NEW RING CLOSING METATHESIS BASED METHODOLOGY FOR THE SYNTHESIS OF MONOMERIC FLAVONOIDS

Dissertation submitted in fulfilment of the requirements of the degree

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by

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Tanya Pieterse

Declaration of authenticity:

I declare that the research project, 'New ring closing metathesis based methodology for the synthesis of monomeric flavonoids', is my own work and that each source of information used has been acknowledged by means of a complete reference. This dissertation has not been submitted before for any other research project, degree or examination at any university.

T. Pieterse

February 2017

Randburg, South Africa

A section of the work presented in this thesis has already led to the following publications:

Miller, B. J.; Pieterse, T.; Marais, C.; Bezuidenhoudt, B. C. B. *Tetrahedron Lett.* **2012**, *53*, 4708–4710.

Pieterse, T.; Visser, M.; Marais, C.; Bezuidenhoudt, B. C. B *Synlett* **2016**, *27* (10), 1541–1546

Contents

Abbreviations

Adamantane	=	Tricyclo[3.1.1.1^{3,7}]decane
ADMET	=	Acyclic diene metathesis
AD-mix-α	=	Asymmetric dihydroxylation mix-α
AD-mix-β	=	Asymmetric dihydroxylation mix-β
AIBN	=	Azobisisobutyronitrile
BHT	=	Butylated hydroxytoluene
[bmim]BF_4	=	1-Butyl-3-methylimidazolium tetrafluoroborate
[bmim]PF_6	=	1-Butyl-3-methylimidazolium hexafluorophosphate
BQC	=	Quinidine benzylchloride
BQdC	=	Quinine benzylchloride
CM	=	Cross metathesis
DBU	=	1,8-Diazabicycloundec-7-ene
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	=	Diisopropylazodicarboxylate
DIBAL	=	Di-isobutylaluminium hydride
DMA	=	*N*,*N*-dimethylacetamide
DMAP	=	*N*,*N*-dimethylaminopyridine
DMDO	=	Dimethyldioxirane
DMF	=	*N*,*N*-dimethylformamide
DMS	=	Dimethylsulfide
DMSO	=	Dimethylsulfoxide
DPEphos	=	Bis[(2-diphenylphosphino)phenyl] ether
dppf	=	Bis(diphenylphosphino)ferrocene
dppp	=	1,3-Bis(diphenylphosphino)propane
EDG	=	Electron donating group
ER	=	Electron-rich
EtOH	=	Ethanol
EWG	=	Electron withdrawing group
FGI	=	Functional group interconversion
GC-MS	=	Gas chromatography-mass spectrometry

HPLC	=	High performance liquid chromatography
3-HQD	=	3-Hydroxynuclidine
IBD	=	Iodobenzene diacetate
IBX	=	*O*-iodoxybenzoic acid
LA	=	Lewis acid
LDA	=	Lithium diisopropylamide
LICA	=	Lithium isopropylcyclohexamide
LiHDMS	=	Litium-bis(trimethylsilyl)amide
MAP	=	Monoaryloxide pyrrolide
m-CPBA	=	*meta*-Chloroperoxybenzoic acid
MEK	=	Methyl ethyl ketone
Mes_2Bitet	=	3,3'-Mesityl-2'-(tert-butyldimethylsilyl silanyloxy)
Min.	=	Minutes
MOM	=	Methoxymethyl ether
MS	=	Molecular sieves
MS(EI)	=	Mass spectrometry (electron impact)
MTPPB	=	Methyltriphenylphosphonium bromide
MW	=	Microwave
NAP-MgO	=	Nanocrystalline aerogel prepared MgO particles
NBS	=	*N*-bromosuccinimide
NCA	=	*N*-carboxanhydride
NHC	=	*N*-heterocyclic carbene
NMMO	=	*N*-methylmorpholine N-oxide
NSFI	=	*N*-fluorobenzenesulfonamide
OHIPT	=	2,6-(2,4,6-*i*-$Pr_3C_6H_2)_2C_6H_3O$]
PCC	=	Pyridinium chlorochromate
PCy_3	=	Tricyclohexylphosphine
PG	=	Protecting group
PPMP	=	Phenyl-2-palmitoylamino-3-morpholino-1-propanol
PTC	=	Phase transfer catalyst
p-TSA (TsOH)	=	*para*-Toluenesulfonic acid
Py	=	Pyridine
RCM	=	Ring closing metathesis

ROM	=	Ring opening metathesis
ROMP	=	Ring opening metathesis polymerisation
Rt.	=	Room temperature
SIMES	=	Saturated mesityl substituted N-heterocyclic carbene
TBAF	=	Tetra-*n*-butylammonium fluoride
TBDPS	=	*tert*-Butyldiphenylsilyl ether
TBS	=	*tert*-Butyldimethylsilyl ether
TEMPO	=	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	=	Triethylsilyl ether
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TLC	=	Thin layer chromatography
TMEDA	=	Tetramethylethylenediamine
TMS	=	Trimethylsilyl
TPP	=	Triphenylphosphine
Trip	=	2,4,6-*i*-$Pr_3C_6H_2$
TTN	=	Thallium(III) nitrate

Literature Overview

Chapter 1: Introduction

Flavonoids, which are present in a wide range of plants, represent an extensive group (> 8000 analogues are known) of naturally occurring polyphenolic compounds constituting a basic C_6-C_3-C_6 skeleton. Although these compounds are usually synthesised by plants in response to pathogenic attacks, they may also act as antioxidants, photoreceptors and visual attractors.[1] While some analogues display an acyclic C_3 moiety, the vast majority of flavonoids contain a phenylchroman type structure. The flavonoids are divided into three subclasses depending on the position of the phenyl substituent (B-ring) on the hetero-atomic C-ring and are known as flavonoids (**1**), isoflavonoids (**2**) and neoflavonoids (**3**).

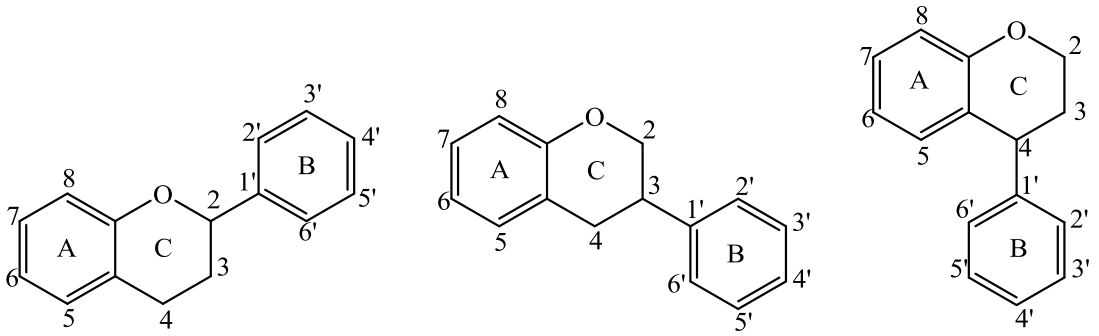


Figure 1.1 Flavonoid classes

Researchers first became interested in flavonoids in the late 1930's when a new substance, called vitamin P [also known as rutin (**4**)], was isolated from oranges. This compound formed part of what was thought to be a new class of vitamins. However, in the 1950's flavonoids lost their vitamin status and in the 1970's the flavonoid quercetin (**5**) was suspected to be carcinogenic. It was only after further research in the 1980's that the tainted reputation of the flavonoids changed when it was found that these compounds in fact showed significant anti-carcinogenic properties.[1,2] Thereafter, with the discovery of the French paradox (the association of decreased cardiovascular mortalities in Mediterranean populations who generally have a higher intake of red wine and saturated fat), research in the field of flavonoids expanded considerably.[2]

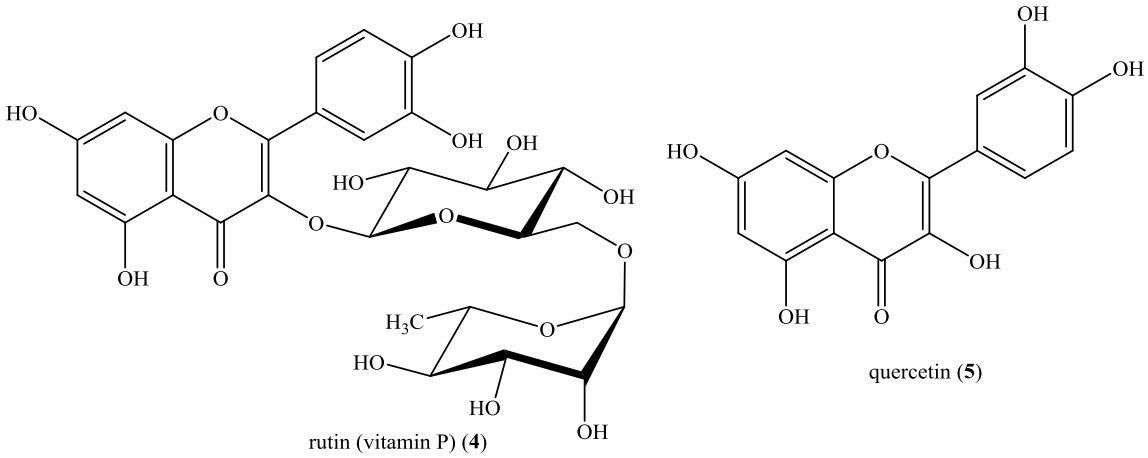


Figure 1.2 Rutin (vitamin P) and quercetin

1.1 Structural diversity

The structural diversity observed amongst the flavonoids can be ascribed to the level of saturation, oxygenation, the presence of other heterocylic rings and additional aromatic rings fused onto the basic flavonoid skeleton. While flavonoids like laxiflorane (**6**) and myristinin A (**7**) represent the saturated flavonoids, haginin D (**8**) and dalbergichromene (**9**) each contain a heterocyclic double bond (Figure 1.3). Higher levels of oxygenation may be present in the saturated [butin (**10**) and (-)-vestitone (**11**)] or unsaturated C-ring [luteolin (**12**), genistein (**13**) and melannein (**14**)] containing the carbonyl functionality (Figure 1.3), whereas oxygenation is also observed in compounds containing the carbonyl moiety as well as a hydroxy group in the saturated [taxifolin (**15**)] or unsaturated [kaempferol (**16**)] heterocyclic ring or two C-ring hydroxy groups as in leucodelphinidin (**17**) (Figure 1.4).

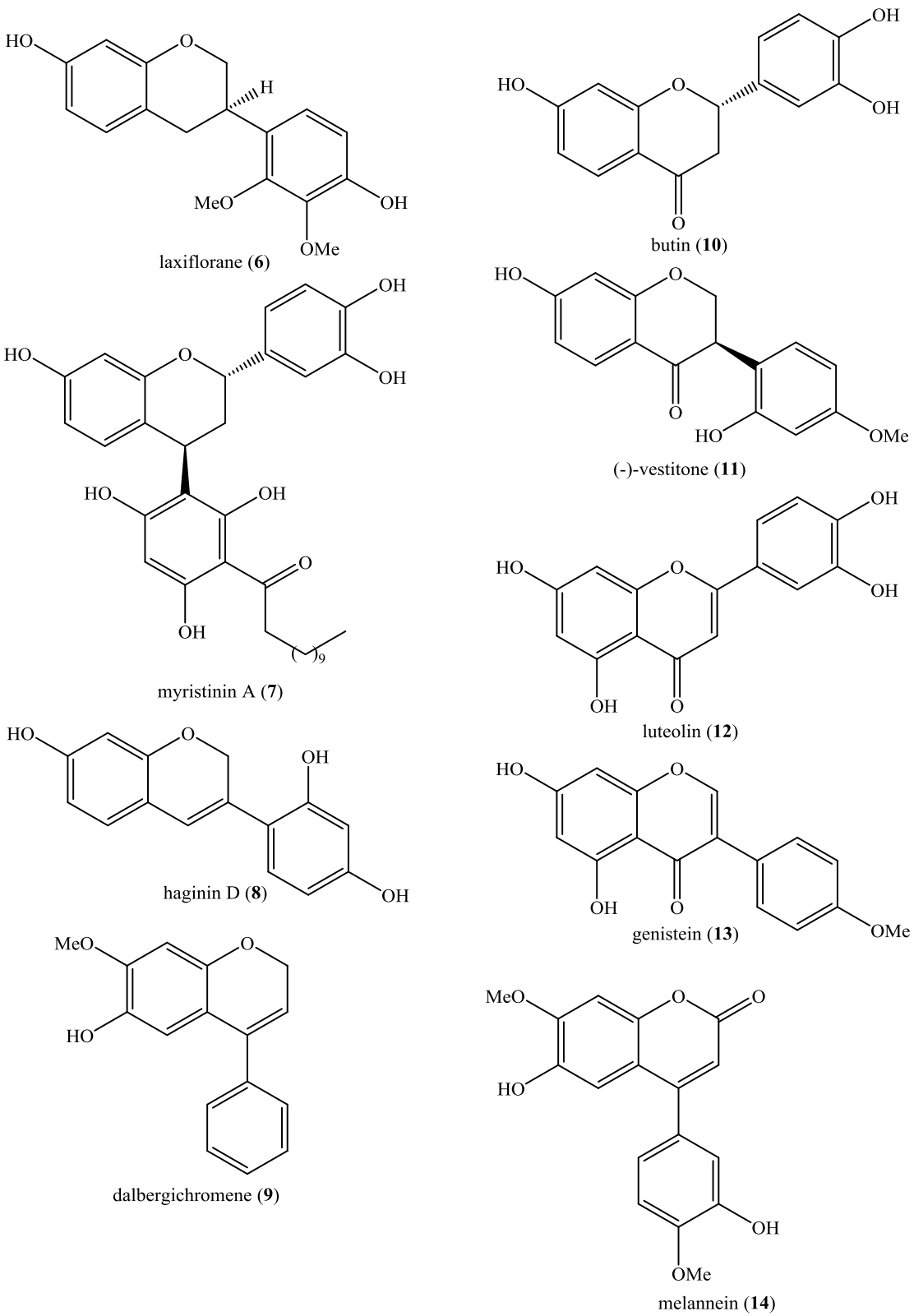


Figure 1.3 Flavonoid diversity: Saturation and oxygenation

The flavonoids obtain further diversity when other aromatic or heterocyclic rings are fused to the flavonoid skeleton [phaseolin (**18**) and coumestrol (**19**)] or when having a sugar moiety attached to one of the aromatic - [talosin A (**20**)] (Figure 1.4) or heterocyclic rings - [rutin (**4**)] (Figure 1.2) as substituent.

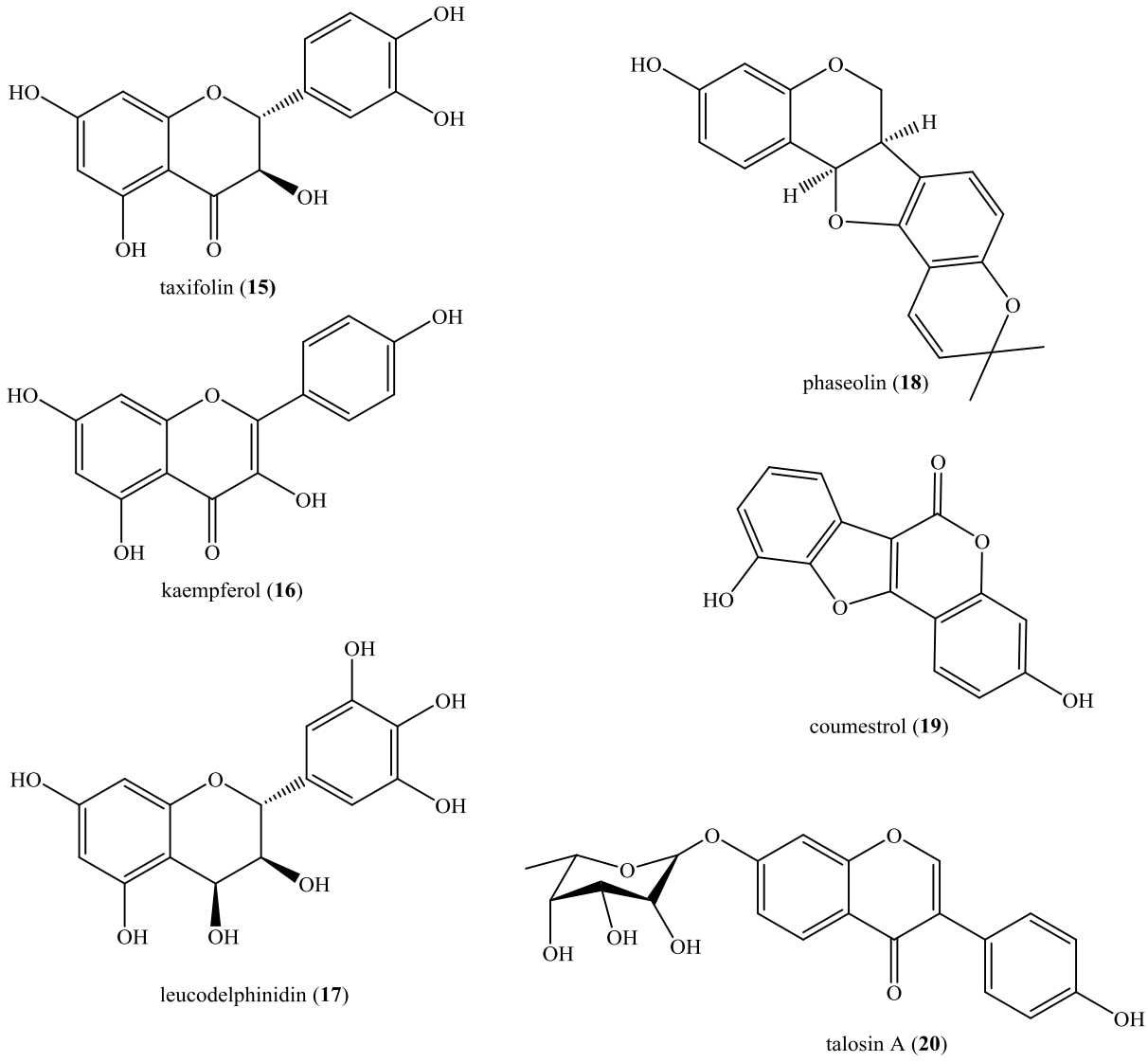


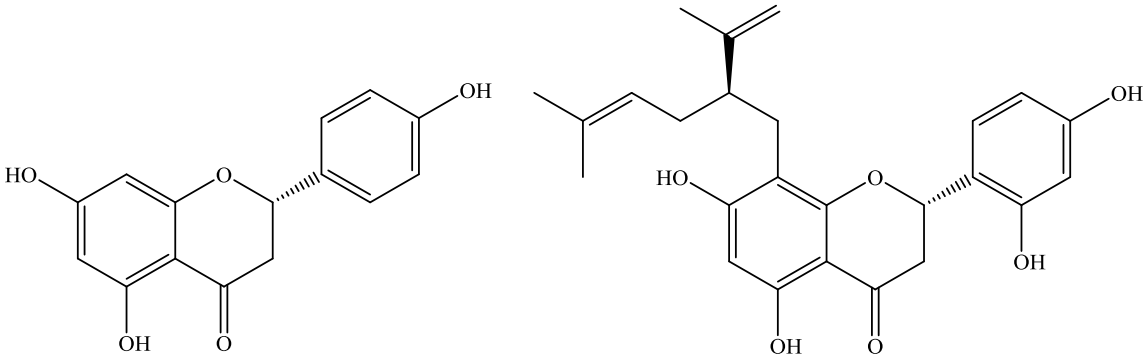
Figure 1.4 Flavonoid diversity: Oxygenation and ring varieties

1.2 Biological activity

While the flavonoids in red wine seem to be beneficial for cardiac health through blood flow improvement, these compounds are also known to display a vast array of other biological activities. Amongst these, anti-oxidant activity, antimicrobial, antifungal and anti-inflammatory properties[3,4,5] as well as significant anticancer activity are included.[6,7]

The mechanism of anti-oxidant activity is thought mainly to entail metal chelation, radical scavenging and enzyme inhibition.[8,9] With the carbonyl functionality and multiple hydroxy groups present in flavonoids, the 'capturing' of metal ions is made possible and during this process the redox potential of the metal is often altered, rendering it inactive.[10] Radical scavenging occurs *via* H-atom transfer from the anti-oxidant, leading to a newly formed radical which is usually stable enough to delay or prevent further radical chain reactions.[10] Enzyme inhibition has been shown to occur in, for example, tyrosinase enzymes when flavonols like kaempferol (**16**) and quercetin (**5**) chelate copper ions situated in the active site of the enzyme, thus leading to permanent deactivation.[1,2,11]

Since flavonoids are mainly produced in plants in response to microbial attacks, the interaction between the flavonoid and pathogen is based on protein complexation through nonspecific hydrogen bonding, covalent bond formation and/or hydrophobic effects. Naringenin (**21**) and sophoraflavanone G (**22**), for example, show quite potent antibacterial activity against MRSA (methicillin resistant *Straphylococcus areus*) and other streptococci spp. due to the ability to alter the fluidity of bacterial cell membranes.[1,3]



naringenin (**21**) sophoraflavanone G (**22**)

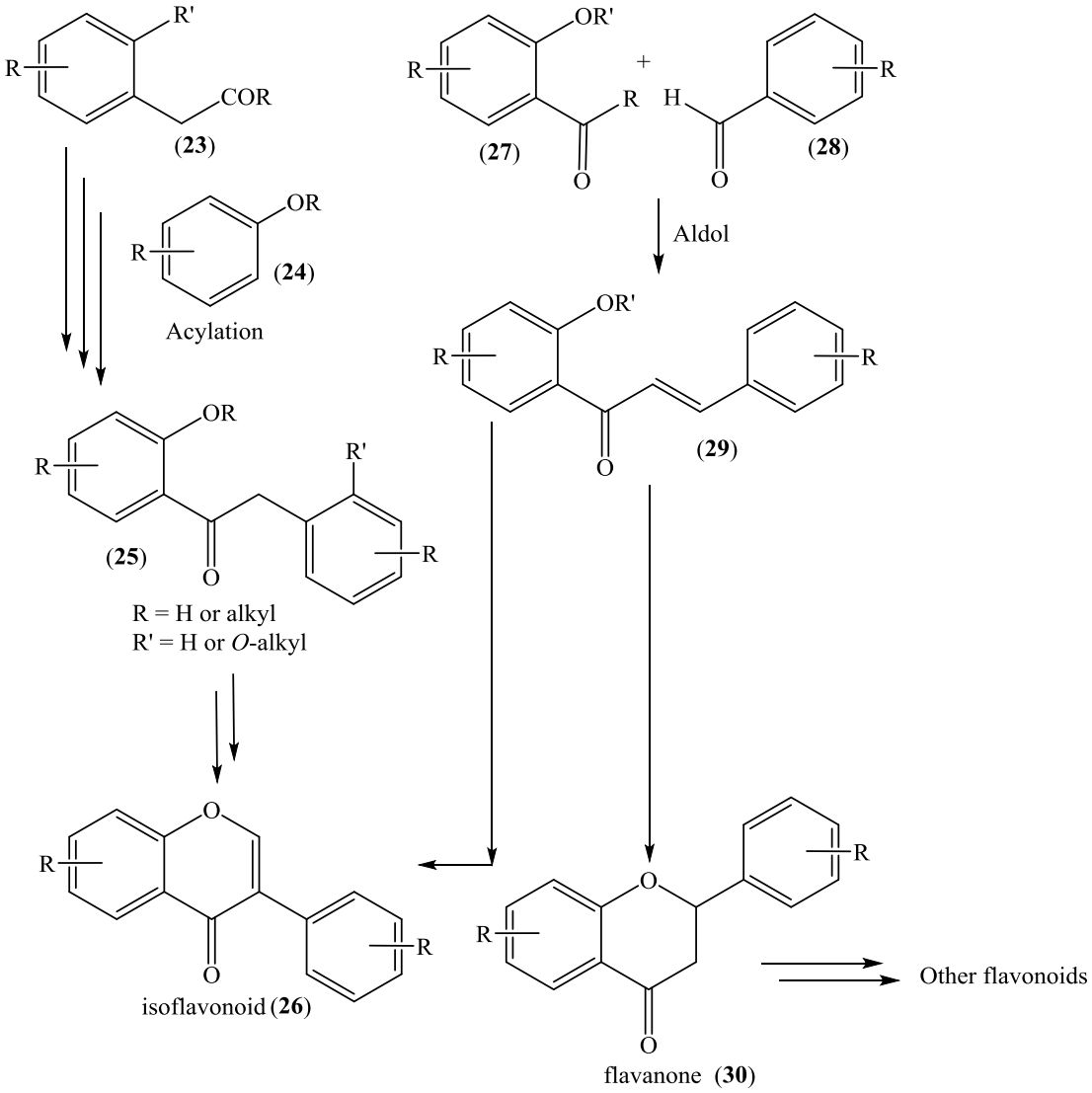
Figure 1.5 Antibacterial flavonoids

Furthermore, the intake of quercetin (**5**), found in high concentrations in apples and onions, was found to be inversely related to the incidence of breast, lung, stomach and prostate cancer.[1,12] Numerous other studies also supported the critical relationship between dietary flavonoid intake and cancer chemoprevention.[1,6,7,12,13] Since free radicals cause permanent damage in DNA, such as base pair mutations, deletions, insertions and rearrangements, and can affect the expression of stress hormones influencing cell differentiation and growth, flavonoids assist in cancer chemoprevention through scavenging of these reactive oxygen species (*vide supra*).[14] Furthermore, flavonoids have been shown to induce apoptosis

(controlled cell death) in cancerous cells, although the exact mechanism is not well understood,[14,15] and while appropriate cell cycle progression is altered in tumour cells, flavonoids can cause cell cycle arrest in these cells, not only due to their anti-oxidant activity but also due to its interference with intracellular signalling *via* enzyme inhibition.[14,16]

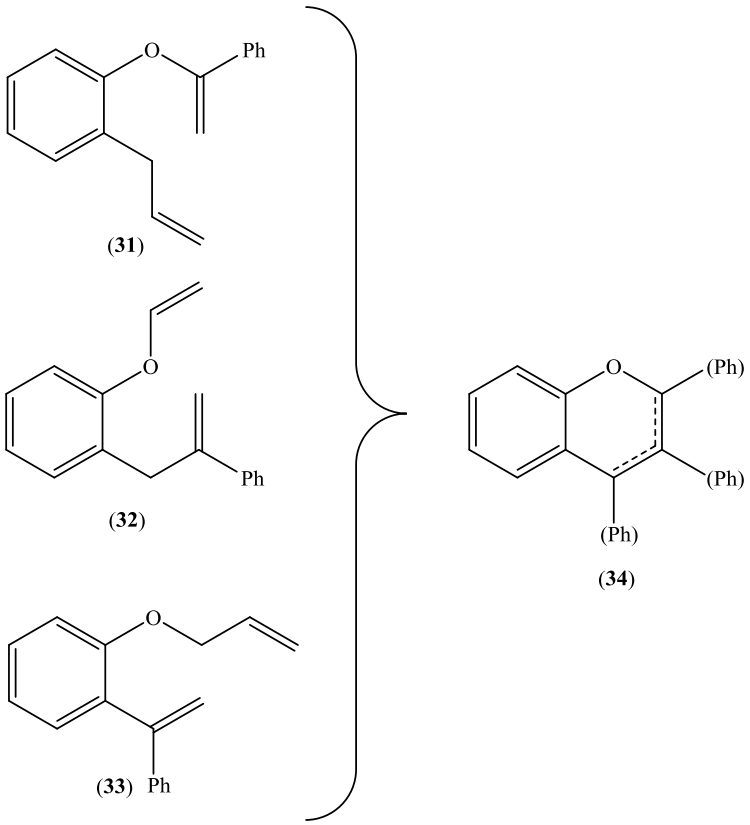
1.3 Synthesis of flavonoids

Although the physiological activity of flavonoids (*vide supra*) stimulated investigations into more efficient synthetic methods for the preparation of these compounds, many of these routes entail multiple steps (Scheme 1.1) and require the utilization of stoichiometric and often toxic reagents. Known methodologies are also hampered by difficulties surrounding the isolation of the desired product and often leads to inseparable mixtures, low yields,[13,17] and tedious synthesis processes.[18,19]



Scheme 1.1 Synthesis of flavonoids

To circumvent these problems and to align the synthesis of flavonoids with modern synthesis methodologies, it was decided to embark on a process of preparing the different classes of flavonoids through the application of catalyst-based reactions. The discovery of the metathesis reaction and its resulting application in the field of organic chemistry[20] prompted an investigation into the utilization of this reaction in the synthesis of flavonoids. It was therefore envisaged that the ring closing metathesis (RCM) reaction has the potential to be utilised in the synthesis of all flavonoids with unsaturation present in the heterocyclic ring (Scheme 1.2). All the different classes of flavonoids would therefore be reachable from readily available starting materials through a few reaction steps and the application of basically a single catalytic reaction in the last step.



Scheme 1.2 All flavonoid classes *via* RCM

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Chapter 2: Synthesis of Flavonoids

Introduction

Researchers became interested in flavonoids in the late 1930's when vitamin P [also known as rutin (**4**)] was isolated from oranges and the discovery of further physiological properties associated with flavonoids (*cf.* par. 1.2) since the mid 1980's,[1] served as additional impetus towards the development of several new methods for the synthesis of these compounds. While many methodologies based on new reactions have emerged in the field of flavonoid synthesis, a number of classical preparations are still the best options for constructing the flavonoid skeleton.

Two general approaches towards the synthesis of flavonoids have been followed over the years i.e., constructing the basic C_6-C_3-C_6 skeleton, followed by transformations to the wanted analogue and direct formation of the desired flavonoid molecule by a combination of the appropriate fragments. Furthermore, due to the enormous body of knowledge involving the synthesis of the different types of flavonoids, this overview will be limited to the construction of the basic flavonoid skeletons and will, apart from a few examples, not cover the preparation of the plethora of natural products isolated.

2.1 Flavonoids

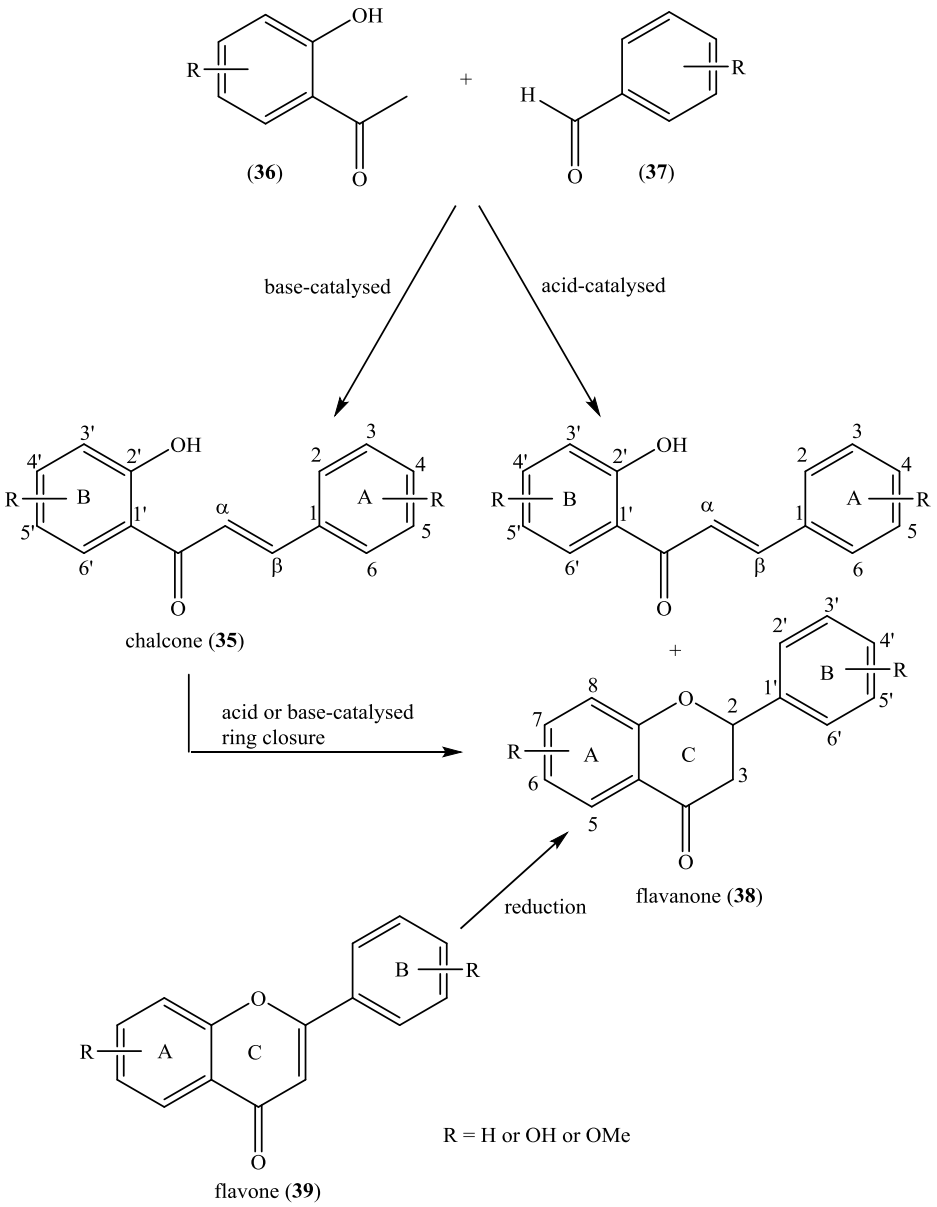
Due to the fact that chalcones [e.g. (**35**)] already contain the C_6-C_3-C_6 skeleton of flavonoids and that these acyclic compounds can easily be transformed into the 2-phenylchromane type structure of the flavonoids, chalcones have for a very long time occupied the position of central precursor in the synthesis of flavonoids.

2.1.1 Synthesis of chalcones

Chalcones are obtained by either acid or base catalysed aldol condensation of a C_6-C_2 moiety [2-hydroxyacetophenones (**36**)] and a C_6-C_1 unit [benzaldehydes (**37**)] (Scheme 2.1). This cross-aldol reaction between an aromatic ketone and an aromatic aldehyde, is also known as the Claisen-Schmidt reaction.[2,3,4]

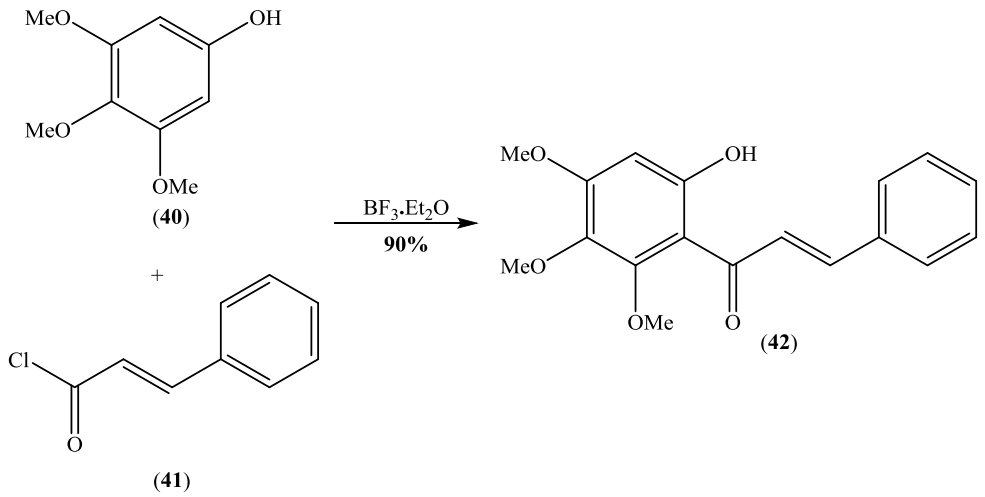
The acid catalysed reaction is usually performed in the presence of HCl[5] but may, however, favour the cyclisation of the chalcone to the flavanone (**38**) in the presence of an unprotected 2'-OH.[2,6] Base catalysed aldol condensation is therefore the method of choice. While the use

of aq. KOH or NaOH has become the standard choice for chalcone synthesis, yields vary between 16 – 93%.[7,8] NaH[9] has, however, led to very satisfactory high yielding aldol reactions (quantitative yield of chalcones with phloroglucinol B- and catechol A-rings protected with Bn, Me and MOM groups),[10] whereas LiHDMS [litium-bis(trimethylsilyl)amide][11] can be used in the presence of alkali-sensitive protecting groups, such as silyls, to prepare chalcones in up to 50% yield. More recent techniques in basic media include solvent free grinding of acetophenone (**36**) and benzaldehyde (**37**) with $Ba(OH)_2$,[12] solid KOH,[13,14] ultrasound assisted aldol condensation utilising LiOH[15] and microwave radiation in the presence of K_2CO_3,[16] whereas acid mediated processes include the utilisation of *p*-toluenesulfonic acid,[17] $SOCl_2$/EtOH (*in situ* HCl),[18] $ZrCl_4$,[19] and sulfonic acid ionic liquids.[20]



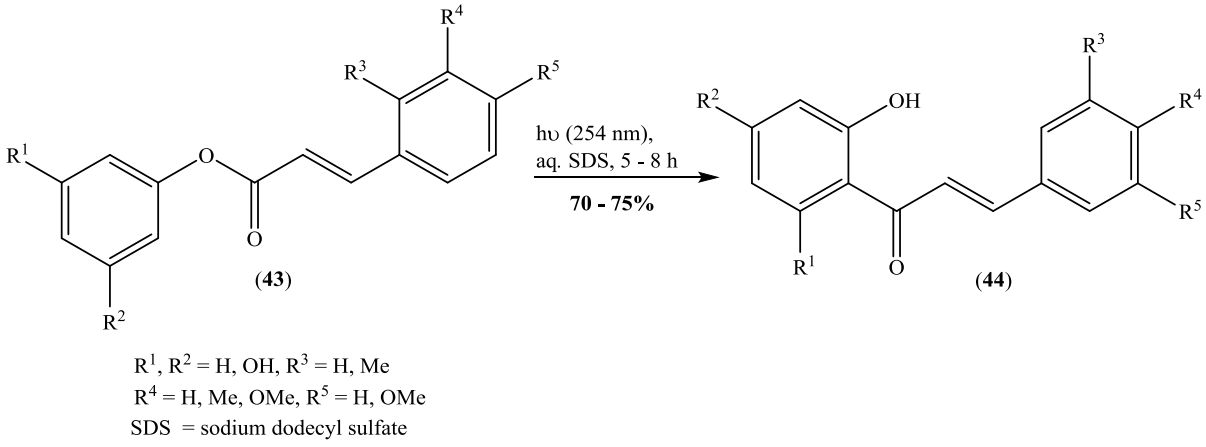
Scheme 2.1 Flavanone synthesis

Another approach toward chalcone preparation entails acylation of a C_6 unit (e.g. phenol) with the C_6-C_3 unit of a cinnamic acid derivative or other equivalent moiety in the presence of $AlCl_3$[21,22] in a Friedel-Crafts type acylation.[23] This process was extended to the utilisation of BF_3**.**Et_2O with coupling of 3,4,5-trimethoxyphenol (**40**) and cinnamoyl chloride (**41**) to give the corresponding chalcone (**42**) in 90% yield (Scheme 2.2).[5,24,25]



Scheme 2.2 Chalcone synthesis *via* Friedel-Crafts acylation

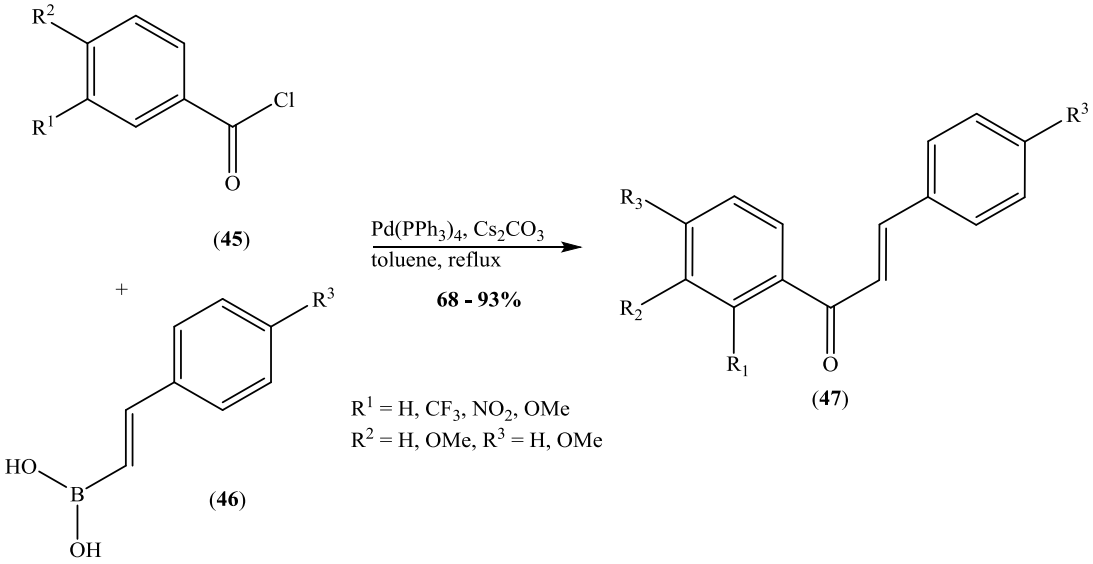
While this methodology might be preferred over aldol condensation due to higher yields, it suffers from drawbacks such as the relatively higher price of Lewis acids compared to the base used in aldol condensations and the fact that substituted cinnamoyl chlorides are not readily available and entails tedious processes to prepare.[26,27] The related Photo-Fries rearrangement of phenyl cinnamates (**43**) (Scheme 2.3), was demonstrated to be compatible with free phenolic and protected oxygenated phenyl cinnamates, amongst others, and formed chalcones (**44**) in good yields (70 – 75%). [28,29]



Scheme 2.3 Photo-Fries rearrangement of phenyl cinnamates

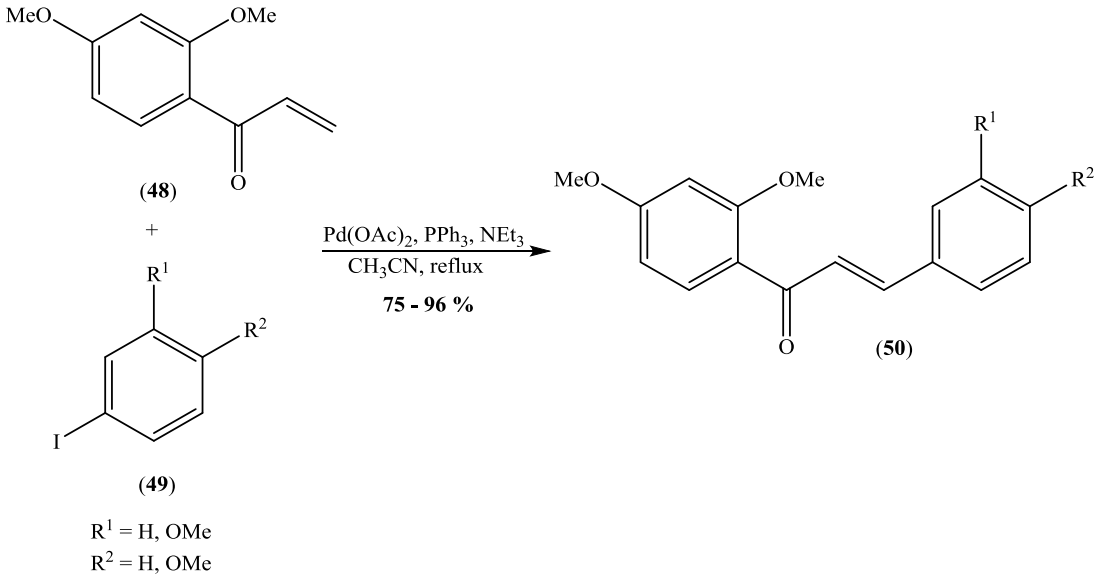
Pd-catalysed C-C bond formation reactions such as the Suzuki-Miyaura reaction,[30,31] Heck reaction,[32,33,34] Sonogashira coupling[35] and carbonylative versions,[34,36] have since emerged as powerful synthesis tools.

Suzuki coupling between benzoyl chloride (**45**) and phenylvinyl boronic acid (**46**) (Scheme 2.4) gave chalcones (**47**) in 68 – 93% yield and shows promise for the preparation of oxygenated chalcones as 3',4,4'-trimethoxychalcone could be obtained in 81% yield.[30]



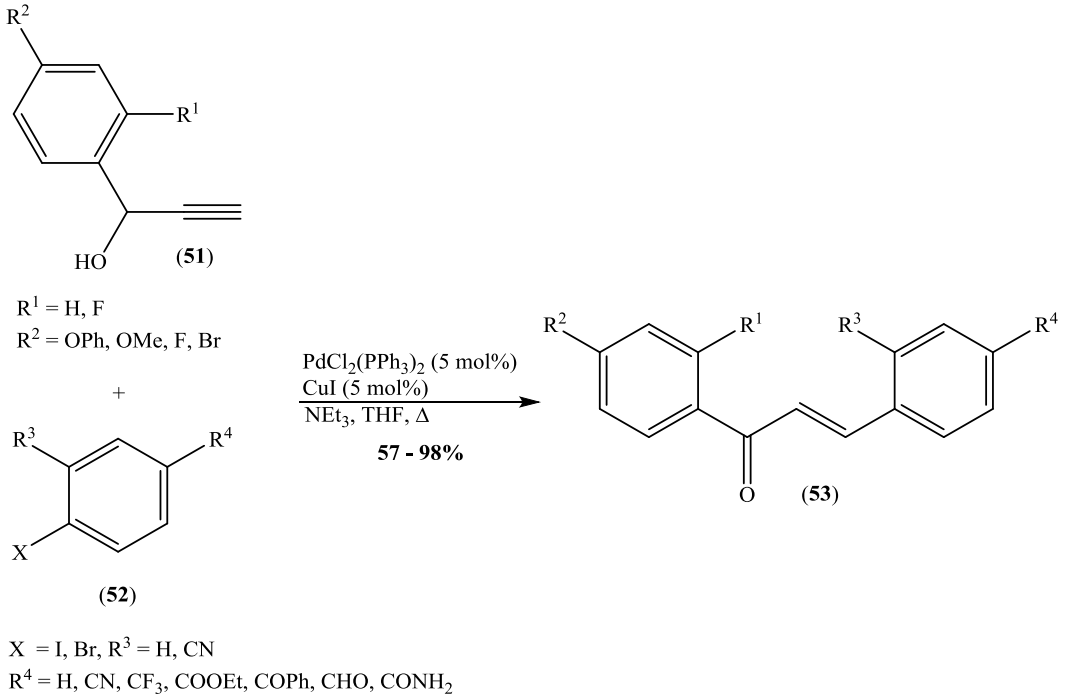
Scheme 2.4 Suzuki-Miyaura reaction of phenylvinyl boronic acids and benzoyl chlorides

Bianco *et al.*[37,38] first applied the Heck reaction to the synthesis of chalcones and were able to obtain oxygenated chalcones (**50**) in 75 – 96% yield (Scheme 2.5), whereas Guo *et al.*[32] modified the procedure to generate the vinyl ketone (**48**) *in situ* from 3-chloropropiophenones in a domino dehydrochlorination/Heck reaction.



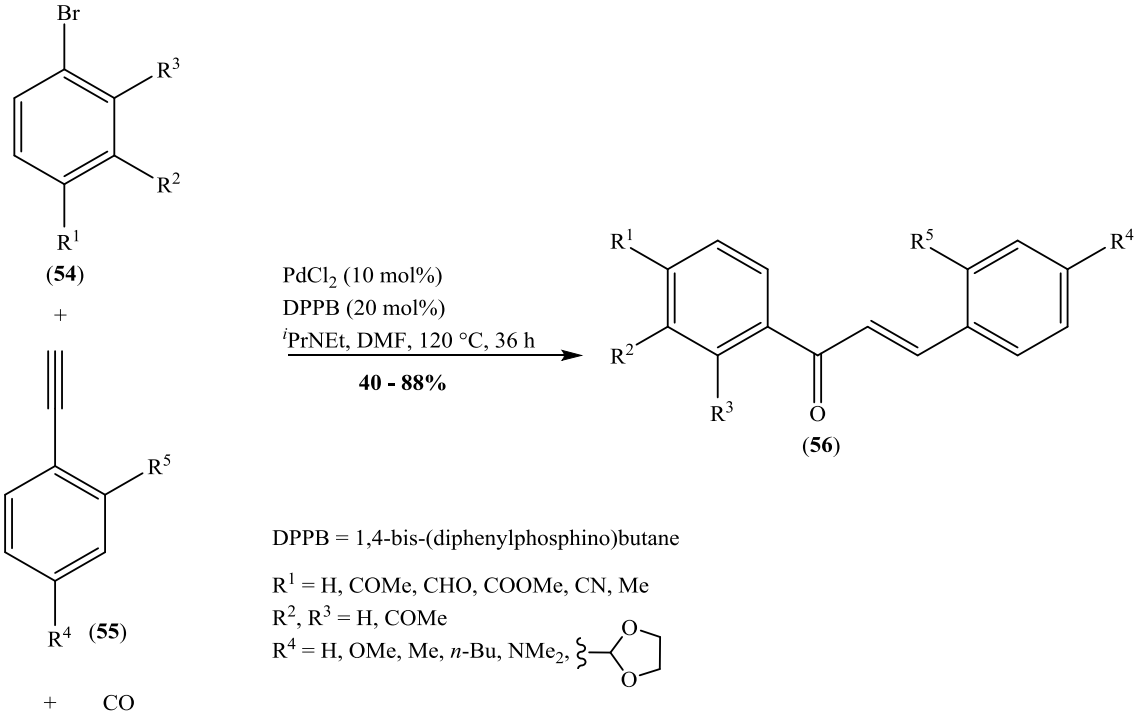
Scheme 2.5 Heck reaction of vinyl ketones and aryl halides

Braun *et al.*[35] successfully prepared chalcones (**53**) in 57 – 98% yield *via* the consecutive Sonogashira coupling of 1-aryl-1-propargyl alcohols (**51**) and aryl halides (**52**) and domino isomerization of the former to the corresponding α,β-unsaturated ketones (**53**) (Scheme 2.6).



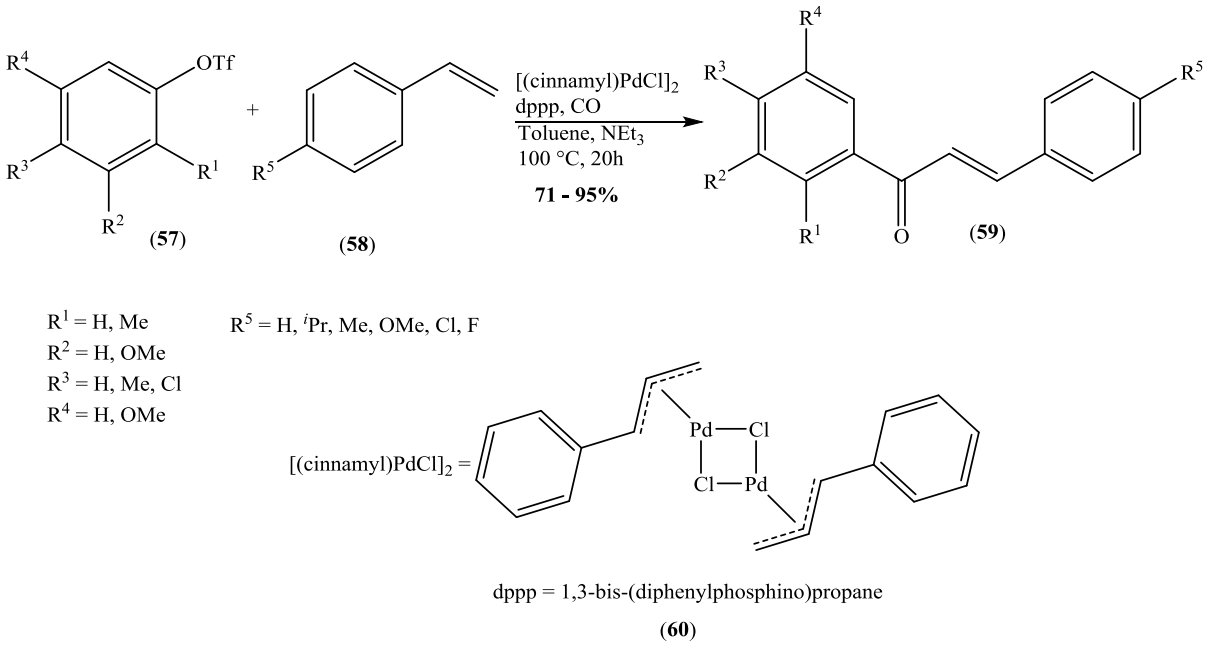
Scheme 2.6 Sonogashira coupling of aryl halides and 1-aryl-1-propargyl alcohols

Zhang and co-workers[32] reported on a selective carbonylative addition of aryl halides (**54**), terminal aryl alkynes (**55**) and carbon monoxide to give chalcones (**56**) in 40 – 88% yield. This method failed to produce chalcone for aryl alkynes with electron withdrawing groups (formyl and F) in the *para*-position or bromobenzene with a *p*-nitro substituent, though (Scheme 2.7).



Scheme 2.7 Carbonylative addition of terminal aryl alkynes, aryl halides and carbon monoxide

In another carbonylative approach, Wu, Neumann and Beller[34] obtained chalcones in 71 – 95% yield from aryl triflates (**57**) and styrenes (**58**) under Heck conditions in the presence of carbon monoxide (Scheme 2.8). Using this methodology, 4-methoxy- and 3',5'-dimethoxychalcone could be obtained in 92% and 79% yield, respectively.



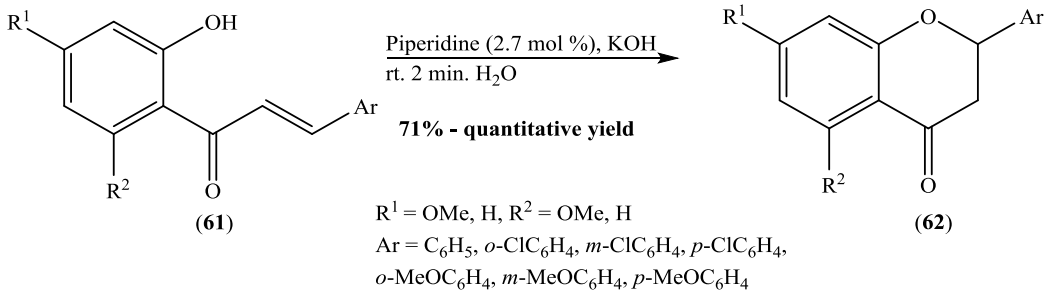
Scheme 2.8 Carbonylative Heck reaction of styrenes, aryl triflates and carbon monoxide

Even though these methods have been successful, they suffer from some drawbacks such as tedious raw material preparation processes, harsh reaction conditions, poor yield, prolonged reaction times and low selectivity.[5,39]

2.1.2 Synthesis of flavanones

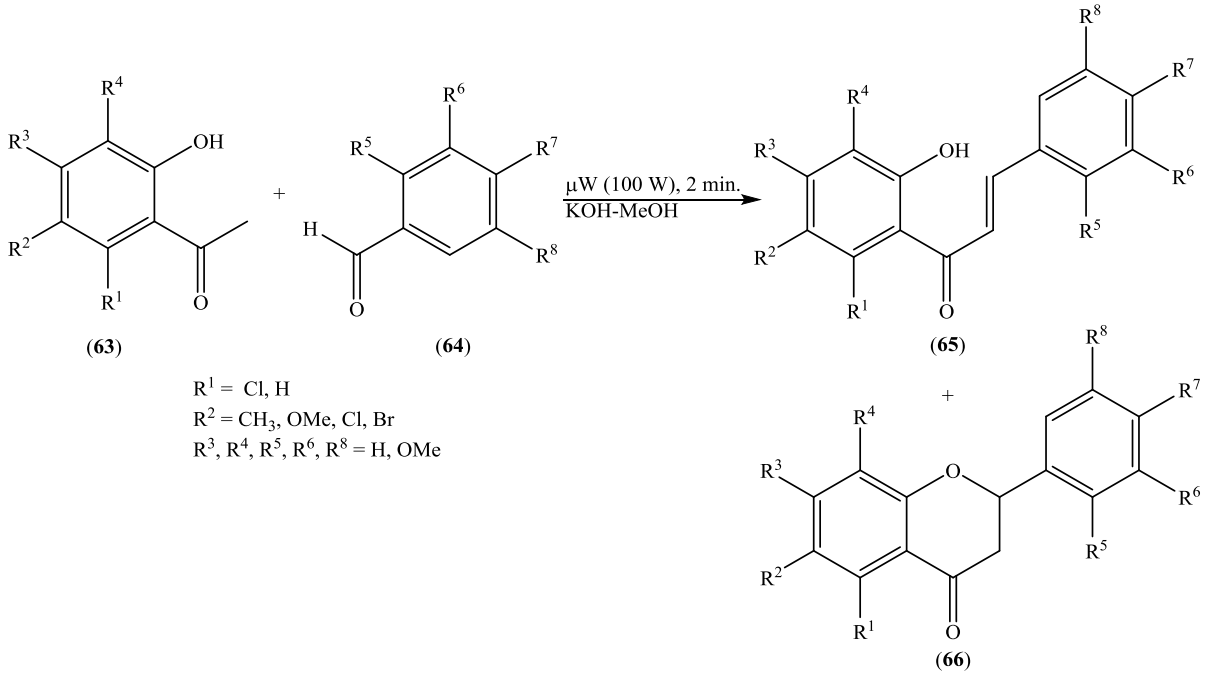
The cyclisation of 2'-hydroxychalcones (**35**) to flavanones (**38**) can be achieved in either basic (e.g. NaOAc,[40] K_2CO_3,[41] NEt_3,[42] KF/MeOH[43]) or acidic (e.g. H_2SO_4,[44] HOAc,[45] HCl[46]) medium with or without heating, but yields of the flavanone may vary quite significantly with differently substituted chalcones (30 – 70%).[47,48]

Zheng and co-workers[49] reported on a highly efficient procedure for chalcone (**61**) cyclisation in the presence of piperidine and KOH at rt. within only 1 – 2 min. which led to the formation of flavanones (**62**) in high yield (Scheme 2.9) and found that *p*-OMe substitution on the Ar-moiety (A-ring of the chalcone) led to a lower yield (71%) compared to *m*-OMe and *o*-OMe substitution (99% and 91% yields, respectively). An unsubstituted A-ring with or without methoxy substitution in the R^1 position of the B-ring led to the highest yields (>99% and 95%, respectively).



Scheme 2.9 Cyclisation by Zheng and co-workers[49]

Al-Bogami and co-workers[50] recently improved on existing synthetic protocols for flavanone synthesis by using microwave irradiation in the presence of KOH and were able to synthesise a range of flavanones (**66**) in a one-step process from the corresponding acetophenones (**63**) and benzaldehydes (**64**) (Scheme 2.10). 2'-Hydroxyacetophenones with substitution at carbon-5 (OCH_3, CH_3, Cl or Br) reacted with aromatic aldehydes with one or no substituents under these conditions to form flavanones (**66**) in 81 – 94% yield, whereas the formation of chalcones (**65**) (80 – 94% yield) were favoured in the absence of a 5-substituent.

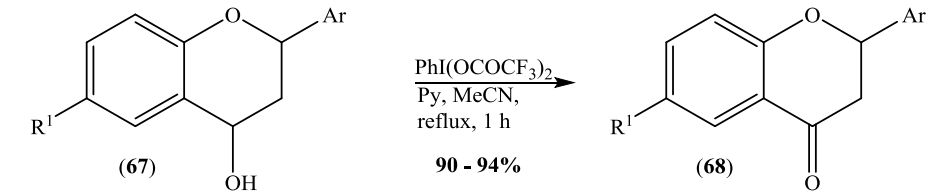


Scheme 2.10 One-pot flavanone synthesis by Al-Bogami and co-workers[50]

The majority of advances in the synthesis of flavanones still entail cyclisation of the chalcone precursor, but the methodology for effecting this transformation has been altered considerably by various research groups under basic (e.g. aminopyridyl functionalized silica,[51] L-proline/DMF,[52] L-alanine/NaOH,[53] $Fe(HSO_4)_3/SiO_2$/aniline,[54] *N*-methylimidazole in DMSO,[55] tetramethylguanidinum-based ionic liquid,[56] CuO nanocatalysis[57]) and acidic (e.g. sulfated zirconia,[58] phosphomolybdic acid supported on silica,[59] CH_3SO_3H/HOAc,[47] microwave/trifluroacetic acid[60]) conditions. Choudary *et al.*[61] utilised recyclable aerogel prepared nanocrystalline MgO particles in a one-pot Claisen–Schmidt condensation of benzaldehydes (**37**) and 2'-hydroxyacetophenones (**36**) and concomitant isomerization of the resulting chalcones to the corresponding flavanones (**38**). Electron donating *ortho*- and *para*-substituents on the aldehyde led to average-high conversions (50 – 80%) while electron withdrawing groups consistently led to conversions over 90%.

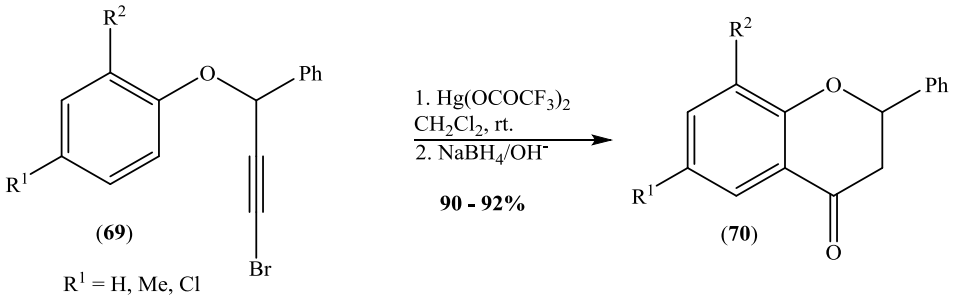
Alternative procedures for the preparation of flavanones include oxidation of flavan-4-ols (**67**) in the presence of hypervalent iodine [$(PhI(OCOCF_3)_2$] to flavanones in 90 – 94% yield for oxygenated and chlorinated substrates (Scheme 2.11);[62] 3-bromo-1-phenylprop-2-ynyl aryl ethers (**69**) cyclisation in the presence of $Hg(OCOCF_3)_2$, giving high yields (90 – 92%) for unsubstituted, methylated or chlorinated aryl ethers, but failing to produce any product with methoxy substitution on the A-ring (Scheme 2.12),[63] or the reaction of unsubstituted 1,3-diaryl-1,3-propanedione (**71**) with electron-rich and electron-poor aldehydes (**72**) in basic

medium (morpholine, EtOH) to afford flavanones (**73**) in 73 – 78% yield (Scheme 2.13).[64] Julia-Kocienski olefination of 2-benzo[*d*]thiazol-2-ylsulfonyl)-1-phenylethanone (**74**) with aromatic aldehydes (**75**) in the presence of DBU/THF has also led to flavanone (**76**) formation from aromatic aldehydes containing EDG or EWG (62 – 68%), but displayed lower tolerance to a free hydroxy group (40% yield) (Scheme 2.14).[65] Intramolecular dehydration of 3-hydroxy-1-(2-hydroxyphenyl)-3-arylpropan-1-ones (**77**) in the presence of a modified Mitsonobu reagent [DIAD (diisopropylazodicarboxylate)/TPP (triphenylphosphine)/Et_3N] gave flavanones (**78**) in 75 – 84% yield (Scheme 2.15). Unfortunately, no oxygenated substrates were included in the investigation.[66] Through a three component Mannich reaction of aromatic aldehydes, aniline and enolizable ketone (**79**) in the presence of iodine (30 mol%), flavanone synthesis was achieved in 63 – 88% yield for a variety of products (**80**) containing electron rich and/or electron poor aromatic entities, but failed to yield any product in the presence of dimethoxy substituted ketones (Scheme 2.16).[67] Microwave assisted Fries rearrangement of cinnamyl esters (**81**) in the presence of silica supported $AlCl_3$-$ZnCl_2$ led to the formation of flavanones (**82**) in 87 and 73% yield for methyl and methoxy substituted A-rings to be (Scheme 2.17), but the investigation was not extended to substrates containing B-ring substitution[68]



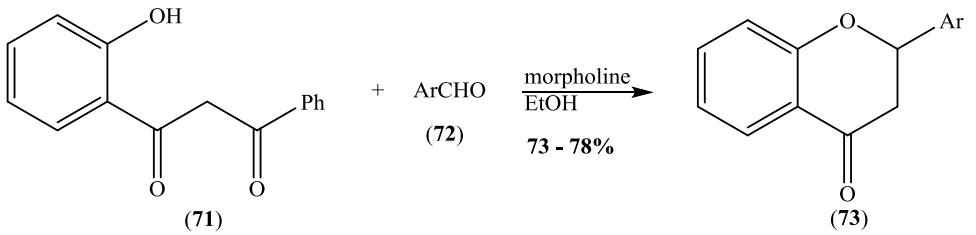
R^1 = H, Cl, Me
Ar = C_6H_5, 4-$OMeC_6H_4$, 4-ClC_6H_4

Scheme 2.11 $PhI(OCOCF_3)_2$ oxidation of flavan-4-ols



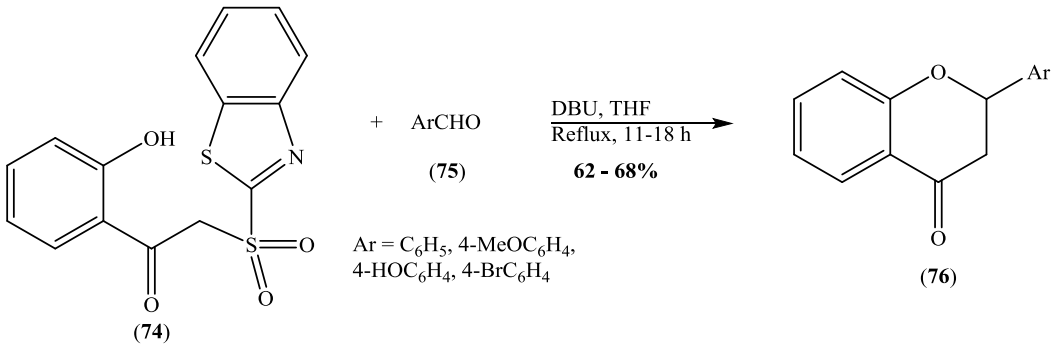
R^1 = H, Me, Cl
R^2 = H, Me

Scheme 2.12 $Hg(OCOCF_3)_2$ cyclisation of 3-bromo-1-phenylprop-2-ynyl aryl ethers



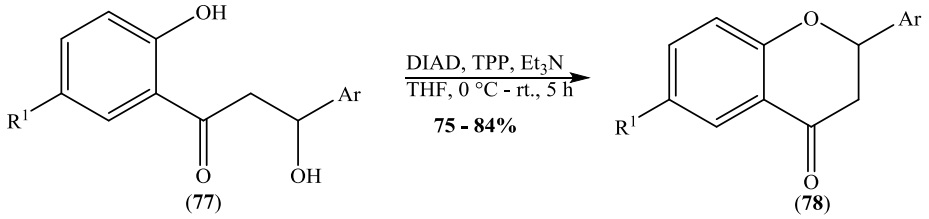
Ar = C_6H_5, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 2.13 Reaction of unsubstituted 1,3-diaryl-1,3-propanedione with aldehydes



Ar = C_6H_5, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-BrC_6H_4

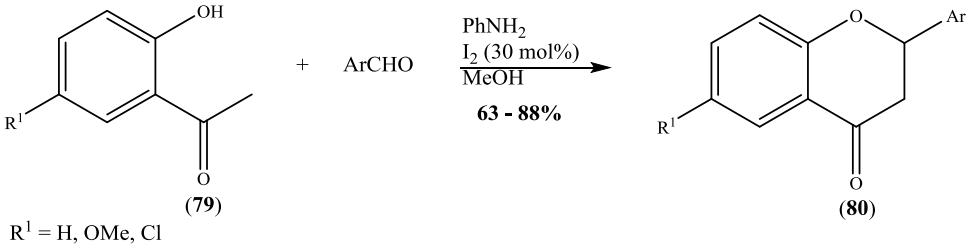
Scheme 2.14 Julia-Kocienski olefination of 2-benzo[*d*]thiazol-2-ylsulfonyl)-1-phenylethanone with aromatic aldehydes



R^1 = H, Cl

Ar = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-Br-C_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-FC_6H_4, 4-BrC_6H_4

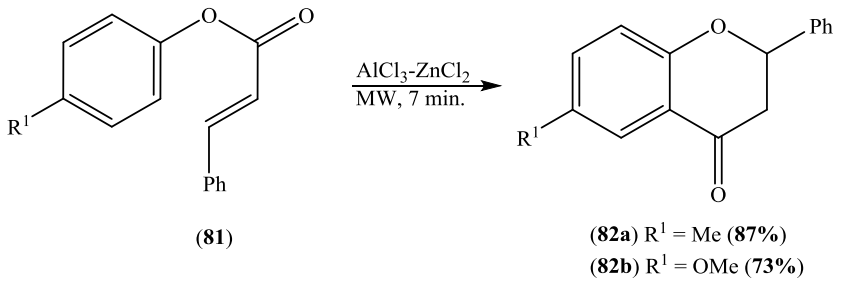
Scheme 2.15 Intramolecular dehydration of 3-hydroxy-1-(2-hydroxyphenyl)-3-arylpropan-1-ones



R^1 = H, OMe, Cl

Ar = C_6H_5, 2-$OMeC_6H_4$, 2-FC_6H_4, 2-$NO_2C_6H_4$, 3-$OMeC_6H_4$, 3-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 2.16 Mannich reaction of aromatic aldehydes, aniline and enolizable ketone



(**81**)

(**82a**) R^1 = Me (**87%**)
(**82b**) R^1 = OMe (**73%**)

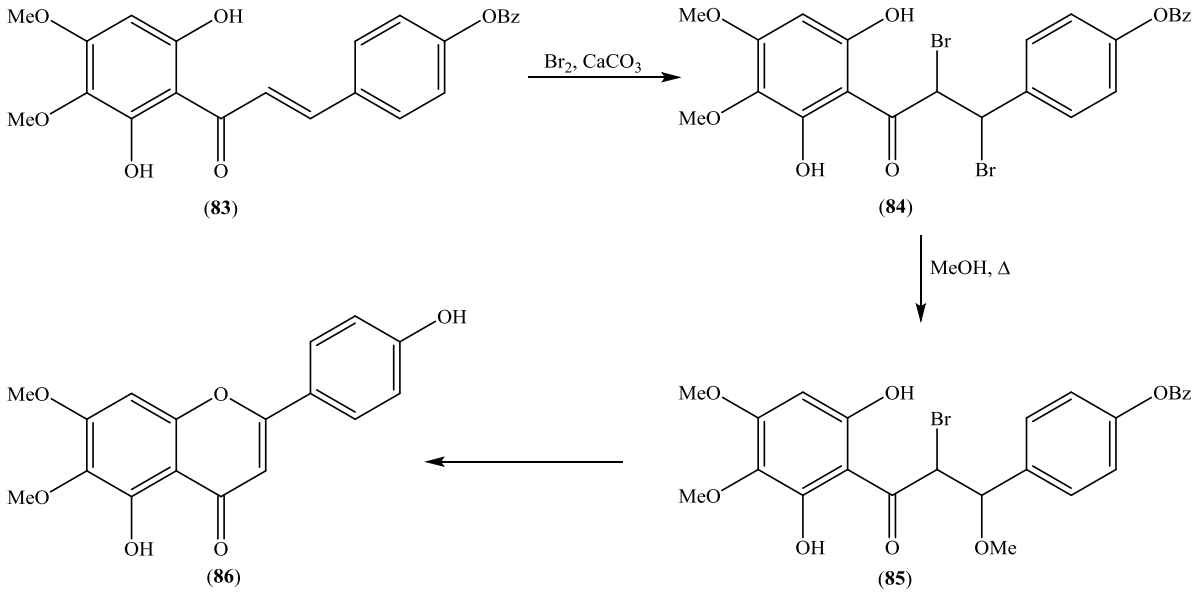
Scheme 2.17 Microwave assisted Fries rearrangement

2.1.3 Flavones

Flavones have mainly been prepared by the halogenation-cyclisation or dehydrogenation-cyclisation of 2'-hydroxychalcones (**35**), the dehydrogenation of flavanones (**38**), the oxidation of flavenes (**98**), the Baker-Venkataraman rearrangement of 1,3-diketones or the Allan and Robinson condensation reaction of *o*-hydroxyacetophenones (**36**) with anhydrides.[69,70]

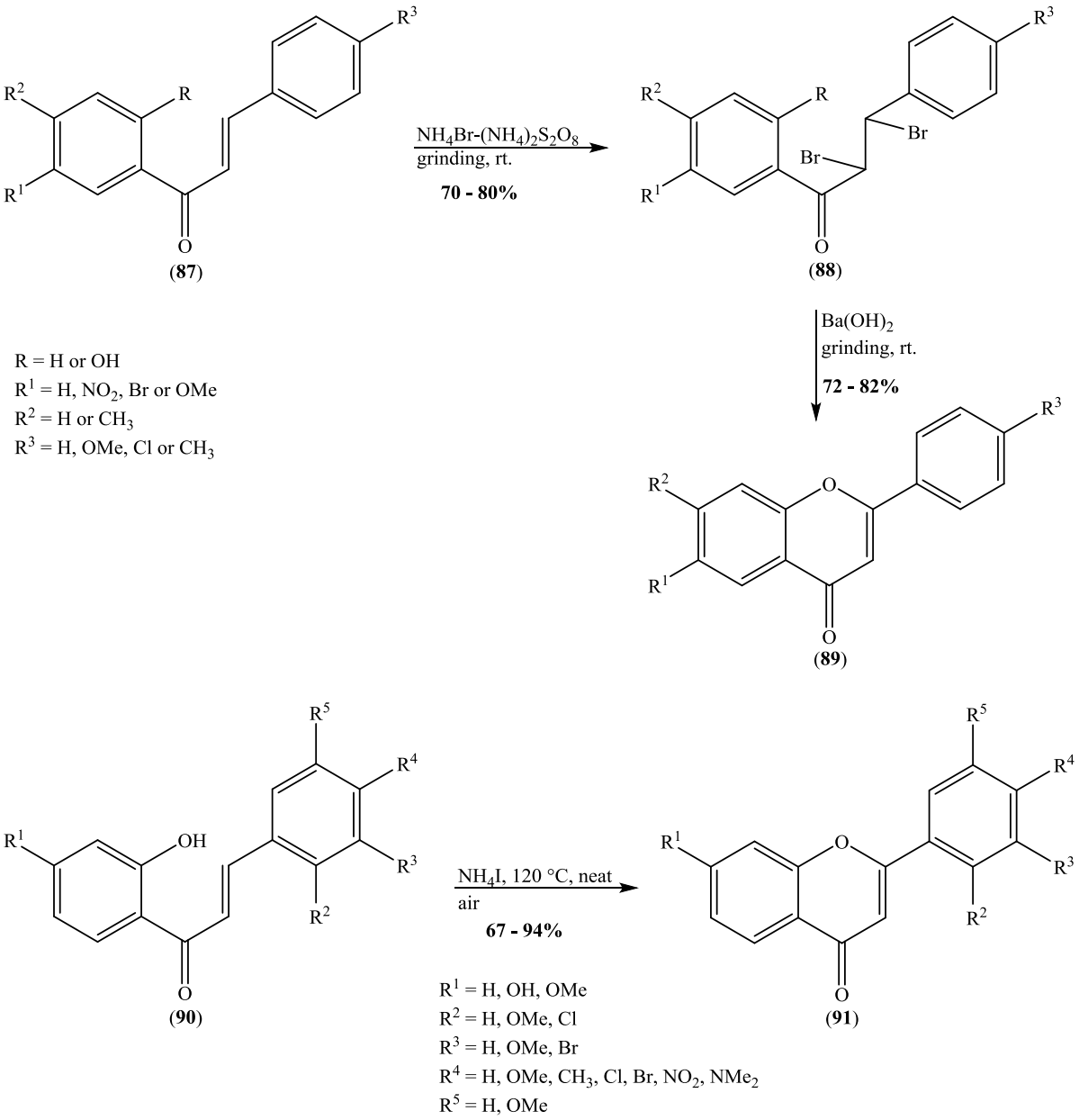
2.1.3.1 Flavones from 2'-hydroxychalcones

The earliest synthetic protocols for flavone preparation utilised 2'-hydroxychalcones (**35**) as starting materials.[71] One of the oldest and most successful methods for the preparation of flavones was developed by Farkas *et al.*[69,72] and involved bromination of the α,β-double bond of the chalcone (**83**) in the presence of $CaCO_3$, followed by boiling the dibromo product (**84**) in MeOH to obtain the flavone (**86**) after thermal cyclisation and HBr elimination (Scheme 2.18). Even though this methodology has been improved upon by the utilisation of numerous other halogenation agents (e.g. tetrabutylammonium tribromide,[73] phenyl trimethylammonium bromide,[74] DMSO/I_2,[75] Br_2-NaOH,[76] etc.), nuclear halogenation of the aromatic rings of the chalcone places a serious limitation on the applicability of this methodology and often leads to low yields being obtained.[77]



Scheme 2.18 Flavone formation from chalcones *via* halogenation

Due to the general drive towards 'green' methods in recent years, many groups have focused on utilising efficient one-pot procedures and/or eco-friendly reaction conditions. In this regard, Jakhar and Makrandi[77] reported an eco-friendly grinding method that involves the bromination of 2'-hydroxychalcones (**87**) in the presence of ammonium bromide and ammonium persulfate in a minimum amount of water and subsequent cyclisation and dehydrohalogenation with barium hydroxide (Scheme 2.19). The Kulkarni group[78] employed catalytic (10 mol%) amounts of ammonium iodide in air to effect the halogenation - cyclisation - dehydrohalogenation (Scheme 2.19). This method proved to be tolerant of a wide range of functional groups (EWG and EDG, including methoxy groups), leading to good yields throughout (72 – 94%), but showed poorer yields in the presence of free hydroxy groups on the aromatic rings (67 – 71%). Lahyani and Trabelsi[79] extended this protocol to ICl/DMSO and ultrasound, whereas Sarda *et al.*[80] reported a solvent-free reaction with I_2–Al_2O_3 under microwave irradiation.



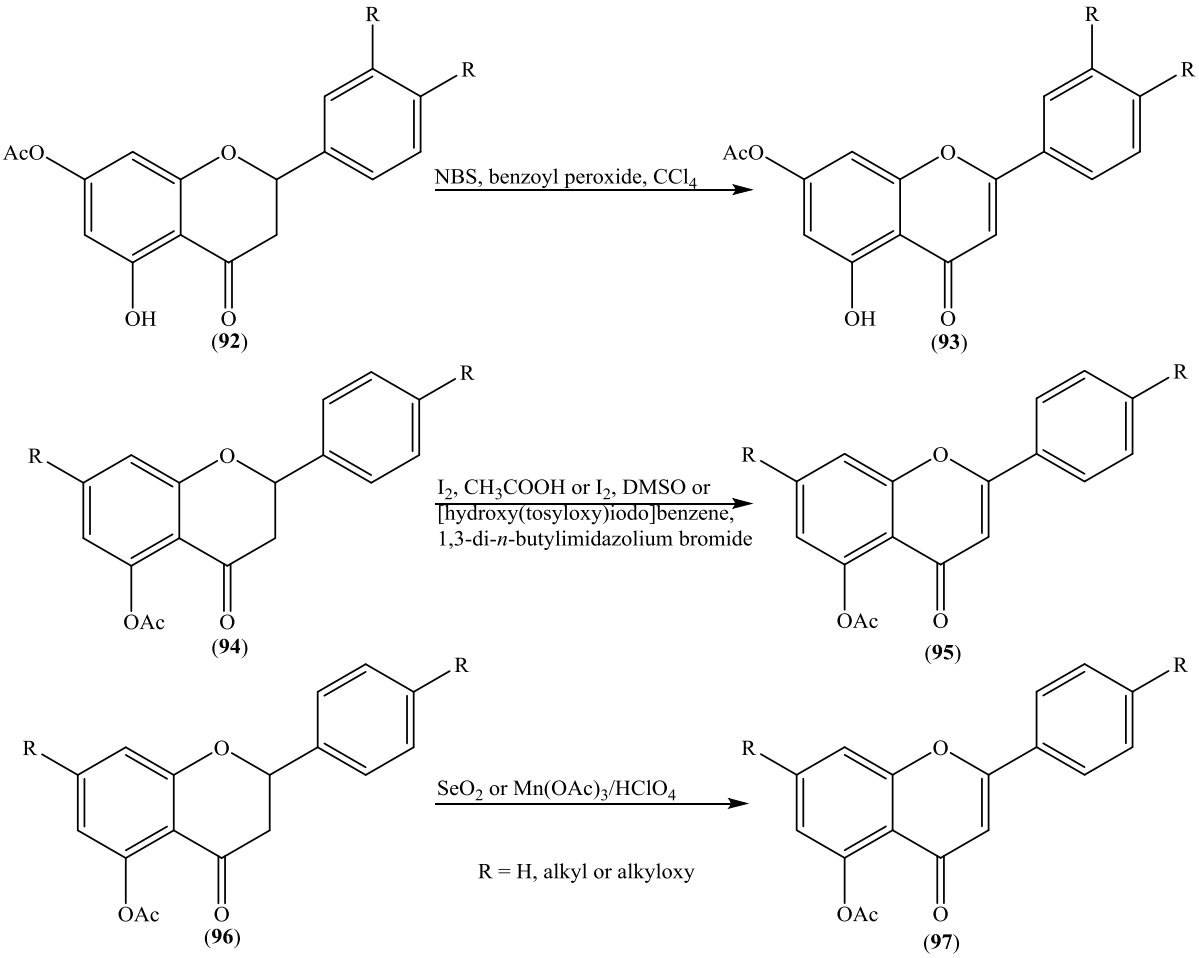
Scheme 2.19 Eco-friendly halogenation and cyclisation-dehalogenation of chalcones

Oxidative cyclisation of the appropriate 2'-hydroxychalcones could alternatively be established with $NaIO_4$/DMSO,[81] DDQ,[82] Na_2TeO_3/DMSO,[83] SeO_2/dioxane[84] and CuI/O_2.[85]

A modification of chalcone dehydrogenation was developed utilising 2',4'-dihydroxychalcones. Bose and co-workers[86] reported on successful cyclisation with simultaneous dehydrogenation in the presence of Pd/C to yield flavone.

2.1.3.2 Flavones from flavanones

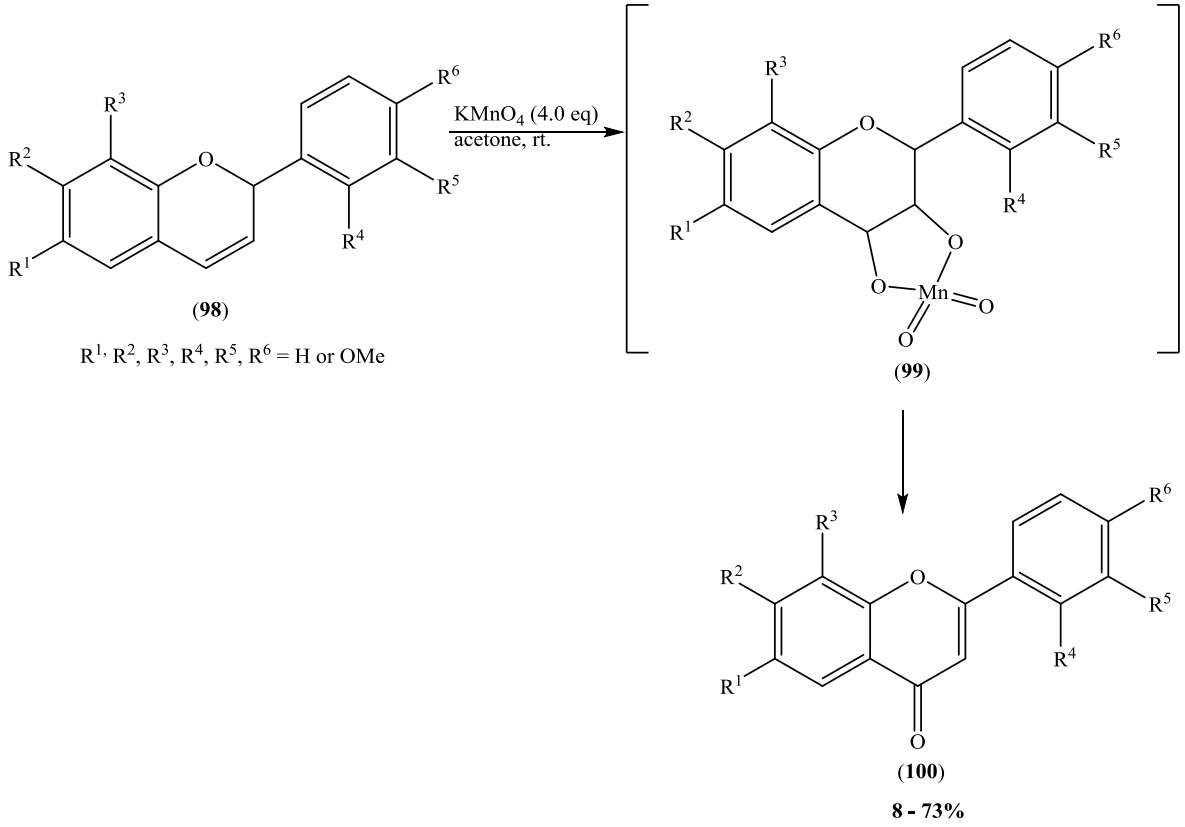
Two major methodologies were reported for the oxidative formation of flavones from flavanones, i.e. benzoyl peroxide-catalysed bromination of partially acetylated flavanones (**92**) with NBS (*N*-bromosuccinimide) in CCl_4 followed by dehydrohalogenation,[87] and treatment of partially methylated flavanones (**94**) with iodine in glacial acetic acid[88] or I_2/DMSO,[75] which led to the formation of the corresponding flavones (**93**) and (**95**) in good yields (70 – 75% and 59 – 87%, respectively) (Scheme 2.20).[89,90] Hypervalent iodine, [hydroxy(tosyloxy)iodo]benzene, in an ionic liquid[91] was demonstrated to convert flavanones to flavones at room temperature in 74 – 90 % yield. However, no oxygenated substrates were included in the evaluation. Flavanone (**96**) dehydrogenation with SeO_2[92,93] or oxidation with $Mn(OAc)_3/HClO_4$,[94] also offer alternatives for the preparation of flavones (**97**) (35% and 90 – 96% yield, respectively) (Scheme 2.20).



Scheme 2.20 Halogenation-elimination and dehydrogenation of flavanones

2.1.3.3 Flavones from flav-3-enes

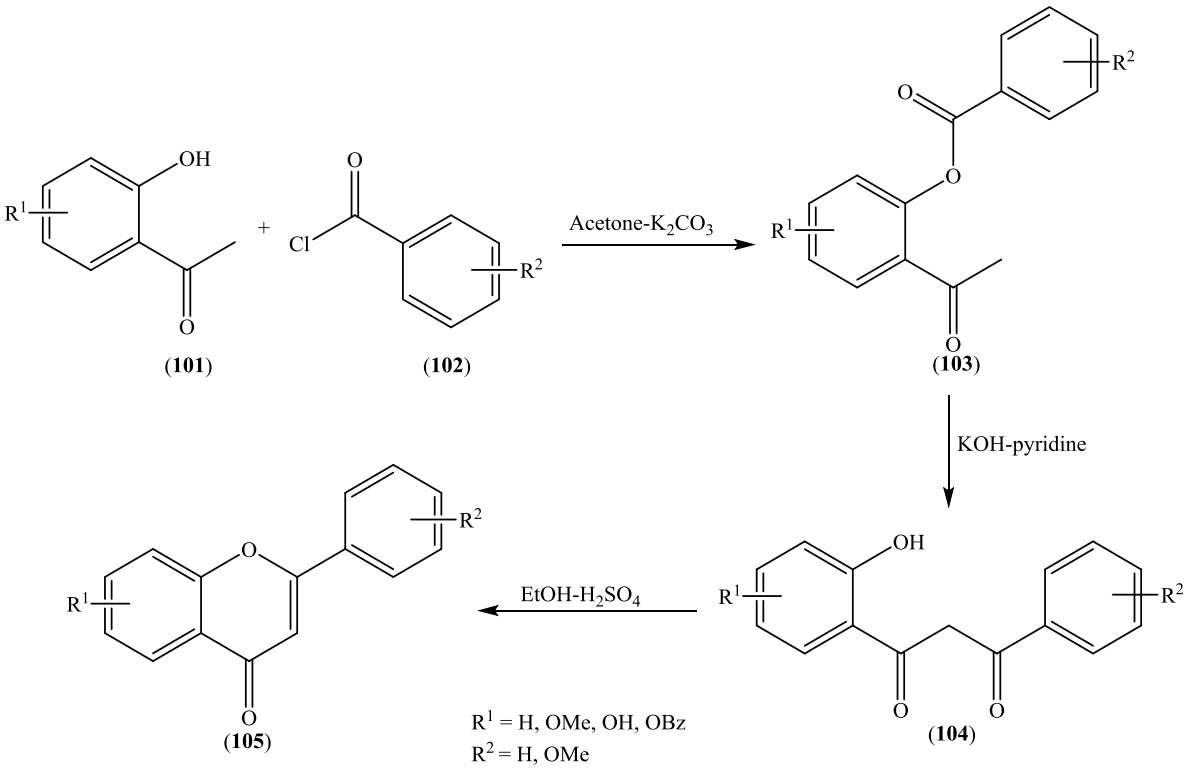
The oxidation of flav-3-enes (**98**) in the presence of $KMnO_4$ and acetone affords flavones (**100**) in variable yields (8 – 73%) but is of limited practical value since this transformation depends upon the availability of appropriately substituted flav-3-enes as substrates (Scheme 2.21).[95]



Scheme 2.21 Oxidation of flav-3-enes

2.1.3.4 Baker-Venkataraman rearrangement

In this method, a 2'-hydroxyacetophenone (**101**) is esterified with an aromatic acid chloride (**102**) in acetone-K_2CO_3 or pyridine. Subsequent base catalysed rearrangement with KOH-pyridine or NaH[96] produces the 1,3-diketone (**104**) which is then transformed into the desired flavone (**105**) through the utilization of EtOH-H_2SO_4 or glacial acetic acid (e.g. Scheme 2.22).[69,97] Other reagents such as benzene-NaOH/$BuN_4^+.HSO_4^-$,[98] CsF/CaO,[99] $InCl_3$,[100] $Ga(OTf)_3$,[101] $TiO_2/H_2PW_{12}O_{40}$,[102] $KHSO_4$,[103] gold nanoparticles[104] or bis-(trichloromethyl)carbonate/DMF have also been effective for this transformation.[105]

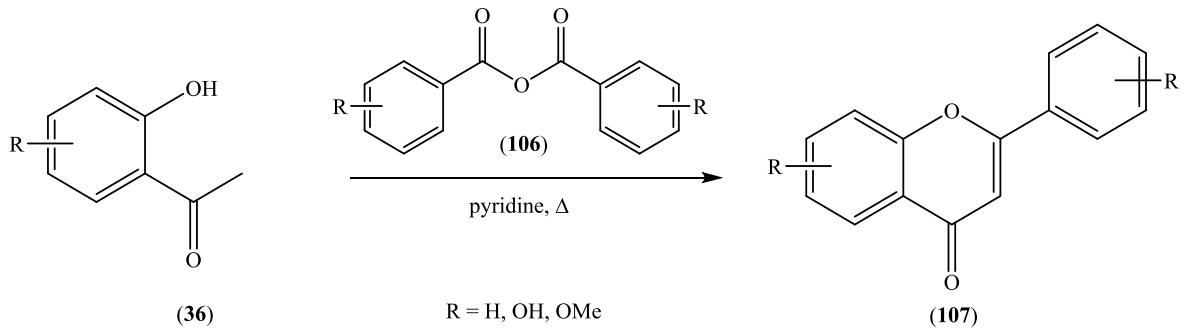


Scheme 2.22 Flavone preparation through the Baker-Venkataraman rearrangement

A catalytic process developed by the Zhao group[106] entails 1,3-dione cyclisation with the utilization of a catalytic quantity of K_2CO_3 in DMF (75 – 98% yield for substrates with H, OMe, Br and Cl substituents), while Bennardi *et al.*[107] employed the heterogenous silica supported Wells-Dawson acid ($H_6P_2W_{18}O_{62}.24H_2O$) as a recyclable catalyst to effect cyclisation (82 – 88% yield for substrates with H, OMe, Br and Cl substituents). Microwave irradiation in catalytic processes with $CuCl_2$[108] or the ionic liquid, ethyl ammonium nitrate,[109] have also been utilised to effect the cyclisation to flavones in yields above 80%.

2.1.3.5 Allan-Robinson condensation

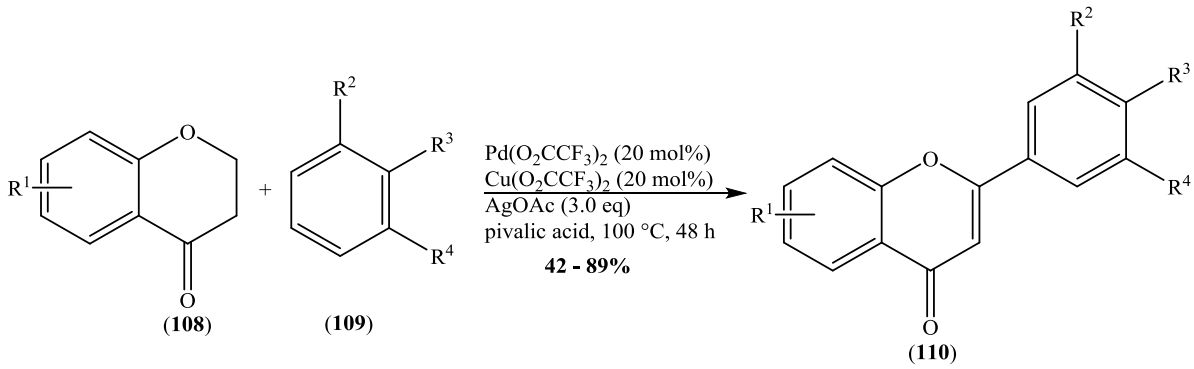
In a similar, but one-step process, developed by Allan and Robinson,[110] an *o*-hydroxyacetophenone (**36**) is reacted with the anhydride of an aromatic acid (**106**). This reaction is performed in the presence of the conjugated salt of the acid corresponding to the anhydride and pyridine or trimethylamine and leads to the flavone (**107**) *via* the β-diketone in a one-pot process (Scheme 2.23).[69,111] The Allan-Robinson and Baker-Venkataraman methods are both hampered by the availability of the substituted acid anhydride/chloride, especially if highly substituted analogues are to be prepared.



Scheme 2.23 Allan-Robinson condensation

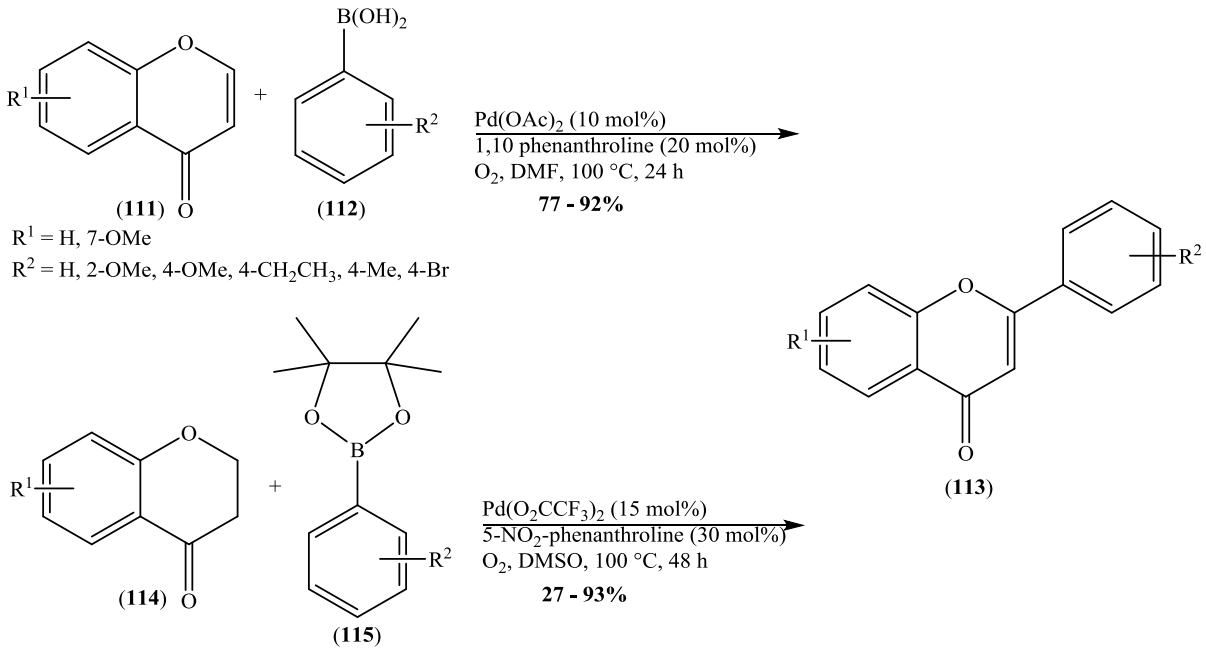
2.1.3.6 Advances in flavone synthesis

Several novel processes for the synthesis of flavones have been developed in recent years.[112] One of these protocols include the regioselective arylation of chromanones or chromenones *via* the Heck reaction.[113,114,115] The Moon group[114] obtained moderate-high yields (42 – 89%) when utilising their catalytic system [$Pd(O_2CCF_3)_2$, $Cu(O_2CCF_3)_2$, AgOAc, pivalic acid] in the coupling of chromanones (**108**) with substituted benzenes (**109**) (Scheme 2.24), while Khoobi and co-workers[115] and Lee *et al.*[113] utilised chromenones (**111**) and chromanones (**114**) in coupling reactions with phenylboronic acids (**112**) and phenylboronic acid pinacol esters (**115**), respectively (Scheme 2.25).



R^1 = H, 6-Me, 6-Cl, 6-F, 7-OMe, 7-OH, 7-OAc, 7-OTf
R^2 = H, CF_3, R^3 = H, Me, Cl, R^4 = H, Me, Cl, F, CF_3

Scheme 2.24 Coupling of chromanones with substituted benzenes

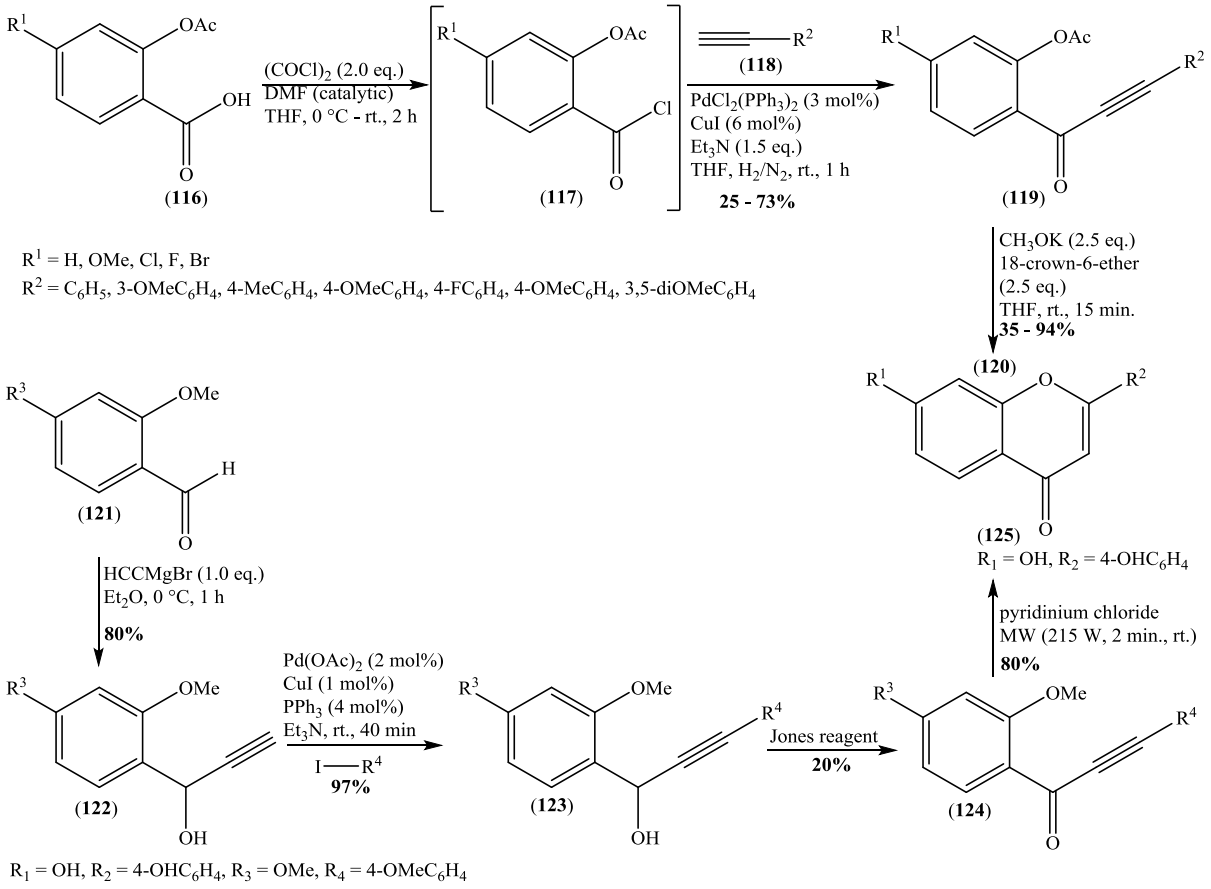


Scheme 2.25 Flavone synthesis *via* Heck reaction

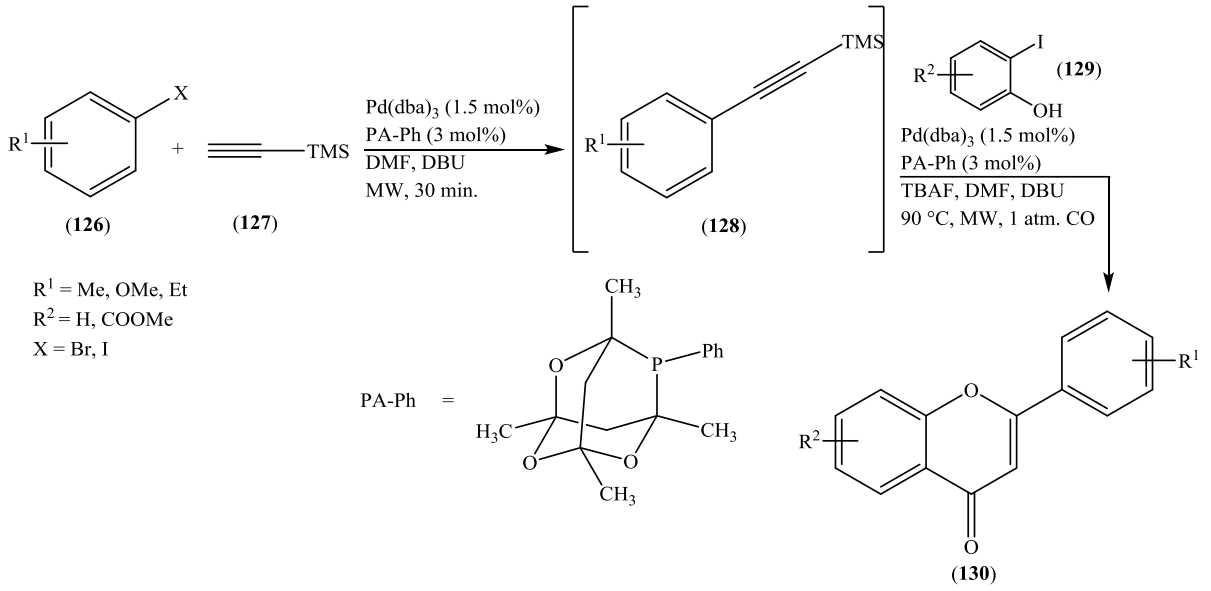
All these methodologies proved to be tolerant of a wide range of functional groups, giving high yields in the presence of electron donating and electron withdrawing substituents. Moon[114] and Lee,[113] however, noted that a significantly lower yield (42 and 27%, respectively) was obtained in the presence of $–CF_3$ entities on the aryl moiety, while Khoobi *et al.*[115] could not achieve flavone formation when employing a nitro-substituted aryl boronic acid.

Sonogashira coupling between *o*-acetylsalicoyl chloride (**117**) and terminal acetylenes (**118**) in the presence of $PdCl_2(PPh_3)_2$/CuI/Et_3N, followed by base catalysed cyclisation gave flavones (**120**) in 35 – 94% yield (final step). It was noted that fluorine substitution on the acetylene aryl ring leads to significantly lower yield (35%). Another Sonogashira process was followed by oxidation with the Jones reagent (CrO_3/H_2SO_4/acetone) and afforded 4',7-dihydroxyflavone (**125**)[116] (Scheme 2.26), while Awuah and Capretta[117] developed a catalytic system wherein flavones were prepared *via* a microwave facilitated Sonogashira-carbonylation-cyclisation reaction. The aryl alkyne (**128**) obtained from the Sonogashira coupling of an aryl halide (**126**) and TMS acetylene (**127**) was transferred to a second reaction vessel containing the iodophenol (**129**), fresh catalyst, solvent, base and TBAF (for desilylation) and CO introduced. The desired flavone (**130**) was thus obtained following a second Sonogashira coupling, carbonylation and cyclisation. Average yields (46 – 67%) were

achieved and a *p*-OMe substituent on the aryl halide was tolerated (56% yield) (Scheme 2.27).



Scheme 2.26 Flavone synthesis *via* multistep processes and Sonogashira coupling



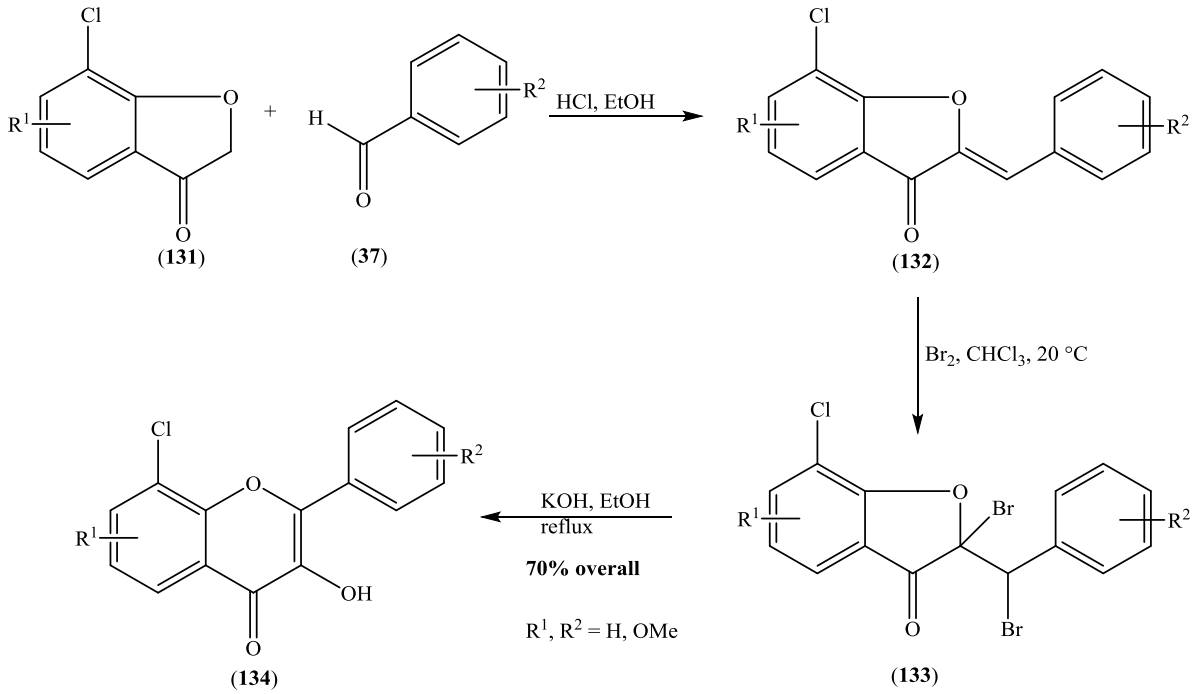
Scheme 2.27 Flavone synthesis *via* Sonogashira coupling and carbonylative annulation

2.1.4 Flavonols (3-hydroxyflavones)

Flavonols are most frequently synthesised *via* the Auwers synthesis or oxidative cyclisation of 2'-hydroxychalcones according to the AFO (Algar-Flynn-Oyamada) reaction.[118]

2.1.4.1 Auwers flavonol synthesis

The first step in the Auwers flavonol synthesis entails acid catalysed aldol condensation between a benzaldehyde (**37**) and coumaranone (**131**). After bromination of the resulting α,β-unsaturated analogue (**132**) (aurone), the dibromo adduct (**133**) is transformed into the desired flavonol (**134**) in the presence of KOH (Scheme 2.28).[119]

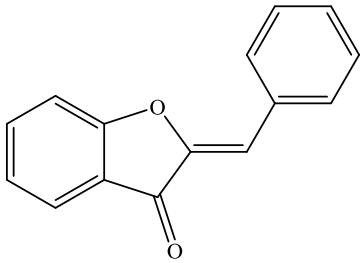


Scheme 2.28 Auwers[119] method for flavonol synthesis

2.1.4.2 The Algar-Flynn-Oyamada reaction

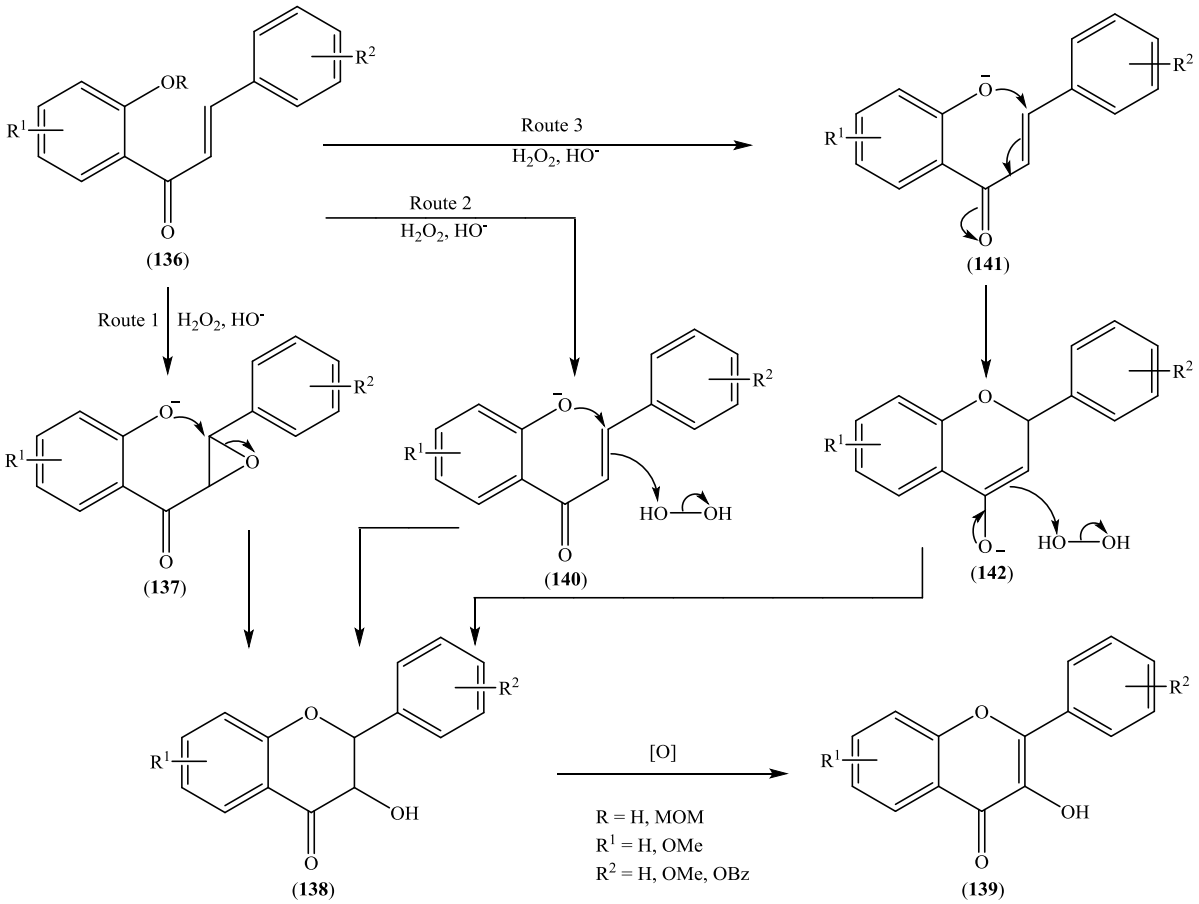
In this procedure, 2'-hydroxychalcones (**35**) are converted into the corresponding flavonols (**134**) in a one-step procedure in the presence of alkaline H_2O_2. Yields are, however, often low (20 – 40%). 2',2,4-Trihydroxychalcones lacking a 6'-methoxy substituent, predominantly yields flavonols while 2'-hydroxychalcones containing a 6'-methoxy substituent, but lacking a 2- and 4-hydroxy group, give a mixture of flavonols and aurones (**135**) (Fig. 2.1). Aurone (**135**) formation is furthermore favoured by low temperatures, while high temperatures predominantly lead to flavonol production.[118,120]

When the 2'-OH group is protected, the reaction proceeds *via* a chalcone epoxide intermediate (**137**),[121,122,123] whereas routes 2 (cyclisation, enolization, hydroxylation) or 3 (concerted cyclisation and hydroxylation) are favoured when this hydroxy group is unprotected (Scheme 2.29).[124,125,126] Following deprotection, acid-mediated (e.g. BF_3-Et_2O)[135] intramolecular cyclisation of the 2'-hydroxychalcone epoxide under dry conditions, will afford the corresponding dihydroflavonol (**138**) that can be oxidized to the desired flavonol (**139**).



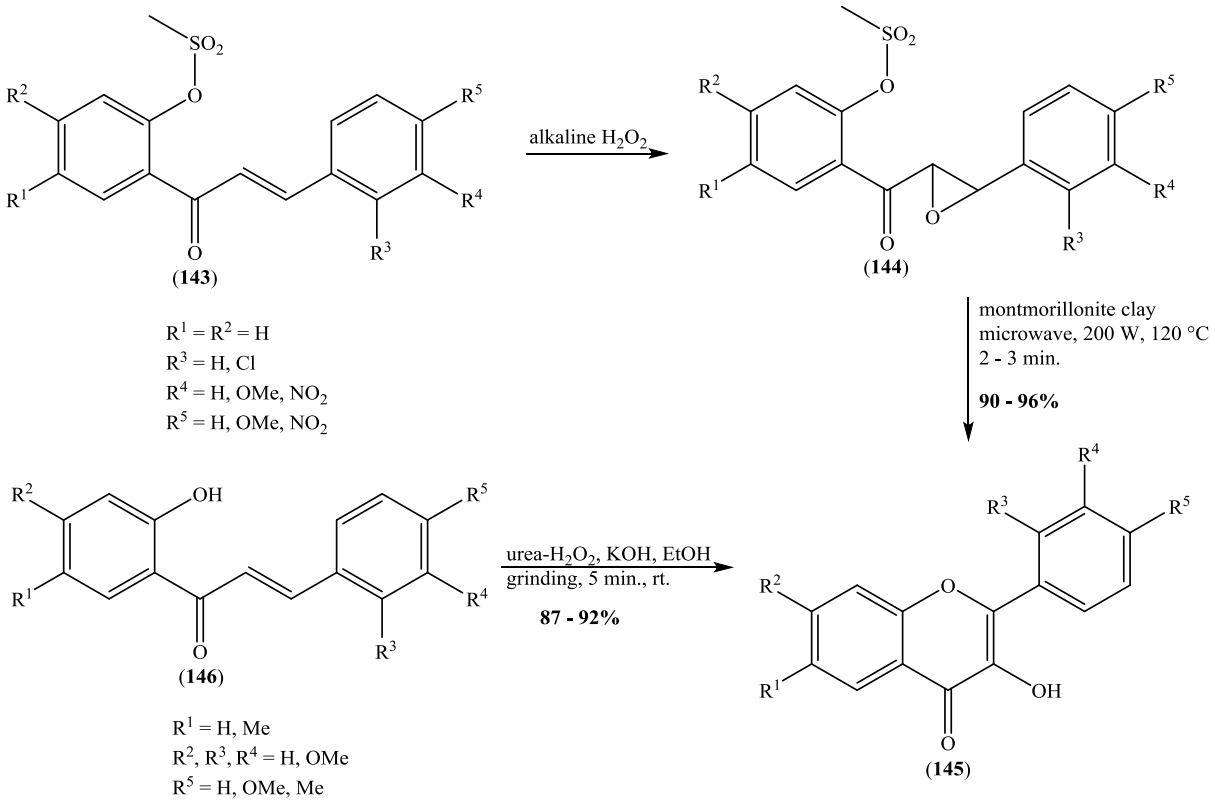
(**135**)

Fig. 2.1 General aurone structure



Scheme 2.29 AFO reaction mechanism

More recent developments focused on environmentally benign processes. Babu *et al.*[127] reported on a microwave assisted, solvent free cyclisation of chalcone epoxides promoted by montmorillonite clay, whereas Kumar and co-workers[128] modified the AFO reaction by grinding a mixture of 2'-hydroxychalcone (**146**) and urea-H_2O_2 complex with pulverised KOH. Flavonols (**145**) were obtained in excellent yield for substrates with oxygenation as well as substrates containing electron withdrawing entities (Scheme 2.30) in both methods.

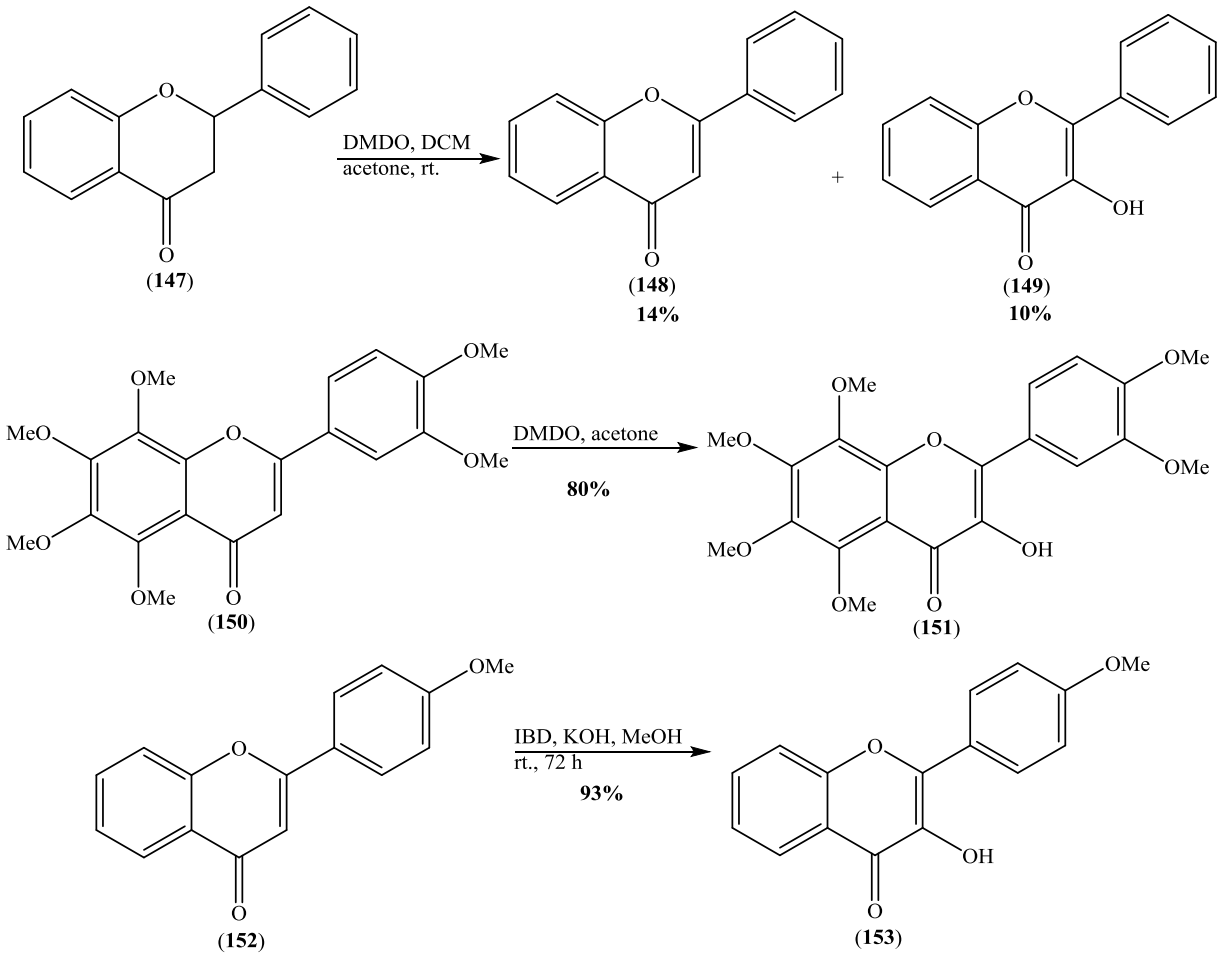


Scheme 2.30 Environmentally benign chalcone cyclisation to flavonol

2.1.4.3 Advances in the synthesis of flavonols

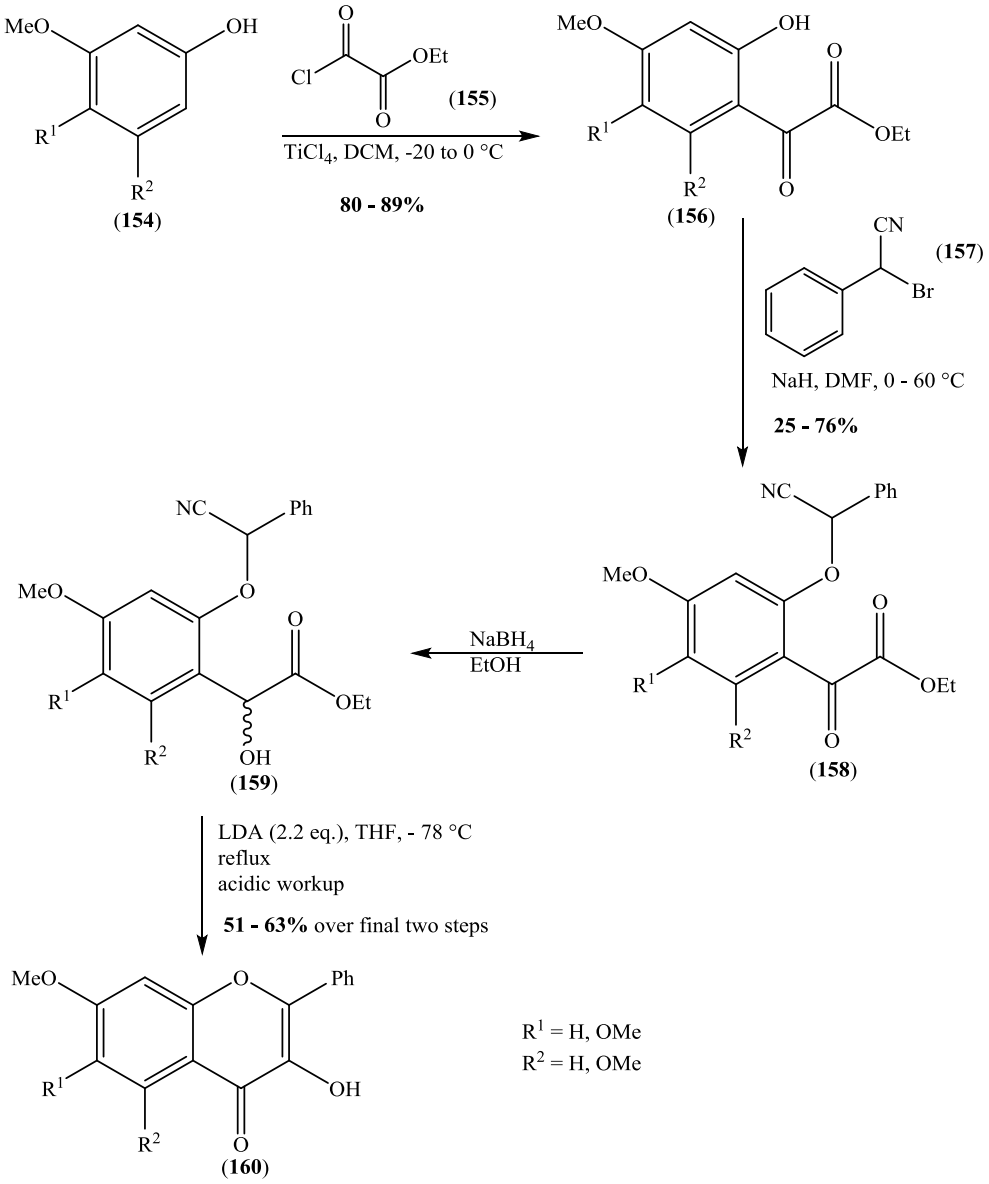
While some new methods for flavonol synthesis were developed a few decades ago, like C-3 hydroxylation of flavanones using the Fenton reagent (a solution of hydrogen peroxide and ferrous iron catalyst),[118] the conversion of flavanones to the 3-acetoxy derivatives with $Pb(OAc)_4$, followed by hydrolysis of the acetate and oxidation of the dihydroflavonol[129] and the treatment of 2-aryl-3-nitrochromenes with alkaline hydrogen peroxide,[130] these procedures proved to be of limited practical value.

More recently, flavonol synthesis was achieved *via* transformation of the preceding flavanone or flavone in the presence of dimethyldioxirane (DMDO) or iodobenzene diacetate (IBD). The Bernini group[131] reported on the oxidation of flavanone (**147**) utilising DMDO and acetone at room temperature to form flavone (**148**) in 14% yield and the flavonol (**149**) in only 10% yield, while Chu, Wu and Lee[132] improved on flavonol synthesis by reacting flavone (**150**) in the presence of DMDO and acetone to afford the desired flavonol (**151**) in 80% yield. Sagrera *et al.*[60] utilised flavone (**152**) in the presence if IBD and obtained the desired product (**153**) in 93% yield. (Scheme 2.31).



Scheme 2.31 Flavonol synthesis in the presence of dimethyldioxirane or iodobenzene diacetate

The Kraus group[133] had a completely new approach and utilised readily available phenols (**154**) in a coupling reaction with ethyl chlorooxoacetate (**155**) under Friedel Crafts conditions with $TiCl_4$. The resulting keto phenols (**156**) were subjected to *O*-alkylation with α-bromophenylacetonitrile (**157**) and subsequent selective reduction ($NaBH_4$) and intramolecular cyclisation in the presence of LDA to produce the desired flavonols (**160**) in moderate yield (Scheme 2.32). Although this process provides a new alternative route to flavonol synthesis, it requires strong base, entails numerous synthetic steps and affords products in variable yields.



Scheme 2.32 Flavonol synthesis *via* base mediated cyclisation

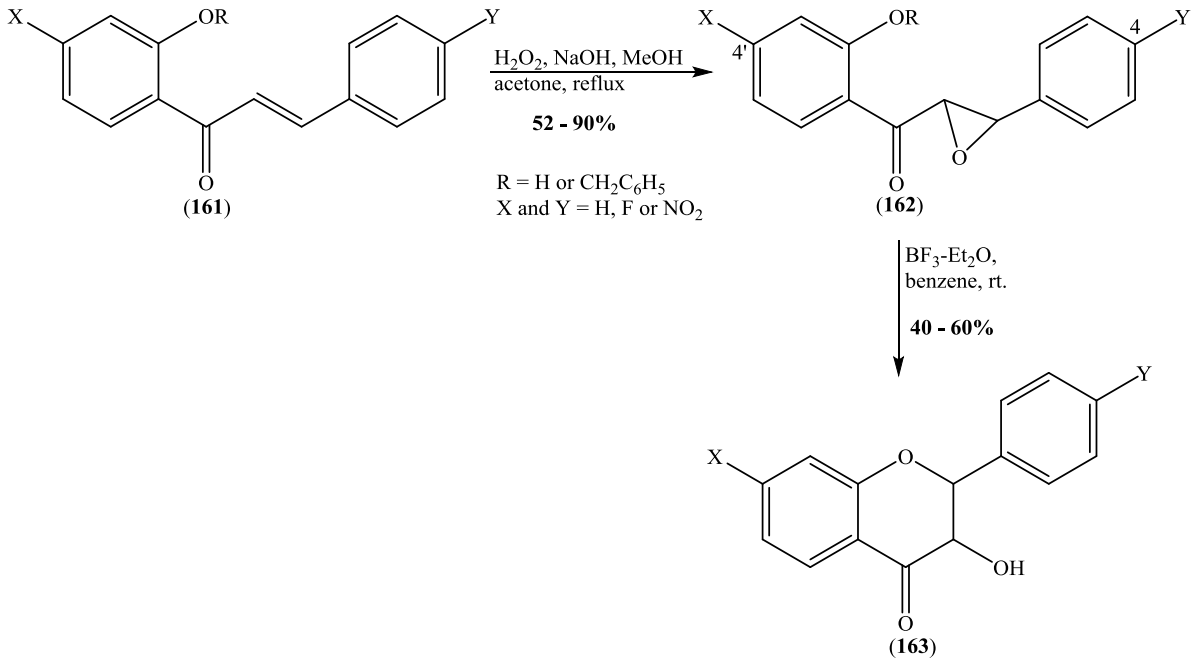
2.1.5 Dihydroflavonols (3-hydroxyflavanones)

Dihydroflavonols (**138**) may be obtained through the cyclisation of 2'-hydroxy-α-methoxychalcone using mild conditions like sodium acetate in ethanol.[134] However, the preparation of flavonols using the AFO oxidation of 2'-hydroxychalcones (**35**) proceeds *via* the dihydroflavonol intermediate (**138**) (*cf.* Scheme 2.29), which therefore also provides a suitable protocol toward dihydroflavonol synthesis.

A more preferred method based on the AFO reaction, involves epoxidation of the 2'-protected 2'-hydroxychalcone, which can then be subjected to acid-mediated intramolecular cyclisation under dry conditions. In this process, however, isoflavone formation takes place as a side

reaction under acidic reaction conditions and can be attributed to cleavage of the highly reactive epoxide functionality prior to deprotection of the 2'-hydroxy group and aryl migration (*vide infra* par. 2.2.1.2). To prevent isoflavone formation, nucleophilic opening of the epoxide functionality is effective. Utilising a phenylmethanethiol (BnSH)-tin(IV)chloride ($SnCl_4$) (Lewis acid-mercaptan) system for cleavage of the oxirane at -20 °C followed by treatment with silver tetrafluroborate as thiophilic Lewis acid, yields dihydroflavonols exclusively (*vide infra* par. 2.4.3)[4,134,135]

The Khlebnikova group[123] synthesised a range of 3-hydroxyflavanones (**163**) in 40 – 60% yield *via* boron trifluoride diethyletherate (BF_3**.**Et_2O) catalysed cyclisation of 2'-hydroxychalcone epoxides (**162**) (Scheme 2.33) and noted that compounds with 4-fluoro or 4,4'-difluoro substituents, gave yields of 40 – 42%, while a combination of 4'-F and 4-NO_2 substituents gave the 3-hydroxyflavanones in 60% yield.



Scheme 2.33 3-Hydroxyflavanone synthesis

2.2 Isoflavonoids

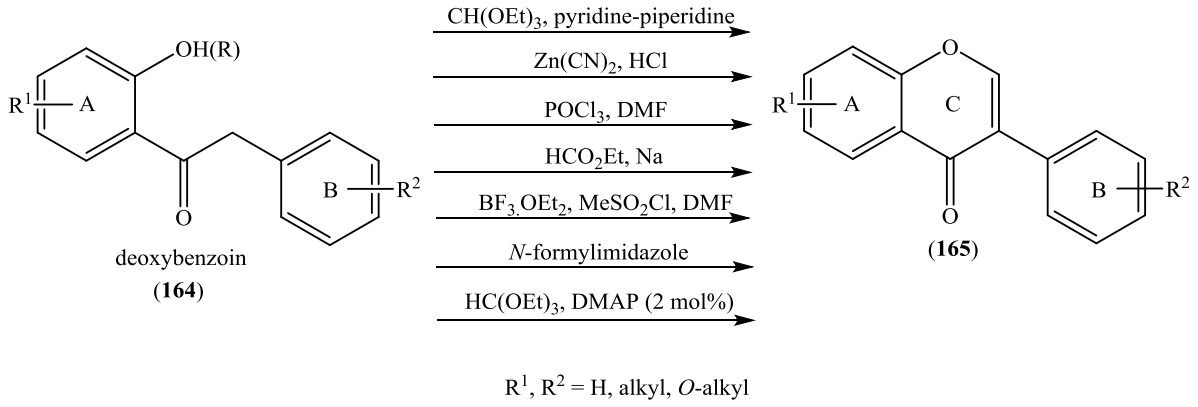
Compounds belonging to the isoflavonoid class of flavonoids also contain the basic C_6-C_3-C_6 skeleton, but with the phenyl (B-ring) moiety attached to the 3-position of the heterocyclic C-ring.

2.2.1 Isoflavones

Since isoflavones often serve as precursor for the preparation of a number of other isoflavonoids (isoflavans, isoflavanones, pterocarpans, etc.), the synthesis of isoflavones has received considerable attention over the years.[136,137,138,139]

2.2.1.1 Isoflavones *via* deoxybenzoins

The first protocol towards the synthesis of isoflavones (**165**), reported by Baker *et al.*,[140] was based on a deoxybenzoin (**164**) as key starting material. This procedure requires the addition of a C_1 moiety to affect ring-closure and several reagents have been utilised to achieve this crucial conversion (Scheme 2.34).



