SYNTHESIS, CONFORMATION ANALYSIS, AND CHARACTERIZATION OF PHYSIOLOGICALLY IMPORTANT FLAVONOIDS AND ISOFLAVONOIDS

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SYNTHESIS, CONFORMATION ANALYSIS, AND CHARACTERIZATION OF PHYSIOLOGICALLY IMPORTANT FLAVONOIDS AND ISOFLAVONOIDS

Thesis submitted in fulfilment of the requirements for the degree

DOCTOR OF PHILOSOPHY

in the

Department of Chemistry

Faculty of Natural and Agricultural Science

at the

University of the Free State

Bloemfontein

by

Chen-Miao Kuo

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Co-supervisor: **Prof. J. Conradie**

March 2018

Declaration

March 2018

I declare that the dissertation/thesis hereby submitted by me for the **DOCTOR OF PHILOSOPHY** degree at the University of the Free State is my own independent work and has not previously been submitted by me at another university/faculty. I further more cede copyright of the dissertation/thesis in favour of the University of the Free State.

Chen-Miao Kuo

ACKNOWLEDGEMENTS

First of all I wish to pay an immense gratitude to the almighty God for making it possible, by providing me with wisdom, good health, courage, knowledgeable supervisors, and a supportive family.

I feel a deep sense of gratitude to the following people who contributed towards the preparation and production of this thesis.

Prof. B.C.B. Bezuidenhoudt, my supervisor, big thanks for your support, encouragement, assistance, perseverance and invaluable advice throughout this project, without which completion of this thesis would have been impossible. I am indeed so fortunate to have you as my supervisor and for your inspiration throughout the project.

Prof. J. Conradie, my co-supervisor, thank you for great advice and assistance, especially your guidance and assistance on the conformational analysis. I really learnt a lot from you.

Dr. C. Marais, I appreciate your help and advice, and for always being a good assistant for me.

Special thanks to Maretha Du Plessis and Jireh Smit for doing all the mass spectrometry work, and my fellow colleagues, Johannes van Tonder, Rudi Swarts, especially IPC group, thanks for being my friends and it's my honour to have worked with you.

My parents, Kun-Cheng and Hu-Su, for your lifetime support, love, encouragement and for being a constant inspiration. To all my family and friends, thank you for your continued love, support and patience.

Thank you to the UFS and SASOL for financial assistance, without which this work would never have materialized.

Chen-Miao Kuo

A part of this study resulted in the following publications:

1. *Determination of the relationship between theoretical vibrational frequencies and experimental IR absorbance bands in organic molecules: computational study of oxane, chromane and flavan*

   Kuo, C.-M.; Bezuidenhoudt, B.C.B.; Conradie, J. *J. Phys. Org. Chem.* **2013**, *26*, 327.

2. *Crystal structure of 3-bromo-4,6-dibenzyloxy-2-hydroxy acetophenone, $C_{22}H_{19}BrO_4$*

   Hill, T.N.; Kuo, C.-M.; Bezuidenhoudt, B.C.B. *Z. Kristallogr.* NCS **230**, 2015, 2014.

3. *1-(3-Benzyl-4,6-dibenzyloxy-2-hydroxyphenyl)ethanone*

   Hill, T.N.; Kuo, C.-M.; Bezuidenhoudt, B.C.B. Z. *Acta Cryst.*, **2012**, E68, po2863.

4. *Crystal structure of 7-benzyloxy-5,6-dihydroxyflavone, $C_{22}H_{16}O_5$*

   Kuo, C.-M.; Hill, T.N.; Bezuidenhoudt, B.C.B. *Z. Kristallogr.* NCS **230**, 2015, 193.

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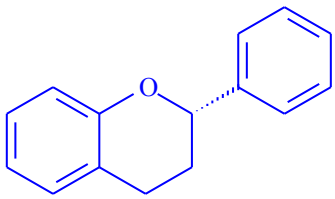
LITERATURE REVIEW

1 Introduction

Polyphenolic compounds are secondary metabolites with structures characterized by the presence of one or more aromatic rings bearing hydroxy substituent(s).[1,2] Typically the flavonoid family of compounds consists of a C_6-C_3-C_6 structure with the chromane ring of cyclic analogues bearing a second aromatic ring in either the 2, 3 or 4 position of the tetrahydrobenzo pyran moiety. The flavonoids, with a C-2 substituted chromane ring (**1.1**), are the most studied compounds in this class of polyphenolic derivatives.



(**1.1**)

The flavonoid pigments, one of the most numerous and widespread groups of natural constituents, are of importance and interest, not only because of their significant natural functions in the economy of the plant, but also because certain members of the group are physiologically active in humans.[3] Many flavonoids, found in vascular plants, are biologically important as they show anti-inflammatory, antiallergic, antischemic, antiplatelet, immunomodulatory, and

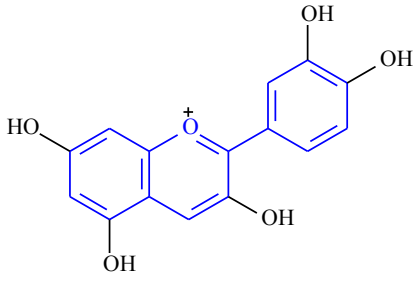
1 Parr, A.J.; Bolwell, G.P. *J. Sci. Food Agric*. **2000**, *80*, 985.

2 Robards, K.; Prenzler, P.D.; Tucker, G.; Swatsitang, P.; Glover, W. *Food Chem*. **1999**, *66*, 401.

3 Harborne, J.B. In *Natural Products of Woody Plants I*, Springer-Verlag Berlin Heidelberg New York, **1989**, 533.

antitumoral activities.[4,5,6] Flavonoids also exhibit antioxidant properties, many of which change metabolic processes and have a positive impact on health.[7]

Anthocyanins (**1.2**), one of the classes of flavonoids, are abundant in soft plant tissue, are intensely coloured and are, therefore, responsible for the red and blue colours in flowers, fruits, and other coloured plant parts.[3] Two other classes of yellow phenolic anthochlor pigments constituting an acyclic C_6-C_3-C_6 skeleton – the chalcones (**1.7**) and aurones (**1.8**) – are of restricted distribution in the plant kingdom[8,9] (Figure 1). These two classes are related in that **1.8** is formed from **1.7** by a dehydrogenation process and related chalcone-aurone pairs tend to be found together in the same plant source. The main occurrence of chalcones and aurones are in the floral tissues of members of the Asteraceae, where they are responsible for the yellow colour in certain families and genera, e.g. in *Coreopsis*. In wood, however, the less intense coloured flavonoids, namely, flavanones (**1.3**), flavones (**1.4**), flavonols (**1.5**), and dihydroflavonols (**1.6**) are more dominant (Figure 1).



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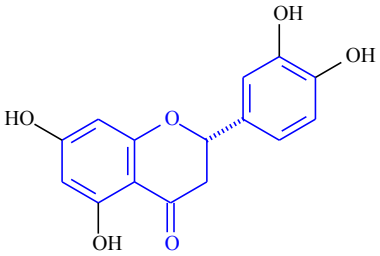

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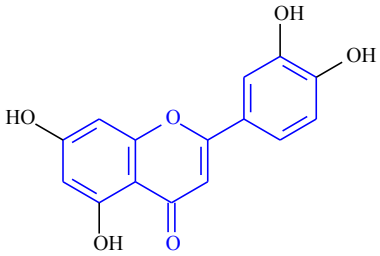


(**1.4**)

[4] Prior, R.L.; Cao, G. *Nutr. Clin. Care* **2000**, *3*, 279.

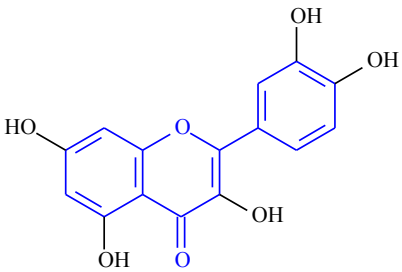
[5] Ielpo, M.T.L.; Basile, A.; Mirando, R.; Moscatello, V.; Nappo, C.; Sorbo, S.; Laghi, E.; Ricciardi, M.M.; Ricciardi, L.; Vuotto, M.L. *Fitoterapia* **2000**, *71*, S101.

[6] Craig, W.J. *Am. J. Clin. Nutr.* **1999**, *70*, 491S.

[7] Beecher, G.R. *J. Nutr.* **2003**, *133*, 3248S.

[8] Harborne, J.B.; Mabry, T.J.(eds) *The Flavonoids: Advances in Research*. Chapman & Hall London, **1982**, 744.

[9] Harborne, J.B.; Mabry, T.J.; Mabry, H.(eds) *The Flavonoids: Advances in Research*. Chapman & Hall London, **1975**, 1204.



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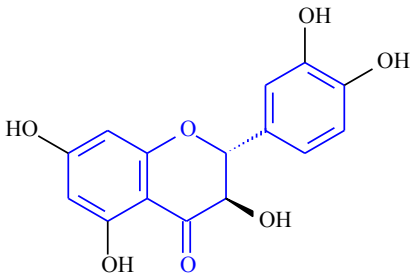

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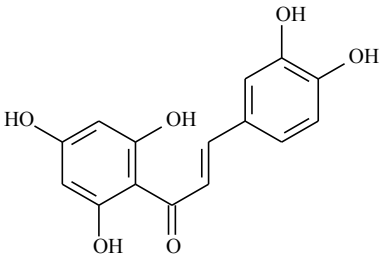
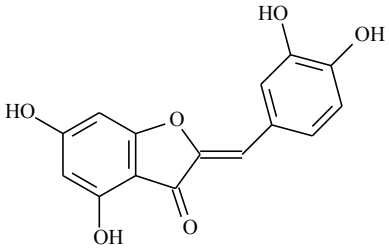


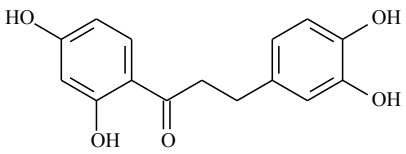
(**1.7**)



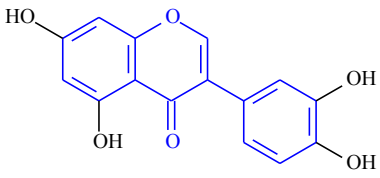
(**1.8**)

Figure 1. Examples of the seven classes of monomeric flavonoids.

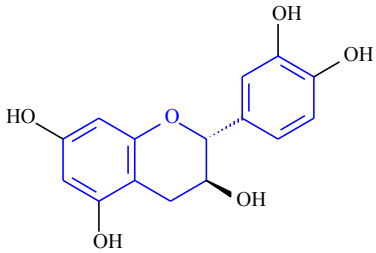
Flavonoids are also components in the diet of numerous herbivores and omnivores, including humans.[10] They are mainly found in fruits, vegetables, and beverage such as red wine, tea, beer and their intake may reach 1 g/day.[11] Various herbs also contain flavonoids.[12] Almost all the flavonoid classes are present in herbs with proven therapeutic activity, including (**1.4**), (**1.5**), (**1.6**), dihydrochalcones (**1.9**) [directly related to chalcones (**1.7**) and derived from them by reduction of the α,β-double bond], isoflavones (**1.10**), flavanols (**1.11**), flavonolignans (**1.12**)[13] (Figure 2).



(**1.9**)



(**1.10**)



(**1.11**)

[10] Karakaya, S.; Nehir, S.E.L. *Food Chem*. **1999**, *66*, 289.

[11] Petersen, J.; Dwyer, J. *Nutr*. *Res*. **1998**, *18*, 1995.

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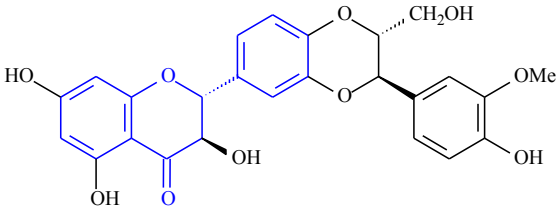
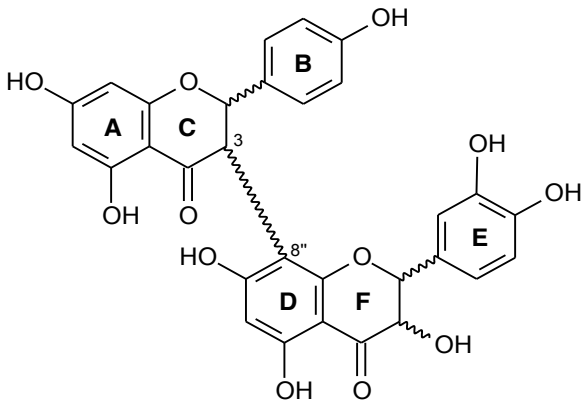
[13] Rice-Evans, C.A.; Packer, L. *Flavonoids in health and disease*. New York: Marcel Dekker, **2003**, 43.



(**1.12**)

Figure 2. Examples of other non-coloured classes of flavonoids.

Over the past decade, scientists have become increasingly interested in the potential of various dietary flavonoids to explain some of the health benefits associated with fruit- and vegetable-rich diets. Many studies were aimed at exploring these important molecules in terms of their relationship between molecular structure and geometry and physiological activity.[14,15,16,17]



GB-2 (**1.13**)

14 Lameira, J.; Alves, C.N.; Moliner, V.; Silla, E. *Eur. J. Med. Chem.* **2006**, *41*, 616.

15 Mendoza-Wilson, A.M.; Glossman-Mitnik, D. *J. Mol. Struct. (THEOCHEM)* **2004**, *681*, 70.

16 van Acker, S.A.B.E.; de Groot, M.J.; van den Berg, D.-J.; Tromp, M.N.J.L.; den Kelder, G.D.-O.; van der Vijgh, W.J.F.; Bast, A. *Chem. Res. Toxicol.* **1996**, *9*, 1305.

17 Antonczak, S. *J. Mol. Struct. (THEOCHEM)* **2008**, *856*, 38.

Since many types of flavonoids contain one or more stereogenic centres {e.g. flavanones (one), flavan-3-ols (two), flavan-3,4-diols (three), flavanone-dihydroflavonols [like GB-2[18] (**1.13**)] (four), catechin-catechin [B3] (five) etc.} (Scheme 1), structure elucidation of these compounds has always been plagued by determination of the absolute configuration at these centres and have included an element of optical measurement in order to define the stereochemistry. Historically, optical rotation and/or electronic circular dichroism (ECD) measurements have found widespread application in determining the absolute configuration of flavonoid compounds.[19,20] While determining the absolute configuration at a single chiral centre in a molecule through application of these methods is quite simple, this aspect in the structure elucidation of compounds with numerous chiral centres represents a challenge.[21,22] The fact that a single Cotton-effect represents the combined effects of several stereogenic centres in more complex molecules, requires the involvement of computational or other methods to determine the collective effect of all the chiral centres. Due to the complexity of the contribution of each chiral centre to the combined Cotton-effect, the relative stereochemistry of the groups attached to the C-ring, as determined by NMR coupling constants, has been used together with ECD measurements to determine the absolute configuration at all the prevailing chiral centres in more complex molecules[19,23,24] The coupling constants of the protons present in the C-ring is, however, not only a function of the relative configuration of the substituents attached to this ring, but also of the conformation of the C-ring, which is also influenced by the number and type of substituents attached to this ring and adjacent to it.[20]

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18 Ding, Y.; Li, X.C.; Ferreira, D. *J*. *Org*. *Chem*. **2007**, *72*, 9010.

19 Xu, Y.J.; Foubert, K.; Dhooghe, L.; Lemière, F.; Maregesi, S.; Coleman, C.M.; Zou, Y.; Ferreira, D.; Apers, S.; Pieters, L. *Phytochemistry* **2012**, *79*, 121.

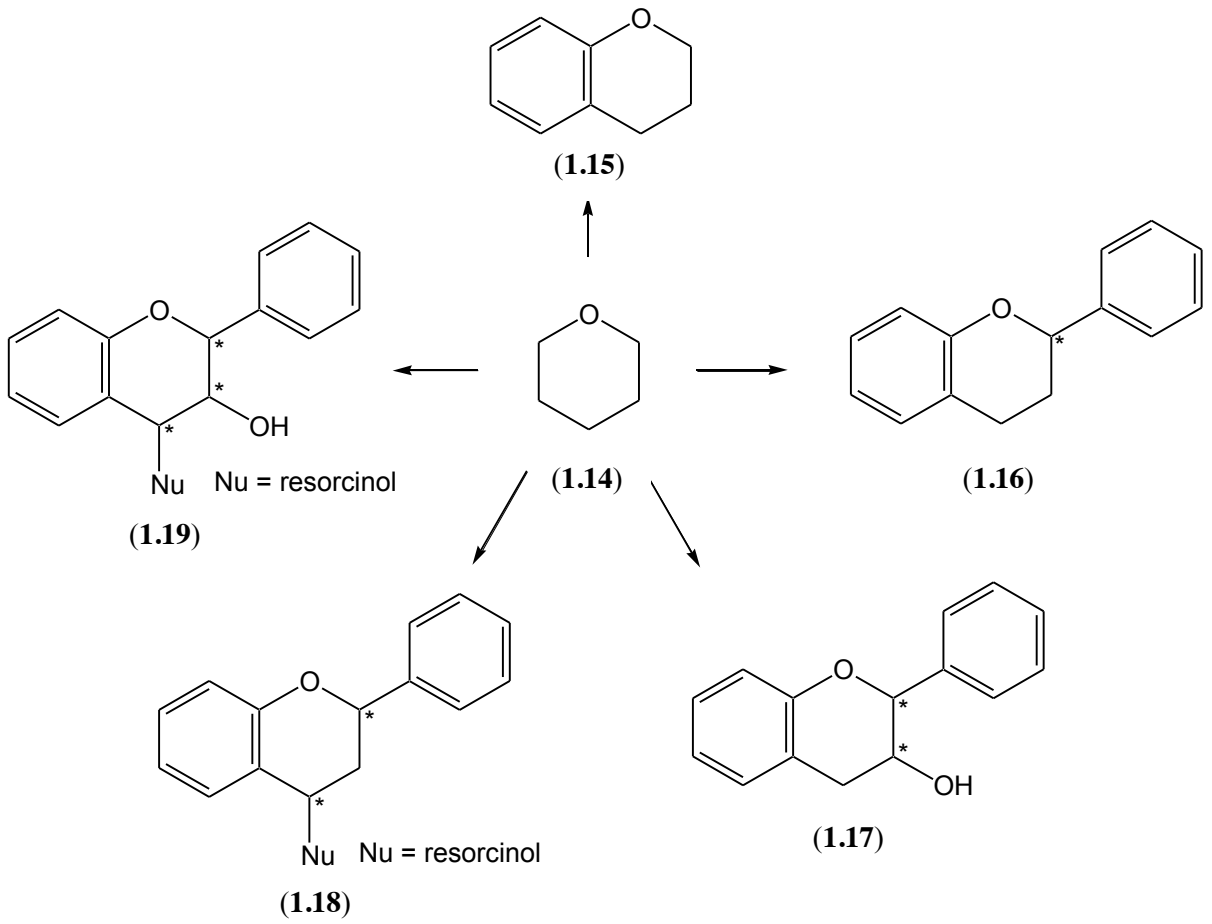
20 Ding, Y.; Li, X.C.; Ferreira, D. *J*. *Nat*. *Prod*. **2010**, *73*, 435.

21 Li, X.C.; Joshi, A.S.; Tan, B.; ElSohly, H.N.; Walker, L.A.; Zjawiony, J.K.; Ferreira, D. *Tetrahedron* **2002**, *58*, 8709.

22 Li, X.C.; Ferreira, D.; Ding Y. *Curr*. *Org*. *Chem*. **2010**, *14*, 1678.

23 Ren, Y.; Lantvit, D.D.; Carcache de Blanco, E.J.; Kardono, L.B.S.; Riswan, S.; Chai, H.; Cottrell, C.E.; Farnsworth, N.R.; Swanson, S.M.; Ding, Y.; Li, X.C.; Marais, J.P.J.; Ferreira, D.; Kinghorn, A.D. *Tetrahedron* **2010**, *66*, 5311.

24 Zhang, F.; Yang, Y.N.; Song, X.Y.; Shao, S.Y.; Feng, Z.M.; Jiang, J.S.; Li, L.; Chen, N.H.; Zhang, P.C. J. *Nat*. *Prod*. **2015**, *78*, 2390.



Scheme 1. Organic molecules for modelling analysis.

During the last decade or two, vibrational circular dichroism (VCD),[25] has emerged as a method of determining the three-dimensional structure of molecules. This fundamentally infrared red (IR) based method can be associated with the chromophores present in a molecule and is a function of the absolute configuration (AC) for the molecule in the vicinity of that chromophore. The enantiomers of a chiral molecule exhibit mirror-image VCD spectra, *i.e.*, at any frequency the VCD intensities of the two enantiomers are equal in magnitude and opposite in sign. As a result, in principle, the VCD spectrum of a chiral molecule of unknown AC allows for the determination of its AC.[26] Both the IR and VCD spectra of diasteriomers—e.g., (R,R) vs. (R,S)—differ; however, for enantiomers—(R,R) vs. (S,S)—the IR spectra are again identical, but the VCD spectra are of opposite sign.

25 P. J. Stephens, F. J. Devlin, *Chirality* **2000**, *12*, 172.

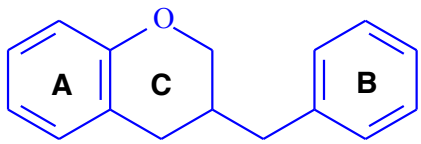
26 Stephens, P.J.; Aamouche, A.; Devlin, F.J. *J. Org. Chem.* **2001,** *66*, 3671.

In order to be able to apply VCD technology to the problem of determining the AC at each stereogenic centre in complex flavonoid molecules, which is the ultimate objective of the study started during this research project, several preliminary investigations had to be completed. In this regard a correlation between the observed IR absorption bands in solution and the chromophore in the molecule responsible for that particular band had to be determined. Since the absorption of a chromophore would be influenced by the structure of the molecule in its vicinity, knowledge of the preferred conformation or set of low energy conformations of the molecule would be required. The initial objective of the current study therefore was to determine the preferred conformation or set of low energy conformations of typical flavonoid molecules starting from simple analogues and progressing to more complex molecules (Scheme 1) by molecular modelling methods. Secondly, the relationship between gas phase theoretical vibrational frequencies, obtained by modelling, and experimental IR absorbance bands of flavonoid molecules in solution were determined and possible VCD spectra calculated. While a comparison between calculated and experimentally obtained VCD spectra would be the desired final outcome of a comprehensive investigation in this regard allowing for the validation of VCD as a tool for determining the AC of different flavonoid molecules, this would require all compounds investigated in the current study to be prepared in enantiomericly pure form and the absolute configuration at every chiral centre determined unambiguously. Since that will entail a full enantioselective flavonoid synthesis project, it will be the theme of a follow-up investigation and does not form part of the current study.

2 Homoisoflavonoids: Structure and Synthesis

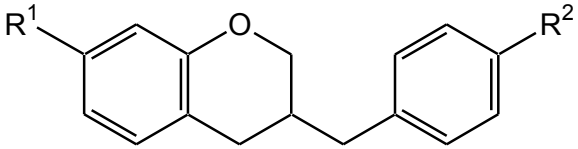
2.1 Introduction

Homoisoflavonoids (e.g. **2.1**) are structurally related to flavonoids,[1] but with their B- and C-rings connected by an additional CH_2 group (Figure 1). Although homoisoflavonoids forms a small sub-group of the natural flavonoids, ca 240 examples of these compounds have nevertheless been isolated from nature. The homoisoflavonoid family of compounds consists of mainly 4 basic classes differing by the position of the double bond and the level of unsaturation and oxygenation presented in the heterocyclic ring, i.e. 3-benzylchromans (**2.2**), 3-benzylchroman-4-ones (**2.3**), 3-benzylidenechroman-4-ones (**2.4**) and 3-benzyl-4-chromones (**2.5**) (Figure 2). Some representative examples of these classes of naturally occurring homoisoflavonoids will be discussed in the following paragraphs.

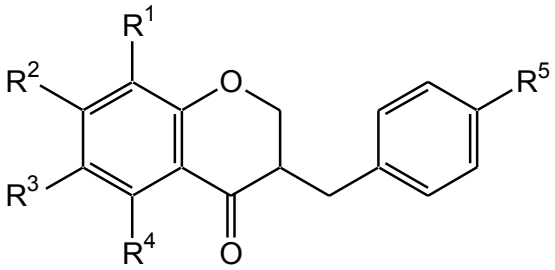


(**2.1**)

Figure 1. Basic skeleton for homoisoflavonoids.

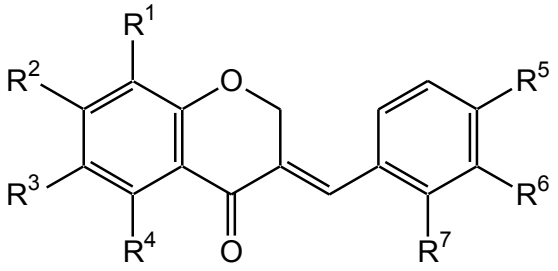


(**2.2**)

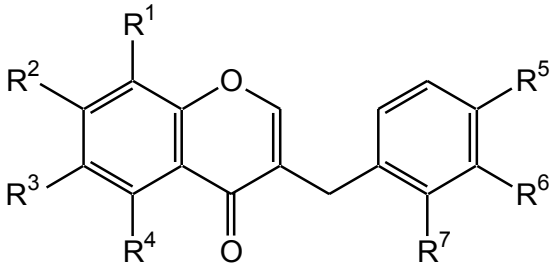


(**2.3**)

[1] Lockhart, I.M. *In The Chemistry of Heterocyclic Compounds Chromenes, Chromanones and Chromones*; Ellis, G. P., Ed.; Wiley: New York, **1977**.



(**2.4**)



(**2.5**)

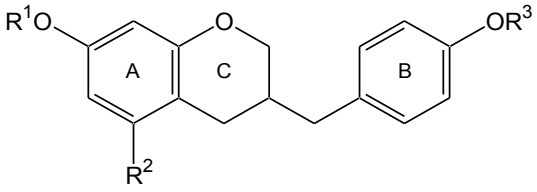
Figure 2. Classes of homoisoflavonoids.

2.2 Structure variation in natural homoisoflavonoids

2.2.1 3-Benzylchromans (2.2)

The isoflavan equivalent of the homoisoflavonoid series, 3-benzylchromans (**2.2**), also contains a saturated heterocyclic ring with no oxygenation present and can be regarded as the most basic structure of all the homoisoflavonoids. While only three examples of this type of compound, with a resorcinol or phloroglucinol A-ring and *para*-substituted B-ring (Table 1), have been isolated to date, these homoisoflavonoids are quite widespread in the plant kingdom and have been found in different plants of the Agavaceae family, including *Dracaena cinnabari*, *Dracaena draco*, *Dracaena cochinchinensis*, *Dracaena loureiri* and *Agave Americana*. Although limited in structural diversity, one of these compounds, **2.7**, has been found to show antioxidant activity.[2]

Table 1. 3-Benzylchromans found in nature.



Compound	R^1	R^2	R^3	Plant source
(**2.6**)	H	H	Me	*Agave barbadensis*,[3] *Anemarrhena asphodeloides*[3]
(**2.7**)	H	H	H	*Dracaena draco*,[4] *D. loureiri*,[3] *D. cochinchinensis*,[3]

2 Gupta, D.; Bleakley, B.; Gupta, R.K. *J. Ethnopharmacol*. **2008**, *115*, 361.

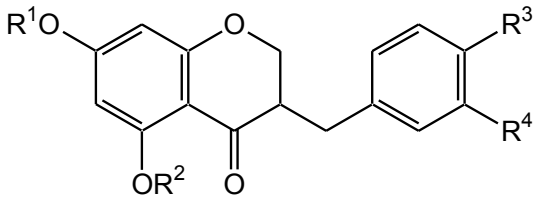
3 Yu. Y.C.; Zhu, S.; Lu, X.W.; Wu, Y.; Liu, B. *Eur. J. Org. Chem*. **2015**, 4964.

				D. cambodiana[3]
(**2.8**)	Me	OMe	H	*Dracaena draco*[5]

2.2.2 3-Benzylchroman-4-ones (2.3)

3-Benzylchroman-4-ones (**2.3**), with a carbonyl group at C4, commonly display a phloroglucinol type A-ring and a 4- or 3,4 disubstituted B-ring. All of the oxygen functions can either be free phenolic (eg. **2.9**) or partly (eg. **2.11** and **2.15**) or fully methylated (eg. **2.12**) (Table 2). Compound **2.13**, obtained from *Scilla nervosa*, however, was isolated as a natural 4'-acetoxy derivative.

Table 2. Examples of 3-benzylchroman-4-ones with phloroglucinol type A-ring.



Cpd no.	Substituents				Plant sources
	R^1	R^2	R^3	R^4	
(**2.9**)	H	H	OH	H	*Ledebouria revoluta*[6]
(**2.10**)	H	H	OMe	H	
(**2.11**)	Me	H	OMe	H	*Scilla nervosa*[7,8]
(**2.12**)	Me	Me	OMe	H	
(**2.13**)	Me	Me	OAc	H	
(**2.14**)	H	H	OMe	OH	*Scilla kraussii*[9]
(**2.15**)	H	H	OH	OMe	*Scilla zebrina*[10]

4 Kirkiacharian, B.S.; Tongo, H.G.; Bastide, J.; Bastide, P.; Grenie, M.M. *Eur. J. Med. Chem.* **1989**, *24*, 541.

5 González, A.G.; León, F.; Sánchez-Pinto, L.; Padrón, J.I.; Bermejo, J. *J. Nat. Prod.* **2000**, *63*, 1297.

6 Moodley, N.; Crouch, N.R.; Mulholland, D.A.; Slade, D.; Ferreira, D. *S. Afr. J. Bot.* **2006**, *72*, 517.

7 Silayo, A.; Ngadjui, B.T.; Abegaz, B.M. *Phytochemistry* **1999**, *52*, 947.

8 Bangani, V.; Crouch, N.R.; Mulholland, D.A. *Phytochemistry* **1999**, *51*, 947.

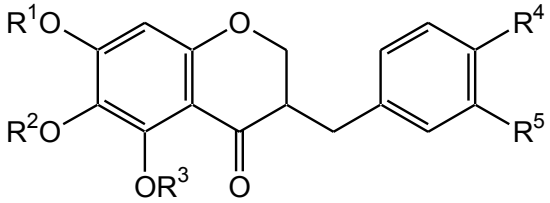
9 Crouch, N.R.; Bangani, V.; Mulholland, D.A. *Phytochemistry* **1999**, *51*, 943.

10 Mulholland, D.A.; Crouch, N.R.; Koorbanally, C.; Moodley, N.; Pohl, T. *Biochem. Syst. Ecol.* **2006**, *34*, 251.

(**2.16**)	H	H	OMe	OMe	*Scilla nervosa*
(**2.17**)	Me	H	OH	OMe	
(**2.18**)	Me	H	OMe	OH	

In addition to a phloroglucinal type A-ring, it is also common to find homoisoflavanones with a 5,6,7-trioxygenated substitution pattern. While these oxygen functions may all be methylated (eg **2.23**), it is more common to find one methoxy group, which may either be at positions 6 (eg. **2.19**) or 7 (eg. **2.27**), or two methoxy functions, which may be at positions 5 and 7 (eg. **2.21**), or 6 and 7 (eg. **2.26**), of the A-ring. One compound (**2.23**) with a fully methoxylated A-ring have also been isolated from *Scilla nervosa* (Table 3). Again the B-ring of these compounds may display a *para*-hydroxy (eg. **2.19**) or methoxy (eg. **2.20**) substituent or catechol type B-ring with one (eg. **2.24** and **2.26**) of these functions being methylated (Table 3). One of the phloroglucinol type analogues (**2.9**) from *Ledebouria revoluta* has been screened and found to show primary cytotoxic and antiproliferative properties.

Table 3. 3-Benzylchroman-4-ones with trioxygenated A-rings.

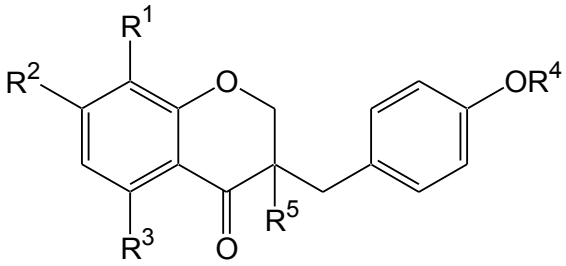


Cpd no.	Substituents					Plant sources
	R^1	**R^2**	**R^3**	**R^4**	**R^5**	
(**2.19**)	H	Me	H	OH	H	*Scilla dracomontana*,[9] *S. Nervosa*, *S. natalensis*[9]
(**2.20**)	H	Me	H	OMe	H	*Scilla dracomontana*
(**2.21**)	Me	H	Me	OMe	H	*Scilla nervosa*
(**2.22**)	Me	H	Me	OH	H	*Scilla zebrina*
(**2.23**)	Me	Me	Me	OH	H	*Scilla nervosa*
(**2.24**)	H	Me	H	OMe	OH	*Scilla natalensis*, *S. dracomontana*

(**2.25**)	H	Me	H	OMe	OH	*Scilla plumbea*[11]
(**2.26**)	Me	Me	H	OH	OMe	*Scilla nervosa*
(**2.27**)	Me	H	H	OH	OMe	*Scilla zebrina*
(**2.28**)	Me	H	Me	OH	OMe	
(**2.29**)	Me	Me	H	OH	OH	*Scilla scilloides*[12]
(**2.30**)	H	H	H	OMe	OH	*Scilla dracomontana, S. nervosa*

While 5,6,7-trioxygenation seems to be quite common amongst the homoisoflavanones, two compounds lacking oxygenation at the 6 position, but with a hydroxy group (**2.31**) and methoxy substituent (**2.32**) at the 8-position, have also been found in *Scilla nervosa* and *Ledebouria revolute*, respectively. Again these analogues display a methoxy and hydroxy function respectively in the *para*-position of the B-ring, while the oxygen functions at the positions 5 and 7 positions are free phenolic for (**2.32**) and methylated in (**2.31**) (Table 4). Compound (**2.33**), isolated from *Chlorophytum inornatum,* displayed a rare methylenedioxy moiety at positions 7 and 8, together with *p*-methoxy substituted B-ring and showed antimycobacterial acitivity. A single example of these homoisoflavonoids with a hydroxy moiety attached to C3 of the heterocyclic ring, Eucomol (**2.34**), has also been isolated from *Scilla dracomontana* by Mulholland *et al*.[9]

Table 4. 3-Benzylchroman-4-ones exhibiting 'other' substitution patterns.



Cpd no.	Substituents					Plant sources
	R^1	**R^2**	**R^3**	**R^4**	**R^5**	
(**2.31**)	OH	OMe	OMe	Me	H	*Scilla nervosa*

11 Pohl, T.; Koorbanally, C.; Crouch, N.R.; Mulholland, D.A. *Biochem. Syst. Ecol.* **2001**, *29*, 857.

12 Nishida, Y.; Eto, M.; Miyashita, H.; Ikeda, T.; Yamaguchi, K.; Yoshimitsu, H.; Nohara, T.; Ono, M. *Chem. Pharm. Bull.* **2008**, *56*, 1022.

(**2.32**)	OMe	OH	OH	H	H	*Ledebouria revoluta*[6]
(**2.33**)	OCH_2O		H	Me	H	*Chlorophytum inornatum*[13]
(**2.34**)	H	OH	OH	Me	OH	*Scilla dracomontana*

2.2.3 3-Benzylidenechroman-4-ones (2.4)

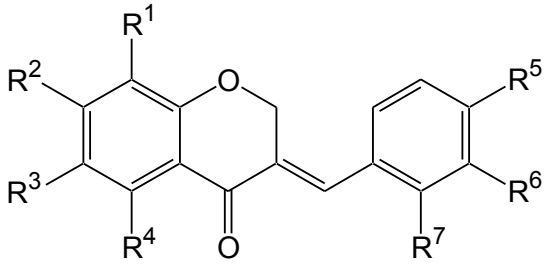
3-Benzylidene-chroman-4-ones (**2.4**), with an exocyclic double bond at C3, are also wide-spread in plants containing homoisoflavonoids and are characterized by a singulet CH resonance at δ 7.6 – 7.9 (d, H-9) and δ 5.2 -5.4 (d, 2-CH_2) in the ^{1}H NMR spectra of the E-isomers.[14,15] These compounds may act as growth inhibitors of the sporogeneses and the enzymes involved in the infection mechanism of *Phytophthora parasitica* and exhibit anti-inflammatory, antifungal, antioxidant, anti-aggregating, analgesic, platet, and hypocholestrolenic activities.[8] As indicated in Table 5 the family of naturally occurring (E)-3-benzylidene-chroman-4-ones currently consists of ca 17 compounds with the majority having a oxygen function, which can be free phenolic (eg. **2.35**) or methylated (eg. **2.39**) at the 7-position of the A-ring and a 4- (eg. **2.36**) or 3,4-dioxygenated (eg. **2.43**) B-ring. Five of the known 3-benzylidene-chroman-4-ones, i.e **2.35** – **2.39**, have a 5,7-dioxygenated A-ring, while three (**2.40** – **2.42**) display a pyrogallol A-ring and another three analogues (**2.36**, **2.37** and **2.43**) exhibit 6,7-dioxygenation. While 3',4'-dihydroxy, 3',4'-hydroxy-methoxy and 3',4'-dimethoxy substituents are quite common for these benzylidene-chroman-4-ones, some examples with a 3',4'-methylenedioxy substitution pattern on the B-ring (eg. **2.45** and **2.47**), have also been isolated. In contrast to other isoflavonoids where 2',4'-dihydroxylation (on the B-ring) is a common feature, only one benzylidene-chroman-4-one (**2.51**) with this substitution pattern on the B-ring has been found in nature to date.

13 Zhang, L.; Zhang, W.G.; Kang, J.; Bao, K.; Dai, Y.; Yao, X.S. *J. Asian Nat. Prod. Res.* **2008**, *10*, 909.

14 Silayo, A.; Ngadjui, B.T.; Abegaz, B.M. *Phytochemistry* **1999**, *52*, 947.

15 Maheswara, M.; Siddaiah, V.; Venkata Rao, C. *Chem. Pharm. Bull.* **2006**, *54*, 1193.

Table 5. (E)-3-Benzylidene-chroman-4-ones isolated from plants.



Cpd no.	Substituents							Trivial name	Plant sources
	R_1	R_2	R_3	R_4	R_5	R_6	R_7		
(**2.35**)	H	OH	H	OH	OMe	H	H	-	*Eucomis bicolor*[16]
(**2.36**)	H	OH	OMe	OH	OH	H	H	-	*Scilla nervosa*
(**2.37**)	H	OH	OMe	OH	OMe	H	H	-	
(**2.38**)	H	OH	H	OH	OH	H	H	-	
(**2.39**)	H	OMe	H	OH	OH	H	H	-	
(**2.40**)	OH	OH	H	H	OMe	H	H	Intricatinol	*Hoffmanosseggia intricata*[17,18]
(**2.41**)	OH	OMe	H	H	OMe	H	H	Intricatin	
(**2.42**)	OMe	OH	H	H	OMe	H	H	8-Methoxy bonducellin	
(**2.43**)	H	OMe	OMe	H	OMe	OH	H	-	*Caesalpinia pulcherrima*[15,19,20]
(**2.44**)	H	OH	H	H	OMe	OH	H	-	
(**2.45**)	H	OMe	H	H	OCH_2O		H	-	
(**2.46**)	H	OMe	H	H	OMe	OMe	H	-	
(**2.47**)	H	OH	H	H	OCH_2O		H	-	

16 Alipour, E.; Mousavi, Z.; Safaei, Z.; Pordeli, M.; Safavi, M.; Firoozpour, L.; Mohammadhosseini, N.; Saeedi, M.; Ardestani, S.K.; Shafiee, A.; Foroumadi, A. *DARU J. Pharm. Sci.* **2014**.

17 Wall, M.E.; Wani, M.C.; Manikumar, H.T.; Taylor, H.; McGivney, R.J. *Nat. Prod.* **1989**, *52*, 774.

18 Siddaiah, V.; Maheswara, M.; Rao, C.V.; Venkateswarlu, S.; Subbaraju, G.V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 288.

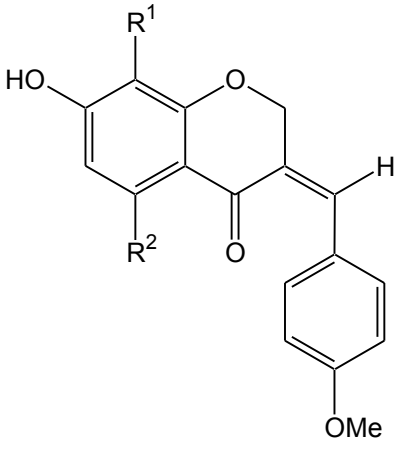
19 Thirupathi, P., Chemical investigation on Natural and Synthetic Heterocyclic Compounds, Ph.D Thesis, Indian Institute of Chemical Technology, Hyderabad, **2008**.

20 Das, B.; Thirupathi, P.; Ravikanth, B.; Kumar, R.A.; Sarma, A.V.S.; Basha, S.J. *Chem. Pharm. Bull.* **2009**, *57*, 1139.

(**2.48**)	H	OH	H	H	OMe	H	H	Bonducellin	
(**2.49**)	H	OMe	H	H	OMe	H	H	7-*O*-methyl bonducellin	
(**2.50**)	H	OH	H	H	OH	OH	H	Sappanone A	
(**2.51**)	H	OH	H	H	OMe	H	OMe	2'-Methoxy bonducellin	

Although most of the 3-benzylidene-chroman-4-ones have been isolated with the E-geometry, a few analogues have also been found in natural sources with a Z-benzylidene system (Table 6). The Z-geometry of these compounds forces the C9 proton away from the anisotropic region of the carbonyl group and causes this vinyl proton to display an upfield chemical shift to ca δ 6.7 – 7.0, while the 2-methylene group is also shifted upfield to ca δ 4.9 – 5.0 (*vs* δ 7.6 – 7.9 and δ 5.2 -5.4 respectively for the E-isomers).[14,15,21] Since it has been demonstrated that the E and Z-isomers are prone to light induced E/Z isomerizarion,[22,23] the fact that, in many instances, both isomers have been isolated from the same plant may be due to this isomerisation taking place during the isolation and purification process and that these analogues may be viewed as artefacts of the real compound present in the plant.

Table 6. Examples of naturally occurring Z-3-benzylidene-chroman-4-ones. [18,21]



21 Roy, S.K.; Agrahari, U.C.; Gautam, R.; Srivastava, A.; Jachak, S.M. *Nat*. *Prod*. *Research* **2012**, *26*, 690.

22 Boehler, P.; Tamm, Ch. *Tetrahedron Lett*. **1967**, *36*, 3479.

23 Siddaiah, V.; Rao, C.V.; Venkateswarlu, S.; Krishnaraju, A.V.; Subbaraju, G.V. *Bioorg*. *Med*. *Chem*. **2006**, *14*, 2545.

Cpd no.	Substituents		Trivial name	Plant sources
	R_1	R_2		
(**2.52**)	H	H	Isobonducellin	*Caesalpinia pulcherrima*
(**2.53**)	H	OH	Eucomine	*Eucomis bicolor*
(**2.54**)	OMe	H	-	*Hoffmanosseggia intricata*
(**2.55**)	OH	H	-	

2.2.4 Homoisoflavones (2.5)

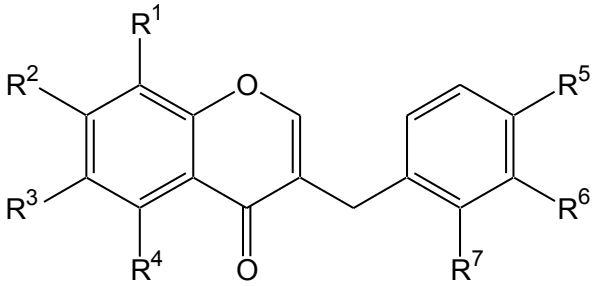
While a large number of homoisoflavones (3-benzyl-4-chromones) have been synthesised en route to other homoisoflavonoids, only about ten of these compounds have been isolated as natural products (Table 7). While these analogues also contain a methylene group and a single double bonded proton, they can be distinguished from the previously mentioned benzylidene analogues (*cf* paragraph 2.2.3) by the fact that the 2-proton appears down-field from that of the benzylidene compounds (δ 7.9 – 8.2 *vs* 6.7 - 7.9), while the CH_2 group appears up-field wrt that in the 3-benzylidene-chroman-4-ones (δ 3.5 – 3.7 *vs* 4.9 – 5.4). The first homoisoflavone (**2.57**), isolated form *Ophiopogon jaburan*,[24] displayed 5,7-dihydroxy substitution on the A-ring and a *p*-hydroxy function on the B-ring and was reported by Rao *et al*.[25] to show angioprotective, antiallergic and antihistaminic properties.[26] While about half of the currently known homoisoflavones (**2.56** to **2.59**) carry only oxygenated (hydroxy, methoxy and methylenedioxy) substitutents, a number of these compounds have been found where methyl substituents are attached to the 6 and/or 8 positions of the A-ring (**2.60** to **2.65**).

24 Watanabe, Y.; Sanada, S.; Ida, Y.; Shoji, J. *Chem*. *Pharm*. *Bull*. **1985**, *33*, 5358.

25 Rao, V.M.; Damu, G.L.V.; Sudhakar, D.; Siddaiah, V.; Rao, C.V. *Arkivoc* **2008**, *xi*, 285.

26 Kirkiacharian, B.S.; Tongo, H.G.; Bastide, J.; Bastide, P.; Grenie, M.M. *Eur*. *J*. *Med*. *Chem*. **1989**, *24*, 541.

Table 7. Examples of homoisoflavones.[5,15,24,27,28]



Cpd no.	Substituents							Trivial name	Plant sources
	R^1	**R^2**	**R^3**	**R^4**	**R^5**	**R^6**	**R^7**		
(**2.56**)	H	OH	H	H	OH	H	H	-	*Dracaena draco*
(**2.57**)	H	OH	H	OH	OH	H	H	-	*Ophiopogon jaburan*
(**2.58**)	H	OH	H	OH	OMe	H	H	-	*Furcraea bedinghausii* Koch
(**2.59**)	H	OH	H	OH	OCH_2O		H	-	
(**2.60**)	OMe	OH	CH_3	OH	OMe	H	OH	-	
(**2.61**)	H	OH	CH_3	OH	OH	H	H	-	*Ophiopogon jaburan*
(**2.62**)	H	OMe	CH_3	OH	OH	OH	H	-	
(**2.63**)	CH_3	OH	H	OH	OCH_2O		OH	-	
(**2.64**)	CH_3	OH	CH_3	OH	OCH_2O		H	8-Methyl-ophiopogonone A	*Ophiopogon japonicus*
(**2.65**)	CH_3	OH	CH_3	OH	OCH_2O		OH	-	

2.2.5 Other types of homoisoflavonoids

Apart from the above mentioned homoisoflavonoid classes, some compounds with extraordinary structures have also been isolated (Figure 3). One homoisoflav-3-ene (**2.66**) have been obtained from the heartwood of *Caesalpinia sappan* L,[29] while a homoisoflavanone containing a benzyl

27 Li, N.; Zhang, J.Y.; Zeng, K.W.; Zhang, L.; Che, Y.Y.; Tu, P.F. *Fitoterapia* **2012**, *83*, 1042.

28 Teponno, R.B.; Ponou, B.K.; Fiorini, D.; Barboni, L.; Tapondjou, L.A. *Int. Lett. Chem. Phys. Astron.* **2013**, *16*, 9.

29 Zhao, H.; Bai, H.; Wang, Y.; Li, W.; Koike, K. *J. Nat. Med.* **2008**, *62*, 325.

alcohol moiety (**2.67**) was found in *Polygonum ferrugineum* (Polygonaceae) by López *et al.*[30] Quite a number of homoisoflavans with 3,4-dioxygenated heterocyclic rings were also obtained. In this regard, Sappanol (**2.68**) as isolated from *Caesalpinia sappan*[31] can be viewed as a reduced form of the 3-hydroxyhomoisoflavanone (**2.34**), while analogues with a 4-methoxy group, i.e. 3',4-di-*O*-methylepisappanol (**2.69**),[32] 3'-deoxy-4-*O*-methylsappanol (**2.70**)[33] and 3'-deoxy-4-*O*-methylepisappanol (**2.71**)[34] were obtained from traditional Chinese medicines and medicinal plants like, *Caesalpinia sappan* and the roots of *C. decapetala*.

(+)-Scillavone A (**2.72**), (from *Scilla scilloides*[35]), Scillascillin (**2.73**)[36] and 2-hydroxy-7-*O*-methylscillascillin (**2.74**) (from *Scilla scilloides*[39]) contain a rare spiro cyclobutane type linkage between the aromatic B-ring and C-3 of the heterocyclic C-ring, while (**2.74**) also exhibits an unusual OH function attached to the 2-position of the heterocyclic C-ring. Furthermore, Heller and Tamm[37] reported the isolation of Brazilin[33,38] (**2.75**) and Hematoxylin[39] (**2.76**) from the heartwood of *Caesalpinia sappan* and *Haematoxylon campechianum* L., respectively; both compounds which contain a cyclopentane ring fused between the aromatic B-ring and position 4 of the heterocyclic C- ring.

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30 López, S.N.; Sierra, M.G.; Gattuso, S.J.; Furlán, R.L.; Zacchino, S.A. *Phytochemistry* **2006**, *67*, 2152.

31 Namikoshi, M.; Nakata, H.; Yamada, H.; Nagai, M.; Saitoh, T. *Chem. Pharm. Bull.* **1987**, *35*, 2761.

32 Zhao, H.; Wang, X.; Li, W.; Koike, K.; Bai, H. *Nat. Prod. Res.: Formerly Natural Product Letters* **2014**, *28*, 102.

33 Mitani, K.; Takano, F.; Kawabata, T.; Allam, A.E.; Ota, M.; Takahashi, T.; Yahagi, N.; Sakurada, C.; Fushiya, S.; Ohta, T. *Planta Med.* **2013**, *79*, 37.

34 Moon, H.I.; Chung, I.M.; Seo, S.H.; Kang, E.Y. *Phytother Res.* **2010**, 24, 463.

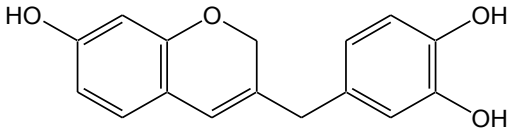
35 Nishida, Y.; Eto, M.; Miyashita, H.; Ikeda, T.; Yamaguchi, K.; Yoshimitsu, H.; Nohara, T.; Ono, M. *Chem. Pharm. Bull.* **2008**, *56*, 1022.

36 Rawal, V.H.; Cava, M.P. *Tetrahedron Lett.* **1983**, *24*, 5581.

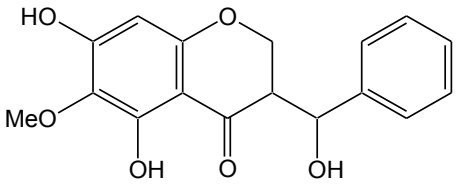
37 Cadby, P.A.; Cooke, R.G.; Edwards, J.M.; Heller, W.; Jefford, C.W.; Lederer, E.; Lefrancier, P.; Dev, S.; Tamm, C. *Prog. Chem. Org. Nat. Prod.* **2012**, page 106.

38 Wang, X.; Zhang, H.; Yang, X.; Zhao, J.; Pan, C. *Chem. Commun.* **2013**, *49*, 5405.

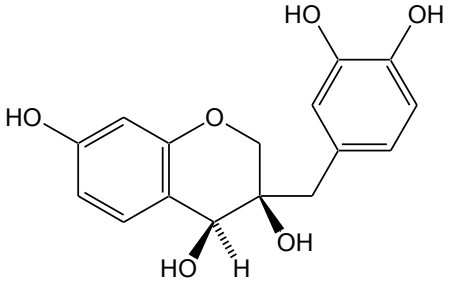
39 Lin, L.G.; Xie, H.; Li, H.L.; Tong, L.J.; Tang, C.P.; Ke, C.Q.; Liu, Q.F.; Lin, L.P.; Geng, M.Y.; Jiang, H.; Zhao, W.M.; Ding, J.; Ye, Y. *J. Med. Chem.* **2008**, *51*, 4419.



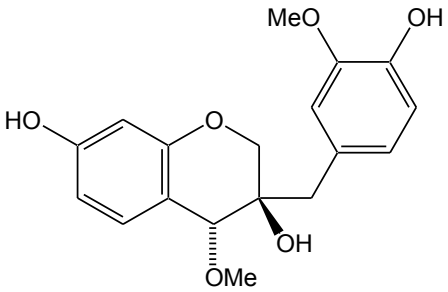
(**2.66**)



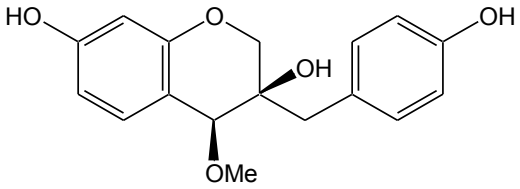
(**2.67**)



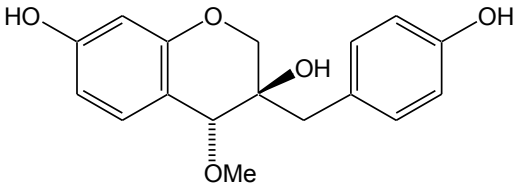
(**2.68**) Sappanol



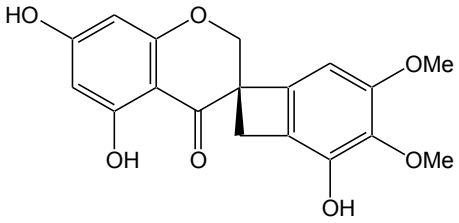
(**2.69**) 3',4-di-*O*-methylepisappanol



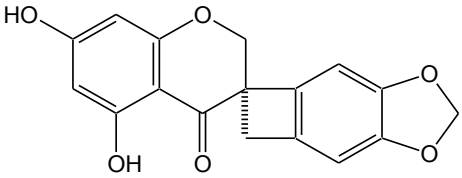
(**2.70**) 3'-Deoxy-4-*O*-methylsappanol



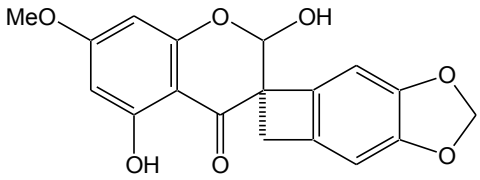
(**2.71**) 3'-Deoxy-4-*O*-methylepisappanol



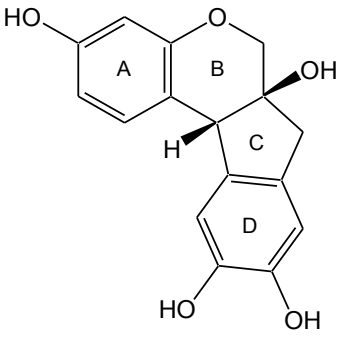
(**2.72**) (+)-Scillavone A



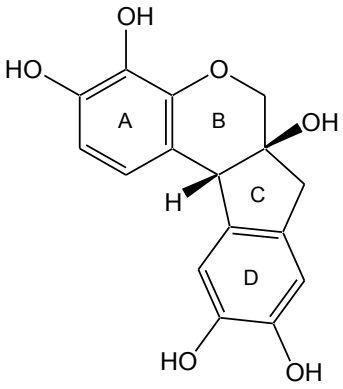
(**2.73**) Scillascillin



(**2.74**) 2-Hydroxy-7-*O*-methylscillascillin



(**2.75**) Brazilin



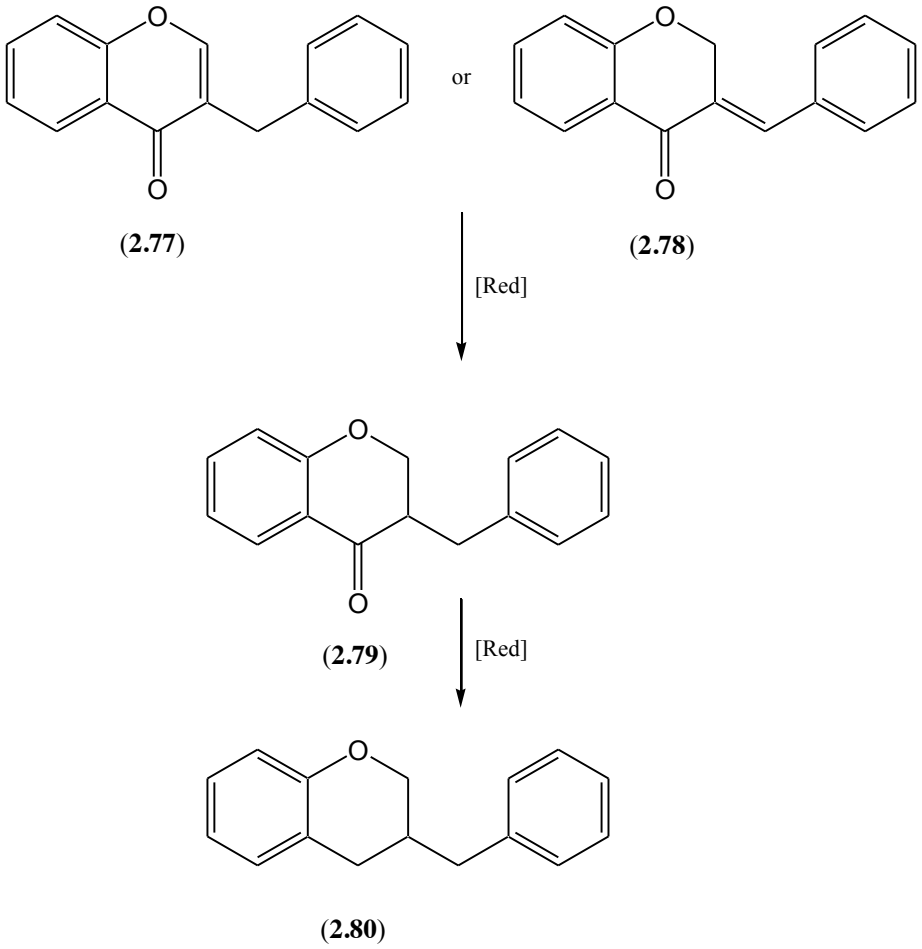
(**2.76**) Hematoxylin

Figure 3. Some isolated rare homoisoflavonoids.

2.3 Synthesis of homoisoflavonoids

2.3.1 Introduction

Since most classes of homoisoflavonoids can be reached through some reductive transformation of the corresponding homoisoflavone (**2.77**) or 3-benzylidenechroman-4-one (**2.78**) (Scheme 1), procedures for the synthesis of many types of homoisoflavonoids have been dominated by the development of methodology for the formation of homoisoflavones and 3-benzylidenechroman-4-ones.



Scheme 1. Reductive transformation of homoisoflavones or 3-benzylidenechroman-4-ones to homoisoflavans.

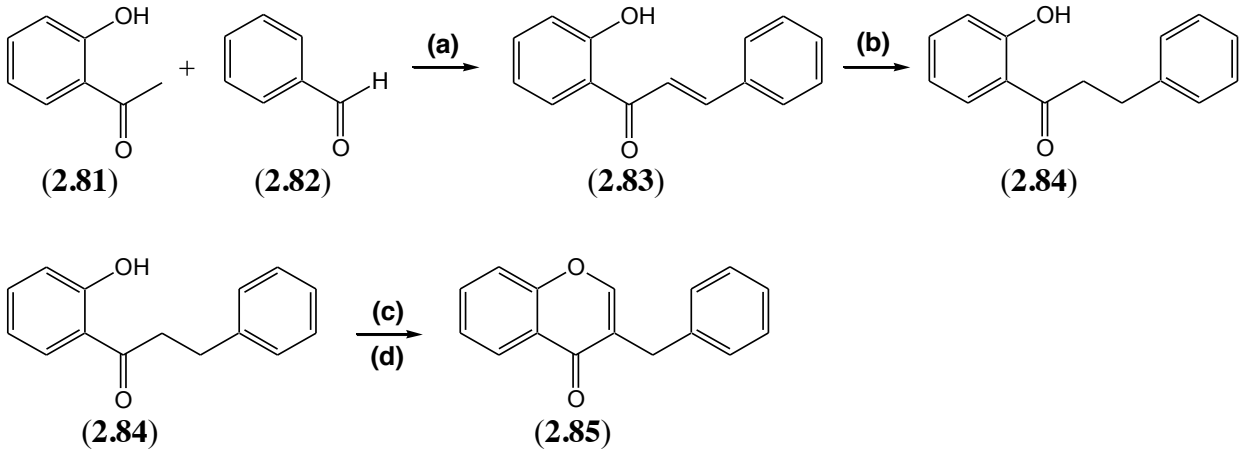
2.3.2 Homoisoflavone preparation

(i) *By introducing a C1 unit into a dihydrochalcone entity*

While the most obvious route towards the formation of homoisoflavones would be through the addition of a C1 unit to an appropriate dihydrochalcone (DHC) analogue, this approach has been followed by most of the earlier workers in the field of homoisoflavone synthesis and still remains one of the favoured methods for the preparation of these compounds. Base catalysed aldol condensation between an appropriate acetophenone (**2.81**) and benzaldehyde (**2.82**) would lead to the chalcone (**2.83**), which could easily be hydrogenated/reduced to the corresponding DHC (**2.84**) (Scheme 2), before introducing the C1 unit. The pivotal step in this approach, i.e. attachment of the C1 fragment to the α-carbon of the DHC, have been effected by the utilization of several reagent systems like BF_3-etherate/DMF/PCl_5,[40] HCO_2Et/Na,[41] 2,4,6-trichloro-1,3,5-

[40] Siddaiah, V.; Rao, C.V.; Venkateswarlu, S.; Subbaraju, G.V. *Tetrahedron* **2006**, *62*, 841.

triazine/DMF [42] and the Vilsmeier reagent (generated from phthaloyl dichloride/DMF). [43] Subsequent cyclization involving the 2'-OH function of the DHC (**2.84**) and a leaving group on the newly introduced carbon would then complete the heterocyclic ring and lead to the homoisoflavone (**2.85**).



Scheme 2. Reagents and conditions: (a) EtOH, KOH at 0 ^{o}C; (b) $NaBH_4$, EtOH; (c) $HC(OEt)_3$, 70% $HClO_4$; (d) H_2O, reflux.

It is worth mentioning that over 80% yields were obtained for homoisoflavones by the treatment of 2'-hydroxydihydrochalcones (**2.84**) with triethylorthoformate and 70% perchloric acid followed by aqueous hydrolysis of the intermediate perchlorates[44] (Scheme 2). Kirkiacharian and co-workers[45,46] reported the utilization of ethyl formate in acetic acid and dimethylaminodimethoxymethane as C1 fragment.

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41 Davis, .F.A.; Chen, B-C. *J. Org. Chem.* **1993**, 58, 1751.

42 Basha, G.M.; Yadav, S.K.; Srinuvasarao, R.; Prasanthi, S.; Ramu, T.; Mangarao, N.; Siddaiah, V. *Can. J. Chem.* **2013**, *91* 763.

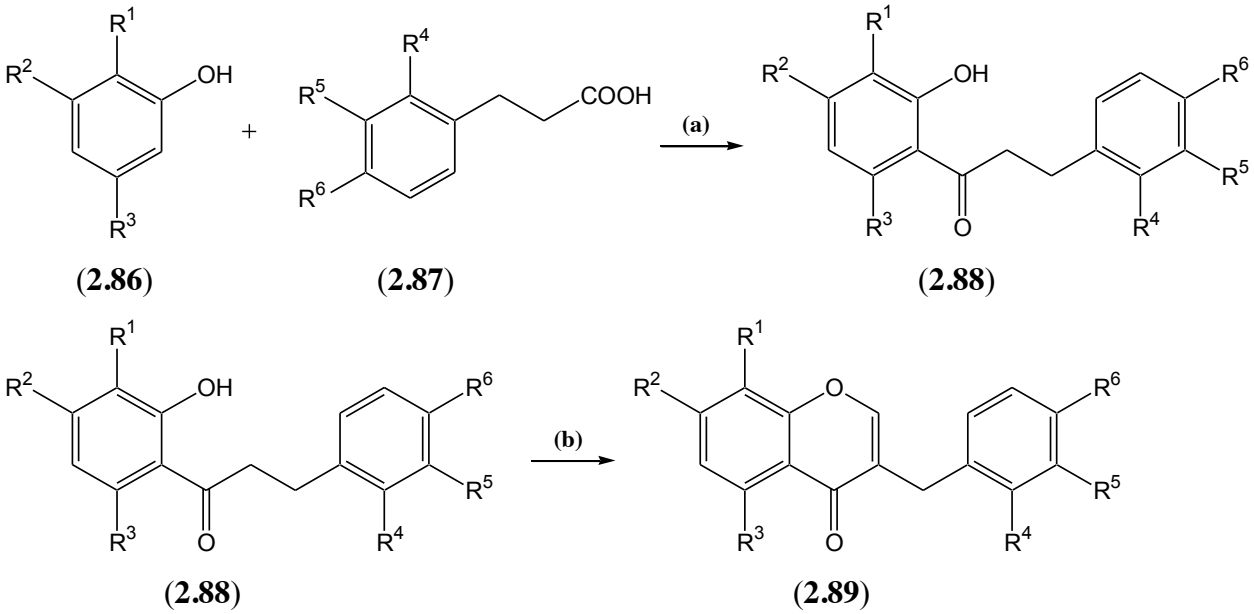
43 Yadav, S.K. *Int. J. Org. Chem.* **2014**, *4*, 236.

44 Rao, V.M.; Damu, G.L.V.; Sudhakar, D.; Siddaiah, V.; Rao, C.V. *Arkivoc* **2008**, *xi*, 285.

45 Kirkiacharian, S.; Tongo, H.G.; Bastide, J.; Bastide, P.; Grenie, M.M. *Eur. J. Med. Chem.* **1989**, *24*, 541.

46 Kirkiacharian, S.; Gomis, M. *Synth. Commun.* **2005**, *35*, 563.

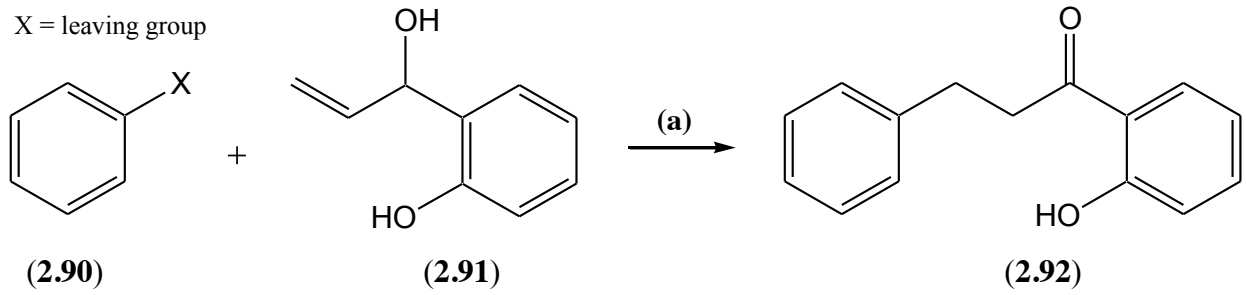
Although many of the dihydrochalcones were obtained in a two step process through aldol condensation between an appropriate acetophenone and benzaldehyde *via* the chalcone intermediate, some workers utilised other methods for reaching this key intermediate. In an improvement on the multi-step chalcone approach, Siddaiah *et al*.[40] utilised a Friedel-Crafts acylation reaction between a phenol (**2.86**) and a dihydrocinnamic acid derivative (**2.87**) to prepare the polyhydroxydihydrochalcone (**2.88**) in a single step (30-71% yield) (Scheme 3). The Vilsmeier reagent with BF_3-etherate/DMF/PCl_5 was utilized in this instance for attaching the C-1 fragment to the α-carbon of the DHC (**2.89**).



Scheme 3. Reagents and conditions: (a) $BF_3 \cdot Et_2O$, 80-90 °C; (b) $BF_3 \cdot Et_2O$, DMF/PCl_5, rt.

Briot *et al*.[47] utilised the Heck-reaction in their quest to synthesise dihydrochalcones in a single step. Thus an aryl halide (**2.90**) and the allyl alcohol (**2.91**) were reacted to give the required dihydrochalcone (**2.92**) in 12-80% yield (Scheme 4). Although this methodology represents a single reaction step for the formation of the dihydrochalcone, 1-aryl-2-propen-1-ols with the required hydroxylation pattern like (**2.91**) are not that freely available and may require quite a number of steps to prepare.

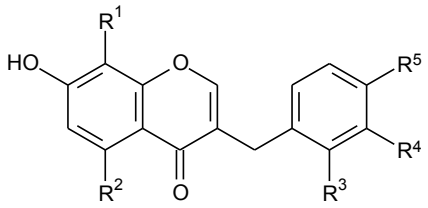
47 Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J*. *Org*. *Chem*. **2004**, *69*, 1374.



(**2.90**) (**2.91**) (**2.92**)

Scheme 4. Reagents and conditions: (a) $Pd(OAc)_2$, NEt_3, CH_3CN.

Some of the homoisoflavones synthesised through the utilization of DHC's as intermediate are listed in Figure 4.



Cpd	R^1	R^2	R^3	R^4	R^5
2.93	H	H	H	H	OH
2.94	H	H	H	H	OCH_3
2.95	H	H	H	OH	OH
2.96	H	H	H	OCH_3	OCH_3
2.97	H	H	OCH_3	H	OCH_3
2.98	OH	H	H	H	OH
2.99	OH	H	H	H	OCH_3
2.100	H	OH	H	H	OH

Figure 4. Some of the homoisoflavones synthesised through DHC intermediates.

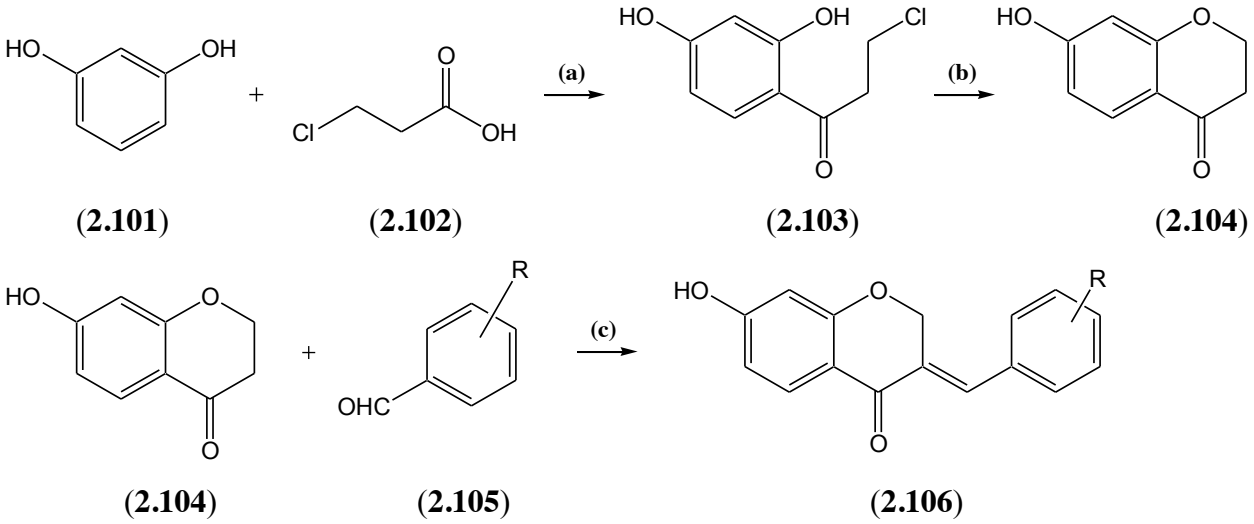
2.3.3 Preparation of 3-benzylidenechroman-4-ones

Although the dihydrochalcone methodology is frequently used to prepare homoisoflavanones, two other routes have recently been developed in this regard. The preparation of 3-benzylidenechroman-4-one can be done by either the condensation of chromanone with benzaldehyde or by utilization of the Baylis-Hillman between the acrylic acid and a substituted benzaldehyde.

(i) *By condensation of chromanone*[20]

One of the most popular methods for preparing 3-benzylidenechroman-4-ones entails aldol-type addition, which could either be acid or base catalysed, of an appropriate benzaldehyde to a

chromanone.[23,48,49,50] The required chromanone (**2.104**) is usually made available by Friedel-Crafts acylation of a resorcinol unit (like **2.101**) with a 3-halopropionic acid (like **2.102**) in the presence of triflic acid. Subsequent base catalysed cyclization would then give the envisaged chromanone (Scheme 5).



Scheme 5. Reagents and conditions: (a) CF_3SO_3H (3 eqv.), 75-80 ^oC, 1 h, 44%; (b) 2 M NaOH, 2 h, 73%; (c) acetic acid, dry HCl gas, rt, 24 h, 20-97%.

In an attempt to use more benign conditions and to improve the yield of the key chromanone, Siddaiah *et al*.[51] reported, the utilization of a *β*-haloacrylonitrile instead of the *β*-halopropionic acid during the preparation of the chromanone. Yields were, however, only marginally improved from 46% to 54% with this process which utilised H_2SO_4 for the formation of the chromanone and piperidine as base for the final aldol reaction. Siddaiah *et al*.[23] also reported the utilization of perchloric acid on silica gel ($HClO_4$-SiO_2) and solvent-free conditions for the aldol reaction between the aldehyde (**2.110**) and chromanone (**2.109**) and were able to improve the yield of the last step in the process to ca 70% in this way (Scheme 6). The photochemical isomerization[23] of 3-benzylidenechroman-4-one from the E- to Z-isomers is presented in Scheme 7.

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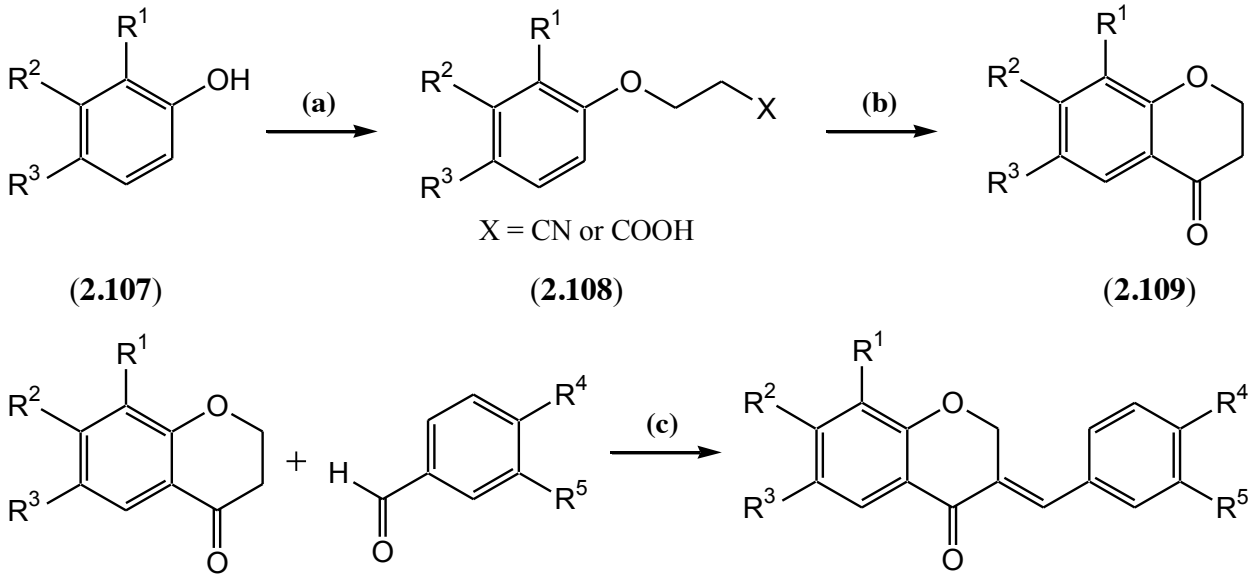
48 Roy, S.K.; Kumari, N.; Gupta, S.; Pahwa, S.; Nandanwar, H.; Jachak, S.M. *J*. *Med*. *Chem*. **2013**, *66*, 499.

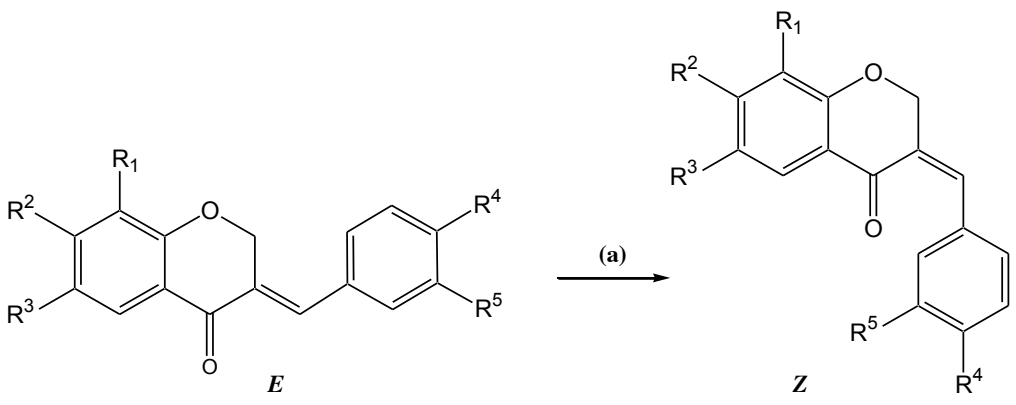
49 Yen, C.T.; Nakagawa-Goto, K.; Hwang, T.L.; Wu, P.C.; Morris-Natschke, S.L.; Lai, W.C.; Bastow, K.F.; Chang, F.R.; Wu, Y.C.; Lee, K.H. *Bioorg*. *Med*. *Chem*. *Lett*. **2010**, *20*, 1037.

50 Jagtap, P.G.; Degterev, A.; Choi, S.; Keys, H.; Yuan, J.; Cuny, G.D. *J*. *Med*. *Chem*. **2007**, *50*, 1886.

51 Siddaiah, V.; Maheswara, M.; Rao, C.V.; Venkateswarlu, S.; Subbaraju, G.V. *Bioorg*. *Med*. *Chem*. *Lett*. **2007**, *17*, 1288.



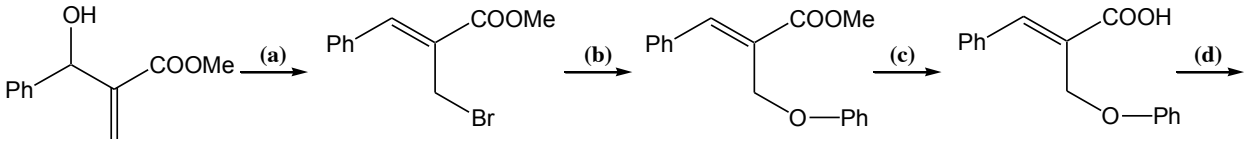
Scheme 6. Reagents and conditions for X = CN: (a) acrylonitrile, NaOMe, 70-80 ^{o}C, 35%; (b) H_2SO_4, 95-100 ^{o}C, 54%; (c) piperidine, 70-80 ^{o}C, 60%. For X = COOH: (a) Bromopropionic acid, NaH, DMF, 70-80 ^{o}C, 30%; (b) polyphosphoric acid (PPA), 80 ^{o}C, 46%; (c) piperidine, 70-80 ^{o}C, (43-72%) or $HClO_4$-SiO_2, 90-100 ^{o}C (71%) or neat 90-100 ^{o}C (68%).



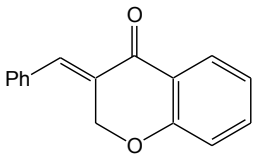
Scheme 7. Reagents and conditions: (a) hv, benzene, 4 h, 32-54%.

(ii) *By utilization of the Baylis-Hillman reaction*

Since polyhydroxylated acetophenones are not always available, Kim *et al*.[52] and Basavaiah *et al*.[53] followed a Baylis-Hillman approach for attaching the two aromatic rings to the isobutyl entity. In this methodology, the Baylis-Hillman adduct (**2.115**) containing the first aromatic ring, is turned into a phenolic ether (**2.116**) by reaction with HBr followed by the appropriate phenol. Trifluoroaqcetic anhydride (TFAA) mediated Friedel-Crafts type cyclization finally produces the 3-benzylidenechroman-4-one (**2.118**) (Scheme 8).



(**2.114**) (**2.115**) (**2.116**) (**2.117**)



(**2.118**)

Scheme 8. Reagents and conditions: (a) HBr, H_2O, 30 min, rt, 95%; (b) K_2CO_3, PhOH, acetone, 3 h, reflux, 94%; (c) KOH, aq THF, 3 h, 40-50 ^oC, 91%; (d) TFAA, CH_2Cl_2, 1 h, reflux, 90%.

2.3.4 Homoisoflavan/homoisoflavanone

Due to the key position of homoisoflavones (**2.3**) and 3-benzylidene-chroman-4-ones (**2.4**) in methodology towards the synthesis many of homoisoflavonoids and the ease of reduction processes in general, many endeavours towards the preparation of homoisoflavanes or homoisoflavanones included the reduction of one of these compounds.

(i) *Reduction of 3-benzylidene-chroman-4-ones or homoisoflavones*

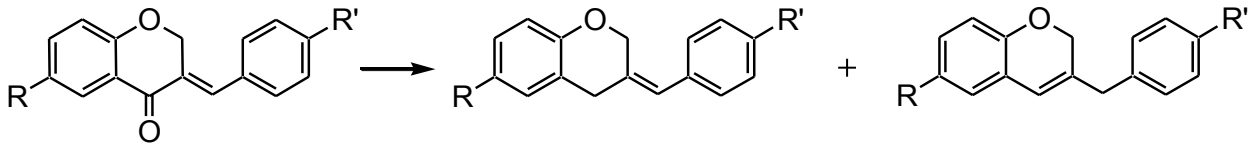
Conti and Desideri[54] found that the reduction of 3-benzylidene-chroman-4-ones with $LiAlH_4$ in the presence of aluminium chloride gave a 3 : 1 mixture (in a ca 50% combined yield) of the 3-

52 Kim, S.H.; Kim, S.H.; Kim, J.N. *Bull*. *Korean Chem*. *Soc*. **2008**, *29*, 2039.

53 Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem*. *Commun*. **1998**, 1639.

54 Conti, C.; Desideri, N. *Bioorg*. *Med*. *Chem*. **2009**, *17*, 3720.

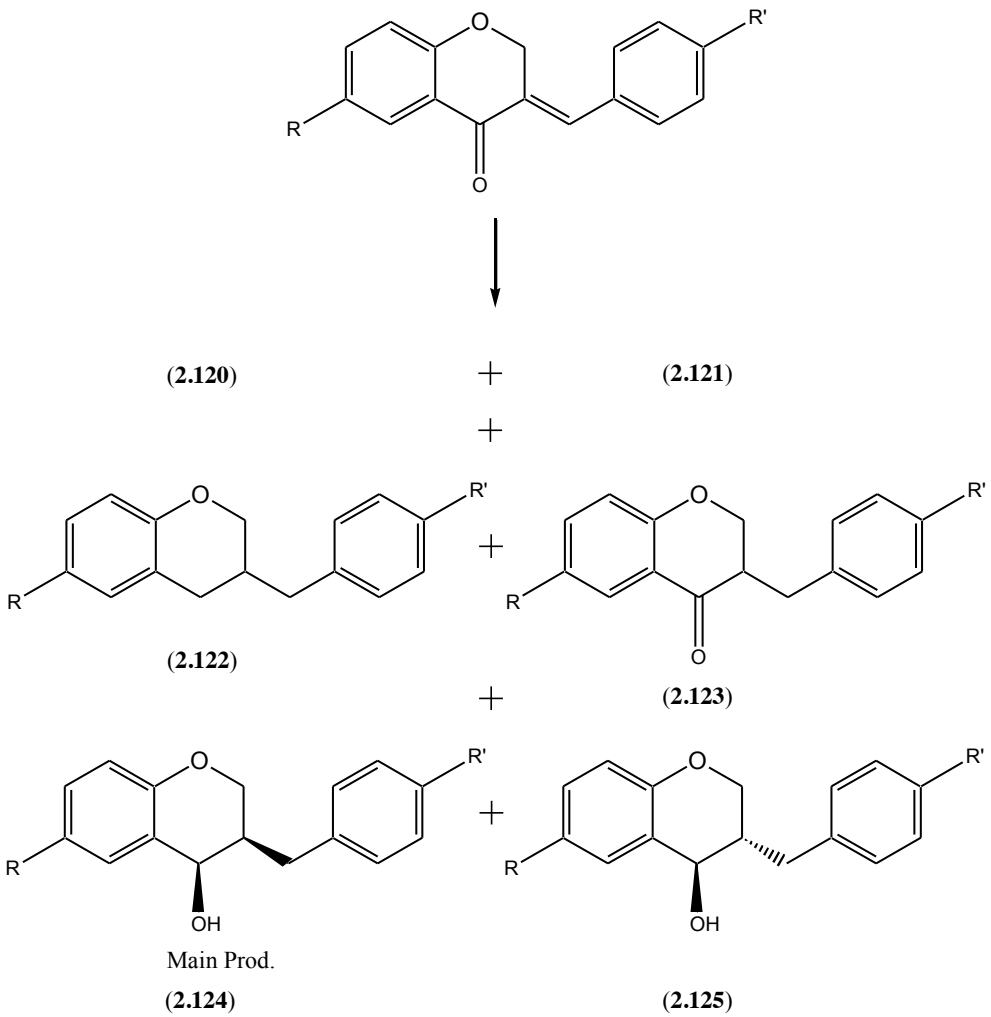
benzylidene-chroman (**2.120**) and homoisoflavene (**2.121**) (Scheme 9), while changing the reducing system to sodium cyanoborohydride and zinc iodide led to a complex mixture of reduced products containing ca 5 and 11% of the homoisoflavans (**2.122**) and homoisoflavanones (**2.123**), respectively (Scheme 10).



(**2.119**) (**2.120**) (**2.121**)

R = H or Cl R' = H or Cl

Scheme 9. Reagents and conditions: $LiAlH_4$,$AlCl_3$, Et_2O, reflux, 30 min.



(**2.120**) + (**2.121**)

+

(**2.122**) + (**2.123**)

+

Main Prod.

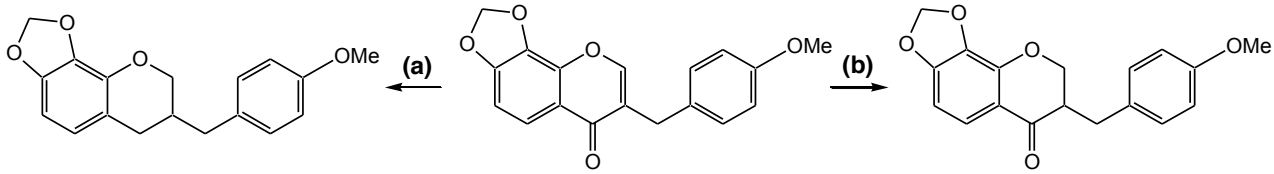
(**2.124**) (**2.125**)

R = H or Cl R' = H or Cl

Scheme 10. Reagents and conditions: $NaCNBH_4$, ZnI_2, DCM, reflux, 20 h.

When Conti and Desideri[55] changed the starting material to the isoflavanone (**2.123**) they were able to obtain the desired homoisoflavans (**2.122**) in 60-70% yields with the same $LiAlH_4$ - $AlCl_3$ reducing system.

Zhang *et al*.[13] reported the formation of the homoisoflavanone (**2.128**) when the homoisoflavone (**2.127**) was reduced over a Raney Nickel catalyst in ethanol, while the corresponding homoisoflavan (**2.126**) was obtained when 10% Pd/C was used as catalyst in either MeOH or EtOAc (Scheme 11).



(**2.126**) (**2.127**) (**2.128**)

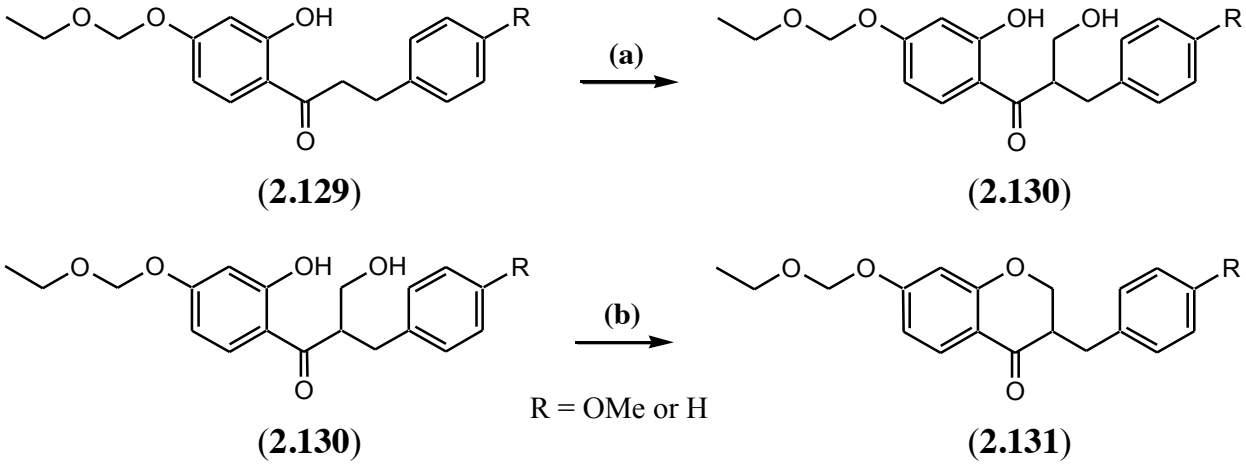
Scheme 11. Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, rt, 12 h, 89%; (b) H_2, Raney Ni, EtOH, rt, 10 h, 80%.

(ii) *Cyclization of dihydrochalcone*

The first direct synthetic route to homoisoflavanones was reported by Jain and Mehta[56] in 1985 when they reacted the 4'-protected dihydrochalcone (**2.129**) with ethoxymethyl chloride to give the α-alkylated intermediates (**2.130**). These products (**2.130**) were cyclized by treatment with ethanolic sodium carbonate to afford the homoisoflavanones (**2.131**) in 38-41% yield, before removal of the protecting group gave the desired final products (Scheme 12).

55 Conti, C.; Desideri, N. *Bioorg*. *Med*. *Chem*. **2009**, *17*, 3720.

56 Jain, A.C.; Mehta, A. *Tetrahedron* **1985**, *41*, 5933.



(**2.129**) (**2.130**)

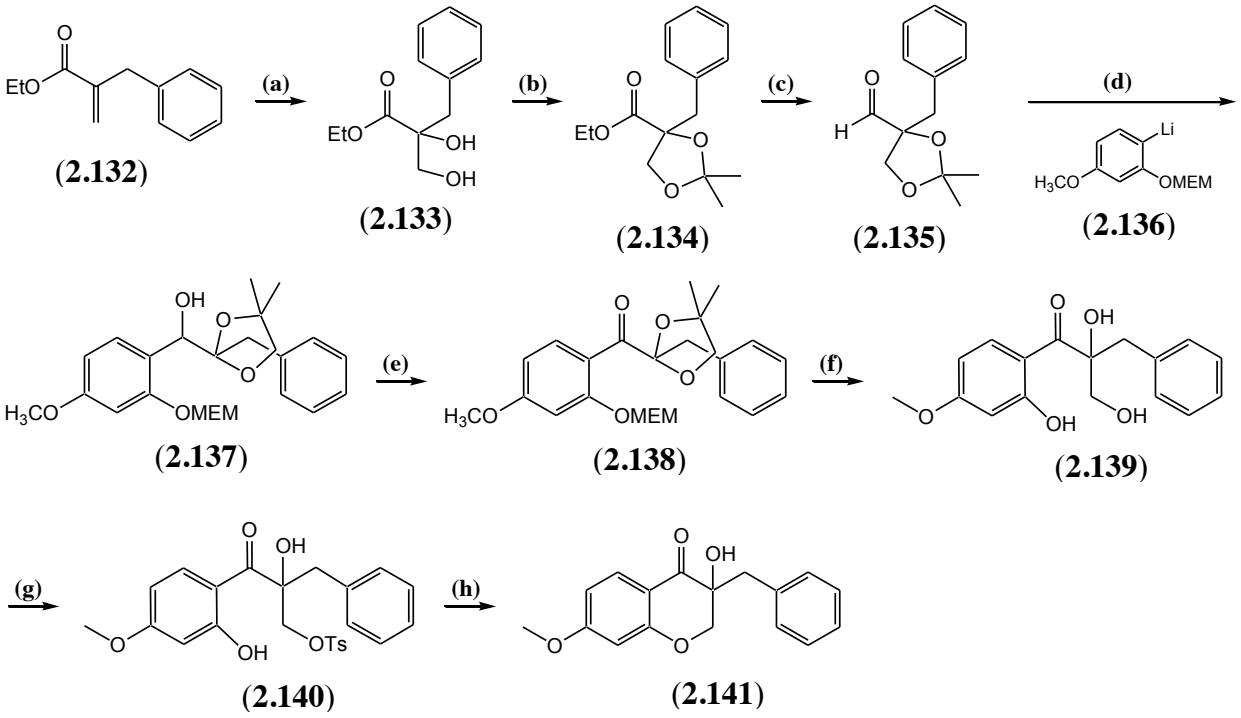
(**2.130**) (**2.131**)

Scheme 12. Reagents and conditions: (a) $ClCH_2OEt$, K_2CO_3, Me_2CO, 60-70 ^oC; (b) 4% *aq*. alc. Na_2CO_3.

2.3.5 3-Hydroxyhomoisoflavanones

Since only one homoisoflavanone has been isolated with a hydroxy function in the 3-position (*cf*. paragraph 2.2.2), development of methodology for the synthesis this type of compound has been rather limited and only Jew *et al.* [57] attempted the synthesis of this novel type of homoisoflavonoid. The synthetic protocol followed by these workers started with the OsO_4 catalysed dihydroxylation of ester (**2.132**) (86%) followed by protection of the diol as isopropylidene derivative (**2.134**) (83%). Subsequent reduction of the ester functionality with DIBAL-H afforded aldehyde (**2.135**) (60%), which was treated with a substituted phenyllithium (**2.136**) to give the protected triol derivative (**2.137**) (56%). PCC oxidation of the benzylic alcohol entity gave the propanone (**2.138**) (79%), which was transformed into the wanted 3-hydroxyhomoisoflavanone (**2.141**) in 74% yield by deprotection of the diol, tosylation of the primary hydroxy function, deprotection of the 2'-hydroxy group and finally base catalysed substitution of the primary OH function for formation of the heterocyclic C-ring (Scheme 13). In summary, the complete synthesis of 3-hydroxyhomoisoflavanone (**2.141**) was prepared through eight steps from the ester (**2.132**) in overall yield 5.9%.

[57] Jew, S.S.; Kim, H.A.; Park, H.G. *Arch*. *Pharm*. *Res*. **1997**, *20*, 144.



Scheme 13. Reagents and conditions: (a) OsO_4, NMO, *tert*-BuOH, H_2O, acetone, rt, 18 h; (b) 2,2-dimethoxypropane, *p*-TsOH, THF, rt, 20 h; (c) DIBAL-H, toluene, -78 ^oC, 30 min; (d) THF, -78 ^oC to rt, 18 h; (e) PCC, NaOAc, CH_2Cl_2, rt, 16 h; (f) 2% HCl in MeOH, 50 ^oC, 2 h; (g) p-TsCl, pyridine, $CHCl_3$, rt, 43 h; (h) K_2CO_3, MeOH, rt, 5 h.

2.3.6 Enantionselective synthesis of homoisoflavans, homoisoflavanones and 3-hydroxyhomoisoflavanones

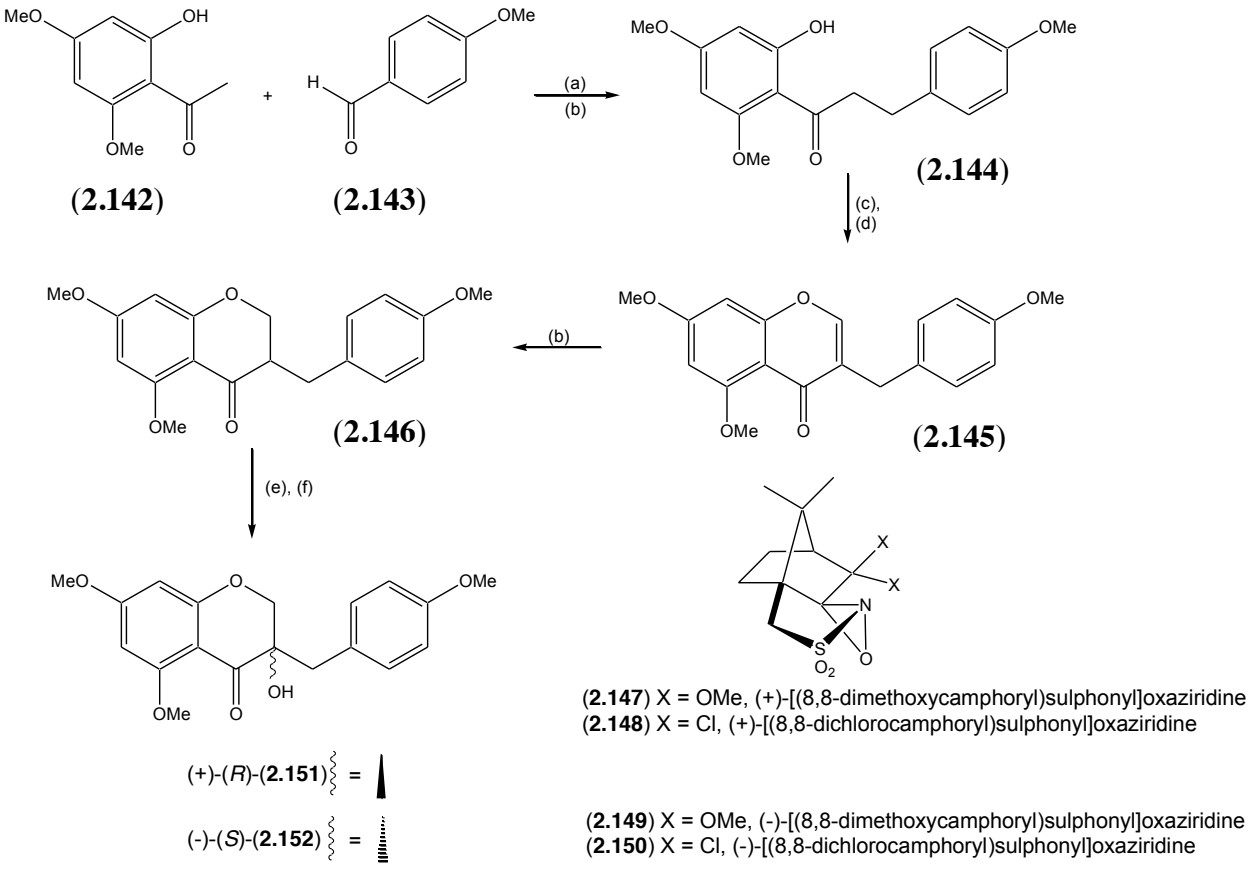
While all the homoisoflavonoids with a reduced C-ring, *i.e*. homoisoflavans, homoisoflavanones and 3-hydroxyhomoisoflavanones, contain a chiral centre associated with this C-ring, the majority of these natural products have been isolated and reported without assignment of the absolute configuration at C-3.[58]

(i) *3-Hydroxyhomoisoflavanones*

Although 3-hydroxyhomoisoflavanones (*cf*. paragraph 2.3.5) are structurally more complex than their 3-deoxy counterparts, the homoisoflavans and homoisoflavanones, 3-hydroxyhomoisoflavanones were the first class of homoisoflavonoids to receive attention wrt methodology for the stereoselective preparation of some analogues. In this regard, Davis and

58 Yu, Y.-C.; Zhu, S.; Lu, X.-W.; Wu, Y.; Liu, B. *Eur*. *J*. *Org*. *Chem*. **2015**, *22*, 4964.

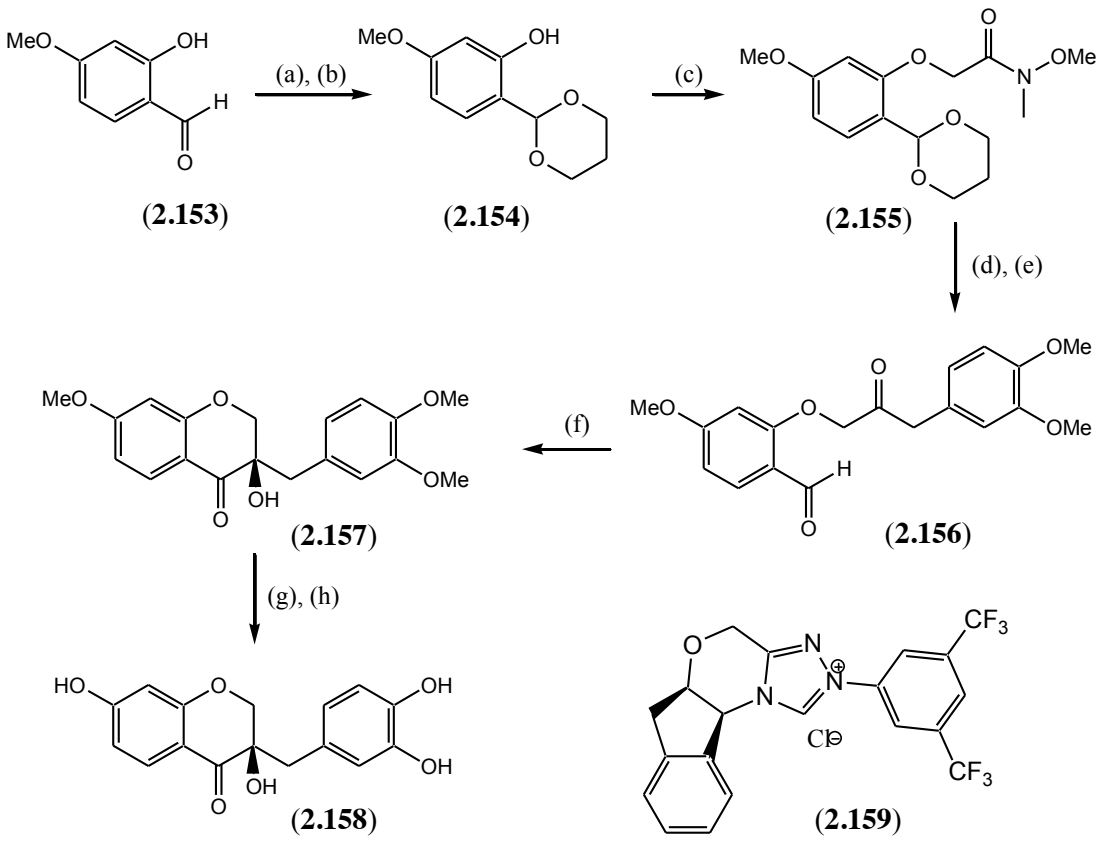
Chen [59] utilized the opportunity to demonstrate the application of their enantioselective α-hydroxylation of ketones for the synthesis of the natural 3-hydroxyhomoisoflavanone, eucomol (**2.34**). While the first 5 steps of the synthetic protocol centered around known racemic reactions, asymmetric induction was achieved in the last step by oxidizing the lithium enolate of the homoisoflavanone (**2.146**) with the two enantiomer of either [(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine [(**2.147**) or (**2.149**)] or [(8,8-dichlorocamphoryl)-sulfonyl]oxaziridine [(**2.148**) or (**2.150**)] (Scheme 14). When the (+)-enantiomers of the oxidizing agents were used, the (+)-(*R*)-isomer of eucomol (**2.151**) was formed in 66-77% yield, while the (-)-isomer of the oxaziridine [(**2.149**) or (**2.150**)] led to (-)-(*S*)-eucomol (**2.152**) in 72% yield. The authors also found that when LDA was used for the formation of the enolate and it was oxidized with the dimethoxyoxaziridines (**2.147**) and (**2.149**), the best ee's (> 96%) were observed.



Scheme 14. Reagents and conditions: (a) 50% aq. KOH, MeOH, 15 min., 91%; (b) H_2, 10% Pd/C, 98%; (c) HCOOEt, Na sand, 0 ^oC to rt., 14 h; (d) EtOH, cat, H_2SO_4, reflux, 2 h; (e) LDA, THF, -78 ^oC; (f) (**2.147**) or (**2.148**), -78 to 0 ^oC, 66-77%.

59 Davis, F.A.; Chen, B.-C.; *Tetrahedron Lett*. **1990**, *31*, 6823.

Takikawa and Suzuki [60] reported the enantioselective synthesis of (+)-Sappanone B in a catalytic process utilizing triazolium salts like (**2.159**) for asymmetric induction during a modified Stetter reaction (Scheme 15). This 6-step process entailed formation of an α-phenoxyacetophenone containing and aldehyde function on the phenoxy ring (**2.155**), through alkylation and Grignard based introduction of the acetophenone entity to the aldehyde starting material accompanied by a series of protection-deprotection steps. Final treatment of the α-phenoxyacetophenone (**2.156**) with the triazolium catalyst (**2.159**) and triethylamine gave the (*R*)-isomer of tri-*O*-methyl sappanone B (**2.157**) in 92% and 95% yield and enantiomeric selectivity, respectively. Although excellent yield and selectivity values were obtained for the preparation of the (*R*)-isomer of the product, the authors are, however, not mentioned anything regarding the preparation of the (*S*)-enantiomer of this compoound.

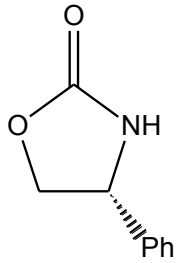


Scheme 15. Reagents and conditions: (a) Ac_2O, Py; (b) *n*-$Bu_4N^+Br_3^-$, $HC(OEt)_3$, $HO(CH_2)_3OH$, then K_2CO_3, MeOH, 95% over the two steps; (c) $ClCH_2CONMe(OMe)$, K_2CO_3, acetone, reflux, quant.; (d) 3,4-$(MeO)_2C_6H_3CH_2MgCl$, THF, -20 °C, 15 min.; (e) 1 M HCl, THF, 0 °C, 2 h, 86% over two steps; (f) (**2.159**) (7.5 mol%), Et_3N (7.5 mol%), toluene, rt, 12 h, 92%, 95% ee; (g) $NaSC_{12}H_{25}$, DMF, 80 °C, 5 h, 92%; (h) BBr_3, DCM, 0 °C, 30 min., 85%.

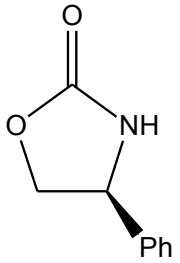
60 Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713.

(ii) *Homoisoflavans and homoisoflavanones*

In another attempt to address the lack of knowledge about the stereoselective synthesis of homoisoflavonoids, the research group of Liu[58] recently attempted and reported the enantioselective synthesis of some homoisoflavans and homoisoflavanones. These workers used (*R*)- and (*S*)-4-phenyloxazolidinones (**2.160** and **2.161**) as chiral auxiliary in their endeavors and started their method development with the selective preparation of the two homoisoflavan enantiomers [(*R*)-(**2.173**)] and [(*S*)-(**2.175**)] (Scheme 17 and Scheme 18).

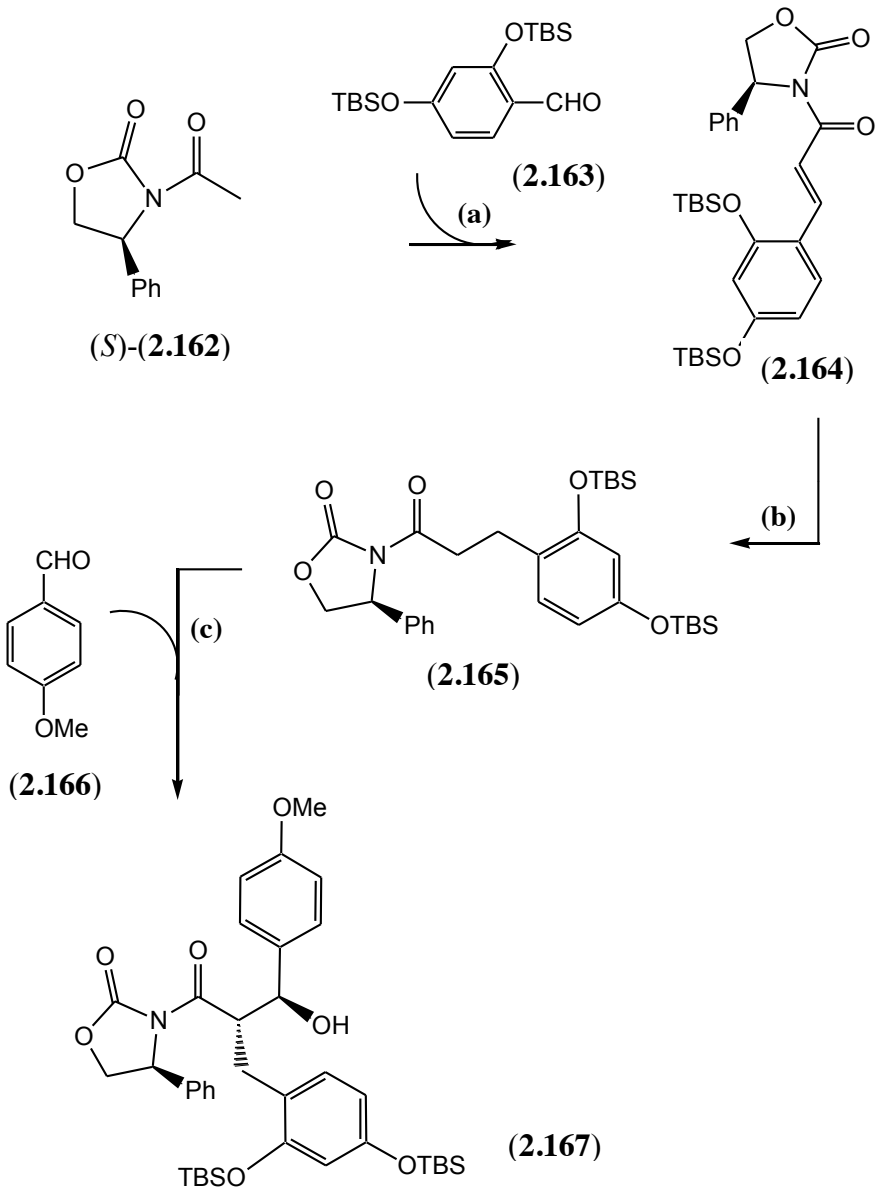


(*R*)-(**2.160**)



(*S*)-(**2.161**)

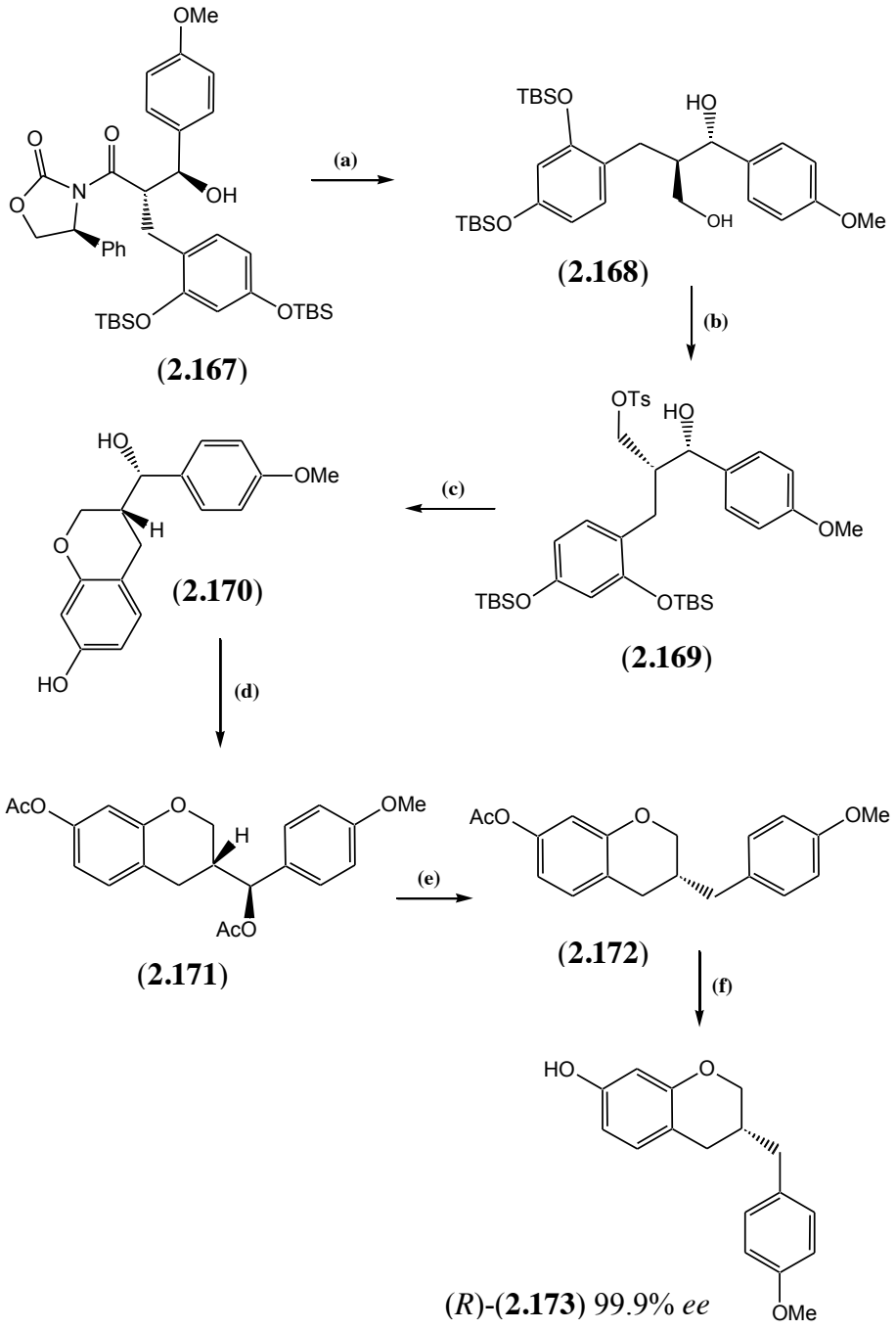
After attaching the chiral auxiliary to the dihydrocinnamic acid entity through a Lewis acid catalyzed aldol reaction between the N-acetyl-4-phenyloxazolidinone [(*S*)-**2.162**)] and the *m*-disubstituted benzaldehyde (**2.163**) followed by Pd/C catalyzed hydrogenation, the C6-C3-C6 framework of the final product was constructed by a second aldol condensation with *p*-anisaldehyde (**2.166**) in 66% yield (Scheme 16).



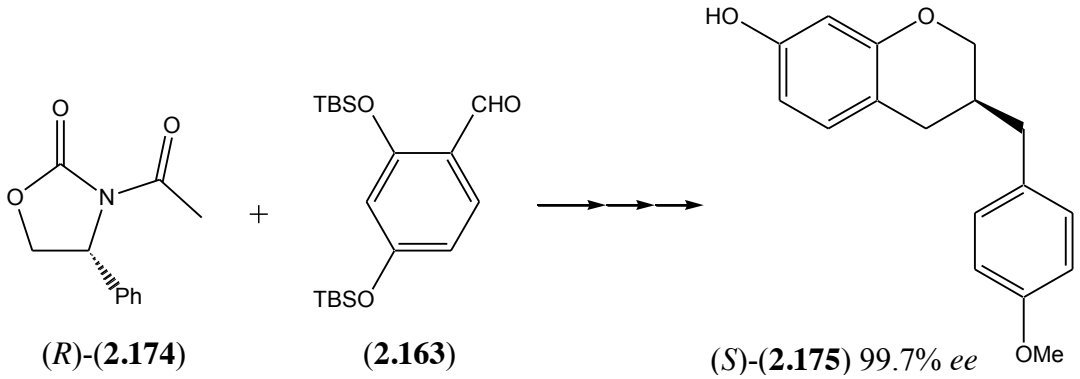
Scheme 16. Reagents and conditions: (a) $TiCl_4$, (+)-sparteine, CH_2Cl_2, 0 ^oC, 2 h, 86%; (b) H_2 (1 atm), Pd/C, EtOAc, rt, 5 h, 93%; (c) $TiCl_4$, TMEDA, CH_2Cl_2, -20 ^oC, 2 h, 66%.

With the absolute configuration at the chiral centres established, $NaBH_4$ reduction led to the removal of the chiral auxiliary in 80% yield, before tosylation of the primary OH function, desilylation of the phenolic hydroxy groups and subsequent cyclization of the diol (**2.168**) gave the hydroxybenzylhomoisoflavan (**2.170**) in 90% yield. Direct reductive removal of the benzylic hydroxy group in (**2.170**), however, failed, so it had to be acetylated, before it could be reductively removed resulting in the formation of the (*R*)-(-)-7-hydroxy-4'-methoxy-homoisoflavan (**2.173**) in 90% yield and > 99% ee, after deacetylation (Scheme 17). By replacing the (*S*)-N-acetyl-4-phenyloxazolidinone (**2.162**) with its (*R*)-isomer (**2.174**), and

following the same protocol, the authors were also able to prepare the (*S*)-(+)-7-hydroxy-4'-methoxyhomoisoflavan (**2.175**) in 92% yield and > 99% ee (Scheme 18).



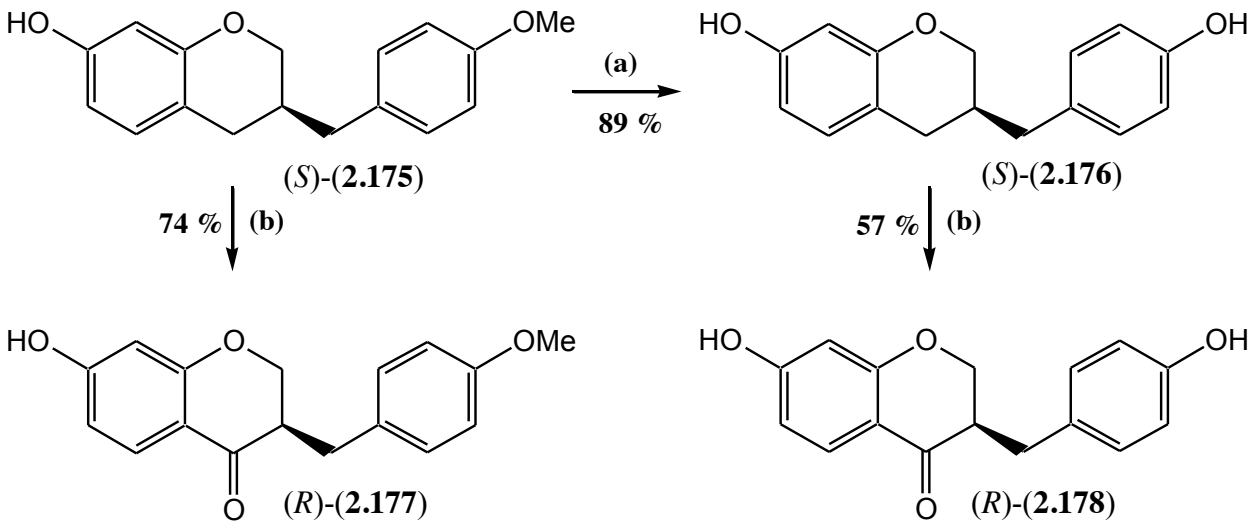
Scheme 17. Reagents and conditions: (a) $NaBH_4$, THF/H_2O, 5 h, 80%; (b) *p*-TsCl, *n*Bu_2SnO, DMAP, Et_3N, MeCN, rt, 3 h, 87%; (c) *n*Bu_4NF, THF, rt, 30 min, 90%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 30 min, 93%; (e) Et_3SiH, CF_3CO_2H, CH_2Cl_2, 0 ^oC, 30 min, 86%; (f) K_2CO_3, MeOH, rt, 30 min., 90%.



(*R*)-(**2.174**) (**2.163**) (*S*)-(**2.175**) 99.7% *ee*

Scheme 18. The synthesis of (*S*)-(+)-7-hydroxy-4'-methoxyhomoisoflavan (**2.175**).

With the homoisoflavans in hand, Liu *et al*. turned their attention towards the conversion of one of these isomers into the corresponding homoisoflavanones. Regioselective oxidation of the (*S*)-homoisoflavan (**2.175**) with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) led to the corresponding (*R*)-homoisoflavanones (**2.177**) in 74% yield (Scheme 19). BBr_3 induced demethylation of the (*S*)-homoisoflavan (**2.175**) afforded the free phenolic analogue (*S*)-(**2.176**) (in 89% yield), which was also transformed into the corresponding (*R*)-homoisoflavanone (**2.178**) in 57% yield (Scheme 19); thus leading to the enantioselective synthesis of two (*R*)-homoisoflavanones for the first time. Unfortunately, the authors did not report on the enantiomeric purity of these homoisoflavanones.



Scheme 19. Reagents and conditions: (a) BBr_3, CH_2Cl_2, rt, 1 h; (b) DDQ, dioxane, H_2O, rt, 30 min.

3 Determination of the absolute configuration of flavonoids

3.1 Introduction

Since many types of flavonoids contain one or more stereogenic centres, structure elucidation of those compounds have always been plagued by the determination of the absolute configuration at these stereocentres. While optical rotation values have been used extensively for this purpose in early investigations, this method does not supply information as to the absolute configuration at individual chiral centres in molecules containing more that one stereogenic centre. Two techniques, i.e. optical rotation dispersion (ORD) and circular dichroism (CD) have been developed since the middle 1960's to assist in defining the absolute configuration(s) in these chiral molecules. The more sensitive technique, circular dichroism, is a form of spectroscopy that basically measures the differential absorption between left- and right-handed circularly polarised light as a function of wavelength. Depending on the stereochemistry of the sample molecule which the light passes through, the difference in absorption between the left- and right-handed circularly polarised light can either be negative or positive and when plotted against wavelength can give rise to either a positive or negative curve, the so-called (+) or (-) Cotton-effect.[1] Due to the fact that steroids were receiving a lot of attention from scientists during the middle of the previous century and these compounds contain a carbonyl group as well as at least one stereogenic centre, chiral carbonyl compounds were the first to be investigated with the 'new' technique of circular dichroism. In order to correlate the absolute configuration of a carbonyl containing compound with the observed Cotton-effect in the CD spectrum Moffitt *et al*.[2,3] formulated an empirical rule, the so-called Octant rule, which could be used to relate the sign of the observed CE with the absolute configuration of the molecule. Since the 1970's and 80's this technique was extended to include other types of compounds and used together with several other empirical rules or by comparison of the CD spectrum of the new compound having

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1 Djerassi, C., In : Snatzke, G. (Ed.), *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*. Heyden and Son Limited, London, **1967**, 16.

2 Moffitt, W., Woodward, R.B., Moscowitz, A., Klyne, W., and Djerassi, C. *J. Am. Chem. Soc*. **1961**, 83, 4013.

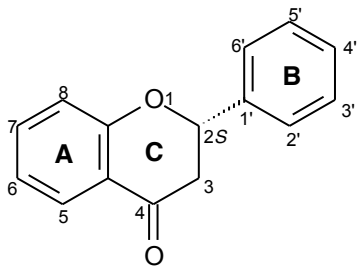
3 Snatzke, G. *Tetrahedron* **1965a**, *21*, 413.

unknown AC to those of analogous compounds of known AC,[4] to define the absolute configuration of, amongst others, a number of non-planar flavonoids.[5]

3.2 Determination of absolute configuration through application of empirical rules

3.2.1 Flavanones

Since flavanones (e.g. **3.1**) represent one of the few classes of flavonoids containing only one stereogenic centre (at C-2) as well as a carbonyl chromophore, the flavanone naringenin became one of the first flavonoids to be subjected to the determination of absolute configuration by CD.



(2*S*)-Flavanone (**3.1**)

In the process of determining the absolute configuration at C2 of flavanones Gaffield[6] extended the modified octant rule for the relationship between the chirality of α,β-unsaturated ketones and the sign of the high wavelength CE [320 – 330 nm (associated with the n → π* transition)] to aryl ketones (acetophenones). Thus flavanones with 2*S*-configuration possessing a conformation with *P*-helicity of the heterocyclic ring and a C2 equatorial aryl group [(**3.1**) and Figure 1],[6] will exhibited a positive CE at the n → π* absorption band (320 – 330 nm) and negative CE at the π → π* transition band (270 – 290 nm). The n → π* absorption band is in this instance used for configurational assignment because the sign of this transition is not effected by the substitution pattern of the aromatic ring system.[7] It must however be remembered that the n → π* transition at longer wavelengths tends to diminish with increasing amounts of the opposite enantiomers.[8]

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4 Nugroho, A.E.; Morita, H. *J. Nat. Med.* **2014**, *68*, 1.

5 Slade, D.; Ferreira, D.; Marais, J.P.J. *Phytochemistry* **2005**, *66*, 2177.

6 Gaffield, W. *Tetrahedron* **1970**, *26*, 4093.

7 Snatzke, G.; Znatzke, F.; Tökés, A.L.; Rákosi, M.; Bognár, R. *Tetrahedron* **1973**, *29*, 909.

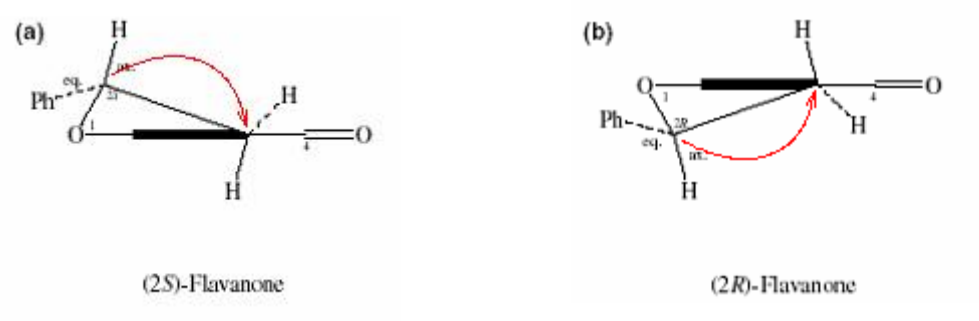
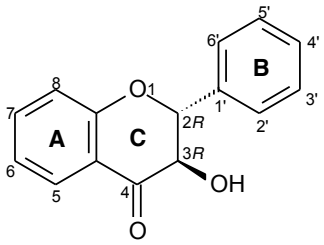


Figure 1. Heterocyclic ring conformations (helicities) of the enantiometic flavanones with equatorial C2-aryl groups.

3.2.2 Dihydroflavonols (3-hydroxyflavanones)



(**3.2**)

Dihydroflavonols (e.g. **3.2**) which possess chiral centres at C2 and C3 can be viewed as flavanones with an additional OH substituent at C3. Having two stereocentres, dihydroflavonols exhibit four possible stereoisomers, i.e. (2*R*,3*R*), (2*R*,3*S*), (2*S*,3*R*), and (2*S*,3*S*). The assignment of absolute configuration to dihydroflavonols has to be done in two steps: In the first step NMR coupling constants ($J_{2,3}$) is utilised to identify the relative configuration of the C2 and C3 substituents as either *trans* or *cis*. For the *trans*-isomers the thermodynamically more stable conformation is the one that has both H2 and H3 axial, thus the absolute configuration (AC) has to be either (2*R*,3*R*) or (2*S*,3*S*), while the *cis*-configuration posses (2*R*,3*S*) or (2*S*,3*R*) stereochemistry with H2 axial and H3 in the equatorial position (Table 1). Subsequently, CD is used to determine the AC at C2 where a positive n → π* CE at ca. 300 - 340 nm is indicative of a 2*R* configuration, whereas 2*S* configuration will show a negative n → π* CE in that region (Table 1). As for the flavanones, the sign of the n → π* transition depends on the helicity of the heterocyclic ring, which in addition with the relative configuration and the equatorial orientation

[8] Li, X.C.; Joshi, A.S.; Tan, B.; ElSohly, H.N.; Walker, L.A.; Zjawiony, J.K.; Ferreira, D. *Tetrahedron* **2002**, *58*, 8709.

of the C2-aryl group establishes the AC. It should be emphasised that (2*R*,*3R*) dihydroflavonols and 2*S* flavanones are homochiral due to the change in Cahn-Ingold-Prelog priorities of the groups round the C2 chiral centre (See Figure 1 and Figure 2).

Table 1. Dihydroflavonol C2 and C3-geometry and configuration.

NMR: $J_{2,3}$	Result of coupling constant analysis	CE at n → π* (ca. 300–340 nm)	Result of CD measurement	Absolute configuration
trans	(2*R*, 3*R*)	Positive	2*R*	(2*R*, 3*R*)
J = 11.5 Hz	**or**			
	(2*S*, 3*S*)	Negative	2*S*	(2*S*, 3*S*)
cis	(2*R*, 3*S*)	Positive	2*R*	(2*R*, 3*S*)
J = 3.5 Hz	**or**			
	(2*S*, 3*R*)	Negative	2*S*	(2*S*, 3*R*)

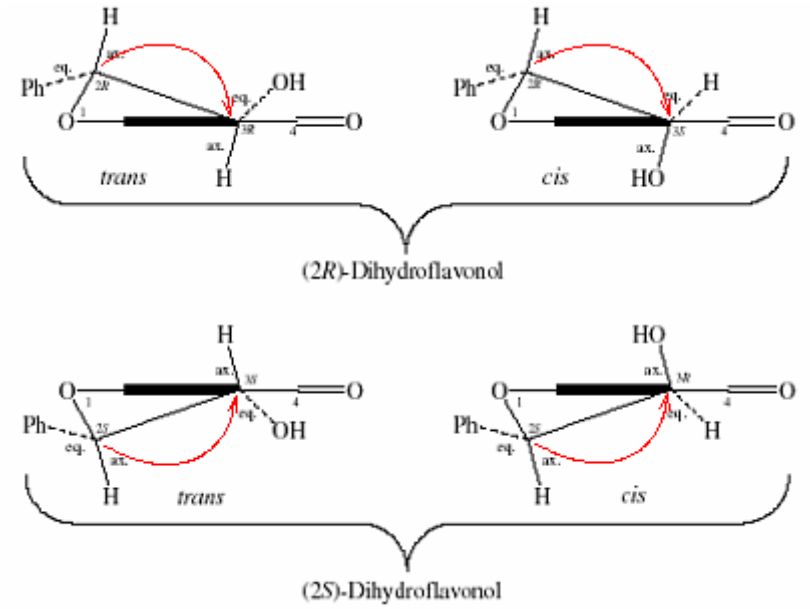
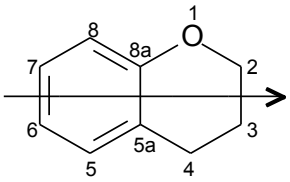


Figure 2. Heterocyclic ring conformations (helicities) of the enantiometic diastereomeric dihydroflavonols with equatorial C2-aryl groups.

3.2.3 Flavan-3-ols

Although flavan-3- and -4-ols do not contain a carbonyl group, the chroman chromophore (**3.3**) is found in these naturally occurring *O*-heterocycles and this entity can then be used for determining the AC of these compounds by CD. The achiral benzene A-ring chromophore in these compounds is chirally perturbed by the fused chiral heterocycle and the substituents attached to it. This gives rise to the observed CEs at ca. 260 - 280 nm (^1L_b band) and ca. 200 - 240 nm (^1L_a band). If the relationship between the helicity of the heterocyclic ring and the sign of the ^1L_b band is known, the chirality (conformation) of the C-ring can be deduced from the CD spectrum. This, in conjunction with the NMR coupling constants which give the relative stereochemistry of the groups attached to the C-ring, can then be used for determining the absolute configuration of the compound.

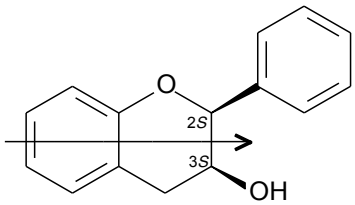


(**3.3**)

(The arrow indicates the direction of projection.)

Since the benzene rings in most of these natural products are substituted, the influence of the achiral substituents on the chiroptical properties had to be determined for each chromophore in order to be able to apply CD correctly. It was, however, found that methoxy and hydroxyl groups at C2, C3, C5 and C7 do not change the chroman helicity rule.[9]

Flavan-3-ols, like catechins (**3.4**), have two stereocentres and four possible diastereomers, namely, (2*R*,3*S*)-2,3-*trans*, (2*S*,3*R*)-2,3-*trans*, (2*R*,3*R*)-2,3-*cis*, and (2*S*,3*S*)-2,3-*cis* exist (Figure 3).



(3.4)

[9] Antus, S.; Kurtán, T.; Juhász, L.; Kiss, L.; Hollósi, M.; Májer, Z. S. *Chirality* **2001**, *13*, 493.

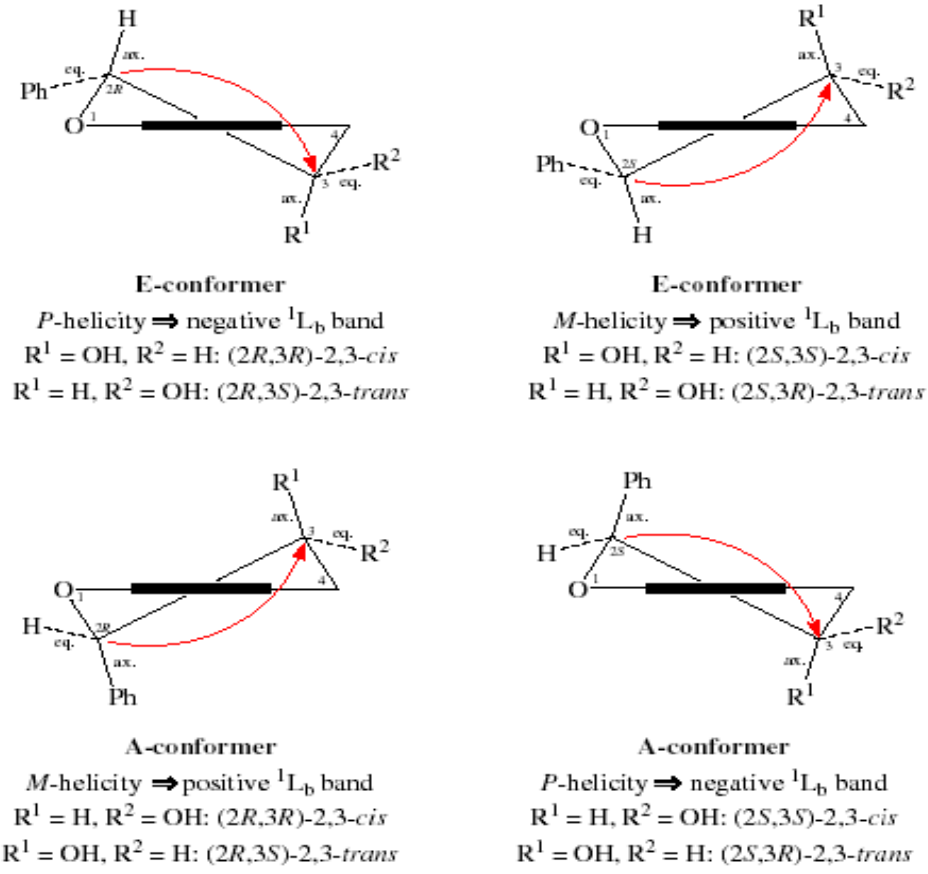


Figure 3. *P*- and *M*-helicity of the chroman C-ring of flavan-3-ols (**3.4**).

The chirality of the heterocyclic C-ring of flavan-3-ols not only determines the sign of the CE within each absorption band, but also plays a significant part in the magnitude. The chirality of the C-ring on the other hand is determined by the preference of the B-ring to be in the equatorial orientation, with the absolute configuration at the C3-OH only having a minor influence (Figure 3).[10] Thus according to the helicity rule for the chroman ring system *M*-helicity and a subsequent (+)-CE in the ^1L_b band region is displayed by flavan-3-ols having a 2*S* AC. Flavan-3-ols with a 2*R* AC on the other hand display *P*-helicity and a negative CE in this region (Figure 3). It should be noted that the helicity of the C-ring is inverted if the B-ring is forced into the axial orientation (A-conformer). The fact that the 3-OH group will, in this instance be, in the equatorial position for 2,3-*cis* flavan-3-ols allows the A conformer to be higher populated, which leads to a reduced magnitude for the ^1L_b band CE.

10 Clark-Lewis, J.W. *Aust. J. Chem.* **1968**, *21*, 2059.

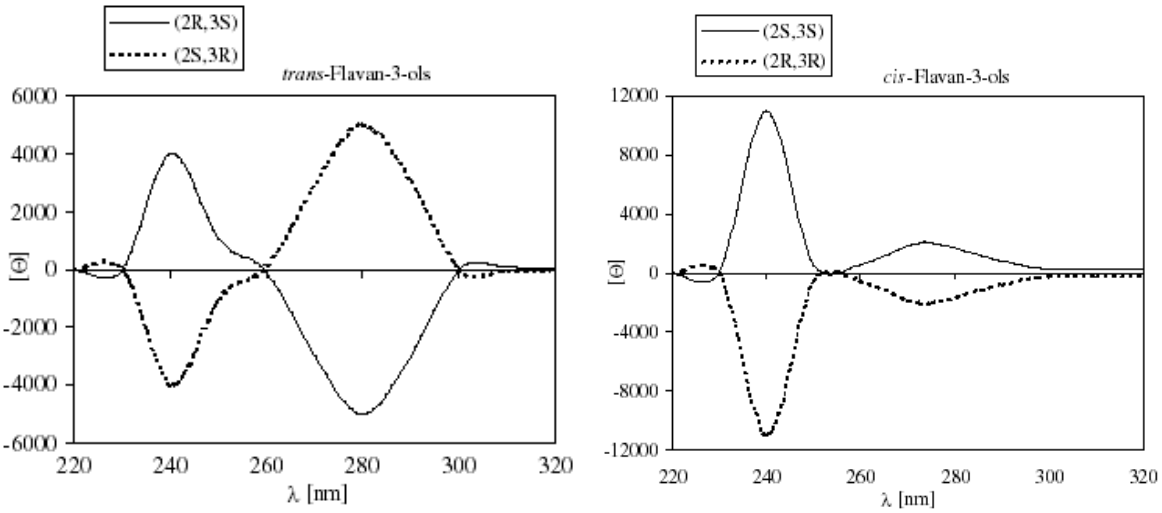
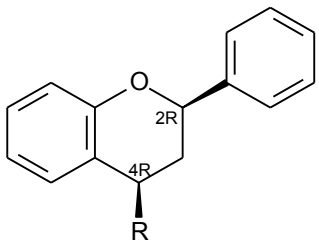


Figure 4. CD spectra of *trans*- and *cis*-flavan-3-ols.

In contrast to the ^1L_b transition (ca. 280 nm) where both sets of *cis*-and *trans*-enantiomers display opposite CEs, only the *trans* enantiomers [(2*R*,3*S*) and (2*S*,3*R*)] have CEs of opposite sign for the ^1L_a transition (ca. 240 nm). The *cis*-enantiomers [(2*R*,3*R*) and (2*S*,3*S*)] in this instance display CEs of the same sign, thus leading to CD spectra as indicated in Figure 4.

3.2.4 Flavan-4-ols

In contrast to flavan-3-ols where the half-chair is the preferred conformation of the heterocyclic C-ring, this ring of flavan-4-ols can either adopt a half-chair or sofa conformation [(**3.5**), Figure 5 and Figure 6].



(2*R*, 4*R*)-*cis*-flavan (**3.5**)

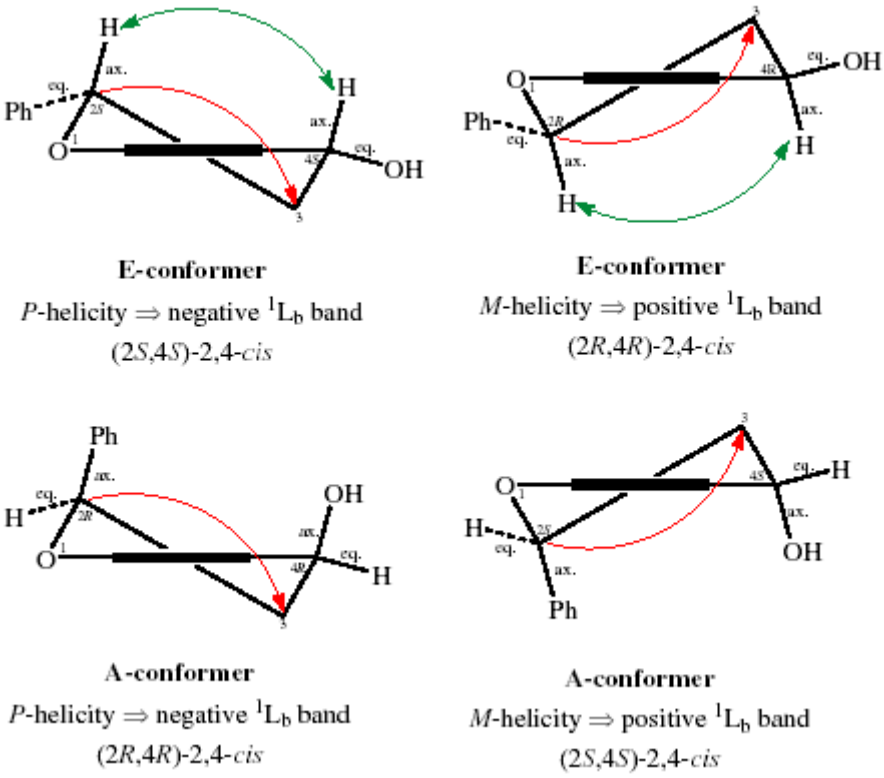


Figure 5. Half-chair conformations for 2,4-*cis*-flavan-4-ols.

With a half-chair conformation of the C-ring, however, the C4-OH of the 2,4-*cis* isomers would be forced into the unfavourable pseudo-equatorial position, while in the other possible half-chair conformation, the C2-phenyl group would adopt an equally unfavourable axial orientation (Figure 5). In the sofa conformation, the C4-OH is oriented in such a way that *peri*-interaction is avoided, while the C2-phenyl group remains in the equatorial position. The sofa conformation therefore seems to be the preferred conformation for both 2,4-*cis* enantiomers (Figure 6).

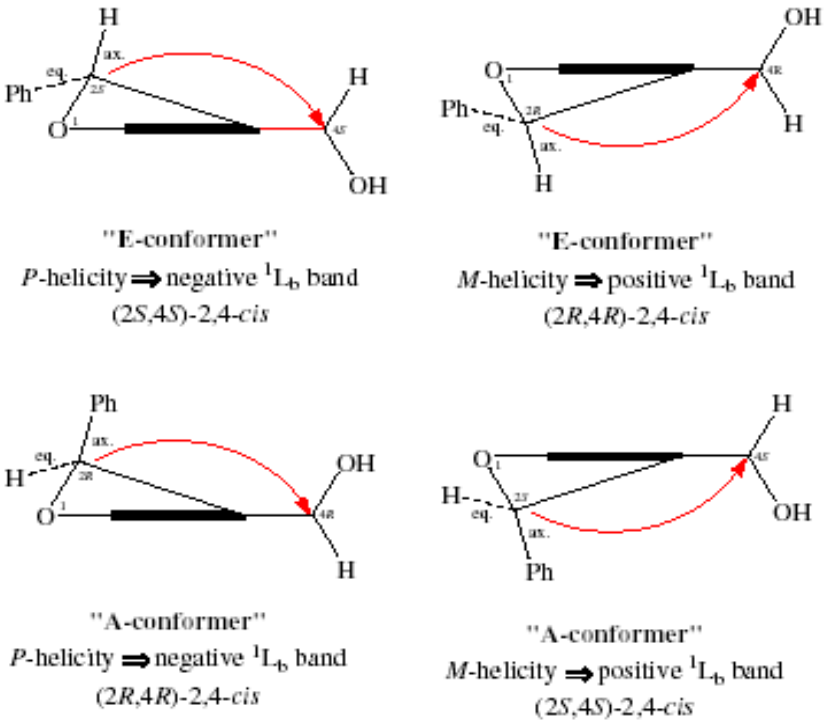


Figure 6. Sofa conformations for 2,4-*cis*-flavan-4-ols.

For the 2,4–*trans* isomers the situation is such that conformation analysis (by NMR) cannot differentiate between the sofa and half-chair conformations. While the C2-phenyl ring remains in the favourable equatorial orientation, the 4-OH now assumes a quasi-axial position in both the half-chair and sofa conformations.

In both conformations (half-chair and sofa) of both *cis*- and *trans*-flavan-4-ols, the helicity is governed by the equatorial orientation of the C2-phenyl group in both enantiomers. *P*- and *M*-helicity of the heterocyclic ring in the chroman chromophore of 2,4-*cis* isomers are reflected by negative – and positive CEs respectively within the $^{1}L_{b}$ band of the CD spectrum, while the opposite (*P* - positive and *M* - negative) is observed for the 2,4-*trans* isomers (Figure 7 and Figure 8).

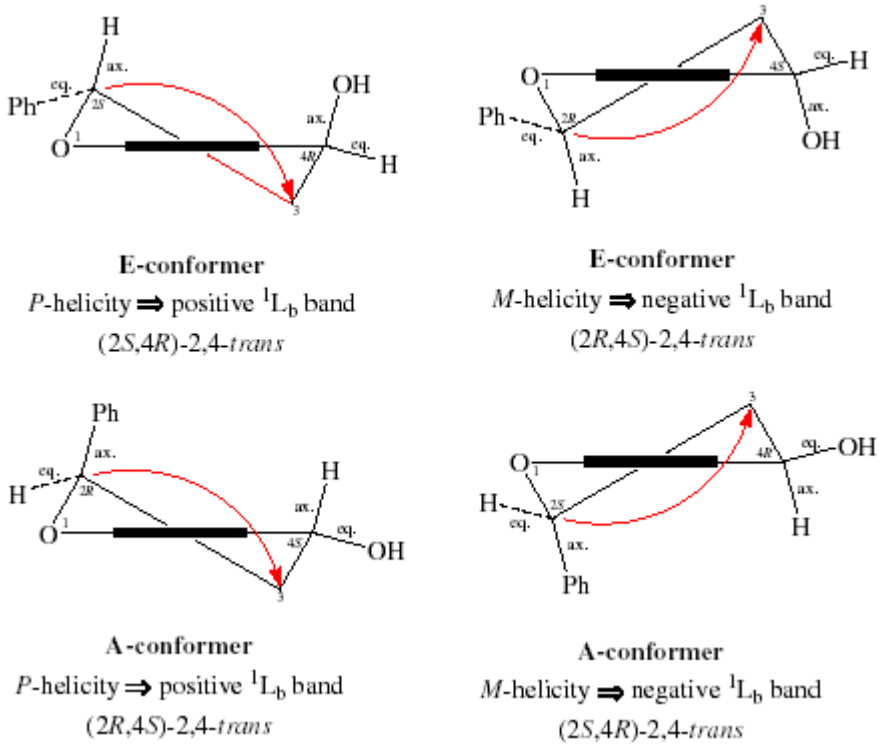


Figure 7. Half-chair conformations for 2,4-*trans*-flavan-4-ols.

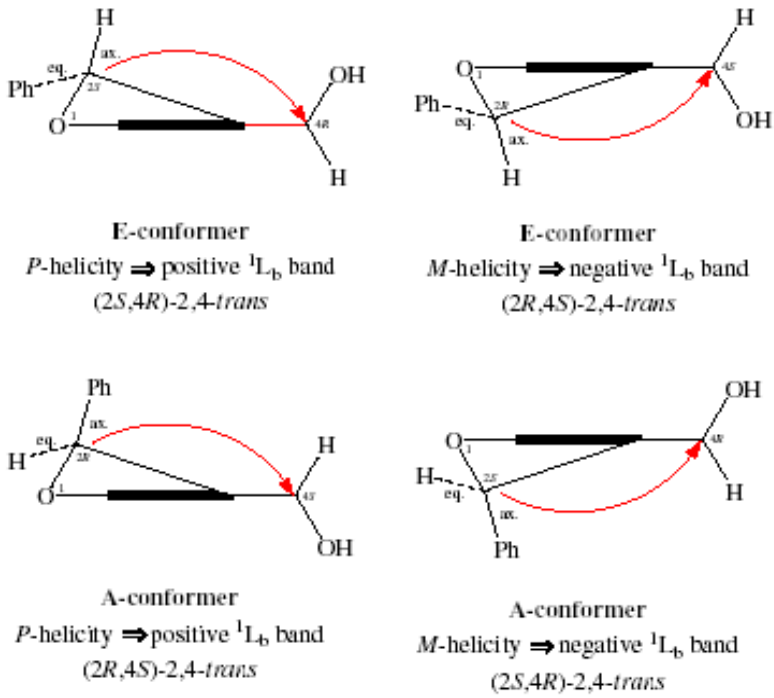


Figure 8. Sofa conformations for 2,4-*trans*-flavan-4-ols.

The final sign and amplitude of the CE of both ^1L_a and ^1L_b bands in the flavan-4-ols is also dependant on the contribution of the C4-OH. This substituent is expected to have a positive contribution to the CEs in both the ^1L_a and ^1L_b bands for the 4*R* stereoisomers and a negative contribution for the 4*S* isomers[11] (Table 2 and Figure 9).

Table 2. CD spectral data of flavan-4-ols. Solvent: acetonitrile.

Flavan-4-ol	λ_{max} ($\Delta\varepsilon$)
(2*R*, 4*R*)-*cis*	283 (+1.22), 276 (+1.28), 227 (+2.23)
(2*R*, 4*S*)-*trans*	282 (-1.17), 276 (-1.17), 226 (-7.62)
(2*S*, 4*R*)-*trans*	282 (+1.44), 276 (+1.41), 226 (+0.80)

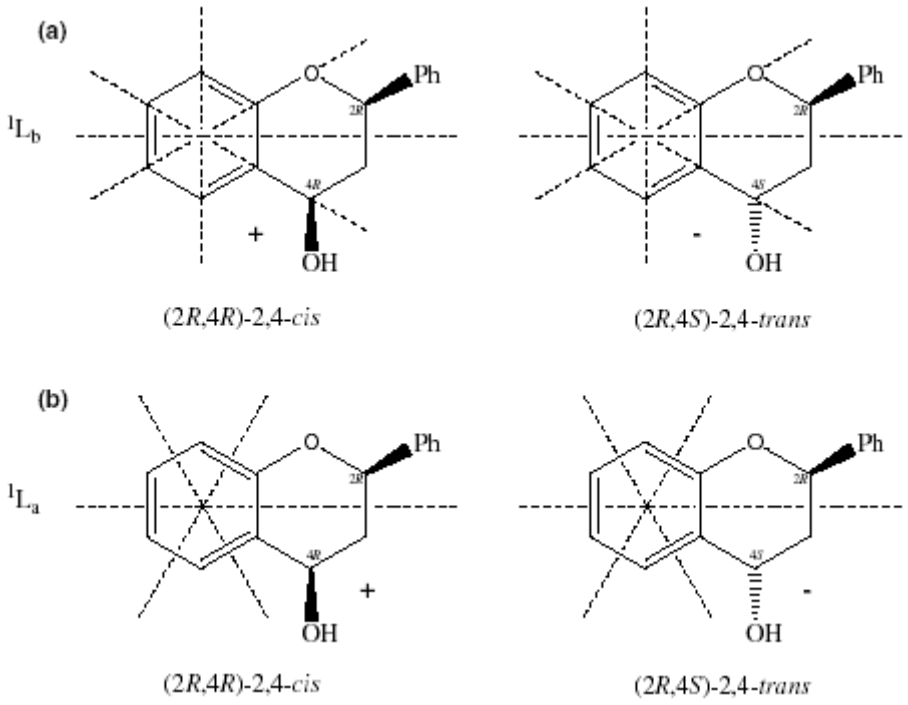


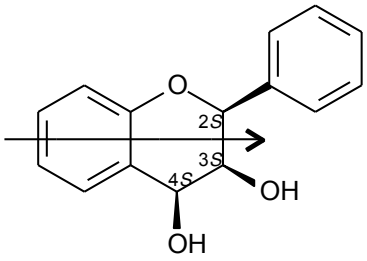
Figure 9. Sector rule for third-sphere contributions to the (a) ^1L_b and (b) ^1L_a bands.

3.2.5 Flavan-3,4-diols

As for the other classes of flavonoids, determination of the absolute configuration at the three stereogenic centres of flavan-3,4-diols (**3.6**) starts with the definition of the relative

11 Snatzke, G.; Znatzke, F.; Tökés, A.L.; Rákosi, M.; Bognár, R. *Tetrahedron* **1973**, *29*, 909.

stereochemistry, which can easily be done by NMR. For most compounds the $^{3}J_{H,H}$ coupling constants of the C-ring protons give a clear indication as to the relative stereochemistry of the substituents attached to the C-ring. In cases where these values showed small differences, i.e. the 2,3-*cis*-3,4-*trans* and 2,3-*cis*-3,4-*cis* isomers, the relative stereochemistry can be confirmed by appropriate NOE experiments.



(**3.6**)

3.2.5.1 The $^{1}L_{b}$ transition

Similar to the flavan-3- and -4-ols, the sign and magnitude of the CE within each absorption band ($^{1}L_{a}$ and $^{1}L_{b}$) of the CD spectrum of flavan-3,4-diols are determined by the preferred conformation of the C-ring. As for the previous cases (flavan-3- and 4-ols) the preferred conformation of the C-ring would in this instance also be the half-chair/C2-sofa with the B-ring in the equatorial position. In general, this implies that *P*-helicity associated with a 2*R* configuration of the C-ring would lead to a negative $^{1}L_{b}$ CE, while *M*-helicity (2*S* configuration) would be associated with a positive CE for the same transition (Figure 10). In agreement with what was concluded for the flavan-3-ols, the absolute configuration of the 3-OH group has a minor influence on the sign of the CE of the $^{1}L_{b}$ transition.

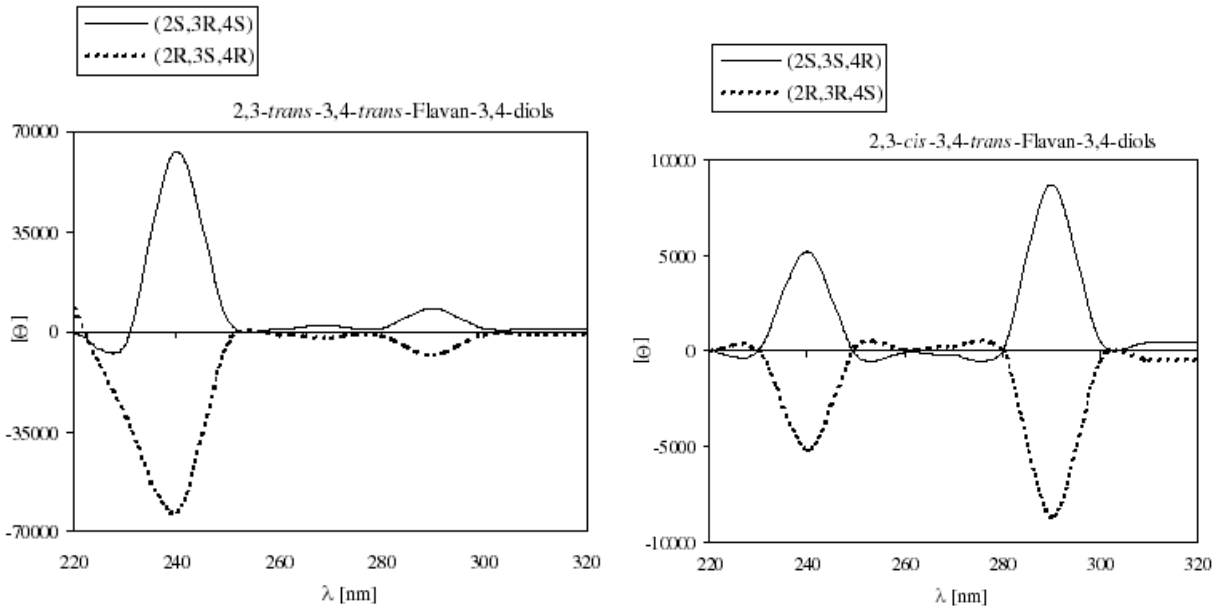
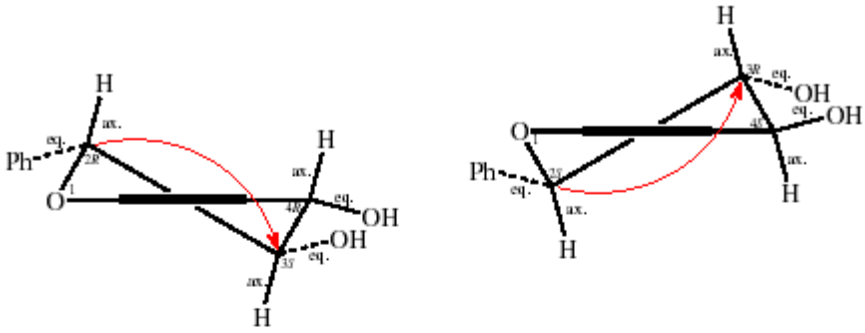


Figure 10. CD spectra of 2,3-*trans*(*cis)*-3,4-*trans*-flavan-3,4-diols.

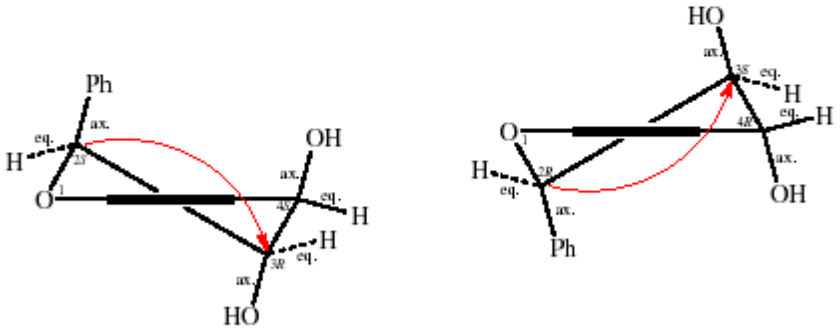
The E-conformer of the all-*trans* analogues, (2*R*,3*S*,4*R*)- and (2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*-flavan-3,4diol, however, experiences allylic strain between the C4-OH and H5. This results in a conformational change to alleviate the strain and leads to a relatively stable inversed half-chair/C2 sofa A-conformation[12] with *M*- as opposed to *P*-helicity for the 2*R*-all-*trans*-flavan-3,4-diols and vice versa for the 2*S* analogues (Figure 11). The net effect of this conformational change is a reduced amplitude of the ^1L_b CE for the all-*trans* analogues compared to the 2,3-*trans*-3,4-*cis* compounds. The A-conformer of these flavan-3,4-diols, as well as the (2*R*,3*R*,4*R*)- and (2*S*,3*S*,4*S*)-2,3-*cis*-3,4-*cis* isomers (all the 2,4-*cis*-analogues) may be stabilised through hydrogen bonding between the C4-OH and the aromatic B-ring (Figure 12).

[12] Porter, L.J.; Wong, R.Y.; Benson, M.; Chan, B.G.; Vishwanadhan, V.N.; Gandour, R.D.; Mattice, W.L. *J. Chem. Res*. **1986**, 86.



E-conformer
P-helicity ⇒ negative ^1L_b band
(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*

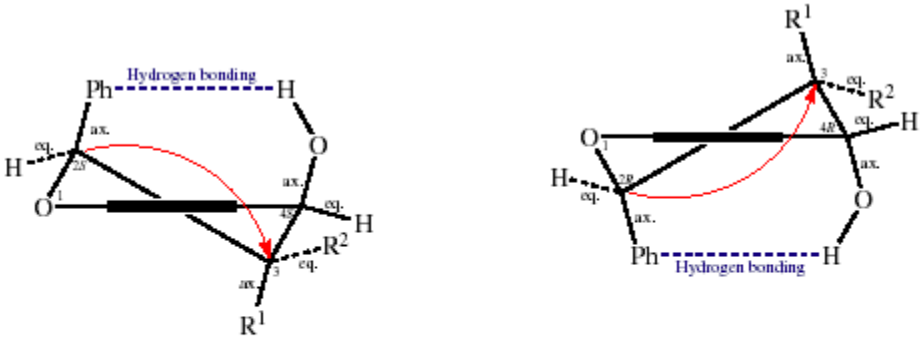
E-conformer
M-helicity ⇒ positive ^1L_b band
(2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*



A-conformer
P-helicity ⇒ negative ^1L_b band
(2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*

A-conformer
M-helicity ⇒ positive ^1L_b band
(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*

Figure 11. A-conformer half-chair conformations for all-*trans*-flavan-3,4-diols.



A-conformer
P-helicity ⇒ negative ^1L_b band
R^1 = H, R^2 = OH: (2*S*,3*S*,4*S*)-2,3-*cis*-3,4-*cis*
R^1 = OH, R^2 = H: (2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*

A-conformer
M-helicity ⇒ positive ^1L_b band
R^1 = H, R^2 = OH: (2*R*,3*R*,4*R*)-2,3-*cis*-3,4-*cis*
R^1 = OH, R^2 = H: (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*

Figure 12. A-conformation 2,4-*cis*-diaxial hydrogen bonding.

The E-conformer of the all-*cis* analogues [(2*R*,3*R*,4*R*)- and (2*S*,3*S*,4*S*) compounds] is also stabilized by hydrogen bonding between the axial C3-OH and the *O*-heteroatom of the C-ring (Figure 13).

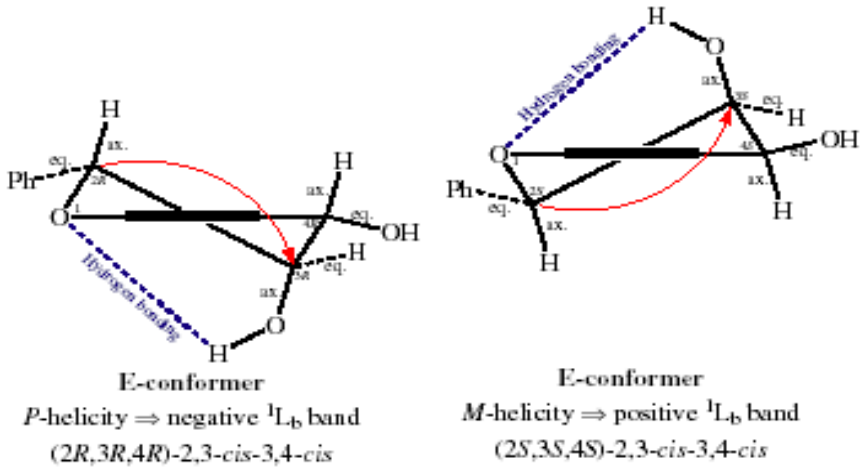


Figure 13. E-conformation all-*cis* hydrogen bonding.

3.2.5.2 The ^1L_a transition

Ferreira *et al*.[13] reported the sign of the ^1L_a CE (ca 240 nm) to be the same as that of the ^1L_b CE (ca 280 nm) for the all-*trans*-, all-*cis*- and 2,3-*cis*-3,4-*trans*-flavan-3,4-diols, while the sign of the ^1L_a CE seems to be opposite to the ^1L_b CE for the 2,3-*trans*-3,4-*cis*-flavan-3,4-diols, except for 2,3-*trans*-3,4-*cis*-leucocyanidin. It was also concluded that the CEs of all the compounds under investigation did not obey the aromatic quadrant rule for correlating the sign of the ^1L_a CE with the absolute configuration at C4.[14]

3.2.6 Flavans

Flavans are formed by a double reduction of a flavanone and their ORD and CD analysis revealed that the 2*S* absolute configuration can be assigned to all natural flavans. Like other flavonoids, flavans adopt a half-chair conformation with the C2-phenyl group in an equatorial orientation and they follow the familiar rule of *P*- and *M*- helicity of the *O*-heterocyclic ring in the chroman chromophore resulting in negative and positive CEs within the ^1L_b band respectively (Figure 14). This implies that a negative ^1L_b CE is observed for 2*S* absolute configuration and a positive ^1L_b CE comes form a 2*R* configuration.

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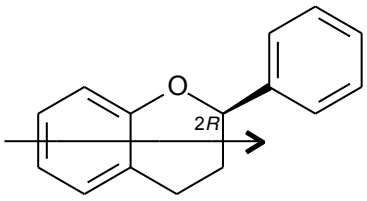
13 Ferreira, D.; Marais, J.P.J.; Slade, D.; Walker, L.A. *J. Nat. Prod.* **2004**, *67*, 174.

14 DeAngelis, G.G.; Wildman, W.C. *Tetrahedron* **1969**, *25*, 5099.



(**3.7**)

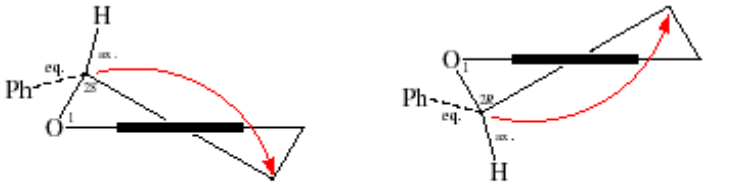
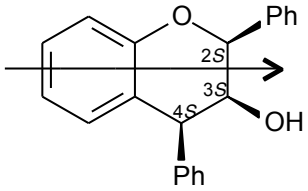


Figure 14. Flavan (**3.7**) *P*- and *M*-helicity.

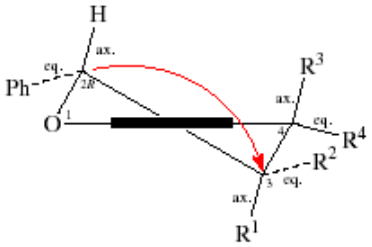
3.2.7 4-Arylflavan-3-ols



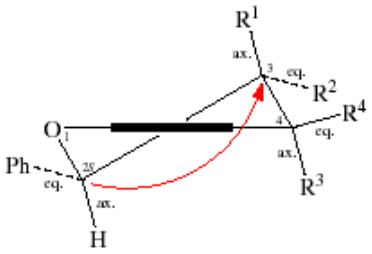
(**3.8**)

While the absolute configuration of the classes of flavonoids discussed thus far can easily be determined by application of the helicity rule and the preference of the C2-phenyl ring towards an equatorial orientation, the situation with 4-arylflavan-3-ols is much more complicated. In this instance the preferred conformation of the C-ring is not that clear since three substituents, of which two are phenyl rings, are attached to adjacent carbon atoms and steric interaction (A- or 1,3-allylic strain) between the D-ring and a possible 5-substituentuent on the A-ring, which plays a significant role in the conformation of the heterocyclic C-ring, may be present. These facts in conjunction with the presence of another aromatic ring close to the A-ring chromophore have a profound influence on the observed Cotton effect(s). Although the helicity of the C-ring (Figure 15 and Figure 16) can easily be concluded, if the preferred conformation of the C-ring (half-chair or C2 sofa) is known, very few reports where the CE has been related to the helicity is found in

literature. In contrast to this, several workers utilised the aromatic quadrant rule[15] (Figure 17) in their efforts to relate the 220 to 240 nm CE with the absolute configuration of 4-arylflavan-3-ols.



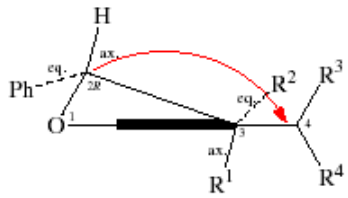
C2/C3	C3/C4	C2	C3	C4	R^1	R^2	R^3	R^4	Helicity
cis	*cis*	*R*	*R*	*R*	OH	H	H	Ph	*P*
trans	*trans*	*R*	*S*	*R*	H	OH	H	Ph	*P*
cis	*trans*	*R*	*R*	*S*	OH	H	Ph	H	*P*
trans	*cis*	*R*	*S*	*S*	H	OH	Ph	H	*P*



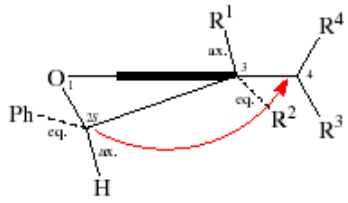
C2/C3	C3/C4	C2	C3	C4	R^1	R^2	R^3	R^4	Helicity
cis	*cis*	*S*	*S*	*S*	OH	H	H	Ph	*M*
trans	*trans*	*S*	*R*	*S*	H	OH	H	Ph	*M*
cis	*trans*	*S*	*S*	*R*	OH	H	Ph	H	*M*
trans	*cis*	*S*	*R*	*R*	H	OH	Ph	H	*M*

Figure 15. Half-chair conformation for 4-arylflavan-3-ols.

15 DeAngelis, G.G.; Wildman, W.C. *Tetrahedron* **1969**, *25*, 5099.



C2/C3	C3/C4	C2	C3	C4	R^1	R^2	R^3	R^4	Helicity
cis	*cis*	*R*	*R*	*R*	OH	H	H	Ph	*P*
trans	*trans*	*R*	*S*	*R*	H	OH	H	Ph	*P*
cis	*trans*	*R*	*R*	*S*	OH	H	Ph	H	*P*
trans	*cis*	*R*	*S*	*S*	H	OH	Ph	H	*P*



C2/C3	C3/C4	C2	C3	C4	R^1	R^2	R^3	R^4	Helicity
cis	*cis*	*S*	*S*	*S*	OH	H	H	Ph	*M*
trans	*trans*	*S*	*R*	*S*	H	OH	H	Ph	*M*
cis	*trans*	*S*	*S*	*R*	OH	H	Ph	H	*M*
trans	*cis*	*S*	*R*	*R*	H	OH	Ph	H	*M*

Figure 16. Sofa conformation for 4-arylflavan-3-ols.

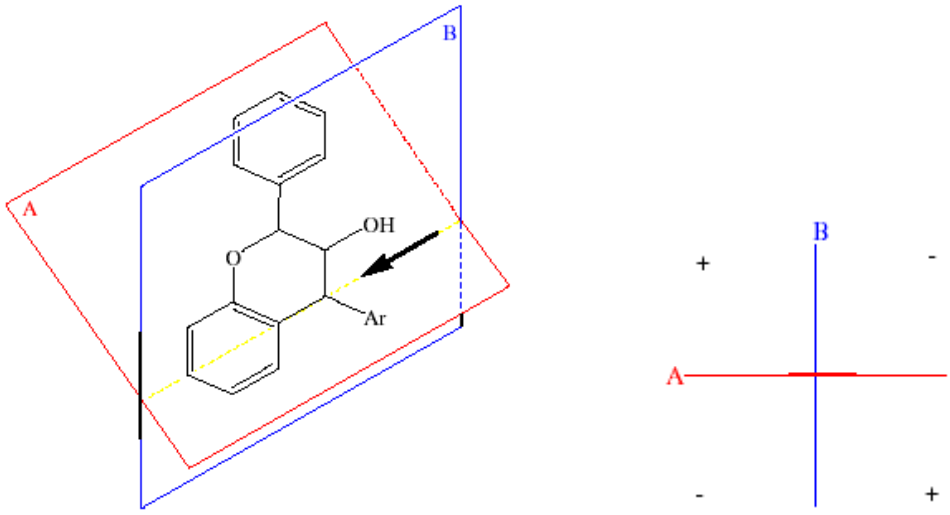
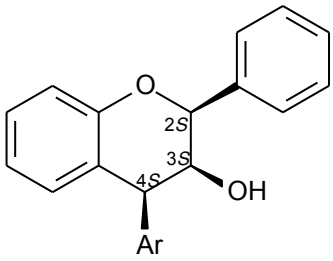


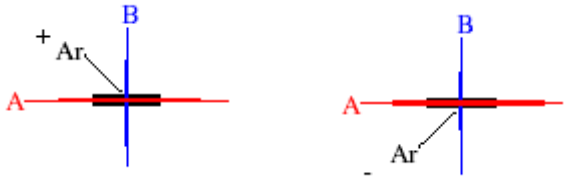
Figure 17. Aromatic quadrant rule.

Studies on a series of 2,3-*trans*- and 2,3-*cis*-4-arylflavan-3-ols where phloroglucinol and resorcinol were coupled to flavan-3,4-diols of known absolute configuration in indicated the CD

spectra of these compounds to be dominated by multiple CEs contributed by the C4-aryl chromophore when compared to the CEs of flavan-3-ols.[16] The CD curves of the methyl ether 3-acetates of these compounds further indicated that CEs due to chirality at C2 and C3 are completely dominated by the high amplitude CEs of the C4-aryl chromophore (220 - 240 nm). Through application of the aromatic quadrant rule these workers determined that a positive CE represents a quasi-axial (extending above the plane of the A-ring) C4-aryl group and a negative CE indicates a quasi-equatorial (below the plane of the A-ring) C4-aryl group (Figure 18).



(**3.9**)



Positive CE	**Negative CE**
(2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*	(2*S*,3*R*,4*R*)-2,3-*trans*-3,4-*cis*
(2*R*,3*R*,4*S*)-2,3-*cis*-3,4-*trans*	(2*S*,3*S*,4*R*)-2,3-*cis*-3,4-*trans*
(2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*trans*	(2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*

Figure 18. The aromatic quadrant rule for 2,3-*trans*-3,4-*trans*-, 2,3-*trans*-3,4-*cis*- and 2,3-*cis*-3,4-*trans*-4-arylflavan-3-ols.*

CD data of the methyl ether acetates of 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ols and the catechin-4α-phloroglucinol analogue with abnormal coupling constants ($J_{2,3}$ 6.5, $J_{3,4}$ 5.5 Hz), however, display inverse CEs to the above rule.[17] This indicates that deviations form the normal dihedral angles between substituents on the heterocyclic ring and therefore form the expected half-chair conformation significantly influences the sign of the CE. While these abnormal CEs were

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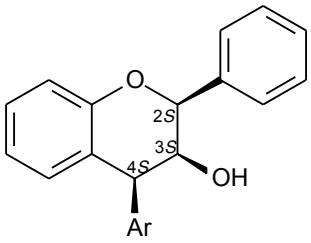
16 Botha, J.J.; Ferreira, D.; Roux, D.G. *J Chem Soc., Chem. Commun.* **1978**, *16*, 698.

* Care should be taken with assignment of *R* and *S* absolute configuration at C4, since substituents on the D-ring influences the CIP priorities.

17 Van der Westhuizen, J.H.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1220.

originally explained by invoking boat-conformations for these compounds (Figure 19), modelling studies [18] indicated profound contributions by A-conformers to the C-ring conformation of isomers with a 2,4-*cis*-relative configuration when compared to 2,4-*trans*-isomers (Figure 20). The CD data of 5-deoxy analogues do not show these irregularities indicating the predominance of the E-conformers and the absence of A-strain for both the 2,4-*trans*- and 2,4-*cis*-isomers. Although 1,3-diaxial arrangements are generally avoided on energetic grounds, the stability of A- relative to E-conformers for the 2,4-cis-sisomers appears to be an exception by virtue of π-stacking between the C2 and C4 aromatic rings (Figure 21).



(**3.10**)

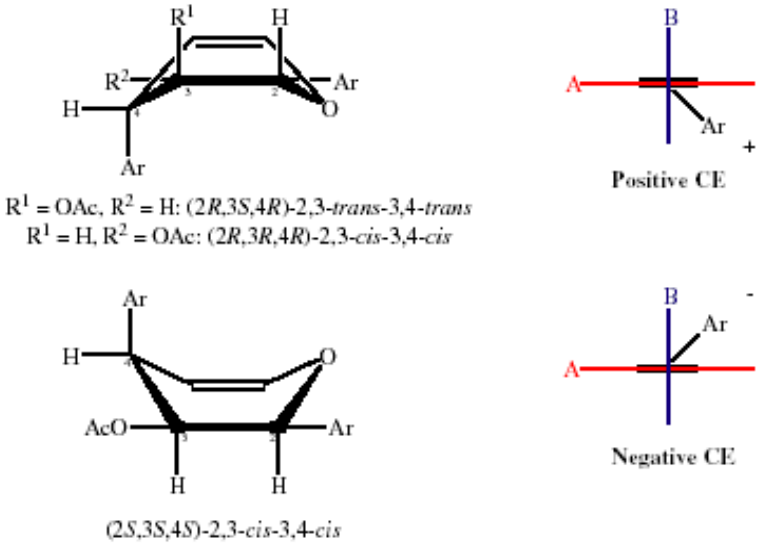


Figure 19. Boat-conformations for 2,3-*cis*-3,4-*cis*-4-arylflavan-3-ols and the catechin-4α-phloroglucinol analogue.

18 Steynberg, J.P.; Brandt, E.V.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1569.

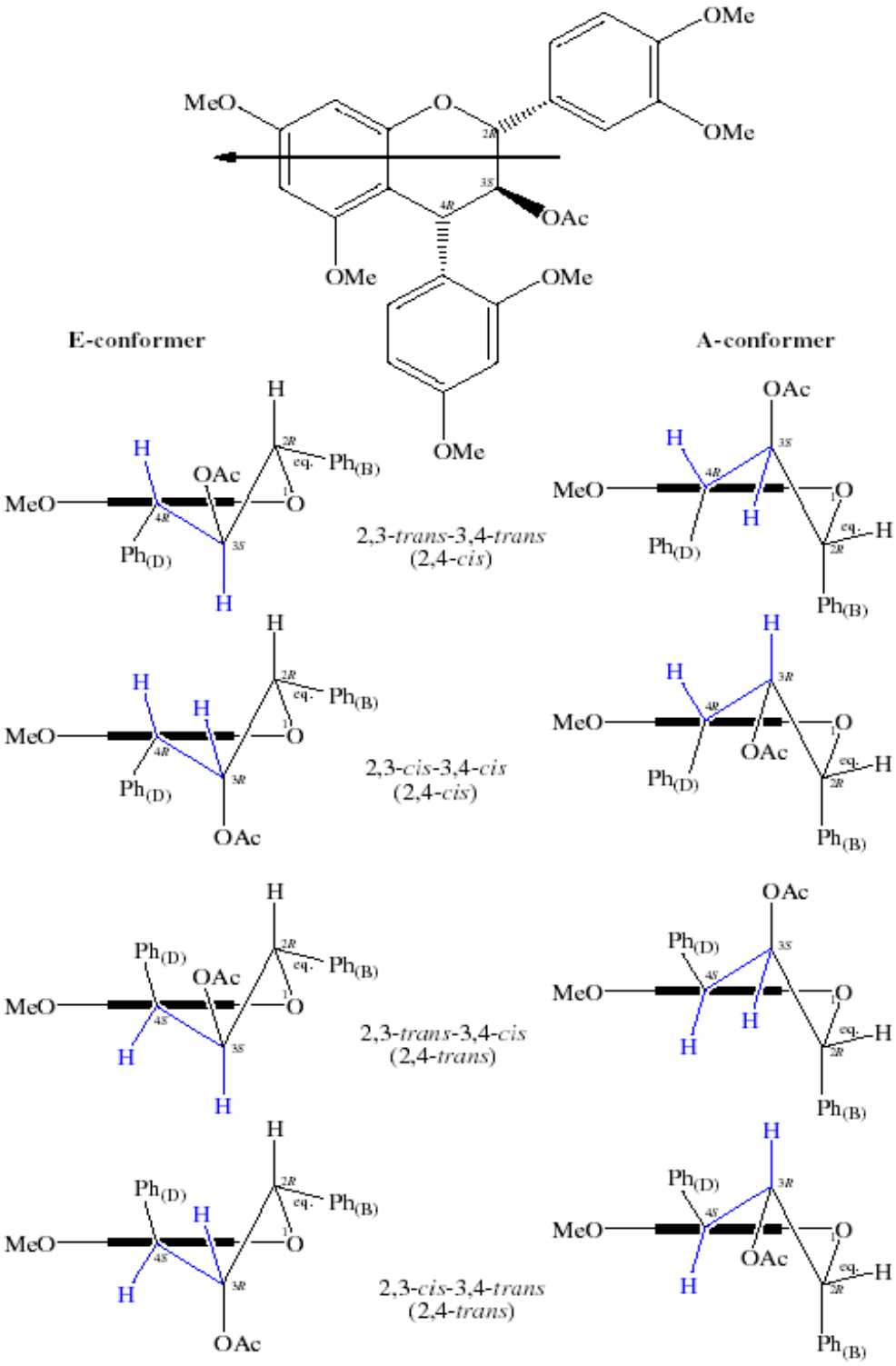


Figure 20. E- and A-conformations.

(H3-C3-C4-H4 angles indicated in blue.)

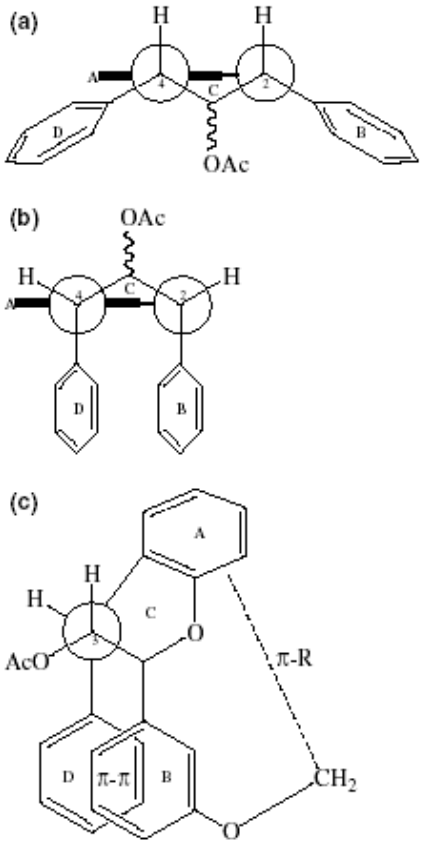


Figure 21. 2,4-*cis*-4-Resorcyl-5-oxyflavan-4-ols. (a) E-conformer viewed along the C2-O1 and C4-C5a bonds, (b) A-conformer viewed along the C2-O1 and C4-C5a bonds, and (c) A-conformer viewed along the C3-C4 bond.

Finally, it has to be pointed out that Van Zyl *et al*.[19] found that the CE at 220 – 240 nm of a (2*R*,3*S*)-2,3-*trans*-3,4-*trans*flavn-3-ol changes form negative for the free phenolic form to positive for the methyl ether acetate of the same compound.

3.2.8 Conclusions

Although CD has found wide application in the determination of the absolute configuration of different classes of flavonoids, this technique is to a large extent dependant on the conformation of the heterocyclic C-ring of the specific flavonoid. As was clearly shown in particular for the 4-arylflavan-3-ols, the conformation of the C-ring can change dramatically with small changes in the relative orientation of the substituents attached to this ring and/or substituents on the A-ring of the flavonoid. The fact that the NMR coupling constants, which are used to determine the relative stereochemistry, and the interpretation of the CE spectrum depend on the same

19 Van Zyl, P.W.; Steynberg, J.P.; Brandt, E.V.; Ferreira, D. *Magn*. *Reson*. *Chem*. **1993**, *31*, 1057.

phenomenon, i.e. conformation of the C-ring, casts some doubt as to the accuracy of results obtained in this way. If some uncertainty in this regard exists for the monomeric flavonoids, it has to be pointed out that the situation would be worse for the oligomeric analogues where two or more heterocyclic rings, each with its own conformation and absolute configuration at at least two chiral centres, are present in the molecule. Methodology or a technique that would allow the assessment of the absolute configuration at each chiral centre independently would therefore make an important contribution to this area of natural product research.

3.3 Molecular modelling in combination with electronic CD (ECD) measurements

3.3.1 Introduction

Since the past decade has witnessed revolutionary advancements in the area of quantum chemical calculations, it became possible to use time-dependent density functional theory (TDDFT), calculations to calculate the electronic circular dichroism (ECD) spectra of chiral molecules and therefore determine the AC of the molecule by comparing the calculated spectrum with the experimentally determined version. ECD is experienced in a very sensitive manner in fact that using 0.1-1 mg of the sample could obtain a good spectrum. The chiral molecule will display absorptions in the UV/vis wavelength range for those appropriate chromophores in order to have ECD absorptions or Cotton effects. In general, the ECD calculations involve the two basic steps. Firstly, through the conformational analysis can find the least energy conformers hence to calculate the ECD spectra of the conformers. In principle, it is the comparison between the calculated and experimental ECD spectra. In other words, the more they match, the more accurate result for the AC assignment can be concluded.[20]

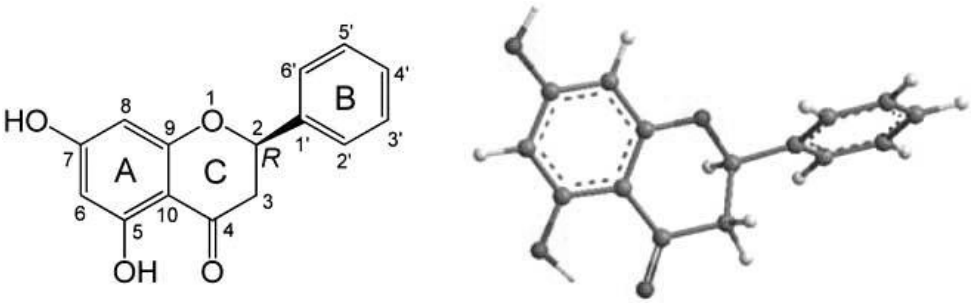
In order to compute the ECD calculations, the relative configuration or possible relative configuration of the stereogenic carbons that close to the chromophore of the compound must be known. It has been found that CD can only detect the stereochemical difference that close to the chromophore in a molecule with multiple stereogenic centers. However, the ECD calculation determines the AC of one or two stereogenic carbons and the NMR spectroscopy can be introduced to determine the AC of the remaining stereogenic centers. The ECD calculation is

20 Li, X.C.; Ferreira, D.; Ding, Y. *Curr*. *Org*. *Chem*. **2010**, *14*, 1678.

also possible to determine the AC of complex chiral molecules by quantifying the contribution of individual conformers and the interaction of multiple chromospheres.

3.3.2 Flavanones

The determination of AC of flavonoids was acchieved by CD experiment which can be the most powerful tool, [21] until 1970 Gaffield reported that (2*S*)-flavanone and (2*R*, 3*R*)-3-hydroxyflavanone resulted the same negative Cotton effect at about 290 nm for the acetophenone $\pi \rightarrow \pi^*$ transitions and a postive Cotton effect at about 330 nm for the acetophenone $n \rightarrow \pi^*$ transitions, see paragraph 3.2.1. Their enantiomers however gave opposite Cotton effects; moreover, these CD patterns are the foundation for all chiral flavonoids for AC assignmant. In order to furnish theoretical evidence with the aforementioned explanation and evaluate the reliability of the ECD calculation a chiral flavonoid, (2*R*)-pinocembrin **(3.11)** (Figure 22) was used as model compound by Li *et al*.[20]



(3.11)

Figure 22. Structure and optimized geometry of (2*R*)-pinocembrin.

(2*R*)-Pinocembrin (**3.11**) possesses one single stereogenic center at C2 and according to NMR investigation that this type of compound reveals the phenyl ring is equatorially oriented and the OH at 5-position makes an intramolecular hydrogen bond with the C4 carbonyl group. Hence, the conformational analysis of this compound is straightforward to afford only one preferred conformer which was presented at the B3LYP/6-31G* basis set in the gas phase (Figure 22). The heterocyclic C-ring orientats a half-chair conformation with an equatorial phenyl B-ring rotated to be almost perpendicular to the A/C-ring plane. The calculated ECD spectra is presented in different basis sets and overall is consistent with its experimental data in the region of 260-350 nm, see Figure 23. It is also observed that the maximum absorption is slightly shifted

21 Slade, D.; Ferreira, D.; Marais, J.P.J. *Phytochemistry* **2005**, *66*, 2177.

toward the low wavelength region at about 270 nm in the calculated ECD *vs* about 285 nm in the experimental ECD spectrum.

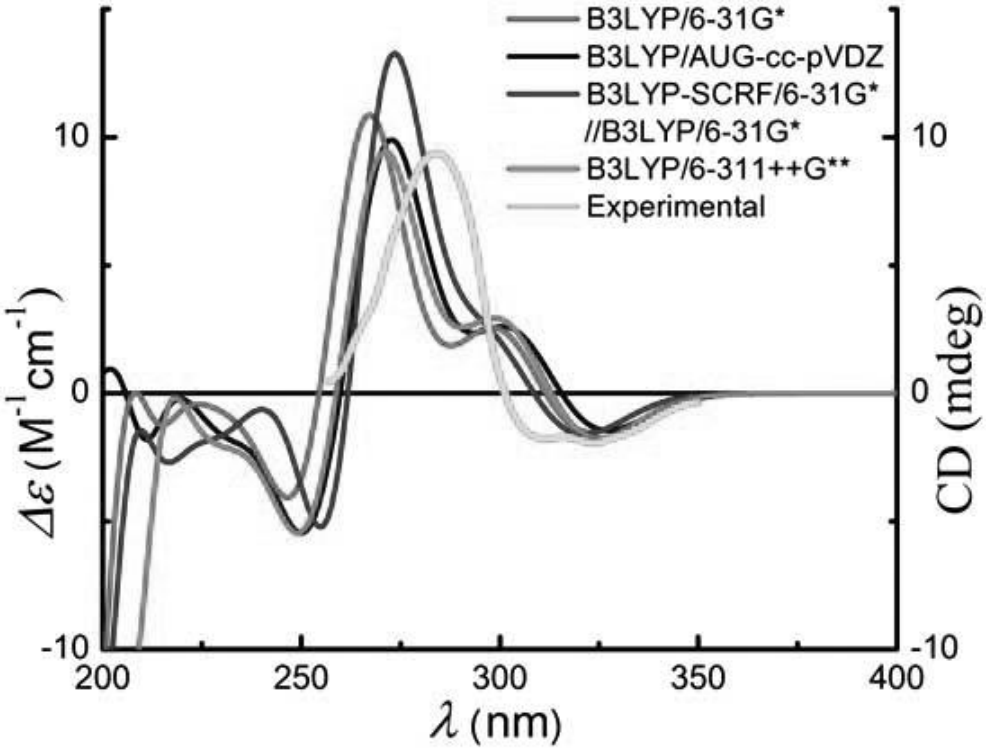


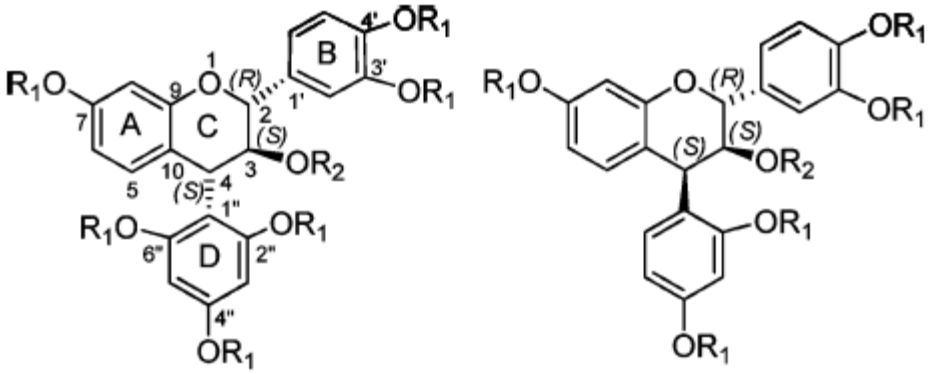
Figure 23. Calculated ECD spectra of (2*R*)-pinocembrin (**3.11**) at different basis sets and its experimental ECD spectrum in the range of 260-350 nm.

3.3.3 4-Arylflavan-3-ols

Proanthocyanidins play an important role in the naturally occurring polyphenols and the biological and industrial applications are based on their composition, configuration, and conformational behaviour including rotation the interflavanyl bonds and preferred conformations of the heterocyclic dihydropyran rings. The conformation analysis of the heterocyclic dihydropyran rings can be determined by ^{1}H NMR coupling constants its AC assignment is possiblily be done on ECD calculation.[22] The results of the calculated ECD spectra of the compounds give the significant information for their conformation and configuration. In other words, the closer the calculated and experimental ECD spectra are matched, the better the calculated conformation and configuration reflect the compound character in solution. Ding *et al*.[22] displayed a series of 4-arylflavan-3-ols as model compounds for the study of AC

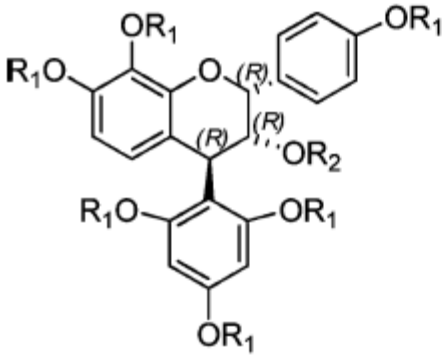
22 Ding, Y.; Li, X.C.; Ferreira, D. *J*. *Nat*. *Prod*. **2010**, *73*, 435.

determination by ECD technique and in this section we presented only two examples e.g. (**3.13**) and (**3.18**) to demonstrate how the ECD works for this class of flavonoids (Figure 24).

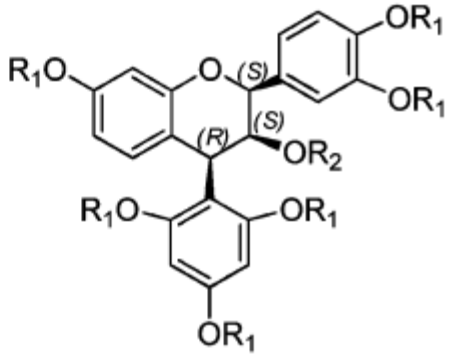


	R_1	R_2
(3.12)	**H**	**H**
(3.13)	**Me**	**Ac**

	R_1	R_2
(3.14)	**H**	**H**
(3.15)	**Me**	**Ac**



	R_1	R_2
(3.16)	**H**	**H**
(3.17)	**Me**	**Ac**



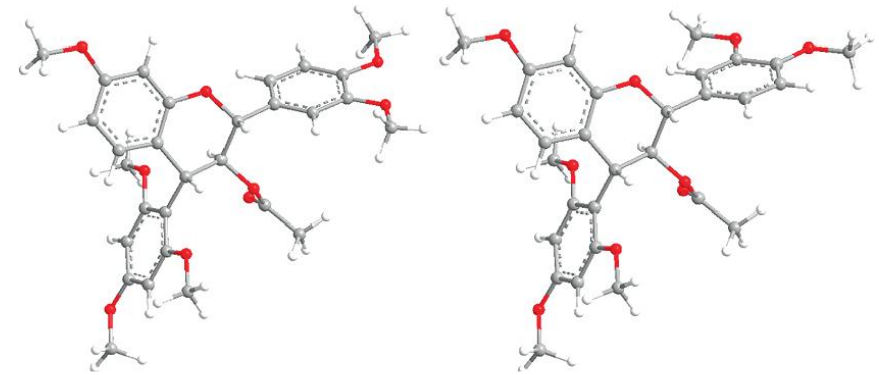
	R_1	R_2
(3.18)	**H**	**H**
(3.19)	**Me**	**Ac**

Figure 24. The models: 4-arylflavan-3-ols (**3.12-3.19**).

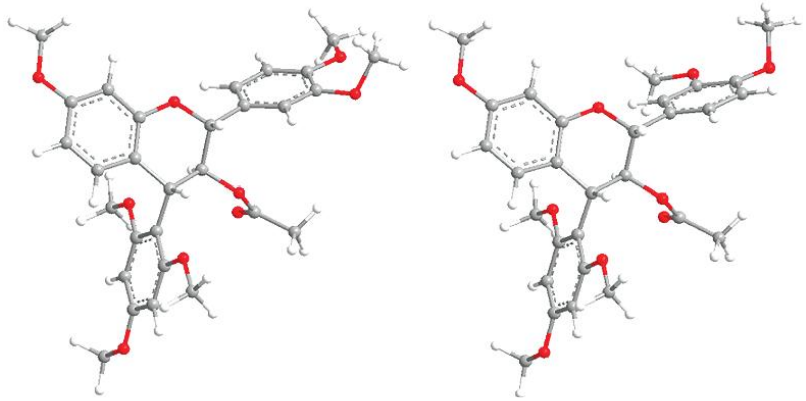
Four 4-arylflavan-3-ols, (**3.12**), (**3.14**), (**3.16**) and (**3.18**) and their corresponding phenolic methyl ether 3-*O*-acetates (**3.13**), (**3.15**), (**3.17**) and (**3.19**) were selected as models. Compounds (**3.16**) and (**3.17**) with 4α-aryl group thus, 4*S* absolute configuration exhibits negative Cotton effect (CE) in the 220-240 nm region, however compounds (**3.14-3.19**) with 4β-aryl groups [4*S* AC for (**3.14**) and (**3.15**)]; 4*R* AC for (**3.17**) and (**3.19**), gave positive CEs in the same region.

The conformational search was performed for compound (**3.13**) to generate 153 conformers in the Boltzmann population. The B-ring acetoxy group and D-ring are equatorially positioned and C4 is coplanar with the A-ring for the first 50 conformers. The next 25 lowest energies

comformers were geometrically optimized and afforded four predominant conformers, (3.13a-3.13d) which were relocated with a Boltzmann distribution of 17.3%, 44.6%, 19.1% and 19.0%. The orientation of the B-ring and *O*-methyl groups are caused the major differences among the four conformers (Figure 25).



(3.13a) **(3.13b)**



(3.13c) **(3.13d)**

Figure 25. Optimized geometries of four predominant conformers, (**3.13a-3.13d**).

The dihedral angle, H-C2-C3-H, in (**3.13a-3.13d**) ranges from 173° – 178° which corresponding a large coupling constant of 10 Hz between H-2 and H-3 in the experimental ^{1}H NMR spectrum, however the dihedral angle, H-C3-C4-H of 166° – 168° is consistent with a $^3J_{3,4}$ value of 9.0 – 9.8 Hz.[23] The calculated ECD spectra of the predominant conforrmer (**3.13b**) and the weighted ECD spectra of the four conformers (**3.13a-3.13d**) are presented in Figure 26. It is shown that this result reveals an excellent match of the calculated and experimental ECD spectra for

[23] (a) Botha, J.J.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Chem. Commun*. **1978**, 698. (b) Botha, J.J.; Young, D. A.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1213. (c) Van der Westhuizen, J.H.; Ferreira, D.; Roux, D.G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1220. (d) Steynberg, J.P.; Burger, J.F.W.; Young, D.A.; Brandt, E.V.; Ferreira, D. *Heterocycles* **1989**, *28*, 923. (e) Van Zyl, P.W.; Steynberg, J.P.; Brandt, E.V.; Ferreira, D. *Magn. Reson. Chem*. **1993**, *31*, 1057.

compound (**3.13**), hence indicates such computational methods are reliable for the conformational and configurational analysis of this class of compounds.

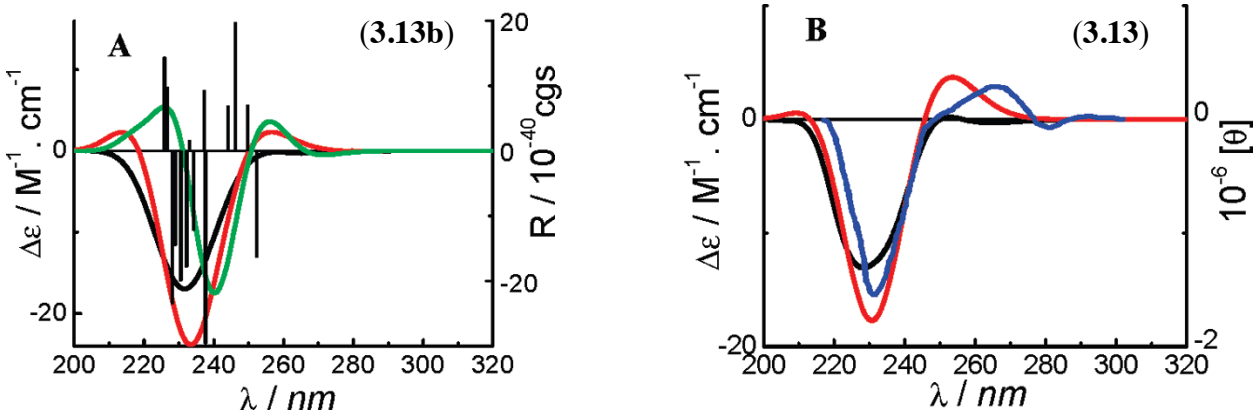


Figure 26. Calculated ECD spectra of conformer (**3.13b**) (A) and weighted and experimental ECD spectra of compound (**3.13**) (B).

The second example, (**3.18**) in this study is that the B- and D-rings were similarly equatorially oriented and the PES was scaned by rotating the C2-C1' - and C4-C1" bonds at B3LYP/6-31G* basis set to afford six conformers (Figure 27). The four conformers, (**3.18a-3.18d**) were found to possess the C2"OH···OC3 hydrogen bonding (C2"O···HOC3 hydrogen bonding for the other two conformers) indicating a Boltzmann distribution of 28%, 50%, 8% and 14% for the predominant conformers (**3.18a-3.18d**) respectively. These differ as far as the orientation of 3-hydroxy group is concerned (Figure 28).

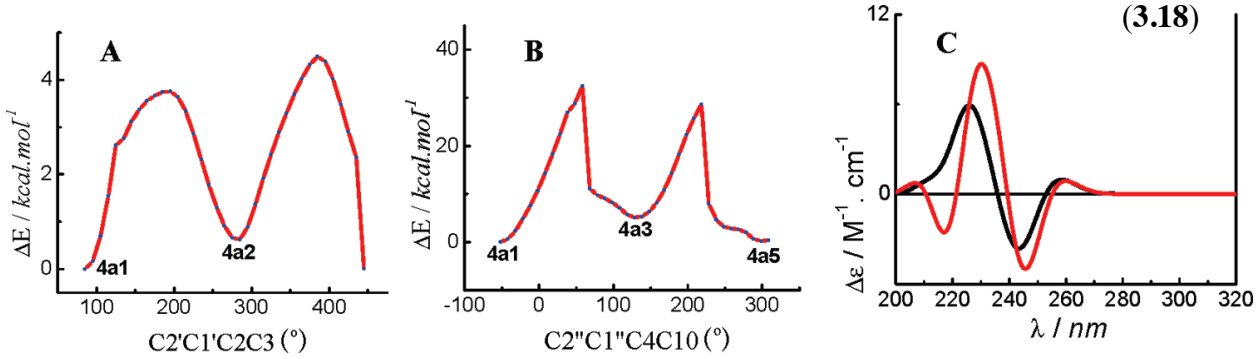
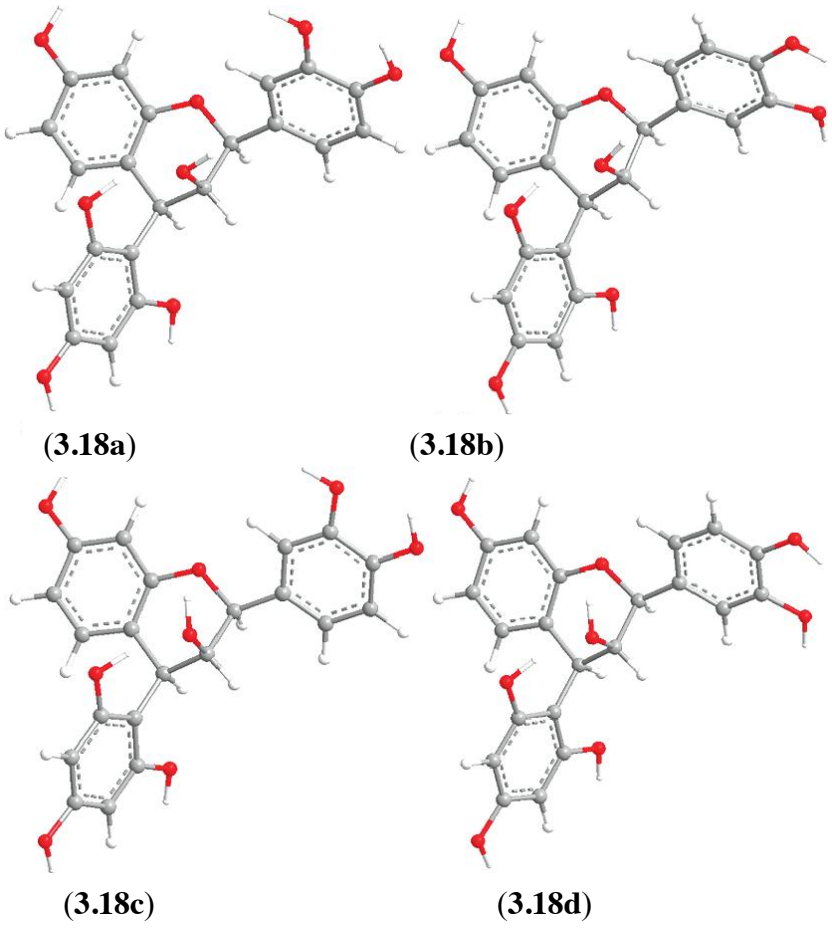


Figure 27. PES of compound (**3.18**) (A, B) at B3LYP/6-31G* level and its weighted ECD spectra (C).

Although the dihedral angles C1"-C4-C10-C9 in (**3.18a-3.18d**) increased to about 153°, the 4-aryl substituent (D-ring) is located in the upper left quadrant, thus compound (**3.18**) would display a positive CE in the 220 – 240 nm region of the ECD spectrum. While experimentally

positive CE at 236 nm was observed this was corresponded to the prediction. In order wards, the conformational inversion of the C-ring will not change the sign of the positive CE in the 220 – 240 nm region. The calculated ECD spectra of (**3.18**) indicating a strong positive CE in the 220 – 240 nm CD region (Figure 27) given theoretical evidence to validate the application of the aromatic quadrant rule to the AC assignment at C4 of 4-arylflavan-3-ols.



(**3.18a**) (**3.18b**)

(**3.18c**) (**3.18d**)

Figure 28. Optimized geometries of four predominant conformers at B3LYP/6-31G* level.

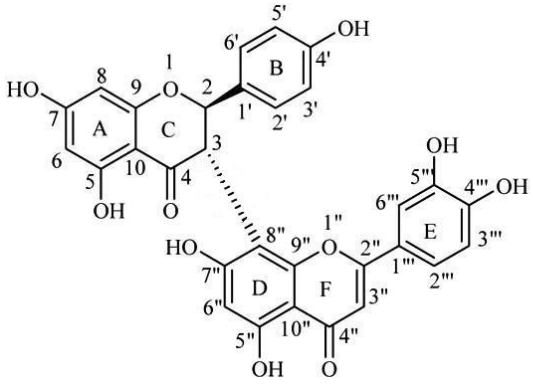
3.3.4 Biflavonoids

3.3.4.1 Morelloflavone

In natural product research, the determination of AC is one of the most challenging topics in the structural elucidation of chiral products or those complex structures. Since the application of ECD is used popularly in AC determining for flavonoids compounds as mentioned, the more complex molecules e.g. biflavonoids are also studied in detailed. Li *et al*.[24,25,26,27] have started a

[24] Li, X.-C.; Joshi, A.S.; Tan, B.; ElSohly, H.N.; Walker, L.A.; Zjawiony, J.K.; Ferreira, D. *Tetrahedron* **2002**, *58*,

series studies on the stereochemistry of morelloflavone where the conformation analysis, AC and chiral properties are presented. In 1967 the first flavanone-(3 → 8")-flavone biflavonoid, morelloflavone (**3.20**) is a rotationally restricted type biflavonoid with two stereogenic centers and one chiral axis and was isolated and identified from the seeds of *Garcinia morella*.[28]



(**3.20**)

Since the biflavonoids biosynthetically play an important role of natural products with significant biological activities, morelloflavone (**3.20**) was first determined its AC with regards to conformations and chiral stability by NMR, CD and ECD analysis. In 1978, a proposed 2*R*, 3*S*-absolute stereochemistry for morelloflavone was obtained by examination of ^{13}C NMR and CD spectra of some biflavonoids from *Garcinia* species[29] unfortunately, the source and optical rotation of (**3.20**) was not clearly indicated. Gaffield has demonstrated that the Cotton effect of the $\pi \rightarrow \pi^*$ transition about 290 nm is more reliable for the determination of the C-2 stereochemistry than the Cotton effect of the $n \rightarrow \pi^*$ transition at longer wavelength.[30] In addition, the CD curve of (**3.20**) indicated (+) Cotton effects for both the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions near 340 and 290 nm respectively. The high-amplitude (+) Cotton effects near 290 nm indicating 2β-orientation of the B-ring hence 2*R* AC for the morelloflavone (**3.20**). Apart

8709.

25 Ding, Y.; Li, X.-C.; Ferreira, D. *J*. *Org*. *Chem*. **2007**, *72*, 9010.

26 Ren, Y.; Lantvit, D.D.; Carcache de Blanco, E.J.; Kardono, L.B.S.; Riswan, S.; Chai, H.; Cottrell, C.E.; Farnsworth, N.R.; Swanson, S.M.; Ding, Y.; Li, X.-C.; Marais, J.P.J.; Ferreira, D.; Kinghorn, A.D. *Tetrahedron* **2010**, *66*, 5311.

27 Li, X.-C.; Ferreira, D.; Ding, Y. *Curr*. *Org*. *Chem*. **2010**, *14*, 1678.

28 Karanjgaokar, C.G.; Radhakrishnan, P.V.; Venkatarama, K. *Tetrahedron Lett*. **1967**, 3195.

29 Duddeck, H.; Snatzke, G.; Yemul, S.S. *Phytochemistry* **1978**, *17*, 1369.

30 Gaffield, W. *Tetrahedron* **1970**, *26*, 4093.

from the CD data, the ^{1}H NMR coupling constants of morelloflavone (**3.20**) ($^{3}J_{2,3}$, ~12 Hz), therefore to confirm the assignment of 2,3-*trans* relative configuration and thus 3*S* AC.

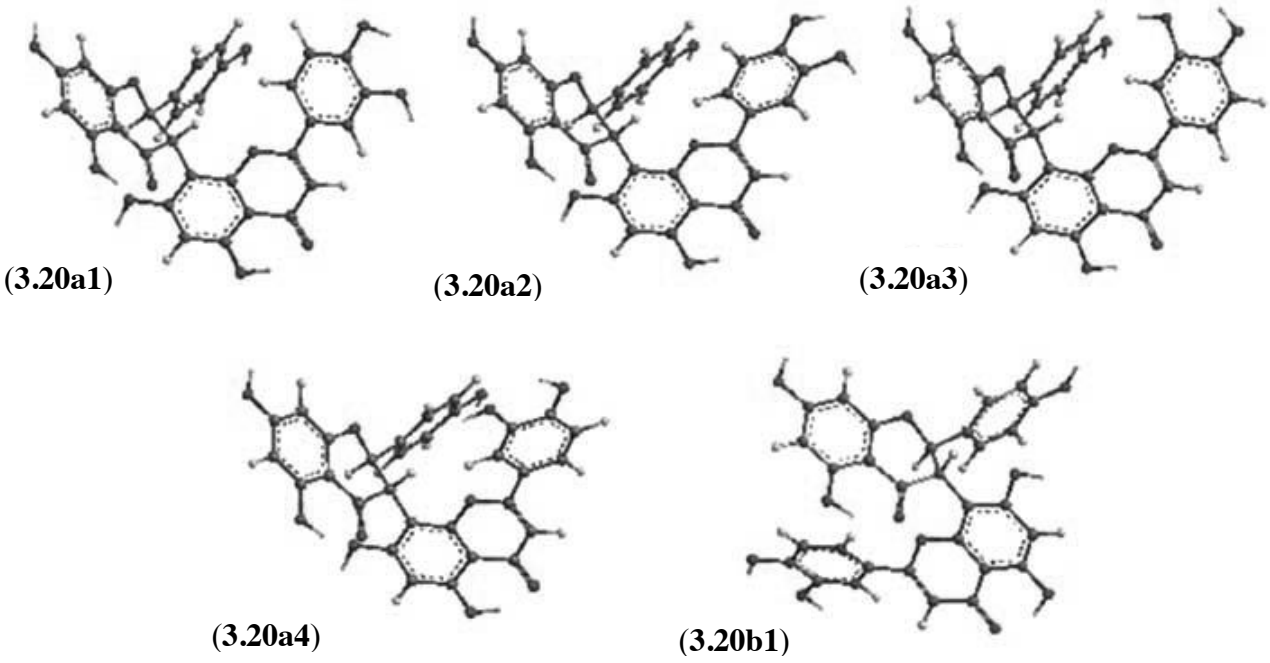


Figure 29. Optimized geometries of conformers of (2*R*,3*S*)-morelloflavone (**3.20**) at the B3LYP/6-31G* level in the gas phase.

The ECD study of such a relatively big and conformationally flexible morelloflavone (**3.20**) to confirm the previous AC assignment was a challenge. However, the work was obtained firstly by conformational analysis to afford a major and minor conformers (**3.20a**) and (**3.20b**) in 73 to 27% respectively.[27] Secondly, the potential energy surface (PES) was obtained for the two stable conformers (**3.20a**) and (**3.20b**) and thirdly, the optimization of individual conformers were performed to confirm the minima and lastly, the PES of the minima conformers were relocated and only four major conformers **3.20a1** (23.4%), **3.20a2** (30.8%), **3.20a3** (3.5%), **3.20a4** (15.2%) and one minor conformer **3.20b1** (26.1%) are predominant (see Figure 29). The ECD calculations of conformers (A→E) were calculated based on the conformational analysis of morelloflavone (**3.20**) (see Figure 30). There are differences among these comformers, conformer (A) has (+) CEs around 285 and 340 nm which is very close to the experimental ECD spectrum indicating (+) CEs about 290 and 350 nm (Figure 30A). The two conformers (B) and (D) produce (+) CEs about 285 and 340 nm and (E) the minor conformer produces a (+) CEs around 350 nm. A weighted ECD spectrum based on the populations of the mentioned five conformers is reported (see Figure 30F), which is agreed with the experimental ECD in methanol

especially for the two (+) CEs around 290 and 350 nm. Therefore, it is concluded that the (2*R*,3*S*)-AC is assigned to morelloflavone (**3.20**).

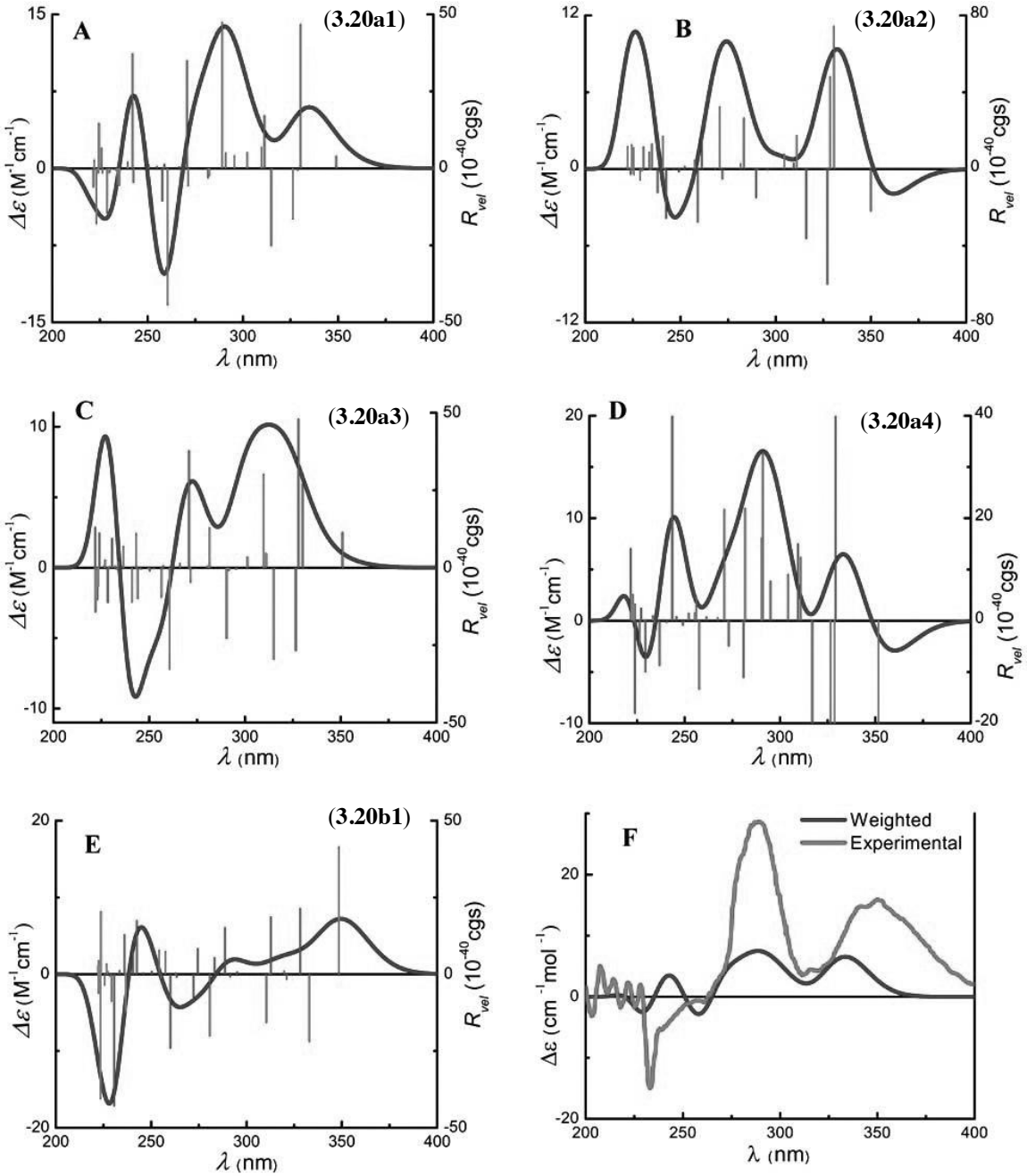
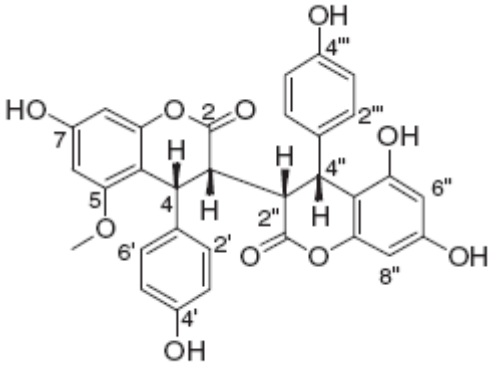


Figure 30. Calculated ECD spectra of conformers (A→E) by TDDFT at the B3LYP-SCRF/6-31G*//B3LYP/6-31G* level in methanol and the weighted ECD (F) and the experimental ECD spectrum of morelloflavone (**3.20**) in methanol (F).

3.3.4.2 5-*O*-Methyldiphysin *vs* 5-5''-di-*O*-methyldiphysin

Having this powerful technique of ECD to determine sucessfully the AC of more complex compound like biflavonoids, more and more biologically active nature products have targeted to

explore their stereochemistry. The characterstic of AC determination of chiral molecules is where only 1 mg or less of a given compound is needed in conjuction with the experimental and theoretically calculated ECD spectra.[31] A new compound, 5-*O*-methyldiphysin (**3.21**) was determined by ECD calculations together with NMR data to determine AC[32] which was isolated and identified from natural product, *Ormocarpum kirkii*. The small coupling constant of H-3 (δ_H 2.91, dd, J = 2.0 and 4.4 Hz) and H-4 (δ_H 4.76, br *s*) afforded a 3,4-*cis*-relative configuration for both conformers of the 5-*O*-methyldiphysin dimer (**3.21**) as well as a *cis*-oriented H-3/H-3" interneoflavanyl bond similar to that of 5,5"-di-*O*-methyldiphysin. Although relative configuration could be assigned by ^3J NMR coupling constant, the AC could only be defined based on application of the non-empirical aromatic quadrant rule,[33] thus to have 3*R*, 4*S* AC of the constituent neoflavanyl moieties of 5,5"-di-*O*-methyldiphysin. However, the calculated ECD spectra of the 3*S*, 4*R* diastereoisomer in both gas and solution phases generated data that matched with experimental data for 5,5"-di-*O*-methyldiphysin, therefore the AC assignment for both 5,5"-di-*O*-methyldiphysin and 5-*O*-methyldiphysin (**3.21**) is opposite to the previously reported for 5,5"-di-*O*-methyldiphysin, being 3S, 4*R* instead of 3*R*, 4*S*. In this case, through the ECD calculations to show that the non-empirical aromatic quadrant rule is not applicable for defining the C-4 configuration of the neoflavonoid type of compounds.



(**3.21**)

31 Warnke, I.; Furche, F. Circular dichroism: electronic. Wiley *Rev.-Comput. Mol. Sci*. **2012**, *2*, 150.

32 Xu, Y.-J.; Foubert, K.; Dhooghe, L.; Lemière, F.; Maregesi, S.; Coleman, C.M.; Zou, Y.; Ferreira, D.; Apers, S.; Pieters, L. *Phytochemistry* **2012**, *79*, 121.

33 De Angelis, G.G.; Wildman, W.C. *Tetrahedron* **1968**, *25*, 5099.

In order to obtain the ECD calculations, conformational analysis is done to afford five low energy conformers (a→e) (Figure 31) and through optimization analysis of these low energy conformers indicating that conformer (b) is the most stable with 99.97% of the Boltzmann population in both the gas and solution phases. The theoretical ECD spectra is calculated using TDDFT (Time Dependent Density Functional Theory) method at the B3LYP/6-31G(d,p) basis set in both the gas phase and methanol.

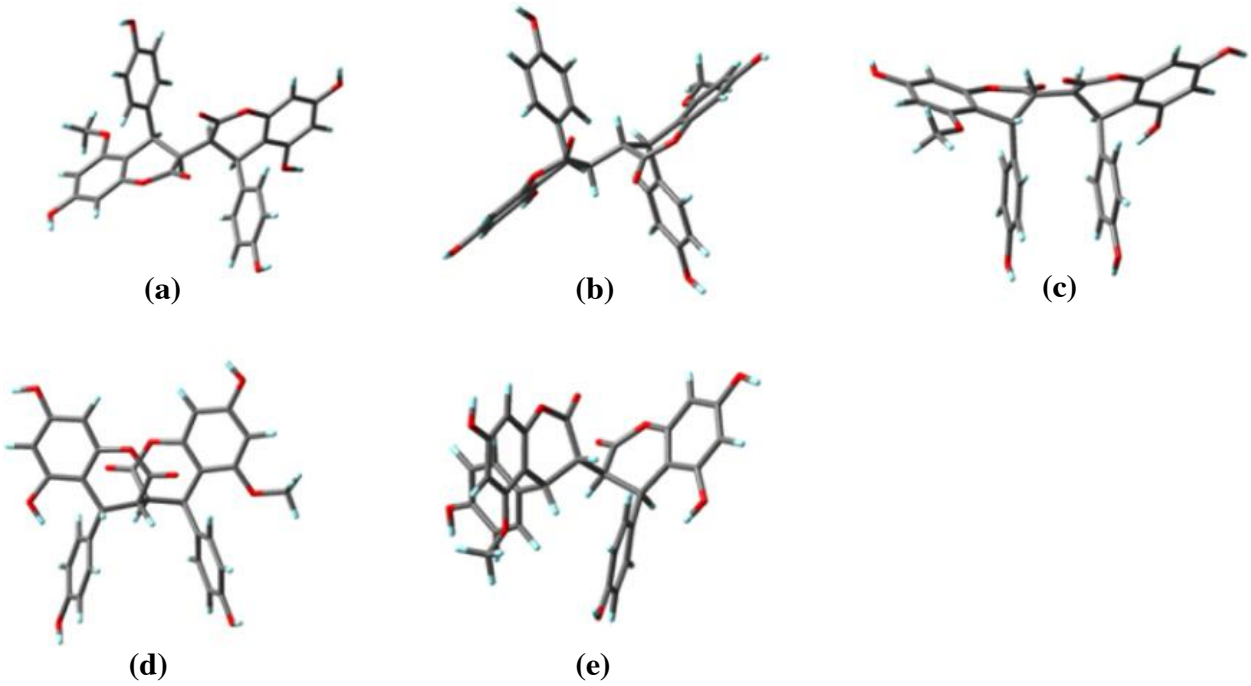


Figure 31. Low energy conformations (a→e) of 5-*O*-methyldiphysin (**3.21**).

