SYNTHESIS OF ISOFLAVONOID-NEOFLAVONOID OLIGOMERS

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Philosophiae Doctor

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at the University of the Orange Free State.

August 1999

Promotor: **Prof Daneel Ferreira**

Co-promotor: .....

Signed: **Prof E. Vincent Brandt**

DECLARATION

I declare that the thesis hereby submitted by me for the degree of *Philosophiae Doctor* at the University of the Orange Free State is my own, independent work and has not previously been submitted by me at another university/faculty. I furthermore cede copyright of the thesis in favour of the University of the Orange Free State.

Mark Rohwer

Mark Bernhard Rohwer

Signed at Bloemfontein, this 6th day of August 1999.

Acknowledgements

This research project would not have been successful without the continued guidance of my supervisor, **Prof Daneel Ferreira**. My sincere thanks, Prof, for your confidence in taking me on as a research student, and for nurturing a keen sense of scientific debate.

I also wish to express my gratitude to my initial supervisors. **Prof Ben Bezuidenhoudt** initiated me in the field of isoflavonoid chemistry. Many of his suggestions carried and inspired my work long after his departure from the UOFS. **Dr Pieter van Heerden** provided much-needed advice during the following 21 months. Fortunately, Pieter and I could see the main synthesis come to fruition before he also left the UOFS.

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Abbreviations

A	=	acetone
aq.	=	aqueous
ax	=	axial (NMR)
B	=	benzene
br	=	broadened (NMR)
d	=	doublet (NMR)
DCM	=	dichloromethane
dd	=	doublet of doublets (NMR)
ddd	=	doublet of doublets of doublets (NMR)
dil.	=	dilute
DMAP	=	4-(N,N-dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
DMTSF	=	dimethyl(methylthio)sulphonium tetrafluoroborate
dq	=	doublet of quartets (NMR)
dt	=	doublet of triplets (NMR)
EA	=	ethyl acetate
eq.	=	equivalent(s) (molar, except if specified otherwise)
eq	=	equatorial (NMR)
FCC	=	flash column chromatography
H	=	hexane
h.	=	hour(s)
HMPA	=	hexamethylphosphoric triamide
m	=	multiplet (NMR)
m/m	=	mass per mass
min.	=	minute(s)
m.p.	=	melting point
MTPACl	=	α-methoxy-α-trifluoromethylphenylacetylchloride
NBS	=	N-bromosuccinimide
NMO	=	N-methylmorpholine-N-oxide
PLC	=	preparative thin layer chromatography
ppm	=	parts per million
Py	=	pyridine
r.t.	=	room temperature
s	=	singlet (NMR)

sat.	=	saturated
t	=	triplet (NMR)
TASF	=	tris(dimethylamino)sulphonium difluorotrimethylsilicate
TBDMSCl	=	*t*-butyldimethylsilyl chloride
TFA	=	2,2,2-trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	qualitative thin layer chromatography
TMEDA	=	N,N,N',N'-tetramethylethylenediamine
v/m	=	volume (cm^3) per mass (g)
v/v	=	volume per volume

Contents

1. LITERATURE SURVEY

1.1. Structure: an introduction

The flavonoids, isoflavonoids and neoflavonoids all contain a benzopyran (chroman) skeleton which is substituted respectively at C-2, C-3 or C-4 with a phenyl ring:

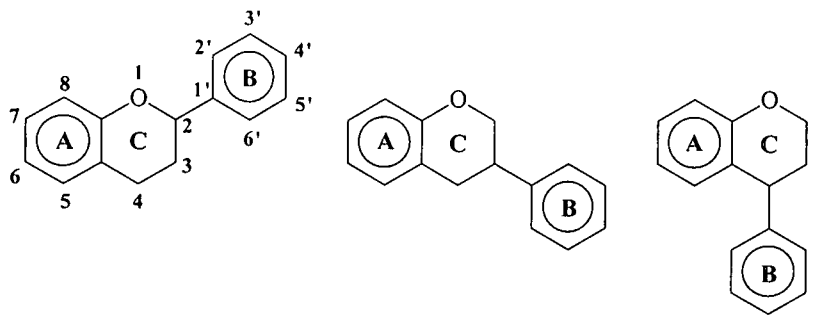


Figure 1: General structure of a flavonoid, an isoflavonoid and a neoflavonoid

Pterocarpans are closely related to the isoflavonoids, but they contain a second heterocyclic ring originating from an ether linkage (C-11a → O-11), and are consequently numbered somewhat differently:

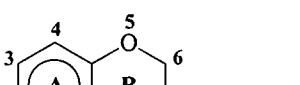


Figure 2: General structure of a pterocarpan

The members of these compound classes vary in the degree and pattern of aromatic and heterocyclic oxygenation, as well as the oxidation state of the heterocyclic ring(s).

1.2. Occurrence of flavonoids and isoflavonoids in plant sources

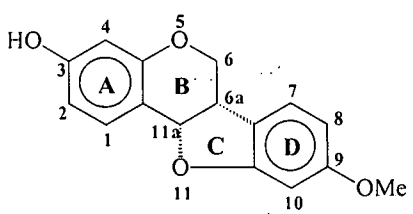
Flavonoids are by far the most abundant of the abovementioned compounds, and occur in most higher, vascular plants.[1] In contrast, isoflavonoids are relatively scarce, and they are encountered almost exclusively in the subfamily Papilionoideae (Lotoideae) of the Leguminosae.[1-4] Accordingly, isoflavonoid-neoflavonoid oligomers, topical to this discussion, are not as widespread as the flavonoid analogues (see Section 1.4.)

1.3. Biological activity of isoflavonoids

Isoflavonoids usually serve a dual purpose in plants, *viz.* protection against phytophageous fungi and feeding insects. Furthermore, some isoflavonoids also display biological activity in mammals. The following paragraphs provide a few examples in each of these categories.

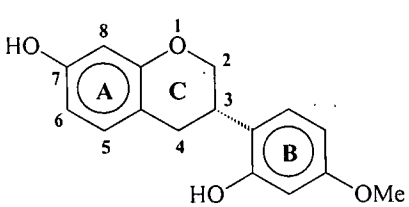
1.3.1. Fungitoxins and phytoalexins

Some isoflavonoids biosynthesized by plants serve as leaf surface fungitoxic agents, *i.e.* they inhibit the germination of fungal spores on the leaf. Most antifungal isoflavonoids, however, are only formed by plants once they are infected by the pathogen.[5] They thus fall into the class of socalled phytoalexins, defined as antimicrobial compounds produced by plants in response to infections by pathogens.[6] Of all flavonoid compounds the most widespread phytoalexins are isoflavonoids,[7,8a-e] in particular pterocarpans (most commonly medicarpin, **1**) and isoflavans (most commonly vestitol, **2**).[9]



Medicarpin (1)

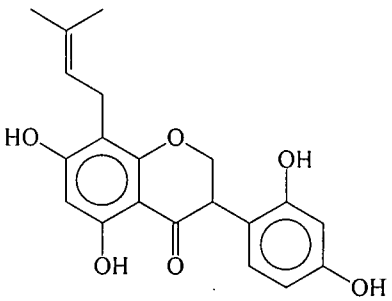
(Note: only the (+)-(6a*S*, 11a*S*) enantiomer is shown)



Vestitol (2)

(Note: only the (+)-(3*S*) isomer is shown)

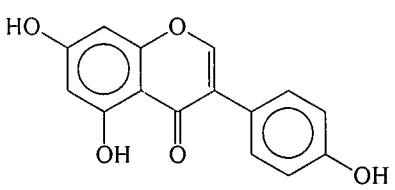
In most cases of plants investigated for phytoalexins, the root cause of disease is fungal infection. Phytoalexins are not only fungicidal, however, but rather generally biologically toxic. Some studies have revealed that isoflavonoid phytoalexins possess bactericidal and bacteriostatic properties, and can even cause lysis of red blood cells and inhibition of mitochondrial respiration. Kievitone (**3**) has been shown to inhibit three human pathogens.[10]



Kievitone (3)

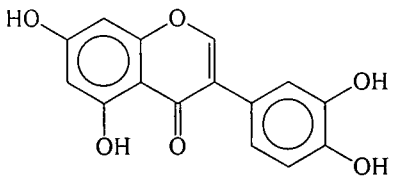
1.3.2. Insect feeding deterrents and insecticides

Genistein (**4**) is a known antibacterial compound, inhibiting the growth of, *e.g.*, *Pseudomonas maltophilia* and *Enterobacter cloacae*. These bacteria are found in the gut of some insects, *e.g.* the tobacco budworm, and thus genistein imparts insect-resistant properties to the parent plant.[11]

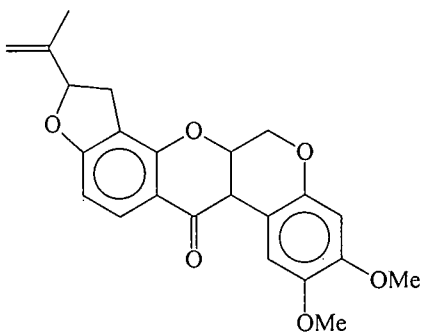


Genistein (4)

Insect antifeeding and insecticidal properties have also been ascribed to orobol (**5**)[12] and several rotenoids including rotenone (**6**). Some of these compounds have been used as commercial insecticides because of their relatively low toxicity to mammals.[13]



Orobol (5)



Rotenone (6)

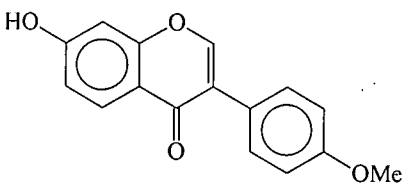
A characteristic structural element of most flavonoids inhibiting insect growth is vicinal oxygenation, *i.e.* they possess *ortho*-dihydroxy or –methoxy substitution on an aromatic ring.[12]

1.3.3. Effects on mammals

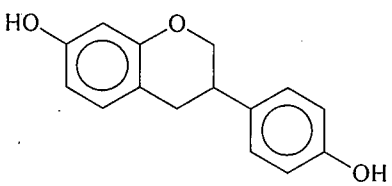
Flavonoids, isoflavonoids and/or neoflavonoids are prevalent in many dietary sources of humans and animals, *e.g.* fruit, vegetables, nuts, seeds, stems, flowers, tea and wine,[14] and a typical Western diet comprises *ca.* 1 g of mixed flavonoids per day.[15] Although these compounds are probably most renowned for their antioxidative properties [14,16], numerous other physiological effects have also been ascribed to them, most notably antiallergic, anti-inflammatory, antiviral, antiproliferative and anticarcinogenic properties,[17-25] as well as enzyme-inducing, free-radical scavenging and metal cation chelating activities,[14] and effects on cellular protein phosphorylation.[14] A few examples of isoflavonoids with biological activity in mammalian systems are given below:

Some isoflavones present in certain lupin varieties, amongst them genistein (**4**), have been reported to induce oestrogenic effects in mammals.[26] Not only could this lead to irregularities in the reproductive cycle of livestock feeding on the lupin; similar effects in humans must also be considered, since lupin is receiving increased attention as a food source for humans.[27]

Bennetts *et al.*[28] described an infertility syndrome in West Australian. sheep that ingested certain species of clover containing formononetin, **7**. This oestrogenic isoflavone is metabolized in the mammalian gut to an oestrogenic isoflavan, equol (**8**).[29] Equol has been found in human urine,[30] and might be accountable for human infertility.

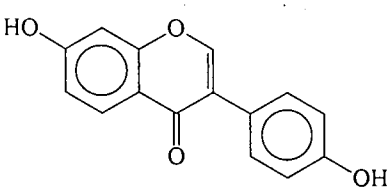


Formononetin (7)



Equol (8)

A further oestrogenic isoflavone which has been detected in human urine is daidzein, **9**.[31] This compound and other phyto-oestrogens bind relatively strongly to oestrogen receptors of human mammary tumour cells,[32] and may thus be responsible for inhibiting breast cancer growth mediated by oestrogen.



Daidzein (9)

The extracts of Jamaican dogwood (*Piscidia erythrina*) exhibit spasmolytic properties in mammalian smooth muscle tissue.[33] This effect is ascribed to various isoflavones related to rotenone, **6**, itself a known spasmolytic agent.[34]

Orobol (**5**) is an inhibitor of dihydroxyphenylalanine (DOPA) decarboxylase and shows significant hypotensive activity in rats. It also inhibits histidine decarboxylase, thus lowering histamine-induced secretion of gastric acid.[35]

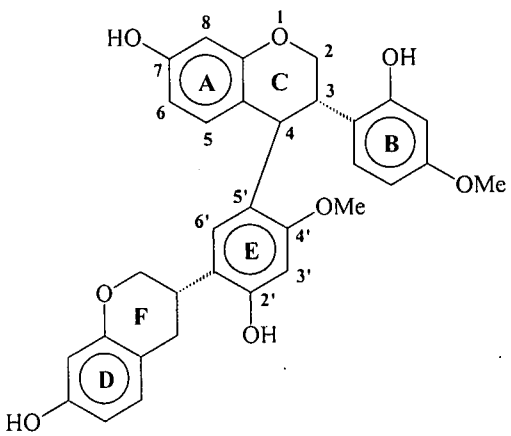
Chimura *et al.*[36] reported that three isoflavones inhibit catechol-*O*-methyltransferase (COMT), a catecholamine-metabolizing enzyme. The possible physiological effect of this inhibition is an adrenaline-sparing action.[37,38]

Genistein (**4**) inhibits protein tyrosinase kinases (PTK),[39] which are enzymes involved in cell growth, gene expression, cell-cell adhesion, cell motility and shape.[40] Topoisomerases I and II, participating in genetic processes such as replication, transcription, recombination, integration and transposition, are also sensitive to genistein.[41] Furthermore, this isoflavone also inhibits T-cell proliferation, an inflammatory reaction of the mammalian body to stimulation by antibodies.[42] These findings make genistein a potential immunosuppressant, useful in, *e.g.*, the rejection of tissue grafts. In addition, genistein can cause differentiation of as yet undifferentiated cancerous cells into cells which exhibit the phenotypic characteristics of the mature cancer.[43-46] These findings may prove valuable in the early detection of cancer.

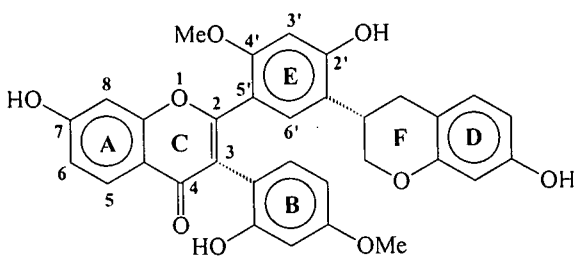
1.4. Isoflavonoid oligomers

Very little is known about the biological activity of isoflavonoid-based oligomers, but it is possible that they possess similar biological properties as the constituent monomers. Not only are isoflavonoid monomers less abundant in nature than flavonoids, but a similar distribution also holds true for the corresponding oligomers.[47] The existence of natural isoflavonoid oligomers was only confirmed in a recent review.[48] A number of these compounds were subsequently identified, however, including isoflavonoid-isoflavonoid, isoflavonoid-flavonoid, isoflavonoid-stilbene and isoflavonoid-phenylpropanoid dimers.[49]

The prominence of the *Dalbergia* genus amongst the quoted plant sources is conspicuous. *Dalbergia nitidula*, for example, contains the isoflavan dimer (3*S*)-vestitol-(4→5')-(3*S*)-vestitol **10**, as well as the isoflavone-isoflavan dimer 2'-hydroxyformononetin-(2→5')-(3S)-vestitol **11**.[50]

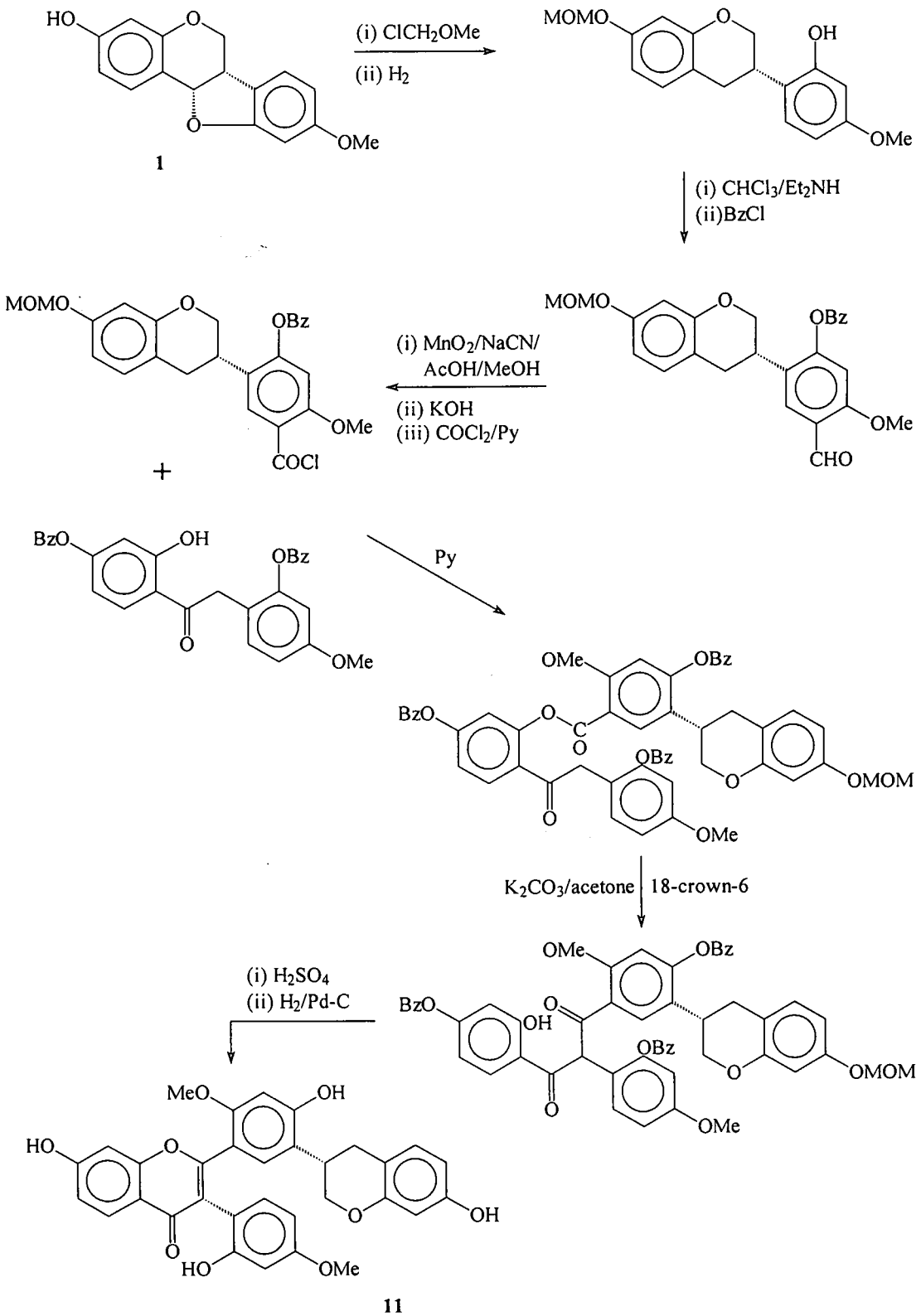


(3*S*)-Vestitol-(4→5')-(3*S*)-vestitol (10)



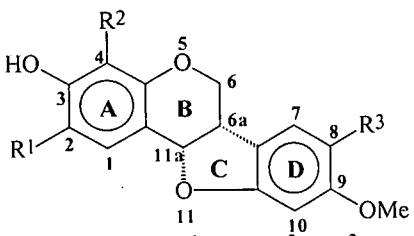
2'-Hydroxyformononetin-(2→5')-(3S)-vestitol (11)

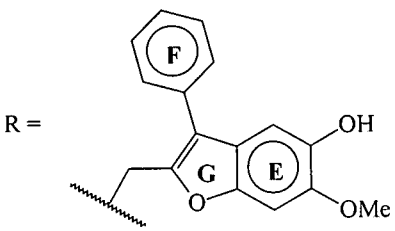
The synthesis of the latter compound from (+)-(6a*S*, 11a*S*)-medicarpin (**1**) is outlined below:[49]



Scheme 1

The novel pterocarpan-neoflavonoid dimers Daljanelins A-C (**12-14**) and the new isoflavan-neoflavonoid dimer Daljanelin D (**15**) were also isolated from *D. nitidula*.[51] The structure of Daljanelin C has already been confirmed by synthesis in these laboratories (see chapter 2),[51] and this dissertation concerns the subsequent syntheses of Daljanelins A, B and D.

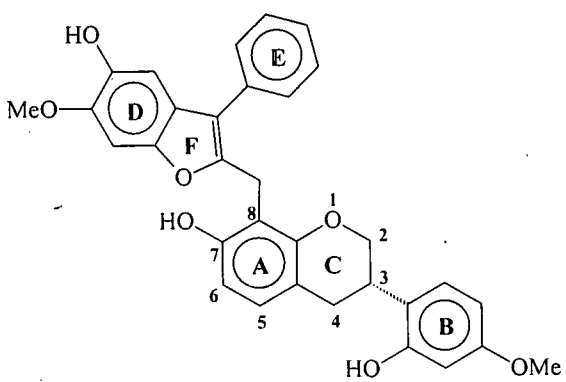




Daljanelin A (12): R^1 = R, R^2 = R^3 = H

Daljanelin B (13): R^1 = R^3 = H, R^2 = R

Daljanelin C (14): R^1 = R^2 = H, R^3 = R



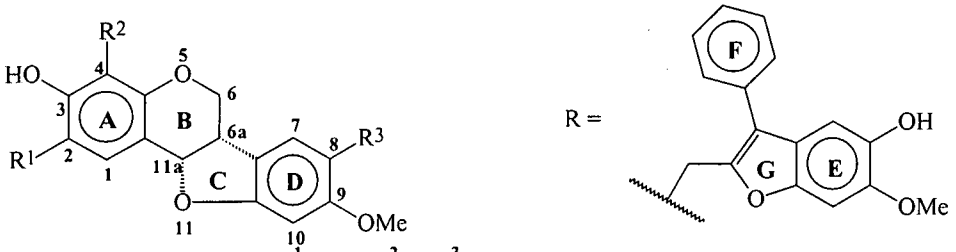
Daljanelin D (15)

2. DISCUSSION

2.1. Considerations regarding the synthesis of the Daljanelins

2.1.1. Structural elucidation of the natural products

The figures below show the structures of Daljanelins A–C (**12–14**) and that of Daljanelin D (**15**):

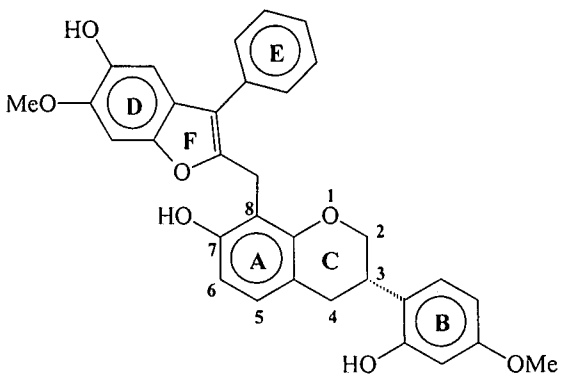


Daljanelin A (12; R^1 = R, R^2 = R^3 = H)

Daljanelin B (13; R^2 = R, R^1 = R^3 = H)

Daljanelin C (14; R^3 = R, R^1 = R^2 = H)

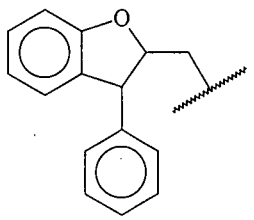
Note that Daljanelins A–C all contain a pterocarpan fragment and a neoflavonoid fragment, and that they differ only in the respective *position* on the pterocarpan to which the neoflavonoid is bonded with a C_1 bridge.



Daljanelin D (15)

Daljanelin D is related closely to Daljanelin B, but contains an isoflavonoid unit in stead of a pterocarpan. It may thus be regarded as the C-11a – O-11 reduced form of Daljanelin B.

Early NMR experiments on the Daljanelins isolated from *Dalbergia nitidula* were not conclusive in establishing whether the constituent pterocarpan (isoflavonoid) and neoflavonoid monomers were bonded through an exocyclic C_1 bridge, the neoflavonoid heterocyclic ring being five-membered (see general neoflavonoid structure 1, below), or whether the interflavanyl bond was situated between two cyclic C atoms, *i.e.*, the neoflavonoid possessing a six-membered heterocyclic ring (structure 2).



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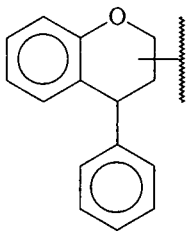
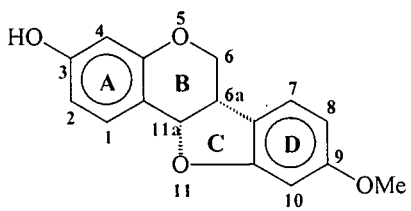


2

Possible general structures for the neoflavonoid fragment in the Daljanelins

The first synthesis of Daljanelin C was performed in these laboratories,[51] and the dimer was characterised as possessing an exocyclic C_1 coupling fragment and a five-membered heterocyclic ring in the neoflavonoid unit, *i.e.* general structure 1 shown above. It still remained to be demonstrated, however, that the neoflavonoid constituents of the other Daljanelins were of the same general structure. Assuming this, the pivotal task in each case was the introduction of a suitable C_1 bridge to the relevant position on (+)-(6a*S*, 11a*S*)-medicarpin **1**, readily available from *Dalbergia nitidula*.



1

2.1.2. Development of a synthetic route towards Daljanelin-type dimers

The syntheses performed in this research project were further motivated by the need for a general synthetic route towards the abovementioned dimers, mainly to address and circumvent the usual difficulties in the functionalization of pterocarpan A-rings, *viz.*:

i) the low nucleophilicity of the A-ring, probably due to the electron withdrawing effect of the C-11a → O-11 ether linkage;

ii) the sensitivity of the pterocarpan C-ring to Lewis and Brønsted acids: the abovementioned cyclic ether is prone to cleavage under such conditions, leading potentially to epimerisation at C-6a and C-11a, and also to oligomerization *via* regiochemical self-condensation initiated by an incipient carbocation at the equivalent of C-11a.

iii) differentiating between C-2 and C-4: if encountered at all, electrophilic aromatic substitution on the pterocarpan A-ring *usually* takes place at C-2, and a general method had to be found to functionalize position 4 selectively. An analogous situation is encountered in the 5-deoxyflavonoids, where substitution is found almost exclusively at C-6, but hardly ever at C-8;[52]

iv) the sensitivity of the phenolic centres to many reaction conditions, in particular, the aptitude of the A-rings of pterocarpans and isoflavonoids to form quinone methides under oxidative conditions, leading to undesired side products.

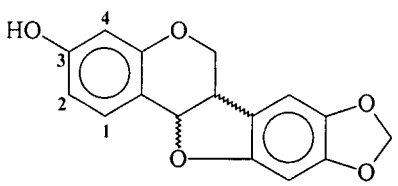
Thus, any attempt to synthesize a Daljanelin should not only take cognizance of these constraints, but should have the potential to bypass the associated pitfalls.

2.2. Synthesis of Daljanelin B (13)

It should be noted that although the medicarpin A- and D-rings are very similar, the free phenolic nature of position 3 provides a suitable focal point for differentiation between the two aromatic systems, *i.e.* between Daljanelins A, B and D on the one hand, and Daljanelin C on the other.

2.2.1. Retrosynthesis

The only hitherto documented instance of introducing a carbon substituent to C-4 of a pterocarpan[53] involves allylation of the corresponding phenolic centre of (±)-maakiain, **16**, and a subsequent Claisen-type rearrangement.



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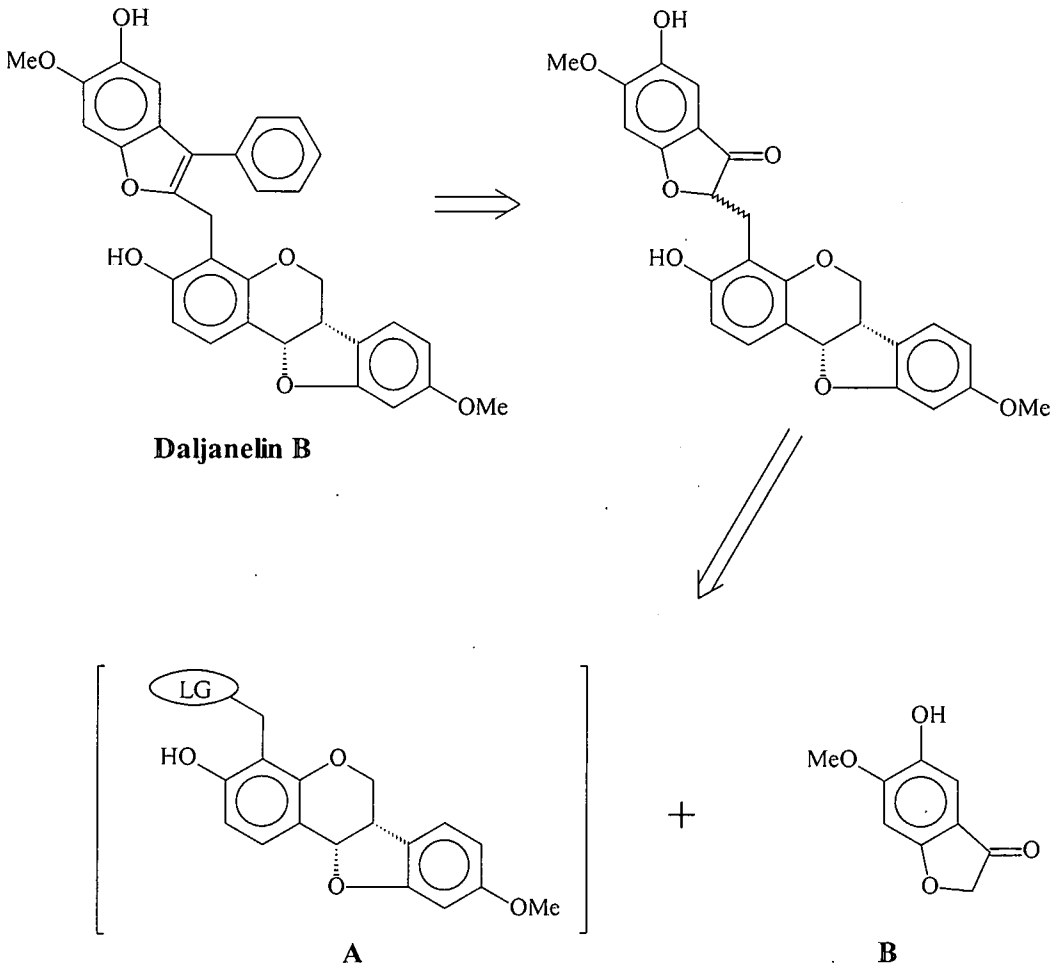
Thus, the following retrosynthetic scheme towards Daljanelin B was proposed:



Scheme 2: Retrosynthesis of Daljanelin B (13)

2.2.2. Proposed synthesis

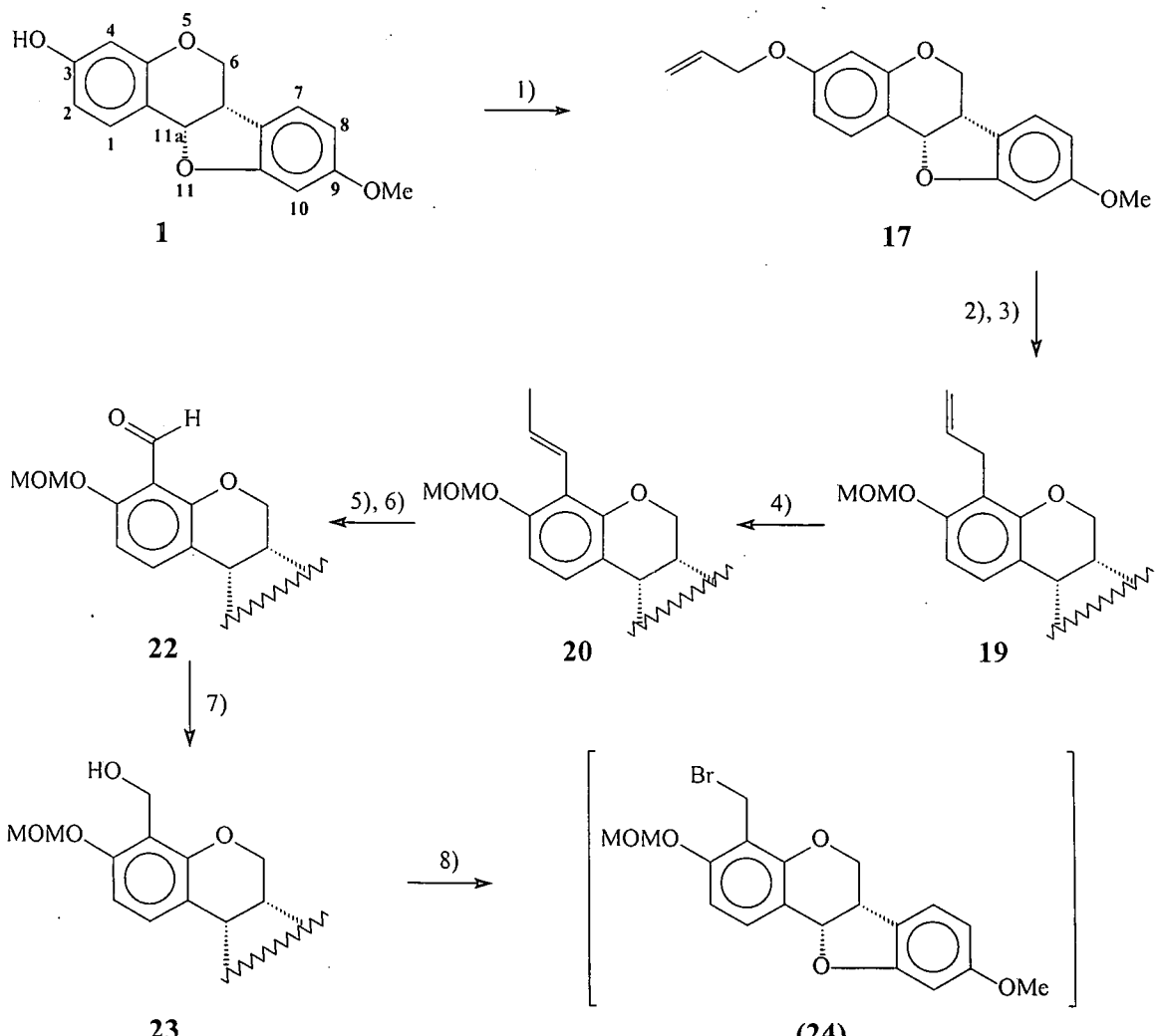
The proposed synthetic route towards Daljanelin B thus consists of three different phases, *viz.*

1) Introduction of a suitable C_1 fragment to C-4 of (+)-(6a*S*, 11a*S*)-medicarpin **1**, to obtain a compound of type **A**, as shown in Scheme 2;
2) Synthesis of a benzofuranoid precursor to the neoflavonoid fragment, *i.e.* of a compound of type **B** (Scheme 2);
3) Coupling of the two monomers, introduction of the remaining C_6 fragment, and subsequent dehydration.

2.2.2.1. Functionalization at C-4 of (+)-(6a*S*, 11a*S*)-medicarpin (1)

This proposed functionalization comprised the following eight steps, and is illustrated in Scheme 3 (steps 2 and 3, as well as steps 5 and 6, have been combined in Scheme 3):

1) 3-*O*-allylation of (+)-medicarpin (**1**);
2) Thermal rearrangement of the allyl ether **17** to an allylphenol **18** (and if necessary, separation of the 2- and 4-allyl isomers);
3) Protection of the 3-hydroxy group in **18** as the corresponding methoxymethyl ether **19**;
4) Isomerization of the allyl group in **19** to a prop-1-enyl group in **20**;
5) Osmilation and dihydroxylation of the resulting conjugated olefinic centre in **20**;
6) Oxidative cleavage of the vicinal diol **21**;
7) Reduction of the resulting benzaldehyde **22** to the corresponding benzyl alcohol **23**;
8) *In situ* conversion to the benzyl bromide **24**.

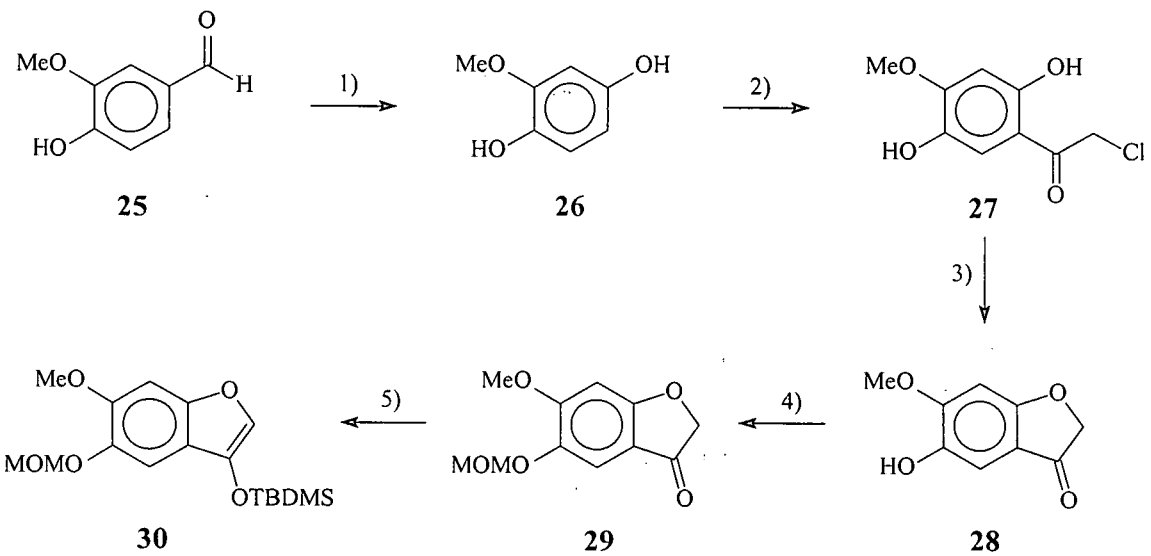


Scheme 3: Proposed functionalization at C-4 of (+)-(6a*S*, 11a*S*)-medicarpin (1)

2.2.2.2. Synthesis of the $C_6.C_2$ fragment of the neoflavonoid constituent unit

Scheme 4 shows the conversion of vanillin **25** to the benzofuranoid precursor required for coupling with the protected 4-bromomethylmedicarpin **24**, according to the following sequence:

1) Dakin-oxidation of vanillin **25** to methoxy-*p*-hydroquinone **26**;
2) Hoesch-acylation of **26** with chloroacetonitrile to acetophenone **27**;
3) Base-catalyzed cyclization of **27** to benzofuranone **28**;
4) Protection of the phenol in **28** as the methoxymethyl ether **29**;
5) Conversion to the enol silyl ether **30**.



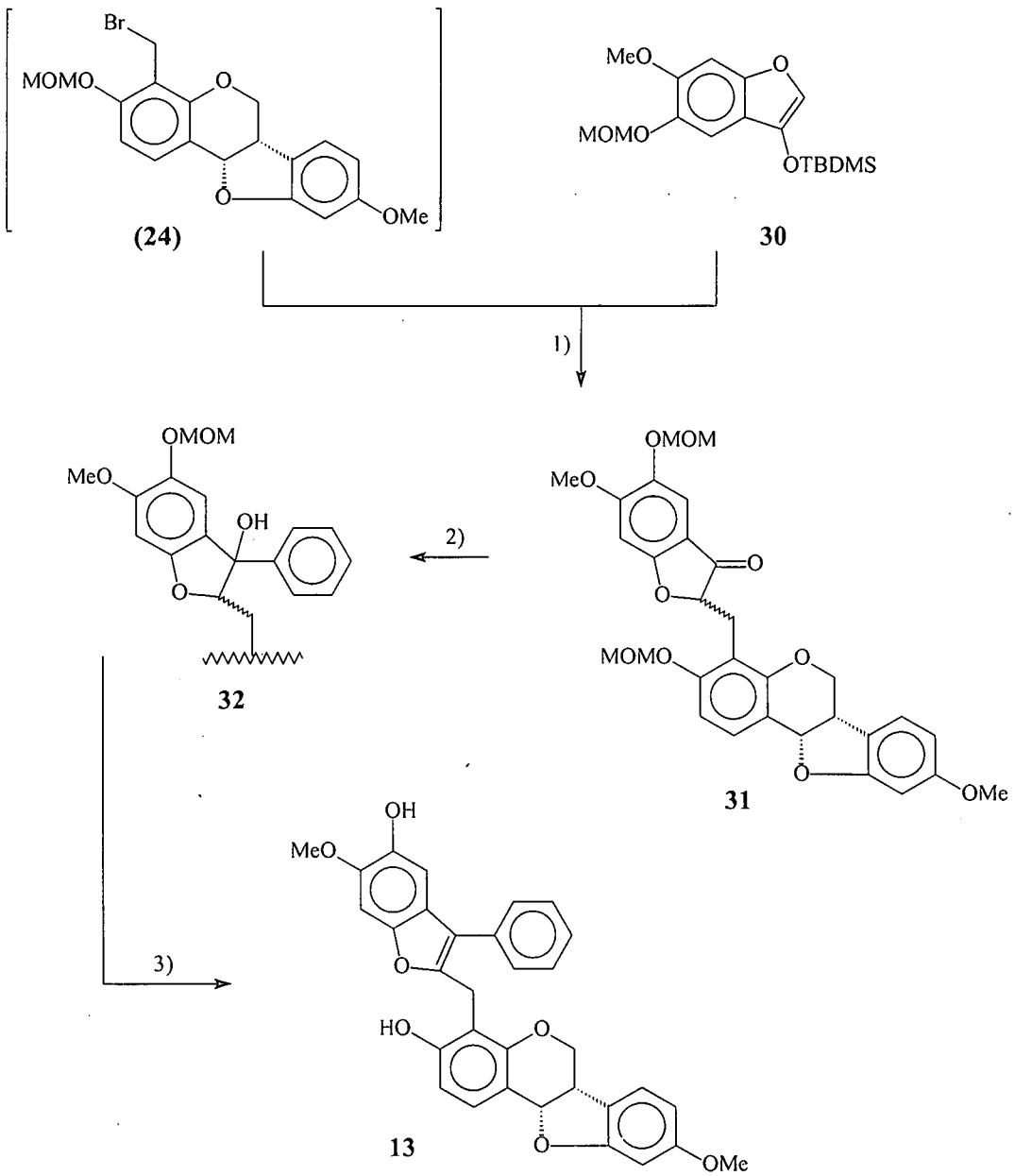
25 **26** **27** **28** **29** **30**

Scheme 4: Synthesis of the benzofuranoid fragment

2.2.2.3. Coupling of the enol silyl ether (30) and benzyl bromide (24)

The last three steps are identical to those utilized in the earlier synthesis of Daljanelin C:[51]

1) Desilylation of the enol silyl ether **30** (Scheme 4) and nucleophilic coupling with the functionalized medicarpin **24** (Scheme 3), giving the dimer **31**;
2) Grignard reaction with PhMgBr to introduce the remaining C_6 fragment in **32**;
3) Dehydration and concomitant 3-*O*-deprotection of **32**, giving Daljanelin B (**13**).



Scheme 5: Nucleophilic coupling and final functionalizations

Section 2.2.3. provides a detailed discussion of the practical execution of each of the aforementioned synthetic steps.

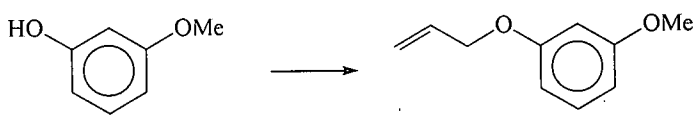
2.2.3. Model reactions and eventual synthesis of Daljanelin B (13)

In order to observe the behaviour of a series of model substrates in the proposed synthetic transformations on (+)-(6a*S*, 11a*S*)-medicarpin **1**, a number of phenolic compounds were subjected to the sequence of reactions outlined in Section 2.2.2.1. and Scheme 3. The simplest model compound, simulating only the medicarpin A-ring, was 3-methoxyphenol,**33**. The medicarpin A- and B-rings, as well as the benzylic oxygen at position 11, were simulated with 4-hydroxy-2-methoxybenzyl alcohol **34** and 1-(4-hydroxy-2-methoxy)-phenylethanol **35**, and three isoflavonoids (**7**, **36** and **37**) were selected to emulate the combined effects of the A-, B- and D-rings in medicarpin.

2.2.3.1. Allylation of resorcylic substrates

Direct C-allylation of 3-methoxyphenol (**33**) with allyl alcohol in 2,2,2-trifluoroethanol was attempted but no product formation was observed. When HCl (c) was added and the mixture heated, the strongly acidic conditions led to decomposition. Baruah[54] has reported the direct, aromatic *ortho*-allylation of some phenols, promoted by anhydrous $Cu(ClO_4)_2$. Owing to the known sensitivity of pterocarpan nuclei to Brønsted and Lewis acids, it was anticipated that neither of the abovementioned routes would be suitable for C-4 allylation of (+)-(6a*S*, 11a*S*)-medicarpin **1.** They were thus abandonded in favour of *O*-allylation and thermal allyl rearrangement.

The first step of the synthesis, *i.e.* *O*-allylation of the phenol, was tested initially on 3-methoxyphenol, **33**:

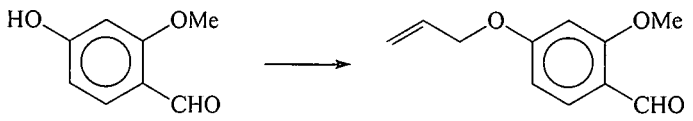


33 **38**

Scheme 6

The starting material was allylated with allyl bromide and K_2CO_3 in dry acetone to give the allyl ether **38**. Although this allylation was found to be slower than that of 3,5-dimethoxyphenol,[55] it proceeded remarkably cleanly. No further purification of the crude product, isolated in 92% yield, was necessary before performing the intended thermal rearrangement.

Allylation of 4-hydroxy-2-methoxybenzaldehyde **39** would provide, after reduction of the allyloxybenzaldehyde **40** to the corresponding benzyl alcohol **41**, a model compound more closely resembling the substituted medicarpin A-ring:

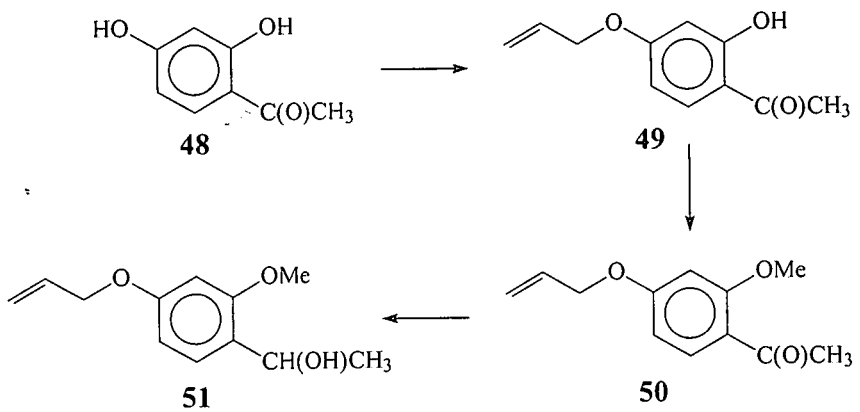


39 **40**

Scheme 7

As the starting material for this allylation was not readily available, it was envisaged to allylate only the *p*-hydroxy group of 2,4-dihydroxybenzaldehyde **42** with allyl bromide and K_2CO_3, and to methylate the remaining free phenol. Selective *p*-allylation, however, proved problematic, as the putative hydrogen bond between the *o*-hydroxy group and the aldehyde functionality was too weak to prevent *o*-allylation. This procedure led mainly to the isolation of 2,4-diallyloxybenzaldehyde, **43**, and only 4% of the desired monoallyl compound, **44**. A similar result was obtained with the use of NaH and allyl bromide in dry THF. Because of the low yields of **44**, 2-*O*-methylation of the product was not investigated, but rather, a higher yielding method for selective 4-*O*-allylation of the dihydroxybenzaldehyde **42** was sought. This entailed protection of the *p*-hydroxy group of **42** as the benzyl ether, methylation of the *o*-hydroxy group, *p*-deprotection and subsequent allylation with allyl bromide and K_2CO_3. This procedure, however, was also unsuccessful: after benzylation of **42**, only 2,4-dibenzyloxybenzaldehyde, **45**, and an inseparable mixture of the 2- and 4-monobenzyl ethers (respectively **46** and **47**) were obtained, and the latter mixture still proved inseparable after methylation with MeI.

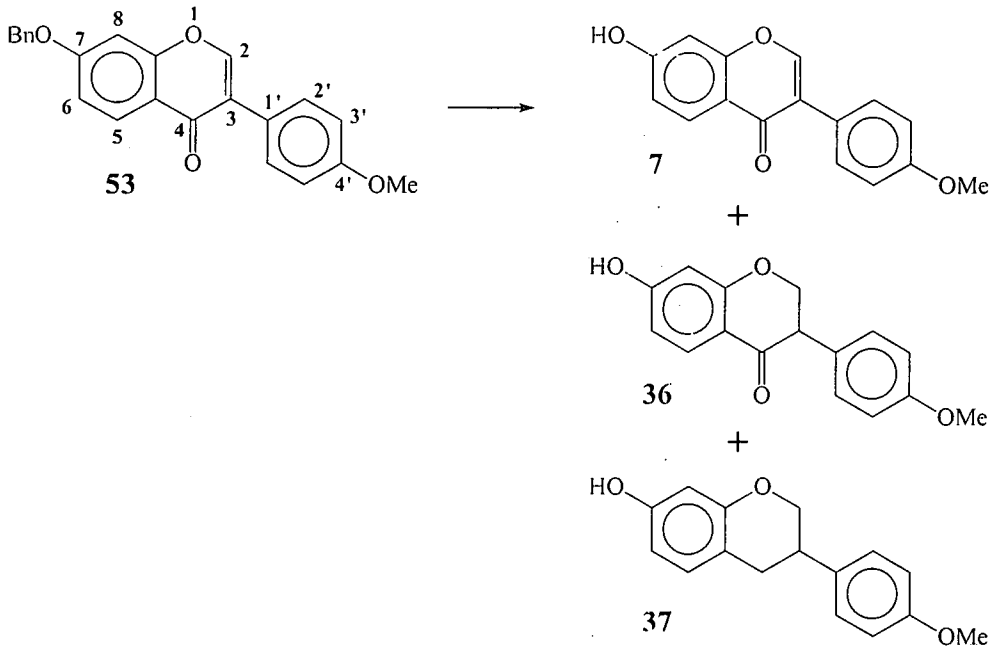
The abovementioned route was not investigated further. Instead, it was envisaged to convert the corresponding 2,4-dihydroxyacetophenone **48** *via* selective *p*-allylation (**49**), subsequent *o*-methylation (**50**) and reduction to 1-(4-allyloxy-2-methoxy)-phenylethanol **51**, a secondary benzylic alcohol which would be an even better model substrate for the allylated medicarpin A-ring:



Scheme 8

Initial attempts to allylate the dihydroxyacetophenone **48** with NaH and allyl bromide presented similar selectivity problems as before, *i.e.* only 4% of 2,4-diallyloxyacetophenone, **52**, and only 3% of 4-allyloxy-2-hydroxyacetophenone, **49**, could be isolated. In contrast, the originally employed method of allylation, *viz.* allyl bromide and K_2CO_3 in dry acetone, led to the formation of the desired monoallyl ether **49** in 55% yield, after which methylation with dimethyl sulphate gave the corresponding 2-methyl ether **50** (79%). Carbonyl reduction with $NaBH_4$ subsequently afforded the desired phenylethanol **51** cleanly and without any purification in 89% yield.

In order to obtain the three isoflavonoids chosen to emulate the medicarpin A-, B- and D-ring system, it was envisaged to hydrogenate 7-*O*-benzyl-4'-methoxyisoflavone **53** catalytically to a mixture of 7-hydroxy-4'-methoxyisoflavone (formononetin) **7**, 7-hydroxy-4'-methoxyisoflavanone **36** and 7-hydroxy-4'methoxyisoflavan **37**:

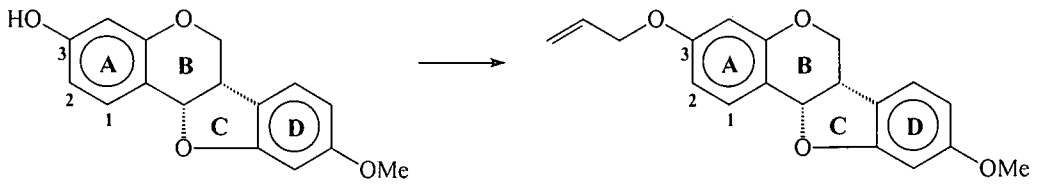


Scheme 9

Catalytic hydrogenations of **53** on 10-40% m/m Pd-C (5 or 10%) gave access to **7**, **36** and **37**. It should be noted that the extent and selectivity of hydrogenation were difficult to control. The best results (**7** : **36** : **37** = 22-35%:24-26%:9-16%; 22-27% recovery of starting material) were obtained by employing EtOH as solvent. Performing the reactions in acetone, itself a reducible ketone, proved valuable in terminating hydrogenation at the isoflavanone stage, if so desired. Furthermore, the isoflavan **37** was extremely difficult to separate from a product tentatively identified as its 4-*O*-ethyl ether.

The three phenolic isoflavonoid substrates **7**, **36** and crude **37** were subsequently allylated with allyl bromide and K_2CO_3 in dry acetone, giving the corresponding allyl ethers **54**, **55** and **56** in respective yields of 91%, 81% and 30%. The low yield of **56** may be ascribed to the significant contamination of the isoflavan **37** after hydrogenation.

Finally, (+)-(6a*S*, 11a*S*)-medicarpin (**1**) was converted to its 3-*O*-allyl ether **17** in 80% yield, again using allyl bromide and K_2CO_3:

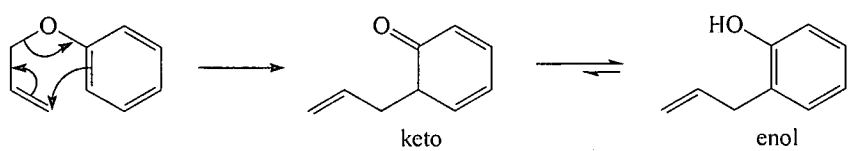


1 **17**

Scheme 10

2.2.3.2. Thermal rearrangement of resorcylic allyl ethers

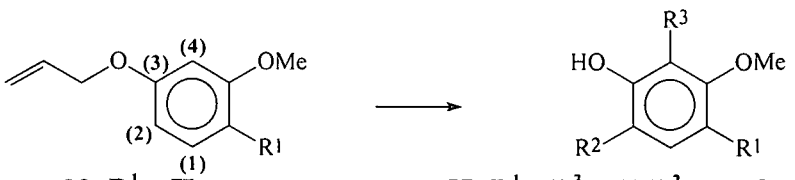
The 1,3- and 3,3-rearrangement of aryl allyl ethers to *o*- and *p*-allylphenols, is referred to as the aromatic Claisen rearrangement and has received wide interest in synthetic organic chemistry.[56a-h] Although some alternative methods have been reported, including catalysis by montmorillonite clay[57,58] and by Florisil®,[59] the reaction historically and usually entails purely thermal rearrangement. The classic mechanism describes a 1,3- or 3,3-sigmatropic rearrangement, the latter shown below:



Scheme 11: 3,3-Sigmatropic rearrangement of an aryl allyl ether

The first step of this mechanism is nucleophilic attack of the aromatic system on the allylic π-system. It is, in essence, an intramolecular S_EAr step, and as such, dictates that if both *ortho*-carbons in the starting material are unsubstituted, the allyl group in the final product will be bonded to the one at which the HOMO of the starting material possesses a higher electron density.

The resorcylic allyl ethers **38**, **50**, **51**, **54**, **55**, **56** and **17** (Section 2.2.3.1.) were all subjected to reflux in N,N-dimethylaniline (*ca.* 200°C) under an Argon atmosphere.[53] Scheme 12 shows the attempted thermal rearrangements of the simpler substrates:



38: R^1 = H

50: R^1 = C(O)CH_3

51: R^1 = CH(OH)CH_3

57: R^1 = R^3 = H, R^2 = allyl

58: R^1 = R^2 = H, R^3 = allyl

59: R^1 = C(O)CH_3, R^2 = allyl, R^3 = H

60: R^1 = C(O)CH_3, R^2 = H, R^3 = allyl

61: R^1 = CH(OH)CH_3. R^2 = allyl, R^3 = H

62: R^1 = CH(OH)CH_3. R^2 = H, R^3 = allyl

Scheme 12

The numbering shown parenthetically in Scheme 12 has been chosen to represent that of the analogous medicarpin A-ring in order to facilitate a direct comparison of the respective reactivities with respect to thermal rearrangement of the allyl group. This numbering will be used in quotation marks when applied to the resorcinol-based model compounds in the further discussion. Table 1 summarizes the results obtained with these model substrates:

Table 1

Allyl ether	"2"-Allylphenol	Yield (%)	"4"-Allylphenol	Yield (%)
38	**57**	52	**58**	39
50	**59**	38 (47)	**60**	20 (25)
51	**61**	0	**62**	0

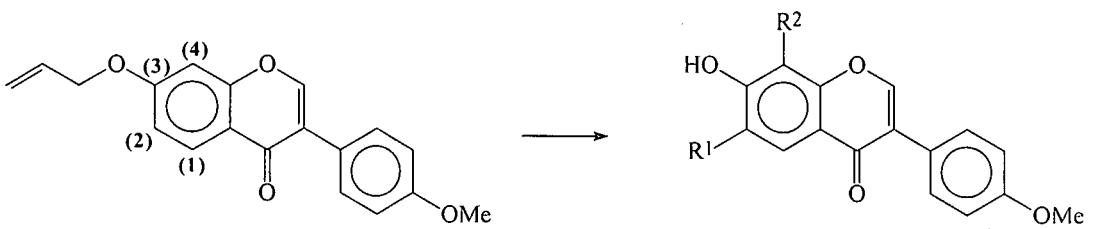
Note: the respective yields for recovery of the starting materials were 0%, 19% and 0%, and the yields by *conversion* are shown in brackets.

The third reaction shown in Table 1, *i.e.* that of the 1-phenylethanol **51**, led to thermal decomposition of the starting material. It can be assumed that the benzylic alcohol functionality is too labile to survive the drastic conditions.

An alternative method of allylic rearrangement was investigated with the *O*-allyl substituted acetophenone **50** and 1-phenylethanol **51** by subjecting these substrates to 100% m/m K10 montmorillonite clay (as supplied by Aldrich) in benzene. The acetophenone seems relatively

inert to these conditions, even after an overnight reaction at 60°C, as only starting material (58%) could be isolated after preparative TLC of the reaction mixture. Once again, the benzylic alcohol proved too labile, as preparative TLC of the mixture gave only three small fractions (3%, 9% and 4%, each in itself a mixture) of unidentified material.

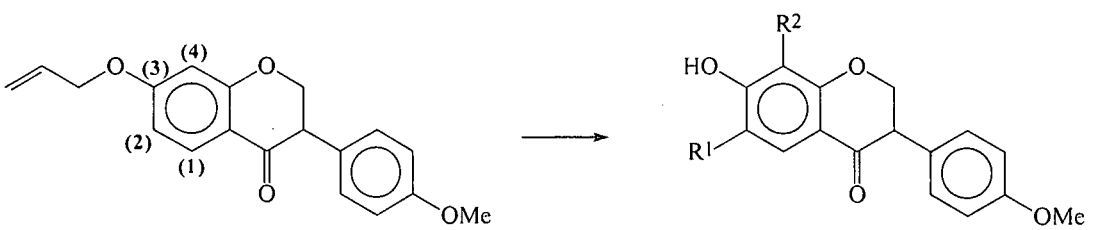
The next step in the chemical modelling of the formation of (6a*S*, 11a*S*)-4-allylmedicarpin (**18**) was to reflux the isoflavonoid-based "3"-*O*-allyl ethers **54**, **55** and **56** (Section 2.2.3.1.) in N,N-dimethylaniline. Schemes 13-15 illustrate the reactions, using parenthetic pterocarpan-based numbering as before:



54 **63: R^1 = allyl, R^2 = H**

64: R^1 = H, R^2 = allyl

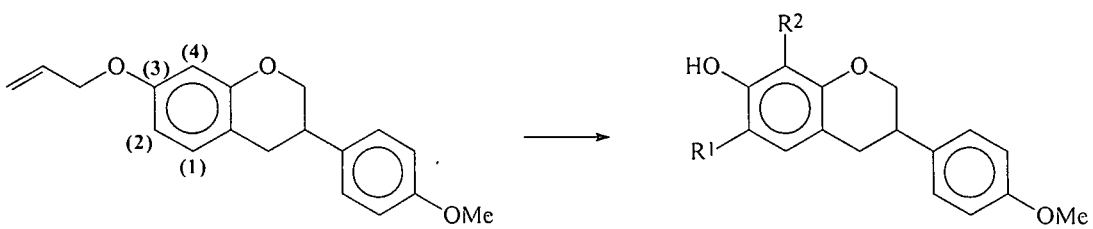
Scheme 13



55 **65: R^1 = allyl, R^2 = H**

66: R^1 = H, R^2 = allyl

Scheme 14



56 **67: R^1 = allyl, R^2 = H**

68: R^1 = H, R^2 = allyl

Scheme 15

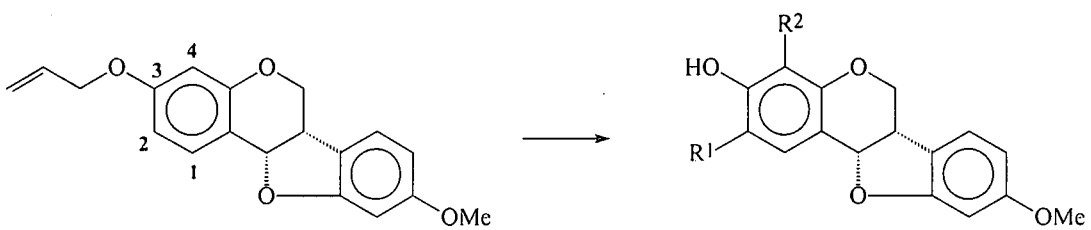
Table 2 provides a summary of the obtained results:

Table 2

Allyl ether	"2"-Allylphenol	Yield (%)	"4"-Allylphenol	Yield (%)
54	**63**	0	**64**	34 (40)
55	**65**	0	**66**	23 (40)
56	**67**	0	**68**	33 (37)

Note: the respective yields for recovery of the starting materials were 15%, 42% and 13%, and the yields by *conversion* are shown in brackets.

As before, the pterocarpan analogue was finally subjected to the same conditions as the model substrates, *i.e.* (6a*S*, 11a*S*)-3-*O*-allylmedicarpin (**17**) was refluxed in N,N-dimethylaniline:



17 **69: R^1 = allyl, R^2 = H**

18: R^1 = H, R^2 = allyl

Scheme 16

Table 3 summarizes the result of this reaction and, by way of comparison, lists the analogous result for thermal rearrangement of (±)-3-*O*-allylmaakiain **70**:[53]

Table 3

Allyl ether	2-Allylpterocarpan	Yield (%)	4-Allylpterocarpan	Yield (%)
17	**69**	0	**18**	55[†]
70	**71**	0	**72**	55

[†] The starting material was recovered in 24% yield.