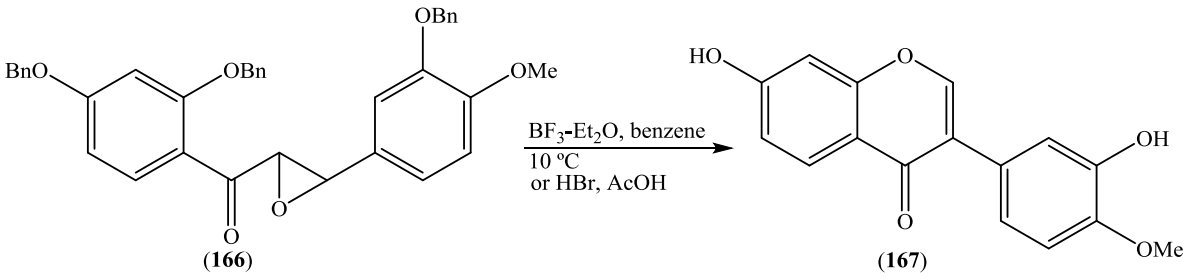
Scheme 2.34 Deoxybenzoin route for the preparation of isoflavones

While ring-closure involving triethylorthoformate in boiling pyridine-piperidine is applicable to a wide range of deoxybenzoin (**164**) substitution patterns, compounds with phloroglucinol-type substitution (2,4,6-trihydroxy) on the A-ring fail to produce the desired isoflavone,[141] whereas the ethyl formate/sodium methodology was found to be compatible with deoxybenzoins containing free hydroxy groups.[141,142] Formylations with zinc cyanide as well as the Vilsmeier reagent ($POCl_3$, DMF) are restricted to ketones with a resorcinol-type substitution (2,4-dialkoxy) pattern.[141,143] Subsequent research utilising methanesulfonyl chloride and boron trifluoride diethyletherate in DMF also proved to afford isoflavones (**165**)

in high yields,[143,144,145] while moderate to high yields were obtained utilising *N*-formylimidazole (prepared from *N*,*N*-carbonyldiimidazole and formic acid) as C_1 unit.[139] Triethylformate in the presence of DMAP has also proven to yield isoflavones containing various oxygenation patterns in high yield (90 – 95%).[146] Although several isoflavone preparations have been successful *via* C_1 insertion into a deoxybenzoin substrate, the latter is not easily accessible in various oxygenation patterns.[142]

2.2.1.2 Isoflavones *via* chalcones

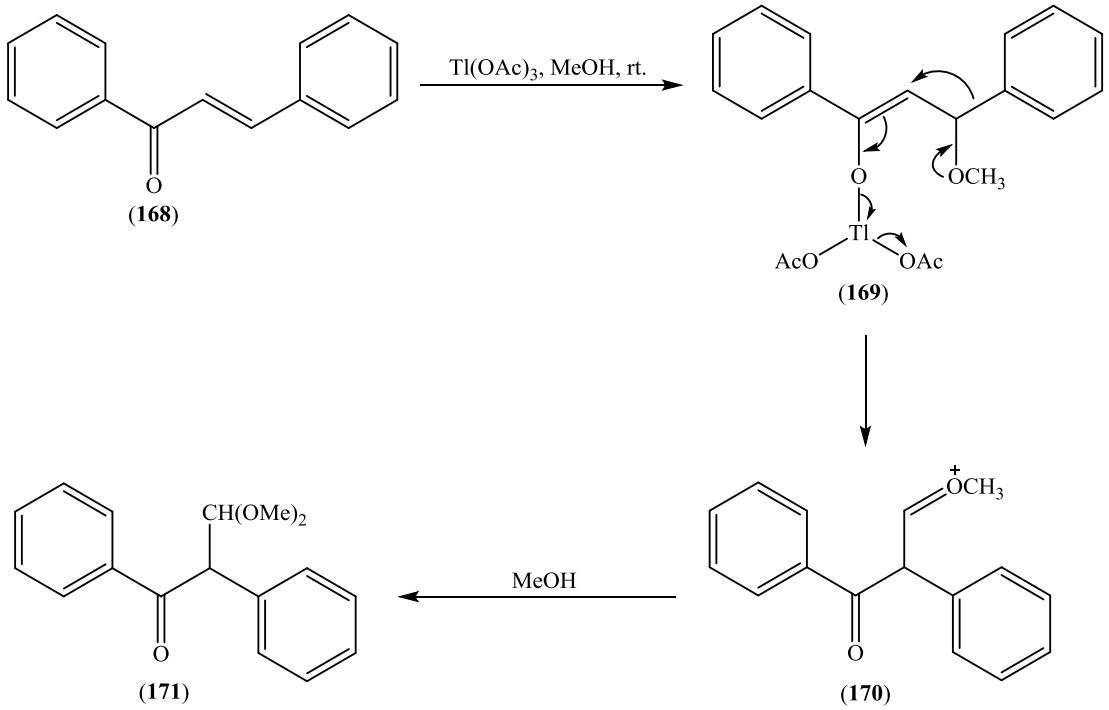
Chalcones, in contrast to deoxybenzoins, are readily available as starting materials for the synthesis of isoflavonoids. Initial investigations centered on rearrangement reactions leading to isoflavones and it was found that 2'-hydroxychalcone epoxides [e.g. (**166**)] could be rearranged to the desired isoflavone (**167**) in the presence of HBr/acetic acid or boron trifluoride etherate, albeit in low yields, with the main products being the dihydroflavonols (**138**) or flavonols (**139**) depending on the substitution pattern of the chalcone epoxide (Scheme 2.35) (*vide supra* par. 2.1.4.2).[135,147,148]



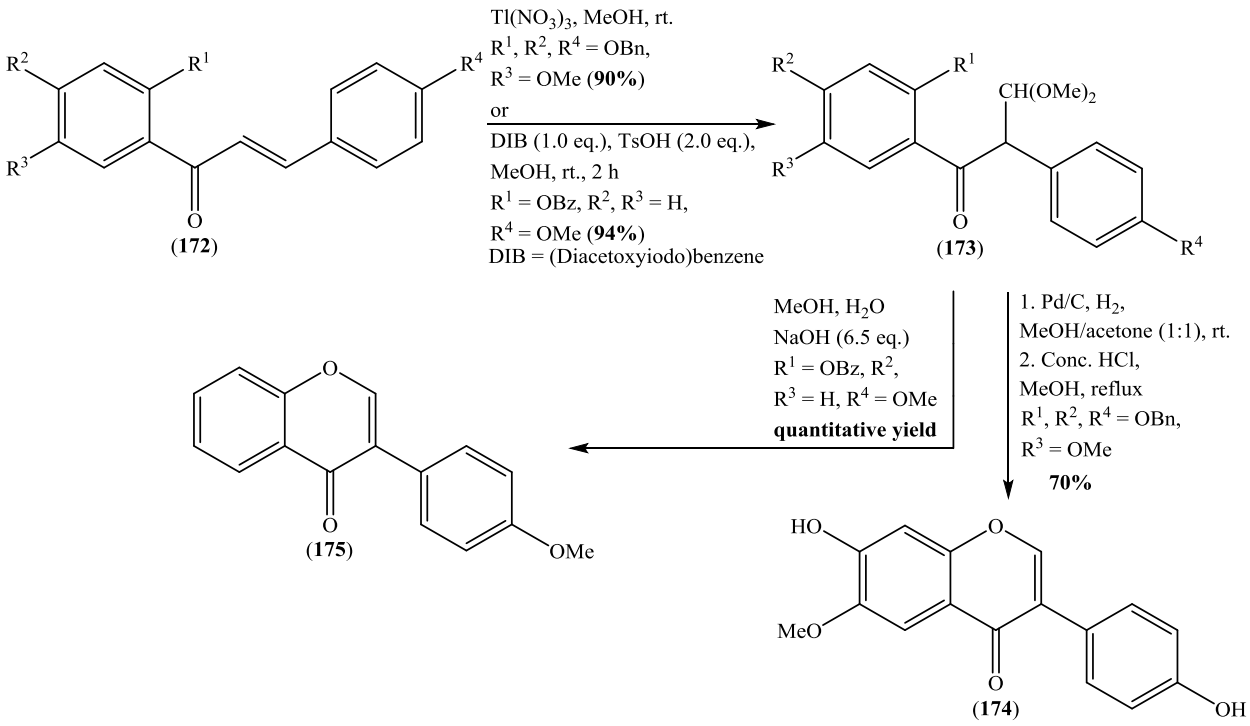
Scheme 2.35 Chalcone epoxide rearrangement to isoflavone

A substantial improvement to the synthesis of isoflavones came from the Ollis group[149] when it was discovered that chalcones (**168**) could be rearranged to isoflavones (**165**) through intermediates (**169**) to (**171**) by thallium(III) acetate in methanol (Scheme 2.36).[150] This procedure was improved by the utilization of thallium(III) nitrate (TTN), which gave access to the isoflavone (**174**) following acid catalysed cyclisation upon deprotection of a 2'-OH group (Scheme 2.37).[151] It was established that the electronic properties of chalcone B-ring *para*-substituents determines the formation of isoflavones or aurones (**135**) (*cf.* Fig. 2.1) and that strong electron donating substituents (e.g. OH, OMe) affords isoflavones exclusively, while weakly electron donating entities (e.g. ethyl) leads to a *ca.* 1:1 ratio of chalcone and aurone and electron withdrawing groups (e.g. Cl, CHO, NO_2) leads to aurone formation.[152] This methodology currently represents the standard method for preparing isoflavones. Koser's reagent ([hydroxy(tosyloxy)iodo]benzene) has also been employed in an oxidative

rearrangement similar to the TTN methodology for the transformation of chalcones (**172**) to the corresponding acetals (**173**) (94% yield), followed by cyclisation in basic medium to afford the isoflavone (**175**) in quantitative yield (Scheme 2.37).[153]



Scheme 2.36 Oxidative rearrangement of chalcones with $Tl(OAc)_3$

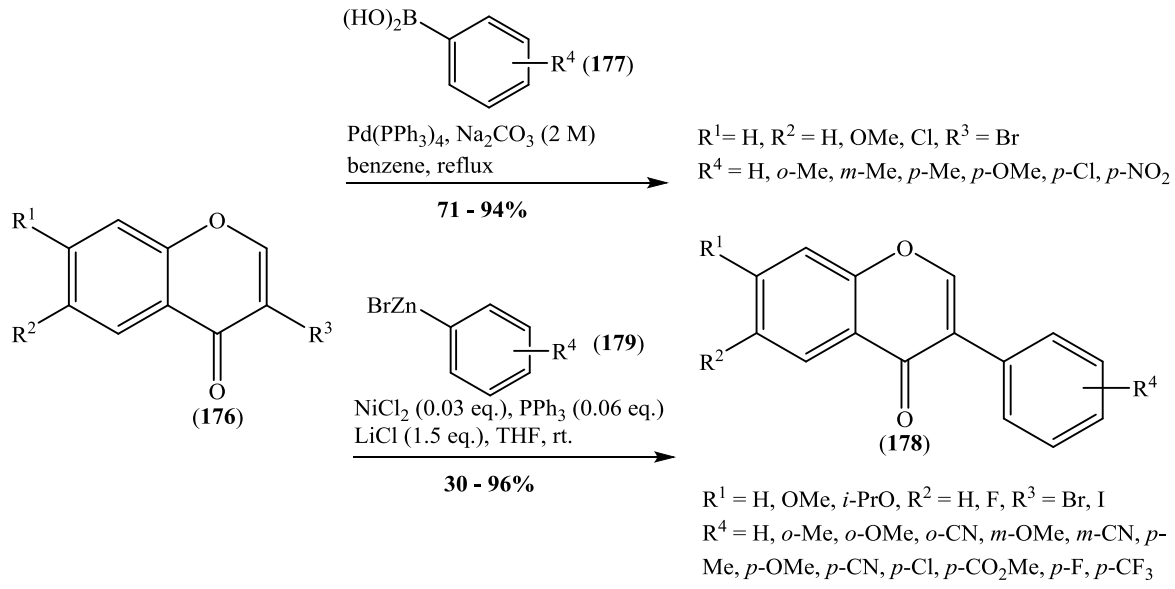


Scheme 2.37 Oxidative rearrangement of chalcones with $Tl(NO_3)_3$ or Koser's reagent

2.2.1.3 Various routes to isoflavone synthesis

Although the TTN induced rearrangement of chalcones remains the method of choice for the preparation of isoflavones, some more recently developed reactions have also found application in the preparation of isoflavones.

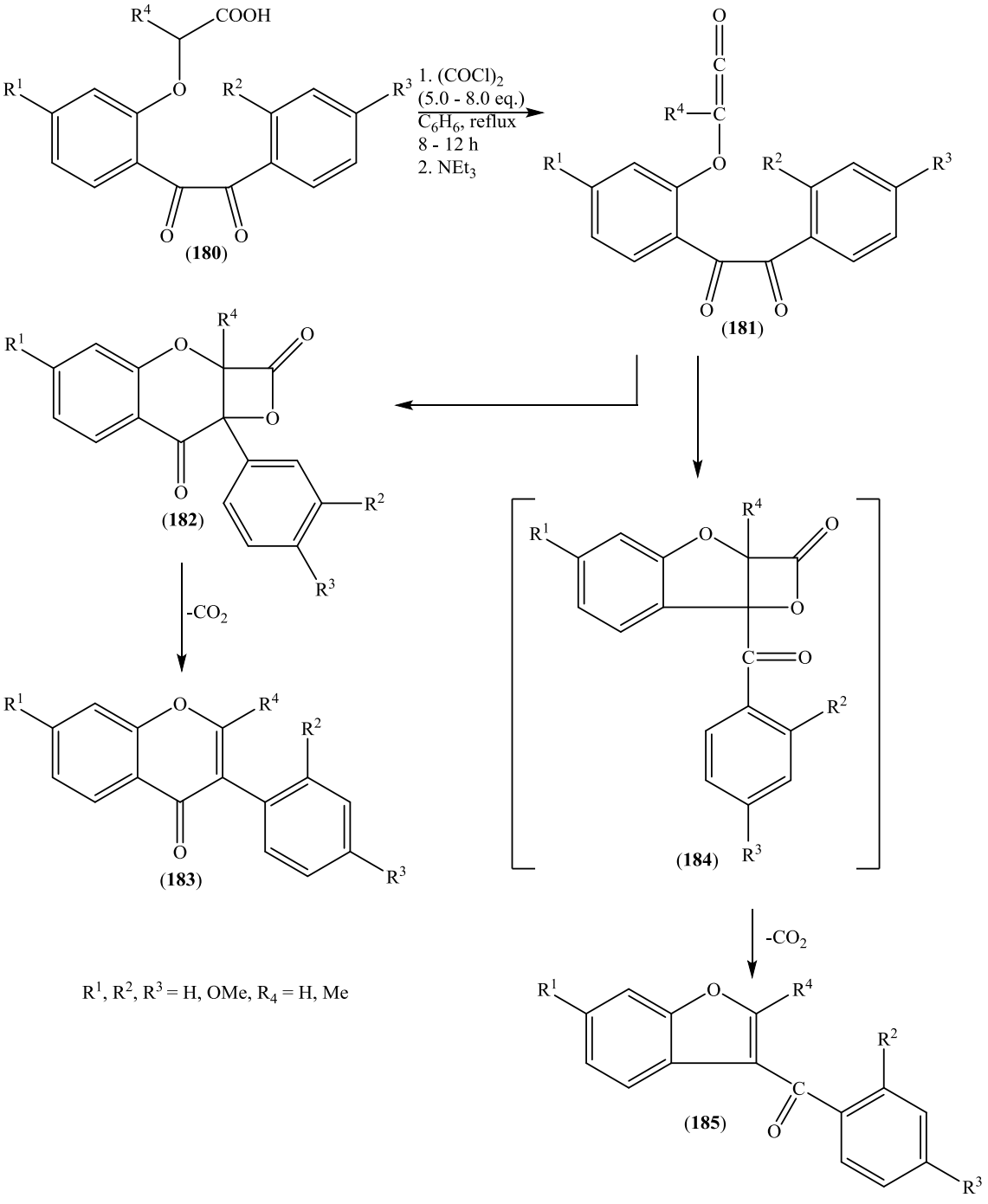
Suzuki cross-coupling between 3-bromochromones (**176**) and arylboronic acids (**177**) produce the desired isoflavones (**178**) in high yield (Scheme 2.38).[138] While 3-bromochromones can be readily prepared from commercially available *o*-hydroxyacetophenones, arylboronic acids are conveniently prepared *via* the reaction of trialkylborates with aryl-Grignard reagents.[154] Methoxy groups on the 3-bromochromone as well as the aryl boronic acid were well tolerated (87 and 94% yield, respectively). In a similar approach, the Zhang group[155] utilised 3-iodo or 3-bromochromones (**176**) and arylzinc bromides (**179**) in a a nickel-catalysed Negishi coupling, which led to moderate to excellent yields (53 – 96% yield) for chromones and arylzinc bromides containing electron deficient and/or electron donating substituents, –CN substituted arylzinc bromides excluded (30 – 41% yield) (Scheme 2.38).



Scheme 2.38 Isoflavone *via* Suzuki and Negishi cross-coupling

Brady and Gu[156] reported on an intramolecular ketene [2+2] cycloaddition reaction yielding isoflavones in moderate yields. This process was achieved by subjecting 2-(carboxyalkoxy)benzils (**180**) to an excess of oxalyl chloride (5.0 – 8.0 eq.) in anhydrous benzene (8 – 12 hours) to form the acid chloride. Dehydrochlorination of the acid chloride by

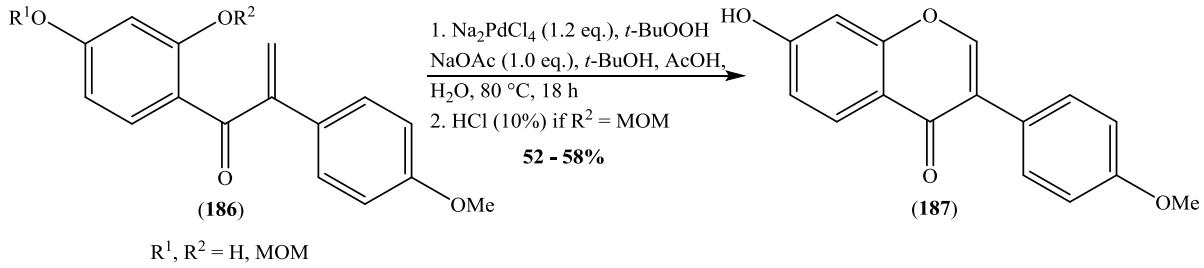
triethylamine to form a ketene (**181**) and subsequent intramolecular [2 + 2] cycloaddition and decarboxylation gave the corresponding isoflavone (**183**). A major drawback of this process however is that isoflavones are not formed exclusively and that 3-aroylbenzofurans (**185**) can be obtained depending on the substitution pattern of the preceding benzil acids (**184**) (Scheme 2.39).



(**180**) (**181**) (**182**) (**183**) (**184**) (**185**)

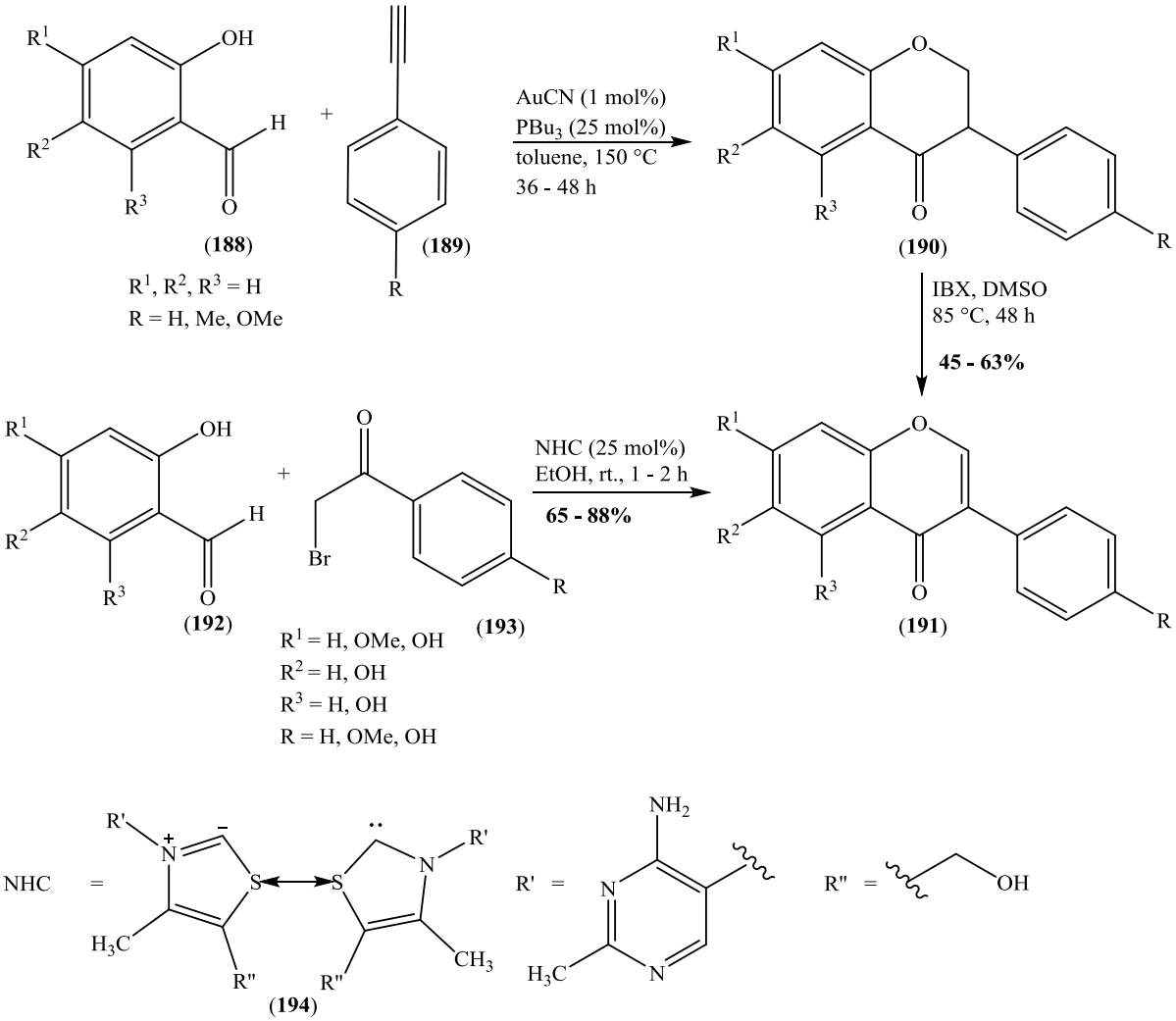
Scheme 2.39 Isoflavone *via* ketene cycloaddition

An alternative route to isoflavone formation involves the Wacker-Cook oxidative Pd-catalysed cyclisation of α-methylenedeoxybenzoins (**186**) to afford the desired products (**187**) in yields of 52 – 58% (Scheme 2.40).[157]



Scheme 2.40 Isoflavone *via* Wacker-Cook oxidative Pd-catalysed cyclisation

Skouta and Li[158,159] achieved isoflavone synthesis in a catalytic process where *para*-substituted alkynebenzenes (**189**) were utilised in a gold(I) catalysed annulation with salicylaldehyde (**188**). Subsequently, these isoflavanones (**190**) were oxidised to the desired isoflavones (**191**) in the presence of IBX (*o*-iodoxybenzoic acid) and DMSO (Scheme 2.41). Alkynebenzenes can easily be prepared *via* Sonogashira coupling from bromobenzenes[160] and it was reported that yields increased as the electron donating properties of the substituent increases, which bodes well for the synthesis of natural oxygenated compounds. Another novel catalytic approach has recently been developed by the Mishra group,[161] who reported on NHC (*N*-heterocyclic carbene) (**194**) facilitated cyclisation of a 2-(2-oxo-2-phenylethoxy)benzaldehyde obtained from the appropriate phenacyl bromide (**193**) and salicylaldehyde (**192**). The isoflavone (**191**) was obtained in high yield (65 – 88%) upon dehydration and methoxy groups as well as hydroxy substituents on either or both rings were well tolerated (Scheme 2.41).



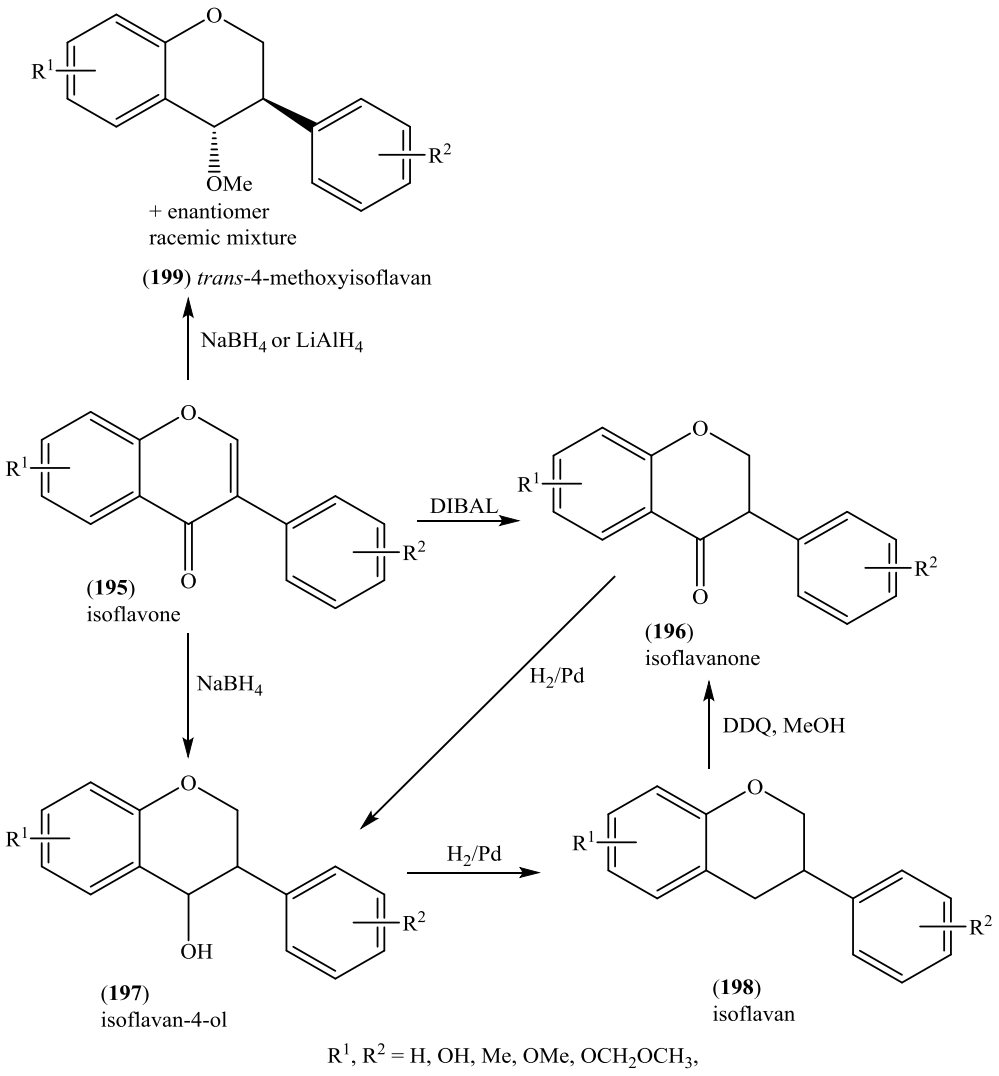
Scheme 2.41 Isoflavone *via* AuCN catalytic annulation or NHC facilitated coupling

2.2.2 Isoflavanones and isoflavans

Since the isoflavanones (**196**) and isoflavans (**198**) structurally resemble isoflavones (**195**), the obvious route toward their synthesis would be reduction of isoflavones. The reaction is complicated by the fact that, if the isoflavanone is desired, over-reduction to the isoflavan-4-ol (**197**) and ultimately isoflavan (**198**) may also occur.[162] In this regard, Farkas *et al.*[163] reported on the hydrogenation of isoflavones with H_2/Pd-C (10%) in acetic acid to produce isoflavanones (**196**), but found the selectivities to be rather low when the substrate does not have substitution in the 5-position. When the solvent was changed to acetone, no reduction of the carbonyl was observed.[164]

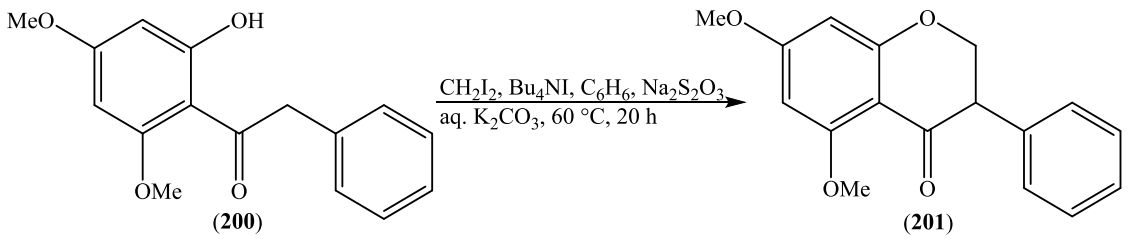
Krishnamurty *et al.*[165] reported on the transfer hydrogenation of isoflavones over Pd/C (10%) with formic acid as hydrogen donor and obtained fair yields of the isoflavanone (40 – 62%).

Isoflavone (**195**) reduction *via* metal hydrides, like $NaBH_4$ and $LiAlH_4$ has led to the formation of the epimeric isoflavan-4-ols (**197**) (Scheme 2.42).[142,166,167] Selectivity towards isoflavanones has been obtained with DIBAL (di-isobutylaluminium hydride) in 60 – 88% yield.[167] Isoflavanones (**196**) can also be prepared *via* DDQ oxidation of isoflavans (**198**) in MeOH (Scheme 2.42). In this process, benzylic oxidation to isoflavones (**195**) proceeds in acceptable yields (61 – 91%) when the 7- and 2'-hydroxy groups are protected with methoxymethyl and methyl groups, respectively, or when a 7-hydroxy substituted isoflavan (**198**) lacks 2'-substitution. However, when 7-hydroxy-2'-methoxyisoflavan was oxidised, a mixture of isoflavanone (**196**) and *trans*-4-methoxyisoflavan (**199**) was obtained (8 and 6% yields, respectively) and the isoflavan (**199**) is presumably formed *via* 1,6 addition of MeOH to an intermediate quinone methide.[168]



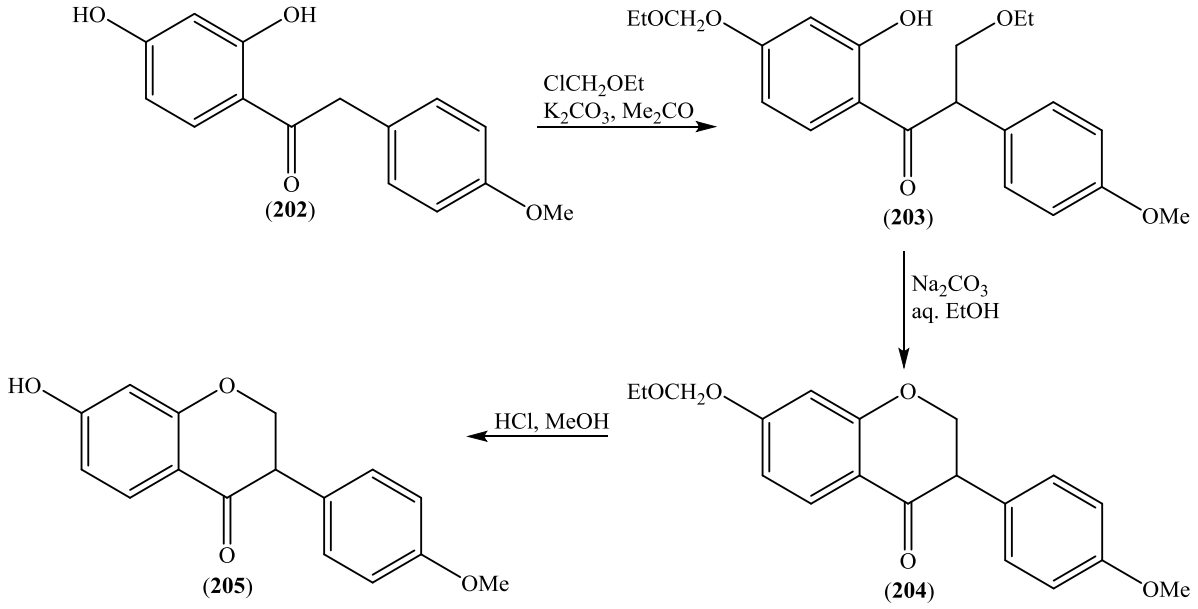
Scheme 2.42 Isoflavanone and isoflavan synthesis

Singh *et al.*[169] revisited the utilization of deoxybenzoin (**200**) as starting material and found that this substrate could be treated with methylene iodide as one-carbon unit for the formation of the heterocyclic C-ring of isoflavanones. Phase transfer conditions were employed using tetra-*n*-butylammonium iodide, aq. K_2CO_3 and sodium thiosulphate in benzene, permitting the preparation of isoflavanones [e.g. (**201**)] in 60 – 70% yield (e.g. Scheme 2.43).[169]



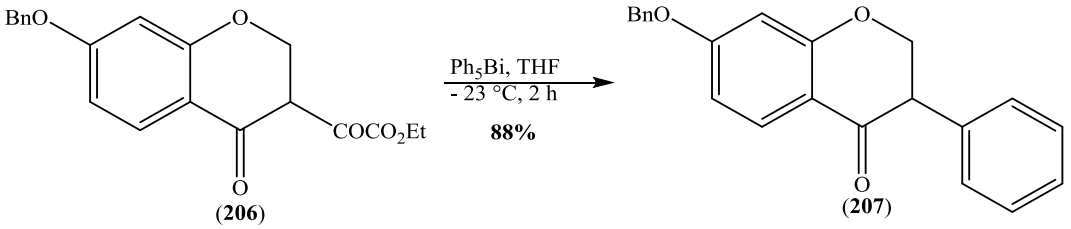
Scheme 2.43 Isoflavanone *via* deoxybenzoin precursor

Other methods involving C_1 moieties like formaldehyde [HCHO, K_2CO_3, $CHCl_3$-H_2O, (n-$Bu)_4N^+HSO_4^-$][170,171] and ethoxymethyl chloride ($ClCH_2OEt$, K_2CO_3, acetone)[170,171] have also been utilised to afford the desired compounds in moderate yields after cyclisation (e.g. Scheme 2.44). This route may be preferred since it also entails *in situ* protection of any free hydroxy group if ethoxymethyl chloride is used, though it suffers from all the difficulties associated with the preparation of deoxybenzoins. Nonetheless, overall yields of 47 – 73% were generally obtained when employing ethoxymethyl chloride as C_1 unit.[172]

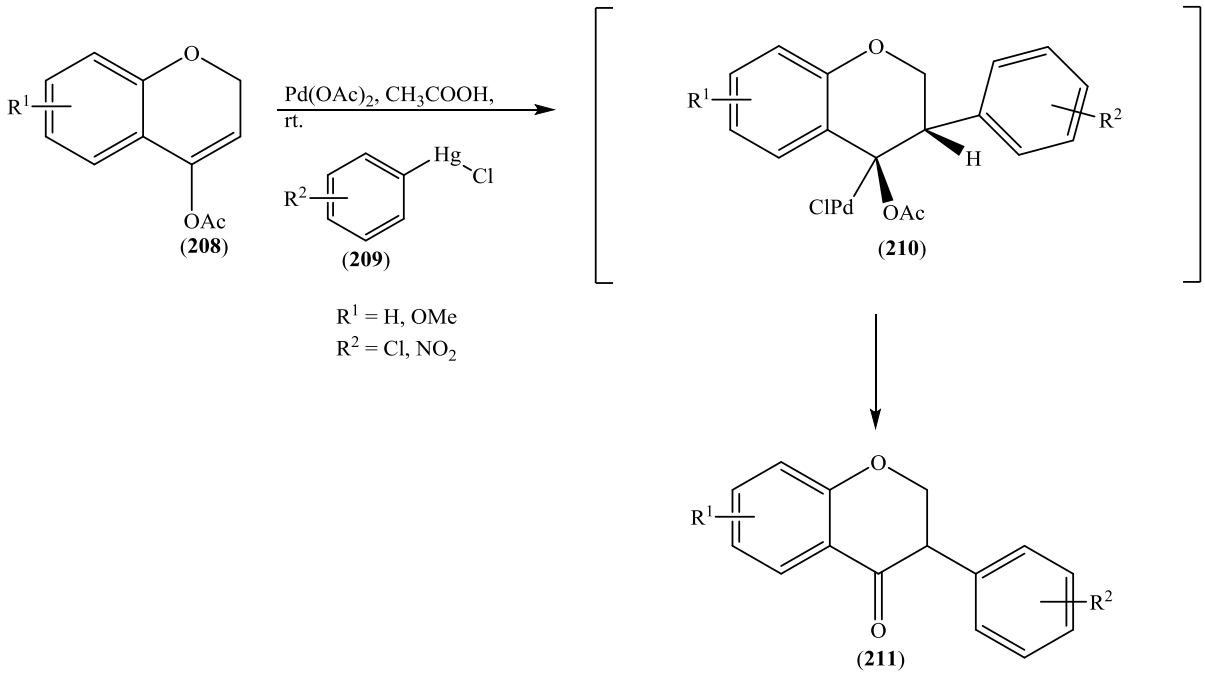


Scheme 2.44 Dihydroformononetin synthesis

Isoflavanone synthesis is also possible through chroman-4-one precursor molecules and derivatives thereof. For example, pentaphenylbismuth has been employed for the arylation of 3-oxalylchroman-4-ones (**206**) or 3-formylchroman-4-ones and is successful for the preparation of isoflavanones (e.g. Scheme 2.45). Isoflavanone formation has also been achieved by reacting an arylmercuric halide (**209**) with the enol ester derivative of chroman-4-one (**208**) in a palladium catalysed Heck reaction (Scheme 2.46). This process is successful with a variety of substitution patterns on both the A and B rings, such as *o*-OMe and *p*-OMe groups on the A-ring in combination with chloro or nitro groups on the B-ring, and led to yields of 60 – 75%. A major drawback of this process, however, is the requirement for a large amount of noxious arylmercury intermediates and expensive $Pd(OAc)_2$ employed in quantitative amounts.[173]

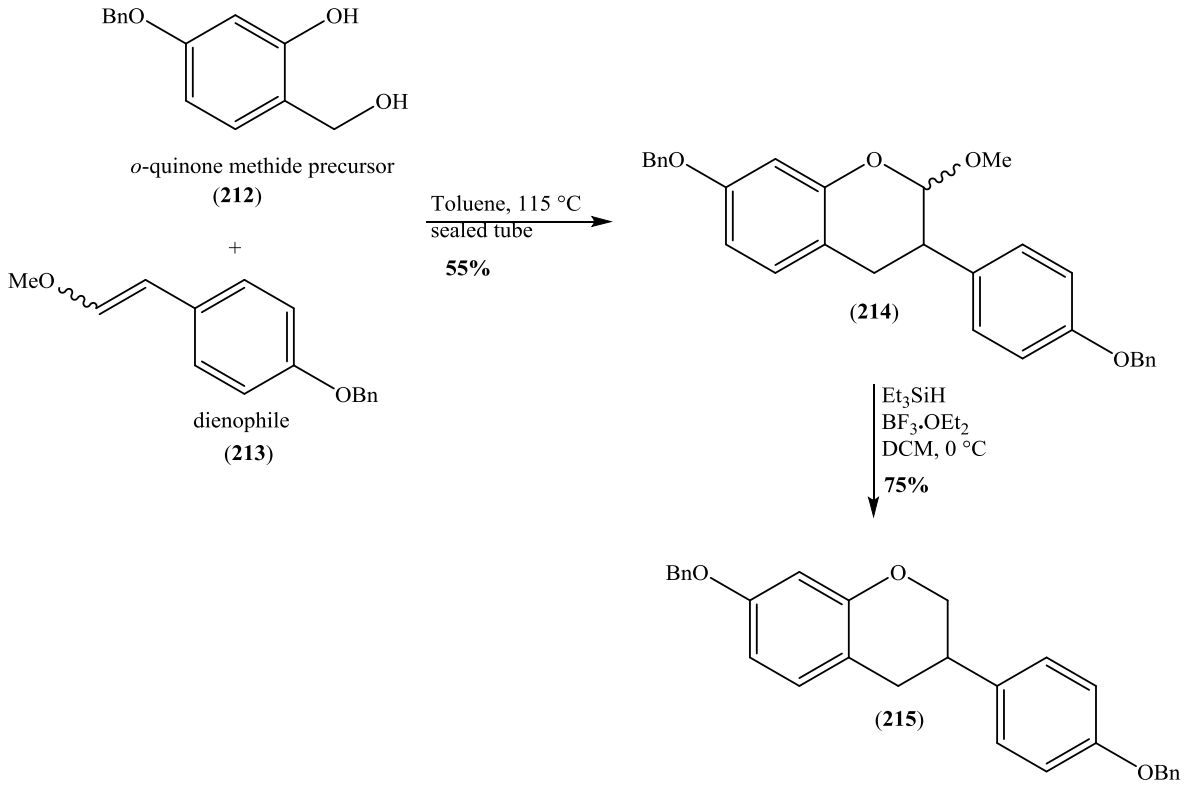


Scheme 2.45 Isoflavanone synthesis *via* pentaphenylbismuth mediated arylation



Scheme 2.46 Isoflavanone synthesis *via* Heck reaction

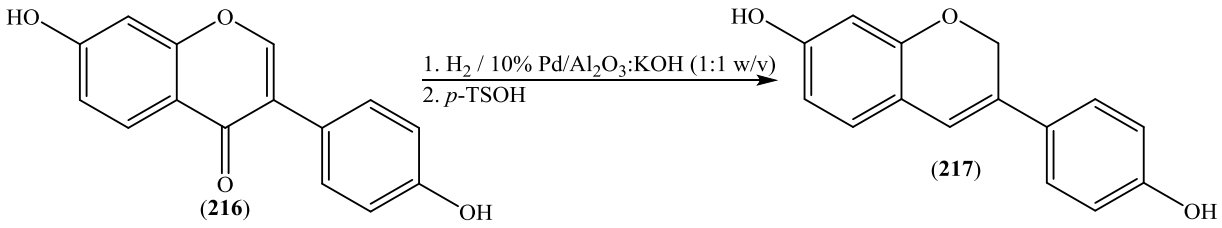
In other recent research published by Gharpure *et al*.,[174] a concise strategy was developed utilising *o*-quinone methide precursors [e.g. (**212**)] in a Diels-Alder reaction with aryl-substituted enol ethers [e.g. (**213**)] followed by a reductive cleavage of the methoxy functionality in (**214**). Although this process can be applied to the synthesis of various oxygenated compounds, the diene (**212**) and dienophile (**213**) raw materials are not readily available and need to be prepared beforehand (Scheme 2.47).



Scheme 2.47 Isoflavan synthesis *via* Diels-Alder reaction

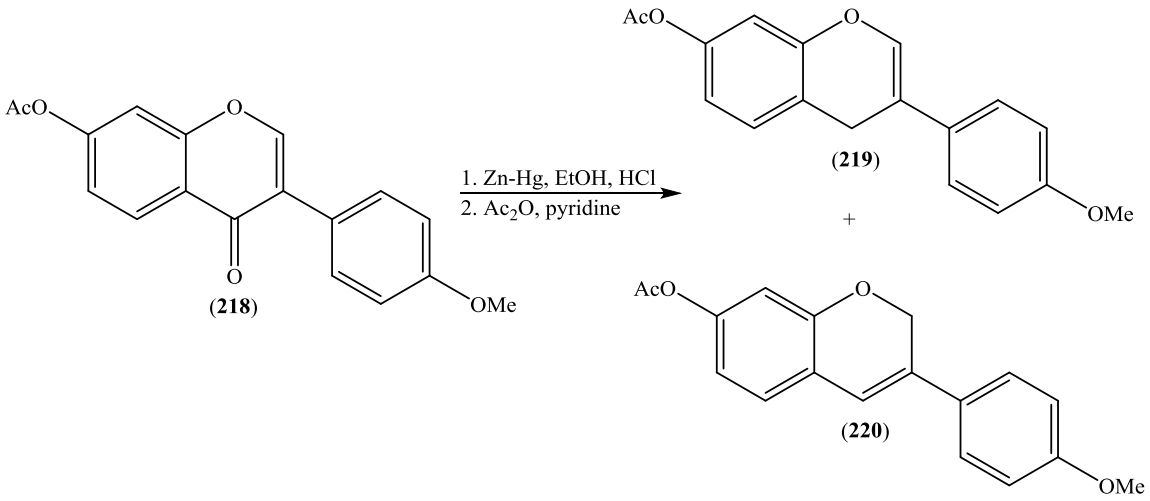
2.2.3 Isoflavenes

Due to the fact that the distribution of isoflav-2-enes and isoflav-3-enes are rather limited in nature, these compounds have not received a lot of attention w.r.t. their synthesis. Isoflav-3-enes can be formed by the dehydration of isoflavan-4-ols derived from the reduction of isoflavones and isoflavanones.[175,176] Heaton and Jeffreys[176] recently patented a one-pot synthesis of isoflav-3-enes by reduction of the corresponding isoflavones by utilising a palladium on alumina catalyst. Hydrogenation of isoflavones *via* this procedure did not require protection of hydroxy substituents and dehydroequol (**217**) was prepared from daidzein (**216**) in excellent yield (Scheme 2.48).



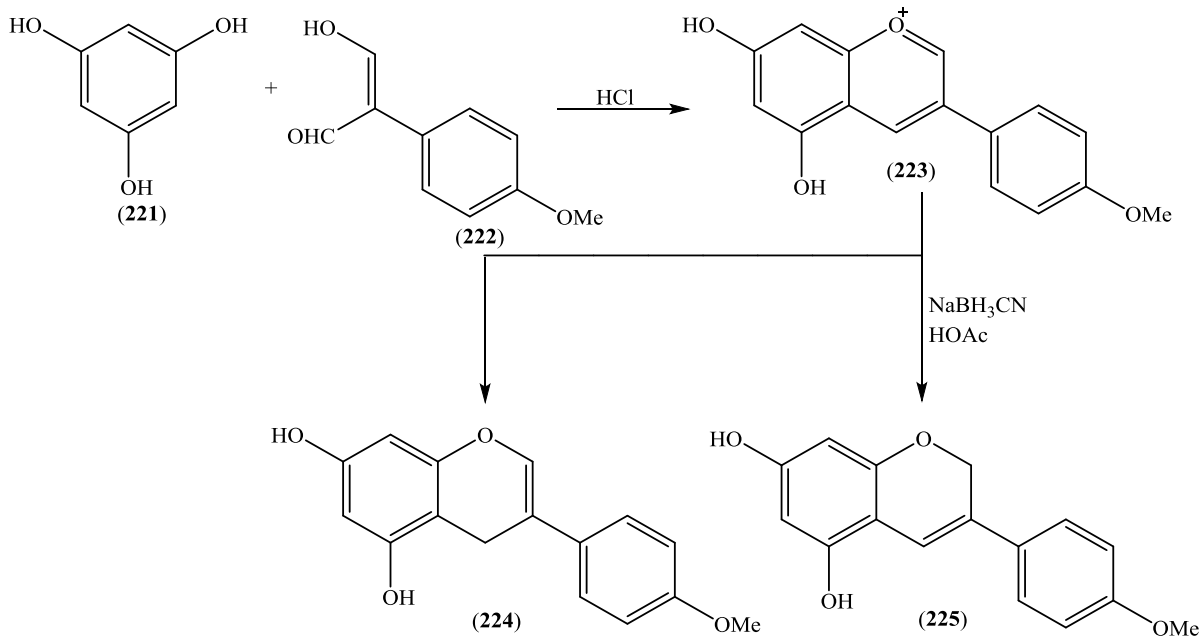
Scheme 2.48 Palladium catalysed reduction of isoflavones.

While isoflav-3-enes [e.g. (**217**)] are available by these simple procedures, their 2-ene analogues are more evasive and not so easy to prepare. Dudley *et al.*[177] utilised the Clemmensen reduction to transform isoflavones (**218**) into a mixture of isoflav-2-enes [e.g. (**219**)] and isoflav-3-enes [e.g. (**220**)] in (15 – 35% yield), with the 2-isomer being present in *ca*. 20 – 30% in the mixture (Scheme 2.49).



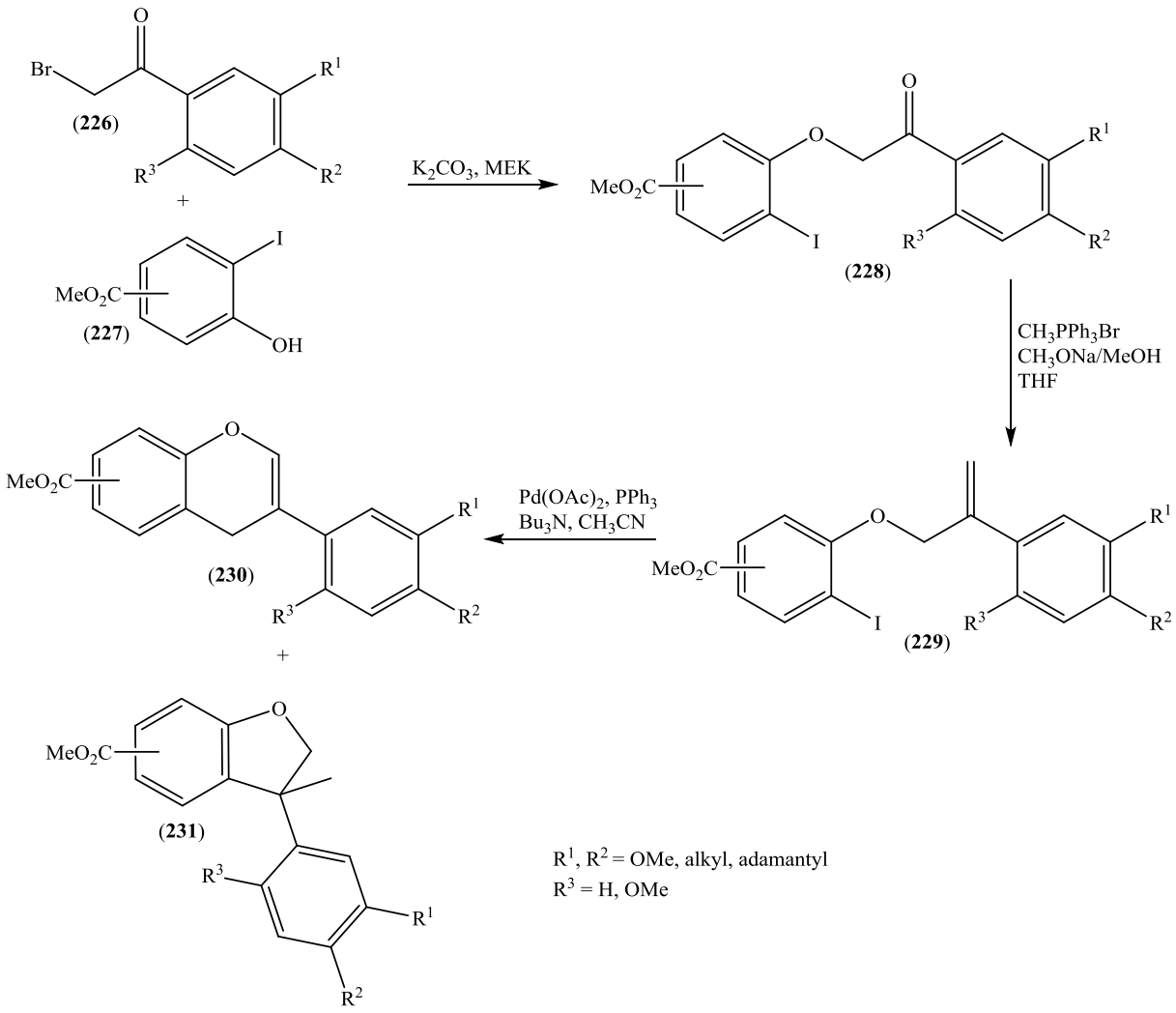
Scheme 2.49 Isoflavenes *via* Clemmensen reduction of isoflavones

In a different, non-isoflavone approach, Liepa[178] reported the formation of isoflavenes during the reduction of isoflavylium salts [e.g. (**223**)] (Scheme 2.50). This method does, however, suffer from some serious drawbacks since the outcome of the reaction depends on the nature of the reducing agent as well as the substitution pattern on the isoflavylium salt. For example, when sodium cyanoborohydride ($NaBH_3CN$) was utilised in the reduction of 5,7,4'-trihydroxyisoflavylium chloride, the corresponding isoflav-3-ene was isolated as major product, whereas the reduction of the 5,7-dihydroxy-4'-methoxyisoflavylium salt (**223**) produced a 1:1 mixture of the isoflav-2-ene (**224**) and isoflav-3-ene (**225**). This method is further hampered by difficulties surrounding the synthesis of starting materials and is not considered to be very valuable.



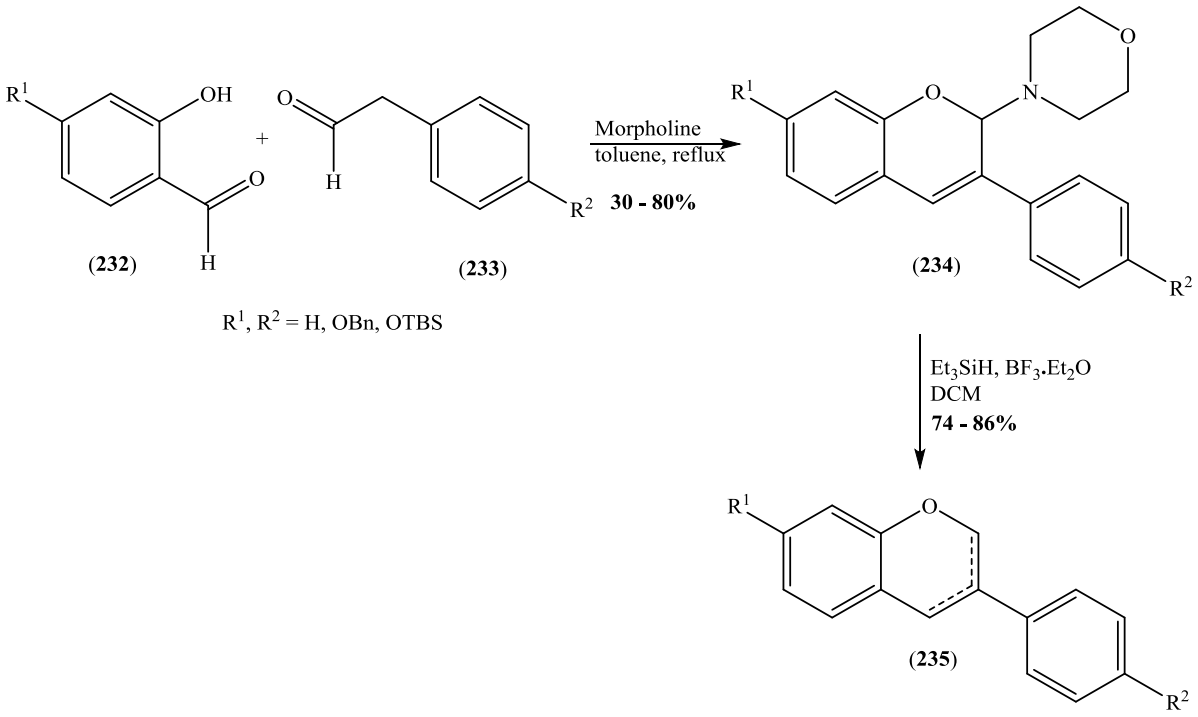
Scheme 2.50 Isoflavene *via* isoflavylium salt

A Heck reaction based method for the preparation of isoflav-2-enes (**230**) was reported by the Diaz group.[179] In this procedure, 2-bromoacetophenones (**226**) and iodophenol analogues (**227**) were reacted to the give the α-phenoxy ketone (**228**), which could then be transformed into the vinyl ether analogue (**229**) by Wittig methodology and cyclised under Heck conditions (Scheme 2.51). This process, however, led to moderate to low yields of the isoflavene and produced mainly the benzofuran side-product (**231**).



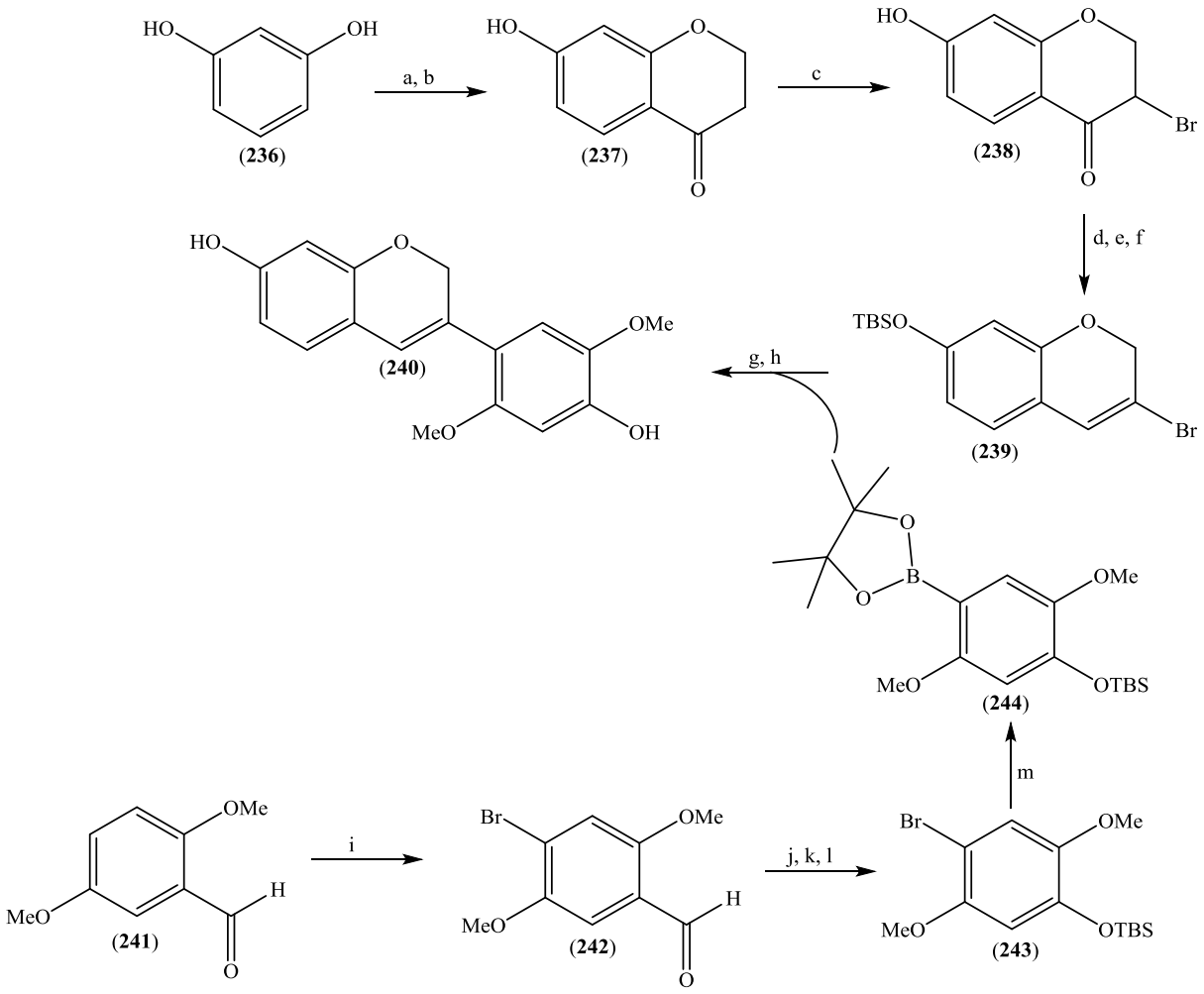
Scheme 2.51 Heck reaction based isoflav-2-ene preparation

Recently, Tilley *et al.*[180] reported on a process for the preparation of isoflavenes wherein phenylacetaldehyde (**233**) and morpholine reacts and leads to the formation of *N*-styrylmorpholine which is then allowed to react with salicylaldehyde (**232**) in a second step to produce 2-morpholinoisoflav-3-ene (**234**) in one pot. Subsequent reduction in the presence of triethylsilane and BF_3**.**Et_2O led to a mixture of isoflav-2-ene and isoflav-3-ene (**235**) in a 1:4 ratio in high yield (74 – 86%) (Scheme 2.52).



Scheme 2.52 Isoflavenes *via* morpholine intermediate

The Koo group[181] also discovered a novel way for the preparation of isoflavene during their investigation towards the total synthesis of eryvarin H (**240**). Vinyl bromide (**239**) and arylboronic ester (**244**) were synthesised separately as shown in Scheme 2.53 and then coupled in a Suzuki-Miyaura reaction. Deprotection in HF and pyridine gave the target compound in 15% overall yield. While this methodology represents a novel process to isoflavene synthesis, it is a lengthy procedure, requiring protection/deprotection, with low overall yield.



a: 3-chloropropionic acid, TfOH, 80 °C, 2h. b: 2N NaOH, 0 °C – rt., 3 h, **62%**. c: $CuBr_2$, EtOAc-$CHCl_3$-MeOH, 70 °C, 4 h, **67%**. d: TBSCl, imidazole, DCM, rt. 1 h. e: $NaBH_4$, EtOH, rt. 1 h. f: TsOH-H_2O, toluene, 80 °C, 120 W μW, 20 min., **61%**. g: $Pd(PPh_3)_4$, Na_2CO_3, toluene-EtOH-H_2O, 80 °C, 2 h. h: HF/pyridine, THF, rt. 3 h, **73%**. i: Br_2, acetic acid, rt. 12 h, **62%**. j: *m*-CPBA, DCM, rt. 3 h. k: NaOH, MeOH, rt. 3 h. l: TBSCl, imidazole, DCM, rt, 3 h, **95%**. m: Pinacolborane, $Pd(OAc)_2$, DPEphos, triethylamine, 1,4-dioxane, 100 °C, 12 h, **63%**.

DPEphos = Bis[(2-diphenylphosphino)phenyl] ether

Scheme 2.53 Total synthesis of eryvarin H

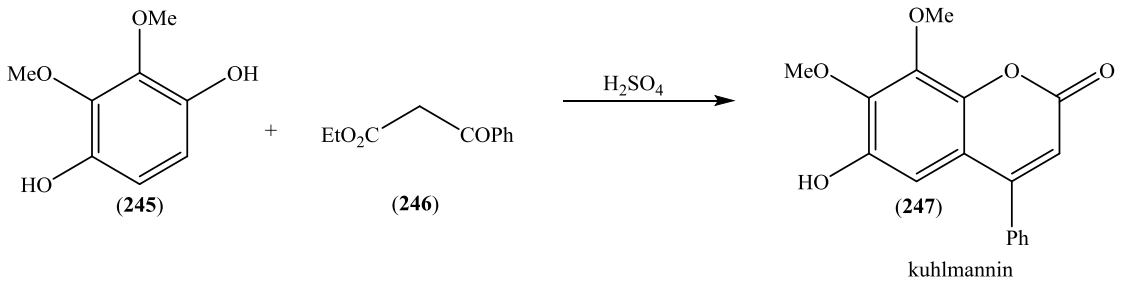
2.3 Neoflavonoids

The neoflavonoids are a class of compounds with a 1,1-diarylpropane skeleton and includes cyclic (e.g. neoflavenes, 4-arylcoumarins) as well as acyclic (e.g. dalbergiones, 3,3-diarylpropenes) compounds.

2.3.1 4-Arylcoumarins

2.3.1.1 Methods based on classical reactions

Since 4-phenylcoumarins were the first group of neoflavonoids to be isolated and characterized during the mid 1950's, these compounds were also the first to be synthesised. One of the first, and still widely used methods for the preparation of 4-phenylcoumarins [e.g. kuhlmannin (**247**)], entails the Von Pechmann condensation of β-ketoesters [e.g. (**246**)] and suitably substituted phenols [e.g. (**245**)] in the presence of protic or Lewis acids (Scheme 2.54).[182,183, 184,185] Even though the Von Pechmann condensation provides a route to obtain 4-arylcoumarins, the reaction is applicable only to highly activated phenols, especially with an electron donating group in the *meta* position, while the availability of the appropriately substituted β-ketoesters are questionable.[185]

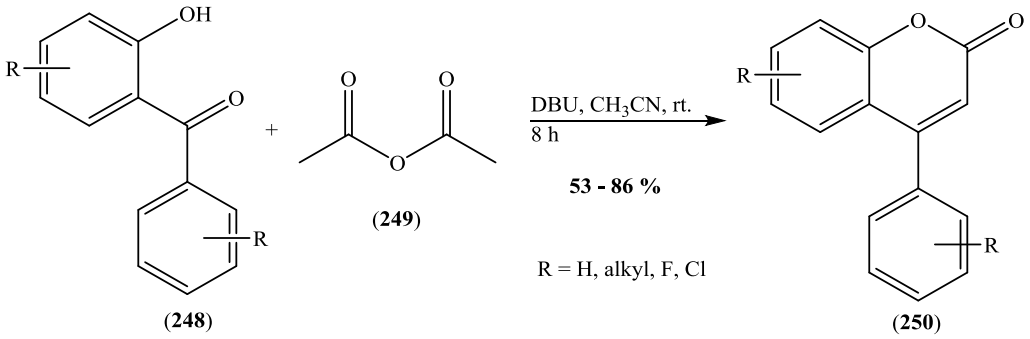


Scheme 2.54 Von Pechmann condensation

Potdar and co-workers[186] improved on this condensation in utilising [bmim]BF_4 or [bmim]PF_6 ionic liquids with catalytic amounts of $POCl_3$ and obtained high yields (90 – 95%) of 4-arylcoumarin products.

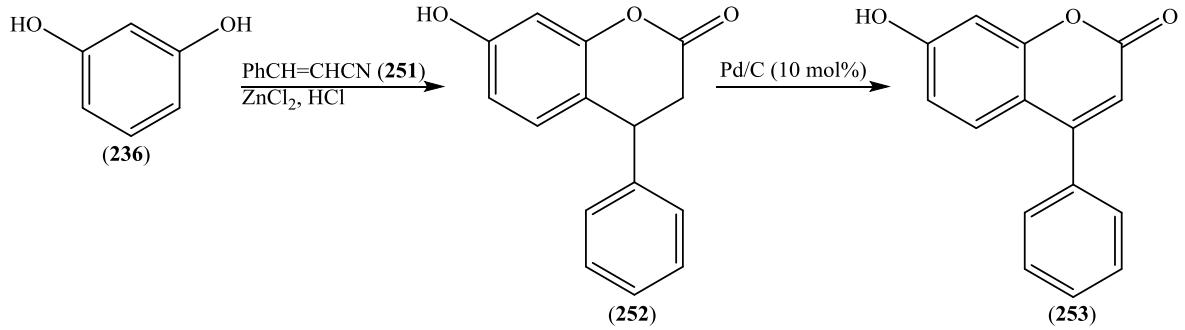
4-Arylcoumarins have also been prepared by a Perkin cyclisation of substituted benzophenones with acetic anhydride in the presence of sodium or potassium acetate.[182] The Hwang group[185] recently reported on a facile new process for the synthesis of highly functionalized 4-arylcoumarins (**250**) *via* an improved Perkin-type reaction of 2-hydroxybenzophenones (**248**) and acyl halides or acyl anhydrides (**249**) in the presence of

base (Scheme 2.55). In this process, the choice of base is vital to the outcome in yield of the desired compound and it was found that organic bases such as amidines were most effective. DBU in acetonitrile led to yields of up to 86%.



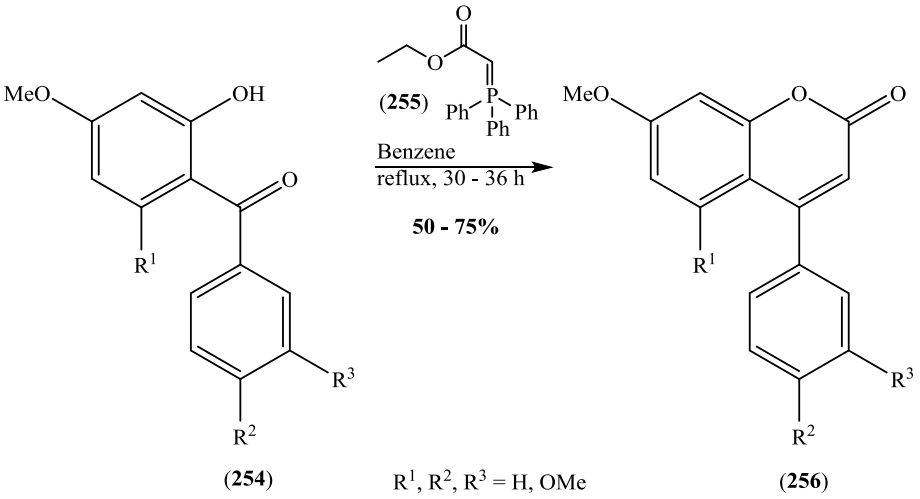
Scheme 2.55 4-Arylcoumarins *via* improved Perkin reaction

Houben-Hoesch type reactions between phenols [e.g. (**236**)] and 3-phenylacrylonitriles [e.g. (**251**)] yields 3,4-dihydrocoumarin (**252**),[187] and dehydrogenation in the presence of Pd/C gave the 4-phenylcoumarins (**253**) in 60 – 65% overall yields.[188]



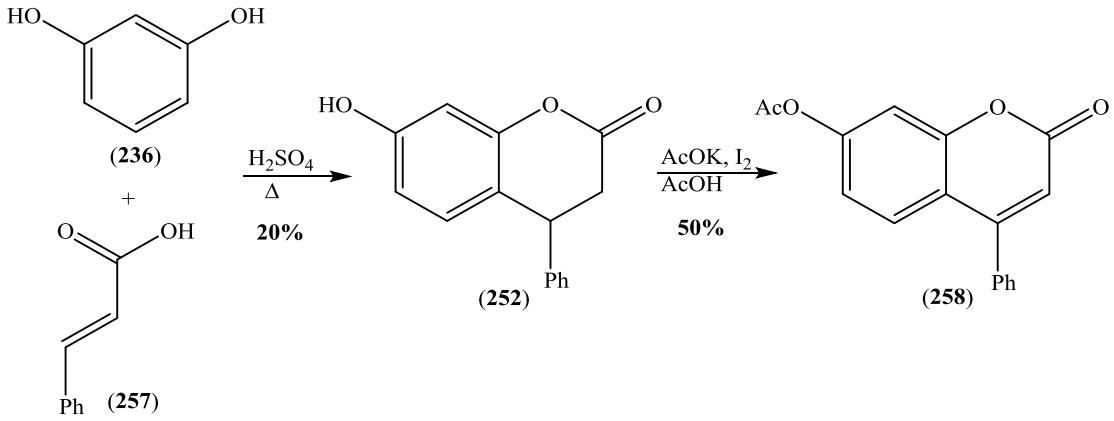
Scheme 2.56 Houben-Hoesch reaction toward 4-arylcoumarin

4-Arylcoumarin synthesis based on the Wittig reaction entails 2-hydroxybenzophenones (**254**) reacting with (ethoxycarbonylmethylene)triphenylphoshorane (**255**) in anhydrous benzene.[189] While moderate to high yields (Scheme 2.57) were obtained, lengthy reaction times are a requirement for full conversion and additional synthesis steps may be required when utilising highly oxygenated 2-hydroxybenzophenones.



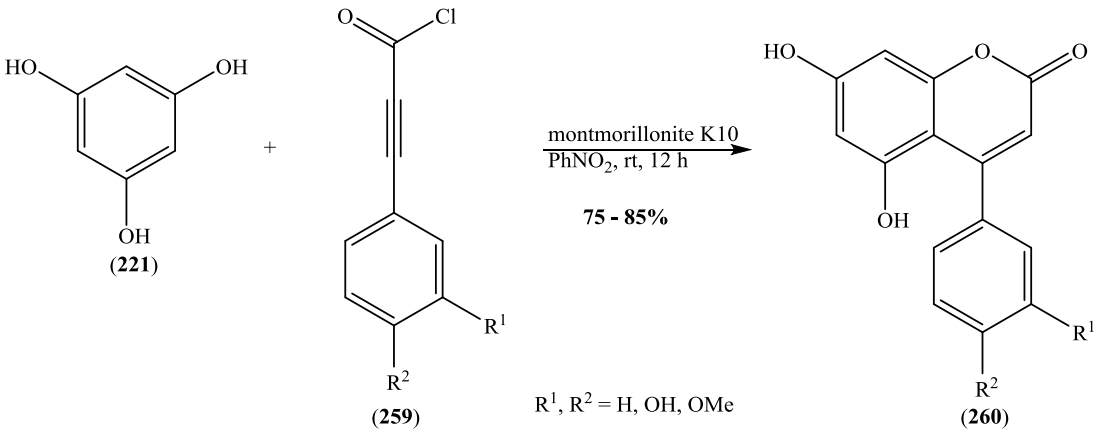
Scheme 2.57 Wittig reaction directed toward 4-phenylcoumarin synthesis

Another approach entails the Ponndorf reaction of cinnamic acids with phenols in the presence of sulfuric acid at high temperature to form 3,4-dihydrocoumarins.[190] For example, the reaction of resorcinol (**236**) and cinnamic acid (**257**), in the presence of concentrated sulfuric acid at 150 – 160 °C, leads to the formation of 3,4-dihydro-7-hydroxy-4-phenylcoumarin (**252**) in low yield. Subsequent protection and dehydrogenation led to the target compound (**258**) in 50% yield (Scheme 2.58).[191,192]



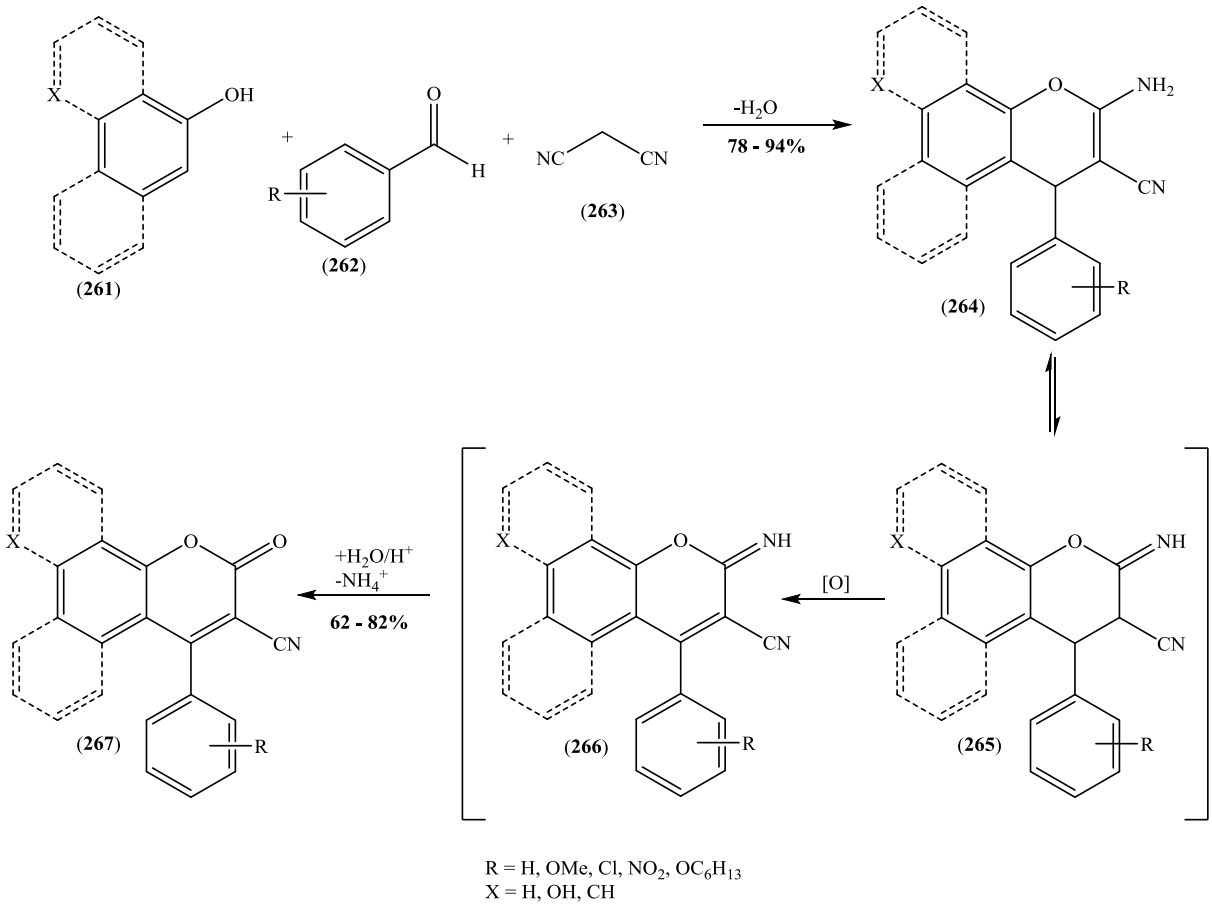
Scheme 2.58 Ponndorf reaction to 7-acetoxy-4-phenylcoumarin

4-Phenylcoumarin preparation can also be achieved by the arylation of propargylic acid derivatives.[190] The Lee group[193] reported on the preparation of various 5,7-dihydroxy-4-phenylcoumarins (**260**) in up to 85% yield by employing phloroglucinol (**221**) and arylpropargylic acids (**259**) in the presence of montmorillonite K10 (Scheme 2.59). The preparation of substituted raw materials, in this case arylpropargylic acids, once again involves a tedious process.



Scheme 2.59 Arylation of phloroglucinol with propargylic acids

Bardasov and co-workers[194] recently also demonstrated that 4-arylcoumarins could be prepared from 2-amino-4-aryl-4*H*-chromene-3-carbonitriles (**264**) *via* oxidation and hydrolysis in the presence of $I_2O_5/CH_3COOH/H_2O$ and although acceptable yields for the desired products (**267**) were obtained (62 – 82%) (Scheme 2.60), this methodology is of limited practical value since the raw material is not readily available and needs to be synthesised in various steps beforehand.

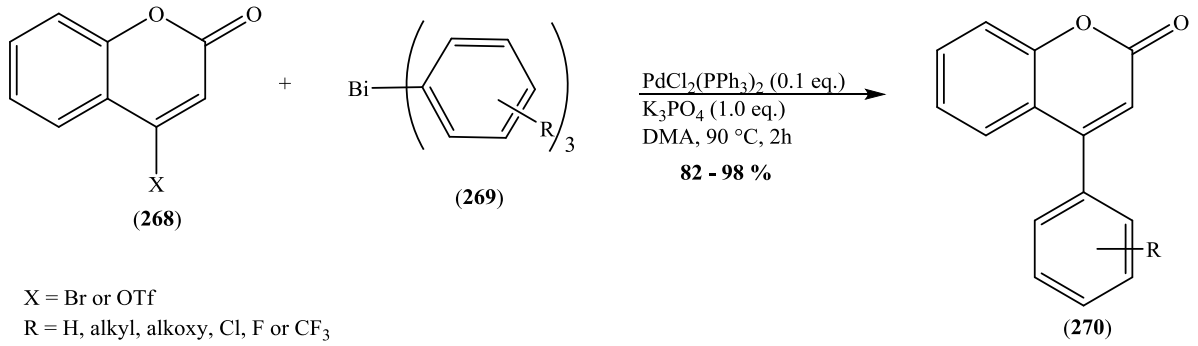


Scheme 2.60 Oxidation and hydrolysis of 2-amino-4-aryl-4*H*-chromene-3-carbonitriles

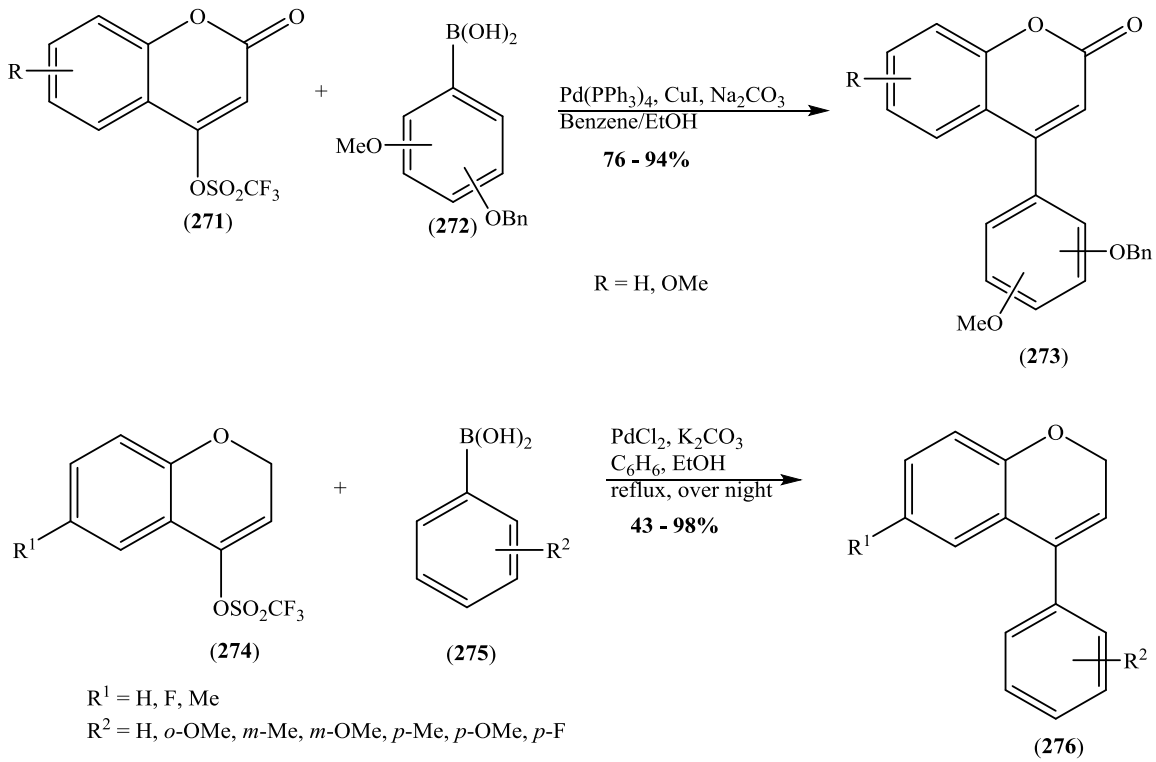
2.3.1.2 Metal catalysed preparations of 4-arylcoumarins

Many recent endeavours involving catalytic processes have led to improved processes in terms of yield and availability of starting materials compared to the classical methods described previously. For example, the Rao group[195] developed an efficient palladium-catalysed cross coupling between triarylbismuth compounds (**269**) and 4-bromo- or 4-(trifluoromethanesulfonyloxy)coumarins (**268**) in dimethyl acetamide (Scheme 2.61), while Donnelly and co-workers[196] utilised the Suzuki coupling reaction between 4-trifluoromethanesulfonyloxycoumarins (**271**) and arylboronic acids (**272**) to achieve neoflavone synthesis. This reaction was also catalysed by palladium, but CuI was employed as co-catalyst (Scheme 2.62).[190] In a similar process, 4-trifluoromethylsulfonyloxy-2*H*-chromenes (**274**) were utililsed in a $PdCl_2$ catalysed coupling process with arylboronic acids (**275**) (Scheme 2.62). Yields remained high in the presence of electron donating or withdrawing moieties whereas an *o*-OMe on the arylboronic acid resulted in the formation of the product in low yield, presumably due to steric hindrance or electronic deactivation of the

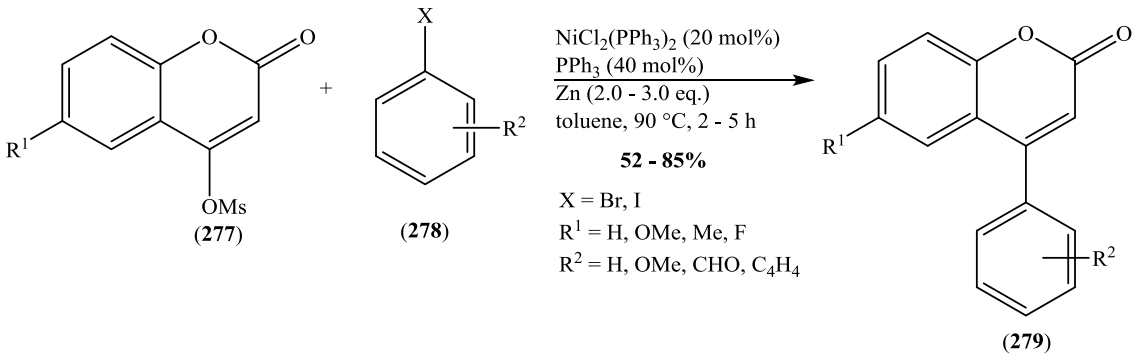
reactive centre.[197] Lei *et al.*[198] reported on an efficient $NiCl_2(PPh_3)_2/PPh_3$/Zn/toluene system for the Ullmann coupling of 4-mesylcoumarins (**277**) with aryl halides (**278**) and obtained moderate-high (52 – 85%) yields for the desired 4-arylcoumarins (**279**) (Scheme 2.63).



Scheme 2.61 Pd-catalysed 4-arylcoumarin synthesis with triarylbismuth

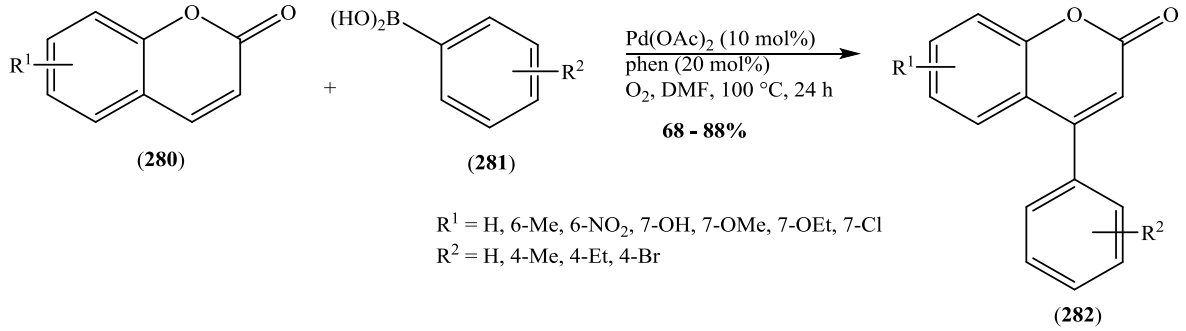


Scheme 2.62 Neoflavone synthesis *via* modified Suzuki coupling



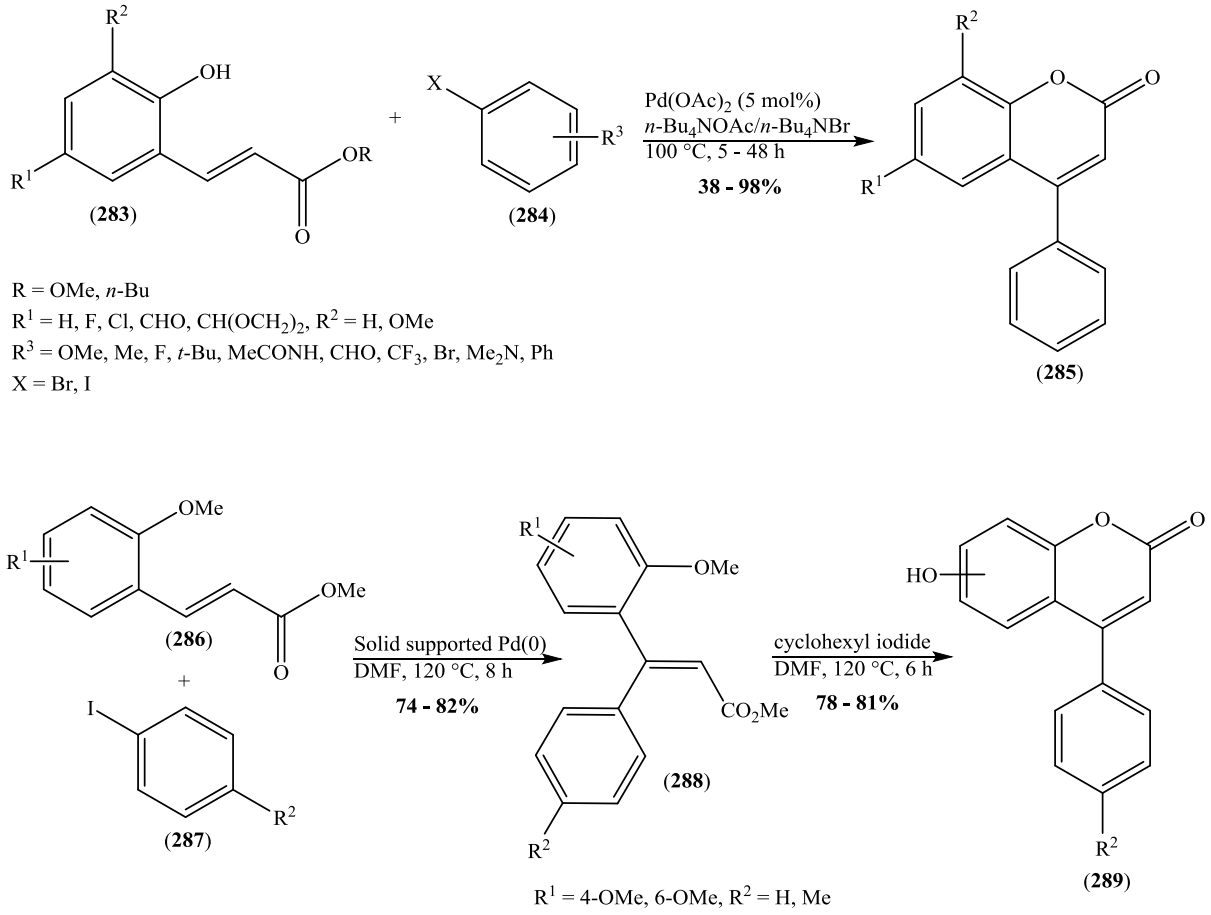
Scheme 2.63 $NiCl_2(PPh_3)_2$ catalysed neoflavone synthesis

A few years later, the Koobi group[115] investigated the preparation of neoflavones that would be of biological importance and reported on the direct arylation of coumarins in a palladium catalysed oxidative Heck reaction. This protocol utilises organoboron reagents (**281**) and allows for the synthesis of neoflavones (**282**) containing various electron withdrawing and electron donating substituents in good yields (Scheme 2.64).

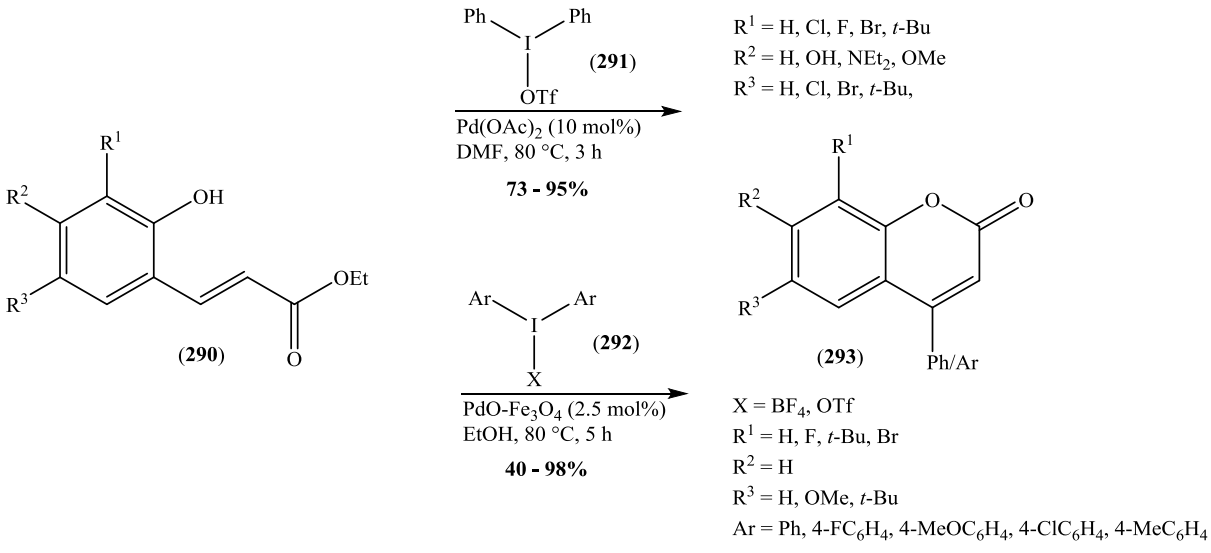


Scheme 2.64 Neoflavone synthesis *via* oxidative Heck reaction

A few palladium catalysed processes involving *o*-hydroxy or *o*-methoxycinnamates (**283**) with aryl halides (**284**) have also been investigated during the past decade utilising, for e.g. $Pd(OAc)_2$ in molten *n*-Bu_4NOAc/*n*-Bu_4NBr[199] or solid supported Pd(0) in Heck processes[200] (Scheme 2.65). Yang and co-workers, [201] however, developed a novel and interesting process entailing an arylation-cyclisation of *o*-hydroxycinnamates (**290**) with diaryliodonium(III) salts (**291**) in a $Pd(OAc)_2$ catalysed reaction while Pérez and co-workers[202] extended this methodology with the utilisation of recyclable palladium(II) oxide (2.5 mol%) impregnated on magnetite (Fe_3O_4) in an effort to make the transformation environmentally benign (Scheme 2.66).



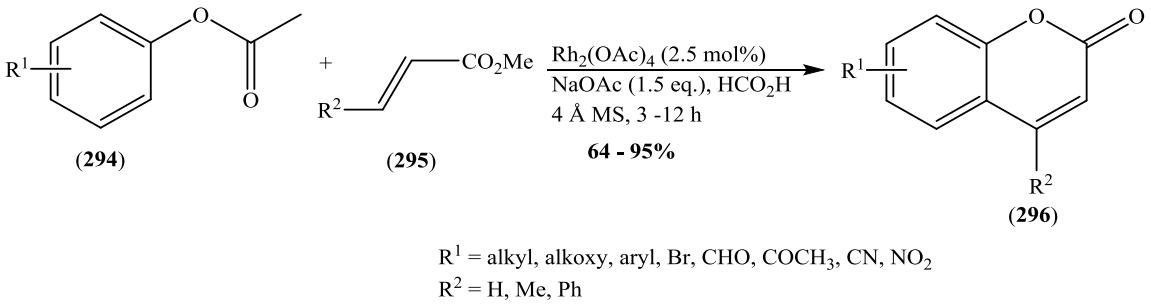
Scheme 2.65 Neoflavone synthesis *via* Pd-catalysed processes utilising *o*-hydroxy or *o*-methoxycinnamates



Scheme 2.66 Neoflavone synthesis *via* diaryliodonium salts

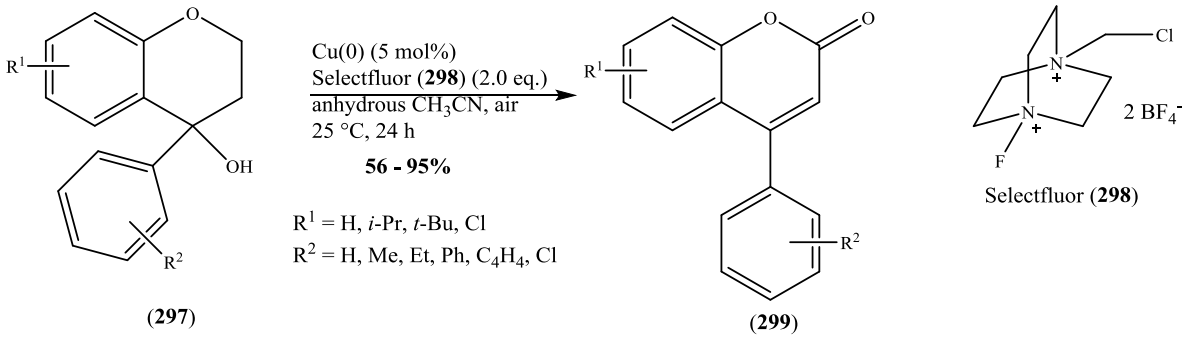
Gadakh *et al.*[203] developed an efficient strategy for the synthesis of coumarins in a rhodium catalysed process. It is envisaged that formic acid reduces $Rh_2(OAc)_4$ to a Rh(I) species.

Ortho-metallation of the phenolic acetate (**294**) to the Rh(I)-species, followed by acrylate (**295**) coordination, insertion and finally β-hydride elimination are believed to give access to the corresponding cinnamate. Deacetylation of the latter under the acidic reaction conditions and subsequent cyclisation finally produce the coumarin (**296**) in high yield (64 – 95%) (Scheme 2.67). This process proves to be successful for both electron rich and electron deficient phenolic acetates and the addition of NaOAc leads to increased yields. Overall, excellent regioselectivity has been observed.



Scheme 2.67 Rhodium catalysed neoflavone preparation

Another recent development published by Ren *et al.*[204] demonstrated the successful dehydration-oxidation of 4-hydroxyneoflavans (**297**) in the presence of Cu(0) and selectfluor (**298**). Although their methodology led to the desired 4-arylcoumarins (**299**) in acceptable yields (56 – 95%), it relies on the availability of the neoflavan skeleton (Scheme 2.68).

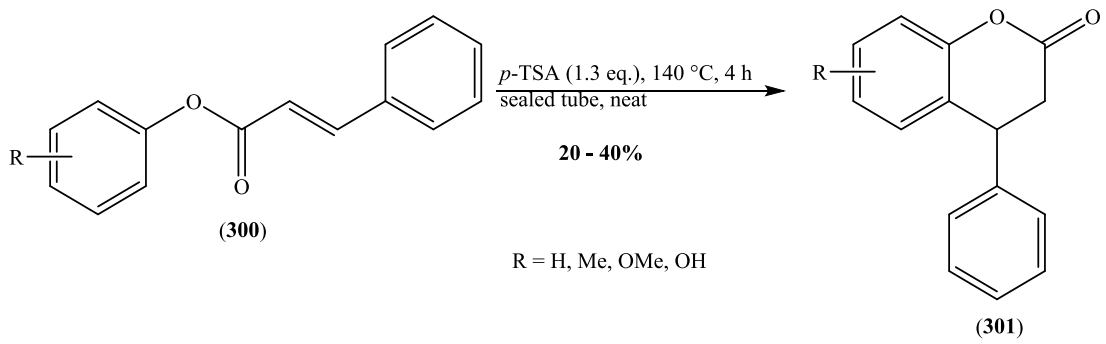


Scheme 2.68 Dehydration-oxidation of 4-hydroxyneoflavans

2.3.2 3,4-Dihydro-4-arylcoumarins

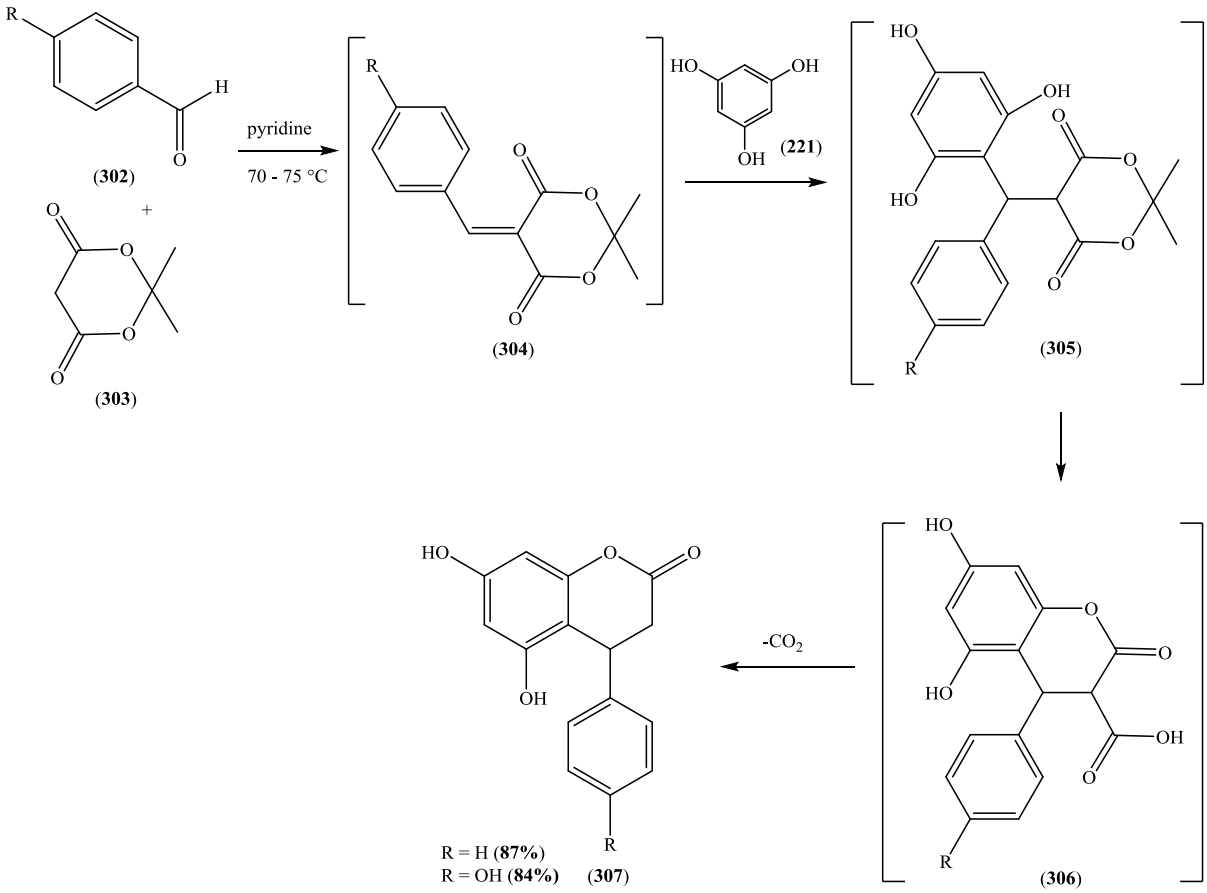
Various routes for the preparation of 3,4-dihydro-4-arylcoumarins have been developed. One of these methods involves the sulfuric acid catalysed Ponndorf reaction of cinnamic acids with phenols (*cf.* par 2.3.1.1, Scheme 2.58). Jeon *et al.*[205] demonstrated that aryl cinnamates (**300**) (prepared from cinnamoyl chloride and a substituted phenol) may, in a similar way, be

utilised in an intramolecular cyclisation reaction catalysed by *p*-TSA to produce 3,4-dihydro-4-arylcoumarins (**301**), albeit in low isolated yields (Scheme 2.69).



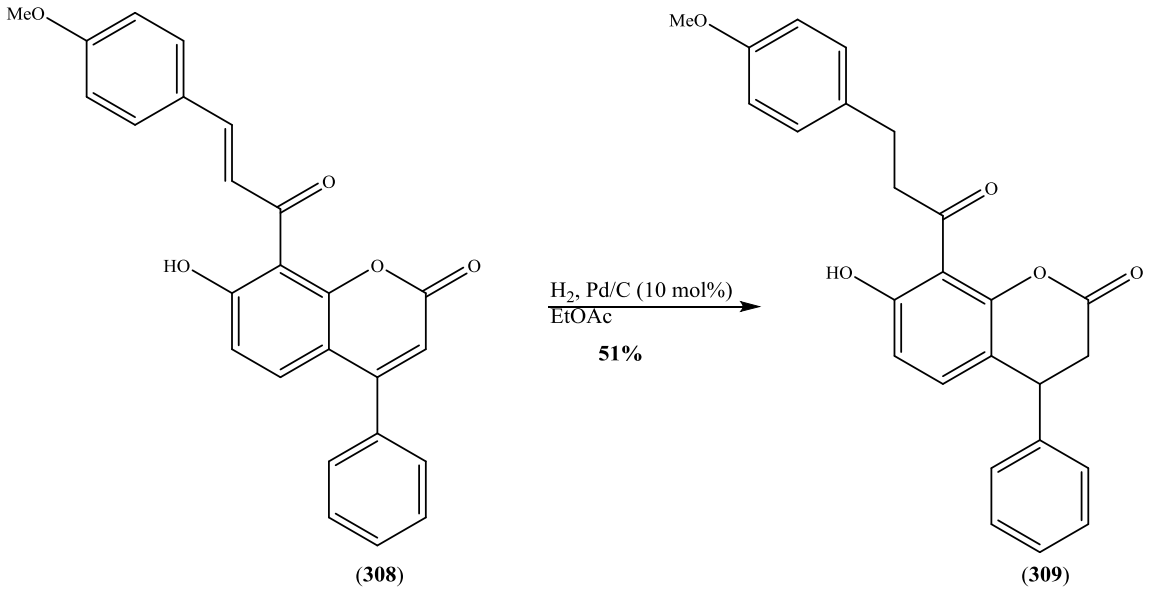
Scheme 2.69 Intramolecular 3,4-dihydro-4-arylcoumarin preparation

Certain 3,4-dihydro-4-arylcoumarins can be prepared in high yield (> 80%) from the appropriate aldehyde (**302**), Meldrum's acid (**303**) and phloroglucinol (**221**) in the presence of a mild base such as pyridine (Scheme 2.70).[206,207] This process entails the formation of an alkylidene Meldrum's acid (**304**) and subsequent nucleophilic attack by a phenol to give access to 3,4-dihydro-4-arylcoumarins (**307**).



Scheme 2.70 3,4-Dihydro-4-arylcoumarin preparation with Meldrum's acid

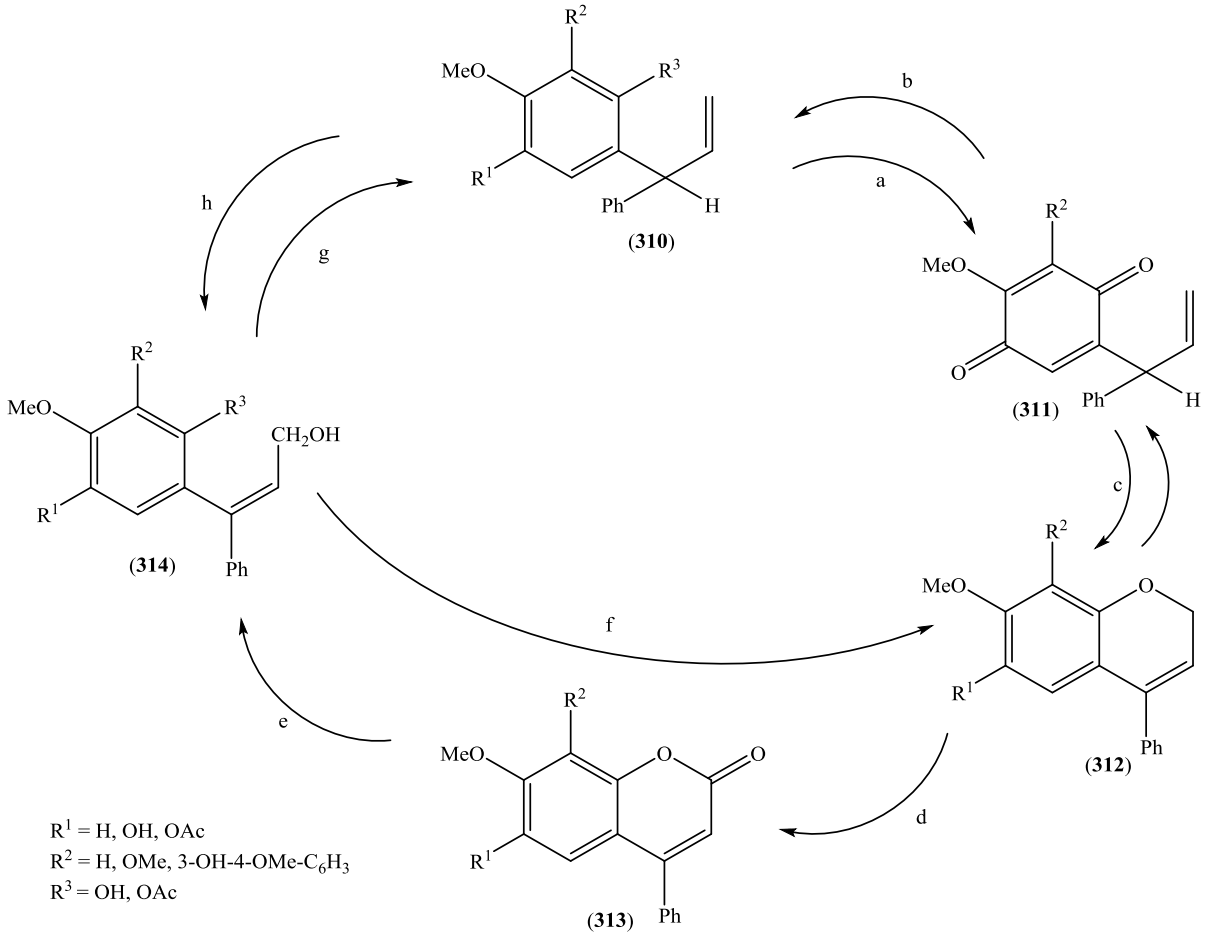
3,4-Dihydro-4-arylcoumarins can also be obtained by the hydrogenation of neoflavones in the presence of Pd/C, which gives the target compound [e.g. (**309**)] in moderate yield (Scheme 2.71). [206]



Scheme 2.71 Neoflavone hydrogenation

2.3.3 Dalbergiones, dalbergiquinols and neoflavenes

The general availability of 4-phenylcoumarins (**313**) through Von Pechmann condensation (*cf.* par. 2.3.1.1) resulted in the first acyclic neoflavonoids to be synthesised by reductive ring opening of the coumarin analogues. Lithium aluminium hydride cleavage of the heterocyclic 4-phenylcoumarin ring leads to 3,3-diarylprop-2-en-1-ol (**314**) in acceptable yields (Scheme 2.72 (e)).[208] Since the dalbergiones (**311**), dalbergiquinols (**310**) and neoflavenes (**312**) are easily interconvertible,[209,210] access to one of these compounds opens up the possibility of transforming it into any one of the other analogues by chemical transformation (Scheme 2.72).[182,191,209]

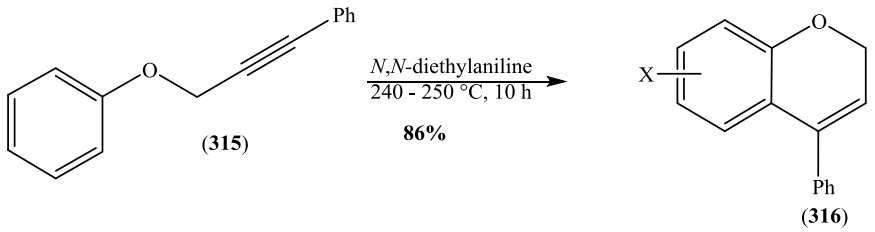


a: DDQ, C_6H_6, b: sodium dithionite, c: *N*, *N*-dimethylaminopyridine, $CHCl_3$, d:CrO_3-pyridine, e:$LiAlH_4$, Et_2O, f: HCl, EtOH, g: DMF/Zn/HCl, h: $Hg(OAc)_2$, HOAc

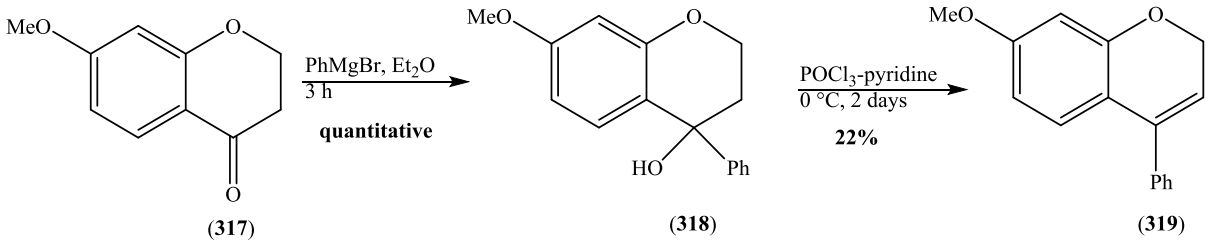
Scheme 2.72 Neoflavonoid interconversions

Apart from the reduction of 4-phenylcoumarins, the cyclic neoflavonoids, like neoflavenes (**316**), could also be prepared by direct routes like heat-induced cyclisation of phenyl

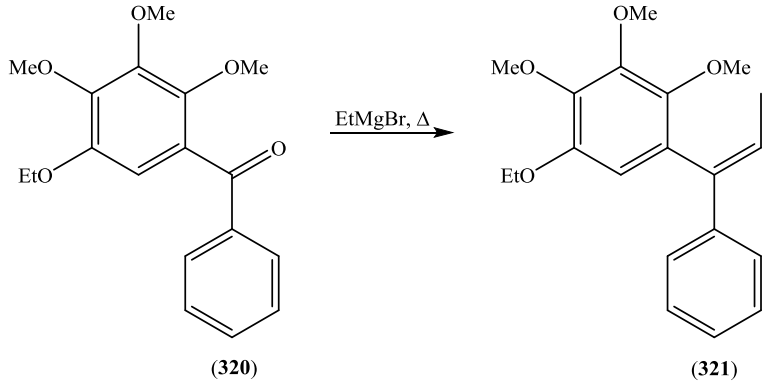
propargyl ethers (**315**), available by etherification (K_2CO_3, acetone, reflux) of phenyl propargyl bromide with a phenol analogue in 52 – 97% yield[211] (e.g. Scheme 2.73). Donnelly *et al.*[191] utilised $AgBF_4$ in the cyclisation of the phenyl propargyl ethers whereas Iwai and Ide[211] reported the preparation of 7-methoxyneoflav-3-ene (**319**) *via* Grignard addition (PhMgBr) to 7-methoxychromanone (**317**), followed by dehydration (Scheme 2.74). Ollis *et al.*[183] constructed the dalbergiquinol (**321**) skeleton *via* the Grignard reaction of ethylmagnesium bromide and 5-ethoxy-2,3,4-trimethoxybenzophenone (**320**) (Scheme 2.75).



Scheme 2.73 Heat-induced cyclisation of phenyl propargyl ether



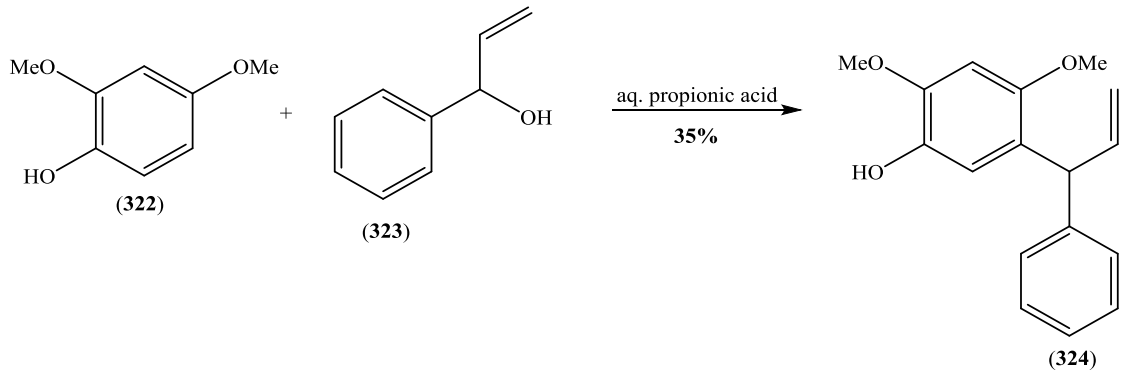
Scheme 2.74 Grignard addition-elimination for neoflav-3-ene preparation



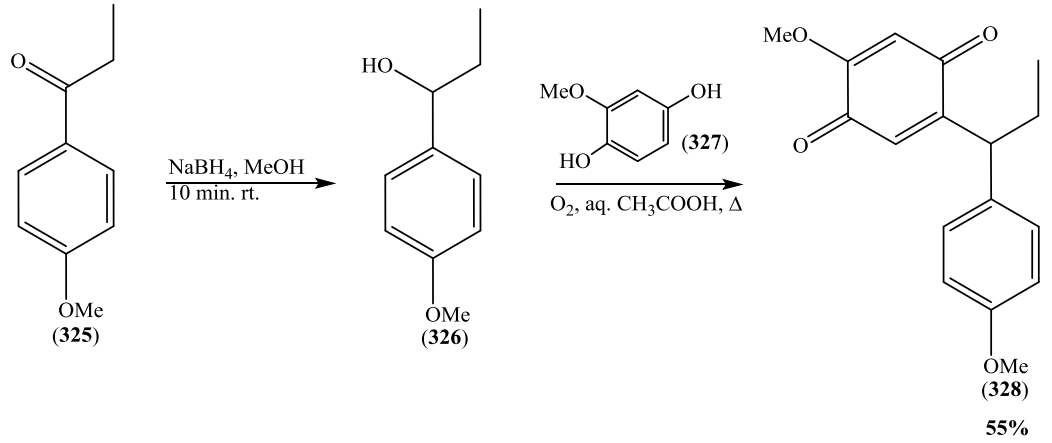
Scheme 2.75 Grignard addition-elimination for dalbergiquinol synthesis

Mageswaran *et al.*[212] entered the field of the dalbergione-dalbergiquinol-neoflavene group of compounds with the preparation of 2,4-dimethoxydalberginol (**324**) through the reaction of 1-phenylprop-2-ene-1-ol (**323**) with 1-hydroxy-2,4-dimethoxybenzene (**322**) under propionic acid catalysis (Scheme 2.76). Jurd[213] prepared 4,4'-dimethoxydalbergione (**328**) *via* the aq.

acetic acid catalysed reaction of 1-(4'-methoxyphenyl)-1-propanol (**326**), available by reduction of the propiophenone analogue (**325**), with 1,4-dihydroxy-2-methoxybenzene (**327**) under aerobic conditions (Scheme 2.77). These workers also reported that the reaction of cinnamyl alcohol with pyrogallol in aq. acetic acid gives the dalbergiquinol as side product.



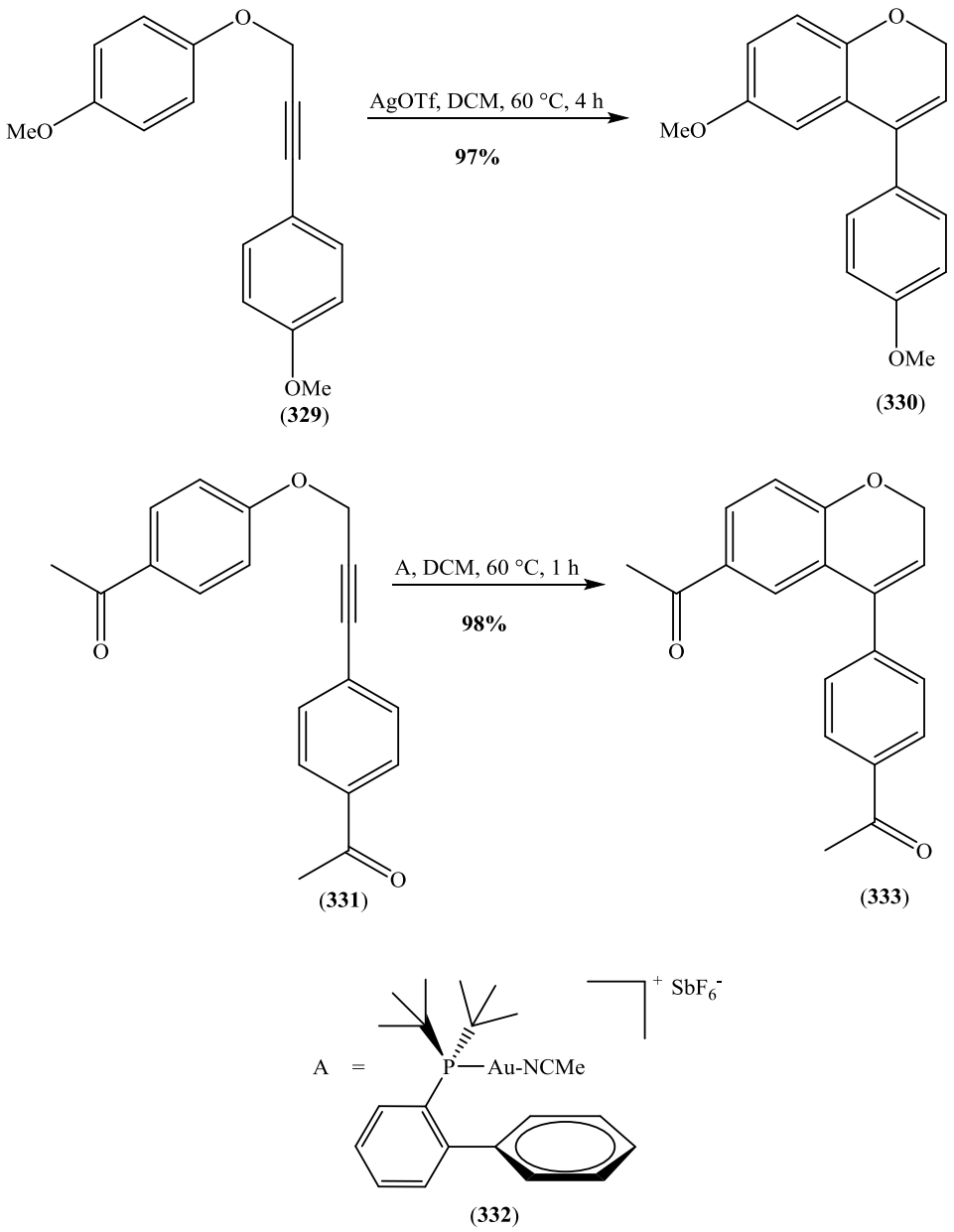
Scheme 2.76 Dalbergiquinol synthesis



Scheme 2.77 Dalbergione synthesis by Jurd[213]

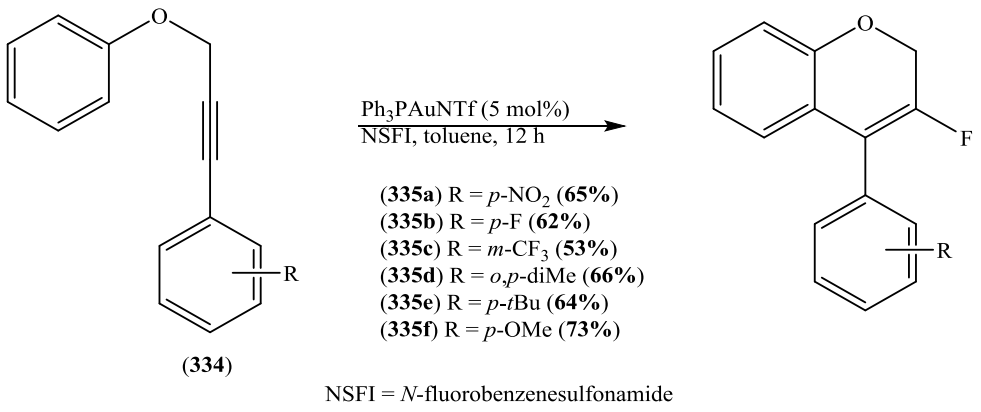
2.3.4 Recent methodologies

One of the more recent approaches to neoflavene synthesis involves catalytic intramolecular cyclisation of propargylic ethers (**329**) and (**331**) in the presence AgOTf[110] and gold(I) (**332**),[214] respectively. Arcadi *et al.*[215] concluded that AgOTf is an effective catalyst for cyclisations where the A and B rings contain electron donating groups, while gold catalysis was very effective for cyclisations wherein the A and B rings contain electron deficient groups (Scheme 2.78).



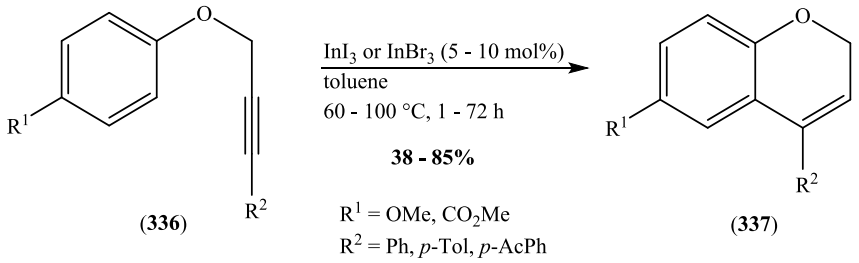
Scheme 2.78 Gold(I) *vs*. silver(I) catalysed intramolecular annulation

Shao and Huang[214] also developed a gold-catalysed hydroarylation-fluorination process utilising propargyl ethers (**334**) and noted that slightly higher yields were obtained for electron donating groups on the B-ring than electron withdrawing groups (Scheme 2.79).

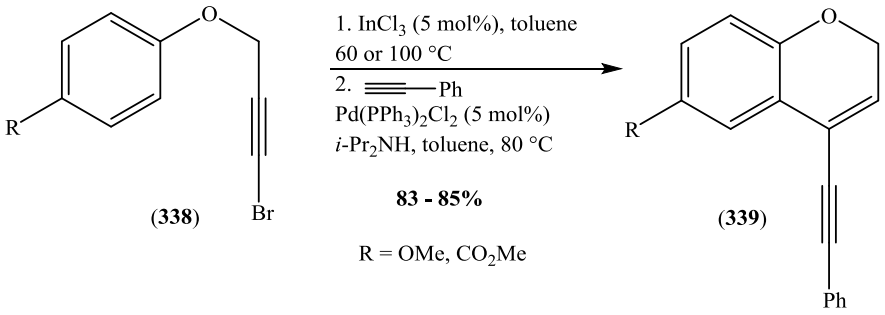


Scheme 2.79 Gold catalysed hydroalrylation/fluorination cascade reaction

Similarly, it has been reported that indium(III) halides are potent catalysts for intramolecular hydroarylation of propargylic ethers. InI_3 and $InBr_3$ have particularly been effective in catalysing this reaction for various substrates bearing electron rich and electron deficient groups on the aryl moieties and for both terminal and internal alkynes, with $–CO_2Me$ substitution in the R^1 position leading to lower yields (38 – 45%) and –OMe substitution in this position affording neoflav-3-enes (**337**) in higher yields of 65 – 85% (Scheme 2.80). The robustness of the catalyst was further demonstrated when this annulation reaction was combined with a palladium-catalysed Sonogashira coupling in one pot (Scheme 2.81).[216]

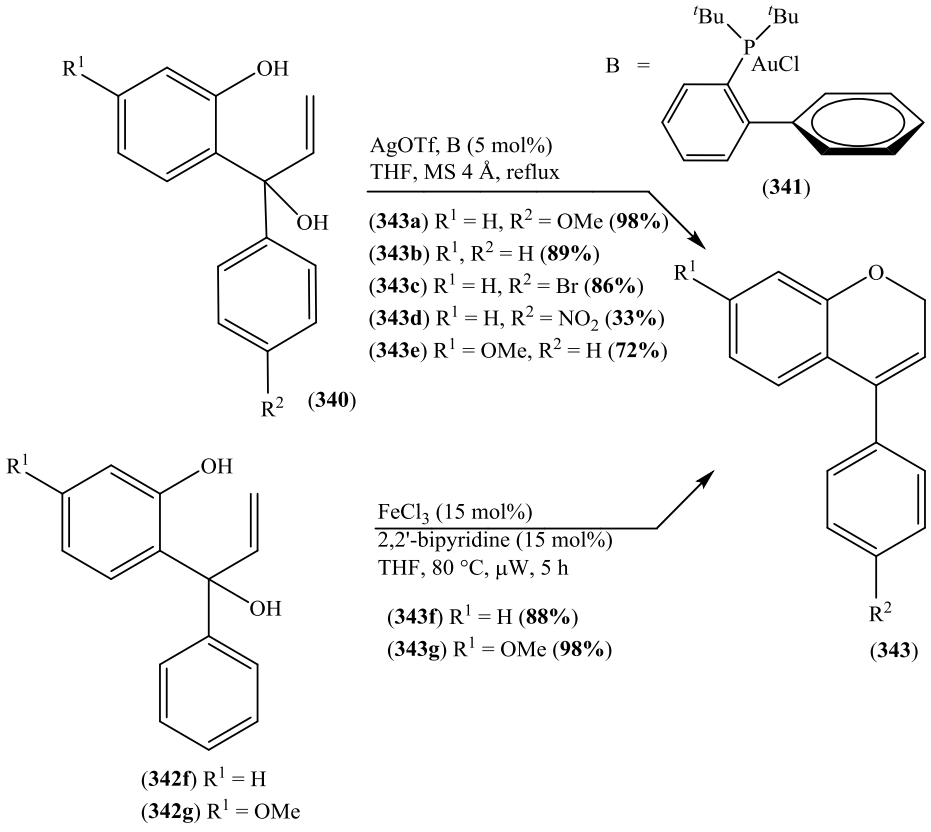


Scheme 2.80 InI_3 catalysed annulation of propargyl ethers



Scheme 2.81 One pot intramolecular hydroarylation and Sonogashira coupling

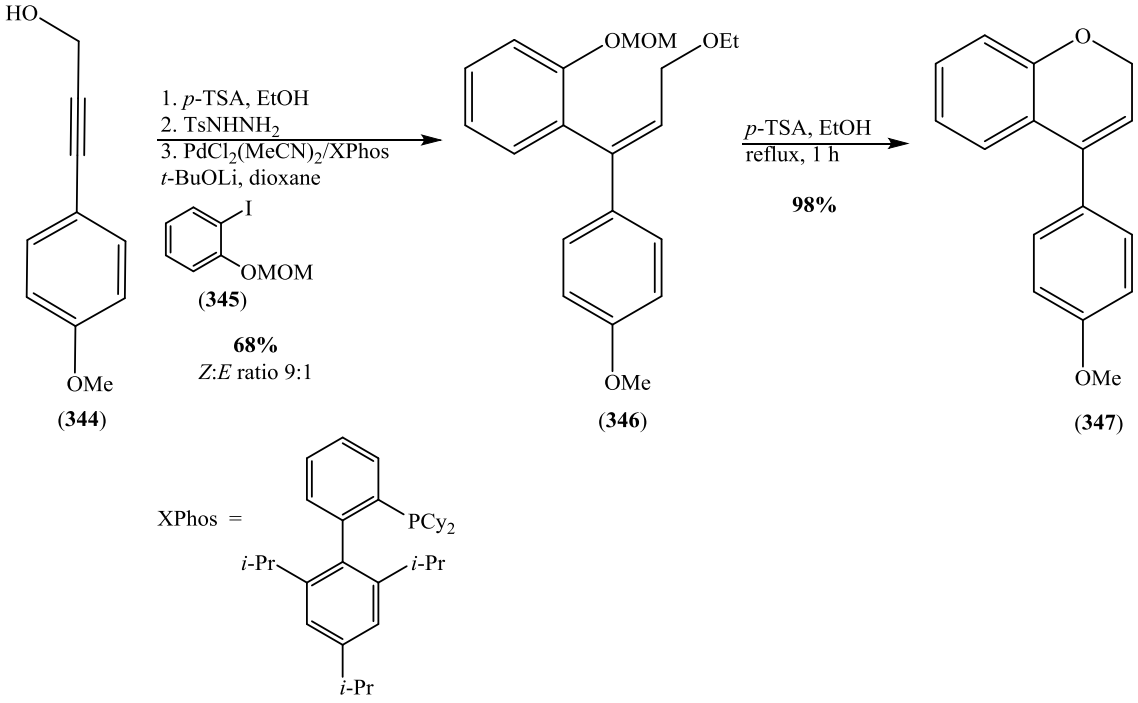
In another approach reported by Aponick, Biannic and Jong[217] a mixture of gold and silver catalysts was used to effect transformation of *o*-(1-hydroxyallyl)phenols (**340**) to chromenes. Their optimized reaction conditions employed 5 mol% AgOTf and Au-catalyst B (**341**) (Scheme 2.82) in THF at reflux and was also effective for a wide variety of electron donating and withdrawing substituents. Utilising this process, they were able to synthesise various neoflavenes in 33 – 98% isolated yields. Similarly, neoflav-3-enes (**343f**) and (**343g**) were synthesised from allylic alcohols (**342f**) and (**342g**), respectively, in a microwave assisted iron(III) chloride catalysed process in excellent yields (Scheme 2.82).[218]



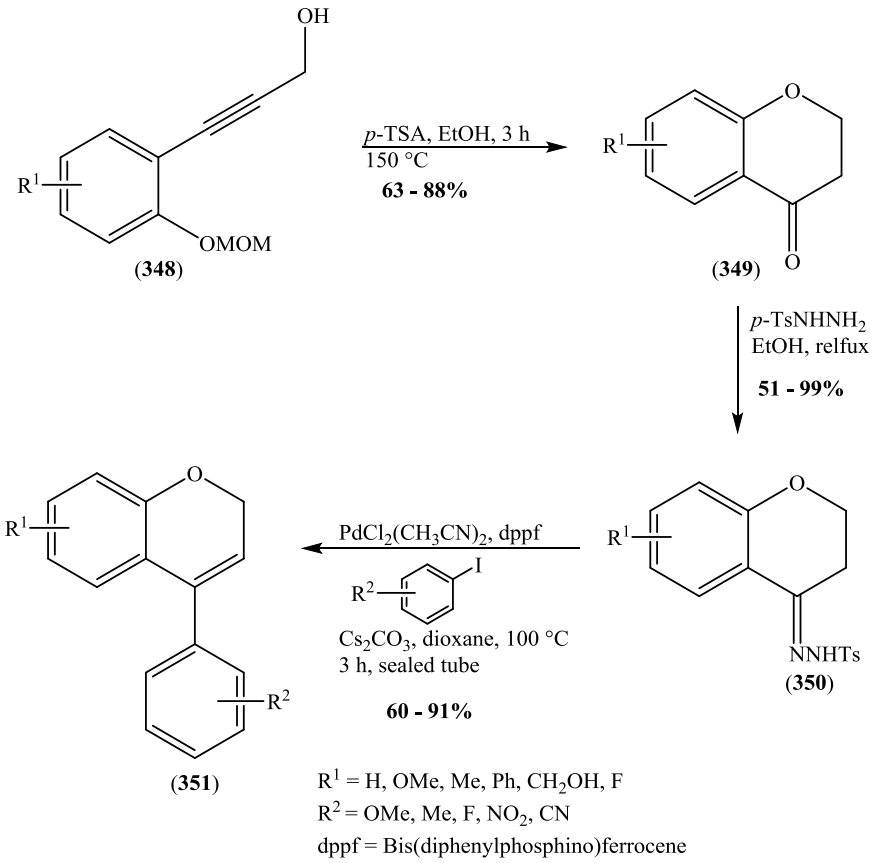
Scheme 2.82 Cyclisation of *o*-(1-hydroxyallyl)phenols

The synthesis of 4'-methoxyneoflav-3-ene (**347**) was also made possible *via* a three step one-pot process involving alkyne hydration, hydrazone formation and palladium-catalysed coupling with an *ortho*-oxygenated aryl halide (**345**) to yield a trisubstutited olefin (**346**). This olefin is subjected to cyclisation in the presence of *p*-TSA to form the desired neoflavene in 98% yield (Scheme 2.83).[219] In a similar process, the Provot group[220,221] transformed a variety of *ortho*-oxygenated arylalkynols (**348**) into 4-chromanones (**349**) in a process consisting of hydration of the triple bond, etherification, MOM-cleavage and cyclisation under microwave irradiation. The corresponding 4-arylchromenes (**351**) were then

obtained after hydrazone formation and subsequent palladium catalysed coupling of the latter with aryl halides (Scheme 2.84).



Scheme 2.83 Synthesis of 4'-methoxyneoflav-3-ene *via* a three step one-pot process

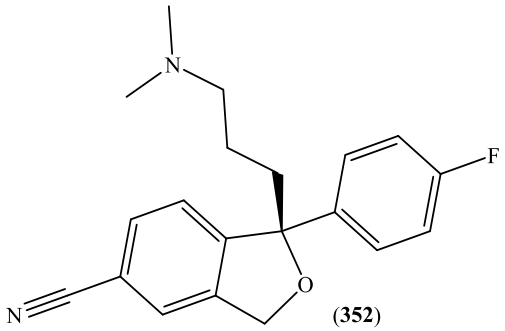


Scheme 2.84 *N*-tosylhydrazone formation and coupling with aryl iodides

2.4 Stereoselective synthesis of flavonoids

Stereoselective synthesis has emerged as an imperative aspect in the field of flavonoid synthesis since 1960 when Forsyth and Roberts[222] isolated and identified various oligomeric flavonoids in optically active form for the first time.

Thereafter, the need for stereoselective synthesis arose from the realization that many biological building blocks, such as sugars and enzymes, are produced as one enantiomer exclusively. Consequently, a high level of chemical chirality is found in living systems and different enantiomers will almost always lead to different reaction outcomes. In this regard the pharmaceutical industry often relies on optically pure compounds as drug effectiveness and safety are affected. Although the anti-depressant drug known as citalopram (**352**) is produced and sold as a racemic mixture, for example, studies have shown that it is only the (S)-(+)-enantiomer that is effective in treating the illness.[223]



(**352**)

Figure 2.2 (S)-(+)-Citalopram

While considerable progress has been made in the past *ca*. 50 years in the study of optically pure compounds in general, the stereoselective synthesis of flavonoids has been hampered by limited availability of starting materials in enantiomerically pure form, while the isolation of such compounds usually involves tedious processes. The preparation of flavonoid monomers in enantiomerically enriched form remains a challenge and thus far the stereoselective synthesis of flavonoids has been limited to a few classes of compounds as discussed in the following sections. Although more elaborate compounds like pterocarpans, 6a-hydroxypterocarpans, etc. have also been prepared in optically active form, the discussion in this paragraph will be limited to compounds relevant to the current investigation.

2.4.1 Chalcone epoxides

Chalcones can be viewed as the key precursor in the preparation of many flavonoids and isoflavonoids (*cf.* par 2.1.1 and 2.2.1.2). If these compounds could therefore be converted into chiral analogues, like chalcone epoxides, in high ee (enantiomeric excess), the asymmetric synthesis of many flavonoids would become possible.

Wynberg *et al.*,[224,225] first attempted the preparation of chalcone epoxides in optically enriched form by utilising the chiral phase transfer catalysts (PTC) BQdC (**353**) (quinidine benzylchloride) and BQC (**354**) (quinine benzylchloride) in a Weitz–Scheffer reaction (30% aq. H_2O_2/NaOH/toluene) and managed to obtain the (–)-*trans*-chalcone epoxides and (+)-*trans*-chalcone epoxides (**356a/b**), in moderate to high yields (38 – 92%), but with poor enantiomeric excess (25 – 48%) (Scheme 2.85).[134]

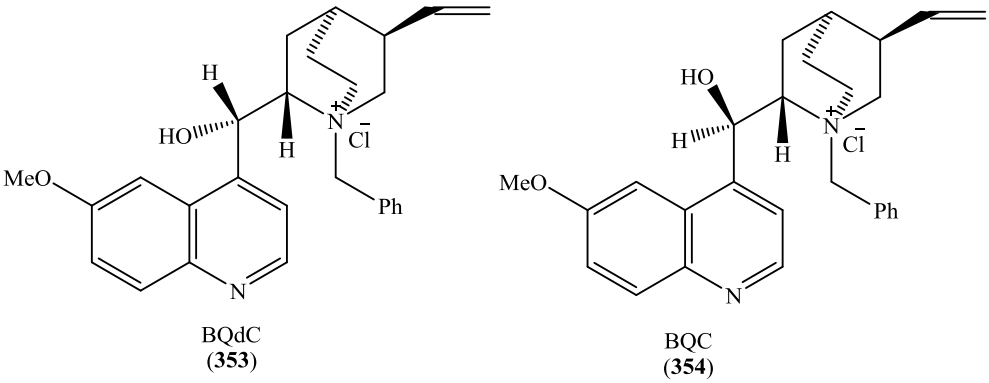
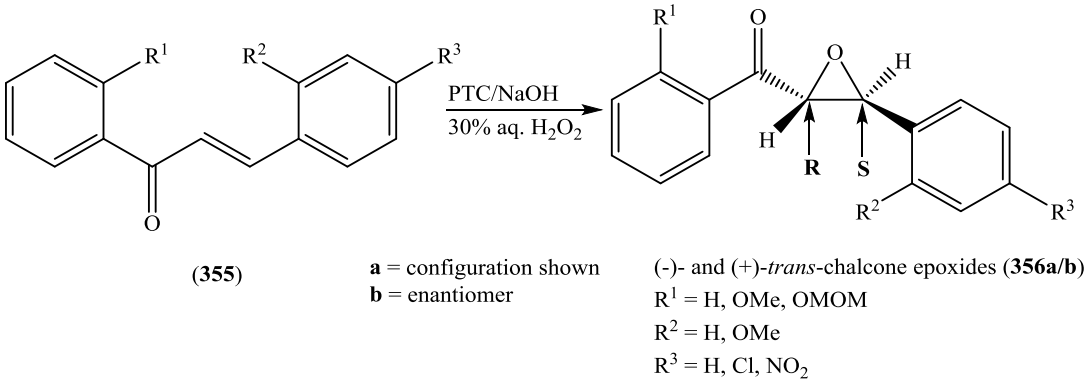


Figure 2.3 Chiral phase transfer catalysts



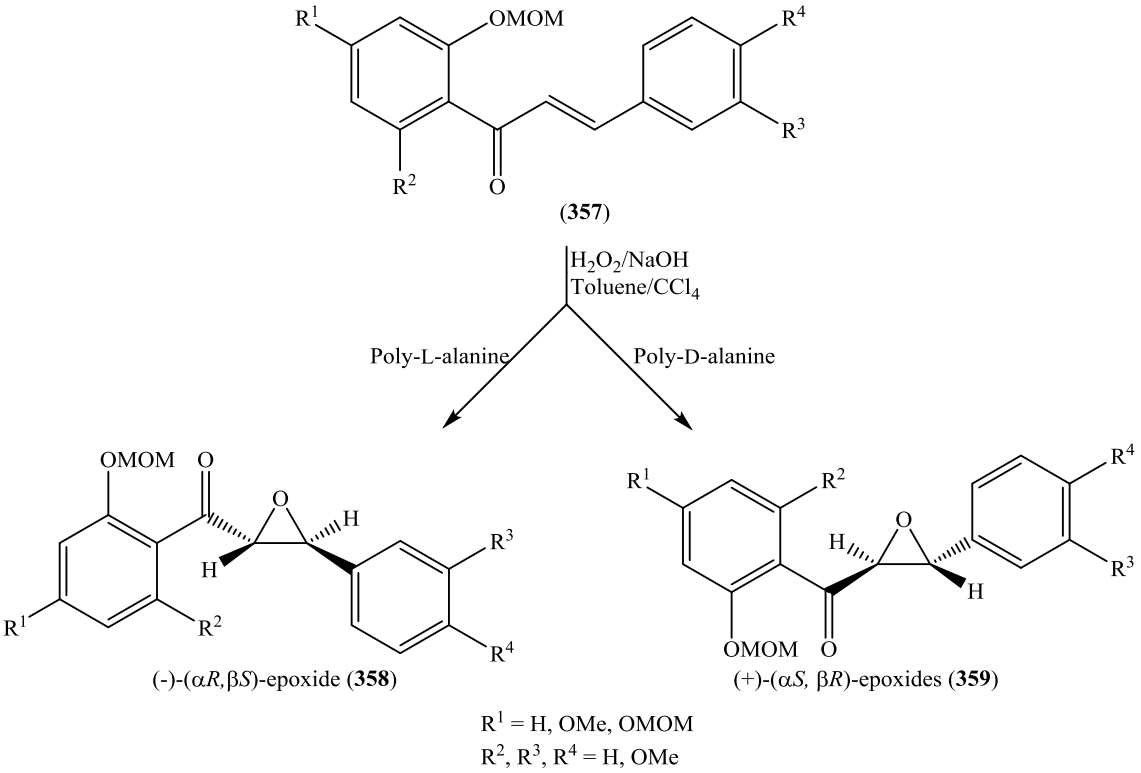
(**355**)

a = configuration shown
b = enantiomer

(-)- and (+)-*trans*-chalcone epoxides (**356a/b**)
R^1 = H, OMe, OMOM
R^2 = H, OMe
R^3 = H, Cl, NO_2

Scheme 2.85 Chiral epoxidation of chalcones with hydrogen peroxide under PTC conditions

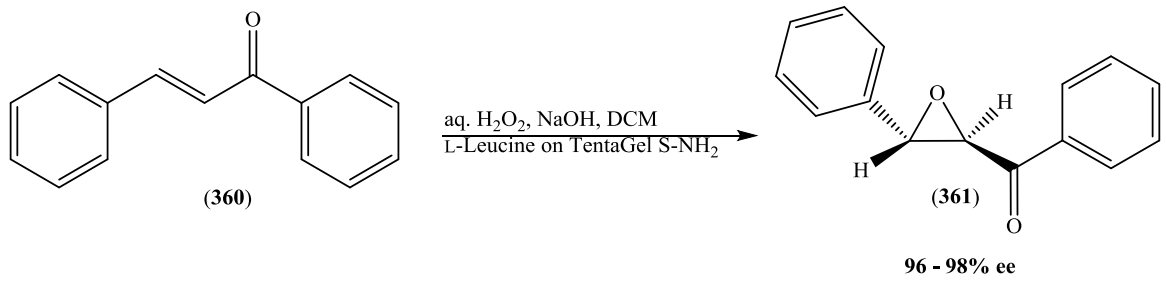
While Wynberg and co-workers[225] managed to obtain optically active chalcone epoxides in moderate to excellent yields and moderate enantiomeric excess, these workers did not address the issue of naturally occurring substitution patterns during their investigation and only included two entries with mono-methoxy substitution on the A- as well as B-rings of the chalcone into their research. Building on the principle of phase transfer catalysis, Julia *et al.*[226] reported an alternative process for achieving the stereoselective epoxidation of chalcones utilising synthetic peptides. Poly-L- or poly-D-alanine and alkaline H_2O_2 in toluene or CCl_4 was used in a triphasic system to afford chiral chalcone epoxides in 40 – 92% chemical yield and 14 – 65% ee.[134] The Ferreira group[227] were able to achieve higher yields (e.g. 74%) and up to 84% ee's for the desired products when they extended this synthetic protocol to compounds displaying natural substitution patterns (Scheme 2.86).