Figure 32 indicated the experimental ECD spectra for 5,5"-di-*O*-methyldiphysin and the Boltzmann averaged spectra for 5-*O*-methyldiphysin were compared to show that the (-) CEs at 205 and 250 nm were shifted to 210 and 260 nm separately, and the (+) CE at 225 nm was shifted to 235 nm. Therefore, the consistent of the experimental ECD spectra with calculated gas and methanol phase spectra, thus to confirm the (3*S*, 4*R*, 3"*S*, 4"*R*) configuration of the diphysin derivatives.

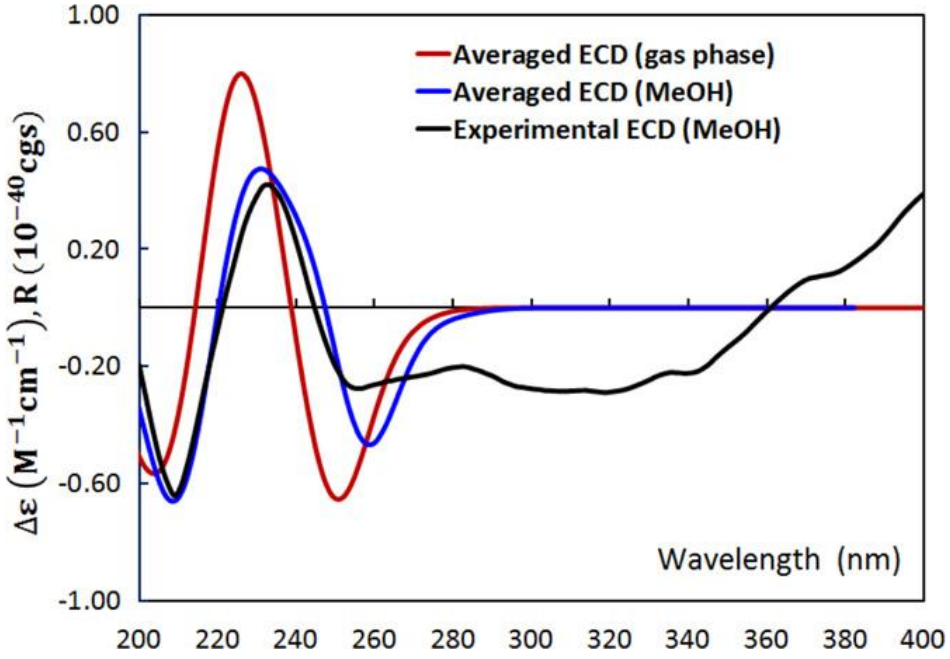


Figure 32. Experimental ECD spectrum for 5,5''-di-*O*-methyldiphysin and Boltzmann averaged calculated ECD spectra of 5-*O*-methyldiphysin (**3.21**).

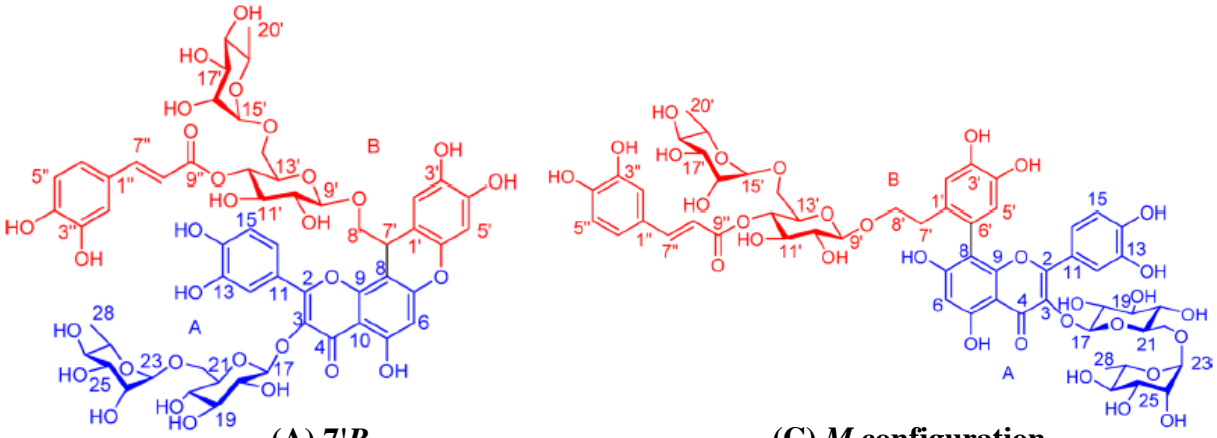
3.3.5 Miscellaneous flavonoids

3.3.5.1 Forsythoneosides

Forsythoneosides (A→D) (Figure 33) are the four unusual adducts of a flavonoid unit fused to a phenylethanoid glycoside through a pyran ring or carbon – carbon bond which isolated from the fruits of *Forsythia suspensa*.[34] The ECD spectrum of (A) showed (+) CE around 367 nm and (-) CEs around 274 and 217 nm, thus the 7'*R* configuration is determined by comparing the calculated and experimental ECD data.[35] The ECD spectrum of (B) however indicated an opposite CE of that observed for (A). From the ECD analysis shows that compound (A) and (B) are diastereoisomers with opposite configurations at C-7'.

34 Zhang, F.; Yang, Y.N.; Song, X.Y.; Shao, S.Y.; Feng, Z.M.; Jiang, J.S.; Li, L.; Chen, N.H.; Zhang, P.C. *J*. *Nat*. *Prod*. **2015**, *78*, 2390.

35 Li, F.S.; Zhan, Z.L.; Liu, F.; Yang, Y.N.; Li, L.; Feng, Z.M.; Jiang, J.S.; Zhang, P.C. *Org*. *Lett*. **2013**, *15*, 674.



(A) 7'*R*

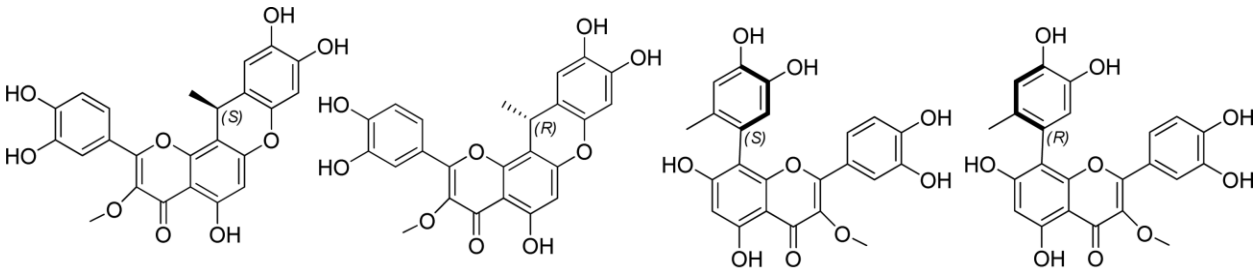
(B) 7'*S*

(C) *M* configuration

(D) *P* configuration

Figure 33. Forsythoneosides (A→D).

The AC of forsythoneosides (A) and (B) were determined by comparing the experimental and calculated ECD data. Firstly, the conformational analysis was scanned to afford two stable conformers (A-1) and (A-2) (Figure 34) and the preferred conformers were optimized using TDDFT method at the B3LYP/6-31G(d) basis set. The calculated ECD spectra of (A-1) and (A-2) were established by Boltzmann population of the lowest energy conformers.



(A-1) **(A-2)** **(C-1)** **(C-2)**

Figure 34. Stable conformers of forsythoneosides.

The entire outcome of the calculated ECD data of (A-1) and (A-2) was in consistent with the experimental data obtained for (B) and (A) respectively (Figure 35). Therefore, the AC of C-7' in forsythoneosides (A) and (B) were established to be *R* and *S* respectively.

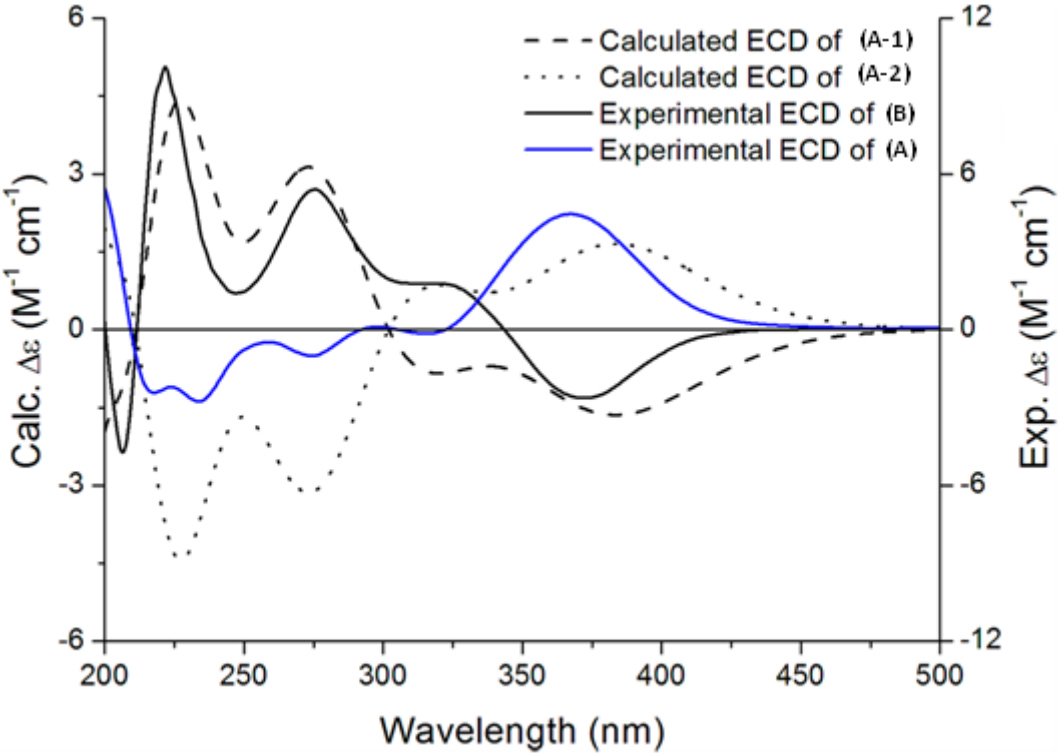


Figure 35. Experimental ECD curves of (A) and (B) and calculated ECD curves of (A-1) and (A-2) in methanol.

The ECD spectrum of forsythoneoside (C) showed (+) CEs around 342 and 264 nm and (-) CE around 225 nm, thus the *M* configuration is determined by comparing the calculated and experimental ECD data. The ECD spectrum of (D) however indicated an opposite CE of that observed for (C) at around 220, 270 and 350 nm suggesting that compounds (C) and (D) are diastereoisomers with the opposite axial chirality at C-8 – C-6'.[34] The AC of conformers (C) and (D) were determined by the same method applied to (A) and (B) where compound (C) was scanned for the conformational analysis and optimization was performed to afford (C-1) and (C-2) (Figure 34). Therefore, the theoretically calculated and experimental ECD spectra were compared to determine the assignment of the AC of *M* and *P* to (C) and (D) respectively (Figure 36).

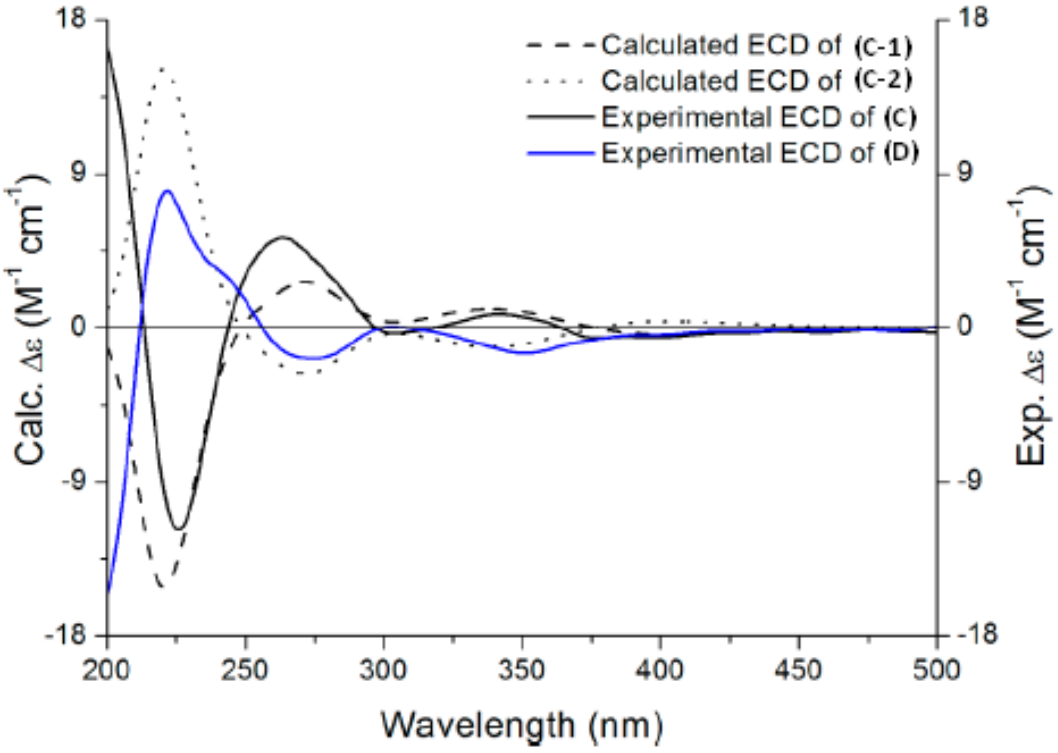


Figure 36. Experimental ECD curves of (C) and (D) and calculated ECD curves of (C-1) and (C-2) in methanol.

3.3.5.2 Bibenzofuranoids

The biflavonoids with rare benzofuranoid moieties were discovered from the heartwood of *Berchemia zeyheri*.[36,37] The stereochemistry of such unusual compounds was studied by NMR, CD method and the computational analysis. This investigation however was to compare the new class of benzofuranoid oligomers with two benzofuranoid moieties (Figure 37).[38]

[36] Volsteedt, F.; Du, R.; Roux, D.G. *Tetrahedron Lett*. **1971**, 1647.

[37] Bekker, R.; Brandt, E.V.; Ferreira, D. *Chem*. *Commun*. **1996**, 957.

[38] Bekker, R.; Ferreira, D.; Swart, K.J.; Brandt, E.V. *Tetrahedron* **2000**, *56*, 5297.

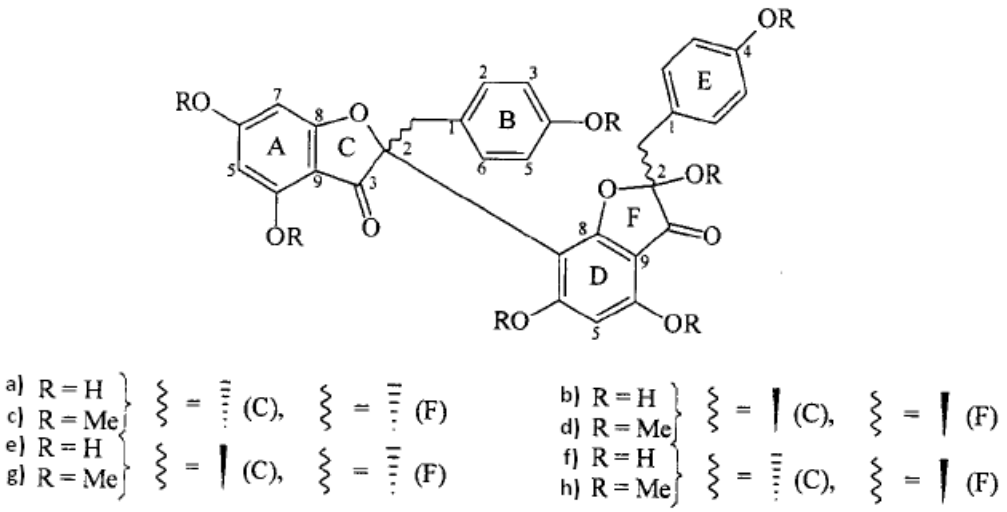


Figure 37. The bibenzofuranoids oligomers and their diastereomers.

R. Bekker *et al*.[38] have reported that possible AC to 2*R*(C):2*S*(F) or 2*S*(C):2*R*(F) for compound (c) (Figure 37 and Figure 38). The ECD unequivocally showed an abundance of one of the enantiomers, however contributed little towards differentiation between the two possibilities when it was compared with the CD curve of its diastereomer (g) (Figure 37 and Figure 38).

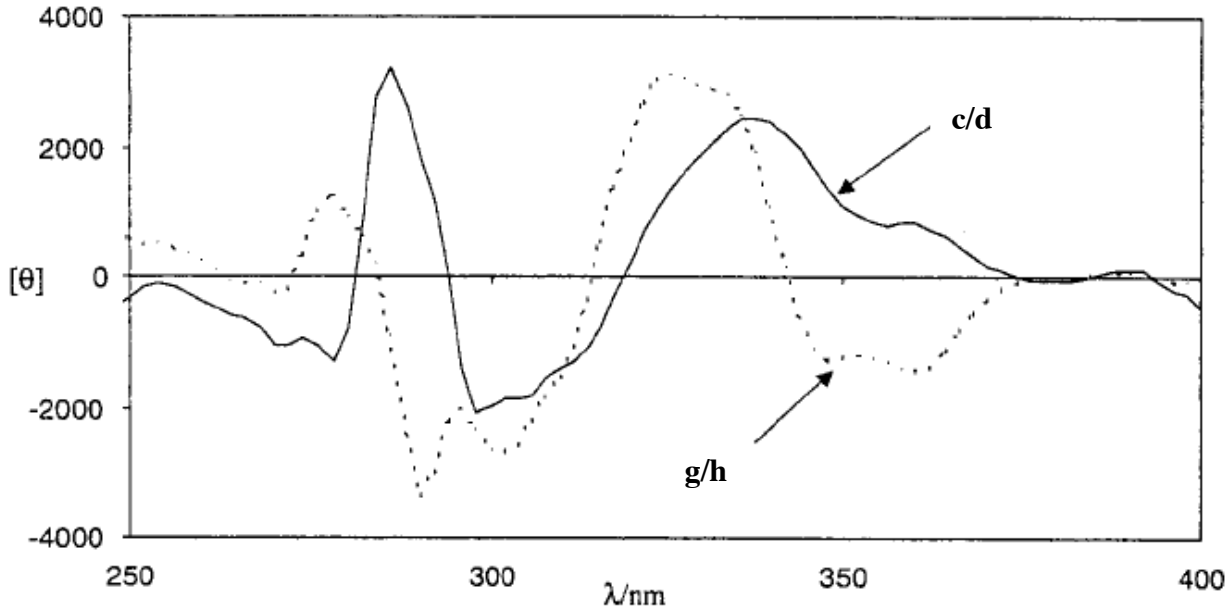
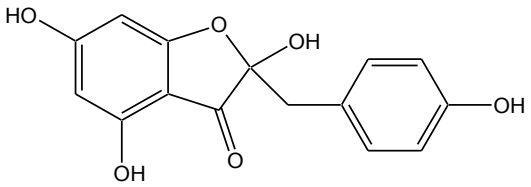


Figure 38. CD curves of the biflavonoid diastereomers c/d and g/h.

The CD curves of enantiomers (c) and (d) each exhibited five CEs in the regions of 230 – 380 nm (Figure 39). Since it is not possible to correlate the respective effects with specific chromophores, the CEs for the n → π* transition in the 330 – 365 nm region have been compared to the AC of the compound, maesopsin (**3.22**) units permitted positive and negative

CEs indicating 2*R* and 2*S* configurations, respectively. The significance of the CE in the region 330 – 365 nm must be accounted in order to differentiate between the 2*R*(C):2*S*(F) and 2*S*(C):2*R*(F) AC for the enantiomers (c) and (d) from the X-ray crystal structure. The PES of the enantiomer 2*S*(C):2*R*(F) was scanned to determine the minimum energy of the conformer implied that the (+) CE exhibited for the n → π* transition in the CD curve of (c), therefore permitted a 2*R*(F) AC for the enantiomer and thus a 2*S*(C):2*R*(F) absolute stereochemistry from the X-ray data. However, the stereochemistry of its enantiomer (d) is assigned for 2*R*(C):2*S*(F).



(**3.22**)

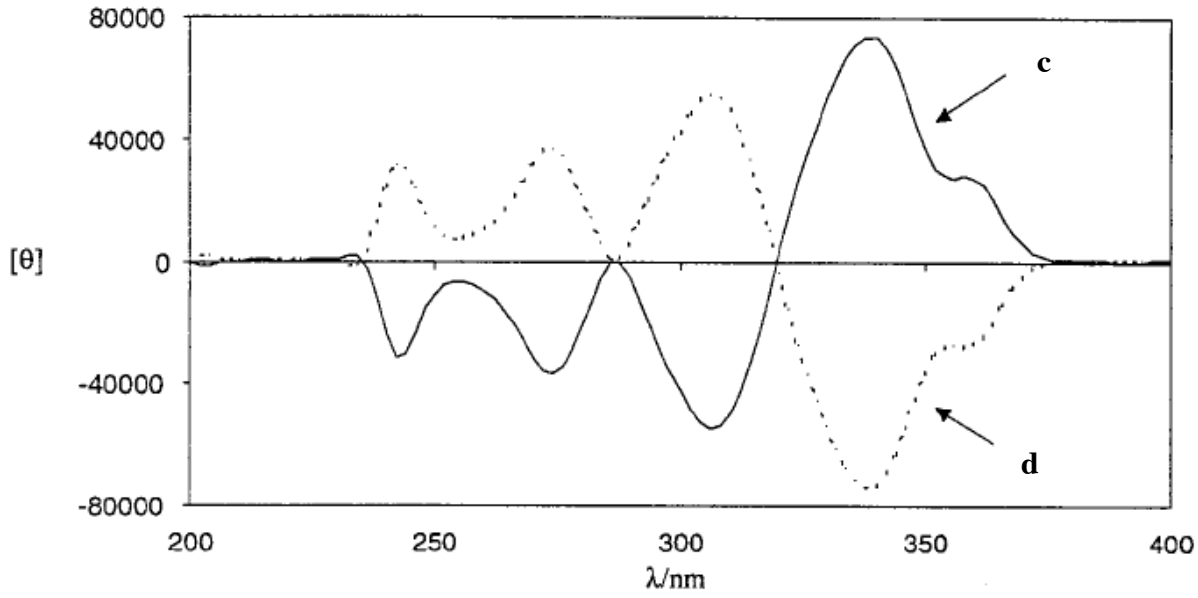


Figure 39. CD curves of the biflavonoid enantiomers (c) and (d).

Same method applied to the 2*S*(C):2*S*(F) enantiomer, the (-) CE was observed for the n → π* transition in the CD curve of (h) permits a 2*S*(F) absolute configuration and hence a 2*S*(C):2*S*(F) configuration for conformer (h) (Figure 40). However, its enantiomer (g) displays 2*R*(C):2*R*(F) configuration as indicated by the (+) CE in the 350 – 370 nm region.

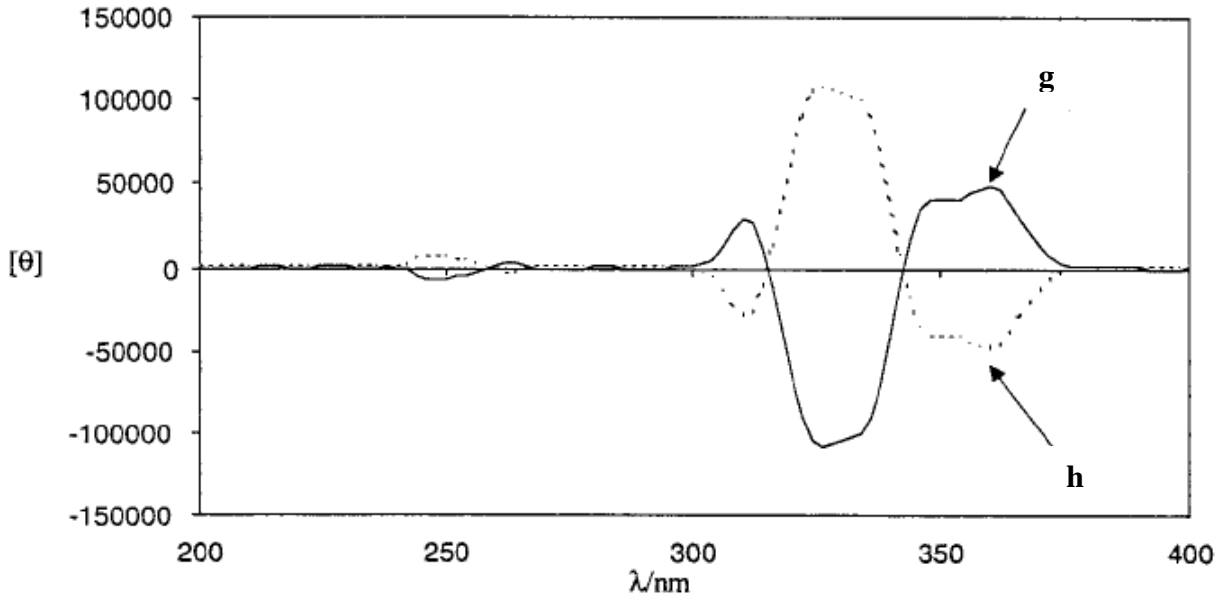


Figure 40. CD curves of the biflavonoid enantiomers (g) and (h).

3.3.6 Conclusions

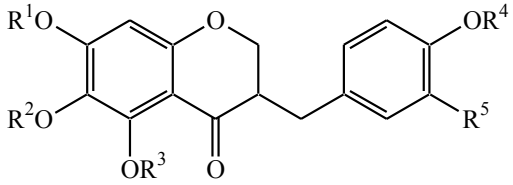
Although the NMR is a useful tool to employ in elucidating the relative configuration, this study however reveals the determination of absolute configuration in natural products research which has become more unequivocal by effectively utilizing 1D and 2D NMR, CD method together with the ECD modelling calculation to assess the absolute stereochemistry of flavonoids, biflavonoids and other oligomer types of flavonoids. Therefore, this feasible strategy may significant speed up the research process in natural products.

DISCUSSION

4 Synthesis of the previously isolated homoisoflavanone and analogues

4.1 Introduction

While homoisoflavonoids have been isolated from several plant species, examples of this type of isoflavonoid with a trisubstituted A-ring bearing two hydroxy groups and one methoxy on the A-ring are rare and are currently limited to only four known compounds, i.e. 5,7-dihydroxy-6-methoxy-3-(4-hydroxybenzyl)chroman-4-one (**4.1**), 5,7-dihydroxy-6-methoxy-3-(4-methoxy-benzyl)-chroman-4-one (**4.2**), 5,7-dihydroxy-6-methoxy-3-(3-hydroxy-4-methoxybenzyl)-chroman-4-one (**4.3**) and 5,6-dihydroxy-7-methoxy-3-(4-hydroxy-3-methoxybenzyl)chroman-4-one (**4.4**), were isolated by Mulholland *et al*[1,2,3] (Figure 1). During a previous phytochemical investigation into the chemical composition of *Scilla natalensis*, another example of this type of homoisoflavonoid, isolated as the peracetate[4] (**4.5**) (Figure 1) was obtained. In order to unambiguously confirm the structure of the newly isolated homoisoflavanone (**4.5**), it was decided to synthesise this compound.



(**4.1**) $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$
(**4.2**) $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = Me$
(**4.3**) $R^1 = R^3 = H$, $R^2 = R^4 = Me$, $R^5 = OH$
(**4.4**) $R^2 = R^3 = R^4 = H$, $R^1 = Me$, $R^5 = OMe$

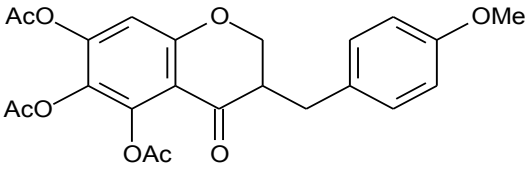
---

1 Crouch, N.R.; Bangani, V.; Mulholland, D.A. *Phytochemistry* **1999**, *51*, 943.

2 Pohl, T.; Koorbanally, C.; Crouch, N.R.; Mulholland, D.A. *Biochem. Syst. Ecol.* **2001**, *29*, 857.

3 Mulholland, D.A.; Crouch, N.R.; Koorbanally, C.; Moodley, N.; Pohl, T. *Biochem. Syst. Ecol.* **2006**, *34*, 251.

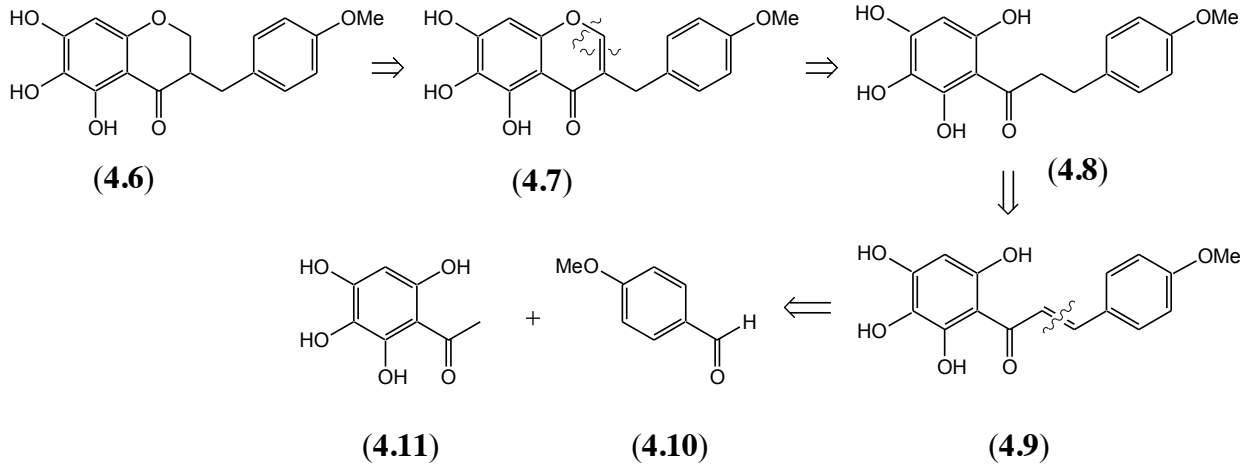
4 Kuo, C.-M. Structure and Synthesis of a Novel Homoisoflavanone from *Scilla natalensis* and Synthesis of Selected Procyanidins through the C-4 Functionalization of Flavan-3-ols. MSc. Thesis, University of the Free State, Bloemfontein, S.A., **2008**.



(**4.5**)

Figure 1. Four isolated homoisoflavonoids with tri-oxygenated A-rings.

Since methodology for the construction of the homoisoflavonoid skeleton is well documented, it was decided to utilize the chalcone-dihydrochalcone route[5,6] for the synthesis of the envisaged homoisoflavanone (Scheme 1). The tetrahydroxyacetophenone (**4.11**), required as starting material for this approach could, however, not be obtained commercially in free phenolic form and had to be synthesised.



(**4.6**) (**4.7**) (**4.8**)

(**4.11**) (**4.10**) (**4.9**)

Scheme 1. Retro-synthesis of chalcone-type approach.

[5] Siddaiah, V.; Rao, C.V.; Venkateswarlu, S.; Subbaraju, G.V. *Tetrahedron* **2006**, *62*, 841.

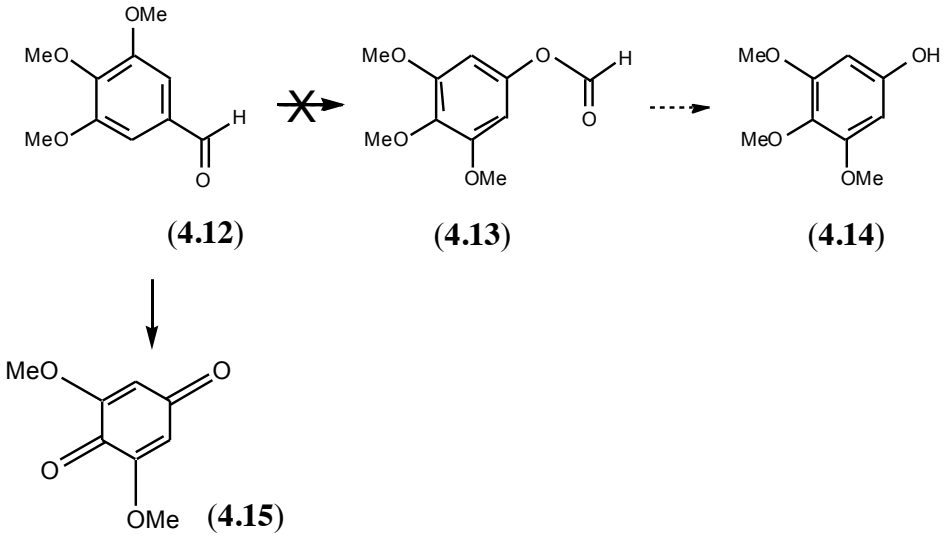
[6] Rao, V.M.; Damu, G.L.V.; Sudhakar, D.; Siddaiah, V.; Rao, C.V. *Arkivoc* **2008**, *6*, 285.

4.2 Synthesis of 2,3,4,6-tetrahydroxyacetophenone analogues

Since the required 2,3,4,6-tetrahydroxyacetophenone could not be obtained commercially, it was decided to approach the synthesis of this fragment through the hydroxylation of a suitably protected pyrogallol analogue followed by subsequent Friedel-Crafts acylation.

4.2.1 Protected tetraoxygenated equivalents

Due to the commercial availability of 3,4,5-trimethoxybenzaldehyde (**4.12**), this compound was viewed as an appropriate model compound that could be transformed into 3,4,5-trimethoxyphenol (**4.14**) through utilization of Baeyer-Villiger oxidation methodology[7,8,9,10,11] followed by hydrolysis of the intermediate ester product (Scheme 2).



Scheme 2. Preparation of 3,4,5-trimethoxyphenol *via* Baeyer-Villiger oxidation methodology.

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[7] Berkessel, A.; Andreae, M.R.M.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4481.

[8] Kolotuchin, S.V.; Meyers, A.I. *J. Org. Chem.* **1999**, *64*, 7921.

[9] Minami, N.; Kijima, S. *Chem. Pharm. Bull.* **1980**, *28*, 1648.

[10] Godfrey, I.M.; Sargent, M.V.; Elix, J.A. *J. Chem. Soc. Perkin I* **1974**, 1353.

[11] Djura, P.; Sargent, M.V.; Vogel, P. *J. Chem. Soc. Perkin I* **1976**, 147.

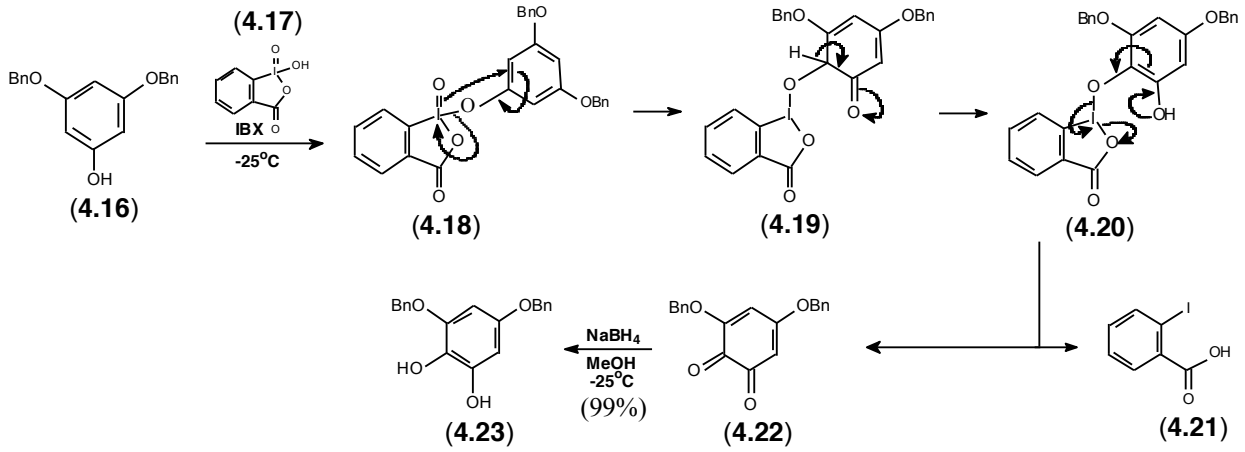
When 3,4,5-trimethoxybenzaldehyde (**4.12**) was treated with 30% H_2O_2 and sulfuric acid in methanol, however, only the quinone product, 2,6-dimethoxy-1,4-benzoquinone[12] (**4.15**) could be obtained in 12% yield. The ^{1}H NMR spectrum of the 1,4-benzoquinone (**4.15**) (Plate 1a) displayed a singlet at δ 3.84 ppm indicating two methoxy groups to be present in the molecule, while another singlet resonance representing the 3 and 5 protons was observed at δ 5.87 ppm. The proposed structure for the product was confirmed by the presence of a molecular ion at *m*/*z* = 168 (M^+, 11%) in the MS spectrum as well as the ^{13}C NMR spectrum (Plate 1b) where 5 carbon resonances at δ_C 186.8, 157.3, 107.4 and 56.5 ppm were visible. Although this compound could in principle be reduced to the diol and thus used in the subsequent synthetic sequence, the yield was unacceptably low (12%) and another step would be added to the process for the preparation of the different homoisoflavanones. In an effort to avoid the additional process step and improved on the yield, it was decided to investigate the application of several other oxidation systems in the Bayer-Villiger oxidation reaction. As indicated in Table 1, replacing the aqueous hydrogen peroxide oxidant with its urea adduct, led to an increase in 1,4-benzoquinone (**4.15**) yield to 69%, while the utilization of H_2O_2 together with *para*-toluenesulfonic acid (PTSA) in hexafluoroisopropanol (HFPI) gave only 20% of the 1,4-benzoquinone (**4.15**). All other reagent systems failed to give any identifiable product (Table 1).

Table 1. Baeyer-Villiger oxidation of 3,4,5-trimethoxybenzaldehyde (**4.12**) with different oxidants.

Entry	Reagents	Yield of 1,4-benzoquinone (**4.15**) (%)
1	30% H_2O_2, H_2SO_4, MeOH	12
2	H_2O_2-urea, H_2SO_4, MeOH	69
3	30% H_2O_2, PTSA, HFIP	20
4	*m*-CPBA, DCM	-
5	PAA, H_2SO_4, MeOH	
6	30% H_2O_2, HCl, MeOH/THF	

[12] Aghoramurthy, K.; Visweswara Rao, K.; Seshadri, T.R.; Sc, F.A. *Proc*. *Ind*. *Acad*. *Sci*. **1953**, 798.

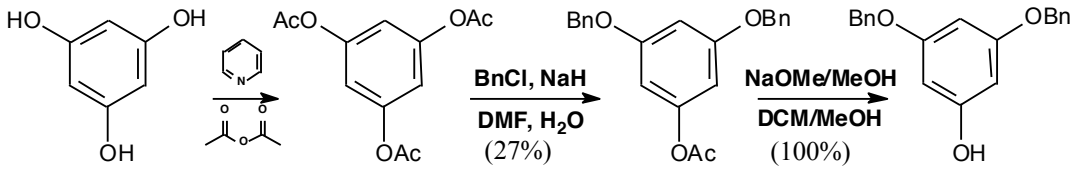
Since it has been reported that 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (IBX), has the ability to hydroxylate phenolic compounds,[13] it was decided to evaluate this reagent for the introduction of the additional hydroxy function into the aromatic ring of a trihydroxyacetophenone analogue. Reaction of 2,4,6-trihydroxyacetophenone with IBX at -25 ^{o}C followed by reductive work-up, however, led to no identifiable product being obtained. While it is apparent from literature and the proposed mechanism for the reaction (Scheme 3) that a free hydroxy function would be required for the hydroxylation to be successfull, it was felt that may be the perhydroxylated aromatic ring in the substrate could be the cause of the failure. It was therefore decided to change the substrate to the double benzylted equivalent and repeat the reaction. Once again no identifiable product could be isolated, so it was decided that the cause of the failure might be situated in the low nucleophilicity of the aromatic phenolic functions due to the presence of the electron-withdrawing carbonyl group. Subjecting 3,5-dibenzyloxyphenol (**4.16**) (prepared accoding to Scheme 4)[14] to the IBX oxidation process proved to be successful and led to the 3,5-dibenzyloxycatechol (**4.23**) to be formed in 99% yield. The ^{1}H NMR of the product (Plate 2) displayed two benzyloxy groups with aromatic resonanes at δ 7.44 – 7.35 ppm (10H) and benzylic methylenes entities at δ 5.04 and δ 5.03 ppm together with two *meta*-coupled single proton resonances at δ 5.91 and δ 5.73 ppm; thus confirming the double benzylated nature of the tetrahydroxybenzene product.



Scheme 3. Proposed mechanism for the hydroxylation of dibenzyloxyphloroglucinol with IBX.

[13] Pezzella, A.; Lista, L.; Napolitano, A.; d'Ischia, M. *Tetrahedron Lett*. **2005**, *46*, 3541.

[14] Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Synth*. *Commun*. **1996**, *26*, 531.



(**4.24**) (**4.25**) (**4.26**) (**4.16**)

Scheme 4. Dibenzylation of phloroglucinol (**4.24**) *via* its triacetate (**4.25**).

4.2.2 Friedel-Crafts acylation of tetraoxygenated benzene analogues

With the tetrahydroxylated aromatic substrate in hand, attention was turned towards the Friedel-Crafts acylation[15] step of the envisaged methodology. Since 3,4,5-trimethoxyphenol (**4.14**) is commercially available and the reaction would not be complicated by the presence of acid labile protecting groups, this substrate was selected as model for the testing of the envisaged Friedel-Crafts acylation reaction. Treatment of (**4.14**) with anhydrous $ZnCl_2$ in acetic acid under refluxing conditions, however, gave the expected acetophenone (**4.27**) in only 2% yield (Scheme 5). The ^{1}H NMR of the product (Plate 3) displayed a broad singlet at δ 13.45 ppm (OH) and a singlet at δ 6.25 ppm (1H) indicating the presence of the aromatic system, while three methoxy resonances at δ 4.02, 3.91 and 3.80 ppm and a singlet at δ 2.67 ppm (3H), indicative of the aromatic acyl group, confirmed the structure of the product to be (**4.27**). The desired acetophenone (**4.27**) was accompanied by another product at R_f 0.45, (T:A = 7:3), which was obtained as a yellow solid in 15% yield. The ^{1}H NMR spectrum of the R_f 0.45 product (**4.15**) (Plate 1a) displayed a singlet at δ 3.84 ppm integrating for six protons as well as another singlet at δ 5.87 ppm representing two protons. These NMR resonances together with a molecular ion of m/z = 168 (M^+, 11%) and the ^{13}C NMR spectrum (Plate 1b) where two carbonyl resonances (δ_C 186.8 ppm) were clearly visible, confirmed the 'other product' to be the benzoquinone (**4.15**). Since the 1,4-benzoquinone has been found before when reactions were performed under oxidative conditions the formation of this compound during the acylation reaction may again be ascribed to oxidative removal of the methyl group in the *para*-position wrt the free hydroxy function and underlines the fact that this type of phenolic compound is extremely prone to oxidative quinone formation.

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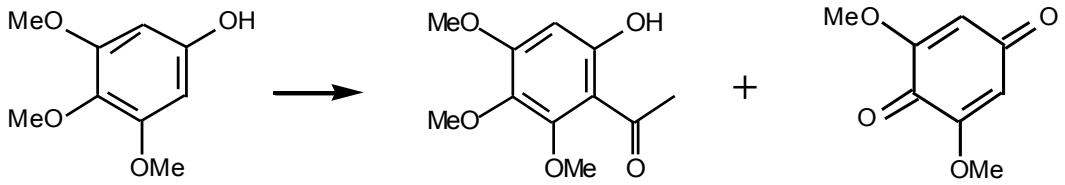
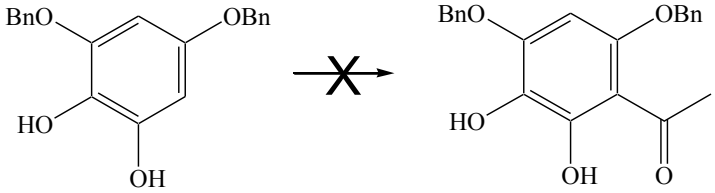
15 Pezzella, A.; Lista, L.; Napolitano, A.; d'Ischia, M. *Tetrahedron Lett*. **2005**, *46*, 3541.



(2%) (15%)

(**4.14**) (**4.27**) (**4.15**)

Scheme 5. Friedel-Crafts acylation of 3,4,5-trimethoxyphenol (**4.14**) with anhydrous $ZnCl_2$ in boiling acetic acid.

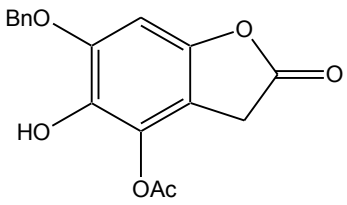


(**4.23**) (**4.28**)

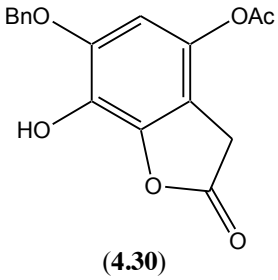
Scheme 6. Friedel-Crafts acylation of 3,5-dibenzyloxycatechol (**4.23**) with anhydrous $ZnCl_2$ in boiling acetic acid.

Since it was available from the IBX oxygenation reaction, it was decided to subject 3,5-dibenzyloxycatechol (**4.23**) to the same Friedel-Crafts acylation conditions despite the low yield obtained in the previous reaction. While only one product was obtained from the reaction mixture in 41% yield (Scheme 6 and Scheme 7), it was evident from the ^{1}H NMR spectrum (Plate 4) of this product (**4.29**) that it was not the desired acetophenone (**4.28**). Apart from the aromatic resonances of the benzyl group at δ 7.43 (5H, br s), the ^{1}H NMR spectrum of this compound also displayed a singlet at δ 5.53 (1H), two doublets at δ 5.16 (1H, J = 10.6 Hz) and δ 5.10 (1H, J = 11.3 Hz), another pair of doublets at δ 3.10 (1H, J = 17.5 Hz) and δ 2.95 (1H, J = 17.5 Hz), and a singlet at δ 2.37 (3H), indicative of one acetoxy group. Although the methylene of a benzyl protecting group usually appears in the ^{1}H NMR spectrum as a singlet at ca δ 5 ppm, steric crowding that prevents free rotation may cause these protons to become non-equivalent and therefore show up in the spectrum as a pair of doublets. The pair of doublets at δ 5.16 ppm and δ 5.10 ppm could therefore be assigned to the benzylic methylene group. Since the sigulet at δ 5.53 showed close resemblance to the chemical shift of the *m*-coupled doublets in the spectrum of the free phenolic starting material (δ 5.91 and 5.73), this resonance could be allocated to a single residual proton on the aromatic ring of the product. This, taken in conjunction with the

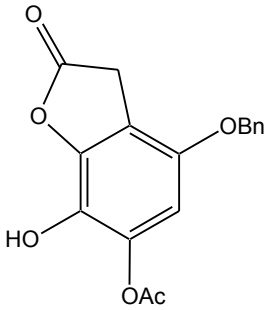
fact that only one benzyloxygroup remained attached to the aromatic ring, implied a heterocyclic ring containing one methylene group to be attached to the aromatic system. A structure like (**4.29**) or an isomer of it like (**4.30**) or (**4.31**) could therefore possibly be assigned to the unexpected product from the reaction (Scheme 7).



(**4.29**)

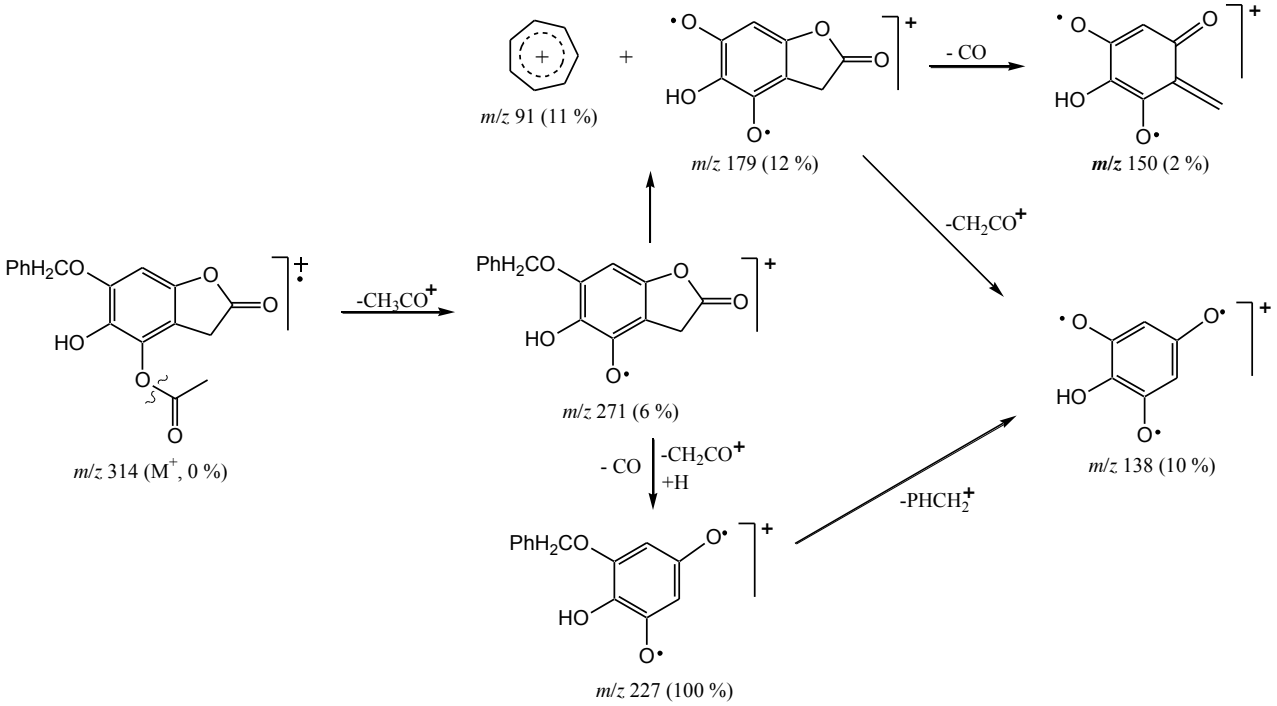


(**4.30**)

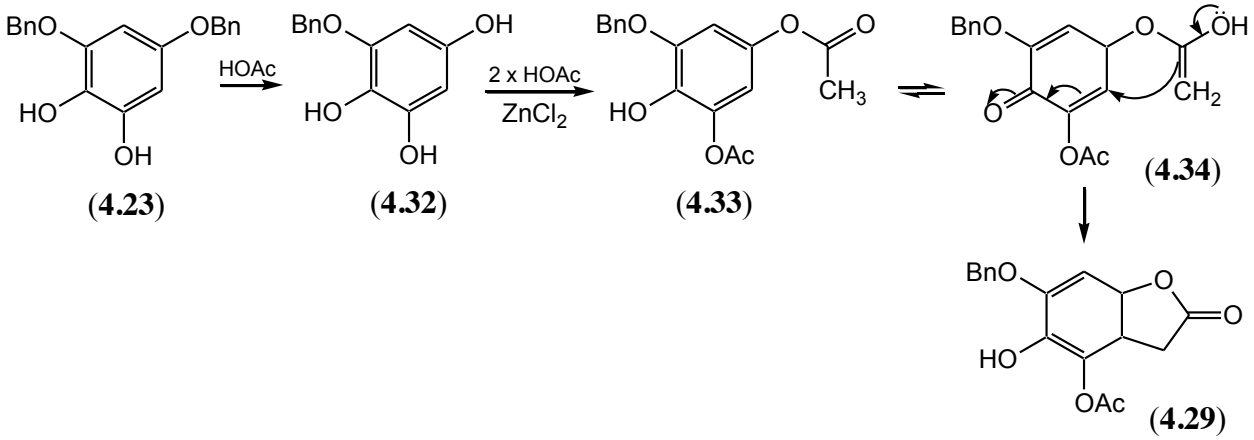


(**4.31**)

Scheme 7. Possible structures for the unexpected product from the acylation of 3,5-dibenzyloxycatechol (**4.23**).



Scheme 8. Electron Impact (EI) fragmentation of (**4.29**).



Scheme 9. Possible mechanism for the formation of (**4.29**).

4.2.3 Acylation by Directed *ortho* Metalation[16]

Since the Friedel-Crafts acylation of the tetraoxygenated benzene nucleus could not be achieved in decent yields, it was decided to revert to a directed *ortho*-metallation (DoM) strategy in order to introduce the wanted acyl function into the aromatic nucleus (Scheme 10).

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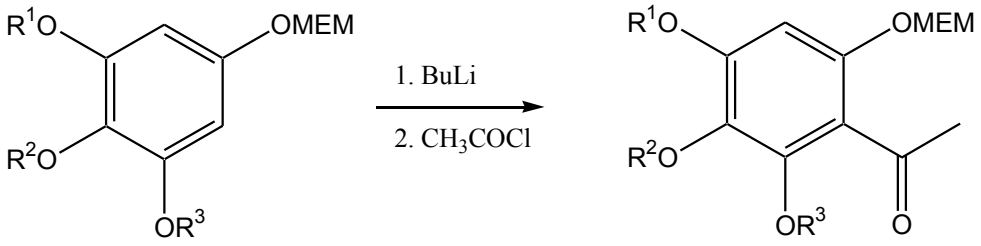
16 Nerdinger, S.; Kendall, C.; Cai, X.; Marchart, R.; Riebel, P.; Johnson, M.R.; Yin, C.-F.; Hénaff, N.; Eltis, L.D.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 5960.

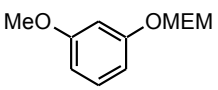
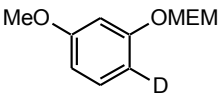
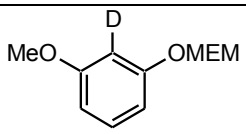
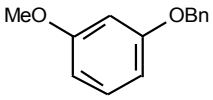
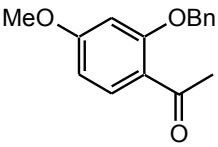
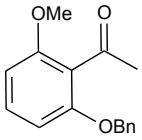


(**4.35**) (**4.36**)

Scheme 10. The Directed *Ortho*-Metalation reaction.

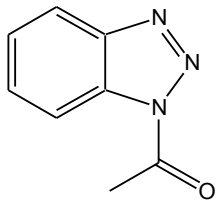
As model reaction the carbanion of 1-methoxy-3-[(2-methoxyethoxy)methoxy]benzene (**4.37**) was quenched with deuterium oxide to determine if the *ortho*-metalation in fact occurred under the prevailing conditions (1. *n*-BuLi/OEt_2 in TMEDA at -70°C; 2. D_2O) and to determine which *ortho*-position would be preferred during the metalation process. 1-Methoxy-3-[(2-methoxyethoxy)methoxy](2-^2H)benzene (**4.39**) was formed in 100% yield, confirming metalation to be directed towards the position between the two substituents (Table 2, entry 1). The structure of the product (**4.39**) was confirmed by the fact that the ^1H NMR spectrum (Plate 5a) did not display the expected ABX system, but a triplet at δ 7.19 (1H, *J* = 8 Hz) and two *ortho*-coupled doublets at δ 6.67 (1H, *J* = 8 Hz) and δ 6.57 (1H, *J* = 8 Hz), which proved the deuterium to be located at C-2 of the benzene ring.

Table 2. Acylation by Directed *ortho*-Metalation.

	Substrate	Target Structure	Reaction Conditions	Obtained Product
1	 (**4.37**)	 (**4.38**)	1. *n*-BuLi/OEt_2, TMEDA, -70 °C, 2. D_2O	 (**4.39**) Yield = 100%
2	 (**4.40**)	 (**4.41**)	1. *n*-BuLi/OEt_2, TMEDA, -70 °C, 2. CH_3COBt (**4.42**)	No Product
3			1. *n*-BuLi/OEt_2, TMEDA, -70 °C, 2. AcOAc	 (**4.43**) Yield = 12%

Although the metallation was directed towards the 'wrong' position in the model reaction indicated above, this could be ascribed to the fact that two directing groups (OMe and OMEM)

worked in tandem towards activating this particular position. In the real substrate, however, both positions next to the main directing group (MEM) would be equally hindered and next to another protecting group (OBn or OMe for example) that might assist in the metallation and acylation process. After optimization of the reaction conditions for the *ortho*-metalation reaction, it was therefore decided to attempt the acylation by DoM methodology anyway. In order to enhance selectivity it was furthermore decided not to utilize acetyl chloride as acylating agent, but rather the less reactive, soft and commercially available alternative, 1-acetyl-1*H*-benzotriazole (CH_3COBt) (**4.42**), in the reaction.[17] Treatment of 1-benzyloxy-3-methoxybenzene (**4.40**) with *n*-BuLi followed by the benzotriazole (**4.42**) at -70 ^{o}C for 30 h, however, failed to produce any of the desired product (Table 2, entry 2). When the electrophile was changed to acetic anhydride, the 2-benzyloxy-6-methoxyacetophenone (**4.43**) was obtained, albeit in only 12% yield. The ^{1}H NMR spectrum (Plate 7a) of this product (**4.43**) again displayed a triplet at δ 7.25 (1H, J = 8 Hz) and two *ortho*-coupled doublets at δ 6.61 (1H, J = 8.3 Hz) and δ 6.58 ppm (1H, J = 8.3 Hz) indicative of substitution between the two directing groups, while a singlet at δ 2.51 (3H) confirmed the presence of acetoxy group. Despite the low yield obtained in the acylation step, it was decided to extend this methodology to the preparation of the 'real' tetraoxygenated acetophenone (**4.11**) anyway.



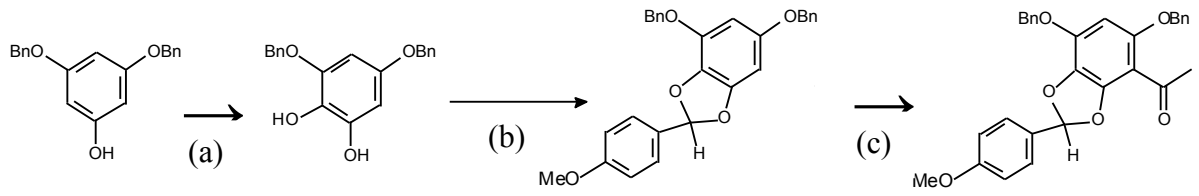
(**4.42**)

4.2.4 Protection of the diol function of 3,5-dibenzyloxycatechol

In order to be able in the end to unambiguously prepare the 6-hydroxy substituted homoisoflavanone and prevent cyclization to the 6-OH group, at least two different protecting groups for the four OH functions attached to the aromatic ring of the acetophenone were required. Since two of the hydroxy groups of the tetraoxygenated benzene entity to be protected (**4.23**), were in an *ortho* orientation, it was decided to utilize a methylene dioxy function as one of the protecting groups and since it had to be taken off again towards the end of the process, the

[17] Katritzky, A.R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679.

acetal of anisole was considered as the appropriate protecting group for this purpose (Scheme 11).



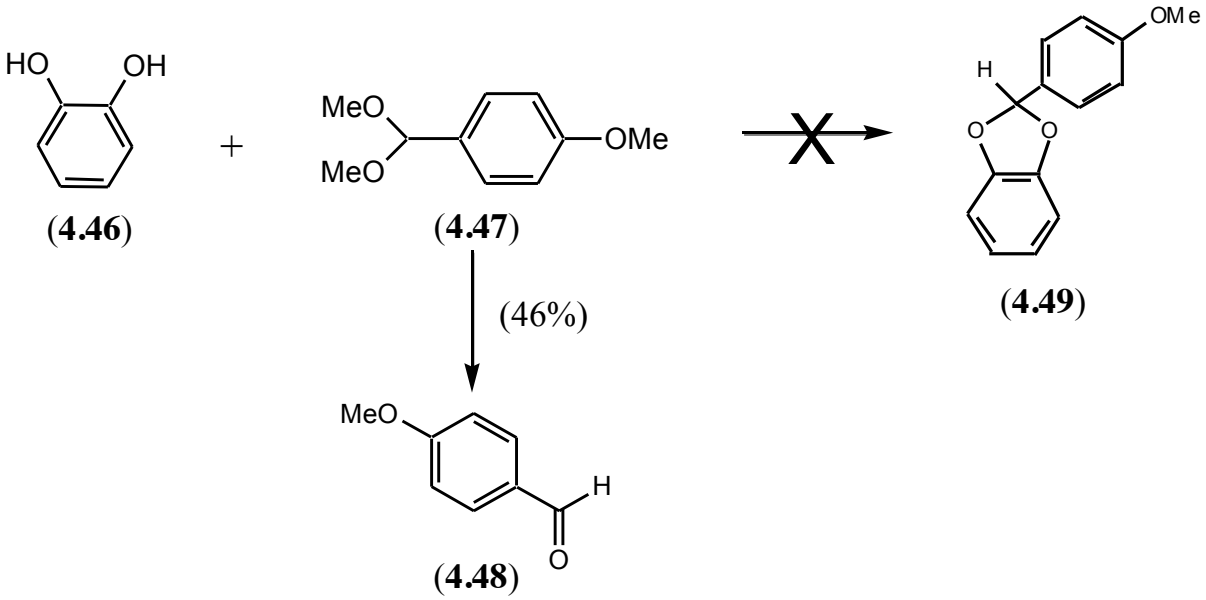
(**4.16**) (**4.23**) (**4.44**) (**4.45**)

Scheme 11. Proposed synthesis of the tetraoxygenated acetophenone (**4.45**).

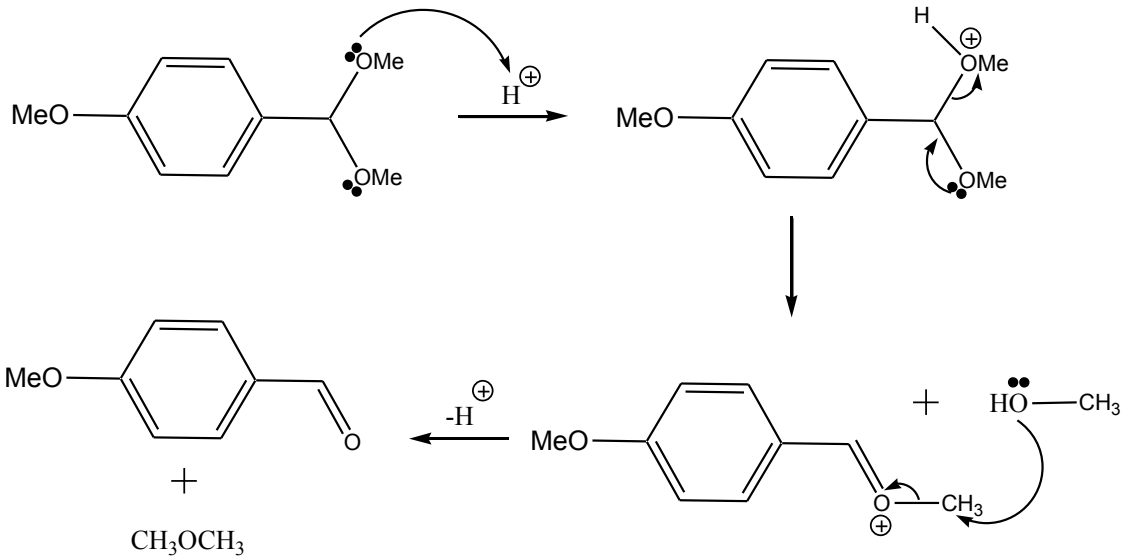
To evaluate the application of 1,2-diol protection technology to the synthesis of the tetrahydroxyacetophenone (**4.11**), it was decided to use catechol (**4.46**) as model substrate and *p*-anisaldehyde dimethyl acetal (**4.47**) as reactant to obtain the methylene dioxy derivative (**4.49**). Reacting catechol (**4.46**) with *p*-anisaldehyde dimethyl acetal (**4.47**) in toluene in the presence of Amberlyst 15,[18] however, failed to give any of the desired acetal product (**4.49**) and only anisaldehyde (**4.48**) was obtained in 46% yield (Scheme 12). Changing the reagents to anisaldehyde (**4.48**) and *p*-toluene sulfonic acid[19] gave the same result. While the formation of anisaldehyde during this reaction could be explained by either or both the acid catalyst and toluene being wet and thus hydrolysing the acetal, it could also originate from acid catalysed dimethyl ether formation as indicated in Scheme 13.

18 Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 1909.

19 Chan, K.-F.; Zhao, Y.; Chow, L.M.C.; Chan, T.H. *Tetrahedron* **2005**, *61*, 4149.



Scheme 12. Methylenedioxy protection of catechol. Reagents: Amberlyst 15, toluene.

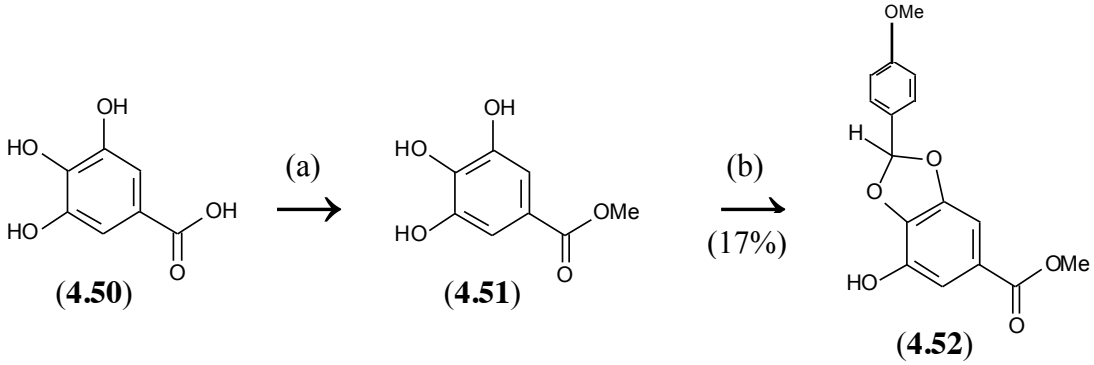


Scheme 13. Acid catalysed transformation of the dimethylacetal into anisaldehyde.

Since catechol did not give any of the desired acetal product, it was decided to utilize a more appropriate substrate as model compound, so methyl 3,4,5-trihydroxybenzoate (**4.51**) (Plate 9), prepared by Fischer-Speier esterification of gallic acid (**4.50**), was subjected to the acetalization conditions and the desired product, methyl 3-hydroxy-4,5-(*p*-methoxyphenyl-methylenedioxy)benzoate[20] (**4.52**) obtained in 17% yield (Scheme 14). The ^{1}H NMR spectrum (Plate 10) of the product (**4.52**) displayed, apart from the expected aromatic *meta*-doublets (δ

[20] Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 1909.

7.12 and 7.07 (each 1H, *J* = 1 Hz), two methoxy singlets (δ 3.85 and 3.84), two *ortho*-doublets [δ 7.57 and 7.02 (each 2H, *J* = 8 Hz)], and a singlet at δ 7.31 ppm typical of a methylene dioxy proton; thus confirming the structure of the product as (**4.52**). Some of the dimethyl acetal reagent (**4.47**) was once again transformed into anisaldehyde (**4.48**), which might have contributed to the low yield being obtained.



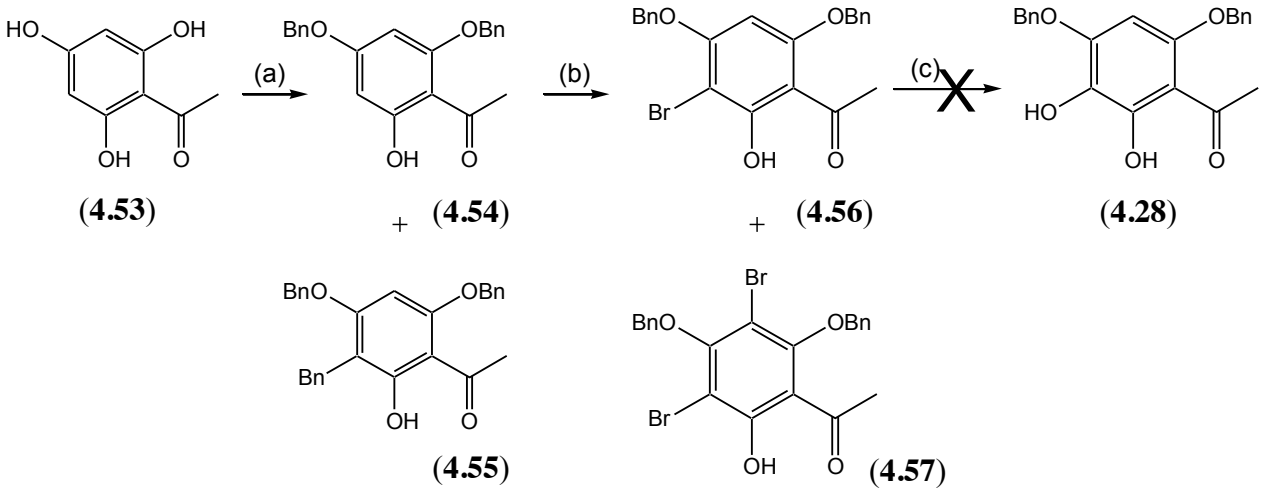
(**4.50**) (**4.51**) (**4.52**)

Scheme 14. Fischer-Speier esterification and acetalization of gallic acid. Reagent: (a) H_2SO_4 (cat.), MeOH, reflux, 24 h; (b) $MeOC_6H_4CH(OMe)_2$, Amberlyst 15, EtOH/benzene reflux, 17 h.

4.2.5 Hydroxylation of phloroacetophenone (4.53)

Since various strategies and several model reactions resulted in low yields, no desired product, or multiple-step reactions, it was decided to re-evaluated the strategy of oxygenation of phloroacetophenone (**4.53**) in order to reach the wanted protected 2,3,4,6-tetraoxygenated acetophenone (**4.11**) and to follow a strategy similar to that of Ellis and Lenger[21] (Scheme 15).

21 Ellis, J.E.; Lenger, S.R. *Synth*. *Commun*. **1998**, *28*, 1517.



Scheme 15. Ellis and Lenger's strategy for the preparation of selectively protected tetrahydroxyacetophenone (**4.28**). Reagents: (a) NaH, BnCl, DMF, rt; (b) Br_2, HOAc; (c) *aq*. NaOH, Cu(m), H_2O/THF reflux.

To be in a position to selectively remove the protecting groups at a later stage in the synthetic process, if required, the 4- and 6-hydroxy groups of phloroacetophenone (**4.53**) not involved in hydrogen bonding, were to be selectively protected by benzylation. Reacting commercially available phloroacetophenone (**4.53**) with sodium hydride and benzyl chloride in DMF, however, led to the desired product (**4.54**) (Plate 11a), which was obtained in 65% yield, to be accompanied by the *C*-alkyled analogue[22] (**4.55**) (Plate 12a) in 20% yield. Placing of the carbon bound benzyl group between the free OH functions and the benzyloxy entity in the *meta*-position wrt the acyl function followed from the NOESY spectrum (Plate 12c) where a strong correlation between the OH and both acyl methyl and benzyl methylene groups were observed.

Bromination of (**4.54**) (Br_2 in HOAc) gave 4,6-dibenzyloxy-3-bromo-2-hydroxyacetophenone[23] (**4.56**) as well as the dibrominated analogue, (**4.57**) in 90% and 10% yield, respectively. The structure of the double brominated product (**4.57**) was confirmed by ^{1}H NMR spectroscopy (Plate 14a) where no aromatic proton resonances were observed and MS which showed a molecular ion at *m/z* = 506 (M^+, 15%). Placing the bromine at C-3 and not C-5 in the monobrominated product (**4.56**) followed from the NOESY spectrum (Plate 13c) where H-5 (δ 6.13 ppm) correlating with both benzyloxy CH_2 groups (at δ 5.20 and 5.08 ppm). Subsequent

22 Hill, T.N.; Kuo, C.-M.; Bezuidenhoudt, B.C.B. *Acta Cryst*. **2012**, *E68*, 02863.

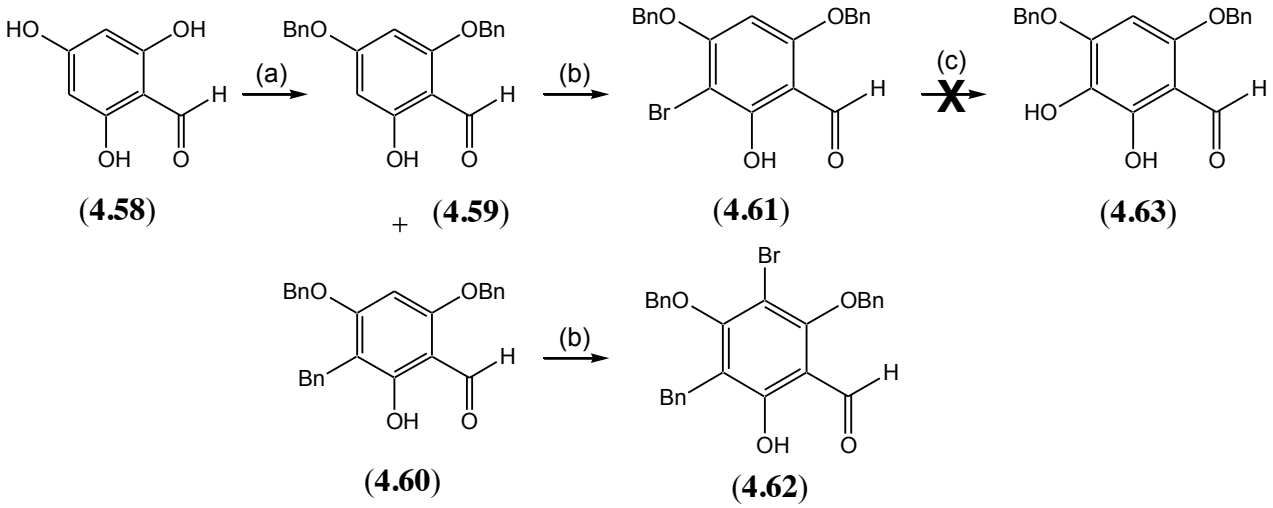
23 Hill, T.N.; Kuo, C.-M.; Bezuidenhoudt, B.C.B. *Z. Kristallogr*. **2015**, *NCS230*.

hydroxy-de-halogenation of (**4.56**) with NaOH in the presence of Cu (m) in refluxing THF/H_2O, however, failed to produce any of the desired dihydroxylated product (**4.28**). This result might probably be ascribed to the competing aldol condensation of the acetophenone or the Cu (m) not being active.

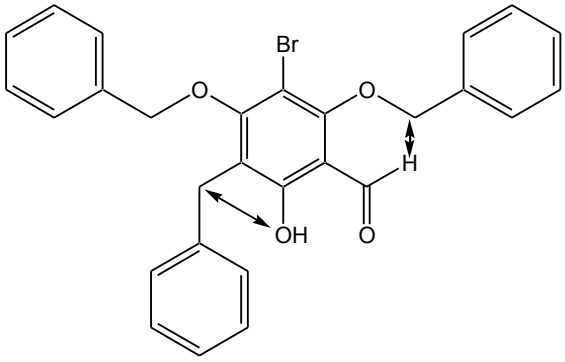
4.2.6 Hydroxylation of 2,4,6-trihydroxybenzaldehyde (4.58)

Since aldol condensation was identified as possible cause of the failure of the hydroxylation of phloroacetophenone (**4.56**), it was decided to replace the acetophenone (**4.56**) with 2-hydroxy-4,6-dibenzyloxybenzaldehyde (**4.59**) as substrate in the hydroxy-de-halogenation[24] reaction. 2,4,6-Trihydroxybenzaldehyde (**4.58**) was therefore protected by benzylation as described above and the product (**4.59**) (Plate 15) obtained in 65% yield; again accompanied by the *C*-benzylated equivlent (**4.60**) in 23% (which could only be isolated by separation after the bromination step). Subsequent bromination also afforded the monobrominated product (**4.61**) in 74% yield (Scheme 16). The ^{1}H NMR spectrum (Plate 16a) of the monobrominated product (**4.61**) showed the residual aromatic proton (H-5) as a singlet at δ 6.14 ppm, as was confirmed by nOe association [NOESY spectrum (Plate 16c)] of this resonance with both benzyl CH_2 groups (at δ 5.21 and 5.10 ppm), while ^{13}C NMR spectrum (Plate 16b) displayed the CHO resonance at δ 191.9 ppm and a Br-C signal at δ 91.7 ppm. The structure of (**4.62**) was confirmed by a benzyl methylene resonance at δ 4.06 ppm in the ^{1}H NMR spectrum (Plate 17a) as well as an aldehyde carbon at δ 193.7 ppm and a Br-C signal at δ 103.1 ppm in the ^{13}C NMR spectrum (Plate 17b). The NOESY spectrum (Plate 17c) showed a correlation between a benzyl methylene (δ 4.06 ppm) and an OH resonance (at δ 12.20 ppm) as well as between the methylene of a benzyloxy group (δ 5.18 ppm) and the aldehyde proton (δ 9.99 ppm); thus confirming the relative positions of the benzyl group and bromine atom.

24 Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew*. *Chem*. *Int*. *Ed*. **2009**, *48*, 8729.



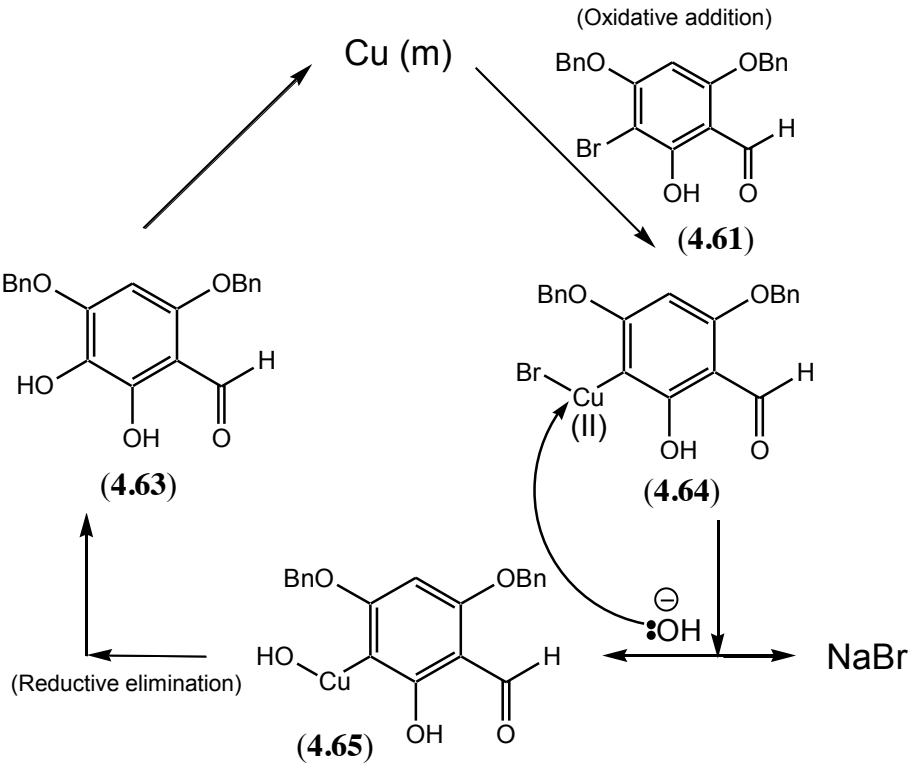
Scheme 16. Preparation of the tetraoxygenated benzyladehyde (**4.63**). Reagents: (a) NaH, BnCl, DMF, rt; (b) Br_2, HOAc; (c) *aq*. NaOH, Cu(m), H_2O/THF reflux.



(**4.62**)

Finally, the Ullmann type hydroxy-de-halogenation reaction (Scheme 17) was performed by treating the bromobenzaldehyde (**4.61**) with copper powder and *aq*. NaOH in THF at refluxing temperatures. Although the copper powder was prepared from $CuSO_4$ and activated with zinc[25] no reaction could again be detected by TLC.

[25] Laflamme, M.; Schiffbauer, J.D.; Dornbos, S.Q. *Quantifying the Evolution of Early Life: Numerical Approaches to the Evalution of Fossils and Ancient Ecosystems*; Springer Science & Business Media, **2011**, 368.



Scheme 17. Proposed catalytic cycle for the Ullman type hydroxy-de-halogenation reaction.

4.2.7 Synthesis of 2,3,4-tribenzyloxy-6-hydroxyacetophenone (4.71) by degradation of the flavone equivalent

Since baicalein (**4.69**), a flavones with a 5,6,7-trihydroxy substituted A-ring is available commercially and this compound could be degraded to the desired tetraoxygenated acetophenone (**4.71**) by treatment with a strong KOH solution,[26] it was decided to embark on this strategy for preparing the wanted 2,3,4-tribenzyloxy-6-hydroxyacetophenone (**4.71**).

In order to evaluate the feasibility of this approach, flavone (**4.66**) was subjected to the degradation reaction conditions, i.e. 18 M aqueous KOH in diethylene glycol - pyridine at 120 ^{o}C (Scheme 18) and the 2-hydroxyacetophenone (**4.67**) (^{1}H NMR spectrum Plate 18) obtained in 20% yield.

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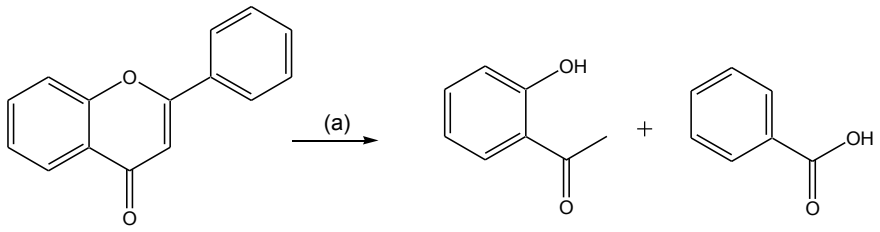
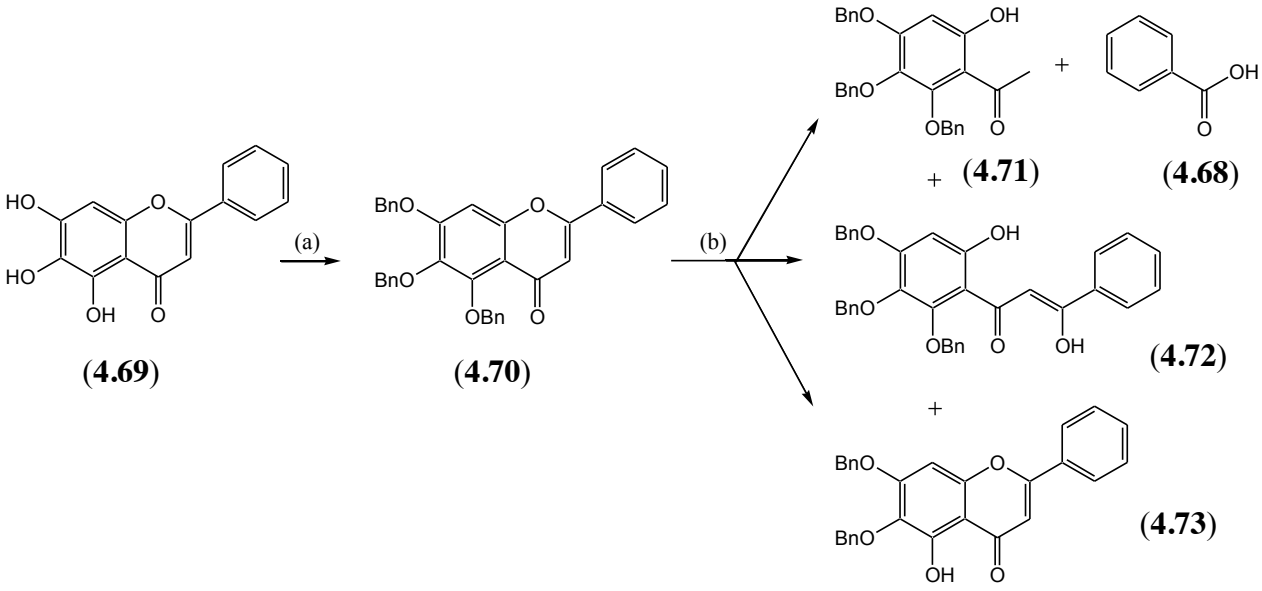
26 Caldwell, S.T.; Petersson, H.M.; Farrugia, L.J.; Mullen, W.; Crozier, A.; Hartley, R.C. *Tetrahedron* **2006**, *62*, 7257.



(**4.66**) (**4.67**) (**4.68**)

Scheme 18. Model reaction for degradation of flavone (**4.66**). Reagents: (a) 18 M aqueous KOH, py-diethylene glycol, 120 ^{o}C, 20% yield.

With the model reaction being successful, baicalein (**4.69**) was perbenzylated[27] (**4.70**) [$PhCH_2Cl$, dry K_2CO_3, dry DMF; 72% yield; (Plate 19a)], to assure a 5,6,7-trihydroxylated final product, and subjected to the degradation conditions to obtain the 2,3,4-tribenzyloxy-6-hydroxy-acetophenone (**4.71**) in 28% yield (Scheme 19). As expected, the ^{1}H NMR spectrum of the product (**4.71**) (Plate 20a) displayed a single aromatic resonance at δ 6.28 ppm (H-5) as well as an acyl CH_3 at δ 2.49 ppm and three benzyloxy methylene resonances at δ 5.23, δ 5.14 and δ 4.97 ppm.

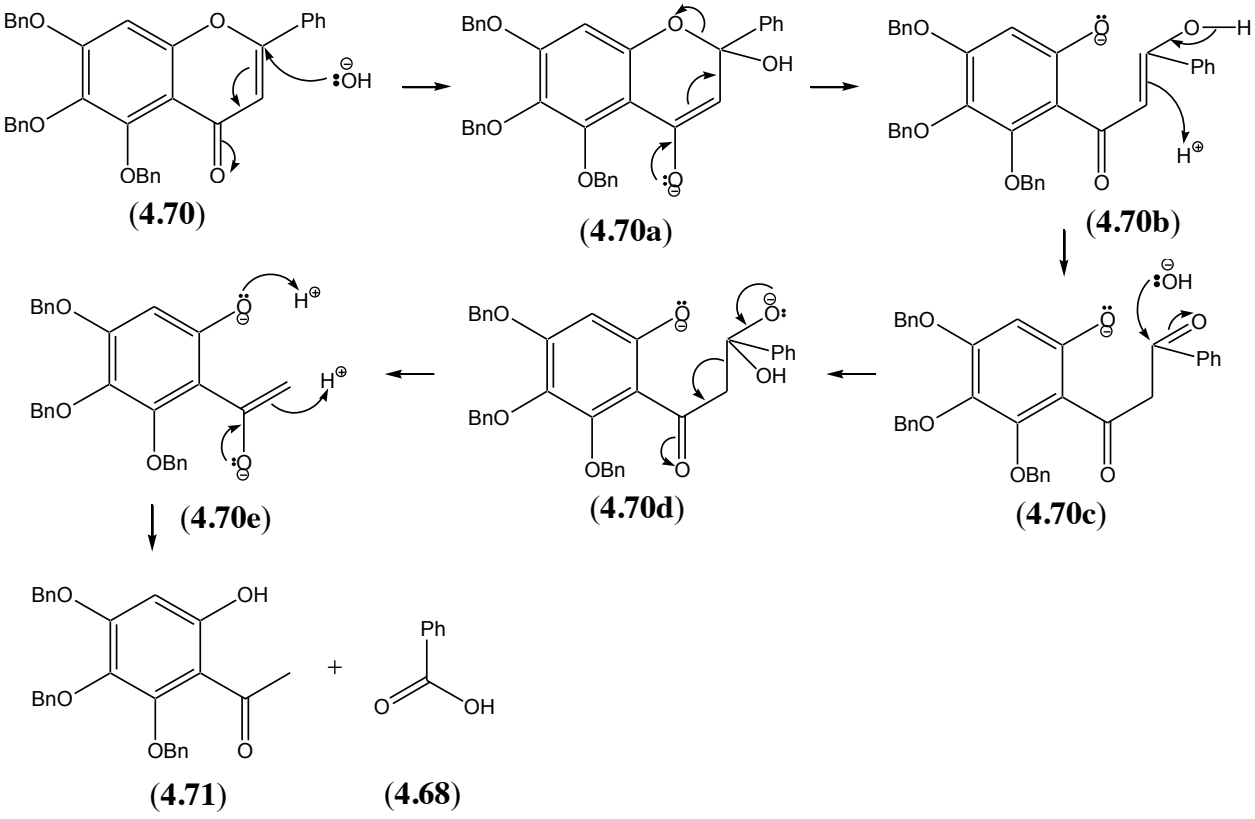


(**4.69**) (**4.70**)

Scheme 19. Synthesis of 2,3,4-tribenzyloxy-6-hydroxyacetophenone (**4.71**). Reagents: (a) $PhCH_2Cl$, dry K_2CO_3, dry DMF; 72% yield; (b) 18 M aqueous KOH, py-diethylene glycol, 100 ^{o}C.

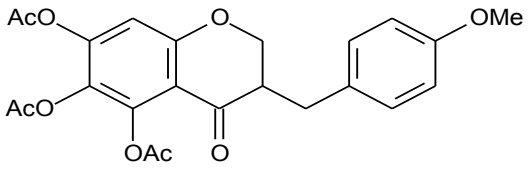
[27] Lee, Y.; Yeo, H.; Liu, S.-H.; Jiang, Z.; Savizky, R.M.; Austin, D.J.; Cheng, Y.-C. *J. Med. Chem.* **2004**, *47*, 5555.

The desired product (**4.71**) was accompanied by two side-products i.e. 2',3',4'-tribenzyloxy-β,6'-dihydroxychalcone (**4.72**) and 6,7-dibenzyloxy-5-hydroxyflavone (**4.73**) (^{1}H NMR spectrum Plate 22a) in 32 and 10% yield, respectively and the expected benzoic acid (**4.68**) (Scheme 19). The ^{1}H NMR spectrum of (**4.72**) (Plate 21a) displayed, apart from the resonances associated with the three benzyl groups and an unsubstituted aromatic ring [δ 5.15, 5.12, and 5.04 (each 2H, each s) and 7.55-7.27 (21H, m, 4 x $C_6\underline{H}_5$ and α-$\underline{H}$)], only one singlet at δ 6.44 ppm, and two hydroxy resonances (δ 15.61 ppm and δ 13.01 ppm) to confirm the structure of the product. The formation of the 2',3',4'-tribenzyloxy-β,6'-dihydroxychalcone (**4.72**) is probably explicable in terms of it being an intermediate product in the degradation of baicalein and the isolation of it indicating that the reaction was not allowed to go to completion as is indicated in Scheme 20.



Scheme 20. Proposed mechanism for the degradation of perbenzylated baicalein (**4.70**).

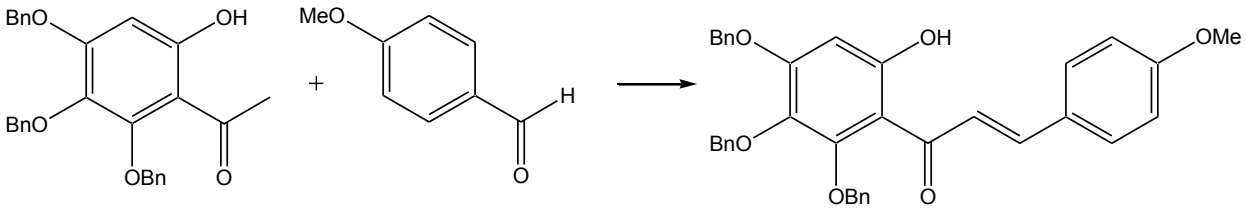
4.3 Synthesis of 5,6,7-triacetoxy-4'-methoxyhomo-isoflavanone (4.5)



(**4.5**)

4.3.1 Aldol condensation of 2,3,4-tribenzyloxy-6-hydroxyaceto-phenone (4.71) with anisaldehyde (4.10) and subsequent reduction of the chalcone product

With the 2,3,4-tribenzyloxy-6-hydroxyacetophenone (**4.71**) in hand, attention was turned towards constructing the chalcone intermediate an route to the homoisoflavanone (**4.5**). Aldol condensation between the benzylated acetophenone (**4.71**) and anisaldehyde (**4.10**) gave 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**) in 76% yield (Scheme 21). The ^{1}H NMR spectrum (Plate 24a) of the product (**4.74**) confirmed it to be the desired chalcone (**4.74**) as the α,β-unsaturated carbonyl system was clearly visible with the resonance of the α-proton appearing at δ 7.91 ppm (1H, d, *J* = 16 Hz) and the β-hydrogen at δ 7.82 ppm (1H, d, *J* = 16 Hz).



(**4.71**) (**4.10**) (**4.74**)

Scheme 21. Synthesis of 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**). Reagents: EtOH, KOH at 0 ^{o}C, 76% yield.

In order to introduce the C1-fragment needed to complete the homoisoflavonoid skeleton into the chalcone molecule, it was envisaged that the double bond of the chalcone could be reduced to give the dihydrochalcone (**4.8**), which could then be transformed into the homoisoflavone

analogue by (Scheme 1) Vilsmeier formylation followed by cyclization. Since $NaBH_4$ is known to be a soft reducing agent, this compound was chosen as reagent for this transformation. Treatment of the 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**) with $NaBH_4$ in EtOH, however, resulted in the flav-3-ene (**4.75**) being formed in 45% yield (Scheme 22). Apart from the expected aromatic [δ 7.35 (2H, d, *J* = 9 Hz, H-2',6'); 6.90 (2H, d, *J* = 9 Hz, H-3',5'); 6.30 (1H, s, H-8) and δ 7.44-7.31 (15H, m, 3 x $C_6\underline{H}_5$)], benzyloxy [δ 5.15 (1H, d, *J* = 11.Hz, $O\underline{CH_2}C_6H_5$); 5.12 (1H, d, *J* = 11 Hz, $O\underline{CH_2}C_6H_5$); 5.03 (2H, s, $O\underline{CH_2}C_6H_5$); 5.01 (2H, s, $O\underline{CH_2}C_6H_5$)], and single methoxy resonance [δ 3.83 (3H, s)], the ^{1}H NMR spectrum (Plate 25a) of the product (**4.75**) displayed two doublets of doublets (*J* = 10 and 1 Hz and *J* = 10 and 3 Hz, respectively) at δ 6.75 and 5.63 and a multiplet at 5.76 (1H, br s). Since no OH group showing hydrogen bonding was observed, it could be concluded that the product contains a three carbon heterocyclic ring with three hydrogens attached to the carbon atoms. The unsaturated heterocyclic ring could therefore constitute a flav-2-ene or flav-3-ene. As the CH_2 of a flav-2-ene would display a methylene resonance in the δ 3 - 4 ppm region,[28] this option could be excluded as structure for product (**4.75**). The flav-3-ene nature of product (**4.75**) was confirmed by a good agreement of the chemical shift values of the heterocyclic resonances with those reported in literature for these compounds [δ 6.75 (1H, dd, *J* = 10 and 1 Hz, H-4), 5.76 (1H, br s, H-2), and 5.63 (1H, dd, *J* = 10 and 3 Hz, H-3)].[29] Confirmation of the flav-3-ene structure of the product (**4.75**) came from the ^{13}C NMR spectrum (Plate 25b) where C-2 was detected at δ 76.8 and the heterocyclic vinyl system at δ 128.2 and 127.5 and MS where a molecular ion was observed at *m/z* 556 (M^+, 3%). The formation of the flav-3-ene is probably explicable in trems of a 1,2 reduction of the carbonyl group, followed by Lewis acid assisted dehydrative cyclization through attack of the free 2'-hydroxy group at the β-carbon of the allylic alcohol intermediate (**4.74a**) (Scheme 22).

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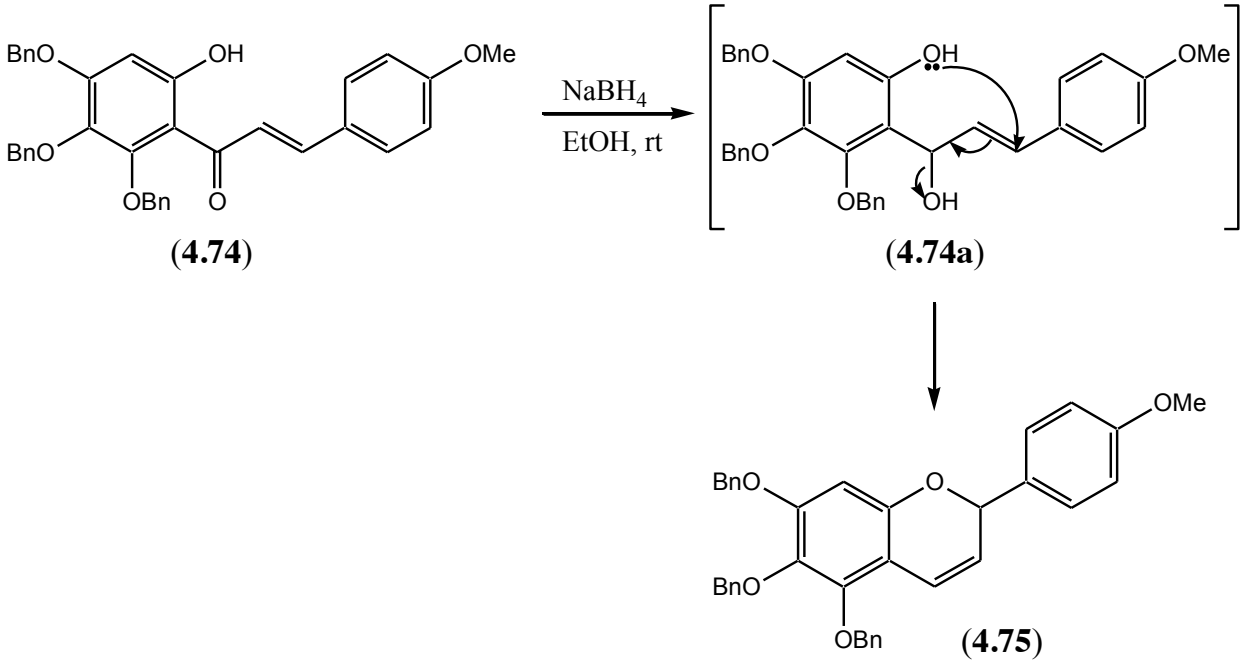
28 Miller, BJ; Pieterse, T; Marais, C; Bezuidenhoudt BCB, *Tetrahedron Lett*. **2012**, *53*, 4708-4710 and Clark-Lewis, JW; Baig, MI, *Aust*. *J*. *Chem*., **1971**, 24, 2581.

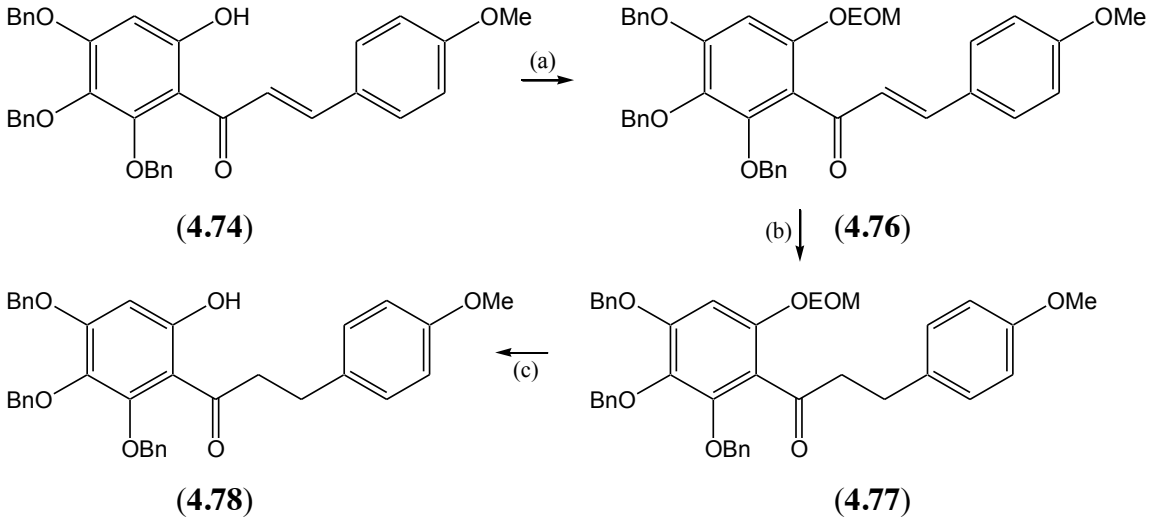
29 Krohn, K; Ahmed, I; John, M, *Synthesis*, **2009**, 779-786; Devakaram, R, Black, DS, Andrews, KT, Fisher, GM, Davis, RA, Kumar, N, *Bioorg*. *Med*. *Chem*., **2011**, *19*, 5199-5206 and Clark-Lewis, JW; Baig, MI, *Aust*. *J*. *Chem*., **1971**, *24*, 2581.



(**4.74**) (**4.74a**) (**4.75**)

Scheme 22. $NaBH_4$ reduction of 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**). Reagents: $NaBH_4$, EtOH, rt, 45% yield.

To prevent the formation of the flavene, as discussed above, it was decided to protect the 6'-hydroxy group of (**4.74**) with the easily removable ethoxymethyl (EOM) group before the reduction (Scheme 23). Treatment of the chalcone (**4.74**) with chloromethyl ethyl ether ($EtOCH_2Cl$) in the presence of Adogen 464 and NaOH led to the pure protected chalcone (**4.76**) being formed in quantitative yield within 1 hour. The ^1H NMR spectrum (Plate 26) of the product (**4.76**) confirmed protection of the free OH function by showing the methylene and ethoxy resonances of the EOM group at δ 5.02 (s), 3.63 (2H, q, J = 7 Hz), and δ 1.60 (3H, t, J = 7 Hz), respectively. Subsequent $NaBH_4$ reduction of the protected chalcone (**4.76**) eventually gave the dihydrochalcone (**4.77**) (Plate 27a) in 26% yield, which was deprotedted [HCl(c), MeOH, reflux] to obtain the desired 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone (**4.78**) (Plate 28a) in quantitive yield.

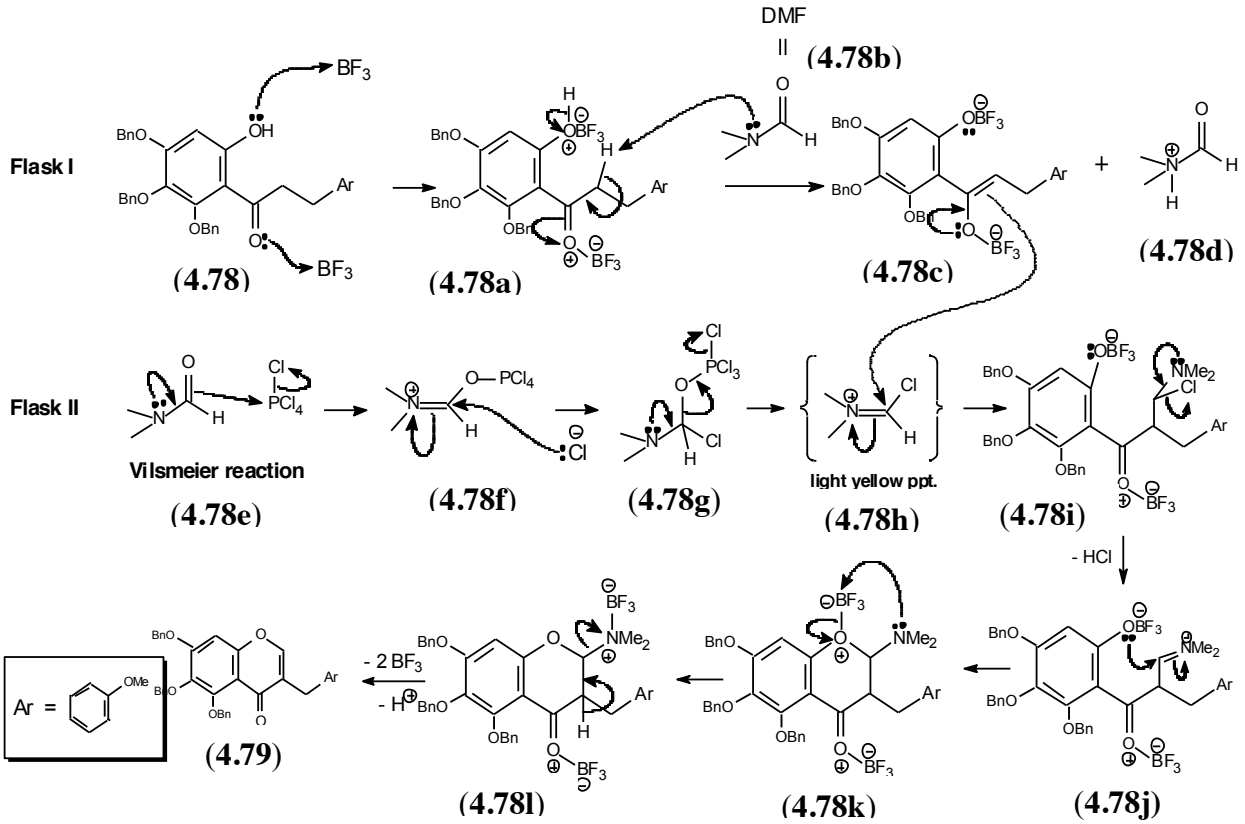


Scheme 23. Preparation of 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone (**4.78**). Reagents: (a) Chloromethyl ethyl ether, Adogen 464, 2M *aq*. NaOH, DCM, rt, 100% yield; (b) $NaBH_4$, EtOH, 26% yield; (c) 3 M HCl, MeOH, rt, 100% yield.

4.3.2 Formation of the heterocyclic ring *via* Vilsmeier formylation

Since it was found during the candidate's MSc[4] study that a model analogue of the wanted 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**), 3',5'-dimethoxyhomoisoflavone, could be prepared by a BF_3 catalysed Vilsmeier reaction, this methodology was also applied to the preparation of the 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**), which was obtained in 29% yield by reacting the corresponding dihydrochalcone (**4.78**) with BF_3 etherate and freshly prepared Vilsmeier reagent[30] (**4.78e**) (Scheme 24). In addition to the expected aromatic signals, the ^{1}H NMR spectrum (Plate 29a) of the homoisoflavone (**4.79**) displayed a methylene resonance at δ 3.69 ppm (2H, s) and a singlet at δ 7.85 ppm; characteristic of the H-2 resonance of isoflavones. The ^{13}C NMR spectrum (Plate 29b) of the product (**4.79**) displayed a carbonyl carbon at δ 176.0 ppm (C-4) as well as an α,β-unsaturated system at δ 114.0 ppm (C-3) and δ 154.9 ppm (C-2) together with a methylene carbon [δ 30.1 ppm (C-9)], while HRMS indicated a molecular ion + Na at *m/z* 607.2102 (Calcd for $C_{38}H_{32}O_6Na$: 607.65 g/mol); thus confirming 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**) as the product.

30 Davis, F.A.; Chen, B-C. *J. Org. Chem.* **1993**, *58*, 1751.



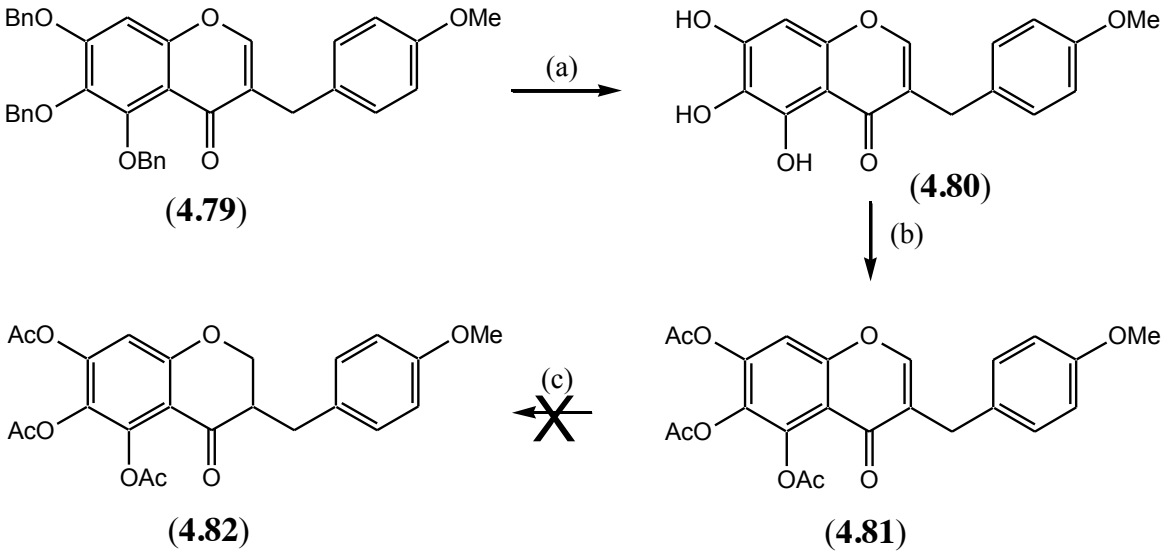
Scheme 24. Cyclization of dihydrochalcone (**4.78**) *via* Vilsmeier formylation.

4.3.3 Reduction and deprotection of the 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (4.79)

In order to obtain the wanted 5,6,7-triacetoxy-4'-methoxyhomoisoflavanone (**4.5**) it was envisaged that selective hydrogenation would be a way to remove the benzyl groups from the aromatic nucleus as well as saturate the hetrocyclic ring in a one-step process. Palladium on carbon catalysed hydrogenation of the homoisoflavone (**4.79**) in actone for 45 min., however, only yielded the trihydroxy-analogue (**4.80**) in 92% yield (Scheme 25), while extended reaction times resulted in the homoisoflavone to be reduced to the homoflavan quivalent. The ^{1}H NMR spectrum (Plate 30) of the trihydroxyisoflavone (**4.80**) clearly revealed no benzyloxy groups to be present, while the chemical shift of the aromatic proton at C-8 moved up-field from δ 7.03 ppm to δ 6.49 ppm.

Since reduction of the heterocyclic double bond could not be achieved selectively through catalytic hydrogenation and $NaBH_4$ does not reduce esters, it was subsequently decided to

acetylate the free OH groups and remove the double bond by reduction with this reagent. Acetylation of the trihydroxyhomoisoflavone (**4.80**) gave the peracetate (**4.81**) (NMR spectra: Plate 31) in 59% yield. Unfortunately, reduction with the borohydride reagent again only led to removal of the acetoxy protecting groups and did not result in saturation of the double bond at all (Scheme 25).



Scheme 25. Catalytic hydrogenation of the tribenzyloxyhomoisoflavone (**4.79**) followed by acetylation and reduction. Reagents: (a) H_2, 5% Pd/C, acetone, 45 min, 92% yield; (b) acetic anhydride, pyridine (ratio 2:1), 60 °C, overnight, 59% yield; (c) $NaBH_4$, EtOH.

Since Baker *et al*.[31] reported ligand bound CuH to be a mild reducing agent for 1,4-reductions of activated alkenes and alkynes, it was decided to evaluate this reagent in the selective reduction of the double bond in the homoisoflavone analogue (**4.79**). Treatment of flavone (**4.66**), as model substrate, with *in sito* prepared *o*-BDPPBCuH (Scheme 26) yielded the flavanone (**4.85**) in 48% yield. The ^{1}H NMR spectrum (Plate 32a) of the flavanone clearly displayed the saturated nature of the heterocyclic ring with resonances at δ 5.52 ppm (1H, dd, J = 13.5 and 2.6 Hz, H-2) and δ 3.12 ppm [1H, dd, J = 13.5 and 3.3 Hz, H-3(a)], δ 2.92 [1H, dd, J = 16.9 and 2.8 Hz, H-3(b)]. In order to evaluate the effect, if any, that a highly substituted aromatic A-ring might have on the outcome of the reaction, perbenzylated baicalein (**4.70**) and peracetylated baicalein (**4.87**) was also subjected to the reductive reaction conditions (Scheme 27), but no identifiable reduced product could be obtained; thus indicating the adverse effect of the highly oxygenated A-ring on the reaction.

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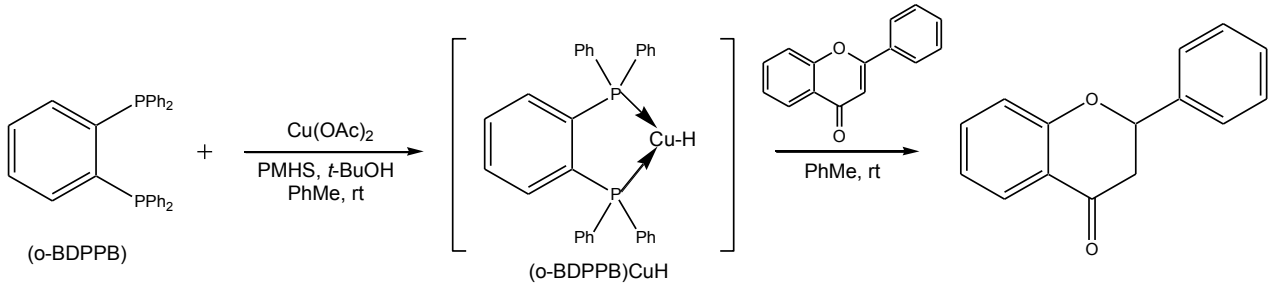
31 Baker, B.A.; Bošković, Ž.V.; Lipshutz, B.H. *Org*. *Lett*. **2008**, *10*, 289.



(**4.83**) (**4.84**) (**4.85**)

Scheme 26. Reduction of flavone (**4.66**) with *o*-BDPPBCuH.

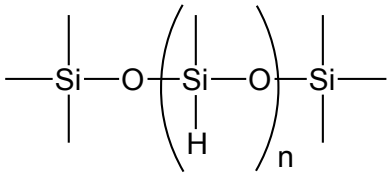
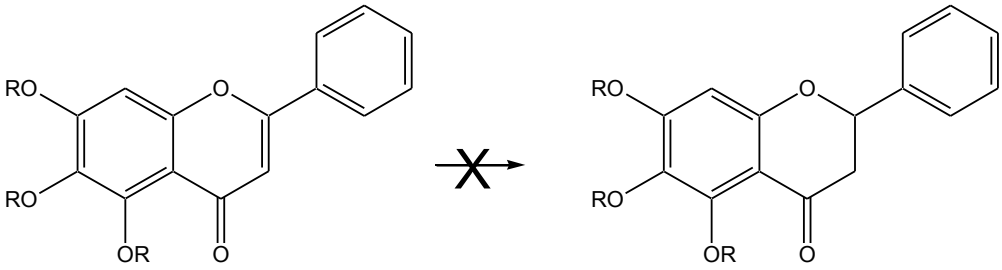


Figure 2. PMHS, Polymethylhydrosiloxane.



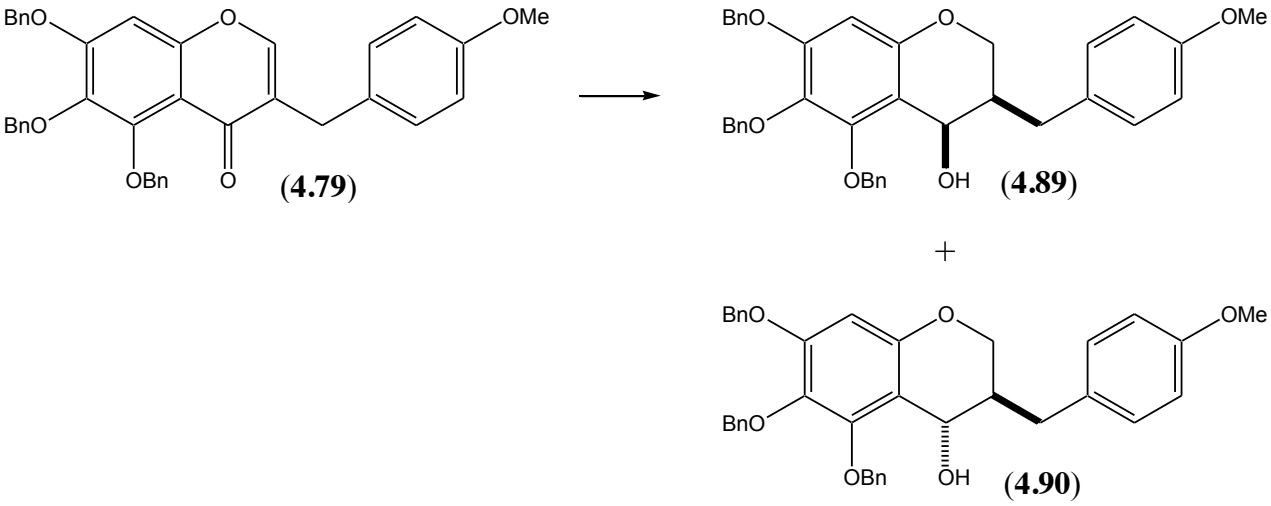
(**4.70**) R = Bn
(**4.87**) R = Ac

(**4.86**) R = Bn
(**4.88**) R = Ac

Scheme 27. Reduction on perbenzyloxy (**4.70**) and peracetoxy baicalein (**4.87**) with *o*-BDPPBCuH. Reagents and conditions: $Cu(OAc)_2$, *o*-BDPPB, *t*-BuOH, PMHS, dry toluene, rt.

With the trioxygenated A-ring compounds being resistant to CuH reduction of the 2,3-double bond, it was decided to once again utilize $NaBH_4$ as reducing agent, albeit on the perbenzylated homoisoflavone (**4.79**). In this instance treatment of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**) with $NaBH_4$ in ethanol gave a mixture of the *cis*- (**4.89**) and *trans*- (**4.90**) isomers of the homoisoflavan-4-ol in 8% combined yield (Scheme 28). The ^1H NMR spectrum (Plate 33a) of the *cis*-homoisoflavan-4-ol (**4.89**) showed three benzyloxy groups [δ 7.46-7.26 (m, 15H, 3 x $C_6\underline{H}_5$), δ 5.29 and 5.03 (each 1H, each d, J = 11 Hz, O$\underline{CH_2}$Ph), 5.07 (2H, s, O$\underline{CH_2}$Ph)

and 4.99 (2H, s, O$\underline{CH_2}$Ph)], an AA'BB' system [δ 7.18 (2H, d, *J* = 8.6 Hz, H-2' and H-6') and δ 6.88 (2H, d, *J* = 8.6 Hz, H-3' and H-5')], an aromatic singulet at δ 6.30 (1H, s, H-8) and a methoxy group at δ 3.84 (3H, s). The exocyclic methylene appeared as two doublets of doublets at δ 2.82 [(1H, dd, *J* = 13.6 Hz and 8.4 Hz, H-9(a)] and δ 2.58 [(1H, dd, *J* = 13.7 Hz and 7.3 Hz, H-9(b)], while the hetrocyclic ring protons were represented by multiplets at δ 2.03 – 2.08 (1H, H-3) and δ 3.98 – 4.00 (2H, H-2) and a doublet at δ 4.54 (1H, *J* = 2.3 Hz, H-4) to confirmed the structure as that of the *cis*-compound (**4.89**). The ^{13}C NMR spectrum (Plate 33b) of the *cis*-homoisoflavan-4-ol (**4.89**) displayed, apart from the expected aromatic carbon resonances, an oxygenated benzylic carbon (C-4) at δ 59.9 ppm, the heterocyclic methylene carbon resonance (C-2) at δ 70.7 ppm and the exocyclic methylene carbon (C-9) at δ 29.7 ppm to give further credence to the structure of the product. The ^{1}H NMR spectrum (Plate 34a) of the *trans*-isomer (**4.90**) displayed, apart from the expected benzyloxy [δ 7.49-7.33 (15H, m, 3 x $CH_2\underline{C_6H_5}$), and 5.02 – 5.35 (6H, m, 3 x $\underline{CH_2}$Ph)], aromatic [δ 7.09 (2H, d, *J* = 8.5 Hz, H-2',6'), δ 6.85 (2H, d, *J* = 8.5 Hz, H-3',5') and δ 6.38 (1H, s, H-8)] and methoxy resonances [δ 3.80 (3H, s)], signals from two methylene groups [δ 2.42 (1H, dd, *J* = 13.9 and 6.0 Hz) and 2.34 – 2.36 (m, 9-CH_2 and 4-OH) and [δ 4.06 (1H, dd, *J* = 10.9 Hz and 2.1 Hz) and δ 3.88 (1H, dd, *J* = 10.8 and 1.9 Hz)]. These resonances were accompanied by a multiplet at δ 2.07 – 2.11 (H-3) and a broad singlet at δ 4.45 (1H) that confirmed the structure of the product as (**4.90**). The ^{13}C NMR spectrum (Plate 34b) of (**4.90**) again displayed the expected heterocyclic carbon resonances at δ_C 55.3, 70.8 and 40.4 (C-4, 2-CH_2 and C-3, respectively) and 9-CH_2 at δ_C 29.7 to confirm the structure of the product.

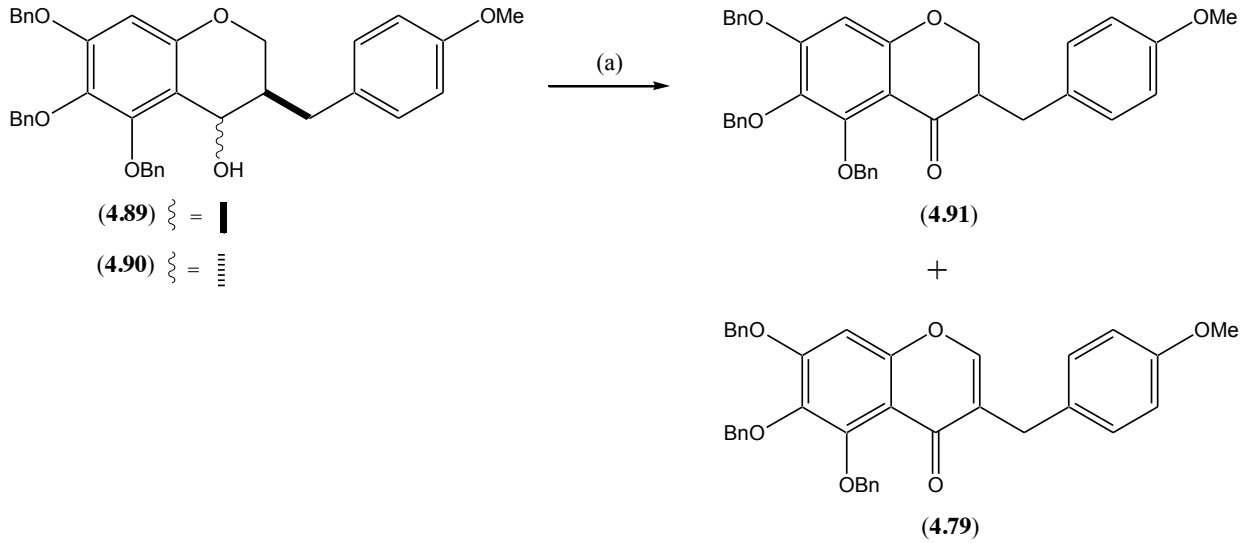


Scheme 28. Sodiumborohydride reduction of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**). Reagents: $NaBH_4$, EtOH, THF, 8% combined yield.

Although the yields for the homoisoflavan-4-ols (**4.89**) and (**4.90**) were not great, it was decided to continue with the 4-hydroxy analogues, since the main objective of the preparation was only to get enough of the final homoisoflavan for comparison of its NMR data with that of the natural product (**4.5**). Furthermore, completion of the synthetic process would only require oxidizing the 4-hydroxy group of both the flavan-4-ols (**4.89** and **4.90**) back to the ketone and transform the benzyloxy protecting groups into acetates.

Since IBX (*o*-iodoxybenzoic acid)[32] is known to be a very mild oxidizing agent that is capable of oxidizing primary and secondary alcohols to aldehydes and ketones, this reagent was selected for this purpose. Refluxing *cis*- and *trans*-5,6,7-tribenzyloxy-4'-methoxyhomoisoflavan-4-ols (**4.89** and **4.90**) in acetonitrile containing IBX, yielded the desired homoisoflavanone (**4.91**) in 80% yield (Scheme 29). Apart from the expected aromatic and benzyl resonances [δ 7.63-7.29 (15H, m, 3 x $CH_2\underline{C_6H_5}$), δ 7.18 (2H, d, *J* = 8.6 Hz, H-2' and H-6') and δ 6.88 (2H, d, *J* = 8.6 Hz, H-3' and H-5')] the ^{1}H NMR spectrum (Plate 35a) of the product (**4.91**) displayed a multiplet at δ 2.73 – 2.77 (1H) for H-3, together with two sets of methylene doublets at δ 4.29 [1H dd, *J* = 11.3 and 3.9 Hz, H-2(a)] and 4.13 [1H, dd, *J* = 11.4 and 6.8 Hz, H-2(b)] and δ 3.22 [1H, dd, *J* = 13.8 and 4.0 Hz, H-9(a)] and 2.67 [1H, dd, *J* = 13.7 and 11.1 Hz, H-9(b)]; thus confirming the product to be the homoisoflavanone (**4.91**). The structure of the wanted product (**4.91**) was further confirmed by the ^{13}C NMR spectrum (Plate 35b), which displayed the carbonyl carbon at δ 191.5 ppm (C-4) together with two methylene carbons [δ 32.0 ppm (C-9) and δ 68.9 (C-2)], and HRMS (Found: *m/z* 609.2258. Calcd for $C_{38}H_{34}O_6Na$: *m/z* 609.67).

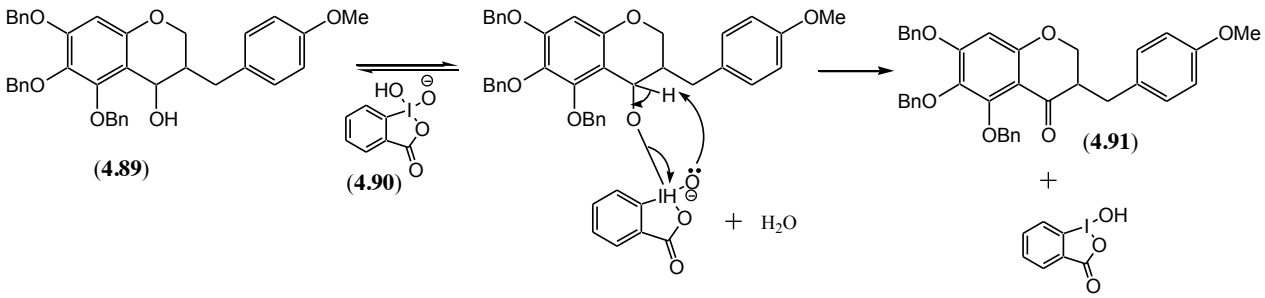
32 Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.



Scheme 29. IBX oxidation of the *cis*- and *trans*-5,6,7-tribenzyloxy-4'-methoxyhomoisoflavan-4-ols (**4.89**) and (**4.90**). Reagents: IBX, dry acetonitrile, reflux, yield for (**4.91**) and (**4.79**) **=** 80 and 20%, respectively.

The wanted homoisoflavanone (**4.91**) was accompanied by an unexpected side-product (20%), which could be identified as the 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**). The formation of the homoisoflavone during this reaction indicated the extreme ease of over oxidation to the unsaturated analogue (Scheme 29).

The mechanism[33,34] for the oxidation of the benzylic alcohols to 5,6,7-tribenzyloxy-4'-methoxy-homoisoflavanone (**4.91**) with IBX is shown in the Scheme 30 below.



Scheme 30. Mechanism for the IBX oxidation of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavan-4-ols (**4.89**) and (**4.90**).

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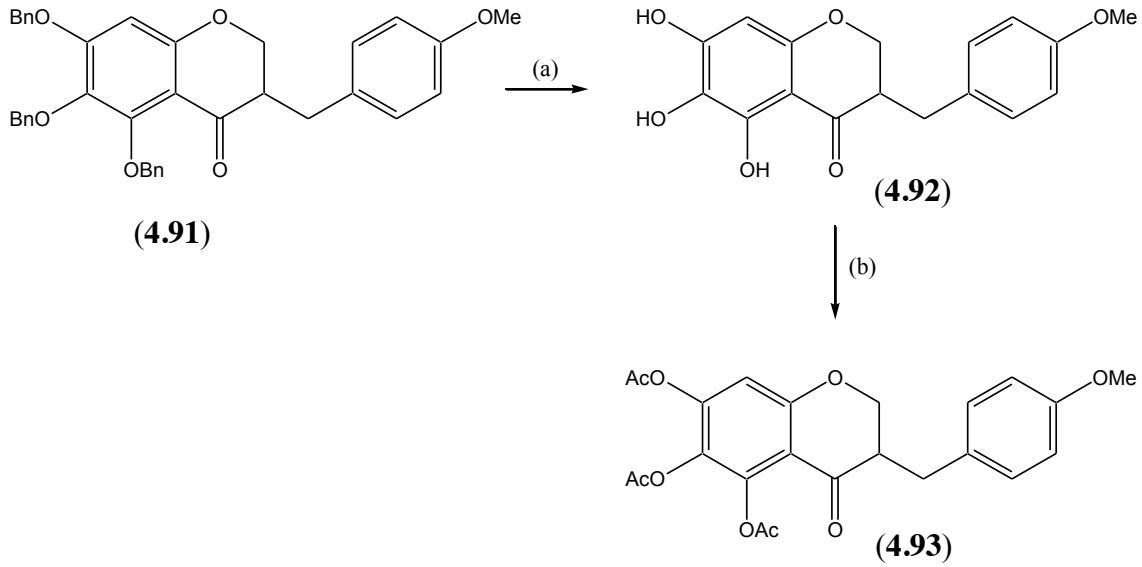
33 Frigerio, M.; Santagostino, M., Sputori, S., Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

34 De Munari, S.; Frigerio, M.; Santagostino, M., *J. Org. Chem.* **1996**, *61*, 9272.

With the 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavanone (**4.91**) in hand, this compound (**4.91**) was debenzylated by catalytic hydrogenation over 5% Pd on carbon in acetone and the free phenolic product (**4.92**) (^{1}H NMR and ^{13}C NMR spectra Plate 36a and b, respectively) isolated in 56% yield. Finally, acetylation (pyridine-acetic anhydride, 60 °C) of the free phenolic homoisoflavanone (**4.92**) resulted in, what was presumed, the protected natural product analogue, 5,6,7-triacetoxy-4'-methoxyhomoisoflavanone (**4.93**) (Plate 37a, Table 3) in quantitive yield (Scheme 31).



Scheme 31. Debenzylation followed by acetylation of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavanone (**4.91**). Reagents: (a) H_2, 5% Pd/C, acetone, 56%; (b) Acetic anhydride, pyridine, 60 °C, overnight, 100%.

A comparison the the NMR data of the synthetic 5,6,7-triacetoxy-4'-methoxyhomoisoflavanone (**4.93**) with that of the natural product (**4.5**) (Table 3), however showed the isolated (**4.5**) and synthesized products (**4.93**) not to be identical. While the chemical shift differences of the heterocyclic- and 9-methylene protons were relatively small (< δ 0.1 ppm), confirming both compounds to be homoisoflavanones, the values for the aromatic hydrogens were quite different, i.e. δ 6.49 *vs* δ 6.86 ppm for H-8, δ 7.23 *vs* 7.12 for H-2',6', and δ 7.06 *vs* 6.87 for H-3',5'. Due to the fact that the resonances for both B-ring protons were down field for the natural product when compared to that of the synthetic equivalent and it was the other way round for the proton at C-8, it could be concluded that the A-ring of the natural product contained the methoxy substituent and was therefore not fully acetylated, while the methoxy group was also not attached to the 4'-position of the B-ring. Structure (**4.5**) could therefore not be assigned to the isolated natural

product. Since Mulholland *et al*.[1,2] previously isolated a homoisoflavanone with a 5,7-dihydroxy-6-methoxy substituted A-ring from a Scilla species, it was felt that the natural product obtained as the peracetate from *Scilla natalensis* during the candidate's MSc studies might therefore be the 4',5,7-trihydroxy-6-methoxyhomoisoflavanone (**4.1**).

Table 3. ^{1}H NMR resonances of the isolated natural product (**4.5**) *vs* the synthesized 5,6,7-triacetoxy-4'-methoxyhomoisoflavanone (**4.93**).

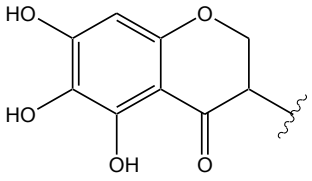
Ring	Proton	$CDCl_3$, 298 K	
		Isolated compound (4.5)	**Synthesized compound (4.93)**
A	H-8	6.49 (s)	6.86 (s)
B	H-2', H-6'	7.23 (d, *J* = 8 Hz)	7.12 (d, *J* = 8.5 Hz)
	H-3', H-5'	7.06 (d, *J* = 8 Hz)	6.87 (d, *J* = 8.5 Hz)
C	H-2(a)	4.47 (dd, *J* = 12 and 4 Hz)	4.36 (dd, *J* = 11.5 and 4.2 Hz)
	H-2(b)	4.27 (dd, *J* = 12 and 9 Hz)	4.18 (dd, *J* = 11.5 and 8.2 Hz)
	H-3	2.92-2.85 (m)	2.83-2.78 (m)
	H-9(a)	3.28 (dd, *J* = 14 and 4 Hz)	3.18 (dd, *J* = 13.9 and 4.6 Hz)
	H-9(b)	2.66 (dd, *J* = 14 and 11 Hz)	2.65 (dd, *J* = 14.2 and 10.7 Hz)
	OAc	2.40 (s)	2.41 (s)
		2.35 (s)	2.32 (s)
		2.32 (s)	2.30 (s)
	OMe	3.85 (s)	3.81 (s)

4.4 Synthesis of A-ring monomethoxy homoisoflavanones

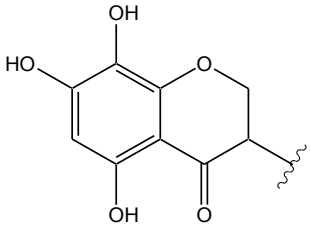
4.4.1 Introduction

Although it was felt that the natural homoisoflavanone isolated from *Scilla natalensis* could have structure (**4.1**), no proof of the position of the methoxy group could be obtained from, for example, nOe association to a neighbouring proton, while the fact that it was isolated as the peracetate hampered comparison of the proton chemical shift of H-8 and the chemical shift values of carbon atoms to those of similar compounds described in literature.

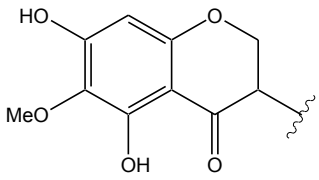
As is amply demonstrated by the wrong structure assigned to the previously isolated compound, structure elucidation of homoisoflavonoids having a tri-oxygenated A-ring is further hampered by the fact that the compounds can either be the 5,6,7 (**4.94**) or the 5,7,8-analogue (**4.95**); both of which having only a single singlet resonance originating from the A-ring in the ^{1}H NMR spectrum available for distinction. Due to the very similar electronic environment, little differences in the chemical shift of the residual 6 or 8-proton as well as the relavant carbon atoms is also eminent. If the unknown compound is isolated in free phenolic form, complexation with $AlCl_3$ and NaOAC together with a bathochromic shift in the UV absorption spectrum as well as ^{13}C NMR spectroscopy have been used to distinguish between the two possible isomers (5,6,7 or 5,7,8) (Figure 3).[35] The presence of a single methoxy group at one of the positions adds another complicating factor to the structure elucidation, as it might not be in a position to allow any nOe effect to the adjacent proton to be visible, i.e. 5- or 6-OMe to H-8 or 8-OMe to H-6 (Figure 3), while isolation as another derivative, like the percetate, renders chemical shift comparison to other known analogues and thus identification of the new compound, very risky.



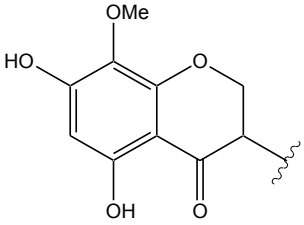
(**4.94**)



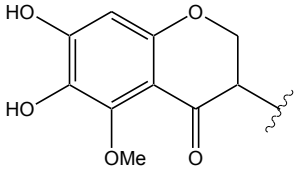
(**4.95**)



(**4.96**)



(**4.97**)

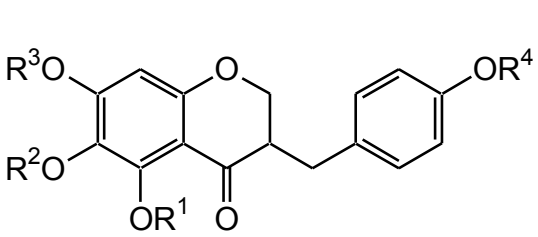


(**4.98**)

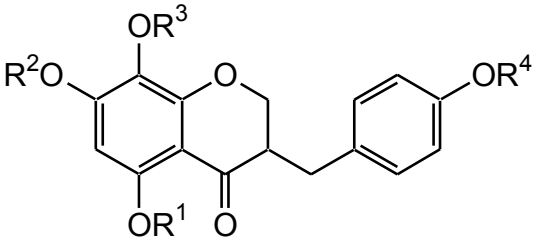
Figure 3. Two possible isomers (5,6,7 and 5,7,8- analogue).

35 Vanitha, P.; Valliappan, R.; Charles, A.; Sukumar, D. *J. Chem. Pharm. Res.*, **2012**, *4*, 3665.

It was therefore decided to embark on the unambiguous synthesis of a series of homoisoflavonoids, including the natural product from *Scilla natalensis*, with oxygenation in the 6- or 8-position and a mono methoxy substituent at all of the possible positions in both the 6- and 8-oxygenated series of compounds (Figure 4) and to obtaind the NMR data (^{1}H and ^{13}C) for all of these compounds both in the free phenolic and acetylated forms.



(**4.99**) $R^1 = Me, R^2 = R^3 = R^4 = H$
(**4.100**) $R^1 = Me, R^2 = R^3 = R^4 = Ac$
(**4.101**) $R^2 = Me, R^1 = R^3 = R^4 = H$
(**4.102**) $R^2 = Me, R^1 = R^3 = R^4 = Ac$
(**4.103**) $R^3 = Me, R^1 = R^2 = R^4 = H$
(**4.104**) $R^3 = Me, R^1 = R^2 = R^4 = Ac$

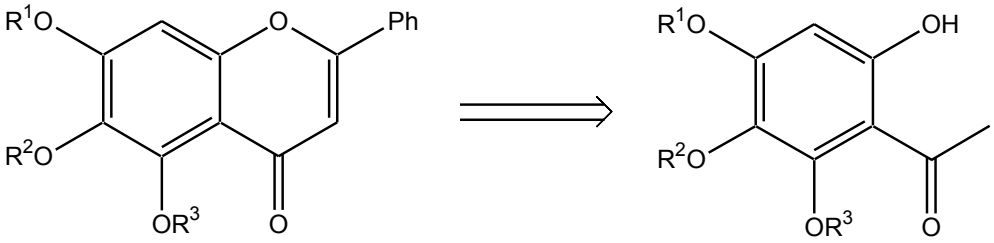


(**4.105**) $R^1 = Me, R^2 = R^3 = R^4 = H$
(**4.106**) $R^1 = Me, R^2 = R^3 = R^4 = Ac$
(**4.107**) $R^2 = Me, R^1 = R^3 = R^4 = H$
(**4.108**) $R^2 = Me, R^1 = R^3 = R^4 = Ac$
(**4.109**) $R^3 = Me, R^1 = R^2 = R^4 = H$
(**4.110**) $R^3 = Me, R^1 = R^2 = R^4 = Ac$

Figure 4. Possible methylated positions in both the 6- and 8-oxygenated series of homoisoflavanones.

4.4.2 Preparation of acetophenones with different protecting groups

The necessity of no ambiguity as to the position of the different substituents in the envisaged final homoisoflavanones, to be synthesized, required the preparation of protected tetra-oxygenated acetophenones with the methoxy substituent in all the predefined positions with no uncertainty as to where the methoxy group is going to be situated in the final product. The first step in the development of the synthetic methodology would therefore be to attach a series of removable protecting groups to the A-ring of the flavone, baicalein (**4.69**), that would lead to the desired monomethoxyacetophenone in the downstream process. Since benzyl and ethoxymethyl groups are easily removable these were selected as first choice for the protection of the baicalein A-ring. Acetophenones (**4.116**, **4.120** and **4.125**) were therefore selected as target molecules for the preparation of the series of 5,6,7-trioxygenated monomethoxyhomoisoflavanones (Scheme 32).



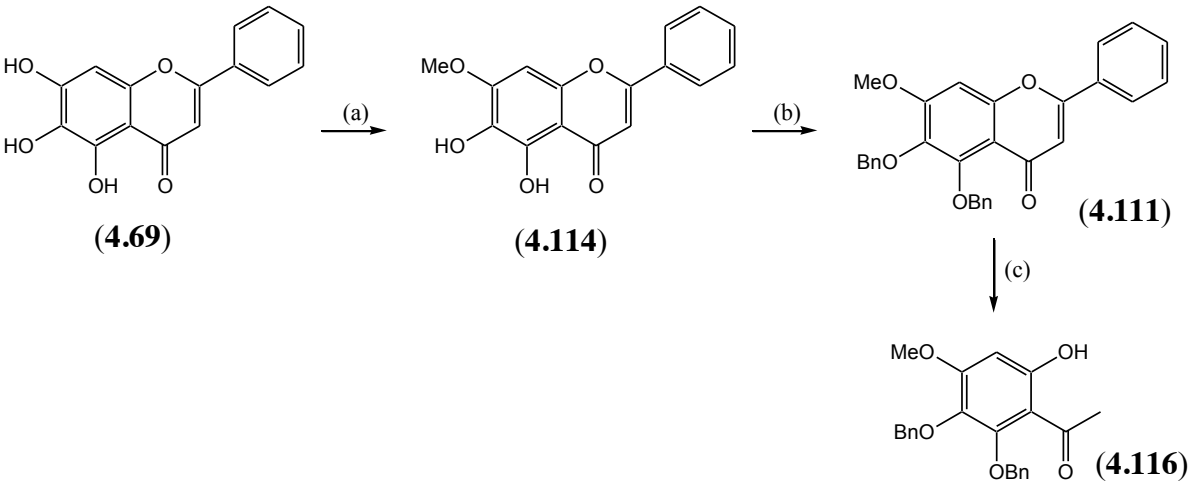
(**4.111**) R^1 = OMe, $R^2 = R^3$ = Bn
(**4.112**) $R^1 = R^3$ = Bn, R^2 = Me
(**4.113**) $R^1 = R^2$ = Bn, R^3 = Me

(**4.116**) R^1 = OMe, $R^2 = R^3$ = Bn
(**4.120**) $R^1 = R^3$ = Bn, R^2 = Me
(**4.125**) $R^1 = R^2$ = Bn, R^3 = Me

Scheme 32. Protection of the baicalein A-ring to give the desired acetophenones (**4.116**, **4.120** and **4.125**).

4.4.2.1 Preparation of 2,3-dibenzyloxy-6-hydroxy-4-methoxyacetophenone (4.116)

Preparation of acetophenone (**4.116**) required selective methylation of the 7-hydroxy function of baicalein, followed by benzylation of the other two hydroxy functions (Scheme 33).



(**4.69**) (**4.114**) (**4.111**) (**4.116**)

Scheme 33. Preparation of acetophenone (**4.116**). Reagents: (a) MeI, Cs_2CO_3, 0 °C, 58% yield; (b) BnBr, K_2CO_3, 60 °C, 37% yield; (c) diethylene glycol, pyridine, 18 M *aq*. KOH, reflux, 4% yield.

Since cesium carbonate (Cs_2CO_3)[36] often gives better yields than potassium carbonate (K_2CO_3) due to its better solubility in organic solvents[37] and it has been demonstrated that this compound

[36] Flessner, T.; Doye, S. *J*. *Prakt*. *Chem*. **1999**, *341*, 186.

[37] Lautens, M.; Piguel, S. *Angew*. *Chem*. *Int*. *Ed*. **2000**, *112*, 1087.

lead to accelerated reation rates,[36] this base was used together with methyl iodide in dry acetonitrile at 0 ^{o}C to selectively methyl baicalein (Scheme 33). Under these conditions the desired 5,6-dihydroxy-7-methoxyflavone (**4.114**) was obtained in 58% yield. The ^{1}H NMR spectrum (Plate 38a) of (**4.114**) displayed the single methoxy resonance at δ 4.04, while the ^{13}C NMR spectrum (Plate 38b) also indicated a single methoxy carbon resonance at δ 56.5 ppm to confirm the structure of the product to be the monomethylated analogue of baicalein. Placing of the methoxy group at C-7 was confirmed by comparing the NMR data of the product (**4.114**) with chemical shift values reported by Shoja, M.[38] for the same compound. Although the monomethoxy derivative proved to be the main product, it was accompanied by 6,7-dimethoxy-5-hydroxy analogue (**4.115**) albeit in low yield (10%). The ^{1}H NMR spectrum of (**4.115**) (Plate 39a) displayed two methoxy groups at δ 4.00 and 3.95 ppm confirming the structure of the product to (**4.115**).

After obtaining the wanted 5,6-dihydroxy-7-methoxyflavone (**4.114**), the remaining free hydroxy groups were to be benzylated, since this protecting group would be prone to removal by a variety of methods, like hydrogenolysis and acid-catalyzed hydrolysis.[39,40] Subsequent benzylation of 5,6-dihydroxy-7-methoxyflavone (**4.114**)[38] with benzyl bromide and K_2CO_3 at 60 ^{o}C yielded the desired dibenzylated product (**4.111**) (^{1}H NMR plate 40a) in 37% yield, before (Scheme 33) degradation with 18 M *aq*. KOH in refluxing pyridine - diethylene glycol gave the acetophenone (**4.116**) in the unacceptable yield of only 4% and the corresponding carboxylic acid as side product.[26,41] The ^{1}H and ^{13}C NMR spectra (Plates 41a and b, respectively) of the acetophenone (**4.116**) confirmed the presence of an acyl group at δ 2.59 (3H, s) and δ 32.30 respectively, while also reflecting the two benzyloxy [δ_H 7.43 – 7.35 (10H, m, 2 x $OCH_2\underline{Ph}$) and δ_H 5.21 and 4.96 (each 2H, each s)] and 7-methoxy [δ 3.89 (3H, s)] entities.

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38 Shoja, M. *Acta Cryst*. **1994**, C50, 771.

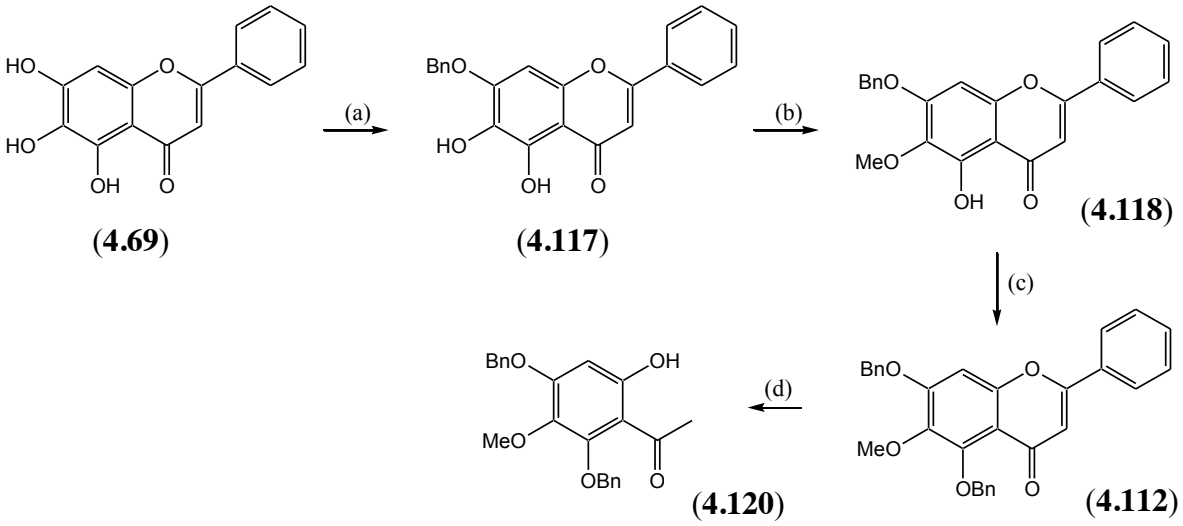
39 Büchi, G.; Weinreb, S.M. *J*. *Am*. *Chem*. *Soc*. **1971**, *93*, 746.

40 Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. *J*. *Org*. *Chem*. **1978**, *43*, 4194.

41 Hauteville, M.; Chadenson, M.; Chopin, *J*. *Bull*. *Soc*. *Chim*. *Fr*. **1979**, *II*, 125.

4.4.2.2 Preparation of 2,4-dibenzyloxy-6-hydroxy-3-methoxyacetophenone (4.120)

Preparation of acetophenone (**4.120**) required selective benzylation of the 7-hydroxy group of baicalein, followed by selective methylation of the 6-hydroxy function and subsequent benzylation of the 5-hydroxy entity (Scheme 34).



Scheme 34. Preparation of acetophenone (**4.120**). Reagents: (a) BnBr, NaH, -40 ^{o}C, 37% yield; (b) MeI, Cs_2CO_3, 0 ^{o}C, 21% yield; (c) BnBr, Cs_2CO_3, 60 ^{o}C, 30% yield; (d) 18 M *aq*. KOH, diethylene glycol, pyridine, reflux, 64% yield.

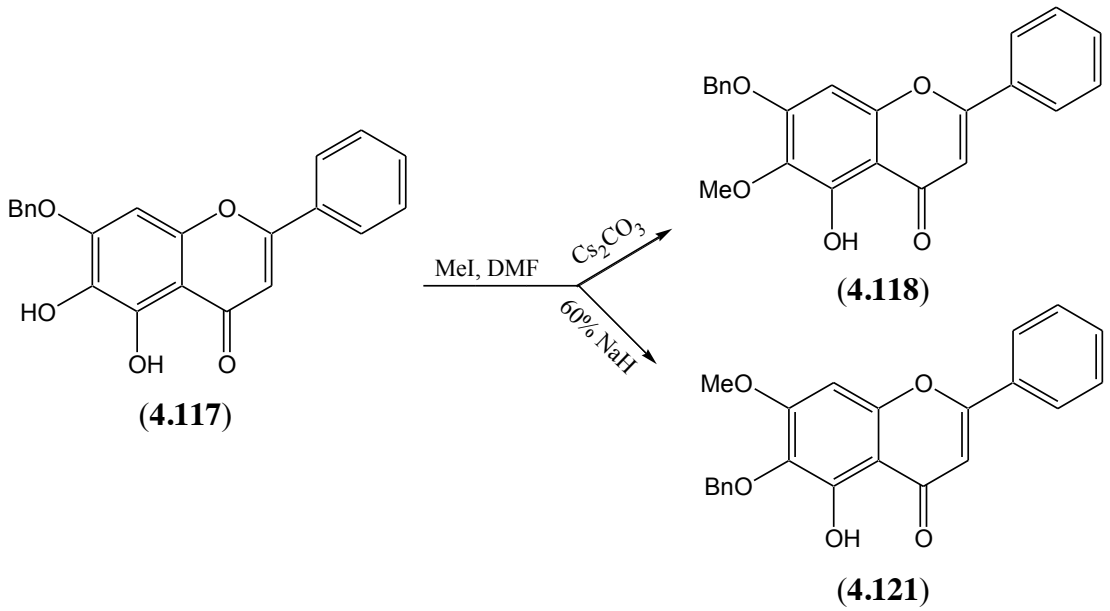
In order to induce selectivity towards the benzylation of only the most acidic 7-hydroxy function, baicalein (**4.69**) was treating with NaH at -40 ^{o}C followed benzyl bromide to give the 7-benzyloxy-5,6-dihydroxyflavone (**4.117**), albeit in only 37% yield. The ^{1}H NMR spectrum (Plate 43a) of (**4.117**) displayed a benzyloxy methylene group at δ 5.28 (2H, s), while the ^{13}C NMR spectrum (Plate 43b) confirmed the presence of the benzyloxy function with a resonance at δ 78.10. The structure the product was finally confirmed as (**4.117**) by single crystal X-ray crystallography.[42]

With the benzyloxy derivative (**4.117**) in hand, attention was turned towards selectively methylating the 6-hydroxy function. Reacting the 7-*O*-benzylbaicalein (**4.117**) with MeI and Cs_2CO_3, however, resulted in the formation of the desired 7-benzyloxy-5-hydroxy-6-methoxyflavone (**4.118**) in only 21% yield, with the fully methylated analogue (**4.119**) being the major product (42%) (Scheme 35). The ^{1}H and ^{13}C NMR spectra (Plate 44a and b respectively)

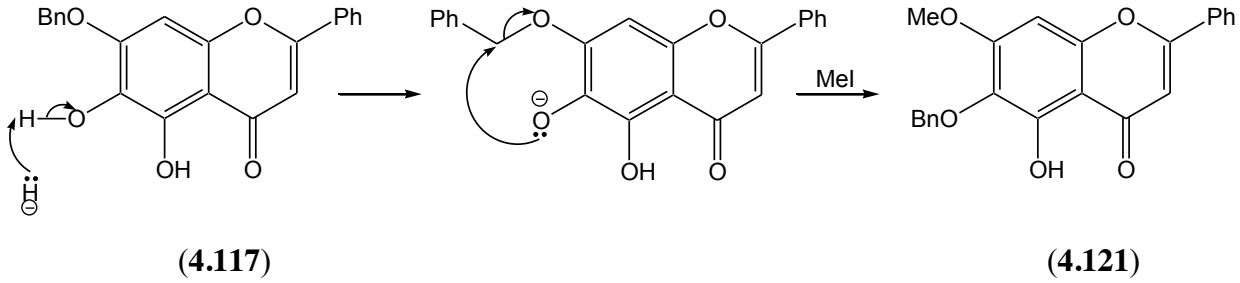
42 Kuo, C.-M.; Hill, T.N.; Bezuidenhoudt, B.C.B. *Z. Kristallogr. NCS*, ***2015***, *230*, 193.

of (**4.118**) confirmed the introduction of only one methoxy group with resonances at δ_H 3.97 (3H, s) and δ_C 60.9 respectivey, while the ^{1}H NMR spectrum (Plate 45a) of (**4.119**) displayed two methoxy resonances at δ 4.02 and 3.94 (each 3H, each s); thus confirming the side-product to be (**4.119**).

In order to improve the yield of the wanted monomethylated product and avoid over methylation, it was decided to use a different base, so the reaction was repeated with NaH. While a monomethylated product was again obtained [δ 3.93 (3H, s)] in 13% yield, it was clear from a comparison of the ^{1}H NMR spectra of the two compounds (plates 44a and 46a) that a different compound to the one isolated when Cs_2CO_3 was used, was formed. Close inspection of the ^{1}H NMR spectrum (Plate 46a) of this monomethylated product (**4.121**) revealed the chemical shift of H-8 (δ 6.55) to be different to that of the same proton of (**4.118**) (δ 6.62), while a a small but significant difference in the chemical shifts of the methoxy [δ 3.97 for (**4.118**) *vs* δ 3.93 for (**4.121**)] and benzyloxy protons [δ 5.27 for (**4.118**) *vs* δ 5.15 for (**4.121**)] were also observed. The differences in chemical shift of the benzyloxy and methoxy groups and C-8 proton pointed towards the two products being isomers, so the possibility of the methoxy group to be at position 5 and not 6 as expected, was considered as explanation for the two different compounds with the same substitution pattern. The chemical shift of the methoxy protons (δ 3.93), however, also did not resemble that of the 5-methoxy entity in the 5,6-dimethoxy analogue (**4.119**) (δ 4.02) obtained during the previous reaction (*vide supra*) or that of the 6,7-dibenzyloxy-5-methoxyflavone (**4.113**) (δ 4.05) (*cf* paragraph 4.4.2.3). In an effort to unambiguously determine the position of the additional methoxy group, an NMR NOESY experiment (Plate 46c) showed a strong correlation between the methoxy group (at δ 3.93) and H-8 (at δ 6.55); thus confirming the benzyloxy group to be at position 6 and the methoxy entity to be at position 7. Structure (**4.121**) could therefore be assigned to the product form the methylation reaction involving NaH as base (Scheme 35). The formation of (**4.121**), where the positions of the methoxy and benzyloxy groups are inverted, is probably explicable in term of an unusual base catalysed migration of the benzyloxy group before methylation as indicated in Scheme 36. The driving force behind this migration might be found in the relative stability of the 6- and 7-phenolates where the latter be more stable than its 6-counterpart due to the electron-withdrawing effect of the carbonyl group in the *para*-position.



Scheme 35. Methylation of 7-O-benzylbaicalein with Cs_2CO_3 and NaH as bases.



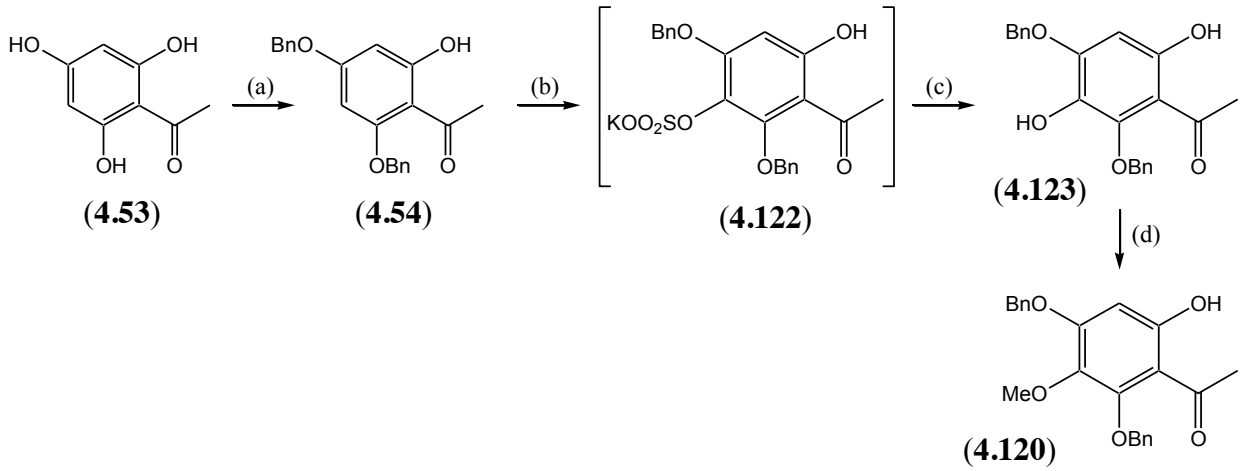
(**4.117**) (**4.121**)

Scheme 36. Possible mechanism for migration of the benzyl group during methylation with NaH.

Althought the yield of the desired 7-benzyloxy-5-hydroxy-6-methoxyflavone (**4.118**) from the Cs_2CO_3 reaction was not great, it was decided to nevertheless continue with the benzylation of the 5-hydroxy function, so the reactant (**4.118**) was treated again with benzyl bromide and Cs_2CO_3 at 60 ^oC and the fully benzylated product (**4.112**) obtained in a disappointing yield of only 30% (Scheme 34). The ^1H and ^{13}C NMR spectra (Plates 47a and b) of the product (**4.112**) proved it to be the 5,7-dibenzyloxy-6-methoxyflavone. Degradation of the flavone as before (18 M *aq*. KOH, pyridine, diethylene glycol, reflux) yielded the wanted acetophenone (**4.120**) in 64% yield. The ^1H and ^{13}C NMR spectra (Plate 48a and b) of (**4.120**) confirmed the structure to be the acetophenone by displaying the acyl group resonances at δ_H 2.59 (3H, s) and δ_C 32.30.

Since both benzylation steps as well as the methylation reaction gave unacceptable low yields (37, 30 and 21% respectively) of the protected flavone and thus the final acetophenone,

alternative methods for the preparation of the desired appropriately protected acetophenone (**4.120**) were considered. Although the Elbs oxidation has been reported for the first time as far back as 1893, some recent applications[43,44] of this method for introducing a hydroxy function into a phenol looked promising, so this potassium persulfate based protocol was persued in order to prepare the wanted tetraoxygenated acetophenone (**4.120**) (Scheme 37).



(**4.53**) (**4.54**) (**4.122**) (**4.123**) (**4.120**)

Scheme 37. Elbs persulfate oxidation for the preparation of tetraoxygenated acetophenone (**4.120**). Reagents: (a) BnCl, K_2CO_3, DMF, reflux, 53% yield; (b) $K_2S_2O_8$, pyridine, 10% NaOH/H_2O; (c) HCl, 5% yield; (d) MeI, Cs_2CO_3, DMF, -10 ^oC, 21% yield.

Benzylation of phloroacetophenone (**4.53**) (BnCl, K_2CO_3, DMF, reflux) gave the 4,6-dibenzyloxy-2-hydroxyacetophenone (**4.54**)[45] (Plate 11a) in 53% yield, which was subsequently subjected to the Elbs persulfate oxidation conditions ($K_2S_2O_8$, pyridine, 10% NaOH/H_2O then HCl) in order to introduce a 5-hydroxy function into the aromatic nucleus. Although the wanted 2,4-dibenzyloxy-3,6-dihydroxyacetophenone (**4.123**) was obtained from the reaction, the yield once again proved to be very poor (5%). The ^{1}H NMR spectrum (Plate 49a) of (**4.123**) displayed an aromatic singlet at δ 6.38 (1H), thus confirming the tetraoxygenated nature of the acetophenone, while the presence of the acyl function and benzyloxy groups were evident form singulets at δ 2.61 (3H), and δ 5.17 (2H) and 5.20 (3H), respectively. The poor yield obtained

43 Sethna, S.M. *The Institute of Science* **1951**, 91.

44 Kavvadias, D.; Sand, P.; Youdim, K.A.; Qaiser, M.Z.; Rice-Evans, C.; Baur, R.; Sigel, E.; Rausch, W-D; Riederer, P.; Schreier, P. *Br. J. Pharmacol*. **2004**, *142*, 811.

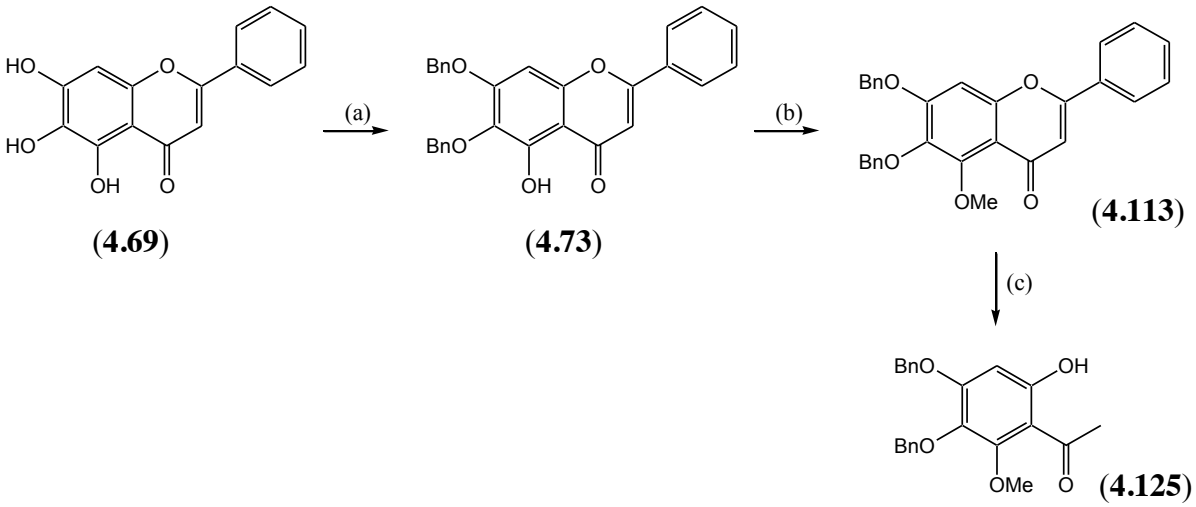
45 Smith, K.A., Structure and synthesis of phloroglucinol derivatives from *Hypericum roeperianum*, MSc Thesis, University of KwaZulu-Natal Pietermaritzburg, **2010**, page 86.

during the oxidation reaction is probably explicable in terms of the tendency of the *p*-dihydroxy entity to be oxidized to the quinine under the prevailing oxidizing conditions.

Selective methylation (MeI, Cs_2CO_3, DMF, -10 ^oC) finally gave the 4,6-dibenzyloxy-2-hydroxy-5-methyoxyacetophenone (**4.120**) in 21% yield, which was accompanied by 11% of the fully methylated analogue (**4.124**). The ^1H and ^{13}C NMR spectra of this monomethylated product (**4.120**) were identical to those obtained for the same acetophenone prepared by degradation of baicalein (**4.69**), while the dimethylated compound (**4.124**) was characterised by two methoxy resonances (δ 3.88 and 3.74) in the ^1H NMR spectrum (Plate 50a).

4.4.2.3 Preparation of 3,4-dibenzyloxy-6-hydroxy-2-methoxyacetophenone (4.125)

Although the direct synthesis of the presious acetophenone (**4.120**) proved to be possible by Elbs persulphate oxidation, the yield for the oxidation step was so low that it was decided to revert back to the degradation methodology for preparing the outstanding acetophenone, despite it requiring an additional process step. Preparation of the last acetophenone, i.e. the 5-methoxy substituted analogue, could be achieved through selective benzylation of the 6- and 7-hydroxy groups followed by methylation of the 5-hydroxy function of baicalein (Scheme 38).



(**4.69**) (**4.73**) (**4.113**) (**4.125**)

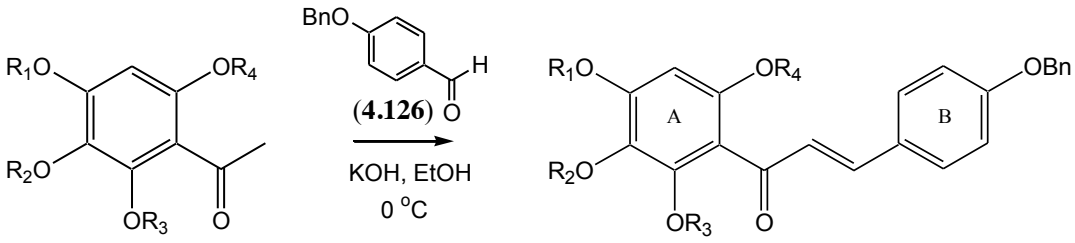
Scheme 38. Preparation of acetophenone (**4.125**). Reagents: (a) BnBr, Cs_2CO_3, DMF, 0 ^oC, 68% yield; (b) MeI, Cs_2CO_3, DMF, 60 ^oC, 89% yield; (c) 18 M *aq*. KOH, diethylene glycol, pyridine, reflux, 36% yield.

Baicalein (**4.69**) was therefore benzylated (BnBr, Cs_2CO_3, DMF, 0 ^oC) to give the wanted 6,7-dibenzyloxy-5-hydroxyflavone (**4.73**) in an acceptable yield of 68%. The ^1H and ^{13}C NMR spectra of (**4.73**) (Plate 22a and b) confirmed the presence of two benzyloxy groups by displaying two methylene resonances at δ_H 5.19 (2H, s) and 5.17 (2H, s) and the corresponding carbons at δ_C 74.9 and 71.0, respectively. Methylation (MeI, Cs_2CO_3, 60 ^oC) of the remaining OH-function proceeded smoothly and the 5-methoxyflavone (**4.113**) could be obtained in 89% yield; the structure of which was confirmed by a methoxy resonance at δ 4.05 (3H, s) in the ^1H NMR spectrum (Plate 51a). Treatment of the protected flavone (**4.113**) with NaOH in diethylene glycol-pyridine (18 M *aq*. KOH, diethylene glycol, pyridine, reflux) finally gave the desired acetophenone (**4.125**), albeit in only 36% yield. The ^1H as well as ^{13}C NMR spectra (Plates 52a and b) of (**4.125**) confirmed the structure of the product as 3,4-dibenzyloxy-6-hydroxy-2-methoxyacetophenone by displaying the appropriate functional group resonances [δ_H 5.13 and 4.94 (each 2H, each s, 2 x O$\underline{CH_2}C_6H_5$), 4.03 (3H, s, OMe) and 2.70 (3H, s, CO$\underline{CH_3}$) and δ_C 203.4 (CO), 75.5 ($\underline{CH_2}$Ph), 70.7 ($\underline{CH_2}$Ph), 61.3 (OMe) and 32.0 (CO$\underline{CH_3}$)] and residual aromatic proton [δ 6.35 (1H, s)].

4.4.3 Preparation of 4',5,6,7-tetraoxygenated homoisoflavanones (4.150), (4.151) and (4.152)

4.4.3.1 Preparation of pentaoxygenated chalcones and dihydrochalcones

With the suitably protected acetophenones in hand, attention was truned towards the aldol condensation reaction for assembling the pentaoxygenated chalcones (Table 4). Aldol condensation between the protected acetophenones (**4.116**, **4.120** and **4.125**) with *p*-benzyloxybenzaldehyde (**4.126**) (Scheme 39) [prepared by benzylation (BnCl, anhydrous K_2CO_3, acetonitrile, reflux) of *p*-hydroxybenzaldehyde] in EtOH at 0 ^oC with freshly powdered KOH yielded the chalcones (**4.127**) – (**4.129**) in 23 - 67% yields (Table 4).



Scheme 39. Aldol condensation between acetophenones and *p*-benzyloxybenzaldehyde.

Table 4. Pentaoxygenated chalcones prepared.

Aceto-phenone	**Chalcone**	**Substituents**				**Yield**	**Chemical shift (ppm)**		**^{1}H NMR**
		R_1	**R_2**	**R_3**	**R_4**	**(%)**	**H-α**	**H-β**	**Plate**
(4.116)	**(4.127)**	Me	Bn	Bn	H	67	δ 7.81	δ 7.90	53a
(4.120)	**(4.128)**	Bn	Me	Bn	H	34	δ 7.80	δ 7.89	54a
(4.125)	**(4.129)**	Bn	Bn	Me	H	23	δ 7.46	δ 7.87	55a

In order to prevent reduction to the allylic alcohol and subsequent cyclization to the flavene, as found during the attempted preparation of the naturally occurring homoisoflavanone (*cf* paragraph 4.3.1, Scheme 22) protection of the 2'-hydroxy function of the chalcone was required at this stage. Since the protecting group had to be removed again in the end for the construction of the homoisoflavanone C-ring to be possible, an easily removable protecting group[46] different to a benzyl entity was required. Treatment of the free phenolic chalcones (**4.127**), (**4.128**) and (**4.129**) with chloromethyl ethyl ether[47] and *aq*. NaOH in DCM containing the phase transfer catalyst, Adogen 464, led to the fully protected chalcones (**4.130**), (**4.131**) and (**4.132**) to be formed in 71 – 93% yield (Table 5). The structures of the fully protected chalcones were confirmed by ^{1}H and ^{13}C NMR spectroscopy (Plates 56 – 58 a and b, respectively) where resonances for the α- β-protons as well as EOM group were clearly visible.

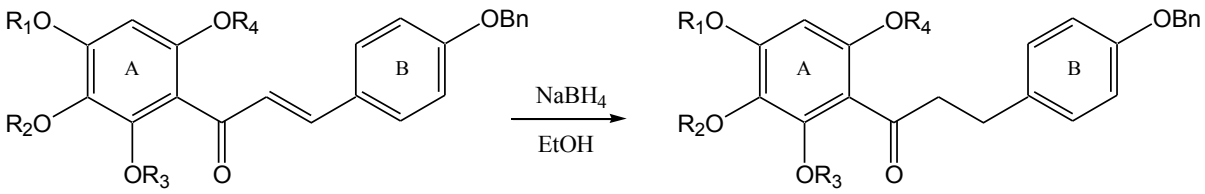
46 Auerbach, J.; Weinreb, S.M. *J. Chem. Soc., Chem. Commun*. **1974**, 298.

47 Markey, M.D. *PhD*. dissertation, The Graduate School of Arts and Science, Boston College, **2008**, 119.

Table 5. Preparation of pentaoxygenated ethoxymethylated chalcones.

EOM-chalcone	Substituents				Yield	Chemical shift (ppm)		^{1}H NMR
	R_1	R_2	R_3	R_4	(%)	H-α	H-β	Plate
(4.130)	Me	Bn	Bn	EOM	77	δ 6.85	δ 7.45	56a
(4.131)	Bn	Me	Bn	EOM	71	δ 6.84	δ 7.40	57a
(4.132)	Bn	Bn	Me	EOM	93	δ 6.88	δ 7.49	58a

Since $NaBH_4$ reduction worked well during the preparation of the perceived natural homoisoflavanone (**4.5**) this reagent was also used for the reduction of the protected chalcones (**4.130**) and (**4.132**) to give the dihydrochalcones (**4.133**) and (**4.134**) in 29 and 41% yields, respectively (Scheme 40 and Table 6).



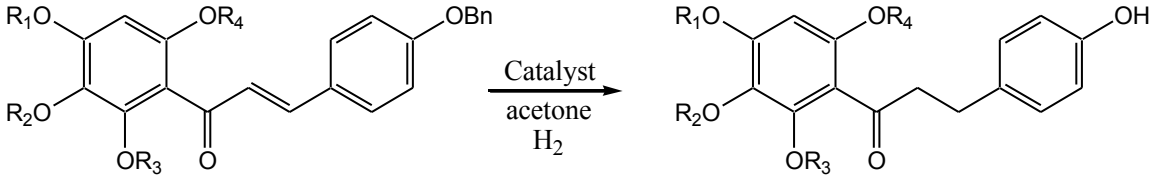
Scheme 40. Preparation of dihydrochalcones by $NaBH_4$ reduction of the respective chalcones.

Table 6. Dihydrochalcones prepared by $NaBH_4$.

Dihydro-chalcone	Substituents				Yield	Chemical shift (ppm)		^{1}H NMR
	R_1	R_2	R_3	R_4	(%)	α-CH_2	β-CH_2	Plate
(4.133)	Me	Bn	Bn	EOM	29	δ 3.00	δ 2.92	59a
(4.134)	Bn	Bn	Me	EOM	41	δ 3.07	δ 2.98	60a
(4.136)	Bn	Bn	Bn	Me	30	δ 3.03	δ 2.94	61a

Due to the fact that the yields of the $NaBH_4$ reductions were not that great (29 - 41%)) and the benzyl protecting groups would have to be removed at some point during the preparation of the homoisoflavanones anyway, it was decided at point of the project to also evaluate the reduction of the double bond of the chalcones by catalytic hydrogenation. Catalytic hydrogenation of the benzyloxy protected chalcone (**4.131**) and 4,4',5',6'-tetrabenzyloxy-2'-methoxydihydrochalcone (**4.136**) over 5% Pd on carbon in acetone led to the removal of the benzyl group protecting as

well as saturation of the double bond giving the 6'-protected free phenolic dihydrochalcones (**4.135**) and (**4.137**) in 52 and 35% yield, respectively (Scheme 41, Table 7). When the catalyst was changed to $Pd(OH)_2$, some improvement in the yields (52 and 35%) were obtained for the 2- and 3-methoxychalcone analogues analogues (**4.132**) and (**4.131**) respectively, but for the 4-methoxy dihydrochalcone (**4.133**) gave an even worse yield (7%) than what was found with the $NaBH_4$ reduction reaction (Table 7).



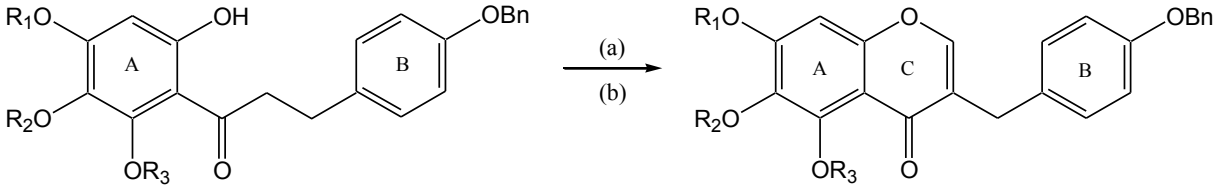
Scheme 41. Catalytic hydrogenation of chalcones (**4.131**), (**4.136**) and (**4.133**) over 5% Pd on carbon or $Pd(OH)_2$.

Table 7. Dihydrochalcones prepared by 5% Pd on carbon and $Pd(OH)_2$

Dihydro-chalcone	Substituents				Yield	Chemical shift (ppm)		Catalyst	^{1}H NMR
	R_1	R_2	R_3	R_4	(%)	α-CH_2	β-CH_2		Plate
(4.135)	H	Me	H	EOM	52	δ 2.96	δ 3.32	5 % Pd/C	62a
(4.137)	H	H	H	Me	35	δ 3.27	δ 2.87	5 % Pd/C	63a
(4.138)	Me	H	H	EOM	7	δ 2.66	δ 2.62	$Pd(OH)_2$	64a

4.4.3.2 Cyclization of dihydrochalcones

Acidification (3 M HCl in MeOH solution) of 6'-ethoxymethoxydihydrochalcones (**4.130**, **4.131** and **4.132**) followed by the Vilsmeier[30] formylation afforded the homoisoflavone derivatives (**4.142**, **4.143** and **4.144**) for the synthesis of 5,6,7-trioxygenated mono-methoxyhomoisoflavanones (Scheme 42, Table 8).



(**4.139**) R_1 = Me, R_2 = R_3 = Bn

(**4.140**) R_1 = R_3 = Bn, R_2 = Me

(**4.141**) R_1 = R_2 = Bn, R_3 = Me

(**4.142**) R_1 = Me, R_2 = R_3 = Bn

(**4.143**) R_1 = R_3 = Bn, R_2 = Me

(**4.144**) R_1 = R_2 = Bn, R_3 = Me

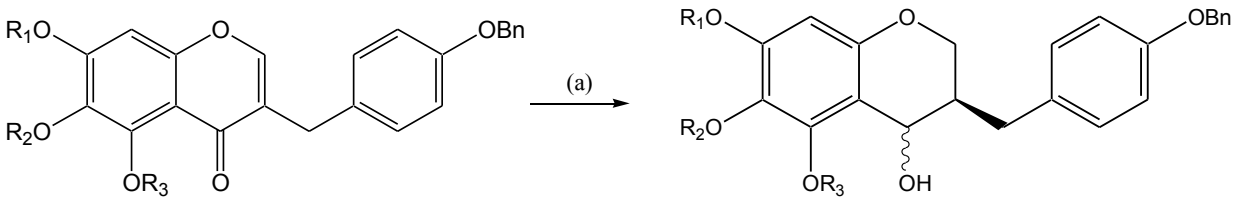
Scheme 42. Cyclization of dihydrochalcone for the synthesis of 5,6,7-trioxygenated mono-methoxyhomoisoflavanones. Reagents: (a) 3 M HCl, MeOH solution; (b) Vilsmeier reagent as prepared before.

Table 8. Preparation of homoisoflavone derivatives.

Homoisoflavone	**Substituents**			**Yield**	**Chemical shift (ppm)**		**^{1}H NMR**
	R_1	**R_2**	**R_3**	**(%)**	**H-2**	**H-9**	**Plate**
(4.142)	**Me**	Bn	Bn	76	δ 7.42	δ 3.78	68a
(4.143)	Bn	**Me**	Bn	65	δ 7.32	δ 3.75	69a
(4.144)	Bn	Bn	**Me**	46	δ 7.45	δ 3.74	70a

4.4.3.3 $NaBH_4$ reduction of homoisoflavones followed by IBX oxidation

Treatment of the homoisoflavones (**4.142** and **4.144**) with $NaBH_4$ resulted in the *cis*- and *trans*-homoisoflavan-4-ols of (**4.145** and **4.146**) to be formed in 61-82% yields (Scheme 43). The NMR data of the *cis*- and *trans*-homoisoflavans are given in Table 9.



(**4.142**) R_1 = Me, R_2 = R_3 = Bn

(**4.144**) R_1 = R_2 = Bn, R_3 = Me

(**4.145**) *cis* and *trans*-homoisoflavan-4-ols

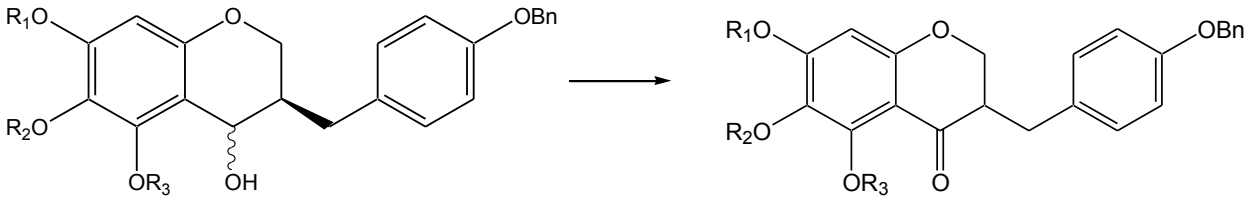
(**4.146**) *cis* and *trans*-homoisoflavan-4-ols

Scheme 43. Reduction of homoisoflavone (**4.142** and **4.144**). Reagents: (a) $NaBH_4$, EtOH, THF.

Table 9. The NMR data of the *cis*- and *trans*-homoisoflavan-4-ols.

Homo-isoflavan	*Cis*-isomer			*Trans*-isomer		
	Chemical shift (ppm)	Yield (%)	^{1}H NMR Plate	Chemical shift (ppm)	Yield (%)	^{1}H NMR Plate
(4.145)	δ 4.01-3.98 (m, 2-CH_2) δ 2.07-2.02 (m, H-3) δ 4.52 (d, *J* = 3.2 Hz, H-4) δ 2.82 [dd, *J* = 13.6 and 8.4 Hz, H-9(a)], 2.58 [dd, *J* = 13.6 and 7.2 Hz, H-9(b)]	44	71a	δ 3.90-3.84 (m, 2-CH_2) δ 2.11-2.07 (m, H-3) δ 4.07 (dd, *J* = 10.9 and 2.0 Hz, H-4) δ 2.40 [dd, *J* = 6.3 and 14.0 Hz, H-9(a)], 2.34 [dd, *J* = 9.8 and 13.6 Hz, H-9(b)]	17	72a
(4.146)	δ 4.02 (d, *J* = 9 Hz, 2-CH_2) δ 2.19-2.15 (m, H-3) δ 4.74 (d, *J* = 3.3 Hz, H-4) δ 2.93 [dd, *J* = 13.9 and 7.8 Hz, H-9(a)] 2.65 [dd, *J* = 13.9 and 7.8 Hz, H-9(b)]	48	73a	δ 4.13 [dd, *J* = 10.9 and 2.3 Hz, H-2(a)], 3.95 [dd, *J* = 10.9 and 2.3 Hz, H-2(b)] δ 2.22-2.18 (m, H-3) δ 4.64 (d, *J* = 2.0 Hz, H-4) δ 2.65-2.59 [m, H-9(a)], 2.51 [dd, *J* = 13.9 and 9.3 Hz, H-9(b)]	34	74a

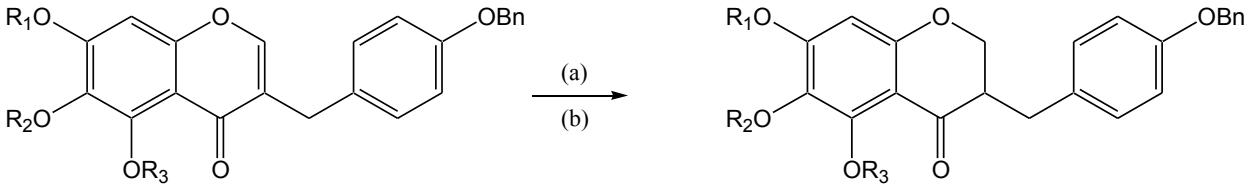
IBX oxidation of the homoisoflavan-4-ols (**4.145**) and (**4.146**) led to the corresponding homoisoflavanones (**4.147**) and (**4.148**) in 73 and 46% yields (Scheme 44, Table 10). In an effort to possibly improve on the yields, one of the homoisoflavone derivatives (**4.143**) were reduced and oxidized with IBX to the corresponding homoisoflavanone (**4.149**) without isolation of the homoisoflavan-4-ol intermediate (Scheme 45) (Table 10). While the desired homoisoflavanone (**4.149**) was still obtained in only 26% overall yield, the 'one-pot' process had the advantage of eliminating one separation step.



(**4.145**) R_1 = Me, R_2 = R_3 = Bn (**4.147**) R_1 = Me, R_2 = R_3 = Bn

(**4.146**) R_1 = R_2 = Bn, R_3 = Me (**4.148**) R_1 = R_2 = Bn, R_3 = Me

Scheme 44. IBX oxidation of *cis*- and *trans*-homoisoflavan-4-ols (**4.145**, **4.146**). Reagents: IBX, acetonitrile.



(**4.143**) R_1 = R_3 = Bn, R_2 = Me (**4.149**) R_1 = R_3 = Bn, R_2 = Me

Scheme 45. Reduction - Oxidation of homoisoflavone (**4.143**). Reagents: (a) $NaBH_4$, EtOH, THF; (b) IBX, acetonitrile.

Table 10. ^{1}H NMR data of homoisoflavanones (**4.147**, **4.148** and **4.149**).

Homoiso-flavanone	**Substituents**			**Yield**	**Chemical shift (ppm)**			**^{1}H NMR**
	R_1	**R_2**	**R_3**	**(%)**	**H-2**	**H-3**	**H-9**	**Plate**
(4.147)	**Me**	Bn	Bn	73	δ 4.30 [(dd, *J* = 11.4 and 3.5 Hz, H-2(a)] δ 4.14 [(dd, *J* = 11.1 and 6.9 Hz, H-2(b)]	δ 2.78-2.72 (m)	δ 3.21 [(dd, *J* = 13.6 and 3.4 Hz, H-9(a)] δ 2.67 [(dd, *J* = 11.4 and 7.3 Hz, H-9(b)]	75a
(4.148)	Bn	Bn	**Me**	46	δ 4.30 [(dd, *J* = 11.3 and 4.1 Hz, H-2(a)] δ 4.12 [(dd, *J* = 11.4 and 7.6 Hz, H-2(b)]	δ 2.80-2.75 (m)	δ 3.23 [(dd, *J* = 13.9 and 4.2 Hz, H-9(a)] δ 2.68 [(dd, *J* = 13.9 and 10.7 Hz, H-9(b)]	76a

(4.149)	Bn	**Me**	Bn	26	δ 4.27 [(dd, *J* = 11.4 and 4.0 Hz, H-2(a)] δ 4.10 [(dd, *J* = 11.4 and 6.9 Hz, H-2(b)]	δ 2.75-2.71 (m)	δ 3.19 [(dd, *J* = 13.8 and 4.0 Hz, H-9(a)] δ 2.64 [(dd, *J* = 11.4 and 13.8 Hz, H-9(b)]	77a

4.4.3.4 Debenzylation and acetylation of homoisoflavanones (4.147, 4.148, and 4.149)

Since 5% Pd/C represents one of the standard catalysts for removal of benzyl groups, this catalyst was used to debenzylate compounds (**4.147**) and (**4.148**) leading to the monomethoxy products (**4.150**) and (**4.151**), albeit in only 18 and 25% yields, respectively. It was therefore decided to utilize $Pd(OH)_2$ in acetone as alternative catalyst for hydrogenation of the remaining benzylated compound (**4.149**). In this instance a substantial improvement in yield was found and the monomethoxylated product (**4.152**) was recovered in of 45%. The ^1H NMR spectra (Plates 78a, 79a, and 80a) of the monomethoxyhomoisoflavanones (**4.150**, **4.151**, and **4.152**) confirmed the absence of the benzyl groups by displaying no methylene resonances in the δ 4.80 to 5.20 ppm region.

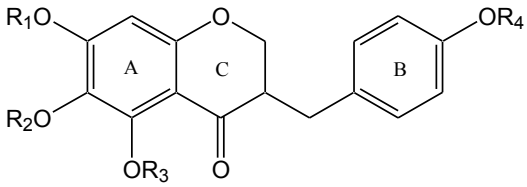
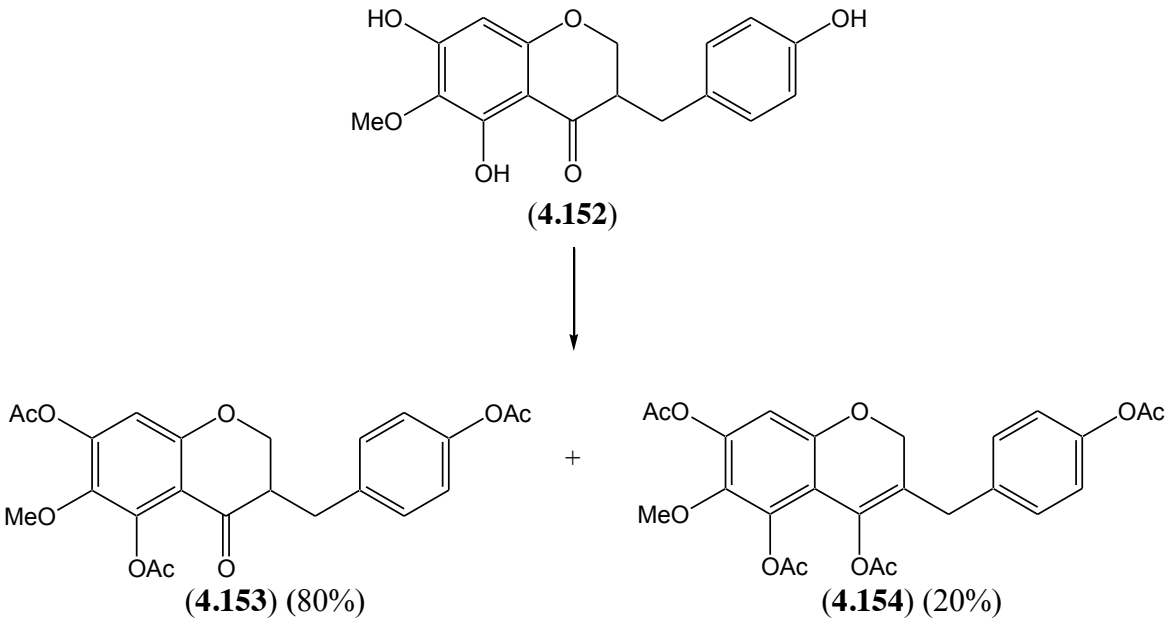


Figure 5. Homoisoflavanones.

Table 11. Catalytic [5% Pd/C or $Pd(OH)_2$] debenzylation of homoisoflavanones (**4.147**, **4.148**, and **4.149**).

Homoisoflavanone		**Yield**
Benzylated	**Debenzylated**	**%**
(4.147) R_1 = Me, R_2 = R_3 = R_4 = Bn	**(4.150)** R_1 = Me, R_2 = R_3 = R_4 = H	18
(4.148) R_1 = R_2 = R_4 = Bn, R_3 = Me	**(4.151)** R_1 = R_2 = R_4 = H, R_3 = Me	25
(4.149) R_1 = R_3 = R_4 = Bn, R_2 = Me	**(4.152)** R_1 = R_3 = R_4 = H, R_2 = Me	45

Acetylation of compound (**4.152**) yielded the peracetylated analogues (**4.153**) and (**4.154**) in quantitative yield and a 4 : 1 ratio (Scheme 46). The structure of the peracetylated compound (**4.153**) were confirmed by ^{1}H NMR spectroscopy (Table 12) where the spectrum (Plate 81a) of the product displayed the methyl group {δ 3.23 [1H, dd, *J* = 14.8 and 3.6 Hz, H-9(a)], 2.67 [1H, dd, *J* = 14.8 and 10.7 Hz, H-9(b)]} and three acetoxy functions at δ 2.46-2.32. After acetylation, it was, however, found that the desired product (**4.153**) is accompanied by a side-product, which was formed in 20% yield. Careful analysis of the ^{1}H NMR spectrum (Plate 82a) of the side-product revealed an additional acetoxy resonance to be present, while the two methine resonances (H-3 and H-4) were absent and a down-field shift in the appearance of the two methylene groups were observed [δ 4.59 and 3.45 vs ca 4.3 – 4.1 and 3.2 – 2.6 in the homoisoflavanones (*cf* Table 10)]. The second product (**4.154**) was therefore identified as the enol acetate of (**4.153**), i,e. 3-(4-acetoxybenzyl)-4,5,7-triacetoxy-6-methoxy homoisoflav-3-ene**.**



Scheme 46. Acetylation of homoisoflavanone (**4.152**). Reagents: acetic anhydride, pyridine (ratio 4:1), 60 °C, overnight, 100% yield.

Table 12. ^{1}H NMR data of the synthetic free phenolic (**4.152**), (**4.151**) and (**4.150**), the peracetylated monomethoxyhomoisoflavanone (**4.153**) and the peracetylated monomethoxy natural product (**4.5**).

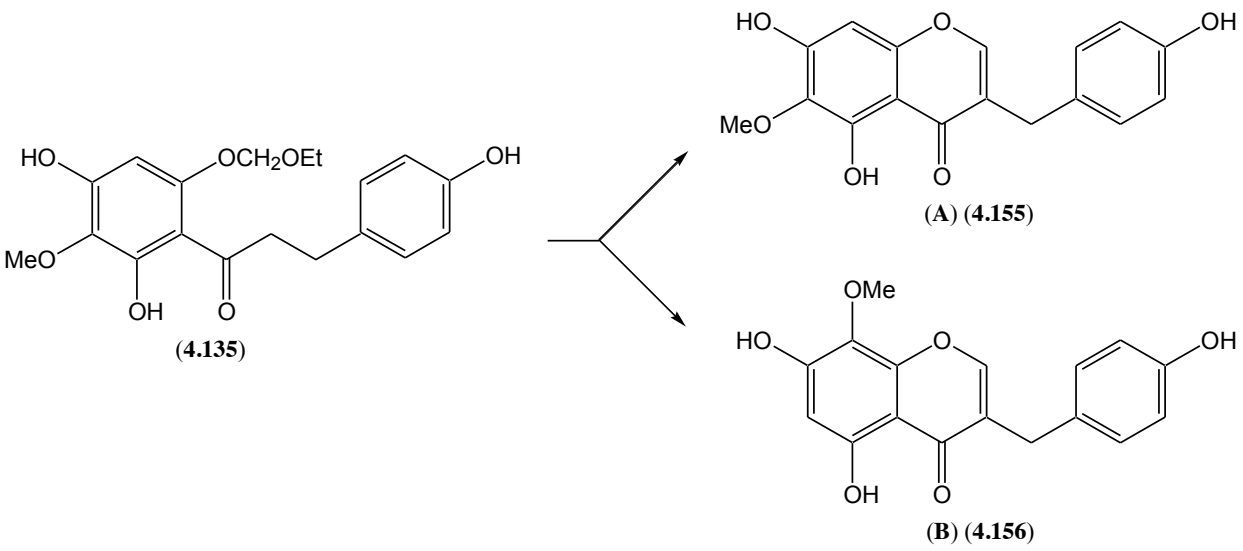
Proton	Natural peracetate (4.5)	6-Methoxy peracetate (4.153)	6-Methoxy-trihydroxy (4.152)	5-Methoxy-trihydroxy (4.151)	7-Methoxy-trihydroxy (4.150)
H-6/8	6.49 (s)	6.69(s)	5.96 (s)	6.23 (s)	6.15 (s)
H-2',6'	7.23 (d, *J* = 8 Hz)	7.22 (d, *J* = 8.4 Hz)	7.13 (d, *J* = 8.4 Hz)	7.21 (d, *J* = 8.6 Hz)	7.12 (d, *J* = 8.5 Hz)
H-3',5'	7.06 (d, *J* = 8 Hz)	7.06 (d, *J* = 8.4 Hz)	6.81 (d, *J* = 8.4 Hz)	6.98 (d, *J* = 8.6 Hz)	6.81 (d, *J* = 8.5 Hz)
H-2(a)	4.47 (dd, *J* = 12 and 4 Hz)	4.34 (dd, *J* = 11.5 and 4.1 Hz)	4.32 (dd, *J* = 11.4 and 4.5 Hz)	4.27 (dd, *J* = 11.4 and 4.3 Hz)	4.32 (dd, *J* = 11.4 and 4.4 Hz)
H-2(b)	4.27 (dd, *J* = 12 and 9 Hz)	4.16 (dd, *J* = 11.5 and 8.2 Hz)	4.13 (dd, *J* = 11.4 and 8.2 Hz)	4.06 (dd, *J* = 11.4 and 8.3 Hz)	4.13 (dd, *J* = 11.3 and 8.3 Hz)
H-3	2.92-2.85 (m)	2.85-2.80 (m)	2.96-2.91 (m)	2.76-2.72 (m)	2.95-2.91 (m)
H-9(a)	3.28 (dd, *J* = 14 and 4 Hz)	3.23 (dd, *J* = 14.8 and 3.6 Hz)	3.14 (dd, *J* = 14.1 and 4.7 Hz)	3.13 (dd, *J* = 14.1 and 4.7 Hz)	3.14 (dd, *J* = 14.0 and 4.7 Hz)
H-9(b)	2.66 (dd, *J* = 14 and 11 Hz)	2.67 (dd, *J* = 14.8 and 10.7 Hz)	2.70 (dd, *J* = 14.1 and 10.1 Hz)	2.71 (dd, *J* = 14.1 and 10.1 Hz)	2.68 (dd, *J* = 14.0 and 10.1 Hz)
OAc	2.40 (s) 2.35 (s) 2.32 (s)	2.46 (s) 2.36 (s) 2.32 (s)	- - -	- - -	- - -
OMe	3.85 (s)	3.79 (s)	3.78	3.80	3.90

With the perceived peracetate of the isolated natural product (**4.153**) in hand, the chemical shift of the residual proton of the A-ring (H-8) was compared to that of the real isolated natural product (**4.5**). Sureprisingly a significant difference (δ 6.49 vs 6.69, Table 12) was, however, observed, so it could be concluded that the natural product in fact did not display the 5,7-diacetoxy-6-methoxy substitution pattern on the A-ring. Since no nOe from the methoxy group to an aromatic proton was observed, two other possibilities for the structure of the natural product, i.e. the 6,7-diacetoxy-5-methoxy - or the 5,7-diacetoxy-8-methoxy analogue could be considered for the structure of the natural product. Since the 6'-ethoxymethoxy-2',4,4'-trihydroxy-3'-methoxydihydrochalcone (**4.135**) (Table 7) was available due to its formation

during the catalytic hydrogenation of the chalcone equivalent (**4.131**) (Table 5) (*cf* paragraph 4.4.3.1), it was decided to utilize this starting material for the formation of the 4',5,7-triacetoxy-8-methoxyhomoisoflavanone and compare the chemical shift value of the residuel aromatic proton of this compound with that of the natural product.

4.5 Preparation of 4',5,7-triacetoxy-8-methoxyhomo-isoflavanone (4.160)

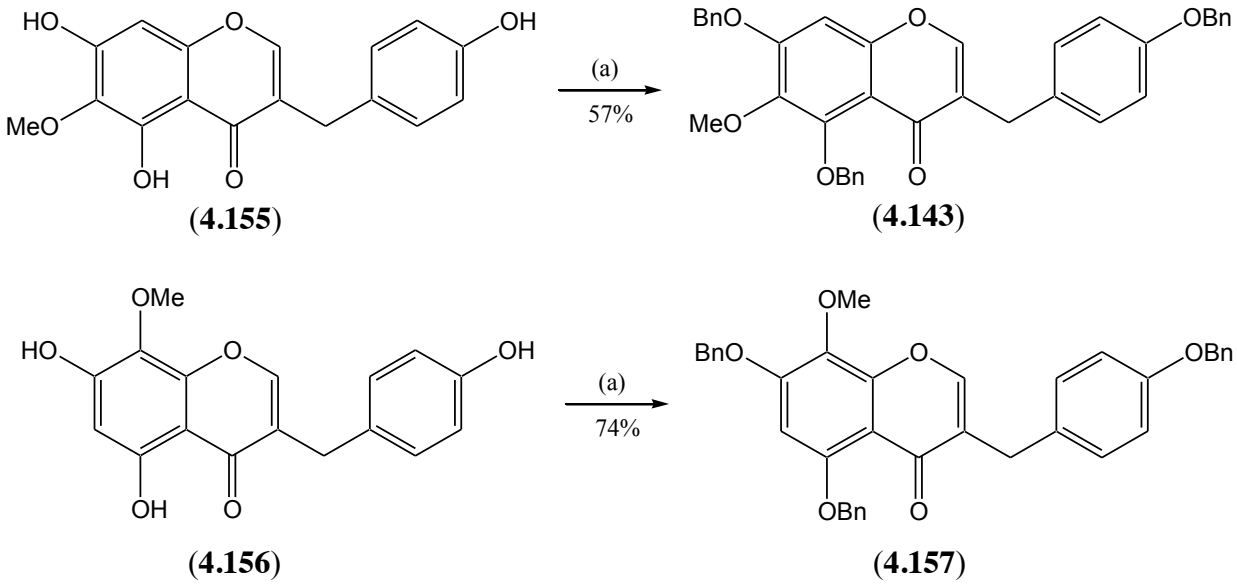
In order to synthesise one of the 'other' natural product possibilities, i.e. 4',5,7-triacetoxy-8-methoxyhomoisoflavanone, the 6'-ethoxymethoxy-3'-methoxy-2',4',4-trihydroxydihydrochalcone (**4.135**), formed during the Pd/C catalysed hydrogenation of the tribenzyloxychalcone analogue (**4.131**), was treated with the Vilsmeier reagent as before (*cf* paragraph 4.3.2). The reaction, however, led to the isolation of two products (**4.155** and **4.156**) with R_f values 0.47 [(2%), Plate 83a] and 0.39 [(36%), Plate 84a], respectively (Scheme 47).



Scheme 47. Vilsmeier formylation and cyclization of dihydrochalcone (**4.135**) during the synthesis of the 5,7,8-trioxygenated monomethoxyhomoisoflavanone (**4.159**). Reagents: Vilsmeier reagent as prepared before.

In order to distinguish between the two products, both were benzylated as before (*cf* paragraph 4.4.2.2) (Scheme 48). The ^{1}H NMR spectrum (Plate 83a) of the perbenzylated derivative of the 5,6,7-trioxygenated monomethoxyhomoisoflavone (**4.155**) proved to be identical to that of (**4.143**) prepared in paragraph 0, while the structure of the benzylated 5,7,8-trioxygenated monomethoxyhomoisoflavone analogue (**4.157**) (obtained in 74% yield) followed from its ^{1}H NMR spectrum (Plate 85a). The spectrum clearly displayed, apart from the expected aromatic resonances originating from the benzyl groups and the B-ring [δ 6.95 (2H, d, *J* = 8.6 Hz, H-3',5') and 7.23 (2H, d, *J* = 8.6 Hz, H-2',6')], three benzyloxy CH_2 groups at δ 5.17, 5.15 and 5.07 (each s) as well as a single methoxy signal (δ 3.88) and a benzylic methylene atδ 3.74. These signals were accompanied by a singlet at δ 6.47 (1H, H-6) in the aromatic region, while H-2 were hidded under the aromatic resonances originating from the benzyl groups.

The formation of compound (**4.155**) in low yield (2%) is probably explicable in terms of the acid labile EOM group not being stable enough to withstand the Lewis acid action during the Vilsmeier formylation and cyclization processes.



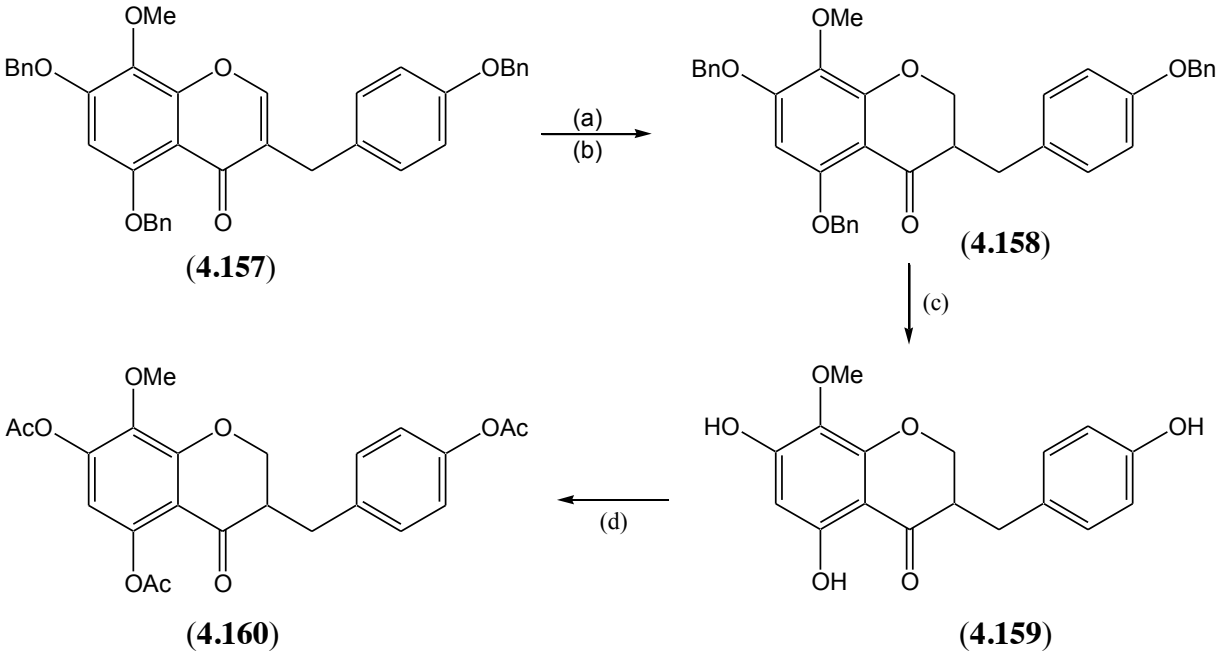
(**4.155**) (**4.143**)

(**4.156**) (**4.157**)

Scheme 48. Benzylation of homoisoflavones (**4.155**) and (**4.156**). Reagents: (a) BnBr, Cs_2CO_3, 60 ^oC, 57 and 74% yield.

The one-pot reduction – oxidiation of the benzylated homoisoflavone (**4.157**) with $NaBH_4$ followed by IBX oxidation subsequently gave the protected homoisoflavanone (**4.158**) in 21%

yield; the structure of which was confirmed by its ^{1}H NMR spectrum (Plate 86a) where the absence of the double bond was evident from the presence of a heterocyclic methine [δ 2.82-2.77 (m, H-3)] and methylene groups {δ 4.38 [dd, *J* = 11.4 and 4.1 Hz, H-2(a)] and 4.23 [dd, *J* = 11.4 and 7.4 Hz, H-2(b)]}. Finally, catalytic hydrogenation over $Pd(OH)_2$ afforded the free phenolic 8-methoxyhomoisoflavanone (**4.159**) in 50% yield, which was acetylated (33% yield) to compare its spectral data (Plate 88a) with that of the acetylated natural product (**4.5**) (Scheme 49).



Scheme 49. Reagents: (a) $NaBH_4$, EtOH, THF; (b) IBX, acetonitrile, 21%; (c) H_2, $Pd(OH)_2$, acetone, 50%; (d) acetic anhydride, pyridine, 60 ^oC, 33%.

As is evident from Table 13 the peracetylated monomethoxyhomoisoflavanone (**4.160**) proved to be identical to the acetylaed natural product peracetate (**4.5**). The natural product was therefore unambiguously identified as 5,7,4'-triacetoxy-8-methoxyhomoisoflavanone, which renders it a new natural product and only the second example of an 8-methoxyhomoisoflavanone isolated form a natural source.

Table 13. ^{1}H NMR data of the synthetic free phenolic (**4.159**) and peracetylated monomethoxy-homoisoflavanone (**4.160**) and the peracetylated monomethoxy natural product (**4.5**).

Proton	Natural peracetate (4.5)	8-Methoxy peracetate (4.160)	8-Methoxy-4',5,7-trihydroxyhomoisoflavanone (4.159)
H-6	6.49 (s)	6.49 (s)	5.99 (s)
H-2',6'	7.23 (d, *J* = 8 Hz)	7.23 (d, *J* = 8 Hz)	7.14 (d, *J* = 8.4 Hz)
H-3',5'	7.06 (d, *J* = 8 Hz)	7.06 (d, *J* = 8 Hz)	6.82 (d, *J* = 8.4 Hz)
H-2(a)	4.47 (dd, *J* = 12 and 4 Hz)	4.47 (dd, *J* = 12 and 4 Hz)	4.24 (dd, *J* = 11.4 and 4.4 Hz)
H-2(b)	4.27 (dd, *J* = 12 and 9 Hz)	4.27 (dd, *J* = 12 and 9 Hz)	4.20 (dd, *J* = 11.4 and 8.1 Hz)
H-3	2.92-2.85 (m)	2.92-2.85 (m)	2.98-2.93 (m)
H-9(a)	3.28 (dd, *J* = 14 and 4 Hz)	3.28 (dd, *J* = 14 and 4 Hz)	3.15 (dd, *J* = 14.1 and 4.9 Hz)
H-9(b)	2.66 (dd, *J* = 14 and 11 Hz)	2.66 (dd, *J* = 14 and 11 Hz)	2.72 (dd, *J* = 14.1 and 10 Hz)
OAc	2.40 (s) 2.35 (s) 2.32 (s)	2.40 (s) 2.35 (s) 2.32 (s)	- - -
OMe	3.85 (s)	3.85 (s)	3.73 (s)

4.6 Conclusions and future work

While the novel homoisoflavanone isolated from *Scilla natalensis* as the peracetate (**4.5**) has unambiguously been proven by synthesis to have the 5,7,4'-triacetoxy-8-methoxy structure during this investigation, it has also been pointed out that great care should be taken in the assignment of the structures of these compound by comparison of proton chemical shifts. This is especially true when a single methoxy group is situated on a trioxygenated A-ring as there might not be an nOe association between the methyl protons and any aromatic hydrogen. The situation may further be aggravated by the fact that natural products may be isolated as derivatives, like peracetates, of the naturally occurring free phenolic analogues due to separation difficulties.

Although only two of the possible 6 A-ring trioxygenated homoisoflavanones (*cf* paragraph 4.4.1) have been synthesised, it is envisaged that the remaining four compounds will also be prepared so the ^{1}H and ^{13}C NMR data of all these compounds both as free phenols and peracetates can be reported. This will be a valuable tool to assist researchers during the isolation

and structure elucidation of this class of natural product during future phytochemical investigations.

5 Conformational analysis of C-ring substituted flavans and analogues

5.1 Introduction

As indicated in chapter 1, structure elucidation of flavonoids with a saturated heterocyclic ring has always been difficult due to ambiguity in determining the absolute configuration at the one or more chiral centres present in the molecule. Historically optical rotation and/or electronic circular dichroism (ECD) measurements have found widespread application in determining the absolute configuration of these flavonoids.[1,2] While determining the absolute configuration at a single chiral centre in a molecule through application of these methods is usually not complicated, this aspect in the structure elucidation of compounds with numerous chiral centres represents a challenge.[3,4] The fact that a single Cotton-effect represents the combined effects of several stereogenic centres in more complex molecules, requires the involvement of computational or other methods to determine the collective effect of all the chiral centres. Due to the complexity of the contribution of each chiral centre to the combined Cotton-effect, the relative stereochemistry of the groups attached to the C-ring, as determined by NMR coupling constants, has been used together with ECD measurements to determine the absolute configuration at all the prevailing chiral centres in more complex molecules[5,6] The coupling constants of the protons present in the C-ring are, however, not only a function of the relative configuration of the substituents attached to this ring, but also of the conformation of the C-ring,

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1 Xu, Y.J.; Foubert, K.; Dhooghe, L.; Lemière, F.; Maregesi, S.; Coleman, C.M.; Zou, Y.; Ferreira, D.; Apers, S.; Pieters, L. *Phytochemistry* **2012**, *79*, 121.

2 Ding, Y.; Li, X.C.; Ferreira, D. *J. Nat. Prod.* **2010**, *73*, 435.

3 Li, X.C.; Joshi, A.S.; Tan, B.; ElSohly, H.N.; Walker, L.A.; Zjawiony, J.K.; Ferreira, D. *Tetrahedron* **2002**, *58*, 8709.

4 Li, X.C.; Ferreira, D.; Ding, Y. *Curr. Org. Chem.* **2010**, *14*, 1678.

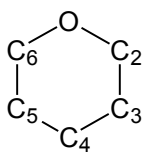
5 Ren, Y.; Lantvit, D.D.; Carcache de Blanco, E.J.; Kardono, L.B.S.; Riswan, S.; Chai, H.; Cottrell, C.E.; Farnsworth, N.R.; Swanson, S.M.; Ding, Y.; Li, X.C.; Marais, J.P.J.; Ferreira, D.; Kinghorn, A.D. *Tetrahedron* **2010**, *66*, 5311.

6 Zhang, F.; Yang, Y.N.; Song, X.Y.; Shao, S.Y.; Feng, Z.M.; Jiang, J.S.; Li, L.; Chen, N.H.; Zhang, P.C. *J. Nat. Prod.* **2015**, *78*, 2390.

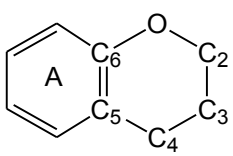
which is also influenced by the number and type of substituents attached to this ring and/or adjacent to it.[2]

In an effort to divulge the effect of the individual stereocenters form each other, and thus the combined effet obtained by ECD, it was decided to investigate the chromophore based method of VCD as measurement of absolute configuration at the different stereogenic centres. If a correlation between the IR absorption band(s) at certain wave numbers and a specific chromophore in a molecule could be established, it should, in principle, be possible to define the absolute comfiguration at that point in the molecule by VCD. In order to find a possible relationship between chromophores and IR absorption bands in flavonoids and related molecules, a molecular modelling study to determine the preferred conformation of the heterocyclic ring of these compounds as well as establish a possible correlation between the chromophore present in the molecule and IR band(s) was embarked upon. In this regard, the preferred conformation(s) of the series of heterocyclic molecules (*vide infra*) with increasing order of complexity, i.e. no substituent to three heterocyclic substituents (Figure 1), were determined and correlated with the respective modelled IR frequencies as well as the experimental absorption bands in the IR spectrum.

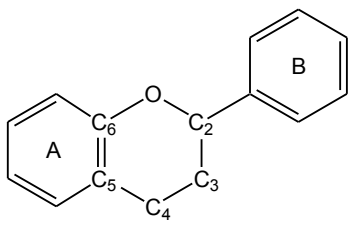
- oxane (tetrahydro-2*H*-pyran, THP); the simplest saturated six-membered heterocyclic compound (**5.1**),
- chromane (3,4-dihydro-2*H*-chromane), a bicyclic heterocycle in which a benzene ring is fused onto the oxane (**5.2**),
- flavan (2-phenyl-3,4-dihydro-2*H*-1-benzopyran or 2-phenylchromane), the basic structure of saturated monomeric flavonoids with 1 stereogenic centre (**5.3**),
- flavan-3-ol (2-phenyl-3,4-dihydro-2*H*-chromen-3-ol) (**5.4**) and 4-arylflavan (4-aryl-2-phenylchromane) (**5.5**) with 2 stereogenic centres and
- 4-arylflavan-3-ol (4-aryl-2-phenylchromane-3-ol) (**5.6**) with 3 stereogenic centres.



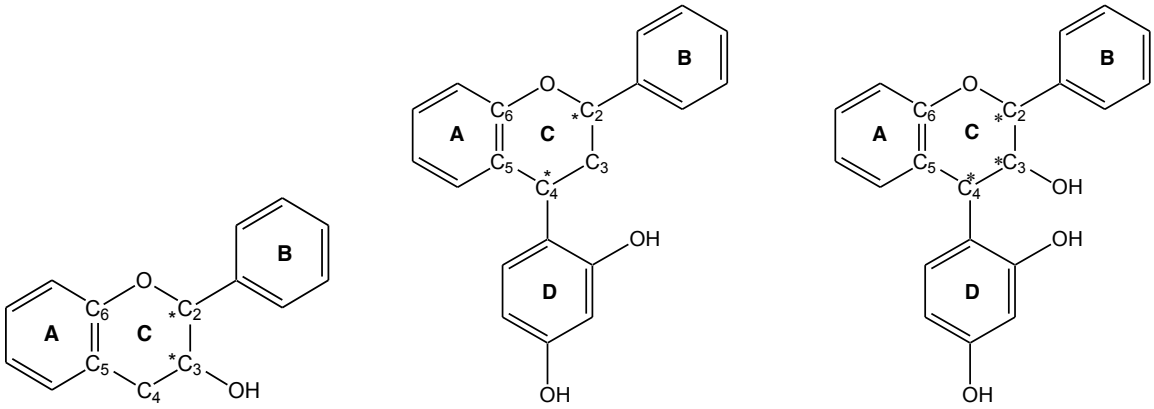
(**5.1**) oxane



(**5.2**) chromane



(**5.3**) flavan



(**5.4**) flavan-3-ol (**5.5**) 4-arylflavan (**5.6**) 4-arylflavan-3-ol

Figure 1. Molecules modelled in this study.

Density functional theory (DFT) calculations were used to determine the preferred conformations and predicted absorption bands of compounds (**5.1**) – (**5.6**), which were then compared to the experimental IR spectra of these substrates. Apart from the *ab initio* approach, the DFT with gradient-corrected functionals and hybrid methodology gave satisfactory efficiency and accuracy with economical computational costs to be able to determine energies, geometries, vibrational frequencies, NMR analysis as well as some significant molecular properties of medium-sized and even larger molecules.[7]

Parts of the research done for this PhD study related to the geometry, PES and IR of complexes (**5.1**) – (**5.3**) have been published in Kuo, C.-M., Bezuidenhoudt, B.C.B. and Conradie, J. "Determination of the relationship between theoretical vibrational frequencies and experimental IR absorption bands in organic molecules: Computational study of oxane, chromane and flavan", Journal of Physical Organic Chemistry, 2013, 26 327–334 DOI: 10.1002/poc.3092.[8] Permission to reuse the figures and tables in this thesis has been obtained by JOHN WILEY AND SONS, License Number 3775170594979 on Dec 24, 2015.

7 Jensen, F. *Introduction to Computational Chemistry*; Wiley: New York, **1999**.

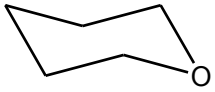
8 Kuo, C.-M., Bezuidenhoudt, B.C.B. and Conradie, J. "Determination of the relationship between theoretical vibrational frequencies and experimental IR absorption bands in organic molecules: Computational study of oxane, chromane and flavan", *J*. *Phys*. *Org*. *Chem*. **2013**, 26 327. DOI: 10.1002/poc.3092.

5.2 Geometry

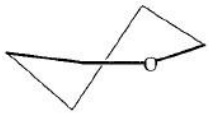
In this section results on the DFT calculated geometries of the different stereoisomers possible for each of (**5.1**) – (**5.6**) are presented.

5.2.1 Oxane

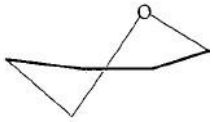
As indicated in Figure 2, various conformations such as chair, boat, half-chair, sofa, skewed/twisted boat and planar of the six-menbered ring of oxane, are possible. The presence of the oxygen in the ring increases the number of conformations possible for a six-menbered ring from 6 to 13. For example, the skewed/twisted boat results in 4 possible conformations, e.g. 1,4-boat and 2,5-boat, 1,4-twisted boat and 2,5-twisted boat, each with a different energy. Although some theoretical studies on the conformational of oxane have appeared, none of them addressed the issue of the relationship between vibrational frequencies and the experimental IR spectrum of this molecule. A DFT study to determine the geometry, energy and population of the different conformations of oxane were therefore embarked upon in order to compare the DFT calculated absorption bands of the equilibrium mixture of the different isomers to the experimental IR spectrum.



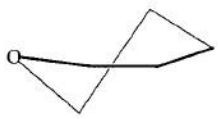
1 Chair
(5.7)



2a Half chair
(5.8)



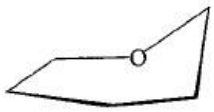
2b Half chair
(5.9)



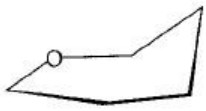
2c Half chair
(5.10)

3a Sofa
(5.11)

3b Sofa
(5.12)



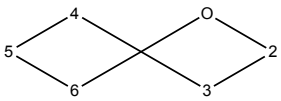
3c Sofa
(5.13)



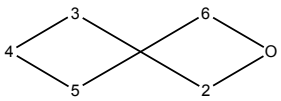
3d Sofa
(5.14)

1,4-Boat
(5.15)

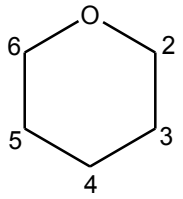
2,5-Boat
(5.16)



2,5-Twisted/Skewed boat (5.17)



1,4-Twisted/Skewed boat (5.18)



Planar (**5.19**)

Figure 2. Different oxane conformers.

A potential energy surface (PES) of oxane as function of the two dihedral angles OC2C3C4 and OC6C5C4 between -80 and +80° is shown in Figure 3. To the best of our knowledge, Figure 3 presents the first entire conformational surface of oxane. From the 3-D potential energy surface (PES) it is obvious that oxane is a symmetrical molecule, in which one half of the PES determines enantiomers of the other half. A chair conformer is found at the global minimum at *ca* (+55°, -55°) and (-55°, +55°) for angles OC2C3C4 and its enantiomer, OC6C5C4, respectively. However, the 2,5-twisted boat and 1,4-twisted boat conformers are represented by the two local minima, which indicated at (-25°, -30°) and (60°, 60°) together with their enantiomers at (25°, +30°) and (-60°, -60°), respectively.