Purification of the slightly contaminated allylphenol **18** by chromatography, crystallization, 3-*O*-methoxymethylation or -acetylation was unsuccessful, and it was finally characterized in 26% overall yield (35% by conversion) *via* crystallization as the 3-*O*-(3',5'-dinitro)benzoate **73**.

1% KOH/MeOH was found to be a very effective reagent for deacetylating the crude 3-*O*-acetate of the rearranged product so that it could be purified as the dinitrobenzoate **73**.

Preliminary HOMO density calculations[60] on the pterocarpan framework show that the HOMO possesses a greater electron density at C-2 than at C-4. The same observation was made for "C-2" and "C-4" of the monocyclic and isoflavonoid model substrates. Normal Claisen rearrangement (intramolecular S_EAr) should thus give the "2"-allyl isomer as the main product, as confirmed by Table 1. From the second entry it can be deduced that the introduction of a benzylic oxygen functionality *para* to the rearranging allyl ether does not affect the preferred rearrangement to position "2", at least not if such an oxygen functionality is a ketone.

This effect is reversed, however, in the isoflavonoid model substrates: Table 2 clearly demonstrates the superior reactivity of "C-4" with respect to aryl-allyl bond formation. A similar preference for allylic rearrangement to C-4 can be observed in pterocarpans (see Table 3). Thus, the isoflavonoid model substrates above correlate with medicarpin in the sense that thermal rearrangement of the "3"-*O*-allyl ether gives only the "4"-allylphenol.

It appears that the exclusive thermal allyl rearrangement in the pterocarpans to the position *less* favoured by normal intra- and intermolecular S_EAr reactions, must be ascribed to a combination of the following factors:

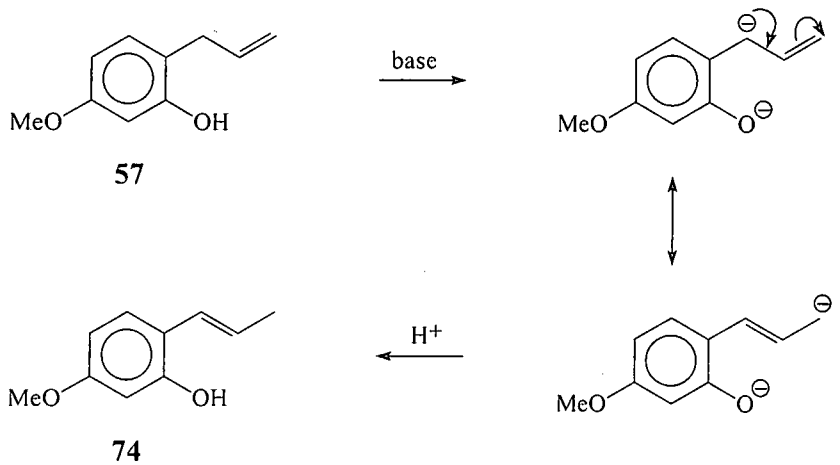
1) The thermal allyl rearrangement possibly proceeds *via* a *different* mechanism than normal Claisen rearrangement;
2) The benzylic, ether-linked oxygen (O-11 in the pterocarpan framework) attenuates the nucleophilicity of C-2 to an extent not predicted by HOMO calculations;
3) The nucleophilicity of "C-2" is decreased by the electronic properties intrinsic to the pterocarpan and isoflavonoid skeletons.

2.2.3.3. Isomerization of the allylic π-system

The earlier synthesis of Daljanelin C (**14**)[51] in our laboratories demonstrated, at least for this dimer, that the neoflavonoid heterocyclic ring was five membered, and that the two monomers were joined by a C_1 bridge. Assuming that the same skeletal configuration held true for Daljanelin B (**13**), retrosynthetic principles (see Scheme 2 in Section 2.2.1) dictated that the allyl group on C-4 should first be isomerized to a prop-1-enyl group, after which

oxidative cleavage would render the precursor to a benzylic, electrophilic C_1 coupling site, as shown earlier in Scheme 3.

One of the products of an earlier allyl rearrangement, 2-allyl-5-methoxyphenol, **57**, was used to test whether deprotonation of the benzylic/allylic carbon would lead to thermodynamic equilibration of the resulting benzylic/allylic anion, to give the corresponding prop-1-enyl isomer **74** after quenching, as shown in Scheme 17:



Scheme 17

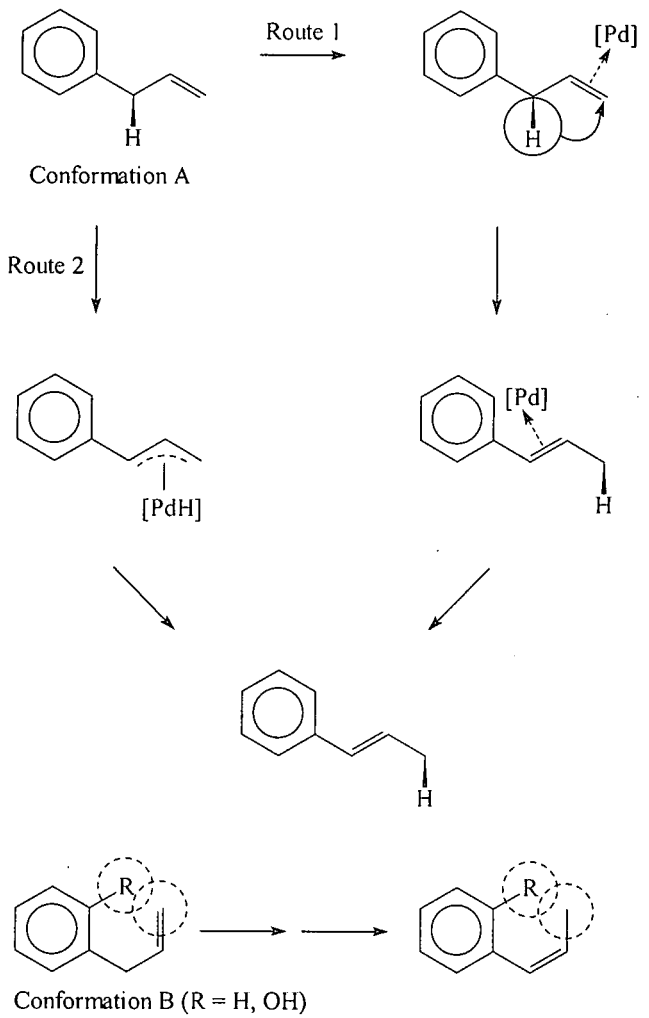
(Note: only the *E*-isomer **74** of the product is shown)

Compound **57** was thus subjected to *n*-BuLi (2.1 eq. were used to provide for deprotonation of the phenol), but conversion to the desired conjugated isomer **74**, inseparable by chromatography from the starting material **57**, could only be achieved in *ca.* 40% yield, and a more highly yielding method was sought.

Golborn and Scheinmann[61] reported the isomerization of several allyl phenyl ethers and allylphenols with $PdCl_2(PhCN)_2$ in refluxing benzene. This catalyst converted allyl phenyl ethers predominantly to (*Z*)-prop-1-enyl phenyl ethers, whereas allylphenols gave mostly (*E*)-prop-1-enylphenols. In both cases, isomerization of the π-system can proceed *via* one of two possible mechanisms:[62-67]

1) A π-allyl(hydrido)-palladium complex is formed, after which hydrogen delivery to C-3 of the carbon chain and dissociation of the π-allyl-palladium complex gives the prop-1-enyl compound, or
2) coordination of palladium with the double bond allows a concerted 1,3-migration of hydrogen on the opposite side of the complex.

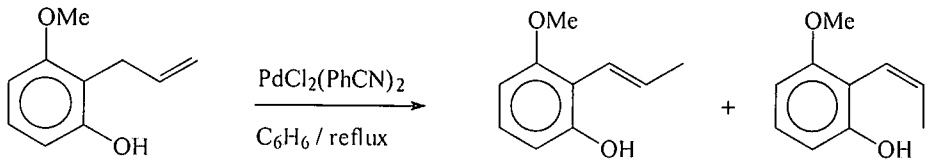
The 1,3-transfer of hydrogen is suprafacial in both cases, but this is of no significance if the allyl group bears no substituents on C-1 and C-3. Scheme 18 illustrates the two mechanistic routes for a general allylarene:



Scheme 18

It can be seen that the conformation of the starting material determines the geometry of the double bond in the product: the s-*trans* conformation A leads to the formation of the *E*-isomer, while the s-*cis* conformation B gives the *Z*-isomer. The fact that allylphenols are isomerized predominantly to (*E*)-prop-1-enylphenols, was ascribed to the steric hindrance between the side chain and the adjacent aromatic hydrogen or hydroxy group in starting materials and products possessing non-preferred conformation B. Although a similar steric interaction between the prop-1-enyl palladium complex and the adjacent aromatic substituent seems likely for conformation A, Route 1, no mention was made of this.

The catalyst, prepared easily according to the method described by Kharasch *et al.*,[68] was tested on a substrate available from earlier studies, *viz.* 2-allyl-3-methoxyphenol, **58**. The reaction is illustrated in Scheme 19:

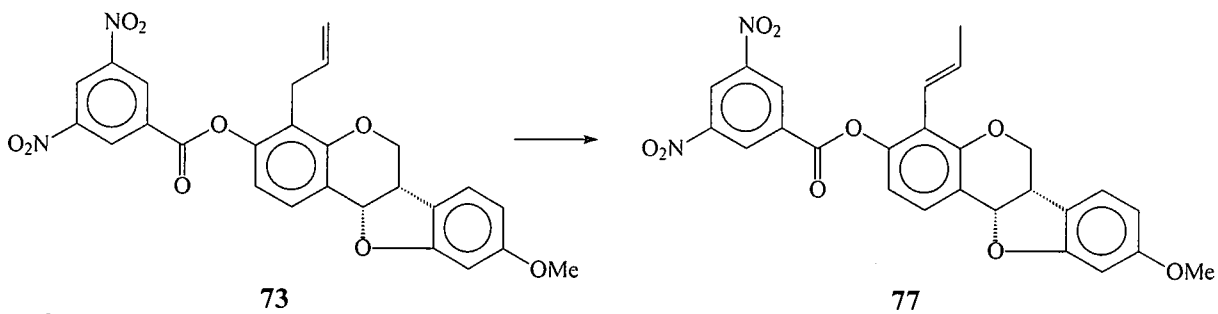


58 **75** **76**

Scheme 19

^{1}H NMR spectra of reaction aliquots showed complete conversion of the allylphenol **58** to a mixture of the (*E*)- and (*Z*)-prop-1-enyl isomers (**75** and **76**, respectively) within 2 h. Chromatography of the product mixture yielded 70% of a similar mixture.

Although the model reaction above was performed on a phenolic substrate, it was decided to subject (6a*S*, 11a*S*)-3-*O*-(3',5'-dinitrobenzoyl)-4-allylmedicarpin **73** to similar conditions without prior debenzoylation, as a protecting group would probably be required for the next proposed synthetic transformation, *i.e.* oxidative cleavage of the isomerized double bond. ^{1}H NMR spectra of reaction aliquots in a small-scale test run indicated that **73** underwent smooth, near-quantitative olefin isomerization in 40 min.:



73 **77**

Scheme 20

(Note: only the *E*-isomer **77** of the product is shown.)

On scale-up, however, it was found that a much longer reaction time (*ca.* 18h.) and considerably more catalyst than the usual 10% m/m were needed to achieve a satisfactory degree of isomerization. The crude product, which did not crystallize on cooling of the reaction mixture, was difficult to purify with preparative thin plate chromatography, as the applied sample crystallized on the silica. Flash column chromatography, however, emerged as the purification technique of choice. After diverse repetitions of the reaction, including

crystallizations and resubmission of incompletely converted mixtures to the catalyst, the combined yield of isomerization could be increased to 94%. The isolated product mixtures varied, according to ^{1}H NMR spectroscopy, in their relative content of *E*- and *Z*-isomers (respectively **77** and **78**), but all reactions showed >95% conversion to a mixture of the prop-1-enyl isomers. In one instance, 99% of >95% isomerically pure product could be isolated after a 22 h. reaction.

2.2.3.4. Osmilation and dihydroxylation of the prop-1-enyl group[69]

The newly introduced conjugated olefin had to be cleaved oxidatively in order to obtain the desired C_1 fragment on the medicarpin A-ring. A commonly used procedure for this transformation is the reaction with catalytic OsO_4 and a co-oxidant (usually *N*-methylmorpholine-*N*-oxide, NMO)[70] and subsequent cleavage of the resulting *vic*-diol with $NaIO_4$.

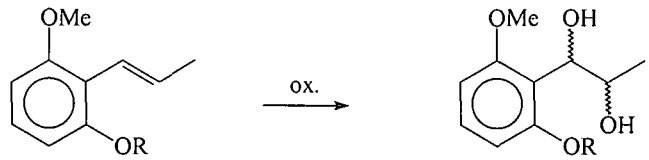
Since the protocol of asymmetric dihydroxylation (so-called AD) of olefins with AD-mix is well-established in our laboratories,[71] this reagent was evaluated to effect the proposed dihydroxylation step. AD-mix is, in essence, a mixture of a catalytic amount of potassium osmate [$K_2OsO_2(OH)_4$] and one of two possible chiral ligands in a carrier.[72] Although no chiral selection was required in this case, AD-mix is nevertheless an extremely convenient reagent, as it alleviates the serious health risk of working with OsO_4 in its pure, highly toxic form.

An experimental dihydroxylation of (*E*/*Z*)-(6a*S*, 11a*S*)-3-*O*-(3',5'-dinitrobenzoyl)-4-(prop-1-enyl)medicarpin, **77**/**78**, with AD-mix gave no conversion of the starting material, probably due to the steric hindrance caused by the *ortho*-dinitrobenzoate group. A further test reaction of the same substrate with OsO_4/NMO indicated lability of the dinitrobenzoate under such conditions, although it had proven stable when exposed to the strongly basic conditions associated with AD-mix in aqueous medium. Two series of model dihydroxylations, one with AD-mix and one with OsO_4, were then performed in order to address the following questions:

1) What degree of steric hindrance between the two *ortho*-substituents and the reaction site is tolerable?
2) Is the 3,5-dinitrobenzoyl ester stable during dihydroxylation?

3) If the dinitrobenzoyl group proves too large or too unstable under these oxidative conditions, can such compounds be dihydroxylated in their free phenolic form?
4) If the free phenol is not suited for direct dihydroxylation, is the methoxymethyl ether a suitable alternative protecting group?

The model reactions are summarized in Scheme 21 and Table 4:



75: R = H **79: R = H**

80: R = CH_2OCH_3 **81: R = CH_2OCH_3**

82: R = $C(O)C_6H_3(NO_2)_2$ **83: R = $C(O)C_6H_3(NO_2)_2$**

Scheme 21

(Note: only the (*E*)-prop-1-enyl isomers of the starting materials are shown.)

Table 4

Compound	Product	Yield: AD-mix (%)	Yield: OsO_4 (%)
75	**79**	0†	0†
80	**81**	>95‡	87
82	**83**	0*	0†

† Decomposition

‡ Determined by ^1H NMR of the crude product

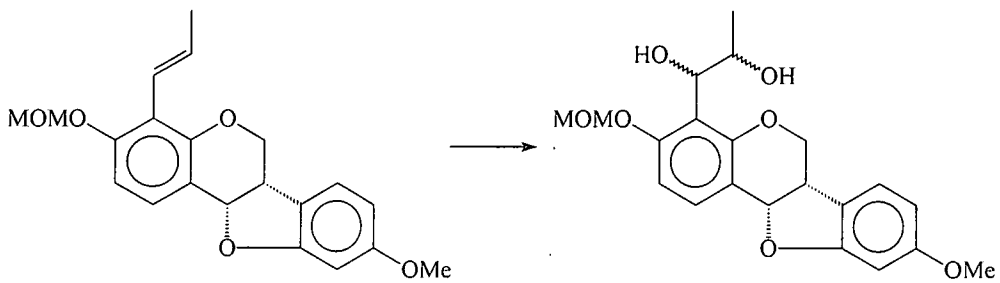
* Starting material recovered

These results provided the following answers to the four questions raised above:

1) It is probable that the 3,5-dinitrobenzoyl group was too large to allow effective attack by the oxidative reagent – at least in the case of AD-mix;
2) The dinitrobenzoyl ester was labile when exposed to OsO_4;
3) Both methods of dihydroxylation led to decomposition of the phenolic substrate;
4) The methoxymethyl-protected compound **80** could be dihydroxylated successfully by either method. According to TLC-analyses of the respective reaction mixtures, however, the OsO_4-catalyzed reaction proceeded more cleanly.

It was thus decided to debenzoylate and methoxymethylate the stock of current synthetic intermediate **77/78** before attempting to transform it to the corresponding *vic*-diol. The first of these steps was achieved with 1% KOH/MeOH to give (*E*/*Z*)-(6a*S*, 11a*S*)-4-(prop-1-enyl)medicarpin **84** in 74% yield, and the second by standard procedure to give the corresponding 3-O-methoxymethyl ether **20** in 61% yield. Although methoxymethylation is usually a near-quantitative reaction, the occasional instability of the products during chromatography accounts for some loss of material, as observed in this case.

(6a*S*, 11a*S*)-(*E*/*Z*)-3-*O*-methoxymethyl-4-(prop-1-enyl)medicarpin **20** was subsequently dihydroxylated with OsO_4/NMO, giving 61% of the corresponding propane-1,2-diol, **21**:



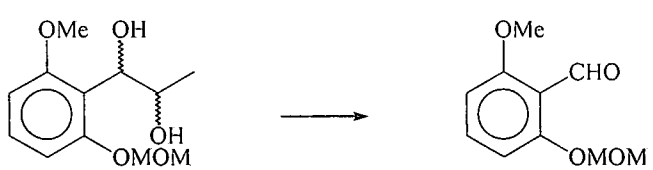
20 **21**

Scheme 22

The usual combination of reaction solvents, *i.e.* water:acetone:*t*-BuOH = 10:5:2, had to be supplemented with *ca.* 20 additional parts of acetone to expedite solution of the organic substrate. As before, loss of yield can probably be ascribed to some decomposition during chromatography.

2.2.3.5. Oxidative cleavage of the 1,2-diol

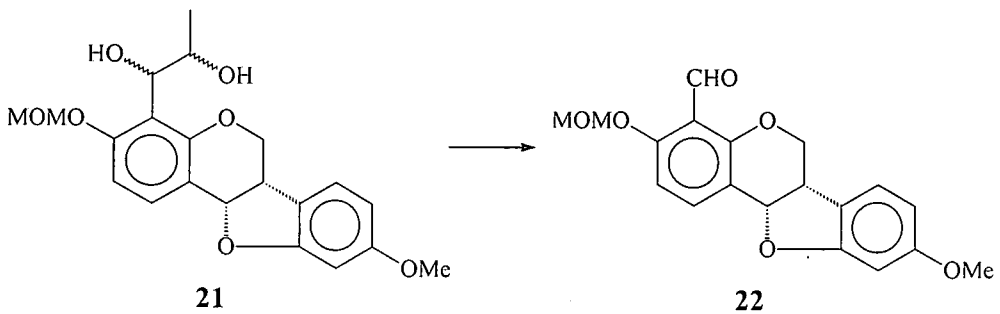
The C_3 fragment introduced to the pterocarpan A-ring could now be truncated by means of oxidative cleavage with $NaIO_4$ in moist MeOH (*ca.* 10% water). As in previous cases, the feasibility of the reaction was first determined using a model compound, in this case **81**:



81 **85**

Scheme 23

The desired 2-methoxy-6-*O*-methoxymethylbenzaldehyde **85** was obtained in 88% yield after 5 min., and the analogous reaction on the pterocarpan-based substrate **21** gave 73% of the desired (6a*S*, 11a*S*)-4-formyl-3-*O*-methoxymethylmedicarpin **22** after 70 min.:



21 **22**

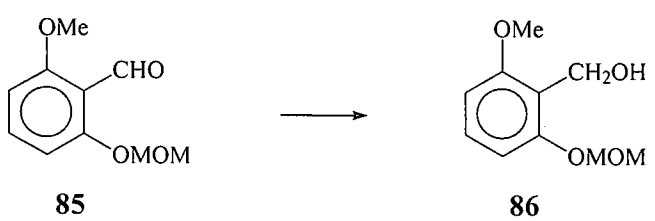
Scheme 24

The pivotal task of introducing a C_1 bridge to C-4 of the medicarpin framework, had thus been achieved.

2.2.3.6. Benzylic reduction

The overall synthetic route, outlined earlier in Scheme 3, conceived preparation of the aforementiond C_1 bridge for an anionic coupling reaction by reduction to the corresponding benzyl alcohol and *in situ* bromination.

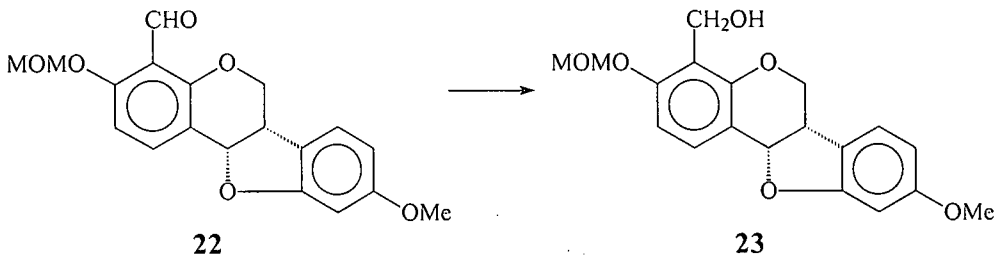
Mild benzylic reduction, using $NaBH_4$ in THF/EtOH (1:1) was tested on the model benzaldehyde **85**:



85 **86**

Scheme 25

The reaction proceeded smoothly and yielded 99% of the benzyl alcohol **86** after 5 min. The medicarpin analogue **22** was converted within 3 min. under similar conditions to (6a*S*, 11a*S*)-4-hydroxymethyl-3-*O*-methoxymethylmedicarpin, **23**:



22 23

Scheme 26

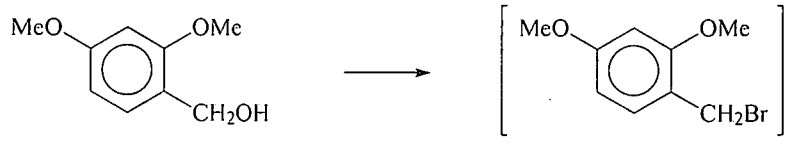
Synthesis of the precursor to the neoflavonoid monomer (see Schemes 2 and 4, and section 2.2.3.8. below) required that the C-4 functionalization of (+)-(6a*S*, 11a*S*)-medicarpin **1** be stopped temporarily at this stage. The corresponding benzyl bromide **24** was expected to be highly unstable (see section 2.2.3.7. below), and would only be synthesized once the required benzofuranone enol silyl ether was ready for the envisaged coupling reaction. For the purposes of linearity, however, conversion of the hydroxymethyl group to the bromomethyl group will be discussed at this point.

2.2.3.7. Benzylic bromination

In order to facilitate coupling of the C_1 functionalized medicarpin **23** with a nucleophilic benzofuranoid precursor of the neoflavonoid unit (see Scheme 2), the newly introduced benzylic alcohol functionality on C-4 of the pterocarpan skeleton had to be converted to an electrophilic centre. To this end, it was envisaged to apply exactly the same method as that used earlier in the synthesis of Daljanelin C,[51] *i.e.* conversion of the benzylic hydroxymethyl group to the corresponding benzyl bromide, to give a compound of the type (**A**) in Scheme 2 (LG = Br). Extensive research on this field had been entered into by the author, as it had been found that the benzyl bromide on C-8 of medicarpin was highly labile.[51] The only method that had resulted in effective benzylic bromination was the Collington-Meyers protocol,[73] using methanesulfonyl anhydride, lithium bromide and 2,6-lutidine in dry THF. The conversion of the benzyl alcohol to the benzyl bromide was monitored with ^{1}H NMR spectra of reaction aliquots, and as soon as quantitative *in situ* bromination was observed, the labile product was used directly for coupling with a benzofuranone enol silyl ether.

In order to test the applicability of the Collington-Meyers protocol to the novel 4-hydroxymethyl analogue **23** on hand, the ideal model compound would have been 2-methoxy-6-*O*-methoxymethylbenzyl alcohol **86** (Scheme 25), but as no sufficient quantity

of this substrate was available, a closely related model compound, 2,4-dimethoxybenzyl alcohol **87**, was subjected to the reagents described above:

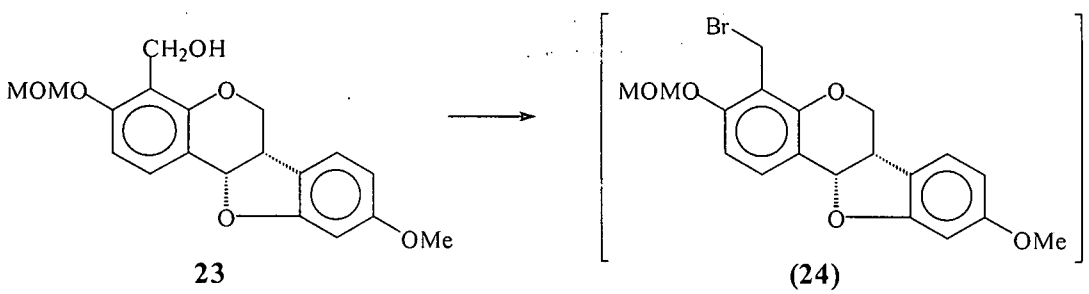


87 **(88)**

Scheme 27

The starting material **87** for this model reaction was obtained easily in 96% yield from readily available 2,4-dimethoxybenzaldehyde **89** *via* reduction with $NaBH_4$ in THF/EtOH (1:1). In an initial attempt at bromination, ^{1}H NMR showed only *ca.* 60% *in situ* conversion of the benzyl alcohol, but during subsequent iterations, the observed yield of **88** was increased to *ca.* 80% and finally to >95%, *i.e.* no traces of starting material could be detected with ^{1}H NMR. This optimization was achieved mainly by increasing the stoichiometric amounts of the oven-dried LiBr (from 2 to 3 eq.) and the methanesulfonyl anhydride [$(CH_3SO_2)_2O$] (from 1.2 to 1.5 eq.). It should be stressed that all reagents have to be dried well, and that the reaction has to be performed under rigorously anhydrous conditions.

Using the optimized stoichiometry as described above, (6a*S*, 11a*S*)-4-hydroxymethyl-3-*O*-methoxymethylmedicarpin, **23**, was subsequently converted *in situ* to the corresponding benzyl bromide **24** in a yield, according to ^{1}H NMR, of >95%, and the product was used immediately for the coupling reaction discussed later under section 2.2.3.9.



23 **(24)**

Scheme 28

Ferreira[51] observed during the synthesis of Daljanelin C that in the ^{1}H NMR spectrum used to monitor the [bromination] reaction, the 8-methylene protons of [the benzyl bromide] resonate as an AB system in contrast to the single doublet that was observed in the spectrum of the benzyl alcohol [...]. Interestingly, a similar observation was made in this case, *i.e.* the 4-methylene protons of the benzyl bromide **24** displayed a dd signal in ^{1}H NMR, whereas

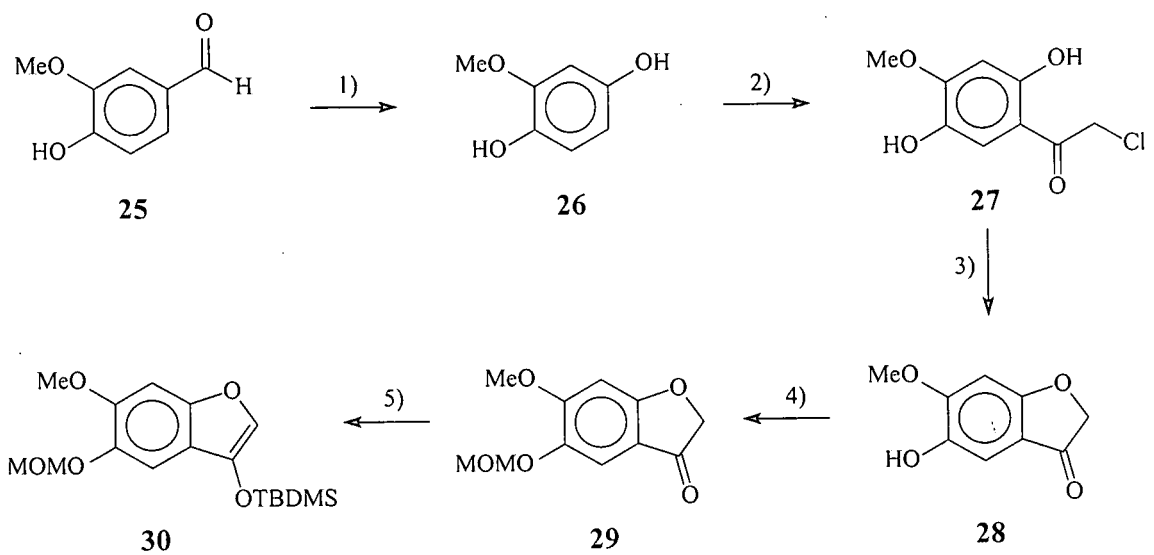
those of the benzyl alcohol **23** exhibited a broadened multiplet. This phenomenon indicates that both benzyl bromides possess a more rigid conformation than the corresponding benzyl alcohols, thus making the methylene protons diastereotopic. This might be explained in terms of hindered rotation around the Ar-CH_2(Br) bond, possibly due to

1) the atomic size of Br, and/or
2) complexation of the bromide, *e.g.* "solvent cage" formation, with Li^+, 2,6-lutidine and THF.

The second hypothesis is improbable, however, as the ^{1}H NMR spectra were recorded from very dilute solutions in C_6D_6.

2.2.3.8. Synthesis of the neoflavonoid precursor

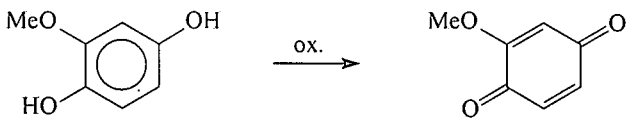
Scheme 4, introduced under section 2.2.2.2, illustrates the sequence of steps required to transform vanillin **25** into the benzufuranone enol silyl ether **30**, which can then be used as a nucleophile after desilylation:



Scheme 4: Synthesis of the benzofuranoid fragment

Based on the assumption that all four Daljanelins contain the same neoflavonoid fragment (see Section 2.1.1.), it was decided to follow the above synthesis exactly as used earlier in these laboratories during the synthesis of Daljanelin C (**14**).[51] A few points deserve attention, though:

1) Dakin oxidation of vanillin (**25**) to methoxy-*p*-hydroquinone (**26**), as monitored by TLC, appears a high-yielding reaction, but substantial amounts of the product were lost during the necessary purification by FCC, resulting in typical yields of 50-60%. This observation emphasizes once again the sensitivity of many phenolic compounds to chromatography. Hydroquinones are particularly susceptible to oxidation, yielding quinones, *e.g.*



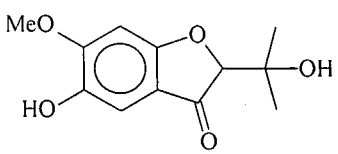
26 **90**

Scheme 29

Sublimation of the crude product,[51] even under relatively high vacuum (*ca.* 1 mm Hg) and elevated temperatures (*ca.* 80°C), gave neither high yields nor good product purity.

2) Houben-Hoesch acylation of the methoxyhydroquinone **26** with chloroacetonitrile was inevitably accompanied by the formation of many side products. As observed by Ferreira,[51] the acylated hydroquinone **27** is easily oxidized, rendering purification by recrystallization ineffective. Chromatography of the worked up reaction mixture is hampered by the same difficulties, and thus the product was used in its crude form for base-catalyzed cyclization.

3) An investigation into an alternative method for base-catalyzed cyclization of the chloroacetohydroquinone **27** to the benzofuranone **28**, *viz.* K_2CO_3/acetone in stead of the previously documented NaOAc/ethanol,[51] demonstrated that the former reaction conditions are not suitable for this reaction. The yield of the desired benzofuranone **28** was only low to moderate, and the main product was assigned tentatively as the acetone aldol adduct **91**:



91

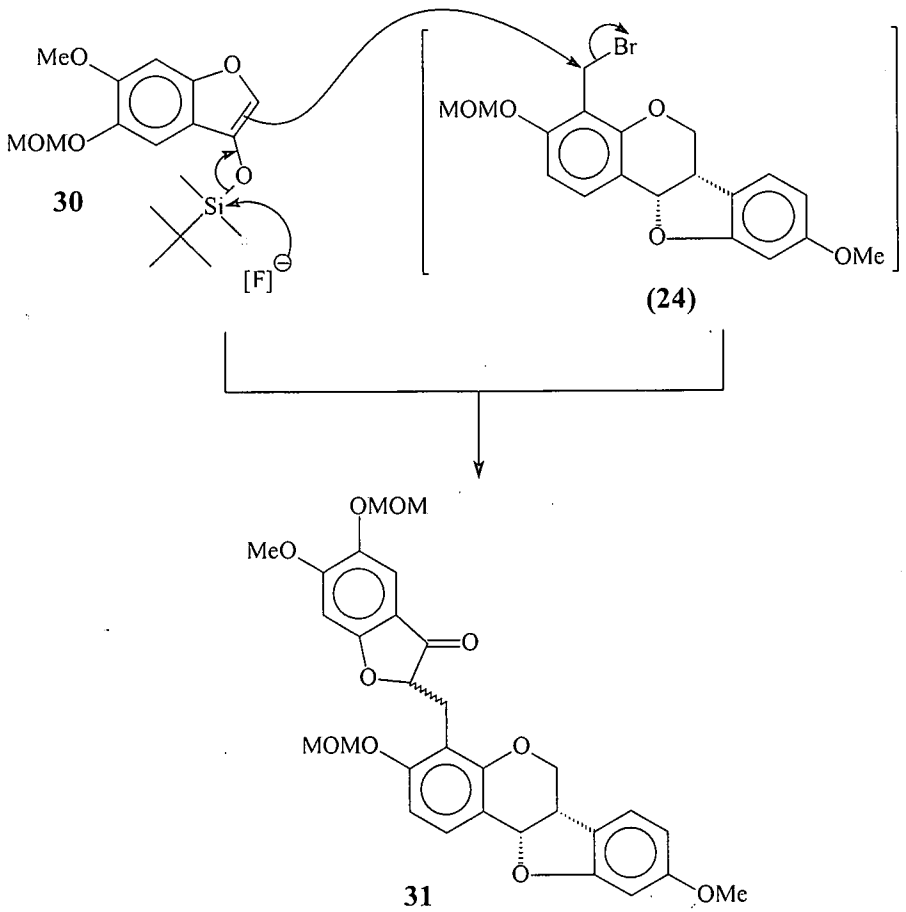
This observation indicates that the α-protons in the benzofuranone heterocyclic ring are sufficiently acidic to be abstracted by K_2CO_3. Both NaOAc/EtOH and NEt_3/EtOH were incapable of accomplishing a retro-aldol reaction of the proposed adduct, to give the desired benzofuranone, and thus the original conditions for cyclization of **27**, *i.e.* NaOAc/EtOH, were employed.

4) Protection of the phenol **28** as its 5-*O*-methoxymethyl ether **29** proceeded smoothly, using dry DMF as solvent. Care had to be taken, however, not to over-acidify the water-quenched reaction mixture. Although washing the organic extract with dilute acid would have facilitated easy removal of all DMF, the methoxymethyl ether **29** proved quite labile under acidic conditions. Thus, the organic extract was rather washed repeatedly with water. This is one of only a few methoxymethylations which cannot be performed well in the standard solvent (*i.e.*, THF) because of low solubility.

5) Ferreira *et al.*[51] noted that the TMS enol ether of the protected benzofuranone **29** was too unstable for further use during the synthesis of Daljanelin C (**14**), and that various coupling reactions with the free enolate of **29** had met only with limited success. The eventual method of choice had been to isolate the enol TBDMS ether **30** (Scheme 4) *before* nucleophilic coupling with a benzylic bromide. Following this procedure, benzofuranone **29** was thus silylated with TBDMSCl, dry NaI and dry NEt_3 in dry CH_3CN to give the enol TBDMS ether **30**. If due care was taken to maintain the extraction of the product with pentane between 0°C and 10°C, up to 96% of the silyl ether could be isolated in sufficient purity for direct further use. A lower extraction temperature incurred a loss of yield, whereas higher temperatures resulted in contamination of the product. Once isolated, the enol silyl ether **30** was quite stable under N_2 in a freezer, and could be used as required.

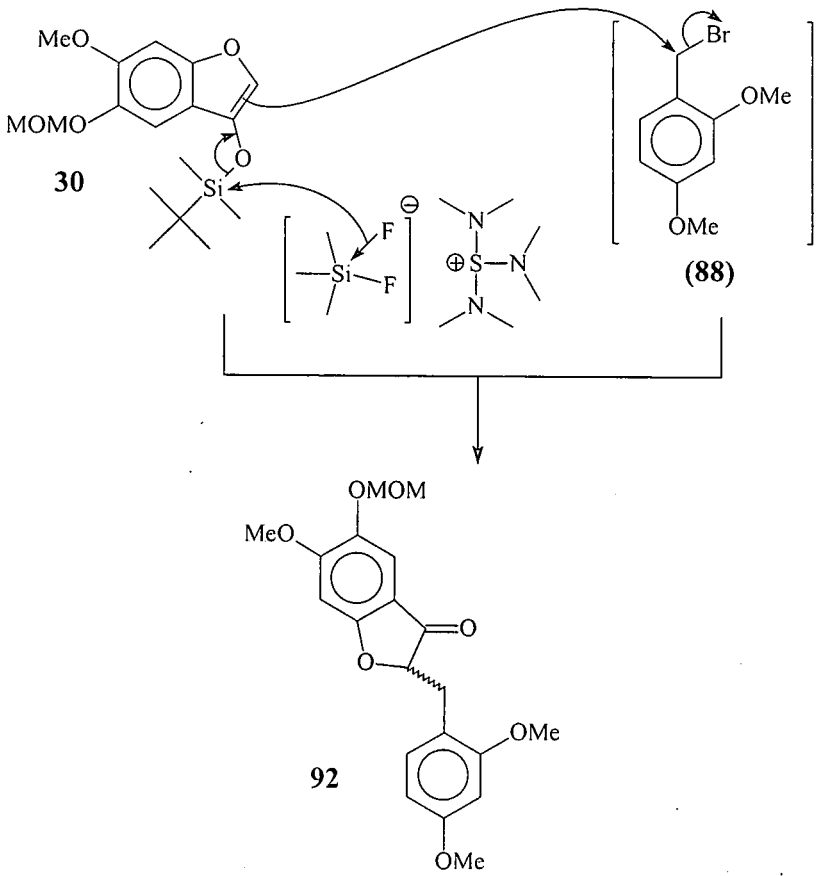
2.2.3.9. Desilylation and nucleophilic coupling

It was envisaged to couple the two precursors **30** and **24** to Daljanelin B (**13**), as follows:



Scheme 30: Simultaneous desilylation of 30 with a fluoride-based siliconophile and nucleophilic coupling with 24

In order to become acquainted with this procedure, a model **88** of the benzylic bromide **24** was prepared *in situ* (see Scheme 27) and coupled with the benzofuranoid fragment **30**:



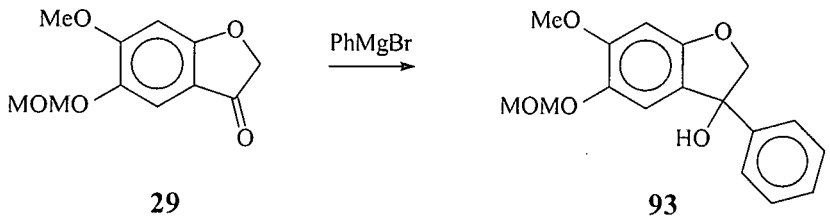
Scheme 31

To liberate an appropriately reactive enolate[51] from the enol silyl ether **30**, the powerful siliconophile, tris(dimethylamino)sulphonium difluorotrimethylsilicate (TASF)[74,75] was used. Care had to be taken when working with this slightly hygroscopic reagent, as the nucleophilic coupling reaction was highly intolerant of any moisture. As the model bromide **88** was readily available, it was used in excess (3.1 eq. relative to the enol silyl ether **30**). The dimer **92** was isolated in 20% yield (relative to the enol silyl ether **30**).

For the analogous reaction with (6a*S*, 11a*S*)-4-bromomethyl-3-*O*-methoxymethylmedicarpin **24** (Scheme 30), it was decided rather to use an excess of the enol silyl ether **30**, as only 50 mg of the starting material for the *in situ* bromination, *i.e.* the 4-hydroxymethylmedicarpin **23**, was available. As soon as ^{1}H NMR indicated near-complete conversion to the benzylic bromide **24**, the mixture was allowed to react with 2.5 eq. of the enol silyl ether **30** in the presence of TASF. The pterocarpan-benzofuranone dimer **31** was isolated after work-up and preparative TLC in 28% yield, a slight improvement on the 22% yield reported for the analogous dimeric precursor to Daljanelin C (**14**).[51]

2.2.3.10. Introduction of the C_6 fragment by Grignard reaction with PhMgBr

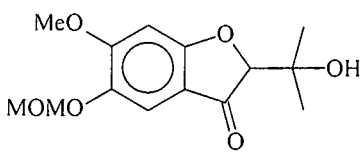
The last step in the construction of the $C_6.C_3.C_6$ backbone of the neoflavonoid constituent unit was reaction of the benzofuranone carbonyl functionality with PhMgBr (see Scheme 5).[51] As the low-yielding model coupling reaction (Scheme 31) had only furnished 11 mg of the model dimer **92**, it was decided to test the proposed Grignard reaction on the parent benzofuranone **29**, of which a slightly larger quantity was still available:



29 **93**

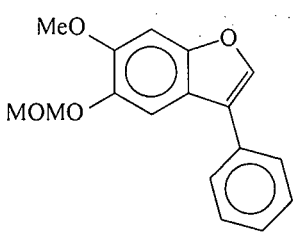
Scheme 32

Interestingly, the main product isolated from this reaction was tentatively identified as the acetone aldol adduct **94**:



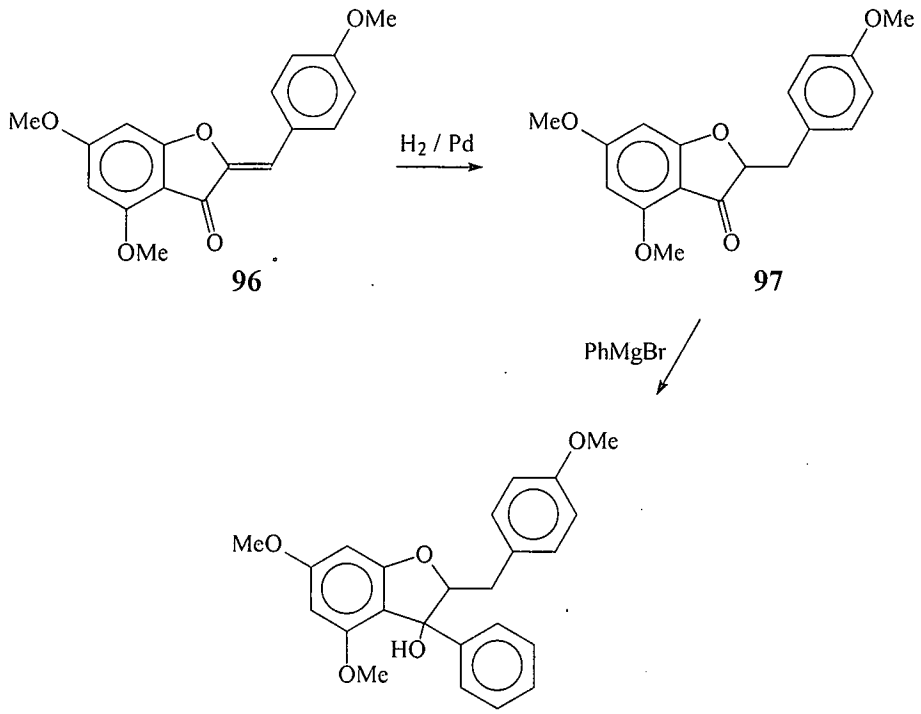
94

Its formation remains unclear, but can possibly be ascribed to the use of acetone in the TLC solvent system which was used. The reaction yielded no benzylic alcohol **93**, but instead, 4% of the 2,3-dehydrated product **95**:



95

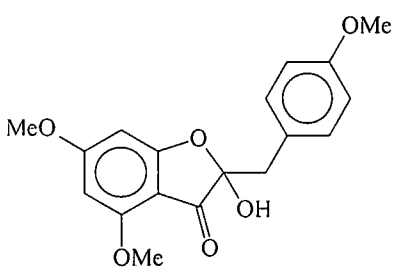
A further test substrate was prepared by catalytic hydrogenation of the aurone **96**, after which the resulting dihydroaurone **97** was subjected to reaction with PhMgBr:



96 **97** **98**

Scheme 33

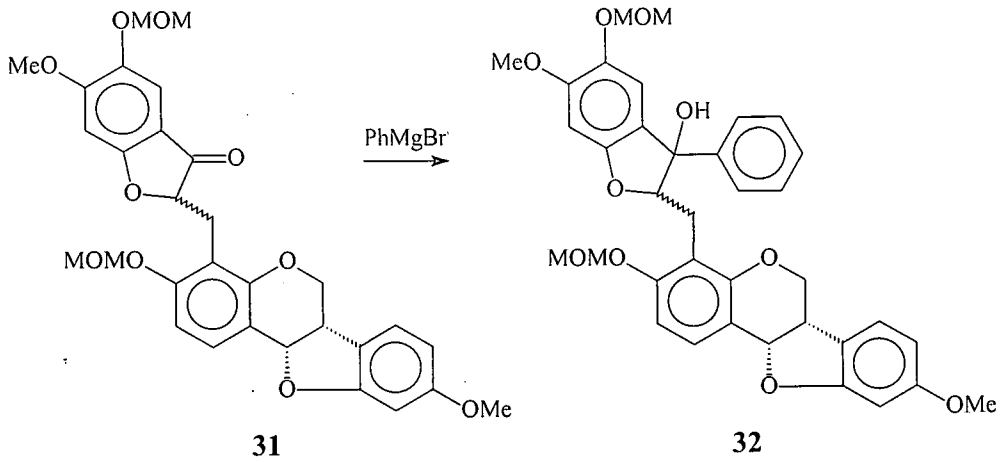
In this case, 67% of the Grignard adduct **98** was isolated, but no formation of a dehydrated product could be detected. Furthermore, it is interesting to note that if the catalytic hydrogenation of aurone **96** was performed in EtOH, some hydration of the double bond took place: in one instance, maesopsin **99** was isolated in 13% yield:



99

This side reaction could be prevented, however, by employing commercially available absolute EtOH as solvent for the hydrogenation.

The pterocarpan-benzofuranone dimer **31** was subsequently reacted with PhMgBr, giving the C_6-adduct **32** in 22% yield:

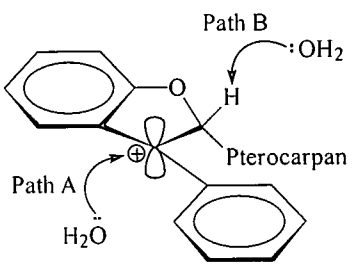


31 **32**

Scheme 34

(Note: the starting material **31** was recovered in 15% yield.)

Although Ferreira[51] reported that the analogous reaction of the precursor to Daljanelin C (**14**) gave a mixture of the dehydrated product (13%) and the carbinol (47%), no dehydrated product could be isolated in this instance. This result is in accordance with the author's hypothesis that the conspicuous stability of the carbinol (**32**, in this instance) [...] may, presumably, be attributed to the high degree of stabilization of the double-benzylic carbocation (**100**, in this instance):



100

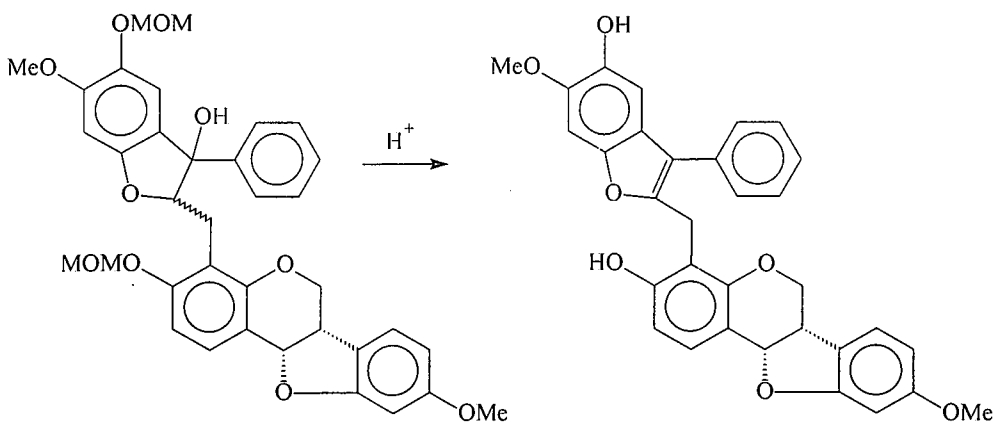
Scheme 35

The distribution of products is thus the result of a kinetic effect, [...] the carbocation (**100**, in this case) being formed rapidly from the carbinol (**32**, in this instance) in a reversible step (path A) due to a small activation energy term. Subsequent formation of the thermodynamically favoured product [of elimination] then proceeds slowly under the relatively mild acidic conditions [...].

The slow formation of the eliminated product is of little import for the overall synthesis of Daljanelin B (**13**), however, as the following step (see Section 2.2.3.11.) would lead to dehydration of the newly formed alcohol **32** in any event.

2.2.3.11. Phenolic deprotection and concomitant dehydration

It had been demonstrated during the synthesis of Daljanelin C (**14**)[51] that reflux in 0.1M HCl in MeOH (1 : 1 v/v) did not affect the heterocyclic ether linkages of the medicarpin framework adversely, but was nevertheless effective in achieving phenolic demethoxymethylation and concomitant dehydration. Thus, the protocol was applied directly to the intermediate **32**, and the deprotected, dehydrated product **13** was isolated after preparative TLC in 24% yield:



32 **13**

Scheme 36

Comparison of ^{1}H NMR and CD data showed that synthetic Daljanelin B (**13**) was chemically identical to the natural product, and that the stereochemistry of the pterocarpan skeleton had been retained during the synthesis.

2.2.4. Concluding remarks: overall yield

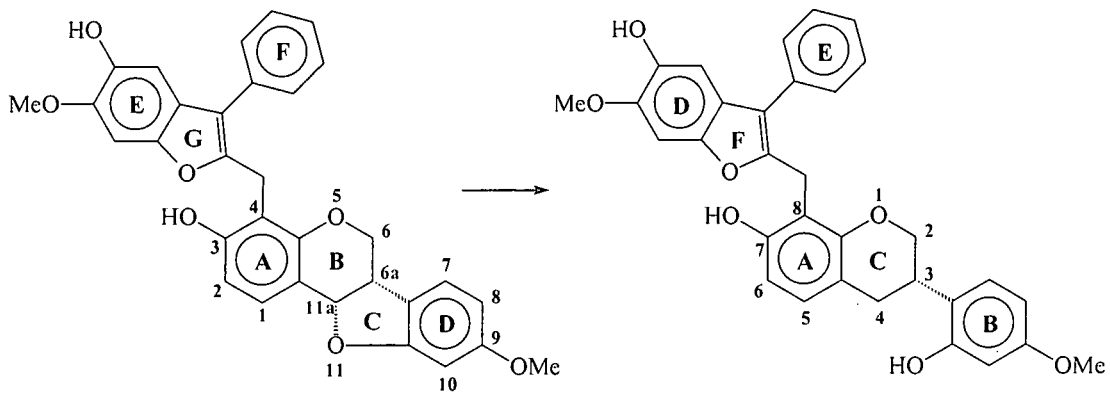
The following discussion serves to alert the reader to the greatest drawback of any long synthetic procedure, *viz.* low overall yields:

Daljanelin B (**13**) has been synthesized for the first time in 11 linear steps (see Schemes 3 and 5). In total, *ca.* 2.5 g (*ca.* 9.25 mmol) of the starting material, (+)-(6a*S*, 11a*S*)-medicarpin (**1**) was used, and 1 mg (1.91 μmol)of the final product was isolated. This gives an overall yield of 0.02% and an average yield of 46% per step. It should be borne in mind, however, that as early as the second step, *i.e.* thermal allylic rearrangement, *ca.* 60% of the material had already been lost. Furthermore, if all of the *actual* transformations performed on the starting material are taken into account, the synthesis comprises a total of 13 steps with an effective yield of 52% each. Due consideration should also be given to the fact that some material is inevitably lost in unsuccessful test reactions.

The need for a shorter synthesis becomes quite evident, and some suggestions to this end are made in Section 2.5.

2.3. Synthesis of Daljanelin D (15)

Daljanelin D (**15**) may be regarded as the C-11a – O-11 reduced form of Daljanelin B (**13**), and it was envisaged that benzylic ether cleavage of the C-ring in Daljanelin B should give direct access to Daljanelin D:



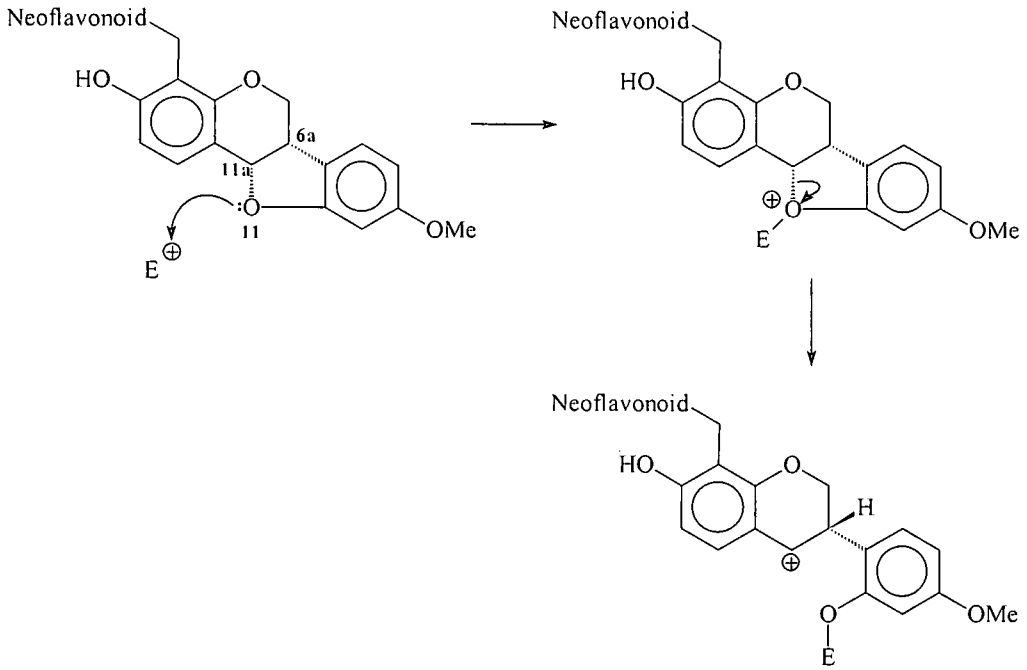
13 **15**

Scheme 37: Reduction of the O-11 – C-11a bond

In selecting a suitable reaction protocol, the following constraints had to be taken into consideration:

1) Only 1 mg (1.91 μmol) of Daljanelin B (**13**) was available. Thus, the reaction should be as clean and quantitative as possible;
2) In order to obtain Daljanelin D (**15**) exclusively in the 3*S*-configuration, cleavage of the C-11a → O-11 ether linkage in Daljanelin B (**13**) should not cause epimerization or racemization at the adjacent C-6a.

Brønsted or Lewis acids (designated as electrophiles, E^+, in Scheme 38) were precluded from the selection of reagents, as they were liable to form a carbocation at the equivalent of C-11a:

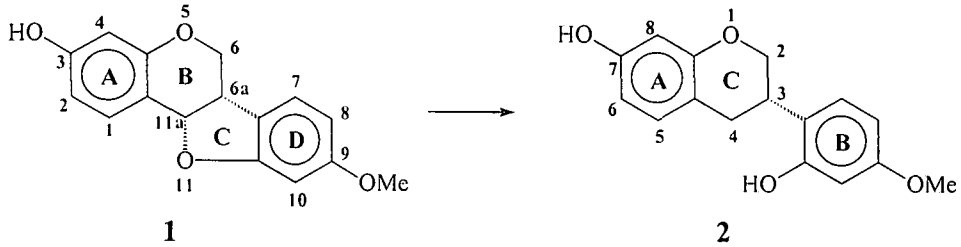


Scheme 38

This carbocation could lead to the following undesired effects:

1) Racemization at the equivalent of C-6a *via* β-elimination and reprotonation, or even
2) Oligomerization *via* nucleophilic attack of one of the activated aromatic functionalities of a second dimer on the carbocation.

The common method used for benzylic ether cleavage, *i.e.* catalytic hydrogenolysis, would not present any of the above problems, but might lead to saturation of the electron rich neoflavonoid heterocyclic ring. A further risk was the loss of material due to partially irreversible adsorption on the catalyst. Catalytic hydrogenation was thus first tested on the pterocarpan constituent unit, (+)-(6a*S*, 11a*S*)-medicarpin (**1**), using the following catalysts: Raney-Ni, Pd-$BaSO_4$, Pd-$CaCO_3$, Pd-alumina and Pd-C. Pd-$CaCO_3$ would be an ideal catalyst for this hydrogenation, since this carrier ensures a neutral reaction medium.[76] The reactions were monitored with TLC against a reference of the anticipated product, (+)-(3*S*)-vestitol (**2**):



1 2

Scheme 39

Remarkably, no significant degree of hydrogenolysis, *i.e.* deannulation, could be observed for any of the catalysts.

A previous research project in these laboratories focussed on the reductive cleavage of interflavanyl C-C and C-O bonds, using $Na(CN)BH_3$[77] in 2,2,2-trifluoroacetic acid (TFA).[78,79] It was envisaged that cleavage of the pterocarpan C-ring with retention of optical activity could be attained if the borohydride was kept in excess and the TFA was added very slowly and dilutely. Any acid-generated carbocation at the equivalent of C-11a (Scheme 38) would immediately be quenched with the equivalent of a hydride ion, before β-elimination could take place.

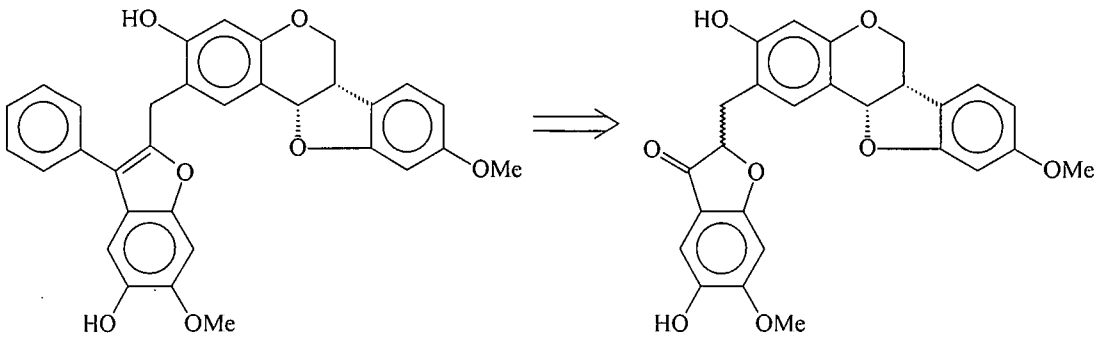
The borohydride reagent, recrystallized according to the procedure described by Wade *et al.*,[80] was thus tested on (+)-(6a*S*, 11a*S*)-medicarpin (**1**) (Scheme 39). After optimization of the conditions, (+)-(3*S*)-vestitol (**2**) was isolated in 85% yield. Mosher esterification of both phenolic centres in the product indicated that no detectable racemization had taken place during the cleavage, as the ^1H NMR spectrum of the Mosher ester **101** displayed only one set of signals. Although a remote possibility of chemical equivalence of diastereomers exists, this spectrum is accepted as conclusive proof of retention of chirality.

Synthetic Daljanelin B (**13**) was subsequently subjected to the same reagents (see Scheme 37). The purified product, isolated in 70% yield, was identical by ^1H NMR and CD to natural Daljanelin D, **15**.