Scheme 2.86 Asymmetric epoxidation of chalcones in a triphasic system

The most satisfactory chiral epoxidation of chalcones was reported by Bentley and Roberts[228] who employed an immobilized poly-amino acid, a non-nucleophilic base and organic solvent in a non-aqueous two-phase system. Their process led to high yields and ee's of over 95%.[134] The Yi group[229] utilised silica-grafted poly-L-leucine catalysts in an improved Juliá-Colonna asymmetric chalcone epoxidation and obtained yields of 50 – 94% and ee's of 70 – 93%, while Geller *et al.*[230] developed a modified Juliá-Colonna epoxidation system wherein a more effective catalyst was prepared *via* polymerisation of leucine-*N*-carboxanhydride (NCA) at elevated temperature (111 °C). This catalyst (ht-poly-L-leucine) was utilised in a triphasic system and in the epoxidation of *trans*-chalcone, a conversion of 59% and ee of 91% was observed within 90 minutes, whereas standard poly-L-leucine gave virtually no conversion within the same time period.

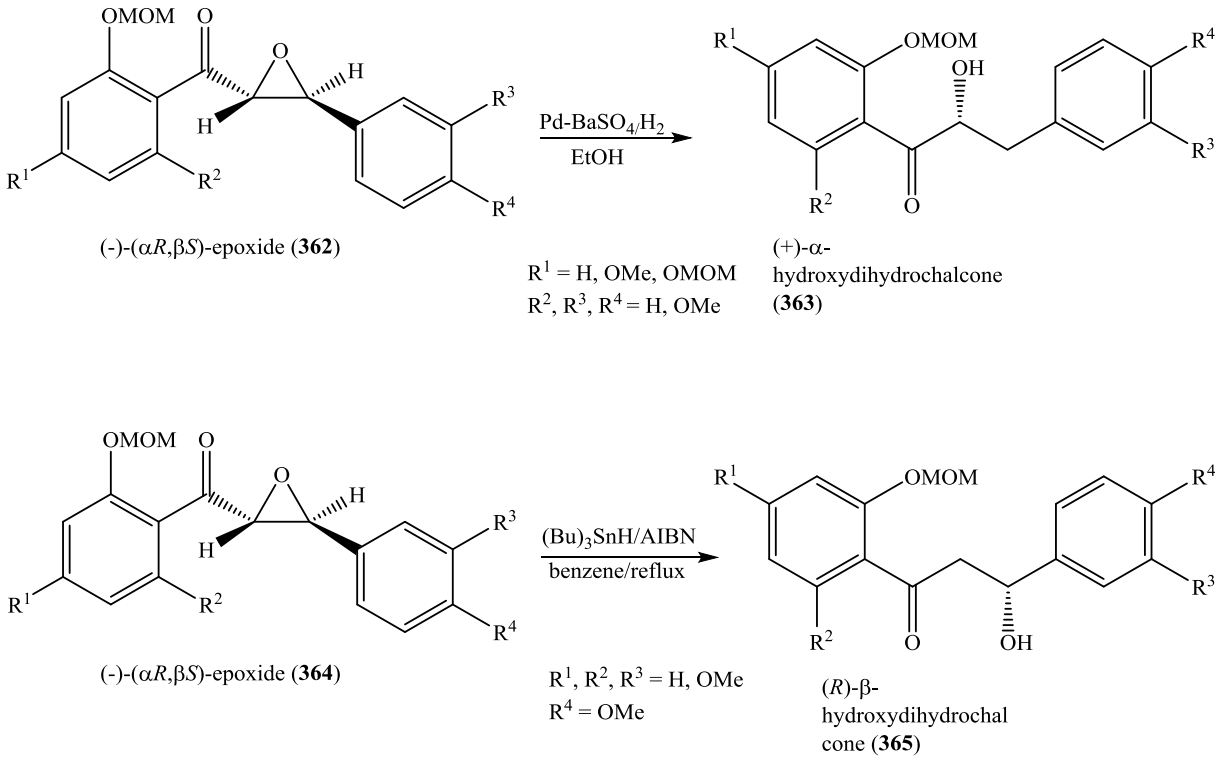
Berkessel *et al.*[231] applied the Juliá-Colonna chalcone epoxidation *via* a system of L-leucine oligomers of varying chain lengths linked to TentaGel^{TM} S-NH_2 resin by means of the amine groups. Stereoselective catalysis is achieved through binding of the enone to the *N*-terminus, while epoxide configuration is determined by the helicity of the peptide which directs the face-selective approach of the hydroperoxide ion. Chalcone epoxides were obtained with ee's of 96 – 98% (Scheme 2.87).



Scheme 2.87 Improved Juliá-Colonna chalcone epoxidation

2.4.2 α- and β-Hydroxydihydrochalcones

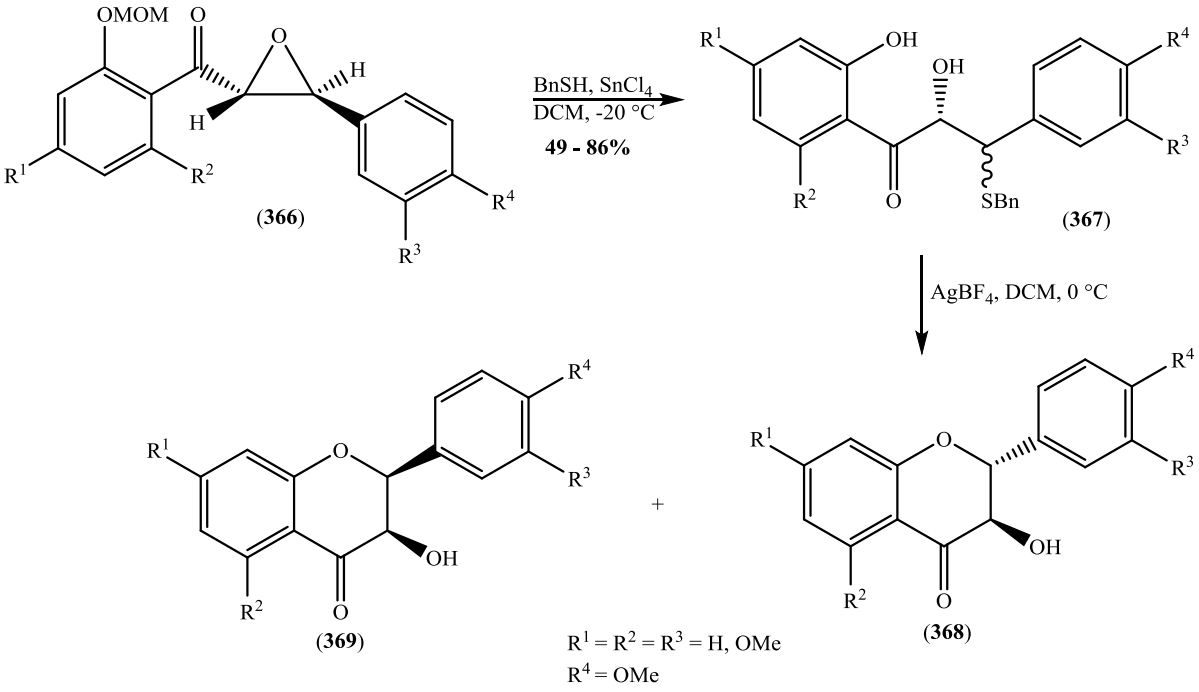
With enantiomerically enriched chalcone epoxides (**362**) and (**364**) available, α- and β-hydroxydihydrochalcones (**363**) and (**365**) could easily be prepared in optically enriched form. Catalytic hydrogenation (Pd-C/H_2 or Pd-$BaSO_4$/H_2) of the epoxide (**362**) produces the α-hydroxydihydrochalcones (**363**) without any significant loss in ee and moderate to excellent chemical yields (40 – 92%), whereas a radical process [$(Bu)_3SnH$/AIBN in benzene under reflux] affords β-hydroxydihydrochalcones (**365**) in up to 91% ee's and yields of *ca.* 70% (Scheme 2.88).[134,227,232,233]



Scheme 2.88 α- and β-Hydroxydihydrochalcone synthesis

2.4.3 Dihydroflavonols

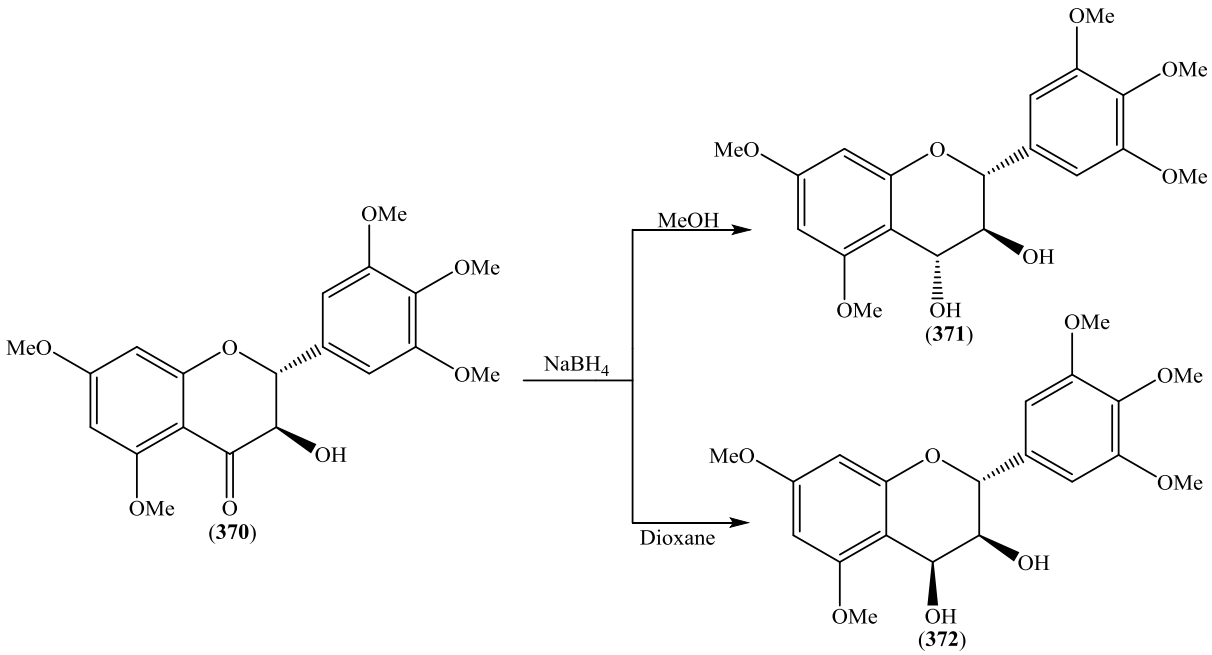
Since chalcone epoxides are suitable precursors for the synthesis of dihydroflavonols, Van Rensburg and co-workers[234,235,236] developed processes aimed at nucleophilic opening of the oxirane moiety with concomitant formation of the heterocyclic C-ring of the dihydroflavonol. Utilising BnSH (benzylmercaptan) and tin tetrachloride to selectively cleave the C_β-O bond of the epoxide (**366**) and to deprotect the 2'-hydroxy function of the dihydrochalcone intermediate, and silver tetrafluoroborate to facilitate the cyclisation, these workers were able to form the 2,3-*trans*-dihydroflavanols (**368**) in up to 86% yield and 83% ee. The 2,3-*cis*-analogues (**369**) were also obtained albeit in poor yield (Scheme 2.89).[134]



Scheme 2.89 Stereoselective dihydroflavonol synthesis

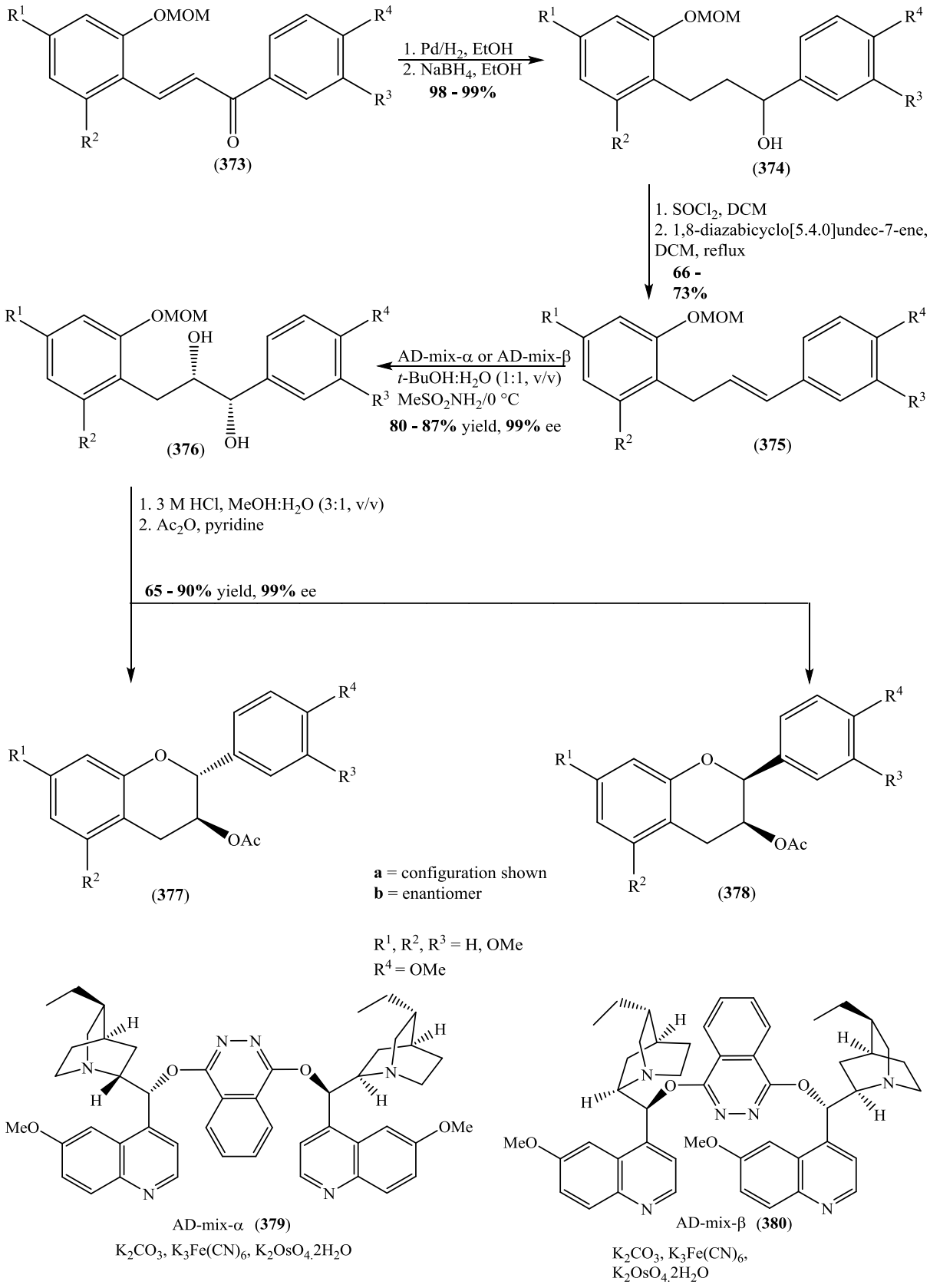
2.4.4 Flavan-3-ols and flavan-3,4-diols

Although the synthesis of the first optically pure flavan-3-ols and flavan-3,4-diols were reported by Weinges *et al.*[237,238] and Onda *et al.*,[239] respectively, these authors obtained the desired compounds by reduction of optically pure dihydroflavonols, either from natural sources (flavan-3-ol preparation) or HPLC purification of enantiomerically enriched starting materials. Onda *et al.*,[239] found that the utilization of $NaBH_4$ in MeOH leads to the preparation of 2,3-*trans*-3,4-*trans*-flavan-3,4-diols (**371**), whereas, if the reaction is executed in dioxane, the 2,3-*trans*-3,4-*cis*-isomers (**372**) are obtained (Scheme 2.90).



Scheme 2.90 Stereoselective flavan-3,4-diol synthesis

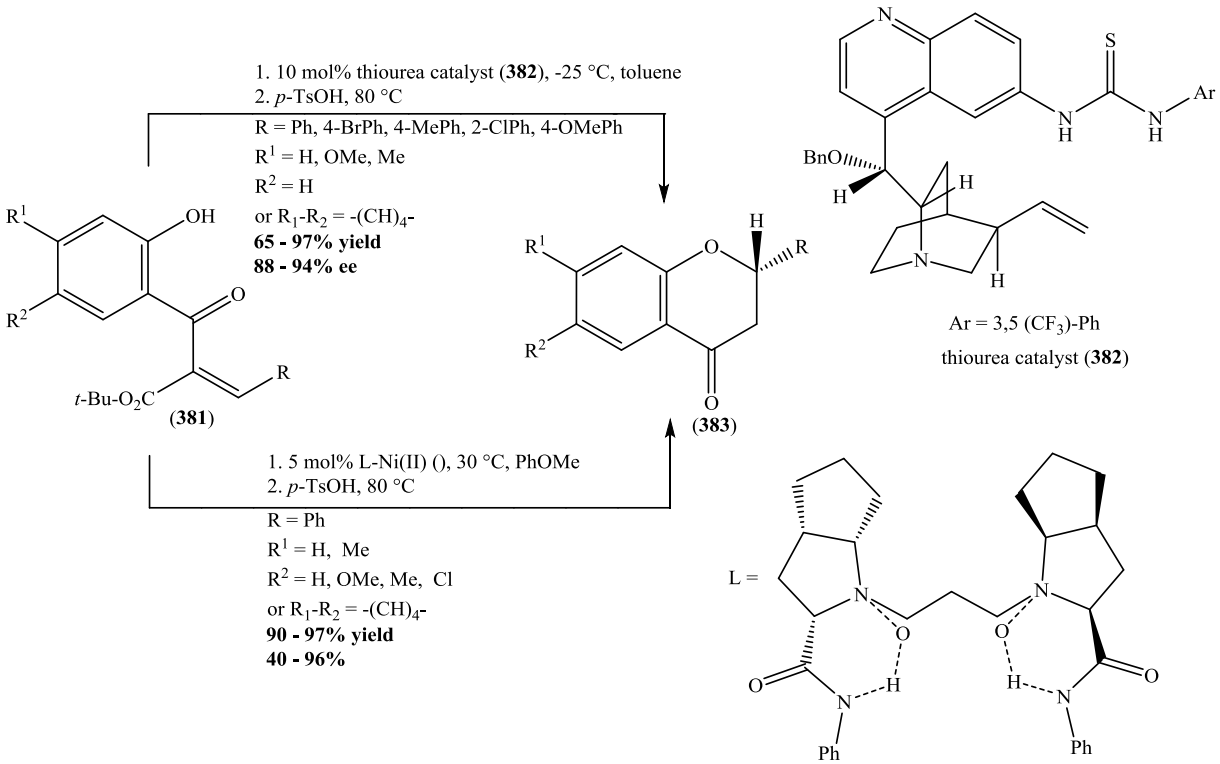
During the mid 1990's, Ferreira and co-workers[235,236] reported the first truly enantioselective synthesis of flavan-3-ols [(**377**) and (**378**)] from achiral starting materials. After preparing the 1,3-diarylpropenes (**375**), these authors utilised the Sharpless asymmetric dihydroxylation with AD-mix-α (**379**) or AD-mix-β (**380**) to enantioselectively prepare the dihydroxy analogues (**376**). 2'-Hydroxy deprotection, followed by cyclisation led to the desired flavan-3-ols [(**377**) and (**378**)] in 65 – 90% yield and 99% ee (Scheme 2.91). This methodology was subsequently extended to cover the synthesis of a full range of naturally occurring flavan-3-ols by Nel *et al*.[240]



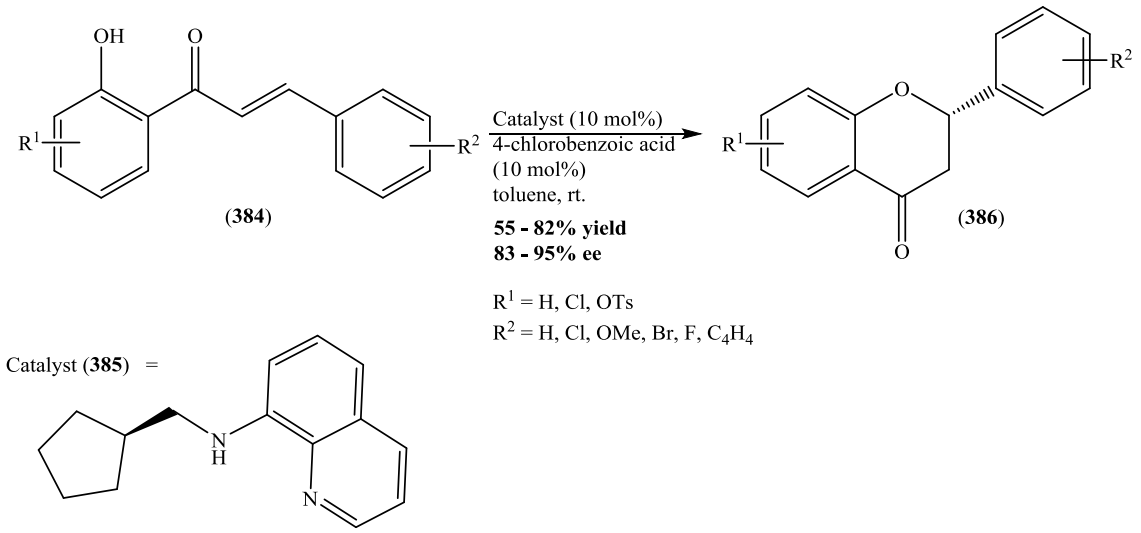
Scheme 2.91 Stereoselective flavan-3-ol synthesis

2.4.5 Flavanones

Only a limited number of methodologies have been developed for the stereoselective synthesis of flavanones and asymmetric catalysis providing a direct route to optically active flavanones has mostly been investigated. The Biddle group[241] studied the application of chiral thioureas in a catalytic intramolecular conjugate addition of α-substituted chalcones to prepare flavanones. Utilising α-CO_2-*t*-Bu substituted chalcones (**381**) to enhance reactivity and promote cyclisation with a thiourea catalyst (**382**) in toluene at -25 °C, followed by decarboxylation upon heating with *p*-TsOH, produced various flavanones in 88 – 94% ee and 65 – 97% yields (Scheme 2.92). The same type of cyclisation could be achieved in the presence of a chiral *N*,*N*'-dioxide nickel(II) complex, tolerant to moisture and air, giving high yield (90 – 97%) and enantioselectivity (80 – 96% and 40% if R^2 = Cl) (Scheme 2.92),[242] while cyclisation of chalcones in the presence of a newly developed L-proline based organocatalyst (**385**) led to the production of flavanones in 83 – 95% ee and 55 – 82% yields (Scheme 2.93).[243]

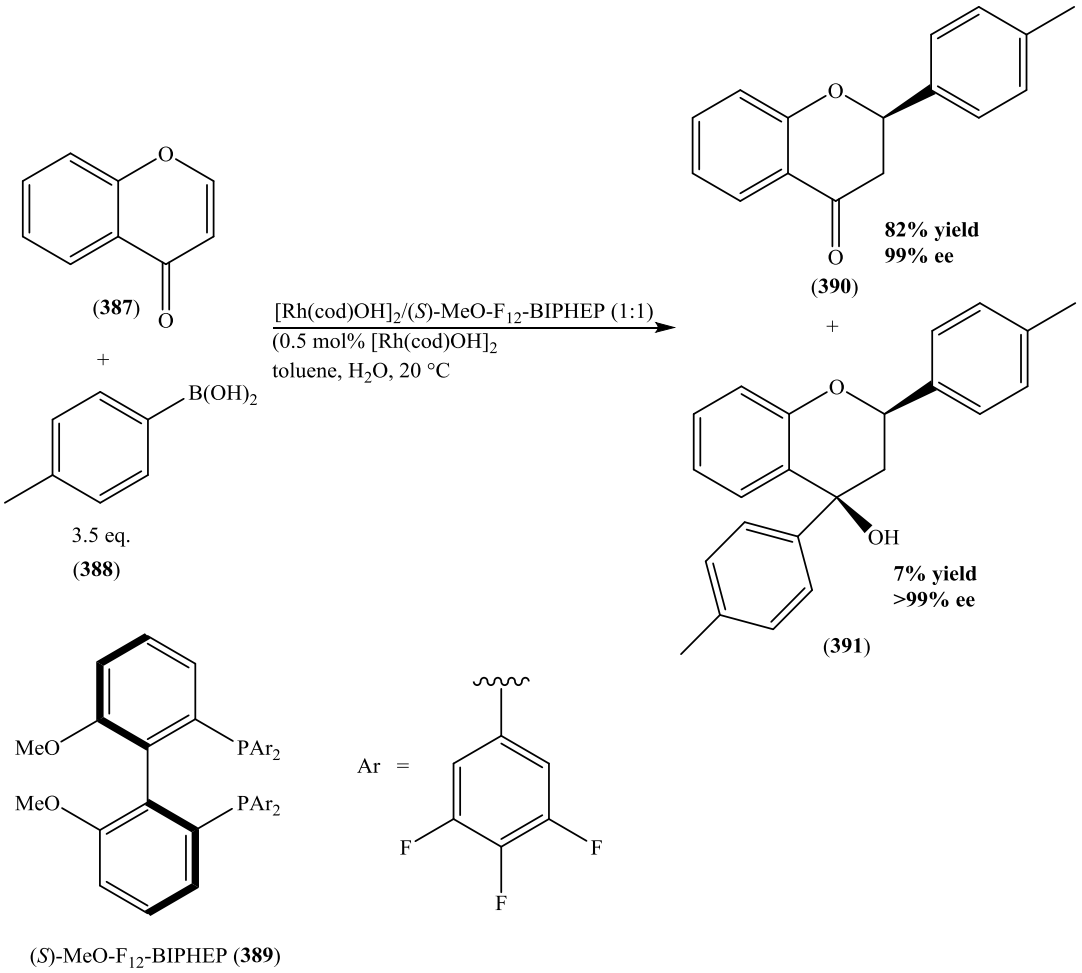


Scheme 2.92 Stereoselective flavanone synthesis with thiourea or Ni(II) catalyst

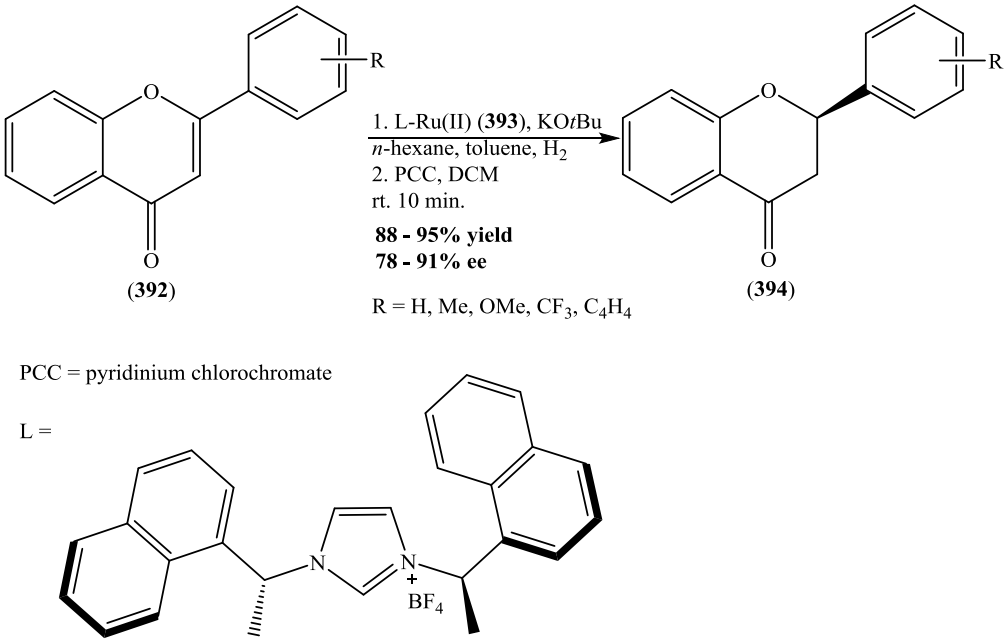


Scheme 2.93 Stereoselective flavanone synthesis with L-proline based catalyst

Korenaga *et al.*[244] utilised a rhodium-based catalyst to initiate 1,4-addition of arylboronic acids (**388**) to chromones (**387**) and obtained high yields (80 – 95%) and ee's (≥99%) for flavanones (**390**), but also observed the formation of a bis-arylated benzopyran-4-ol (**391**) byproduct in low yield [e.g. (Scheme 2.94)]. The Zhao group[245] on the other hand utilised a chiral ruthenium catalyst (**393**) to effect asymmetric hydrogenation of flavones (**392**) to optically active flavan-4-ols, which were subsequently oxidised by PCC (pyridinium chlorochromate) to give the desired flavanones (**394**) in 78 – 91% ee and 88 – 95% yield (Scheme 2.95).



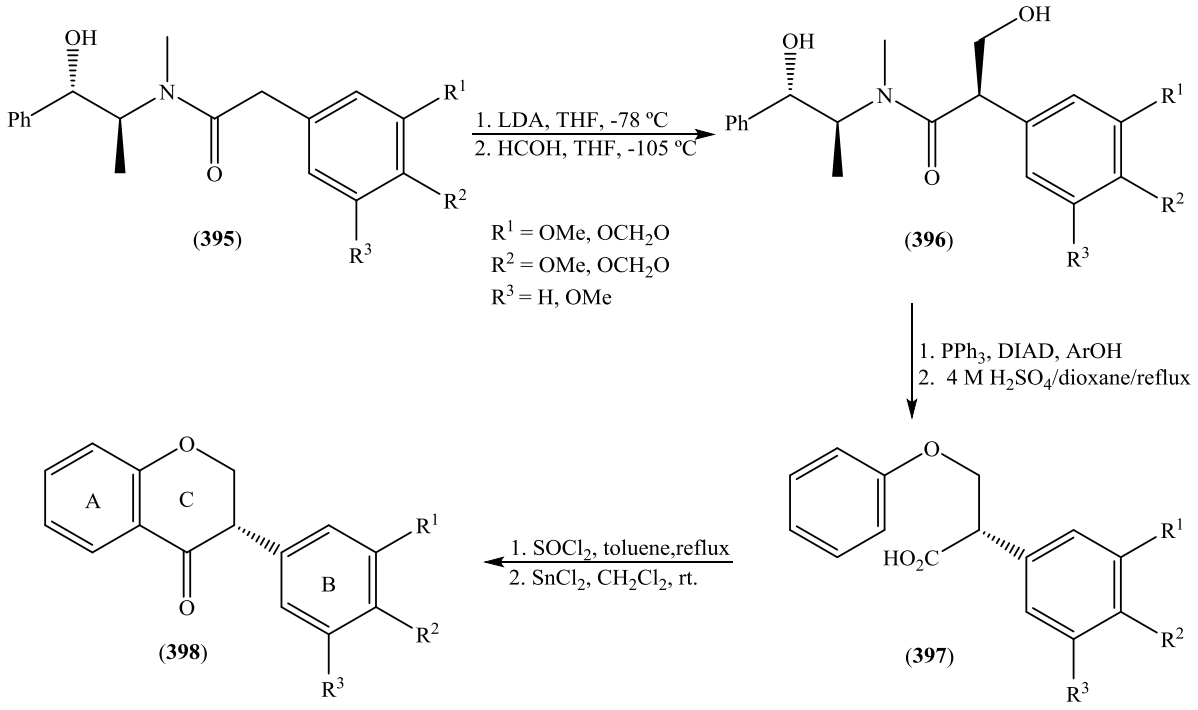
Scheme 2.94 Rh-catalysed stereoselective flavanone synthesis



Scheme 2.95 Ru-catalysed asymmetric flavone hydrogenation

2.4.6 Isoflavanones

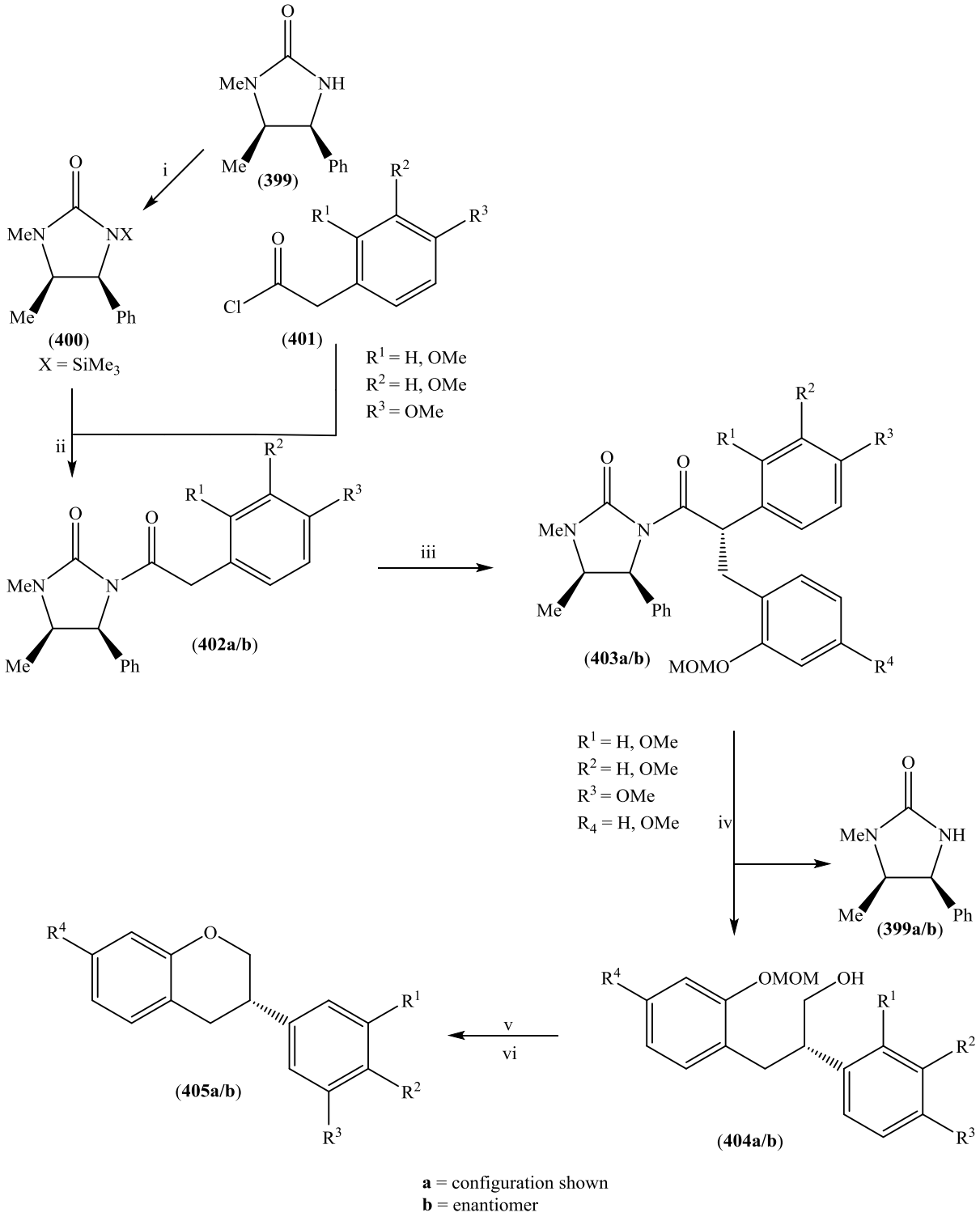
Chirality could be introduced at C-3 of the isoflavanone framework by applying a stereocontrolled aldol reaction of formaldehyde with (*S*,*S*)-(+)-pseudoephedrine arylacetamides (**395**). Subsequent aryl ether formation under Mitsunobu conditions, hydrolysis and intramolecular Friedel-Crafts acylation permitted the formation of the C-ring of the isoflavanone skeleton. In this way, the Vicario group[246] were able to synthesise optically enriched isoflavanones (**398**) in high yields (69 – 71%) and over 99% ee's (Scheme 2.96).[247]



Scheme 2.96 Stereoselective isoflavanone synthesis

2.4.7 Isoflavans

Versteeg *et al.*[248,249,250] addressed the issue of stereocontrol at the 3-position of the isoflavan (**405**) skeleton through the asymmetric α-benzylation of phenylacetic acid derivatives (**401**). Imidazolin-2-ones (**399**) were utilised to introduce chirality and subsequent reductive cleavage ($LiAlH_4$) of these auxiliaries was followed by cyclisation under Mitsunobu conditions to give the final products (**405a/b**) in excellent chemical yields (75 – 92%) and ee's of 96 – 99% (Scheme 2.97).



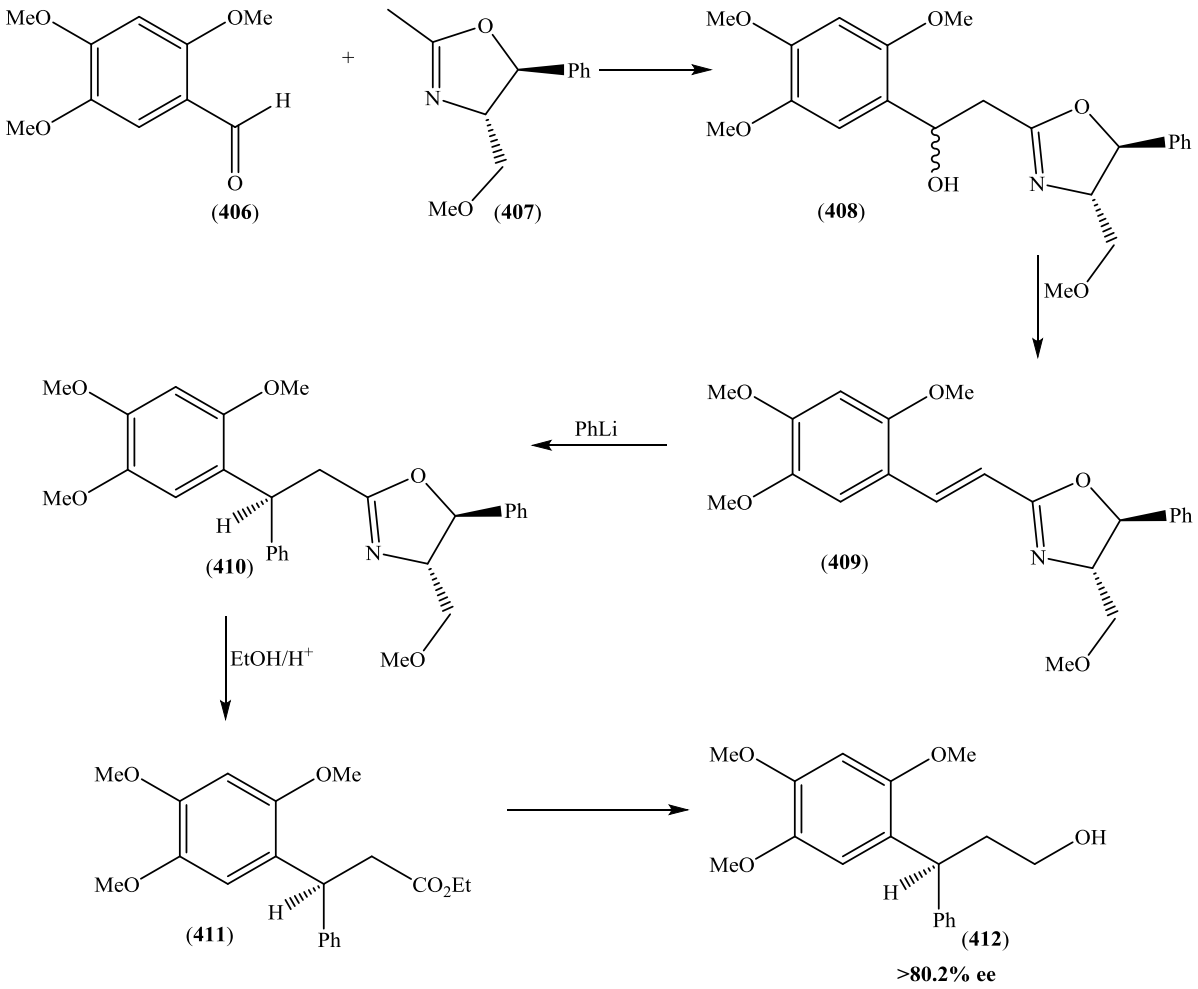
a = configuration shown
b = enantiomer

i. BuLi, Ph_3CH (catalytic), THF, 0 ºC; then Me_3SiCl, -78 ºC to rt.; ii. tetrabutylammonium fluoride (TBAF), MeCN, rt.; iii, lithium isopropylcyclohexylamide (LICA), 2-*O*-Methoxymethylbenzyl bromide, THF–CH_2Cl_2, -40 ºC; iv. $LiAlH_4$/THF or $LiBH_4/Et_2O$, -24 ºC to rt.; v. 3 M HCl, MeOH, reflux, vi. PPh_3, DIAD, THF, rt.

Scheme 2.97 Stereoselective isoflavan synthesis

2.4.8 Dalbergiquinols

The synthesis of *S*-3-(2',4',5'-trimethoxybenzene)-3-phenylpropan-1-ol (**412**) has been achieved utilising chiral 2-methyloxazoline (**407**) in a condensation reaction with 2,4,5-trimethoxybenzaldehyde (**406**) and afforded a diastereomeric mixture (1:1) of the hydroxyoxazoline analogue (**408**). Subsequent dehydration led to the formation of *E*-vinyloxazoline (**409**) and nucleophilic addition of PhLi afforded a diastereomeric adduct (**410**). This compound was hydrolysed and esterified (EtOH/H^+) and subsequently reduced to give the desired *S*-alcohol (**412**) in >80.2% ee (Scheme 2.98).[251]

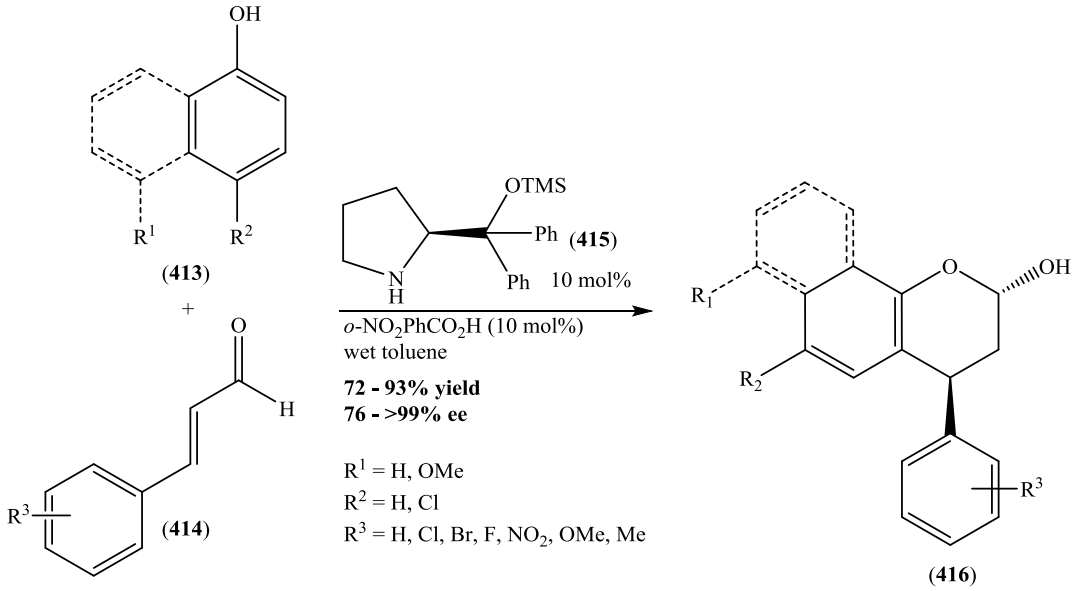


Scheme 2.98 Stereoselective dalbergiquinol synthesis

2.4.9 Neoflavonols and neoflavones

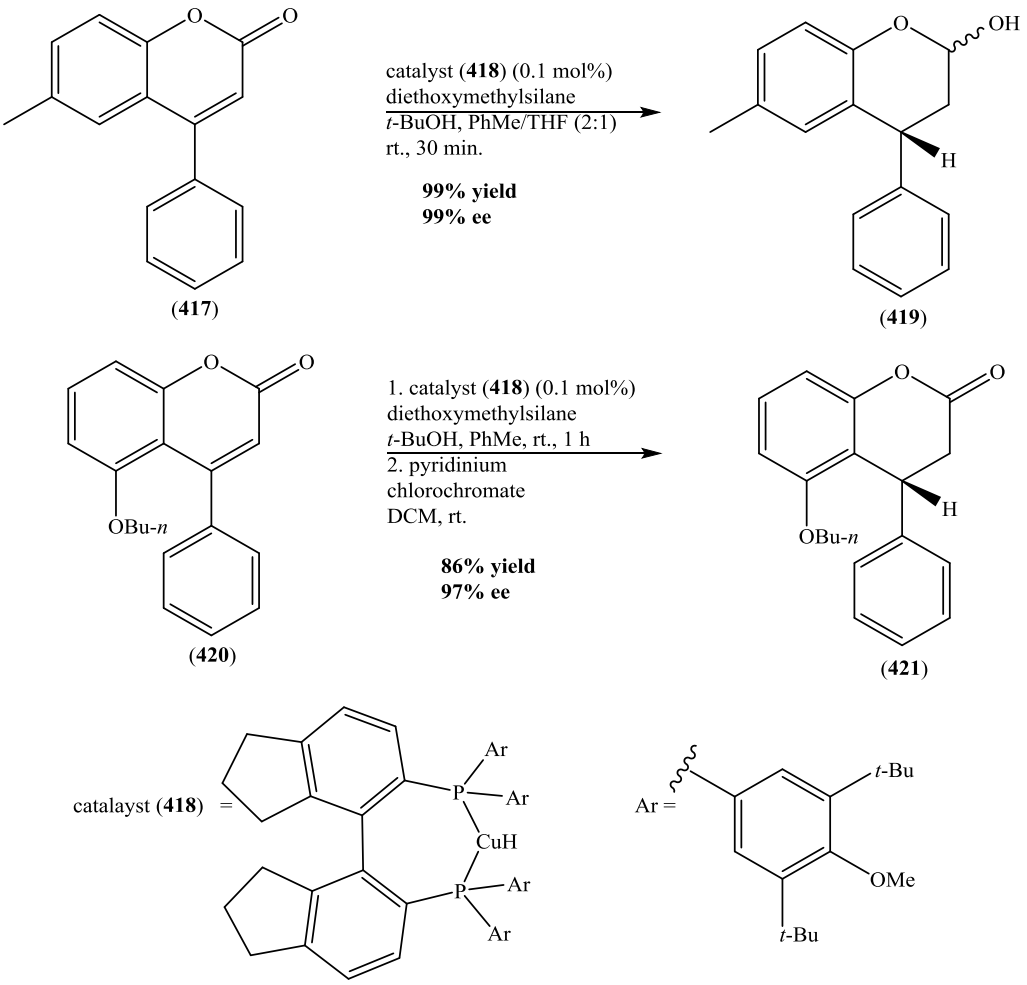
Stereoselective synthesis of 4-phenylchroman-2-ols (neoflavanols) has been achieved *via* a Friedel-Crafts alkylation and cyclisation cascade process wherein phenols or 1-naphthols

(**413**) reacted with α,β-unsaturated aldehydes (**414**) in the presence of organocatalyst (**415**). Good enantioselectivities were achieved over a broad scope of phenols/naphthols but varied with the electronic nature of different aldehydes. Aldehydes bearing electron donating groups generally led to lower yields and enantioselectivities (68 – 79% yield, 80 – 82% ee) while electron withdrawing groups led to high yield and enantioselectivities (73 – 93% yield, 84 – 90% ee) (Scheme 2.99).[252]



Scheme 2.99 Stereoselective neoflavonol synthesis

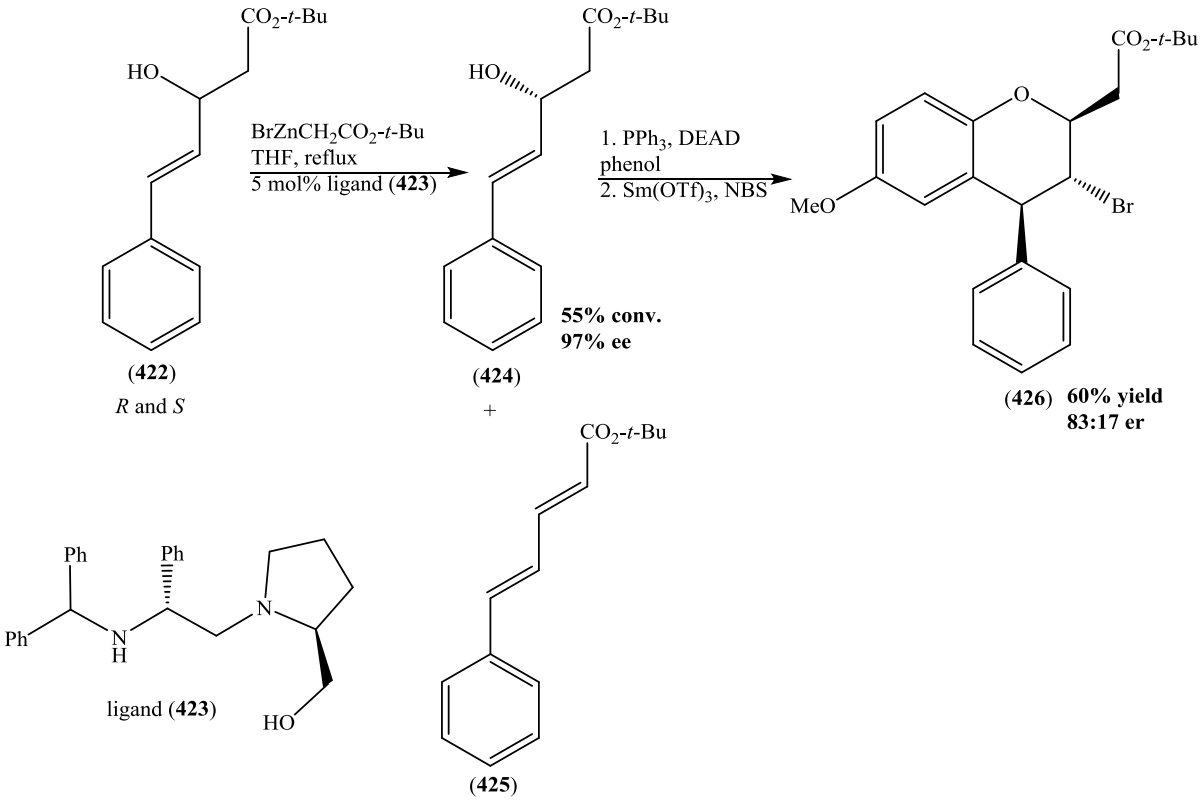
Gallegher *et al.*[253] developed a process for the asymmetric reduction of 4-arylcoumarins (**417**) and (**420**) to neoflavanols (**419**) and neoflavanones (**420**), respectively, in the presence of a chiral copper catalyst (**418**) with exceptional yields and enantioselectivities being achieved (Scheme 2.100).



Scheme 2.100 Asymmetric reduction of 4-arylcoumarins

2.4.10 Neoflavans

Stereoselective synthesis of neoflavonoids has been achieved through an asymmetric dehydration of racemic *tert*-butyl 3-hydroxy-5-phenylpent-4-enoate (**422**) to provide the dienoate (**425**) together with the desired *R*-enantiomer of *tert*-butyl 3-hydroxy-5-phenylpent-4-enoate (**424**) in 37% yield. Subsequent etherification of the latter (**424**) with phenol under Mitsunobu conditions, followed by bromoarylation led to the formation of 4-phenylchroman (**426**) in 60% yield and 83:17 er (Scheme 2.101).[254]



Scheme 2.101 Stereoselective neoflavan synthesis

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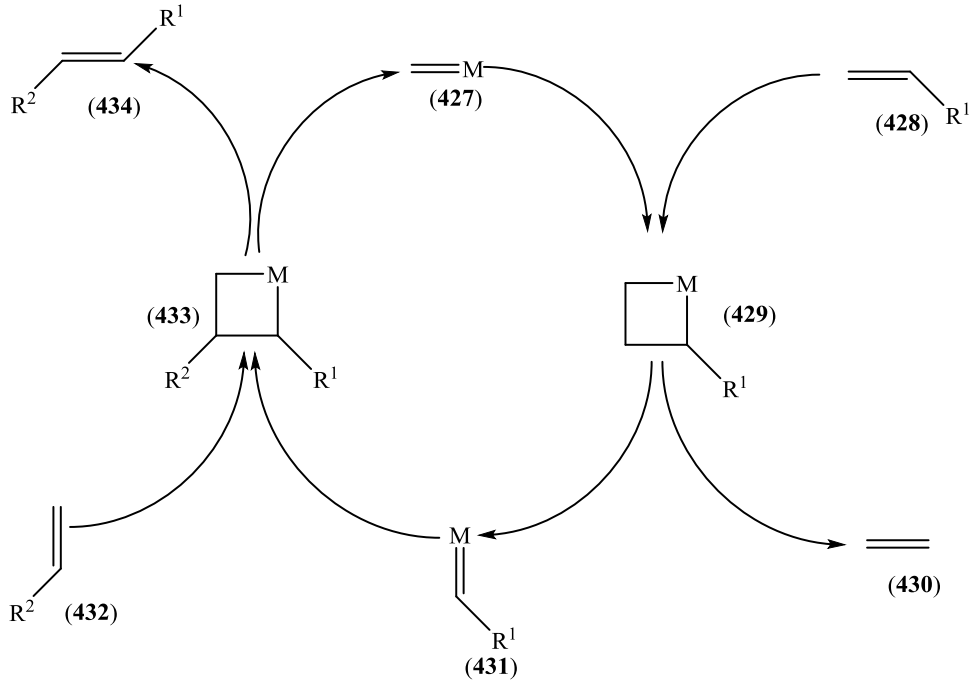
Chapter 3: Metathesis

Introduction

Olefins are vital functional groups both in terms of their prevalence in natural products and in organic synthesis as they can be modified quite readily into a vast array of other functional moieties. Olefin metathesis has become an integral part of modern organic chemistry synthesis since its discovery in the 1950's and it has enabled revolutionary advances in chemical biology,[1] medicinal chemistry[2] and materials science.[3] This led to Nobel Prize awards in Chemistry to the pioneers in the field, Robert H. Grubbs, Yves Chauvin and Richard R. Schrock, in 2005.[4]

3.1 Mechanism

Olefin metathesis is based on the redistribution of alkene fragments through the cleavage and regeneration of carbon-carbon double bonds. Hérisson and Chauvin[5] originally proposed the widely accepted catalytic cycle in 1971 (Scheme 3.1).

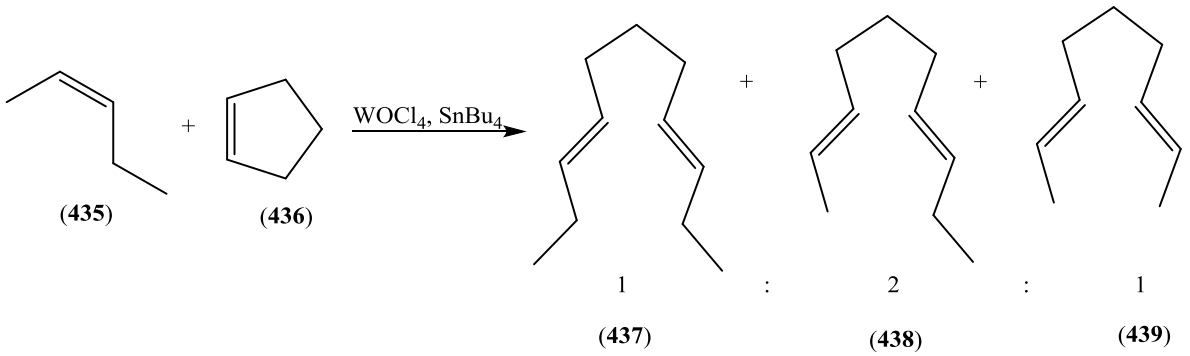


Scheme 3.1 Metathesis mechanism

According to the Chauvin metathesis mechanism, the reaction proceeds *via* a [2+2] cycloaddition of an olefin (**428**) and a transition metal carbene (**427**). The resulting metallocyclobutane intermediate (**429**) then undergoes [2+2] cycloreversion, generating

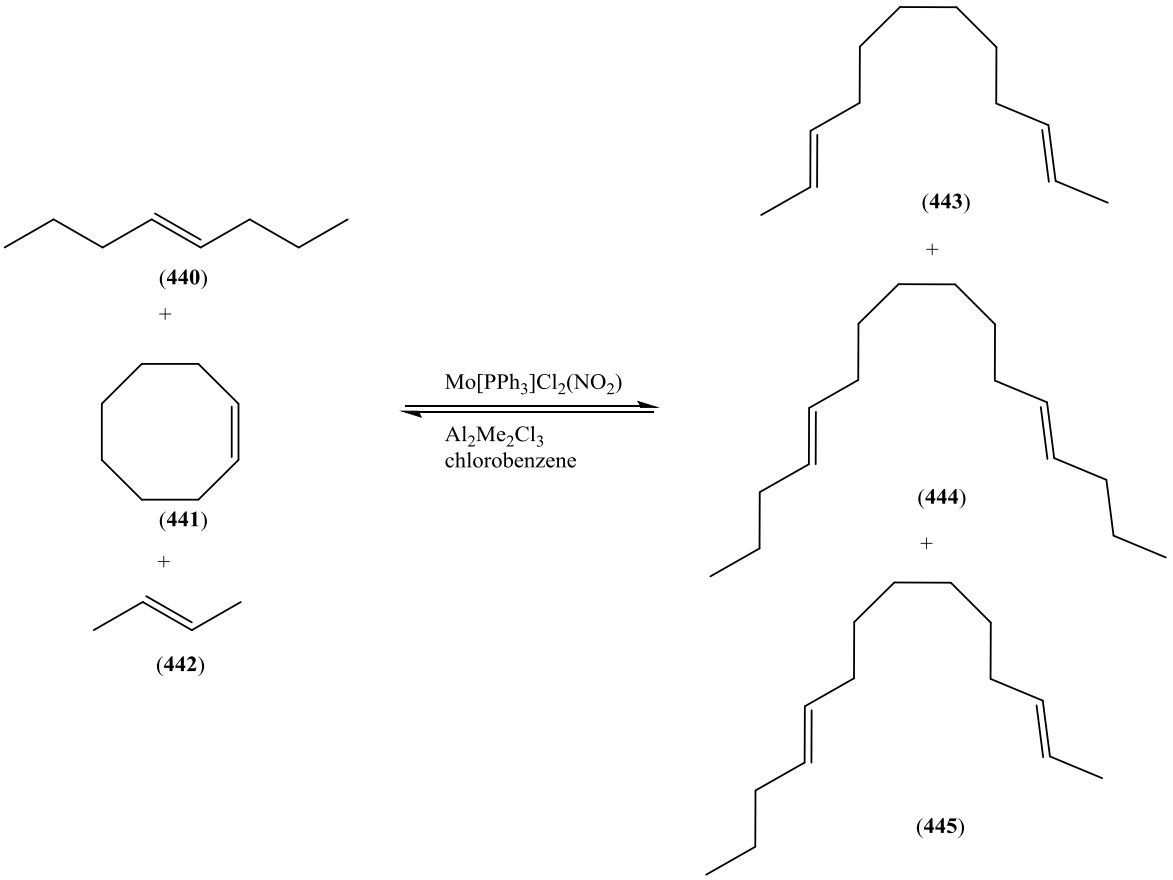
either the original (degenerative metathesis) or a new (productive metathesis) metal alkylidene (**431**) together with the original or metathesized alkene [ethylene (**430**) in the case of a terminal alkene]. The newly formed metal carbene (**431**) reacts with another olefin (**432**) in the same manner to release the product (**434**) and an active metal carbene species (**427**). This process is, like most organic reactions, thermodynamically controlled.[6]

Chauvin found experimental evidence for the proposed step-wise mechanism based on a reaction of 2-pentene (**435**) and cyclopentene (**436**) in the presence of $WOCl_4$ and $SnBu_4$ and obtained the products (**437**), (**438**) and (**439**) in a 1:2:1 ratio, regardless of conversion (Scheme 3.2).[7,8]



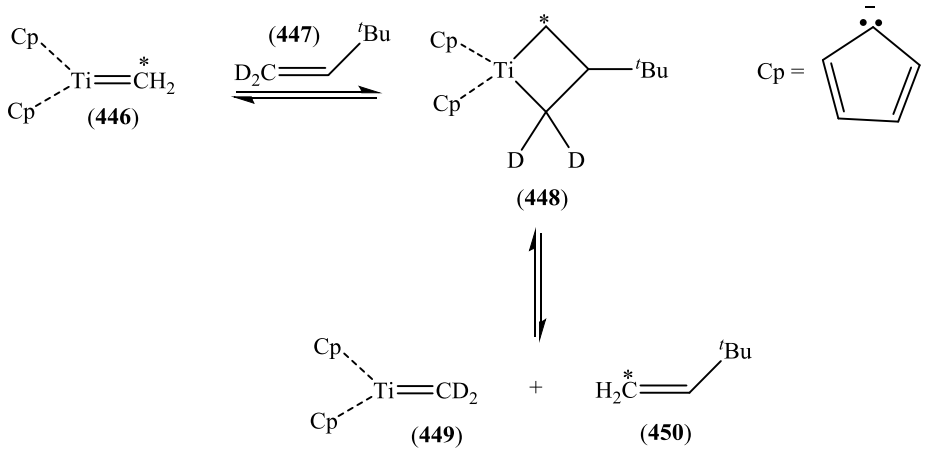
Scheme 3.2 Statistical distribution of metathesis products

In 1975, Katz and McGinnis[9] found additional evidence for the existence of a metallocyclobutane (**429**) intermediate in the mechanism as proposed by Chauvin when they reacted cyclooctene (**441**), but-2-ene (**442**) and oct-4-ene (**440**) in the presence of a molybdenum catalyst and found the C_{16} product (**444**) to be present from the start (Scheme 3.3).



Scheme 3.3 Metathesis by the Katz group[9]

Finally, Grubbs *et al.* [10,11] provided further support for the metallocyclobutane intermediate (**448**) in the mechanism proposed by Chauvin through the utilization of ^{13}C and deuterium labelling of the metal carbene (**446**) and alkene (**447**) (Scheme 3.4), respectively, although they did not rule out the possibility of a 5-membered 4-carbon intermediate.



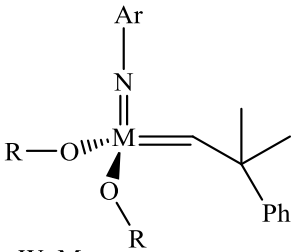
Scheme 3.4 Confirmation of metathesis mechanism by Grubbs

3.2 Metathesis catalysts

Since the discovery of the metathesis reaction, the drive toward developing effective and stable catalysts has led to research focusing on a vast array of transition metal complexes including Mo, Ru, Re, W, Os, Ir, V, Ti, Co, Cr, Ta, Rh and Nb. While initial investigations utilised Lewis acid co-catalysts such as Et_2AlCl_2, R_3Al, R_3AlCl_2 and R_4Sn (R = Me, Et, Bu, Ph), promoters like EtOH, or PhOH or other compounds containing oxygen, have also been utilised extensively.[12] In early developments, tungsten and molybdenum appeared to be the most suitable metals, but difficulties in obtaining an active but stable alkylidene catalyst, hampered the utilization of metathesis reactions in many organic synthesis processes.[12,13]

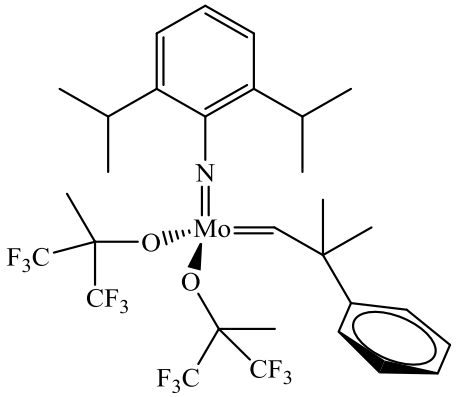
3.2.1 Tungsten and molybdenum carbene complexes

The first well-defined catalysts capable of giving high turn-over numbers were developed by Schrock and co-workers[13,14,15] when they constructed tungsten and molybdenum imido alkylidene complexes with general formula [$M(=CHCMe_2Ph)(=N\text{-}Ar)(OR)_2$, with R a bulky group] and found these compounds to be quite stable [e.g. (**451**) Fig. 3.1].[14,15] A molybdenum version containing two hexafluoro-*tert*-butoxy groups is currently widely known as the Schrock metathesis catalyst (**452**) (Fig. 3.1) and finds application in reactions where high reactivity is required, while it also reacts well with both terminal and internal alkenes. Being highly oxophilic, the molybdenum metal centre, however, renders this catalyst, similar to others based on early transition metals, highly sensitive to moisture and oxygen. The Schrock-type catalysts have limited functional group tolerance and is incompatible with aldehydes and alcohols, for example.[16]



M = W, Mo
Ar = 2,6-diisopropylphenyl
R = *t*-Bu, $C(CH_3)_2CF_3$

(**451**)

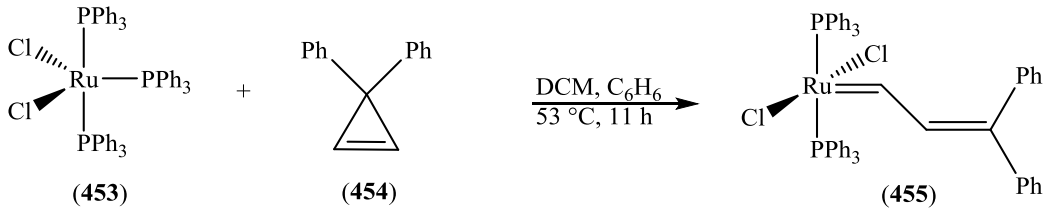


(**452**) Schrock

Figure 3.1 First stable Mo and W metathesis catalysts

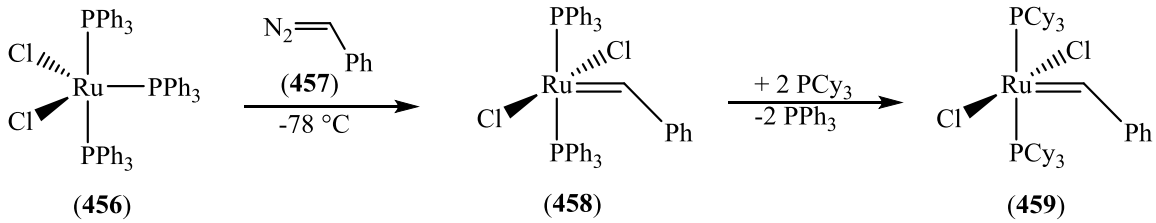
3.2.2 Ruthenium based catalysts

While Schrock and collaborators were focussing on the utilization of tungsten and molybdenum in metathesis catalysts, Grubbs became active in the field as well and developed ruthenium based catalysts.[17,18] The first active ruthenium based metathesis initiator, vinylidene $(PPh_3)_2Cl_2Ru{=}CH{-}CH{=}CPh_2$ (**455**), was prepared from 3,3-diphenylcyclopropene (**454**) and $RuCl_2(PPh_3)_3$ (**453**) (Scheme 3.5). This catalyst proved to be active towards living ring opening metathesis polymerisation (*vide infra*, par. 3.4.4) of norbornene[17] and other highly strained cyclic olefins.[19] It also showed exceptional stability in the presence of acids, water and a wide variety of functional groups.[16]



Scheme 3.5 Synthesis of 1st active ruthenium-based metathesis catalyst

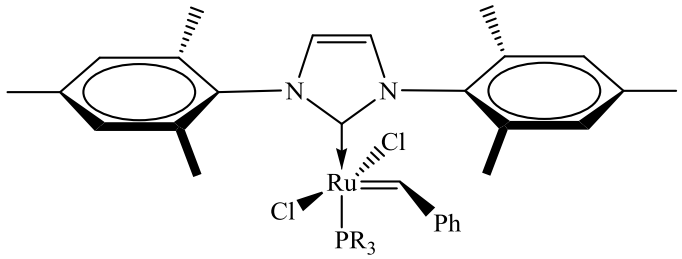
Further research toward Ru-based metathesis catalysts were centered on the development of complexes that could initiate the metathesis of acyclic and low-strain cyclic compounds.[19] When the PPh_3-groups were replaced by PCy_3 (Cy = cyclohexyl) entities in 1992, this catalyst was found to initiate the metathesis of *cis*-2-pentene.[16,19] During subsequent years, the Grubbs group[20,21] investigated processes towards more accessible ruthenium-based metathesis catalysts suitable for commercial scale production. Phenyldiazomethane (**457**) was utilised in the initial synthesis step with $Cl_2Ru(PPh_3)_3$ (**456**) to produce a ruthenium-benzylidene complex (**458**) at -78 °C. Subsequent phosphine exchange with PCy_3 produced an active catalyst (**459**) in high purity (> 95%) and yield (> 90%) (Scheme 3.6). This catalyst, which became known as the Grubbs 1st generation catalyst, demonstrated the capacity to initiate metathesis in the presence of most functional groups (amines, nitriles and basic media excluded).[22] It is readily available due to a viable large-scale production and commercialisation and has become one of the 'workhorse' metathesis catalysts.[16, 23]



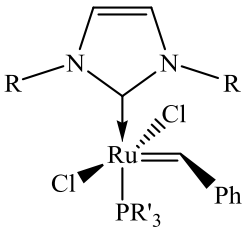
Scheme 3.6 Synthesis of Grubbs I catalyst

Ruthenium based metathesis catalysts soon proved to be the most versatile when compared to the titanium, molybdenum or tungsten counterparts due to their higher reactivity to C-C double bonds and tolerance towards most other functional groups.[23]

In 1999, the groups of Nolan,[24] Grubbs[25] and Hermann[26] reported on the synthesis of heteroleptic catalysts (Fig. 3.2) with one phosphine and one *N*-heterocyclic carbene (NHC) ligand.[27] These heteroleptic catalysts benefitted from the lability of the phoshine group, stabilisation of both the pre-catalyst and active catalyst through σ-donation from the NHC to the metal and steric protection of the metal center by the NHC.



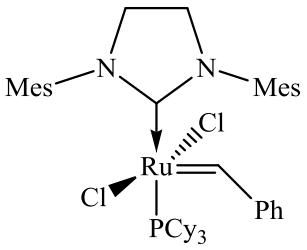
(**460a**) R = cyclohexyl
(**460b**) R = Ph



(**461a**) R *t*-Bu, R' = Ph
(**461b**) R, R' = cyclohexyl
(**461c**) R = 4-Me-C_6H_4 R' = cyclohexyl
(**461d**) R = 4-Cl-C_6H_4, R' cyclohexyl

Figure 3.2 Heteroleptic catalysts

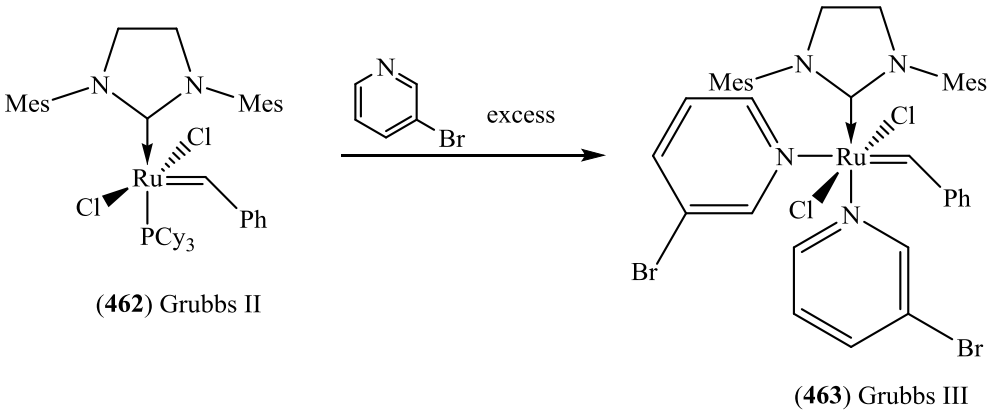
These first reports on the synthesis of heteroleptic catalysts led to one of the most significant breakthroughs in the field of alkene metathesis. Being mindful of the stabilising effect of NHC ligands, Grubbs[25] discovered that catalyst (**462**) containing the NHC ligand with a saturated skeleton displayed even higher activity compared to its unsaturated counterpart (**460a**). It is currently widely known as the Grubbs 2nd generation catalyst.[23] Not only has this catalyst proven to be air and water tolerant, but it also has a tolerance for a wide variety of functional groups and expanded the scope of ruthenium based metathesis catalysts to RCM (*vide infra* par. 3.4.1) of sterically hindered dienes, ROMP (*vide infra* par. 3.4.4) of low strain compounds and various CM reactions (*vide infra* par. 3.4.2).[28]



(**462**) Grubbs II

Figure 3.3 Grubbs II catalyst (Mes = 1,3,5-trimethylbenzyl)

Replacement of the phosphine in (**462**) with two 3-bromopyridine ligands resulted in a catalyst which is 10^4 times more active than the Grubbs 1st generation catalyst and has since become known as the Grubbs 3rd generation catalyst (**463**).[27,29]

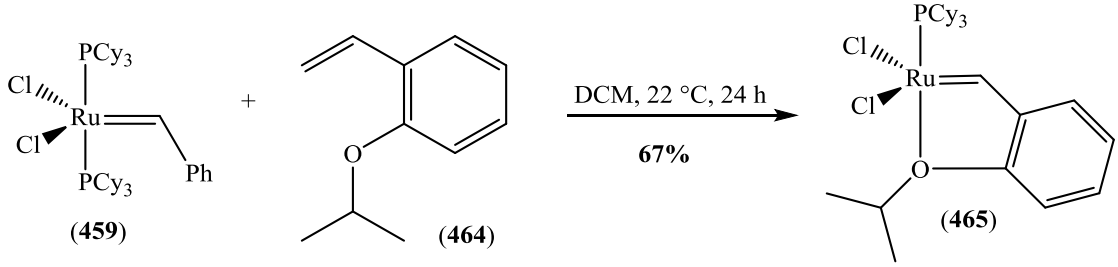


(**462**) Grubbs II

(**463**) Grubbs III

Scheme 3.7 Synthesis of Grubbs III catalyst

Another evolution in catalyst stability came from the Hoveyda group[30] who reported on the synthesis of a ruthenium isopropoxystyrene chelate complex (**465**) utilising the Grubbs 1st generation catalyst (Scheme 3.8). This 1st generation Hoveyda-Grubbs catalyst displayed astonishing stability and could be recycled *via* column chromatography and stored in chloroform for *ca.* 2 weeks without any significant decomposition.[27]

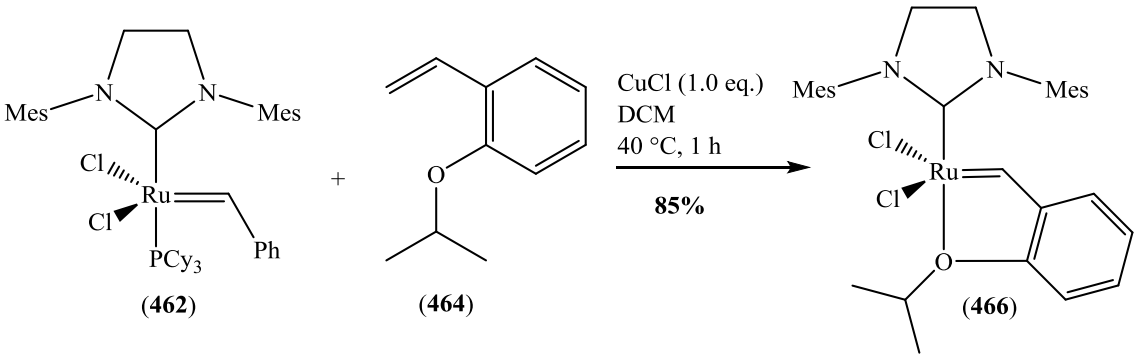


(**459**) (**464**) (**465**)

Scheme 3.8 Synthesis of 1st generation Hoveyda-Grubbs catalyst

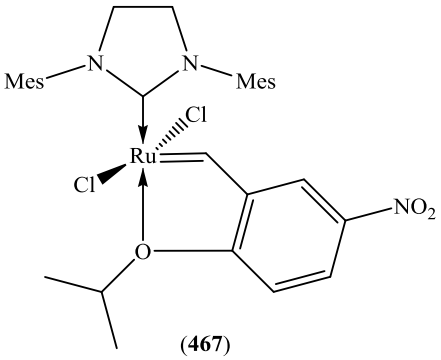
However, metathesis in the presence of this catalyst proceeded extremely slowly and the Hoveyda group postulated that the increased stability of the ruthenium chelate is accompanied by decreased activity.[27]

Subsequent research on what was to become known as the 2nd generation Hoveyda-Grubbs phosphine free catalyst (**466**) (Scheme 3.9), a catalyst with NHC as well as chelating *ortho*-isopropoxy benzylidene ligands, was published nearly simultaneously by Hoveyda[30,31] and Blechert.[27,32] Due to its high stability, the Hoveyda-Grubbs 2nd generation catalyst (**466**) gained popularity even though it is a slower metathesis initiator than the Grubbs II catalyst.[28] The Hoveyda-Grubbs 2nd generation catalyst proved to be highly efficient in cross metathesis (*vide infra*, par. 3.4.2) and the ring closing metathesis (*vide infra*, par. 3.4.1) of trisubstituted alkenes.



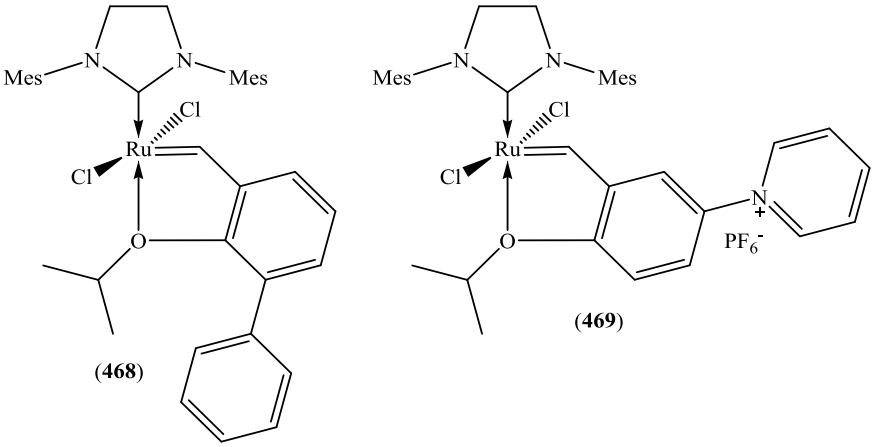
Scheme 3.9 Synthesis of 2nd generation Hoveyda-Grubbs catalyst

Another approach toward catalyst design entails the introduction of substituents on the benzylidene moiety. Grela and co-workers[33] improved upon the catalytic activity of the Hoveyda-Grubbs (**466**) catalyst by introducing the strongly electron withdrawing nitro moiety to the isopropoxy benzylidene ligand (Figure 3.4) in order to obtain an electronically destabilized metal-ether bond. Blechert's group[34] introduced a phenyl group to the benzylidene ligand to achieve a sterically destabilized ruthenium-ligand bond (Figure 3.5). This type of catalyst has since evolved into other forms as well.[6,32] An ammonium group, for example, has been introduced to render (**469**) soluble in water, thus allowing for easier removal of the catalyst *via* liquid-liquid extraction after completion of the reaction.[6,35]



(**467**)

Figure 3.4 Grela's[33] new metathesis catalyst

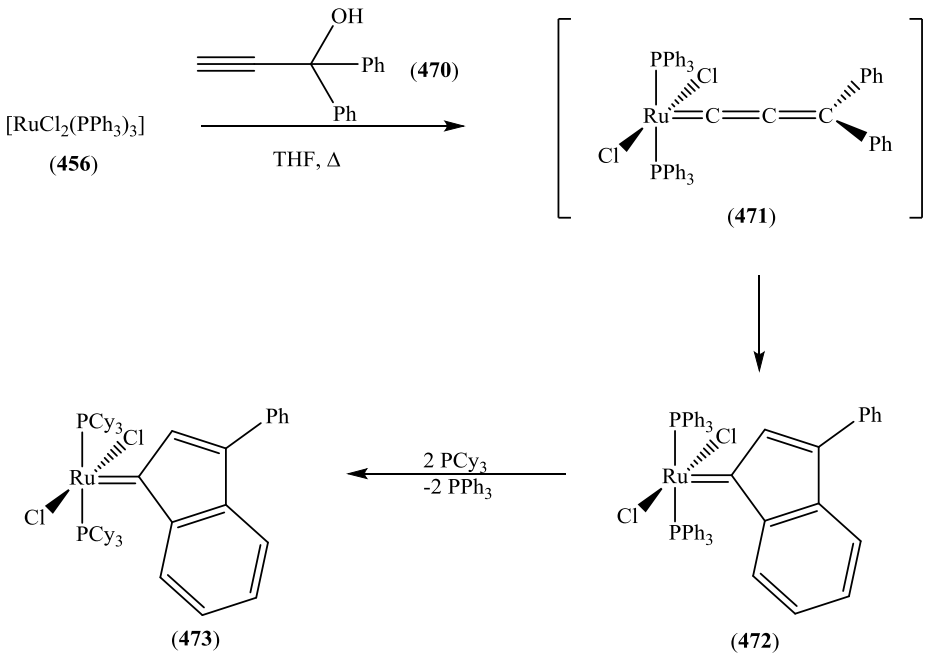


(**468**) (**469**)

Figure 3.5 New benzylidene substituents by Blechert *et al*.[34]

Fürstner[36,37] and Nolan[38,39] constructed indenylidene complexes (**473**) and (**474**), respectively. These complexes are easy to prepare (Scheme 3.10) and are reported to be robust catalysts.[6, 23,36] Indenylidene catalysts contributed mostly to the synthesis of polymer materials and are especially efficient for ROMP (*vide infra*, par. 3.4.4) due to their tolerance for various functional groups and ability to effect copolymer synthesis.[6,27]

Furthermore, indenylidene catalysts such as (**474**) (Fig 3.6) was prepared as alternative to benzylidene catalysts and widely applied to natural product synthesis. These catalysts displayed superiority to their benzylidene counterparts regarding thermal stability and showed good activity and selectivity, but require higher temperature than their benzylidene analogues to effect initiation.[23,40]



Scheme 3.10 Ru-indenylidene metathesis catalyst synthesis

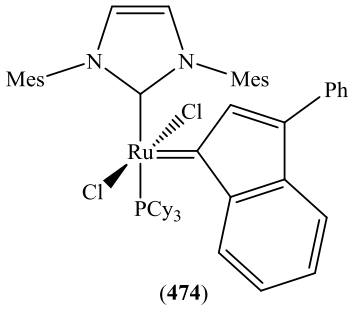
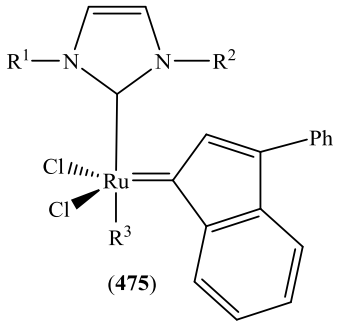


Figure 3.6 Ru-indenylidene catalyst containing NHC ligand

Interestingly, Ru-indenylidene catalysts such as (**474**) (Fig. 3.6) containing the NHC and PCy_3 ligands have also proven effective for the synthesis of tetrasubstituted cycloalkenes *via* RCM (*vide infra*, par. 3.4.1) of the corresponding diene precursor molecules – a process that is usually not possible or severely restricted with diphosphane ruthenium alkylidene catalysts due to their limited thermal stability and tolerance toward functional groups especially in highly substituted olefins.[40]

Recently, research was published on a series of metathesis catalysts (Fig. 3.7) featuring a less sterically hindered NHC entity than found in the conventionally utilised Grubbs 2nd generation catalyst. Known as the Apeiron catalysts, these compounds proved to be effective in RCM (*vide infra*, par 3.4.1) for the synthesis of tetrasubstituted olefins.[41] Even though the synthesis of tetrasubstituted olefins *via* RCM has been reported,[40,42,43] these catalysts can be

utilised at a lower loading and shows higher stability. Interestingly, an unexpectedly high rate of initiation has been observed despite their stability.[41,44]

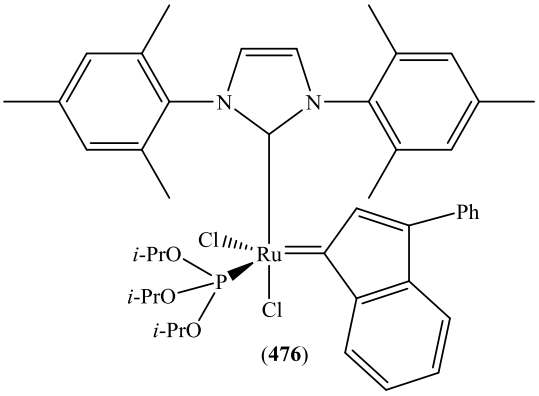


(**475**)

$R^1 = R^2$ = 2-methylbenzene, 2,5-dimethylbenzene
R^3 = pyridine, PCy_3, PPh_3

Figure 3.7 Apeiron catalyst series

Cazin[45] patented a catalyst wherein the phosphine ligands present in Grubbs type catalysts are replaced with phosphite moieties (Fig. 3.8). This variation leads to a more stable catalyst taking advantage of the increased π-acidity of the phosphite entities and shows the same or higher activity than Grubbs type catalysts.[41]



(**476**)

Figure 3.8 Phosphite containing catalyst

Recently patented metathesis catalysts feature ligation *via* nitrogen, a halogen or sulfur. This ligation allows for modification of catalyst properties such as stability, activity and sensitivity to additives and temperature.[41] For example, the initiation rate of catalyst (**477**) with bis-ligation *via* an imine and ester can be tuned by the temperature or additives such as TMSCl and HCl,[46] while ligation with bromine or iodine affords catalysts (**478**) which are highly sensitive to temperature and are able to catalyse the ene-yne metathesis of highly hindered substrates.[47] The sulfur-containing catalysts [e.g. (**479**)] show modest activity toward RCM

(*vide infra*, par. 3.4.1). However, their reactivity can be enhanced by BCl_3 co-catalysis and these complexes are especially useful in rubber depolymerisation.[48]

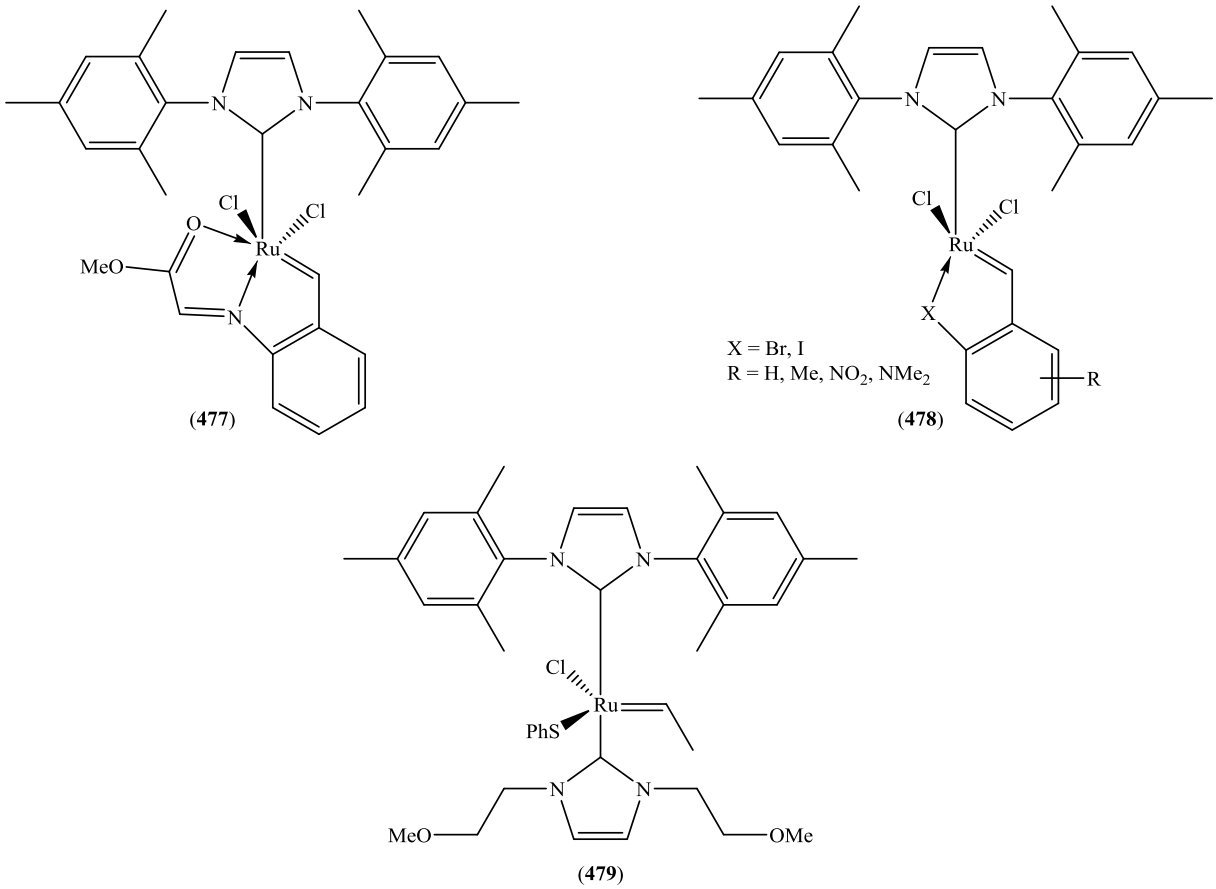
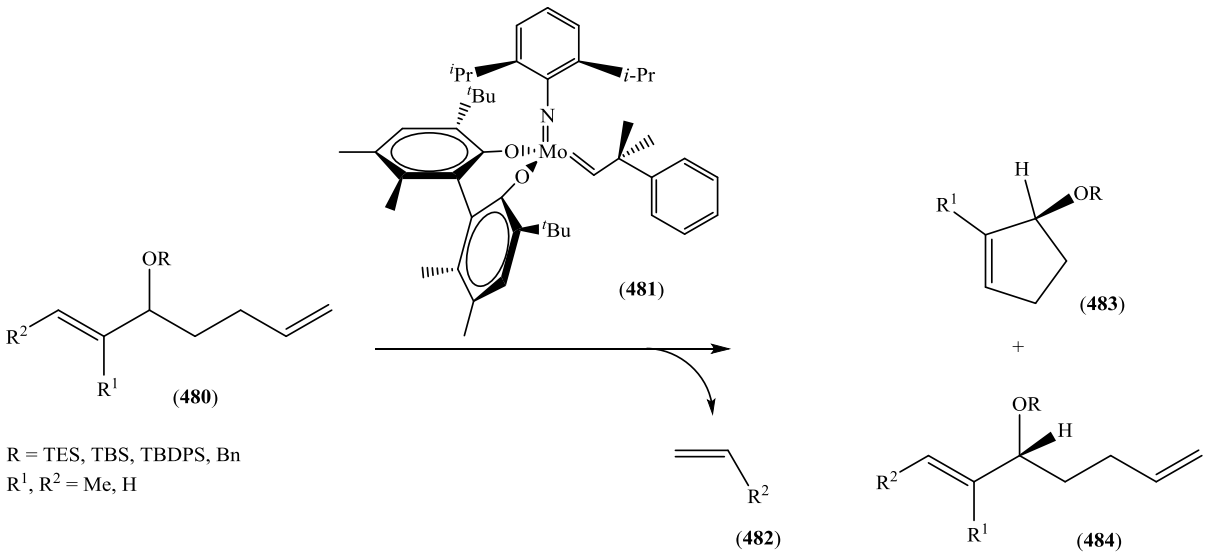


Figure 3.9 Catalysts with ligation *via* nitrogen, oxygen, sulfur or halogens

3.3 Stereoselective metathesis reactions

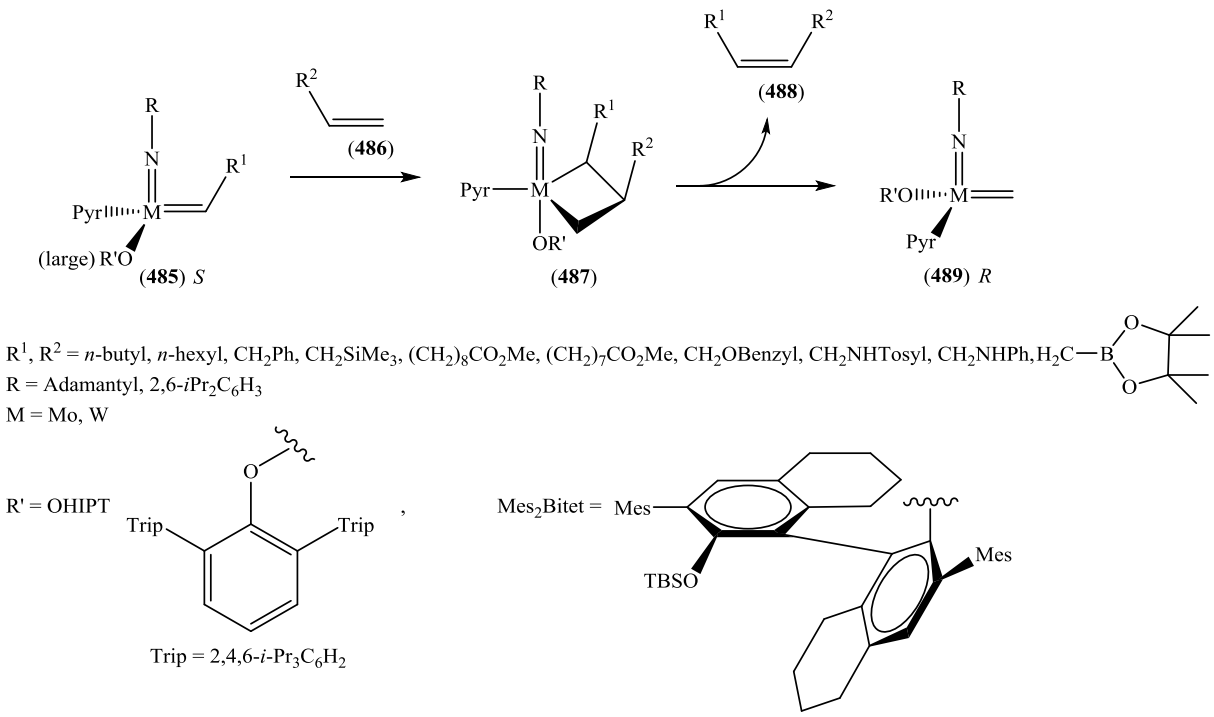
Although major advances have been achieved in the past few decades with respect to olefin metathesis, issues on stereoselectivity were left to thermodynamic preferences and the notable drawback of olefin metathesis is the predominant formation of *E*-olefins.[49] An effective solution to this issue required the development of novel catalysts that are structurally distinct from previously utilised molecules.

Hoveyda and co-workers[50,51] first reported on the development of a chiral molybdenum catalyst (**481**) which allows 1,6-dienes that bear a siloxy or alkoxy moiety to yield either the recovered non-racemic diene (**484**) or cycloalkenyl product (**483**) *via* asymmetric ring closing metathesis (ARCM) (*vide infra*, par. 3.4.1) in > 90% ee, depending upon the level of alkene substitution (Scheme 3.11).



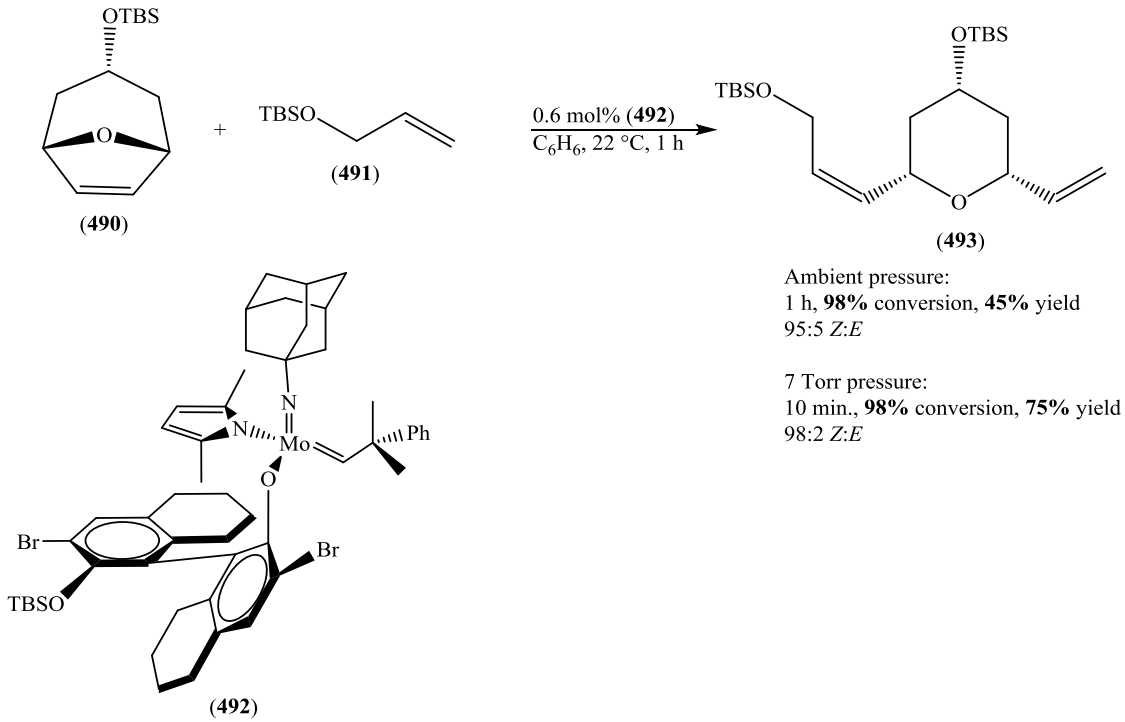
Scheme 3.11 Enantioselective ring closing metathesis with chiral Mo-complex

However, active catalysts promoting *Z*-selectivity were only discovered in 2009.[52] The Schrock group[53,54] developed a new class of Mo and W monoaryloxide pyrrolide (MAP) metathesis catalysts [e.g. (**485**)] for *Z*-selective homo-coupling of olefins. In this process, the olefin preferentially binds to the catalyst in a *trans* configuration with respect to the pyrrolide (pyr) ligand with the R^1 and R^2 groups facing away from the axial bulky OR' moiety, thus leading to *Z* alkenes (**488**) (Scheme 3.12).



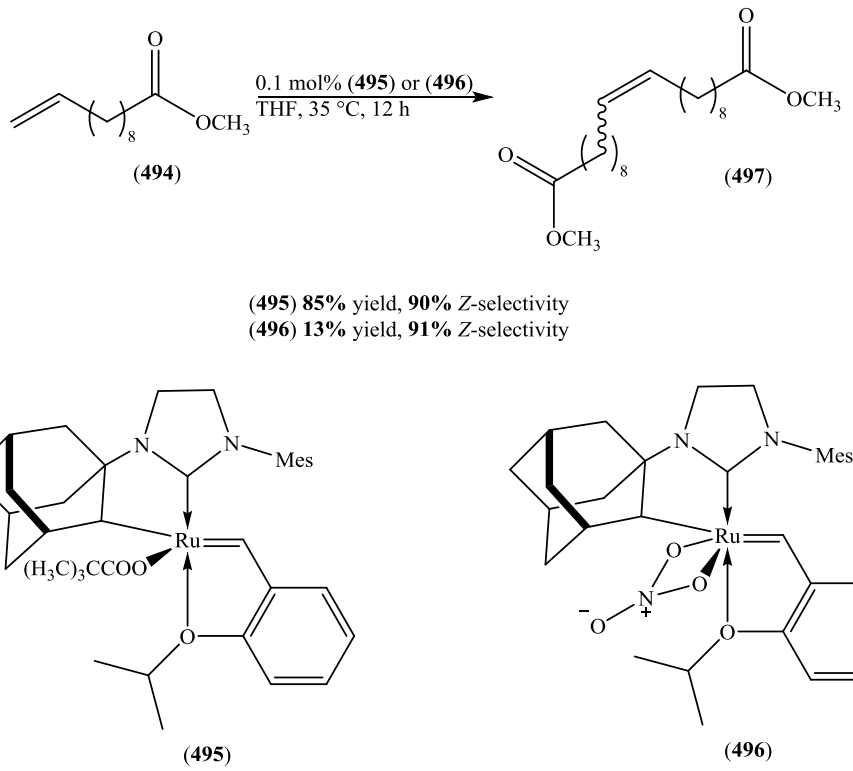
Scheme 3.12 *Z*-selective metathesis catalysts

With this new technology they were able to obtain the desired homo-metathesis products in variable conversions (33 – 88%) and moderate to high *Z*-selectivity (68 – 98%). Soon afterwards, this protocol was extended to ring opening cross metathesis (ROCM) (*vide infra*, par. 3.4.3) reactions based on a similar molybdenum catalyst (**492**) containing an adamantylimido moiety.[49] The beneficial effects of applying vacuum was also demonstrated for this process where reaction time was shortened by 50 minutes and yield improved by 30% (Scheme 3.13).[49]



Scheme 3.13 *Z*-selective ROCM

In 2012, Grubbs *et al.*[55] complemented the work of Schrock by creating ruthenium based, functional group tolerant catalysts suitable for *Z*-selective cross metathesis. They synthesised various C-H activated catalysts [e.g. (**495**) and (**496**)] and screening of these complexes revealed that an adamantyl moiety on the NHC (*N*-heterocyclic carbene) ligand is necessary to effect selectivity, while *ortho*-substitution of the NHC-aryl moiety prevents undesired C-H activation and thus affords stability. They further reported that bidentate ligands leads to increased activity over monodentate ligands and that nitrato-type ligands offers higher stability and activity over carboxylates, with turnover numbers (TON's) of up to 1000 h^{-1} and high *Z*-selectivity (≥ 90%) (e.g. Scheme 3.14).[6]



Scheme 3.14 Ruthenium catalysed *Z*-selective metathesis

In 2016 the Grubbs group[56] published research on the applications of catalyst (**496**) (shown above) and an even more improved catalyst (**497**) (Fig. 3.10) in the homo-dimerization of terminal alkenes containing alcohol and ester functionalities with over 95% *Z*-selectivity and TON's of up to 7400 h^{-1}.[41]

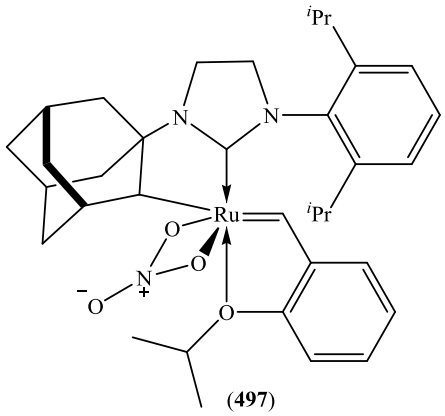
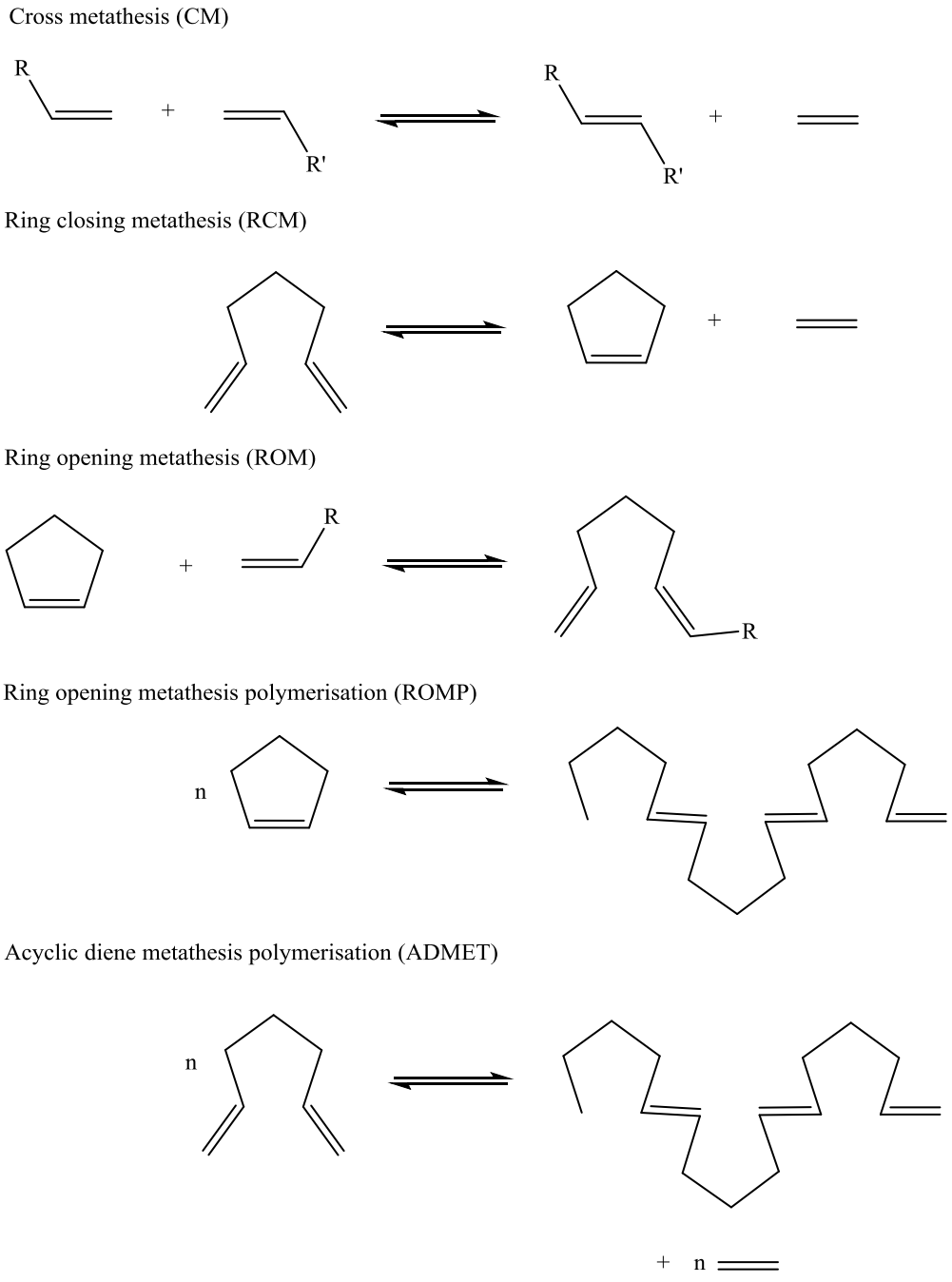


Fig. 3.10 Highly *Z*-selective catalyst by the Grubbs group[56]

3.4 Applications of the metathesis reaction

In its host of reaction paradigms (Scheme 3.15), olefin metathesis has certainly influenced the landscape of organic synthesis more than any other single process within the last two

decades.[57] The wealth of synthesis transformations that has been achieved *via* this reaction is astounding and in the following sections just a few examples thereof are discussed.

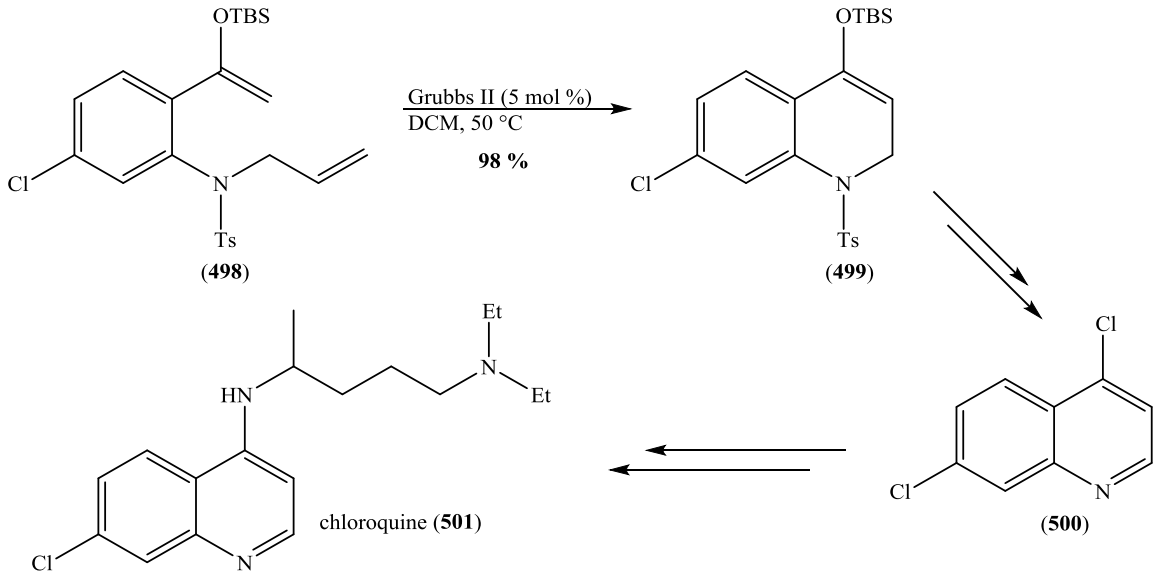


Scheme 3.15 Classes of metathesis reactions

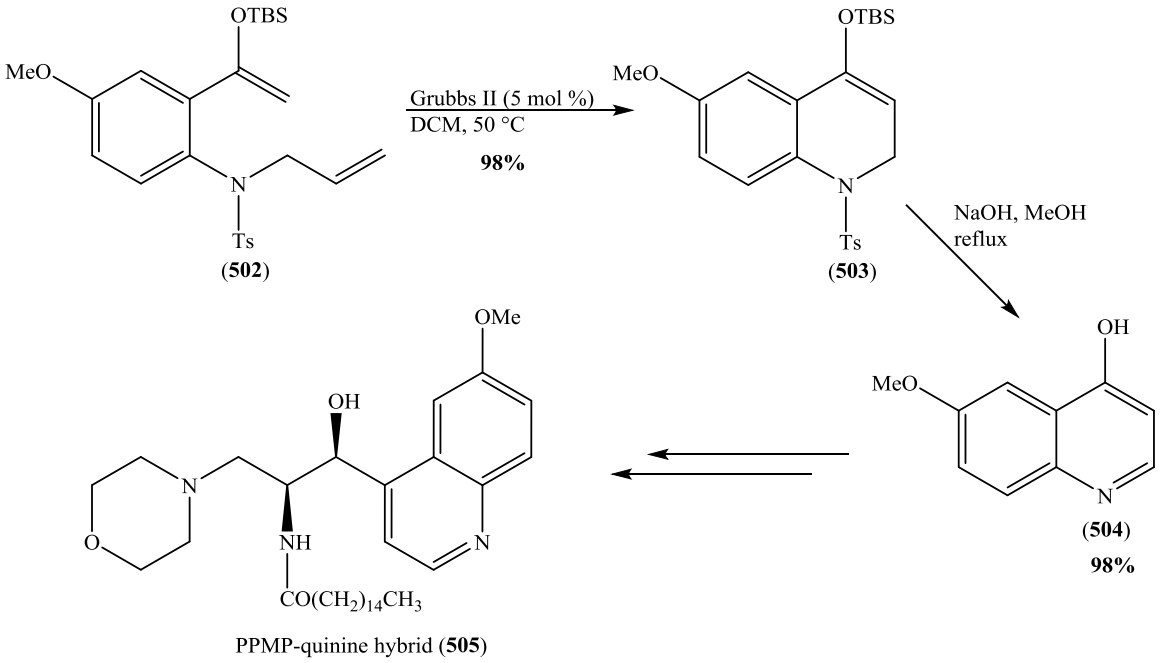
3.4.1 Ring closing metathesis

Access to various natural compounds have been made possible by utilising ring closing metathesis (RCM) and Nishida *et al.*[58] extended the protocol developed by Nakagawa *et al.*[59] in their synthesis of dihydroquinolines to the preparation of various antimalarial drugs such

as chloroquine (**501**) and (PPMP)-quinine (**505**). Utilising standard Grubbs II conditions, the metathesis steps yielded the desired intermediates, both in 98% yield (Scheme 3.16 and 3.17).



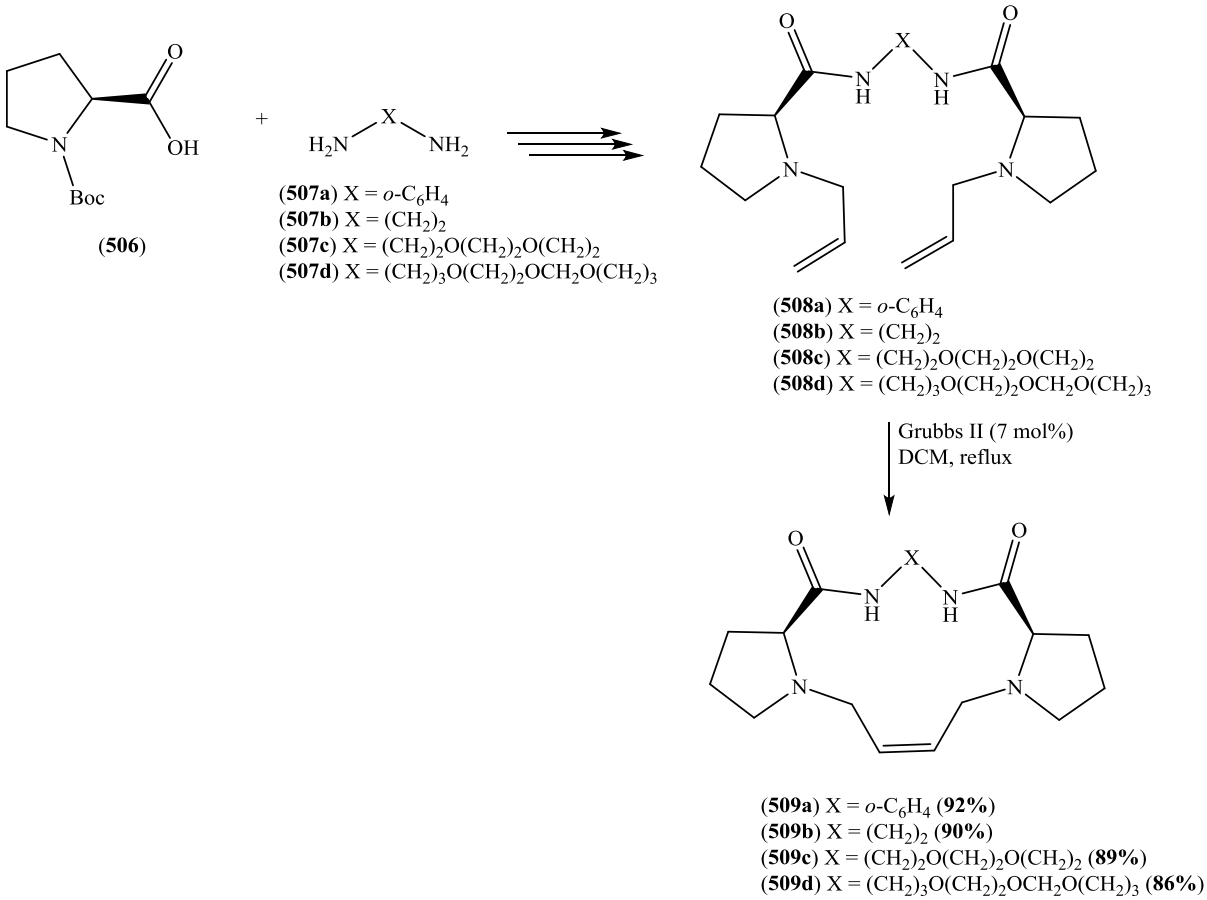
Scheme 3.16 Chloroquine synthesis



Scheme 3.17 PPMP-quinine hybrid synthesis

Another interesting application of RCM is found in the synthesis of macrocyclic compounds, that often exibit antibiotic, antibacterial and cytotoxic properties.[60,61] The Vinodh group[62] recently utilised ring closing metathesis in their synthesis of L-proline based macrolides, which finds application as enantiodiscriminating agents. The target bis-amides (**509a**),

(**509b**), (**509c**) and (**509d**) were prepared by employing the Grubbs II catalyst and were obtained in excellent yield (86 – 92%) (Scheme 3.18).



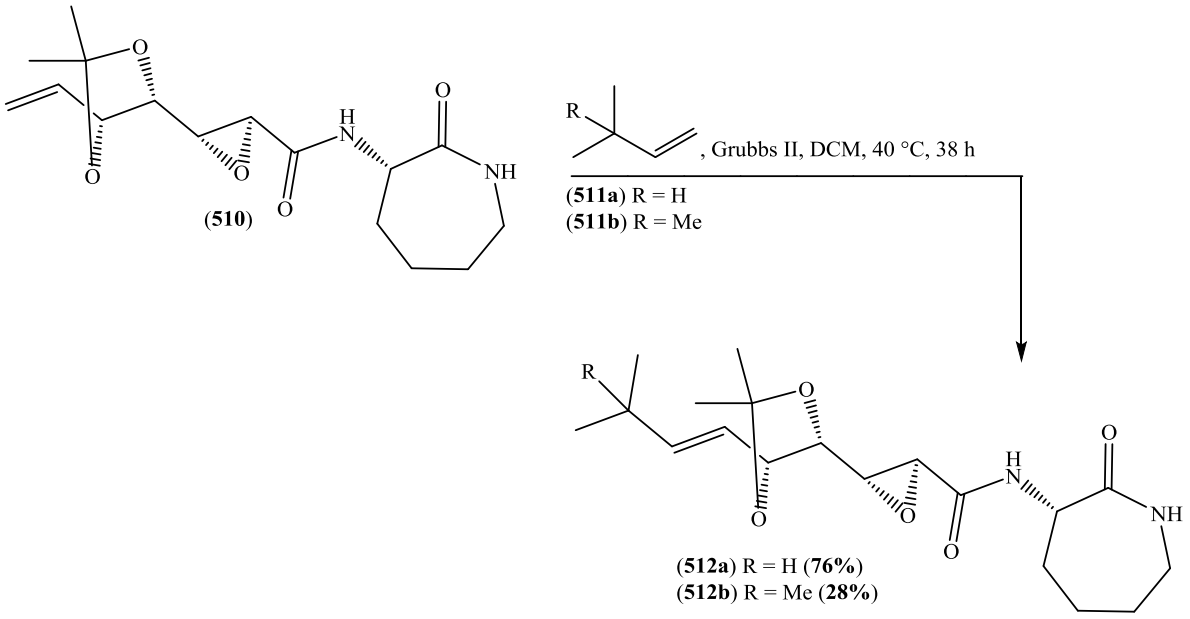
Scheme 3.18 Synthesis of L-proline based macrolides

3.4.2 Cross metathesis

Due to the stereoselectivity difficulties (*cf.* par 3.3) and formation of homo-coupled products that plague the cross metathesis (CM) reaction, it actually emerged later than RCM. Only with the development of advanced second generation Grubbs catalysts, could these challenges be overcome. One of the great advantages of CM over other cross-coupling reactions, such as the Suzuki or Stille couplings, is that preparation of a sophisticated coupling partner is not required in cross metathesis.[63]

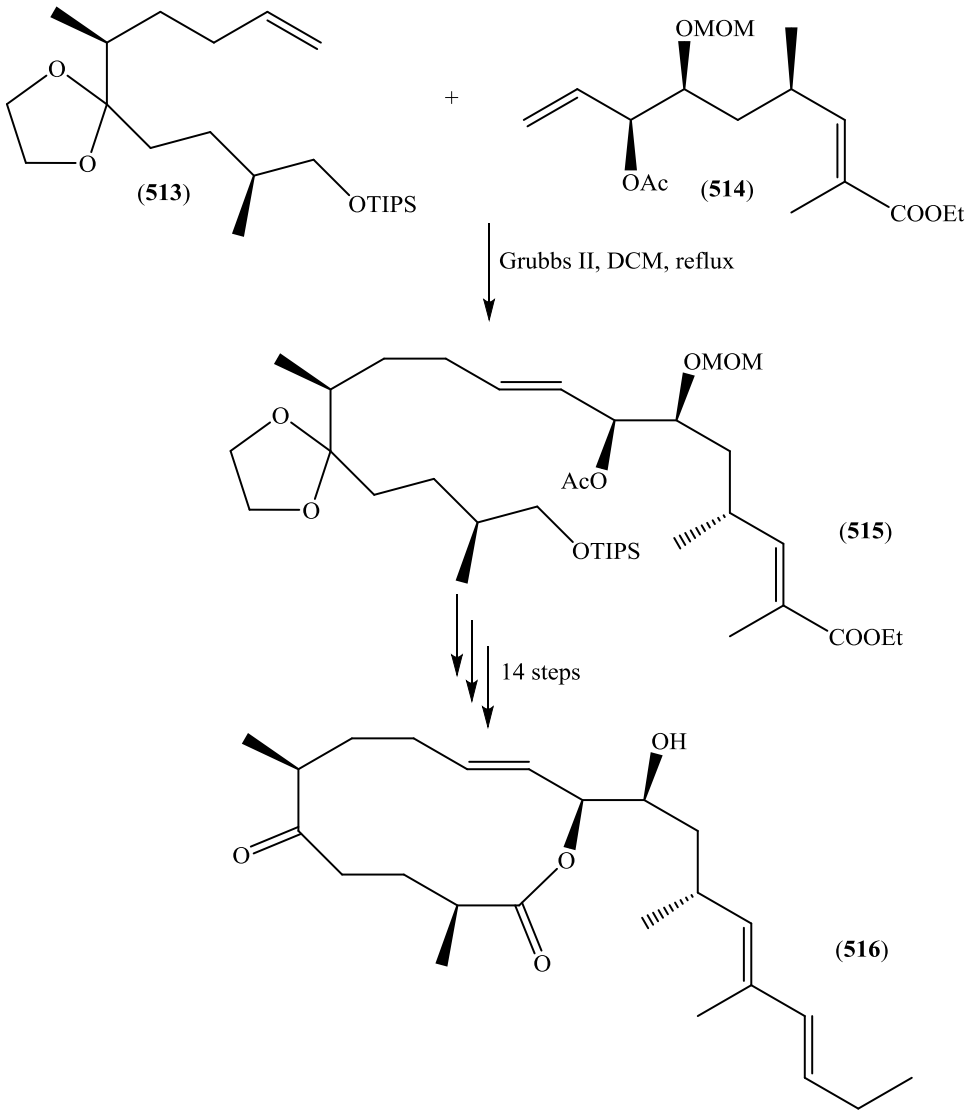
CM between terminal alkenes have found wide application in natural product synthesis[64,65,66,67] and the Sarabia group,[68] for example, utilised CM in their preparation of precursor molecules for bengamides, compounds that exhibit antibiotic, antitumor and antihelmintic properties. Two different alkenes were employed under Grubbs II conditions and while 3-methyl-1-butene (**511a**) led to 76% yield (*E*:*Z* 9:1), the more hindered 3,3-

dimethyl-1-butene (**511b**) gave only 28% (*E*:*Z* 9:1) yield, proving the sensitivity of metathesis to steric bulk (Scheme 3.19).



Scheme 3.19 Bengamide precursor synthesis *via* CM

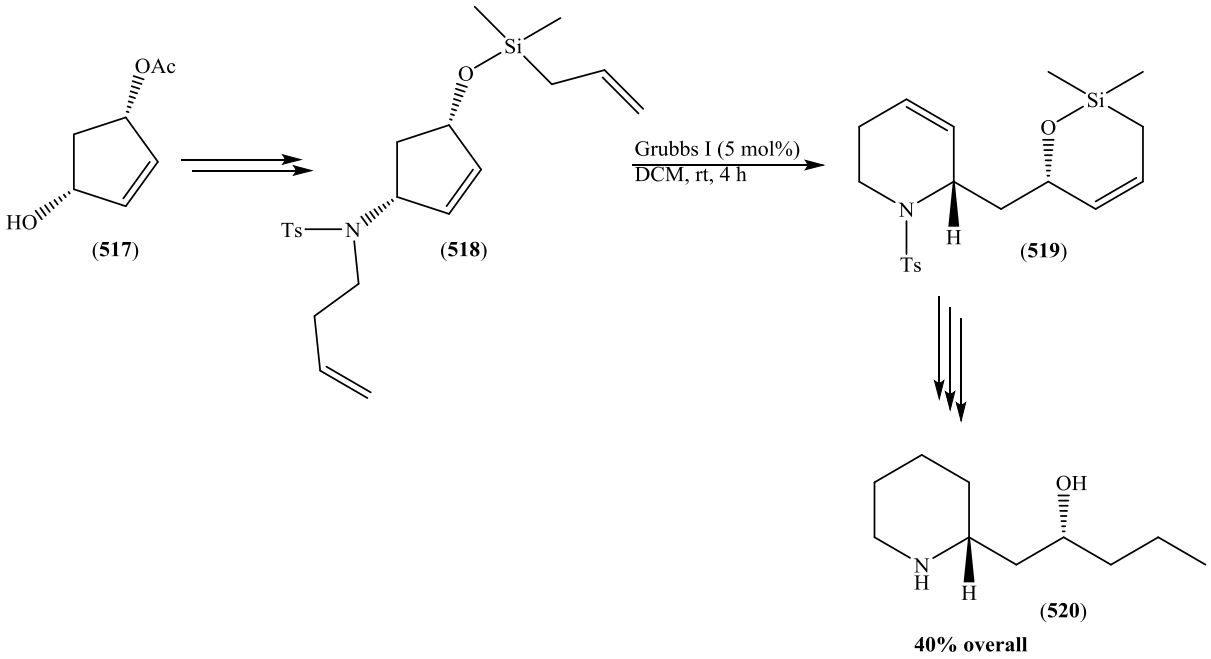
Ghosh and Ghong[69] also employed CM as one of the synthetic steps in their preparation of amphidinolide W (**516**), a cytotoxic 12-membered macrolide. The metathesis methodology was optimised when utilising Grubbs II conditions (DCM, reflux) and an acetate protecting group for the allylic alcohol (**514**) and yielded the precursor compound (**515**) in 85% yield with an *E*:*Z* ratio of 11:1 (Scheme 3.20).



Scheme 3.20 (+)-Amphidinolide W precursor synthesis *via* CM

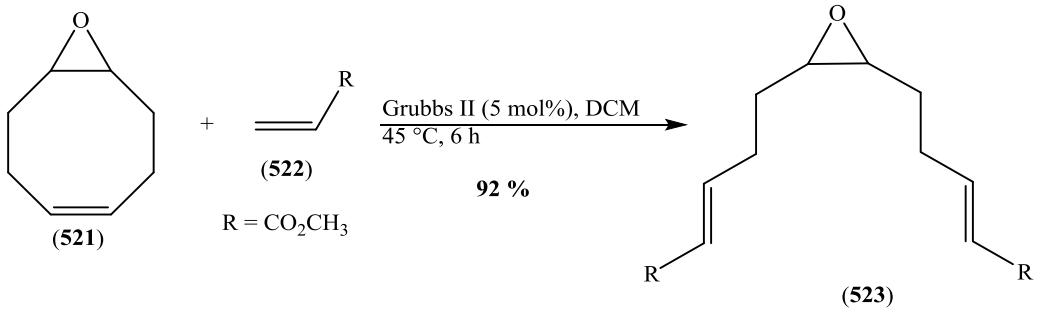
3.4.3 Ring opening metathesis

Ring opening metathesis (ROM) is driven by the release of ring strain and has often been applied to the preparation of polymers through ring opening metathesis polymerisation (ROMP, *vide infra*, par 3.4.4). However, prevention of polymerisation can be achieved when ROM is immediately followed by CM or RCM. As in the synthesis of the alkaloid, (-)-halosaline (**520**), this tandem methodology is an elegant process wherein the stereochemistry of one ring can be transferred to another (Scheme 3.21).[70]



Scheme 3.21 Synthesis of (-)-halosaline

The ROM-CM process of unstrained cycloalkenes have also been studied by Blechert *et al.*[71] It was found that this process takes place under mild conditions and it was concluded that the phosphine free Grubbs II catalyst showed superior reactivity to Grubbs I. An example is shown in Scheme 3.22 where the target compound was obtained in 92% yield.

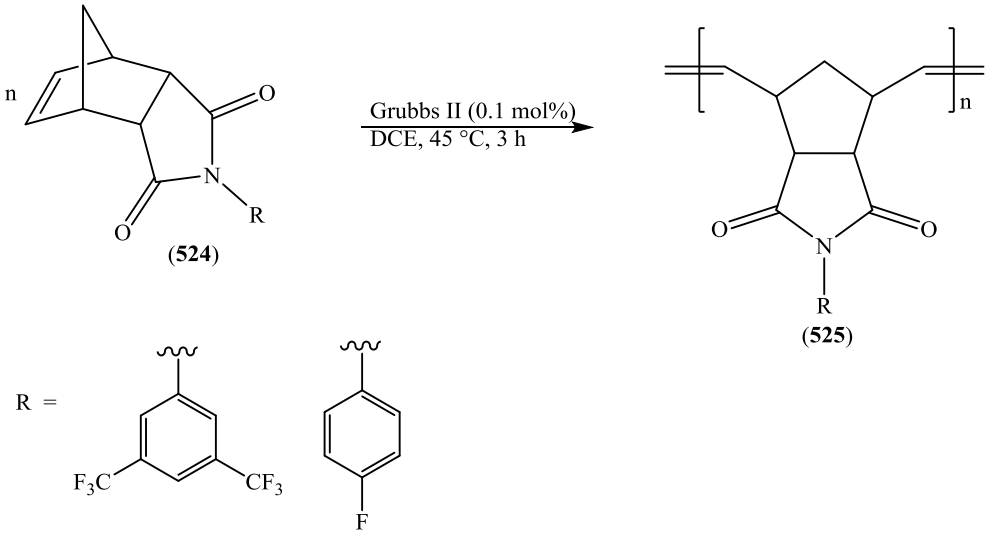


Scheme 3.22 ROM/CM of unstrained cycloalkenes

3.4.4 Ring opening metathesis polymerisation

Similar to ROM, the driving force behind ring opening metathesis polymerisation (ROMP) lies within the opening of strained cyclo-alkenes like cyclobutene, cyclopentene, cyclooctene and cyclopentadiene. Advances in the polymer industry has largely been attributed to the choice of catalyst, where Ru-benzylidene and Ru-indenylidene initiators have been most effective due to their high functional group tolerance.[6,72]

For example, Vargas *et al.*[73] investigated ROMP of *N*-fluorinated phenylnorbornene dicarboxamides (**524**) utilising Grubbs 2nd generation catalyst in the preparation of a membrane with good mechanical and thermal resistance and higher gas permeability and selectivity than non-fluorinated polymers. Under inert conditions in dichloroethane (DCE), differently fluorinated polymers were obtained in excellent yields (> 90%) while subsequent hydrogenation yielded the target compounds in up to 98% conversion (Scheme 3.23).



Scheme 3.23 ROMP of *N*-fluorinated phenylnorbornene dicarboxamides

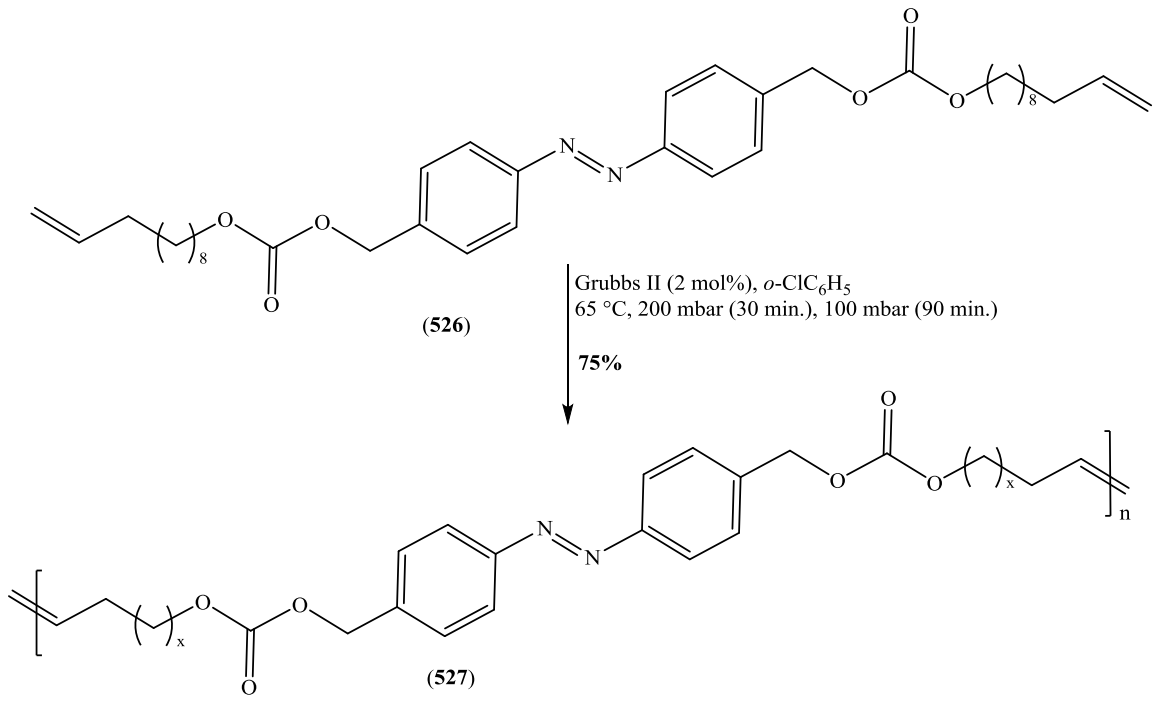
Other ROMP applications have been found in the synthesis of commercial products like Norsorex@, which is a polymer used as a moulding powder, and Zeonex@, which is a transparent amorphous polymer known for its low absorption properties and suitability for application in lenses, prisms and discs.[12]

3.4.5 Acyclic diene metathesis polymerisation

In addition to ROMP, acyclic diene metathesis polymerisation (ADMET) has also found its applications within the polymer industry and, like other metathesis reactions, its driving force lies within the formation of ethylene gas. This reaction proceeds if the terminal diene is sterically hindered enough so that RCM is inhibited.[6]

Mutlu and Barner-Kowollik[74] recently investigated the formation of an enzyme degradable polymer due to the increased drive toward environmentally benign and sustainable processes. A monomer (**526**) containing an azo-functionality was utilised due to the unique properties this moiety exhibits in its capability of responding to environmental changes and enzymatic cleavage *via* reduction. Subsequent ADMET of this monomer led to the target polymer (**527**)

in 75% in the presence of Grubbs II (Scheme 3.24). Studies towards various applications of this polymer are still underway and are currently directed at uses in imaging.



Scheme 3.24 ADMET of azo-containing monomer

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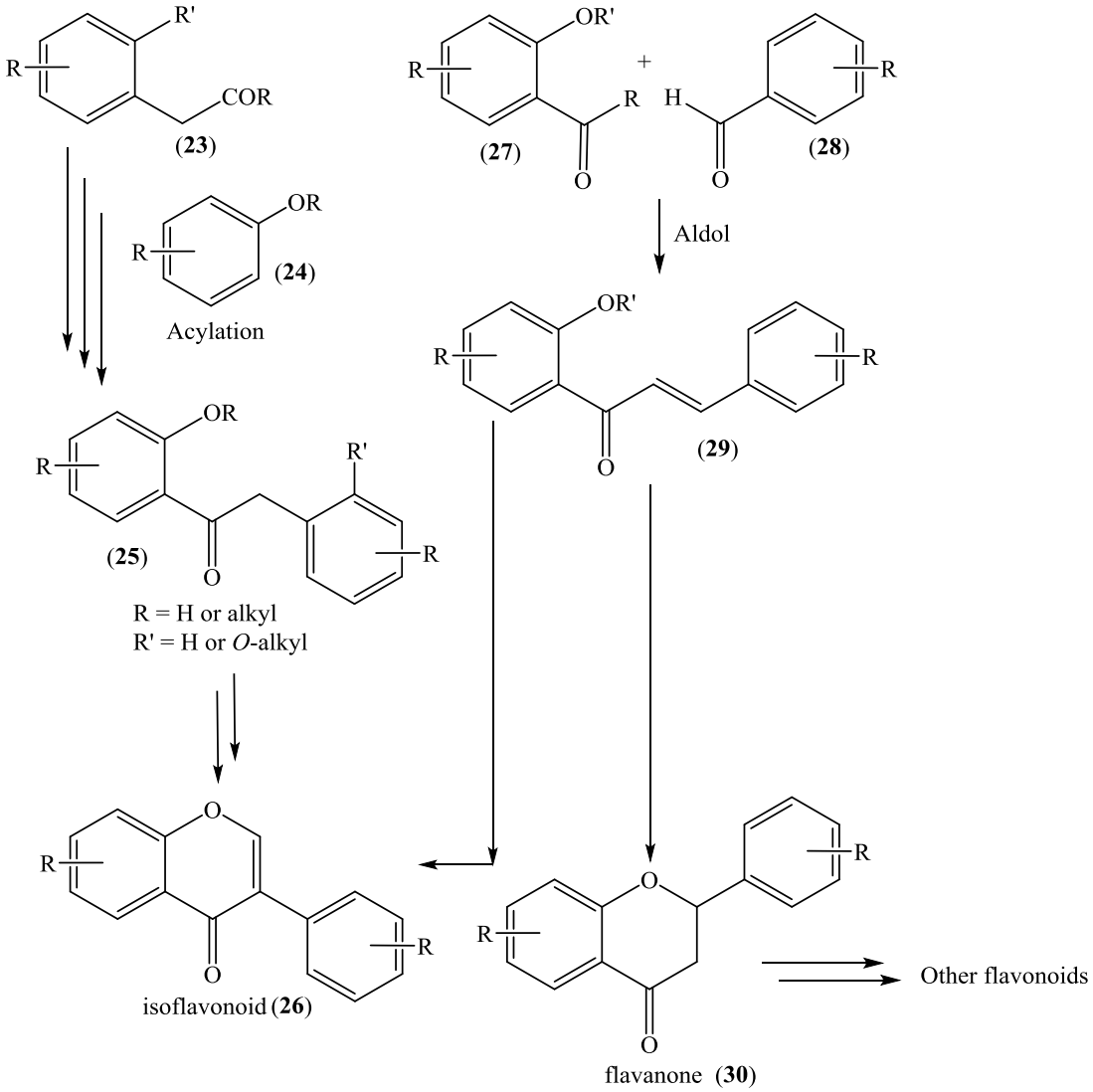
Results and Discussion

Chapter 4: Introduction

Studies directed at the synthesis of flavonoids have emerged from the increased interest in the beneficial physiological effects of these compounds. As mentioned earlier (*cf.* chapter 1), the flavonoids represent a group of compounds exhibiting many interesting biological properties including application as antimalarial[1] and antibacterial[2,3] drugs and the prevention of cancer[4] and depression,[5] among many others.