Figure 4 shows the DFT optimized geometry, reoptimized without any constraints of the chair, 2,5 twisted boat and 1,4 twisted boat conformers of oxane and Table 1 gives the relative energies of the different conformers of oxane with the number of imaginary vibrational frequencies obtained and the constraints used in the geometry optimization. These results show that the chair, 2,5-twisted boat and 1,4-twisted boat are stable conformers of oxane. Table 2 gives geometrical parameters (bond lengths Å and angles °) of selected crystal structures and the calculated minimum structures of oxane.[9] Reasonable agreement between the experimental bond lengths and angles and the DFT calculated bond lengths and angles were obtained.

[9] Hehre, W.J.; Radom, L.; Schleyer, P.V.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1986**.

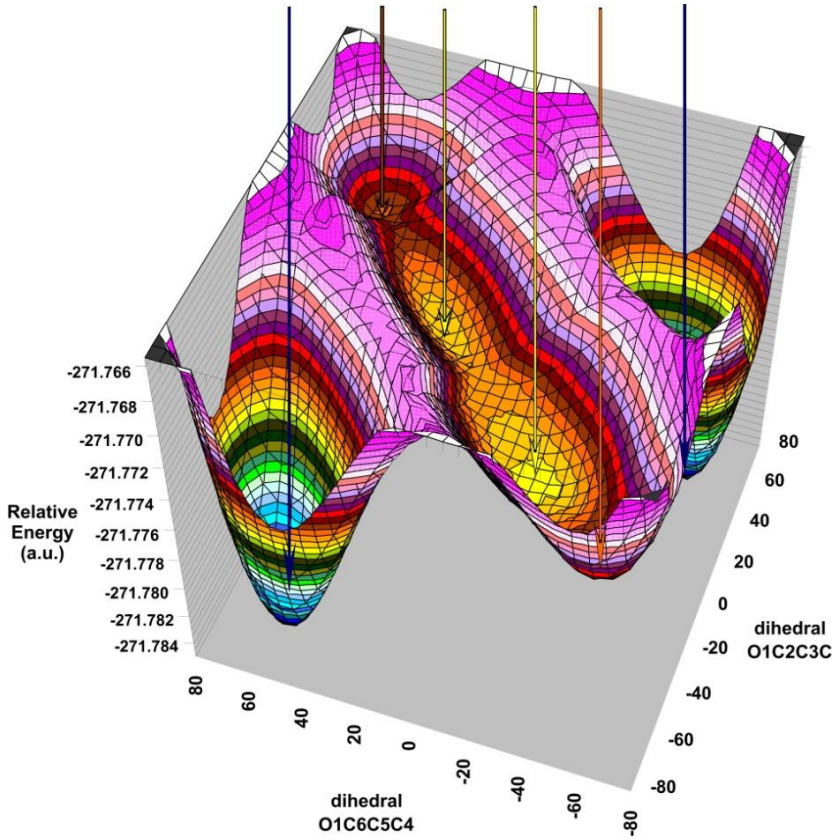


Figure 3. 3-D potential energy surface (PES) of oxane. The arrows show minima:

dark blue arrows:

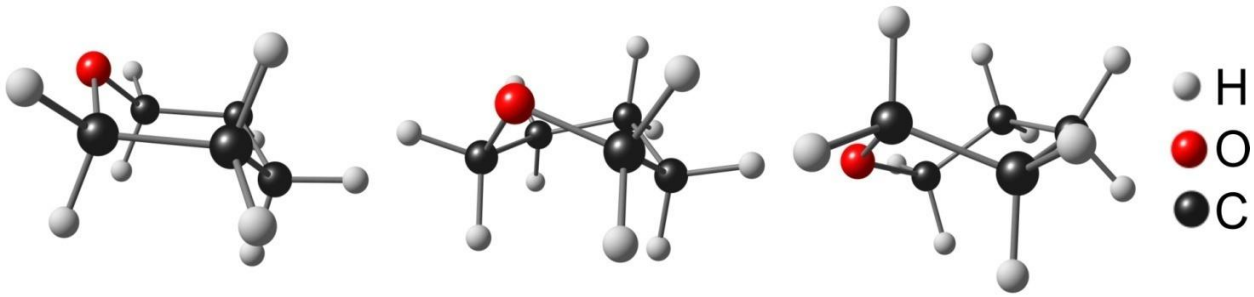
global minima at (-55°, 55°) and (55°, -55°) for the two chair mirror images

yellow arrows:

local minima at (-25°, -30°) and (55°, 35°) for the two 2,5 twisted boat mirror images

orange arrows:

local minima at (55°, 55°) and (-55°, -55°) for the two 1,4 twisted boat mirror images



(**5.20**) (**5.21**) (**5.22**)

Figure 4. The DFT optimized geometry of the chair, 2,5 twisted boat and 1,4 twisted boat conformers of oxane.

Results obtained in this study is in agreement with previous studies by Freeman *et al*.[10] who reported that among 13 possible conformers, the chair, 2,5-twisted boat and 1,4-boat are the most stable conformers. However, the 2,5-twisted boat and 1,4-boat conformers are less stable than the chair conformer by *ca* 25 kJ/mol and 29 kJ/mol, respectively. It has also been determined that the hypothetical planar oxane possesses three imaginary vibrational frequencies, while one imaginary vibrational frequency is found for each of the half chair, sofa, 1,4-boat, and the 2,5-boat conformers and the real vibrational frequencies are assigned for the chair, 2,5-twisted boat and 1,4-twisted boat conformers.

Based on the singlet ground state calculations of oxane, Naumov *et al*.[11] reported the chair to be the most stable conformer before the 2,5-twisted boat and 1,4-twisted boat, moreover, the boat and sofa conformers are in transition states, while the planar oxane is a third-order saddle point. According to the DFT calculations by Smith *et al*.[12] showing that oxane has three minima e.g. chair, 2,5-twisted boat and 1,4-twisted boat that are calculated between 23.6 and 25.9 kJ mol^{-1}.

Table 1. Relative energies of the different conformers of oxane (see Figure 4). The number of imaginary vibrational frequencies obtained and the constraints used in the geometry optimization, are also indicated.

Geometry	**Relative Energy (kJ/mol)**	**No. of imaginary frequencies**	**Optimized with constraints**
Chair	0.0	0	none
2,5 twisted boat	24.9	0	none
1,4 twisted boat	29.0	0	none
Half chair 2	39.9	1	4 atoms in the same plane
Half chair 1	40.5	1	4 atoms in the same plane
Sofa 1	41.4	1	5 atoms in the same plane
Sofa 2	42.1	1	5 atoms in the same plane
Half chair 3	44.0	1	4 atoms in the same plane
Sofa 3	44.5	1	5 atoms in the same plane
Sofa 4	45.9	1	5 atoms in the same plane
Planar	100.9	3	6 atoms in the same plane

10 Stortz, C.A. *J*. *Phys*. *Org*. *Chem*. **2010**, *23*, 1173.

11 Naumov, S.; Janovský, I.; Knolle, W.; Mehnert, R. *Phys*. *Chem*. *Chem*. *Phys*. **2003**, *5*, 3133.

12 Smith, B.J. *J*. *Phys*. *Chem*. *A*. **1998**, *102*, 3756.

Table 2. Geometrical parameters (bond lengths Å and angles °) of selected crystal structures and the calculated minimum structures of oxane.

	CSD code	**GIHPIX**	**HETCIS**	**JAZKOL**	**Calculated**		
Conformation		Chair	Chair	Chair	Chair	2,5 twist boat	1,4 twist boat
Temperature(K)		183	150	173			
Bond lengths	O1-C2	1.434	1.429	1.434	1.423	1.428	1.428
	C2-C3	1.518	1.503	1.498	1.531	1.545	1.528
	C3-C4	1.530	1.516	1.515	1.537	1.534	1.547
	C4-C5	1.522	1.512	1.517	1.537	1.545	1.547
	C5-C6	1.513	1.499	1.502	1.531	1.544	1.528
	C6-O1	1.438	1.427	1.458	1.423	1.422	1.429
Dihedrals	O1C2C3C4	57.4	56.2	56.8	55.8	25.0	61.7
	O1C6C5C4	56.4	55.6	56.1	55.8	29.8	61.8
Angles	O1C2C3	111.3	111.2	111.3	111.8	112.7	112.7
	C2C3C4	109.8	110.9	110.7	110.2	109.6	110.6
	C3C4C5	110.1	110.1	110.3	110.1	110.0	110.8
	C4C5C6	110.7	110.5	111.5	110.2	110.0	110.6
	C5C6O1	111.2	112.2	110.0	111.8	110.9	112.7
	C6O1C2	110.9	111.4	111.1	112.1	112.0	115.4
Reference		[13]	[14]	[15]			

5.2.2 Chromane

Since the basic idea of this study was to determine the preferred conformations of chiral flavonoid molecules, chromane (**5.2**) was selected as second target molecule for the investigation as it could be considered as the main building block of flavonoids with a saturated heterocyclic ring. The PES of chromane as a function of the O1C6C5C4 dihedral angle is presented in Figure 5. From the structural analysis it is clear that the tetrahydropyran ring of chromane is hardly represented by the boat conformation due to the planarity of the benzene ring. The two minima at (0^o, 60^o) and (0^o,-60^o) of the PES of chromane present the two enantiomeric forms of oxane, which are the two half-chair mirror images (Figure 5). The DFT optimized geometry of the half-chair optimized conformer of chromane and its conformational enantiomer are shown in Figure 6.

13 Spingler, B.; Antoni, P.M. *Chem*. *Eur*. *J*. **2007**, *13*, 6617.

14 Bock, H.; John, A.; Nather, C. *Chem*. *Commun*. **1994**, 1939.

15 Bieller, S.; Bolte, M.; Lerner, H.-W.; Wagner, M. *Inorg*. *Chem*. **2005**, *44*, 9489.

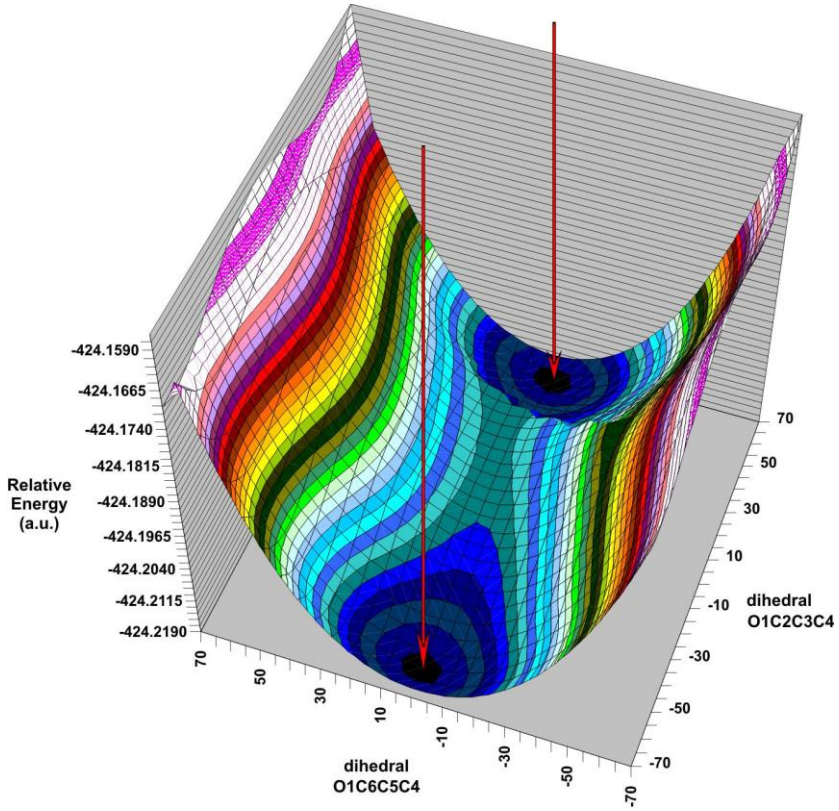
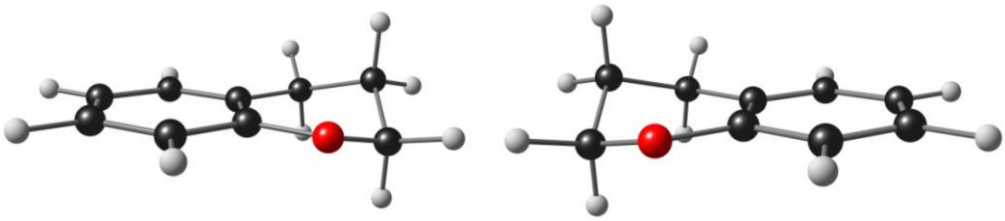


Figure 5. 3-D potential energy surface (PES) of chromane. The red arrows show the global minima at (0^o, 60^o) and (0^o,-60^o) for the two half chair enantiomers.



(**5.23**) (**5.24**)

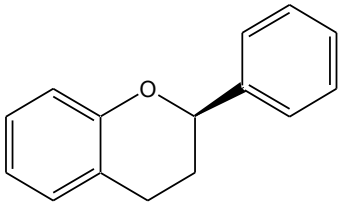
Figure 6. The DFT optimized geometry of the half-chair optimized conformer of chromane and its mirror image. [Colour code (online version): C grey, H white, O red.]

On a DFT level of theory, Setiadi *et al.*[16] investigated ring inversions of chromane on the molecular geometries and activation energy. During the optimization analysis, they showed the half-chair conformation of a planar benzene ring connected to an oxane ring; in addition, for the ring inversion the united heterocyclic oxane ring reveals an extremely twisted boat orientation in the transition state. The Boltzman distribution between the half-chair (lowest energy conformation) and second lowest energy conformation of chromane is 50.4% and 49.6% population respectively.

[16] Setiadi, D.H.; Chass, G.A.; Torday, L.L.; Varro, A.; Papp, J.G. *J. Mol. Struct. (THEOCHEM)* **2002**, *594*, 161.

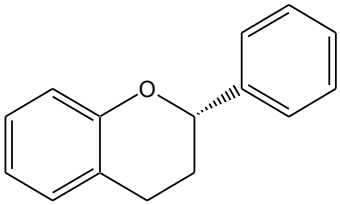
5.2.3 Flavan

The first real flavonoid compound to be investigated, flavan (**5.3**), is a chiral molecule containing one stereogenic centre at C2 and thus may exist as two enantiomers e.g. (2*R*) and (2*S*) with two conformations (axial and equatorial) of the phenyl substituent being possible (Figure 7). In Figure 8 and 9 the 3-D potential energy surface (PES) of the (2*R*)- and (2*S*)-enantiomers of flavan is displayed.



(2*R*)

(**5.25**)



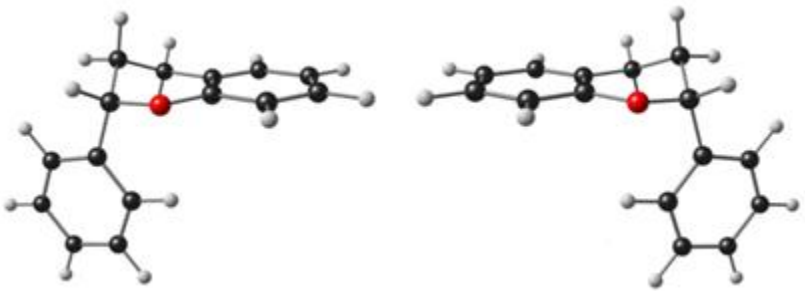
(2*S*)

(**5.26**)

Figure 7. (2*R*)- and (2*S*)-enantiomers of flavan.

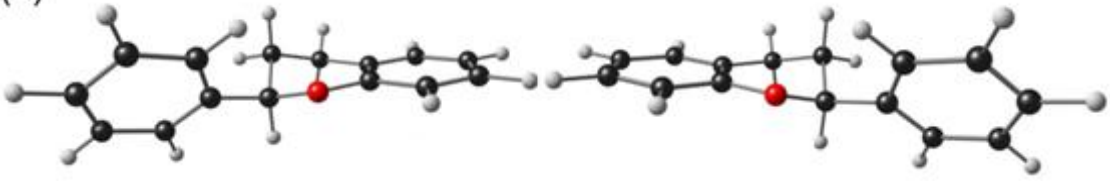
Similar to chromane, the PES of the (*R*)-isomer of flavan showed two minima, namely a global minimum and a local minimum at (0^o, 60^o) and (0^o,-60^o), respectively. Optimization of the aforementioned minimum energy geometries with the PES scanned without any constraints afforded two half chair conformations, the (2*R*)-*equatorial* (**5.29**) and the (2*R*)-*axial* (**5.28**) conformers with dihedral angles (0^o, 61^o) and (0^o, -58^o). The (2*R*)-*axial* conformer [Figure 8 (a)] was found to be 6.2 kJ/mol less stable than the (2*R*)-*equatorial* isomer [Figure 8 (b)].

(a)



(2*S*)-*axial* conformation (**5.27**) (2*R*)-*axia*l conformation (**5.28**)

(b)



(2*R*)-*equatorial* conformation (**5.29**) (2*S*)-*equatorial* conformation (**5.30**)

Figure 8. The DFT optimized geometry of the two *equatorial*-conformers [(2*R*)-*equatorial*- and (2*S*)-*equatorial*)] and the two *axial*-isomers [(2*S*)-*axial*- and (2*R*)-*axia*l] of flavan. The populations of the two *axial*-isomers *vs*. two *equatorial*-isomers of flavan according to Boltzman equation is (a) 7.6% and (b) 92.4%. Colour code (online version): C grey, H white, O red.

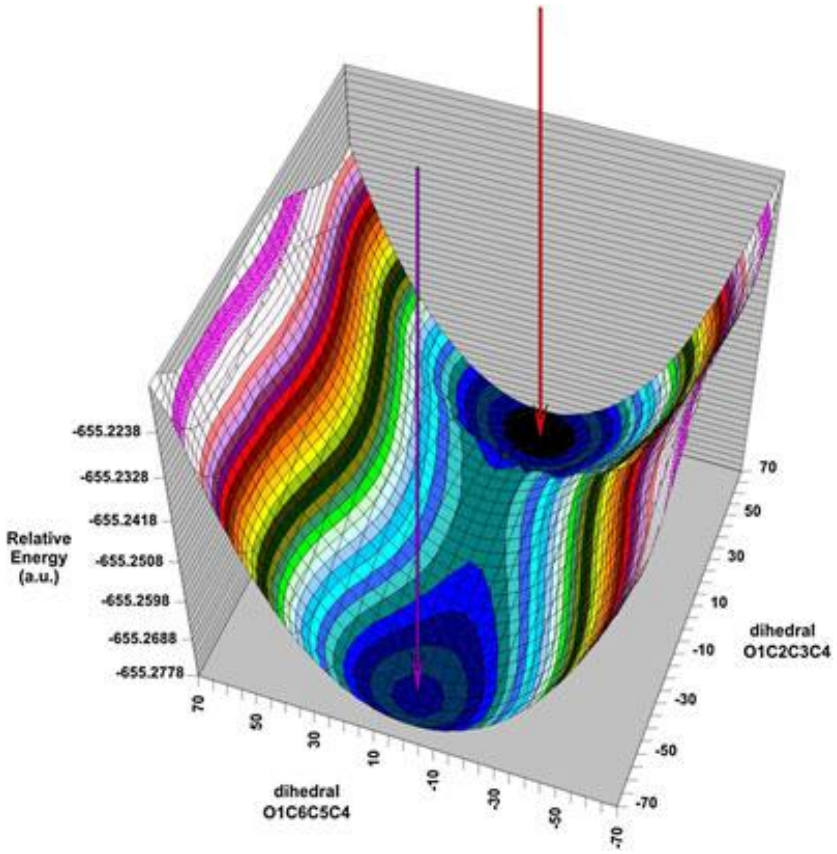


Figure 9. 3-D potential energy surface (PES) of the (2*R*)-*equatorial*- and (2*R*)-*axial* conformers of flavan. The arrows show minima: red arrow, global minimum at (0^o, 60^o) for the (2*R*) *equatorial*-isomer, purple arrow, local minimum at (0^o,-60^o) for the (2*R*)-*axial* conformer.

The PES of the (*S*)-isomer of flavan also showed two minima; a global minimum at (0^o, -60^o) as well as a local minimum at (0^o, 60^o) (Figure 10). Optimization of these minimum energy geometries on the PES scan without any constraints gave the (2*S*)-*equatorial*- and the (2*S*)-*axial* isomer of flavan with dihedral angles (0^o, -58^o) and (0^o, 61^o). The (2*S*)-*axial* isomer in Figure 8 (a) is 6.2 kJ/mol less stable than the (2*S*)-*equatorial* isomer of flavan in Figure 8 (b).

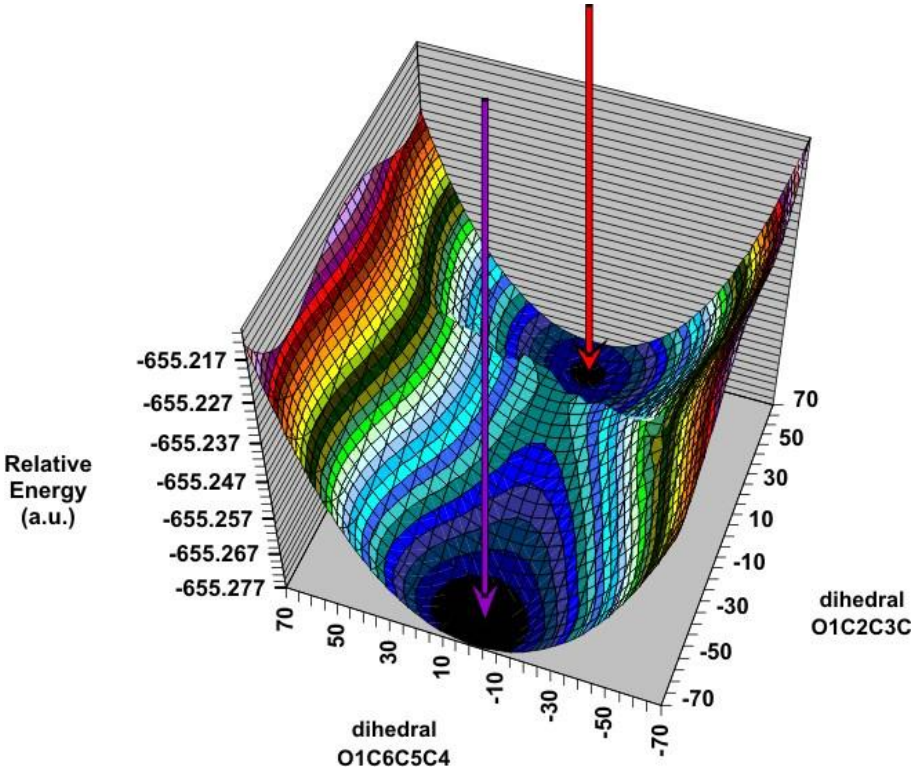


Figure 10. 3-D potential energy surface (PES) of the (2*S*)-*equatorial*- and the (2*S*)-*axial* conformers of flavan. The global minimum at (0^o, 60^o) for the (2*S*)-*equatorial* isomer, purple arrow, local minimum at (0^o, -60^o) for the (2*S*)-*axial* isomer, red arrow.

Table 3 summarize the results obtained from the PES for global and local minima and Boltzman populations for the (2*R*)- and (2*S*)-configurations of flavan. The (2*R*)-*equatorial* conformer as well as its (2*S*)-*equatorial* isomer have a Boltzman calculated population of 92.4%, while (2*R*)-*axial* conformer as well as its (2*S*)-*axial* isomer have a population of only 7.6%. The (2*R*)-*equatorial*- and (2*S*)-*equatorial* isomers are therefore more stable than their respective *axial*-conformers by 6.2 kJ/mol (Figure 8).

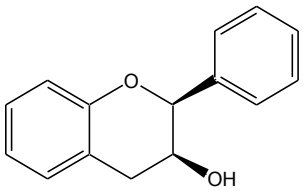
Table 3. PES results and Boltzman populations study for all conformations and enantiomers of flavan.

Flavan (starting geometry)	**Degrees Global minimum**	**Degrees Local minimum**	**Boltzman % population [a] (Global : Local)**
(2*R*)	(0^o, 60^o) (2*R*)-*equatorial* (**5.29**)	(0^o,-60^o) (2*R*)-*axial* (**5.28**)	92.4 : 7.6
(2*S*)	(0^o,60^o) (2*S*)-*equatorial* (**5.30**)	(0^o, -60^o) (2*S*)-*axial* (**5.27**)	92.4 : 7.6

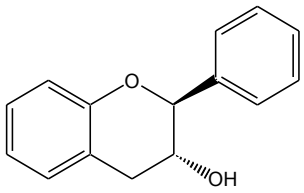
[a] Population determined from the energies of the geometries at the indicated minima, reoptimized without any geometry constraint.

5.2.4 Flavan-3-ols

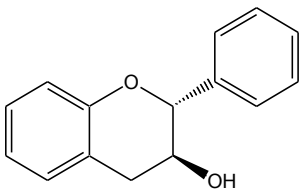
Due to the presence of two stereogenic centres, flavan-3-ols may exist in any of four stereoisomers, namely (2*S*,3*S*)-*cis*, (2*S*,3*R*)-*trans*, (2*R*,3*S*)-*trans* and (2*R*,3*R*)-*cis* isomers (Figure 11). Since the (2*S*,3*S*)-*cis* isomer (**5.31**) and the (2*S*,3*R)-trans* isomer (**5.32**) have enantiomeric relationships with the (2*R*,3*R*)-*cis* isomer (**5.34**) and (2*R*,3*S*)-*trans* isomers (**5.33**), respectively, the physical data of the pairs of enantiomers are the same in all aspects, except in the interaction with polarized light (ORD or CD), so only the results for the (2*S*,3*S*)-*cis* isomer (**5.31**) and (2*S*,3*R*)-*trans* isomer (**5.32**) will be discussed.



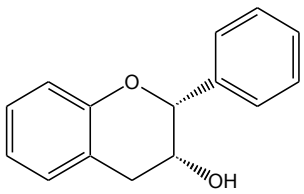
(2*S*,3*S*)-*cis* isomer (**5.31**)



(2*S*,3*R*)-*trans* isomer (**5.32**)



(2*R*,3*S*)-*trans* isomer (**5.33**)



(2*R*,3*R*)-*cis* isomer (**5.34**)

Figure 11. (2*S*,3*S*), (2*S*,3*R*), (2*R*,3*S*) and (2*R*,3*R*) stereoisomers of flavan-3-ols.

A PES as a function of the dihedral angles O1C2C3C4 between -80° and +80° is shown in Figure 12 for flavan-3-ols. The PES of the two stereoisomers e.g. (2*S*,3*S*)-*cis* isomer (**5.31**) and (2*S*,3*R*)-*trans* isomer (**5.32**) were determined separately. Geometries corresponding to the global minimum and the local minimum of the different PES were reoptimized without any geometry constraints. From the energies the population of the two stereoisomers of flavan-3-ols according to Boltzman equation were anaylzed and the results are given in Table 4.

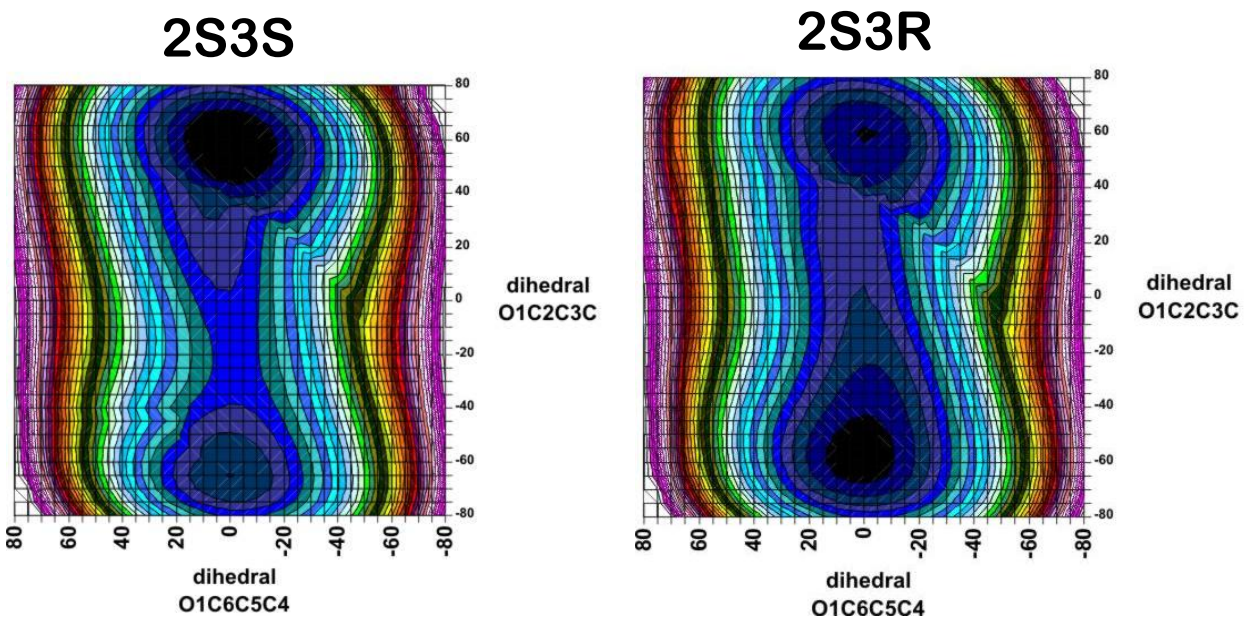


Figure 12. 2-D PES of the two stereoisomers of flavan-3-ols: (2*S*,3*S*)-*cis* isomer (**5.31**) and (2*S*,3*R*)-*trans* isomer (**5.32**). Energies are in Hartrees (a.u.) according to colour coding right.

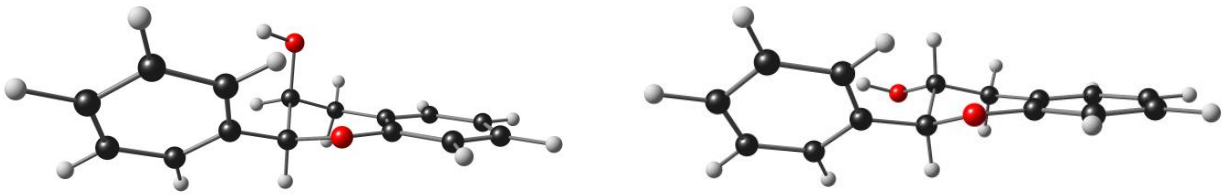
Table 4 gives a summary of the minima of the PES and the calculated Boltzman population of four conformations for flavan-3-ols. Each PES exhibits two minima, a global and a local minimum. The (2*S*,3*S*)-geometry consists of [(2*S*)-*equatorial*, (3*S*)-*axial* isomer (**5.35**)] *vs*. [(2*S*)-*axial*, (3*S*)-*equatorial* isomer (**5.36**)] and the Boltzman population of the former is 99.2% *vs*. 0.8%, respectively. This implies that the [(2*S*)-*axial*, (3*S*)-*equatorial* isomer (**5.36**)] is less stable and therefore less populated than the other conformer (**5.35**). For the (2*S*,3*R*)-geometry was calculated that the most stable conformation would be the [(2*S*)-*equatorial*, (3*R*)-*equatorial* isomer (**5.37**)] over the [(2*S*)-*equatorial*, (3*R*)-*axial* isomer (**5.38**)] at global minimum (0°, -60°) and local minimum (0°, 60°) with Boltzman population of 99.2% *vs* 0.8% for the axial isomer.

Table 4. PES results and Boltzman equation study for isomers of flavan-3-ols.

Flavan-3-ol (starting geometry)	**Degrees Global minimum**	**Degrees Local minimum**	**Boltzman % population [a] (Global : Local)**
(2*S*,3*S*)	(0°, 60°) (2*S*)-*equatorial*, (3*S*)-*axial* isomer (**5.35**)	(0°, -65°) (2*S*)-*axial*, (3*S*)-*equatorial* isomer (**5.36**)	99.2 : 0.8
(2*S*,3*R*)	(0°, -60°) (2*S*)-*equatorial*, (3*R*)-*equatorial* isomer (**5.37**)	(0°, 60°) (2*S*)-*equatorial*, (3*R*)-*axial* isomer (**5.38**)	99.2 : 0.8

[a] Population determined from the energies of the geometries at the indicated minima, reoptimized without any geometry constraint.

The most stable conformations which obtaining the highest Boltzman population of 99.2% are [(2*S*)-*equatorial*, (3*S*)-*axial* isomer (**5.35**)] and [(2*S*)-*equatorial*, (3*R*)-*equatorial* isomer (**5.37**)] (see Figure 13) which was in the agreement with the ^{1}H NMR indicating a *trans*-stereochemistry in flavan-3-ols due to the large coupling constant *J* 7.9 Hz.



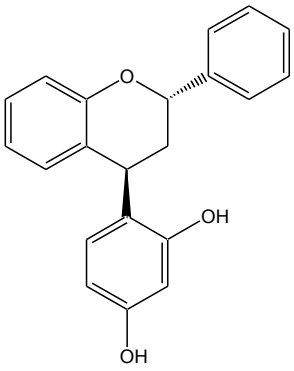
(2*S*)-*equatorial*, (3*S*)-*axial* (**5.35**) (2*S*)-*equatorial*, (3*R*)-*equatorial* (**5.37**)

Figure 13. The DFT optimized geometry of the preferred conformations (**5.35**) and (**5.37**) of flavan-3-ols.

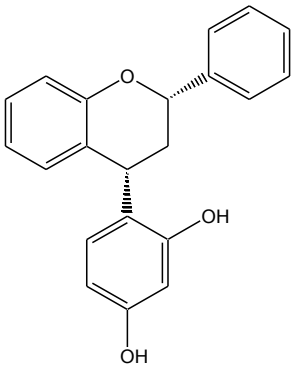
5.2.5 4-Arylflavan

Although not natural products in abundance, the 4-arylflavans containing two stereogenic centres (at C2 and C4) which can exist as four stereoisomers, namely (2*S*,4*R*)-*trans* isomer (**5.39**), (2*S*,4*S*)-*cis* isomer (**5.40**), (2*R*,4*R*)-*cis* isomer (**5.41**) and (2*R*,4*S*)-*trans* isomer (**5.42**) (Figure 14), were the next group of compounds to be investigated. Since the (2*S*,4*R*)-*trans* isomer (**5.39**) and (2*S*,4*S*)-*cis* isomer (**5.40**) have enantiomeric relationships with the (2*R*,4*S*)-*trans* isomer (**5.42**) and (2*R*,4*R*)-*cis* isomers (**5.41**), respectively, the physical data of the pairs of enantiomers are the

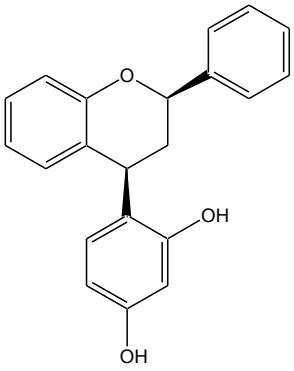
same in all aspects, except in the interaction with polarized light (ORD or CD), so only the results for the (2*S*,4*R*)-*trans* isomer (**5.39**) and (2*S*,4*S*)-*cis* isomer (**5.40**) will be discussed. PES as a function of the dihedral angles O1C2C3C4 between -80° and +80° is shown in Figure 15 for the two stereoisomers of 4-arylflavan.



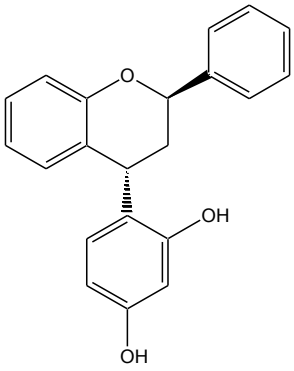
(2*S*,4*R*)-*trans* isomer (**5.39**)



(2*S*,4*S*)-*cis* isomer (**5.40**)



(2*R*,4*R*)-*cis* isomer (**5.41**)



(2*R*,4*S*)-*trans* isomer (**5.42**)

Figure 14. All stereoisomers: (2*S*,4*R*), (2*S*,4*S*), (2*R*,4*R*) and (2*R*,4*S*) of 4-arylflavans.

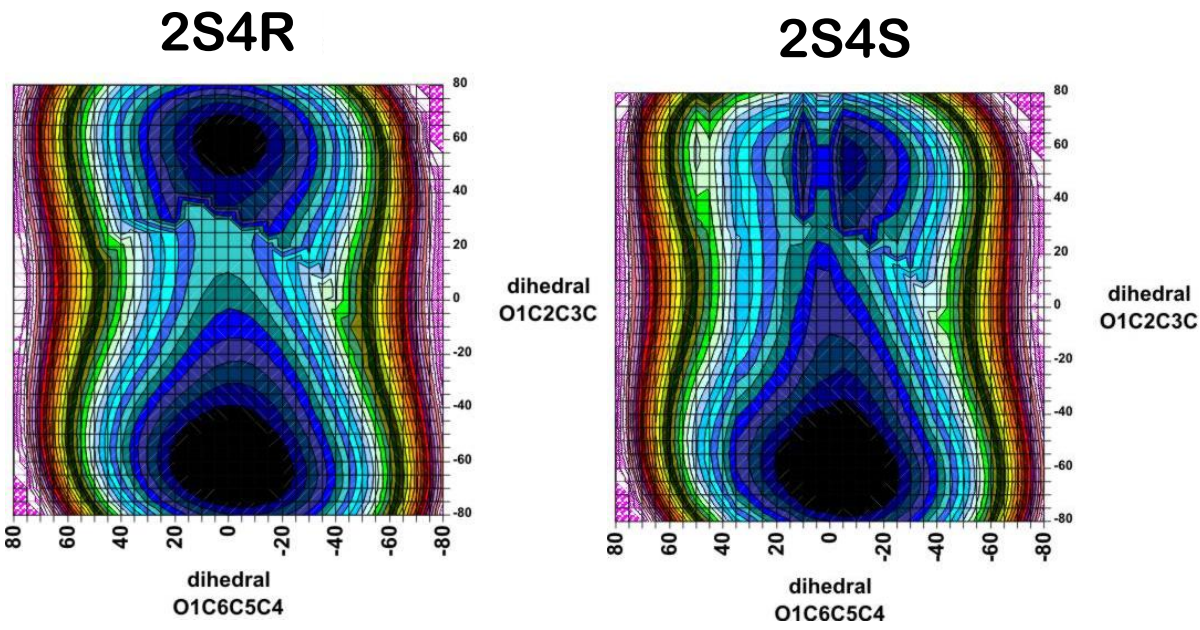


Figure 15. 2-D PES of the two stereoisomers of 4-arylflavan: (2*S*,4*R*)-*trans* isomer (**5.39**) and (2*S*,4*S*)-*cis* isomer (**5.40**). Energies are in Hartrees (a.u.) according to colour coding right.

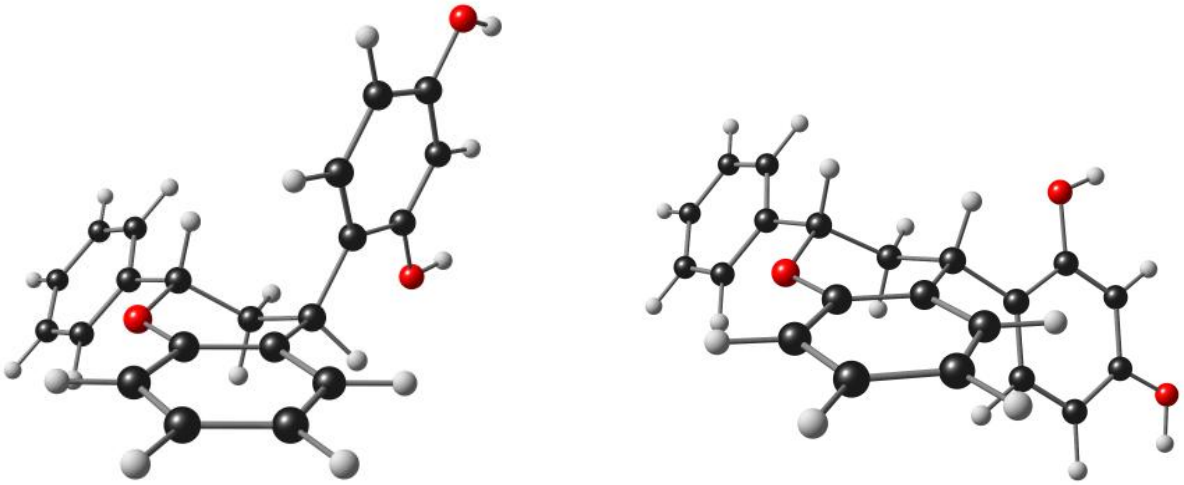
Table 5 gives a summary of the Boltzman distribution of the four conformations of 4-arylflavan. Each PES exhibits two minima, a global and a local minimum. The (2*S*,4*R*)-geometry consists of [(2*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.43**)] *vs*. [(2*S*)-*axial*, (4*R*)-*equatorial* isomer (**5.44**)] with Boltzman population of 97.9% at global minimum (0°, -60°) and 2.1% at local minimum (0°, 60°) respectively. For the (2*S*,4*S*)-geometry, it was calculated that the most stable conformation of 99.8% *vs*. 0.2% Boltzman population would be the [(2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45**)] *vs*. [(2*S*)-*axial*, (4*S*)-*axial* isomer (**5.46**)] at global minimum (-5°, -60°) and local minimum (-5°, 55°), respectively.

Table 5. PES results and Boltzman equation study for isomers of 4-arylflavan.

4-Arylflavan (starting geometry)	**Degrees Global minimum**	**Degrees Local minimum**	**Boltzman % population [a] (Global : Local)**
(2*S*,4*R*)	(0°, -60°) (2*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.43**)	(0°, 60°) (2*S*)-*axial*, (4*R*)-*equatorial* isomer (**5.44**)	97.9 : 2.1
(2*S*,4*S*)	(-5°, -60°) (2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45**)	(-5°, 55°) (2*S*)-*axial*, (4*S*)-*axial* isomer (**5.46**)	99.8 : 0.2

[a] Population determined from the energies of the geometries at the indicated minima, reoptimized without any geometry constraint.

[(2*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.43**)] has the higher Boltzman population of 97.9% which is the most stable conformation of (2*S*,4*R*)-geometry. [(2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45**)] is the most stable preferred conformation with the lowest energy and a DFT calculated Boltzman population of 99.8%, see Figure 16.



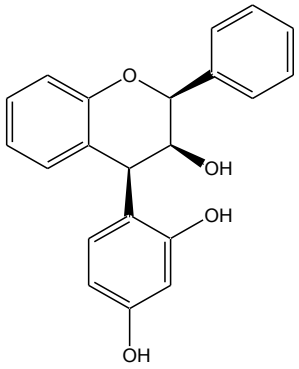
(2*S*)-*equatorial*, (4*R*)-*axial* (**5.43**) (2*S*)-*equatorial*, (4*S*)-*equatorial* (**5.45**)

Figure 16. The DFT optimized geometry of the preferred conformations (**5.43**) and (**5.45**) of 4-arylflavan.

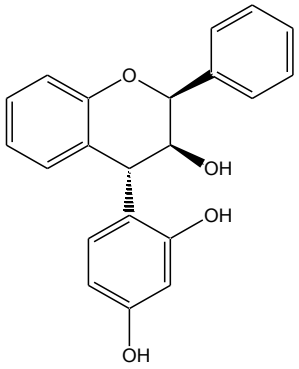
5.2.6 4-Arylflavan-3-ols

Apart from the two stereogenic centres complexes presented in section 4 (flavan-3-ols) and section 5 (4-arylflavan), 4-arylflavan-3-ols which possesses three stereogenic centres has been investigated in this regard. 4-Arylflavan-3-ols has three stereogenic centres at C2, C3 and C4, and it's therefore a chiral molecule with eight stereoisomers (Figure 17), namely (2*S*,3*S*,4*R*)-*cis-cis* isomer (**5.47**), (2*S*,3*S*,4*S*)-*cis-trans* isomer (**5.48**), (2*S*,3*R*,4*R*)-*trans-trans* isomer (**5.49**) and (2*S*,3*R*,4*S*)-*trans-cis* isomer (**5.50**) plus four of their enantiomers (**5.51**) - (**5.54**). Since the (2*S*,3*S*,4*R*)- (**5.47**), (2*S*,3*S*,4*S*)- (**5.48**), (2*S*,3*R*,4*R*)- (**5.49**) and (2*S*,3*R*,4*S*)- (**5.50**) have enantiomeric relationships with the (2*R*,3*R*,4*S*)- (**5.54**), (2*R*,3*R*,4*R*)- (**5.53**), (2*R*,3*S*,4*S*)- (**5.52**) and (2*R*,3*S*,4*R*)- (**5.51**), respectively, the physical data of the pairs of enantiomers are the same in all aspects, except in the interaction with polarized light (ORD or CD), so only the results for the four isomers (**5.47**) – (**5.50**) will be discussed. A PES of the four stereoisomers of 4-arylflavan-

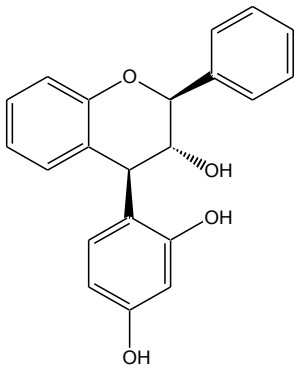
3-ols as a function of the dihedral angles O1C2C3C4 between -80° and +80° is shown in Figure 18.



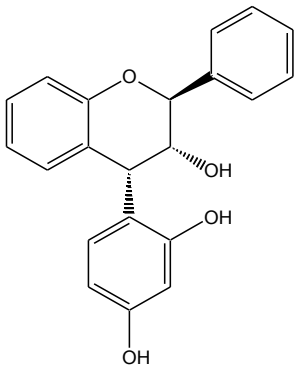
(2*S*,3*S*,4*R*)-*cis*-*cis* isomer (**5.47**)



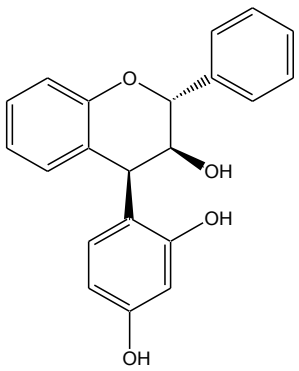
(2*S*,3*S*,4*S*)-*cis*-*trans* isomer (**5.48**)



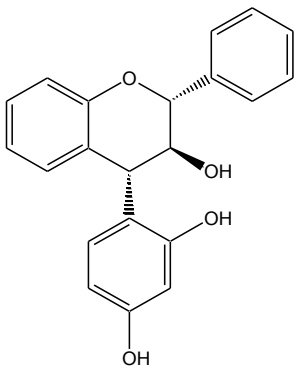
(2*S*,3*R*,4*R*)-*trans*-*trans* isomer (**5.49**)



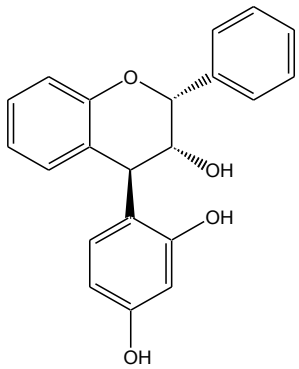
(2*S*,3*R*,4*S*)-*trans*-*cis* isomer (**5.50**)



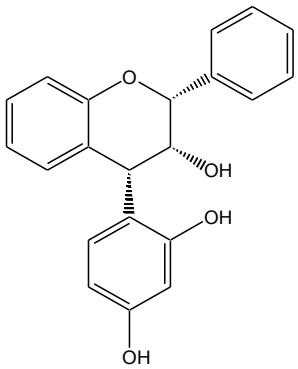
(2*R*,3*S*,4*R*)-*trans*-*cis* isomer (**5.51**)



(2*R*,3*S*,4*S*)-*trans*-*trans* isomer (**5.52**)



(2*R*,3*R*,4*R*)-*cis*-*trans* isomer (**5.53**)



(2*R*,3*R*,4*S*)-*cis*-*cis* isomer (**5.54**)

Figure 17. All stereoisomers of 4-arylflavan-3-ols.

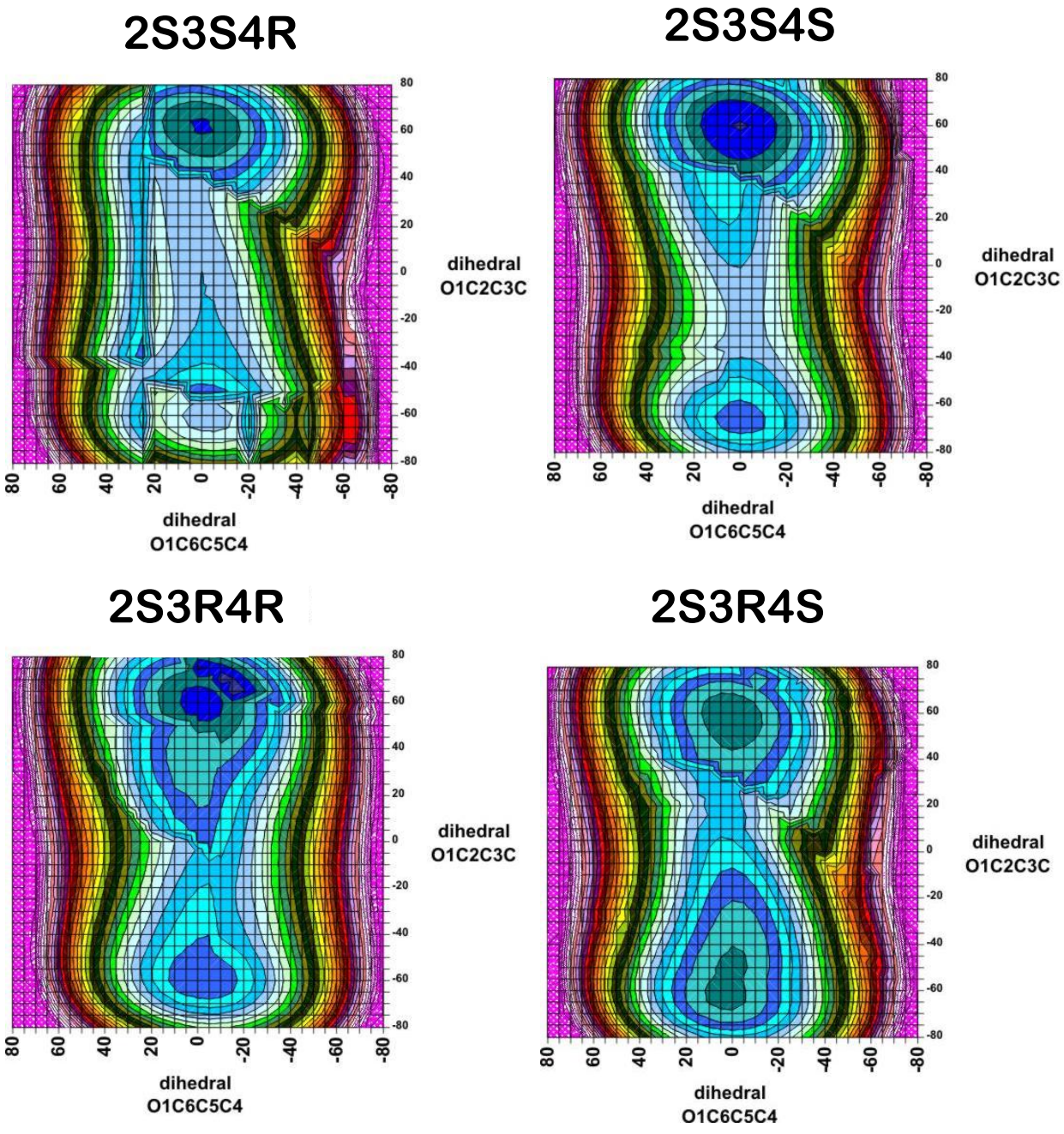


Figure 18. 2-D PES of the (2*S*,3*S*,4*R*)- (**5.47**), (2*S*,3*S*,4*S*)- (**5.48**), (2*S*,3*R*,4*R*)- (**5.49**) and (2*S*,3*R*,4*S*)- (**5.50**) stereoisomers of 4-arylflavan-3-ols. Energies are in Hartrees (a.u.) according to colour coding right.

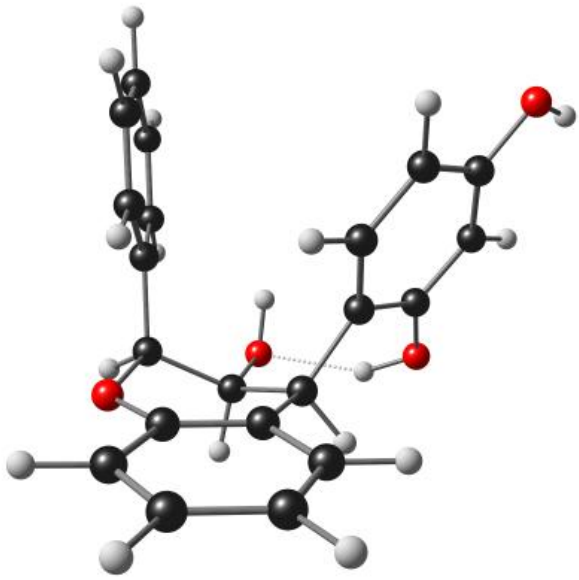
Table 6 gives a summary of the minima of the PES and the calculated Boltzman population of the eight conformations of 4-arylflavan-3-ols. It is clearly indicated that confirmations [(2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.55**)], [(2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*axial* isomer (**5.57**)], [(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial* isomer (**5.59**)] and [(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**)] have the highest Boltzman population of 86%, 51.3%, 100% and 76.5%, respectively, therefore, the most stable conformations of 4-arylflavan-3-ols (see Figure 19).

Table 6. PES results and Boltzman equation study for the conformations of 4-arylflavan-3-ols.

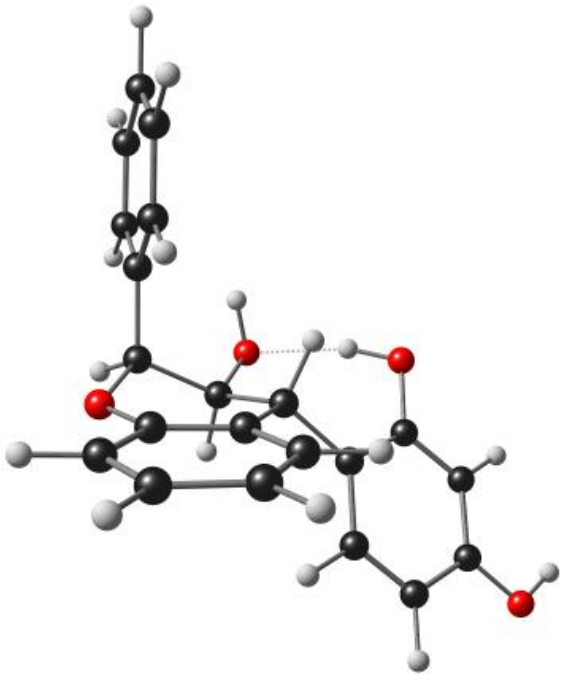
4-Arylflavan-3-ols (starting geometry)	**Degrees Global minimum**	**Degrees Local minimum**	**Boltzman % population [a] (Global : Local)**
(2*S*,3*S*,4*R*)	(0°, -50°) (2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.55**)	(0°, 65°) (2*S*)-*equatorial*, (3*S*)-*axial*, (4*R*)-*equatorial* isomer (**5.56**)	86 : 14
(2*S*,3*S*,4*S*)	(0°, -65°) (2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.57**)	(0°, 60°) (2*S*)-*equatorial*, (3*S*)-*axial*, (4*S*)-*axial* isomer (**5.58**)	51.3 : 48.7
(2*S*,3*R*,4*R*)	(-15°, 65°) (2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial* isomer (**5.59**)	(0°, -60°) (2*S*)-*axial*, (3*R*)-*axial*, (4*R*)-*axial* isomer (**5.60**)	100 : 0
(2*S*,3*R*,4*S*)	(0°, 60°) (2*S*)-*equatorial*,	(5°, -60°) (2*S*)-*axial*,	76.5 : 23.5

(3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**)	(3*R*)-*axial*, (4*S*)-*equatorial* isomer (**5.62**)

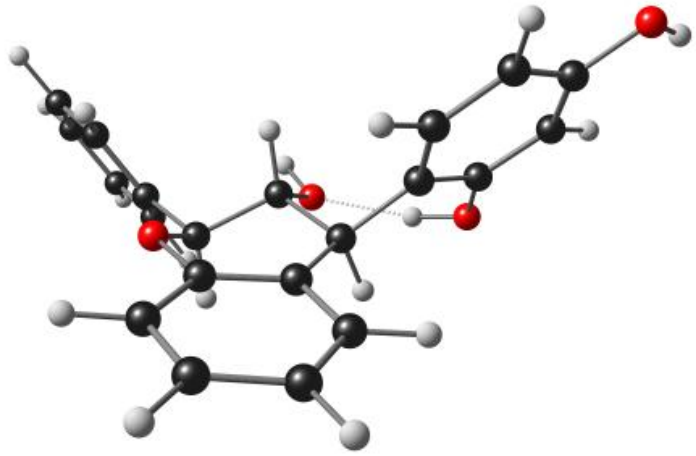
[a] Population determined from the energies of the geometries at the indicated minima, reoptimized without any geometry constraint.



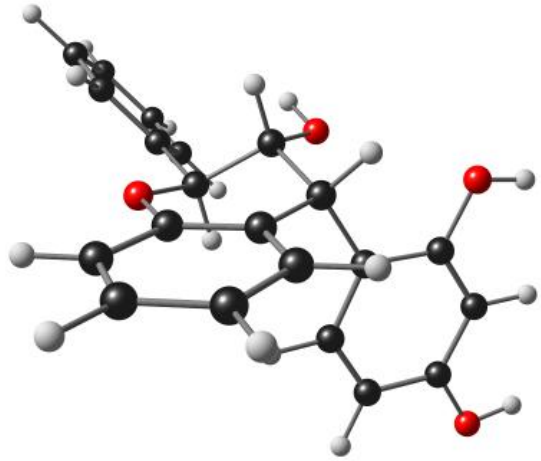
(2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.55**)



(2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.57**)



(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial* isomer (**5.59**)



(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**)

Figure 19. The DFT optimized geometry of the preferred conformations, (**5.55**), (**5.57**), (**5.59**) and (**5.61**) of 4-arylflavan-3-ols.

5.2.7 Comparison of conformations between 4-arylflavan and 4-arylflavan-3-ols

5.2.7.1 Geometry

According to the PES and Boltzman equation study of the componds, 4-arylflavan and 4-arylflavan-3-ols the substituents of the most stable conformaions are indicated as equatorial. It is found that the most stable conformation of oxane ring of all corresponded compounds is assigned as a chair /half chair conformation, see Table 7.

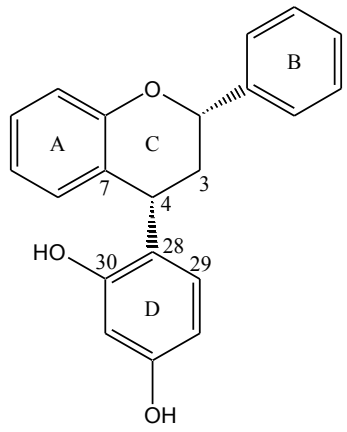
Table 7. The most stable conformations of 4-arylflavan and 4-arylflavan-3-ols.

Compounds	Most stable conformations
4-Arylflavan	(2*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.43**) – 97.9%
	(2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45**) – 99.8%
4-Arylflavan-3-ols	(2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.55**) – 86%
	(2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.57**) – 51.3%
	(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial* isomer (**5.59**) – 100%
	(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**) – 76.5%

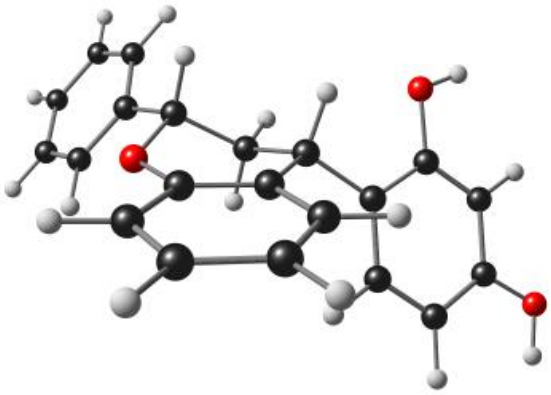
5.2.7.2 Barrier to rotation of D-ring in 4-arylflavan

(i) (2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45***)* of 4-Arylflavan

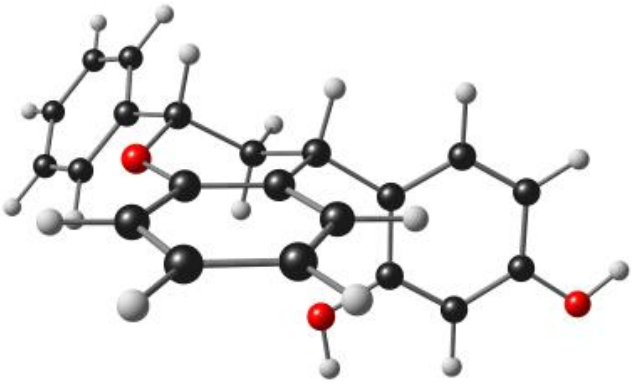
The energy of the conformation, (2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45**) of 4-arylflavan as a function of the dihedral angle C3, C4, C28 and C30 (D37) was calculated between -180 and 180 degrees in order to investigate the barrier to rotation of D-ring. It was found that there are two minimum energies at 90° (0 kcal/mol) and -60° (0.75 kcal/mol) degrees (chair conformation) and two maxima at -140° (20.53 kcal/mol) and 50° (15.24 kcal/mol) (boat conformation) as shown in Table 8 and Figure 20. The barrier to rotation of the D-ring to rotate from -180° to 180° was found to be 20.53 kcal/mol. This maximum energy value of 20.53 kcal/mol corresponds to a geometry of 4-arylflavan where there is a large steric interaction between the OH on C30 and hydrogens on C3.



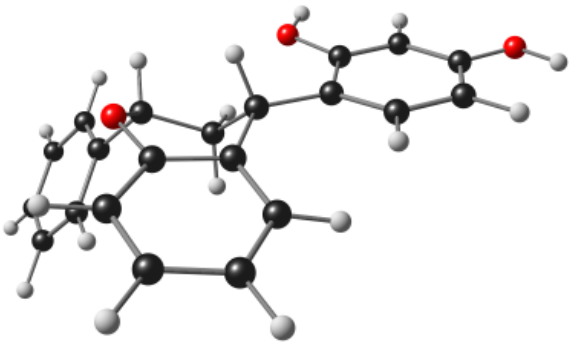
(2*S*,4*S*)-*cis* isomer (**5.40**)



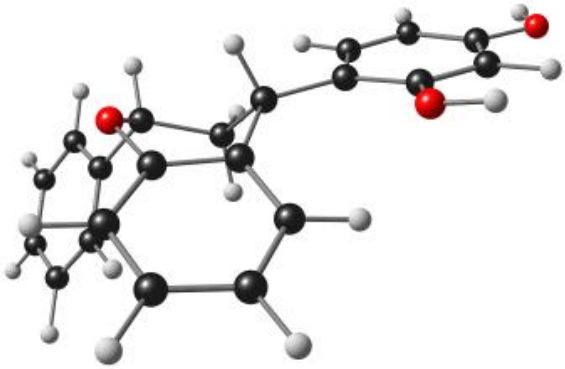
Minimum energies at 90° (0 kcal/mol) (**5.63**)



Minimum energies at -60° (0.75 kcal/mol) (**5.64**)



Maximum energies at 50° (15.24 kcal/mol) (**5.65**)



Maximum energies at -140° (20.53 kcal/mol) (**5.66**)

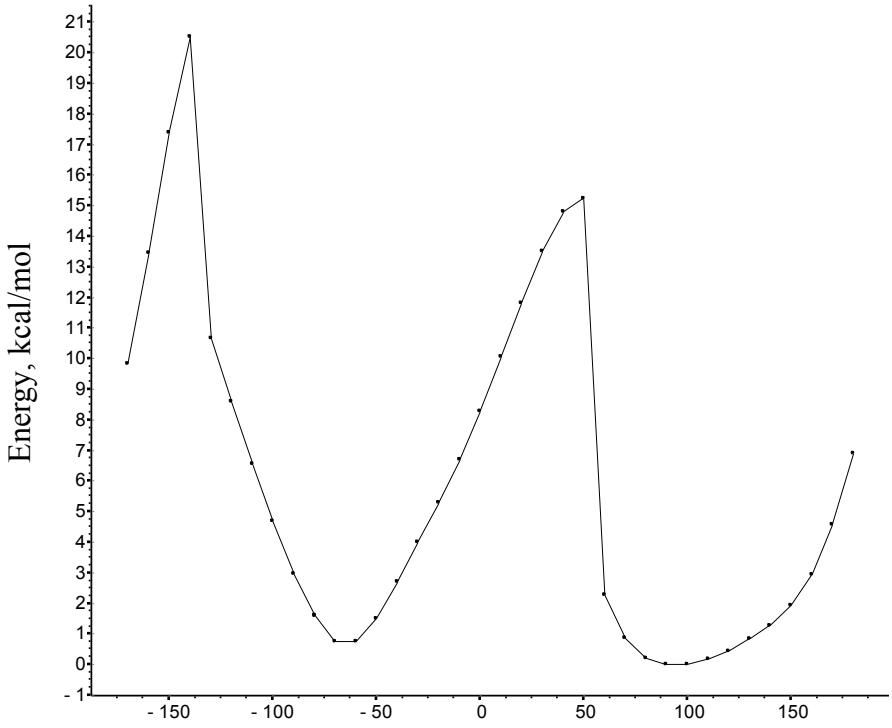


Figure 20. 2-D PES of the energy *vs*. dihedral angle calculated on rotation of D-ring for (2*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.45**) of 4-arylflavans.

Table 8. The dihedral angles associated with the maximum and minimum energy.

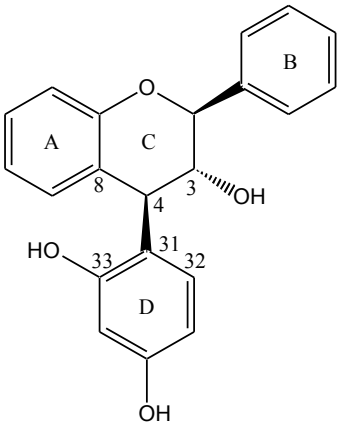
Dihedral angles	Energy, kcal/mol	Conformations
90°	0	Chair
-60°	0.75	Chair
50°	15.24	Boat
-140°	20.53	Boat

5.2.7.3 Barrier to rotation of D-ring in 4-arylflavan-3-ols

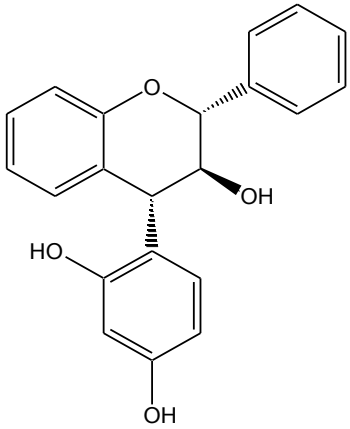
(i) (2*R*)-*equatorial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.52**) of 4-Arylflava n-3-ols

The rotation of D-ring for (2*R*,3*S*,4*S*)-*trans*-*trans* isomer (**5.52**) was calculated instead of (2*S*,3*R*,4*R*)-*trans*-*trans* isomer (**5.49**). Since one isomer has enantiomeric relationships with the other one, the physical data of the pair of enantiomers are the same in all aspects. Therefore, the study of barrier to rotation of D-ring will focus on (2*R*,3*S*,4*S*)-*trans*-*trans* isomer (**5.52**) (see Figure 21).

The energy of dihedral angle C3, C4, C31 and C33 were calculated between -180 and 180 degrees of the (2*R*)-*equatorial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* (**5.52**) isomer of 4-arylflavan-3-ols in order to investigate the barrier to rotation of the D-ring. There are three minimum energies at 80 (0 kcal/mol), -20 (6.53 kcal/mol) and -70 (3.13 kcal/mol) degrees (chair conformation) and three maxima at -120 (29.42 kcal/mol), -30 (10.28 kcal/mol) and 50 (19.99 kcal/mol) degrees (chair/boat conformation) as shown in Table 9 and Figure 22. The barrier to rotation of the D-ring to rotate from -180° to 180° was therefore found to be 29.42 kcal/mol, which is about 9 kcal/mol more than that observed for the D-ring of 4-arylflavan (20.53 kcal/mol). The reason for the higher energy barrier is probably situated in the steric hinderance between the OH on the C-ring and the *ortho*-OH of ring-D.

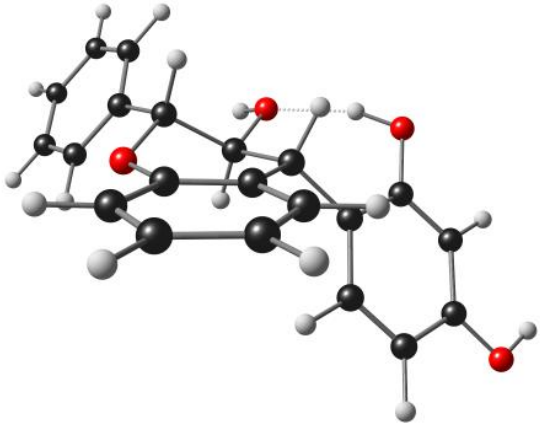


(2*S*,3*R*,4*R*)-*trans*-*trans* isomer (**5.49**)

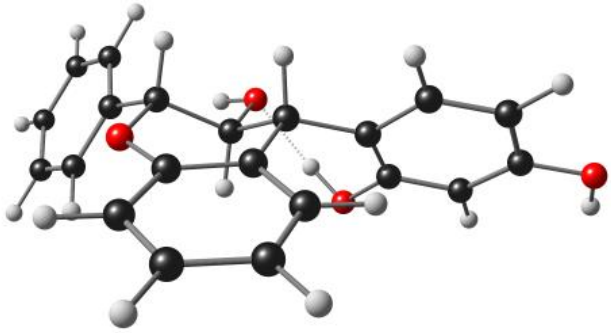


(2*R*,3*S*,4*S*)-*trans*-*trans* isomer (**5.52**)

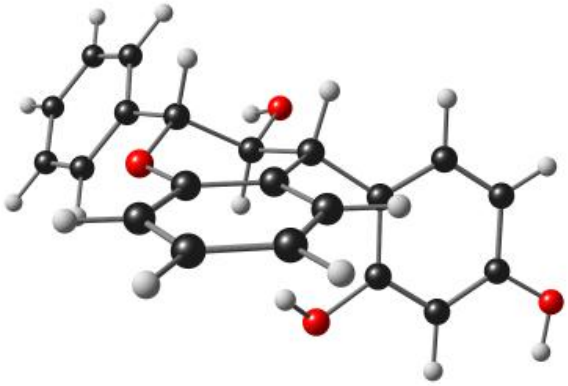
Figure 21. The pair of enantiomers.



Minimum energies at 80° (0 kcal/mol) (**5.67**)

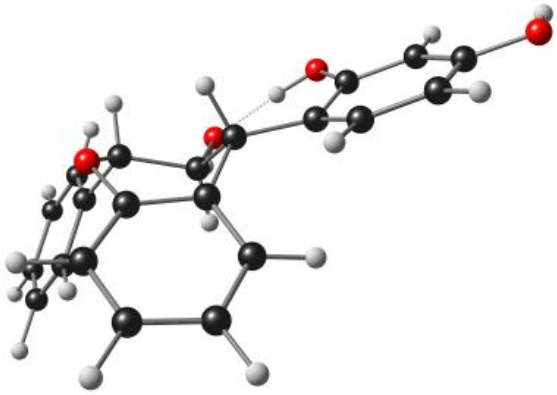


Minimum energies at -20° (6.53 kcal/mol) (**5.68**)

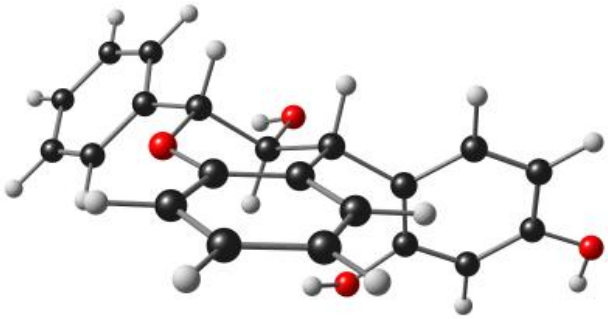


Minimum energies at -70° (3.13 kcal/mol) (**5.69**)

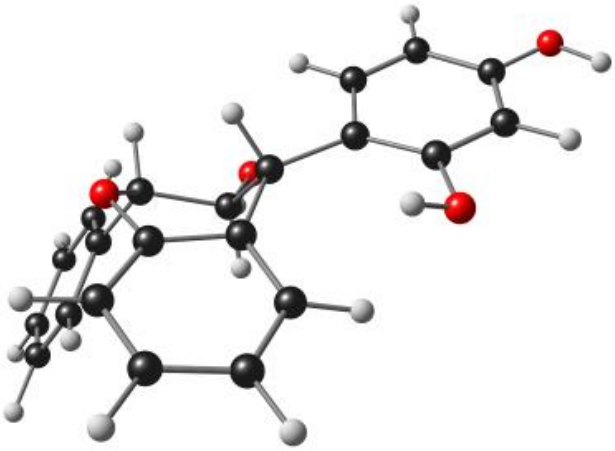
Figure 21(a). The 3-D conformations of (2*R*,3*S*,4*S*)-*trans*-*trans* isomer (**5.52**) in minimum energy state.



Maximum energies at 50° (19.99 kcal/mol) (**5.70**)



Maximum energies at -30° (10.28 kcal/mol) (**5.71**)



Maximum energies at -120° (29.42 kcal/mol) (**5.72**)

Figure 21(b). The 3-D conformations of (2*R*,3*S*,4*S*)-*trans*-*trans* isomer (**5.52**) in maximum energy state.

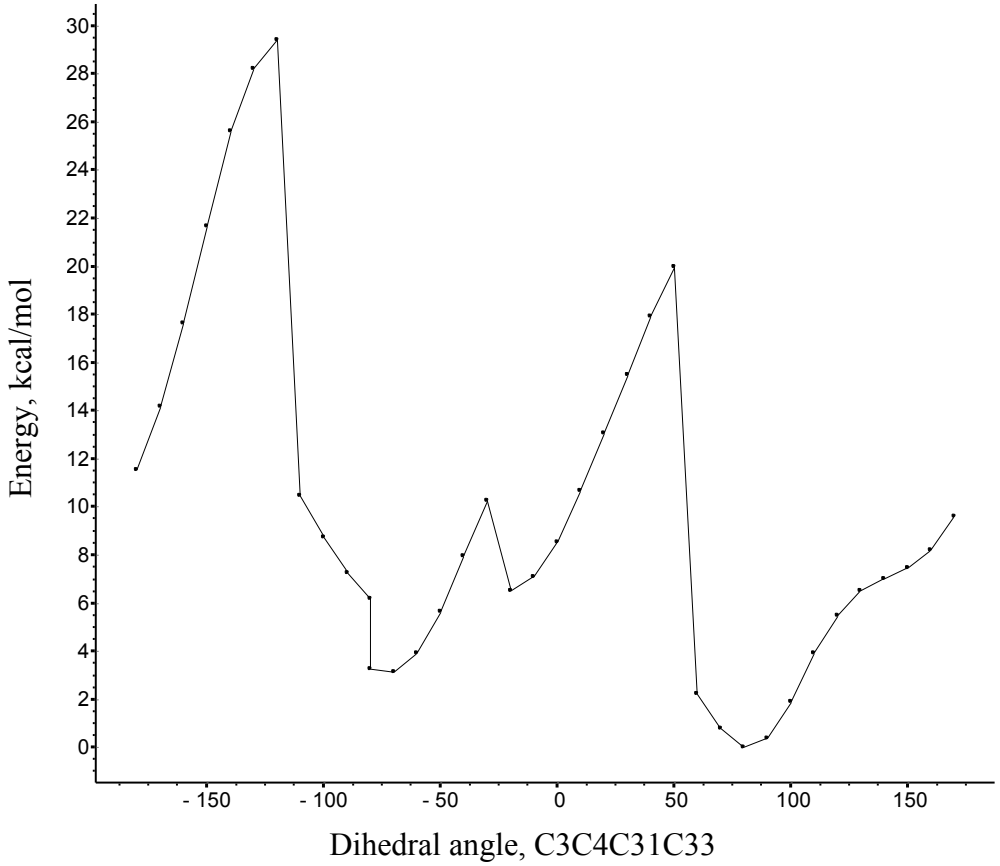


Figure 22. 2-D PES of the energy *vs*. dihedral angle (C3C4C31C33) calculated for rotation of the D-ring of (2*R*)-*equatorial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.52**) of 4-arylflavan-3-ols.

Table 9. The dihedral angles associated with the maximum and minimum energy.

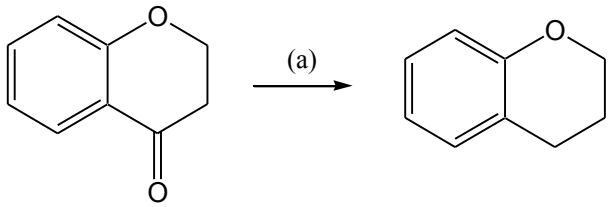
Dihedral angles	Energy, kcal/mol	Conformations
80°	0	Chair
-20°	6.53	Chair
-70°	3.13	Chair
50°	19.99	Boat
-30°	10.28	Chair
-120°	29.42	Boat

5.3 Synthesis of chromane, flavan, flavan-3-ols, 4-aryl-flavan and 4-arylflavan-3-ols

In order to be able to compare the DFT calculated and experimental IR absorbance spectra of the different compounds, a process for the preparation of these compounds was embarked upon.

5.3.1 Chromane (5.2)

The chromane (**5.2**) was obtained in 87% yield by the hydrogenation of commercially available 4-chromanone (**5.73**) over $Pd(OH)_2$ (Scheme 1). The ^1H NMR spectrum (Plate 89a) of (**5.2**) displayed an additional methylene signal at δ 2.86 (t, 2H, J = 6 Hz and 7 Hz, 4-CH_2) when compared to the spectrum of the starting material; thus proving the integrity of the product.



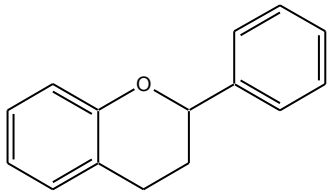
(**5.73**) (**5.2**)

Scheme 1. Preparation of chromane. Reagents: H_2, $Pd(OH)_2$, EtOH, 87%.

5.3.2 Flavan (5.3)

A racemic mixture of flavan (**5.3**) was obtained from J.H. Van Tonder[17] and therefore not prepared. The ^1H NMR (Plate 90a) of (**5.3**) displayed two methylene groups at [δ 3.09 - 3.01 (m, 1H, H-4) and 2.88 - 2.82 (m, 1H, H-4)] and [δ 2.28 - 2.24 (m, 1H, H-3) and δ 2.18 - 2.11 (m, 1H, H-3)], while the absence of carbonyl group was confirmed by the ^{13}C NMR spectrum of the product (Plate 90b) where the carbonyl resonance was replaced by a CH_2.

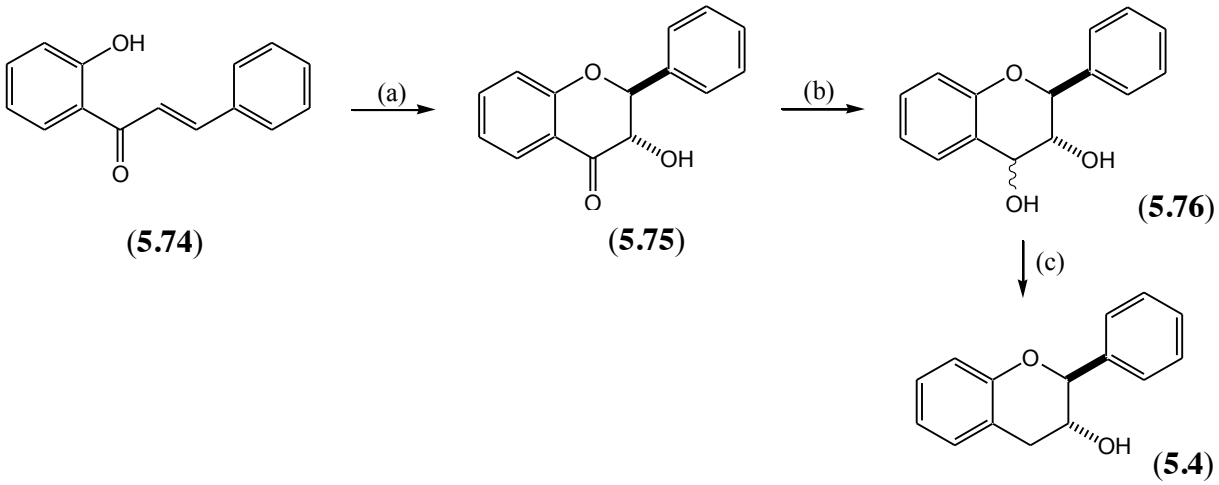
[17] Van Tonder, J.H. Studies Directed at the Stereoselective Synthesis of Flavonoids through the Hydrogenation of Prochiral Precursors. MSc. Thesis, University of the Free State, Bloemfontein, S.A., **2008**.



(**5.3**)

5.3.3 2,3-*trans*-Flavan-3-ol (5.4)

As indicated in Scheme 2, a racemic mixture of the flavan-3-ol (**5.4**) was prepared in 50% overall yield by standard methodology involving chalcone formation (EtOH, KOH) followd by oxidative cyclization to the dihydroflavonol (**5.75**) (30% H_2O_2, 1,4-dioxane, diethylamine) and eventually reduction ($NaBH_4$, EtOH). The structure of (**5.4**) was confirmed by its ^1H NMRspectrum (Plate 94a) where the methylene resonances at δ 3.11 [dd, 1H, *J* = 16.0 and 5.3 Hz, H-4(a)], δ 2.95 [dd, 1H, *J* = 16.0 and 8.9 Hz, H-4(b)] were accompanied by resonances at δ 4.84 (1H, d, *J* = 7.9 Hz, H-2) and δ 4.17-7.13 (1H, m, H-3). The 2,3-*trans* relative configuration of the flavan-3-ol (**5.4**) followed form the relatively large coupling constant (7.9 Hz) between H-2 and 3 in the ^1H NMR spectrum.

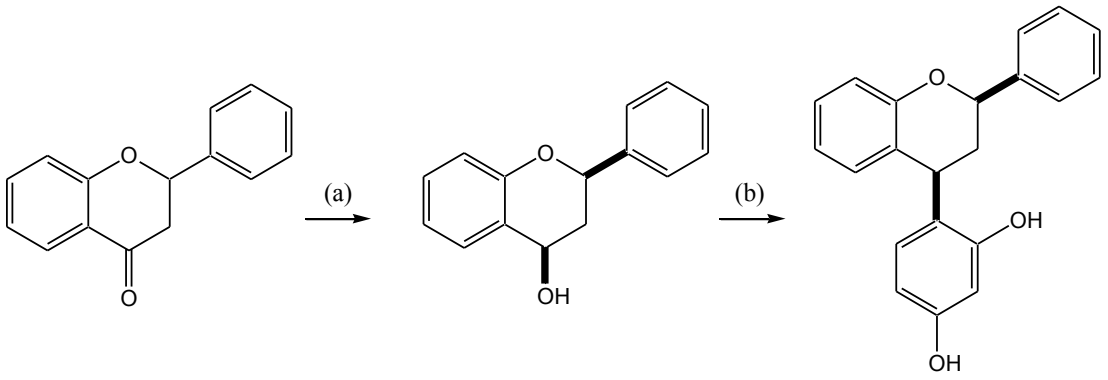


Scheme 2. Synthesis of 2,3-*trans*-flavan-3-ol. Reagents: (a) 30% H_2O_2, 1,4-dioxane, diethylamine, 0 ^oC, 43%; (b) $NaBH_4$, EtOH, 29%; (c) H_2, 5% Pd/C, EtOH, 50%.

5.3.4 1,4-*cis*-4-Arylflavan (5.5)

The 4-arylflavan (**5.5**) was obtained as a racemate in 27% overall yield from the flavanone (**5.77**) by $NaBH_4$ reduction followed by treatment of the flavan-4-ol (**5.78**) with resorcinol and PTSA in trifluoroethanol (Scheme 3). Apart from the expected aromatic resonances originating from the

unsubstituted A- and B-rings, the ^{1}H NMR spectrum (Plate 97a) of (**5.5**) displayed an aromatic ABX system [δ 6.58 (d, 1H, *J* = 8.3 Hz, H-6"), δ 6.42 (d, 1H, *J* = 2.4 Hz, H-3") and δ 6.29 (dd, 1 H, *J* = 8.3 Hz and 2.4 Hz, H-5")] together with two methine signals at δ 4.51 (m, 1H, H-4) and δ 5.01 (dd, 1H, *J* = 3.0 and 10.2 Hz, H-2).



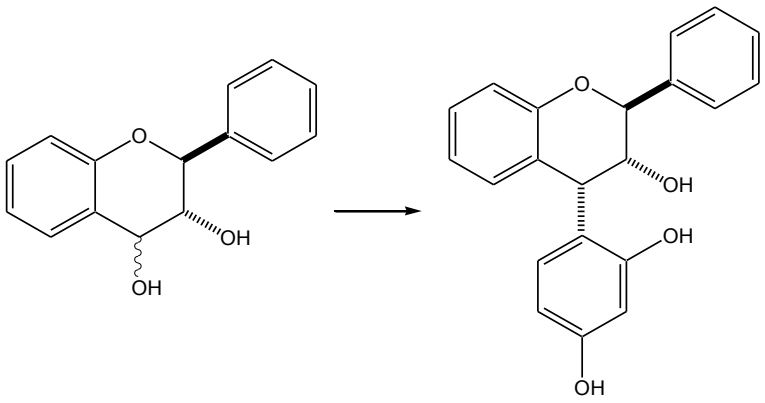
(**5.77**) (**5.78**) (**5.5**)

Scheme 3. Preparation of 1,4-*cis*-4-arylflavan. Reagents: (a) $NaBH_4$, EtOH, 63%; (b) resorcinol, CF_3CH_2OH, *p*-TSA, 43%.

5.3.5 2,3-*trans*-3,4-*cis*-4-Arylflavan-3-ol (5.6)

The racemic mixture of the 2,3-*trans*-3,4-*cis*-4-arylflavan-3-ol (**5.6**) was obtained from the 2,3-*trans*-flavan-3,4-diol (**5.79**) by reaction with resorcinol in the presence of *p*-TSA (1.5 eq) in CF_3CH_2OH (3 mL) (Scheme 4). The ^{1}H NMR spectrum (Plate 98a) of (**5.6**) displayed the ABX spin system expected form the resorcinol D-ring [δ 6.48 (d, 1H, *J* = 8.4 Hz, H-6"), δ 6.39 - 6.37 (m, 1H, H-3") and δ 6.30 (dd, 1 H, *J* = 8.4 and 2.1 Hz, H-5")], while also indicating three methine resonances at δ 4.93 (d, 1H, *J* = 8.3 Hz, H-2), 4.53 - 4.51 (m, 1H, H-4) and δ 4.38 (dd, 1H, *J* = 4.8 and 8.3 Hz, H-3). The relative stereochemistry around the heteocyclic C-ring followed from the coupling constant of 4.8 Hz between H-3 and 4 indicating it to be the 3,4-*cis*-isomer. However, this coupling constant was found to be in agreement with the modelling studies of Professor Ferreira[18] with regards to 2,4-*trans*- relative configuration (2,3-*trans*-3,4-*cis*).

18 Steynberg, J.P.; Brandt, E.V.; Ferreira, D. *J. Chem.* Soc., *Perkin Trans. 2* **1991**, 1569.



(**5.76**) (**5.6**)

Scheme 4. Preparation of 2,3-*trans*-3,4-*cis*-4-arylflavan-3-ol (**5.6**). Reagents: Resorcinol (0.027 g), *p*-TSA (1.5 eq.), CF_3CH_2OH (3 mL), 42%.

5.4 Comparison of calculated vibrational absorption bands with experimental IR spectra

5.4.1 Oxane

The Boltzmann distribution of 99.9949%, 0.0043% and 0.0008% in respect to the chair, 2,5-twisted boat and 1,4-twisted boat confomations in terms of the relative energies, showed that the most stable conformer of the oxane is the chair conformation (*cf* paragraph 5.2.1). The application of harmonic approximation in DFT vibrational frequency determination is permitting fundamental vibrational transitions only, which can be predicted within an *N*-atom molecule law theoretically, as $3N - 6$ fundamental transitions equivalent to the $3N$-6 normal modes. Therefore, for the chair conformation of oxane 42 fundamental transitions could be visualised as spikes in the calculated IR absorption spectrum (Figure 23). The absorption regions of the main functional groups e.g. C-C and C-O (800-1300 cm^{-1}), C=C and C=O (1500-1900 cm^{-1}), C≡C (2000-2300 cm^{-1}) and C-H (2700-3800 cm^{-1})[19] are found in a specific wavelength region. The DFT calculated IR spectrum of the chair conformation of oxane was therefore compared to the experimental IR absorbance spectrum of oxane which was obtained from Sigma Aldrich without analysis (Figure 23) and it was found that both the calculated and experimental IR spectrum of oxane are matched each other.

[19] Carey, F. Organic Chemistry: Oxidation of Alcohols: Preparation of Cyclohexanone, 5th ed.; Boulder, **2003**.

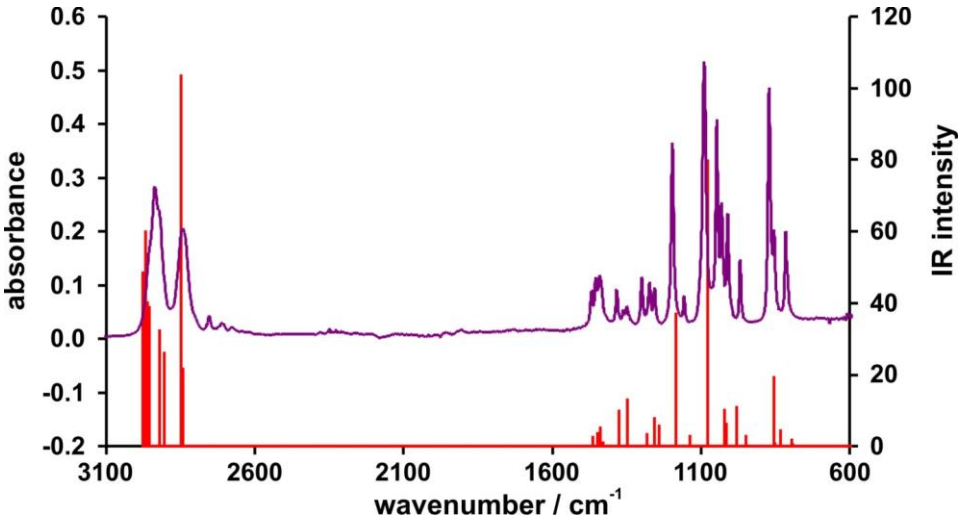


Figure 23. The DFT calculated (red spikes, y axis right) and experimental IR absorbance spectrum (purple smooth line, y axis left) of oxane. A scaling factor of 0.961 for the wavenumber of the calculated spectra was used.

A comparison between the calculated and experimental IR absorption bands for the chair conformation of an oxane as well as the type of vibrational movement observed for the relevant atoms are given in Table 10. It was also found that the calculated stretching frequencies are averagely *ca*. 30 cm^{-1} higher than the experimental peaks of the absorption bands between 800 and 1200 cm^{-1}. However, the calculated stretching frequencies are having less differences with scaled factor than unscaled frequency as to the experimental peaks bewteen 1200 and 1250 cm^{-1}. Finally, a good match was observed with scaled factor stretching frequency with experimental peaks between 1400 and 1500 cm^{-1}. In order to get a better agreement with the experimental IR spectrum, different scalling factors[20] can be applied to the calculated IR stretching frequencies.

Table 10. Assignment of calculated IR absorption bands of the chair conformer of oxane with atomic vibrations*.

No. spikes	**Calculated frequency (cm^{-1}) unscaled**	**frequency (cm^{-1}) scaled with 0.961**	**IR intensity**	**Experimental frequency (cm^{-1})**	**Type of motion**
1	244	234	0.5	below exp range	ring tor
2	252	242	3.6	below exp range	ring def

[20] National Institute of Standards and Technology. Computational Chemistry Comparison and Benchmark Database. http://cccbdb.nist.gov (accessed Dec 4, 2017).

3	401	385	4.3	below exp range	ring def
4	439	422	1.7	below exp range	ring def
5	466	448	0.0	below exp range	ring def
6	567	545	3.6	below exp range	ring def
7	825	793	0.7	not observed	ring def
8	827	795	2.2	815	ring def
9	868	834	4.6	854	ring def
10	886	851	1.0	not observed	CC str
11	889	854	19.6	871	CO str
12	989	950	3.3	968	CH_2 rock, wag
13	1020	980	11.3	1010	CC str
14	1056	1015	6.5	1030	CC str
15	1065	1023	10.3	1047	CC str
16	1120	1076	80.0	1090	CO str, CC str
17	1184	1138	3.2	1155	ring tor, CH_2 rock
18	1199	1152	0.0	not observed	CH_2 rock, twi
19	1231	1183	37.3	1195	CO str, CH_2 twi
20	1291	1241	5.9	1256	CH_2 wag
21	1308	1257	8.1	1272	CH_2 wag
22	1334	1282	3.6	1297	CH_2 twist
23	1361	1308	0.0	not observed	CH_2 wag
24	1387	1333	0.3	not observed	CH_2 twi
25	1390	1336	0.1	not observed	CH_2 wag, twi, rock
26	1403	1348	13.3	1358	CH_2 wag
27	1433	1377	10.3	1382	CH_2 wag, twi, scis
28	1488	1430	1.3	1424	CH_2 scis
29	1496	1438	5.4	1438	CH_2 scis
30	1507	1448	4.0	1453	CH_2 scis
31	1507	1448	0.1	not observed	CH_2 scis
32	1522	1463	2.8	1464	CH_2 scis
33	2956	2841	21.9	2837 broad peak	CH str
34	2963	2847	103.7		CH str
35	3024	2906	26.5	2918 broad peak	CH str
36	3037	2919	32.6		CH str

37	3038	2920	14.3		CH str
38	3076	2956	39.3	2925 broad peak	CH str
39	3081	2961	40.3		CH str
40	3087	2967	60.3		CH str
41	3095	2974	47.2		CH str
42	3097	2976	48.7		CH str

*Abbreviations: str, stretching; rock, rocking; wag, wagging; scis, scissoring; twi, twisting; def, deformation; tor, torsion.

5.4.2 Chromane

The DFT calculated and experimental IR (Solvent, $CHCl_3$) absorbance spectrum of chromane with scalling factor 0.961 is displeayed in Figure 24. The calculated IR spectrum of chromane has 54 fundamental transitions. The proposed assignments of the theoretical calculated IR absorbance bands for chromane are given in Table 11. It is also observed that the calculated and experimental spectra are very similar qualitatively.

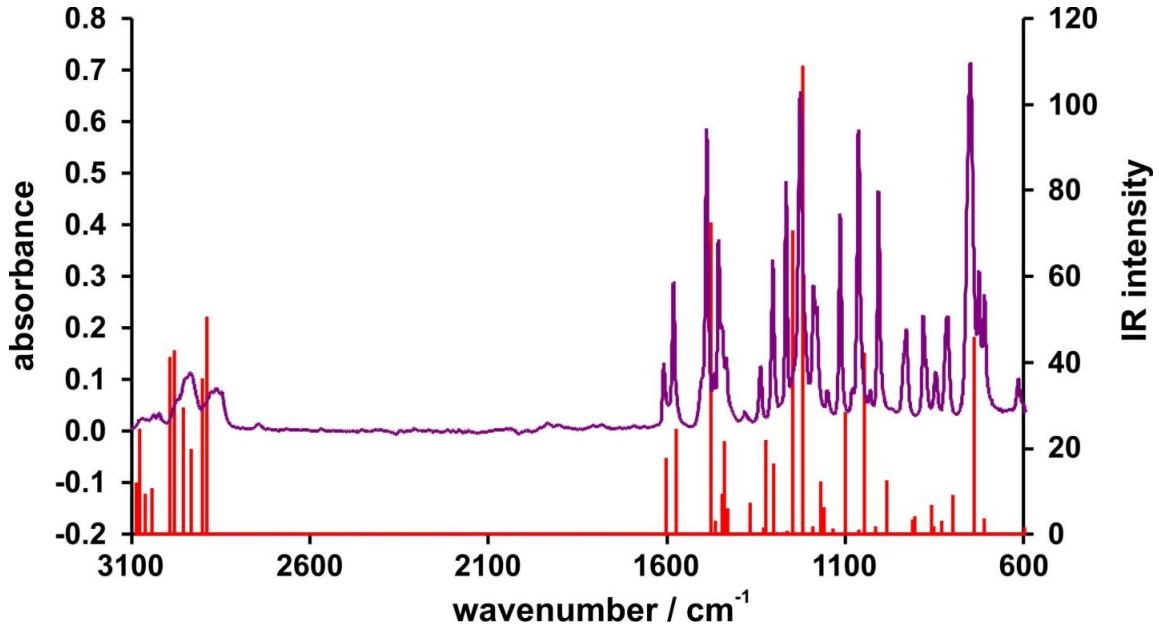


Figure 24. The DFT calculated (red spikes, y axis right) and experimental IR absorbance spectrum (purple smooth line, y axis left) of chromane. A scaling factor of 0.961 for the wavenumber of the calculated spectra was used.

5.4.3 Flavan

The DFT predicted IR spectrum of flavan was calculated according to the Boltzmann distribution of the two isomers, i.e (2*R*)-*equatoria*- and *axial* and was found to be in good agreement with the experimental spectrum (Solvent, $CHCl_3$) (Figure 25). The calculated IR spectrum of flavan has 84 fundamental transitions. The proposed identification of the 54 calculated peaks of chromane and the 84 peaks of flavan is given in Table 11.

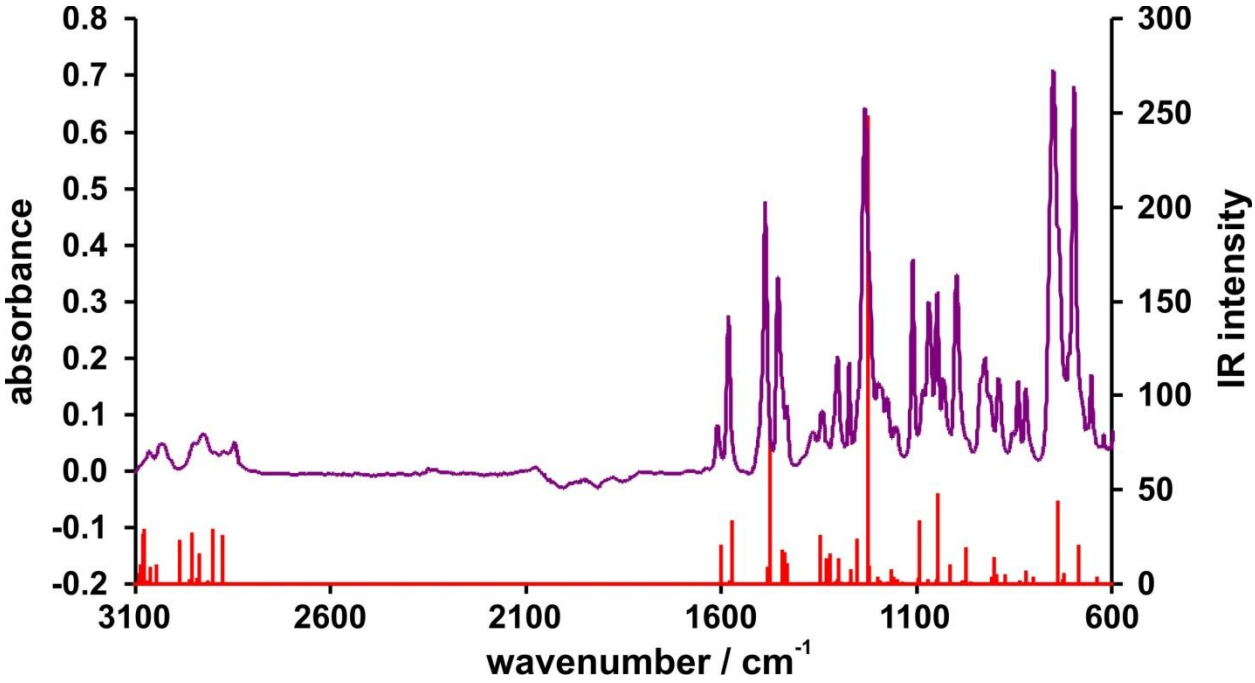
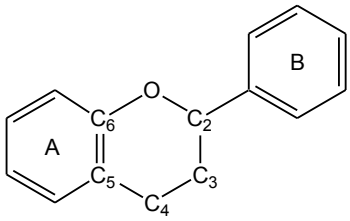


Figure 25. The DFT calculated (red spikes, y axis right) and experimental IR absorbance spectrum (purple smooth line, y axis left) of flavan. A scaling factor of 0.961 for the wavenumber of the calculated spectra was applied.



(**5.3**) Flavan

Table 11. Proposed assignment to theoretical calculated IR absorbance bands for chromane and flavan. The calculated bands with an intensity larger than 20 is indicated in bolt font.

Chromane				Flavan				
No. spikes	**calc. f (cm^{-1})**	**calc. f with 0.961 (cm^{-1})**	**calc. inten-sity**	**No. spikes**	**calc. f (cm^{-1})**	**calc. f with 0.961 (cm^{-1})**	**calc. inten-sity**	**Type of motion**
				1	28	27	0.1	C2 wag (B-ring wag)
1	97	93	2.5	2	44	42	0.5	C2 rock
				3	80	77	0.1	C2 wag
2	157	151	1.3	4	141	136	2.7	C3 rock
				5	162	156	0.6	C2 and C4 rock
				6	247	237	0.5	C2 twist
				7	262	252	0.4	C-ring twist
3	282	271	0.6	8	279	268	0.6	C-ring twist
4	310	298	3.8	9	296	284	1	C-ring twist
5	362	348	1.7	10	385	370	0.7	C-ring twist
				11	416	400	0.4	B-ring twist
6	441	424	1.8	12	443	426	1.3	A- and C-ring str
7	467	449	1.3	13	468	450	2.9	A- and C-ring twist
8	482	463	0.5	14	527	506	3.1	A-, B- and C-ring twist
				15	533	512	1.6	A-, B- and C-ring twist
9	546	525	0.8	16	548	527	0.8	A-, B- and C-ring twist
10	583	560	1.9	17	585	562	4.4	A-, B- and C-ring twist
11	623	599	1.7	18	603	579	0.4	A-, B- and C-ring twist
				19	635	610	0.2	B-ring twist
				20	665	639	4	A-, B- and C-ring twist
				21	715	687	**21**	**B-ring wag**
12	721	693	0.3	22	721	693	0.5	A-ring wag
13	740	711	3.5	23	750	721	5.7	A- and C-ring twist
14	768	738	**45.8**	24	768	738	**26.8**	**CH wag (A-ring)**
				25	770	740	**47.4**	**CH rock (A- and C-ring)**
15	830	798	9.1	26	832	800	3.7	CH_2 CH rock
16	864	830	3.3	27	853	820	7.3	A- and C-ring twist
				28	863	829	0	CH wag (B-ring)

17	887	852	1.9	29	871	837	1.5	CH wag (A-ring)
18	894	859	6.8	30	908	873	5.1	C-ring twist
				31	930	894	5.1	B- and C-ring twist
19	942	905	4.1	32	936	899	15.5	A-, B- and C-ring twist
20	947	910	3.5	33	945	908	3.9	CH rock (A-ring)
21	974	936	0	34	975	937	0	CH rock (A-ring)
				35	975	937	0.1	CH rock (B-ring)
				36	1000	961	1.2	CH rock (B-ring)
22	1024	984	12.5	37	1013	973	**21.1**	C3 str
				38	1017	977	0.6	B-ring twist
				39	1055	1014	11.2	B-ring twist
23	1058	1017	1.9	40	1057	1016	2	A-, B- and C-ring twist
				41	1073	1031	13.8	A-, B- and C-ring twist
24	1090	1047	**42.3**	42	1089	1047	**51.9**	C3 and C4 str
25	1104	1061	1.2	43	1113	1070	8.6	CH wag (B-ring)
26	1144	1099	**28.4**	44	1137	1093	**36.7**	CH rock (A-ring)
27	1181	1135	1.2	45	1181	1135	1.3	CH rock (A-ring)
				46	1187	1141	0.1	CH rock (B-ring)
28	1206	1159	6.3	47	1195	1148	2.4	CH_2 wag (C3,C4); CH wag (C2)
				48	1205	1158	3.8	CH wag (B-ring)
29	1215	1168	12.2	49	1213	1166	8.2	A-, B- and C-ring twist
				50	1223	1175	1.4	A-, B- and C-ring twist
30	1239	1191	2	51	1242	1194	1.6	A-, B- and C-ring twist
31	1268	1219	**109.2**	52	1274	1224	**269**	**CO str + A-ring twist**
32	1298	1247	**70.8**	53	1304	1253	**22.8**	CH_2 wag + CH wag (A-ring)
33	1313	1262	0.9	54	1321	1269	8.1	CH_2 wag + CH wag (B-ring)
				55	1345	1293	0.9	CH_2 wag + CH wag (B-ring)
34	1353	1300	16.5	56	1353	1300	14.4	A-, B- and C-ring twist
				57	1362	1309	0.9	B-ring twist
35	1375	1321	**21.9**	58	1375	1321	17.6	CH_2 wag (C3,C4); A-ring twist
36	1382	1328	1.7	59	1384	1330	14.6	CH, CH_2 twist (C2, C3, C4)
37	1423	1368	7.4	60	1402	1347	**28.1**	CH, CH_2 twist (C2, C3), B-ring twist
38	1488	1430	6.1	61	1488	1430	10.2	CH_2 sci (C3 & C4)

				62	1494	1436	18.4	CH_2 scis, A- and B-ring twist
39	1496	1438	**21.6**	63	1499	1441	5.2	CH_2 scis, A- and B-ring twist
40	1503	1444	9.5	4	1501	1442	19.8	CH_2 scis, A-ring twist
41	1522	1463	3.1					
42	1538	1478	**72.5**	65	1534	1474	**95.2**	4-CH_2 scis, A-ring twist
				66	1541	1481	9.4	B-ring twist
43	1637	1573	**24.6**	67	1637	1573	**36.4**	A- and B-ring twist
				68	1644	1580	1.9	A- and B-ring twist
				69	1664	1599	1.1	A- and B-ring twist
44	1666	1601	17.9	70	1666	1601	**22.5**	A- and B-ring twist
45	3007	2890	**50.7**	71	2993	2876	**27.7**	CH wag (C2)
46	3019	2901	**36.4**	72	3019	2901	**31.8**	CH_2 sym str (C4)
47	3051	2932	19.9	73	3054	2935	17.6	CH_2 sym str (C3)
48	3074	2954	**29.5**	74	3074	2954	**29.2**	CH_2 asym str (C4)
49	3099	2978	**42.8**	75	3106	2985	**25.1**	CH_2 asym str (C3)
50	3112	2991	**41.2**					
51	3167	3043	10.7	76	3168	3044	10.4	CH str (A-ring)
				77	3169	3045	8.7	CH str (B-ring)
				78	3181	3057	0.4	CH str (B-ring)
52	3185	3061	9.4	79	3186	3062	9.5	CH str (A-ring)
				80	3191	3067	**25.2**	CH str (B-ring)
53	3202	3077	**24.6**	81	3202	3077	**29.7**	CH str (A-ring)
				82	3204	3079	**28.6**	CH str (B-ring)
54	3212	3087	11.9	83	3213	3088	11.3	CH str (A-ring)
				84	3216	3091	5.9	CH str (B-ring)

*Abbreviations: calc, calculated; f, frequency; str, stretching; rock, rocking; wag, wagging; scis, scissoring; twi, twisting; def, deformation; tor, torsion.

As is indicated in Figure 26, *axial* and *equatorial* conformers of flavan have different IR absorption bands in the vicinity of the stereogenic center (C-2) with the (2*R*)-*axial*- and (2*R*)-*equatorial* conformers displaying bands at 2929 and 2876 cm^{-1} respectively. A symmetric C-H stretching at C4 with frequencies 2914 and 2901 cm^{-1} in respect to (2*R*)-*axial*)- and (2*R*)-*equatorial* conformers separately was also observed.

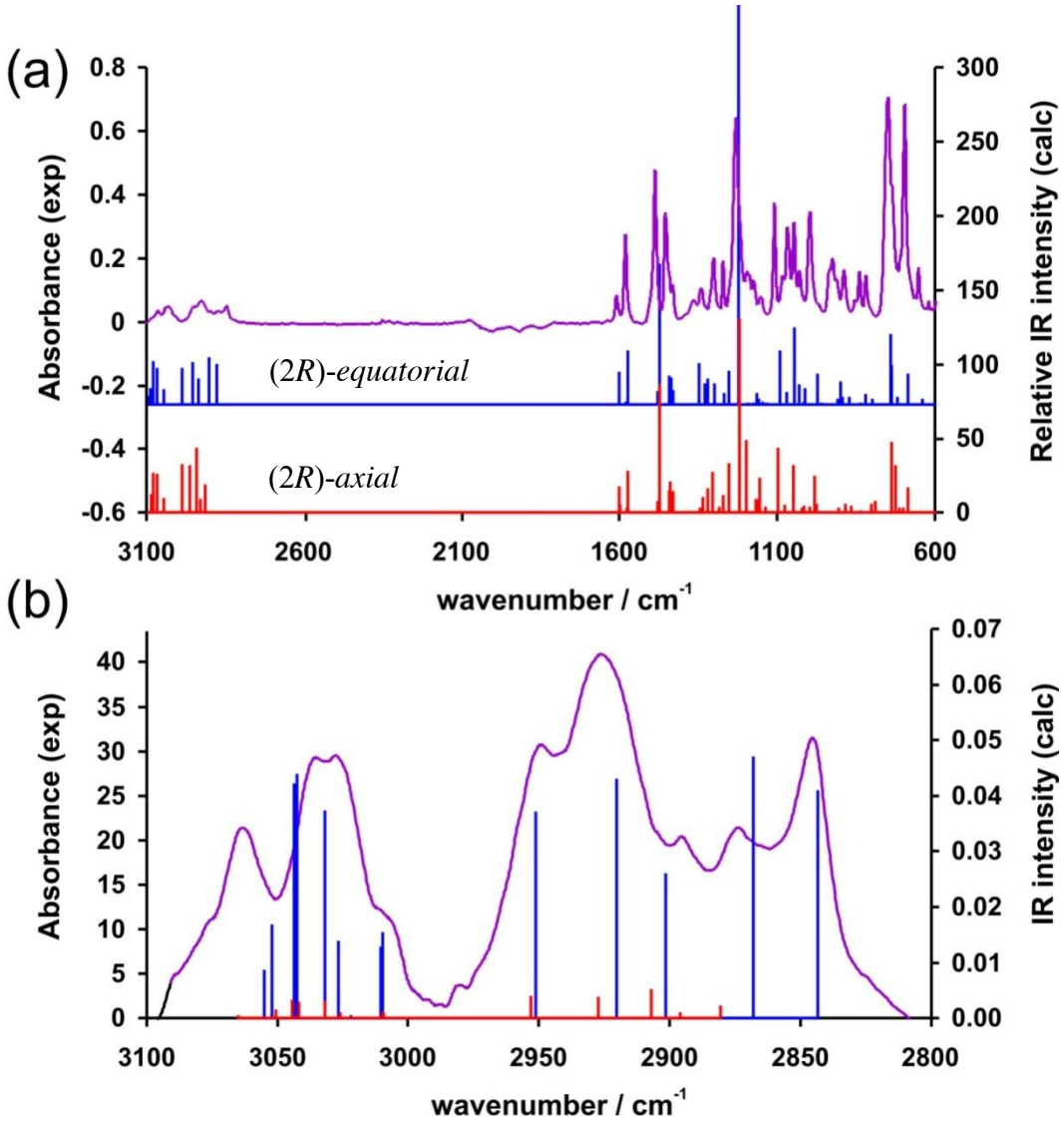


Figure 26. (a) The DFT calculated (red spikes (2*R*)-*axial* conformer, blue spikes and (2*R*)-*equatorial* conformer, y axis right) and experimental IR absorbance spectrum (purple smooth line, y axis left) of flavan. A scaling factor of 0.961 for the wavenumber of the calculated spectra was used.

Figure 27 gives an overlay of the experimental and calculated spectra of chromane (green) and flavan (magenta) and the values are compared in Table 13. The difference between flavan and chromane is observed by a fingerprint peak at 697 cm^{-1} experimentally, which was assigned to the CH wagging of the B-ring of chromane. The absorption bands at 749 and 737 cm^{-1} experimentally were assigned to the CH wagging of A-ring and were found to be very similar in wavelength for flavan and oxane. The other similar wavelengths for both chromane and flavan were detected at 1113 and 1109 cm^{-1} respectively for CH rocking of A-ring. The motion of CH_2

scissoring and CH rocking of the A-ring is observed for chromane and flavan at a very identical wavelengths of 1488 and 1487 cm^{-1} respectively, see Table 13.

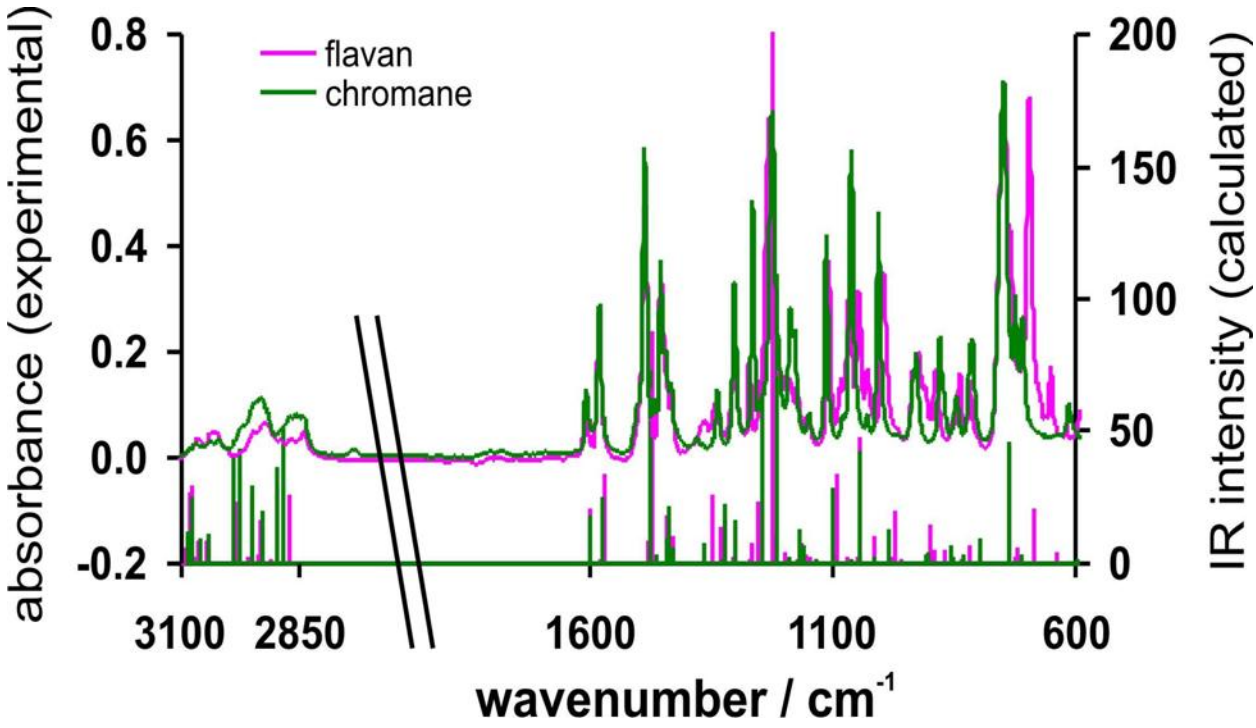


Figure 27. Overlay of the experimental (smooth lines) and calculated (spikes) spectra of chromane (green) and flavan (magenta).

Table 12. Assignment of the main calculated IR absorbance bands for oxane, chromane and flavan.

Oxane			**Chromane**			**Flavan**			**Type of motion**
freq. (cm^{-1}) unscaled	freq. (cm^{-1}) scaled	inten-sity	freq. (cm^{-1}) unscaled	freq. (cm^{-1}) scaled	inten-sity	freq. (cm^{-1}) unscaled	freq. (cm^{-1}) scaled	inten-sity	
-	-	-	768	738	46	768	738	28	CH bending out of plane (ring A)
-	-	-	-	-	-	770	740	44	CH bending out of plane (ring B)
889	854	20	864	830	3	853	819	7	CO symmetric stretching
1120	1076	80	1090	1047	42	1039	1046	48	CO asymmetric stretching + CH_2 twist + CH rock
1231	1183	38	1268	1219	109	1274	1224	249	CO asymmetric stretching
-	-	-	1538	1478	73	1534	1475	88	CH bending in plane (ring A)

The main calculated frequency bands of oxane, chromane and flavan are presented in Table 12. It was found that all three molecules containing CH stretching motions lie at the frequency region 2900 – 3100 cm^{-1}. The peak at 854 cm^{-1} was assigned as a strong symmetric C-O stretching for oxane, however, chromane and flavan have weak symmetric C-O stretching due to the fused benzene A-ring affect. The asymmetric C-O stretching frequency is observed separately for oxane, chromane and flavan in Table 12. The A-ring in both chromane and flavan affordeds peaks at 738 and *ca*. 1476 cm^{-1} represent strong out of plane CH bending and in plane CH bending motion, respectively. The B-ring in flavan was assigned to the out of plane CH bending motion at 740 cm^{-1}.

Table 13. Comparison of the main IR absorbance bands of chromane and flavan.

Chromane					**Flavan**					**Type of motion**
No.	calc. f unscaled (cm^{-1})	calc. f scaled with 0.961 (cm^{-1})	exp. f (cm^{-1})	calc. inten-sity	No.	calc. f unscaled (cm^{-1})	calc. f scaled with 0.961 (cm^{-1})	exp. f (cm^{-1})	calc. inten-sity	
					21	715	687	697	21	CH wag (B-ring)
14	768	738	749	45.8	24	768	738	737	26.8	CH wag (A-ring)
		0			25	770	740	749	47.4	CH_2 + CH rock
24	1090	1047	1063	42.3	42	1089	1047	1046	51.9	CH_2 wag + CH rock (A-ring)
26	1144	1099	1113	28.4	44	1137	1093	1109	36.7	CH rock (A-ring)
31	1268	1219	1225	109.2	52	1274	1224	1230	269	CO str + CH_2 twist + CH rock
42	1538	1478	1488	72.5	65	1534	1474	1487	95.2	CH_2 scis + CH rock (A-ring)

5.4.4 2,3-*trans*-Flavan-3-ol

Figure 28 gives the DFT calculated IR absorbance spectra of the most populated conformation of flavan-3-ols, (2*S*)-*equatorial*, (3*S*)-*axial* (**5.35**) (99.2%) and Figure 29 gives an overlay of the DFT calculated and experimental IR absorbance spectra of the second most populated conformation, (2*S*)-*equatorial*, (3*R*)-*equatorial* (**5.37**) (99.2%) of flavan-3-ol (Solvent, $CHCl_3$). The assignment and comparison of the main calculated IR absorbance bands between flavan and flavan-3-ol was investigated, see Table 14. The calculated IR spectrum of flavan-3-ols (31 atoms) has 87 fundamental transitions. The proposed assignment of the main calculated peaks of 2,3-*trans*-flavan-3-ol is given in Table 14. The IR spectrum shows good correlation between

calculated and experimental of absorption bands at 700 cm^{-1} and 1600 cm^{-1} and at 2800 cm^{-1} and 3100 cm^{-1}.

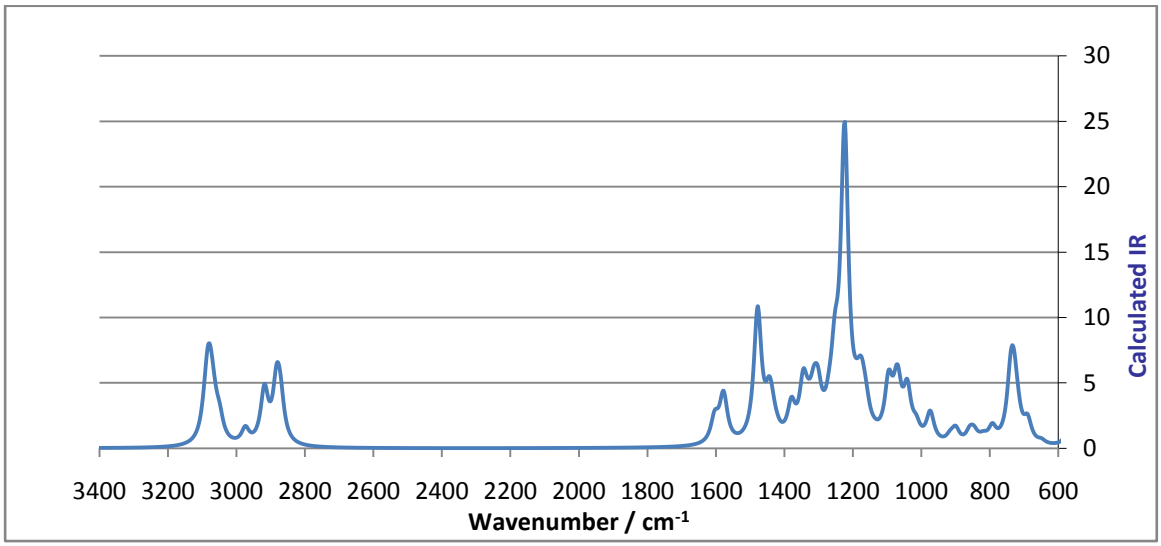


Figure 28. The DFT calculated IR absorbance spectrum of (2*S*)-*equatorial*, (3*S*)-*axial* (**5.35**) of flavan-3-ol.

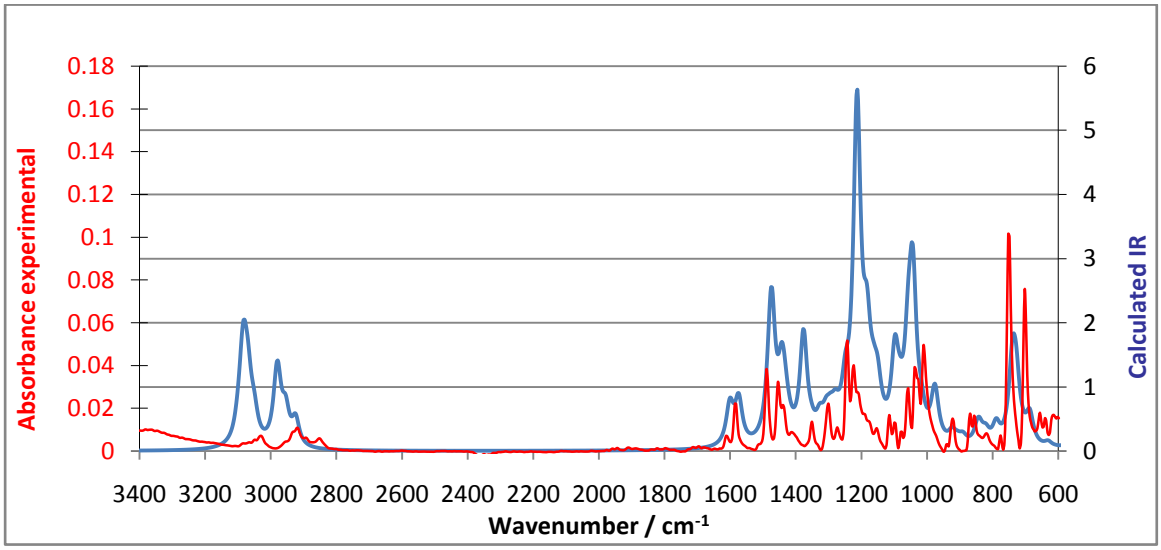


Figure 29. The DFT calculated (blue smooth line, y axis right) and experimental (red smooth line, y axis left) IR absorbance spectrum of (2*S*)-*equatorial*, (3*R*)-*equatorial* (**5.37**) of flavan-3-ol.

Table 14 gives assignment and comparison of the main calculated IR absorbance bands (between 700 cm^{-1} to 1600 cm^{-1}) for flavan and flavan-3-ol. The absorption band at *ca* 740 cm^{-1} is attributable to CH bending out-of-plane vibration and C-O symmetric stretching at 1014 cm^{-1} is assigned for both compounds. The C-O asymmetric stretching at *ca* 1225 cm^{-1} and the CH bending vibration at *ca* 1475 cm^{-1} is detected in both compounds.

Table 14. Assignment and comparison of the main calculated IR absorbance bands between flavan and flavan-3-ols. Frequencies (cm^{-1}) scaled with 0.962.

Flavan			Flavan-3-ols			Type of motion
freq. (cm^{-1})	freq. (cm^{-1})	intensity	freq. (cm^{-1})	freq. (cm^{-1})	intensity	
unscaled	scaled		unscaled	scaled		
768	738	27	769	738	13	CH bending out-of-plane
770	740	47	770	740	58	CH bending out-of-plane
853	819	7	-	-	-	CO symmetric stretching /CH wag/ring twist
1055	1014	11	1056	1014	0.8	CO symmetric stretching + CH_2 twist + CH rock
1274	1224	269	1275	1225	214	CO asymmetric stretching/CH_2 wag + CH wag
1534	1475	95	1535	1475	97	CH bending in plane (ring A)

5.4.5 1,4-*cis*-4-Arylflavan

The DFT calculated IR absorbance spectra of the most populated conformations (2*S*)-*equatorial*, (4*R*)-*axial* (**5.43**) (97.9%) (Figure 30) and (2*S*)-*equatorial*, (4*S*)-*equatorial* (**5.45**) (99.8%) (Figure 31) which shows an overlay of the DFT calculated and experimental IR absorbance spectra of of 4-arylflavan (Solvent, $CHCl_3$). The assignment and comparison of the main calculated IR absorbance bands bewteen flavan-3-ol and 4-arylflavan was investigated, see Table 15. The calculated IR spectrum of 4-arylflavan (42 atoms) has 120 fundamental transitions. The proposed assignment of the main calculated peaks of 1,4-*cis*-4-arylflavan is given in Table 15.

Since the real compound, 1,4-*cis*-4-arylflavan is made with (2*R*4*R*) configuration (*cf* paragraph 5.3.4, Scheme 3), and it has the enantiomeric relationships with the (2*S*4*S*) isomer. Therefore, the comparison between the calculated and experimental IR absorbance spectrum will focus on (2*S*)-*equatorial*, (4*S*)-*equatorial* (**5.45**) isomer.

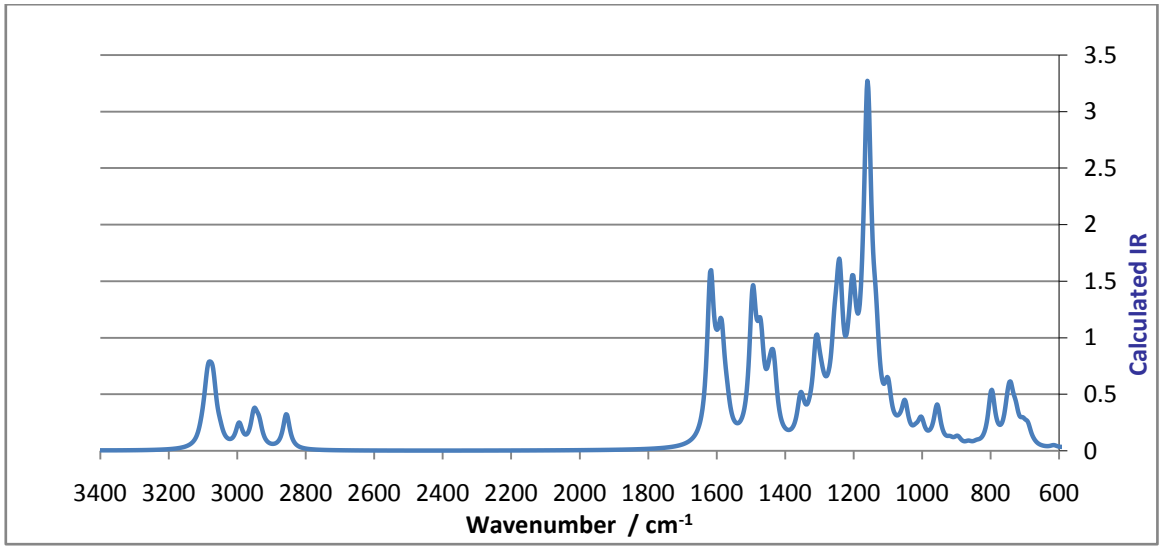


Figure 30. The DFT calculated IR absorbance spectrum of (2*S*)-*equatorial*, (4*R*)-*axial* (**5.43**) of 4-arylflavan. A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

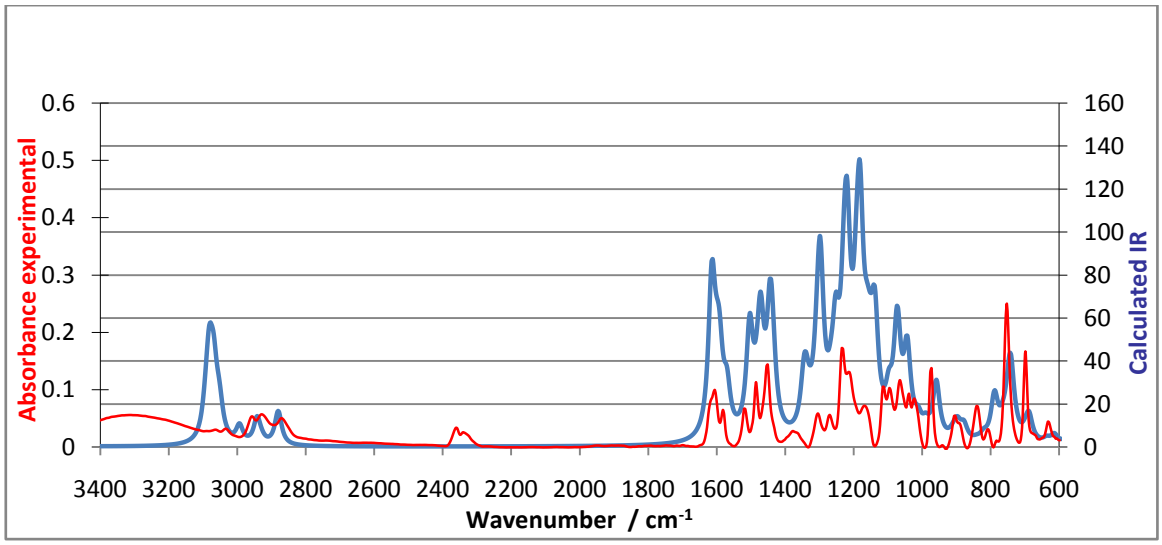


Figure 31. The DFT calculated (blue smooth line, y axis right) and experimental (red smooth line, y axis left) IR absorbance spectrum of (2*S*)-*equatorial*, (4*S*)-*equatorial* (**5.45**) of 4-arylflavan. A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

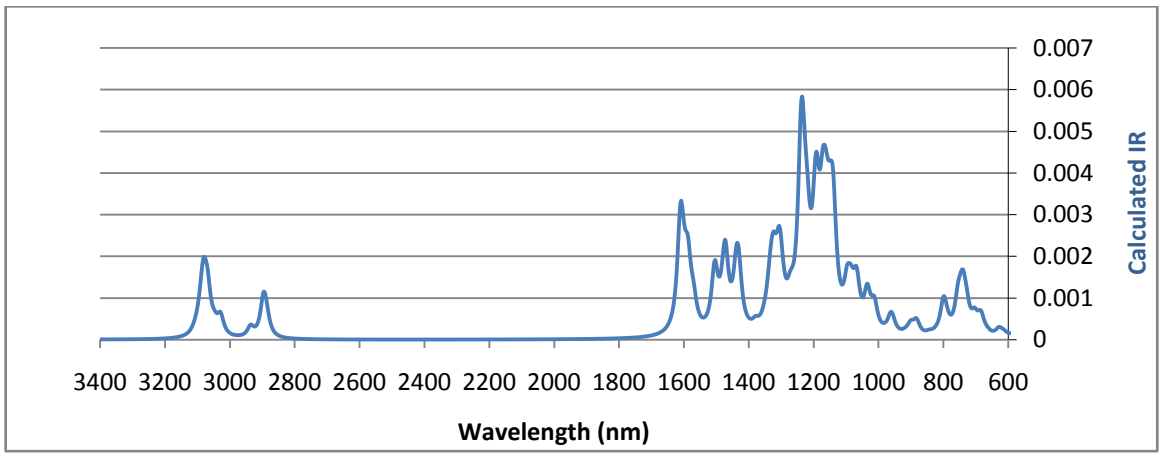
The IR spectrum shows good correlation between calculated and experimental of absorption band at 600 cm^{-1} and 1700 cm^{-1} and at 2800 cm^{-1} and 3000 cm^{-1}. Assignment of IR absorbance frequency at 819 cm^{-1} the C-O symmetric stretching vibration is activated and the absorption band at 1226 cm^{-1} attributable to the C-O asymmetric stretching. The CH bending in plane of A-ring has absorption band at 1470 cm^{-1} (see Table 15).

Table 15. Assignment and comparison of the main calculated IR absorbance bands between flavan-3-ol and 4-arylflavan. Frequencies (cm^{-1}) scaled with 0.962.

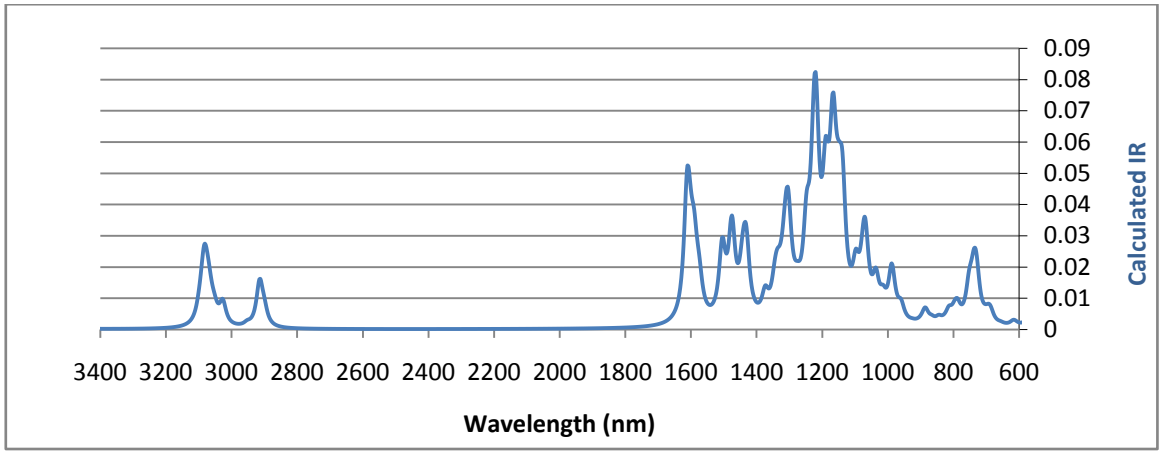
Flavan-3-ols			4-Arylflavan			Type of motion
freq. (cm^{-1}) unscaled	freq. (cm^{-1}) scaled	intensity	freq. (cm^{-1}) unscaled	freq. (cm^{-1}) scaled	intensity	
769	738	13	769	739	38	CH bending out-of-plane
770	740	58	773	743	29	CH bending out-of-plane
-	-	-	852	819	5	CO symmetric stretching /CH wag/ring twist
1056	1014	0.8	1029	989	9	CO symmetric stretching + CH_2 twist + CH rock
1275	1225	214	1276	1226	76	CO asymmetric stretching/CH_2 wag + CH wag
1535	1475	97	1530	1470	90	CH bending in plane (ring A)

5.4.6 2,3-*trans*-3,4-*cis*-4-Arylflavan-3-ols

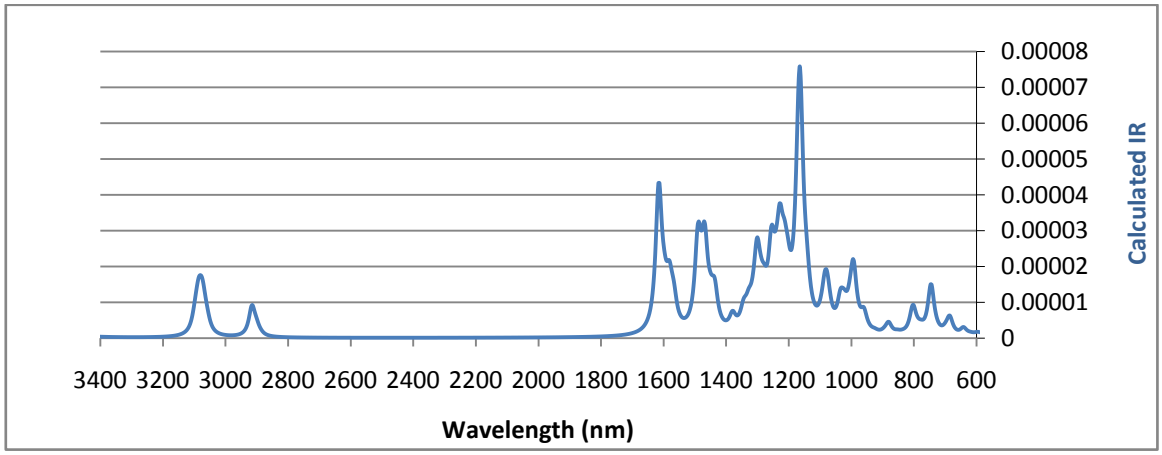
Figure 32 gives an overlay of the DFT calculated and experimental IR absorbance spectra of (2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**) (76.5%) of 4-arylflavan-3-ols (Solvent, $CHCl_3$). The DFT calculated IR absorbance spectra of the most populated conformations of 4-arylflavan-3-ols, (**5.55**) (86%), (**5.57**) (51.3%) and (**5.59**) (100%) were also inspected and given in Figure 32. The calculated IR spectrum of the 4-arylflavan-3-ol (43 atoms) has 123 fundamental transitions. The assignment and comparison of the main calculated IR absorbance bands bewteen 4-arylflavan and 4-arylflavan-3-ol was investigated and is given in Table 16.



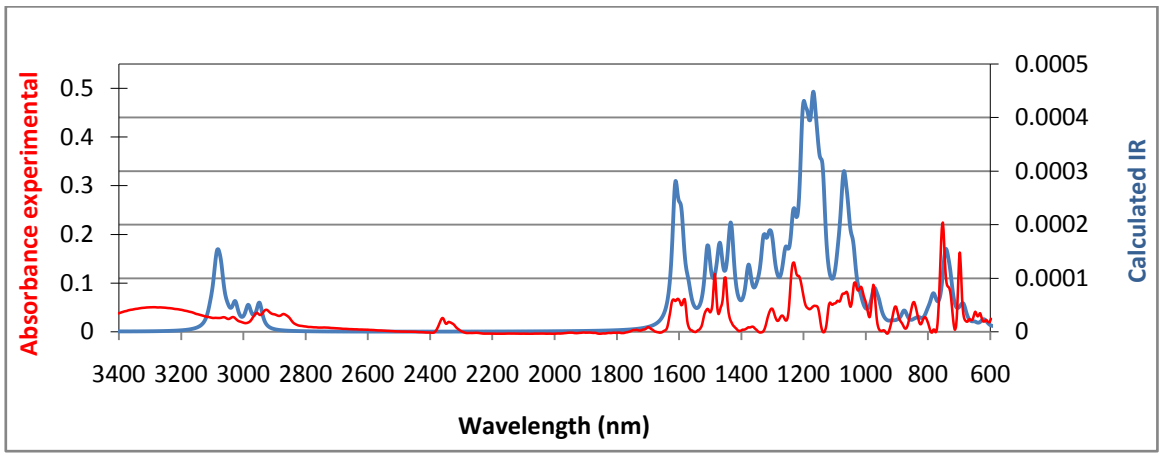
(a) (2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.55**).



(b) (2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.57**).



(c) (2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial* isomer (**5.59**).



(d) (2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**).

Figure 32. The DFT calculated IR absorbance spectrum of (a) – (c) (**5.55**), (**5.57**) and (**5.59**) and the calculated (blue smooth line, y axis right) and experimental (red smooth line, y axis left) IR absorbance spectrum of (d) (**5.61**) of 4-arylflavan-3-ol. A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

The IR spectrum shows good correlation between calculated and experimental of absorption band at 800 cm^{-1} and 1700 cm^{-1}. Assignment of IR absorbance peaks between 4-arylflavan and 4-arylflavan-3-ols is given in Table 16. The absorption band at *ca* 740 cm^{-1} is attributable to CH bending out-of-plane vibration for both compounds. The C-O symmetric stretching is assigned for both 4-arylflavan and 4-arylflavan-3-ols at 819 cm^{-1} and 833 cm^{-1} respectively. The C-O asymmetric stretching at *ca* 1220 cm^{-1} and the CH bending vibration at *ca* 1470 cm^{-1} is assigned separately for both compounds.

Table 16. Assignment and comparison of the main calculated IR absorbance bands between 4-arylflavan and 4-arylflavan-3-ols. Frequencies (cm^{-1}) scaled with 0.961.

4-Arylflavan			**4-Arylflavan-3-ols**			**Type of motion**
freq. (cm^{-1})	freq. (cm^{-1})	intensity	freq. (cm^{-1})	freq. (cm^{-1})	intensity	
unscaled	scaled		unscaled	scaled		
769	739	38	772	743	53	CH bending out-of-plane
773	743	29	775	745	16	CH bending out-of-plane
852	819	5	867	833	0.5	CO symmetric stretching /CH wag/ring twist
1029	989	9	1027	987	1.1	CO symmetric stretching + CH_2 twist + CH rock
1276	1226	76	1270	1220	130	CO asymmetric stretching/CH_2 wag + CH wag
1530	1470	90	1531	1471	84	CH bending in plane (ring A)

5.5 VCD spectra* of flavan, flavan-3-ol, 4-arylflavan and 4-arylflavan-3-ol

5.5.1 Flavan

Since flavan has a chiral centre, a VCD spectrum can be used to distinguish between the R and S enantiomers of flavan. Unlike the experimental IR we could only obtain the calculated VCD spectrum for flavan. The calculated VCD spectrum was done by DFT calculations using B3LYP Becke hybrid functional and the 6-31G* basis set and the optimized geometry of the different stable conformations flavan.

Figure 33 gives the calculated VCD spectra of flavan of the highest population, (2*R*)-*equatorial* (**5.29**) (92.4%). The most dominated peak is where the absorption bands going from 738 cm^{-1} at (+) intensity to 740 cm^{-1} at (-) intensity. Apart from the most donimated peaks, (+) intensity at 1224 and 1330 cm^{-1} and (-) intensity at 2954 cm^{-1} is also significant. However, over much of the spectrum, VCD intensities are weaker below 740 cm^{-1} for the conformation.

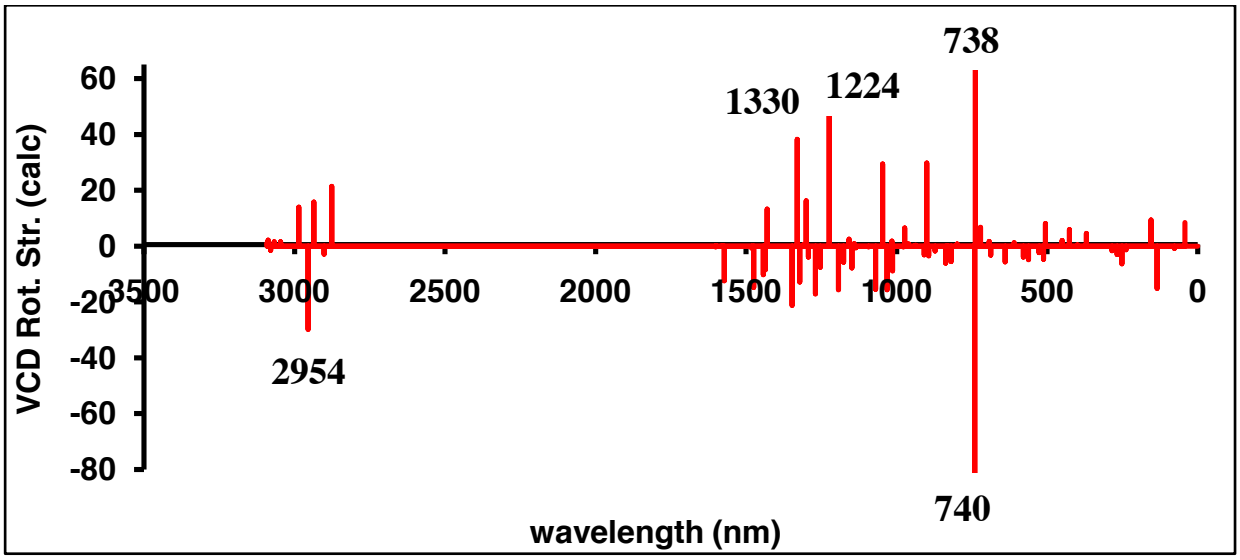
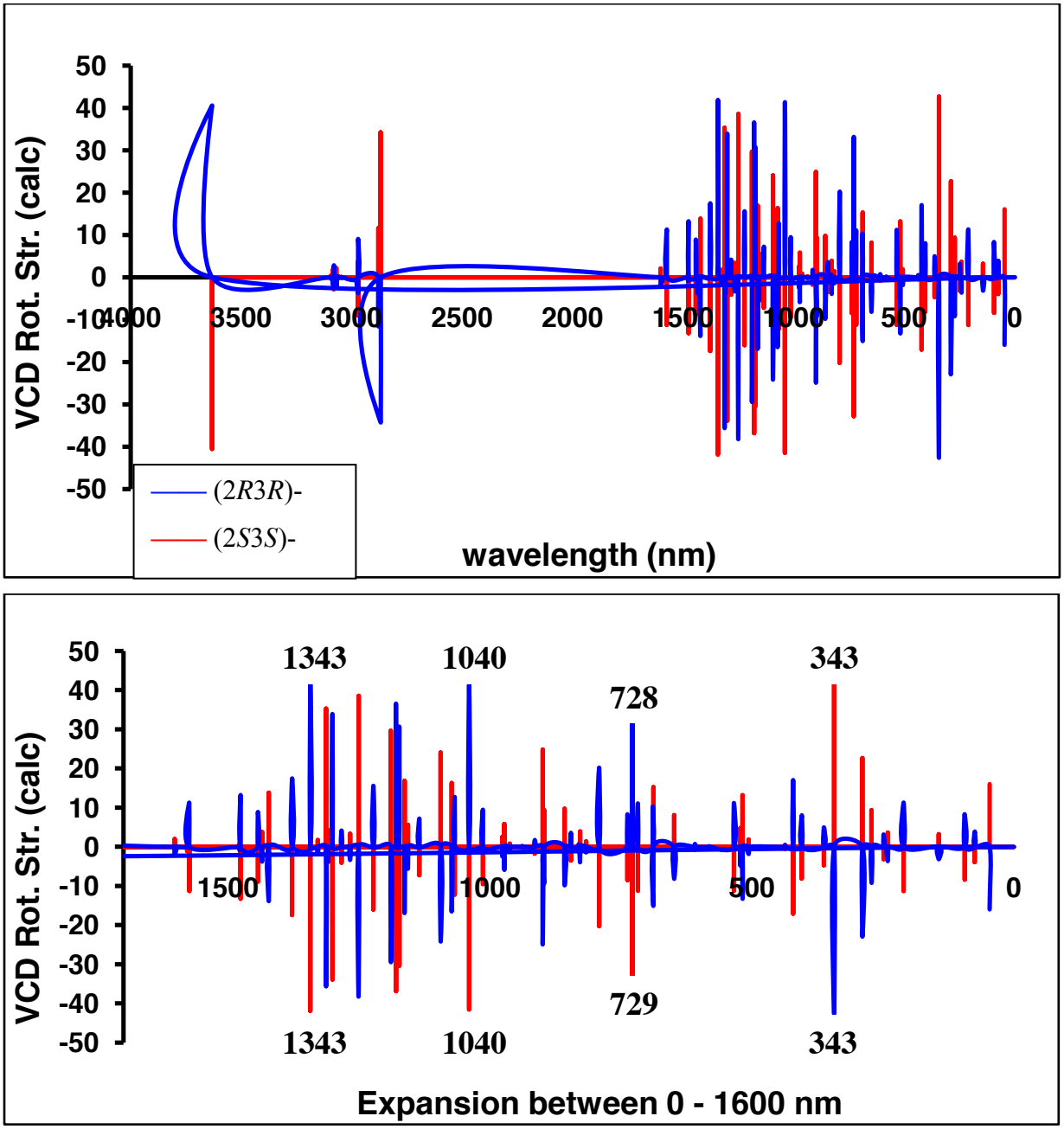


Figure 33. The calculated VCD spectra of flavan of the highest population (2*R*)-*equatorial* isomer (**5.29**). A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

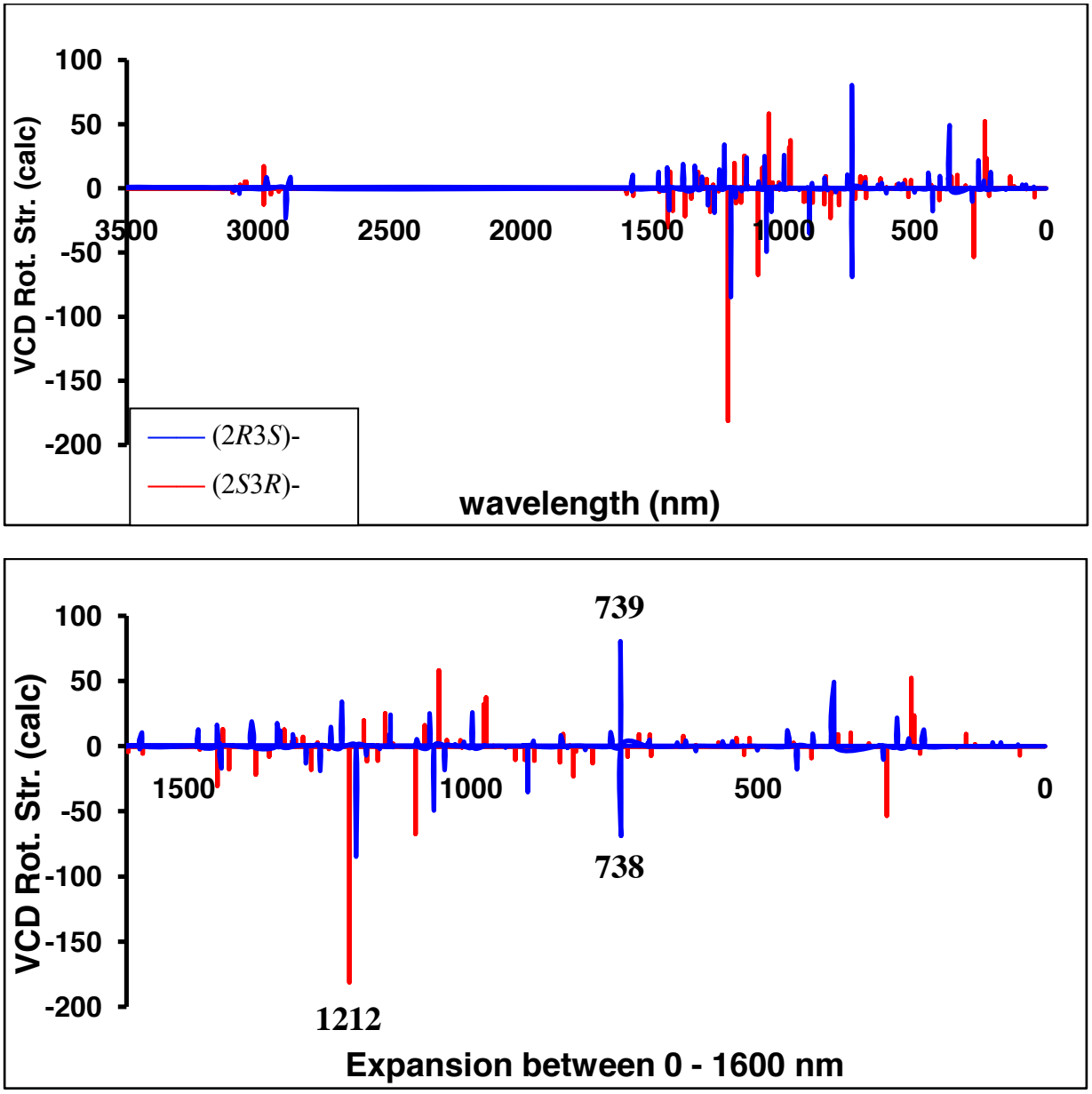
5.5.2 2,3-*trans*-Flavan-3-ol

Figure 34 gives the calculated VCD spectra of the (a) (2*S*)-*equatorial*, (3*S*)-*axial* (**5.35**) *vs*. its enantiomer and (b) (2*S*)-*equatorial*, (3*R*)-*equatorial* (**5.37**) *vs*. its enantiomer of flavan-3-ols. The VCD spectrum of the most dominated peaks of (**5.35**) and its enantiomer at 343 cm^{-1}, 728 cm^{-1}, 1040 cm^{-1} and 1343 cm^{-1} are showing (+) and (-) intensity of one another. It is clearly see that the calculated VCD shows two conformations in opposite intensity. The conformation of (2*R*3*S*) shows (-) intensity at 738 cm^{-1} to (+) intensity at 738 cm^{-1} and (-) intensity at 1212 cm^{-1} of (2*S*3*R*) (**5.37**) are the dominated peaks.

* Preparing all flavonoids compounds for experimental VCD purposes in enantiomeric enriched form would require intense additional efforts. A VCD spectrophotometer is not available in South Africa, so obtaining VCD spectra would be the objective of a follow up study.



(a) Calculated VCD spectrum of (2*S*)-*equatorial*, (3*S*)-*axial* (**5.35**) *vs*. its enantiomer



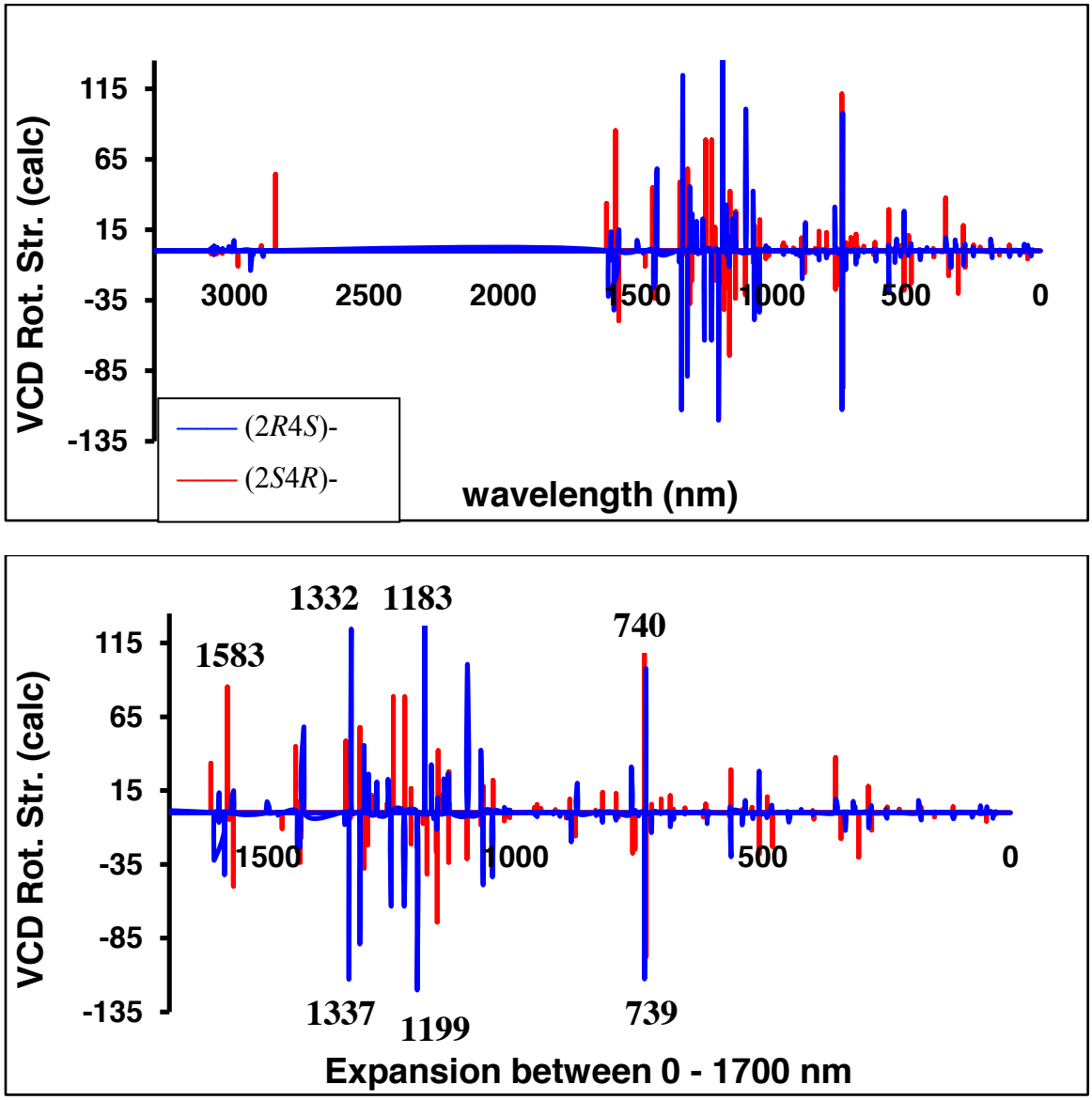
(b) Calculated VCD spectrum for (2*S*)-*equatorial*, (3*R*)-*equatorial* (**5.37**) *vs*. its enantiomer

Figure 34. The calculated VCD spectra of flavan-3-ol of the (a) [(2*S*)-*equatorial*, (3*S*)-*axial*] and (b) [(2*S*)-*equatorial*, (3*R*)-*equatorial*] are presented. A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

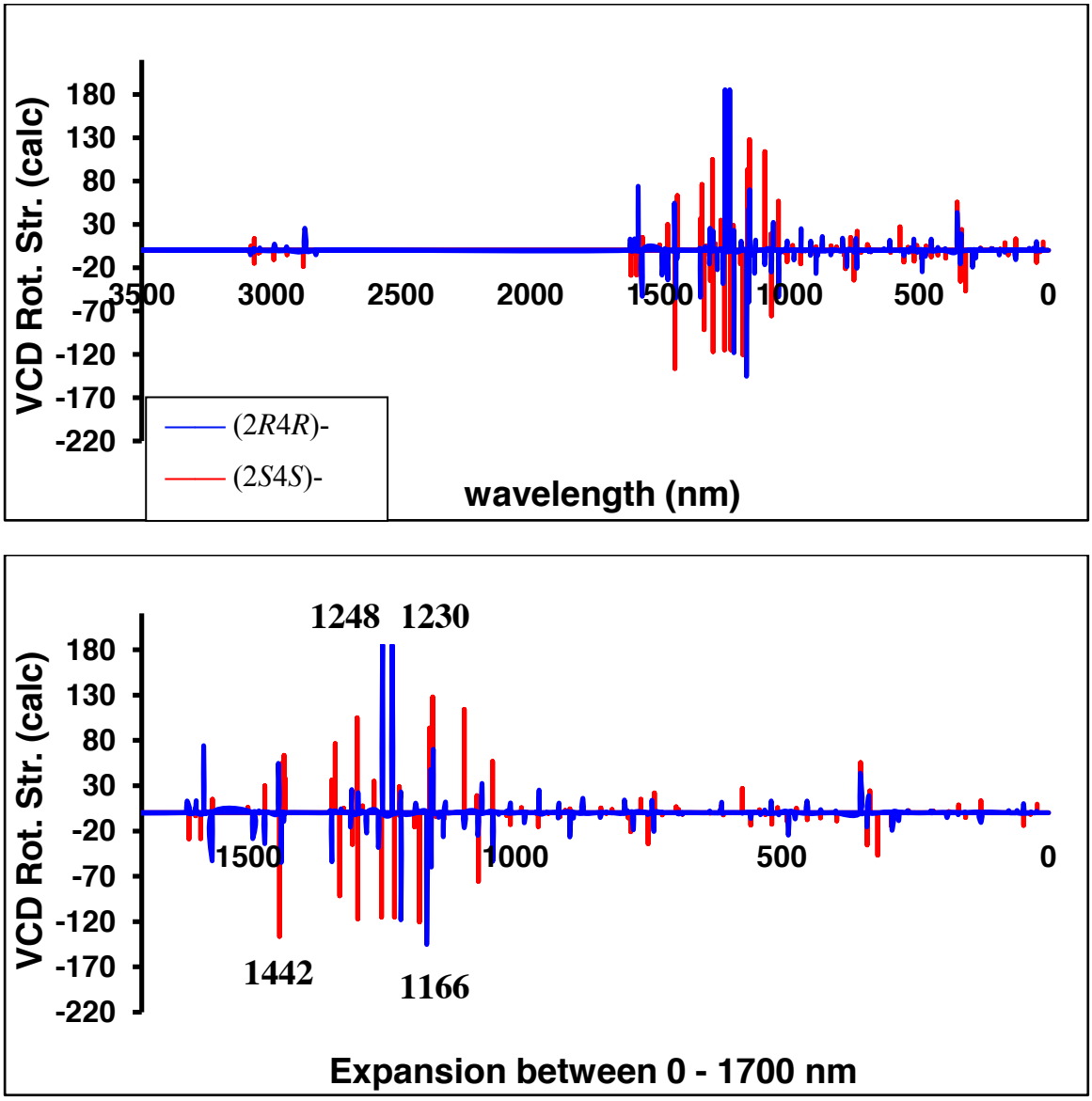
5.5.3 1,4-*cis*-4-Arylflavan

Unlike the VCD spectra of flavan (84 peaks) and flavan-3-ol (87 peaks), 4-arylflavan (120 peaks) has more complicated VCD especially for the absorption band between 1000 cm^{-1} and 1500 cm^{-1}, see Figure 35. This is due to the large molecule 4-arylflavan containing more atoms. The VCD spectrum of (2*S*4*R*) (**5.43**) and its enantiomer (2*R*4*S*) showing an overlap at (-) 739 cm^{-1} to (+) 740 cm^{-1}; at (+) 1183 cm^{-1} to (-) 1199 cm^{-1} and at (+) 1332 cm^{-1} to (-) 1337 cm^{-1} of

(2*R*4*S*) and (+) 1583 cm^{-1} of (2*S*4*R*) are the dominated peaks. The conformation (2*R*4*R*) showing (-) 1166 cm^{-1} and (+) 1230 and 1248 cm^{-1} whereas (2*S*4*S*) giving (-) 1442 cm^{-1} are the most significant peaks for 4-arylflavan.



(a) Calculated VCD spectrum for (2*S*)-*equatorial*, (4*R*)-*axial* (**5.43**) *vs*. its enantiomer



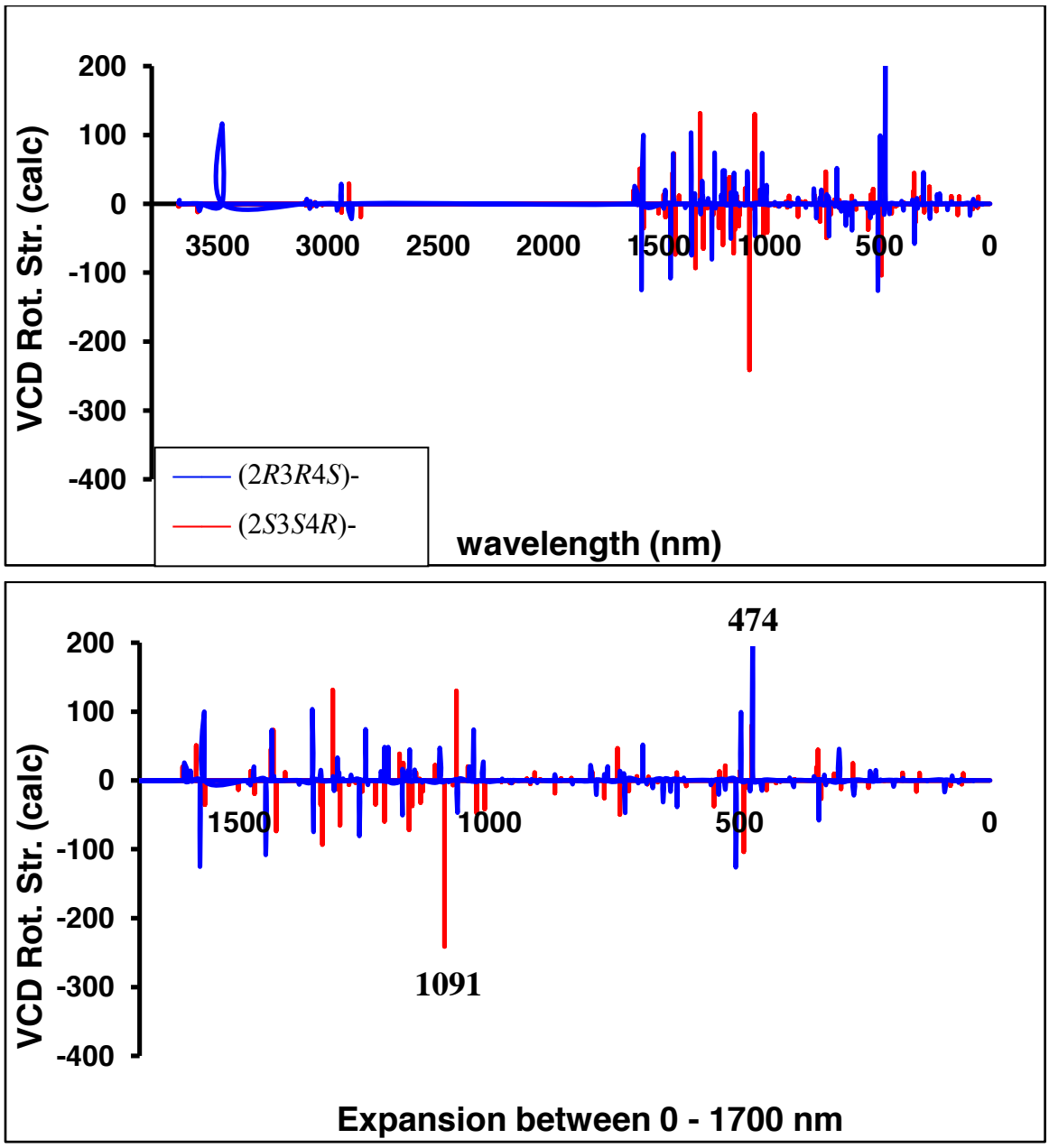
(b) Calculated VCD spectrum for (2*S*)-*equatorial*, (4*S*)-*equatorial* (**5.45**) *vs*. its enantiomer

Figure 35. The calculated VCD spectra of 4-arylflavan of the (a) [(2*S*)-*equatorial*, (4*R*)-*axial*] and (b) [(2*S*)-*equatorial*, (4*S*)-*equatorial*] isomer are presented. A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

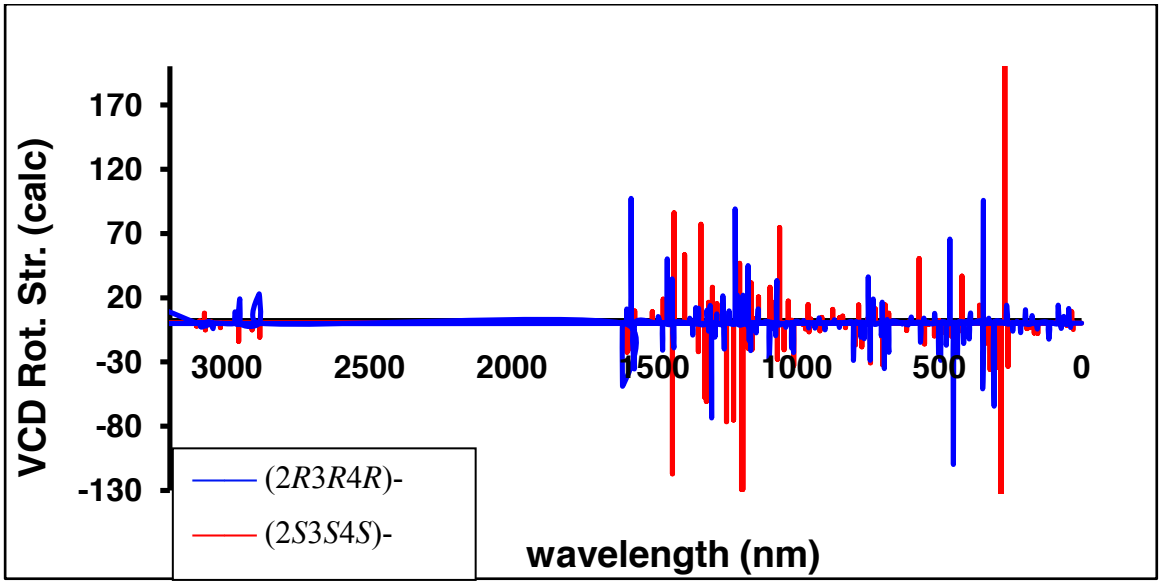
5.5.4 2,3-*trans*-3,4-*cis*-4-Arylflavan-3-ol

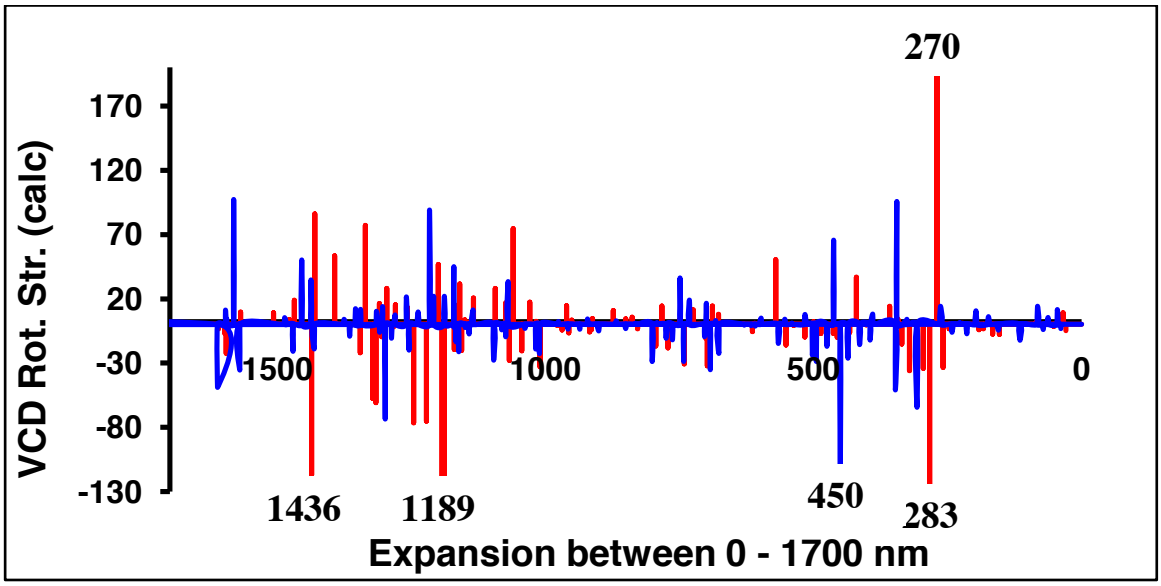
Unlike the VCD spectra of flavan, flavan-3-ol and 4-arylflavan, 4-arylflavan-3-ol has more complicated and difficult measurable VCD aross the absorption band between 1000 cm^{-1} and 1500 cm^{-1}, see Figure 36. By attaching a resorcinal ring and a hydroxyl group to the flavan causing more CH and CH_2 stretching vibrations. The VCD spectrum of the most stable conformations of (2*S*3*S*4*R*) (**5.55**), (2*S*3*S*4*S*) (**5.57**), (2*S*3*R*4*R*) (**5.59**) and (2*S*3*R*4*S*) (**5.61**) of 4-arylflavan-3-ol is discussed. Since 4-arylflavan-3-ol has 43 atoms, the VCD spectrum exsists of

123 peaks. For the conformation (2*R*3*R*4*S*), the VCD spectrum shows the dominated peaks at (+) 474 cm^{-1} and (-) 1091 cm^{-1} for (2*S*3*S*4*R*) (**5.55**) [(Figure 36, (a)]. For the conformation (2*S*3*S*4*S*) (**5.57**), the VCD spectrum shows the dominated peaks at (+) 270 cm^{-1}, (-) 283 cm^{-1}, (-) 1189cm^{-1} and (-) 1436 cm^{-1}, however the conformation (2*R*3*R*4*R*) shows (-) 450 cm^{-1} [(Figure 36, (b)]. For the conformation (2*S*3*R*4*R*) (**5.59**), the dominated peak at (-) 1227 cm^{-1} and (+) 1221 cm^{-1} for (2*R*3*S*4*S*) [(Figure 36, (c)]. Lastly the conformation (2*S*3*R*4*S*) (**5.61**) of 4-arylflavan-3-ol has dominated peaks at (-) 1240 cm^{-1} and (+) 1332 cm^{-1} where (2*R*3*S*4*R*) has dominated peaks at (-) 1081 cm^{-1} and (+) 1201 cm^{-1}. The overlap peaks at (-) 736 cm^{-1} and (+) 739 cm^{-1} indicated for both conformations [(Figure 36, (d)].

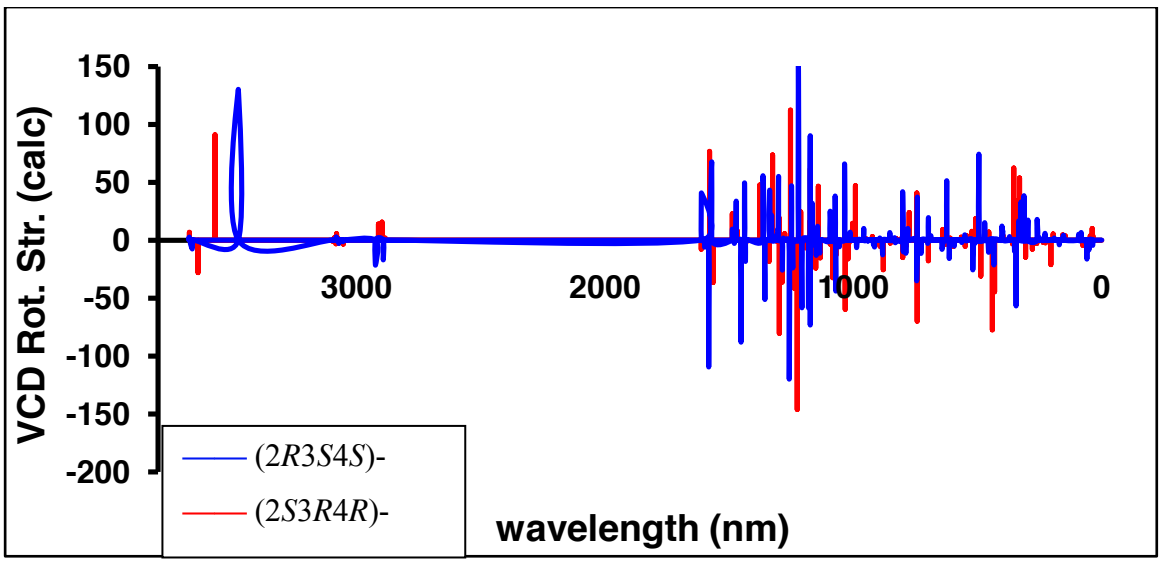


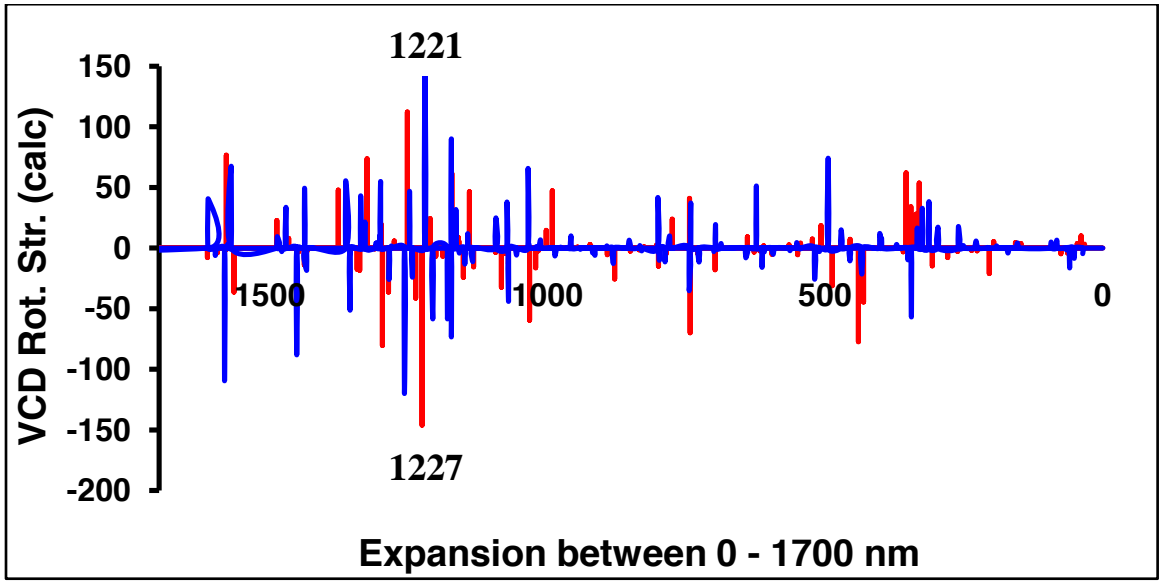
(a) (2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial* isomer (**5.55**) *vs*. its enantiomer



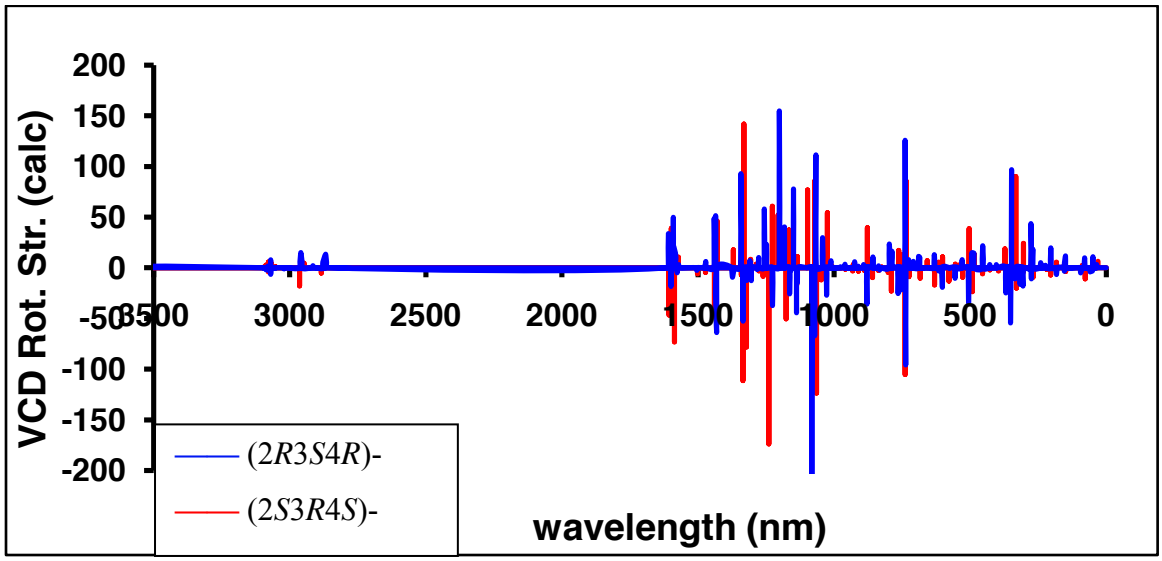


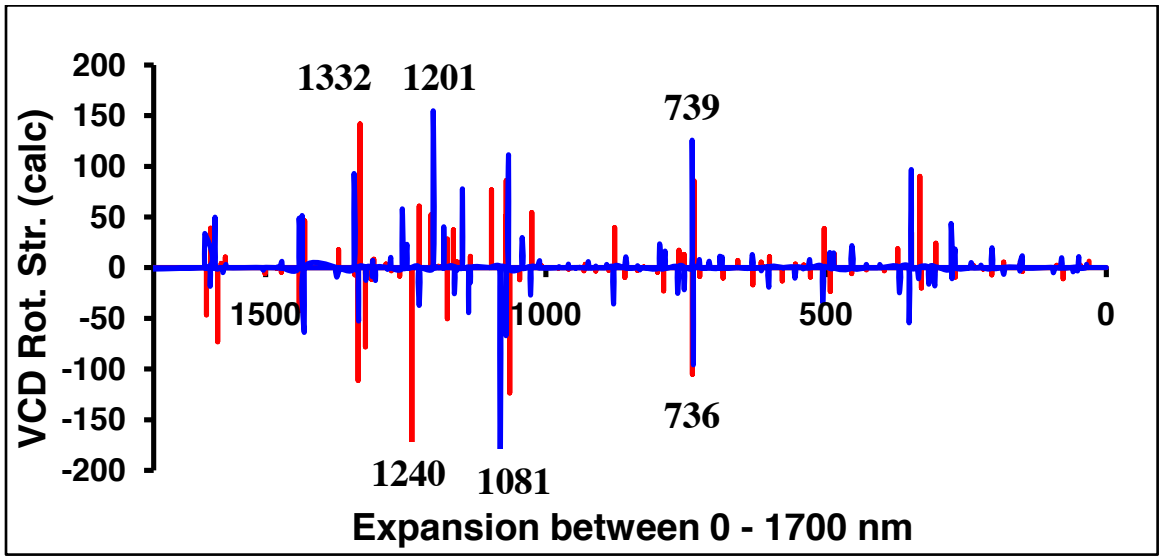
(b) (2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial* isomer (**5.57**) *vs*. its enantiomer





(c) (2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial* isomer (**5.59**) *vs*. its enatiomer





(d) (2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial* isomer (**5.61**) *vs*. its enatiomer

Figure 36. The calculated VCD spectrum of the most stable conformations (global minimum) of 4-arylflavan-3-ol is presented. A scalling factor of 0.962 for the wavenumber of the calculated spectra is used.

5.6 Conclusions

In this study a complete conformational surface of flavan-3-ols, 4-arylflavan and 4-arylflavan-3-ols is presented to give the global and local minima which reulted in finding the most stable conformations. The assignment of IR absorption from theoretical spectra is presented and the excellent match between theoretical and experimental IR analysis is achieved. We evidently concluded that the method of using TDDFT calculations together with infrared spectroscopy to determine the most stable or preferred conformation was achieved for flavonoid compounds. The determining of absolute configuration at a chiral centre in selected flavonoid compounds and understanding of its IR spectra is currently under investigation with the same approach. The calculated VCD spectrum of 4-arylflavan-3-ol was also achieved successfully.

EXPERIMENTAL

6 Experimental

6.1 Chromatographic techniques

6.1.1 Gravity column chromatography (CC)

CC separations were performed in glass columns packed with a suspension of Macherey-Nagel Silica 60 (0.063 – 0.2 mm) in the appropriate solvent. The crude product was dissolved in a minimum quantity of the appropriate solvent and applied to the column. Elution was performed at a flow rate of ca. 1 mL/min and fractions of ca. 20 mL were collected.

6.1.2 Flash column chromatography (FCC)

FCC was performed in a glass column (5 cm diameter) charged with 100 g of Macherey-Nagel Silica 60 (0.063 – 0.2 mm) for every 1 g of the crude material. Air was displaced by elution with the appropriate solvent under N_2-pressure (*ca.* ~ 40 kPa). The crude product was dissolved in a minimum volume of the appropriate solvent and applied to the column. The purified product was recovered by elution under N_2-pressure in 15 mL fractions.

6.1.3 Thin-layer chromatography (TLC)

Qualitative TLC was performed on Macherey-Nagel Alugram® Xtra Sil G UV_{254} pre-coated aluminum sheets (0.2 mm layer) divided into strips of ca. 2.5 x 5.0 cm. R_f values reported are those observed in these qualitative TLC assessments.

6.1.4 Preparative thin-layer chromatography (PLC)

Glass plates (20 x 20 cm) were coated with a water suspension of Merck Silica gel 60 PF_{254} for preparative thin layer chromatography Kieselgel 60 PF_{254} (1.0 mm) and allowed to dry in air. The crude product was applied to these plates (10-15 mg per plate) and developed with the

appropriate eluent in a closed development chamber. The plates were dried in a stream of air and the bands distinguished by UV light (254 nm). Each band was physically removed and the compounds eluted from the adsorbent with acetone. Small-scale separations were conducted in a similar manner on Macherey-Nagel Alugram® Xtra Sil G UV_{254} pre-coated aluminum sheets (0.2 mm layer) charged with 3-5 mg of the crude product per plate.

6.1.5 Development of thin-layer chromatograms

Ferric chloride - perchloric acid

A mixture of 35% (v/v) aq. perchloric acid (100 mL) and 0.5 M aq. ferric chloride (5 mL) was prepared and diluted with EtOH (1:9). Thin-layer chromatograms were dipped in the solution and developed with heat to give coloured spots.

Sulfuric acid

Thin-layer chromatograms were dipped in a solution of concentrated sulfuric acid (10 mL) and EtOH (90 mL), and developed with heat to yield grey spots.

6.1.6 Solvent abbreviations

The following abbreviations for solvents are used through out the experimental section:

A	=	acetone	EtOH	=	ethanol
$CHCl_3$	=	chloroform	H	=	hexane
DCM	=	dichloromethane	MeOH	=	methanol
DMF	=	dimethylformamide	THF	=	tetrahydrofuran
Et_2O	=	diethyl ether	T	=	toluene
EA	=	ethyl acetate	TMEDA	=	tetramethylethylenediamine
rt	=	room temperature			

6.2 Spectroscopical methods

Electron-Impact Ionization Mass Spectrometry (EIMS)

EIMS analysis was conducted on a Shimadzu gas chromatograph (GC-2010) fitted with a mass spectrometer (GCMS-QP2010) by means of the direct sample inlet unit (DI-2010).

High-Resolution Mass Spectrometry (HRMS)

HRMS analyses were conducted at the University of KwaZulu-Natal (UKZN), Pietermaritzburg, South Africa.

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded on a Bruker AVANCE DPX_{600} spectrometer with tetramethylsilane an internal standard. The solvents used were deuteriochloroform ($CDCl_3$, δ_H 7.24) and deuterioacetone [$(CD_3)_2CO$/acetone d_6, δ_H 2.04]. Chemical shifts are reported in parts per million (ppm) on the δ-scale and coupling constants were measured in Hz. Abbreviations are used as follows:

Abbreviations used in describing ^{1}H NMR signal multiplicities.

Abbreviation	Signal multiplicity
s	singlet
d	doublet
t	triplet
dd	doublet of doublets
br	broadened
m	multiplet
ddd	doublet of doublets of doublets

6.3 General procedures

6.3.1 Anhydrous solvents

a) Acetone was passively dried over molecular sieves followed by distillation under N_2 prior to use.
b) DCM was passively dried over calcium chloride. The predried DCM was freshly distilled under N_2 from calcium hydride prior to use.
c) DMF was purchased from Sigma-Aldrich as an anhydrous solvent.

d) THF was passively dried over sodium metal. The predried THF was refluxed over sodium/benzophenone under N_2 until a dark blue colour persisted with subsequent fresh distillation prior to use.

6.3.2 Acetylation[1]

Dry phenolic material was dissolved in a minimum volume of pyridine. Twice the amount of acetic anhydride was added. After 8-12 hours at ambient temperatures, crushed ice was added to precipitate the acetylated material which was filtered and excess pyridine washed out with cold water.

6.3.3 Baeyer-Villiger oxidation[2,3]

The benzaldehyde (0.100 g, 0.510 mmol, 1 eq.) was dissolved in solvent (1 mL) followed by addition of the oxidant (0.021 mL, 0.67 mmol, 1.31 eq.) and acid (0.01 mL). Stirring was continued at rt for 24 h. The reaction mixture was extracted into EA (20 mL) and washed with brine (3 x 20 mL). The organic phase was dried over Na_2SO_4, concentrated *in vacuo* and the product(s) isolated by means of PLC.

6.3.4 Friedel-Crafts acylation[4]

Anhydrous zinc chloride was dissolved glacial acetic acid and the solution heated to reflux under argon. The substrate was added to the hot solution and refluxing continued for 24 h. After cooling down for 20 minutes, the solution was diluted with 5 M HCl and the dark red solution cooled in an ice bath. The resulting precipitate was filtered and washed with 3 M HCl (3 x 20 mL). The crude product was dried and purified by PLC.

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2 Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740.

3 Berkessel, A.; Andreae, M.R.M.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4481.

4 Wan, S.B.; Chan, T.H. *Tetrahedron* **2004**, *60*, 8207.

6.3.5 DOM (Directed *Ortho* Metalation) acylation[5]

A solution of TMEDA (0.2 mL, 0.518 mmol, 1.1 eq.) and *n*-BuLi (0.2 mL, 0.518 mmol, 1.1 eq.) in dry Et_2O (4 mL) was stirred for 20 min at -20 °C under argon. The phenolic compound in dry Et_2O (1 mL) was added dropwise and stirring continued for 30 h at 0 °C. D_2O (3-4 drops) was added and the reaction mixture stirred for 30 min. before it was allowed to warm up to rt. Saturated aqueous NH_4Cl was added and the product extracted into ether (3 x 20 mL). The organic phase was washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by PLC afforded the desired product

6.3.6 Aryl bromination[6]

To a solution of substrate (0.5 – 0.8 g) in glacial acetic acid (10 mL), bromine (1 eq.) in glacial acetic acid (1 mL) was added dropwise at rt over a period of 30 min and the reaction mixture stirred for 4 h at the same temperature. The reaction was quenched by the addition of water and the resulting solid was filtered off. The crude product was separated by prep. TLC to afford the product.

6.3.7 Flavone degradation[7]

Diethylene glycol (19.6 eq.) was added slowly to a stirring mixture of flavone (1 eq.) in pyridine (20.4 eq.) and 18 M KOH (60 eq.). The solution was heated at 100 ^oC for 24 h. After cooling, the solution was acidified to pH 1 with 3 M HCl. The reaction mixture was washed with water (3 x 20 mL) then extracted into EA (3 x 20 mL). The organics were washed with saturated $NaHCO_3$ (20 mL) solution then dried over Na_2SO_4 and concentrated under vacuum. The crude product was isolated by PLC.

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5 Nerdinger, S.; Kendall, C.; Cai, X.; Marchart, R.; Riebel, P.; Johnson, M.R.; Yin, C.-F.; Hénaff, N.; Eltis, L.D.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 5960.

6 Yang, Z.; Liu, H.B.; Lee, C.M.; Chang, H.M.; Wong, N.C. *J. Org. Chem.* **1992**, *57*, 7248.

7 Caldwell, S.T.; Petersson, H.M.; Farrugia, L.J.; Mullen, W.; Crozier, A.; Hartley, R.C. *Tetrahedron* **2006**, *62*, 7257.

6.3.8 Aldol condensation

Acetophenone and benzaldehyde were dissolved in EtOH:THF = 5:1 and stirred at 0 ^{o}C. Freshly powdered KOH was added and stirred at rt overnight. Water was added and the reaction mixture was neutralized with 3 M HCl. The residue was extracted with EA (3 x 20 mL) and the organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Purification by PLC separation.

6.3.9 Alkylation

To a solution of chalcone (1 eq.) in DCM (20 mL), was added adogen 464 (0.5 mL) followed by *aq*. NaOH (2 M, 5 mL). The reaction mixture was stirred vigorously at rt for 30 minutes before chloromethyl ethyl ether (EOMCl) (3 eq.) was added with continuous stirring. After completion of the reaction, water (20 mL) was added and the reaction mixture was extracted with DCM (3 x 20 mL), washed with brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the product isolated by PLC.

6.3.10 Reduction by $NaBH_4$

The chalcone was dissolved in EtOH. Finely powder $NaBH_4$ was added to the solution and it was stirred at rt until completion of the reduction process (TLC). Acetone was then added to the reaction mixture and stirred for 30 min. The reaction mixture was evaporated to dryness. The crude product was extracted with EA (3 x 20 mL) and washed with water (3 x 20 mL). The organic layers were collected and dried over Na_2SO_4 and evaporated under reduced pressure. Purification by PLC yielded dihydrochalcone.

6.3.11 Hydrogenation

To a mixture of starting material (1 eq.) in acetone (10 mL) was added 5% Pd/C or $Pd(OH)_2$ (substract:catalyst = 1:1) and the reaction mixture was then hydrogenated at atmospheric pressure. After completion, the catalyst was filtered off and the solvent removed by distillation under reduced pressure to obtain the product.

6.3.12 Acidification for dealkylation

3 M HCl in MeOH solution (2 – 10 mL) was added to the solution of dihydrochalcone which was dissolved in minimum THF (1 – 3 mL). The reaction mixture was stirred at rt for 2 h. After completion, the solvent was evaporated and diluted with EtOH (10 mL). The product was collected after evaporation under reduced pressure. No purification was necessary to yield the product.

6.3.13 Cyclization

A mixture of dihydrochalcone (1 eq.) in DMF (2 mL) was added dropwise to a $BF_3.Et_2O$ solution (0.20 mL, 1.5 mmol, 18 eq.) and cooled to 10 ^oC. In a second flask, DMF (2 mL) was cooled to 10 ^oC and PCl_5 (0.105 g, 0.504 mmol, 6 eq.) was added in small portions. The mixture was subsequently stirred at 55 ^oC until a light yellow colour indicated *N*,*N*'-dimethyl(chloromethylene)ammonium chloride was formed (20 min.). The mixture was then slowly added to the first flask at 20 – 25 ^oC. The reaction mixture was stirred at rt for 24 h, before it was slowly added to boiling diluted HCl (10 mL) and cooled to rt. The solution was extracted with EA (3 x 20 mL) and the combined organic layers washed with water (3 x 20 mL) and brine (20 mL) and the combined organic phases dried over Na_2SO_4. The residue after in vacuo concentration was purified by PLC to afford homoisoflavone derivatives.

6.3.14 Reduction-oxidation of homoisoflavones

The reduction and the oxidation of a homoisoflavone can be done consecutively, therefore, isolation of some *cis*- and *trans*-homoisoflavans were not reported.

6.3.14.1 Reduction of homoisoflavones

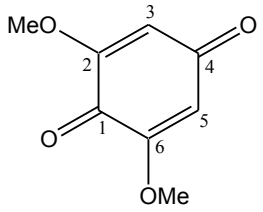
Homoisoflavone (1 eq.) was dissolved in THF and EtOH (ratio = 1:4, 0.5 mL:2 mL). $NaBH_4$ (15 – 20 eq.) was added to the solution and it was stirred at rt until completion. Acetone (10 – 20 mL) was added and the reaction mixture stirred for another 30 min. The reaction mixture was evaporated to dryness. The crude product was extracted with EA (3 x 20 mL) and washed with water (20 mL). The organic layers were collected and dried over Na_2SO_4 and evaporated under reduced pressure and PLC afforded *cis*- and *trans*-homoisoflavan.

6.3.14.2 Oxidation with IBX of homoisoflavones

The combined *cis*- and *trans*-homoisoflavan (0.026 g, 1 eq) was dissolved in a minimum dry acetonitrile (5 mL). IBX (1.5 eq.) was added to the reaction and the reaction mixture refluxed for 6.5 h. After completion, solids was filtered off and the filtrate was extracted into Et_2O (20 mL) and washed with H_2O (20 mL). The organic layer was dried over Na_2SO_4 and PLC gave the homoisoflavanone.

6.4 Synthesis of tetraoxygenated acetophenones

6.4.1 2,6-Dimethoxy-1,4-benzoquinone (4.15)[8,9]



(**4.15**)

Prepared as described in general Bayer-Villiger oxidation procedure (*cf* paragraph 6.3.3):

Method A: 3,4,5-Trimethoxybenzaldehyde (**4.12**) (0.100 g, 0.510 mmol, 1 eq.), 30% aqueous hydrogen peroxide (0.021 mL, 0.67 mmol, 1.31 eq.), MeOH (1 mL), and H_2SO_4 (0.01 mL). Yield of 2,6-dimethoxy-1,4-benzoquinone (**4.15**) 0.010 g (12%).

Method B: 3,4,5-Trimethoxybenzaldehyde (**4.12**) (0.100 g, 0.510 mmol, 1 eq.), hydrogen peroxide-urea adduct (0.096 g, 1.02 mmol, 2 eq.), MeOH (10 mL), and H_2SO_4 (0.5 mL). Yield of 2,6-dimethoxy-1,4-benzoquinone (**4.15**) 0.059 g (69%).

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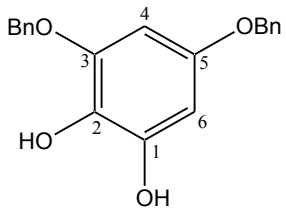
8 Brambilla, G.; Robbiano, L.; Cajelli, E.; Martelli, A.; Turmolini, F.; Mazzei, M. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 1011.

9 Aghoramurthy, K.; Visweswara Rao, K.; Seshadri, T.R. *Bangalore Press.* **1953**, 798.

Method C: 3,4,5-Trimethoxybenzaldehyde (**4.12**) (0.100 g, 0.510 mmol, 1 eq.), 1,1,1,3,3,3,-hexafluoro-2-propanol (HFIP) (0.63 mL, 6.02 mmol, 11.8 eq.), *para*-toluenesulfonic acid (0.97 mg), and 30% aqueous hydrogen peroxide (2 eq., 0.1 mL). Yield of 2,6-dimethoxy-1,4-benzoquinone (**4.15**) 0.017 g (20%).

Yellow solid; R_f 0.45 (T:A = 7:3); ^{1}H NMR (Plate 1a, 600 MHz, $CDCl_3$) δ 5.87 (2H, s, H-3,5), 3.84 (6H, s, 2 x OCH_3); ^{13}C NMR (Plate 1b, 600 MHz, $CDCl_3$) δ 186.8, 157.3, 107.4, 56.5. EIMS (70 eV) *m/z* 168 (M^+, 11%).

6.4.2 3,5-Dibenzyloxycatechol (4.23)[10]



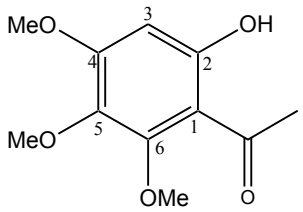
(**4.23**)

Solid IBX (0.070 g, 0.248 mmol, 2 eq.) was added to a solution of 3,5-dibenzyloxyphenol (**4.16**) (0.038 g, 0.124 mmol, 1 eq.) in $CHCl_3$/MeOH 4:1 v/v (10 mL) at -25 °C. A pink-to-red colour developed and the mixture was stirred for 2 h. Methanolic $NaBH_4$ (15 mg in 1 mL) was then added at -25 °C under vigorous stirring until the colour disappeared. Acetone (20 mL) was added to the reaction mixture and then evaporated off to afford 3,5-dibenzyloxycatechol (**4.23**) 0.046 g (100%).

Red liquid; R_f 0.33 (T:EA = 8:2); ^{1}H NMR (Plate 2, 600 MHz, $CDCl_3$) δ 7.44-7.35 (10H, m, 2 x Ar-H), 5.90 (1H, d, *J* = 2 Hz, H-4), 5.71 (1H, d, *J* = 2 Hz, H-6), 5.02 (2H, s, OCH_2Ph), 5.01 (2H, s, OCH_2Ph).

[10] Pezzella, A.; Lista, L.; Napolitano, A.; d'Ischia, M. *Tetrahedron Lett*. **2005**, *46*, 3541.

6.4.3 2-Hydroxy-4,5,6,-trimethoxyacetophenone (4.27)[11,12]

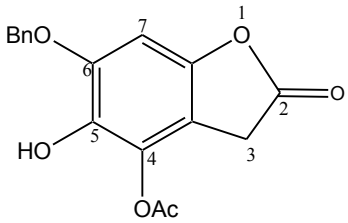


(**4.27**)

Prepared as described in general Friedel-Crafts acylation procedure (*cf* paragraph 6.3.4): 3,4,5-Trimethoxyphenol (**4.14**) (0.500 g, 2.71 mmol, 1 eq.), $ZnCl_2$ (1 g, 7.35 mmol, 2.7 eq.) and acetic acid (10 mL). Yield of 2-hydroxy-4,5,6-trimethoxyacetophenone (**4.27**) 0.009 g (2%).

Brown liquid; R_f 0.35 (T:A = 8:2); ^{1}H NMR[13] (Plate 3, 600 MHz, $CDCl_3$) δ 13.45 (1H, s, O<u>H</u>), 6.25 (1H, s, H-5), 4.02 (3H, s, OC<u>H</u>$_3$), 3.91 (3H, s, OC<u>H</u>$_3$), 3.80 (3H, s, OC<u>H</u>$_3$), 2.67 (3H, s, COC<u>H</u>$_3$).

6.4.4 *4-Acetoxy-6-benzyloxy-5-hydroxy-2,3-dihydrobenzofuran-2-one* (4.29)



(**4.29**)

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11 Krishna Rao, G.S.; Visweswara Rao, K.; Seshadri, T.R. *Proceedings of the Indian Academy of Sciences – Section A*, **1948**, *27*, 245.

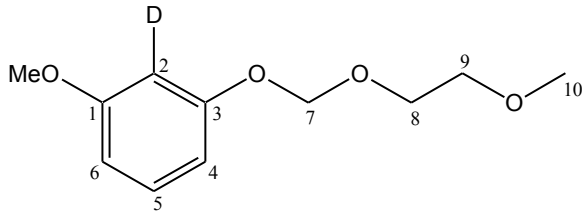
12 Kuroda, C. *RIKEN* **1929**, 765.

13 Dong, Z.-X.; Li, N.-G.; Zhang, P.-X.; Gu, T.; Wu, W.-Y.; Shi, Z.-H. *Molecules* **2016**, *21*, 263.

Prepared as described in general Friedel-Crafts acylation procedure (*cf* paragraph 6.3.4):
3,5-Dibenzyloxy-1,2-dihydroxybenzene (**4.23**) (0.150 g, 0.47 mmol, 1 eq.), $ZnCl_2$ (0.5 g, 3.67 mmol, 7.8 eq.) and acetic acid (5 mL). Yield of *4-acetoxy-6-benzyloxy-5-hydroxy-2,3-dihydrobenzofuran-2-one* (**4.29**) 0.006 g (41%).

Brown solid; R_f 0.41 (T:A = 8:2); ^{1}H NMR (Plate 4, 600 MHz, $CDCl_3$) δ 7.43 (5H, br s, Ar-H), 5.53 (1H, s, H-7), 5.16 (1H, d, *J* = 10.6 Hz, OCH_2Ph), 5.10 (1H, d, *J* = 11.3 Hz, OCH_2Ph), 3.10 [1H, d, *J* = 17.5 Hz, H-3(a)], 2.95 [1H, d, *J* = 17.5 Hz, H-3(b)], 2.37 (3H, s, $COCH_3$). EIMS (70 eV) *m/z* 271 (M^+ -Ac, 6%), 227 (100%), 179 (12%), 150 (2%), 138 (10%).

6.4.5 1-Methoxy-3-[(2-methoxyethoxy)methoxy](2-^{2}*H*)benzene (4.39)

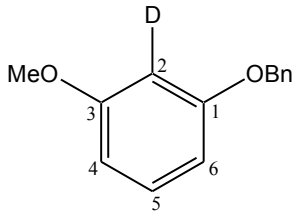


(**4.39**)

Prepared as described in general DOM (Directed *Ortho* Metalation) acylation procedure (*cf* paragraph 6.3.5):
TMEDA (0.2 mL, 0.518 mmol, 1.1 eq.), *n*-BuLi (0.2 mL, 0.518 mmol, 1.1 eq.), dry Et_2O (4 mL), phenolic compound (**4.37**) (100 mg, 0.471 mmol, 1 eq.), dry Et_2O (1 mL) and D_2O (3-4 drops). Yield of 1-methoxy-3-[(2-methoxyethoxy)methoxy](2-^{2}*H*)benzene (**4.39**) 0.134 g (100%).

Clear liquid; R_f 0.41 (H:A = 8:2); ^{1}H NMR (Plate 5a, 600 MHz, $CDCl_3$) δ 7.19 (1H, t, *J* = 8 Hz, H-5), 6.67 (1H, d, *J* = 8 Hz, H-4), 6.57 (1H, d, *J* = 8 Hz, H-6), 5.27 [2H, s, H-7(a),(b)], 3.84 [2H, t, *J* = 5 Hz, H-8(a),(b)], 3.79 (3H, s, OCH_3), 3.57 [2H, t, *J* = 5 Hz, H-9(a),(b)], 3.39 [3H, s, H-10(a),(b),(c)]; ^{13}C NMR (Plate 5b, 600 MHz, $CDCl_3$) δ 160.7, 158.5, 129.9, 108.4, 107.6, 93.5, 71.6, 67.6, 59.0, 55.3. EIMS (70 eV) *m/z* 213 (M^+, 10%).

6.4.6 *1-Benzyloxy-3-methoxy-2-(^{2}H)benzene* (4.161)



(**4.161**)

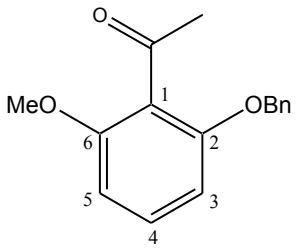
Prepared as described in general DOM (Directed *Ortho* Metalation) acylation procedure (*cf* paragraph 6.3.5):
TMEDA (0.2 mL, 0.518 mmol, 1.1 eq.), *n*-BuLi (0.2 mL, 0.518 mmol, 1.1 eq.), dry Et_2O (4 mL), 1-benzyloxy-3-methoxybenzene (**4.40**) (0.150 g, 0.700 mmol, 1 eq.) and dry Et_2O (1 mL). Yield of *1-benzyloxy-3-methoxy-2-(^{2}H)benzene* (**4.161**) 0.145 g (100%).

Clear liquid; R_f 0.51 (H:A = 8:2); ^{1}H NMR (Plate 6a, 600 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 7.5 Hz, Ar-H), 7.47 (2H, t, *J* = 7.3 Hz, Ar-H), 7.41 (1H, t, *J* = 7.3 Hz, Ar-H), 7.28 (1H, t, *J* = 8.2 Hz, H-5), 6.69 (1H, dd, *J* = 8.2 and 1.2 Hz, H-4), 6.63 (1H, dd, *J* = 8.2 and 1.2 Hz, H-6), 5.12 (2H, s, OCH_2Ph), 3.85 (3H, s, OCH_3); ^{13}C NMR (Plate 6b, 600 MHz, $CDCl_3$) δ 160.9, 160.2, 137.1, 130.1, 128.7, 128.1, 127.6, 107.1, 106.7, 101.5, 70.1, 55.3. EIMS (70 eV) *m/z* 214 (M^+, 35%).

6.4.7 Acylation of 1-benzyloxy-3-methoxybenzene (4.40)

A solution of TMEDA (0.2 mL, 0.518 mmol, 1.1 eq.) and *n*-BuLi (0.2 mL, 0.518 mmol, 1.1 eq.) in dry Et_2O (4 mL) was stirred for 20 min at -20 °C under argon. 1-Benzyloxy-3-methoxybenzene (**4.40**) (0.100 g, 0.467 mmol, 1 eq.) in dry Et_2O (1 mL) was added dropwise and stirring continued for 30 min at 0 °C. A few drops of acetic anhydride were added and the reaction mixture stirred for 30 min.before it was allowed to warm up to rt. Saturated aqueous NH_4Cl was added and the product extracted into ether (3 x 20 mL). The organic phase was washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by PLC (T:EA, 95:5) yielded two identifiable products with R_f values of 0.71 and 0.64 (T:EA, 9.5:0.5).

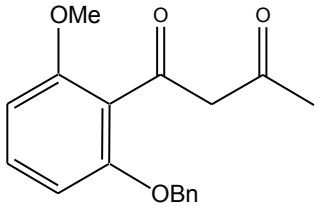
6.4.7.1 2-Benzyloxy-6-methoxyacetophenone (4.43)[14]



(**4.43**)

The first compound (R_f 0.71); obtained as a clear liquid; 0.014 g (12%); was identified as the 2-benzyloxy-6-methoxyacetophenone (**4.43**); ^{1}H NMR (Plate 7a, 600 MHz, $CDCl_3$) δ 7.40-7.36 (4H, m, Ar-H), 7.34-7.30 (1H, m, Ar-H), 7.25 (1H, t, *J* = 8 Hz, H-4), 6.61 (1H, d, *J* = 8.3 Hz, H-3), 6.58 (1H, d, *J* = 8.3 Hz, H-5), 5.10 (2H, s, OCH_2Ph), 3.82 (3H, s, OCH_3), 2.51 (3H, s, $COCH_3$); ^{13}C NMR (Plate 7b, 600 MHz, $CDCl_3$) δ 202.7, 156.7, 155.8, 136.6, 130.6, 128.6, 127.9, 127.0, 121.2, 105.5, 104.3, 70.5, 55.9, 32.4. EIMS (70 eV) *m/z* 256 (M^+, 5%).

6.4.7.2 *1-(2-Benzyloxy-6-methoxy-phenyl)-butane-1,3-dione* (4.162)



(**4.162**)

The second compound (R_f 0.64); obtained as a yellow liquid; 0.003 g (2%); was identified as the *1-(2-benzyloxy-6-methoxy-phenyl)-butane-1,3-dione* (**4.162**); ^{1}H NMR (Plate 8a, 600 MHz, $CDCl_3$) δ 7.43-7.28 (5H, m, Ar-H), 7.21 (1H, t, *J* = 8 Hz, H-4), 6.58 (1H, d, *J* = 8 Hz, H-5), 6.57 (1H, d, *J* = 8 Hz, H-3), 5.39 (1H, d, *J* = 1 Hz, $COCH_2COCH_3$), 5.16 (1H, d, *J* = 1 Hz, $COCH_2COCH_3$), 5.12 (2H, s, OCH_2Ph), 3.84 (3H, s, OCH_3), 2.04 (3H, s, $COCH_2COCH_3$); ^{13}C NMR (Plate 8b, 600 MHz, $CDCl_3$) δ 168.6, 158.4, 157.3, 145.8, 137.1, 130.1, 128.5, 127.7, 126.9, 108.2, 105.5, 104.2, 70.4, 56.0, 21.2. EIMS (70 eV) *m/z* 298 (M^+, 2%).

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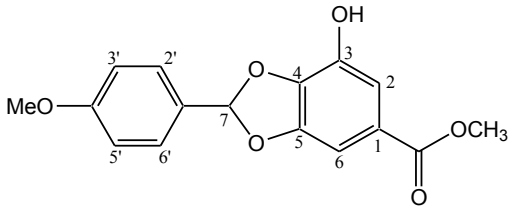
14 Sethna, S.M. *Chem. Rev.* **1951**, *49*, 91.

6.4.8 Methyl 3-hydroxy-4,5-(*p*-methoxyphenylmethylenedioxy)-benzoate (4.52)[15]



(**4.52**)

A mixture of methyl 3,4,5-trihydroxybenzoic (**4.51**) (0.200 g, 1.086 mmol, 1 eq.), Amberlyst 15 (0.100 g), and *p*-anisaldehyde dimethylacetal (0.555 mL, 3.258 mmol, 3 eq.) (**4.47**) in benzene (20 mL) was refluxed for 17 h with azeotropic removal of the EtOH/benzene mixture by using the Dean Stark trap. After completion, the reaction mixture was filtered through filter paper, the solvent concentrated *in vacuo* and the product separated by PLC.

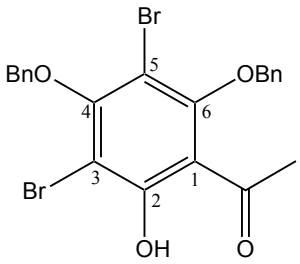
Light yellow solid; 0.057 g (17%); R_f 0.39 (H:A = 7:3); ^{1}H NMR (Plate 10, 600 MHz, Acetone) δ 8.86 (1H, s, OH), 7.57 (2H, d, *J* = 8 Hz, H-2',6'), 7.31 (1H, s, H-7), 7.12 (1H, d, *J* = 1 Hz, H-2), 7.07 (1H, d, *J* = 1 Hz, H-6), 7.02 (2H, d, *J* = 8 Hz, H-3',5'), 3.85 (3H, s, OC$\underline{H}_3$), 3.84 (3H, s, OC$\underline{H}_3$).

6.4.9 Bromination of 4,6-dibenzyloxy-2-hydroxyacetophenone (4.54)

Treatment of 4,6-dibenzyloxy-2-hydroxyacetophenone (**4.54**) [0.780 g, 2.239 mmol, 1 eq. in glacial acetic acid (10 mL)], with bromine (0.13 mL, 2.239 mmol, 1 eq. in glacial acetic acid (2 mL)] and work-up of the reaction mixture according to the general procedure given above (*cf* paragraph 6.3.6). Purification by PLC (H:A = 8:2) yielded two identifiable products with R_f values of 0.56 and 0.38.

15 Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 1909.

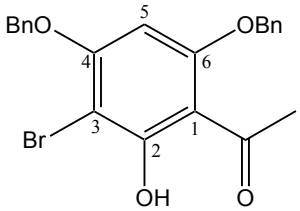
6.4.9.1 4,6-Dibenzyloxy-3,5-dibromo-2-hydroxyacetophenone (**4.57**)



(**4.57**)

The first compound (R_f 0.56); obtained as yellow needles; 0.057 g (10%); was identified as the *4,6-dibenzyloxy-3,5-dibromo-2-hydroxyacetophenone* (**4.57**); ^{1}H NMR (Plate 14a, 600 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 7.1 Hz, Ar-H), 7.51 (2H, d, *J* = 6.7 Hz, Ar-H), 7.46-7.40 (6H, m, Ar-H), 5.15 (2H, s, OCH_2Ph), 5.05 (2H, s, OCH_2Ph), 2.67 (3H, s, $COCH_3$); ^{13}C NMR (Plate 14b, 600 MHz, $CDCl_3$) δ 204.1, 160.6, 159.4, 158.0, 135.7, 135.3, 128.9-128.2, 114.4, 104.9, 75.0, 31.9. EIMS (70 eV) *m/z* 506 (M^+, 15%).

6.4.9.2 4,6-Dibenzyloxy-3-bromo-2-hydroxyacetophenone (**4.56**)



(**4.56**)

The second compound (R_f 0.38); obtained as a grey solid; 0.58 g (90%); was identified as the *4,6-dibenzyloxy-3-bromo-2-hydroxyacetophenone* (**4.56**); ^{1}H NMR [16] (Plate 13a, 600 MHz, $CDCl_3$) δ 14.60 (1H, s, OH), 7.45-7.35 (10H, m, 2 x Ar-H), 6.13 (1H, s, H-5), 5.20 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 2.58 (3H, s, $COCH_3$); ^{13}C NMR (Plate 13b, 600 MHz, $CDCl_3$) δ 205.3, 164.5, 163.9, 163.2, 138.2, 137.8, 130.6-129.2, 108.5, 93.3, 92.4, 73.4, 72.6, 34.5; NOESY (Plate 13c, 600 MHz, $CDCl_3$).

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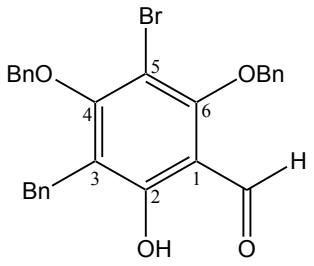
16 Hill, T.N.; Kuo, C.-M.; Bezuidenhoudt, B.C.B. *Z. Kristallogr*. NCS 230, **2015**, 2014.

6.4.10 Bromination of 2-hydroxy-4,6-dibenzyloxybenzaldehyde (4.59)

Prepared as described in general bromination procedure (*cf* paragraph 6.3.6):

2-Hydroxy-4,6-dibenzyloxybenzaldehyde (**4.59**)[17] (0.556 g, 1.663 mmol, 1 eq.), glacial acetic acid (10 mL), bromine (0.266 g, 0.09 mL, 1.663 mmol, 1 eq.) and glacial acetic acid (1 mL). Purification by PLC (H:A = 9:1) yielded two identifiable products with R_f values of 0.57 and 0.28.

6.4.10.1 3-Benzyl-4,6-dibenzyloxy-5-bromo-2-hydroxybenzaldehyde (4.62)

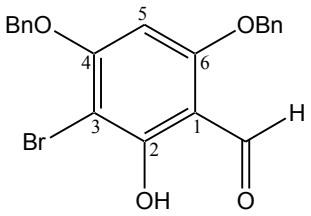


(**4.62**)

The first compound (R_f 0.57); obtained as brown needles; 0.09 g (13%); was identified as the *3-benzyl-4,6-dibenzyloxy-5-bromo-2-hydroxybenzaldehyde* (**4.62**); ^{1}H NMR (Plate 17a, 600 MHz, $CDCl_3$) δ 12.20 (1H, s, OH), 9.99 (1H, s, C<u>H</u>O), 7.51-7.48 (4H, m, Ar-<u>H</u>), 7.46-7.41 (6H, m, Ar-<u>H</u>), 7.30-7.27 (4H, m, $CH_2C_6\underline{H}_5$), 7.23-7.19 (1H, m, $CH_2C_6\underline{H}_5$), 5.18 (2H, s, $OC\underline{H}_2Ph$), 4.97 (2H, s, $OC\underline{H}_2Ph$), 4.06 (2H, s, $OC\underline{H}_2Ph$); ^{13}C NMR (Plate 17b, 600 MHz, $CDCl_3$) δ 193.7, 162.2, 161.9, 158.8, 140.1, 136.2, 135.3, 128.9-126.2, 121.8, 113.4, 103.1, 78.0, 75.6, 29.4; NOESY (Plate 17c, 600 MHz, $CDCl_3$). EIMS (70 eV) *m/z* 503 (M^+, 2%).

[17] Anderson, J.C.; Headley, C.; Stapleton, P.D.; Taylor, P.W. *Tetrahedron* **2005**, *61*, 7703.

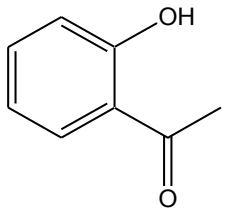
6.4.10.2 4,6-Dibenzyloxy-3-bromo-2-hydroxybenzaldehyde (**4.61**)



(**4.61**)

The second compound (R_f 0.28); obtained as a brown solid; 0.089 g (74%); was identified as the *4,6-dibenzyloxy-3-bromo-2-hydroxybenzaldehyde* (**4.61**); ^{1}H NMR (Plate 16a, 600 MHz, $CDCl_3$) δ 12.97 (1H, s, OH), 10.16 (1H, s, CHO), 7.44-7.36 (10H, m, 2 x Ar-H), 6.14 (1H, s, H-5), 5.21 (2H, s, OCH_2Ph), 5.10 (2H, s, OCH_2Ph); ^{13}C NMR (Plate 16b, 600 MHz, $CDCl_3$) δ 191.9, 162.7, 162.2, 161.5, 135.4, 135.3, 128.9-126.9, 106.8, 91.7, 90.0, 71.1, 71.0; NOESY (Plate 16c, 600 MHz, $CDCl_3$). EIMS (70 eV) *m/z* 413 (M^+, 3%).

6.4.11 2-Hydroxyacetophenone (4.67)



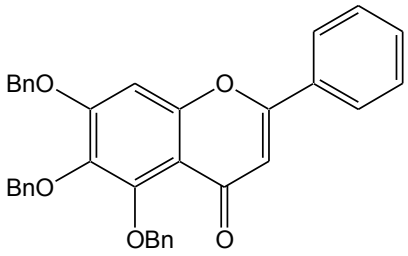
(**4.67**)

Prepared as described in general flavone degradation procedure (*cf* paragraph 6.3.7):
Diethylene glycol (0.84 mL, 8.82 mmol, 19.6 eq.), flavone (**4.66**) (0.100 g, 0.45 mmol, 1 eq.), pyridine (0.74 mL, 9.18 mmol, 20.4 eq.) and 18 M KOH (0.74 mL, 27 mmol, 60 eq.). Yield of 2-hydroxyacetophenone (**4.67**) 0.012 g (20%).

Yellow solid; R_f 0.58 (H:A = 8:2); ^{1}H NMR (Plate 18, 600 MHz, $CDCl_3$) δ 12.27 (1H, s, OH), 7.75 (1H, dd, *J* = 8 Hz and 2 Hz, H-6), 7.49 (1H, dt, *J* = 7 Hz, H-4), 7.00 (1H, dd, *J* = 8 Hz and 2

Hz, H-3), 6.92 (1H, dt, *J* = 8 Hz, H-5), 2.66 (3H, s, COC<u>H</u>$_3$). EIMS[18] (70 eV) *m/z* 136 (M^+, 60%).

6.4.12 5,6,7-Tribenzyloxyflavone (4.70)



(**4.70**)

Baicalein (**4.69**) (0.500 g, 1.850 mmol, 1 eq.) and K_2CO_3 (1.023 g, 7.401 mmol, 4 eq.) in DMF (20 mL) was stirred at 60 ^oC. The reaction mixture was then treated with BnBr (0.9 mL, 7.401 mmol, 4 eq.) at the same temperature for 12 h. The crude mixture was acidified with 3 M HCl (5 mL) and extracted with EA (3 x 20 mL), washed with water (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* and the product obtained by PLC.

Brown solid; 1.928 g (72%); R_f 0.34 (H:EA:A = 8:1:1); ^{1}H NMR[19] (Plate 19a, 600 MHz, $CDCl_3$) δ 7.88 (2H, dd, *J* = 7.9 and 2.3 Hz, H-3',5'), 7.72 (2H, d, *J* = 7.2 Hz, H-2',6'), 7.53-7.28 (16H, m, 3 x Ar-<u>H</u>, H-4'), 6.93 (1H, s, H-3), 6.72 (1H, s, H-8), 5.21 (2H, s, OC<u>H</u>$_2$Ph), 5.19 (2H, s, OC<u>H</u>$_2$Ph), 5.09 (2H, s, OC<u>H</u>$_2$Ph); ^{13}C NMR[19] (Plate 19b, 600 MHz, $CDCl_3$) δ_C (ppm): 177.2, 161.2, 157.2, 154.6, 151.8, 140.1, 137.2, 135.6, 131.6, 131.3, 129.4, 128.1, 127.5, 126.0, 113.6, 108.4, 97.9, 76.8, 76.0, 71.1.