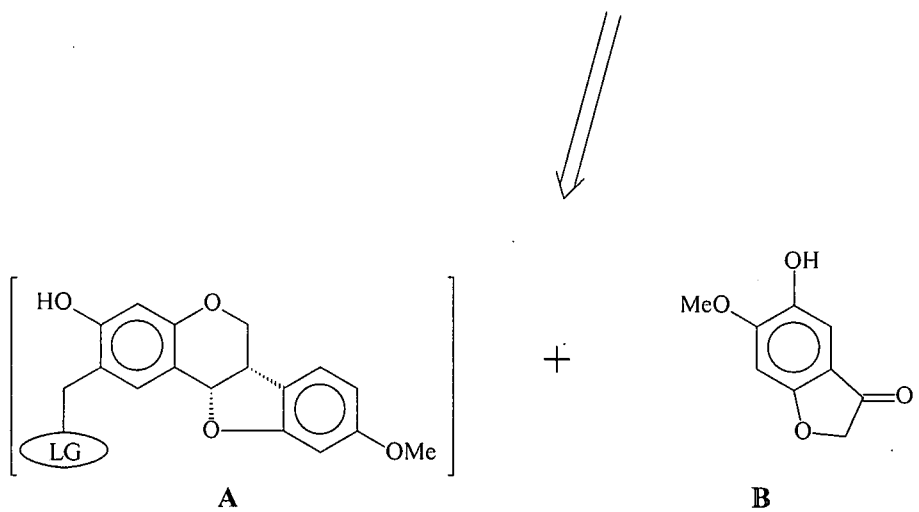
2.4. Synthesis of Daljanelin A (12)

2.4.1 Retrosynthesis

The same retrosynthetic principles that were used for Dajanelins B (**13**) (Scheme 2) and C (**14**),[51] can be applied to Daljanelin A (**12**) as follows:



Daljanelin A



A **B**

LG = leaving group

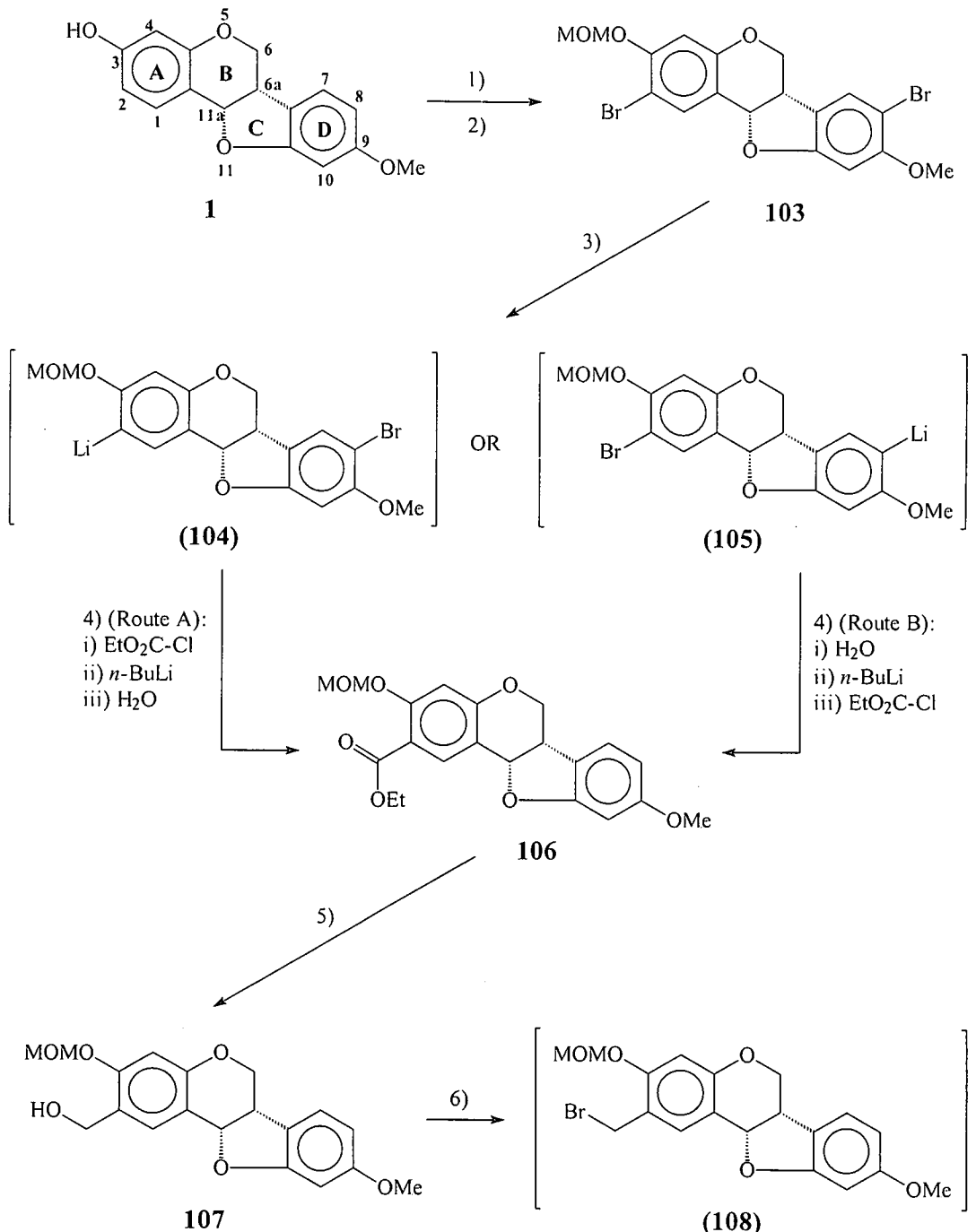
Scheme 40: Retrosynthesis of Daljanelin A (12)

2.4.2 Proposed synthesis

It is clear that the cornerstone in a synthesis of Daljanelin A **12** is the introduction of an electrophilic C_1 coupling site at C-2 of (+)-(6a*S*, 11a*S*)-medicarpin (**1**). Once this has been achieved, the rest of the synthesis may be performed analogous to those of Daljanelins B **13** and C **14** (Schemes 4 and 5).

(+)-(6a*S*, 11a*S*)-Medicarpin (**1**) has been formylated at C-2 in these laboratories (Scheme 46, Section 2.5.), but the reaction was low-yielding. Efforts to improve the yield by opening the C-ring first (Scheme 39, Section 2.3.) *i.e.* removing the deactivating effect of the 11a-oxygen function, then formylating the A-ring of the resulting vestitol **2** and finally recyclizing, were unsuccessful. It was thus envisaged to introduce the required electrophilic C_1 fragment to C-2 *via* the following novel protocol (steps 1 and 2 have been combined in Scheme 41):

1) 2,8-dibromination of (+)-(6a*S*, 11a*S*)-medicarpin (**1**) to give **102**;
2) Protection of **102** as the 3-*O*-methoxymethyl ether **103**;
3) Selective lithiation of **103** *via* metal-halogen exchange, *either* at C-2 *or* at C-8, giving one of the respective aryllithium intermediates **104** or **105**;
4) Conversion of **104** or **105** to the ester **106** by the applicable route (respectively A or B);
5) Selective reduction of **106** to obtain the benzyl alcohol **107**;
6) *In situ* bromination of **107** *via* the Collington-Meyers protocol[73] to give the benzyl bromide **108**.



Scheme 41

Proposed reagents and conditions:

1) Br_2/dioxane, Py.HBr.Br_2/MeOH[81,82] or HBr/DMSO[83]

2) NaH/THF/$ClCH_2OCH_3$

3) 1 eq. *n*-BuLi/THF, possibly solvated with TMEDA

5) $LiAlH_4$[51]

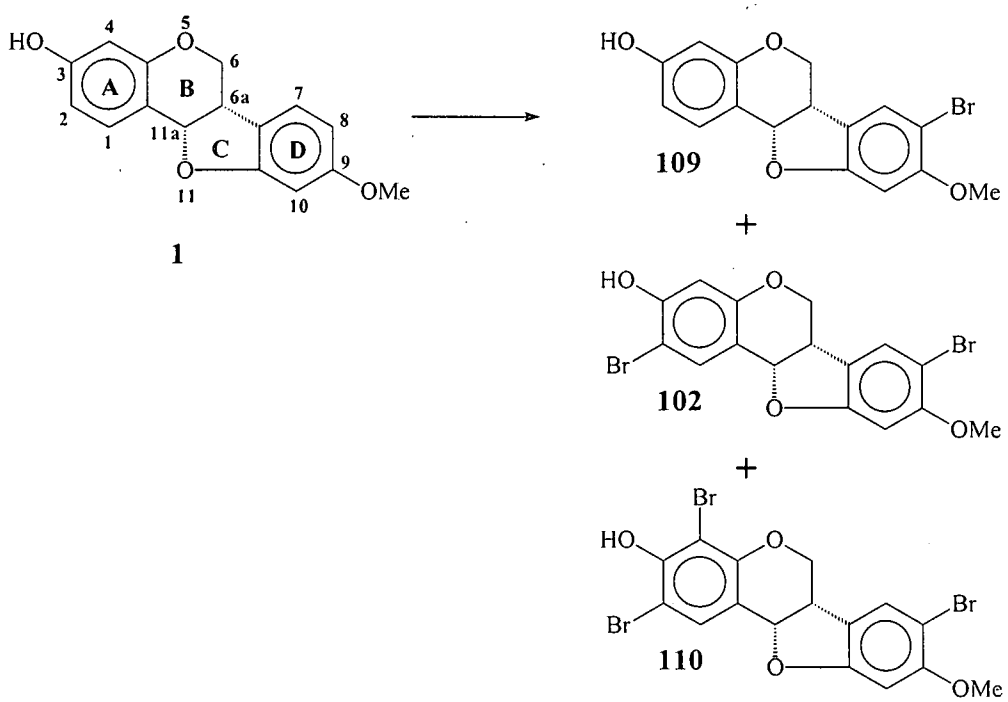
6) $(CH_3SO_2)_2O$/LiBr/2,6-lutidine/THF[73]

The key to this synthetic sequence is twofold:

1) When subjected to electrophilic aromatic bromination, (+)-(6a*S*, 11a*S*)-medicarpin (**1**) displays remarkable selectivity in that C-8 is brominated first, then C-2, and finally C-4. This phenomenon was used in the synthesis of Daljanelin C (**14**),[51] by terminating bromination after the first step and lithiating at C-8. For the synthesis of Daljanelin A (**12**), it was envisaged to terminate bromination of **1** only after the second step.
2) If a method could be found to lithiate the protected (6a*S*, 11a*S*)-2,8-dibromomedicarpin **103** selectively (either at C-2 or at C-8, but not both), then the precursor **106** could be synthesized as shown in Scheme 41: should lithiation of the dibromo compound **103** take place mainly at C-2, Route A would be followed, whereas Route B made provision for lithiation of **103** at C-8.

2.4.3 Eventual synthesis of Daljanelin A (12)

2.4.3.1 Bromination of (+)-(6a*S*, 11a*S*)-medicarpin (1)



Scheme 42

The conditions used to brominate (+)-(6a*S*, 11a*S*)-medicarpin (**1**) in the synthesis of Daljanelin C (**14**),[51] *viz.* NBS/methyl acetate, were not used in this synthesis, as they lead mainly to the formation of the monobrominated product **109**. Three alternative reagents, *viz.* Br_2/dioxane, Py.HBr.Br_2/MeOH[81,82] and HBr/DMSO,[83] were thus tested on (+)-(6a*S*, 11a*S*)-medicarpin (**1**). The results, obtained after preparative TLC of small-scale reactions, are shown below:

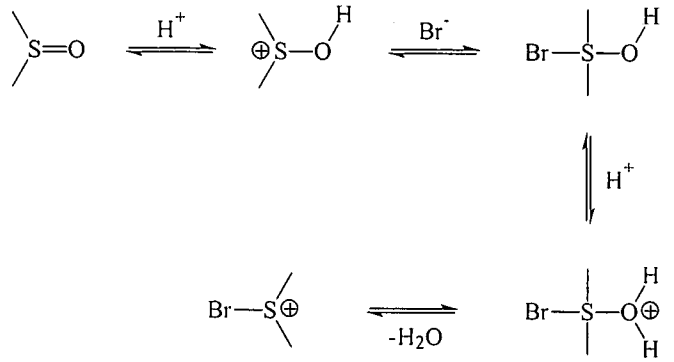
Table 5

Brominating agent	Yields (%) of brominated products		
	109	**102**	**110**
Br_2/dioxane	0†	0†	0†
Py.HBr.Br_2/MeOH	0	38	12
HBr/DMSO	39	16	0

† Decomposition

Br_2/dioxane caused severe decomposition of (+)-(6a*S*, 11a*S*)-medicarpin (**1**) and was not utilized further. Significant loss of material (*ca.* 50%) was also observed when using the other two methods, but they gave moderate yields of the desired 2,8-dibromo derivative **102**. Although HBr/DMSO gave a lower yield of **102** than Py.HBr.Br_2, the former method had the advantage that over-bromination (*i.e.* formation of **110**) was easier to curb, and some monobrominated compound (**109**) could be recovered for subsequent use. In larger, preparative iterations of the procedures, the excess of bromine in the reaction mixture was quenched with $Na_2S_2O_3$, and the unpurified product was always methoxymethylated directly (Section 2.4.3.2.), in order to avoid further loss of phenolic material during chromatography.

HBr/DMSO is a milder, and thus more selective reagent for aromatic bromination than solutions of molecular bromine, and it eliminates the need to handle the toxic and corrosive bromine.[83] The active species, bromodimethylsulfonium bromide, is formed *in situ* as follows:[84]



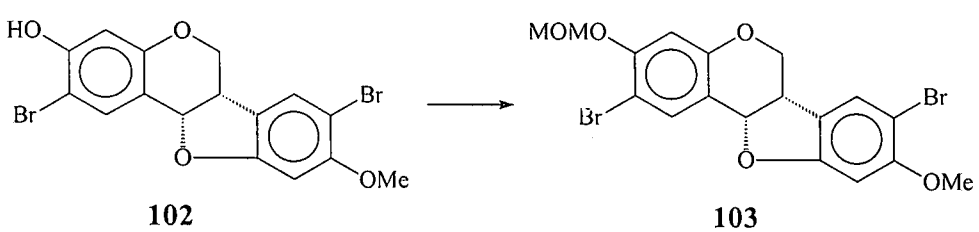
Scheme 43

The brominating agents above supply activated, electrophilic bromine ("Br^+") to the substrate. This active species, and even the parent species, *i.e.* the polarizable bromine molecule, can be regarded as Lewis acids. Furthermore, a stoichiometric amount of HBr (*i.e.* a Brønsted acid) is always formed during bromination. The sensitivity of the medicarpin C-11a→ O-11 ether linkage to such conditions (*cf.* Scheme 38) explains the complete or partial decomposition of starting material and the relatively low yields of brominated products.

Although TLC of reaction aliquots (spotted *vs.* the three possible products, **109**, **102** and **110**) clearly showed that bromination takes place first at C-8, then at C-2 and finally at C-4, it was found that even under carefully controlled stoichiometry, at least two of the three products occurred in equilibrium. The reactions were terminated as soon as the dibromo compound **102** appeared, by TLC, to be the major product.

2.4.3.2 3-*O*-Methoxymethylation

Protection of the phenol on a small quantity of pure (6a*S*, 11a*S*)-2,8-dibromomedicarpin **102** was achieved in 79% yield using standard reagents and conditions, and presented no difficulties.



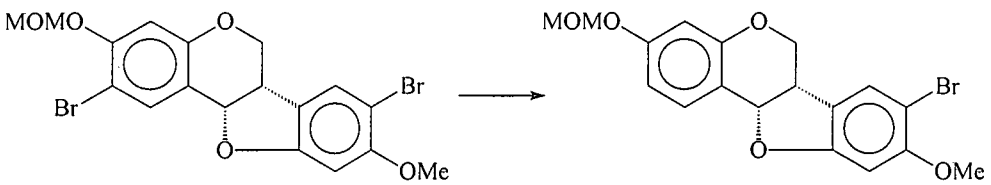
102 **103**

Scheme 44

As mentioned above, when working on a preparative scale, the crude mixture of mono-, di- and tribrominated compounds (respectively **109**, **102** and **110**) was methoxymethylated without prior purification, and the target 2,8-dibromomedicarpin was isolated in its 3-*O*-methoxymethylated form **103**, typically in a combined yield of 30%.

2.4.3.3 Lithium-bromine exchange reactions

A small-scale test reaction was performed on (6a*S*, 11a*S*)-2,8-dibromo-3-*O*-methoxymethylmedicarpin **103**, using 1.1 eq. of *n*-BuLi and subsequent protic quenching, leading to the formation of (6a*S*, 11a*S*)-8-bromo-3-*O*-methoxymethylmedicarpin (**111**) in 20% yield:



103 **111**

Scheme 45

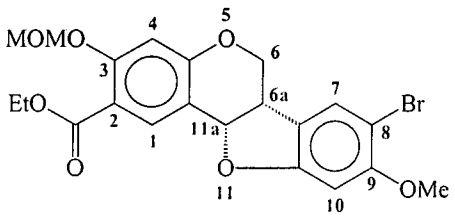
Note: the structure of **111** was assigned with ^{1}H NMR NOESY.

The fully debrominated analogue, *i.e.* (6a*S*, 11a*S*)-3-*O*-methoxymethylmedicarpin **112**, was obtained in 13% yield, while 17% of the starting material was recovered. No 2-bromo isomer could be isolated.

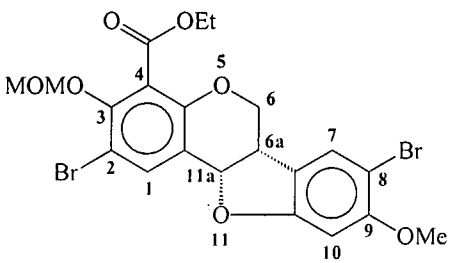
This result revealed that although lithiation of **103** can occur both at C-2 and C-8, it does so regioselectively at C-2. The relative order of debromination thus mirrored that of bromination. This knowledge was applied to the envisaged synthesis of Daljanelin A (**12**) by selecting the ensuing sequence according to Route A (Scheme 41): **103** would first have to be lithiated at C-2 and the aryllithium **104** substituted with ethyl chloroformate, and only then would C-8 be debrominated.

2.4.3.4 C-2-Carboxylation and C-8-debromination

In a preliminary experiment, (6a*S*, 11a*S*)-2,8-dibromo-3-*O*-methoxymethylmedicarpin **103** was thus allowed to react for 30 min. with 1.1 eq. of *n*-BuLi (solvated with 2.5 eq. of TMEDA) and 6 eq. of ethyl chloroformate. Other than recovered starting material (42%), the only product that could be isolated was, interestingly, not the expected 2-ethoxycarbonyl-8-bromo derivative **113**, but rather compound **114**:



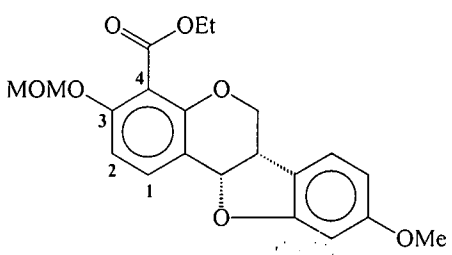
113



114

114, isolated in 14% yield, was characterized as follows:

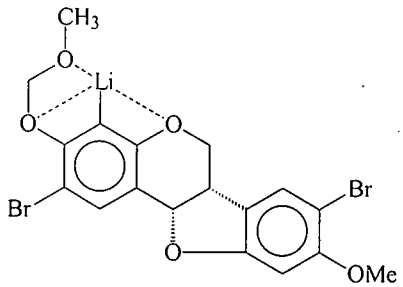
1) NOESY experiments demonstrated that there were aromatic protons present on C-1, C-7 and C-10, but not on C-4;
2) After full debromination (*i.e.* subjection of **114** to an excess of *n*-BuLi and protic quenching), the following compound was obtained:



115

The formation of **114** (confirmed by repetition) is highly unusual, because it has been established that exposure of the parent compound **103** to *n*-BuLi preferentially generates the C-2-lithiated intermediate **104** (Schemes 41 and 45); yet **114** can only be formed *via* aromatic deprotonation at C-4 *at the expense* of lithiation at C-2. Lithium-halogen exchange with *n*-BuLi is usually a fast and facile reaction,[85] and can even compete with the protonation of the organolithium by H_2O, T_2O or an intramolecular carboxylic acid.[86,87] It is thus remarkable that instead of lithium-bromine exchange at C-2, deprotonation of the weakly acidic aromatic ring takes place. The observed reaction can be rationalized in two ways:

1) C-4-lithiation may be aided by double or triple complexation of the resulting aryllithium **116**, *i.e.* a resorcylic "directed *ortho* metalation" (D*o*M):[88a,b]



116

or

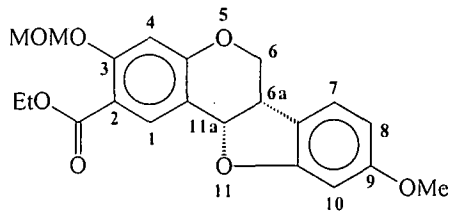
2) The C-2-lithiated intermediate **104** is evidently a good base, capable of deprotonating water, hence the formation of the 2-*de*bromo compound **111**; but in spite of its basicity, **104** seems to be a weak nucleophile, incapable of nucleophilic attack on ethyl chloroformate, hence no formation of the 2-ethoxycarbonyl compound **113**.

Eventually however, it was possible to isolate the desired 8-bromo-2-ethoxycarbonylmedicarpin **113** by adding the ethyl chloroformate much sooner (*ca.* 3 min.) after the *n*-BuLi and TMEDA. Although **113** was isolated in 14% yield, it was still accompanied by 6% of **114**. If the ethyl chloroformate was added even sooner, it was found that the parent dibromide **103** did not have sufficient time to react with the *n*-BuLi, leading mainly to the recovery of starting material.

113 was characterized as follows:

1) ^{1}H NMR demonstrated that there were aromatic protons present on C-1, C-4, C-7 and C-10, *i.e.* two aromatic AX systems;
2) The ethoxycarbonyl moiety could not be bonded to C-8, as it had been demonstrated (Section 2.4.3.3.) that monolithiation of the parent dibromide **103** takes place preferentially at C-2 and not at C-8;

3) After full debromination (*i.e.* subjection of **113** to an excess of *n*-BuLi and protic quenching), the following compound was obtained:



106

The ^{1}H NMR spectrum of **106** showed characteristic deshielding of H-1 by the adjacent benzylic carbonyl moiety, and that the D-ring had been converted from an AX system into an ABX system. Furthermore, NOESY experiments revealed a correlation between H-1 (singlet) and H-11a, thus eliminating any possibility that the ethoxycarbonyl group could be bonded to C-8.

When performing the C-8-debromination of **113**, to give **106**, care had to be taken to prevent nucleophilic attack of the *n*-BuLi on the benzoate ester. If 3 eq. or more of *n*-BuLi was used, and the reaction left for 15 – 30 min. at 0°C before protic quenching, conversion of the starting material **113** was good, but inevitably *n*-BuLi had also attacked the ethoxycarbonyl group. On the other hand, 1 – 1.5 eq. of *n*-BuLi did not lead to a satisfactory conversion of the starting material. The best results were obtained on a small-scale test reaction, using 2.2 eq. of *n*-BuLi (solvated with 2.5 eq. of TMEDA) at –78°C, warming to 0°C and immediate protic quenching. This procedure led to the isolation of the desired 2-ethoxycarbonylmedicarpin **106** in 34% yield and the recovery of starting material **113** in 29% yield.

2.4.4 Concluding remarks

The aromatic ethoxycarbonyl group is reducible with $LiAlH_4$ to the corresponding benzylic alcohol.[51] Thus, it is a direct precursor to the electrophilic C_1 fragment required at C-2 of (+)-(6a*S*, 11a*S*)-medicarpin (**1**) (Schemes 40 and 41). The feasibility of the reactions following the introduction of such a C_1 fragment has been sufficiently demonstrated during the syntheses of Daljanelins B (**13**, see Section 2.2.) and C (**14**).[51] The greatest synthetic challenge in the synthesis of Daljanelin A (**12**) has thus ended, as the compound should be readily accessible *via* ester reduction, *in situ* bromination, nucleophilic coupling with the

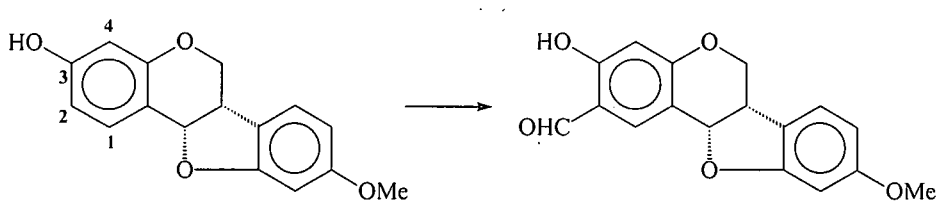
benzofuranone enol TBDMS ether **30**, Grignard reaction with PhMgBr and final dehydration / deprotection.

The CD curve of the 2-ethoxycarbonylmedicarpin **106** exhibits a similar Cotton effect as that of the parent compound, (+)-(6a*S*, 11a*S*)-medicarpin (**1**), albeit with somewhat different amplitudes at slightly altered wavelengths. It can thus be assumed that the synthetic steps discussed in this section have left the stereocentres at C-6a and C-11a intact.

2.5. Future perspectives

Direct introduction of the requisite C_1 fragment at the correct site on the pterocarpan A-ring would simplify the total synthesis of Daljanelins A (**12**), B (**13**) and D (**15**) considerably. Most of the commonly used methods for aromatic formylation, *e.g.* the Reimer-Tiemann, Gattermann and Vilsmeyer-Haack protocols, are immediately precluded by the known sensitivity of the heterocyclic ether linkages in the pterocarpan skeleton to Brønsted and Lewis acids (Section 2.1.2.).

Some preliminary experiments have, however, been performed in these laboratories with the formilating agent tris(phenylthio)methane, $(PhS)_3CH$, and the soft, thiophilic Lewis acid dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF).[89,90] As expected from normal A-ring nucleophilicity (Section 2.1.2.), this combination of reagents led to the C-2-formylation of (+)-(6a*S*, 11a*S*)-medicarpin (**1**) in 36% yield:

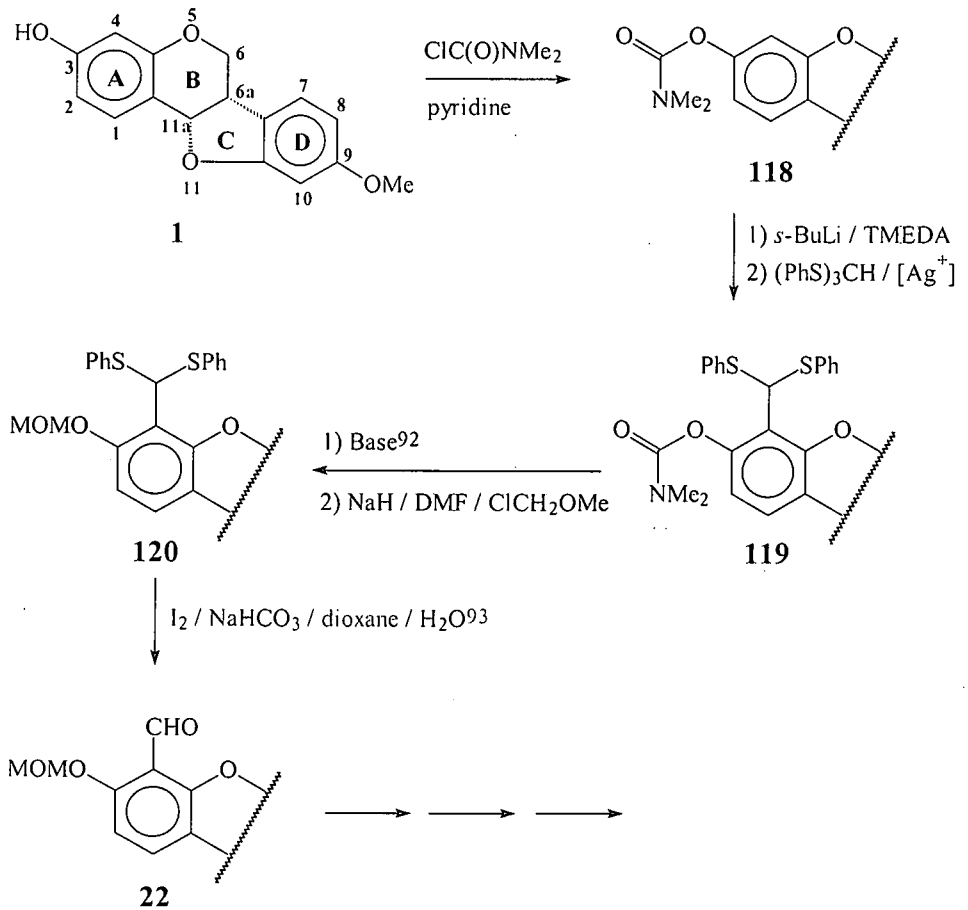


1 **117**

Scheme 46

DMTSF is a highly hygroscopic reagent, and often it already contains some moisture as commercially supplied. Its advantage over other Lewis acids is, however, that it is relatively soft, and because of sulphur's tendency to catenate,[91] it does not coordinate strongly with the benzylic oxygen of medicarpin. Alternative thiophilic Lewis acids for this application might be $AgBF_4$ and AgOTf, although it remains to be shown that they do not attack the heterocyclic ether linkage(s) of the pterocarpan (*cf.* Scheme 38).

In order to achieve C-4-formylation, *i.e.* to synthesize the precursor **22** to Daljanelins B (**13**) and D (**15**), this reaction could possibly be adapted in a variation of the DoM (directed *ortho* metalation) protocol[88a,b] as follows:



Scheme 47

(Note: $[Ag^+]$ denotes a thiophilic Lewis acid, *e.g.* $AgBF_4$, AgOTf *etc.*)

3. EXPERIMENTAL

3.1. Chromatographic techniques

Qualitative thin layer chromatography (TLC) was performed on pre-coated Merck plastic or aluminium sheets (silica gel PF_{254}, 0.2 mm) divided into strips of *ca.* 3 x 6 cm.

Preparative TLC (PLC)was conducted on glass plates (20 x 20 cm) coated with Kieselgel PF_{254} (1.0 mm; 100g Kieselgel stirred in 230 ml of distilled water per 5 plates). The plates were air dried and used without prior activation. Micro-scale separations (<5mg per plate) were performed on pre-coated Merck aluminium sheets (silica gel PF_{254}, 0.2 mm) or glass plates (silica gel 60 PF_{254}, 0.25 mm). After development in the appropriate eluent, the plates were dried in a fast stream of air and the bands distinguished under UV light (254 nm). The bands were eluted with acetone and the solvent removed under reduced pressure.

Flash column chromatography (FCC) was performed according to Still *et al.*[94] by charging a glass column of the appropriate diameter with Merck silica gel 60 (230 – 400 mesh) to a height of 15 – 20 cm (*ca.* 100g for every 1g of crude product). The crude product was either adsorbed on a minimum of the same stationary phase and carefully added to the top of the column, or adsorbed directly on the column. The purified product was recovered by elution under N_2 pressure (*ca.* 40 kPa, but not faster than *ca.* 5 cm/min.) and collection in *ca.* 15 cm^3 fractions.

3.2. Spraying agents

TLC plates were sprayed lightly with a 2% (v/v) solution of **formaldehyde** (40%) in concentrated sulphuric acid and subsequently heated with a Bunsen burner to achieve optimal colour development.[95]

All chromatograms involving divalent sulphur derivatives were sprayed with a 0.02 M **$PdCl_2$** solution in 6% HCl.

3.3. Purification and dessication of reagents and solvents

LiBr, K_2CO_3 and molecular sieves were oven-dried for 24 h. at 200°C and immediately cooled in a vacuum dessicator prior to use.

$ZnCl_2$ was fused immediately before use.

Acetone was left over dry K_2CO_3 for 24 h. The K_2CO_3 was filtered off and the solvent subsequently distilled over 3 Å molecular sieves and stored under N_2.

Benzene, diethyl ether, THF, DMF, NEt_3 and 2,6-lutidine were refluxed over Na wire / benzophenone under N_2 until a dark blue or purple colour persisted, followed by fresh distillation under N_2 prior to use.

Ethyl chloroformate was distilled over $CaSO_4$ ("Drierite") under N_2, and TMEDA was similarly distilled over CaH_2.

CH_3CN, DCM and DMF were refluxed over CaH_2 under N_2 for 12 h., followed by fresh distillation under N_2 prior to use.

Allyl bromide, chloromethyl methyl ether, HMPA and N,N-dimethylaniline were distilled (the last two under vacuum) and stored under N_2.

Pyridine was stored over NaOH pellets.

3.4. Standardization of commercial reagent solutions

3.4.1. *n*-Butyllithium

A solution of *n*-BuLi in hexanes was added *via* a syringe under N_2 to a stirred solution of 1,10-phenanthroline (*ca.* 1 mg) in anhydrous THF (*ca.* 1 cm^3) until persistence of a dark red colour. *s*-BuOH was added dropwise from a microsyringe until the first permanent colour change (dark red → yellow) was observed. *n*-BuLi (exactly 100 µl) was then added and the mixture subsequently titrated with *s*-BuOH. The double burette titration was repeated until consistent titre figures had been obtained (reaction stoichiometry: 1 mol *s*-BuOH for 1 mol *n*-BuLi).

3.4.2. Phenylmagnesium bromide

A solution of this reagent in THF was standardized by the same procedure as *n*-BuLi (see above).

3.5. Spectrometric and spectroscopic methods

3.5.1. Nuclear magnetic resonance spectrometry

^{1}H NMR spectra were recorded on a Bruker AM-300 FT spectrometer at 296K (23°C) with $CDCl_3$, $(CD_3)_2CO$ or C_6D_6 as solvent and internal standard. Chemical shifts are reported in ppm on the δ scale, and coupling constants were measured in Hz.

3.5.2. Circular dichroism

CD spectra were recorded on a Jasco J-710 spectropolarimeter. Samples were dissolved in spectrophotometric grade MeOH.

3.6. Melting points

Melting points were determined using a Reichert Thermopan microscope with a Koffler hotstage, and are uncorrected.

3.7. General chemical methods

3.7.1. Allylation of phenols

A solution of the phenolic compound (1 eq.) and allyl bromide (*ca.* 10 eq., unless specified otherwise) in anhydrous acetone (*ca.* 10 eq. v/m) was refluxed over anhydrous K_2CO_3 (2 – 5 eq. m/m) under N_2 until TLC indicated complete conversion of the starting material. The K_2CO_3 was filtered off, the solid residues washed with anhydrous acetone, the filtrates combined and the acetone removed under reduced pressure. If required, the product was purified by FCC or PLC.

3.7.2. Thermal rearrangement of aryl allyl ethers[53]

A solution of the aryl allyl ether in N,N-dimethylaniline (*ca.* 10 eq. v/m) was refluxed under Ar until TLC indicated complete or near-complete conversion of the starting material. A copious amount of ice was added to the cooled reaction mixture, and 3 M HCl (*ca.* 10 volumes) was added slowly. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with ice-cold 3 M HCl, sat. aq. $NaHCO_3$ and brine. The extract was dried over $MgSO_4$ and the solvent removed under reduced pressure. FCC or PLC gave the purified product(s).

3.7.3. Methoxymethylation of phenols[96]

The phenolic compound (1.0 eq.) was dissolved in anhydrous THF (except if stated to the contrary) and added under N_2 to an ice-cooled, stirred suspension of NaH (1.5 eq.) in the same anhydrous solvent. The mixture was stirred for 10 min., chloromethyl methyl ether (1.2 eq.) added and stirring continued on ice until TLC indicated complete conversion of the starting material. Crushed ice was added slowly to the mixture and the aqueous phase extracted with EtOAc. The organic extracts were combined, washed with H_2O , dried ($MgSO_4$) and the solvent removed under reduced pressure. The pure methoxymethyl ether was obtained after FCC or PLC.

3.7.4. Acetylation of phenols[97]

The dry phenolic material was dissolved in a minimal volume of pyridine, *ca.* twice the volume of Ac_2O added, the reaction vessel sealed and the mixture left standing at *ca.* 30°C for *ca.* 12 h. The reaction was quenched by addition of ice, and the excess of pyridine was washed out with H_2O.

3.7.5. (3',5'-Dinitro)benzoylation of phenols

The dry phenolic material was dissolved in a minimal volume of pyridine, 3,5-dinitrobenzoyl chloride (1.5 eq.) added, and the mixture left standing at *ca.* 30°C for *ca.* 12 h. The reaction was quenched by addition of ice and the crude product was taken up in EtOAc. The organic phase was washed successively with H_2O, sat. aq. $CuSO_4$ (twice), H_2O, sat. aq. $NaHCO_3$ and

H_2O, dried over $MgSO_4$, and the solvent was removed under reduced pressure. PLC or recrystallization gave the pure dinitrobenzoate.

3.7.6. Hydrolysis of phenyl acetates and phenyl 3,5-dinitrobenzoates

The phenyl ester was dissolved in MeOH (*ca.* 10 eq. v/m) and a 2% solution of KOH in MeOH (*ca.* 10 eq. v/m) was added slowly. The mixture was stirred at r.t. (or at gentle reflux, if necessary) until TLC indicated no further conversion of starting material. The cooled mixture was poured into an excess of ice water, and the aqueous phase was acidified to *p*H 5 and extracted with EtOAc. The combined organic extracts were washed with sat. aq. $NaHCO_3$ and H_2O, dried over $MgSO_4$ and the solvent removed under reduced pressure. If required, the product was purified by FCC or PLC.

3.7.7. Pd(II)-catalyzed isomerization of allylarenes[61]

$PdCl_2(PhCN)_2$ was prepared[68] as follows: $PdCl_2$ (500 mg; 2.82 mmol) was heated in PhCN (*ca.* 8 cm^3) under Ar to 100°C until dissolution, the mixture was cooled and any solids filtered. A second crop of product was precipitated from the mother liquor with petroleum ether (40-60) and filtered. The combined precipitates were washed with petroleum ether (40-60), dried in a vacuum oven at *ca.* 35°C and stored under Ar until use. Yield: 792 mg (73%).

A solution of the allylic substrate (1 eq.) and $PdCl_2(PhCN)_2$ (5–10 eq. m/m) was refluxed in benzene under Ar until ^1H NMR spectra of reaction aliquots indicated complete or near-complete conversion of the allyl group to a prop-1-enyl group. The catalyst was removed by elution with acetone through a short silica gel plug, and the eluate was concentrated under reduced pressure. If required, the product was purified by FCC, PLC or crystallization.

3.7.8. Dihydroxylation of prop-1-enylarenes with AD-mix[72]

(procedure given per mmol of olefin)

A round-bottomed flask, equipped with a magnetic stirrer, was charged with 5 cm^3 of *t*-BuOH, 5 cm^3 of water and 1.4 g of AD-mix-α or AD-mix-β. Stirring at r.t. produced two clear phases; the lower aqueous phase appeared bright yellow. Methanesulfonamide (95 mg;

1 eq. based on 1 mmol of olefin) was added and the mixture was cooled to 0°C, whereupon some of the dissolved salts precipitated. One mmol of olefin was added at once, and the heterogeneous slurry was stirred vigorously at 0°C until TLC indicated no further conversion of starting material (typically 3-24 h.). While the mixture was stirred at 0°C, solid Na_2SO_3 (1.5 g) was added and the mixture was allowed to warm to r.t. and stirred for 30–60 min. EtOAc (10 cm^3) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 x 5 cm^3). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give the crude product, which was analyzed by ^1H NMR without prior purification.

3.7.9. Dihydroxylation of prop-1-enylarenes with OsO_4 / NMO[70]

(procedure given per mmol of olefin)

To a mixture of NMO (150 mg; 1.1 eq. based on 1 mmol of olefin), H_2O (5 cm^3), acetone (2.5 cm^3) and OsO_4 (13-51 mg; 5-20 mol%) in *t*-BuOH (1 cm^3) was added 1 mmol of the olefin. The mixture was stirred at r.t. under N_2 until TLC indicated no further conversion of starting material (typically 3-18 h.). The reaction was quenched by the addition of a slurry of $NaHSO_3$ (100 mg) and commercial Florisil® (1 g) in H_2O (50 cm^3). After filtration and washing (acetone, 3 x 10 cm^3) of the Florisil®, the combined filtrates were neutralized to *p*H 7 with 3 M HCl, the acetone removed under reduced pressure, the aqueous residue cooled by the addition of ice and acidified further to *p*H 2. The solution was saturated with NaCl and extracted with EtOAc (3 x 50 cm^3), the combined extracts washed successively with sat. aq. $NaHCO_3$ and H_2O, dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by PLC.

3.7.10. Oxidative cleavage of 1,2-diols

(procedure given per mmol of 1,2-diol)

A solution of $NaIO_4$ (535 mg; 2.5 eq. based on 1 mmol of 1,2-diol) in water (*ca.* 1 cm^3) was added slowly to a solution of the 1,2-diol (1 mmol) in MeOH (*ca.* 10 cm^3) and the mixture was stirred at r.t. until TLC indicated complete conversion of the starting material. The MeOH was evaporated under reduced pressure, the residue taken up in H_2O and the aqueous phase extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, the solvent removed under reduced pressure and the crude product purified by PLC.

3.7.11. Benzylic reduction

(procedure given per mmol of acetophenone or benzaldehyde)

Finely powdered $NaBH_4$ (95 mg; 2.5 eq. based on 1 mmol of substrate) was added in small portions to a stirred solution of the substrate (1 mmol) in a mixture of THF (*ca.* 1 cm^3) and EtOH (*ca.* 1 cm^3). The resulting mixture was stirred at r.t. until TLC indicated complete conversion of the starting material. The excess of borohydride was quenched by the slow addition of acetone (*ca.* 2 cm^3) and the mixture was concentrated under reduced pressure. The residue was taken up in H_2O, the aqueous phase extracted with Et_2O and the combined organic extracts dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the product, which was sufficiently pure to be used directly in a subsequent reaction.

3.7.12. Bromination of benzylic alcohols[73]

(procedure given per mmol of benzylic alcohol)

2,6-Lutidine (120 μl; 2 eq. based on 1 mmol of benzylic alcohol) was added to a stirred solution of the benzyl alcohol (1 mmol) and oven-dried LiBr (260 mg; 3 eq. based on 1 mmol of benzylic alcohol) in anhydrous THF (*ca.* 5 cm^3) under Ar, and stirring was continued at r.t. until all LiBr had dissolved. The mixture was cooled to 0°C and a solution of methanesulfonyl anhydride (260 mg; 1.5 eq. based on 1 mmol of benzylic alcohol) in anhydrous THF (*ca.* 2 cm^3) was added to it under Ar. The resulting suspension was stirred at r.t. until ^1H NMR of reaction aliquots indicated complete conversion of the benzylic alcohol into the corresponding bromide. The latter compound was used directly for coupling with a benzofuranone enol silyl ether (Section 3.8.9.).

3.7.13. Grignard reaction with PhMgBr

(procedure given per mmol of benzofuranoid substrate)

A standardized solution of PhMgBr in THF (2 eq. based on 1 mmol of substrate) was added slowly *via* a syringe or microsyringe to a stirred solution of the substrate (1 mmol) in anhydrous THF (*ca.* 5 cm^3) under N_2 at 0°C, and the resulting mixture was stirred at r.t. until TLC of reaction aliquots indicated complete conversion of the starting material. Crushed ice and an excess of sat. aq. NH_4Cl was added to the mixture which was then extracted with EtOAc. The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by PLC.

3.8. Model reactions and eventual synthesis of Daljanelin B (13)

Note: unless specified otherwise, all ^{1}H NMR data of products are given in Table 6.1 (monocyclic allyl compounds), Table 6.2 (other monocyclic model compounds), Table 7 (isoflavonoid model compounds), Table 8.1 (medicarpin and its derivatives) and Table 9 (benzofuranoid precursors to the neoflavonoid fragment) in Section 4.1. CD spectra are given in Section 4.2.

3.8.1. Allylation of phenols

1-*O*-Allyl-3-methoxyphenol **38**

3-Methoxyphenol **33** (5 g; 40.3 mmol) was allylated according to general procedure 3.7.1. The product **38** (6.08 g; 92%), a viscous, light yellow oil, was sufficiently pure to be used further without any purification.

^{1}H NMR: Plate 1 / Table 6.1.

4-Allyloxy-2-hydroxybenzaldehyde **44**

Method 1:

2,4-Dihydroxybenzaldehyde **42** (1 g; 7.24 mmol) was allylated according to general procedure 3.7.1., but only 1.1 eq. (963 mg) of allyl bromide were used in order to attempt monoallylation. FCC (H:EA 9:1) provided the title compound **44** (52 mg; 4%; R_f: 0.3) as a colourless oil, and 2,4-diallyloxybenzaldehyde **43** (322 mg; 20%; R_f: 0.2) as a light yellow oil.

Method 2:

A solution of 2,4-dihydroxybenzaldehyde **42** (1 g; 7.24 mmol) in anhydrous THF (*ca.* 10 cm^3) was added slowly to a stirred suspension of NaH (220 mg of an 80% supension in mineral oil; 7.33 mmol) in anhydrous THF (*ca.* 10 cm^3) under Ar at 0°C. The resulting mixture was stirred at 0°C for 30 min. and allyl bromide (615 µl; 7.27 mmol) was added dropwise *via* a syringe. The mixture was heated to 60°C and stirred for 18 h., cooled and quenched with crushed ice. After careful acidification with 3 M HCl, the aqueous phase was extracted with EtOAc (3 x 30 cm^3), the combined extracts were washed with sat. aq. $NaHCO_3$, dried over

$MgSO_4$ and the solvent removed under reduced pressure. FCC of the residue (H:EA 9:1) gave the title compound **44** (65 mg; 5%; R_f: 0.3) as a yellow oil, and 2,4-diallyloxybenzaldehyde **43** (29 mg; 2%; R_f: 0.2) as a colourless oil.

^{1}H NMR spectra: **44**: Plate 2 / Table 6.1.
43: Plate 3 / Table 6.1.

4-Allyloxy-2-hydroxyacetophenone **49**

Method 1:

A solution of 2,4-dihydroxyacetophenone **48** (550 mg; 3.61 mmol) in anhydrous THF (*ca.* 5 cm^3) was added slowly to a stirred suspension of NaH (110 mg of an 80% supension in mineral oil; 3.67 mmol) in anhydrous THF (*ca.* 5 cm^3) under Ar at 0°C. The resulting mixture was stirred at 0°C for 30 min. and allyl bromide (310 µl; 3.66 mmol) was added dropwise *via* a a syringe. The mixture was heated to 60°C and stirred for 18 h., cooled and quenched with crushed ice. After careful acidification with 3 M HCl, the aqueous phase was extracted with EtOAc (3 x 20 cm^3), the combined extracts were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and the solvent removed under reduced pressure. FCC of the residue (H:EA 9:1) gave the title compound **49** (30 mg; 4%; R_f: 0.35), and 2,4-diallyloxyacetophenone **52** (26 mg; 3%; R_f: 0.25), both as amorphous white solids. 110 mg (20%) of the starting material **48** was recovered (R_f: 0.1).

Method 2:

2,4-Dihydroxyacetophenone **48** (550 mg; 3.61 mmol) was allylated according to general procedure 3.7.1., but only 1.1 eq. (480 mg) of allyl bromide were used in order to effect monoallylation. FCC (H:EA 9:1) provided the title compound **49** (384 mg; 55 %; R_f: 0.35) as a colourless oil, and 2,4-diallyloxyacetophenone **52** (93 mg; 11%; R_f: 0.25) as an amorphous, white solid.

^{1}H NMR spectra: **49**: Plate 4 / Table 6.1.
52: Plate 5 / Table 6.1.

4-Allyloxy-2-methoxyacetophenone **50**

A solution of 4-allyloxy-2-hydroxyacetophenone **49** (100 mg; 520 μmol) and dimethyl sulphate (165 mg; 2.5 eq.) in anhydrous acetone (*ca.* 10 cm^3) was refluxed over anhydrous K_2CO_3 (*ca.* 5 g) under N_2 for 18 h. The K_2CO_3 was filtered off, the solid residues washed with anhydrous acetone, the filtrates combined and the acetone removed under reduced pressure. PLC of the residue (H:EA 8:2) gave the title compound **50** (85 mg; 79%) as a colourless oil (R_f: 0.4).

^{1}H NMR: Plate 6 / Table 6.1.

1-(4-Allyloxy-2-methoxy)phenylethanol **51**

4-Allyloxy-2-methoxyacetophenone **50** (70 mg; 339 μmol) was reduced according to general procedure 3.7.11., to give the title compound **51** (63 mg: 89%) as a light yellow oil.

^{1}H NMR: Plate 7 / Table 6.1.

Preparation of free phenolic isoflavonoid substrates **7**, **36** and **37**

10% Pd-C (430 mg; 35% m/m) was added to a solution of 7-*O*-benzyl-4'-methoxyisoflavone **53** (1.23 g; 3.43 mmol) in EtOH (*ca.* 50 cm^3) and the resulting mixture was stirred vigorously under H_2 until TLC of reaction aliquots indicated optimal formation of all possible products. The catalyst was removed by elution (EtOH) through a short Celite plug, the eluate concentrated under reduced pressure, and the residue purified by FCC (B:A 98:2), to give 7-hydroxy-4'-methoxyisoflavone **7** (204 mg; 22%; R_f: 0.1), 7-hydroxy-4'-methoxyisoflavanone **36** (243 mg; 26%; R_f: 0.15) and 7-hydroxy-4'-methoxyisoflavan **37** (81 mg; 9%; R_f: 0.25), all as amorphous, white solids. 338 mg (27%) of the starting material **53** was recovered (R_f: 0.4).

^{1}H NMR spectra: **53**: Plate 8 / Table 7.
7: Plate 9 / Table 7.
36: Plate 10 / Table 7.
37: Plate 11 / Table 7.

7-Allyloxy-4'-methoxyisoflavone **54**

7-Hydroxy-4'-methoxyisoflavone **7** (200 mg; 746 μmol) was allylated according to general procedure 3.7.1. PLC (B:A 9:1) gave the title compound **54** (209 mg; 91%) as an amorphous, white solid (R_f: 0.65).

^{1}H NMR: Plate 12 / Table 7.

7-Allyloxy-4'-methoxyisoflavanone **55**

7-Hydroxy-4'-methoxyisoflavanone **36** (220 mg; 814 μmol) was allylated according to general procedure 3.7.1. PLC (B:A 92:8) gave the title compound **55** (205 mg; 81%) as an amorphous, cream-coloured solid (R_f: 0.65).

^{1}H NMR: Plate 13 / Table 7.

7-Allyloxy-4'-methoxyisoflavan **56**

7-Hydroxy-4'-methoxyisoflavan **37** (84 mg; 328 μmol) was allylated according to general procedure 3.7.1. PLC (B:A 98:2) gave the title compound **56** (29 mg; 30%) as an amorphous, white solid (R_f: 0.7).

^{1}H NMR: Plate 14 / Table 7.

(6a*S*, 11a*S*)-3-*O*-Allylmedicarpin **17**

(+)-(6a*S*, 11a*S*)-Medicarpin **1** (500 mg; 1.85 mmol) was allylated according to general procedure 3.7.1. PLC (H:B:A 5:4:1) gave the title compound **17** (457 mg; 80%) as a viscous, light yellow oil (R_f: 0.6).

^{1}H NMR spectra: **1**: Plate 15 / Table 8.1.
17: Plate 16 / Table 8.1.

3.8.2. Thermal rearrangement of aryl allyl ethers

Thermal rearrangement of 1-*O*-allyl-3-methoxyphenol **38**

1-*O*-Allyl-3-methoxyphenol **38** (1 g; 6.09 mmol) was treated according to general procedure 3.7.2. FCC (H:EA 9:1) gave 2-allyl-3-methoxyphenol **58** (394 mg; 39%; R_f: 0.35) as a colourless oil, and 2-allyl-5-methoxyphenol **57** (517 mg; 52%; R_f: 0.25) as a yellow oil.

^{1}H NMR spectra: **58**: Plate 17 / Table 6.1.
57: Plate 18 / Table 6.1.

Thermal rearrangement of 4-allyloxy-2-methoxyacetophenone **50**

4-Allyloxy-2-methoxyacetophenone **50** (100 mg; 485 μmol) was treated according to general procedure 3.7.2. FCC (H:EA 6:4) gave 3-allyl-4-hydroxy-2-methoxyacetophenone **60** (20 mg; 20%; R_f: 0.4) as a light yellow oil, and 5-allyl-4-hydroxy-2-methoxyacetophenone **59** (38 mg; 38%; R_f: 0.25) as an amorphous, white solid. 19 mg (19%) of the starting material **50** was recovered (R_f: 0.6).

^{1}H NMR spectra: **60**: Plate 19 / Table 6.1.
59: Plate 20 / Table 6.1.

8-Allyl-7-hydroxy-4'-methoxyisoflavone **64**

7-Allyloxy-4'-methoxyisoflavone **54** (100 mg; 324 μmol) was treated according to general procedure 3.7.2. PLC (B:A 9:1) gave the title compound **64** (34mg; 34%) as an amorphous, white solid (R_f: 0.15), and 15mg (15%) of the starting material **54** was recovered (R_f: 0.6).

^{1}H NMR: Plate 21 / Table 7.

8-Allyl-7-hydroxy-4'-methoxyisoflavanone **66**

7-Allyloxy-4'-methoxyisoflavanone **55** (90 mg; 290 μmol) was treated according to general procedure 3.7.2. PLC (B:A 85:15) gave the title compound **66** (21mg; 23%) as an amorphous, light yellow solid (R_f: 0.4), and 38mg (42%) of the starting material **55** was recovered (R_f: 0.7).

^{1}H NMR: Plate 22 / Table 7.

8-Allyl-7-hydroxy-4'-methoxyisoflavan **68**

7-Allyloxy-4'-methoxyisoflavan **56** (40 mg; 135 μmol) was treated according to general procedure 3.7.2. PLC (B:A 98:2) gave the title compound **68** (13mg; 33%) as a viscous, light yellow oil (R_f: 0.45), and 5 mg (13%) of the starting material **56** was recovered (R_f: 0.7).

^{1}H NMR: Plate 23 / Table 7.

(6a*S*, 11a*S*)-4-Allylmedicarpin **18**

(6a*S*, 11a*S*)-3-*O*-Allylmedicarpin **17** (1 g; 3.22 mmol) was treated according to general procedure 3.7.2. FCC (H:EA 8:2) gave the title compound **18** (553 mg; 55%) as a viscous, light brown oil (R_f: 0.3), and 239 mg (24%) of the starting material **17** was recovered (R_f: 0.5).

^{1}H NMR: Plate 24 / Table 8.1.

Note: the title compound **18** could not be purified further by chromatography, crystallization, 3-*O*-methoxymethylation (general procedure 3.7.3) or –acetylation (general procedure3.7.4), and was finally converted to the 3-*O*-(3',5'-dinitro)benzoate **73** (see below).

(6a*S*, 11a*S*)-4-Allyl-3-*O*-(3',5'-dinitro)benzoylmedicarpin **73**

The contaminated (6a*S*, 11a*S*)-4-allylmedicarpin **18** was treated according to general procedure 3.7.5. Crystallization from EtOAc gave the title compound **73** (429 mg; 26% based on 1 g of (6a*S*, 11a*S*)-3-*O*-allylmedicarpin **17**) as orange needles (m.p.: 186-187°C).

^{1}H NMR: Plate 25 / Table 8.1.

3.8.3. Isomerization of allylarenes

5-Methoxy-2-(prop-1-enyl)phenol **74**

A solution of 2-allyl-5-methoxyphenol **57** (87 mg; 530 μmol) in anhydrous THF (*ca.* 5 cm^3) was cooled to –78°C under Ar. *n*-BuLi (690 μl of a 1.63 M solution in hexanes; 2.1 eq.) was added, and the mixture was stirred at 0°C until ^{1}H NMR of reaction aliquots indicated no further conversion of the allyl group. The reaction was quenched with sat. aq. NH_4Cl (*ca.* 2 cm^3), the mixture diluted with H_2O and the aqueous phase extracted with EtOAc (3 x 10 cm^3). The combined organic extracts were dried over $MgSO_4$, the solvent removed under reduced pressure and the residue purified by PLC (H:EA 8:2), to give an inseparable mixture (33 mg; 38%) of the title compound **74** and the starting material **57** as a light brown oil (R_f: 0.35).

(*E*/*Z*)-3-Methoxy-2-(prop-1-enyl)phenol **75/76**

2-Allyl-3-methoxyphenol **58** (100 mg; 609 μmol) was isomerized according to general procedure 3.7.7. PLC (benzene) gave an inseparable *E*/*Z*-mixture (70 mg; 70%) of the respective title compounds **75** and **76** as a viscous, yellow oil (R_f: 0.5).

^{1}H NMR: Plate 26 / Table 6.2.

(*E/Z*)-(6a*S*, 11a*S*)-3-*O*-(3',5'-Dinitro)benzoyl-4-(prop-1-enyl)medicarpin **77/78**

(6a*S*, 11a*S*)-4-Allyl-3-*O*-(3',5'-dinitro)benzoylmedicarpin **73** (306 mg; 607 μmol) was isomerized according to general procedure 3.7.7. FCC (H:B:A 60:35:5) gave an inseparable *E/Z*-mixture (302 mg; 99%; R_f: 0.25) of the respective title compounds **77** and **78** as yellow needles (m.p.: 195-196°C).

^{1}H NMR: Plate 27 / Table 8.1.

3.8.4. Dihydroxylation of prop-1-enylarenes

Attempted dihydroxylation of (*E/Z*)-3-methoxy-2-(prop-1-enyl)phenol **75/76**

(*E/Z*)-3-Methoxy-2-(prop-1-enyl)phenol **75/76** (50 mg; 304 μmol) was treated according to general procedure 3.7.8. TLC indicated that the starting material decomposed, and no product could be isolated.

Treatment of the starting material **75/76** according to general procedure 3.7.9. led to a similar result.

2-(1,2-Dihydroxy)propyl-3-methoxy-1-*O*-methoxymethylphenol **81**

(*E/Z*)-3-Methoxy-2-(prop-1-enyl)phenol **75/76** (500 mg; 3.04 mmol) was methoxymethylated according to general procedure 3.7.3. PLC (H:EA 9:1) gave (*E/Z*)-3-methoxy-1-*O*-methoxymethyl-2-(prop-1-enyl)phenol **80** (449 mg; 71%) as a colourless oil (R_f: 0.5).

^{1}H NMR: Plate 28 / Table 6.2.

(*E/Z*)-3-Methoxy-1-*O*-methoxymethyl-2-(prop-1-enyl)phenol **80** (63 mg; 303 μmol) was dihydroxylated according to general procedure 3.7.8. ^{1}H NMR of the crude product (79 mg of a colourless oil) indicated >95% conversion of the starting material to the title compound **81**.

(*E/Z*)-3-Methoxy-1-*O*-methoxymethyl-2-(prop-1-enyl)phenol **80** (63 mg; 303 μmol) was dihydroxylated according to general procedure 3.7.9. PLC (H:A 6:4) gave the title compound **81** (64 mg; 87%) as a light yellow oil (R_f: 0.35).

^{1}H NMR: Plate 29 / Table 6.2.

Attempted dihydroxylation of 3-methoxy-1-*O*-(3',5'-dinitro)benzoyl-2-(prop-1-enyl)phenol **82**

(*E/Z*)-3-Methoxy-2-(prop-1-enyl)phenol **75/76** (500 mg; 3.04 mmol) was dinitrobenzoylated according to general procedure 3.7.5. Crystallization from EtOAc gave (*E/Z*)-3-methoxy-1-*O*-(3',5'-dinitro)benzoyl-2-(prop-1-enyl)phenol **82** (471 mg; 43%) as yellow needles (m.p.:143-145°C).

^{1}H NMR: Plate 30 / Table 6.2.

Note: the yield was not optimized by any further crystallization from the mother liquor.

(*E/Z*)-3-Methoxy-1-*O*-(3',5'-dinitro)benzoyl-2-(prop-1-enyl)phenol **82** (109 mg; 304 μmol) was treated according to general procedure 3.7.8. TLC indicated that no conversion of the starting material **82** had taken place after 24 h.

(*E/Z*)-3-Methoxy-1-*O*-(3',5'-dinitro)benzoyl-2-(prop-1-enyl)phenol **82** (109 mg; 304 μmol) was treated according to general procedure 3.7.9. TLC indicated that the starting material **82** decomposed, and no product could be isolated.

(6a*S*, 11a*S*)-4-(1,2-Dihydroxy)propyl-3-*O*-methoxymethylmedicarpin **21**

(*E/Z*)-(6a*S*, 11a*S*)-3-*O*-(3',5'-Dinitro)benzoyl-4-(prop-1-enyl)medicarpin **77/78** (623 mg; 1.24 mmol) was debenzoylated according to general procedure 3.7.6. PLC (H:EA 7:3) gave (*E/Z*)-(6a*S*, 11a*S*)-4-(prop-1-enyl)medicarpin **84** (283 mg; 74%) as a light green oil (R_f: 0.35).

^{1}H NMR: Plate 31 / Table 8.1.

The phenolic medicarpin **84** (300 mg; 967 μmol) was methoxymethylated according to general procedure 3.7.3. PLC (H:EA 6:4) gave (*E*/*Z*)-(6a*S*, 11a*S*)-3-*O*-methoxymethyl-4-(prop-1-enyl)medicarpin **20** (201 mg; 61%) as an amorphous, white solid (R_f: 0.6).

^{1}H NMR: Plate 32 / Table 8.1.

(*E*/*Z*)-(6a*S*, 11a*S*)-3-*O*-Methoxymethyl-4-(prop-1-enyl)medicarpin **20** (180 mg; 508 μmol) was dihydroxylated according to general procedure 3.7.9., using a solvent system consisting of H_2O (15 cm^3), acetone (30 cm^3) and *t*-BuOH (3 cm^3). FCC (EA:H 6:4) gave the title compound **21** (121 mg; 61%) as an amorphous, white solid (R_f: 0.4).

^{1}H NMR: Plate 33 / Table 8.1.

3.8.5. Oxidative cleavage of 1,2-diols

2-Methoxy-6-*O*-methoxymethylbenzaldehyde **85**

2-(1,2-Dihydroxy)propyl-3-methoxy-1-*O*-methoxymethylphenol **81** (70 mg; 289 μmol) was oxidized according to general procedure 3.7.10. PLC (H:EA 6:4) gave the title compound **85** (50 mg; 88%) as a viscous, light yellow oil (R_f: 0.35).

^{1}H NMR: Plate 34 / Table 6.2.

(6a*S*, 11a*S*)-4-Formyl-3-*O*-methoxymethylmedicarpin **22**

(6a*S*, 11a*S*)-4-(1,2-Dihydroxy)propyl-3-*O*-methoxymethylmedicarpin **21** (110 mg; 283 μmol) was oxidized according to general procedure 3.7.10. PLC (H:EA 6:4) gave the title compound **22** (71 mg; 73%) as a viscous, light yellow oil (R_f: 0.3).

^{1}H NMR: Plate 35 / Table 8.1.

3.8.6. Reduction of benzaldehydes

2-Methoxy-6-*O*-methoxymethylbenzyl alcohol **86**

2-Methoxy-6-*O*-methoxymethylbenzaldehyde **85** (10 mg; 51.0 μmol) was reduced according to general procedure 3.7.11., giving the title compound **86** (10 mg; 99%) as a viscous, light yellow oil.

Note: due to instability of the product, no clean ^{1}H NMR spectrum could be obtained.

(6a*S*, 11a*S*)-4-Hydroxymethyl-3-*O*-methoxymethylmedicarpin **23**

(6a*S*, 11a*S*)-4-Formyl-3-*O*-methoxymethylmedicarpin **22** (60 mg; 175 μmol) was reduced according to general procedure 3.7.11., giving the title compound **23** (51 mg; 85%) as an amorphous, white solid.

^{1}H NMR: Plate 36 / Table 8.1.

3.8.7. *In situ* bromination of benzyl alcohols

2,4-Dimethoxybenzyl bromide **88**

2,4-Dimethoxybenzaldehyde **89** (2 g; 12.04 mmol) was reduced according to general procedure 3.7.11., giving 2,4-dimethoxybenzyl alcohol **87** (1.945 g; 96%) as a colourless oil.

^{1}H NMR: Plate 37 / Table 6.2.

2,4-Dimethoxybenzyl alcohol **87** (76 mg; 452 μmol) was brominated according to general procedure 3.7.12., to give the title compound **88**, which was used directly for coupling with a benzofuranone enol silyl ether (Section 3.8.9.).

(6a*S*, 11a*S*)-4-Bromomethyl-3-*O*-methoxymethylmedicarpin **24**

(6a*S*, 11a*S*)-4-Hydroxymethyl-3-*O*-methoxymethylmedicarpin **23** (45 mg; 131 μmol) was brominated according to general procedure 3.7.12., to give the title compound **24**, which was used directly for coupling with a benzofuranone enol silyl ether (Section 3.8.9.).

3.8.8. The neoflavonoid fragment[51]

Methoxy-*p*-hydroquinone **26**

A 6% aq. solution of H_2O_2 (150 cm^3) at 0°C was slowly added under N_2 to an N_2-purged solution of vanillin **25** (20 g; 131 mmol) in 2 M NaOH (200 cm^3) at 0°C. The cream-coloured suspension turned dark brown within 15 min. after the addition of H_2O_2 had commenced. The mixture was stirred at 0°C for 30 min. and subsequently at r.t. for 45 min. After acidification with HCl (c), the mixture was extracted with Et_2O (3 x 100 cm^3), the extracts were combined and $Na_2S_2O_5$ (excess) was added to them. After filtration, the solution was washed with H_2O (100 cm^3), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. FCC ($CHCl_3$:EA 9:1) gave the title compound **26** (10.7 g; 58%) as a light brown solid (R_f: 0.25).

^{1}H NMR: Plate 38:
δ_H 6.78 (d, 9; H-6), 6.47 (d, 3; H-3), 6.33 (dd; 9, 3; H-5), 5.26 (br s; O<u>H</u>), 4.81 (br s; O<u>H</u>) and 3.86 (s; OC<u>H</u>$_3$).