While many studies focussing on the effects of flavonoids for potential human benefits used isolation from plants as a means to obtain the active compounds, these methods are frequently hampered by low yields of the desired analogue and mixtures of compounds being obtained.[6,7] Although many synthesis endeavours have led to the desired compounds being obtained in decent quantities, several of these methods suffer from serious drawbacks like multi-step tedious processes, utilization of poisonous reagents in stoichiometric amounts and poor overall yields. The availability of different types of flavonoids are also complicated by the fact that a single process that can be utilised for the preparation of all groups of flavonoids has not been developed as yet.[8,9] While flavonoids and isoflavonoids can be obtained through similar synthetic routes (Scheme 4.1), the preparation of neoflavonoids has received little attention and the reported synthesis processes differ quite significantly from those used for the preparation of flavonoids and isoflavonoids (*cf.* chapter 2.).



Scheme 4.1 Flavonoid and isoflavonoid synthesis

Since the discovery of the metathesis reaction and its development into a viable synthesis tool, the construction of various new compounds became possible,[10,11,12] while it has also been applied to the improved preparation of many molecules.[13,14,15] The fact that many classes of flavonoids contain a double bond in the heterocyclic ring (Figure 4.1) render these compounds ideal substrates to be synthesised by application of metathesis based methodology. Ring closing metathesis (RCM) was therefore identified as the final step which could be utilised for the preparation of the basic skeleton of all classes of flavonoids.

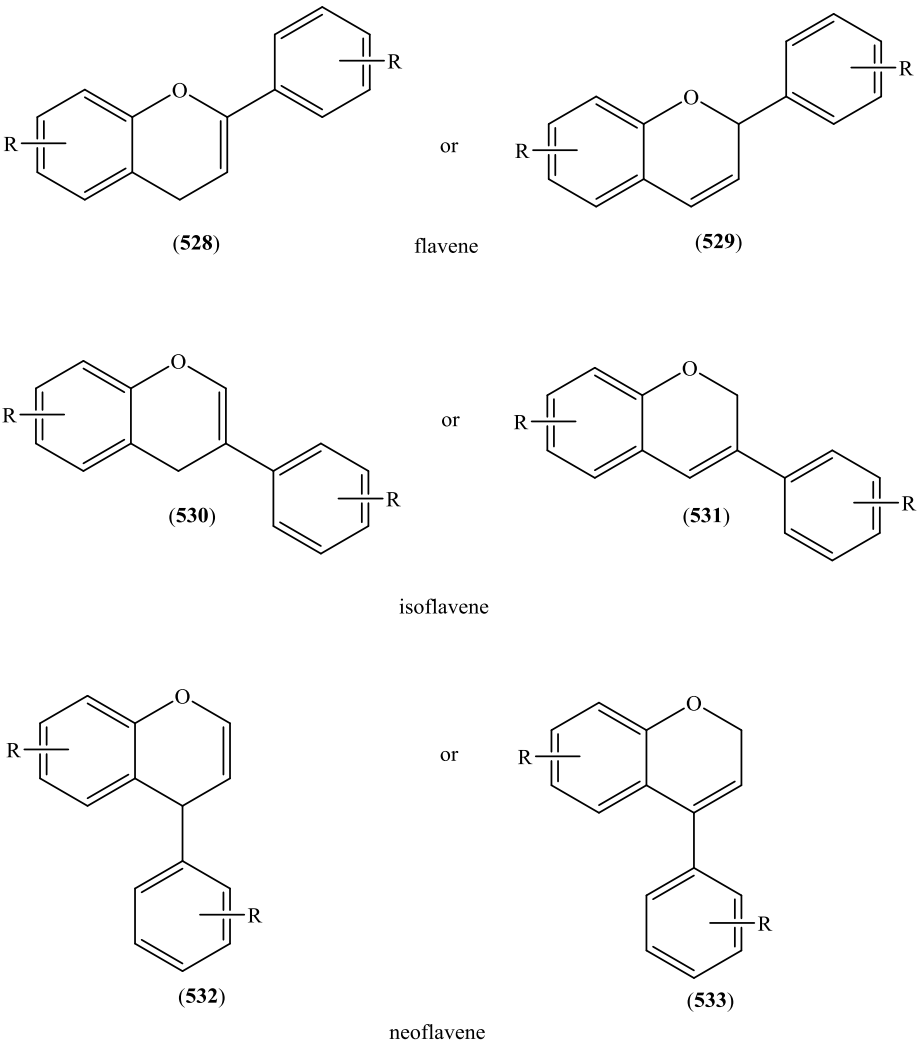
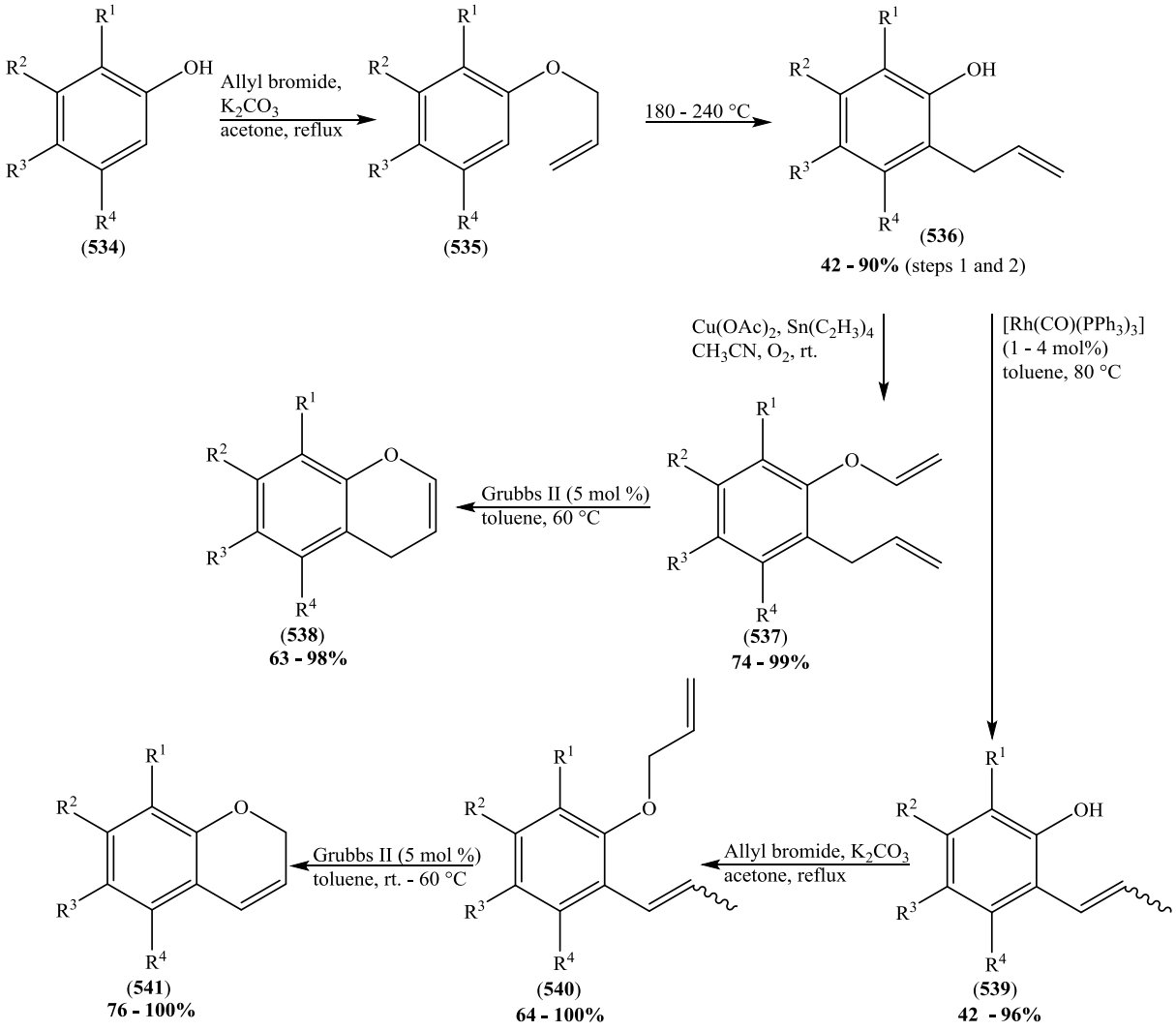


Figure 4.1 Basic flavene, isoflavene and neoflavene skeletons

Additional impetus for the application of RCM to the synthesis of all groups of flavonoids, came from the work of Van Otterlo and co-workers[16,17,18] who applied this reaction to the synthesis of various heterocyclic unsubstituted chromenes [(**538**) and (**541**)] (Scheme 4.2).



Scheme 4.2 Synthesis of 4*H*-chromenes and 2*H*-chromenes

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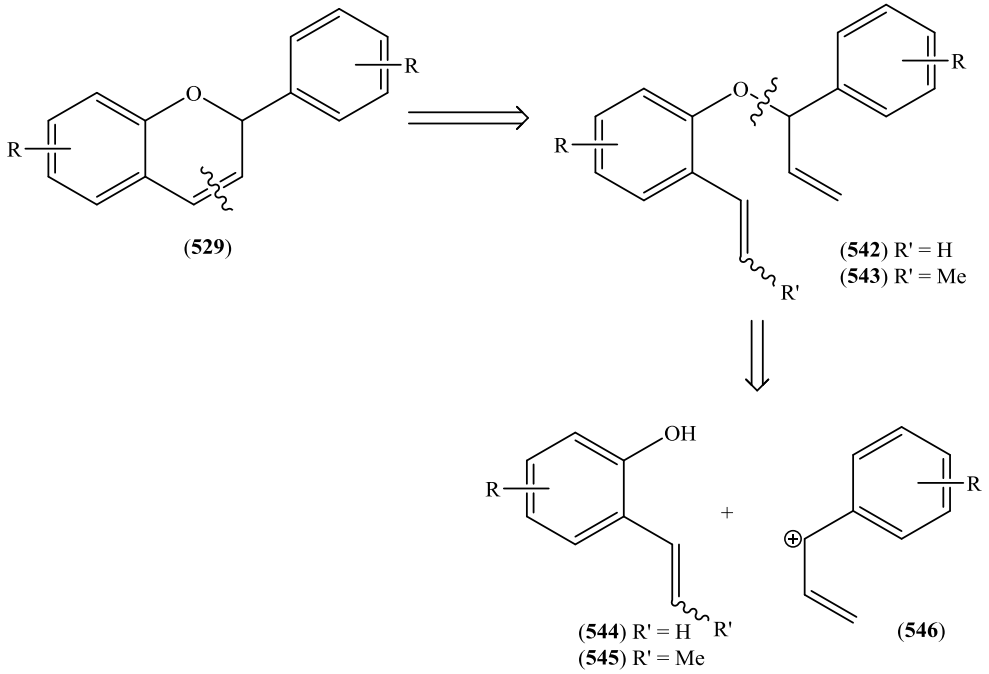
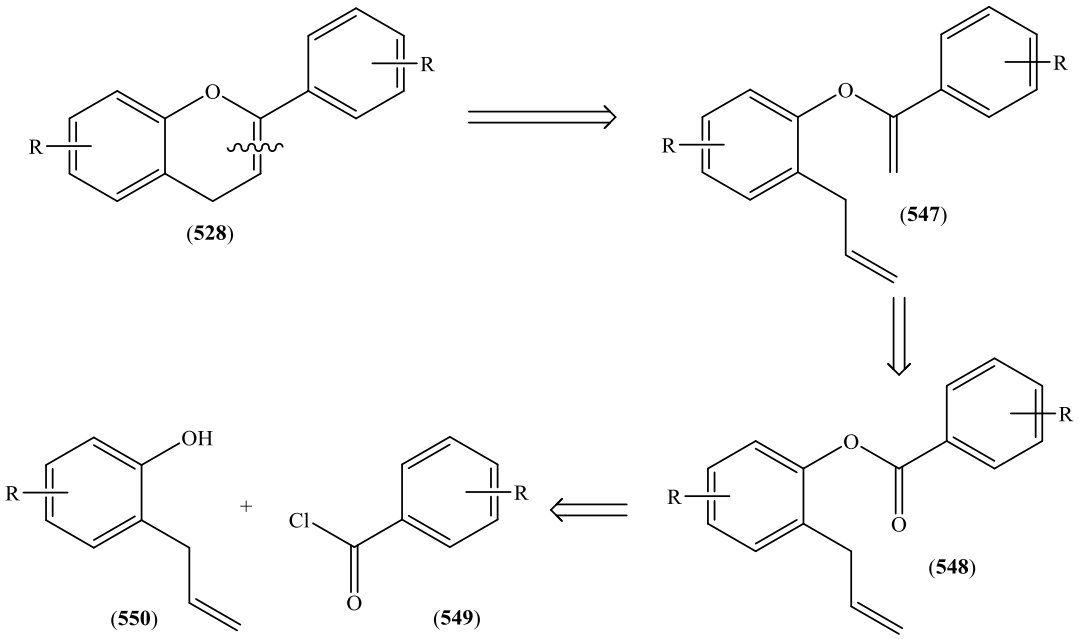
Chapter 5: Synthesis of Flavenes

Introduction

While the basic flavonoid skeleton could readily be obtained through RCM, two positions for the final double bond in the heterocyclic C-ring of the flavenes would be possible, i.e. through preparation of the flav-3-ene (**529**) or flav-2-ene (**528**) as indicated in schemes 5.1 and 5.2.



Scheme 5.1 Flav-3-ene retrosynthesis



Scheme 5.2 Flav-2-ene retrosynthesis

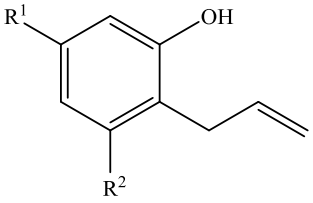
Even though the synthesis protocol for the formation of the flav-3-enes (**529**) would be possible, it requires the preparation of a phenyl substituted vinyl ether [(**542**) or (**543**)], the starting material of which might be difficult to prepare and handle due to stability issues, especially when higher oxygenated analogues are to be utilised. The flav-2-ene strategy (Scheme 5.2), on the other hand, utilises readily available starting materials like allyl benzenes (**550**), and a facile esterification process with, for example, substituted benzoyl chlorides (**549**), before Tebbe-type[1,2,3,4] methylenation of the ester carbonyl would lead to the desired intermediate (**547**) to be subjected to the RCM reaction.

5.1 *C*-allylation of phenols

While unsubstituted 1-allyl-2-hydroxybenzene (**551**) could be purchased for subsequent esterification with various benzoyl chlorides, 1-allyl-2-hydroxy-4-methoxybenzene (**552**) and 1-allyl-2-hydroxy-4,6-dimethoxybenzene (**553**) had to be prepared (Fig. 5.1).

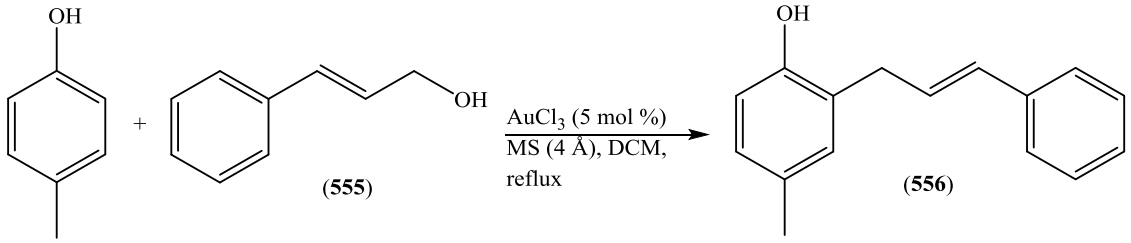
Since the synthesis of the substituted allyl benzenes, 1-allyl-2-hydroxy-4-methoxybenzene (**552**) and 1-allyl-2-hydroxy-4,6-dimethoxybenzene (**553**), would require two steps, i.e. *O*-allylation with a halogenated allyl moiety followed by Claisen rearrangement, direct *C*-allylation was investigated in order to eliminate one step and make the methodology more economical and environmentally friendly. Due to the fact that Rao and Chan[5] reported on a gold catalysed direct *C*-allylation process for aromatic compounds with allylic alcohol, this

method was evaluated as a starting point for *C*-alkylation during the current investigation. The model substrate, 1-hydroxy-4-methylbenzene (**554**), was therefore reacted with cinnamyl alcohol (**555**) under Rao-Chan[5] conditions and the reaction mixture analysed by MS (EI). Since the molecular ion of the desired product (**556**) was observed at *m/z* 224 (Scheme 5.3), it was concluded that this method could be applied to the direct preparation of the required allylated phenols.



(**551**) R^1, R^2 = H
(**552**) R^1 = OMe, R^2 = H
(**553**) R^1, R^2 = OMe

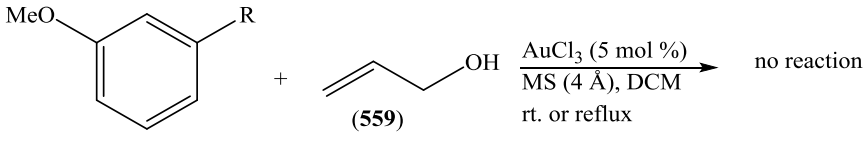
Figure 5.1 1-Allyl-2-hydroxybenzenes



(**554**) (**555**) (**556**)

Scheme 5.3 Gold(III) catalysed *C*-alkylation

Encouraged by the success of the model reaction, this methodology was applied to the reaction of methoxybenzenes, (**557**) and (**558**) and allyl alcohol (**559**), but only unreacted starting material could be recovered from the reaction mixture, even under refluxing conditions after 24 h (Scheme 5.4). These results are explicable in terms of the lower reactivity of the primary allylic alcohol (**559**) employed during the current attempts when compared to the secondary alcohols utilised by the Rao group.[5]



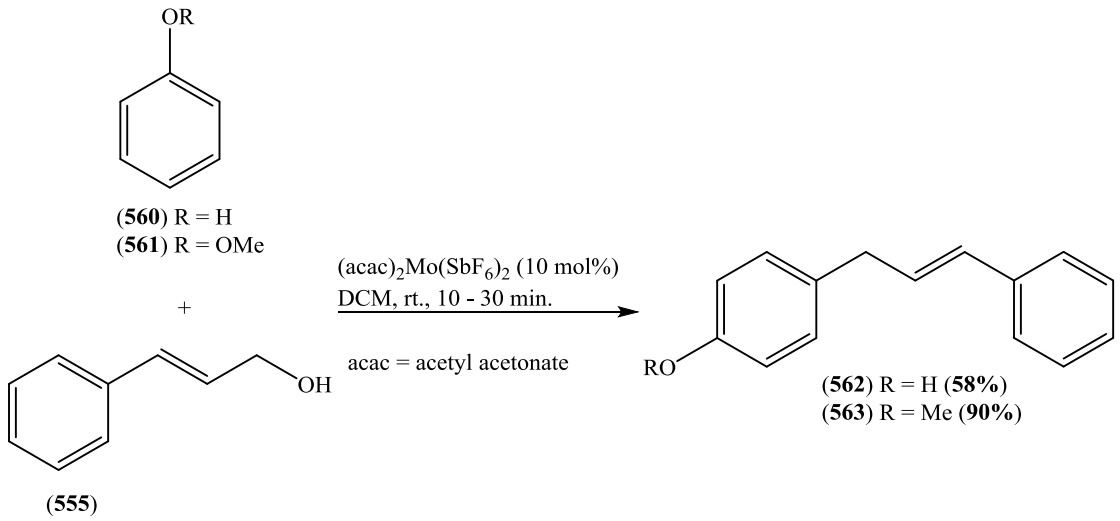
(**559**)

(**557**) R = H
(**558**) R = OH

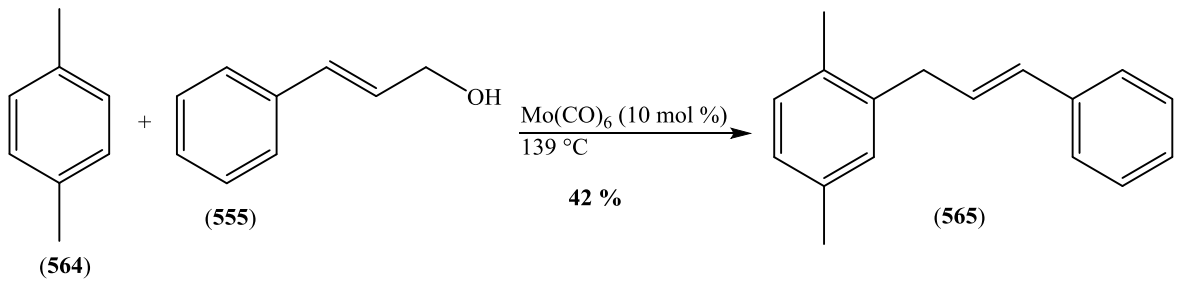
Scheme 5.4 Attempted *C*-allylation of methoxybenzenes

As the presence of the free hydroxy group attached to the aromatic moiety of the substrate did not complicate or interfere with the allylation process during the gold(III) chloride catalysed reaction of 1-hydroxy-4-methylbenzene (**554**) and cinnamyl alcohol (**555**) (*cf.* Scheme 5.3), the allylation of 1-hydroxy-3-methoxybenzene (**558**) with allyl alcohol (**559**) was repeated with other catalysts under a variety of reaction conditions to investigate the possibility of increased substrate activity.

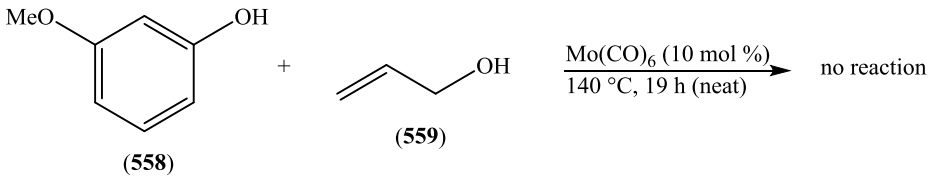
Since Malkov *et al.*[6] reported on the use of $(acac)_2Mo(SbF_6)_2$ as catalyst in the allylation of hydroxy- (**560**) and methoxybenzene (**561**) with cinnamyl alcohol (**555**) (Scheme 5.5) and Shimizu *et al.*[7] utilised the same alcohol (**555**) to allylate *p*-xylene (**564**) in the presence of $Mo(CO)_6$ (Scheme 5.6), it was decided to use this methodology for the preparation of the required allyl benzenes. $Mo(CO)_6$ catalysed reaction of 1-hydroxy-3-methoxybenzene (**558**) with allyl alcohol (**559**), however, again resulted in no identifiable product being formed (Scheme 5.7).



Scheme 5.5 $(Acac)_2Mo(SbF_6)_2$ catalysed allylation of PhOH or PhOMe

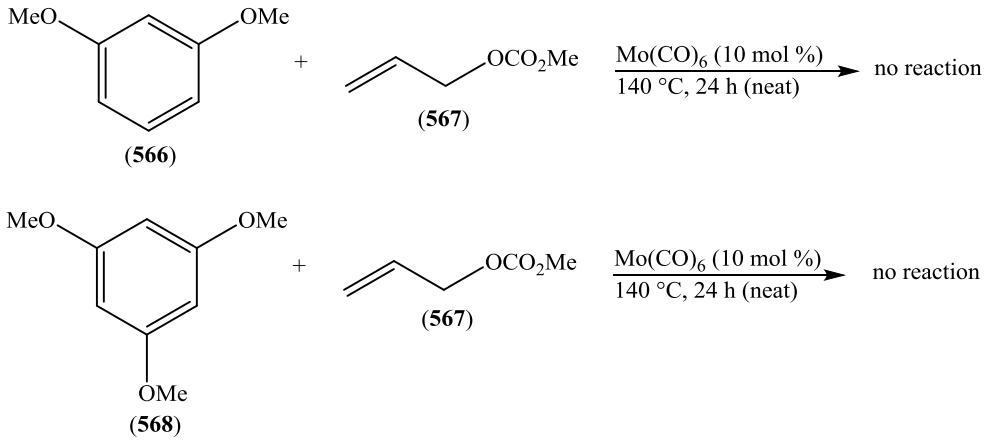


Scheme 5.6 $Mo(CO)_6$ catalysed allylation of *p*-xylene



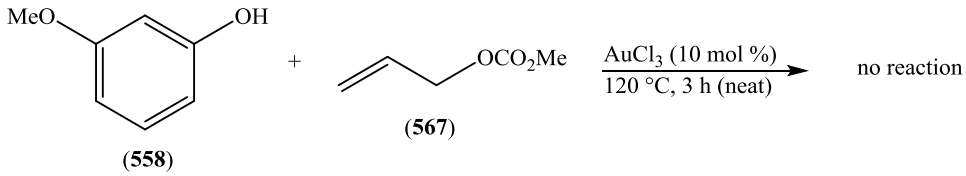
Scheme 5.7 Attempted molybdenum catalysed allylation of *m*-methoxyphenol

Due to the fact that Shimizu *et al.*[7] also reported the successful synthesis of 1-allyl-3,4-dimethoxybenzene when 3,4-dimethoxybenzene was treated with allyl methyl carbonate (**567**) in the presence of $Mo(CO)_6$, this protocol was subsequently applied to the allylation of 1,3-dimethoxybenzene (**566**) and 1,3,5-trimethoxybenzene (**568**) (Scheme 5.8). However, after 24 hours at 140 ºC, only starting material could be recovered from the reaction mixture.



Scheme 5.8 Molybdenum catalysed allylations with allyl methyl carbonate

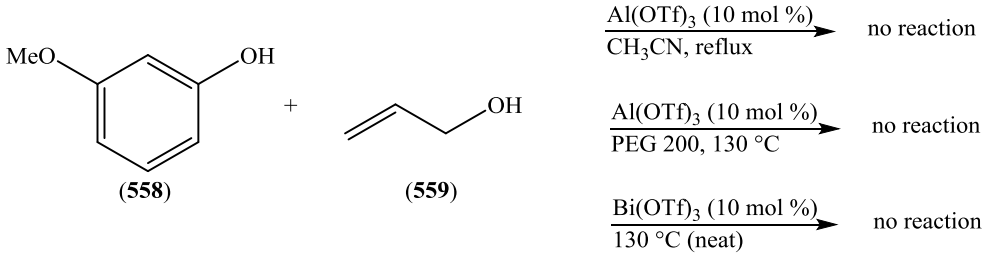
Since it was felt that the poor leaving abilities of the hydroxy function of the allyl alcohol (**559**) could be the cause of failure for the gold-catalysed reaction, the $AuCl_3$ methodology was also applied to the allylic carbonate substrate (**567**) (Scheme 5.9), but once again the desired product could not be obtained.



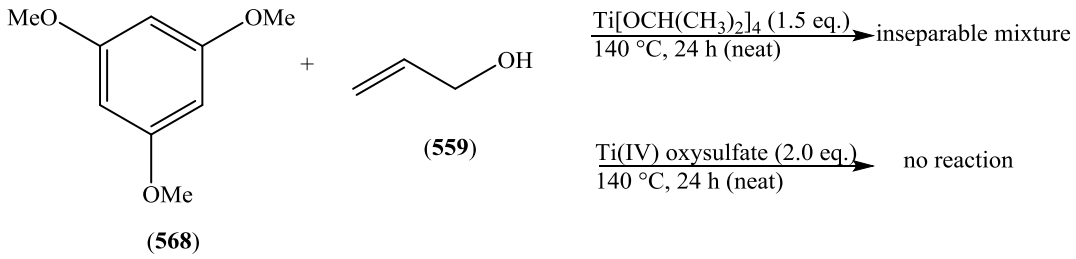
Scheme 5.9 Gold catalysed allylation with allyl methyl carbonate

Due to the oxophilic Lewis acid properties of metal triflates and titanium reagents, $Al(OTf)_3$, $Bi(OTf)_3$, titanium(IV) isopropoxide as well as titanium oxysulfate were subsequently evaluated as catalysts in the reaction between 1-hydroxy-3-methoxybenzene (**558**) and allyl

alcohol (**559**) for the triflate reactions, and trimethoxybenzene (**568**) and allyl alcohol (**559**) for the titanium reactions (Schemes 5.10 and 5.11).



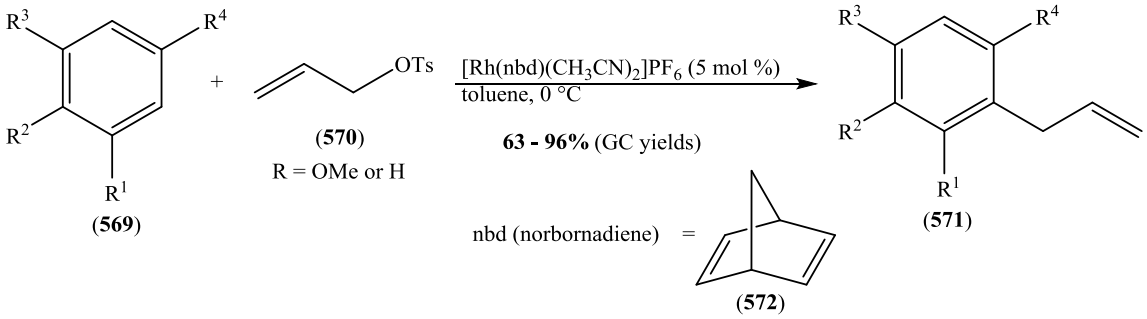
Scheme 5.10 *C*-Allylations with triflates



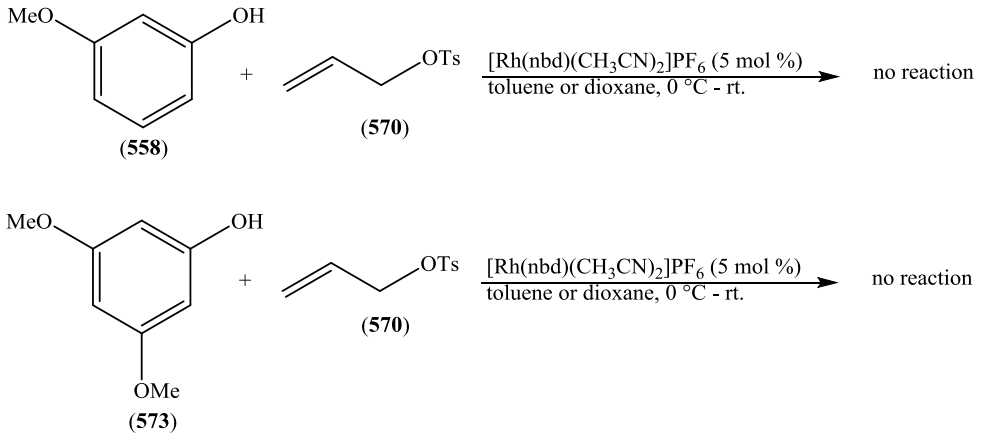
Scheme 5.11 *C*-Allylations with titanium(IV) catalysts

None of the triflate-catalysed as well as the titanium(IV) oxysulfate reactions, however, yielded any of the desired allylated products, while the titanium(IV) isopropoxide reaction gave an inseparable mixture of compounds with no indication of the desired product being present (GC-MS).

Since Tsukada *et al.*[8] reported the allylation of electron-rich arenes (**569**) with allyl tosylates (**570**) in the presence of $[Rh(nbd)(CH_3CN)_2]PF_6$ in 63 – 96% yields (Scheme 5.12), this method was subsequently evaluated for the direct synthesis of the required allyl benzenes. Allyl tosylate (**570**) [^{1}H NMR: plate 1a; MS (EI) *m/z* 212 (M^+, 3%); obtained by esterification of allyl alcohol (**559**) with tosyl chloride in $CHCl_3$ - pyridine in 68% yield] was therefore reacted with 1-hydroxy-3-methoxybenzene (**558**) and 1-hydroxy-3,5-dimethoxybenzene (**573**), respectively, under Tsukada conditions [toluene or dioxane, 0 °C – rt., $[Rh(nbd)(CH_3CN)_2]PF_6$ (10 mol%)] (Scheme 5.13), but no allylated products could be isolated, even under refluxing conditions in toluene and in dioxane.



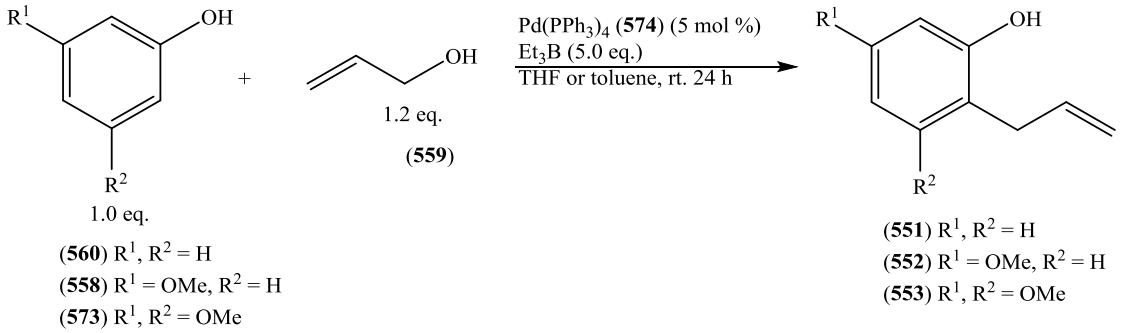
Scheme 5.12 Rhodium catalysed *C*-allylation



Scheme 5.13 Allylation of methoxyphenols with $[Rh(nbd)(CH_3CN)_2]PF_6$

Although many synthesis protocols were tested without any noticeable success, Pd-cataysed allylation reported by Kimura *et al.*[9] was attempted as a last resort towards a one-step process for this new methodology. 1-Hydroxybenzene (**560**), 1-hydroxy-3-methoxybenzene (**558**) and 1-hydroxy-3,5-dimethoxybenzene (**573**) were therefore treated with allyl alcohol (**559**) over 5 mol% $Pd(PPh_3)_4$ and Et_3B in THF[9] at rt. for 24 hours (Scheme 5.14).

Unfortunately none of the desired products could be isolated even when the $Pd(PPh_3)_4$ concentration was increased to 10 mol% and the reaction temperature raised to refluxing conditions. Since Kimura *et al.*[9] also reported toluene as suitable solvent for this reaction, the solvent was also changed to toluene, but only for the reaction of 1-hydroxy-3,5-dimethoxybenzene (**573**). In this instance a double allylated product could be identified by mass spectrometry through the presence of a molecular ion of *m/z* 232 (M^+, 100%).

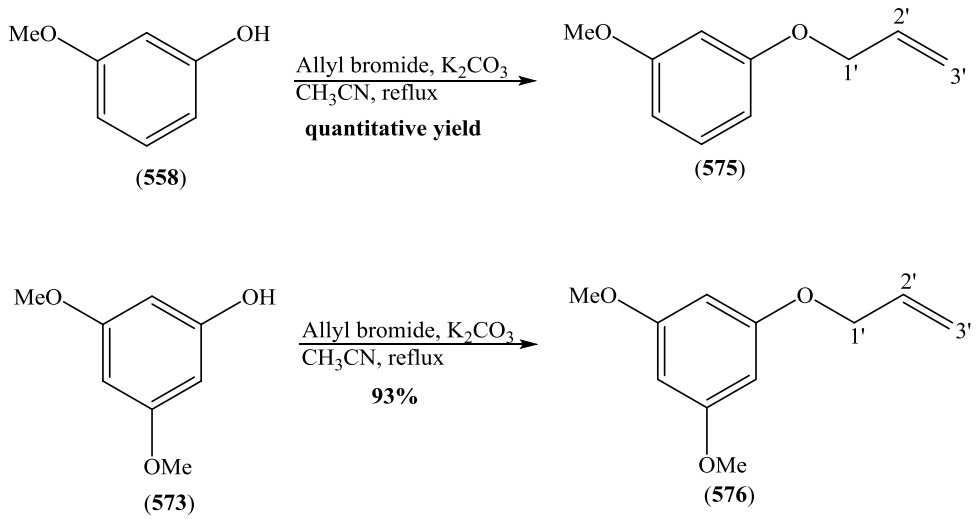


Scheme 5.14 Pd catalysed *C*-allylation under Kimura[9] conditions

While direct *C*-allylation would be very advantageous in the overall synthesis of the envisaged flavenes (**528**), none of the reactions investigated led to a positive outcome for the desired substrates, so it was decided that these compounds should rather be obtained from 1-allyloxy-3-methoxybenzene (**575**) and 1-allyloxy-3,5-dimethoxybenzene (**576**) *via* Claisen rearrangement and that this aspect of the new technology should receive more attention at a later stage when the other steps have been developed successfully.

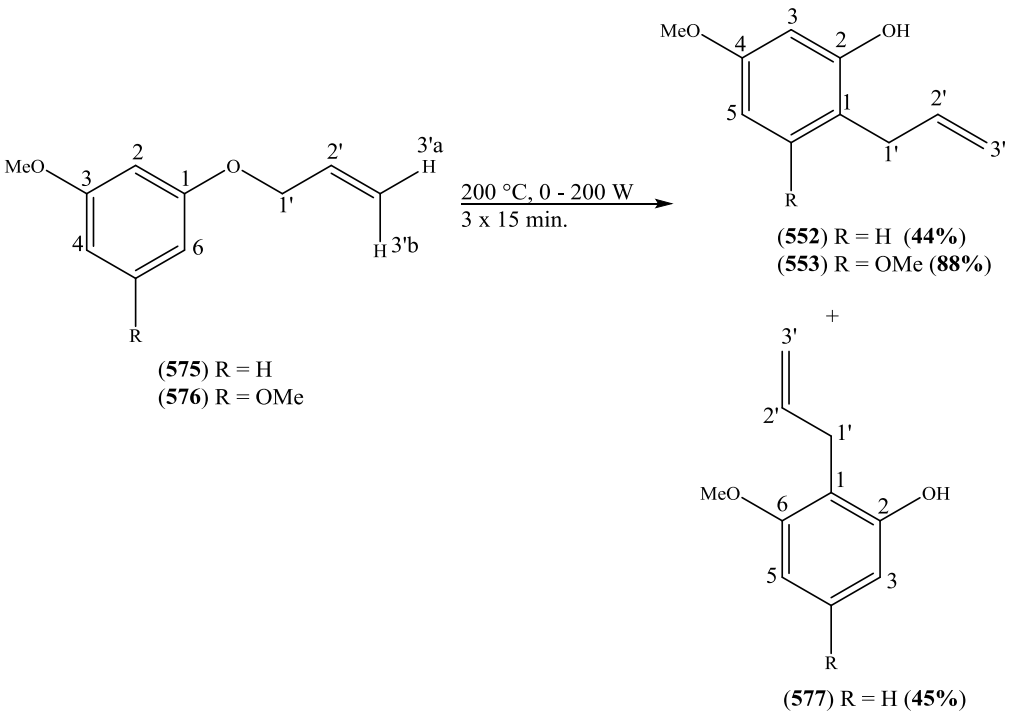
5.2 *O*-Allylation of phenols followed by Claisen rearrangement

1-Allyloxy-3-methoxybenzene (**575**) and 1-allyloxy-3,5-dimethoxybenzene (**576**) were prepared *via* standard Williamson etherification [K_2CO_3(2.0 eq.), CH_3CN, reflux][10] of the phenols and the desired products (**575**) and (**576**) obtained in almost quantitative yields (Scheme 5.15). The structures (**575**) and (**576**) were confirmed by ^{1}H NMR spectroscopy (plates 3a and 4a) where the expected aromatic resonances [δ 7.20 (1H, dd, *J* = 8.2, 8.2 Hz), 6.56 – 6.54 (2H, m), 6.53 (1H, dd, *J* = 2.3, 2.3 Hz) and δ 6.11 (2H, d, *J* = 2.10 Hz), 6.10 – 6.09 (1H, m), respectively] were observed, as well as the characteristic allylic proton resonances at δ 6.08 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz, H-2'), 5.44 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, H-3'b), 5.32 (1H, ddt, *J* = 10.5, 1.4, 1.4 Hz, H-3'a), 4.55 (2H, ddd, *J* = 5.3, 1.4, 1,4 Hz, H-1') and at δ 6.05 (1H, ddt, *J* = 17.3, 10.4, 5.6 Hz, H-2'), 5.41 (1H, ddt, *J* = 17.3, 1.4, 1.4 Hz, H-3'b), 5.29 (1H, ddt, *J* = 10.4, 1.4, 1.4 Hz, H-3'a), 4.49 (2H, ddd, *J* = 5.6, 1.4, 1.4 Hz, H-1') for (**575**) and (**576**), respectively. Additional confirmation for the proposed structures was obtained from mass spectrometry (EI) where molecular ions for (**575**) and (**576**) were observed at *m/z* 164 (100%) and *m/z* 194 (100%), respectively.



Scheme 5.15 Preparation of *O*-allylated methoxybenzenes *via* Williamson etherification

While Claisen rearrangements are classically performed in high boiling solvents like *N*,*N*-dimethylaniline under refluxing conditions, this is a tedious process and usually requires reaction times of > 8 h. Microwave irradiation was therefore investigated in order to speed up the transformations to the target allyl benzenes (**552**) and (**553**). Microwave irradiation (200 W, 0 – 200 °C, neat) of 1-allyloxy-3-methoxybenzene (**575**) for 45 minutes led to the formation of the desired 1-allyl-2-hydroxy-4-methoxybenzene (**552**) (plate 15) in 44% yield as well as the isomeric, 1-allyl-2-hydoxy-6-methoxybenzene (**577**) (plate 16) in 45% yield (Scheme 5.16), while the 3,5-dimethoxy analogue gave the desired product (**553**) (plate 17) in 88% yield.



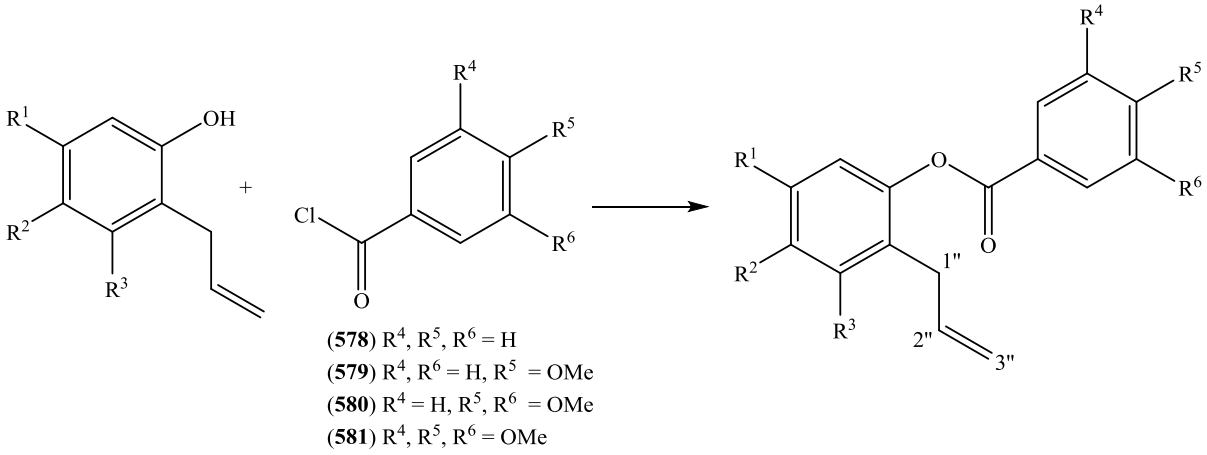
Scheme 5.16 Claisen rearrangement of allyloxymethoxybenzenes

Formation of the *C*-allylated products (**552**), (**577**) and (**553**) were confirmed by –O<u>H</u> resonances (δ 5.23, δ 5.15 and δ 5.25), as well as allylic systems [δ 6.01 (1H, ddt, *J* = 16.9, 10.4, 6.4 Hz, H-2'), 5.17 – 5.13 (1H, m, H-3'a and H-3'b), 3.36 (2H, br. d, *J* = 6.4 Hz, H-1') for (**552**), δ 5.99 (1H, ddt, *J* = 17.2, 10.1, 6.3 Hz, H-2'), 5.13 – 5.07 (2H, m, H-3'a and H-3'b), 3.48 (2H, ddd, *J* = 6.3, 1.6, 1.6 Hz, H-1') for (**577**) and δ 5.96 (1H, ddt, *J* = 17.3, 10.9, 5.9 Hz, H-2'), 5.13 – 5.07 (2H, m, H-3'a and H-3'b), 3.39 (2H, ddd, *J* = 5.9, 1.7, 1.7 Hz, H-1') for (**553**)] in the ^{1}H NMR spectra (plates 15a, 16a and 17a, respectively) of the three products (**552**), (**577**), and (**553**). Final proof of the envisaged structures (**552**), (**577**) and (**553**) came from the MS spectra where the respective molecular ions [*m/z* 164 (M^{+}, 100%), *m/z* 164 (M^{+}, 100%), and *m/z* 194 (M^{+}, 100%)] were observed.

<u>5.3 Benzoylation of 1-allyl-2-hydroxybenzenes</u>

With the desired 1-allyl-2-hydroxybenzenes, (**552**) and (**553**) in hand, attention was turned towards esterification of these substrates and the alcohols reacted with benzoyl chloride (**578**), 4-methoxybenzoyl chloride (**579**), 3,4-dimethoxybenzoyl chloride (**580**) and 3,4,5-trimethoxybenzoyl chloride (**581**) to obtain the corresponding esters (**582**) – (**589**). Since the esterification reactions of phenolic substrates were reported to work well in aqueous alkaline solution,[11] the reaction of 1-allyl-2-hydroxybenzene (**551**) with benzoyl chloride (**578**) and 4-

methoxybenzoyl chloride (**579**) were performed under these conditions. Modest yields, 68% and 74%, of the wanted products (**582**) and (**583**) were, however, obtained so the conditions were changed to the well-known pyridine-DMAP system in refluxing DCM, which led to the desired esters (**584**) – (**589**) being obtained in excellent yields (75 – 98%) (Table 5.1).



(**578**) R^4, R^5, R^6 = H
(**579**) R^4, R^6 = H, R^5 = OMe
(**580**) R^4 = H, R^5, R^6 = OMe
(**581**) R^4, R^5, R^6 = OMe

Table 5.1 Ester syntheses

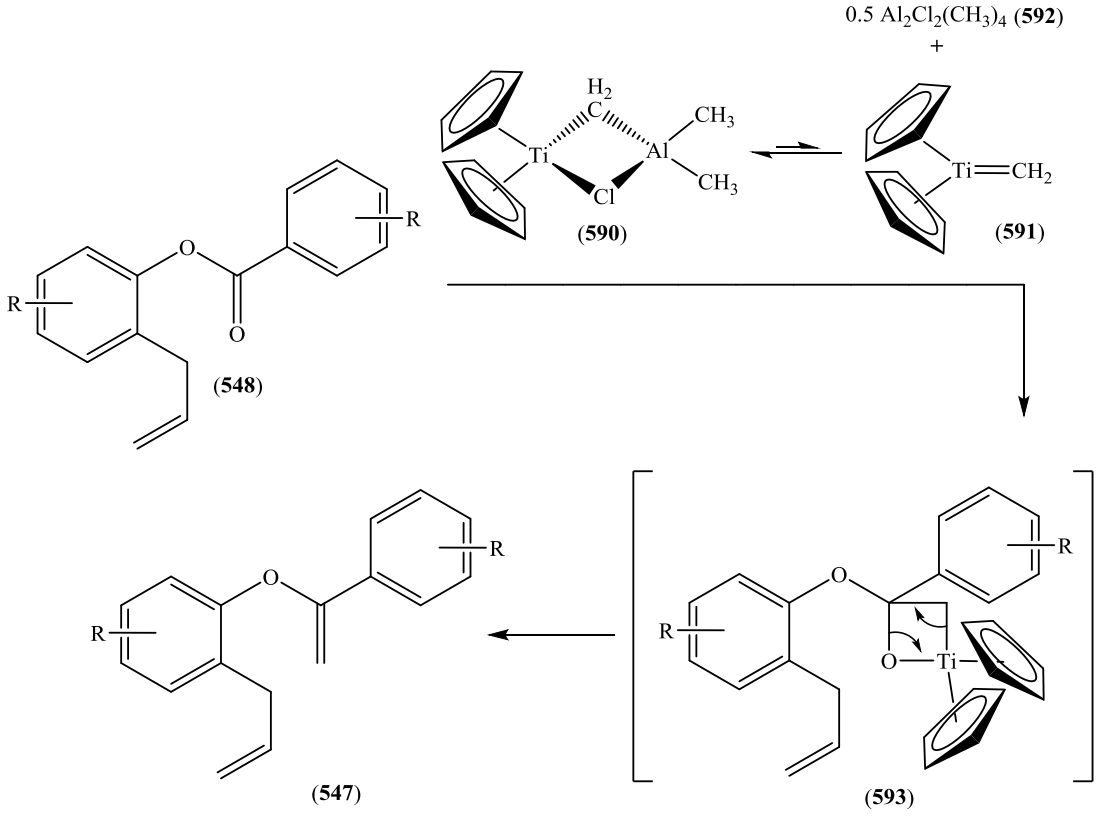
Plate	Substitution	^{1}H NMR: Allylic system	^{13}C NMR: Carbonyl	MS	Yield (%)
18 (**582**)	R^1, R^2, R^3, R^4, R^5, R^6 = H	δ 5.96 (1H, ddt, *J* = 16.8, 10.1, 6.6 Hz, H-2"), 5.08 – 5.03 (2H, m, H-3"), 3.40 (2H, br. d, *J* = 6.6 Hz, H-1")	δ 165.08	238[a] (9%)	68[c]
19 (**583**)	R^1, R^2, R^3, R^4, R^6 = H R^5 = OMe	δ 5.95 (1H, ddt, *J* = 16.8, 10.2, 6.6 Hz, H-2"), 5.07 – 5.02 (2H, m, H-3"), 3.38 (2H, br. d, *J* = 6.6 Hz, H-1")	δ 164.80	291[b]	74[c]
20 (**584**)	R^1, R^2, R^3, R^6 = H R^4, R^5 = OMe	δ 5.11 (1H, ddt, *J* = 16.7, 10.1, 6.6 Hz, H-2"), 4.22 – 4.16 (2H, m, H-3"), 2.54 (2H, br. d, *J*	δ 165.13	321[b]	93[d]

		= 6.6 Hz, H-1")			
21 (**585**)	R^1, R^2, R^3 = H R^4, R^5, R^6 = OMe	δ 5.96 (1H, ddt, *J* = 16.7, 10.1, 6.6 Hz, H-2"), 5.04 (2H, m, H-3"), 3.39 (2H, br. d, *J* = 6.6 Hz, H-1")	δ 165.01	351[b]	93[d]
22 (**586**)	R^2, R^3, R^6 = H R^1, R^4, R^5 = OMe	δ 5.91 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, H-2"), 5.01 – 4.95 (2H, m, H-3"), 3.28 (2H, br. d, *J* = 6.6 Hz, H-1")	δ 164.97	351[b]	75[d]
23 (**587**)	R^2, R^3 = H R^1, R^4, R^5, R^6 = OMe	δ 5.91 (1H, ddt, *J* = 16.7, 10.1, 6.5 Hz, H-2"), 5.03 – 4.97 (2H, m, H-3"), 3.28 (2H, br. d, *J* = 6.5 Hz, H-1")	δ 164.90	381[b]	98[d]
24 (**588**)	R^2, R^6 = H R^1, R^3, R^4, R^5 = OMe	δ 5.83 (1H, ddt, *J* = 16.4, 10.0, 6.3 Hz, H-2"), 4.90 – 4.83 (2H, m, H-3"), 3.25 (2H, br. d, *J* = 6.3 Hz, H-1")	δ 164.98	381[b]	89[d]
25 (**589**)	R^2 = H R^1, R^3, R^4, R^5, R^6 = OMe	δ 5.85 (1H, ddt, *J* = 16.3, 10.1, 6.2 Hz, H-2"), 4.93 – 4.87 (2H, m, H-3"), 3.27 (2H, br. d, *J* = 6.2 Hz, H-1")	δ 164.82	411[b]	97[d]

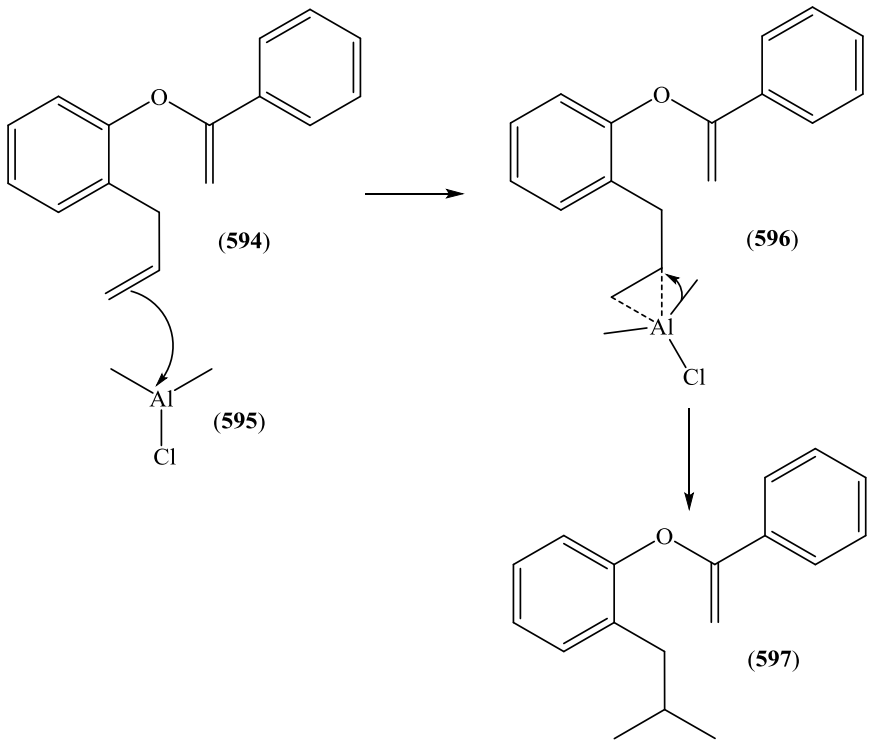
[a]GC-MS [M^+] [b]HR-MS ([M + Na]$^+$) [c]Conditions: aq. NaOH (2.0 M), rt. [d]Conditions: Pyridine, DMAP, DCM, reflux

5.4 Vinyl ether preparation

With all the desired benzoates available, attention was turned towards preparing the vinyl ether analogues. Since the Tebbe reagent was shown to be the reagent of choice for this transformation in a previous study (Scheme 5.17),[12] this reagent was selected for the current investigation as well. During the previous investigation, however, it was found that the Lewis acid used for the preparation of the Tebbe reagent may cause methylation of the allylic double bond (after carbonyl methylenation) leading to the isobutyl analogue (**597**) as side product (Scheme 5.18).[12] The methylenation reaction was therefore performed at low temperature to avoid this unwanted side-reaction.

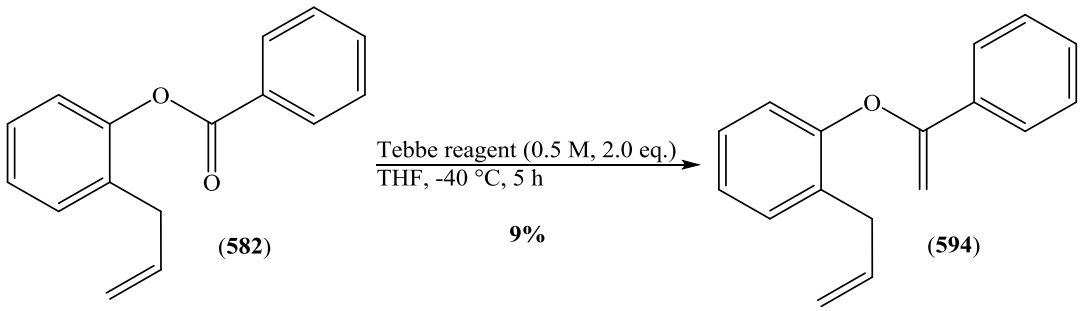


Scheme 5.17 Methylenation of benzoates with Tebbe reagent



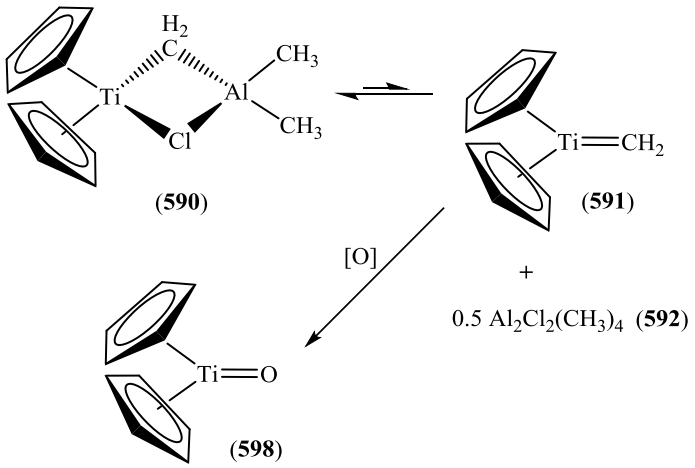
Scheme 5.18 Lewis-acid assisted methylation of allylic double bond during reaction with the Tebbe reagent

Treatment of 2-allylphenyl benzoate (**582**) with the Tebbe reagent in dry THF at -40 °C for 5 hours gave the desired 2-allyl-1-(1-phenylvinyloxy)benzene (**594**), albeit in low yield (9%) (Scheme 5.19). The structure of the product (**594**) was confirmed by ^{1}H NMR data (plate 26a) where the expected aromatic resonances [δ 7.76 – 7.74 (2H, m), 7.42 – 7.37 (3H, m), 7.28 (1H, dd, *J* = 7.6, 1.6 Hz), 7.22 (1H, ddd *J* = 8.0, 8.0, 1.6 Hz), 7.13 (1H, ddd, *J* = 8.0, 7.6, 1.3 Hz), 7.06 (1H, dd, *J* = 8.0, 1.3 Hz)] were accompanied by signals from the allylic system [δ 6.00 (1H, ddt, *J* = 16.9, 10.1, 6.7 Hz), 5.11 – 5.06 (2H, m), 3.41 (2H, br. d, *J* = 6.7 Hz)] and the newly introduced vinyl group [δ 4.92 (1H, d, *J* = 2.6 Hz), 4.16 (1H, d, *J* = 2.6 Hz)]. In the ^{13}C NMR spectrum (plate 26b) the presence of the vinyl group was confirmed by resonances at δ 159.75 and δ 89.20, while HR-MS (EI) showed the expected protonated molecular ion $[M + H]^{+}$ at *m/z* 237.



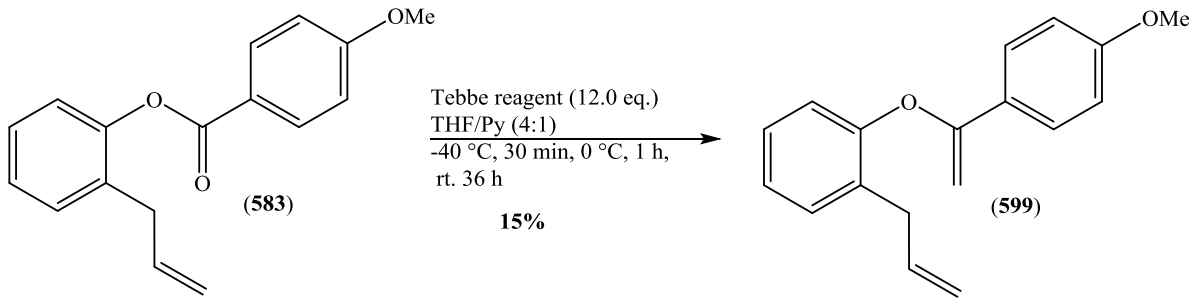
Scheme 5.19 Methylenation of 2-allylphenyl benzoate with Tebbe reagent

In order to improve the yield to acceptable levels and since no by-product formation could be detected during the reaction, it was decided to repeat the reaction and allow the reaction mixture to slowly warm up to rt. after being kept -40 °C for 4 hours. Under these conditions, however, the yield decreased even further to only 5%. Since a large amount of starting material remained unreacted after 6 hours of reaction time even with excess Tebbe reagent being present, it was concluded that the reagent might have been deactivated through reaction with oxygen during handling and storage of the commercial Tebbe reagent (Scheme 5.20) or due to incomplete formation during the preparation process. Due to the fact that Hartley and McKiernen[2] as well as Berget and Schore[13] reported on the integration of a Lewis base such as THF and/or pyridine into the reaction mixture not only to facilitate formation of the highly reactive titanocene methylidene species (**590**) necessary for the methylenation process, but also to reverse the formation of oxidised titanium compound (**598**), this alteration to the process was subsequently investigated in order to improve on the yield. Methylenation of 2-allylphenyl benzoate (**582**) with 2.0 eq. of Tebbe reagent in a mixture of THF and pyridine (4:1; 15 mL) at -40 °C (1 h) followed by stirring at rt. for 3 hours led to an increase in yield to 25%.



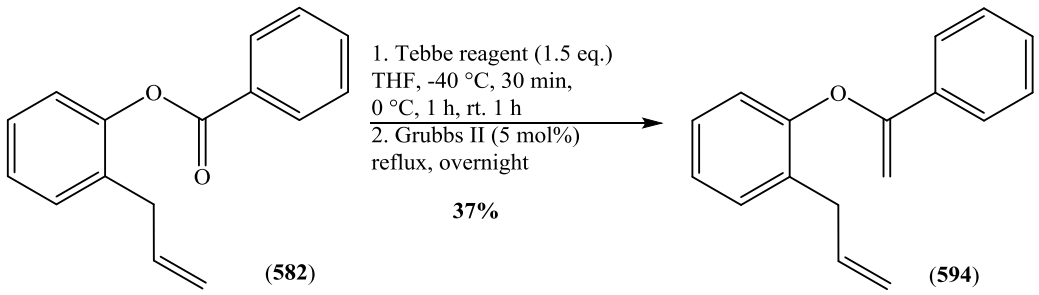
Scheme 5.20 Possible formation of a titanium oxo species through reaction of the Tebbe reagent with oxygen

While the yield for the methylenation of 2-allylphenyl benzoate (**582**) remained unsatisfactory, it was decided to investigate the reactivity of some of the other benzoates towards the Tebbe reagent first and return to the optimization of the reaction conditions for the current substrate (**582**) at a later stage. 2-Allylphenyl 4-methoxybenzoate (**583**) was therefore reacted with Tebbe reagent (*ca*. 12.0 eq. to ensure excess reagent) in THF-pyridine (4:1) at -40 ºC (30 min.), then 0 ºC for 1 hour and subsequently for 36 hours at room temperature. The desired product (**599**) was obtained, albeit in only 15% yield (Scheme 5.21). The structure of the product (**599**) was confirmed by ^{1}H NMR (plate 27a) where the expected aromatic resonances [δ 7.71 (2H, d, *J* = 9.2 Hz), 7.31 (1H, dd, *J* = 7.6, 1.4 Hz), 7.25 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.14 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.05 (1H, dd, *J* = 7.6, 1.4 Hz), 6.97 (2H, d, *J* = 9.2 Hz)] were accompanied by signals from the allylic system [δ 6.00 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz), 5.05 – 5.01 (1H, m, H-3'"a), 3.40 (2H, br. d, *J* = 6.7 Hz)] and the newly introduced vinyl group [δ 4.91 (1H, d, *J* = 2.5 Hz), 4.03 (1H, d, *J* = 2.5 Hz)]. In the ^{13}C NMR spectrum (plate 27b) the presence of the vinyl group was confirmed by the –$\underline{C}H_2$ resonance at δ 88.16, while MS (EI) showed the molecular ion at *m/z* 266 (2%).



Scheme 5.21 Methylenation of 2-allylphenyl 4-methoxybenzoate with 12.0 eq. of Tebbe reagent.

In an effort to improve the yield of the desired product and have a more efficient process, it was subsequently decided to embark on a strategy of converting the vinyl ether (**599**) to the desired flavene before suspected deactivation of the Tebbe reagent could take place. In this regard a one-pot tandem methylenation-metathesis protocol was investigated for the synthesis of the desired flav-2-ene and 2-allylphenyl benzoate (**582**) treated with Tebbe reagent (1.5 eq.) [THF/Py 4:1 (15 mL), -40^{o}C (30 min.), then 0 ^{o}C (1 h), then rt. (1 h)], before Grubbs II catalyst (5 mol%) was added and the mixture refluxed overnight. While the desired methylenated product (**594**) was formed in 37% yield during this reaction, it was still accompanied in the reaction mixture by unreacted starting material (**582**), while no flavene could be detected. (Scheme 5.22).



Scheme 5.22 Attempted one-pot Tebbe methylenation and RCM

Since Yang *et al.*[14] reported on Grubbs-type ring closing metathesis catalysts being deactivated in the presence of Lewis acids like $AlCl_3$ and $La(OTf)_3$, the lack of flavene formation in the previous reaction could be ascribed to the presence of Me_2AlCl (*cf.* Scheme 5.20) in the reaction mixture, originating from the formation of the titanocene methylidene complex (Tebbe reagent). It was therefore decided to revert back to the optimization of the methylenation step and return to the one-pot methylenation-metathesis approach at a later stage.

Careful re-examination of the literature revealed a 1985 report by Pine *et al.*[4] where these authors were able to form the vinyl ether (**594**) of 2-allylphenyl benzoate (**582**) in 94% yield after only 30 min. when the reaction was carried out on *ca*. 200 mg of substrate in 2 – 3 mL of THF at 0 ºC with excess Tebbe reagent (1.3 eq.). The substrate concentration was therefore increased to 400 mg in 2 mL of THF and the desired product (**594**) was obtained after 30 minutes at 0 ºC, 1 hour at rt. and another 2 hours at reflux followed by filtration through a short column of basic alumina in 81% yield. Following the success of the methylenation on the model substrate (**582**), the reaction was repeated on all the remaining benzoates utilising these conditions. The structures of all the vinyl ethers (**594**) and (**599**) – (**603**) were elucidated *via* ^{1}H NMR data where the characteristic resonances indicative of the vinyl group were observed as doublets with small coupling constants between δ 4.03 and 5.02 as well as the resonances of the allylic system in the ^{1}H NMR spectra and $\underline{C}H_2$ resonances in the ^{13}C NMR spectra between δ 88.16 and δ 90.15 (Table 5.2).

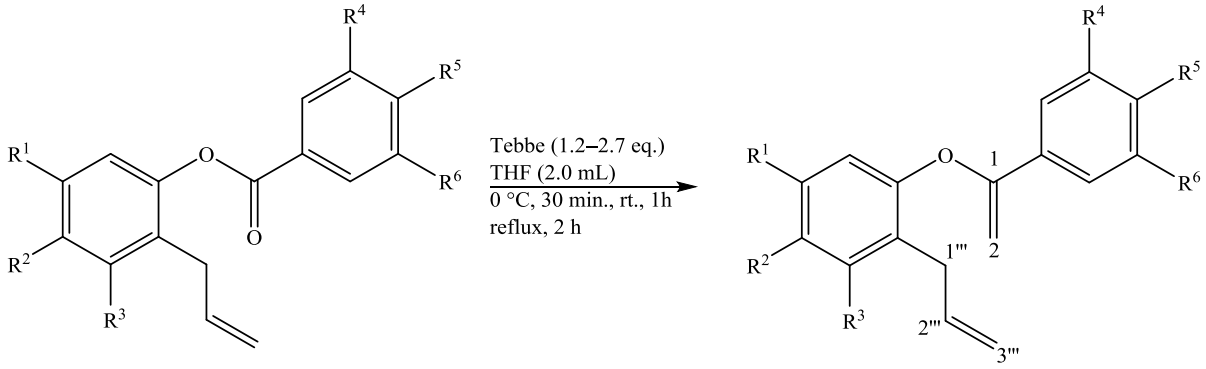


Table 5.2 Vinyl ether syntheses

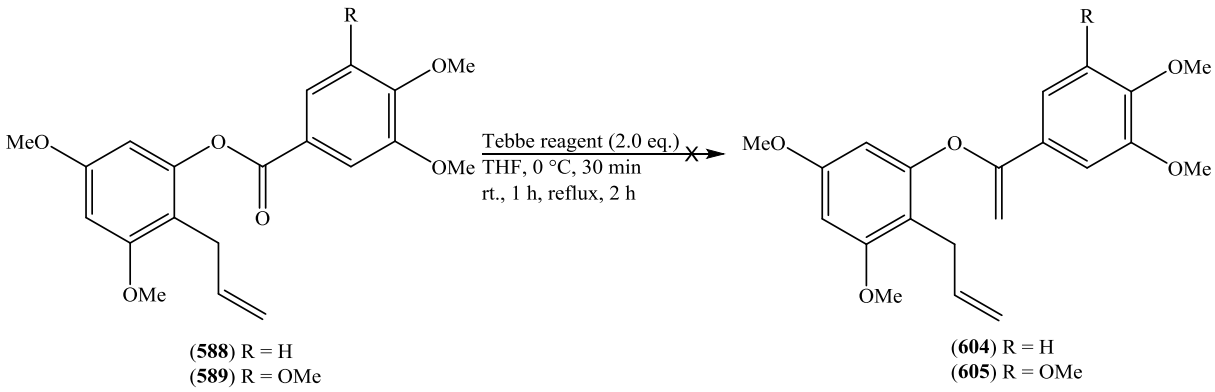
Plate	Substitution	^{1}H NMR: Allylic and vinyl systems	^{13}C NMR: Vinyl-$\underline{C}H_2$	MS	Tebbe (eq.)	Yield (%)
26 (**594**)	R^1, R^2, R^3, R^4, R^5, R^6 = H	δ 6.00 (1H, ddt, *J* = 16.9, 10.1, 6.7 Hz, H-2'''), 5.11 – 5.06 (2H, m, H-3'''), 4.92 (1H, d, *J* = 2.6 Hz, H-2), 4.16 (1H, d, *J* = 2.6 Hz, H-2), 3.41	δ 89.20	237[a]	1.3	81

		(2H, br. d, *J* = 6.7 Hz, H-1''')				
27 (**599**)	R^1, R^2, R^3, R^4, R^6 = H R^5 = OMe	δ 6.00 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05 – 5.01 (1H, m, H-3'''a), 4.91 (1H, d, *J* = 2.5 Hz, H-2), 4.03 (1H, d, *J* = 2.5 Hz, H-2), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1''')	δ 88.16	266[c] (2%)	2.0	71
28 (**600**)	R^1, R^2, R^3, R^6 = H R^4, R^5 = OMe	δ 6.01 (1H, ddt, *J* = 17.0, 10.0, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05 – 5.02 (1H, m, H-3'''a), 4.95 (1H, d, *J* = 2.5 Hz, H-2), 4.05 (1H, d, *J* = 2.5 Hz, H-2), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1''')	δ 88.45	319[b]	1.4	94
29 (**601**)	R^1, R^2, R^3 = H R^4, R^5, R^6 = OMe	δ 6.02 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-2'''), 5.08 (1H, ddt, *J* = 17.0, 1.8, 1.8 Hz, H-3'''b), 5.05 (1H, ddt, *J* = 10.1, 1.8, 1.8 Hz, H-3'''a), 5.02 (1H, d, *J* = 2.6 Hz,	δ 89.49	351[b]	1.4	85

		H-2), 4.11 (1H, d, *J* = 2.6 Hz, H-2), 3.41 (1H, br. d, *J* = 6.7 Hz, H-1''')				
30 (**602**)	R^2, R^3, R^6 = H R^1, R^4, R^5 = OMe	δ 5.98 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H-2'''), 5.07 – 5.03 (1H, m, H-3'''b), 5.03 – 4.99 (1H, m, H-3'''a), 4.97 (1H, d, *J* = 2.4 Hz, H-2), 4.14 (1H, d, *J* = 2.4 Hz, H-2), 3.33 (2H, br. d, *J* = 6.6 Hz, H-1''')	δ 89.19	349[b]	1.2	87
31 (**603**)	R^2, R^3 = H R^1, R^4, R^5, R^6 = OMe	δ 5.99 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H-2'''), 5.07 – 5.00 (2H, m, H-3'''), 5.04 (1H, d, *J* = 2.6 Hz, H-2), 4.18 (1H, d, *J* = 2.6 Hz, H-2), 3.32 (2H, br. d, *J* = 6.6 Hz, H-1''')	δ 90.15	379 [b]	2.7	75

[a] HR-MS ($[M + 1]^+$) [b]HR-MS ($[M + Na]^+$) [c]GC-MS [M^+]

While the oxygenated esters (**579**) – (**587**) gave the vinyl ethers in excellent yields (71 – 94%) when treated with the Tebbe reagent, the analogues with a phloroglucinol-type substitution pattern on the allyl benzene entity, i.e. (**588**) and (**589**), led to inseparable mixtures of products from which the desired enol ethers (**604**) and (**605**) could not be obtained even though full conversion of the substrates were observed on TLC (Scheme 5.23). The failure of these reactions is probably explicable in terms of the high level of oxygenation displayed by these compounds on what would become the A-rings of the flav-2-enes.



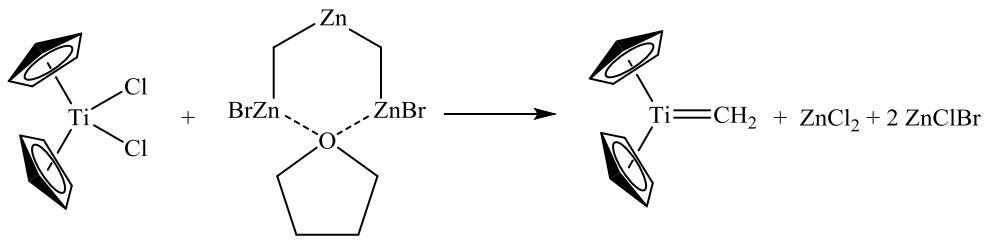
(**588**) R = H
(**589**) R = OMe

(**604**) R = H
(**605**) R = OMe

Scheme 5.23 Attempted syntheses of highly oxygenated vinyl ethers

Due to the fact that the vinyl ether products from these compounds might be unstable and therefore undergo decomposition during the work-up and/or separation process, these reactions were repeated on the above mentioned substrates and the product mixture, after work-up, directly subjected to ring closing metathesis conditions (Grubbs II, DCM, reflux). Unfortunately an inseparable mixture of products were still obtained with no indication of the desired flavenes being present in the reaction mixture [MS (EI) analysis].

Since it is known that the Tebbe reagent may lose reactivity over time and that that could be the cause of these substrates not giving the desired products, alternative methods for preparing the required titanocene methylidene (**591**) reagent were investigated. In order to eliminate the usage of $AlMe_3$ during the preparation of titanocene methylidene (**591**), it was decided to utilise the Nysted reagent (**607**) to generate the reactive titanocene methylidene moiety *in situ* through microwave irradiation (Scheme 5.24).[15] Application of the Haahr, Rankovic and Hartley methodology[15] for preparing the methylidene moiety and subsequent reaction with 2-allylphenyl benzoate (**582**) under microwave radiation conditions (75 °C, 100 W, 2 h), however, led to only starting material being recovered.



(**606**)
2.0 eq.

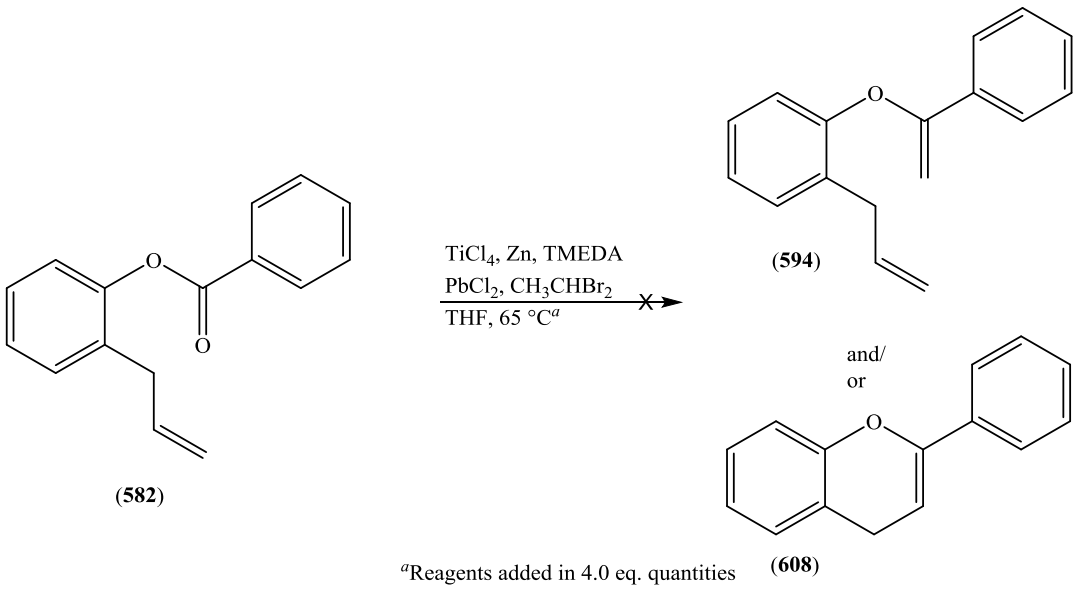
Nysted reagent (**607**)
1.0 eq.

(**591**)
2.0 eq.

Scheme 5.24 Formation of titanocene methylidene through reaction with Nysted reagent[15]

In another effort to transform the phloroglucinol-based benzoates (**588**) and (**589**) into the corresponding vinyl ethers, it was decided to investigate the titanium-zinc methylenation of esters ($TiCl_4$, Zn, $PbCl_2$, TMEDA and CH_2Br_2 in THF) reported by Iyer and Rainier.[16]

Reaction of 2-allylphenyl benzoate (**582**) as model substrate with the Rainer reagent, however, did again not lead to any product formation [vinyl ether (**594**) or flav-2-ene (**608**); MS analysis of the reaction mixture], even after 20 hours of reaction time (Scheme 5.25).



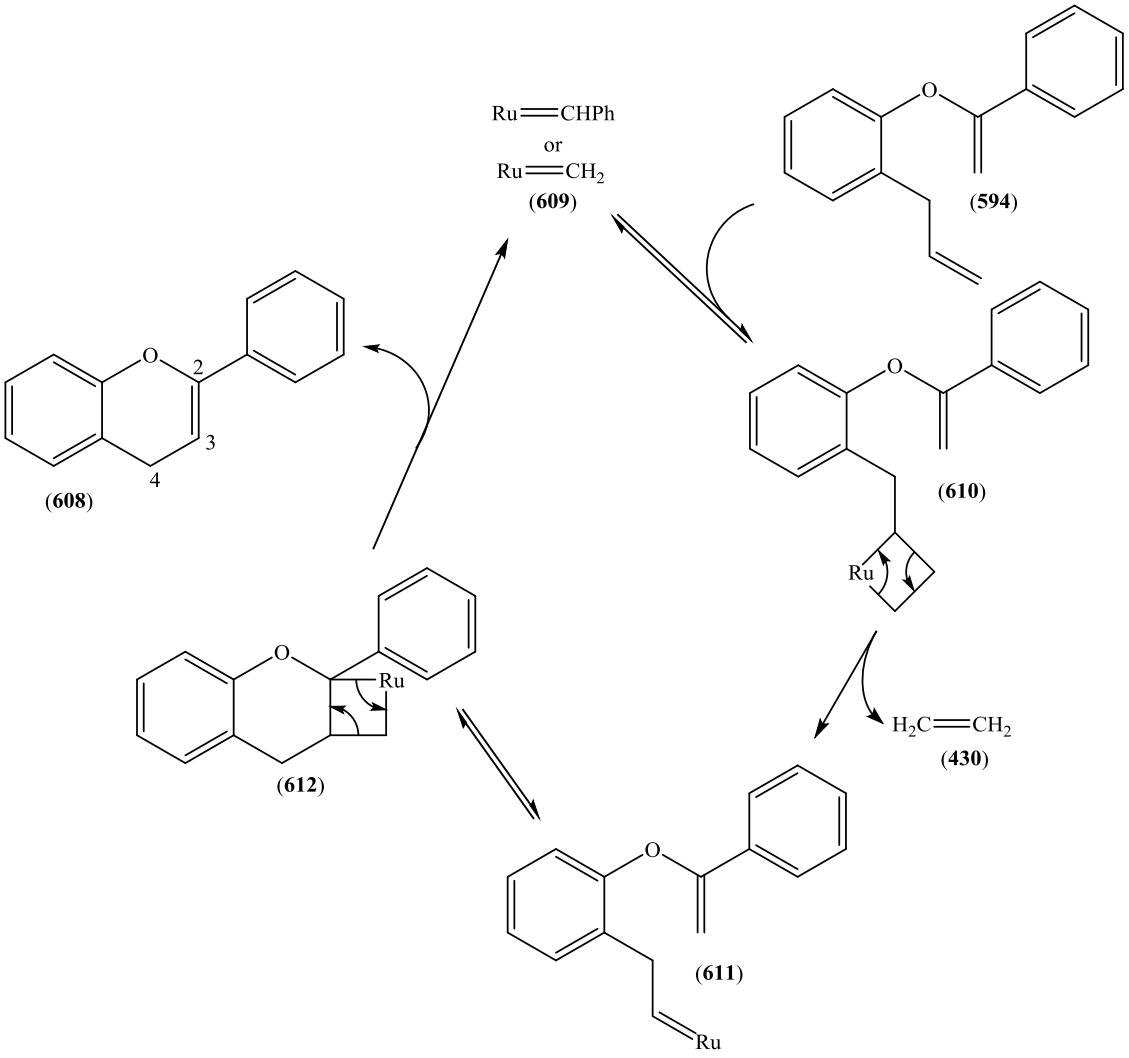
Scheme 5.25 Attempted methylenation-RCM through application of the Iyer and Rainier[16] method.

While several methods for the preparation of the titanium methylidene complex (**591**) have been investigated, all of these reagents led to no improvement in the outcome of the reaction and it may therefore be concluded that this would not be a viable protocol for the preparation of the flav-2-enes with the phloroglucinol A-ring substitution pattern. Unless new methodology for converting benzoates (**588**) and (**589**) into vinyl ethers is found, this method would not be suitable for the preparation of flavonoids with a phloroglucinol type A-ring and it is therefore proposed that the flav-3-ene route (Scheme 5.1) be investigated as means of obtaining the envisaged flavonoids *via* catalytic metathesis-based technology.

5.5 RCM of vinyl ethers: Synthesis of flav-2-enes

Although the vinyl ethers with phloroglucinol rings (**604**) and (**605**) could not be prepared, focus was subsequently turned towards the preparation of the flav-2-enes from the available vinyl ethers (**594**) and (**599**) – (**603**) *via* ring closing metathesis. The process was initiated utilising the unsubstituted model substrate, 2-allyl-1-(1-phenylvinyloxy)benzene (**594**), in

anhydrous DCM in the presence of Grubbs II catalyst under refluxing conditions. These reaction conditions led to the isolation of the desired flav-2-ene (**608**) as a dark orange oil in 92% yield (Scheme 5.26).



Scheme 5.26 Ring closing metathesis catalytic cycle

The structure of the flav-2-ene (**608**) product was confirmed through ^{1}H NMR (plate 32a), where a doublet of doublets resonance appeared at δ 5.67 (1H, *J* = 3.9, 3.9 Hz, H-3) and a broad doublet at δ 3.57 (2H, *J* = 3.9 Hz, H-4) indicative of the coupled protons present in the newly formed heterocyclic C-ring. The structure of the product was further confirmed by carbon resonances at δ 97.55 and 24.93 in the ^{13}C NMR spectrum (plate 32b) originating from C-3 and C-4, respectively, as well as mass spectrometry (EI) where the deprotonated molecular ion at *m/z* 207 $[M\text{-}H]^{+}$ (100%) was clearly visible.

With the RCM procedure being effective, the same methodology was applied to all the remaining vinyl ethers (Table 5.3).

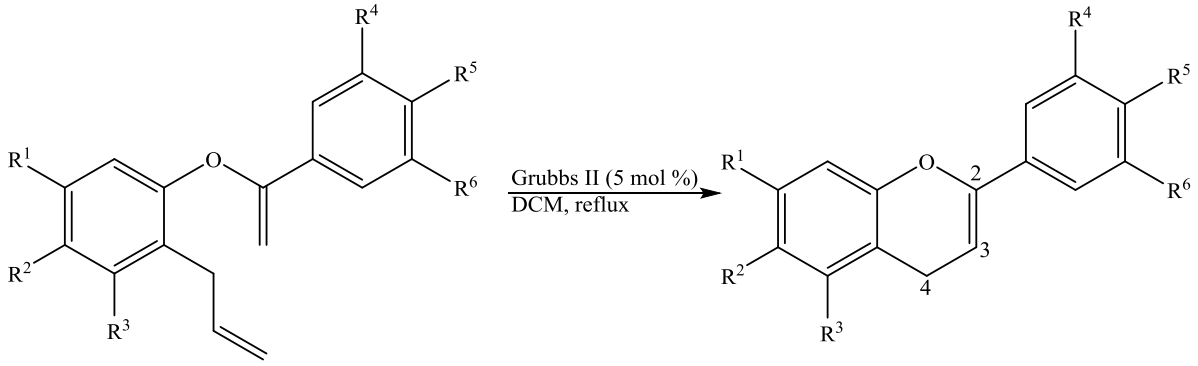


Table 5.3 Flav-2-ene syntheses

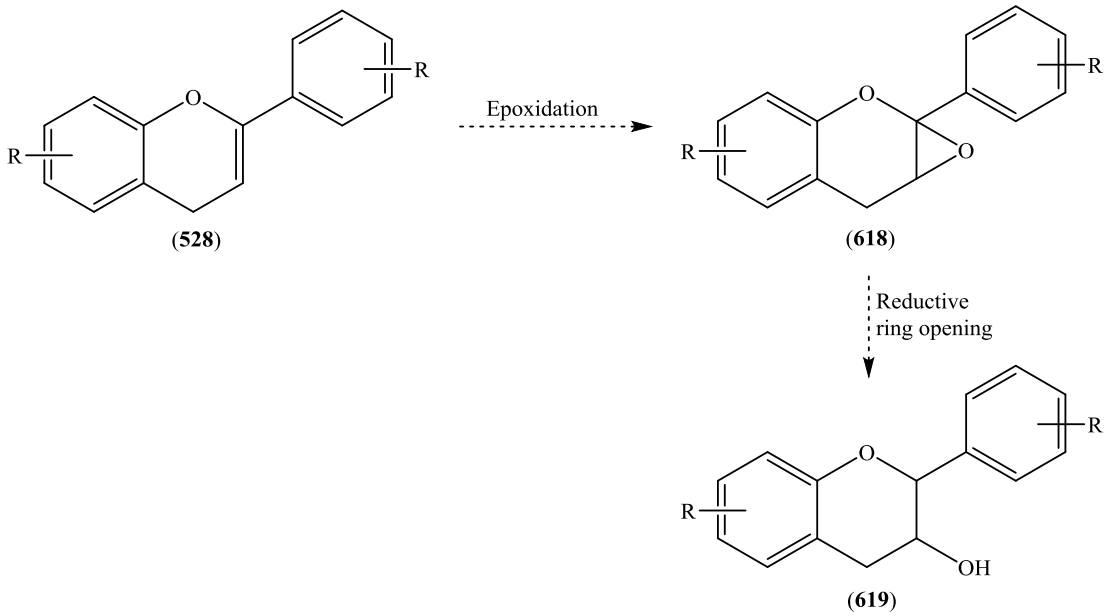
Plate	Substitution	^{1}H NMR: H-3, H-4	^{13}C NMR: C-3, C-4	MS	Yield (%)
32 (**608**)	R^1, R^2, R^3, R^4, R^5, R^6 = H	δ 5.67 (1H, dd, *J* = 3.9, 3.9 Hz) δ 3.57 (2H, br. d, *J* = 3.9 Hz)	δ 97.55 δ 24.93	207 [d] (100%)	92
33 (**613**)	R^1, R^2, R^3, R^4, R^6 = H R^5 = OMe	δ 5.54 (1H, dd, *J* = 3.9, 3.9 Hz) δ 3.55 (2H, br. d, *J* = 3.9 Hz)	δ 95.49 δ 24.81	239[a]	87
34 (**614**)	R^1, R^2, R^3, R^6 = H R^4, R^5 = OMe	δ 5.57 (1H, dd, *J* = 3.9, 3.9 Hz) δ 3.55 (2H, br. d, *J* = 3.9 Hz)	δ 95.85 δ 24.91	268 [c] (100%)	96
35 (**615**)	R^1, R^2, R^3 = H R^4, R^5, R^6 = OMe	δ 5.66 (1H, dd, *J* = 3.9, 3.9 Hz) δ 3.57 (2H, br. d, *J* = 3.9 Hz)	δ 97.15 δ 24.92	321[b]	96
36 (**616**)	R^2, R^3, R^6 = H R^1, R^4, R^5 =	δ 5.57 (1H, dd, *J* = 3.9, 3.9 Hz) δ 3.48 (2H, br. d, *J* = 3.9 Hz)	δ 96.21 δ 24.27	321[b]	76

	OMe				
37	R^2, R^3 = H	δ 5.65 (1H, dd, *J* = 3.9, 3.9 Hz)	δ 97.42	351[b]	41
(**617**)	R^1, R^4, R^5, R^6 = OMe	δ 3.48 (2H, br. d, *J* = 3.9 Hz)	δ 24.20		

[a] HR-MS ($[M + H]^+$) [b]HR-MS ($[M + Na]^+$) [c]GC-MS ($[M^+]$ [d]GC-MS ($[M-H]^+$)

5.6 Flav-2-ene epoxidation and isomerisation

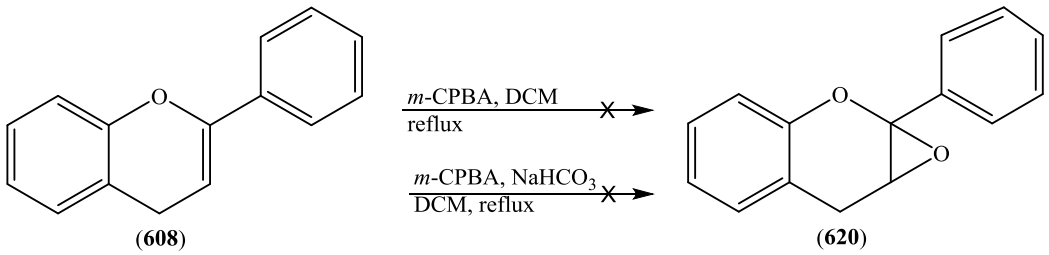
While flavenes show significant biological activity,[17] the hydroxylated analogues, like flavan-3-ols (**619**), are more abundant in plants[18] and also of more importance from a physiological point of view. It was therefore decided to investigate the obvious transformation of flav-2-enes (**528**) into the more abundant flavan-3-ols *via* an epoxidation step (Scheme 5.27).



Scheme 5.27 Proposed flavan-3-ols preparation from flav-2-enes

Subsequently, flav-2-ene (**608**) was treated with freshly recrystallized and dried *m*-CPBA (*m*-chloroperbenzoic acid) in DCM at rt. (Scheme 5.28). However, no desired product formation was detected under these conditions [MS(EI)]. Since the flav-2-ene epoxide (**620**), essentially represents an acetal moiety at C-2 and this compound might not be stable under the acidic conditions (*meta*-chlorobenzoic acid formed from the peracid) prevailing during the epoxidation process, it was decided to repeat the reaction in the presence of $NaHCO_3$ (2.0 eq.),[19] which would neutralise any acid present and possibly prevent decomposition of the

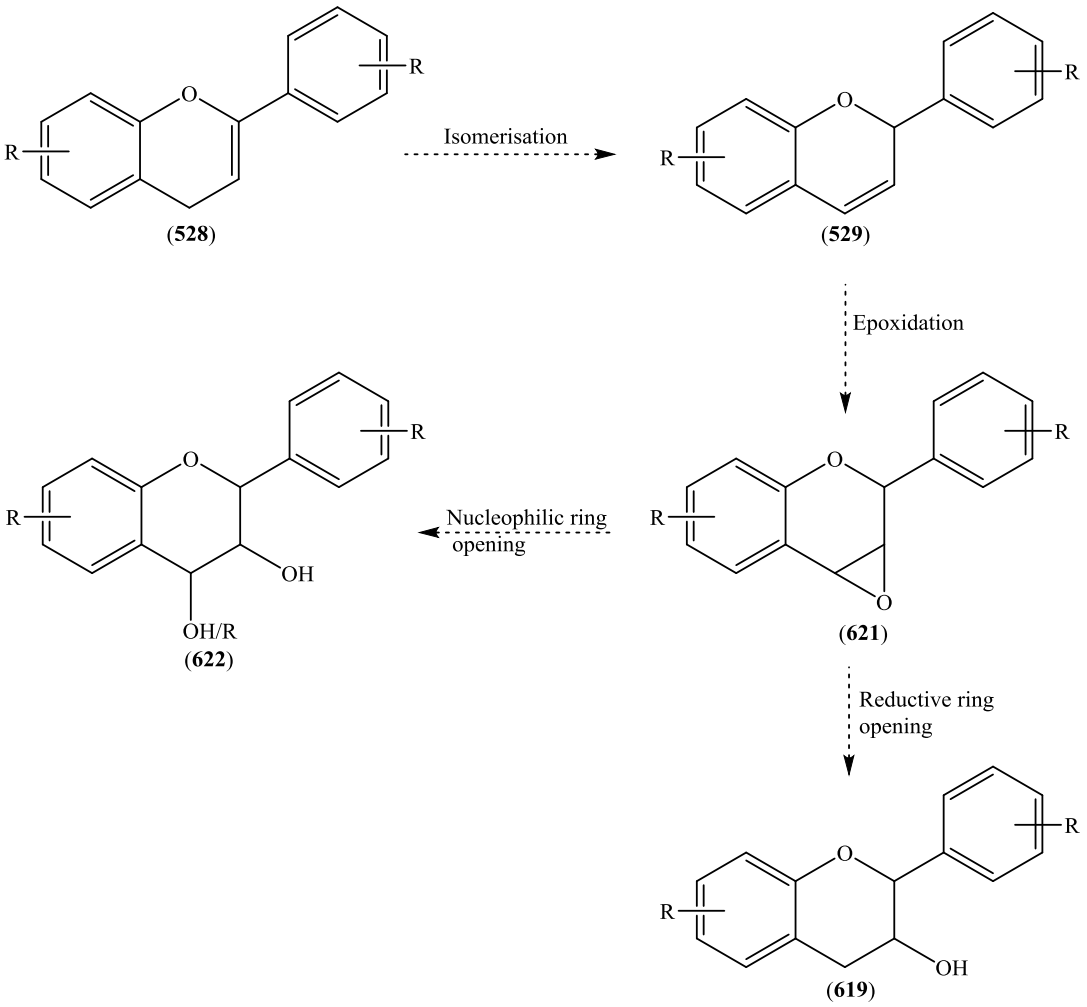
epoxide product. Again no product formation could be detected, so it was concluded that even under neutral conditions, the epoxide may not be stable enough to be isolated.



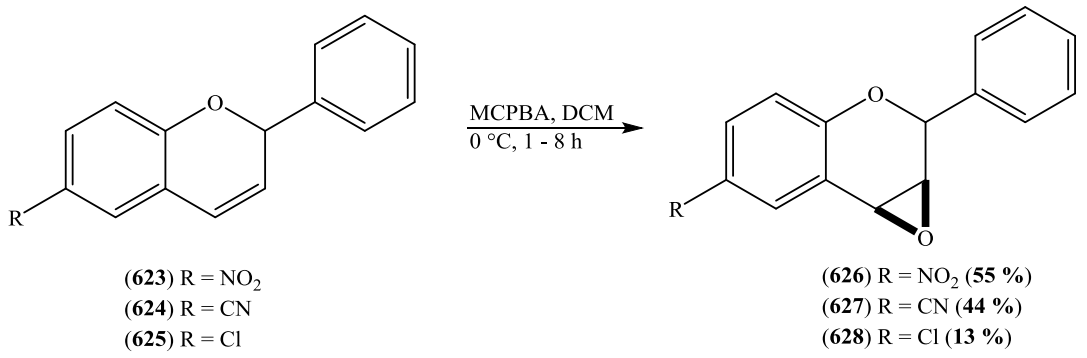
(**608**) (**620**)

Scheme 5.28 Flav-2-ene epoxidation

Since the flav-2-ene epoxide (**620**) could not be obtained and the corresponding flav-3-enes (**529**) could in principle be transformed into both flavan-3-ols (**619**) and flavan-3,4-diols (**622**), it was decided to investigate an isomerization process for preparing the desired flavonoid analogues (Scheme 5.29). Additional impetus for this approach came from a report by Page *et al*.[20] where it was shown that flav-3-enes (**623**), (**624**) and (**625**) containing electron withdrawing groups attached to the A-ring could be epoxidized in 13 – 55% yield by reaction with *m*-CPBA in DCM (Scheme 5.30).



Scheme 5.29 Possible flav-3-ene transformations into flavan-3-ols and flavan-3,4-diols



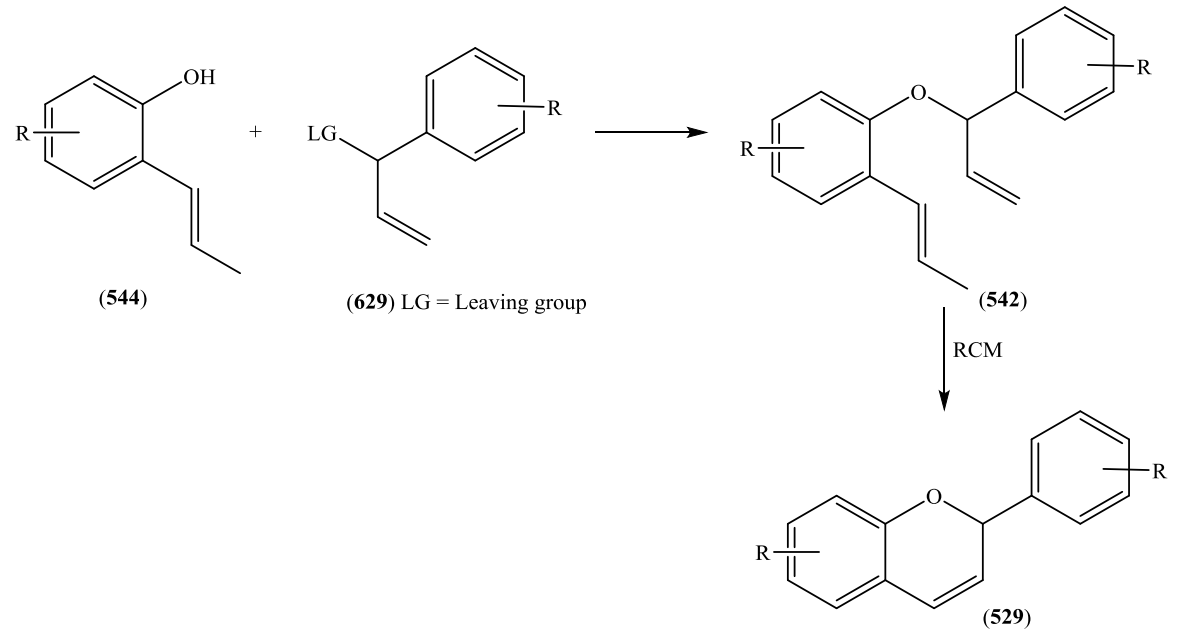
Scheme 5.30 Reported epoxidation of electron-poor flav-3-enes with *m*-CPBA

Treatment of 3',4',5',7-tetramethoxyflav-2-ene (**617**) with Grubbs isomerization catalyst, carbonylchlorohydridotris(triphenylphosphine)ruthenium(II), however, yielded only the starting material even after 8 hours of refluxing (GC-MS). Since the flav-2-ene contains a trisubstituted double bond and isomerization to the 3-position would mean moving to a disubstituted double bond, this process was expected to be energetically unfavourable and

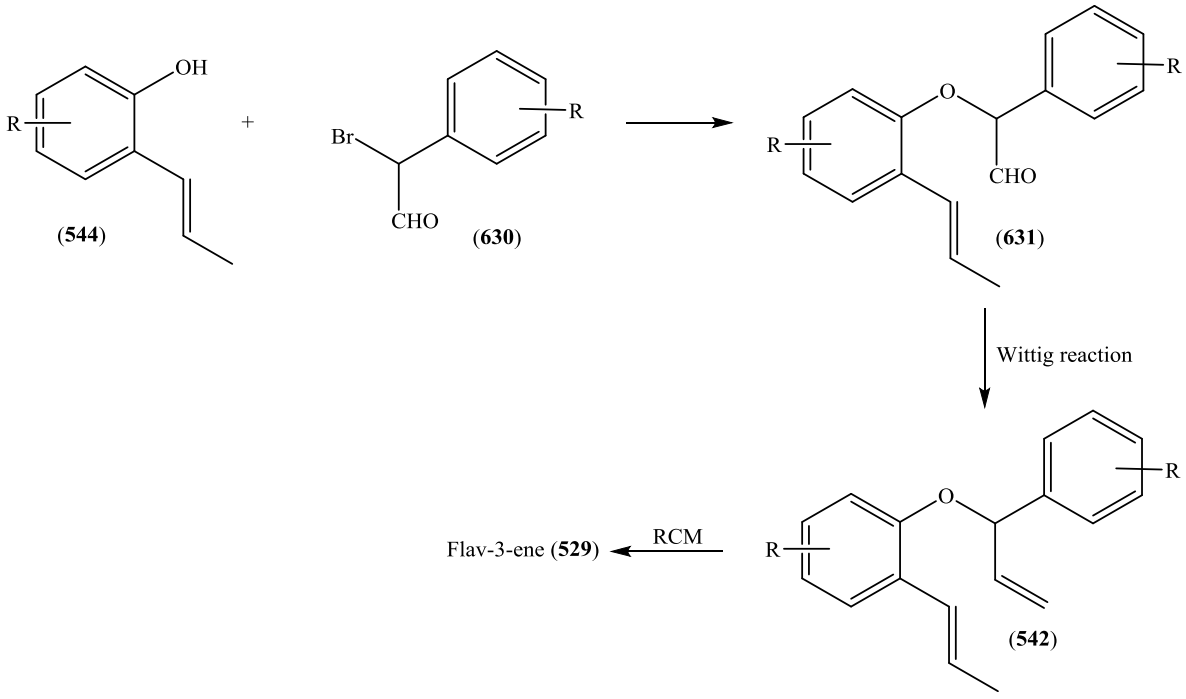
thus slow, if possible at all. Since it has been reported that the flav-3-enes can be isomerised into the flav-2-ene analogues by refluxing under basic conditions in benzene,[21] no further attention was given to this aspect of the methodology.

5.7 Conclusions and future work

Although several attempts at the direct *C*-allylation of phenols were investigated, these were not successful and the desired *C*-allylated phenols were subsequently obtained by Claisen rearrangement of the allyloxybenzenes (**575**) and (**576**) under neat microwave conditions, which led to the desired 1-allyl-2-hydroxybenzenes (**552**) and (**553**) to be synthesised in 44% and 88% yields, respectively, without tedious acidic work-up procedures. The 1-allyl-2-hydroxybenzenes could be esterified with 3-methoxy substituted benzoyl chlorides (**579**), (**580**) and (**581**), before the esters (**583**) – (**587**) were converted to the corresponding vinyl ethers (**599**) – (**603**) by treatment with the Tebbe reagent. High yields (71 – 94%) were obtained with an increase in the concentration of the reactants (2-allylphenyl benzoate: 400 mg in 1 – 2 mL THF and 2.0 eq of the Tebbe reagent) and a brief period of refluxing (2 h), after initially keeping the temp. at 0 ^{o}C for 30 min. and rt. for an hour. Despite evaluating a variety of conditions with the Tebbe reagent as well as other methylenation reagents (Nysted reagent and a mixture of $TiCl_4$, Zn, $PbCl_2$, TMEDA, CH_2Br_2 in THF) the two esters containing a phloroglucinol type allyl phenol entity (**588**) and (**589**) could not be converted into the vinyl ethers required for RCM. A one-pot methylenation-RCM approach also did not give any positive results and led to inseparable mixtures of products with no indication of the desired compounds being present (MS). Finally, RCM of the six available vinyl ethers (**594**) and (**599**) – (**603**), under standard metathesis conditions [Grubbs (II), DCM, reflux] led to the desired flav-2-enes (**608**) and (**613**) – (**617**) in 41 – 96% yields, which proved that flav-2-enes and thus the basic flavonoid skeleton could in fact be constructed by the envisaged metathesis based methodology. If preparation of phloroglucinol type vinyl ethers proved to be completely impossible during subsequent investigations, this methodology could be adapted to the preparation of the flav-3-ene analogues (**529**) through RCM of the 1-vinyl benzyl ether analogues [e.g. (**542**)], available as indicated in either Scheme 5.31 or 5.32.



Scheme 5.31 Flav-3-ene synthesis through RCM of 1-vinyl benzyl ether



Scheme 5.31 Alternative flav-3-ene synthesis through RCM of 1-vinyl benzyl ether

Although attempts at converting the available flav-2-enes into examples of 'real' flavonoid analogues were not successful, this aspect of the methodology was not exhaustively investigated and only one epoxidizing system (*m*-CPBA) was evaluated in this regard. Since many more modern epoxidizing agents, like different dioxiranes and hydroperoxides could

still yield the desired products, this aspect of the research will receive attention during a follow-up investigation.

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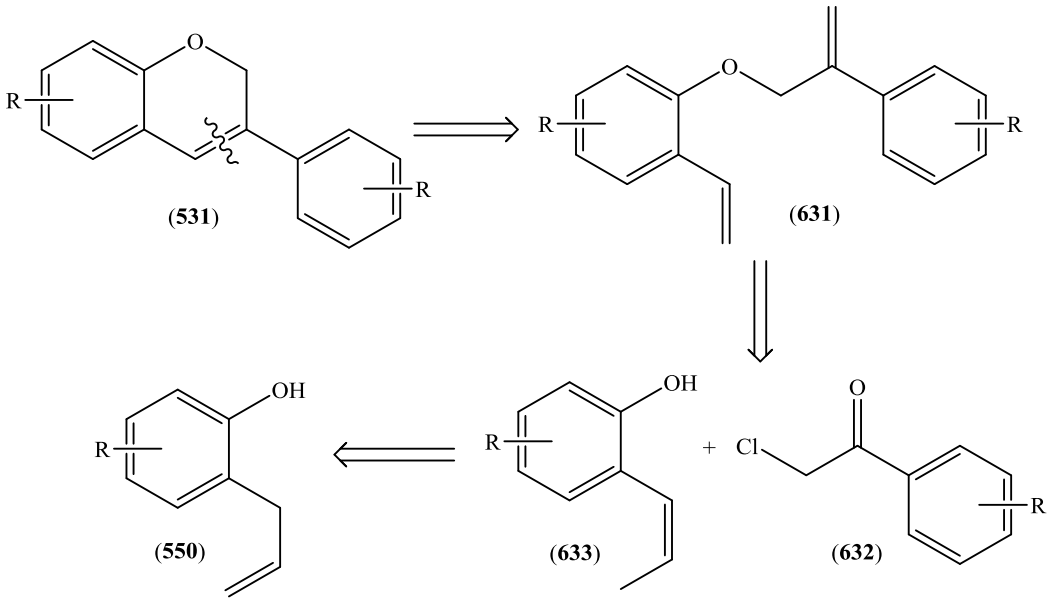
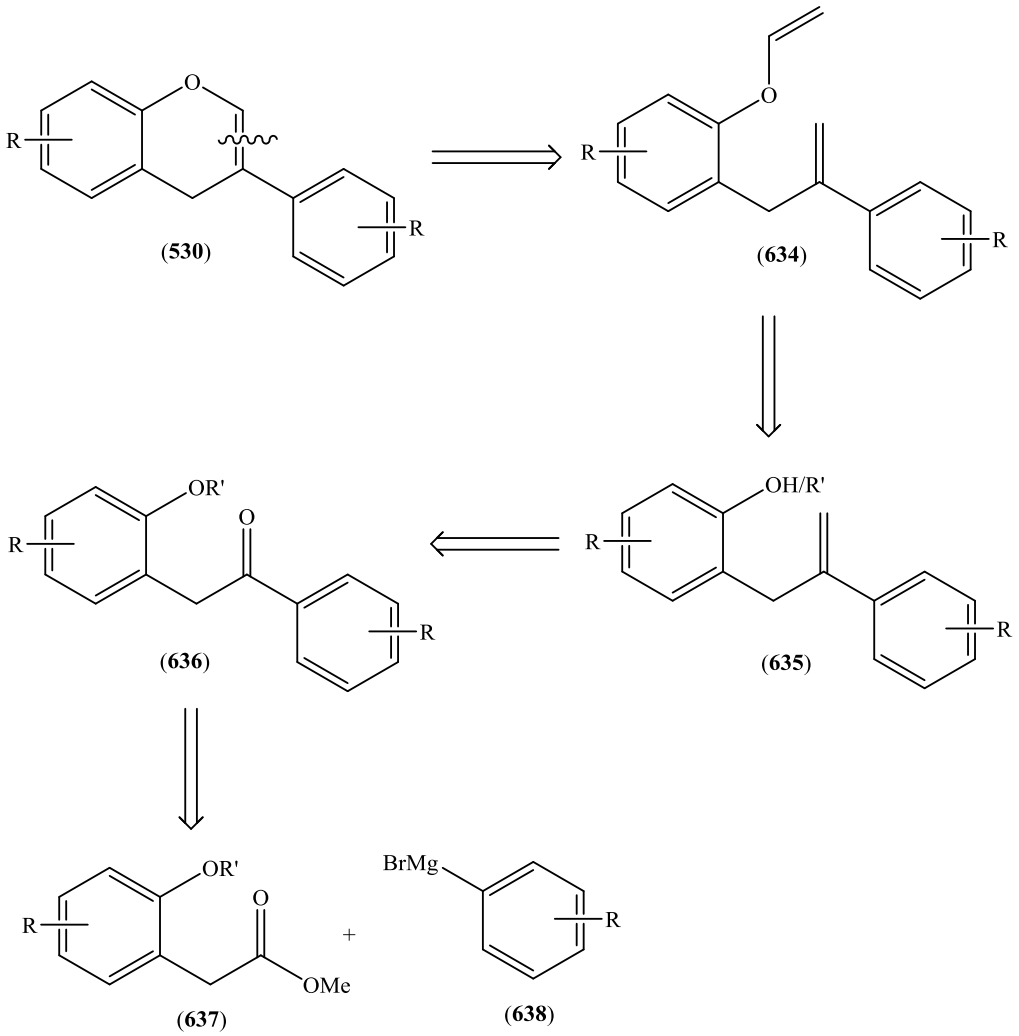
Chapter 6: Synthesis of Isoflavenes

Introduction

Similar to the flavene skeleton, the isoflavene framework can be obtained either as the isoflav-3-ene (**531**) or isoflav-2-ene (**530**) as depicted in the retrosynthesis presentations below (Scheme 6.1 and 6.2).



Scheme 6.1 Isoflav-3-ene retrosynthesis



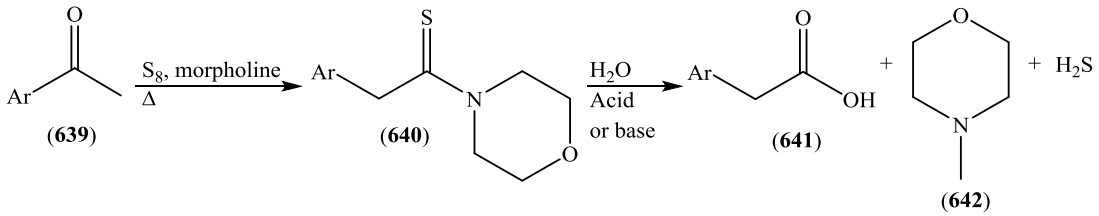
Scheme 6.2 Isoflav-2-ene retrosynthesis

Even though the first retrosynthesis approach represents a promising synthesis route, the second disconnection would require a phenacyl halide (**632**) and while this step might not be problematic, the process could be complicated when utilising oxygenated phenacyl analogues. The second retrosynthesis approach, on the other hand, utilises the deoxybenzoin intermediate (**636**), which could be prepared from the appropriate ester (**637**) and Grignard reagent (**638**) and would therefore involve, a known chemical transformation followed by *O*-vinylation of a 2'-hydroxy entity which is known to proceed in the presence of tetravinyl tin.[1,2] It was therefore decided to construct the isoflav-2-ene (**530**) skeleton through the deoxybenzoin (**636**) and phenylacetic acid (**637**) approach as indicated in Scheme 6.2.

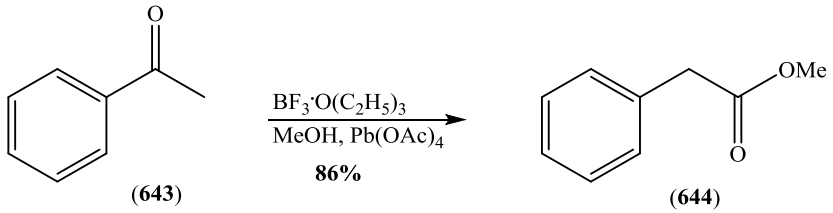
6.1 Isoflav-2-ene synthesis

6.1.1 Preparation of phenylacetic acid derivatives

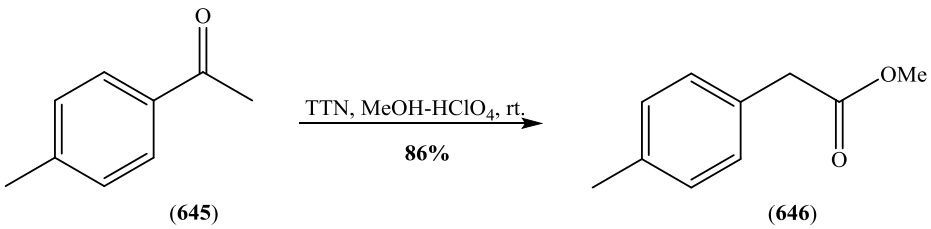
While several methods for the preparation of phenylacetic acid derivatives like the Willgerodt-Kindler reaction[3,4,5,6] (Scheme 6.3), lead(IV) acetate or $Tl(NO_3)_3$ oxidative rearrangements[3,7] (Scheme 6.4 and 6.5) and other reactions[5] (Scheme 6.6, 6.7 and 6.8) are known, most of these methods are hampered by serious limitations. The Willgerodt-Kindler reaction is complicated by the requirement of high reaction temperatures and excessive quantities of elemental sulphur leading to the formation of large amounts of odorous side-products, while yields are also variable.[3,4,5] The methodologies developed by McKillop[3] [$Tl(NO_3)_3$] and Myrboh[8] [lead(IV) acetate] utilises toxic heavy metal reagents[9] and are also not always high yielding and compatible with all substitution patterns, while the Grignard reaction is hampered by side-reactions including dimeric alkyl halide coupling.[10] Palladium catalysed carbonylation, requires benzyl halides as starting materials which may be difficult to prepare when oxygenated, while nitrile hydrolysis requires stoichiometric amounts of acid and high temperature and could lead to substitution with water.



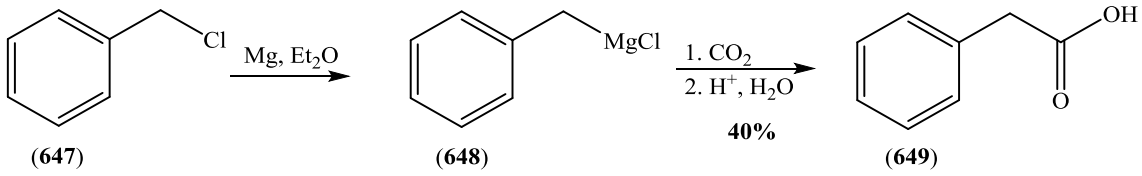
Scheme 6.3 Willgerodt-Kindler reaction



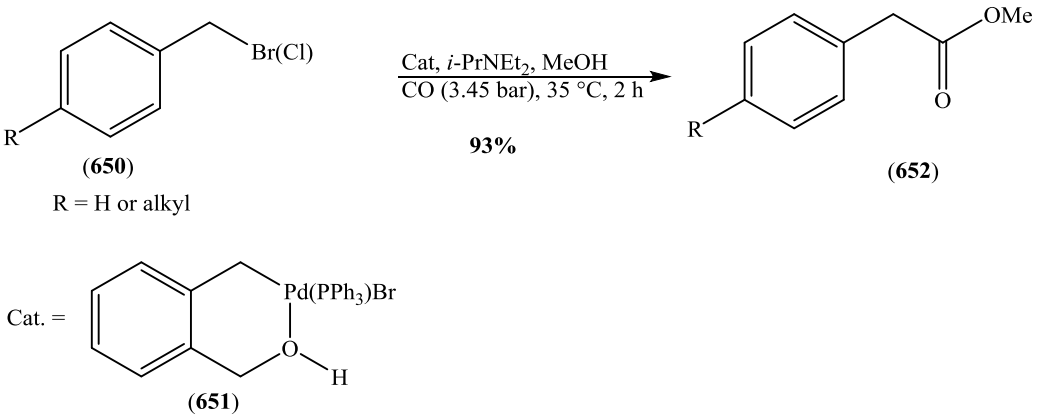
Scheme 6.4 Myrboh Process



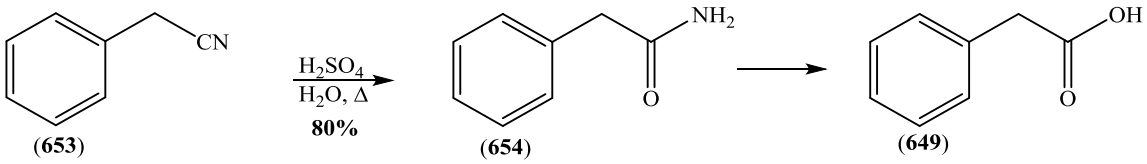
Scheme 6.5 TTN Rearrangement of benzophenones (McKillop synthesis)



Scheme 6.6 Grignard reactions with CO_2



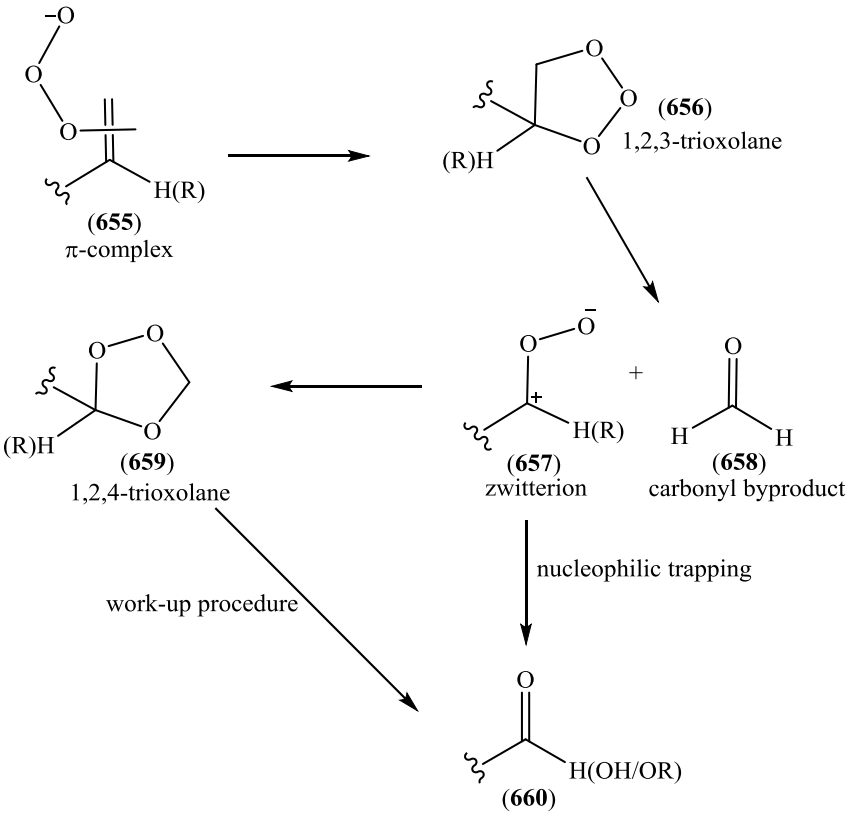
Scheme 6.7 Pd-catalysed carbonylation of benzyl halides



Scheme 6.8 Acid catalysed hydrolysis of benzonitriles

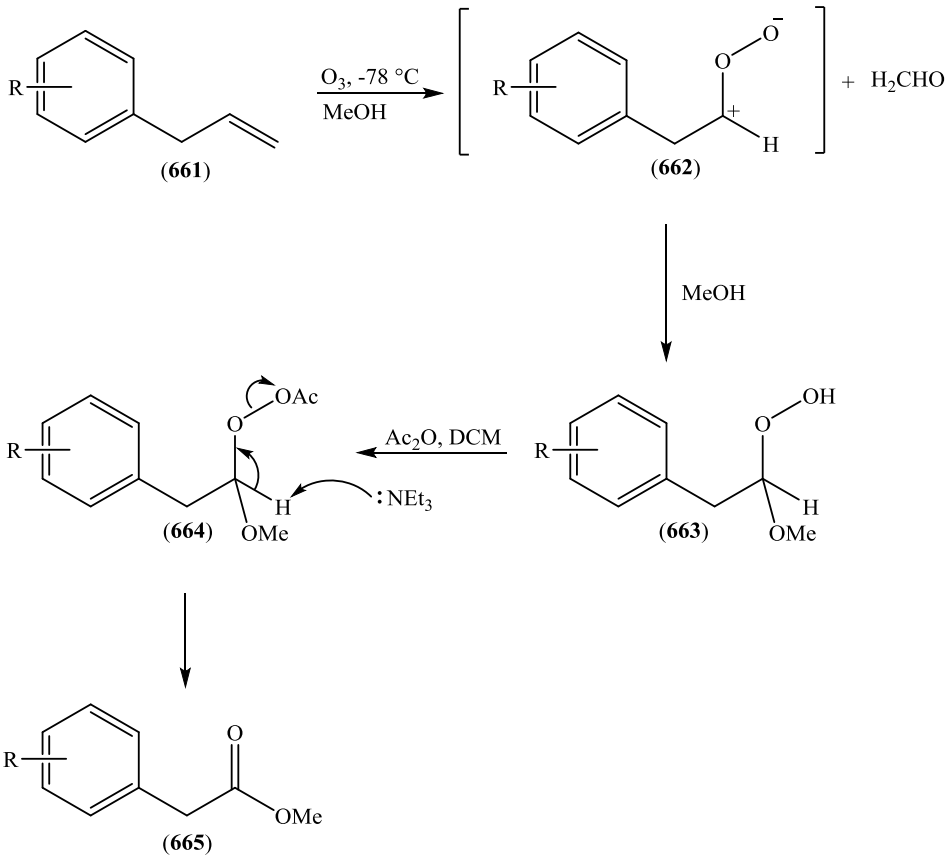
It was therefore decided to develop a benign synthesis route for the preparation of phenylacetic acid derivatives that would utilise readily available starting materials and be compatible with the substitution patterns of naturally occurring isoflavonoids. Since ozonolysis of substituted allyl benzenes has the potential to meet these requirements, this reaction was investigated as methodology for the preparation of phenylacetic acid derivatives from allyl benzenes.

The initial interaction between the dipolar O_3 and the olefinic substrate can be viewed as the formation of a π-complex (**655**), which is subsequently transformed into a primary ozonide [1,2,3-trioxolane (**656**)] *via* a highly exothermic cycloaddition.[11,12] The primary ozonide, the 1,2,3-trioxolane (**656**), is short lived and almost immediate transformed into a bipolar zwitterion (**657**) and carbonyl byproduct (**658**) before recyclisation to the 1,2,4-trioxolane (**659**) according to the accepted Criegee mechanism.[13] The 1,2,4-trioxolane (**659**) may now be converted to an aldehyde if a reductive work-up procedure is followed or an acid if oxidative conditions are prevailing (Scheme 6.9).[11,12,14]



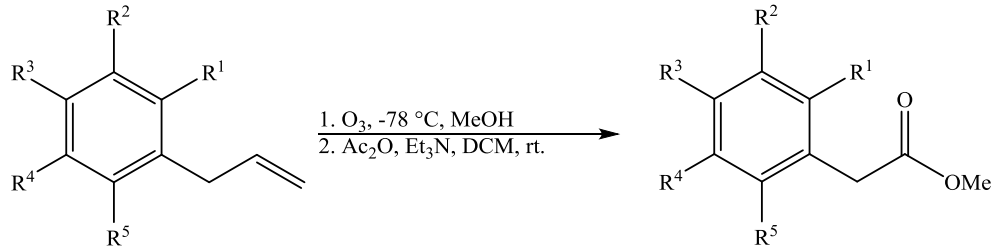
Scheme 6.9 Criegee ozonolysis mechanism

Since methyl phenylacetates (**665**) were the desired products from the ozonolysis reaction, allyl benzene substrates (**661**) were treated with ozone in methanol and the intermediate peroxide (**663**) decomposed by acetylation and treatment with triethylamine (Scheme 6.10).[15]



Scheme 6.10 Mechanism of the ozonolysis of allyl benzenes in methanol

Although initial yields for substrates (**666**) – (**669**) were low, increasing the scale of the reactions to *ca*. 500 mg led to the desired products (**670**) – (**673**) in 80 – 99% yield (Scheme 6.11).



(**666**) R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = H
(**667**) R^1 = H, R^2 = H, R^3 = CF_3, R^4 = H, R^5 = H
(**668**) R^1 = H, R^2 = H, R^3 = OTf, R^4 = OMe, R^5 = H
(**669**) R^1 = H, R^2 = OMe, R^3 = OTf, R^4 = OMe, R^5 = H

(**670**) R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = H (**99%**)
(**671**) R^1 = H, R^2 = H, R^3 = CF_3, R^4 = H, R^5 = H (**96%**)
(**672**) R^1 = H, R^2 = H, R^3 = OTf, R^4 = OMe, R^5 = H (**80%**)
(**673**) R^1 = H, R^2 = OMe, R^3 = OTf, R^4 = OMe, R^5 = H (**88%**)

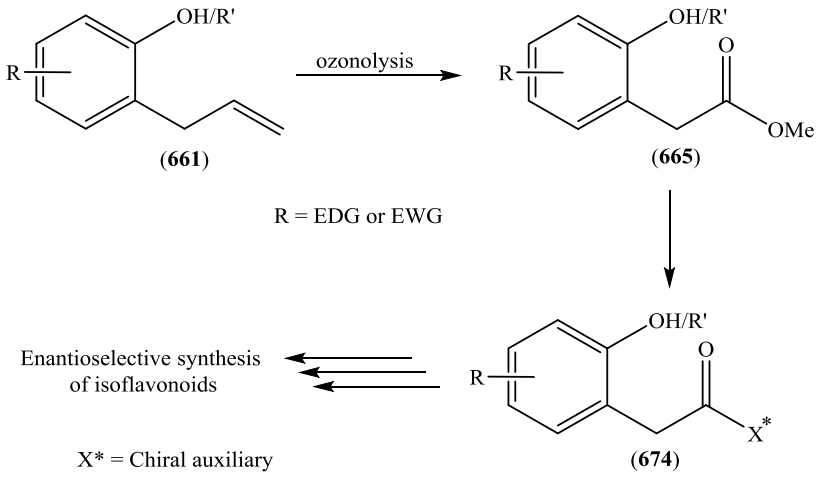
Scheme 6.11 Preparation of methyl phenylacetates through ozonolysis

The structures of (**670**), (**671**), (**672**) and (**673**) were confirmed by ^{1}H NMR spectroscopy (plates 38a, 39a, 40a and 41a) where the -C<u>H</u>$_2$- moieties were clearly visible as singlets at δ

3.57, 3.69, 3.63, 3.59 and the -COOMe groups as singlets at δ 3.68, 3.71, 3.72 and 3.72, respectively. Further confirmation of the structures of the products were obtained by MS (EI) where the molecular ions were observed at *m/z* 180 (23%), 217 (38%), 328 (30%) and 358 (15%) for (**670**), (**671**), (**672**) and (**673**), respectively.

Although it has been found that phenylacetates with a variety of substitution patterns could be prepared in excellent yields *via* ozonolysis, the transformation of these compounds into the required deoxybenzoins (**636**) were hampered by the inability (even at temperatures as low as -78 ^{o}C) of stopping the reaction of the phenyl Grignard reagent (PhMgBr) with the ester at the ketone stage. Due to the fact that ketones are more reactive towards Grignard reagents than esters, the tertiary alcohols from these reactions were always isolated as the only product. Since Grignard reagents would not be compatible with methyl phenylacetates containing a free 2'-hydroxy group, this protocol would furthermore require another protection-deprotection step, which would render it too tedious for the economical preparation of the isoflav-2-enes. The focus of the current technology development was therefore shifted towards the synthesis of isoflav-3-enes (**531**) as general precursor for the preparation of isoflavonoids by RCM (*cf.* Scheme 6.1).

While the development of improved methodology for the preparation of phenylacetates (**665**) through ozonolysis of allyl benzenes (**661**) did not lead to new technology for the synthesis of isoflavonoids *via* RCM, it has the potential of improving the enantioselective synthesis of these compounds through the method reported by Versteeg *et al.*[16,17] (Scheme 6.12) and was therefore of value to the synthesis of isoflavonoids in general.

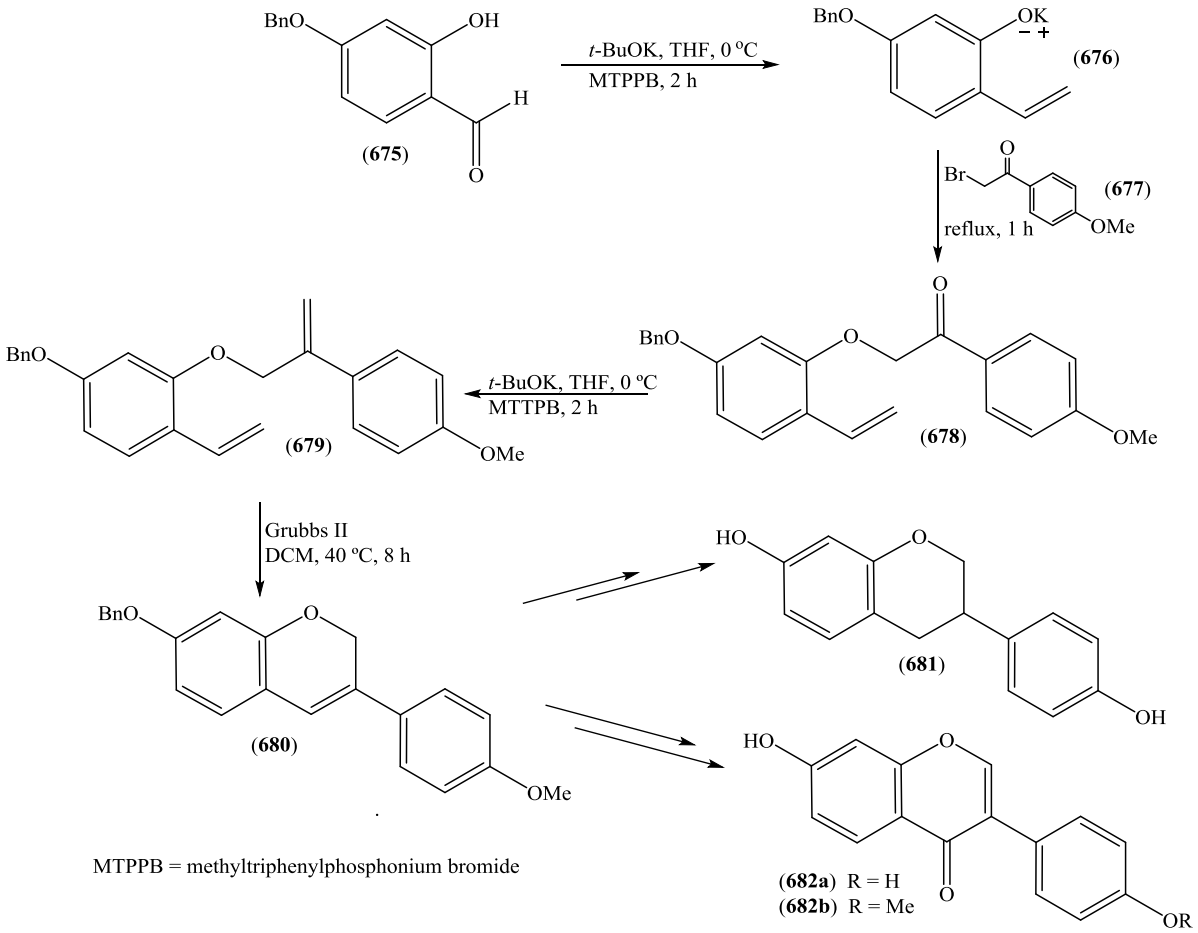


Scheme 6.12 Enantioselective synthesis of isoflavonoids

6.2 Preparation of isoflav-3-enes

6.2.1 Preparation of styrene derivatives

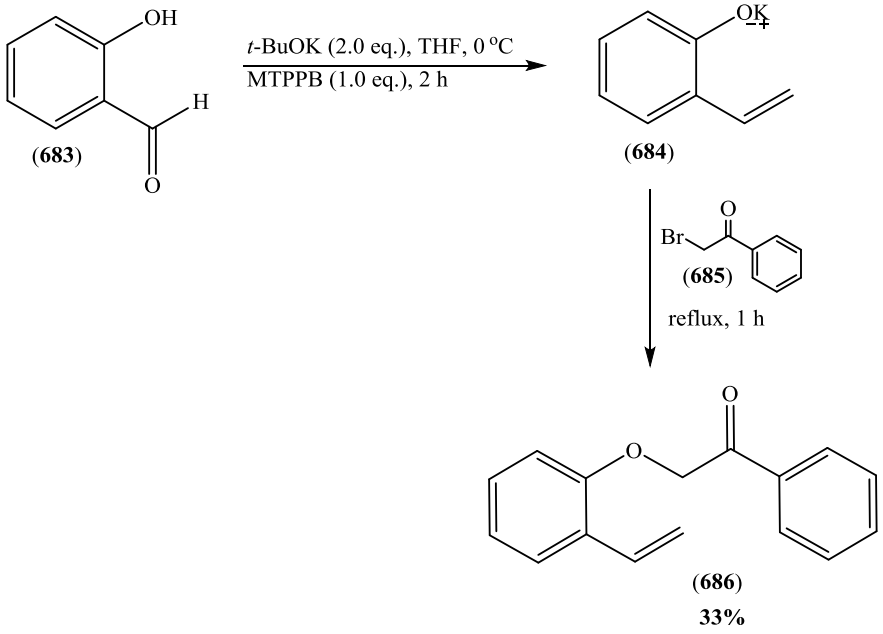
Since Li *et al.*[18] reported the synthesis of *rac*-equol (**681**), daidzein (**682a**) and formononetin (**682b**) through the preparation of the styrene precursors (**679**) *via* phenacyl ether formation and double Wittig reaction (Scheme 6.13), it was decided to follow this approach for the synthesis of the envisaged series of isoflav-3-enes.



Scheme 6.13 Isoflav-3-enes through RCM of styrene intermediates

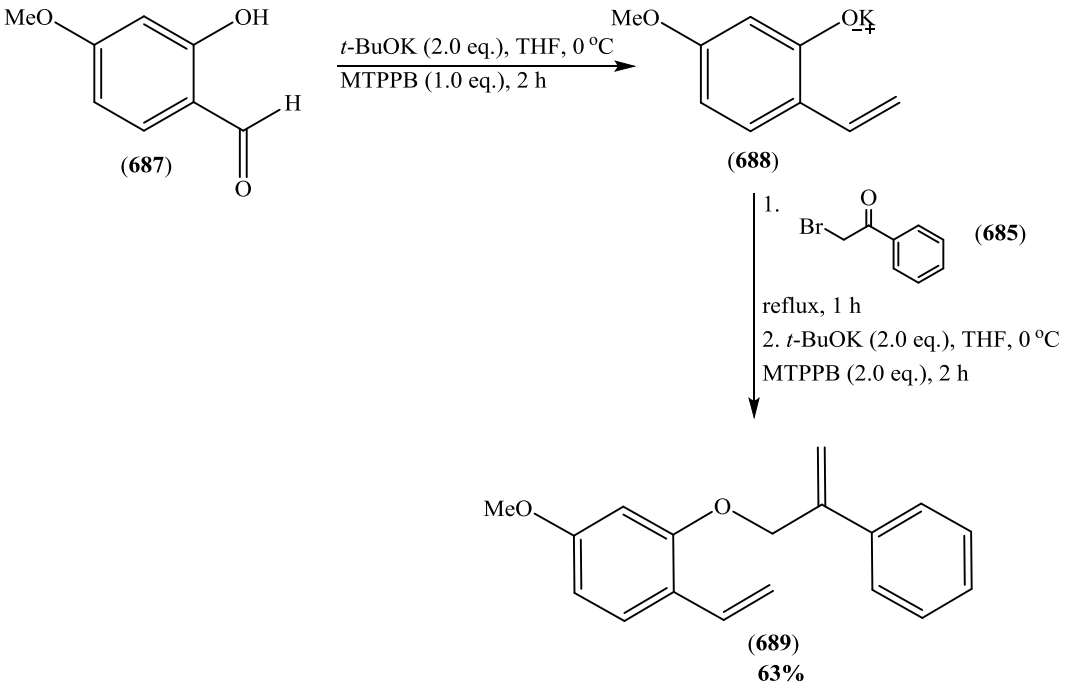
Reaction of 2-hydroxybenzaldehyde (**683**) with potassium *tert*-butoxide (2.0 eq.), methyltriphenylphosphonium bromide (MTPPB) and 2-bromoacetophenone (**685**) gave the desired 2-(2-vinylphenoxy)acetophenone (**686**) in 33% yield (Scheme 6.14). The structure of the phenoxyacetophenone (**686**) was confirmed by the ^{1}H NMR spectrum (plate 42a) where, apart from all the expected aromatic resonances, the -C$\underline{H_2}$- moiety was observed at δ 5.57 (2H, s) and the vinyl protons appeared at δ 7.16 (1H, dd, *J* = 17.8, 11.3 Hz), δ 5.88 (1H, dd, *J* = 17.8, 1.6 Hz) and δ 5.25 (1H, dd, *J* = 11.3, 1.6 Hz). Furthermore, the resonance of the

carbonyl functionality was observed at δ 194.76 in the ^{13}C NMR spectrum (plate 42b), while a molecular ion of *m/z* 238 (22%) was present in the mass spectrum.