6.4.13 Degradation of 5,6,7-tribenzyloxyflavone (4.70)

Prepared as described in general flavone degradation procedure (*cf* paragraph 6.3.7):

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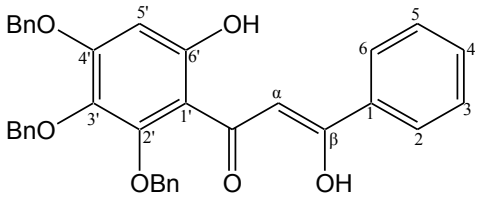
18 Pal, P.; Pahari, S.K.; Sinhamahapatra, A.; Giri, A.K.; Bajaj, H.C.; Panda, A.B. *RSC* **2013**.

19 Yuichi, K.; Yukinori, M.; Tsuyoshi, T. *Yakugaku Zasshi* **1991**, *111*, 424.

Diethylene glycol (1.12 mL, 5.370 mmol, 19.6 eq.), flavone (**4.70**) (0.148 g, 0.274 mmol, 1 eq.), pyridine (1.07 mL, 5.590 mmol, 20.4 eq.) and 18 M KOH (2.04 mL, 16.44 mmol, 60 eq.). Purification by PLC (T:EA = 9.5:0.5) yielded three identifiable products with R_f values of 0.73, 0.62 and 0.27

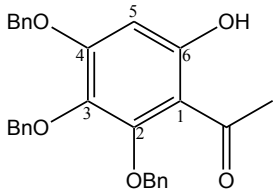
6.4.13.1 2',3',4'-Tribenzyloxy-β,6'-dihydroxychalcone (4.72)



(**4.72**)

The first compound (R_f 0.73); obtained as a yellow solid; 0.040 g (32%); was identified as the 2',3',4'-tribenzyloxy-β,6'-dihydroxychalcone (**4.72**); ^{1}H NMR (Plate 21a, 600 MHz, $CDCl_3$) δ 15.61 (1H, s, OH), 13.01 (1H, s, OH), 7.55-7.27 (21H, m, 4 x $C_6\underline{H}_5$ and α-$\underline{H}$)], 6.44 (1H, s, H-5'), 5.15 (2H, s, OC$\underline{H}_2$Ph), 5.12 (2H, s, OC$\underline{H}_2$Ph), 5.04 (2H, s, OC$\underline{H}_2$Ph); ^{13}C NMR (Plate 21b, 600 MHz, $CDCl_3$) δ 193.7, 176.8, 161.5, 158.6, 153.7, 137.3, 136.6, 135.8, 135.0, 133.7, 131.8, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 127.7, 126.8, 107.9, 98.3, 97.6, 76.7, 76.0, 70.7.

6.4.13.2 2,3,4-Tribenzyloxy-6-hydroxyacetophenone (4.71)[20]



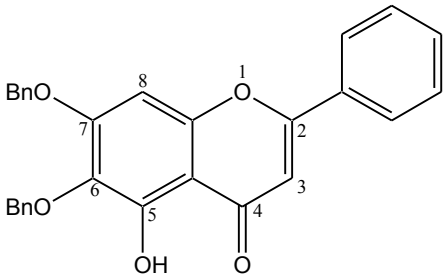
(**4.71**)

The second compound (R_f 0.62); obtained as a yellow solid; 0.036 g (28%); was identified as the *2,3,4-tribenzyloxy-6-hydroxyacetophenone* (**4.71**); ^{1}H NMR (Plate 20a, 600 MHz, $CDCl_3$) δ 13.37 (1H, s, O$\underline{H}$), 7.47-7.27 (15H, m, 3 x Ar-$\underline{H}$), 6.28 (1H, s, H-5), 5.23 (2H, s, OC$\underline{H}_2$Ph), 5.14 (2H, s, OC$\underline{H}_2$Ph), 4.97 (2H, s, OC$\underline{H}_2$Ph), 2.49 (3H, s, COC$\underline{H}_3$); ^{13}C NMR (Plate 20b, 600 MHz,

[20] Kuo, C.-M.; Hill, T.N.; Bezuidenhoudt, B.C.B. *Z. Kristallogr. NCS* **2016**, *231*, 1155.

$CDCl_3$) δ 203.6, 161.9, 159.4, 154.6, 137.0, 136.7, 135.7, 134.0, 128.8, 128.7, 128.6, 128.4, 128.4, 128.2, 127.7, 109.3, 97.6, 76.3, 75.8, 70.8, 32.3. HRMS: calcd for $C_{29}H_{26}O_5Na$: 477.1600 g/mol. Found: *m/z* 477.1677.

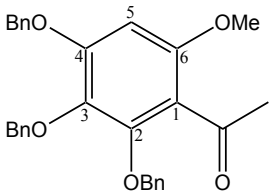
6.4.13.3 6,7-Dibenzyloxy-5-hydroxyflavone (**4.73**)[21]



(**4.73**)

The third compound (R_f 0.27); obtained as a white solid; 0.012 g (10%); was identified as the *6,7-dibenzyloxy-5-hydroxyflavone* (**4.73**); ^{1}H NMR (Plate 22a, 600 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 6.9 Hz, H-2',6'), 7.57-7.50 (5H, m, Ar-H), 7.43-7.41 (4H, m, Ar-H), 7.37-7.40 (1H, m, Ar-H), 7.32-7.30 (3H, m, Ar-H), 6.69 (1H, s, H-3), 6.60 (1H, s, H-8), 5.19 (2H, s, OCH_2Ph), 5.17 (2H, s, OCH_2Ph); ^{13}C NMR (Plate 22b, 600 MHz, $CDCl_3$) δ 164.0, 153.3, 137.5, 135.8, 131.9, 131.4, 129.1, 128.8, 128.7, 128.7, 128.3, 128.2, 128.0, 127.3, 126.3, 105.7, 92.0, 74.9, 71.0, 29.7. EIMS (70 eV) *m/z* 450 (M^+, 2%).

6.4.14 2,3,4-Tribenzyloxy-6-methoxyacetophenone (4.163)



(**4.163**)

2,3,4-Tribenzyloxy-6-hydroxyacetophenone (**4.71**) (0.137 g, 0.301 mmol, 1 eq.) was treated with Cs_2CO_3 (0.12 g, 0.362 mmol, 1.2 eq.) in DMF (4 mL), the reaction was stirred at rt for 30 min.

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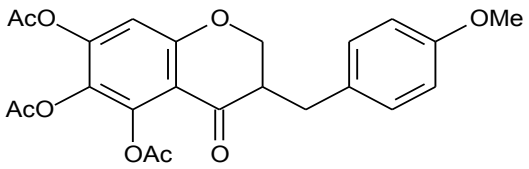
21 Lee, Y.; Yeo, H.; Liu, S.-H.; Jiang, Z.; Savizky, R.M.; Austin, D.J.; Cheng, Y.-C. *J. Med. Chem.* **2004**, *47*, 5555.

After 30 min. MeI (0.02 mL, 0.362 mmol, 1.2 eq.) was added dropwise at the same temperature and the mixture stirred for 1 hour. The reaction mixture was acidified with 3 M HCl (5 mL) and extracted with EA (3 x 20 mL), washed with water (20 mL), dried over Na_2SO_4 and concentrated. The crude product was separated by PTL. Yield of 2,3,4-tribenzyloxy-6-methoxyacetophenone (**4.163**) 0.012 g (9%).

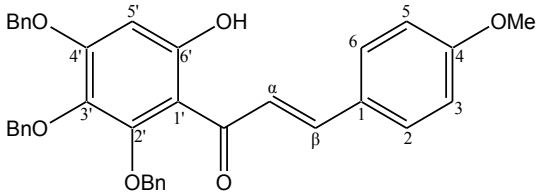
Yellow solid; R_f 0.34 (H:EA = 8:2); ^{1}H NMR (Plate 23a, 600 MHz, $CDCl_3$) δ 7.47-7.45 (2H, m, Ar-H), 7.43-7.41 (4H, m, Ar-H), 7.39-7.35 (5H, m, Ar-H), 7.34-7.32 (4H, m, Ar-H), 6.37 (1H, s, H-5), 5.16 (2H, s, OCH_2Ph), 5.11 (2H, s, OCH_2Ph), 5.01 (2H, s, OCH_2Ph), 3.77 (3H, s, OCH_3), 2.39 (3H, s, $COCH_3$); ^{13}C NMR (Plate 23b, 600 MHz, $CDCl_3$) δ 201.3, 154.2, 152.8, 150.3, 137.4, 137.1, 136.5, 136.0, 128.8, 128.7, 128.7, 128.4, 128.4, 128.2, 128.2, 128.1, 127.6, 119.6, 94.6, 76.6, 75.8, 71.4, 56.0, 32.6.

6.5 Synethsis of 5,6,7-triacetoxy-4'-methoxyhomoisoflavan-one (4.5)



(**4.5**)

6.5.1 *2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxychalcone* (4.74)

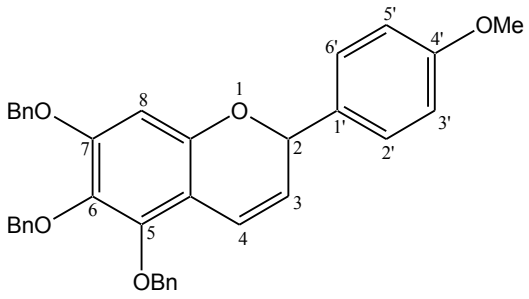


(**4.74**)

2,3,4-Tribenzyloxy-6-hydroxyacetophenone (**4.71**) (0.152 g, 0.334 mmol, 1 eq.) and *p*-methoxybenzaldehyde (**4.10**) (0.05 mL, 0.401 mmol, 1.2 eq.) were dissolved in EtOH:THF = 5:1 (10 mL : 2 mL) and stirring at 0 ^{o}C. Freshly powder KOH (0.1 g, 1.67 mmol, 5 eq.) was added and stirred at rt overnight. Water (30 mL) was added and the reaction mixture was neutralized with 3 M HCl. The residue was extracted with EA (3 x 20 mL) and the organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Purification by PLC yielded *2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxychalcone* (**4.74**) 0.146 g (76%).

Yellow solid; R_f 0.23 (H:EA:A = 9:0.5:0.5); ^{1}H NMR (Plate 24a, 600 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 16 Hz, H-α), 7.82 (1H, d, *J* = 16 Hz, H-β), 7.47-7.45 (2H, m, Ar-H), 7.44-7.41 (4H, m, Ar-H), 7.40-7.39 (1H, m, Ar-H), 7.36-7.31 (6H, m, Ar-H), 7.29-7.26 (4H, m, Ar-H, H-2,6), 6.81 (2H, d, *J* = 8 Hz, H-3,5), 6.44 (1H, s, H-5'), 5.16 (2H, s, OCH_2Ph), 5.09 (2H, s, OCH_2Ph), 5.04 (2H, s, OCH_2Ph), 3.87 (3H, s, OCH_3); ^{13}C NMR (Plate 24b, 600 MHz, $CDCl_3$) δ 192.8, 162.9, 161.5, 159.2, 154.3, 143.8, 137.3, 136.5, 135.7, 134.7, 130.6, 129.0-127.7(9), 124.3, 114.2, 109.4, 98.0, 76.0, 70.8, 55.4. HRMS: calcd for $C_{37}H_{32}O_6Na$: 595.2018 g/mol. Found: *m/z* 595.2087.

6.5.2 *5,6,7-Tribenzyloxy-4'-methoxyflav-3-ene* (4.75)



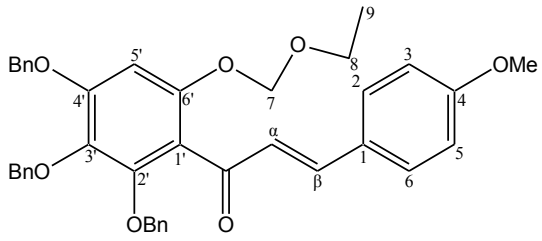
(**4.75**)

2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**) (0.100 g, 0.175 mmol, 1 eq.) was dissolved in EtOH (10 mL). Finely powder $NaBH_4$ (20 eq.) was added to the solution and it was stirred at rt until completion (TLC). Acetone was added to the reaction mixture and it was stirred for 30 min. The reaction mixture was evaporated to dryness under reduced pressure. The crude product was dissolved in EA (60 mL) and washed with water (30 mL). The organic layer was

dried over Na_2SO_4 and evaporated under reduced pressure. Purification by PLC yielded *5,6,7-tribenzyloxy-4'-methoxyflav-3-ene* (**4.75**) 0.045 g (45%).

Orange solid; R_f 0.47 (H:EA:A = 8:1:1); ^{1}H NMR (Plate 25a, 600 MHz, $CDCl_3$) δ 7.44-7.31 (15H, m, 3 x Ar-H), 7.35 (2H, d, *J* = 9 Hz, H-2',6'), 6.90 (2H, d, *J* = 9 Hz, H-3',5'), 6.75 (1H, dd, *J* = 10 and 1 Hz, H-4), 6.30 (1H, s, H-8), 5.76 (1H, br s, H-2), 5.63 (1H, dd, *J* = 10 and 3 Hz, H-3), 5.15 (1H, d, *J* = 11 Hz, OCH_2Ph), 5.12 (1H, d, *J* = 11 Hz, OCH_2Ph), 5.03 (2H, s, OCH_2Ph), 5.01 (2H, s, OCH_2Ph), 3.83 (3H, s, OCH_3); ^{13}C NMR (Plate 25b, 600 MHz, $CDCl_3$) δ 159.8, 153.3, 149.6, 148.6, 137.7, 137.4, 136.7, 135.8, 132.6, 128.9-127.5 (10), 121.7, 119.3, 114.0, 109.3, 98.2, 76.8, 76.0, 75.8, 70.8, 55.3. EIMS (70 eV) *m/z* 556 (M^+, 3%).

6.5.3 *2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxychalcone* (4.76)



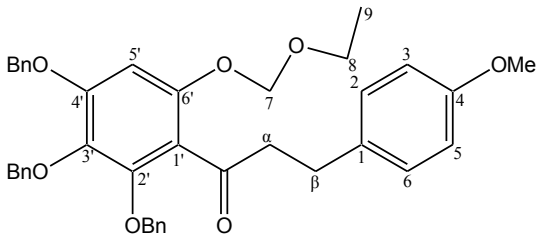
(**4.76**)

To a solution of 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**) (0.200 g, 0.349 mmol, 1 eq.) and adogen 464 (0.5 mL) in DCM (10 mL) was added *aq*. NaOH (2 M, 5 mL). The reaction mixture was stirred vigorously at rt for 30 minutes and then chloromethyl ethylether (EOMCl) (0.1 mL, 0.524 mmol, 3 eq.) was added with continuous stirring for 30 min. After completion of the reaction, water (20 mL) was added and the reaction mixture was extracted with DCM (3 x 20 mL), washed with brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and yielded *2',3',4'-tribenzyloxy-6'-ethoxymethoxy-4-methoxychalcone* (**4.76**) 0.220 g (100%).

Yellow oil; R_f 0.33 (H:EA = 8:2); ^{1}H NMR (Plate 26, 600 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8 Hz, H-2,6), 7.44-7.37 (7H, m, Ar-H), 7.30-7.27 (5H, m, Ar-H, H-β), 7.24-7.21 (4H, m, Ar-H), 6.88 (2H, d, *J* = 8 Hz, H-3,5), 6.82 (1H, d, *J* = 16 Hz, H-α), 6.74 (1H, s, H-5'), 5.16 (2H, s, OCH_2Ph),

5.12 (2H, s, OC<u>H</u>$_2$Ph), 5.08 (2H, s, OC<u>H</u>$_2$Ph), 5.02 [2H, s, H-7(a),(b)], 3.84 (3H, s, OC<u>H</u>$_3$), 3.63 [2H, q, *J* = 7 Hz, H-8(a),(b)], 1.60 [3H, t, *J* = 7 Hz, H-9(a),(b),(c)].

6.5.4 *2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxydihydrochalcone* (4.77)

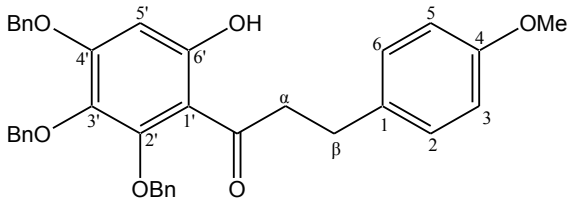


(**4.77**)

2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxychalcone (**4.76**) (0.100 g, 0.159 mmol, 1 eq.) was dissolved in EtOH (10 mL). Finely powder $NaBH_4$ (0.120 g, 3.18 mmol, 20 eq.) was added to the solution and it was stirred at rt until completion. Acetone (20 mL) was added to the reaction mixture and stirred for 30 min. The reaction mixture was evaporated to dryness. The crude product was dissolved in EA (60 mL) and washed with water (3 x 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Purification by PLC yielded *2',3',4'-tribenzyloxy-6'-ethoxymethoxy-4-methoxydihydrochalcone* (**4.77**) 0.026 g (26%).

Yellow solid; R_f 0.38 (H:EA = 8:2); ^{1}H NMR (Plate 27a, 600 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 7.3 Hz, Ar-<u>H</u>), 7.41-7.31 (13H, m, Ar-<u>H</u>), 7.07 (2H, d, *J* = 8 Hz, H-2,6), 6.78 (2H, d, *J* = 8 Hz, H-3,5), 6.70 (1H, s, H-5'), 5.13 (2H, s, OC<u>H</u>$_2$Ph), 5.10 (2H, s, OC<u>H</u>$_2$Ph), 5.08 (2H, s, OC<u>H</u>$_2$Ph), 5.00 [2H, s, H-7(a),(b)], 3.78 (3H, s, OC<u>H</u>$_3$), 3.66 [2H, q, *J* = 7 Hz, H-8(a),(b)], 2.98 (2H, t, *J* = 7 Hz, α-CH_2), 2.90 (2H, t, *J* = 7 Hz, β-CH_2), 1.21 [3H, t, *J* = 7 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 27b, 600 MHz, $CDCl_3$) δ 202.8, 157.8, 154.0, 150.4, 150.0, 137.4, 137.2, 136.7, 136.4, 133.4, 129.3-127.7 (8), 120.3, 113.7, 98.0, 94.0, 76.6, 75.7, 71.1, 64.4, 55.3, 46.7, 28.8, 15.1. HRMS: calcd for $C_{40}H_{40}O_7Na$: 655.2674 g/mol. Found: *m/z* 655.2681.

6.5.5 *2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone* (4.78)

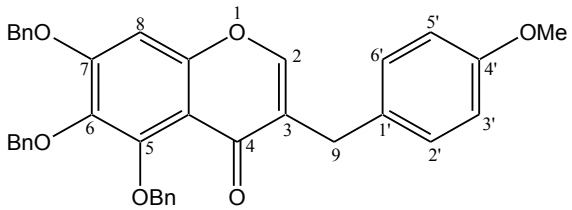


(**4.78**)

3 M HCl (1 mL) in MeOH solution (10 mL) was added to a solution of 2',3',4'-tribenzyloxy-6'-ethoxymethoxy-4-methoxydihydrochalcone (**4.77**) (0.200 g, 0.316 mmol, 1 eq.) in THF (3 mL). The reaction mixture was stirred at rt for 2 h. After completion of the reaction, the solvent was evaporated and diluted in EtOH (20 mL). The product was collected after evaporated under reduced pressure. Yield of *2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone* (**4.78**) 0.182 g (100%).

Brown solid; R_f 0.34 (H:EA = 8:2); ^{1}H NMR (Plate 28a, 600 MHz, $CDCl_3$) δ 7.45-7.38 (6H, m, Ar-H), 7.34-7.32 (3H, m, Ar-H), 7.31-7.26 (6H, m, Ar-H), 6.95 (2H, d, *J* = 9 Hz, H-2,6), 6.77 (2H, d, *J* = 9 Hz, H-3,5), 6.38 (1H, s, H-5'), 5.18 (2H, s, OCH_2Ph), 5.13 (2H, s, OCH_2Ph), 4.96 (2H, s, OCH_2Ph), 3.81 (3H, s, OCH_3), 3.30 (2H, t, *J* = 8 Hz, α-CH_2), 2.86 (2H, t, *J* = 8 Hz, β-CH_2); ^{13}C NMR (Plate 28b, 600 MHz, $CDCl_3$) δ 205.0, 161.8, 159.1, 157.7, 154.4, 137.0, 136.4, 135.7, 134.0, 133.3, 129.3-127.7 (9), 113.7, 108.9, 97.7, 76.4, 75.8, 70.8, 55.3, 45.5, 29.3. HRMS: calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2257.

6.5.6 *5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavone* (4.79)

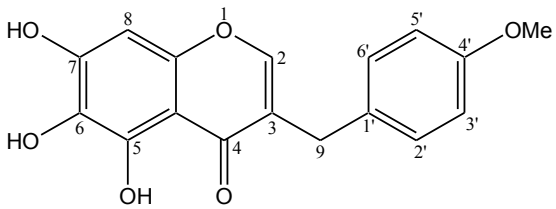


(**4.79**)

To a solution of 2',3',4'-tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone (**4.78**) (0.050 g, 0.087 mmol, 1 eq.) in DMF (2 mL) was added dropwise $BF_3.Et_2O$ (0.03 mL, 0.183 mmol, 3 eq.) and the mixture cooled to 10 ^oC. In a second flask, DMF (2 mL) was cooled to 10 ^oC and PCl_5 (0.027 g, 0.131 mmol, 1.5 eq.) was added in small portions.[22] The DMF-PCl_5 mixture was stirred at 55 ^oC until a light yellow colour indicative of *N*,*N*'-dimethyl(chloromethylene) ammonium chloride was observed (20 min.) and then slowly added to the flask containing the dihydrochalcone solution at 20 – 25 ^oC. The reaction mixture was stirred at rt for 24 h, slowly added to boiling diluted HCl (10 mL) and cooled. The solution was extracted with EA (3 x 10 mL) and the combined organic layers washed with water (10 mL) and brine (10 mL) and the combined organic phases dried over Na_2SO_4. The residue after *in vacuo* concentration was purified by PLC to afford the title compound, *5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone* (**4.79**) 0.015 g (29%).

Light yellow amorphous solid; R_f 0.31 (H:EA:A = 8:1:1); ^1H NMR (Plate 29a, 600 MHz, Acetone) δ 7.85 (1H, s, H-2), 7.66-7.27 (17H, m, H-2',6', 3 x Ar-H), 7.03 (1H, s, H-8), 6.85 (2H, d, *J* = 8.5 Hz, H-3',5'), 5.32 (2H, s, OCH_2Ph), 5.09 (2H, s, OCH_2Ph), 5.02 (2H, s, OCH_2Ph), 3.76 (3H, s, OCH_3), 3.69 (2H, s, 9-CH_2); ^{13}C NMR (Plate 29b, 600 MHz, Acetone) δ 176.0, 158.3, 157.0, 154.9, 151.5, 151.2, 139.8, 138.0, 137.7, 136.3, 131.5, 129.8, 128.7, 128.7, 128.4, 128.3, 128.3, 128.1, 128.0, 127.5, 127.3, 125.0, 114.0, 113.4, 97.9, 75.9, 75.3, 70.8, 54.5, 30.1. HRMS: calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2102.

6.5.7 *5,6,7-Trihydroxy-4'-methoxyhomoisoflav*one (4.80)



(**4.80**)

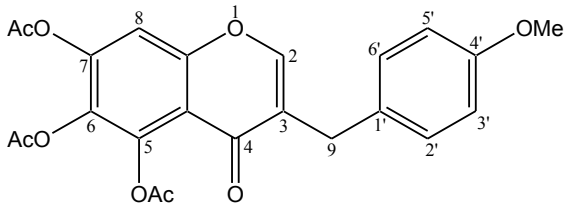
A mixture of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**) (0.024 g, 0.041 mmol) in acetone (15 mL) was added 5% Pd/C (20 mg) in a ratio of 1:1 and the reaction mixture was

[22] Davis, F.A.; Chen, B-C. *J. Org. Chem.* **1993**, *58*, 1751.

hydrogenated at rt under atmospheric pressure. The reaction stopped after 45 min. The catalyst was filtered off. Yield of *5,6,7-trihydroxy-4'-methoxyhomoisoflavone* (**4.80**) 0.012 g (92%).

Light yellow solid; R_f 0.14 (H:EA:A = 7:2:1); ^{1}H NMR (Plate 30, 600 MHz, Acetone) δ 7.98 (1H, s, H-2), 7.26 (2H, d, *J* = 9 Hz, H-2',6'), 6.85 (2H, d, *J* = 9 Hz, H-3',5'), 6.49 (1H, s, H-8), 3.76 (3H, s, OC<u>H</u>$_3$), 3.69 (2H, s, 9-C<u>H</u>$_2$).

6.5.8 *<u>5,6,7-Triacetoxy-4'-methoxyhomoisoflavone</u>* (<u>4.81</u>)

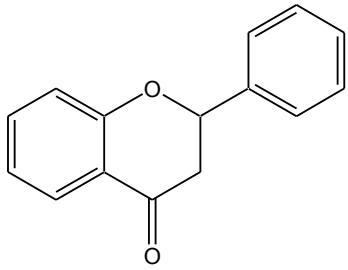


(**4.81**)

5,6,7-Trihydroxy-4'-methoxyhomoisoflavone (**4.80**) (0.012 g, 0.038 mmol, 1 eq.) was added to a mixture of pyridine (1 mL) and acetic anhydride (2 mL) in a ratio 1:2. The reaction mixture was heated at 60 °C overnight. Ice water (10 mL) was added to the reaction mixture, whereafter the precipitate was filtered off and washed with cold water several times (3 x 10 mL) to remove the pyridine. Yield of *5,6,7-triacetoxy-4'-methoxyhomoisoflavone* (**4.81**) 0.010 g (59%).

Brown solid; R_f 0.24 (H:EA:A = 7:2:1); ^{1}H NMR (Plate 31, 600 MHz, CDCl3) δ 7.59 (1H, s, H-2), 7.18 (2H, d, *J* = 9 Hz, H-2',6'), 6.88 (2H, d, *J* = 9 Hz, H-3',5'), 6.82 (1H, s, H-8), 3.82 (3H, s, OC<u>H</u>$_3$), 3.74 (2H, s, 9-C<u>H</u>$_2$), 2.37 (3H, s, COC<u>H</u>$_3$), 2.34 (3H, s, COC<u>H</u>$_3$), 2.20 (3H, s, COC<u>H</u>$_3$).

6.5.9 Flavanone (4.85)



(**4.85**)

Copper (II) acetate monohydrate (0.001 mg, 0.0045 mmol) and 1,2-bis(diphenylphosphino)benzene (0.0002 mg, 0.0005 mmol) were dissolved in degassed *t*-BuOH (0.1 mL) and 2 mL dry toluene under argon.[23] The reaction mixture was allowed to stir for 30 min at rt before poly(methylhydrosiloxane) (0.24 mL, 0.9 mmol) was added. The solution changed colour from blue to golden over 20 min period. Flavone (0.1 g, 1 eq) (**4.66**) was added and the reaction was run for 5 h. The reaction worked up after 5 h which indicated the product was formed. The mixture was diluted with EA (10 mL) and washed with 1 N KOH (10 mL) followed by 1 M HCl (10 mL) and sat. *aq*. NaCl (10 mL). The aqueous layyers was combined and back washed with EA (10 mL). The organic layers was collected and dried over anhydrous $MgSO_4$. Purification by PLC yielded of flavanone (**4.85**) 0.08 g (48%).

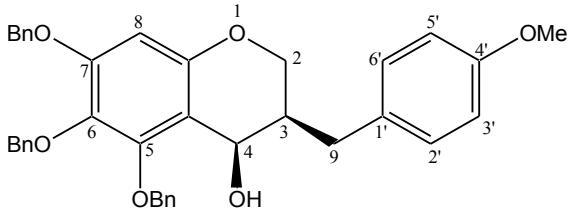
White solid; R_f 0.31 (H:EA = 8:2); ^{1}H NMR[18] (Plate 32a, 600 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J* = 8.0 Hz and 1.5 Hz, H-5), 7.55-7.44 (5H, m, H-2', H-3', H-4', H-5', H-6'), 7.41 (1H, m, H-7), 7.09 (2H, m, H-6 and H-8), 5.52 (1H, dd, *J* = 13.5 Hz and 2.6 Hz, H-2), 3.12 [(1H, dd, *J* = 13.5 Hz and 3.3 Hz, H-3(a)], 2.92 [(1H, dd, *J* = 16.9 Hz and 2.8 Hz, H-3(b)]; ^{13}C NMR (Plate 32b, 600 MHz, $CDCl_3$) δ 192.0, 161.6, 138.7, 136.2, 128.9, 128.8, 127.1, 126.2, 121.7, 120.9, 118.2, 79.6, 44.7.

23 Baker, B.A.; Bošković, Ž.V.; Lipshutz, B.H. *Org*. *Lett*. **2008**, *10*, 289.

6.5.10 Reduction of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone (4.79)

5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**) (0.050 g, 0.086 mmol, 1 eq.) was dissolved in THF (0.5 mL) and EtOH (5 mL). Finely powder $NaBH_4$ (0.06 g, 1.59 mmol, 20 eq.) was added to the solution and stirred at rt until completion. Acetone (10 mL) was added to the reaction mixture and stirred for 30 min. The reaction mixture was evaporated to dryness. The crude product was extracted with EA (3 x 20 mL) and washed with water (30 mL). The organic layers were collected and dried over Na_2SO_4 and evaporated under reduced pressure. Purification by PLC (H:EA = 8:2) yielded two identifiable products with R_f values of 0.45 and 0.32.

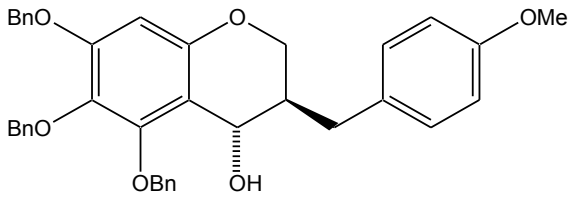
6.5.10.1 cis-5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavan-4-ol (4.89)



(**4.89**)

The first compound (R_f 0.45); obtained as brown oil; 0.002 g (4%); was identified as the *cis-5,6,7-tribenzyloxy-4'-methoxyhomoisoflavan-4-ol* (**4.89**); ^{1}H NMR (Plate 33a, 600 MHz, $CDCl_3$) δ 7.46-7.26 (15H, m, 3 x Ar-H), 7.18 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.88 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.30 (1H, s, H-8), 5.29 (1H, d, *J* = 11 Hz, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 5.03 (1H, d, *J* = 11 Hz, OCH_2Ph), 4.99 (2H, s, OCH_2Ph), 4.54 (1H, d, *J* = 2.3 Hz, H-4), 4.00-3.98 (2H, m, 2-CH_2), 3.84 (3H, s, OCH_3), 2.82 [1H, dd, *J* = 13.6 and 8.4 Hz, H-9(a)], 2.58 [1H, dd, *J* = 13.7 and 7.3 Hz, H-9(b)], 2.08-2.03 (1H, m, H-3), 1.50 (1H, d, *J* = 2.3 Hz, OH); ^{13}C NMR (Plate 33b, 600 MHz, $CDCl_3$) δ_C (ppm): 158.0, 153.6, 151.0, 150.9, 137.5, 137.2, 136.6, 135.0, 131.4, 130.1, 128.7, 128.6, 128.4, 128.0, 127.5, 113.9, 111.7, 97.6, 75.8, 75.7, 70.7, 65.1, 59.9, 55.3, 40.1, 32.0, 29.7.

6.5.10.2 trans-5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavan-4-ol (**4.90**)



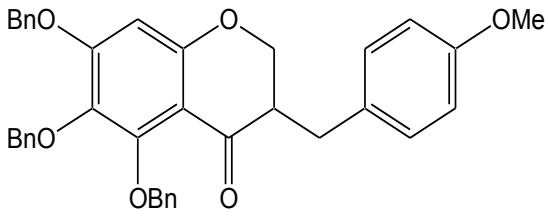
(**4.90**)

The second compound (R_f 0.32); obtained as a brown solid; 0.002 g (4%); was identified as the *trans-5,6,7-tribenzyloxy-4'-methoxyhomoisoflavan-4-ol* (**4.90**); ^{1}H NMR (Plate 34a, 600 MHz, $CDCl_3$) δ 7.49-7.33 (15H, m, 3 x Ar-H), 7.09 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.85 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.38 (1H, s, H-8), 5.35 (1H, d, *J* = 11.1 Hz, OCH_2Ph), 5.13 (1H, d, *J* = 9.8 Hz, OCH_2Ph), 5.11 (1H, d, *J* = 9.8 Hz, OCH_2Ph), 5.08 (1H, d, *J* = 11.1 Hz, OCH_2Ph), 5.02 (2H, s, OCH_2Ph), 4.45 (1H, br s, H-4), 4.06 [1H, dd, *J* = 10.9 and 2.1 Hz, H-2(a)], 3.88 [1H, dd, *J* = 10.8 and 1.9 Hz, H-2(b)], 3.80 (3H, s, OCH_3), 2.42 [1H, dd, *J* = 13.9 and 6.0 Hz, H-9(a)], 2.36-2.34 [2H, m, H-9(b), OH)], 2.11-2.07 (1H, m, H-3); ^{13}C NMR (Plate 34b, 600 MHz, $CDCl_3$) δ 153.7, 151.7, 150.8, 137.5, 137.1, 136.6, 135.2, 131.4, 130.1, 128.8, 128.7, 128.6, 128.4, 128.1, 127.6, 113.9, 110.2, 97.7, 75.8, 70.8, 63.2, 55.3, 40.4, 33.4, 29.7.

6.5.11 Oxidation of homoisoflavan-4-ol

The *cis-* and *trans*-5,6,7-tribenzyloxy-4'-methoxyhomoisoflavan-4-ols (**4.89**) and (**4.90**) (0.010 g, 0.017 mmol) were dissolved in minimum dry acetonitrile (1 mL). IBX (0.010 g, 0.034 mmol, 2 eq.) was added to the reaction and refluxed for 6.5 h. After completion, IBX was filtered off and the filtrate was extracted into Et_2O (2 x 10 mL) and washed with H_2O (20 mL). The organic layer was dried over $MgSO_4$. Purification by PLC (H:EA:A = 8:1:1) yielded two identifiable products with R_f values of 0.40 and 0.33.

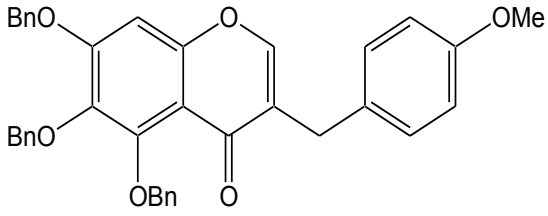
6.5.11.1 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavanone (**4.91**)



(**4.91**)

The first compound (R_f 0.40); obtained as brown oil; 0.008 g (80%); was identified as the *5,6,7-tribenzyloxy-4'-methoxyhomoisoflavanone* (**4.91**); ^{1}H NMR (Plate 35a, 600 MHz, $CDCl_3$) δ 7.63-7.29 (15H, m, 3 x Ar-H), 7.18 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.88 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.38 (1H, s, H-8), 5.12 (2H, d, *J* = 2.1 Hz, OCH_2Ph), 5.11 (2H, d, *J* = 3.8 Hz, OCH_2Ph), 4.97 (2H, s, OCH_2Ph), 4.29 [1H, dd, *J* = 11.3 and 3.9 Hz, H-2(a)], 4.13 [1H, dd, *J* = 11.4 and 6.8 Hz, H-2(b)], 3.82 (3H, s, OCH_3), 3.22 [1H, dd, *J* = 13.8 and 4.0 Hz, H-9(a)], 2.77-2.73 (1H, m, H-3), 2.67 [1H, dd, *J* = 13.7 and 11.1 Hz, H-9(b)]; ^{13}C NMR (Plate 35b, 600 MHz, $CDCl_3$) δ 191.5, 159.7, 158.6, 158.3, 153.5, 137.3, 137.2, 135.7, 130.4, 130.2, 129.2, 128.9, 128.7, 128.4, 128.3, 128.1, 127.5, 114.1, 109.4, 97.5, 76.0, 75.9, 70.8, 68.9, 55.3, 48.7, 32.0. HRMS: calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2258.

6.5.11.2 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**)

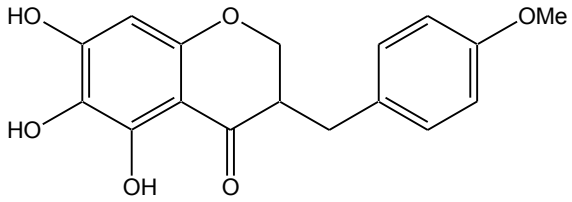


(**4.79**)

The second compound (R_f 0.33); obtained as a light yellow amorphous solid; 0.002 g (20%); was identified as the *5,6,7-tribenzyloxy-4'-methoxyhomoisoflavone* (**4.79**); ^{1}H NMR (Plate 29a, 600 MHz, $CDCl_3$) δ 7.66-7.24 (16H, m, H-2, Ar-H), 7.21 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.86 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.69 (1H, s, H-8), 5.14 (2H, s, OCH_2Ph), 5.12 (2H, s, OCH_2Ph), 5.01 (2H, s, OCH_2Ph), 3.80 (3H, s, OCH_3), 3.75 (2H, s, 9-CH_2); ^{13}C NMR (Plate 29b, 600 MHz, $CDCl_3$) δ 176.0, 158.2, 156.9, 154.8, 151.9, 139.8, 137.3, 137.2, 135.5, 130.7, 130.2, 129.2, 128.9, 128.7,

128.7, 128.4, 128.3, 128.3, 128.1, 128.0, 127.5, 127.3, 125.4, 114.0, 97.6, 76.6, 75.9, 70.9, 55.3, 30.6. HRMS: calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2102.

6.5.12 *5,6,7-Trihydroxy-4'-methoxyhomoisoflavanone* (4.92)

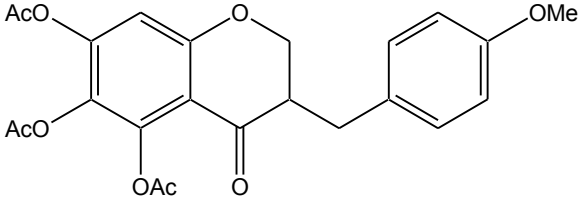


(**4.92**)

A mixture of 5,6,7-tribenzyloxy-4'-methoxyhomoisoflavanone (**4.91**) (0.013 g, 0.017 mmol) in acetone (5 mL) was added 5% Pd/C (15 mg) in a ratio of 1:1 and the reaction mixture was hydrogenated at rt and atmospheric pressure. The reaction was stopped after desired times. The catalyst was filtered off and yielded the *5,6,7-trihydroxy-4'-methoxyhomoisoflavanone* (**4.92**) 0.003 g (56%).

Yellow solid; R_f 0.18 (H:A = 7:3); ^{1}H NMR (Plate 36a, 600 MHz, Acetone) δ 7.22 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.90 (2H, d, *J* = 8.4 Hz, H-3',5'), 5.98 (1H, s, H-8), 4.29 [1H, dd, *J* = 11.3 and 4.5 Hz, H-2(a)], 4.10 [1H, dd, *J* = 11.3 and 8.2 Hz, H-2(b)], 3.79 (3H, s, OC$\underline{H}_3$), 3.17 [1H, dd, *J* = 14.0 and 4.8 Hz, H-9(a)], 2.96-2.91 (1H, m, H-3), 2.83 (3H, br s, 3 x O$\underline{H}$), 2.73 [1H, dd, *J* = 14.0 and 9.9 Hz, H-9(b)]; ^{13}C NMR (Plate 36b, 600 MHz, Acetone) δ 198.7, 158.6, 156.0, 130.2, 130.1, 113.9, 101.7, 94.3, 69.3, 54.6, 46.6, 31.4.

6.5.13 *5,6,7-Triacetoxy-4'-methoxyhomoisoflavanone* (4.93)



(**4.93**)

5,6,7-Trihydroxy-4'-methoxyhomoisoflavanone (**4.92**) (0.003 g, 0.0095 mmol, 1 eq.) was added to a mixture of pyridine (0.1 mL) and acetic anhydride (0.2 mL) in a ration 1:2. The reaction mixture was heated at 60 °C for overnight. Ice water (10 mL) was added to the reaction mixture, whereafter the precipitate was filtered off and washed with cold water several times to remove the pyridine. Yield of *5,6,7-triacetoxy-4'-methoxyhomoisoflavanone* (**4.93**) 0.005 g (100%).

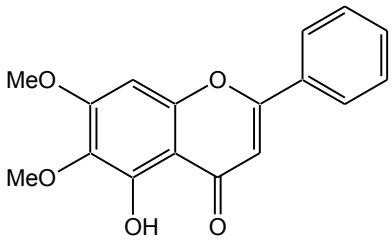
Brown oil; R_f 0.25 (H:A = 7:3); ^{1}H NMR (Plate 37a, 600 MHz, $CDCl_3$) δ 7.12 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.87 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.86 (1H, s, H-8), 4.36 [1H, dd, *J* = 11.5 and 4.2 Hz, H-2(a)], 4.18 [1H, dd, *J* = 11.5 and 8.2 Hz, H-2(b)], 3.81 (3H, s, OC<u>H</u>$_3$), 3.18 [1H, dd, *J* = 13.9 and 4.6 Hz, H-9(a)], 2.83-2.78 (1H, m, H-3), 2.65 [1H, dd, *J* = 14.2 and 10.7 Hz, H-9(b)], 2.41 (3H, s, COC<u>H</u>$_3$), 2.32 (3H, s, COC<u>H</u>$_3$), 2.30 (3H, s, COC<u>H</u>$_3$); ^{13}C NMR (Plate 37b, 600 MHz, $CDCl_3$) δ 191.1, 168.1, 167.5, 167.0, 159.8, 158.5, 148.4, 143.4, 130.0, 129.7, 114.2, 110.0, 69.3, 55.3, 48.1, 31.4, 29.7, 29.7, 20.8, 20.1. HRMS: calcd for $C_{23}H_{22}O_9Na$: 465.1164 g/mol. Found: *m/z* 465.1157.

6.6 Synthesis of a series of A-ring monomethoxy homoisoflavanones: Preparation of acetophenone (A)

6.6.1 Bromination of baicalein (4.69)

Baicalein (**4.69**) (0.200 g, 0.740 mmol, 1 eq.) was treated with Cs_2CO_3 (0.482 g, 1.480 mmol, 2 eq.) in DMF (15 mL) at 0 ^{o}C. After 20 min. MeI (0.06 mL, 0.888 mmol, 1.2 eq.) was added dropwise at corresponded temperature for 12 h. The crude was acidified with 3 M HCl and extracted with EA (3 x 20 mL) washed with water (30 mL), dried over Na_2SO_4 and concentrated. Purification by PLC (H:A = 7:3) yielded two identifiable products with R_f values of 0.39 and 0.25.

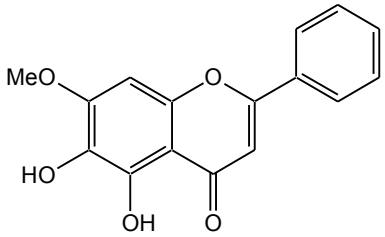
6.6.1.1 6,7-Dimethoxy-5-hydroxyflavone (4.115)



(**4.115**)

The first compound (R_f 0.39); obtained as a yellow solid; 0.010 g (10%); was identified as the 6,7-dimethoxy-5-hydroxyflavone (**4.115**); ^{1}H NMR[24] (Plate 39a, 600 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 6.8 Hz, H-2',6'), 7.59-7.54 (3H, m, H-3',5',4'), 6.71 (1H, s, H-3), 6.60 (1H, s, H-8), 4.00 (3H, s, OC<u>H</u>$_3$), 3.95 (3H, s, OC<u>H</u>$_3$). ^{13}C NMR[24] (Plate 39b, 600 MHz, $CDCl_3$) δ_C (ppm): 207.0, 182.8, 164.0, 158.9, 153.4, 153.1, 132.7, 131.9, 131.4, 129.1, 126.3, 106.3, 105.7, 90.7, 60.9, 56.4, 31.0, 29.7, 22.7, 14.1.

6.6.1.2 5,6-Dihydroxy-7-methoxyflavone (4.114)



(**4.114**)

The second compound (R_f 0.25); obtained as a yellow crystals; 0.121 g (58%); was identified as the 5,6-dihydroxy-7-methoxyflavone (**4.114**); ^{1}H NMR[25] (Plate 38a, 600 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 6.8 Hz, H-2',6'), 7.59-7.53 (3H, m, H-3',5',4'), 6.71 (1H, s, H-3), 6.65 (1H, s, H-8), 4.04 (3H, s, OC<u>H</u>$_3$). ^{13}C NMR[25] (Plate 38b, 600 MHz, $CDCl_3$) δ_C (ppm): 182.7, 164.2, 152.9, 150.8, 145.6, 131.8, 131.5, 129.6, 129.1, 126.3, 105.5, 90.5, 56.5, 29.7. IR (KBr) 3445, 3077, 2929, 2844, 1649, 1612, 1586, 1500, 1362, 1249, 1201, 1111, 1091, 763, 677.

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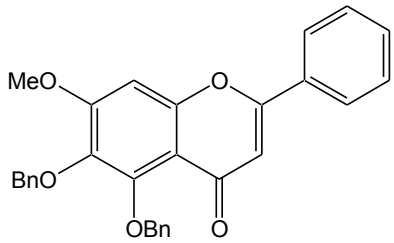
24 Ab Ghani, N.; Ahmat, N.; Ismail, N.H.; Zakaria, I. *Aust*. *J*. *Basic Appl*. *Sci*. **2011**, *5*, 154.

25 Zhang, C.-L.; Feng, S.-X.; Wang, Q.; Wang, P.; Xu, J.; Chen, T. *Chem*. *Nat*. *Compd*. **2014**, *50*, 254.

6.6.2 *5,6-Dibenzyloxy-7-methoxyflavone* (4.111)

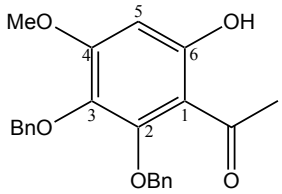


(4.111)

The reaction mixture of 5,6-dihydroxy-7-methoxyflavone (**4.114**) (0.050 g, 0.175 mmol, 1 eq.) and K_2CO_3 (0.054 g, 0.385 mmol, 2.2 eq.) in DMF (5 mL) was then treated with BnBr (0.05 mL, 0.774 mmol, 2.2 eq.) were stirred at 60 ^oC for 24 h. The crude mixture was acidified with 3 M HCl (5 mL) and extracted with EA (3 x 10 mL), washed with water (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by PLC (H:A = 7:3) yielded of *5,6-dibenzyloxy-7-methoxyflavone* (**4.111**) 0.030 g (37%).

Brown solid; R_f 0.34 (H:A = 7:3); ^1H NMR (Plate 40a, 600 MHz, $CDCl_3$) δ 7.91-7.89 (2H, m, Ar-H), 7.68 (2H, d, *J* = 7 Hz, H-2',6'), 7.55-7.51 (2H, m, Ar-H), 7.47 (2H, *J* = 7 Hz, H-3',5'), 7.40-7.23 (7H, m, Ar-H), 6.85 (1H, s, H-3), 6.71 (1H, s, H-8), 5.17 (2H, s, OCH_2Ph), 5.06 (2H, s, OCH_2Ph), 3.96 (3H, s, OCH_3); ^{13}C NMR (Plate 40b, 600 MHz, $CDCl_3$) δ_C (ppm): 177.3, 161.2, 158.2, 154.8, 151.6, 139.7, 137.2, 137.1, 131.6, 131.3, 129.4, 129.0, 128.8, 128.3, 128.1, 126.0, 113.4, 108.4, 96.6, 76.8, 75.9, 56.3. HRMS: calcd for $C_{30}H_{24}O_5Na$: 487.1524 g/mol. Found: *m/z* 487.1526.

6.6.3 *2,3-Dibenzyloxy-6-hydroxy-4-methoxyacetophenone* (A) (4.116)[26]

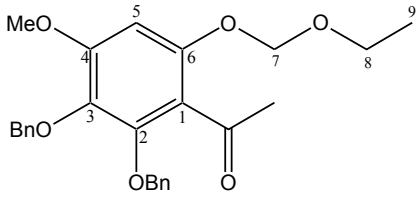


(**A**) (**4.116**)

Diethylene glycol (13 mL, 140.17 mmol, 20 eq.) was added slowly to a stirring mixture of flavone (**4.111**) (3.322 g, 7.15 mmol, 1 eq.) in pyridine (11 mL, 145.86 mmol, 20.4 eq.) and 18 M KOH (11 mL, 429 mmol, 60 eq.). The solution was heated at 100 ^{o}C for 24 h. After cooling, the solution was acidified to pH 1 with 3 M HCl. The reaction mixture was washed with water (3 x 20 mL) then extracted into EA (3 x 20 mL). The organics were washed with saturated $NaHCO_3$ (20 mL) solution then dried over Na_2SO_4 and concentrated under vacuum. The crude product was isolated by PLC to yield *2,3-dibenzyloxy-6-hydroxy-4-methoxyacetophenone* (**A**) (**4.116**) 0.115 g (4%).

Brown oil; R_f 0.49 (H:A = 7:3); ^{1}H NMR (Plate 41a, 600 MHz, $CDCl_3$) δ 7.43-7.35 (10H, m, 2 x Ar-H), 6.30 (1H, s, H-5), 5.21 (2H, s, OCH_2Ph), 4.96 (2H, s, OCH_2Ph), 3.89 (3H, s, OCH_3), 2.59 (3H, s, $COCH_3$); ^{13}C NMR (Plate 41b, 600 MHz, $CDCl_3$) δ 203.5, 162.1, 160.3, 154.4, 137.1, 136.6, 133.7, 128.7, 128.6, 128.4, 128.2, 109.1, 96.5, 76.3, 75.8, 56.1, 32.3.

6.6.4 *2,3-Dibenzyloxy-6-ethoxymethoxy-4-methoxyacetophenone* (4.164)



(**4.164**)

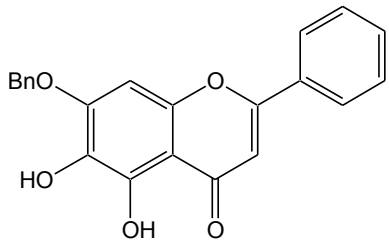
[26] Bhaskar, A.; Seshadri, T.R. *Indian J. Chem.* **1974**, *12*, 557.

To a solution of 2,3-dibenzyloxy-6-hydroxy-4-methoxyacetophenone (**4.116**) (0.097 g, 0.256 mmol, 1 eq.) in DCM (4 mL), adogen 464 (4 mL) was added and followed by *aq*. NaOH (2 M, 6 mL). The reaction mixture stirred vigorously at rt for 30 minutes and then chloromethyl ethylether (EOMCl) (0.04 mL, 0.513 mmol, 2 eq.) was added with continuous stirring for 2 hours. After completion, water (20 mL) was added and the reaction mixture was extracted with DCM (2 x 20 mL), washed with brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and isolated by PLC to yield *2,3-dibenzyloxy-6-ethoxymethoxy-4-methoxyacetophenone* (**4.164**) 0.054 g (48%).

Yellow oil; R_f 0.34 (H:EA:A = 8:1:1); ^{1}H NMR (Plate 42a, 600 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 6.9 Hz, Ar-H), 7.45 (1H, d, *J* = 7.1 Hz, Ar-H), 7.39-7.30 (7H, m, Ar-H), 6.62 (1H, d, *J* = 7.5 Hz, H-5), 5.21 (2H, d, *J* = 6.3 Hz, OCH_2Ph), 5.10 (2H, s, OCH_2Ph), 5.00 [1H, s, H-7(a)], 3.90-3.88 (3H, m, OCH_3), 3.86 [1H, s, H-7(b)], 3.76-3.72 [2H, m, H-8(a),(b)], 2.39 (3H, s, COCH_3), 1.27-1.24 [3H, m, H-9(a),(b),(c)]; ^{13}C NMR (Plate 42b, 600 MHz, $CDCl_3$) δ 201.2, 155.1, 154.8, 150.7, 150.5, 149.8, 149.6, 137.4, 137.3, 137.2, 137.1, 136.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 120.3, 120.2, 96.3, 96.2, 94.1, 76.6, 76.4, 75.7, 64.5, 61.2, 56.2, 32.6, 15.1.

6.7 Preparation of acetophenone (B)

6.7.1 7-Benzyloxy-5,6-dihydroxyflavone (4.117)[27]



(**4.117**)

Baicalein (**4.69**) (0.100 g, 0.370 mmol, 1 eq.), 60% NaH (0.011 g, 0.444 mmol, 1.2 eq.), and BnBr (0.05 mL, 0.444 mmol, 1.2 eq.) in DMF (8 mL) were stirred at -40 ^{o}C for 30 min, before

27 Wang, J.-F.; Ding, N.; Zhang, W.; Wang, P.; Li, Y.-X. *Helv*. *Chim*. *Acta* **2011**, *94*, 2221.

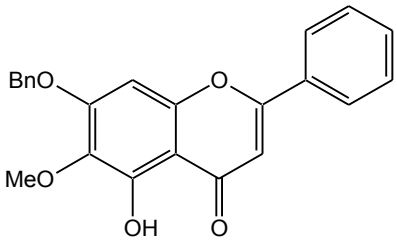
the temperature was allowed to rise to 0 °C and stirring continued for 2 days. Standard work-up and PLC gave 7-benzyloxy-5,6-dihydroxyflavone (**4.117**) 0.021 g (16%).

Brown crystals; R_f 0.30 (H:A = 7:3); ^{1}H NMR[28] (Plate 43a, 600 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 6.9 Hz, H-2",6"), 7.58-7.52 (3H, m, Ar-H), 7.49 (2H, d, *J* = 7.3 Hz, H-2',6'), 7.45 (2H, t, *J* = 7.3 Hz, H-3',5'), 7.40 (1H, t, *J* = 7.3 Hz, H-4'), 6.70 (1H, s, H-3), 6.68 (1H, s, H-8), 5.40 (1H, s, OH), 5.28 (2H, s, OCH_2Ph); ^{13}C NMR[19] (Plate 43b, 600 MHz, $CDCl_3$) δ 182.7, 164.2, 151.9, 150.5, 146.0, 135.4, 132.3, 131.5, 130.1, 129.6, 129.5, 129.3, 129.1, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1, 127.2, 126.9, 126.8, 126.8, 125.9, 125.7, 106.3, 105.2, 104.8, 91.6, 91.2, 78.1, 77.6, 77.6, 71.4.

6.7.2 Methylation of 7-benzyloxy-5,6-dihydroxyflavone (4.117)

7-Benzyloxy-5,6-dihydroxyflavone (**4.117**) (0.064 g, 0.178 mmol, 1 eq.) was treated with Cs_2CO_3 (0.087 g, 0.267 mmol, 1.5 eq.) in DMF (5 mL) at 0 °C for 45 min. After 20 min. MeI (0.02 mL, 0.267 mmol, 1.5 eq.) was added dropwise at corresponded temperature for 12 h. The crude was acidified with 3 M HCl and extracted with EA (3 x 20 mL) washed with water (30 mL), dried over Na_2SO_4 and concentrated. Purification by PLC (H:A = 7:3) yielded two identifiable products with R_f values of 0.33 and 0.24.

6.7.2.1 7-Benzyloxy-5-hydroxy-6-methoxyflavone (4.118)[29]



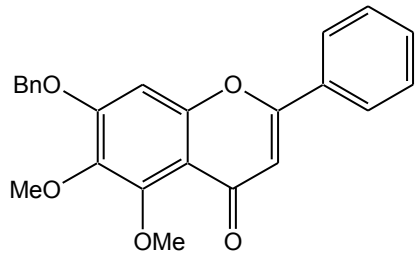
(**4.118**)

28 Kuo, C.-M.; Hill, T.N.; Bezuidenhoudt, B.C.B. *Z. Kristallogr. NCS*, ***2015***, *230*, 193.

29 Bhardwaj, D.K.; Neelakantan, S.; Seshadri, T.R. *Indian J. Chem.* **1965**, *3*, 559.

The first compound (R_f 0.33); obtained as a yellow solid; 0.014 g (21%); was identified as the 7-benzyloxy-5-hydroxy-6-methoxyflavone (**4.118**); ^{1}H NMR (Plate 44a, 600 MHz, $CDCl_3$) δ 7.88-7.42 (10H, m, Ar-H), 6.69 (1H, s, H-3), 6.62 (1H, s, H-8), 5.27 (2H, s, OCH_2Ph), 3.97 (3H, s, OCH_3); ^{13}C NMR (Plate 44b, 600 MHz, $CDCl_3$) δ 182.8, 164.0, 158.0, 153.3, 153.2, 135.8, 133.2, 131.9, 131.3, 129.1, 128.8, 128.3, 127.2, 126.3, 105.6, 92.2, 70.9, 60.9.

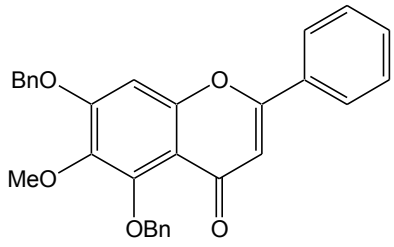
6.7.2.2 7-Benzyloxy-5,6-dimethoxyflavone (4.119)



(**4.119**)

The second compound (R_f 0.24); obtained as a yellow solid; 0.028 g (42%); was identified as the 7-benzyloxy-5,6-dimethoxyflavone (**4.119**); ^{1}H NMR (Plate 45a, 600 MHz, $CDCl_3$) δ 7.87-7.37 (10H, m, Ar-H), 6.88 (1H, s, H-3), 6.67 (1H, s, H-8), 5.24 (2H, s, OCH_2Ph), 4.02 (3H, s, OCH_3), 3.94 (3H, s, OCH_3); ^{13}C NMR (Plate 45b, 600 MHz, $CDCl_3$) δ 177.2, 161.2, 156.9, 154.4, 152.8, 140.7, 135.6, 131.3, 129.0, 128.8, 128.4, 127.3, 126.0, 108.4, 97.7, 70.9, 62.3, 61.6.

6.7.3 *5,7-Dibenzyloxy-6-methoxyflavone* (4.112)



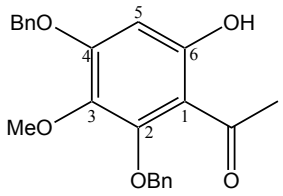
(**4.112**)

7-Benzyloxy-5-hydroxy-6-methoxyflavone (**4.118**) (0.027 g, 0.072 mmol, 1 eq.), Cs_2CO_3 (0.035 g, 0.108 mmol, 1.5 eq.) and BnBr (0.01 mL, 0.108 mmol, 1.5 eq.) in DMF (2 mL) were attired at

60 °C for 2 hours. After completion of the reaction, standard work-up and PLC gave *5,7-dibenzyloxy-6-methoxyflavone* (**4.112**) 0.010 g (30%).

Yellow solid; R_f 0.27 (H:EA = 8:2); ^{1}H NMR (Plate 47a, 600 MHz, $CDCl_3$) δ 7.90-7.88 (2H, m, Ar-H), 7.72 (2H, d, *J* = 7.2 Hz, 2-C_6H_5), 7.55-7.50 (4H, m, Ar-H), 7.47-7.35 (7H, m, Ar-H), 6.92 (1H, s, H-3), 6.70 (1H, s, H-8), 5.26 (2H, s, OCH_2Ph), 5.17 (2H, s, OCH_2Ph), 3.93 (3H, s, OCH_3); ^{13}C NMR (Plate 47b, 600 MHz, $CDCl_3$) δ 177.2, 161.2, 156.9, 154.5, 151.5, 141.2, 137.3, 135.6, 131.6, 131.3, 129.1, 129.0, 128.8, 128.4, 128.4, 128.1, 127.3, 126.0, 113.6, 108.4, 97.9, 76.6, 71.0, 61.6, 29.7. HRMS: calcd for $C_{30}H_{24}O_5Na$: 487.1524 g/mol. Found: *m/z* 487.1521.

6.7.4 2,4-Dibenzyloxy-6-hydroxy-3-methoxyacetophenone (B) (4.120)[30]



(B) (4.120)

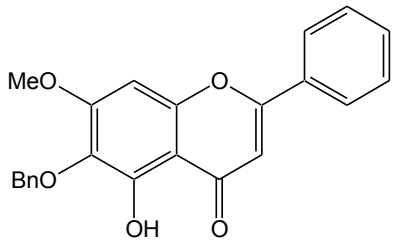
Diethylene glycol (0.6 mL, 6.028 mmol, 19.6 eq.) was added slowly to a stirring mixture of flavone (**4.112**) (0.140 g, 0.301 mmol, 1 eq.) in pyridine (0.5 mL, 6.14 mmol, 20.4 eq.) and 18 M KOH (0.5 mL, 18.06 mmol, 60 eq.). The solution was heated at 100 °C for 24 h. After cooling, the solution was acidified to pH 1 with 3 M HCl. The reaction mixture was washed with water (3 x 20 mL) then extracted into EA (3 x 20 mL). The organics were washed with saturated $NaHCO_3$ (20 mL) solution then dried over Na_2SO_4 and concentrated under vacuum. The crude product was isolated by PLC to yield 2,4-dibenzyloxy-6-hydroxy-3-methoxyacetophenone (**B**) (**4.120**) 0.073 g (64%).

Yellow oil; R_f 0.39 (H:A = 7:3); ^{1}H NMR (Plate 48a, 600 MHz, $CDCl_3$) δ 7.48-7.40 (10H, m, 2 x Ar-H), 6.35 (1H, s, H-5), 5.22 (2H, s, OCH_2Ph), 5.17 (2H, s, OCH_2Ph), 3.84 (3H, s, OCH_3),

30 Xie, X.; Du, W.; Yang, X.; Li, X.; Zou, Q. *Faming Zhuanli Shenqing*, **2008**.

2.59 (3H, s, COC<u>H</u>$_3$); ^{13}C NMR (Plate 48b, 600 MHz, $CDCl_3$) δ 203.6, 161.7, 159.2, 154.3, 136.8, 135.8, 128.7, 128.6, 128.4, 127.4, 109.2, 97.6, 76.2, 70.6, 61.3, 32.3.

6.7.5 6-Benzyloxy-5-hydroxy-7-methoxyflavone (4.121)



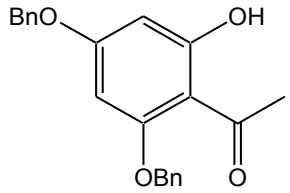
(**4.121**)

7-Benzyloxy-5,6-dihydroxyflavone (**4.117**) [*cf* chapter 4 (p117), scheme 35 and 36] (0.015 g, 0.042 mmol, 1 eq.) was treated with 60% NaH (0.0012 g, 0.050 mmol, 1.2 eq.) in DMF (2 mL) at 0 ^{o}C for 1 hour. After 20 min. MeI (0.003 mL, 0.042 mmol, 1 eq.) was added dropwise at corresponded temperature for 12 h. The crude was acidified with 3 M HCl and extracted with EA (3 x 20 mL) washed with water (30 mL), dried over Na_2SO_4 and concentrated. Purification by PLC to yield 6-benzyloxy-5-hydroxy-7-methoxyflavone (**4.121**) 0.002 g (13%).

Brown solid; R_f 0.44 (H:A = 7:3); ^{1}H NMR (Plate 46a, 600 MHz, $CDCl_3$) δ 7.90-7.89 (2H, d, *J* = 7.1 Hz, Ar-<u>H</u>), 7.58-7.53 (5H, m, Ar-<u>H</u>), 7.38-7.31 (3H, m, Ar-<u>H</u>), 6.70 (1H, s, H-3), 6.55 (1H, s, H-8), 5.15 (2H, s, OC<u>H</u>$_2$Ph), 3.93 (3H, s, OC<u>H</u>$_3$); ^{13}C NMR (Plate 46b, 600 MHz, $CDCl_3$) δ 182.8, 167.8, 159.2, 153.5, 153.3, 137.4, 131.9, 130.9, 129.1, 128.8, 128.6, 128.2, 128.0, 126.3, 105.7, 90.6, 74.9, 68.2, 56.3. NOESY (Plate 46c, 600 MHz, $CDCl_3$).

6.8 The Elbs persulfate oxidation, an alternative method to the preparation of acetophenone (B)

6.8.1 4,6-Dibenzyloxy-2-hydroxyacetophenone (4.54)[31]



(**4.54**)

To a mixture of 2,4,6-trihydroxyacetophenone (**4.53**) (1.00 g, 5.37 mmol, 1 eq.) in DMF (20 mL) was added K_2CO_3 (2.21 g, 16.00 mmol, 2.98 eq.) and the mixture stirred for 15 min. BnCl (1.2 mL, 10.74 mmol, 2 eq.) in DMF (3 mL) was added and the mixture refluxed for 2 h. Standard work-up followed by PLC gave 4,6-dibenzyloxy-2-hydroxyacetophenone (**4.54**) 0.98 g (53%).

Yellow solid; R_f 0.46 (H:A = 7:3); ^{1}H NMR[32] (Plate 11a, 600 MHz, $CDCl_3$) δ 7.43-7.37 (10H, m, 2 x Ar-H), 6.19 (1H, d, *J* = 2.2 Hz, H-5), 6.12 (1H, d, *J* = 2.2 Hz, H-3), 5.08 (4H, s, 2 x OCH_2Ph), 2.57 (3H, s, $COCH_3$); ^{13}C NMR[33] (Plate 11b**,** 600 MHz, $CDCl_3$) δ 203.2, 167.6, 165.1, 162.0, 135.8, 135.6, 128.8, 128.5, 128.4, 128.0, 127.7, 106.3, 94.7, 92.4, 71.1, 70.3, 33.4.

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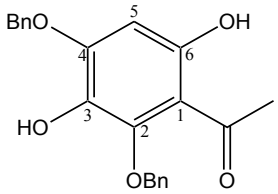
31 Huang, C.; Zhang, Z.; Li, S.; Li, Y. *J. Chem. Research (S)* **1999**, 148.

32 Caldwell, S.T.; Petersson, H.M.; Farrugia, L.J.; Mullen, W.; Crozier, A.; Hartley, R.C. *Tetrahedron* **2006**, *62*, 7257.

33 Smith, K.A. STRUCTURE AND SYNTHESIS OF PHLOROGLUCINOL DERIVATIVES FROM *HYPERICUM ROEPERIANUM*, MSc Thesis, University of Kwazulu-Natal, Pietermaritzburg, **2010**, p59.

6.8.2 2,4-Dibenzyloxy-3,6-dihydroxyacetophenone (4.123)[34]



(**4.123**)

In flask one, 4,6-dibenzyloxy-2-hydroxyacetophenone (**4.54**) (0.20 g, 0.574 mmol, 1 eq.) and NaOH (0.4 g) were added H_2O (4 mL) and pyridine (0.5 mL). In flask two, potassium persulfate (0.55 g, 2.03 mmol, 3.5 eq.) was added H_2O (10 mL). The potassium persulfate solution was added to flask one at 15 ^oC and the reaction mixture was stirred at rt for 24 h or more. After completion, the RM was acidified to pH 5 with $HCl_{conc.}$ (1 mL) and Et_2O (6 mL) was added to reflux for 2 h. RM was extracted with EA (3 x 20 mL) and dried over $NaSO_4$. Purification by PLC to yield 2,4-dibenzyloxy-3,6-dihydroxyacetophenone (**4.123**) 0.010 g (5%).

Brown oil; R_f 0.36 (H:EA = 8:2); ^1H NMR (Plate 49a, 600 MHz, $CDCl_3$) δ 7.49 (2H, *J* = 7 Hz, Ar-H), 7.45-7.36 (8H, m, Ar-H), 6.38 (1H, s, H-5), 5.20 (2H, s, OCH_2Ph), 5.17 (2H, s, OCH_2Ph), 2.61 (3H, s, $COCH_3$); ^{13}C NMR (Plate 49b, 600 MHz, $CDCl_3$) δ 203.7, 158.7, 153.0, 146.3, 136.7, 135.1, 131.4, 128.9, 128.8, 128.6, 128.4, 128.0, 109.3, 96.7, 75.4, 71.3, 32.2

6.8.3 Methylation of 2,4-dibenzyloxy-3,6-dihydroxyacetophenone (4.123)

2,4-Dibenzyloxy-3,6-dihydroxyacetophenone (**4.123**) (0.094 g, 0.258 mmol, 1 eq.) was treated with Cs_2CO_3 (0.084 g, 0.258 mmol, 1 eq.) in DMF (8 mL) at -10 ^oC. After 20 min, MeI (0.016 mL, 0.258 mmol, 1 eq.) was added dropwise and temperature allowed rising at 0 ^oC for 12 hours. The crude was acidified with 3 M HCl and extracted with EA (3 x 20 mL) washed with water (30 mL), dried over Na_2SO_4 and concentrated. Purification by PLC (H:EA:A = 8:1:1) yielded two identifiable products with R_f values of 0.49 and 0.13.

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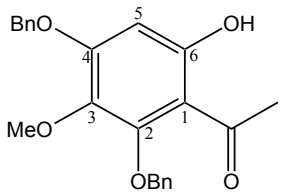
[34] Kavvadias, D.; Sand, P.; Youdim, K.A.; Qaiser, M.Z.; Rice-Evans, C.; Baur, R.; Sigel, E.; Rausch, W-D; Riederer, P.; Schreier, P. *Br. J. Pharmacol.* **2004**, *142*, 811.

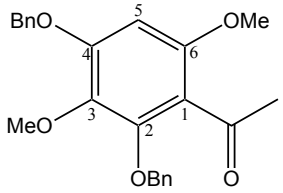
6.8.3.1 2,4-Dibenzyloxy-6-hydroxy-3-methoxyacetophenone (B) (4.120)[35]



(**B**) (**4.120**)

The first compound (R_f 0.49); obtained as yellow oil; 0.020 g (21%); was identified as the 2,4-dibenzyloxy-6-hydroxy-3-methoxyacetophenone (**4.120**); ^{1}H NMR (Plate 48a, 600 MHz, $CDCl_3$) δ 7.48-7.40 (10H, m, 2 x Ar-H), 6.35 (1H, s, H-5), 5.22 (2H, s, OCH_2Ph), 5.17 (2H, s, OCH_2Ph), 3.84 (3H, s, OCH_3), 2.59 (3H, s, $COCH_3$); ^{13}C NMR (Plate 48b, 600 MHz, $CDCl_3$) δ 203.6, 161.7, 159.2, 154.3, 136.8, 135.8, 128.7, 128.6, 128.4, 127.4, 109.2, 97.6, 76.2, 70.6, 61.3, 32.3.

6.8.3.2 2,4-Dibenzyloxy-3,6-dimethoxyacetophenone (4.124)



(**4.124**)

The second compound (R_f 0.13); obtained as a red solid; 0.011 g (11%); was identified as the 2,4-dibenzyloxy-3,6-dimethoxyacetophenone (**4.124**); ^{1}H NMR (Plate 50a, 600 MHz, $CDCl_3$) δ 7.49-7.32 (10H, m, 2 x Ar-H), 6.34 (1H, s, H-5), 5.19 (2H, s, OCH_2Ph), 5.11 (2H, s, OCH_2Ph), 3.88 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.37 (3H, s, $COCH_3$); ^{13}C NMR (Plate 50b, 600 MHz, $CDCl_3$) δ 201.3, 153.9, 152.5, 150.0, 137.2, 136.6, 128.7, 128.6, 128.5, 127.3, 119.6, 94.8, 76.4, 71.3, 61.3, 56.0, 32.5, 29.7.

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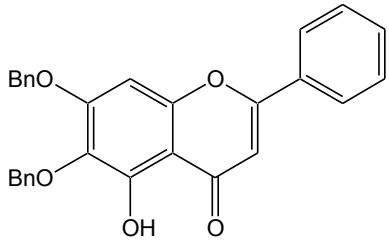
35 Xie, X.; Du, W.; Yang, X.; Li, X.; Zou, Q. *Faming Zhuanli Shenqing*, **2008**.

6.9 Preparation of acetophenone (C)

6.9.1 *6,7-Dibenzyloxy-5-hydroxyflavone* (4.73)[36]



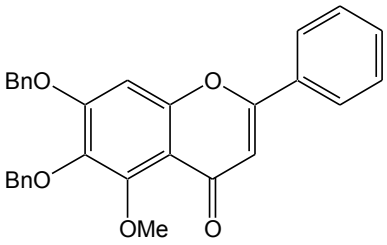
(**4.73**)

Baicalein (**4.69**) (0.500 g, 1.850 mmol, 1 eq.) and Cs_2CO_3 (1.21 g, 3.70 mmol, 2 eq.) in DMF (20 mL) was stirred at at 0 ^oC for 30 min. The reaction mixture was then treated with BnBr (0.27 mL, 2.22 mmol, 1.2 eq.) and the temperature was allowed to rise to rt and stirring continued for 2 days. Standard work-up and PLC gave *6,7-dibenzyloxy-5-hydroxyflavone* (**4.73**) 0.567 g (68%).

White solid; R_f 0.48 (H:A = 7:3); ^1H NMR (Plate 22a, 600 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 6.9 Hz, H-2',6'), 7.57-7.50 (6H, m, Ar-H), 7.42-7.36 (4H, m, Ar-H), 7.33-7.31 (3H, m, Ar-H), 6.69 (1H, s, H-3), 6.60 (1H, s, H-8), 5.19 (2H, s, OCH_2Ph), 5.17 (2H, s, OCH_2Ph); ^{13}C NMR (Plate 22b, 600 MHz, $CDCl_3$) δ 164.0, 153.3, 137.5, 135.8, 131.9, 131.4, 129.1, 128.8, 128.7, 128.7, 128.3, 128.2, 128.0, 127.3, 126.3, 105.7, 92.0, 74.9, 71.0, 29.7. EIMS (70 eV) *m/z* 450 (M^+, 2%).

[36] Cheng, Y.-C.; Lee, Y.; Yeo, H. *PCT Int*. *Appl*., **2005**.

6.9.2 *6,7-Dibenzyloxy-5-methoxyflavone* (4.113)

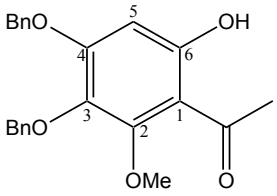


(**4.113**)

6,7-Dibenzyloxy-5-hydroxyflavone (**4.73**) (0.330 g, 0.733 mmol, 1 eq.) was treated with Cs_2CO_3 (0.29 g, 0.879 mmol, 1.2 eq.) in DMF (15 mL) at 60 ^oC. After 20 min. MeI (0.06 mL, 0.880 mmol, 1.2 eq.) was added dropwise and temperature allowed rising at 0 ^oC for 6 h. Standard work-up and PLC gave *6,7-dibenzyloxy-5-methoxyflavone* (**4.113**) 0.301 g (89%).

Yellow solid; R_f 0.27 (H:A = 7:3); ^1H NMR (Plate 51a, 600 MHz, $CDCl_3$) δ 7.91-7.89 (2H, m, Ar-H), 7.56-7.53 (3H, m, Ar-H), 7.50-7.41 (7H, m, Ar-H), 7.35-7.33 (3H, m, Ar-H), 6.90 (1H, s, H-3), 6.71 (1H, s, H-8), 5.22 (2H, s, OCH_2Ph), 5.12 (2H, s, OCH_2Ph), 4.05 (3H,s, OCH_3); ^{13}C NMR (Plate 51b, 600 MHz, $CDCl_3$) δ 177.2, 161.2, 157.1, 154.6, 153.1, 139.7, 137.3, 135.6, 131.7, 131.3, 129.0, 128.8, 128.7, 128.4, 128.3, 128.1, 127.5, 127.3, 126.0, 113.3, 108.5, 97.6, 75.9, 71.0, 62.2. HRMS: calcd for $C_{30}H_{24}O_5Na$: 487.1524 g/mol. Found: *m/z* 487.1524.

6.9.3 3,4-Dibenzyloxy-6-hydroxy-2-methoxyacetophenone (C) (4.125)[37]



(**C**) (**4.125**)

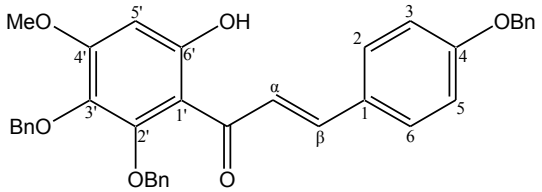
[37] Chawla, H.M.; Gambhir, I.; Kathuria, L. *J. Chromatogr.* **1980**, *188*, 289.

Diethylene glycol (1.455 mL, 13.713 mmol, 19.6 eq.) was added slowly to a stirring mixture of flavone (**4.113**) (0.325 g, 0.700 mmol, 1 eq.) in pyridine (1.2 mL, 14.280 mmol, 20.4 eq.) and 18 M KOH (1.2 mL, 42 mmol, 60 eq.). The solution was heated at 100 ^{o}C for 24 h. After cooling, the solution was acidified to pH 1 with 3 M HCl. The reaction mixture was washed with water (3 x 20 mL) then extracted into EA (3 x 20 mL). The organics were washed with saturated $NaHCO_3$ solution (20 mL) then dried over Na_2SO_4 and concentrated under vacuum. The crude product was isolated by PLC yielded 3,4-dibenzyloxy-6-hydroxy-2-methoxyacetophenone (**C**) (**4.125**) 0.093 g (36%).

Yellow liquid; R_f 0.40 (H:A = 7:3); ^{1}H NMR (Plate 52a, 600 MHz, $CDCl_3$) δ 7.45-7.38 (7H, m, Ar-H), 7.35-7.33 (3H, m, Ar-H), 6.35 (1H, s, H-5), 5.13 (2H, s, OCH_2Ph), 4.94 (2H, s, OCH_2Ph), 4.03 (3H, s, OCH_3), 2.70 (3H, s, $COCH_3$); ^{13}C NMR (Plate 52b, 600 MHz, $CDCl_3$) δ 203.4, 161.9, 159.3, 155.8, 137.2, 135.7, 133.8, 128.7, 128.6, 128.4, 128.1, 127.6, 108.7, 97.3, 75.5, 70.7, 61.3, 32.0.

6.10 Preparation of 4',5,6,7-tetraoxygenated homoisoflavanones and 4',5,7-trihydroxy-8-methoxyisoflavanone

6.10.1 *4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxychalcone* (4.127)



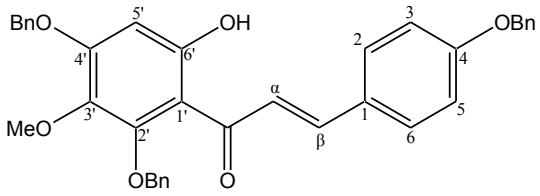
(**4.127**)

Prepared as described in general Aldol condensation procedure (*cf* paragraph 6.3.8):
2,3-Dibenzyloxy-6-hydroxy-4-methoxyacetophenone (**4.116**) (0.117 g, 0.309 mmol, 1 eq.), *p*-benzyloxybenzaldehyde (**4.126**) (0.08 g, 0.371 mmol, 1.2 eq.), EtOH:THF (10:2 mL) and

Freshly powder KOH (0.20 g, 2.472 mmol, 6 eq.). Yield of *4,2',3'-tribenzyloxy-6'-hydroxy-4'-methoxychalcone* (**4.127**) 0.119 g (67%).

Yellow solid; R_f 0.34 (H:DCM = 6:4); ^{1}H NMR (Plate 53a, 600 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 15.6 Hz, H-β), 7.81 (2H, d, *J* = 15.6 Hz, H-α), 7.51 (2H, d, *J* = 6.4 Hz, Ar-H), 7.47-7.43 (5H, m, Ar-H), 7.40-7.36 (4H, m, Ar-H), 7.33 (2H, d, *J* = 8.3 Hz, H-2,6), 7.26-7.21 (4H, m, Ar-H), 6.87 (2H, d, *J* = 8.7 Hz, H-3,5), 6.35 (1H, s, H-5'), 5.13 (2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 5.03 (2H, s, OCH_2Ph), 3.91 (3H, s, OCH_3); ^{13}C NMR (Plate 53b, 600 MHz, $CDCl_3$) δ 192.8, 163.1, 160.6, 160.2, 154.1, 143.6, 137.3, 136.5, 136.4, 134.4, 130.6, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.5, 124.4, 115.1, 109.2, 96.9, 75.9, 70.1, 56.1, 29.7. HRMS: calcd for $C_{37}H_{32}O_6Na$: 595.2118 g/mol. Found: *m/z* 595.2101.

6.10.2 *4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxychalcone* (4.128)



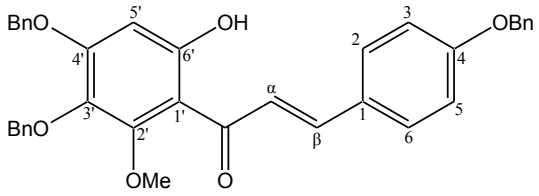
(**4.128**)

Prepared as described in general Aldol condensation procedure (*cf* paragraph 6.3.8): 2,4-Dibenzyloxy-6-hydroxy-3-methoxyacetophenone (**4.120**) (0.100 g, 0.264 mmol, 1 eq.), *p*-benzyloxybenzaldehyde (**4.126**) (0.067 g, 0.317 mmol, 1.2 eq), EtOH:THF (10:2 mL) and Freshly powder KOH (0.074 g, 1.32 mmol, 5 eq.). Yield of *4,2',4'-tribenzyloxy-6'-hydroxy-3'-methoxychalcone* (**4.128**) 0.051 g (34%).

Yellow solid; R_f 0.34 (H:EA:A = 9:0.5:0.5); ^{1}H NMR (Plate 54a, 600 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 15.5 Hz, H-β), 7.80 (1H, d, *J* = 15.5 Hz, H-α), 7.49-7.42 (11H, m, Ar-H), 7.39-7.36 (2H, m, Ar-H), 7.32-7.29 (2H, m, Ar-H), 7.24 (2H, d, *J* = 8.7 Hz, H-2,6), 6.86 (2H, d, *J* = 8.7 Hz, H-3,5), 6.41 (1H, s, H-5'), 5.19 (2H, s, OCH_2Ph), 5.12 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 3.92 (3H, s, OCH_3); ^{13}C NMR (Plate 54b, 600 MHz, $CDCl_3$) δ 192.8, 162.8, 160.6, 159.1, 154.0, 143.6, 136.6, 136.5, 135.8, 130.5, 128.9, 128.7, 128.7, 128.6, 128.4, 128.3, 128.2, 127.5, 127.4,

124.4, 115.1, 109.3, 98.1, 70.6, 70.1, 61.5. HRMS: calcd for $C_{37}H_{32}O_6Na$: 595.2118 g/mol. Found: *m/z* 595.2103.

6.10.3 *4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxychalcone* (4.129)



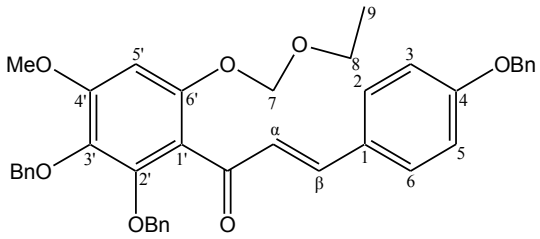
(**4.129**)

Prepared as described in general Aldol condensation procedure (*cf* paragraph 6.3.8): 3,4-Dibenzyloxy-6-hydroxy-2-methoxyacetophenone (**4.125**) (0.266 g, 0.703 mmol, 1 eq.), *p*-benzyloxybenzaldehyde (**4.126**) (0.179 g, 0.843 mmol, 1.2 eq.), EtOH:THF (25:5 mL) and Freshly powder KOH (0.197 g, 3.515 mmol, 5 eq.). Yield of 4,*3'*,*4'*-*tribenzyloxy-6'-hydroxy-2'-methoxychalcone* (**4.129**) 0.091 g (23%).

Yellow oil; R_f 0.36 (H:DCM = 5:5); ^{1}H NMR (Plate 55a, 600 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 8.4 Hz, H-β), 7.63 (2H, d, *J* = 8.8 Hz, H-2,6), 7.47-7.40 (12H, m, H-α, Ar-H), 7.39-7.37 (2H, m, Ar-H), 7.34-7.33 (2H, m, Ar-H), 7.04 (2H, d, *J* = 8.8 Hz, H-3,5), 6.39 (1H, s, H-5'), 5.14 (4H, s, 2 x OCH_2Ph), 4.99 (2H, s, OCH_2Ph), 3.95 (3H, s, OCH_3); ^{13}C NMR (Plate 55b, 600 MHz, $CDCl_3$) δ 192.9, 162.7, 160.7, 159.3, 143.4, 137.4, 136.4, 135.7, 134.4, 130.3, 128.7, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.6, 127.5, 124.2, 115.3, 97.8, 75.7, 70.7, 70.1, 62.1. HRMS: calcd for $C_{37}H_{32}O_6Na$: 595.2018 g/mol. Found: *m/z* 595.2095.

6.11 Preparation of pentaoxygenated ethoxymethylated-chalcones

6.11.1 *4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxy-chalcone* (4.130)

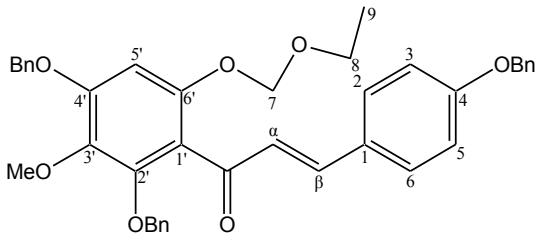


(**4.130**)

Prepared as described in general Alkylation procedure (*cf* paragraph 6.3.9): 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxychalcone (**4.127**) (0.205 g, 0.358 mmol, 1 eq.), DCM (20 mL), adogen 464 (0.5 mL), *aq*. NaOH (2 M, 5 mL) and chloromethyl ethylether (0.06 mL, 0.716 mmol, 2 eq.). Standard work-up and PLC yield of *4,2',3'-tribenzyloxy-6'-ethoxymethoxy-4'-methoxychalcone* (**4.130**) 0.174 g (77%).

Yellow oil; R_f 0.30 (H:EA = 8:2); ^{1}H NMR (Plate 56a, 600 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.1 Hz, Ar-H), 7.45-7.40 (7H, m, H-β, H-2,6, Ar-H), 7.37-7.33 (4H, m, Ar-H), 7.31-7.26 (2H, m, Ar-H), 7.25-7.21 (3H, m, Ar-H), 6.97 (2H, d, *J* = 8.8 Hz, H-3,5), 6.85 (1H, d, *J* = 16.0 Hz, H-α), 6.66 (1H, s, H-5'), 5.17 [2H, s, H-7(a),(b)], 5.11 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.02 (2H, s, OCH_2Ph), 3.91 (3H, s, OCH_3), 3.67 [2H, q, *J* = 7.0 Hz, H-8(a),(b)], 1.20 [3H, t, *J* = 7.0 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 56b, 600 MHz, $CDCl_3$) δ 193.7, 160.7, 155.0, 151.0, 150.5, 145.0, 137.5, 137.1, 136.4, 136.3, 130.2, 128.7, 128.6, 128.3, 128.2, 128.2, 128.0, 127.9, 127.7, 127.5, 127.0, 118.4, 115.2, 96.4, 94.0, 76.3, 75.6, 71.7, 71.1, 70.1, 64.4, 61.9, 56.2, 15.1. HRMS: calcd for $C_{40}H_{38}O_7Na$: 653.2518 g/mol. Found: *m/z* 653.2539.

6.11.2 *4,2',4'-Tribenzyloxy-6'-ethoxymethoxy-3'-methoxy-chalcone* (4.131)

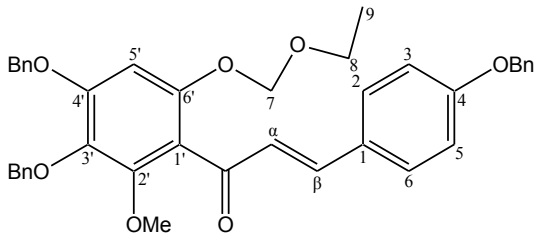


(**4.131**)

Prepared as described in general Alkylation procedure (*cf* paragraph 6.3.9): 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxychalcone (**4.128**) (0.051 g, 0.089 mmol, 1 eq.), DCM (6 mL), adogen 464 (0.2 mL), *aq*. NaOH (2 M, 2 mL) and chloromethyl ethylether (0.023 mL, 0.267 mmol, 3 eq.). Standard work-up and PLC yield of *4,2',4'-tribenzyloxy-6'-ethoxymethoxy-3'-methoxychalcone* (**4.131**) 0.040 g (71%).

Yellow oil; R_f 0.24 (H:EA = 8:2); ^{1}H NMR (Plate 57a, 600 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 7.4 Hz, Ar-H), 7.45-7.42 (8H, m, Ar-H), 7.40-7.36 (4H, m, H-β, H-2,6, Ar-H), 7.29-7.26 (3H, m, Ar-H), 7.24-7.22 (1H, m, Ar-H), 6.97 (2H, d, *J* = 8.8 Hz, H-3,5), 6.84 (1H, d, *J* = 16.0 Hz, H-α), 6.74 (1H, s, H-5'), 5.20 [2H, s, H-7(a),(b)], 5.12 (2H, s, OCH_2Ph), 5.11 (4H, s, OCH_2Ph), 3.91 (3H, s, OCH_3), 3.64 [2H, q, *J* = 7.1 Hz, H-8(a),(b)], 1.17 [3H, t, *J* = 7.1 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 57b, 600 MHz, $CDCl_3$) δ 193.7, 160.7, 153.8, 150.7, 150.4, 145.0, 137.8, 137.2, 136.6, 136.4, 130.2, 128.7, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 126.9, 118.7, 115.2, 98.2, 94.0, 76.1, 71.0, 70.1, 64.4, 61.3, 15.1. HRMS: calcd for $C_{40}H_{38}O_7Na$: 653.2518 g/mol. Found: *m/z* 653.2517.

6.11.3 *4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxy-chalcone* (4.132)



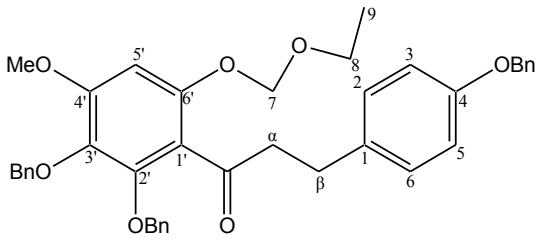
(**4.132**)

Prepared as described in general Alkylation procedure (*cf* paragraph 6.3.9): 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxychalcone (**4.129**) (0.091 g, 0.159 mmol, 1 eq.), DCM (10 mL), adogen 464 (0.5 mL), *aq*. NaOH (2 M, 5 mL) and chloromethyl ethylether (0.04 mL, 0.477 mmol, 3 eq.). Standard work-up and PLC yield of *4,3',4'-tribenzyloxy-6'-ethoxymethoxy-2'-methoxychalcone* (**4.132**) 0.093 g (93%).

Yellow oil; R_f 0.33 (H:EA = 8:2); ^{1}H NMR (Plate 58a, 600 MHz, $CDCl_3$) δ 7.49-7.40 (14H, m, H-β, Ar-H, H-2,6), 7.38-7.36 (2H, m, Ar-H), 7.33-7.30 (2H, m, Ar-H), 6.99 (2H, d, *J* = 8.8 Hz, H-3,5), 6.88 (1H, d, *J* = 16.3 Hz, H-α), 6.71 (1H, s, H-5'), 5.15 (2H, s, OCH_2Ph), 5.12 (4H, s, OCH_2Ph), 5.03 [2H, s, H-7(a),(b)], 3.88 (3H, s, OCH_3), 3.65 [2H, q, *J* = 7.0 Hz, H-8(a),(b)], 1.17 [3H, t, *J* = 7.0 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 58b, 600 MHz, $CDCl_3$) δ 193.9, 160.8, 154.0, 151.8, 150.8, 145.3, 137.5, 136.5, 136.4, 130.2, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.0, 118.2, 115.3, 97.9, 94.0, 71.1, 70.1, 64.4, 62.1, 15.1. HRMS: calcd for $C_{40}H_{38}O_7Na$: 653.2518 g/mol. Found: *m/z* 653.2516.

6.12 Preparation of pentaoxygenated dihydrochalcones

6.12.1 *4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxydihydrochalcone* (4.133)

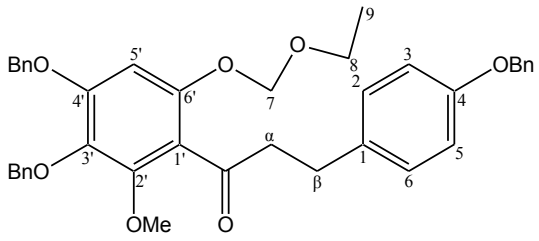


(**4.133**)

Prepared as described in general Reduction procedure (*cf* paragraph 6.3.10): 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxychalcone (**4.130**) (0.174 g, 0.276 mmol, 1 eq.), EtOH (15 mL), finely powder $NaBH_4$ (0.020 g, 0.529 mmol, 2 eq.), and acetone (20 mL). Standard work-up and PLC yield of *4,2',3'-tribenzyloxy-6'-ethoxymethoxy-4'-methoxy-dihydrochalcone* (**4.133**) 0.051 g (29%).

Light yellow oil; R_f 0.47 (H:EA = 8:2); ^{1}H NMR (Plate 59a, 600 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.1 Hz, Ar-H), 7.46 (2H, d, *J* = 7.2 Hz, Ar-H), 7.42-7.38 (5H, m, Ar-H), 7.37-7.34 (6H, m, Ar-H), 7.09 (2H, d, *J* = 8.6 Hz, H-2,6), 6.88 (2H, d, *J* = 8.6 Hz, H-3,5), 6.63 (1H, s, H-5'), 5.15 (2H, s, OCH_2Ph), 5.09 (2H, s, OCH_2Ph), 5.05 (2H, s, OCH_2Ph), 5.01 [2H, s, H-7(a),(b)], 3.89 (3H, s, OCH_3), 3.70 [2H, q, *J* = 7.1 Hz, H-8(a),(b)], 3.00 (2H, t, *J* = 7.6 Hz, α-CH_2), 2.92 (2H, t, *J* = 7.7 Hz, β-CH_2), 1.26 [3H, t, *J* = 7.1 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 59b, 600 MHz, $CDCl_3$) δ 202.9, 157.0, 155.0, 150.6, 149.9, 137.4, 137.2, 137.2, 136.2, 133.8, 129.4, 128.7, 128.6, 128.4, 128.1, 127.9, 127.5, 119.9, 114.7, 96.3, 94.0, 76.6, 75.7, 70.0, 64.5, 56.2, 46.8, 28.8, 15.2. HRMS: calcd for $C_{40}H_{40}O_7Na$: 655.2674 g/mol. Found: *m/z* 655.2676.

6.12.2 *4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxydihydrochalcone* (4.134)

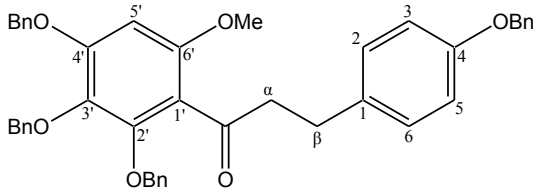


(**4.134**)

Prepared as described in general Reduction procedure (*cf* paragraph 6.3.10): 4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxychalcone (**4.132**) (0.093 g, 0.147 mmol, 1 eq.), EtOH (10 mL), finely powder $NaBH_4$ (0.022 g, 0.590 mmol, 4 eq.), and acetone (20 mL). Standard work-up and PLC yield of *4,3',4'-tribenzyloxy-6'-ethoxymethoxy-2'-methoxy-dihydrochalcone* (**4.134**) 0.038 g (41%).

Yellow solid; R_f 0.39 (H:EA = 8:2); ^{1}H NMR (Plate 60a, 600 MHz, $CDCl_3$) δ 7.45-7.44 (5H, m, Ar-H), 7.41-7.38 (5H, m, Ar-H), 7.37-7.33 (5H, m, Ar-H), 7.17 (2H, d, *J* = 8.6 Hz, H-2,6), 6.91 (2H, d, *J* = 8.6 Hz, H-3,5), 6.66 (1H, s, H-5'), 5.11 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.06 (2H, s, OCH_2Ph), 4.98 [2H, s, H-7(a),(b)], 3.84 (3H, s, OCH_3), 3.65 [2H, q, *J* = 7.1 Hz, H-8(a),(b)], 3.07 (2H, t, *J* = 7.8 Hz, α-CH_2), 2.98 (2H, t, *J* = 7.8 Hz, β-CH_2), 1.20 [3H, t, *J* = 7.1 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 60b, 600 MHz, $CDCl_3$) δ 202.9, 157.0, 154.0, 151.2, 150.3, 137.4, 137.2, 136.4, 136.3, 133.8, 129.4, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6, 127.5, 114.7, 97.6, 94.0, 75.5, 71.0, 70.0, 64.4, 62.2, 46.7, 28.9, 15.1.

6.12.3 *4,2',3',4'-Tetrabenzyloxy-6'-methoxydihydrochalcone* (4.136)

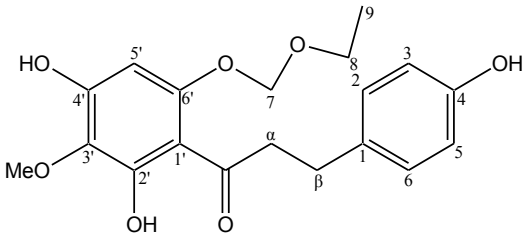


(**4.136**)

Prepared as described in general Reduction procedure (*cf* paragraph 6.3.10): 4,2',3',4'-Tetrabenzyloxy-6'-methoxychalcone (0.176 g, 0.266 mmol, 1 eq.), EtOH (15 mL), fine powder $NaBH_4$ (0.040 g, 1.064 mmol, 4 eq.) and acetone (20 mL). Standard work-up and PLC yield of *4,2',3',4'-tetrabenzyloxy-6'-methoxydihydrochalcone* (**4.136**) 0.053 g (30%).

Yellow oil; R_f 0.57 (H:EA:A = 7:2:1); ^{1}H NMR (Plate 61a, 600 MHz, $CDCl_3$) δ 7.50-7.41 (12H, m, Ar-H), 7.39-7.34 (8H, m, Ar-H), 7.11 (2H, d, *J* = 8.6 Hz, H-2,6), 6.90 (2H, d, *J* = 8.6 Hz, H-3,5), 6.40 (1H, s, H-5'), 5.19 (2H, s, OCH_2Ph), 5.13 (2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 5.04 (2H, s, OCH_2Ph), 3.75 (3H, s, OCH_3), 3.03 (2H, t, *J* = 7.3 Hz, α-CH_2), 2.94 (2H, t, *J* = 7.3 Hz, β-CH_2); ^{13}C NMR (Plate 61b, 600 MHz, $CDCl_3$) δ 203.1, 157.1, 154.1, 152.7, 150.4, 137.4, 137.3, 137.2, 136.5, 135.9, 133.8, 129.4, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.6, 127.5, 119.3, 114.7, 94.7, 76.6, 75.8, 71.4, 70.1, 56.0, 46.7, 28.9.

6.12.4 *6'-Ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone* (4.135)



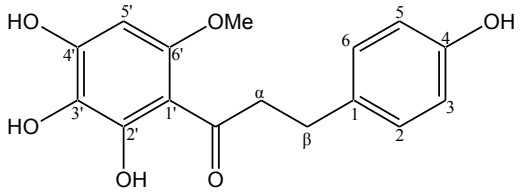
(**4.135**)

Prepared as described in general Hydrogenation procedure (*cf* paragraph 6.3.11): 4,2',4'-Tribenzyloxy-6'-ethoxymethoxy-3'-methoxychalcone (**4.131**) (0.040 g, 0.063 mmol, 1 eq.), acetone (10 mL) and 5% Pd/C (40 mg). Standard work-up and yield of *6'-ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone* (**4.135**) 0.012 g (52%).

Brown oil; R_f 0.22 (H:A = 7:3); ^{1}H NMR (Plate 62a, 600 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 8.3 Hz, H-2,6), 6.78 (2H, d, *J* = 8.3 Hz, H-3,5), 6.29 (1H, s, H-5'), 5.26 [2H, s, H-7(a),(b)], 3.92 (3H, s, OCH_3), 3.69 [2H, q, *J* = 7.0 Hz, H-8(a),(b)], 3.32 (2H, t, *J* = 7.5 Hz, α-CH_2), 2.96 (2H, t, *J* = 7.5 Hz, β-CH_2), 1.22 [3H, t, *J* = 7.1 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 62b, 600 MHz, $CDCl_3$)

δ 205.4, 158.1, 156.6, 155.0, 153.9, 133.6, 129.5, 128.9, 115.3, 106.3, 93.5, 92.3, 65.1, 60.9, 46.2, 29.7, 15.0. HRMS: calcd for $C_{19}H_{22}O_7Na$: 385.1285 g/mol. Found: *m/z* 385.1262.

6.12.5 *4,2',3',4'-Tetrahydroxy-6'-methoxydihydrochalcone* (4.137)

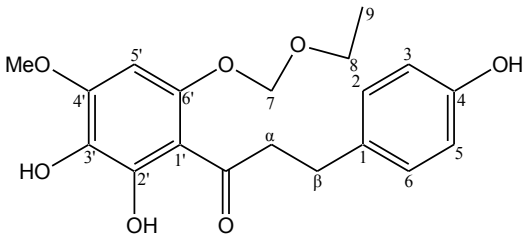


(**4.137**)

Prepared as described in general Hydrogenation procedure (*cf* paragraph 6.3.11): 4,2',3',4'-Tetrabenzyloxy-6'-methoxydihydrochalcone (**4.136**) (0.063 g, 0.095 mmol, 1 eq.), acetone (10 mL) and $Pd(OH)_2$ (60 mg). Standard work-up and yield of *4,2',3',4'-tetrahydroxy-6'-methoxydihydrochalcone* (**4.137**) 0.010 g (35%).

Yellow solid; R_f 0.16 (H:A = 7:3); ^{1}H NMR (Plate 63a, 600 MHz, acetone) δ 7.10 (2H, d, *J* = 8.4 Hz, H-2,6), 6.76 (2H, d, *J* = 8.4 Hz, H-3,5), 6.10 (1H, s, H-5'), 3.87 (3H, s, $OC\underline{H}_3$), 3.27 (2H, t, *J* = 7.6 Hz, α-CH_2), 2.87 (2H, t, *J* = 7.5 Hz, β-CH_2); ^{13}C NMR (Plate 63b, 600 MHz, acetone) δ 205.1, 156.2, 155.6, 153.8, 152.1, 132.4, 129.3, 126.0, 115.1, 104.5, 90.7, 55.3, 46.1, 29.8.

6.12.6 *6'-Ethoxymethoxy-4,2',3'-trihydroxy-4'-methoxydihydrochalcone* (4.138)



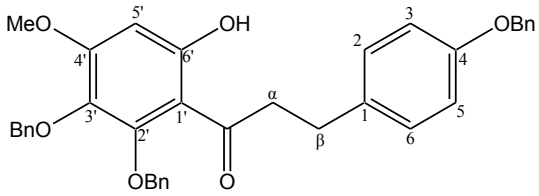
(**4.138**)

Prepared as described in general Hydrogenation procedure (*cf* paragraph 6.3.11): 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxydihydrochalcone (**4.133**) (0.025 g, 0.040 mmol, 1 eq.), acetone (3 mL) and $Pd(OH)_2$ (25 mg). Standard work-up and gave *6'-ethoxymethoxy-4,2',3'-trihydroxy-4'-methoxydihydrochalcone* (**4.138**) 0.001 g (7%).

Colourless oil; R_f 0.11 (H:A = 7:3); ^{1}H NMR (Plate 64a, 600 MHz, $CDCl_3$) δ 7.10 (2H, d, *J* = 8.5 Hz, H-2,6), 6.75 (2H, d, *J* = 8.5 Hz, H-3,5), 6.38 (1H, s, H-5'), 5.14 [2H, s, H-7(a),(b)], 3.86 (3H, s, OC<u>H</u>$_3$), 3.72 [2H, q, *J* = 7.1 Hz, H-8(a),(b)], 2.66 (2H, t, *J* = 7.7 Hz, α-CH_2), 2.62 (2H, t, *J* = 8 Hz, β-CH_2), 1.25 [3H, t, *J* = 7.1 Hz, H-9(a),(b),(c)]; ^{13}C NMR (Plate 64b, 600 MHz, $CDCl_3$) δ 207.1, 149.2, 138.5, 138.3, 138.0, 135.2, 133.7, 129.5, 114.9, 94.4, 92.0, 64.1, 56.2, 34.9, 31.0, 15.2.

6.13 Acidification of pentaoxygenated dihydrochalcones

6.13.1 *4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxydihydrochalcone* (4.139)



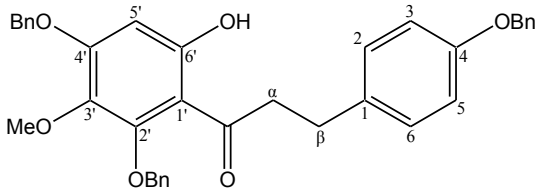
(**4.139**)

Prepared as described in general Acidification for dealkylation procedure (*cf* paragraph 6.3.12): 3 M HCl (1 mL), MeOH solution (2 mL), 4,2',3'-tribenzyloxy-6'-ethoxymethoxy-4'-methoxydihydrochalcone (**4.130**) (0.060 g, 0.095 mmol, 1 eq.) and THF (1 mL). Standard work-up and yield of *4,2',3'-tribenzyloxy-6'-hydroxy-4'-methoxydihydrochalcone* (**4.139**) 0.048 g (89%).

Brown solid; R_f 0.44 (H:EA = 8:2); ^{1}H NMR (Plate 65a, 600 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 7.1 Hz, Ar-<u>H</u>), 7.43-7.40 (4H, m, Ar-<u>H</u>), 7.36-7.33 (4H, m, Ar-<u>H</u>), 7.31-7.29 (2H, m, Ar-<u>H</u>), 7.25-7.24 (3H, m, Ar-<u>H</u>), 6.93 (2H, d, *J* = 8.6 Hz, H-2,6), 6.84 (2H, d, *J* = 8.3 Hz, H-3,5), 6.30 (1H, s,

H-5'), 5.17 (2H, s, OC$\underline{H}_2$Ph), 5.07 (2H, s, OC$\underline{H}_2$Ph), 4.95 (2H, s, OC$\underline{H}_2$Ph), 3.89 (3H, s, OC$\underline{H}_3$), 3.28 (2H, t, J = 7.4 Hz, α-CH_2), 2.85 (2H, t, J = 7.8 Hz, β-CH_2); ^{13}C NMR (Plate 65b, 600 MHz, $CDCl_3$) δ 205.0, 162.0, 160.1, 157.0, 154.3, 137.3, 137.1, 136.4, 133.7, 133.6, 129.3, 128.7, 128.6, 128.4, 128.2, 127.9, 127.5, 114.7, 96.6, 76.4, 75.7, 70.0, 56.1, 45.4, 29.3. HRMS: calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2264.

6.13.2 *4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxydihydrochalcone* (4.140)

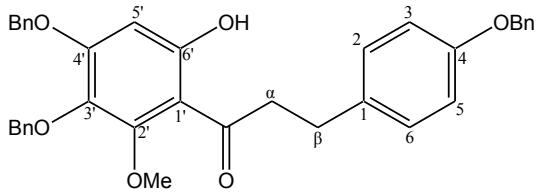


(**4.140**)

Prepared as described in general Acidification for dealkylation procedure (*cf* paragraph 6.3.12): 3 M HCl (1 mL), MeOH solution (2 mL), 4,2',4'-tribenzyloxy-6'-ethoxymethoxy-3'-methoxy-dihydrochalcone **4.165**) (0.070 g, 0.111 mmol, 1 eq.) and THF (2 mL). Standard work-up and yield of *4,2',4'-tribenzyloxy-6'-hydroxy-3'-methoxydihydrochalcone* (**4.140**) 0.055 g (86%).

Yellow oil; R_f 0.49 (H:EA = 8:2); ^{1}H NMR (Plate 66a, 600 MHz, $CDCl_3$) δ 7.46 (2H, d, J = 7.4 Hz, Ar-$\underline{H}$), 7.44-7.40 (5H, m, Ar-$\underline{H}$), 7.38-7.30 (8H, m, Ar-$\underline{H}$), 6.94 (2H, d, J = 8.4 Hz, H-2,6), 6.84 (2H, d, J = 8.4 Hz, H-3,5), 6.36 (1H, s, H-5'), 5.19 (2H, s, OC$\underline{H}_2$Ph), 5.17 (2H, s, OC$\underline{H}_2$Ph), 5.07 (2H, s, OC$\underline{H}_2$Ph), 3.84 (3H, s, OC$\underline{H}_3$), 3.29 (2H, t, J = 7.6 Hz, α-CH_2), 2.87 (2H, t, J = 7.6 Hz, β-CH_2); ^{13}C NMR (Plate 66b, 600 MHz, $CDCl_3$) δ 205.0, 161.6, 158.9, 157.0, 154.1, 137.3, 136.5, 135.8, 135.2, 133.6, 129.3, 128.8, 128.6, 128.4, 128.3, 127.9, 127.5, 127.4, 114.7, 97.7, 76.3, 70.6, 70.1, 61.3, 45.4, 29.7, 29.3. HRMS: calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2246.

6.13.3 *4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxydihydrochalcone* (4.141)



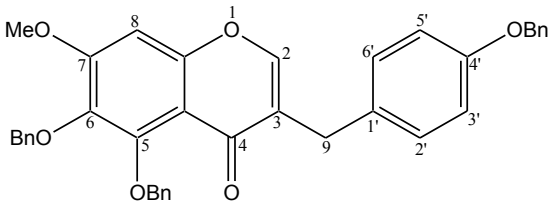
(**4.141**)

Prepared as described in general Acidification for dealkylation procedure (*cf* paragraph 6.3.12): 3 M HCl (1 mL), MeOH solution (10 mL), 4,3',4'-tribenzyloxy-6'-ethoxymethoxy-2'-methoxy-dihydrochalcone (**4.132**) (0.080 g, 0.139 mmol, 1 eq.) and THF (3 mL). Standard work-up and yield of *4,3',4'-tribenzyloxy-6'-hydroxy-2'-methoxydihydrochalcone* (**4.141**) 0.053 g (66%).

Brown oil; R_f 0.61 (H:EA = 8:2); ^{1}H NMR (Plate 67a, 600 MHz, $CDCl_3$) δ 7.49-7.46 (4H, m, Ar-H), 7.44-7.40 (9H, m, Ar-H), 7.35-7.34 (2H, m, Ar-H), 7.21 (2H, d, *J* = 8.3 Hz, H-2,6), 6.96 (2H, d, *J* = 8.3 Hz, H-3,5), 6.37 (1H, s, H-5'), 5.13 (2H, s, OCH_2Ph), 5.09 (2H, s, OCH_2Ph), 4.95 (2H, s, OCH_2Ph), 4.00 (3H, s, OCH_3), 3.38 (2H, t, *J* = 7.5 Hz, α-CH_2), 3.01 (2H, t, *J* = 7.5 Hz, β-CH_2); ^{13}C NMR (Plate 67b, 600 MHz, $CDCl_3$) δ 205.0, 161.9, 159.2, 157.2, 155.7, 137.2, 135.7, 133.9, 129.4, 128.8, 128.7, 128.6, 128.4, 128.4, 128.2, 128.0, 127.6, 127.5, 127.4, 114.9, 97.4, 75.5, 70.7, 70.1, 61.4, 45.2, 29.7. HRMS: calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2257.

6.14 Cyclization of dihydrochalcones

6.14.1 *5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavone* (4.142)

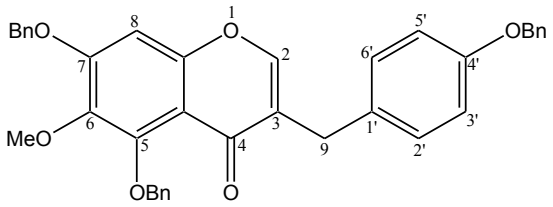


(**4.142**)

Prepared as described in general Cyclization procedure (*cf* paragraph 6.3.13): 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxydihydrochalcone (**4.139**) (0.048 g, 0.084 mmol, 1 eq.), DMF (2 mL), $BF_3.Et_2O$ (0.20 mL, 1.5 mmol, 18 eq.), DMF (2 mL) and PCl_5 (0.105 g, 0.504 mmol, 6 eq.). Standard work-up and PLC gave *5,6,4'-tribenzyloxy-7-methoxyhomoisoflavone* (**4.142**) 0.037 g (76%).

Yellow oil; R_f 0.41 (H:EA = 8:2); ^{1}H NMR (Plate 68a, 600 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 6.9 Hz, Ar-H), 7.47 (2H, d, *J* = 7.3 Hz, Ar-H), 7.44-7.34 (12H, m, H-2, Ar-H), 7.24 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.96 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.65 (1H, s, H-8), 5.16 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.02 (2H, s, OCH_2Ph), 3.90 (3H, s, OCH_3), 3.78 (2H, s, 9-CH_2); ^{13}C NMR (Plate 68b, 600 MHz, $CDCl_3$) δ 176.1, 157.9, 157.5, 155.0, 151.7, 151.2, 139.5, 137.2, 137.1, 131.0, 130.3, 129.2, 128.8, 128.6, 128.3, 128.1, 128.0, 128.0, 127.5, 125.3, 115.0, 113.4, 96.3, 76.6, 75.8, 70.1, 56.2, 30.7. HRMS: calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2111.

6.14.2 *5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavone* (4.143)

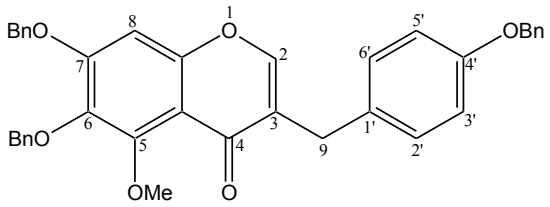


(**4.143**)

Prepared as described in general Cyclization procedure (*cf* paragraph 6.3.13): 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxydihydrochalcone (**4.140**) (0.065 g, 0.113 mmol, 1 eq.), DMF (2 mL), $BF_3.Et_2O$ (0.14 mL, 1.131 mmol, 10 eq.), DMF (3 mL) and PCl_5 (0.141 g, 0.678 mmol, 6 eq.). Standard work-up and PLC yield of *5,7,4'-tribenzyloxy-6-methoxyhomo-isoflavone* (**4.143**) 0.043 g (65%).

Yellow oil; R_f 0.36 (H:A = 7:3); ^{1}H NMR (Plate 69a, 600 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 7.1 Hz, Ar-H), 7.47-7.33 (13H, m, Ar-H), 7.32 (1H, s, H-2), 7.22 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.95 (2H, d, *J* = 8.4 Hz, H-3',5'), 6.70 (1H, s, H-8), 5.20 (2H, s, OCH_2Ph), 5.16 (2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 3.88 (3H, s, OCH_3), 3.75 (2H, s, 9-CH_2); ^{13}C NMR (Plate 69b, 600 MHz, $CDCl_3$) δ 176.0, 157.5, 156.6, 154.6, 151.6, 151.1, 141.0, 137.5, 137.1, 135.7, 131.0, 130.2, 128.9, 128.8, 128.6, 128.4, 128.3, 127.9, 127.5, 127.3, 125.3, 115.0, 113.6, 97.7, 76.5, 70.9, 70.1, 61.5, 30.6. HRMS: calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2103.

6.14.3 *6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavone* (4.144)



(**4.144**)

Prepared as described in general Cyclization procedure (*cf* paragraph 6.3.13): 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxydihydrochalcone (**4.141**) (0.080 g, 0.139 mmol, 1 eq.), DMF (5 mL), $BF_3.Et_2O$ (0.11 mL, 0.835 mmol, 6 eq.), DMF (4 mL) and PCl_5 (0.09 g, 0.417 mmol, 3 eq.). Standard work-up and PLC yield of *6,7,4'-tribenzyloxy-5-methoxyhomoisoflavone* (**4.144**) 0.037 g (46%).

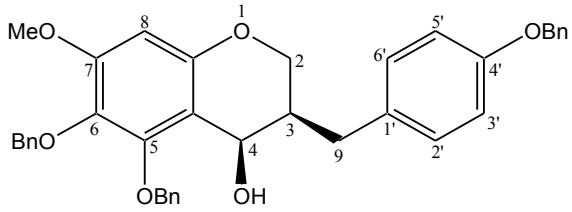
Yellow oil; R_f 0.28 (H:EA = 8:2); ^{1}H NMR (Plate 70a, 600 MHz, $CDCl_3$) δ 7.48-7.46 (3H, m, Ar-H), 7.45 (1H, s, H-2), 7.43-7.40 (8H, m, Ar-H), 7.36-7.33 (4H, m, Ar-H), 7.24 (2H, d, *J* = 8.7 Hz, H-2',6'), 6.95 (2H, d, *J* = 8.7 Hz, H-3',5'), 6.69 (1H, s, H-8), 5.14 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 4.03 (3H, s, OCH_3), 3.74 (2H, s, 9-CH_2); ^{13}C NMR (Plate 70b, 600 MHz, $CDCl_3$) δ 176.1, 157.5, 156.9, 154.8, 153.1, 151.1, 139.5, 137.3, 137.1, 135.6, 131.1, 130.2, 128.7, 128.6, 128.4, 128.1, 128.0, 127.5, 125.3, 115.0, 113.3, 97.3, 75.8, 70.9, 70.1, 62.1, 30.7. HRMS: calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2100.

6.15 Reduction-oxidation of homoisoflavones

6.15.1 Reduction-oxidation of 5,6,4'-tribenzyloxy-7-methoxy-homoisoflavone (4.142)

Prepared as described in general Reduction-oxidation of homoisoflavones procedure (*cf* paragraph 6.3.14):
5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavone (**4.142**) (0.041 g, 0.070 mmol, 1 eq.), THF (0.5 mL), EtOH (2 mL), $NaBH_4$ (0.003 g, 0.070 mmol, 15 eq.) and acetone (10 mL). Purification by PLC (H:EA = 8:2) yielded two identifiable products *cis*- and *trans*-homoisoflavan with R_f values of 0.39 and 0.32.

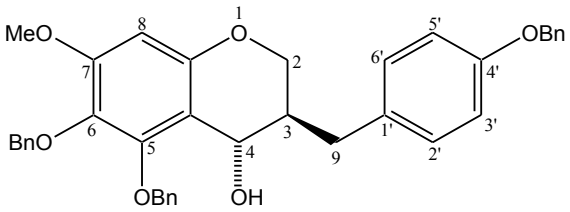
6.15.1.1 *cis-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol* (**4.145-*cis***)



(**4.145-*cis***)

The first compound (R_f 0.39); obtained as yellow oil; 0.018 g (44%); was identified as the *cis-5,6,4'-tribenzyloxy-7-methoxyhomoisoflavan-4-ol* (**4.145-*cis***); ^{1}H NMR (Plate 71a, 600 MHz, $CDCl_3$) δ 7.50-7.47 (4H, m, Ar-H), 7.42-7.30 (9H, m, Ar-H), 7.26-7.24 (2H, m, Ar-H), 7.18 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.96 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.23 (1H, s, H-8), 5.27 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 5.09 (2H, s, OCH_2Ph), 5.02 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.98 (2H, s, OCH_2Ph), 4.52 (1H, d, *J* = 3.2 Hz, H-4), 4.01-3.98 (2H, m, 2-CH_2), 3.83 (3H, s, OCH_3), 2.82 [1H, dd, *J* = 13.6 and 8.4 Hz, H-9(a)], 2.58 [1H, dd, *J* = 13.6 and 7.2 Hz, H-9(b)], 2.07-2.02 (1H, m, H-3); ^{13}C NMR (Plate 71b, 600 MHz, $CDCl_3$) δ 157.3, 154.5, 151.0, 137.6, 137.2, 137.1, 131.8, 130.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.5, 114.8, 111.3, 96.1, 75.7, 75.6, 70.1, 65.1, 59.9, 55.9, 40.1, 32.0.

6.15.1.2 ***trans-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol*** **(4.145-*trans*)**



(**4.145-*trans***)

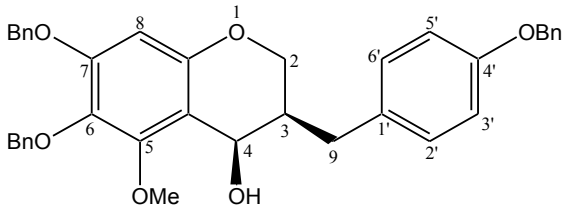
The second compound (R_f 0.32); obtained as yellow oil; 0.007 g (17%); was identified as the *trans-5,6,4'-tribenzyloxy-7-methoxyhomoisoflavan-4-ol* (**4.145-*trans***); ^{1}H NMR (Plate 72a, 600 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 7.2 Hz, Ar-H), 7.45 (2H, d, *J* = 7.3 Hz, Ar-H), 7.42-7.38 (4H, m, Ar-H), 7.36-7.33 (7H, m, Ar-H), 7.09 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.93 (2H, d, *J* = 8.4 Hz, H-3',5'), 6.30 (1H, s, H-8), 5.33 (1H, d, *J* = 11.1 Hz, OCH_2Ph), 5.11 (1H, d, *J* = 11.1 Hz, OCH_2Ph), 5.05 (2H, s, OCH_2Ph), 5.01 (2H, d, *J* = 3.4 Hz, OCH_2Ph), 4.44 (1H, br s, OH), 4.07 (1H, dd, *J* = 10.9 and 2.0 Hz, H-4), 3.90-3.84 (2H, m, 2-CH_2), 3.86 (3H, s, OCH_3), 2.40 [1H, dd, *J* = 6.3 and 14.0 Hz, H-9(a)], 2.34 [1H, dd, *J* = 9.8 and 13.6 Hz, H-9(b)], 2.11-2.07 (1H, m, H-3); ^{13}C NMR (Plate 72b, 600 MHz, $CDCl_3$) δ 157.3, 154.5, 151.5, 150.8, 137.6, 137.1, 134.8, 131.8, 130.1, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.5, 114.8, 109.8, 96.2, 75.7, 70.1, 63.9, 63.2, 55.9, 40.4, 33.4, 31.0.

6.15.2 Reduction-oxidation of 6,7,4'-tribenzyloxy-5-methoxy-homoisoflavone (4.144)

Prepared as described in general Reduction-oxidation of homoisoflavones procedure (*cf* paragraph 6.3.14):

6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavone (**4.144**) (0.058 g, 0.099 mmol, 1 eq.), THF (0.5 mL), EtOH (2 mL), $NaBH_4$ (0.06 g, 0.002 mmol, 15 eq.) and acetone (10 mL). Purification by PLC (H:EA = 8:2) yielded two identifiable products *cis*- and *trans*-homoisoflavan with R_f values of 0.53 and 0.45.

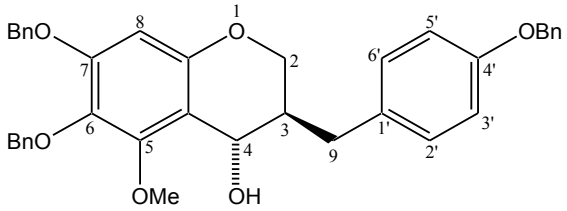
6.15.2.1 *cis-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol* (**4.146-*cis***)



(**4.146-*cis***)

The first compound (R_f 0.53); obtained as yellow oil; 0.028 g (48%); was identified as the *cis-6,7,4'-tribenzyloxy-5-methoxyhomoisoflavan-4-ol* (**4.146-*cis***); ^{1}H NMR (Plate 73a, 600 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 7.5 Hz, Ar-H), 7.45-7.38 (8H, m, Ar-H), 7.37-7.33 (5H, m, Ar-H), 7.22 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.97 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.29 (1H, s, H-8), 5.09 (2H, s, OCH_2Ph), 5.06 (2H, s, OCH_2Ph), 4.96 (2H, s, OCH_2Ph), 4.74 (1H, d, *J* = 3.3 Hz, H-4), 4.02 (2H, d, *J* = 9 Hz, 2-CH_2), 4.00 (3H, s, OCH_3), 2.93 [1H, dd, *J* = 13.9 and 7.8 Hz, H-9(a)], 2.65 [1H, dd, *J* = 13.9 and 7.8 Hz, H-9(b)], 2.20 (1H, br s, OH), 2.19-2.15 (1H, m, H-3); ^{13}C NMR (Plate 73b, 600 MHz, $CDCl_3$) δ 157.3, 153.7, 152.4, 150.9, 137.6, 137.2, 136.7, 134.7, 131.8, 130.1, 128.6, 128.3, 128.0, 127.5, 114.9, 111.0, 97.3, 75.6, 70.7, 70.1, 65.1, 61.6, 60.4, 40.2, 32.1.

6.15.2.2 *trans-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol* (**4.146-*trans***)

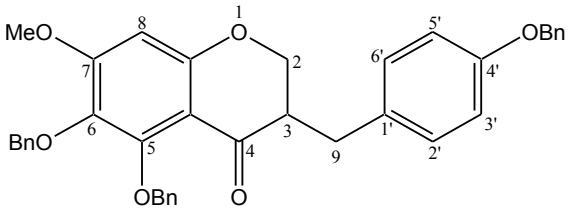


(**4.146-*trans***)

The second compound (R_f 0.45); obtained as yellow oil; 0.020 g (34%); was identified as the *trans-6,7,4'-tribenzyloxy-5-methoxyhomoisoflavan-4-ol* (**4.146-*trans***); ^{1}H NMR (Plate 74a, 600 MHz, $CDCl_3$) δ 7.47-7.44 (6H, m, Ar-H), 7.43-7.40 (4H, m, Ar-H), 7.38-7.33 (5H, m, Ar-H), 7.14 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.95 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.35 (1H, s, H-8), 5.10 (1H, d, *J* = 11.7 Hz, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 5.06 (1H, d, *J* = 11.7 Hz, OCH_2Ph), 4.99 (2H, s, OCH_2Ph), 4.64 (1H, d, *J* = 2.0 Hz, H-4), 4.13 [1H, dd, *J* = 10.9 and 2.3 Hz, H-2(a)], 3.95 [1H,

dd, *J* = 10.9 and 2.3 Hz, H-2(b)], 4.01 (3H, s, OC<u>H</u>$_3$), 2.65-2.59 [(2H, m, H-9(a), O<u>H</u>)], 2.51 [1H, dd, *J* = 13.9 and 9.3 Hz, H-9(b)], 2.22-2.18 (1H, m, H-3); ^{13}C NMR (Plate 74b, 600 MHz, $CDCl_3$) δ 157.4, 153.7, 153.0, 150.7, 137.6, 137.1, 136.6, 134.9, 131.7, 130.1, 128.6, 128.5, 128.3, 128.0, 127.5, 114.9, 109.6, 97.4, 75.6, 70.7, 70.1, 64.4, 63.1, 61.5, 40.7, 33.8.

6.15.3 *5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavanone* (4.147)



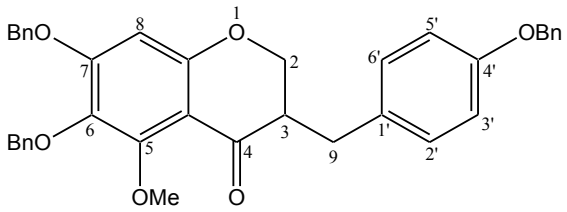
(**4.147**)

Prepared as described in general Reduction-oxidation of homoisoflavones procedure (*cf* paragraph 6.3.14):

cis- and *trans*-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol (**4.145-*cis*** and **4.145-*trans***) (0.026 g, 0.044 mmol, 1 eq.), dry acetonitrile (2 mL) and IBX (0.020 g, 0.066 mmol, 1.5 eq.). Standard work-up and PLC yield of *5,6,4'-tribenzyloxy-7-methoxyhomoisoflavanone* (**4.147**) 0.019 g (73%).

Yellow oil; R_f 0.59 (H:EA:A = 7:2:1); ^{1}H NMR (Plate 75a, 600 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 7.1 Hz, Ar-<u>H</u>), 7.46-7.34 (13H, m, Ar-<u>H</u>), 7.18 (2H, d, *J* = 8.1 Hz, H-2',6'), 6.96 (2H, d, *J* = 8.1 Hz, H-3',5'), 6.30 (1H, s, H-8), 5.10 (2H, br s, OC<u>H</u>$_2$Ph), 5.07 (2H, s, OC<u>H</u>$_2$Ph), 4.96 (2H, s, OC<u>H</u>$_2$Ph), 4.30 [1H, dd, *J* = 11.4 and 3.5 Hz, H-2(a)], 4.14 [1H, dd, *J* = 11.1 and 6.9 Hz, H-2(b)], 3.87 (3H, s, OC<u>H</u>$_3$), 3.21 [1H, dd, *J* = 13.6 and 3.4 Hz, H-9(a)], 2.78-2.72 (1H, m, H-3), 2.67 [1H, dd, *J* = 11.4 and 7.3 Hz, H-9(b)]; ^{13}C NMR (Plate 75b, 600 MHz, $CDCl_3$) δ 191.4, 159.8, 159.6, 157.6, 153.4, 137.4, 137.2, 137.1, 137.0, 130.8, 130.2, 129.2, 128.7, 128.6, 128.3, 128.1, 128.0, 127.5, 115.1, 109.2, 96.3, 76.0, 75.8, 70.1, 69.0, 56.1, 48.6, 32.1. HRMS: calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2269.

6.15.4 *6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavanone* (4.148)

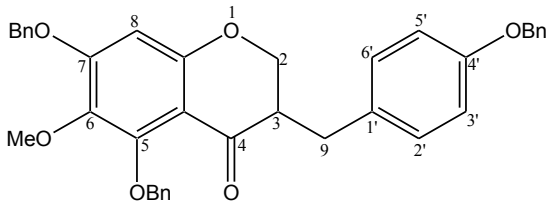


(**4.148**)

Prepared as described in general Reduction-oxidation of homoisoflavones procedure (*cf* paragraph 6.3.14):
cis- and *trans*-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol (**4.146-*cis*** and **4.146-*trans***) (0.050 g, 0.085 mmol, 1 eq.), dry acetonitrile (2 mL) and IBX (0.036 g, 0.127 mmol, 1.5 eq.). Standard work-up and PLC yield of *6,7,4'-tribenzyloxy-5-methoxyhomoisoflavanone* (**4.148**) 0.023 g (46%).

Brown oil; R_f 0.59 (H:EA:A = 7:2:1); ^{1}H NMR (Plate 76a, 600 MHz, $CDCl_3$) δ 7.47-7.45 (4H, m, Ar-H), 7.43-7.40 (6H, m, Ar-H), 7.37-7.32 (5H, m, Ar-H), 7.18 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.95 (2H, d, *J* = 8.4 Hz, H-3',5'), 6.34 (1H, s, H-8), 5.11 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 4.99 (2H, s, OCH_2Ph), 4.30 [1H, dd, *J* = 11.3 and 4.1 Hz, H-2(a)], 4.12 [1H, dd, *J* = 11.4 and 7.6 Hz, H-2(b)], 3.98 (3H, s, OCH_3), 3.23 [1H, dd, *J* = 13.9 and 4.2 Hz, H-9(a)], 2.80-2.75 (1H, m, H-3), 2.68 [1H, dd, *J* = 13.9 and 10.7 Hz, H-9(b)]; ^{13}C NMR (Plate 76b, 600 MHz, $CDCl_3$) δ 191.5, 159.7, 158.6, 157.6, 154.9, 137.5, 137.0, 136.8, 135.7, 130.8, 130.2, 128.7, 128.6, 128.3, 128.1, 128.0, 127.5, 115.0, 109.0, 97.3, 75.8, 70.7, 70.1, 69.1, 61.7, 48.5, 32.0. HRMS: calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2261.

6.15.5 *5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavanone* (4.149)



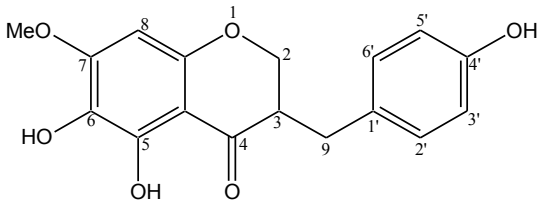
(**4.149**)

5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavone (**4.143**) (0.043 g, 0.074 mmol, 1 eq.) was dissolved in minimum THF (1 mL) and EtOH (6 mL). $NaBH_4$ (0.043 g, 1.137 mmol, 15 eq.) was added to the reaction mixture and stirred at rt for 24 h. Acetone (20 mL) was added to the reaction mixture and stirred for 30 min. Standard work-up and the crude product (0.043 g, 0.073 mmol, 1 eq.) was dissolved in minimum dry acetonitrile (5 mL). IBX (0.031 g, 0.110 mmol, 1.5 eq.) was added to the reaction and refluxed for overnight. Standard work-up and PLC yield of *5,7,4'-tribenzyloxy-6-methoxyhomoisoflavanone* (**4.149**) 0.011 g (26%).

Yellow oil; R_f 0.32 (H:EA = 8:2); ^{1}H NMR (Plate 77a, 600 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 7.2 Hz, Ar-H), 7.47-7.44 (4H, m, Ar-H), 7.43-7.39 (6H, m, Ar-H), 7.38-7.34 (3H, m, Ar-H), 7.17 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.95 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.36 (1H, s, H-8), 5.17 (2H, br s, OCH_2Ph), 5.11 (2H, br s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 4.27 [1H, dd, *J* = 11.4 and 4.0 Hz, H-2(a)], 4.10 [1H, dd, *J* = 11.4 and 6.9 Hz, H-2(b)], 3.85 (3H, s, OCH_3), 3.19 [1H, dd, *J* = 13.8 and 4.0 Hz, H-9(a)], 2.75-2.71 (1H, m, H-3), 2.64 [1H, dd, *J* = 11.4 and 13.8 Hz, H-9(b)]; ^{13}C NMR (Plate 77b, 600 MHz, $CDCl_3$) δ 191.4, 159.5, 158.4, 157.6, 153.3, 138.3, 137.4, 137.1, 135.8, 130.7, 130.2, 128.9, 128.8, 128.6, 128.4, 128.3, 128.0, 127.5, 127.3, 115.0, 109.5, 97.6, 75.9, 70.7, 70.1, 69.0, 61.4, 48.6, 32.0. HRMS: calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2264.

6.16 Hydrogenation

6.16.1 *5,6,4'-Trihydroxy-7-methoxyhomoisoflavanone* (4.150)[38]



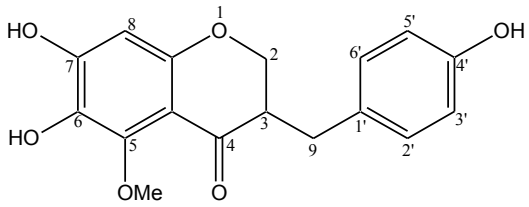
(**4.150**)

Prepared as described in general Hydrogenation procedure (*cf* paragraph 6.3.11): 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavanone (**4.147**) (0.010 g, 0.017 mmol, 1 eq.), acetone (5 mL) and 5% Pd/C (10 mg). Yield of *5,6,4'-trihydroxy-7-methoxyhomoisoflavanone* (**4.150**) 0.001 g (18%).

Brown solid; R_f 0.19 (H:A = 7:3); ^{1}H NMR (Plate 78a, 600 MHz, Acetone) δ 7.12 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.81 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.15 (1H, s, H-8), 4.32 [1H, dd, *J* = 11.4 and 4.4 Hz, H-2(a)], 4.13 [1H, dd, *J* = 11.3 and 8.3 Hz, H-2(b)], 3.90 (3H, s, OC$\underline{H}_3$), 3.14 [1H, dd, *J* = 14 and 4.7 Hz, H-9(a)], 2.95-2.91 (1H, m, H-3), 2.68 [1H, dd, *J* = 14 and 10.1 Hz, H-9(b)]; ^{13}C NMR (Plate 78b, 600 MHz, Acetone) δ 199.1, 156.1, 155.8, 130.1, 115.3, 91.0, 69.3, 55.7, 46.7, 31.4.

[38] Koorbanally, C.; Mulholland, D.A.; Crouch, N.R. *Biochem. Syst. Ecol.* **2006**, *34*, 588.

6.16.2 *6,7,4'-Trihydroxy-5-methoxyhomoisoflavanone* (4.151)

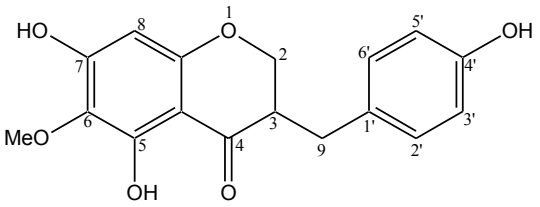


(**4.151**)

Prepared as described in general Hydrogenation procedure (*cf* paragraph 6.3.11): 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavanone (**4.148**) (0.015 g, 0.026 mmol, 1 eq.), acetone (5 mL) and 5% Pd/C (15 mg). The reaction mixture was taken to hydrogenation with 1 bar atmospheric pressure. Yield of *6,7,4'-trihydroxy-5-methoxyhomoisoflavanone* (**4.151**) 0.002 g (25%).

Yellow solid; R_f 0.13 (H:A = 7:3); ^{1}H NMR (Plate 79a, 600 MHz, Acetone) δ 7.21 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.98 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.23 (1H, s, H-8), 4.27 [1H, dd, *J* = 11.4 and 4.3 Hz, H-2(a)], 4.06 [1H, dd, *J* = 11.4 and 8.3 Hz, H-2(b)], 3.80 (3H, s, OC$\underline{H}_3$), 3.13 [1H, dd, *J* = 14.1 and 4.7 Hz, H-9(a)], 2.76-2.72 (1H, m, H-3), 2.71 [1H, dd, *J* = 14.1 and 10.1 Hz, H-9(b)]; ^{13}C NMR (Plate 79b, 600 MHz, Acetone) δ 201.1, 158.6, 156.3, 130.3, 130.2, 115.3, 103.6, 95.2, 69.5, 57.0, 46.7, 31.4. HRMS: calcd for $C_{17}H_{16}O_6Na$: 339.0847 g/mol. Found: *m/z* 339.0845.

6.16.3 *5,7,4'-Trihydroxy-6-methoxyhomoisoflavanone* (4.152)



(**4.152**)

Prepared as described in general Hydrogenation procedure (*cf* paragraph 6.3.11): 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavanone (**4.149**) (0.004 g, 0.0068 mmol, 1 eq.), acetone (5 mL) and $Pd(OH)_2$ (4 mg). Yield of *5,7,4'-trihydroxy-6-methoxyhomoisoflavanone* (**4.152**) 0.001 g (45%).

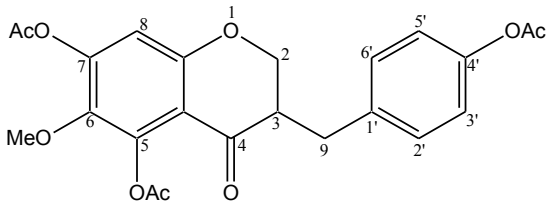
Green solid; R_f 0.20 (H:A = 7:3); ^{1}H NMR (Plate 80a, 600 MHz, Acetone) δ 7.13 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.81 (2H, d, *J* = 8.4 Hz, H-3',5'), 5.96 (1H, s, H-8), 4.32 [1H, dd, *J* = 11.4 and 4.5 Hz, H-2(a)], 4.13 [1H, dd, *J* = 11.4 and 8.2 Hz, H-2(b)], 3.78 (3H, s, OC$\underline{H}_3$), 3.14 [1H, dd, *J* = 14.1 and 4.7 Hz, H-9(a)], 2.96-2.91 (1H, m, H-3), 2.70 [1H, dd, *J* = 14.1 and 10.1 Hz, H-9(b)]; ^{13}C NMR (Plate 80b, 600 MHz, Acetone) δ 198.9, 158.9, 158.6, 156.1, 155.7, 130.1, 128.8, 115.4, 102.0, 94.4, 69.2, 59.8, 46.5, 31.4.

6.17 Acetylation

6.17.1 Acetylation of 5,7,4'-trihydroxy-6-methoxyhomoiso-flavanone (4.150)

Prepared as described in general Acetylation procedure (*cf* paragraph 6.3.2): 5,7,4'-Trihydroxy-6-methoxyhomoisoflavanone (**4.150**) (0.001 g, 0.0032 mmol, 1 eq.), pyridine (0.5 mL) and acetic anhydride (1 mL). Purification by PLC (H:A = 7:3) yielded two identifiable products with R_f values of 0.55 and 0.41.

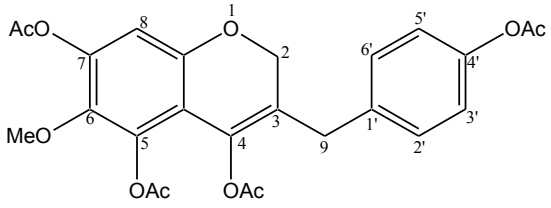
6.17.1.1 *5,7,4'-Triacetoxy-6-methoxyhomoisoflavanone* (**4.153**)



(**4.153**)

The first compound (R_f 0.55); obtained as yellow oil; 0.006 g (80%); was identified as the 5,*7*,*4'*-*triacetoxy-6-methoxyhomoisoflavanone* (**4.153**); ^{1}H NMR (Plate 81a, 600 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.4 Hz, H-2',6'), 7.06 (2H, d, *J* = 8.4 Hz, H-3',5'), 6.69 (1H, s, H-8), 4.34 [1H, dd, *J* = 11.5 and 4.1 Hz, H-2(a)], 4.16 [1H, dd, *J* = 11.5 and 8.2 Hz, H-2(b)], 3.79 (3H, s, OC$\underline{H}_3$), 3.23 [1H, dd, *J* = 14.8 and 3.6 Hz, H-9(a)], 2.85-2.80 (1H, m, H-3), 2.67 [1H, dd, *J* = 14.8 and 10.7 Hz, H-9(b)], 2.46 (3H, s, COC$\underline{H}_3$), 2.36 (3H, s, COC$\underline{H}_3$), 2.32 (3H, s, COC$\underline{H}_3$); ^{13}C NMR (Plate 81b, 600 MHz, $CDCl_3$) δ 191.2, 169.5, 169.0, 168.0, 158.0, 150.0, 149.5, 144.1, 130.0, 121.8, 112.1, 109.9, 69.1, 61.6, 48.0, 31.6, 29.7, 21.0, 20.7. HRMS: calcd for $C_{23}H_{22}O_9Na$: 465.1164 g/mol. Found: *m/z* 465.1158.

6.17.1.2 *3-(4-Acetoxybenzyl)-4,5,7-triacetoxy-6-methoxyhomoisoflav-3-ene* (**4.154**)



(**4.154**)

The second compound (R_f 0.41); obtained as colourless oil; 0.002 g (20%); was identified as the *3-(4-acetoxybenzyl)-4,5,7-triacetoxy-6-methoxyhomoisoflav-3-ene* (**4.154**); ^{1}H NMR (Plate 82a, 600 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.03 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.57 (1H, s, H-8), 4.59 (2H, s, 2-CH_2), 3.73 (3H, s, OC$\underline{H}_3$), 3.45 (2H, s, H-4), 2.35 (3H, s, COC$\underline{H}_3$), 2.32 (3H, s, COC$\underline{H}_3$), 2.31 (3H, s, COC$\underline{H}_3$), 2.28 (3H, s, COC$\underline{H}_3$); ^{13}C NMR (Plate 82b, 600 MHz, $CDCl_3$) δ 168.3, 168.1, 149.6, 144.1, 136.7, 134.2, 129.7, 122.1, 121.9, 112.5, 109.2, 67.7, 61.3,

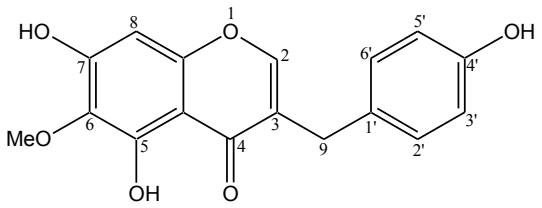
32.6, 29.7, 21.1, 20.7, 20.7, 20.5. HRMS: calcd for $C_{25}H_{24}O_{10}Na$: 507.1269 g/mol. Found: *m/z* 507.1260.

6.18 Preparation of 4',5,7-triacetoxy-8-methoxyhomoiso-flavanone

6.18.1 Cyclization of 6'-ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone (4.135)

A mixture of 6'-ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone (**4.135**) (0.065 g, 0.179 mmol, 1 eq.) and DMF (2 mL) was added dropwise $BF_3.Et_2O$ (0.2 mL, 1.611 mmol, 9.0 eq.) and cooled to 10 ^oC. In a second flask, DMF (3 mL) was cooled to 10 ^oC and PCl_5 (0.224 g, 1.074 mmol, 6.0 eq.) was added in small portions. The latter mixture was thus stirred at 55 ^oC until a light yellow colour indicative of (*N*,*N*'-dimethyl(chloromethylene)ammonium chloride) was observed (20 min.) and then slowly added to the first flask at 20 – 25 ^oC. The reaction mixture was stirred at rt for 24 h, slowly added to boiling diluted HCl (10 mL) and cooled. Purification by PLC (H:EA:A = 7:2:1) yielded two identifiable products with R_f values of 0.47 and 0.39.

6.18.1.1 *5,7,4'-Trihydroxy-6-methoxyhomoisoflavone* (4.155)

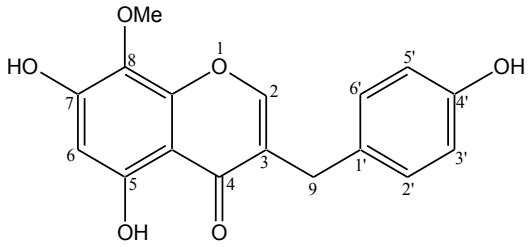


(**4.155**)

The first compound (R_f 0.47); obtained as yellow oil; 0.001 g (2%); was identified as the 5,*7,4'-trihydroxy-6-methoxyhomoisoflavone* (**4.155**); ^1H NMR (Plate 83a, 600 MHz, Acetone) δ 7.97 (1H, s, H-2), 7.17 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.77 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.45 (1H, s, H-8),

3.85 (3H, s, OC<u>H</u>$_3$), 3.66 (2H, s, 9-C<u>H</u>$_2$); ^{13}C NMR (Plate 83b, 600 MHz, Acetone) δ 181.9, 156.9, 155.9, 154.0, 153.6, 153.1, 131.1, 129.8, 127.6, 122.5, 115.1, 105.4, 98.8, 59.8, 29.4.

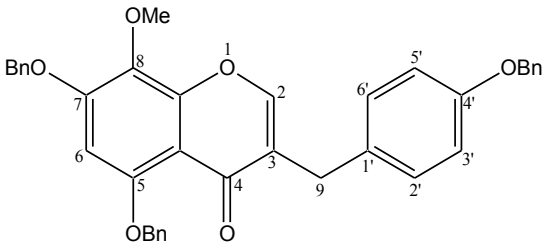
6.18.1.2 *5,7,4'-Trihydroxy-8-methoxyhomoisoflavone* (4.156)



(**4.156**)

The second compound (R_f 0.39); obtained as yellow oil; 0.019 g (36%); was identified as the *5,7,4'-trihydroxy-8-methoxyhomoisoflavone* (**4.156**); ^{1}H NMR (Plate 84a, 600 MHz, Acetone) δ 8.02 (1H, s, H-2), 7.18 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.77 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.30 (1H, s, H-6), 3.83 (3H, s, OC<u>H</u>$_3$), 3.66 (2H, s, 9-C<u>H</u>$_2$); ^{13}C NMR (Plate 84b, 600 MHz, Acetone) δ 181.5, 157.4, 156.6, 155.9, 153.7, 150.4, 129.9, 129.6, 127.5, 123.0, 115.2, 104.9, 98.7, 60.8, 29.4.

6.18.2 *5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavone (4.157)*



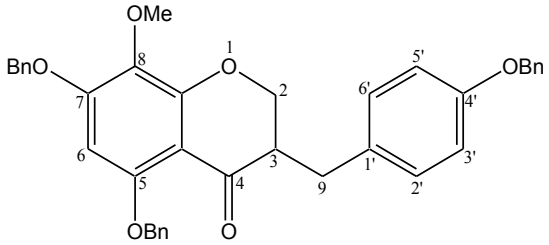
(**4.157**)

To a solution of 5,7,4'-trihydroxy-8-methoxyhomoisoflavone (**4.156**) (0.019 g, 0.060 mmol, 1 eq.) in DMF (5 mL) was added Cs_2CO_3 (0.027 g, 0.193 mmol, 3.2 eq.) and the mixture stirred for 20 min at 60 ^{o}C. Benzyl bromide (0.023 mL, 0.193 mmol, 3.2 eq.) was added and stirring continued for overnight before the reaction mixture was acidified with 3 M HCl (15 mL) and the product extracted into EA (3 x 20 mL), washed with water (30 mL), dried over $MgSO_4$ and

concentrated *in vacuo*. Purification by PLC yield of *5,7,4'-tribenzyloxy-8-methoxyhomoisoflavone* (**4.157**) 0.026 g (74%).

White solid; R_f 0.36 (H:A = 7:3); ^{1}H NMR (Plate 85a, 600 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 7.4 Hz, Ar-H), 7.45 (2H, d, *J* = 7.4 Hz, Ar-H), 7.42-7.38 (8H, m, Ar-H), 7.36-7.31 (3H, m, Ar-H), 7.23 (2H, d, *J* = 8.6 Hz, H-2',6'), 6.95 (2H, d, *J* = 8.6 Hz, H-3',5'), 6.47 (1H, s, H-6), 5.17 (2H, s, OCH_2Ph), 5.15 (2H, s, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 4.72 (1H, s, H-2); 3.88 (3H, s, OCH_3), 3.74 (2H, s, 9-CH_2); ^{13}C NMR (Plate 85b, 600 MHz, $CDCl_3$) δ 176.3, 157.5, 154.9, 152.4, 150.9, 137.2, 136.6, 136.0, 131.3, 131.0, 130.2, 128.8, 128.7, 128.6, 128.4, 127.9, 127.8, 127.6, 127.5, 127.3, 127.0, 126.9, 115.0, 110.2, 97.1, 71.5, 71.1, 70.1, 65.4, 61.6, 30.6. HRMS: calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2112.

6.18.3 *5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavanone* (4.158)



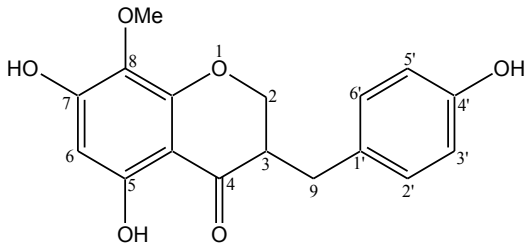
(**4.158**)

5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavone (**4.157**) (0.026 g, 0.044 mmol, 1 eq.) was dissolved in minimum THF (1 mL) and EtOH (6 mL). $NaBH_4$ (0.026 g, 0.687 mmol, 15.6 eq.) was added to the reaction mixture and stirred at rt for 24 h. Acetone (20 mL) was added to the mixture and stirred for 30 min. Standard work-up and the crude product (0.024 g, 0.041 mmol, 1 eq.) was dissolved in minimum dry acetonitrile (5 mL). IBX (0.023 g, 0.082 mmol, 2 eq.) was added to the reaction and refluxed for overnight. Standard work-up and PLC yield of *5,7,4'-tribenzyloxy-8-methoxyhomoisoflavanone* (**4.158**) 0.005 g (21%).

Colourless oil; R_f 0.28 (H:EA:DCM = 7:2:1); ^{1}H NMR (Plate 86a, 600 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 7.7 Hz, Ar-H), 7.46-7.44 (3H, m, Ar-H), 7.42-7.38 (7H, m, Ar-H), 7.37-7.31 (3H, m, Ar-H), 7.17 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.94 (2H, d, *J* = 8.5 Hz, H-3',5'), 6.21 (1H, s, H-6), 5.16 (2H, s, OCH_2Ph), 5.10 (2H, d, *J* = 3.2 Hz, OCH_2Ph), 5.07 (2H, s, OCH_2Ph), 4.38 [1H, dd, *J* =

11.4 and 4.1 Hz, H-2(a)], 4.23 [1H, dd, *J* = 11.4 and 7.4 Hz, H-2(b)], 3.83 (3H, s, OC<u>H</u>$_3$), 3.25 [1H, dd, *J* = 14.0 and 4.1 Hz, H-9(a)], 2.82-2.77 (1H, m, H-3), 2.67 [1H, dd, *J* = 14.0 and 11.0 Hz, H-9(b)]; ^{13}C NMR (Plate 86b, 600 MHz, $CDCl_3$) δ 191.4, 157.5, 157.4, 156.7, 156.5, 141.8, 137.1, 136.5, 136.1, 130.8, 130.2, 128.8, 128.6, 128.3, 128.0, 127.8, 127.5, 127.2, 126.7, 115.0, 106.6, 93.4, 70.9, 70.1, 69.2, 68.2, 61.2, 48.8, 31.9. HRMS: calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2264.

6.18.4 *5,7,4'-Trihydroxy-8-methoxyhomoisoflavanone* (4.159)

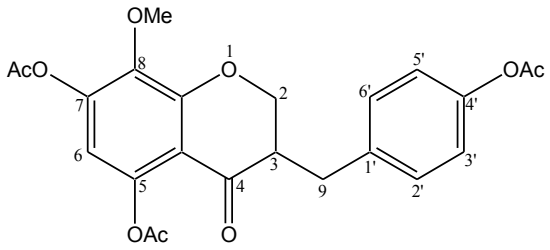


(**4.159**)

A mixture of 5,7,4'-tribenzyloxy-8-methoxyhomoisoflavanone (**4.158**) (0.007 g, 0.012 mmol, 1 eq.) in acetone (5 mL) was added $Pd(OH)_2$ (10 mg) and the reaction mixture was taken to hydrogenation with 1 bar atmospheric pressure. The reaction stopped after completion and the catalyst was filtered off and yield of *5,7,4'-trihydroxy-8-methoxyhomoisoflavanone* (**4.159**) 0.002 g (50%).

Yellow oil; R_f 0.20 (H:A = 7:3); ^{1}H NMR (Plate 87a, 600 MHz, Acetone) δ 7.14 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.82 (2H, d, *J* = 8.4 Hz, H-3',5'), 5.99 (1H, s, H-6), 4.24 [1H, dd, *J* = 11.4 and 4.4 Hz, H-2(a)], 4.20 [1H, dd, *J* = 11.4 and 8.1 Hz, H-2(b)], 3.73 (3H, s, OC<u>H</u>$_3$), 3.15 [1H, dd, *J* = 14.1 and 4.9 Hz, H-9(a)], 2.98-2.93 (1H, m, H-3), 2.72 [1H, dd, *J* = 14.1 and 10.0 Hz, H-9(b)]; ^{13}C NMR (Plate 87b, 600 MHz, Acetone) δ 198.18; 159.91; 159.49; 156.38; 154.30; 130.11; 128.82; 115.33; 102.06; 95.87; 69.39; 60.37; 46.43; 31.42. HRMS: calcd for $C_{17}H_{16}O_6$: 316.0847 g/mol. Found: *m/z* 316.0893.

6.18.5 *5,7,4'-Triacetoxy-8-methoxyhomoisoflavanone* (4.160)



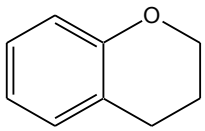
(**4.160**)

5,7,4'-Trihydroxy-8-methoxyhomoisoflavanone (**1.159**) (0.004 g, 0.013 mmol, 1 eq.) was added to a mixture of pyridine (0.5 mL) and acetic anhydride (1 mL). The reaction mixture was heated at 60 °C for overnight. Standard work-up and yield of *5,7,4'-triacetoxy-8-methoxyhomoiso-flavanone* (**4.160**) 0.002 g (33%).

Colourless oil; R_f 0.27 (H:A = 7:3); ^{1}H NMR (Plate 88a, 600 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8 Hz, H-2',6'), 7.06 (2H, d, *J* = 8 Hz, H-3',5'), 6.49 (1H, s, H-6), 4.47 [1H, dd, *J* = 12 and 4 Hz, H-2(a)], 4.27 [1H, dd, *J* = 12 and 9 Hz, H-2(b)], 3.85 (3H, s, OC$\underline{H}_3$), 3.28 [1H, dd, *J* = 14 and 4 Hz, H-9(a)], 2.92-2.85 (1H, m, H-3), 2.66 [1H, dd, *J* = 14 and 11 Hz, H-9(b)], 2.40 (3H, s, COC$\underline{H}_3$), 2.35 (3H, s, COC$\underline{H}_3$), 2.32 (3H, s, COC$\underline{H}_3$); ^{13}C NMR (Plate 88b, 600 MHz, $CDCl_3$) δ 190.9, 169.6, 168.0, 156.4, 149.5, 148.6, 145.7, 138.9, 135.4, 130.0, 121.9, 112.5, 111.0, 69.5, 61.0, 47.8, 31.5, 21.2, 21.0, 20.7. HRMS: calcd for $C_{23}H_{22}O_9Na$: 465.1164 g/mol. Found: *m/z* 465.1146.

6.19 Synthesis of compounds for modelling analysis

6.19.1 3,4-Dihydro-2*H*-chromen (chroman)[39]



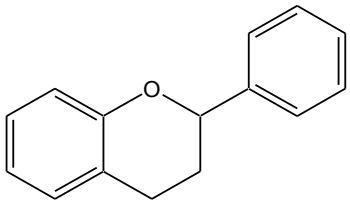
(**5.2**)

A mixture 4-chromanone (**5.73**) (1.000 g, 6.75 mmol, 1 eq.) in EtOH (50 mL) was added $Pd(OH)_2/C$ (0.3 g) and the reaction mixture was taken to hydrogenation with 1 bar atmospheric pressure. The reaction stopped after 4 hours. The catalyst was filtered off through filtered paper and yield of chroman (**5.2**) 0.79 g (87%).

Colourless liquid; R_f 0.68 (H:EA=8.5:1.5); ^{1}H NMR (Plate 89a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.17 (1H, ddd, *J* = 8, 8 and 1 Hz, Ar-H), 7.12 (1H, dd, *J* = 8 and 1 Hz, Ar-H), 6.92-6.88 (2H, m, Ar-H), 4.26 (2H, t, *J* = 5 Hz, 2-CH_2), 2.86 (2H, t, *J* = 6 Hz, 4-CH_2), 2.10-2.06 (2H, m, 3-CH_2). ^{13}C NMR (Plate 89b, 600 MHz, $CDCl_3$) δ_C (ppm): 155.0, 129.9, 127.3, 122.3, 120.2, 116.8, 66.5, 25.0, 22.5.

[39] Van Tonder, J.H. STUDIES DIRECTED AT THE STEREOSELECTIVE SYNTHESIS OF FLAVONOIDS THROUGH THE HYDROGENATION OF PROCHIRAL PRECURSORS, *MSc*. thesis, University of the Free State, Bloemfontein, S.A., **2008**, p101.

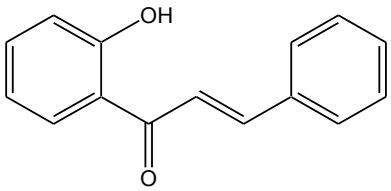
6.19.2 2-Phenylchromane (flavan)[39]



(**5.3**)

Compound 2-phenylchromane (**5.3**) was contributed by J.H. van Tonder. ^{1}H NMR (Plate 90a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.48-7.36 (5H, m, Ar-H), 7.19-7.13 (2H, m, Ar-H), 6.98-6.92 (2H, m, Ar-H), 5.12 (1H, dd, *J* = 10.0 and 2.5 Hz, H-2), 3.05 [1H, ddd, *J* = 6.0, 11.0 and 16.5 Hz, H-4(a)], 2.85 [1H, ddd, *J* = 3.6, 4.7 and 16.5 Hz, H-4(b)], 2.28-2.24 [(1H, m, H-3(a)], 2.18-2.11 [(1H, m, H-3(b)]. ^{13}C NMR (Plate 90b, 600 MHz, $CDCl_3$) δ_C (ppm): 155.2, 141.8, 129.6, 128.6, 127.9, 127.4, 126.0, 121.9, 120.4, 117.0, 77.8, 30.0, 25.1.

6.19.3 2'-Hydroxychalcone (5.74)[40]



(**5.74**)

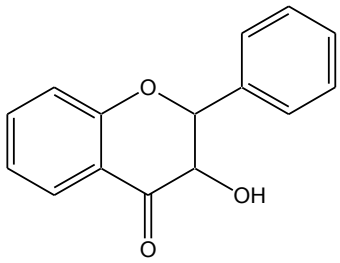
2-Hydroxyacetophenone (**4.67**) (2 g, 14.69 mmol, 1 eq.) and benzaldehyde (**5.79**) (1.87 mL, 17.63 mmol, 1.2 eq.) were dissolved in EtOH (40 mL) and stirring at 0 ^{o}C. Freshly powder KOH (4.94 g, 44.07 mmol, 6 eq.) was added and stirred at rt overnight. Water (50 mL) was added and the reaction mixture was neutralized with 3 M HCl (1 mL). The residue was extracted with EA (3 x 50 mL) and the organic layers were combined, washed with brine (30 mL), dried (Na_2SO_4)

[40] March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, 3rd edition; John Wiley and Sons, **1985**, 832.

and evaporated under reduced pressure. Purification by PLC yield of 2'-hydroxychalcone (**5.74**) 1.138 g (35%).

Yellow solid; R_f 0.61 (H:EA = 9.5:0.5,); ^{1}H NMR (Plate 91a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.96-7.94 (2H, m, H-β, Ar-H), 7.71-7.68 (3H, m, H-α, Ar-H), 7.53 (1H, t, *J* = 8.5 Hz, Ar-H), 7.47-7.46 (3H, m, Ar-H), 7.06 (1H, d, *J* = 8.4 Hz, Ar-H), 6.98 (1H, t, *J* = 8.1 Hz, Ar-H). ^{13}C NMR (Plate 91b, 600 MHz, $CDCl_3$) δ_C (ppm): 193.8, 163.6, 145.5, 136.5, 134.6, 131.0, 129.7, 129.1, 128.7, 120.1, 120.0, 118.9, 118.7.

6.19.4 Dihydroflavonol (5.75)[41]



(**5.75**)

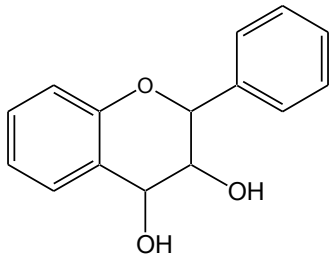
To a solution of 2'-hydroxychalcone (**5.74**) (0.40 g, 1.784 mmol, 1 eq.) in 1,4-dioxane (15 mL) at 0 ^oC was added diethylamine (0.66 g, 8.919 mmol, 5 eq.) and 30% H_2O_2 (15 mL) over 20 min. The reaction mixture left in refrigerator for 24 hour and then stirred at rt. After completion of the reaction, ice water (10 mL) was added and the products extracted with EA (3 x 20 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by PLC yield dihydroflavonol (**5.75**) 0.185 g (43%).

Light yellow needlelike crystals; R_f 0.32 (H:EA = 8:2); ^{1}H NMR (Plate 92a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.95 (1H, dd, *J* = 8 and 1 Hz, H-5), 7.61 (2H, d, *J* = 8 Hz, H-2',6'), 7.58 (1H, dt, *J* = 9 and 2 Hz, H-6), 7.51-7.45 (3H, m, H-3',5',4'), 7.14 (1H, t, *J* = 8 Hz, H-7), 7.07 (1H, d, *J* = 8 Hz, H-8), 5.16 (1H, d, *J* = 12 Hz, H-3), 4.66 (1H, d, *J* = 12 Hz, H-2), 3.70 (1H, s, OH). ^{13}C NMR

[41] Van Rensburg, H.; van Heerden, P.S.; Ferreira, D. *J. Chem. Soc., Perkins Trans. I* **1997**, 3415.

(Plate 92b, 600 MHz, $CDCl_3$) δ_C (ppm): 194.3, 161.7, 137.0, 136.3, 129.4, 128.8, 127.6, 127.4, 122.2, 118.5, 118.2, 83.9, 73.6.

6.19.5 Flavan-3,4-diol (5.76)[42]



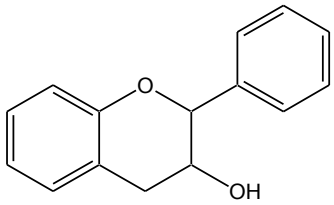
(**5.76**)

Dihydroflavonol (**5.75**) (0.021 g, 0.0874 mmol, 1 eq.) was dissolved in EtOH (5 mL). $NaBH_4$ (0.0078 g, 0.206 mmol, 2.36 eq.) was added to the reaction mixture and stirred at rt. After completion acetone (10 mL) was added to the mixture and evaporated off. The solution was extracted into Et_2O (3 x 10 mL), washed with H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. Purification by PLC yield flavan-3,4-diol (**5.76**) 0.006 g (29%).

Yellow needlelike crystals; R_f 0.32 (H:EA:A = 9:0.5:0.5); ^{1}H NMR (Plate 93a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.56 (1H, d, *J* = 7.7 Hz, H-5), 7.53-7.51 (2H, m, Ar-H), 7.48-7.45 (2H, m, Ar-H), 7.44-7.41 (1H, m, Ar-H), 7.24 (1H, t, *J* = 8.3 Hz, H-6), 7.05 (1H, t, *J* = 8.3 Hz, H-7), 6.90 (1H, d, *J* = 8.3 Hz, H-8), 4.93 (1H, d, *J* = 8.4 Hz, H-2), 4.88 (1H, d, *J* = 9.9 Hz, H-4), 3.93 (1H, dd, *J* = 8.4 and 9.9 Hz, H-3). ^{13}C NMR (Plate 93b, 600 MHz, $CDCl_3$) δ_C (ppm): 153.7, 137.0, 129.3, 129.2, 128.9, 127.7, 127.4, 123.5, 121.6, 116.3, 80.6, 74.1, 71.5.

[42] Elphimoff-Felkin, Sarda, P. *Org*. *Synth*. **1988**, *Coll*. *Vol*. *6*, 769.

6.19.6 Flavan-3-ol (5.4)[43]



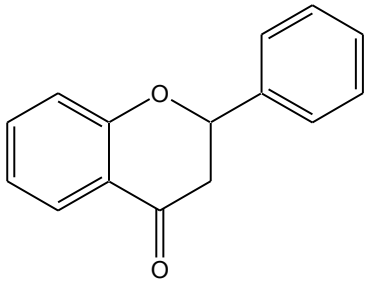
(**5.4**)

A mixture of flavan-3,4-diol (**5.76**) (0.050 g, 0.206 mmol, 1 eq.) in EtOH (10 mL) was added 5% Pd/C (0.10 g) with a few drops of conc. H_2SO_4 and the reaction mixture was taken to hydrogenation with 1 bar atmospheric pressure. The reaction stopped after completion. The catalyst was filtered off through filtered paper and yield flavan-3-ol (**5.4**) 0.017 g (50%).

Whie solid; R_f 0.15 (H:A=7:3); ^{1}H NMR (Plate 94a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.48-7.40 (5H, m, Ar-H), 7.18 (1H, t, *J* = 7.4 and 7.8 Hz, H-7), 7.14 (1H, d, *J* = 7.4 Hz, H-5), 6.95 (2H, t, *J* = 7.8 and 7.4 Hz, H-6,8), 4.84 (1H, d, *J* = 7.9 Hz, H-2), 4.17-7.13 (1H, m, H-3), 3.11 [1H, dd, *J* = 5.3 and 16.0 Hz, H-4(a)], 2.95 [1H, dd, *J* = 8.9 and 16.0 Hz, H-4(b)]. ^{13}C NMR (Plate 94b, 600 MHz, $CDCl_3$) δ_C (ppm): 154.1, 138.1, 130.0, 128.9, 128.7, 127.8, 127.2, 121.1, 120.1, 116.5, 81.9, 68.2, 32.8.

43 Grotewold, E. (2006). *The Science of Flavonoids*. New York, NY: Springer.

6.19.7 Flavanone (5.77)[44]



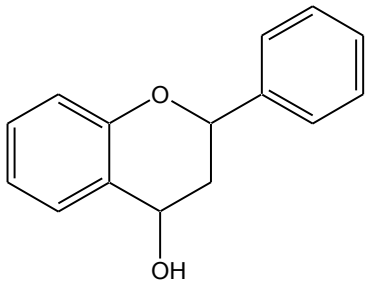
(**5.77**)

To a solution of 2'-hydroxychalcone (**5.74**) (0.40 g, 1.784 mmol, 1 eq.) in 1,4-dioxane (15 mL) at 0 ^{o}C was added diethylamine (0.66 g, 8.919 mmol, 5 eq.) and 30% H_2O_2 (15 mL) over 20 min. The reaction mixture left in refrigerator for 24 hour and then stirred at rt. After completion of the reaction, ice water (10 mL) was added and the products extracted with EA (3 x 20 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by PLC yield flavanone (**5.77**) 0.112 g (38%).

Light yellow solid; R_f 0.32 (H:EA = 8:2); ^{1}H NMR (Plate 95a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.96 (1H, dd, *J* = 8.1 and 1.8 Hz, H-5), 7.55-7.45 (5H, m, Ar-H), 7.43-7.40 (1H, m, H-7), 7.10-7.07 (2H, m, H-6,8), 5.52 (1H, dd, *J* = 13.5 and 2.8 Hz, H-2), 3.12 [1H, dd, *J* = 13.5 and 16.9 Hz, H-3(a)], 2.93 [1H, dd, *J* = 2.8 and 16.9 Hz, H-3(b)]. ^{13}C NMR (Plate 95b, 600 MHz, $CDCl_3$) δ_C (ppm): 192.1, 161.6, 138.7, 136.3, 128.9, 128.8, 127.1, 126.2, 121.7, 120.9, 118.2, 79.6, 44.7.

44 Van Tonder, J.H. STUDIES DIRECTED AT THE STEREOSELECTIVE SYNTHESIS OF FLAVONOIDS THROUGH THE HYDROGENATION OF PROCHIRAL PRECURSORS, *MSc*. thesis, University of the Free State, Bloemfontein, S.A., **2008**, p16.

6.19.8 Flavan-4-ol (5.78)[39]

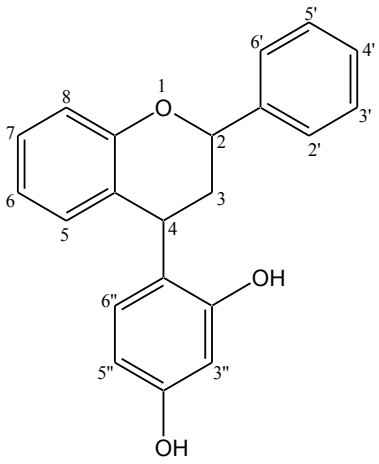


(**5.78**)

Flavanone (**5.77**) (0.352 g, 1.57 mmol, 1 eq.) was dissolved in EtOH (14 mL). $NaBH_4$ (0.178 g, 4.71 mmol, 3 eq.) was added to the reaction mixture and stirred at rt. After completion acetone (10 mL) was added to the mixture and evaporated off. The solution was extracted into EA (3 x 10 mL), washed with H_2O (20 mL) and dried over $MgSO_4$. Purification by PLC yield flavan-4-ol (**5.78**) 0.225 g (63%).

White solid; R_f 0.22 (H:EA = 8:2); ^{1}H NMR (Plate 96a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.55 (1H, d, *J* = 7.6 Hz, H-5), 7.48-7.37 (5H, m, Ar-H), 7.24 (1H, t, *J* = 7.3 Hz, H-7), 7.02 (1H, t, *J* = 7.3 Hz, H-6), 6.93 (1H, d, *J* = 8.2 Hz, H-8), 5.21 (1H, d, *J* = 10.5 Hz, H-2), 5.14-5.10 (1H, m, H-4), 2.56-2.52 [1H, m, H-3(a)], 2.20-2.14 [1H, m, H-3(b)], 1.90 (1H, d, *J* = 7.9 Hz, OH). ^{13}C NMR (Plate 96b, 600 MHz, $CDCl_3$) δ_C (ppm): 154.5, 140.5, 129.2, 128.7, 128.3, 127.0, 126.1, 125.7, 121.0, 116.8, 65.9, 40.1.

6.19.9 4-Aryl-2-phenylchromane (4-arylflavan)[45]



(**5.5**)

A mixture of flavan-4-ol (**5.78**) (0.050 g, 0.22 mmol, 1 eq.) and resorcinol (0.04 g, 0.33 mmol, 1.5 eq.) in CF_3CH_2OH (3 mL) was stirred at rt. *p*-TSA (0.063 g, 0.33 mmol, 1.5 eq.) was added to the reaction mixture. The reaction stopped after completion. Purification by PLC yield 4-arylflavan (**5.5**) 0.030 g (43%).

Red oil; R_f 0.44 (T:EA:A=7:2:1); ^{1}H NMR (Plate 97a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.49 (1H, d, *J* = 7.3 Hz, H-5), 7.37-7.32 (3H, m, Ar-H), 7.29 (1H, m, Ar-H), 7.20 (1H, m, Ar-H), 7.03-7.01 (2H, m, H-7,8), 6.89 (1H, t, *J* = 7.3 Hz, H-6), 6.58 (1H, d, *J* = 8.3 Hz, H-6"), 6.42 (1H, d, *J* = 2.4 Hz, H-3"), 6.29 (1H, dd, *J* = 2.4 and 8.3 Hz, H-5"), 5.01 (1H, dd, *J* = 3.0 and 10.2 Hz, H-2), 4.51-4.50 (1H, m, H-4), 2.38-2.30 (2H, m, 2 x H-3). ^{13}C NMR (Plate 97b, 600 MHz, $CDCl_3$) δ_C (ppm): 155.8, 155.5, 154.4, 141.6, 131.5, 130.8, 128.5, 128.4, 127.8, 127.7, 126.3, 126.2, 124.6, 123.6, 120.5, 116.9, 106.7, 102.8, 73.7, 36.0.

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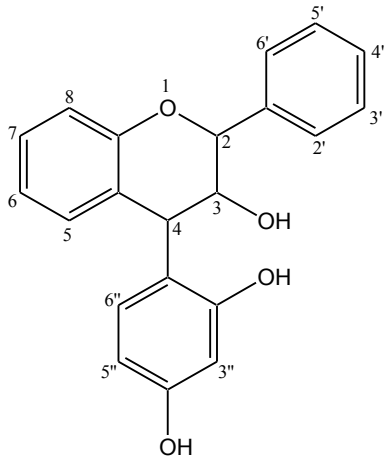
45 Kuo, C.-M. STRUCTURE AND SYNTHESIS OF A NOVEL HOMOISOFLAVANONE FROM *SCILLA NATALENSIS* AND SYNTHESIS OF SELECTED PROCYANIDINS THROUGH THE C-4 FUNCTIONALIZATION OF FLAVAN-3-OLS, *MSc*. thesis, University of the Free State, Bloemfontein, S.A., **2008**, page122.

6.19.10 4-Aryl-2-phenylchromane-3-ol (4-arylflavan-3-ol)[45]



(**5.6**)

A mixture of flavan-3,4-diol (**5.76**) (0.050 g, 0.206 mmol, 1 eq.) and resorcinol (0.027 g, 0.247 mmol, 1.2 eq.) in CF_3CH_2OH (3 mL) was stirred at rt. *p*-TSA (0.059 g, 0.310 mmol, 1.5 eq.) was added to the reaction mixture. The reaction stopped after completion. Purification by PLC yield 4-arylflavan-3-ol (**5.6**) 0.029 g (42%).

Brown oil; R_f 0.24 (T:A=8:2); ^{1}H NMR (Plate 98a, 600 MHz, $CDCl_3$) δ_H (ppm): 7.38-7.29 (5H, m, Ar-H), 7.25-7.22 (1H, m, H-7), 7.01 (1H, d, *J* = 8.3 Hz, H-5), 6.93-6.90 (2H, m, H-6,8), 6.48 (1H, d, *J* = 8.4 Hz, H-6"), 6.39 - 6.37 (1H, br s, H-3"), 6.30 (1H, dd, *J* = 8.4 and 2.1 Hz, H-5"), 4.93 (1H, d, *J* = 8.3 Hz, H-2), 4.53 - 4.51 (1H, br s, H-4), 4.38 (1H, dd, *J* = 4.8 and 8.3 Hz, H-3). ^{13}C NMR (Plate 98b, 600 MHz, $CDCl_3$) δ_C (ppm): 156.2, 155.8, 154.3, 137.8, 133.1, 130.5, 128.8, 128.7, 128.6, 127.9, 127.3, 122.1, 121.3, 119.9, 116.3, 108.1, 104.7, 72.7, 41.0, 29.1.

6.20 Experimental of modelling analysis

Density functional theory (DFT) calculations were performed using the B3LYP/6-31G(d,p)[46] functional and basis set (6-31G**) as implemented in the GAUSSIAN 03 package.[47] The global and local minimum structures of oxane are determined by constructing a potential energy surface (PES) as a function of the dihedral angles O1C2C3C4 and O1C6C5C4. In this way the energy of all different (unsymmetrical) conformations of oxane was calculated. No symmetry limitations were imposed during these calculations. Additionally the energy of oxane in C_s symmetry as a function of dihedral O1C2C3C4 = O1C6C5C4 was calculated. All minimum structures were confirmed by a frequency analysis.

The accuracy of the global minimum geometry obtained was evaluated by comparing the geometrical parameters with the optimized molecular structure and selected crystal structures.[48] Accurate geometries generally refer to bond lengths that are within about 0.01 to 0.02 Å of experiment and bond and dihedral angles that are within 1° to 2° of the experimentally measured value.[49]

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46 (a) Becke, A.D. *Phys*. *Rev*. *A* **1988**, *38*, 3098; (b) Lee, C.; Yang, W.; Parr, R.G. *Phys*. *Rev*. *B* **1988**, *37*, 785.

47 Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr. T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

48 Cambridge Structural Database (CSD), version 5.31, August 2011 update.

49 Foresman, J.B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*; Gaussian, Inc.: Pittsburgh, **1996**.

In the case of flavan-3-ol, it contains two stereogenic centres at C2 and C3 which according to the law of stereochemistry, n stereogenic centres = 2^n possible stereoisomers provided there are non-equivalent stereocenters thus, flavan-3-ol will have a maximum of four stereoisomers. The PES energy of four stereoisomers was calculated. However, 4-arylflavan has two stereogenic centres at C2 and C4 which have four stereoisomers and the PES energy of which was determined. All minimum structures were confirmed by a frequency analysis.

Theoretically calculated *ab initio* harmonic vibrational frequencies are typically larger than the fundamental frequencies observed experimentally[50] and thus have to be scaled according to the method and basis set used. The overestimation of *ab initio* harmonic vibrational frequencies is, however, found to be relatively uniform and as a result generic frequency scaling factors are often applied. Good overall agreement between the scaled theoretical harmonic frequencies and the unharmonic experimental frequencies can then usually be obtained. The determination of appropriate scale factors for estimating experimental fundamental frequencies from theoretical harmonic frequencies has received considerable attention in the literature.[51,52] The scaling factor for B3LYP/6-31G(d,p) as obtained from the Computational Chemistry Comparison and Benchmark Data Base is 0.961.[53] The combined spectrum of the two conformations of flavan was obtained by adding the separate spectra together in the ratio of their relative population as determined by the Boltzmann equation.

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50 Hehre, W.J.; Radom, P.L.; Schleyer, V.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, **1986**.

51 Scott, A.P.; Radom, L. *J. Phys. Chem.* **1996**, *100,* 16502.

52 Merrick, J.P.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007**, *111,* 11683.

53 NIST Computational Chemistry Comparison and Benchmark Database, NIST Standard Reference Database Number 101, Release 15b, August 2011, Editor: Russell D. Johnson III, http://cccbdb.nist.gov/

SUMMARY

Summary

This work contains two parts of study: Synthesis of a series of homoisoflavonoid analogues in order to investigate a difference between 6- and 8- homoisoflavanone which isolated from *Scilla Natalensis* and Part II contains conformational analysis of C-ring substituted flavans and analogues.

While the novel homoisoflavanone isolated from *Scilla natalensis* as the peracetate has unambiguously been proven by synthesis to have the 5,7,4'-triacetoxy-8-methoxy structure during this investigation. The control of the substituents (protecting groups) is determined the A-ring of a homoisoflavanone which has also been pointed out that great care should be taken in the assignment of the structures of these compound by comparison of proton chemical shifts. This is especially true when a single methoxy group is situated on a trioxygenated A-ring as there might not be an nOe association between the methyl protons and any aromatic hydrogen. The situation may further be aggravated by the fact that natural products may be isolated as derivatives, like peracetates, of the naturally occurring free phenolic analogues due to separation difficulties.

Although only two of the possible 6 A-ring trioxygenated homoisoflavanones have been synthesised e.g. 5,7,4'-trihydroxy-6-methoxyhomoisoflavanone and 5,7,4'-trihydroxy-8-methoxyhomoisoflavanone, it is envisaged that the remaining four compounds will also be prepared so the ^{1}H and ^{13}C NMR data of all these compounds both as free phenols and peracetates can be reported. This will be a valuable tool to assist researchers during the isolation and structure elucidation of this class of natural product during future phytochemical investigations.

In an effort to divulge the effect of the individual stereocenters form each other, and thus the combined effet obtained by ECD, it was decided to investigate the chromophore based method of VCD as measurement of absolute configuration at the different stereogenic centres. If a correlation between the IR absorption band(s) at certain wave numbers and a specific chromophore in a molecule could be established, it should, in principle, be possible to define the absolute comfiguration at that point in the molecule by VCD. In order to find a possible relationship between chromophores and IR absorption bands in flavonoids and related molecules,

a molecular modelling study to determine the preferred conformation of the heterocyclic ring of these compounds as well as establish a possible correlation between the chromophore present in the molecule and IR band(s) was embarked upon. In this regard, the preferred conformation(s) of the series of heterocyclic molecules with increasing order of complexity, i.e. no substituent to three heterocyclic substituents, were determined and correlated with the respective modelled IR frequencies as well as the experimental absorption bands in the IR spectrum.

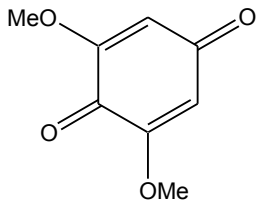
In this study a complete conformational surface of oxane, chromane, flavan, flavan-3-ols, 4-arylflavan and 4-arylflavan-3-ols is presented to give the global and local minima which reulted in finding the most stable conformations. However, the most stable conformations for these compounds are the chair, 2,5-twisted boat and 1,4-twisted boat (oxane); half chair (chromane); [(2*R*)-*equatorial* and (2*S*)-*equatorial* (flavan)]; [(2*S*)-*equatorial*, (3*S*)-*axial* and (2*S*)-*equatorial*, (3*R*)-*equatorial* (flavan-3-ol)]; [(2*S*)-*equatorial*, (4*R*)-*axial* and (2*S*)-*equatorial*, (4*S*)-*equatorial* (4-arylflavan)] and {[(2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial*], [(2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial*], [(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial*] and [(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial*] (4-arylflavan-3-ols)}. The assignment of IR absorption from theoretical spectra is presented and the excellent match between theoretical and experimental IR analysis is achieved. It's evidently concluded that the method of using TDDFT calculations together with infrared spectroscopy to determine the most stable or preferred conformation was achieved for flavonoid compounds. The determining of absolute configuration at a chiral centre in selected flavonoid compounds and understanding of its IR spectra is currently under investigation with the same approach.

The calculated VCD spectrums of the highest populated conformations are presented e.g. [(2*R*)-*equatorial* (flavan)]; [(2*S*)-*equatorial*, (3*S*)-*axial* and (2*S*)-*equatorial*, (3*R*)-*equatorial* (flavan-3-ol)]; [(2*S*)-*equatorial*, (4*R*)-*axial* and (2*S*)-*equatorial*, (4*S*)-*equatorial* (4-arylflavan)] and {[(2*S*)-*axial*, (3*S*)-*equatorial*, (4*R*)-*axial*], [(2*S*)-*axial*, (3*S*)-*equatorial*, (4*S*)-*equatorial*], [(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*R*)-*equatorial*] and [(2*S*)-*equatorial*, (3*R*)-*equatorial*, (4*S*)-*axial*] (4-arylflavan-3-ols)} were also achieved successfully.

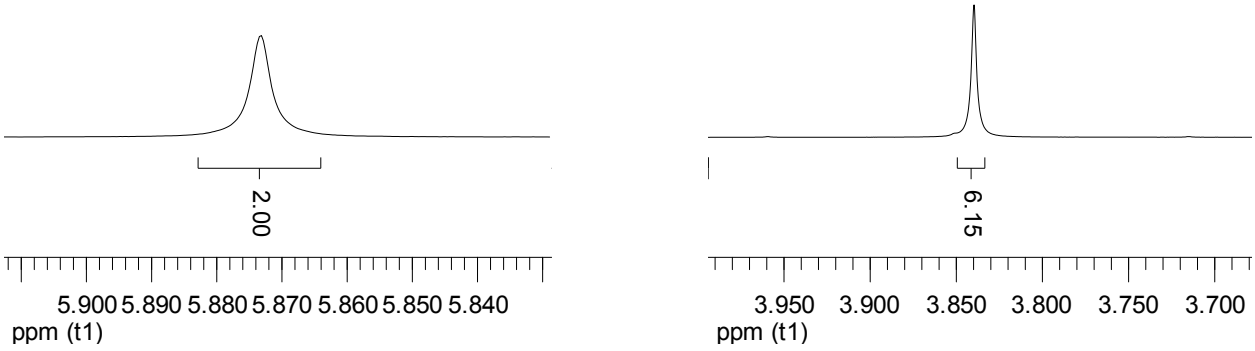
APPENDIX A

NMR SPECTRA

Plate 1a: ^{1}H NMR of 2,6-Dimethoxy-1,4-benzoquinone, $CDCl_3$ (298 K)



(**4.15**)



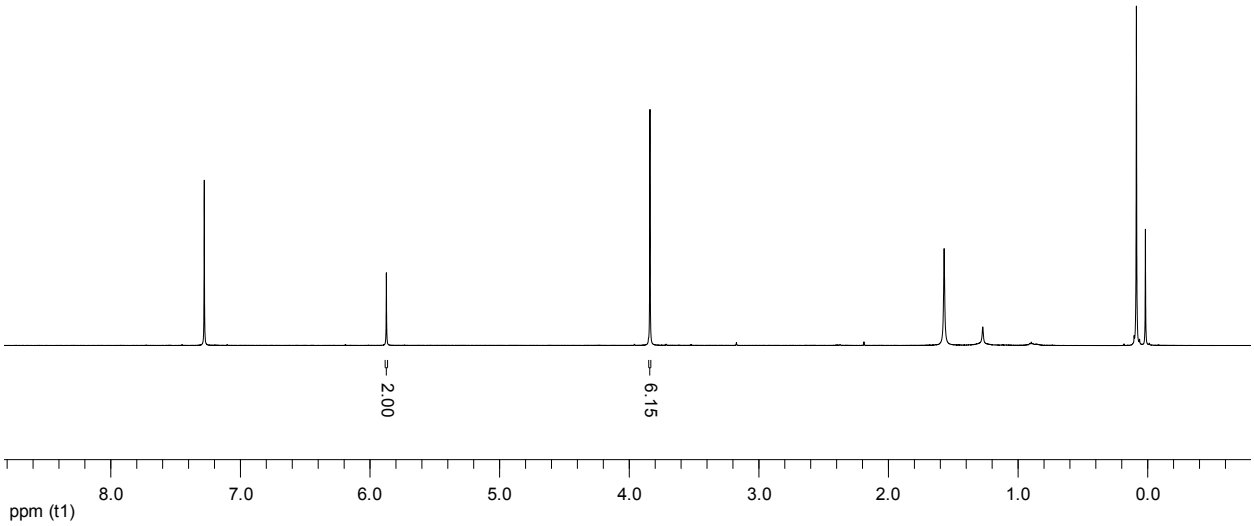
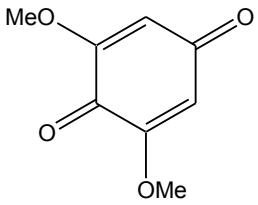


Plate 1b: ^{13}C NMR of 2,6-Dimethoxy-1,4-benzoquinone, $CDCl_3$ (298 K)



(**4.15**)

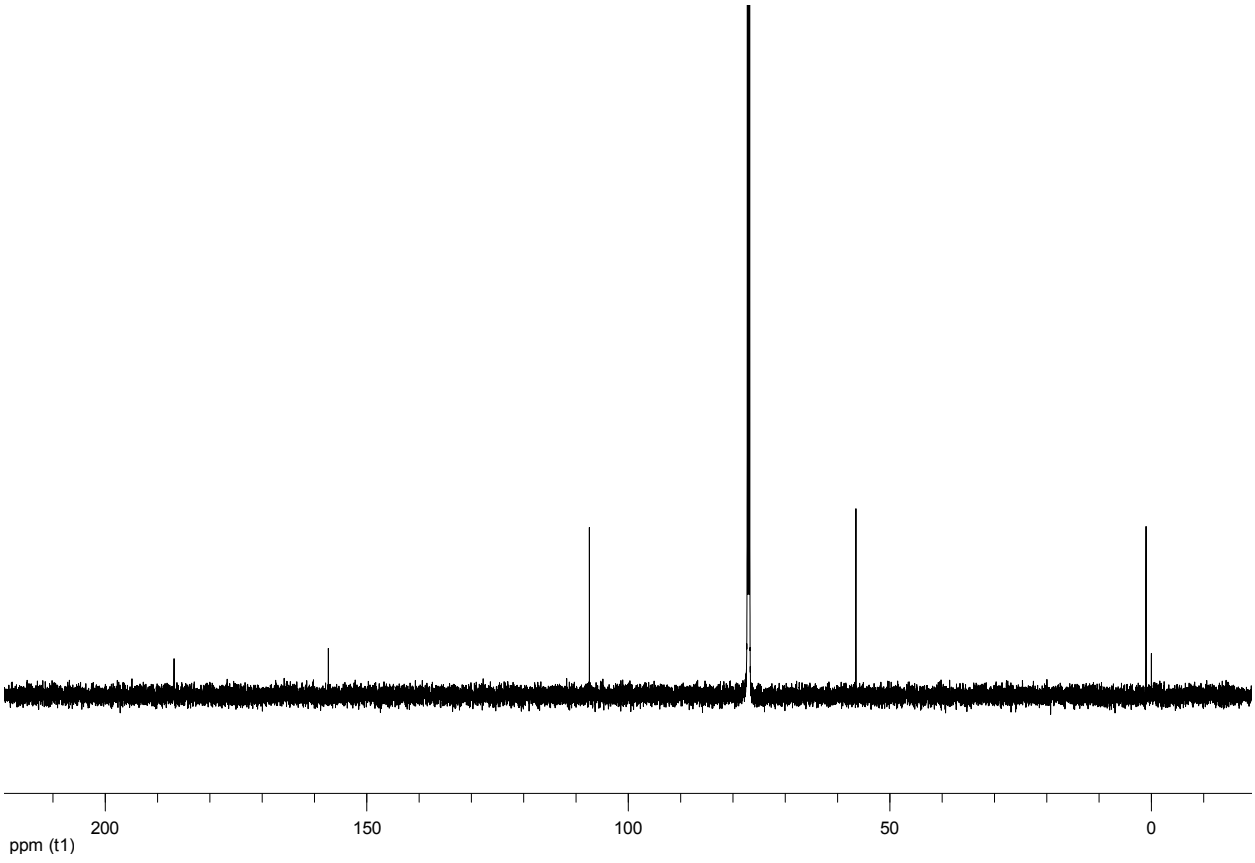
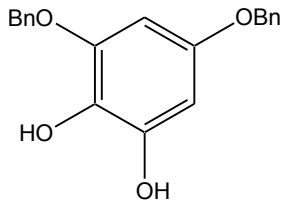
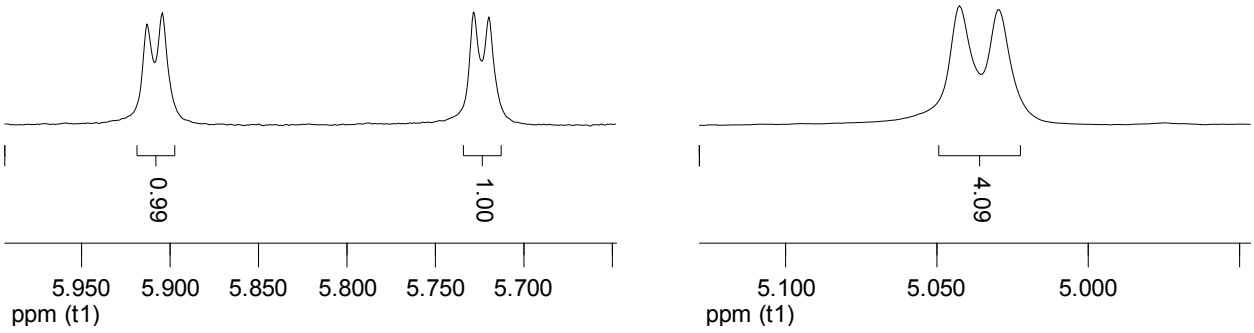


Plate 2: ^{1}H NMR of 3,5-Dibenzyloxycatechol, $CDCl_3$ (298 K)



(**4.23**)



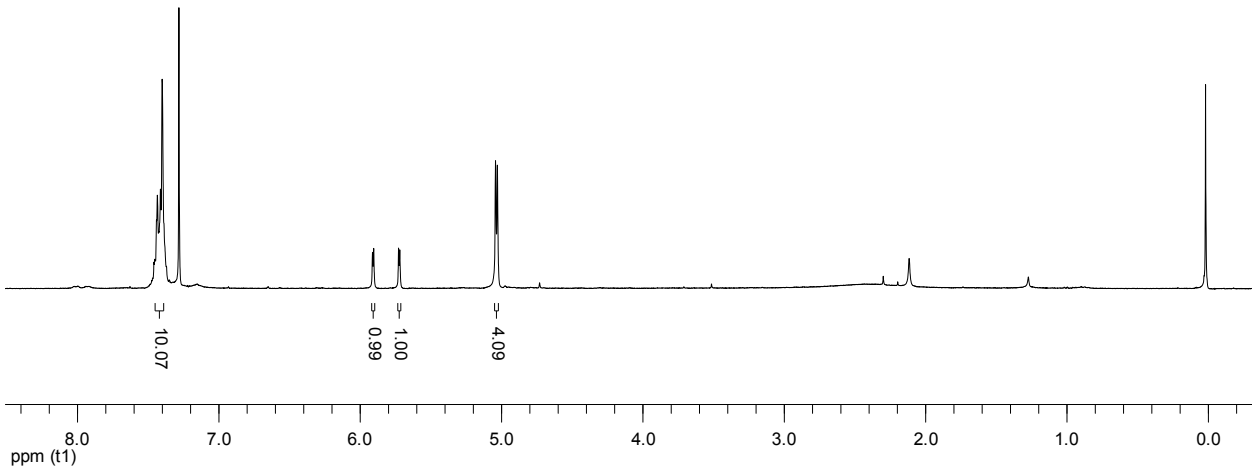
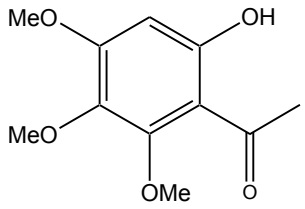


Plate 3: ^{1}H NMR of 2-Hydroxy-4,5,6-trimethoxyacetophenone, $CDCl_3$ (298 K)



(**4.27**)

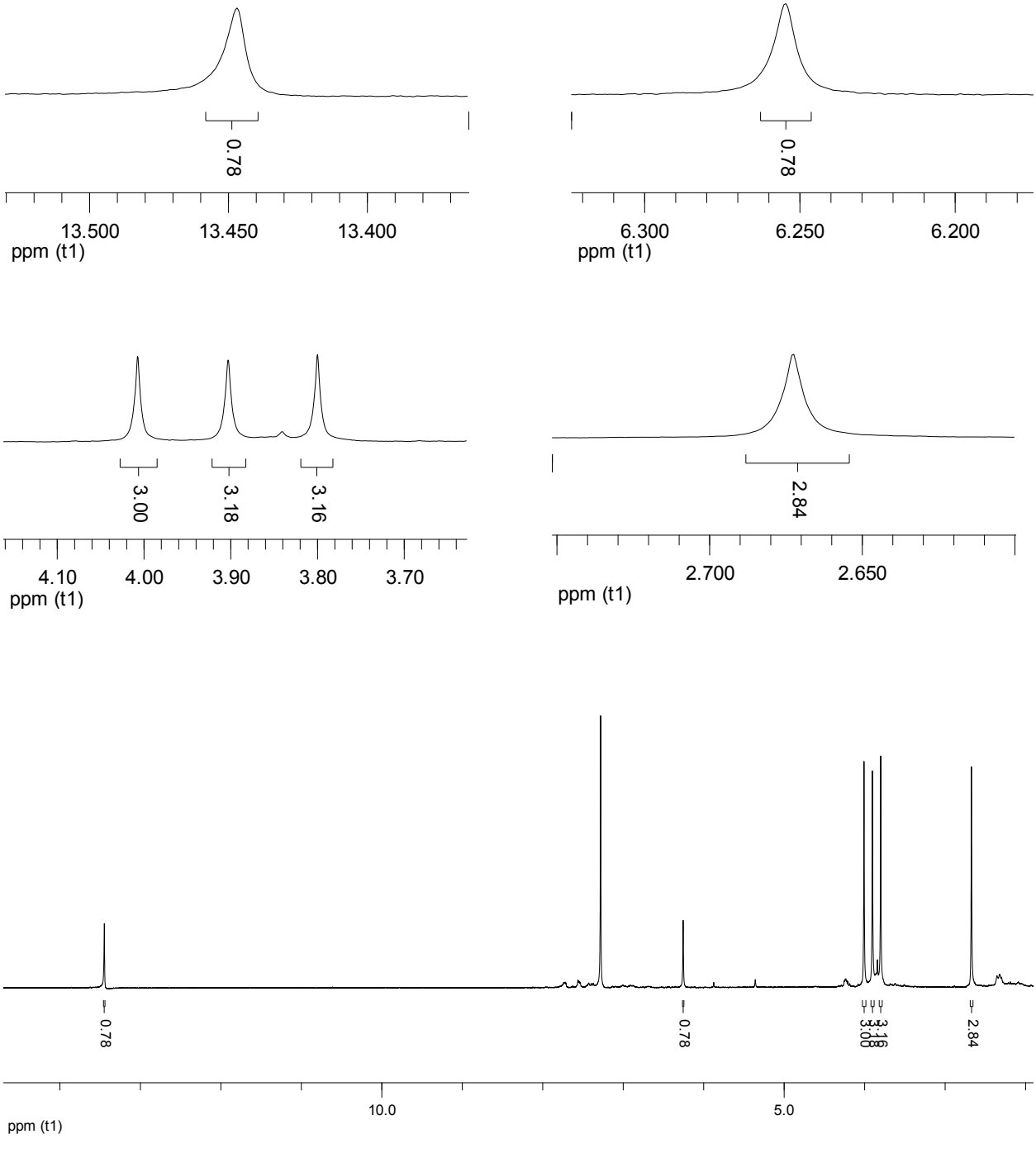
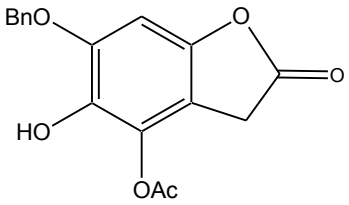


Plate 4: ^{1}H NMR of 4-Acetoxy-6-benzyloxy-5-hydroxy-2,3-dihydrobenzofuran-2-one, $CDCl_3$ (298 K)



(**4.29**)

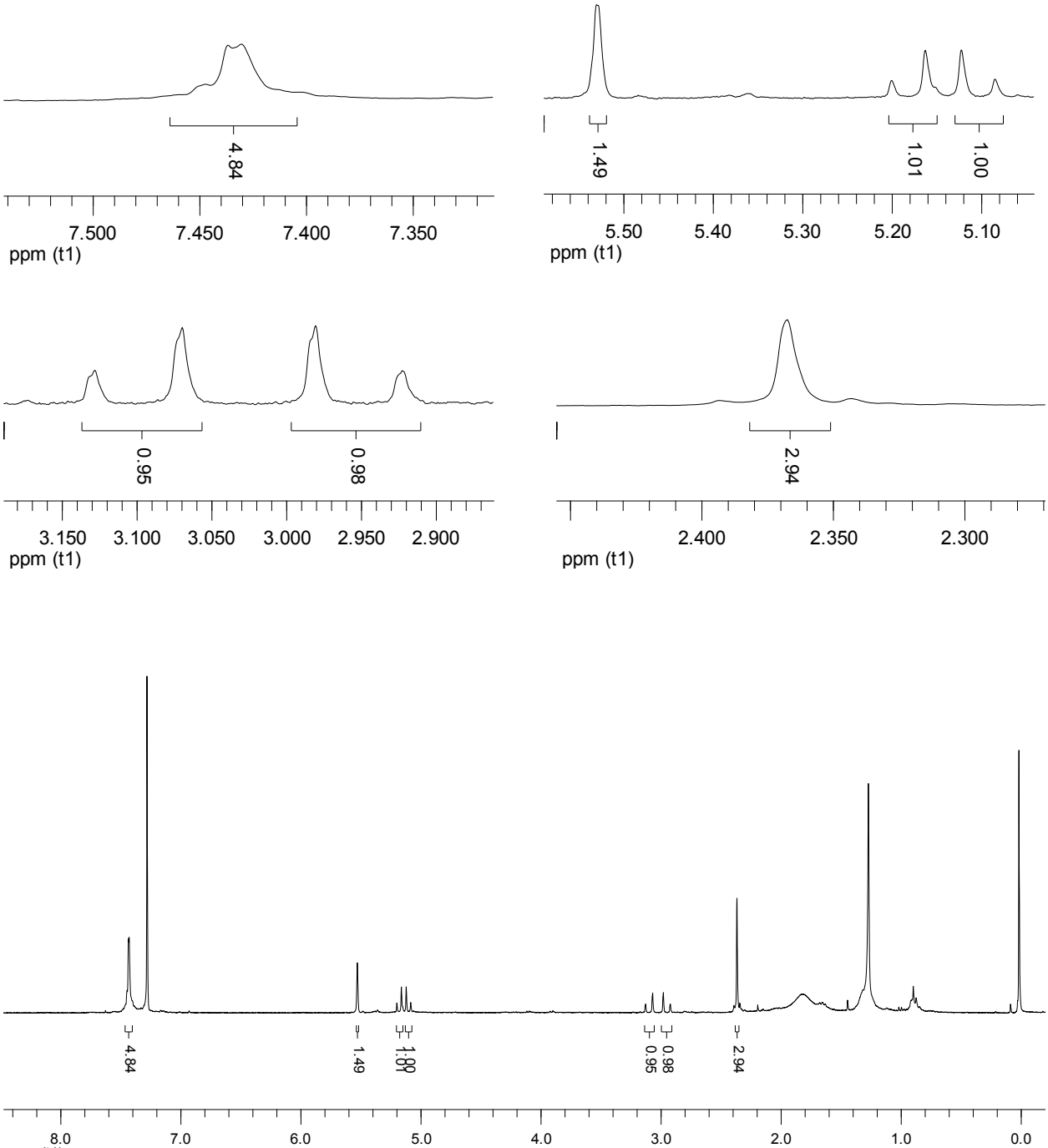
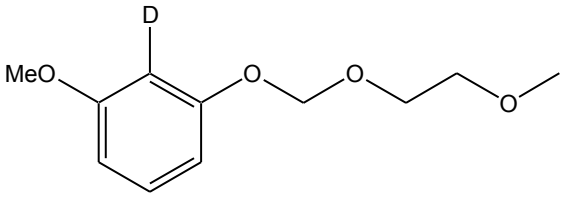
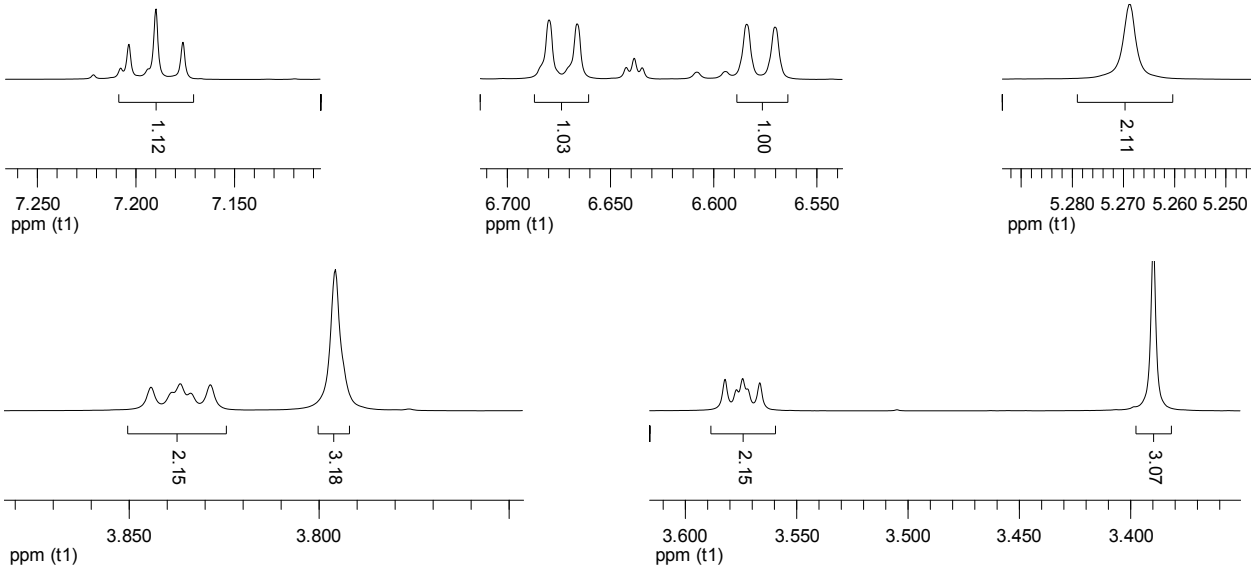


Plate 5a: ^{1}H NMR of 1-Methoxy-3-[(2-methoxyethoxy)methoxy](2-^{2}H)benzene, $CDCl_3$ (298 K)



(**4.39**)



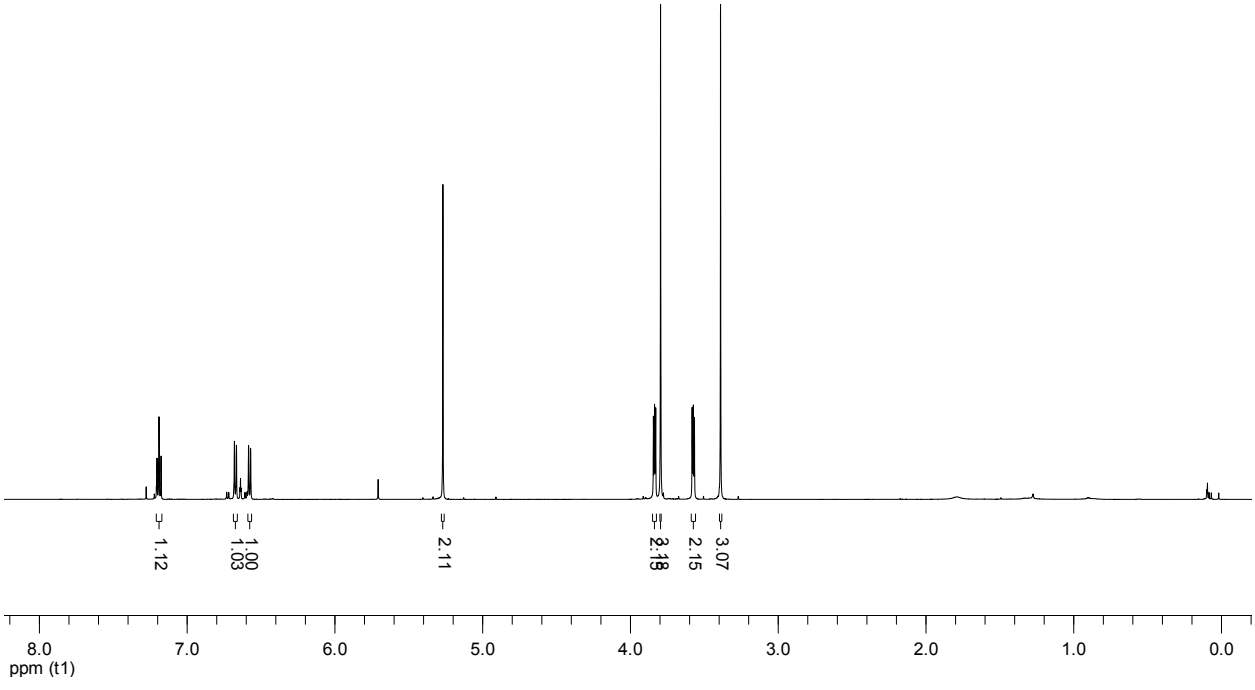
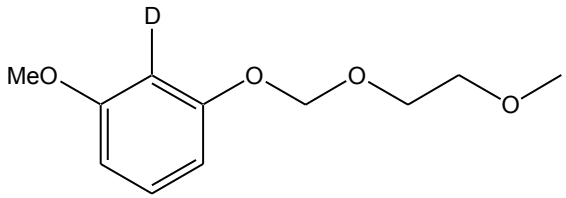


Plate 5b: ^{13}C NMR of 1-Methoxy-3-[(2-methoxyethoxy)methoxy](2-^{2}H)benzene, $CDCl_3$ (298 K)



(**4.39**)

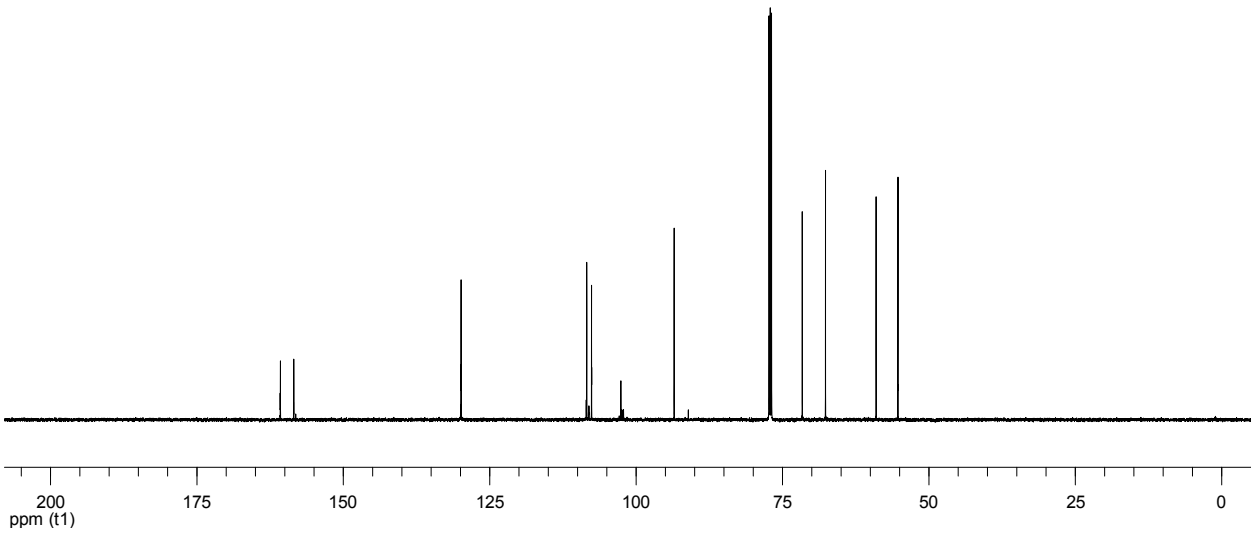
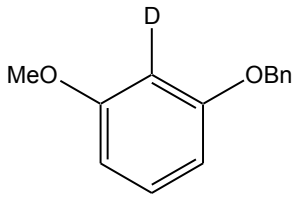


Plate 6a: ^{1}H NMR of 1-Benzyloxy-3-methoxy-2-(^{2}H)benzene, $CDCl_3$ (298 K)



(**4.161**)

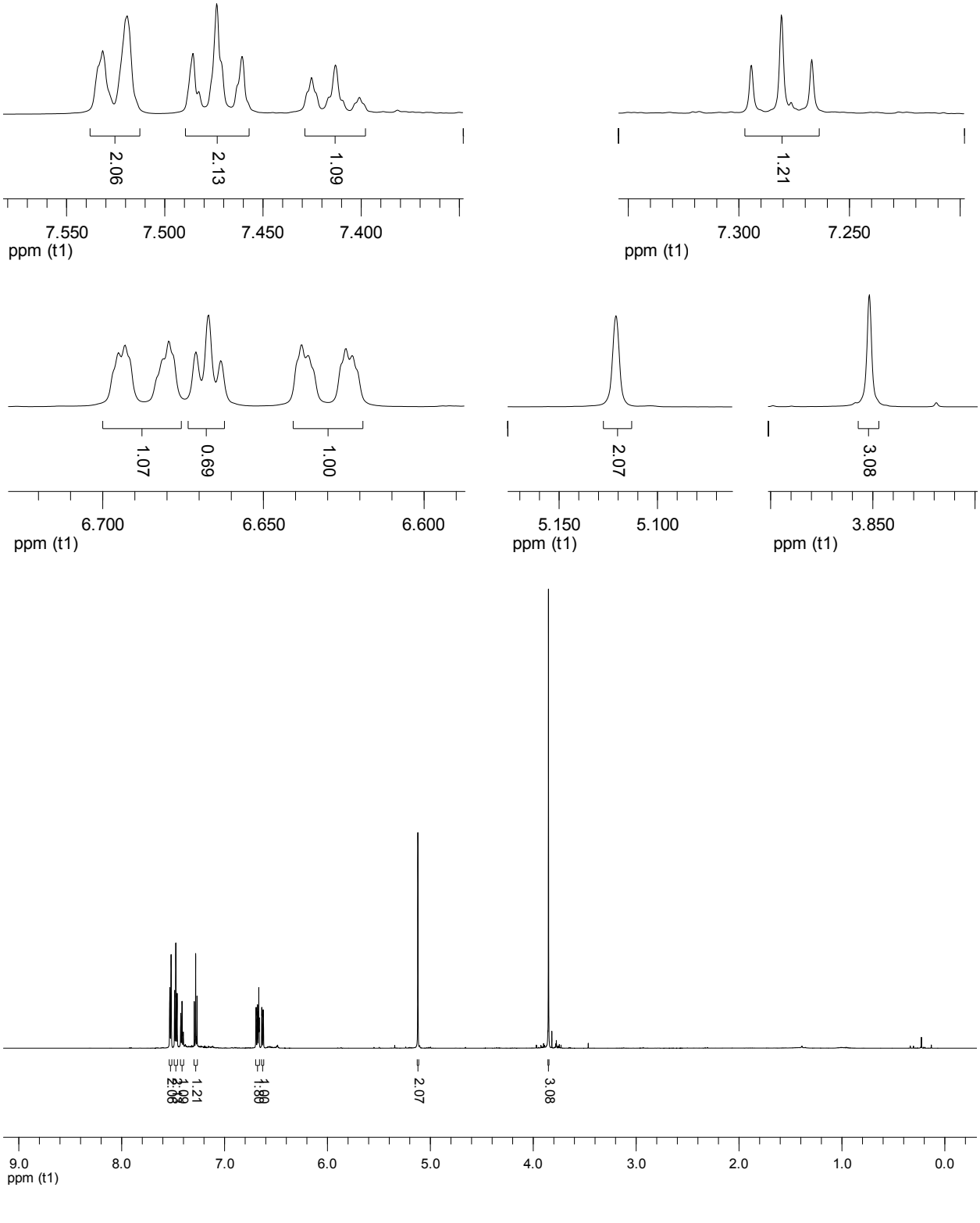
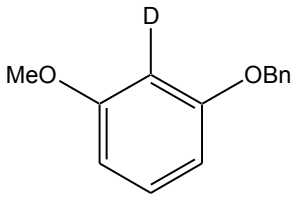


Plate 6b: ^{1}H NMR of 1-Benzyloxy-3-methoxy-2-(^{2}*H*)benzene, $CDCl_3$ (298 K)



(**4.161**)

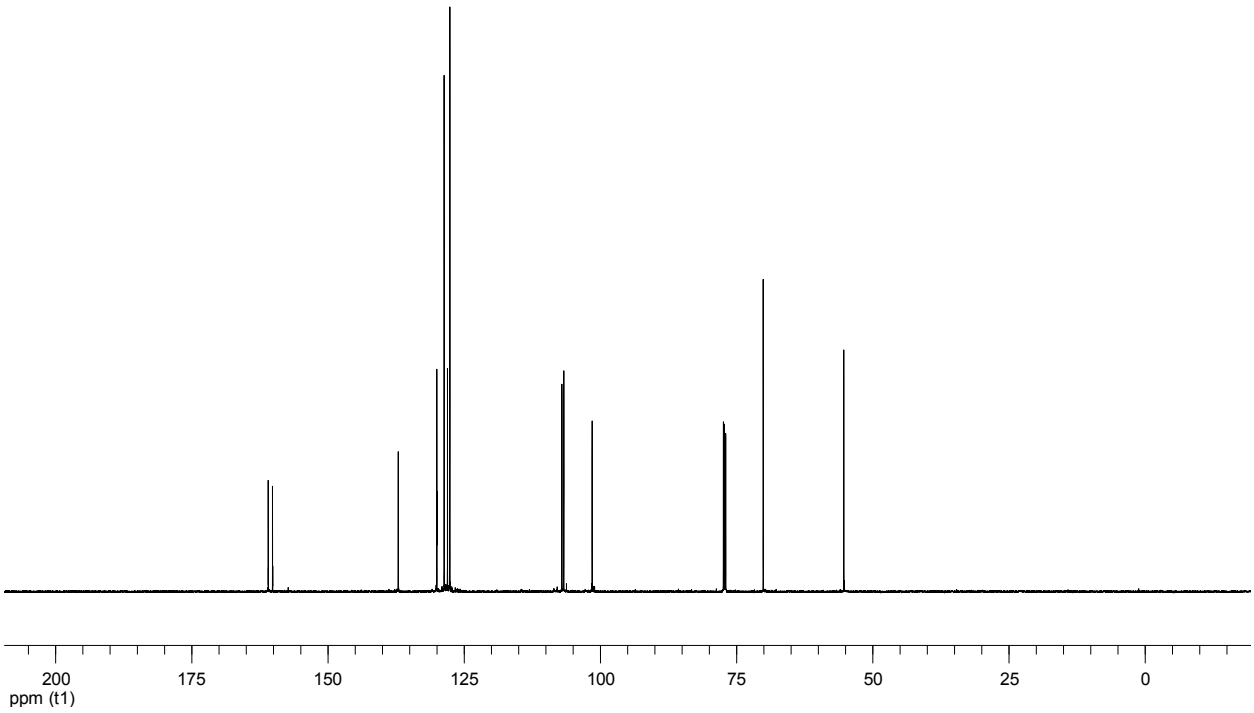
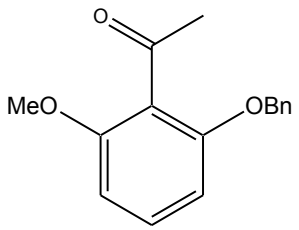


Plate 7a: ^{1}H NMR of 2-Benzyloxy-6-methoxyacetophenone, $CDCl_3$ (298 K)



(**4.43**)

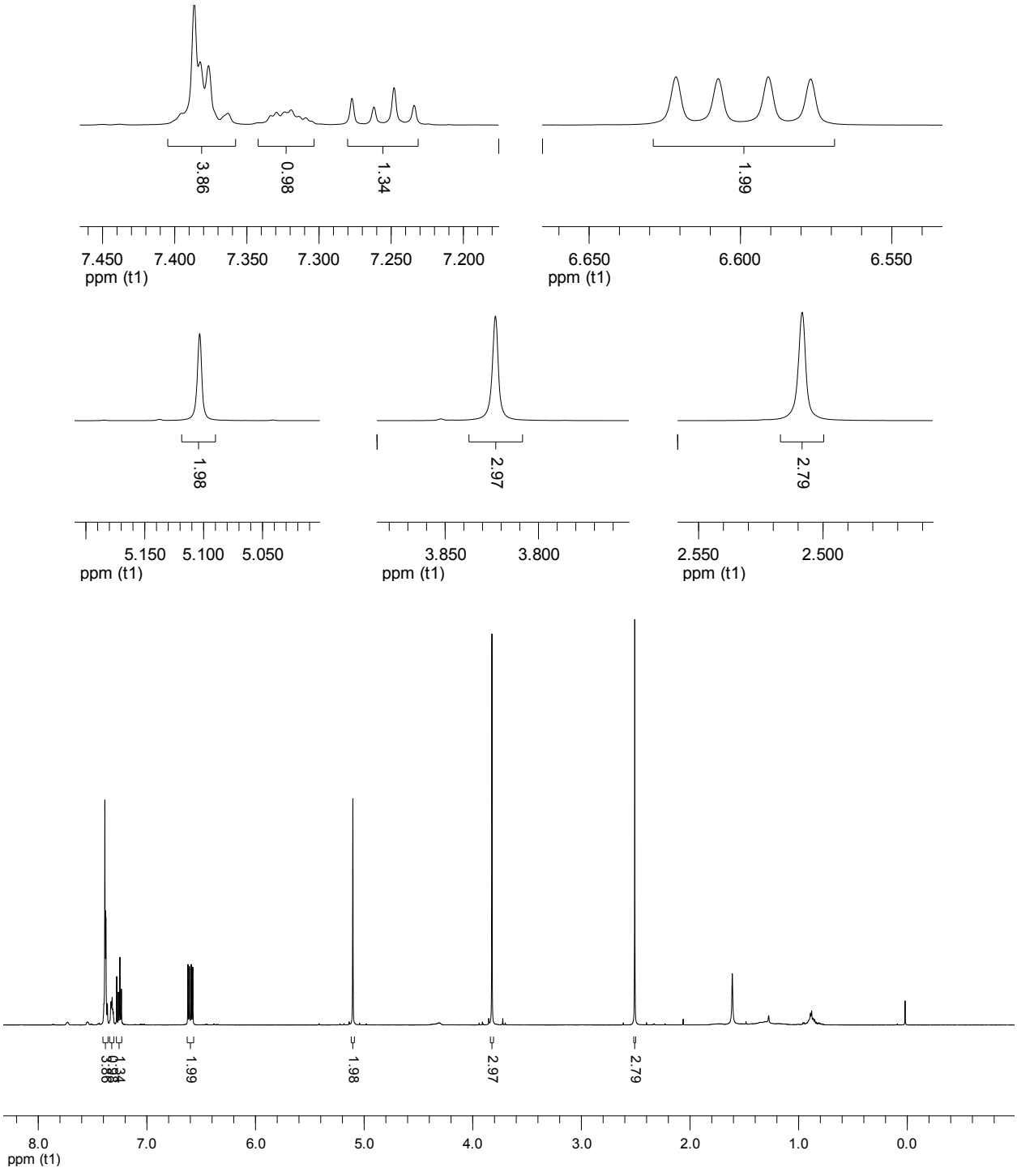
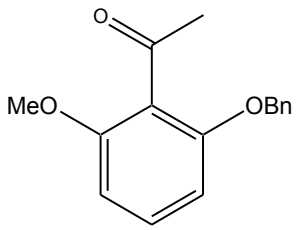