2-Chloro-2',5'-dihydroxy-4'-methoxyacetophenone **27**

HCl (g), dried over H_2SO_4 (c) was bubbled through a mixture of methoxy-*p*-hydroquinone **26** (5 g; 35.7 mmol) and freshly fused $ZnCl_2$ (9.7 g; 2 eq.) in anhydrous Et_2O (25 cm^3) at r.t. under N_2 for 90 min. A solution of freshly distilled chloroacetonitrile (2.5 cm^3; 1.1 eq.) in anhydrous Et_2O (25 cm^3) was subsequently added to the mixture over 1 h. under N_2 and HCl-bubbling was continued for 6 h. to give a dark green paste. The mixture was left at 4°C for 30 h., the solvent decanted and H_2O (excess) added to the residue, giving a yellow solution. This solution was refluxed for 2 h. and left at 4°C for 5 h. to give the crude title compound **27** as a brown precipitate (6.5 g; 84%). The product was not recrystallized or

chromatographed owing to its susceptibility to oxidation, and was used directly in the cyclization step.

^{1}H NMR: Plate 39 (crude product):
δ_H 11.98 (s; 2'-OH), 7.17 (s; H-6'), 6.50 (s; H-3'), 5.3 (br s; 5'-OH), 4.63 (s; 2-CH_2Cl) and 3.97 (s; OCH_3).

5-Hydroxy-6-methoxy-2,3-dihydrobenzo[b]furan-3-one **28**

A suspension of 2-chloro-2',5'-dihydroxy-4'-methoxyacetophenone **27** (6.5 g; 30.0 mmol) and NaOAc (7.4 g; 3 eq.) in EtOH (100 cm^3) was refluxed for 3 h. under N_2. Crushed ice was added and the resulting brown precipitate filtered off. Recrystallization from H_2O gave the title compound **28** (4.8 g; 90%) as light brown needles (m.p.: 182-184°C).

^{1}H NMR: Plate 40 / Table 9.

6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one **29**

The phenolic benzofuranone **28** (4.8 g; 26.6 mmol) was methoxymethylated according to general procedure 3.7.3., using anhydrous DMF as solvent. FCC ($CHCl_3$:EA 95:5) gave the title compound **29** (5.2 g; 87%) as light yellow needles (m.p.: 161-163°C; R_f: 0.25).

^{1}H NMR: Plate 41 / Table 9.

3-*t*-Butyldimethylsilyloxy-6-methoxy-5-*O*-methoxymethylbenzo[b]furan **30**

NEt_3 (500 µl; 1.5 eq.) was added slowly *via* a syringe to a stirred solution of 6-methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one **29** (500 mg; 2.23 mmol) and oven-dried NaI (500 mg; 1.5 eq.) in anhydrous CH_3CN (10 cm^3). A solution of TBDMSCl (500 mg; 1.5 eq.) in anhydrous CH_3CN (3 cm^3) was added slowly at r.t. to the mixture, and stirring at r.t. continued for 12 h. The mixture was diluted with cold H_2O (20 cm^3) and the aqueous phase extracted exhaustively with cold pentane (0-10°C). The combined organic extracts were kept

at *ca.* 0°C and washed with chilled H_2O, dried over $MgSO_4$, and the solvent evaporated to give the title compound **30** (724 mg; 96%) as a yellow oil.

^{1}H NMR: Plate 42 / Table 9.

3.8.9. Desilylation and nucleophilic coupling

6-Methoxy-2-(2',4'-dimethoxybenzyl)-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one **92**

A solution of the silyloxybenzofuran **30** (50 mg; 148 μmol) in anhydrous THF (0.5 cm^3) was added slowly to a stirred suspension of TASF (43 mg; 1.06 eq.) in anhydrous THF (0.5 cm^3) at -78°C under Ar. The mixture was stirred for 15 min., HMPA (130 μl; 5 eq.) added and stirring continued for 15 min. The suspension containing the aforementioned 2,4-dimethoxybenzyl bromide **88** (452 μmol; 3.1 eq.) was added slowly to the mixture by filtration under Ar through a septum-capped syringe (5 cm^3) charged with cotton wool. The cotton wool was rinsed once with anhydrous THF (2 cm^3), and the resulting mixture was stirred (5 h.: -78 → -30°C), quenched at -30°C with sat. aq. NH_4Cl (2 cm^3), warmed to r.t., diluted with H_2O, extracted with Et_2O (5 x 10 cm^3) and the combined organic extracts dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and PLC ($CHCl_3$:MeOH 98:2) gave the title compound **92** (11 mg; 20%) as a yellow oil (R_f: 0.7). Further purification by PLC was unsuccessful.

^{1}H NMR: Plate 43 (contaminated):
δ_H 7.38 (s; H-4), 7.13 (d, 8; H-6'), 6.58 (s; H-7), 6.50 (d, 2; H-3'), 6.47 (dd; 8, 2; H-5'), 5.19 (s; $OC\underline{H}_2OCH_3$), 4.88 (dd; 10, 4; H-2), 3.94/3.85/3.83 (3 x s; 3 x $OC\underline{H}_3$), 3.53 (s; $OCH_2OC\underline{H}_3$), 3.43 (dd; 15, 4; 2-$C\underline{H}_2$) and 2.68 (dd; 15, 10; 2-$C\underline{H}_2$).

(6a*S*, 11a*S*)-4-(6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **31**

A solution of the silyloxybenzofuran **30** (112 mg; 328 μmol; 2.5 eq. relative to the benzyl bromide **24**) in anhydrous THF (1 cm^3) was added slowly to a stirred suspension of TASF (95 mg; 1.05 eq. relative to the silyloxybenzofuran **30**) in anhydrous THF (1 cm^3) at -78°C under Ar. The mixture was stirred for 15 min., HMPA (300 μl; 5 eq. relative to the

silyloxybenzofuran **30**) added and stirring continued for 15 min. The suspension containing the aforementioned (6a*S*, 11a*S*)-4-bromomethyl-3-*O*-methoxymethylmedicarpin **24** (452 μmol; 1 eq.) was added slowly to the mixture by filtration under Ar through a septum-capped syringe (5 cm^3) charged with cotton wool. The cotton wool was rinsed once with anhydrous THF (2 cm^3), and the resulting mixture was stirred (1 h.: -78 → -30°C; 15h.: -30°C), quenched at -30°C with sat. aq. NH_4Cl (2 cm^3), warmed to r.t., diluted with H_2O, extracted with Et_2O (5 x 10 cm^3) and the combined organic extracts dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and PLC (first $CHCl_3$:MeOH 98:2, R_f: 0.4; then H:B:A 5:4:1, R_f: 0.25) gave the title compound **31** (20 mg; 28%) as a viscous, colourless oil.

^{1}H NMR: Plate 44 (unresolved diastereomeric mixture):

δ_H 7.44 (2 x d, 9; 2 x H-1(A)), 7.39/7.38 (2 x s; 2 x H-4(E)), 7.15 (2 x d, 9; 2 x H-7(D)), 6.92/6.91 (2 x d, 9; 2 x H-2(A)), 6.51/6.48 (2 x s; 2 x H-7(E)), 6.47 (dd; 9, 3; 2 x H-8(D)), 6.47/6.44 (2 x d, 3; 2 x H-10(D)), 5.57/5.56 (2 x d, 7; 2 x H-11a), 5.24/5.22/5.20/5.19 (4 x s; 2 x 3(A)-OC$\underline{H}_2$OCH$_3$ and 2 x 5(E)-OC$\underline{H}_2$OCH$_3$), 4.91/4.88 (2 x dd; 10, 4/5; 2 x H-2(G)), 4.35-4.25 (m; 2 x H-6*eq*), 3.94/3.90/3.79/3.78 (4 x s; 2 x 9(D)-OC$\underline{H}_3$ and 2 x 6(E)-OC$\underline{H}_3$), 3.68-3.57 (m; 2 x H-6*ax* and 2 x H-6(B)), 3.53/3.52/3.48/3.48 (4 x s; 2 x 3(A)-OCH$_2$OC$\underline{H}_3$ and 2 x 5(E)-OCH$_2$OC$\underline{H}_3$), 3.27/3.26 (2 x dd; 14, 4/5; 2 x 4(A)-C$\underline{H}_2$) and 3.14/3.12 (2 x dd; 14, 10; 2 x 4(A)-C$\underline{H}_2$).

3.8.10. Grignard reactions with PhMgBr

6-Methoxy-5-*O*-methoxymethyl-3-phenylbenzo[b]furan **95**

6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one **29** (100 mg; 446 μmol) was treated according to general procedure 3.7.13. PLC (H:B:A 35:35:30) gave the title compound **95** (6 mg; 4%) as a colourless oil (R_f: 0.65).

^{1}H NMR: Plate 45 / Table 9.

3-Hydroxy-4,6-dimethoxy-2-(4-methoxybenzyl)-3-phenyl-2,3-dihydrobenzo[b]furan **98**

5% Pd-C (20 mg; 10% m/m) was added to a solution of 4,4',6-trimethoxyaurone **96** (200 mg; 640 μmol) in commercial absolute EtOH (*ca.* 20 cm^3) and the resulting mixture was stirred vigorously under H_2 until TLC of reaction aliquots indicated complete conversion of the starting material. The catalyst was removed by elution (EtOH) through a short Celite plug, the eluate concentrated under reduced pressure, and the residue purified by PLC (B:A 85:15), to give 4,6-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydrobenzo[b]furan-3-one **97** (131 mg; 65%) as a light yellow oil (R_f: 0.5).

^{1}H NMR: Plate 46 / Table 9.

The benzofuranone **97** (50 mg; 159 μmol) was treated according to general procedure 3.7.13. PLC (B:A 9:1) gave the title compound **98** (42 mg; 67%) as a viscous, colourless oil (R_f: 0.6).

^{1}H NMR: Plate 47 / Table 9.

(6a*S*, 11a*S*)-4-(3-Hydroxy-6-methoxy-5-*O*-methoxymethyl-3-phenyl-2,3-dihydrobenzo[b] furan-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **32**

(6a*S*, 11a*S*)-4-(6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **31** (20 mg; 36.3 μmol) was treated according to general procedure 3.7.13. PLC (B:A 9:1) gave the title compound **32** (5 mg; 22%; R_f: 0.25), and 3 mg (15%) of the starting material **31** (R_f: 0.4) was recovered.

^{1}H NMR: Plate 48 (unresolved diastereomeric mixture):
δ_H 7.35-7.29/7.26-7.11 (2 x m; 2 x H-1(A), 2 x H-7(D) and 2 x $C_6\underline{H}_5$(F)), 6.78/6.78 (2 x s; 2 x H-4(E)), 6.74 (2 x d, 9; 2 x H-2(A)), 6.54/6.45 (2 x s; 2 x H-7(E)), 6.51-6.44 (m; 2 x H-8(D) and 2 x H-10(D)), 5.44/5.42 (2 x d, 7; 2 x H-11a), 5.05/5.04/5.02/5.02 (4 x s; 2 x 3(A)-OC$\underline{H}_2$OCH$_3$ and 2 x 5(E)-OC$\underline{H}_2$OCH$_3$), 5.11-4.92 (m; 2 x H-2(G)), 4.22/4.14 (2 x ddd; 10, 4/5, 1; 2 x H-6*eq*), 3.87/3.86/3.79/3.78 (4 x s; 2 x 9(D)-OC$\underline{H}_3$ and 2 x 6(E)-OC$\underline{H}_3$), 3.63-3.46 (m; 2 x H-6*ax* and 2 x H-6(B)), 3.45/3.44/3.38/3.35 (4 x s; 2 x 3(A)-OCH$_2$OC$\underline{H}_3$ and 2 x 5(E)-OCH$_2$OC$\underline{H}_3$), 3.33-3.20 (m; 2 x 4(A)-C$\underline{H}_2$) and 2.91 (s; 2 x 3(G)-O$\underline{H}$).

3.8.11. Phenolic deprotection and dehydration

(6a*S*, 11a*S*)-4-(5-Hydroxy-6-methoxy-3-phenylbenzo[b]furan-2-ylmethyl)medicarpin **13**

(6a*S*, 11a*S*)-4-(3-Hydroxy-6-methoxy-5-*O*-methoxymethyl-3-phenyl-2,3-dihydrobenzo[b] furan-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **32** (5 mg; 7.95 μmol) was refluxed for 3 h. in a mixture of 0.1 M HCl (1 cm^3) and MeOH (1 cm^3) . The mixture was cooled to r.t., neutralized with sat. aq. $NaHCO_3$ and extracted with Et_2O (5 x 5 cm^3). The combined moist organic extracts were homogenized with EtOH (*ca.* 0.5 cm^3), concentrated under reduced pressure and the residue subjected directly to PLC (B:A 8:2) to give the title compound **13** (1 mg; 24%; R_f: 0.55).

^{1}H NMR: Plate 49:

δ_H 7.67-7.63 (m; 2 x H(F)), 7.45 (s; H-4(E)), 7.41 (d, 8; H-1(A)), 7.39-7.29 (m; 3 x H(F)), 6.81 (d, 8; H-7(D)), 6.66 (d, 2; H-10(D)), 6.60 (s; H-7(E)), 6.53 (d, 8; H-2(A)), 6.51 (dd; 8, 2; H-8(D)), 5.52/5.46 (2 x br s; 3(A)-O<u>H</u> and 5(E)-O<u>H</u>), 5.30 (d, 7; H-11a), 4.36 (s; 4(A)-C<u>H</u>$_2$), 3.92 (ddd; 11, 5, 1; H-6*eq*), 3.45 (t, 11; H-6*ax*), 3.34/3.14 (2 x s; 9(A)-OC<u>H</u>$_3$ and 6(E)-OC<u>H</u>$_3$) and 3.12-3.01 (m; H-6a).

CD: Plate 1 (synthetic *vs.* natural compounds)

3.9. Model reaction and synthesis of Daljanelin D (15)

Note: CD spectra are given in Section 4.2.

3.9.1. Reduction of (+)-(6a*S*, 11a*S*)-medicarpin (1)

(+)-(3*S*)-Vestitol **2**

TFA (17 µl; 1.2 eq.) was added slowly *via* a microsyringe to a stirred suspension of (+)-(6a*S*, 11a*S*)-medicarpin **1** (50 mg; 185 µmol) and $Na(CN)BH_3$ (17 mg; 1.5 eq.) in anhydrous DCM (2 cm^3) at -10°C under N_2. Stirring was continued (1 h.: -10 → 0°C), the reaction quenched with H_2O (excess), the mixture neutralized with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (H:B:A 4:4:2) of the residue gave the title compound **2** (43 mg; 85%) as a light brown solid (R_f: 0.25). The retention of chirality at the equivalent of C-6a was demonstrated by Mosher esterification (see below).

^1H NMR: Plate 50:

δ_H 7.03 (d, 9; H-6'), 6.96 (d, 8; H-5), 6.50 (dd; 9, 2; H-5'), 6.41 (dd; 8, 2; H-6), 6.38 (d, 2; H-8), 6.37 (d, 2; H-3'), 4.96/4.70 (2 x br s; 7-O<u>H</u> and 2'-O<u>H</u>), 4.35 (ddd; 11, 4, 2; H-2*eq*), 4.06 (dd; 10, 10; H-2*ax*), 3.79 (s, 4'-OC<u>H</u>$_3$), 3.57-3.47 (m; H-3), 3.02 (ddd; 16, 10, 1; H-4*ax*) and 2.91 (ddd; 16, 6, 2; H-4-*eq*).

(3*S*)-{2'-*O*,7-*O*-Di-[(α*R*)-α-trifluoromethyl-α-methoxyphenylacetyl}vestitol **101**[98]

The vestitol **2** described above (11 mg; 40.4 µmol), NEt_3 (60 µl; 5.3 eq. per phenol) and DMAP (8 mg; 0.8 eq. per phenol) were dissolved in anhydrous DCM (2 cm^3) under N_2. The mixture was added to *S*-(+)-MTPACl (7 cm^3 of a 21.4 mM solution in anhydrous DCM; 1.9 eq. per phenol), stirred at r.t. under N_2 for 2 h., neutralized with 0.1 M HCl and extracted with EtOAc (4 x 5 cm^3). The combined extracts were washed with sat. aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, the solvent evaporated under reduced pressure and the residue purified with PLC (H:B:A 5:4:1) to give the title compound **101** (13 mg; 44%) as a colourless oil (R_f: 0.55).

^{1}H NMR: Plate 51:

δ_H 7.70-7.66/7.64-7.60/7.52-7.47/7.32-7.28 (4 x m; 2 x $C_6\underline{H}_5$), 7.10 (d, 9; H-6'), 6.99 (d, 8; H-5), 6.84 (dd; 9, 3; H-5'), 6.69 (d, 3; H-3'), 6.64 (dd; 8, 2; H-6), 6.62 (d, 2; H-8), 4.16 (ddd; 11, 4, 2; H-2*eq*), 3.91 (dd; 11, 10; H-2*ax*), 3.82 (s, 4'-OC$\underline{H}_3$), 3.73/3.69 (2 x q, 1; 2 x PhC(CF_3)OC$\underline{H}_3$), 2.95-2.86 (m; H-3) and 2.85-2.67 (m; H-4*ax* and H-4-*eq*).

3.9.2. Reduction of Daljanelin B (13)

Daljanelin D **15**

TFA (200 µl of a 0.1% solution in anhydrous DCM; 1.4 eq.) was added slowly *via* a microsyringe to a stirred suspension of Daljanelin B **13** (1 mg; 1.91 µmol) and Na(CN)BH_3 (*ca.* 0.5 mg; 4.2 eq.) in anhydrous DCM (1 cm^3) at -10°C under N_2. Stirring was continued (1 h.: -10 → 0°C), the reaction quenched with H_2O (excess), the mixture neutralized with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 5 cm^3). The combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (B:A 8:2) of the residue gave Daljanelin D **15** (0.7 mg; 70%; R_f: 0.3).

^{1}H NMR: Plate 52:

δ_H 7.62-7.59/7.50-7.44/7.37-7.33 (3 x m; 5 x H(E)), 7.06 (s; H-4(D)), 7.02 (s; H-7(D)), 6.99 (d, 9; H-6'(B)), 6.88 (d, 8; H-5(A)), 6.50 (d, 8; H-6(A)), 6.45 (dd; 8, 3; H-5'(B)), 6.38 (d, 3; H-3'(B)), 4.24-4.18 (m; 4(A)-C$\underline{H}_2$ and H-2*eq*), 3.94/3.78 (2 x s; 4'(B)-OC$\underline{H}_3$ and 6(D)-OC$\underline{H}_3$), 3.93 (dd; 10, 10; H-2*ax*), 3.49-3.41 (m; H-3(C)) and 3.05-2.87 (m; H-4*ax* and H-4*eq*).

CD: Plate 2 (synthetic *vs.* natural compounds).

3.10. Synthesis of Daljanelin A (12)

Note: all ^{1}H NMR data of products are given in Table 8.2 (derivatives of medicarpin) in Section 4.1. CD spectra are given in Section 4.2.

3.10.1. Bromination of (+)-(6a*S*, 11a*S*)-medicarpin (1)

(6a*S*, 11a*S*)-2,8-Dibromomedicarpin **102**

Note: the purification and isolation described in the two procedures below pertains only to small-scale test reactions. When working on a preparative scale, the excess of bromine was quenched with $Na_2S_2O_3$, and the crude brominated products were methoxymethylated directly after extraction (EtOAc) from the quenched reaction mixture (Section 3.10.2.).

Method 1: Py.HBr.Br_2/MeOH[81,82]

A solution of Py.HBr.Br_2 (130 mg; 2.2 eq.) in MeOH (2 cm^3) was added slowly to a stirred solution of (+)-(6a*S*, 11a*S*)-medicarpin **1** (50 mg; 185 μmol) in MeOH (2 cm^3) at 0°C. The mixture was stirred at 50°C for 45 min., concentrated under reduced pressure, and the residue subjected to PLC (H:B:A 5:4:1) to give the title compound **102** (30 mg; 38%) as a white solid (R_f: 0.4), and 2,4,8-tribromomedicarpin **110** (11 mg; 12%) as a yellow solid (R_f: 0.5).

Method 2: HBr/DMSO[83]

A solution of HBr(c) (3 cm^3) in DMSO (4 cm^3) was added dropwise to a stirred solution of (+)-(6a*S*, 11a*S*)-medicarpin **1** (300 mg; 1.11 mmol) in DMSO (5 cm^3) kept just above freezing point (*ca.* 5°C). The mixture was stirred at r.t. for 1 h., diluted with H_2O, carefully neutralized with Na_2CO_3 (s), the *p*H adjusted to 6 with 3 M HCl, and extracted with EtOAc (3 x 20 cm^3). The combined organic extracts were washed with H_2O (3 x 10 cm^3), dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (H:B:A 5:4:1) gave the title compound **102** (74 mg; 16%; R_f: 0.4) and 8-bromomedicarpin **109** (151 mg; 39%; R_f: 0.3), both as cream-coloured solids.

^{1}H NMR spectra: **109**: Plate 53 / Table 8.2.
102: Plate 54 / Table 8.2.
110: Plate 55 / Table 8.2.

3.10.2. Methoxymethylation

(6a*S*, 11a*S*)-2,8-Dibromo-3-*O*-methoxymethylmedicarpin **103**

(6a*S*, 11a*S*)-2,8-Dibromomedicarpin **102** (30 mg; 70.1 μmol) was methoxymethylated according to general procedure 3.7.3. PLC (H:B:A 5:4:1) gave the title compound **103** (26 mg; 79%) as a colourless oil (R_f: 0.75).

^{1}H NMR: Plate 56 / Table 8.2.

Note: when working on a preparative scale, the crude mixture of phenolic, brominated products (Section 3.10.1.) was methoxymethylated directly, giving the title compound **103** in a typical overall yield of 30%.

3.10.3. Selective lithiation

(6a*S*, 11a*S*)-8-Bromo-3-*O*-methoxymethylmedicarpin **111**

n-BuLi (20 μl of a 1.30 M solution in hexanes; 1.02 eq.) was added *via* a microsyringe to a stirred solution of (6a*S*, 11a*S*)-2,8-dibromo-3-*O*-methoxymethylmedicarpin **103** (12 mg; 25.4 μmol) in anhydrous THF (*ca.* 1 cm^3) under N_2 at -78°C. The mixture was stirred at -78°C for 30 min., quenched with sat. aq. NH_4Cl (excess), warmed to r.t., diluted with H_2O and extracted with EtOAc (4 x 5 cm^3). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (benzene) gave the title compound **111** (2 mg; 20%; R_f: 0.55) and (6a*S*, 11a*S*)-3-*O*-methoxymethylmedicarpin **112** (1 mg; 13%; R_f: 0.45). 2 mg (17%) of the starting material **103** was recovered (R_f: 0.7).

^{1}H NMR spectra: **111**: Plate 57 / Table 8.2.
112: Plate 58 / Table 8.2.

3.10.4. Carboxylation

(6a*S*, 11a*S*)-8-Bromo-2-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **113**

(6a*S*, 11a*S*)-2,8-Dibromo-3-*O*-methoxymethylmedicarpin **103** (45 mg; 95.3 μmol) was dissolved in anhydrous THF (*ca.* 1 cm^3) and the solution was cooled under N_2 to -78°C. *n*-BuLi (64 μl of a 1.64 M solution in hexanes; 1.1 eq.) and TMEDA (35 μl; 2.4 eq.) were added successively *via* microsyringes to the stirred solution, and ethyl chloroformate (45 μl; 4.9 eq.) was added *via* a microsyringe to the mixture 3 min. after the addition of the TMEDA. The resulting mixture was warmed to 0°C and stirred for 90 min., quenched with sat. aq. NH_4Cl (excess), warmed to r.t., diluted with H_2O and extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (benzene) gave the title compound **113** (6 mg; 14%; R_f: 0.15) and 2,8-dibromo-4-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **114** (3 mg; 6%; R_f: 0.25).

^{1}H NMR spectra: **113**: Plate 59 / Table 8.2.
114: Plate 60 / Table 8.2.

3.10.5. Aromatic debromination

(6a*S*, 11a*S*)-2-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **106**

(6a*S*, 11a*S*)-8-Bromo-2-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **113** (3.5 mg; 7.52 μmol) was dissolved in anhydrous THF (*ca.* 0.5 cm^3) and the solution was cooled under N_2 to -78°C. *n*-BuLi (10 μl of a 1.64 M solution in hexanes; 2.2 eq.) and TMEDA (3 μl; 2.6 eq.) were added successively *via* microsyringes to the stirred solution. The resulting mixture was stirred at -78°C for 10 min., warmed to 0°C and quenched immediately with sat. aq. NH_4Cl (excess), warmed to r.t., diluted with H_2O and extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (B:A 95:5) gave the title compound **106** (1 mg; 34%; R_f: 0.6), and 1 mg (29%) of the starting material **113** was recovered (R_f: 0.7).

^{1}H NMR: Plate 61 / Table 8.2.
CD: Plate 3 (*vs.* (+)-(6a*S*, 11a*S*)-medicarpin **1**).

(6a*S*, 11a*S*)-4-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **115**

(6a*S*, 11a*S*)-2,8-Dibromo-4-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **114** (5 mg; 9.19 μmol) was dissolved in anhydrous THF (*ca.* 0.5 cm^3) and the solution was cooled under N_2 to -78°C. *n*-BuLi (18 μl of a 1.60 M solution in hexanes; 3.1 eq.) was added *via* a microsyringe to the stirred solution. The resulting mixture was stirred at -78°C for 10 min., then at 0°C for 45 min., and quenched with sat. aq. NH_4Cl (excess), warmed to r.t., diluted with H_2O and extracted with EtOAc (4 x 5 cm^3). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. PLC (B:A 95:5) gave the title compound **115** (2 mg; 56%; R_f: 0.75).

^{1}H NMR: Plate 62 / Table 8.2.

4. APPENDICES

4.1. Appendix A: ^{1}H NMR spectra

Table 6.1: ^{1}H NMR spectra of monocyclic model compounds: Part 1 – allyl compounds (Plate number shown next to compound number)

Assignment	**38** (1)	**44** (2)	**43** (3)	**49** (4)	**52** (5)	**50** (6)	**51** (7)	**58** (17)	**57** (18)	**60** (19)	**59** (20)
H-2	6.56-6.51 (m)	-	-	-	-	-	-	-	-	-	-
H-3	-	6.41 (d, 2)	6.44 (d, 3)	6.46 (d, 3)	6.45 (d, 2)	6.46 (d, 2)	6.48 (d, 2)	-	6.98 (d, 8)	-	6.49 (s)
H-4	6.56-6.51 (m)	-	-	-	-	-	-	6.51 (dd; 8, 1)	6.44 (dd; 8, 3)	-	-
H-5	7.19 (ddd; 8, 8, 1)	6.53 (dd; 9, 2)	6.52(dd; 9, 3)	6.42 (dd; 9, 3)	6.50 (dd; 9, 2)	6.49 (dd; 9, 2)	6.45 (dd; 8, 2)	7.11 (dd; 8, 8)	-	7.59 (d, 9)	-
H-6	6.56-6.51 (m)	7.40 (d, 9)	7.78 d, 9)	7.61 d, 9)	7.80 (d, 9)	7.79 (d, 9)	7.20 (d, 8)	6.53 (dd; 8, 1)	6.40 (d, 3)	6.71 (d, 9)	7.68 (s)
Ar-OH	-	11.45 (s)	-	12.71 (s)	-	-	-	5.07 (br s)	5.67 (br s)	6.10 (br s)	6.4 (br s)
Ar-CHO	-	9.69 (s)	10.32 (s)	-	-	-	-	-	-	-	-
Ar-C(R)CH_3	-	-	-	2.54 (s)	2.58 (s)	2.54 (s)	1.47 (d, 6)	-	-	2.64 (s)	2.60 (s)
Ar-CH(OH)CH_3	-	-	-	-	-	-	5.02 (q, 6)	-	-	-	-
Ar-CH(OH)CH_3	-	-	-	-	-	-	2.6 (br s)	-	-	-	-
Ar-OCH_3	3.79 (s)	-	-	-	-	3.85 (s)	3.81 (s)	3.83 (s)	3.74 (s)	3.77 (s)	3.87 (s)
allyl group(s):											
1'-CH_2	4.52 (dt; 5, 2)	4.56 (dt; 5, 2)	4.60-4.54 (m, 4 x H)	4.55 (dt; 5, 2)	4.59/4.55 (dt; 5, 2)	4.55 (dt; 5, 2)	4.51 (dt; 5, 2)	3.49 (dt; 6, 2)	3.33 (dt; 6, 2)	3.53 (dt; 6, 2)	3.39 (dt; 6, 2)
H-2'	6.13-6.01 (m)	6.07-5.94 (m)	6.10-5.95 (m, 2 x H)	6.08-5.95 (m)	6.13-5.95 m, 2 x H)	6.08-5.95 (m)	6.10-5.97 (m)	6.08-5.95 (m)	6.05-5.92 (m)	6.13-6.00 (m)	6.07-5.94 (m)
3'-CH_A	5.43 (dq; 17, 2)	5.40 (dq; 17, 2)	5.46-5.27 (m, 4 x H)	5.40 (dq; 17, 2)	5.42/5.40 (dq; 17, 2)	5.40 (dq; 17, 2)	5.40 (dq; 17, 2)	5.14 (dq; 17, 2)	5.15-5.08 (m, 2 x H)	5.15 (dq; 17, 2)	5.22-5.15 (m, 2 x H)
3'-CH_B	5.30 (dq; 11, 2)	5.31 (dq; 10, 2)		5.30 (dq; 10, 2)	5.33-5.27 (m, 2 x H)	5.29 (dq; 11, 2)	5.27 (dq; 10, 2)	5.11 (dq; 10, 2)		5.17 (dq; 10, 2)	

Table 6.2: ^{1}H NMR spectra of monocyclic model compounds: Part 2 (Plate number shown next to compound number)

Assignment	75/76* (26)	80* (28)	81† (29)	82* (30)	85 (34)	87 (37)
H-3	-	-	-	-	6.64 (br d, 8)	6.48 (d, 2)
H-4	6.46 (dd; 8, 1)	6.69-6.55 (m)	6.64/6.62 (dd; 8, 1)	6.95 (dd; 8, 1)	7.45 (dd; 9, 9)	-
H-5	7.18/7.09 (dd; 8, 8)	7.21/7.11 (dd; 8, 8)	7.22/7.21 (dd; 8, 8)	7.31 (dd; 8, 8)	6.81 (dd; 8, 1)	6.46 (dd; 8, 2)
H-6	6.58 (dd; 8, 1)	6.82/6.77 (dd; 8, 1))	6.82/6.80 (dd; 8, 1)	7.02 (dd; 8, 1)	-	7.18 (d, 8)
Ar-OH	5.6 (br s)	-	-	-	-	-
Ar-*O*-R:						
CH_3	3.83 (s)	3.86/3.85 (s)	3.88/3.87 (s)	3.93 (s)	3.92 (s)	3.85 (s) 3.82 (s)
CH_2OCH_3	-	5.22/5.19 (s)	5.23/5.22 (d, 2/1)	-	5.28 (s)	-
CH_2OCH_3	-	3.51/3.50 (s)	3.50/3.49	-	3.52 (s)	-
$COC_6H_3(NO_2)_2$	-	-	-	9.26 (s)	-	-
C_3 fragment:						
1'-CH_n-R	6.49-6.42 (m)	6.69-6.55 (m)	5.10/4.91 (d, 6/9)	6.40 (dd; 7, 5; 2 x H)	-	-
2'-CH-R	6.15 (dq; 17, 6)	6.28/5.97 (dq; 11, 2/6)	4.12-4.02 (m)		-	-
3'-CH_n	1.98/1.67 (dd; 7, 2)	1.95/1.62 (dd; 2/7, 2)	1.26/1.04 (d, 6)	1.74/1.59 (dd; 2/7, 2)	-	-
C_1 fragment:						
CHO	-	-	-	-	10.55 (s)	-
CH_2-OH	-	-	-	-		4.62 (br d, 6)
CH_2-OH	-	-	-	-		2.35 (dt; 6, 2)

Note: signal duplication respectively due to an unresolved *E/Z* mixture (*) and an unresolved diastereomeric mixture (†).

Table 7: ^{1}H NMR spectra of isoflavonoid model compounds (Plate number shown next to compound number)

Assignment	**53** (8)	**7** (9)	**36** (10)	**37** (11)	**54** (12)	**55** (13)	**56** (14)	**64** (21)	**66** (22)	**68** (23)
2-CH_n	7.94 (s)	8.20 (s)	4.65 (2 x d; 8, 6)	*eq*: 4.21 (ddd; 10, 4, 2) *ax*: 3.97 (dd; 10, 10)	8.23 (s)	4.68 (2 x d; 8, 6)	*eq*: 4.24 (ddd; 10, 4, 2) *ax*: 3.99 (dd; 10, 10)	8.27 (s)	4.68 (d, 7)	*eq*: 4.38 (ddd; 11, 4, 2) *ax*: 3.98 (dd; 11, 11)
H-3	-	-	3.92 (dd; 8, 6)	3.17-3.04 (m)	-	3.95 (dd; 8, 6)	3.19-3.09 (m)	-	3.90 (dd; 7, 7)	3.24-3.13 (m)
4-CH_2	-	-	-	2.94-2.86 (m)	-	-	3.01-2.81 (m)	-	-	3.00-2.95 (m)
H-5	8.24 (d, 9)	8.08 (d, 9)	7.76 (d, 9)	6.91 (d, 8)	8.12 (d, 9)	7.80 (d, 9)	7.00 (d, 8)	7.98 (d, 9)	7.66 (d, 9)	6.88 (d, 8)
H-6	7.09 (dd; 9, 2)	7.02 (dd; 9, 2)	6.59 (dd; 9,2)	6.38 (dd; 8,2)	7.11 (dd; 9, 3)	6.69 (dd; 9, 2)	6.49 (dd; 8, 3)	7.08 (d, 9)	6.66 (d, 9)	6.45 (d, 8)
7-OH	-	*	9.6 (br s)	8.25 (s)	-	-	-	*	9.4 (br s)	4.9 (br s)
H-8	6.95 (d, 2)	6.93 (d, 2)	6.42 (d, 2)	6.30 (d, 2)	7.07 (d, 2)	6.55 (d, 2)	6.39 (d, 3)	-	-	-
H-2', H-6'	7.52 (d, 9)	7.57 (d, 9)	7.24 (d, 9)	7.27 (d, 9)	7.58 (d, 9)	7.25 (d, 9)	7.27 d, 9)	7.59 (d, 9)	7.25 (d, 9)	7.19 (d, 9)
H-3', H-5'	6.99 (d, 9)	6.99 (d, 9)	6.90 (d, 9)	6.92 (d, 9)	6.99 (d, 9)	6.91 (d, 9)	6.93 (d, 9)	6.99 (d, 9)	6.89 (d, 9)	6.92 (d, 9)
4'-OCH_3	3.86 (s)	3.89 (s)	3.78 (s)	3.79 (s)	3.84 (s)	3.79 (s)	3.80 (s)	3.84 (s)	3.78 (s)	3.83 (s)
allyl group:										
1''-CH_2	-	-	-	-	4.77 (dt; 5, 2)	4.69 (dt; 5, 2)	4.53 (dt; 5, 2)	3.64 (dt; 6, 2)	3.41 (dt; 6, 2)	3.48 (dt; 6, 2)
H-2''	-	-	-	-	6.20-6.08 (m)	6.18-6.03 (m)	6.14-6.01 (m)	6.10-5.97 (m)	6.02-5.88 (m)	6.09-5.96 (m)
3''-CH_A					5.50 (dq; 17, 2)	5.46 (dq; 17, 2)	5.41 (dq; 17, 2)	5.06 (dq; 17, 2)	5.01 (dq; 17, 2)	5.16 (dq; 17, 2)
3''-CH_B	-	-	-	-	5.34 (dq; 11, 2)	5.31 (dq; 11, 2)	5.24 (dq; 11, 2)	5.00 (dq; 10, 2)	4.94 (dq; 10, 2)	5.12 (dq; 10, 2)
7-*O*-Bn:										
$CH_2C_6H_5$	5.19 (s)	-	-	-	-	-	-	-	-	-
$CH_2C_6H_5$	7.48-7.39 (m)	-	-	-	-	-	-	-	-	-

* Not visible

Table 8.1: ^{1}H NMR spectra of (+)-(6a*S*, 11a*S*)-medicarpin and derivatives: synthesis of Daljanelin B (13) (Plate number shown next to compound number)

Assignment	**1** (15)	**17** (16)	**18** (24)	**73** (25)	**77/78** (27)	**84*** (31)	**20*** (32)	**21** (33)	**22** (35)	**23** (36)
H-1	7.41(d, 9)	7.45 (d; 9)	7.33 (d, 8)	7.57 (d, 9)	7.52 (d, 8)	7.40/7.31 (d, 8)	7.34 (d, 9)	7.45 (d, 9)	7.69 (d, 9)	7.46 (d, 9)
H-2	6.57 (dd; 8, 2)	6.69 (dd; 8, 3)	6.60 (d, 9)	6.97 (d, 8)	6.93 (d, 8)	6.72/6.67 (d, 8)	6.93/6.88 (d, 8)	6.92 (d, 9)	6.94 (d, 9)	6.89 (d, 9)
3-OH	5.0 (br s)	-	5.3 (br s)	-	-	5.66 (br s)	-	-	-	-
H-4	6.44 (d, 3)	6.48 (d, 2)	-	-	-	-	-	-	-	-
H-6*eq*	4.26 (ddd; 11, 5, 1)	4.27 (ddd; 11 5, 1)	4.33-4.28 (m)	4.44-4.35 (m)	4.43-4.38 (m)	4.30 (ddd; 11, 5, 1)	4.34 (ddd; 10, 5, 1)	4.40-4.29 (m)	4.43 (ddd; 10, 4, 1)	4.35 (ddd; 10, 5, 1)
H-6*ax*	3.64 (t; 11, 11)	3.65 (t; 11, 11)	3.61 (t; 11, 10)	3.69-3.59 (m, 2 x H)	3.69 (t; 11, 10)	3.69 (t; 11, 11)	3.65 (t; 11, 10)	3.68-3.58 (m, 2 x H)	3.67 (t; 11, 10)	3.67 (t; 11, 10)
H-6a	3.59-3.51 (m)	3.59-3.51 (m)	3.57-3.51 (m)		3.65-3.59 (m)	3.59-3.48 (m)	3.59-3.56 (m)		3.63-3.57 (m)	3.69-3.54 (m)
H-7	7.15 (d, 9)	7.15 (d, 9)	7.15 (d, 9)	7.18 (d, 9)	7.19 (d, 9)	7.15 (d, 9)	7.16 (d, 8)	7.15 (d, 9)	7.17 (d, 8)	7.16 (d, 9)
H-8	6.48 (dd; 9, 3)	6.48 (dd; 9, 3)	6.47 (dd; 9, 2)	6.50 (dd; 9, 3)	6.50 (dd; 9, 2)	6.47 (dd; 9, 2)	6.48 (dd; 9, 2)	6.48 (dd; 9, 2)	6.49 (dd; 8, 2)	6.48 (dd; 9, 2)
9-OCH_3	3.79 (s)	3.79 (s)	3.79 (s)	3.81 (s)	3.81 (s)	3.79 (s)	3.79 (s)	3.79 (s)	3.79 (s)	3.79 (s)
H-10	6.47 (d, 2)	6.51 (d; 2)	6.47 (d, 2)	6.50 (d, 2)	6.50 (d, 2)	6.47 (d, 2)	6.47 (d, 2)	6.46 (d, 2)	6.47 (d, 2)	6.47 (d, 2)
H-11a	5.52 (d, 6)	5.53 (d; 7)	5.54 (d, 7)	5.60 (d, 5)	5.59 (d, 7)	5.52 (d, 7)	5.54 (d, 6)	5.52 (d, 6)	5.49 (d, 6)	5.54 (d, 6)
3-*O*-R:										
CH_2OCH_3	-	-	-	-	-	-	5.24 (dd; 9, 7)	5.28-5.22 (m)	5.32 (s)	5.26 (dd; 8, 7)
CH_2OCH_3	-	-	-	-	-	-	3.51 (s)	3.50 (s)	3.53 (s)	3.51 (s)
$COC_6H_3(NO_2)_2$	-	-	-	9.34 (s)	9.34 (s)	-	-	-	-	-
C_3 fragment:										
1'-CH_n-R	-	4.55 (dt; 5, 2)	3.48 (dt; (6, 2)	3.44-3.40 (m)	6.40-6.28 (m, 2 x H)	6.43-6.41 (m)	6.64-6.60 (m, 2 x H)	4.92/4.88 (d, 9)	-	-
2'-CH-R	-	6.13-6.00 (m)	6.05-5.92 (m)	5.93-5.80 (m)		6.24-6.12 (m)		4.10-4.00 (m)	-	-
3'-CH_n	-	H_A: 5.44 (dq; 17, 2) H_B: 5.32 (dq; 11, 2)	H_A: 5.14 (dq; 10, 2) H_B: 5.09 (dq; 3, 2)	H_A: 4.89 (dq; 17, 2) H_B: 4.97 (dq; 10, 2)	1.81 (dd; 2, 2)	1.97/1.67 dd; 7, 2)	1.95/1.61 (dd; 3/7, 2)	1.04/1.03 (d, 6)	-	-
C_1 fragment:										
CHO	-	-	-	-	-	-	-	-	10.52 (s)	-
CH_2-OH	-	-	-	-	-	-	-	-	-	4.88-4.75 (m)
CH_2-OH	-	-	-	-	-	-	-	-	-	2.41 (br t)

Note: signal duplication respectively due to an unresolved *E/Z* mixture (*) and an unresolved diastereomeric mixture (').

Table 8.2: ^{1}H NMR spectra of derivatives of (+)-(6a*S*, 11a*S*)-medicarpin: synthesis of Daljanelin A (12) (Plate number shown next to compound number)

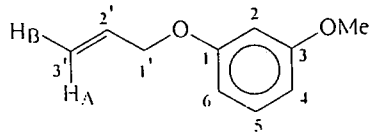
Assignment	**109** (53)	**102** (54)	**110** (55)	**103** (56)	**111** (57)	**112** (58)	**113** (59)	**114** (60)	**106** (61)	**115** (62)
H-1	7.38 (d, 9)	7.62 (s)	7.65 (s)	7.69 (s)	7.43 (d, 9)	7.46 (d, 9)	8.08 (s)	7.83 (s)	8.11 (s)	7.53 (d, 9)
H-2	6.58 (dd; 8, 3)	-	-	-	6.78 (dd; 9, 3)	6.77 (dd; 9, 3)	-	-	-	6.92 (d, 9)
3-OH	5.4 (br s)	5.59 (br s)	6.1 (br s)	-	-	-	-	-	-	-
H-4	6.44 (d, 3)	6.64 (s)	-	6.78 (s)	6.66 (d, 3)	6.66 (d, 3)	6.77 (s)	-	6.77 (s)	-
H-6*eq*	4.25 (ddd; 10, 4, 1)	4.27 (ddd; 10, 4, 1)	4.41 (ddd; 11, 5, 1)	4.28 (ddd; 10, 4, 1)	4.27 (ddd; 10, 4, 1)	4.27 (ddd; 10, 5, 1)	4.32 (dd; 11, 5)	4.46 (dd; 11, 4)	4.32 (ddd; 11, 5, 1)	4.36 (dd; 16, 10)
H-6*ax*	3.66 (t; 11, 10)	3.67 (t; 11, 10)	3.77 (t; 11, 11)	3.68 (t; 10, 10)	3.68 (t; 11, 10)	3.65 (t; 11, 10)	3.72 (t; 11, 11)	3.95 (t; 8, 9)	3.69 (t; 11, 11)	3.75-3.67 (m, 2 x H)
H-6a	3.61-3.54 (m)	3.63-3.57 (m)	3.70-3.61 (m)	3.64-3.57 (m)	3.63-3.56 (m)	3.60-3.52 (m)	3.65-3.58 (m)	3.91-3.88 (m)	3.62-3.56 (m)	
H-7	7.39 (s)	7.39 (s)	7.41 (s)	7.39 (s)	7.39 (s)	7.15 (d, 9)	7.40 (s)	7.56 (s)	7.16 (d, 9)	7.26 (d, 8)
H-8	-	-	-	-	-	6.47 (dd; 9, 2)	-	-	6.49 (dd; 9, 2)	6.48 (dd; 8, 2)
9-OCH_3	3.85 (s)	3.86 (s)	3.87 (s)	3.87 (s)	3.86 (s)	3.79 (s)	3.86 (s)	3.86 (s)	3.79 (s)	3.76 (s)
H-10	6.50 (s)	6.50 (s)	6.50 (s)	6.50 (s)	6.50 (s)	6.47 (d, 2)	6.52 (s)	6.63 (s)	6.48 (d, 2)	6.40 (d, 2)
H-11a	5.55 (d, 7)	5.52 (d, 7)	5.55 (d, 7)	5.53 (d, 7)	5.57 (d, 7)	5.53 (d, 7)	5.56 (d, 7)	5.76 (d, 7)	5.53 (d, 7)	5.60 (d, 6)
3-*O*-R:										
CH_2OCH_3	-	-	-	5.25 (s)	5.18 (dd; 8, 7)	5.18 (dd; 8, 7)	5.26 (s)	5.12 (s)	5.26 (s)	5.24 (s)
CH_2OCH_3	-	-	-	3.52 (s)	3.48 (s)	3.48 (s)	3.53 (s)	3.54 (s)	3.53 (s)	3.44 (s)
Ar-CO_2Et:										
CH_2	-	-	-	-	-	-	4.36 (q, 7)	4.34 (q, 7)	4.36 (q, 7)	4.30 (q, 7)
CH_3	-	-	-	-	-	-	1.41 (t, 7)	1.32 (t, 7)	1.41 (t, 7)	1.30 (t, 7)

Table 9: ^{1}H NMR spectra of benzofuranoid compounds (Plate number shown next to compound number)

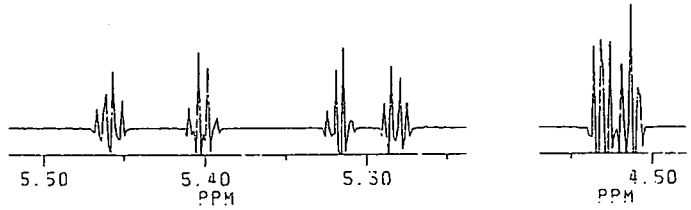
Assignment	**28** (40)	**29** (41)	**30** (42)	**95** (45)	**97** (46)	**98** (47)
2-CH_n	4.59 (s)	4.62 (s)	7.22 (s)	7.13 (s)	4.74 (dd; 9, 4)	4.60 (dd; 8, 5)
3-CH_n	-	-	-	-	-	-
H-4	6.92 (s)	7.37 (s)	7.27 (s)	7.73 (s)	-	-
H-5	-	-	-	-	5.99 (d, 2)	6.05 (d, 2)
H-6	-	-	-	-	-	-
H-7	6.79 (s)	6.61 (s)	6.96 (s)	7.57 (s)	6.14 (d, 2)	6.16 (d, 2)
Ar-*O*-R:						
H	7.9 (br s)	-	-	-	-	-
CH_3	3.99 (s)	3.97 (s)	3.92 (s)	3.97 (s)	3.91/3.86/ 3.79 (3 x s)	3.81/3.79/ 3.61 (3 x s)
CH_2OCH_3	-	5.19 (s)	5.25 (s)	5.28 (s)	-	-
CH_2OCH_3	-	3.51 (s)	3.57 (s)	3.57 (s)	-	-
3-R						
OH	-	-	-	-	-	2.45 (br s)
$OSi(CH_3)_2C(CH_3)_3$	-	-	1.03 (s)	-	-	-
$OSi(CH_3)_2C(CH_3)_3$	-	-	0.23 (s)	-	-	-
C_6H_5	-	-	-	7.65-7.62/ 7.53-7.47/ 7.41-7.35 (3 x m)	-	7.47-7.43/ 7.39-7.25 (2 x m)
2-$CH_2C_6H_4(OCH_3)$:						
CH_2	-	-	-	-	3.31/2.92 (2 x dd; 15, 4/9)	3.13/3.12 2 x br d, 8/5)
H-2', H-6'	-	-	-	-	7.24 (d, 9)	7.18 (d, 9)
H-3', H-5'	-	-	-	-	6.84 (d, 9)	6.83 (d, 9)

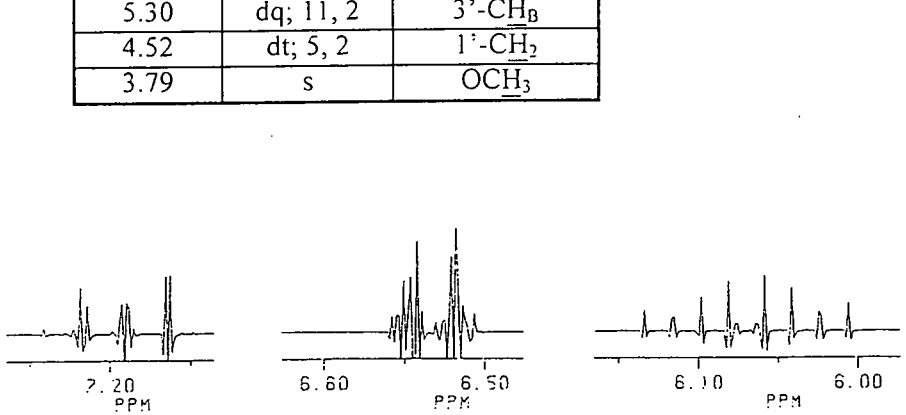
Plate 1: 1-*O*-Allyl-3-methoxyphenol **38**

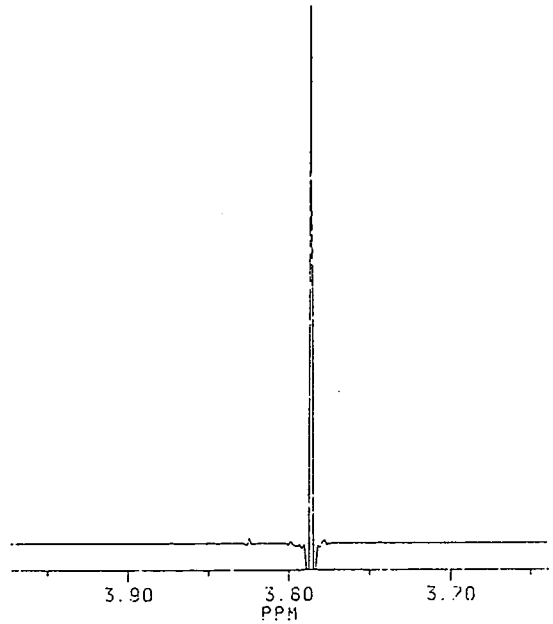
($CDCl_3$)



δ_H	Signal	Assignment
7.19	ddd; 8, 8, 1	H-5
6.56-6.51	m	H-2, H-4, H-6
6.13-6.01	m	H-2'
5.43	dq; 17, 2	3'-CH_A
5.30	dq; 11, 2	3'-CH_B
4.52	dt; 5, 2	1'-CH_2
3.79	s	OCH_3







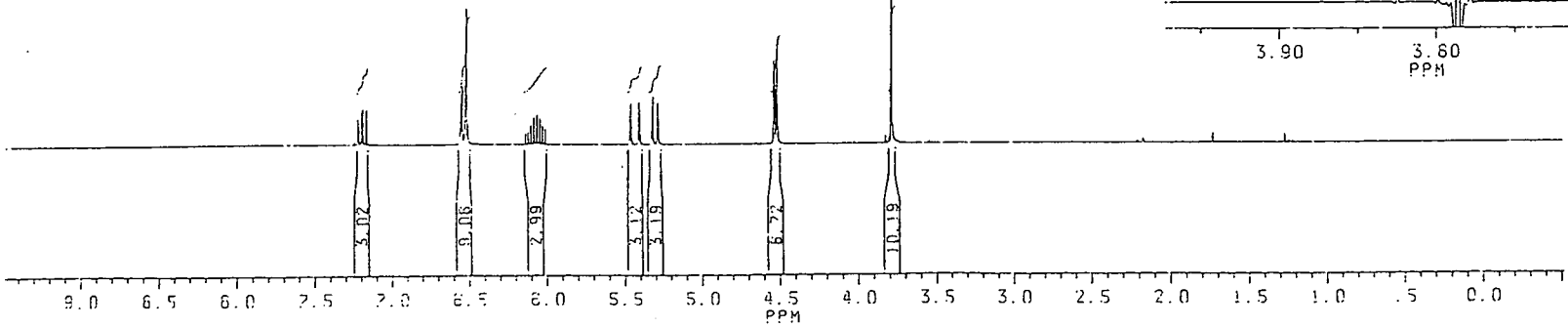
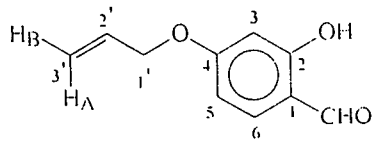


Plate 2: 4-Allyloxy-2-hydroxybenzaldehyde 44

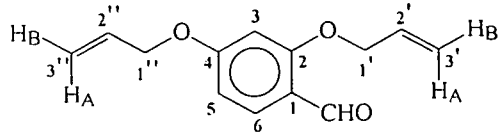
($CDCl_3$)



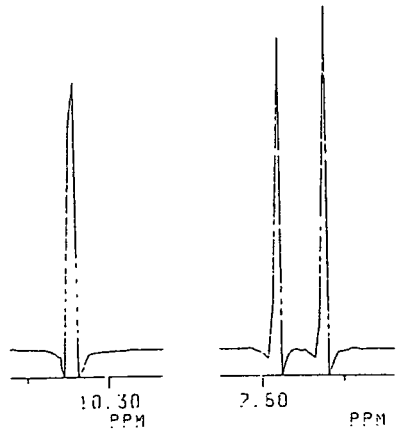
δ_H	Signal	Assignment
11.45	s	O<u>H</u>
9.69	s	C<u>H</u>O
7.40	d, 9	H-6
6.53	dd; 9, 2	H-5
6.41	d, 2	H-3
6.07-5.94	m	H-2'
5.40	dq; 17, 2	3'-C<u>H</u>$_A$
5.31	dq; 10, 2	3'-C<u>H</u>$_B$
4.56	dt; 5, 2	1'-C<u>H</u>$_2$

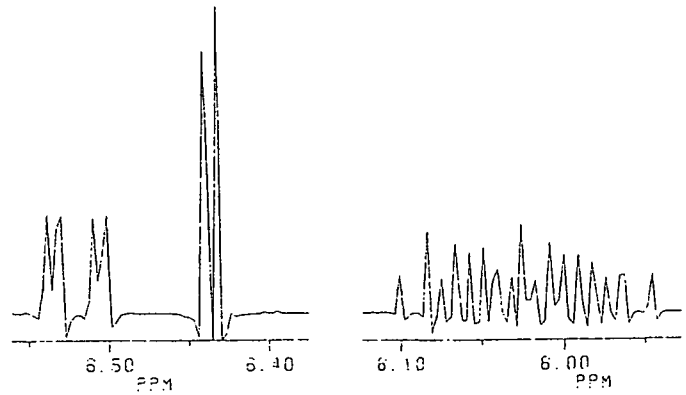
Plate 3: 2,4-Diallyloxybenzaldehyde **43**

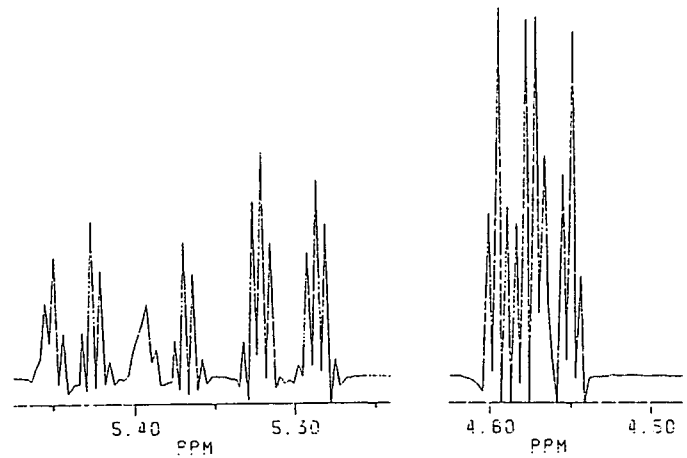
($CDCl_3$)



δ_H	Signal	Assignment
10.32	s	C<u>H</u>O
7.78	d, 9	H-6
6.52	dd; 9, 3	H-5
6.44	d, 3	H-3
6.10-5.95	m	H-2', H-2''
5.46-5.27	m	3'-C<u>H</u>$_2$, 3''-C<u>H</u>$_2$
4.60-4.54	m	1'-C<u>H</u>$_2$, 1''-C<u>H</u>$_2$







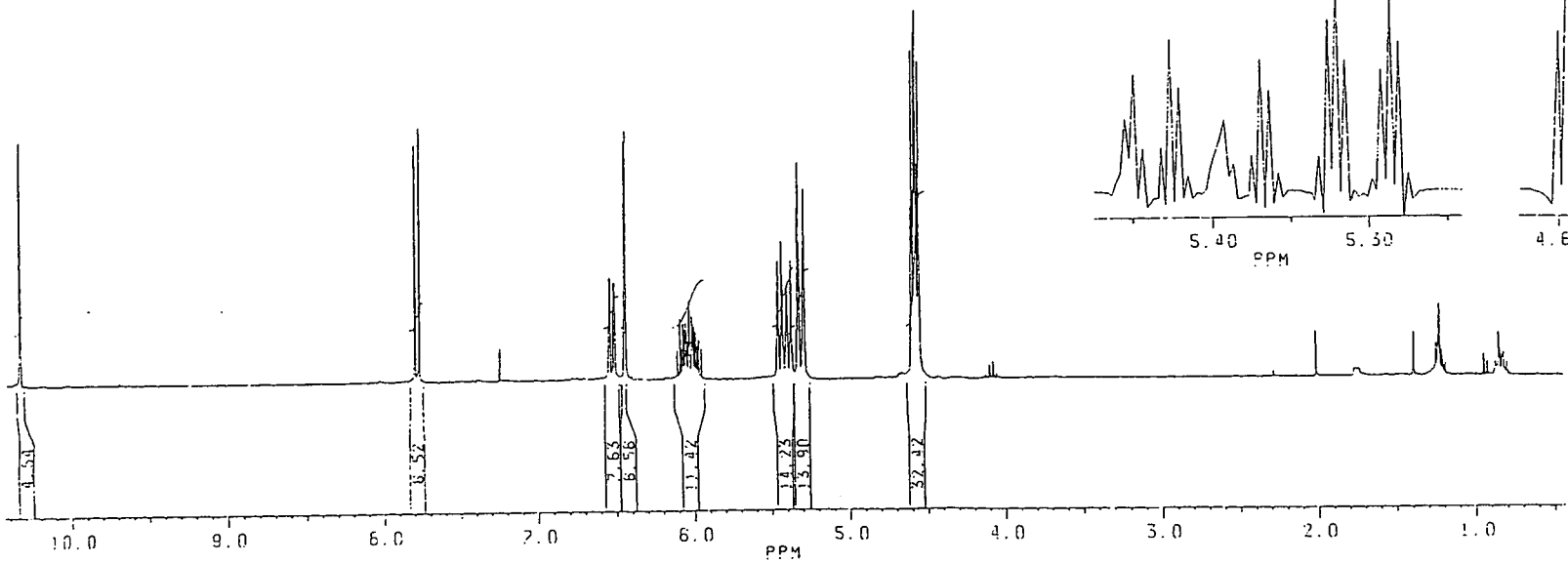
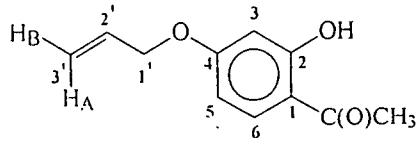
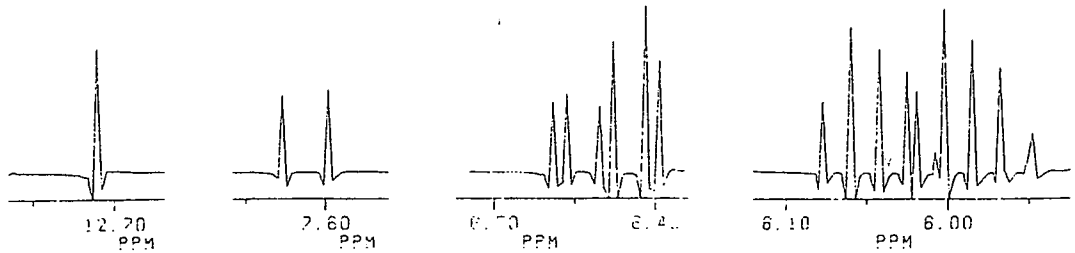


Plate 4: 4-Allyloxy-2-hydroxyacetophenone **49**

($CDCl_3$)



δ_H	Signal	Assignment
12.71	s	O<u>H</u>
7.61	d, 9	H-6
6.46	d, 3	H-3
6.42	dd; 9, 3	H-5
6.08-5.95	m	H-2'
5.40	dq; 17, 2	3'-C<u>H</u>$_A$
5.30	dq; 10, 2	3'-C<u>H</u>$_B$
4.55	dt; 5, 2	1'-C<u>H</u>$_2$
2.54	s	C(O)C<u>H</u>$_3$



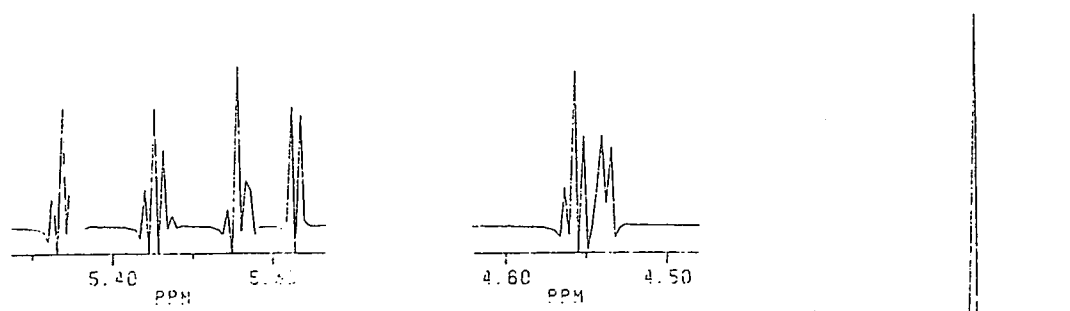
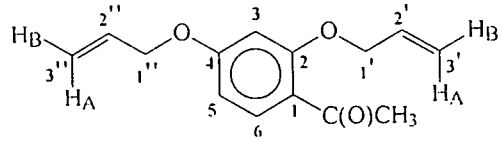


Plate 5: 2,4-Diallyloxyacetophenone **52**

($CDCl_3$)



δ_H	Signal	Assignment
7.80	d, 9	H-6
6.50	dd; 9, 2	H-5
6.45	d, 2	H-3
6.13-5.95	m	H-2', H-2''
5.42/5.40	dq; 17, 2	3'-CH_A, 3''-CH_A
5.33-5.27	m	3'-CH_B, 3''-CH_B
4.59/4.55	dt; 5, 2	1'-CH_2, 1''-CH_2
2.58	s	$C(O)CH_3$