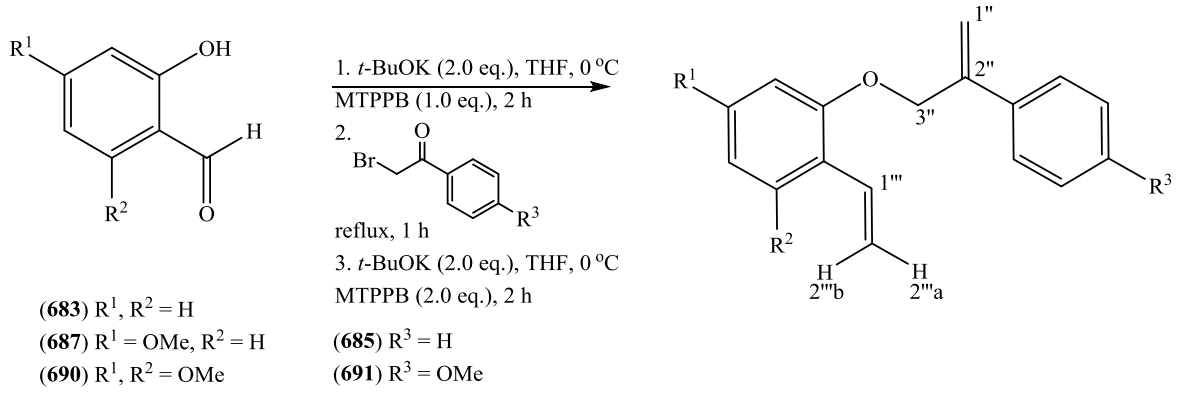
Scheme 6.14 2-(2-Vinylphenoxy)-acetophenone synthesis

Subsequent treatment of the phenoxyacetophenone (**686**) with one equivalent of the MTPPB ylide in a new reaction pot at room temperature, however, led to only starting material (**686**) being recovered even after 12 hours of reaction time. However, when the synthesis protocol was repeated with 2-hydroxy-4-methoxybenzaldehyde (**687**) and 2-bromoacetophenone (**685**), the desired product, (**689**), was obtained, albeit in only 35% yield. Increasing the concentration of the Wittig reagent to two equivalents (2.0 eq. of MTPPB and *t*-BuOK) in the final reaction resulted in the desired protected vinyl benzene (**689**) being formed in 63% (Scheme 6.15).



Scheme 6.15 4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene synthesis

Extending this synthetic protocol to the reactions of 2-hydroxybenzaldehyde (**683**), 2-hydroxy-4-methoxybenzaldehyde (**687**) and 2-hydroxy-4,6-dimethoxybenzaldehyde (**690**) with 2-bromoacetophenone (**685**) and 2-bromo-4'-methoxyacetophenone (**691**) led to the formation and isolation of all the desired products in excellent yields (Table 6.1). Thus the vinyl benzene starting materials for the synthesis of isoflav-3-enes exhibiting the substitution pattern of most naturally occurring isoflavonoids were obtained. The structures of the vinyl benzene products (**689**) and (**692**) – (**695**) were confirmed by ^{1}H and ^{13}C NMR as well as MS data (Table 6.1).



(**683**) R^1, R^2 = H
(**687**) R^1 = OMe, R^2 = H
(**690**) R^1, R^2 = OMe

(**685**) R^3 = H
(**691**) R^3 = OMe

Table 6.1 Vinyl benzene syntheses

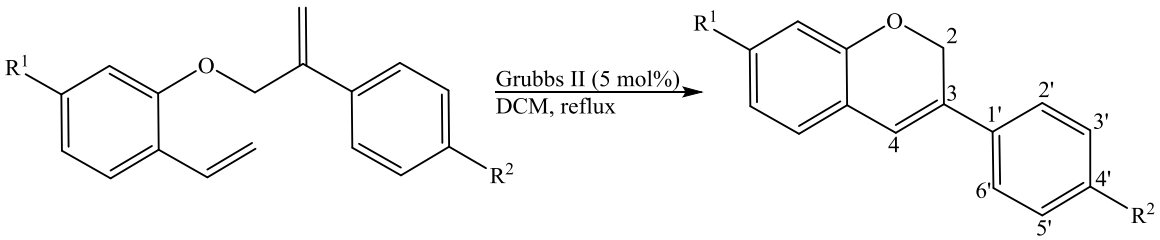
Plate	Substitution	^{1}H NMR: Double bonds	MS	Yield (%)
43 (**689**)	R^1 = OMe, R^2 = R^3 = H	δ 6.90 (1H, dd, *J* = 17.8, 11.2 Hz, H-1'''); δ 5.68 – 5.67 (1H, m, H-1''); δ 5.60 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b); δ 5.55 – 5.53 (1H, m, H-1''); δ 5.03 (2H, br. s, H-3''); δ 5.02 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a)	267[a]	63
44 (**692**)	R^1 = R^2 = OMe, R^3 = H	δ 6.86 (1H, dd, *J* = 17.9, 12.0 Hz, H-1'''); δ 5.87 (1H, dd, *J* = 17.9, 3.0 Hz, H-2'''b); δ 5.66 – 5.64 (1H, m, H-1''); δ 5.53 – 5.52 (1H, m, H-1''); δ 5.10 (1H, dd, *J* = 12.0, 3.0 Hz, H-2'''a); δ 5.01 (2H, br. s, H-3'')	319[b]	76
45 (**693**)	R^1 = R^2 = H, R^3 = OMe	δ 7.00 (1H, dd, *J* = 17.8, 11.2 Hz, H-1'''); δ 5.73 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b)	267[a]	89

		δ 5.57 – 5.56 (1H, m, H-1") δ 5.41 – 5.40 (1H, m, H-1") δ 5.16 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'"a) δ 4.98 (2H, br. s, H-3")		
46 (**694**)	$R^1 = R^3$ = OMe R^2 = H	δ 6.96 – 6.90 (1H, m, H-1'") δ 5.61 (dd, *J* = 17.8, 1.6 Hz, H-2'"b), δ 5.58 (1H, br. s, H-1") δ 5.43 – 5.42 (1H, m, H-1") δ 5.04 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'"a) δ 4.97 (2H, br. s, H-3")	296 [c] (100%)	61
47 (**695**)	R^1, R^2, R^3 = OMe	δ 6.85 (1H, dd, *J* = 18.0, 12.3 Hz, H-1'") δ 5.86 (1H, dd, *J* = 18.0, 3.0 Hz, H-2'"b) δ 5.57 (1H, br. s, H-1") δ 5.43 – 5.41 (1H, m, H-1") δ 5.09 (1H, dd, *J* = 12.3, 3.0 Hz, H-2'"a) δ 4.99 (2H, br. s, H-3")	349[b]	70

[a]HR-MS ($[M + H]^+$) [b]HR-MS ($[M + Na]^+$) [c]GC-MS ($[M^+]$)

6.2.2 Construction of the heterocyclic ring of the isoflav-3-enes

With the desired vinyl benzenes in hand, attention was turned towards transforming these compounds to the isoflav-3-ene analogues with RCM. When the standard ring closing metathesis conditions [Grubbs II (5 mol%), DCM, reflux] were applied to the mono- and di-oxygenated phenyl ethers (**689**), (**693**) and (**694**) it resulted in the isoflav-3-enes (**696**), (**697**) and (**698**) being formed in 57% to quantitative yields (Scheme 6.16).



(**689**) R^1 = OMe, R^2 = H
(**693**) R^1 = H, R^2 = OMe
(**694**) R^1 = R^2 =OMe

(**696**) R^1 = OMe, R^2 = H (**quantitative**)
(**697**) R^1 = H, R^2 = OMe (**86%**)
(**698**) R^1 = R^2 =OMe (**57%**)

Scheme 6.16 Isoflav-3-enes *via* RCM of styrene derivatives

The structures of the isoflav-3-enes (**696**), (**697**) and (**698**) were confirmed by ^{1}H NMR spectra (plates 48a, 50a and 52a) where the vinyl proton resonances (H-4) appeared at δ 6.97, 6.87 and 6.84 (1H, br. s), respectively, and the heterocyclic methylene signals (H-2) as sets of singlets at δ 5.18 and 5.17, 5.15 and 5.14 and 5.13 and 5.13 respectively for (**696**), (**697**) and (**698**). While geminal coupling of these protons (d, J ~ 1.1 Hz) is expected, the methylene protons for each compound in this instance appear as two singlets, which is difficult to explain at this stage. Final confirmation of the structures of the isoflav-3-enes (**696**), (**697**) and (**698**) were obtained from the ^{13}C NMR spectra (plate 48b, 50b, 52b) where the heterocyclic carbon resonances were clearly visible [δ 129.55 (C-3), 120.54 (C-4), 67.67 (C-2) for (**696**), 132.42 (C-3), 118.65 (C-4), 67.53 (C-2) for (**697**) and 129.35 (C-3), 118.61 (C-4), 67.73 (C-2) for (**698**)] and by mass spectrometry where the molecular ions were present at *m/z* 238 (M^+, 100%), 238 (M^+, 100%) and 268 (M^+, 100%) for (**696**), (**697**) and (**698**), respectively.

Although the 4'-methoxyisoflav-3-ene (**697**) was obtained in 86% yield, the desired product was accompanied by a small amount of a side product (5%). With all the resonances of the aromatic rings [(δ 7.60 – 7.58 (1H, m), 7.54 – 7.52 (1H, m), 7.46 (2H, d, J = 9.0 Hz, H-2' and H-6'), 7.35 – 7.32 (1H, m), 7.25 – 7.22 (1H, m), 6.94 (2H, d, J = 9.03 Hz, H-3' and H-5')] and the methoxy signal (δ 3.85) still present in the ^{1}H NMR spectrum (plate 51a) of this side-product, it was clear that the structure of this compound closely resembles that of the target isoflav-3-ene (**697**). The heterocyclic region of the spectrum, however, displayed two doublets with small coupling (J = 1.0 Hz) at δ 5.94 and δ 5.41, each integrating for a single proton, while a broad singlet was also observed at δ 6.66, also integrating for one proton. The presence of these resonances in addition to the fact that the mass spectrum indicated a molecular ion of *m/z* 250 (100%), which is 12 more than the corresponding isoflav-3-ene (**697**), indicated the side-product to contain an additional methylidene group attached to the

heterocyclic ring. Since the chemical shift values and coupling constant of the additional heterocyclic resonances showed some resemblance to those of the isolated methylidene group of the 1,1-disubstituted compounds prepared in the previous chapter and paragraph 6.3.1, it could be concluded that the side-product might be one of the two methylidene isoflavene isomers (**699**) and (**700**) or benzofuran derivatives (**701**) or (**702**) indicated in Figure 6.1. The HMBC spectrum of the by-product (plate 51d), however, showed a strong cross-peak between the methylidene hydrogens and the aromatic quaternary carbon at δ 132.10, which could be assigned to C-1 of the B-ring, since it also gave a strong cross-peak to H-3 and H-5 of the B-ring. Since only structure **A** (**701**) could account for this phenomenon, it could be concluded that structure (**701**) could be assigned to the side-product from the reaction. The proposed structure was further confirmed by all the expected C-H cross-peaks, i.e. H-2" and H-6" to C-4" and C-1", H-4 and H-6 to C-7a, H-5 to C-3a, H-3 to C-7a and H-2' to C-2, in the HMBC spectrum as well as NOE associations between only one of the CH_2 hydrogens and H-2",6" and between H-4 and H-5. The presence of a free hydroxy moiety was furthermore eliminated by no change in the resonance multiplicity when D_2O was added to the solvent and the ^1H NMR spectrum recorded again.

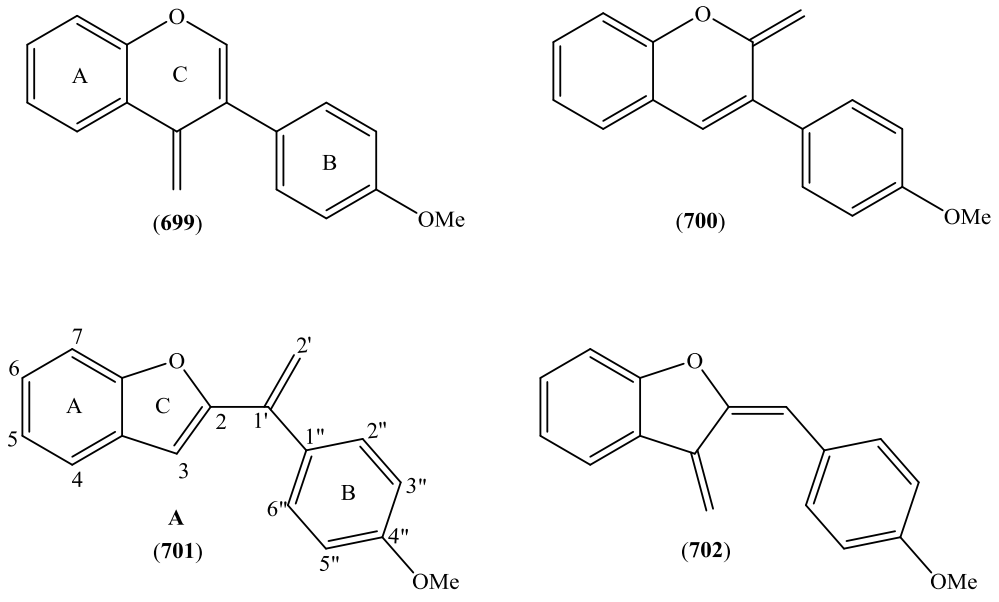
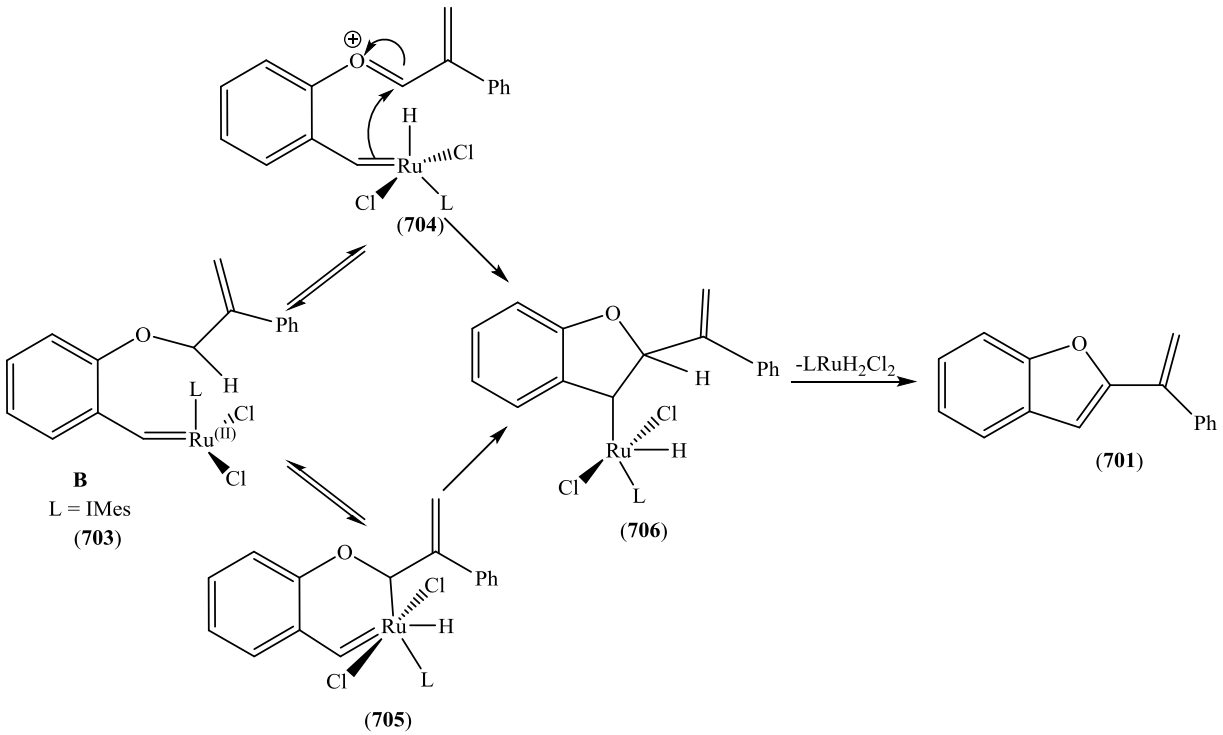


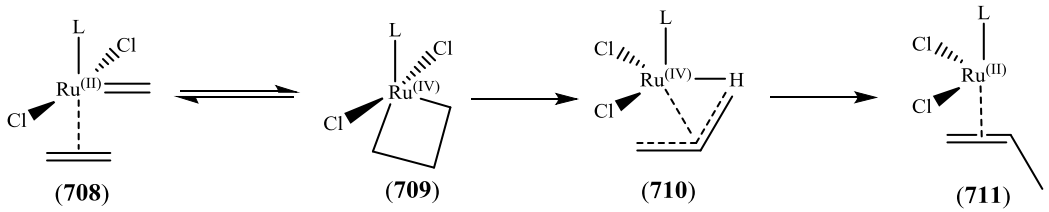
Figure 6.1 Possible structures for the side-product obtained during RCM of 1-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene

The formation of the side-product (**701**) is explicable in terms of either oxidative addition or hydride transfer to the ruthenium benzylidene complex **B** (**703**) to give (**705**) and (**704**)

respectively. Carbene attack directed at the carbon of the oxonium intermediate (**704**) followed by deprotonation would lead to the final product (**701**) in this instance, while some type of reductive elimination followed by β-hydride elimination would lead to the product (**701**) in the oxidative pathway (Scheme 6.17). Since Janse van Rensburg *et al.*[19] proposed and demonstrated a β-hydride transfer step from the ruthenacyclobutane intermediate as a catalyst deactivation route during ruthenium catalysed metathesis reactions, the former (hydride transfer) mechanism seems to be a plausible explanation for the formation of the observed side-product (**701**) (Scmeme 6.18). Jeganmohan and Manikandan,[20] on the other hand, postulated an oxidative addition pathway for C-H activation during the ruthenium(II) catalysed hydroarylation of alkynes, so the second option could also be a possible explanation for the formation of the observed side-product (**701**).



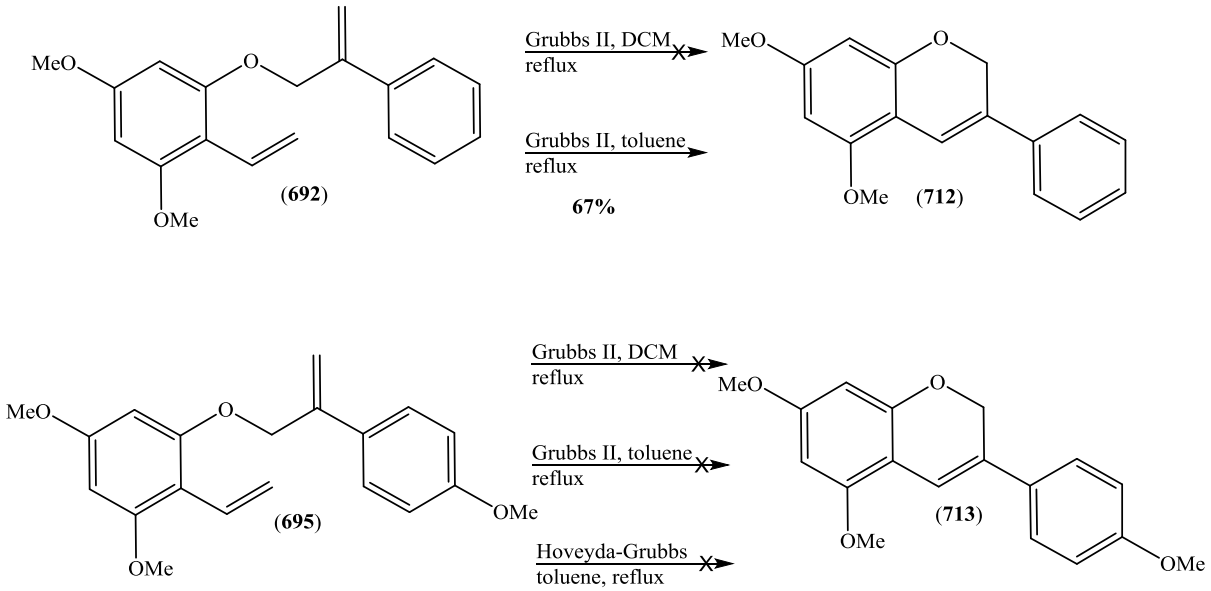
Scheme 6.17 Possible mechanisms for the formation of (**701**) through β-hydride transfer and oxidative addition during Ru catalysed RCM



L = PCy_3, IMes

Scheme 6.18 Catalyst deactivation by β-hydride transfer during Ru catalysed metathesis reactions

With the standard RCM conditions [Grubbs(II) (5 mol%), DCM, reflux] being successful for the preparation of the flav-2-enes and mono- and dioxygenated isoflav-3-enes (**696**), (**697**) and (**698**), this procedure was extended to to the synthesis of the analogues with a phloroglucinol-type A-ring (**712**) and (**713**). Exposure of divinylbenzenes (**692**) and (**695**) to the standard metathesis reaction conditions, however, yielded only starting material even after prolonged reaction times of 72 hours (Scheme 6.19). Changing the solvent to toluene with the associated increase in reaction temperature at reflux resulted in the 5,7-dimethoxyisoflav-3-ene (**712**) to be formed in 67% yield, but with still no observable product formation for the B-ring methoxylated equivalent (**713**), even when the Hoveyda-Grubbs equivalent was used as catalyst.



Scheme 6.19 RCM of phloroglucinol-type divinylbenzenes

The structure of the isoflav-3-ene (**712**) was confirmed by the ^{1}H NMR spectrum (plate 49a) where the heterocyclic resonances were clearly visible at δ 7.12 (1H, br. s, H-4) and 5.10 (1H, s, H-2), 5.10 (1H, s, H-2) and further corroborated by the ^{13}C NMR spectrum (plate 49b) where the heterocyclic carbons resonate at δ 127.48 (C-3), 115.56 (C-4) and 67.53 (C-2) and MS (EI) with a molecular ion at *m/z* 268 (M^{+}, 100%).

In a study aimed at suppressing isomerisation side-reactions during metathesis, Grubbs *et al.*[21] found that the addition of additives, like 1,4-benzoquinone and acetic acid, to the reaction mixture during ring closing metathesis reactions could enhance the formation of the desired RCM product from < 5% to > 90% (Table 6.2).

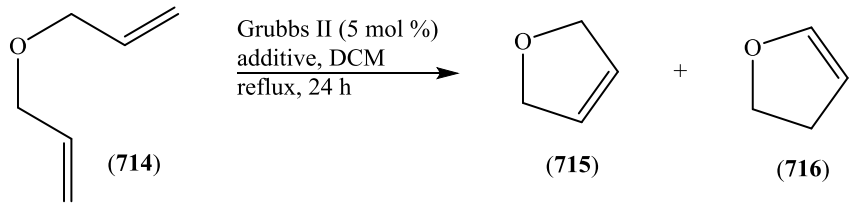
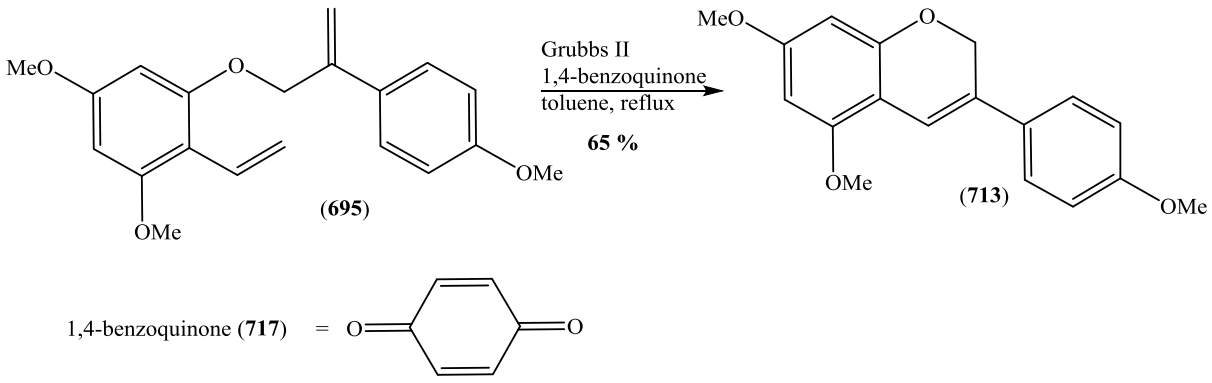


Table 6.2 Metathesis isomerisation side-reactions

additive	equivalents	product distribution[a]	
		(**715**)	(**716**)
none	None	< 5% [b]	> 95%[c]
acetic acid	0.1	> 95%	none
1,4-benzoquinone	0.1	> 95%	none
galvinoxyl	0.2	80%	20%
TEMPO	0.5	7%	93%
4-methoxyphenol	0.5	17%	83%
BHT	0.5	4%	93%

[a] Determined by ^{1}H NMR, [b] Yield ~ 80 %, 1 h. [c] Yield ~ 20 %, 1 h

Although it was not clear whether isomerisation could be the cause of the RCM reaction of (**695**) being unsuccessful, it was decided to investigate the effect, if any, that the addition of 1,4-benzoquinone might have on the RCM reaction of this substrate (**695**) (Scheme 6.20). When the reaction of divinylbezene (**695**) was repeated over the Grubbs II catalyst in refluxing toluene in the presence of 1,4-benzoquinone (**717**), the desired isoflav-3-ene (**713**) was obtained in 65% yield.

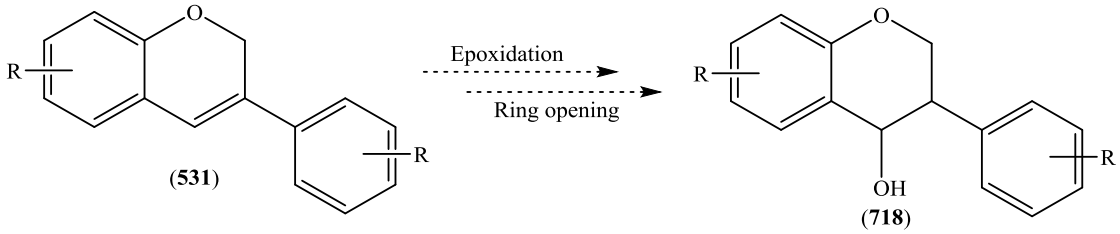


Scheme 6.20 Synthesis of 4',5,7-trimethoxyisoflav-3-ene (**713**)

The ^{1}H NMR and ^{13}C NMR spectra (plates 53a and 53b respectively) confirmed the proposed structure for the product (**713**) by displaying the heterocyclic resonances at δ_H 7.01 – 6.99 (1H, m, H-4) and 5.07 (1H, s, H-2), 5.07 (1H, s, H-2) and δc 127.16 (C-3), 113.51 (C-4) and 67.50 (C-2), while MS (EI) indicated the presence of the molecular ion at *m/z* 298 (M^{+}, 100%).

6.3 Isoflav-3-ene epoxidation

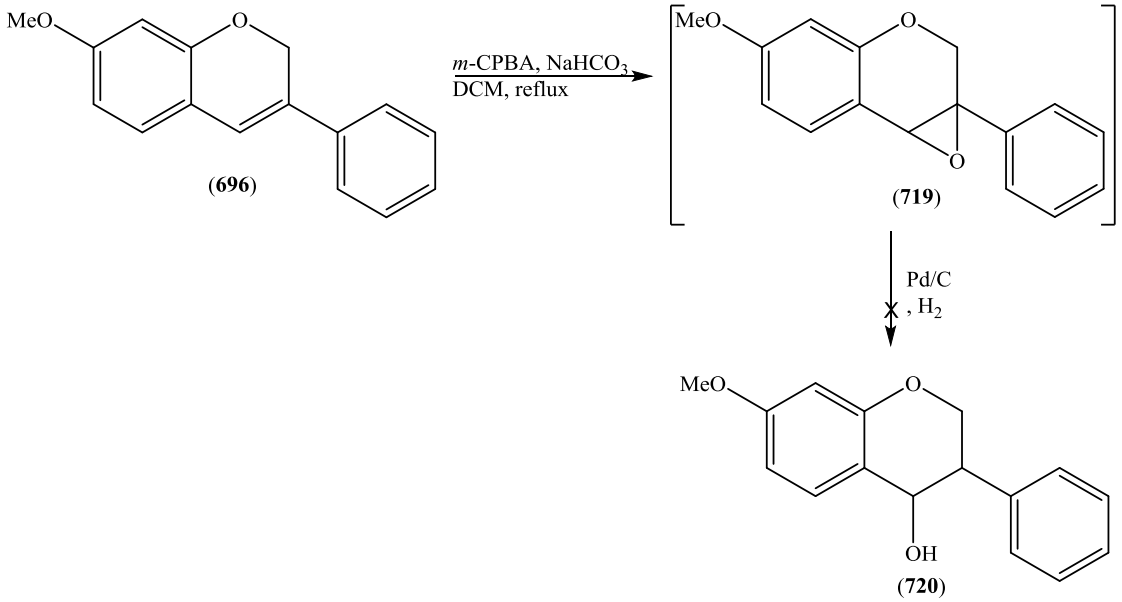
Like flavonoids, most isoflavonoids contain at least one oxygen function attached to the heterocyclic ring, so epoxidation of the isoflav-3-enes in hand were attempted to transform these products into analogues found in nature or precursors of natural compounds (Scheme 6.21).



Scheme 6.21 Preparation of isoflavan-4-ols through epoxidation of isoflav-3-enes

Since isoflav-3-ene epoxides might be unstable under the prevailing acidic conditions during treatment with *m*-CPBA, the epoxidation reaction was performed in the presence of $NaHCO_3$ (2.0 eq.). After disappearance of the starting material, TLC indicated product formation, but after PLC purification no epoxidation product could be isolated (only an inseparable mixture of products), even with the addition of Et_3N (10%) to the eluent system during the separation process. In an effort to prevent the apparent decomposition of the epoxide during purification,

it was decided to proceed directly to the reductive opening of the oxirane ring by *in situ* treatment of the reaction mixture with hydrogen over Pd on carbon (Scheme 6.22). No isoflavan-4-ol (**720**) could, however, again be isolated from the reaction mixture.



Scheme 6.22 Attempted transformation of 7-methoxyisoflav-3-ene into the corresponding isoflavanol

Even though 7-methoxyisoflav-3-ene (**696**) could not be epoxidised successfully with *m*-CPBA, the utilization of other, more recently developed, reagents, like oxones[22] and dioxiranes,[23] might be the answer to this challenge and will be investigated in a subsequent follow-up study.

6.4 Conclusions

While a series of substituted phenylacetates could be prepared in excellent yields (80 – 99%) through ozonolysis of the corresponding allyl benzenes, transforming these compounds into the required deoxybenzoins en route to the isoflav-2-enes by RCM, proved to be difficult. It was therefore decided to change the strategy for the synthesis of isoflavonoids by RCM to the preparation of the isoflav-3-enes as key intermediates. Through the application of a one-pot double Wittig reaction involving methyltriphenylphosphonium bromide, substituted salicyl aldehydes and bromoacetophenone derivatives, the envisaged vinyl benzene intermediates (**689**) and (**692**) – (**695**) became available in 61 – 89% yield. Subsequent ring closing metathesis of the 7- and/or 4' substituted vinylbenzenes (**696**), (**697**) and (**698**) proceeded smoothly under refluxing conditions in DCM over Grubbs II catalyst resulting in the isoflav-3-enes to be obtained in 57% – quantitative yield. RCM of the phloroglucinol type substituted

vinylbenzenes (**692**) and (**695**), however, required higher temperatures (toluene) and/or the addition of 1,4-benzoquinone as additive for the reaction to be successful and the isoflav-3-enes (**712**) and (**713**) were formed in 67% and 65% yields, respectively. Epoxidation of 7-methoxyisoflav-3-ene (**696**) with *m*-CPBA in the presence of $NaHCO_3$ gave indications of the epoxide to be present (TLC and GC-MS), but the desired product could not be isolated. Attempts at reducing the seemingly unstable epoxide by catalytic hydrogenation over Pd/C, howver, failed to produce any hydroxylated isoflavan (TLC).

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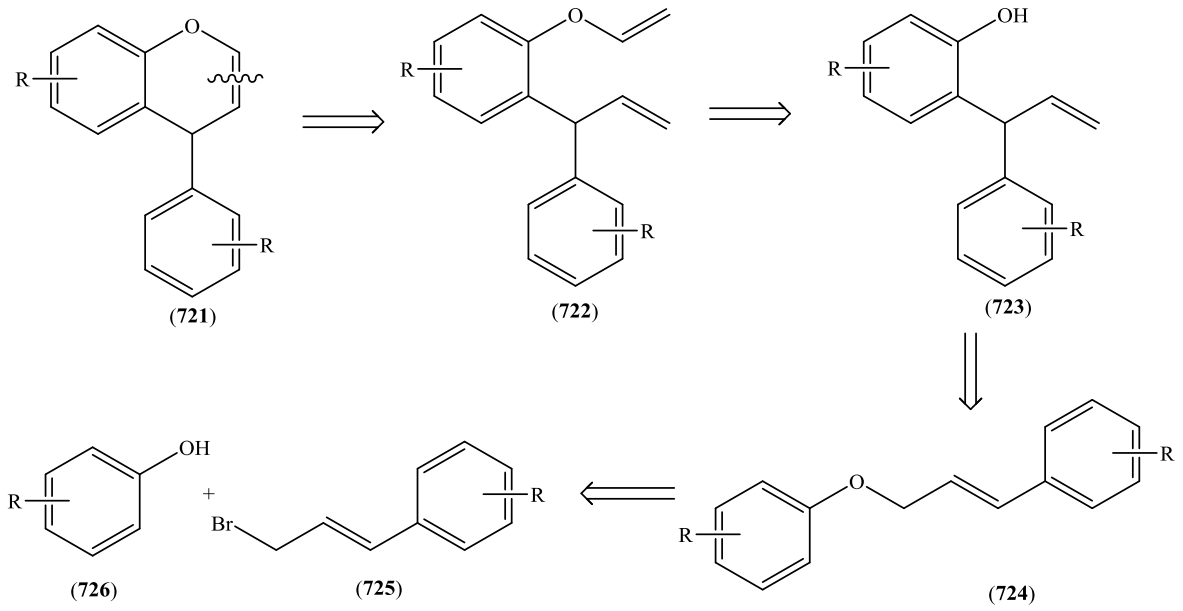
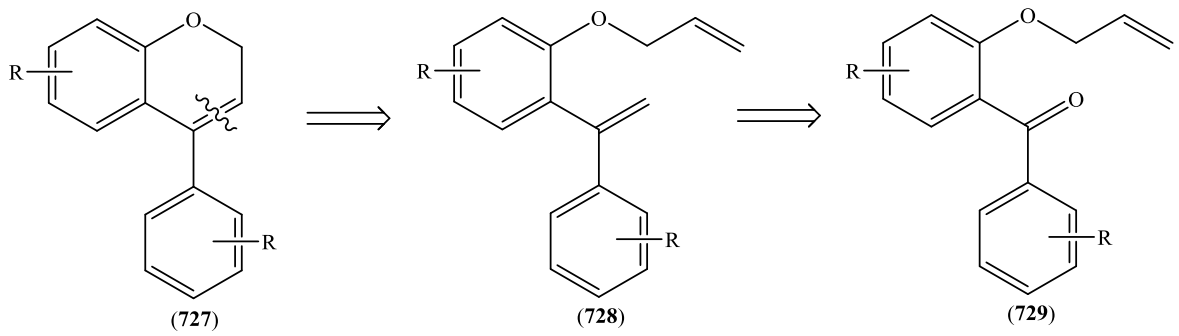
Chapter 7: Synthesis of Neoflavenes

Introduction

With the preparation of several flav-2-enes and isoflav-3-enes completed, attention was turned to the other major class of flavonoids, i.e. the neoflavonoids, and in particular neoflavene-based compounds. As for the other classes of compounds the heterocyclic ring in the neoflavenes could be constructed by preparing the neoflav-2-ene (**721**) (Scheme 7.1) or the 3-ene equivalent (**727**) (Scheme 7.2). While the preparation of the neoflav-2-enes (**721**) would require simple transformations such as the Williamson ether synthesis,[1] Claisen rearrangement,[2] and vinylation of the 2-OH group, which has been reported by Van Otterlo *et al.*,[3] the neoflav-3-ene equivalents (**727**) would be reachable by converting the carbonyl group of a suitably substituted benzophenone (**729**) into a 1,1-diarylethylene (**728**). Since benzophenones with substitution patterns on both aromatic rings resembling those found in natural products, are not readily available and may be more demanding to prepare, initial attempts at the synthesis of neoflavenes were directed towards the utilization of the known reaction methodology, i.e etherification followed by Claisen rearrangement and vinylation and thus neoflav-2-ene preparation as indicated in Scheme 7.1.



Scheme 7.1 Neoflav-2-ene retrosynthesis

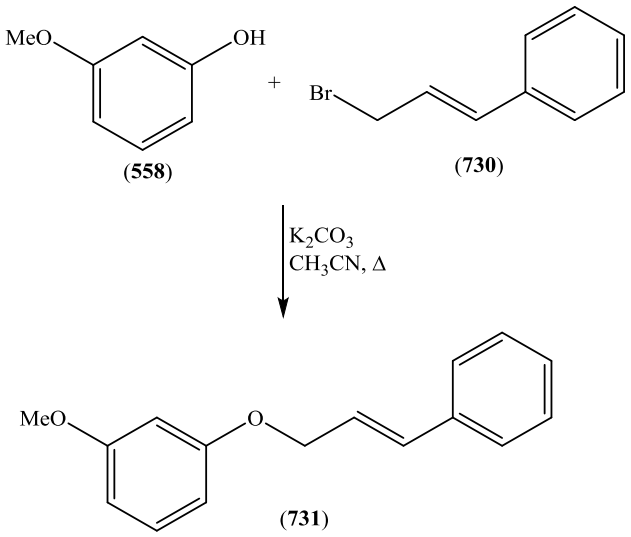


Scheme 7.2 Neoflav-3-ene retrosynthesis

7.1 Neoflav-2-ene synthesis

7.1.1 Etherification with cinnamyl bromide

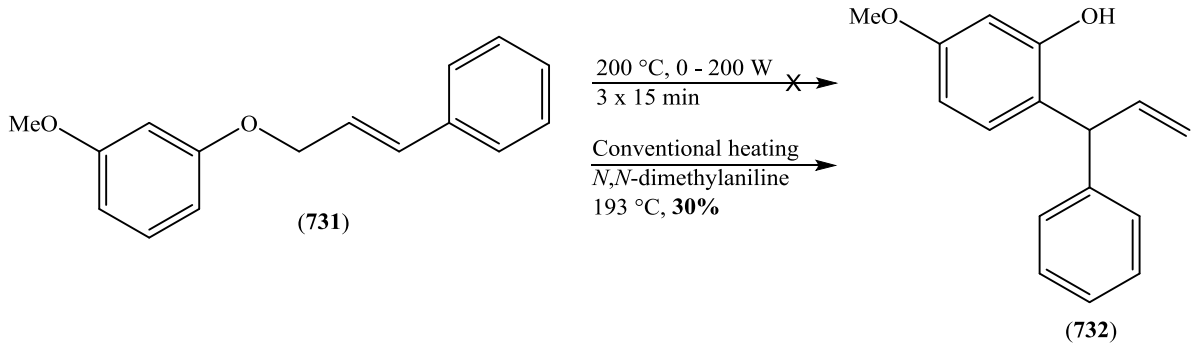
To test the etherification-vinylation strategy, 1-hydroxy-3-methoxybenzene (**558**) was reacted with cinnamyl bromide (**730**) under standard Williamson etherification conditions (K_2CO_3, refluxing acetonitrile) and the product (**731**) obtained in 73% yield (Scheme 7.3). The structure of the product (**731**) was confirmed by the ^{1}H NMR spectrum (plate 5a) where all the expected aromatic resonances [δ 7.45 (2H, d, *J* = 7.2 Hz), 7.36 (2H, dd, *J* = 7.9, 7.2 Hz), 7.31 – 7.28 (1H, m), 7.23 (1H, t, *J* = 8.2 Hz), 6.63 – 6.55 (3H, m, Ar-H)] were observed as well as the allylic moiety at δ 6.77 (1H, br. d, *J* = 16.1 Hz), 6.45 (1H, dt, *J* = 16.1, 5.8 Hz), 4.71 (2H, dd, *J* = 5.8, 1.5 Hz), while HR-MS confirmed the envisaged structure (**731**) (found: *m/z* 241.1228 $[M + H]^+$; calculated: *m/z* 241.1223).



Scheme 7.3 Synthesis of 1-cinnamyloxy-3-methoxybenzene

7.1.2 Claisen Rearrangement

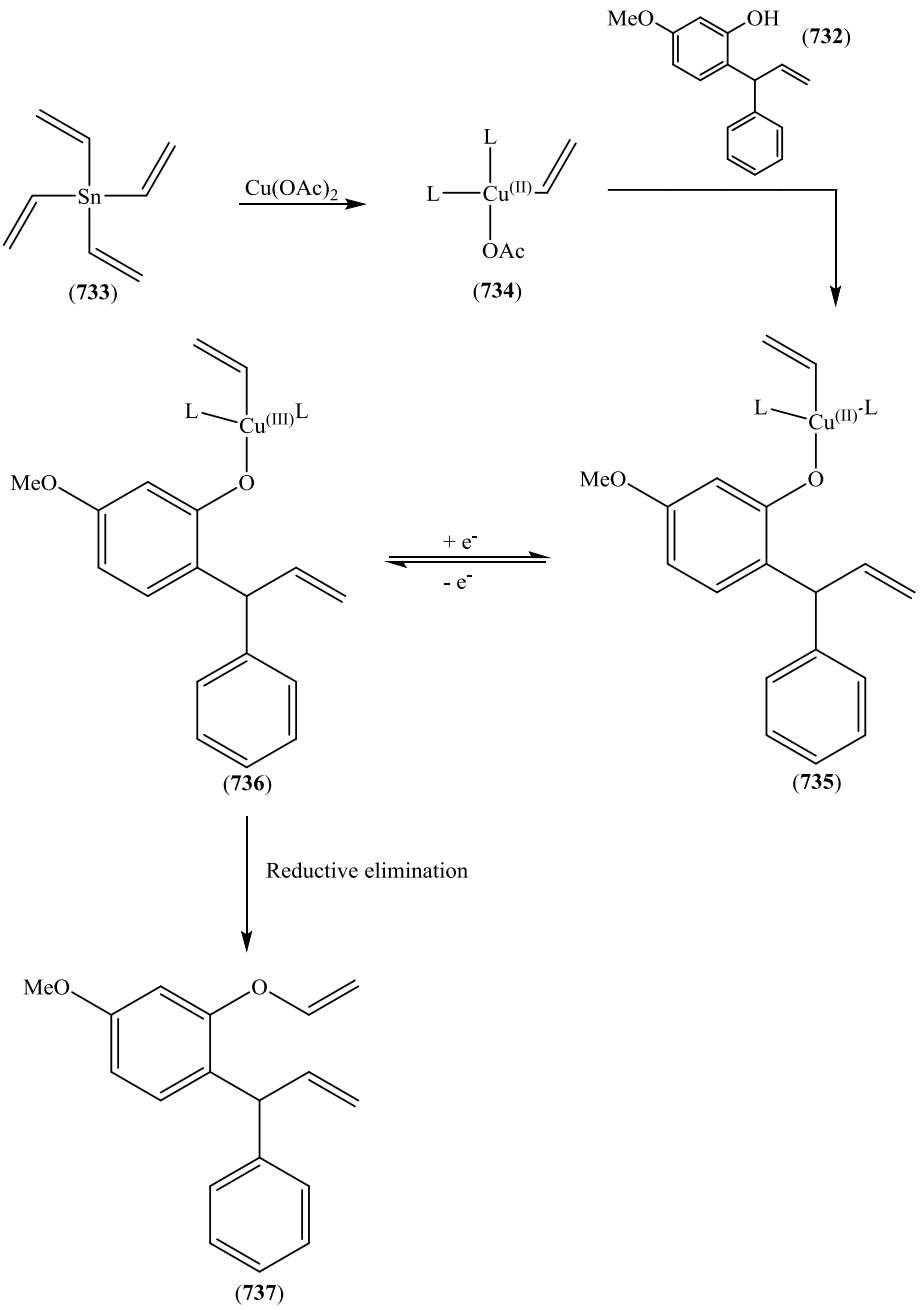
Since the Claisen rearrangement of the allyl benzenes under microwave irradiation out-performed the same reaction under conventional heating conditions for the preparation of the flavene preqursors (*cf.* par. 5.3), the microwave mediated process was applied to the rearrangement of 1-cinnamyloxy-3-methoxybenzene (**731**), but in this instance, a mixture of difficult to separate products was obtained (Scheme 7.4). Subsequent, conventional reflux in *N*,*N*-dimethylaniline for 8 hours, however, gave the desired product (**732**) in 30% yield after acidification with HCl, extraction into diethyl ether and PLC purification. Apart from the expected aromatic resonances, the ^{1}H NMR spectrum of the product (**732**) (plate 14a) also displayed signals indicative of an allylic moiety [δ 6.33 (1H, ddd, *J* = 17.3, 10.2, 6.5 Hz), 5.30 (1H, ddd, *J* = 10.2, 1.5, 1.5 Hz), 5.02 (1H, ddd, *J* = 17.3, 1.5, 1.5 Hz), 4.88 (1H, br. d, *J* = 6.5 Hz)], while the ^{13}C NMR spectrum (plate 14b) confirmed the proposed structure (**732**). Finally, the protonated molecular ion for the product was observed in the MS (EI) spectrum [*m/z* 241 ($[M + H]^+$, 18%)].



Scheme 7.4 Claisen rearrangement of 1-cinnamyloxy-3-methoxybenzene

7.1.3 Vinylation

Since Van Otterlo *et al.*[4] reported utilising Sn(vinyl)$_4$ (**733**) and Cu(OAc)$_2$ for the vinylation of free hydroxy groups, this protocol was employed for the vinylation of 5-methoxy-2-(1-phenylallyl)phenol (**732**) and the product (**737**) was obtained in 12% yield after work-up and PLC purification (Scheme 7.5).



Scheme 7.5 Vinylation of allyl phenol with tetravinyltin and copper acetate.

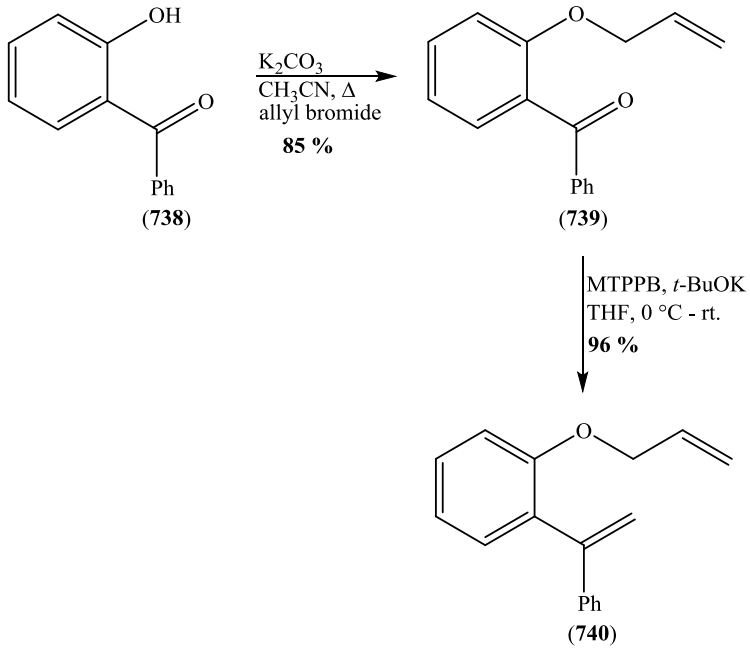
The presence of the vinyloxy group in the product (**737**) was confirmed by resonances at δ 6.50 (1H, br. dd, *J* = 13.8, 6.1 Hz), 4.64 (1H, dd, *J* = 13.8, 1.4 Hz) and 4.35 (1H, dd, *J* = 6.1, 1.4 Hz) in the ^{1}H NMR spectrum (plate 13a) of the compound, while the expected aromatic and allylic proton signals [δ 7.30 – 7.26 (2H, m), 7.20 – 7.17 (3H, m), 7.05 (1H, d, *J* = 8.5 Hz), 6.61 (1H, dd, *J* = 8.5, 2.5 Hz), 6.54 (1H, d, *J* = 2.5 Hz), 6.27 (1H, ddd, *J* = 17.1, 10.2, 6.7 Hz), 5.20 (1H, br. d, *J* = 10.2 Hz), 5.05 (1H, br. d, *J* = 6.7 Hz), 4.92 (1H, br. d, *J* = 17.1 Hz)] remained unchanged. Additional confirmation for the structure came from MS(EI)

where the molecular ion was observed at *m/z* 266 (M^+, 95%) and the ^{13}C NMR spectrum (plate 13b).

Even though the correct intermediate products could be obtained *via* this route, yields were moderate to low with difficulties being experienced during the separation of the products from the Claisen rearrangement. Furthermore it was also realised that if biologically active neoflavonoids were to be prepared, cinnamyl bromides containing higher oxygenation must be utilised, which were not readily available. It was therefore decided to evaluate the alternative benzophenone process (Scheme 7.2) for preparing the neoflav-3ene analogues and return to the current methodology, if necessary.

7.2 Neoflav-3-ene synthesis *via* benzophenone intermediates

Allylation of 2-hydroxybenzophenone (**738**) (allyl bromide, K_2CO_3, CH_3CN) yielded the desired allylated product (**739**) [^1H NMR (plate 10a) and EI-MS *m/z* 238 (M^+, 11%)] as a yellow oil (85%), which was subsequently subjected to a Wittig reaction with methyltriphenylphosphonium bromide (MTPPB) and ^{t}BuOK to form the diarylethene (**740**) in 96% yield (Scheme 7.6).

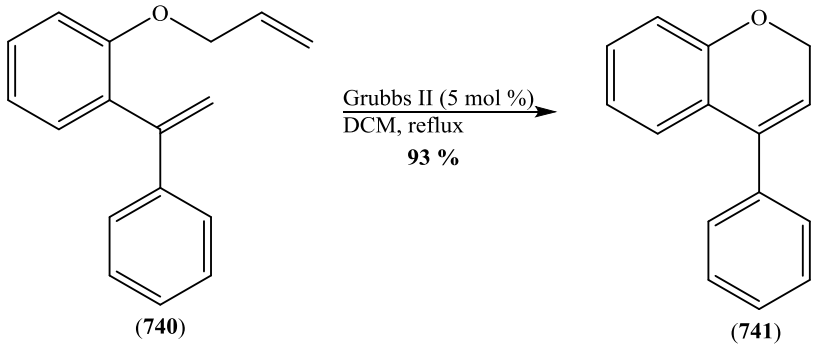


Scheme 7.6 Allyltion of 2-hydroxybenzophenone

The structure of the product (**740**) was confirmed *via* ^1H NMR spectroscopy (plate 54a) where the allylic resonances were observed at δ 5.67 (1H, ddt, *J* = 17.3, 10.6, 4.8 Hz), 5.03 (1H, ddt, *J* = 17.3, 1.8, 1.8 Hz), 4.98 (1H, ddt, *J* = 10.6, 1.8, 1.8 Hz), 4.39 (2H, ddd, *J* = 4.8,

1.8, 1.8 Hz) in addition to those of the vinyl group at δ 5.70 (1H, d, *J* = 1.5 Hz) and 5.28 (1H, d, *J* = 1.5 Hz). The additional -$\underline{C}H_2$ resonance at δ 115.54 in the ^{13}C NMR spectrum of the product (plate 54b) as well as the disappearance of the carbonyl carbon when compared to the starting material gave additional credence to the proposed structure, while final structure confirmation was obtained *via* mass spectrometry (EI), which showed a molecular ion at *m/z* 236 (M^+, 3%).

With the desired styrene intermediate (**740**) in hand, the final step in the process, i.e. to form the neoflav-3-ene (**741**) was attempted by treating the vinyl styrene (**740**) with Grubbs II catalyst in refluxing DCM and the product was obtained in 93% yield (Scheme 7.7). The structure of the neoflav-3-ene (**741**) was confirmed by the ^1H NMR spectrum (plate 63a) where, apart from the expected aromatic resonances [δ 7.45 – 7.41 (2H, m), 7.40 – 7.37 (1H, m), 7.36 – 7.33 (2H, m), 7.19 – 7.15 (1H, m), 6.97 (1H, dd, *J* = 7.6, 1.6 Hz), 6.88 – 6.85 (2H, m)], the characteristic heterocyclic protons* were clearly visible at δ 5.88 (1H, t, *J* = 4.0 Hz, H-3) and 4.82 (2H, d, *J* = 4.0 Hz, H-2) while the molecular ion was present in the MS spectrum at *m/z* 207 ($[M-H]^+$, 100%). The ^{13}C NMR spectrum (plate 63b) also contained resonances from the three heterocyclic carbons [δ 137.68 (C-4), 122.04 or 121.57 (C-3) and 65.89 (C-2)] in addition to the expected aromatic carbon signals [δ 130.23, 129.45, 129.43, 128.80, 126.50, 122.04 or 121.57, 117.10].



(**740**) (**741**)

Scheme 7.7 RCM of 1-(allyloxy)-2-(1-phenylvinyl)benzene

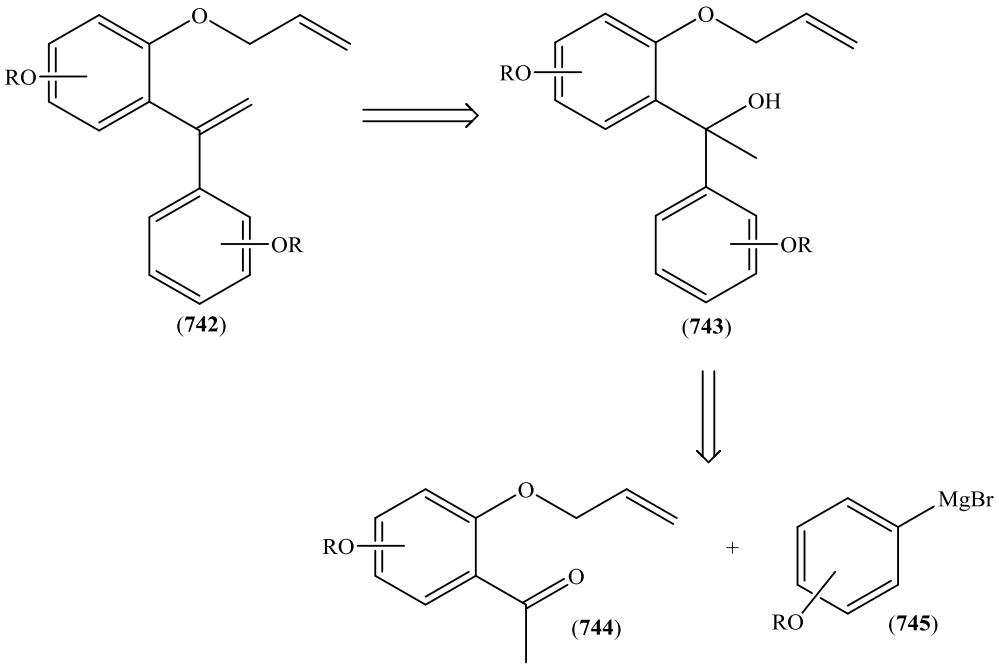
Although this protocol for the synthesis of neoflavenes seemed very promising, the availability of benzophenones with oxygenation patterns resembling those of naturally occurring neoflavonoids are rather limited and these compounds would therefore have to be

* As for the isoflav-3-enes, the enantiotopic-CH_2 protons in the neoflav-3-enes appeared to be magnetically equivalent when acetone-d_6 is used as NMR solvent.

prepared adding at least two other steps to the methodology. In order to address this issue, it was decided to investigate the possibility of transforming the readily available acetophenones or benzaldehydes into the required α-phenylstyrenes (**742**) with a minimum number of additional steps.

7.3 Preparation of neoflav-3-enes through acetophenone intermediates

As indicated in retrosynthesis Scheme 7.8, the envisaged α-phenylstyrenes (**742**) could become available by addition of a suitable phenolic nucleophile, like a phenyl Grignard reagent, to a protected 2-hydroxyacetophenone analogue (**744**). If this could be achieved in a high-yielding process, it would only add two extra steps to the general methodology and thus render it still feasible.

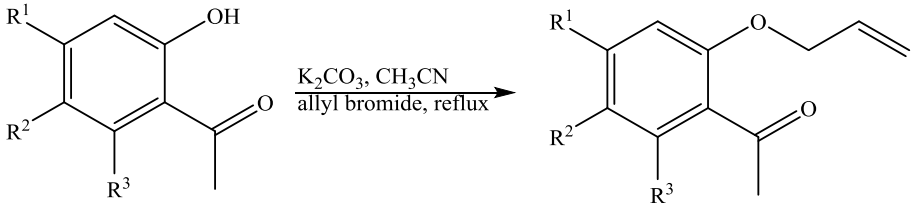


Scheme 7.8 Grignard reaction based transformation of acetophenones into α-phenylstyrenes

7.3.1 Addition of phenolic nucleophiles to allyloxyacetophenones

To investigate this new approach toward the preparation of the envisaged α-phenylstyrenes (**742**), it was decided to follow a strategy of Grignard addition of a phenolic nucleophile to the acetophenone followed by $CuSO_4$ catalysed dehydration of the tertiary alcohol. Thus 2-allyloxyacetophenones (**750**), (**751**), (**752**), and (**753**) were prepared in 74 – 96% yield by reacting the 2'-hydroxyacetophenones (**746**), (**747**), (**748**) and (**749**) with allyl bromide and K_2CO_3 in refluxing CH_3CN (Scheme 7.9). When (**750**) was reacted as model substrate with

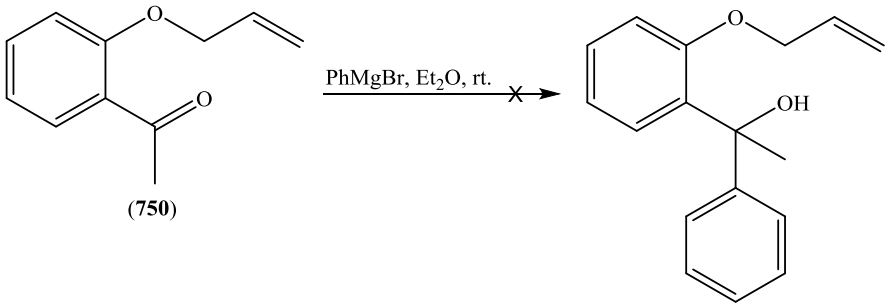
phenylmagnesium bromide in diethyl ether at room temperature over night, the Grignard reaction did, however, not proceed at all and virtually only starting material and biphenyl could be recovered from the crude mixture (Scheme 7.10).



(**746**) $R^1 = R^2 = R^3 = H$
(**747**) $R^1 = OMe$, $R^2 = R^3 = H$
(**748**) $R^1 = R^3 = OMe$, $R^2 = H$
(**749**) $R^1 = R^2 = OMe$, $R^3 = H$

(**750**) $R^1 = R^2 = R^3 = H$ (**96%**)
(**751**) $R^1 = OMe$, $R^2 = R^3 = H$ (**96%**)
(**752**) $R^1 = R^3 = OMe$, $R^2 = H$ (**74%**)
(**753**) $R^1 = R^2 = OMe$, $R^3 = H$ (**99%**)

Scheme 7.9 Allylation of 2-hydroxyacetophenones

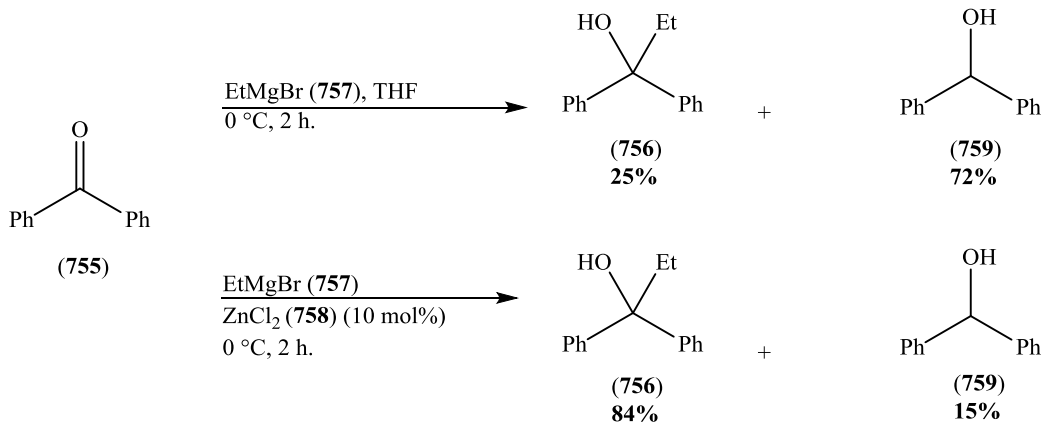


(**750**)

(**754**)

Scheme 7.10 Grignard reaction between allyloxyacetphenone and phenylmagnesium bromide

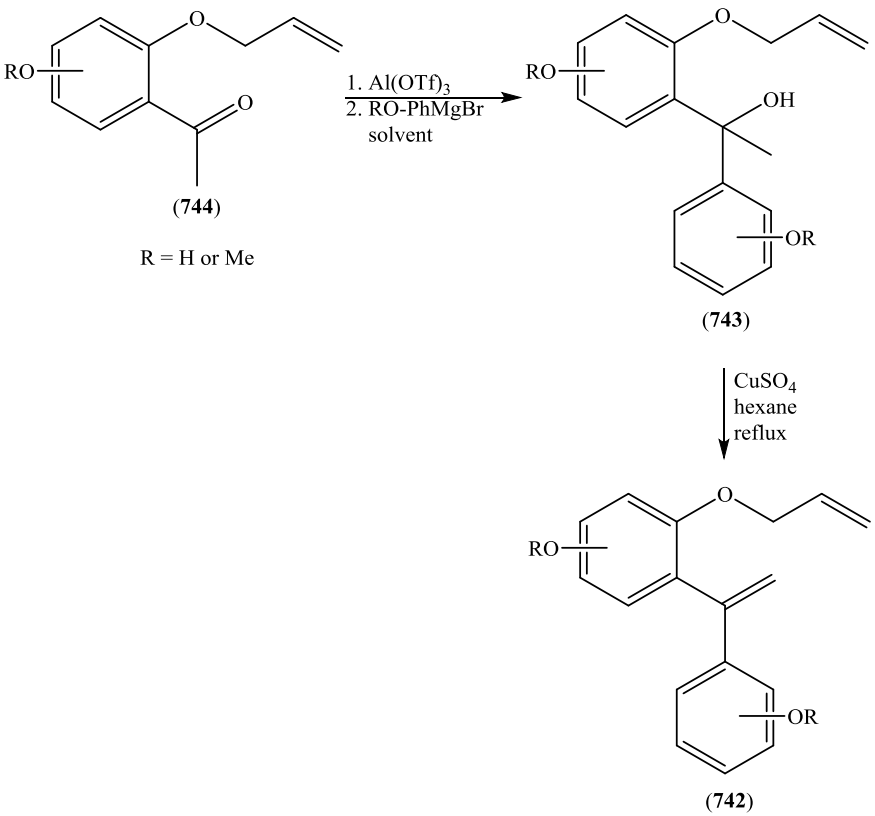
While the addition of phenyl Grignard reagents to benzaldehydes has been well-documented over many decades and represents a high yielding transformation,[5] addition of these reagents to ketones and especially acetophenones often entails enol formation, which many times become the prevailing reaction over the desired addition and thereby deactivating the substrate for Grignard addition.[6] For quite some years, endeavours towards minimizing enol formation and other Grignard side reactions, such as conjugate addition, homo-coupling and reduction, included changing the solvent, from THF to 2-methyltetrahydrofuran[7] for example, and/or utilising additives such as $CeCl_3$,[6] Li salts[8] and Ti complexes.[9] Hatano and co-workers[10] improved the addition of Grignard reagents to ketones by utilising $ZnCl_2$ [forming trialkylzinc(II)ate complexes] as additive in catalytic amounts, which led to the alcohol formation in good yields (Scheme 7.11)



Scheme 7.11 $ZnCl_2$ enhanced Grignard addition reactions

Even though these processes were reported to be effective in some cases, additives had to be prepared in a separate step, added in equimolar or excess quantities and general applicability were lacking. A new approach involving activation of the carbonyl functionality in 2-allyloxyacetophenones would therefore be beneficial and worth investigating.

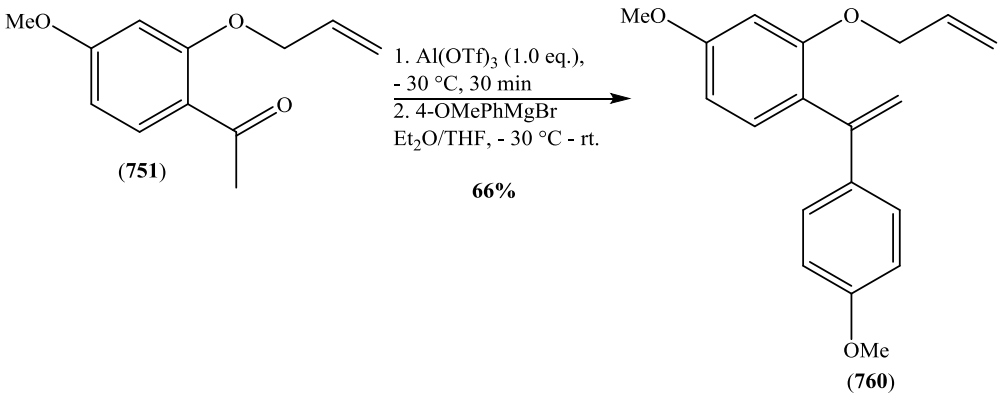
Since $Al(OTf)_3$ is known for its oxophilic Lewis acid properties and has been used efficiently as catalyst in cascading addition/substitution-cyclisation reactions[11,12] and ionic hydrogenation processes[13,14] as well as Michael type addition reactions,[15] this catalyst was envisaged as an ideal candidate for enhancing the addition of Grignard nucleophiles to acetophenones through Lewis acid activity. Furthermore, $Al(OTf)_3$ is generally less expensive than other metal triflates, quite tolerant to various functional groups and reaction conditions and can be recycled.[16] If activation of the acetophenone (**744**) could be achieved utilising $Al(OTf)_3$, the desired alcohols should be transformable into the styrene analogues (**742**) by treatment with anhydrous $CuSO_4$ (Scheme 7.12).



Scheme 7.12 Envisaged $Al(OTf)_3$ activated Grignard reaction

Since Cardillo *et al.*[17] reported good to excellent yields during the conjugate addition of Grignard reagents to substituted α,β-unsaturated esters by adding the Lewis acid to the substrate at –30 °C and allowing the reaction mixture to stir for 30 minutes before addition of the Grignard reagent, it was decided to utilise this procedure as starting point for the subsequent investigation. With the unsubstituted neoflav-3-ene (**741**) already prepared, the envisaged new process was evaluated by subjecting 2'-allyloxy-4'-methoxyacetophenone (**751**) to these reaction conditions. 2'-Allyloxy-4'-methoxyacetophenone (**751**) was therefore dissolved in dry Et_2O and cooled to –30 °C before $Al(OTf)_3$ was added and stirring continued for 30 minutes. Thereafter, 4-methoxyphenylmagnesium bromide was added to the reaction mixture and the temperature allowed to rise to room temperature and stirring continued over night when TLC indicated the starting material to be completely consumed (Scheme 7.13). The ^{1}H NMR spectrum (plate 55a) of the product (**760**), which was obtained in 66% yield after work-up and PLC, however, indicated no methyl resonance, while, apart from the expected aromatic [δ 7.22 (2H, d, *J* = 8.8 Hz), 7.14 (1H, d, *J* = 9.2 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 6.57 (1H, dd, *J* = 9.2, 2.3 Hz), 6.57 (1H, d, *J* = 2.3 Hz)] and allyl signals [5.72 (1H, ddt, *J* = 17.3, 10.7, 4.7 Hz), 5.07 (1H, *J* = 17.3, 1.9, 1.9 Hz), 5.01 (1H, ddt, *J* = 10.7, 1.9, 1.9 Hz), 4.40 (1H, ddd, *J* = 4.7, 1.9, 1.9 Hz)], two additional one-proton doublets (*J* = 1.7 Hz) were

observed at δ 5.54 and 5.12. Since the chemical shift and small coupling constant resembled those of the styrene derivatives prepared during the synthesis of the isoflav-3-enes, e.g. 1-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**) (*ca.* δ 5.7 and 5.2 and *ca.*1.6 Hz) it became evident that the product in fact was not the expected alcohol (**743**), but the 1-arylsubstituted styrene (**760**) and that addition of the nucleophile was accompanied by concomitant dehydration. Confirmation of the structure of the 1-arylsubstituted styrene (**760**) came from the ^{13}C NMR spectrum (plate 55b) where the -$\underline{C}H_2$ carbon could be identified at δ 113.34 and MS (EI) showing the molecular ion at *m/z* 296 (M^+, 28%).



Scheme 7.13 Direct styrene formation *via* Grignard reaction with $Al(OTf)_3$ activation

Delighted by this serendipitous result, the novel process was extended to the direct preparation of the other target 1-arylstyrenes (**761**), (**762**) and (**763**), which could be prepared in moderate to high yields (52 – 94%).* The structures of these compounds (**761**), (**762**) and (**763**) were all confirmed by ^{1}H and ^{13}C NMR as well as MS (Table 7.1).

*The mechanism of this reaction is discussed in Chapter 8.

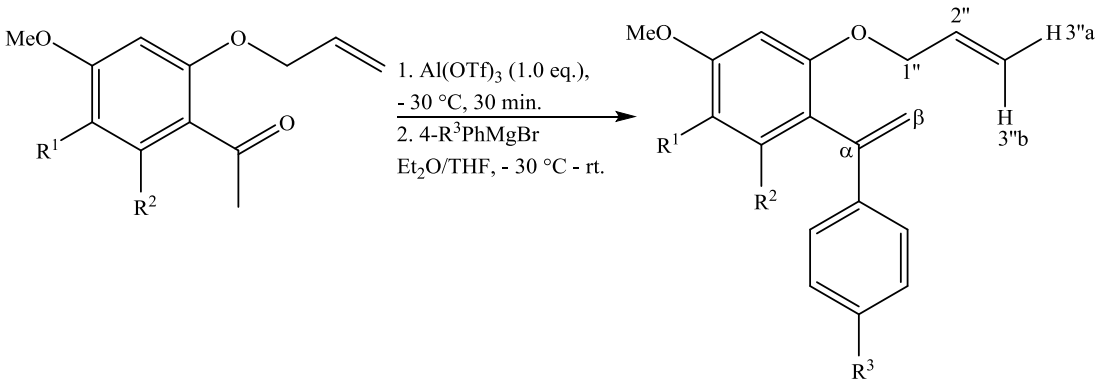


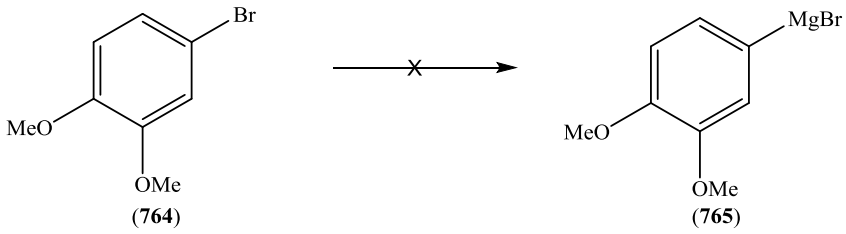
Table 7.1 1-Arylstyrene syntheses

Plate	Substitution	^{1}H NMR: Allylic and vinyl system	^{13}C NMR: Vinyl –$\underline{C}H_2$	MS	Yield (%)
56 (**761**)	R^1, R^3 = H; R^2 = OMe	δ 5.87 (1H, d, *J* = 1.7 Hz, H-β), 5.81 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, H-2"), 5.22 (1H, ddt, *J* = 17.3, 1.7, 1.7 Hz, H-3"b), 5.13 (1H, d, *J* = 1.7 Hz, H-β), 5.06 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3"a), 4.45 (2H, ddd, *J* = 4.7, 1.7, 1.7 Hz, H-1")	δ 142.35 (C-α); δ 116.53 (C-β)	319[a]	94
57 (**762**)	R^1 = H; R^2, R^3 = OMe	5.84 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, H-2"), 5.76 (1H, d, *J* = 1.6 Hz, H-β), 5.23 (1H, ddt, *J* = 17.3, 1.8, 1.8 Hz, H-3"b), 5.07 (1H, ddt, *J* = 10.6, 1.8, 1.8 Hz, H-3"a), 4.98 (1H, d, *J* = 1.6 Hz, H-β), 4.45 (2H, ddd, *J* = 4.7, 1.8, 1.8 Hz, H-1")	δ 141.76 (C-α); δ 114.44 (C-β)	349[a]	65
58	R^1, R^3 =	5.70 (1H, ddt, *J* = 17.2,	δ 147.77	349[a]	52

(**763**)	OMe R^2 = H	10.7, 5.0 Hz, H-2"), 5.55 (1H, d, *J* = 1.6 Hz, H-β), 5.16 (1H, d, *J* = 1.6 Hz, H-β), 5.08 (1H, ddt, *J* = 17.2, 1.8, 1.8 Hz, H-3"b), 5.00 (1H, ddt, *J* = 10.7, 1.8, 1.8 Hz, H-3"a), 4.36 (2H, ddd, *J* = 5.0, 1.8, 1.8 Hz, H-1")	(C-α) δ 113.55 (C-β)

[a]HR-MS ([M + Na]$^+$)

In order to complete the series of neoflavene analogues with naturally occurring substitution patterns, the next step in the methodology development required addition of 3,4-dimethoxyphenylmagnesium bromide (**765**) to the substituted acetophenones. Preparation of this Grignard reagent, however, proved to be no simple task and led to extensive variation in reaction conditions to be evaluated (Scheme 7.14).



Method A: Mg (2.0 eq.), Et_2O, reflux, 1 h

Method B: Mg (2.0 eq.), THF, reflux, 1 h

Method C: Mg (2.0 eq.), I_2 (cat.), THF, reflux, 1 h

Method D: Mg (2.0 eq.), I_2 (1.0 eq.), THF, reflux, 1 h

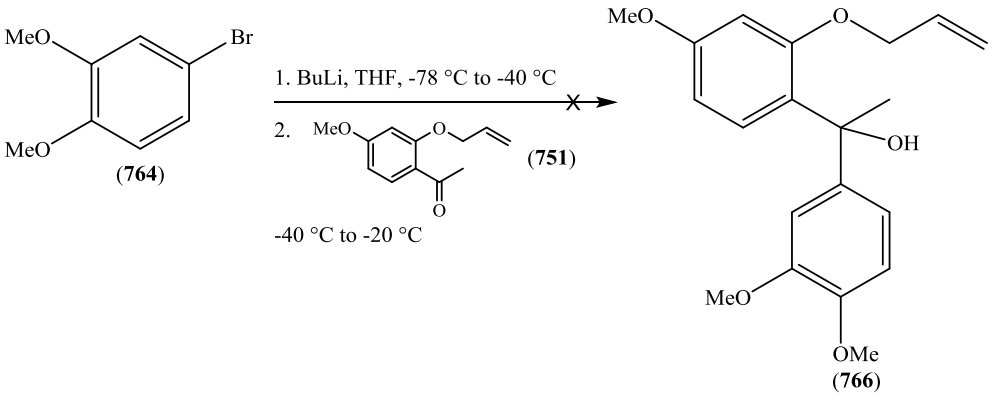
Method E: Mg (2.0 eq.), I_2 (1.0 eq.), THF, reflux, over night

Scheme 7.14 Attempts at preparing 3,4-dimethoxyphenylmagnesium bromide

Since the reaction mixture never started to reflux spontaneously (as expected when preparing Grignard reagents), the initial thought that the product could be very reactive and therefore reacting with itself to form the biphenyl, or some other side-reaction, could be discarded and it was realised that 4-bromo-1,2-dimethoxybenzene (**764**) was a lousy substrate for reaction with magnesium. The temperature for the reaction was therefore raised to refluxing conditions and the solvent changed to THF to be able to reach those higher temperatures, but

even with I_2 activation under these conditions, no indication of the Grignard reagent being formed, could be found.

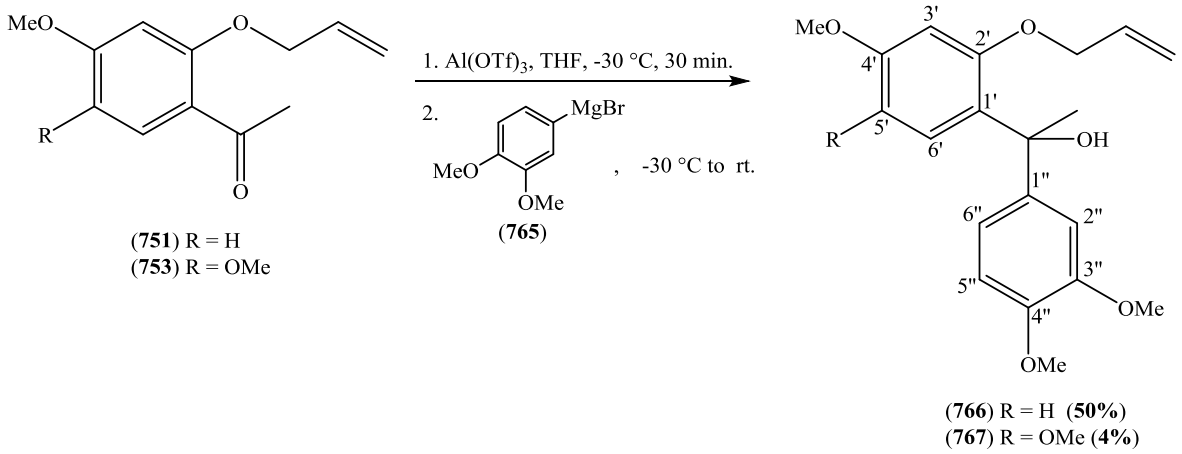
In another approach towards preparing the desired 1-arylstyrenes (or alcohol analogues) having a 3,4-dimethoxy substitution pattern, it was decided to utilise a transmetallation process (treatment with BuLi at low temp.) for forming the aromatic nucleophile and reacting that with the acetophenone (**751**). However, this synthetic protocol also yielded only starting materials (Scheme 7.15).



Scheme 7.15 Attempted tertiary alcohol prepatation *via* transmetallation with BuLi

Since Sivaraman and Aidhen[18] described the preparation of 3,4,5-trimethoxyphenyl-magnesium bromide through the addition of I_2 and MeI to the reaction mixture, this procedure was subsequently followed for the preparation of the desired 3,4-dimethoxy-phenylmagnesium bromide. Additional drying of the bromobenzene (**764**) by azeotropic distillation with benzene, flame drying all glassware and activating the magnesium by washing with HCl followed by diethyl ether and air drying, led to the successful formation of the Grignard reagent as was confirmed by reaction with benzaldehyde and GC-MS analysis of the latter reaction mixture.

With the desired 3,4-dimethoxyphenylmagnesium bromide (**765**) in hand, attention was subsequently focused on transforming 2'-allyloxy-4'-methoxyacetophenone (**751**) and 2'-allyloxy-4',5'-dimethoxyacetophenone (**753**) into the styrene analogues. When the $Al(OTf)_3$ enhanced Grignard reaction conditions were applied to these substrates, the alcohols (**766**) and (**767**) were, however, obtained in 50 and 4% yields, respectively (Scheme 7.16).

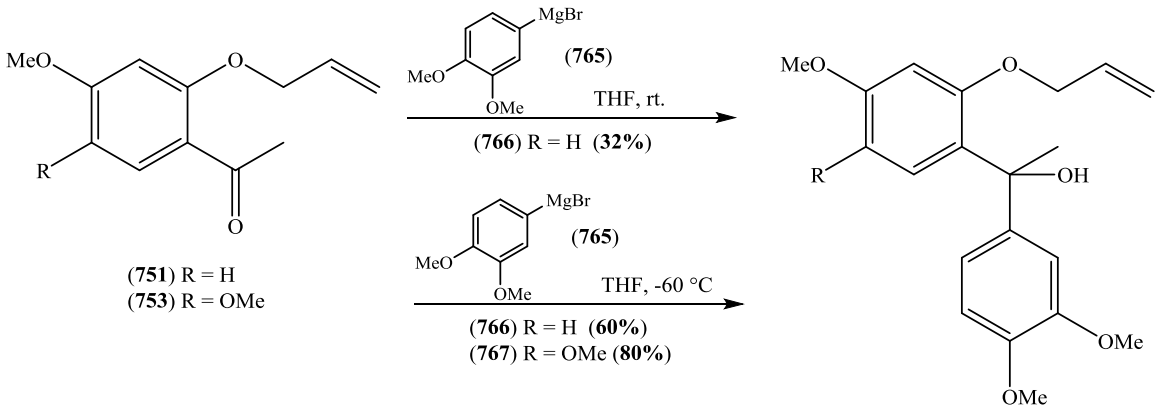


Scheme 7.16 Tertiary alcohols from the reaction of the acetophenone analogues (**751**) and (**753**) with 3,4-dimethoxyphenylmagnesium bromide in the presence of $Al(OTf)_3$

^{1}H NMR spectra (plates 59a and 60a) of alcohols (**766**) and (**767**) confirmed the structures of these products by showing the expected two aromatic ABX systems [δ 7.48 (1H, d, *J* = 8.4 Hz, H-6'), 7.03 (1H, d, *J* = 2.1 Hz, H-2"), 6.79 (1H, d, *J* = 8.4 Hz, H-5"), 6.75 (1H, dd, *J* = 8.4, 2.1 Hz, H-6"), 6.56 (H, dd, *J* = 8.4, 2.5 Hz, H-5'), 6.55 (1H, d, *J* = 2.5 Hz, H-3')] and an aromatic ABX system accompanied by two aromatic singlets [δ 7.03 (1H, d, *J* = 2.0 Hz, H-2"), 6.98 (1H, s, H-6'), 6.71 (1H, d, *J* = 8.4 Hz, H-5"), 6.66 (1H, dd, *J* = 8.4, 2.0 Hz, H-6"), 6.52 (1H, s, H-3')], respectively, while both spectra also contained a methyl resonance at δ 1.80 and 1.81, respectively, as well as an OH signal respectively at δ 4.50 and 4.57, apart from the resonances typical of the allyl group. The ^{13}C NMR DEPT spectra (plates 59e and 60e) further confirmed the presence of the methyl carbon at δ 30.35 and 30.36, respectively, while high resolution mass spectrometry revealed the presence of the desired compounds by showing sodium adduct molecular ions at *m/z* 367.1520 (calculated: *m/z* 367.1516) and *m/z* 397.1629 (calculated: *m/z* 397.1627) (both $[M + Na]^+$) for (**766**) and (**767**), respectively.

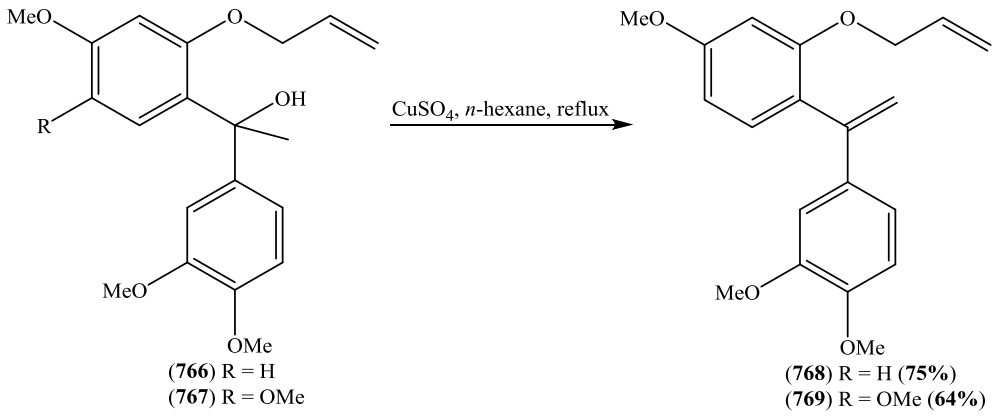
Although formation of the alcohols would add an extra process step to the methodology, it was not detrimental to the synthesis protocol, since these compounds could easily be transformed into the styrene analogues by elimination of water. Attention was therefore first turned towards improving the yields of the alcohol formation process. Repeating the Grignard reaction on 2'-allyloxy-4'-methoxyacetophenone (**751**) at lower temperature (-60 °C) in the presence of $Al(OTf)_3$, however, did not result in any product formation. Since it seemed as if the addition of $Al(OTf)_3$ might not have an effect on the outcome of the reaction in this case, the Lewis acid was omitted from the reaction mixture and the reaction repeated with only the Grignard reagent in THF at room temp. In this case, the alcohol (**766**) could only be obtained

in a decreased yield of 32% (Scheme 7.17). Repeating the reaction once more without $Al(OTf)_3$, but at -60 °C, led to the desired alcohol (**766**) being isolated in an acceptable yield of 60%. Applying the low temperature Grignard conditions without $Al(OTf)_3$ to the other substrate, 2'-allyloxy-4',5'-dimethoxyacetophenone (**753**), resulted in the desired alcohol (**767**) being formed in an excellent yield of 80%.



Scheme 7.17 Improved methodology for the synthesis of tertiary alcohols

With the desired alcohols in hand the dehydration process with anhydrous $CuSO_4$ in refluxing hexane was attempted and corresponding styrenes, (**768**) and (**769**) obtained good yields (75% and 64%, respectively) (Scheme 7.18).



Scheme 7.18 Dehydration of *tert*-alcohols by treatment with anhydrous copper sulfate

The ^1H (plates 61a and 62a) and ^{13}C NMR spectra (plates 61b and 62b) of the products (**768**) and (**769**) clearly indicated the presence of the 1,1-disubstituted vinyl group exhibiting resonances at δ_H 5.56 (1H, d, J = 1.6 Hz), and 5.14 (1H, d, J = 1.6 Hz) and at δ_H 5.58 (1H, d, J = 1.6 Hz) and 5.17 (1H, d, J = 1.6 Hz), respectively, while the carbon spectra also revealed

the -$\underline{C}H_2$ groups at δ 113.48 and δ 113.84, respectively. High resolution mass spectrometry yielded the sodium adduct molecular ion at *m/z* 349.1418 (calculated: *m/z* 349.1416) and 379.1523 (calculated: *m/z* 379.1521), respectively.

7.3.2 Construction of the neoflav-3-ene heterocyclic ring *via* RCM

With all the styrene substrates being prepared in good yields, the final step in the synthetic protocol, i.e. RCM, was embarked upon. Since the utilization of the Grubbs II catalyst in refluxing DCM proved to be the method of choice for the preparation of most flav-2-enes and isoflav-3-enes, this methodology was also applied to the ring closing metathesis reaction for the preparation of the neoflav-3-enes and the products (**770**) - (**775**), which could be obtained in 67% to quantitative yields (Table 7.2).

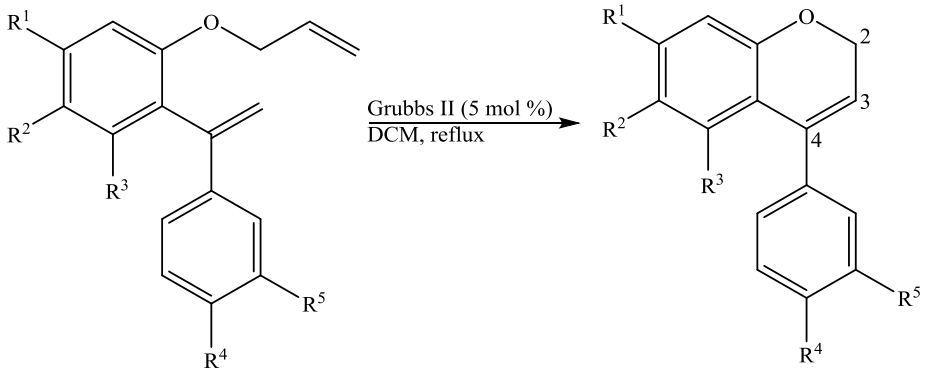


Table 7.2 Neoflav-3-ene syntheses

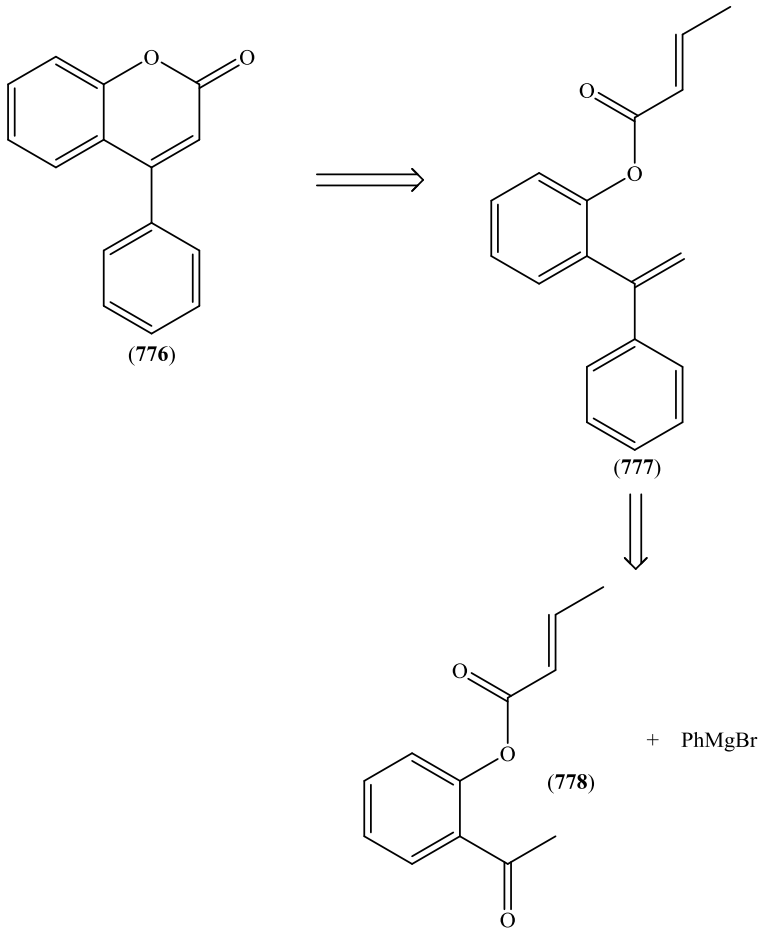
Plate	Substitution	^{1}H NMR: Heterocyclic protons	^{13}C NMR:	MS	Yield (%)
63 (**741**)	R^1, R^2, R^3, R^4, R^5 = H	δ 5.88 (1H, t, *J* = 4.0 Hz, H-3), 4.82 (2H, d, *J* = 4.0 Hz, H-2)	δ 137.68 (C-4) δ 121.57 or 122.04 (C-3) δ 65.89 (C-2)	207 [d] (100%)	93
64 (**770**)	R^1, R^4 = OMe R^2, R^3, R^5 = H	δ 5.68 (1H, t, *J* = 4.0 Hz, H-3), 4.78 (2H, d, *J* = 4.0	δ 137.22 (C-4) δ 117.49 (C-3)	268 [c] (100%)	95

		Hz, H-2)	δ 66.10 (C-2)		
65 (**771**)	R^1, R^3 = OMe R^2, R^4, R^5 = H	δ 5.71 (1H, t, *J* = 4.7 Hz, H-3), 4.57 (2H, d, *J* = 4.7 Hz, H-2)	δ 137.47 (C-4) δ 118.65 (C-3) δ 65.38 (C-2)	291[b]	Quant.
66 (**772**)	R^1, R^3, R^4 = OMe R^2, R^5 = H	δ 5.67 (1H, t, *J* = 4.7 Hz, H-3), 4.54 (2H, d, *J* = 4.7 Hz, H-2)	δ 137.10 (C-4) δ 117.62 (C-3) δ 65.42 (C-2)	595[e]	73
67 (**773**)	R^1, R^2, R^4 = OMe R^3, R^5 = H	δ 5.72 (1H, t, *J* = 4.1 Hz, H-3), 4.72 (2H, d, *J* = 4.1 Hz, H-2)	δ 137.49 (C-4) δ 117.53 (C-3) δ 65.86 (C-2)	298 [c] (100%)	79
68 (**774**)	R^1, R^4, R^5 = OMe R^2, R^3 = H	δ 5.72 (1H, t, *J* = 4.0 Hz, H-3), 4.78 (2H, d, *J* = 4.0 Hz, H-2)	δ 137.40 (C-4) δ 117.48 (C-3) δ 66.06 (C-2)	321[b]	67
69 (**775**)	R^1, R^2, R^4, R^5 = OMe R^3 = H	δ 5.75 (1H, t, *J* = 4.1 Hz, H-3), 4.72 (2H, d, *J* = 4.1 Hz, H-2)	δ 137.62 (C-4) δ 117.51 (C-3) δ 65.79 (C-2)	351[b]	72

[a]HR-MS ($[M + H]^+$) [b]HR-MS ($[M + Na]^+$) [c]GC-MS ($[M^+]$ [d]GC-MS ($[M-H]^+$) [e]($[M^+]$-dimer

7.4 4-Arylcoumarins *via* $Al(OTf)_3$ enhanced Grignard reaction and RCM

With the synthesis of the neoflavenes completed successfully, it was felt that the same basic methodology could be applied to the preparation of 4-arylcoumarins as well. If the $Al(OTf)_3$-based olefination of the crotonated acetophenone (**777**) could be achieved selectively (Scheme 7.19), this might also lead to a novel three step preparation of this biologically important (*cf.* Chapter 2) group of flavonoids.



Scheme 7.19 4-Arylcoumarin retrosynthesis

In this regard, esterification of 2-hydroxyacetophenone (**746**) with crotonoyl chrloride (pyridine, DMAP, refluxing DCM) led to the desired ester (**778**) (plate 2) in 43% yield. Subsequent $Al(OTf)_3$ enhanced addition of phenylmagnesium bromide to the ketone moiety [1. $Al(OTf)_3$ (1.0 eq.), Et_2O, -30 °C, 30 min., 2. PhMgBr (3.0 M, 1.5 eq.), rt., 7 h.] could, however, not be controlled and products originating from interaction of the Grignard reagent with the ester moiety were found in abundance, even at reduced temperatures. Although this complicating process could, in principle, be circumvented by using another protecting group during the Grignard reaction and replacing it afterwards with the crotonyl ester moiety, this would add at least two extra steps to the process; thus rendering it too tedious and not economical when compared to other existing methods for preparing 4-arylcoumarins,[19] so this approach was abandoned for the time being.

7.5 Conclusions

Although neoflav-3-ene (**741**) could be prepared *via* a Claisen rearrangement of the 1-cinnamyloxy-3-methoxybenzene (**731**) followed by vinylation and subsequent RCM, or

Wittig mediated methylenation of 2-allyloxybenzophenone (**739**) followed by RCM, it was found not to be possible to extend these methodologies towards oxygenated substrates without adding a number of process steps. A new process, which proved to be versatile towards several oxygenated substrates, was therefore developed. In this regard, it was found that the addition of $Al(OTf)_3$ to the reaction of 2'-allyloxyacetophenones with phenyl Grignard reagents led to the one-pot preparation of the 1,1-disubstituted styrenes in 52 – 94% yields, when PhMgBr or 4-OMePhMgBr was used in the Grignard reaction. When 3,4-dimethoxyphenylmagnesium bromide (**765**) was utilised together with $Al(OTf)_3$, the analogous alcohols (**766**) and (**767**) were, however, obtained in moderate and low yield (50% and 4%), respectively. Omitting $Al(OTf)_3$ from this Grignard reaction, i.e. reacting 2'-allyloxy-4'-methoxyacetophenone (**751**) and its 4',5'-dimethoxy analogue (**753**) with 3,4-dimethoxyphenylmagnesium bromide (**765**), and performing the reaction under 'normal' Grignard conditions [THF, -60 °C], led to the tertiary alcohols to be obtained in 60 and 80% yield, respectively. Subsequent dehydration of the alcohols (**766**) and (**767**) afforded the desired styrenes (**768**) and (**769**) in 75 and 64% yields, respectively. Subsequent ring closing metathesis of all the styrene intermediates proceeded smoothly over Grubbs II catalyst and the neoflav-3-enes could thus be obtained in good to excellent yields (67% – quant.).

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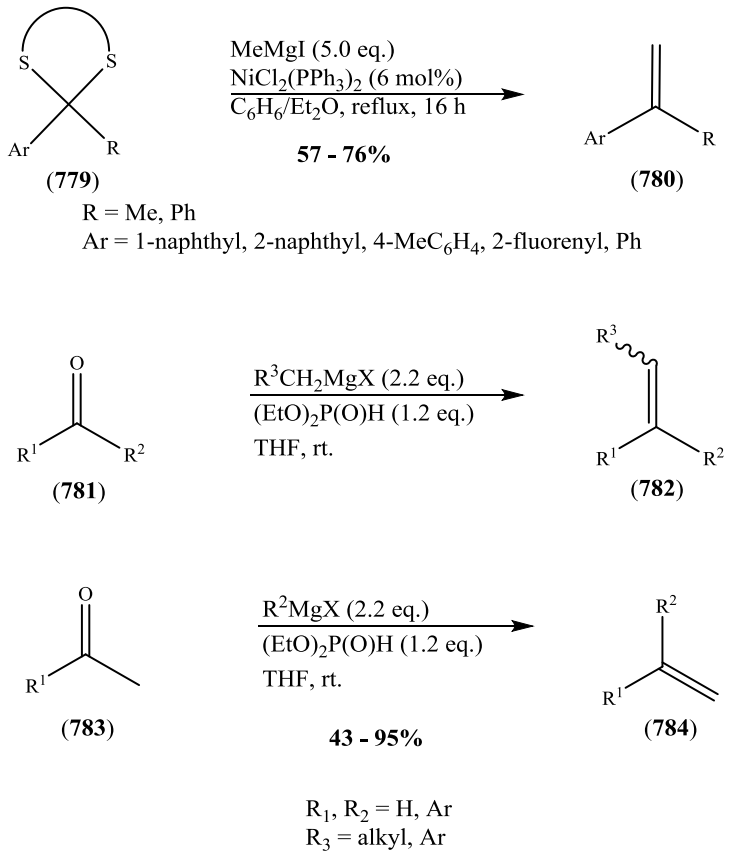
Chapter 8:$Al(OTf)_3$ Enhanced Grignard Reactions

Introduction

Olefination of carbonyl compounds signifies an important transformation in the preparation of various organic molecules. The search for alkenes of a variety of substitution patterns have furthermore been intensified by the development of metathesis based methodology for the preparation of various organic compounds. Although classical methods for the transformation of carbonyl compounds into olefins, like the Wittig reaction and its modifications,[1,2,3] Peterson olefination[4,5] and Julia olefination[6,7,8] exist, many of these processes are hampered by the utilisation of reagents in stoichiometric quantities and strong basic conditions being required, as well as the stepwise generation of intermediates (e.g. ylide). Catalytic alternatives to the Wittig reaction based on several metals (Mo,[9] Re,[10] Fe,[11] Ru,[12] Co,[13] Rh,[14] Cu,[15] and Ir[16]) and ligands have been reported, but these methods require the availability of diazocompounds which are not always commercially available. Moreover, many of these protocols are only high yielding when applied to aldehydes and/or electron-deficient ketones. Lewis acids like $SbCl_5$ and Et_3OBF_4 were also tested as co-catalysts in efforts to increase the electrophilicity of the carbonyl carbon in ketones, but due to undesired side reactions, the olefin yield was below 10% proving that strong Lewis acids do not activate ketones towards olefination under these conditions.[10]

Ketone and aldehyde olefinations utilising Grignard reagents are limited to the research published by Luh *et al.*[17] and the Zhang group.[18] Luh and co-workers[17] employed Grignard reagents and a nickel catalyst to convert dithioacetal *S*-oxides (**779**) (synthesised from the analogous carbonyl compounds) into alkenes, while Zhang *et al.*[18] utilised the aldehydes or ketones directly with Grignard reagent in the presence of diethyl phosphite yielding the corresponding olefins (Scheme 8.1). Although these workers obtained alkenes in acceptable yields from aldehydes and ketones at room temperature, the Grignard reagent was required in excess (2.0 eq.) while stoichiometric quantities of phosphite was required.



Scheme 8.1 Olefination of aldehydes or ketones by Luh *et al.*[17] and Zhang *et al.*[18]

However, it is well known that the addition of cuprates to carbonyl compounds are enhanced by the presence of Lewis acids[19,20,21,22,23] and $CeCl_3$, for example, has been employed to improve the reactivity of various carbonyl substrates toward Grignard additions and improved yields of the alcohols.[24,25,26] Since it has already been established that $Al(OTf)_3$ indeed has an enhancing effect on the addition of Grignard reagents to some electron-rich ketones (*cf.* Chapter 7), it was decided to embark on an investigation into the scope of this novel direct olefination process for activated ketones in general.

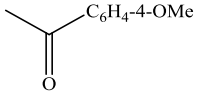
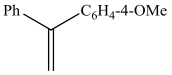
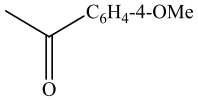
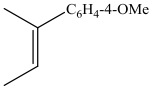
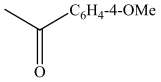
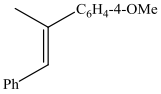
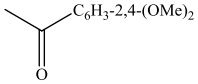
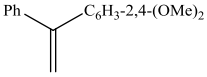
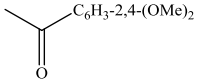
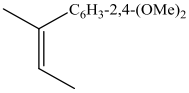
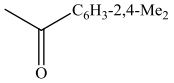
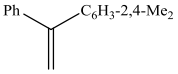
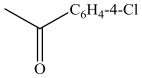
8.1 $Al(OTf)_3$ enhanced Grignard reactions of substituted acetophenones

The investigation was initiated by treating a solution of *p*-methoxyacetophenone (**785**) in dry DCM (5.0 mL) with $Al(OTf)_3$ (1.0 eq.) at -30 ^oC for 30 minutes, followed by the addition of PhMgBr (2.0 eq.) and allowing the reaction mixture to warm up to room temperature and the desired alkene, which proved to be 4-methoxy-α-phenylstyrene (**789**) [^1H, ^{13}C NMR and MS data: Table 8.2 (plate 70)], was obtained in 71% yield. In order to prove that the product was indeed formed during the $Al(OTf)_3$ mediated process, the reaction was repeated at room temperature in the absence of $Al(OTf)_3$ with all other conditions being kept constant. Under

these conditions, however, no olefinic product or alcohol could be detected (GC). While the effect of the temperature profile on the reaction has already been investigated during the preparation of the neoflavonoid precursors, the effect of the ratio between Grignard reagent and $Al(OTf)_3$ has not been assessed, so this aspect of the new methodology was subsequently investigated. The reaction of *p*-methoxyacetophenone (**785**) was therefore repeated with only 1 equivalent of PhMgBr in the presence of 1 equivalent of $Al(OTf)_3$ and it was found that the desired olefin (**789**) was formed in only 40% yield. It was henceforth decided to continue utilising the Grignard reagent in 2 equivalent quantities for the remainder of the investigation.

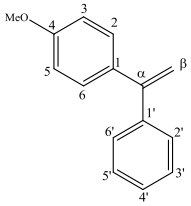
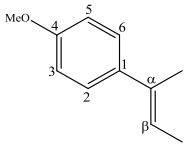
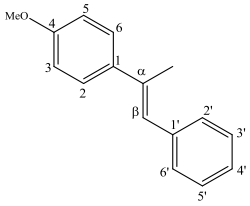
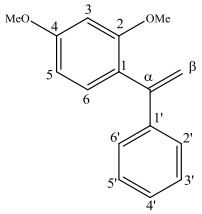
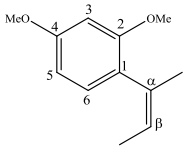
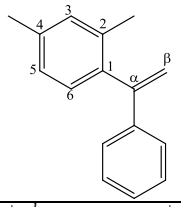
With the optimum conditions determined, the applicability of the new methodology to other Grignard reagents was investigated. The reaction of *p*-methoxyacetophenone (**785**) with EtMgBr and BnMgBr under the aforementioned reaction conditions led to the formation of the alkenes (**790**) and (**791**) in 53 and 67% yields respectively (Table 8.1, entries 2 and 3). The ^{1}H NMR spectra (plates 71a and 72a, Table 8.2) of the products contained only one olefinic proton resonance at δ 5.81 and δ 6.85 – 6.83, respectively, so it could be concluded that the products were in fact the expected trisubstituted alkenes (**790**) and (**791**). Although a mixture of the *cis*- and *trans*-products was expected from each of these reactions, only one product was obtained for every Grignard reaction. Since literature revealed the chemical shift value of the residual proton in aryl substituted alkenes to be diagnostic in terms of the *E* or *Z* geometry of the product with the β-proton of the *E*-isomer of arylsubstituted 2-butenes to resonate between δ 5.78 and 5.90 *vs* δ 5.52 – 5.58 for the *Z*-izomer[27,28,29] and the β-proton in *E* methyl substituted stilbenes to be between δ 6.78 and 6.81 *vs* that of the *Z*-isomer at *ca.* δ 6.32,[30,31,32] it could be concluded that both products from the reactions were the *E*-isomers (**790**) and (**791**), respectively. Control reactions in the absence of $Al(OTf)_3$ in the case of the EtMgBr gave no addition product at all, while (*E*)-4-methoxy-α-methyl-β-phenylstyrene (**791**) was obtained in only 12% yield when BnMgBr was used as Grignard reagent (Table 8.1, entries 2 and 3).

Table 8.1 Reaction of acetophenones with Grignard reagents in the presence of $Al(OTf)_3$

Entry	Substrate	Grignard reagent	Product	Yield (%)	
				With $Al(OTf)_3$	Without $Al(OTf)_3$[a]
1	 (**785**)	PhMgBr	 (**789**)	71	0
2	 (**785**)	EtMgBr	 (**790**)	53	0
3	 (**785**)	BnMgBr	 (**791**)	67	12
4	 (**786**)	PhMgBr	 (**792**)	62	0
5	 (**786**)	EtMgBr	 (**793**)	46	0
6	 (**787**)	PhMgBr	 (**794**)	24	0
7	 (**788**)	PhMgBr	-	0	0[b]

[a]Ketone [200 mg in anhydrous DCM (5 – 10mL)] [b]Repeating the reaction in THF led to the formation of the tertiary alcohol [1-(4-chlorophenyl)-1-phenylethan-1-ol] (**795**) in 51% yield.

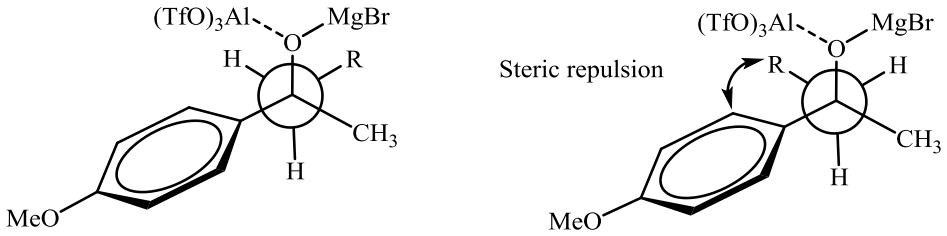
Table 8.2 ^{1}H, ^{13}C NMR data of products from $Al(OTf)_3$ enhanced Grignard reactions

Plate	Product		^{1}H NMR	^{13}C NMR	MS
70		(**789**)	δ 5.41 (1H, d, *J* = 1.2 Hz, H-β), 5.37 (1H, d, *J* = 1.2 Hz, H-β)	δ 112.97 (C-β)	210[a] (100%)
71		(**790**)	δ 5.81 (1H, qq, *J* = 6.8, 1.3 Hz, H-β), 2.04 – 2.02 (3H, m, α-C$\underline{H}_3$), 1.82 – 1.80 (3H, m, β-C$\underline{H}_3$)	δ 120.95 (C-β) δ 15.63 (α-$\underline{C}H_3$) δ 14.40 (β-$\underline{C}H_3$)	162[a] (100%)
72		(**791**)	δ 6.85 – 6.83 (1H, m, H-β), 2.24 (3H, d, *J* = 1.3 Hz, -C$\underline{H}_3$)	δ 126.88 (C-β)	224[a] (100%)
73		(**792**)	δ 5.62 (1H, d, *J* = 1.6 Hz, H-β), 5.21 (1H, d, *J* = 1.6 Hz, H-β)	δ 115.13 (C-β)	240[a] (80%)
74		(**793**)	δ 5.55 (1H, qq, *J* = 6.7, 1.3 Hz, H-β), 2.00 – 1.98 (3H, m, α-C$\underline{H}_3$), 1.80 – 1.78 (3H, m, β-C$\underline{H}_3$)	δ 123.46 (C-β) δ 16.98 (α-$\underline{C}H_3$) δ 14.03 (β-$\underline{C}H_3$)	192[b]
75		(**794**)	δ 5.75 – 5.73 (1H, m, H-β), 5.19 – 5.17 (1H, m, H-β)	δ 114.93 (C-β)	208[a] (31%)

[a]GC-MS [M^+] [b]HR-MS [M^+]

The formation of only the *E*-isomers during the reaction of *p*-methoxyacetophenone (**785**) with the EtMgBr and BnMgBr can be explained in terms of an E2-type $Al(OTf)_3$ mediated elimination of the oxygen moiety where the transition states (**796**) and (**797**) (Figure 8.1) are

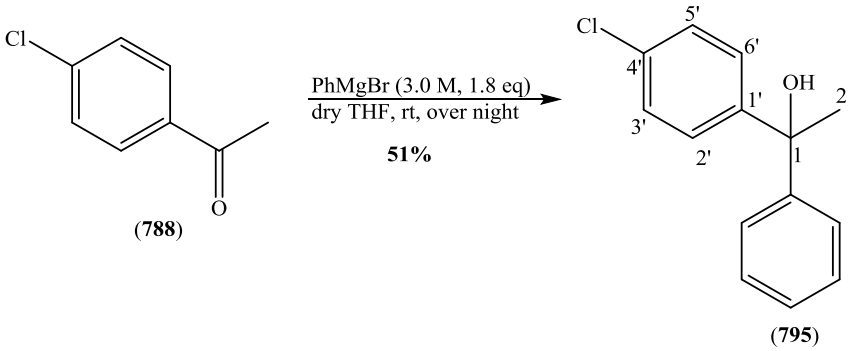
possible during the elimination process. If it is assumed that complexation of the bulky aluminium triflate entity to the Mg-alkoxide function results in it being in a perpendicular alignment with respect to the aromatic ring, steric interaction between the methyl or phenyl moiety and the *ortho*-hydrogens on the aromaric ring would lead to elimination from the gauche conformation (**796**) instead of the anti-conformer (**797**); thus leading to the *E*-isomer of the product being formed in both cases.



(**796**) R = CH_3 or Ph (**797**) R = CH_3 or Ph

Figure 8.1 E2-type elimination transition states

Extending the reaction of PhMgBr to 2,4-dimethoxy- (**786**) and 2,4-dimethylacetophenone (**787**) led to the alkenes (**792**) and (**794**) (^{1}H NMR plates 73a and 75a) being formed in 62 and 24% yields, respectively (Table 8.1, entries 4 and 6). These yields, taken in combination with the fact that 4-chloroacetophenone (**788**) did not yield any alkene at all (Table 8.1, entry 7), serves as indication that, under these reaction conditions, an electron-rich aromatic ring is required for olefin formation. Reacting the electron-rich substrates (**785**) and (**786**) and 4-chloroacetophenone (**788**) under 'normal' Grignard conditions [PhMgBr (3.0 M, 1.8 – 2.0 eq.), DCM, rt.] resulted in no observable alkene or alcohol product to be found. When the solvent for the 4-chloroacetophenone (**788**) reaction was changed to THF, however, the tertiary alcohol (**795**) was obtained in 51% yield in the absence of any $Al(OTf)_3$, while the addition of $Al(OTf)_3$ in this instance did not lead to a change in product formation (Scheme 8.2). The structure of the alcohol (**795**) was confirmed by ^{1}H NMR (plate 80a) where, apart from the expected aromatic resonances [δ 7.51 – 7.47 (4H, m), 7.32 – 7.27 (4H, m), 7.21 – 7.18 (1H, m)] the hydroxy resonance was clearly visible at δ 4.82 (1H, s) and the methyl group at δ 1.93 (3H, s)]. ^{13}C NMR data (plate 80b) further confirmed the structure of (**795**) where the methyl signal was observed at δ 30.93 and HR-MS data gave final confirmation indicating the $[M\text{-}H]^+$ fragment at *m/z* 231.



Scheme 8.2 Reaction of chloroacetophenone with PhMgBr under 'normal' Grignard conditions

When 2,4-dimethoxyacetophenone (**786**) was treated with EtMgBr in the presence of $Al(OTf)_3$ it also led to the formation of the alkene (**793**) (Table 8.2, ^1H NMR plate 74a) in 46% yield. In this instance, however, the chemical shift of the residual alkene proton (δ 5.55) corresponded to that of the *Z*-isomer of the trisubstituted olefinic analogues (*vide supra*). The fact that the *Z*-isomer was obtained in this case *vs* the *E*-isomers (**790**) and (**791**) in previous reactions (*vide supra*), is probably explicable in terms of chelate complexation between the 2,4-dimethoxy substrate (**786**) and the triflate as indicated in Figure 8.2 resulting in the aromatic ring, benzylic carbon and OH group to occupy the same plain, thus allowing free rotation for the ethyl group being possible and subsequent preferred anti-periplanar elimination of the oxygen entity.

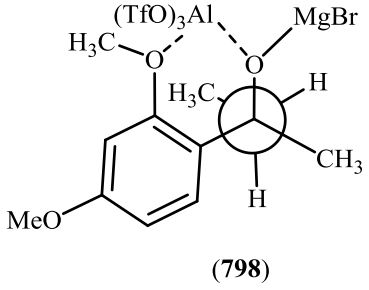


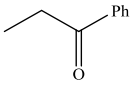
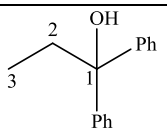
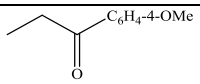
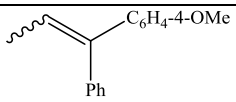
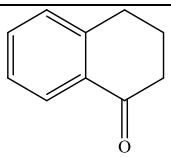
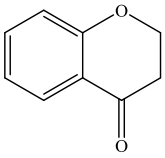
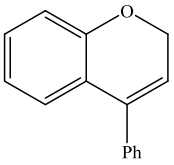
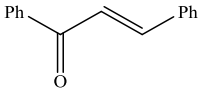
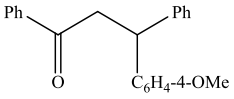
Figure 8.2 Elimination transition state leading to (*Z*)-2,4-dimethoxy-α,β-dimethylstyrene

8.2 Effect of $Al(OTf)_3$ on the reaction of PhMgBr with 'other' ketones

Since results of the new Grignard based one-pot olefination process w.r.t. electron-rich or activated acetophenones looked quite promising, it was decided to expand the investigation to the evaluation of other activated aromatic ketones. Propiophenone (**799**), *p*-methoxypropiophenone (**800**), α-tetralone (**801**) and chromanone (**802**) were therefore treated with $Al(OTf)_3$ and PhMgBr under the optimum conditions found for the acetophenones. While propiophenone (**799**) and α-tetralone (**801**) failed to give any olefinic products, the

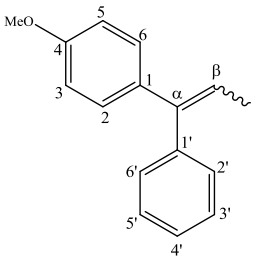
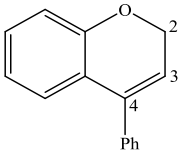
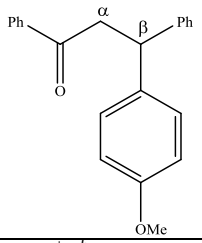
oxygenated analogues (**800**) and (**802**) yielded the expected substituted alkenes (**804**), and (**741**) in 97% and 55% yields, respectively [Table 8.3 entries 2 and 4, Table 8.4 (NMR and MS data)]; thus confirming the prerequisite of an activated aromatic ring for this reaction to be successful. In contrast to what was found for the reactions of the ethyl - and benzyl Grignard reagents with the acetophenones (**785**) and (**786**) (*cf.* paragraph 8.1), the product in the propiophenone case showed no preference for a specific regioisomer and an almost 1:1 mixture of the *E*- and *Z*-isomers were obtained. The formation of the mixture of products is explicable in terms of an E1-type elimination of the oxygen moiety from the double benzylic position in the tertiary alcohol intermediate rather than the aluminium triflate assisted E2 elimination envisaged for the acetophenone derivatives. In order to again prove the effect of aluminium triflate in the Grignard reactions of propiophenone (**799**) and *p*-methoxypropiophenone (**800**), these reactions were repeated without $Al(OTf)_3$ being present and the alcohols (**756**) and (**806**) [^{1}H NMR plates 78a and 79a, δ_H 4.37 (1H, s, -O<u>H</u>), 2.35 (2H, q, *J* = 7.3 Hz, H-2), 0.86 (3H, t, *J* = 7.3 Hz, H-3) for (**756**) and δ_H 4.28 (1H, s, -O<u>H</u>), 2.33 (2H, q, *J* = 7.3 Hz, H-2), 0.87 (1H, t, *J* = 7.3 Hz, H-3) for (**806**); ^{13}C NMR plates 78b and 79b, δ_C 78.23 (C-1), 35.05 (C-2), 8.56 (C-3) for (**756**) and δ_C 77.76 (C-1), 35.04 (C-2), 8.49 (C-3) for (**806**); *m/z* 212 (0.14%) for (**756**) and 242 (3%) for (**806**)] could be isolated in 22% and 85% yields, respectively (Table 8.3, entries 1 and 2).

Table 8.3 Reaction of PhMgBr with 'other' ketones in the presence of $Al(OTf)_3$

Entry	Substrate		Grignard reagent	Product	Yield (%) With $Al(OTf)_3$	Without $Al(OTf)_3$[a]
1		(**799**)	PhMgBr		(**756**) 0	22[b]
2		(**800**)	PhMgBr		(**804**) 97	85[b]
3		(**801**)	PhMgBr	-	0	0
4		(**802**)	PhMgBr		(**741**) 55	0
5		(**803**)	*p*-OMePhMgBr		(**805**) 29	21

[a]Ketone [200 mg in anhydrous DCM (5 – 10mL)] [b]Products were the tertiary alcohols (**756**) (plate 78) and (**806**) (plate 79)

Table 8.4 ^{1}H, ^{13}C NMR data of products from $Al(OTf)_3$ enhanced Grignard reactions

Plate	Product		^{1}H NMR	^{13}C NMR	MS
76		(**804**)	δ 6.14 (1H, q, *J* = 7.0 Hz, H-β (*Z*)), 6.10 (1H, q, *J* = 7.0 Hz, H-β (*E*)), 1.74 (3H, d, *J* = 7.0 Hz, -C<u>H</u>$_3$ (*Z*)), 1.70 (3H, d, *J* = 7.0 Hz, -C<u>H</u>$_3$ (*E*))	δ 124.32 (C-β) δ 122.74 (C-β) δ 16.07 (-<u>C</u>H$_3$) δ 15.92 (-<u>C</u>H$_3$)	225[b]
63		(**741**)	δ 5.88 (1H, t, *J* = 4.0 Hz, H-3), 4.82 (2H, d, *J* = 4.0 Hz, H-2)	δ 137.68 (C-4) δ 121.57 (C-3) δ 65.89 (C-2)	207[a] (100%)
77		(**805**)	δ 4.76 (1H, t, *J* = 7.3 Hz, H-β), 3.84 (2H, d, *J* = 7.3 Hz, H-α)	δ 46.28 (C-β) δ 45.02 (C-α)	339[c]

[a]GC-MS ($[M-H]^+$) [b]HR-MS ($[M^+]$ [c]HR-MS ($[M + Na]^+$)

Finally, it was decided to look into the effect, if any, of $Al(OTf)_3$ on the conjugated addition of Grignard reagents to α,β-unsaturated substrates and it was found that when chalcone (**803**) was reacted with *p*-OMePhMgBr in the presence of $Al(OTf)_3$, the yield of the 1,4-addition product (**805**) could be increased from 21 to 29% (Table 8.3, entry 5).

Although $Al(OTf)_3$ was used in stoichiometric amounts in all of the reactions mentioned above, it was also determined that it could be used in catalytic quantities. In this regard, repeating the reaction of *p*-methoxyacetophenone (**785**) with PhMgBr in the presence of catalytic quantities (10 mol%) of $Al(OTf)_3$ led to the desired 1,1-disubstituted styrene (**789**) being formed in 82% yield.

8.3 Conclusions and future work

From the results reported above, it is evident that aluminium triflate has an enhancing effect on the addition of Grignard reagents to electron-rich ketones like oxygenated aromatic analogues and that this reagent also facilitates the formation of the alkene from the initially formed tertiary alcohol in a one-pot process. It has furthermore been demonstrated that the

reaction is highly stereoselective towards one regio-isomer of the olefin in the case of oxygenated aryl-alkyl substituted substrates [(**785**) and (**786**) reacting with ethyl- or benzyl Grignard reagents] but not when the elimination originates from a double benzylic alcohol intermediate. Finally, it was found that aluminium triflate may be utilised in less than molar quantities, rendering this methodology the first Grignard based catalytic olefination process. Extending the scope of the catalytic addition of aluminium triflate to the Grignard reactions of the other electron-rich substrates in Tables 8.2 and 8.4 will form the basis of a future investigation.

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Chapter 9: Experimental

9.1 Chromatography

9.1.1 Thin layer chromatography (TLC)

Qualitative thin layer chromatography (TLC) was conducted on Merck TLC-aluminium plates: Silica Gel F_{254} (0.2 mm layer) divided into strips of *ca.* 2.5 x 5 cm. R_f values are those observed in these qualitative TLC assessments. Eluent was prepared v/v.

9.1.2 Preparative layer chromatography (PLC)

PLC was conducted on glass plates (20 x 20 cm) coated with a layer (*ca.* 1.0 mm) of Merck Kieselgel 60 PF_{254} that had been air-dried overnight at rt. Eluent was prepared v/v. Crude mixture (15 – 20 mg) was applied to each plate and after development, in the appropriate eluent, the plates were dried in a stream of air. Bands were distinguished under UV-light (254 nm) after which they were removed and the isolated product washed out with acetone or ethyl acetate (EtOAc). All solvent was removed under reduced pressure at *ca.* 40 °C.

9.2 Anhydrous solvents[1]

MeCN, MeOH, Me_2CO, DCM and *n*-hexane were dehydrated by filtering through a small column of activated basic alumina (Sigma Aldrich Brockman I basic alumina, 20% v/v) prior to use.

Et_2O and THF were distilled over Na for 2 h with subsequent fresh distillation under Ar before use.

Pyridine was dried over KOH.

9.3 Spectroscopic and spectrometric methods

9.3.1 Nuclear magnetic resonance spectrometry (NMR)

NMR-spectroscopy was performed on a Bruker AM 600 FT-spectrometer at, unless specified to the contrary, 20 ºC with $CDCl_3$ (deuterochloroform) or $(CD_3)_2CO$ (deuterated acetone) as solvent. Chemical shifts are reported in parts per million (ppm) with the solvent peak for proton spectra at 7.26 ppm for $CDCl_3$ and 2.06 ppm for $(CD_3)_2CO$ and 77.16 ppm for $CDCl_3$ and 206.26 ppm for $(CD_3)_2CO$ on the δ-scale in carbon spectra, whereas coupling constants are given in Hz. Chemical impurity in proton spectra resonating at 1.56 ppm is identified as

moisture in accordance with Gottlieb *et al.*[2] Impurities or solvent peaks are designated I and S, respectively on NMR spectra.

9.3.3 Mass spectrometry (MS)

Mass spectrometry was performed by means of electron impact (EI) ionization on a Shimadzu GC-MS QP-2010 fitted with a J & W DB-5ms capillary column (0.25 μm film thickness, 0.32 mm ID, 30 m), helium as carrier gas at a linear velocity of 27.5 cm/s and an injector temperature of 250 °C. Injections were made in the split mode. The initial column temperature of 50 °C was kept for 3 min, where after it was increased to 250 °C at 10 °C/min and kept at this temperature for the rest of the analysis. Alternatively, MS was performed by means of a Matrix Assisted Laser Desorption Ionization Time-Of-Flight (MALDI-TOF) Bruker Microflex LRF20 in either positive or negative mode with the minimum laser power required to observe signals. High resolution MS (EI-MS, 70 eV) was performed by PMBMS, University of KwaZulu-Natal.

9.4 Melting points

Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP3) apparatus and are uncorrected.

9.5 Microwave irradiation

Reactions were carried out in a CEM Discover® SP microwave reactor utilising the dynamic irradiation program (fixed temperature, variable power) with continuous cooling and power set to a maximum of 200 W.

9.6 Standard work-up procedure

Unless specified otherwise, distilled H_2O was added to the reaction mixture and the aqueous (aq.) phase extracted into EtOAc or Et_2O. The organic extract was dried over Na_2SO_4 and the solvent removed *in vacuo* at *ca*. 40 °C. Subsequent purification *via* PLC afforded the product.

9.7 Ether synthesis

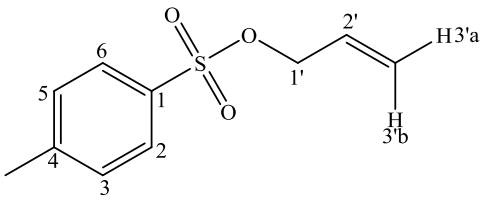
9.7.1 Tosylation of alcohols[3]

To a stirring solution of alcohol (1.0 eq.) and pyridine (3.0 eq.) in $CHCl_3$ (10.0 mL) at 0 °C, *p*-toluenesulfonyl chloride (2.0 eq.) was added slowly. After completion of the reaction, the reaction mixture was acidified with aq. HCl (2.0 N, 30.0 mL) and extracted into Et_2O (3 x 60.0 mL). The organic layer was washed with aq. $NaHCO_3$ (5%, 60.0 mL) and water (60.0

mL) consecutively, dried over Na_2SO_4 and the solvent removed under reduced pressure. The product was purified *via* PLC.

9.7.1.1. 1-Allyl-4-methylbenzenesulfonate (**570**)[4]

Allyl alcohol (**559**) (0.6 mL, 8.8 mmol), pyridine (2.1 mL, 26 mmol, 3.0 eq.), tosyl chloride (3.30 g, 17.3 mmol, 2.0 eq.)



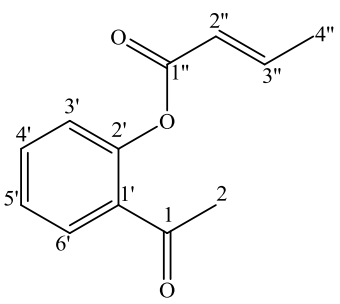
Yielded 1-allyl-4-methylbenzenesulfonate (**570**) as a colourless oil (1.25 g, 68%); R_f : 0.11 (H:A; 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 1a): δ 7.78 (2H, d, *J* = 8.4 Hz, H-2 and H-6), 7.34 (2H, d, *J* = 8.4 Hz, H-3 and H-5), 5.80 (1H, ddt, *J* = 17.1, 10.4, 5.9 Hz, H-2'), 5.30 (1H, ddt, *J* = 17.1, 1.3, 1.3 Hz, H-3'b), 5.24 (1H, ddt, *J* = 10.4, 1.3, 1.3 Hz, H-3'a), 4.51 (2H, ddd, *J* = 5.9, 1.3, 1.3 Hz, H-1'), 2.43 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, plate 1b): δ 144.96 (C-4), 133.22 (C-1), 130.29 (C-2'), 129.95 (C-3 and C-5), 127.98 (C-2 and C-6), 120.36 (C-3'), 70.89 (C-1'), 21.71 (-CH_3); *m/z* (EI) 212 (M^+, 3%).

9.7.2 Ester synthesis

2'-Hydroxyacetophenone (1.0 eq.), DMAP (0.2 eq.) and dry pyridine (1.0 eq.) were dissolved in dry DCM (15.0 mL) under an Ar atmosphere. Crotonoyl chloride (2.0 eq.) was added and the reaction mixture heated to reflux overnight. After completion of the reaction, water (60.0 mL) was added and the product extracted into EtOAc (3 x 60.0 mL) and the solvent removed in *vacuo*. The product was purified *via* PLC.

9.7.2.1 2'-Crotonoyloxyacetophenone (**778**)[5]

2'-Hydroxyacetophenone (**746**) (1.8 mL, 15 mmol), DMAP (0.2 g, 2 mmol, 0.1 eq.), pyridine (2.0 mL, 25 mmol, 1.7 eq.), crotonoyl chloride (2.0 mL, 18 mmol, 1.2 eq.)



Yielded 2'-crotonoyloxyacetophenone (**778**) as a yellow oil (1.40 g, 47%); R_f : 0.34 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 2a): δ 7.78 (1H, dd, *J* = 7.7, 1.7 Hz, H-6'), 7.50 (1H, ddd, *J* = 7.9, 7.7, 1.7 Hz, H-4'), 7.28 (1H, ddd, *J* = 7.7, 7.7, 1.1 Hz, H-5'), 7.20 (1H, dq, *J* = 15.5, 7.0 Hz, H-3''), 7.11 (1H, dd, *J* = 7.9, 1.1 Hz, H-3'), 6.07 (1H, dq, *J* = 15.5, 1.7 Hz, H-2''), 2.51 (3H, s, -C<u>H</u>$_3$), 1.96 (3H, dd, *J* = 7.0, 1.7 Hz, H-4''); ^{13}C NMR (151 MHz, $CDCl_3$, plate 2b): δ 197.76 (C-1),

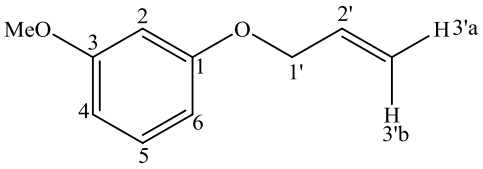
164.59 (C-1''), 149.10 (C-2'), 147.94 (C-3''), 133.29 (C-4'), 131.30 (C-1'), 130.08 (C-6'), 125.96 (C-5'), 123.82 (C-3'), 121.75 (C-2''), 29.79 (C-2), 18.34 (C-4''); *m/z* (EI) 204 (M^+, 2%).

9.7.3 Williamson ether synthesis[6]

K_2CO_3 (2.0 eq.) was added to a mixture of phenol (1.0 eq.) in dry CH_3CN under an Ar atmosphere. Allyl bromide (2.0 eq.) was added slowly while the mixture heated to reflux. Once deemed complete, the reaction mixture was allowed to cool and the K_2CO_3 filtered off. The solvent and excess allyl bromide was removed *in vacuo*. The product was purified *via* PLC.

9.7.3.1 1-Allyloxy-3-methoxybenzene (**575**)[7]

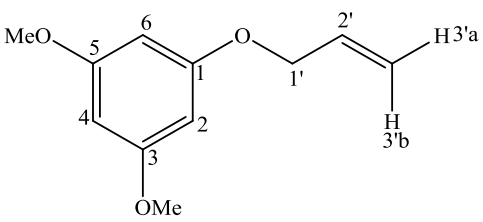
1-Hydroxy-3-methoxybenzene (**558**) (4.4 mL, 41 mmol), K_2CO_3 (11.93 g, 86.3 mmol, 2.1 eq.), allyl bromide (7.0 mL, 81 mmol, 2.0 eq.).



Yielded 1-allyloxy-3-methoxybenzene (**575**) as a bright orange oil (6.56 g, quantitative yield); R_f : 0.6 (H:A; 6:4); ^{1}H NMR (600 MHz, $CDCl_3$, plate 3a): δ 7.20 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 6.56 – 6.54 (2H, m, H-4 and H-6), 6.53 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.08 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz, H-2'), 5.44 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, H-3'b), 5.32 (1H, ddt, *J* = 10.5, 1.4, 1.4 Hz, H-3'a), 4.55 (2H, ddd, *J* = 5.3, 1.4, 1,4 Hz, H-1'), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 3b): δ 160.91 (C-1/3), 159.94 (C-1/3), 133.36 (C-2'), 129.95 (C-5), 117.75 (C-3'), 106.95 (C-4/6), 106.51 (C-4/6), 101.31 (C-2), 68.89 (C-1'), 55.32 (-OMe); *m/z* (EI) 164 (M^+, 100%).

9.7.3.2 1-Allyloxy-3,5-dimethoxybenzene (**576**)[6]

1-Hydroxy-3,5-dimethoxybenzene (**573**) (3.91 g, 25.4 mmol), K_2CO_3 (9.11 g, 65.9 mmol, 2.6 eq.), allyl bromide (5.4 mL, 62 mmol, 2.5 eq.).

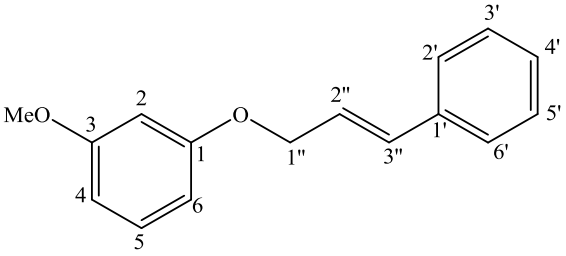


Yielded 1-allyloxy-3,5-dimethoxybenzene (**576**) as a yellow oil (4.56 g, 93%); R_f : 0.54 (H:A; 7:3); ^{1}H NMR (600 MHz, $CDCl_3$, plate 4a): δ 6.11 (2H, d, *J* = 2.10 Hz, H-2 and H-6), 6.10 – 6.09 (1H, m, H-4), 6.05 (1H, ddt, *J* = 17.3, 10.4, 5.6 Hz, H-2'), 5.41 (1H, ddt, *J* = 17.3, 1.4, 1.4 Hz, H-3'b), 5.29

(1H, ddt, *J* = 10.4, 1.4, 1.4 Hz, H-3'a), 4.49 (2H, ddd, *J* = 5.6, 1.4, 1.4 Hz, H-1'), 3.77 (6H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 4b): δ 161.59 (C-3 and C-5), 160.58 (C-1), 133.26 (C-2'), 117.91 (C-3'), 93.71 (C-2 and C-6), 93.20 (C-4), 68.98 (C-1'), 55.44 (-OMe); *m/z* (EI) 194 (M^+, 100%).

9.7.3.3 1-Cinnamyloxy-3-methoxybenzene (**731**)[8]

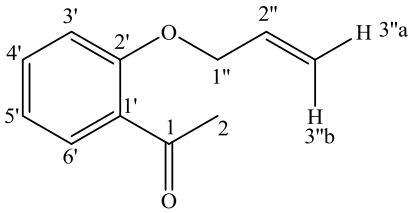
1-Hydroxy-3-methoxybenzene (**558**) (0.9 mL, 8 mmol), K_2CO_3 (2.30 g, 16.7 mmol, 2.1 eq.), cinnamyl bromide (**730**) (1.91 g, 9.67 mmol, 1.2 eq.).



Yielded 1-cinnamyloxy-3-methoxybenzene (**731**) as a yellow oil (1.40 g; 73%); R_f : 0.60 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 5a): δ 7.45 (2H, d, *J* = 7.2 Hz, H-2' and H-6'), 7.36 (2H, dd, *J* = 7.9, 7.2 Hz, H-3' and H-5'), 7.31 – 7.28 (1H, m, H-4'), 7.23 (1H, t, *J* = 8.2 Hz, H-5), 6.77 (1H, br. d, *J* = 16.1 Hz, H-3"), 6.63 – 6.55 (3H, m, Ar-H), 6.45 (1H, dt, *J* = 16.1, 5.8 Hz, H-2"), 4.71 (2H, dd, *J* = 5.8, 1.5 Hz, H-1"), 3.82 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 5b): δ 160.94 (C-3), 159.98 (C-1), 136.56 (C-1'), 133.15 (C-3"), 130.05 (C-5), 128.62 (C-3' and C-5'), 127.97 (C-4'), 126.68 (C-2' and C-6'), 124.47 (C-2"), 106.98 (Ar-C), 106.58 (Ar-C), 101.37 (Ar-C), 68.78 (C-1"), 55.41 (-OMe); HR-MS (ES) *m/z* 241.1228 $(M + H)^+$, $C_{16}H_{17}O_2^+$ requires 241.1223, found 241.1228.

9.7.3.4 2'-Allyloxyacetophenone (**750**)[9]

2'-Hydroxyacetophenone (**746**) (0.4 mL, 4 mmol), K_2CO_3 (1.13 g, 8.14 mmol, 2. eq.), allyl bromide (0.6 mL, 7 mmol, 1.8 eq.)

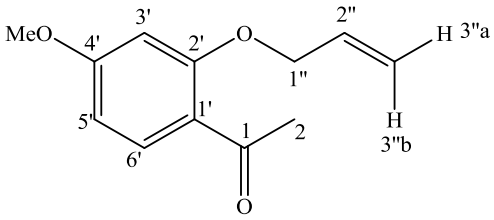


Yielded 2'-allyloxyacetophenone (**750**) as a yellow oil (0.62 g, 96%); R_f : 0.37 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 6a): δ 7.65 (1H, dd, *J* = 7.8, 1.9 Hz, H-6'), 7.48 (1H, ddd, *J* = 8.4, 8.3, 1.9 Hz, H-4'), 7.13 (1H, br. d, *J* = 8.4 Hz, H-3'), 7.01 (1H, ddd, *J* = 8.3, 7.8, 1.0 Hz, H-5'), 6.15 (1H, ddt, *J* = 17.3, 10.6, 5.4 Hz, H-2"), 5.47 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3"b), 5.30 (1H, ddt, *J* = 10.6, 1.5, 1.5 Hz, H-3"a), 4.72 (2H, ddd, *J* = 5.4, 1.5, 1.5 Hz, H-1"), 2.57 (3H, s, -CH_3); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 6b): δ 199.19 (C-1), 158.81 (C-2'), 134.34 (C-4'), 134.22 (C-2"),

130.74 (C-6'), 129.66 (C-1'), 121.48 (C-5'), 118.26 (C-3''), 114.17 (C-3'), 70.15 (C-1''), 32.12 (-<u>C</u>H$_3$); *m/z* (EI) 176 (M$^+$, 7%).

<u>9.7.3.5 2'-Allyloxy-4'-methoxyacetophenone (**751**)</u>[10]

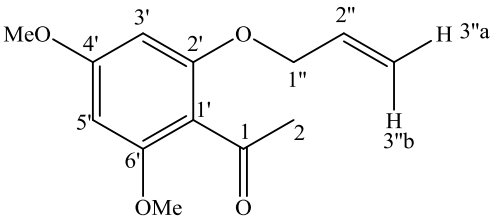
2'-Hydroxy-4'-methoxyacetophenone (**747**) (1.07 g, 5.20 mmol), K_2CO_3 (1.89 g, 13.7 mmol, 2.6 eq.), allyl bromide (1.1 mL, 13 mmol, 2.4 eq.)