Plate 7b: ^{1}H NMR of 2-Benzyloxy-6-methoxyacetophenone, $CDCl_3$ (298 K)



(**4.43**)

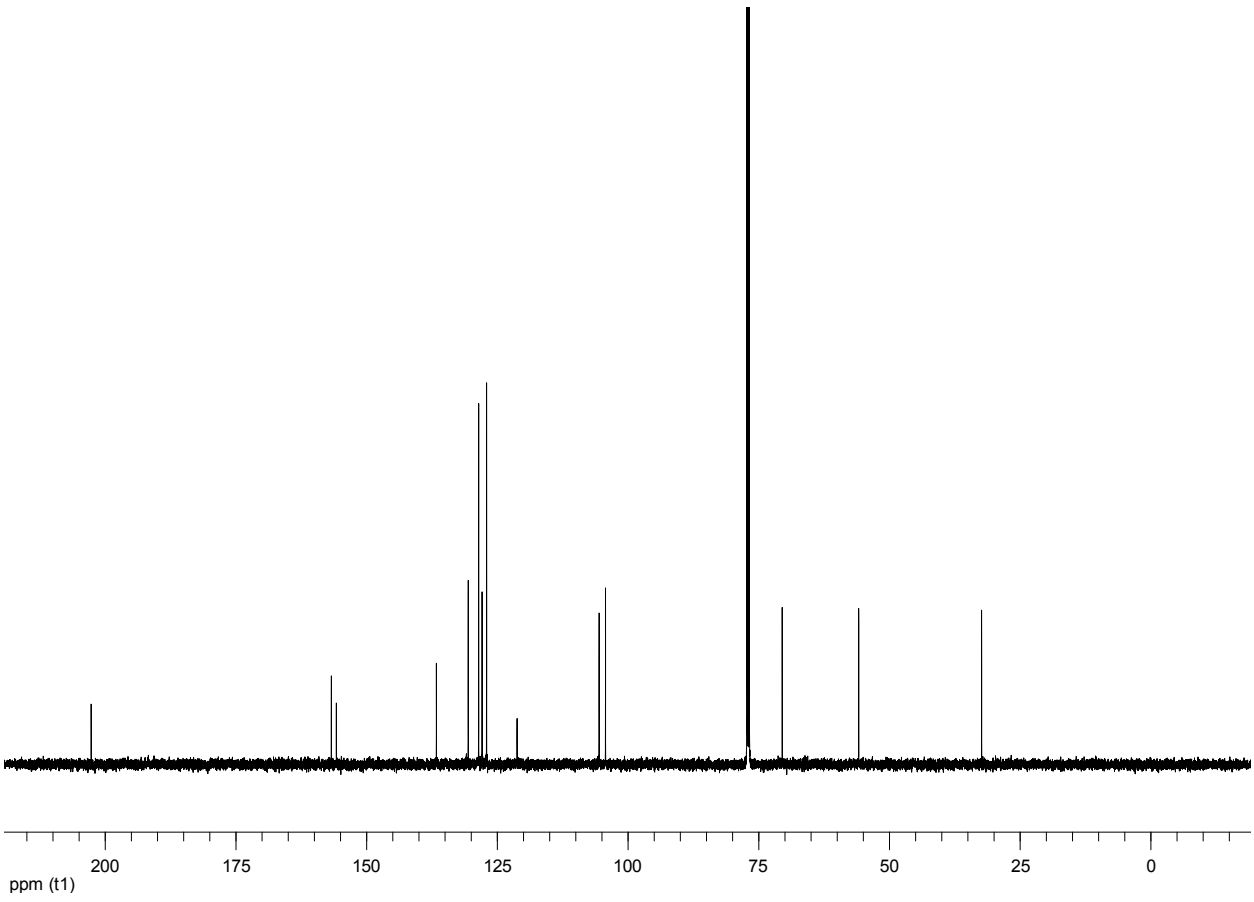
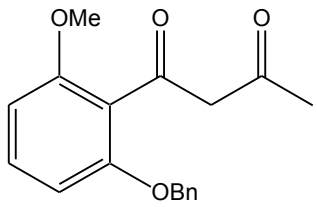


Plate 8a: ^{1}H NMR of 1-(2-Benzyloxy-6-methoxy-phenyl)-butane-1,3-dione, $CDCl_3$ (298 K)



(**4.162**)

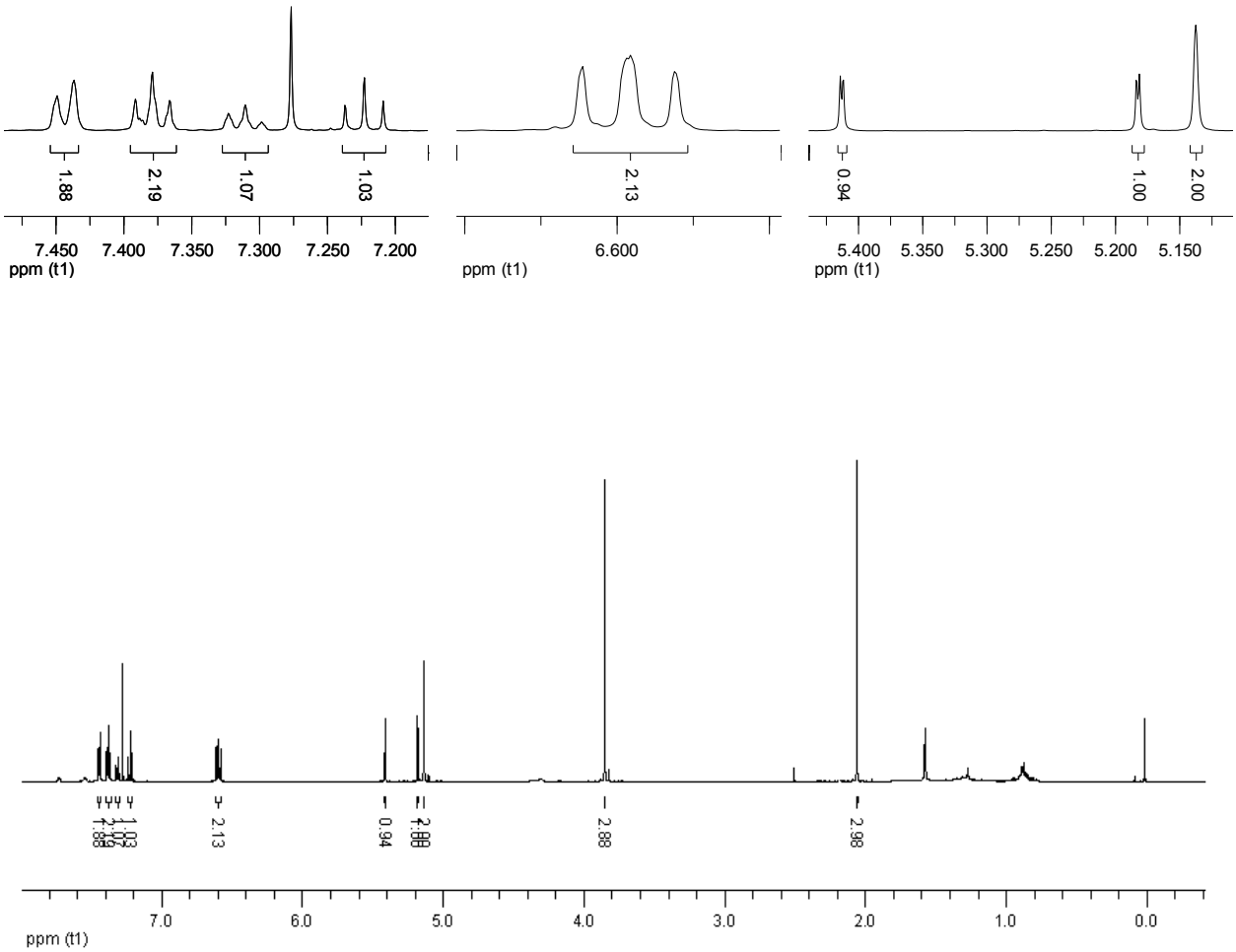
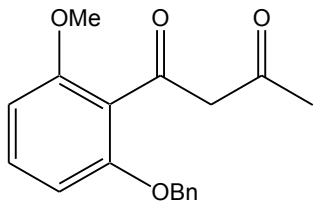


Plate 8b: ^{13}C NMR of 1-(2-Benzyloxy-6-methoxy-phenyl)-butane-1,3-dione, $CDCl_3$ (298 K)



(**4.162**)

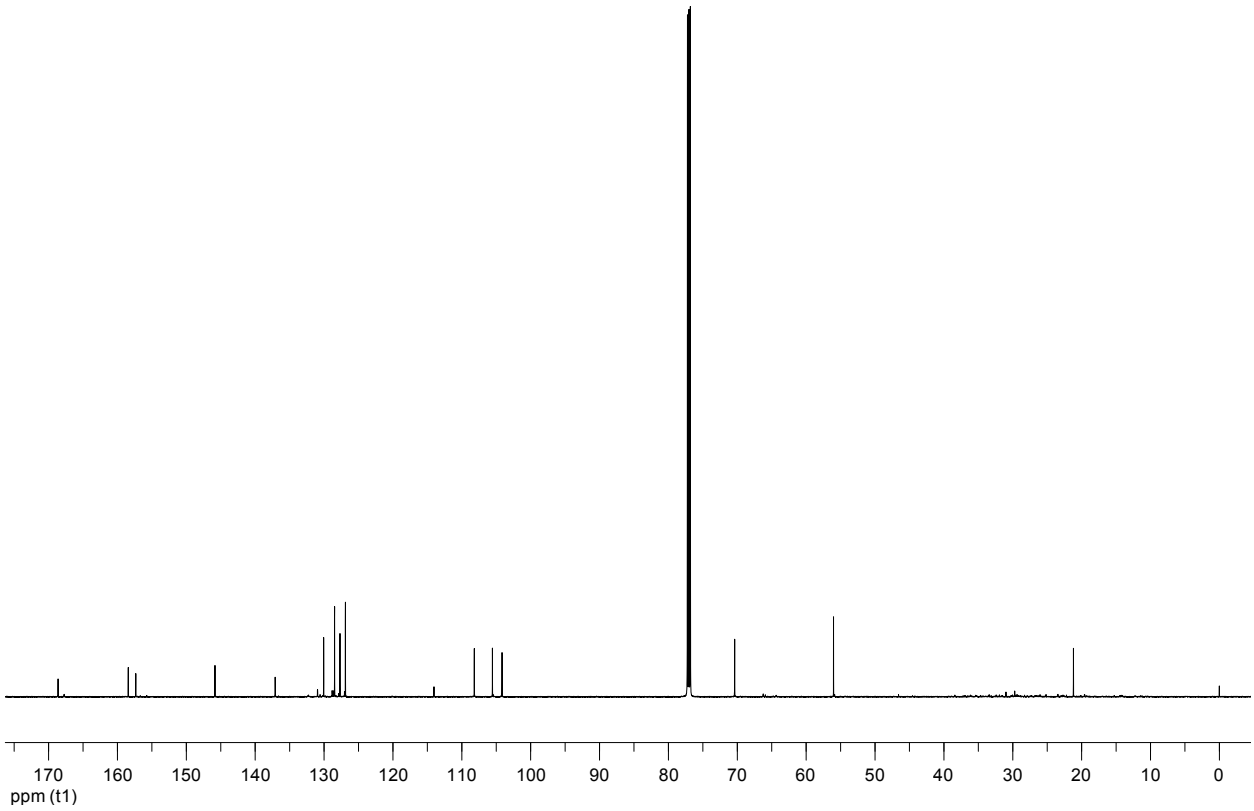
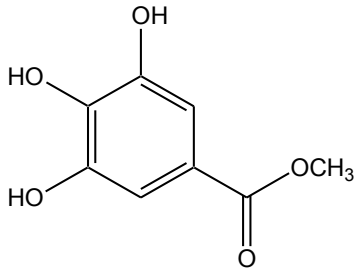


Plate 9: ^{1}H NMR of Methyl 3,4,5-trihydroxybenzoate, acetone (298K)



(**4.51**)

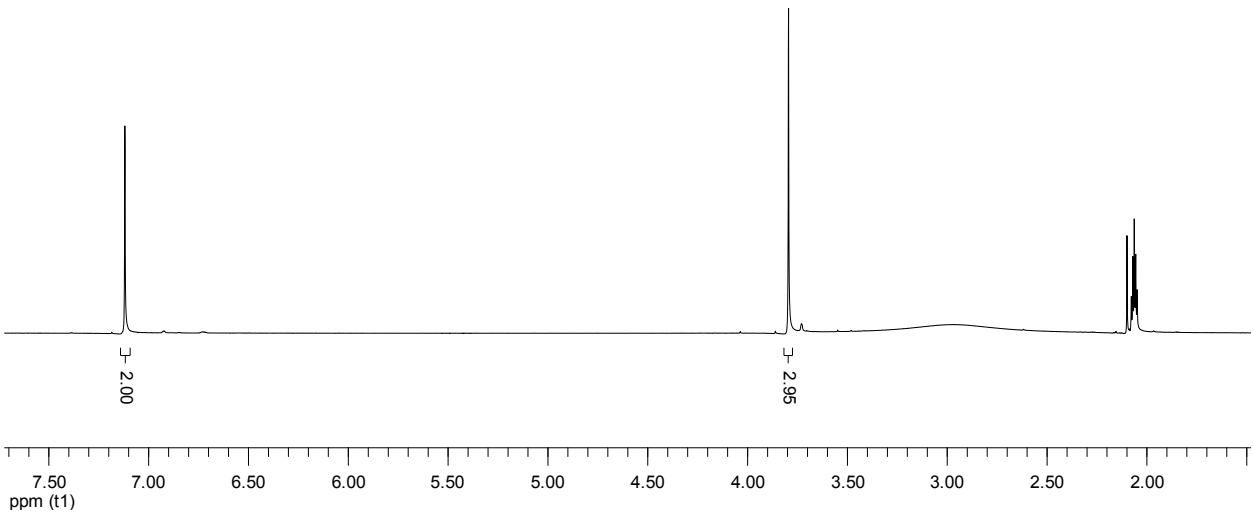
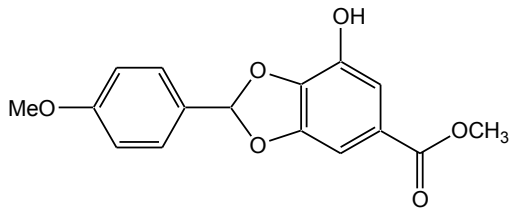
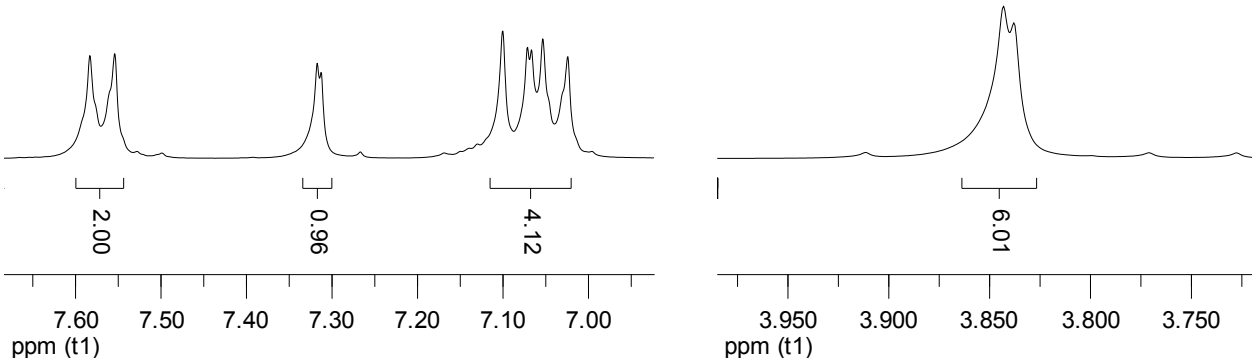


Plate 10: ^{1}H NMR of Methyl 3-hydroxy-4,5-(*p*-methoxyphenylmethylenedioxy)benzoate, acetone (298K)



(**4.52**)



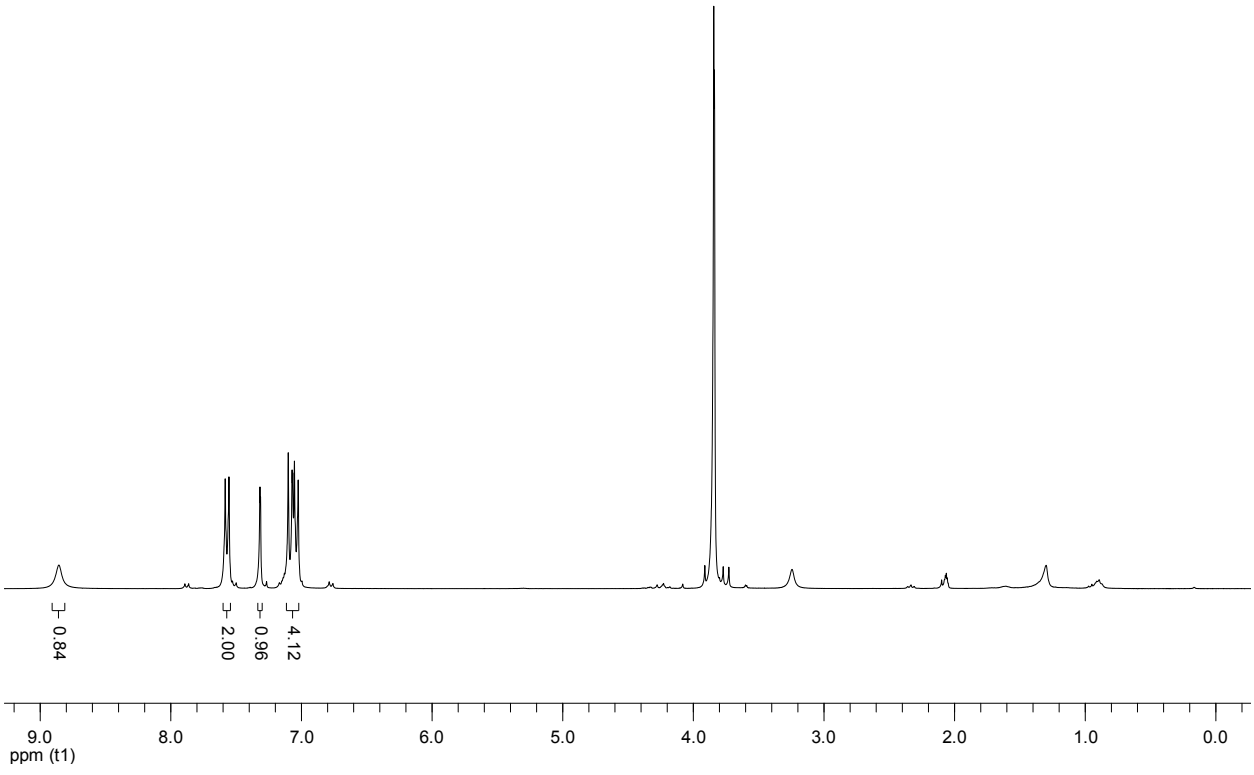
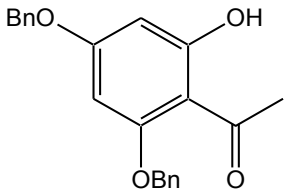
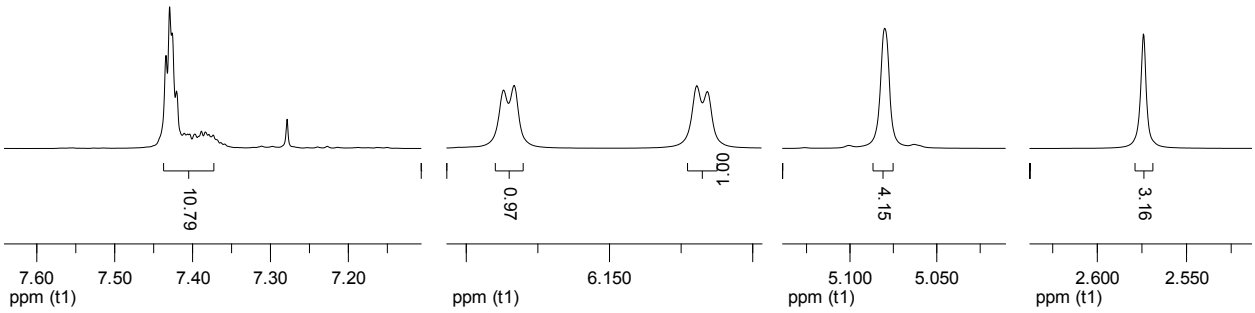


Plate 11a: ^{1}H NMR of 4,6-Dibenzyloxy-2-hydroxyacetophenone, $CDCl_3$ (298K)



(**4.54**)



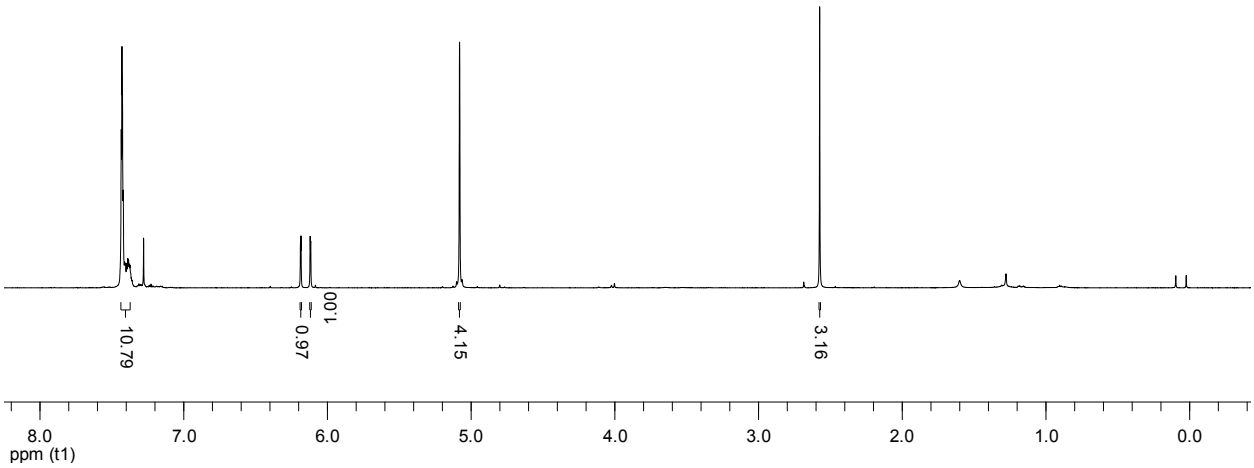
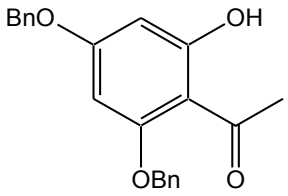


Plate 11b: ^{13}C NMR of 4,6-Dibenzyloxy-2-hydroxyacetophenone, $CDCl_3$ (298K)



(**4.54**)

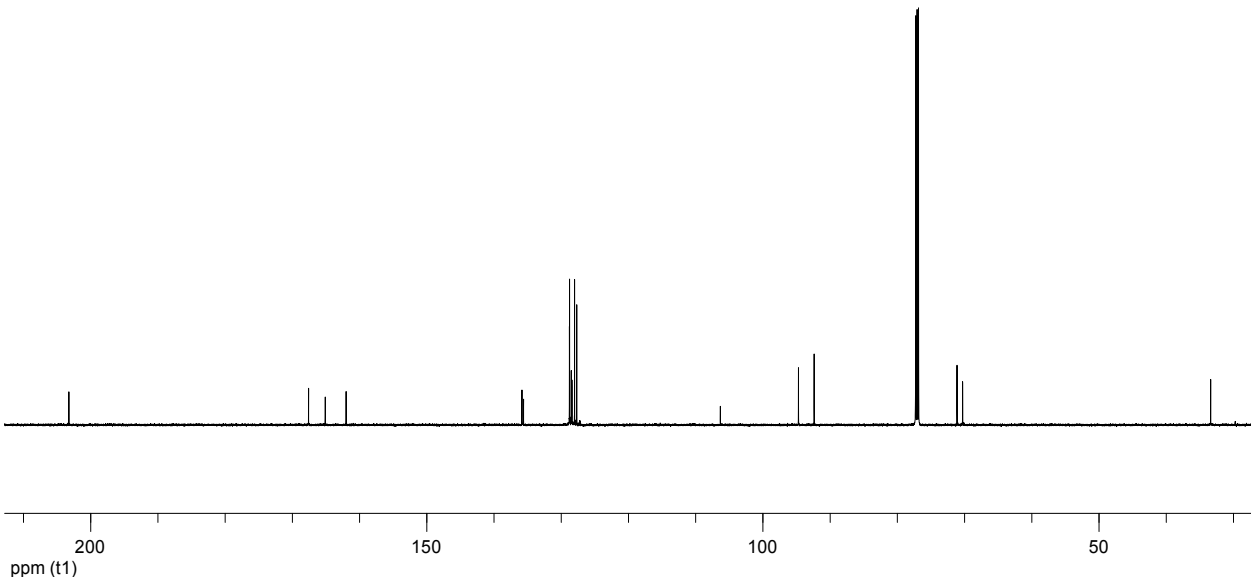
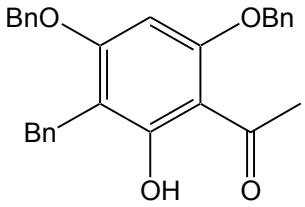


Plate 12a: ^{1}H NMR of 3-Benzyl-4,6-dibenzyloxy-2-hydroxyacetophenone, acetone (298K)



(**4.55**)

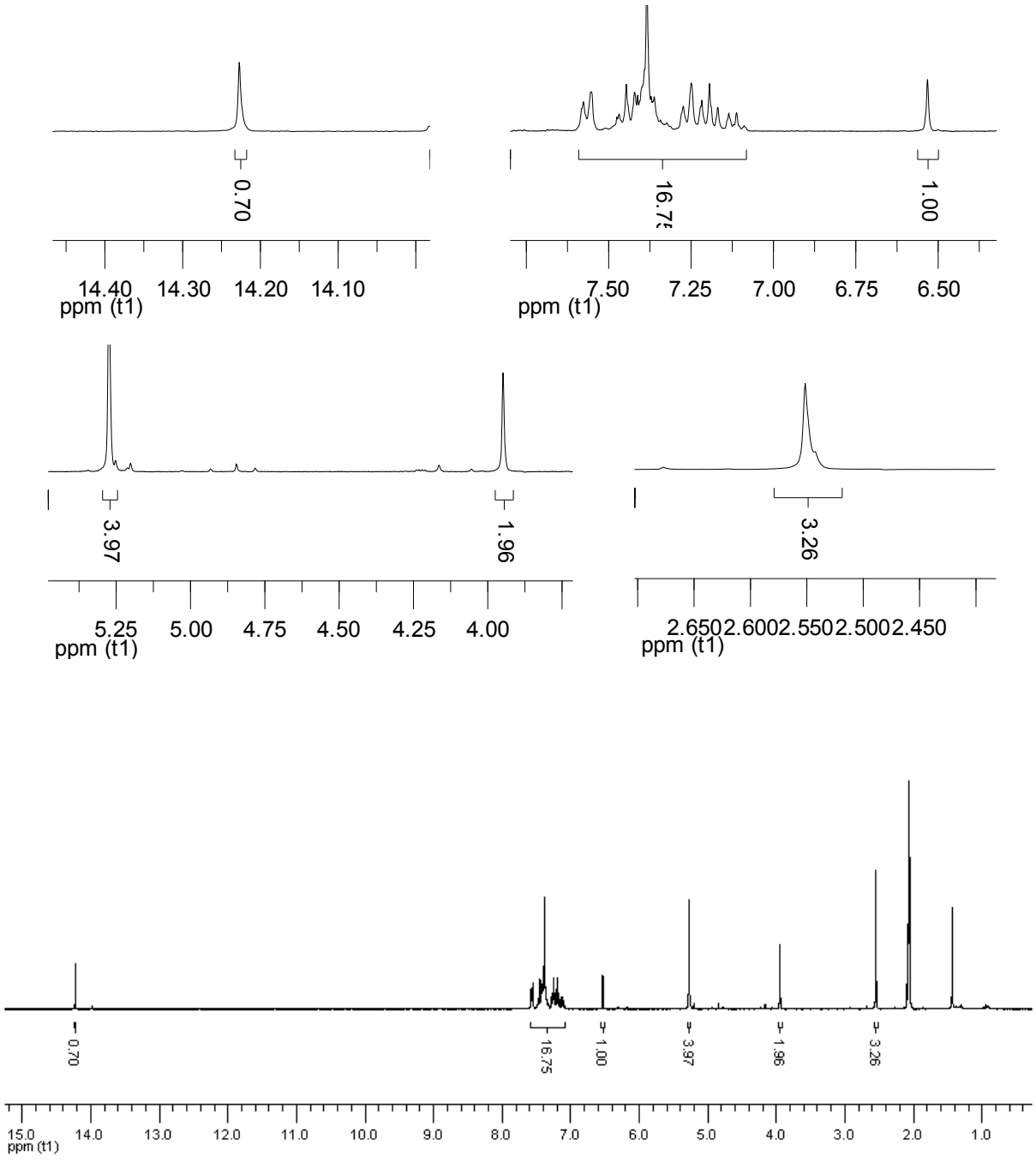
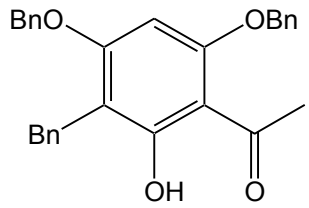


Plate 12b: ^{13}C NMR of 3-Benzyl-4,6-dibenzyloxy-2-hydroxyacetophenone, acetone (298K)



(**4.55**)

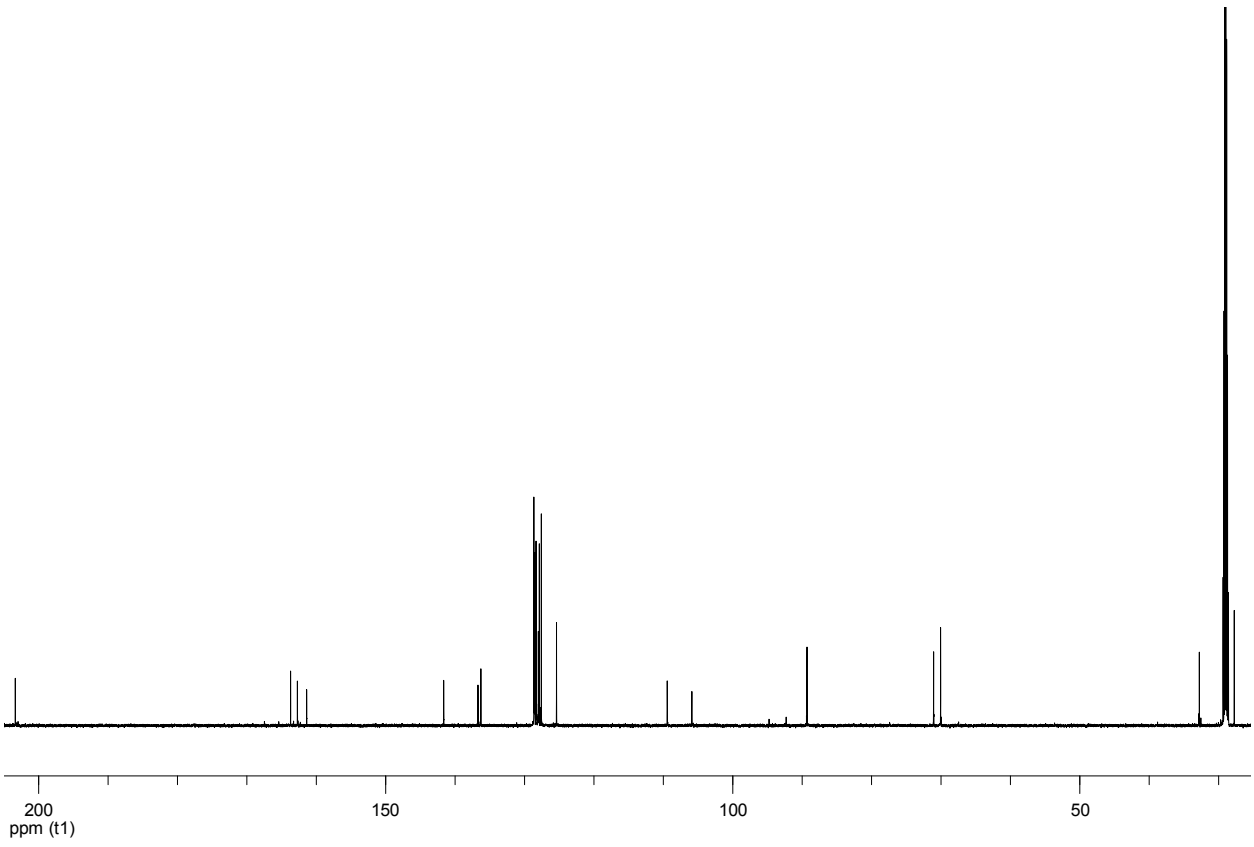
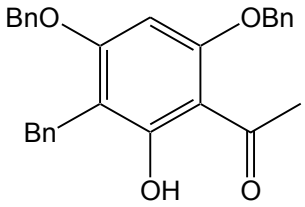


Plate 12c: NOESY of 3-Benzyl-4,6-dibenzyloxy-2-hydroxyacetophenone, acetone (298K)



(**4.55**)

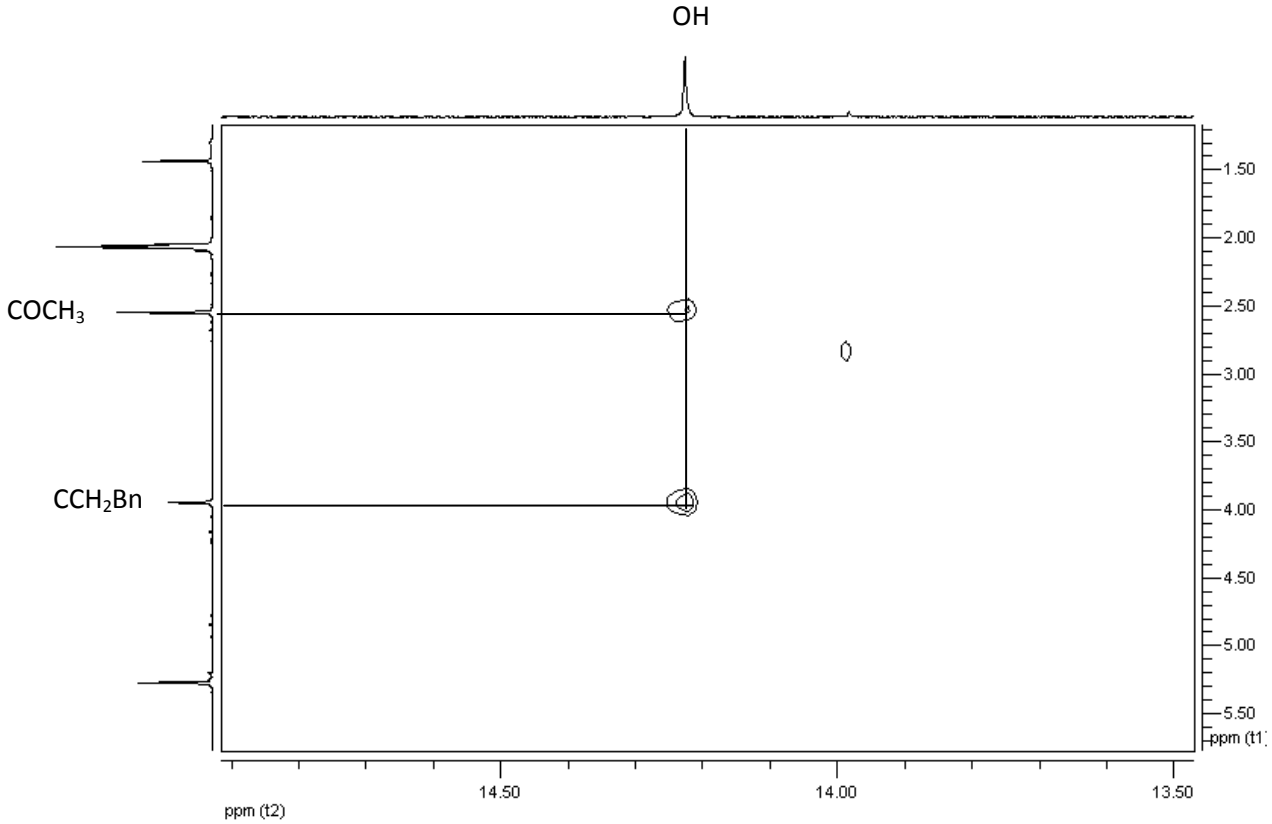
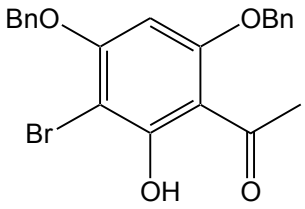
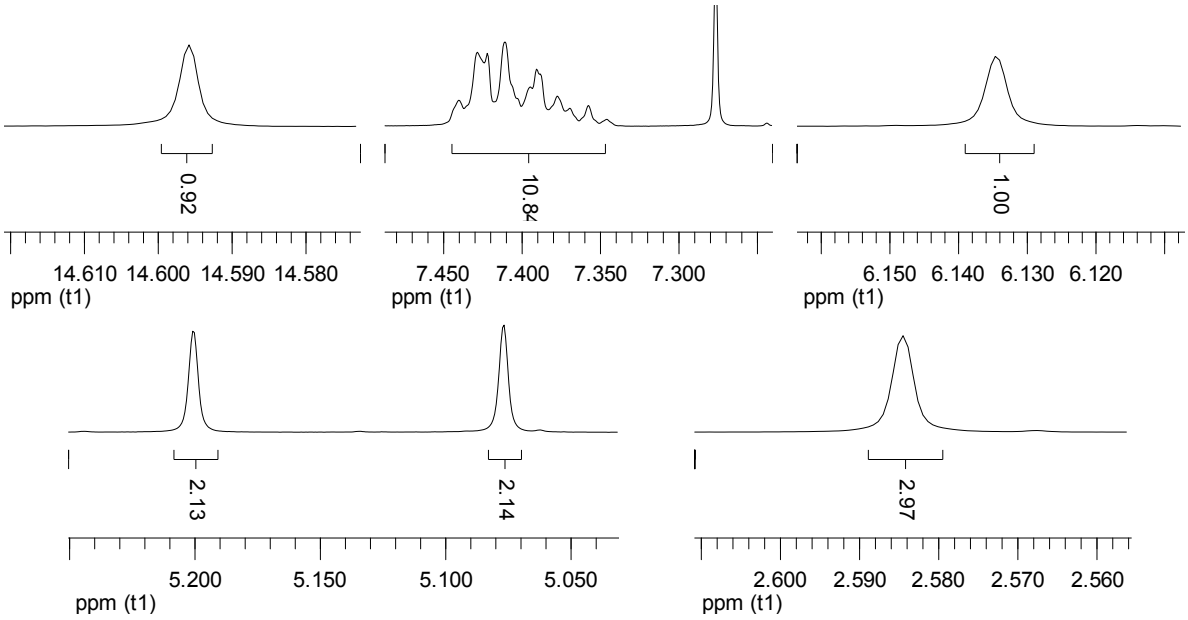


Plate 13a: ^{1}H NMR of 4,6-Dibenzyloxy-3-bromo-2-hydroxyacetophenone, $CDCl_3$ (298 K)



(**4.56**)



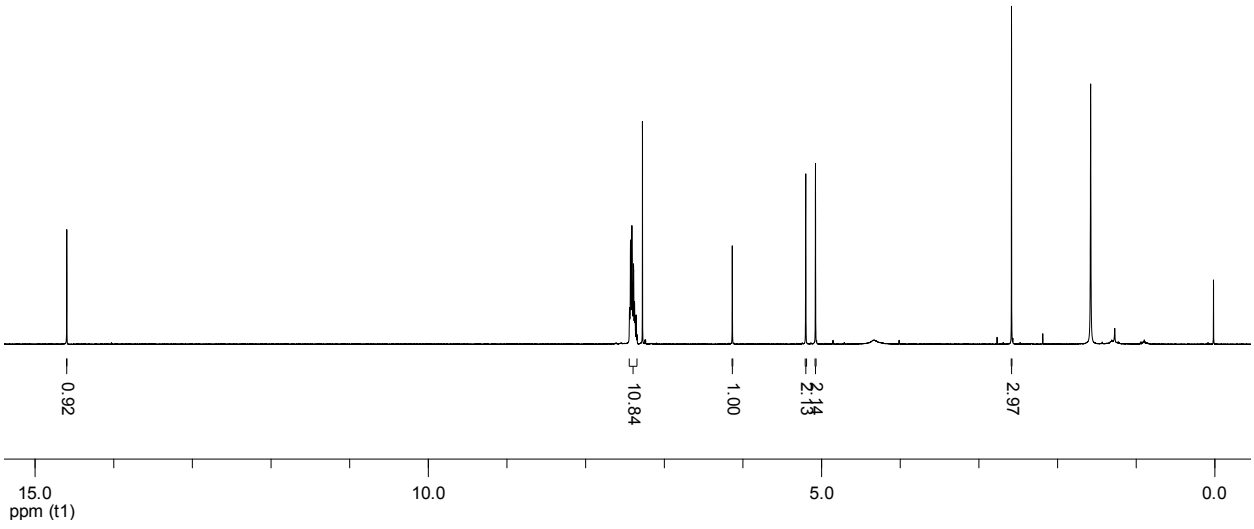
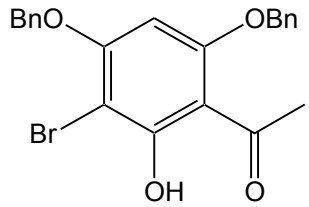


Plate 13b: ^{13}C NMR of 4,6-Dibenzyloxy-3-bromo-2-hydroxyacetophenone, $CDCl_3$ (298 K)



(**4.56**)

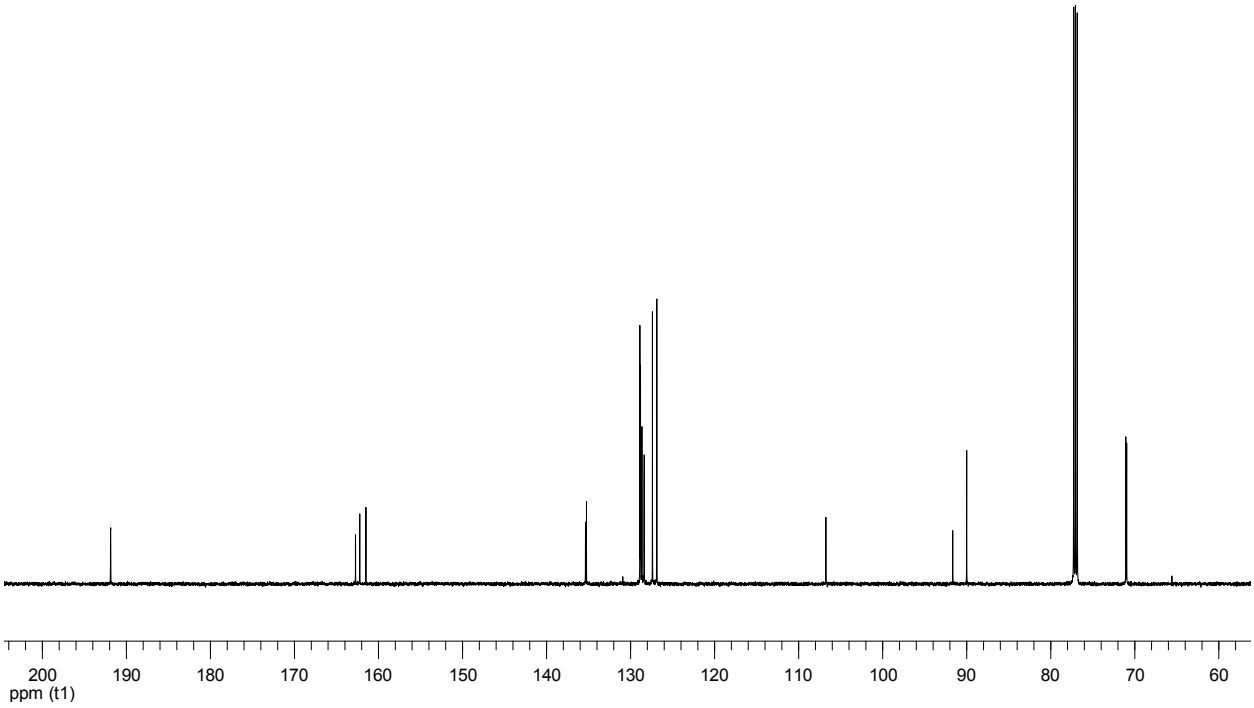
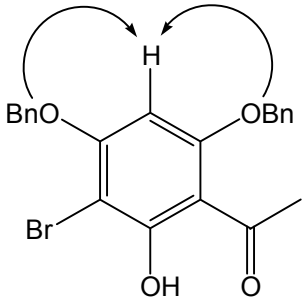


Plate 13c: NOESY of 4,6-Dibenzyloxy-3-bromo-2-hydroxyacetophenone, $CDCl_3$ (298 K)



(**4.56**)

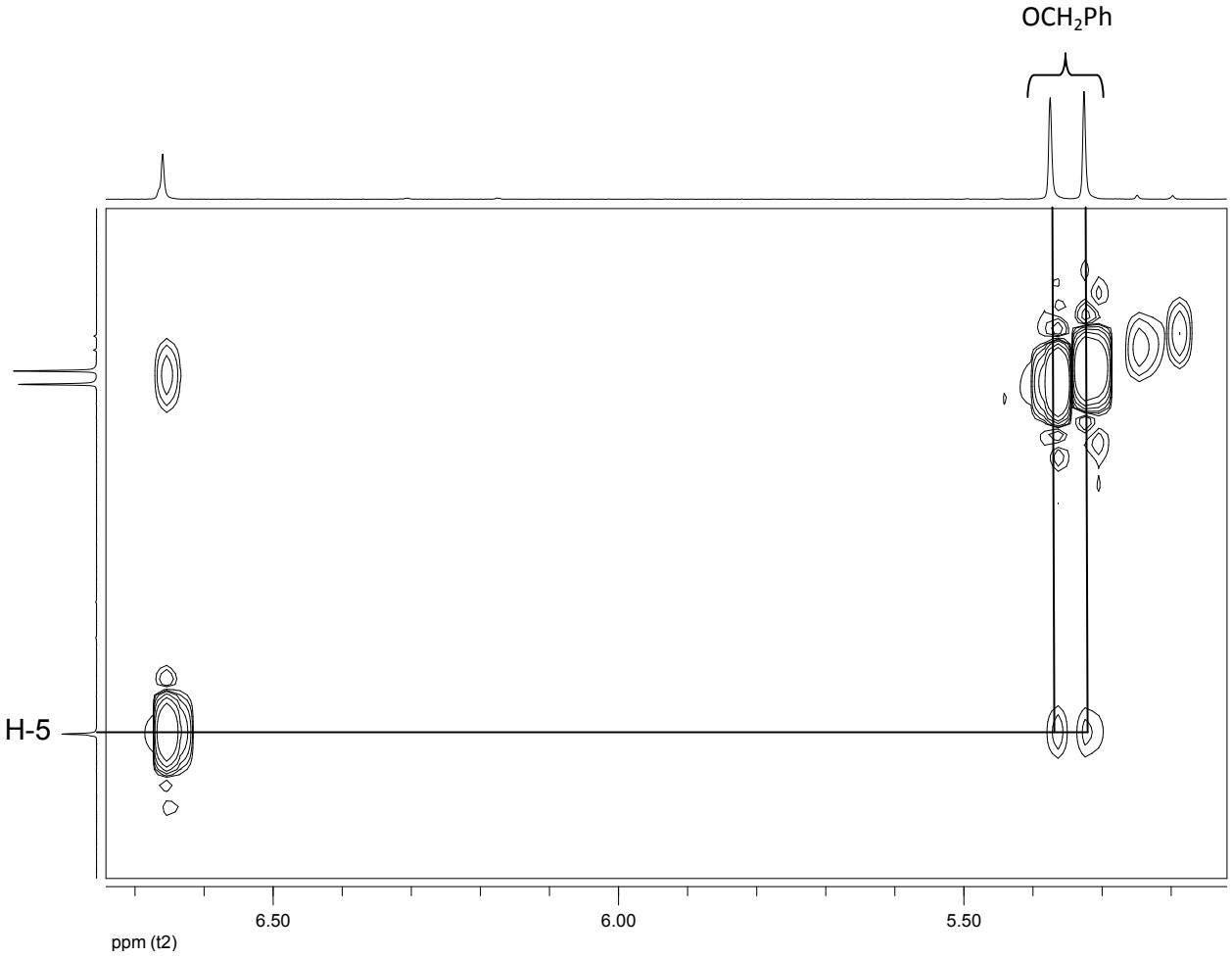
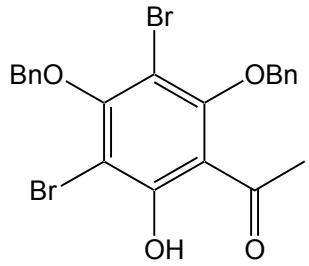
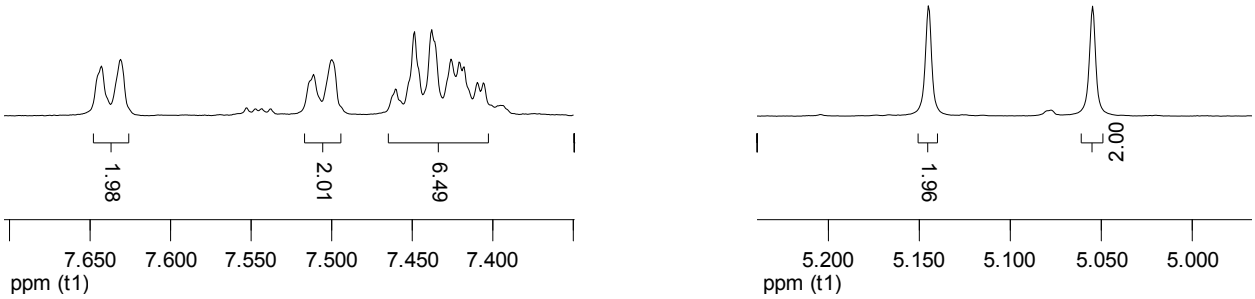


Plate 14a: ^{1}H NMR of 4,6-Dibenzyloxy-3,5-dibromo-2-hydroxyacetophenone, $CDCl_3$ (298 K)



(**4.57**)



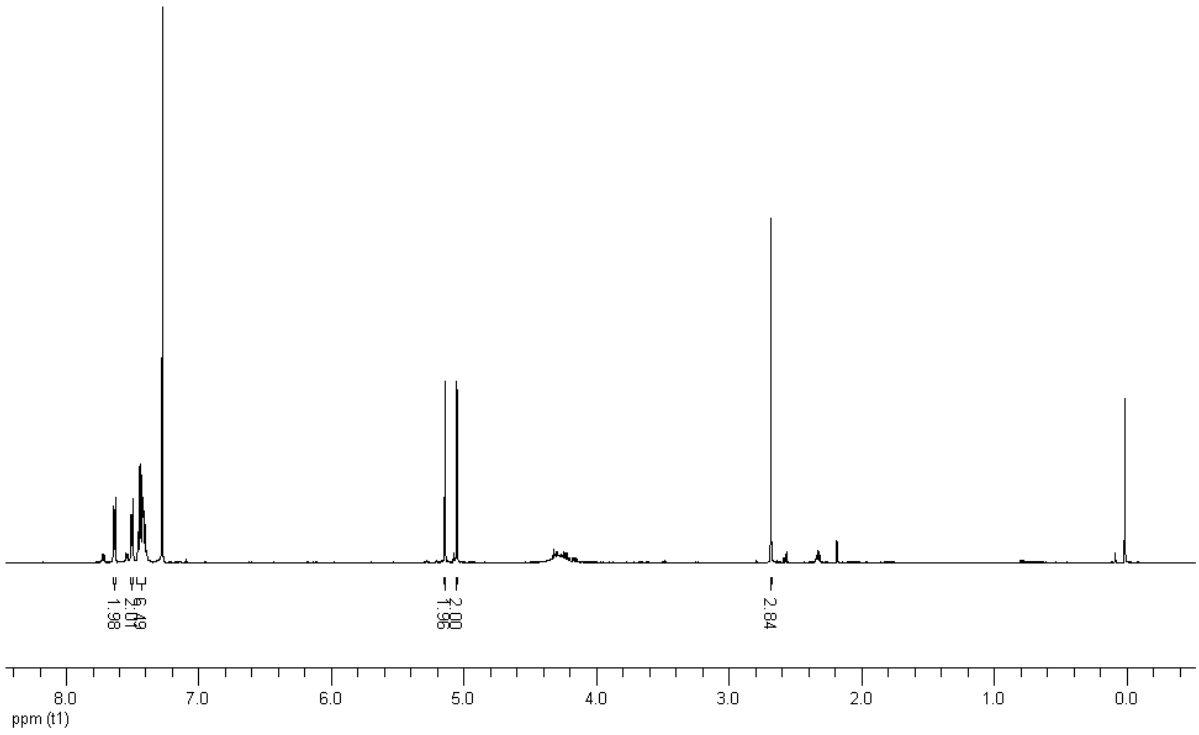
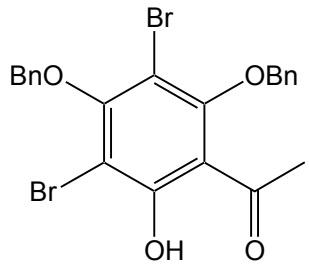


Plate 14b: ^{1}H NMR of 4,6-Dibenzyloxy-3,5-dibromo-2-hydroxyacetophenone, $CDCl_3$ (298 K)



(**4.57**)

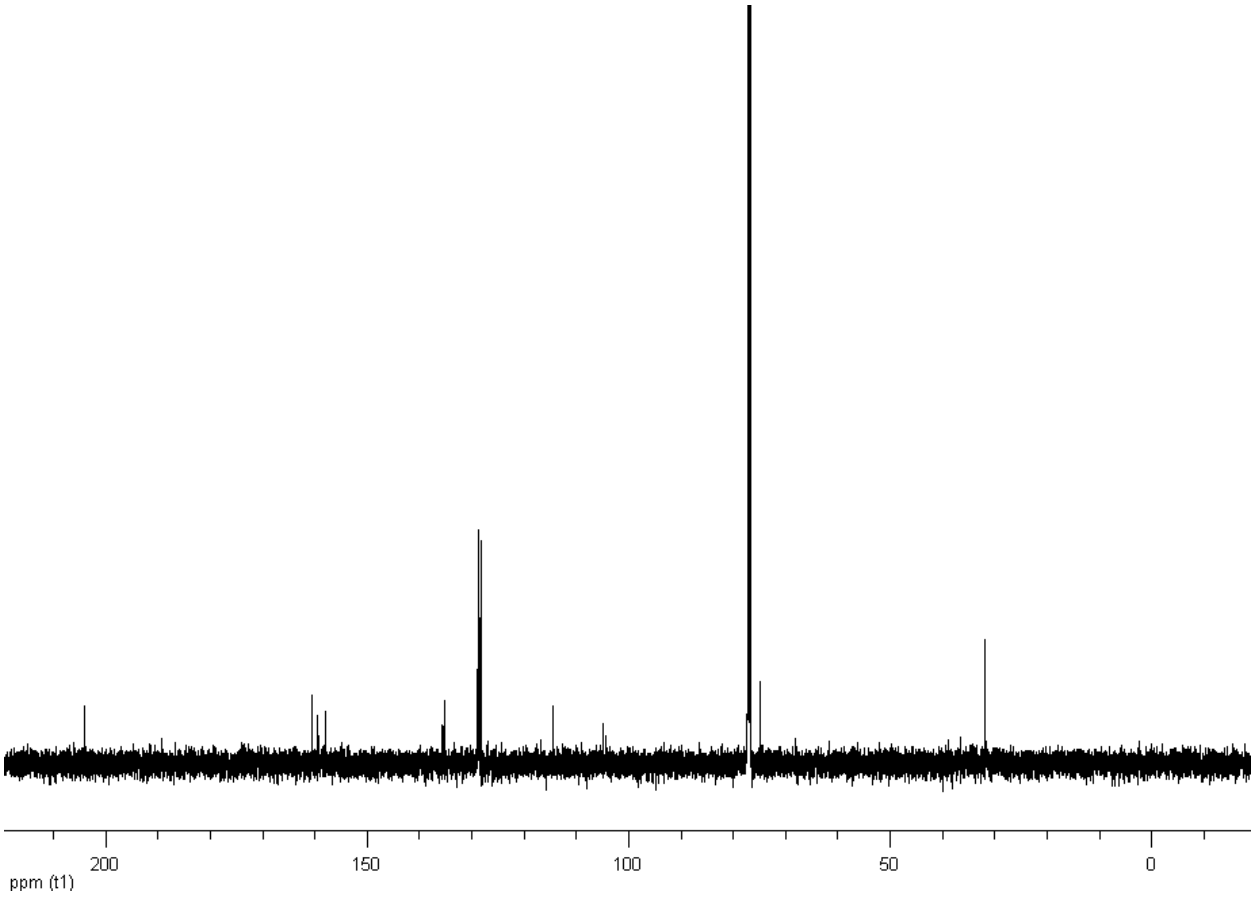
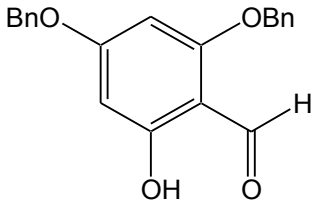


Plate 15: ^{1}H NMR of 2-Hydroxy-4,6-dibenzyloxybenzaldehyde, $CDCl_3$ (298 K)



(**4.59**)

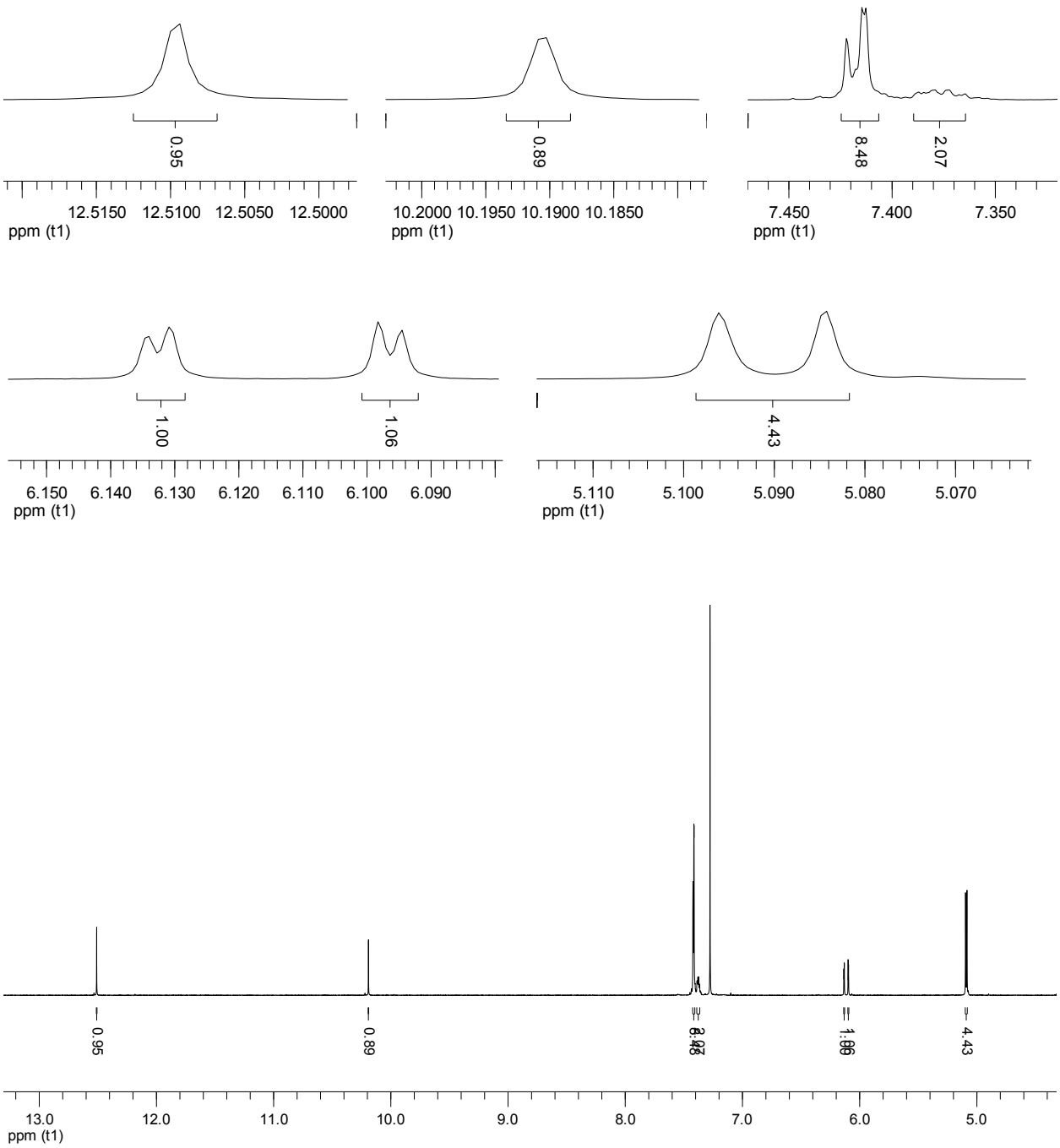
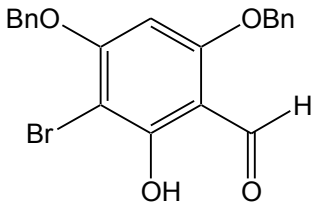
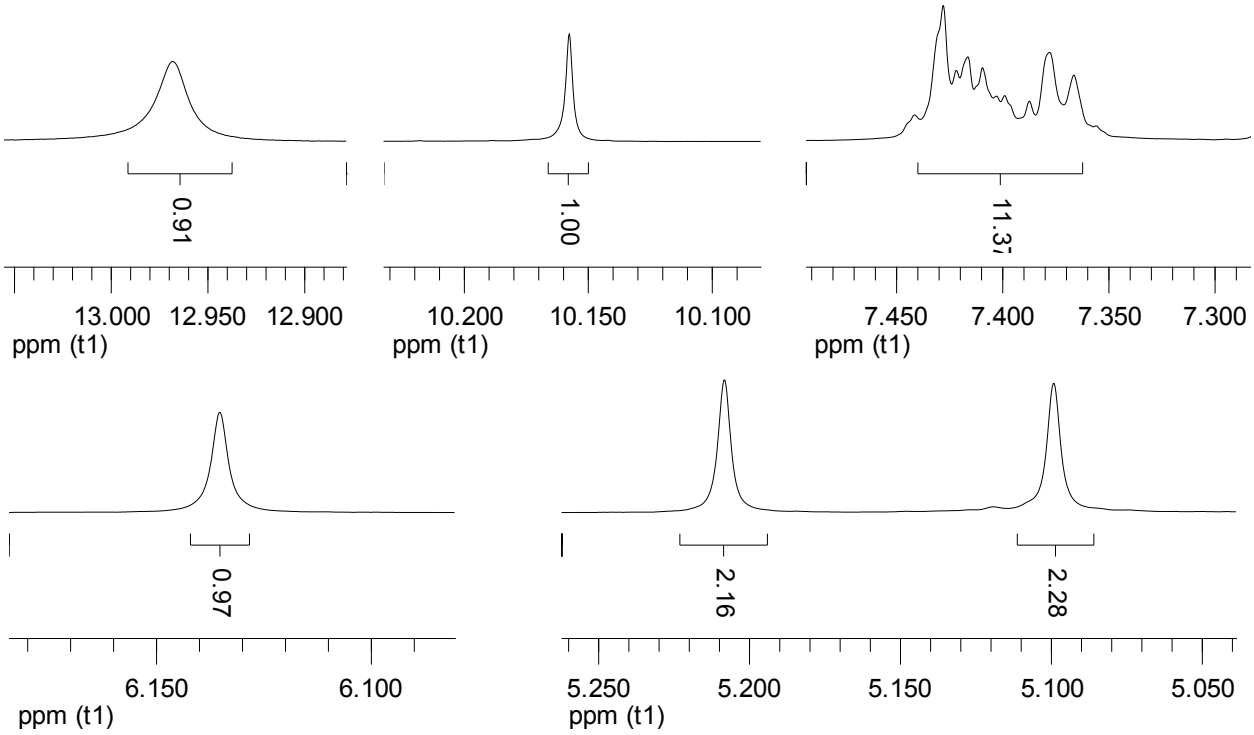


Plate 16a: ^{1}H NMR of 4,6-Dibenzyloxy-3-bromo-2-hydroxybenzaldehyde, $CDCl_3$ (298 K)



(**4.61**)



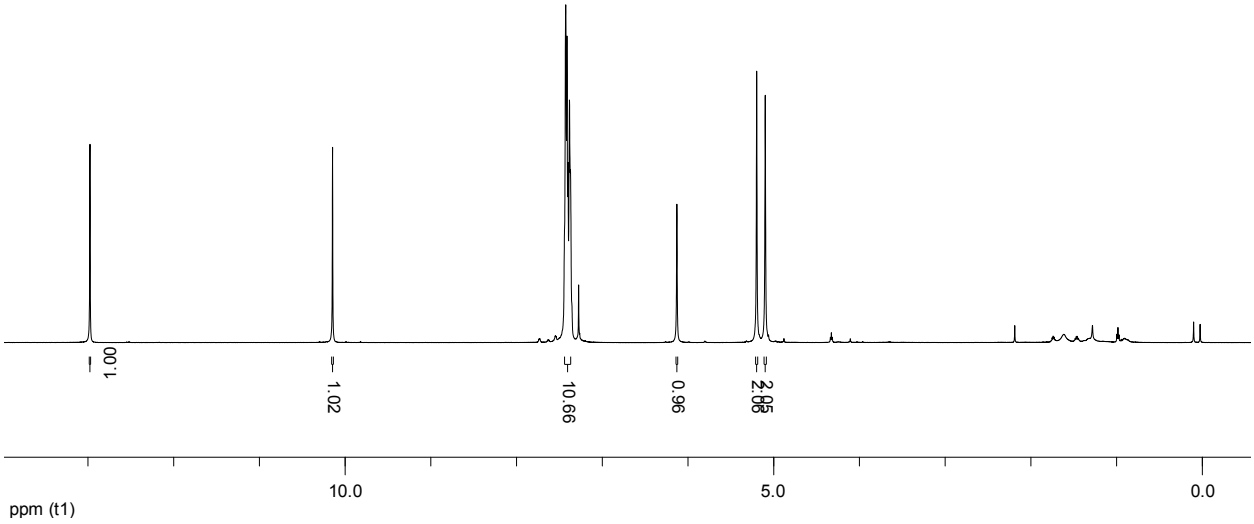
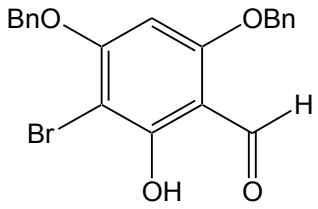


Plate 16b: ^{13}C NMR of 4,6-Dibenzyloxy-3-bromo-2-hydroxybenzaldehyde, $CDCl_3$ (298 K)



(**4.61**)

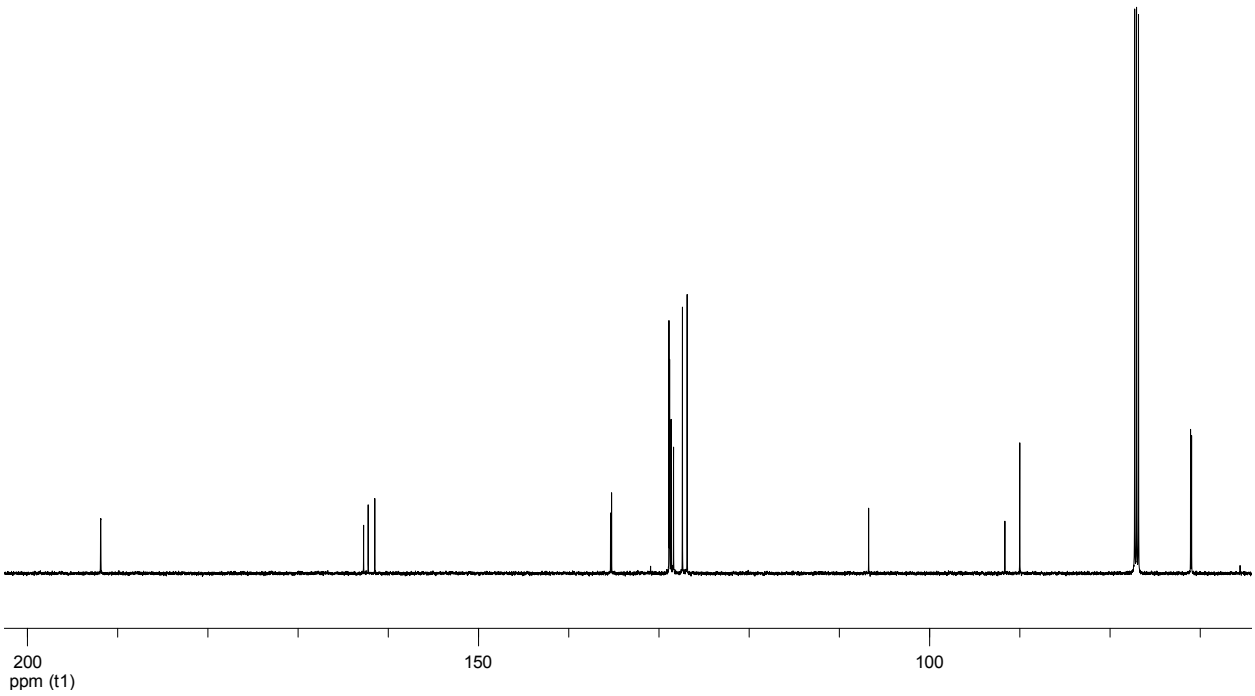
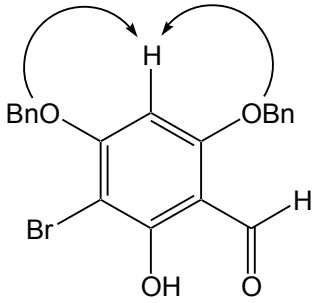


Plate 16c: NOESY of 4,6-Dibenzyloxy-3-bromo-2-hydroxybenzaldehyde, $CDCl_3$ (298 K)



(**4.61**)

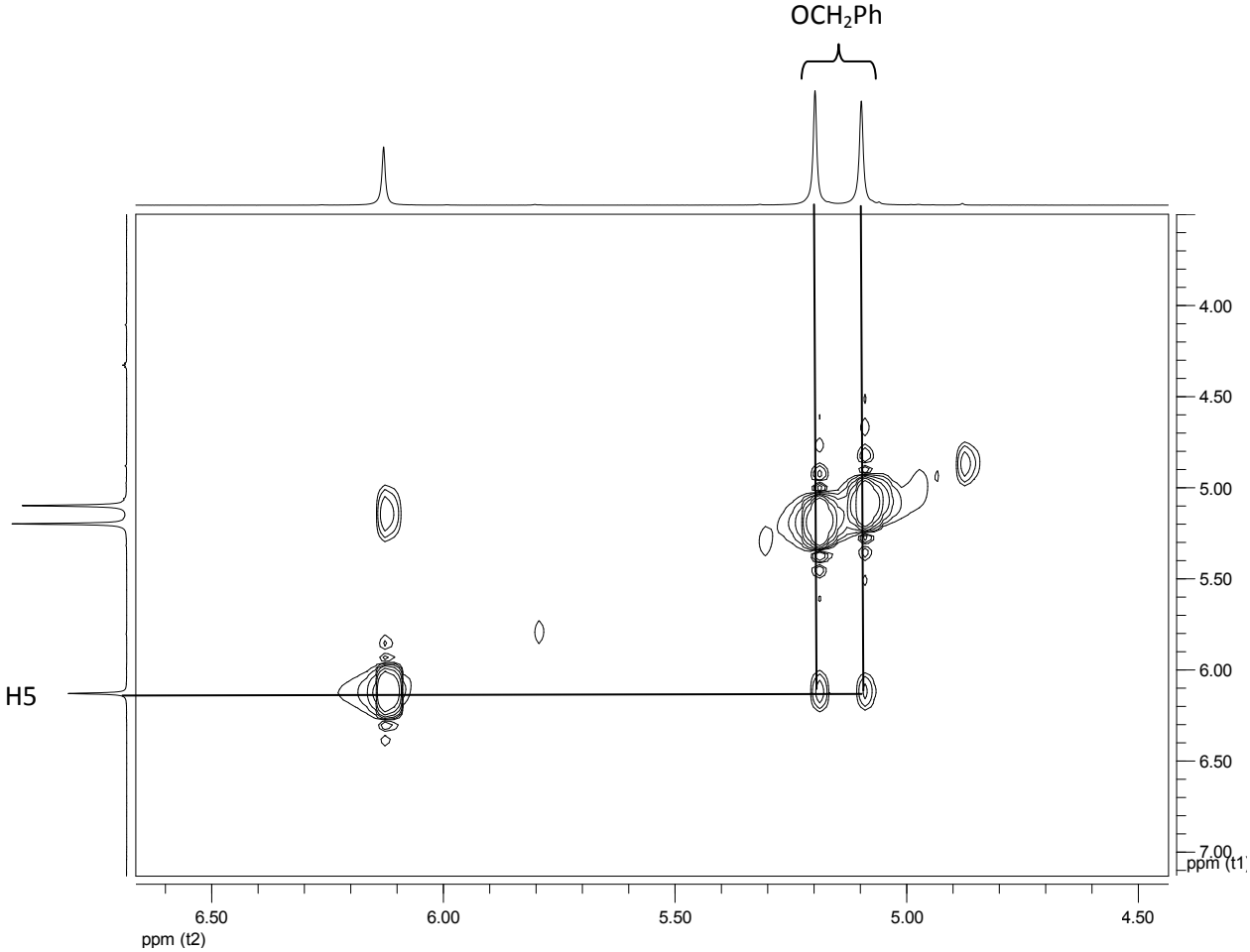
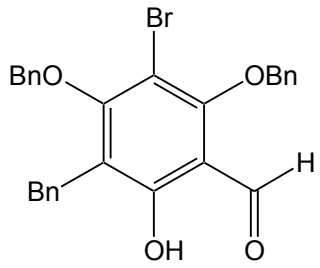
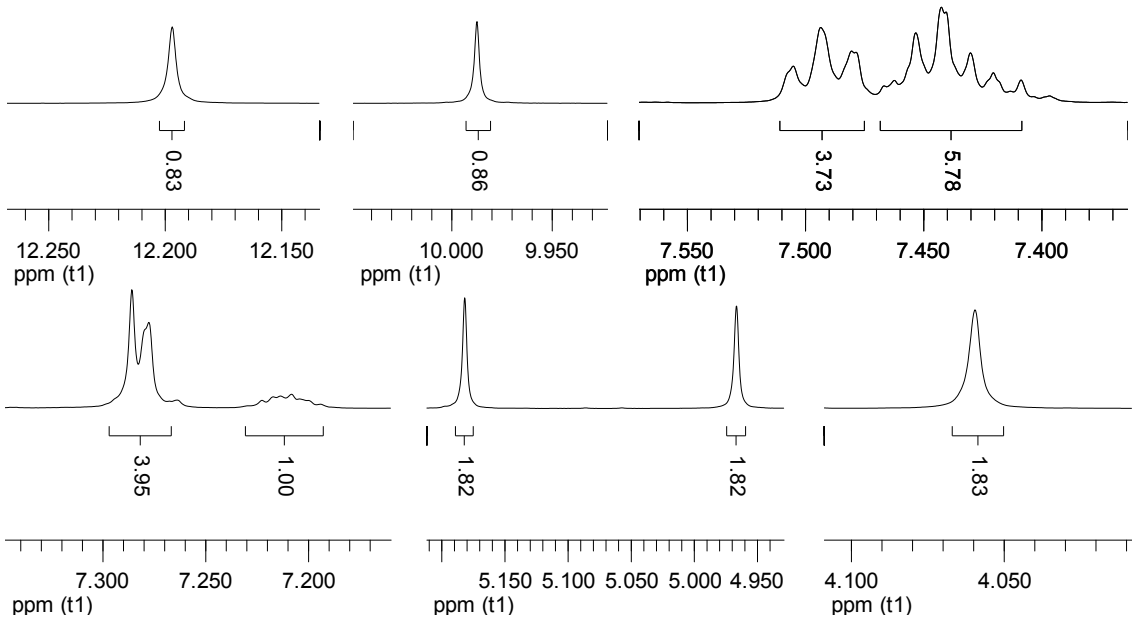


Plate 17a: ^{1}H NMR of 3-Benzyl-4,6-dibenzyloxy-5-bromo-2-hydroxybenzaldehyde, $CDCl_3$ (298 K)



(**4.62**)



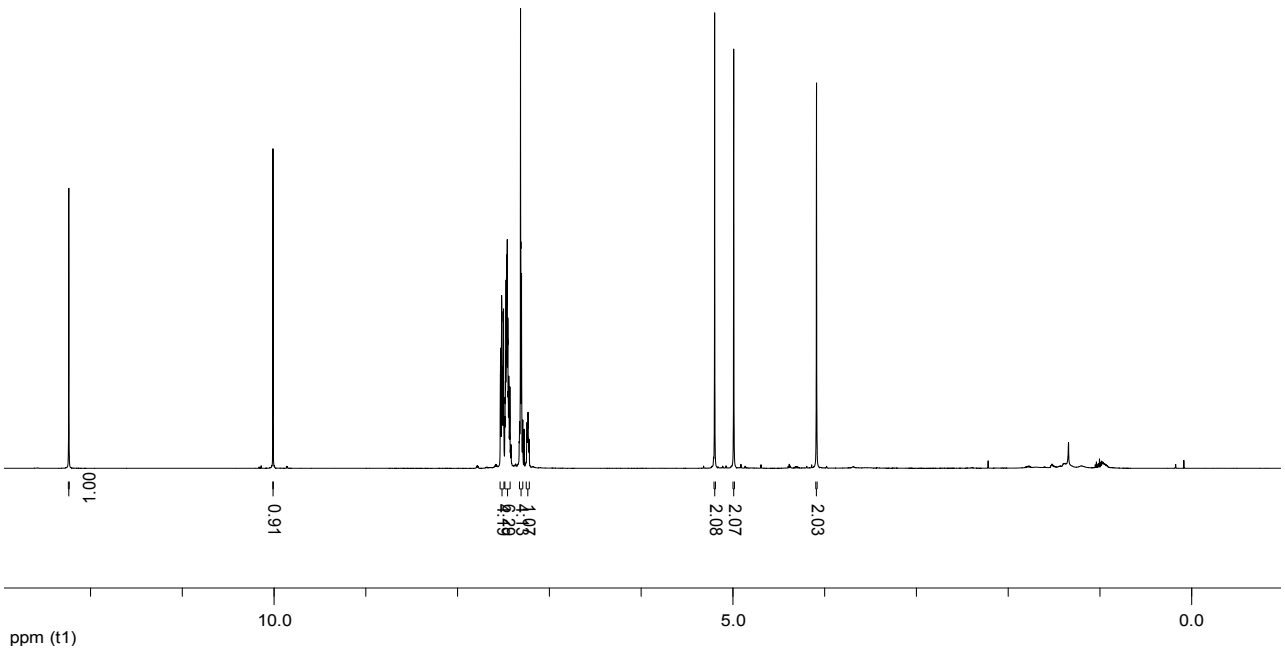
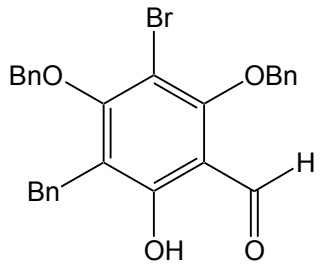


Plate 17b: ^{13}C NMR of 3-Benzyl-4,6-dibenzyloxy-5-bromo-2-hydroxybenzaldehyde, $CDCl_3$ (298 K)



(**4.62**)

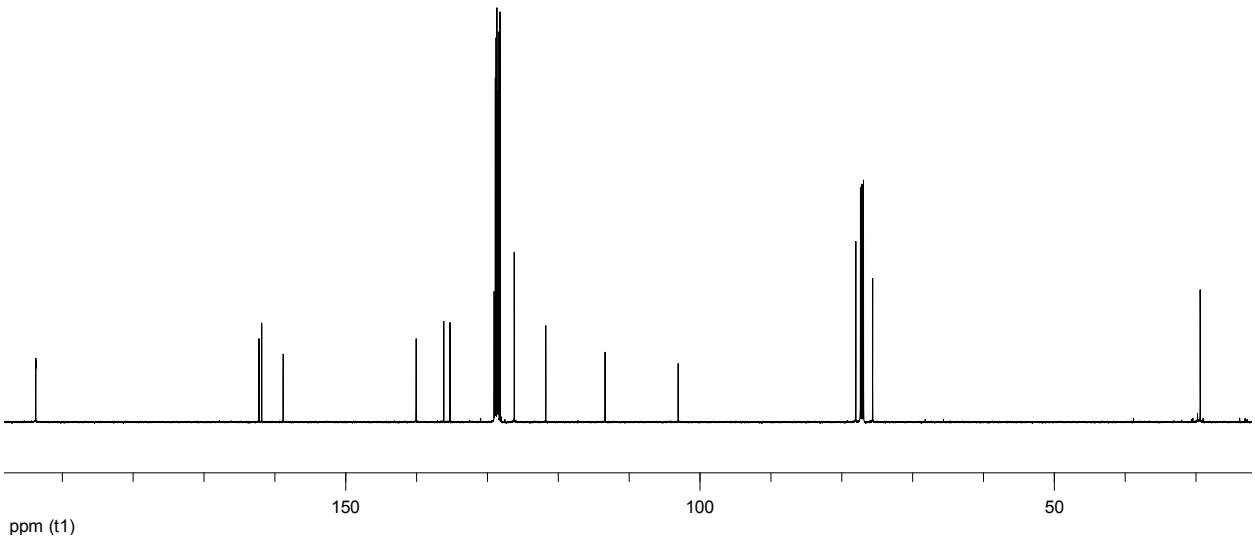
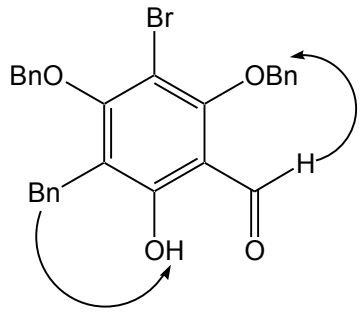


Plate 17c: NOESY of 3-Benzyl-4,6-dibenzyloxy-5-bromo-2-hydroxybenzaldehyde, $CDCl_3$ (298K)



(**4.62**)

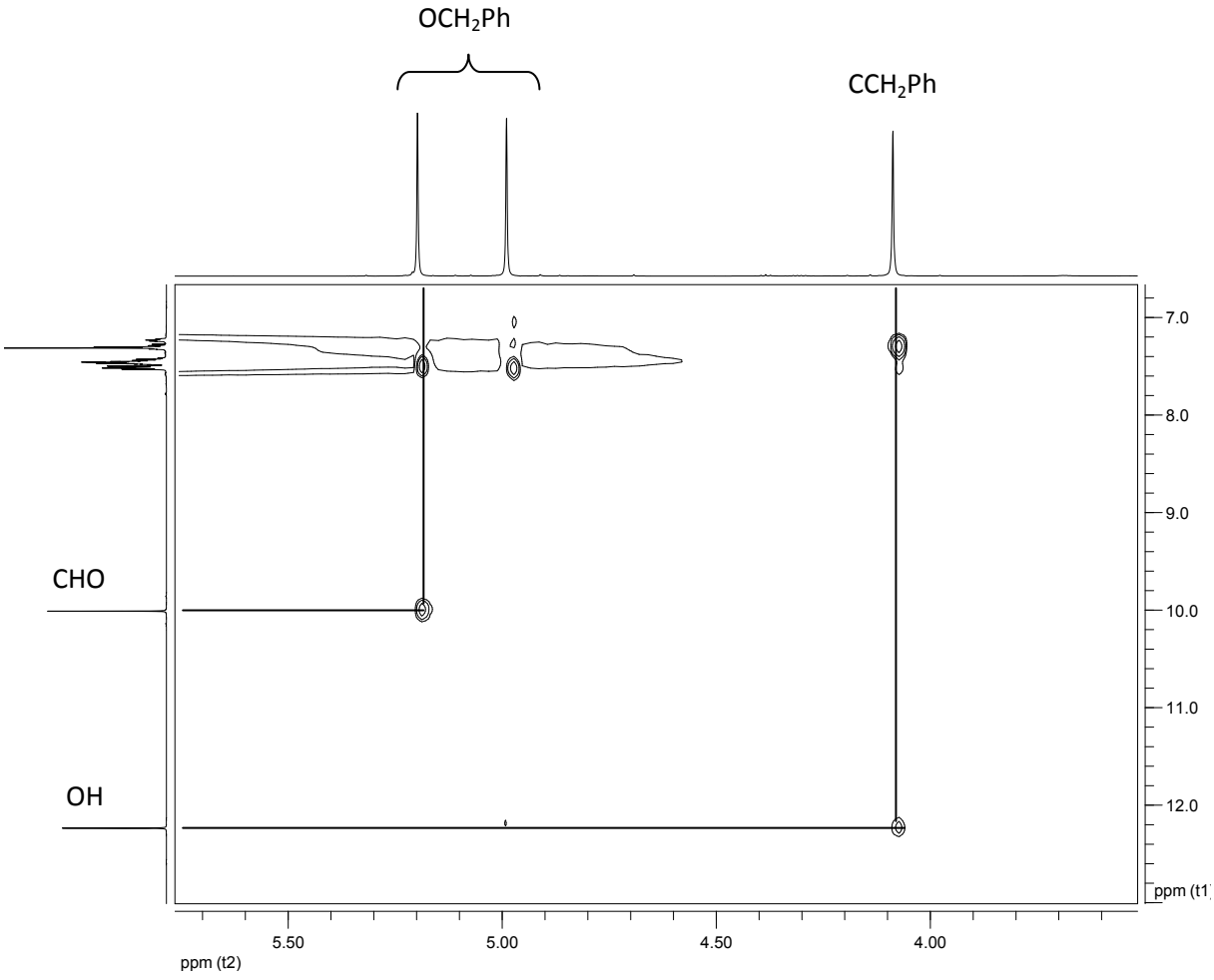
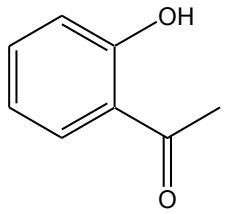
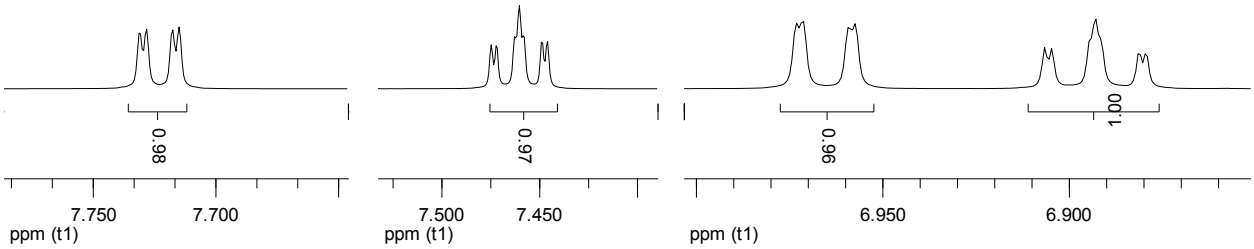


Plate 18: ^{1}H NMR of 2-Hydroxyacetophenone, $CDCl_3$ (298K)



(**4.67**)



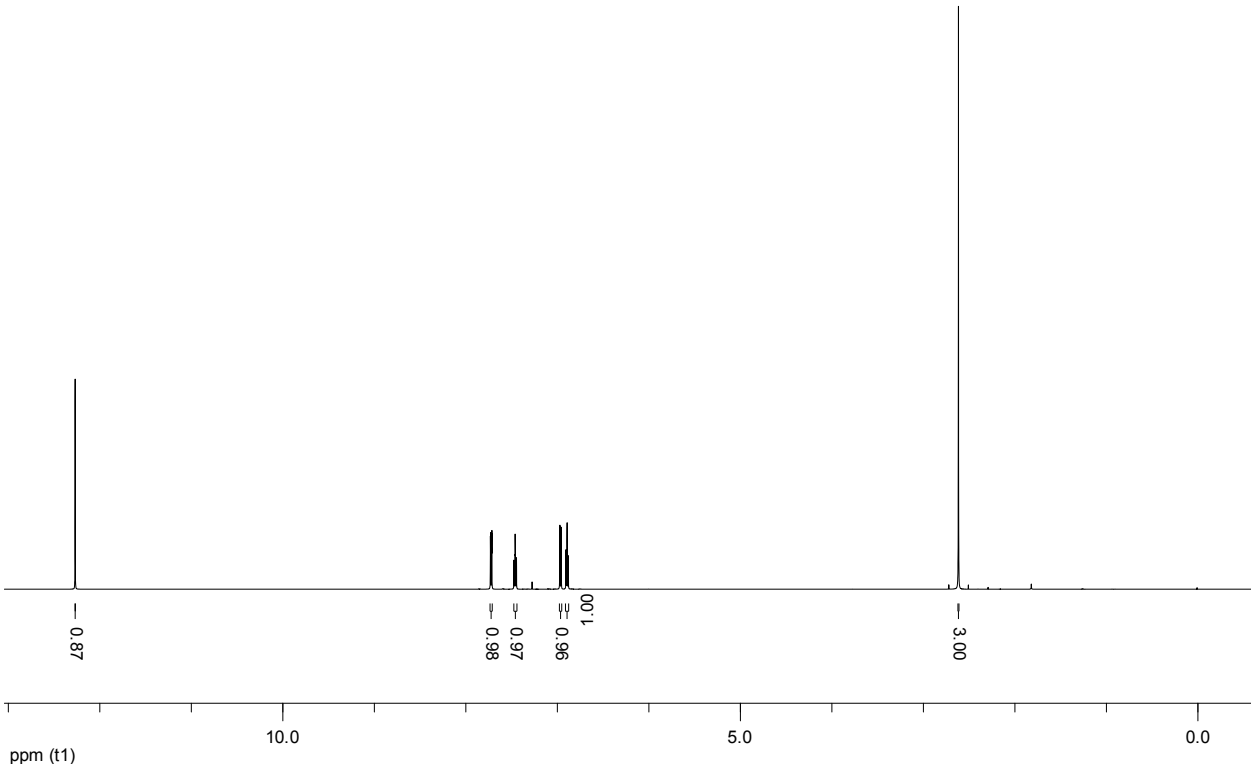
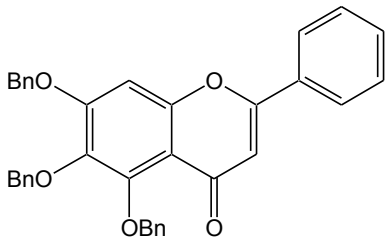
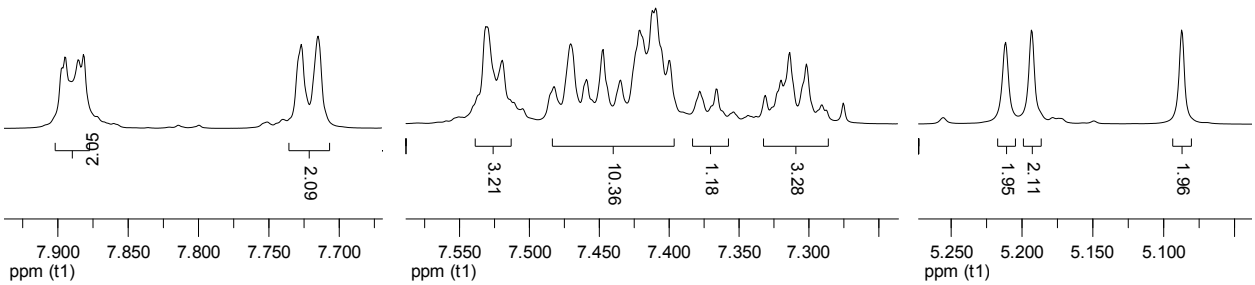


Plate 19a: ^{1}H NMR of 5,6,7-Tribenzyloxyflavone, $CDCl_3$ (298K)



(**4.70**)



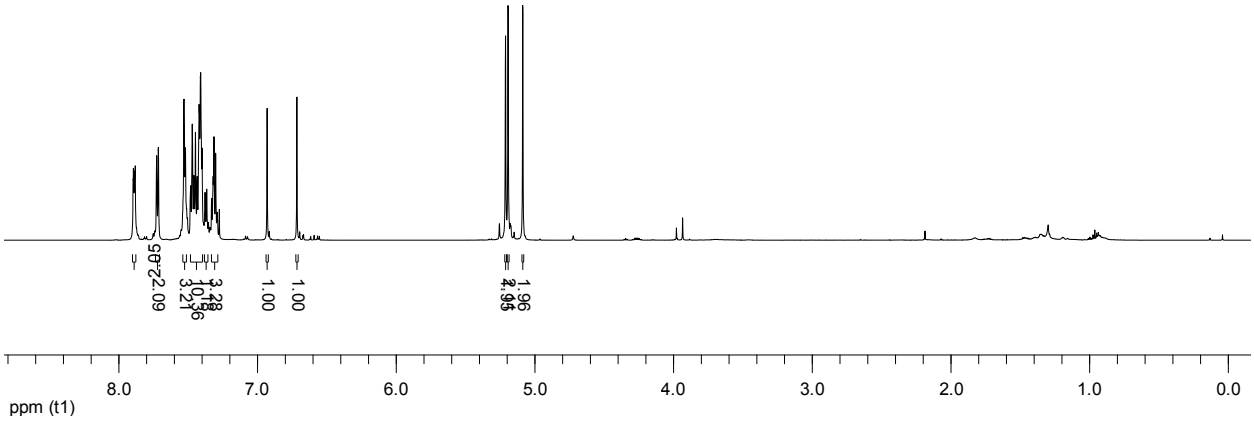
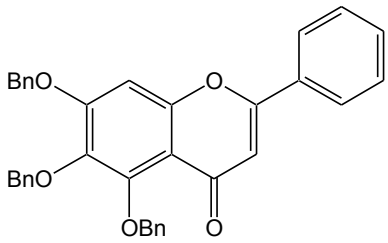


Plate 19b: ^{13}C NMR of 5,6,7-Tribenzyloxyflavone, $CDCl_3$ (298K)



(**4.70**)

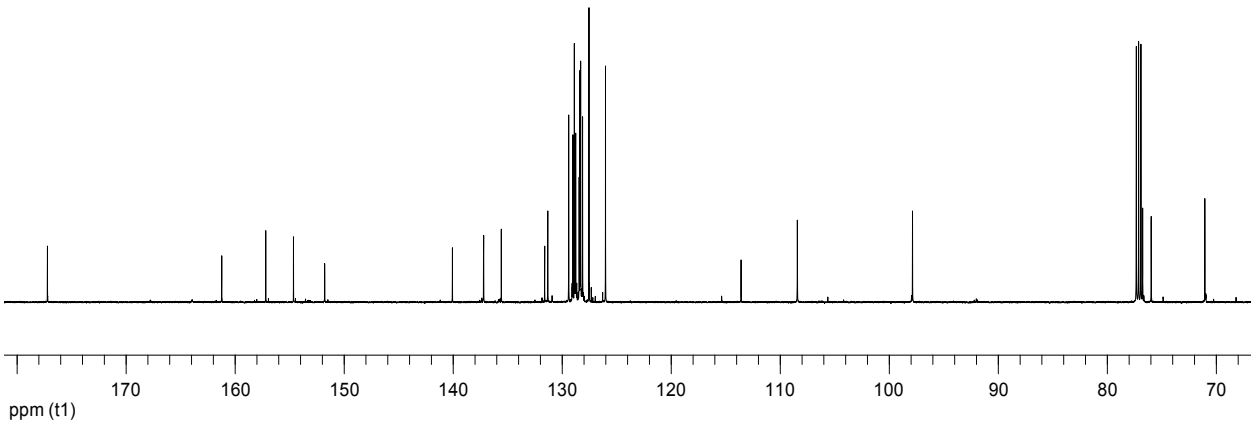
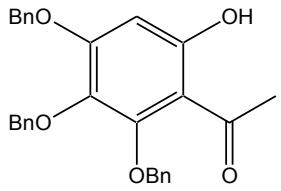
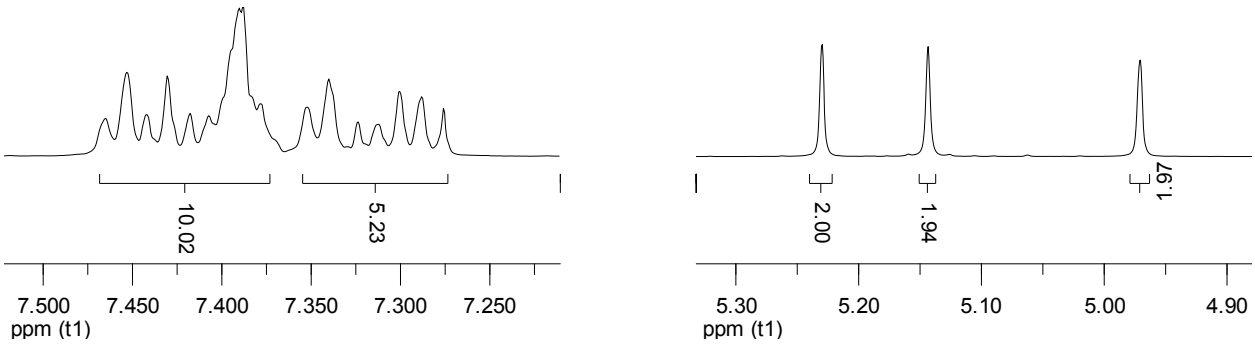


Plate 20a: ^{1}H NMR of 2,3,4-Tribenzyloxy-6-hydroxyacetophenone, $CDCl_3$ (298K)



(**4.71**)



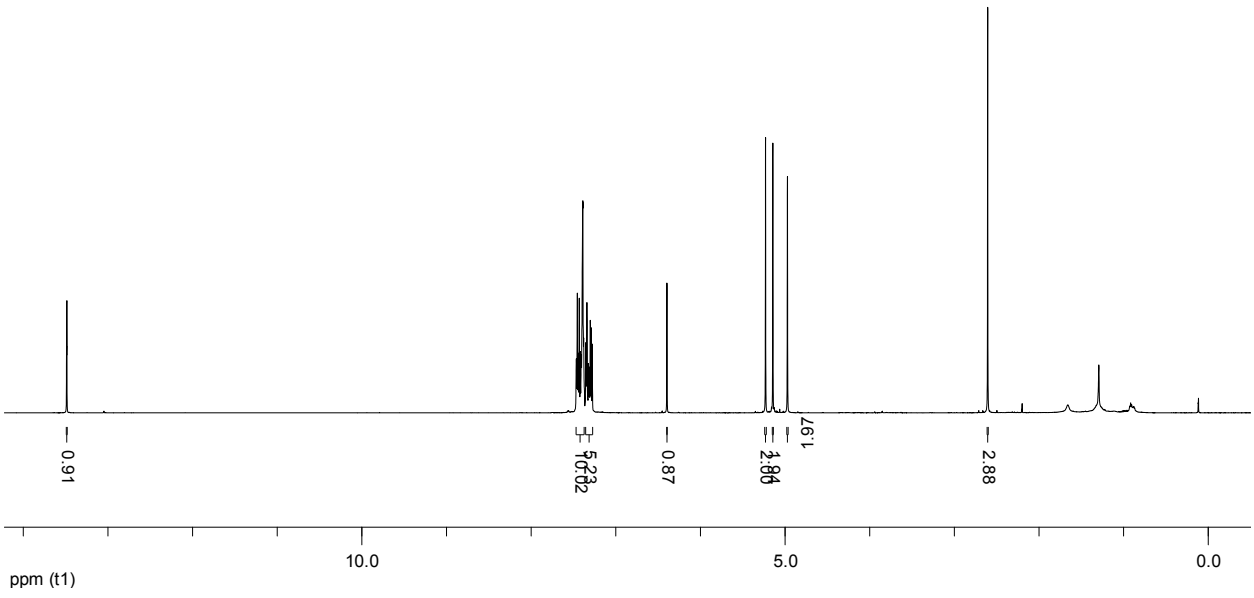
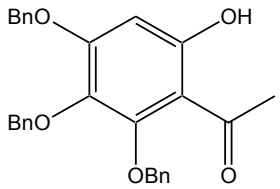


Plate 20b: ^{13}C NMR of 2,3,4-Tribenzyloxy-6-hydroxyacetophenone, $CDCl_3$ (298K)



(**4.71**)

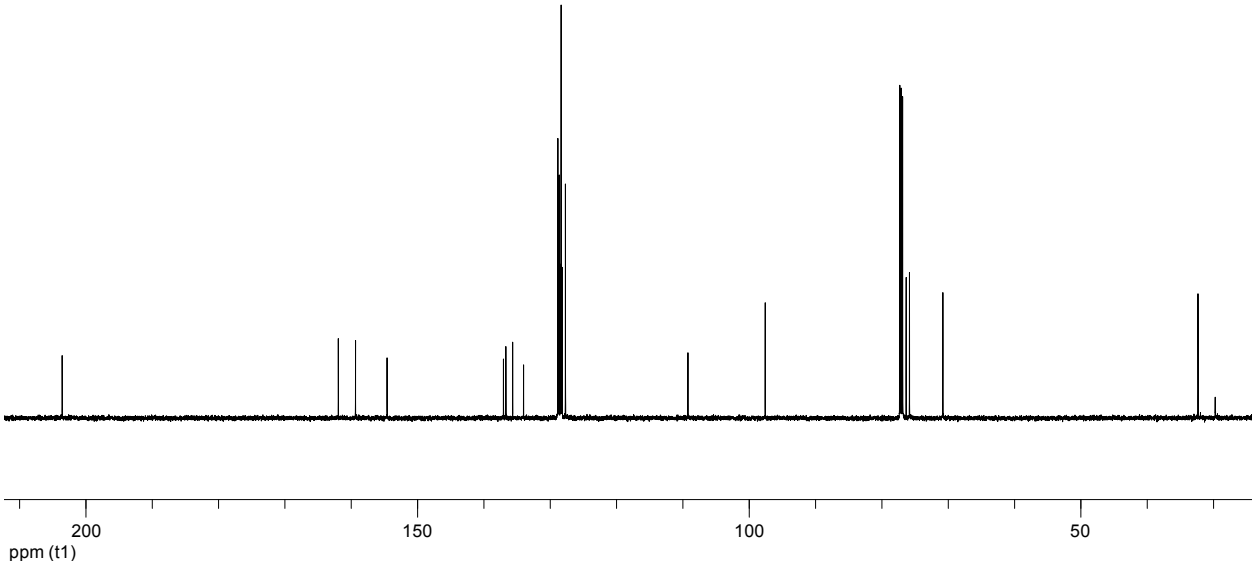
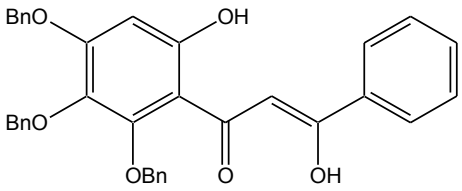
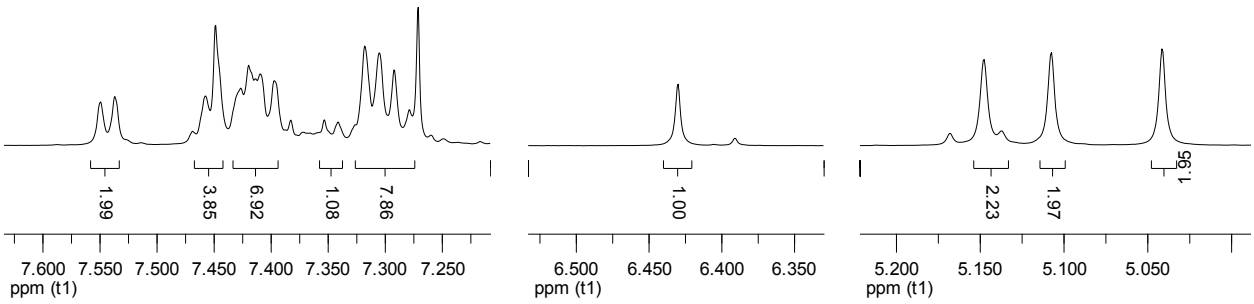


Plate 21a: ^{1}H NMR of 2',3',4'-Tribenzyloxy-β,6'-dihydroxychalcone, $CDCl_3$ (298K)



(**4.72**)



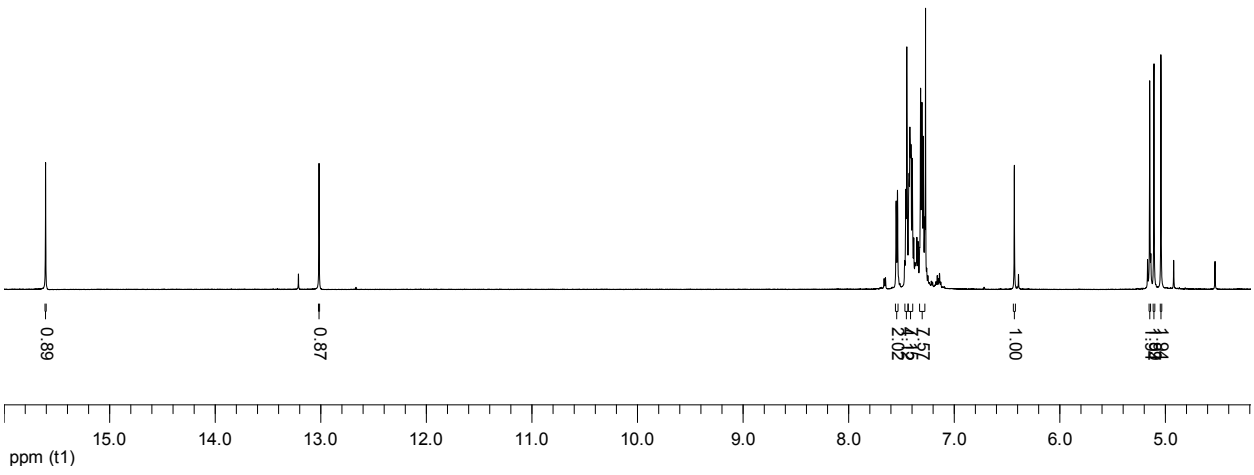
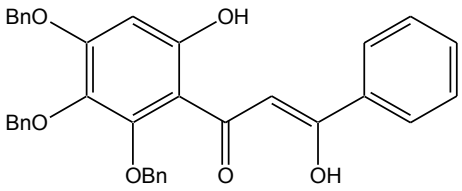


Plate 21b: ^{13}C NMR of 2',3',4'-Tribenzyloxy-β,6'-dihydroxychalcone, $CDCl_3$ (298K)



(**4.72**)

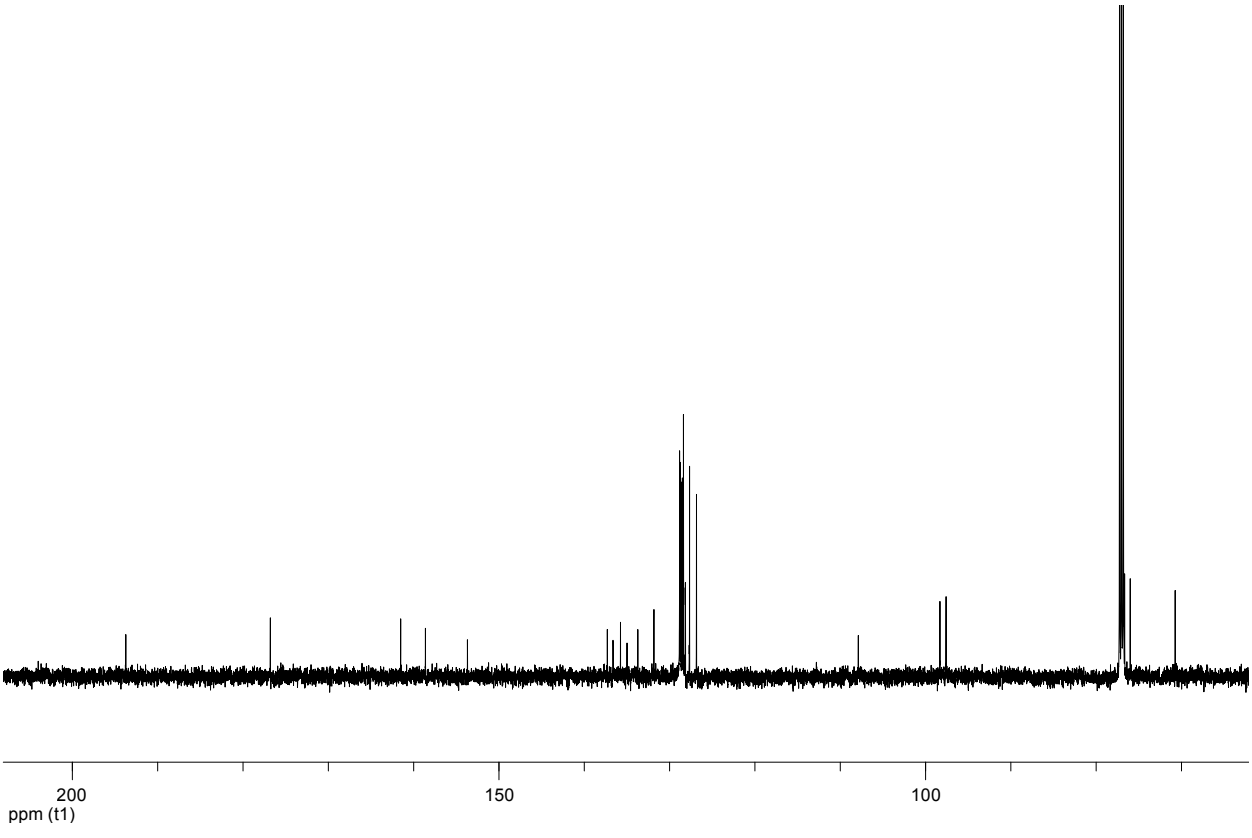
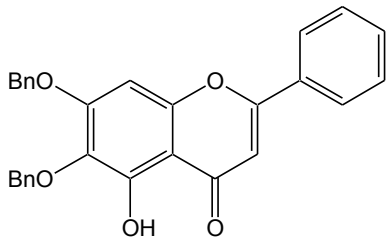
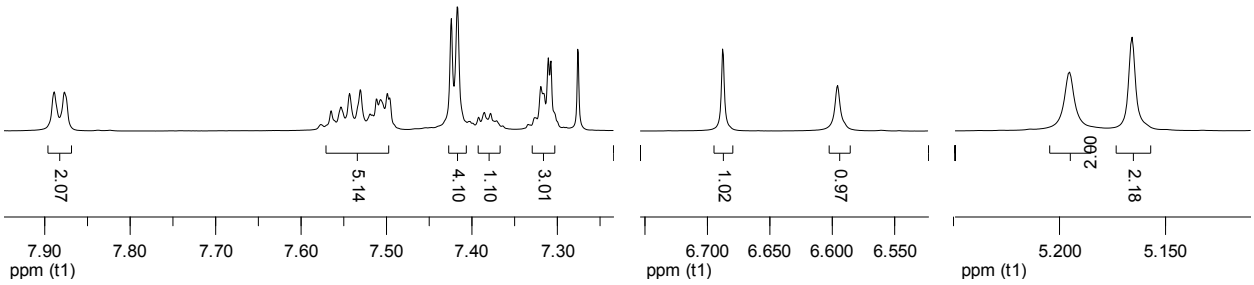


Plate 22a: ^{1}H NMR of 6,7-Dibenzyloxy-5-hydroxyflavone, $CDCl_3$ (298K)



(**4.73**)



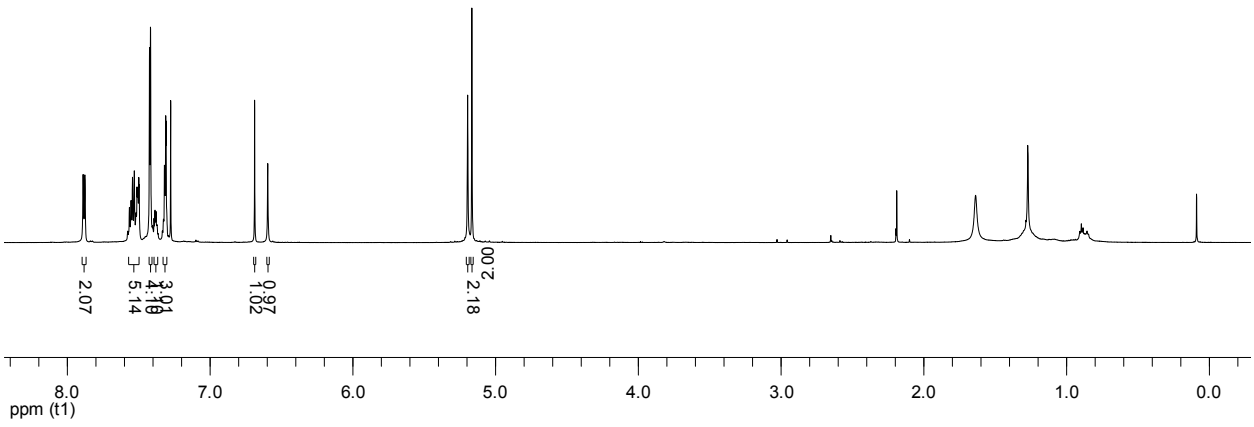
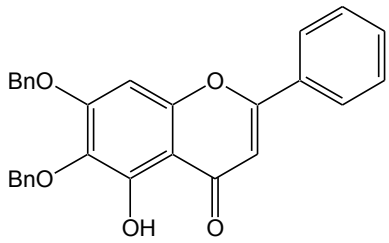


Plate 22b: ^{13}C NMR of 6,7-Dibenzyloxy-5-hydroxyflavone, $CDCl_3$ (298K)



(**4.73**)

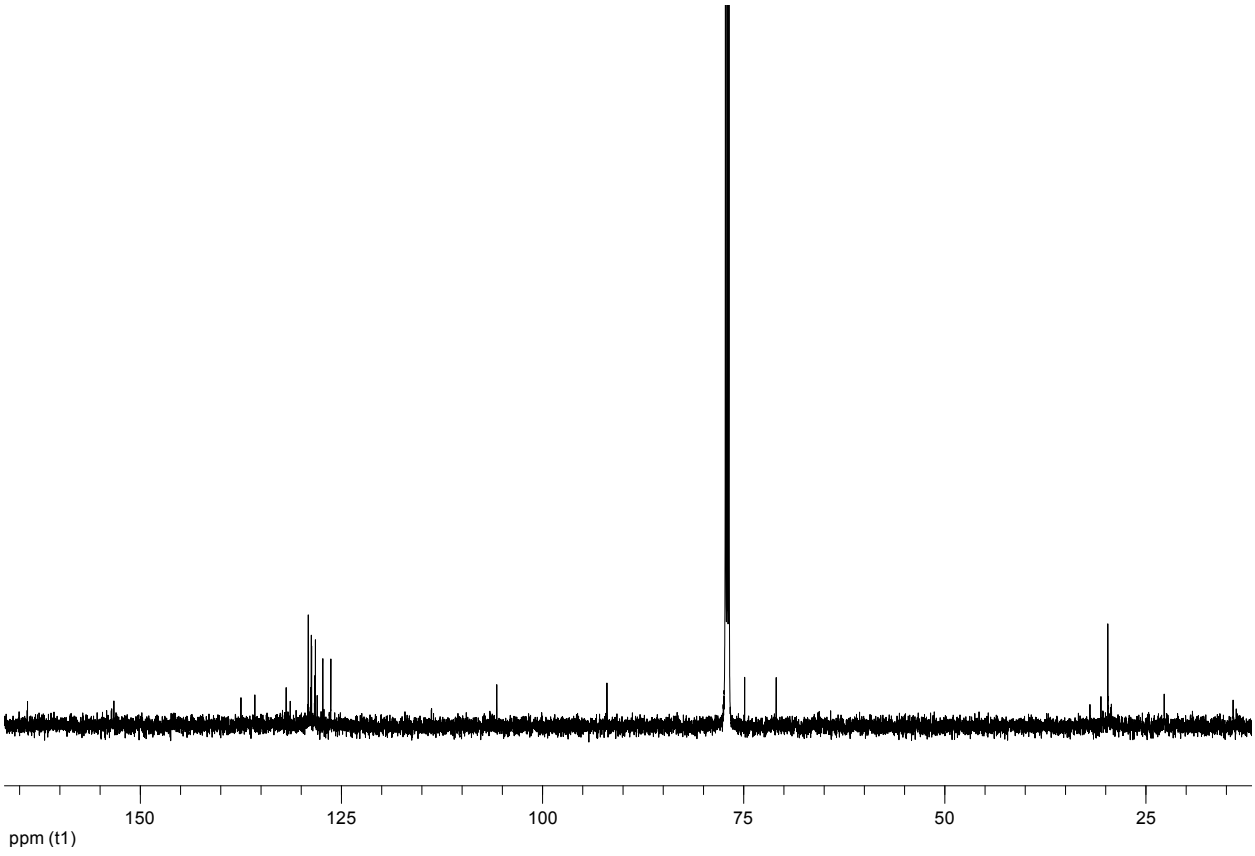
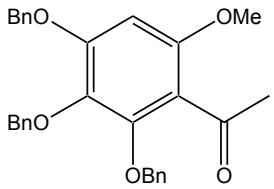
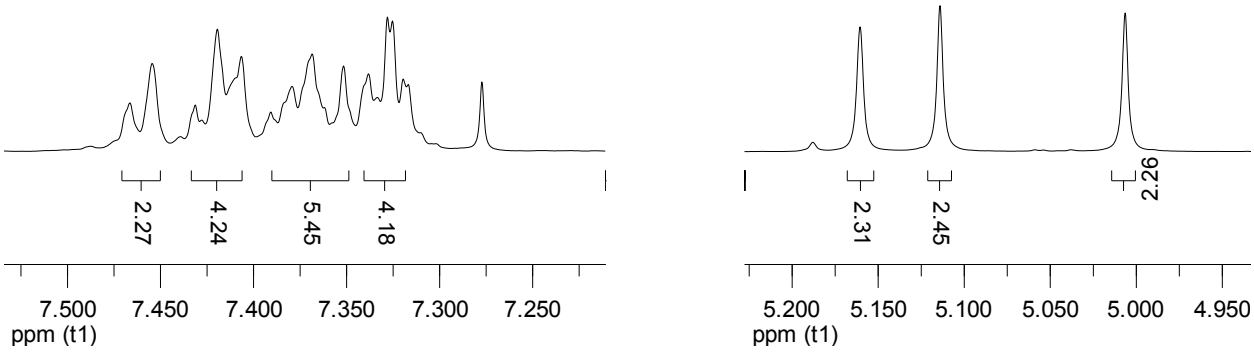


Plate 23a: ^{1}H NMR of 2,3,4-Tribenzyloxy-6-methoxyacetophenone, $CDCl_3$ (298K)



(**4.163**)



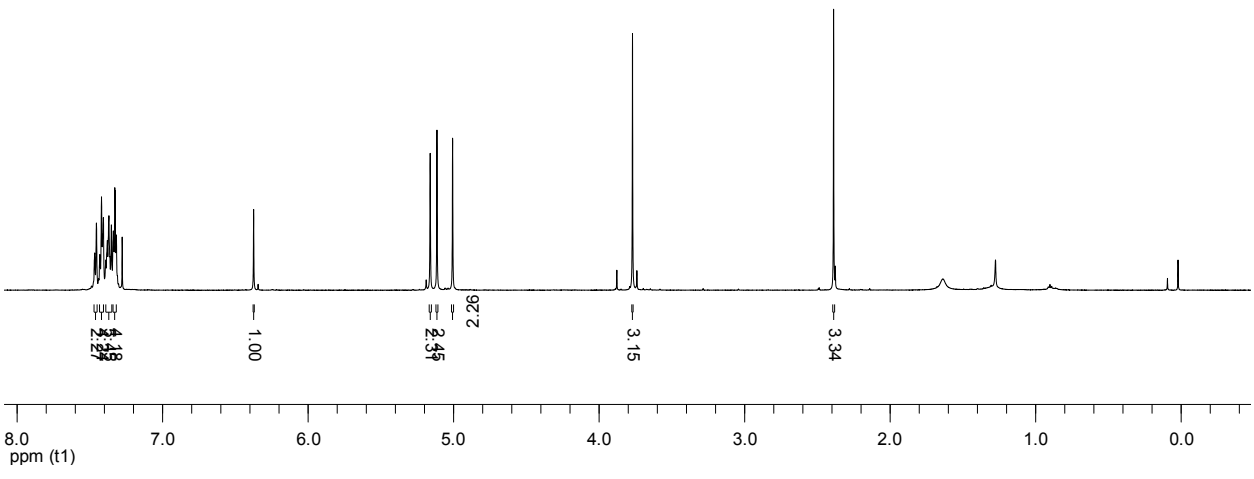
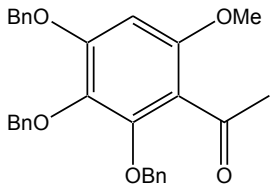


Plate 23b: ^{13}C NMR of 2,3,4-Tribenzyloxy-6-methoxyacetophenone, $CDCl_3$ (298K)



(**4.163**)

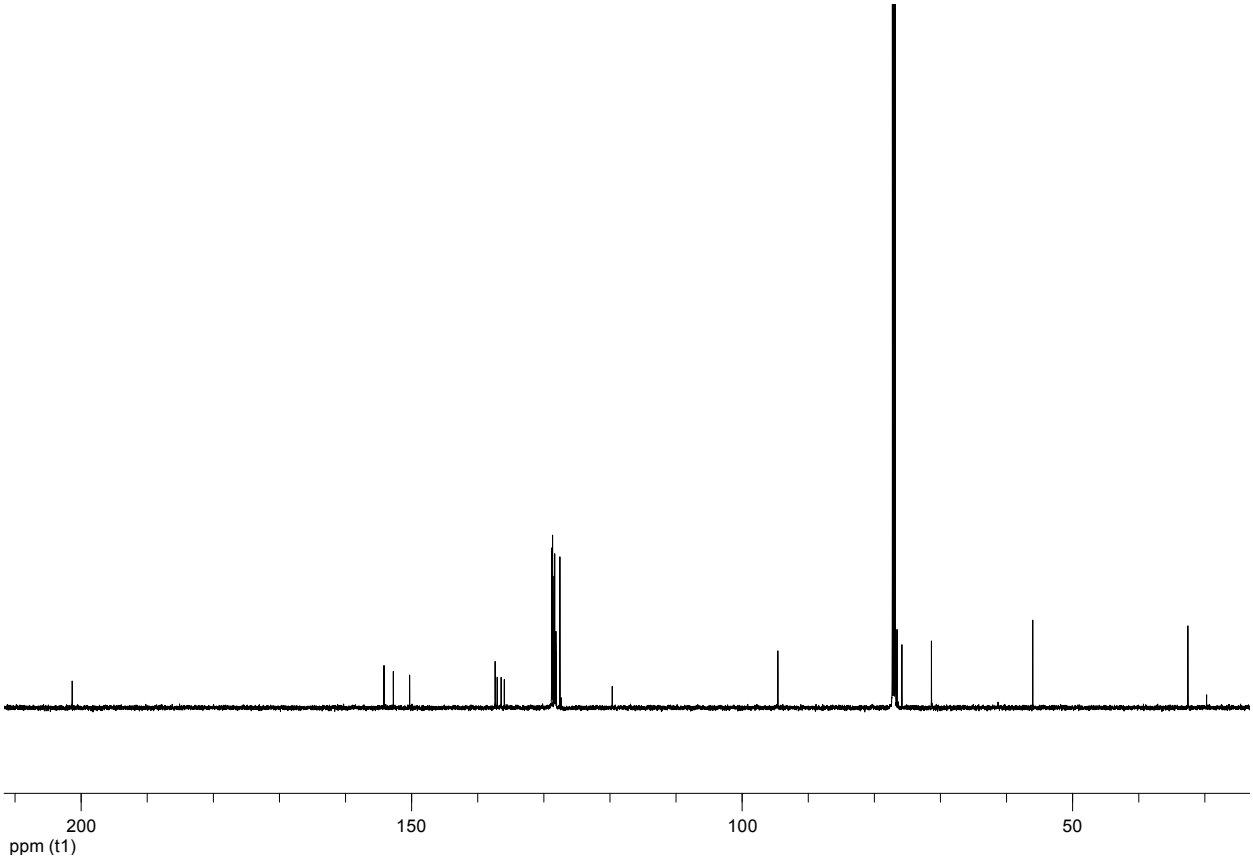
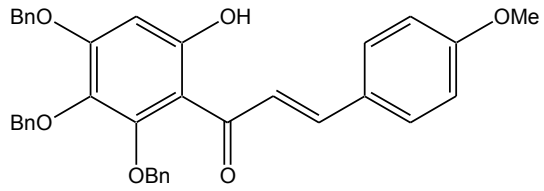


Plate 24a: ^{1}H NMR of 2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxychalcone, $CDCl_3$ (298K)



(**4.74**)

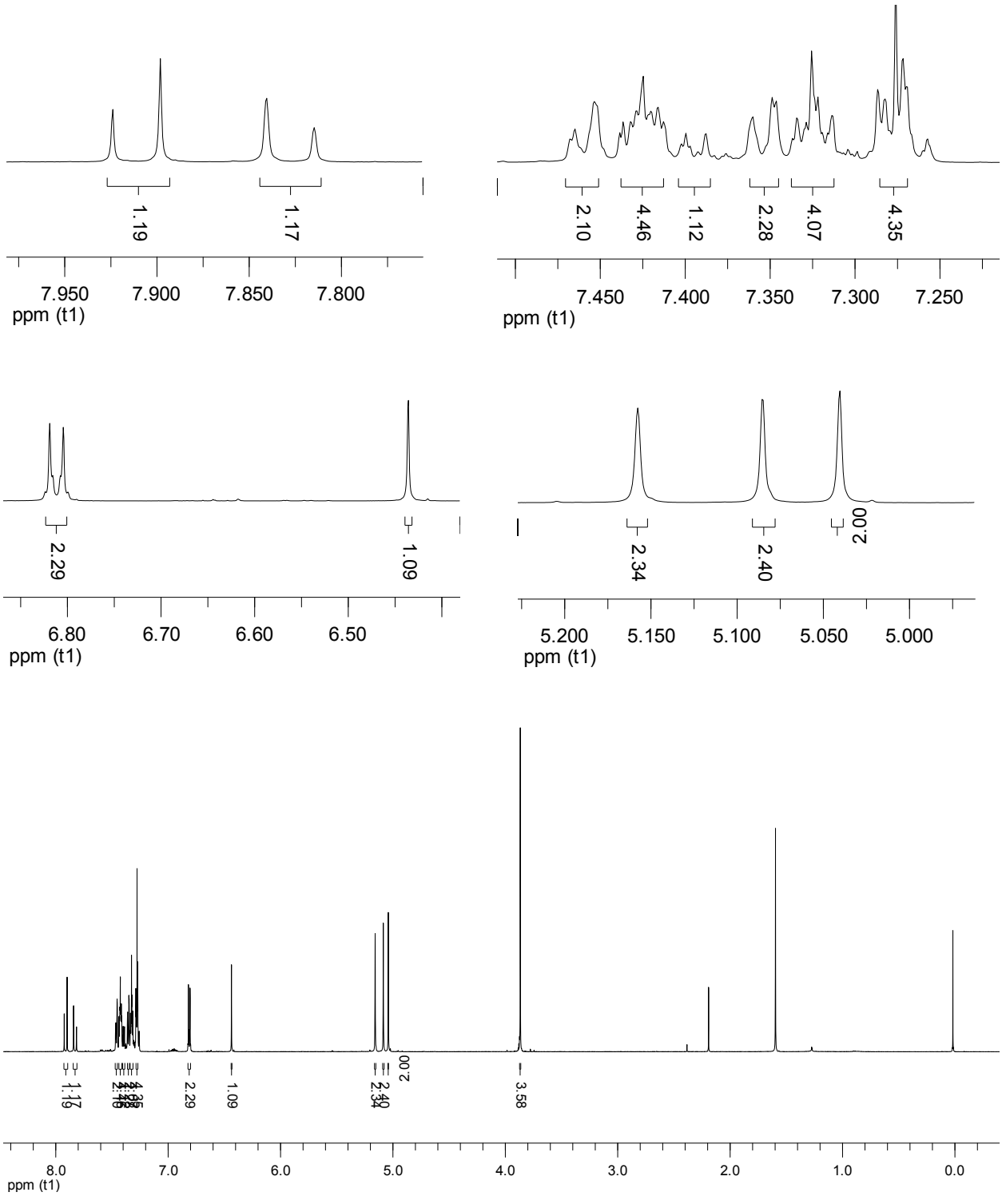
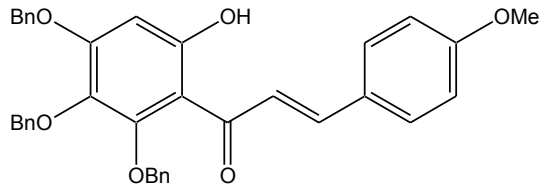


Plate 24b: ^{13}C NMR of 2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxychalcone, $CDCl_3$ (298K)



(**4.74**)

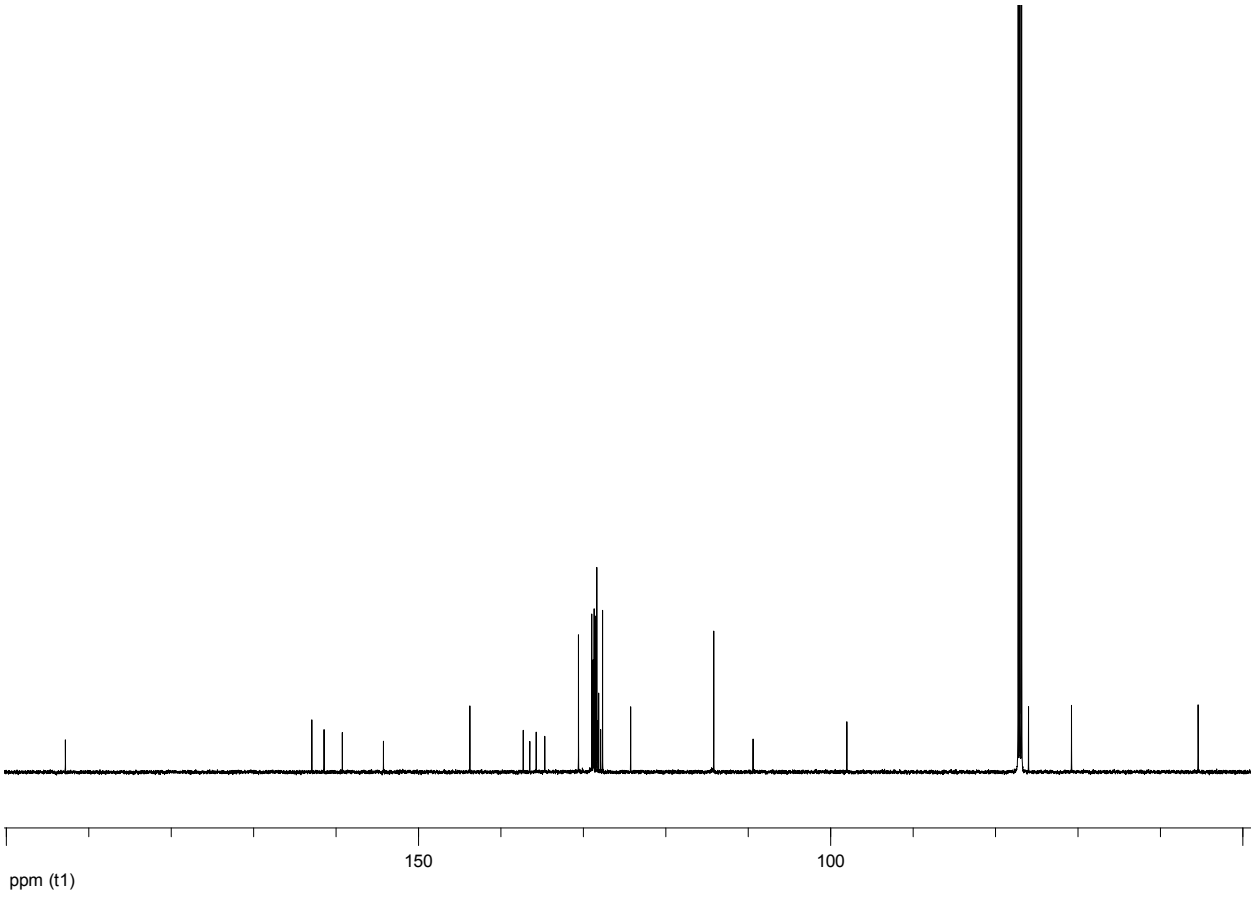
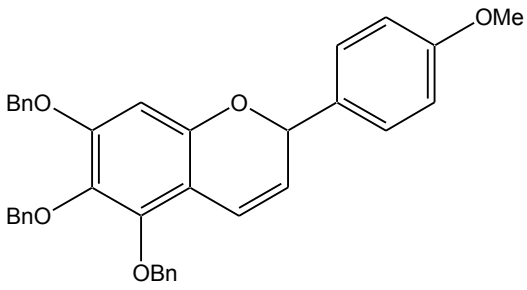


Plate 25a: ^{1}H NMR of 5,6,7-Tribenzyloxy-4'-methoxyflav-3-ene, $CDCl_3$ (298K)



(**4.75**)

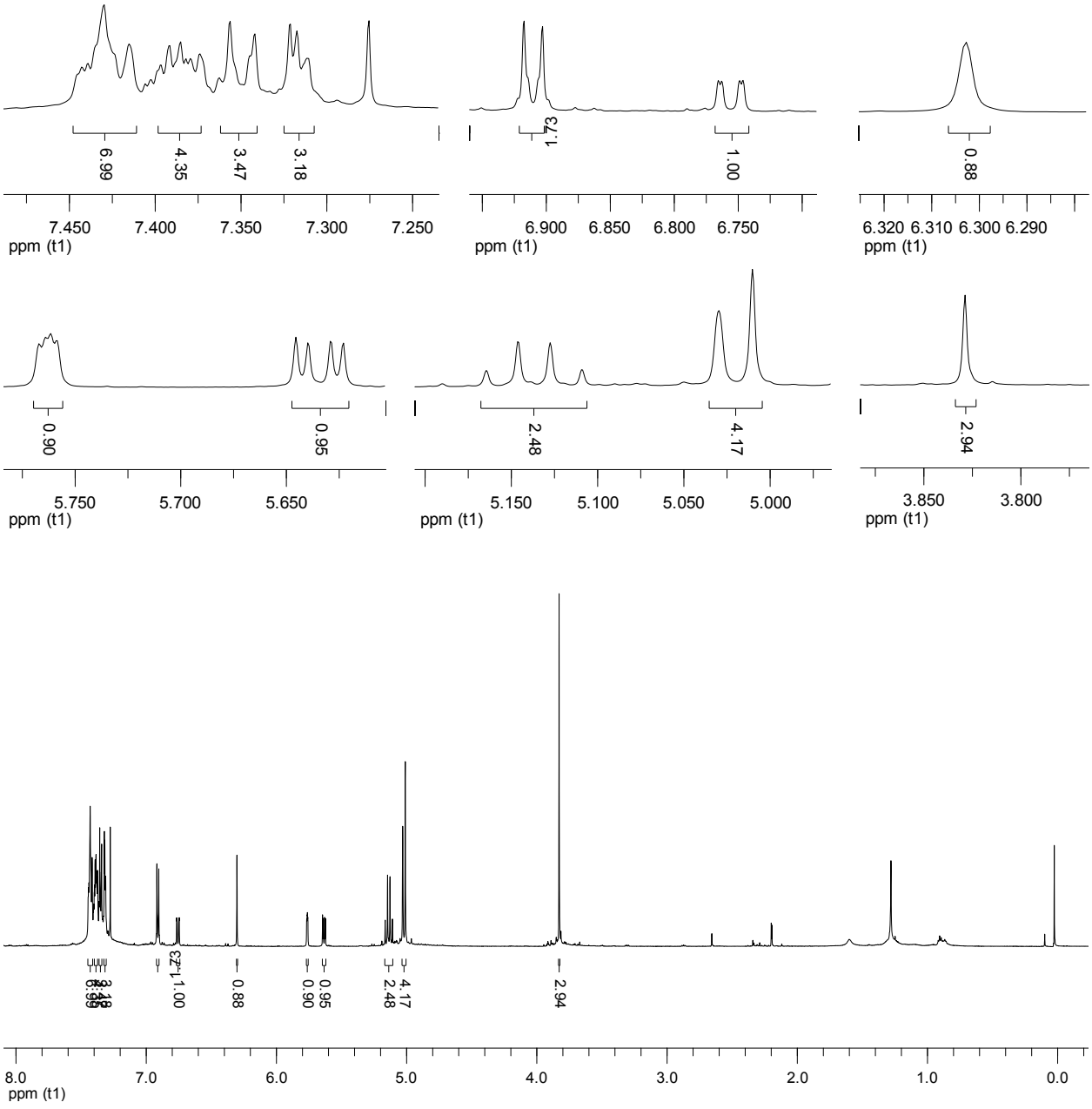
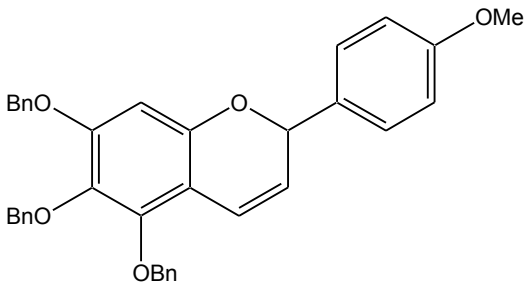


Plate 25b: ^{13}C NMR of 5,6,7-Tribenzyloxy-4'-methoxyflav-3-ene, $CDCl_3$ (298K)



(**4.75**)

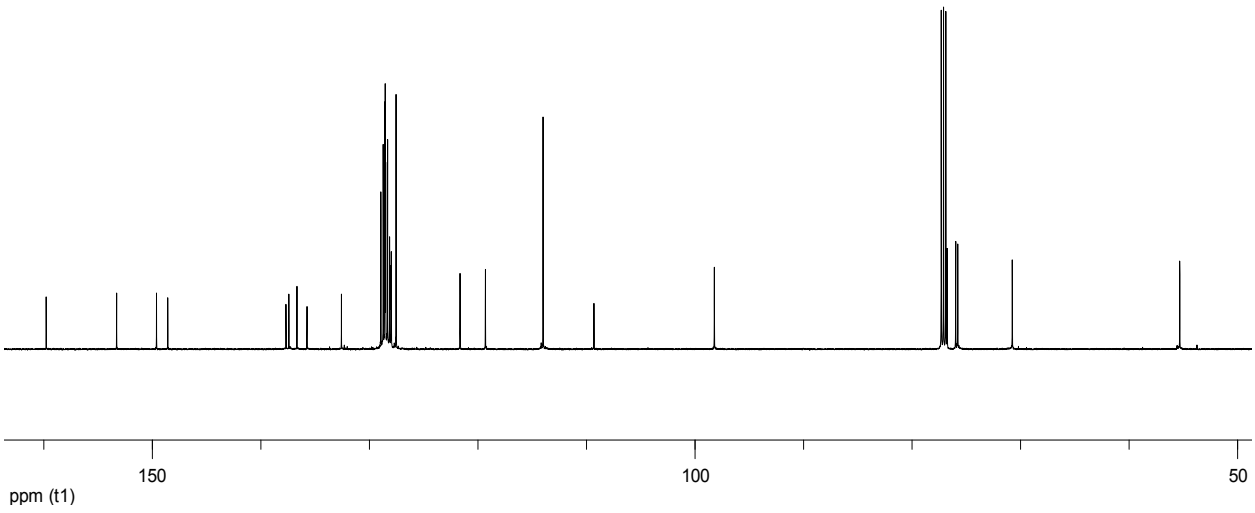
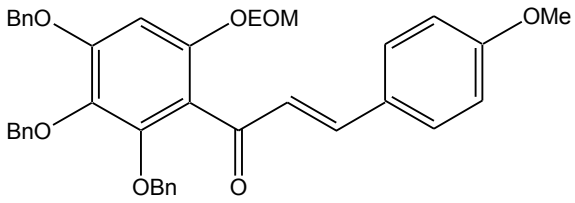


Plate 26: ^{1}H NMR of 2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxychalcone, $CDCl_3$ (298K)



(**4.76**)

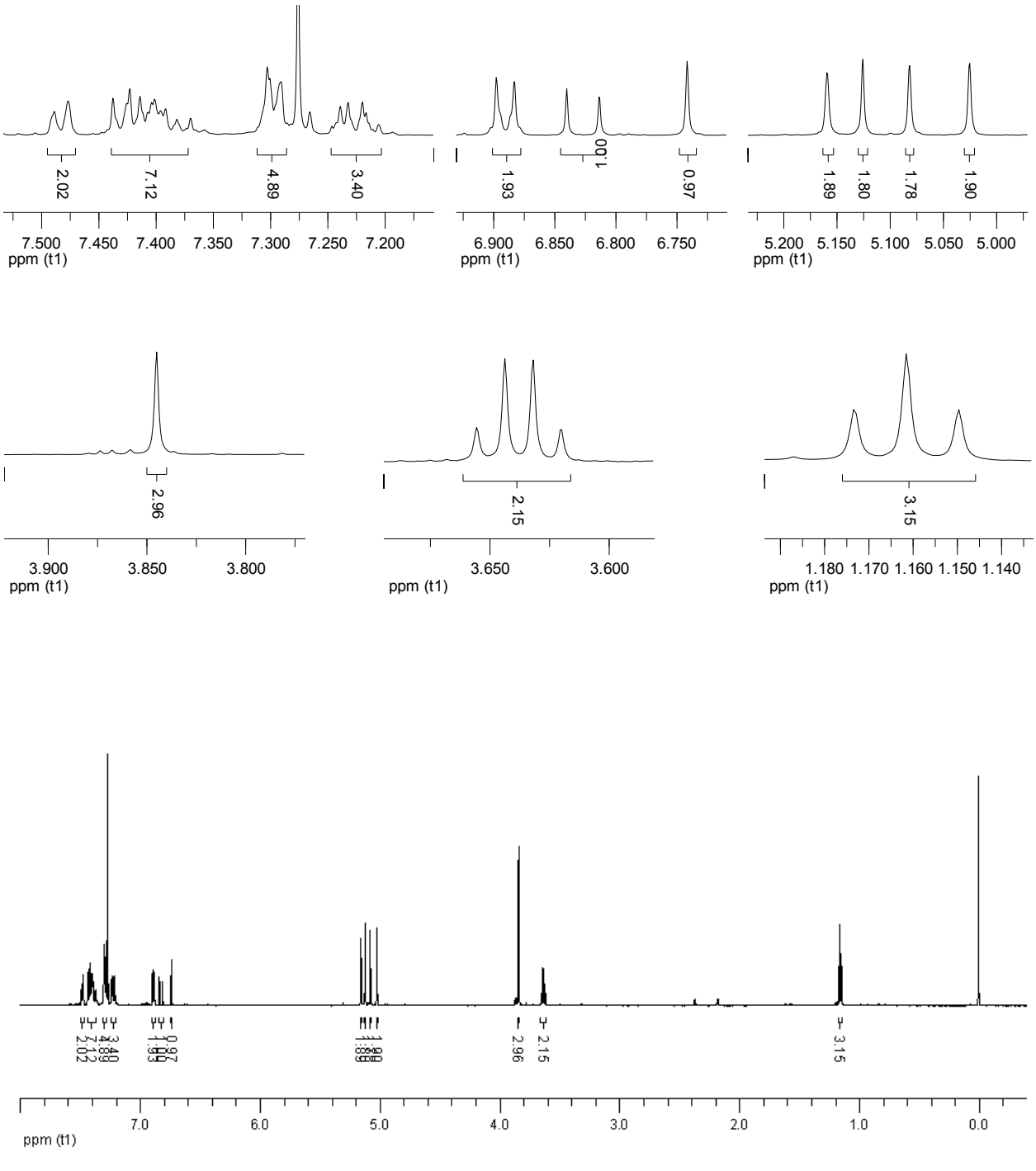
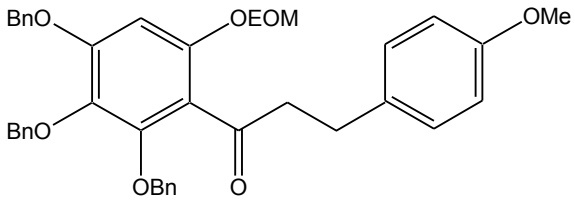


Plate 27a: ^{1}H NMR of 2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.77**)

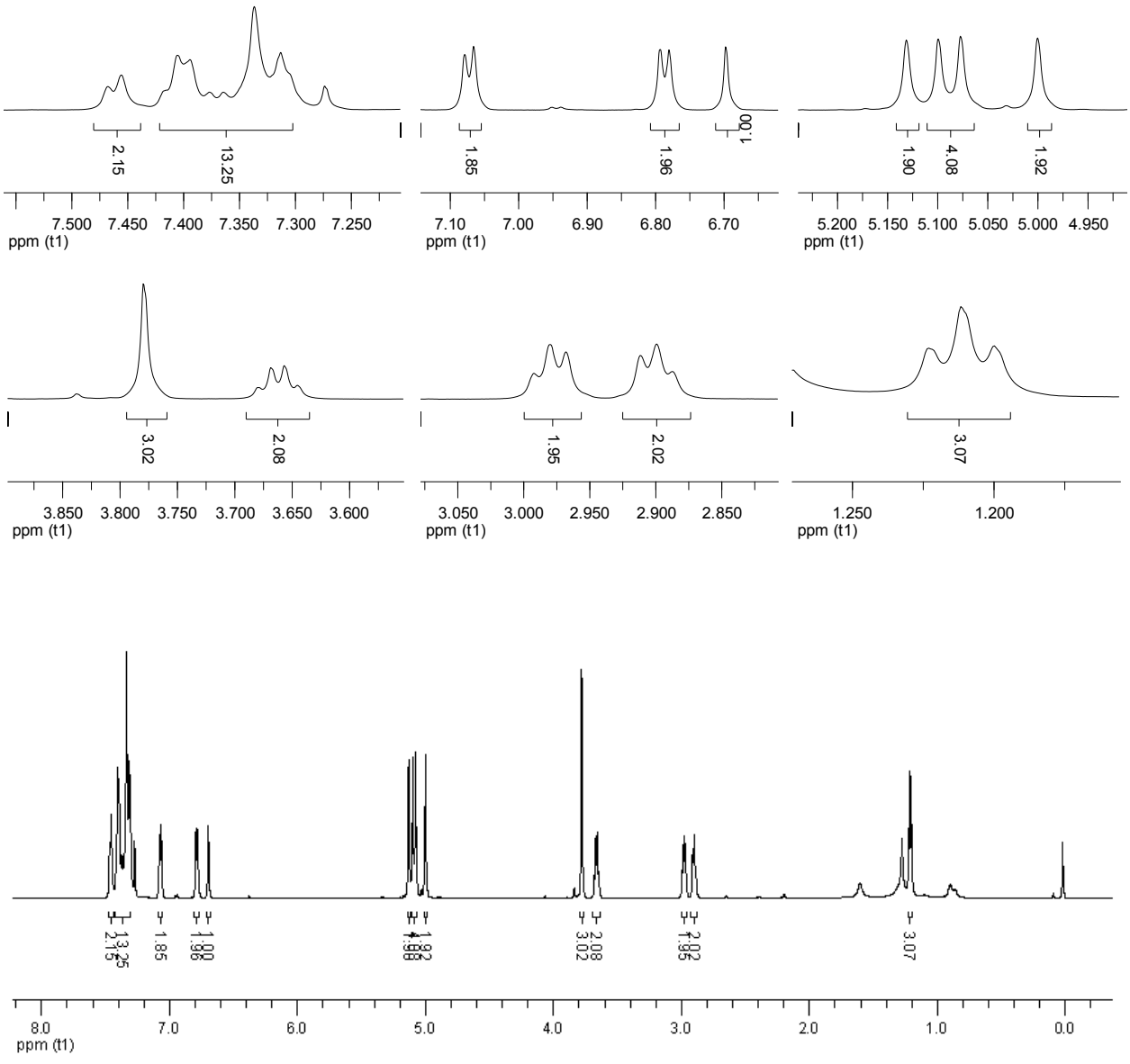
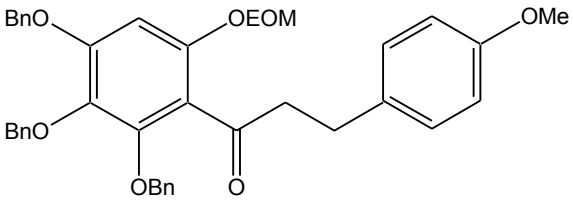


Plate 27b: ^{13}C NMR of 2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.77**)

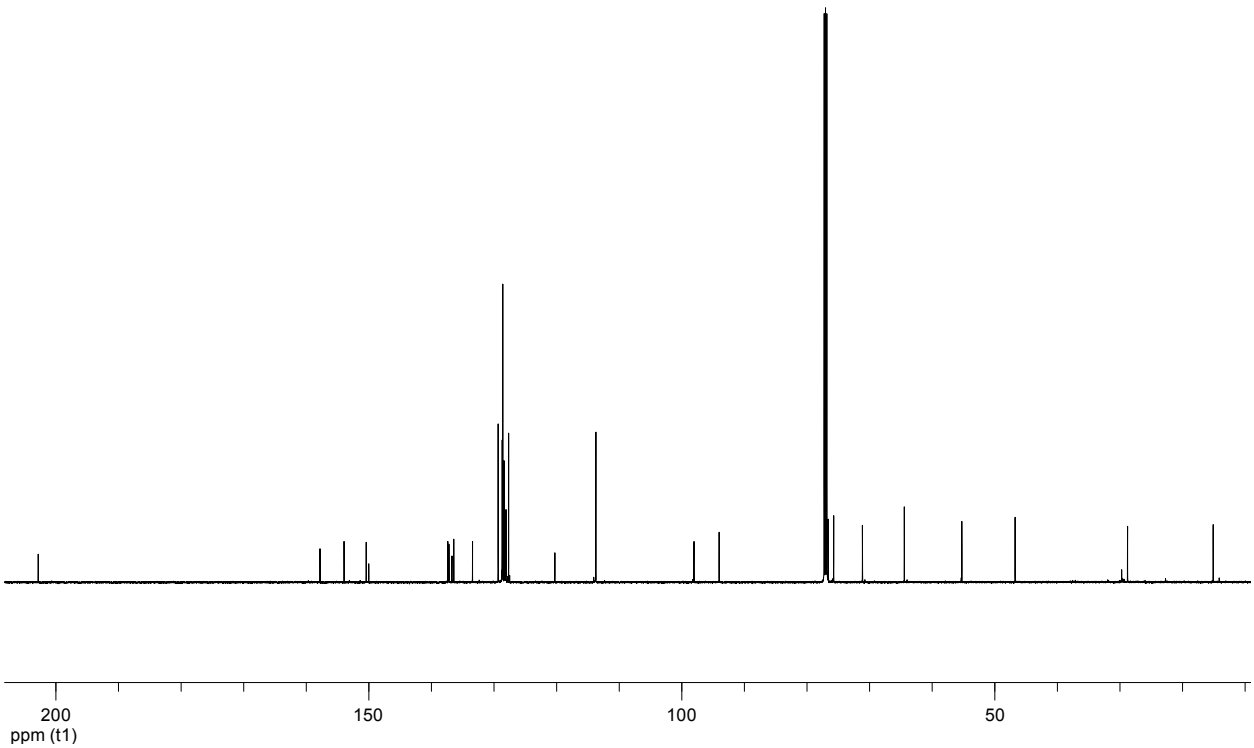
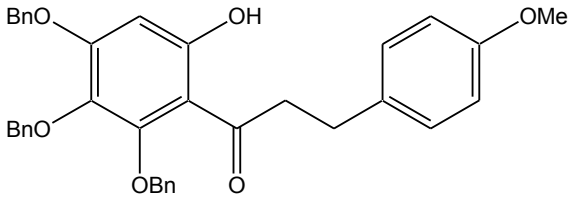
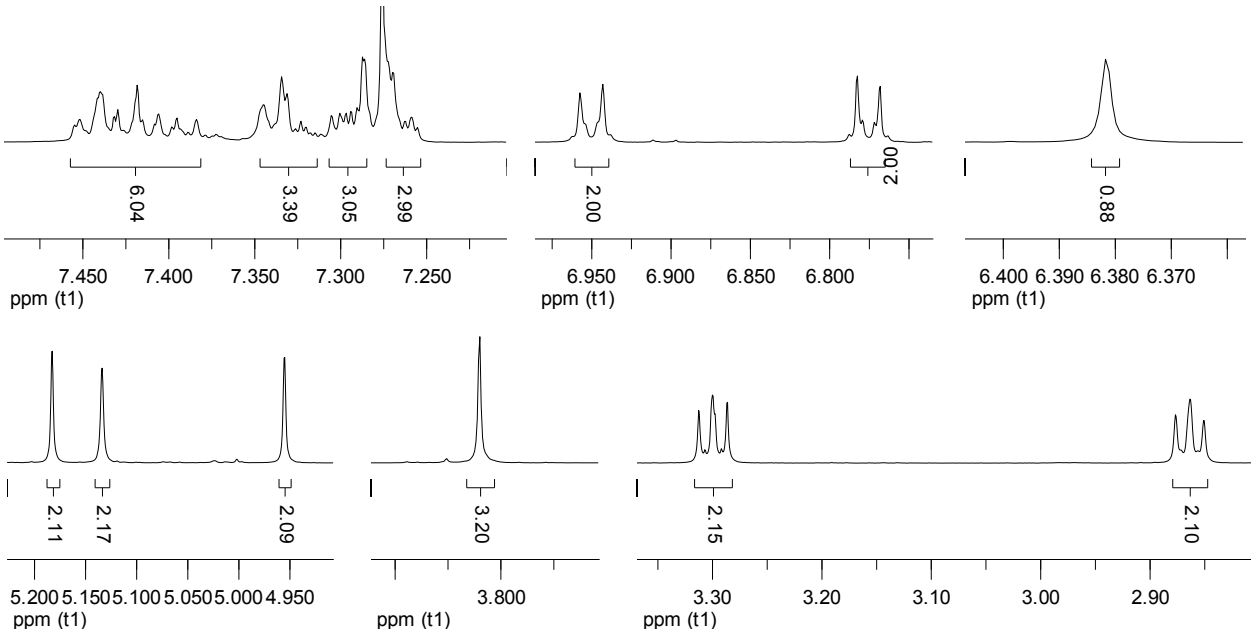


Plate 28a: ^{1}H NMR of 2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.78**)



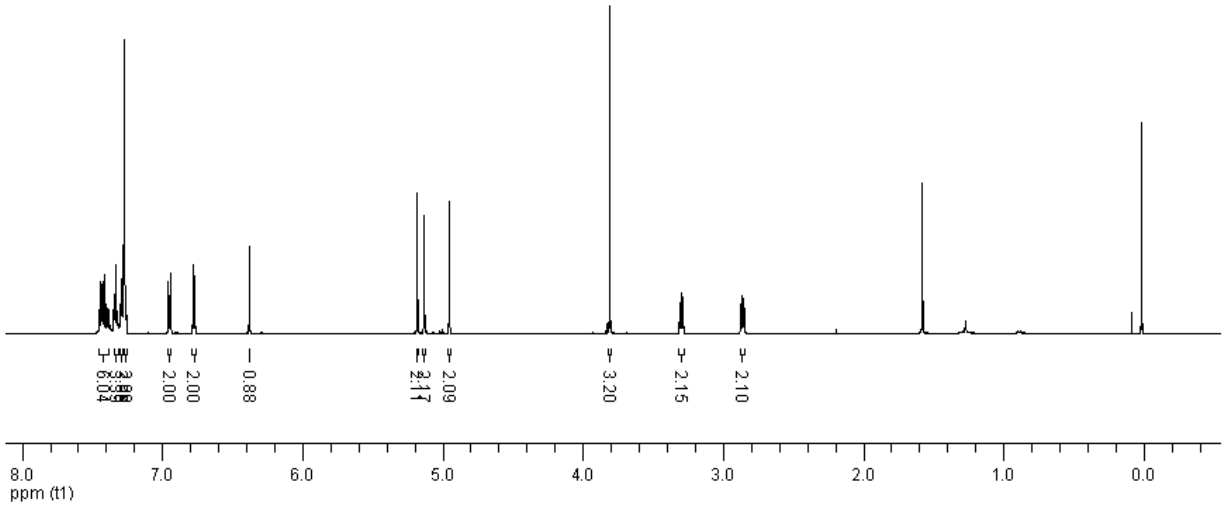
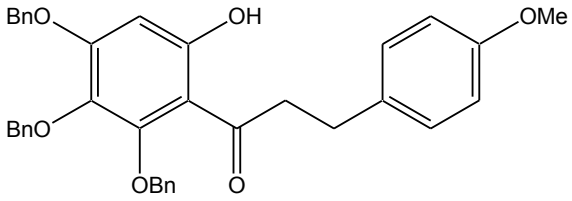


Plate 28b: ^{13}C NMR of 2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.78**)

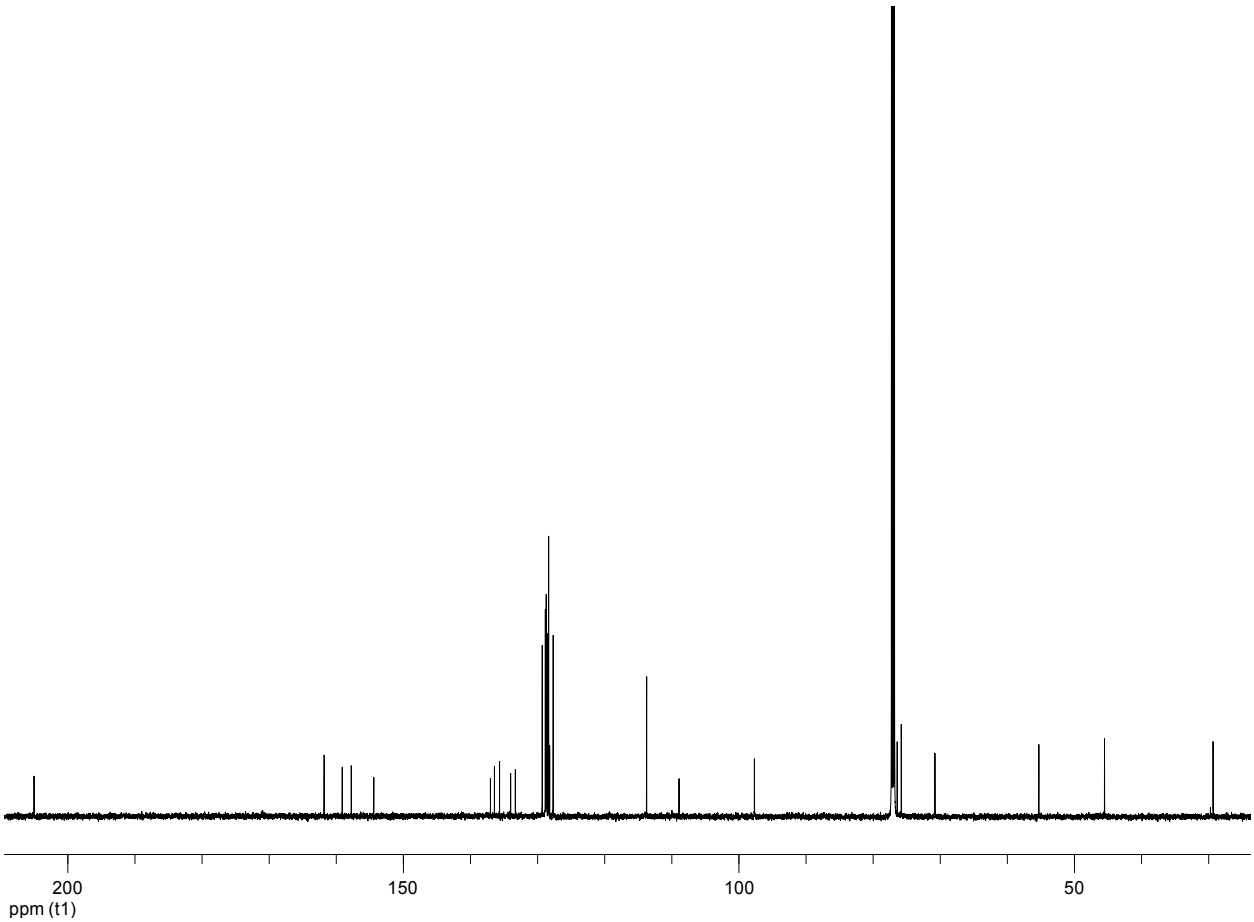
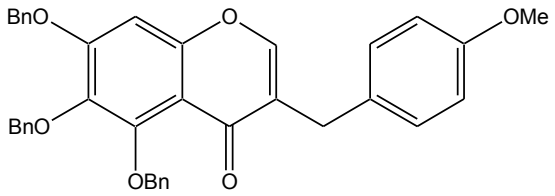
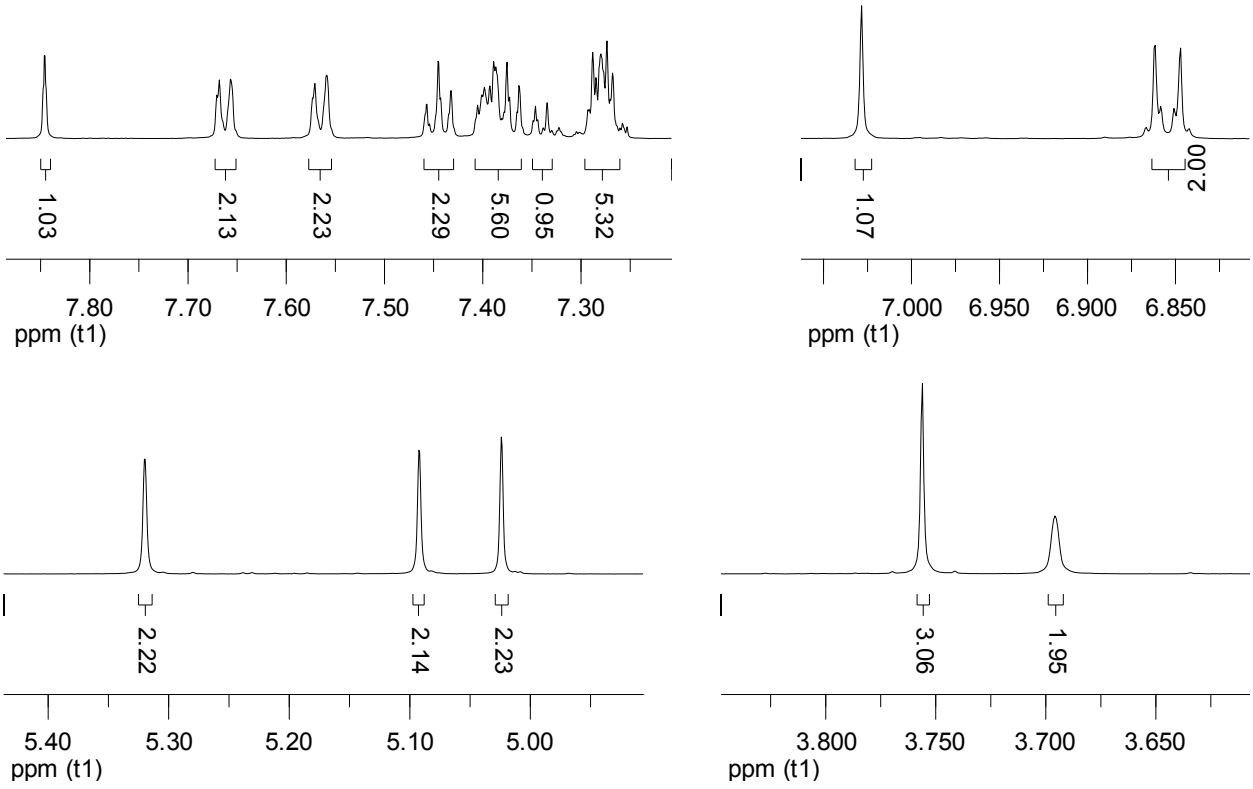


Plate 29a: ^{1}H NMR of 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavone, acetone (298K)



(**4.79**)



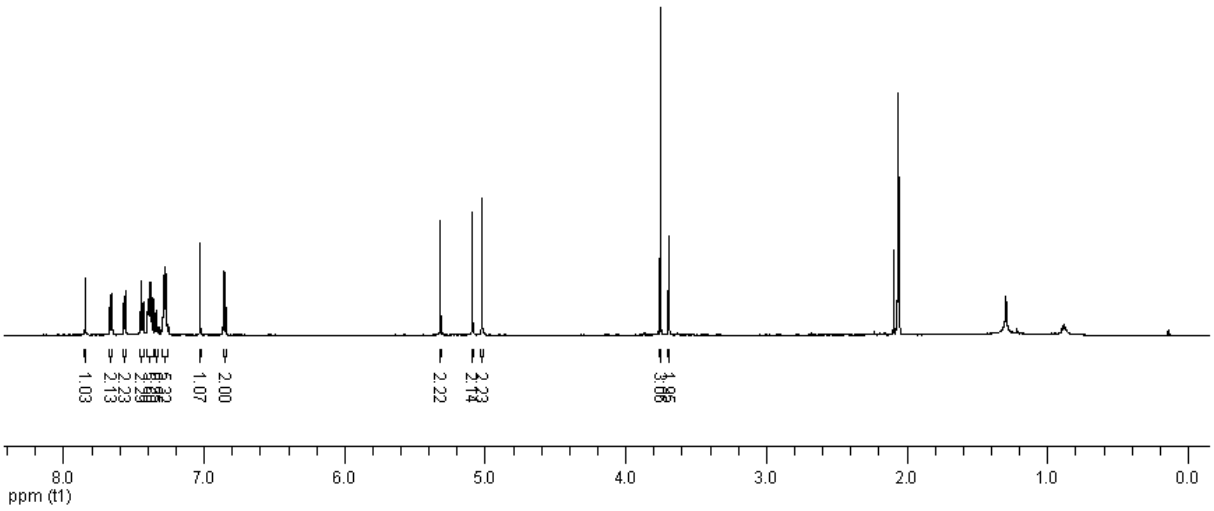
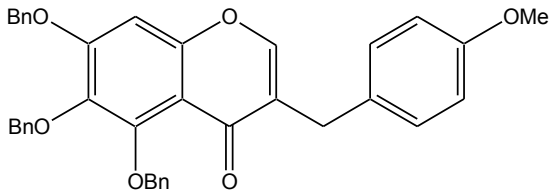


Plate 29b: ^{13}C NMR of 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavone, acetone (298K)



(**4.79**)

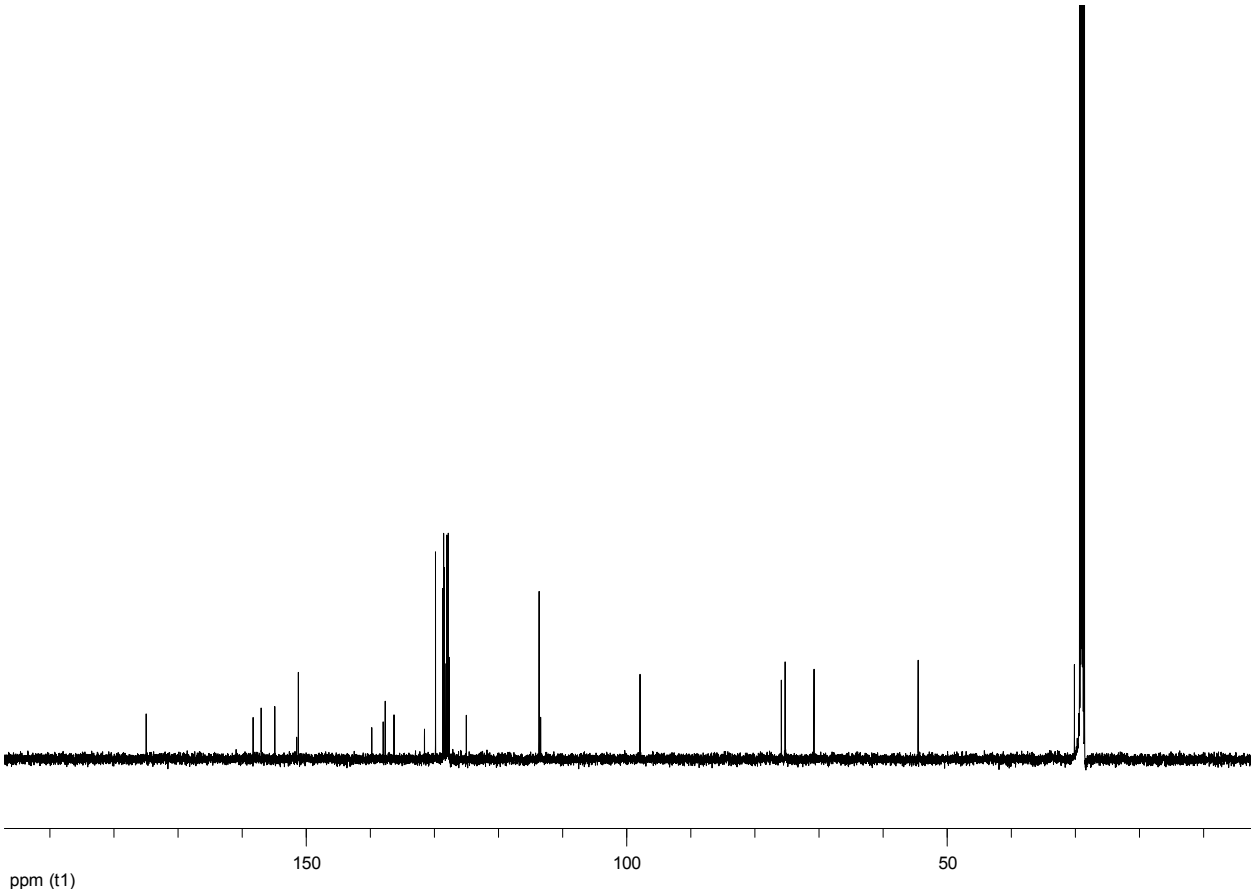
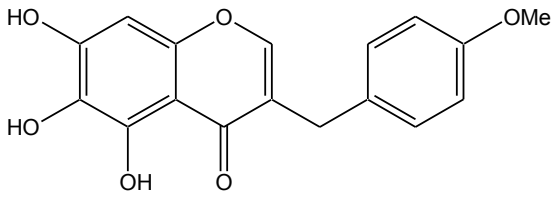
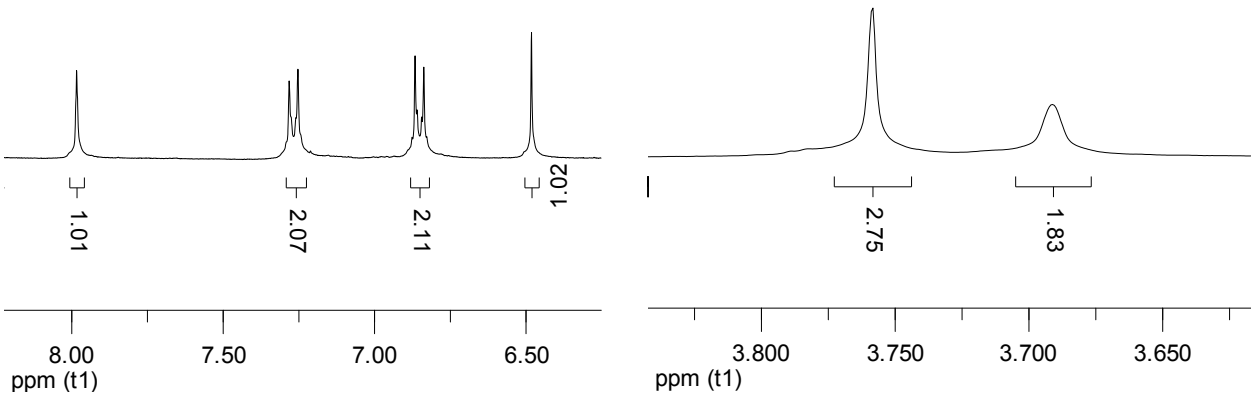


Plate 30: ^{1}H NMR of 5,6,7-Trihydroxy-4'-methoxyhomoisoflavone, acetone (298K)



(**4.80**)



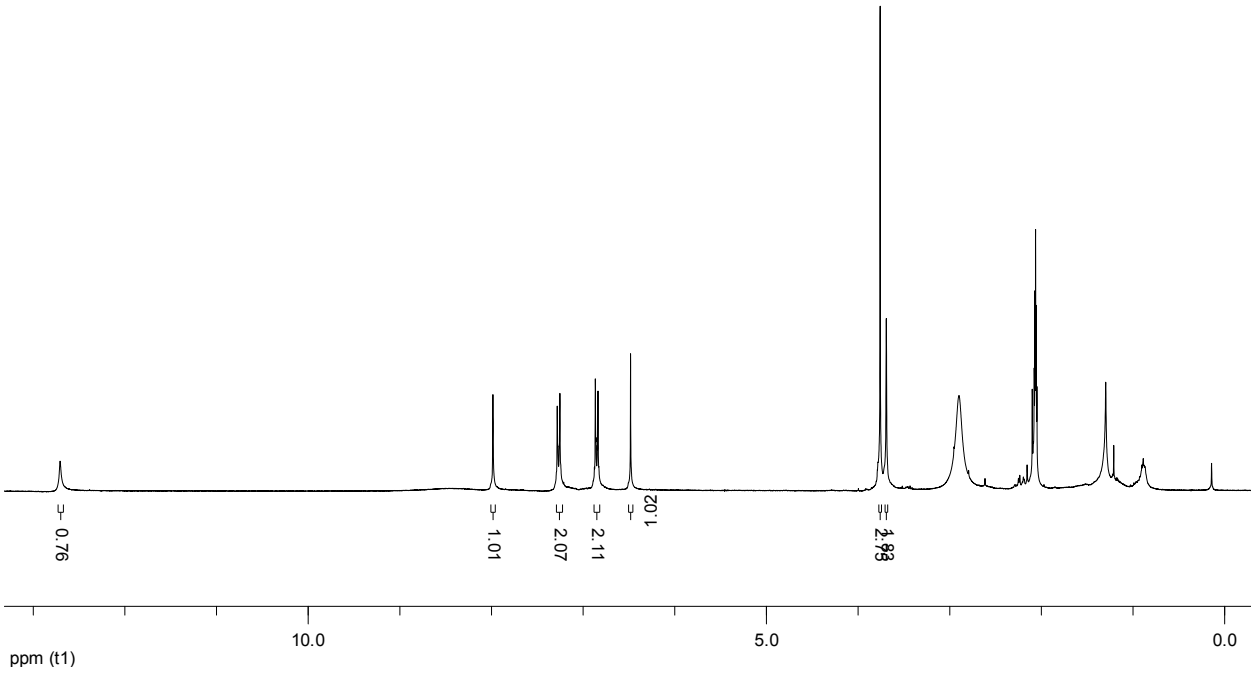
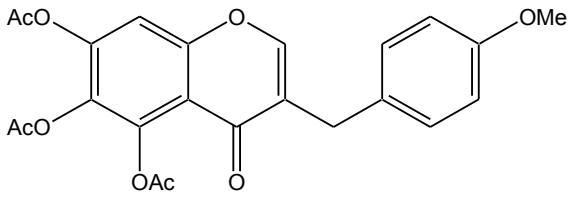
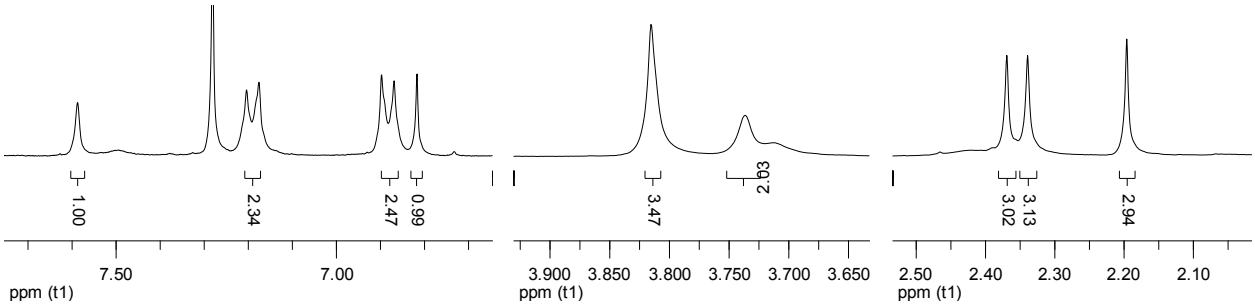


Plate 31: ^{1}H NMR of 5,6,7-Triacetoxy-4'-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.81**)



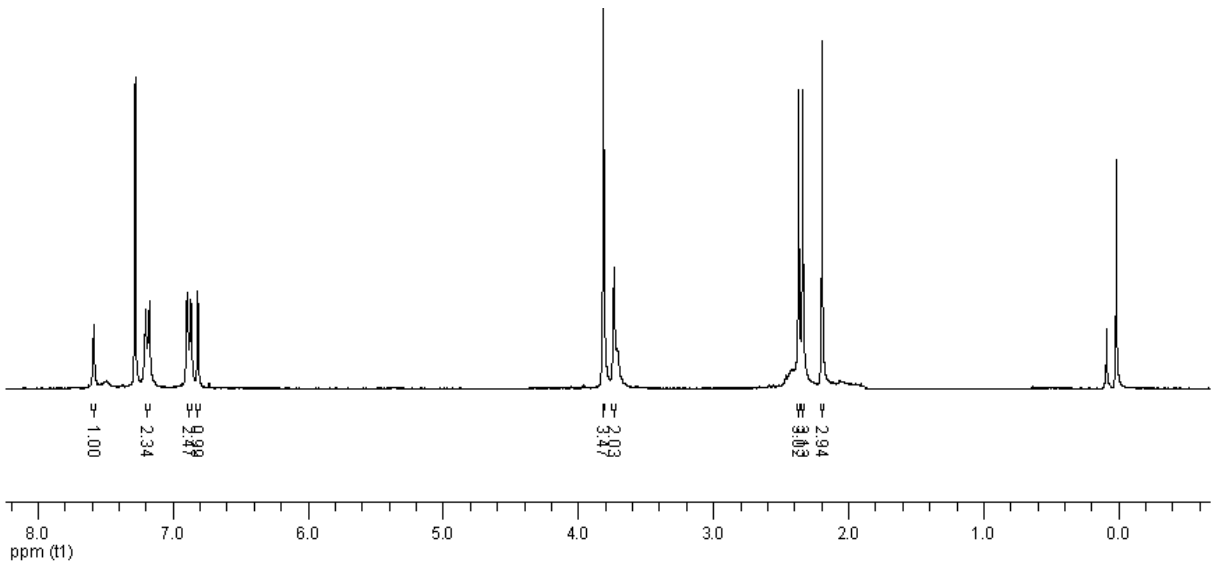
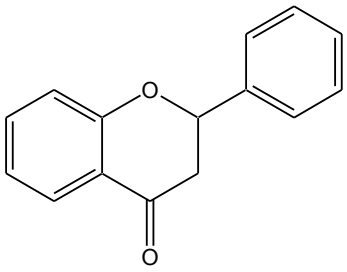


Plate 32a: ^{1}H NMR of Flavanone, $CDCl_3$ (298K)



(**4.85**)

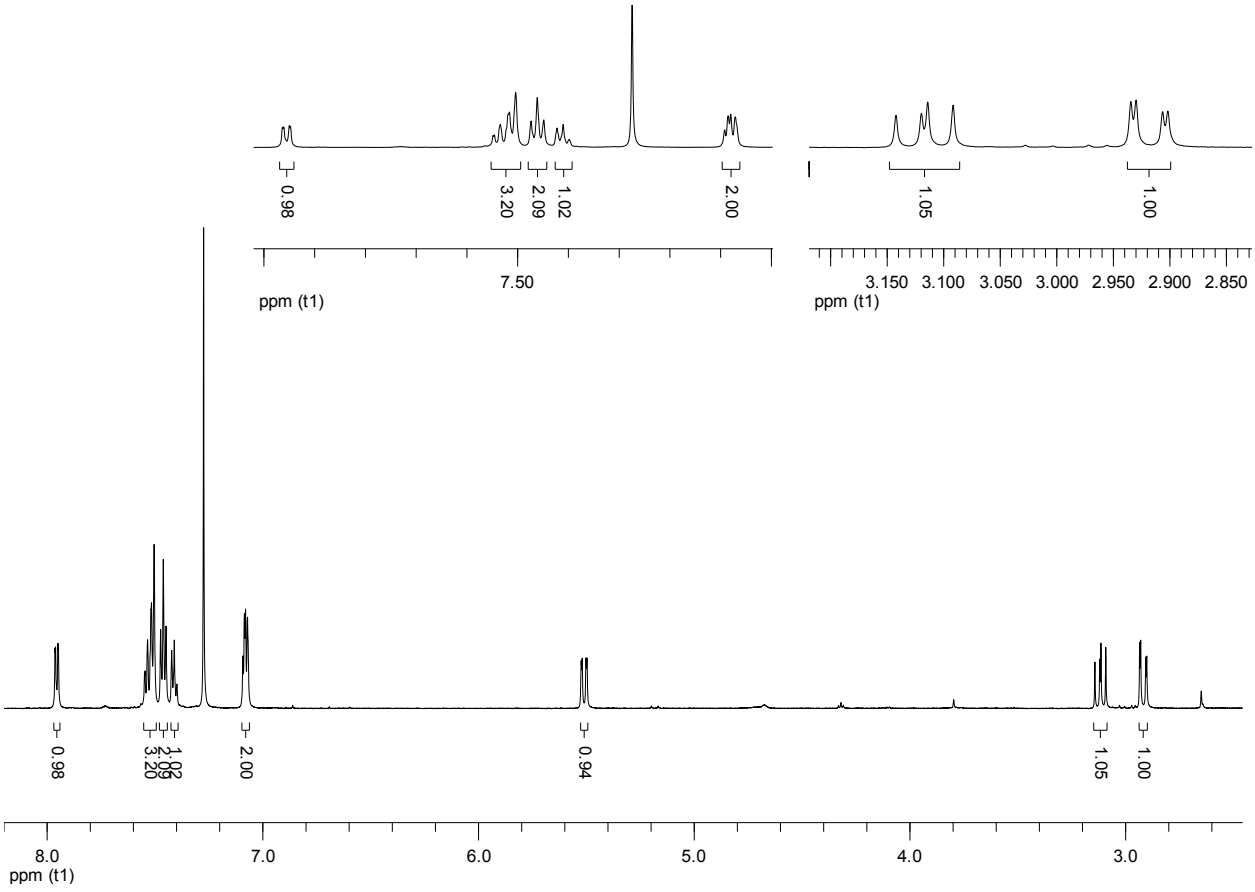
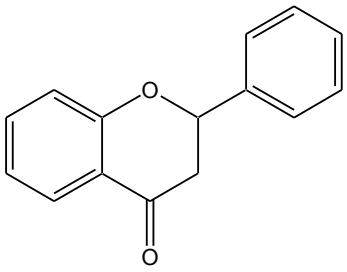


Plate 32b: ^{13}C NMR of Flavanone, $CDCl_3$ (298K)



(**4.85**)

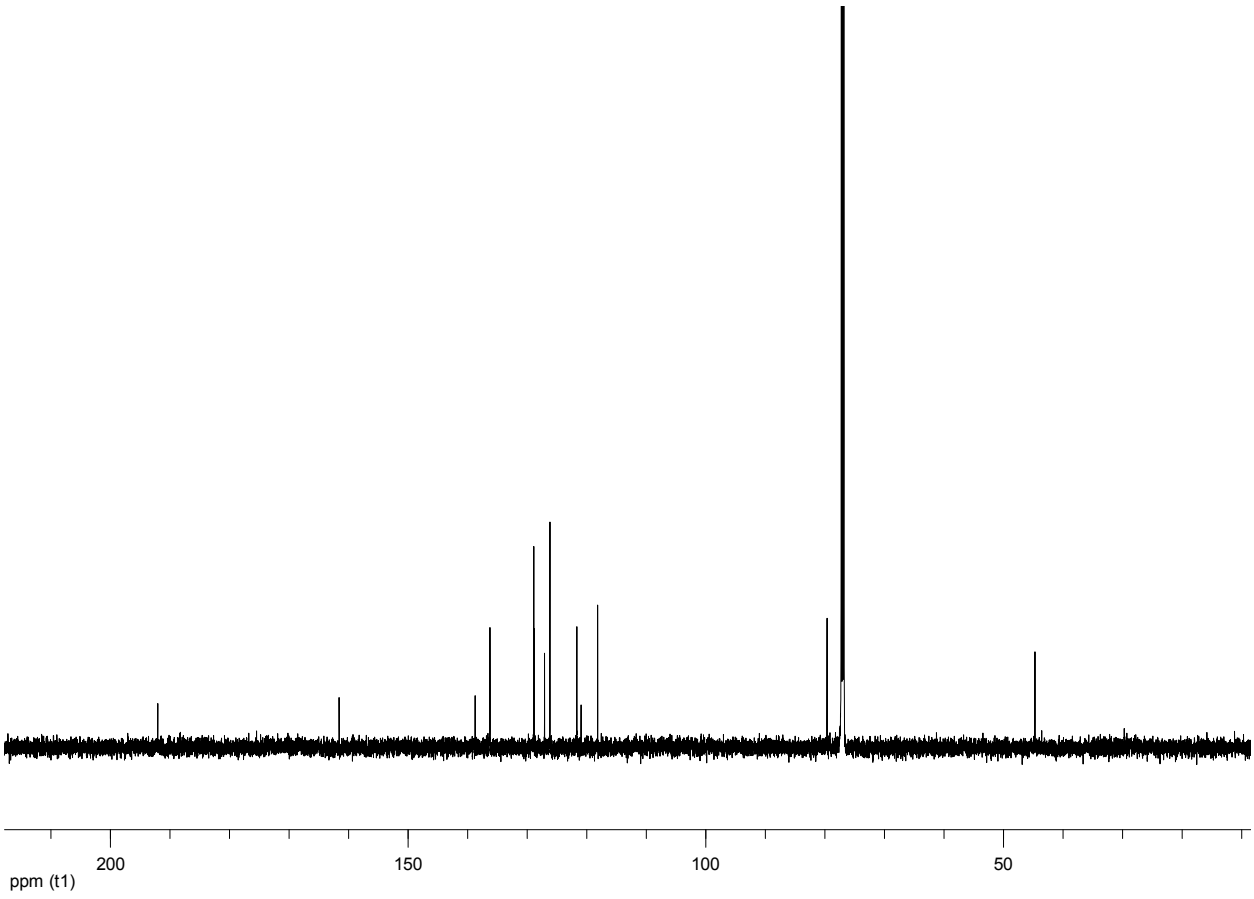
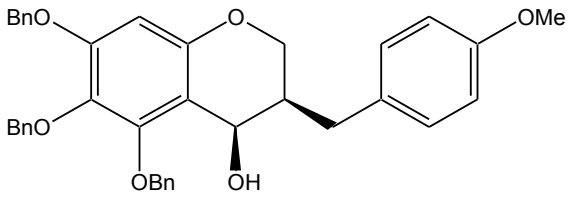
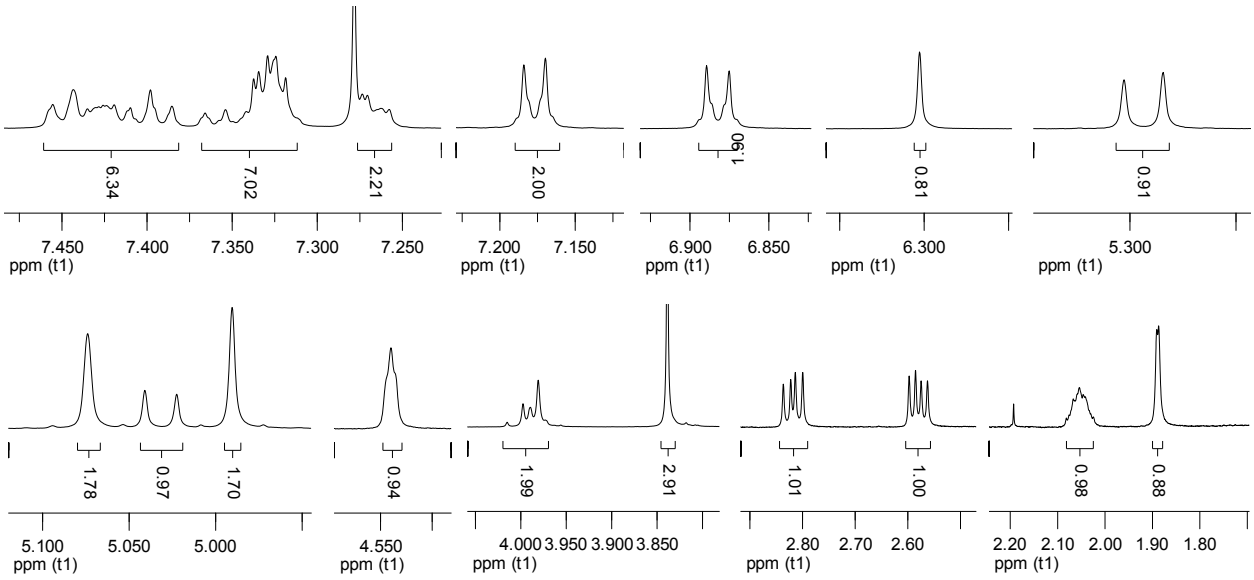


Plate 33a: ^{1}H NMR of *cis*-5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.89**)



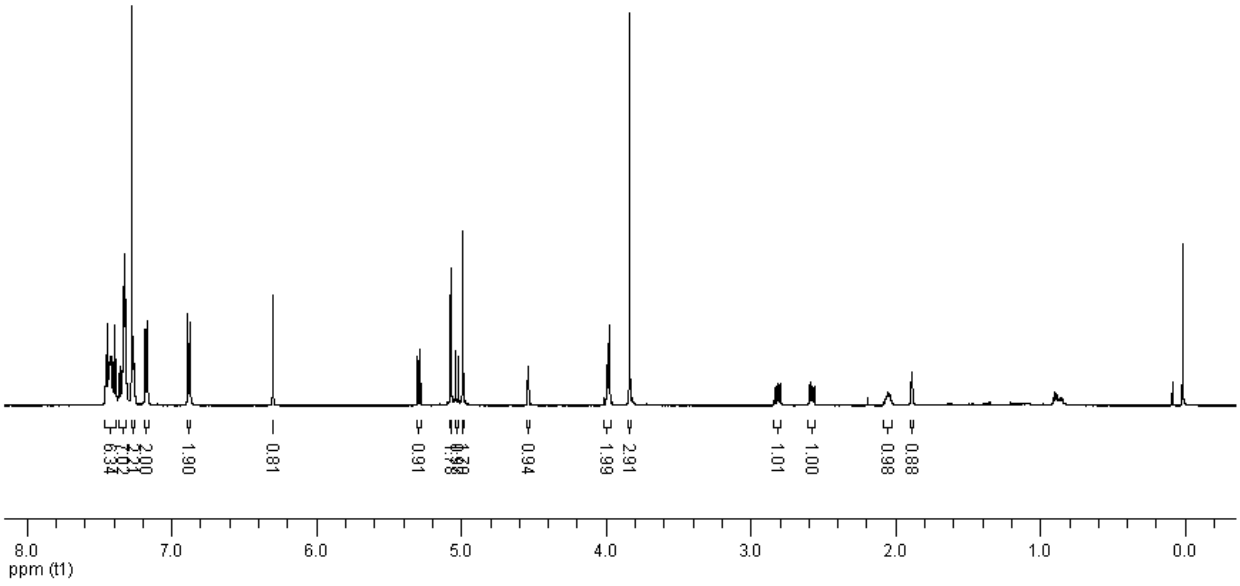
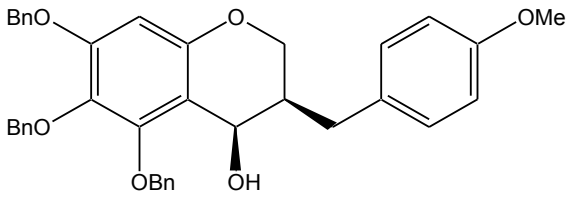


Plate 33b: ^{13}C NMR of *cis*-5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.89**)

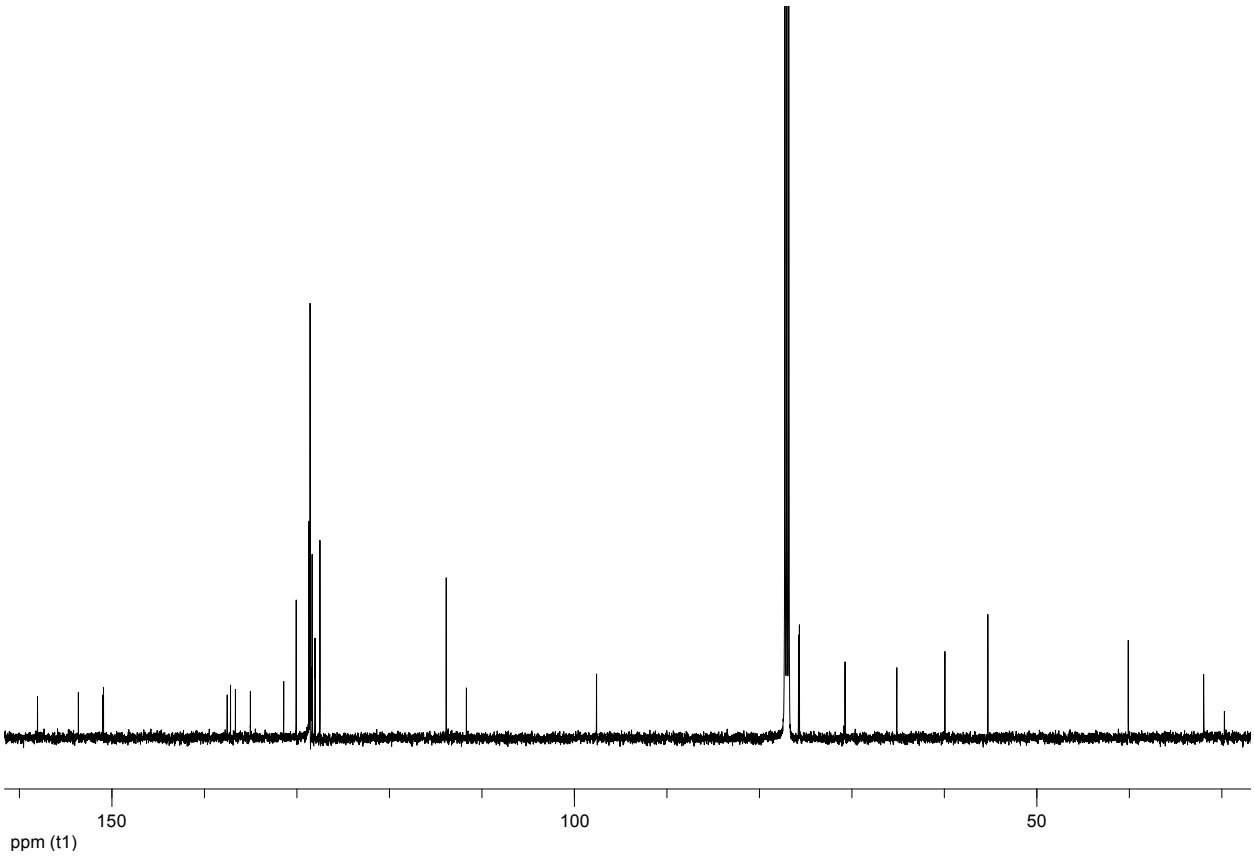
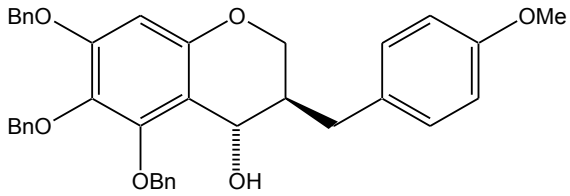
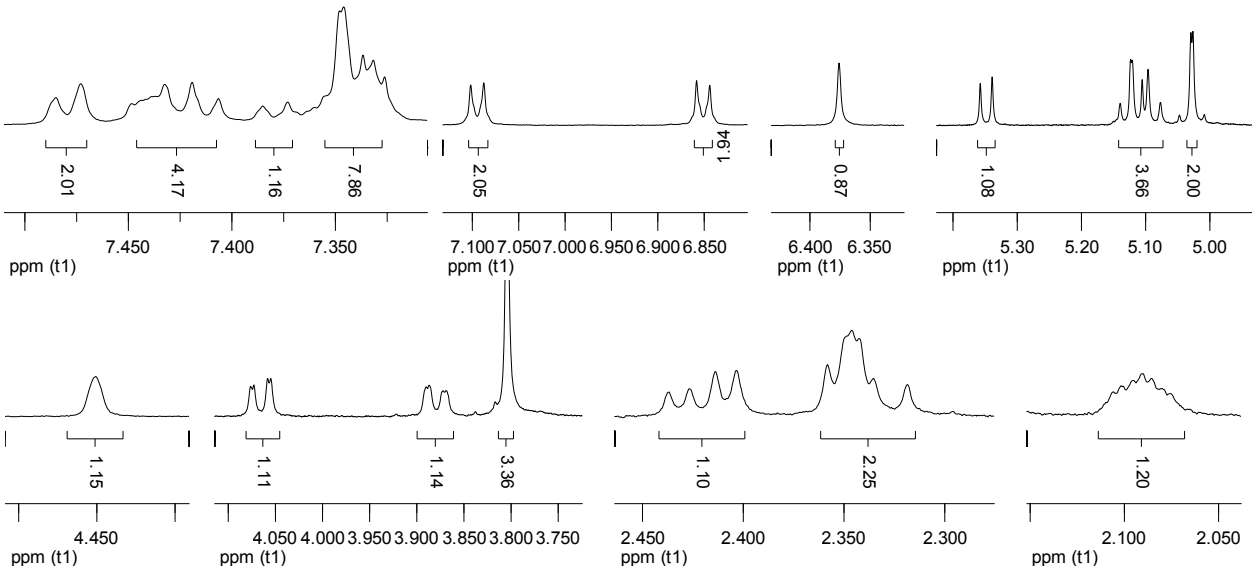


Plate 34a: ^{1}H NMR of *trans*-5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.90**)



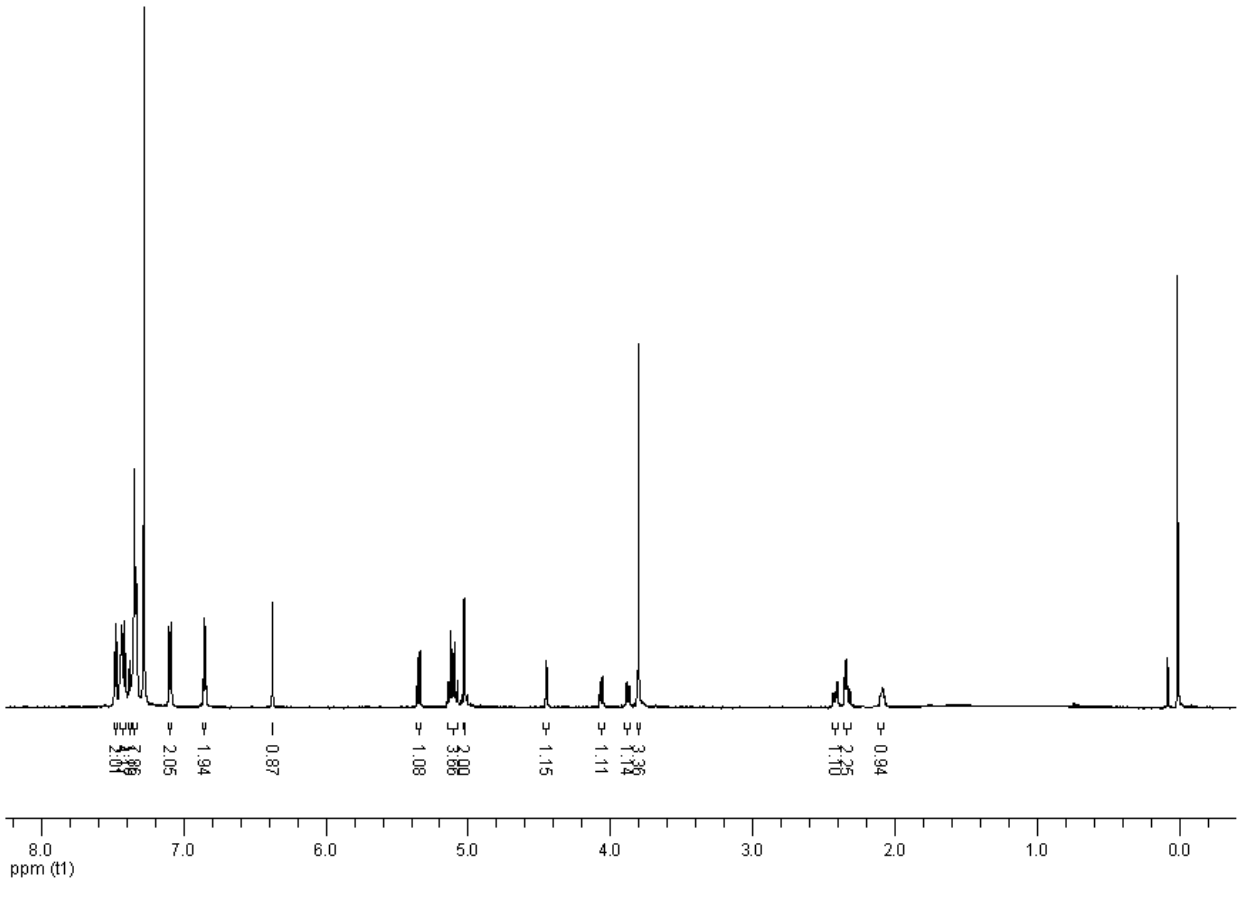
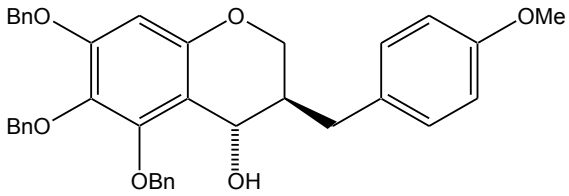


Plate 34b: ^{13}C NMR of *trans*-5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.90**)

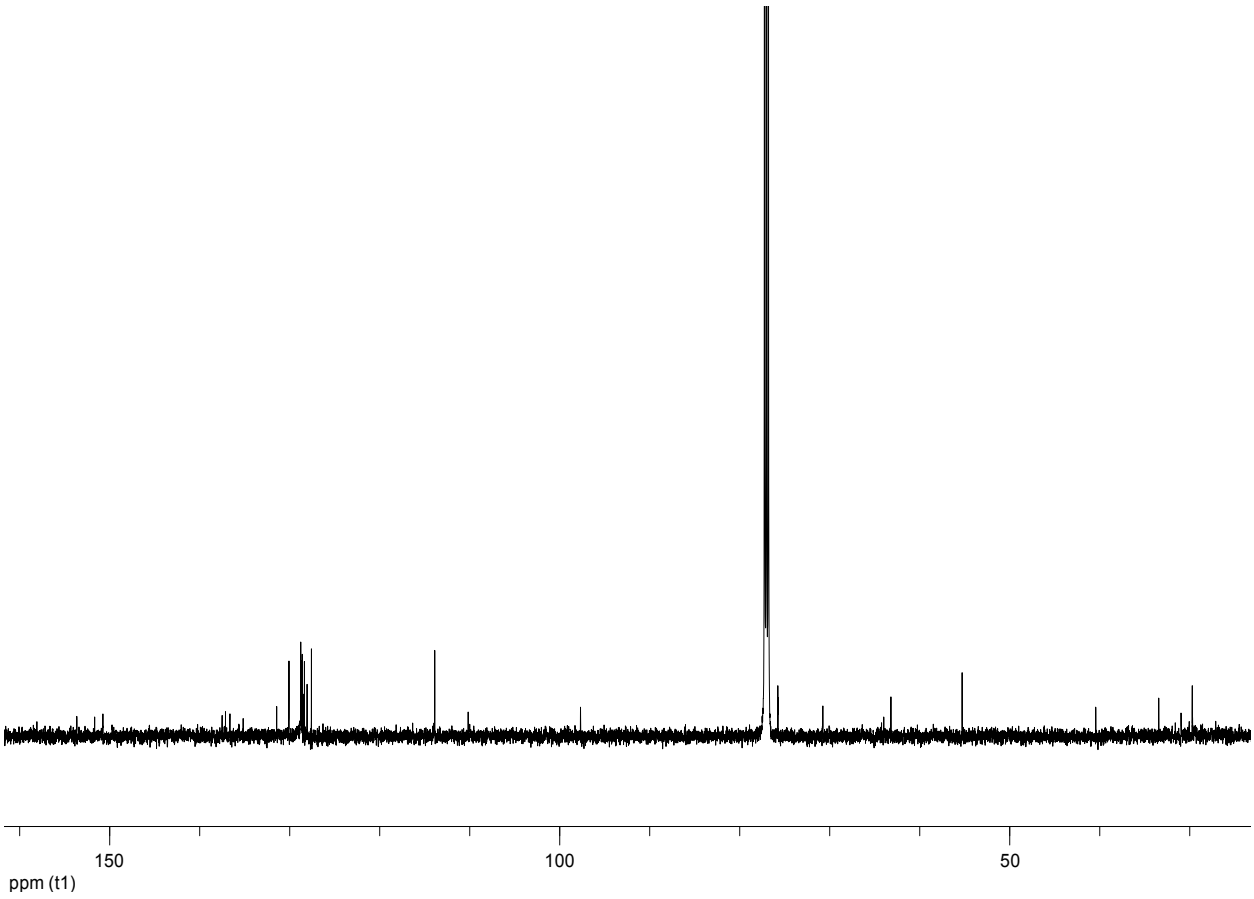
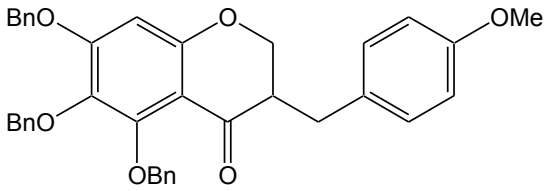
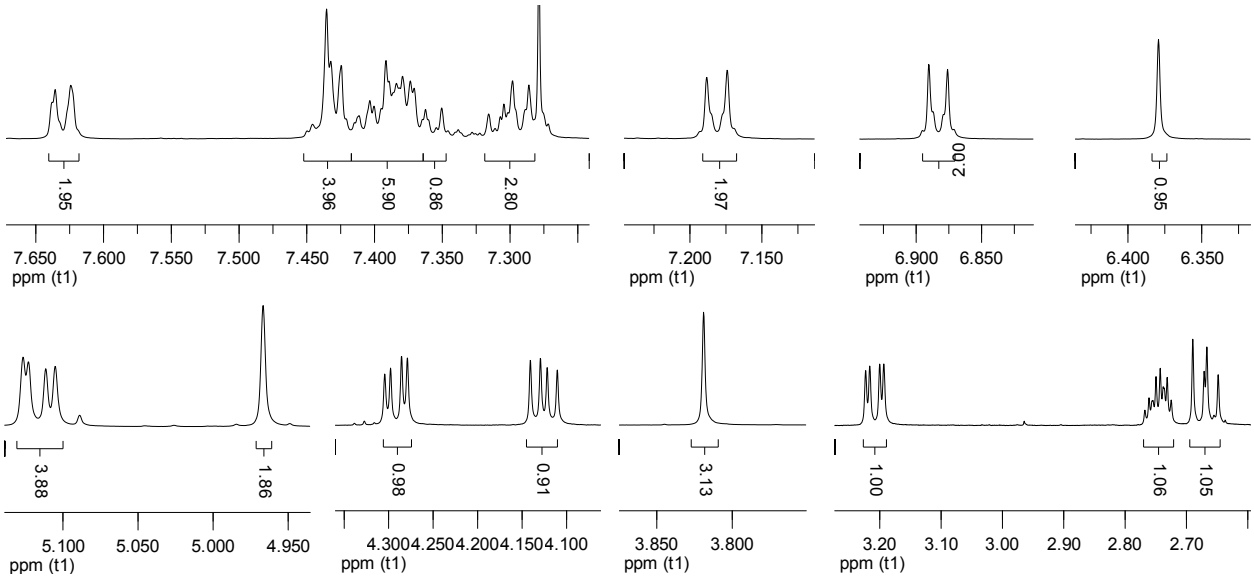


Plate 35a: ^{1}H NMR of 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.91**)



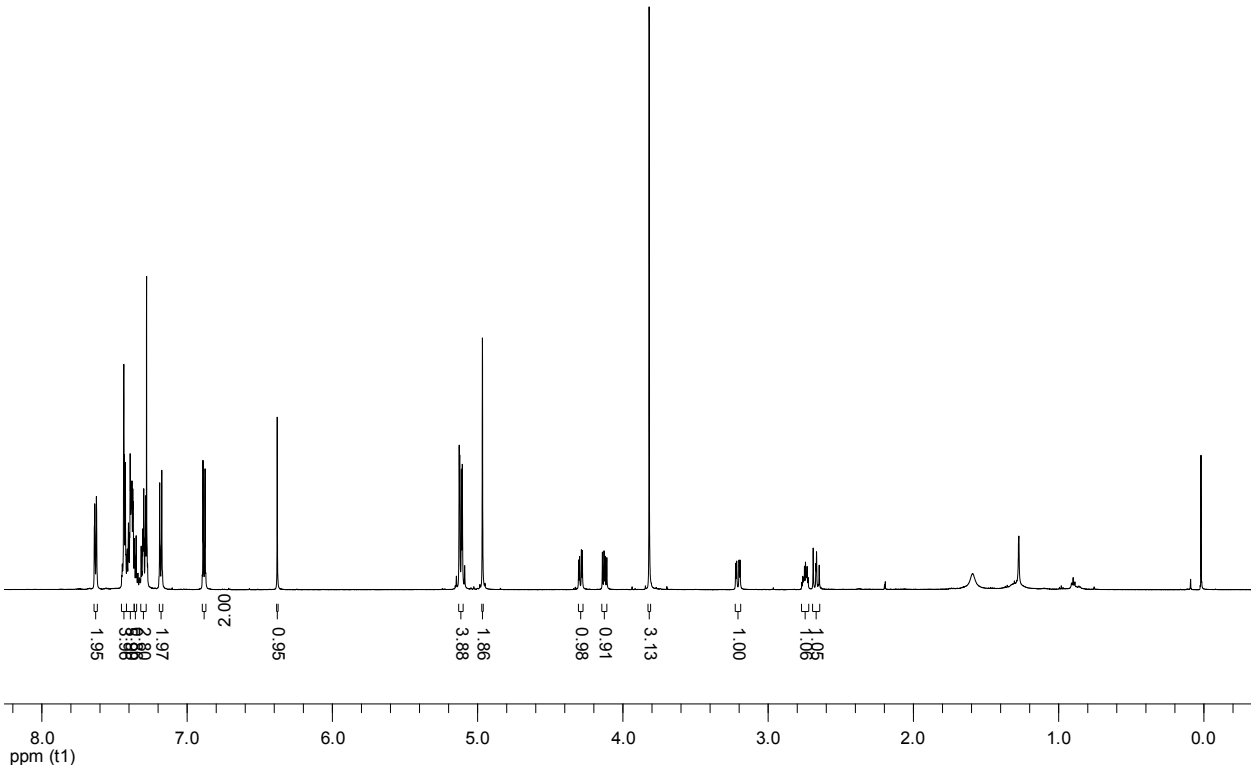
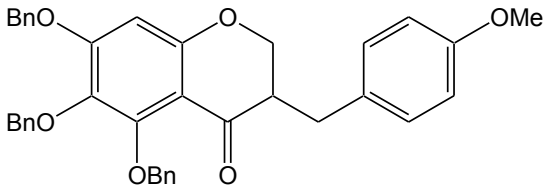


Plate 35b: ^{13}C NMR of 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.91**)

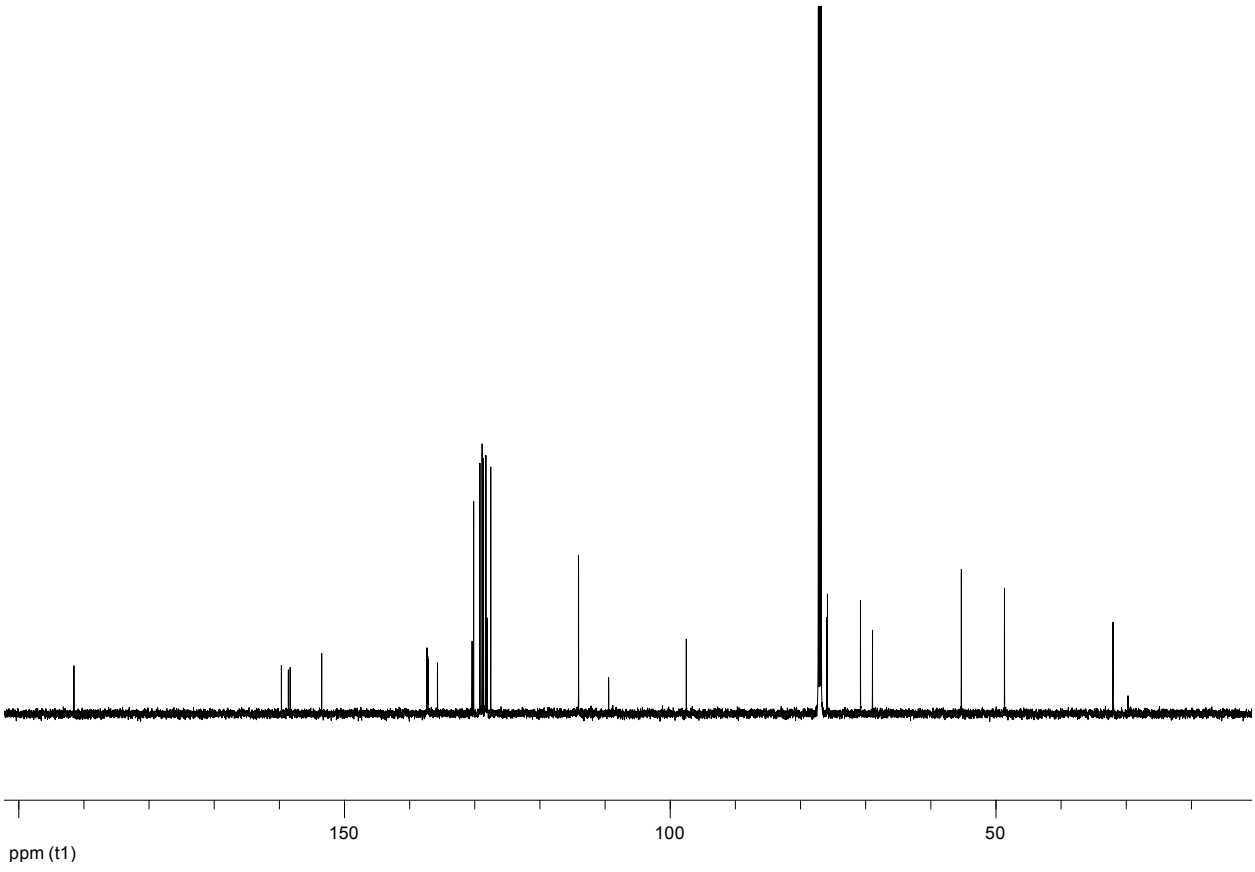
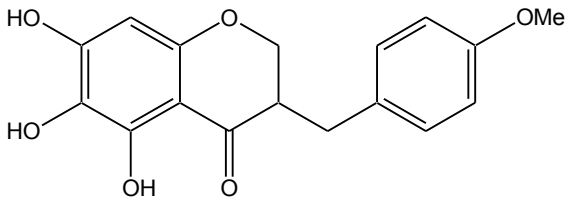
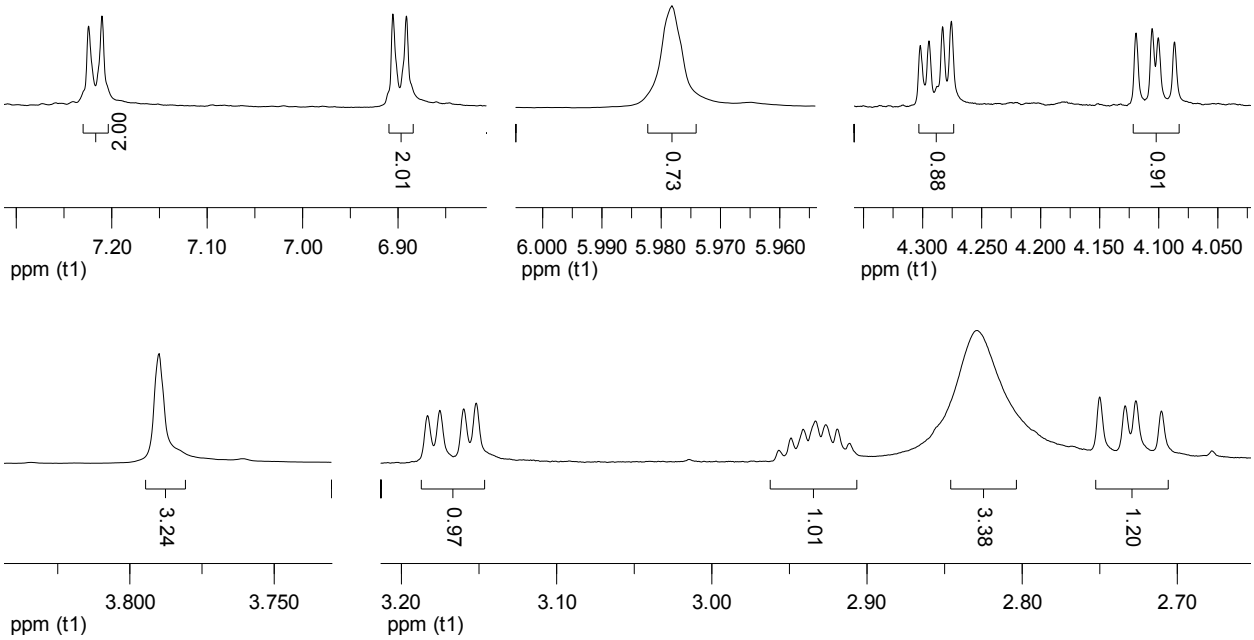


Plate 36a: ^{1}H NMR of 5,6,7-Trihydroxy-4'-methoxyhomoisoflavanone, acetone (298K)



(**4.92**)



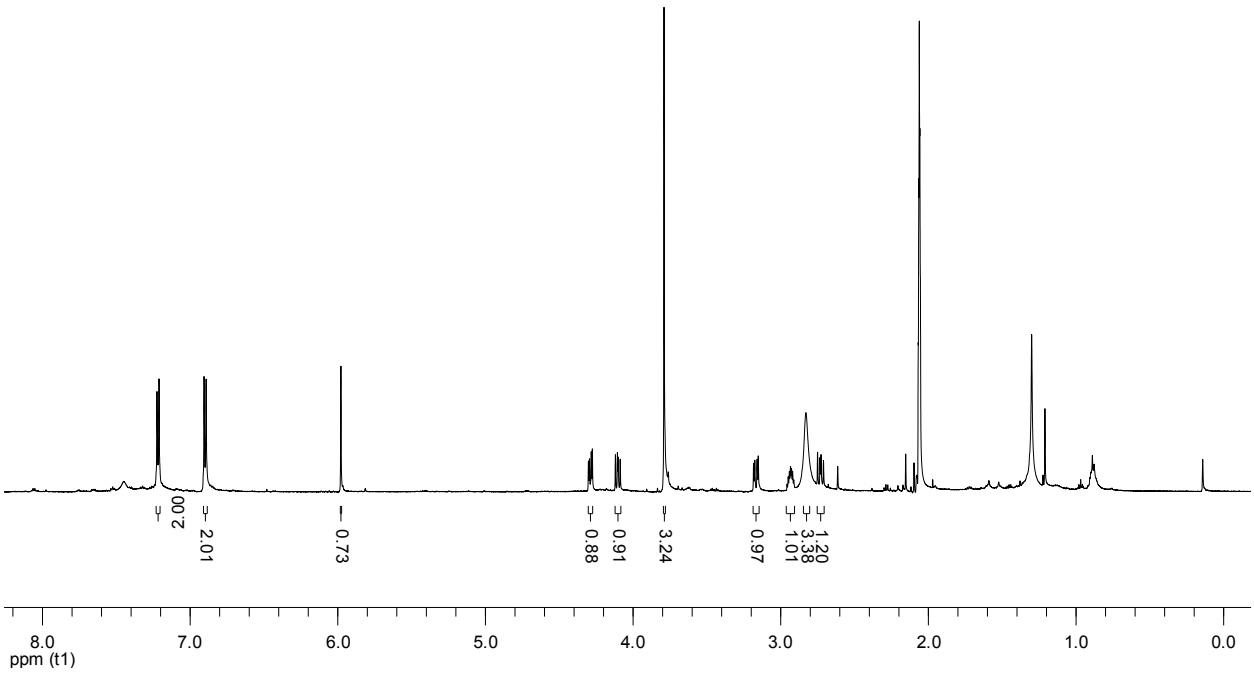
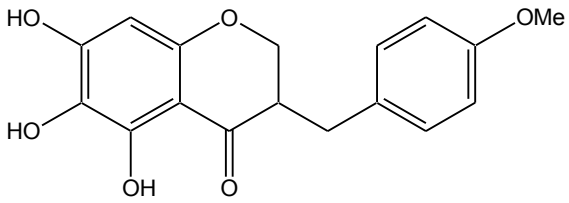


Plate 36b: ^{13}C NMR of 5,6,7-Trihydroxy-4'-methoxyhomoisoflavanone, acetone (298K)



(**4.92**)