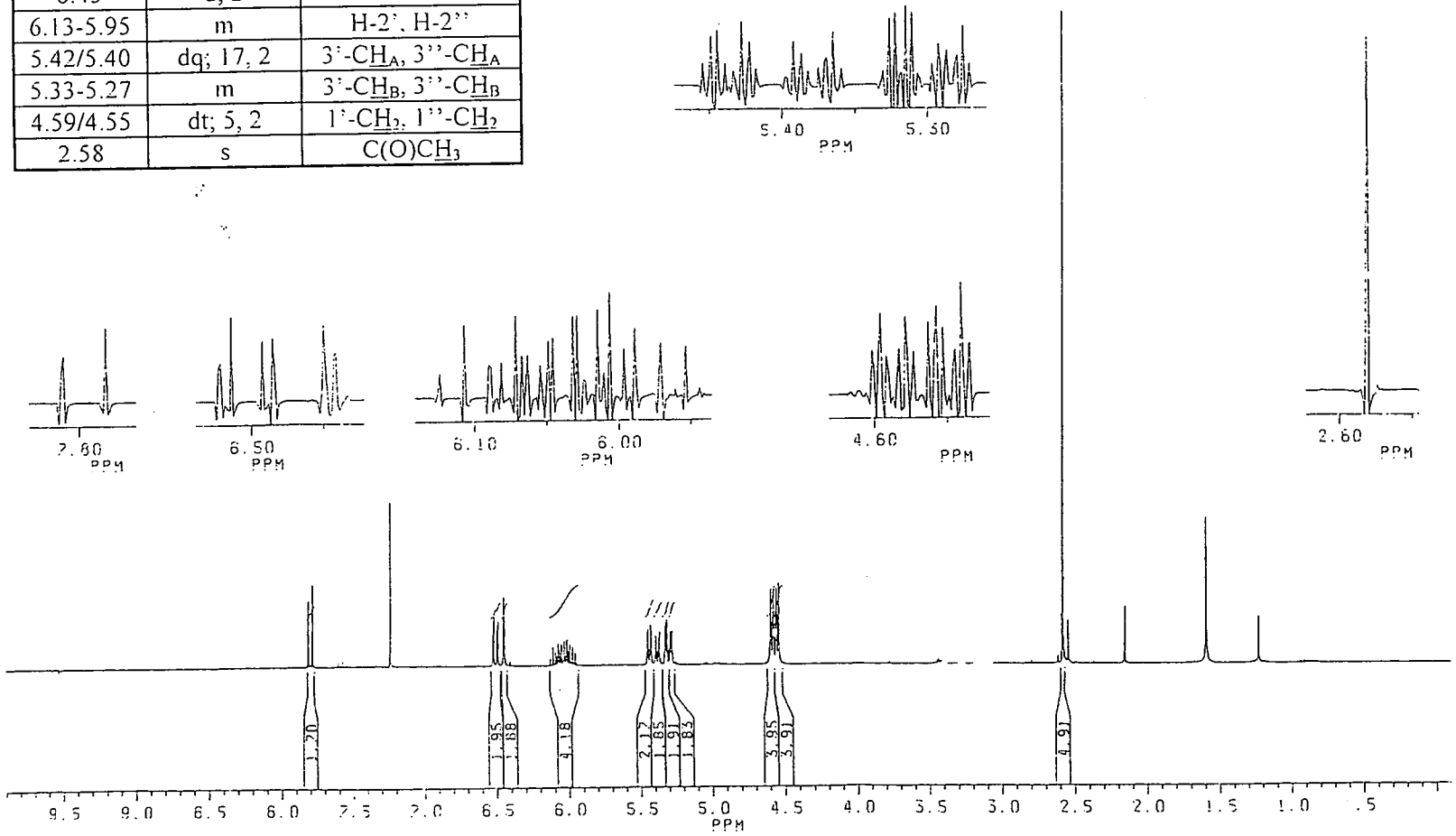
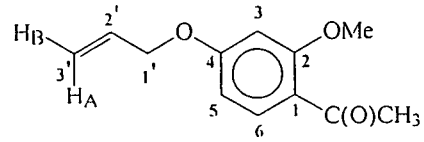


Plate 6: 4-Allyloxy-2-methoxyacetophenone **50**

($CDCl_3$)



δ_H	Signal	Assignment
7.79	d, 9	H-6
6.49	dd; 9, 2	H-5
6.46	d, 2	H-3
6.08-5.95	m	H-2'
5.40	dq; 17, 2	3'-C<u>H</u>$_A$
5.29	dq; 11, 2	3'-C<u>H</u>$_B$
4.55	dt; 5, 2	1'-C<u>H</u>$_2$
3.85	s	OC<u>H</u>$_3$
2.54	s	C(O)C<u>H</u>$_3$

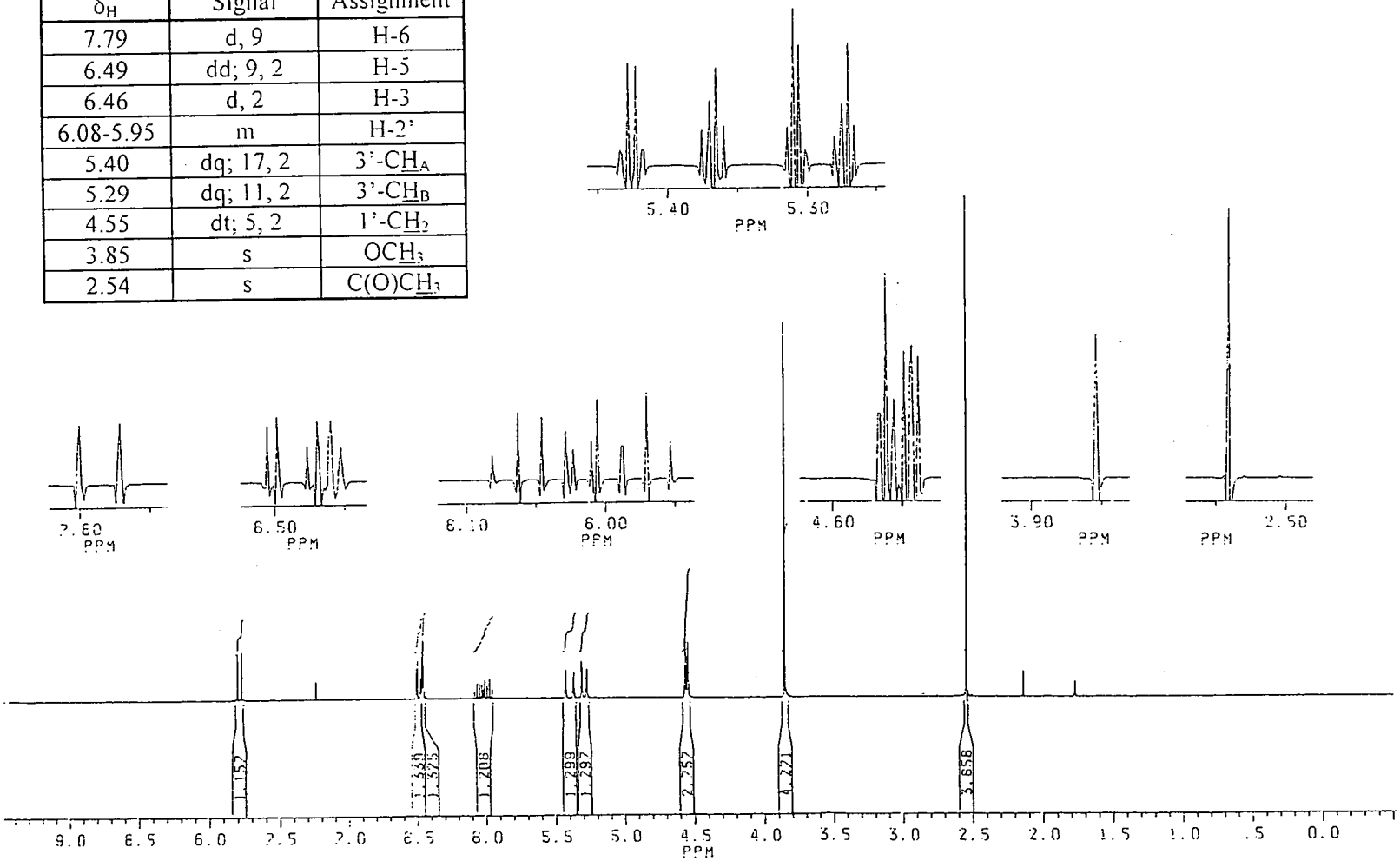
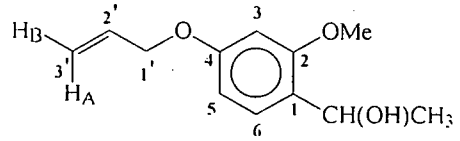


Plate 7: 1-(4-Allyloxy-2-methoxy)phenylethanol **51**

($CDCl_3$)



δ_H	Signal	Assignment
7.20	d, 8	H-6
6.48	d, 2	H-3
6.45	dd; 8, 2	H-5
6.10-5.97	m	H-2'
5.40	dq; 17, 2	3'-C<u>H</u>$_A$
5.27	dq; 10, 2	3'-C<u>H</u>$_B$
5.02	q, 6	C<u>H</u>(OH)CH$_3$
4.51	dt; 5, 2	1'-C<u>H</u>$_2$
3.81	s	OC<u>H</u>$_3$
2.6	br s	CH(O<u>H</u>)CH$_3$
1.47	d, 6	CH(OH)C<u>H</u>$_3$

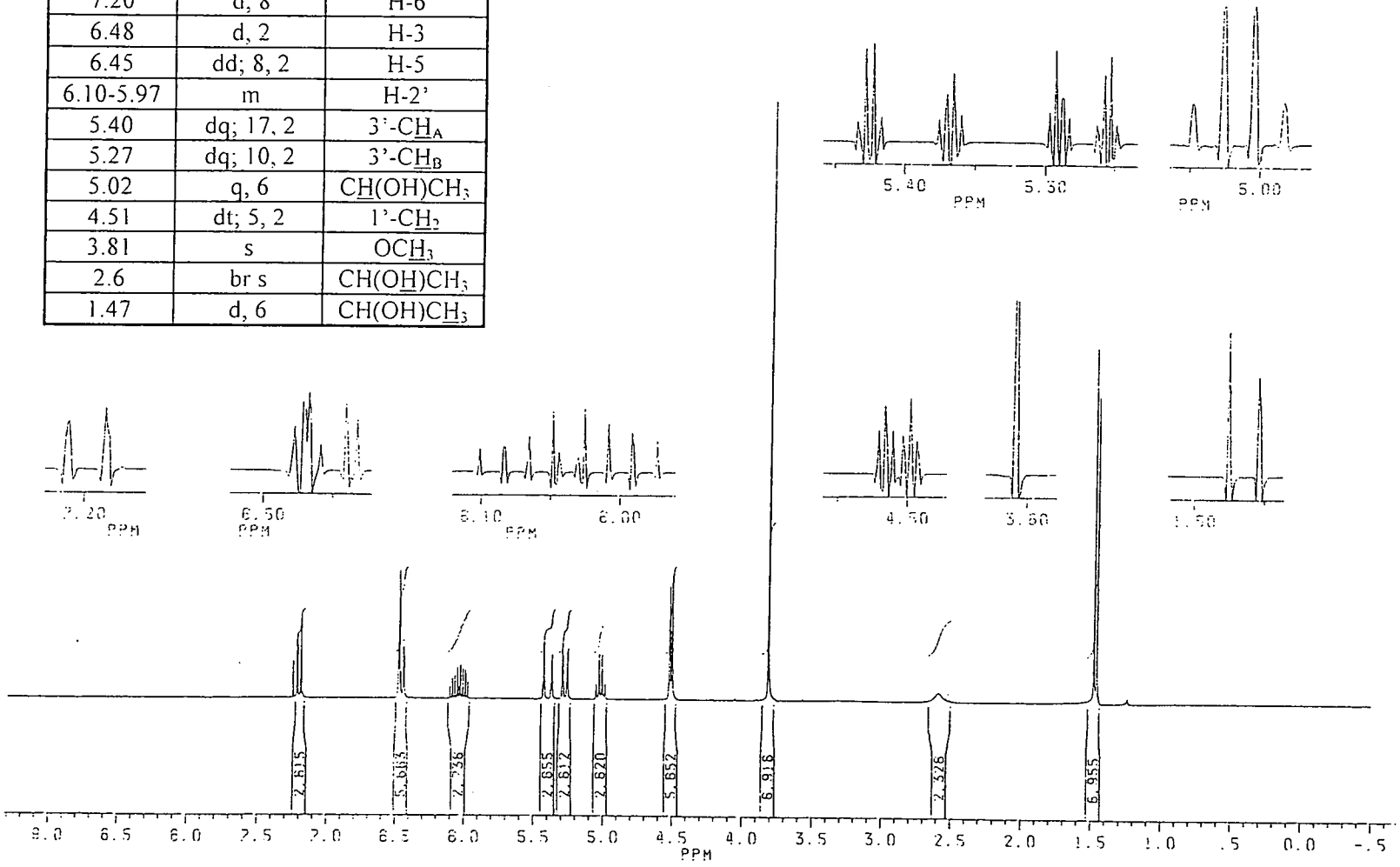
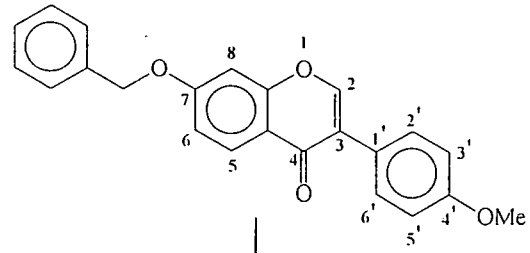


Plate 8: 7-*O*-Benzyl-4'-methoxyisoflavone 53

($CDCl_3$)



δ_H	Signal	Assignment
8.24	d, 9	H-5
7.94	s	H-2
7.52	d, 9	H-2', H-6'
7.48-7.39	m	$CH_2C_6H_5$
7.09	dd; 9, 2	H-6
6.99	d, 9	H-3', H-5'
6.95	d, 2	H-8
5.19	s	$CH_2C_6H_5$
3.86	s	OCH_3

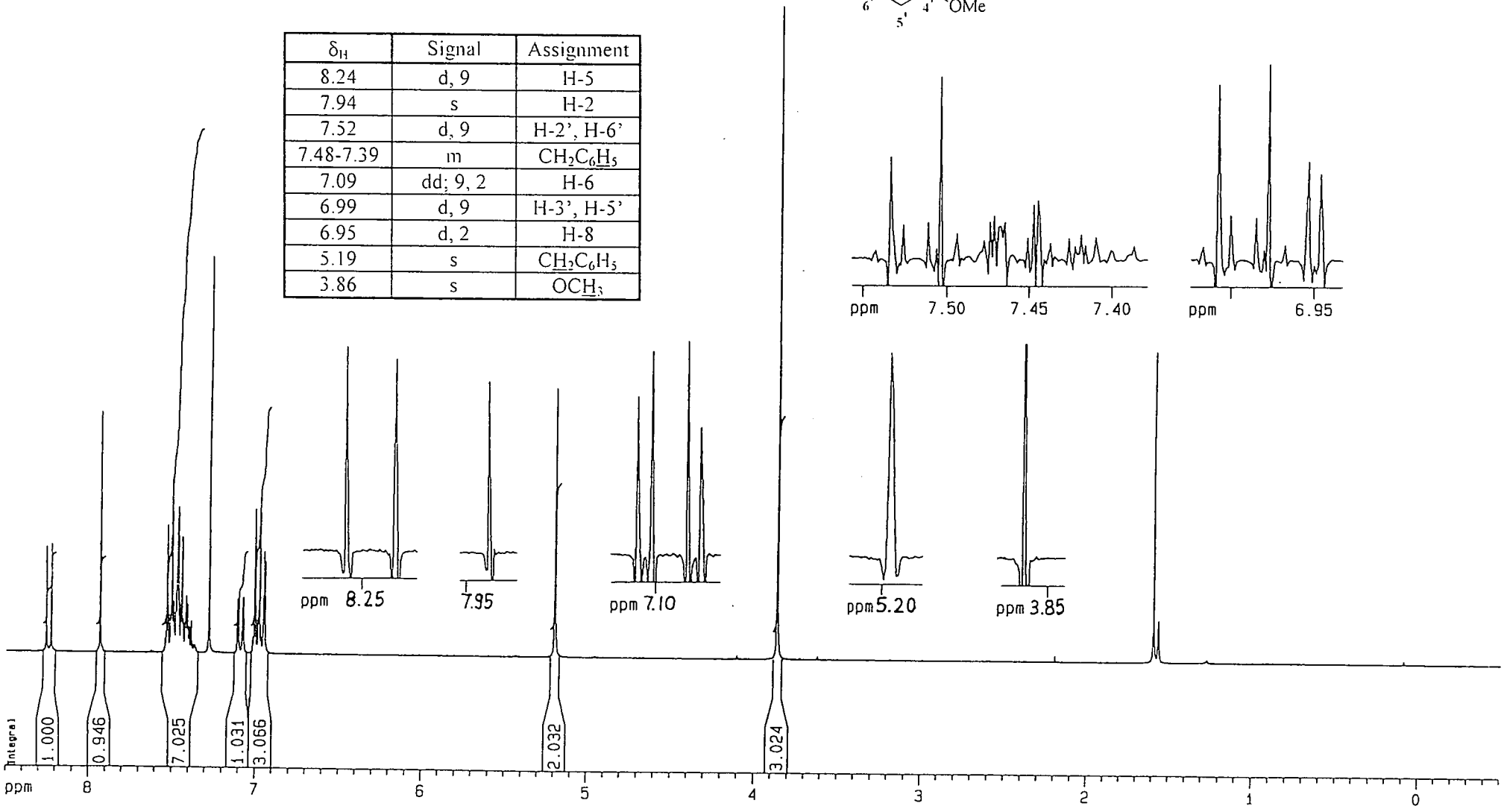
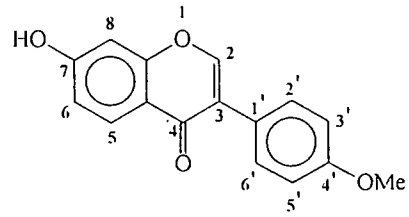


Plate 9: 7-Hydroxy-4'-methoxyisoflavone (formononetin) 7

[$(CD_3)_2CO$]



δ_H	Signal	Assignment
8.20	s	H-2
8.08	d, 9	H-5
7.57	d, 9	H-2', H-6'
7.02	dd; 9, 2	H-6
6.99	d, 9	H-3', H-5'
6.93	d, 2	H-8
3.89	s	OCH_3

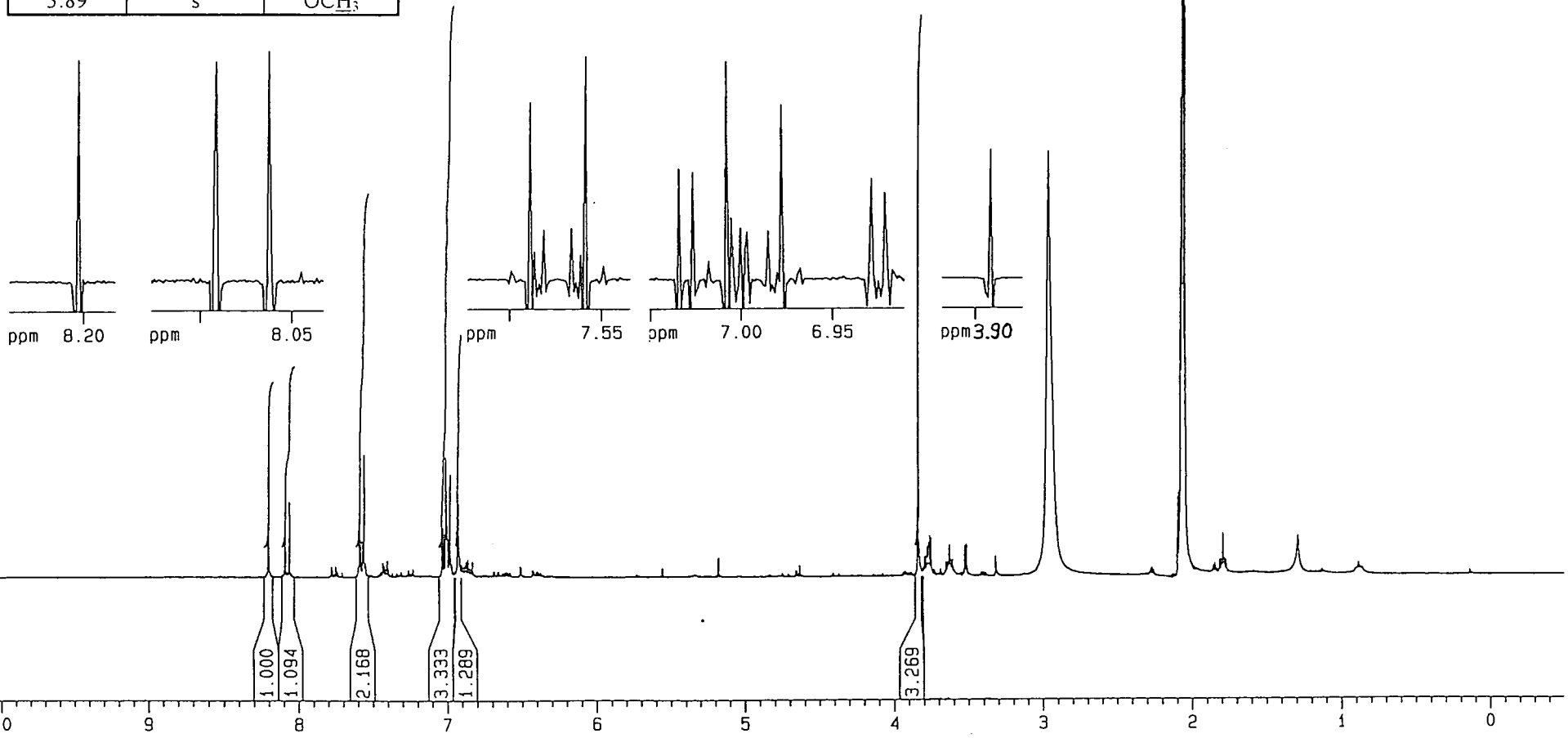
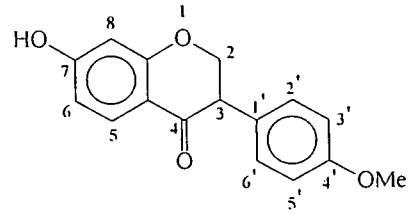


Plate 10: 7-Hydroxy-4'-methoxyisoflavanone 36

$[(CD_3)_2CO]$



δ_H	Signal	Assignment
9.6	br s	OH
7.76	d, 9	H-5
7.24	d, 9	H-2', H-6'
6.90	d, 9	H-3', H-5'
6.59	dd; 9, 2	H-6
6.42	d, 2	H-8
4.65	2 x d; 8, 6	$2\text{-}CH_2$
3.92	dd; 8, 6	H-3
3.78	s	OCH_3

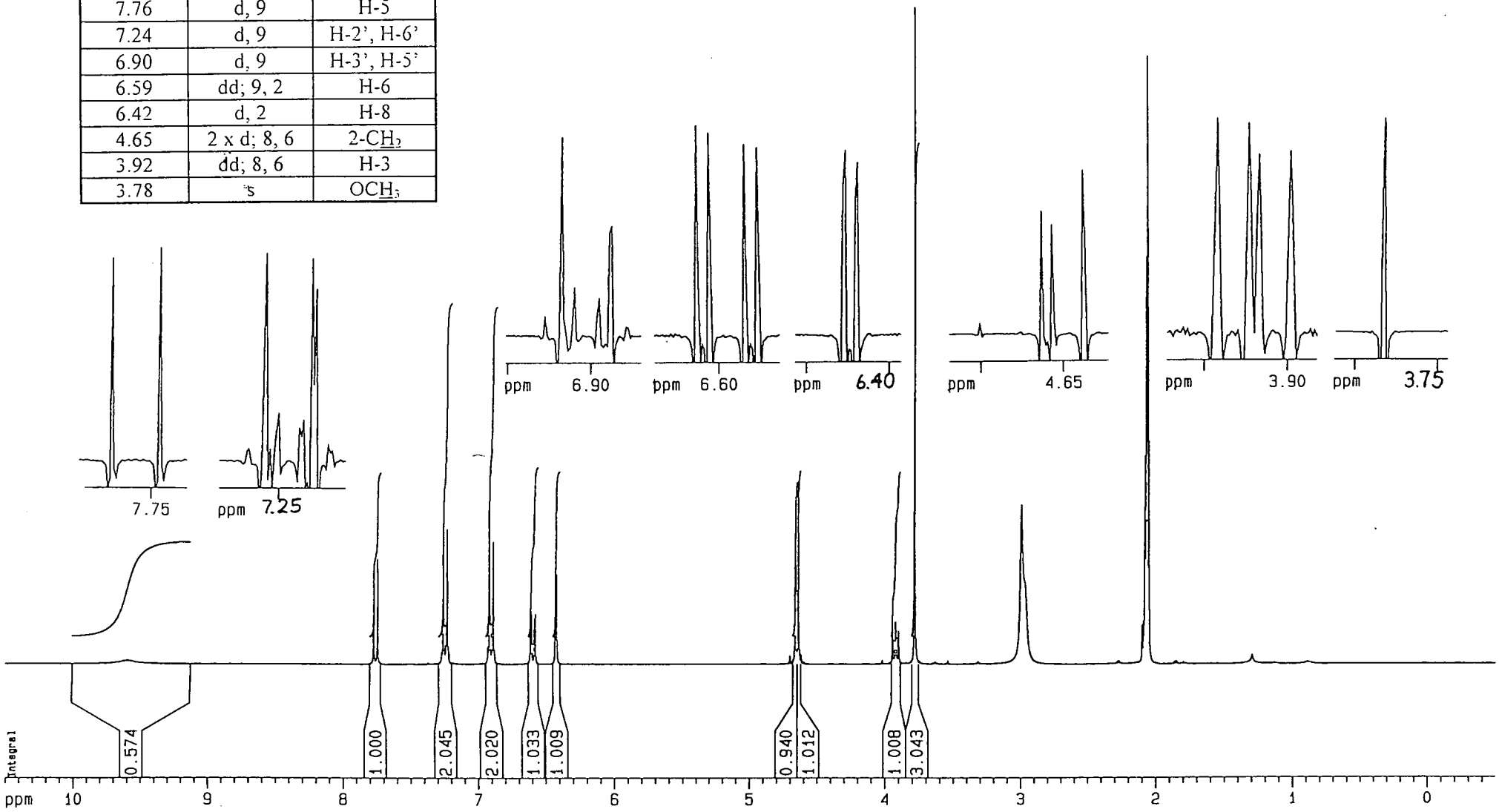
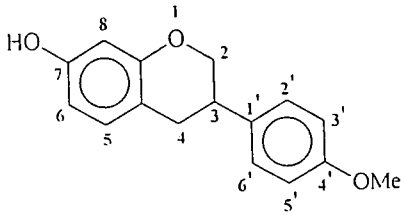


Plate 11: 7-Hydroxy-4'-methoxyisoflavan **37**

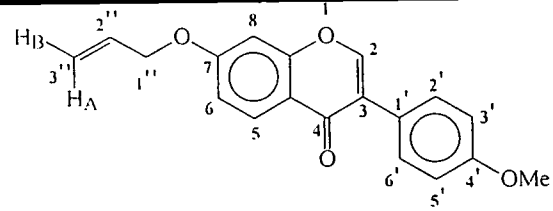
[$(CD_3)_2CO$]



δ_H	Signal	Assignment
8.25	s	OH
7.27	d, 9	H-2', H-6'
6.92	d, 9	H-3', H-5'
6.91	d, 8	H-5
6.38	dd; 8, 2	H-6
6.30	d, 2	H-8
4.21	ddd; 10, 4, 2	H-2*eq*
3.97	dd; 10, 10	H-2*ax*
3.79	s	OCH_3
3.17-3.04	m	H-3
2.94-2.86	m	4-CH_2

Plate 12: 7-Allyloxy-4'-methoxyisoflavone **54**

$[(CD_3)_2CO]$



δ_H	Signal	Assignment
8.23	s	H-2
8.12	d, 9	H-5
7.58	d, 9	H-2', H-6'
7.11	dd; 9, 3	H-6
7.07	d, 2	H-8
6.99	d, 9	H-3', H-5'
6.20-6.08	m	H-2''
5.50	dq; 17, 2	3''-C$\underline{H}_A$
5.34	dq; 11, 2	3''-C$\underline{H}_B$
4.77	dt; 5, 2	1''-C$\underline{H}_2$
3.84	s	OC$\underline{H}_3$

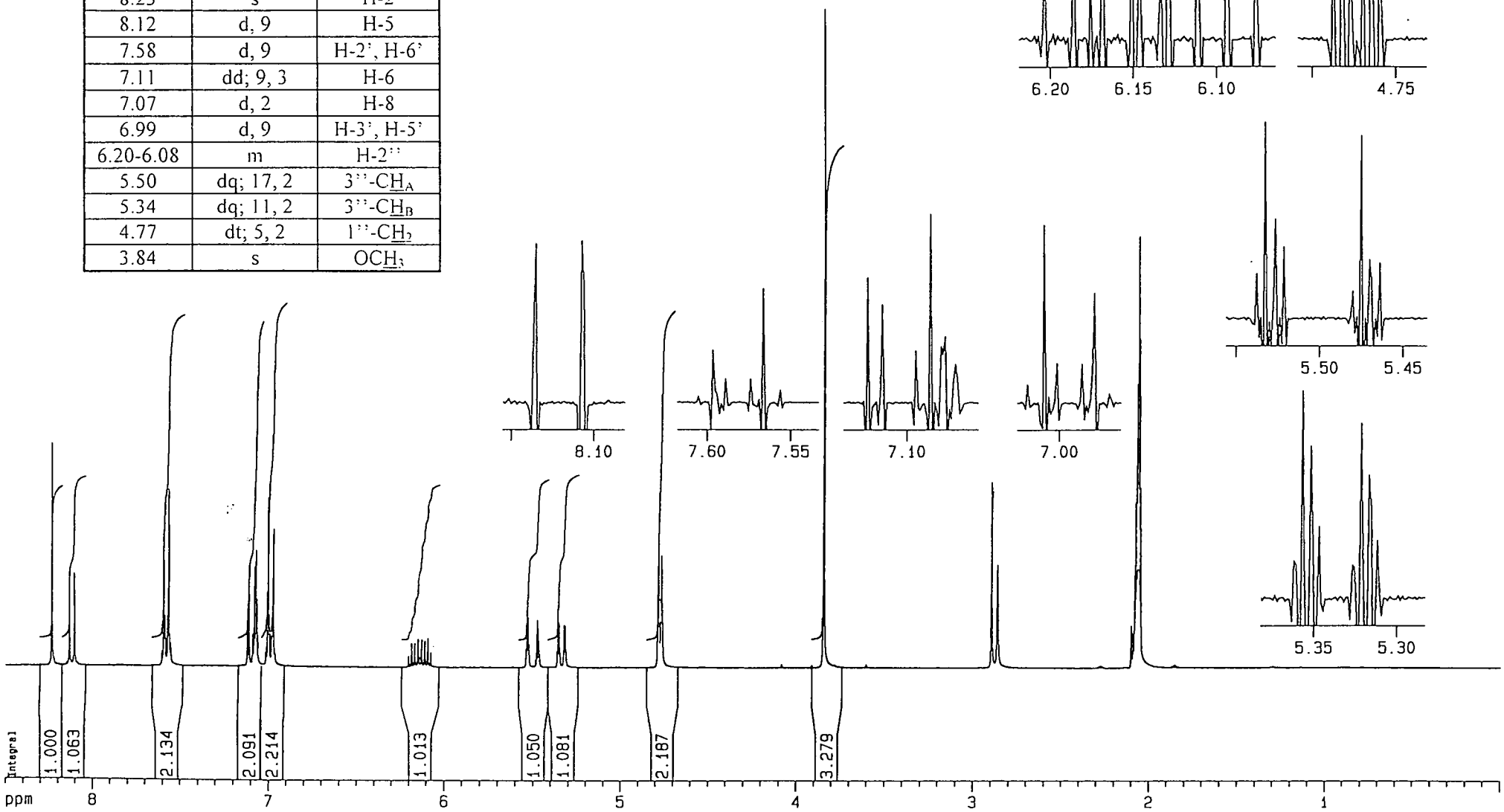
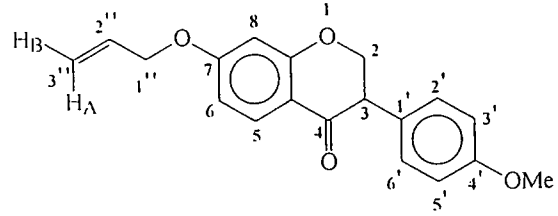
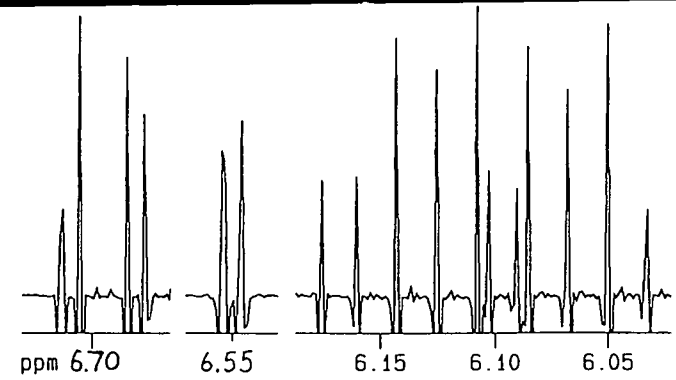


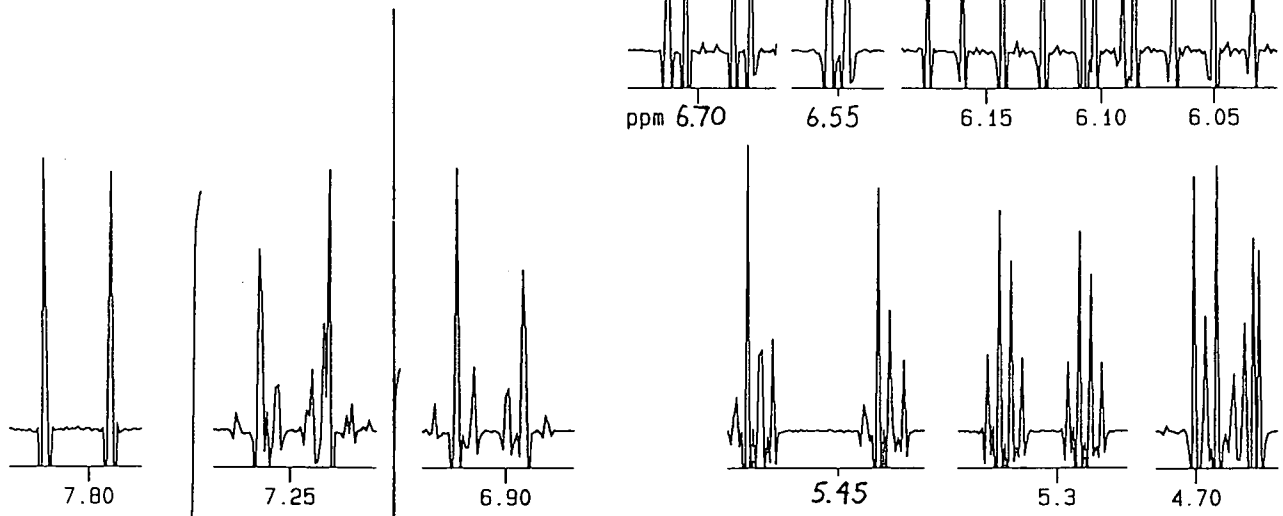
Plate 13: 7-Allyloxy-4'-methoxyisoflavanone 55

[$(CD_3)_2CO$]



δ_H	Signal	Assignment
7.80	d, 9	H-5
7.25	d, 9	H-2', H-6'
6.91	d, 9	H-3', H-5'
6.69	dd; 9, 2	H-6
6.55	d, 2	H-8
6.18-6.03	m	H-2''
5.46	dq; 17, 2	3''-CH_A
5.31	dq; 11, 2	3''-CH_B
4.69	dt; 5, 2	1''-CH_2
4.68	2 x d; 8, 6	2-CH_2
3.95	dd; 8, 6	H-3
3.79	s	OCH_3





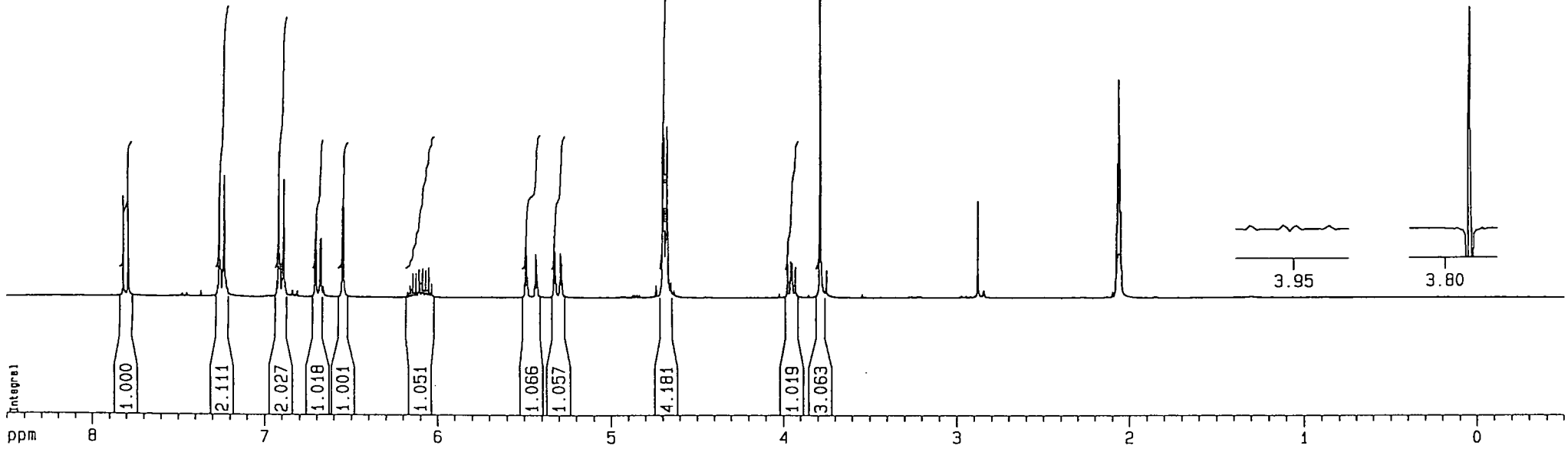
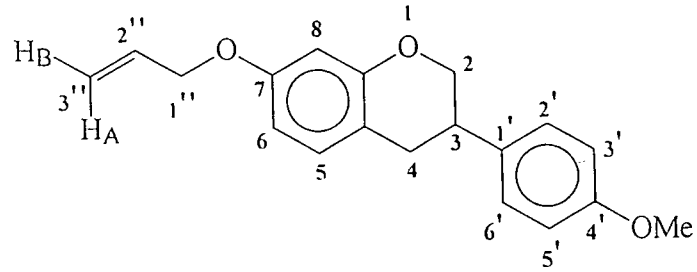
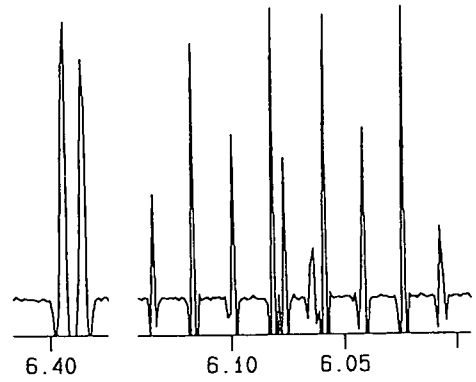


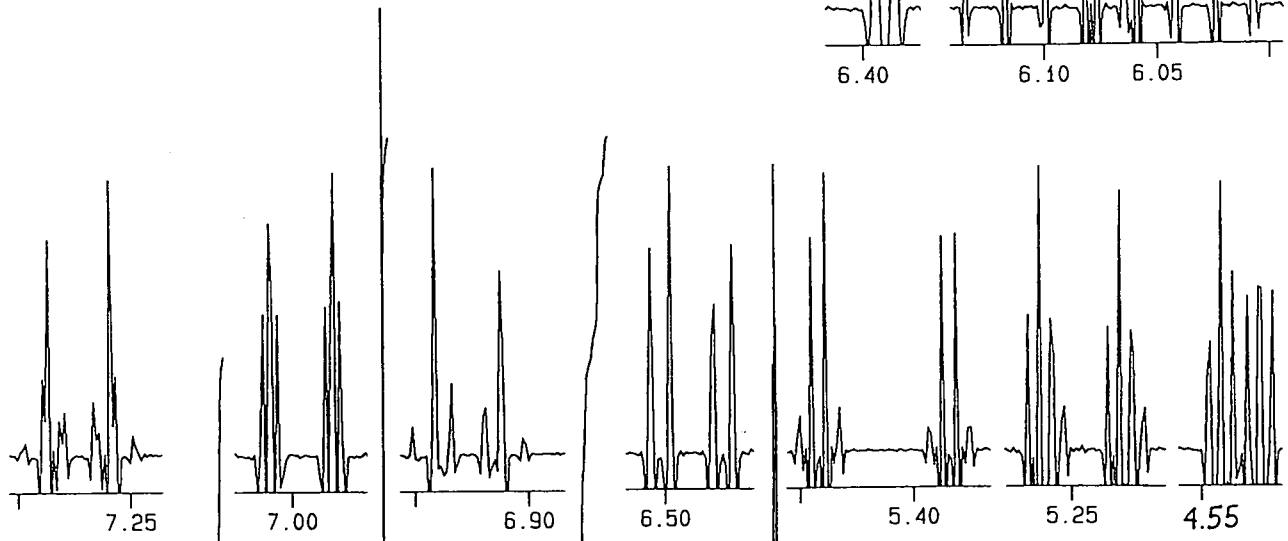
Plate 14: 7-Allyloxy-4'-methoxyisoflavan 56

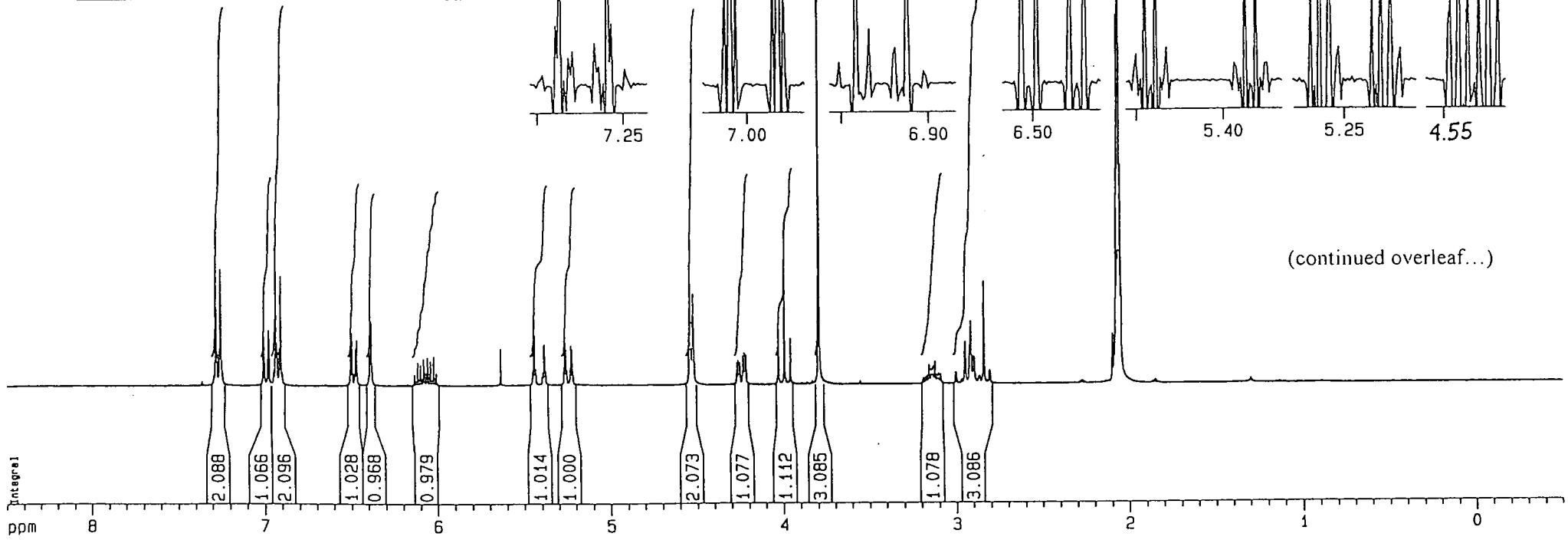
[$(CD_3)_2CO$]

δ_H	Signal	Assignment
7.27	d, 9	H-2', H-6'
7.00	d, 8	H-5
6.93	d, 9	H-3', H-5'
6.49	dd; 8, 3	H-6
6.39	d, 3	H-8
6.14-6.01	m	H-2''
5.41	dq; 17, 2	3''-C$\underline{H}_A$
5.24	dq; 11, 2	3''-C$\underline{H}_B$
4.53	dt; 5, 2	1''-C$\underline{H}_2$
4.24	ddd; 10, 4, 2	H-2*eq*
3.99	dd; 10, 10	H-2*ax*
3.80	s	OC$\underline{H}_3$
3.19-3.09	m	H-3
3.01-2.81	m	4-C$\underline{H}_2$





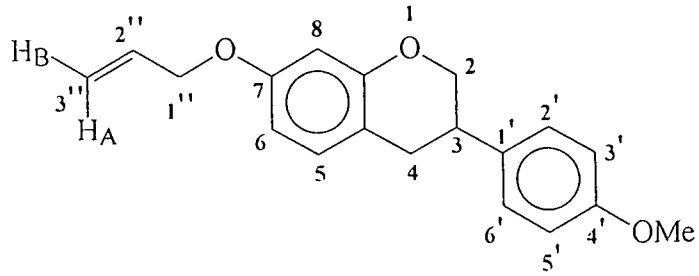




(continued overleaf...)

Plate 14: 7-Allyloxy-4'-methoxyisoflavan 36

(continued)



δ_H	Signal	Assignment
7.27	d, 9	H-2', H-6'
7.00	d, 8	H-5
6.93	d, 9	H-3', H-5'
6.49	dd; 8, 3	H-6
6.39	d, 3	H-8
6.14-6.01	m	H-2''
5.41	dq; 17, 2	3''-C$\underline{H}_A$
5.24	dq; 11, 2	3''-C$\underline{H}_B$
4.53	dt; 5, 2	1''-C$\underline{H}_2$
4.24	ddd; 10, 4, 2	H-2*eq*
3.99	dd; 10, 10	H-2*ax*
3.80	s	O$\underline{CH}_3$
3.19-3.09	m	H-3
3.01-2.81	m	4-C$\underline{H}_2$

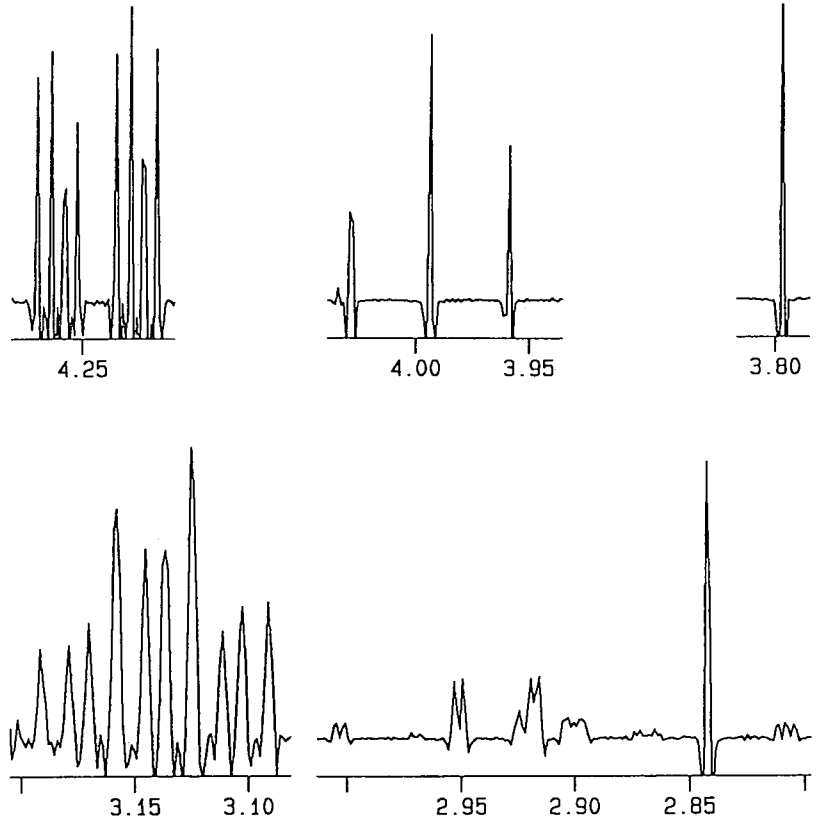
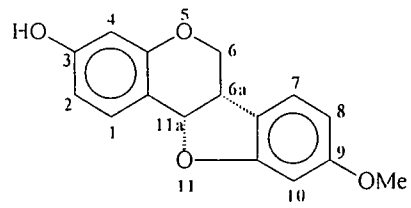


Plate 15: (+)-(6a*S*, 11a*S*)-Medicarpin **1**

($CDCl_3$)

δ_H	Signal	Assignment
7.41	d, 9	H-1
7.15	d, 9	H-7
6.57	dd; 8, 2	H-2
6.48	dd; 9, 3	H-8
6.47	d, 2	H-10
6.44	d, 3	H-4
5.52	d, 6	H-11a
5.0	br s	OH
4.26	ddd; 11, 5, 1	H-6*eq*
3.79	s	OCH_3
3.64	t; 11, 11	H-6*ax*
3.59-3.51	m	H-6a



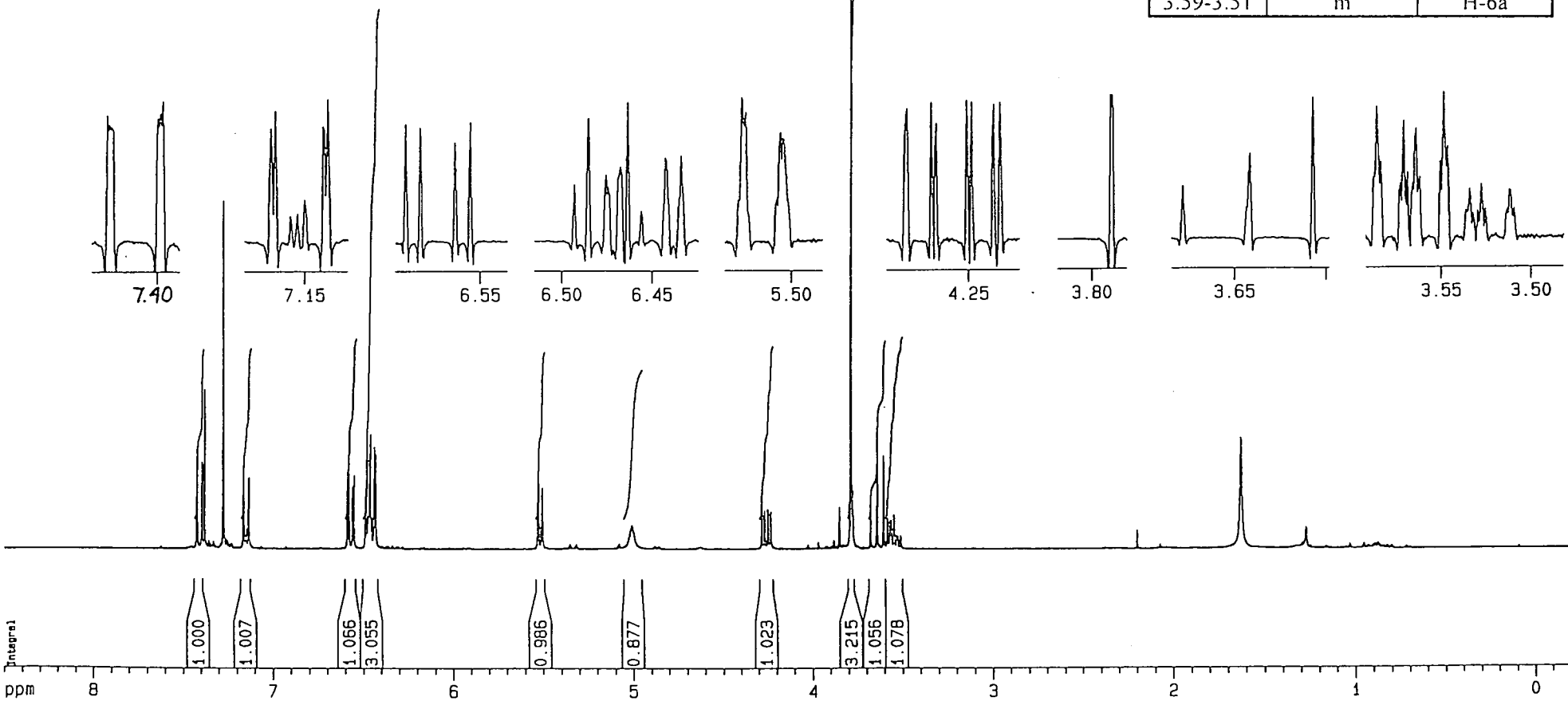
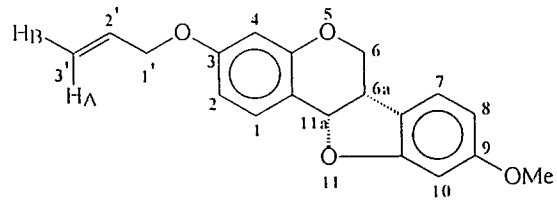
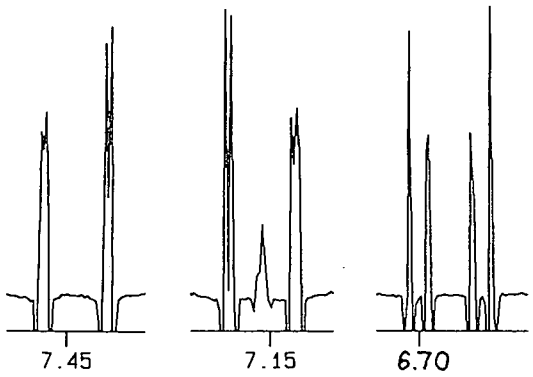


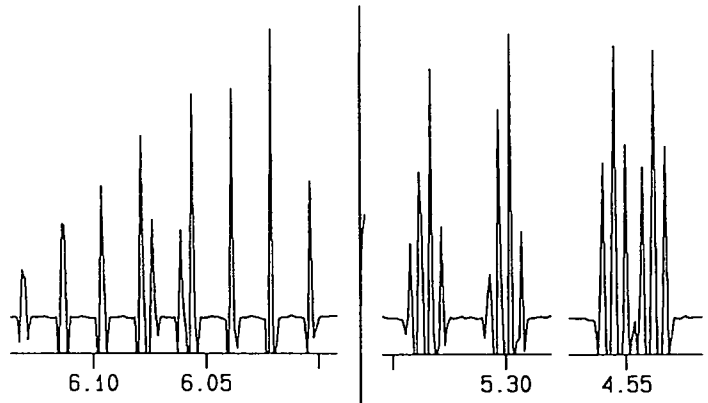
Plate 16: (6aS, 11aS)-3-*O*-Allylmedicarpin 17

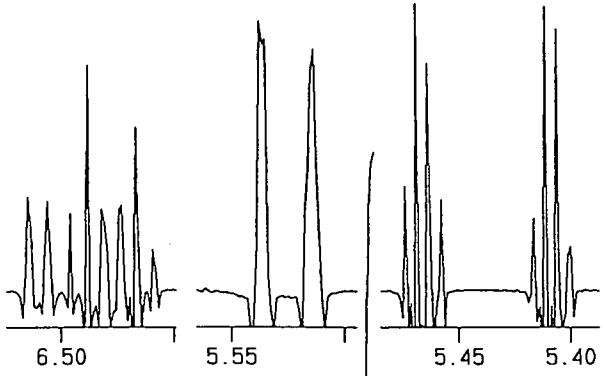
($CDCl_3$)

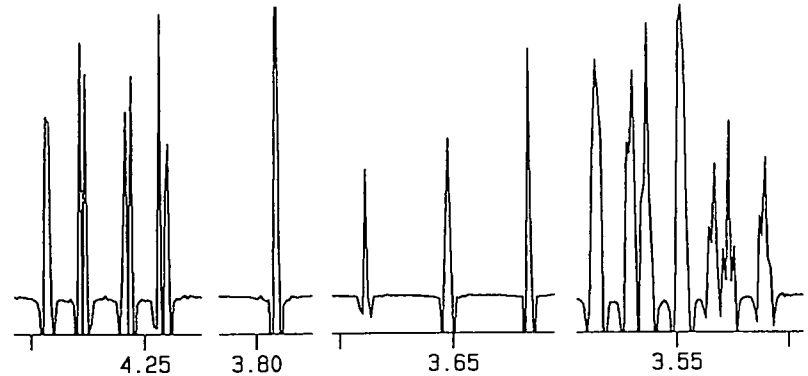


δ_H	Signal	Assignment
7.45	d, 9	H-1
7.15	d, 9	H-7
6.69	dd; 8, 3	H-2
6.51	d, 2	H-10
6.48	dd; 9, 3	H-8
6.48	d, 2	H-4
6.13-6.00	m	H-2'
5.53	d, 7	H-11a
5.44	dq; 17, 2	3'-C$\underline{H}_A$
5.32	dq; 11, 2	3'-C$\underline{H}_B$
4.55	dt; 5, 2	1'-C$\underline{H}_2$
4.27	ddd; 11, 5, 1	H-6*eq*
3.79	s	O$\underline{CH}_3$
3.65	t; 11, 11	H-6*ax*
3.59-3.51	m	H-6a

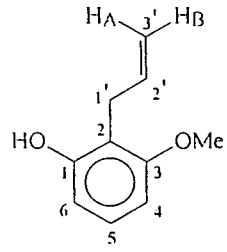








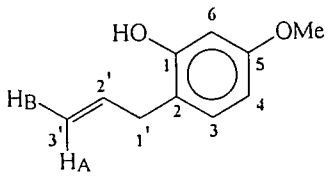
(CDCl$_3$)



δ_H	Signal	Assignment
7.11	dd; 8, 8	H-5
6.53	dd; 8, 1	H-6
6.51	dd; 8, 1	H-4
6.08-5.95	m	H-2'
5.14	dq; 17, 2	3'-C$\underline{H}_A$
5.11	dq; 10, 2	3'-C$\underline{H}_B$
5.07	br s	O$\underline{H}$
3.83	s	OC$\underline{H}_3$
3.49	dt; 6, 2	1'-C$\underline{H}_2$

Plate 18: 2-Allyl-5-methoxyphenol **57**

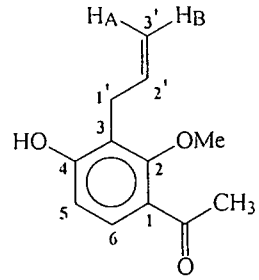
($CDCl_3$)



δ_H	Signal	Assignment
6.98	d, 8	H-3
6.44	dd; 8, 3	H-4
6.40	d, 3	H-6
6.05-5.92	m	H-2'
5.67	br s	O<u>H</u>
5.15-5.08	m	3'-C<u>H</u>$_A$, 3'-C<u>H</u>$_B$
3.74	s	OC<u>H</u>$_3$
3.33	dt; 6, 2	1'-C<u>H</u>$_2$

Plate 19: 3-Allyl-4-hydroxy-2-methoxyacetophenone 60

($CDCl_3$)



δ_H	Signal	Assignment
7.59	d, 9	H-5
6.71	d, 9	H-6
6.13-6.00	m	H-2'
6.10	br s	O<u>H</u>
5.17	dq; 10, 2	3'-C<u>H</u>$_B$
5.15	dq; 17, 2	3'-C<u>H</u>$_A$
3.77	s	OC<u>H</u>$_3$
3.53	dt; 6, 2	1'-C<u>H</u>$_2$
2.64	s	C(O)C<u>H</u>$_3$

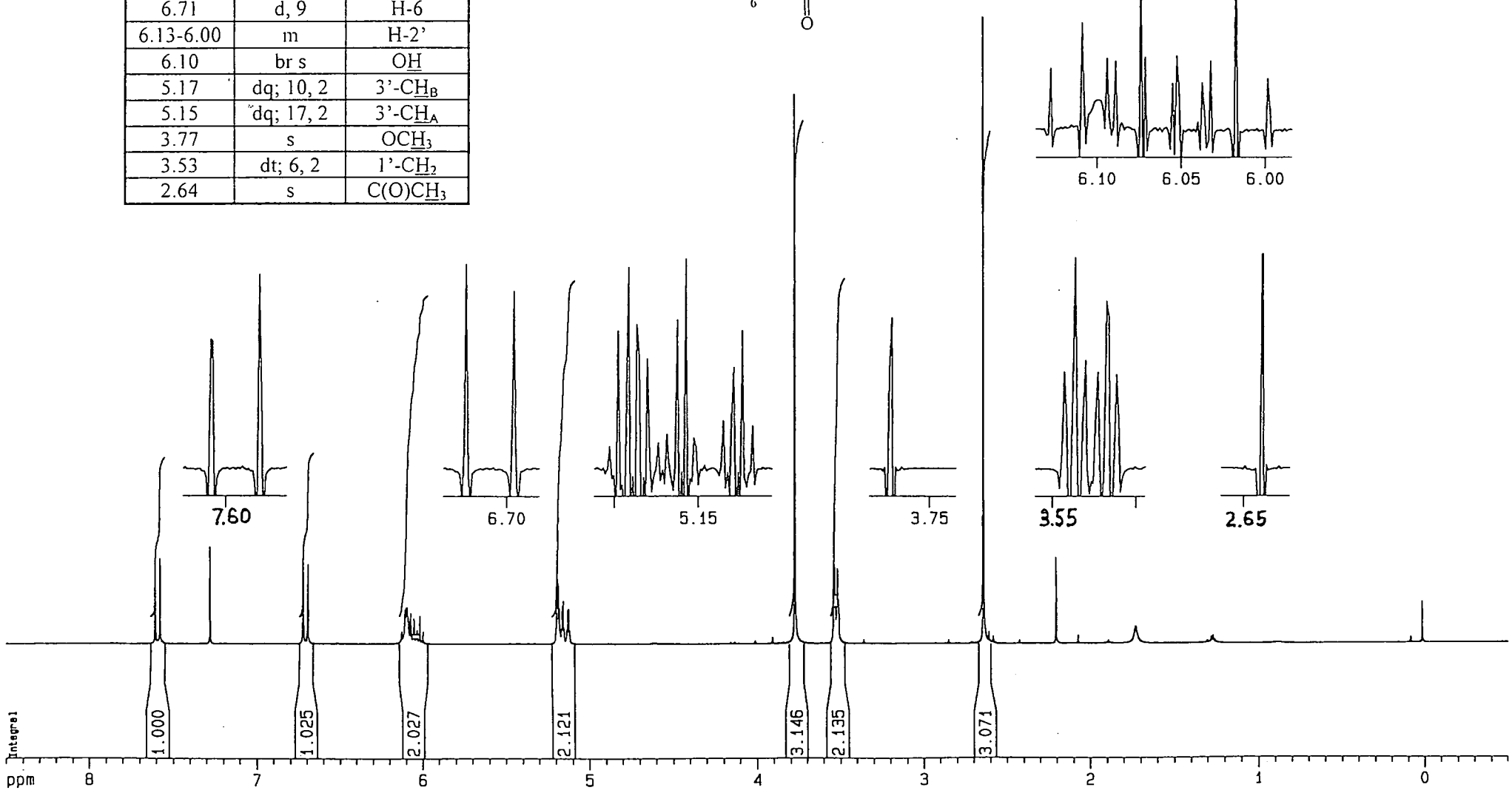
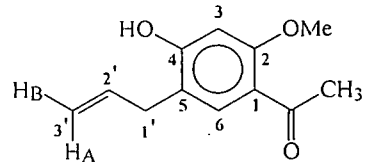


Plate 20: 5-Allyl-4-hydroxy-2-methoxyacetophenone **59**

($CDCl_3$)



δ_H	Signal	Assignment
7.68	s	H-6
6.49	s	H-3
6.4	br s	OH
6.07-5.94	m	H-2'
5.22-5.15	m	3'-CH_A, 3'-CH_B
3.87	s	OCH_3
3.39	dt; 6, 2	1'-CH_2
2.60	s	C(O)CH_3

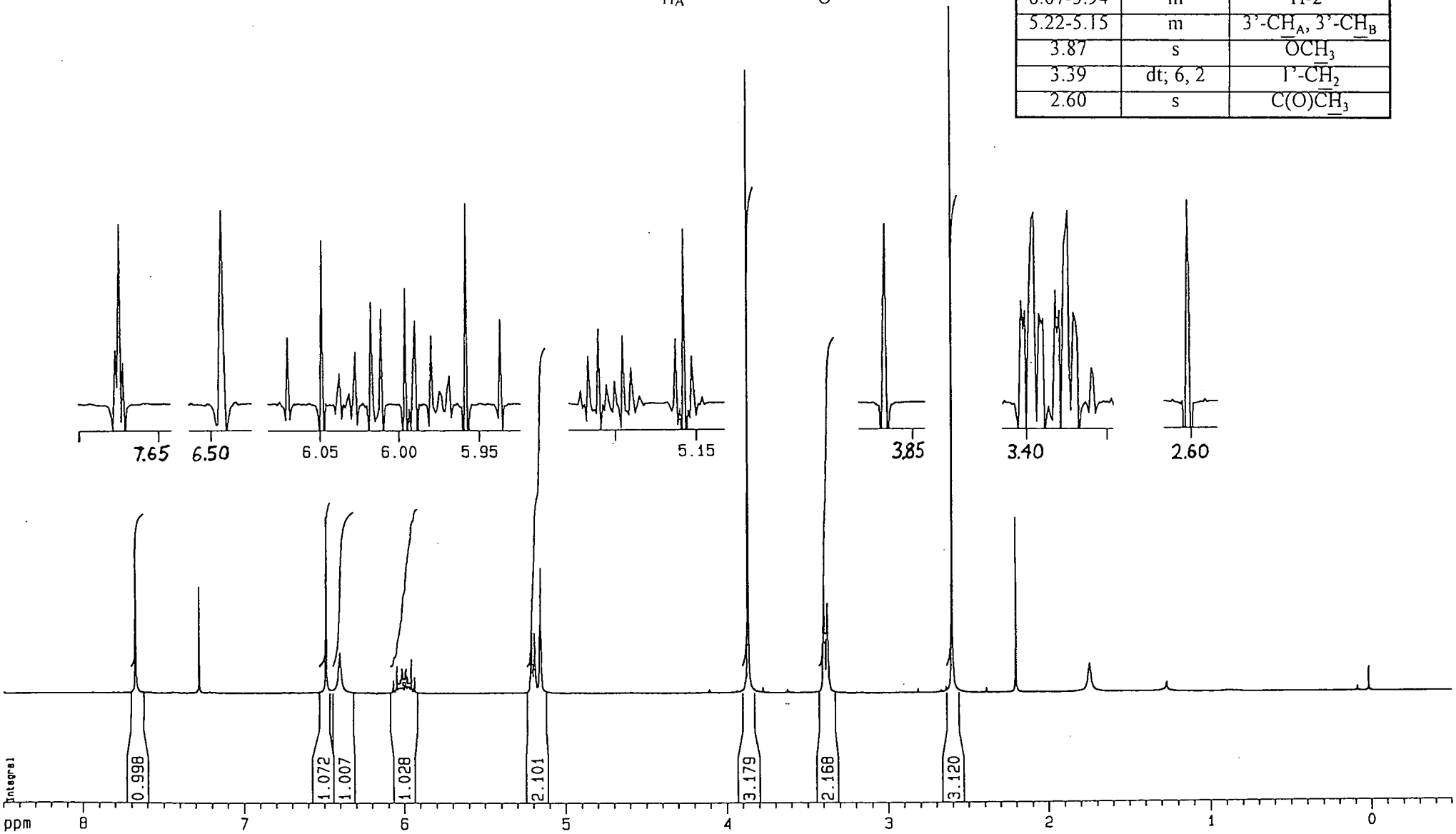
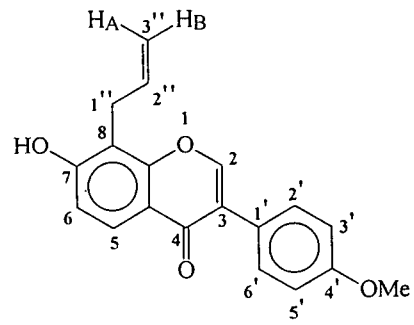


Plate 21: 8-Allyl-7-hydroxy-4'-methoxyisoflavone **64**

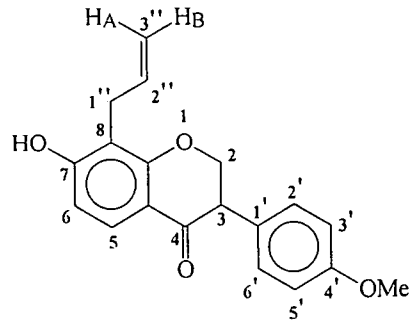
$[(CD_3)_2CO]$



δ_H	Signal	Assignment
8.27	s	H-2
7.98	d, 9	H-5
7.59	d, 9	H-2', H-6'
7.08	d, 9	H-6
6.99	d, 9	H-3', H-5'
6.10-5.97	m	H-2''
5.06	dq; 17, 2	3''-C<u>H</u>$_A$
5.00	dq; 10, 2	3''-C<u>H</u>$_B$
3.84	s	OC<u>H</u>$_3$
3.64	dt; 6, 2	1''-C<u>H</u>$_2$

Plate 22: 8-Allyl-7-hydroxy-4'-methoxyisoflavanone **66**

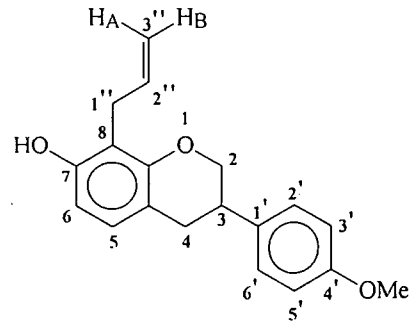
$[(CD_3)_2CO]$



δ_H	Signal	Assignment
9.4	br s	O<u>H</u>
7.66	d, 9	H-5
7.25	d, 9	H-2', H-6'
6.89	d, 9	H-3', H-5'
6.66	d, 9	H-6
6.02-5.88	m	H-2''
5.01	dq; 17, 2	3''-C<u>H</u>$_A$
4.94	dq; 10, 2	3''-C<u>H</u>$_B$
4.68	d, 7	2-C<u>H</u>$_2$
3.90	dd; 7, 7	H-3
3.78	s	OC<u>H</u>$_3$
3.41	dt; 6, 2	1''-C<u>H</u>$_2$

Plate 23: 8-Allyl-7-hydroxy-4'-methoxyisoflavan **68**

($CDCl_3$)

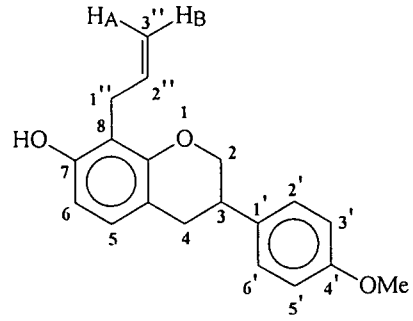


δ_H	Signal	Assignment
7.19	d, 9	H-2', H-6'
6.92	d, 9	H-3', H-5'
6.88	d, 8	H-5
6.45	d, 8	H-6
6.09-5.96	m	H-2''
5.16	dq; 17, 2	3''-C$\underline{H}_A$
5.12	dq; 10, 2	3''-C$\underline{H}_B$
4.9	br s	O$\underline{H}$
4.38	ddd; 11, 4, 2	H-2*eq*
3.98	dd; 11, 11	H-2*ax*
3.83	s	OC$\underline{H}_3$
3.48	dt; 6, 2	1''-C$\underline{H}_2$
3.24-3.13	m	H-3
3.00-2.95	m	4-C$\underline{H}_2$

(continued overleaf...)