Yielded 2'-allyloxy-4'-methoxyacetophenone (**751**) as a light yellow solid (1.27 g, 96%); R_f: 0.36 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 7a): δ 7.74 (1H, d, *J* = 8.7 Hz, H-6'), 6.65 (1H, d, *J* = 2.3 Hz, H-3'), 6.60 (1H, dd, *J* = 8.7, 2.3 Hz, H-5'), 6.18 (1H, ddt, *J* = 17.3, 10.7, 5.4 Hz, H-2''), 5.50 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3''b), 5.33 (1H, ddt, *J* = 10.7, 1.5, 1.5 Hz, H-3''a), 4.75 (2H, ddd, *J* = 5.4, 1.5, 1.5 Hz, H-1''), 3.87 (3H, s, -O<u>Me</u>), 2.53 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 7b): δ 196.73 (C-1), 165.50 (C-4'), 161.10 (C-2'), 134.26 (C-2''), 133.00 (C-6'), 122.13 (C-1'), 118.41 (C-3''), 106.91 (C-5'), 100.14 (C-3'), 70.32 (C-1''), 56.05 (-O<u>Me</u>), 32.26 (-<u>C</u>H$_3$); *m/z* (EI) 206 (M$^+$, 34%).

<u>9.7.3.6 2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**)</u>[11]

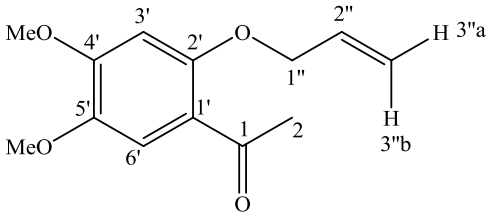
2'-Hydroxy-4',6'-dimethoxyacetophenone (**748**) (0.69 g, 3.5 mmol), K_2CO_3 (1.38 g, 9.99 mmol, 2.9 eq.), allyl bromide (0.7 mL, 8 mmol, 2 eq.)



Yielded 2'-allyloxy-4',6'-dimethoxyacetophenone (**752**) as a yellow oil (0.61 g, 74%); R_f: 0.22 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 8a): δ 6.26 (2H, s, H-3' and H-5'), 6.03 (1H, ddt, *J* = 17.3, 10.6, 5.0 Hz, H-2''), 5.40 (1H, ddt, *J* = 17.3, 1.7, 1,7 Hz, H-3''b), 5.23 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3''a), 4.59 (2H, ddd, *J* = 5.0, 1.7, 1.7 Hz, H-1''), 3.83 (3H, s, -O<u>Me</u>), 3.79 (3H, s, -O<u>Me</u>), 2.36 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 8b): δ 200.28 (C-1), 163.09 (C-4'/6'), 158.85 (C-4'/6'), 157.67 (C-2'), 134.35 (C-2''), 117.40 (C-3''), 115.11 (C-1'), 92.76 (C-3'/5'), 91.87 (C-3'/5'), 69.86 (C-1''), 56.21 (-O<u>Me</u>), 55.85 (-O<u>Me</u>), 32.64 (-<u>C</u>H$_3$); *m/z* (EI) 236 (M$^+$, 22%).

9.7.3.7 2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**)[12]

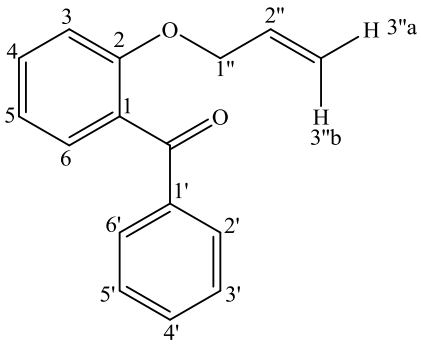
2'-Hydroxy-4',5'-dimethoxyacetophenone (**749**) (0.82 g, 3.5 mmol), K_2CO_3 (1.72 g, 12.4 mmol, 3.4 eq.), allyl bromide (1.0 mL, 12 mmol, 3.3 eq.)



Yielded 2'-allyloxy-4',5'-dimethoxyacetophenone (**753**) as *light yellow needles* (0.97 g, quantitative yield); R_f : 0.28 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 9a): δ 7.34 (1H, s, H-3'/6'), 6.80 (1H, s, H-3'/6'), 6.18 (1H, ddt, *J* = 17.3, 10.6, 5.5 Hz, H-2"), 5.49 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3"b), 5.32 (1H, ddt, *J* = 10.6, 1.5, 1.5 Hz, H-3"a), 4.76 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz, H-1"), 3.91 (3H, s, -O<u>Me</u>), 3.79 (3H, s, -O<u>Me</u>), 2.54 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 9b): δ 196.30 (C-1), 155.56 (4°-C), 155.35 (4°-C), 144.40 (C-4'/5'), 134.62 (C-2"), 120.23 (C-1'), 118.32 (C-3"), 113.59 (C-3'/6'), 99.61 (C-3'/6'), 71.16 (C-1"), 56.53 (-O<u>Me</u>), 56.41 (-O<u>Me</u>), 32.45 (-<u>C</u>H$_3$); *m/z* (EI) 236 (M^+, 46%).

9.7.3.8 2-Allyloxybenzophenone (**739**)[13]

2-Hydroxybenzophenone (**738**) (0.51 g, 2.6 mmol), K_2CO_3 (0.80 g, 5.8 mmol, 2.2 eq.), allyl bromide (0.4 mL, 5 mmol, 2.0 eq.)



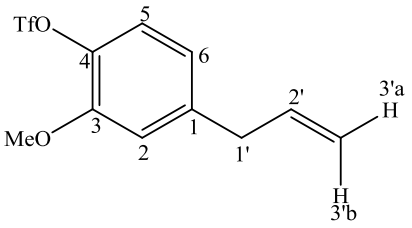
Yielded 2-allyloxybenzophenone (**739**) as a light yellow oil (0.59 g, 85%); R_f: 0.34 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 10a): δ 7.79 – 7.76 (2H, m, H-2' and H-6'), 7.62 – 7.58 (1H, m, H-4'), 7.53 – 7.47 (3H, m, H-4 and H-3' and H-5'), 7.39 (1H, dd, *J* = 7.4, 1.8 Hz, H-6), 7.14 (1H, br. d, *J* = 8.5 Hz, H-3), 7.11 (1H, ddd, *J* = 8.3, 7.4, 1.0 Hz, H-5), 5.73 (1H, ddt, *J* = 16.5, 11.4, 5.0 Hz, H-2"), 5.02 – 4.98 (2H, m, H-3"), 4.51 (2H, ddd, *J* = 5.0, 1.7, 1.7 Hz, H-1"); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 10b): δ 196.50 (<u>C</u>=O), 157.04 (C-2), 138.99 (C-1'), 133.66 (C-4'/2"), 133.61 (C-4'/2"), 132.73 (C-4), 130.19 (C-1), 130.07 (C-6, C-2' and C-6'), 129.15 (C-3' and C-5'), 121.64 (C-5), 116.81 (C-3"), 113.68 (C-3), 69.36 (C-1"); *m/z* (EI) 238 (M^+, 11%).

9.7.4 Trifluoromethanesulfonyloxy-group protection

A solution of phenol (1.0 eq.) in dry DCM (20.0 mL) was cooled to 0 ºC under Ar atmosphere with subsequent addition of DMAP (1.2 eq.). The reaction mixture was allowed to stir for 5 min. where after trifluoromethanesulfonic anhydride (1.2 eq.) was added. The reaction mixture was allowed to warm to rt. after 1 h of stirring. Once the reaction was deemed complete by TLC, the solvent was removed *in vacuo*, the crude reaction mixture passed through a short silica column and purified by PLC.

9.7.4.1 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)[14]

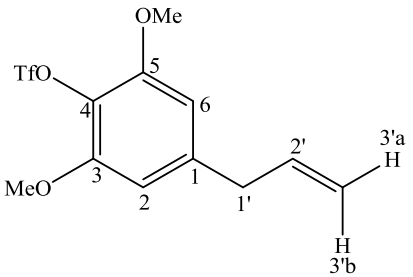
1-Allyl-4-hydroxy-3-methoxybenzene (0.5 mL, 3 mmol), DMAP (0.45 g, 3.7 mmol, 1.0 eq.), trifluoromethanesulfonic anhydride (0.6 mL, 4 mmol, 1.0 eq.).



Yielded 1-allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**) as a light yellow oil (0.74 g; 82%); R_f : 0.62 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 11a): δ 7.13 (1H, d, *J* = 8.3 Hz, H-5), 6.85 (1H, d, *J* = 1.9 Hz, H-2), 6.79 (1H, dd, *J* = 8.3, 1.9 Hz, H-6), 5.94 (1H, ddt, *J* = 17.1, 10.5, 6.7 Hz, H-2'), 5.14 – 5.10 (2H, m, H-3'a and H-3'b), 3.90 (3H, s, -OMe), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$, plate 11b): δ 151.30 (C-3), 141.92 (C-1), 137.23 (C-4), 136.42 (C-2'), 122.29 (C-5), 120.93 (C-6), 118.89 (q, *J* = 320.5 Hz, -OSO_2CF_3), 116.97 (C-3'), 113.45 (C-2), 56.22 (-OMe), 40.15 (C-1'); ^{19}F NMR (565 MHz, $CDCl_3$, plate 11f): δ -74.70 (-$OSOCF_3$); *m/z* (EI) 296 (M^+, 32%).

9.7.4.2 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

1-Allyl-4-hydroxy-3,5-dimethoxybenzene (0.5 mL, 2 mmol), DMAP (0.38 g, 3.1 mmol, 1.6 eq.), trifluoromethanesulfonic anhydride (0.5 mL, 3 mmol, 1.5 eq.).



Yielded 1-allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**) as a *beige amorphous solid* (0.72 g; 71%); R_f : 0.43 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 12a): δ 6.45 (2H, s, H-2 and H-6), 5.97 – 5.90 (1H, m, H-2'), 5.16 – 5.12 (2H, m, H-3'a and H-3'b), 3.87 (6H, s, -OMe), 3.37 (2H, br. d, *J* = 6.7 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$, plate 12b): δ 152.32 (C-3 and C-5), 141.35 (C-1), 136.36 (C-2'), 126.41 (C-4),

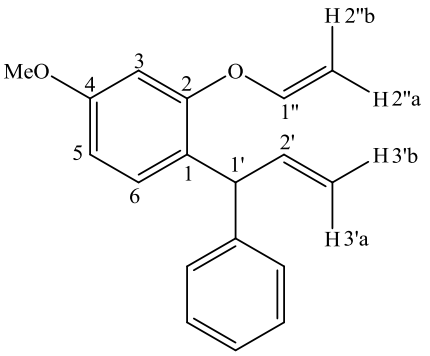
118.05 (q, 320.6 Hz, -$OSO_2\underline{C}F_3$), 117.02 (C-3'), 105.16 (C-2 and C-6), 56.34 (-O<u>Me</u>), 40.77 (C-1'); ^{19}F NMR (565 MHz, $CDCl_3$, plate 12f): δ -76.90 (-OSOC<u>F_3</u>); *m/z* (EI) 327 ($[M + H]^+$, 13%); HR-MS (ES) *m/z* 349.0335 $[M + Na]^+$, $C_{12}H_{13}O_5F_3NaS^+$ requires 349.0333, found 349.0335.

<u>9.7.5 Standard vinylation</u>

The phenolic substrate (1.0 eq.) was dissolved in CH_3CN (4.0 mL) and added to a degassed (Ar) reaction setup after which $Cu(OAc)_2$ (2.0 eq.) was added. $Sn(C_2H_3)_4$ (3.0 eq.) was then added to the reaction mixture and allowed to stir at rt. for 24 hours with positive O_2 pressure. Once the reaction was deemed complete (TLC), NH_4OAc (0.3 M, 20.0 mL) was added and the reaction mixture allowed to stir for another 10 – 15 min. The product was extracted into EtOAc (3 x 10.0 mL) and purified *via* PLC.

<u>9.7.5.1 4-Methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**)</u>[8]

5-Methoxy-2-(1-phenylallyl)phenol (**732**) (0.09 g, 0.4 mmol), $Cu(OAc)_2$ (0.17 g, 0.87 mmol, 2.4 eq.), $Sn(C_2H_3)_4$ (**733**) (0.2 mL, 1 mmol, 3.0 eq.).



Yielded 4-methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**) as a colourless oil (0.01 g, 12%); R_f : 0.63 (H:EtOAc 90:10); ^{1}H NMR (600 MHz, $CDCl_3$, plate 13a): δ 7.30 – 7.26 (2H, m, Ar-H), 7.20 – 7.17 (3H, m, Ar-H), 7.05 (1H, d, *J* = 8.5 Hz, H-6), 6.61 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.54 (1H, d, *J* = 2.5 Hz, H-3), 6.50 (1H, br. dd, *J* = 13.8, 6.1 Hz, H-1"), 6.27 (1H, ddd, *J* = 17.1, 10.2, 6.7 Hz, H-2'), 5.20 (1H, br. d, *J* = 10.2 Hz, H-3'b), 5.05 (1H, br. d, *J* = 6.7 Hz, H-1'), 4.92 (1H, br. d, *J* = 17.1 Hz, H-3'a), 4.64 (1H, dd, *J* = 13.8, 1.4 Hz, H-2"b), 4.35 (1H, dd, *J* = 6.1, 1.4 Hz, H-2"a), 3.78 (3H, s, -O<u>Me</u>); ^{13}C NMR (151 MHz, $CDCl_3$, plate 13b): δ 159.35 (C-4), 155.01 (C-2), 148.88 (C-1"), 143.20 (4°-C), 140.34 (C-2'), 130.27 (C-6), 128.69 (Ar-C), 128.32 (Ar-C), 126.24 (Ar-C), 125.94 (C-1), 116.29 (C-3'), 108.67 (C-5), 103.96 (C-3), 94.74 (C-2"), 55.56 (-O<u>Me</u>), 47.35 (C-1'); *m/z* (EI) 266 (M^+, 95%).

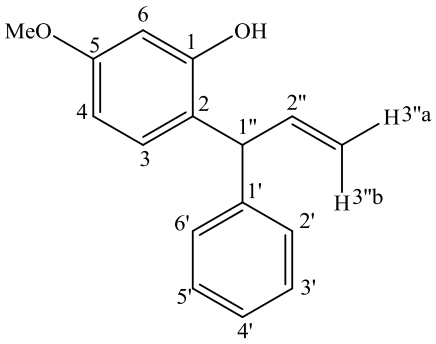
9.8 Claisen rearrangement

9.8.1 Standard Claisen rearrangement

A solution of phenol (1.0 eq.) in *N*,*N*-dimethylaniline (5.0 mL) was heated to *ca*. 200 ºC where refluxing continued for 8 hours. After completion of the reaction, HCl (32% v/v, 40.0 mL) was added to the reaction mixture. The product was extracted into Et_2O (3 x 30.0 mL) and the organic phase washed with H_2O (3 x 30.0 mL). The solvent was removed under reduced pressure and the product purified *via* PLC.

9.8.1.1 5-Methoxy-2-(1-phenylallyl)phenol (**732**)[8]

1-Cinnamyloxy-3-methoxybenzene (**731**) (0.33 g, 1.4 mmol, 1.0 eq.).



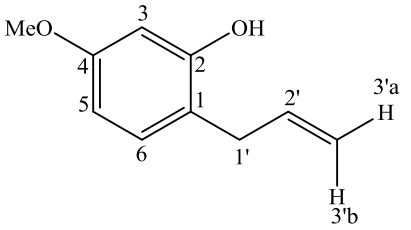
Yielded 5-methoxy-2-(1-phenylallyl)phenol (**732**) as a yellow oil (0.09 g, 30%); R_f : 0.14 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 14a): δ 7.35 – 7.32 (2H, dd, H-3' and H-5'), 7.26 – 7.22 (3H, m, Ar-H), 6.95 (1H, d, *J* = 8.5 Hz, H-3), 6.48 (1H, dd, *J* = 8.5, 2.6 Hz, H-4), 6.42 (1H, d, *J* = 2.6 Hz, H-6), 6.33 (1H, ddd, *J* = 17.3, 10.2, 6.5 Hz, H-2"), 5.30 (1H, ddd, *J* = 10.2, 1.5, 1.5 Hz, H-3"b), 5.02 (1H, ddd, *J* = 17.3, 1.5, 1.5 Hz, H-3"a), 4.88 (1H, br. d, *J* = 6.5 Hz, H-1"), 3.78 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 14b): δ 159.80 (C-5), 154.62 (C-1), 139.79 (C-2"), 130.39 (C-3), 128.80 (Ar-C), 126.92 (Ar-C), 126.37 (Ar-C), 117.03 (C-3"), 106.24 (C-4), 102.57 (C-6), 99.72 (C-1'/2), 91.74 (C-1'/2), 55.44 (-OMe), 48.99 (C-1"); *m/z* (EI) 241 ($[M+H]^+$, 18%).

9.8.2 Microwave assisted Claisen rearrangement

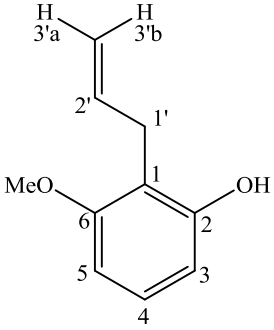
1-Allyloxybenzene was irradiated at 200 °C for 3 sessions of 15 min. each (neat), cooling the sample between sessions. The product was purified *via* PLC.

9.8.2.1 1-Allyl-2-hydroxy-4-methoxybenzene (**552**) and 1-allyl-2-hydroxy-6-methoxybenzene (**577**)[7]

1-Allyloxy-3-methoxybenzene (**575**) (0.50 g, 3.1 mmol).



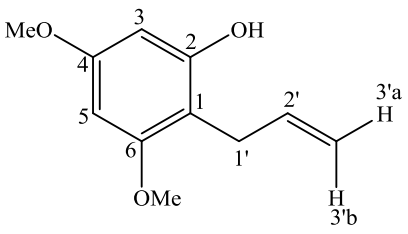
Yielded 1-allyl-2-hydroxy-4-methoxybenzene (**552**) as a light yellow oil (0.12 g, 44%); R_f: 0.54 (H:EtOAc; 9:1). ^{1}H NMR (600 MHz, $CDCl_3$, plate 15a): δ 7.01 (1H, d, *J* = 8.3 Hz, H-6), 6.47 (1H, dd, *J* = 8.3, 2.5 Hz, H-5), 6.43 (1H, d, *J* = 2.5 Hz, H-3), 6.01 (1H, ddt, *J* = 16.9, 10.4, 6.4 Hz, H-2'), 5.23 (1H, s, -O<u>H</u>), 5.17 – 5.13 (1H, m, H-3'a and H-3'b), 3.76 (3H, s, -O<u>Me</u>), 3.36 (2H, br. d, *J* = 6.4 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$, plate 15b): δ 159.65 (C-4), 155.13 (C-2), 136.93 (C-2'), 130.98 (C-6), 117.53 (C-1), 116.36 (C-3'), 106.41 (C-5), 102.12 (C-3), 55.44 (-O<u>Me</u>), 34.64 (C-1'); *m/z* (EI) 164 (M^+, 100%).



Yielded 1-allyl-2-hydoxy-6-methoxybenzene (**577**) as a light yellow oil (0.17 g; 45%); R_f : 0.60 (H:EtOAc; 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 16a): δ 7.08 (1H, dd, *J* = 8.6, 8.1 Hz, H-4), 6.51 – 6.50 (2H, m, H-3 and H-5), 5.99 (1H, ddt, *J* = 17.2, 10.1, 6.3 Hz, H-2'), 5.15 (1H, s, -O<u>H</u>), 5.13 – 5.07 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -O<u>Me</u>), 3.48 (2H, ddd, *J* = 6.3, 1.6, 1.6 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$, plate 16b): δ 158.35 (C-6), 155.28 (C-2), 136.45 (C-2'), 127.66 (C-4), 115.30 (C-3'), 113.73 (C-1), 108.93 (C-3/5), 103.44 (C-3/5), 55.94 (-O<u>Me</u>), 27.47(C-1'); *m/z* (EI) 164 (M^+, 100%).

9.8.2.2 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**553**)[13]

1-Allyloxy-3,5-dimethoxybenzene (**576**) (0.11 g, 0.57 mmol).



Yielded 1-allyl-2-hydroxy-4,6-dimethoxybenzene (**553**) as a red-brown amorphous solid (0.1 g, 88%); R_f : 0.31 (H:EtOAc; 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 17a): δ 6.11 (1H, d, *J* = 2.4 Hz, H-3/5), 6.08 (1H, d, *J* = 2.4 Hz, H-3/5), 5.96 (1H, ddt, *J* = 17.3, 10.9, 5.9 Hz, H-2'), 5.25 (1H, s, -O<u>H</u>), 5.13 – 5.07 (2H, m, H-3'a and H-3'b), 3.78 (3H, s, -O<u>Me</u>), 3.76 (3H, s, -O<u>Me</u>), 3.39 (2H, ddd, *J* = 5.9, 1.7, 1.7 Hz, H-1'); ^{13}C NMR (151 MHz, $CDCl_3$, plate 17b): δ 159.90 (4°-C), 158.69 (4°-C), 155.94 (4°-C), 136.89 (C-2'), 115.41 (C-3'), 105.82 (C-1),

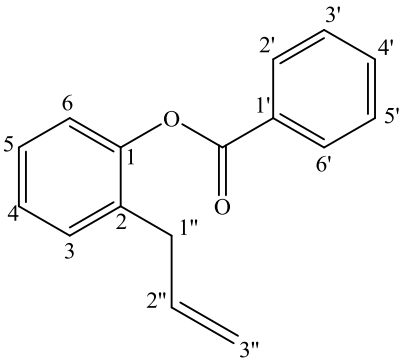
93.88 (C-3/5), 91.67 (C-3/5), 55.93 (-OMe), 55.34 (-OMe), 27.08 (C-1'); *m/z* (EI) 194 (M^+, 100%).

9.9 Benzoate synthesis in aqueous medium

1-Allyl-2-hydroxybenzene (1.0 eq.) was dissolved in aq. NaOH (2.0 M, 40.0 mL). Benzoyl chloride (2.0 eq.) was added and the exothermic reaction mixture allowed to stir until heat generation had ceased and the reaction mixture returned to rt. After completion of the reaction the product was extracted into EtOAc (3 x 60.0 mL) and the solvent removed *in vacuo*.

9.9.1 2-Allylphenyl benzoate (**582**)[8]

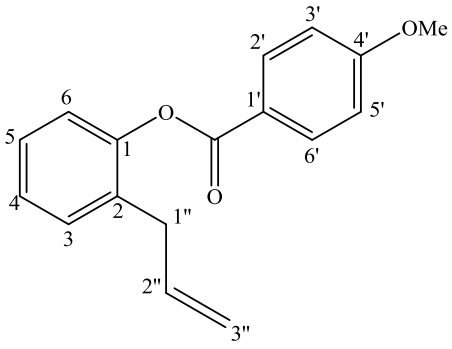
1-Allyl-2-hydroxybenzene (**551**) (2.0 mL, 15 mmol), benzoyl chloride (**578**) (3.5 mL, 30 mmol, 2.0 eq.)



Yielded 2-allylphenyl benzoate (**582**) as a light yellow oil (2.41 g, 68%); R_f : 0.61 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 18a): δ 8.27 – 8.24 (2H, m, H-2' and H-6'), 7.69 – 7.65 (1H, m, H-4'), 7.56 – 7.53 (2H, m, H-3' and H-5'), 7.35 – 7.31 (2H, m, Ar-H), 7.28 – 7.25 (1H, m, Ar-H), 7.22 – 7.20 (1H, m, Ar-H), 5.96 (1H, ddt, *J* = 16.8, 10.1, 6.6 Hz, H-2"), 5.08 – 5.03 (2H, m, H-3"), 3.40 (2H, br. d, *J* = 6.6 Hz, H-1"); ^{13}C NMR (151 MHz, $CDCl_3$, plate 18b): δ 165.08 (C=O), 149.22 (C-1), 135.91 (C-2"), 133.70 (C-4'), 132.21 (C-2), 130.51 (Ar-C), 130.26 (C-2' and C-6'), 129.56 (C-1'), 128.72 (C-3' and C-5'), 127.59 (Ar-C), 126.33 (Ar-C), 122.58 (Ar-C), 116.43 (C-3"), 34.79 (C-1"); *m/z* (EI) 238 (M^+, 9%).

9.9.2 2-Allylphenyl 4-methoxybenzoate (**583**)

1-Allyl-2-hydroxybenzene (**551**) (0.5 mL, 4 mmol), 4-methoxybenzoyl chloride (**579**) (1.3 mL, 9.6 mmol, 2.6 eq.)



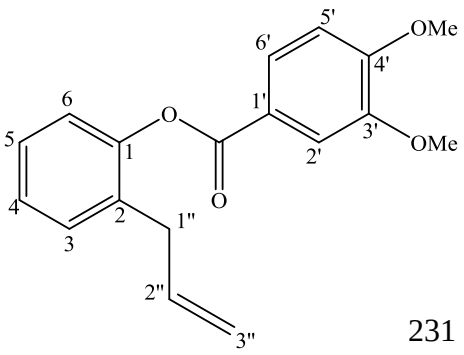
Yielded 2-allylphenyl 4-methoxybenzoate (**583**) as a *colourless oil* (0.74 g, 74%): R_f : 0.34 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 19a): δ 8.19 (2H, d, *J* = 9.3 Hz, H-2' and H-6'), 7.32 – 7.29 (2H, m, Ar-H), 7.25 – 7.22 (1H, m, Ar-H), 7.20 – 7.18 (1H, m, Ar-H), 7.02 – 7.00 (2H, d, *J* = 9.3 Hz, H-3' and H-5'), 5.95 (1H, ddt, *J* = 16.8, 10.2, 6.6 Hz, H-2"), 5.07 – 5.02 (2H, m, H-3"), 3.90 (3H, s, -OMe), 3.38 (2H, br. d, *J* = 6.6 Hz, H-1"); ^{13}C NMR (151 MHz, $CDCl_3$, plate 19b): δ 164.80 (C=O), 164.00 (C-4'), 149.32 (C-1), 136.00 (C-2"), 132.36 (C-2' and C-6'), 132.29 (C-2), 130.39 (Ar-C), 127.78 (Ar-C), 126.17 (Ar-C), 122.67 (Ar-C), 121.86 (C-1'), 116.29 (C-3"), 113.98 (C-3' and C-5'), 55.59 (-OMe), 34.80 (C-1"); HR-MS (ES) *m/z* 291.1003 $[M + Na]^+$, $C_{17}H_{16}O_3Na^+$ requires 291.0992, found 291.1003.

9.10 Benzoate synthesis in anhydrous medium[15]

1-Allyl-2-hydroxybenzene (1.0 eq.), DMAP (0.2 eq.) and dry pyridine (1.0 eq.) were dissolved in dry DCM (15.0 mL) under Ar atmosphere. Benzoyl chloride (2.0 eq.) was added and the reaction mixture heated to reflux overnight. After completion of the reaction, the product was extracted into EtOAc (3 x 60.0 mL) and the solvent removed in *vacuo*. The product was purified *via* PLC.

9.10.1 2-Allylphenyl 3,4-dimethoxybenzoate (**584**)

1-Allyl-2-hydroxybenzene (**551**) (0.5 mL, 3.8 mmol), DMAP (0.09 g, 0.7 mmol, 0.2 eq.), pyridine (0.2 mL, 2 mmol, 0.7 eq.), 3,4-dimethoxybenzoyl chloride (**580**) (0.92 g, 4.6 mmol, 1.2 eq.)

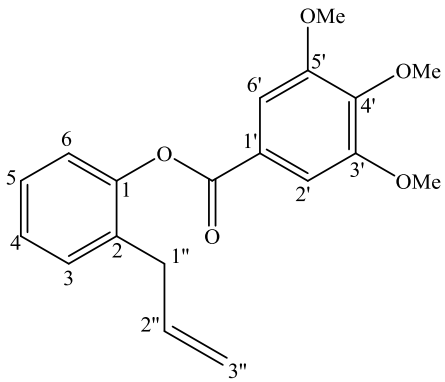


Yielded 2-allylphenyl 3,4-dimethoxybenzoate (**584**) as *white needles* (1.03 g, 93%): R_f : 0.20 (H:EtOAc 9:1); Mp. 92.0 – 93.2 ºC; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 20a): δ 7.02 (1H, dd, *J* = 8.4, 2.0 Hz, H-6'), 6.85 (1H, d, *J* = 2.0 Hz, H-2'), 6.51 – 6.48 (2H, m, Ar-H),

6.43 – 6.40 (1H, m, Ar-H), 6.40 – 6.38 (1H, m, Ar-H), 6.29 (1H, d, *J* = 8.4 Hz, H-5'), 5.11 (1H, ddt, *J* = 16.7, 10.1, 6.6 Hz, H-2''), 4.22 – 4.16 (2H, m, H-3''), 3.10 (3H, s, -OMe), 3.07 (3H, s, -OMe), 2.54 (2H, br. d, *J* = 6.6 Hz, H-1''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 20b): δ 165.13 (C=O), 155.10 (C-4'), 150.47 (C-1), 150.19 (C-3'), 137.13 (C-2''), 133.22 (C-2), 131.19 (Ar-C), 128.30 (Ar-C), 126.91 (Ar-C), 125.02 (C-6'), 123.75 (Ar-C), 122.53 (C-1'), 116.48 (C-3''), 113.32 (C-2'), 111.92 (C-5'), 56.34 (-OMe), 56.25 (-OMe), 35.42 (C-1''); HR-MS (ES) *m/z* 321.1107 $[M + Na]^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1107.

9.10.2 2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**)

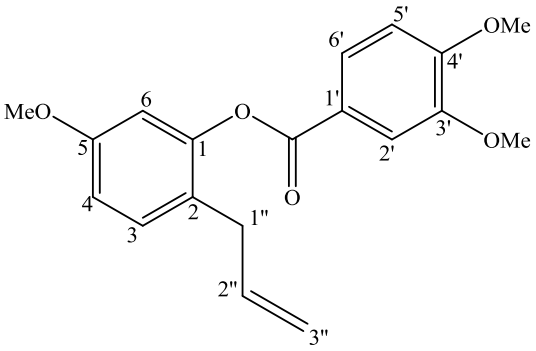
1-Allyl-2-hydroxybenzene (**551**) (0.5 ml, 4 mmol), DMAP (0.06 g, 0.5 mmol, 0.1 eq.), pyridine (0.2 mL, 2 mmol, 0.7 eq.), 3,4,5-trimethoxybenzoyl chloride (**581**) (1.08 g, 4.70 mmol, 1.3 eq.)



Yielded 2-allylphenyl 3,4,5-trimethoxybenzoate (**585**) as *white needles* (1.11 g, 93%): R_f : 0.21 (H:EtOAc 9:1); Mp. 61.9 – 63.2 ºC; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 21a): δ 7.50 (2H, s, H-2' and H-6'), 7.37 – 7.33 (2H, m, Ar-H), 7.29 – 7.26 (1H, m, Ar-H), 7.25 – 7.23 (1H, m, Ar-H), 5.96 (1H, ddt, *J* = 16.7, 10.1, 6.6 Hz, H-2''), 5.04 (2H, m, H-3''), 3.94 (6H, s, -OMe), 3.86 (3H, s, -OMe), 3.39 (2H, br. d, *J* = 6.6 Hz, H-1''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 21b): δ 165.01 (C=O), 154.43 (C-3' and C-5'), 150.42 (C-1), 144.10 (C-4'), 137.13 (C-2''), 133.16 (C-2), 131.29 (Ar-C), 128.38 (Ar-C), 127.07 (Ar-C), 125.32 (C-1'), 123.66 (Ar-C), 116.49 (C-3''), 108.26 (C-2' and C-6'), 60.80 (-OMe), 56.69 (-OMe), 35.41 (C-1''); HR-MS (ES) *m/z* 351.1200 $[M + Na]^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1200.

9.10.3 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**)

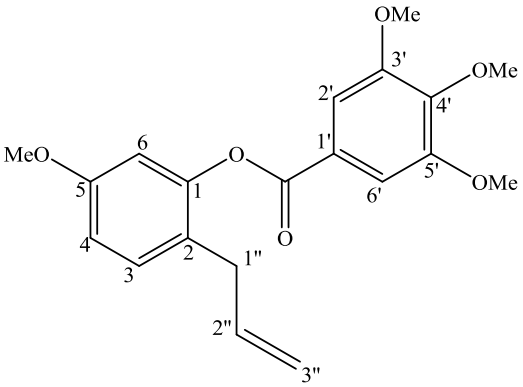
1-Allyl-2-hydroxy-4-methoxybenzene (**552**) (0.44 g, 2.7 mmol), DMAP (0.10 g, 0.80 mmol, 0.3 eq.), pyridine (0.2 mL, 2 mmol, 0.9 eq.), 3,4-dimethoxybenzoyl chloride (**580**) (0.76 g, 3.8 mmol, 1.4 eq.)



Yielded 2-allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**) as *white crystals* (0.66 g, 75%): R_f : 0.14 (H:EtOAc 9:1). Mp. 96.3 – 97.2 ºC. ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 22a); δ 7.83 (1H, dd, *J* = 8.5, 2.0 Hz, H-6'), 7.66 (1H, d, *J* = 2.0 Hz, H-2'), 7.21 (1H, d, *J* = 9.1 Hz, H-3), 7.11 (1H, d, *J* = 8.5 Hz, H-5'), 6.85 – 6.82 (2H, m, H-4 and H-6), 5.91 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, H-2"), 5.01 – 4.95 (2H, m, H-3"), 3.93 (3H, s, 4'-O<u>Me</u>), 3.90 (3H, s, 3'-O<u>Me</u>), 3.80 (3H, s, 5-O<u>Me</u>), 3.28 (2H, br. d, *J* = 6.6 Hz, H-1"); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 22b): δ 164.97 (<u>C</u>=O), 159.97 (C-5), 155.03 (C-4'), 151.01 (C-1), 150.11 (C-3'), 137.53 (C-2"), 131.47 (C-3), 124.97 (C-2/6'), 124.89 (C-2/6'), 122.46 (C-1'), 116.00 (C-3"), 113.25 (C-2'), 112.61 (C-4/6), 111.85 (C-5'), 109.44 (C-4/6), 56.27 (-O<u>Me</u>), 56.18 (-O<u>Me</u>) 55.83 (-O<u>Me</u>), 34.73 (C-1"); HR-MS (ES) *m/z* 351.1206 $[M + Na]^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1206.

9.10.4 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**)

1-Allyl-2-hydroxy-4-methoxybenzene (**552**) (0.70 g, 1.8 mmol), DMAP (0.25 g, 2.1 mmol, 1.2 eq.), pyridine (0.4 mL, 5 mmol, 2.8 eq.), 3,4,5-trimethoxybenzoyl chloride (**581**) (1.56 g, 6.76 mmol, 3.8 eq.)

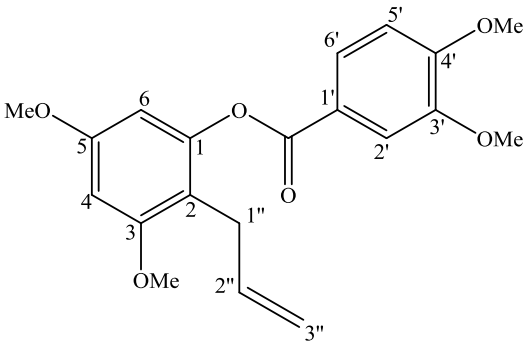


Yielded 2-allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**) as a *white solid* (1.48 g, 98%): R_f : 0.31 (H:EtOAc 9:1); Mp. 93.5 – 94.2 ºC; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 23a): δ 7.47 (2H, s, H-2' and H-6'), 7.22 (1H, d, *J* = 8.9 Hz, H-3), 6.86 – 6.83 (2H, m, H-4 and H-6) 5.91 (1H, ddt, *J* = 16.7, 10.1, 6.5 Hz, H-2"), 5.03 – 4.97 (2H, m, H-3"), 3.92 (6H, s, -O<u>Me</u>), 3.85 (3H, s, -O<u>Me</u>), 3.80 (3H, s, -O<u>Me</u>), 3.28 (2H, br. d, *J* = 6.5 Hz, H-1"); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate

23b): δ 164.90 (C=O), 160.08 (C-5), 154.39 (C-3' and C-5'), 151.00 (C-1), 144.09 (C-4'), 137.57 (C-2"), 131.62 (C-3), 125.29 (C-2/1'), 124.86 (C-2/1'), 116.10 (C-3"), 112.78 (C-4/6), 109.42 (C-4/6), 108.25 (C-2' and C-6'), 60.83 (-OMe), 56.69 (-OMe), 55.91 (-OMe), 34.79 (C-1"); HR-MS (ES) *m/z* 381.1322 $[M + Na]^+$, $C_{20}H_{22}O_6Na^+$ requires 381.1309, found 381.1322.

9.10.5 2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**)

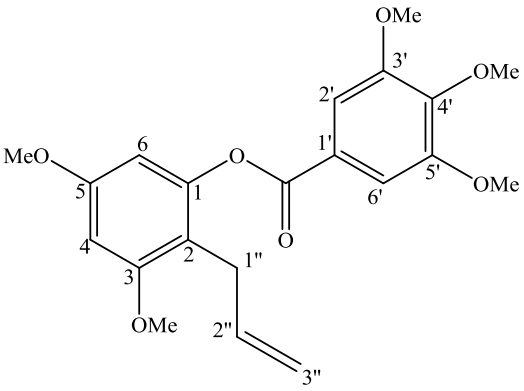
1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**553**) (0.50 g, 1.4 mmol), DMAP (0.09 g, 0.7 mmol, 0.5 eq.) and dry pyridine (0.2 mL, 2 mmol, 1.4 eq.), 3,4-dimethoxybenzoyl chloride (**580**) (0.67 g, 3.3 mmol, 2.4 eq.)



Yielded 2-allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**) as *light yellow crystals* (0.91 g, 89%): R_f: 0.11 (H:EtOAc 9:1); Mp. 109.2 – 110.2 ºC; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 24a): δ 7.81 (1H, dd, *J* = 8.4, 2.0 Hz, H-6'), 7.64 (1H, d, *J* = 2.0 Hz, H-2'), 7.12 (1H, d, *J* = 8.4 Hz, H-5'), 6.50 (1H, d, *J* = 2.4 Hz, H-4/6), 6.44 (1H, d, *J* = 2.4 Hz, H-4/6), 5.83 (1H, ddt, *J* = 16.4, 10.0, 6.3 Hz, H-2"), 4.90 – 4.83 (2H, m, H-3"), 3.93 (3H, s, -OMe), 3.90 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.25 (2H, br. d, *J* = 6.3 Hz, H-1"); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 24b): δ 164.98 (C=O), 160.31 (4º-C), 159.83 (4º-C), 155.06 (4º-C), 151.70 (4º-C), 150.18 (4º-C), 137.27 (C-2"), 124.96 (C-6'), 122.62 (4º-C), 114.91 (C-3"), 113.90 (4º-C), 113.27 (C-2'), 111.92 (C-5'), 100.93 (C-4/6), 97.03 (C-4/6), 56.41 – 55.78 (-OMe), 28.60 (C-1"); HR-MS (ES) *m/z* 381.1310 $[M + Na]^+$, $C_{20}H_{22}O_6Na^+$ requires 381.1314, found 381.1310.

9.10.6 2-Allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**589**)

1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**553**) (0.37 g, 1.9 mmol), DMAP (0.07 g, 0.6 mmol, 0.3 eq.), pyridine (0.2 mL, 2 mmol, 1.3 eq.), 3,4,5-trimethoxybenzoyl chloride (**581**) (0.89 g, 3.9 mmol, 2.1 eq.).



Yielded 2-allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**589**) as a *white solid* (0.66 g, 97%): R_f : 0.25 (H:EtOAc 9:1); Mp. 87.2 – 88.9 ºC; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 25a): δ 7.46 (2H, s, H-2' and H-6'), 6.51 (1H, d, *J* = 2.4 Hz, H-4/6), 6.47 (1H, d, *J* = 2.4 Hz, H-4/6), 5.85 (1H, ddt, *J* = 16.3, 10.1, 6.2 Hz, H-2"), 4.93 – 4.87 (2H, m, H-3"), 3.91 (6H, s, -OMe), 3.86 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.27 (2H, br. d, *J* = 6.2 Hz, H-1"); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 25b): δ 164.82 (C=O), 160.31 (4º-C), 159.81 (4º-C), 154.33 (C-3' and C-5'), 151.60 (4º-C), 143.99 (C-4'), 137.24 (C-2"), 125.32 (4º-C), 114.97 (C-3"), 113.75 (4º-C), 108.14 (C-2' and C-6'), 100.79 (C-4/6), 97.07 (C-4/6), 60.80 (-OMe), 56.63 (-OMe), 56.30 (-OMe), 55.86 (-OMe), 28.56 (C-1"); HR-MS (ES) *m/z* 411.1410 $[M + Na]^+$, $C_{21}H_{24}O_7Na^+$ requires 411.1420, found 411.1410.

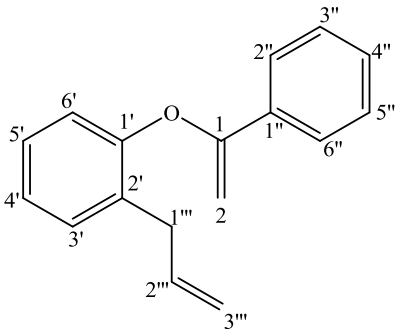
9.11 Vinyl ether synthesis[8]

2-Allylphenyl benzoate (1.0 eq.) in THF (1.0 – 2.0 mL) was cooled to 0 ºC and Tebbe reagent (0.5 M, 2.0 eq.) added. The mixture was allowed to stir at 0 ºC for 30 min. where after it was allowed to reach rt. and stirred for another hour. If the reaction did not run to completion at this stage, the reaction mixture was heated to 90 ºC for an additional 2 hours. The reaction mixture was allowed to cool to rt. and aq. NaOH (2.0 M, 1.0 mL) was added very slowly. Once the exothermic reaction subsided, the reaction mixture was dissolved in Et_2O (200.0 mL) and filtered through a column of activated basic Al_2O_3 (Sigma Aldrich Brockman I activated basic alumina, min. layer thickness: 0.11 mm, column length x width: 150 mm x 30 mm). The solvent was removed *in vacuo* and the crude reaction mixture purified *via* PLC.

9.11.1 2-Allyl-1-(1-phenylvinyloxy)benzene (**594**)[8]

2-Allylphenyl benzoate (**582**) (0.4 g, 2 mmol), Tebbe reagent (4.0 mL, 1.3 mmol, 1.3 eq.).

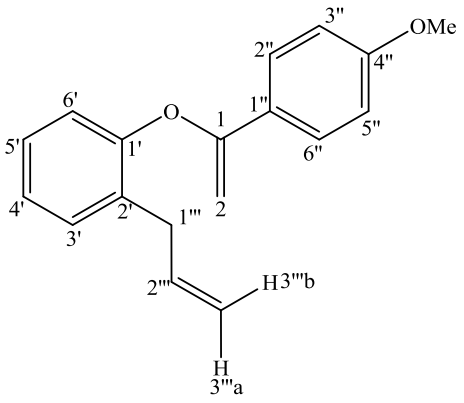
Yielded 2-allyl-1-(1-phenylvinyloxy)benzene (**594**) as a yellow oil (0.31 g, 81%): R_f: 0.81 (H:EtOAc:Et_3N 90:10:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 26a): δ 7.76 – 7.74 (2H, m, Ar-H), 7.42 – 7.37 (3H, m, Ar-H), 7.28 (1H, dd, *J* = 7.6, 1.6 Hz, H-3'), 7.22 (1H, ddd *J* = 8.0, 8.0, 1.6 Hz, H-5'), 7.13 (1H, ddd, *J* = 8.0, 7.6, 1.3 Hz, H-4'), 7.06 (1H, dd, *J* = 8.0, 1.3 Hz, H-6'), 6.00 (1H, ddt, *J* = 16.9, 10.1, 6.7 Hz, H-2'''), 5.11 – 5.06 (2H, m, H-3'''), 4.92 (1H, d, *J* = 2.6 Hz, H-2), 4.16 (1H, d, *J* = 2.6 Hz, H-2), 3.41 (2H, br. d, *J* = 6.7 Hz, H-1'''); ^{13}C NMR (151 MHz, $CDCl_3$, plate 26b): δ 159.75 (C-1), 153.32 (C-1'), 136.74 (C-2'''), 135.38 (C-1''), 132.31 (C-2'), 130.55 (C-3'), 128.96 (Ar-C), 128.49 (Ar-C), 127.68 (C-5'), 125.52 (Ar-C), 124.65 (C-4'), 121.18 (C-6'), 116.12 (C-3'''), 89.20 (C-2), 34.24 (C-1'''); HR-MS (ES) *m/z* 237.1277 $[M+H]^+$, $C_{17}H_{16}O^+$ requires 237.1279, found 237.1277.



9.11.2 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**)[12]

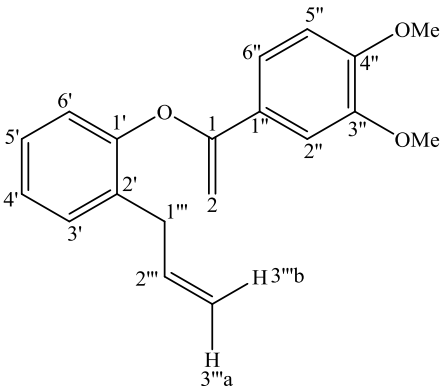
2-Allylphenyl 4-methoxybenzoate (**583**) (0.20 g, 0.77 mmol), Tebbe reagent (3.0 mL, 1.5 mmol, 2.0 eq.).

Yielded 2-allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**) as a *yellow oil* (0.14 g, 71%): R_f: 0.55 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 27a): δ 7.71 (2H, d, *J* = 9.2 Hz, H-2'' and H-6''), 7.31 (1H, dd, *J* = 7.6, 1.4 Hz, H-3'), 7.25 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz, H-5'), 7.14 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz, H-4'), 7.05 (1H, dd, *J* = 7.6, 1.4 Hz, H-6'), 6.97 (2H, d, *J* = 9.2 Hz, H-3'' and H-5''), 6.00 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05 – 5.01 (1H, m, H-3'''a), 4.91 (1H, d, *J* = 2.5 Hz, H-2), 4.03 (1H, d, *J* = 2.5 Hz, H-2), 3.83 (3H, s, -O<u>Me</u>), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1'''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 27b): δ 161.40 (C-4''), 160.42 (4º-C), 154.25 (4º-C), 137.70 (C-2'''), 132.83 (4º-C), 131.42 (C-3'), 128.57 (C-5'), 127.68 (C-2'' and C-6''), 127.29 (C-1''), 125.43 (C-4'), 121.72 (C-6'), 116.29 (C-3'''), 114.63 (C-3'' and C-5''), 88.16 (C-2), 55.72 (-O<u>Me</u>), 34.84 (C-1'''); MS (EI) *m/z* 266 (M^+, 2%).



9.11.3 2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**)

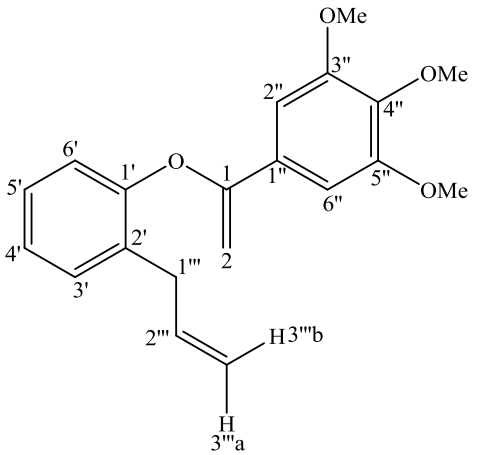
2-Allylphenyl 3,4-dimethoxybenzoate (**584**) (0.21 g, 0.69 mmol), Tebbe reagent (2.0 mL, 1.0 mmol, 1.4 eq.).



Yielded 2-allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**) as a *yellow oil* (0.19 g, 94%): R_f: 0.37 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 28a): δ 7.34 – 7.32 (2H, m, H-2" and H-6"), 7.31 (1H, dd, *J* = 7.4, 1.6 Hz, H-3'), 7.25 (1H, ddd, *J* = 8.0, 7.6, 1.6 Hz, H-5'), 7.14 (1H, ddd, *J* = 7.6, 7.4, 1.3 Hz, H-4'), 7.05 (1H, dd, *J* = 8.0, 1.3 Hz, H-6'), 6.97 (1H, d, *J* = 8.7 Hz, H-5"), 6.01 (1H, ddt, *J* = 17.0, 10.0, 6.7 Hz, H-2"'), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz, H-3"'b), 5.05 – 5.02 (1H, m, H-3"'a), 4.95 (1H, d, *J* = 2.5 Hz, H-2), 4.05 (1H, d, *J* = 2.5 Hz, H-2), 3.84 (6H, s, -OMe), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1"'); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 28b): δ 160.35 (C-1), 154.25 (C-1'), 151.20 (C-3"/4"), 150.11 (C-3"/4"), 137.68 (C-2"'), 132.68 (C-2'), 131.38 (C-3'), 128.77 (C-1"), 128.50 (C-5'), 125.32 (C-4'), 121.58 (C-6'), 119.02 (C-2"/6"), 116.17 (C-3"'), 112.25 (C-5"), 110.02 (C-2"/6"), 88.45 (C-2), 56.08 (-OMe), 34.81 (C-1"'); HR-MS (ES) *m/z* 321.1457 $[M + Na]^+$, $C_{19}H_{20}O_3Na^+$ requires 319.1467, found 319.1457

9.11.4 2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**)

2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**) (0.233 g, 0.708 mmol), Tebbe reagent (2.0 mL, 1.0 mmol, 1.4 eq.).

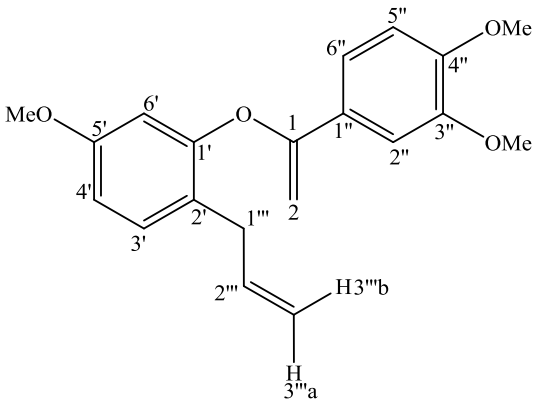


Yielded 2-allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**) as a *yellow oil* (0.20 g, 85%): R_f: 0.29 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 29a): δ 7.31 (1H, dd, *J* = 7.7, 1.8 Hz, H-3'), 7.26 (1H, ddd, *J* = 8.1, 7.7, 1.8 Hz H-5'), 7.15 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz, H-4'), 7.08 (2H, s, H-2" and H-6"), 7.06 (1H, dd, *J* = 8.1, 1.2 Hz, H-6'), 6.02 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-2"'), 5.08 (1H, ddt, *J* = 17.0, 1.8, 1.8 Hz, H-3"'b), 5.05 (1H, ddt, *J* = 10.1, 1.8, 1.8 Hz, H-3"'a), 5.02 (1H, d, *J* = 2.6 Hz, H-2), 4.11 (1H, d, *J* = 2.6 Hz,

H-2), 3.86 (6H, s, -OMe), 3.76 (3H, s, -OMe), 3.41 (1H, br. d, *J* = 6.7 Hz, H-1'''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 29b): δ 160.28 (C-1), 154.29 (4º-C), 154.17 (4º-C), 140.09 (4º-C), 137.69 (C-2'''), 132.71 (4º-C), 131.53 (C-1''), 131.51 (C-3'), 128.58 (C-5'), 125.48 (C-4'), 121.68 (C-6'), 116.21 (C-3'''), 103.87 (C-2'' and C-6''), 89.49 (C-2), 60.62 (-OMe), 56.46 (-OMe), 34.87 (C-1'''); HR-MS (ES) *m/z* 351.1568 $[M + Na]^+$, $C_{20}H_{24}O_4Na^+$ requires 351.1572, found 351.1568.

9.11.5 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**)*

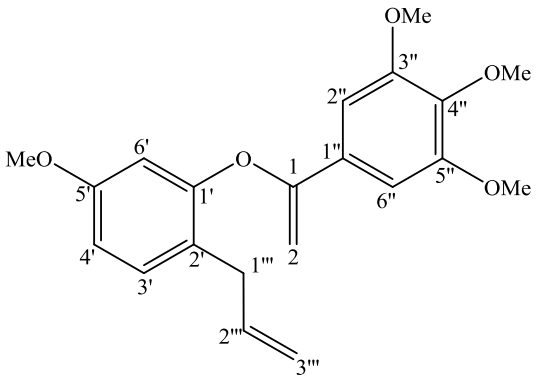
2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**) (0.27 g, 0.81 mmol), Tebbe reagent (2.0 mL, 1.0 mmol, 1.2 eq.).



Yielded 2-allyl-5-methoxyphenyl 1-(3, 4-dimethoxyphenyl)vinyl ether (**602**) as a *yellow oil* (0.23 g, 87%): R_f : 0.21 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 30a): δ 7.33 – 7.31 (2H, m, H-2'' and H-6''), 7.19 (1H, d, *J* = 8.5 Hz, H-3'), 6.96 (1H, d, *J* = 9.0 Hz, H-5''), 6.72 (1H, dd, *J* = 8.5, 2.6 Hz, H-4'), 6.62 (1H, d, *J* = 2.6 Hz, H-6'), 5.98 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H-2'''), 5.07 – 5.03 (1H, m, H-3'''b), 5.03 – 4.99 (1H, m, H-3'''a), 4.97 (1H, d, *J* = 2.4 Hz, H-2), 4.14 (1H, d, *J* = 2.4 Hz, H-2), 3.84 (6H, m, -OMe), 3.75 (3H, s, -OMe), 3.33 (2H, br. d, *J* = 6.6 Hz, H-1'''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 30b): δ 160.44 (4º-C), 160.22 (4º-C), 155.14 (4º-C), 151.39 (4º-C), 150.31 (4º-C), 138.27 (C-2'''), 131.91 (C-3'), 128.91 (4º-C), 124.46 (4º-C), 119.24 (C-2''/6''), 115.89 (C-3'''), 112.49 (C-5''), 110.82 (C-4'), 110.28 (C-2''/6''), 107.40 (C-6'), 89.19 (C-2), 56.28 (-OMe), 55.84 (-OMe), 34.32 (C-1'''); HR-MS (ES) *m/z* 349.1427 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1427.

9.11.6 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**)*

2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**) (0.20 g, 0.56 mmol), Tebbe reagent (3.0 mL, 1.5 mmol, 2.7 eq.).



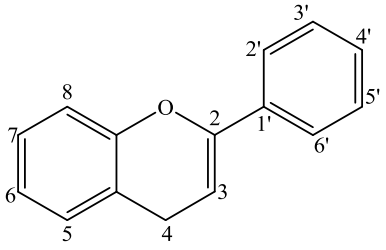
Yielded 2-allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**) as a *yellow oil* (0.15 g, 75%): R_f: 0.22 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 31a): δ 7.20 (1H, d, *J* = 8.5 Hz, H-3'), 7.06 (2H, s, H-2" and H-6"), 6.74 (1H, dd, *J* = 8.5, 2.6 Hz, H-4'), 6.63 (1H, d, *J* = 2.6 Hz, H-6'), 5.99 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H-2'''), 5.07 – 5.00 (2H, m, H-3'''), 5.04 (1H, d, *J* = 2.6 Hz, H-2), 4.18 (1H, d, *J* = 2.6 Hz, H-2), 3.86 (6H, s, -OMe), 3.76 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.32 (2H, br. d, *J* = 6.6 Hz, H-1'''); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 31b): δ 160.42 (4º-C), 160.08 (4º-C), 154.98 (4º-C), 154.39 (C-3" and C-5"), 140.10 (4º-C), 138.22 (C-2'''), 131.96 (C-3'), 131.58 (4º-C), 124.39 (4º-C), 115.85 (C-3'''), 110.95 (C-4'), 107.41 (C-6'), 104.02 (C-2" and C-6"), 90.15 (C-2), 60.68 (-OMe), 56.57 (-OMe), 55.80 (-OMe), 34.30 (C-1'''); HR-MS (ES) *m/z* 379.1322 $[M + Na]^+$, $C_{20}H_{20}O_6Na^+$ requires 379.1314, found 379.1322.

9.12 Flavene synthesis *via* RCM

A solution of vinyl ether (1.0 eq.) and Grubbs II catalyst (5 mol%) in dry DCM (5.0 mL) was heated to reflux and allowed to stir overnight under Ar. After completion of the reaction, the product was directly purified *via* PLC.

9.12.1 Flav-2-ene (**608**)[8]

2-Allyl-1-(1-phenylvinyloxy)benzene (**594**) (0.11 g, 0.46 mmol).

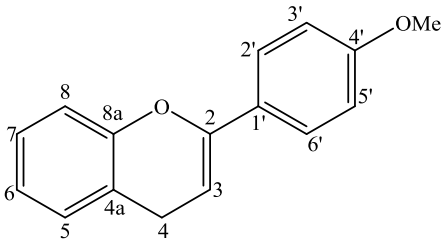


Yielded flav-2-ene (**608**) as a yellow oil (0.09 g, 92%); R_f: 0.66 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 32a): δ 7.74 – 7.72 (2H, m, H-2' and H-6'), 7.42 – 7.39 (2H, m, H-3' and H-5'), 7.36 – 7.33 (1H, m, H-4'), 7.21 – 7.18 (1H, m, H-7), 7.12 (1H, br. d, *J* = 7.5 Hz, H-5), 7.05 (1H, dd, *J* = 8.1, 1.1 Hz, H-8) 7.03 (1H,

ddd, *J* = 8.1, 7.5, 1.1 Hz, H-6), 5.67 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.57 (2H, br. d, *J* = 3.9 Hz, H-4); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 32b): δ 152.82 (4º-C), 149.66 (4º-C), 135.33 (4º-C), 130.04 (C-5), 129.31 (C-3' and C-5'), 129.27 (C-4'), 128.54 (C-7), 125.24 (C-2' and C-6'), 124.40 (C-6), 120.72 (4º-C), 117.36 (C-8), 97.55 (C-3), 24.93 (C-4); *m/z* (EI) 207 ([M-H]$^+$, 100%).

9.12.2 4'-Methoxyflav-2-ene (**613**)

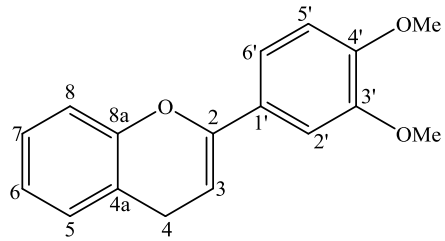
2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**) (0.04 g, 0.2 mmol)



Yielded 4'-methoxyflav-2-ene (**613**) as *white needles* (0.03 g, 87%): R_f : 0.49 (H:EtOAc 9:1); Mp. 102.3 – 105.1 ºC; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 33a): δ 7.66 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.20 – 7.19 (1H, m, H-7), 7.13 – 7.11 (1H, br. d, *J* = 7.2 Hz, H-5), 7.04 – 7.00 (2H, m, H-6 and H-8), 6.96 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 5.54 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.82 (3H, s, -OMe), 3.55 (2H, br. d, *J* = 3.9 Hz, H-4); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 33b): δ 160.91 (C-4'), 152.85 (C-8a), 149.51 (C-2), 129.97 (C-5), 128.42 (C-7), 127.85 (C-1'), 126.58 (C-2' and C-6'), 124.24 (C-6/8), 120.82 (C-4a), 117.27 (C-6/8), 114.57 (C-3' and C-5'), 95.49 (C-3), 55.65 (-OMe), 24.81 (C-4); HR-MS (AP) *m/z* 239.1082 $[M + H]^+$, $C_{16}H_{15}O_2^+$ requires 239.1072, found 239.1082.

9.12.3 3',4'-Dimethoxyflav-2-ene (**614**)[12]

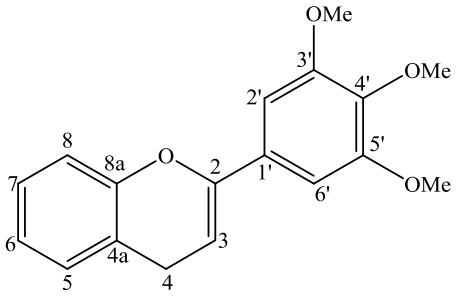
2-Allyl-3-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**) (0.09 g, 0.3 mmol).



Yielded 3',4'-dimethoxyflav-2-ene (**614**) as a *yellow oil* (0.08 g, 96%): R_f : 0.20 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 34a): δ 7.30 – 7.28 (2H, m, H-2' and H-6'), 7.20 – 7.17 (1H, m, H-7), 7.12 (1H, br. d, *J* = 8.0 Hz, H-5), 7.05 – 7.03 (1H, m, H-6), 7.01(1H, dd, *J* = 7.5, 1.2 Hz, H-8), 6.97 (1H, d, *J* = 8.9 Hz, H-5'), 5.57 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.87 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.55 (2H, br. d, *J* = 3.9 Hz, H-4); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 34b): δ 152.93 (C-8a), 150.90 (C-3'/4'), 150.28 (C-3'/4'), 149.65 (C-2), 130.01 (C-5), 128.45 (C-7), 128.26 (C-1'), 124.29 (C-8), 120.88 (C-4a), 118.07 (C-2'/6'), 117.35 (C-6), 112.47 (C-5'), 109.38 (C-2'/6'), 95.85 (C-3), 56.27 (-OMe), 56.20 (-OMe), 24.91 (C-4); *m/z* 268 (M^+, 100%)

9.12.4 3',4',5'-Trimethoxyflav-2-ene (**615**)

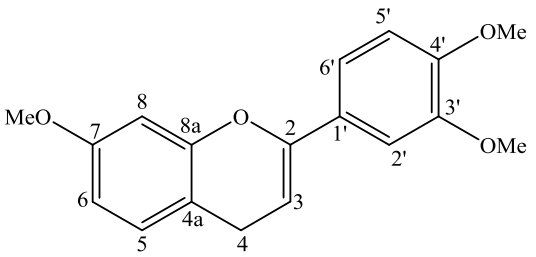
2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**) (0.08 g, 0.3 mmol).



Yielded 3',4',5'-trimethoxyflav-2-ene (**615**) as a *yellow oil* (0.07 g, 96%): R_f : 0.20 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 35a): δ 7.21 – 7.18 (1H, m, H-7), 7.14 – 7.12 (1H, m, H-5), 7.06 – 7.02 (4H, m, H-6, H-8, H-2' and H-6'), 5.66 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.88 (6H, s, -OMe), 3.75 (3H, s, -OMe), 3.57 (2H, br. d, *J* = 3.9 Hz, H-4); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 35b): δ 154.41 (C-3' and C-5'), 152.84 (C-8a), 149.61 (C-2), 139.74 (C-4'), 130.94 (C-1'), 130.01 (C-5), 128.48 (C-7), 124.38 (C-8), 120.75 (C-4a), 117.40 (C-6), 103.12 (C-2' and C-6'), 97.15 (C-3), 60.68 (-OMe), 56.58 (-OMe), 24.92 (C-4); HR-MS (ES) *m/z* 321.1100 $[M + Na]^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1100.

9.12.5 3',4',7-Trimethoxyflav-2-ene (**616**)

2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**) (0.11 g, 0.34 mmol)

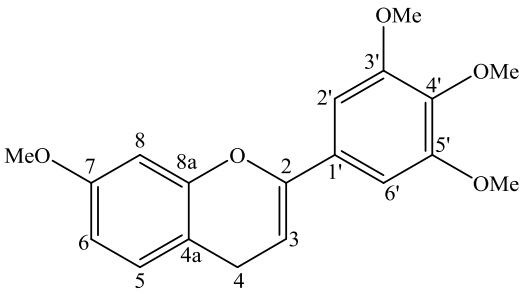


Yielded 3',4',7-trimethoxyflav-2-ene (**616**) as an *orange oil* (0.08 g, 76%): R_f : 0.31 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 36a): δ 7.29 – 7.27 (2H, m, H-2' and H-6'), 7.03 – 7.01 (1H, m, H-5), 6.97 (1H, d, *J* = 8.7 Hz, H-5'), 6.64 – 6.61 (2H, m, H-6 and H-8), 5.57 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.86 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.48 (2H, br. d, *J* = 3.9 Hz, H-4); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 36b): δ 160.37 (C-7), 153.48 (C-8a), 150.85 (C-4'), 150.25 (C-3'), 149.36 (C-2), 130.44 (C-5), 128.24 (C-1'), 118.03 (C-2'/6'), 112.54 (C-4a), 112.40 (C-5'), 110.81 (C-6/8), 109.35 (C-2'/6'), 102.44 (C-6/8), 96.21 (C-3), 56.25 (-OMe), 56.17 (-OMe), 55.77 (-OMe), 24.27 (C-4); HR-MS (ES) *m/z* 321.1109 $[M + Na]^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1109.

9.12.6 3',4',5',7-Tetramethoxyflav-2-ene (**617**)

2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**) (0.09 g, 0.3 mmol)

Yielded 3',4',5',7-tetramethoxyflav-2-ene (**617**) as an *orange amorphous solid* (0.03 g, 41%): R_f : 0.30 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 37a): δ 7.03 (1H, d, *J* = 8.3 Hz, H-5), 7.02 (2H, s, H-2' and H-6'), 6.65 (1H, d, *J* = 2.5 Hz, H-8), 6.63 (1H, dd, *J* = 8.3, 2.5 Hz, H-6), 5.65 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.88 (3H, s, -OMe), 3.78 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.48 (2H, br. d, *J* = 3.9 Hz, H-4); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 37b): δ 160.27 (C-4'/7), 154.28 (C-3' and C-5'), 153.29 (C-8a), 149.22 (C-2), 139.62 (C-4'/7), 130.84 (C-1'), 130.34 (C-5), 112.32 (C-4a), 110.75 (C-6), 103.01 (C-2' and C-6'), 102.42 (C-8), 97.42 (C-3), 60.59 (-OMe), 56.48 (-OMe), 55.68 (-OMe), 24.20 (C-4); HR-MS (ES) *m/z* 351.1216 $[M + Na]^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1216.



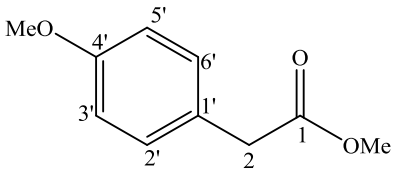
9.13 Ozonolysis of allyl benzenes with oxidative work-up[16]

A mixture of allyl benzene (1.0 eq.) in dry (basic alumina) MeOH (20.0 mL) was cooled to -78 ºC under Ar. A stream of O_3 with a flow rate of 10 – 200 g/Nm^3 and 0.5 MPa inlet pressure was bubbled through the reaction mixture (resulting in a blue colour) where after the mixture was purged with O_2 for 5 minutes. The reaction mixture was allowed to warm to rt. over 2 hours where after the solvent was removed *in vacuo*. The crude reaction material was then dissolved in dry DCM (30.0 mL) and cooled to 0 ºC with subsequent addition of Et_3N (2.0 eq.) and Ac_2O (8.0 eq.). The reaction mixture was stirred at 0 ºC for 30 min. and then for 21 hours at rt. MeOH (2.5 mL) was added and the reaction mixture stirred for 10 – 20 min. with subsequent addition of Et_2O (40.0 mL). The product was extracted into Et_2O (3 x 40.0 mL) and washed with saturated aq. $NaHCO_3$ solution (1 x 40.0 mL) and H_2O (1 x 40.0 mL). The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The product was purified *via* PLC.

9.13.1 Methyl 4-methoxyphenyl acetate (**670**)[17]

1-Allyl-4-methoxybenzene (0.58 g, 3.9 mmol), O_3 (59.9 – 89.5 g/Nm^3, 12 min.), Ac_2O (2.6 mL, 28 mmol, 7.0 eq.), Et_3N (1.0 mL, 7.2 mmol, 1.8 eq).

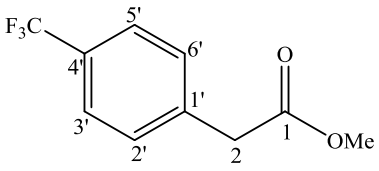
Yielded methyl 4-methoxyphenyl acetate (**670**) as an orange oil (0.70 g, 99%): R_f : 0.49 (H:A 7:3); ^{1}H NMR (300 MHz, $CDCl_3$, plate 38a): δ 7.20 (2H, d, *J* = 8.8 Hz, H-2' and H-6'),



6.86 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 3.79 (3H, s, -OMe), 3.68 (3H, s, -COOMe), 3.57 (2H, s, H-2); *m/z* (EI) 180 (M^+, 23%).

9.13.2 Methyl 4-trifluoromethylphenyl acetate (**671**)[18]

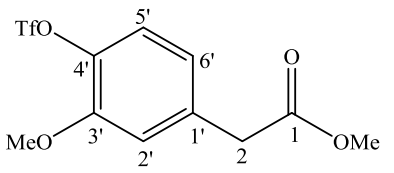
1-Allyl-4-trifluoromethylbenzene () (0.63 g, 2.9 mmol), O_3 (89.3 – 89.8 g/Nm^3, 10 min.), Ac_2O (2.0 mL, 21 mmol, 7.3 eq.), Et_3N (0.8 mL, 6 mmol, 2.0 eq).



Yielded methyl 4-trifluoromethylphenyl acetate (**671**) as an orange oil (0.70 g, 96%): R_f : 0.66 (H:A 6:4); ^{1}H NMR (300 MHz, $CDCl_3$, plate 39a): δ 7.59 (2H, d, *J* = 8.2 Hz, H-3' and H-5'), 7.40 (2H, d, *J* = 8.2 Hz, H-2' and H-6'), 3.71 (3H, s, -COOMe), 3.69 (2H, s, H-2); *m/z* (EI) 217 ($[M-H]^+$, 38%).

9.13.3 Methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate (**672**)[19]

1-Allyl-3-methoxy-4-trifluoromethanesulfonyloxybenzene (**668**) (0.64 g, 2.1 mmol), O_3 (85.6 – 91.8 g/Nm^3, 7 min.), Ac_2O (1.3 mL, 14 mmol, 6.4 eq.), Et_3N (0.5 mL, 4 mmol, 1.7 eq).

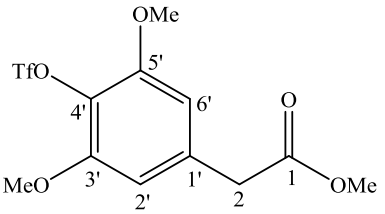


Yielded methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate (**672**) as a yellow oil (0.57 g, 80%): R_f : 0.14 (H:EtOAc:Et_3N 9:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 40a): δ 7.16 (1H, d, *J* = 8.3 Hz, H-5'), 6.98 (1H, d, *J* = 2.0 Hz, H-2'), 6.88 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 3.91 (3H, s, -OMe), 3.72 (3H, s, -COOMe), 3.63 (2H, s, H-2); ^{13}C NMR (151 MHz, $CDCl_3$, plate 40b): δ 171.38 (C-1), 151.41 (C-3'), 137.99 (C-4'), 135.57 (C-1'), 122.52 (C-5'), 121.83 (C-6'), 117.78 (q, *J* = 319.9 Hz, -$OSO_2\underline{C}F_3$), 114.30 (C-2'), 56.33 (-OMe), 52.43 (-COOMe), 41.01 (C-2); *m/z* (EI) 328 (M^+, 30%).

9.13.4 Methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate (**673**)

1-Allyl-3,5-dimethoxy-4-trifluoromethanesulfonyloxybenzene (**669**) (0.51 g, 1.6 mmol), O_3 (60.1 – 72.9 g/Nm^3, 8 min.), Ac_2O (1.2 mL, 13 mmol, 8.1 eq.), Et_3N (0.5 mL, 4 mmol, 2.3 eq).

Yielded methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate (**673**) as a *yellow oil* (0.49 g, 88%): R_f : 0.11 (H:EtOAc:Et_3N; 9:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 41a): δ 6.55 (2H, s, H-2' and H-6'), 3.88 (6H, s, -OMe), 3.72 (3H, s, -COOMe), 3.59 (2H, s, H-2); ^{13}C NMR (151 MHz, $CDCl_3$, plate 41b): δ 171.37 (C-1), 152.43 (C-3' and C-5'), 134.94 (C-1'), 127.19 (C-4'), 118.93 (q, J = 320.2 Hz, -OSO_2CF_3), 106.10 (C-2' and C-6'), 56.43 (-OMe), 52.46 (-COOMe), 41.65 (C-2); *m/z* (EI) 358 (M^+, 15%); HR-MS (ES) *m/z* 381.0233 $[M + Na]^+$, $C_{12}H_{13}O_7F_3NaS^+$ requires 381.0232, found 381.0233.



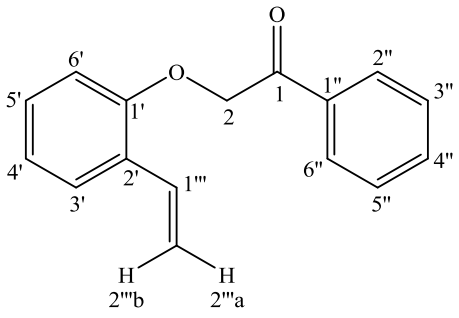
9.14 Vinyl benzene synthesis[20]

A suspension of methyltriphenylphosphonium bromide (MTPPB) (1.2 eq.) and *t*-BuOK (1.2 eq.) in anhydrous THF (5.0 mL) under argon was cooled to 0 °C and stirred for 15 minutes. A mixture of benzaldehyde (1.0 eq.) and *t*-BuOK (1.2 eq.) in THF (5.0 mL) was added and the resulting mixture stirred at 0 °C for 2 hours. The reaction mixture was then heated to reflux and a solution of bromoacetophenone (1.2 eq.) in anhydrous THF (2.0 mL) added dropwise and stirred for 1 hour. The reaction mixture was cooled to 0 °C again and transferred to a solution of MTPPB (1.2 eq.) and *t*-BuOK (1.2 eq.) in anhydrous THF (5.0 mL) already stirred at 0 °C for 15 minutes. The resulting mixture was left to continue stirring at 0 °C for 2 hours after which it was quenched with aq. NH_4Cl (60.0 mL). The product was extracted into EtOAc (3 x 60.0 mL) dried over Na_2SO_4, the solvent removed in *vacuo* and the product purified *via* PLC.

9.14.1 1-Phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**)[19]

MTPPB (0.74 g, 2.1 mmol, 1.3 eq.), *t*-BuOK (0.24 g, 2.1 mmol, 1.3 eq.), 2-hydroxybenzaldehyde (**683**) (0.2 mL, 2 mmol), *t*-BuOK (0.23 g, 2.1 mmol, 1.3 eq.), 2-bromoacetophenone (**685**) (0.41 g, 2.1 mmol, 1.3 eq.), MTPPB (0.75 g, 2.1 mmol, 1.3 eq.), *t*-BuOK (0.22 g, 2.0 mmol, 1.2 eq.).

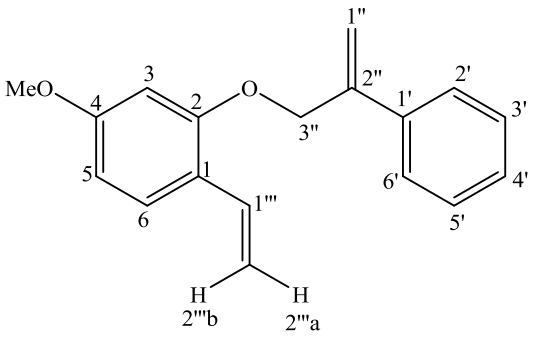
Yielded 1-phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**) as a yellow oil (0.13 g, 33%): R_f : 0.51 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 42a): δ 8.10 – 8.08 (2H, m, H-2" and H-6"), 7.70 – 7.67 (1H, m, H-4"), 7.59 – 7.55 (2H, m, H-3" and H-5"), 7.54 (1H, dd, J =



7.7, 1.7 Hz, H-3'), 7.23 – 7.20 (1H, m, H-5'), 7.16 (1H, dd, *J* = 17.8, 11.3 Hz, H-1'''), 7.00 (1H, dd, *J* = 8.3, 1.0 Hz, H-6'), 6.97 – 6.93 (1H, m, H-4'), 5.88 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.57 (2H, s, H-2), 5.25 (1H, dd, *J* = 11.3, 1.6 Hz, H-2'''a); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 42b): δ 194.76 (C-1), 156.45 (C-1'), 135.84 (C-1''), 134.48 (C-4''), 132.65 (C-1'''), 129.70 (C-5'), 129.66 (C-3'' and C-5''), 128.81 (C-2'' and C-6''), 127.56 (C-2'), 127.36 (C-3'), 121.95 (C-4'), 114.82 (C-2'''), 113.31 (C-6'), 71.49 (C-2); *m/z* (EI) 238 (M^+, 22%).

9.14.2 4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**689**)

MTPPB (1.14 g, 3.19 mmol, 1.2 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 1.2 eq.), 2-hydroxy-4-methoxybenzaldehyde (**687**) (0.41 g, 2.7 mmol, 0.8 eq.), *t*-BuOK (0.38 g, 3.4 mmol, 1.3 eq.), 2-bromoacetophenone (**685**) (0.86 g, 4.3 mmol, 1.6 eq.), MTPPB (2.29 g, 6.41 mmol, 2.4 eq.), *t*-BuOK (0.72 g, 6.4 mmol, 2.4 eq.).

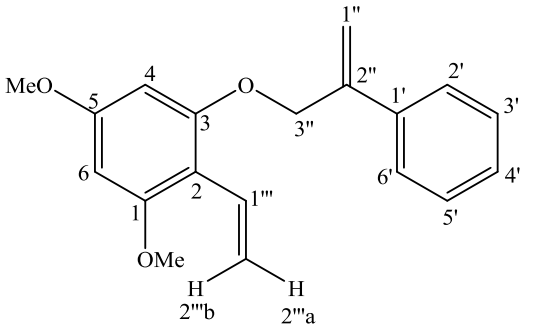


Yielded 4-methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**689**) as a *yellow oil* (0.44 g, 63%): R_f : 0.62 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 43a): δ 7.60 – 7.57 (2H, m, H-2' and H-6'), 7.45 (1H, d, *J* = 8.4 Hz, H-6), 7.40 – 7.37 (2H, m, H-3' and H-5'), 7.35 – 7.31 (1H, m, H-4'), 6.90 (1H, dd, *J* = 17.8, 11.2 Hz, H-1'''), 6.71 (1H, d, *J* = 2.4 Hz, H-3), 6.55 (1H, dd, *J* = 8.4, 2.4 Hz, H-5), 5.68 – 5.67 (1H, m, H-1''), 5.60 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.55 – 5.53 (1H, m, H-1''), 5.03 (2H, br. s H-3''), 5.02 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 43b): δ 161.62 (C-4), 157.60 (C-2), 144.47 (C-1'/2''), 139.14 (C-1'/2''), 131.98 (C-1'''), 129.32 (C-3' and C-5'), 128.73 (C-4'), 127.79 (C-6), 126.82 (C-2' and C-6'), 120.35 (C-1), 114.85 (C-1''), 111.94 (C-2'''), 106.52 (C-5), 100.27 (C-3), 70.50 (C-3''), 55.57 (-OMe); *m/z* (EI) 266 (M^+, 100%); HR-MS (AP) *m/z* 267.1384 ($[M+H]^+$), $C_{18}H_{18}O_2^+$ requires 267.1385, found 267.1384.

9.14.3 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**)

MTPPB (0.71 g, 2.0 mmol, 1.3 eq.), *t*-BuOK (0.23 g, 2.0 mmol, 1.3 eq.), 2-hydroxy-4,6-dimethoxybenzaldehyde (**690**) (0.29 g, 1.6 mmol), *t*-BuOK (0.23 g, 2.0 mmol, 1.3 eq.), 2-bromoacetophenone (**685**) (0.40 g, 2.0 mmol, 1.3 eq.), MTPPB (1.2 g, 3.3 mmol, 2.1 eq.), *t*-BuOK (0.36 g, 3.2 mmol, 2.0 eq.).

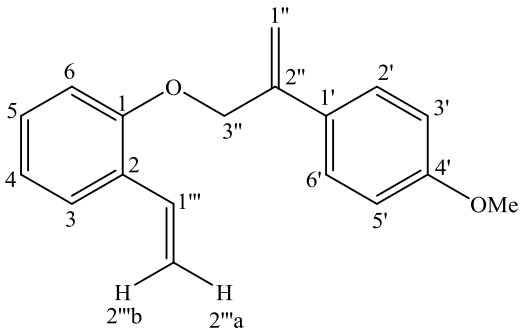
Yielded 1,5-dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**) as a *yellow oil* (0.36 g, 76%): R_f : 0.51 (H:A 6:4); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 44a): δ 7.57 – 7.54 (2H, m, H-2' and H-6'), 7.38 – 7.35 (2H, m, H-3' and H-5'), 7.33 – 7.30 (1H, m, H-4'), 6.86 (1H, dd, *J* = 17.9, 12.0 Hz, H-1'''), 6.39 (1H, d, *J* = 2.3 Hz, H-4), 6.26 (1H, d, *J* = 2.3 Hz, H-6), 5.87 (1H, dd, *J* = 17.9, 3.0 Hz, H-2'''b), 5.66 – 5.64 (1H, m, H-1''), 5.53 – 5.52 (1H, m, H-1''), 5.10 (1H, dd, *J* = 12.0, 3.0 Hz, H-2'''a), 5.01 (2H, br. s, H-3''), 3.82 (3H, s, -OMe), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 44b): δ 161.29 (C-1), 160.48 (C-5), 159.20 (C-3), 144.50 (C-2''), 139.16 (C-1'), 129.18 (C-3' and C-5'), 128.76 (C-4'), 127.91 (C-1'''), 126.78 (C-2' and C-6'), 115.71 (C-2'''), 115.07 (C-1''), 108.80 (C-2), 92.67 (C-4), 91.76 (C-6), 70.84 (C-3''), 55.90 (-OMe), 55.53 (-OMe); *m/z* (EI) 296 (M^+, 97%); HR-MS (ES) *m/z* 319.1309 $[M + Na]^+$, $C_{19}H_{20}O_3Na^+$ requires 319.1310, found 319.1309.



9.14.4 1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**)

MTPPB (1.18 g, 3.30 mmol, 2.0 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 2.0 eq.), 2-hydroxybenzaldehyde (**683**) (0.20 g, 1.6 mmol), *t*-BuOK (0.23 g, 2.1 mmol, 1.3 eq.), 2-bromo-4'-methoxyacetophenone (**691**) (0.46 g, 2.0 mmol, 1.2 eq.), MTPPB (1.17 g, 3.28 mmol, 2.0 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 2.0 eq.).

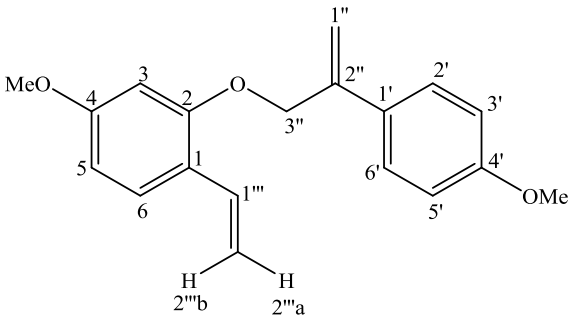
Yielded 1-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**) as a *yellow oil* (0.39 g, 89%): R_f : 0.63 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 45a): δ 7.54 – 7.50 (1H, m, H-3), 7.51 (2H, d, *J* = 9.0, H-2' and H-6'), 7.27 – 7.24 (1H, m, H-5), 7.11 (1H, dd, *J* = 8.3, 1.0 Hz, H-6), 7.00 (1H, dd, *J* = 17.8, 11.2 Hz, H-1'''), 6.96 – 6.94 (1H, m, H-4), 6.93 (2H, d, *J* = 9.0, H-3' and H-5'), 5.73 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.57 – 5.56 (1H, m, H-1''), 5.41 – 5.40 (1H, m, H-1''), 5.16 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a), 4.98 (2H, br. s, H-3''), 3.80 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 45b): δ 160.56 (C-4'), 156.65 (C-1), 143.82 (C-2''), 132.44 (C-1'''), 131.45 (C-1'), 129.81 (C-5), 128.03 (C-2' and C-6'), 127.52 (C-2), 127.04 (C-3), 121.65 (C-4), 114.60 (C-3' and C-5'),



114.42 (C-2'''), 113.48 (C-6), 113.03 (C-1''), 70.68 (C-3''), 55.56 (-OMe); *m/z* (EI) 266 (M^+, 100%); HR-MS (AP) *m/z* 267.1394 ($[M+H]^+$), $C_{18}H_{18}O_2^+$ requires 267.1385, found 267.1394.

9.14.5 4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**)[12]

MTPPB (0.94 g, 2.6 mmol, 1.7 eq.), *t*-BuOK (0.30 g, 2.5 mmol, 0.9 eq.), 2-hydroxy-4-methoxybenzaldehyde (**687**) (0.23 g, 1.5 mmol), *t*-BuOK (0.18 g, 1.6 mmol, 1.1 eq.), 2-bromo-4'-methoxyacetophenone (**691**) (0.37 g, 1.6 mmol, 1.1 eq.), MTPPB (0.95 g, 2.7 mmol, 1.8 eq.), *t*-BuOK (0.32 g, 2.9 mmol, 1.9 eq.).

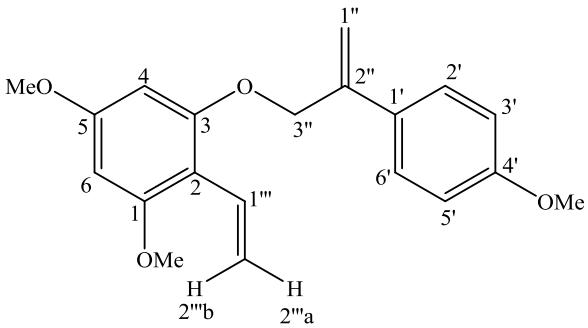


Yielded 4-methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**) as a *colourless oil* (0.27 g, 61%): R_f : 0.13 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 46a): δ 7.51 (2H, d, *J* = 8.5 Hz, H-2' and H-6'), 7.45 (1H, d, *J* = 8.5 Hz, H-6), 6.96 – 6.90 (1H, m, H-1'''), 6.92 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 6.69 (1H, d, *J* = 2.4 Hz, H-3), 6.54 (1H, dd, *J* = 8.5, 2.4 Hz, H-5), 5.61 (dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.58 (1H, br. s H-1''), 5.43 – 5.42 (1H, m, H-1''), 5.04 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a), 4.97 (2H, br. s, H-3''), 3.79 (3H, s, -OMe), 3.78 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 46b): δ 161.56 (C-4), 160.42 (C-4'), 157.61 (C-2), 143.60 (C-2''), 131.99 (C-1'''), 131.29 (C-1'), 128.08 (C-2' and C-6'), 127.93 (C-6), 120.35 (C-1), 114.49 (C-3' and C-5'), 113.07 (C-1''), 111.99 (C-2'''), 106.36 (C-5), 100.28 (C-3), 70.61 (C-3''), 55.56 (-OMe), 55.43 (-OMe); *m/z* (EI) 296 (M^+, 100%).

9.14.6 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**)

MTPPB (0.71 g, 2.0 mmol, 1.2 eq.), *t*-BuOK (0.22 g, 2.0 mmol, 1.2 eq.), 2-hydroxy-4,6-dimethoxybenzaldehyde (**690**) (0.30 g, 1.7 mmol), *t*-BuOK (0.22 g, 2.0 mmol, 1.2 eq.), 2-bromo-4'-methoxyacetophenone (**691**) (0.46 g, 2.0 mmol, 1.2 eq.), MTPPB (1.18 g, 3.30 mmol, 2.0 eq.), *t*-BuOK (0.37 g, 3.3 mmol, 2.0 eq.).

Yielded 1,5-dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**) as a *yellow oil* (0.38 g, 70%); R_f : 0.63 (H:A 6:4); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 47a): δ 7.51 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.93 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.85 (1H, dd, *J* = 18.0, 12.3 Hz, H-1'''), 6.39 (1H, d, *J* = 2.3 Hz, H-4/6), 6.27 (1H, d, *J* = 2.3 Hz, H-4/6), 5.86 (1H, dd, *J* = 18.0, 3.0 Hz, H-2'''b), 5.57 (1H, br. s H-1''), 5.43 – 5.41 (1H, m, H-1''), 5.09 (1H, dd, *J* = 12.3, 3.0 Hz, H-2'''a), 4.99 (2H, br. s, H-3''), 3.84 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.81 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 47b): δ 161.50 (C-5), 160.68 (C-1/4'), 160.67 (C-1/4'), 159.46 (C-3), 144.04 (C-2''), 131.63 (C-1'), 128.18 (C-2' and C-6'), 128.11 (C-1'''), 115.81 (C-2'''), 114.64 (C-3' and C-5'), 113.41 (C-1''), 108.97 (C-2), 92.86 (C-4/6), 91.92 (C-4/6), 71.18 (C-3''), 56.05 (-OMe), 55.70 (-OMe), 55.62 (-OMe); HR-MS (ES) *m/z* 349.1414 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1410, found 349.1414.



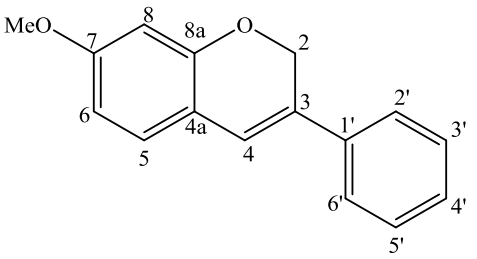
9.15 Isoflavene synthesis *via* RCM[8]

A solution of vinyl ether (1.0 eq.) and Grubbs II catalyst (5 mol%) in dry DCM or toluene (5.0 – 10.0 mL) was heated to reflux and allowed to stir overnight. After completion of the reaction, the product was directly purified *via* PLC. Alternatively a solution of vinyl ether (1.0 eq.), Grubbs II catalyst (5 mol%) and 1,4-benzoquinone (10 mol%) in dry toluene (5.0 – 10.0 mL) was heated to reflux.[21] After completion of the reaction, the product (in solvent) was directly purified *via* PLC.

9.15.1 7-Methoxyisoflav-3-ene (**696**)[19]

4-Methoxy-2-[(2-phenylallyl)oxy]-1-vinylbenzene (**689**) (0.20 g, 0.67 mmol), DCM (5.0 mL).

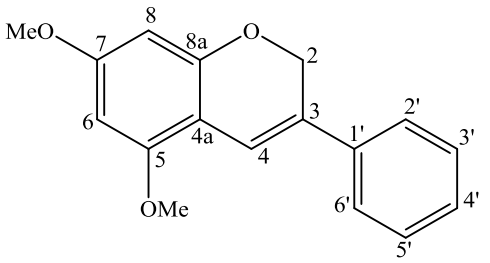
Yielded 7-methoxyisoflav-3-ene (**696**) as a white needles (0.18 g, quantitative yield): R_f : 0.53 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 48a): δ 7.55 – 7.53 (2H, m, H-2' and H-6'), 7.43 – 7.40 (2H, m, H-3' and H-5'), 7.33 – 7.31 (1H, m, H-4'), 7.11 (1H, d, *J* = 8.3 Hz, H-5), 6.97 (1H, br. s, H-4), 6.53 (1H, dd, *J* = 8.3, 2.4 Hz, H-6),



6.44 (1H, d, *J* = 2.4 Hz, H-8), 5.18 (1H, s, H-2), 5.17 (1H, s, H-2), 3.80 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 48b): δ 161.86 (C-7), 155.64 (C-8a), 137.76 (C-1'), 129.55 (C-3), 129.50 (C-3' and C-5'), 128.85 (C-5), 128.47 (C-4'), 125.37 (C-2' and C-6'), 120.54 (C-4), 117.13 (C-4a), 108.19 (C-6), 102.08 (C-8), 67.67 (C-2), 55.72 (-OMe); *m/z* (EI) 238 (M^+, 100%).

9.15.2 5,7-Dimethoxyisoflav-3-ene (**712**)[19]

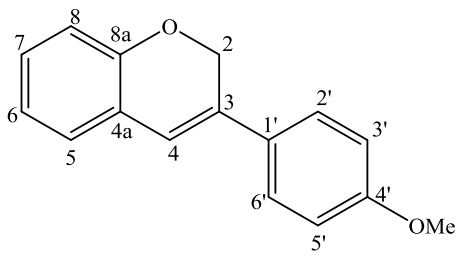
1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**) (0.11 g, 0.34 mmol), toluene (5.0 mL).



Yielded 5,7-dimethoxyisoflav-3-ene (**712**) as a yellow amorphous solid (0.07 g, 67%): R_f : 0.57 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 49a): δ 7.52 – 7.49 (2H, m, H-2' and H-6'), 7.42 – 7.38 (2H, m, H-3' and H-5'), 7.31 – 7.27 (1H, m, H-4'), 7.12 (1H, br. s, H-4), 6.19 (1H, d, *J* = 2.2 Hz, H-6/8), 6.11 (1H, d, *J* = 2.2 Hz, H-6/8), 5.10 (1H, s, H-2), 5.10 (1H, s, H-2), 3.87 (3H, s, -OMe), 3.80 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 49b): δ 162.48 (C-5/7), 157.69 (C-5/7), 156.23 (C-8a), 138.18 (C-1'), 129.62 (C-3' and C-5'), 128.20 (C-4'), 127.48 (C-3), 125.33 (C-2' and C-6'), 115.56 (C-4), 106.62 (C-4a), 94.37 (C-6/8), 92.71 (C-6/8), 67.53 (C-2), 56.14 (-OMe), 55.79 (-OMe); *m/z* (EI) 268 (M^+, 100%).

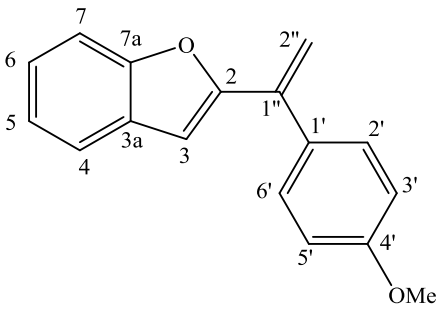
9.15.3 4'-Methoxyisoflav-3-ene (**697**) and 2-[1-(4-methoxyphenyl)vinyl]benzofuran (**701**)[19]

1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**) (0.34 g, 1.3 mmol), DCM (5.0 mL).



Yielded 4'-methoxyisoflav-3-ene (**697**) as a beige amorphous solid (0.26 g, 86%); R_f : 0.46 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 50a): δ 7.50 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.13 (1H, dd, *J* = 7.4, 1.6 Hz, H-5), 7.11 (1H, ddd, *J* = 8.0, 7.7, 1.6 Hz, H-7), 6.97 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.90 (1H, ddd, *J* = 7.7, 7.4, 1.2 Hz, H-6), 6.87 (1H, br. s, H-4), 6.80 (1H, br. d, *J* = 8.0 Hz, H-8), 5.15 (1H, s, H-2), 5.14 (1H, s, H-2), 3.82 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 50b): δ 160.67 (C-4'), 154.02 (C-8a), 132.42 (C-3), 129.74 (C-1'), 129.39 (C-5/7), 127.69 (C-5/7), 126.90 (C-2' and C-6'), 124.20

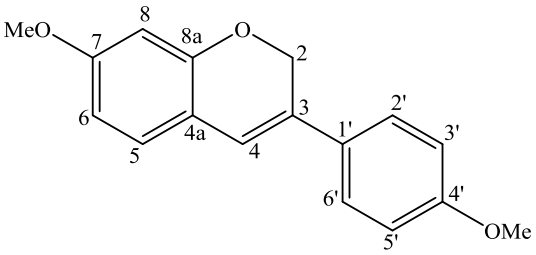
(C-4a), 122.32 (C-6), 118.65 (C-4), 115.97 (C-8), 114.97 (C-3' and C-5'), 67.53 (C-2), 55.61 (-OMe); *m/z* (EI) 238 (M^+, 100%).



Yielded 2-[1-(4-methoxyphenyl)vinyl]benzofuran (**701**)[12] as a *white amorphous solid* (0.02 g, 5%); R_f: 0.54 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 51a): δ 7.60 – 7.58 (1H, m, H-4), 7.54 – 7.52 (1H, m, H-7), 7.46 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 7.35 – 7.32 (1H, m, H-6), 7.25 – 7.22 (1H, m H-5), 6.94 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 6.66 (1H, br. s, H-3), 5.94 (1H, br. d, *J* = 1.0 Hz, H-2"), 5.41 (1H, br. d, *J* = 1.0 Hz, H-2"), 3.85 (3H, s, OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 51b): δ 160.87 (C-4'), 156.92 (C-2), 155.76 (C-7a), 140.01 (C-1"), 132.10 (C-1'), 130.35 (C-2' and C-6'), 129.79 (C-3a), 125.84 (C-6), 123.85 (C-5), 122.23 (C-4), 114.65 (C-3' and C-5'), 114.49 (C-2"), 111.70 (C-7), 106.60 (C-3), 55.62 (OMe); *m/z* (EI) 250 (M^+, 100%).

9.15.4 4',7-Dimethoxyisoflav-3-ene (**698**)[19]

4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**) (0.26 g, 0.84 mmol), DCM (5.0 mL).

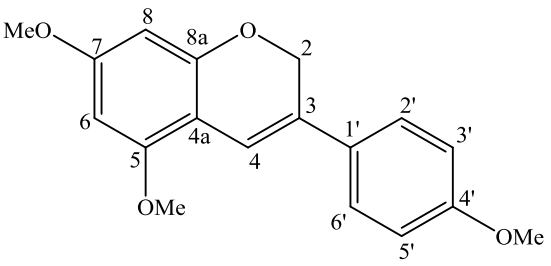


Yielded 4',7-dimethoxyisoflav-3-ene (**698**) as a yellow oil (0.13 g, 57%): R_f: 0.28 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 52a): δ 7.48 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.07 (1H, d, *J* = 8.3 Hz, H-5), 6.97 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.84 (1H, br. s, H-4), 6.51 (1H, dd, *J* = 8.3, 2.5 Hz, H-6), 6.42 (1H, d, *J* = 2.5 Hz, H-8), 5.13 (1H, br. s, H-2), 5.13 (1H, br. s, H-2), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 52b): δ 161.55 (C-7), 160.44 (C-4'), 155.38 (C-8a), 130.18 (C-1'), 129.35 (C-3), 128.49 (C-5), 126.70 (C-2' and C-6'), 118.61 (C-4), 117.40 (C-4a), 115.02 (C-3' and C-5'), 108.09 (C-6), 102.09 (C-8), 67.73 (C-2), 55.72 (-OMe), 55.67 (-OMe); *m/z* (EI) 268 (M^+, 100%).

9.15.5 4',5,7-Trimethoxyisoflav-3-ene (**713**)[19]

1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**) (0.13 g, 0.40 mmol), toluene (5.0 mL), benzoquinone (0.01, 0.09 mmol, 0.2 eq).

Yielded 4',5,7-trimethoxyisoflav-3-ene (**713**) as a yellow oil (0.08 g, 65%): R_f : 0.34 (H:A 7:3). ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 53a): δ 7.46 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.01 – 6.99 (1H, m, H-4), 6.97 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.18 (1H, d, *J* = 2.2 Hz, H-6), 6.09 (1H, dd, *J* = 2.2, 0.5 Hz, H-8), 5.07 (1H, s, H-2), 5.07 (1H, s, H-2), 3.86 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 53b): δ 162.00 (C-5/7), 160.15 (C-4'), 157.36 (C-5/7), 155.83 (C-8a), 130.55 (C-1'), 127.16 (C-3), 126.54 (C-2' and C-6'), 114.91 (C-3' and C-5'), 113.51 (C-4), 106.71 (C-4a), 94.30 (C-8), 92.58 (C-6), 67.50 (C-2), 56.04 (-OMe), 55.69 (-OMe), 55.56 (-OMe); *m/z* (EI) 298 (M^+, 100%).



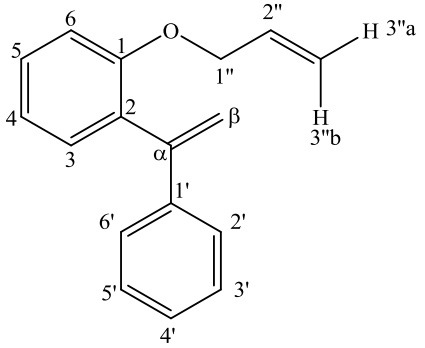
9.16 Allyloxy phenylvinyl benzene synthesis *via* Wittig reaction

A suspension of MTPPB (1.5 eq.) and *t*-BuOK (1.5 eq.) in anhydrous THF (10.0 mL) under argon was cooled to 0 °C and stirred for 15 minutes. 2-Allyloxybenzophenone (1.0 eq.) was added to this mixture and gradually warmed to rt. After completion of the reaction (TLC), a saturated solution of aq. NH_4Cl (60.0 mL) was added and the product extracted into Et_2O (3 x 60.0 mL), dried over Na_2SO_4, the solvent removed in *vacuo* and the product purified *via* PLC.

9.16.1 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**)[13]

2-Allyloxybenzophenone (**739**) (0.51 g, 2.6 mmol), MTPPB (1.13 g, 3.16 g, 1.2 eq.), *t*-BuOK (0.36 g, 3.2 mmol, 1.3 eq.).

Yielded 1-(allyloxy)-2-(1-phenylvinyl)benzene (**740**) as a yellow oil (0.48 g, 96%): R_f : 0.56 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 54a): δ 7.36 – 7.32 (1H, m, H-5), 7.31 – 7.28 (4H, m, H-2', 6', 3' and 5'), 7.28 – 7.23 (2H, m, H-3 and H-4'), 7.03 – 7.00 (2H, m, H-4 and H-6), 5.70 (1H, d, *J* = 1.5 Hz, H-β), 5.67 (1H, ddt, *J* = 17.3, 10.6, 4.8 Hz, H-2"), 5.28 (1H, d, *J* = 1.5 Hz, H-β), 5.03 (1H, ddt, *J* = 17.3, 1.8, 1.8 Hz, H-3"b), 4.98 (1H, ddt, *J* = 10.6, 1.8, 1.8 Hz, H-3"a), 4.39 (2H, ddd, *J* = 4.8, 1.8, 1.8 Hz, H-1"); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 54b): δ 157.03 (C-1), 148.78 (C-α), 142.35 (C-1'), 134.29 (C-2"), 132.20 (C-2), 131.93 (C-3), 130.06 (C-4'),



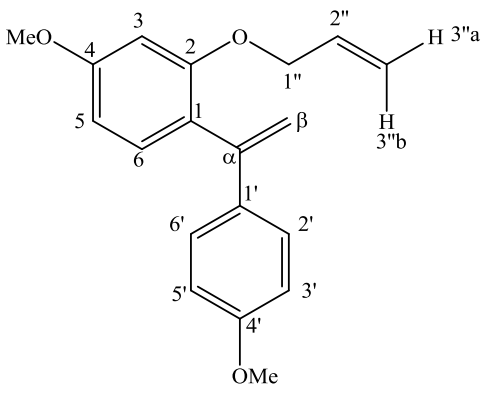
128.89 (C-2' and C-6'), 128.13 (C-5), 127.20 (C-3' and C-5'), 121.64 (C-4), 116.42 (C-3"), 115.54 (C-β), 113.62 (C-6), 69.33 (C-1"); *m/z* (EI) 236 (M^+, 3%).

9.17 Allyloxy phenylvinyl benzene synthesis *via* $Al(OTf)_3$ enhanced Grignard reaction

A mixture of 2'-allyloxyacetophenone (1.0 eq.) and $Al(OTf)_3$ (1.0 eq.) in Et_2O (10.0 mL) was stirred at -30 °C for 30 min. under Ar. where after the magnesium bromide Grignard reagent in Et_2O (3.0 M, 2.0 eq.) was added. The temperature was allowed to increase to rt. while stirring continued. Once the reaction was deemed complete (TLC), the reaction mixture was quenched with aq. NH_4Cl (50.0 mL) and the product extracted into EtOAc (3 x 60.0 mL), dried over Na_2SO_4, the solvent removed in *vacuo* and the product purified *via* PLC.

9.17.1 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**)[13]

2'-Allyloxy-4'-methoxyacetophenone (**751**) (0.17 g, 0.82 mmol), $Al(OTf)_3$ (0.47 g, 0.99 mmol, 1.2 eq.), 4-methoxyphenylmagnesium bromide (0.7 mL, 3.0 M, 2.6 eq.)

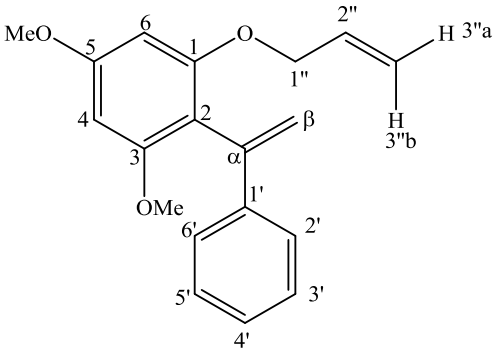


Yielded 2-(allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**) as a yellow oil (0.19 g, 66%): R_f : 0.49 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 55a): δ 7.22 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.14 (1H, d, *J* = 9.2 Hz, H-6), 6.85 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.57 (1H, dd, *J* = 9.2, 2.3 Hz, H-5), 6.57 (1H, d, *J* = 2.3 Hz, H-3), 5.72 (1H, ddt, *J* = 17.3, 10.7, 4.7 Hz, H-2"), 5.54 (1H, d, *J* = 1.7 Hz, H-β), 5.12 (1H, d, *J* = 1.7 Hz, H-β), 5.07 (1H, ddt, *J* = 17.3, 1.9, 1.9 Hz, H-3"b), 5.01 (1H, ddt, *J* = 10.7, 1.9, 1.9 Hz, H-3"a), 4.40 (1H, ddd, *J* = 4.7, 1.9, 1.9 Hz, H-1"), 3.82 (3H, s, -OMe), 3.78 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 55b): δ 161.76 (C-4), 160.19 (C-4'), 158.04 (C-2), 147.85 (C-α), 135.23 (C-1'), 134.33 (C-2"), 132.39 (C-6), 128.41 (C-2' and C-6'), 125.00 (C-1), 116.47 (C-3"), 114.19 (C-3' and C-5'), 113.34 (C-β), 105.78 (C-3/5), 100.91 (C-3/5), 69.36 (C-1"), 55.71 (-OMe), 55.58 (-OMe); *m/z* (EI) 296 (M^+, 28%).

9.17.2 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**)

2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**) (0.22 g, 0.91 mmol), $Al(OTf)_3$ (0.88 g, 1.8 mmol, 2.0 eq.), phenylmagnesium bromide (0.6 mL, 3.0 M, 2.0 eq.)

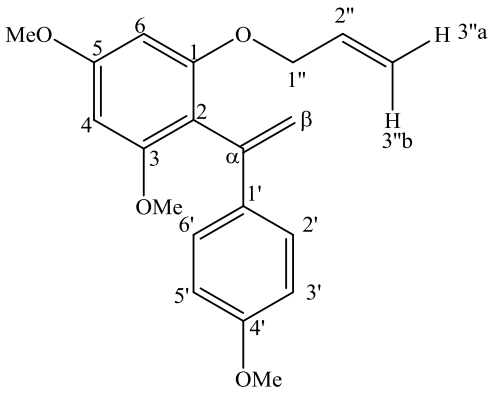
Yielded 1-(allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**) as a *yellow oil* (0.25 g, 94%): R_f : 0.42 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 56a): δ 7.34 – 7.31 (2H, m, H-2' and H-6'), 7.27 – 7.23 (2H, m, H-3' and H-5'), 7.22 – 7.18 (1H, m, H-4'), 6.32 (1H, d, *J* = 2.2 Hz, H-4/6), 6.30 (1H, d, *J* = 2.2 Hz, H-4/6), 5.87 (1H, d, *J* = 1.7 Hz, H-β), 5.81 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, H-2"), 5.22 (1H, ddt, *J* = 17.3, 1.7, 1.7 Hz, H-3"b), 5.13 (1H, d, *J* = 1.7 Hz, H-β), 5.06 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3"a), 4.45 (2H, ddd, *J* = 4.7, 1.7, 1.7 Hz, H-1"), 3.84 (3H, s, -O<u>Me</u>), 3.67 (3H, s, -O<u>Me</u>); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 56b): δ 161.79 (C-3/5), 159.77 (C-3/5), 158.52 (C-1), 142.48 (C-1'), 142.35 (C-α), 134.57 (C-2"), 128.76 (C-3' and C-5'), 127.73 (C-4'), 126.71 (C-2' and C-6'), 116.53 (C-3" and C-β), 113.26 (C-2), 93.00 (C-4/6), 92.00 (C-4/6), 69.56 (C-1"), 56.11 (-O<u>Me</u>), 55.67 (-O<u>Me</u>); *m/z* (EI) 296 (M^+, 26%); HR-MS (ES) *m/z* 319.1307 $[M + Na]^+$, $C_{19}H_{20}O_3Na^+$ requires 319.1310, found 319.1307.



<u>9.17.3 1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**)</u>

2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**) (0.21 g, 0.87 mmol), $Al(OTf)_3$ (0.42 g, 0.88 mmol, 1.0 eq.), 4-methoxyphenylmagnesium bromide (1.0 mL, 3.0 M, 3.5 eq.)

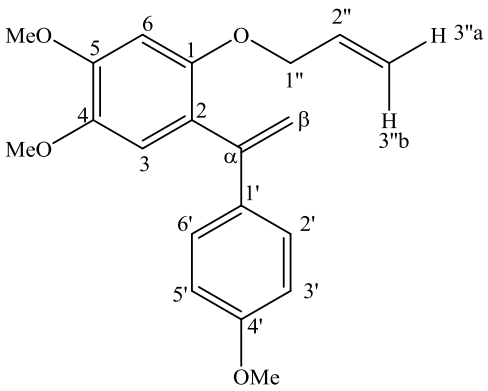
Yielded 1-(allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**) as a *yellow oil* (0.18 g, 65%): R_f : 0.41 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 57a): δ 7.24 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 6.81 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.30 (1H, d, *J* = 2.2 Hz, H-4/6), 6.29 (1H, d, *J* = 2.2 Hz, H-4/6), 5.84 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, H-2"), 5.76 (1H, d, *J* = 1.6 Hz, H-β), 5.23 (1H, ddt, *J* = 17.3, 1.8, 1.8 Hz, H-3"b), 5.07 (1H, ddt, *J* = 10.6, 1.8, 1.8 Hz, H-3"a), 4.98 (1H, d, *J* = 1.6 Hz, H-β), 4.45 (2H, ddd, *J* = 4.7, 1.8, 1.8 Hz, H-1"), 3.84 (3H, s, -O<u>Me</u>), 3.76 (3H, s, -O<u>Me</u>), 3.68 (3H, s, -O<u>Me</u>); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 57b): δ 161.69 (C-3/5), 159.92 (C-3/5/4'), 159.74 (C-3/5/4'), 158.50 (C-1), 141.76 (C-α), 134.83 (C-1'), 134.66 (C-2"), 127.86 (C-2' and C-6'), 116.47 (C-3"), 114.44 (C-β), 114.10 (C-3' and C-5'), 113.59 (C-2), 93.02 (C-4/6), 92.07 (C-4/6), 69.64 (C-1"), 56.11 (-O<u>Me</u>), 55.66 (-O<u>Me</u>), 55.49 (-O<u>Me</u>);



m/z (EI) 326 (M^+, 94%); HR-MS (ES) *m/z* 349.1416 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1416.

9.17.4 1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**)

2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**) (0.21 g, 0.89 mmol), $Al(OTf)_3$ (0.41 g, 0.86 mmol, 1.0 eq.), 4-methoxyphenylmagnesium bromide (2.0 mL, 3.0 M, 6.7 eq.)



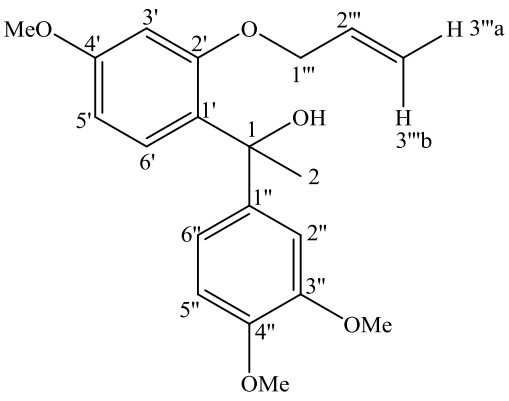
Yielded 1-(allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**) as a *yellow oil* (0.15 g, 52%): R_f : 0.30 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 58a): δ 7.24 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.85 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.82 (1H, s, H-3/6), 6.73 (1H, s, H-3/6), 5.70 (1H, ddt, *J* = 17.2, 10.7, 5.0 Hz, H-2"), 5.55 (1H, d, *J* = 1.6 Hz, H-β), 5.16 (1H, d, *J* = 1.6 Hz, H-β), 5.08 (1H, ddt, *J* = 17.2, 1.8, 1.8 Hz, H-3"b), 5.00 (1H, ddt, *J* = 10.7, 1.8, 1.8 Hz, H-3"a), 4.36 (2H, ddd, *J* = 5.0, 1.8, 1.8 Hz, H-1"), 3.85 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.77 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 58b): δ 160.22 (C-4'), 151.46 (C-4/5), 150.88 (C-1), 147.77 (C-α), 144.53 (C-4/5), 135.14 (C-1'), 134.89 (C-2"), 128.57 (C-2' and C-6'), 124.18 (C-2), 116.61 (C-3/6), 116.45 (C-3"), 114.19 (C-3' and C-5'), 113.55 (C-β), 101.51 (C-3/6), 70.78 (C-1"), 57.01 (-OMe), 56.40 (-OMe), 55.58 (-OMe); *m/z* (EI) 326 (M^+, 48%); HR-MS (ES) *m/z* 349.1418 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1418.

9.18 Synthesis of 1-[2-(allyloxy)phenyl]-1-phenylethan-1-ols *via* Grignard reaction

A mixture of 2'-allyloxyacetophenone (1.0 eq.) and 3,4-dimethoxyphenylmagnesium bromide (0.5 M, 2.0 eq.) in THF (2.0 mL) was stirred at -60 °C for 3 hours where after the temperature was allowed to increase to rt. while stirring continued overnight. Once the reaction was deemed complete (TLC), the reaction mixture was quenched with aq. NH_4Cl (50.0 mL) and the product extracted into EtOAc (3 x 60.0 mL). The organic layer was dried and the solvent removed under reduced pressure. The reaction mixture was purified *via* PLC.

9.18.1 1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**)

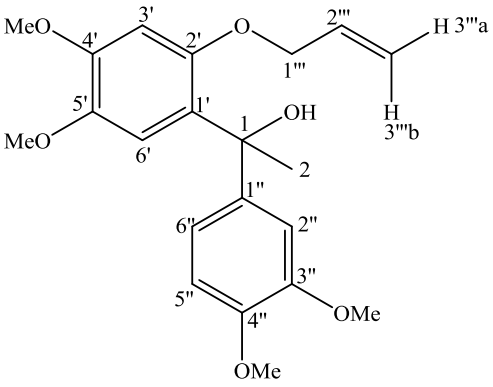
2'-Allyloxy-4'-methoxyacetophenone (**751**) (0.11 g, 0.53 mmol), 3,4-dimethoxyphenylmagnesium bromide (**765**) (2.0 mL, 0.5 M, 1.8 eq.)



Yielded 1-[2-(allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**) as a *yellow oil* (0.11 g, 60%): R_f : 0.19 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 59a): δ 7.48 (1H, d, *J* = 8.4 Hz, H-6'), 7.03 (1H, d, *J* = 2.1 Hz, H-2''), 6.79 (1H, d, *J* = 8.4 Hz, H-5''), 6.75 (1H, dd, *J* = 8.4, 2.1 Hz, H-6''), 6.56 (H, dd, *J* = 8.4, 2.5 Hz, H-5'), 6.55 (1H, d, *J* = 2.5 Hz, H-3'), 5.76 (1H, ddt, *J* = 17.3, 10.4, 5.1 Hz, H-2'''), 5.15 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3'''b), 5.11 (1H, ddt, *J* = 10.4, 1.5, 1.5 Hz, H-3'''a), 4.50 (1H, s, -O<u>H</u>), 4.44 (1H, ddd, *J* = 13.0, 5.1, 1.5 Hz, H-1'''a), 4.35 (1H, ddd, *J* = 13.0, 5.1, 1.5 Hz, H-1'''b), 3.79 (3H, s, -O<u>Me</u>), 3.75 (3H, s, -O<u>Me</u>), 3.73 (3H, s, -O<u>Me</u>), 1.80 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 59b): δ 160.96 (C-4'), 157.67 (C-2'), 149.57 (C-3''), 148.77 (C-4''), 143.81 (C-1''), 134.14 (C-2'''), 129.82 (C-1'), 128.16 (C-6'), 118.51 (C-6''), 117.51 (C-3'''), 112.01 (C-5''), 110.93 (C-2''), 105.21 (C-5'), 101.57 (C-3'), 75.70 (C-1), 69.80 (C-1'''), 56.13 (-O<u>Me</u>), 56.08 (-O<u>Me</u>), 55.58 (-O<u>Me</u>), 30.35 (-<u>C</u>H$_3$); HR-MS (ES) *m/z* 367.1520 $[M + Na]^+$, $C_{20}H_{24}O_5Na^+$ requires 367.1516, found 367.1520.

<u>9.18.2 1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**)</u>

2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**) (0.83 g, 0.35 mmol), 3,4-dimethoxyphenylmagnesium bromide (**765**) (2.0 mL, 0.5 M, 2.8 eq.)



Yielded 1-[2-(allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**) as a *yellow oil* (0.11 g, 80%): R_f : 0.14 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 60a): δ 7.03 (1H, d, *J* = 2.0 Hz, H-2''), 6.98 (1H, s, H-6'), 6.71 (1H, d, *J* = 8.4 Hz, H-5''), 6.66 (1H, dd, *J* = 8.4, 2.0 Hz, H-6''), 6.52 (1H, s, H-3'), 5.68 – 5.61 (1H, m, H-2'''), 5.15 – 5.10 (2H, m, 3'''a and 3'''b), 4.57 (1H, s, -O<u>H</u>), 4.31 (1H, br. dd, *J* = 12.5, 5.7 Hz, H-1'''a), 4.07 (1H, br. dd, *J* = 12.5, 5.7 Hz, H-1'''b), 3.87 (3H, s, -O<u>Me</u>), 3.85 (3H, s, -O<u>Me</u>), 3.83 (3H, s, -O<u>Me</u>), 3.82 (3H, s, -O<u>Me</u>), 1.81 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, plate 60b): δ 150.49 (C-2'), 148.91 (C-4'/4''), 148.44 (C-3'), 147.53 (C-4'/4''), 142.98 (C-5'), 142.95 (C-1''), 132.87 (C-2'''), 128.15 (C-1'), 117.92 (C-3'''), 117.30 (C-6''), 111.73 (C-6'), 110.40 (C-5''), 108.74 (C-2''), 100.55 (C-3'), 75.91 (C-1), 70.82 (C-1'''),

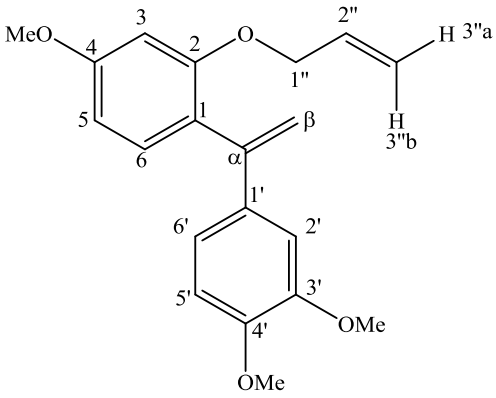
56.94 (-OMe), 56.19 (-OMe), 55.97 (-OMe), 55.94 (-OMe), 30.36 (-CH_3); HR-MS (ES) *m/z* 397.1629 $[M + Na]^+$, $C_{21}H_{26}O_6Na^+$ requires 397.1627, found 397.1629.

9.19 Allyloxy phenylvinyl benzene synthesis *via* dehydration

A mixture of the tertiary alcohol (1.0 eq.) and anhydrous $CuSO_4$ (4.0 eq.) was heated to reflux in dehydrated hexane over night. After completion of the reaction, the mixture was washed with distilled H_2O (30.0 mL) and the product extracted into EtOAc (3 x 30.0 mL). The organic layer was dried and the solvent removed under reduced pressure. The reaction mixture was purified *via* PLC.

9.19.1 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**)

1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**) (0.11 g, 0.33 mmol), $CuSO_4$ (0.21 g, 1.3 mmol, 3.9 eq.)

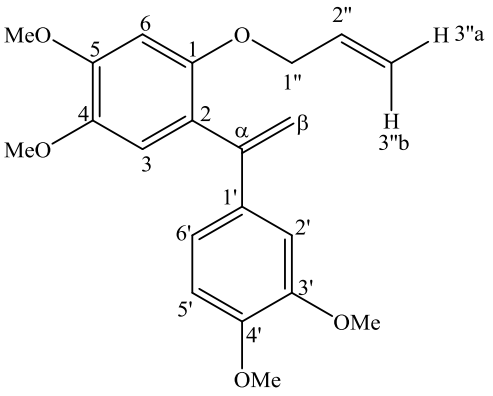


Yielded 2-(allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**) as a *yellow oil* (0.08 g, 75%): R_f : 0.30 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 61a): δ 7.15 (1H, d, *J* = 8.7 Hz, H-6), 6.95 (1H, d, *J* = 2.0 Hz, H-2'), 6.84 (1H, d, *J* = 8.3 Hz, H-5'), 6.77 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 6.59 – 6.56 (2H, m, H-3 and H-5), 5.77 – 5.70 (1H, m, H-2"), 5.56 (1H, d, *J* = 1.6 Hz, H-β), 5.14 (1H, d, *J* = 1.6 Hz, H-β), 5.08 (1H, br. d, *J* = 17.3, 1.7 Hz, H-3"b), 5.02 (1H, br. d, *J* = 10.5, 1.7 Hz, H-3"a), 4.43 – 4.40 (2H, m, H-1"), 3.82 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.75 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 61b): δ 161.63 (C-4), 157.97 (C-2), 149.99 (C-3'/4'), 149.88 (C-3'/4'), 147.92 (C-α), 135.61 (C-1'), 134.25 (C-2"), 132.30 (C-6), 124.85 (C-1), 120.06 (C-6'), 116.35 (C-3"), 113.48 (C-β), 112.18 (C-5'), 111.42 (C-2'), 105.69 (C-5), 100.80 (C-3), 69.27 (C-1"), 56.08 (-OMe), 56.07 (-OMe), 55.59 (-OMe); HR-MS (ES) *m/z* 349.1418 $[M + Na]^+$, $C_{20}H_{22}O_4Na^+$ requires 349.1416, found 349.1418.

9.19.2 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**)

1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**) (0.10 g, 0.27 mmol), $CuSO_4$ (0.19 g, 1.2 mmol, 4.5 eq.).

Yielded 1-(allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**) as a *yellow oil* (0.06 g, 64%): R_f : 0.26 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 62a): δ 6.96 (1H, d, *J* = 2.1 Hz, H-2'), 6.86 (1H, d, *J* = 8.4 Hz, H-5'), 6.81 (1H, s, H-3/6), 6.79 (1H, dd, *J* = 8.4, 2.1 Hz, H-6'), 6.74 (1H, s, H-3/6), 5.72 (1H, ddt, *J* = 17.3, 10.6, 4.9 Hz, H-2"), 5.58 (1H, d, *J* = 1.6 Hz, H-β), 5.17 (1H, d, *J* = 1.6 Hz, H-β), 5.09 (1H, ddt, *J* = 17.3, 1.7, 1.7 Hz, H-3"b), 5.01 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3"a), 4.38 (2H, ddd, *J* = 4.9, 1.7, 1.7 Hz, H-1"), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.77 (3H, s, -OMe), 3.76 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 62b): δ 151.56 (4°-C), 150.89 (4°-C), 150.18 (4°-C), 150.03 (4°-C), 147.94 (C-α), 144.52 (C-4), 135.66 (C-1'), 134.95 (C-2"), 124.17 (C-2), 120.31 (C-6'), 116.64 (C-3/6), 116.46 (C-3"), 113.84 (C-β), 112.31 (C-5'), 111.65 (C-2'), 101.55 (C-3/6), 70.85 (C-1"), 57.02 (-OMe), 56.39 (-OMe), 56.22 (-OMe), 56.19 (-OMe); HR-MS (ES) *m/z* 379.1523 $[M + Na]^+$, $C_{21}H_{24}O_5Na^+$ requires 379.1521, found 379.1523.



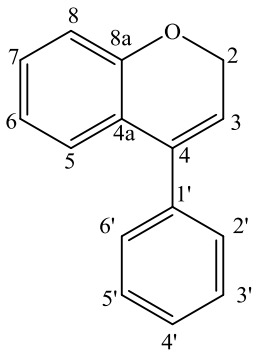
9.20 Neoflavene synthesis *via* RCM[8]

A solution of allyloxy phenylvinyl benzene () (1.0 eq.) and Grubbs II catalyst (5 mol%) in dry DCM (10.0 ml) was heated to reflux and allowed to continue stirring over night. After completion of the reaction, the solvent was removed under reduced pressure and the product purified *via* PLC.

9.21.3 Neoflav-3-ene (**741**)[8,22]

1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**) (0.18 g, 0.72 mmol).

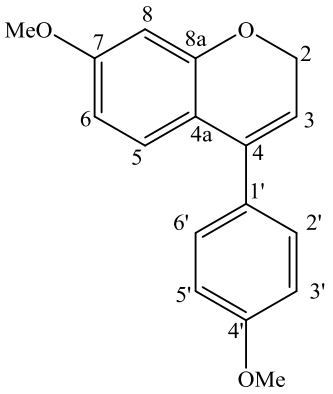
Yielded neoflav-3-ene (**741**) as a yellow oil (0.14 g, 93%): R_f : 0.67 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 63a): δ 7.45 – 7.41 (2H, m, H-2' and H-6') , 7.40 – 7.37 (1H, m, H-4'), 7.36 – 7.33 (2H, m, H-3' and H-5'), 7.19 – 7.15 (1H, m, H-7), 6.97 (1H, dd, *J* = 7.6, 1.6 Hz, H-5), 6.88 – 6.85 (2H, m, H-6 and H-8), 5.88 (1H, t, *J* = 4.0 Hz, H-3), 4.82 (2H, d, *J* = 4.0 Hz, H-2); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 63b): δ 155.96 (C-8a), 139.24 (C-1'), 137.68 (C-4), 130.23 (C-7),



129.45 (C-4'), 129.43 (C-3' and C-5'), 128.80 (C-2' and C-6'), 126.50 (C-5), 124.54 (C-4a), 122.04 (C-3/6), 121.57 (C-3/6), 117.10 (C-8), 65.89 (C-2); *m/z* (EI) 207 ([M-H]$^+$, 100%).

9.20.2 4',7-Dimethoxyneoflav-3-ene (**770**)[13]

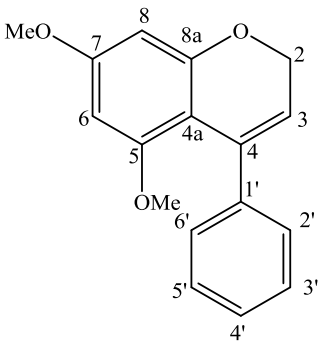
2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**) (0.05 g, 0.2 mmol, 1.0 eq.).



Yielded 4',7-dimethoxyneoflav-3-ene (**770**) as a beige oil (0.04 g, 95%): R_f : 0.38 (H:A 7:3); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 64a): δ 7.27 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.98 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.93 (1H, d, *J* = 8.0 Hz, H-5), 6.49 – 6.46 (2H, m, H-6 and H-8), 5.68 (1H, t, *J* = 4.0 Hz, H-3), 4.78 (2H, d, *J* = 4.0 Hz, H-2), 3.84 (-OMe), 3.79 (-OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 64b): δ 161.72 (C-7), 160.48 (C-4'), 157.37 (C-8a), 137.22 (C-4), 131.63 (C-1'), 130.49 (C-2' and C-6'), 127.44 (C-5), 117.85 (C-4a), 117.49 (C-3), 114.73 (C-3' and C-5'), 107.63 (C-6/8), 102.77 (C-6/8), 66.10 (C-2), 55.73 (-OMe), 55.66 (-OMe); *m/z* (EI) 268 (M$^+$, 100%).

9.20.3 5,7-Dimethoxyneoflav-3-ene (**771**)

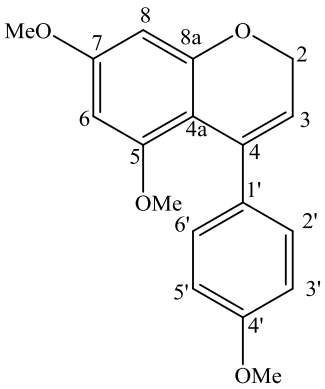
1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**) (0.13 g, 0.43 mmol).



Yielded 5,7-dimethoxyneoflav-3-ene (**771**) as a *yellow oil* (0.12 g, quantitative yield): R_f : 0.34 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 65a): δ 7.31 – 7.27 (2H, m, H-3' and H-5'), 7.27 – 7.23 (1H, m, H-4'), 7.19 – 7.17 (2H, m, H-2' and H-6'), 6.23 (1H, d, *J* = 2.4 Hz, H-6/8), 6.19 (1H, d, *J* = 2.4 Hz, H-6/8), 5.71 (1H, t, *J* = 4.7 Hz, H-3), 4.57 (2H, d, *J* = 4.7 Hz, H-2), 3.81 (-OMe), 3.41 (-OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 65b): δ 162.51 (C-7), 159.22 (C-8a), 158.63 (C-5), 142.02 (C-1'), 137.47 (C-4), 128.25 (Ar-C), 127.78 (Ar-C), 127.39 (C-4'), 118.65 (C-3), 107.45 (C-4a), 94.98 (C-6/8), 94.02 (C-6/8), 65.38 (C-2), 55.73 (-OMe), 55.50 (-OMe); *m/z* (EI) 268 (M$^+$, 100%); HR-MS (ES) *m/z* 291.0995 [M + Na]$^+$, $C_{17}H_{16}O_3Na^+$ requires 291.0997, found 291.0995.

9.20.4 4',5,7-Trimethoxyneoflav-3-ene (**772**)

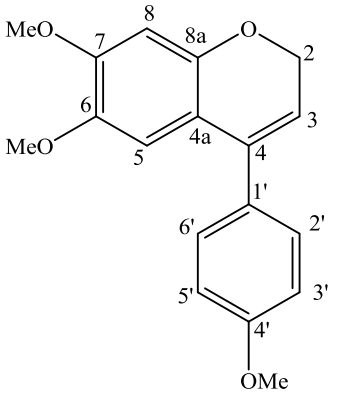
1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**) (0.03 g, 0.1 mmol).



Yielded 4',5,7-trimethoxyneoflav-3-ene (**772**) as an *orange oil* (0.02 g, 73%): R_f : 0.36 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 66a): δ 7.11 (2H, d, *J* = 8.8, H-2' and H-6'), 6.86 (2H, d, *J* = 8.8, H-3' and H-5'), 6.21 (1H, d, *J* = 2.4 Hz, H-6), 6.19 (1H, d, *J* = 2.4 Hz, H-8), 5.67 (1H, t, *J* = 4.7 Hz, H-3), 4.54 (2H, d, *J* = 4.7 Hz, H-2), 3.81 (3H, s, -OMe), 3.81 (3H, s, -OMe), 3.45 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 66b): δ 162.48 (C-7), 159.71 (C-5), 159.40 (C-4'), 158.78 (C-8a), 137.10 (C-4), 134.30 (C-1'), 128.93 (C-2' and C-6'), 117.62 (C-3), 113.67 (C-3' and C-5'), 107.62 (C-4a), 95.01 (C-6/8), 94.09 (C-6/8), 65.42 (C-2), 55.76 (-OMe), 55.64 (-OMe), 55.53 (-OMe); *m/z* (EI) 298 (M^+, 100%); HR-MS (ES) *m/z* 595.2320 [M^+]-dimer, $C_{36}H_{35}O_8^+$ requires 595.2332, found 595.2320.

9.20.5 4',6,7-Trimethoxyneoflav-3-ene (**773**)

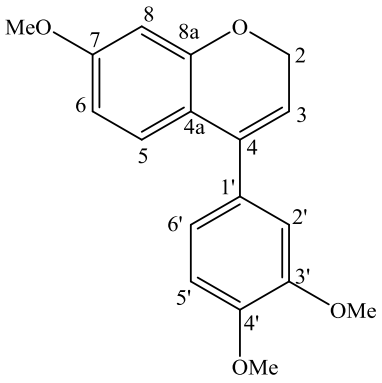
1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**) (0.07 g, 0.2 mmol).



Yielded 4',6,7-trimethoxyneoflav-3-ene (**773**) as a yellow oil (0.05 g, 79%): R_f : 0.28 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 67a): δ 7.31 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 7.00 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 6.61 (1H, s, H-5), 6.56 (1H, s, H-8), 5.72 (1H, t, *J* = 4.1 Hz, H-3), 4.72 (2H, d, *J* = 4.1 Hz, H-2), 3.85 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.62 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 67b): δ 160.58 (C-4'), 151.50 (C-8a), 150.92 (C-7), 144.55 (C-6), 137.49 (C-4), 131.57 (C-1'), 130.49 (C-2' and C-6'), 117.53 (C-3), 116.59 (C-4a), 114.78 (C-3' and C-5'), 111.59 (C-5), 102.04 (C-8), 65.86 (C-2), 57.06 (-OMe), 56.24 (-OMe), 55.65 (-OMe); *m/z* (EI) 298 (M^+, 100%).

9.20.6 3',4',7-Trimethoxyneoflav-3-ene (**774**)

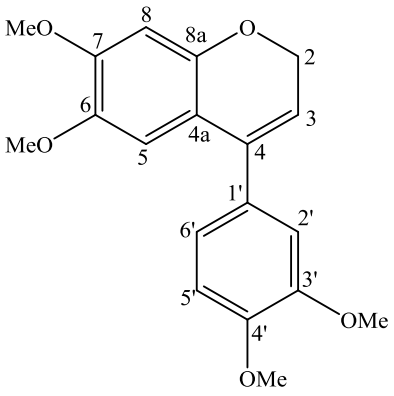
2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**) (0.05 g, 0.2 mmol)



Yielded 3',4',7-trimethoxyneoflav-3-ene (**774**) as a *yellow oil* (0.03 g, 67%): R_f : 0.33 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 68a): δ 6.99 (2H, d, *J* = 8.3 Hz, H-5 and H-5'), 6.90 (1H, d, *J* = 2.0 Hz, H-2'), 6.88 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 6.48 (1H, dd, *J* = 8.3, 2.5 Hz, H-6), 6.46 (1H, d, *J* = 2.5 Hz, H-8), 5.72 (1H, t, *J* = 4.0 Hz, H-3), 4.78 (2H, d, *J* = 4.0 Hz, H-2), 3.85 (3H, s, -OMe), 3.82 (3H, s, -OMe), 3.79 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 68b): δ 161.65 (C-7), 157.31 (C-8a), 150.19 (C-3' and C-4'), 137.40 (C-4), 131.97 (C-1'), 127.52 (C-5/5'), 121.60 (C-6'), 117.77 (C-4a), 117.48 (C-3), 113.14 (C-2'), 112.60 (C-5/5'), 107.61 (C-6'), 102.70 (C-8), 66.06 (C-2), 56.12 (-OMe), 56.10 (-OMe), 55.68 (-OMe); HR-MS (ES) *m/z* 321.1103 $[M + Na]^+$, $C_{18}H_{18}O_4Na^+$ requires 321.1103, found 321.1103.

9.20.7 3',4',6,7-Tetramethoxyneoflav-3-ene (**775**)

1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**) (0.05 g, 0.1 mmol)



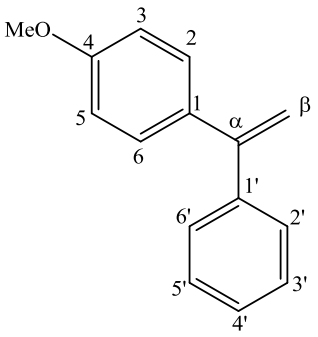
Yielded 3',4',6,7-tetramethoxyneoflav-3-ene (**775**) as an *orange-brown oil* (0.03 g, 72% yield): R_f : 0.27 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 69a): δ 7.01 (1H, d, *J* = 8.7 Hz, H-5'), 6.94 – 6.91 (2H, m, H-2' and H-6'), 6.67 (1H, s, H-5), 6.57 (1H, s, H-8), 5.75 (1H, t, *J* = 4.1 Hz, H-3), 4.72 (2H, d, *J* = 4.1 Hz, H-2), 3.85 (3H, s, -OMe), 3.83 (6H, s, -OMe), 3.64 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 69b): δ 151.33 (C-8a), 150.79 (C-7), 150.19 (C-3'/4'), 150.14 (C-3'/4'), 144.50 (C-6), 137.62 (C-4), 131.88 (C-1'), 121.57 (C-2'/6'), 117.51 (C-3), 116.41 (C-4a), 112.95 (C-2'/6'), 112.59 (C-5'), 111.34 (C-5), 101.93 (C-8), 65.79 (C-2), 56.92 (-OMe), 56.16 (-OMe), 56.10 (-OMe), 56.06 (-OMe); HR-MS (ES) *m/z* 351.1208 $[M + Na]^+$, $C_{19}H_{20}O_5Na^+$ requires 351.1208, found 351.1208.

9.21 $Al(OTf)_3$ enhanced Grignard reaction

A solution of carbonyl compound in dry DCM (2.0 – 5.0 mL) was cooled to -30 °C. $Al(OTf)_3$ (1.0 eq.) was added and the reaction mixture stirred at -30 °C for 30 min. under Ar. Grignard reagent in diethyl ether (3.0 M, 2.0 eq.) was subsequently added and the reaction mixture allowed to warm to rt. while being stirred. Once the reaction was deemed complete (TLC), the reaction mixture was neutralized with aq. NH_4Cl solution and the product extracted into EtOAc (3 x 50.0 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification was done *via* PLC.

9.21.1 4-Methoxy-α-phenylstyrene (**789**)[23]

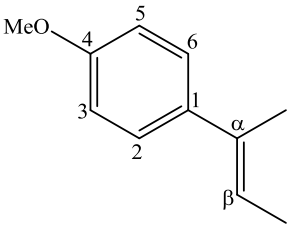
4'-Methoxyacetophenone (**785**) (0.21 g, 1.4 mmol), $Al(OTf)_3$ (0.63 g, 1.3 mmol, 0.9 eq.), DCM (5.0 mL), phenylmagnesium bromide (0.9 mL, 3.0 M, 1.9 eq.)



Yielded 4-methoxy-α-phenylstyrene (**789**) as a white solid (0.23 g, 71%): R_f : 0.54 (H:EtOAc 9:1); Mp. 60 – 63 °C; ^{1}H NMR (600 MHz, $CDCl_3$, plate 70a): δ 7.37 – 7.31 (5H, m, Ar-H), 7.29 (2H, d, *J* = 8.8 Hz, H-2 and H-6), 6.88 (2H, d, *J* = 8.8 Hz, H-3 and H-5), 5.41 (1H, d, *J* = 1.2 Hz, H-β), 5.37 (1H, d, *J* = 1.2 Hz, H-β), 3.82 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 70b): δ 159.37 (C-4), 149.55 (C-α), 141.84 (C-1'), 133.99 (C-1), 129.43 (C-2 and C-6), 128.35 (Ar-C), 128.17 (Ar-C), 127.70 (C-4'), 113.56 (C-3 and C-5), 112.97 (C-β), 55.29 (-OMe); *m/z* (EI) 210 (M^+, 100%).