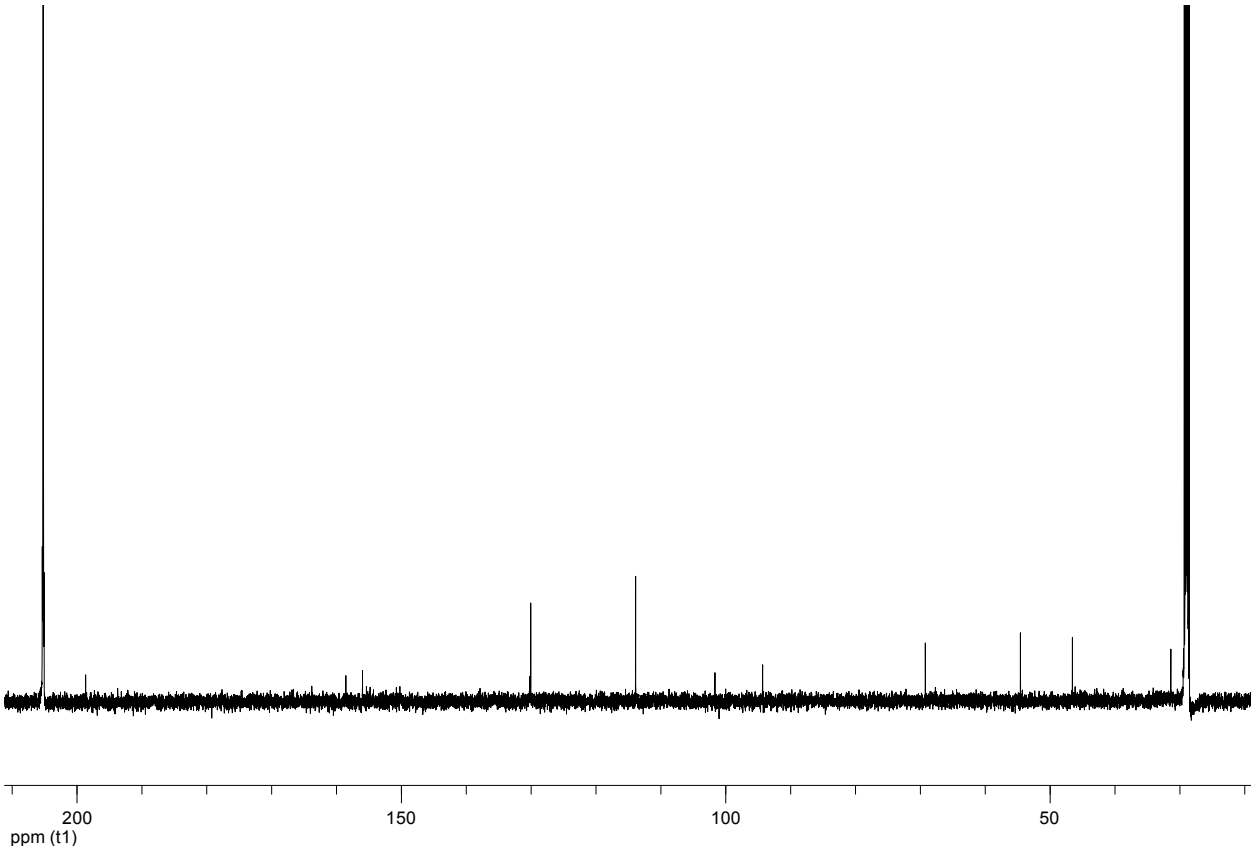
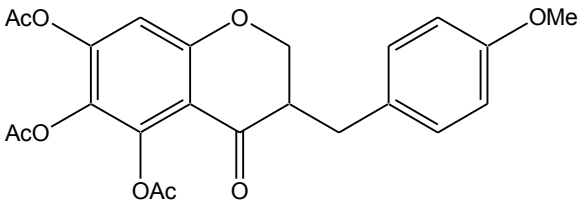
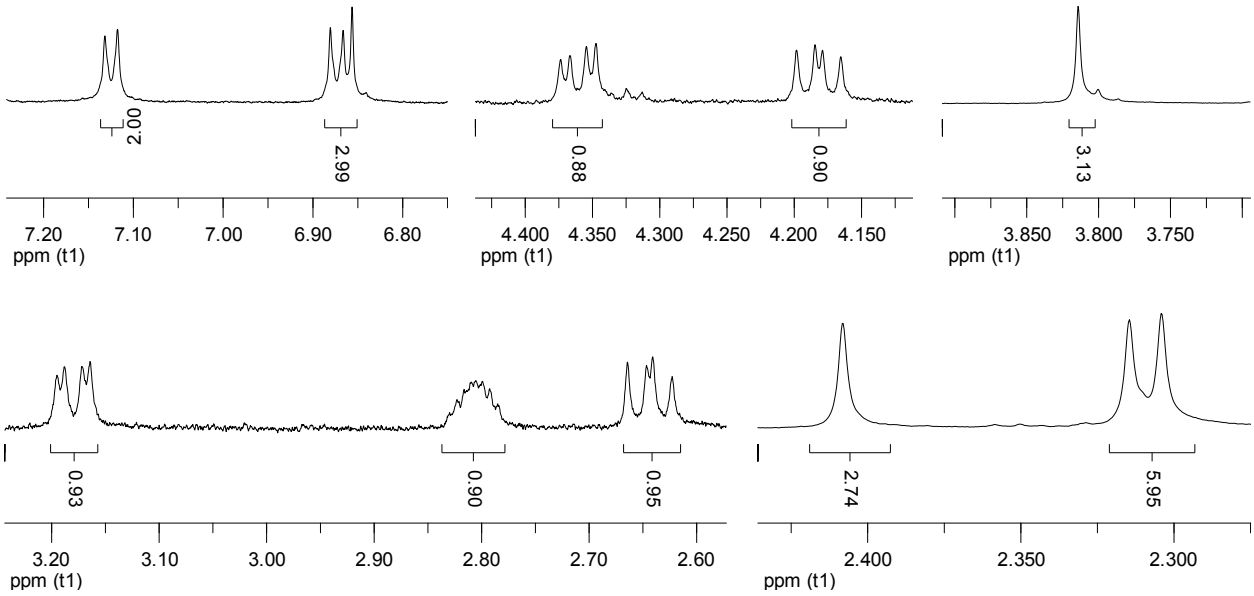


Plate 37a: ^{1}H NMR of 5,6,7-Triacetoxy-4'-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.93**)



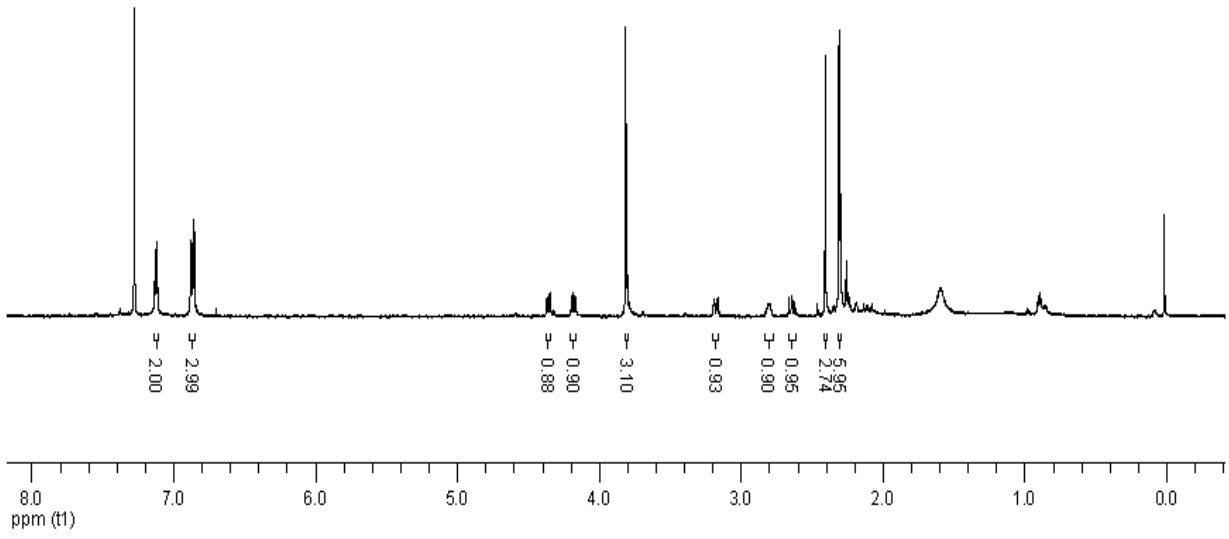
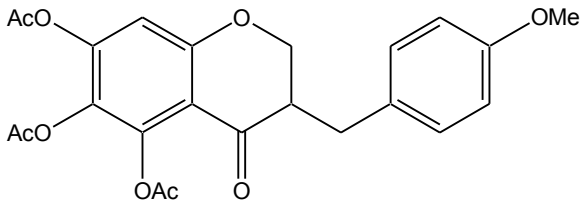


Plate 37b: ^{13}C NMR of 5,6,7-Triacetoxy-4'-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.93**)

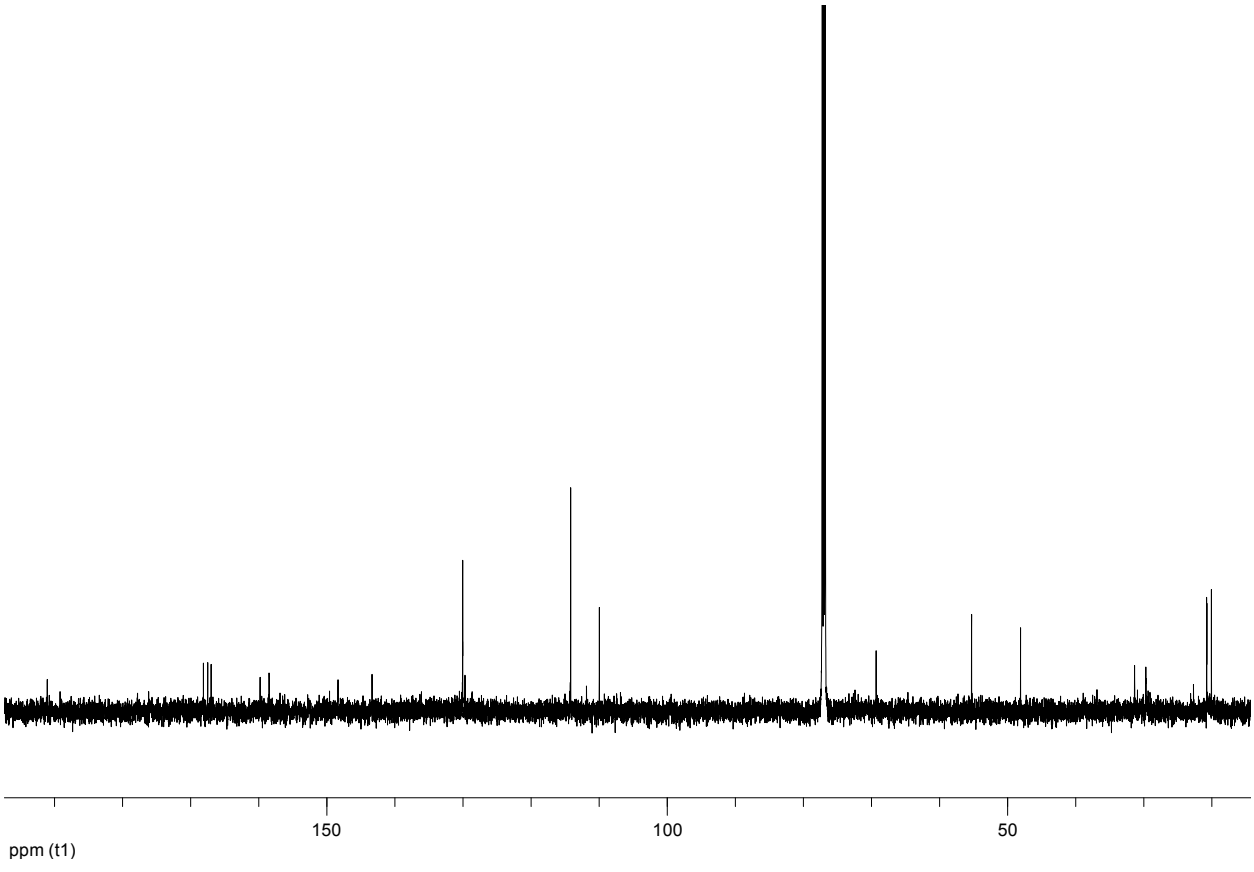
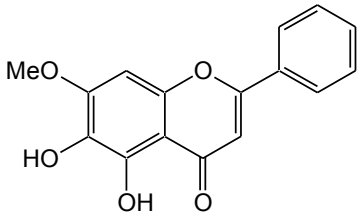
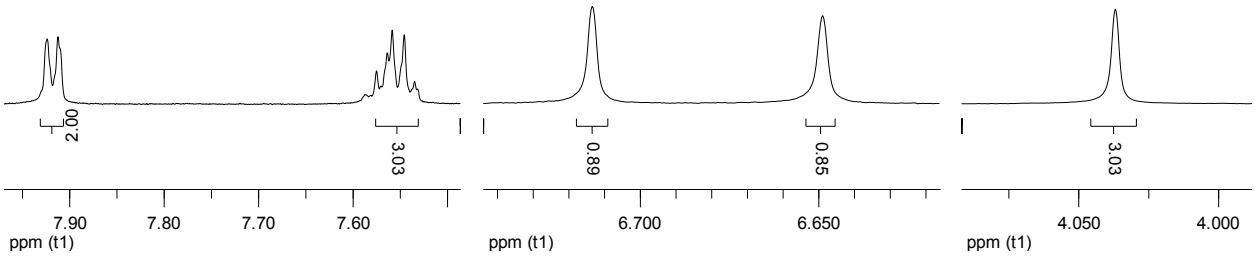


Plate 38a: ^{1}H NMR of 5,6-Dihydroxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.114**)



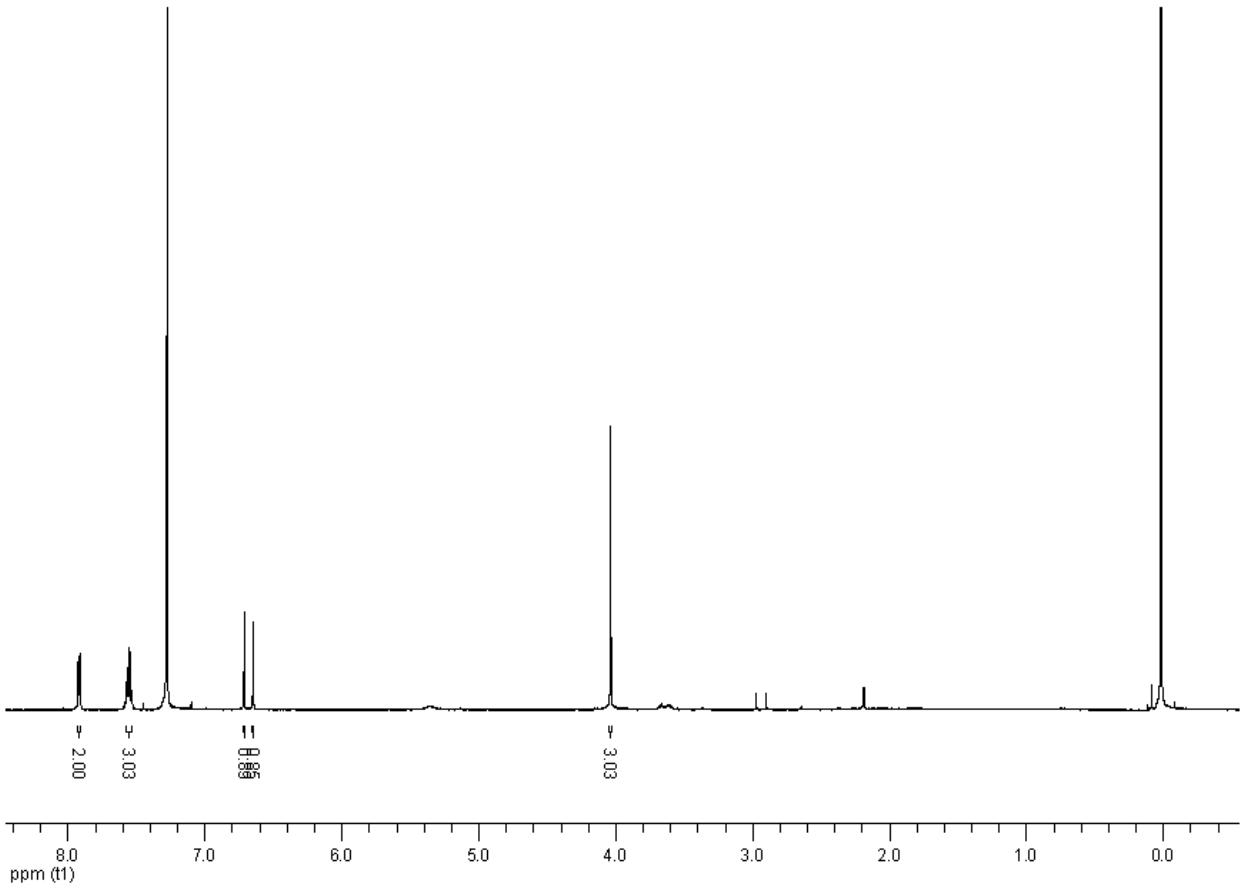
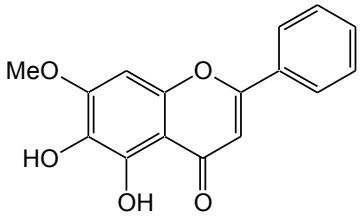


Plate 38b: ^{13}C NMR of 5,6-Dihydroxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.114**)

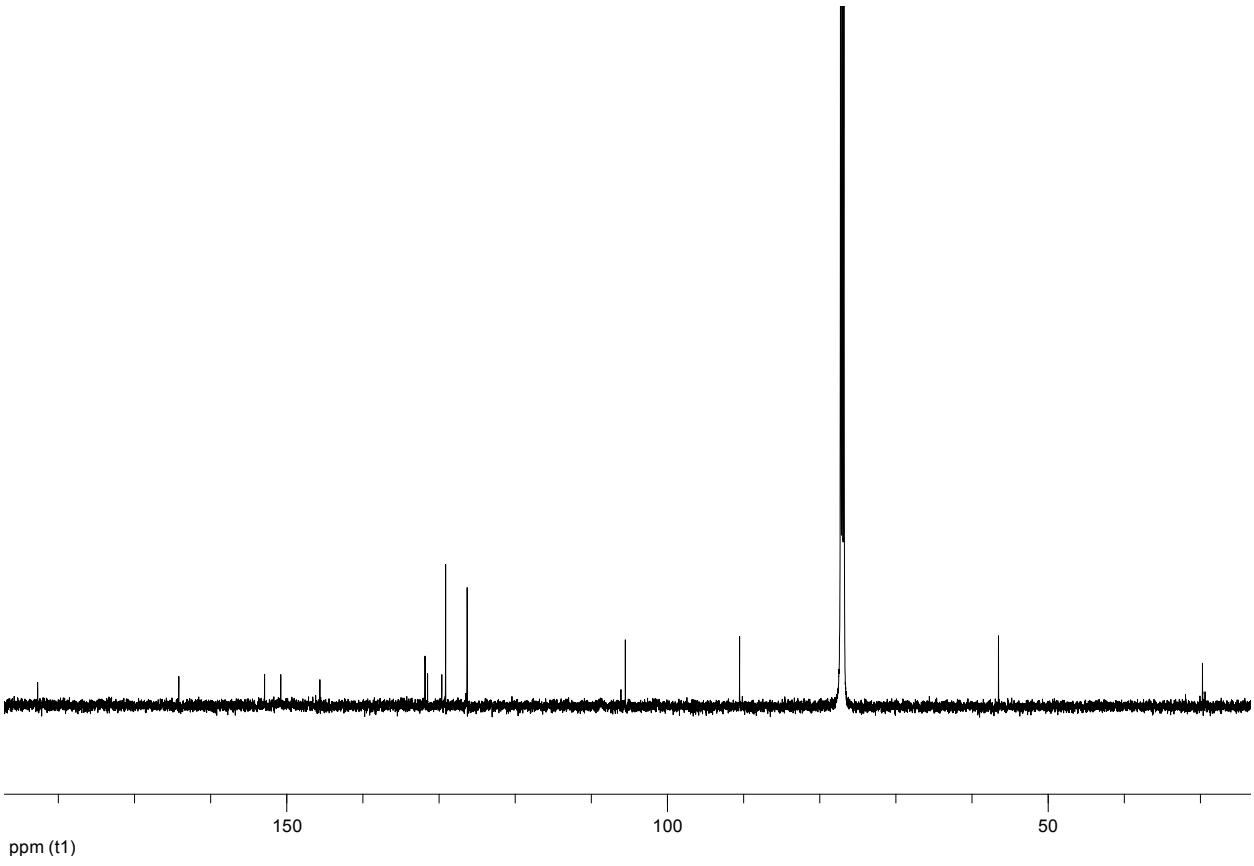
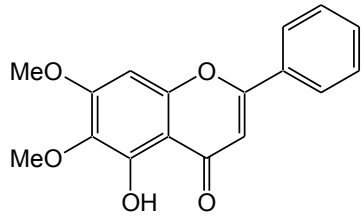
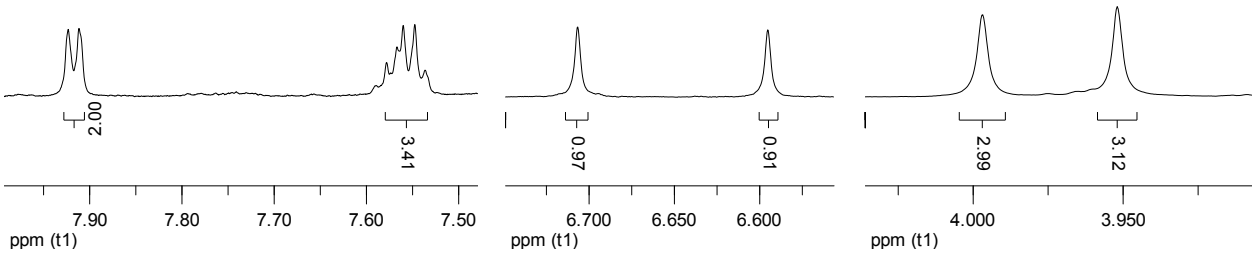


Plate 39a: ^{1}H NMR of 6,7-Dimethoxy-5-hydroxyflavone, $CDCl_3$ (298K)



(**4.115**)



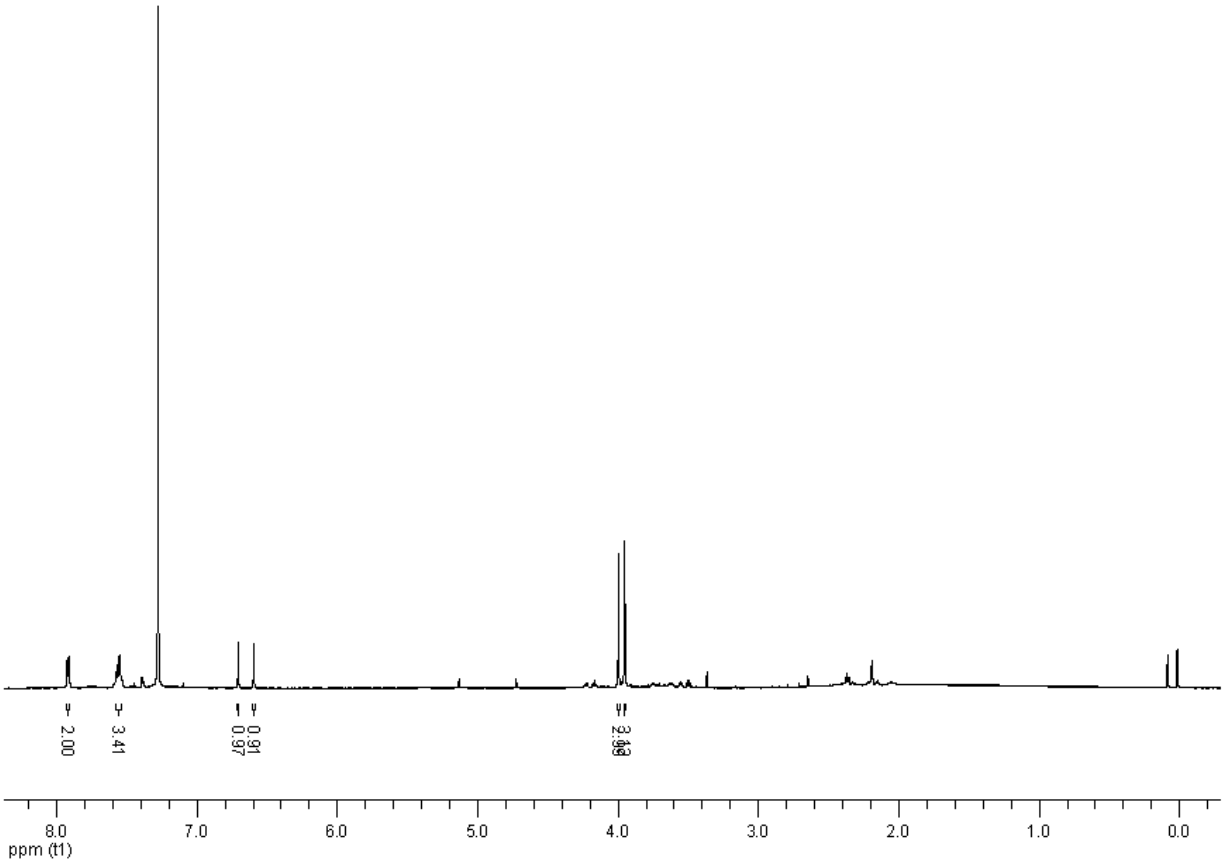
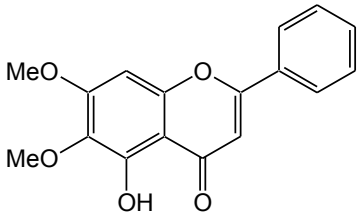


Plate 39b: ^{13}C NMR of 6,7-Dimethoxy-5-hydroxyflavone, $CDCl_3$ (298K)



(**4.115**)

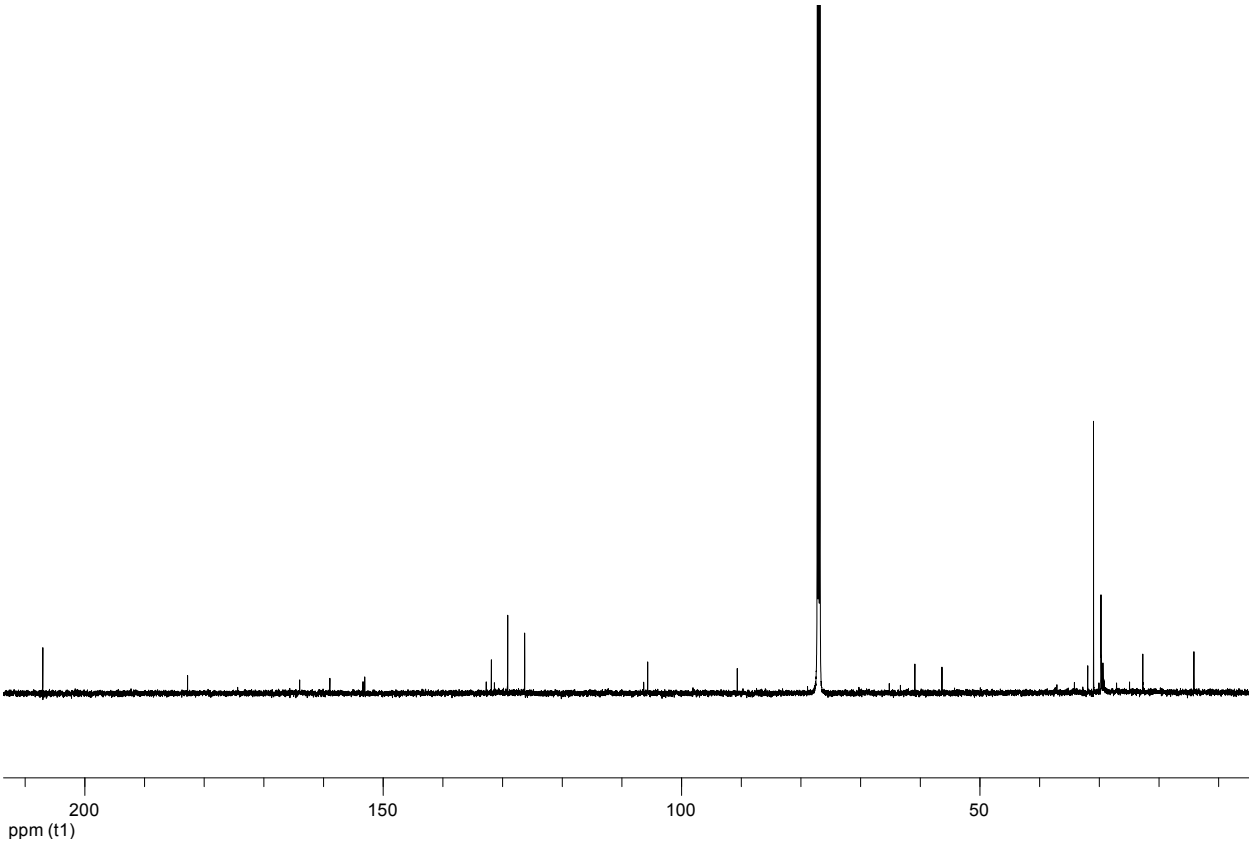
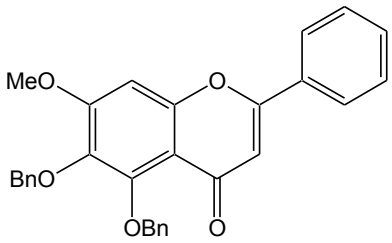
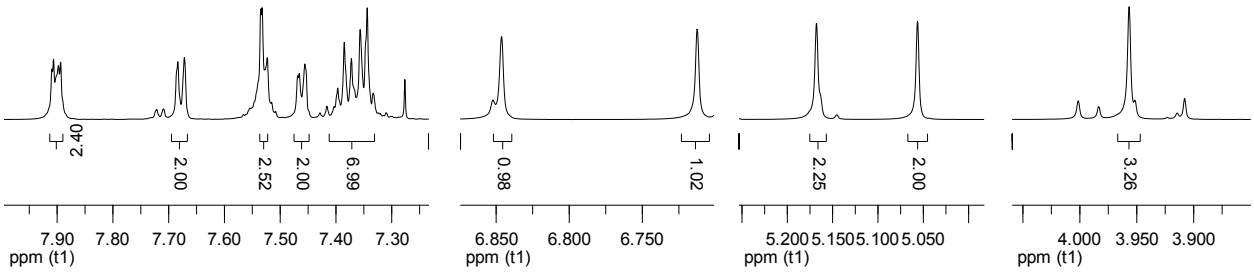


Plate 40a: ^{1}H NMR of 5,6-Dibenzyloxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.111**)



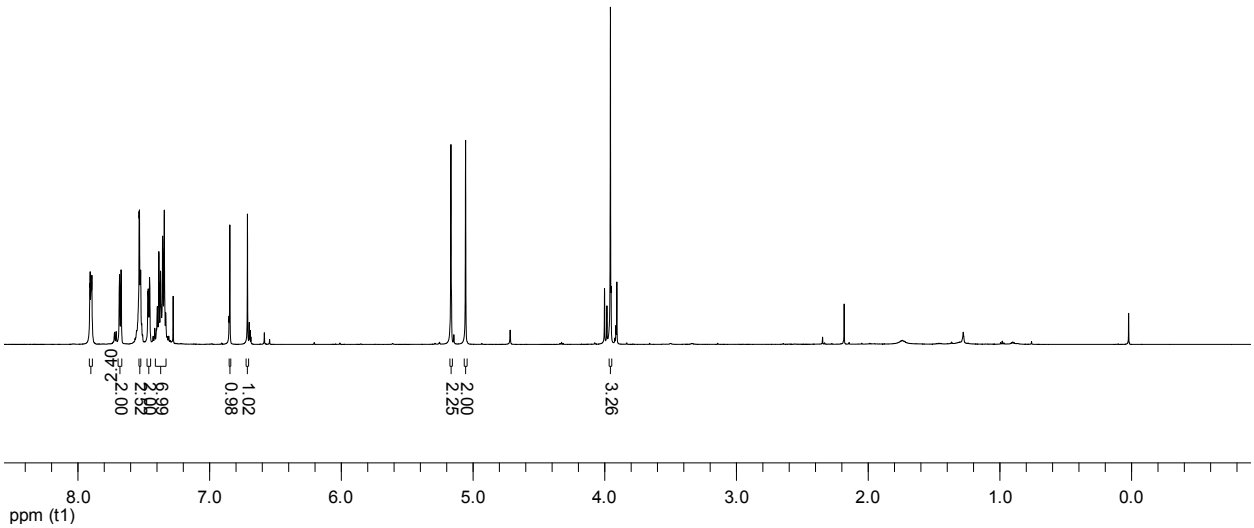
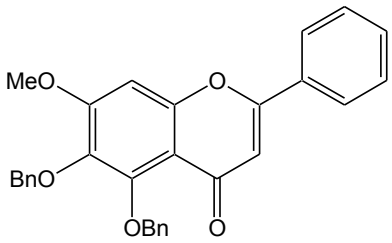


Plate 40b: ^{13}C NMR of 5,6-Dibenzyloxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.111**)

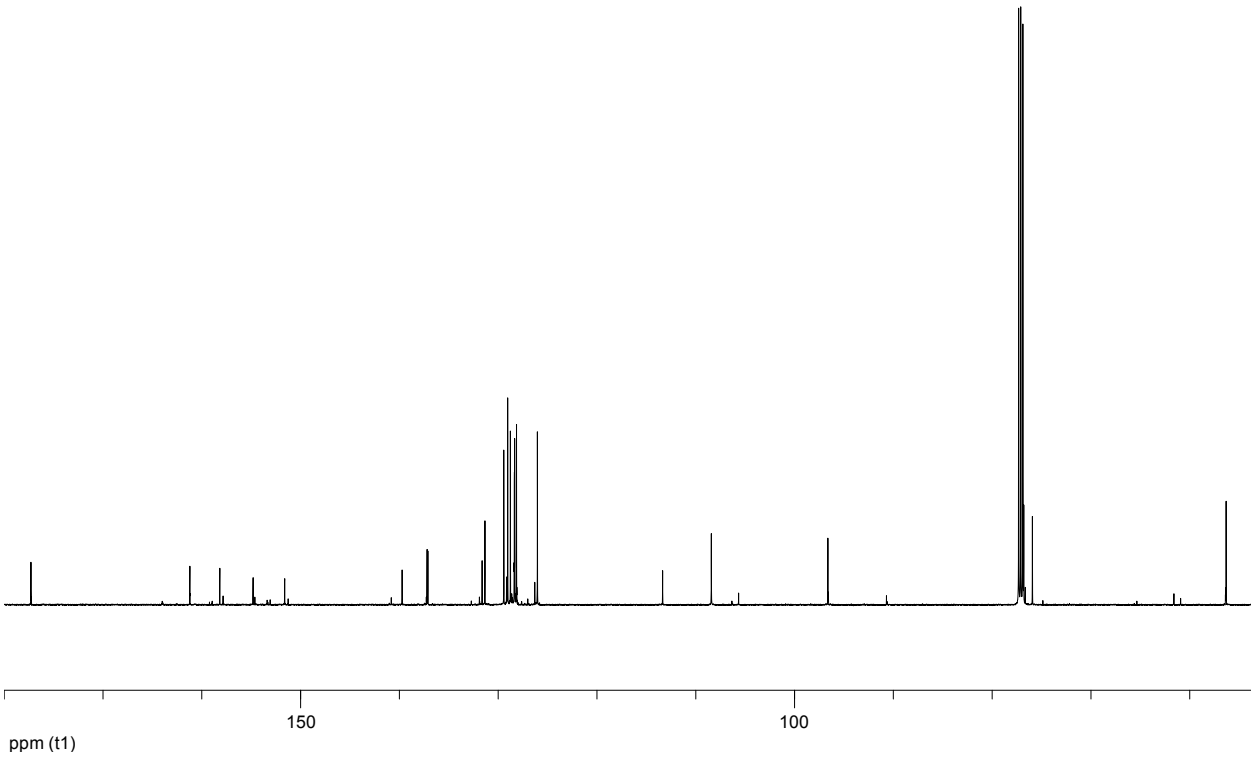
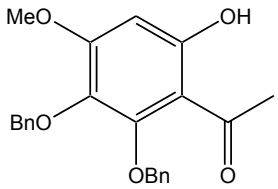
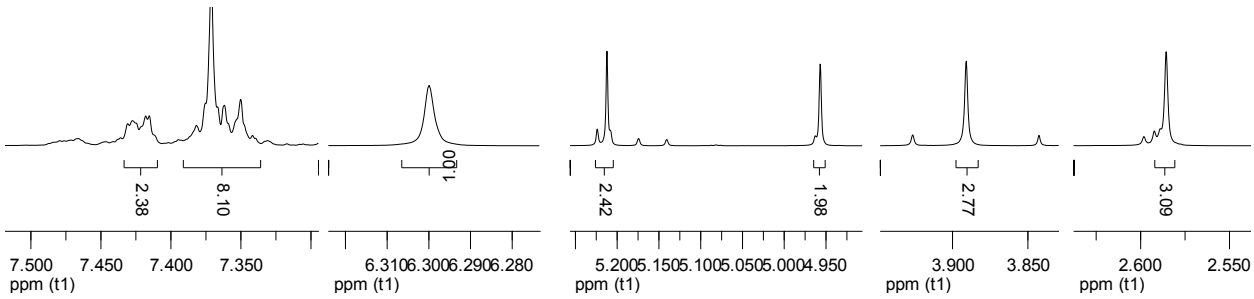


Plate 41a: ^{1}H NMR of 2,3-Dibenzyloxy-6-hydroxy-4-methoxyacetophenone, $CDCl_3$ (298K)



(**4.116**)



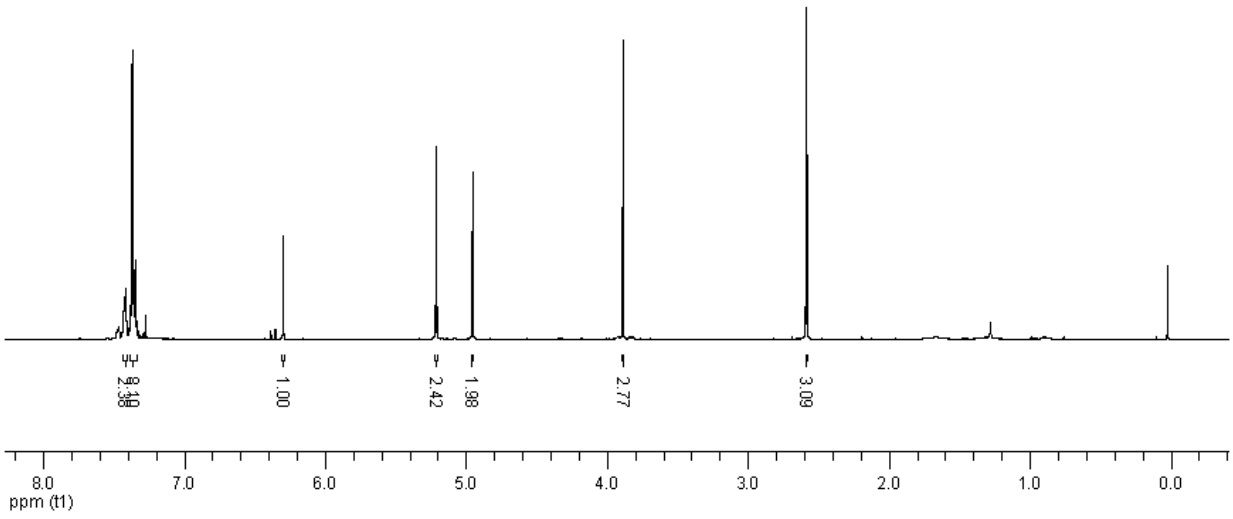
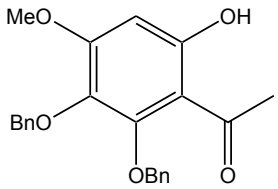


Plate 41b: ^{13}C NMR of 2,3-Dibenzyloxy-6-hydroxy-4-methoxyacetophenone, $CDCl_3$ (298K)



(**4.116**)

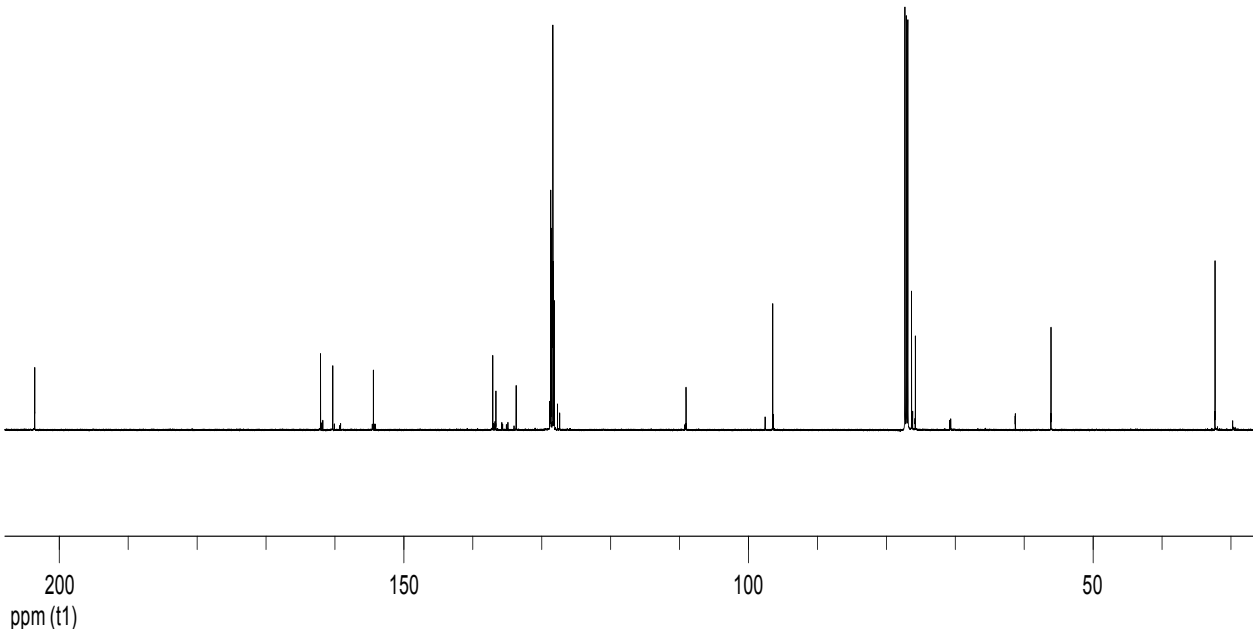
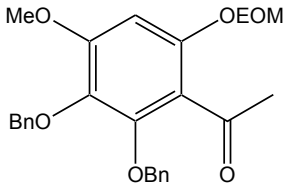
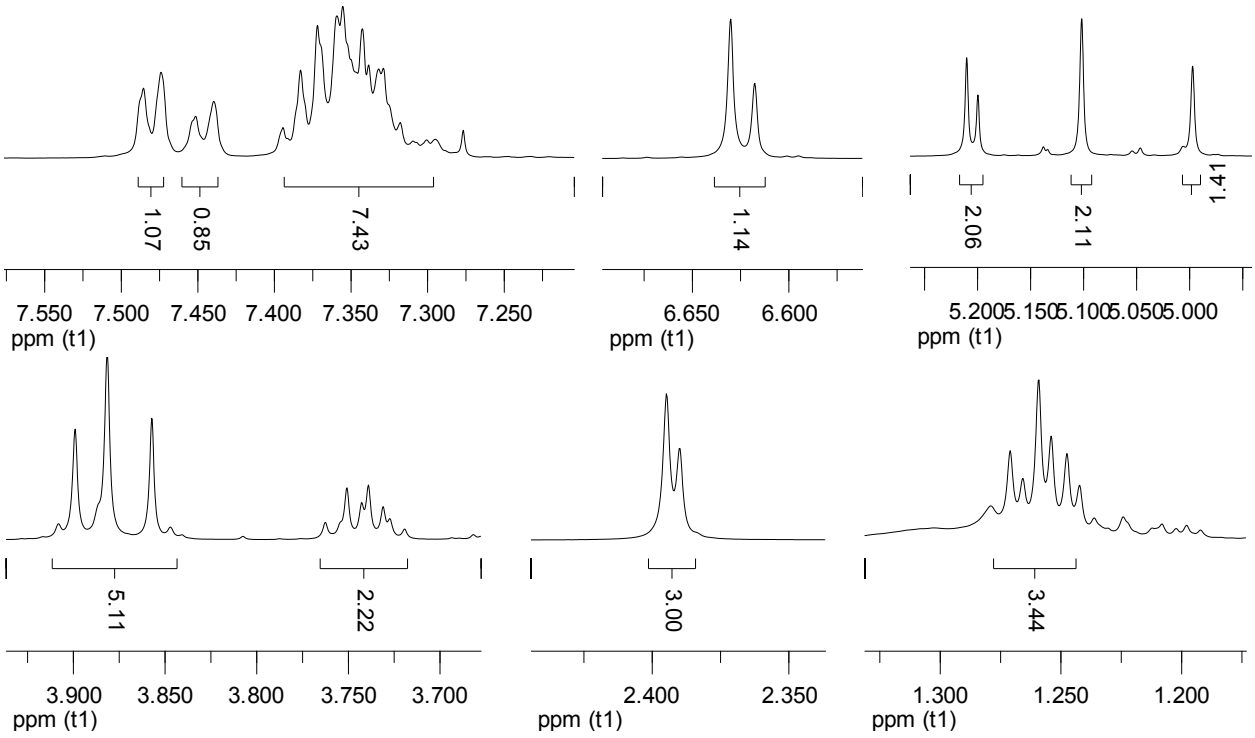


Plate 42a: ^{1}H NMR of 2,3-Dibenzyloxy-6-ethoxymethoxy-4-methoxyacetophenone, $CDCl_3$ (298K)



(**4.164**)



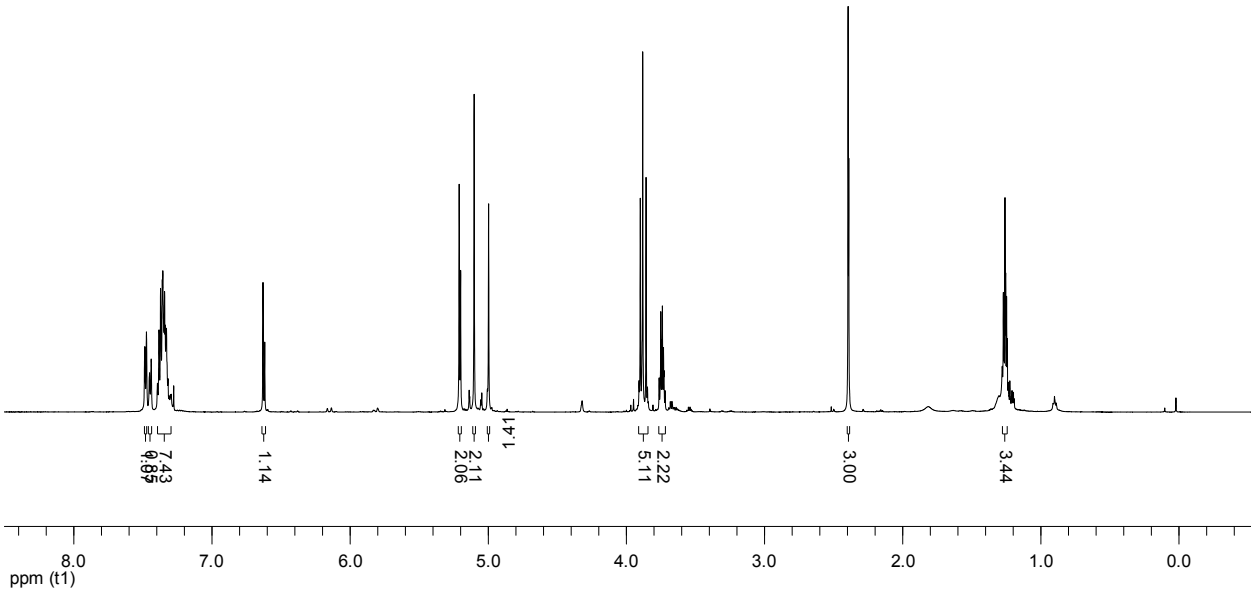
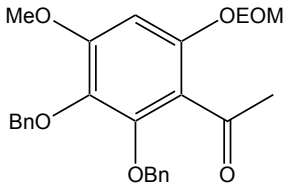


Plate 42b: ^{13}C NMR of 2,3-Dibenzyloxy-6-ethoxymethoxy-4-methoxyacetophenone, $CDCl_3$ (298K)



(**4.164**)

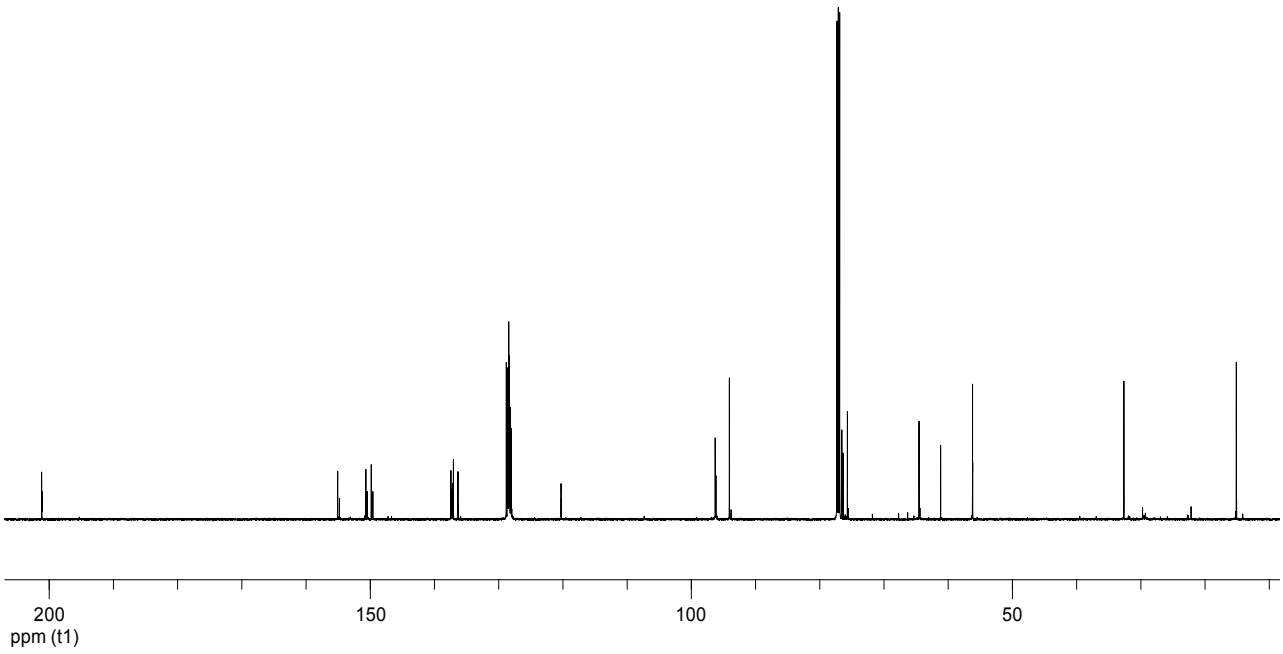
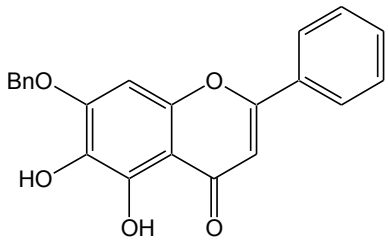
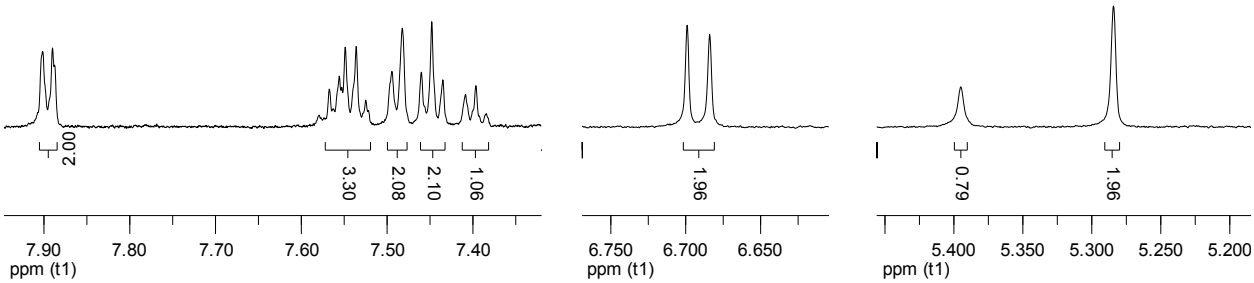


Plate 43a: ^{1}H NMR of 7-Benzyloxy-5,6-dihydroxyflavone, $CDCl_3$ (298K)



(**4.117**)



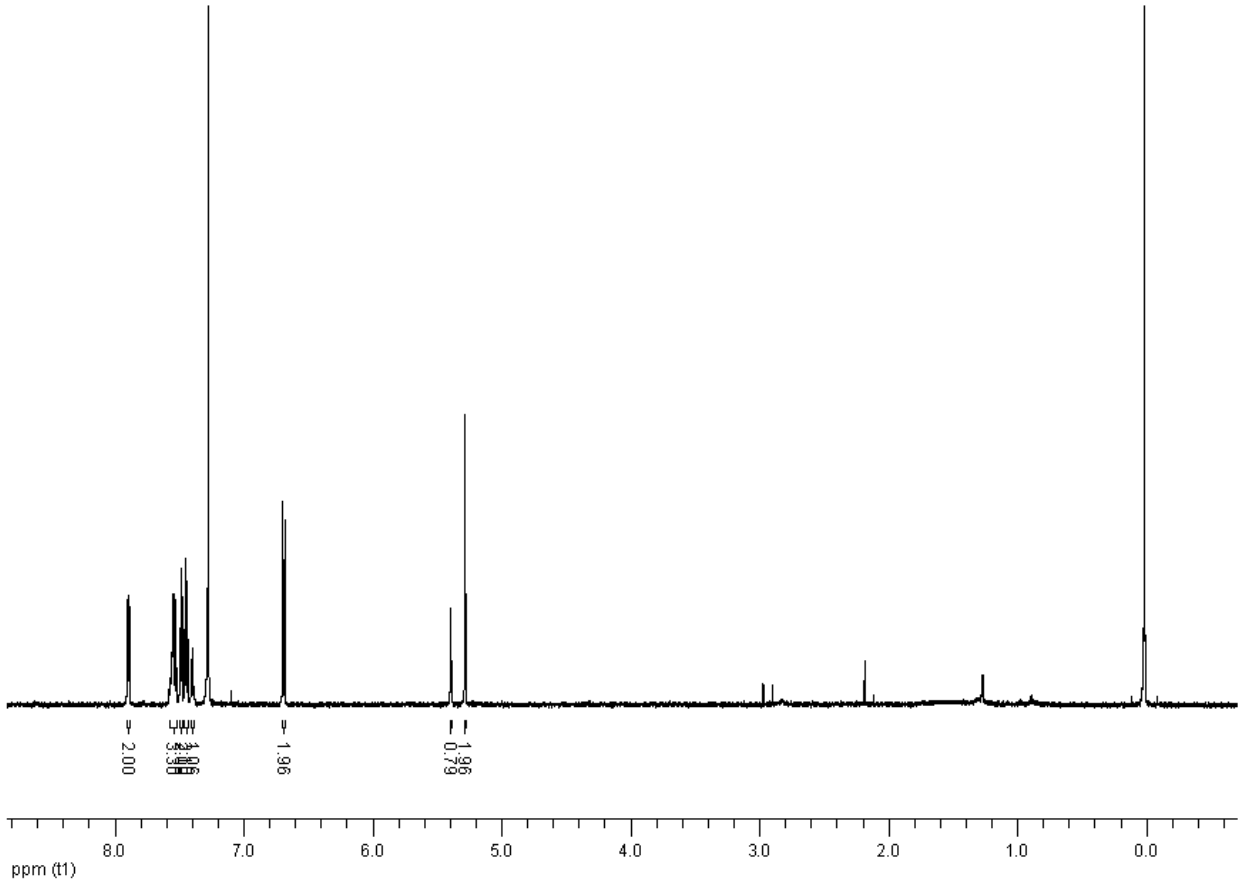
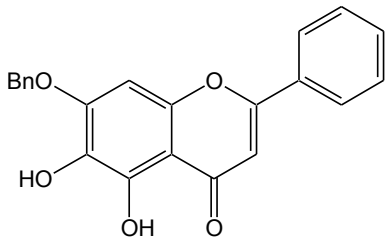


Plate 43b: ^{13}C NMR of 7-Benzyloxy-5,6-dihydroxyflavone, $CDCl_3$ (298K)



(**4.117**)

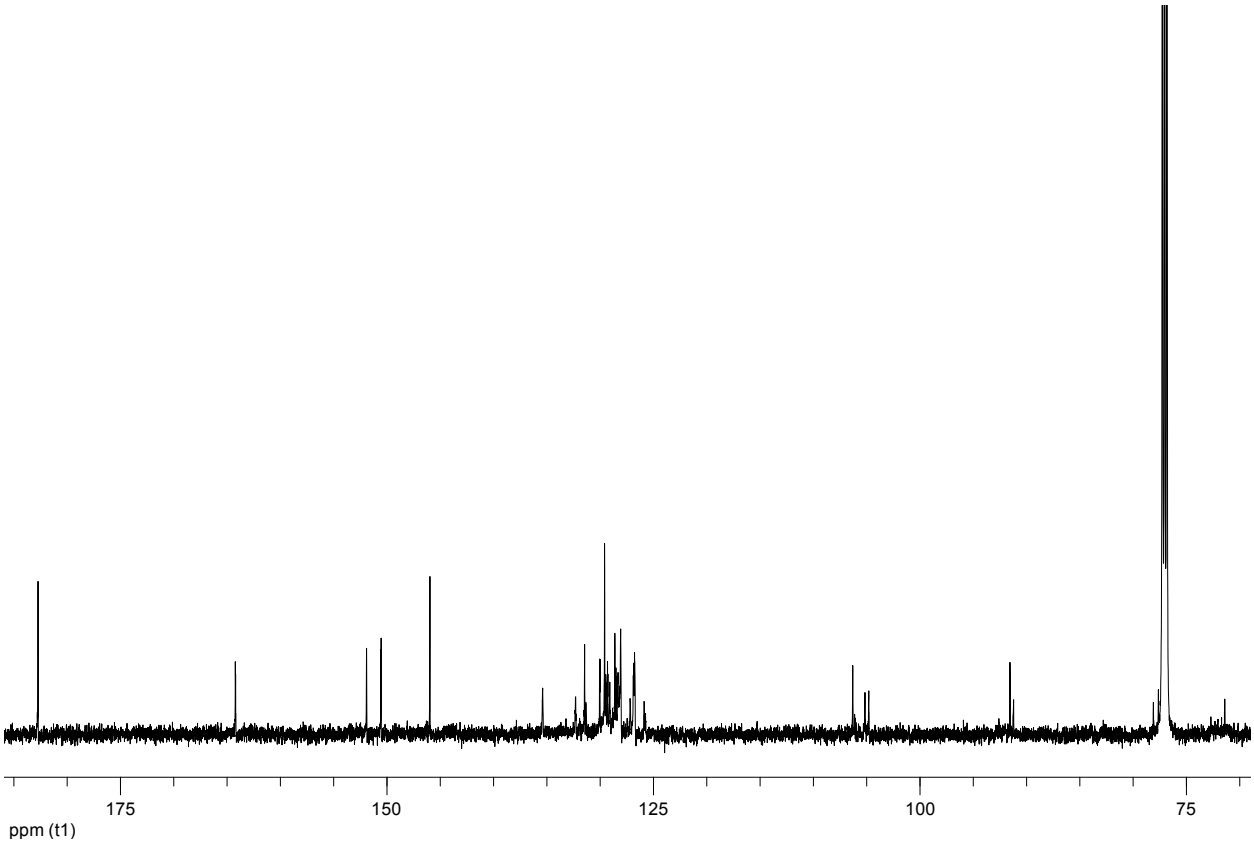
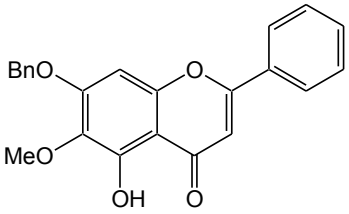
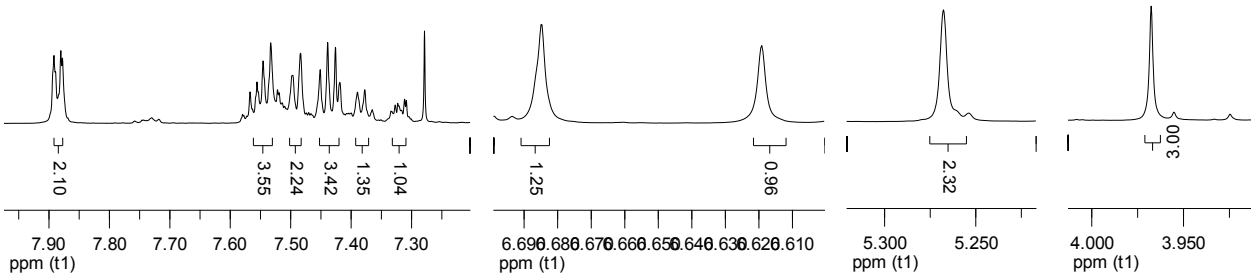


Plate 44a: ^{1}H NMR of 7-Benzyloxy-5-hydroxy-6-methoxyflavone, $CDCl_3$ (298K)



(**4.118**)



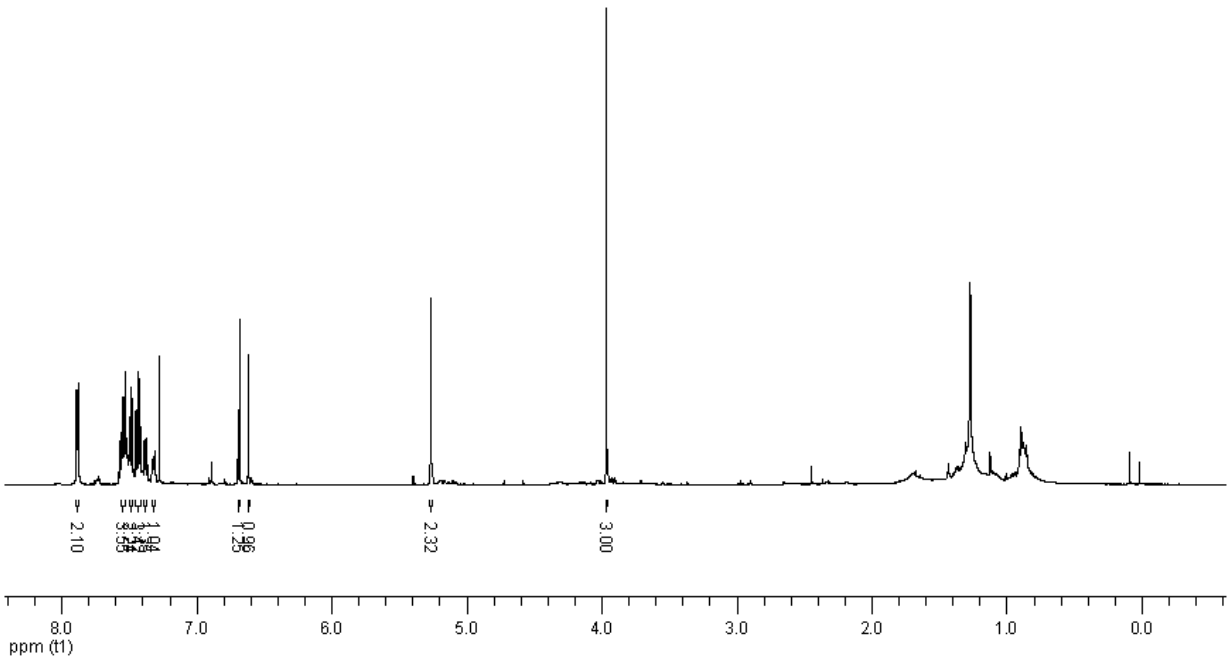
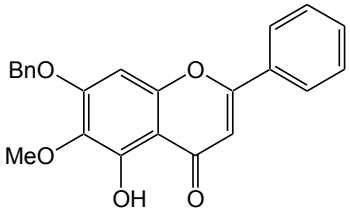


Plate 44b: ^{13}C NMR of 7-Benzyloxy-5-hydroxy-6-methoxyflavone, $CDCl_3$ (298K)



(**4.118**)

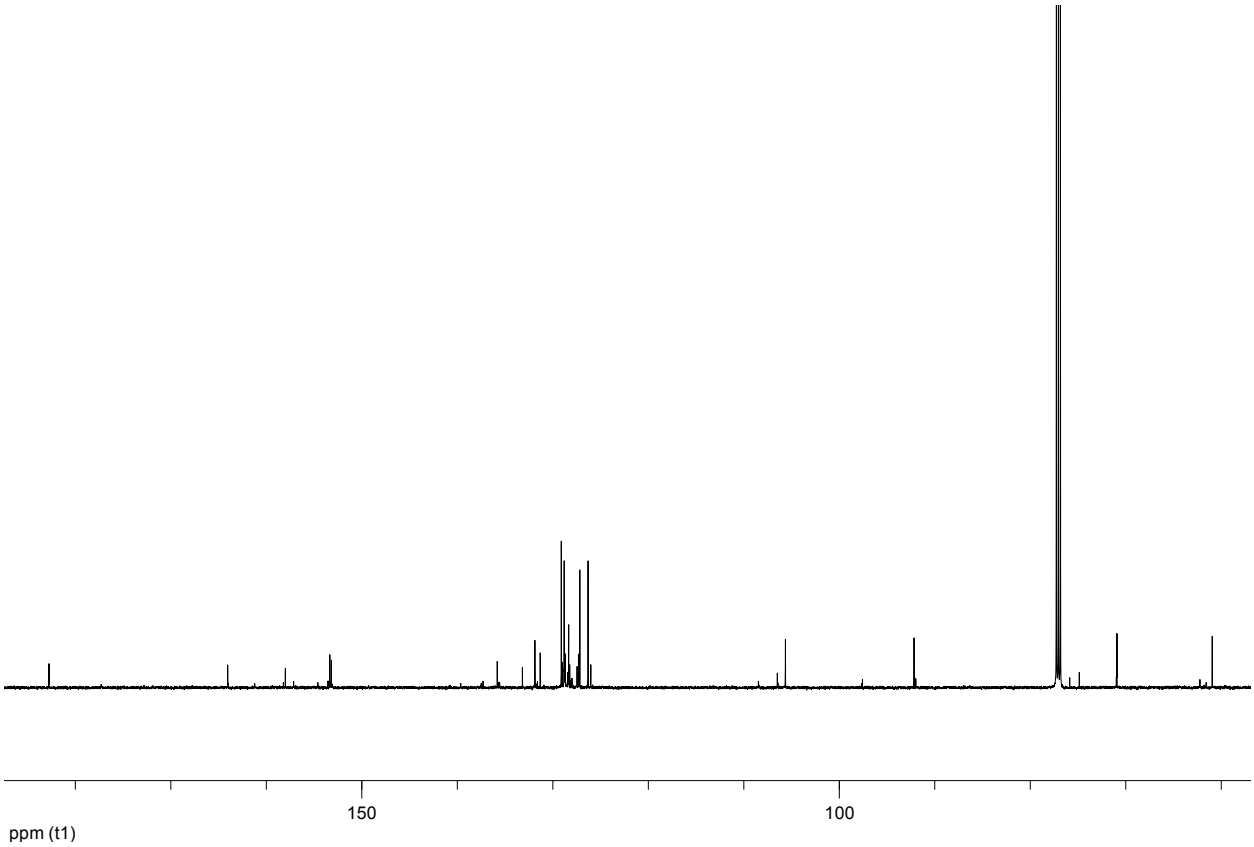
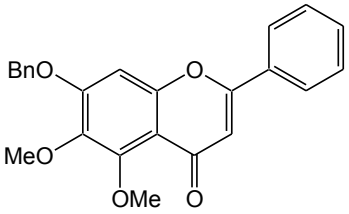
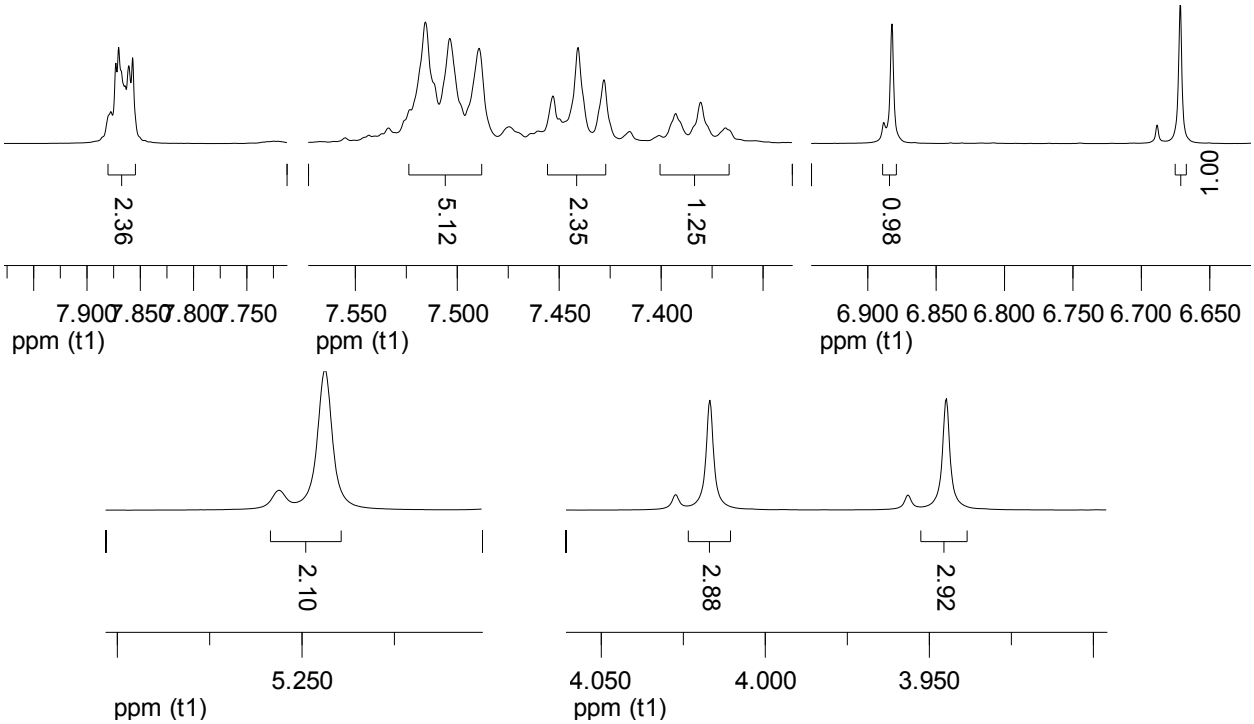


Plate 45a: ^{1}H NMR of 7-Benzyloxy-5,6-dimethoxyflavone, $CDCl_3$ (298K)



(**4.119**)



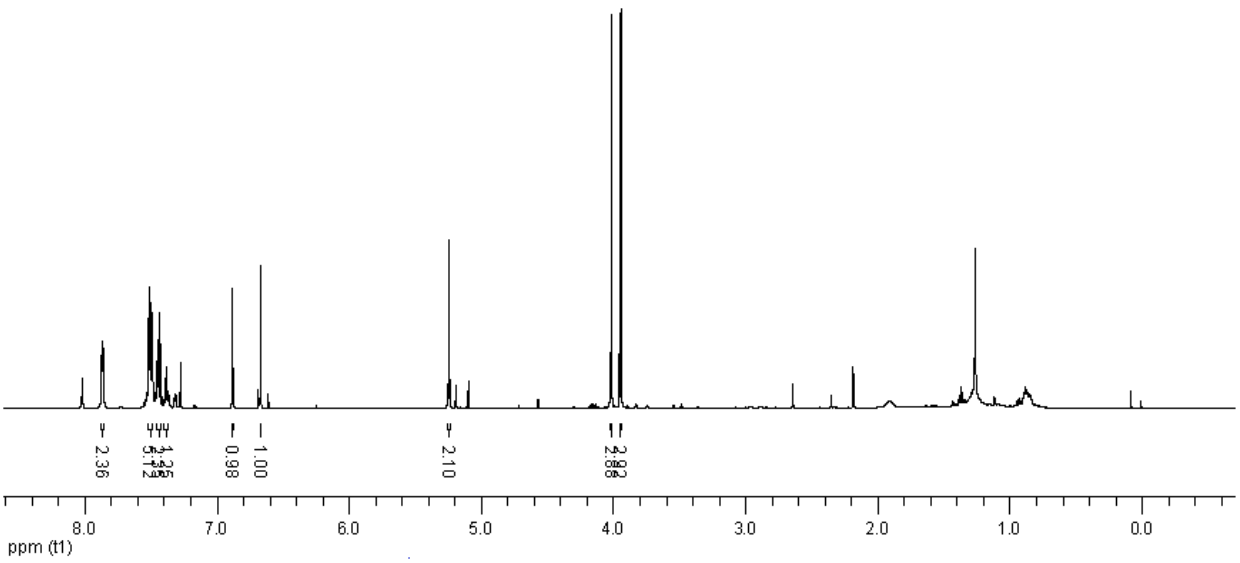
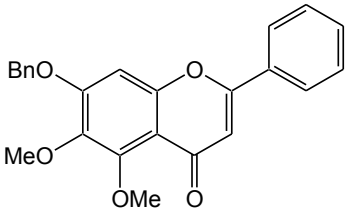


Plate 45b: ^{13}C NMR of 7-Benzyloxy-5,6-dimethoxyflavone, $CDCl_3$ (298K)



(**4.119**)

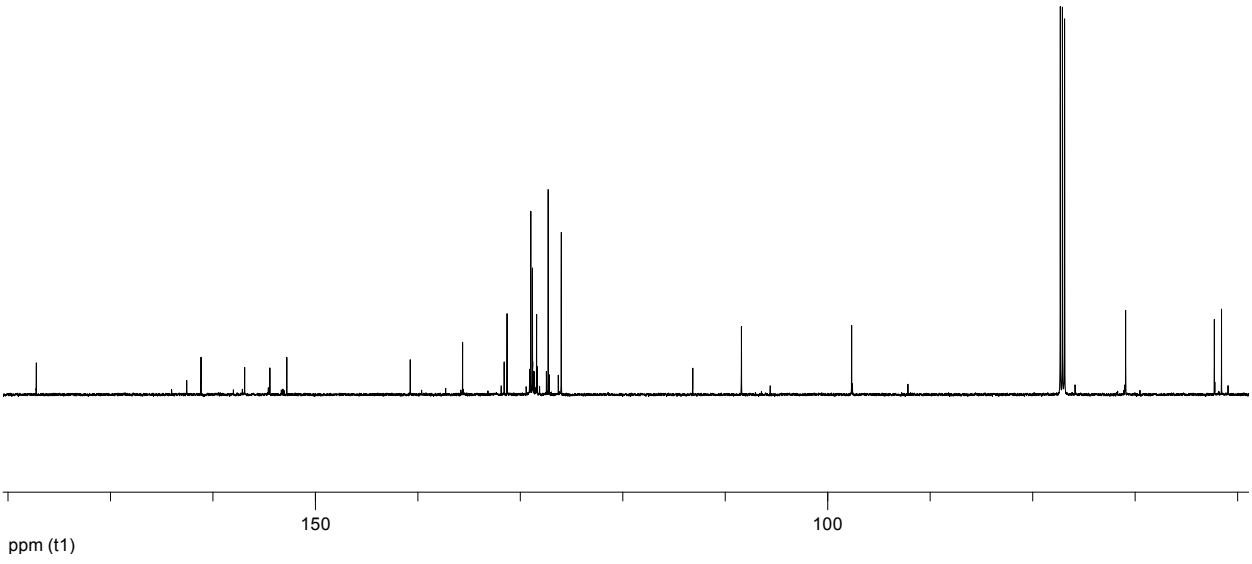
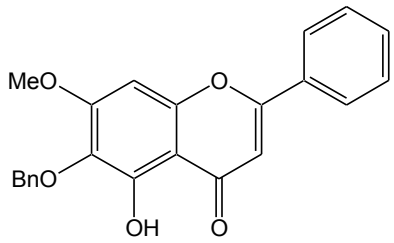
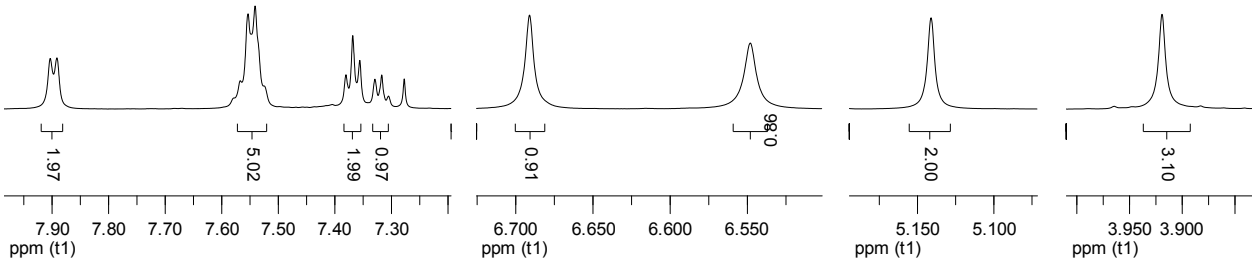


Plate 46a: ^{1}H NMR of 6-Benzyloxy-5-hydroxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.121**)



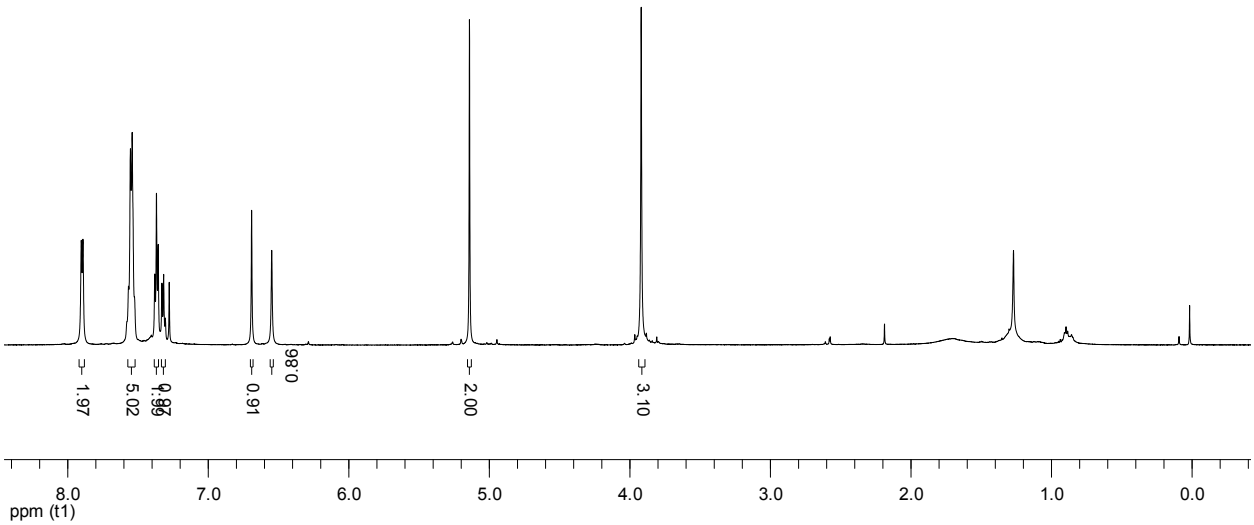
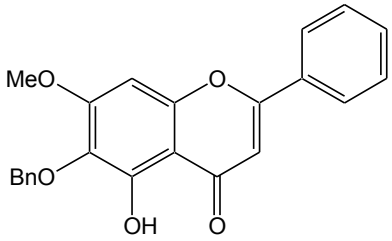


Plate 46b: ^{13}C NMR of 6-Benzyloxy-5-hydroxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.121**)

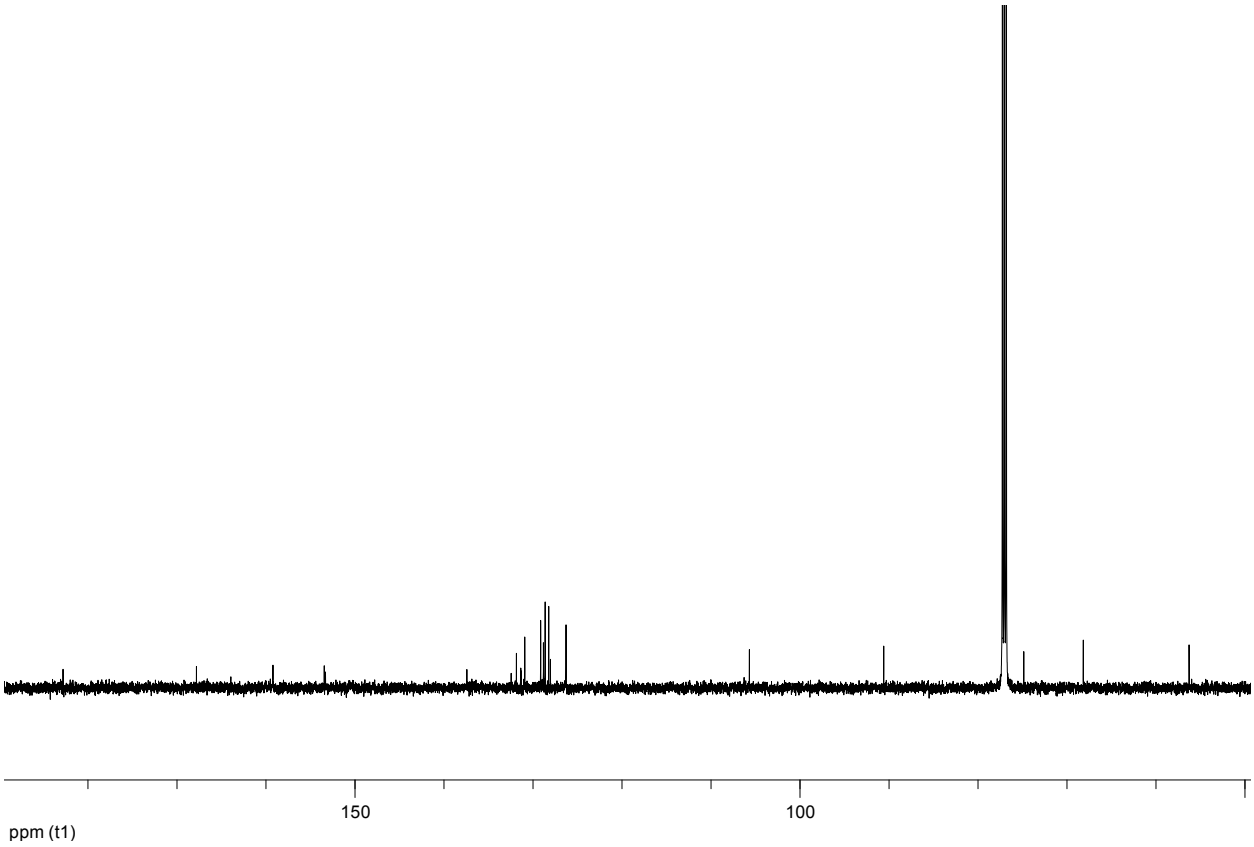
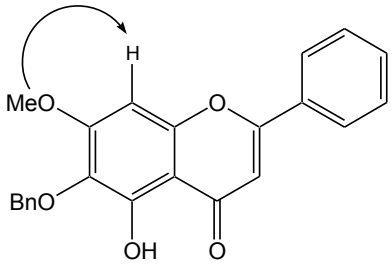


Plate 46c: NOESY of 6-Benzyloxy-5-hydroxy-7-methoxyflavone, $CDCl_3$ (298K)



(**4.121**)

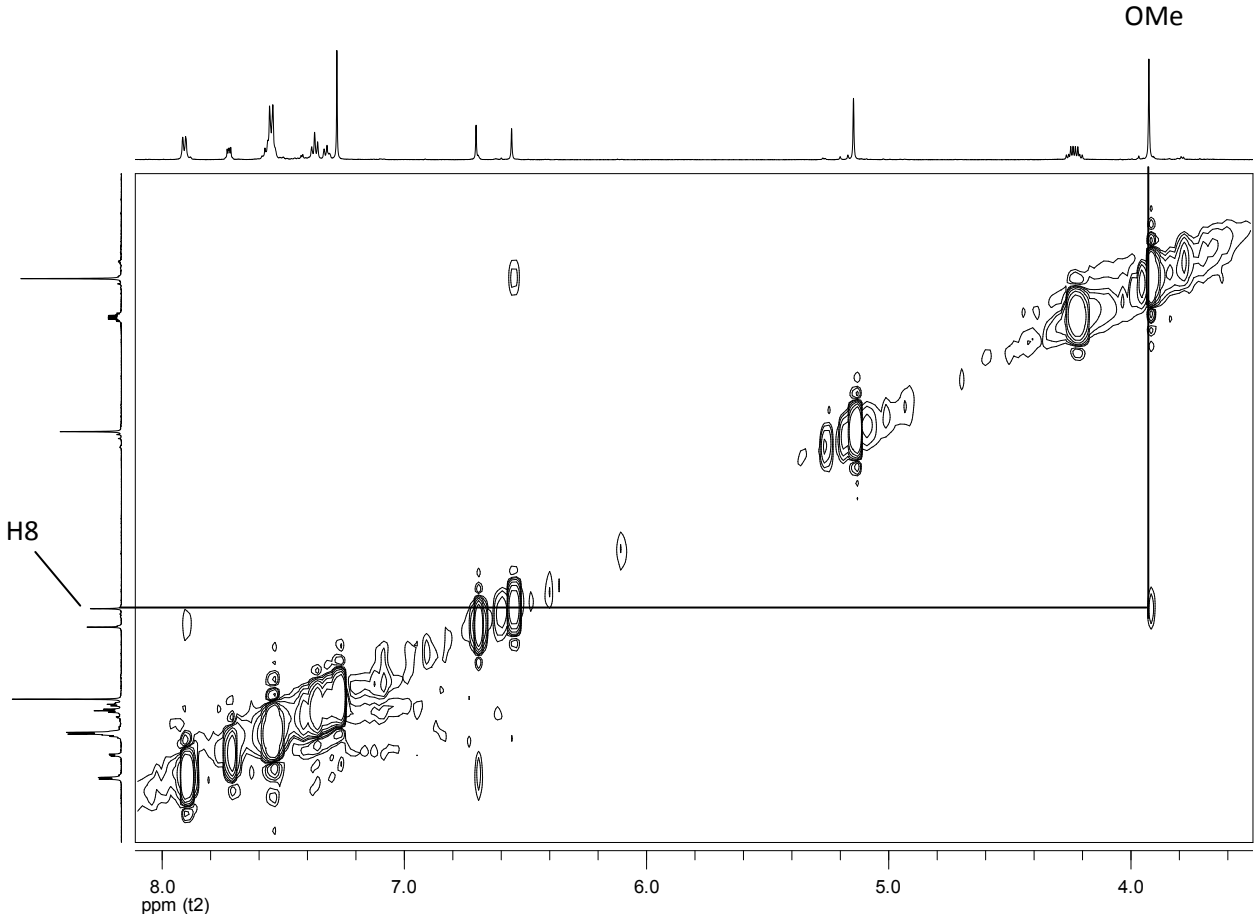
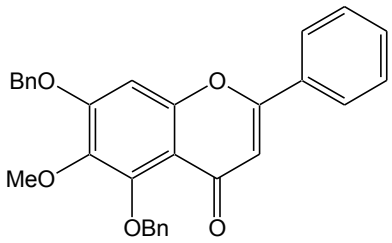


Plate 47a: ^{1}H NMR of 5,7-Dibenzyloxy-6-methoxyflavone, $CDCl_3$ (298K)



(**4.112**)

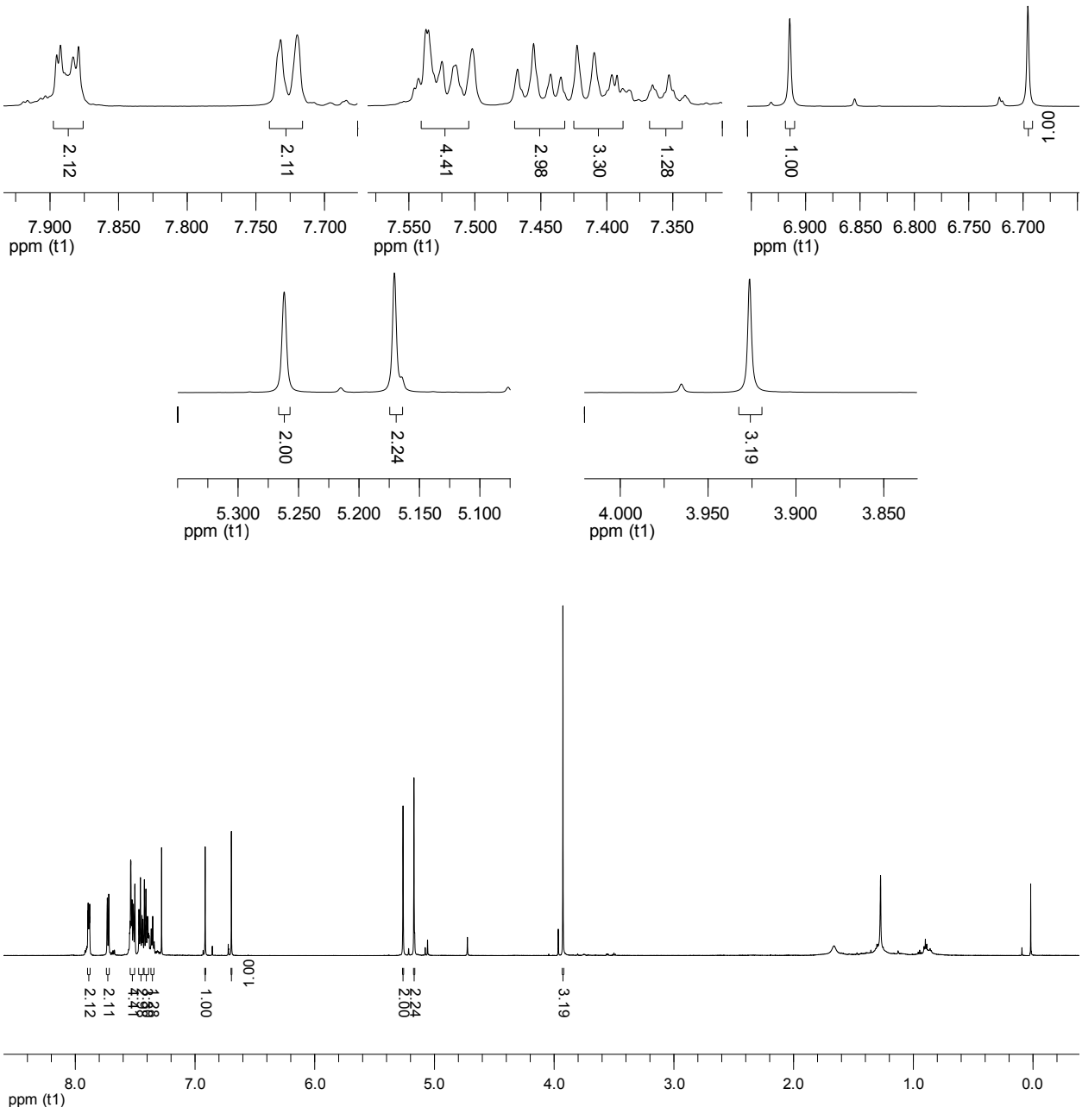
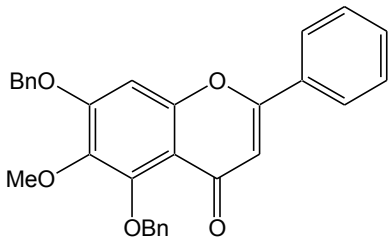


Plate 47b: ^{13}C NMR of 5,7-Dibenzyloxy-6-methoxyflavone, $CDCl_3$ (298K)



(**4.112**)

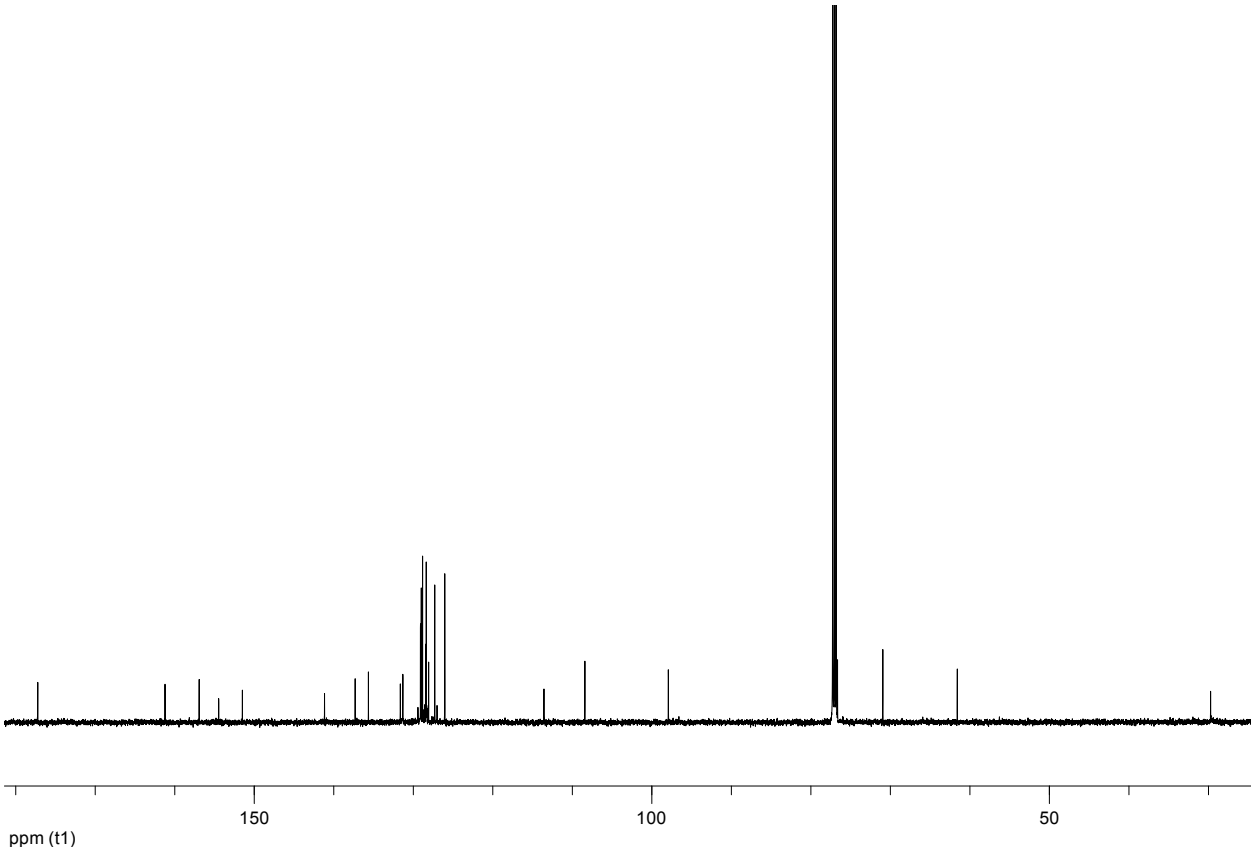
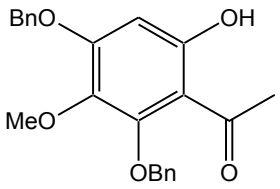
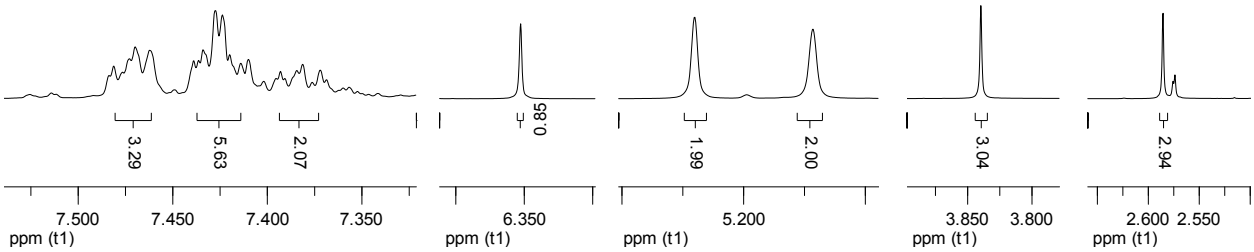


Plate 48a: ^{1}H NMR of 2,4-Dibenzyloxy-6-hydroxy-3-methoxyacetophenone, $CDCl_3$ (298K)



(**4.120**)



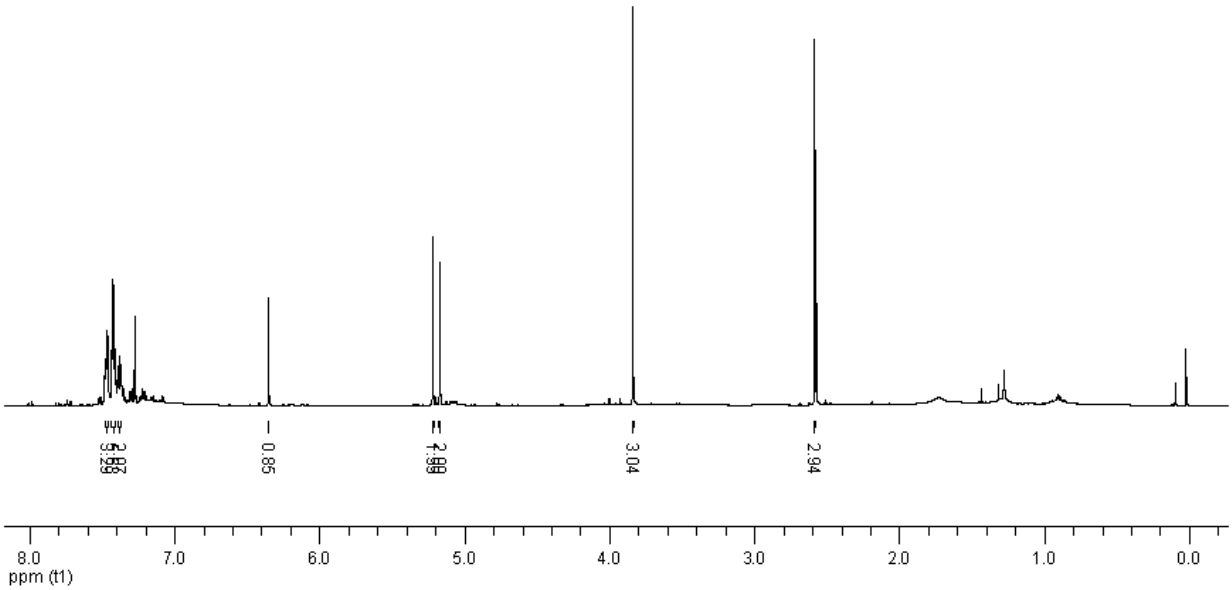
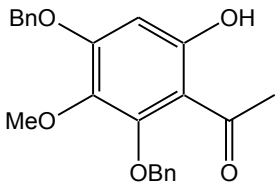


Plate 48b: ^{13}C NMR of 2,4-Dibenzyloxy-6-hydroxy-3-methoxyacetophenone, $CDCl_3$ (298K)



(**4.120**)

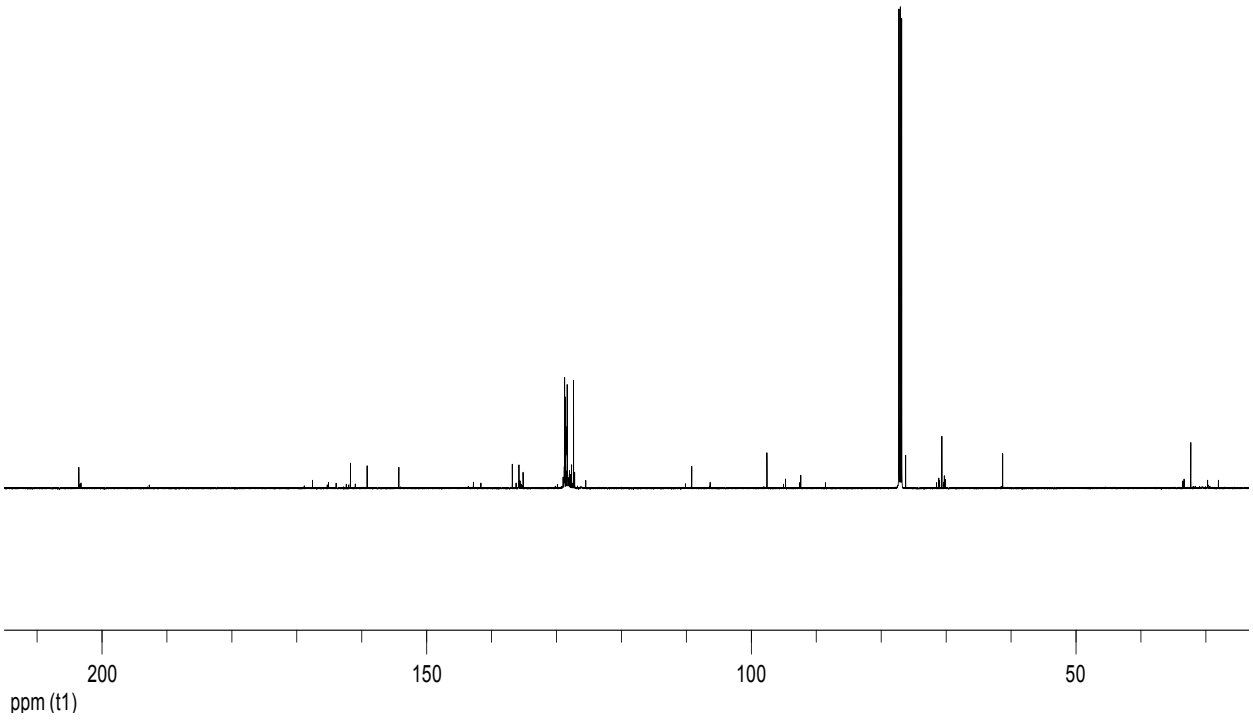
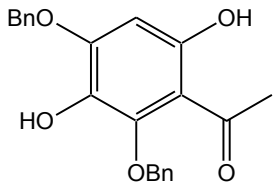
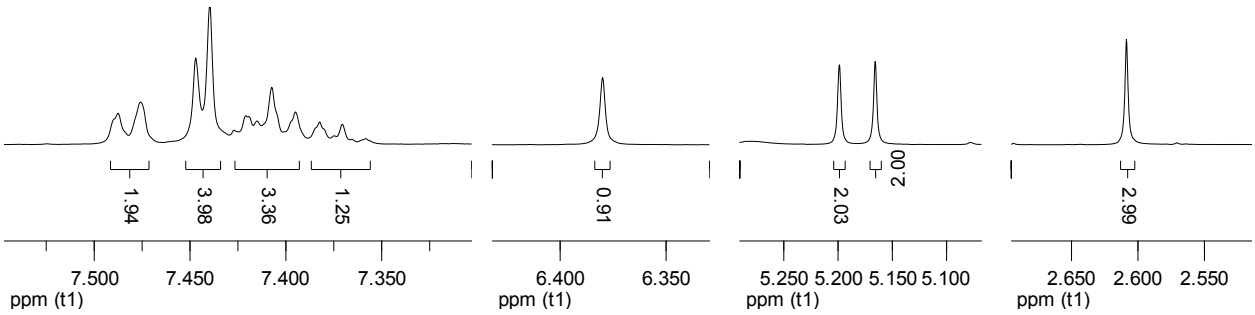


Plate 49a: ^{1}H NMR of 2,4-Dibenzyloxy-3,6-dihydroxyacetophenone, $CDCl_3$ (298K)



(**4.123**)



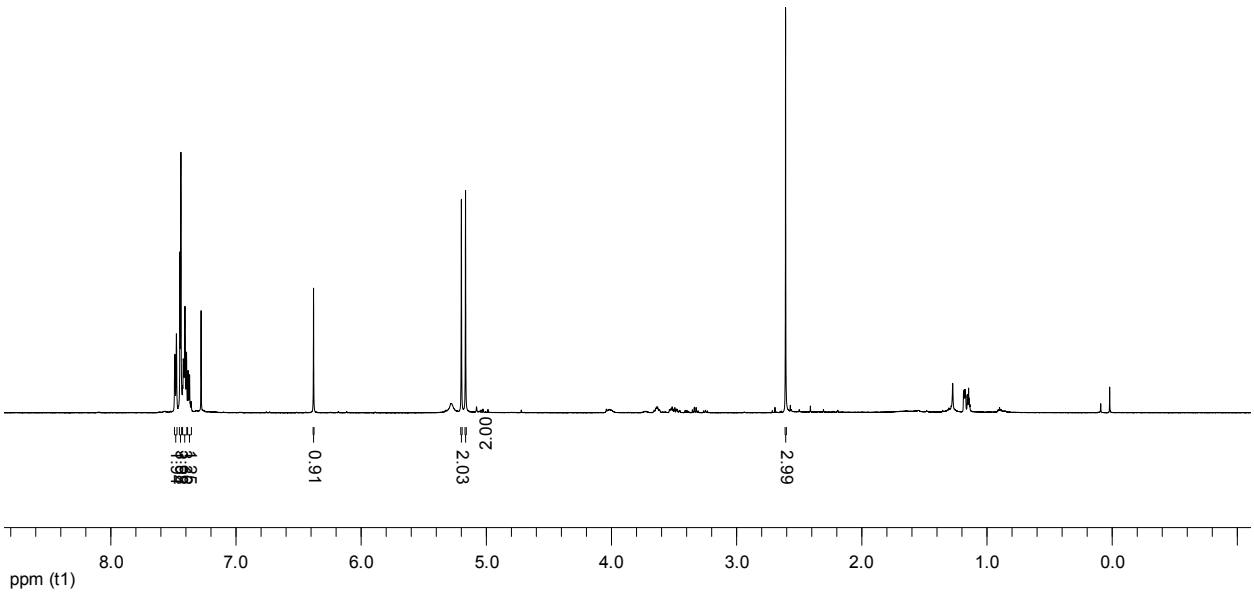
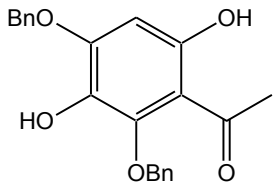


Plate 49b: ^{13}C NMR of 2,4-Dibenzyloxy-3,6-dihydroxyacetophenone, $CDCl_3$ (298K)



(**4.123**)

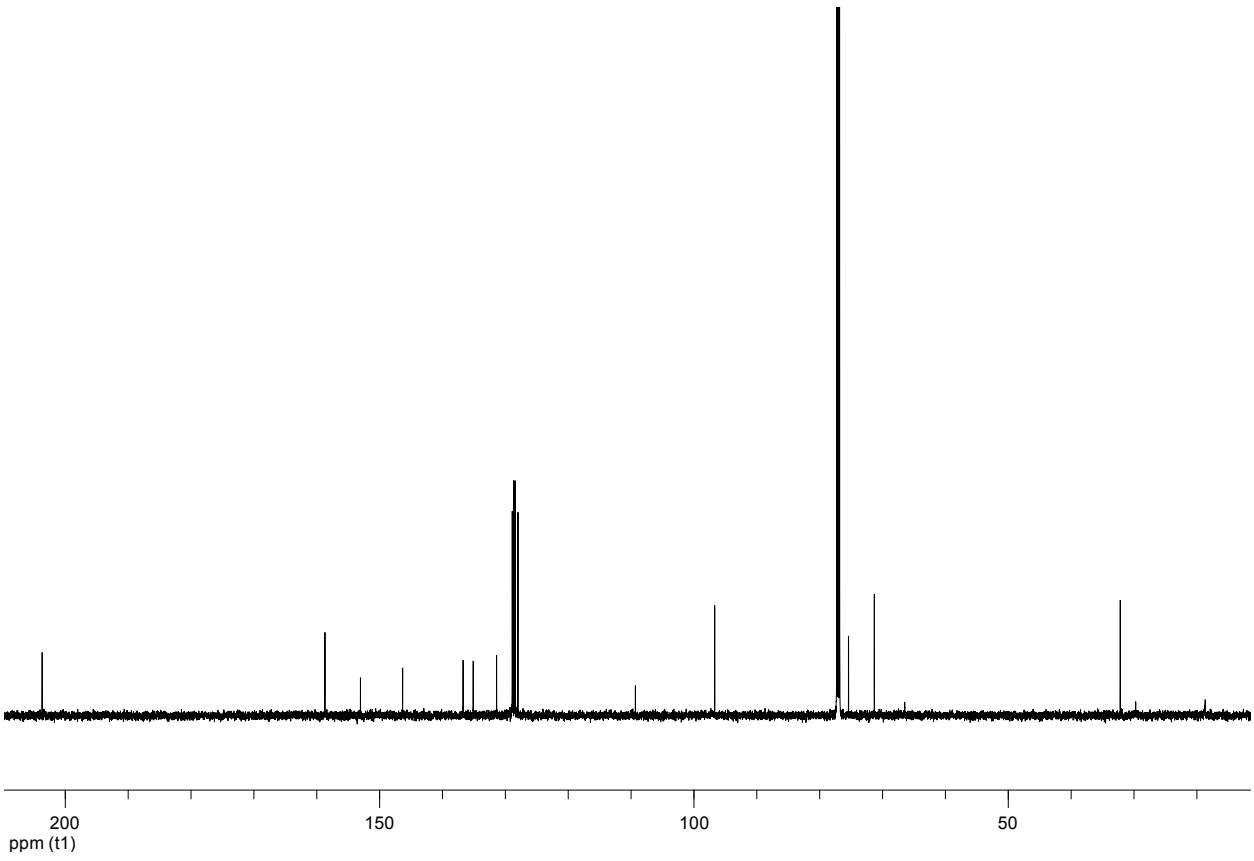
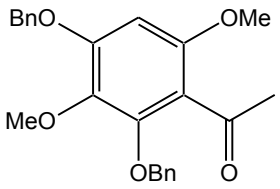
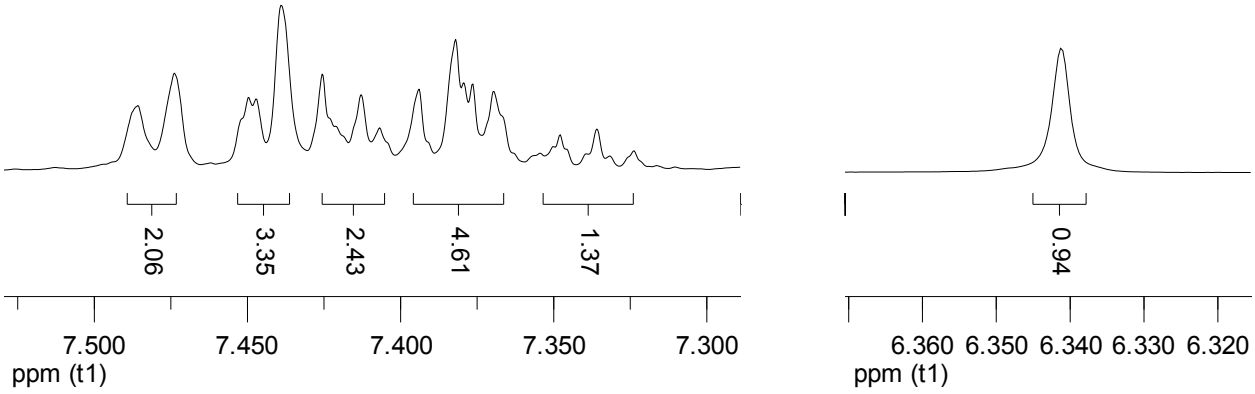
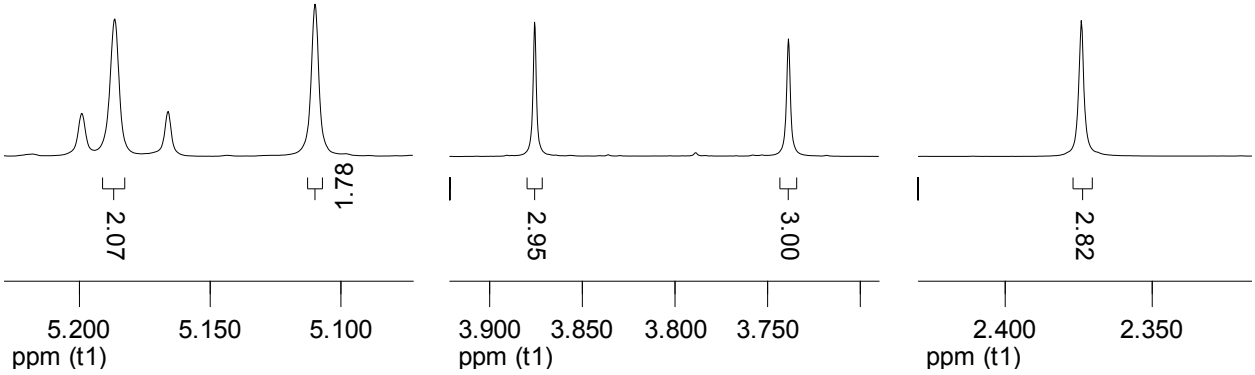


Plate 50a: ^{1}H NMR of 2,4-Dibenzyloxy-3,6-dimethoxyacetophenone, $CDCl_3$ (298K)



(**4.124**)





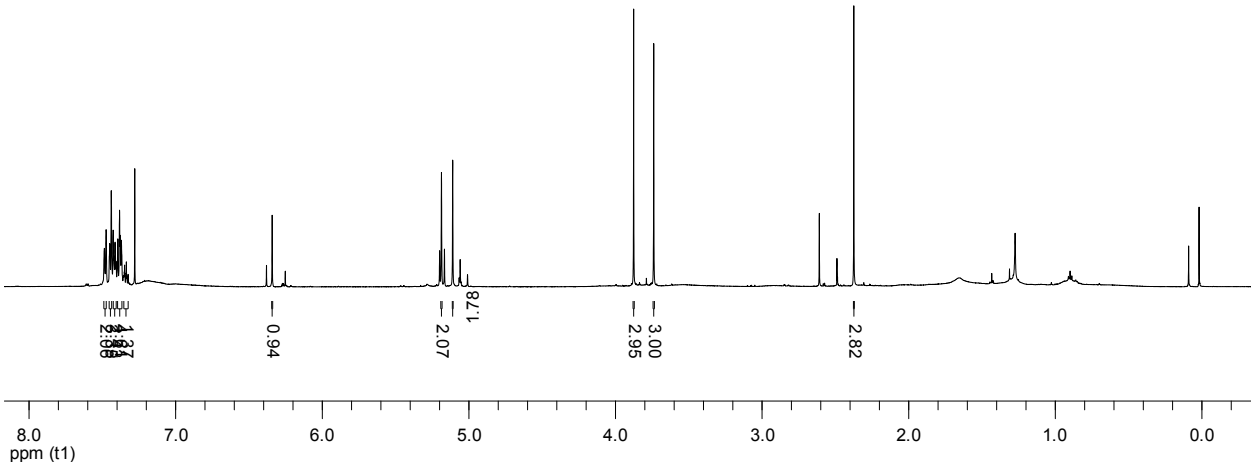
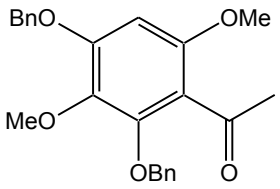


Plate 50b: ^{13}C NMR of 2,4-Dibenzyloxy-3,6-dimethoxyacetophenone, $CDCl_3$ (298K)



(**4.124**)

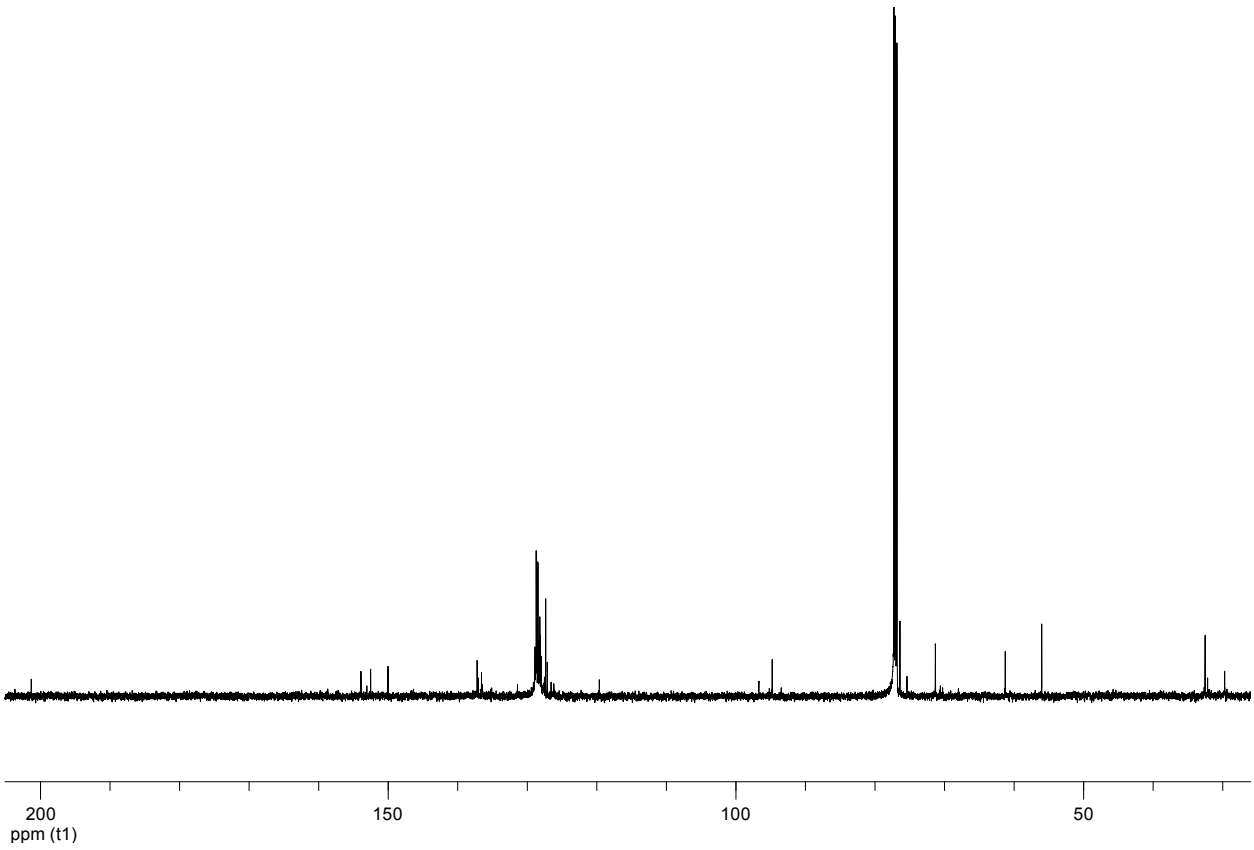
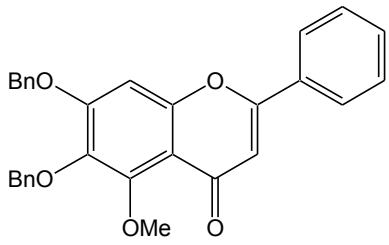
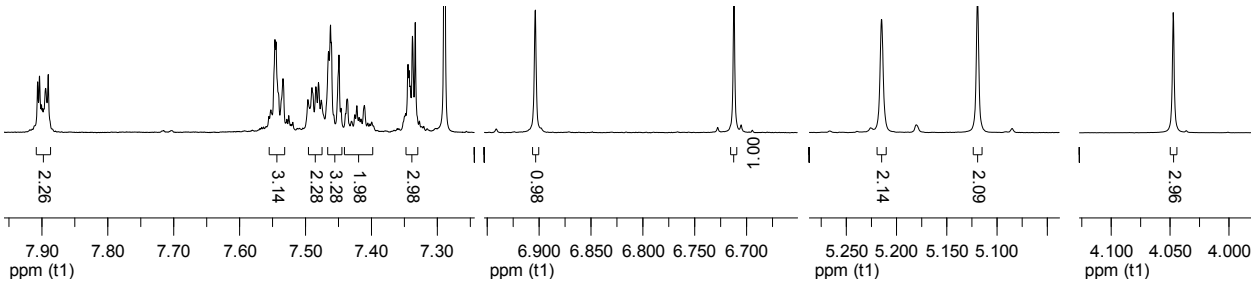


Plate 51a: ^{1}H NMR of 6,7-Dibenzyloxy-5-methoxyflavone, $CDCl_3$ (298K)



(**4.113**)



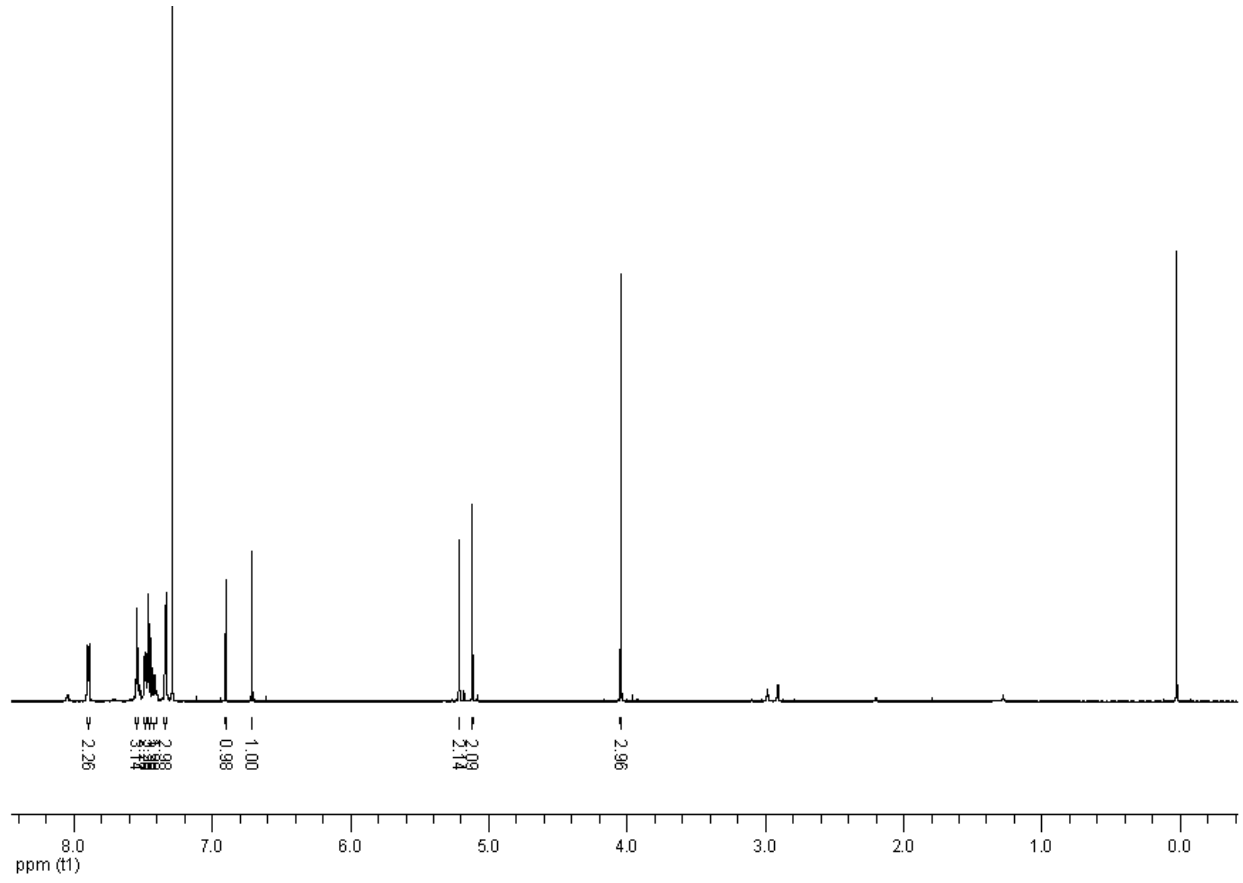
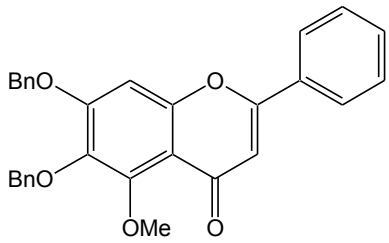


Plate 51b: ^{13}C NMR of 6,7-Dibenzyloxy-5-methoxyflavone, $CDCl_3$ (298K)



(**4.113**)

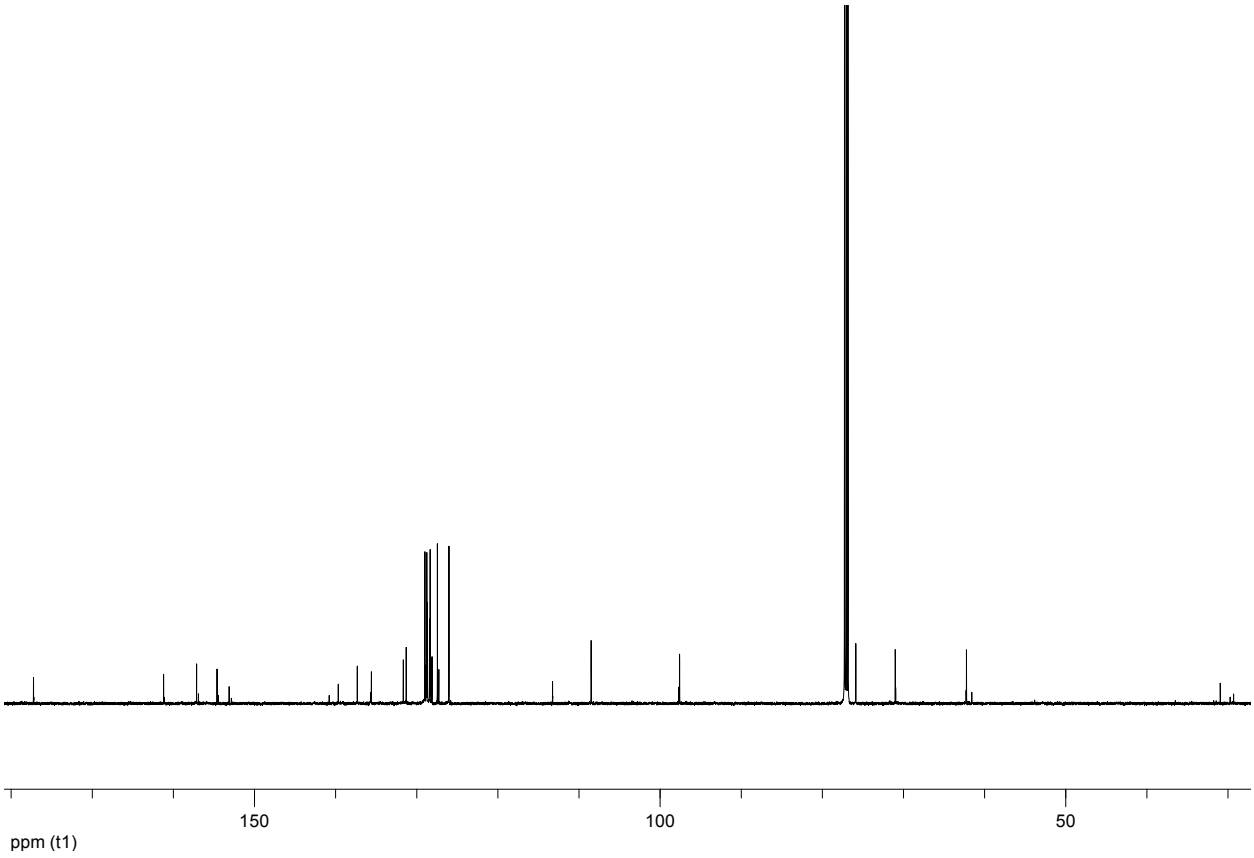
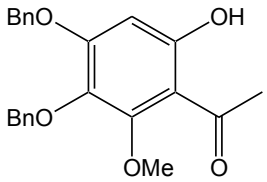
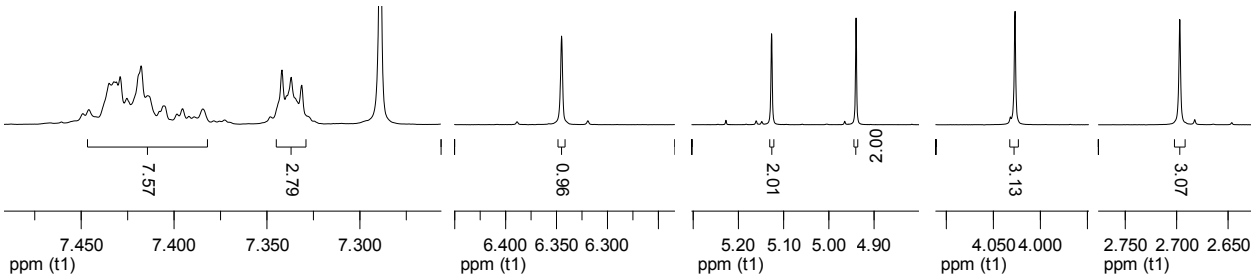


Plate 52a: ^{1}H NMR of 3,4-Dibenzyloxy-6-hydroxy-2-methoxyacetophenone, $CDCl_3$ (298K)



(**4.125**)



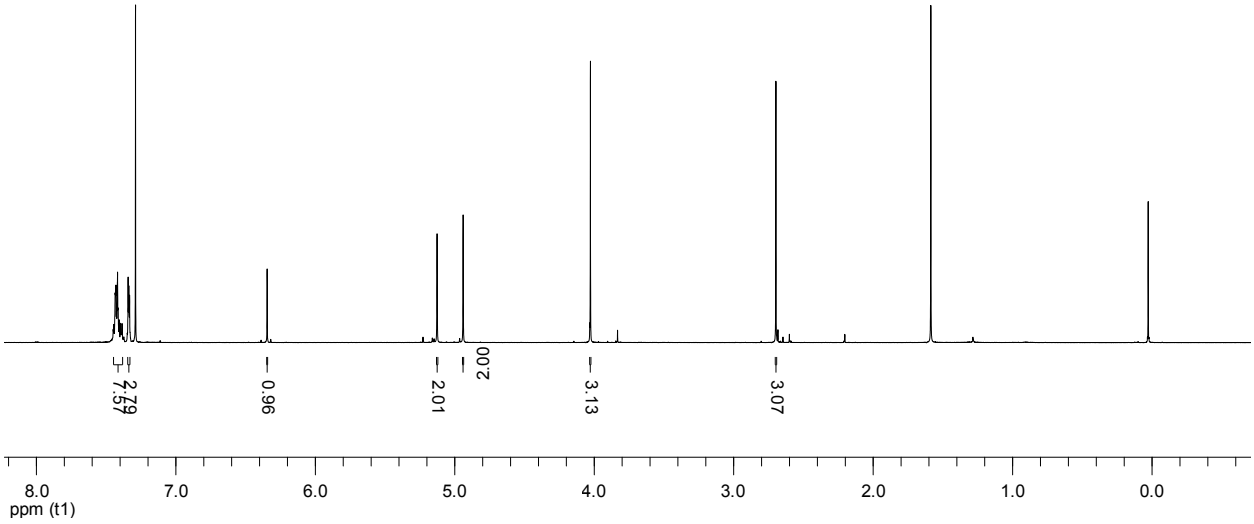
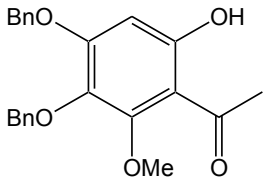


Plate 52b: ^{13}C NMR of 3,4-Dibenzyloxy-6-hydroxy-2-methoxyacetophenone, $CDCl_3$ (298K)



(**4.125**)

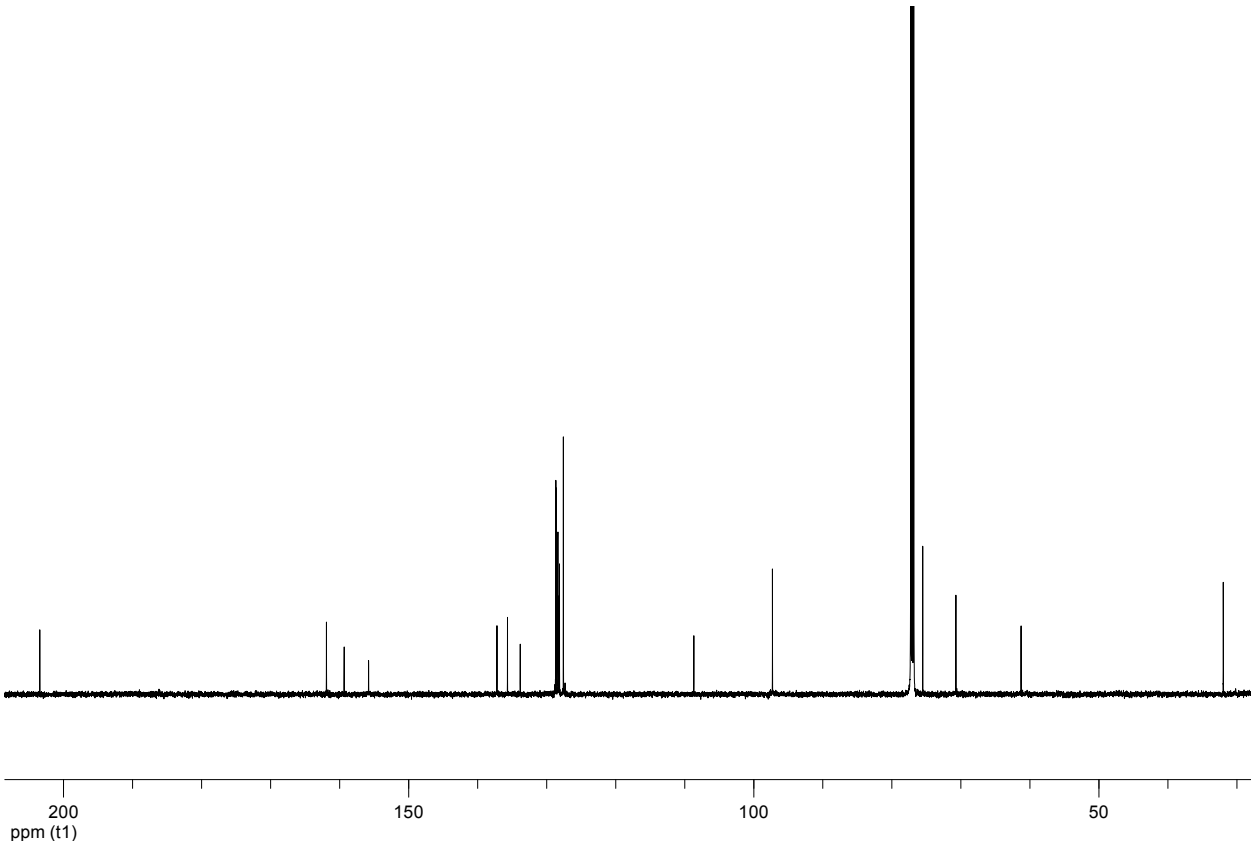
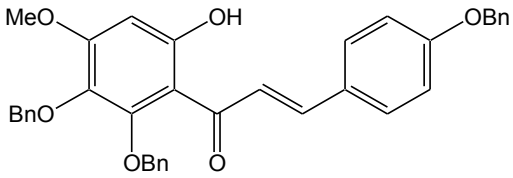
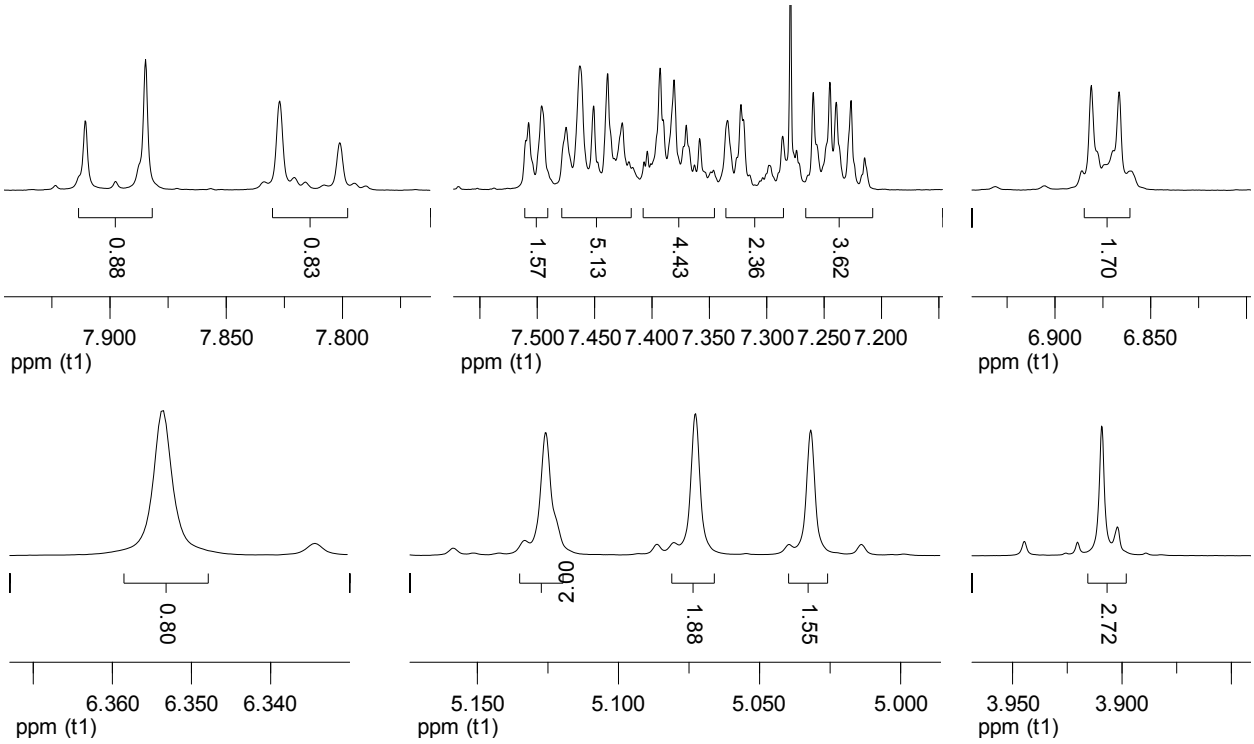


Plate 53a: ^{1}H NMR of 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxychalcone, $CDCl_3$ (298K)



(**4.127**)



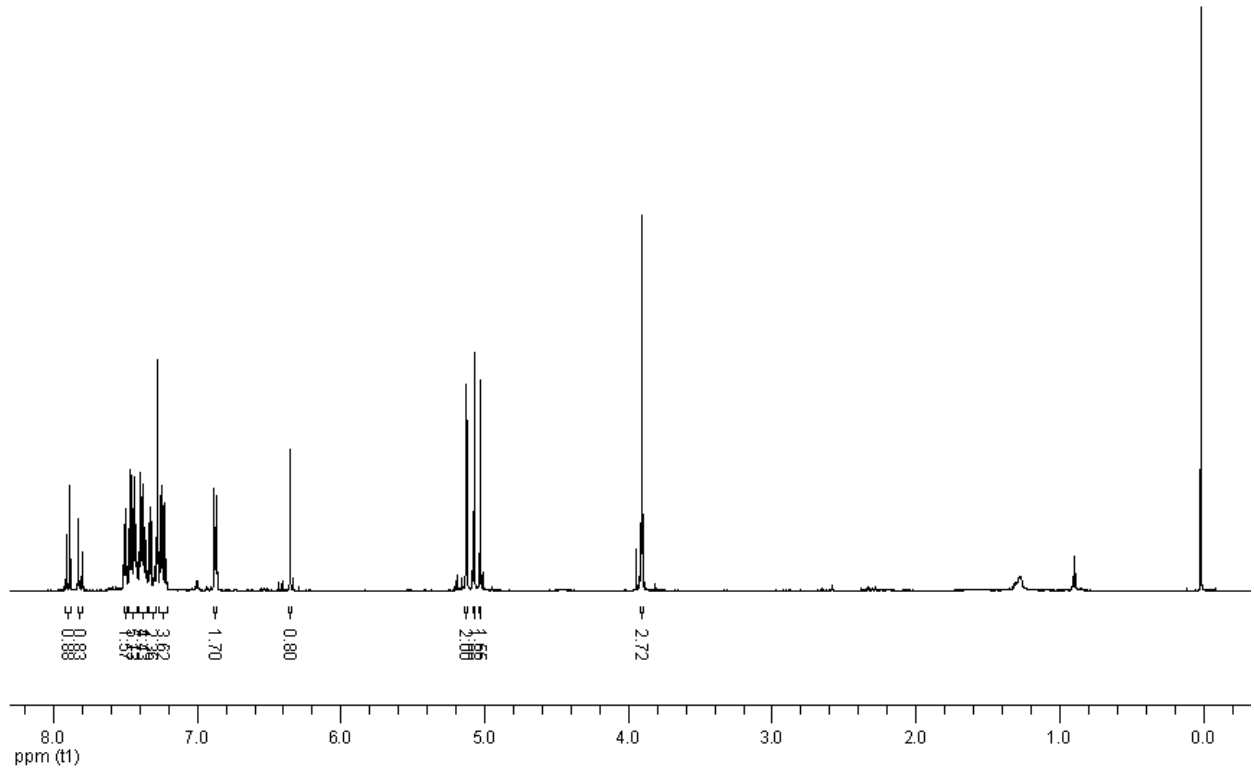
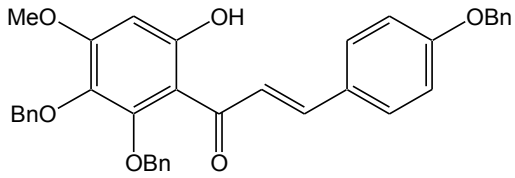


Plate 53b: ^{13}C NMR of 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxychalcone, $CDCl_3$ (298K)



(**4.127**)

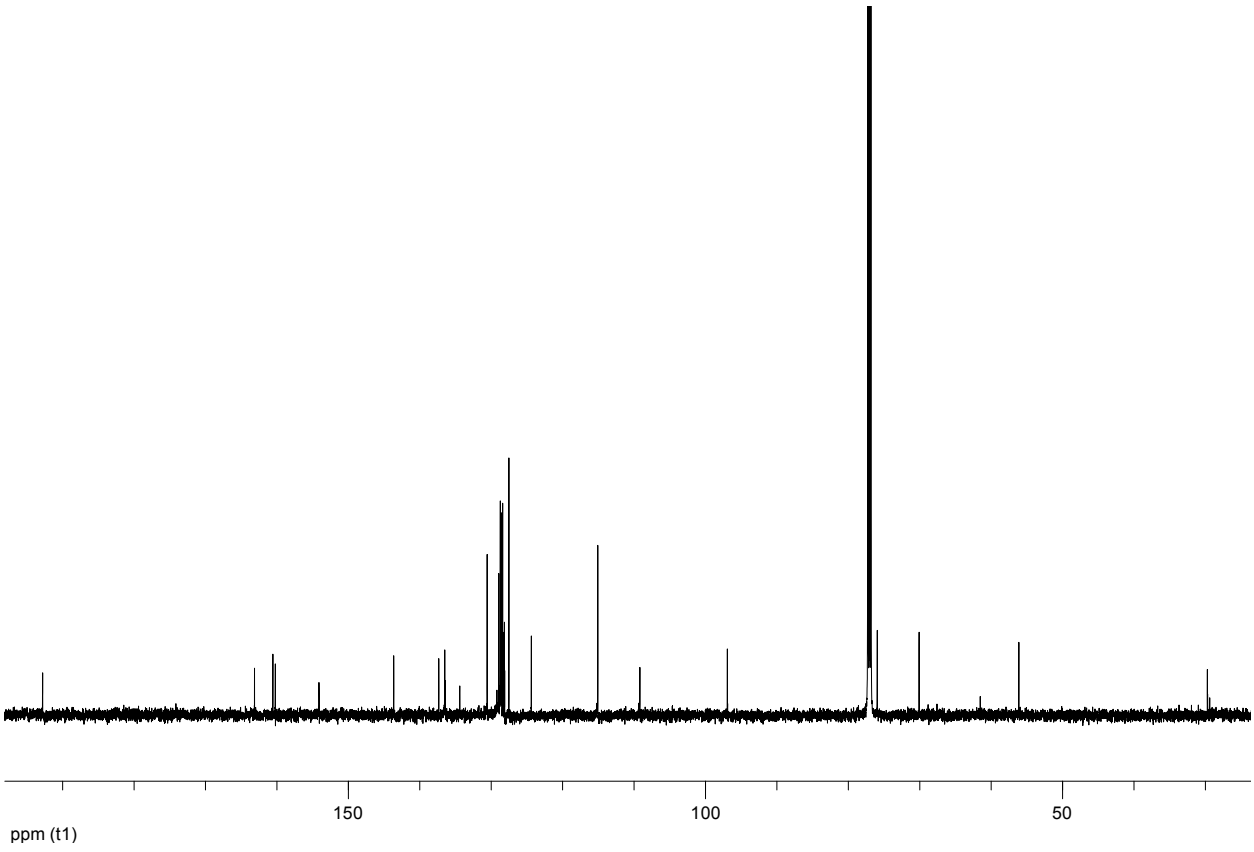
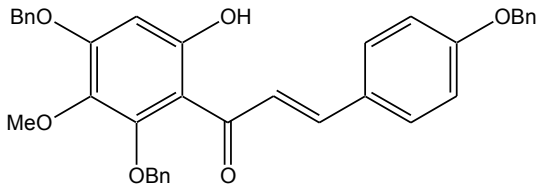
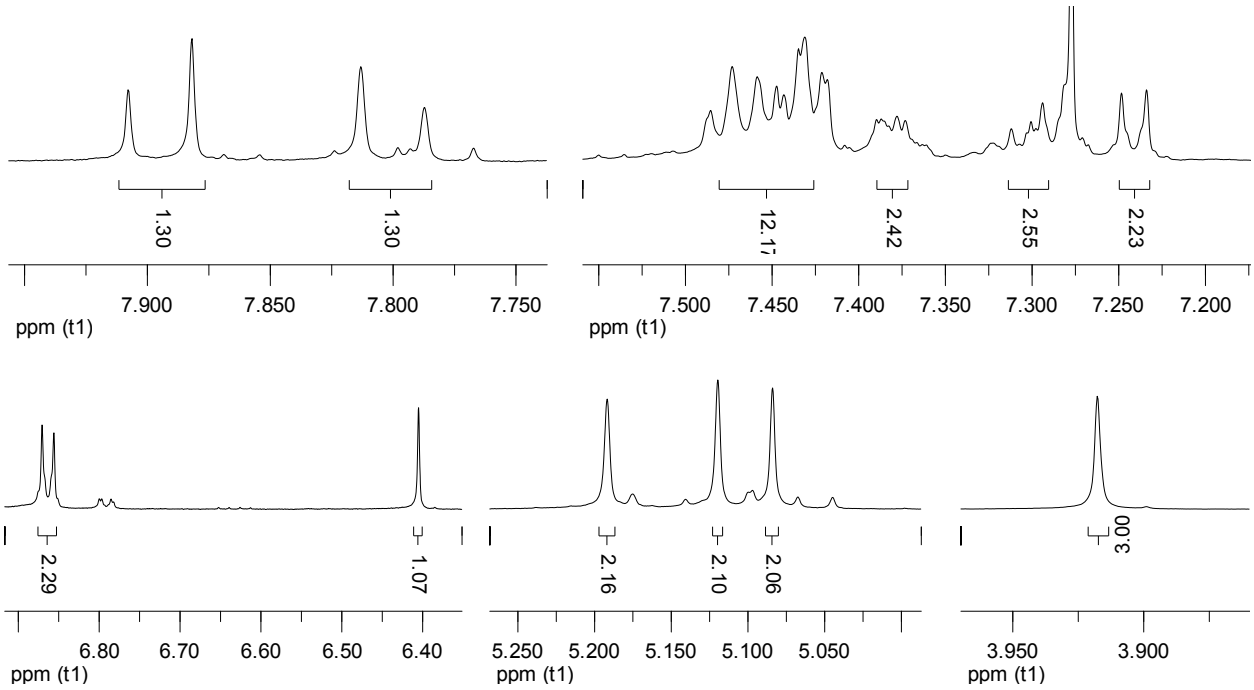


Plate 54a: ^{1}H NMR of 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxychalcone, $CDCl_3$ (298K)



(**4.128**)



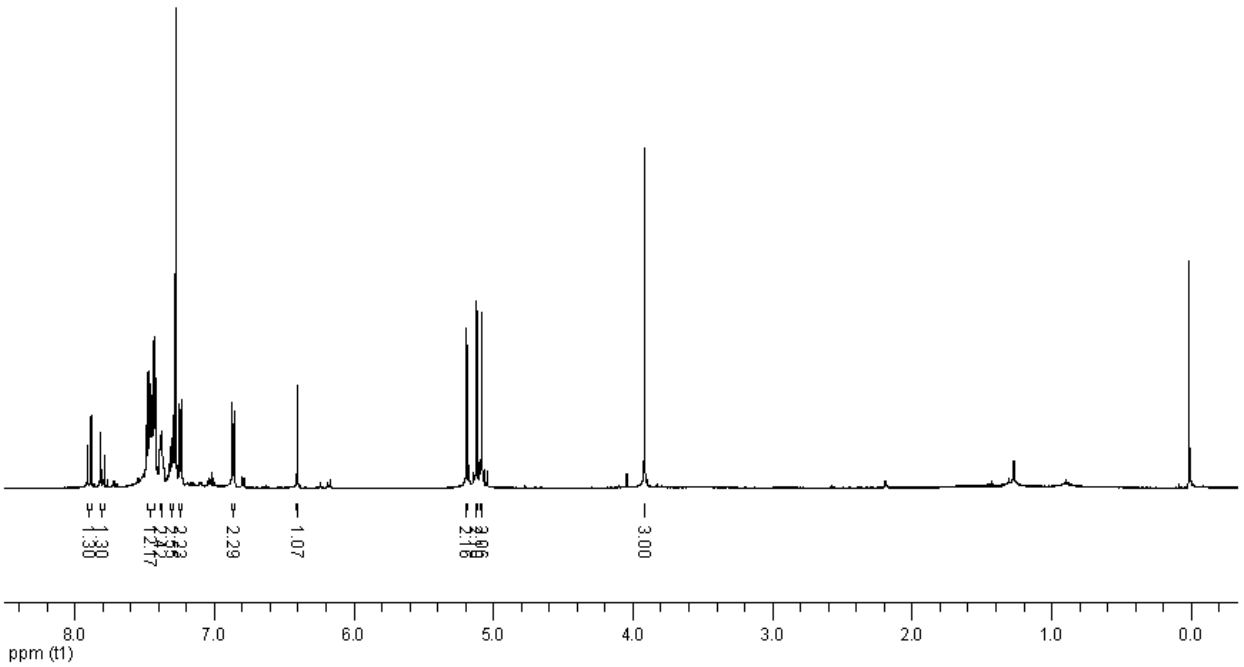
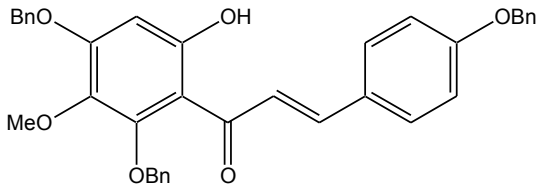


Plate 54b: ^{13}C NMR of 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxychalcone, $CDCl_3$ (298K)



(**4.128**)

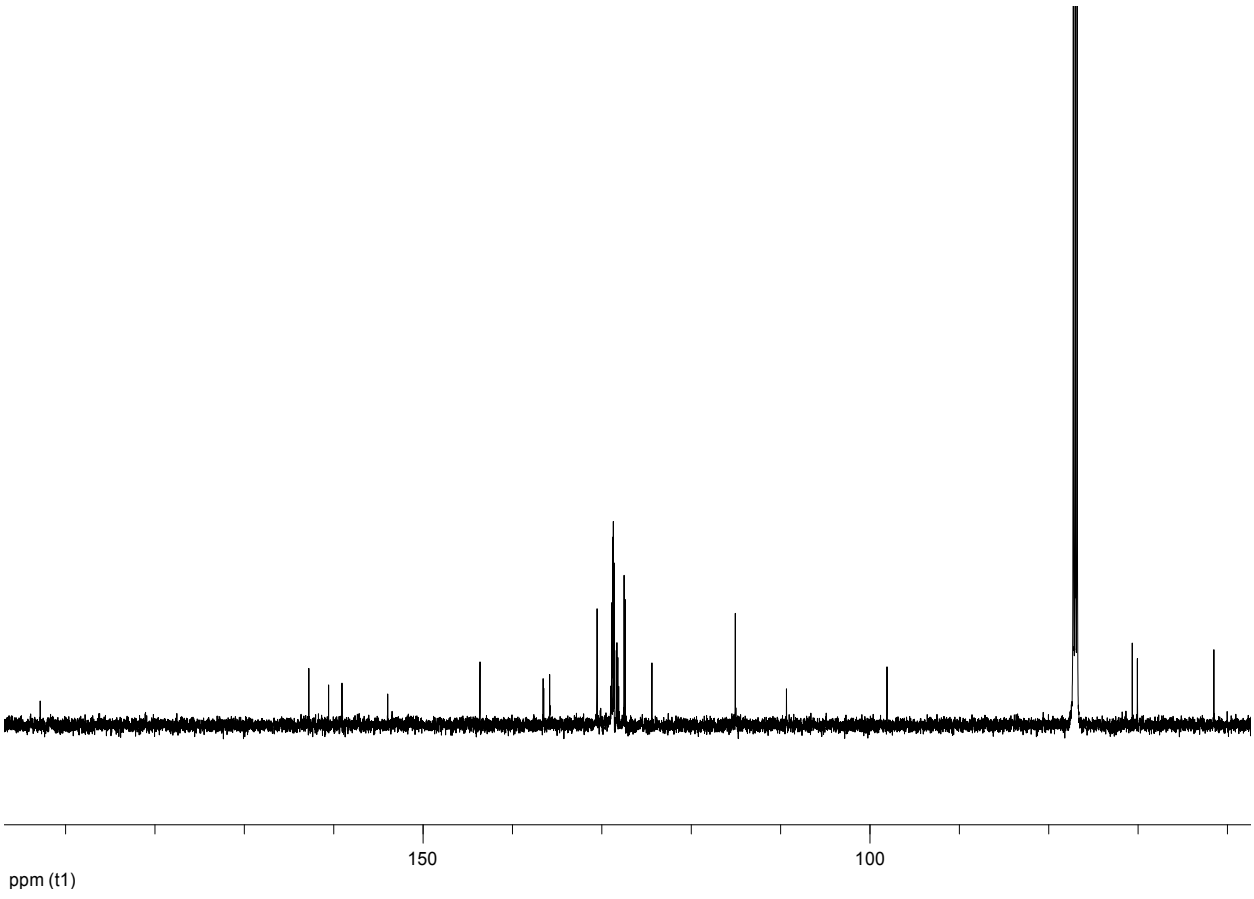
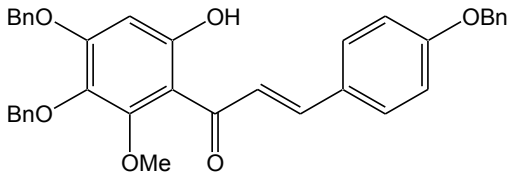


Plate 55a: ^{1}H NMR of 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxychalcone, $CDCl_3$ (298K)



(**4.129**)

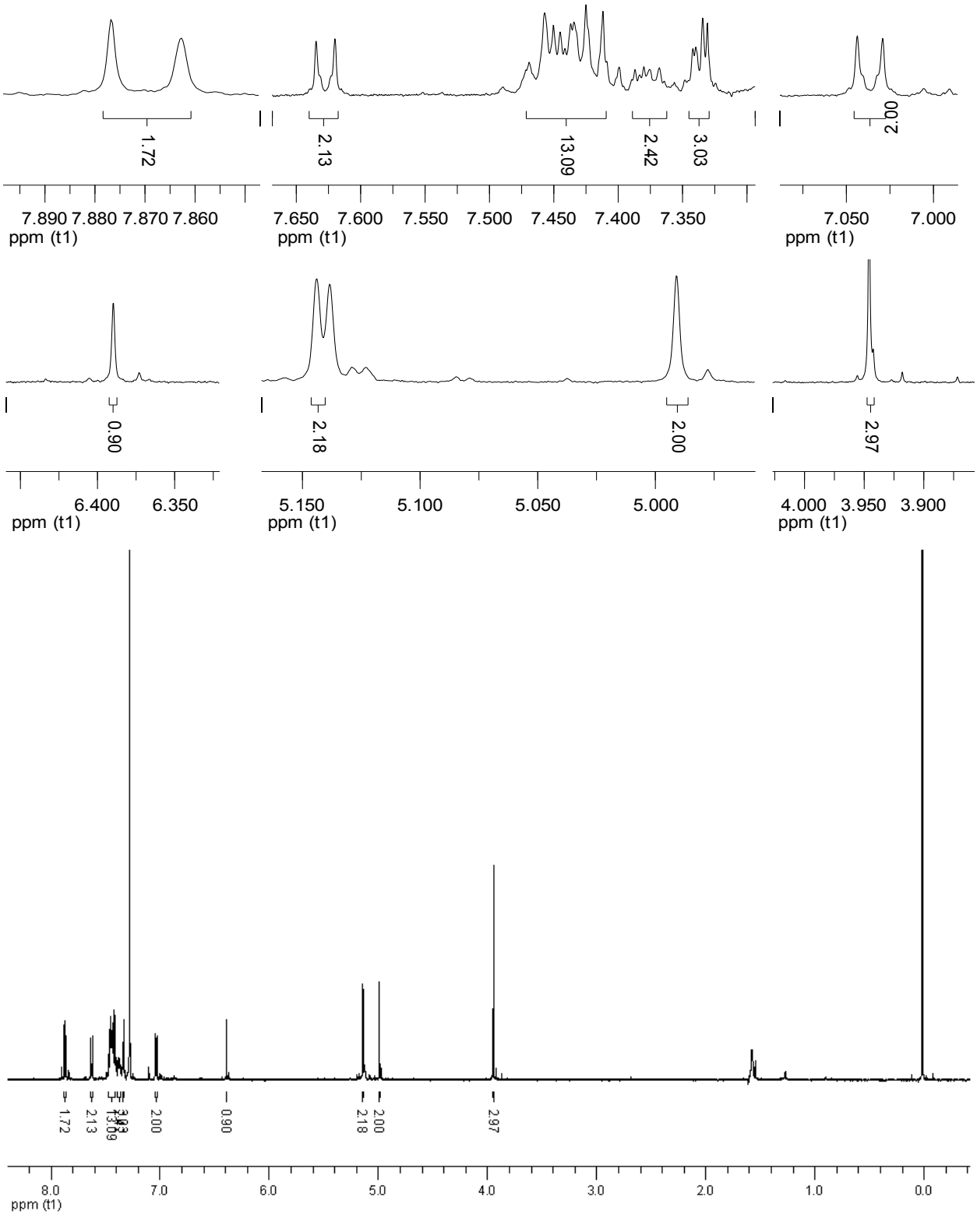
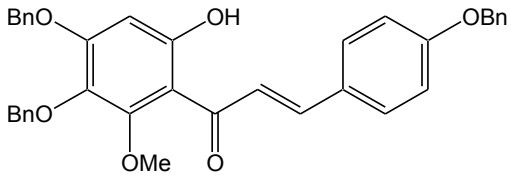


Plate 55b: ^{13}C NMR of 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxychalcone, $CDCl_3$ (298K)



(**4.129**)

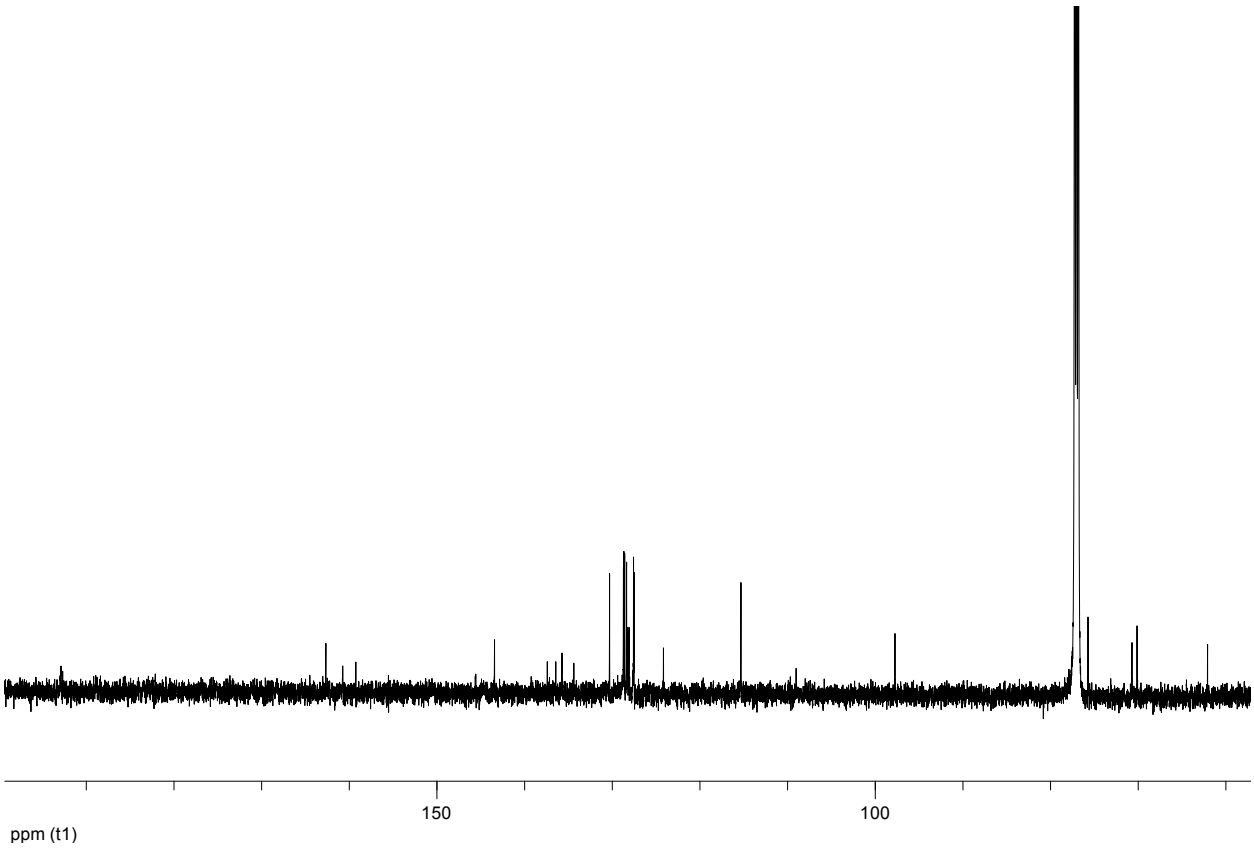
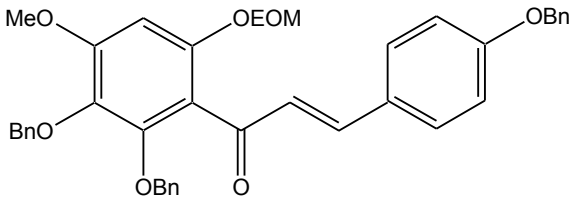


Plate 56a: ^{1}H NMR of 4,2′,3′-Tribenzyloxy-6′-ethoxymethoxy-4′-methoxychalcone, $CDCl_3$ (298K)



(**4.130**)

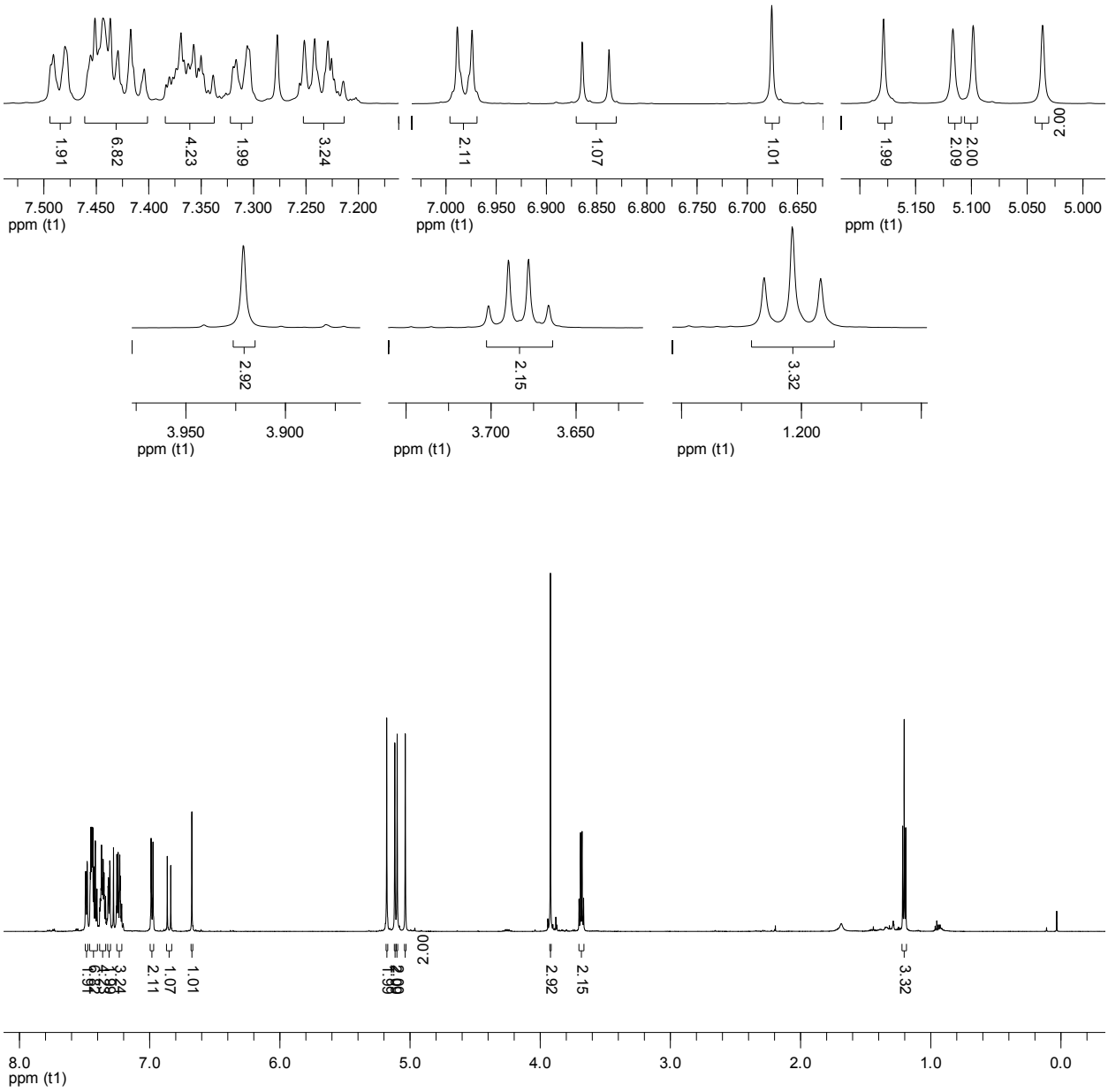
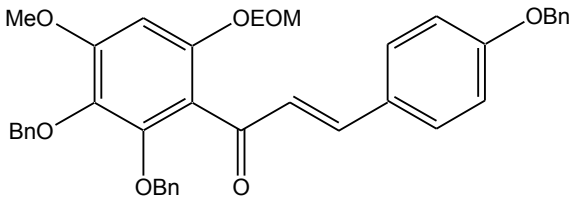


Plate 56b: ^{13}C NMR of 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxychalcone, $CDCl_3$ (298K)



(**4.130**)

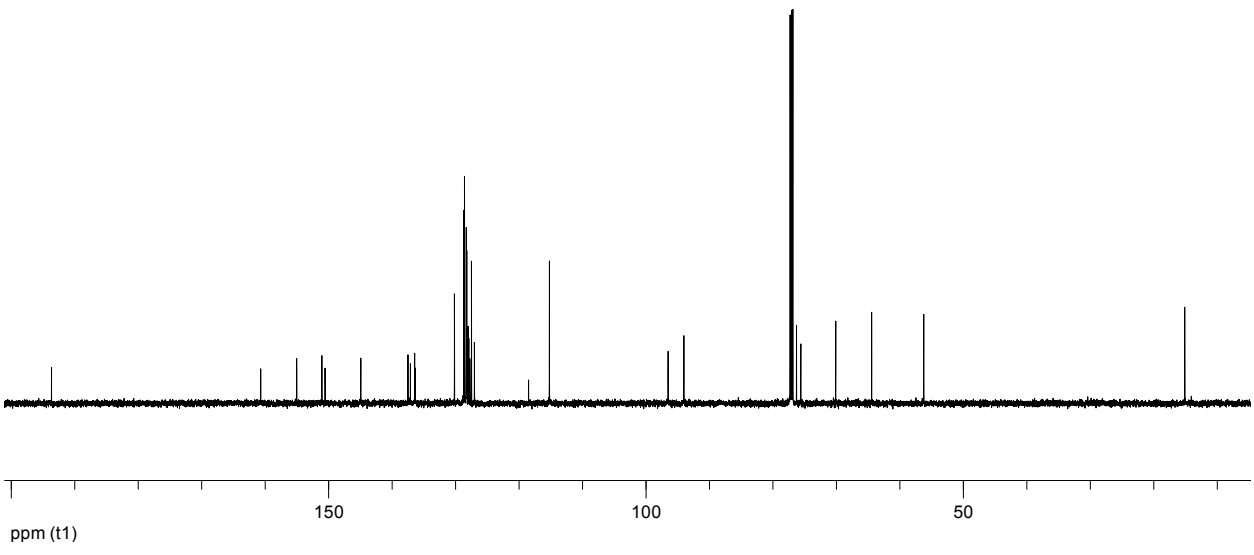
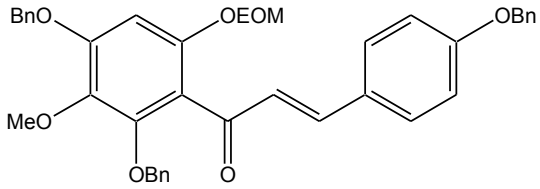
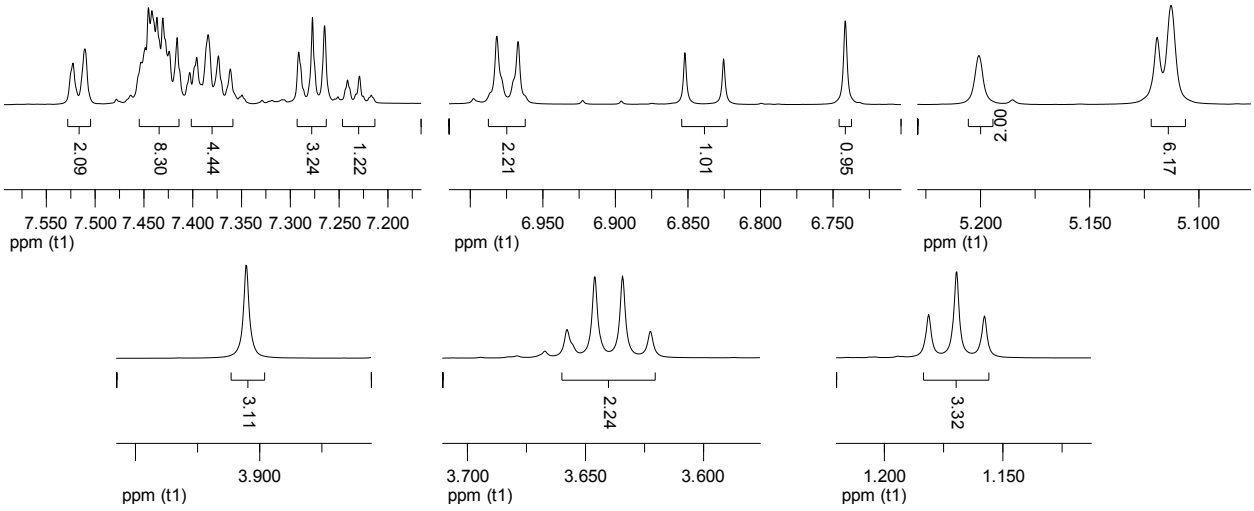


Plate 57a: ^{1}H NMR of 4,2',4'-Tribenzyloxy-6'-ethoxymethoxy-3'-methoxychalcone, $CDCl_3$ (298K)



(**4.131**)



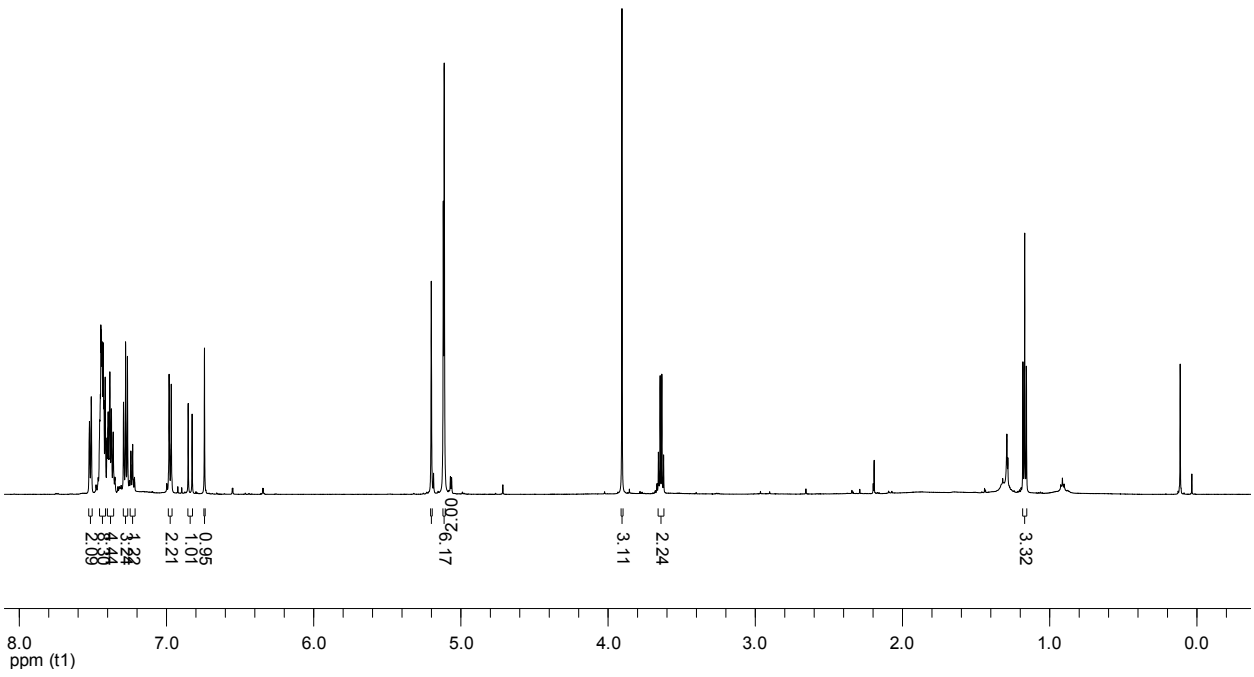
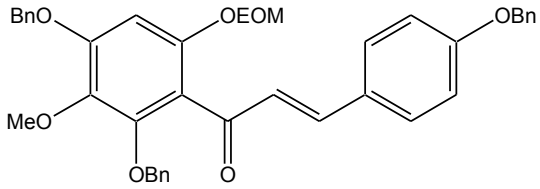


Plate 57b: ^{13}C NMR of 4,2',4'-Tribenzyloxy-6'-ethoxymethoxy-3'-methoxychalcone, $CDCl_3$ (298K)



(**4.131**)

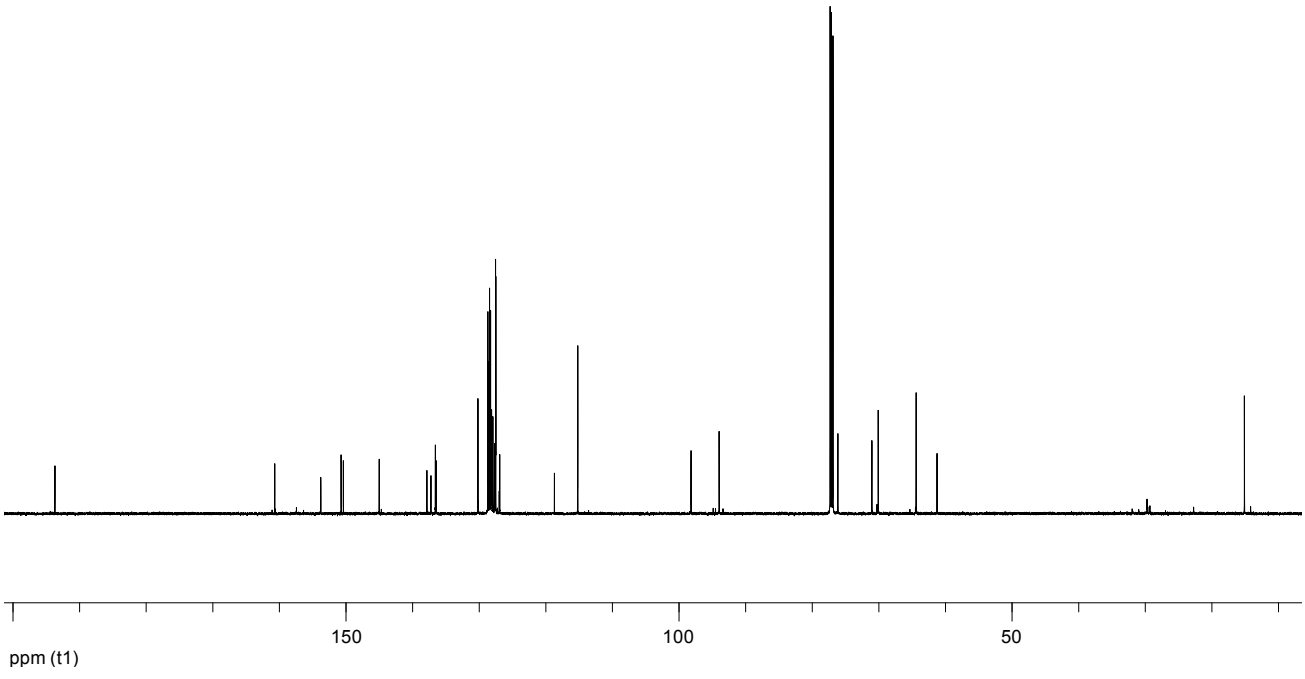
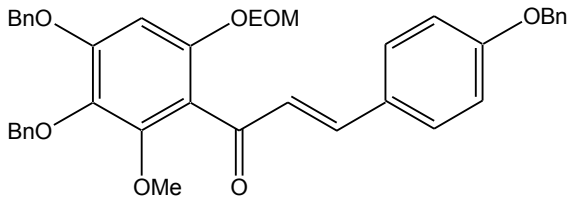


Plate 58a: ^{1}H NMR of 4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxychalcone, $CDCl_3$ (298K)



(4.132)

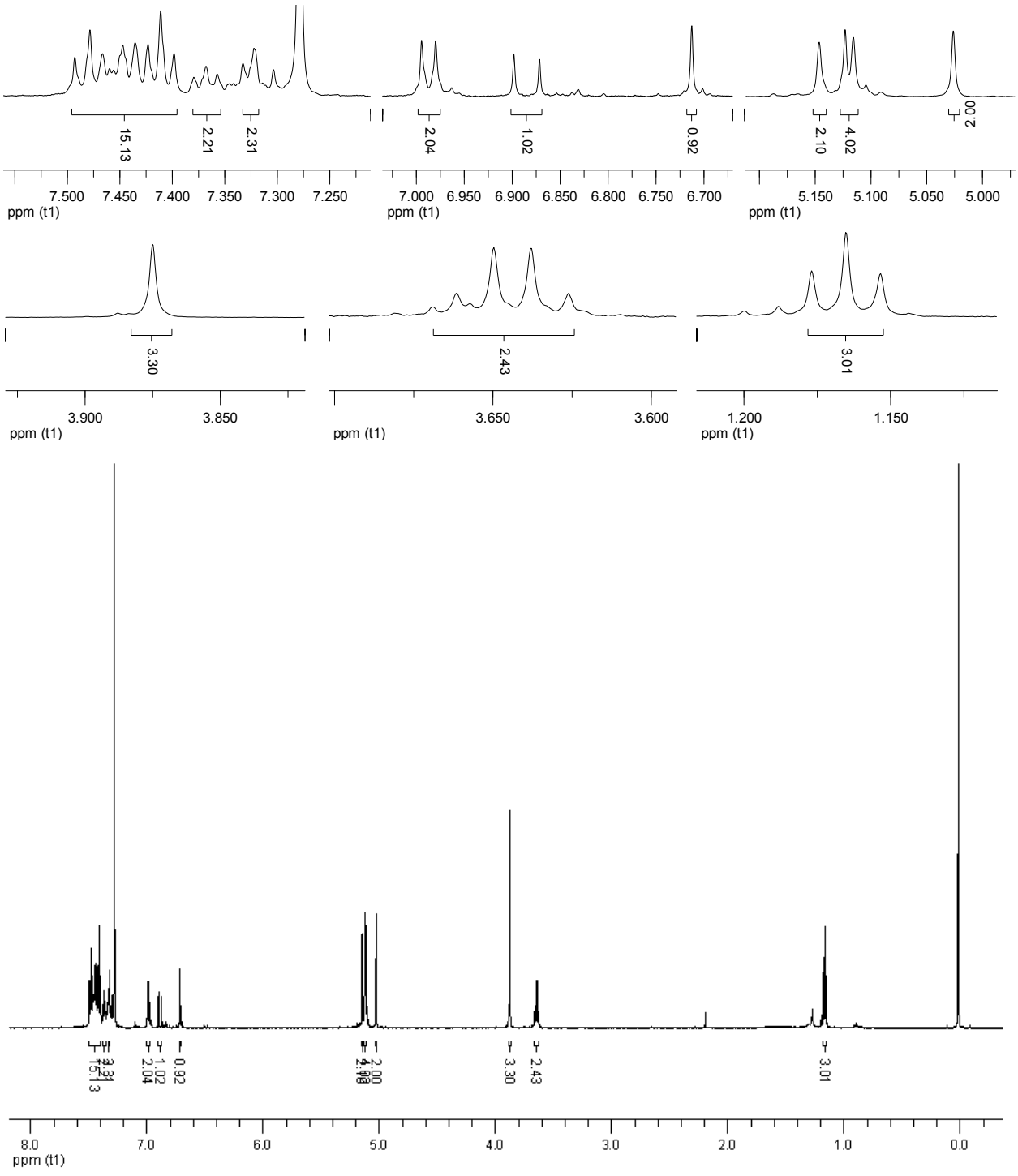
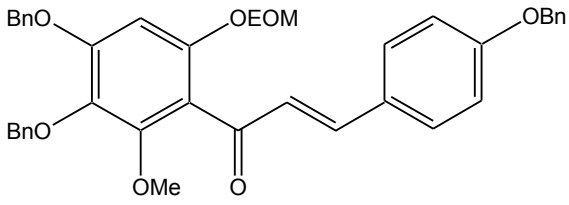


Plate 58b: ^{13}C NMR of 4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxychalcone, $CDCl_3$ (298K)



(**4.132**)

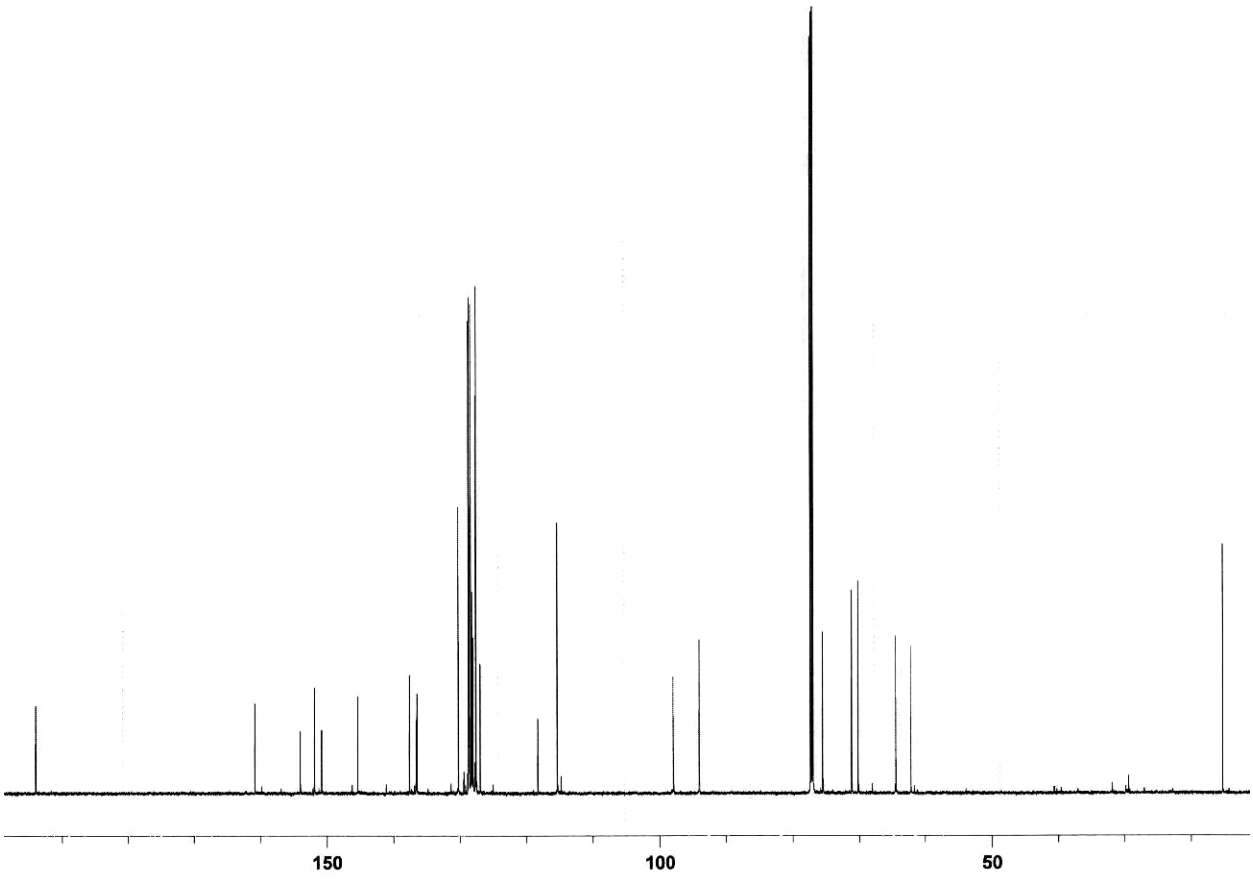
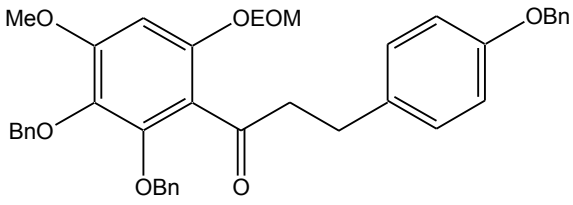


Plate 59a: ^{1}H NMR of 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.133**)

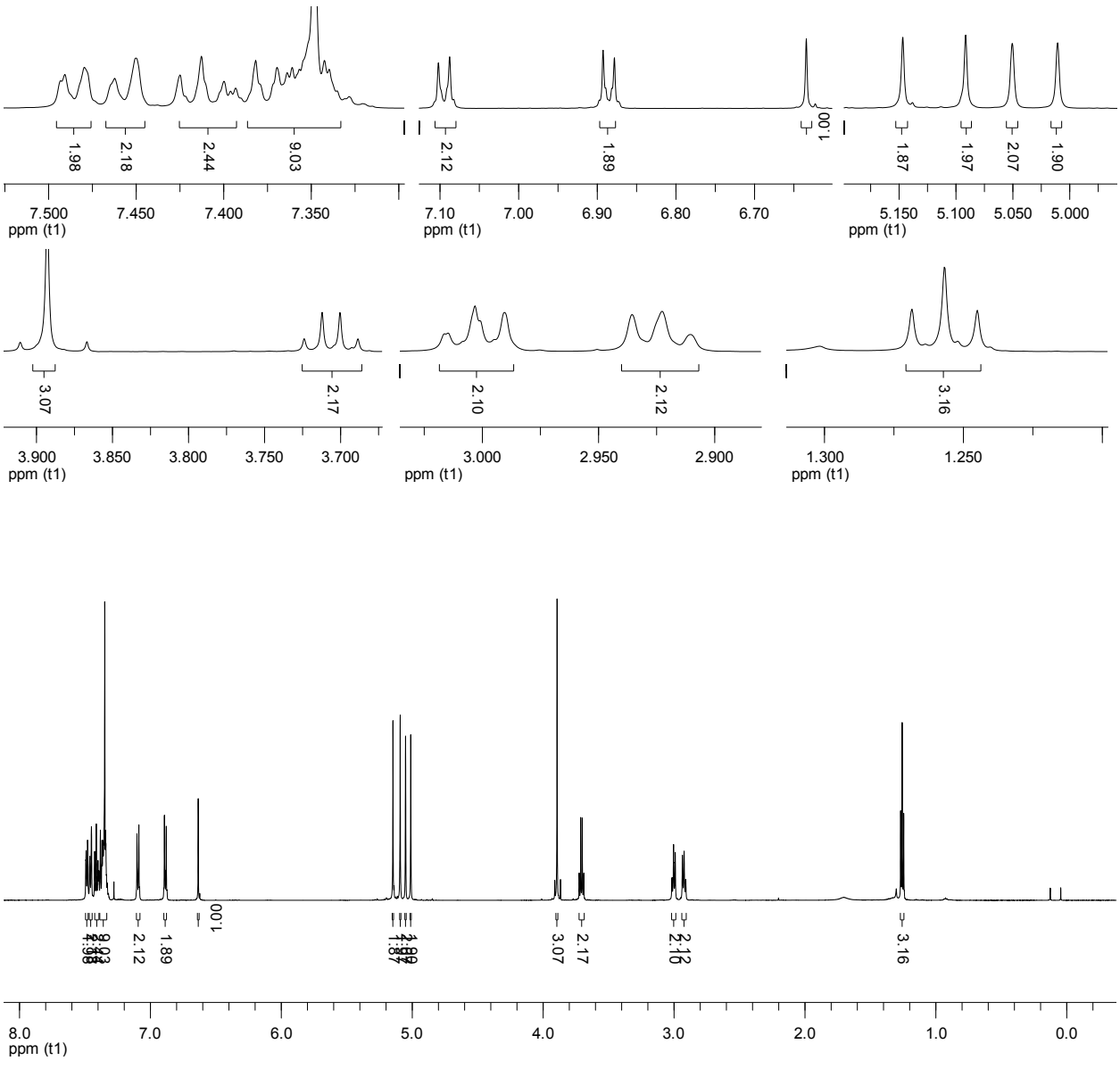
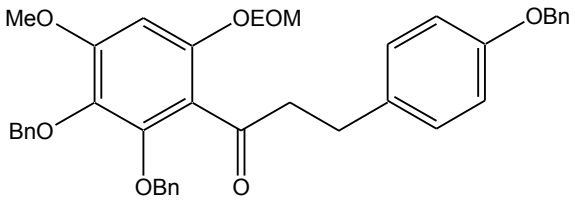


Plate 59b: ^{13}C NMR of 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.133**)

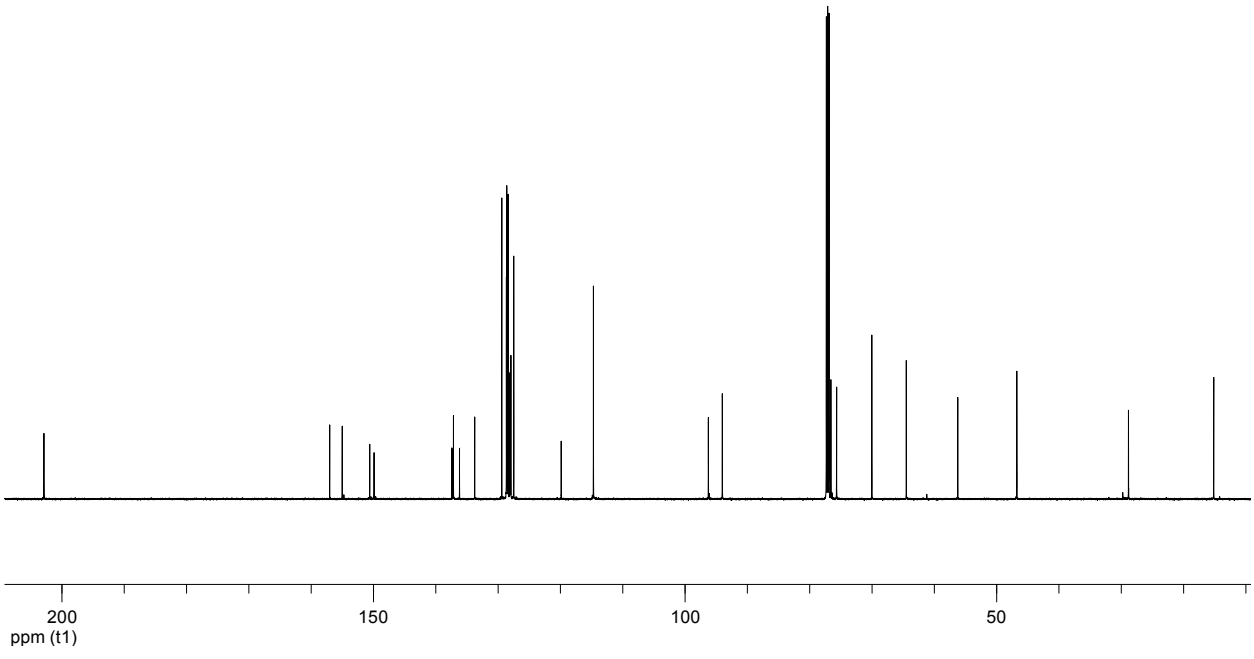
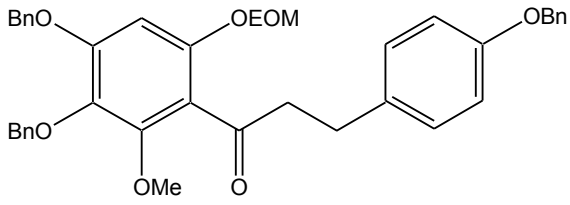
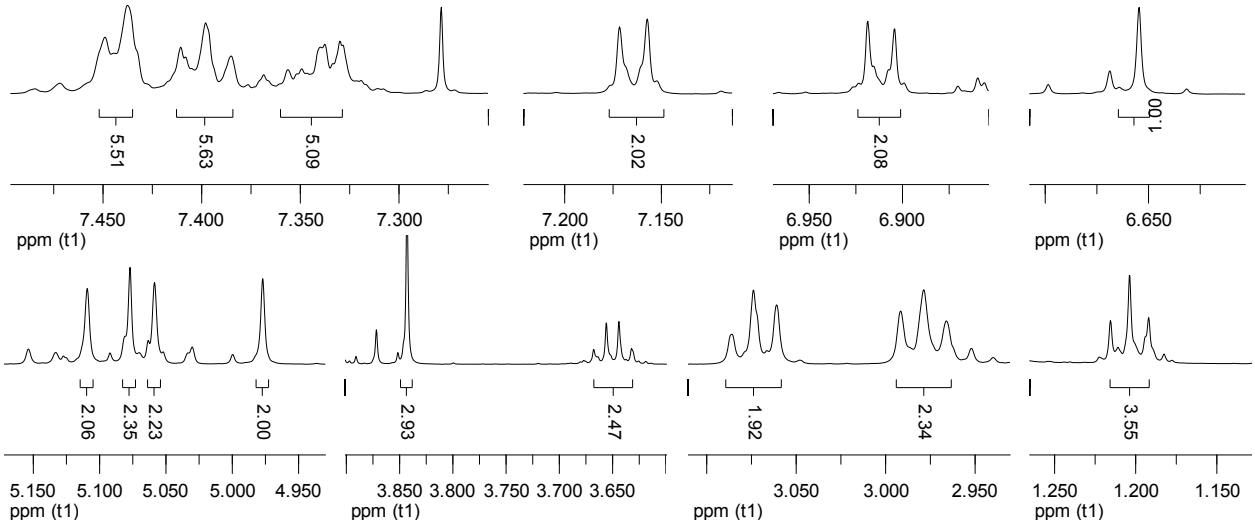


Plate 60a: ^{1}H NMR of 4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.134**)



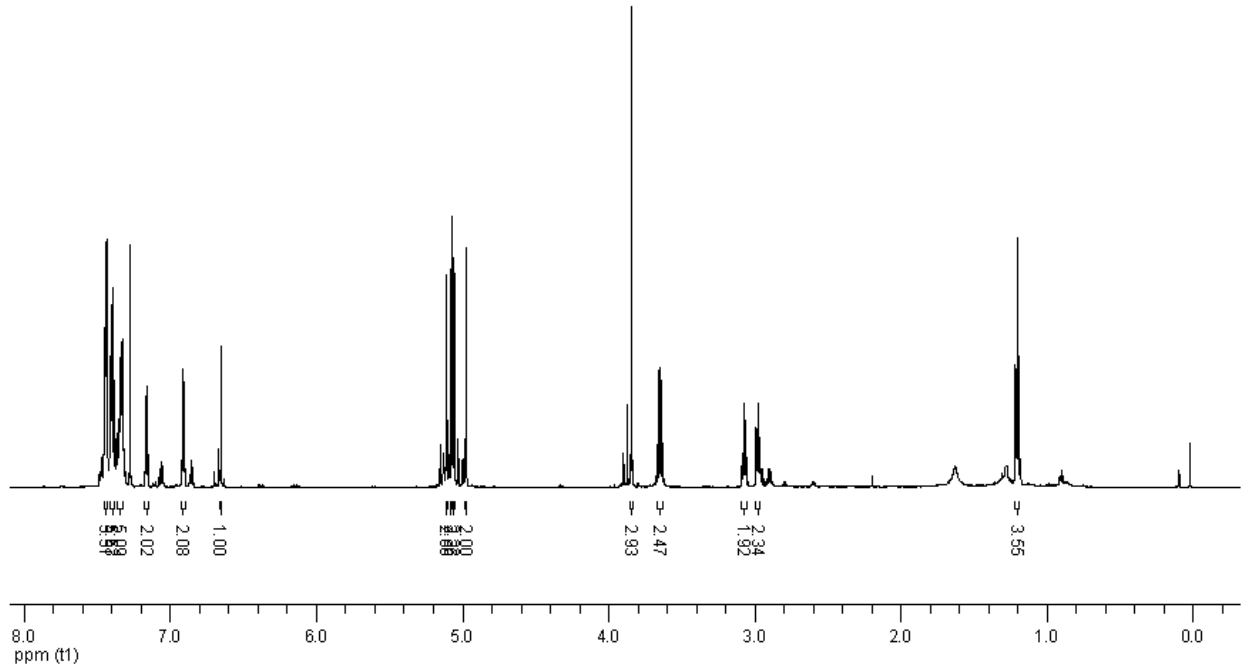
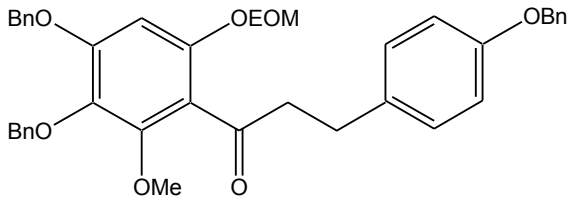


Plate 60b: ^{13}C NMR of 4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.134**)

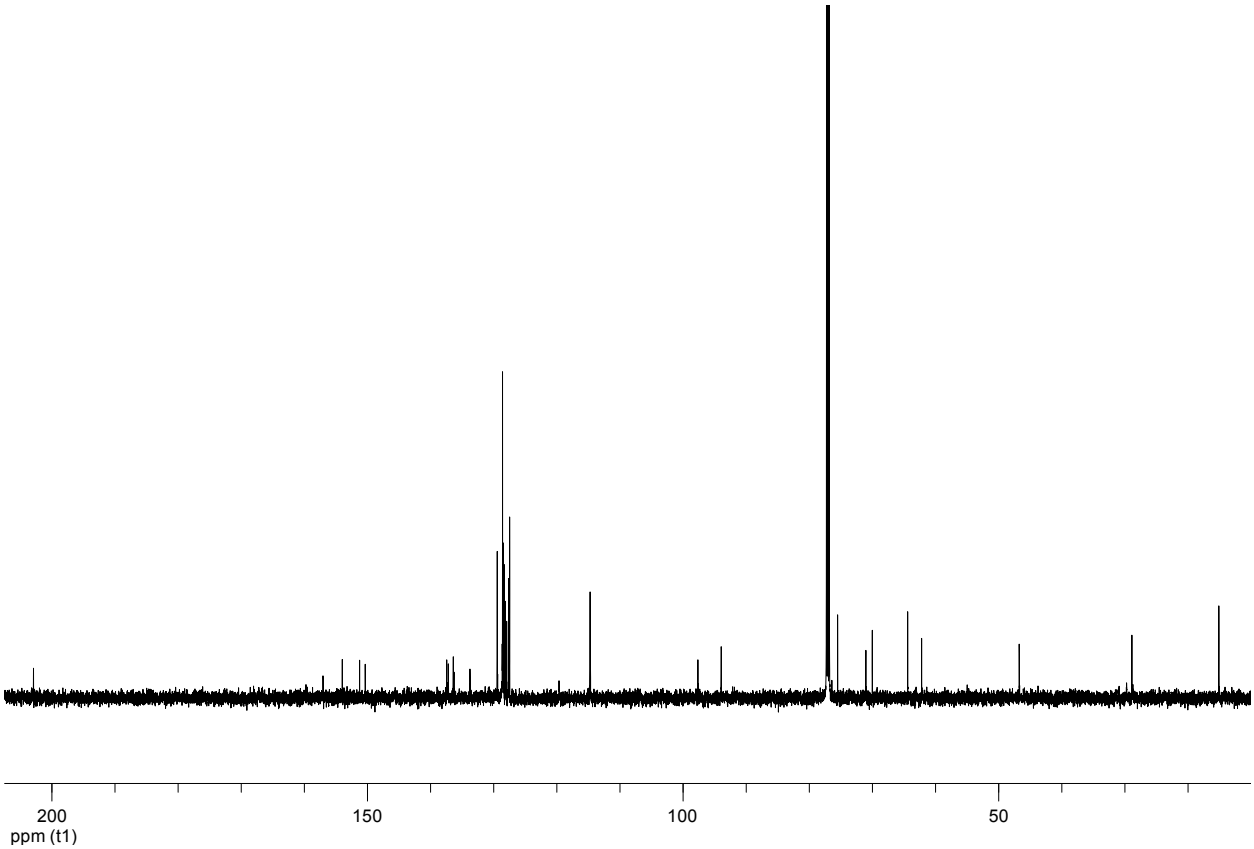
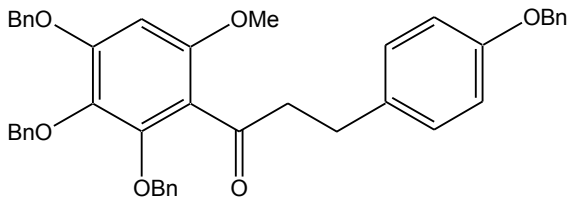
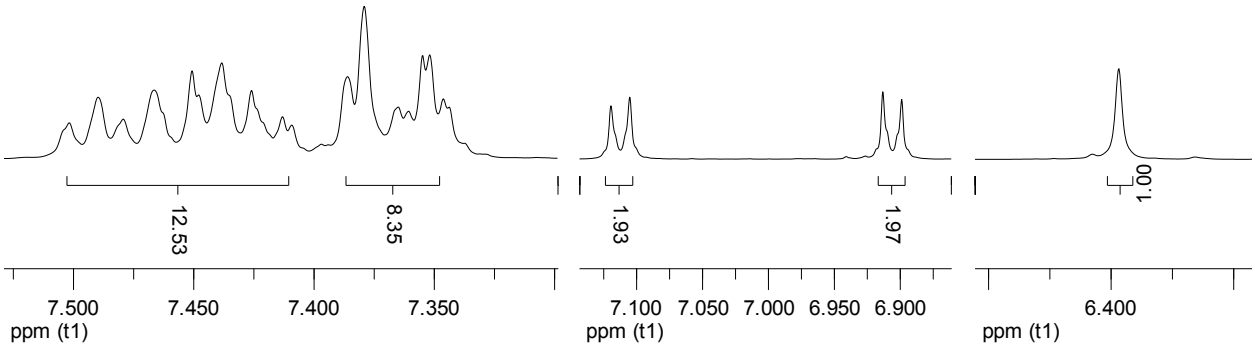
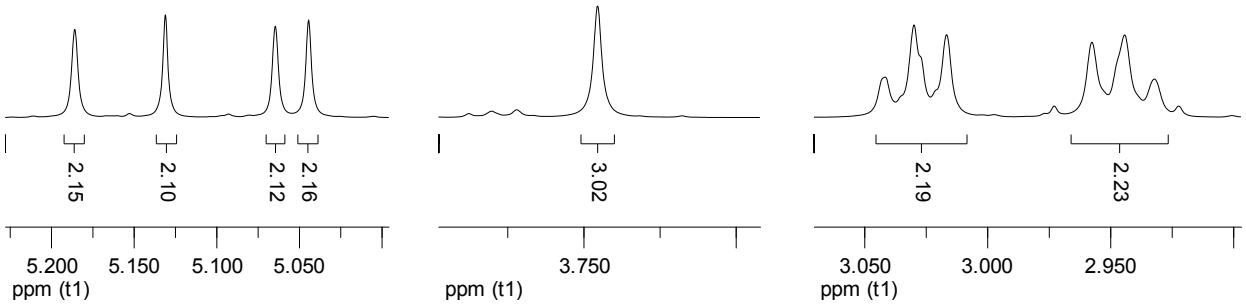


Plate 61a: ^{1}H NMR of 4,2',3',4'-Tetrabenzyloxy-6'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.136**)





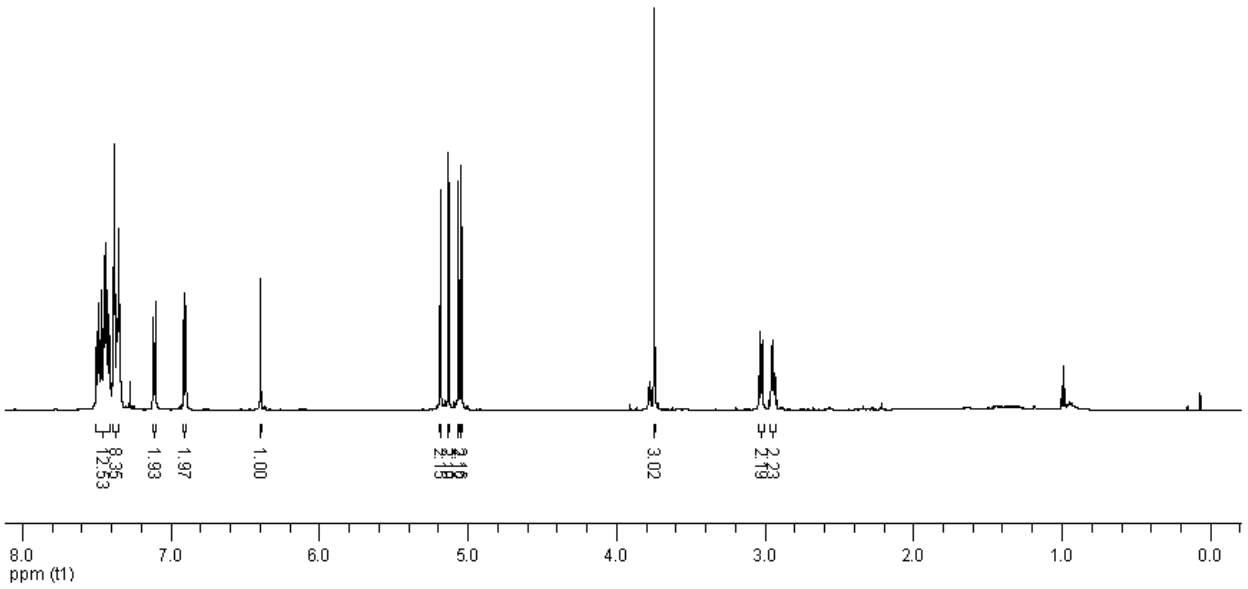
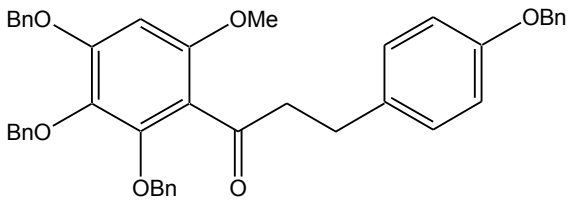


Plate 61b: ^{13}C NMR of 4,2',3',4'-Tetrabenzyloxy-6'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.136**)

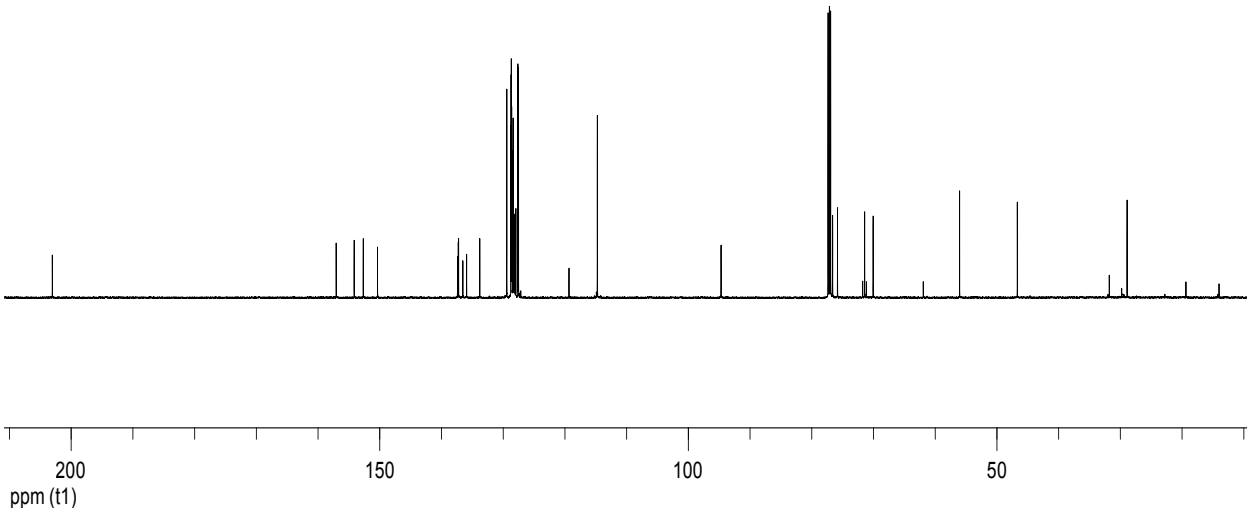
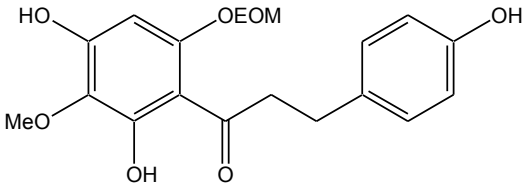


Plate 62a: ^{1}H NMR of 6'-Ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.135**)

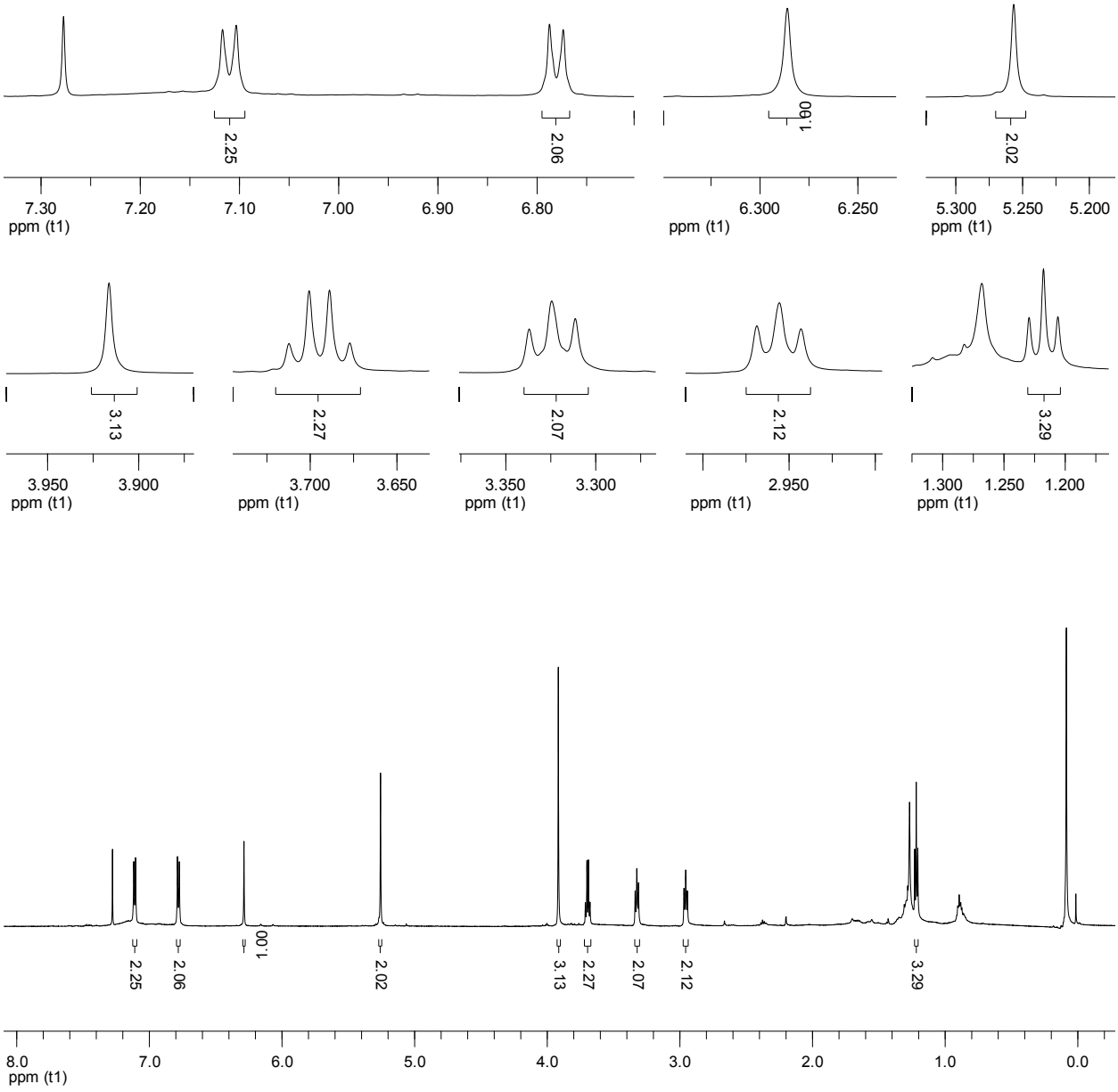
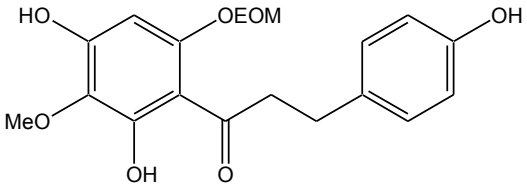


Plate 62b: ^{13}C NMR of 6'-Ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.135**)

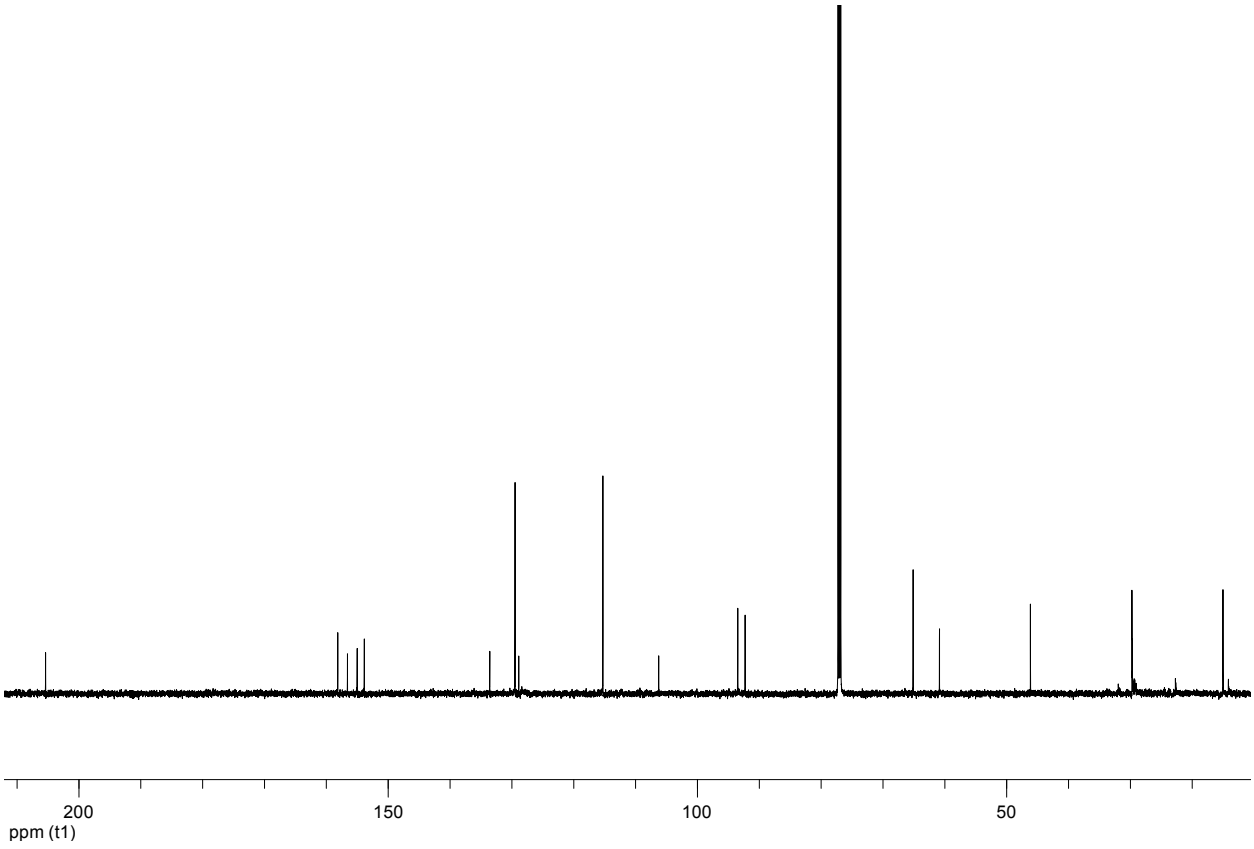
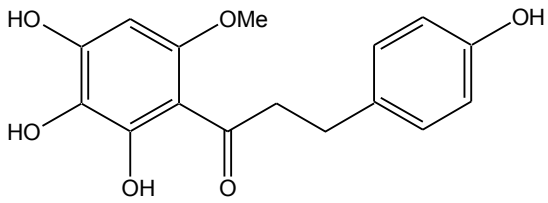
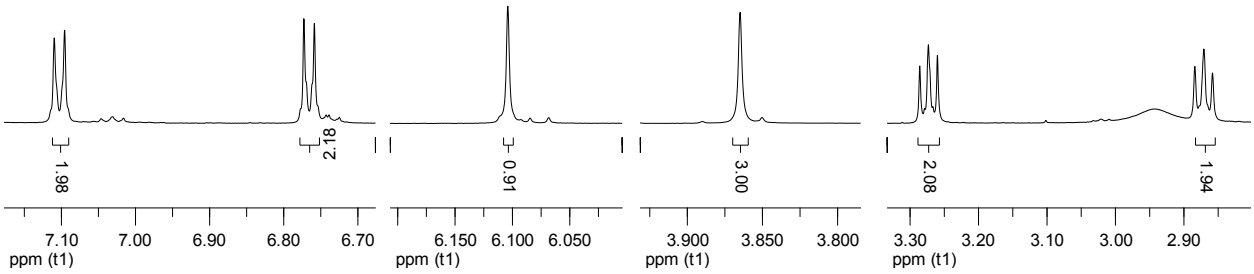


Plate 63a: ^{1}H NMR of 4,2',3',4'-Tetrahydroxy-6'-methoxydihydrochalcone, acetone (298K)



(**4.137**)



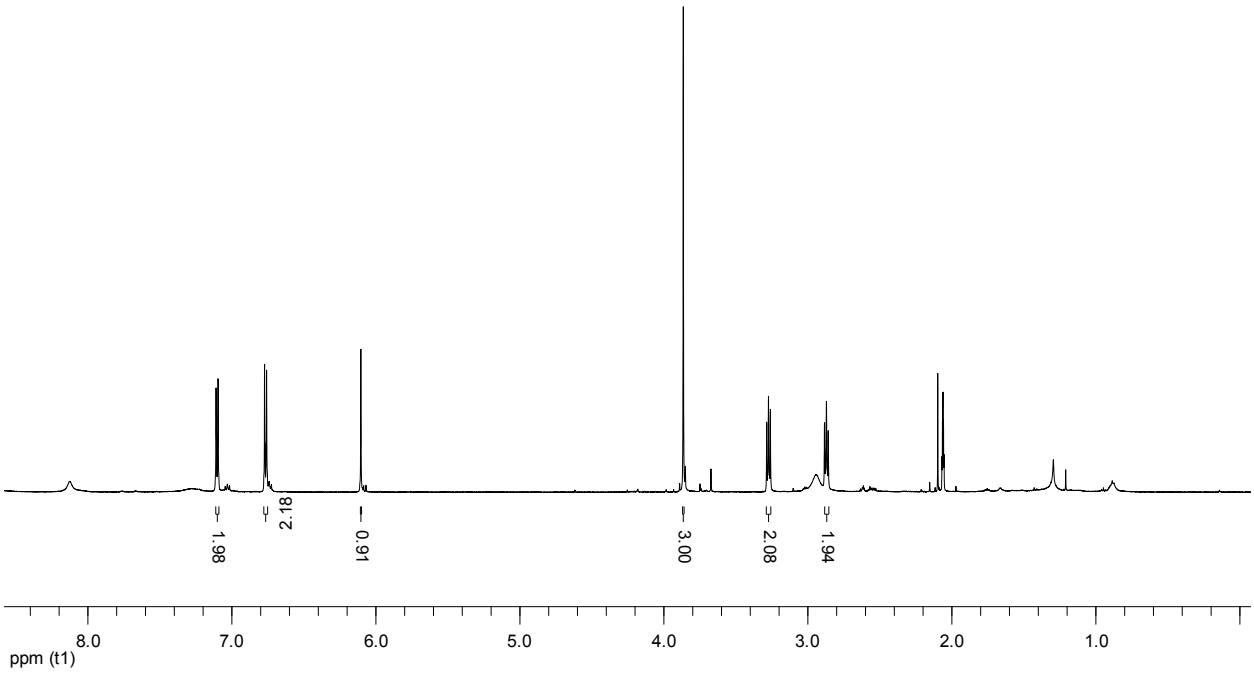
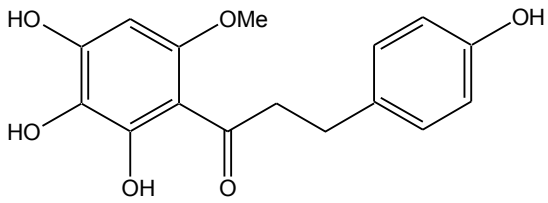