Plate 23: 8-Allyl-7-hydroxy-4'-methoxyisoflavan **68**

(continued)



δ_H	Signal	Assignment
7.19	d, 9	H-2', H-6'
6.92	d, 9	H-3', H-5'
6.88	d, 8	H-5
6.45	d, 8	H-6
6.09-5.96	m	H-2''
5.16	dq; 17, 2	3''-C$\underline{H}_A$
5.12	dq; 10, 2	3''-C$\underline{H}_B$
4.9	br s	O$\underline{H}$
4.38	ddd; 11, 4, 2	H-2*eq*
3.98	dd; 11, 11	H-2*ax*
3.83	s	OC$\underline{H}_3$
3.48	dt; 6, 2	1''-C$\underline{H}_2$
3.24-3.13	m	H-3
3.00-2.95	m	4-C$\underline{H}_2$

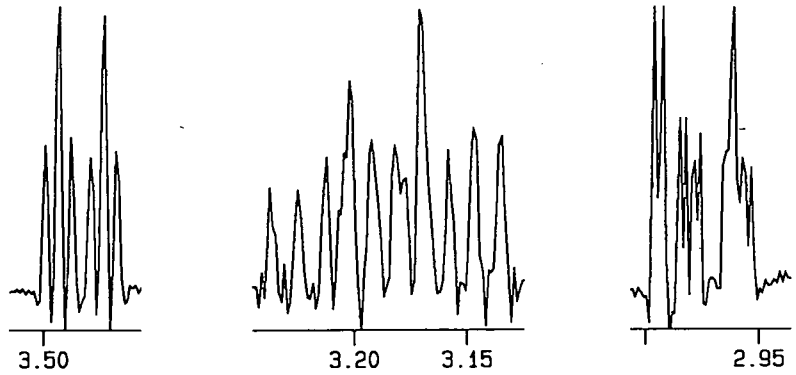
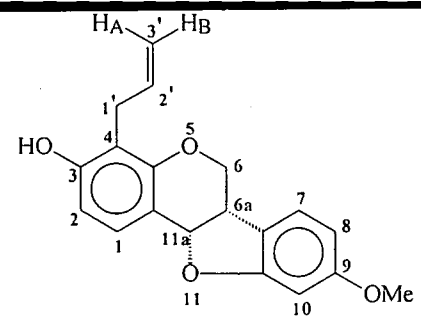
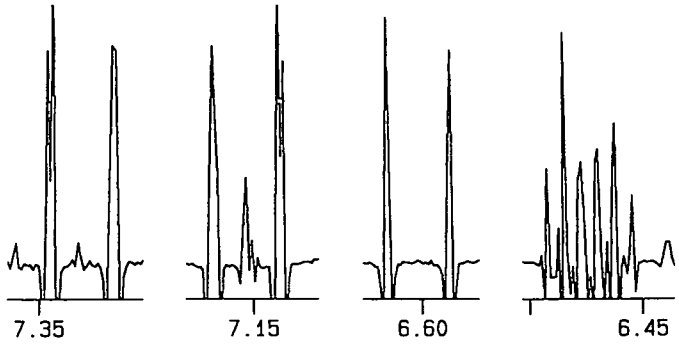


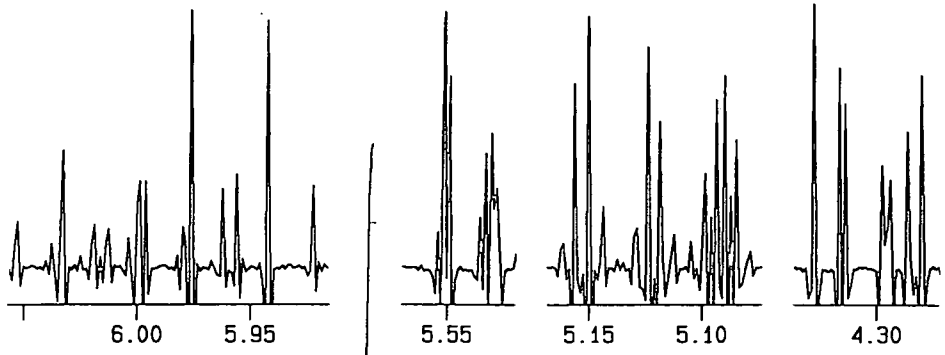
Plate 24: (6a*S*, 11a*S*)-4-Allylmedicarpin **18**

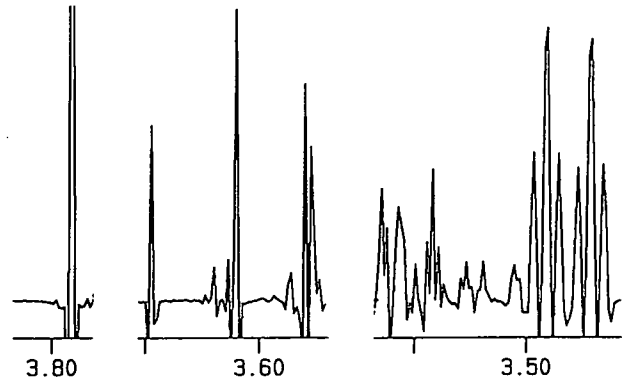
($CDCl_3$)



δ_H	Signal	Assignment
7.33	d, 8	H-1
7.15	d, 9	H-7
6.60	d, 9	H-2
6.47	d, 2	H-10
6.47	dd; 9, 2	H-8
6.05-5.92	m	H-2'
5.54	d, 7	H-11a
5.3	br s	O<u>H</u>
5.14	dq; 10, 2	3'-C<u>H</u>$_A$
5.09	dq; 3, 2	3'-C<u>H</u>$_B$
4.33-4.28	m	H-6*eq*
3.79	s	O<u>CH</u>$_3$
3.61	t; 11, 10	H-6*ax*
3.57-3.51	m	H-6a
3.48	dt; 6, 2	1'-C<u>H</u>$_2$







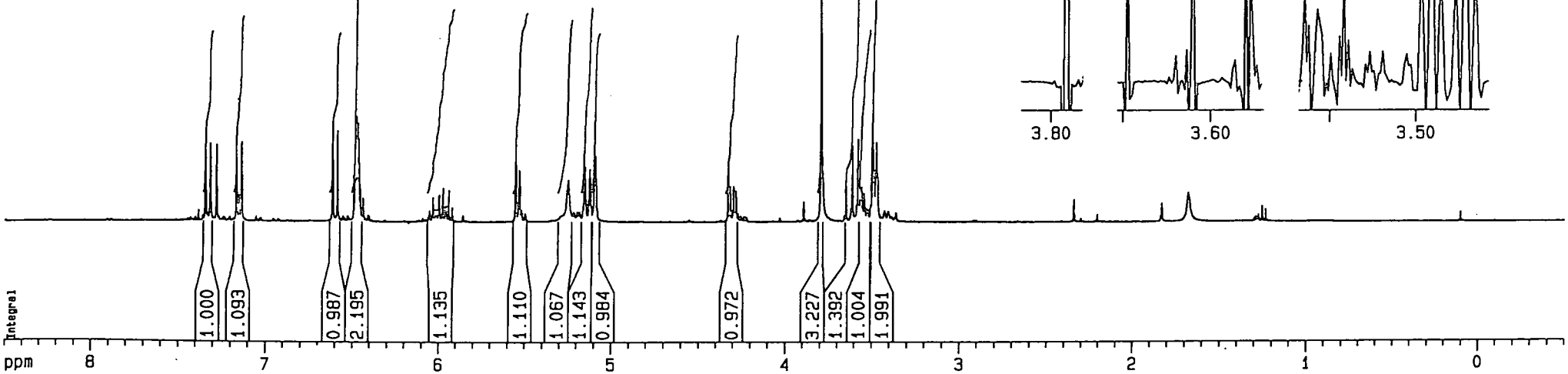


Plate 25: (6a*S*, 11a*S*)-4-Allyl-3-*O*-(3',5'-dinitro)benzoylmedicarpin **73**

($CDCl_3$)

δ_H	Signal	Assignment
9.34	s	$C_6\underline{H}_3(NO_2)_2$
7.57	d, 9	H-1
7.18	d, 9	H-7
6.97	d, 8	H-2
6.50	d, 2	H-10
6.50	dd; 9, 3	H-8
5.93-5.80	m	H-2'
5.60	d, 5	H-11a
4.97	dq; 10, 2	3'-C$\underline{H}_B$
4.89	dq; 17, 2	3'-C$\underline{H}_A$
4.44-4.35	m	H-6*eq*
3.81	s	OC$\underline{H}_3$
3.69-3.59	m	H-6*ax*, H-6a
3.44-3.40	m	1'-C$\underline{H}_2$

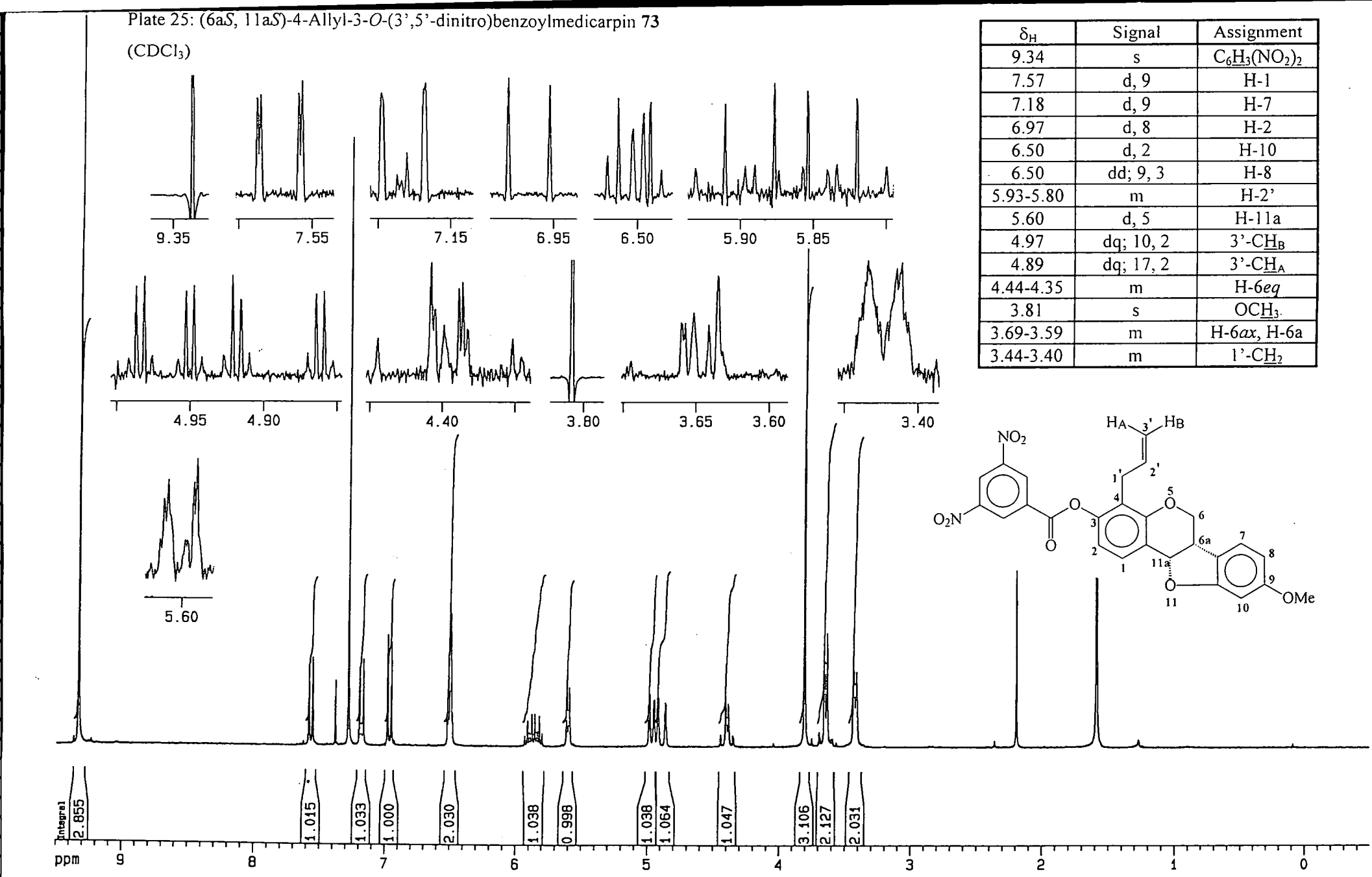
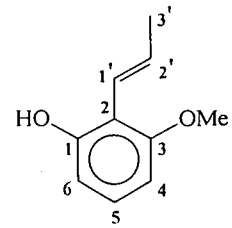


Plate 26: 3-Methoxy-2-(prop-1-enyl)phenol **75/76**

(Unresolved *E*/*Z*-mixture; structure of *E*-isomer shown)

($CDCl_3$)



δ_H	Signal	Assignment
7.18/7.09	dd; 8, 8	H-5
6.58	dd; 8, 1	H-6
6.49-6.42	m	H-1'
6.46	dd; 8, 1	H-4
6.15	dq; 17, 6	H-2'
5.6	br s	O<u>H</u>
3.83	s	O<u>C</u>H$_3$
1.98/1.67	dd; 7, 2	3'-C<u>H</u>$_3$

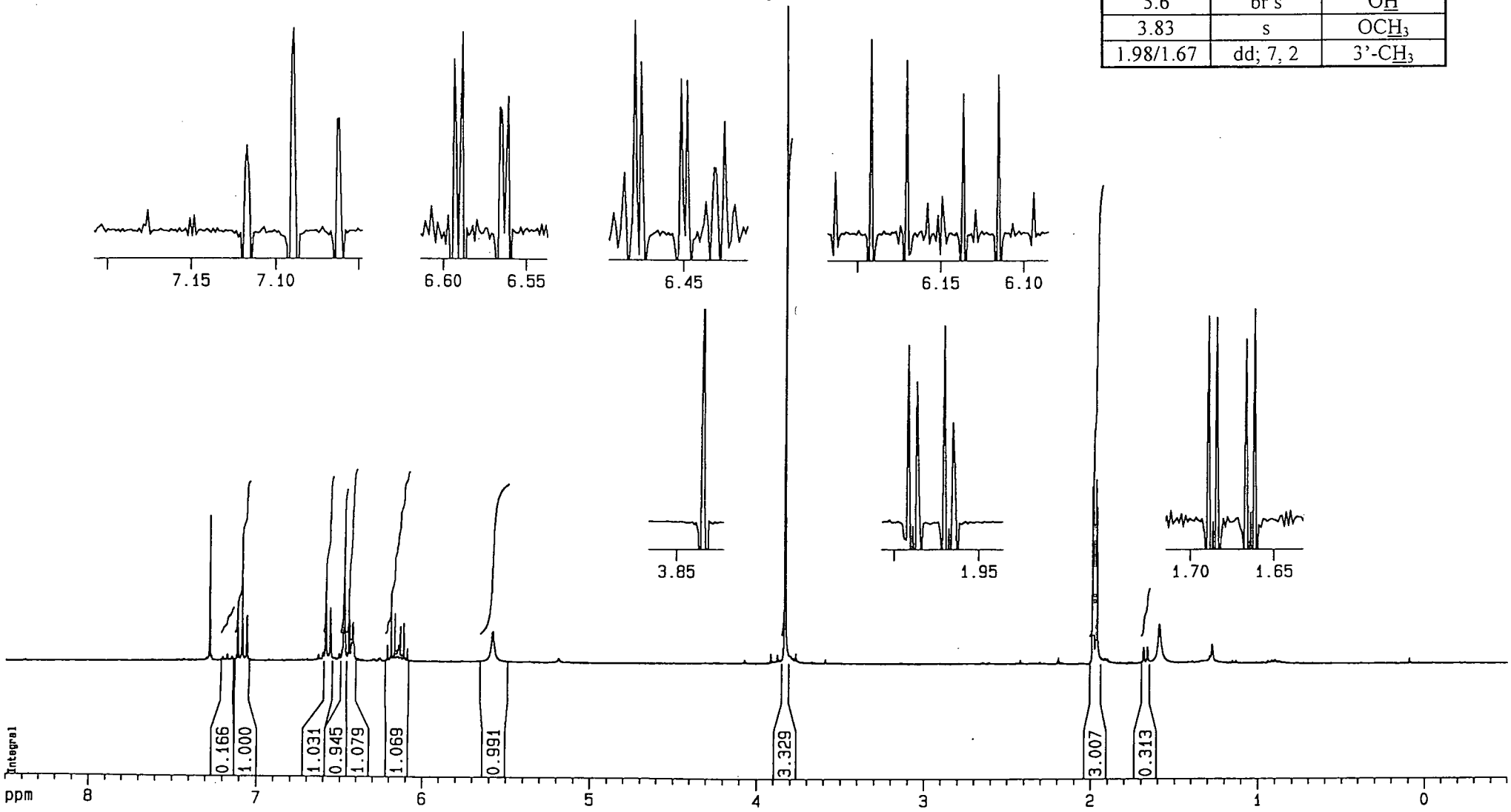
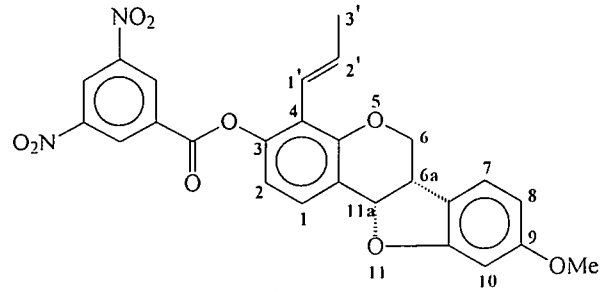


Plate 27: (6a*S*, 11a*S*)-3-*O*-(3',5'-Dinitro)benzoyl-4-(prop-1-enyl)medicarpin **77**/**78**

(Structure of *E*-isomer shown)

($CDCl_3$)



δ_H	Signal	Assignment
9.34	s	$C_6H_3(NO_2)_2$
7.52	d, 8	H-1
7.19	d, 9	H-7
6.93	d, 8	H-2
6.50	d, 2	H-10
6.50	dd; 9, 2	H-8
6.40-6.28	m	H-1', H-2'
5.59	d, 7	H-11a
4.43-4.38	m	H-6*eq*
3.81	s	OCH_3
3.69	t; 11, 10	H-6*ax*
3.65-3.59	m	H-6a
1.81	dd; 2, 2	3'-CH_3

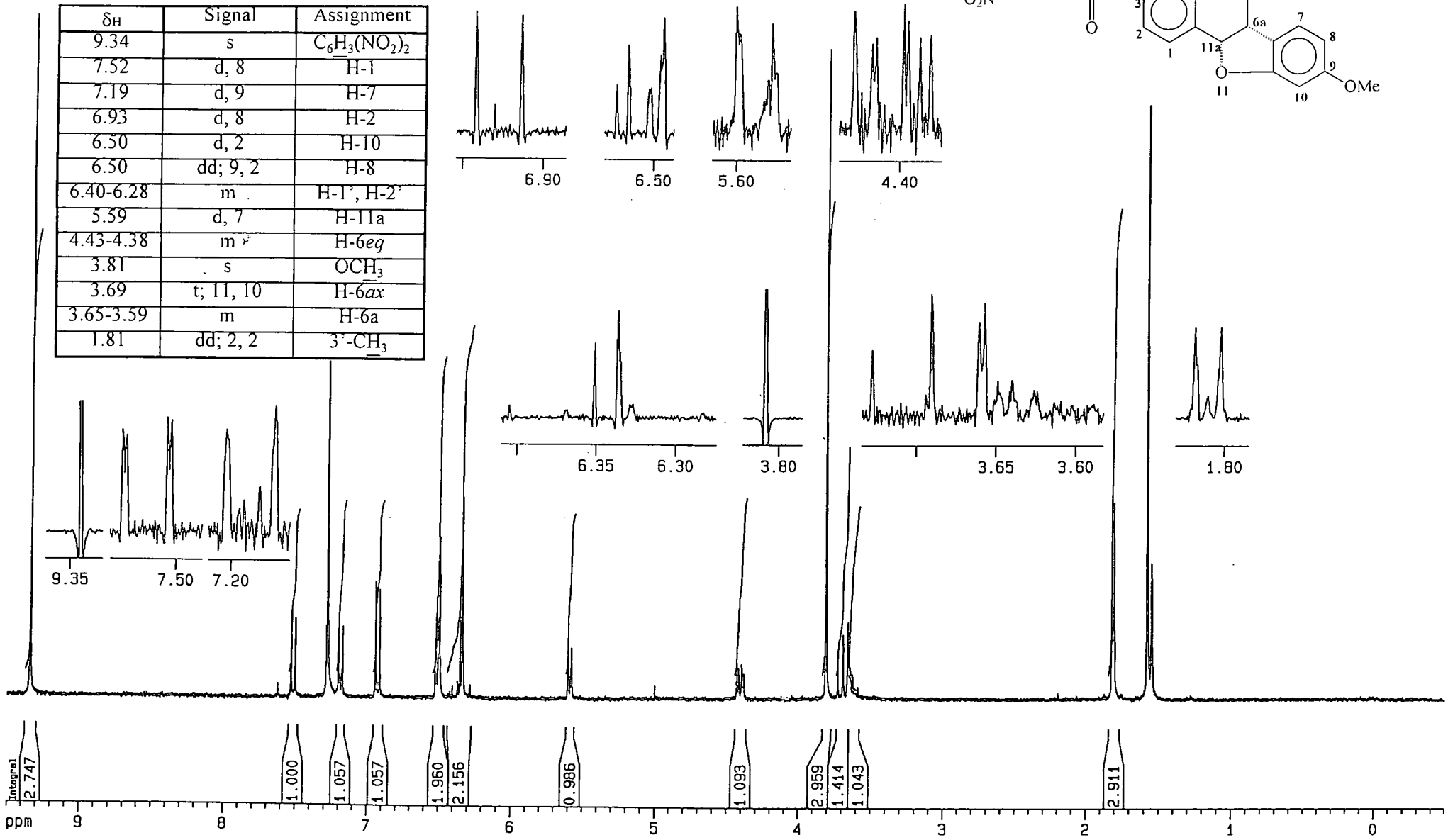
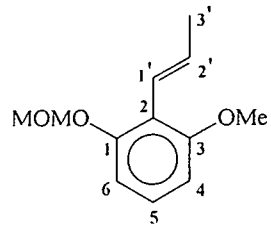


Plate 28: 3-Methoxy-1-*O*-methoxymethyl-2-(prop-1-enyl)phenol **80**

(Unresolved *E*/*Z*-mixture; structure of *E*-isomer shown)

($CDCl_3$)



δ_H	Signal	Assignment
7.21/7.11	dd; 8, 8	H-5
6.82/6.77	dd; 8, 1	H-6
6.69-6.55	m	H-1', H-2', H-4
6.28	dq; 11, 2	H-1' (isomer)
5.97	dq; 11, 6	H-2' (isomer)
5.22/5.19	s	OCH_2OCH_3
3.86/3.85	s	$Ar\text{-}OCH_3$
3.51/3.50	s	OCH_2OCH_3
1.95/1.62	dd; 2/7, 2	$3'\text{-}CH_3$

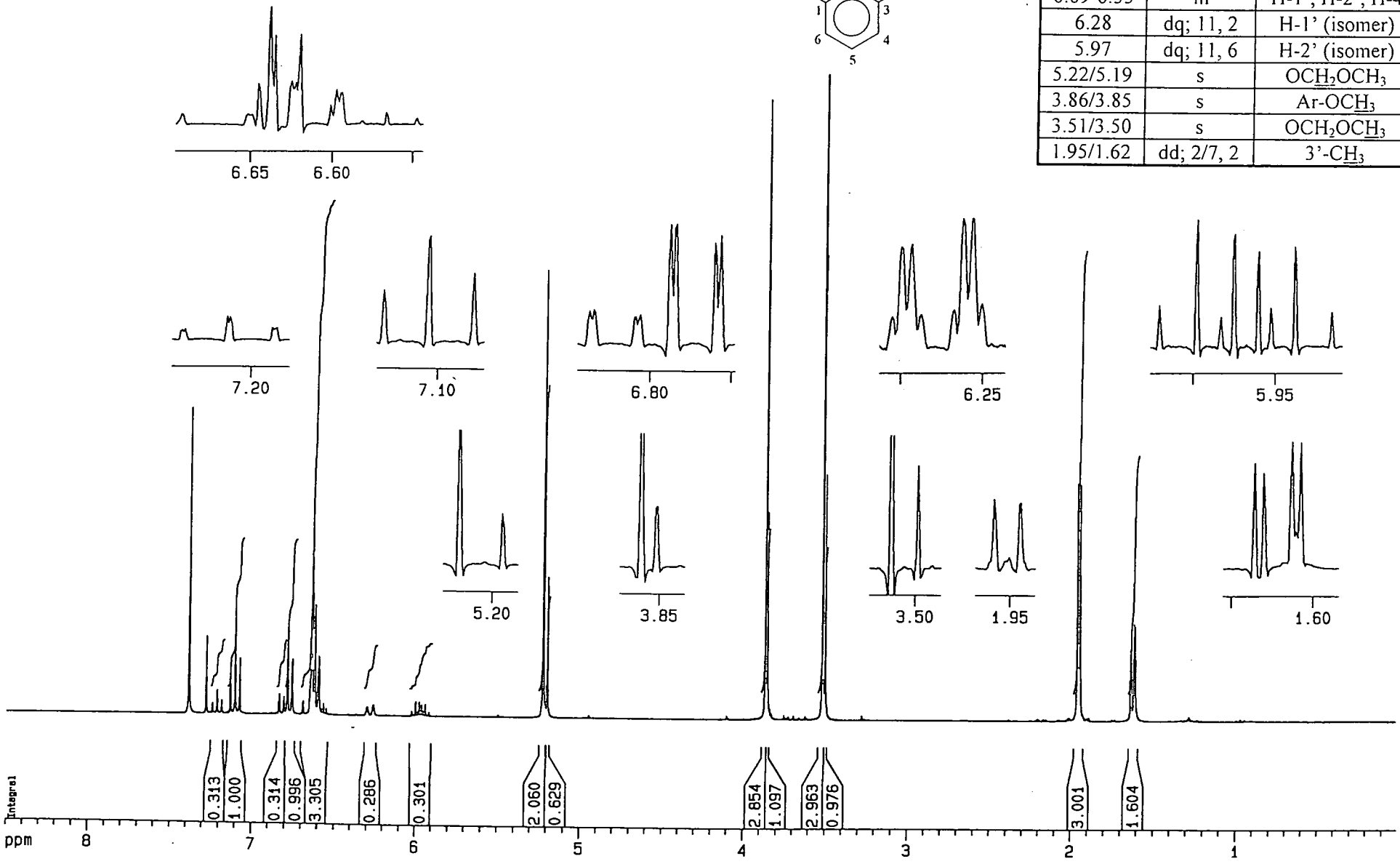
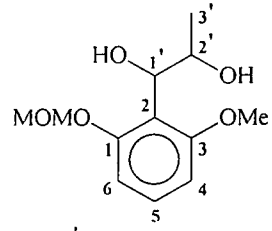


Plate 29: 2-(1,2-Dihydroxy)propyl-3-methoxy-1-*O*-methoxymethylphenol **81**

(Unresolved diastereomeric mixture)

($CDCl_3$)



δ_H	Signal	Assignment
7.22/7.21	dd; 8, 8	H-5
6.82/6.80	dd; 8, 1	H-6
6.64/6.62	dd; 8, 1	H-4
5.23/5.22	d, 2/1	$OC\underline{H}_2OCH_3$
5.10/4.91	d, 6/9	1'-C<u>H</u>OH
4.12-4.02	m	2'-C<u>H</u>OH
3.88/3.87	s	Ar-$OC\underline{H}_3$
3.50/3.49	s	$OCH_2OC\underline{H}_3$
1.26/1.04	d, 6	3'-$C\underline{H}_3$

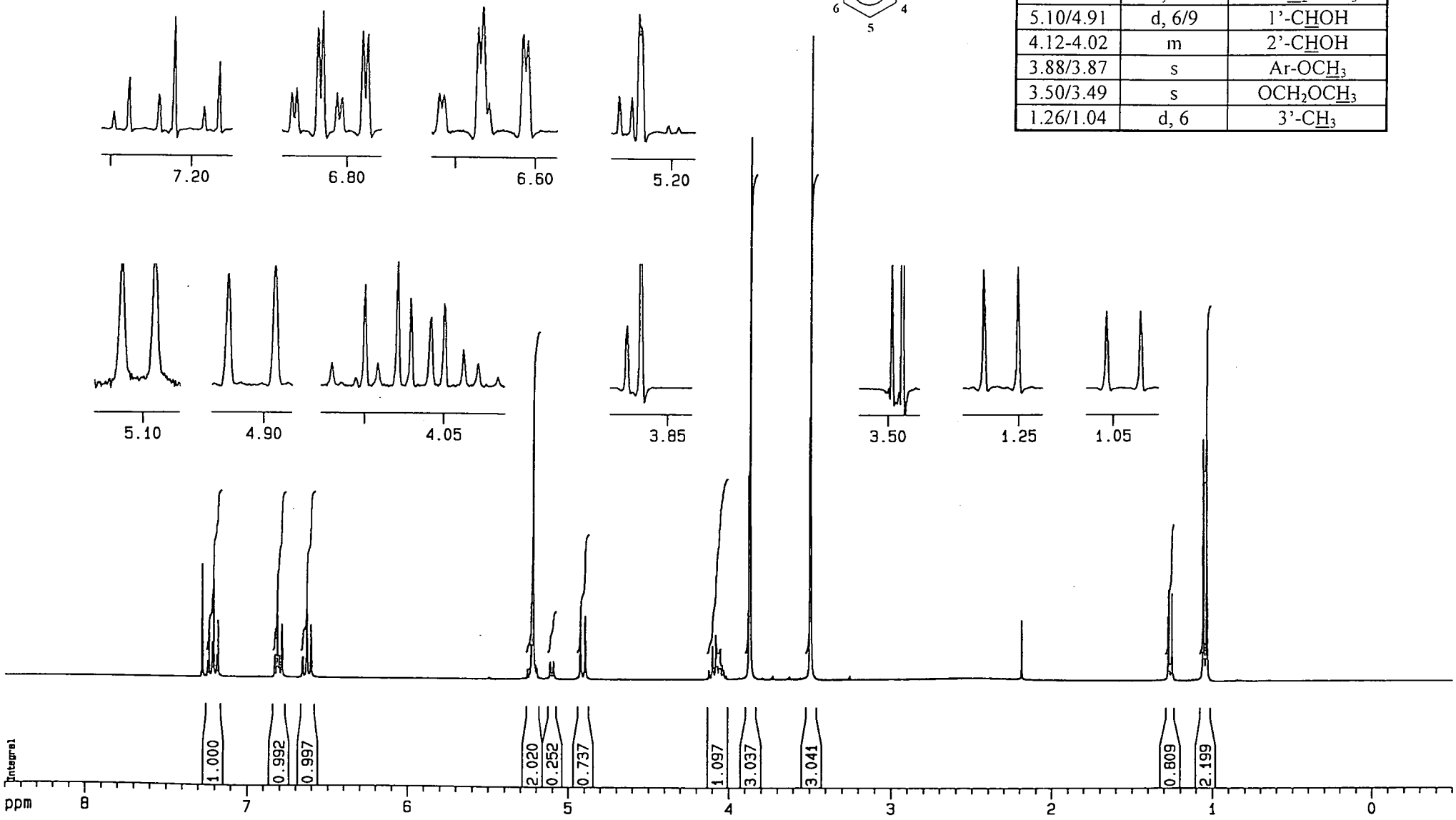
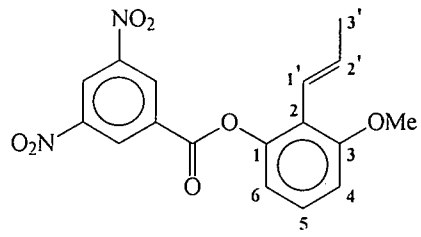


Plate 30: 3-Methoxy-1-*O*-(3',5'-dinitro)benzoyl-2-(prop-1-enyl)phenol **82**

(Unresolved *E*/*Z*-mixture; structure of *E*-isomer shown)

[$(CD_3)_2CO$]



δ_H	Signal	Assignment
9.26	s	$C_6\underline{H}_3(NO_2)_2$
7.31	dd; 8, 8	H-5
7.02	dd; 8, 1	H-6
6.95	dd; 8, 1	H-4
6.40	dd; 7, 5	H-1', H-2'
3.93	s	$O\underline{C}H_3$
1.74/1.59	dd; 2/7, 2	3'-$C\underline{H}_3$

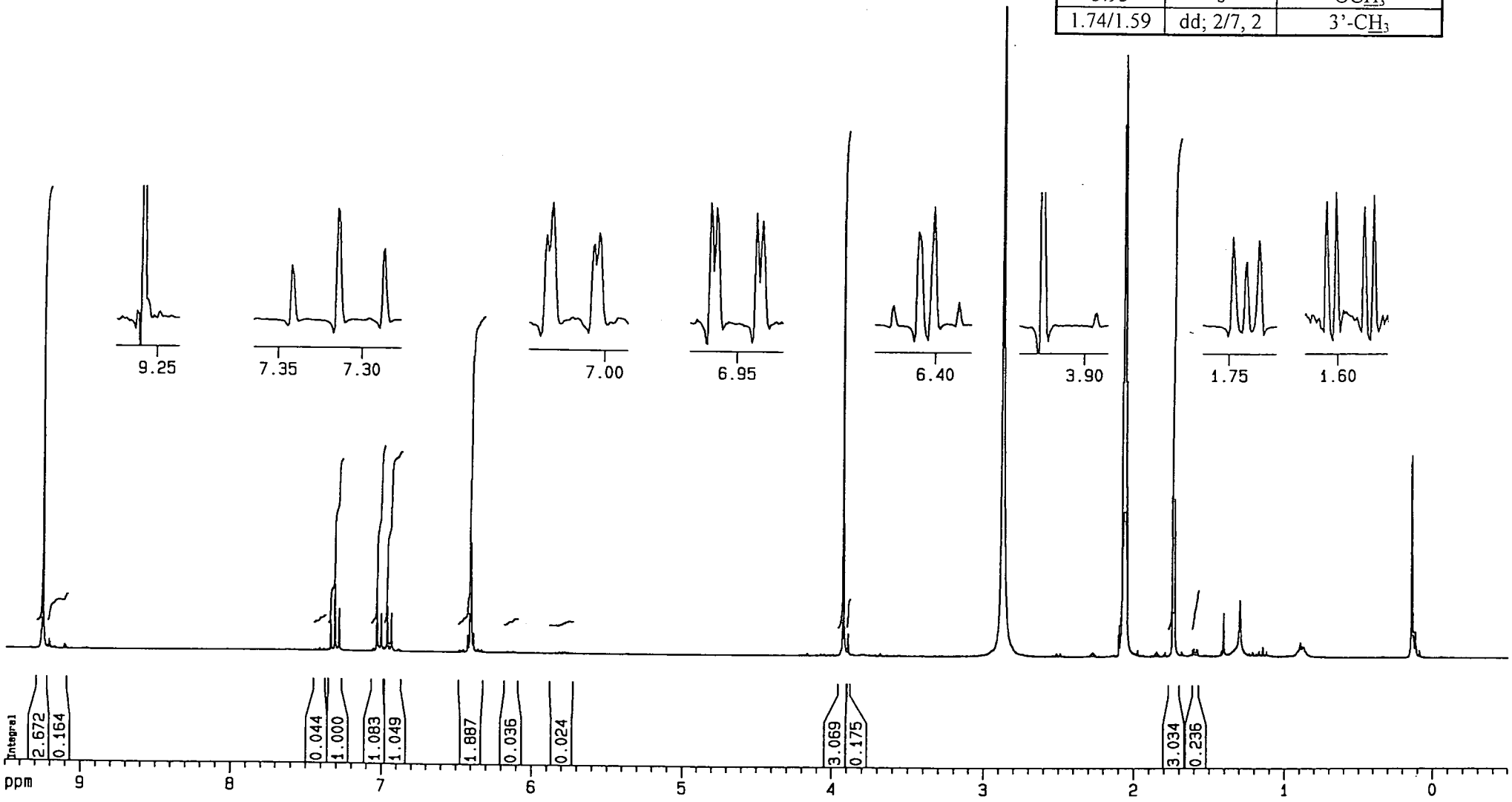
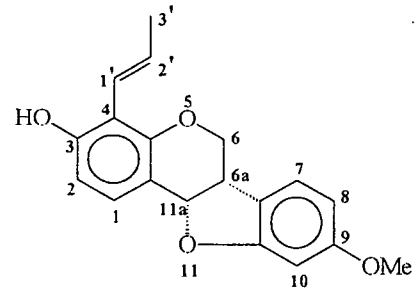


Plate 31: (6a*S*, 11a*S*)-4-(Prop-1-enyl)medicarpin **84**

(Unresolved *E*/*Z*-mixture; structure of *E*-isomer shown)

($CDCl_3$)

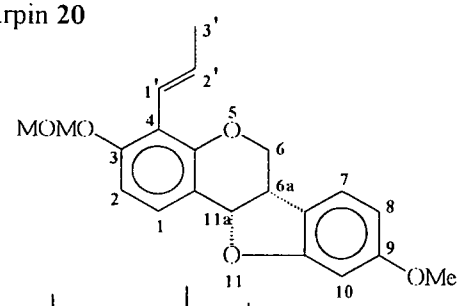


δ_H	Signal	Assignment
7.40/7.31	d, 8	H-1
7.15	d, 9	H-7
6.72/6.67	d, 8	H-2
6.47	d, 2	H-10
6.47	dd; 9, 2	H-8
6.43-6.41	m	H-1'
6.24-6.12	m	H-2'
5.66	br s	O<u>H</u>
5.52	d, 7	H-11a
4.30	ddd; 11, 5, 1	H-6*eq*
3.79	s	O<u>C</u>H$_3$
3.69	t, 11	H-6*ax*
3.59-3.48	m	H-6a
1.97/1.67	dd; 7, 2	3'-C<u>H</u>$_3$

Plate 32: (6a*S*, 11a*S*)-3-*O*-Methoxymethyl-4-(prop-1-enyl)medicarpin **20**

(Unresolved *E*/*Z*-mixture; structure of *E*-isomer shown)

($CDCl_3$)



δ_H	Signal	Assignment
7.34	d, 9	H-1
7.16	d, 8	H-7
6.93/6.88	d, 8	H-2
6.48	dd; 9, 2	H-8
6.47	d, 2	H-10
6.64-6.60/	m	H-1`, H-2`
5.54	d, 6	H-11a
5.24	dd; 9, 7	OCH_2OCH_3
4.34	ddd; 10, 5, 1	H-6*eq*
3.79	s	Ar-OCH_3
3.65	t; 11, 10	H-6*ax*
3.59-3.56	m	H-6a
3.51	s	OCH_2OCH_3
1.95/1.61	dd; 3/7, 2	3`-CH_3

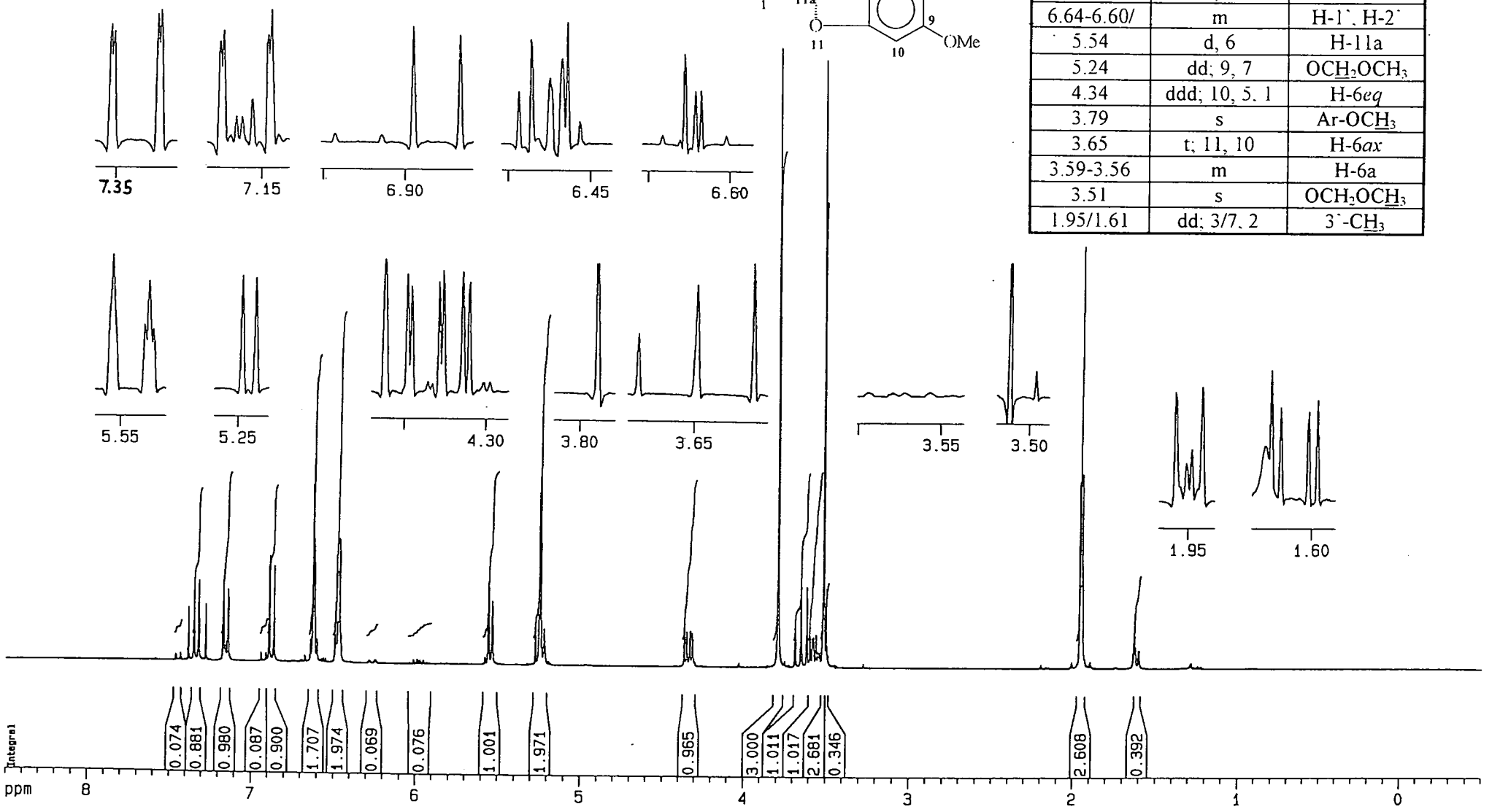
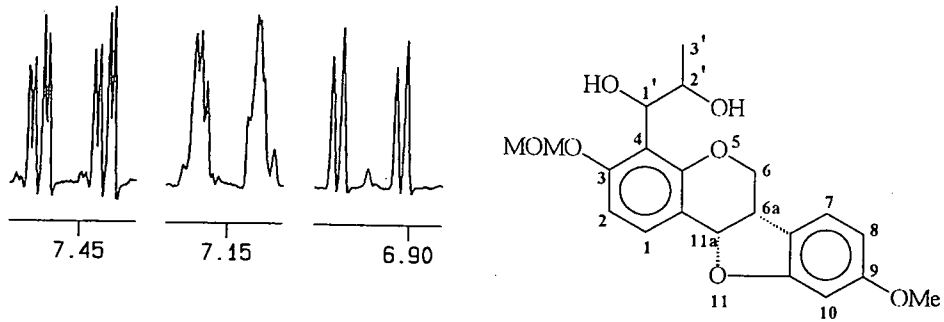


Plate 33: (6a*S*, 11a*S*)-4-(1,2-Dihydroxy)propyl-3-*O*-methoxymethylmedicarpin **21**

(Unresolved diastereomeric mixture)

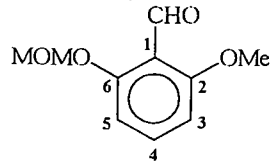
($CDCl_3$)



δ_H	Signal	Assignment
7.45	2 x d, 9	H-1
7.15	d, 9	H-7
6.92	2 x d, 9	H-2
6.48	dd; 9, 2	H-8
6.46	d, 2	H-10
5.52	2 x d, 6	H-11a
5.28-5.22	m	$OC\underline{H}_2OCH_3$
4.92/4.88	d, 9	1'-C<u>H</u>OH
4.40-4.29	m	H-6*eq*
4.10-4.00	m	2'-C<u>H</u>OH
3.79	2 x s	Ar-$OC\underline{H}_3$
3.68-3.58	m	H-6*ax*, H-6a
3.50	s	$OCH_2OC\underline{H}_3$
3.13/1.70	br s	1'-, 2'-CHO<u>H</u>
1.04/1.03	d, 6	3'-$C\underline{H}_3$

Plate 34: 2-Methoxy-6-*O*-methoxymethylbenzaldehyde **85**

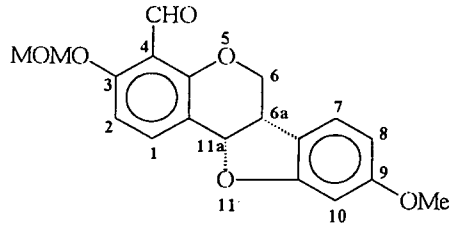
($CDCl_3$)



δ_H	Signal	Assignment
10.55	s	C<u>H</u>O
7.45	dd; 9, 9	H-4
6.81	dd; 8, 1	H-5
6.64	br d, 8	H-3
5.28	s	$OC\underline{H}_2OCH_3$
3.92	s	$Ar\text{-}OC\underline{H}_3$
3.52	s	$OCH_2OC\underline{H}_3$

Plate 35: (6a*S*, 11a*S*)-4-Formyl-3-*O*-methoxymethylmedicarpin **22**

($CDCl_3$)



δ_H	Signal	Assignment
10.52	s	C<u>H</u>O
7.69	d, 9	H-1
7.17	d, 8	H-7
6.94	d, 9	H-2
6.49	dd; 8, 2	H-8
6.47	d, 2	H-10
5.49	d, 6	H-11a
5.32	s	$OC\underline{H}_2OCH_3$
4.43	ddd; 10, 4, 1	H-6*eq*
3.79	s	$Ar\text{-}OC\underline{H}_3$
3. 67	t; 11, 10	H-6*ax*
3.63-3.57	m	H-6a
3.53	s	$OCH_2OC\underline{H}_3$

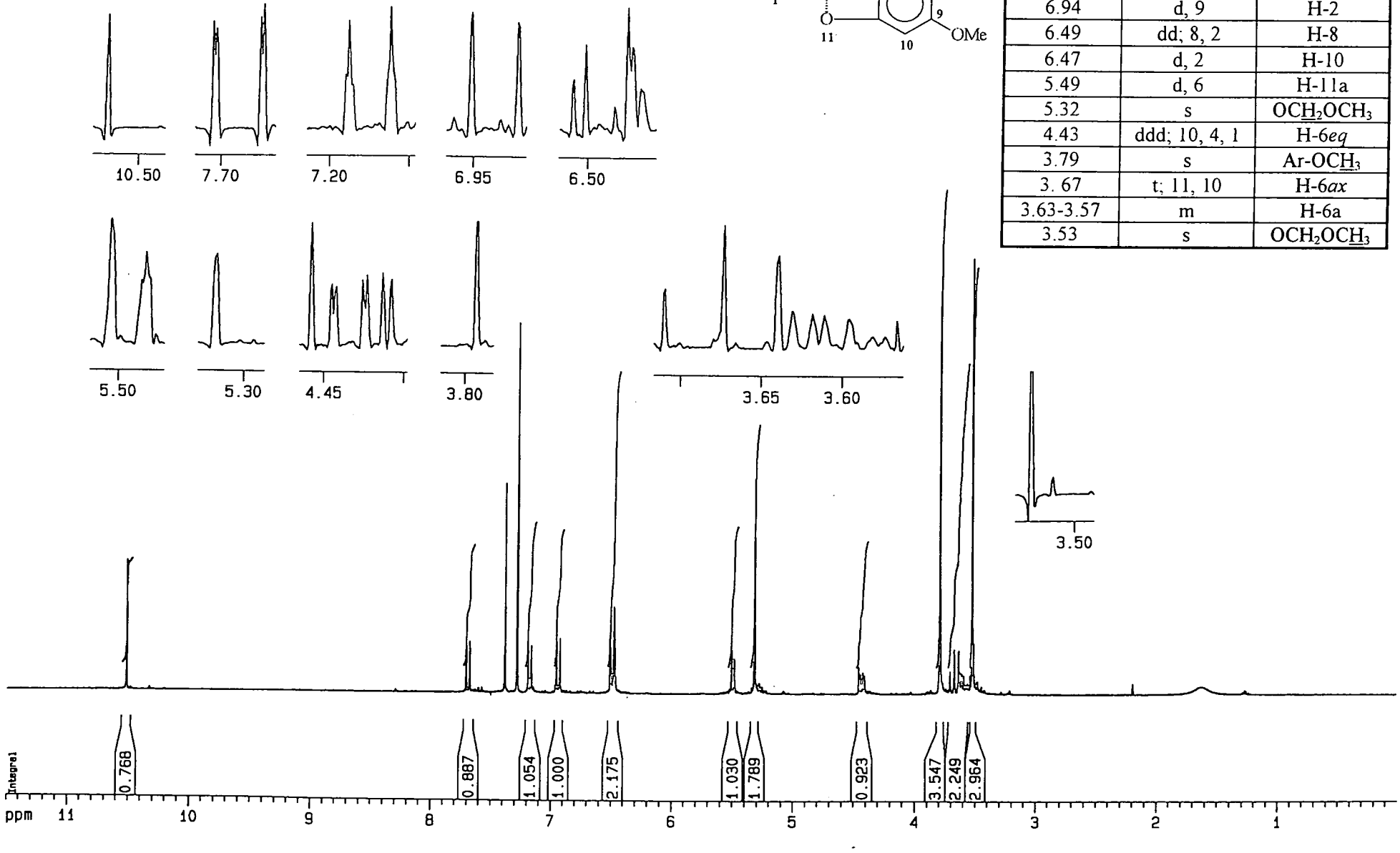
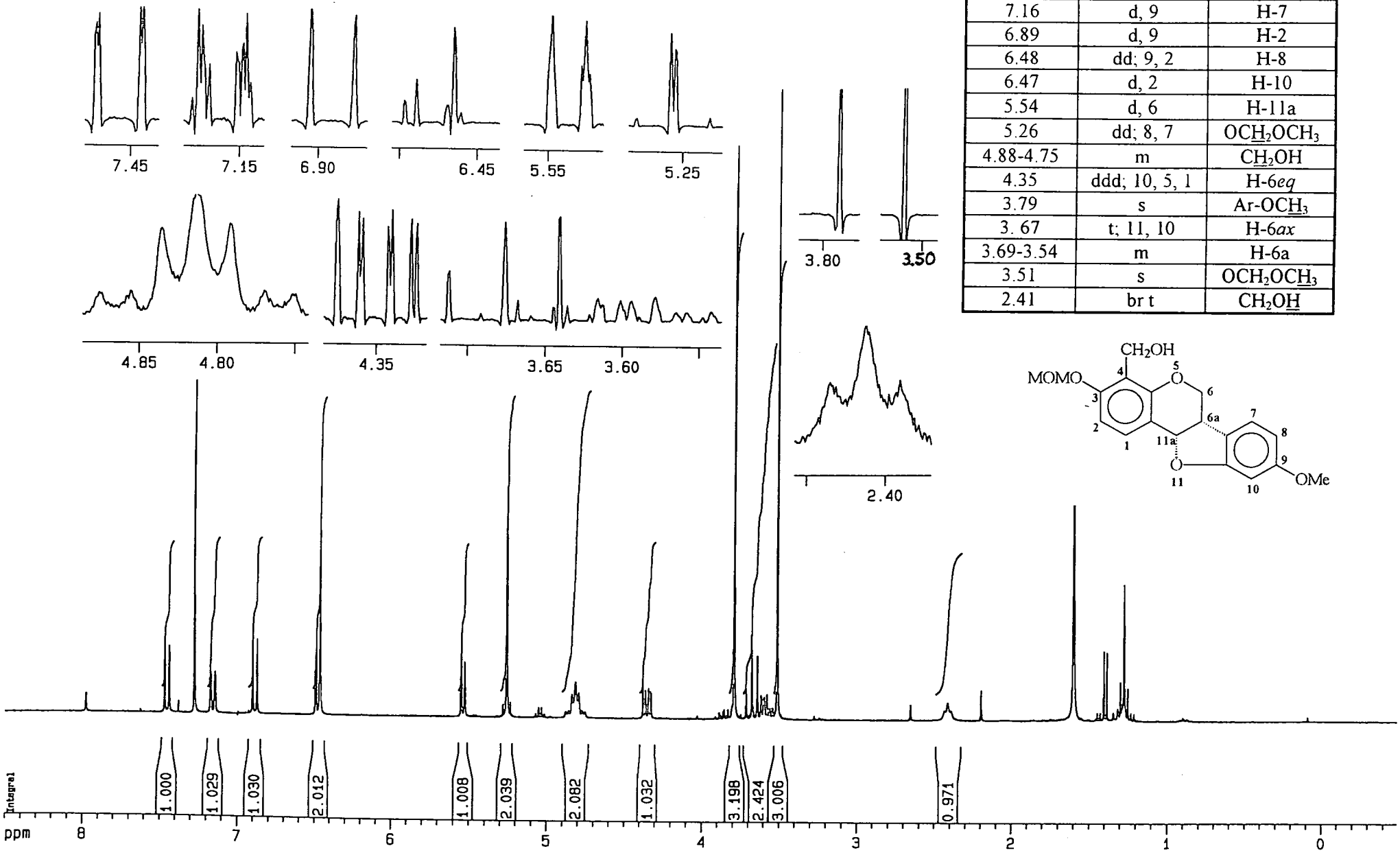


Plate 36: (6a*S*, 11a*S*)-4-Hydroxymethyl-3-*O*-methoxymethylmedicarpin **23**

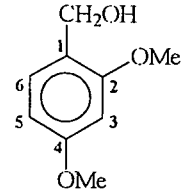
($CDCl_3$)



δ_H	Signal	Assignment
7.46	d, 9	H-1
7.16	d, 9	H-7
6.89	d, 9	H-2
6.48	dd; 9, 2	H-8
6.47	d, 2	H-10
5.54	d, 6	H-11a
5.26	dd; 8, 7	$OC\underline{H}_2OCH_3$
4.88-4.75	m	$C\underline{H}_2OH$
4.35	ddd; 10, 5, 1	H-6*eq*
3.79	s	Ar-$OC\underline{H}_3$
3. 67	t; 11, 10	H-6*ax*
3.69-3.54	m	H-6a
3.51	s	$OCH_2OC\underline{H}_3$
2.41	br t	$CH_2O\underline{H}$

Plate 37: 2,4-Dimethoxybenzyl alcohol **87**

($CDCl_3$)



δ_H	Signal	Assignment
7.18	d, 8	H-6
6.48	d, 2	H-3
6.46	dd; 8, 2	H-5
4.62	br d, 6	$C\underline{H}_2OH$
3.85, 3.82	s	2 x $OC\underline{H}_3$
2.35	dt; 6, 2	$CH_2O\underline{H}$