9.21.2 (*E*)-4-Methoxy-α,β-dimethylstyrene (**790**)[24]

4'-Methoxyacetophenone (**785**) (0.21 g, 1.4 mmol), $Al(OTf)_3$ (0.67 g, 1.4 mmol, 1.0 eq.), DCM (5.0 mL), ethylmagnesium bromide (0.9 mL, 3.0 M, 1.9 eq.)

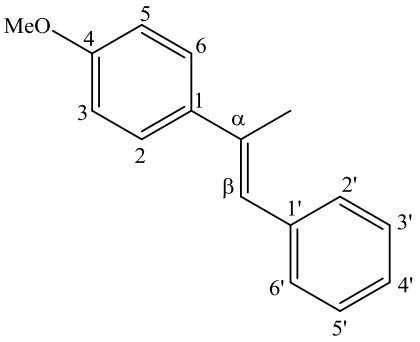


Yielded (*E*)-4-methoxy-α,β-dimethylstyrene (**790**) as a yellow oil (0.121 g, 53%): R_f : 0.74 (H:A 7:3); ^{1}H NMR (600 MHz, $CDCl_3$, plate 71a): δ 7.33 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 6.87 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 5.81 (1H, qq, *J* = 6.8, 1.3 Hz, H-β), 3.82 (3H, s, -OMe), 2.04 – 2.02 (3H, m, α-CH_3), 1.82 – 1.80 (3H, m, β-

C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, plate 71b): δ 158.44 (C-4), 136.75 (C-1), 134.93 (C-α), 126.61 (C-2 and C-6), 120.95 (C-β), 113.55 (C-3 and C-5), 55.34 (-O<u>Me</u>), 15.63 (α-<u>C</u>H$_3$), 14.40 (β-<u>C</u>H$_3$); *m/z* (EI) 162 (M^+, 100%).

<u>9.21.3 (*E*)-4-Methoxy-α-methyl-β-phenylstyrene (**791**)</u>[25]

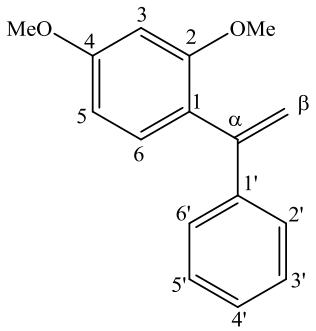
4'-Methoxyacetophenone (**785**) (0.20 g, 1.3 mmol), $Al(OTf)_3$ (0.67 g, 1.4 mmol, 1.1 eq.), DCM (3.0 mL), benzylmagnesium bromide (0.9 mL, 3.0 M, 2.0 eq.)



Yielded (*E*)-4-methoxy-α-methyl-β-phenylstyrene (**791**) as a light yellow solid (0.21 g, 67%): R_f : 0.56 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 72a): δ 7.52 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 7.40 – 7.36 (4H, m, Ar-H), 7.26 – 7.22 (1H, m, Ar-H), 6.94 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 6.85 – 6.83 (1H, m, H-β), 3.81 (3H, s, -O<u>Me</u>), 2.24 (3H, d, *J* = 1.3 Hz, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 72b): δ 160.22 (C-4), 139.55 (C-1'), 137.57 (C-α), 136.99 (C-1), 130.08 (Ar-C), 129.11 (Ar-C), 127.95 (C-2 and C-6), 127.23 (C-4'), 126.88 (C-β), 114.62 (C-3 and C-5), 55.60 (-O<u>Me</u>), 17.68 (-<u>C</u>H$_3$); *m/z* (EI) 224 (M^+, 100%).

<u>9.21.4 2,4-Dimethoxy-α-phenylstyrene (**792**)</u>[26]

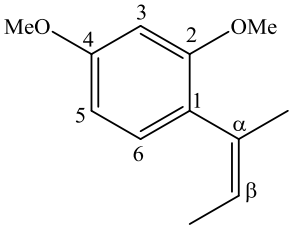
2',4'-Dimethoxyacetophenone (**786**) (0.21 g, 1.2 mmol), $Al(OTf)_3$ (0.52 g, 1.1 mmol, 0.9 eq.), DCM (3.0 mL), phenylmagnesium bromide (0.7 mL, 3.0 M, 1.8 eq.)



Yielded 2,4-dimethoxy-α-phenylstyrene (**792**) as a yellow oil (0.172 g, 62%): R_f : 0.34 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 73a): δ 7.28 – 7.21 (5H, m, Ar-H), 7.10 (1H, d, *J* = 8.1 Hz, H-6), 6.57 (1H, d, *J* = 2.4 Hz, H-3), 6.56 (1H, dd, *J* = 8.1, 2.4 Hz, H-5), 5.62 (1H, d, *J* = 1.6 Hz, H-β), 5.21 (1H, d, *J* = 1.6 Hz, H-β), 3.83 (3H, s, -O<u>Me</u>), 3.59 (3H, s, -O<u>Me</u>); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 73b): δ 162.00 (C-4), 159.25 (C-2), 148.27 (C-α), 142.70 (C-1'), 132.39 (C-6), 128.89 (Ar-C), 128.03 (C-4'), 127.28 (Ar-C), 124.44 (C-1), 115.13 (C-β), 105.55 (C-5), 99.73 (C-3), 55.83 (-O<u>Me</u>), 55.75 (-O<u>Me</u>); *m/z* (EI) 240 (M^+, 80%).

9.21.5 (*Z*)-2,4-Dimethoxy-α,β-dimethylstyrene (**793**)

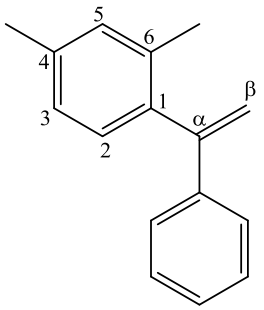
2',4'-Dimethoxyacetophenone (**786**) (0.23 g, 1.2 mmol), $Al(OTf)_3$ (0.53 g, 1.1 mmol, 0.9 eq.), DCM (5.0 mL), ethylmagnesium bromide (0.7 mL, 3.0 M, 1.7 eq.)



Yielded *(Z)-2,4-dimethoxy-α,β-dimethylstyrene* (**793**) as a colourless oil (0.11 g, 46%): R_f : 0.61 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 74a): δ 7.06 (1H, d, *J* = 8.2 Hz, H-6), 6.48 (1H, d, *J* = 2.4 Hz, H-3), 6.46 (1H, dd, *J* = 8.2, 2.4 Hz, H-5), 5.55 (1H, qq, *J* = 6.7, 1.3 Hz, H-β), 3.83 (6H, s, -O<u>Me</u>), 2.00 – 1.98 (3H, m, α-C<u>H</u>$_3$), 1.80 – 1.78 (3H, m, β-C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, plate 74b): δ 159.75 (C-4), 157.60 (C-2), 135.32 (C-α), 129.98 (C-6), 128.06 (C-1), 123.46 (C-β), 103.92 (C-5), 98.67 (C-3), 55.44 (-O<u>Me</u>), 16.98 (α-<u>C</u>H$_3$), 14.03 (β-<u>C</u>H$_3$); HR-MS (ES) *m/z* 192.1147 (M^+), $C_{12}H_{16}O_2^+$ requires 192.1229, found 192.1147 [M^+].

9.21.6 2,4-Dimethyl-α-phenylstyrene (**794**)[27]

2',4'-Dimethylacetophenone (**786**) (0.2 mL, 1 mmol), $Al(OTf)_3$ (0.65 g, 1.4 mmol, 1.0 eq.), DCM (3.0 mL), phenylmagnesium bromide (0.9 mL, 3.0 M, 2.0 eq.)

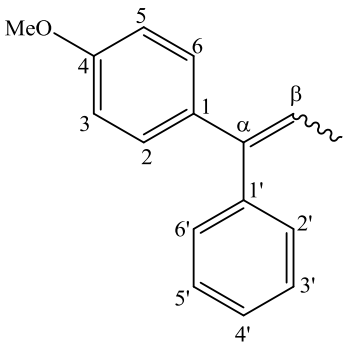


Yielded 2,4-dimethyl-α-phenylstyrene (**794**) as a colourless oil (0.07 g, 24%): R_f : 0.59 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$, plate 75a): δ 7.28 – 7.24 (5H, m, Ar-H), 7.12 (1H, d, *J* = 7.6 Hz, H-2), 7.04 – 7.00 (2H, m, H-3 and H-5), 5.75 – 5.73 (1H, m, H-β), 5.19 – 5.17 (1H, m, H-β), 2.35 (3H, s, -C<u>H</u>$_3$), 2.01 (3H, s, -C<u>H</u>$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, plate 75b): δ 149.52 (4°-C), 140.97 (4°-C), 138.89 (4°-C), 137.28 (C-4/6), 136.10 (C-4/6), 131.03 (C-3/5), 130.12 (C-2), 128.43 (Ar-C), 127.63 (Ar-C), 126.65 (Ar-C), 126.46 (C-3/5), 114.93 (C-β), 21.26 (-<u>C</u>H$_3$), 20.20 (-<u>C</u>H$_3$); *m/z* (EI) 208 (M^+, 31%).

9.21.7 4-Methoxy-α-phenyl-β-methylstyrene (**804**)[28]

4'-Methoxypropiophenone (**800**) (0.2 mL, 1.1 mmol), $Al(OTf)_3$ (0.58 g, 1.2 mmol, 1.1 eq.), DCM (5.0 mL), phenylmagnesium bromide (0.8 mL, 3.0 M, 2.1 eq.)

Yielded a mixture of the *E*- and *Z*-isomers of 4-methoxy-α-phenyl-β-methylstyrene (**804**) as a white amorphous solid (0.28 g, 97%): R_f: 0.72 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 76a): δ 7.42 – 7.38 (2H, m, H-3' and H-5' (*E*)), 7.34 – 7.29 (1H, m, H-4' (*E*)), 7.28 – 7.24 (2H, m, Ar-H (*Z*)), 7.23 – 7.19 (3H, m, Ar-H (*Z*)), 7.17 – 7.15 (2H, m, H-2' and H-6' (*E*)), 7.12 (2H, d, *J* = 8.8 Hz, H-2 and H-6 (*E*)), 7.09 (2H, d, *J* = 8.7 Hz, H-2 and H-6 (*Z*)), 6.96 (2H, d, *J* = 8.8 Hz, H-3 and H-5 (*Z*)), 6.83 (2H, d, *J* = 8.7 Hz, H-3 and H-5 (*E*)), 6.14 (1H, q, *J* = 7.0 Hz, H-β (*Z*)), 6.10 (1H, q, *J* = 7.0 Hz, H-β (*E*)), 3.81 (3H, s, -OMe (*Z*)), 3.76 (3H, s, -OMe (*E*)), 1.74 (3H, d, *J* = 7.0 Hz, -CH_3 (*Z*)), 1.70 (3H, d, *J* = 7.0 Hz, -CH_3 (*E*)); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 76b): δ 159.87 (C-4 (*E*/*Z*)), 159.77 (C-4 (*E*/*Z*)), 144.33 (C-1' (*Z*)), 143.21 (C-α (*E*/*Z*)), 143.05 (C-α (*E*/*Z*)), 141.30 (C-1' (*E*)), 136.40 (C-1 (*E*)), 133.00 (C-1 (*Z*)), 132.01 (Ar-C), 130.82 (Ar-C), 129.19 (Ar-C), 129.08 (Ar-C), 129.02 (Ar-C), 128.10 (Ar-C), 127.84 (Ar-C), 127.67 (Ar-C), 124.32 (C-β (*E*/*Z*)), 122.74 (C-β (*E*/*Z*)), 114.58 (C-3 and C-5 (*E*/*Z*)), 114.43 (C-3 and C-5 (*E*/*Z*)), 55.62 (-OMe (*E* and *Z*)), 16.07 (-CH$_3$ (*E*/*Z*)), 15.92 (-CH$_3$ (*E*/*Z*)); HR-MS (AP) *m/z* 225.1280 [M^+], $C_{16}H_{17}O^+$ requires 225.1279, found 225.1280.



9.21.8 Neoflav-3-ene (**741**)

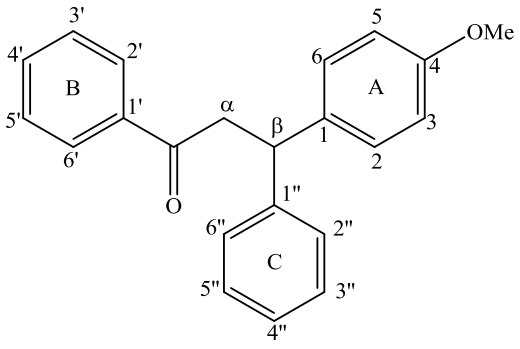
Chromanone (**802**) (0.20 g, 1.4 mmol), $Al(OTf)_3$ (0.64 g, 1.4 mmol, 1.0 eq.), phenylmagnesium bromide (0.9 mL, 3.0 M 2.0 eq.).

Yielded neoflav-3-ene (**741**) as a yellow oil (0.15 g, 55%); (*cf.* par. 9.20.1 for data).

9.21.9 β-Phenyl-4-methoxydihydrochalcone (**805**)[29]

Chalcone (**803**) (0.20 g, 0.90 mmol), $Al(OTf)_3$ (0.46 g, 0.97 mmol, 1.0 eq.), DCM (3.0 mL), 4-methoxyphenylmagnesium bromide (0.6 mL, 3.0 M, 1.9 eq.)

Yielded β-phenyl-4-methoxydihydrochalcone (**805**) as a light yellow solid (0.09 g, 29%): R_f: 0.49 (H:A 7:3); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 77a): δ 8.05 – 8.02 (2H, m, H-2' and H-6'), 7.60 – 7.57 (1H, m, H-4'), 7.50 – 7.46 (2H, m, H-3' and H-5'), 7.39 – 7.36 (2H, m, H-2" and H-6"),



7.29 (2H, d, *J* = 8.8, H-2 and H-6), 7.27 – 7.24 (2H, m, H-3" and H-5"), 7.17 – 7.12 (1H, m, H-4"), 6.82 (2H, d, *J* = 8.8, H-3 and H-5), 4.76 (1H, t, *J* = 7.3 Hz, H-β), 3.84 (2H, d, *J* = 7.3 Hz, H-α), 3.71 (3H, s, -OMe); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 77b): δ 198.39 (C=O), 159.07 (C-4), 146.16 (C-1"), 138.27 (C-1'), 137.68 (C-1), 133.81 (C-4'), 129.71 (Ar-C), 129.49 (Ar-C), 129.23 (Ar-C), 128.92 (Ar-C), 128.70 (Ar-C), 126.90 (C-4"), 114.60 (C-3 and C-5), 55.45 (-OMe), 46.28 (C-β), 45.02 (C-α); HR-MS (ES) *m/z* 339.1348 $[M + Na]^+$, $C_{22}H_{20}O_2Na^+$ requires 339.1361, found 339.1348.

9.22 Control reactions for $Al(OTf)_3$ enhanced Grignard reaction

A solution of carbonyl compound in dry DCM (2.0 – 5.0 mL) and the Grignard reagent in diethyl ether (3.0 M, 2.0 eq.) was stirred under Ar at rt. with the reaction time the same as to achieve the completion of the corresponding $Al(OTf)_3$-enhanced reaction. The reaction mixture was neutralized with aq. NH_4Cl solution and the product extracted into EtOAc (3 x 50.0 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification was done *via* PLC.

9.22.1 4-Methoxy-α-methyl-β-phenylstyrene (**791**)

4'-Methoxyacetophenone (**785**) (0.21 g, 1.4 mmol), benzylmagnesium bromide (0.9 mL, 3.0 M, 1.9 eq.)

Yielded 4-methoxy-α-methyl-β-phenylstyrene (**791**) as a light yellow solid (0.04 g, 12%); (*cf.* par. 9.21.3 for data).

9.22.2 β-Phenyl-4'-methoxychalcone (**805**)

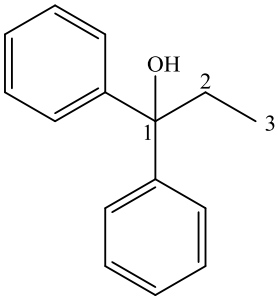
Chalcone (**803**) (0.21 g, 0.98 mmol), 4-methoxyphenylmagnesium bromide (0.6 mL, 3.0 M, 1.8 eq.)

Yielded β-phenyl-4'-methoxychalcone (**805**) as a *light yellow solid* (0.06 g, 21%); (*cf.* par. 9.21.9 for data).

9.22.3 1,1-Diphenylpropanol (**756**)[25]

Propiophenone (**799**) (0.20 g, 1.5 mmol), DCM (5.0 mL), phenylmagnesium bromide (1.0 mL, 3.0 M, 2.0 eq.)

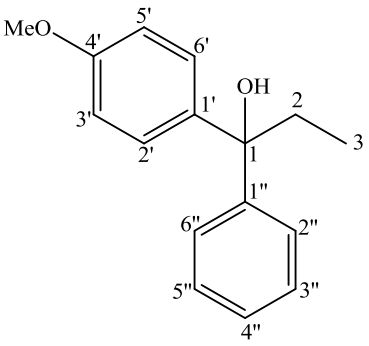
Yielded 1,1-diphenylpropanol (**756**) as a white solid (0.07 g, 22%): R_f: 0.49 (H:A 7:3); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 78a): δ 7.51 – 7.49 (4H, m, Ar-H), 7.29 – 7.26 (4H, m, Ar-H), 7.18 – 7.15 (2H, m, Ar-H), 4.37 (1H, s, -OH), 2.35 (2H, q, *J* = 7.3 Hz, H-2), 0.86 (3H, t, *J* = 7.3 Hz, H-3); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 78b): δ 149.20 (4°-C), 128.64 (Ar-C), 127.03 (Ar-C), 78.23 (4°-C), 35.05 (C-2), 8.56 (C-3); *m/z* (EI) 212 (M^+, 0.14%), 183 ($[M-CH_2CH_3]^+$, 100%).



9.22.4 1-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**806**)[30]

4'-Methoxypropiophenone (**800**) (0.2 mL, 1.1 mmol), DCM (5.0 mL), phenylmagnesium bromide (0.8 mL, 3.0 M, 2.1 eq.)

Yielded 1-(4-methoxyphenyl)-1-phenylpropan-1-ol (**806**) as a white oil (0.25 g, 85%): R_f: 0.35 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 79a): δ 7.49 (2H, dd, *J* = 8.3, 1.0 Hz, H-2" and H-6"), 7.41 (2H, d, *J* = 9.1 Hz, H-2' and H-6'), 7.30 – 7.26 (2H, m, H-3" and H-5"), 7.19 – 7.14 (1H, m, H-4"), 6.85 (2H, d, *J* = 9.1 Hz, H-3' and H-5'), 4.28 (1H, s, OH), 3.74 (3H, s, -OMe), 2.33 (2H, q, *J* = 7.3 Hz, H-2), 0.87 (1H, t, *J* = 7.3 Hz, H-3); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 79b): δ 158.91 (C-4'), 149.24 (C-1"), 141.15 (C-1'), 128.40 (C-3" and C-5"), 128.04 (C-2' and C-6'), 126.81 (C-2" and C-6"), 126.73 (C-4"), 113.75 (C-3' and C-5'), 77.76 (C-1), 55.29 (-OMe), 35.04 (C-2), 8.49 (C-3); *m/z* (EI) 242 (M^+, 3%).

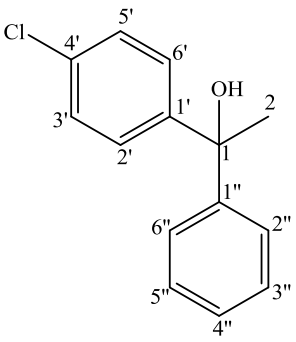


9.23 Control reaction for $Al(OTf)_3$ enhanced Grignard reaction in THF

A solution of carbonyl compound in dry THF (5.0 mL) and the Grignard reagent in diethyl ether (3.0 M, 2.0 eq.) was stirred under Ar at rt. with the reaction time the same as that necessary to achieve completion of the corresponding $Al(OTf)_3$ enhanced reaction. The reaction mixture was neutralized with aq. NH_4Cl solution and the product extracted into EtOAc (3 x 50.0 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification was done *via* PLC.

9.23.1 1-(4-Chlorophenyl)-1-phenylethan-1-ol (**795**)[31]

4'-Chloroacetophenone (**788**) (0.2 mL, 1.5 mmol), THF (5.0 mL), phenylmagnesium bromide (0.9 mL, 3.0 M 1.8 eq.)



Yielded 1-(4-chlorophenyl)-1-phenylethan-1-ol (**795**) as a colourless oil (0.15 g, 51%): R_f : 0.16 (H:EtOAc 9:1); ^{1}H NMR (600 MHz, $(CD_3)_2CO$, plate 80a): δ 7.51 – 7.47 (4H, m, Ar-H), 7.32 – 7.27 (4H, m, Ar-H), 7.21 – 7.18 (1H, m, H-4"), 4.82 (1H, s, -OH), 1.93 (3H, s, H-2); ^{13}C NMR (151 MHz, $(CD_3)_2CO$, plate 80b): δ 149.66 (C-1'/1"), 149.25 (C-1'/1"), 132.44 (C-4'), 128.73 (Ar-C), 128.58 (Ar-C), 128.51 (Ar-C), 127.31 (C-4"), 126.61 (C-2" and C-6"), 75.43 (C-1), 30.93 (C-2); HR-MS (ES) *m/z* 231.0582 $[M-H]^+$, $C_{16}H_{17}O^+$ requires 231.0577, found 231.0582. $[M + Na]^+$

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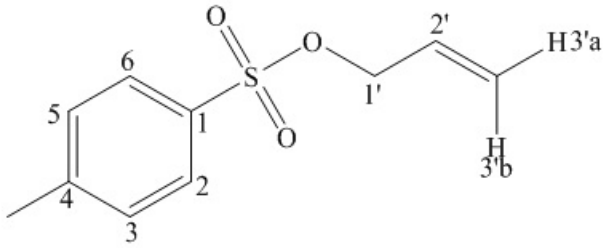
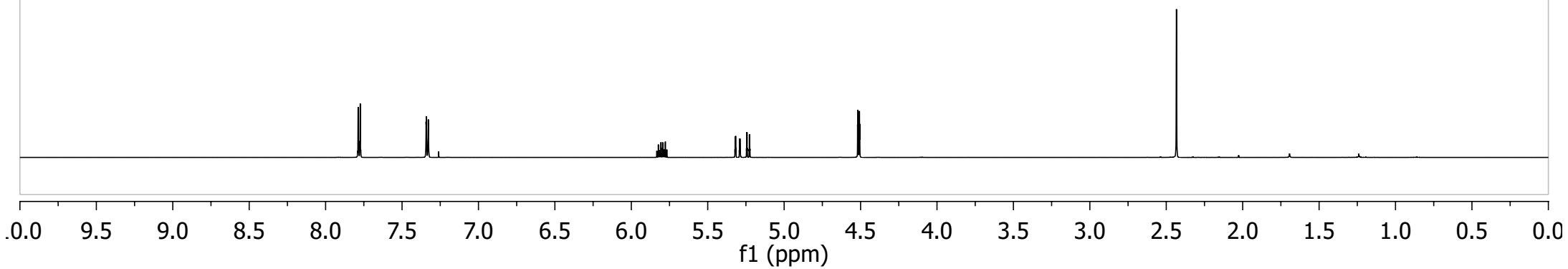
Plate 1a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Allyl-4-methylbenzenesulfonate (**570**)

δ 7.78 (2H, d, *J* = 8.4 Hz, H-2 and H-6), 7.34 (2H, d, *J* = 8.4 Hz, H-3 and H-5), 5.80 (1H, ddt, *J* = 17.1, 10.4, 5.9 Hz, H-2'), 5.30 (1H, ddt, *J* = 17.1, 1.3, 1.3 Hz, H-3'b), 5.24 (1H, ddt, *J* = 10.4, 1.3, 1.3 Hz, H-3'a), 4.51 (2H, ddd, *J* = 5.9, 1.3, 1.3 Hz, H-1'), 2.43 (3H, s, -C<u>H</u>$_3$)





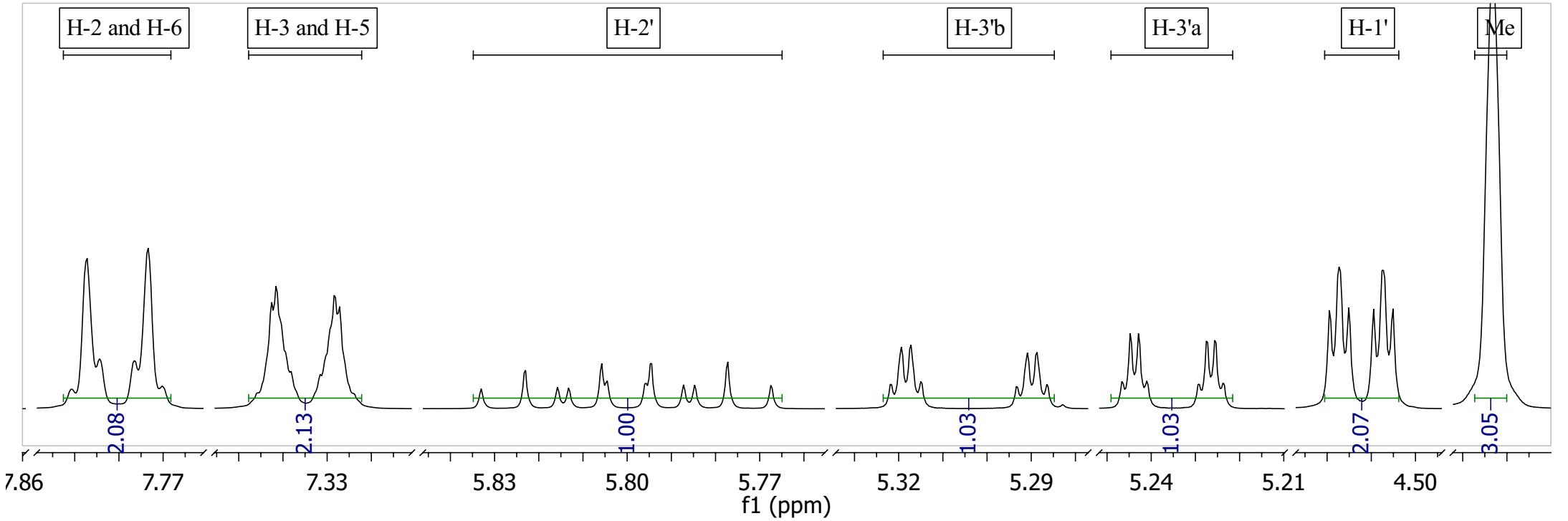
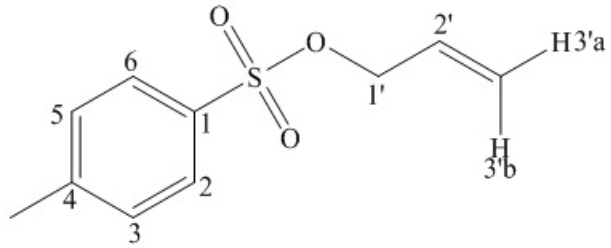


Plate 1b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Allyl-4-methylbenzenesulfonate (**570**)

δ 144.96 (C-4), 133.22 (C-1), 130.29 (C-2'), 129.95 (C-3 and C-5), 127.98 (C-2 and C-6), 120.36 (C-3'), 70.89 (C-1'), 21.71 (-CH_3)



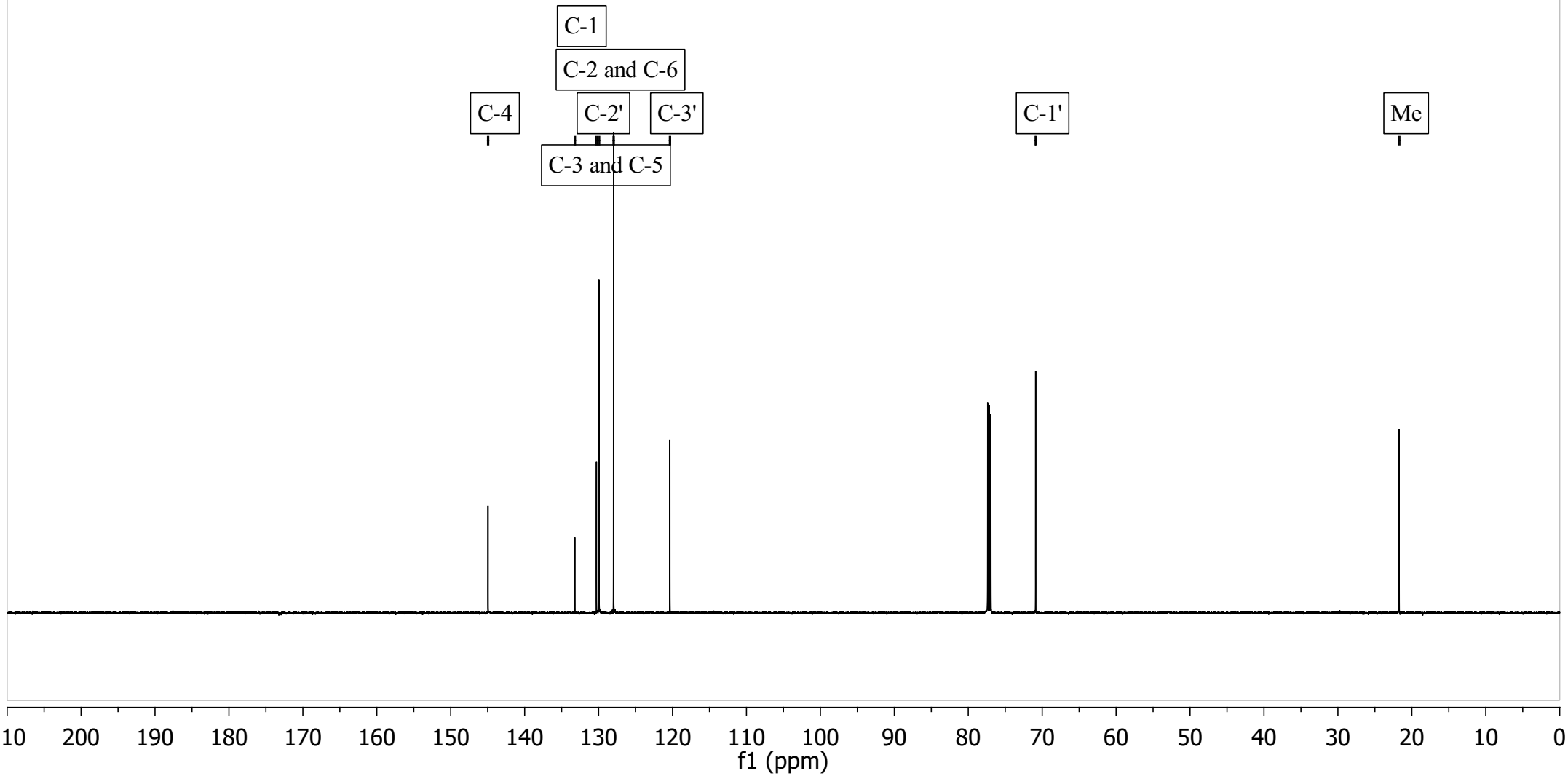


Plate 1c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 1-Allyl-4-methylbenzenesulfonate (**570**)

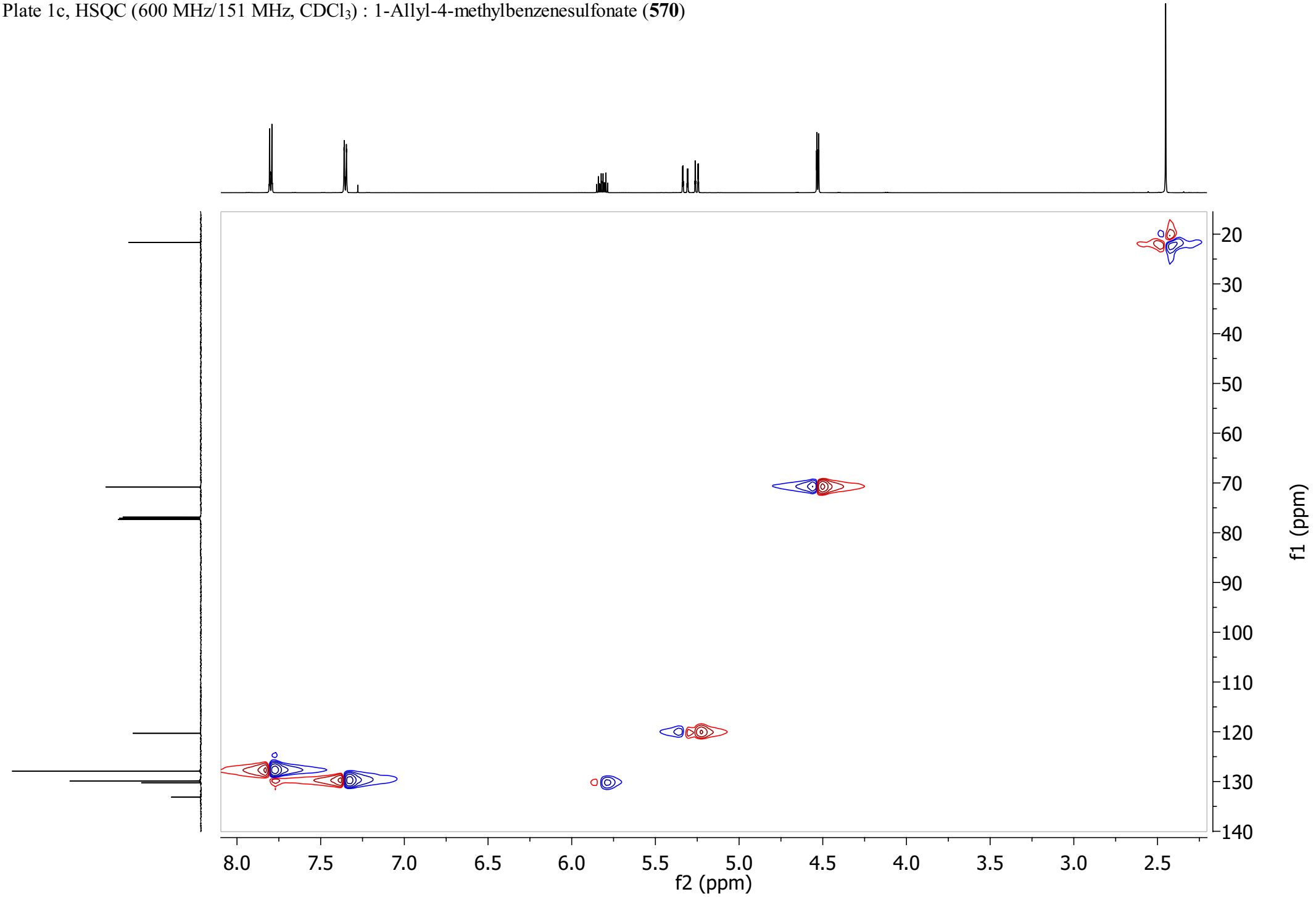


Plate 1d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 1-Allyl-4-methylbenzenesulfonate (**570**)

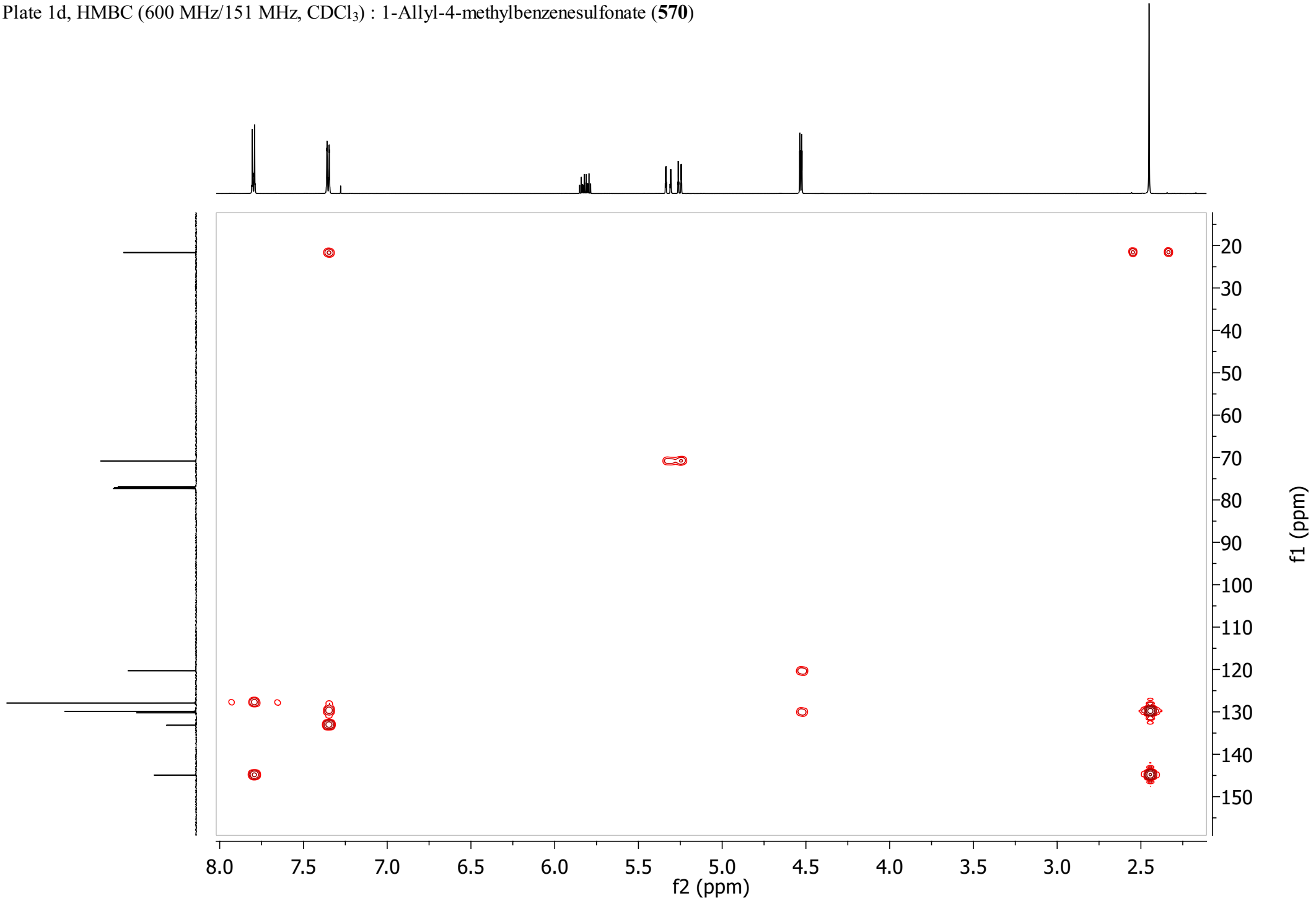


Plate 1e, DEPT (151 MHz, $CDCl_3$) : 1-Allyl-4-methylbenzenesulfonate (**570**)

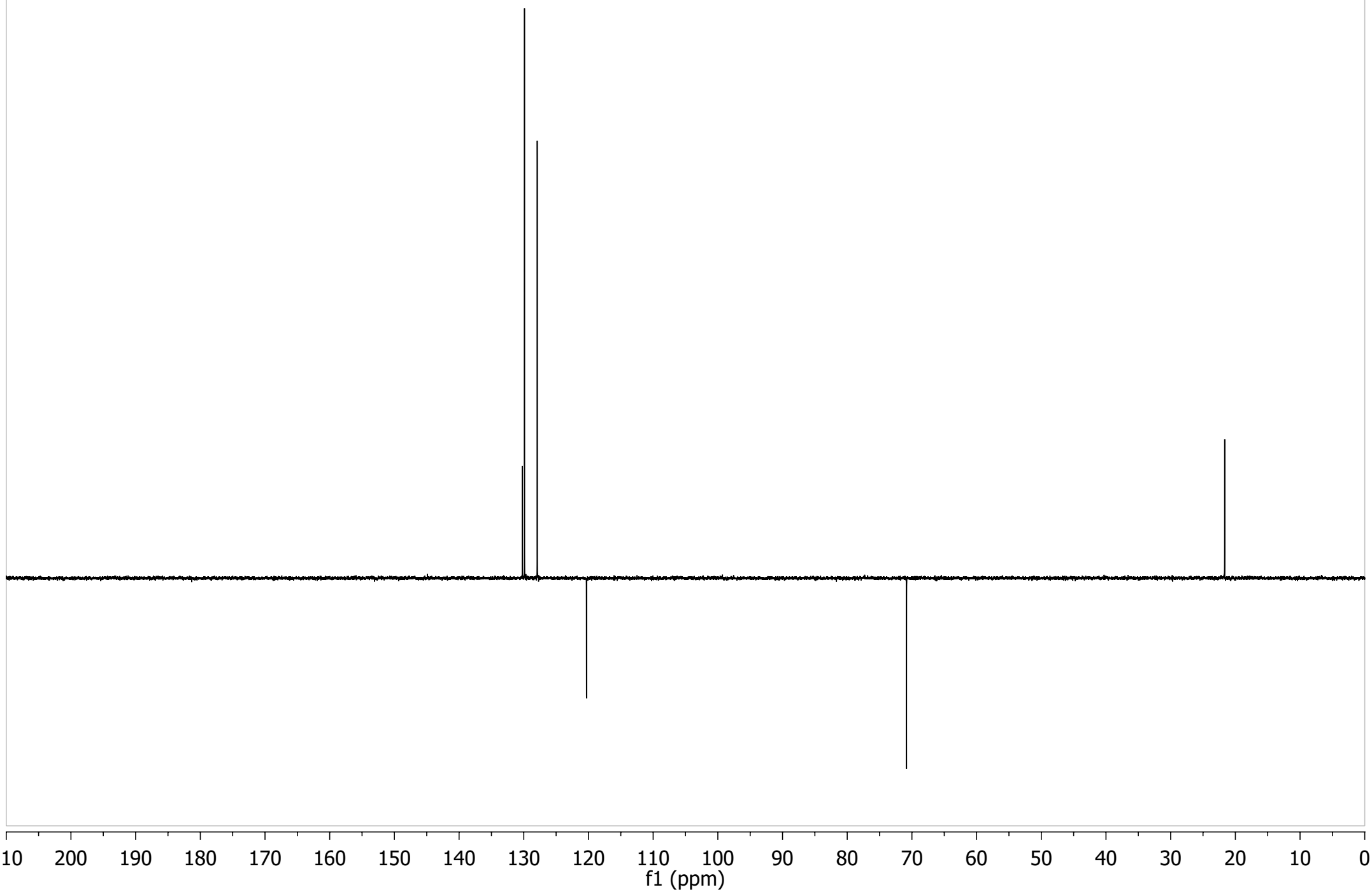
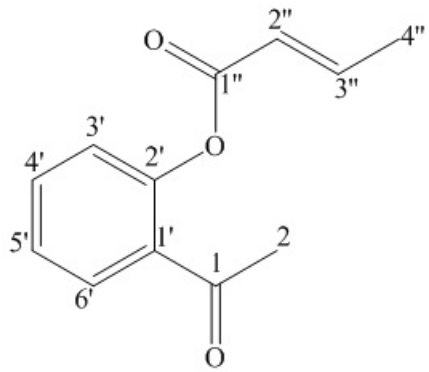
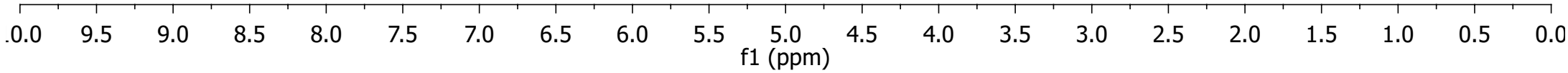


Plate 2a, ^{1}H NMR (600 MHz, $CDCl_3$) : 2'-Crotonoyloxyacetophenone (**778**)

δ 7.78 (1H, dd, *J* = 7.7, 1.7 Hz, H-6'), 7.50 (1H, ddd, *J* = 7.9, 7.7, 1.7 Hz, H-4'), 7.28 (1H, ddd, *J* = 7.7, 7.7, 1.1 Hz, H-5'), 7.20 (1H, dq, *J* = 15.5, 7.0 Hz, H-3''), 7.11 (1H, dd, *J* = 7.9, 1.1 Hz, H-3'), 6.07 (1H, dq, *J* = 15.5, 1.7 Hz, H-2''), 2.51 (3H, s, -C<u>H</u>$_3$), 1.96 (3H, dd, *J* = 7.0, 1.7 Hz, H-4'')





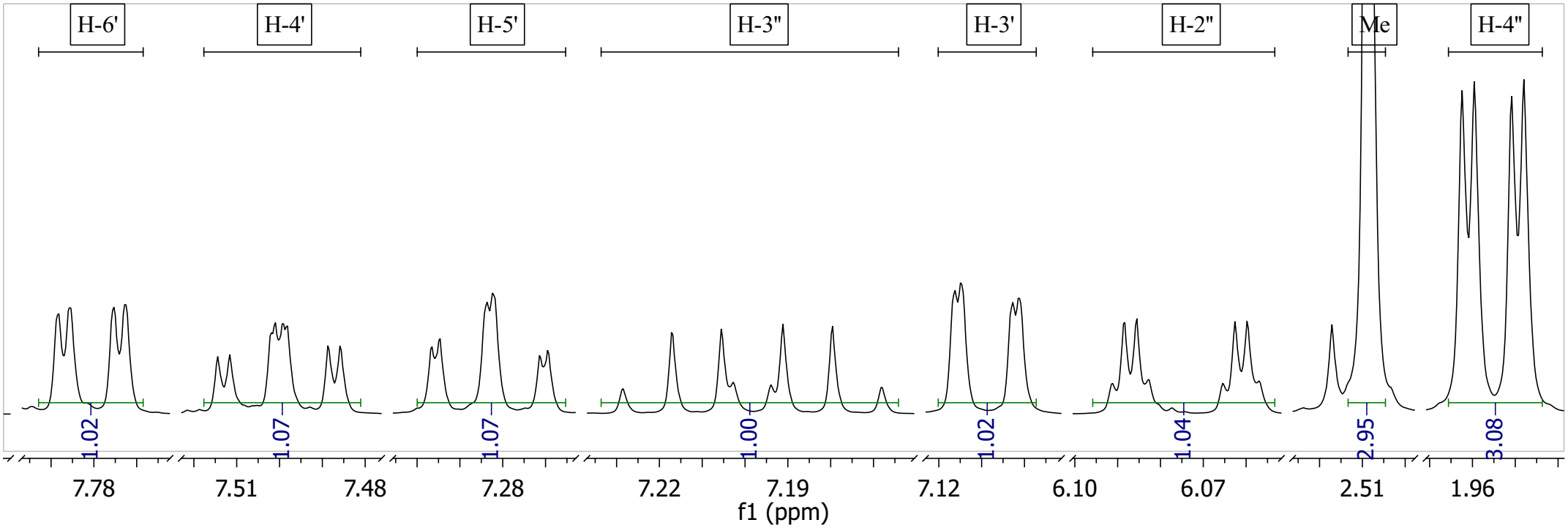
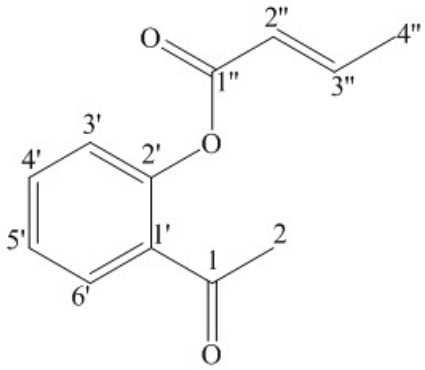


Plate 2b, ^{13}C NMR (151 MHz, $CDCl_3$) : 2'-Crotonoyloxyacetophenone (**778**)

δ 197.76 (C-1), 164.59 (C-1''), 149.10 (C-2'), 147.94 (C-3''), 133.29 (C-4'), 131.30 (C-1'), 130.08 (C-6'), 125.96 (C-5'), 123.82 (C-3'), 121.75 (C-2''), 29.79 (C-2), 18.34 (C-4'')



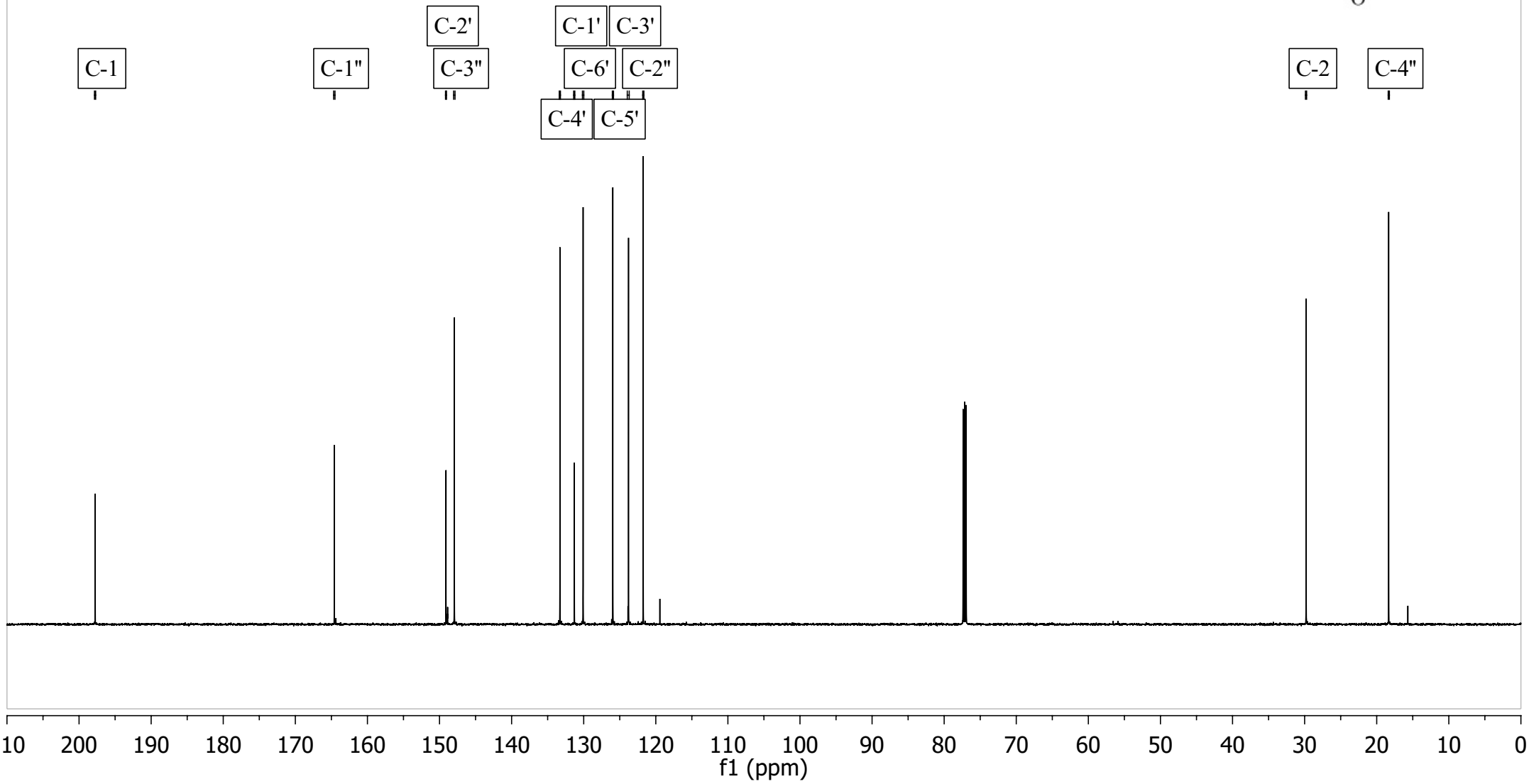


Plate 2c, HSQC (600/151 MHz, $CDCl_3$) : 2'-Crotonoyloxyacetophenone (**778**)

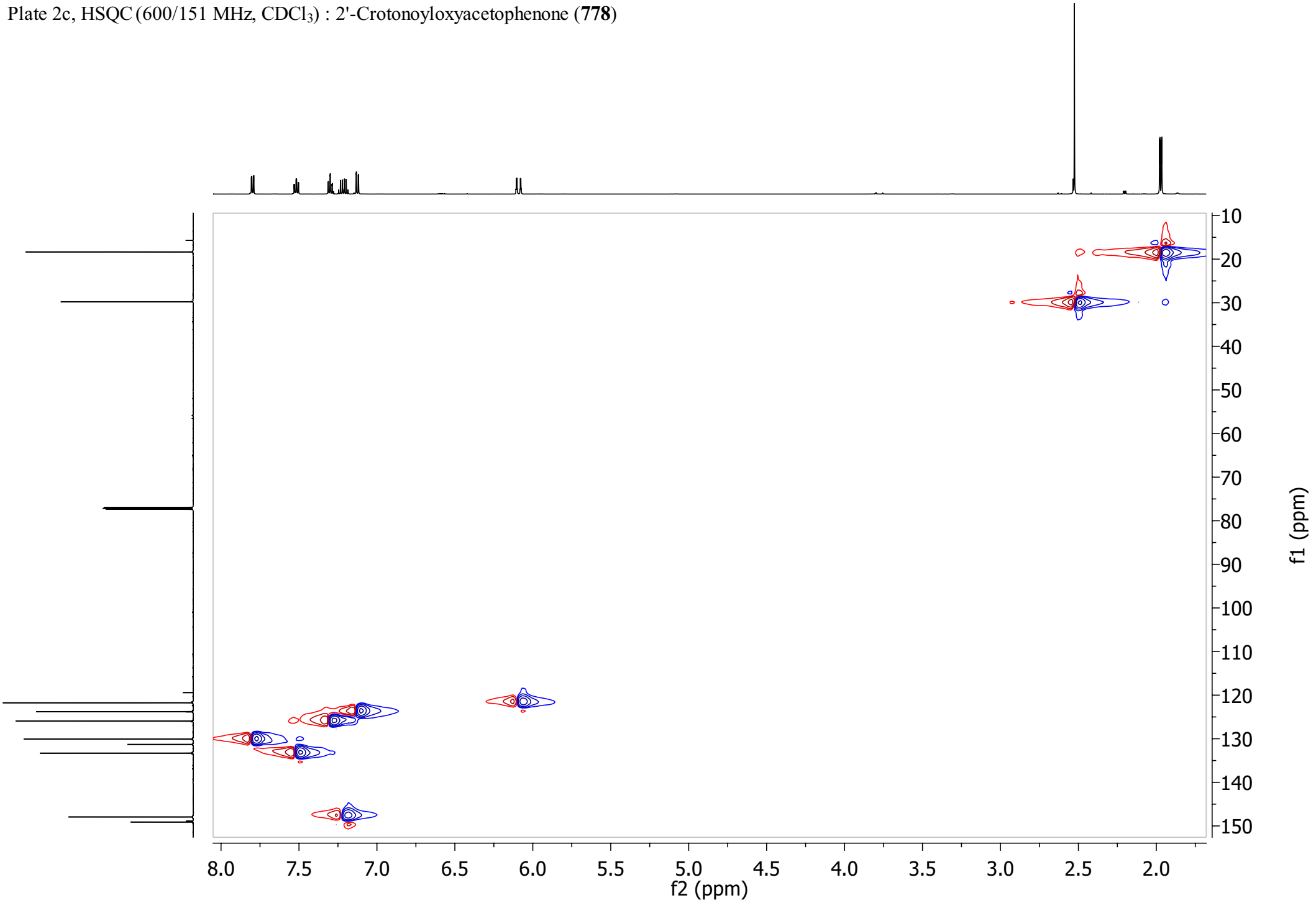


Plate 2d, HMBC (600/151 MHz, $CDCl_3$) : 2'-Crotonoyloxyacetophenone (**778**)

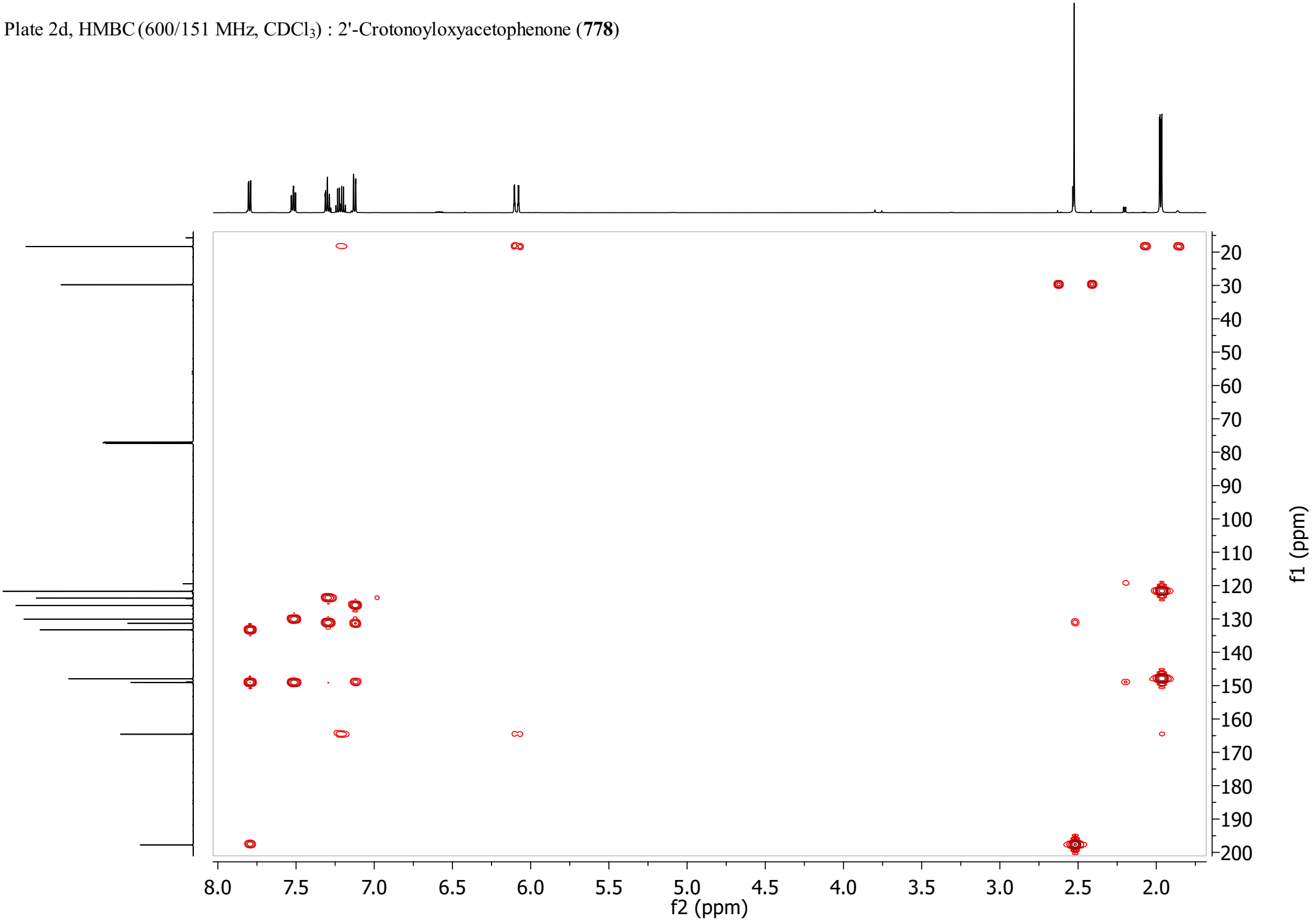


Plate 2e, DEPT (151 MHz, $CDCl_3$) : 2'-Crotonoyloxyacetophenone (**778**)

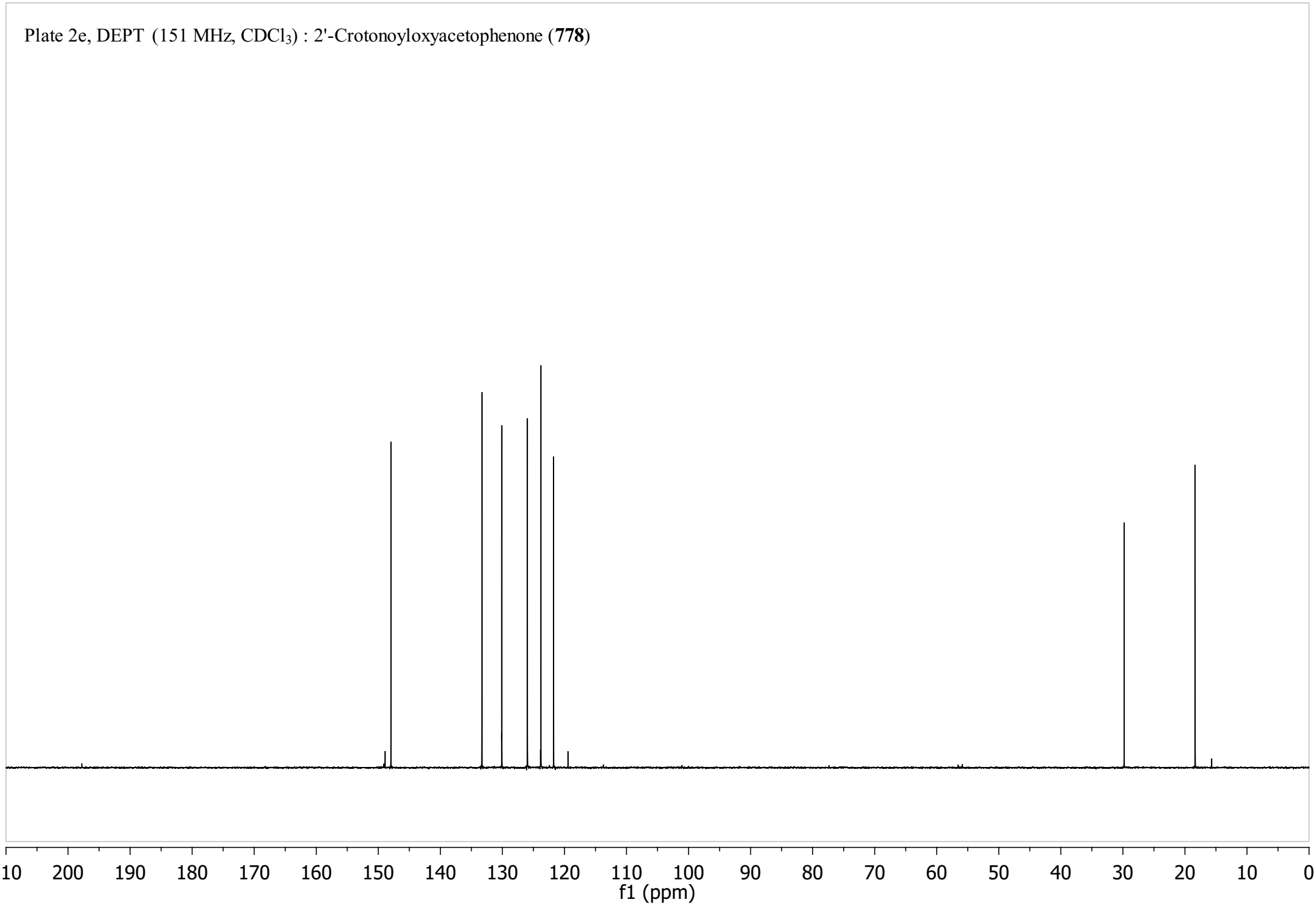
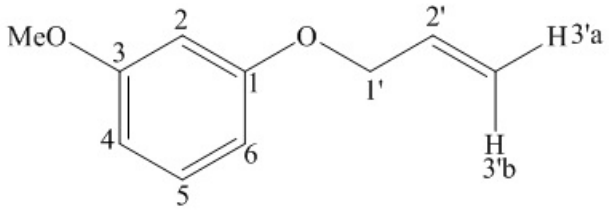
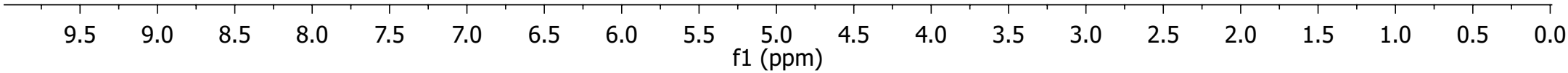


Plate 3a, ^{1}H NMR(600 MHz, $CDCl_3$) : 1-Allyloxy-3-methoxybenzene (**575**)

δ 7.20 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 6.56 – 6.54 (2H, m, H-4 and H-6), 6.53 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.08 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz, H-2'), 5.44 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, H-3'b), 5.32 (1H, ddt, *J* = 10.5, 1.4, 1.4 Hz, H-3'a), 4.55 (2H, ddd, *J* = 5.3, 1.4, 1,4 Hz, H-1'), 3.81 (3H, s, -OMe)





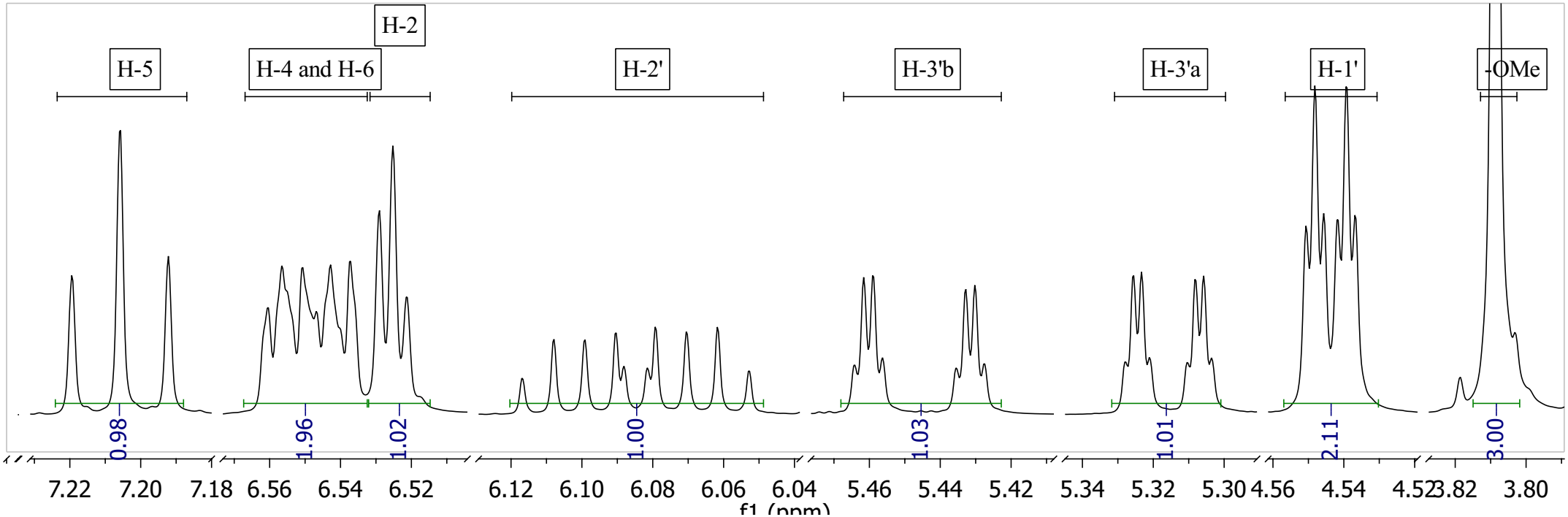
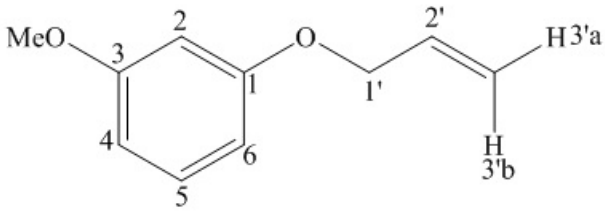


Plate 3b, ^{13}C NMR(151 MHz, $CDCl_3$) : 1-Allyloxy-3-methoxybenzene (**575**)

δ 160.91 (C-1/3), 159.94 (C-1/3), 133.36 (C-2'), 129.95 (C-5), 117.75 (C-3'), 106.95 (C-4/6), 106.51 (C-4/6), 101.31 (C-2), 68.89 (C-1'), 55.32 (-OMe)



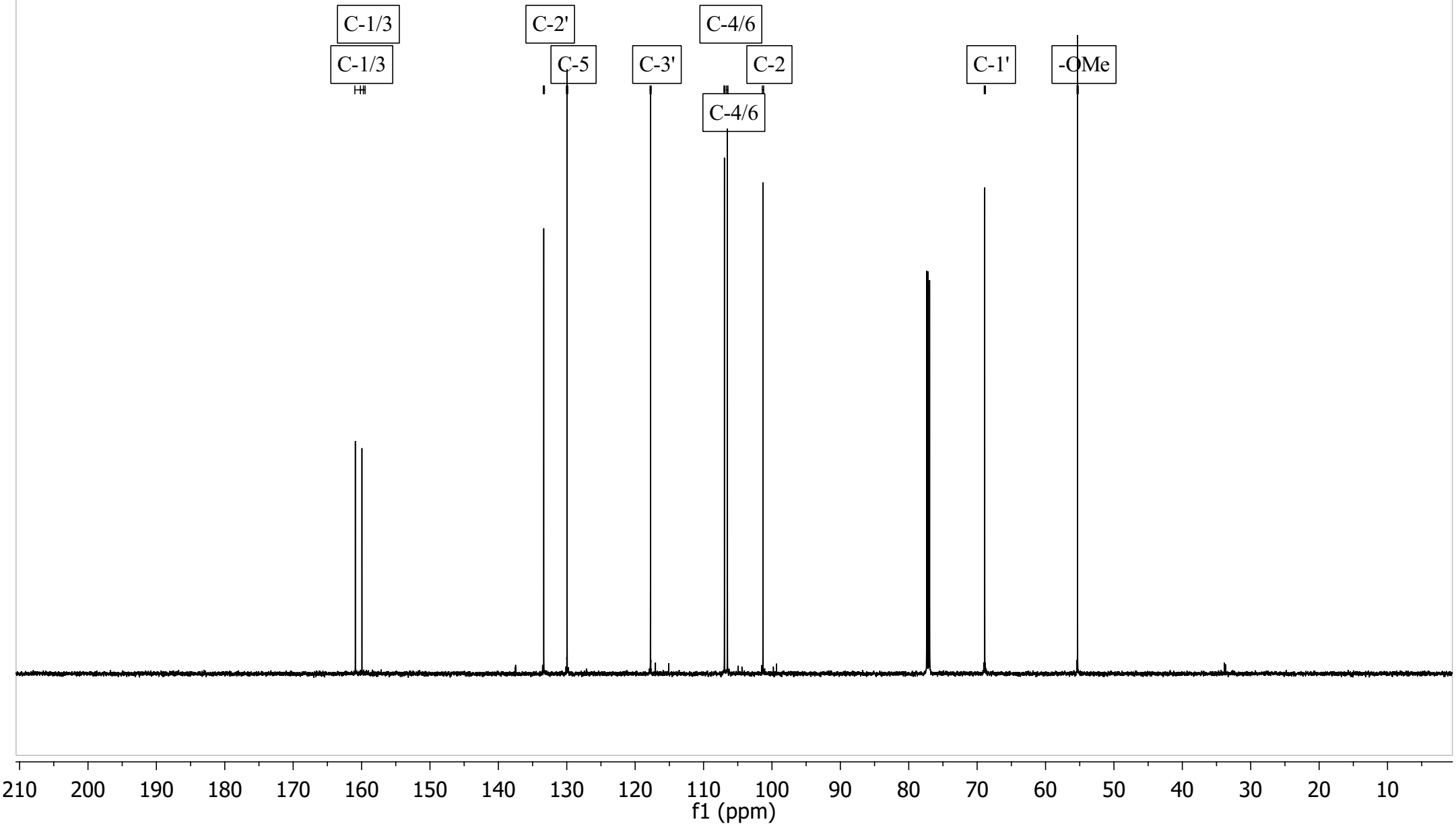


Plate 3c, HSQC(600/151 MHz, $CDCl_3$) : 1-Allyloxy-3-methoxybenzene (**575**)

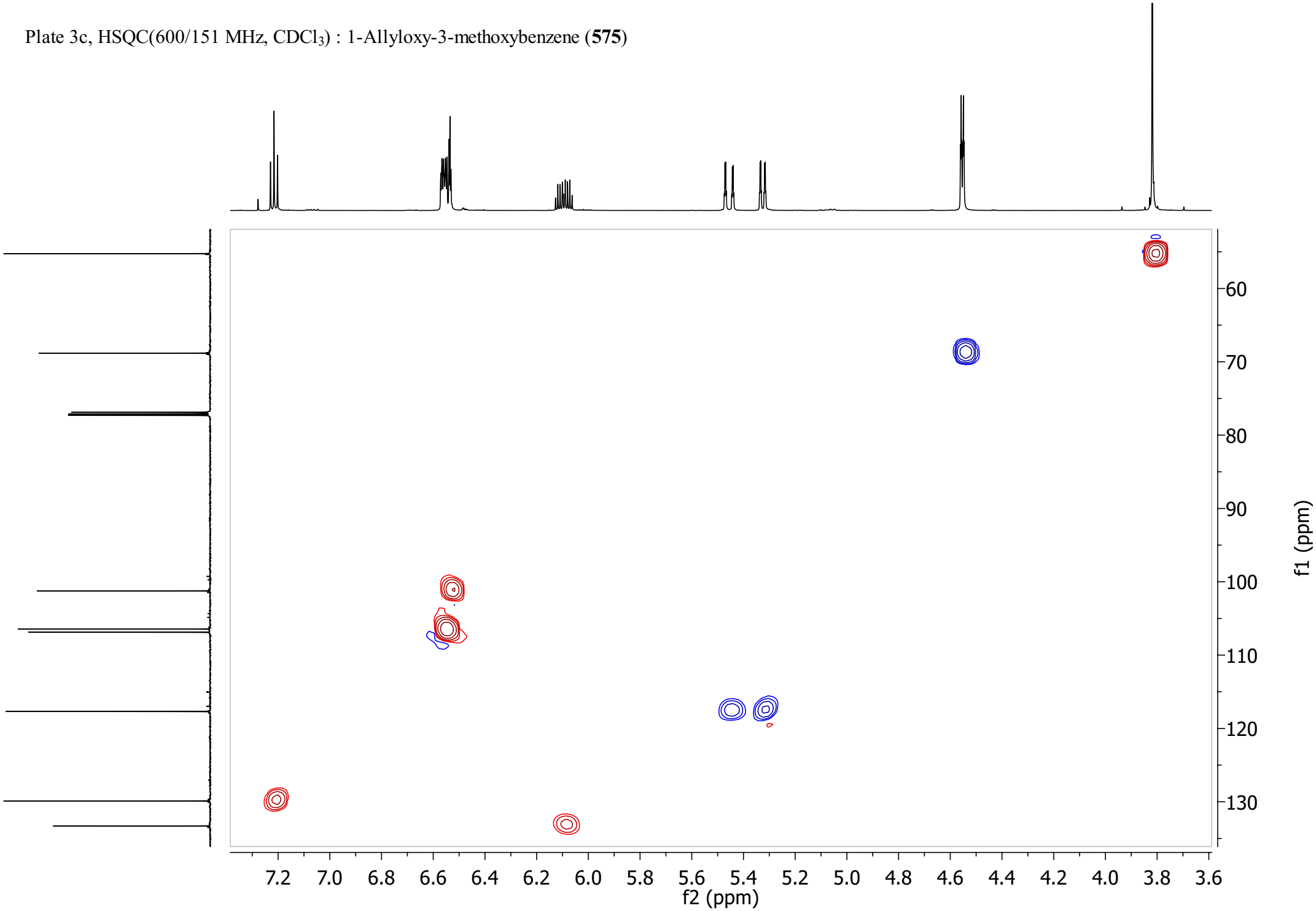


Plate 3d, HMBC(600/151 MHz, $CDCl_3$) : 1-Allyloxy-3-methoxybenzene (**575**)

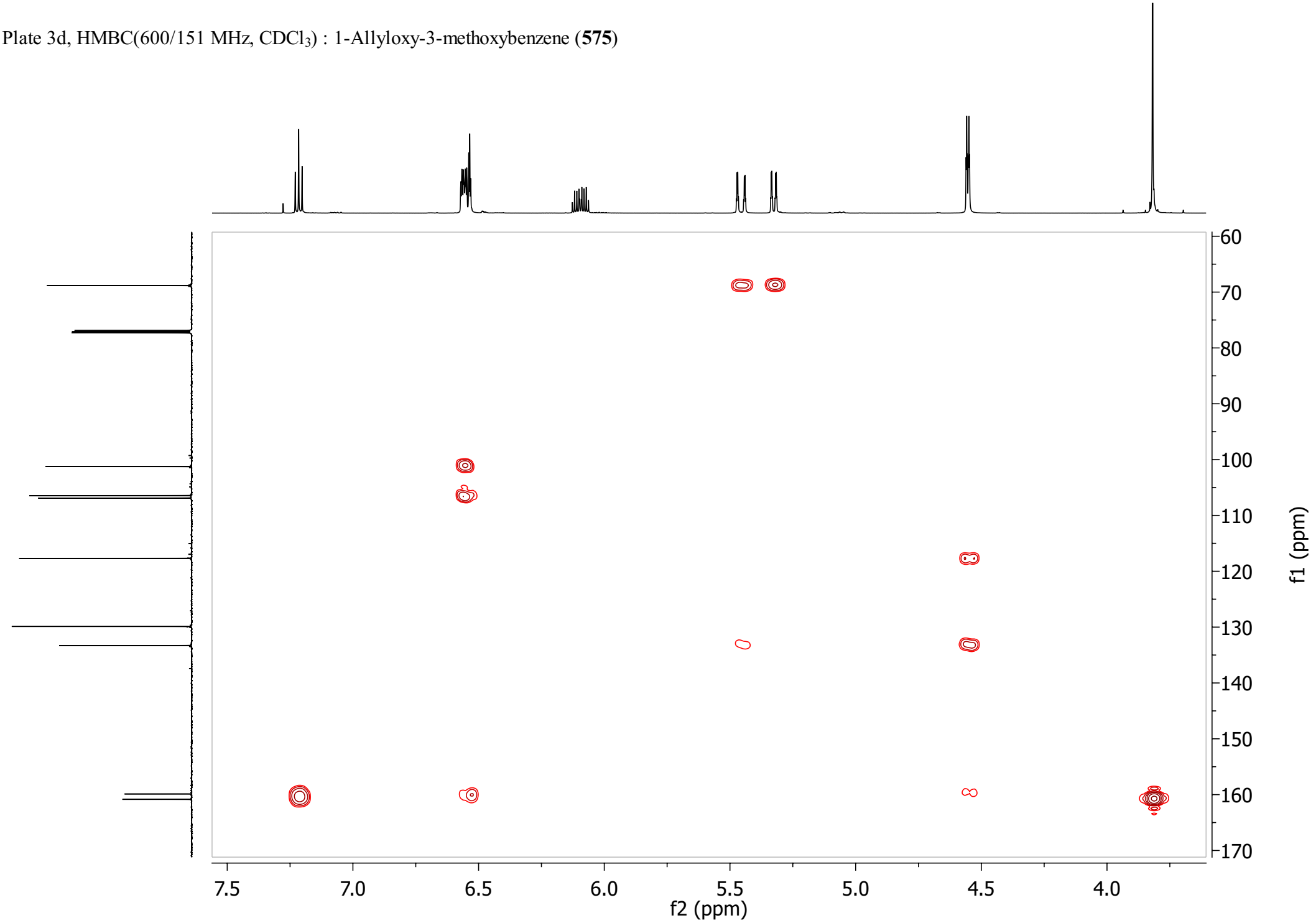


Plate 3e, DEPT (151 MHz, $CDCl_3$) : 1-Allyloxy-3-methoxybenzene (**575**)

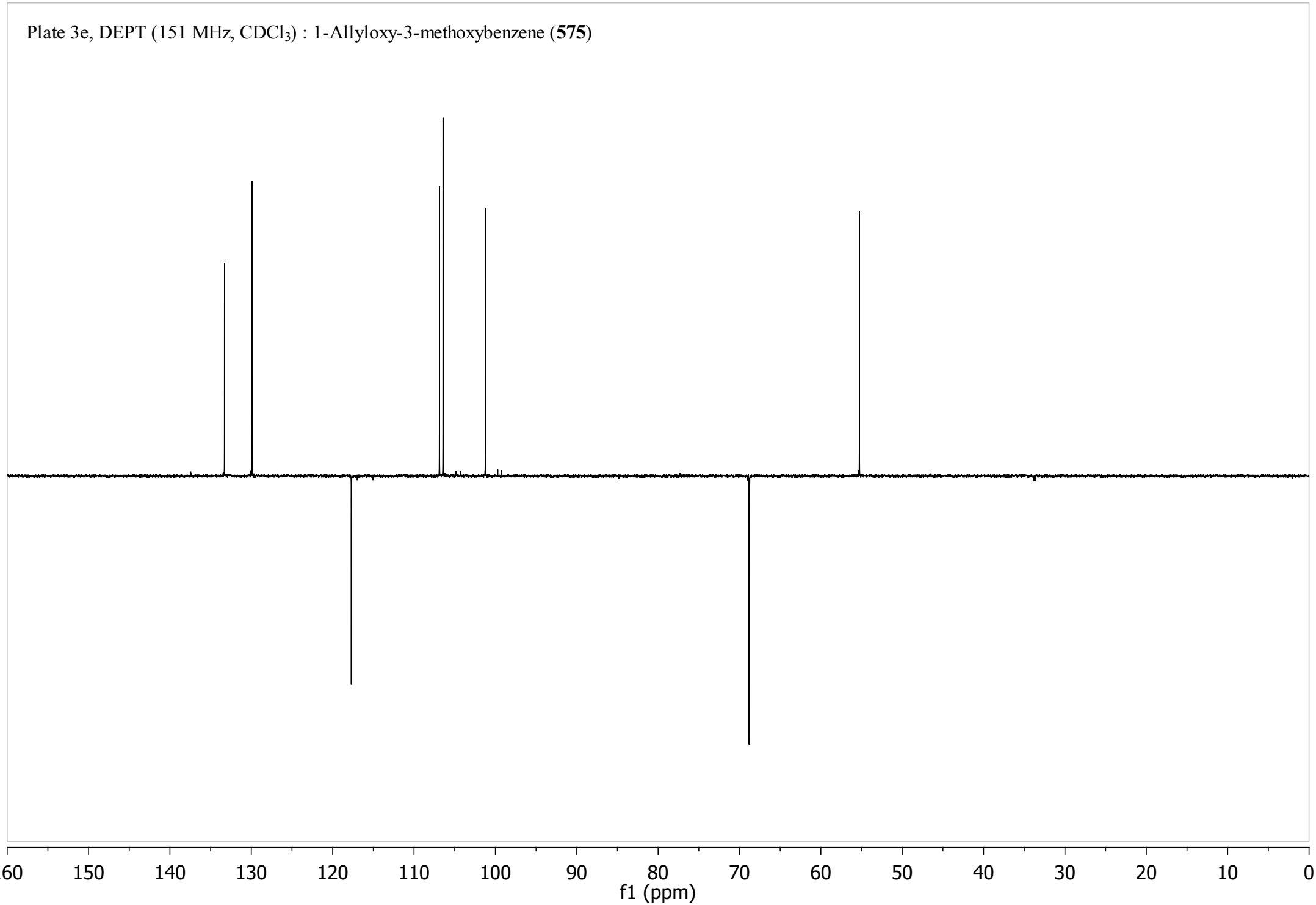
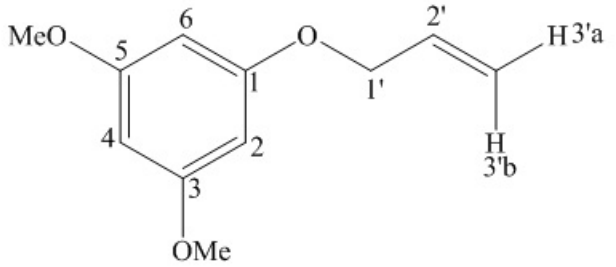


Plate 4a, ^{1}HNMR (600 MHz, $CDCl_3$) : 1-Allyloxy-3,5-dimethoxybenzene (**576**)

δ 6.11 (2H, d, *J* = 2.10 Hz, H-2 and H-6), 6.10 – 6.09 (1H, m, H-4), 6.05 (1H, ddt, *J* = 17.3, 10.4, 5.6 Hz, H-2'), 5.41 (1H, ddt, *J* = 17.3, 1.4, 1.4 Hz, H-3'b), 5.29 (1H, ddt, *J* = 10.4, 1.4, 1.4 Hz, H-3'a), 4.49 (2H, ddd, *J* = 5.6, 1.4, 1.4 Hz, H-1'), 3.77 (6H, s, -OMe)



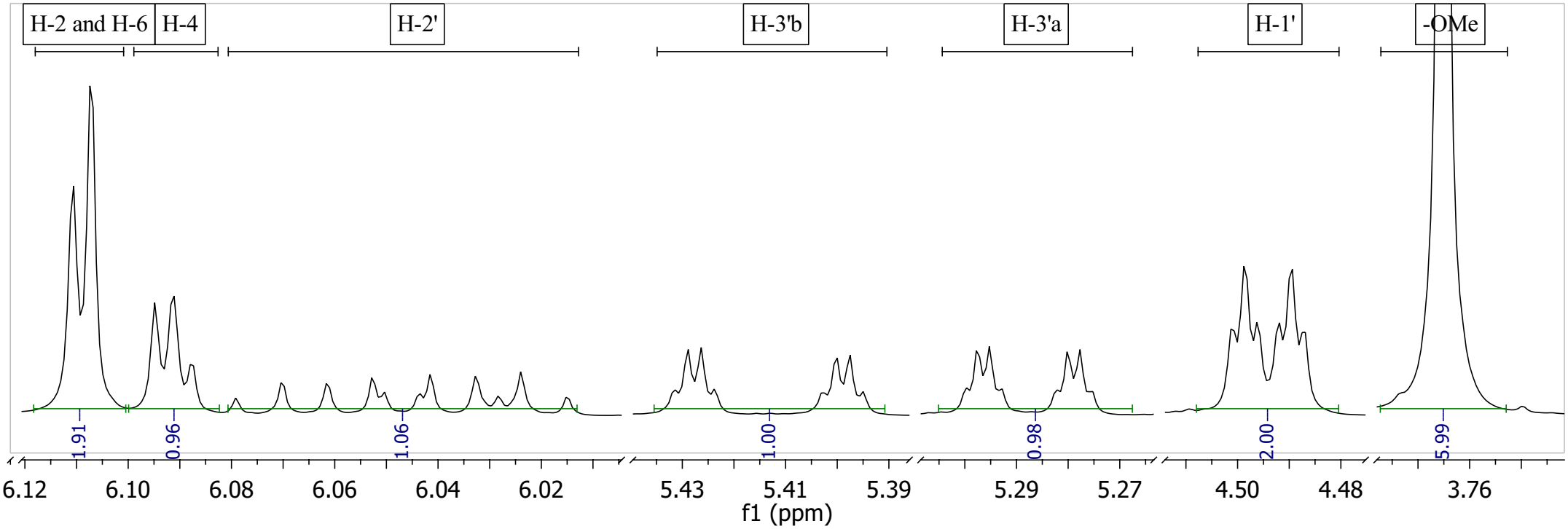
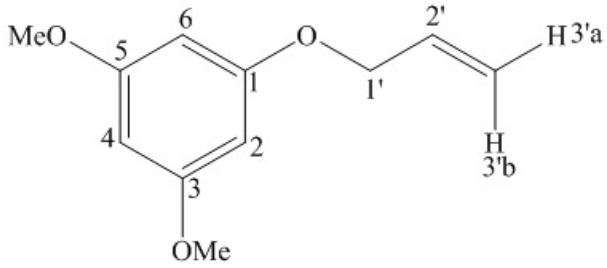


Plate 4b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Allyloxy-3,5-dimethoxybenzene (**576**)

δ 161.59 (C-3 and C-5), 160.58 (C-1), 133.26 (C-2'), 117.91 (C-3'), 93.71 (C-2 and C-6), 93.20 (C-4), 68.98 (C-1'), 55.44 (-O<u>Me</u>)



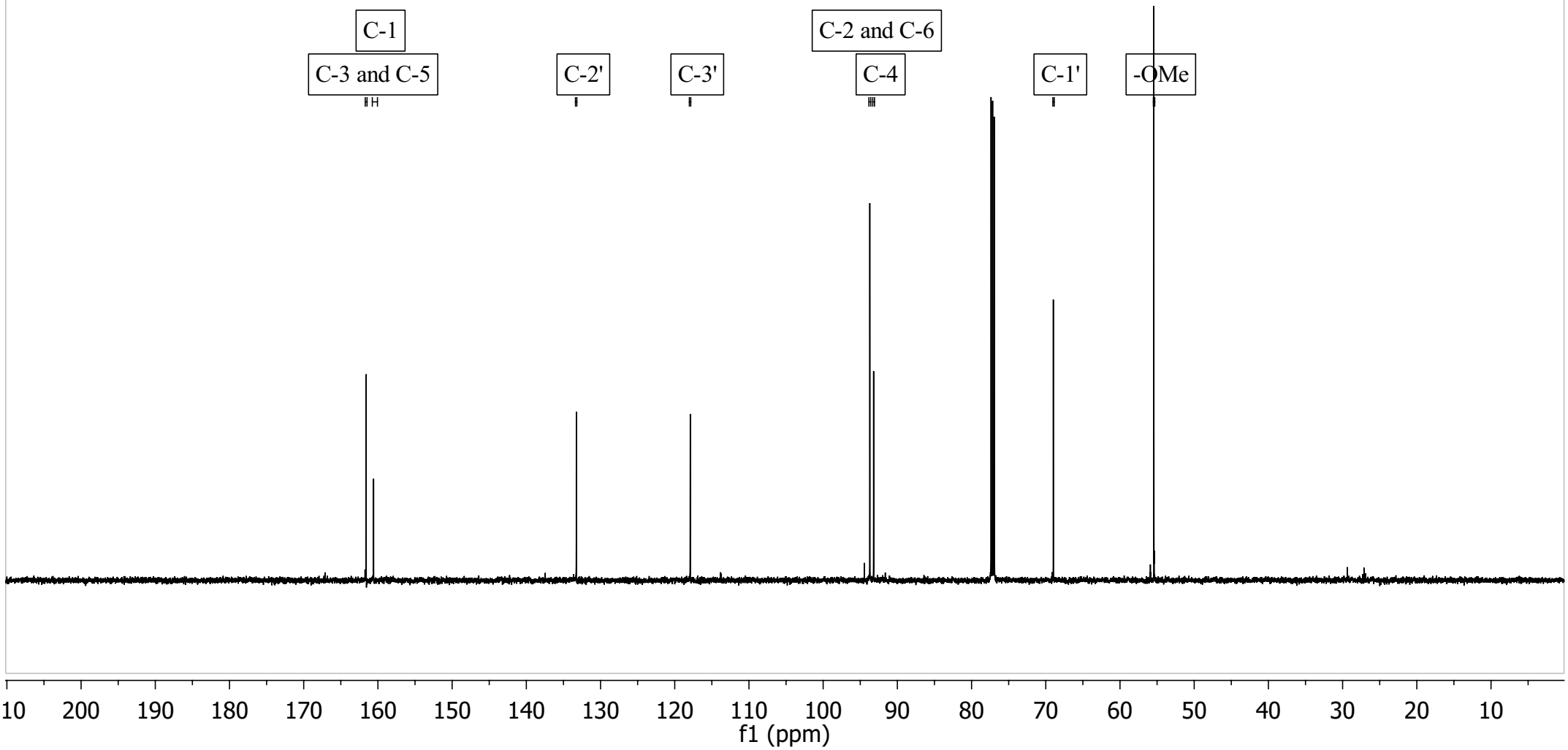


Plate 4c; HSQC (600/151 MHz, $CDCl_3$) : 1-Allyloxy-3,5-dimethoxybenzene (**576**)

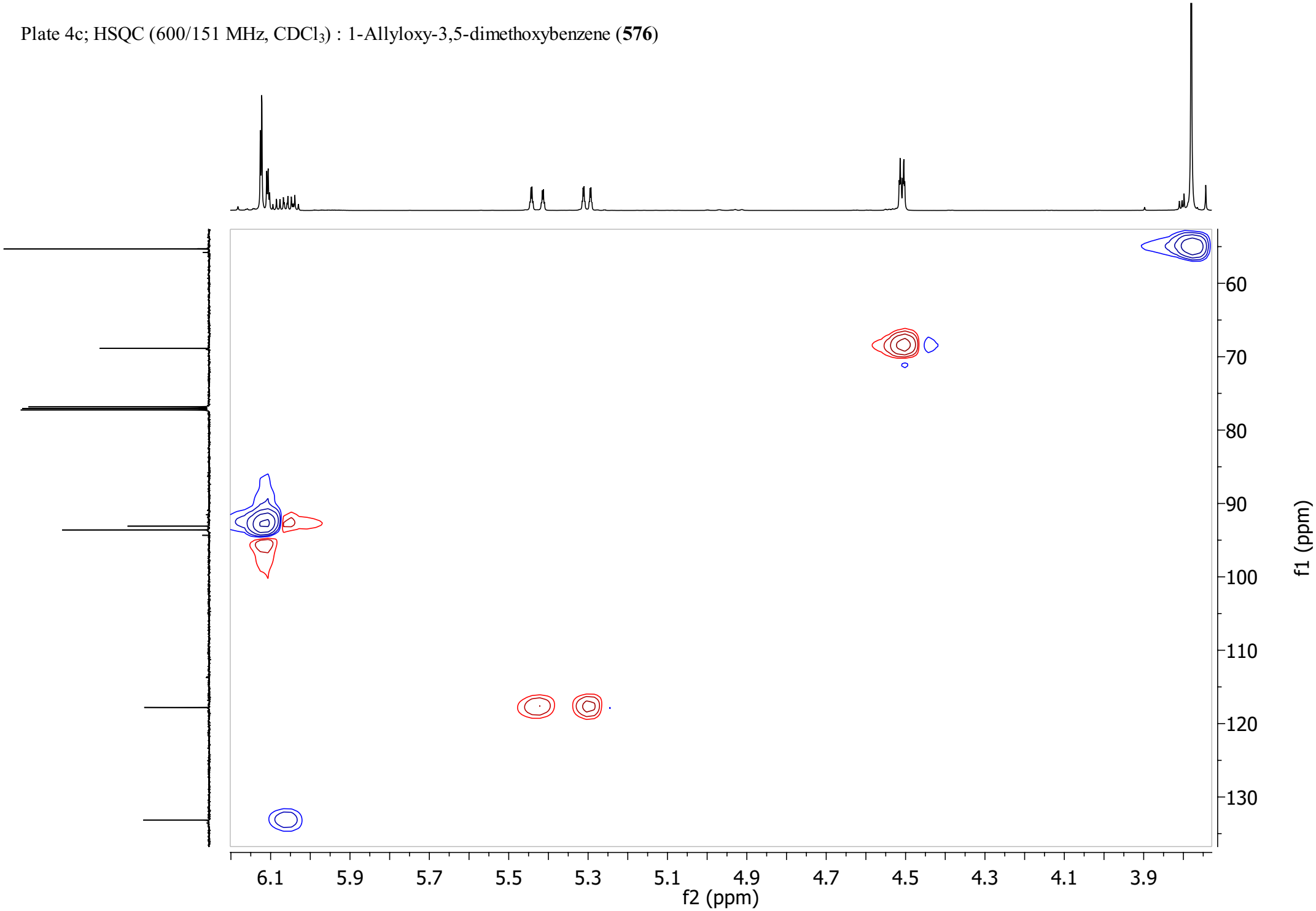
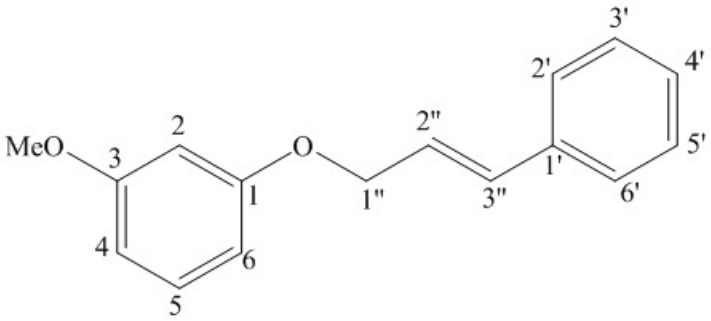
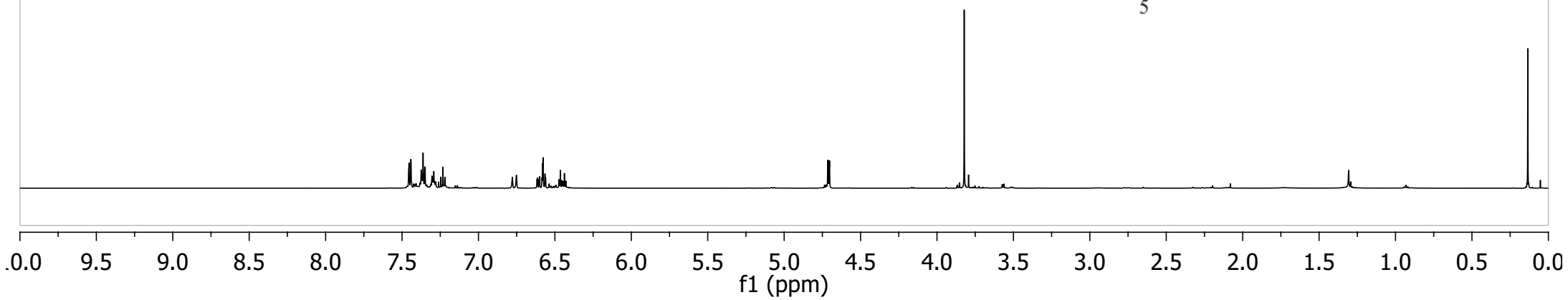


Plate 5a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Cinnamyloxy-3-methoxybenzene (**731**)

δ 7.45 (2H, d, *J* = 7.2 Hz, H-2' and H-6'), 7.36 (2H, dd, *J* = 7.9, 7.2 Hz, H-3' and H-5'), 7.31 – 7.28 (1H, m, H-4'), 7.23 (1H, t, *J* = 8.2 Hz, H-5), 6.77 (1H, br. d, *J* = 16.1 Hz, H-3''), 6.63 – 6.55 (3H, m, Ar-H), 6.45 (1H, dt, *J* = 16.1, 5.8 Hz, H-2''), 4.71 (2H, dd, *J* = 5.8, 1.5 Hz, H-1''), 3.82 (3H, s, -OMe)





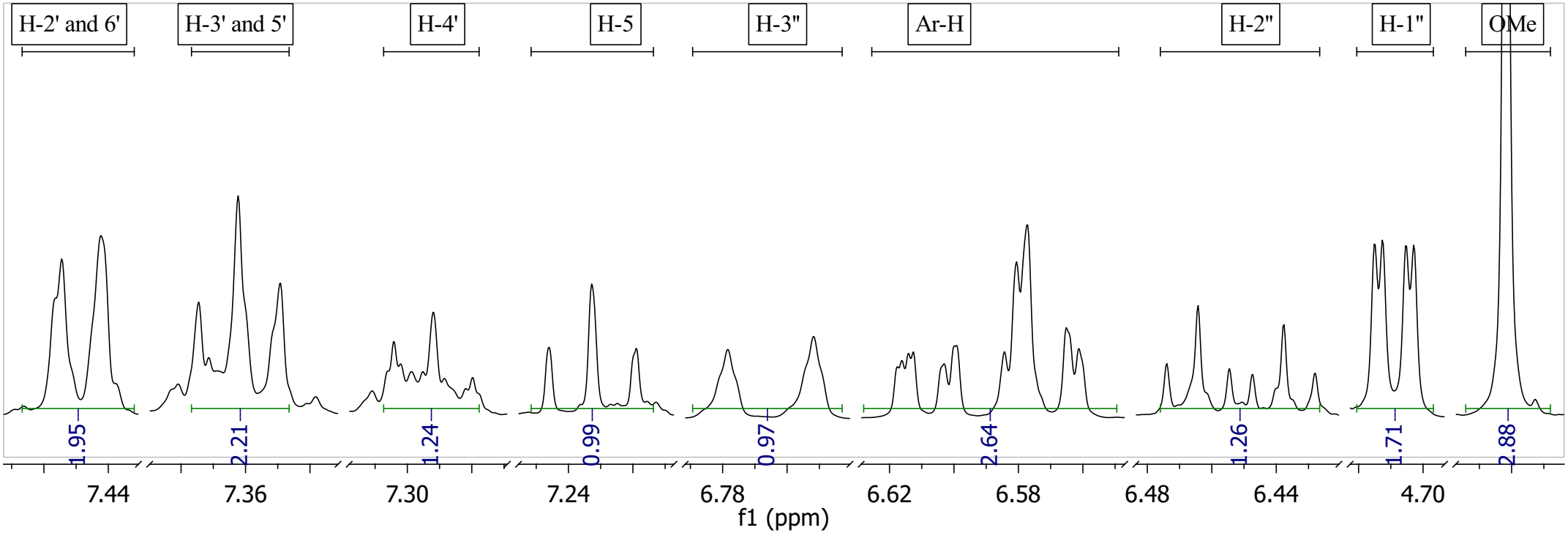
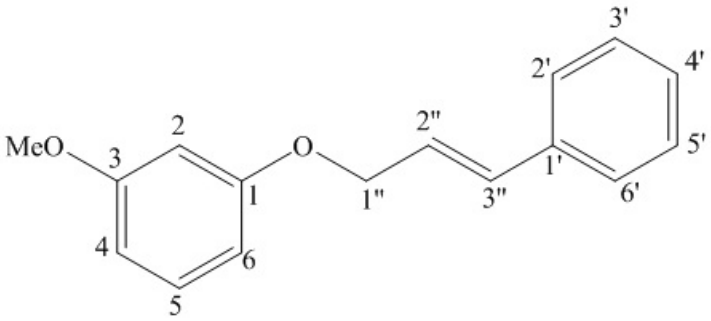


Plate 5b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Cinnamyloxy-3-methoxybenzene (**731**)

δ 160.94 (C-3), 159.98 (C-1), 136.56 (C-1'), 133.15 (C-3''), 130.05 (C-5), 128.62 (C-3' and C-5'), 127.97 (C-4'), 126.68 (C-2' and C-6'), 124.47 (C-2''), 106.98 (Ar-C), 106.58 (Ar-C), 101.37 (Ar-C), 68.78 (C-1''), 55.41 (-OMe)



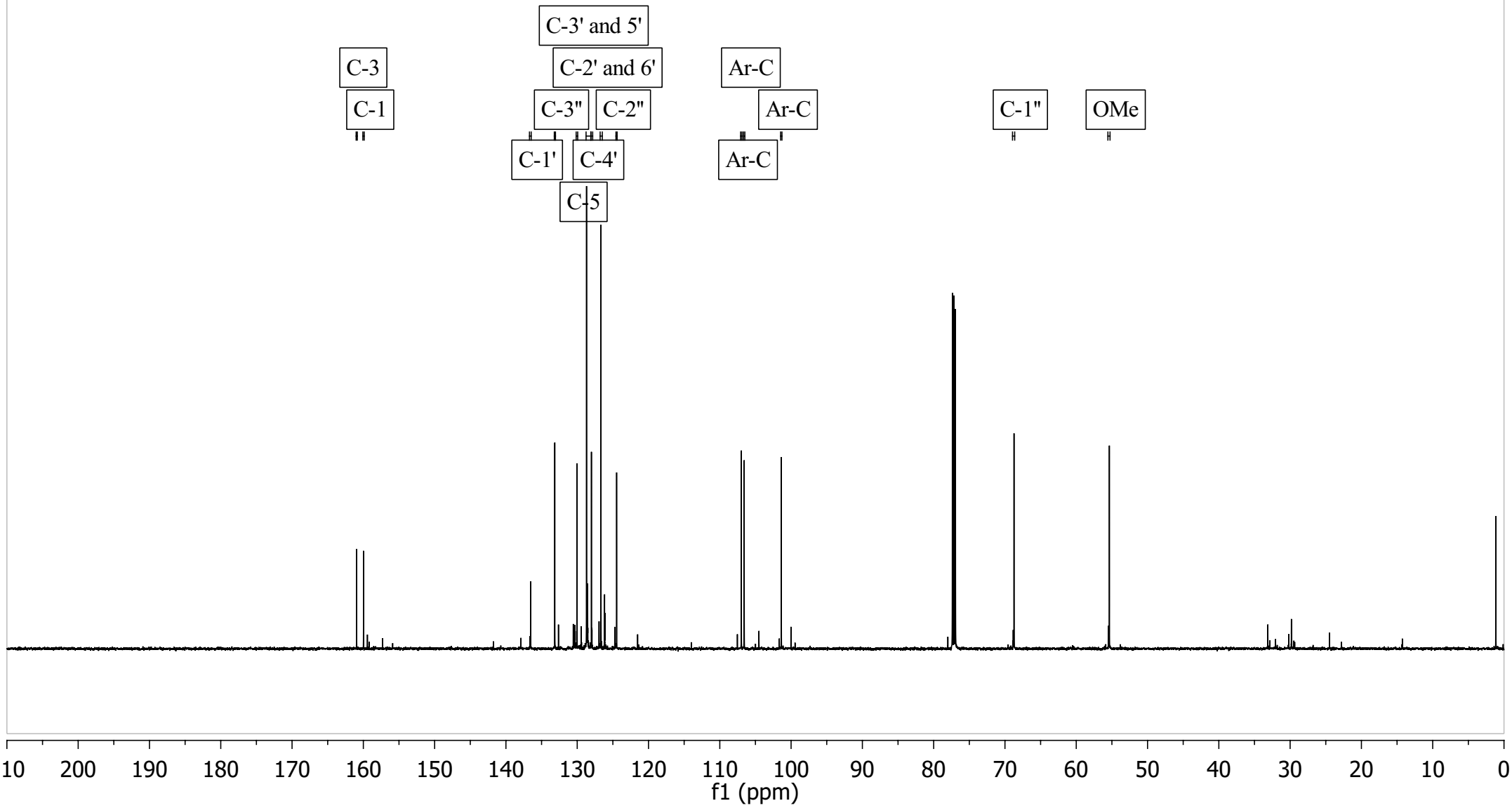


Plate 5c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 1-Cinnamyloxy-3-methoxybenzene (**731**)

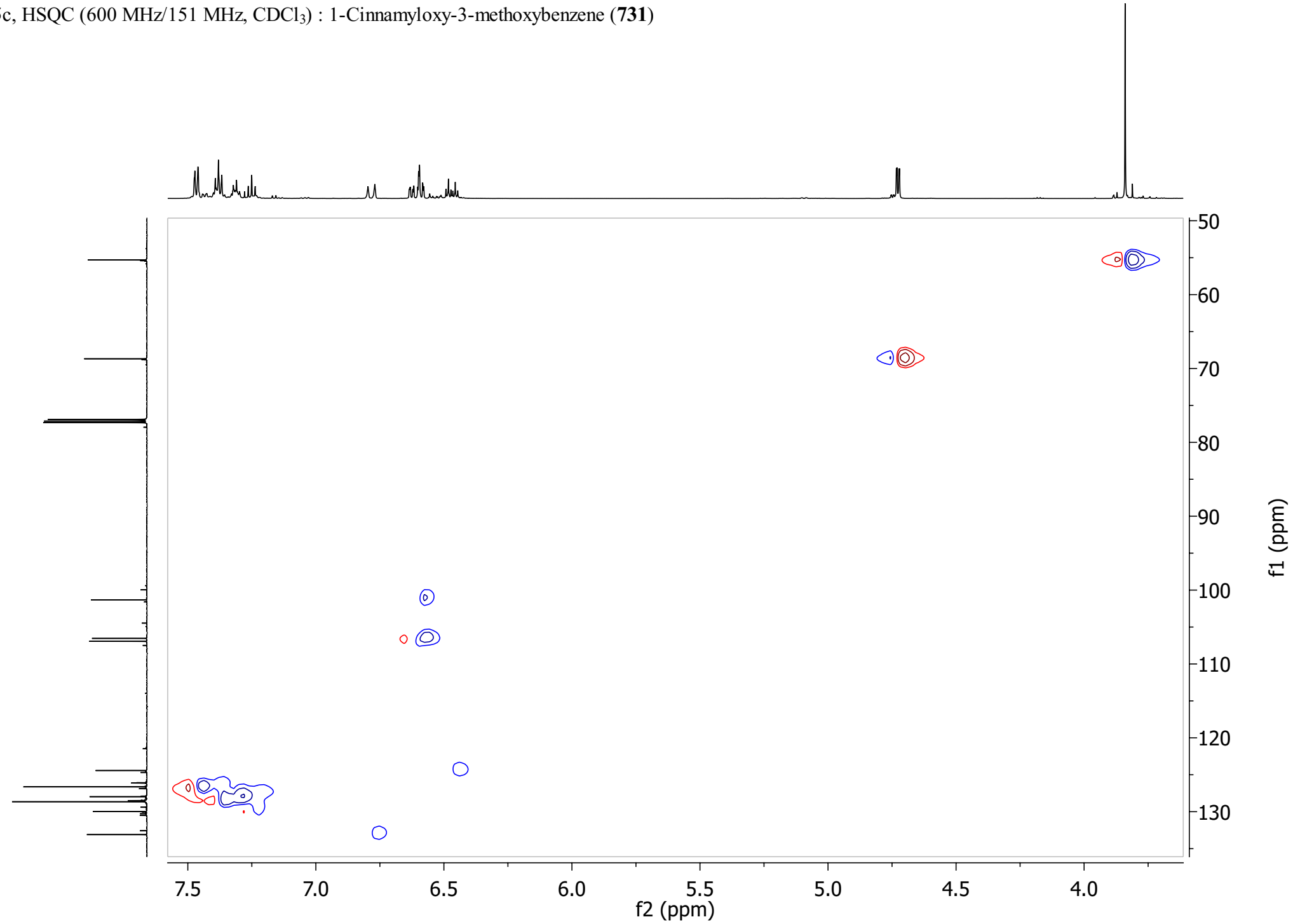


Plate 5d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 1-Cinnamyloxy-3-methoxybenzene (**731**)

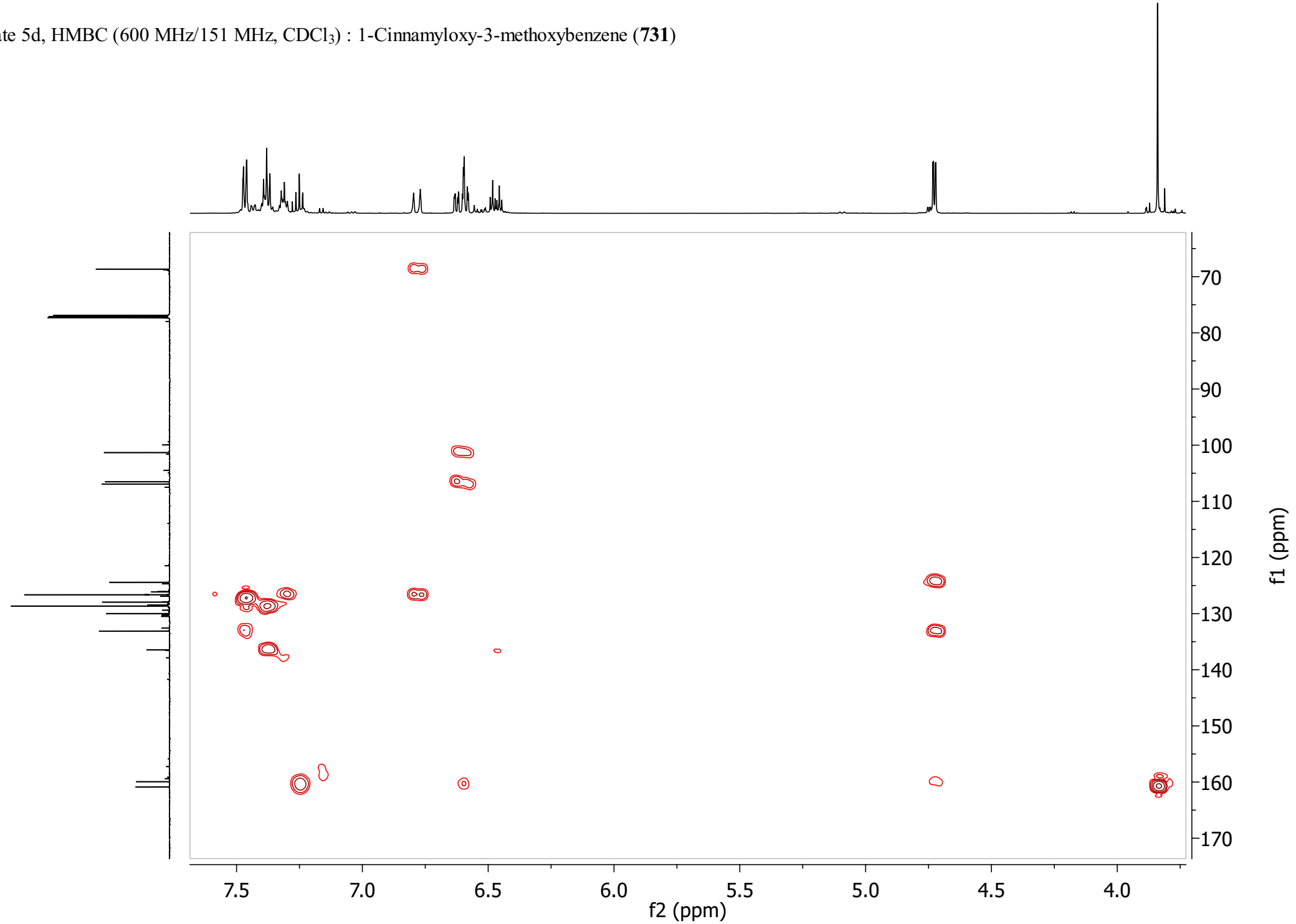


Plate 5e, DEPT (151 MHz, $CDCl_3$) : 1-Cinnamyloxy-3-methoxybenzene (**731**)

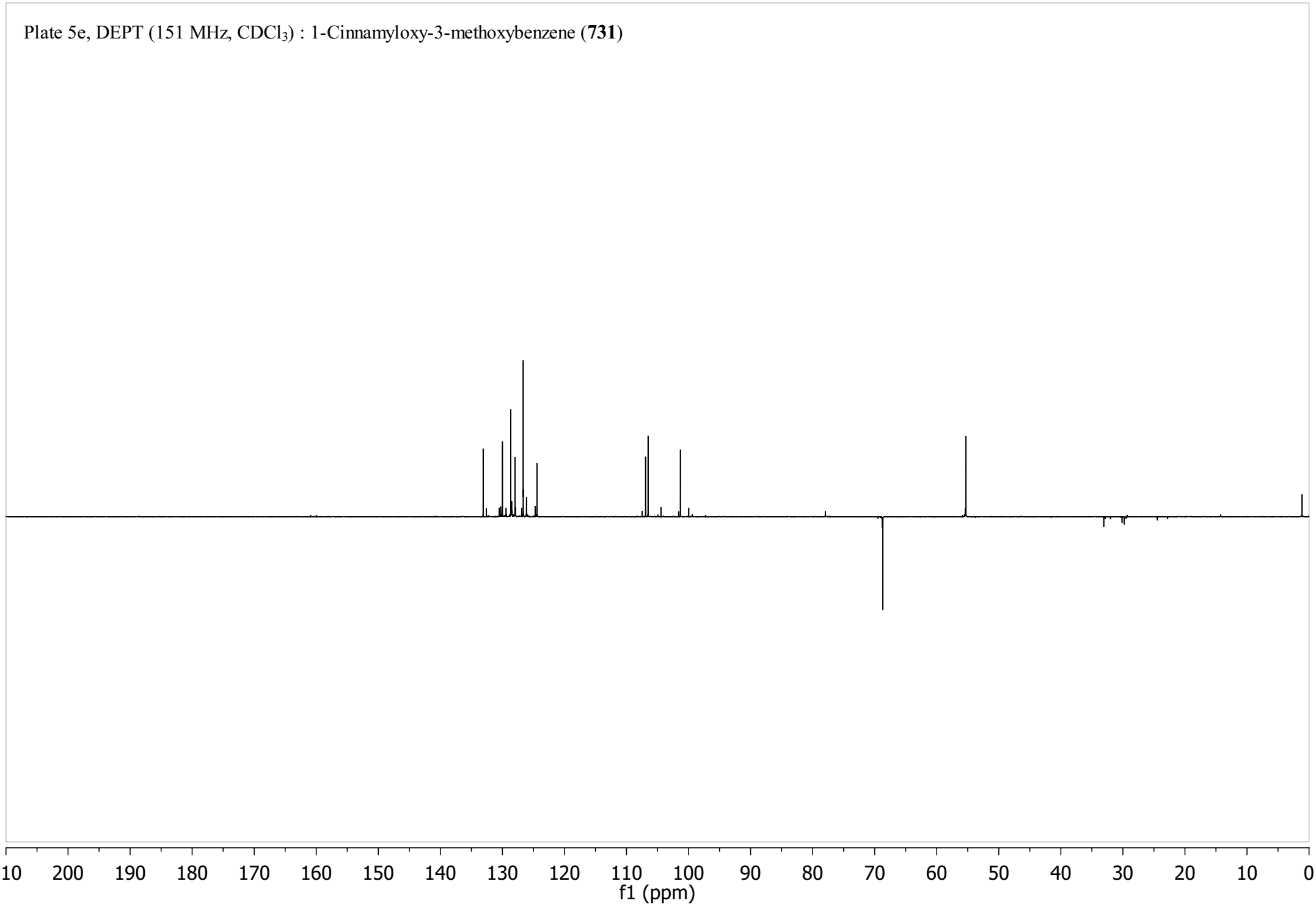
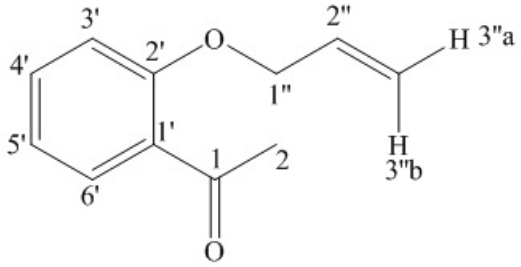
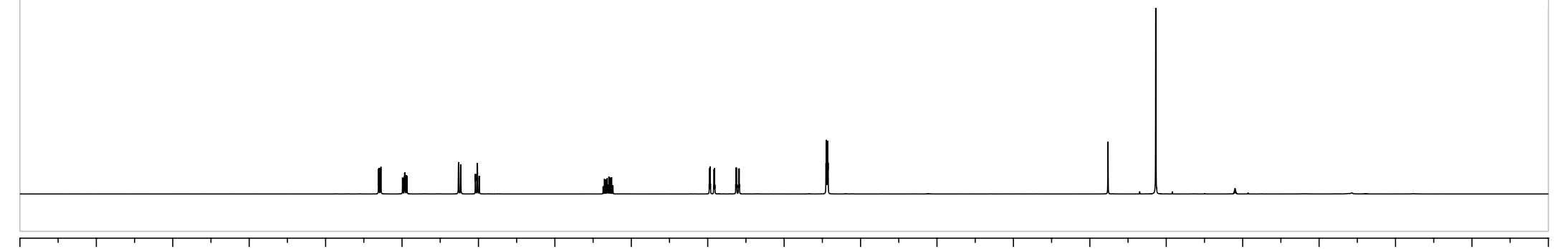


Plate 6a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2'-Allyloxyacetophenone (**750**)

δ 7.65 (1H, dd, *J* = 7.8, 1.9 Hz, H-6'), 7.48 (1H, ddd, *J* = 8.4, 8.3, 1.9 Hz, H-4'), 7.13 (1H, br. d, *J* = 8.4 Hz, H-3'), 7.01 (1H, ddd, *J* = 8.3, 7.8, 1.0 Hz, H-5'), 6.15 (1H, ddt, *J* = 17.3, 10.6, 5.4 Hz, H-2''), 5.47 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3''b), 5.30 (1H, ddt, *J* = 10.6, 1.5, 1.5 Hz, H-3''a), 4.72 (2H, ddd, *J* = 5.4, 1.5, 1.5 Hz, H-1''), 2.57 (3H, s, -C<u>H</u>$_3$)





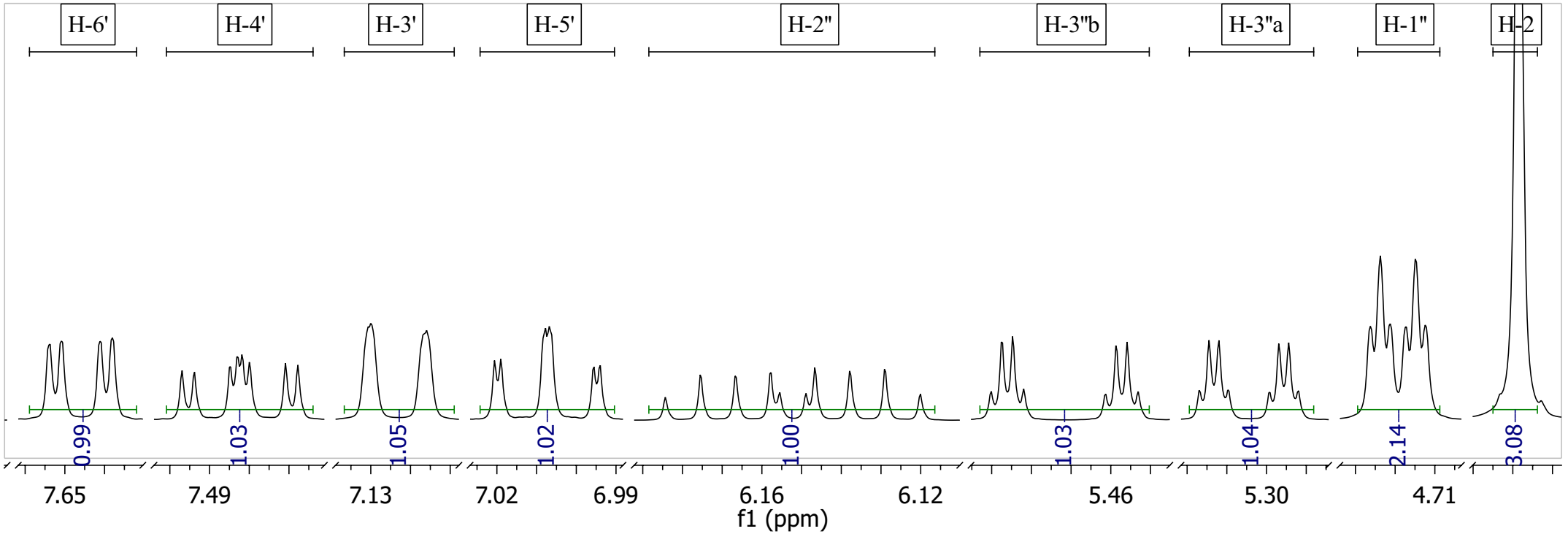
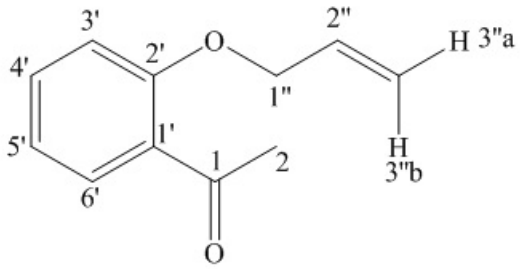


Plate 6b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2'-Allyloxyacetophenone (**750**)

δ 199.19 (C-1), 158.81 (C-2'), 134.34 (C-4'), 134.22 (C-2''), 130.74 (C-6'), 129.66 (C-1'), 121.48 (C-5'), 118.26 (C-3''), 114.17 (C-3'), 70.15 (C-1''), 32.12 (-<u>C</u>H_3)



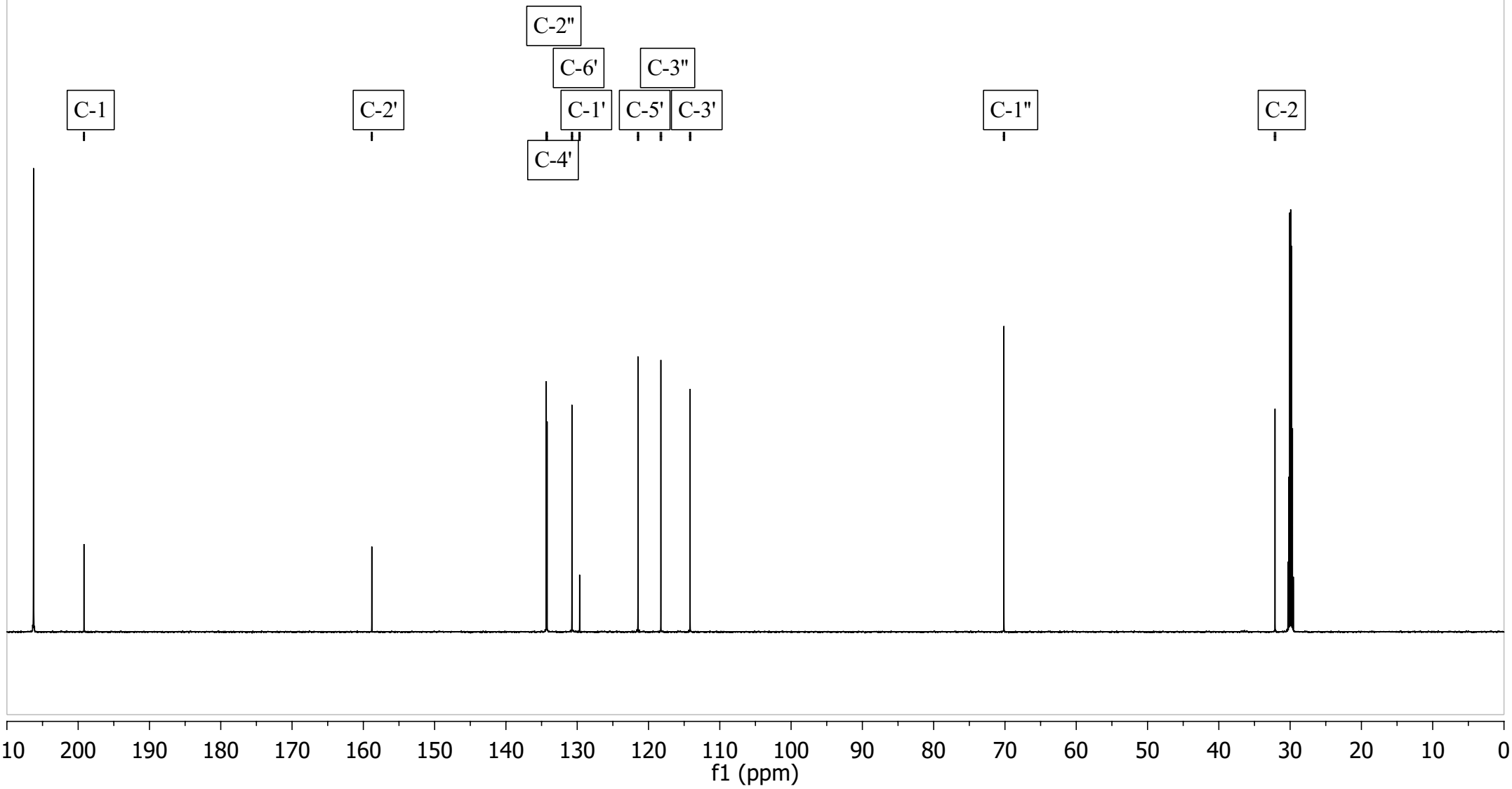


Plate 6c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxyacetophenone (**750**)

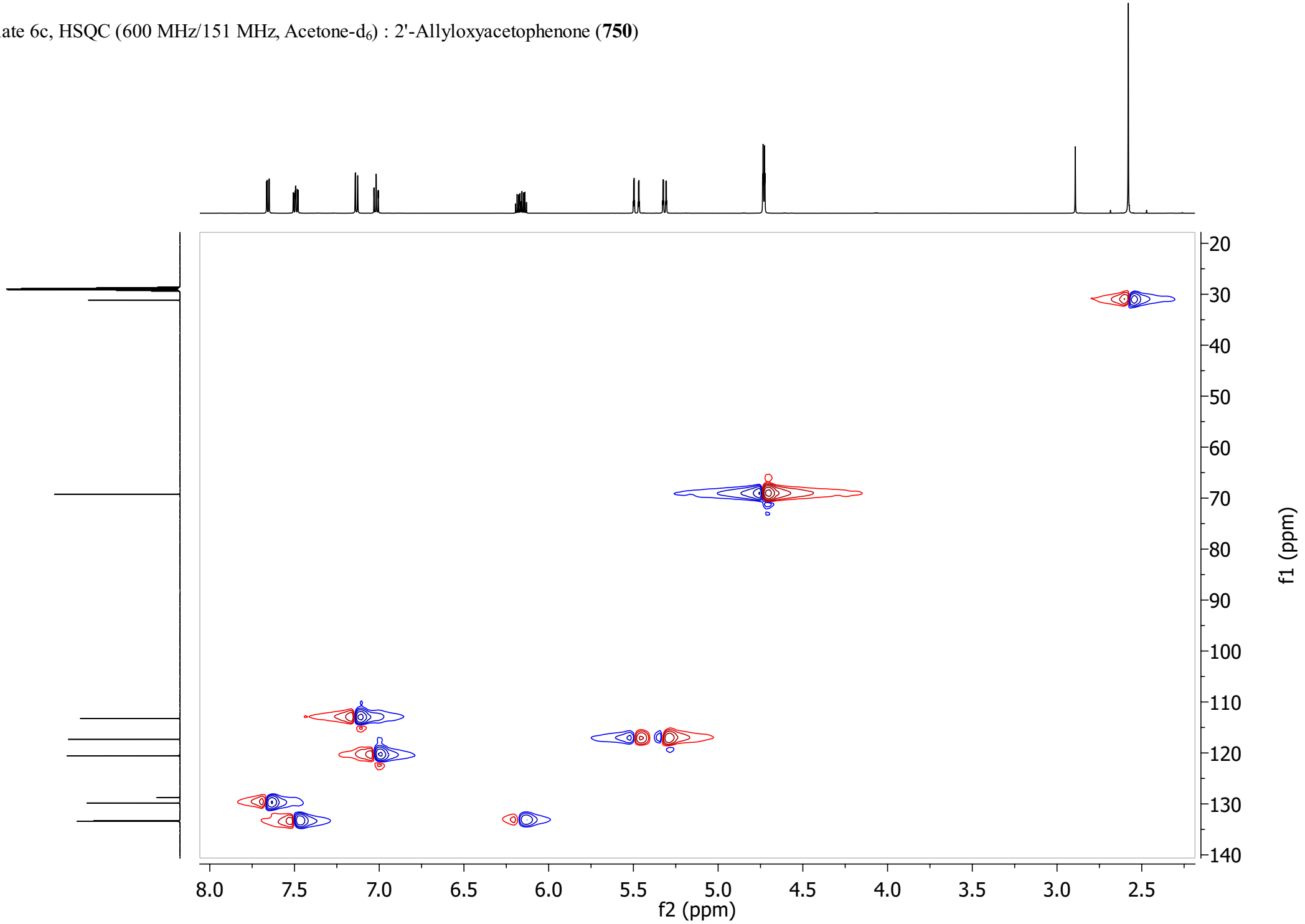


Plate 6d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxyacetophenone (**750**)

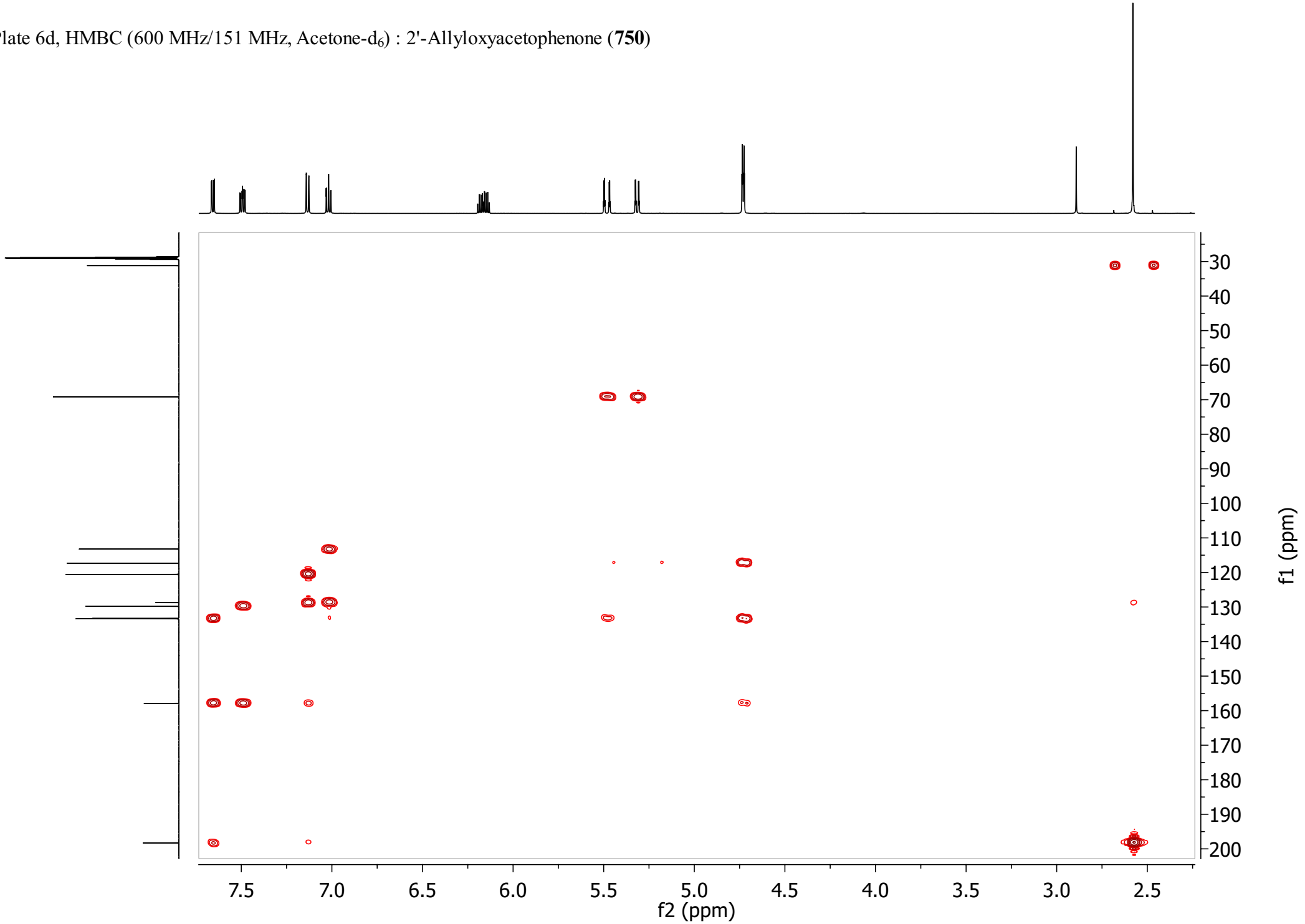


Plate 6e, DEPT (151 MHz, Acetone-d_6) : 2'-Allyloxyacetophenone (**750**)

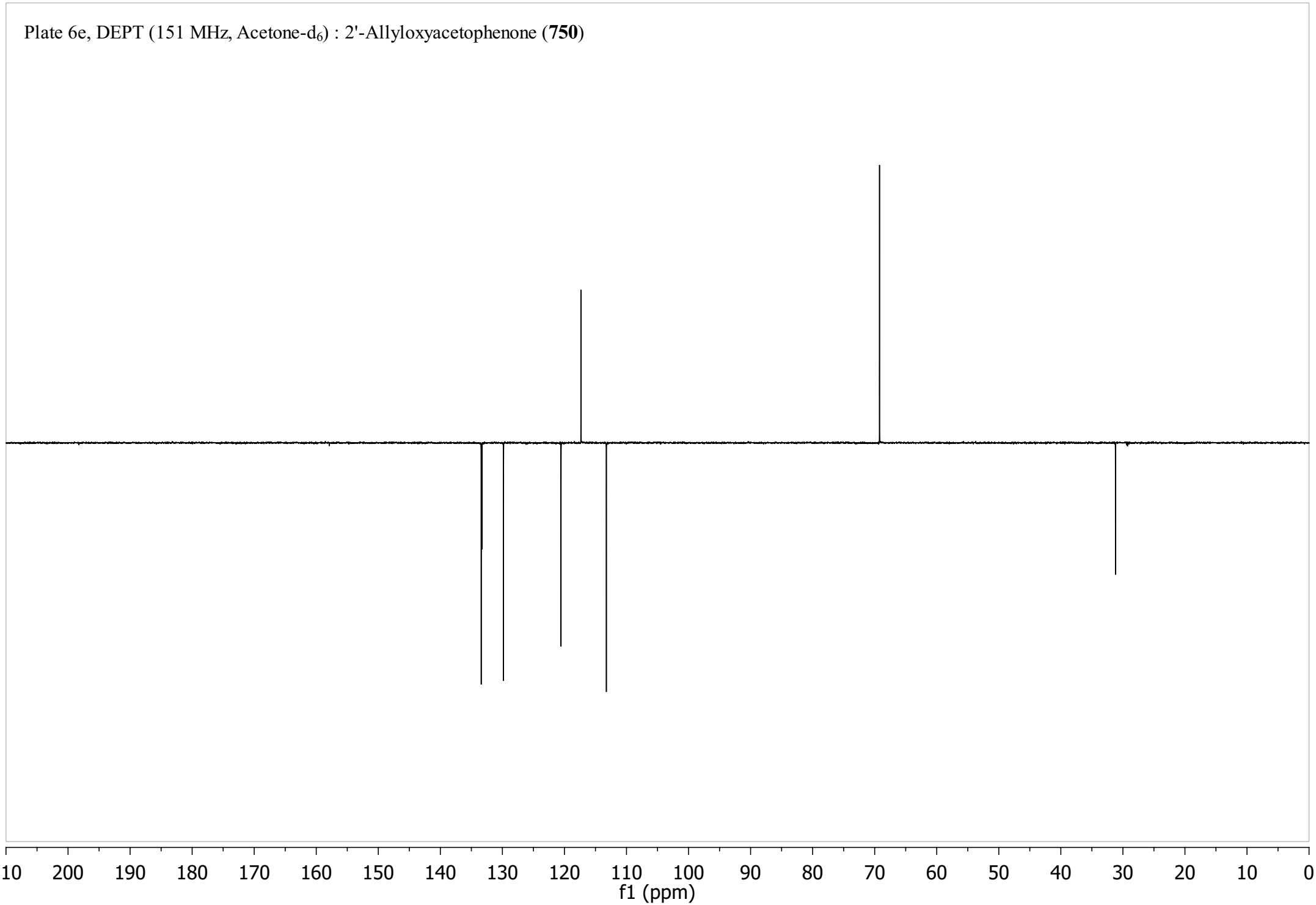
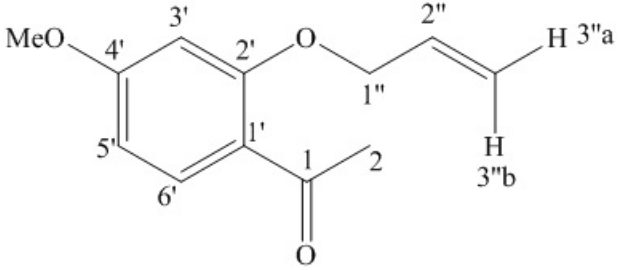
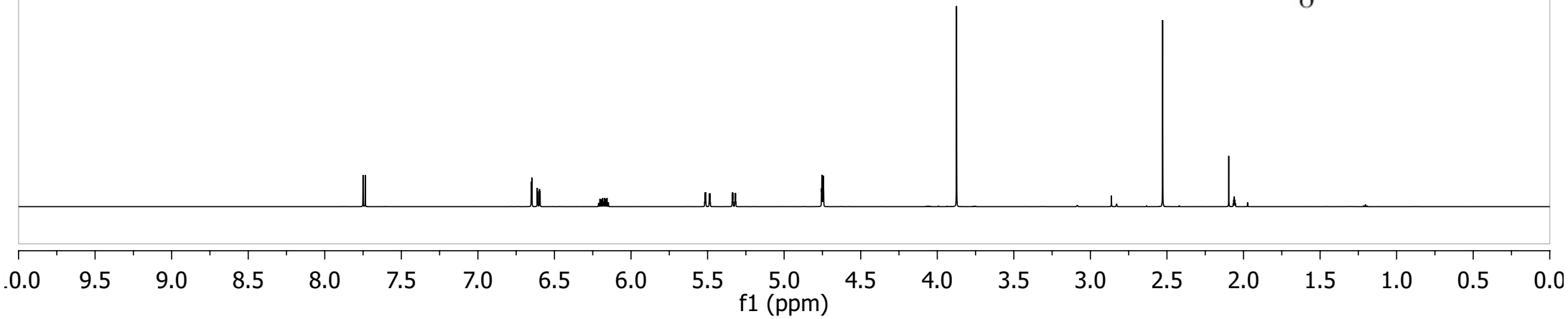