Plate 63b: ^{13}C NMR of 4,2',3',4'-Tetrahydroxy-6'-methoxydihydrochalcone, acetone (298K)



(**4.137**)

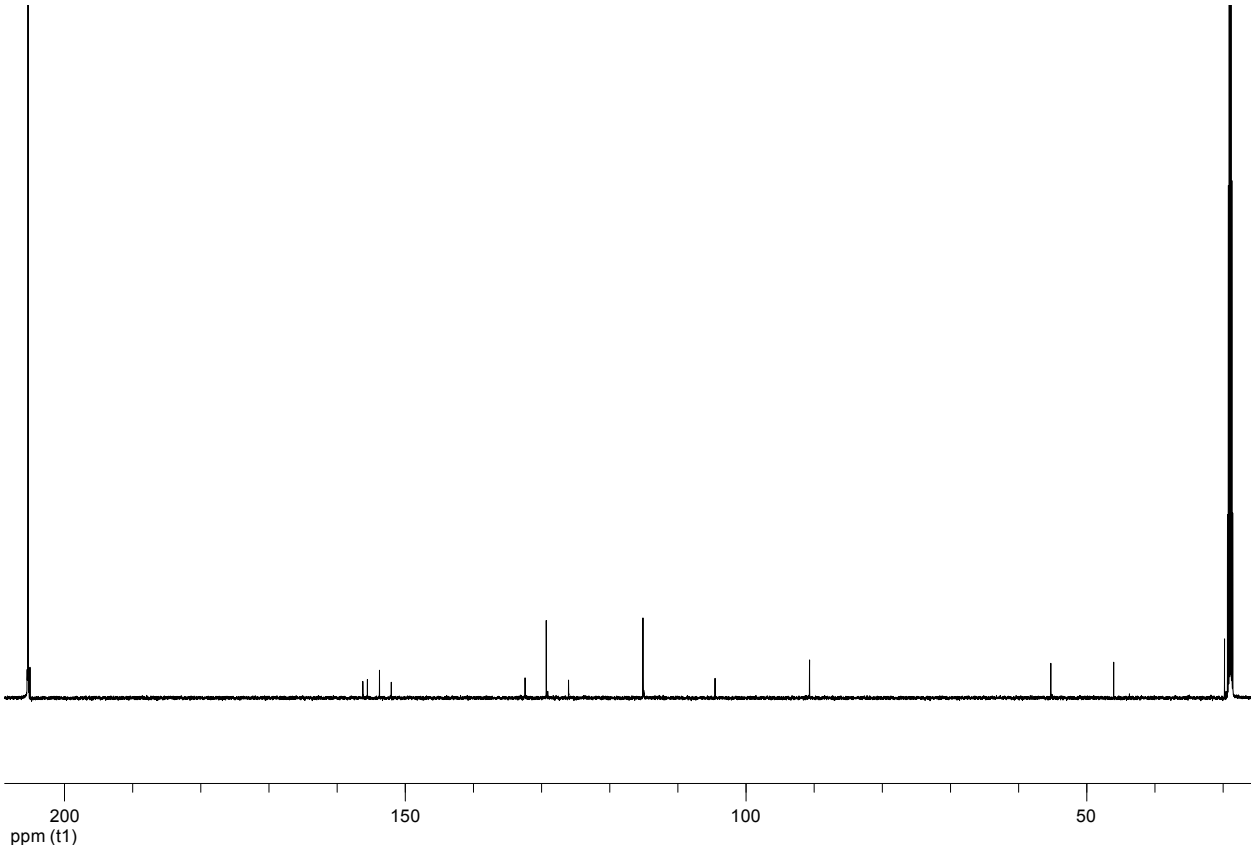
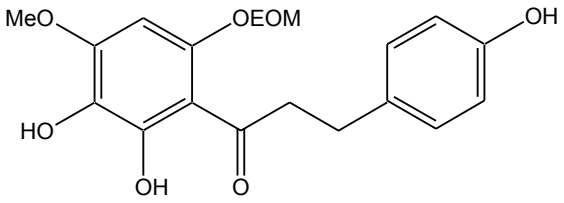
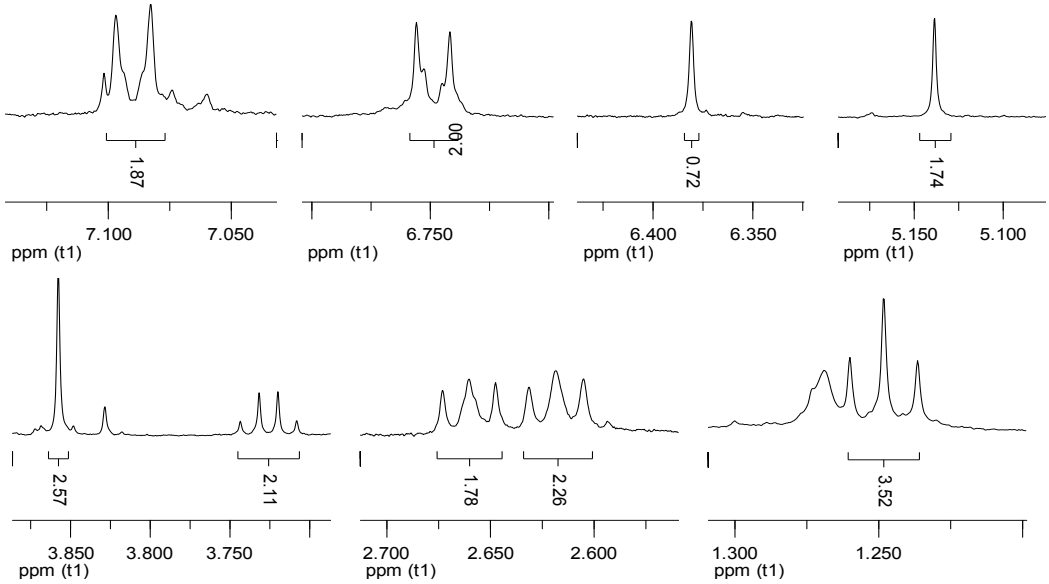


Plate 64a: ^{1}H NMR of 6'-Ethoxymethoxy-4,2',3'-trihydroxy-4'-methoxydihydrochalcone, $CDCl_3$ (298K)



(4.138)



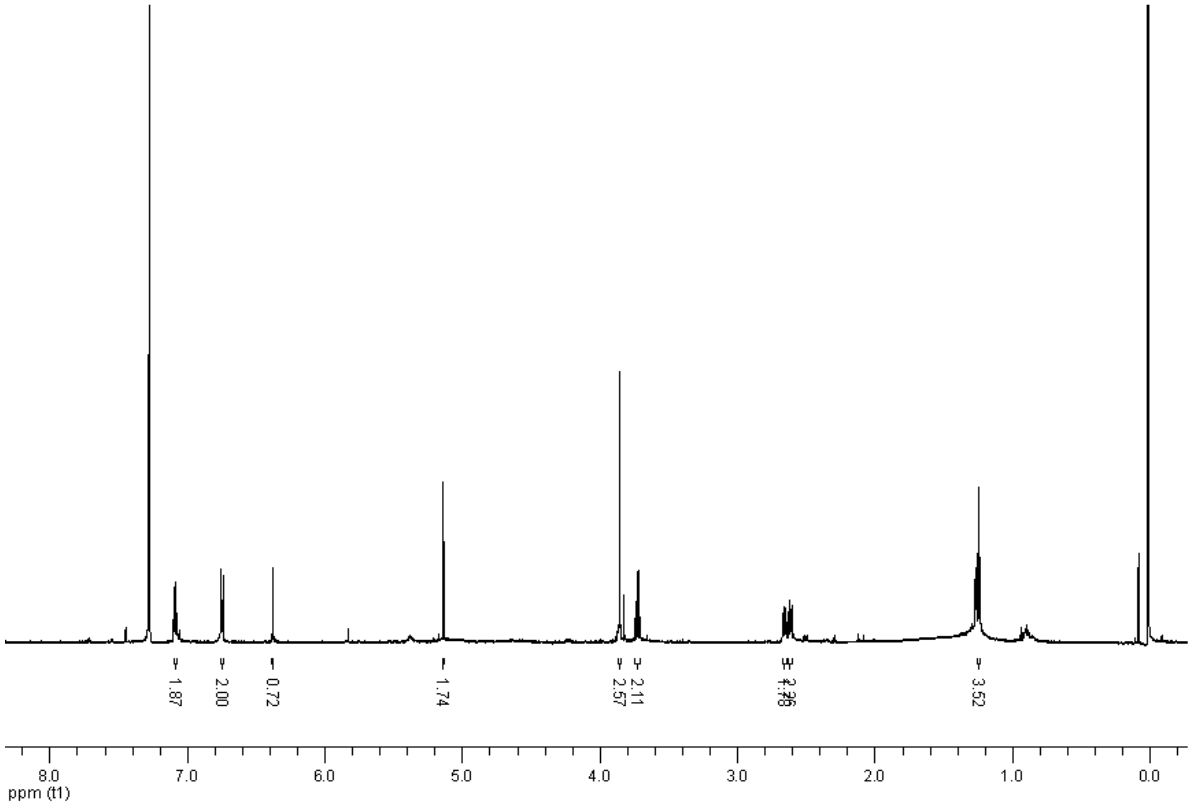
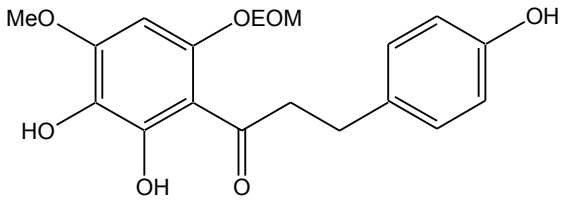


Plate 64b: ^{13}C NMR of 6'-Ethoxymethoxy-4,2',3'-trihydroxy-4'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.138**)

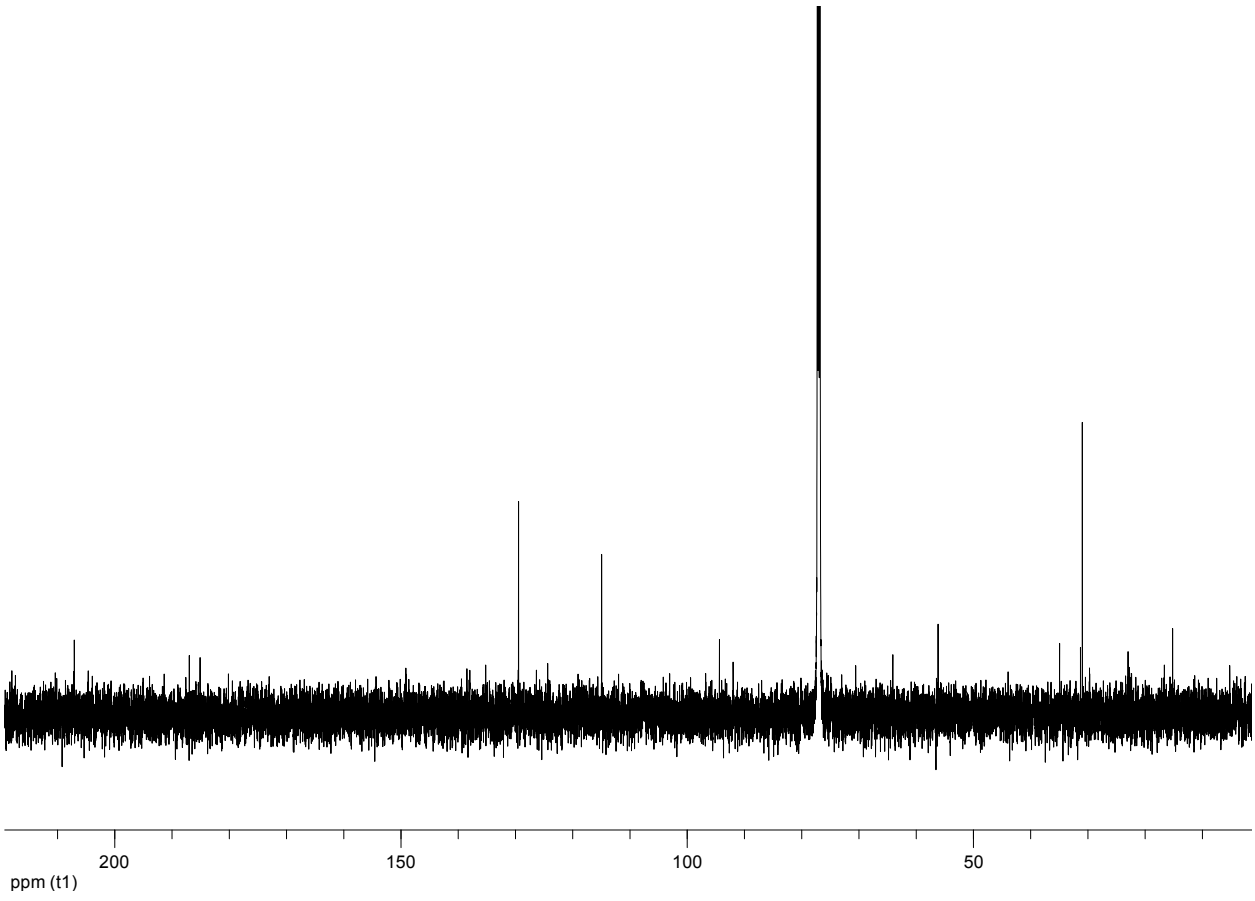
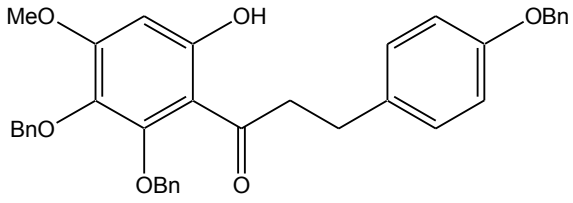


Plate 65a: ^{1}H NMR of 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.139**)

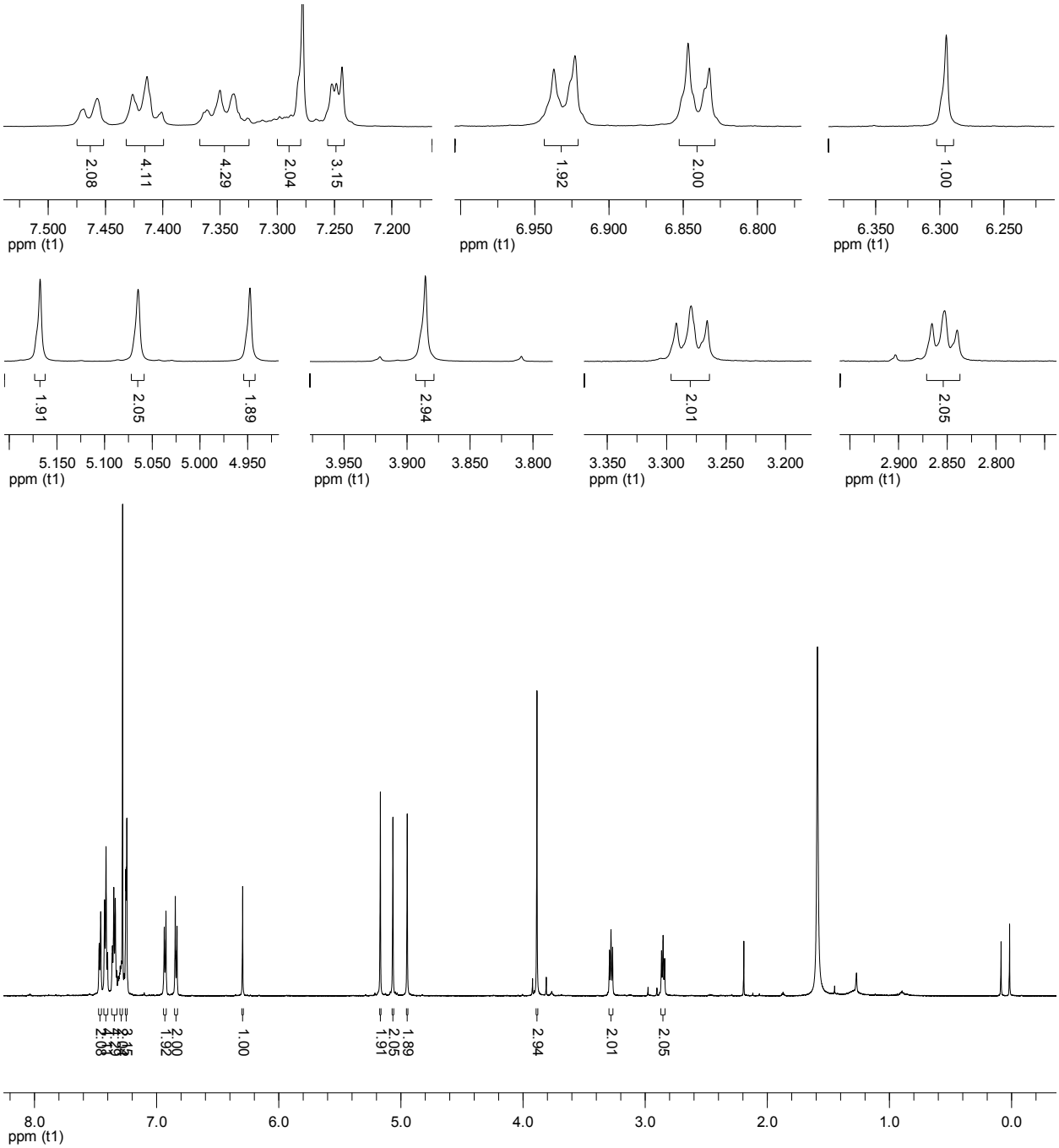
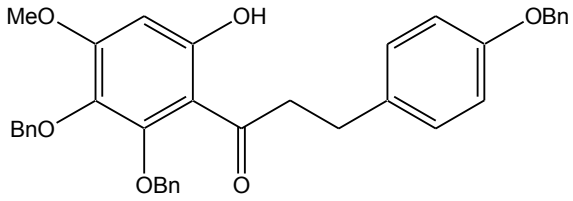


Plate 65b: ^{13}C NMR of 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.139**)

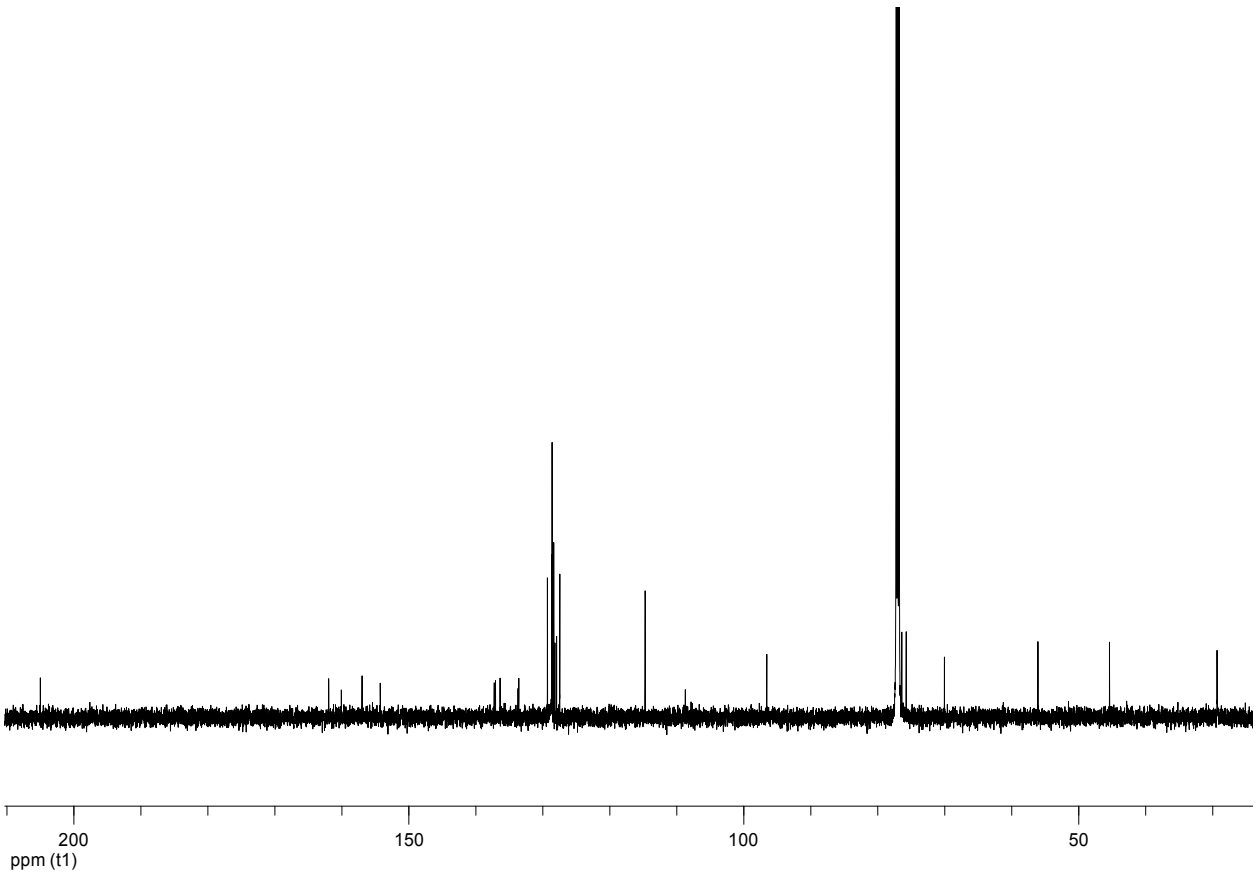
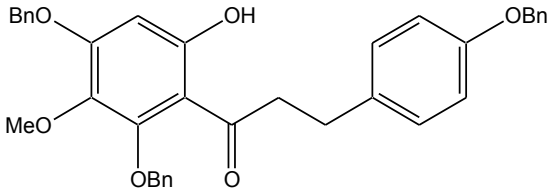
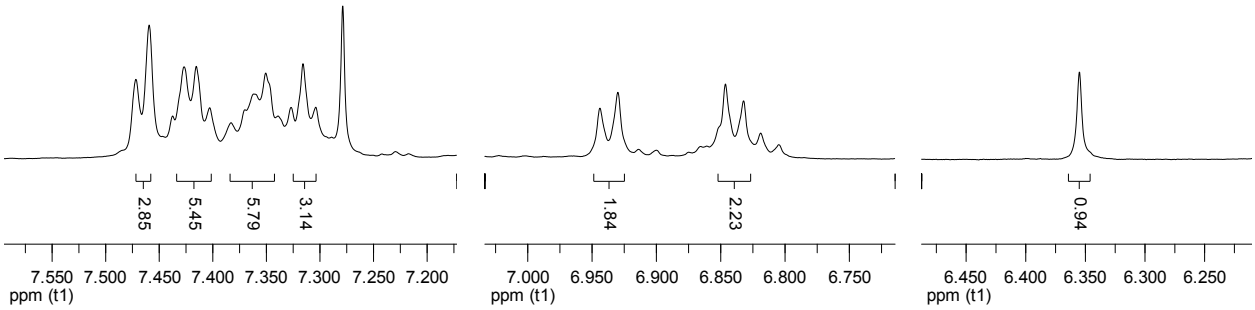
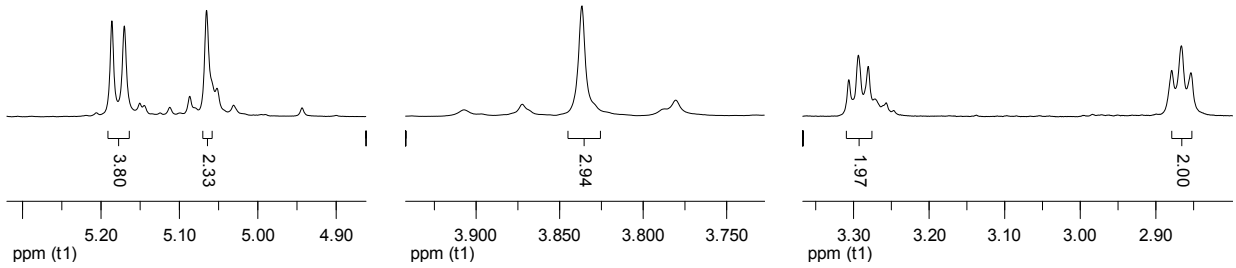


Plate 66a: ^{1}H NMR of 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.140**)





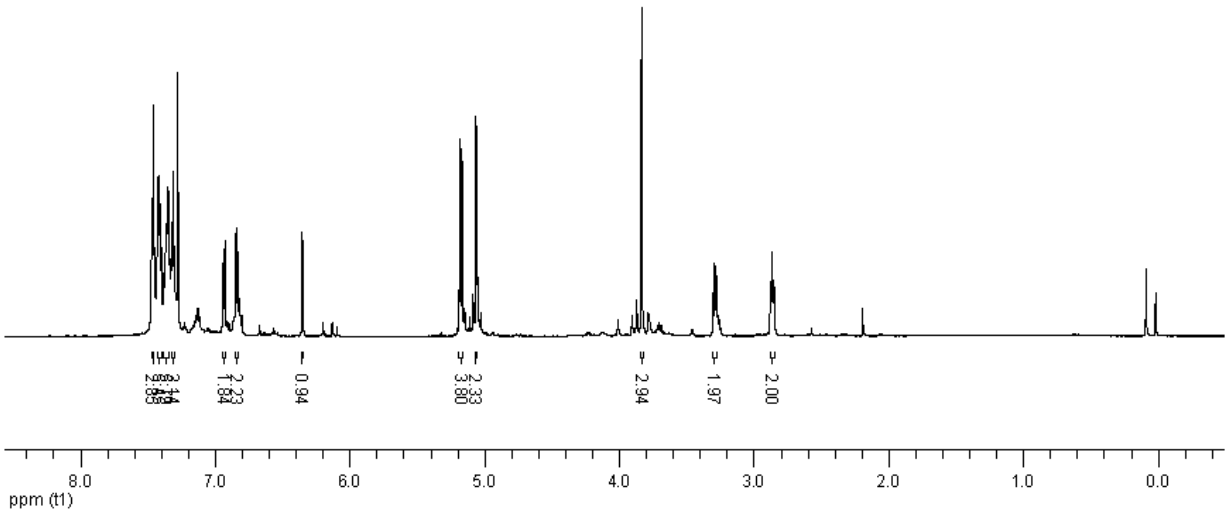
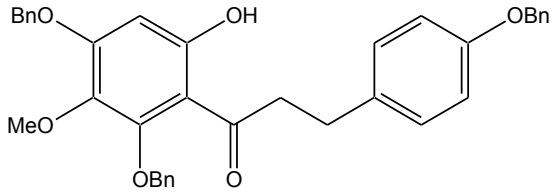


Plate 66b: ^{13}C NMR of 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.140**)

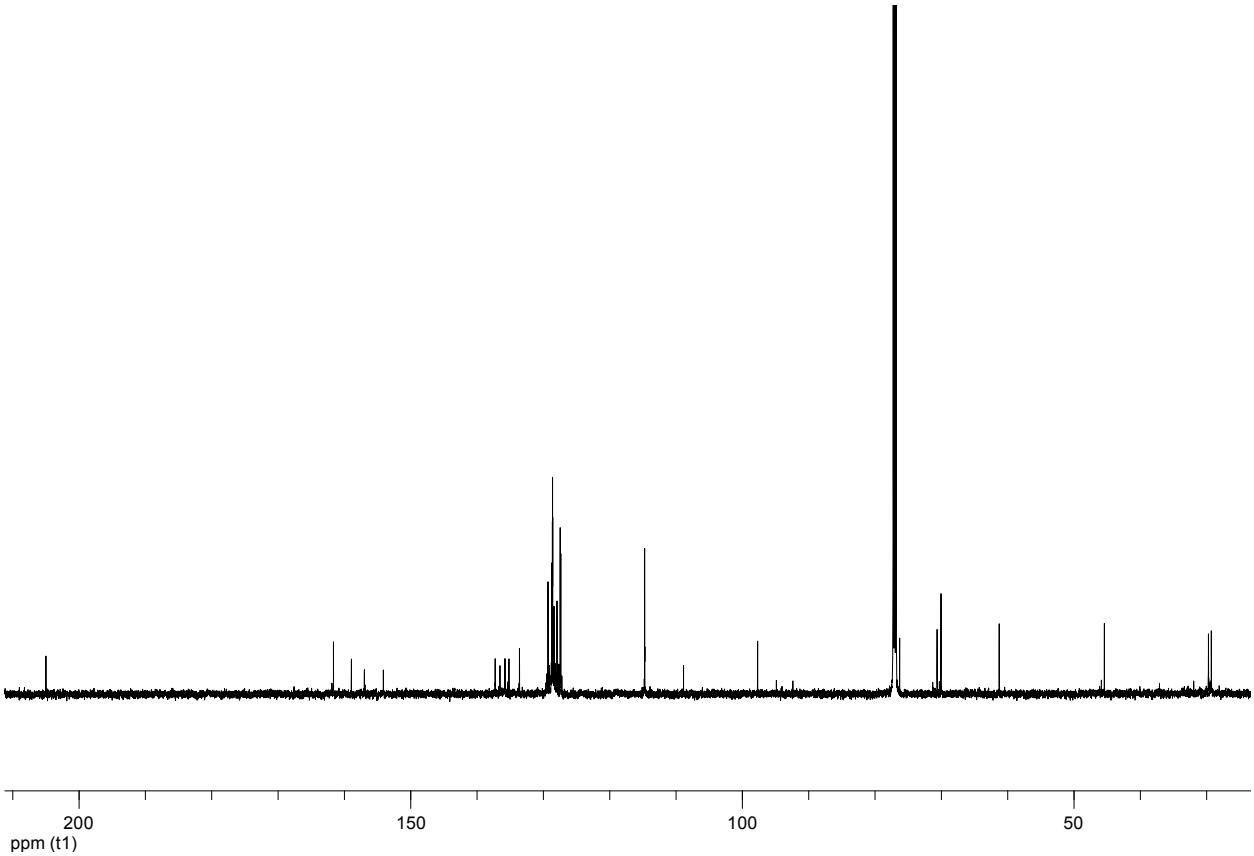
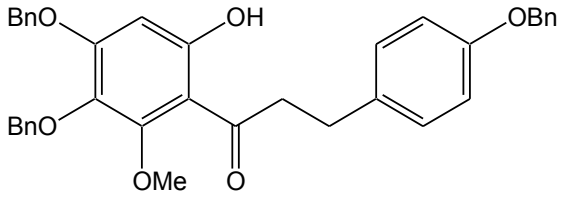
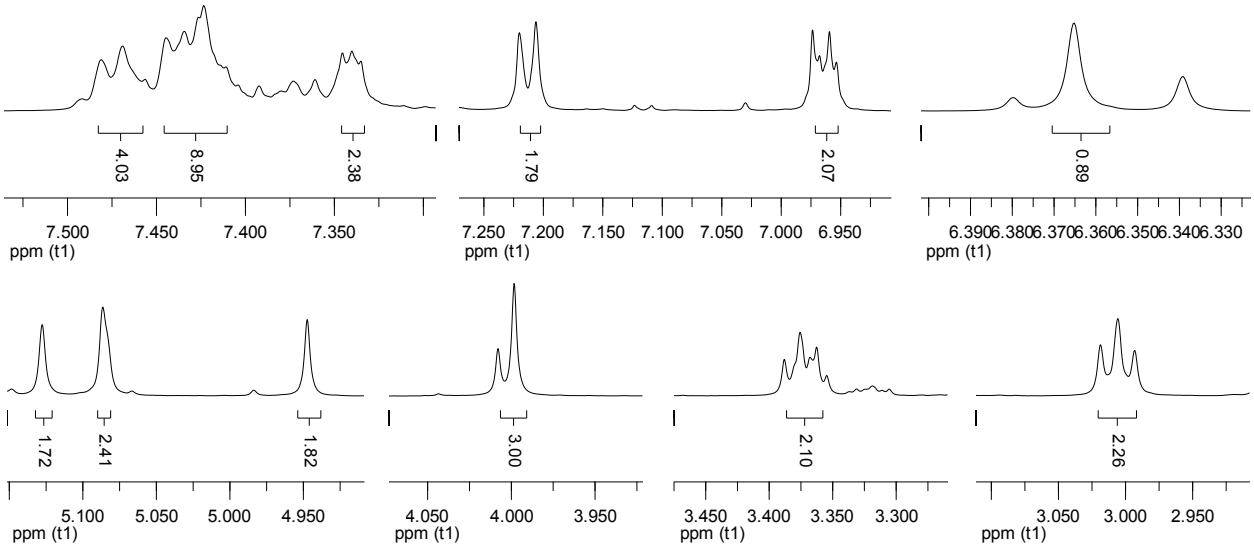


Plate 67a: ^{1}H NMR of 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.141**)



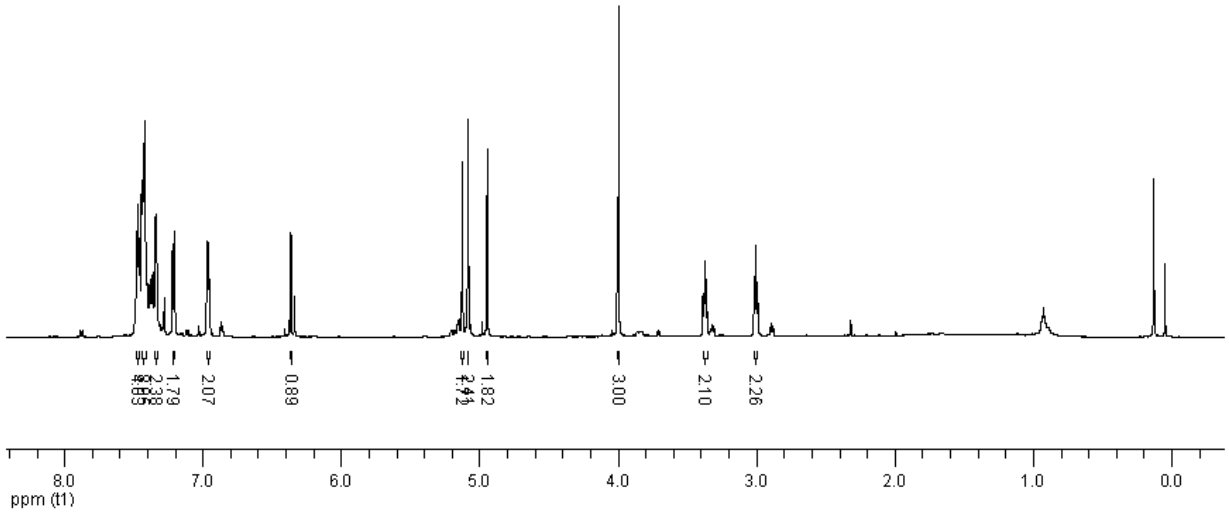
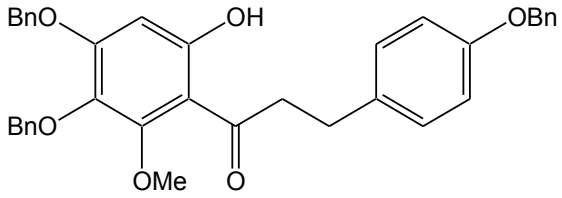


Plate 67b: ^{13}C NMR of 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxydihydrochalcone, $CDCl_3$ (298K)



(**4.141**)

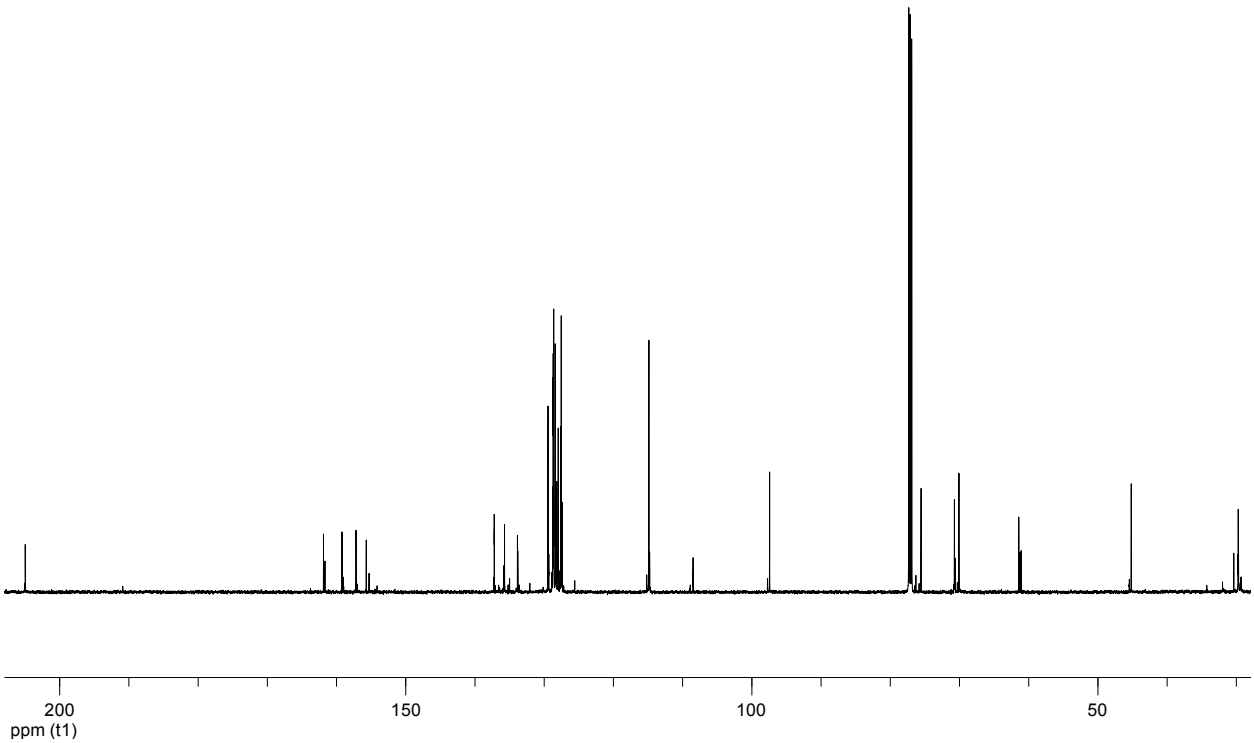
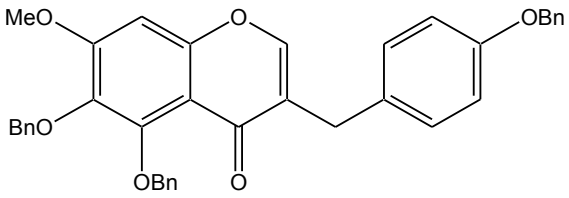


Plate 68a: ^{1}H NMR of 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.142**)

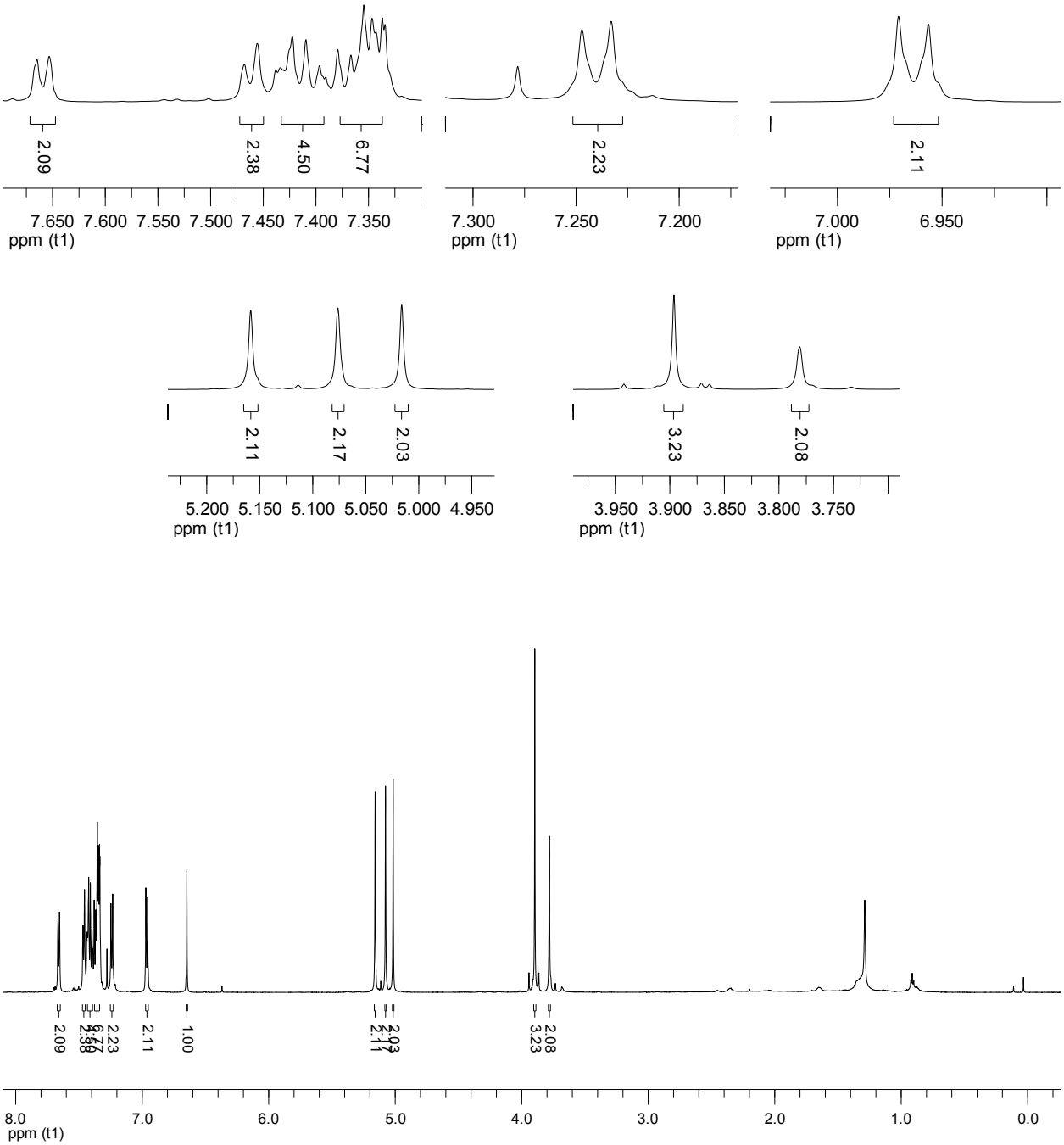
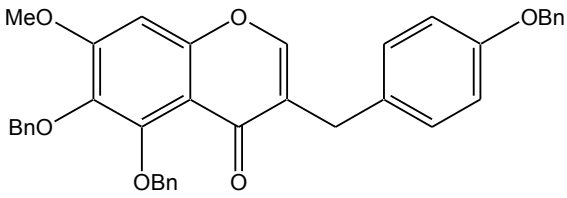


Plate 68b: ^{13}C NMR of 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.142**)

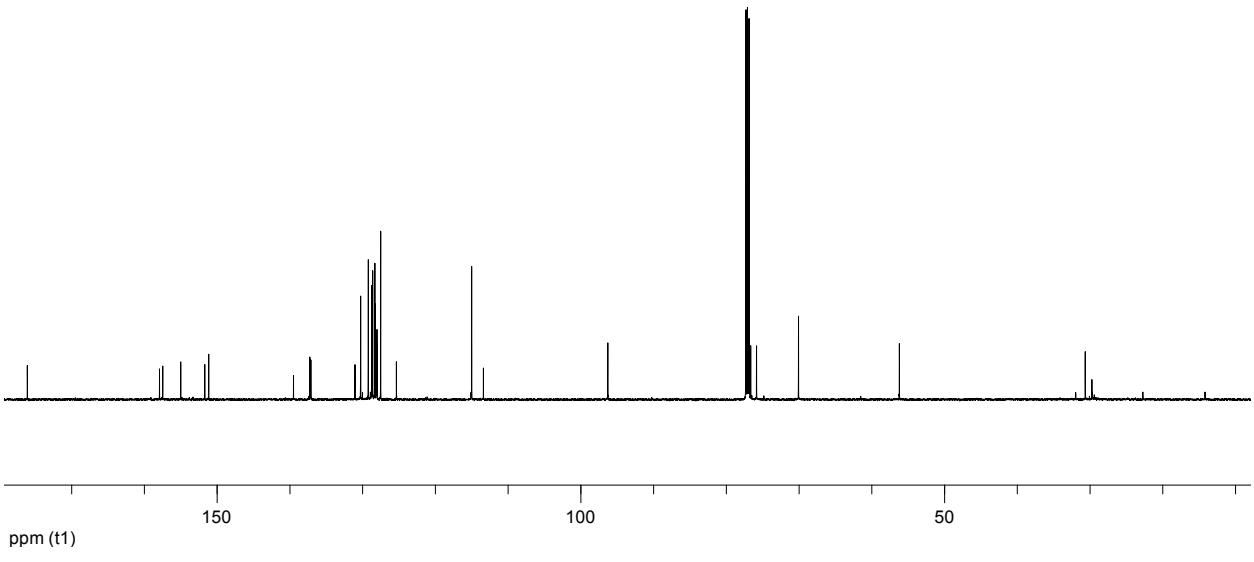
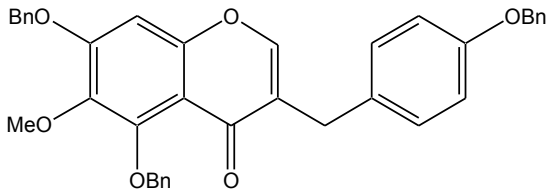


Plate 69a: ^{1}H NMR of 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.143**)

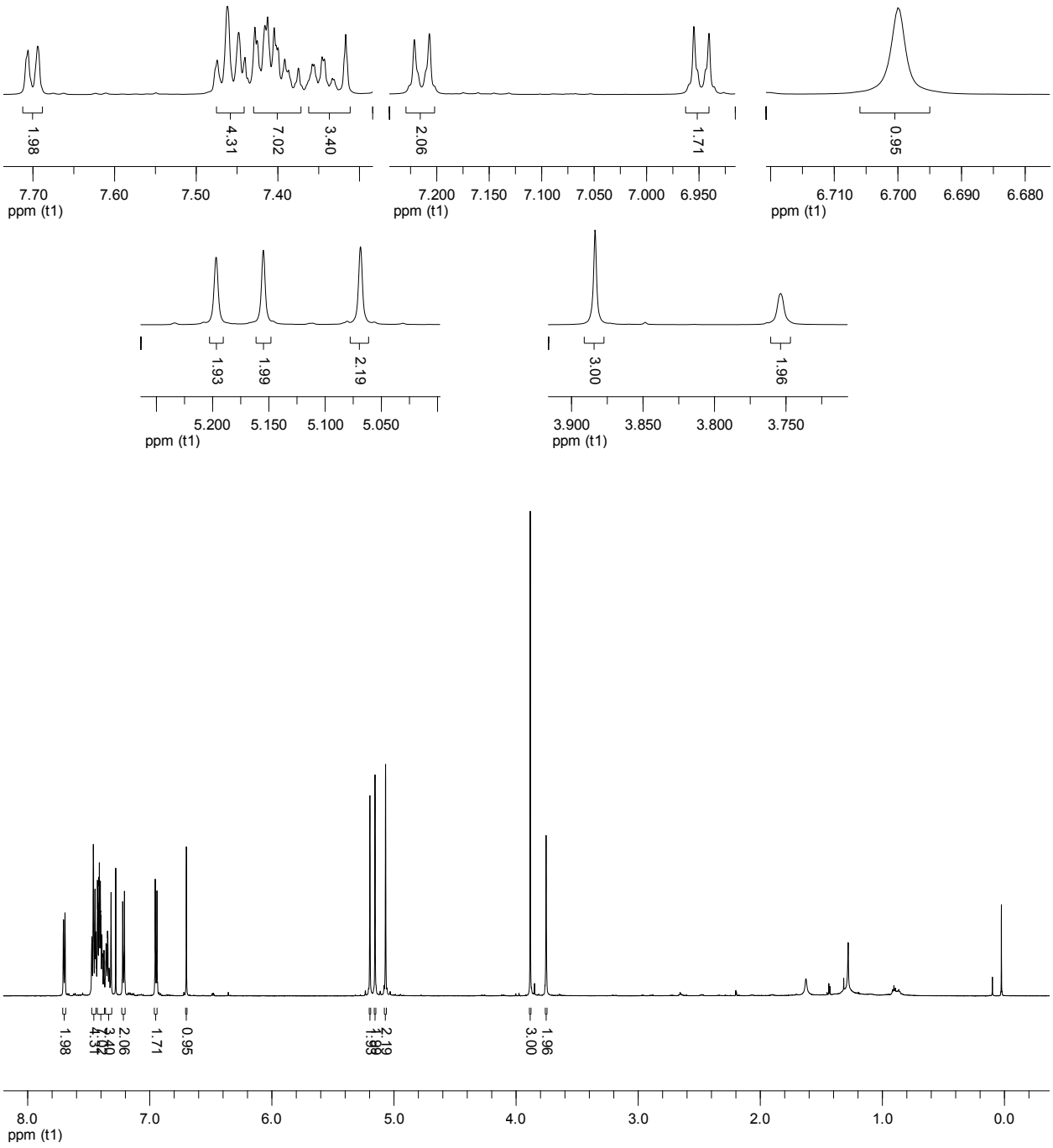
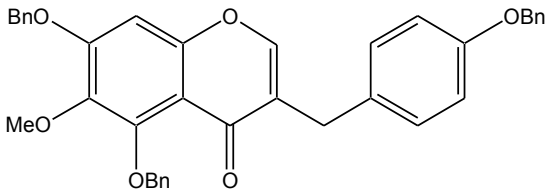


Plate 69b: ^{13}C NMR of 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.143**)

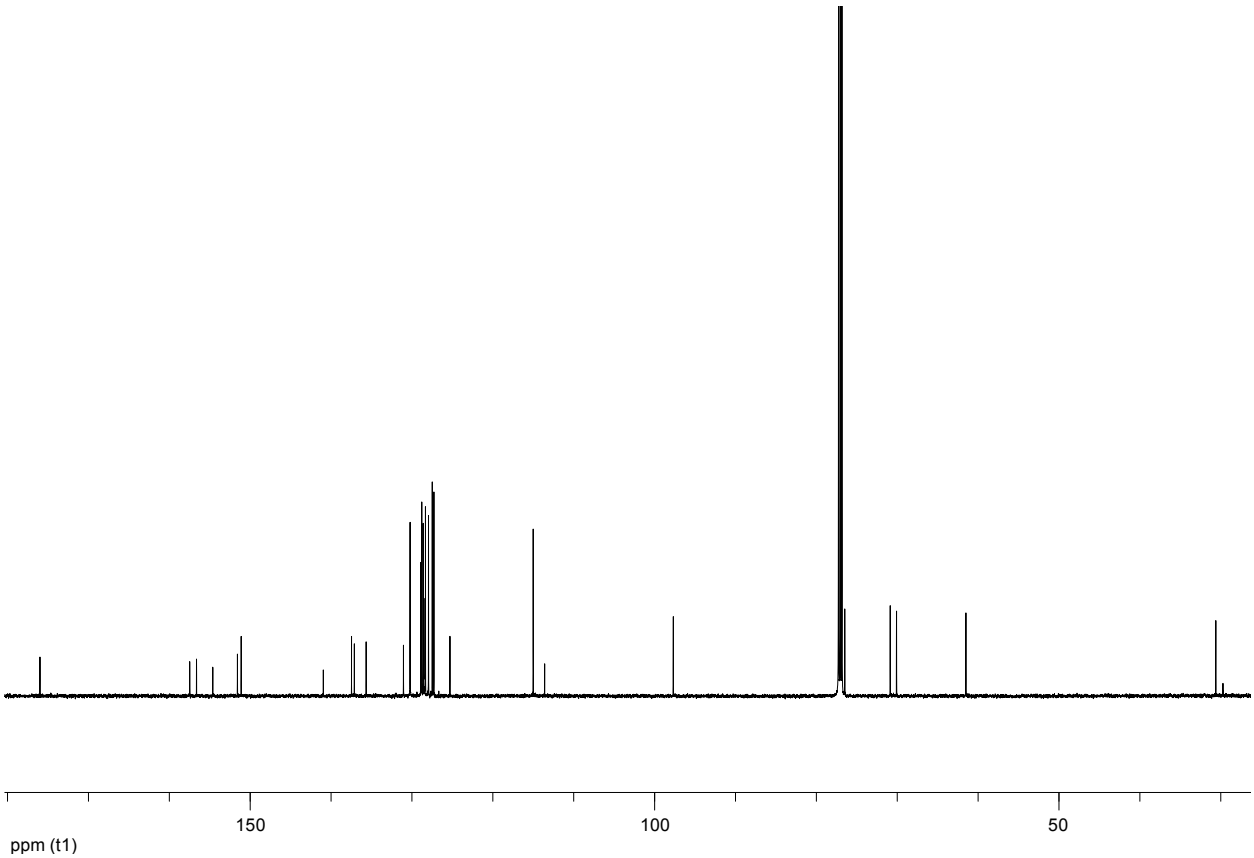
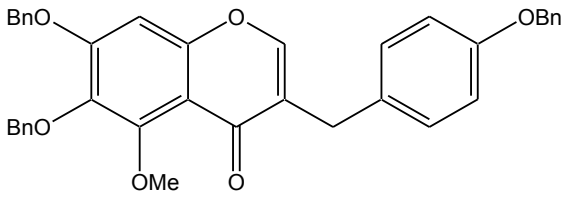


Plate 70a: ^{1}H NMR of 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.144**)

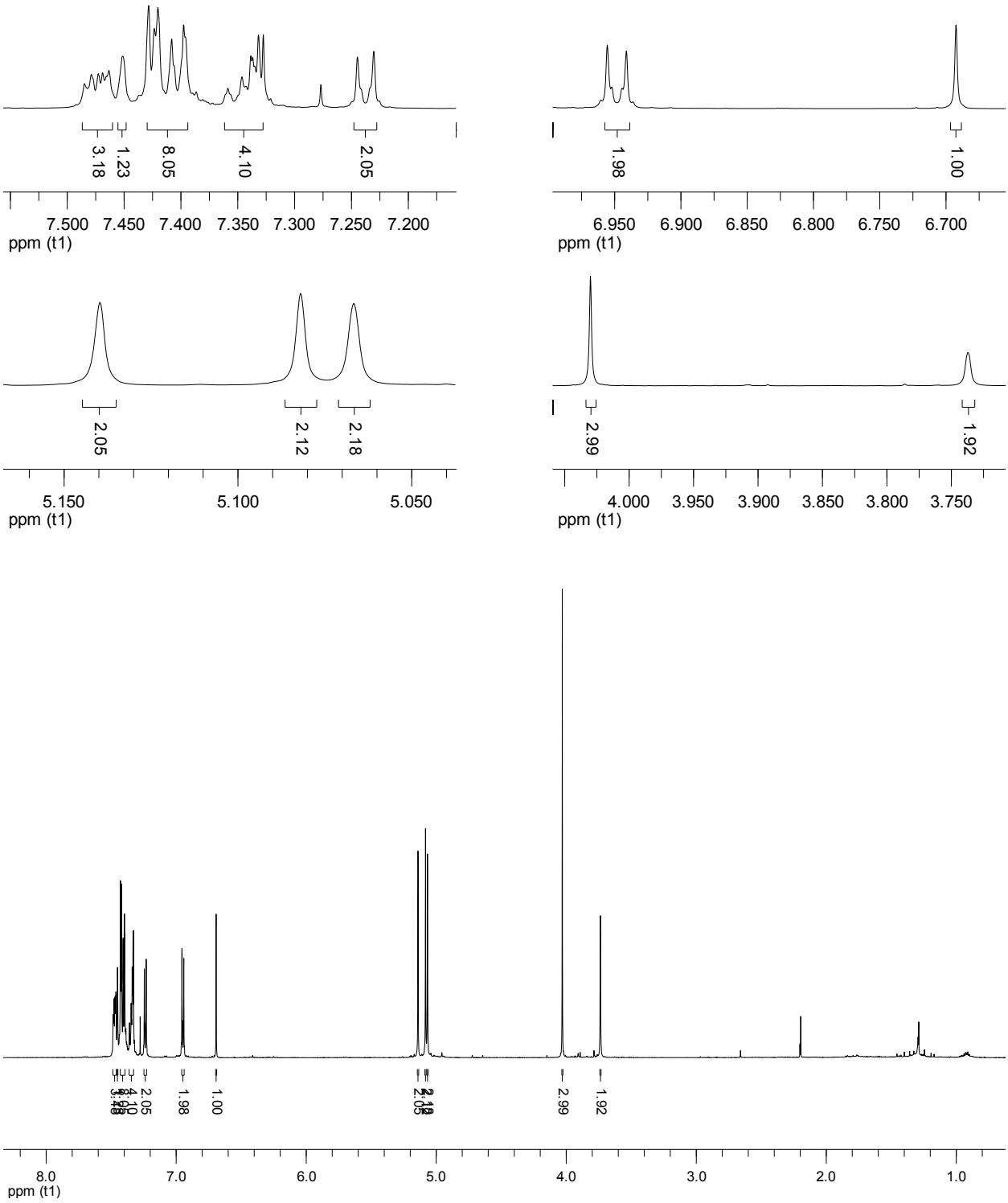
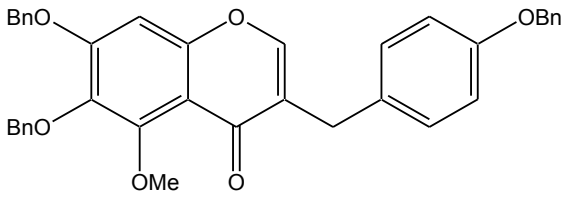


Plate 70b: ^{13}C NMR of 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.144**)

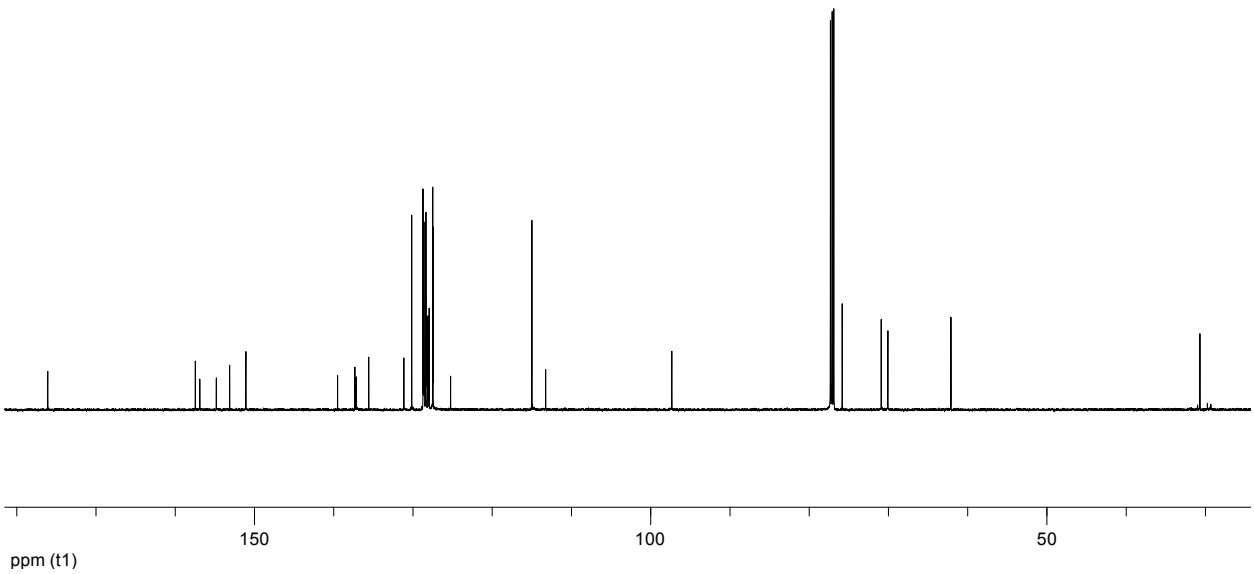
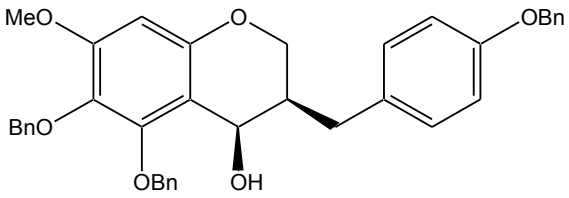
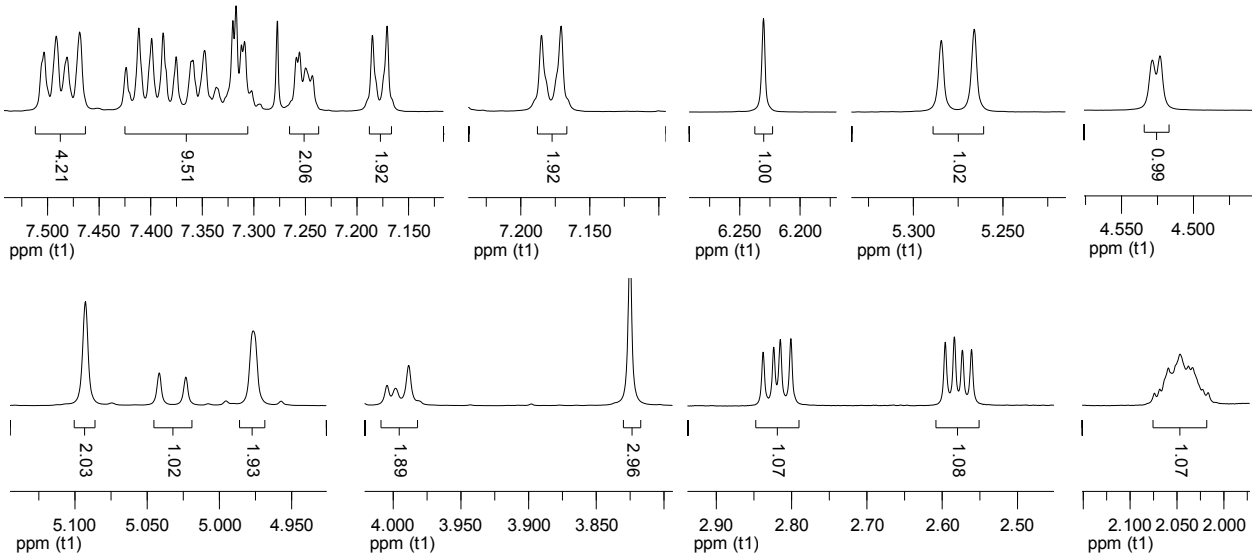


Plate 71a: ^{1}H NMR of *cis*-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.145-*cis***)



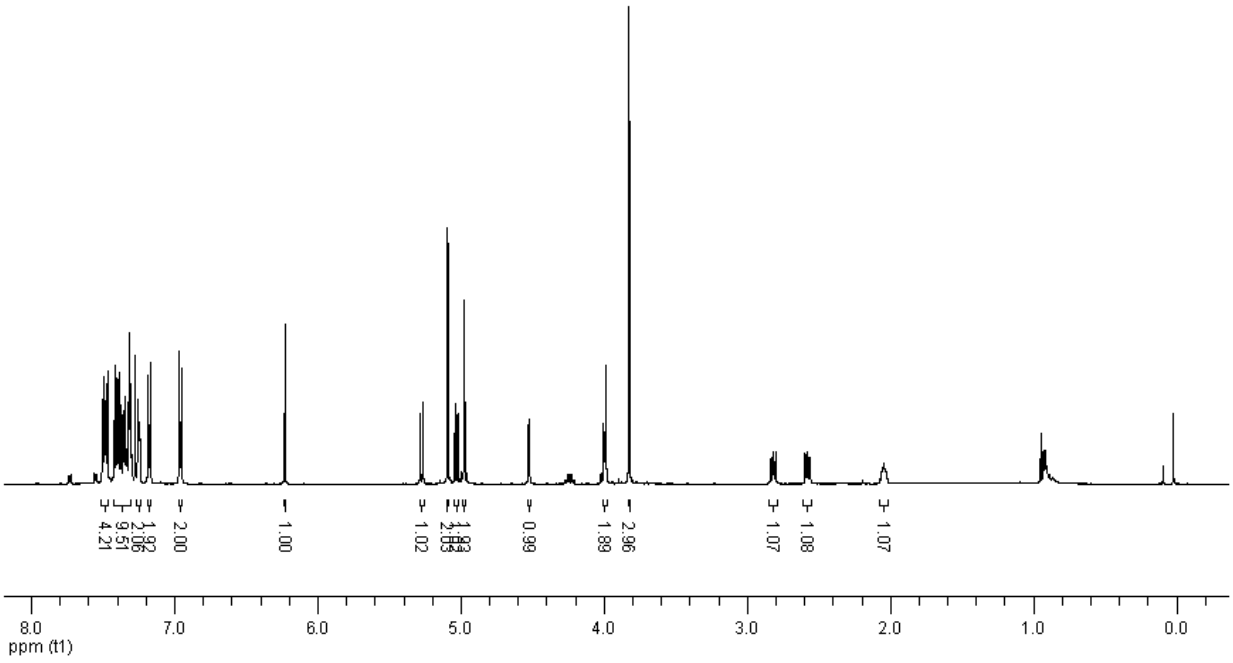
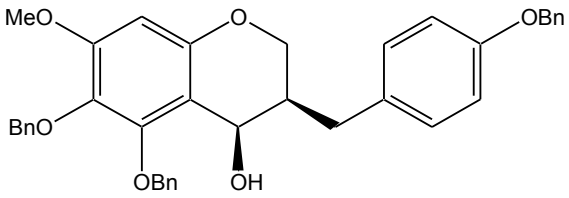


Plate 71b: ^{13}C NMR of *cis*-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.145-*cis***)

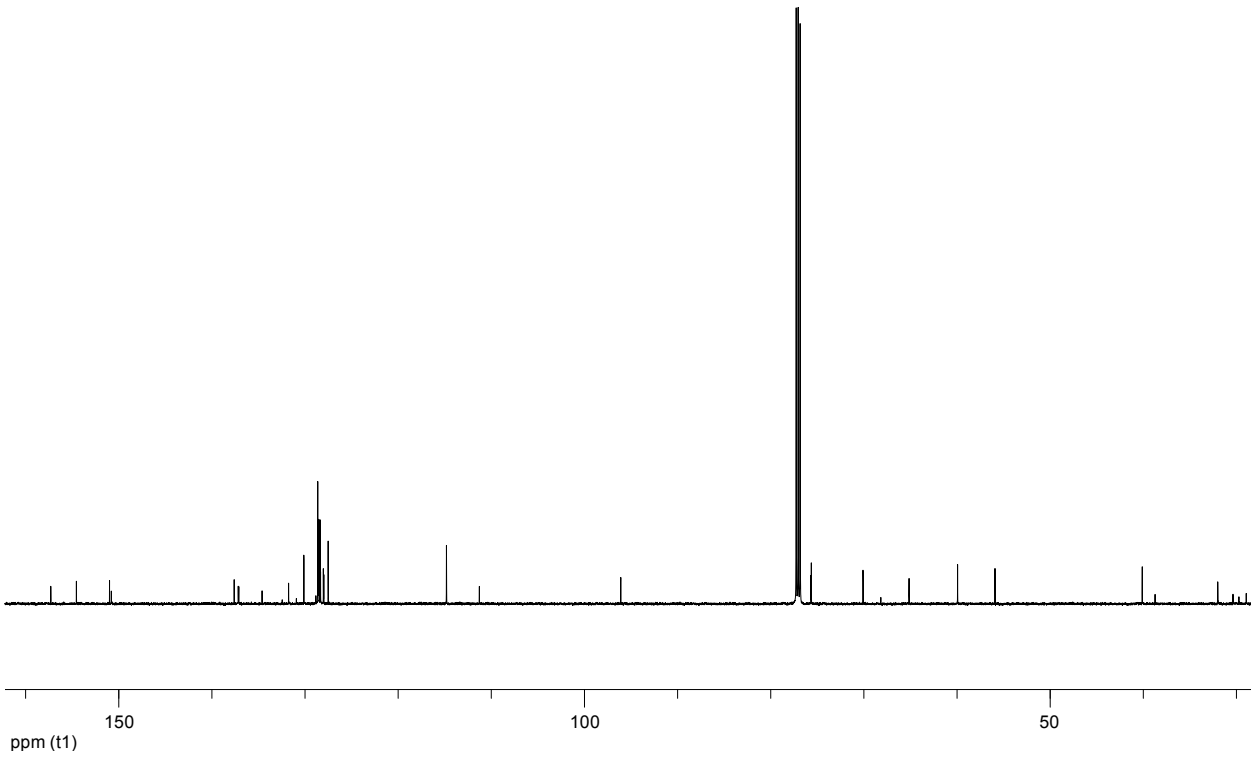
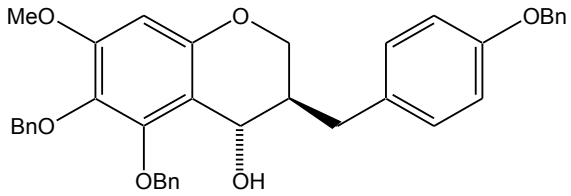
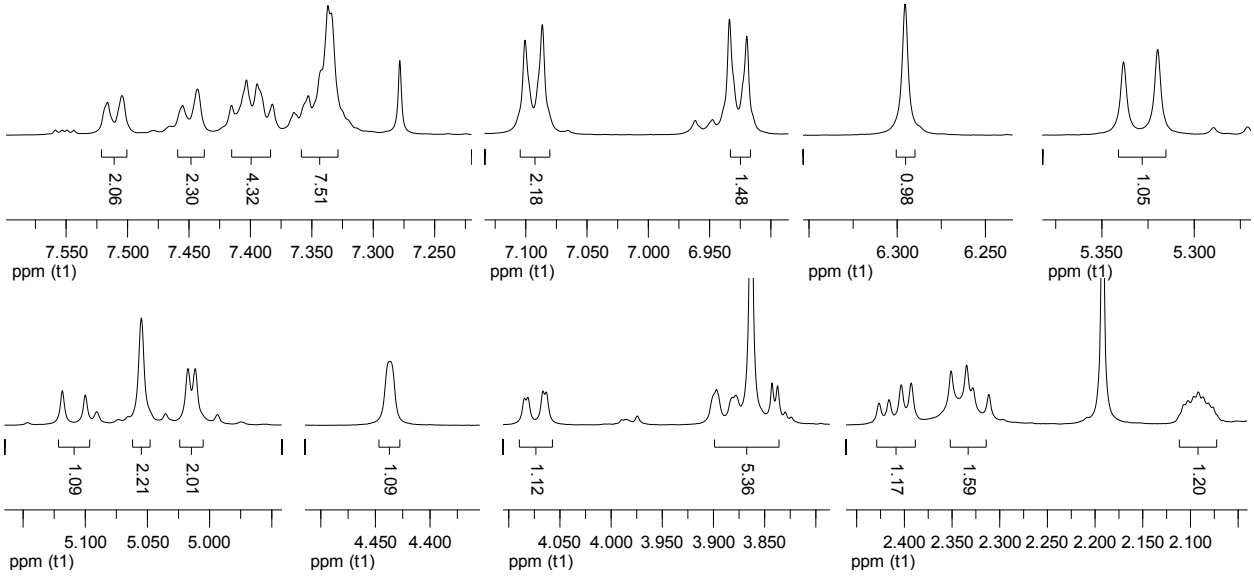


Plate 72a: ^{1}H NMR of *trans*-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.145-*trans***)



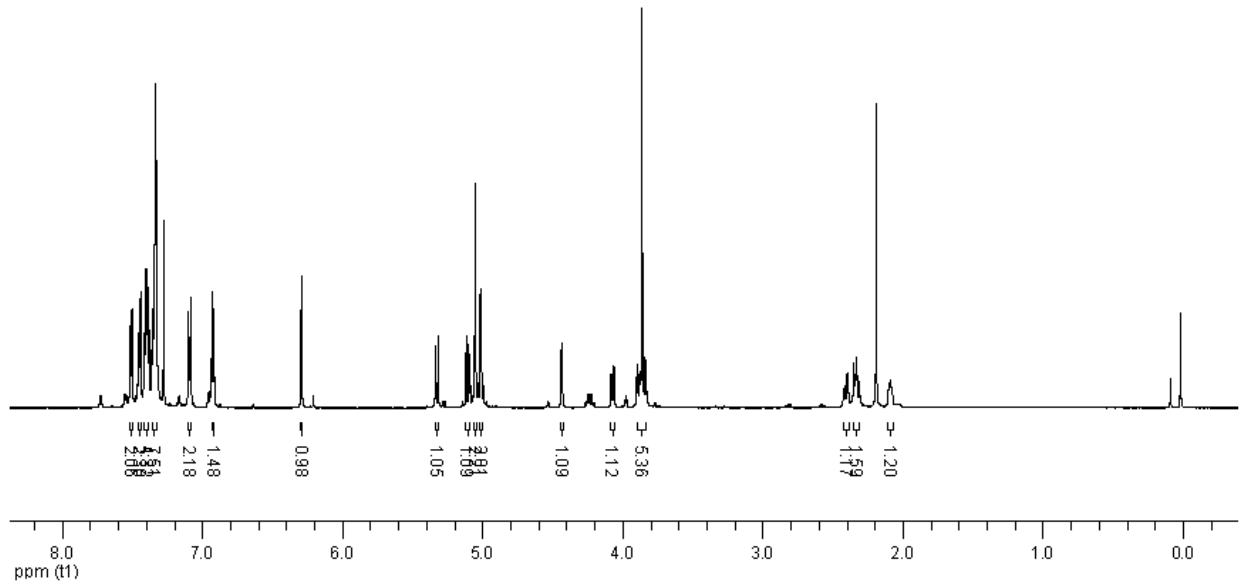
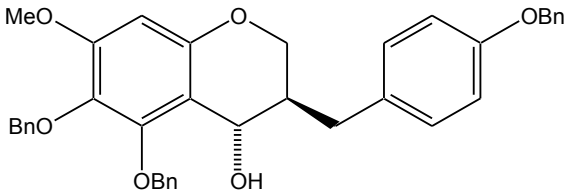


Plate 72b: ^{13}C NMR of *trans*-5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.145-*trans***)

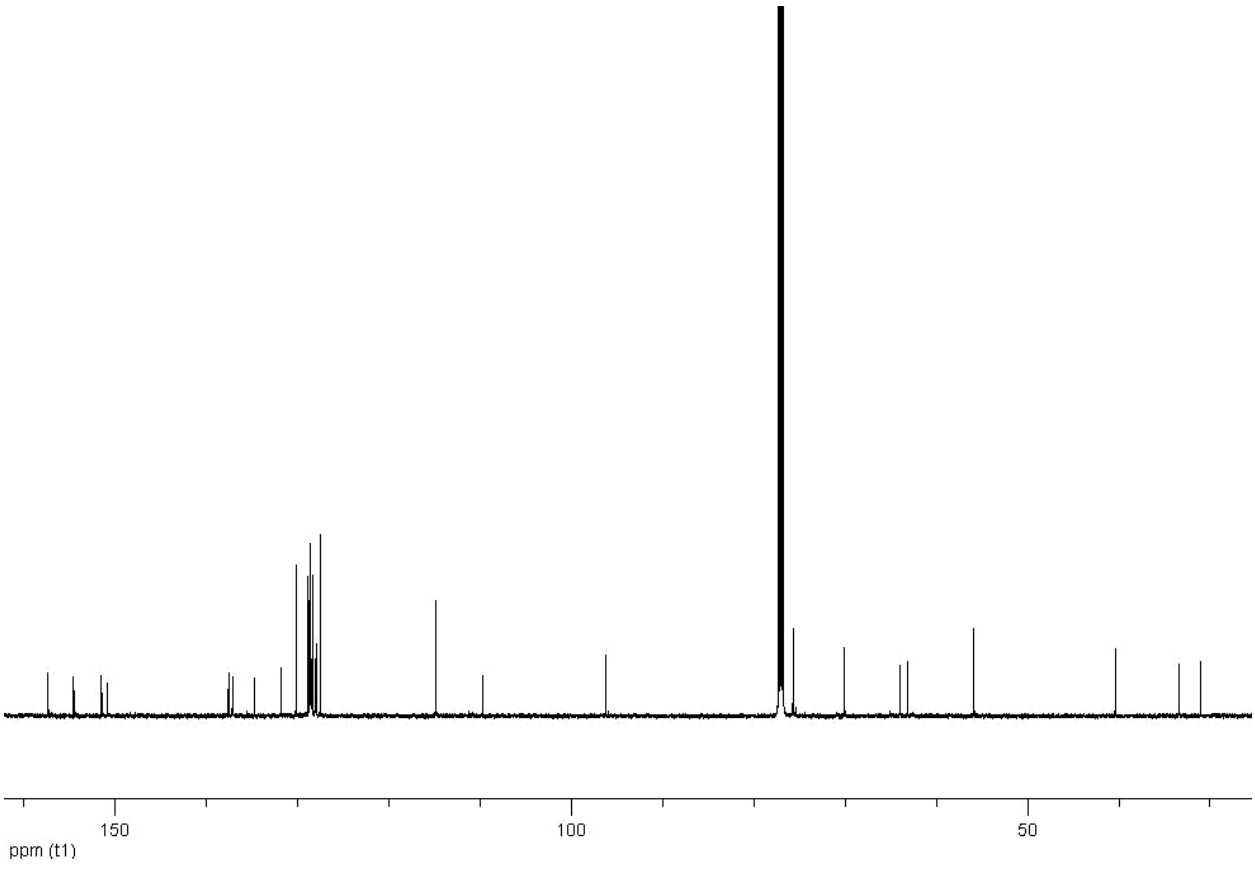
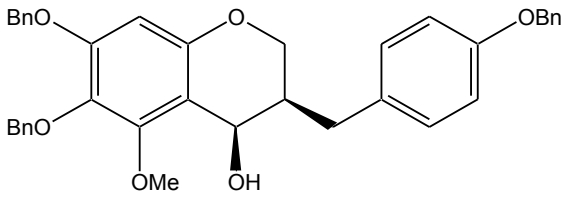
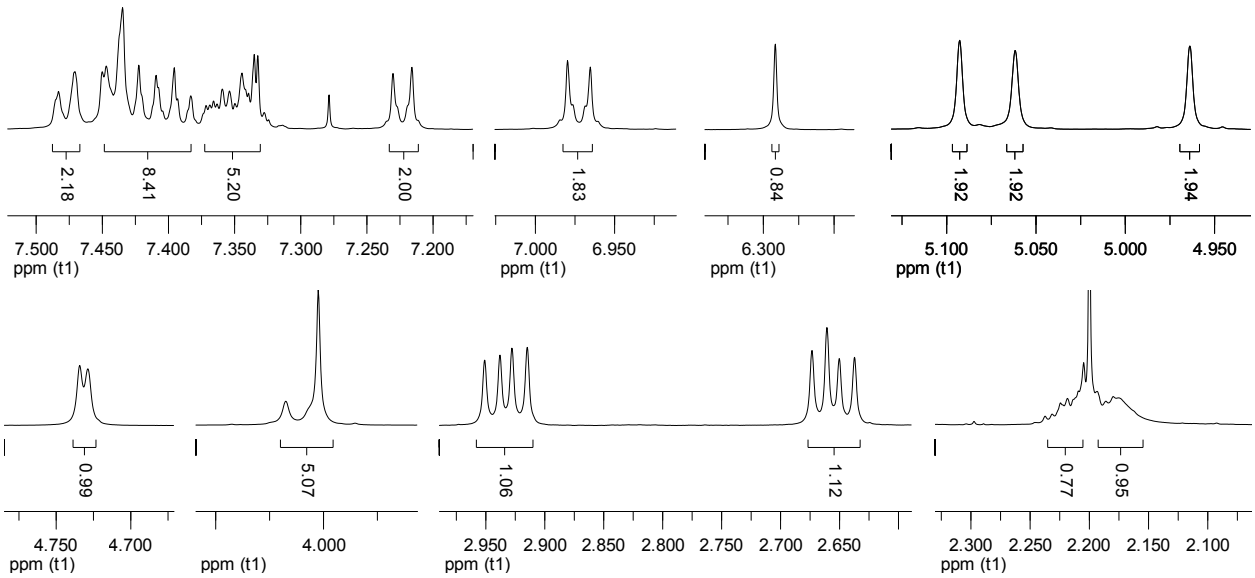


Plate 73a: ^{1}H NMR of *cis*-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.146-*cis***)



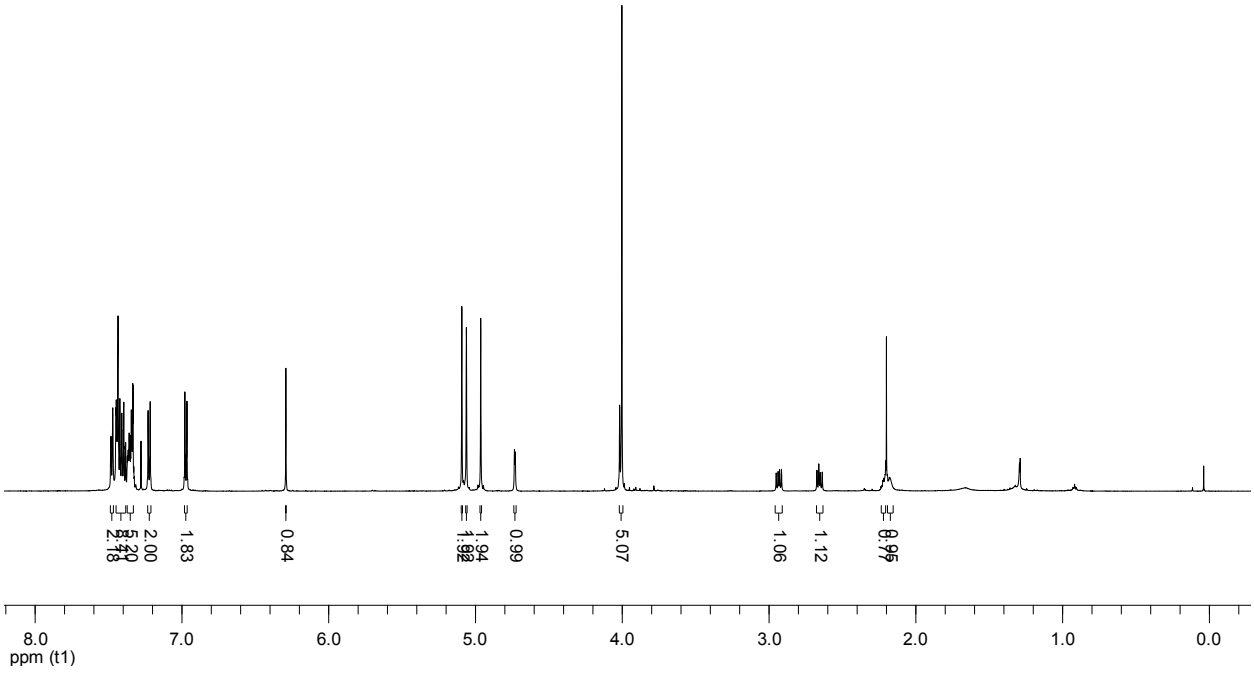
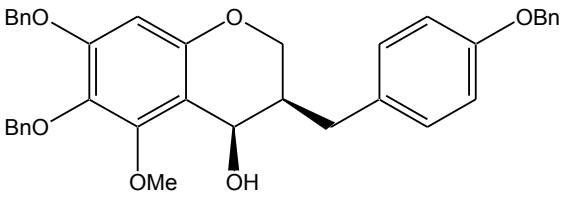


Plate 73b: ^{13}C NMR of *cis*-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.146-*cis***)

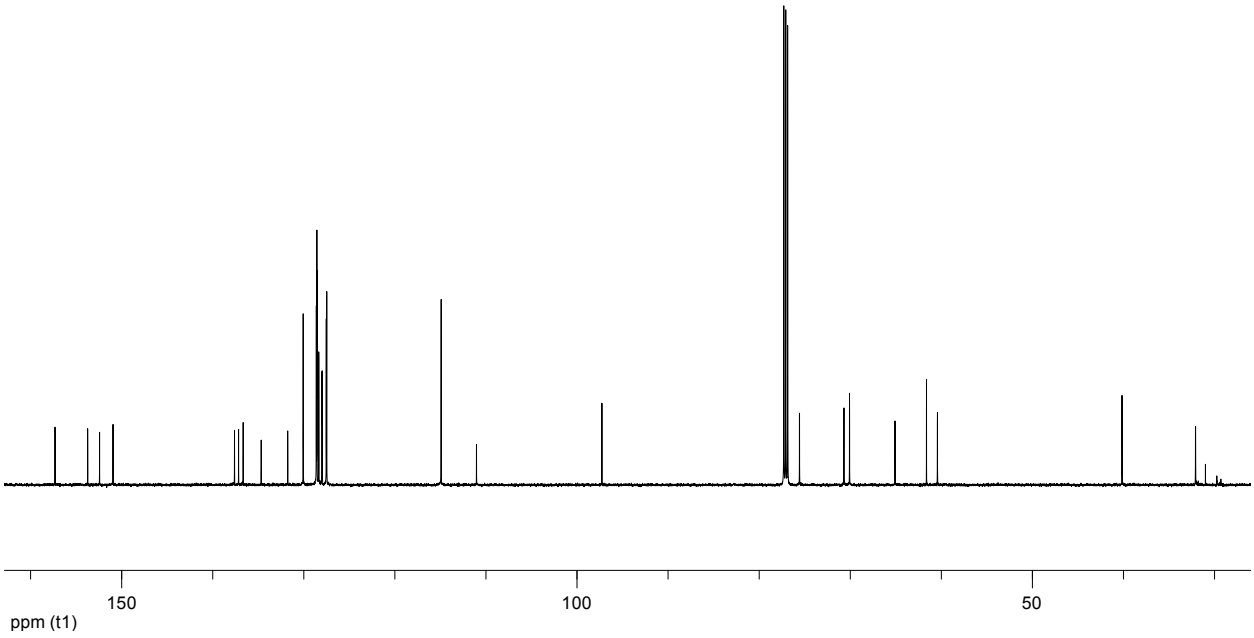
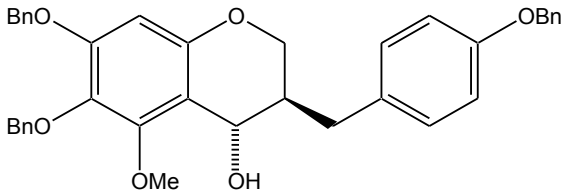
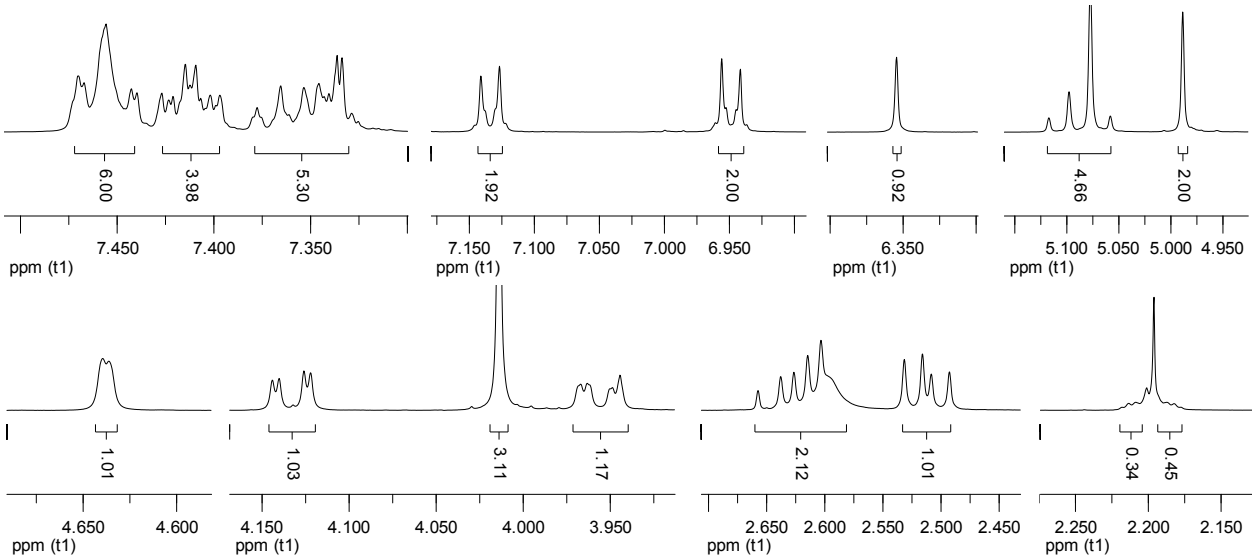


Plate 74a: ^{1}H NMR of *trans*-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.146-*trans***)



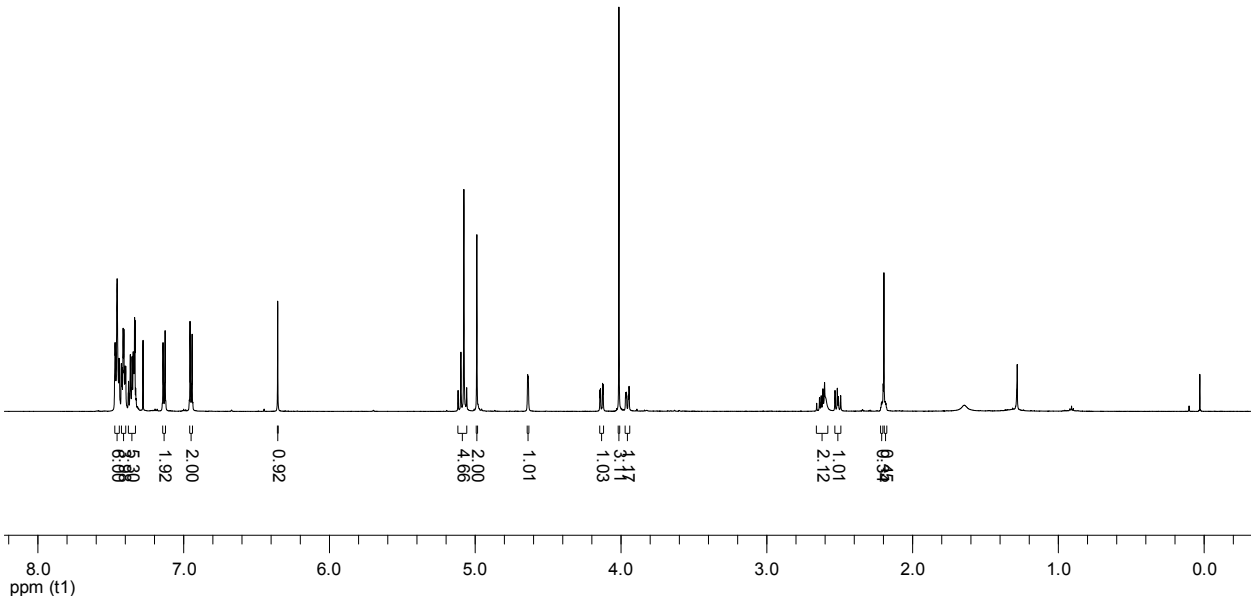
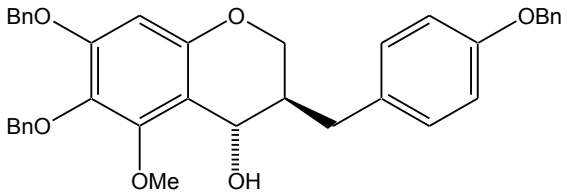


Plate 74b: ^{13}C NMR of *trans*-6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavan-4-ol, $CDCl_3$ (298K)



(**4.146-*trans***)

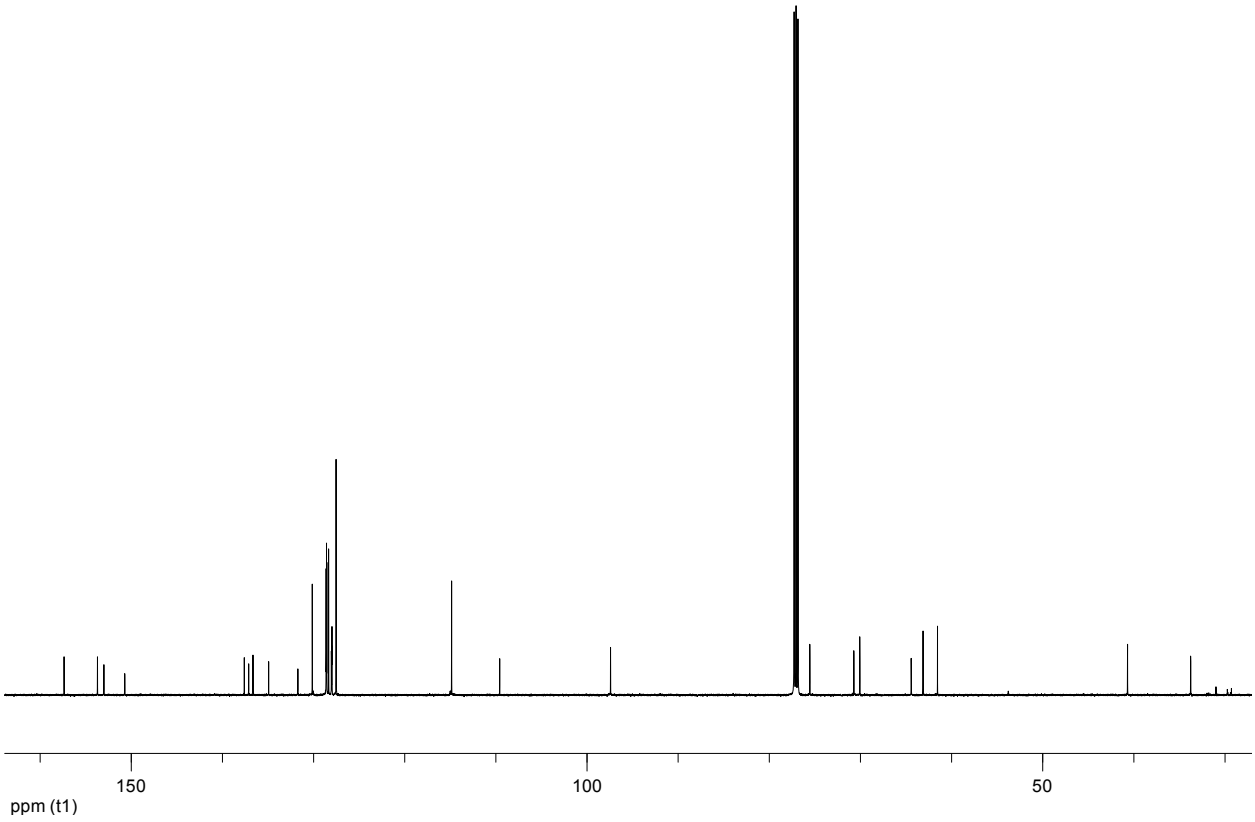
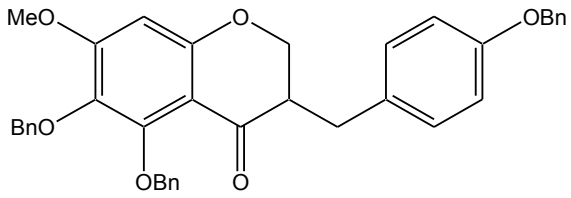


Plate 75a: ^{1}H NMR of 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.147**)

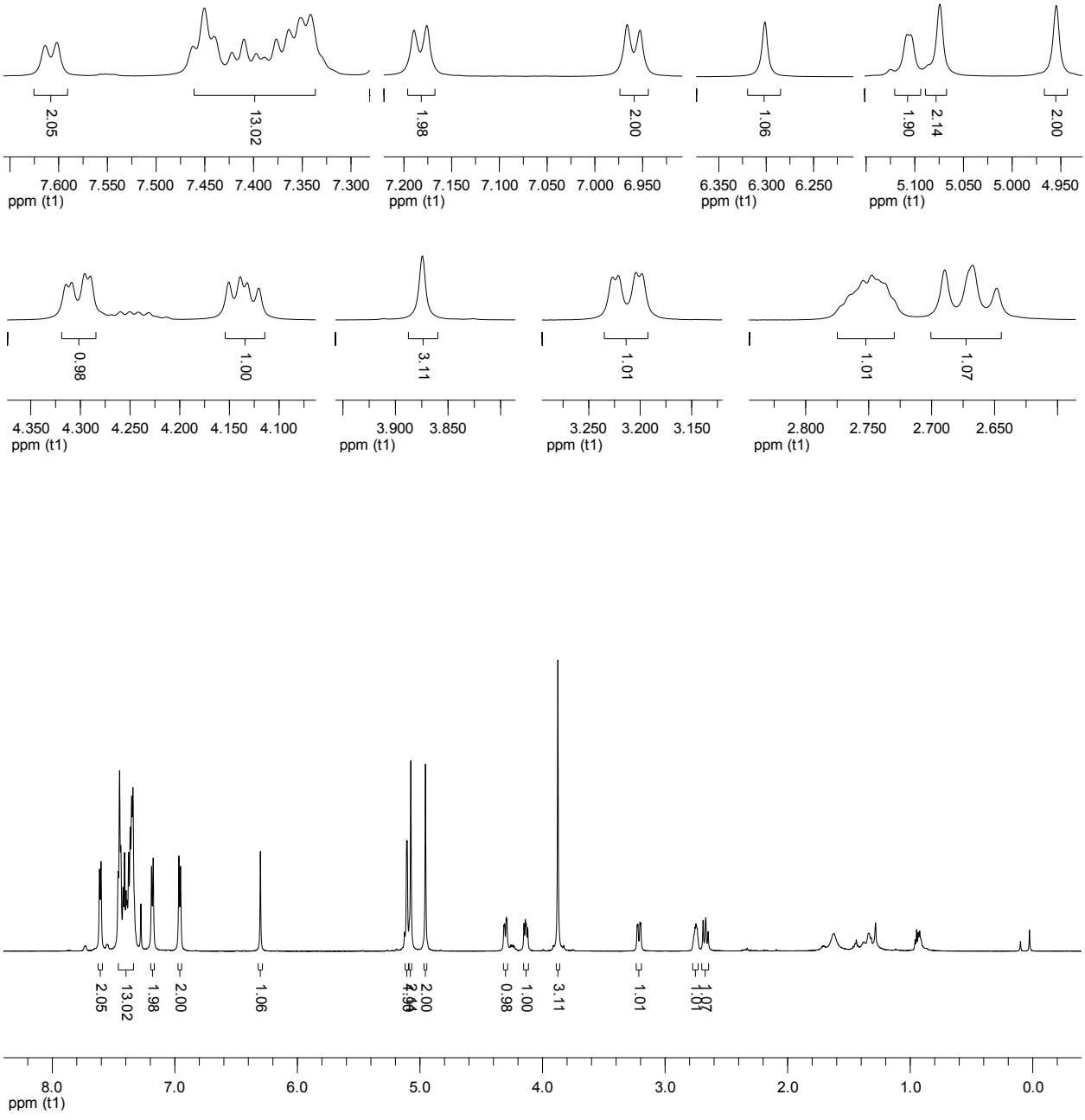
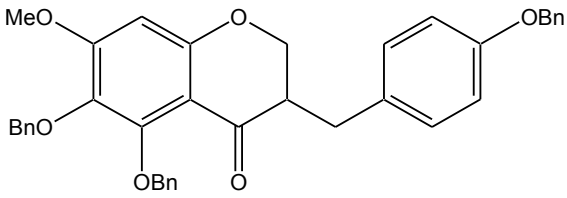


Plate 75b: ^{13}C NMR of 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.147**)

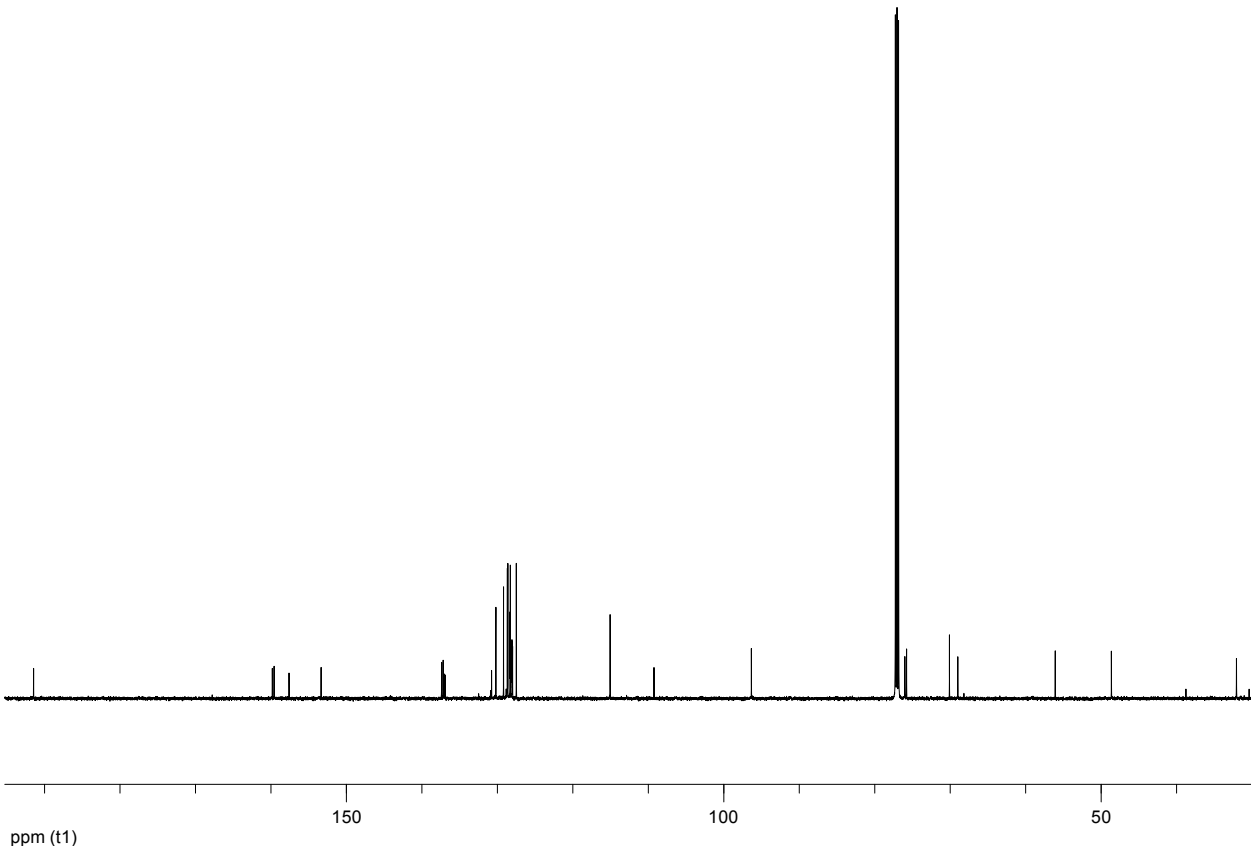
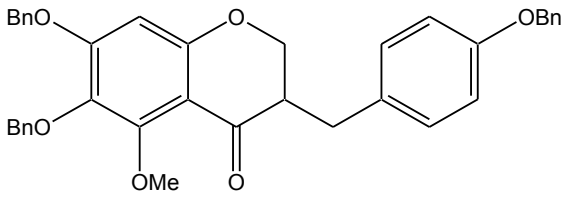


Plate 76a: ^{1}H NMR of 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.148**)

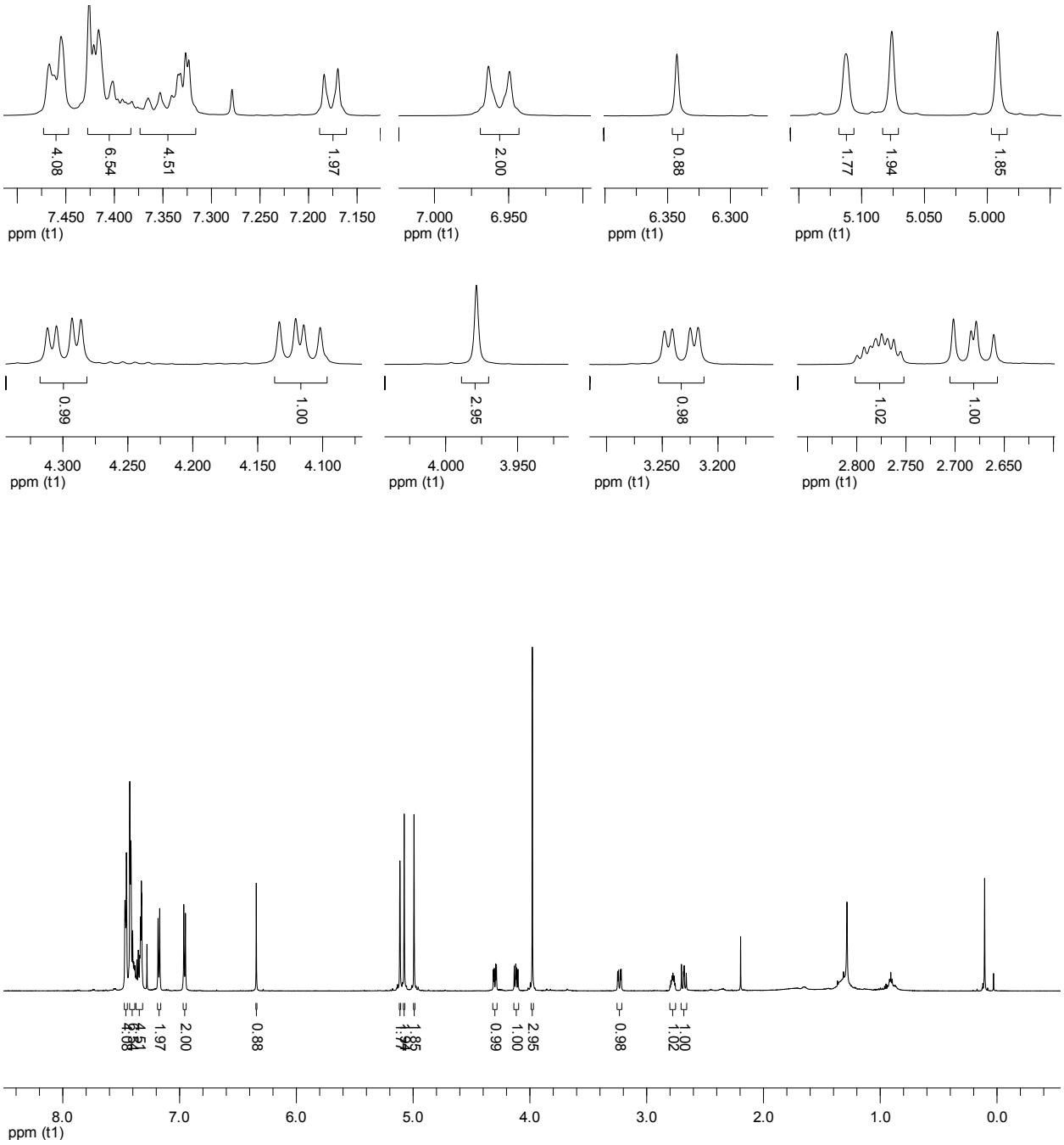
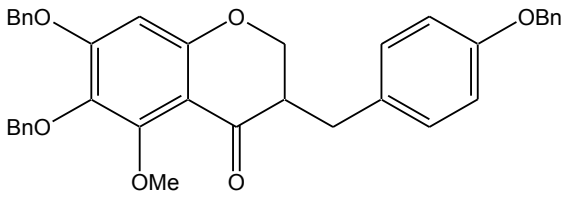


Plate 76b: ^{13}C NMR of 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.148**)

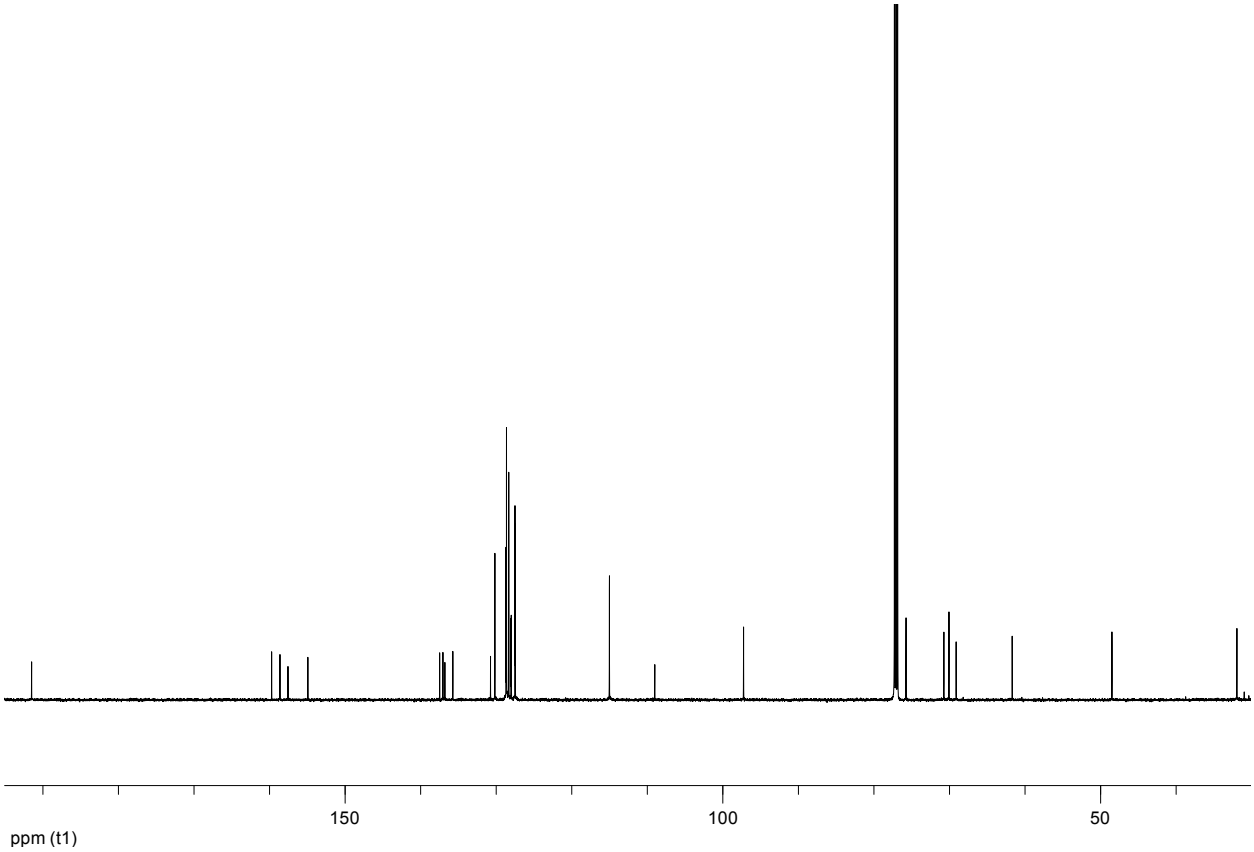
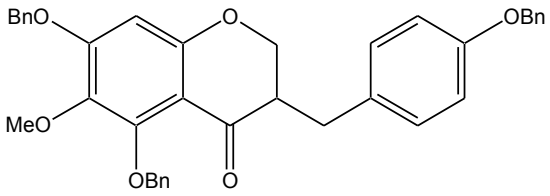
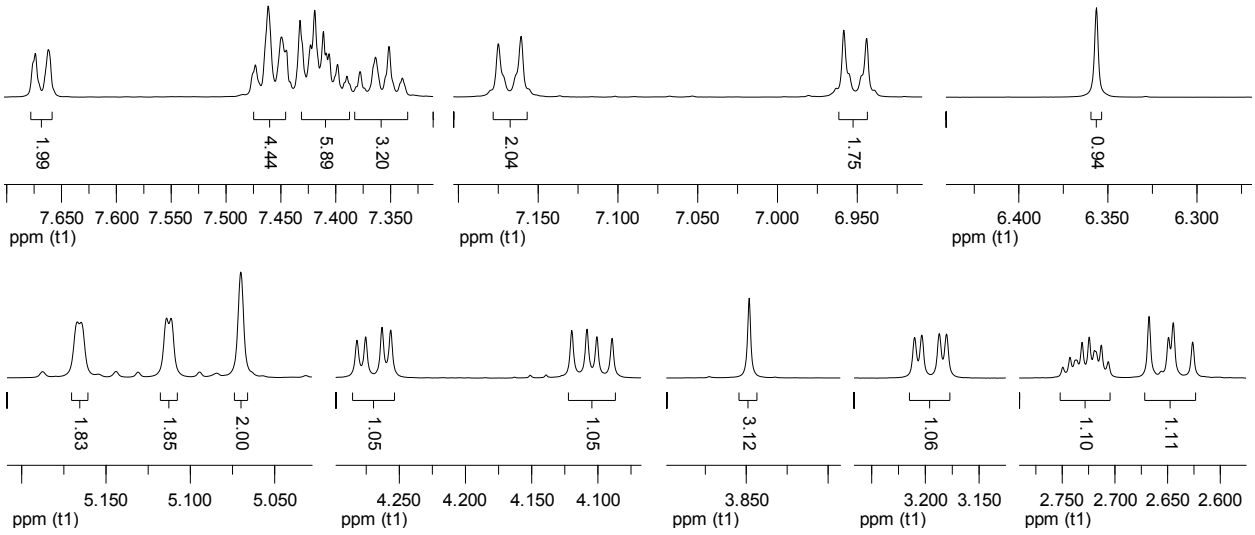


Plate 77a: ^{1}H NMR of 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.149**)



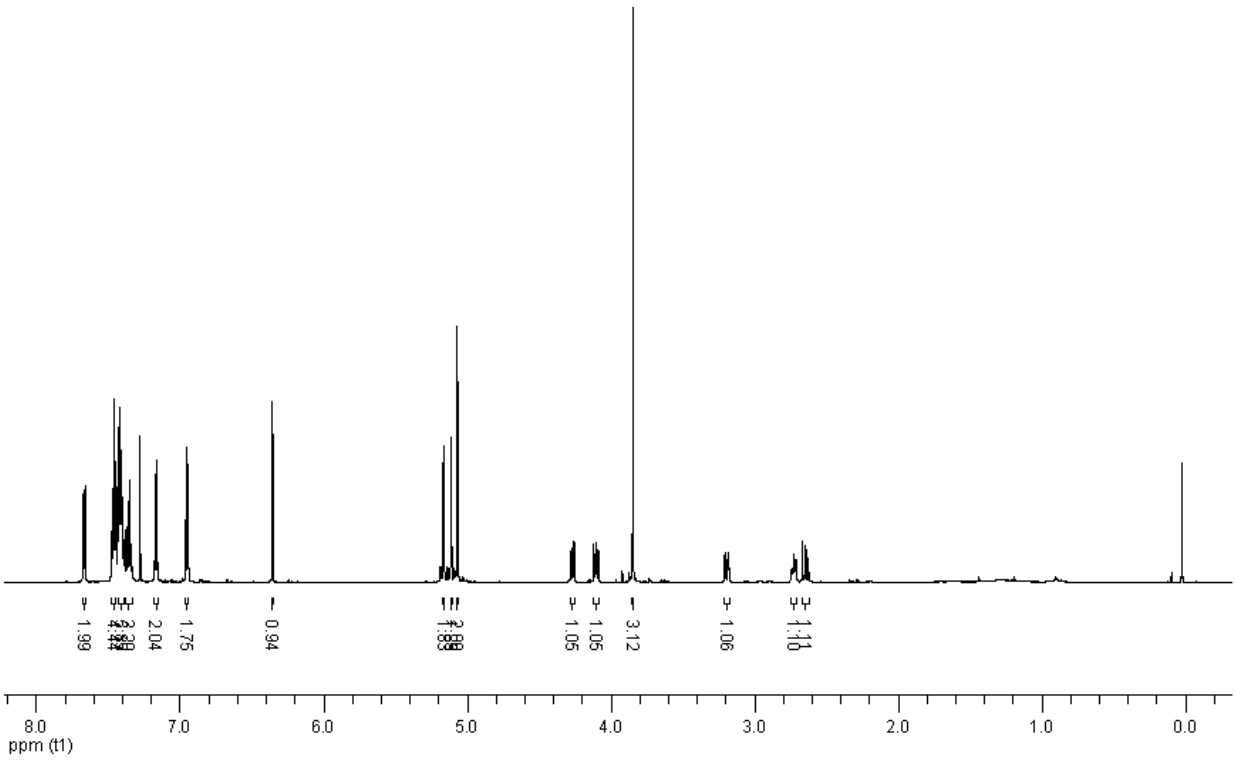
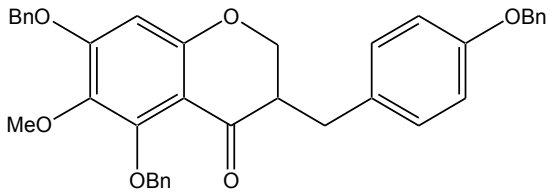


Plate 77b: ^{13}C NMR of 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.149**)

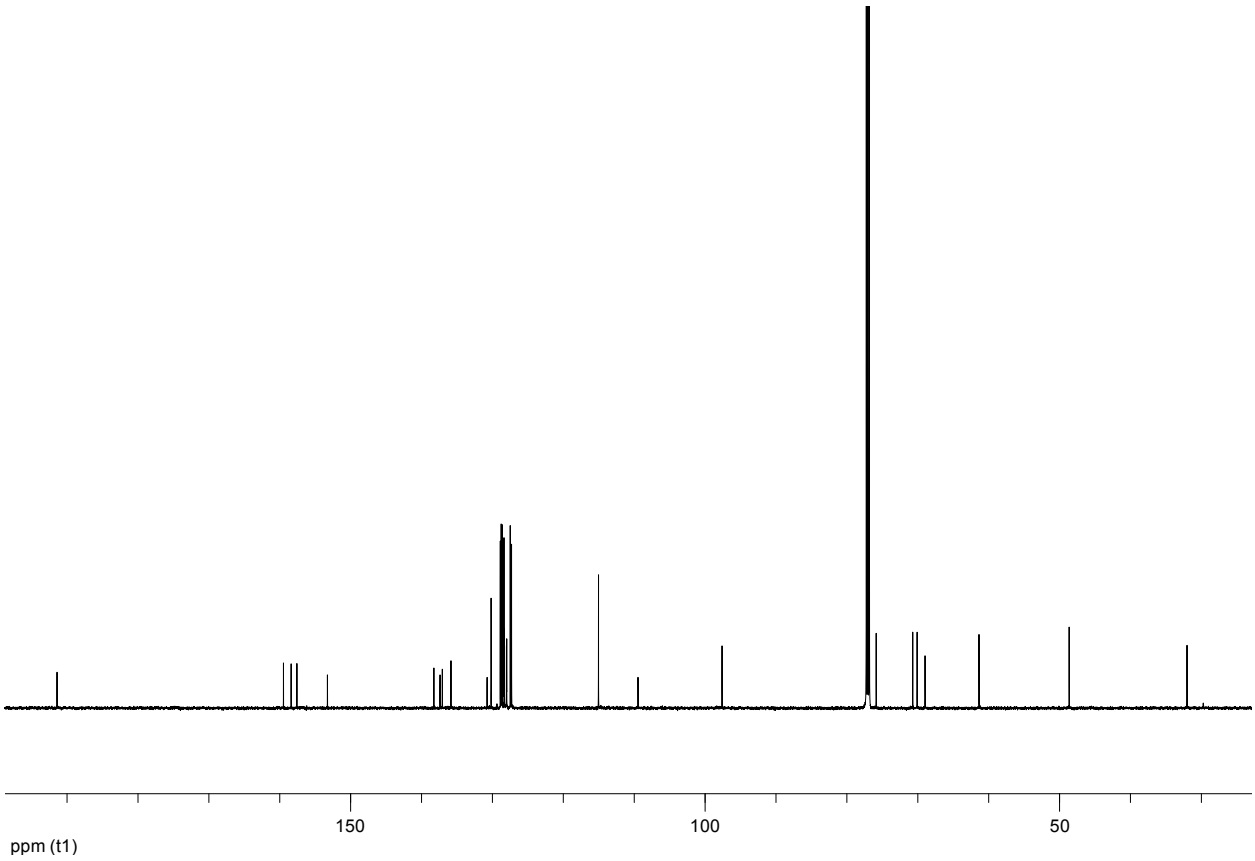
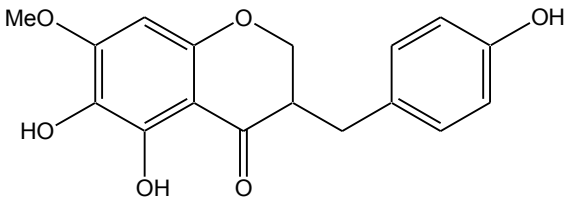
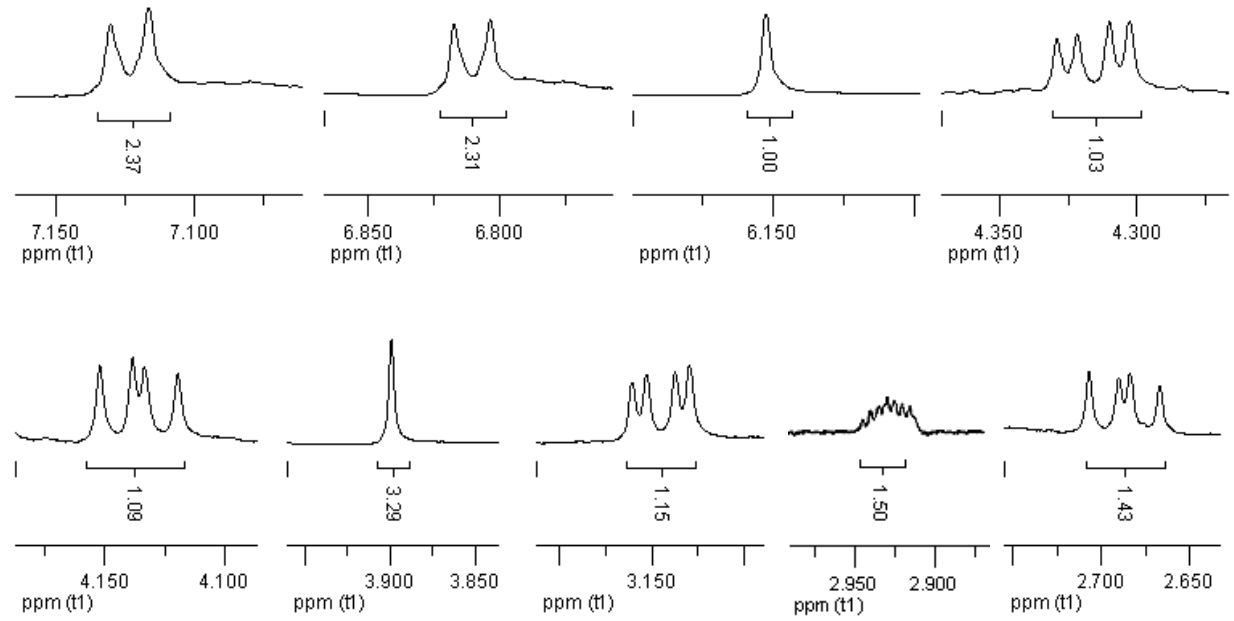


Plate 78a: ^{1}H NMR of 5,6,4'-Trihydroxy-7-methoxyhomoisoflavanone, acetone (298K)



(4.150)



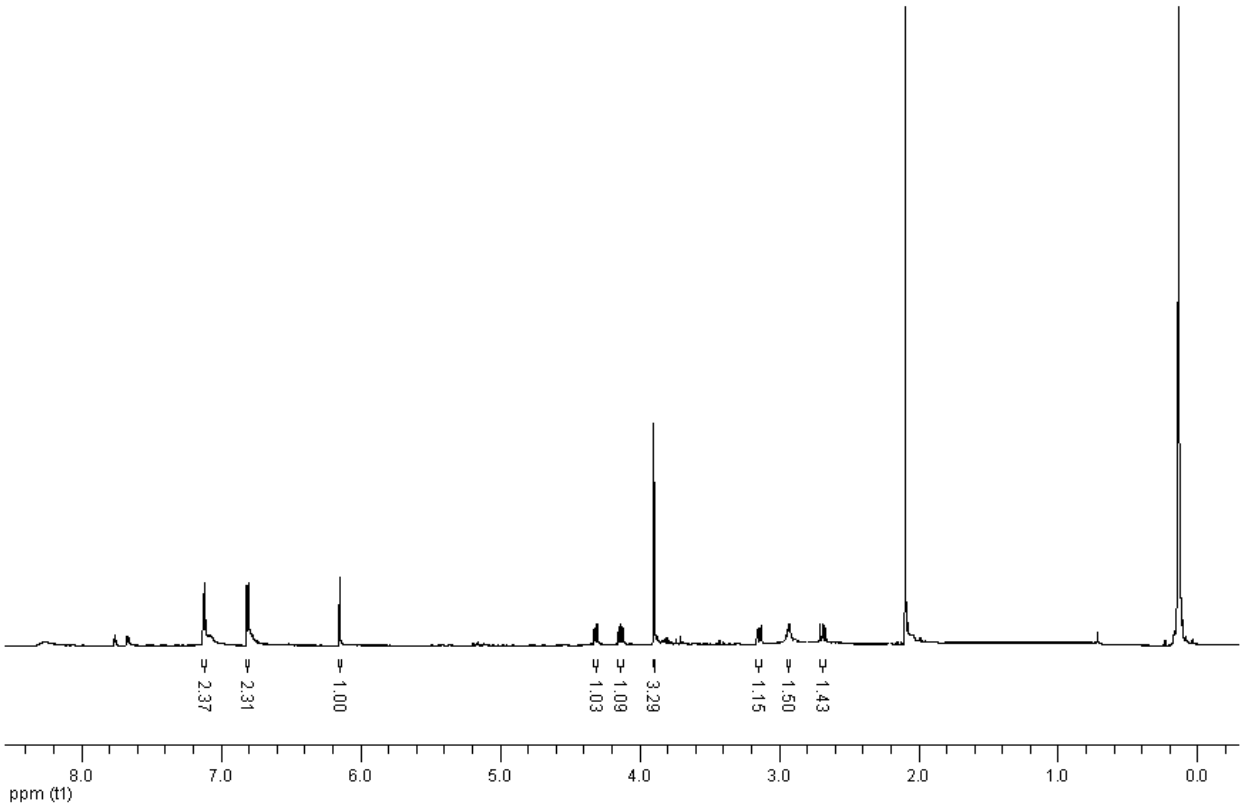
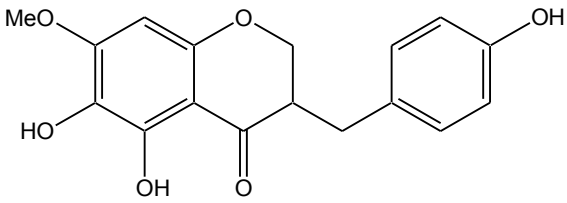


Plate 78b: ^{13}C NMR of 5,6,4'-Trihydroxy-7-methoxyhomoisoflavan, acetone (298K)



(4.150)

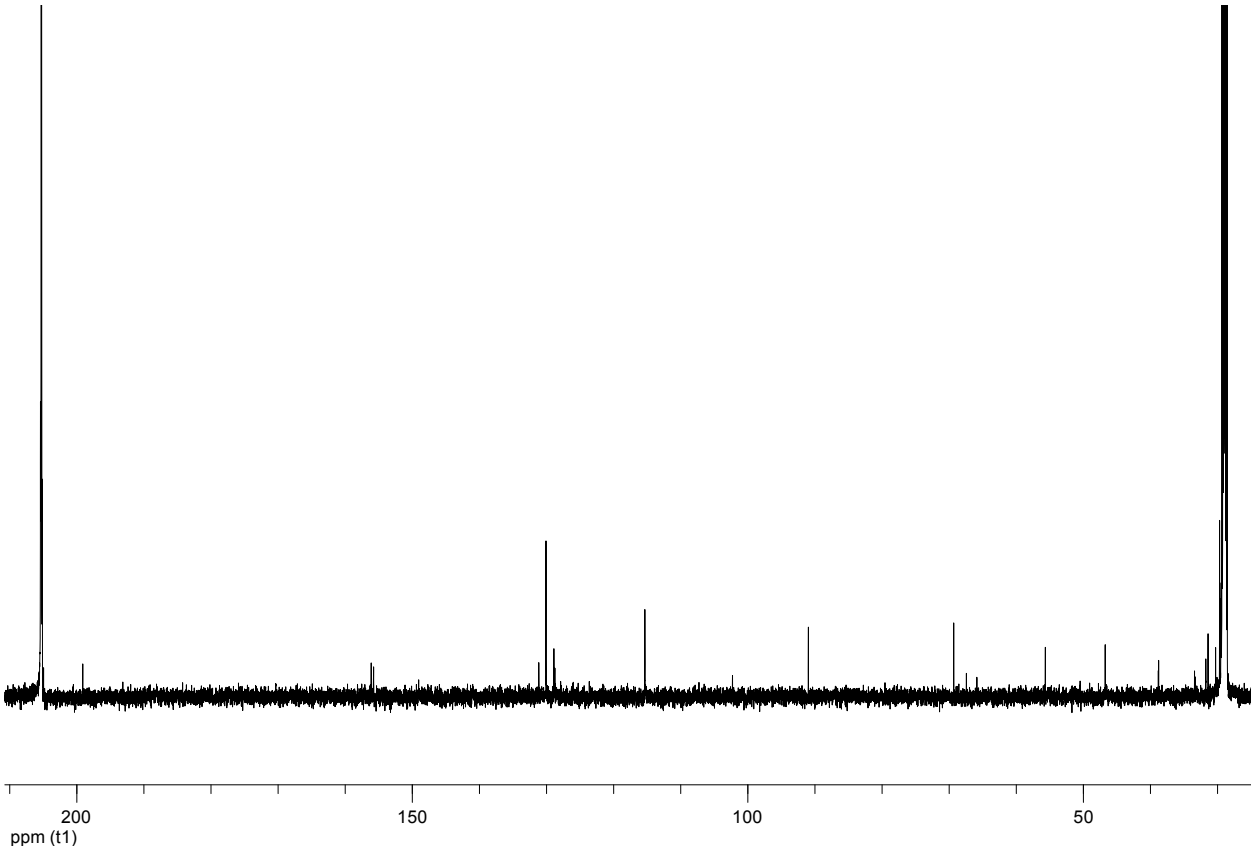
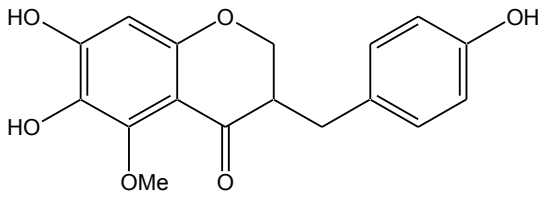
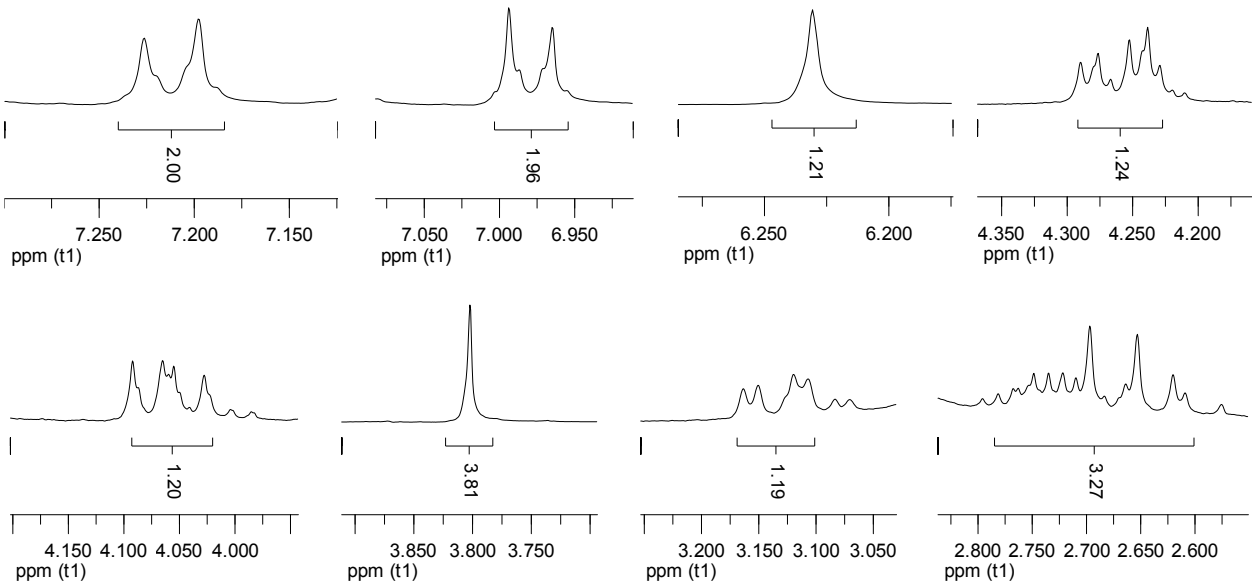


Plate 79a: ^{1}H NMR of 6,7,4'-Trihydroxy-5-methoxyhomoisoflavanone, acetone (298K)



(**4.151**)



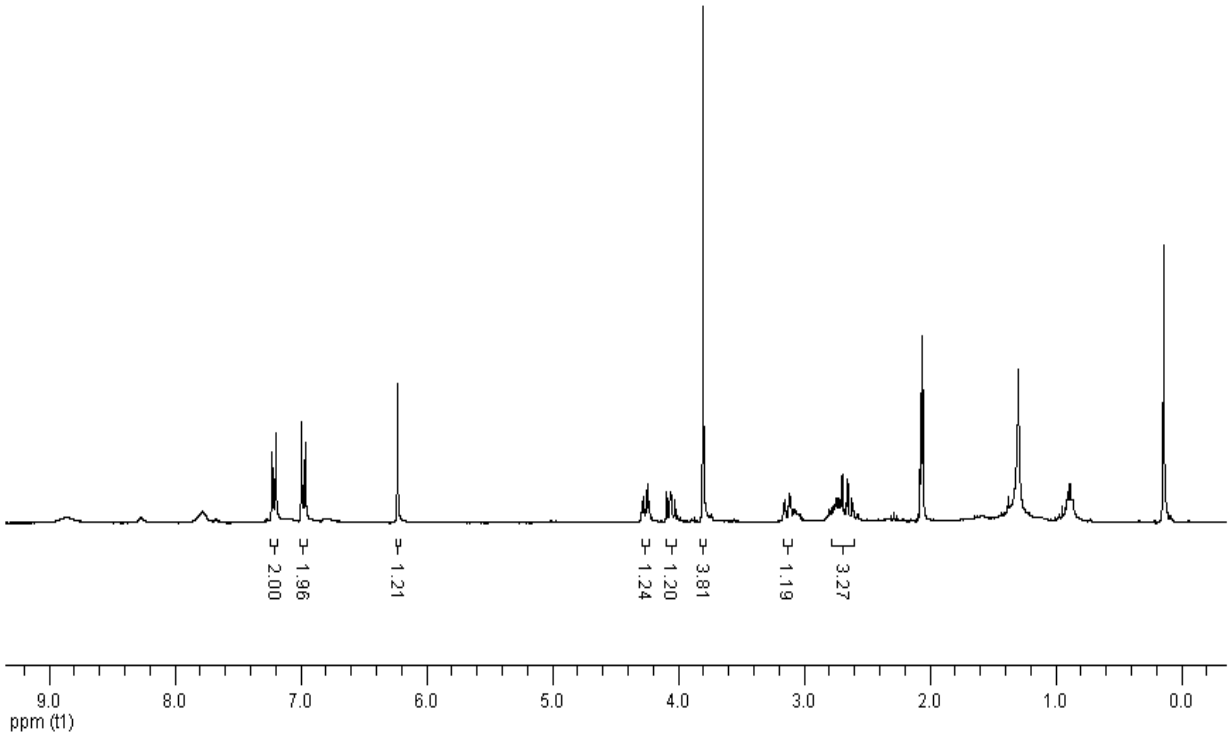
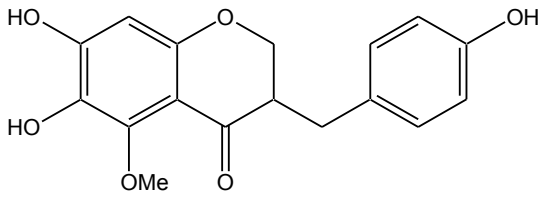


Plate 79b: ^{13}C NMR of 6,7,4'-Trihydroxy-5-methoxyhomoisoflavanone, acetone (298K)



(**4.151**)

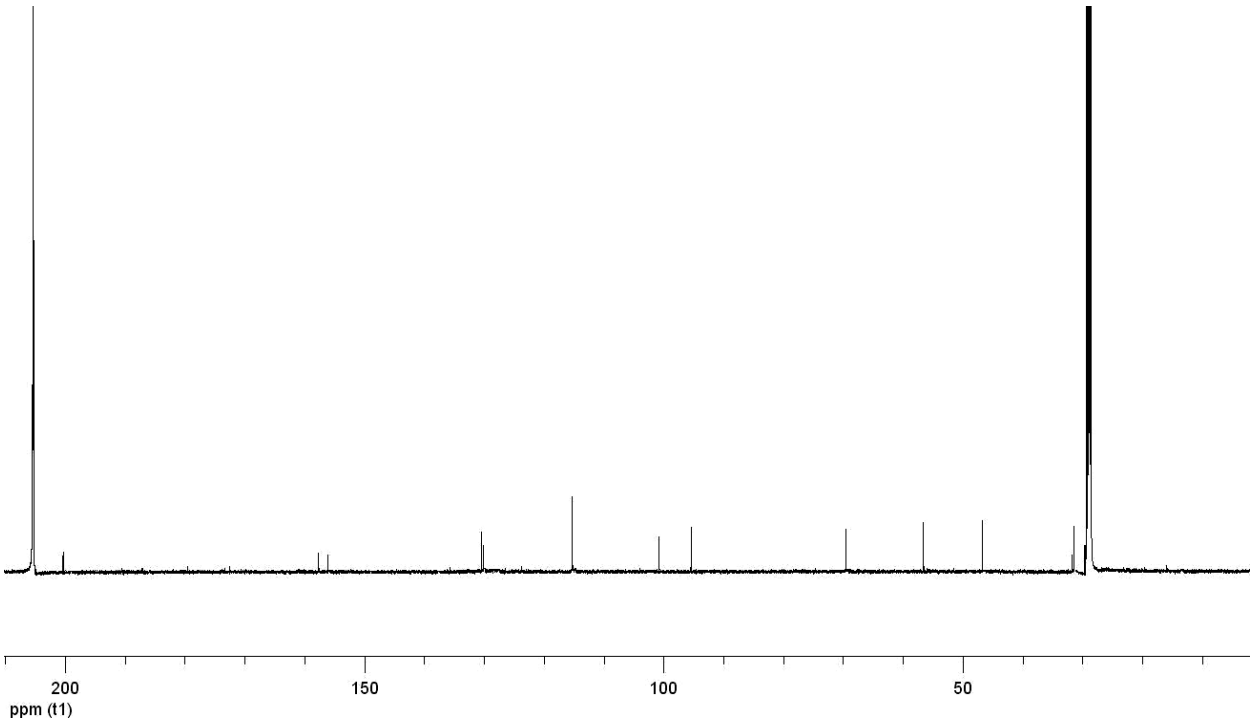
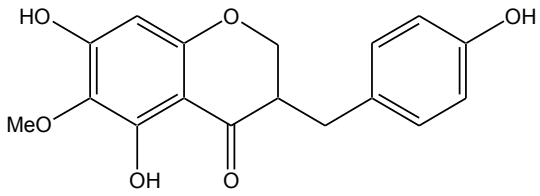
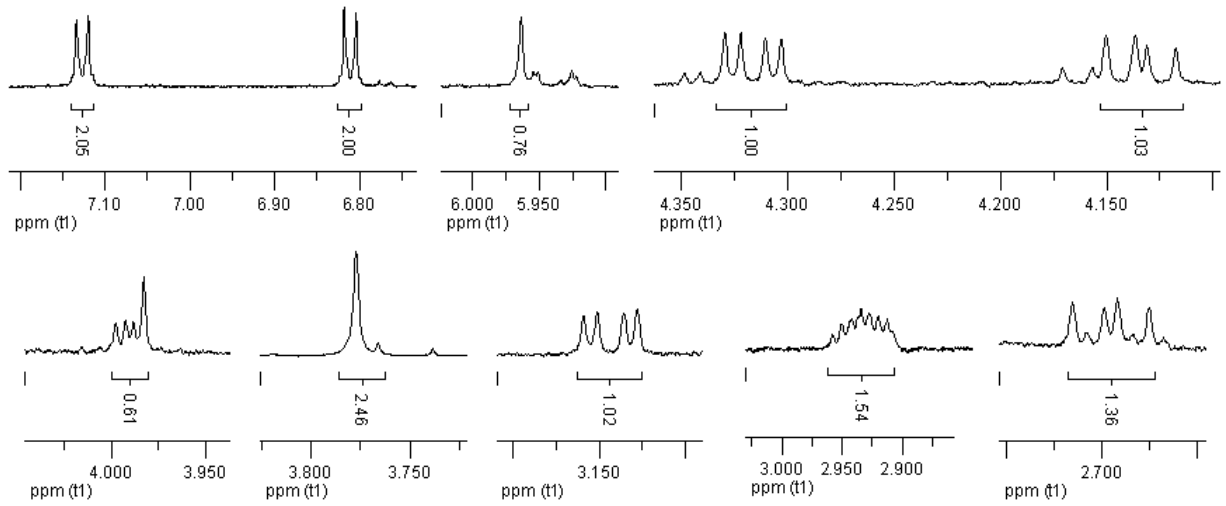


Plate 80a: ^{1}H NMR of 5,7,4'-Trihydroxy-6-methoxyhomoisoflavanone, acetone (298K)



(4.152)



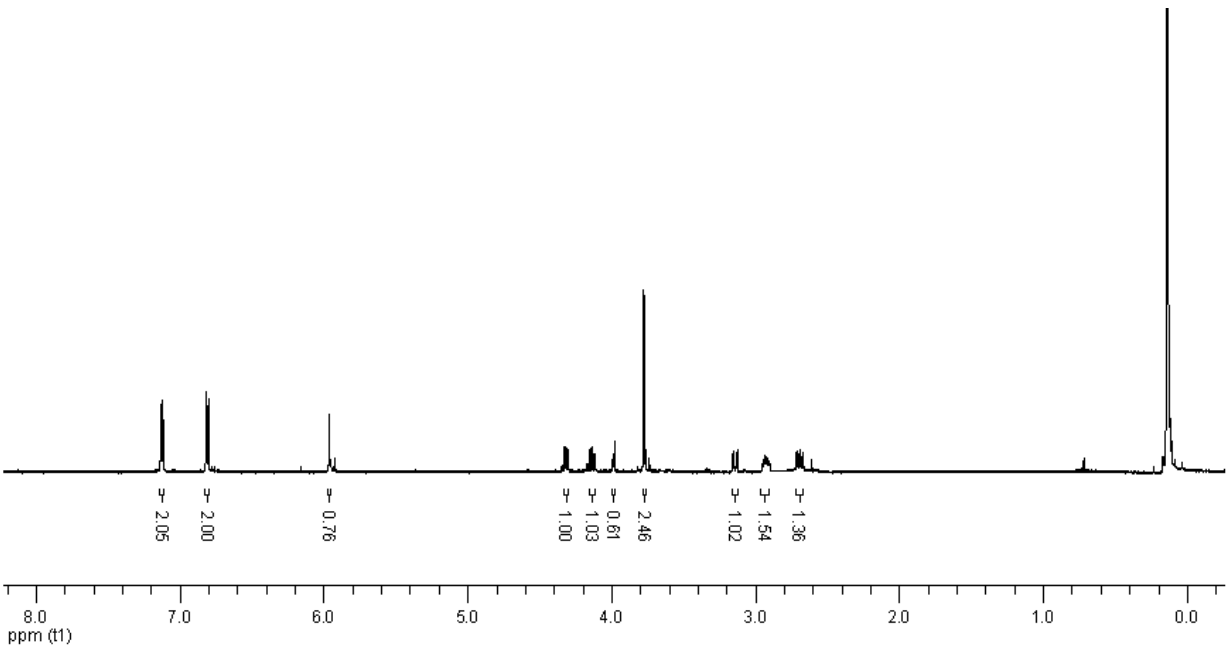
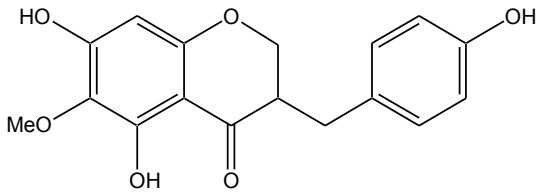


Plate 80b: ^{13}C NMR of 5,7,4'-Trihydroxy-6-methoxyhomoisoflavanone, acetone (298K)



(**4.152**)

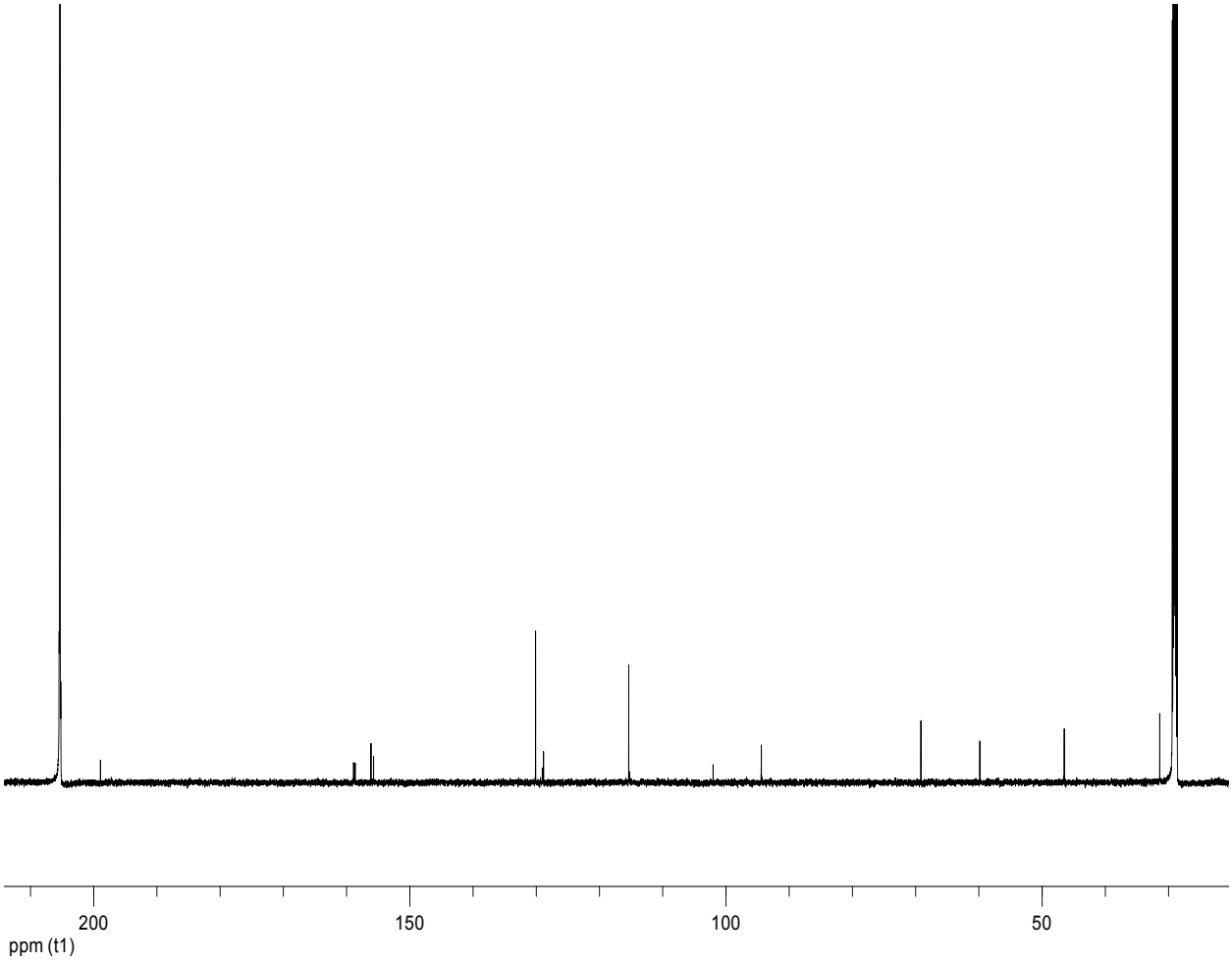
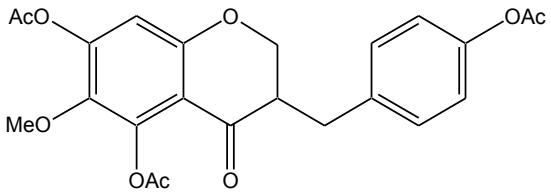
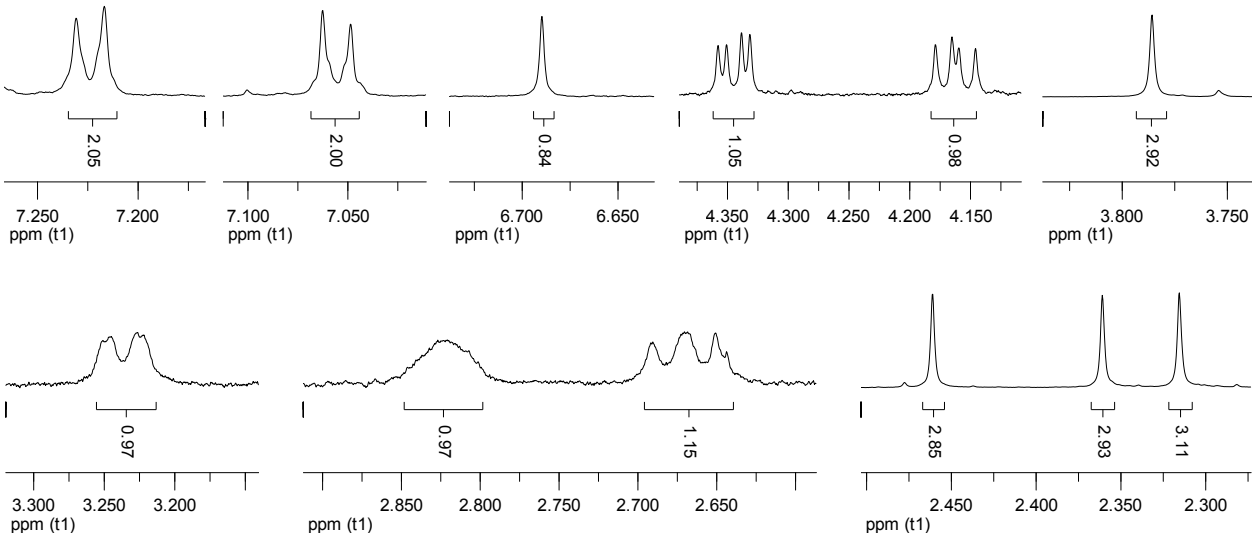


Plate 81a: ^{1}H NMR of 5,7,4'-Triacetoxy-6-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.153**)



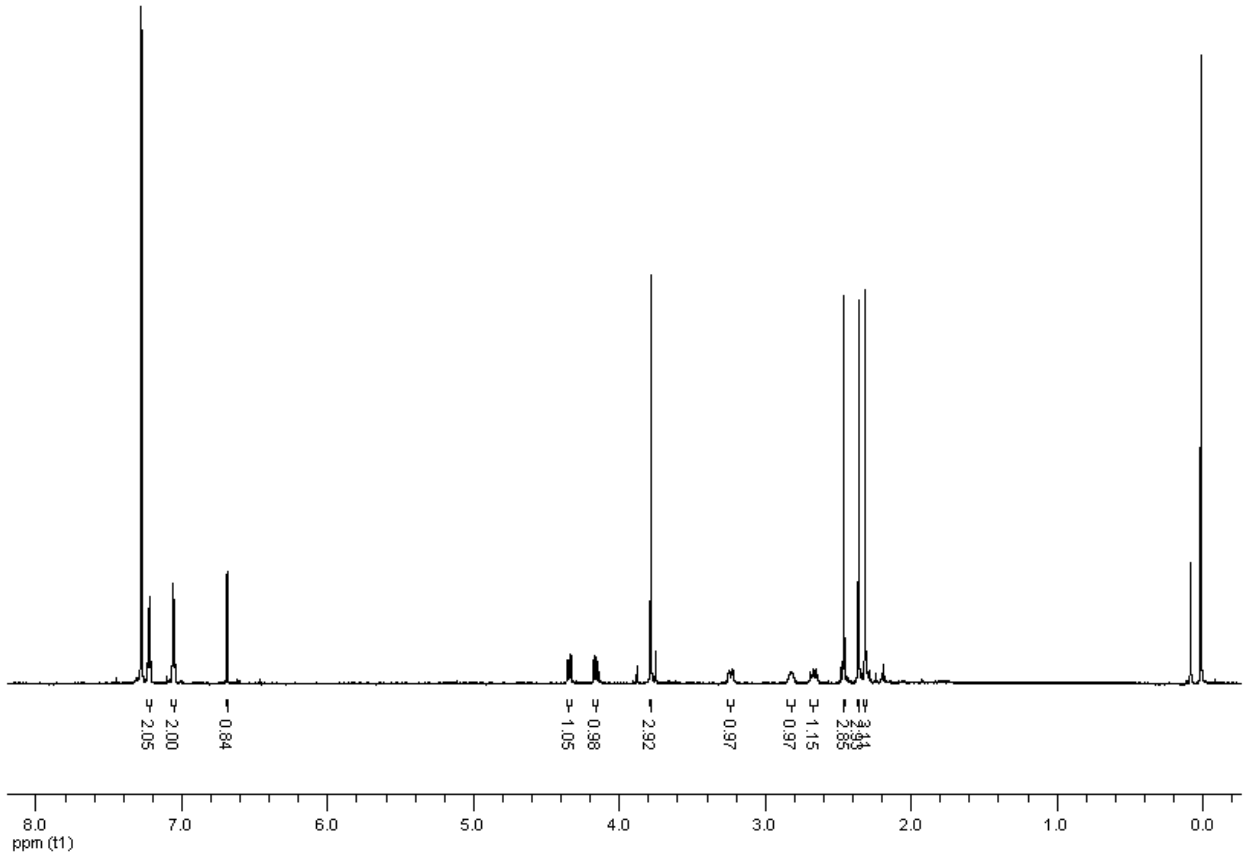
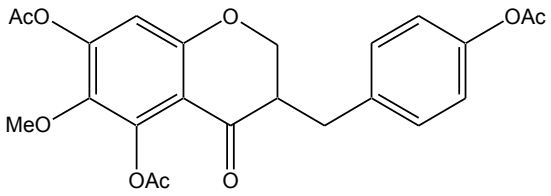


Plate 81b: ^{13}C NMR of 5,7,4'-Triacetoxy-6-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.153**)

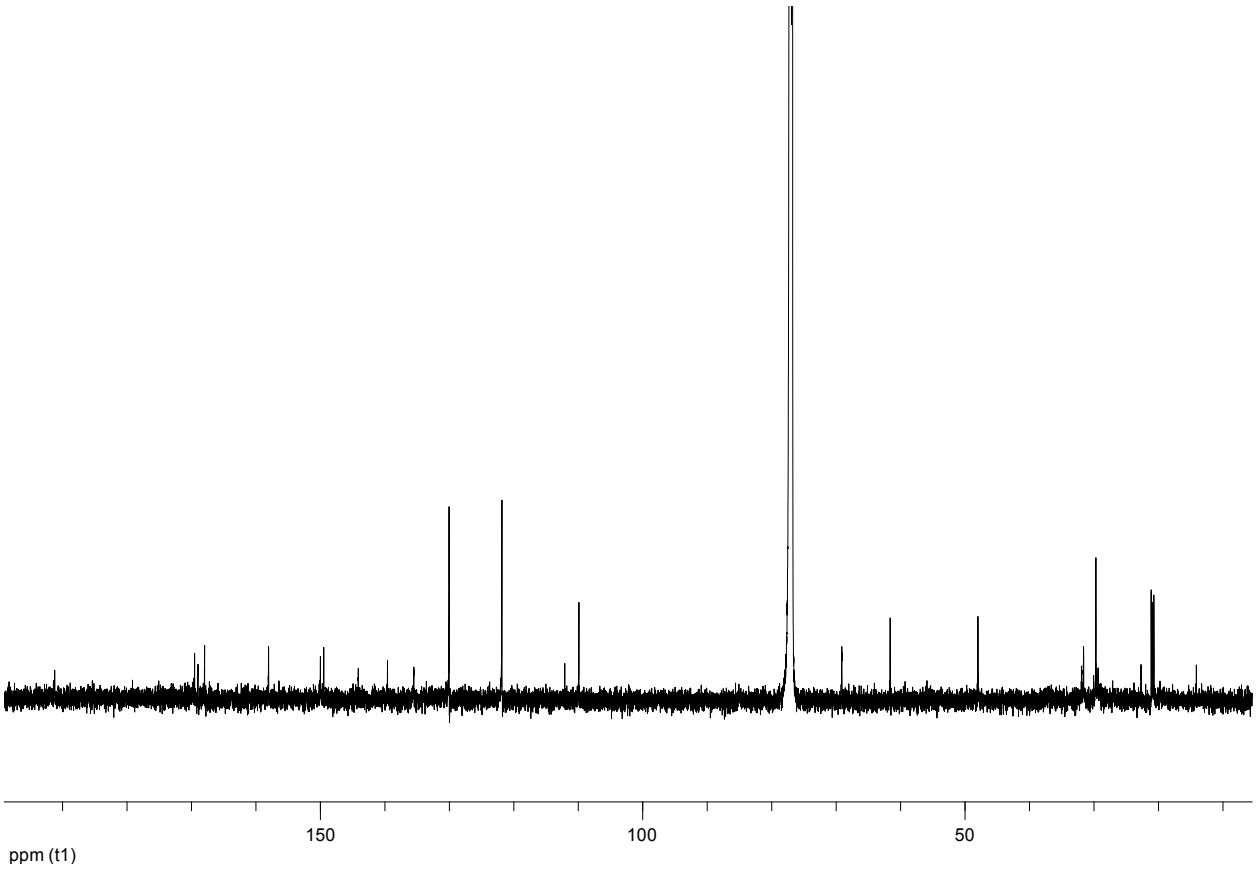
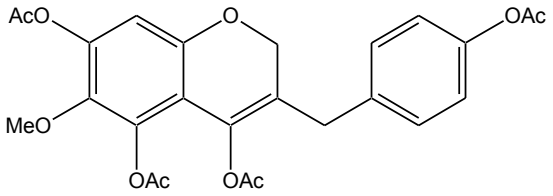
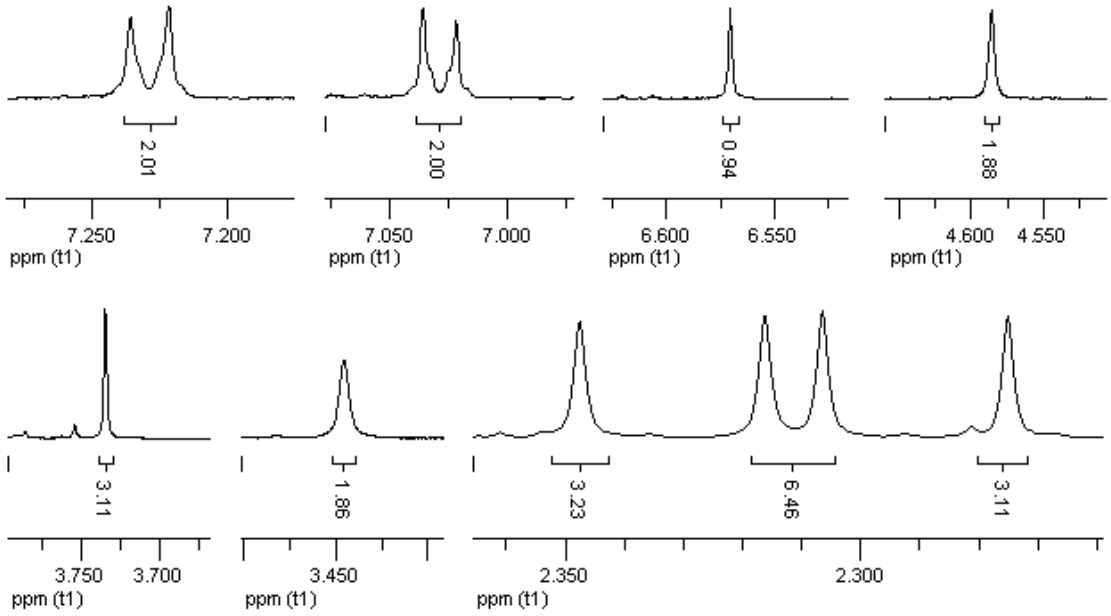


Plate 82a: ^{1}H NMR of 3-(4-Acetoxybenzyl)-4,5,7-triacetoxy-6-methoxyhomoisoflav-3-ene, $CDCl_3$ (298K)



(4.154)



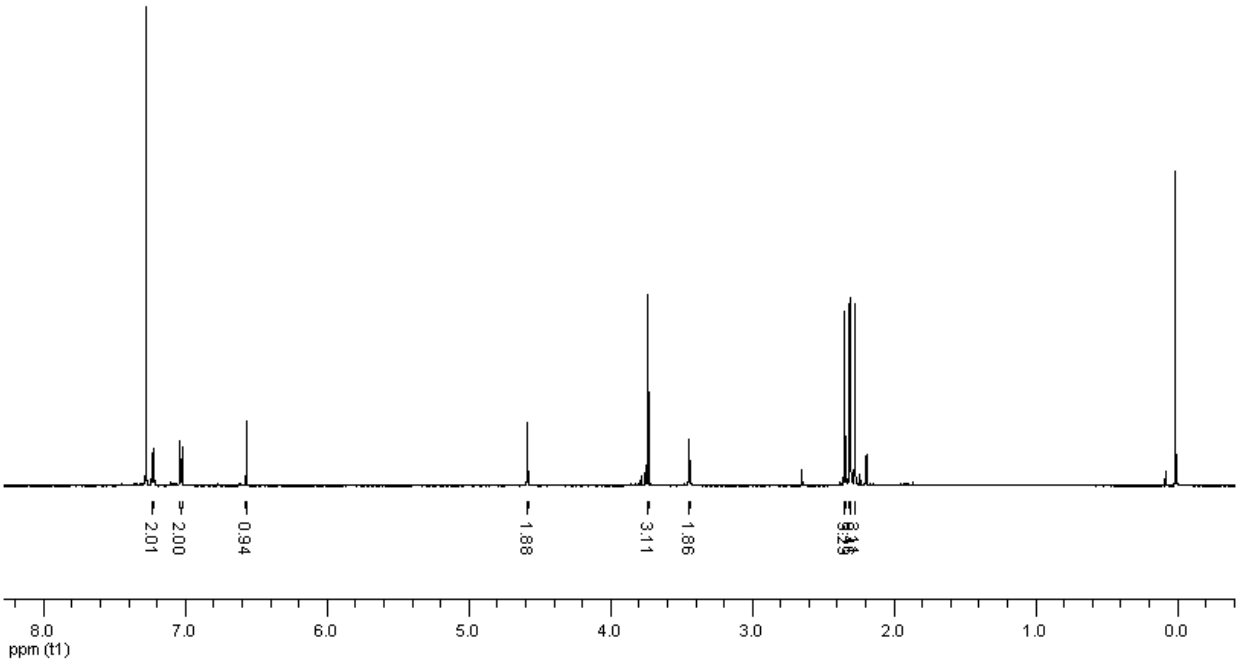
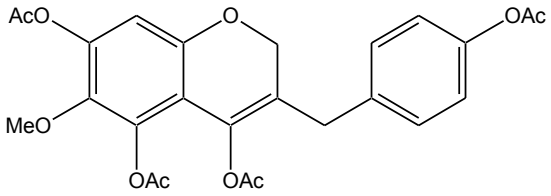


Plate 82b: ^{13}C NMR of 3-(4-Acetoxybenzyl)-4,5,7-triacetoxy-6-methoxyhomoisoflav-3-ene, $CDCl_3$ (298K)



(**4.154**)

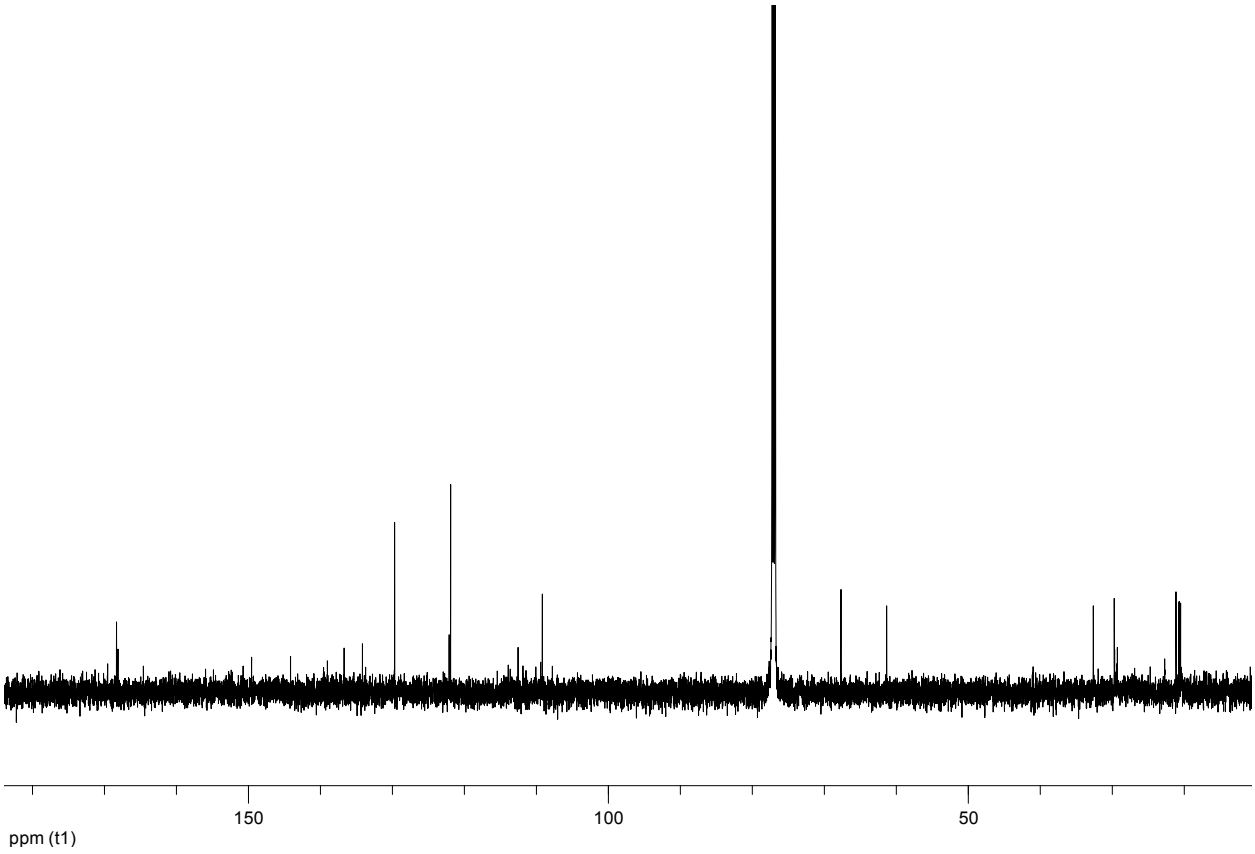
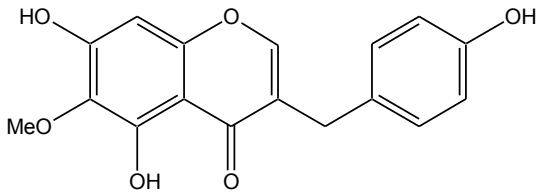


Plate 83a: ^{1}H NMR of 5,7,4',-Trihydroxy-6-methoxyhomoisoflavone, acetone (298K)



(**4.155**)

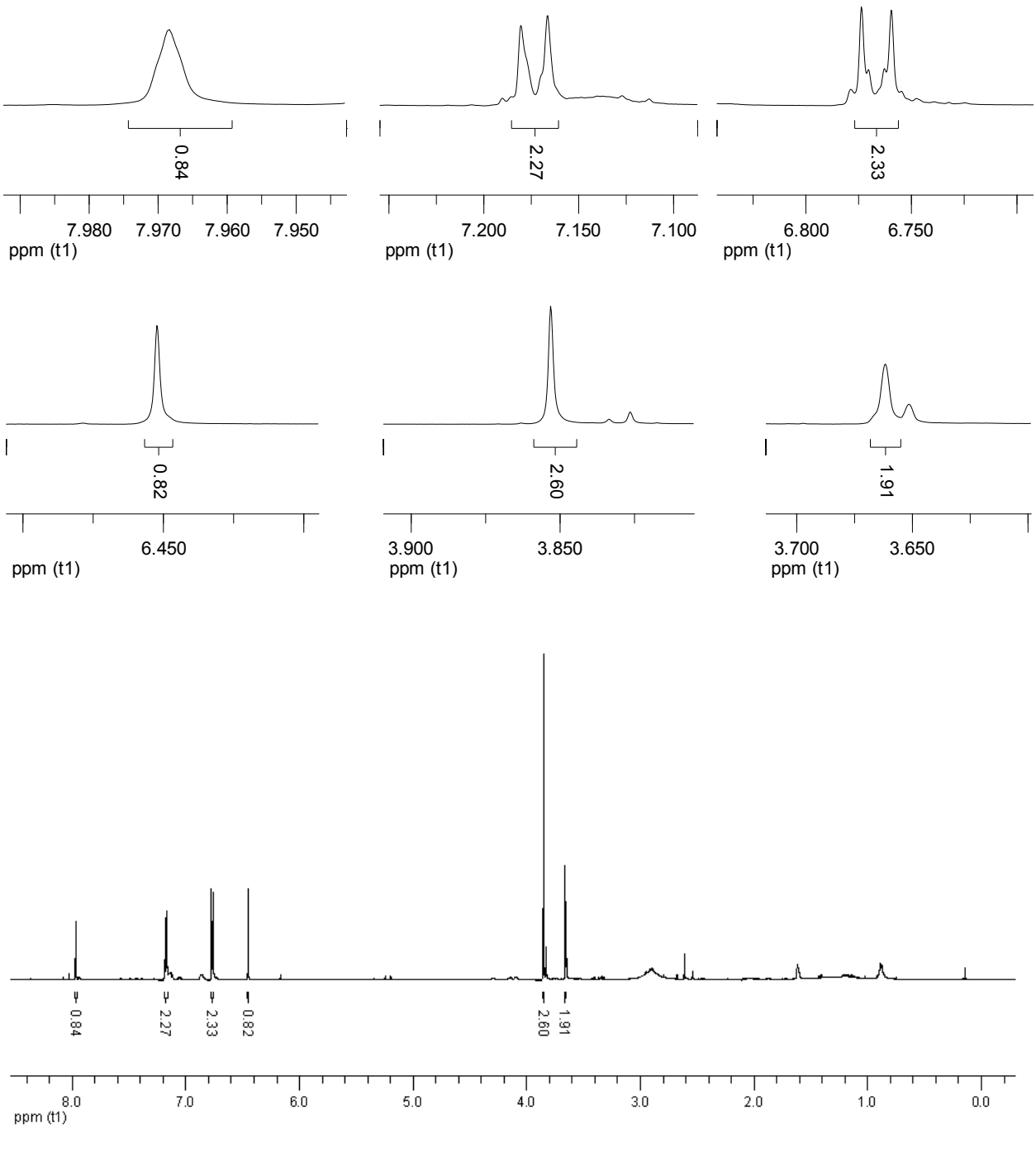
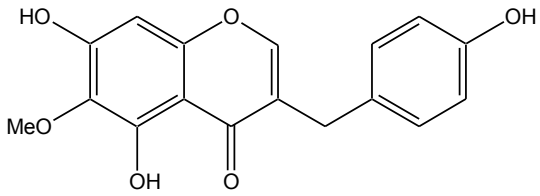


Plate 83b: ^{13}C NMR of 5,7,4',-Trihydroxy-6-methoxyhomoisoflavone, acetone (298K)



(**4.155**)

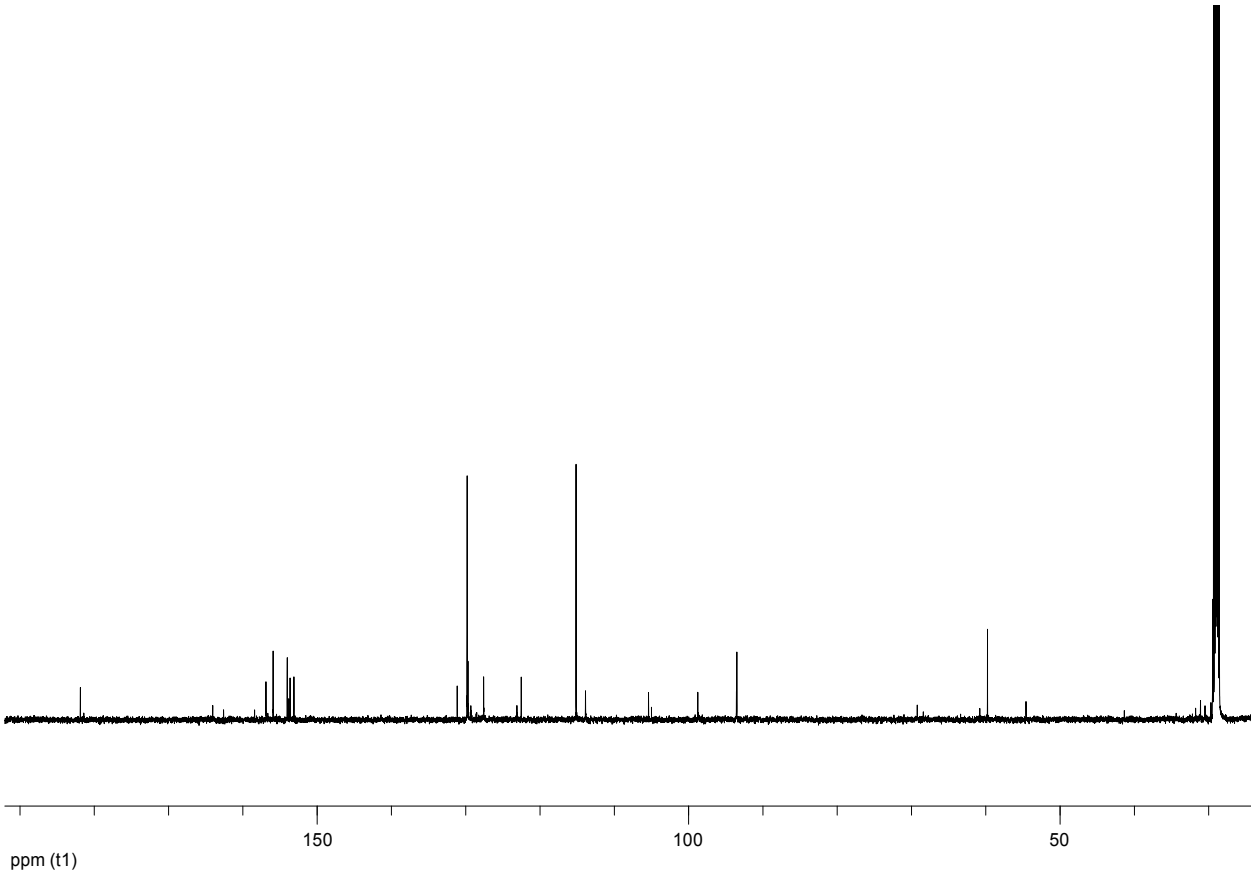
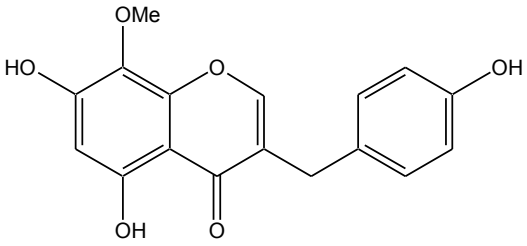
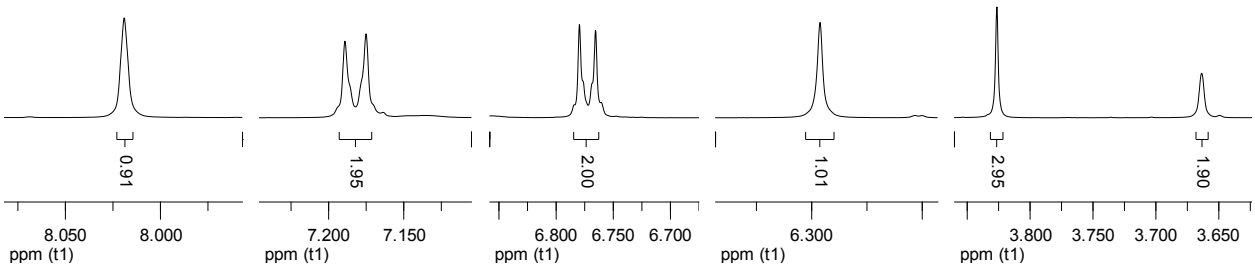


Plate 84a: ^{1}H NMR of 5,7,4'-Trihydroxy-8-methoxyhomoisoflavone, acetone (298K)



(**4.156**)



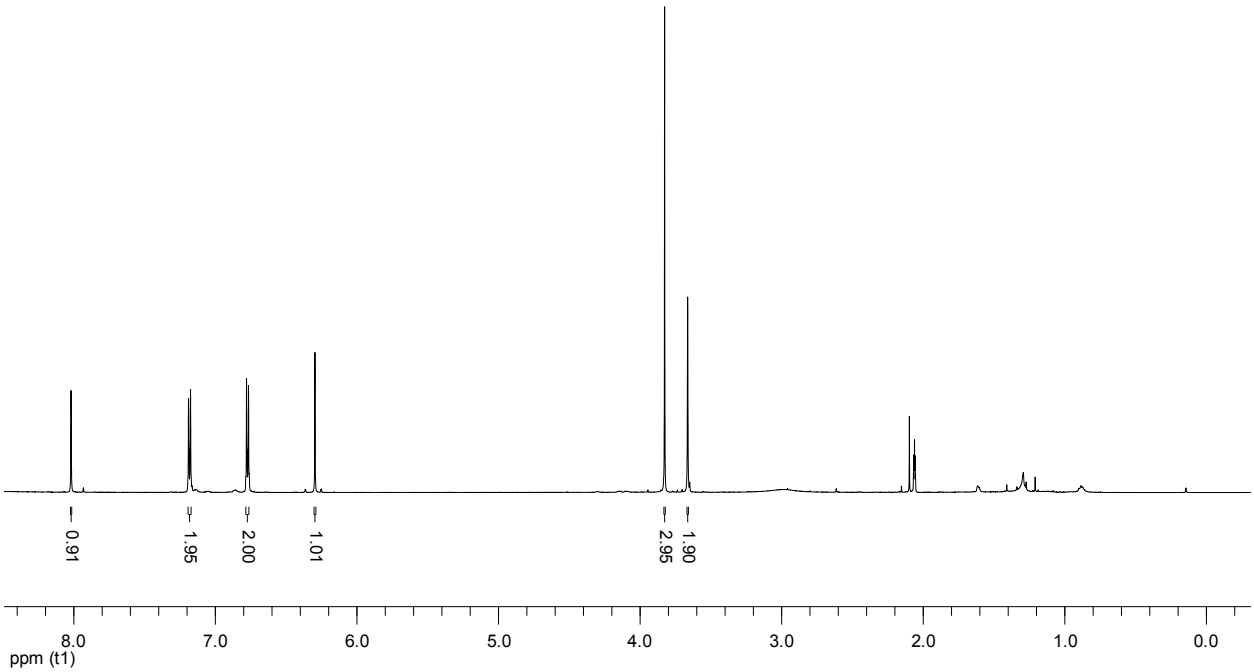
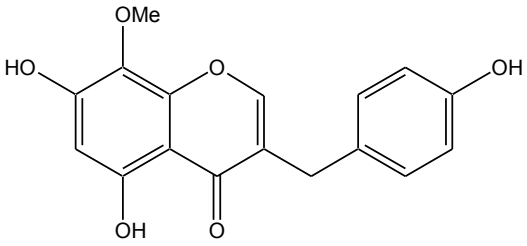


Plate 84b: ^{13}C NMR of 5,7,4'-Trihydroxy-8-methoxyhomoisoflavone, acetone (298K)



(**4.156**)

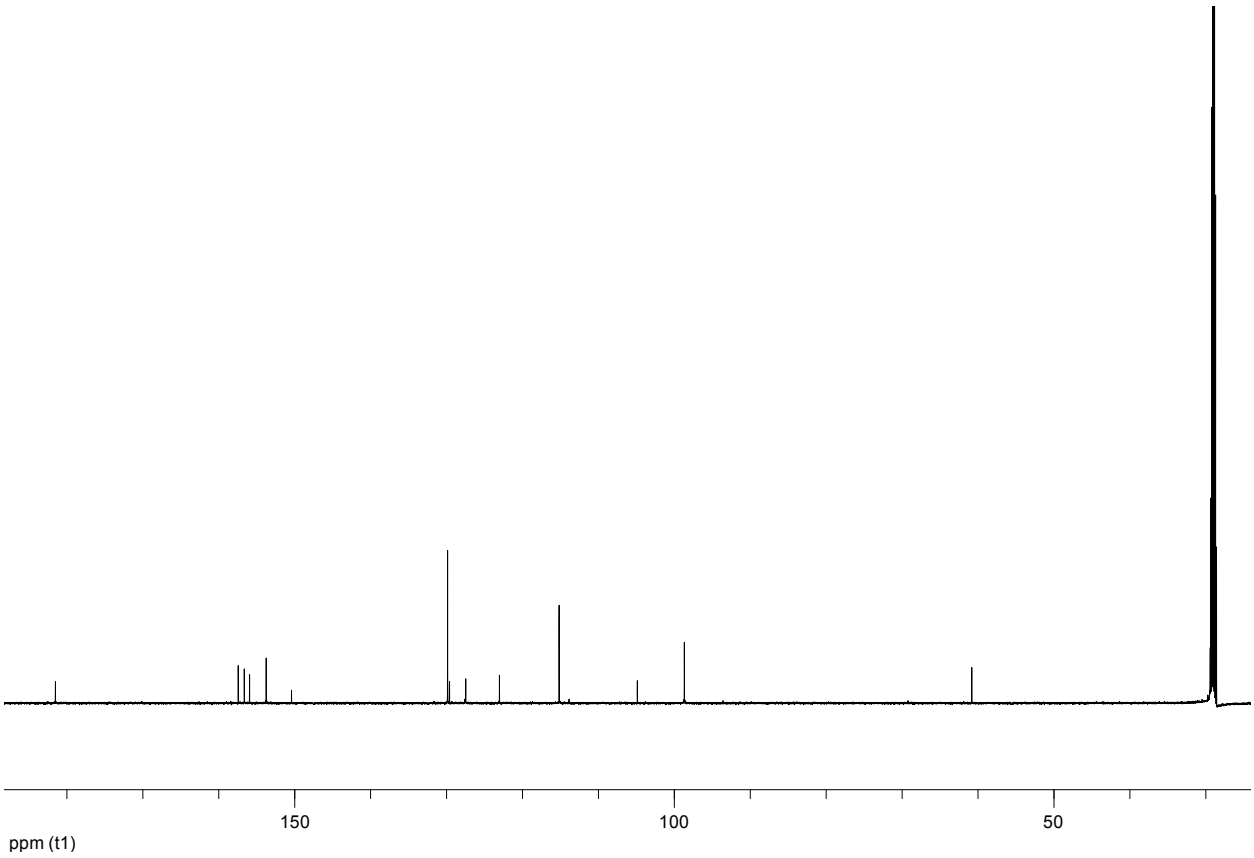
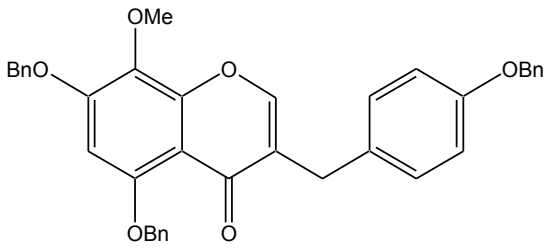
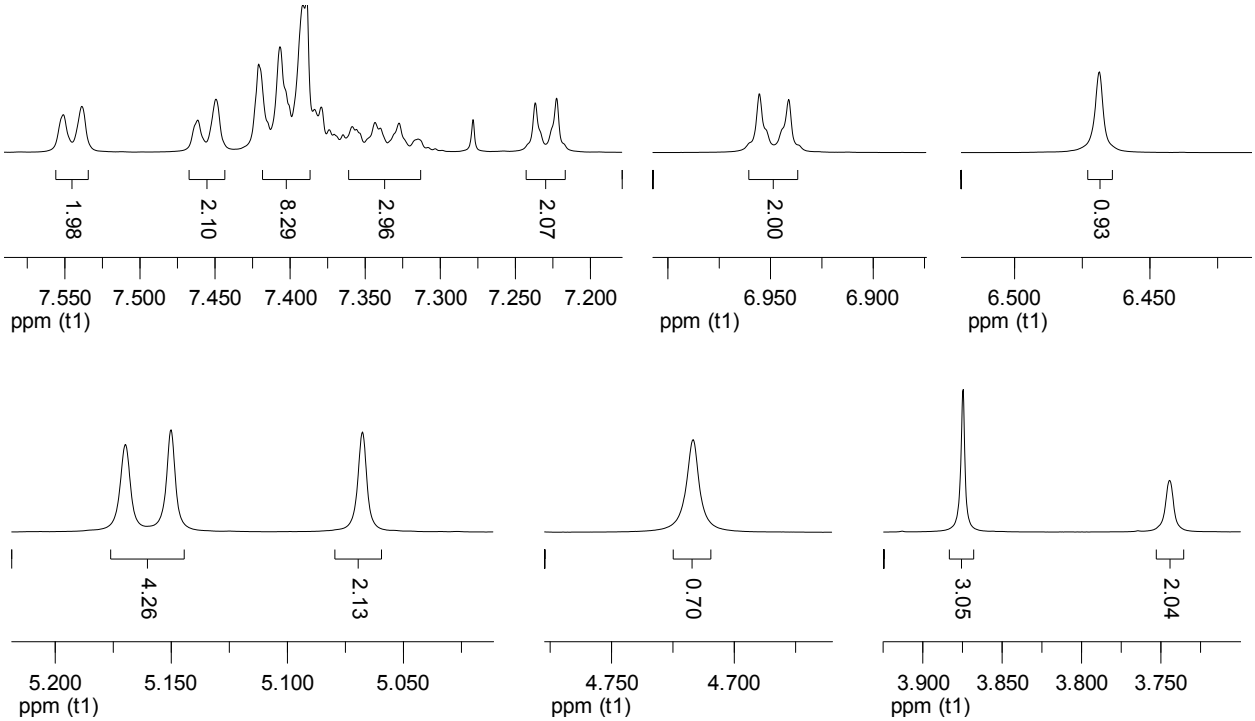


Plate 85a: ^{1}H NMR of 5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.157**)



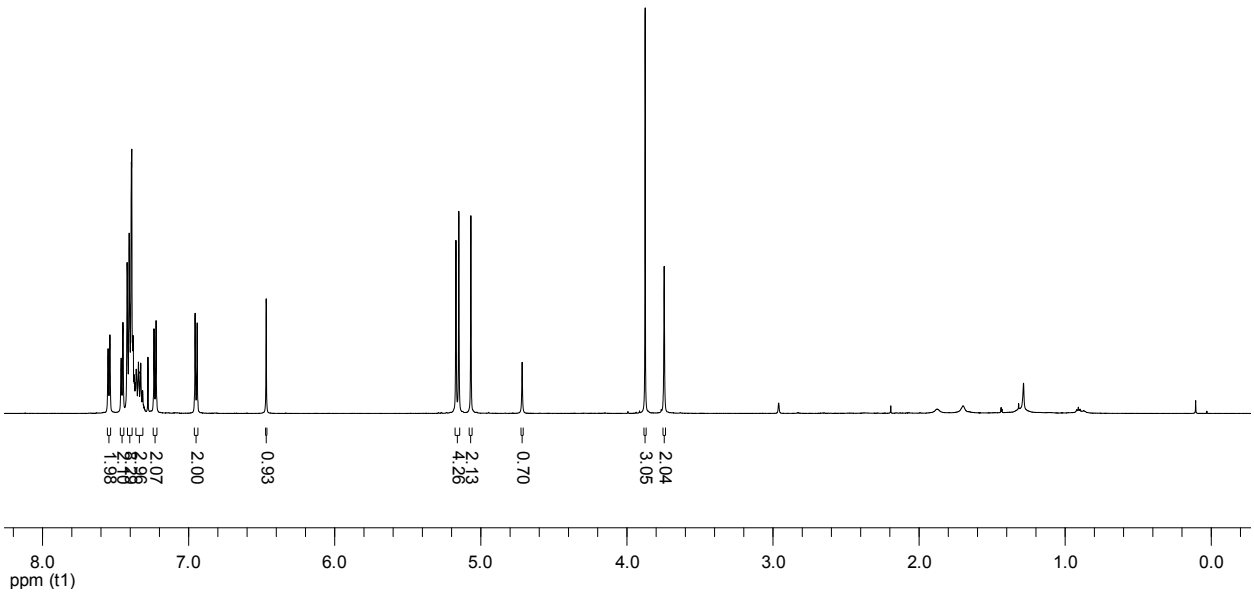
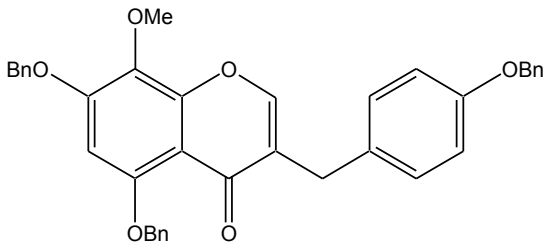


Plate 85b: ^{13}C NMR of 5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavone, $CDCl_3$ (298K)



(**4.157**)

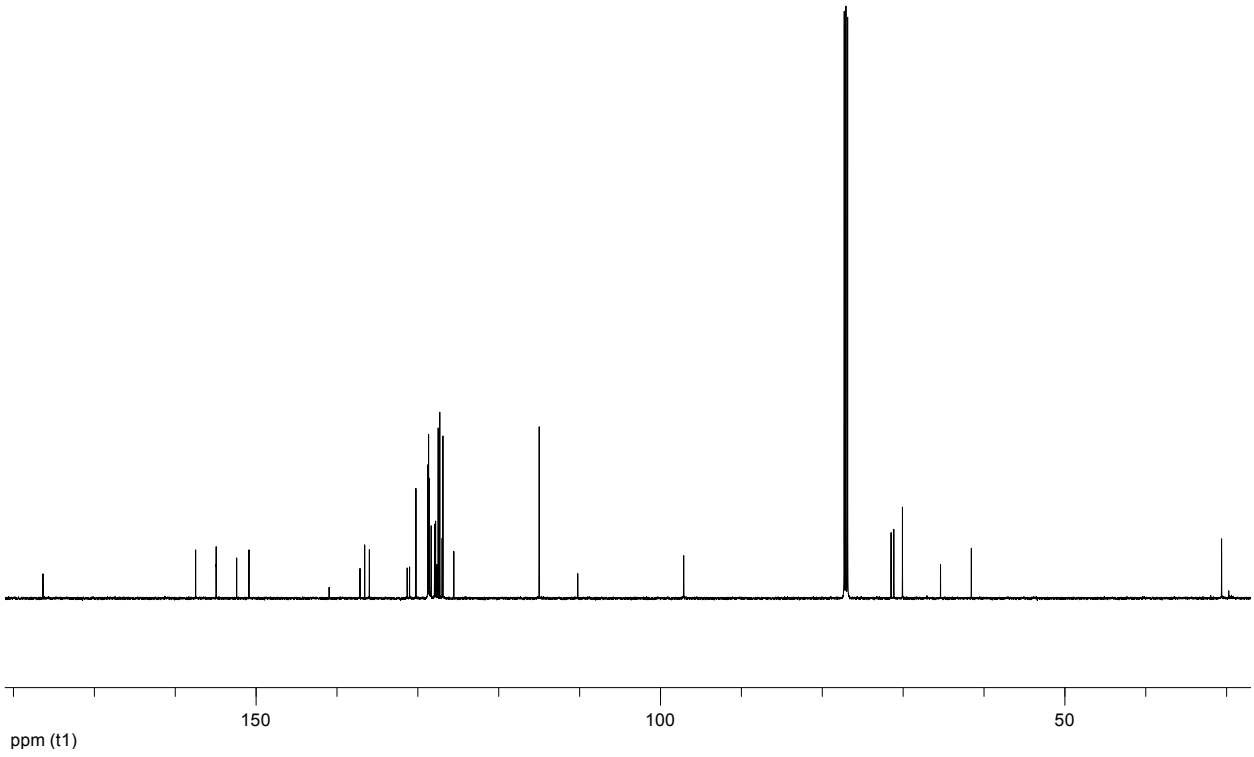
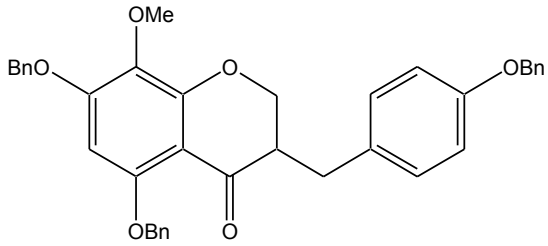
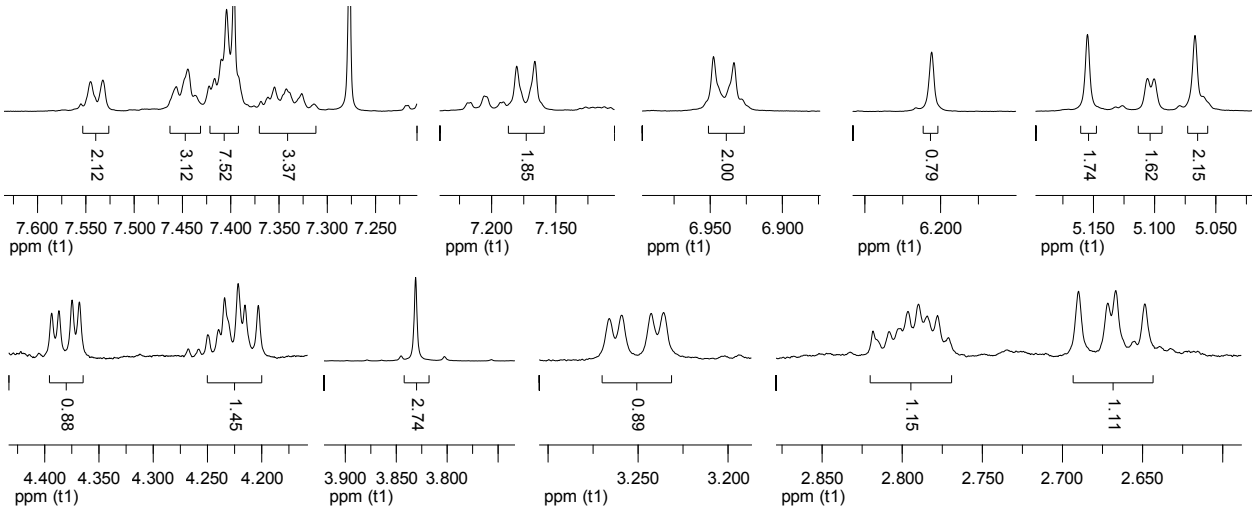


Plate 86a: ^{1}H NMR of 5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.158**)



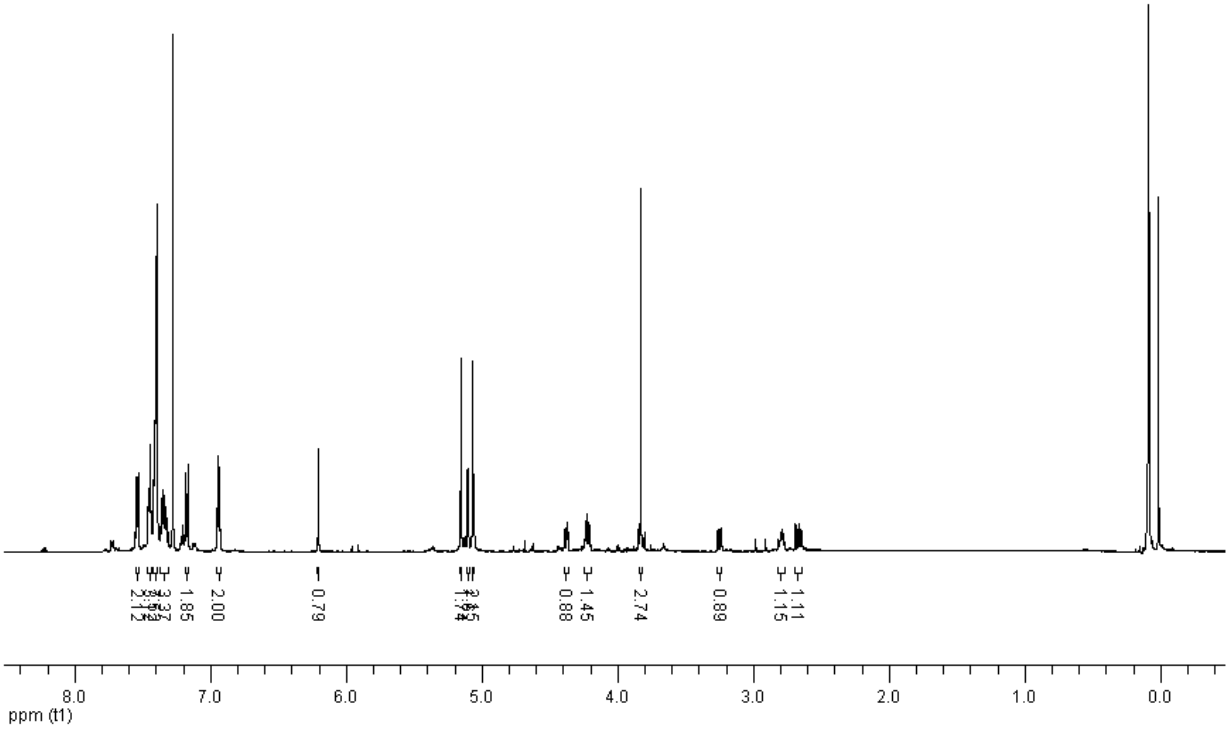
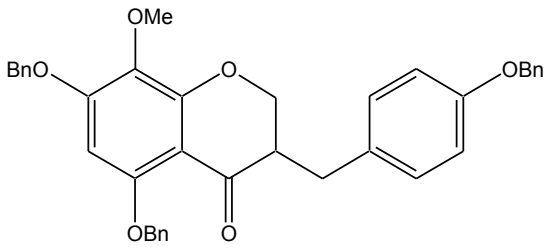


Plate 86b: ^{13}C NMR of 5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.158**)

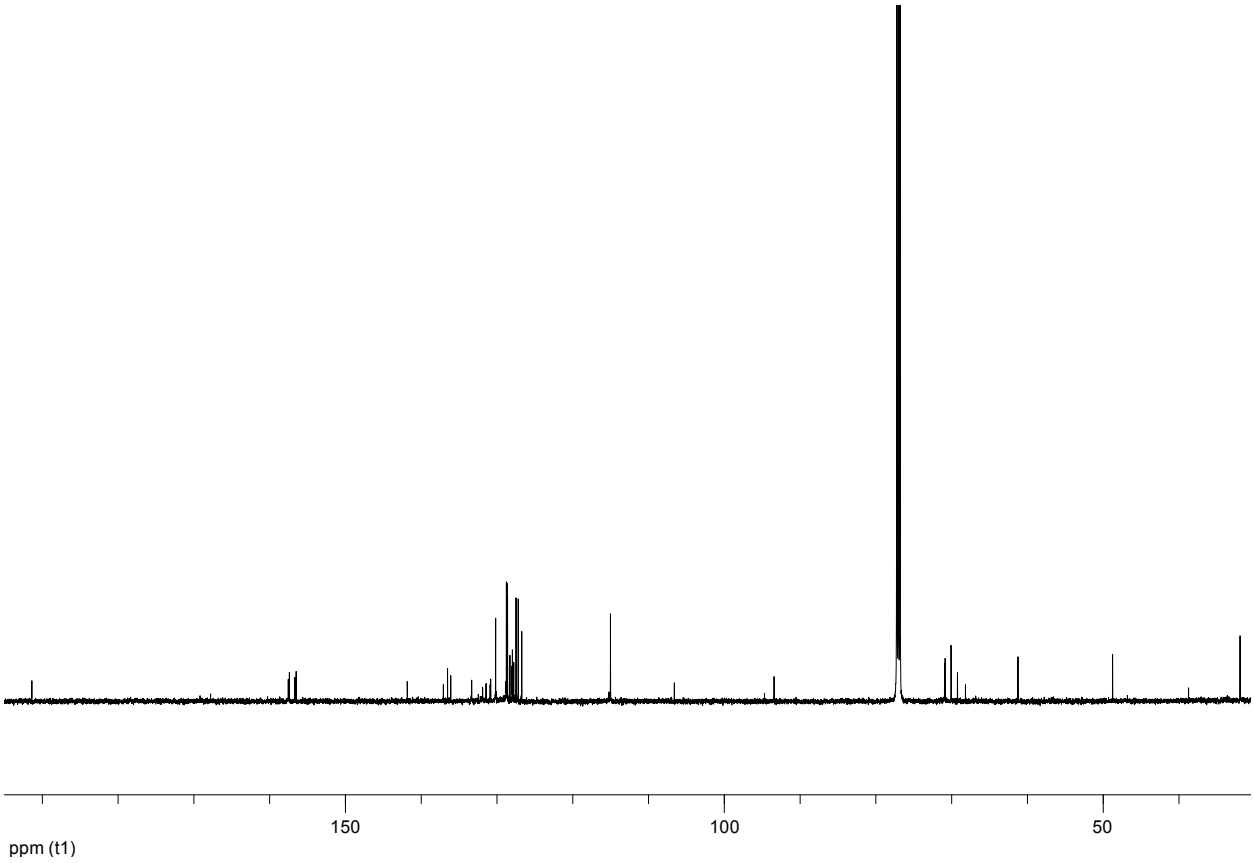
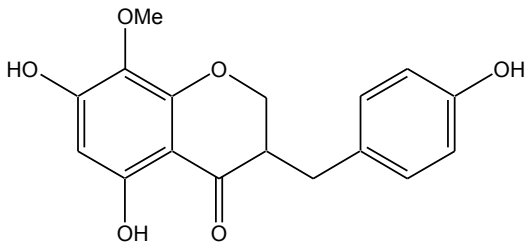
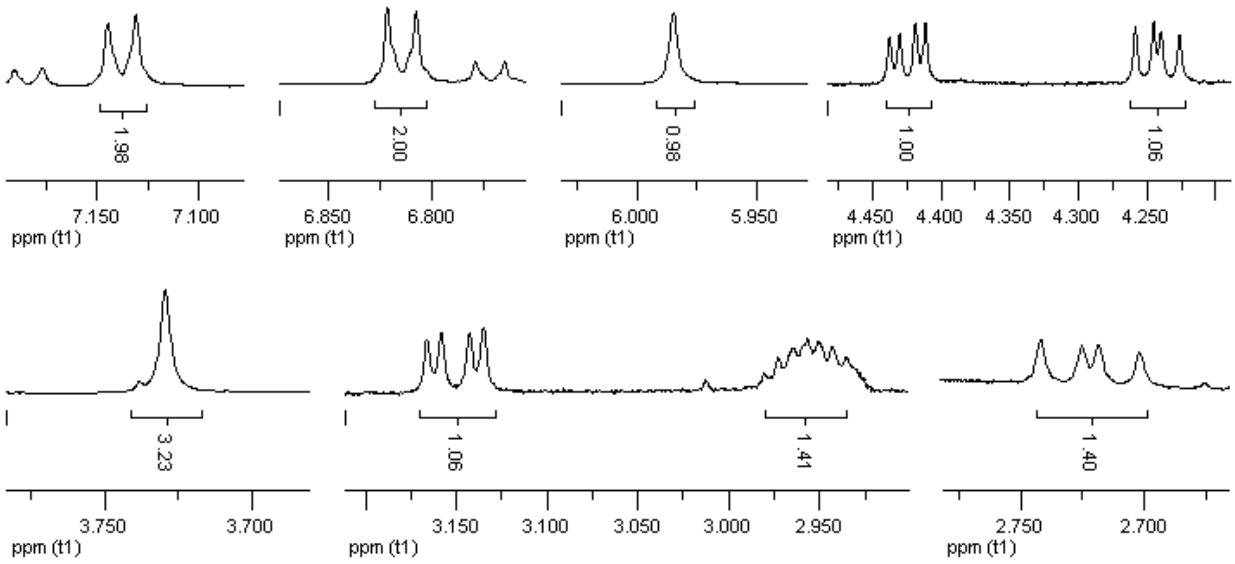


Plate 87a: ^{1}H NMR of 5,7,4'-Trihydroxy-8-methoxyhomoisoflavanone, acetone (298K)



(**4.159**)



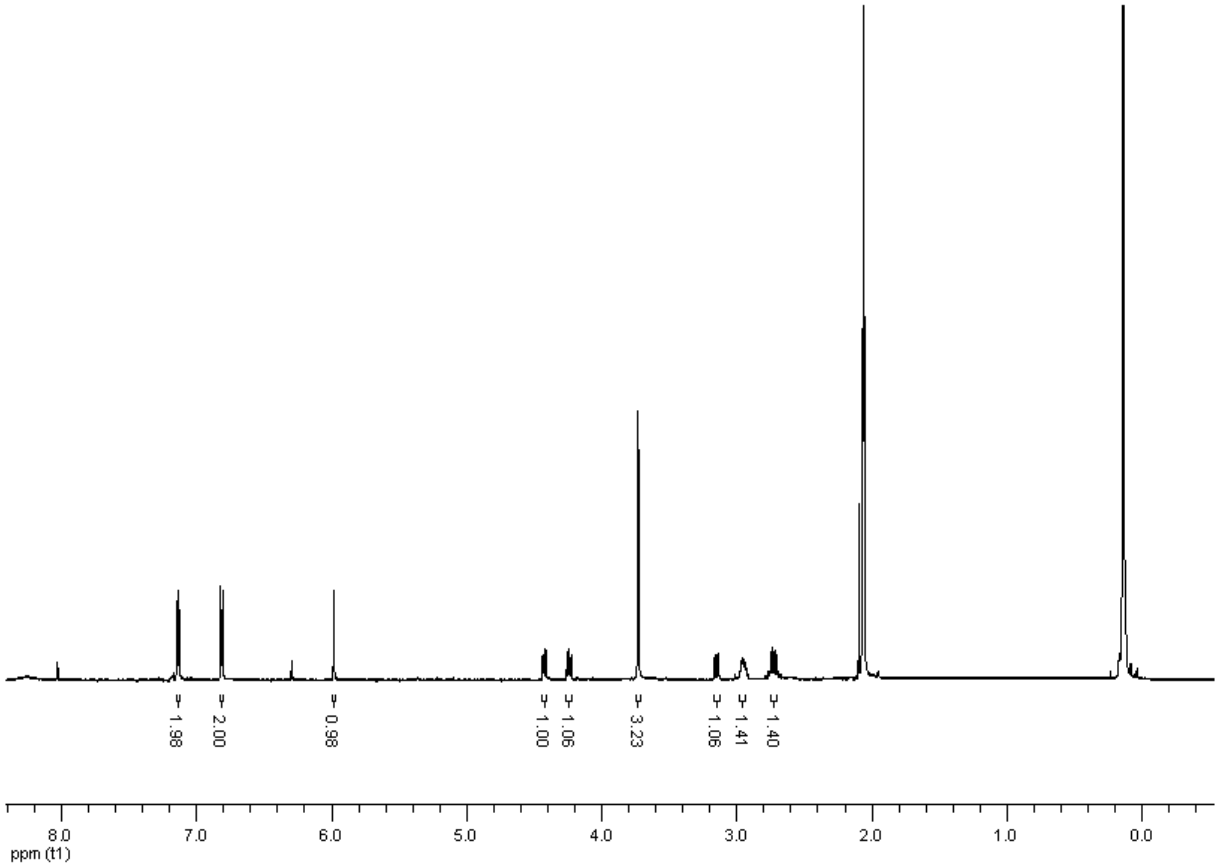
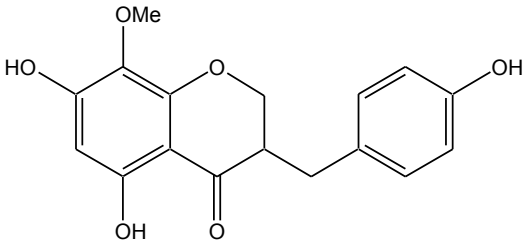


Plate 87b: ^{13}C NMR of 5,7,4'-Trihydroxy-8-methoxyhomoisoflavanone, acetone (298K)



(**4.159**)

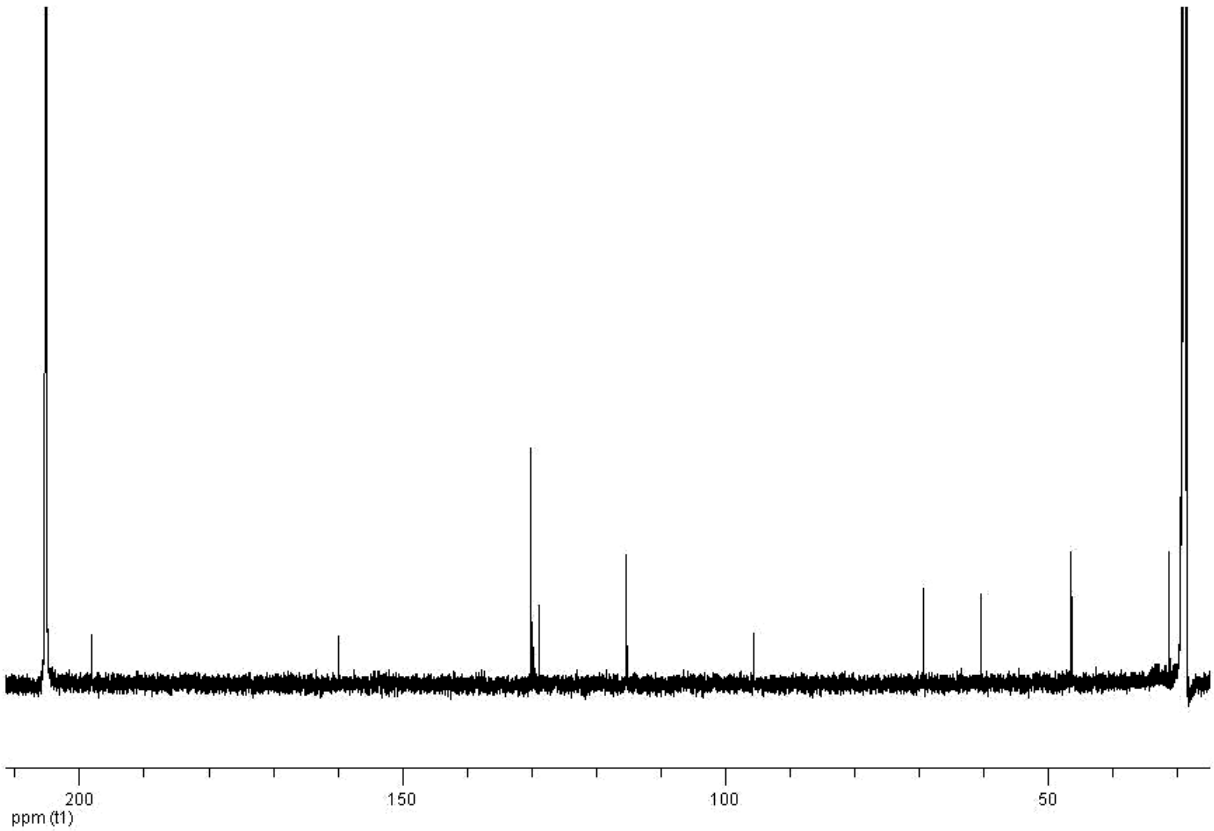
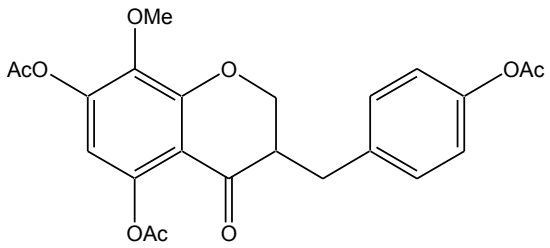
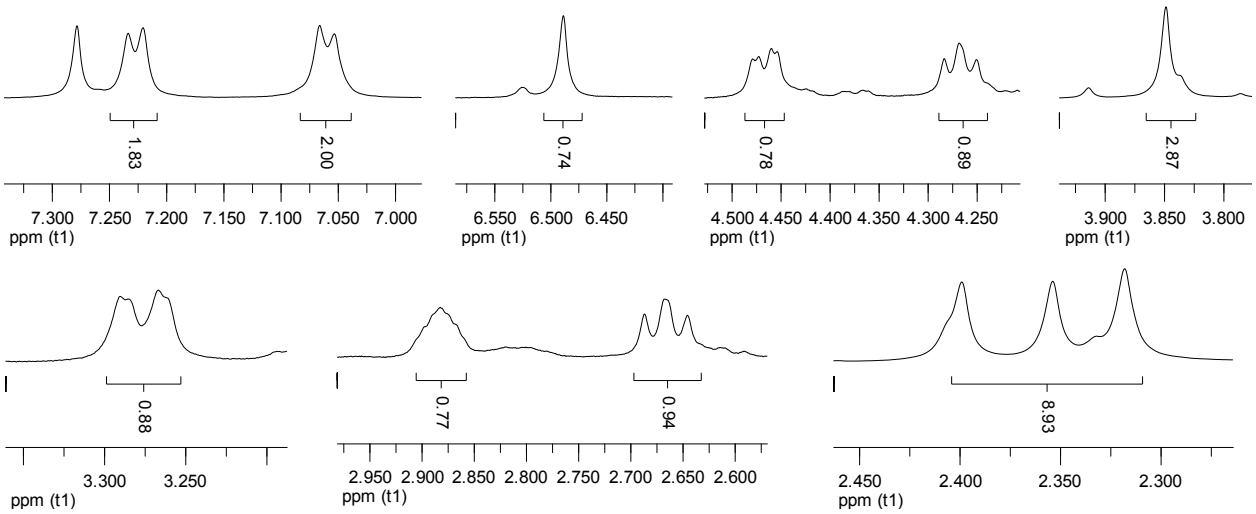


Plate 88a: ^{1}H NMR of 5,7,4'-Triacetoxy-8-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.160**)



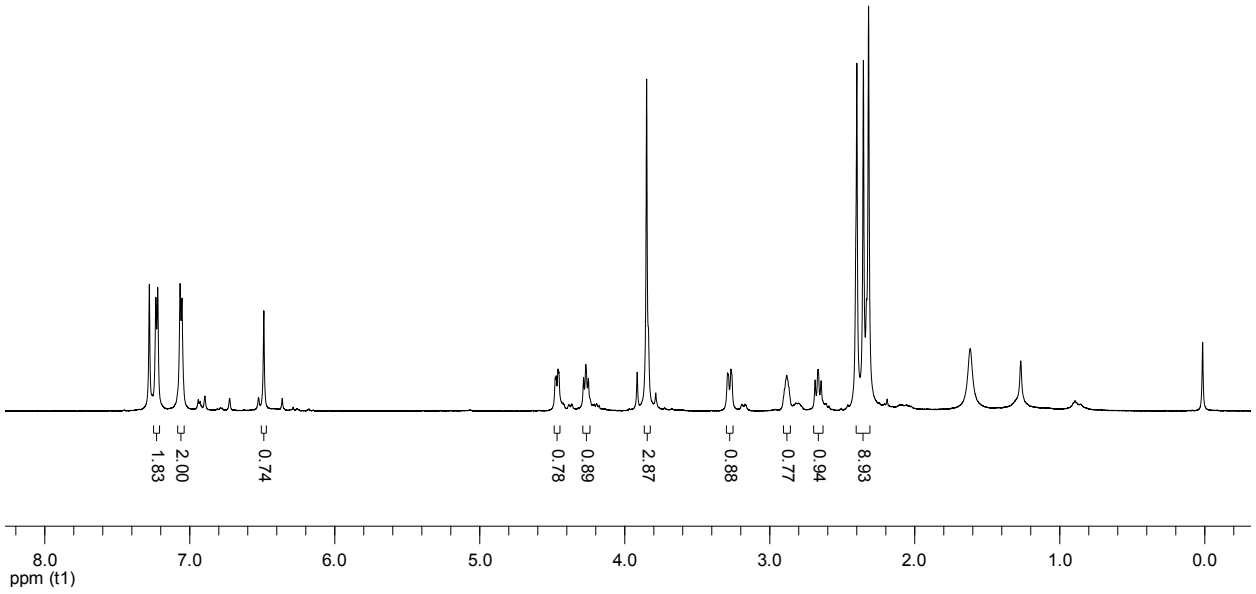
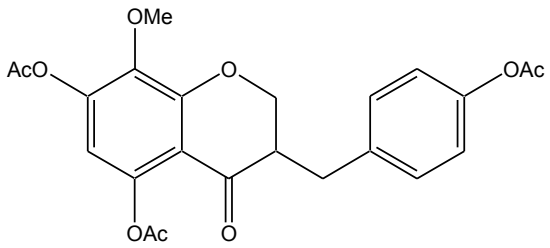


Plate 88b: ^{13}C NMR of 5,7,4'-Triacetoxy-8-methoxyhomoisoflavanone, $CDCl_3$ (298K)



(**4.160**)

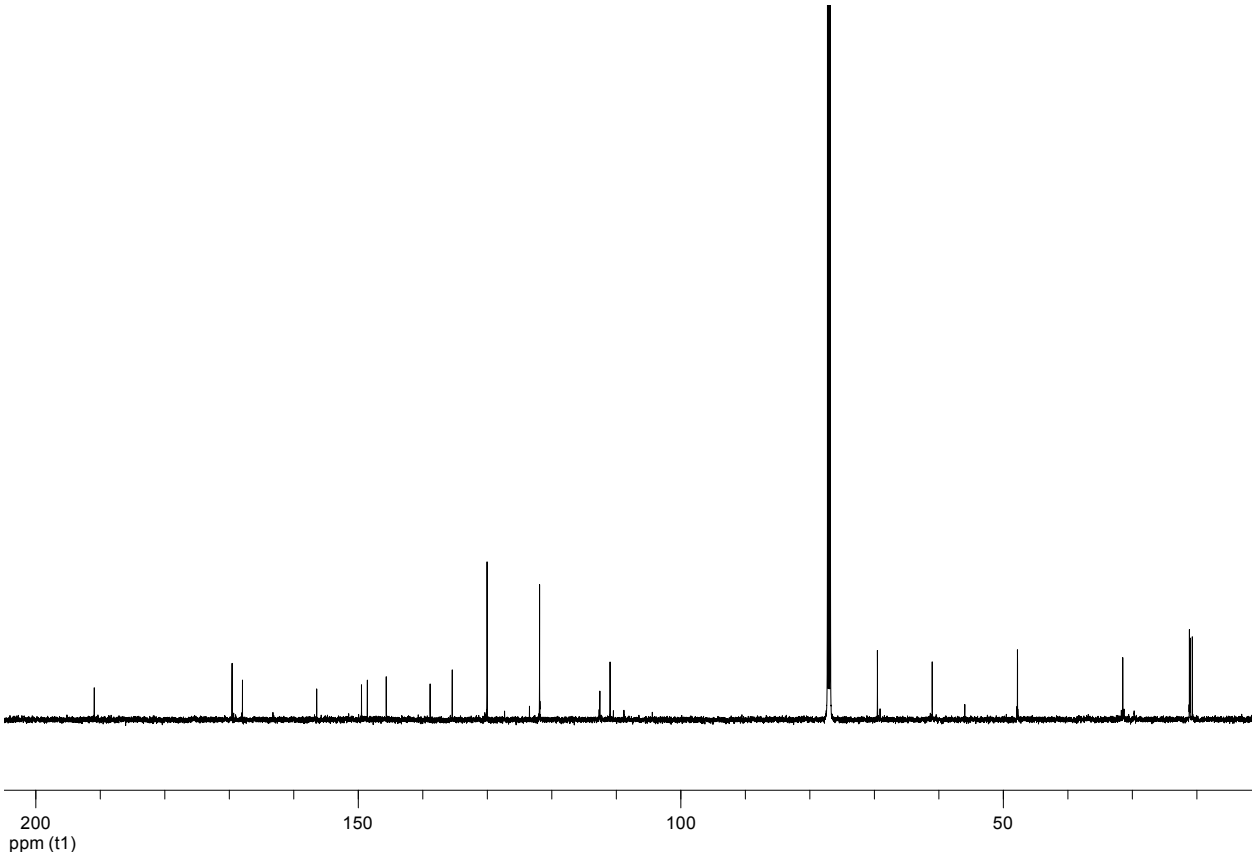
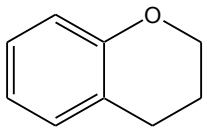


Plate 89a: ^{1}H NMR of 3,4-Dihydro-2*H*-chromen, $CDCl_3$ (298K)



(**5.2**)