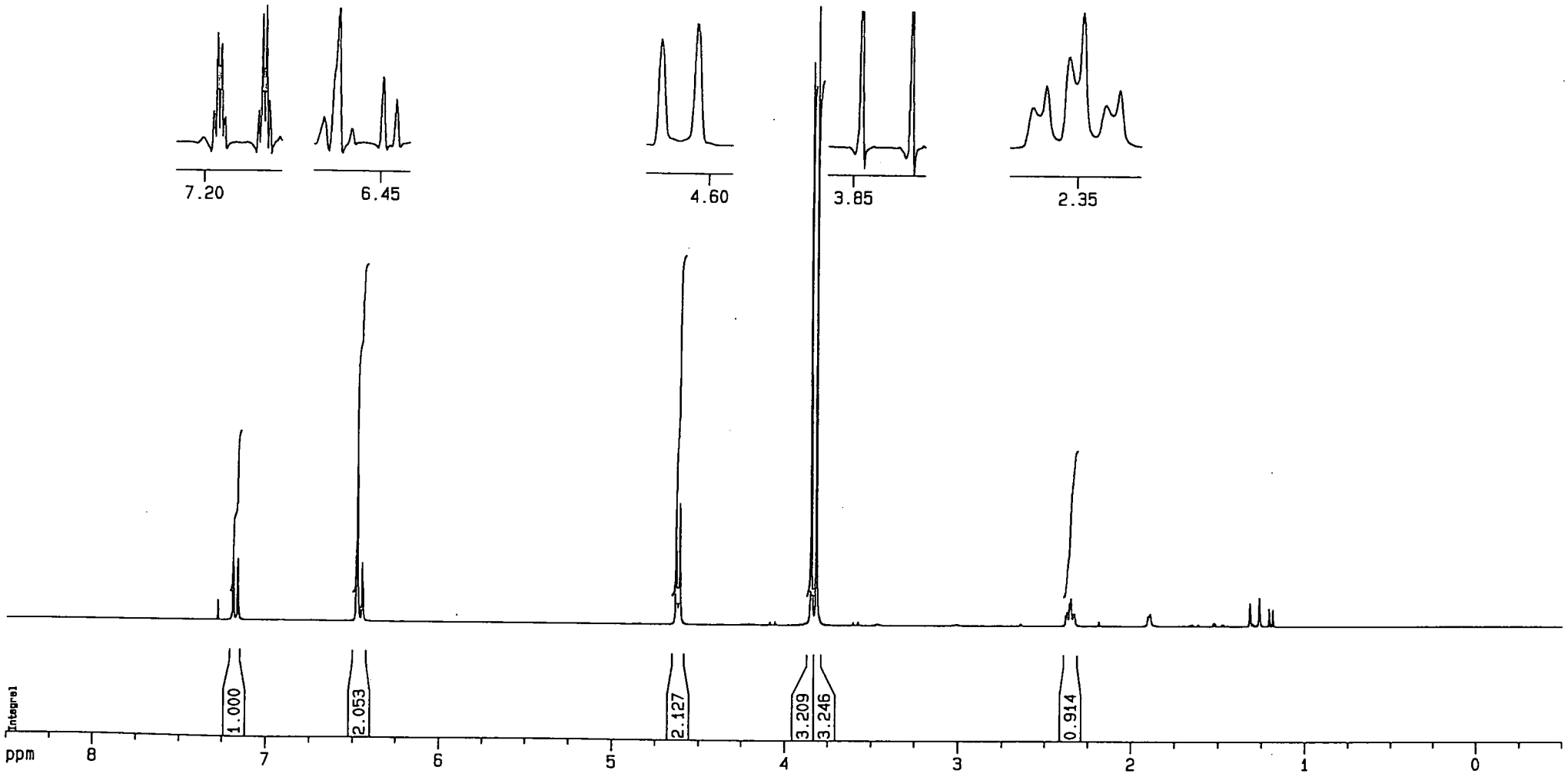
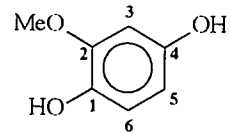


Plate 38: Methoxy-*p*-hydroquinone **26**

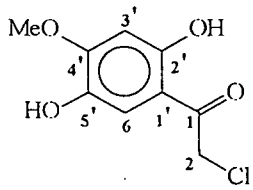
($CDCl_3$)



δ_H	Signal	Assignment
6.78	d, 9	H-6
6.47	d, 3	H-3
6.33	dd; 9, 3	H-5
5.26/4.81	br s	2 x O<u>H</u>
3.86	s	O<u>CH</u>$_3$

Plate 39: 2-Chloro-2',5'-dihydroxy-4'-methoxyacetophenone **27**

($CDCl_3$)



δ_H	Signal	Assignment
11.98	s	2'-O<u>H</u>
7.17	s	H-6'
6.50	s	H-3'
5.3	br s	5'-O<u>H</u>
4.63	s	2-C<u>H</u>$_2$Cl
3.97	s	OC<u>H</u>$_3$

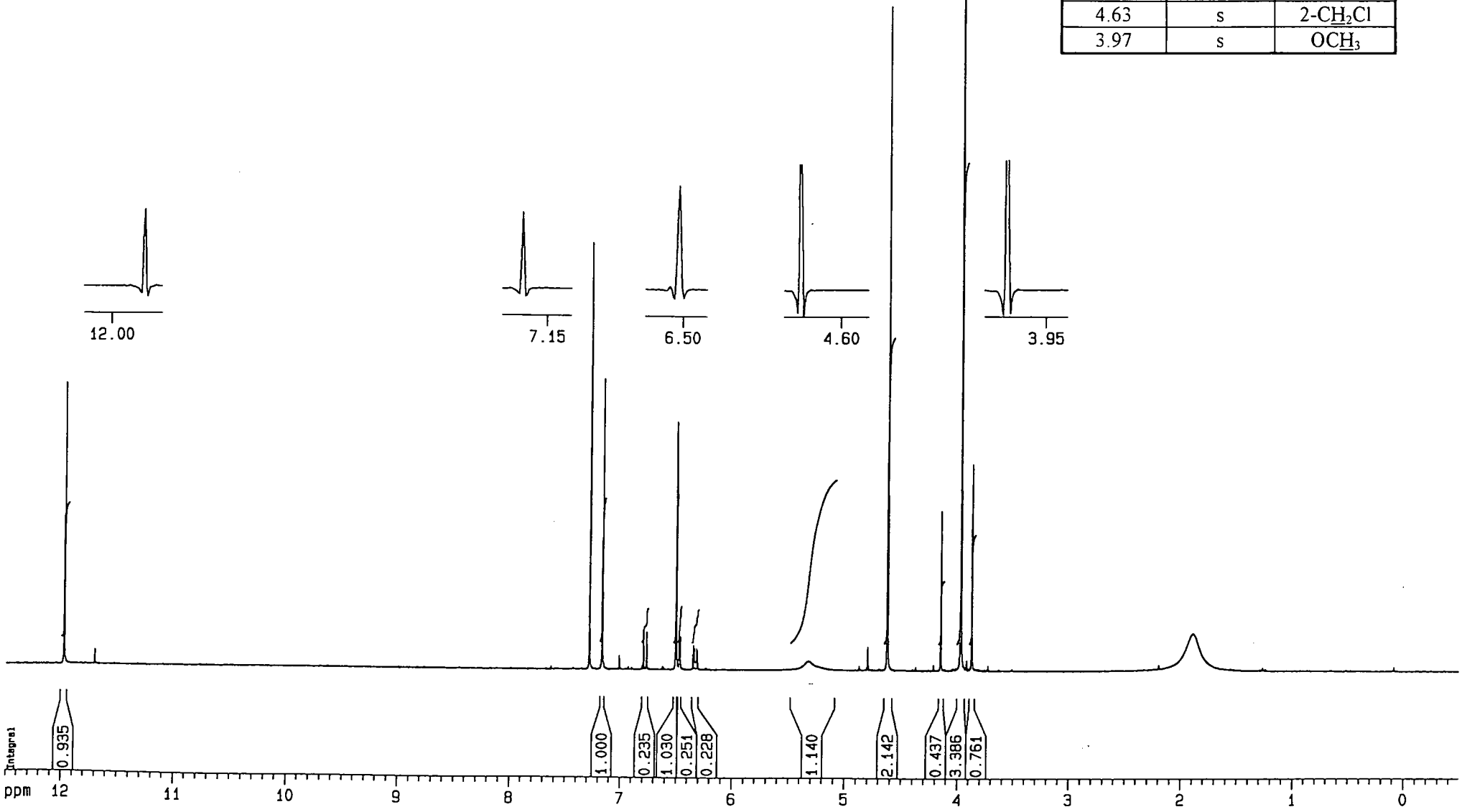
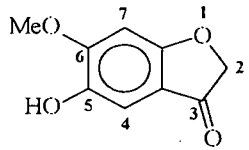


Plate 40: 5-Hydroxy-6-methoxy-2,3-dihydrobenzo[b]furan-3-one **28**

$[(CD_3)_2CO]$



δ_H	Signal	Assignment
7.9	br s	O<u>H</u>
6.92	s	H-4
6.79	s	H-7
4.59	s	2-C<u>H</u>$_2$
3.99	s	OC<u>H</u>$_3$

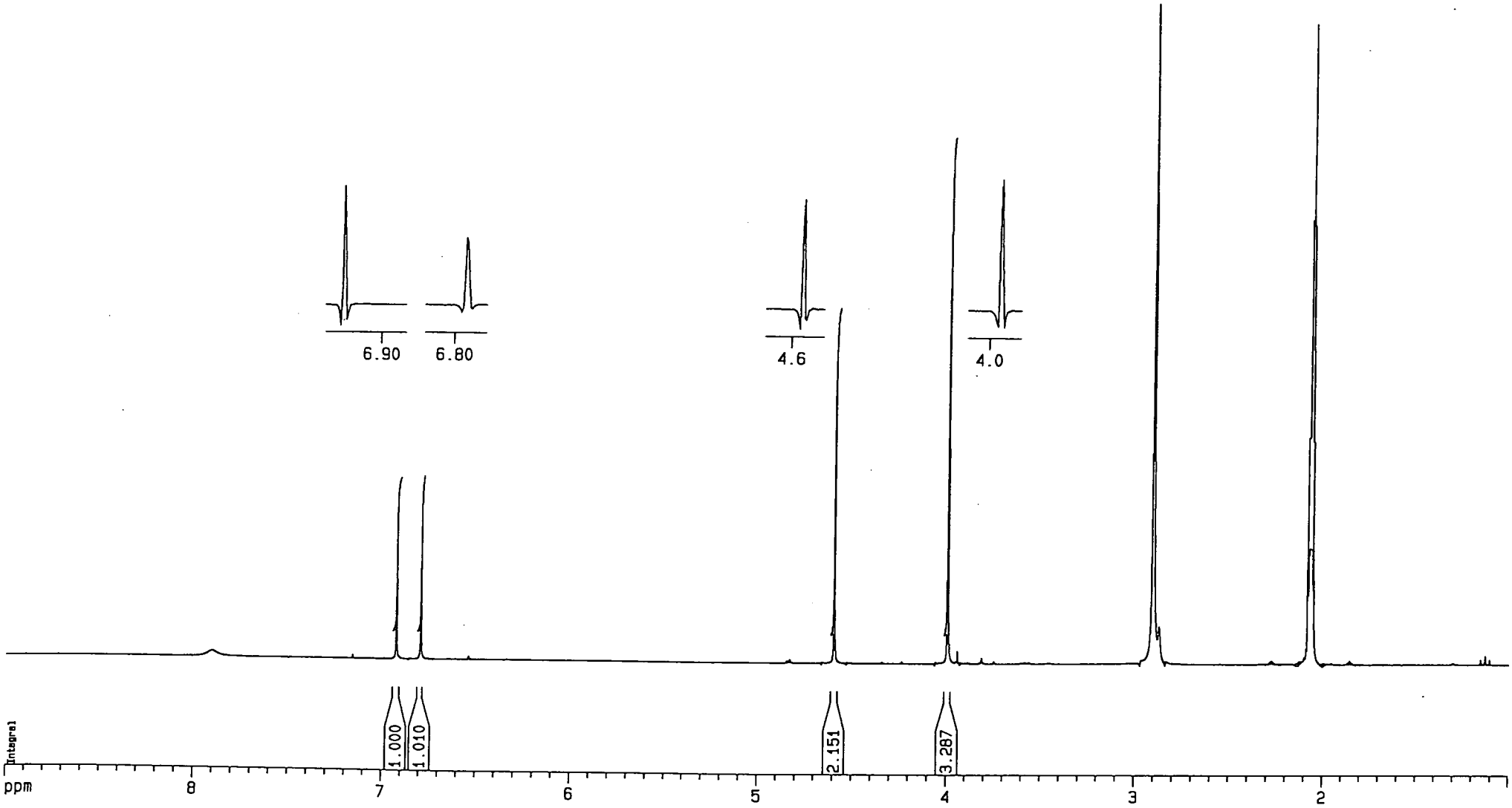
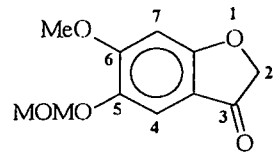


Plate 41: 6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one **29**

($CDCl_3$)



δ_H	Signal	Assignment
7.37	s	H-4
6.61	s	H-7
5.19	s	$OC\underline{H}_2OCH_3$
4.62	s	2-$C\underline{H}_2$
3.97	s	$OC\underline{H}_3$
3.51	s	$OCH_2OC\underline{H}_3$

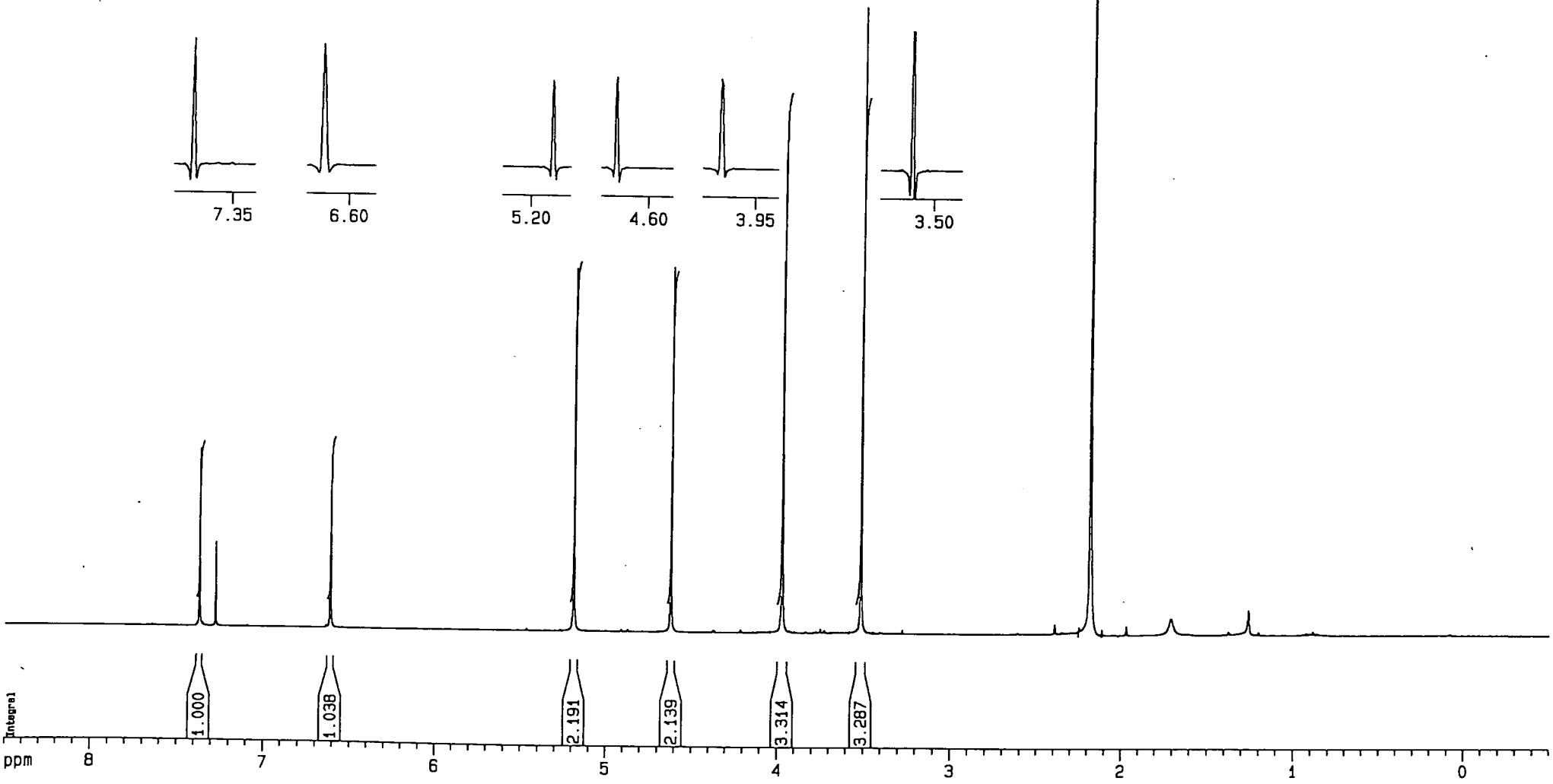
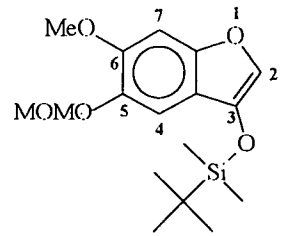


Plate 42: 3-*t*-Butyldimethylsilyloxy-6-methoxy-5-*O*-methoxymethylbenzo[b]furan **30** ($CDCl_3$)



δ_H	Signal	Assignment
7.27	s	H-4
7.22	s	H-2
6.96	s	H-7
5.25	s	$OC\underline{H}_2OCH_3$
3.92	s	$OC\underline{H}_3$
3.57	s	$OCH_2OC\underline{H}_3$
1.03	s	$OSi(C\underline{H}_3)_2C(CH_3)_3$
0.23	s	$OSi(CH_3)_2C(C\underline{H}_3)_3$

Plate 43: 6-Methoxy-2-(2',4'-dimethoxybenzyl)-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one **92** ($CDCl_3$)

δ_H	Signal	Assignment
7.38	s	H-4
7.13	d, 8	H-6'
6.58	s	H-7
6.50	d, 2	H-3'
6.47	dd; 8, 2	H-5'
5.19	s	$OC\underline{H}_2OCH_3$
4.88	dd; 10, 4	H-2
3.94/3.85/3.83	s	3 x $OC\underline{H}_3$
3.53	s	$OCH_2OC\underline{H}_3$
3.43/2.68	dd; 15, 4/10	2-$C\underline{H}_2$

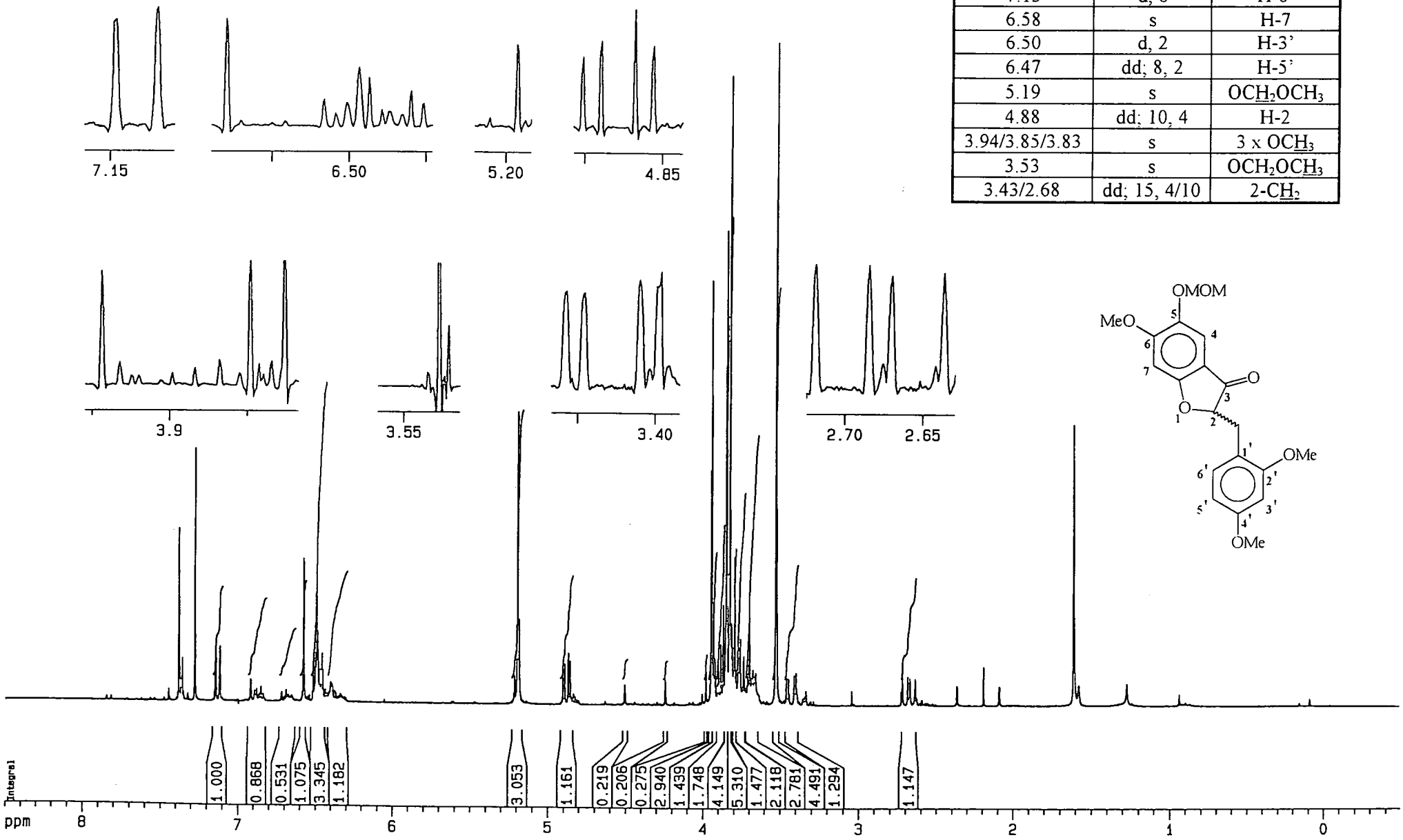
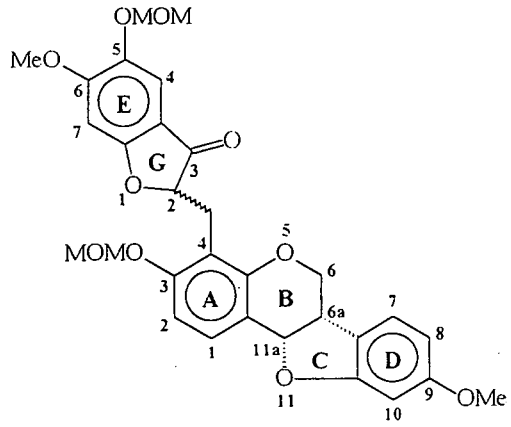


Plate 44: (6a*S*, 11a*S*)-4-(6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **31**

(Unresolved diastereomeric mixture)

($CDCl_3$)



δ_H	Signal	Assignment
7.44	2 x d, 9	2 x H-1(A)
7.39/7.38	s	2 x H-4(E)
7.15	2 x d, 9	2 x H-7(D)
6.92/6.91	d, 9	2 x H-2(A)
6.51/6.48	s	2 x H-7(E)
6.47	dd; 9, 3	2 x H-8(D)
6.47/6.44	d, 3	2 x H-10(D)
5.57/5.56	d, 7	2 x H-11a
5.24/5.22/5.20/5.19	s	2 x 3(A)-$OC\underline{H}_2OCH_3$, 2 x 5(E)-$OC\underline{H}_2OCH_3$
4.91/4.88	dd; 10, 4/5	2 x H-2(G)
4.35-4.25	m	2 x H-6*eq*
3.94/3.90/3.79/3.78	s	2 x 9(D)-$OC\underline{H}_3$, 2 x 6(E)-$OC\underline{H}_3$
3.68-3.57	m	2 x H-6*ax*, 2 x H-6(B)
3.53/3.52/3.48/3.48	s	2 x 3(A)-$OCH_2OC\underline{H}_3$, 2 x 5(E)-$OCH_2OC\underline{H}_3$
3.27/3.26	dd; 14, 4/5	2 x 4(A)-$C\underline{H}_2$
3.14/3.12	dd; 14, 10	2 x 4(A)-$C\underline{H}_2$

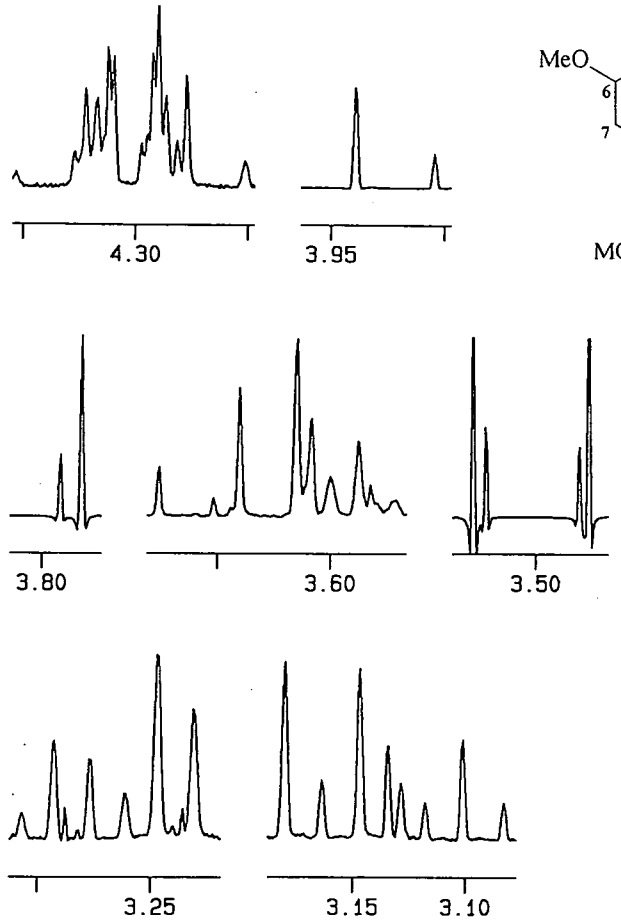
(continued overleaf...)

Plate 44: (6a*S*, 11a*S*)-4-(6-Methoxy-5-*O*-methoxymethyl-2,3-dihydrobenzo[b]furan-3-one-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **31**

(Unresolved diastereomeric mixture)

(continued)

δ_H	Signal	Assignment
7.44	2 x d, 9	2 x H-1(A)
7.39/7.38	s	2 x H-4(E)
7.15	2 x d, 9	2 x H-7(D)
6.92/6.91	d, 9	2 x H-2(A)
6.51/6.48	s	2 x H-7(E)
6.47	dd; 9, 3	2 x H-8(D)
6.47/6.44	d, 3	2 x H-10(D)
5.57/5.56	d, 7	2 x H-11a
5.24/5.22/5.20/5.19	s	2 x 3(A)-$OC\underline{H}_2OCH_3$, 2 x 5(E)-$OC\underline{H}_2OCH_3$
4.91/4.88	dd; 10, 4/5	2 x H-2(G)
4.35-4.25	m	2 x H-6*eq*
3.94/3.90/3.79/3.78	s	2 x 9(D)-$OC\underline{H}_3$, 2 x 6(E)-$OC\underline{H}_3$
3.68-3.57	m	2 x H-6*ax*, 2 x H-6(B)
3.53/3.52/3.48/3.48	s	2 x 3(A)-$OCH_2OC\underline{H}_3$, 2 x 5(E)-$OCH_2OC\underline{H}_3$
3.27/3.26	dd; 14, 4/5	2 x 4(A)-$C\underline{H}_2$
3.14/3.12	dd; 14, 10	2 x 4(A)-$C\underline{H}_2$



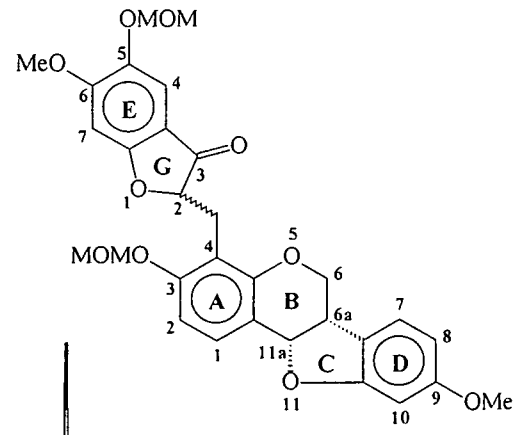
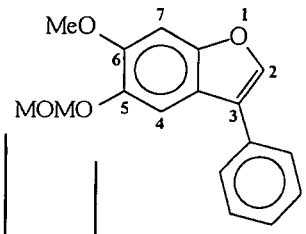


Plate 45: 6-Methoxy-5-*O*-methoxymethyl-3-phenylbenzo[b]furan **95**

($CDCl_3$)



δ_H	Signal	Assignment
7.73	s	H-4
7.65-7.62/ 7.53-7.47/ 7.41-7.35	m	$C_6\underline{H}_5$
7.57	s	H-7
7.13	s	H-2
5.28	s	$OC\underline{H}_2OCH_3$
3.97	s	$Ar\text{-}OC\underline{H}_3$
3.57	s	$OCH_2OC\underline{H}_3$

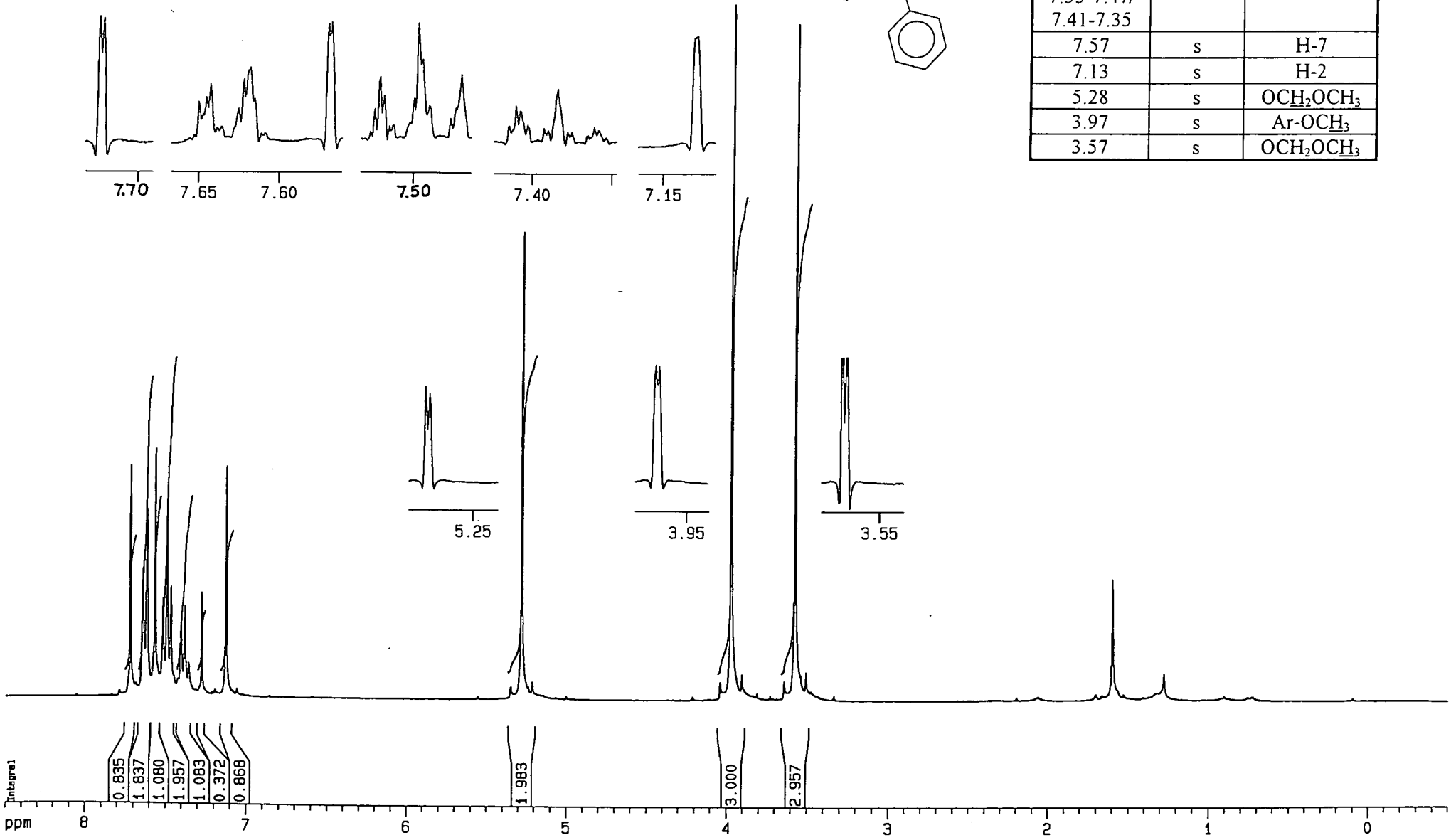


Plate 46: 4,6-Dimethoxy-2-(4-methoxybenzyl)-2,3-dihydrobenzo[b]furan-3-one **97**
($CDCl_3$)

δ_H	Signal	Assignment
7.24	d, 9	H-2', H-6'
6.84	d, 9	H-3', H-5'
6.14	d, 2	H-7
5.99	d, 2	H-5
4.74	dd; 9, 4	H-2
3.91/3.86/3.79	s	3 x $OC\underline{H}_3$
3.31/2.92	dd; 15, 4/9	$C\underline{H}_2$

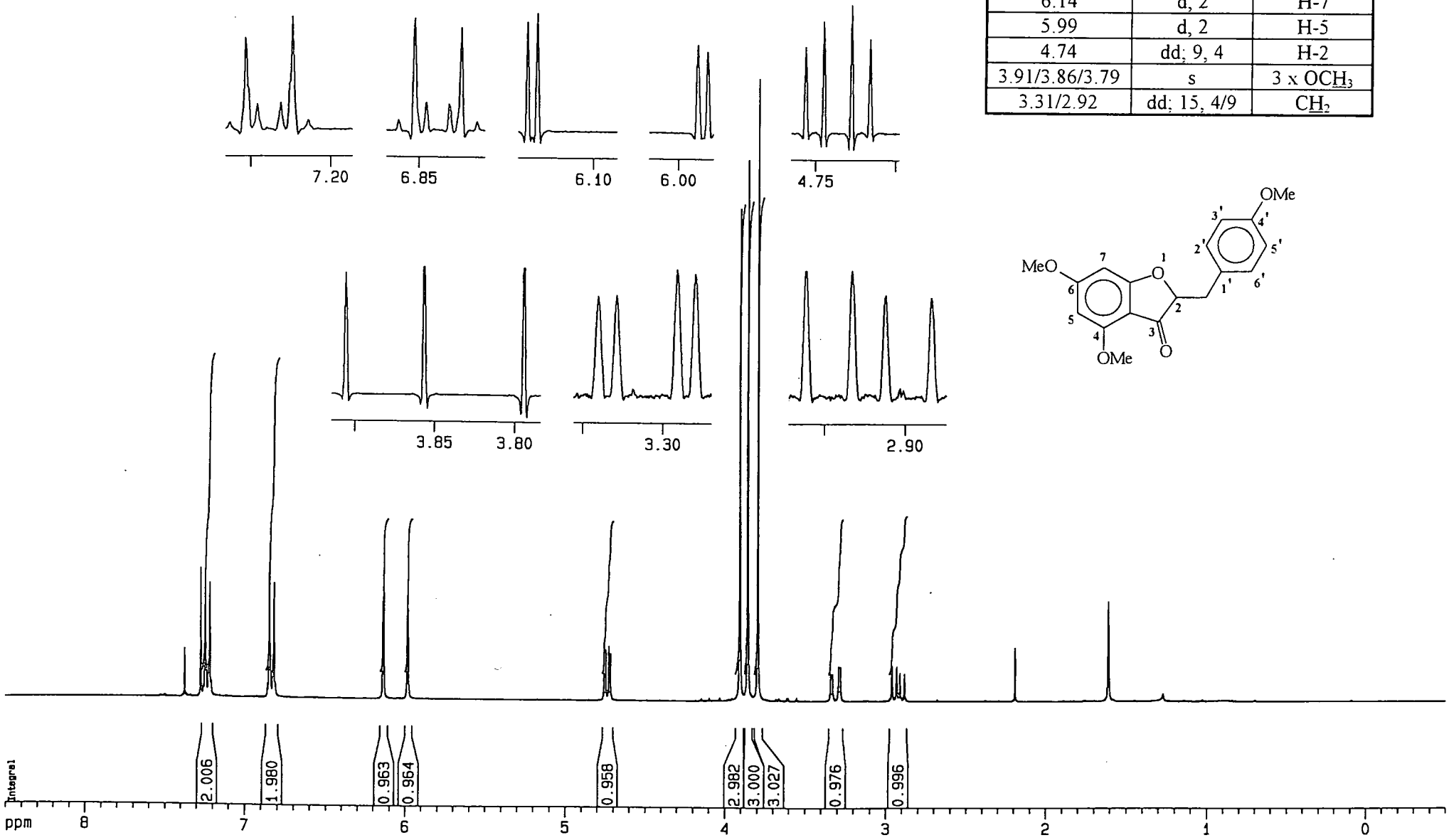


Plate 47: 3-Hydroxy-4,6-dimethoxy-2-(4-methoxybenzyl)-3-phenyl-2,3-dihydrobenzo[b]furan **98** ($CDCl_3$)

δ_H	Signal	Assignment
7.47-7.43/ 7.39-7.25	m	$C_6\underline{H}_5$
7.18	d, 9	H-2', H-6'
6.83	d, 9	H-3', H-5'
6.16	d, 2	H-7
6.05	d, 2	H-5
4.60	dd; 8, 5	H-2
3.81/3.79/3.61	s	3 x $O\underline{CH}_3$
3.13/3.12	br d, 8/5	$\underline{CH}_2$
2.45	br s	$O\underline{H}$

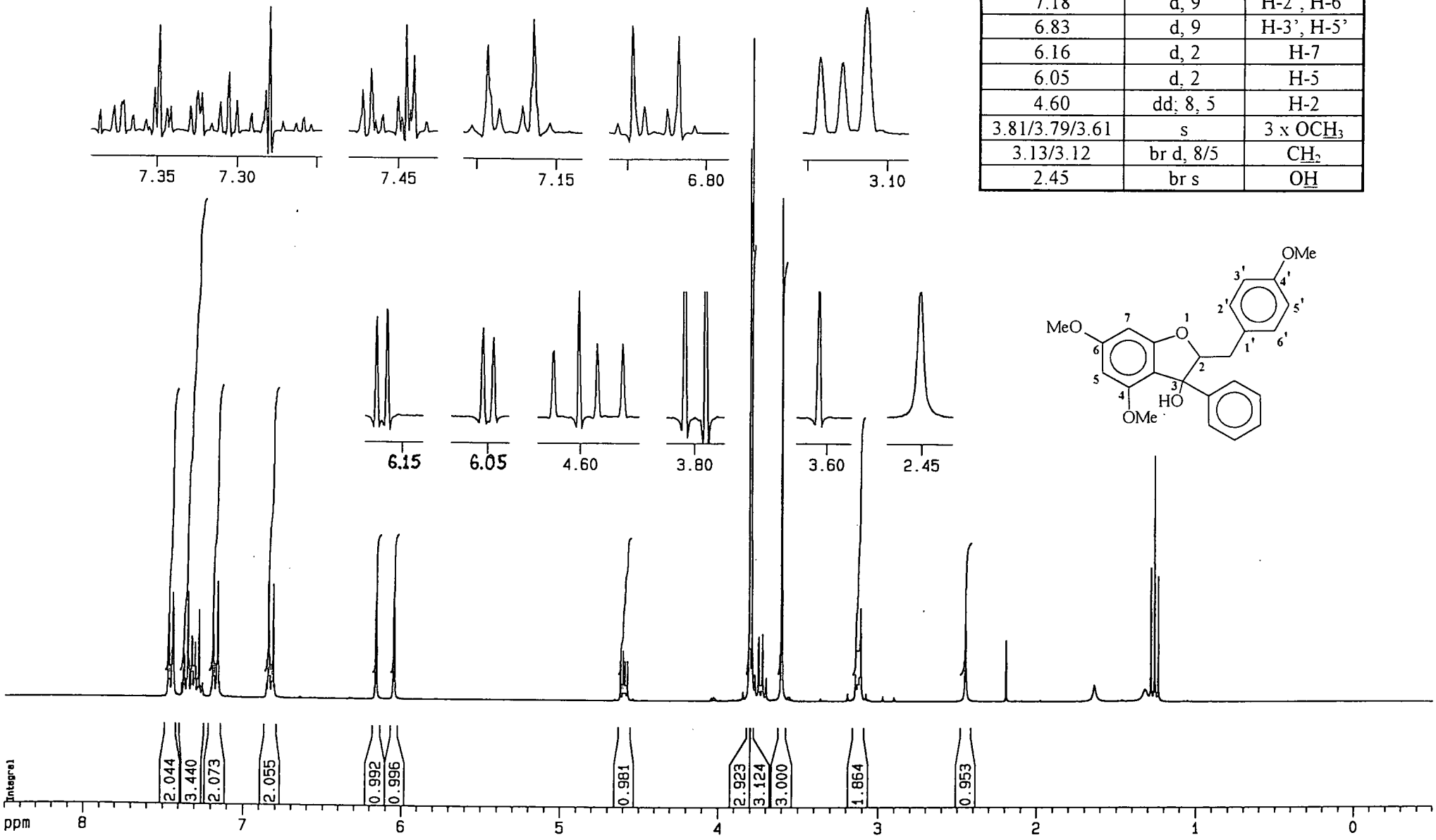
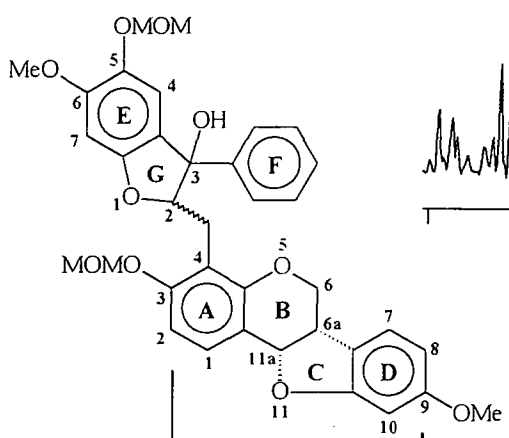


Plate 48: (6a*S*, 11a*S*)-4-(3-Hydroxy-6-methoxy-5-*O*-methoxymethyl-3-phenyl-2,3-dihydrobenzo[b]furan-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **32**

(Unresolved diastereomeric mixture)

($CDCl_3$)



δ_H	Signal	Assignment
7.35-7.29/ 7.26-7.11	m	2 x H-1(A), 2 x H-7(D), 2 x $C_6\underline{H}_5$(F)
6.78/6.78	s	2 x H-4(E)
6.74/6.74	d, 9	2 x H-2(A)
6.54/6.45	s	2 x H-7(E)
6.51-6.44	m	2 x H-8(D), 2 x H-10(D)
5.44/5.42	d, 7	2 x H-11a
5.05/5.04/ 5.02/5.02	s	2 x 3(A)-OC$\underline{H}_2$OCH$_3$, 2 x 5(E)-OC$\underline{H}_2$OCH$_3$
5.11-4.92	m	2 x H-2(G)
4.22/4.14	ddd; 10, 4/5, 1	2 x H-6*eq*
3.87/3.86/ 3.79/3.78	s	2 x 9(D)-OC$\underline{H}_3$, 2 x 6(E)-OC$\underline{H}_3$
3.63-3.46	m	2 x H-6*ax*, 2 x H-6(B)
3.45/3.44/ 3.38/3.35	s	2 x 3(A)-OCH$_2$OC$\underline{H}_3$, 2 x 5(E)-OCH$_2$OC$\underline{H}_3$
3.33-3.20	m	2 x 4(A)-C$\underline{H}_2$
2.91	s	2 x 3(G)-O$\underline{H}$

(continued overleaf...)

Plate 48: (6a*S*, 11a*S*)-4-(3-Hydroxy-6-methoxy-5-*O*-methoxymethyl-3-phenyl-2,3-dihydrobenzo[b]furan-2-ylmethyl)-3-*O*-methoxymethylmedicarpin **32**

(Unresolved diastereomeric mixture)

(continued)

δ_H	Signal	Assignment
7.35-7.29/ 7.26-7.11	m	2 x H-1(A), 2 x H-7(D), 2 x $C_6\underline{H}_5$(F)
6.78/6.78	s	2 x H-4(E)
6.74/6.74	d, 9	2 x H-2(A)
6.54/6.45	s	2 x H-7(E)
6.51-6.44	m	2 x H-8(D), 2 x H-10(D)
5.44/5.42	d, 7	2 x H-11a
5.05/5.04/ 5.02/5.02	s	2 x 3(A)-$OC\underline{H}_2OCH_3$, 2 x 5(E)-$OC\underline{H}_2OCH_3$
5.11-4.92	m	2 x H-2(G)
4.22/4.14	ddd; 10, 4/5, 1	2 x H-6*eq*
3.87/3.86/ 3.79/3.78	s	2 x 9(D)-$OC\underline{H}_3$, 2 x 6(E)-$OC\underline{H}_3$
3.63-3.46	m	2 x H-6*ax*, 2 x H-6(B)
3.45/3.44/ 3.38/3.35	s	2 x 3(A)-$OCH_2OC\underline{H}_3$, 2 x 5(E)-$OCH_2OC\underline{H}_3$
3.33-3.20	m	2 x 4(A)-$C\underline{H}_2$
2.91	s	2 x 3(G)-O<u>H</u>

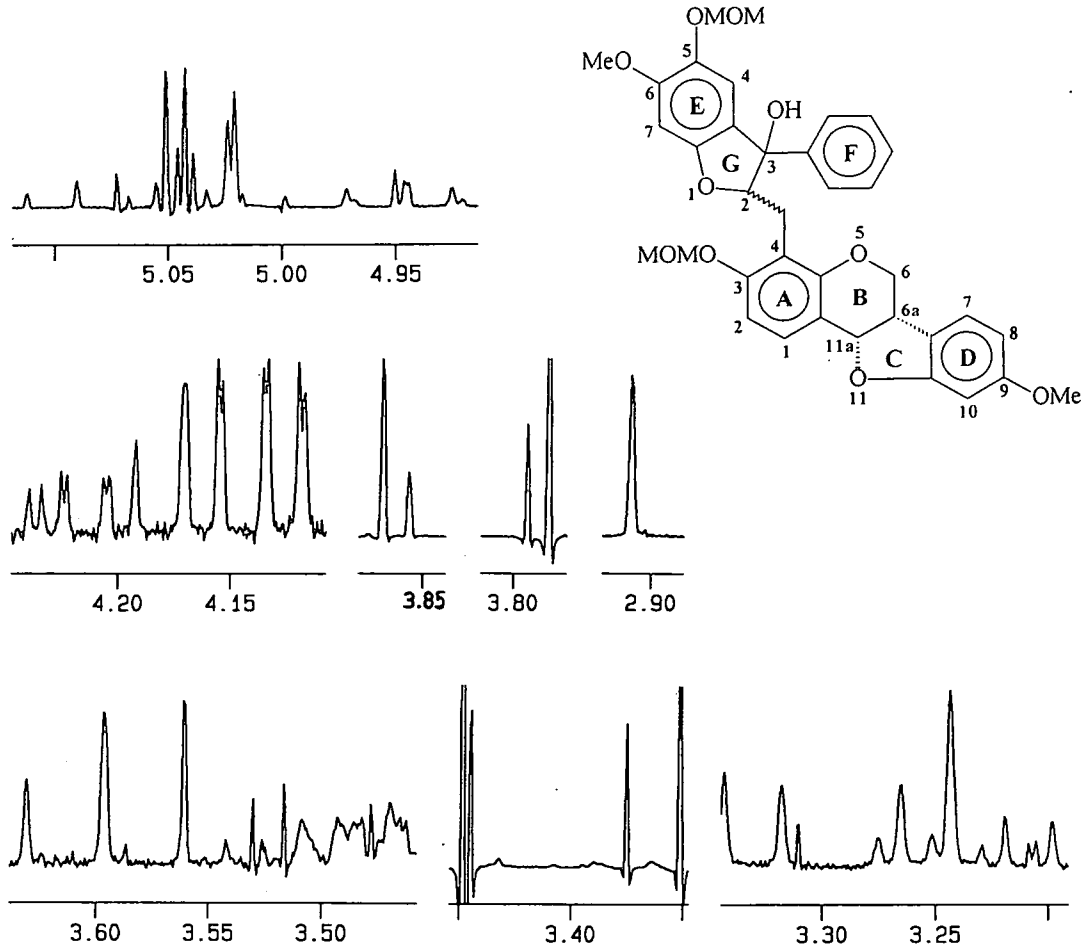
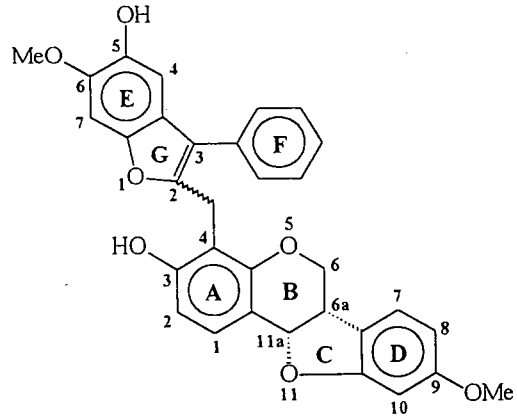


Plate 49: Daljanelin B **13**

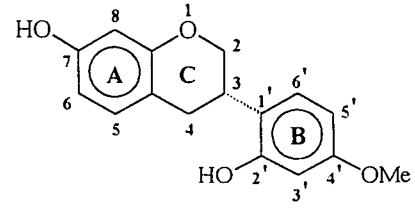
($CDCl_3$)



δ_H	Signal	Assignment
7.67-7.63	m	2 x H(F)
7.45	s	H-4(E)
7.41	d, 8	H-1(A)
7.39-7.29	m	3 x H(F)
6.81	d, 8	H-7(D)
6.66	d, 2	H-10(D)
6.60	s	H-7(E)
6.53	d, 8	H-2(A)
6.51	dd; 8, 2	H-8(D)
5.52/5.46	br s	3(A)-O<u>H</u>, 5(E)-O<u>H</u>
5.30	d, 7	H-11a
4.36	s	4(A)-C<u>H</u>$_2$
3.92	ddd; 11, 5, 1	H-6*eq*
3.45	t, 11	H-6*ax*
3.34/3.14	s	9(A)-OC<u>H</u>$_3$, 6(E)-OC<u>H</u>$_3$
3.12-3.01	m	H-6a

Plate 50: (+)-(3*S*)-Vestitol **2**

($CDCl_3$)



δ_H	Signal	Assignment
7.03	d, 9	H-6'
6.96	d, 8	H-5
6.50	dd; 9, 2	H-5'
6.41	dd; 8, 2	H-6
6.38	d, 2	H-8
6.37	d, 2	H-3'
4.96/4.70	br s	7-O<u>H</u>, 2'-O<u>H</u>
4.35	ddd; 11, 4, 2	H-2*eq*
4.06	dd; 10, 10	H-2*ax*
3.79	s	4'-OC<u>H</u>$_3$
3.57-3.47	m	H-3
3.02	ddd; 16, 10, 1	H-4*ax*
2.91	ddd; 16, 6, 2	H-4-*eq*

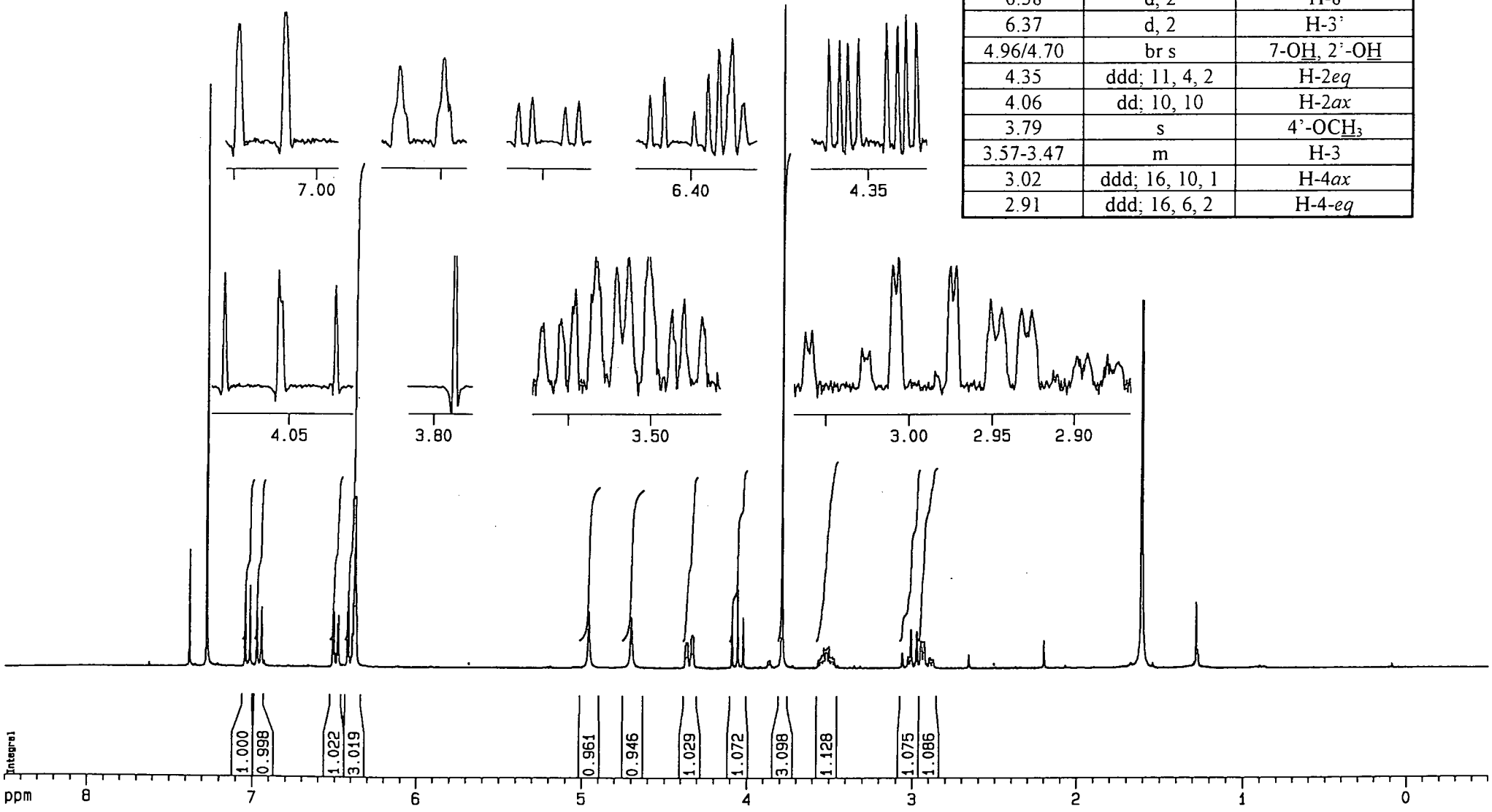


Plate 51: (3*S*)-{2'-*O*,7-*O*-Di-[(α*R*)-α-trifluoromethyl-α-methoxyphenylacetyl}vestitol **101**

($CDCl_3$)

δ_H	Signal	Assignment
7.70-7.66/ 7.64-7.60/ 7.52-7.47/ 7.32-7.28	m	2 x $C_6\underline{H}_5$
7.10	d, 9	H-6'
6.99	d, 8	H-5
6.84	dd; 9, 3	H-5'
6.69	d, 3	H-3'
6.64	dd; 8, 2	H-6
6.62	d, 2	H-8
4.16	ddd; 11, 4, 2	H-2*eq*
3.91	dd; 11, 10	H-2*ax*
3.82	s	4'-$OC\underline{H}_3$
3.73/3.69	q, 1	2 x $PhC(CF_3)OC\underline{H}_3$
2.95-2.86	m	H-3
2.85-2.67	m	H-4*ax*, H-4-*eq*

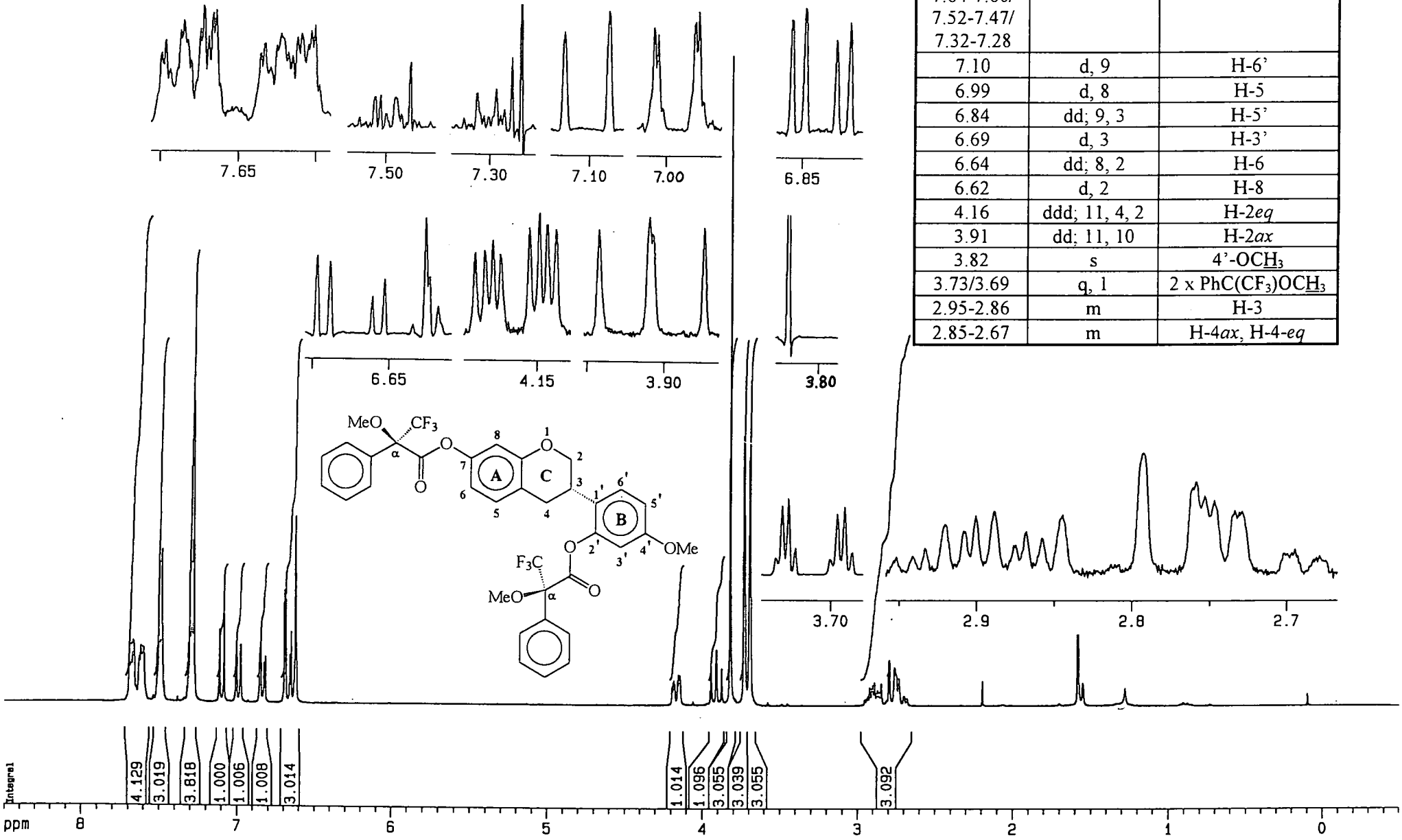
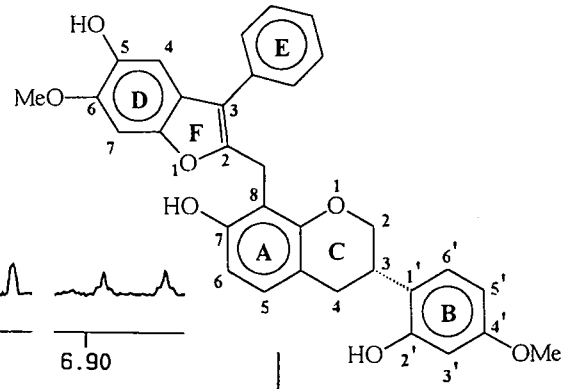


Plate 52: Daljanelin D.15

($CDCl_3$)

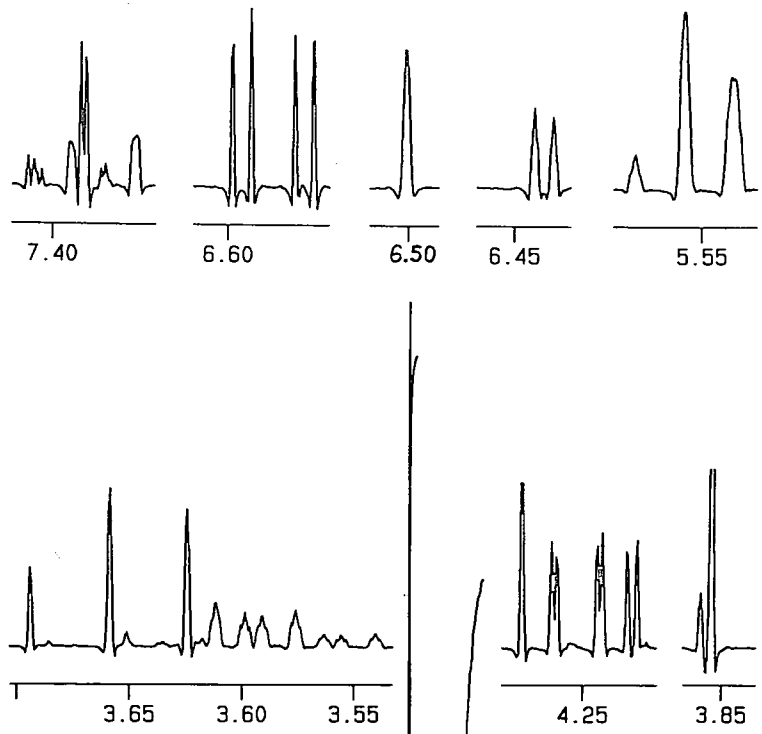


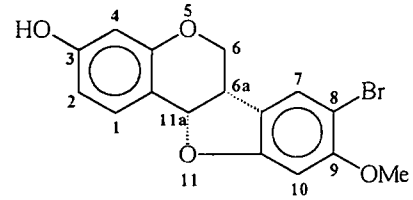
δ_H	Signal	Assignment
7.62-7.59/ 7.50-7.44/ 7.37-7.33	m	5 x H(E)
7.06	s	H-4(D)
7.02	s	H-7(D)
6.99	d, 9	H-6'(B)
6.88	d, 8	H-5(A)
6.50	d, 8	H-6(A)
6.45	dd; 8, 3	H-5'(B)
6.38	d, 3	H-3'(B)
4.24-4.18	m	4(A)-$C\underline{H}_2$, H-2*eq*
3.94/3.78	s	4'(B)-$OC\underline{H}_3$, 6(D)-$OC\underline{H}_3$
3.93	dd; 10, 10	H-2*ax*
3.49-3.41	m	H-3(C)
3.05-2.87	m	H-4*ax*, H-4*eq*