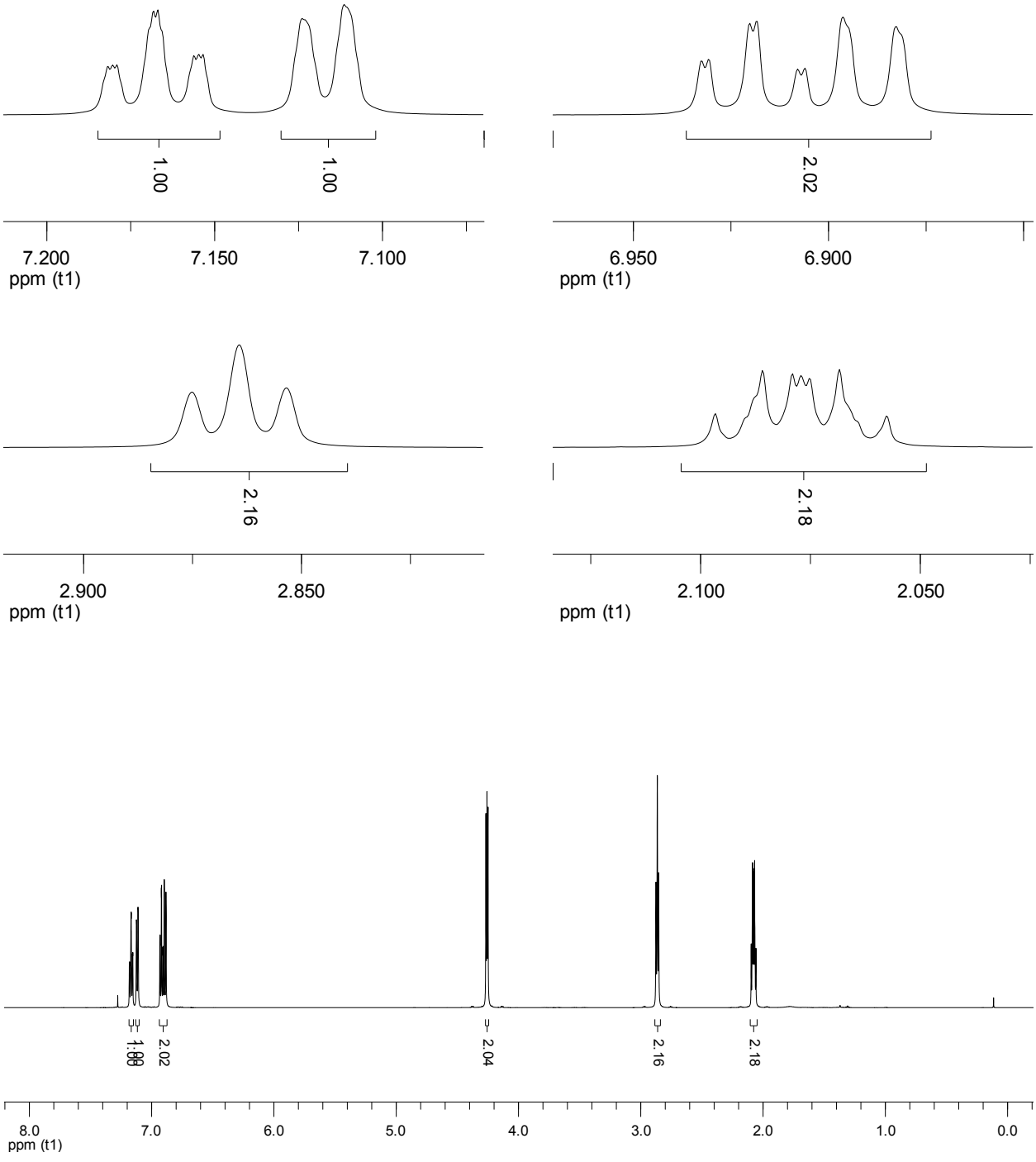
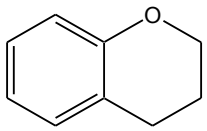


Plate 89b: ^{13}C NMR of 3,4-Dihydro-2*H*-chromen, $CDCl_3$ (298K)



(**5.2**)

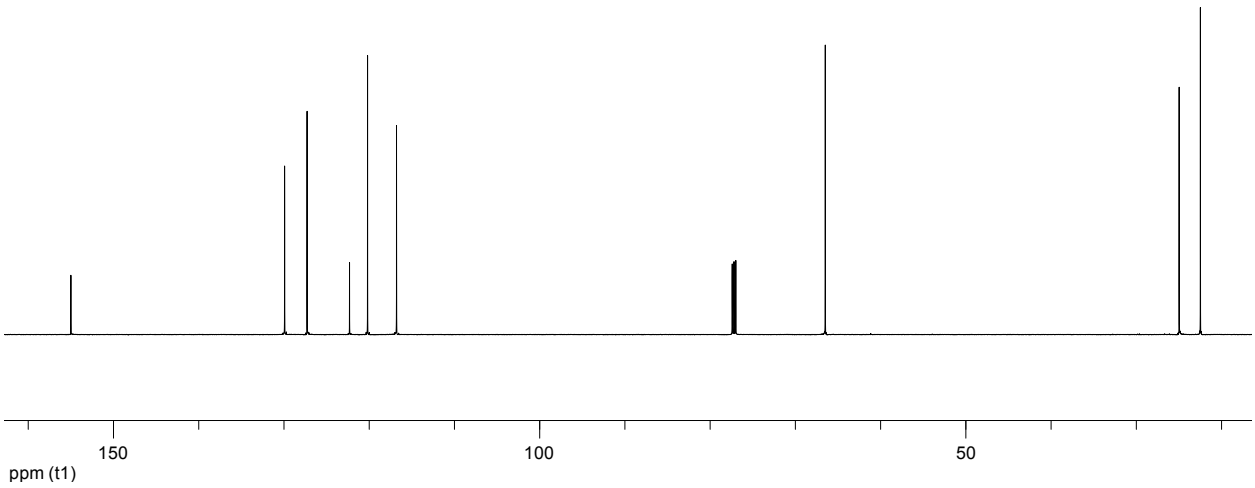
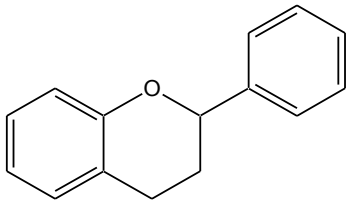


Plate 90a: ^{1}H NMR of 2-Phenylchromane, $CDCl_3$ (298K)



(**5.3**)

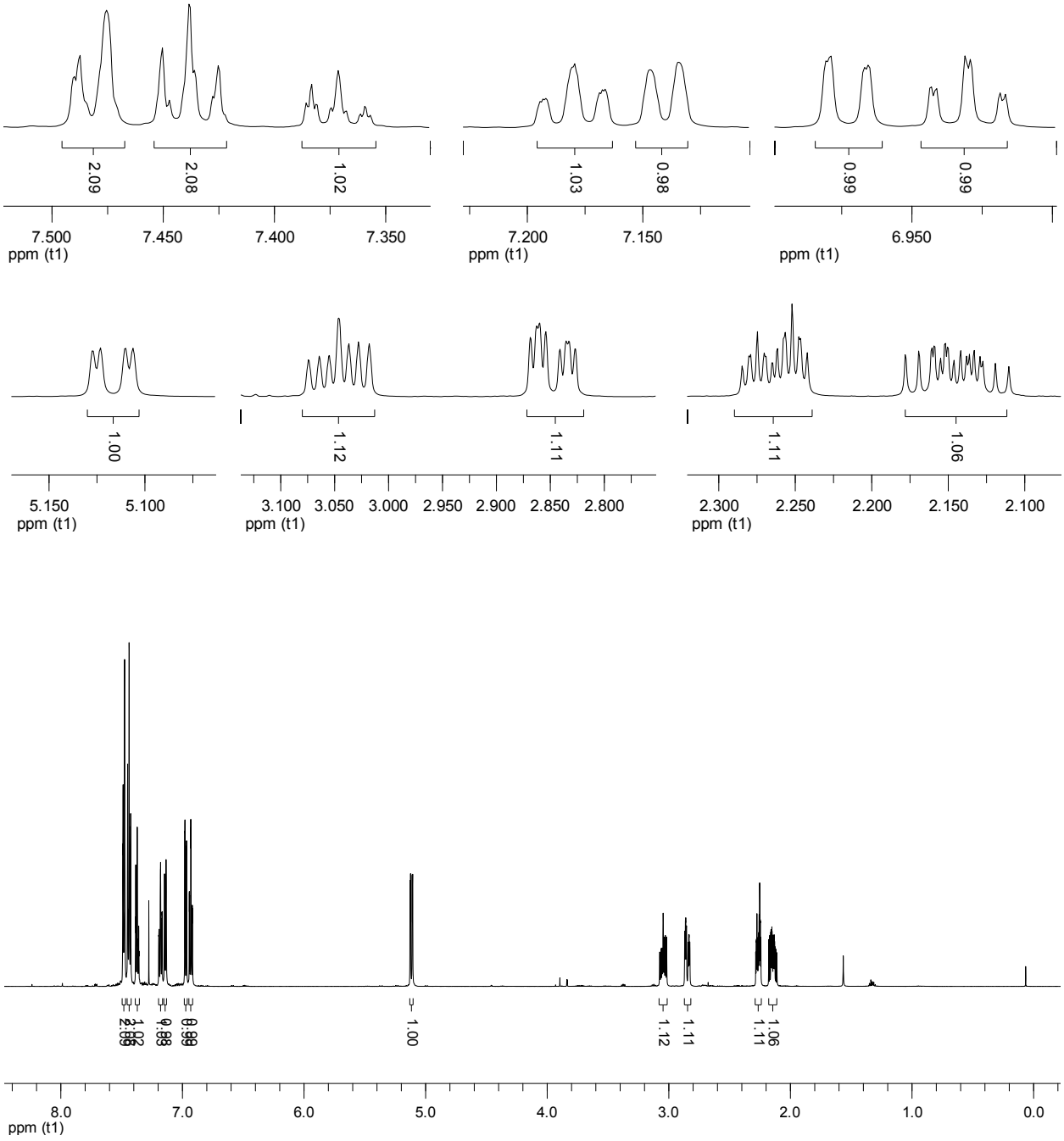
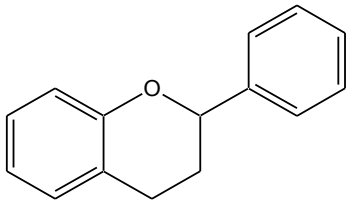


Plate 90b: ^{13}C NMR of 2-Phenylchromane, $CDCl_3$ (298K)



(**5.3**)

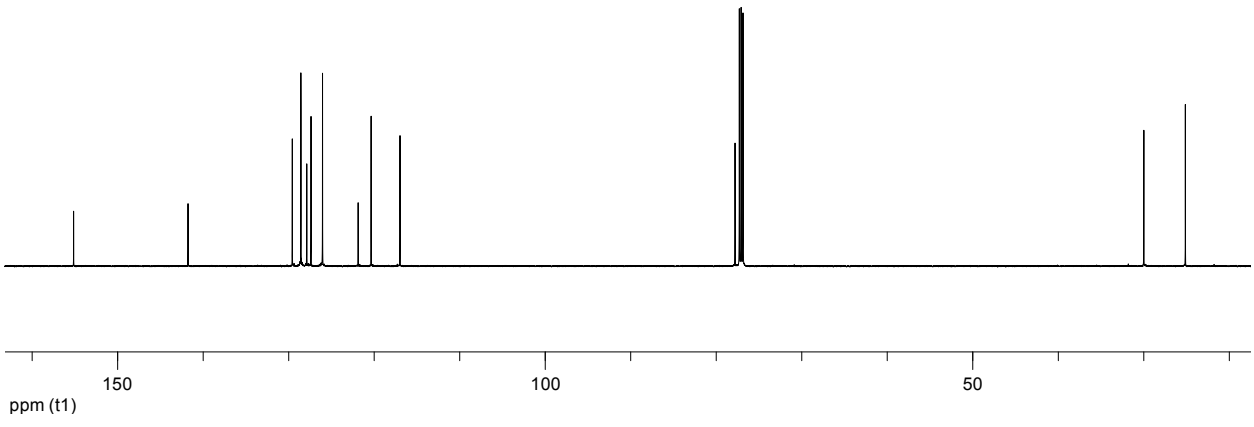
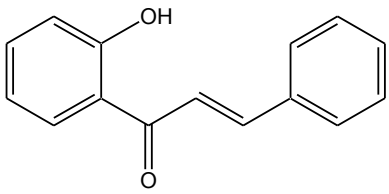
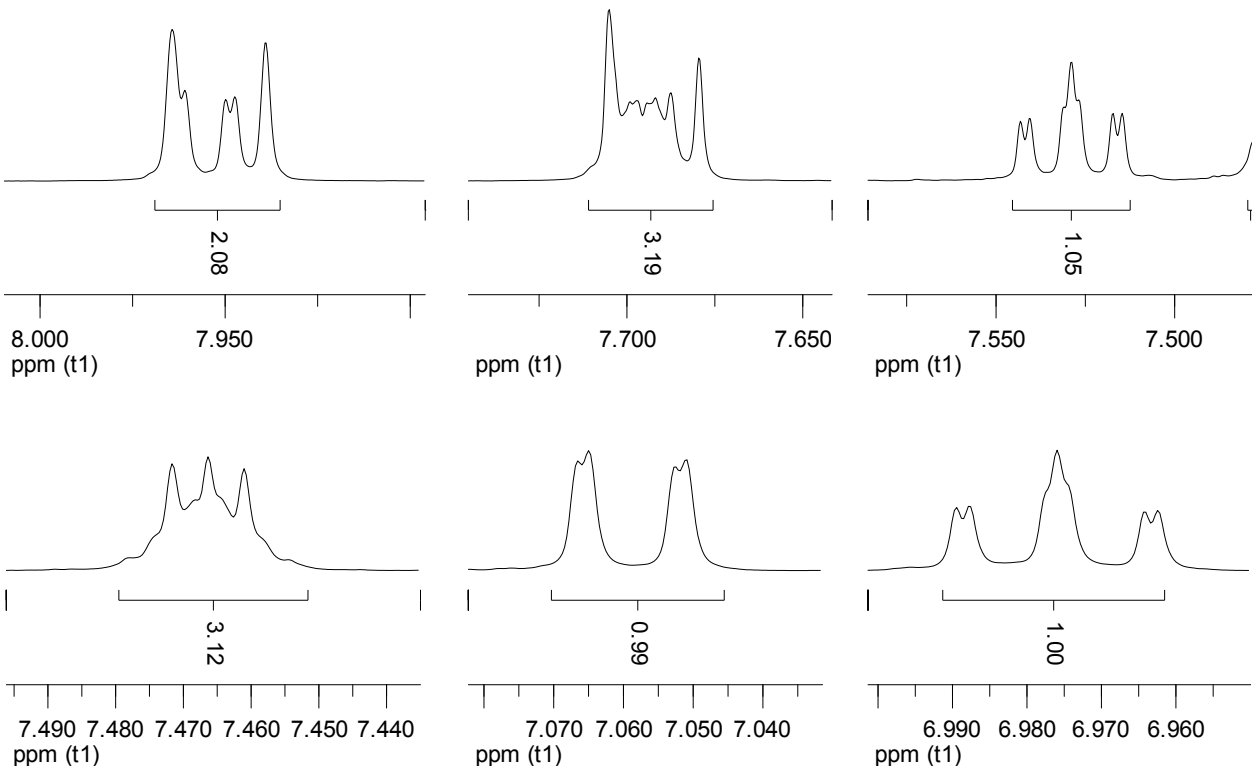


Plate 91a: ^{1}H NMR of 2$^{'}$-Hydroxychalcone, $CDCl_3$ (298K)



(**5.74**)



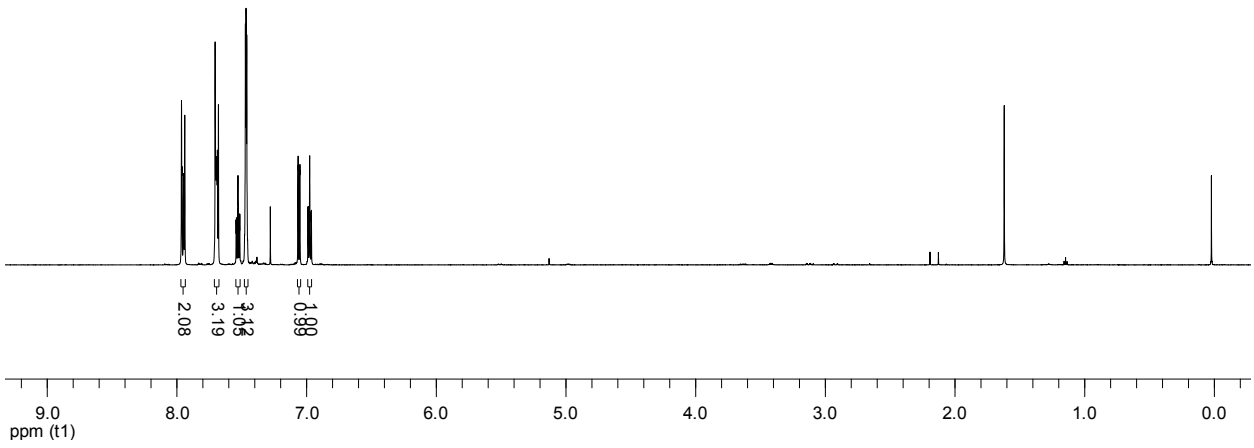
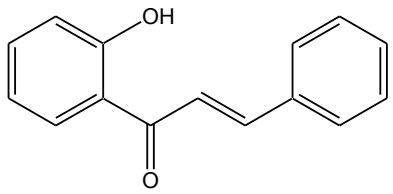


Plate 91b: ^{13}C NMR of 2'-Hydroxychalcone, $CDCl_3$ (298K)



(**5.74**)

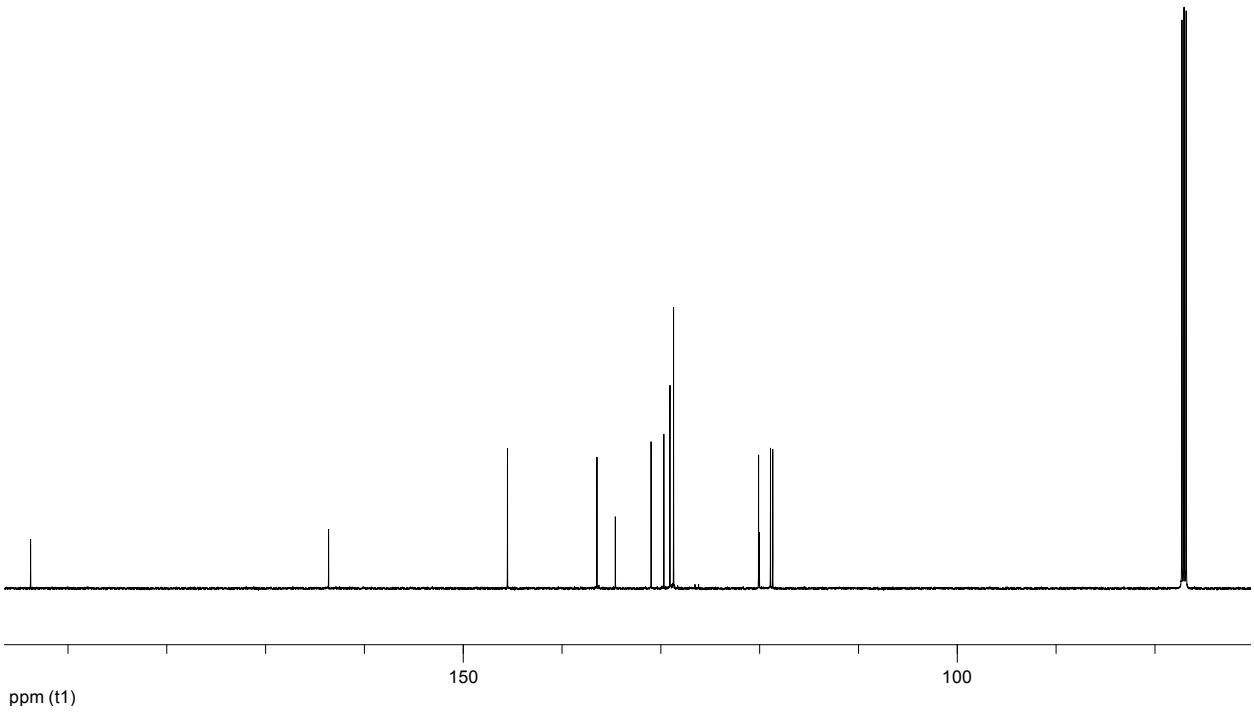
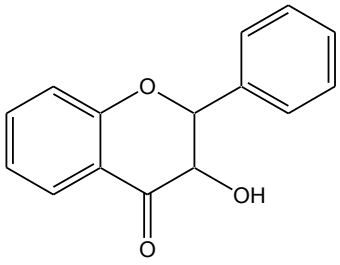
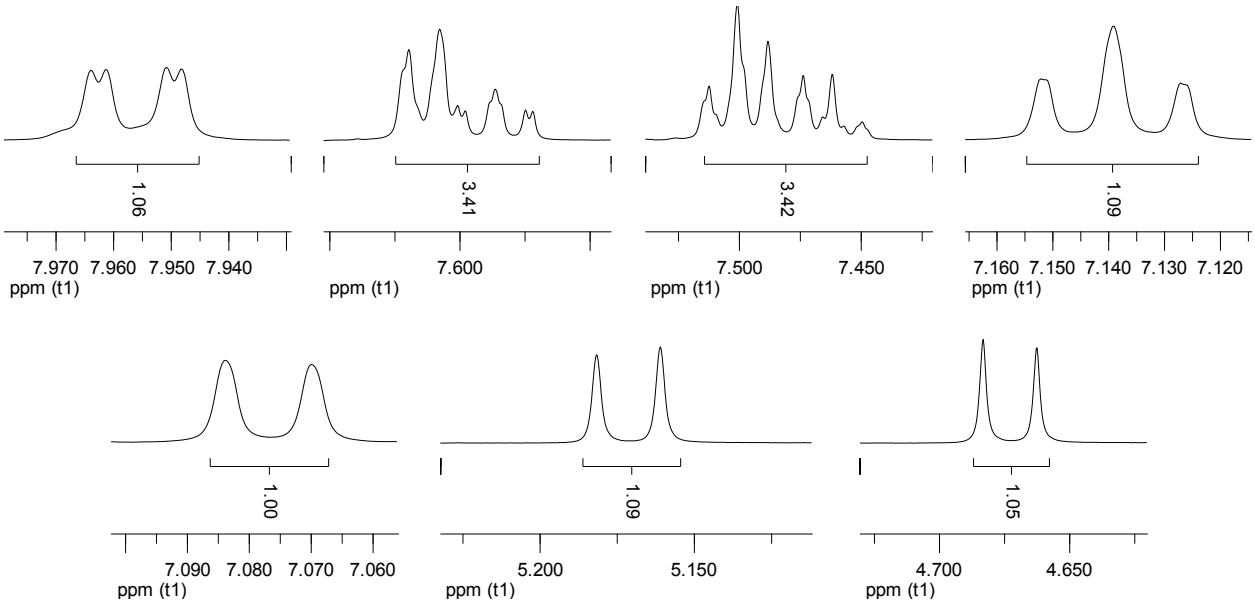


Plate 92a: ^{1}H NMR of Dihydroflavonol, $CDCl_3$ (298K)



(**5.75**)



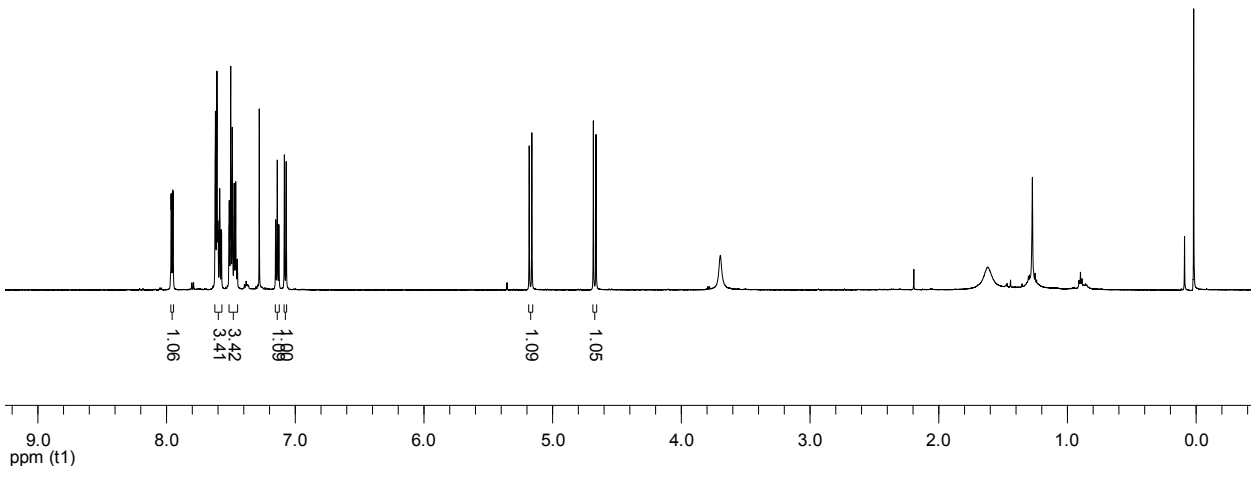
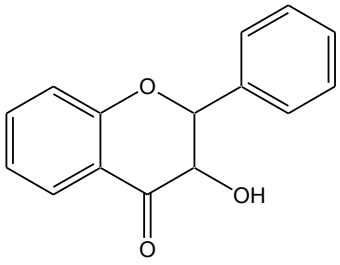


Plate 92b: ^{13}C NMR of Dihydroflavonol, $CDCl_3$ (298K)



(**5.75**)

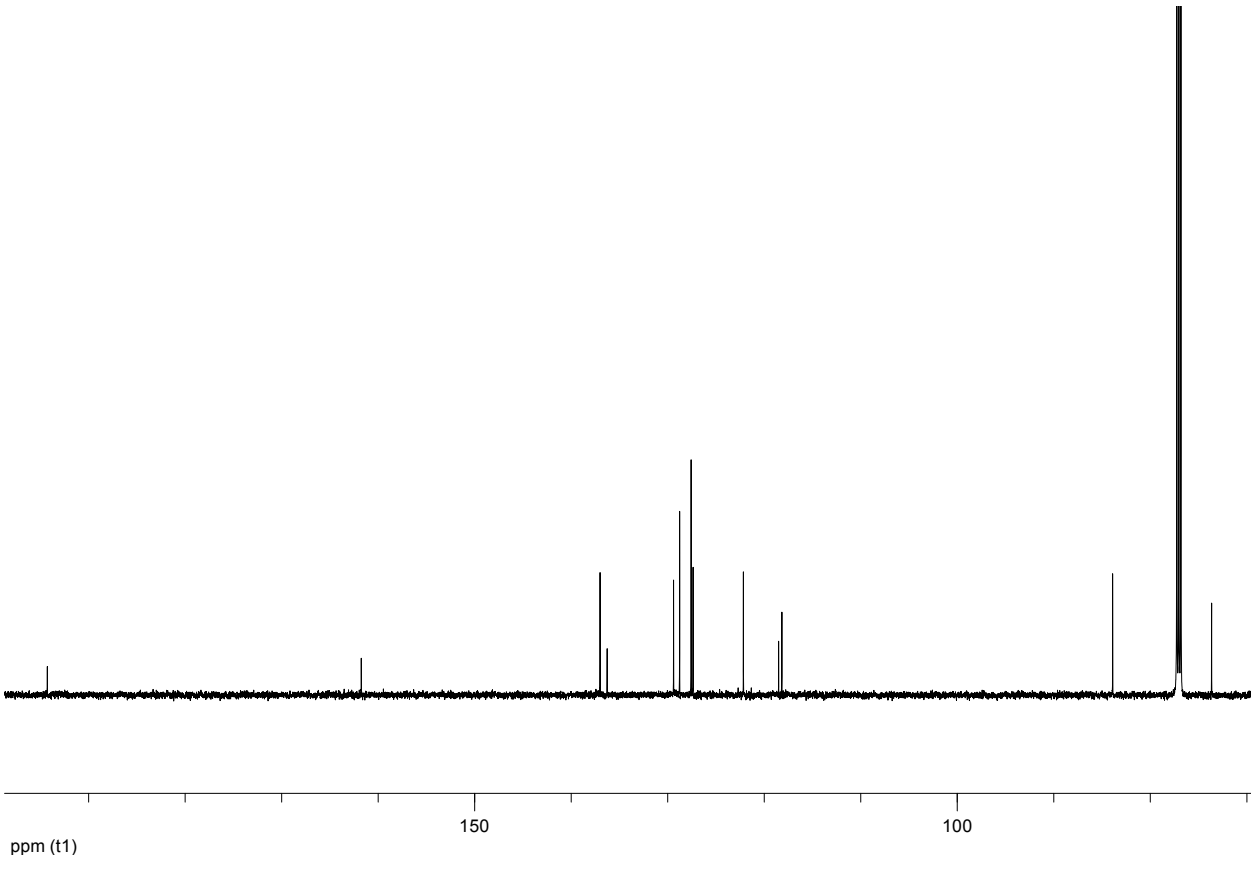
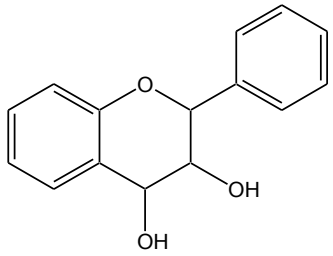
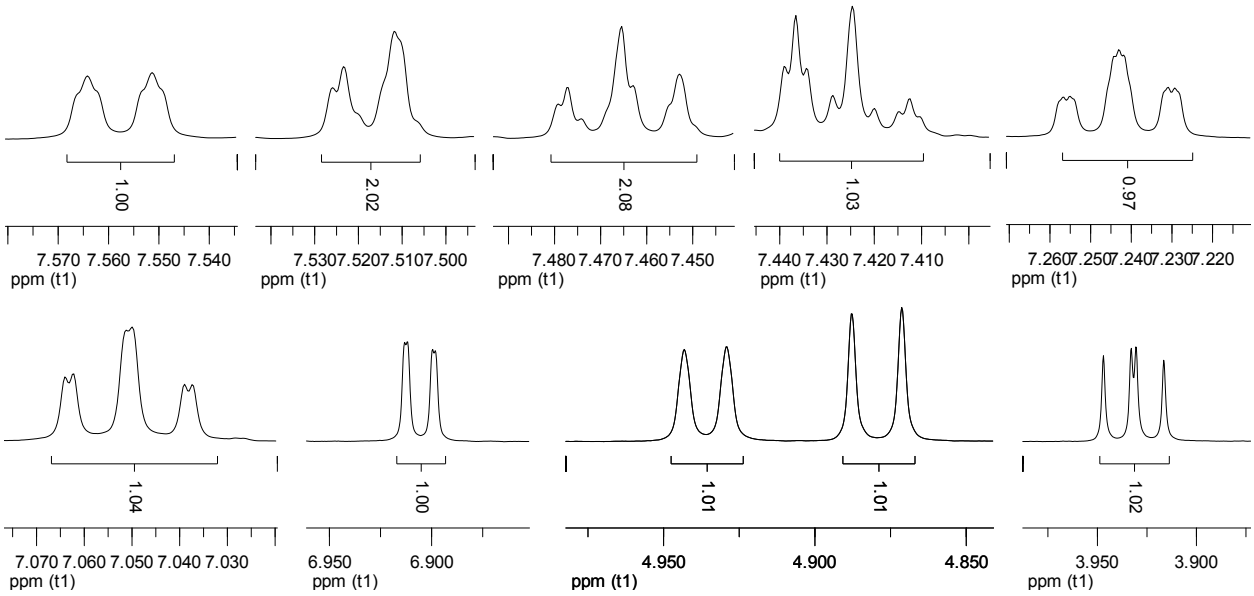


Plate 93a: ^{1}H NMR of Flavan-3,4-diol, $CDCl_3$ (298K)



(**5.76**)



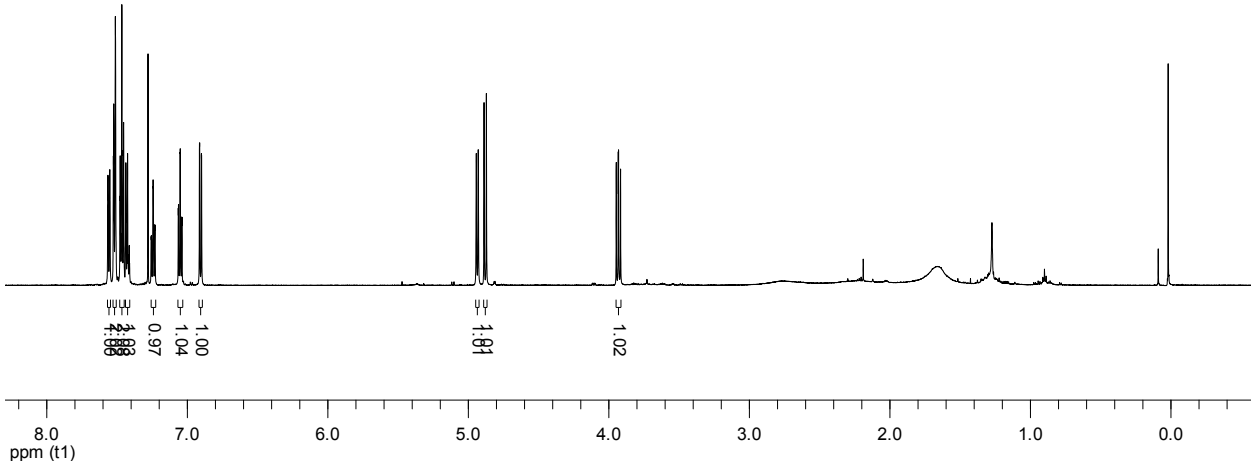
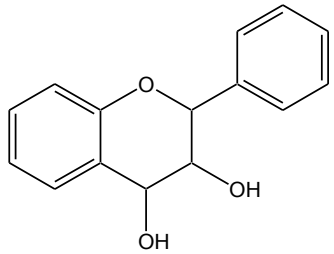


Plate 93b: ^{13}C NMR of Flavan-3,4-diol, $CDCl_3$ (298K)



(**5.76**)

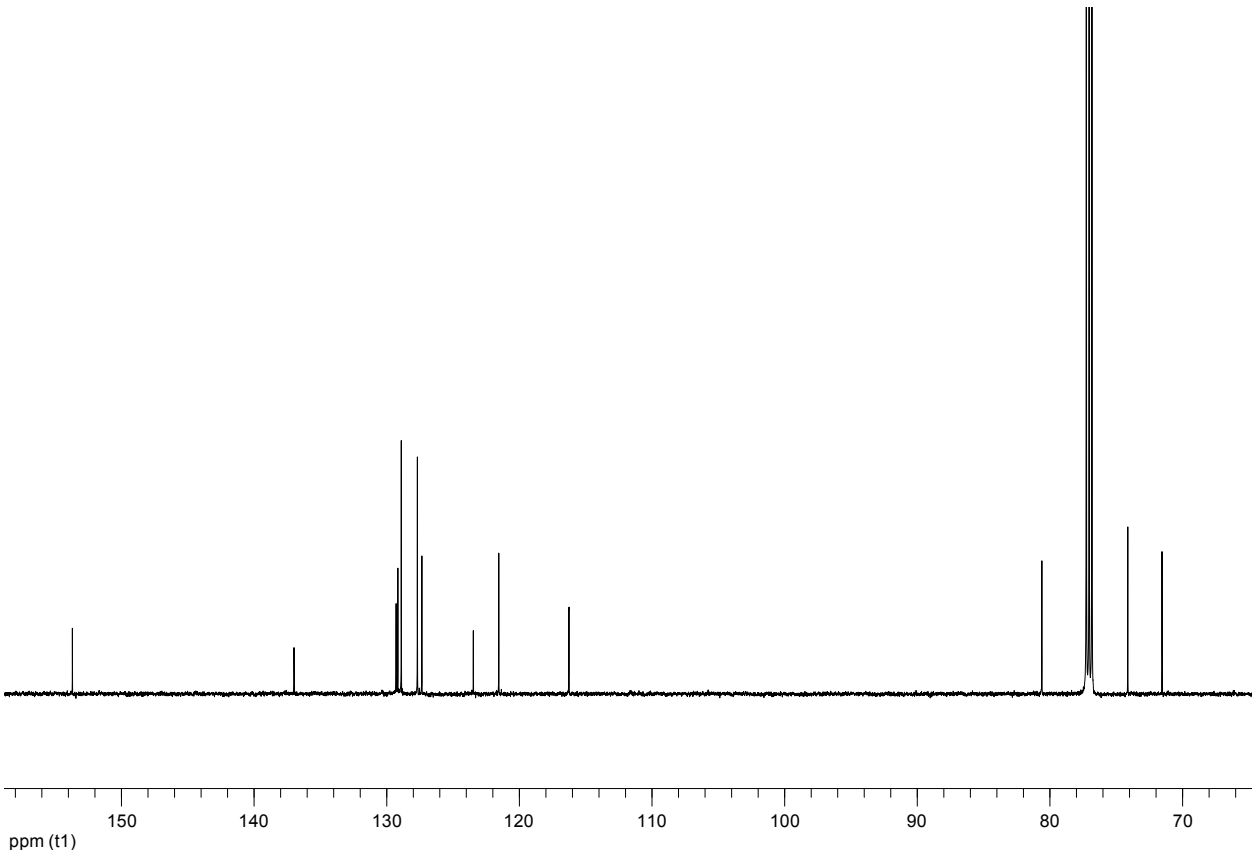
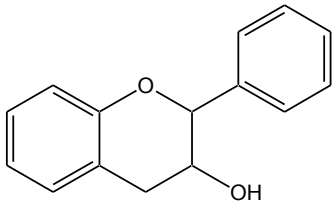
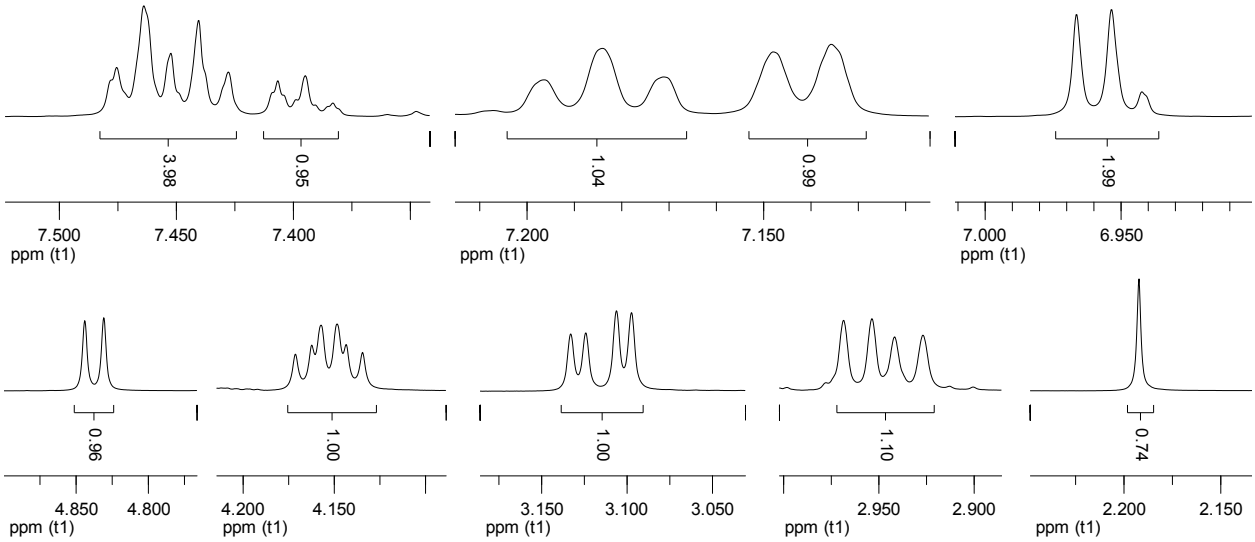


Plate 94a: ^{1}H NMR of Flavan-3-ol, $CDCl_3$ (298K)



(**5.4**)



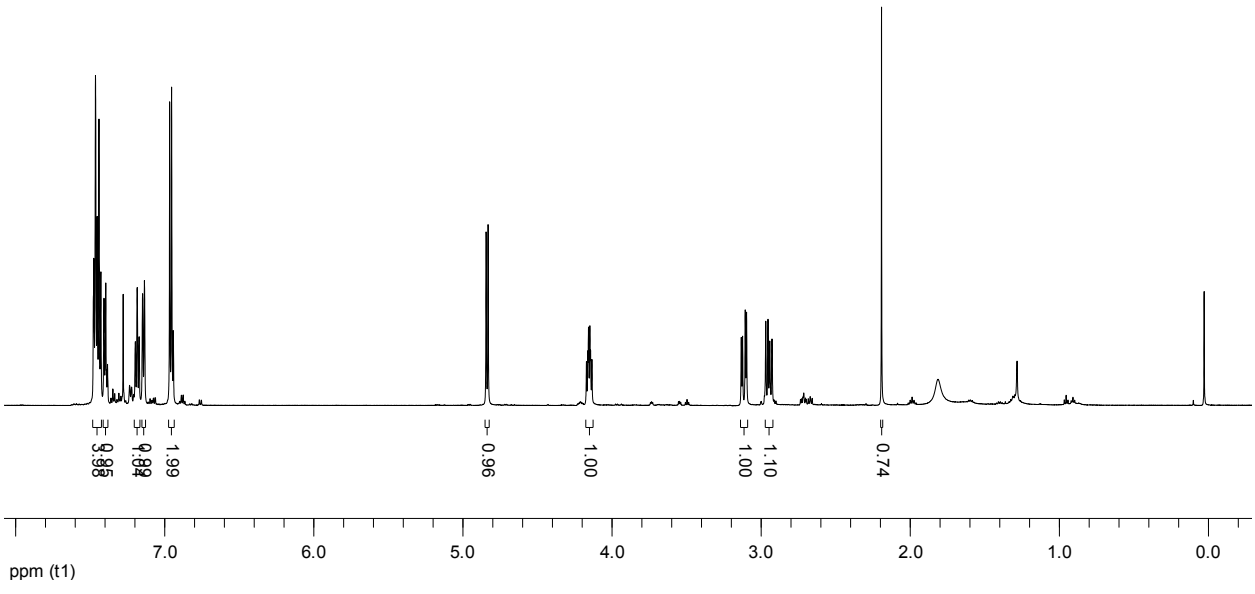
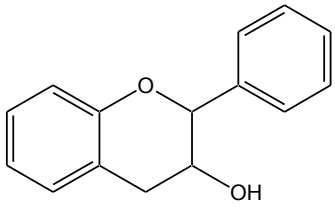


Plate 94b: ^{13}C NMR of Flavan-3-ol, $CDCl_3$ (298K)



(**5.4**)

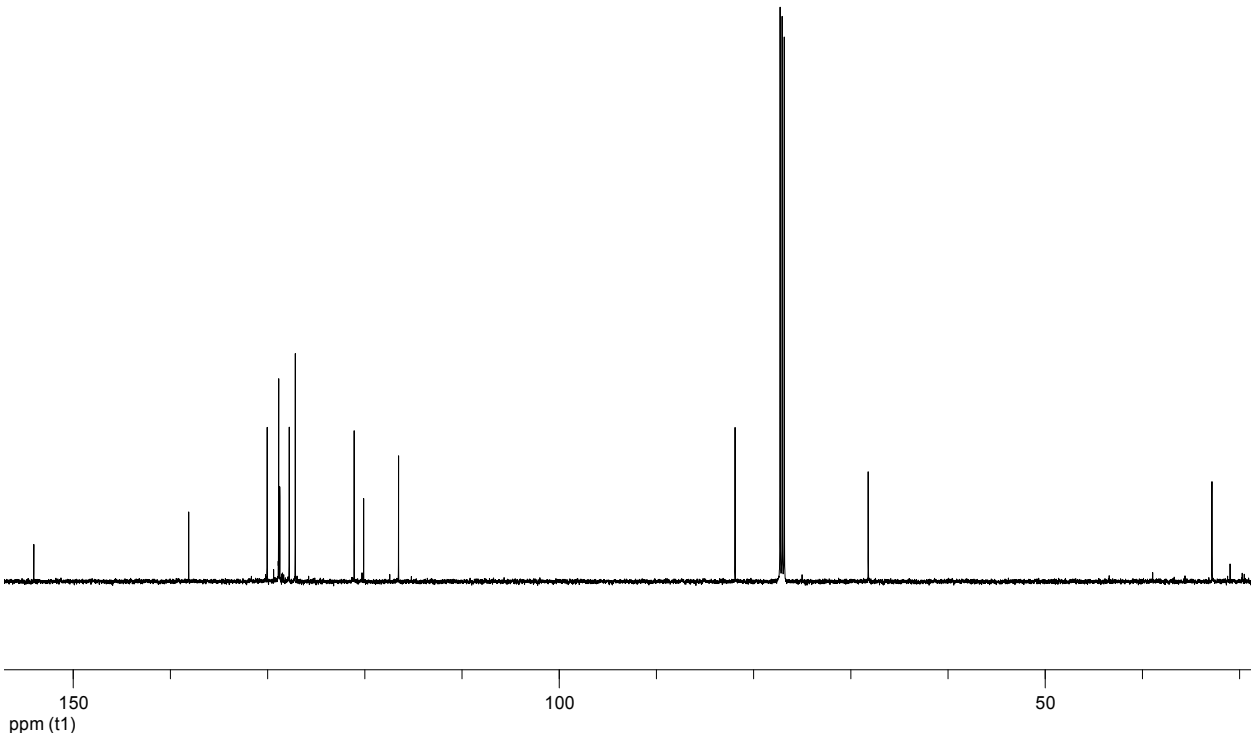
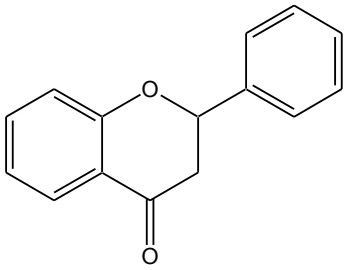
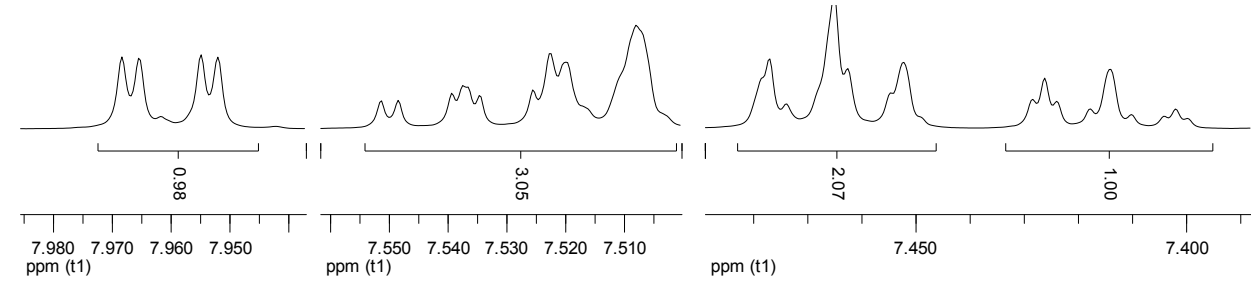
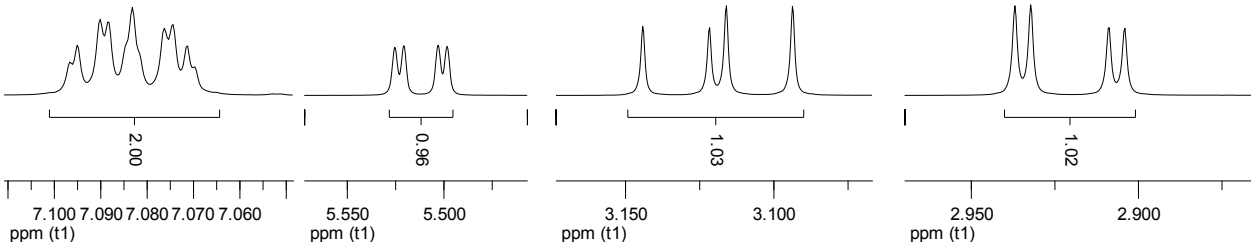


Plate 95a: ^{1}H NMR of Flavanone, $CDCl_3$ (298K)



(**5.77**)





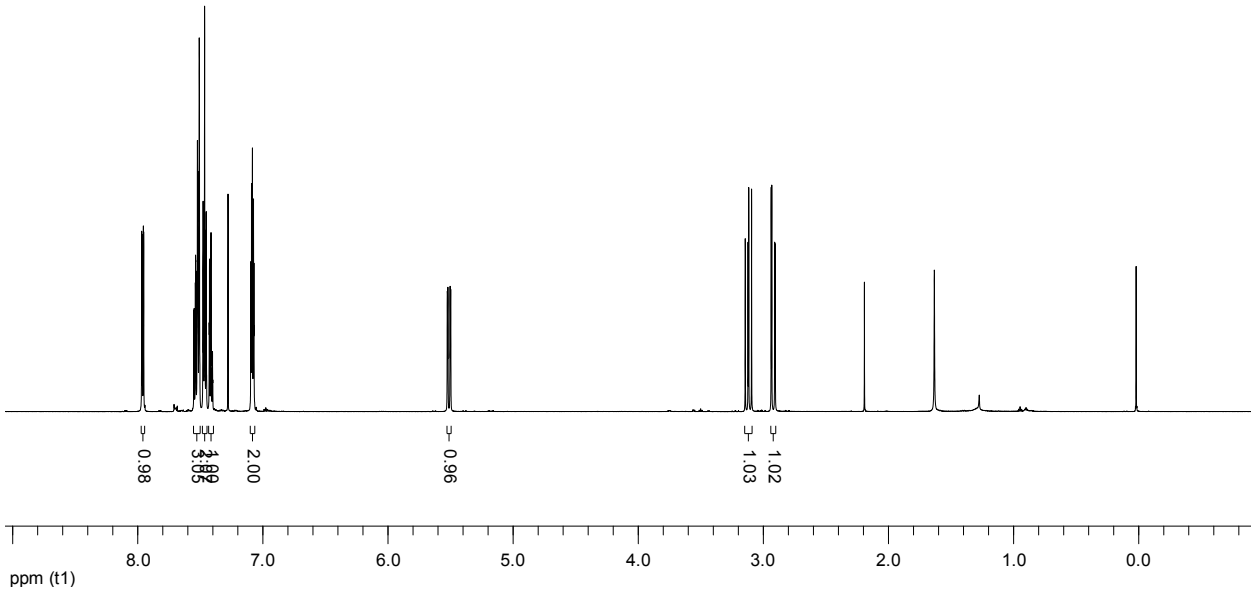
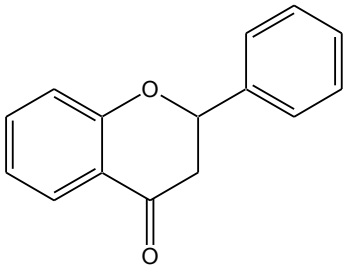


Plate 95b: ^{13}C NMR of Flavanone, $CDCl_3$ (298K)



(**5.77**)

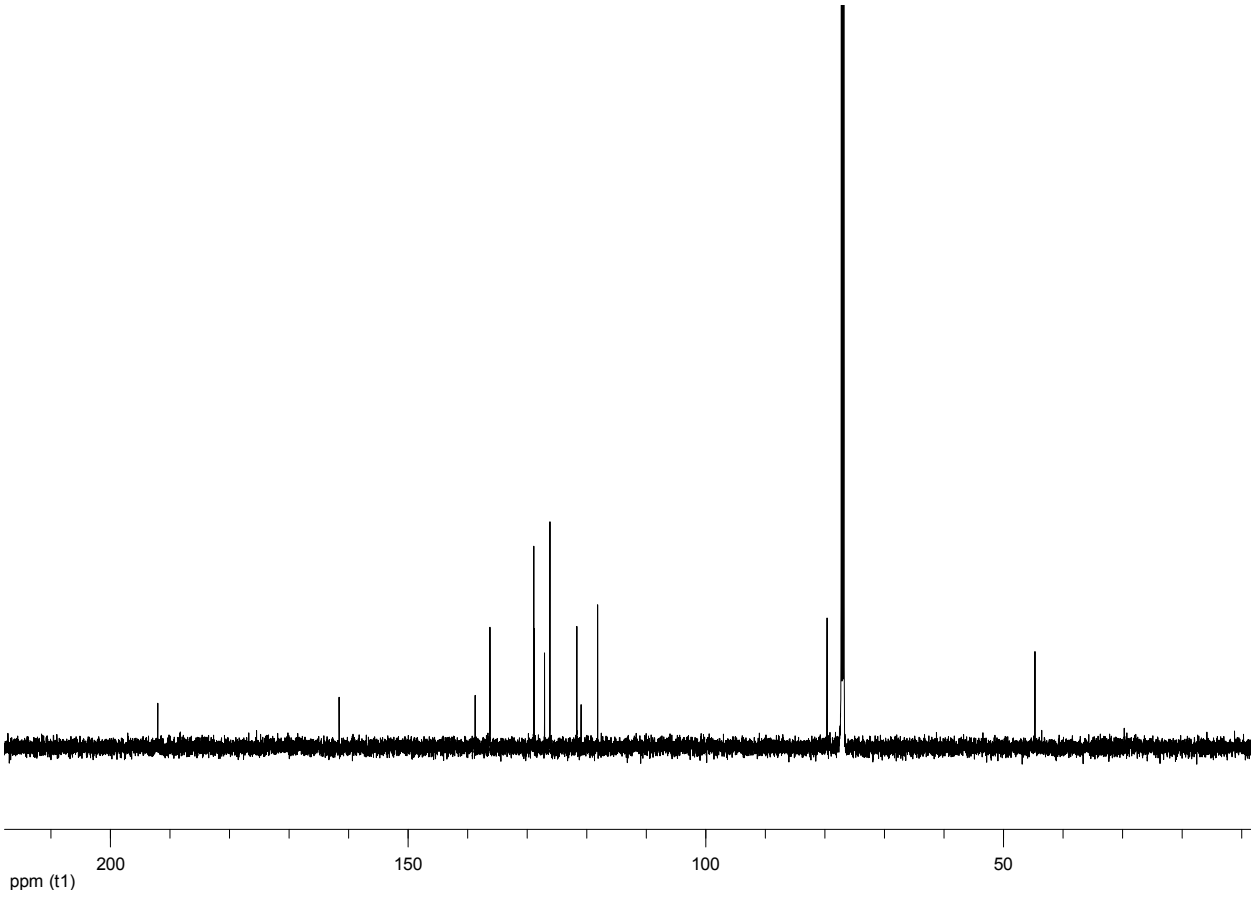
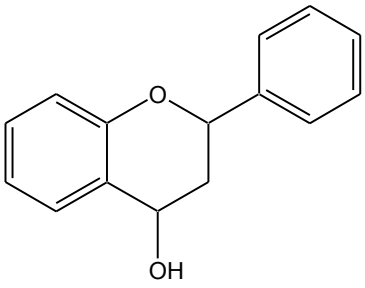
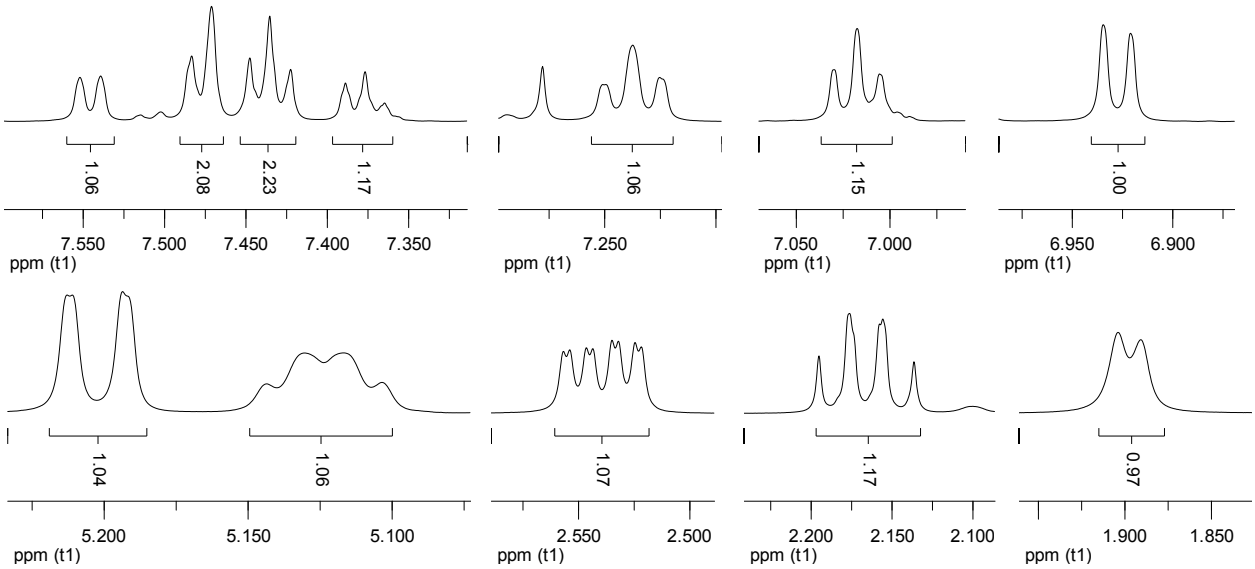


Plate 96a: ^{1}H NMR of Flavan-4-ol, $CDCl_3$ (298K)



(**5.78**)



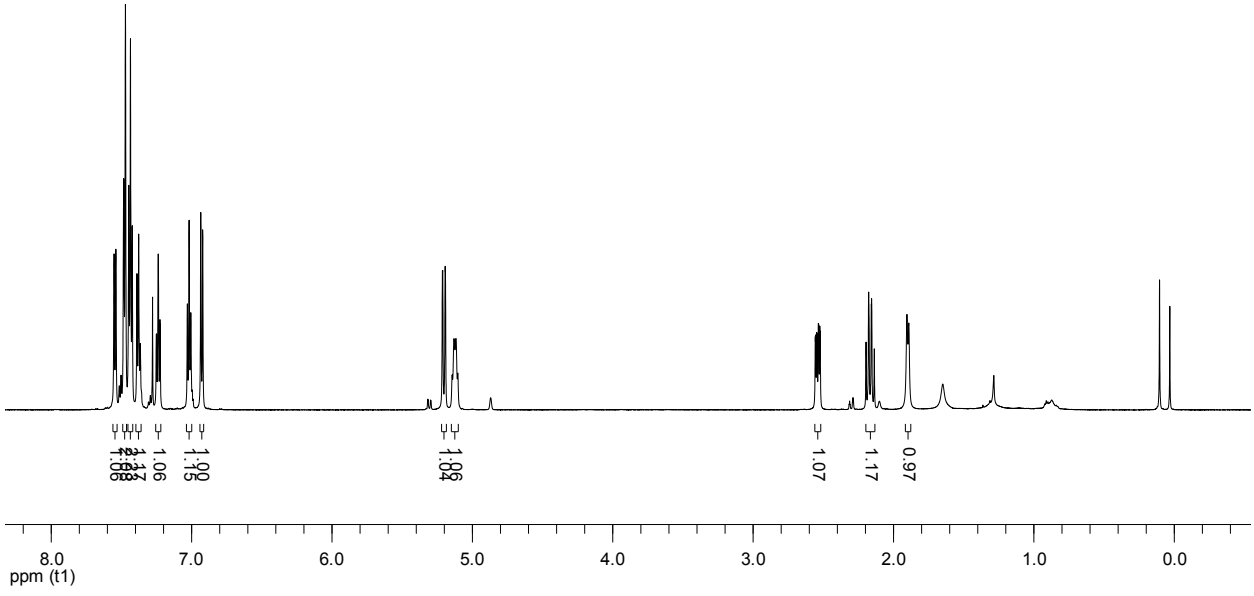
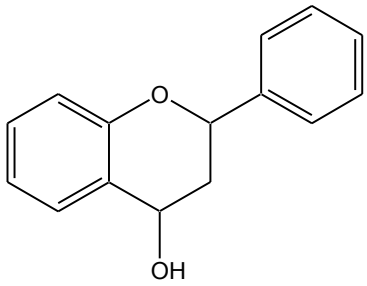


Plate 96b: ^{13}C NMR of Flavan-4-ol, $CDCl_3$ (298K)



(**5.78**)

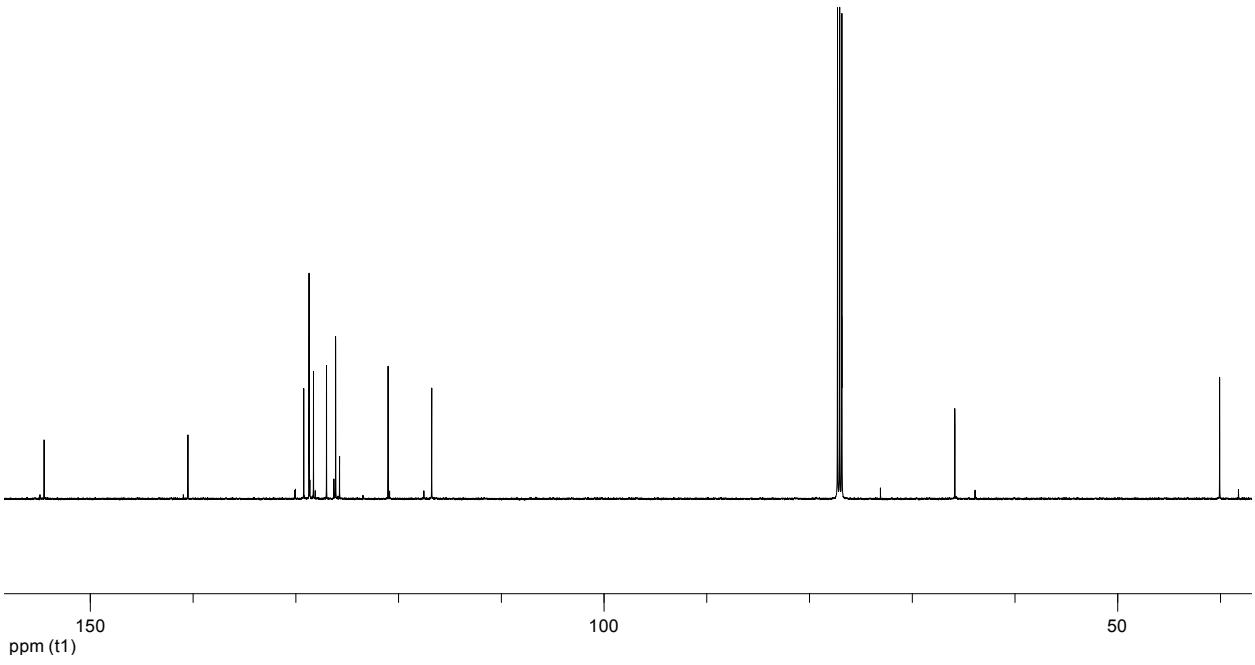
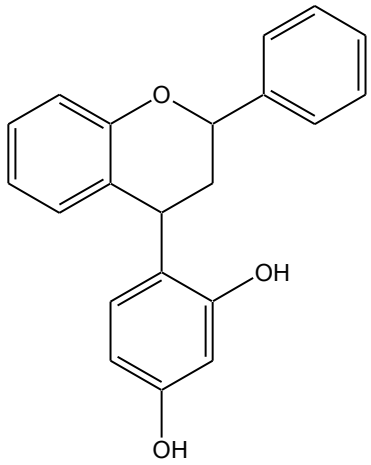


Plate 97a: ^{1}H NMR of 4-Aryl-2-phenylchromane, $CDCl_3$ (298K)



(**5.5**)

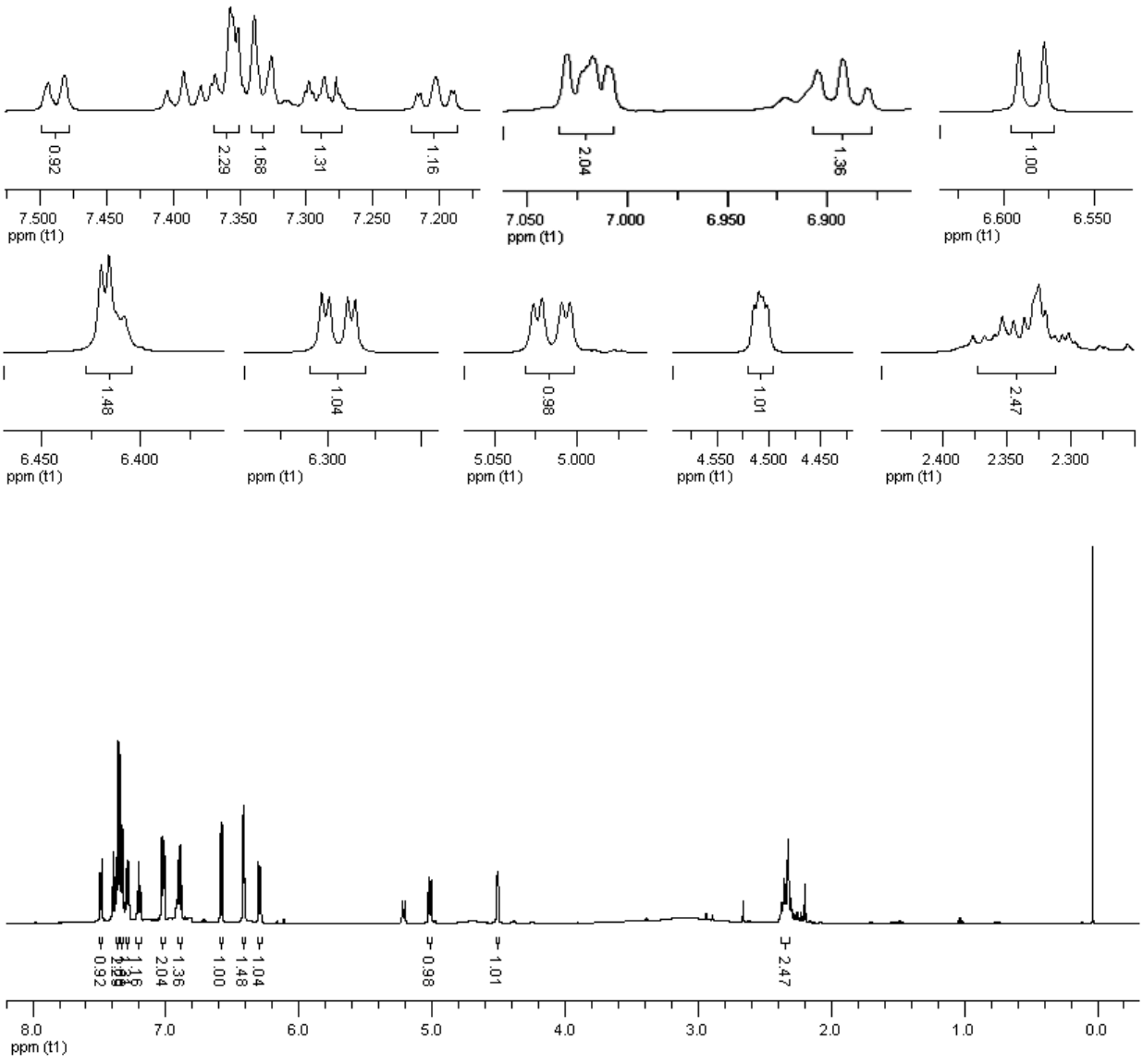
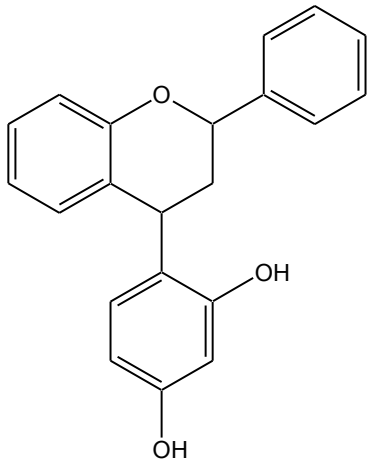


Plate 97b: ^{13}C NMR of 4-Aryl-2-phenylchromane, $CDCl_3$ (298K)



(**5.5**)

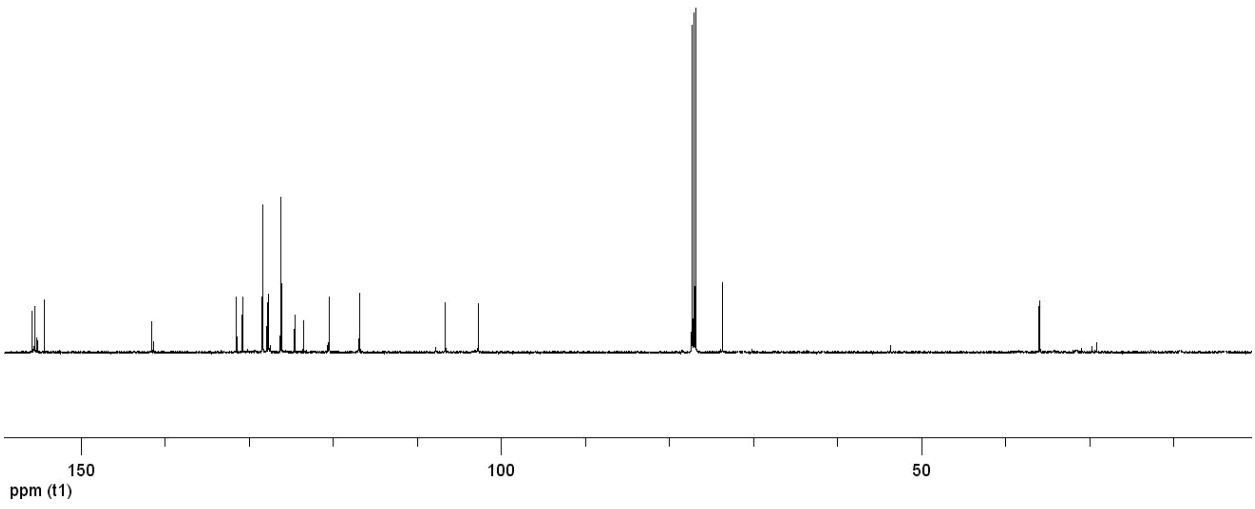
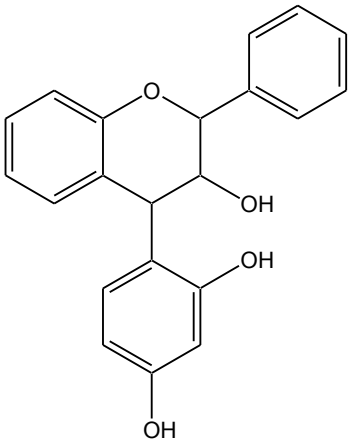


Plate 98a: ^{1}H NMR of 4-Aryl-2-phenylchromane-3-ol, $CDCl_3$ (298K)



(**5.6**)

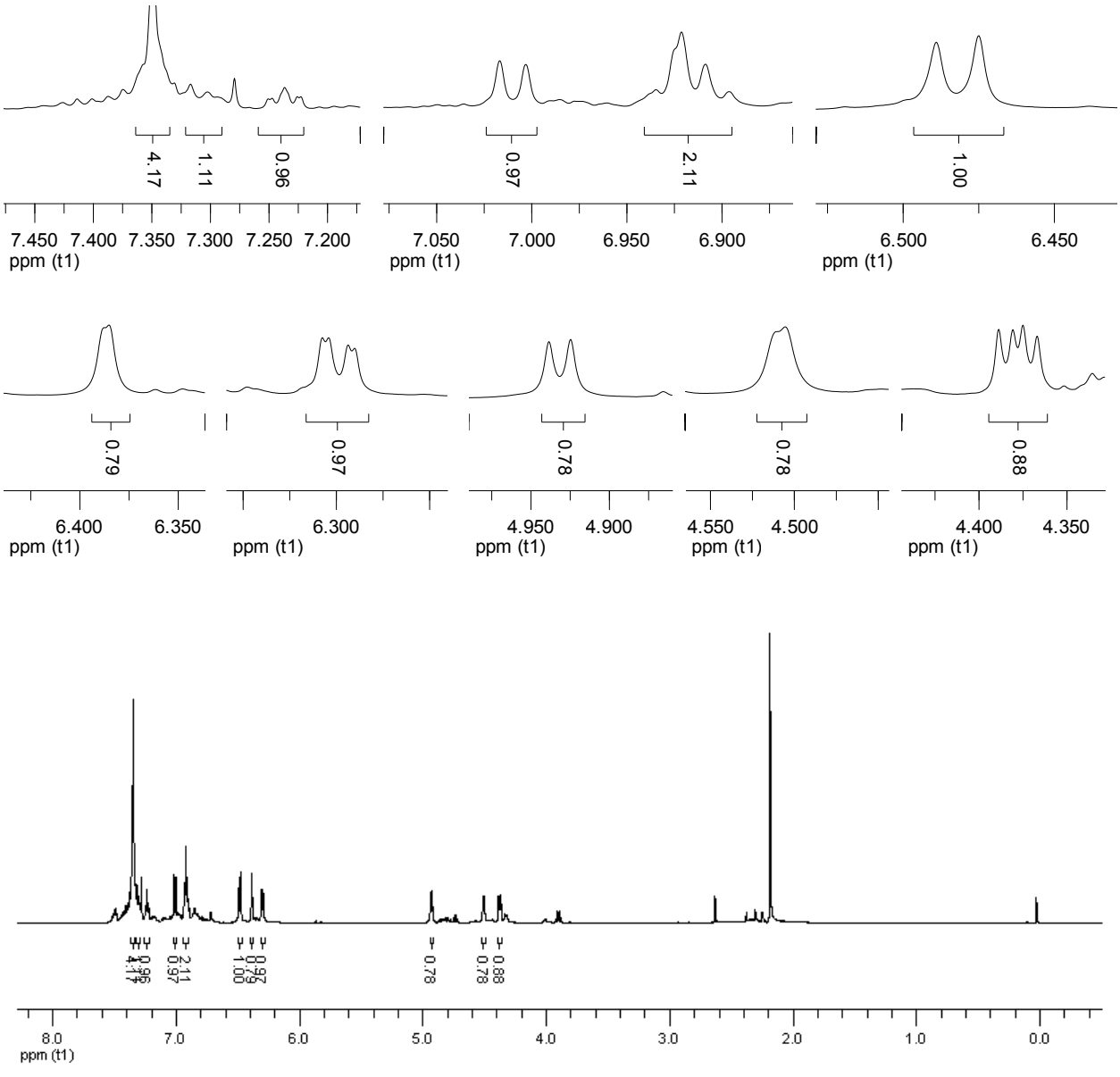
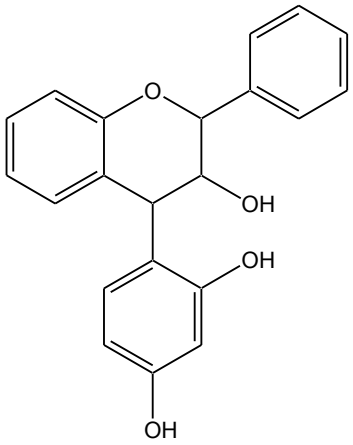
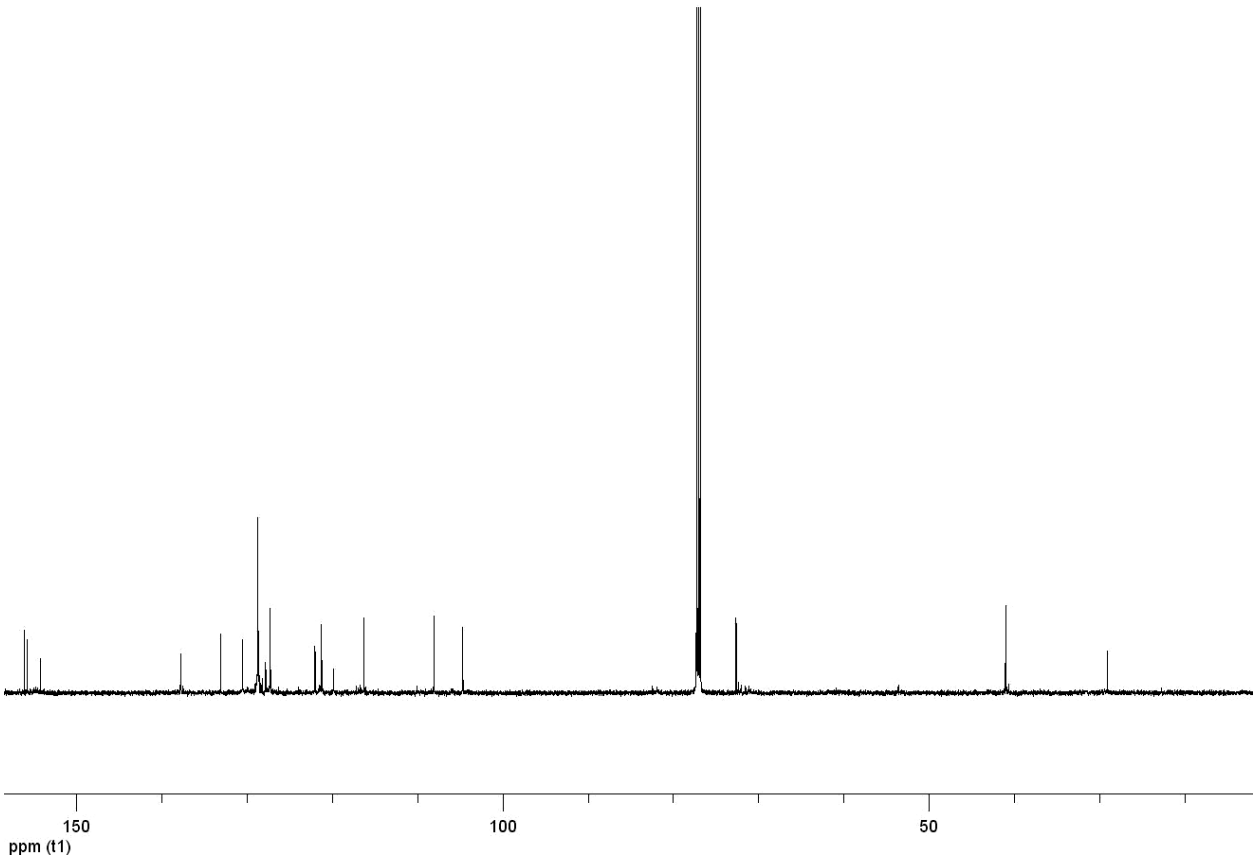


Plate 98b: ^{13}C NMR of 4-Aryl-2-phenylchromane-3-ol, $CDCl_3$ (298K)



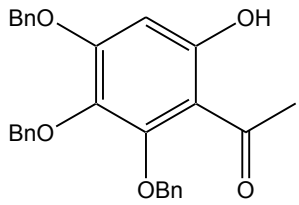
(**5.6**)



APPENDIX B

HRMS ANALYSIS

HRMS Analysis 1: 2,3,4-Tribenzyloxy-6-hydroxyacetophenone (**4.71**)



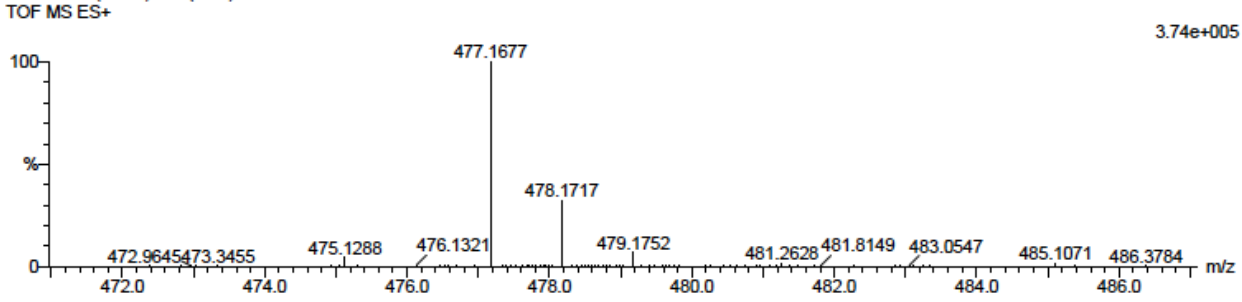
(**4.71**)

Calcd for $C_{29}H_{26}O_5Na$: 477.1600 g/mol. Found: *m/z* 477.1677.

Elemental Composition Report

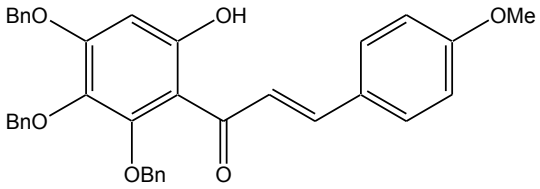
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 25-30 H: 25-30 O: 0-5 Na: 0-1
4-OMe-1 6 (0.169) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
477.1677	477.1678	-0.1	-0.2	16.5	581.5	0.0	C29 H26 O5 Na

HRMS Analysis 2: 2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxychalcone (**4.74**)



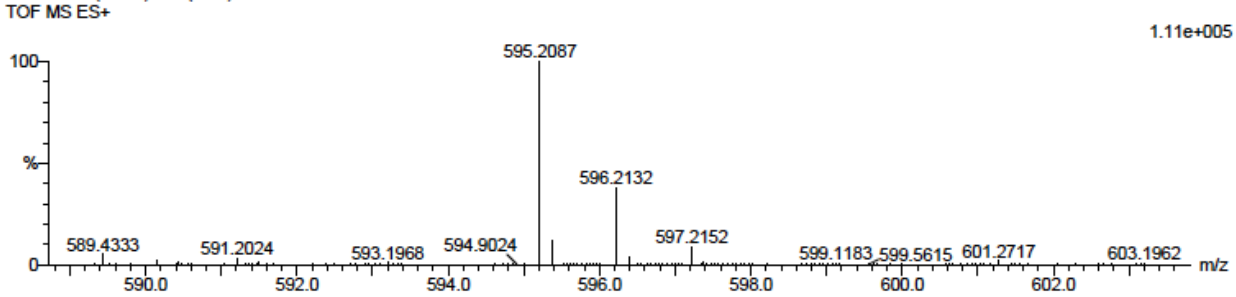
(**4.74**)

Calcd for $C_{37}H_{32}O_6$ Na: 595.2018 g/mol. Found: *m/z* 595.2087.

Elemental Composition Report

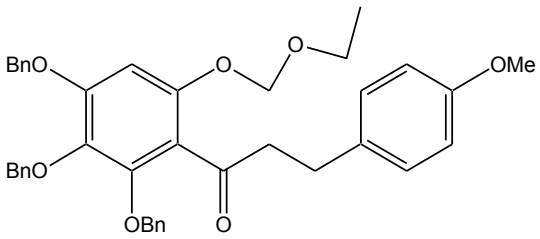
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 5-10 Na: 0-1
4-OMe-2 2 (0.034) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
595.2087	595.2097	-1.0	-1.7	21.5	426.1	0.0	C37 H32 O6 Na

HRMS Analysis 3: 2',3',4'-Tribenzyloxy-6'-ethoxymethoxy-4-methoxydihydrochalcone (**4.77**)



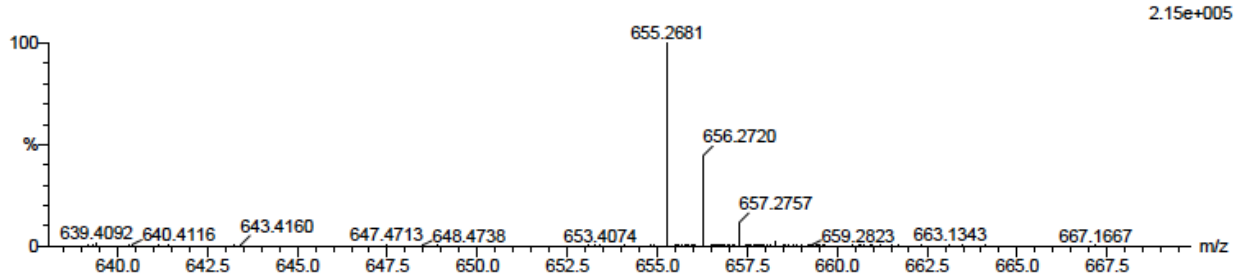
(**4.77**)

Calcd for $C_{40}H_{40}O_7Na$: 655.2674 g/mol. Found: *m/z* 655.2681.

Elemental Composition Report

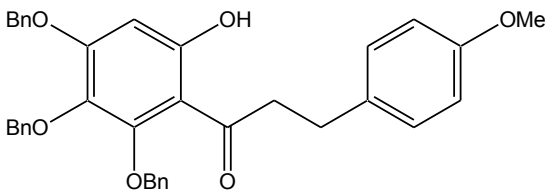
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 40-45 H: 40-45 O: 5-10 Na: 0-1
4-OMe-3 35 (1.146) Cm (1:61)
TOF MS ES+



Minimum:				-1.5					
Maximum:		5.0	5.0	100.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
655.2681	655.2672	0.9	1.4	20.5	443.1	0.0	C40	H40	O7 Na

HRMS Analysis 4: 2',3',4'-Tribenzyloxy-6'-hydroxy-4-methoxydihydrochalcone (**4.78**)



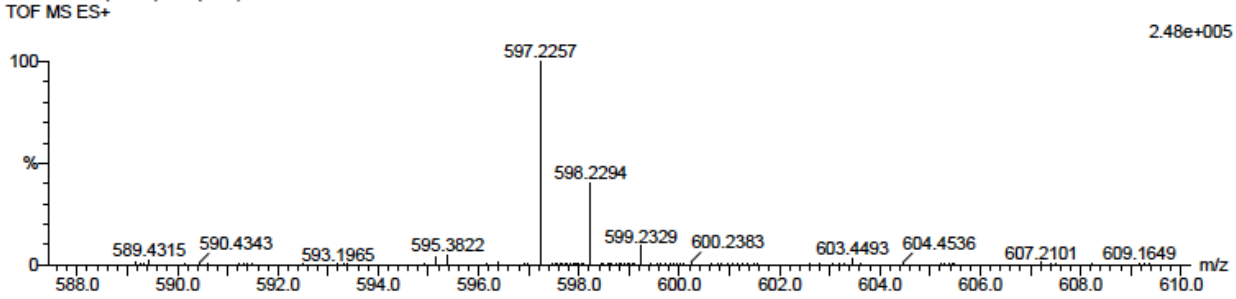
(**4.78**)

Calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2257.

Elemental Composition Report

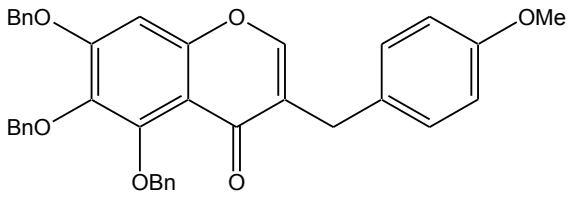
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 5-10 Na: 1-1
4-OMe-4 61 (2.025) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
597.2257	597.2253	0.4	0.7	20.5	490.4	0.0	C37 H34 O6 Na

HRMS Analysis 5: 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavone (**4.79**)



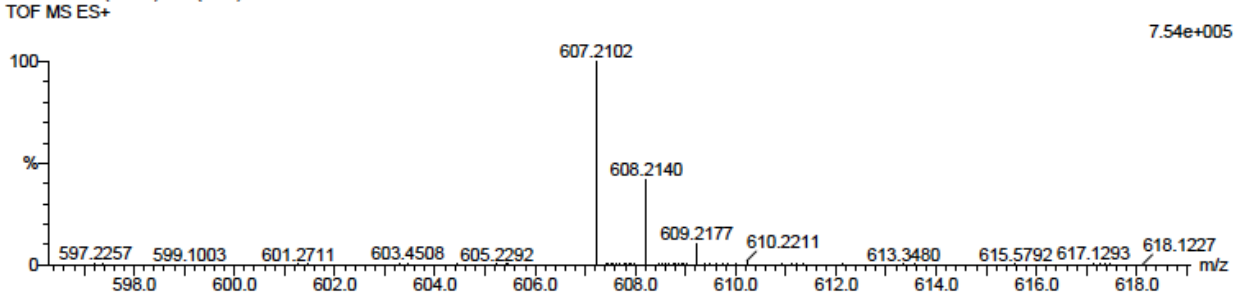
(**4.79**)

Calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2102.

Elemental Composition Report

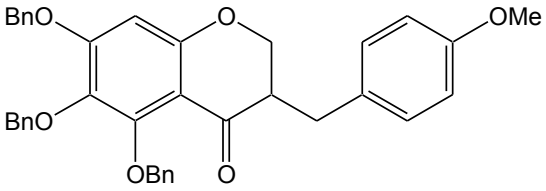
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 5-10 Na: 1-1
4-OMe-5 24 (0.776) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
607.2102	607.2097	0.5	0.8	22.5	531.0	0.0	C38 H32 O6 Na

HRMS Analysis 6: 5,6,7-Tribenzyloxy-4'-methoxyhomoisoflavanone (**4.91**)



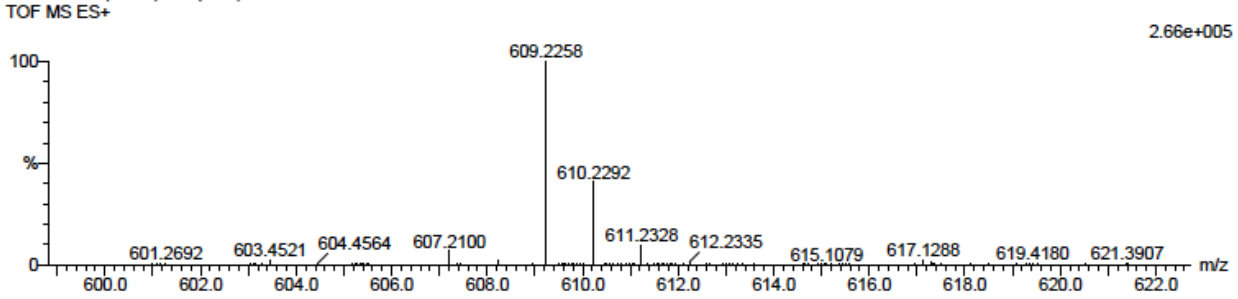
(**4.91**)

Calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2258.

Elemental Composition Report

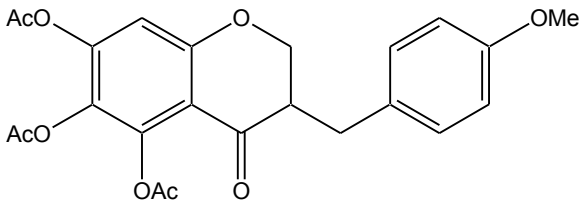
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 5-10 Na: 1-1
4-OMe-6 16 (0.506) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
609.2258	609.2253	0.5	0.8	21.5	518.8	0.0	C38 H34 O6 Na

HRMS Analysis 7: 5,6,7-Triacetoxy-4'-methoxyhomoisoflavanone (**4.93**)



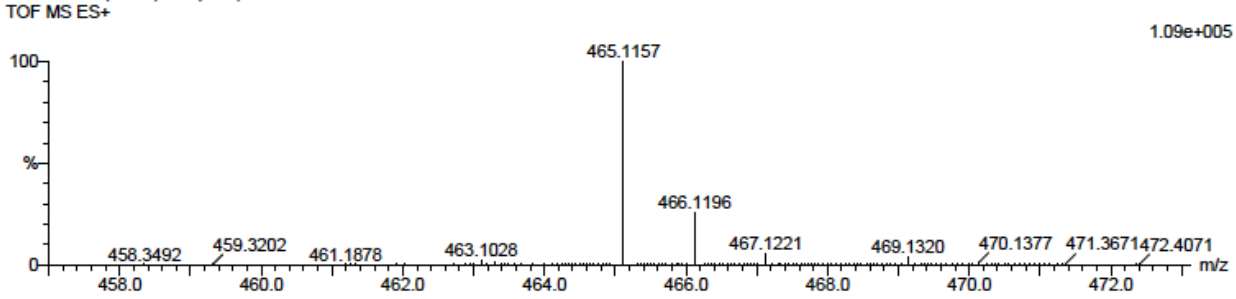
(**4.93**)

Calcd for $C_{23}H_{22}O_9Na$: 465.1164 g/mol. Found: *m/z* 465.1157.

Elemental Composition Report

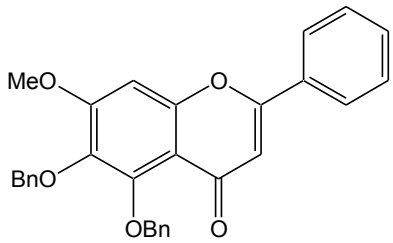
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 O: 5-10 Na: 1-1
4-OMe-7 26 (0.844) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
465.1157	465.1162	-0.5	-1.1	12.5	506.7	0.0	C23 H22 O9 Na

HRMS Analysis 8: 5,6-Dibenzyloxy-7-methoxyflavone (**4.111**)



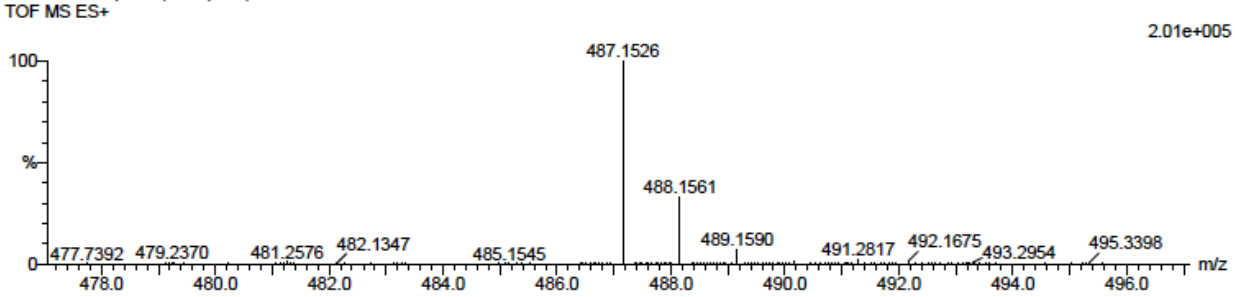
(**4.111**)

Calcd for $C_{30}H_{24}O_5Na$: 487.1524 g/mol. Found: *m/z* 487.1526.

Elemental Composition Report

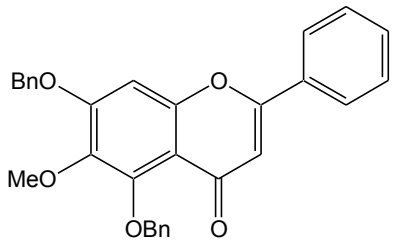
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 25-30 H: 20-25 O: 0-10 Na: 1-1
7-OMe-17 13 (0.405) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
487.1526	487.1521	0.5	1.0	18.5	521.3	0.0	C30 H24 O5 Na

HRMS Analysis 9: 5,7-Dibenzyloxy-6-methoxyflavone (**4.112**)



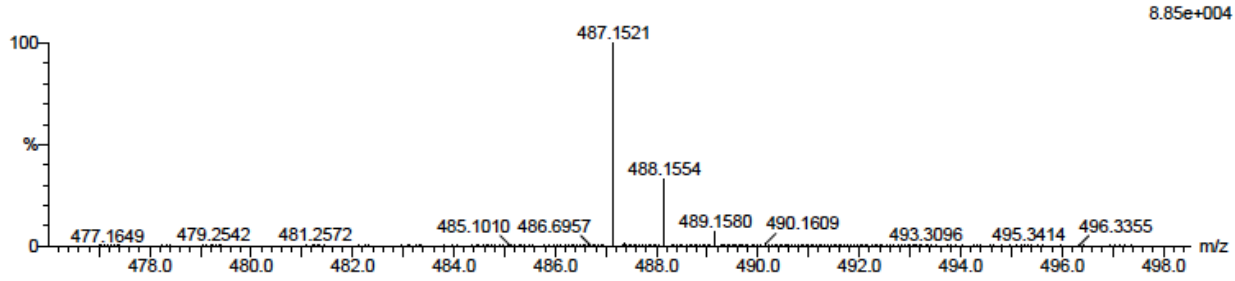
(**4.112**)

Calcd for $C_{30}H_{24}O_5Na$: 487.1524 g/mol. Found: *m/z* 487.1521.

Elemental Composition Report

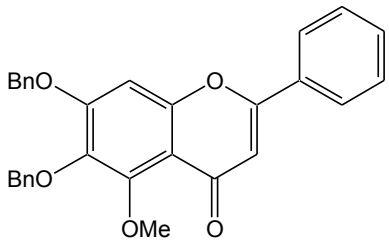
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 30-35 H: 20-25 O: 0-5 Na: 1-1
6-OMe Flavone 4 (0.102) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
487.1521	487.1521	0.0	0.0	18.5	476.5	0.0	C30 H24 O5 Na

HRMS Analysis 10: 6,7-Dibenzyloxy-5-methoxyflavone (**4.113**)



(**4.113**)

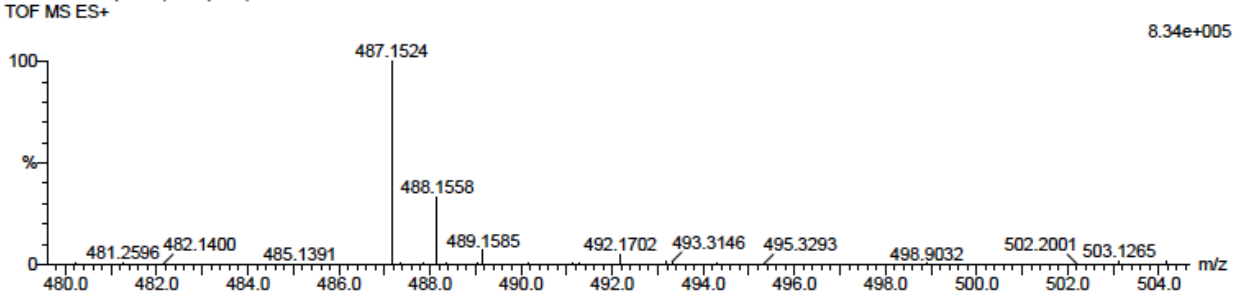
Calcd for $C_{30}H_{24}O_5Na$: 487.1524 g/mol. Found: *m/z* 487.1524.

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

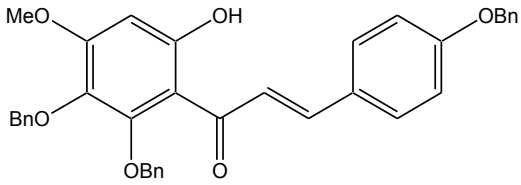
Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 25-30 H: 20-25 O: 0-5 Na: 1-1

5-OMe-10 47 (1.553) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
487.1524	487.1521	0.3	0.6	18.5	628.6	0.0	C30 H24 O5 Na

HRMS Analysis 11: 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxychalcone (**4.127**)



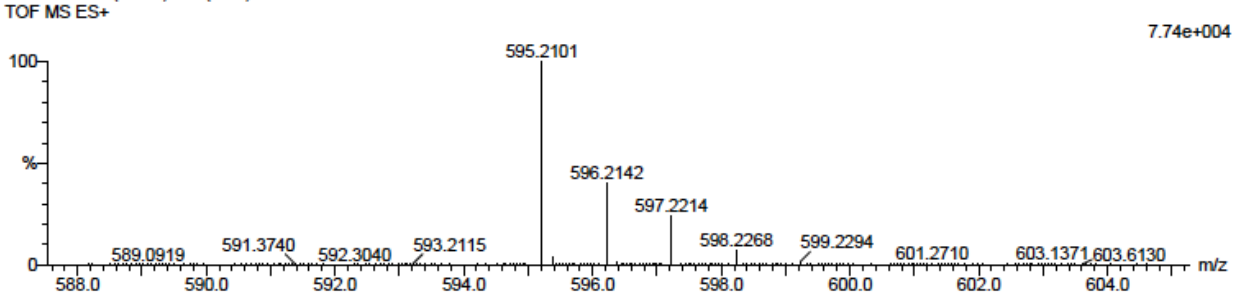
(**4.127**)

Calcd for $C_{37}H_{32}O_6Na$: 595.2118 g/mol. Found: *m/z* 595.2101.

Elemental Composition Report

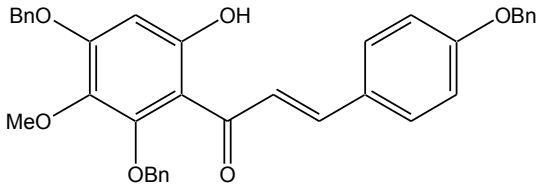
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
7-OMe-18 36 (1.181) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
595.2101	595.2097	0.4	0.7	21.5	457.0	0.0	C37 H32 O6 Na

HRMS Analysis 12: 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxychalcone (**4.128**)



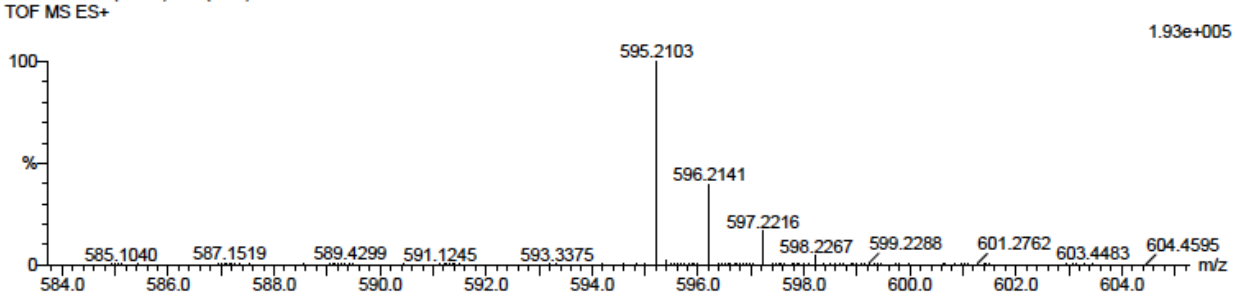
(**4.128**)

Calcd for $C_{37}H_{32}O_6Na$: 595.2118 g/mol. Found: *m/z* 595.2103.

Elemental Composition Report

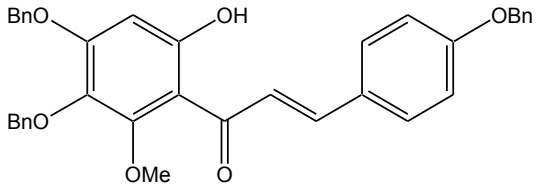
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
6-OMe-24 34 (1.114) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
595.2103	595.2097	0.6	1.0	21.5	498.7	0.0	C37 H32 O6 Na

HRMS Analysis 13: 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxychalcone (**4.129**)



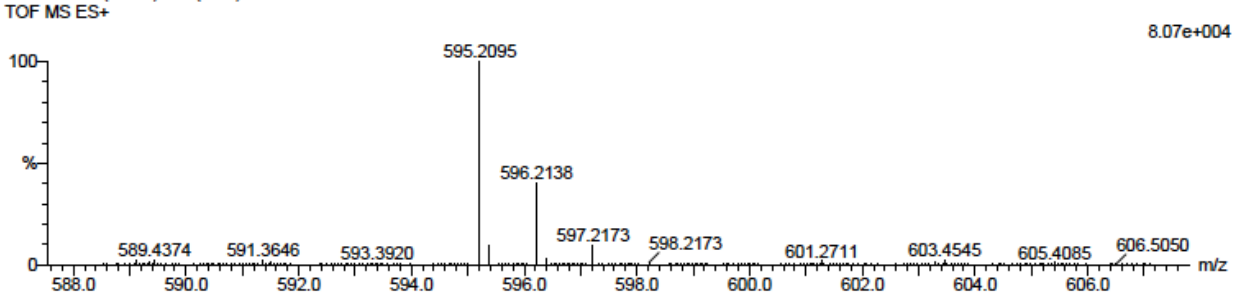
(**4.129**)

Calcd for $C_{37}H_{32}O_6Na$: 595.2018 g/mol. Found: *m/z* 595.2095.

Elemental Composition Report

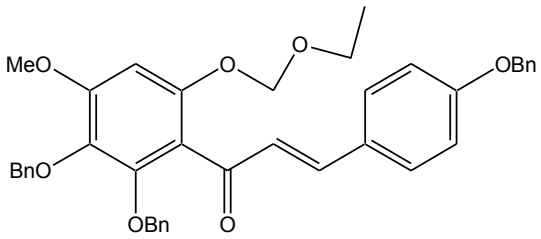
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
5-OMe-11 3 (0.068) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
595.2095	595.2097	-0.2	-0.3	21.5	461.5	0.0	C37 H32 O6 Na

HRMS Analysis 14: 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxychalcone (**4.130**)



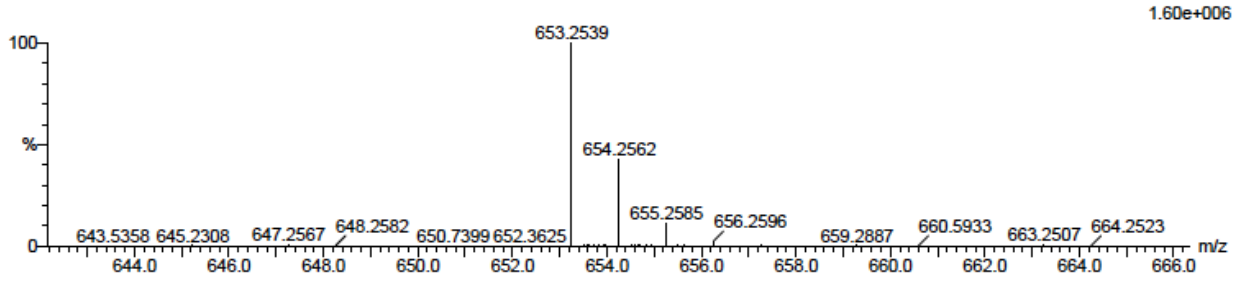
(**4.130**)

Calcd for $C_{40}H_{38}O_7Na$: 653.2518 g/mol. Found: *m/z* 653.2539.

Elemental Composition Report

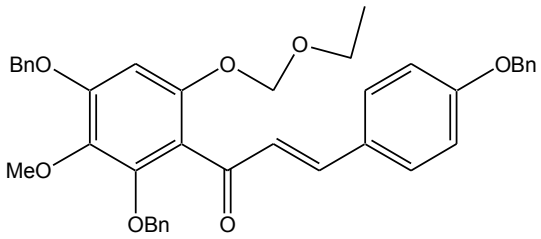
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 35-40 O: 0-10 Na: 1-1
7-OMe-19 18 (0.574) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
653.2539	653.2515	2.4	3.7	21.5	539.5	0.0	C40 H38 O7 Na

HRMS Analysis 15: 4,2',4'-Tribenzyloxy-6'-ethoxymethoxy-3'-methoxychalcone (**4.131**)



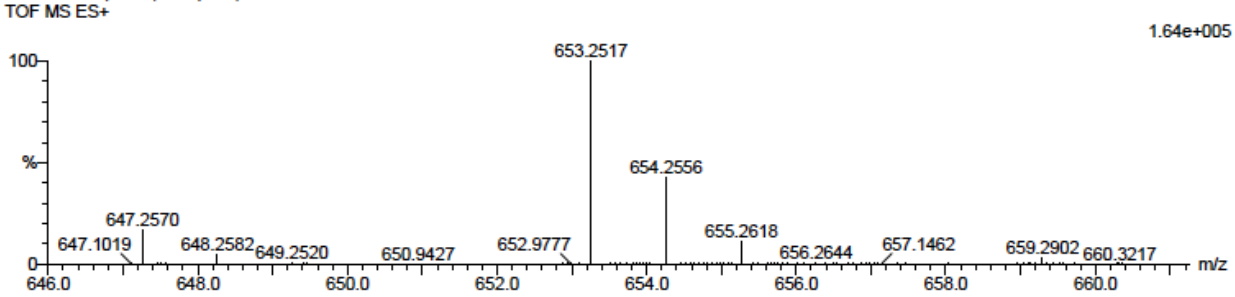
(**4.131**)

Calcd for $C_{40}H_{38}O_7Na$: 653.2518 g/mol. Found: *m/z* 653.2517.

Elemental Composition Report

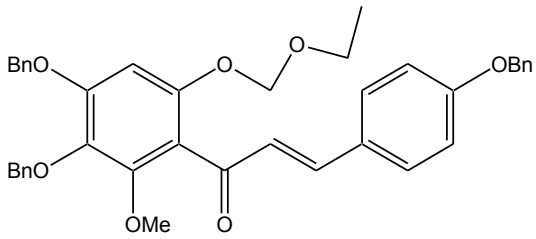
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 35-40 O: 0-10 Na: 1-1
6-OMe-25 2 (0.034) Cm (1:61)
TOF MS ES+



Minimum:				-1.5					
Maximum:		5.0	5.0	100.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
653.2517	653.2515	0.2	0.3	21.5	444.6	0.0	C40	H38	O7 Na

HRMS Analysis 16: 4,3',4'-Tribenzyloxy-6'-ethoxymethoxy-2'-methoxychalcone (**4.132**)



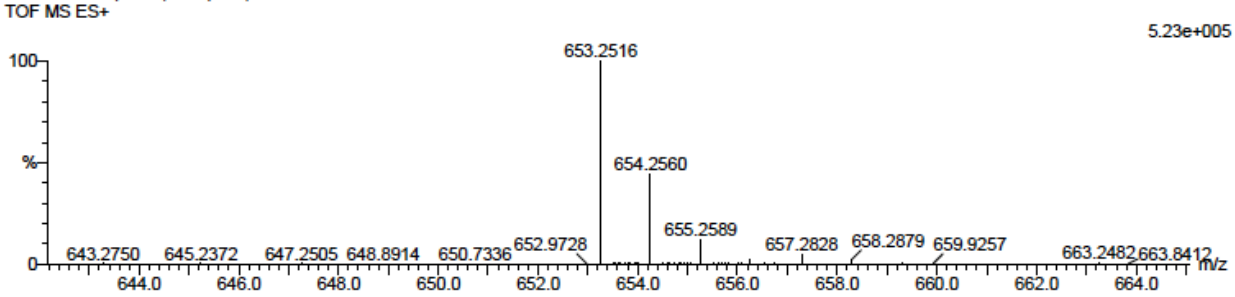
(**4.132**)

Calcd for $C_{40}H_{38}O_7Na$: 653.2518 g/mol. Found: *m/z* 653.2516.

Elemental Composition Report

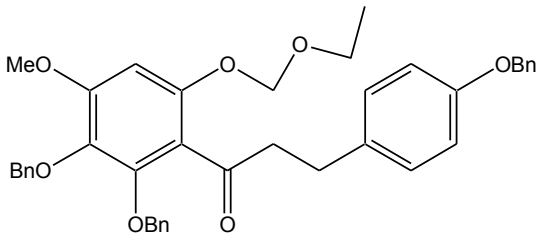
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 35-40 O: 0-10 Na: 1-1
5-OMe-12 32 (1.047) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
653.2516	653.2515	0.1	0.2	21.5	491.0	0.0	C40 H38 O7 Na

HRMS Analysis 17: 4,2',3'-Tribenzyloxy-6'-ethoxymethoxy-4'-methoxydihydrochalcone (**4.133**)



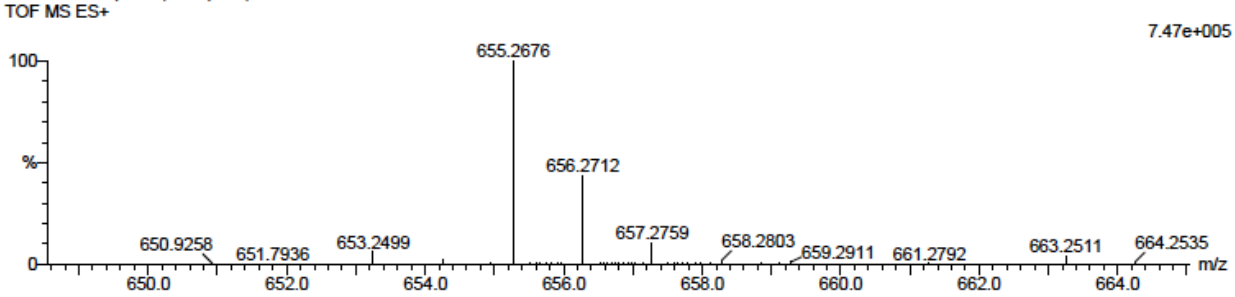
(**4.133**)

Calcd for $C_{40}H_{40}O_7Na$: 655.2674 g/mol. Found: *m/z* 655.2676.

Elemental Composition Report

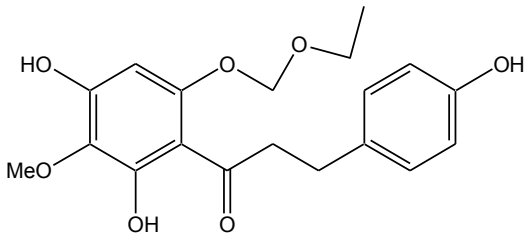
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 35-40 O: 0-10 Na: 1-1
7-OMe-20 47 (1.552) Cm (1:61)
TOF MS ES+



Minimum:				-1.5					
Maximum:		5.0	5.0	100.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
655.2676	655.2672	0.4	0.6	20.5	494.0	0.0	C40	H40	O7 Na

HRMS Analysis 18: 6'-Ethoxymethoxy-2',4',4-trihydroxy-3'-methoxydihydrochalcone (**4.135**)



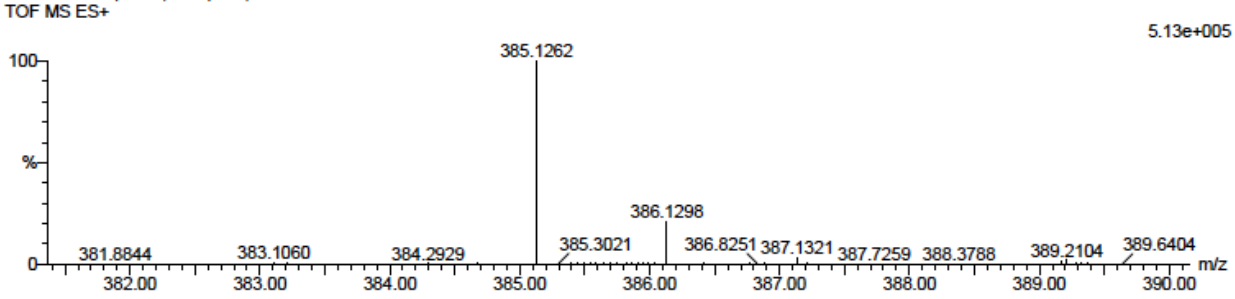
(**4.135**)

Calcd for $C_{19}H_{22}O_7Na$: 385.1285 g/mol. Found: *m/z* 385.1262.

Elemental Composition Report

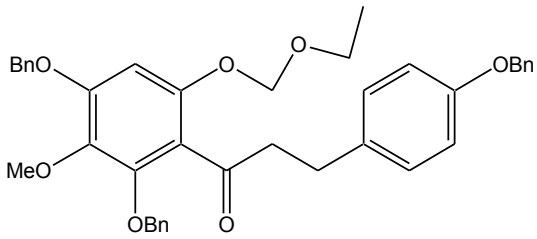
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 20-25 O: 0-10 Na: 1-1
6-OMe-26 25 (0.811) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
385.1262	385.1263	-0.1	-0.3	8.5	562.9	0.0	C19 H22 O7 Na

HRMS Analysis 19: 4,2',4'-Tribenzyloxy-6'-ethoxymethoxy-3'-methoxydihydrochalcone (**4.165**)



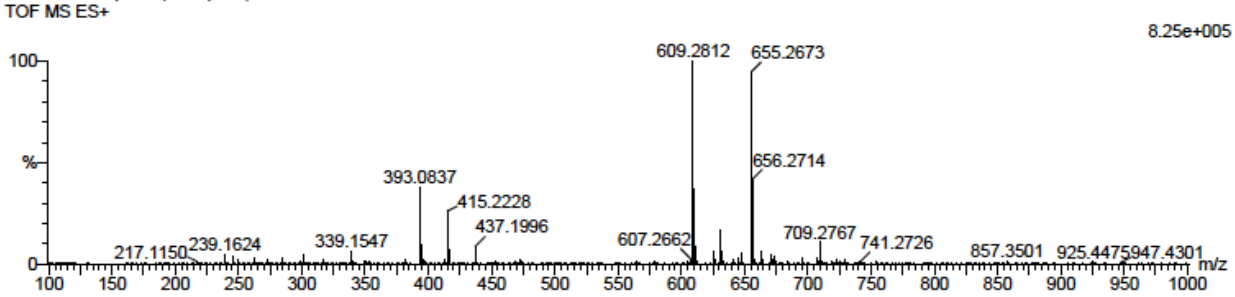
(**4.165**)

Calcd for $C_{19}H_{22}O_7Na$: 655.2674 g/mol. Found: *m/z* 655.2673.

Elemental Composition Report

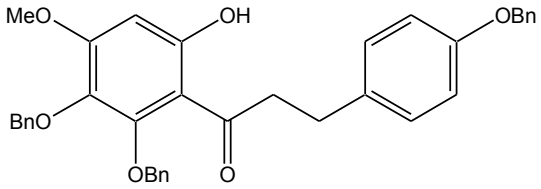
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 35-40 O: 0-10 Na: 1-1
8-OMe-36 15 (0.473) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
655.2673	655.2672	0.1	0.2	20.5	518.7	0.0	C40 H40 O7 Na

HRMS Analysis 20: 4,2',3'-Tribenzyloxy-6'-hydroxy-4'-methoxydihydrochalcone (**4.139**)



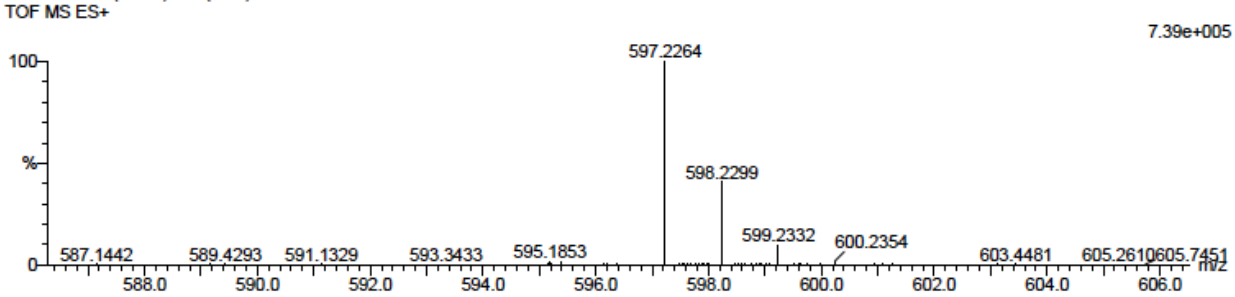
(**4.139**)

Calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2264.

Elemental Composition Report

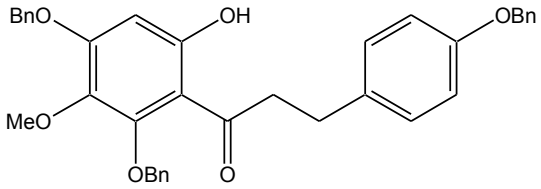
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
7-OMe-21 38 (1.248) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
597.2264	597.2253	1.1	1.8	20.5	528.5	0.0	C37 H34 O6 Na

HRMS Analysis 21: 4,2',4'-Tribenzyloxy-6'-hydroxy-3'-methoxydihydrochalcone (**4.140**)



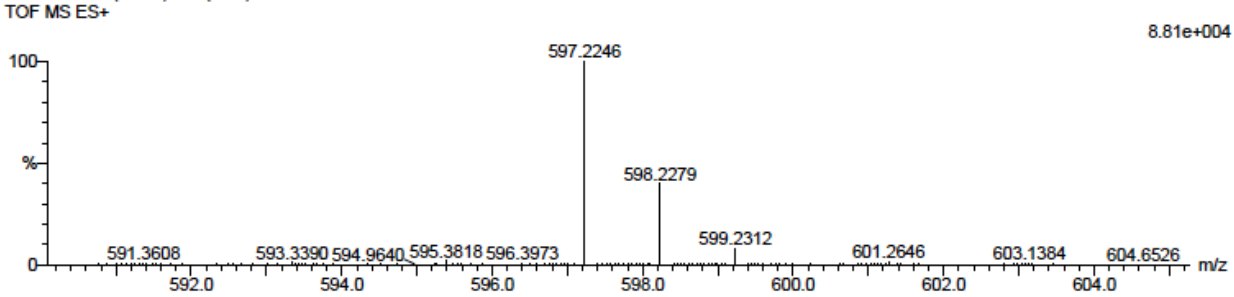
(**4.140**)

Calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2246.

Elemental Composition Report

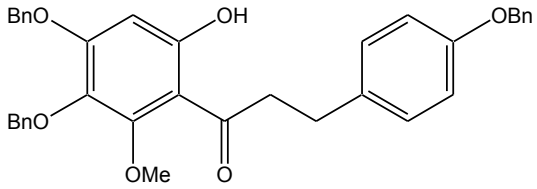
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
8-OMe-35 16 (0.507) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
597.2246	597.2253	-0.7	-1.2	20.5	445.3	0.0	C37 H34 O6 Na

HRMS Analysis 22: 4,3',4'-Tribenzyloxy-6'-hydroxy-2'-methoxydihydrochalcone (**4.141**)



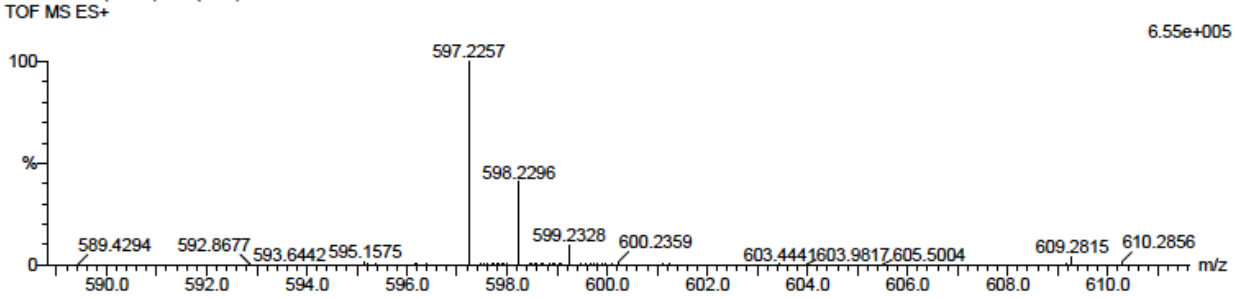
(**4.141**)

Calcd for $C_{37}H_{34}O_6Na$: 597.2275 g/mol. Found: *m/z* 597.2257.

Elemental Composition Report

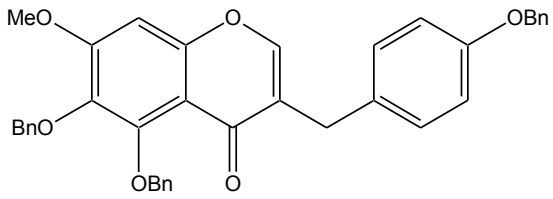
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
5-OMe-13 2 (0.034) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
597.2257	597.2253	0.4	0.7	20.5	510.2	0.0	C37 H34 O6 Na

HRMS Analysis 23: 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavone (**4.142**)



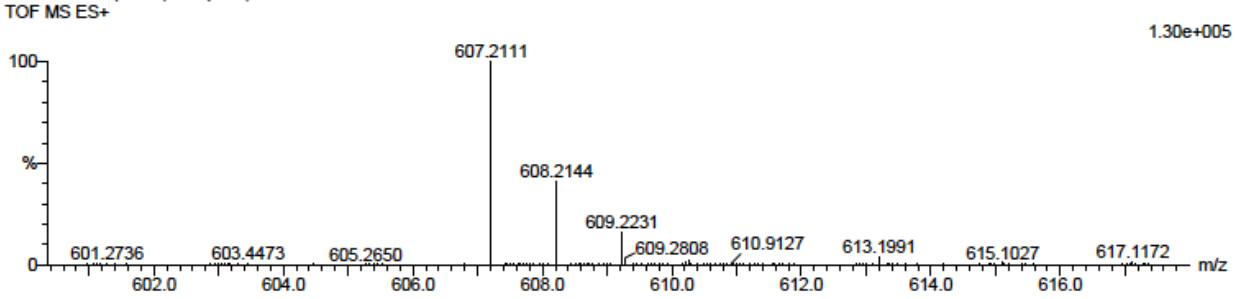
(**4.142**)

Calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2111.

Elemental Composition Report

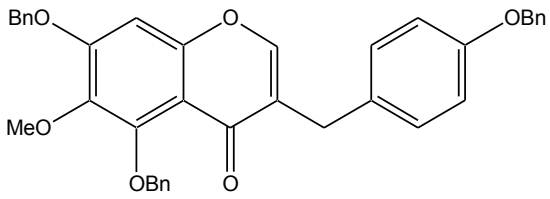
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
7-OMe-22 39 (1.283) Cm (1:61)
TOF MS ES+



Minimum:				-1.5					
Maximum:		5.0	5.0	100.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
607.2111	607.2097	1.4	2.3	22.5	470.2	0.0	C38	H32	O6 Na

HRMS Analysis 24: 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavone (**4.143**)



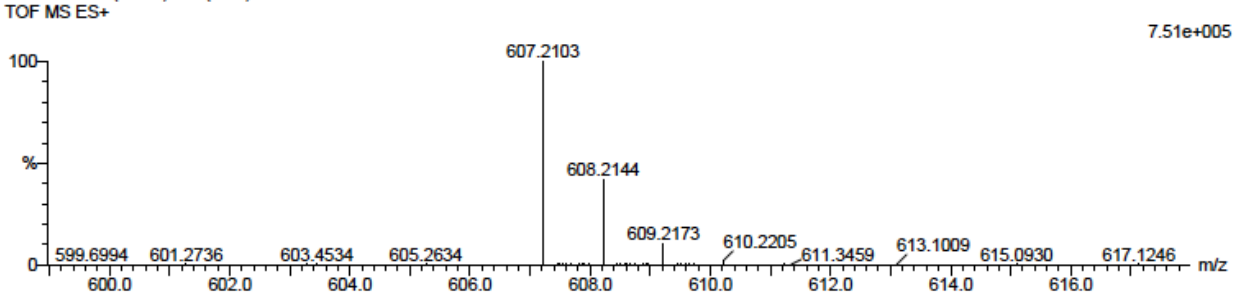
(**4.143**)

Calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2103.

Elemental Composition Report

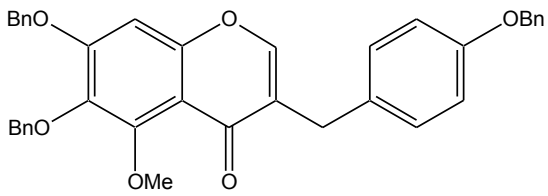
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
8-OMe-33 15 (0.506) Cm (1:60)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
607.2103	607.2097	0.6	1.0	22.5	524.3	0.0	C38 H32 O6 Na

HRMS Analysis 25: 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavone (**4.144**)



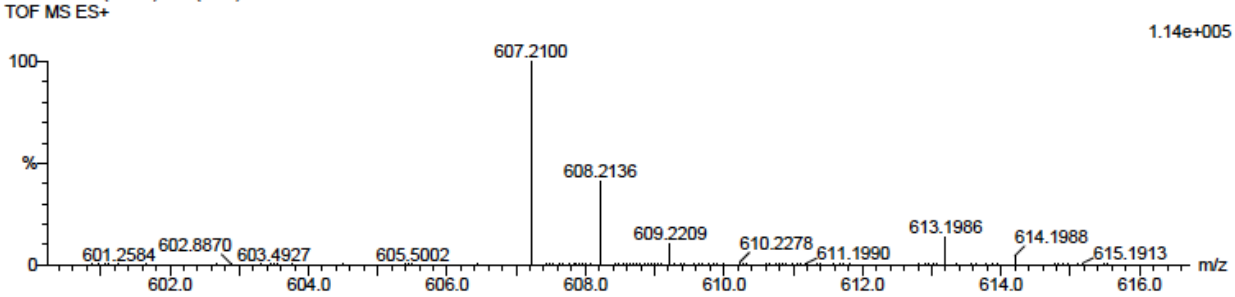
(**4.144**)

Calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2100.

Elemental Composition Report

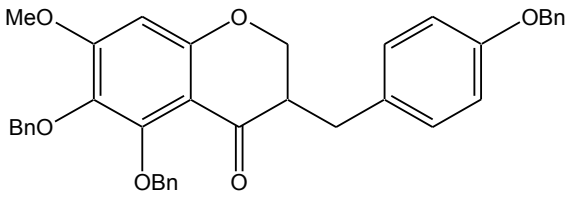
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
5-OMe-14 2 (0.034) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
607.2100	607.2097	0.3	0.5	22.5	440.9	0.0	C38 H32 O6 Na

HRMS Analysis 26: 5,6,4'-Tribenzyloxy-7-methoxyhomoisoflavanone (**4.147**)



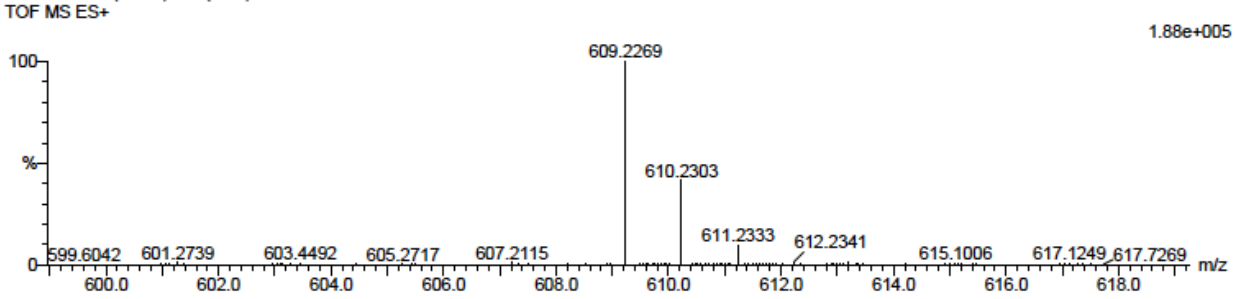
(**4.147**)

Calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2269.

Elemental Composition Report

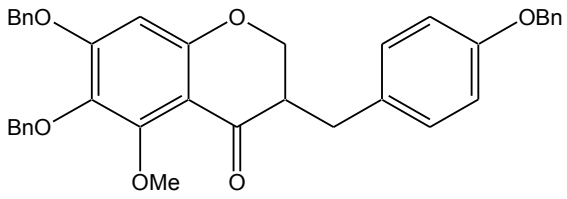
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
7-OMe-23 35 (1.181) Cm (1:60)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
609.2269	609.2253	1.6	2.6	21.5	491.3	0.0	C38 H34 O6 Na

HRMS Analysis 27: 6,7,4'-Tribenzyloxy-5-methoxyhomoisoflavanone (**4.148**)



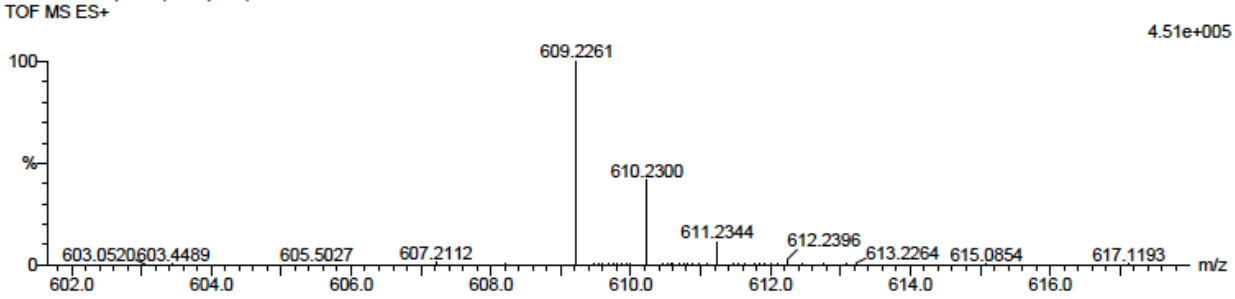
(**4.148**)

Calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2261.

Elemental Composition Report

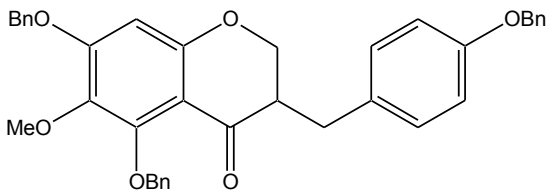
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
5-OMe-15 36 (1.181) Cm (1:61)
TOF MS ES+



Minimum:				-1.5						
Maximum:		5.0	5.0	100.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
609.2261	609.2253	0.8	1.3	21.5	505.4	0.0	C38	H34	O6	Na

HRMS Analysis 28: 5,7,4'-Tribenzyloxy-6-methoxyhomoisoflavanone (**4.149**)



(**4.149**)

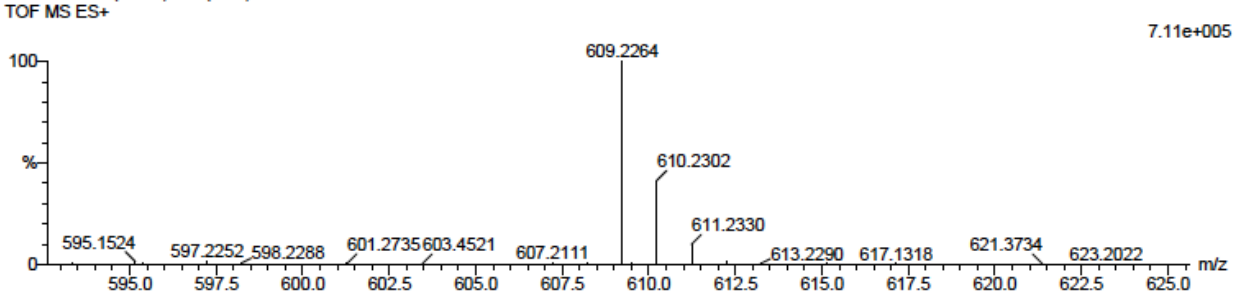
Calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2264.

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

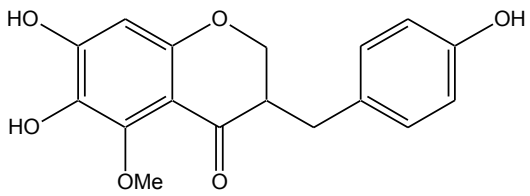
Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1

6-OMe-28 26 (0.844) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
609.2264	609.2253	1.1	1.8	21.5	514.3	0.0	C38 H34 O6 Na

HRMS Analysis 29: 6,7,4'-Trihydroxy-5-methoxyhomoisoflavanone (**4.151**)



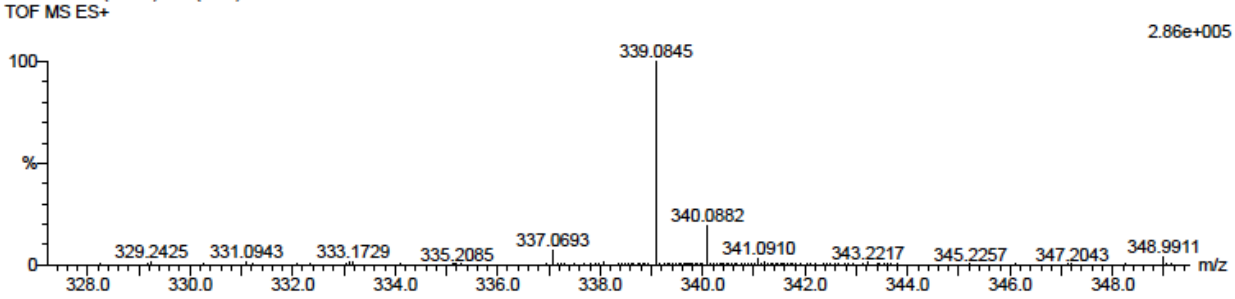
(**4.151**)

Calcd for $C_{17}H_{16}O_6Na$: 339.0847 g/mol. Found: *m/z* 339.0845.

Elemental Composition Report

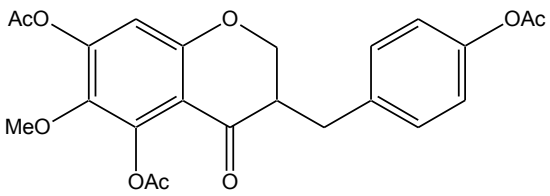
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-10 Na: 1-1
5-OMe-16 7 (0.203) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
339.0845	339.0845	0.0	0.0	9.5	638.8	0.0	C17 H16 O6 Na

HRMS Analysis 30: 5,7,4'-Triacetoxy-6-methoxyhomoisoflavanone (**4.153**)



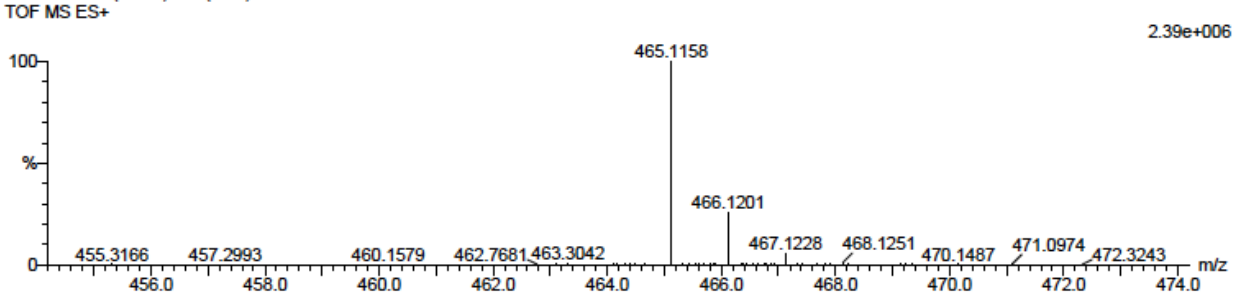
(**4.153**)

Calcd for $C_{23}H_{22}O_9Na$: 465.1164 g/mol. Found: *m/z* 465.1158.

Elemental Composition Report

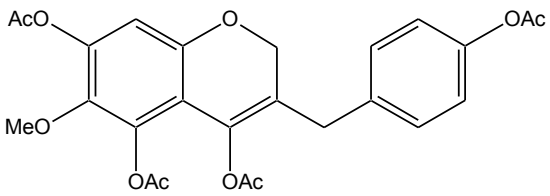
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 O: 0-10 Na: 1-1
6-OMe-29 23 (0.742) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
465.1158	465.1162	-0.4	-0.9	12.5	662.4	0.0	C23 H22 O9 Na

HRMS Analysis 31: 3-(4-Acetoxybenzyl)-4,5,7-triacetoxy-6-methoxyhomoisoflav-3-ene (**4.154**)



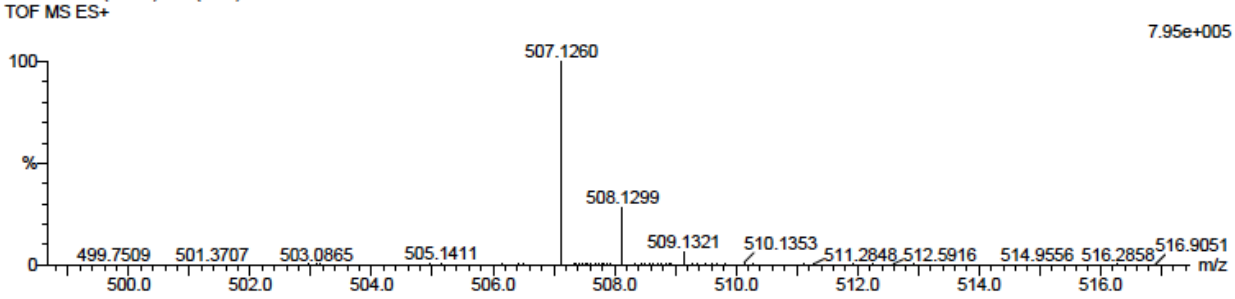
(**4.154**)

Calcd for $C_{25}H_{24}O_{10}Na$: 507.1269 g/mol. Found: *m/z* 507.1260.

Elemental Composition Report

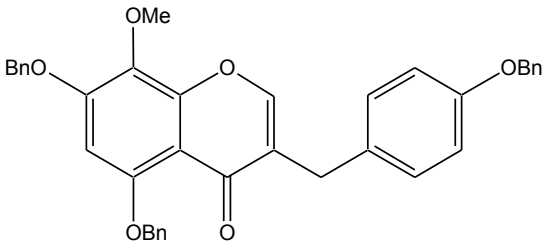
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
8 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 O: 0-10 Na: 1-1
8-OMe-34 9 (0.271) Cm (1:61)
TOF MS ES+



Minimum:				-1.5					
Maximum:		5.0	5.0	100.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
507.1260	507.1267	-0.7	-1.4	13.5	596.8	0.0	C25	H24	O10 Na

HRMS Analysis 32: 5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavone (**4.157**)



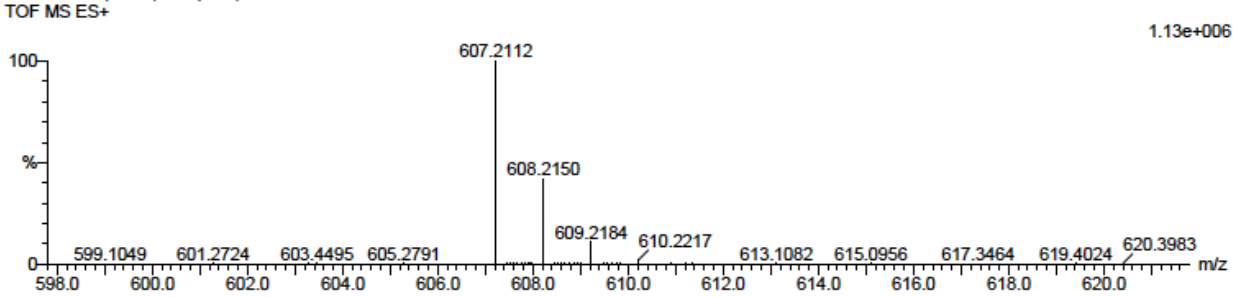
(**4.157**)

Calcd for $C_{38}H_{32}O_6Na$: 607.2199 g/mol. Found: *m/z* 607.2112.

Elemental Composition Report

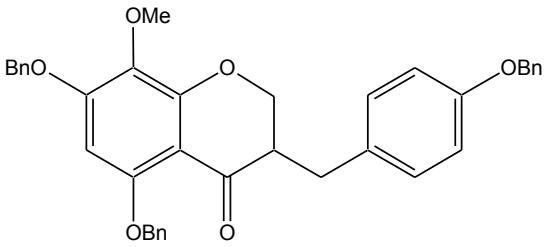
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
8-OMe-32 9 (0.270) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
607.2112	607.2097	1.5	2.5	22.5	559.8	0.0	C38 H32 O6 Na

HRMS Analysis 33: 5,7,4'-Tribenzyloxy-8-methoxyhomoisoflavanone (**4.158**)



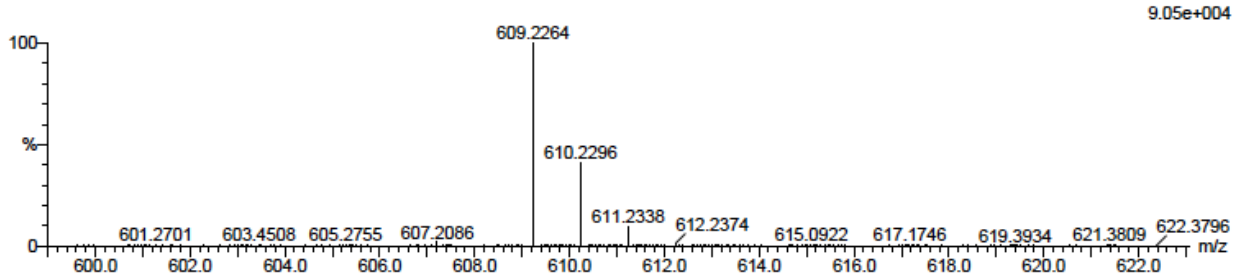
(**4.158**)

Calcd for $C_{38}H_{34}O_6Na$: 609.2255 g/mol. Found: *m/z* 609.2264.

Elemental Composition Report

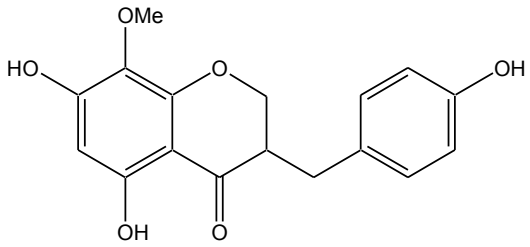
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 35-40 H: 30-35 O: 0-10 Na: 1-1
8-OMe-31 39 (1.283) Cm (1:59)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
609.2264	609.2253	1.1	1.8	21.5	447.1	0.0	C38 H34 O6 Na

HRMS Analysis 34: 5,7,4'-Trihydroxy-8-methoxyhomoisoflavanone (**4.159**)



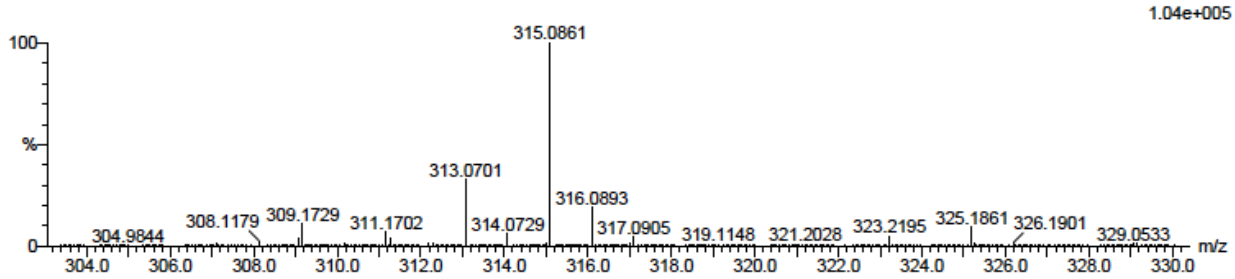
(**4.159**)

Calcd for $C_{17}H_{16}O_6$: 316.0847 g/mol. Found: *m/z* 316.0893.

Elemental Composition Report

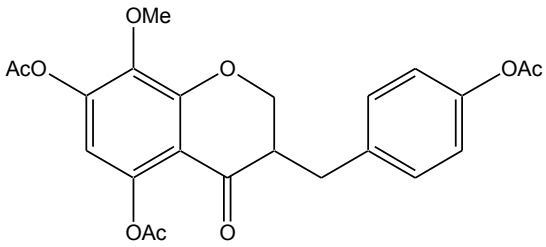
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-10
6-OMe-27 8 (0.236) Cm (1:61)
TOF MS ES-



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
315.0861	315.0869	-0.8	-2.5	10.5	577.9	0.0	C17 H15 O6

HRMS Analysis 35: 5,7,4'-Triacetoxy-8-methoxyhomoisoflavanone (**4.160**)



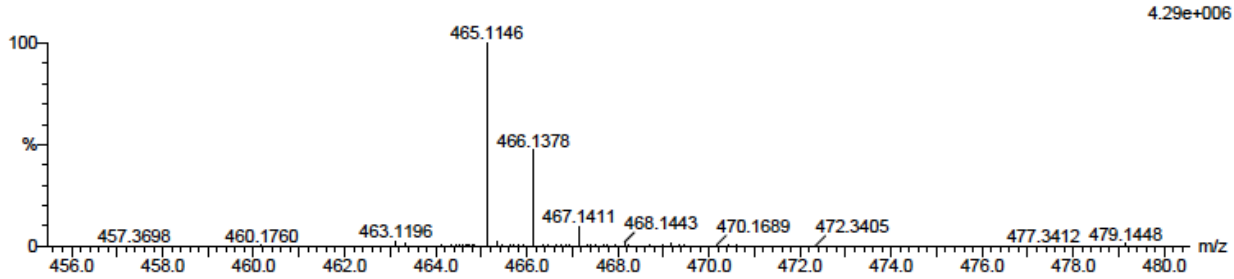
(**4.160**)

Calcd for $C_{23}H_{22}O_9Na$: 465.1164 g/mol. Found: *m/z* 465.1146.

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
6 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 O: 0-10 Na: 1-1
6-OMe-30 57 (1.888) Cm (1:61)
TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
465.1146	465.1162	-1.6	-3.4	12.5	547.8	0.0	C23 H22 O9 Na

APPENDIX C

OPTIMIZED COORDINATES

APPENDIX C: SUPPORTING INFORMATION FOR OPTIMIZED COORDINATES

Contents

Optimized Cartesian coordinates (Å)

All compounds were optimized with B3LYP/6-31G(d,p)

1. *Oxane* (2,5-twisted boat)

O	-1.084569000	0.509069000	0.118034000
C	-0.620895000	0.097185000	-1.167673000
C	0.876583000	-0.282632000	-1.167041000
C	1.589391000	0.443929000	-0.019930000
C	0.978203000	0.020047000	1.333949000
C	-0.527455000	-0.277927000	1.163207000
H	-0.801108000	0.954247000	-1.824923000
H	-1.231511000	-0.743250000	-1.537254000
H	1.321265000	-0.033272000	-2.136611000
H	0.996740000	-1.365899000	-1.039268000
H	1.468154000	1.524916000	-0.153191000
H	2.665392000	0.242015000	-0.037429000
H	1.481629000	-0.874642000	1.721447000
H	1.128382000	0.813916000	2.073288000
H	-1.091134000	-0.031714000	2.067410000
H	-0.690241000	-1.349026000	0.957967000

2. *Oxane* (chair)

O	-1.222956000	0.223966000	0.022949000
C	-0.564541000	-0.219722000	-1.158101000
C	0.873655000	0.298725000	-1.236938000
C	1.655381000	-0.109341000	0.021322000
C	0.874752000	0.295623000	1.281273000
C	-0.563619000	-0.222440000	1.202461000
H	-1.167040000	0.144425000	-1.995721000
H	-0.565767000	-1.324005000	-1.195952000
H	0.848596000	1.392649000	-1.318863000
H	1.357116000	-0.085315000	-2.143581000
H	2.654914000	0.339809000	0.021477000
H	1.799797000	-1.199176000	0.019899000
H	1.358957000	-0.090771000	2.186517000
H	0.849917000	1.389340000	1.365964000
H	-1.165309000	0.139995000	2.041404000
H	-0.565031000	-1.326799000	1.237870000

3. *Chromane*

O	-1.376974000	-0.021585000	-0.279087000
C	-0.554657000	0.668168000	-1.225621000
C	0.823552000	0.029391000	-1.349506000
C	1.532399000	0.092819000	0.008652000
H	-0.460073000	1.721482000	-0.920905000
H	-1.108989000	0.633898000	-2.166794000

H	1.403244000	0.545194000	-2.122677000
H	0.702753000	-1.012445000	-1.668619000
H	2.427651000	-0.539283000	0.008219000
H	1.882680000	1.119239000	0.188210000
C	0.597829000	-0.334857000	1.122965000
C	-0.791531000	-0.363795000	0.913207000
C	1.080464000	-0.724548000	2.378369000
H	2.154976000	-0.711134000	2.548211000
C	-1.661044000	-0.780884000	1.928423000
C	0.224462000	-1.131996000	3.398631000
H	-2.726167000	-0.793863000	1.721305000
H	0.626285000	-1.429191000	4.362294000
C	-1.153684000	-1.162575000	3.165545000
H	-1.834571000	-1.482505000	3.948978000

4. *Flavan (2R)-equatorial*

O	-1.212920000	-0.943308000	-0.614756000
C	-0.454797000	-0.108657000	-1.505012000
C	0.056481000	1.133879000	-0.762749000
C	0.974050000	0.710689000	0.388891000
H	0.413306000	-0.686810000	-1.858832000
H	-0.810983000	1.687817000	-0.385039000
H	0.580242000	1.788461000	-1.466344000
H	1.946998000	0.396255000	-0.014790000
H	1.178898000	1.562549000	1.047349000
C	0.355286000	-0.420234000	1.183027000
C	-0.695139000	-1.174005000	0.635659000
C	0.789389000	-0.740354000	2.475381000
H	1.599103000	-0.158465000	2.910349000
C	-1.294923000	-2.206664000	1.366463000
C	0.206538000	-1.770578000	3.209170000
H	-2.106645000	-2.760540000	0.906228000
H	0.562318000	-1.997304000	4.209384000
C	-0.844575000	-2.502294000	2.648481000
H	-1.312890000	-3.305821000	3.209419000
C	-1.334624000	0.234251000	-2.687721000
C	-2.710813000	0.436498000	-2.532597000
C	-0.760584000	0.408722000	-3.952020000
H	-3.161644000	0.281467000	-1.558336000
H	0.305720000	0.241108000	-4.085925000
C	-3.495421000	0.810437000	-3.623707000
C	-1.543404000	0.789001000	-5.042263000
H	-4.563529000	0.958686000	-3.492340000
H	-1.084013000	0.918159000	-6.018028000
C	-2.914706000	0.991243000	-4.880287000
H	-3.527544000	1.281331000	-5.728750000

5. *Flavan (2R)-axial*

O	-0.415334000	-1.792034000	-1.018245000

C	0.055520000	-0.840533000	-1.985217000
C	1.171661000	0.037123000	-1.395934000
C	0.670613000	0.766041000	-0.146545000
H	0.481308000	-1.465349000	-2.779116000
H	1.518943000	0.744555000	-2.154561000
H	2.017700000	-0.610232000	-1.137334000
H	1.493977000	1.293935000	0.347026000
H	-0.061143000	1.530887000	-0.439642000
C	0.041354000	-0.224515000	0.805585000
C	-0.457816000	-1.439352000	0.309077000
C	-0.051931000	0.012127000	2.182020000
H	0.340151000	0.947640000	2.574874000
C	-1.028400000	-2.385322000	1.169619000
C	-0.625544000	-0.916838000	3.047135000
H	-1.394813000	-3.314926000	0.746252000
H	-0.686352000	-0.707660000	4.110569000
C	-1.112747000	-2.121903000	2.532826000
H	-1.557803000	-2.859413000	3.194403000
C	-1.092837000	-0.034340000	-2.584964000
C	-2.388241000	-0.079050000	-2.060848000
C	-0.849132000	0.764029000	-3.711988000
H	-2.597182000	-0.709731000	-1.204781000
H	0.147041000	0.794033000	-4.147660000
C	-3.413032000	0.673627000	-2.639562000
C	-1.871545000	1.512740000	-4.291722000
H	-4.413150000	0.629338000	-2.217869000
H	-1.664058000	2.123051000	-5.166083000
C	-3.159636000	1.472774000	-3.753420000
H	-3.958397000	2.054820000	-4.203596000

6. *Flavan-3ol (2S)-equatorial, (3S)-axial*

O	-1.295860000	-1.019972000	-0.438928000
C	-0.591670000	-0.223944000	-1.394158000
C	0.078194000	0.997590000	-0.718306000
C	1.055290000	0.512089000	0.349978000
H	0.209608000	-0.829861000	-1.845524000
H	0.626724000	1.547485000	-1.499815000
H	1.964662000	0.143572000	-0.143511000
H	1.352683000	1.367921000	0.964607000
C	0.445223000	-0.572100000	1.210045000
C	-0.685040000	-1.271928000	0.765554000
C	0.973255000	-0.904366000	2.462769000
H	1.844306000	-0.360395000	2.821186000
C	-1.270675000	-2.268907000	1.552746000
C	0.405411000	-1.900510000	3.253804000
H	-2.147113000	-2.782020000	1.170565000
H	0.834932000	-2.139124000	4.221781000
C	-0.725269000	-2.581144000	2.793740000
H	-1.182377000	-3.357196000	3.400651000
C	-1.571611000	0.190384000	-2.470709000

C	-2.922851000	0.411085000	-2.172129000
C	-1.115166000	0.429596000	-3.773281000
H	-3.282106000	0.198689000	-1.171181000
H	-0.070724000	0.251504000	-4.018096000
C	-3.798387000	0.862934000	-3.162139000
C	-1.989423000	0.883865000	-4.759684000
H	-4.845354000	1.022621000	-2.920924000
H	-1.622519000	1.059381000	-5.766738000
C	-3.334848000	1.102985000	-4.455804000
H	-4.017633000	1.451690000	-5.224922000
O	-0.872077000	1.831602000	-0.079921000
H	-1.558409000	2.050299000	-0.727021000

7. *Flavan-3ol (2S)-axial, (3S)-equatorial*

O	-0.318100000	-1.796387000	-0.973659000
C	-0.091952000	-0.729620000	-1.910223000
C	1.069413000	0.131687000	-1.354031000
C	0.624062000	0.813897000	-0.069541000
H	0.266833000	-1.247246000	-2.810024000
H	1.874219000	-0.580081000	-1.114749000
H	1.481080000	1.300379000	0.407799000
H	-0.094460000	1.603907000	-0.322050000
C	0.003474000	-0.209083000	0.858730000
C	-0.425583000	-1.447810000	0.356363000
C	-0.138352000	0.027752000	2.231012000
H	0.195536000	0.982565000	2.630377000
C	-0.964280000	-2.420748000	1.204781000
C	-0.682508000	-0.928949000	3.084959000
H	-1.273722000	-3.368653000	0.776380000
H	-0.779922000	-0.720105000	4.145673000
C	-1.090223000	-2.160744000	2.565779000
H	-1.509613000	-2.919355000	3.220069000
C	-1.392359000	-0.001792000	-2.254615000
C	-2.625380000	-0.559297000	-1.891111000
C	-1.388373000	1.189316000	-2.997976000
H	-2.645275000	-1.485179000	-1.329068000
H	-0.444661000	1.638813000	-3.281571000
C	-3.822878000	0.062680000	-2.246354000
C	-2.587471000	1.809313000	-3.350595000
H	-4.767146000	-0.385457000	-1.950284000
H	-2.562807000	2.734212000	-3.920103000
C	-3.809899000	1.250421000	-2.976738000
H	-4.741916000	1.734874000	-3.253256000
O	1.545664000	1.118688000	-2.260385000
H	1.987776000	0.665827000	-2.990956000

8. *Flavan-3ol (2R)-equatorial, (3R)-axial*

O	-1.479346000	-0.785197000	-0.579676000
C	-0.552318000	-0.284844000	-1.545219000

C	0.903308000	-0.650492000	-1.164373000
C	1.232476000	-0.057572000	0.203729000
H	-0.618858000	0.814166000	-1.570917000
H	1.564663000	-0.210357000	-1.927865000
H	2.169304000	-0.499301000	0.558524000
H	1.412360000	1.019756000	0.088386000
C	0.119978000	-0.303412000	1.198325000
C	-1.162940000	-0.646883000	0.750035000
C	0.329709000	-0.206436000	2.578586000
H	1.324173000	0.049776000	2.937048000
C	-2.201129000	-0.890326000	1.655294000
C	-0.696793000	-0.438094000	3.491341000
H	-3.177283000	-1.157366000	1.263751000
H	-0.507591000	-0.355828000	4.557097000
C	-1.966726000	-0.785611000	3.022454000
H	-2.776360000	-0.973835000	3.721461000
C	-0.940933000	-0.840699000	-2.898361000
C	-1.527755000	-2.107571000	-3.018108000
C	-0.646727000	-0.115026000	-4.059881000
H	-1.781525000	-2.657157000	-2.118319000
H	-0.200873000	0.873397000	-3.977731000
C	-1.813639000	-2.635153000	-4.279380000
C	-0.929473000	-0.644226000	-5.318313000
H	-2.276064000	-3.614732000	-4.359451000
H	-0.701208000	-0.067580000	-6.209917000
C	-1.513468000	-1.907842000	-5.431317000
H	-1.738956000	-2.318511000	-6.411030000
O	1.087438000	-2.052152000	-1.077390000
H	0.771024000	-2.445718000	-1.903593000

9. *Flavan-3ol (2R)-axial, (3R)-equatorial*

O	-1.533717000	0.627997000	-0.677911000
C	-0.618360000	0.535053000	-1.782284000
C	0.810186000	0.721080000	-1.212402000
C	1.151829000	-0.453604000	-0.308530000
H	-0.859915000	1.415167000	-2.393282000
H	0.765708000	1.635376000	-0.601114000
H	1.309219000	-1.342715000	-0.932141000
H	2.093951000	-0.257290000	0.213830000
C	0.026992000	-0.675432000	0.680805000
C	-1.241000000	-0.122367000	0.441573000
C	0.213574000	-1.403939000	1.861408000
H	1.193707000	-1.832154000	2.057902000
C	-2.281252000	-0.282389000	1.362946000
C	-0.816978000	-1.579131000	2.782217000
H	-3.242710000	0.170649000	1.143500000
H	-0.645021000	-2.147574000	3.690799000
C	-2.067446000	-1.008057000	2.530627000
H	-2.878611000	-1.129774000	3.242436000
C	-0.873611000	-0.720696000	-2.617279000

C	-2.045366000	-1.464655000	-2.425672000
C	0.011267000	-1.113933000	-3.634015000
H	-2.744895000	-1.165878000	-1.654372000
H	0.925712000	-0.555427000	-3.791868000
C	-2.320132000	-2.580675000	-3.216961000
C	-0.265847000	-2.230918000	-4.422709000
H	-3.232897000	-3.144960000	-3.047939000
H	0.435095000	-2.522811000	-5.199794000
C	-1.431430000	-2.969980000	-4.218428000
H	-1.645032000	-3.838740000	-4.834416000
O	1.819295000	0.848251000	-2.206347000
H	1.692148000	1.694697000	-2.655387000

10. *Flavan-3ol (2S)-equatorial, (3R)-equatorial*

O	-1.476565000	0.450158000	-0.446626000
C	-0.850326000	0.479478000	-1.734952000
C	0.594368000	1.020144000	-1.604608000
C	1.401217000	0.081295000	-0.715625000
H	-0.786080000	-0.545801000	-2.129241000
H	0.529816000	2.016501000	-1.139038000
H	1.646621000	-0.808067000	-1.311878000
H	2.354872000	0.550097000	-0.450784000
C	0.628653000	-0.301387000	0.527815000
C	-0.758705000	-0.100991000	0.588174000
C	1.261821000	-0.850380000	1.649507000
H	2.337864000	-1.004546000	1.615925000
C	-1.486148000	-0.431953000	1.736464000
C	0.548745000	-1.190207000	2.796750000
H	-2.556978000	-0.256877000	1.739482000
H	1.064178000	-1.613615000	3.653110000
C	-0.831630000	-0.973953000	2.837715000
H	-1.400009000	-1.230203000	3.726942000
C	-1.700291000	1.324748000	-2.656984000
C	-1.689366000	1.074583000	-4.036450000
C	-2.451154000	2.401226000	-2.167558000
H	-1.120836000	0.233135000	-4.423253000
H	-2.474116000	2.586648000	-1.099400000
C	-2.411093000	1.888662000	-4.911392000
C	-3.178311000	3.208361000	-3.042185000
H	-2.396548000	1.680184000	-5.977222000
H	-3.763446000	4.035047000	-2.649588000
C	-3.158050000	2.957794000	-4.415812000
H	-3.725775000	3.587789000	-5.094217000
O	1.245896000	1.079953000	-2.862169000
H	0.769433000	1.718323000	-3.411558000

11. *Flavan-3ol (2S)-equatorial, (3R)-axial*

O	-1.456304000	0.407149000	-0.486385000

C	-0.813120000	0.473276000	-1.768692000
C	0.629843000	1.011033000	-1.611570000
C	1.425380000	0.082703000	-0.691349000
H	-0.749180000	-0.547471000	-2.182377000
H	0.561650000	2.012009000	-1.171565000
H	1.690039000	-0.822699000	-1.261598000
H	2.372627000	0.559290000	-0.417202000
C	0.637578000	-0.301332000	0.541393000
C	-0.753231000	-0.124293000	0.565438000
C	1.255909000	-0.829343000	1.681196000
H	2.335111000	-0.964027000	1.673397000
C	-1.500823000	-0.460266000	1.700024000
C	0.522686000	-1.172768000	2.814378000
H	-2.574195000	-0.303643000	1.677368000
H	1.025204000	-1.579027000	3.686499000
C	-0.862223000	-0.981670000	2.820167000
H	-1.446662000	-1.241128000	3.697971000
C	-1.671952000	1.326516000	-2.674607000
C	-1.724487000	1.058445000	-4.046410000
C	-2.387427000	2.417372000	-2.167647000
H	-1.179262000	0.209360000	-4.449822000
H	-2.364235000	2.617684000	-1.101945000
C	-2.472012000	1.868065000	-4.900870000
C	-3.140093000	3.224615000	-3.020574000
H	-2.503786000	1.646701000	-5.963735000
H	-3.695880000	4.064883000	-2.614315000
C	-3.182738000	2.954608000	-4.389315000
H	-3.770081000	3.583378000	-5.052144000
O	1.269683000	1.188625000	-2.864517000
H	1.455187000	0.312318000	-3.230267000

12. Flavan-3ol (2R)-equatorial, (3S)-equatorial

O	-1.522169000	-0.863904000	-0.530428000
C	-0.620399000	-0.311542000	-1.497240000
C	0.838392000	-0.661752000	-1.115200000
C	1.164659000	-0.037574000	0.236361000
H	-0.710537000	0.785083000	-1.490646000
H	0.904129000	-1.759438000	-1.048546000
H	2.112229000	-0.438922000	0.611003000
H	1.324464000	1.036976000	0.073466000
C	0.051879000	-0.270119000	1.234896000
C	-1.221807000	-0.662053000	0.795884000
C	0.252519000	-0.115547000	2.611935000
H	1.237572000	0.182047000	2.963890000
C	-2.257508000	-0.898583000	1.706116000
C	-0.771511000	-0.341803000	3.528669000
H	-3.225459000	-1.202845000	1.321629000
H	-0.589078000	-0.215642000	4.591260000
C	-2.030278000	-0.739548000	3.069236000
H	-2.837110000	-0.923424000	3.772553000

C	-1.001838000	-0.843215000	-2.860636000
C	-1.568858000	-2.115315000	-3.010430000
C	-0.724548000	-0.083107000	-4.005599000
H	-1.799135000	-2.698278000	-2.125563000
H	-0.297549000	0.910357000	-3.897947000
C	-1.854874000	-2.613906000	-4.281164000
C	-1.003718000	-0.587201000	-5.277260000
H	-2.302293000	-3.598377000	-4.383914000
H	-0.787379000	0.014802000	-6.155016000
C	-1.570344000	-1.854364000	-5.417922000
H	-1.794754000	-2.245209000	-6.406011000
O	1.764002000	-0.145988000	-2.056719000
H	1.595797000	-0.580482000	-2.904824000

13. Flavan-3ol (2R)-axial, (3S)-axial

O	-1.598440000	0.555317000	-0.753155000
C	-0.672319000	0.496429000	-1.852664000
C	0.783851000	0.581372000	-1.346368000
C	1.058376000	-0.560905000	-0.363530000
H	-0.870373000	1.416121000	-2.413244000
H	1.453557000	0.506240000	-2.207352000
H	1.069382000	-1.511764000	-0.911843000
H	2.051628000	-0.427120000	0.076379000
C	-0.004804000	-0.585399000	0.711255000
C	-1.270915000	-0.040480000	0.442205000
C	0.221257000	-1.131041000	1.980828000
H	1.202839000	-1.544806000	2.199825000
C	-2.277962000	-0.047755000	1.415640000
C	-0.774578000	-1.152225000	2.954167000
H	-3.239754000	0.389894000	1.168881000
H	-0.575114000	-1.584386000	3.929633000
C	-2.028589000	-0.605429000	2.665097000
H	-2.813765000	-0.610433000	3.415362000
C	-0.930238000	-0.700697000	-2.754868000
C	-1.775637000	-1.750124000	-2.380563000
C	-0.307154000	-0.750570000	-4.010510000
H	-2.285046000	-1.714609000	-1.424546000
H	0.332946000	0.069122000	-4.328641000
C	-1.978514000	-2.834817000	-3.236645000
C	-0.509930000	-1.832726000	-4.864955000
H	-2.638417000	-3.641697000	-2.931043000
H	-0.020940000	-1.852901000	-5.834640000
C	-1.345519000	-2.882631000	-4.478101000
H	-1.506726000	-3.726016000	-5.142974000
O	1.043323000	1.857048000	-0.777012000
H	0.492498000	1.943889000	0.013938000

14. *4-Arylflavan (2S)-equatorial, (4R)-axial*

O	-0.734790000	-1.285237000	-0.159088000

C	0.120876000	-0.577275000	-1.073339000
C	1.578134000	-1.002436000	-0.871826000
C	2.048332000	-0.658728000	0.561399000
H	0.035899000	0.497567000	-0.855950000
H	2.971445000	-1.222322000	0.739516000
C	1.005397000	-1.145704000	1.551597000
C	-0.303549000	-1.434306000	1.132521000
C	1.325352000	-1.357032000	2.900106000
H	2.337201000	-1.134785000	3.230866000
C	-1.253453000	-1.926902000	2.038475000
C	0.389147000	-1.840100000	3.809122000
H	-2.252089000	-2.140263000	1.671440000
H	0.665356000	-1.995914000	4.847285000
C	-0.907280000	-2.128083000	3.369038000
H	-1.649748000	-2.508775000	4.064462000
C	-0.378688000	-0.837999000	-2.478151000
C	-0.966172000	-2.059177000	-2.827400000
C	-0.206251000	0.139389000	-3.465336000
H	-1.119500000	-2.810585000	-2.060535000
H	0.238029000	1.096301000	-3.201102000
C	-1.369843000	-2.297177000	-4.141534000
C	-0.603502000	-0.100504000	-4.780664000
H	-1.830298000	-3.246956000	-4.398771000
H	-0.465832000	0.668961000	-5.534996000
C	-1.187227000	-1.321404000	-5.122734000
H	-1.503315000	-1.508170000	-6.144955000
C	2.398268000	0.821131000	0.709217000
C	1.566606000	1.759072000	1.331160000
C	3.614355000	1.297994000	0.186133000
H	0.631331000	1.416963000	1.761989000
C	1.900165000	3.108197000	1.434456000
C	3.973862000	2.644664000	0.280620000
H	1.242167000	3.818211000	1.922346000
H	4.923457000	2.983339000	-0.132592000
C	3.112918000	3.552240000	0.905941000
O	4.434367000	0.383325000	-0.424047000
O	3.412694000	4.880271000	1.026264000
H	5.244052000	0.823218000	-0.713302000
H	4.275900000	5.051267000	0.628065000
H	2.214213000	-0.513064000	-1.613022000
H	1.648987000	-2.083685000	-1.040149000

15. *4-Arylflavan (2S)-axial, (4R)-equatorial*

O	-1.761345000	-0.325050000	-0.440482000
C	-0.957760000	0.185263000	-1.512799000
C	0.182789000	1.047202000	-0.960967000
C	1.088757000	0.227859000	-0.019965000
H	-1.646830000	0.827185000	-2.074021000
H	1.537467000	-0.573874000	-0.628928000
C	0.216046000	-0.483881000	1.006689000

C	-1.141913000	-0.714350000	0.723344000
C	0.721723000	-0.971088000	2.219846000
H	1.770668000	-0.807145000	2.446202000
C	-1.966318000	-1.372563000	1.644645000
C	-0.086695000	-1.639247000	3.135712000
H	-3.011382000	-1.514445000	1.389177000
H	0.334256000	-2.002229000	4.068023000
C	-1.440364000	-1.831447000	2.846690000
H	-2.085812000	-2.343369000	3.554417000
C	-0.477587000	-0.927655000	-2.441636000
C	-0.727173000	-2.277111000	-2.171999000
C	0.219660000	-0.592577000	-3.612733000
H	-1.283217000	-2.549957000	-1.282939000
H	0.401657000	0.451584000	-3.855787000
C	-0.272806000	-3.270159000	-3.043226000
C	0.670626000	-1.583585000	-4.483563000
H	-0.473063000	-4.313320000	-2.816190000
H	1.206085000	-1.304274000	-5.386419000
C	0.429297000	-2.929276000	-4.198381000
H	0.780481000	-3.702683000	-4.874948000
C	2.205524000	1.089688000	0.550137000
C	1.991196000	1.937996000	1.647594000
C	3.474840000	1.135509000	-0.057885000
H	1.018493000	1.922911000	2.130212000
C	2.976582000	2.778459000	2.149430000
C	4.483303000	1.969340000	0.437322000
H	2.794283000	3.421890000	3.002578000
H	5.448925000	1.964330000	-0.060733000
C	4.235585000	2.787324000	1.537545000
O	3.815418000	0.395411000	-1.157356000
O	5.185358000	3.620097000	2.058416000
H	3.061880000	-0.138592000	-1.440720000
H	6.000924000	3.525481000	1.549082000
H	-0.245428000	1.889494000	-0.406722000
H	0.769606000	1.467391000	-1.782764000

16. *4-Arylflavan (2R)-equatorial, (4S)-axial*

O	-3.126831000	-1.960848000	2.028561000
C	-2.526615000	-1.347604000	0.874047000
C	-1.430495000	-0.368610000	1.304231000
C	-0.309440000	-1.113350000	2.067101000
H	-2.068697000	-2.141773000	0.266275000
H	0.286517000	-0.352288000	2.583940000
C	-0.940367000	-2.006985000	3.120050000
C	-2.296510000	-2.363161000	3.041069000
C	-0.201907000	-2.470825000	4.217803000
H	0.848943000	-2.198922000	4.284234000
C	-2.889317000	-3.151161000	4.037746000
C	-0.778436000	-3.258074000	5.209762000
H	-3.940993000	-3.399748000	3.939291000

H	-0.182855000	-3.601738000	6.049720000
C	-2.132964000	-3.595270000	5.115426000
H	-2.599862000	-4.206410000	5.882442000
C	-3.625949000	-0.684163000	0.072600000
C	-4.745024000	-0.122104000	0.697209000
C	-3.502055000	-0.582464000	-1.318042000
H	-4.853826000	-0.216912000	1.772094000
H	-2.642153000	-1.026859000	-1.813992000
C	-5.719291000	0.532175000	-0.057298000
C	-4.472363000	0.077329000	-2.072099000
H	-6.586512000	0.959019000	0.438688000
H	-4.363719000	0.145434000	-3.150803000
C	-5.585278000	0.637310000	-1.442652000
H	-6.345481000	1.145976000	-2.028381000
C	0.637180000	-1.847783000	1.119078000
C	0.602441000	-3.229580000	0.900809000
C	1.599598000	-1.114798000	0.400499000
H	-0.115814000	-3.823835000	1.456116000
C	1.464009000	-3.872679000	0.014138000
C	2.477622000	-1.736318000	-0.490832000
H	1.421773000	-4.945035000	-0.138802000
H	3.213556000	-1.141821000	-1.031336000
C	2.408162000	-3.119594000	-0.684940000
O	1.639281000	0.240043000	0.610754000
O	3.240886000	-3.779971000	-1.544290000
H	2.353667000	0.623871000	0.086259000
H	3.844879000	-3.147665000	-1.954544000
H	-1.881968000	0.392902000	1.951320000
H	-1.025033000	0.143866000	0.428774000

17. *4-Arylflavan (2R)-axial, (4S)-equatorial*

O	-3.635999000	-2.911908000	1.754159000
C	-3.388002000	-2.408515000	0.434635000
C	-1.917168000	-2.609909000	0.054539000
C	-0.986379000	-1.874992000	1.039971000
H	-4.009631000	-3.042209000	-0.208685000
H	-1.212880000	-0.800068000	0.949699000
C	-1.379089000	-2.253532000	2.462915000
C	-2.673558000	-2.738799000	2.720303000
C	-0.513116000	-2.092980000	3.553407000
H	0.486070000	-1.711014000	3.368660000
C	-3.064910000	-3.087535000	4.019130000
C	-0.897951000	-2.423326000	4.850143000
H	-4.068751000	-3.472051000	4.167459000
H	-0.203221000	-2.290004000	5.673390000
C	-2.179391000	-2.931653000	5.079151000
H	-2.491684000	-3.201811000	6.083659000
C	-3.858367000	-0.963940000	0.280560000
C	-4.360742000	-0.229070000	1.359267000
C	-3.805209000	-0.354933000	-0.982832000

H	-4.428341000	-0.693009000	2.336129000
H	-3.443017000	-0.916314000	-1.840822000
C	-4.781983000	1.091207000	1.183008000
C	-4.228258000	0.961772000	-1.159181000
H	-5.166490000	1.647855000	2.032790000
H	-4.182019000	1.414856000	-2.145312000
C	-4.714848000	1.692448000	-0.072990000
H	-5.044073000	2.718404000	-0.208115000
C	0.475160000	-2.097063000	0.680018000
C	1.153125000	-3.268064000	1.053077000
C	1.179113000	-1.174722000	-0.117857000
H	0.628944000	-3.995915000	1.665273000
C	2.468644000	-3.521945000	0.686893000
C	2.507277000	-1.408207000	-0.490736000
H	2.977990000	-4.429432000	0.990425000
H	3.011268000	-0.663584000	-1.100685000
C	3.150222000	-2.577091000	-0.089199000
O	0.635888000	-0.010154000	-0.588240000
O	4.444888000	-2.853018000	-0.427700000
H	-0.282817000	0.064557000	-0.299007000
H	4.795015000	-2.123226000	-0.955277000
H	-1.740591000	-2.261227000	-0.966987000
H	-1.689479000	-3.681270000	0.073632000

18. *4-Arylflavan (2S)-equatorial, (4S)-equatorial*

O	-1.994415000	0.897829000	1.148297000
C	-1.709899000	2.301760000	1.250509000
C	-0.281148000	2.578844000	0.774896000
C	0.744001000	1.838208000	1.661109000
H	-1.794449000	2.591276000	2.309732000
H	0.764764000	2.355240000	2.628048000
C	0.276756000	0.408345000	1.913715000
C	-1.052513000	0.034915000	1.649785000
C	1.130157000	-0.565326000	2.452305000
H	2.158314000	-0.289394000	2.667815000
C	-1.493007000	-1.274377000	1.880394000
C	0.699405000	-1.866659000	2.696952000
H	-2.526318000	-1.515541000	1.653194000
H	1.386108000	-2.597444000	3.112926000
C	-0.618997000	-2.222612000	2.398838000
H	-0.968694000	-3.235188000	2.578110000
C	-2.751656000	3.051884000	0.448720000
C	-3.310252000	2.502961000	-0.711126000
C	-3.130622000	4.340953000	0.840913000
H	-3.032620000	1.497131000	-1.006700000
H	-2.710791000	4.771761000	1.747027000
C	-4.229644000	3.233630000	-1.464354000
C	-4.044668000	5.074444000	0.084662000
H	-4.661344000	2.794325000	-2.359270000
H	-4.331354000	6.072546000	0.403281000

C	-4.597455000	4.521552000	-1.071600000
H	-5.314424000	5.088089000	-1.658699000
C	2.141729000	1.954927000	1.069001000
C	2.604000000	1.107073000	0.058891000
C	3.003363000	2.990286000	1.479480000
H	1.961329000	0.297892000	-0.274517000
C	3.864081000	1.251083000	-0.520815000
C	4.270607000	3.151757000	0.918001000
H	4.192212000	0.568080000	-1.300454000
H	4.931792000	3.950290000	1.243398000
C	4.701931000	2.280188000	-0.083843000
O	2.546779000	3.843527000	2.450906000
O	5.952860000	2.488730000	-0.593816000
H	3.239563000	4.484342000	2.656837000
H	6.125086000	1.828335000	-1.277648000
H	-0.083215000	3.654621000	0.794720000
H	-0.193484000	2.248901000	-0.266880000

19. *4-Arylflavan (2S)-axial, (4S)-axial*

O	-2.240341000	1.346866000	2.413998000
C	-1.741466000	2.654939000	2.091977000
C	-0.391077000	2.898724000	2.779849000
C	0.677013000	1.830405000	2.441219000
H	-2.475986000	3.325004000	2.555992000
H	1.404075000	1.869628000	3.261854000
C	0.039241000	0.453115000	2.474944000
C	-1.355507000	0.300240000	2.474695000
C	0.825411000	-0.705164000	2.564670000
H	1.907044000	-0.593460000	2.566023000
C	-1.937207000	-0.972460000	2.568938000
C	0.259818000	-1.973318000	2.650081000
H	-3.020135000	-1.043675000	2.575502000
H	0.894531000	-2.851293000	2.718535000
C	-1.133156000	-2.102130000	2.655725000
H	-1.592863000	-3.083658000	2.727220000
C	-1.786841000	2.912183000	0.586874000
C	-2.290650000	1.957978000	-0.302969000
C	-1.394218000	4.159493000	0.081886000
H	-2.621878000	0.999103000	0.077912000
H	-1.017891000	4.924008000	0.756246000
C	-2.374019000	2.233844000	-1.669478000
C	-1.480145000	4.436993000	-1.280913000
H	-2.764337000	1.478212000	-2.345640000
H	-1.166778000	5.408366000	-1.652834000
C	-1.967276000	3.471748000	-2.164716000
H	-2.034506000	3.687242000	-3.227161000
C	1.470977000	2.128911000	1.169834000
C	1.323316000	1.428158000	-0.027710000
C	2.433533000	3.157949000	1.191342000
H	0.596238000	0.625375000	-0.075682000

C	2.076267000	1.724627000	-1.164338000
C	3.200279000	3.472231000	0.070687000
H	1.928818000	1.160068000	-2.081707000
H	3.939898000	4.267902000	0.099127000
C	3.018916000	2.752462000	-1.112752000
O	2.585622000	3.844740000	2.370718000
O	3.797739000	3.103724000	-2.180786000
H	3.296349000	4.490850000	2.267629000
H	3.568049000	2.538770000	-2.930080000
H	-0.575488000	2.873104000	3.860155000
H	-0.017499000	3.897380000	2.545874000

20. *4-Arylflavan (2R)-equatorial, (4R)-equatorial*

O	-1.188547000	-0.692843000	-0.801601000
C	-0.343115000	0.109878000	-1.640257000
C	0.359908000	1.178908000	-0.799269000
C	1.262515000	0.527120000	0.270888000
H	0.418362000	-0.548136000	-2.087557000
H	2.126293000	0.101646000	-0.254029000
C	0.521839000	-0.622863000	0.945903000
C	-0.642076000	-1.158812000	0.367821000
C	0.989258000	-1.211368000	2.129758000
H	1.891265000	-0.812115000	2.584365000
C	-1.328694000	-2.216355000	0.977402000
C	0.321264000	-2.271092000	2.737765000
H	-2.226738000	-2.590005000	0.496345000
H	0.708660000	-2.703130000	3.655322000
C	-0.850466000	-2.768121000	2.160074000
H	-1.386544000	-3.590283000	2.625269000
C	-1.197158000	0.697785000	-2.742882000
C	-2.537094000	1.036127000	-2.522172000
C	-0.628087000	0.958032000	-3.994889000
H	-2.985698000	0.818083000	-1.559174000
H	0.409157000	0.688199000	-4.179840000
C	-3.291218000	1.626113000	-3.536908000
C	-1.379617000	1.553930000	-5.007581000
H	-4.332270000	1.878312000	-3.355707000
H	-0.925041000	1.747058000	-5.975041000
C	-2.715254000	1.889769000	-4.780719000
H	-3.304549000	2.347872000	-5.569747000
C	1.803085000	1.582310000	1.225914000
C	1.069595000	2.054692000	2.317594000
C	3.056350000	2.179562000	0.990441000
H	0.101235000	1.609188000	2.524495000
C	1.543442000	3.060896000	3.158759000
C	3.554065000	3.184596000	1.820796000
H	0.946992000	3.398686000	4.002646000
H	4.524263000	3.637446000	1.635452000
C	2.796294000	3.625829000	2.907271000
O	3.770838000	1.740931000	-0.094565000

O	3.337625000	4.611723000	3.684022000
H	4.615016000	2.209388000	-0.124799000
H	2.715689000	4.829009000	4.390704000
H	-0.405419000	1.803465000	-0.323812000
H	0.957005000	1.829060000	-1.445535000

21. *4-Arylflavan (2R)-axial, (4R)-axial*

O	-0.642077000	-1.582908000	-1.105773000
C	0.029390000	-0.574613000	-1.877669000
C	1.492287000	-0.442521000	-1.431853000
C	1.654118000	-0.143451000	0.078662000
H	0.028070000	-0.992596000	-2.892087000
H	2.667559000	-0.474435000	0.337626000
C	0.687111000	-1.006745000	0.869098000
C	-0.373397000	-1.672855000	0.236538000
C	0.859563000	-1.209165000	2.246486000
H	1.680430000	-0.696758000	2.742483000
C	-1.225145000	-2.517382000	0.963564000
C	0.016237000	-2.037864000	2.979502000
H	-2.026560000	-3.020460000	0.432061000
H	0.174932000	-2.174668000	4.044628000
C	-1.030767000	-2.697801000	2.327259000
H	-1.696075000	-3.353083000	2.882065000
C	-0.779551000	0.720450000	-1.924255000
C	-2.022771000	0.829094000	-1.292951000
C	-0.314502000	1.804485000	-2.681682000
H	-2.406018000	-0.011138000	-0.726038000
H	0.639322000	1.736409000	-3.197895000
C	-2.770947000	2.004136000	-1.392845000
C	-1.061678000	2.976066000	-2.784821000
H	-3.732664000	2.070978000	-0.891692000
H	-0.681678000	3.806362000	-3.373289000
C	-2.293535000	3.082687000	-2.135699000
H	-2.876510000	3.995666000	-2.215397000
C	1.602804000	1.344090000	0.425032000
C	0.531861000	1.960122000	1.073640000
C	2.703925000	2.160220000	0.097342000
H	-0.328100000	1.358760000	1.346014000
C	0.528104000	3.320860000	1.382009000
C	2.726323000	3.521231000	0.396850000
H	-0.327645000	3.766733000	1.882928000
H	3.581330000	4.140746000	0.139754000
C	1.632016000	4.103606000	1.040879000
O	3.762203000	1.555049000	-0.534660000
O	1.707935000	5.442487000	1.309753000
H	4.462195000	2.207334000	-0.667916000
H	0.890429000	5.717306000	1.745100000
H	2.005925000	0.315111000	-2.026659000
H	1.978674000	-1.400704000	-1.648662000

22. *4-Arylflavan-3-ol (2S)-axial, (3S)-equatorial, (4R)-axial*

O	2.574428000	0.976966000	0.810952000
C	1.327706000	1.264214000	1.450741000
C	0.686672000	-0.048192000	1.970789000
C	0.514590000	-1.155881000	0.899196000
H	1.606339000	1.835953000	2.342777000
H	1.377681000	-0.431910000	2.728140000
H	0.488622000	-2.093967000	1.471501000
C	1.762985000	-1.203017000	0.035468000
C	2.700086000	-0.161047000	0.049694000
C	2.037050000	-2.321938000	-0.765431000
H	1.313878000	-3.133115000	-0.780252000
C	3.872940000	-0.238725000	-0.714827000
C	3.194511000	-2.408858000	-1.531077000
H	4.572782000	0.589066000	-0.668336000
H	3.379931000	-3.286983000	-2.141342000
C	4.117549000	-1.357839000	-1.500593000
H	5.028631000	-1.411020000	-2.089201000
C	0.439511000	2.162916000	0.599023000
C	0.647356000	2.328107000	-0.775174000
C	-0.584091000	2.899472000	1.217355000
H	1.461547000	1.804308000	-1.262255000
H	-0.717084000	2.836926000	2.294354000
C	-0.174035000	3.175160000	-1.519118000
C	-1.411469000	3.739219000	0.470258000
H	0.001855000	3.291071000	-2.584630000
H	-2.199272000	4.298272000	0.966638000
C	-1.212351000	3.875132000	-0.903349000
H	-1.850444000	4.532276000	-1.486409000
O	-0.525361000	0.214303000	2.678866000
H	-1.127562000	0.652929000	2.054413000
C	-0.805753000	-1.129571000	0.122039000
C	-0.898827000	-0.754163000	-1.225472000
C	-1.978129000	-1.626441000	0.735234000
H	-0.010868000	-0.385278000	-1.726137000
C	-2.078278000	-0.865033000	-1.952565000
C	-3.168666000	-1.756842000	0.014126000
H	-2.129016000	-0.574142000	-2.995697000
H	-4.043191000	-2.144499000	0.529575000
C	-3.218304000	-1.381783000	-1.328185000
O	-2.001657000	-2.039528000	2.039322000
O	-4.357617000	-1.486671000	-2.075269000
H	-1.430107000	-1.438680000	2.554662000
H	-5.055669000	-1.873157000	-1.530360000

23. *4-Arylflavan-3-ol (2S)-equatorial, (3S)-axial, (4R)-equatorial*

O	-1.889309000	1.446405000	-0.034701000
C	-1.844163000	0.149708000	0.573924000
C	-0.543698000	-0.572941000	0.193703000

C	0.666464000	0.232361000	0.742540000
H	-1.832328000	0.275300000	1.667499000
H	-0.551104000	-1.561768000	0.676247000
H	0.646028000	0.104085000	1.831307000
C	0.493231000	1.715284000	0.433798000
C	-0.765957000	2.221990000	0.069328000
C	1.555211000	2.624059000	0.540918000
H	2.532596000	2.248544000	0.829748000
C	-0.938506000	3.581661000	-0.217465000
C	1.390828000	3.980752000	0.272533000
H	-1.927387000	3.923133000	-0.505210000
H	2.233683000	4.658900000	0.363489000
C	0.136666000	4.456932000	-0.119255000
H	-0.006268000	5.510817000	-0.339792000
C	-3.098343000	-0.598431000	0.180428000
C	-3.591597000	-0.543556000	-1.128879000
C	-3.764445000	-1.382618000	1.127657000
H	-3.074259000	0.064785000	-1.860859000
H	-3.395386000	-1.420147000	2.150145000
C	-4.733087000	-1.262944000	-1.478236000
C	-4.902386000	-2.110469000	0.775637000
H	-5.110561000	-1.211162000	-2.495613000
H	-5.411218000	-2.713125000	1.522551000
C	-5.390360000	-2.050161000	-0.529544000
H	-6.280089000	-2.608884000	-0.805722000
O	-0.522318000	-0.691471000	-1.216825000
H	0.308263000	-1.123906000	-1.458686000
C	1.970369000	-0.377397000	0.250378000
C	2.527235000	-0.066013000	-0.999422000
C	2.633341000	-1.350870000	1.019856000
H	2.038952000	0.690270000	-1.605453000
C	3.689687000	-0.668254000	-1.474173000
C	3.805881000	-1.962840000	0.566354000
H	4.109036000	-0.408918000	-2.439514000
H	4.301525000	-2.709658000	1.185528000
C	4.334317000	-1.621331000	-0.682021000
O	2.082656000	-1.683512000	2.229681000
O	5.474491000	-2.188492000	-1.173650000
H	2.646493000	-2.331676000	2.670977000
H	5.823736000	-2.819569000	-0.531034000

24. *4-Arylflavan-3-ol (2R)-axial, (3R)-axial, (4S)-axial*

O	-2.630352000	0.963383000	0.625528000
C	-1.409357000	1.410161000	1.221844000
C	-0.722725000	0.232004000	1.959398000
C	-0.479196000	-1.026221000	1.085941000
H	-1.729161000	2.108217000	2.003273000
H	-1.412607000	-0.054831000	2.759449000
H	-0.428770000	-1.856794000	1.804151000
C	-1.702797000	-1.269542000	0.219519000

C	-2.686834000	-0.285620000	0.053351000
C	-1.906461000	-2.512865000	-0.397944000
H	-1.146435000	-3.279612000	-0.272898000
C	-3.837296000	-0.540638000	-0.706572000
C	-3.040974000	-2.776343000	-1.157524000
H	-4.575328000	0.248798000	-0.802945000
H	-3.171639000	-3.747770000	-1.623532000
C	-4.012196000	-1.780525000	-1.308048000
H	-4.906323000	-1.970812000	-1.894297000
C	-0.544802000	2.195141000	0.242888000
C	-0.735901000	2.124511000	-1.141822000
C	0.436721000	3.066875000	0.742254000
H	-1.518867000	1.492922000	-1.544998000
H	0.554040000	3.186732000	1.816193000
C	0.062109000	2.873951000	-2.006291000
C	1.240985000	3.808824000	-0.124009000
H	-0.100395000	2.806501000	-3.078087000
H	1.996378000	4.475303000	0.281899000
C	1.059762000	3.709887000	-1.503284000
H	1.679802000	4.290356000	-2.179722000
O	0.461115000	0.662265000	2.632095000
H	1.060012000	1.013966000	1.951937000
C	0.857882000	-1.067292000	0.338758000
C	0.969467000	-0.908155000	-1.049665000
C	2.033685000	-1.406913000	1.045377000
H	0.080149000	-0.662837000	-1.618995000
C	2.170274000	-1.082173000	-1.727694000
C	3.246253000	-1.598802000	0.376561000
H	2.235525000	-0.959742000	-2.802897000
H	4.122591000	-1.859869000	0.963610000
C	3.314201000	-1.442022000	-1.007531000
O	2.041103000	-1.603449000	2.399413000
O	4.475038000	-1.615437000	-1.707175000
H	1.434525000	-0.952048000	2.800415000
H	5.174483000	-1.878027000	-1.094476000

25. *4-Arylflavan-3-ol (2R)-equatorial, (3R)-axial, (4S)-equatorial*

O	8.040722000	-1.676046000	-0.272669000
C	8.000603000	-2.968194000	0.345858000
C	6.701213000	-3.697385000	-0.026077000
C	5.490176000	-2.891368000	0.519876000
H	7.990872000	-2.834337000	1.438447000
H	6.712455000	-4.682540000	0.463890000
H	5.513184000	-3.012557000	1.609368000
C	5.658975000	-1.410028000	0.201072000
C	6.915740000	-0.902519000	-0.170535000
C	4.594904000	-0.503337000	0.304964000
H	3.619329000	-0.879483000	0.599086000
C	7.083842000	0.455547000	-0.467313000
C	4.754918000	0.851910000	0.026853000

H	8.070952000	0.797580000	-0.760451000
H	3.910540000	1.528439000	0.115686000
C	6.006665000	1.328664000	-0.371950000
H	6.146151000	2.381340000	-0.600317000
C	9.255835000	-3.715937000	-0.044970000
C	9.746898000	-3.668171000	-1.355347000
C	9.925069000	-4.492813000	0.906097000
H	9.227186000	-3.065406000	-2.090259000
H	9.557735000	-4.524680000	1.929396000
C	10.889347000	-4.387367000	-1.702042000
C	11.063947000	-5.220478000	0.556796000
H	11.265103000	-4.341130000	-2.720322000
H	11.575237000	-5.817409000	1.306625000
C	11.549733000	-5.167298000	-0.749529000
H	12.440151000	-5.725943000	-1.023638000
O	6.677021000	-3.826524000	-1.435476000
H	5.846642000	-4.262071000	-1.672448000
C	4.186714000	-3.507082000	0.034170000
C	3.626542000	-3.204282000	-1.216226000
C	3.527453000	-4.477571000	0.810647000
H	4.111510000	-2.450256000	-1.827727000
C	2.464496000	-3.812069000	-1.685082000
C	2.355506000	-5.094944000	0.363302000
H	2.042716000	-3.559186000	-2.651075000
H	1.862733000	-5.839172000	0.987799000
C	1.823784000	-4.762025000	-0.886170000
O	4.081387000	-4.801660000	2.021326000
O	0.684017000	-5.334830000	-1.372075000
H	3.520417000	-5.449366000	2.466831000
H	0.337633000	-5.962972000	-0.725055000

26. *4-Arylflavan-3-ol (2S)-axial, (3S)-equatorial, (4S)-equatorial*

O	-5.236067000	-2.155327000	4.373269000
C	-5.109954000	-3.569253000	4.217435000
C	-3.640964000	-3.948369000	3.908475000
C	-3.034065000	-3.190178000	2.704871000
H	-5.334935000	-3.969672000	5.210684000
H	-3.052812000	-3.712765000	4.800279000
H	-3.375844000	-3.721465000	1.803750000
C	-3.569835000	-1.765421000	2.627367000
C	-4.618012000	-1.338813000	3.454642000
C	-3.065673000	-0.847478000	1.692915000
H	-2.263412000	-1.167879000	1.035454000
C	-5.103306000	-0.026306000	3.393361000
C	-3.549582000	0.454680000	1.610294000
H	-5.907946000	0.256494000	4.063867000
H	-3.135118000	1.142198000	0.879822000
C	-4.565077000	0.869496000	2.477586000
H	-4.945813000	1.885497000	2.431791000
C	-6.126107000	-4.165863000	3.249542000

C	-6.666598000	-5.427990000	3.547486000
C	-6.534880000	-3.525556000	2.069870000
H	-6.390702000	-5.922383000	4.476135000
H	-6.150484000	-2.543423000	1.821614000
C	-7.572371000	-6.046082000	2.682563000
C	-7.448514000	-4.138985000	1.213218000
H	-7.978446000	-7.021157000	2.934680000
H	-7.757750000	-3.625961000	0.307371000
C	-7.965428000	-5.401532000	1.510830000
H	-8.674853000	-5.874002000	0.838218000
O	-3.527456000	-5.369744000	3.732136000
H	-4.315606000	-5.661940000	3.244306000
C	-1.503292000	-3.275503000	2.724085000
C	-0.695514000	-2.242682000	3.221647000
C	-0.850209000	-4.425160000	2.232967000
H	-1.169011000	-1.353880000	3.625727000
C	0.694002000	-2.298763000	3.185969000
C	0.544643000	-4.485987000	2.165354000
H	1.302617000	-1.485410000	3.564794000
H	1.001628000	-5.390173000	1.772297000
C	1.316050000	-3.422525000	2.633088000
O	-1.543473000	-5.516520000	1.790720000
O	2.682752000	-3.437088000	2.595131000
H	-2.295106000	-5.639269000	2.404800000
H	2.975242000	-4.263478000	2.188925000

27. *4-Arylflavan-3-ol (2S)-equatorial, (3S)-axial, (4S)-axial*

O	8.792817000	-5.581342000	-1.169652000
C	8.523414000	-6.957395000	-0.896968000
C	7.804051000	-7.123986000	0.458130000
C	6.460192000	-6.358979000	0.442521000
H	7.850334000	-7.354037000	-1.671327000
H	7.611131000	-8.198962000	0.591144000
H	6.214965000	-6.181927000	1.501442000
C	6.645906000	-4.985671000	-0.176725000
C	7.789974000	-4.679182000	-0.925810000
C	5.696007000	-3.973471000	0.017946000
H	4.805536000	-4.203557000	0.597774000
C	7.979080000	-3.397131000	-1.457288000
C	5.869312000	-2.697930000	-0.509659000
H	8.881329000	-3.203809000	-2.028137000
H	5.117894000	-1.932511000	-0.343702000
C	7.022181000	-2.411583000	-1.248503000
H	7.174000000	-1.419856000	-1.664277000
C	9.836213000	-7.709690000	-0.931547000
C	9.849632000	-9.067683000	-1.275490000
C	11.034969000	-7.091066000	-0.552075000
H	8.926051000	-9.554367000	-1.579482000
H	11.030596000	-6.032866000	-0.314259000
C	11.037544000	-9.796317000	-1.238692000

C	12.224751000	-7.822130000	-0.518786000
H	11.034142000	-10.847020000	-1.513463000
H	13.149361000	-7.330183000	-0.230874000
C	12.229292000	-9.175015000	-0.858359000
H	13.155581000	-9.741285000	-0.833926000
O	8.562705000	-6.608036000	1.538854000
H	9.454873000	-6.981075000	1.481966000
C	5.347717000	-7.196323000	-0.181328000
C	4.846634000	-6.968273000	-1.469988000
C	4.800150000	-8.275636000	0.541169000
H	5.241433000	-6.133259000	-2.039641000
C	3.855504000	-7.763054000	-2.036277000
C	3.800574000	-9.082304000	-0.006891000
H	3.477233000	-7.571816000	-3.033982000
H	3.406294000	-9.899379000	0.590969000
C	3.330731000	-8.827034000	-1.295600000
O	5.211968000	-8.610623000	1.803182000
O	2.356491000	-9.585406000	-1.880223000
H	5.839741000	-7.954562000	2.133022000
H	2.077602000	-10.273349000	-1.261818000

28. *4-Arylflavan-3-ol (2R)-axial, (3R)-equatorial, (4R)-equatorial*

O	1.701295000	1.245079000	1.586411000
C	1.730163000	-0.174765000	1.436550000
C	0.308732000	-0.714816000	1.144761000
C	-0.390302000	-0.033467000	-0.054753000
H	2.008292000	-0.543632000	2.428560000
H	-0.292493000	-0.541424000	2.042089000
H	-0.001092000	-0.527708000	-0.957710000
C	-0.015973000	1.441381000	-0.142438000
C	0.987364000	1.984518000	0.672042000
C	-0.628272000	2.294174000	-1.074024000
H	-1.397164000	1.884459000	-1.721684000
C	1.324104000	3.342307000	0.601559000
C	-0.291953000	3.641420000	-1.165826000
H	2.099587000	3.715005000	1.262404000
H	-0.787511000	4.275972000	-1.893713000
C	0.680645000	4.169387000	-0.310964000
H	0.946378000	5.221001000	-0.363973000
C	2.795654000	-0.660213000	0.459621000
C	3.119197000	0.016107000	-0.726381000
C	3.474815000	-1.853926000	0.755677000
H	2.626544000	0.948939000	-0.973544000
H	3.264681000	-2.371591000	1.688848000
C	4.085834000	-0.496793000	-1.590935000
C	4.434039000	-2.372351000	-0.117023000
H	4.327293000	0.043192000	-2.501701000
H	4.947587000	-3.295716000	0.133758000
C	4.741585000	-1.693524000	-1.294971000
H	5.491652000	-2.087994000	-1.973729000

O	0.350802000	-2.140779000	0.974339000
H	1.161292000	-2.346544000	0.479071000
C	-1.902035000	-0.287138000	-0.019165000
C	-2.813740000	0.652369000	0.483734000
C	-2.429225000	-1.503833000	-0.499949000
H	-2.437072000	1.589621000	0.880136000
C	-4.188883000	0.443305000	0.462815000
C	-3.809508000	-1.718257000	-0.552883000
H	-4.879627000	1.186164000	0.845565000
H	-4.167943000	-2.668873000	-0.938539000
C	-4.688735000	-0.744419000	-0.080242000
O	-1.624339000	-2.513908000	-0.946142000
O	-6.045816000	-0.909666000	-0.103961000
H	-0.857511000	-2.550494000	-0.339762000
H	-6.249459000	-1.764996000	-0.504478000

29. *4-Arylflavan-3-ol (2R)-equatorial, (3R)-axial, (4R)-axial*

O	-1.576913000	1.337570000	-0.633409000
C	-1.309114000	-0.041819000	-0.376445000
C	-0.591059000	-0.224708000	0.977289000
C	0.753619000	0.538984000	0.971656000
H	-0.635787000	-0.430181000	-1.154769000
H	-0.399470000	-1.301366000	1.098093000
H	0.997671000	0.704477000	2.032697000
C	0.570419000	1.919094000	0.366909000
C	-0.572801000	2.235488000	-0.379398000
C	1.521826000	2.927609000	0.572910000
H	2.411706000	2.689870000	1.150556000
C	-0.759666000	3.523520000	-0.896968000
C	1.350778000	4.209079000	0.059069000
H	-1.661352000	3.724453000	-1.466074000
H	2.103342000	4.971446000	0.233662000
C	0.198688000	4.505254000	-0.677076000
H	0.048592000	5.501662000	-1.082144000
C	-2.622642000	-0.792274000	-0.420688000
C	-3.821017000	-0.176821000	-0.034927000
C	-2.637219000	-2.146175000	-0.780354000
H	-3.815709000	0.878548000	0.215139000
H	-1.713932000	-2.630264000	-1.089342000
C	-5.011582000	-0.906974000	-0.010950000
C	-3.825914000	-2.873941000	-0.752825000
H	-5.935890000	-0.417417000	0.281963000
H	-3.823402000	-3.921395000	-1.039743000
C	-5.017291000	-2.255832000	-0.366166000
H	-5.944185000	-2.821375000	-0.348936000
O	-1.350199000	0.279553000	2.063179000
H	-2.242373000	-0.092764000	2.001818000
C	1.866060000	-0.292924000	0.340446000
C	2.369090000	-0.051844000	-0.945082000
C	2.411501000	-1.380385000	1.052261000

H	1.975938000	0.789554000	-1.506424000
C	3.360129000	-0.841670000	-1.518394000
C	3.410959000	-2.182337000	0.497008000
H	3.739929000	-0.640284000	-2.513518000
H	3.803519000	-3.006091000	1.086778000
C	3.882791000	-1.913975000	-0.788289000
O	1.997918000	-1.728116000	2.310198000
O	4.857016000	-2.667157000	-1.379609000
H	1.369176000	-1.075838000	2.645618000
H	5.134316000	-3.361922000	-0.768156000

30. *4-Arylflavan-3-ol (2S)-equatorial, (3R)-equatorial, (4R)-equatorial*

O	3.965592000	6.084032000	3.515279000
C	4.107482000	4.942794000	2.666402000
C	2.846138000	4.067356000	2.797768000
C	1.575660000	4.826069000	2.367552000
H	4.184494000	5.273548000	1.619781000
H	2.755755000	3.756831000	3.847200000
H	1.563150000	4.767701000	1.268982000
C	1.668730000	6.302725000	2.738284000
C	2.839218000	6.842907000	3.290038000
C	0.594047000	7.175434000	2.512684000
H	-0.317345000	6.774797000	2.079240000
C	2.919370000	8.192456000	3.649481000
C	0.664381000	8.522842000	2.854645000
H	3.846024000	8.558179000	4.079245000
H	-0.185371000	9.173113000	2.672204000
C	1.829681000	9.029302000	3.438161000
H	1.893866000	10.077172000	3.715834000
C	5.361403000	4.195788000	3.062754000
C	5.814318000	4.199234000	4.388449000
C	6.050547000	3.433450000	2.109283000
H	5.292305000	4.800783000	5.124424000
H	5.715328000	3.437293000	1.075592000
C	6.937709000	3.456078000	4.750181000
C	7.169659000	2.683339000	2.475335000
H	7.284717000	3.473415000	5.779259000
H	7.697067000	2.101232000	1.725304000
C	7.616128000	2.693478000	3.797223000
H	8.490732000	2.116191000	4.082015000
O	2.944279000	2.923488000	1.941235000
H	3.608218000	2.317264000	2.297229000
C	0.311355000	4.125702000	2.868551000
C	-0.224605000	3.032921000	2.154554000
C	-0.357140000	4.525084000	4.034406000
C	-1.418600000	2.429252000	2.562592000
C	-1.532515000	3.919337000	4.465317000
H	-1.799313000	1.596030000	1.977965000
H	-2.043319000	4.248329000	5.363225000
C	-2.074647000	2.874688000	3.709566000

O	-3.240812000	2.312604000	4.149905000
H	-3.507280000	1.620405000	3.530722000
H	0.042218000	5.355215000	4.608448000
O	0.367186000	2.530126000	1.032034000
H	1.334945000	2.592892000	1.146563000

31. *4-Arylflavan-3-ol (2S)-axial, (3R)-axial, (4R)-axial*

O	0.516947000	8.237735000	3.224094000
C	-0.704680000	8.616319000	3.882049000
C	-1.351080000	7.358833000	4.489951000
C	-1.659241000	6.269011000	3.420660000
H	-0.358995000	9.220123000	4.728546000
H	-2.275713000	7.639963000	4.998832000
H	-1.592621000	5.323357000	3.982487000
C	-0.544869000	6.200357000	2.389969000
C	0.470180000	7.165964000	2.357854000
C	-0.457588000	5.129436000	1.487896000
H	-1.239971000	4.375179000	1.503564000
C	1.540840000	7.060547000	1.460974000
C	0.595344000	5.017525000	0.585737000
H	2.308246000	7.827610000	1.480150000
H	0.635995000	4.178728000	-0.101838000
C	1.601836000	5.989060000	0.578203000
H	2.432744000	5.912190000	-0.116701000
C	-1.601598000	9.481504000	3.006965000
C	-1.217800000	9.868310000	1.718754000
C	-2.807486000	9.973421000	3.526590000
H	-0.274547000	9.523080000	1.312682000
H	-3.115837000	9.707748000	4.534139000
C	-2.037111000	10.702130000	0.954881000
C	-3.623830000	10.806620000	2.764913000
H	-1.725138000	10.987978000	-0.045586000
H	-4.557397000	11.171873000	3.182546000
C	-3.243815000	11.170516000	1.471641000
H	-3.880744000	11.818177000	0.876617000
O	-0.502285000	6.840081000	5.510666000
H	0.389224000	6.776321000	5.137674000
C	-3.072245000	6.361363000	2.852592000
C	-4.161795000	5.999824000	3.669631000
C	-3.361859000	6.793187000	1.552175000
C	-5.475490000	6.071034000	3.200335000
C	-4.661826000	6.875096000	1.067075000
H	-6.282044000	5.776554000	3.866186000
H	-4.869013000	7.216188000	0.059282000
C	-5.724368000	6.510600000	1.900420000
O	-6.989388000	6.601922000	1.390932000
H	-7.621076000	6.316888000	2.064102000
H	-2.540559000	7.079380000	0.904727000
O	-4.015832000	5.573012000	4.963745000
H	-3.080902000	5.459223000	5.178874000

32. *4-Arylflavan-3-ol (2R)-equatorial, (3S)-equatorial, (4S)-equatorial*

O	-1.747512000	1.538099000	0.295720000
C	-1.865394000	0.331879000	-0.462172000
C	-0.596409000	-0.515305000	-0.246153000
C	0.671379000	0.222391000	-0.718688000
H	-1.931839000	0.578216000	-1.532518000
H	-0.517016000	-0.741198000	0.825550000
H	0.699631000	0.077577000	-1.808966000
C	0.557071000	1.722448000	-0.467124000
C	-0.626581000	2.290339000	0.025511000
C	1.625052000	2.587478000	-0.747473000
H	2.546529000	2.164889000	-1.136483000
C	-0.726374000	3.662949000	0.276273000
C	1.535346000	3.956693000	-0.513868000
H	-1.662664000	4.050250000	0.664213000
H	2.380252000	4.600729000	-0.736502000
C	0.356810000	4.493542000	0.013194000
H	0.277439000	5.559177000	0.206523000
C	-3.116237000	-0.396577000	-0.023953000
C	-3.587198000	-0.293907000	1.291466000
C	-3.783828000	-1.240118000	-0.922777000
H	-3.081935000	0.370159000	1.984096000
H	-3.434575000	-1.313924000	-1.949171000
C	-4.707127000	-1.019698000	1.696545000
C	-4.899483000	-1.972450000	-0.512782000
H	-5.068298000	-0.925370000	2.716532000
H	-5.410163000	-2.618285000	-1.221060000
C	-5.364032000	-1.863326000	0.798355000
H	-6.236029000	-2.426824000	1.116774000
O	-0.670351000	-1.724167000	-1.010835000
H	-1.332128000	-2.308485000	-0.616286000
C	1.936354000	-0.420830000	-0.147675000
C	2.584206000	0.077333000	0.991502000
C	2.494211000	-1.559949000	-0.766085000
H	2.167810000	0.945262000	1.492950000
C	3.760092000	-0.478306000	1.484118000
C	3.689008000	-2.115091000	-0.296208000
H	4.254736000	-0.073392000	2.359773000
H	4.086985000	-2.987125000	-0.808220000
C	4.324129000	-1.572707000	0.820402000
O	1.923742000	-2.156774000	-1.853050000
O	5.490220000	-2.084126000	1.318807000
H	0.953838000	-2.096654000	-1.756776000
H	5.772645000	-2.819972000	0.760003000

33. *4-Arylflavan-3-ol (2R)-axial, (3S)-axial, (4S)-axial*

O	-2.586074000	0.769736000	0.883264000
C	-1.317907000	1.062341000	1.494883000

C	-0.661969000	-0.259212000	1.932651000
C	-0.447959000	-1.243564000	0.744113000
H	-1.596769000	1.584211000	2.417117000
H	0.300135000	-0.044266000	2.402888000
H	-0.512776000	-2.238505000	1.213234000
C	-1.618516000	-1.182412000	-0.223129000
C	-2.612924000	-0.203828000	-0.093012000
C	-1.779671000	-2.148796000	-1.227352000
H	-1.014082000	-2.912243000	-1.337960000
C	-3.734875000	-0.195908000	-0.931265000
C	-2.884526000	-2.147259000	-2.072618000
H	-4.483181000	0.576443000	-0.785719000
H	-2.982014000	-2.906640000	-2.841931000
C	-3.869012000	-1.165596000	-1.917623000
H	-4.739552000	-1.154977000	-2.566664000
C	-0.457929000	1.996078000	0.653629000
C	-0.914180000	2.520689000	-0.560111000
C	0.791069000	2.409802000	1.138602000
H	-1.889827000	2.236408000	-0.935801000
H	1.157677000	2.036239000	2.090889000
C	-0.125244000	3.413692000	-1.288284000
C	1.576966000	3.302346000	0.412969000
H	-0.493940000	3.806589000	-2.231505000
H	2.544376000	3.605402000	0.802395000
C	1.123538000	3.804521000	-0.808292000
H	1.736637000	4.498383000	-1.375610000
O	-1.453354000	-0.862401000	2.953179000
H	-2.368527000	-0.874974000	2.636392000
C	0.933924000	-1.130729000	0.108001000
C	1.166679000	-0.567220000	-1.152872000
C	2.053418000	-1.608673000	0.817674000
H	0.321420000	-0.188329000	-1.716505000
C	2.440112000	-0.470193000	-1.701359000
C	3.341067000	-1.524676000	0.282668000
H	2.603537000	-0.026892000	-2.676904000
H	4.172422000	-1.911790000	0.865406000
C	3.533304000	-0.954159000	-0.975308000
O	1.964136000	-2.169124000	2.064919000
O	4.770820000	-0.844604000	-1.545132000
H	1.039627000	-2.259895000	2.330157000
H	5.428420000	-1.217481000	-0.943505000

34. *4-Arylflavan-3-ol (2S)-equatorial, (3R)-equatorial, (4S)-axial*

O	6.081199000	-0.587991000	2.057738000
C	5.852518000	-1.975758000	2.333695000
C	5.120657000	-2.128296000	3.687886000
C	3.736582000	-1.440332000	3.630782000
H	5.208161000	-2.400692000	1.551985000
H	5.728691000	-1.601331000	4.441336000
H	3.406213000	-1.333697000	4.668551000

C	3.912262000	-0.048771000	3.044012000
C	5.054153000	0.289293000	2.303094000
C	2.941675000	0.942923000	3.242998000
H	2.051957000	0.686373000	3.812701000
C	5.220003000	1.580937000	1.785513000
C	3.093498000	2.228276000	2.732788000
H	6.119800000	1.798174000	1.219299000
H	2.326969000	2.977437000	2.904501000
C	4.243457000	2.545531000	2.001975000
H	4.377780000	3.544857000	1.598343000
C	7.189825000	-2.683724000	2.318882000
C	7.252482000	-4.043586000	1.982090000
C	8.366705000	-2.022017000	2.692360000
H	6.346526000	-4.561152000	1.678546000
H	8.323946000	-0.966502000	2.936953000
C	8.467461000	-4.730020000	2.023866000
C	9.581074000	-2.707233000	2.724660000
H	8.501082000	-5.782146000	1.756118000
H	10.487926000	-2.180323000	3.007569000
C	9.635525000	-4.062937000	2.394583000
H	10.582726000	-4.593683000	2.419909000
O	4.946722000	-3.487757000	4.033787000
H	5.826710000	-3.880773000	4.118727000
C	2.676580000	-2.269337000	2.910995000
C	2.456175000	-2.190558000	1.531123000
C	1.866832000	-3.161676000	3.637697000
H	3.034257000	-1.477201000	0.951947000
C	1.509582000	-2.971489000	0.872251000
C	0.907781000	-3.953237000	2.998349000
H	1.355041000	-2.894224000	-0.197857000
H	0.292182000	-4.635733000	3.583708000
C	0.734808000	-3.863998000	1.614381000
O	2.030313000	-3.209953000	4.993798000
O	-0.187166000	-4.618481000	0.943477000
H	1.435919000	-3.875171000	5.362872000
H	-0.653281000	-5.184353000	1.572327000

35. *4-Arylflavan-3-ol (2S)-axial, (3R)-axial, (4S)-equatorial*

O	-2.020281000	1.372394000	1.274437000
C	-1.819579000	-0.036477000	1.485347000
C	-0.309132000	-0.339594000	1.470736000
C	0.284519000	0.015873000	0.084767000
H	-2.167508000	-0.196425000	2.511797000
H	-0.149545000	-1.403847000	1.662123000
H	-0.205009000	-0.658887000	-0.626529000
C	-0.124890000	1.438387000	-0.280829000
C	-1.263875000	2.010167000	0.311269000
C	0.561014000	2.202012000	-1.234767000
H	1.442742000	1.774048000	-1.701331000
C	-1.683583000	3.303130000	-0.020910000

C	0.146705000	3.485542000	-1.583286000
H	-2.562204000	3.703707000	0.474316000
H	0.700185000	4.051041000	-2.326471000
C	-0.978473000	4.039045000	-0.967331000
H	-1.309323000	5.040977000	-1.224489000
C	-2.650459000	-0.896009000	0.546019000
C	-2.706635000	-2.280504000	0.765140000
C	-3.385593000	-0.351477000	-0.511899000
H	-2.160304000	-2.718858000	1.596748000
H	-3.372482000	0.718789000	-0.680951000
C	-3.465990000	-3.103283000	-0.064301000
C	-4.144872000	-1.176826000	-1.344252000
H	-3.498888000	-4.172893000	0.122049000
H	-4.708906000	-0.737900000	-2.162248000
C	-4.186449000	-2.553222000	-1.126541000
H	-4.779993000	-3.192464000	-1.773487000
O	0.317814000	0.344840000	2.546584000
H	0.009008000	1.261984000	2.522918000
C	1.774876000	-0.266062000	0.011848000
C	2.727342000	0.541191000	0.648404000
C	2.252190000	-1.392584000	-0.678902000
H	2.381956000	1.410589000	1.195188000
C	4.090468000	0.269156000	0.605937000
C	3.619259000	-1.686153000	-0.737245000
H	4.812255000	0.906295000	1.104041000
H	3.962357000	-2.564933000	-1.282329000
C	4.538216000	-0.853878000	-0.094377000
O	1.331873000	-2.203119000	-1.292847000
O	5.883918000	-1.091840000	-0.120310000
H	1.792413000	-2.916127000	-1.752986000
H	6.056310000	-1.893884000	-0.630216000

36. *4-Arylflavan-3-ol (2R)-equatorial, (3S)-equatorial, (4R)-axial*

O	-1.597934000	1.422962000	-0.552720000
C	-1.381711000	0.033434000	-0.275473000
C	-0.655831000	-0.124623000	1.081268000
C	0.734156000	0.551746000	1.028592000
H	-0.738135000	-0.397062000	-1.054792000
H	-1.261964000	0.407781000	1.832420000
H	1.061806000	0.656099000	2.067455000
C	0.572019000	1.944502000	0.440742000
C	-0.564525000	2.291815000	-0.304105000
C	1.550125000	2.928161000	0.642729000
H	2.435776000	2.664421000	1.215481000
C	-0.717960000	3.584654000	-0.822499000
C	1.410674000	4.214600000	0.131702000
H	-1.614031000	3.809209000	-1.391758000
H	2.182835000	4.957398000	0.305798000
C	0.265820000	4.541190000	-0.602994000
H	0.141091000	5.541490000	-1.007289000

C	-2.724760000	-0.663473000	-0.294867000
C	-3.897445000	0.007848000	0.074555000
C	-2.797386000	-2.022813000	-0.631860000
H	-3.846878000	1.062963000	0.319369000
H	-1.894665000	-2.547783000	-0.932313000
C	-5.117493000	-0.667409000	0.102636000
C	-4.018080000	-2.699272000	-0.594283000
H	-6.020965000	-0.133058000	0.382390000
H	-4.059386000	-3.751105000	-0.862109000
C	-5.181922000	-2.022617000	-0.227635000
H	-6.133522000	-2.545581000	-0.205606000
O	-0.494439000	-1.485307000	1.428450000
H	-1.377972000	-1.871275000	1.508896000
C	1.789573000	-0.286368000	0.312746000
C	2.015315000	-0.210031000	-1.066404000
C	2.589272000	-1.185253000	1.042529000
H	1.445209000	0.507932000	-1.647795000
C	2.957504000	-0.999194000	-1.721765000
C	3.543748000	-1.985157000	0.406729000
H	3.116322000	-0.923668000	-2.791369000
H	4.151518000	-2.672647000	0.994423000
C	3.722192000	-1.897912000	-0.976668000
O	2.420692000	-1.231665000	2.398047000
O	4.639964000	-2.660492000	-1.644166000
H	3.007877000	-1.902004000	2.769389000
H	5.099117000	-3.230059000	-1.013533000

37. *4-Arylflavan-3-ol (2R)-axial, (3S)-axial, (4R)-equatorial*

O	2.020776000	1.373512000	1.273133000
C	1.820390000	-0.035287000	1.485067000
C	0.309971000	-0.338720000	1.471425000
C	-0.284251000	0.015627000	0.085396000
H	2.168802000	-0.194462000	2.511476000
H	0.150806000	-1.402919000	1.663555000
H	0.205426000	-0.659443000	-0.625488000
C	0.124427000	1.438150000	-0.281023000
C	1.263318000	2.010725000	0.310411000
C	-0.562366000	2.201149000	-1.234824000
H	-1.444016000	1.772517000	-1.700922000
C	1.681921000	3.304004000	-0.021995000
C	-0.149050000	3.484880000	-1.583753000
H	2.560417000	3.705287000	0.472882000
H	-0.703147000	4.049818000	-2.326904000
C	0.975925000	4.039299000	-0.968228000
H	1.305918000	5.041472000	-1.225547000
C	2.650988000	-0.895358000	0.546008000
C	3.385408000	-0.351515000	-0.512761000
C	2.707628000	-2.279671000	0.766221000
H	3.371994000	0.718610000	-0.682638000
H	2.161890000	-2.717472000	1.598516000

C	4.144387000	-1.177376000	-1.344895000
C	3.466669000	-3.102940000	-0.062993000
H	4.707865000	-0.738973000	-2.163554000
H	3.499920000	-4.172391000	0.124200000
C	4.186382000	-2.553577000	-1.126116000
H	4.779690000	-3.193213000	-1.772888000
O	-0.316489000	0.346258000	2.547116000
H	-0.006877000	1.263128000	2.523606000
C	-1.774530000	-0.266831000	0.012656000
C	-2.727033000	0.539347000	0.650569000
C	-2.251791000	-1.392380000	-0.679719000
H	-2.381656000	1.407989000	1.198528000
C	-4.090100000	0.267062000	0.608088000
C	-3.618820000	-1.686168000	-0.738080000
H	-4.811881000	0.903351000	1.107287000
H	-3.961882000	-2.564222000	-1.284360000
C	-4.537789000	-0.855063000	-0.093727000
O	-1.331534000	-2.201776000	-1.295238000
O	-5.883437000	-1.093325000	-0.119610000
H	-1.792104000	-2.914033000	-1.756506000
H	-6.055789000	-1.894556000	-0.630807000