Plate 53: (6a*S*, 11a*S*)-8-Bromomedicarpin **109**

($CDCl_3$)

δ_H	Signal	Assignment
7.39	s	H-7
7.38	d, 9	H-1
6.58	dd; 8, 3	H-2
6.50	s	H-10
6.44	d, 3	H-4
5.55	d, 7	H-11a
5.4	br s	O<u>H</u>
4.25	ddd; 10, 4, 1	H-6*eq*
3.85	s	$OC\underline{H}_3$
3.66	t; 11, 10	H-6*ax*
3.61-3.54	m	H-6a





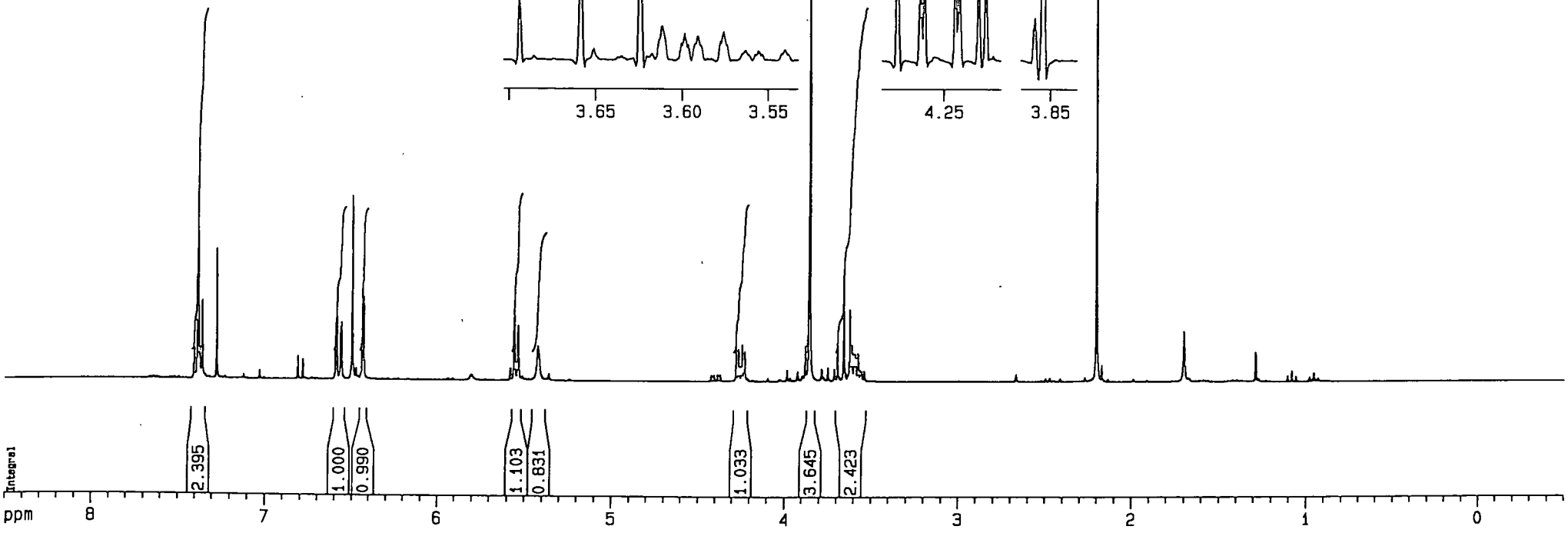
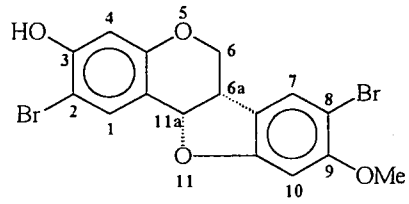


Plate 54: (6a*S*, 11a*S*)-2,8-Dibromomedicarpin **102**

($CDCl_3$)



δ_H	Signal	Assignment
7.62	s	H-1
7.39	s	H-7
6.64	s	H-4
6.50	s	H-10
5.59	br s	O<u>H</u>
5.52	d, 7	H-11a
4.27	ddd; 10, 4, 1	H-6*eq*
3.86	s	O<u>CH</u>$_3$
3.67	t; 11, 10	H-6*ax*
3.63-3.57	m	H-6a

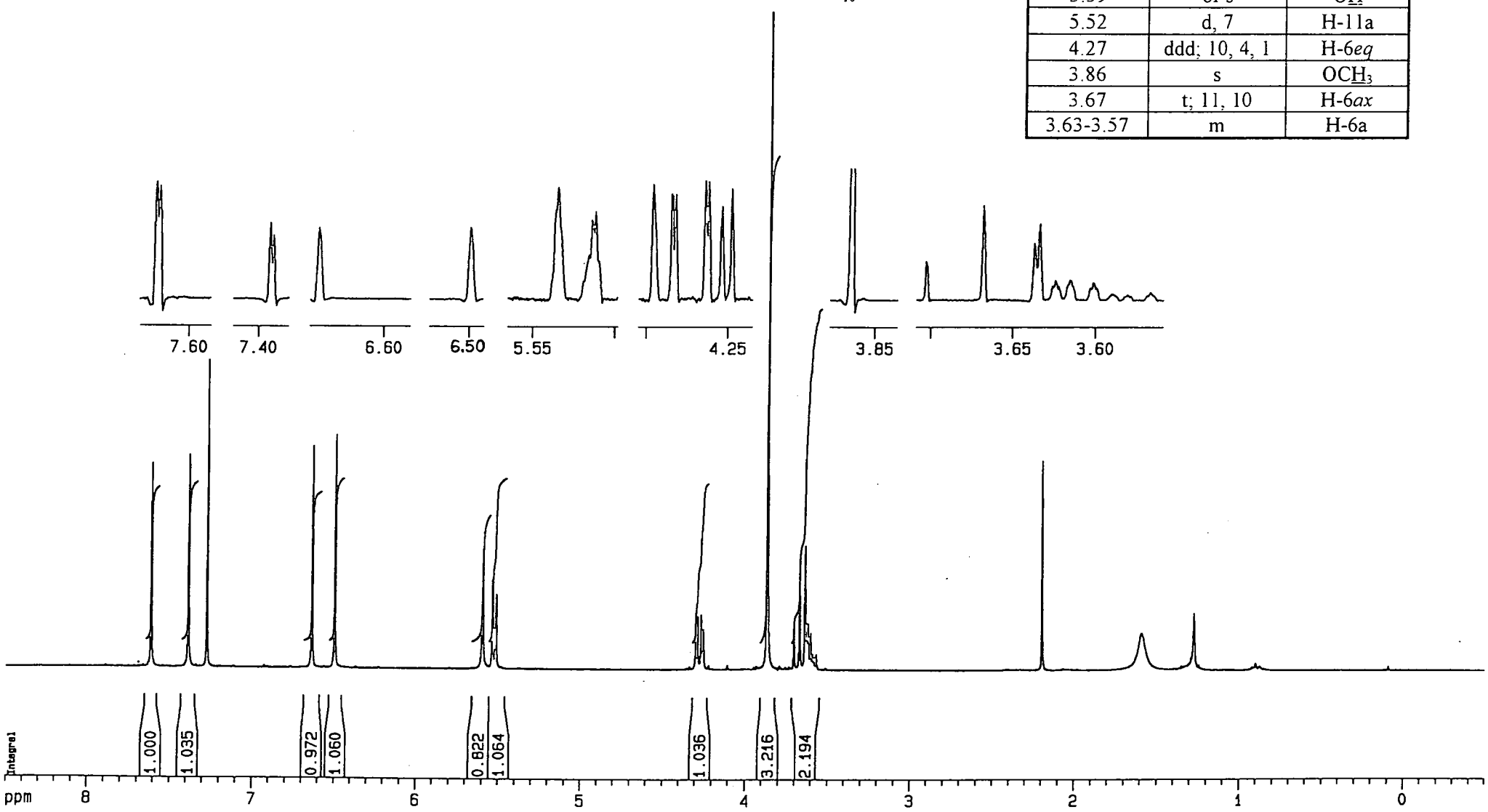
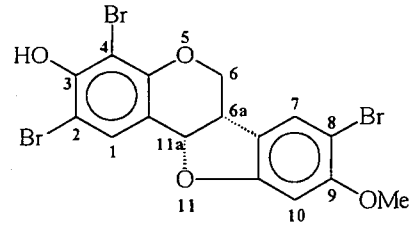


Plate 55: (6a*S*, 11a*S*)-2,4,8-Tribromomedicarpin **110**

($CDCl_3$)



δ_H	Signal	Assignment
7.65	s	H-1
7.41	s	H-7
6.50	s	H-10
6.1	br s	O<u>H</u>
5.55	d, 7	H-11a
4.41	ddd; 11, 5, 1	H-6*eq*
3.87	s	O<u>C</u>H$_3$
3.77	t, 11	H-6*ax*
3.70-3.61	m	H-6a

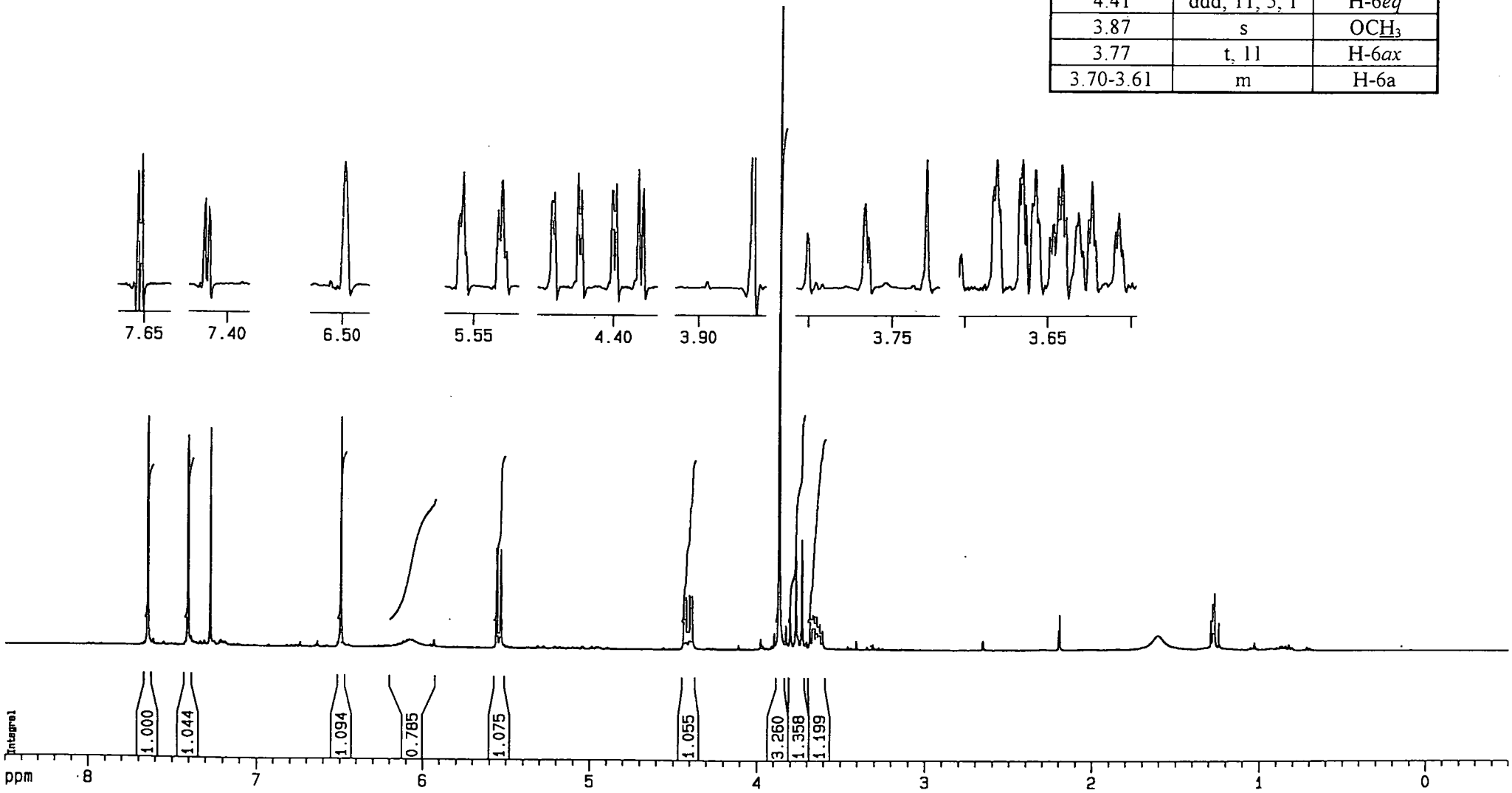


Plate 56: (6a*S*, 11a*S*)-2,8-Dibromo-3-*O*-methoxymethylmedicarpin **103**

($CDCl_3$)

δ_H	Signal	Assignment
7.69	s	H-1
7.39	s	H-7
6.78	s	H-4
6.50	s	H-10
5.53	d, 7	H-11a
5.25	s	$OC\underline{H}_2OCH_3$
4.28	ddd; 10, 4, 1	H-6*eq*
3.87	s	Ar-$OC\underline{H}_3$
3.68	t, 10	H-6*ax*
3.64-3.57	m	H-6a
3.52	s	$OCH_2OC\underline{H}_3$

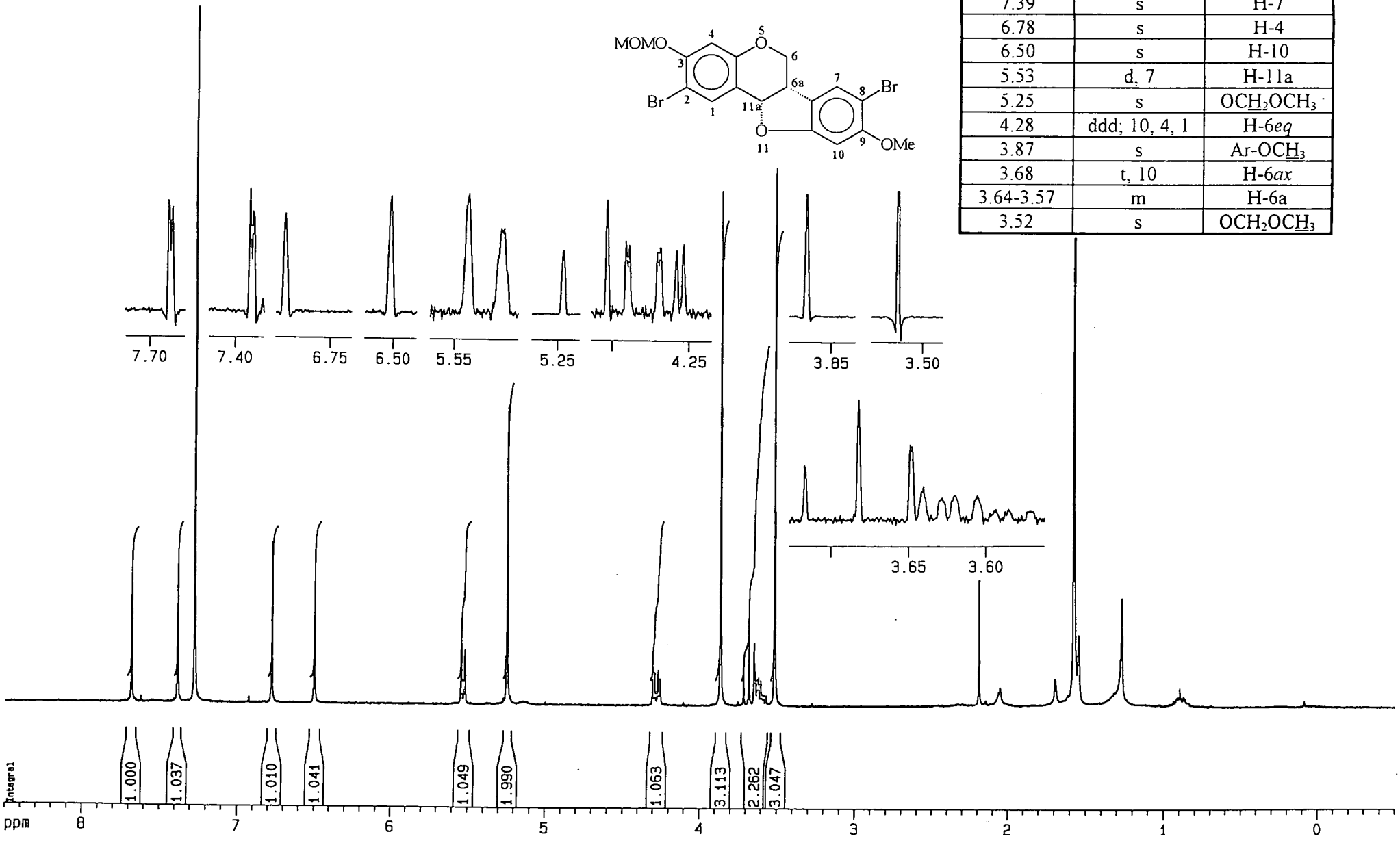
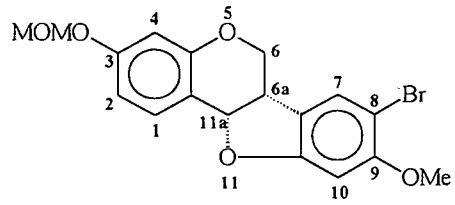


Plate 57: (6a*S*, 11a*S*)-8-Bromo-3-*O*-methoxymethylmedicarpin **111**

($CDCl_3$)



δ_H	Signal	Assignment
7.43	d, 9	H-1
7.39	s	H-7
6.78	dd; 9, 3	H-2
6.66	d, 3	H-4
6.50	s	H-10
5.57	d, 7	H-11a
5.18	dd; 8, 7	$OC\underline{H}_2OCH_3$
4.27	ddd; 10, 4, 1	H-6*eq*
3.86	s	Ar-$OC\underline{H}_3$
3.68	t; 11, 10	H-6*ax*
3.63-3.56	m	H-6a
3.48	s	$OCH_2OC\underline{H}_3$

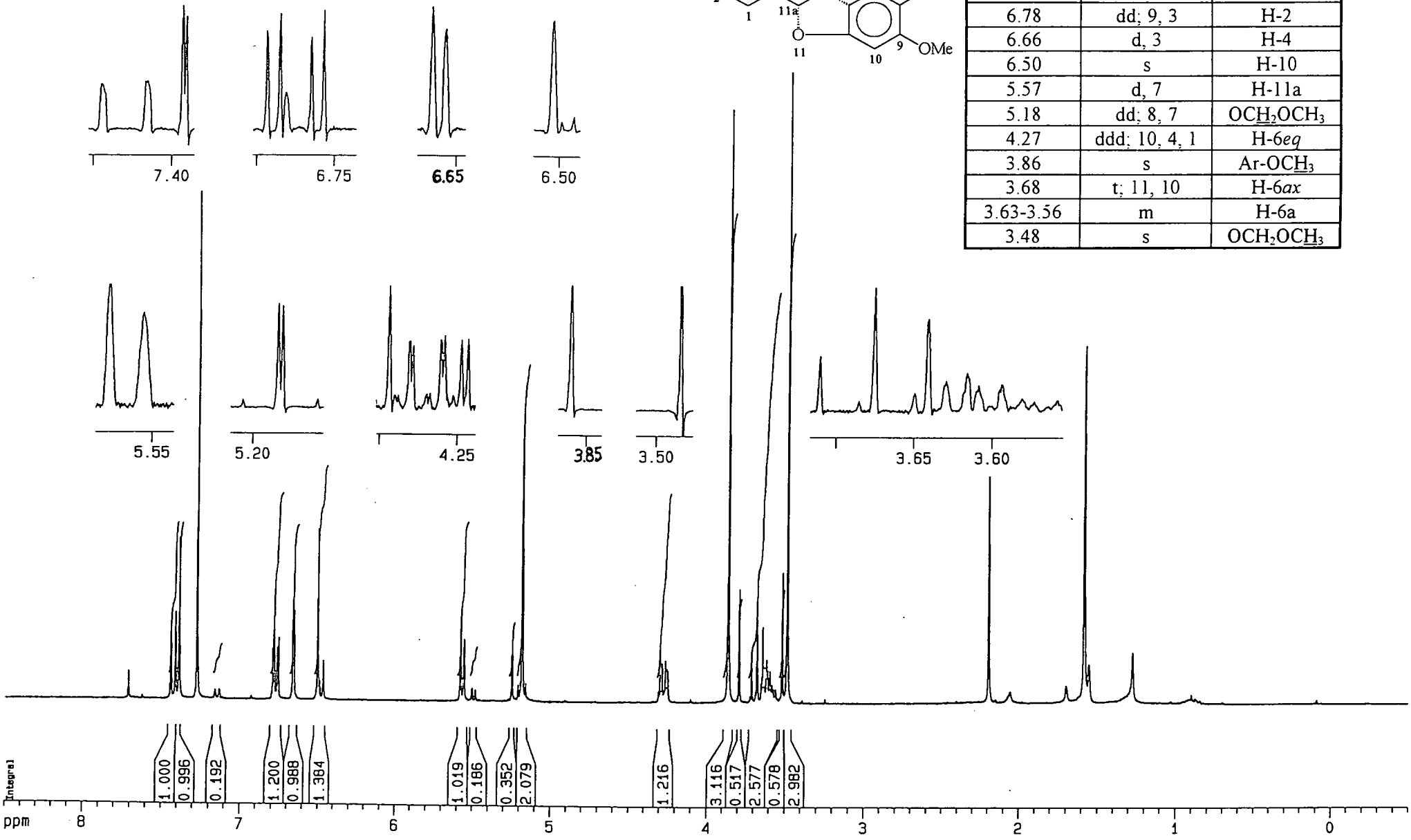
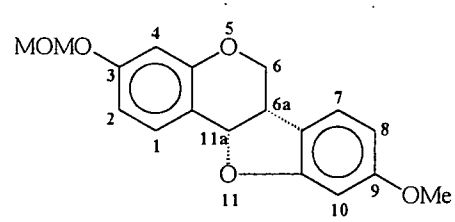


Plate 58: (6a*S*, 11a*S*)-3-*O*-Methoxymethylmedicarpin **112**

($CDCl_3$)



δ_H	Signal	Assignment
7.46	d, 9	H-1
7.15	d, 9	H-7
6.77	dd; 9, 3	H-2
6.66	d, 3	H-4
6.47	dd; 9, 2	H-8
6.47	d, 2	H-10
5.53	d, 7	H-11a
5.18	dd; 8, 7	$OC\underline{H}_2OCH_3$
4.27	ddd; 10, 5, 1	H-6*eq*
3.79	s	$Ar\text{-}OC\underline{H}_3$
3.65	t; 11, 10	H-6*ax*
3.60-3.52	m	H-6a
3.48	s	$OCH_2OC\underline{H}_3$

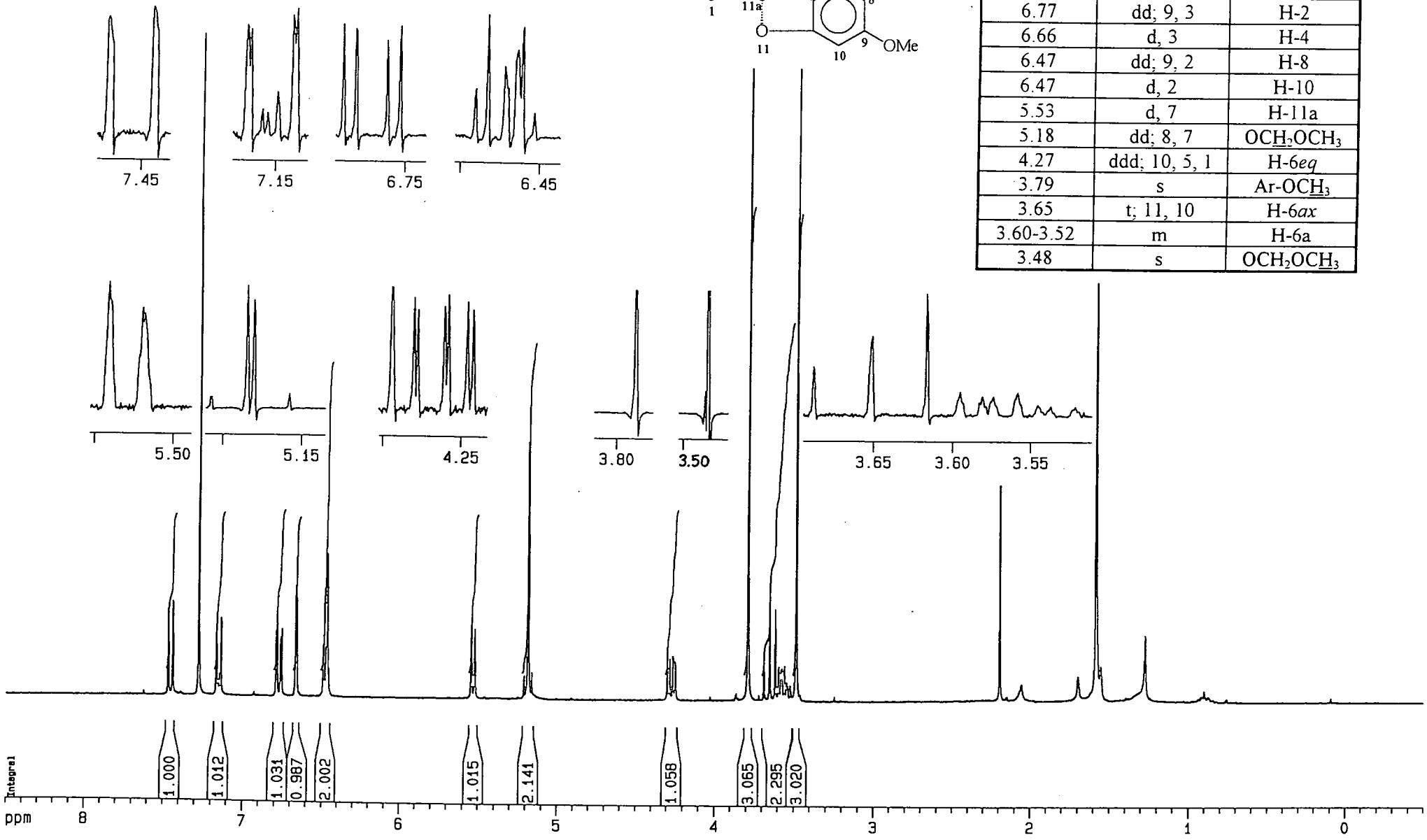


Plate 59: (6a*S*, 11a*S*)-8-Bromo-2-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **113**

($CDCl_3$)

δ_H	Signal	Assignment
8.08	s	H-1
7.40	s	H-7
6.77	s	H-4
6.52	s	H-10
5.56	d, 7	H-11a
5.26	s	OCH_2OCH_3
4.36	q, 7	$CO_2CH_2CH_3$
4.32	dd; 11, 5	H-6*eq*
3.86	s	Ar-OCH_3
3.72	t, 11	H-6*ax*
3.65-3.58	m	H-6a
3.53	s	OCH_2OCH_3
1.41	t, 7	$CO_2CH_2CH_3$

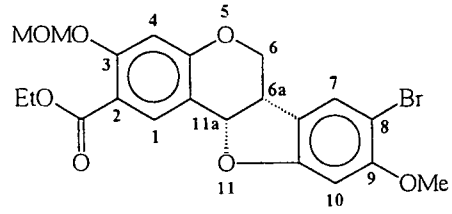


Plate 60: 2,8-Dibromo-4-ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **114**

[$(CD_3)_2CO$]

δ_H	Signal	Assignment
7.83	s	H-1
7.56	s	H-7
6.63	s	H-10
5.76	d, 7	H-11a
5.12	s	$OC\underline{H}_2OCH_3$
4.46	dd; 11, 4	H-6*eq*
4.34	q, 7	$CO_2C\underline{H}_2CH_3$
3.95	t; 8, 9	H-6*ax*
3.91-3.88	m	H-6a
3.86	s	Ar-$OC\underline{H}_3$
3.54	s	$OCH_2OC\underline{H}_3$
1.32	t, 7	$CO_2CH_2C\underline{H}_3$

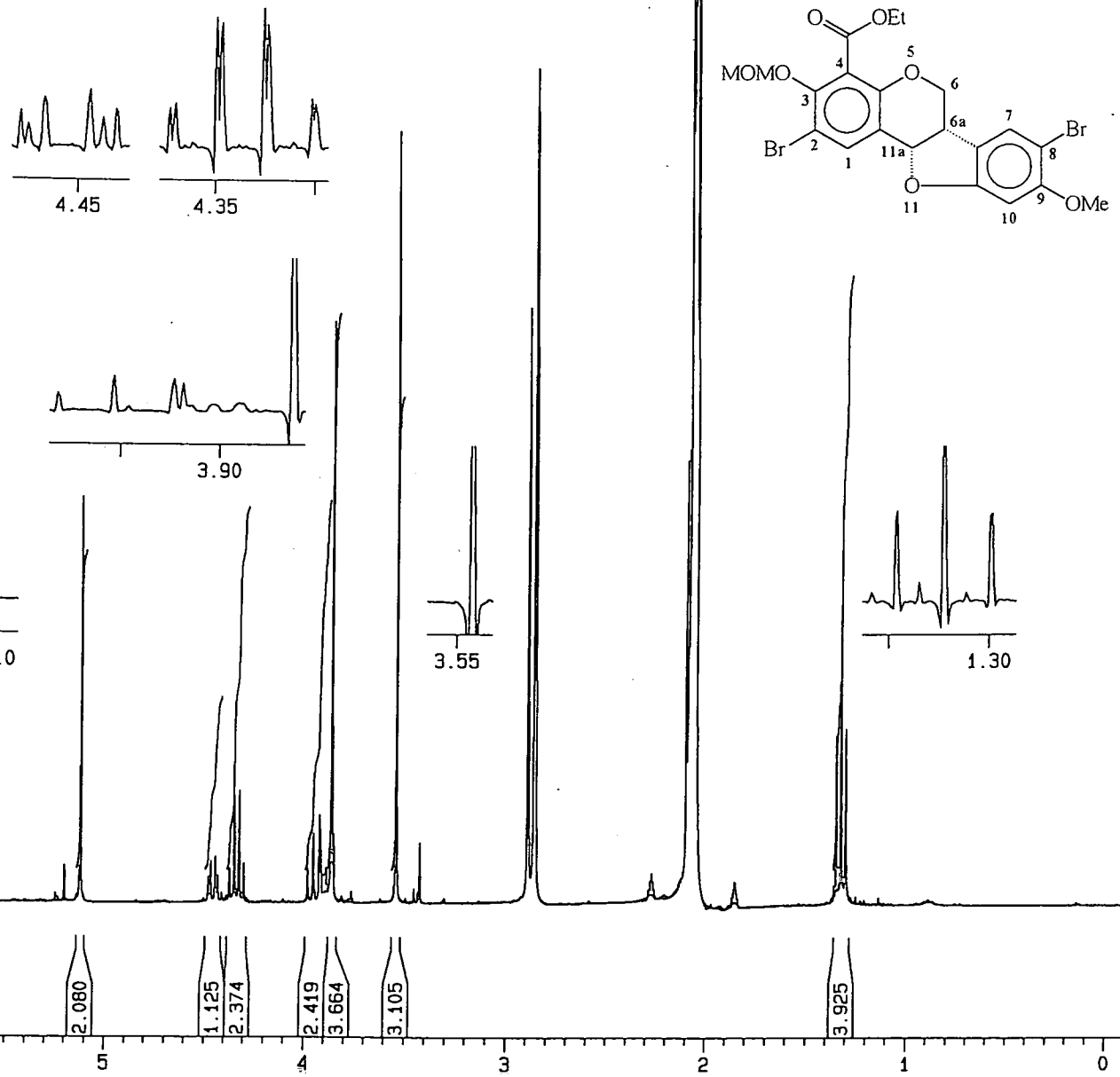


Plate 61: (6a*S*, 11a*S*)-2-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **106**

($CDCl_3$)

δ_H	Signal	Assignment
8.11	s	H-1
7.16	d, 9	H-7
6.77	s	H-4
6.49	dd; 9, 2	H-8
6.48	d, 2	H-10
5.53	d, 7	H-11a
5.26	s	OCH_2OCH_3
4.36	q, 7	$CO_2CH_2CH_3$
4.32	ddd; 11, 5, 1	H-6*eq*
3.79	s	Ar-OCH_3
3.69	t, 11	H-6*ax*
3.62-3.56	m	H-6a
3.53	s	OCH_2OCH_3
1.41	t, 7	$CO_2CH_2CH_3$

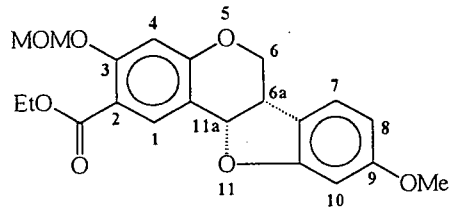
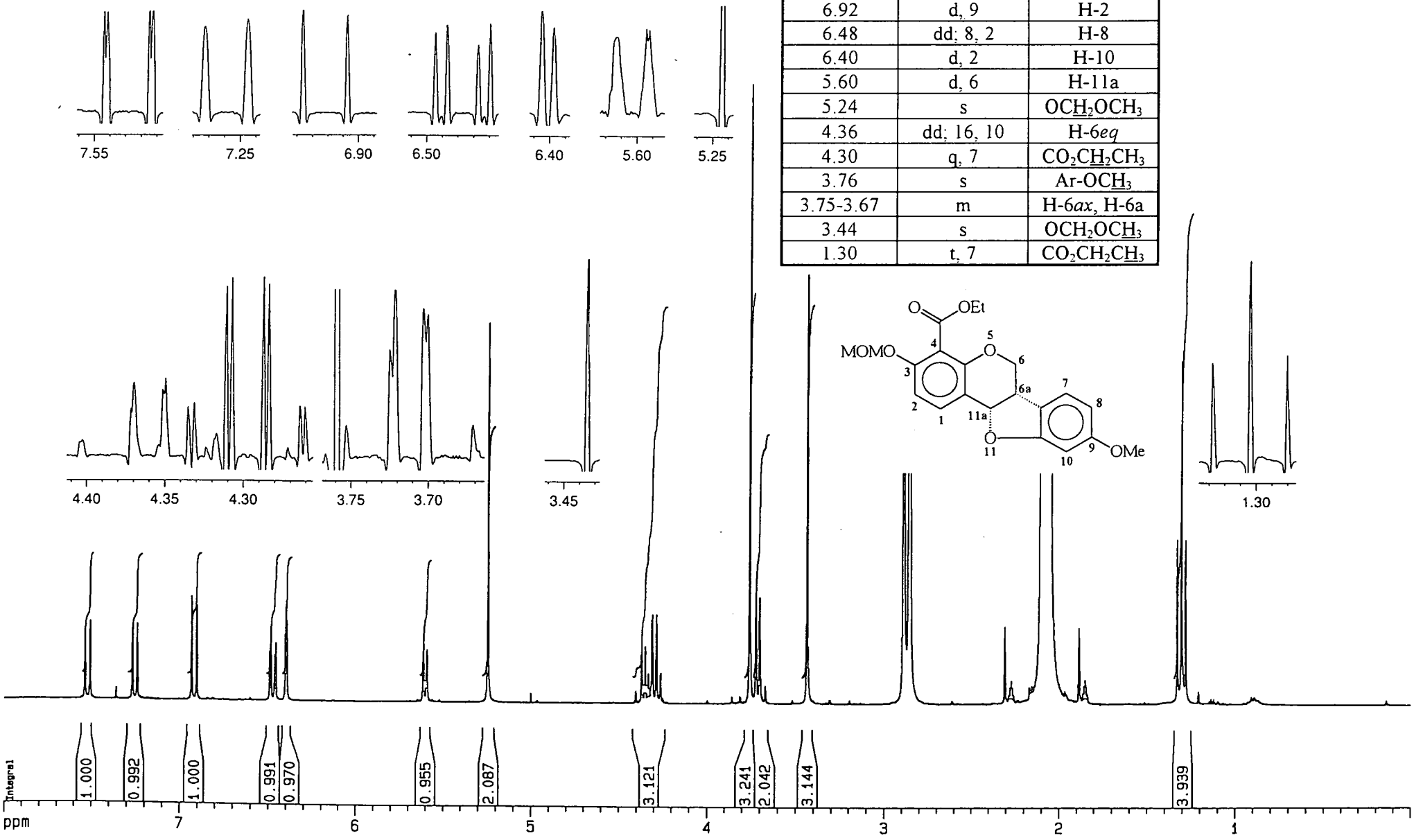


Plate 62: (6a*S*, 11a*S*)-4-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **115**

$[(CD_3)_2CO]$

δ_H	Signal	Assignment
7.53	d, 9	H-1
7.26	d, 8	H-7
6.92	d, 9	H-2
6.48	dd; 8, 2	H-8
6.40	d, 2	H-10
5.60	d, 6	H-11a
5.24	s	$OC\underline{H}_2OCH_3$
4.36	dd; 16, 10	H-6*eq*
4.30	q, 7	$CO_2C\underline{H}_2CH_3$
3.76	s	Ar-$OC\underline{H}_3$
3.75-3.67	m	H-6*ax*, H-6a
3.44	s	$OCH_2OC\underline{H}_3$
1.30	t, 7	$CO_2CH_2C\underline{H}_3$



4.2. Appendix B: CD spectra

Plate 1: Daljanelin B 13

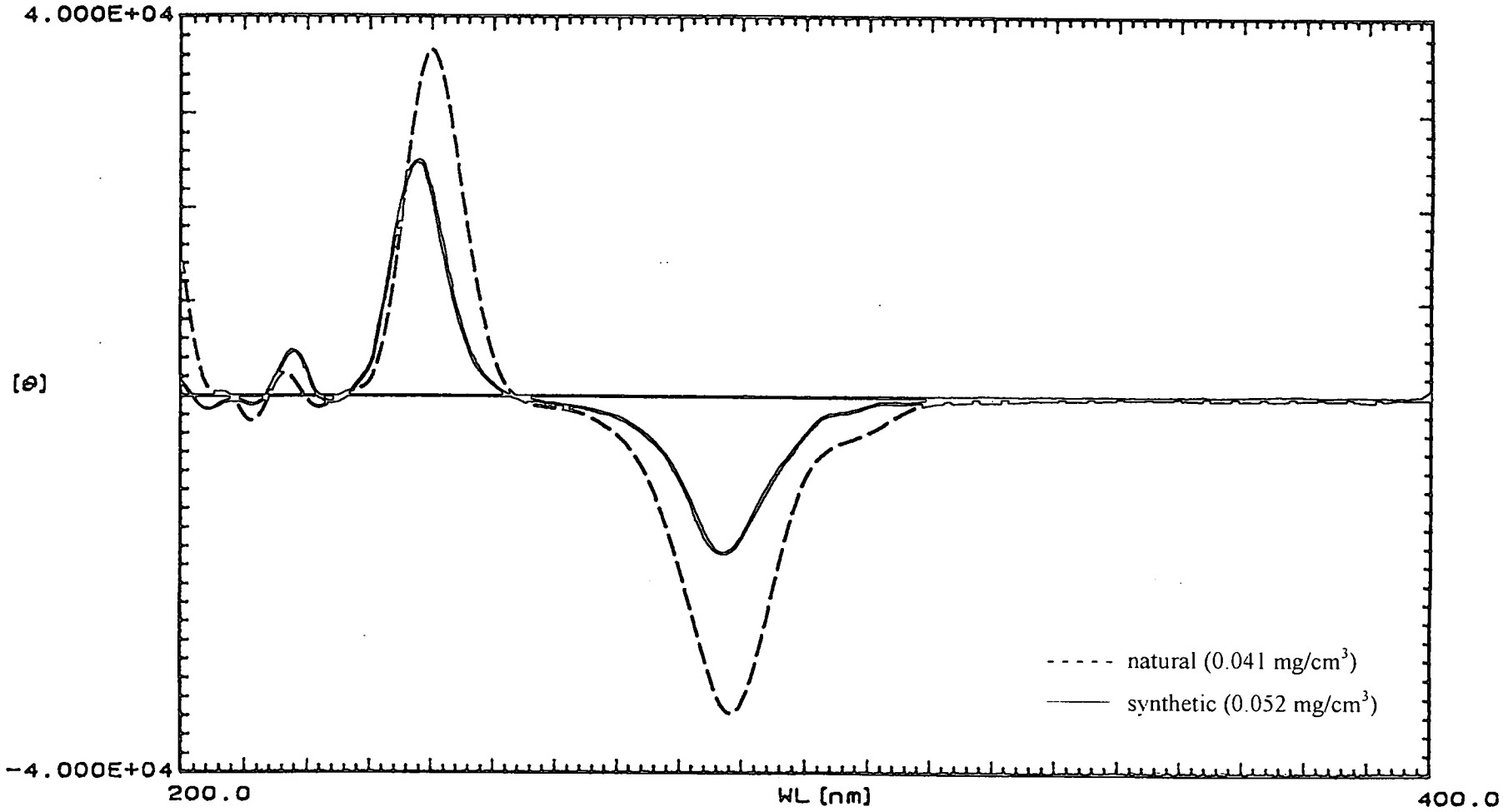
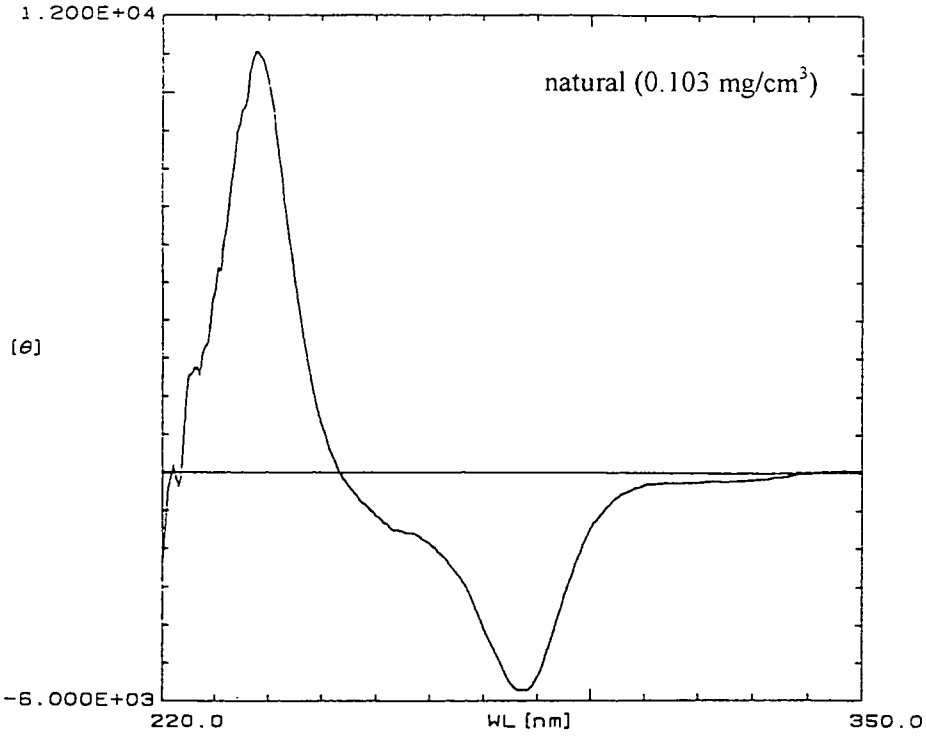


Plate 2: Daljanelin D **15**



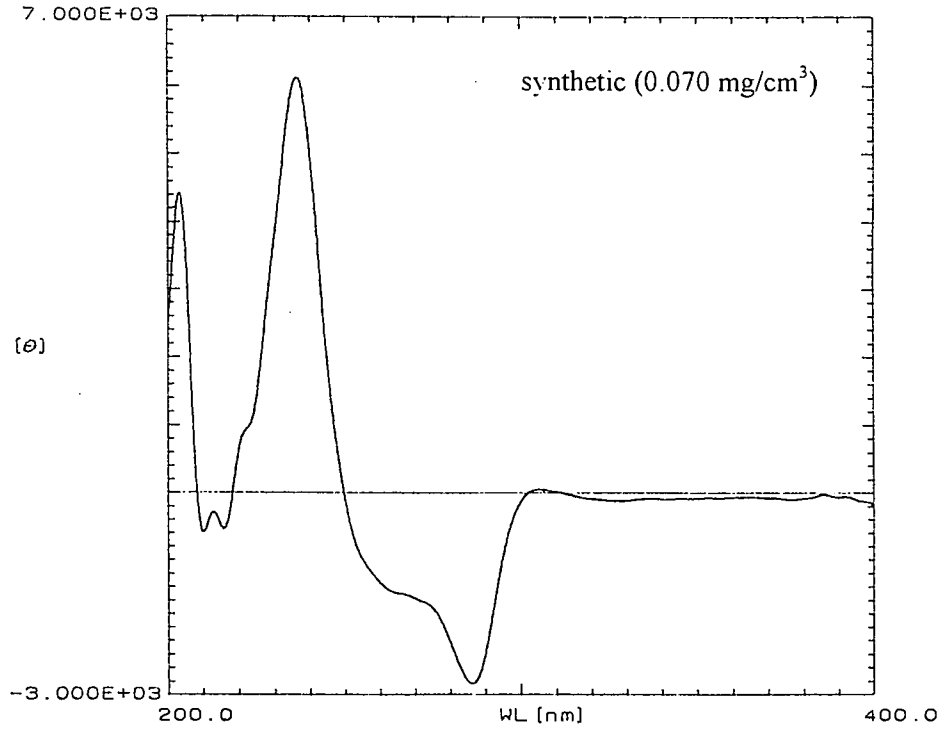
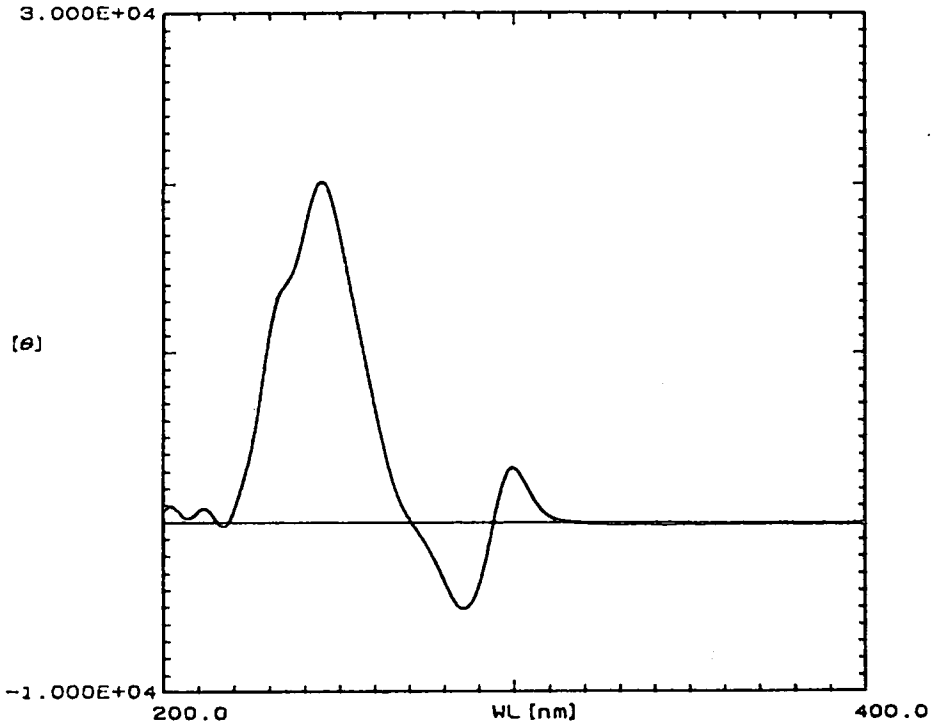
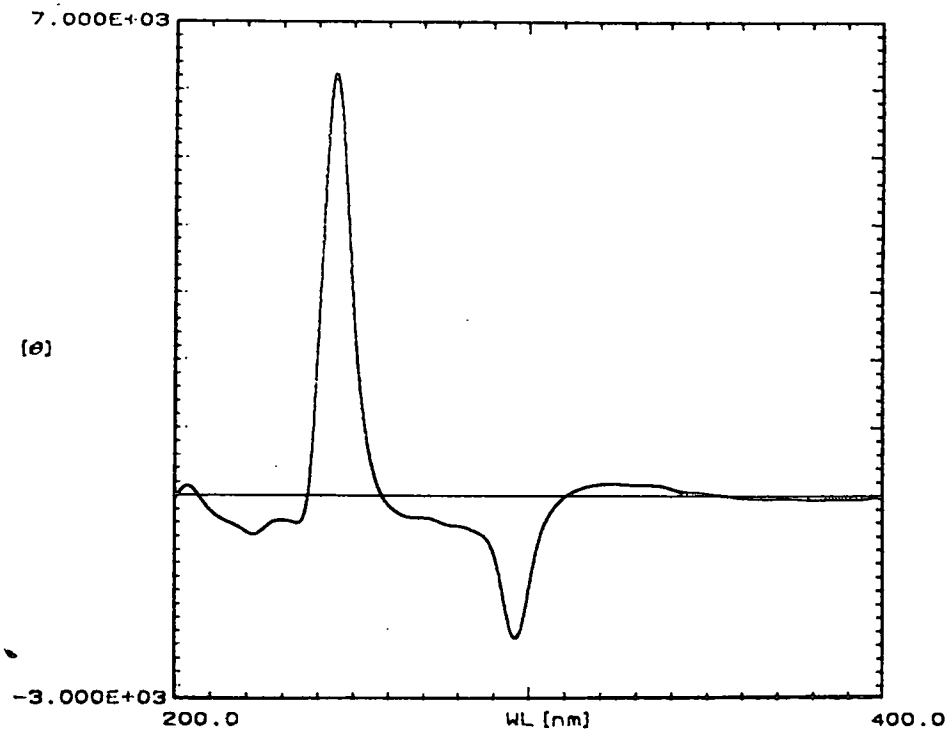


Plate 3: (6a*S*, 11a*S*)-2-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **106** *vs.* (+)-(6a*S*, 11a*S*)-medicarpin **1**



(6a*S*, 11a*S*)-2-Ethoxycarbonyl-3-*O*-methoxymethylmedicarpin **106**

(0.035 mg/cm^3)



(+)-(6a*S*, 11a*S*)-medicarpin **1**

(0.082 mg/cm^3)

5. SUMMARIES AND REGISTER OF KEY TERMS

5.1. Summary (English)

A recent phytochemical study on the heartwood of the Purplewood Dalbergia (*Dalbergia nitidula*) in our laboratories led to the isolation of the first pterocarpan-neoflavonoid dimers, Daljanelins A-C, and an isoflavan-neoflavonoid dimer, Daljanelin D. Although the structure of Daljanelin C has been confirmed by synthesis previously, synthetic evidence regarding the exact structures of Daljanelins A, B and D was still pending. This dissertation outlines the total syntheses of Daljanelins B and D, as well as the preparation of a suitable precursor to Daljanelin A.

The crucial step in the retrosynthesis of Daljanelin B is the nucleophilic coupling of a suitably functionalized pterocarpan precursor with a benzofuranone. The electrophilic methylene bridge required at C-4 of (6a*S*, 11a*S*)-medicarpin was introduced *via* 3-O-allylation, Claisen rearrangement, isomerization and oxidative cleavage of the olefin, benzylic reduction and *in situ* bromination, affording (6a*S*, 11a*S*)-4-bromomethylmedicarpin.

The requisite benzofuranone synthon was synthesized from vanillin by Dakin oxidation, Houben-Hoesch acylation, cyclization, protection of the hydroxy group and conversion to the *tert*-butyldimethylsilyl enol ether.

The subsequent coupling of the pterocarpanoid and benzofuranoid fragments was achieved by means of desilylation of the latter with a strongly siliconophilic fluoride source. Grignard reaction of the resulting dimer with phenyl magnesium bromide and subsequent acid catalyzed dehydration and deprotection then afforded synthetic Daljanelin B, which exhibited the same ^{1}H NMR and CD properties as the natural product.

Reductive cleavage of the pterocarpan C-ring in Daljanelin B afforded Daljanelin D, identical to the natural compound. It should be noted that the standard method for benzylic ether cleavage, *i.e.* hydrogenolysis on Pd(0) catalysts, was ineffectual. Good results were obtained, however, with a $Na(CN)BH_3$-TFA system.

A suitable precursor to Daljanelin A, *i.e.* a 2-ethoxycarbonyl-substituted medicarpin, was synthesized from (6a*S*, 11a*S*)-medicarpin *via* 2,8-dibromination, 3-*O*-methoxymethylation, selective lithium-bromine exchange and carboxylation at C-2, followed by 8-debromination. Reduction of the resulting ethyl benzoate, *in situ* bromination, benzylic coupling to a benzofuranoid, Grignard reaction and phenolic deprotection, as used in the synthesis of

Daljanelin B, should prove instrumental in affording the desired dimer.

Over and above structural elucidation, this research project has led to the following significant results:

- The introduction of a hydroxymethyl group to position 4 of the pterocarpan skeleton constitutes an unusual accomplishment, since substitution on resorcinol-type pterocarpan A-rings is usually hampered by low aromatic nucleophilicity, as well as sensitivity of the C-ring towards the typically employed Brønsted and/or Lewis acids.
- Electrophilic aromatic substitution on such A-rings, if observed at all, takes place in low yields at position 2. An analogue situation is encountered in natural and synthetic 5-deoxyflavonoids, where A-ring substitution is found exclusively at position 6. It is thus hoped that the protocol developed for the synthesis of Daljanelin B will alleviate these difficulties.
- Although the yields in the bromination-carboxylation-debromination protocol towards Daljanelin A are still low, an alternative route for C-2-alkylation of pterocarpans has been established.

The novel synthetic routes towards Daljanelins A and B may thus collaborate in circumventing some of the problems typically associated with flavonoid and isoflavonoid A-ring functionalization.

5.2. Opsomming (Afrikaans)

'n Onlangse fitochemiese ondersoek in ons laboratoriums van die kernhout van die blinkplatboontjie (*Dalbergia nitidula*) het gelei tot die isolering van die eerste pterokarpaan-neoflavonoïed dimere, Daljanelins A-C, asook 'n isoflavaan-neoflavonoïed dimeer, Daljanelin D. Alhoewel die struktuur van Daljanelin C al vantevore m.b.v. totale sintese bevestig is, het soortgelyke struktuurbewyse vir Daljanelins A, B en D tot op hede ontbreek. Hierdie proefskrif beskryf die totale sinteses van Daljanelins B en D, asook die bereiding van 'n geskikte voorloper tot Daljanelin A.

Die grondliggende stap in die retrosintese van Daljanelin B is die nukleofiliese koppeling van 'n bensofuranoon aan 'n geskikte gefunksionaliseerde pterokarpaan. Die nodige elektrofiliese metileenbrug is by C-2 van (6a*S*, 11a*S*)-medikarpin ingestel deur 3-*O*-allilering, Claisenherrangskikking, isomerisasie en oksidatiewe splyting van die olefien, bensiliese reduksie en *in situ* brominering, om (6a*S*, 11a*S*)-4-bromometielmedikarpin te lewer.

Die benodigde bensofuranoon is vanaf vanillien gesintetiseer d.m.v. Dakin-oksidasie, Houben-Hoesch-asilering, siklisering, beskerming van die hidroksigroep en omskakeling na die *tert*-butieldimetielsiliel enol eter.

Die koppeling van die pterokarpaan- en bensofuranoongebaseerde fragmente is vervolgens bewerkstellig deur desililering van die laasgenoemde tussenproduk met 'n sterk silikonofiliese fluoriedbron. Grignardreaksie van die verkrege dimeer met fenielmagnesiumbromied, gevolg deur suurgekataliseerde dehidrasie en ontskerming, het gelei tot sintetiese Daljanelin B, wat volgens ^{1}H KMR en SD identies was aan die natuurproduk.

Reduktiewe splyting van die pterokarpaan-C-ring in Daljanelin B het natuuridentiese Daljanelin D gelewer. Dit is opvallend dat hierdie bensiliese etersplyting nie met die standaardmetode kon bewerkstellig word nie, d.w.s. hidrogenolise op Pd(0)-kataliste. 'n $Na(CN)BH_3$-TFA-sisteem het egter gelei tot goeie resultate.

'n Geskikte voorloper tot Daljanelin A, te wete 'n 2-etoksikarbonielgesubstitueerde medikarpin, is vanaf (6a*S*, 11a*S*)-medikarpin gesintetiseer *via* 2,8-dibrominering, 3-*O*-metoksimetilering, selektiewe litium-broomuitruiling en karboksilering by C-2, gevolg deur 8-debrominering. Daljanelin A behoort sinteties toeganklik te wees deur reduksie van hierdie etielbensoaat, gevolg deur *in situ* brominering, bensiliese koppeling aan 'n

bensofuranoonvoorloper, Grignardreaksie en fenoliese ontskerming, analoog aan die sintese van Daljanelin B.

Afgesien van struktuurbevestigings, het hierdie navorsingsprojek die volgende betekenisvolle resultate gelewer:

- Die hidroksimetilering van C-4 op die pterokarpaanskelet is 'n beduidende mylpaal, aangesien substitusiereaksies van resorsiliese pterokarpaan-A-ringe gewoonlik belemmer word deur lae aromatiese nukleofilisiteit, asook gevoeligheid van die C-ring teenoor die Brønsted- en/of Lewissure wat tipies vir sulke reaksies gebruik word.
- Indien elektrofiliese aromatiese substitusie hoegenaamd op sulke A-ringe waargeneem word, vind dit in lae opbrengste by posisie 2 plaas. Natuurlike en sintetiese 5-deoksiflavonoïede vertoon soortgelyke eienskappe, deurdat A-ringsubstitusie uitsluitlik by posisie 6 aangetref word. Hierdie probleme kan hopelik aangespreek word met die protokol wat vir die sintese van Daljanelin B ontwikkel is.
- Die protokol vir Daljanelin A, d.w.s. brominering, karboksilering en debrominering, vertoon huidig lae opbrengste, maar nietemin is daar 'n alternatiewe roete tot C-2-alkilering van pterokarpane daargestel.

Die nuwe sintetiese roetes tot Daljanelins A en B mag dus behulpsaam wees om sommige probleme te omseil wat tipies geassosieer word met die funksionalisering van flavonoïed- en isoflavonoïed-A-ringe.

5.3. Synopsis (Deutsch)

Eine phytochemische Studie des Kernholzes der *Dalbergia nitidula* führte unlängst in unseren Laboratorien zur Isolation der ersten Pterokarpan-Neoflavonoid-Dimere, Daljaneline A-C, und eines Isoflavan-Neoflavonoid-Dimers, Daljanelin D. Obwohl die Struktur des Daljanelin C schon mittels Synthese bestätigt wurde, lag ein genauer Strukturbeweis der Daljaneline A, B und D bisher nicht vor. Diese Dissertation beschreibt die Totalsynthesen der Daljaneline B und D, sowie die Bereitung eines geeigneten Vorläufers des Daljanelin A.

Der grundliegende Schritt in der Retrosynthese des Daljanelin B ist die nukleophile Anlagerung eines passend funktionalisierten Pterokarpanderivates an ein Benzofuranon. Die dafür erforderliche elektrophile Methylenbrücke am C-4 des (6a*S*, 11a*S*)-Medikarpins wurde mittels 3-*O*-Allylierung, Claisenumstellung, Isomerisation und oxidativer Zerlegung des Olefins, benzylischer Reduktion und *in situ* Brominierung hergestellt, um das (6a*S*, 11a*S*)-4-Bromomethylmedikarpin zu geben.

Das erwünschte Benzofuranon wurde durch Dakin-Oxidation des Vanillins, Houben-Hoesch-Acylierung, Ringschluß, Beschützung der Hydroxylgruppe und Umführung in den *tert*-Butyldimethylsilyl-Enolether synthetisiert.

Die darauffolgende Anlagerung des Benzofuranonfragments an das Pterokarpan wurde durch Desilylierung des ersteren mit einer stark silikonophilen Fluoridquelle erzielt. Grignardreaktion des resultierenden Dimers mit Phenylmagnesiumbromid, säurekatalysierte Wasserabspaltung und gleichzeitige Entschirmung ergab das synthetische Daljanelin B, welches dem Naturprodukt ^{1}H NMR- und CD-spektroskopisch glich.

Reduktive Öffnung des Pterokarpan-C-Ringes im Daljanelin B gab das Daljanelin D als naturidentischen Stoff. Merkwürdigerweise erwies sich die Standardmethode zur Benzyletherreduktion, d.h. katalytische Hydrogenolyse auf Pd(0), als ineffektiv. Ein System aus $Na(CN)BH_3$ und Trifluoressigsäure führte jedoch zu befriedigenden Ergebnissen.

Ein geeigneter Ausgangsstoff des Daljanelin A, nämlich ein 2-Ethoxycarbonylmedikarpin, wurde aus dem (6a*S*, 11a*S*)-Medikarpin durch 2,8-Dibrominierung, 3-*O*-methoxymethylierung, selektiven Lithium-Bromaustausch und Carboxylierung am C-2 und schließlicher 8-Debrominierung synthetisiert. Reduktion des resultierenden Ethylbenzoats, *in situ* Brominierung, benzylische Anlagerung an ein Benzofuranoid, Grignardreaktion und

Phenolentschirmung, wie schon in der Synthese des Daljanelin B verwendet, sollte den Zugang zum erwünschten Dimer ermöglichen.

Abgesehen von Strukturbestätigung der Naturprodukte, führte dies Projekt zu den folgenden bedeutenden Ergebnissen:

- Die Einführung einer Hydroxymethylgruppe in Position 4 des Pterokarpanskeletts ist in sich eine außergewöhnliche Errungenschaft, da die Substitution resorcylischer Pterokarpan-A-Ringe meist durch niedrige aromatische Nukleophilizität, als auch durch Labilität der C-Ringe in Gegenwart der typisch verwendeten Brønsted- und/oder Lewissäuren, erschwert wird.
- Die elektrophile aromatische Substitution solcher A-Ringe findet in niedrigen Ausbeuten, falls überhaupt, auf Position 2 statt. Ein analoges Muster ergibt sich bei natürlichen und synthetischen 5-Deoxyflavonoiden, die ausschließlich auf Position 6 substituiert sind. Das Verfahren, welches zur Synthese des Daljanelin B entwickelt wurde, kann diese Schwierigkeiten möglicherweise beseitigen.
- Obwohl die Ausbeuten im Brominierungs-, Carboxylierungs- und Debrominierungsverfahren zum Daljanelin A noch niedrig sind, ist doch ein alternativer Zugang zu C-2-alkylierten Pterokarpanen eröffnet worden.

Die neuen Syntheserouten zu den Daljanelinen A und B könnten sich demnach als hilfreich erweisen, einige der Probleme zu umgehen, die typisch mit der Funktionalisierung von Flavonoid- und Isoflavonoid-A-Ringen verbunden sind.

5.4. Key terms

- Daljanelins A-D
- Isoflavonoid-neoflavonoid dimers
- Pterocarpan
- Benzofuranone
- A-ring functionalization
- Thermal allyl rearrangement (Claisen rearrangement)
- $PdCl_2(PhCN)_2$-catalyzed isomerization
- Dihydroxylation
- *In situ* benzylic bromination (Collington-Meyers protocol)
- Interflavanyl coupling
- Hydrogenolysis
- Aromatic bromination
- Selective aromatic lithiation
- Carboxylation
- Formylation

6. REFERENCES

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