Plate 7a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2'-Allyloxy-4'-methoxyacetophenone (**751**)

δ 7.74 (1H, d, *J* = 8.7 Hz, H-6'), 6.65 (1H, d, *J* = 2.3 Hz, H-3'), 6.60 (1H, dd, *J* = 8.7, 2.3 Hz, H-5'), 6.18 (1H, ddt, *J* = 17.3, 10.7, 5.4 Hz, H-2''), 5.50 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3''b), 5.33 (1H, ddt, *J* = 10.7, 1.5, 1.5 Hz, H-3''a), 4.75 (2H, ddd, *J* = 5.4, 1.5, 1.5 Hz, H-1''), 3.87 (3H, s, -OMe), 2.53 (3H, s, -CH_3)





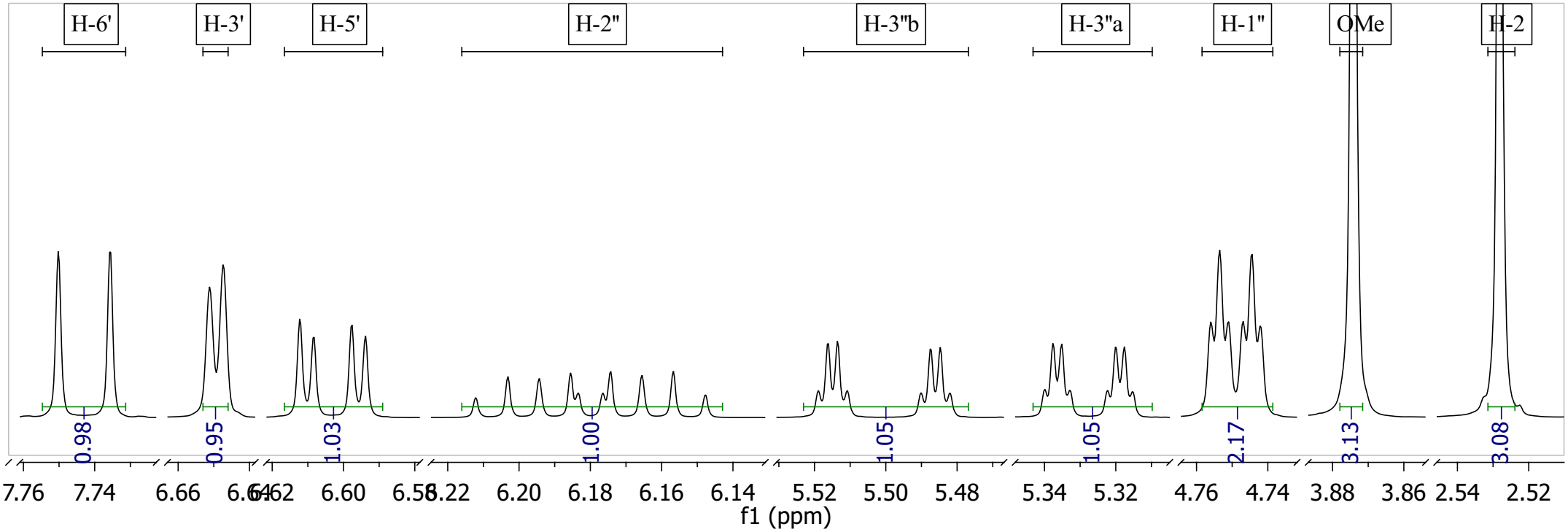
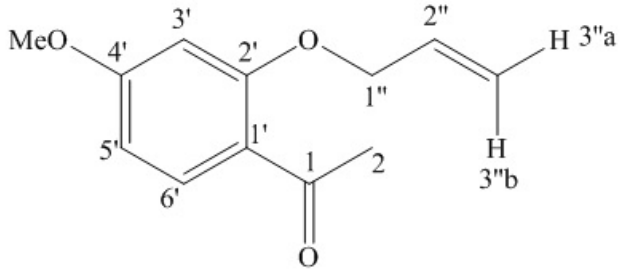


Plate 7b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2'-Allyloxy-4'-methoxyacetophenone (**751**)

δ 196.73 (C-1), 165.50 (C-4'), 161.10 (C-2'), 134.26 (C-2''), 133.00 (C-6'), 122.13 (C-1'), 118.41 (C-3''), 106.91 (C-5'), 100.14 (C-3'), 70.32 (C-1''), 56.05 (-O<u>Me</u>), 32.26 (-<u>C</u>H_3)



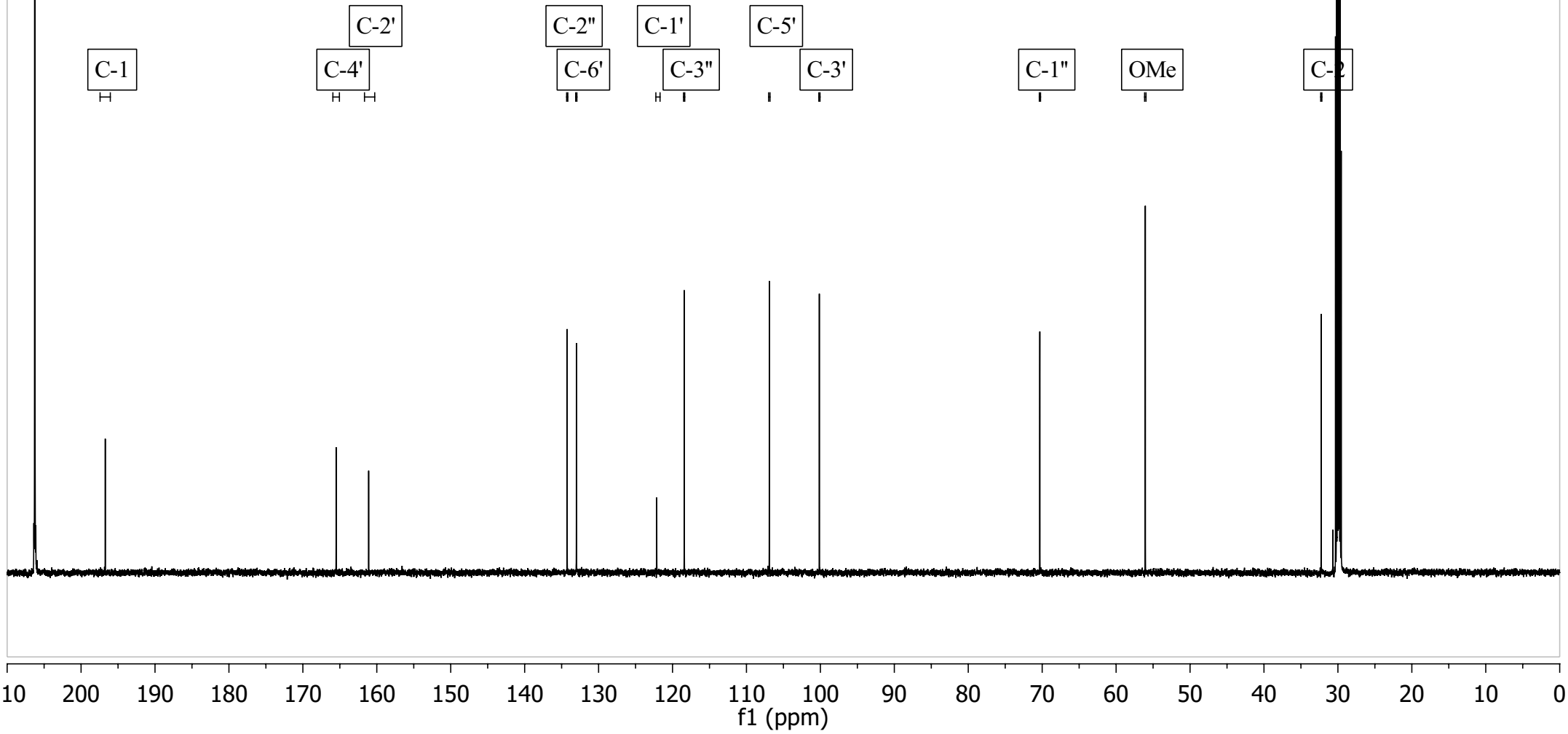


Plate 7c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxy-4'-methoxyacetophenone (**751**)

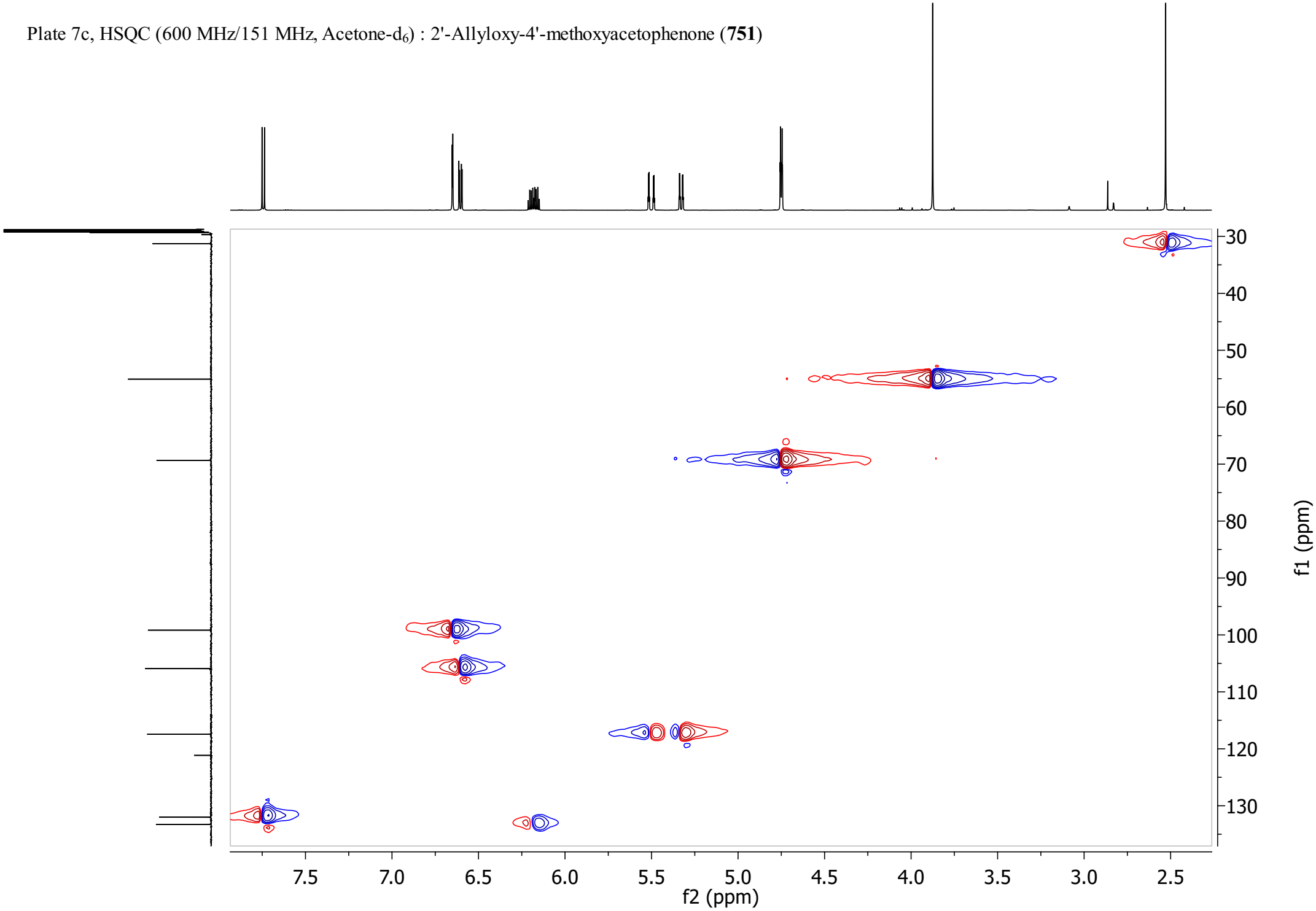


Plate 7d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxy-4'-methoxyacetophenone (**751**)

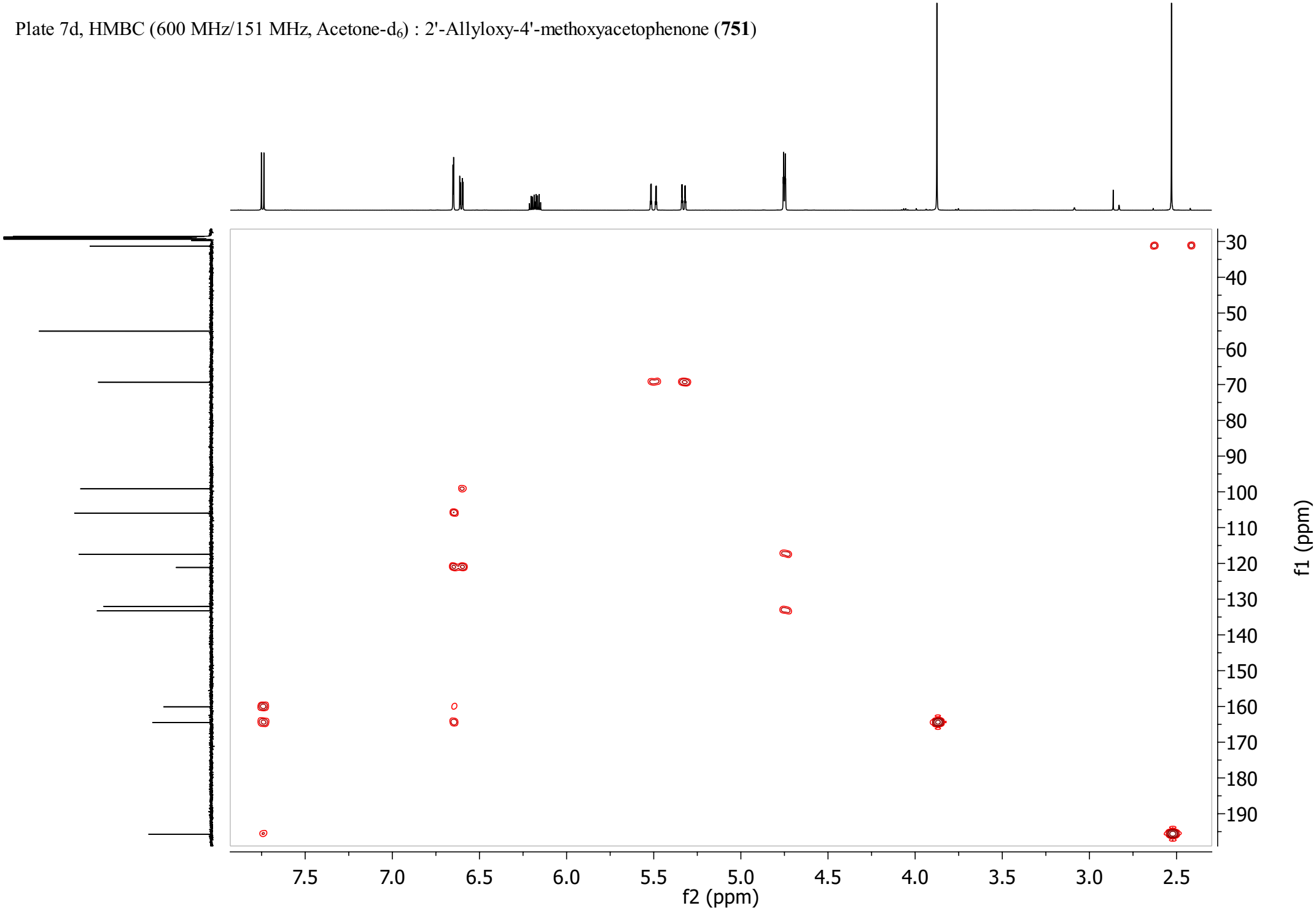


Plate 7e, DEPT (151 MHz, Acetone-d_6) : 2'-Allyloxy-4'-methoxyacetophenone (**751**)

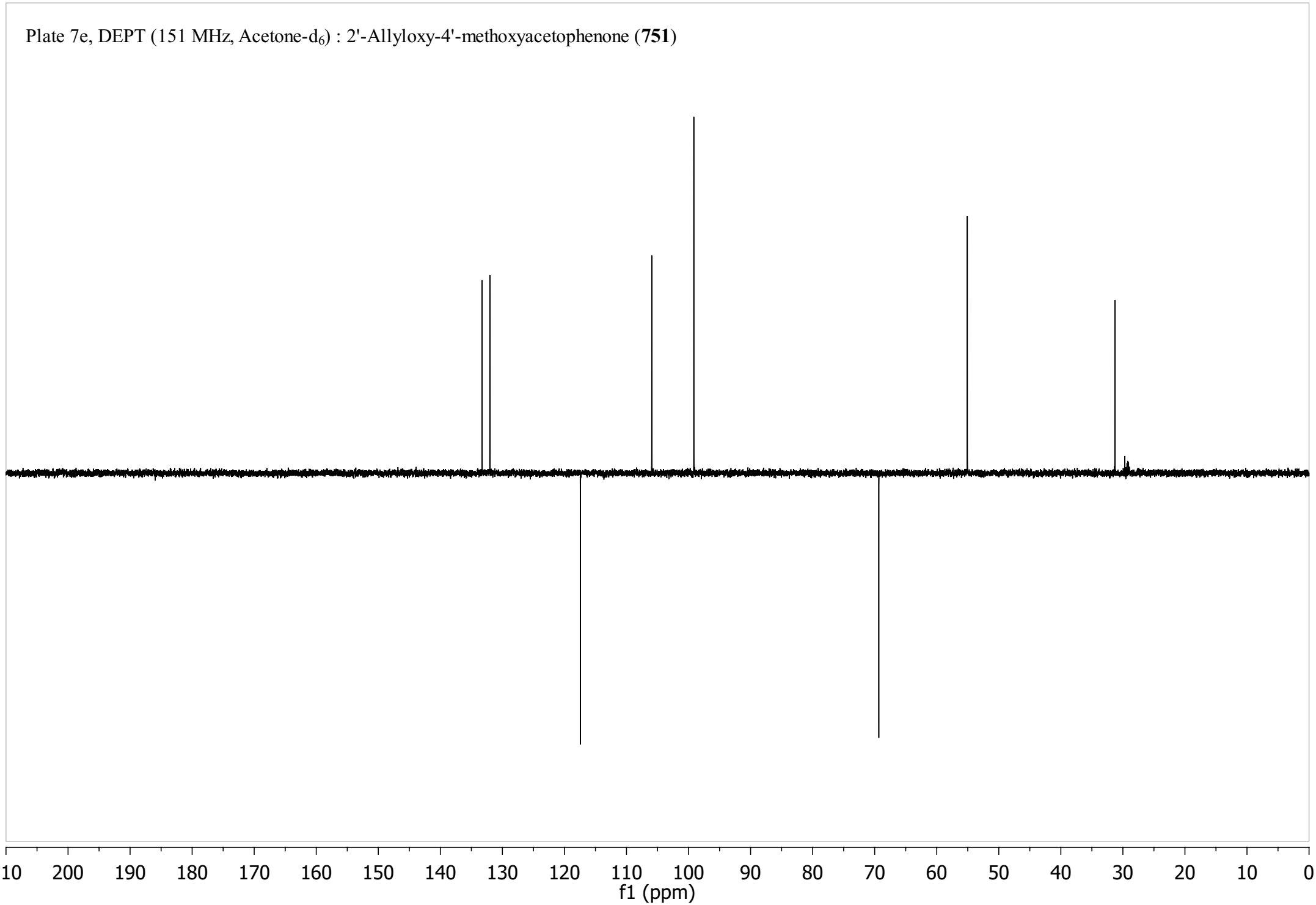
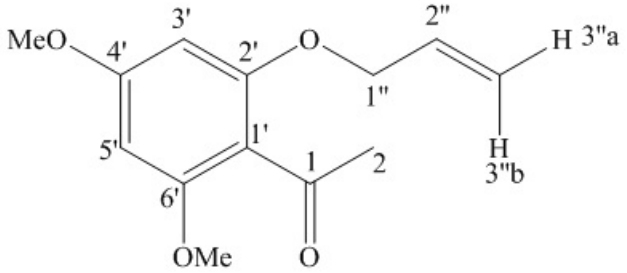
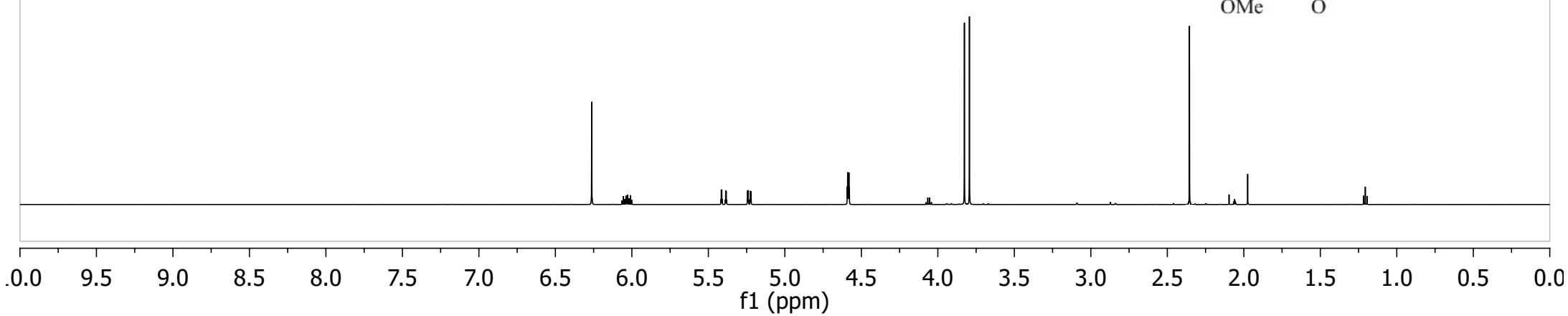


Plate 8a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**)

δ 6.26 (2H, s, H-3' and H-5'), 6.03 (1H, ddt, *J* = 17.3, 10.6, 5.0 Hz, H-2''), 5.40 (1H, ddt, *J* = 17.3, 1.7, 1,7 Hz, H-3''b), 5.23 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3''a), 4.59 (2H, ddd, *J* = 5.0, 1.7, 1.7 Hz, H-1''), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe), 2.36 (3H, s, -CH_3)





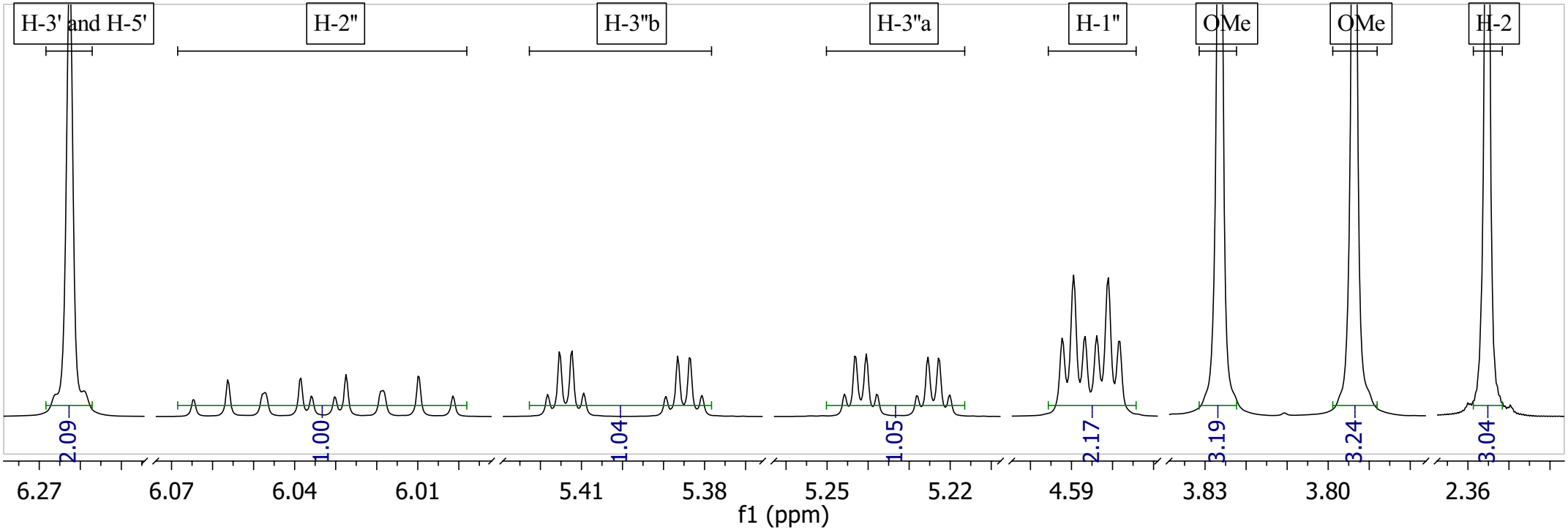
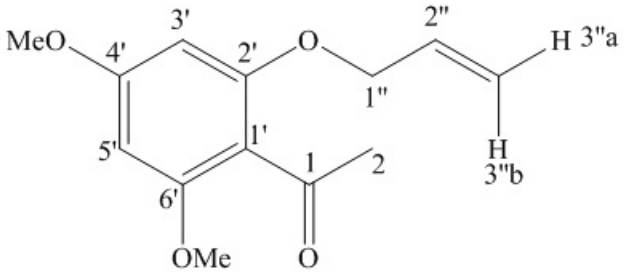


Plate 8b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**)

δ 200.28 (C-1), 163.09 (C-4'/6'), 158.85 (C-4'/6'), 157.67 (C-2'), 134.35 (C-2''), 117.40 (C-3''), 115.11 (C-1'), 92.76 (C-3'/5'), 91.87 (C-3'/5'), 69.86 (C-1''), 56.21 (-O<u>Me</u>), 55.85 (-O<u>Me</u>), 32.64 (-<u>C</u>H_3)



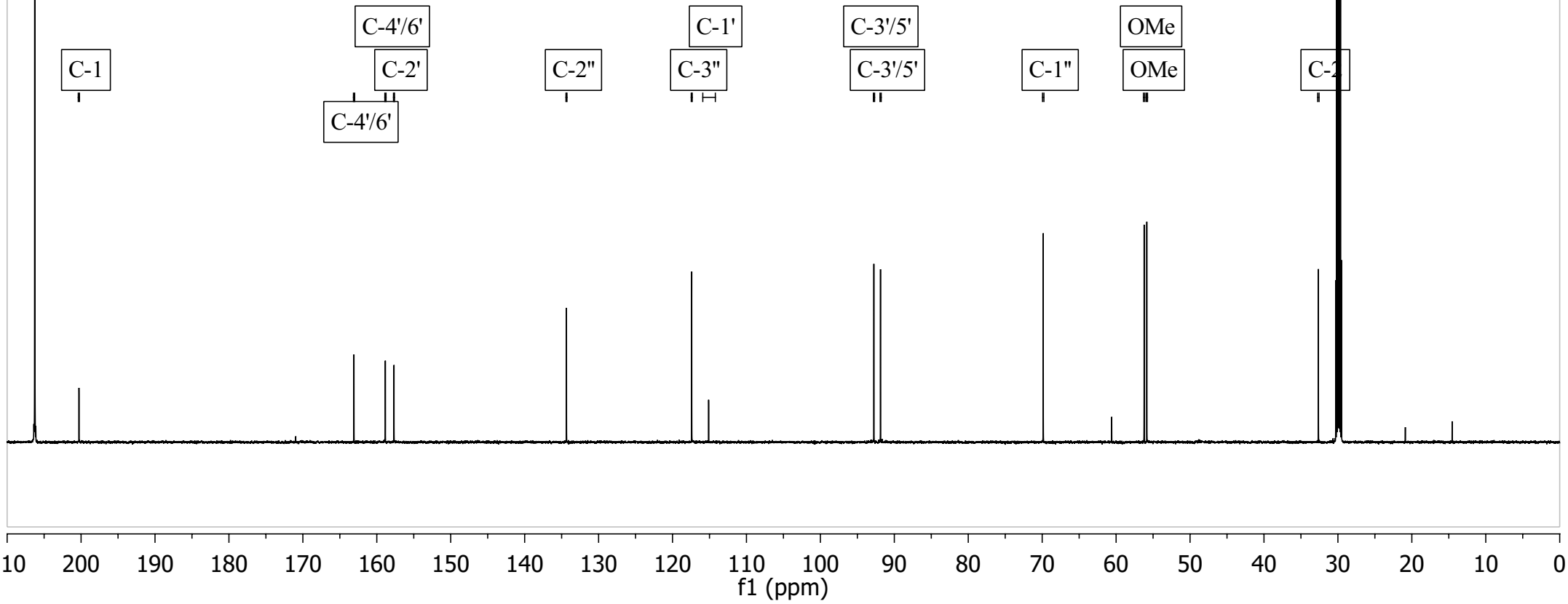


Plate 8c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**)

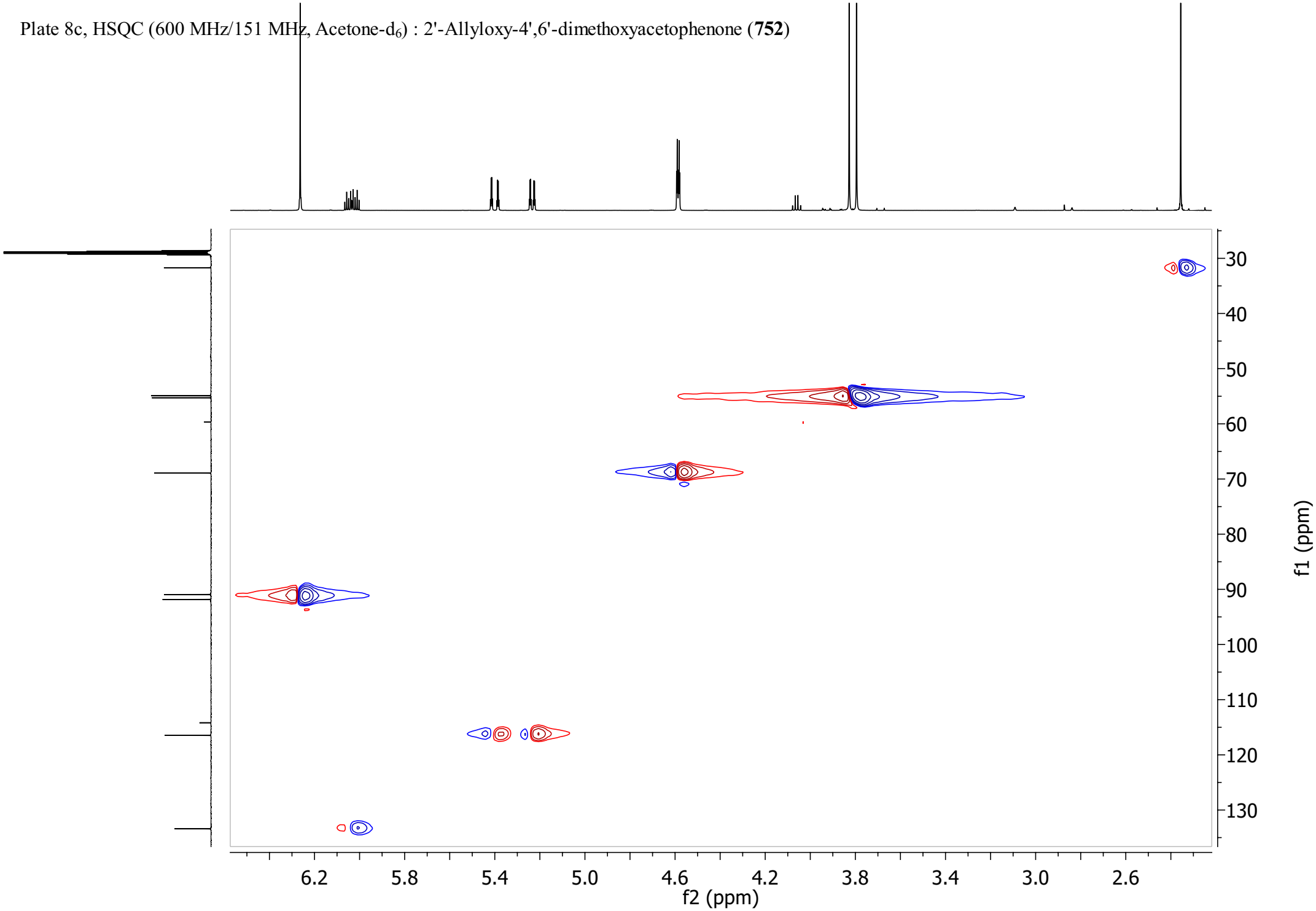


Plate 8d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**)

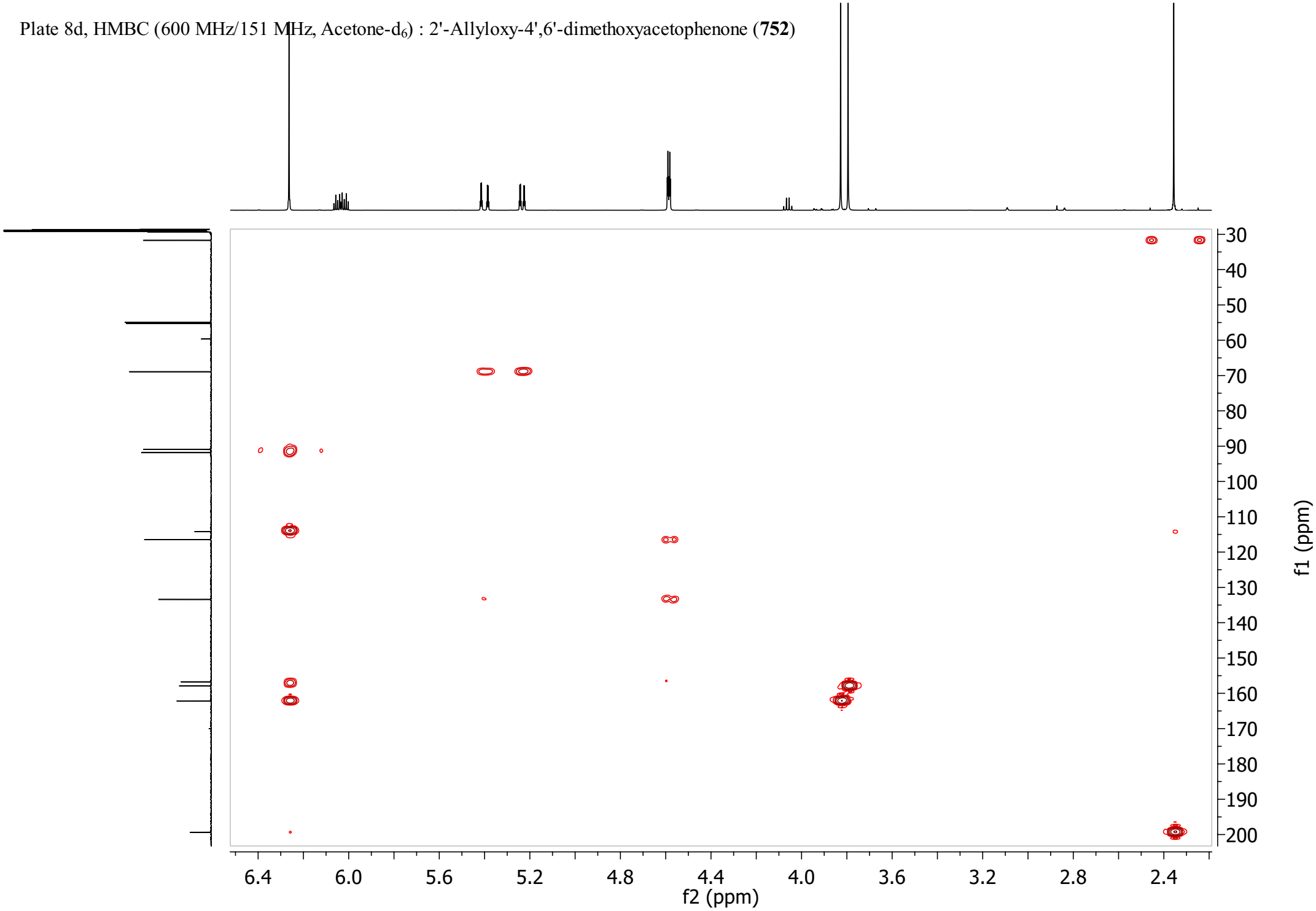


Plate 8e, DEPT (151 MHz, Acetone-d_6) : 2'-Allyloxy-4',6'-dimethoxyacetophenone (**752**)

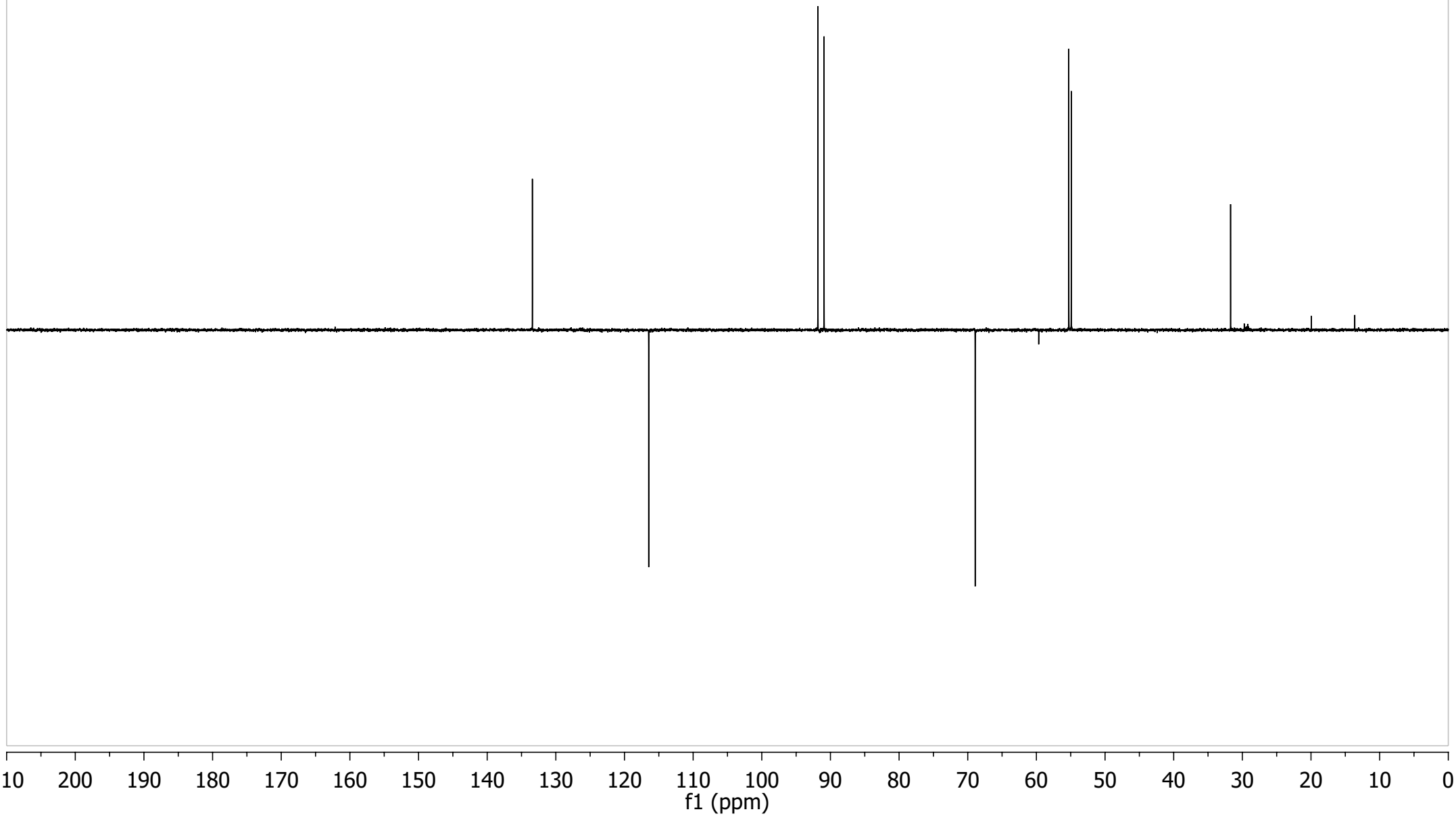
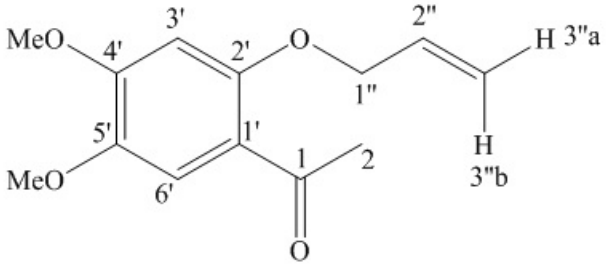
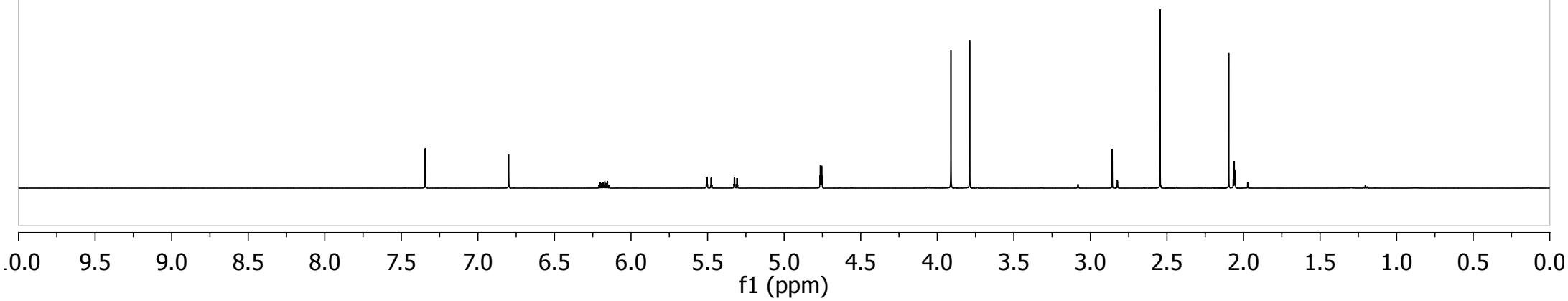


Plate 9a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**)

δ 7.34 (1H, s, H-3'/6'), 6.80 (1H, s, H-3'/6'), 6.18 (1H, ddt, *J* = 17.3, 10.6, 5.5 Hz, H-2''), 5.49 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3''b), 5.32 (1H, ddt, *J* = 10.6, 1.5, 1.5 Hz, H-3''a), 4.76 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz, H-1''), 3.91 (3H, s, -OMe), 3.79 (3H, s, -OMe), 2.54 (3H, s, -CH_3)





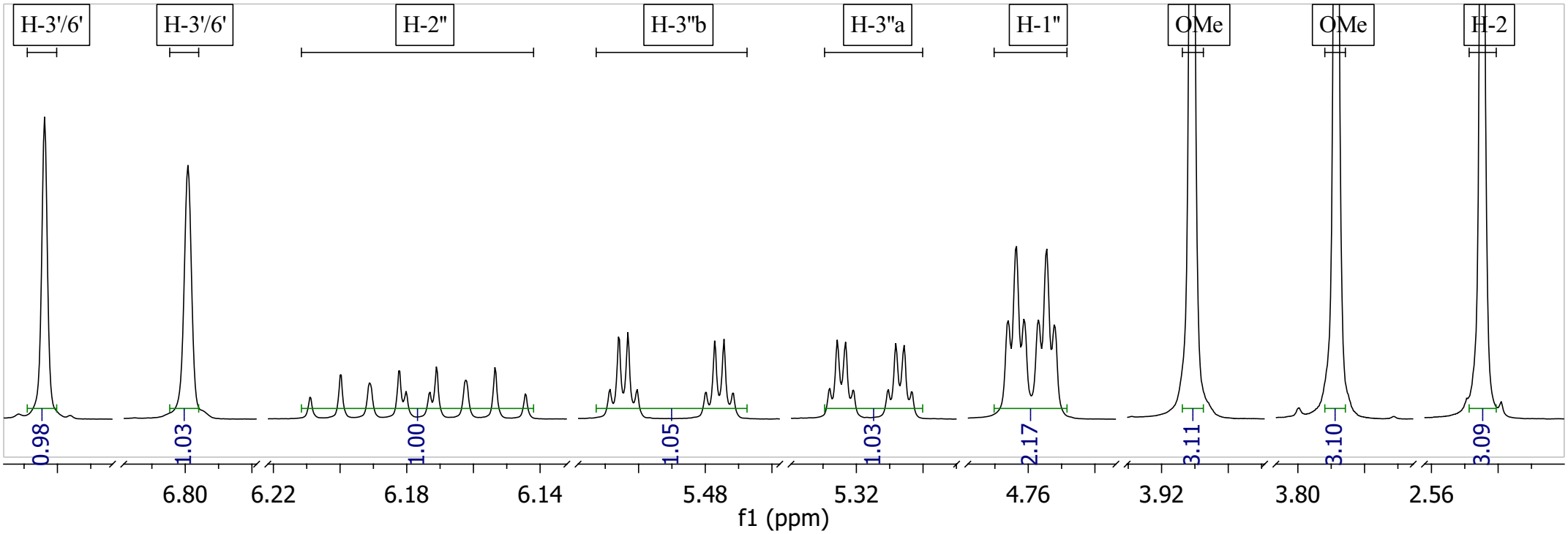
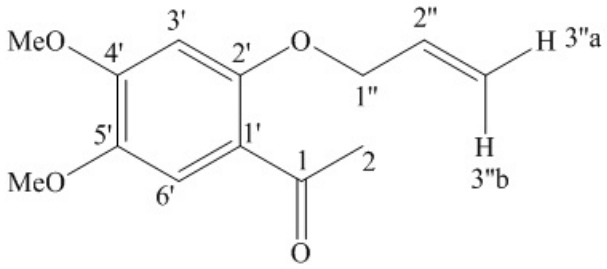


Plate 9b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**)

δ 196.30 (C-1), 155.56 (4°-C), 155.35 (4°-C), 144.40 (C-4'/5'), 134.62 (C-2''), 120.23 (C-1'), 118.32 (C-3''), 113.59 (C-3'/6'), 99.61 (C-3'/6'), 71.16 (C-1''), 56.53 (-O<u>Me</u>), 56.41 (-O<u>Me</u>), 32.45 (-<u>C</u>H_3)



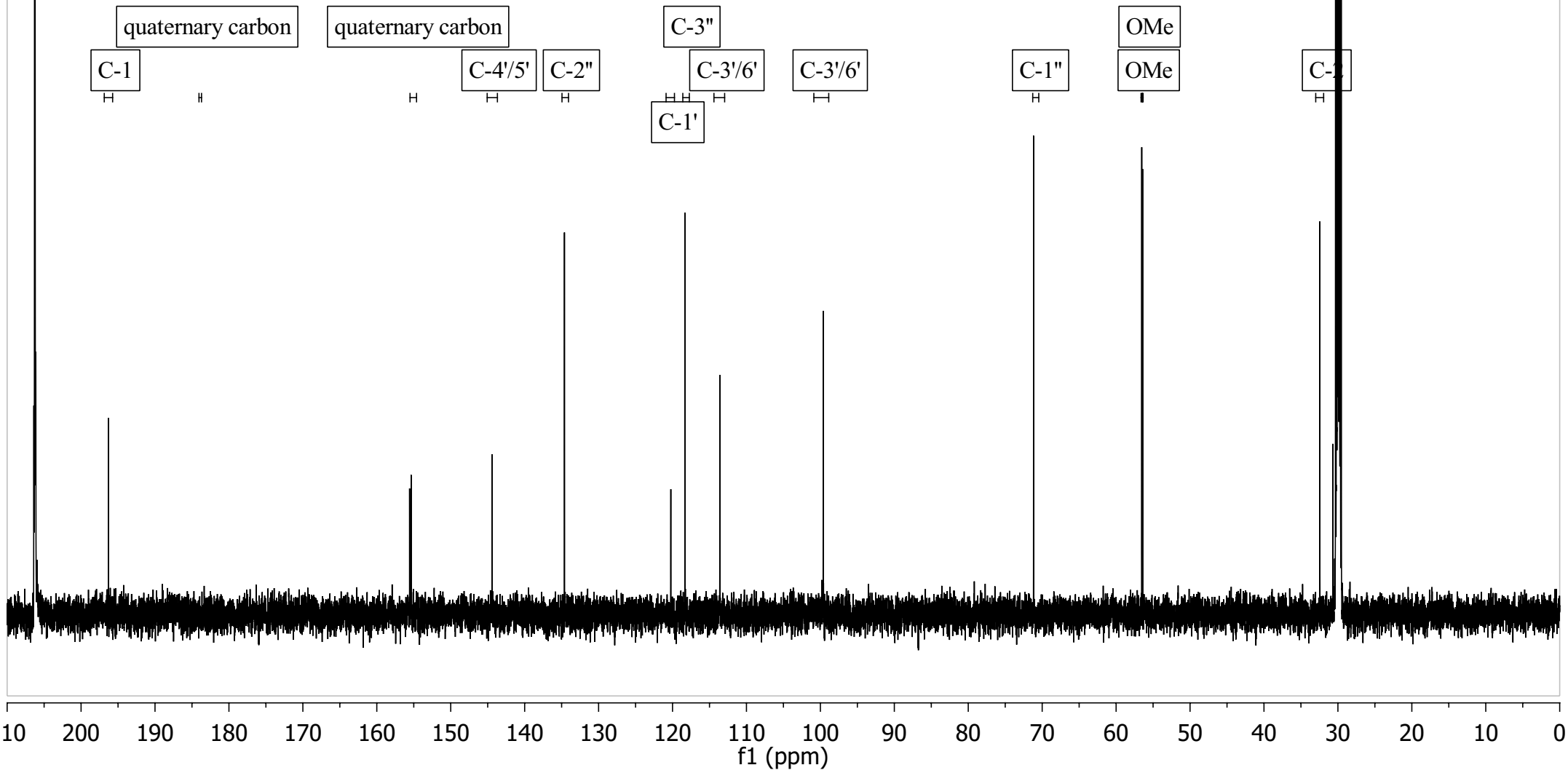


Plate 9c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**)

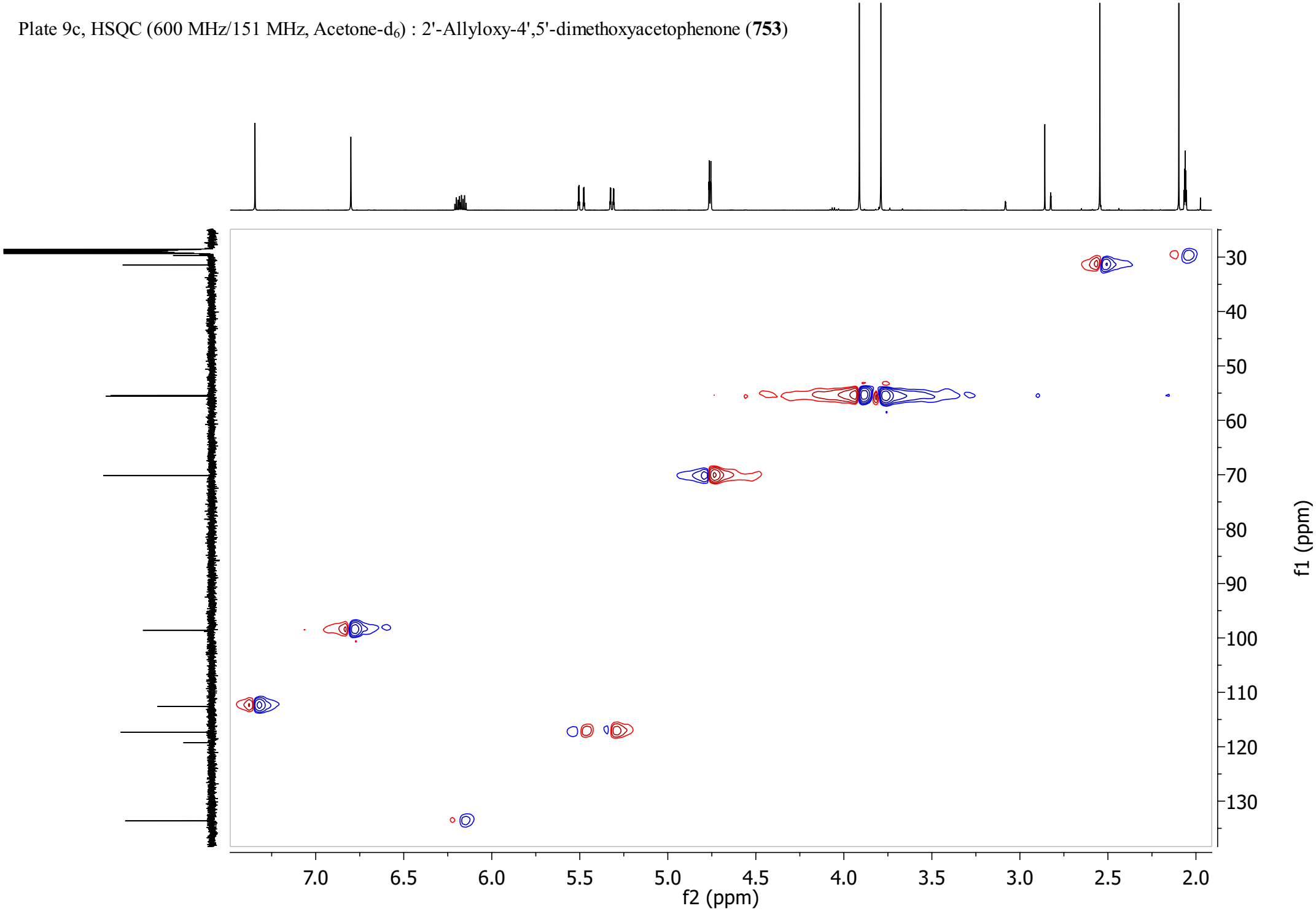


Plate 9d, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**)

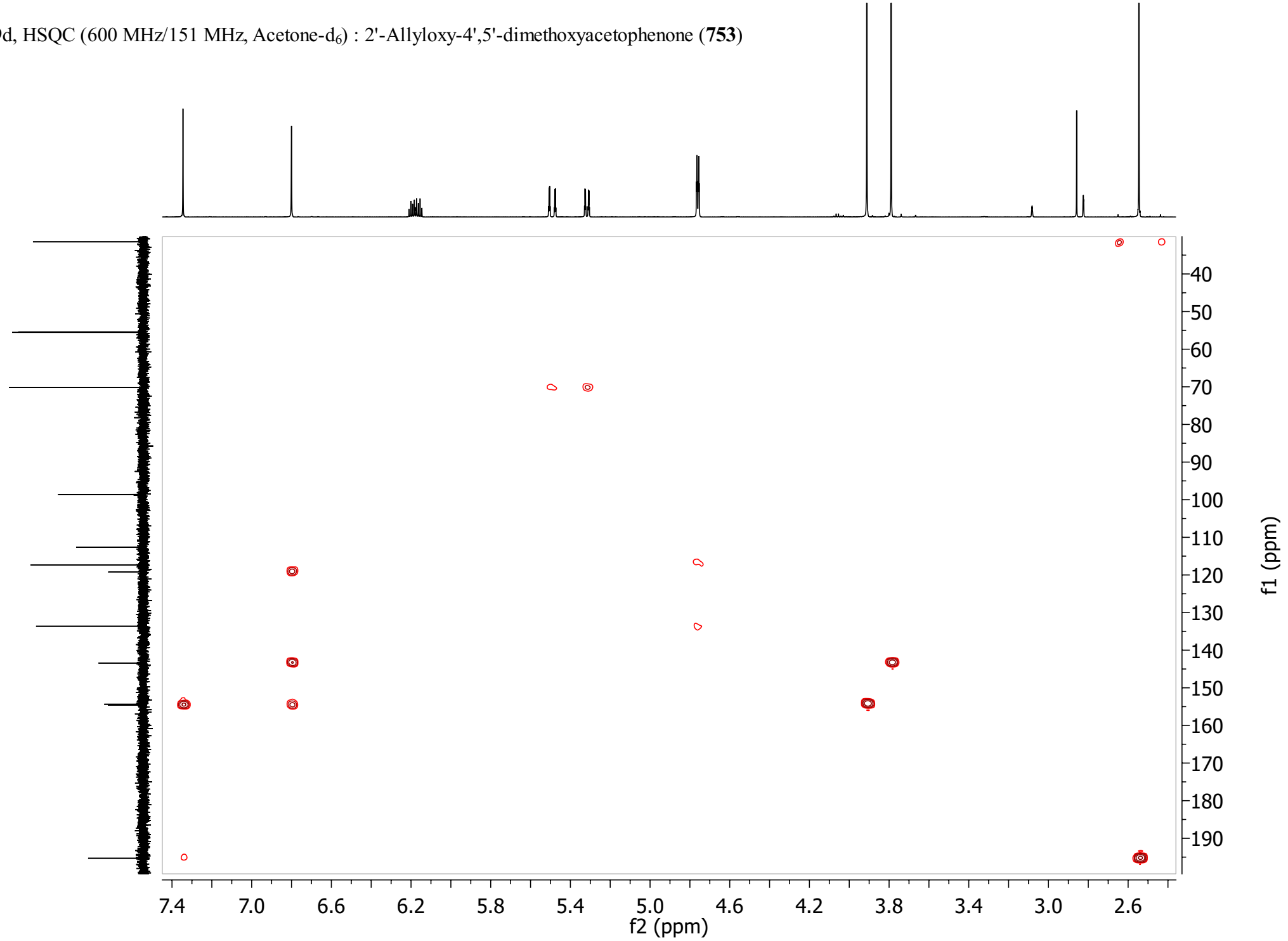
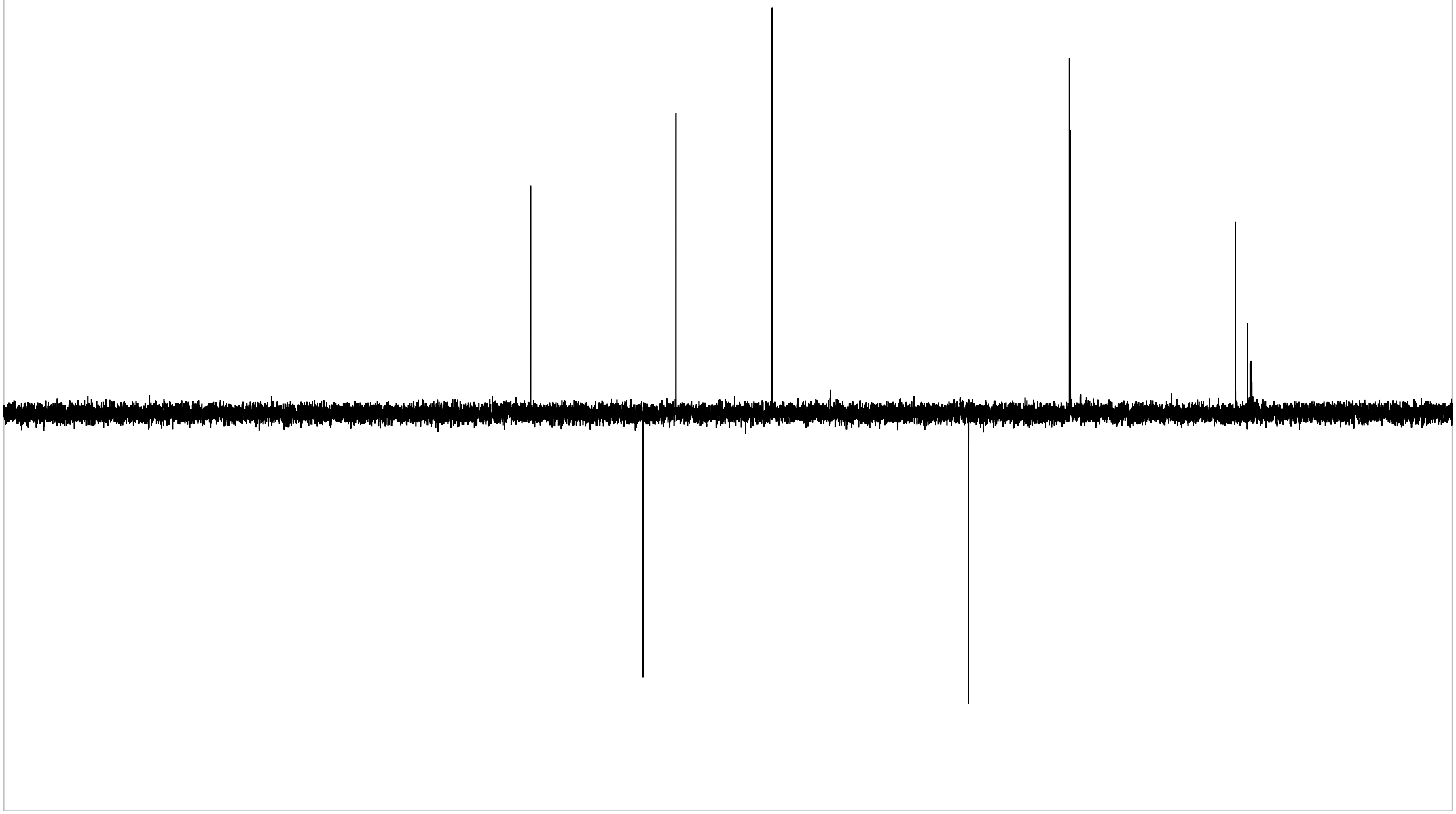


Plate 9e, DEPT (151 MHz, Acetone-d_6) : 2'-Allyloxy-4',5'-dimethoxyacetophenone (**753**)

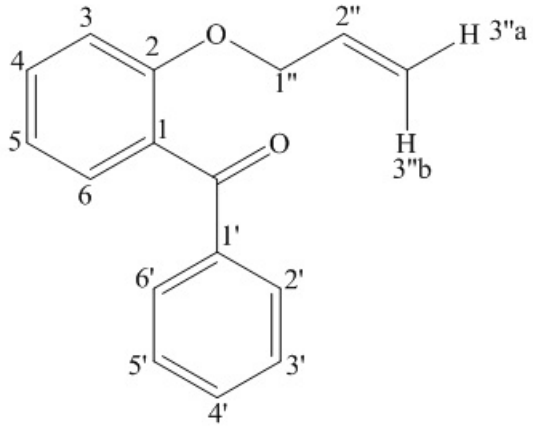


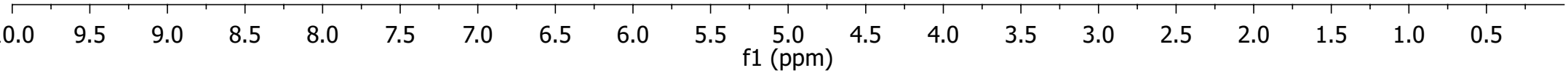
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 10a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyloxybenzophenone (**739**)

δ 7.79 – 7.76 (2H, m, H-2' and H- 6'), 7.62 – 7.58 (1H, m, H-4'), 7.53 – 7.47 (3H, m, H-4 and H-3' and H-5'), 7.39 (1H, dd, *J* = 7.4, 1.8 Hz, H-6), 7.14 (1H, br. d, *J* = 8.5 Hz, H-3), 7.11 (1H, ddd, *J* = 8.3, 7.4, 1.0 Hz, H-5), 5.73 (1H, ddt, *J* = 16.5, 11.4, 5.0 Hz, H-2''), 5.02 – 4.98 (2H, m, H-3''), 4.51 (2H, ddd, *J* = 5.0, 1.7, 1.7 Hz, H-1'')





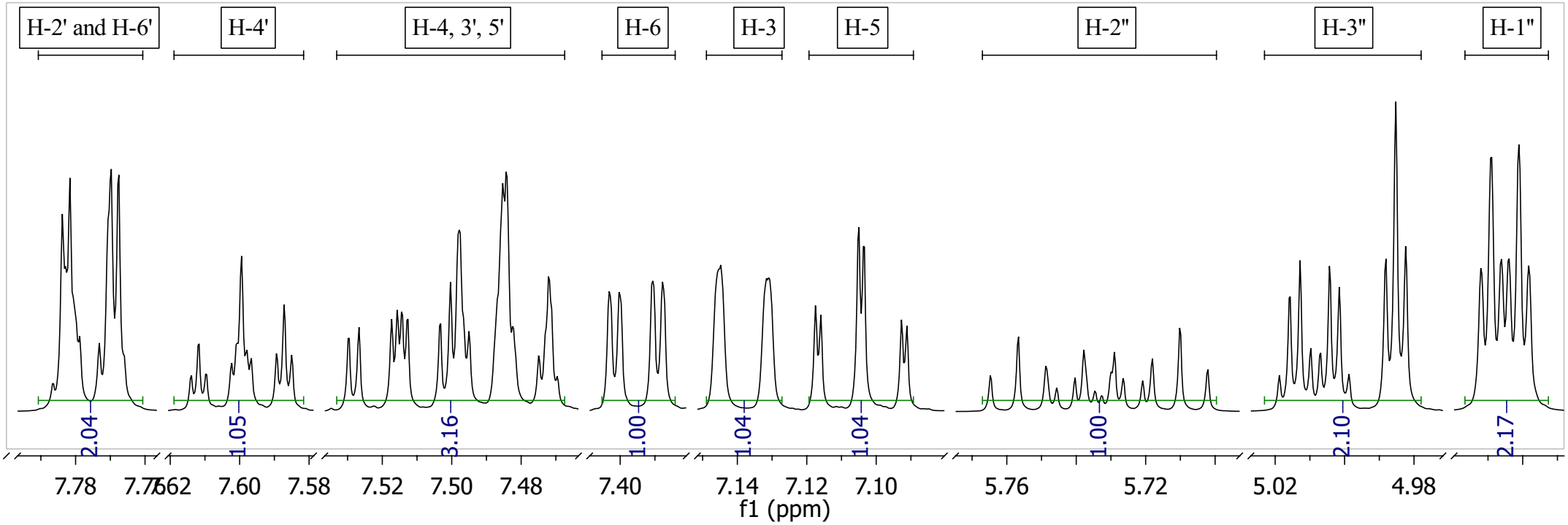
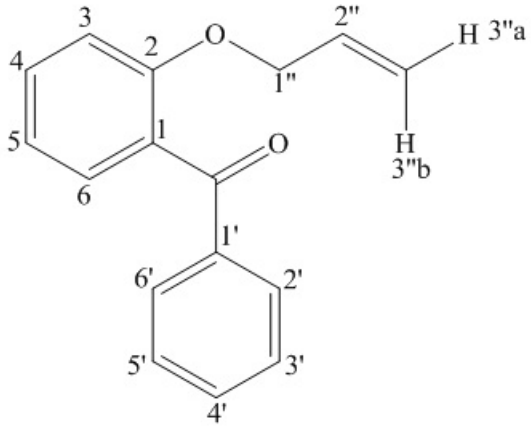


Plate 10b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyloxybenzophenone (**739**)

δ 196.50 (C=O), 157.04 (C-2), 138.99 (C-1'), 133.66 (C-4'/2''), 133.61 (C-4'/2''), 132.73 (C-4), 130.19 (C-1), 130.07 (C-6, C-2' and C-6'), 129.15 (C-3' and C-5'), 121.64 (C-5), 116.81 (C-3''), 113.68 (C-3), 69.36 (C-1'')



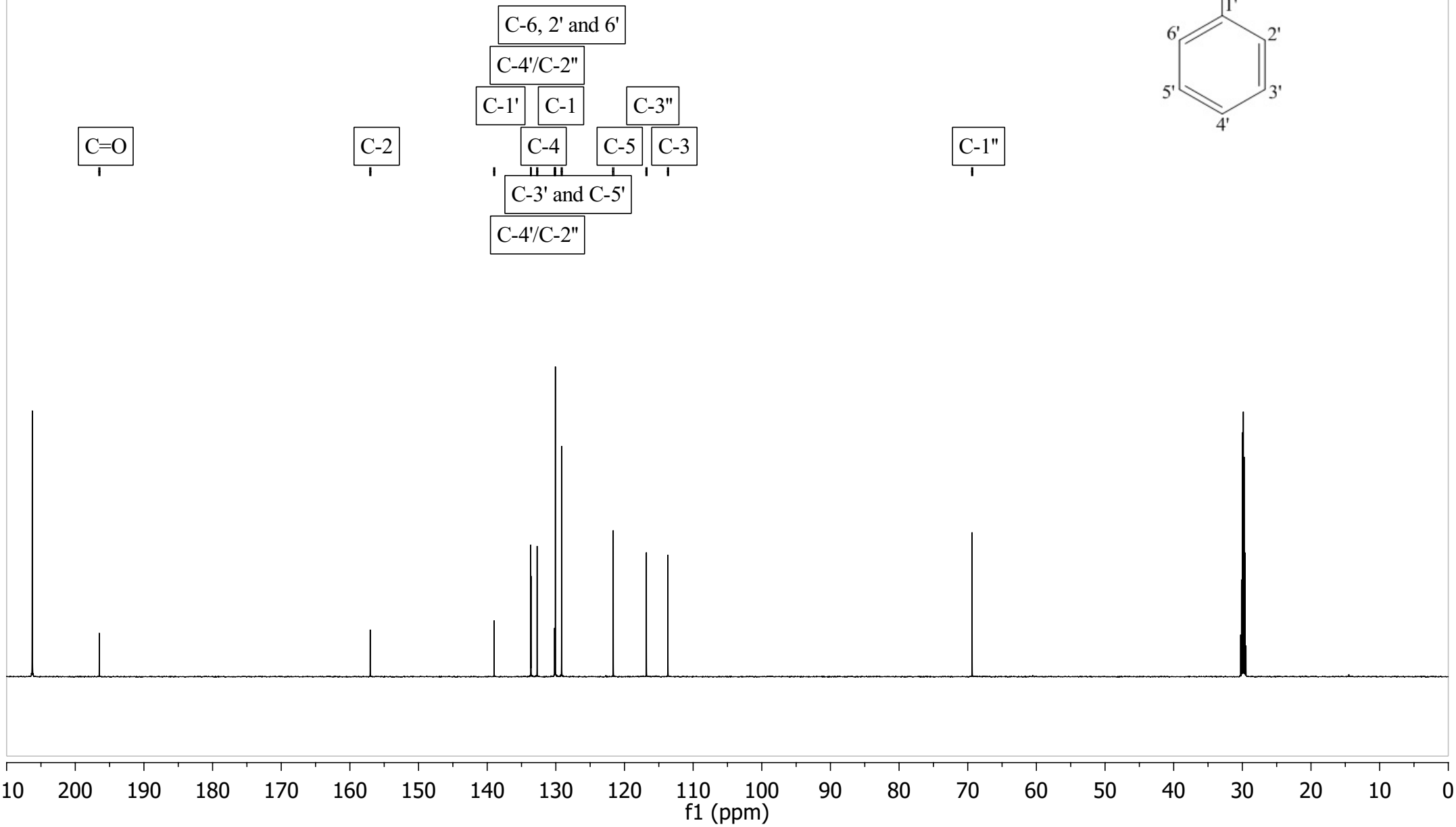


Plate 10c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyloxybenzophenone (**739**)

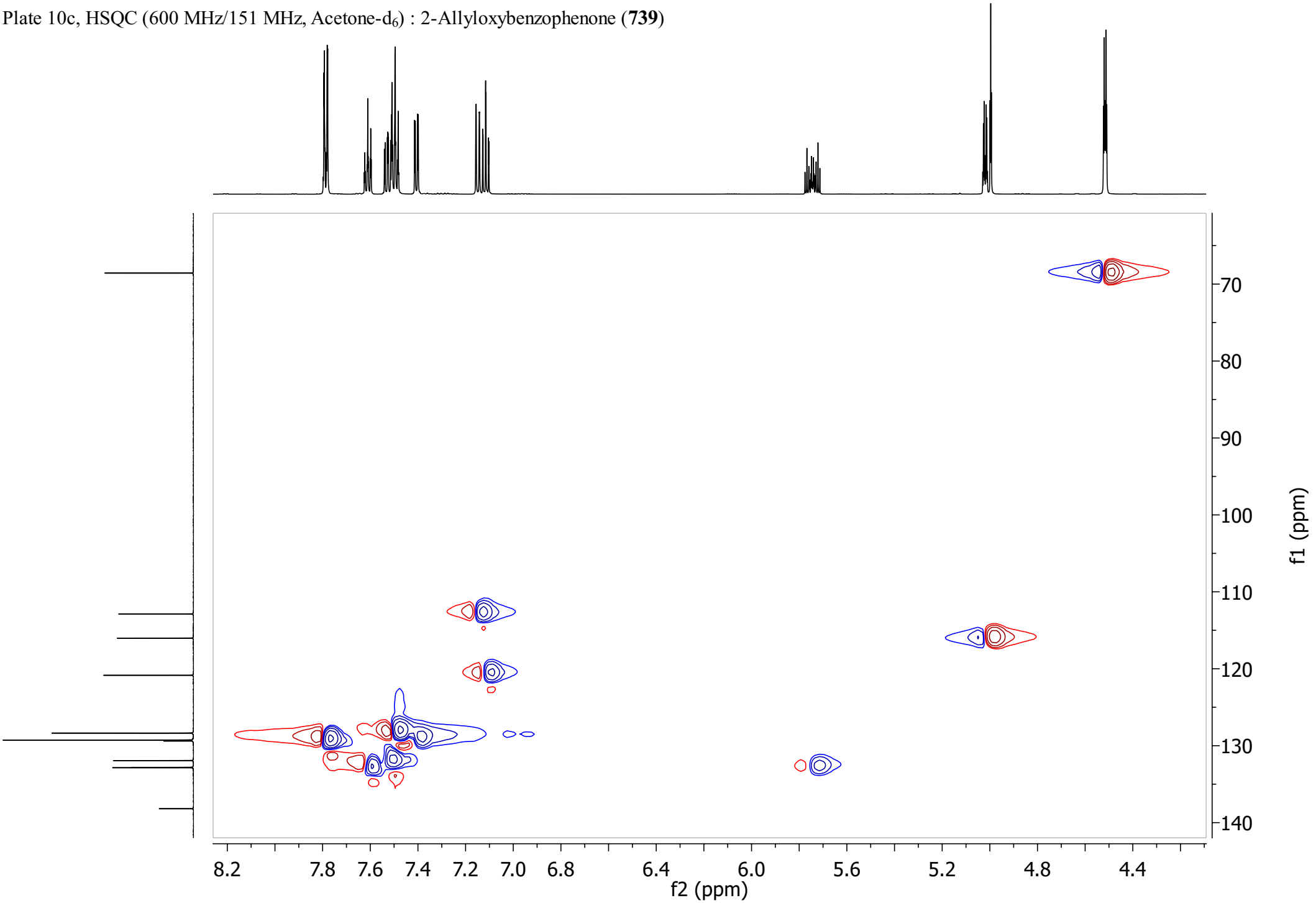


Plate 10d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyloxybenzophenone (**739**)

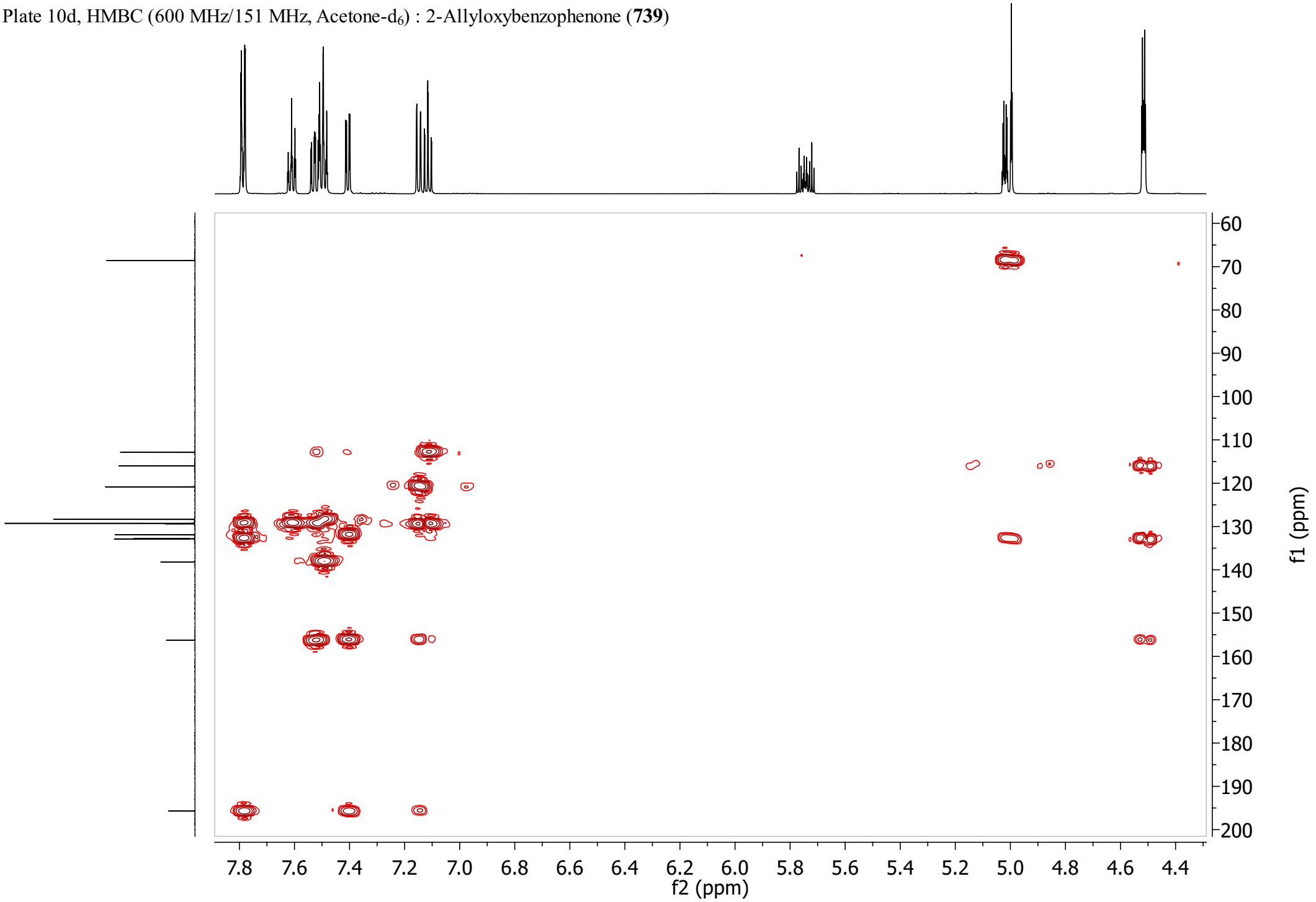


Plate 10e, DEPT (151 MHz, Acetone-d_6) : 2-Allyloxybenzophenone (**739**)

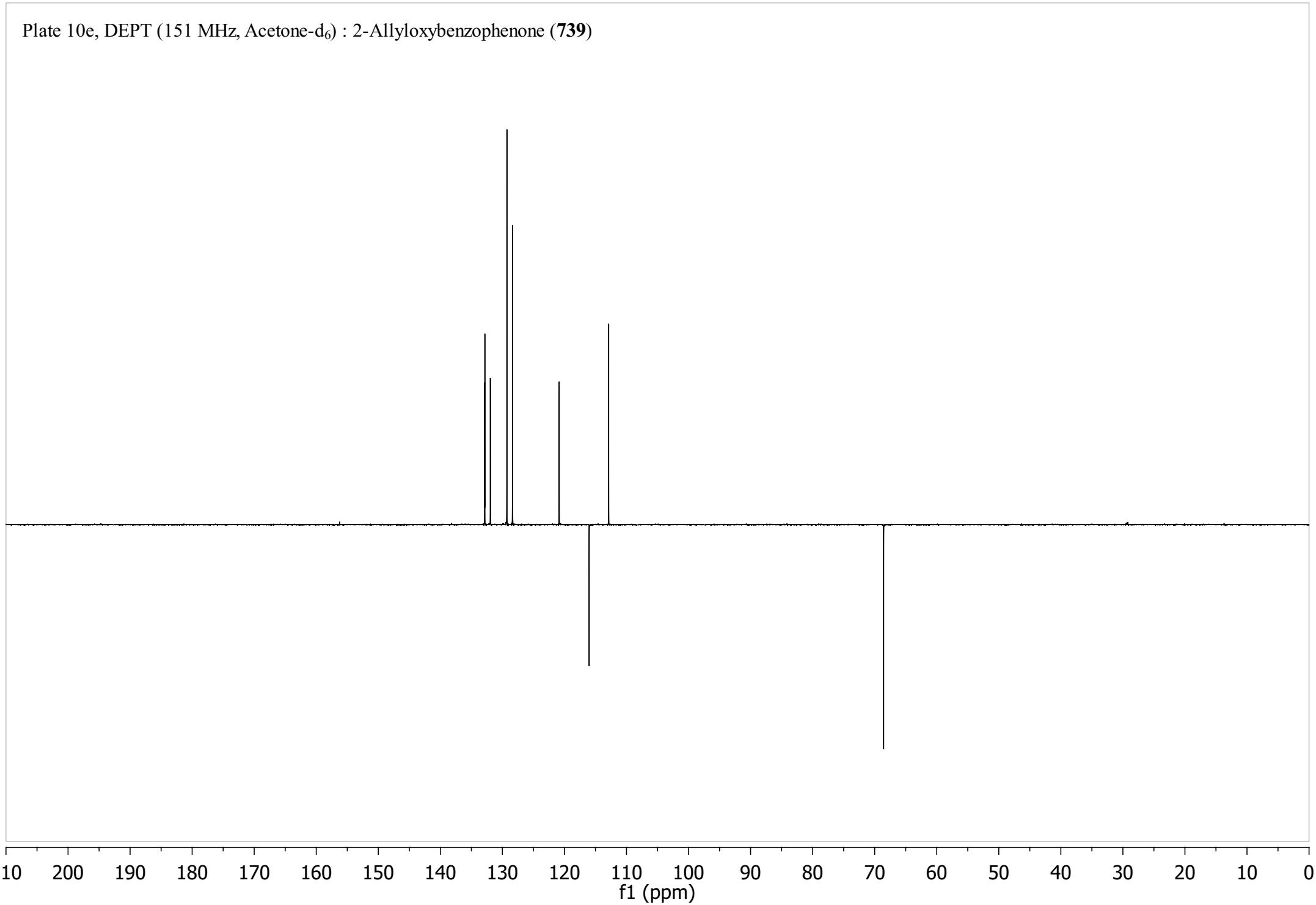
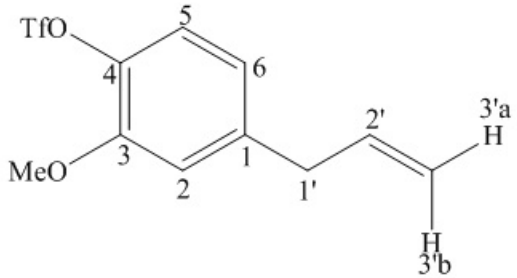
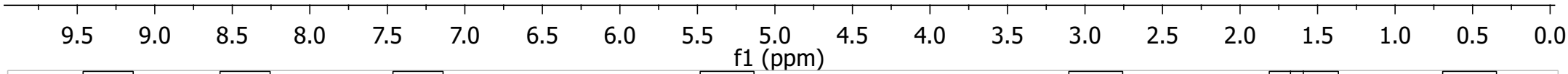


Plate 11a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)

δ 7.13 (1H, d, *J* = 8.3 Hz, H-5), 6.85 (1H, d, *J* = 1.9 Hz, H-2), 6.79 (1H, dd, *J* = 8.3, 1.9 Hz, H-6), 5.94 (1H, ddt, *J* = 17.1, 10.5, 6.7 Hz, H-2'), 5.14 – 5.10 (2H, m, H-3'a and H-3'b), 3.90 (3H, s, -OMe), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1')





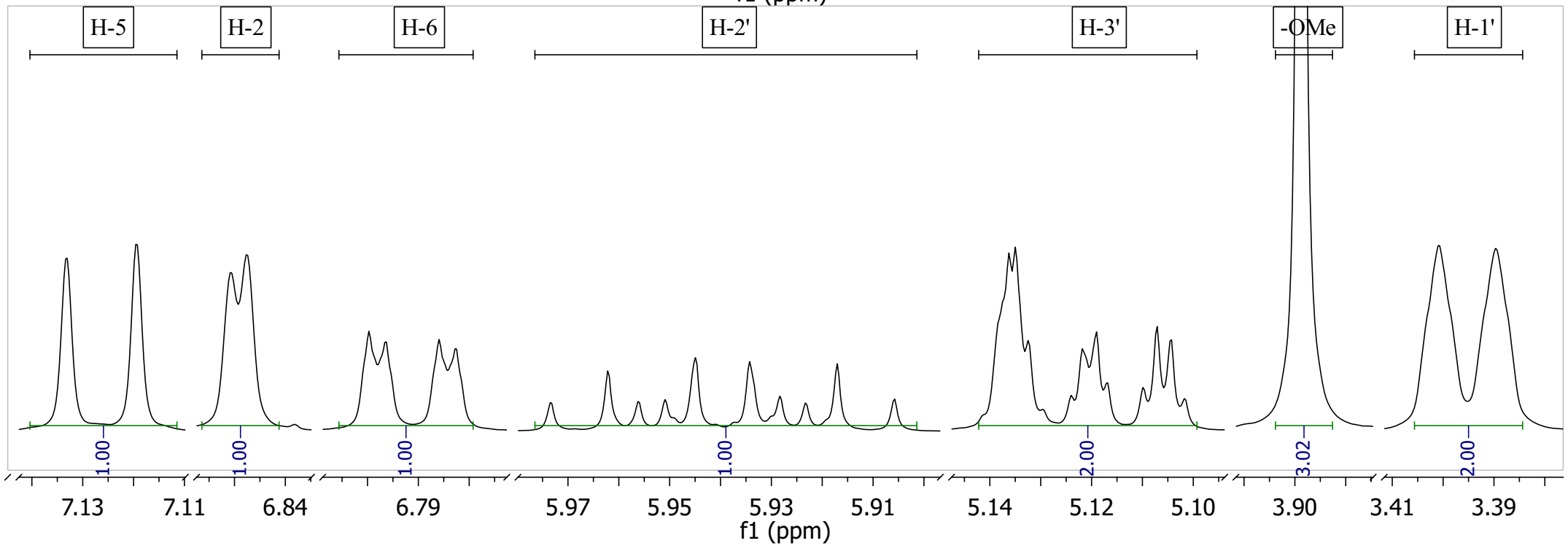
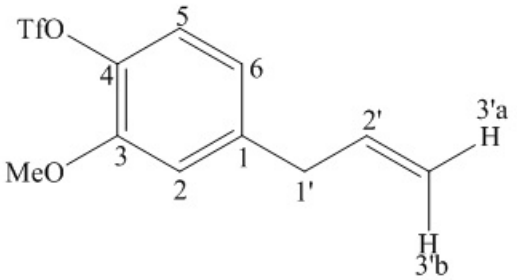
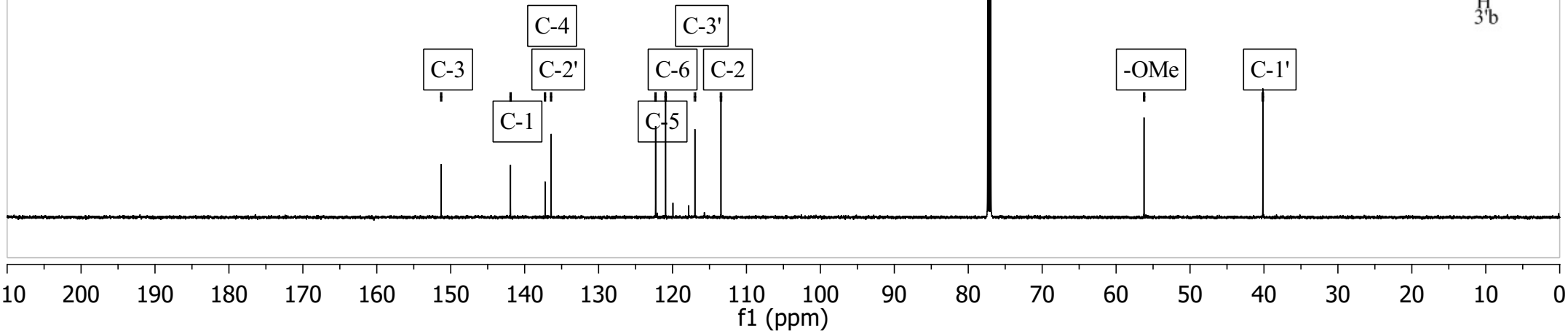


Plate 11b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)

δ 151.30 (C-3), 141.92 (C-1), 137.23 (C-4), 136.42 (C-2'), 122.29 (C-5), 120.93 (C-6), 118.89 (q, J = 320.5 Hz, -$OSO_2\underline{C}F_3$), 116.97 (C-3'), 113.45 (C-2), 56.22 (-O<u>Me</u>), 40.15 (C-1')





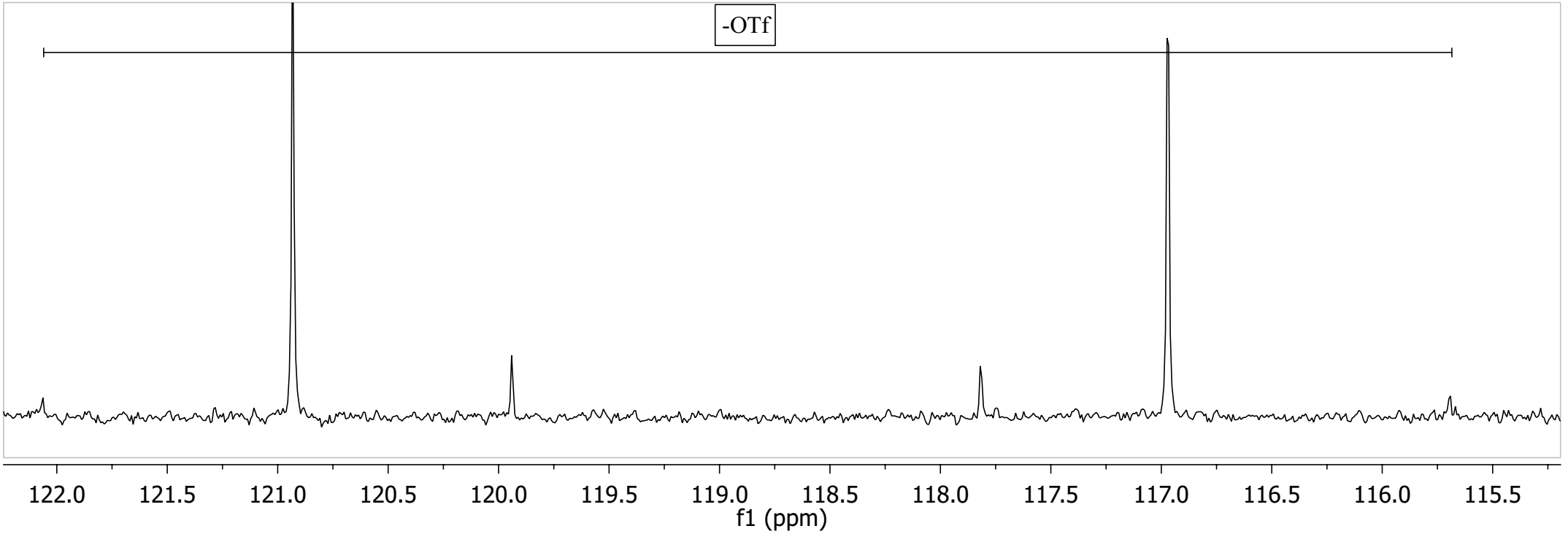


Plate 11c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)

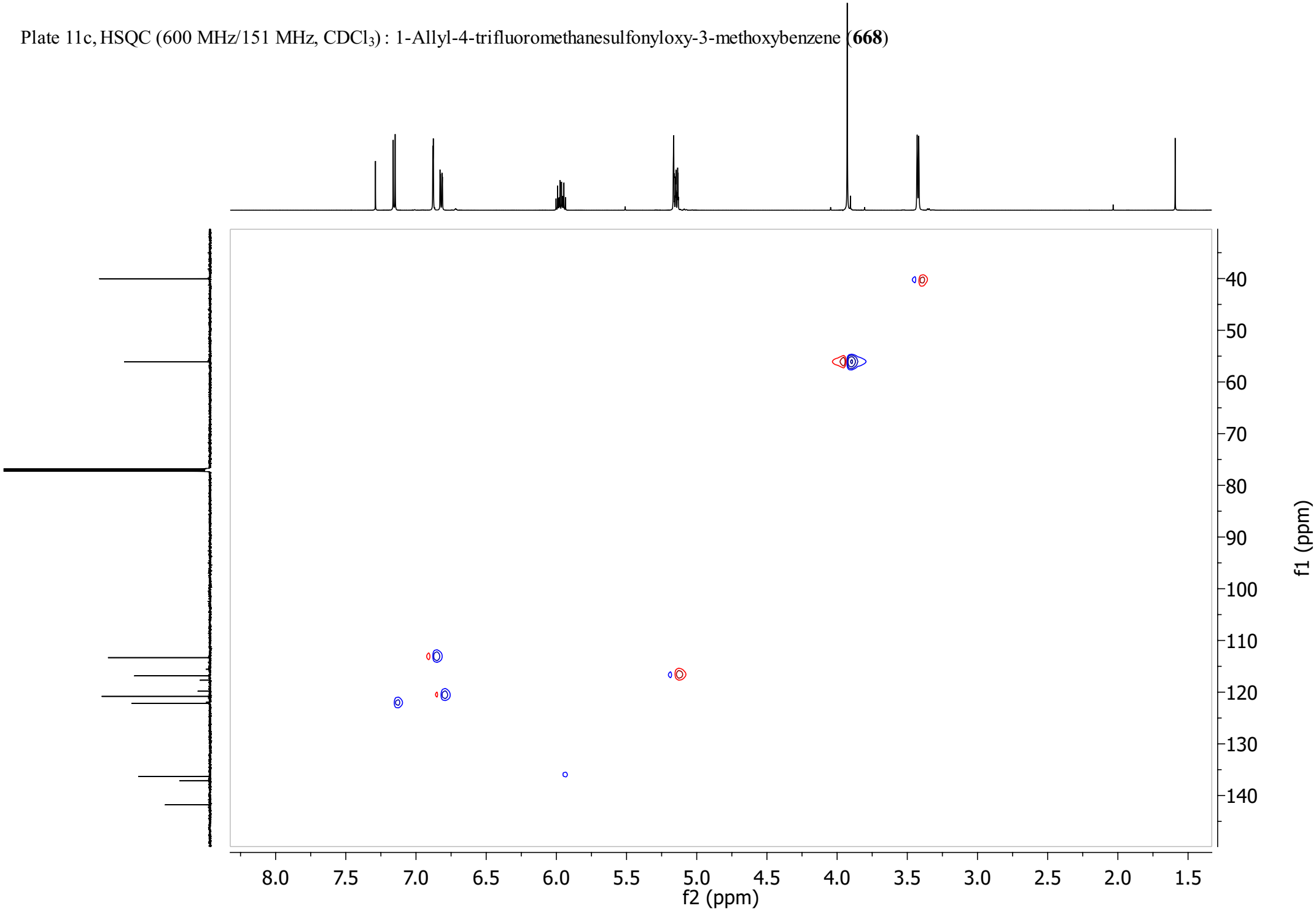


Plate 11d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)

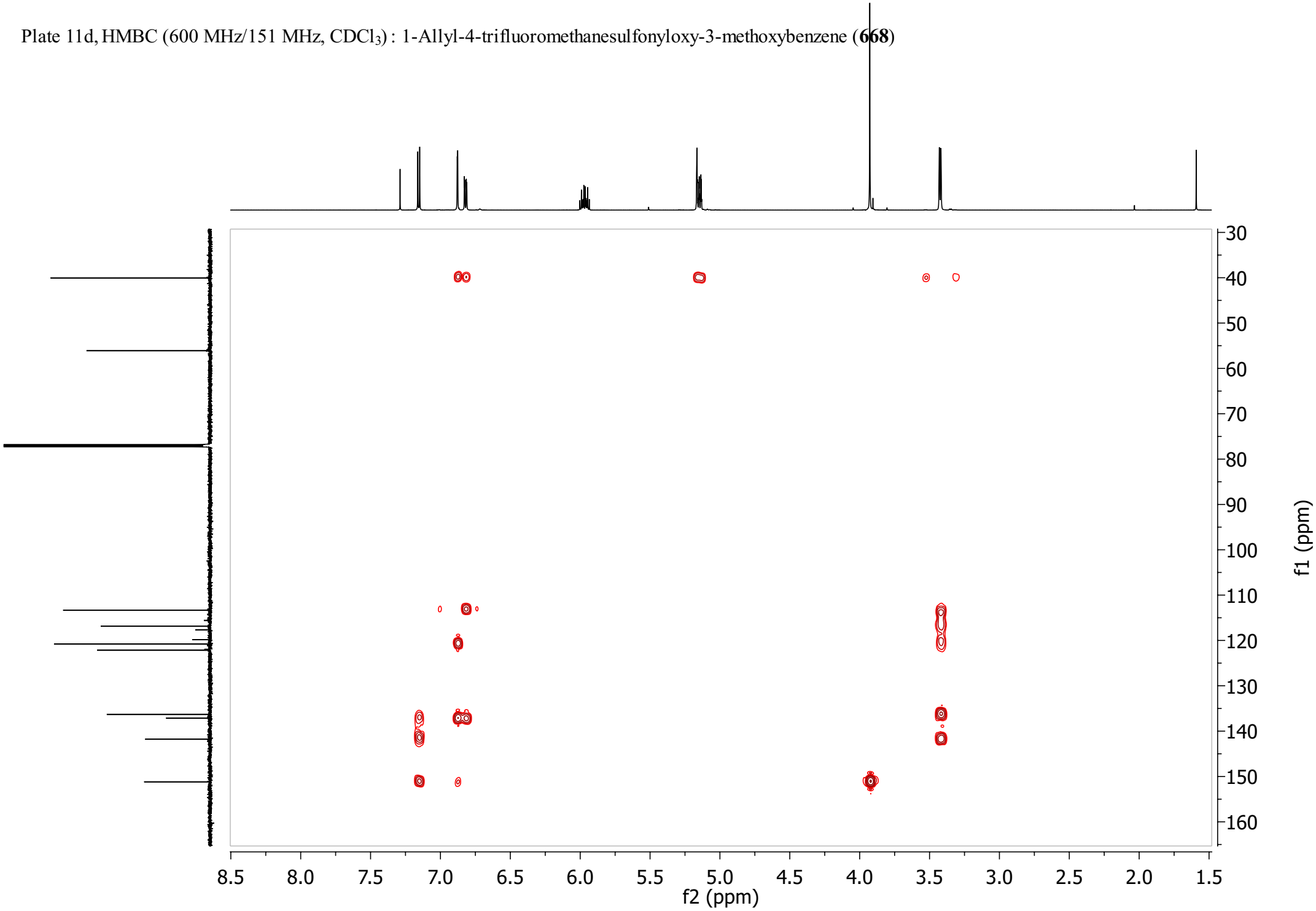


Plate 11e, DEPT (151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)

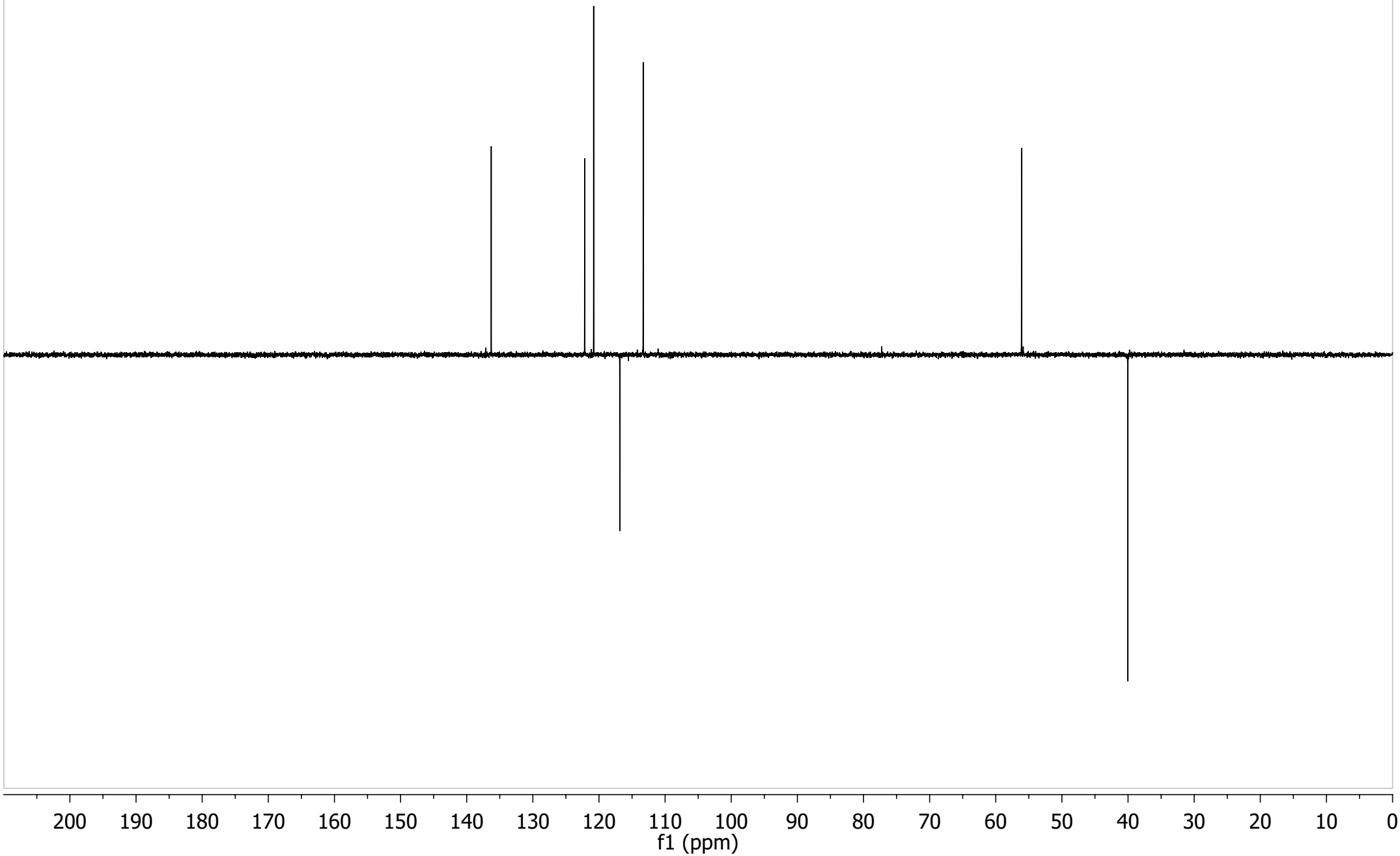


Plate 11f, ^{19}F (565 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**668**)

δ -74.70 (-OSOC<u>F</u>$_3$)

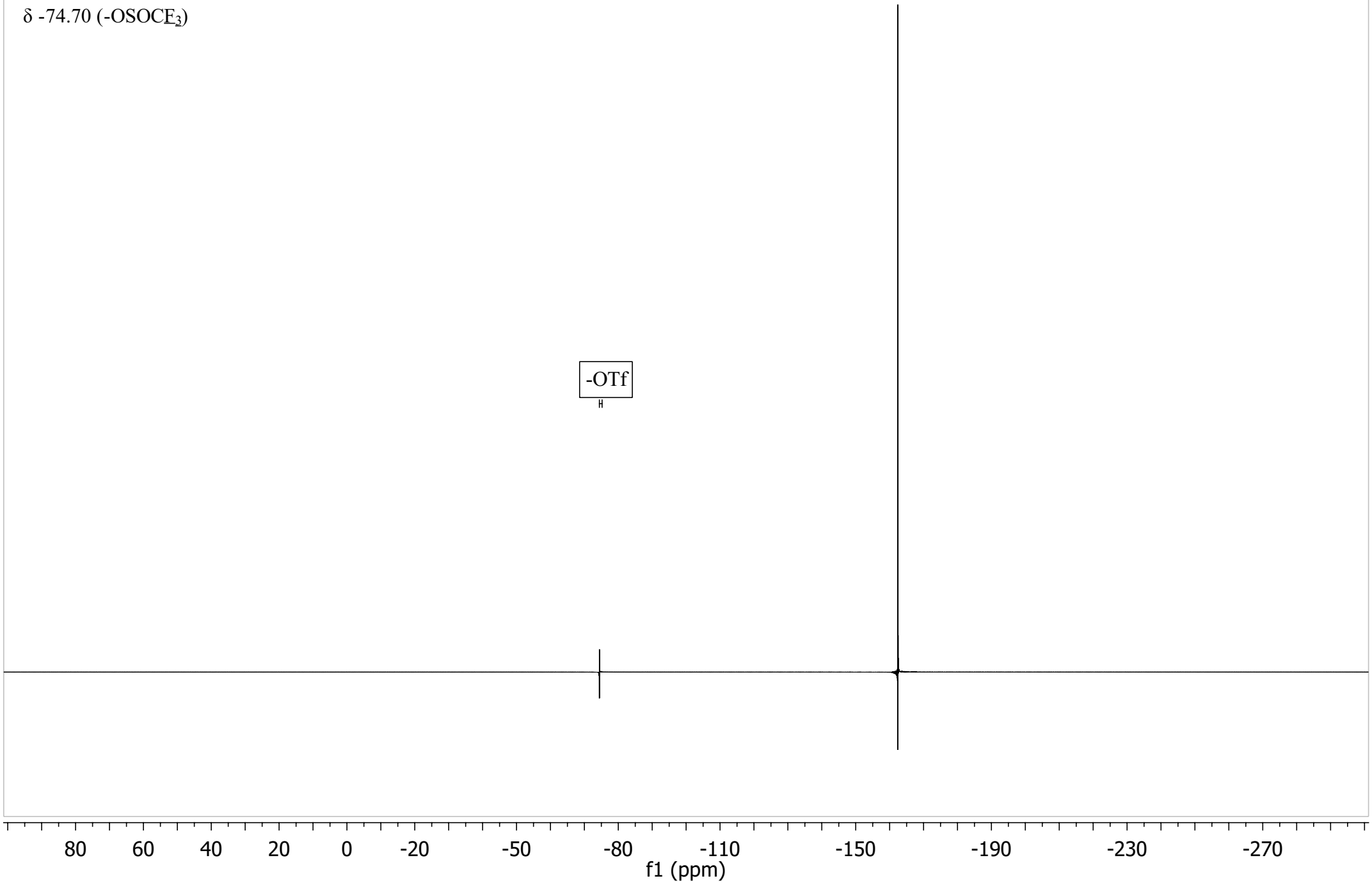
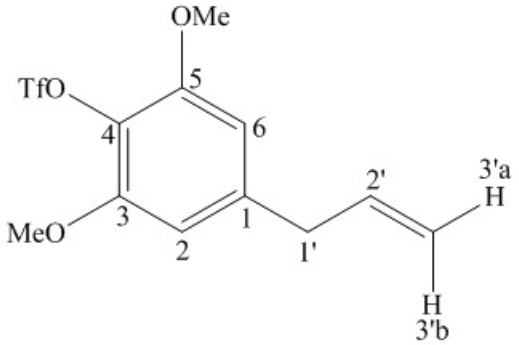
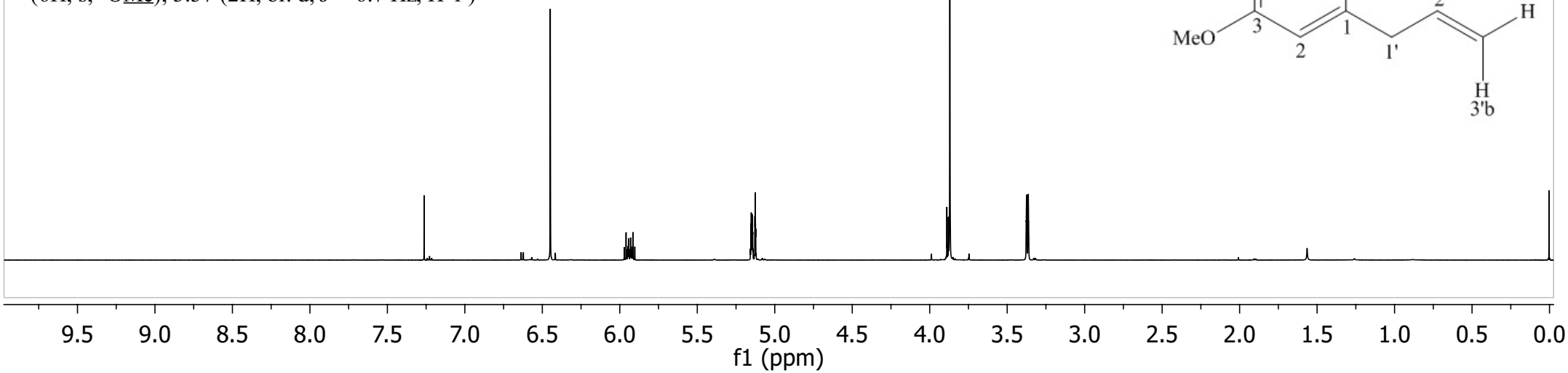


Plate 12a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

δ 6.45 (2H, s, H-2 and H-6), 5.97 – 5.90 (1H, m, H-2'), 5.16 – 5.12 (2H, m, H-3'a and H-3'b), 3.87 (6H, s, -OMe), 3.37 (2H, br. d, *J* = 6.7 Hz, H-1')





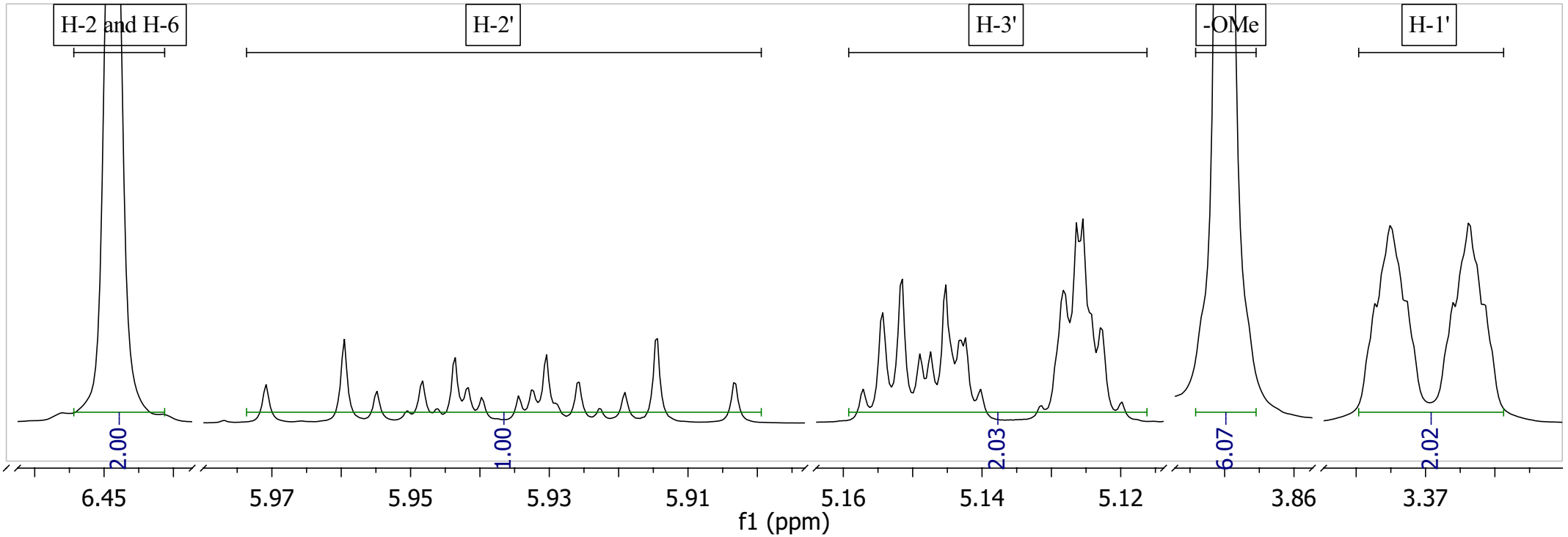
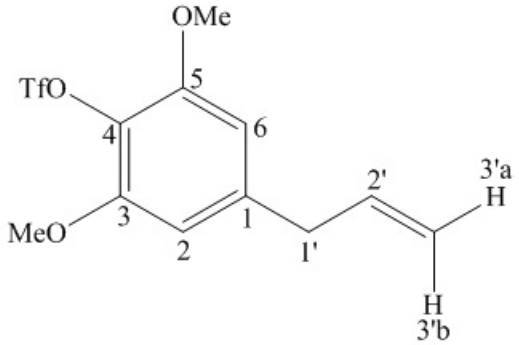
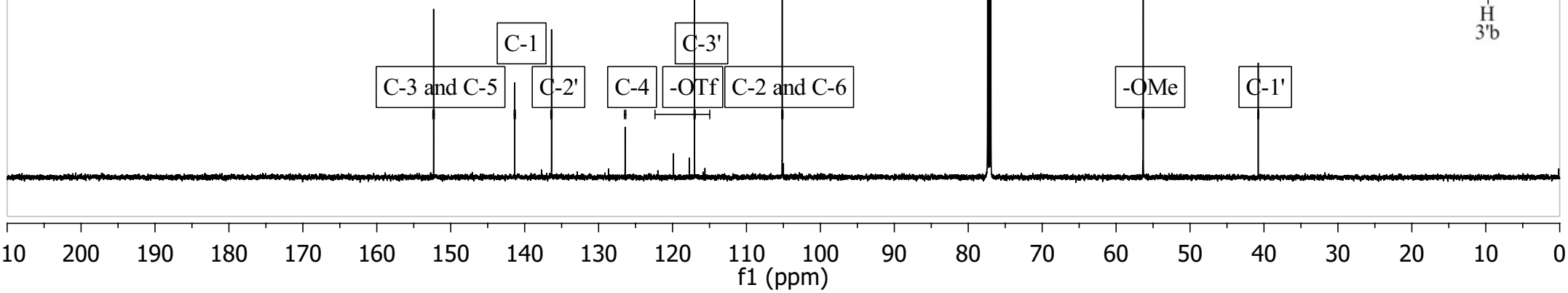


Plate 12b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

δ 152.32 (C-3 and C-5), 141.35 (C-1), 136.36 (C-2'), 126.41 (C-4), 118.05 (q, 320.6 Hz, -$OSO_2\underline{C}F_3$), 117.02 (C-3'), 105.16 (C-2 and C-6), 56.34 (-O<u>Me</u>), 40.77 (C-1')





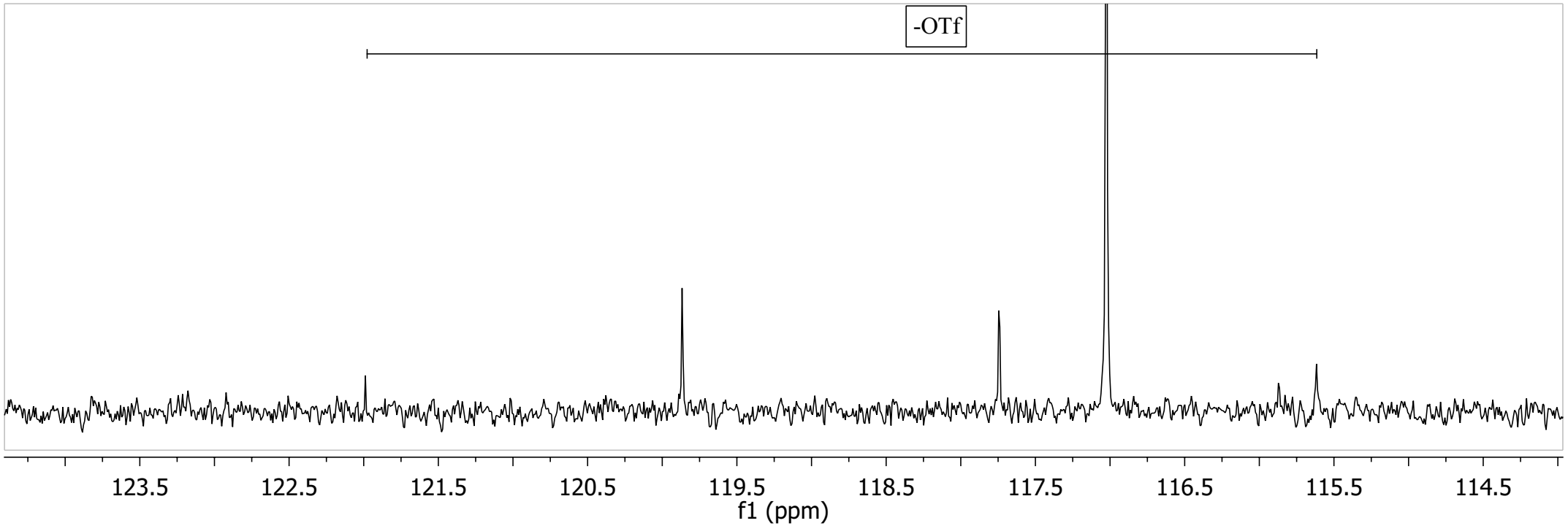


Plate 12d, HSQC (600 MHz/151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

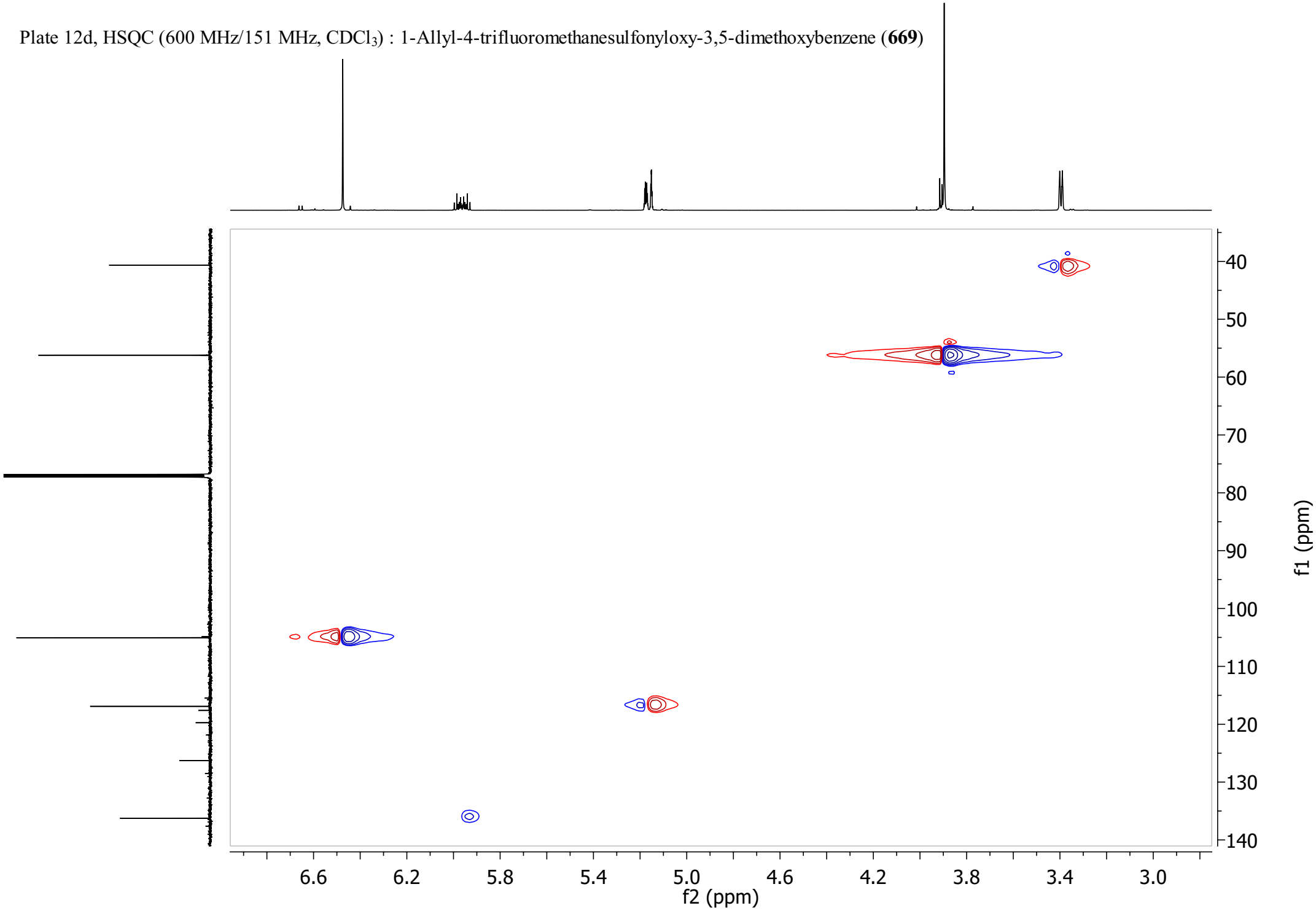


Plate 12d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

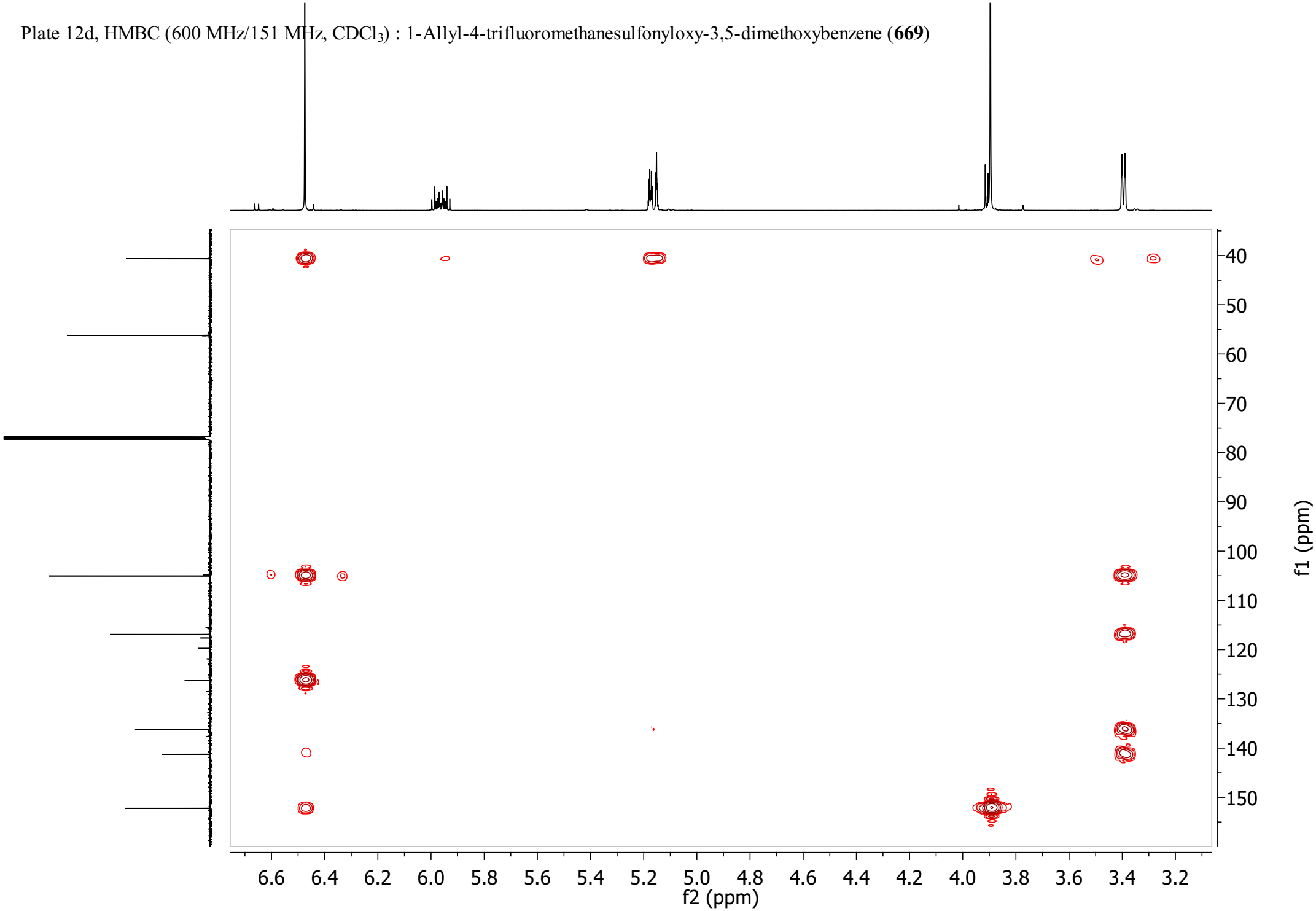


Plate 12e, DEPT (151 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

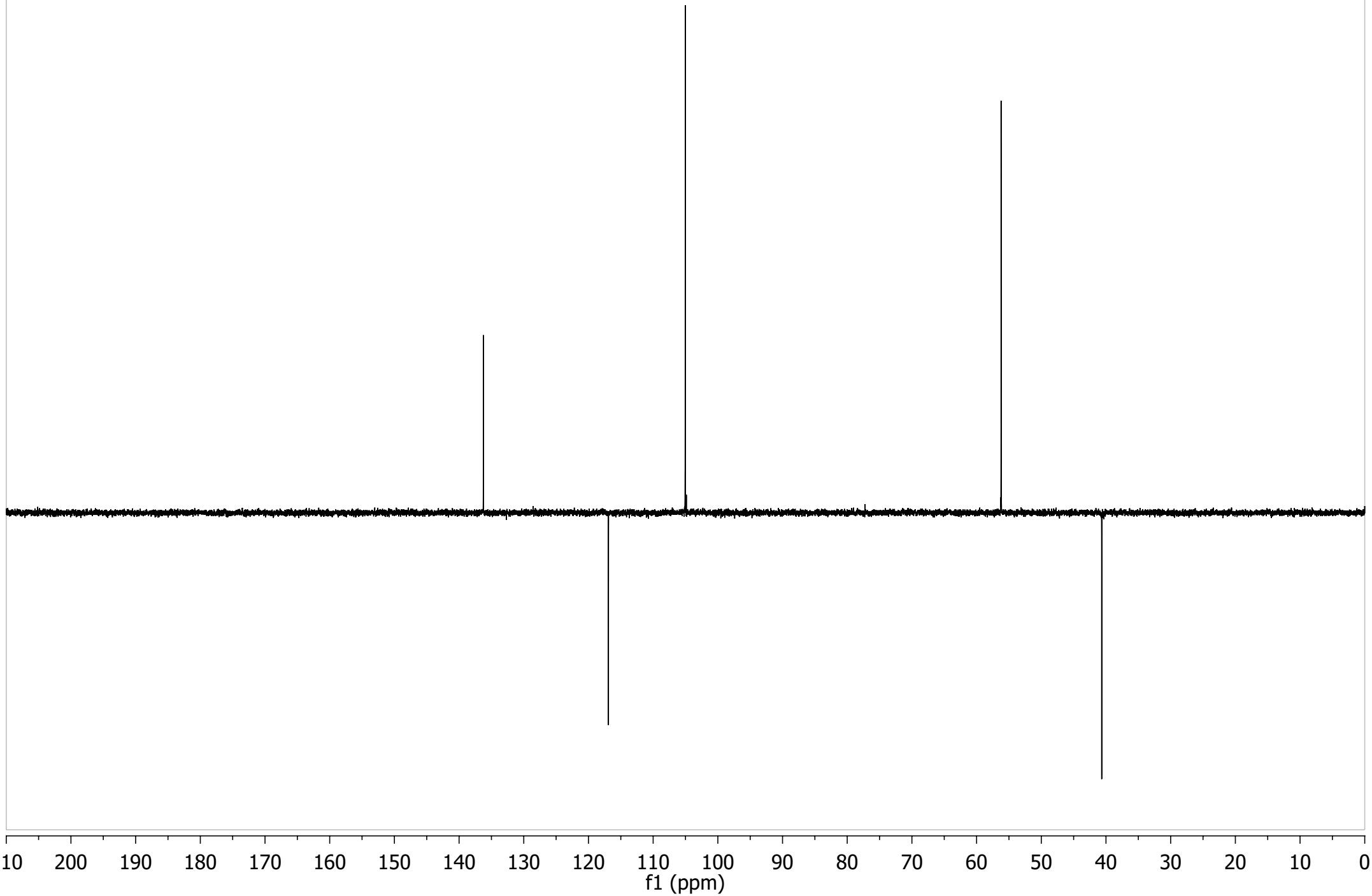


Plate 12f, ^{19}F (565 MHz, $CDCl_3$) : 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**669**)

δ -76.90 (-OSOC<u>F</u>$_3$)

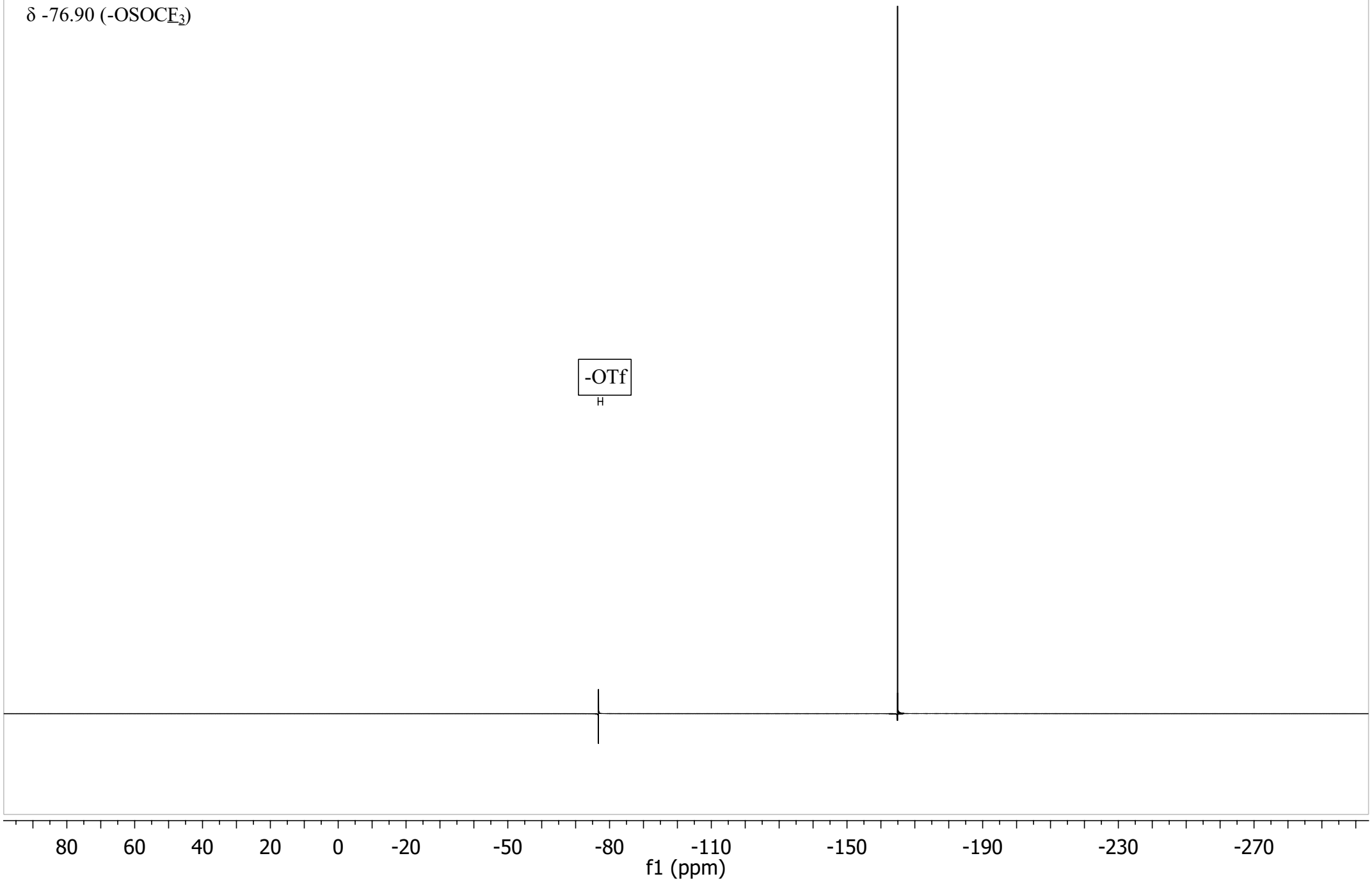
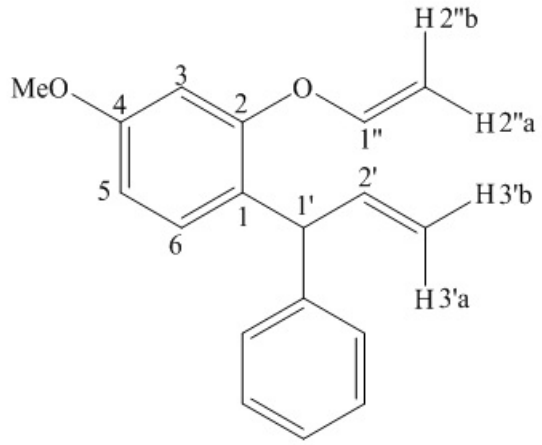
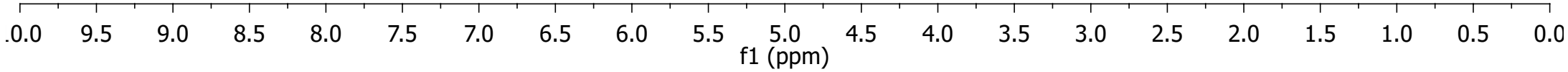


Plate 13a, ^{1}H NMR (600 MHz, $CDCl_3$) : 4-Methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**)

δ 7.30 – 7.26 (2H, m, Ar-H), 7.20 – 7.17 (3H, m, Ar-H), 7.05 (1H, d, *J* = 8.5 Hz, H-6), 6.61 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.54 (1H, d, *J* = 2.5 Hz, H-3), 6.50 (1H, br. dd, *J* = 13.8, 6.1 Hz, H-1''), 6.27 (1H, ddd, *J* = 17.1, 10.2, 6.7 Hz, H-2'), 5.20 (1H, br. d, *J* = 10.2 Hz, H-3'b), 5.05 (1H, br. d, *J* = 6.7 Hz, H-1'), 4.92 (1H, br. d, *J* = 17.1 Hz, H-3'a), 4.64 (1H, dd, *J* = 13.8, 1.4 Hz, H-2''b), 4.35 (1H, dd, *J* = 6.1, 1.4 Hz, H-2''a), 3.78 (3H, s, -OMe)





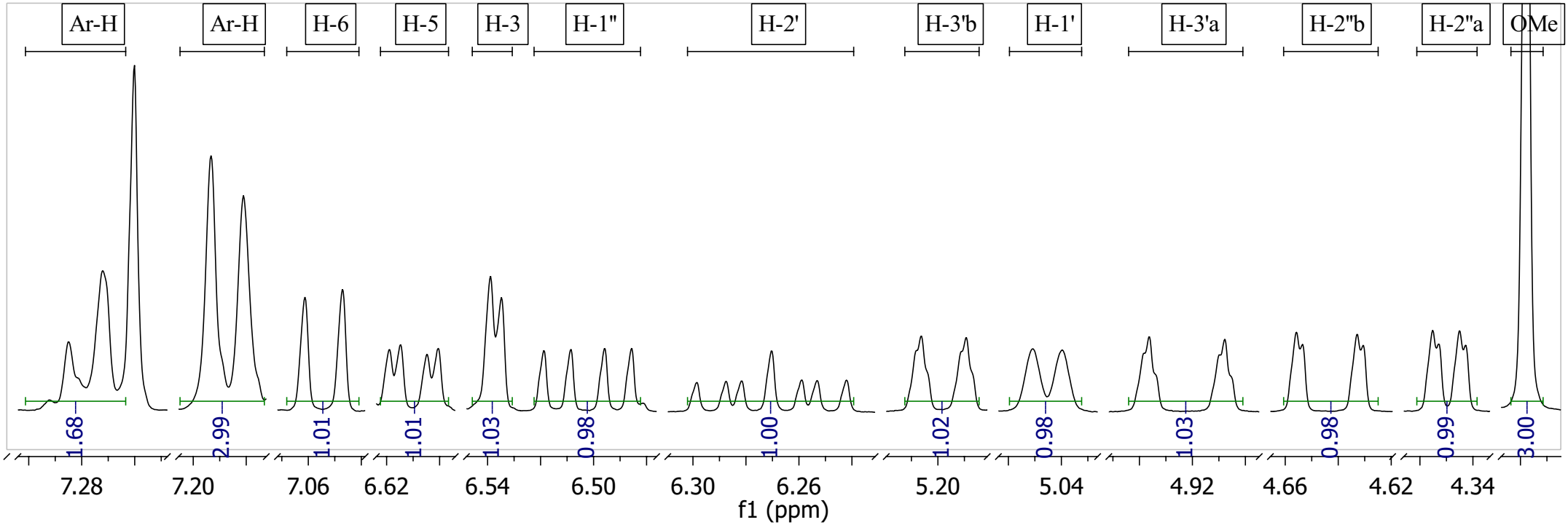
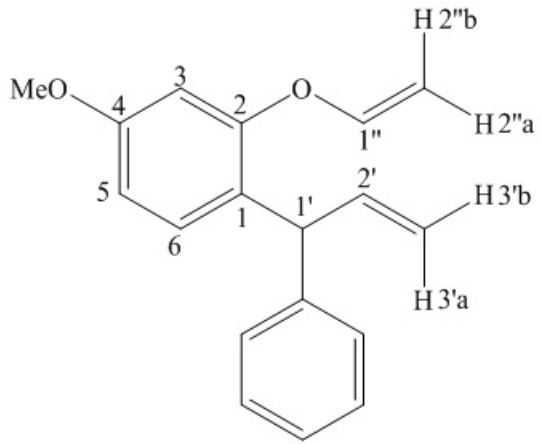


Plate 13b, ^{13}C NMR (151 MHz, $CDCl_3$) : 4-Methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**)

δ 159.35 (C-4), 155.01 (C-2), 148.88 (C-1''), 143.20 (4°-C), 140.34 (C-2'), 130.27 (C-6), 128.69 (Ar-C), 128.32 (Ar-C), 126.24 (Ar-C), 125.94 (C-1), 116.29 (C-3'), 108.67 (C-5), 103.96 (C-3), 94.74 (C-2''), 55.56 (-O<u>Me</u>), 47.35 (C-1')



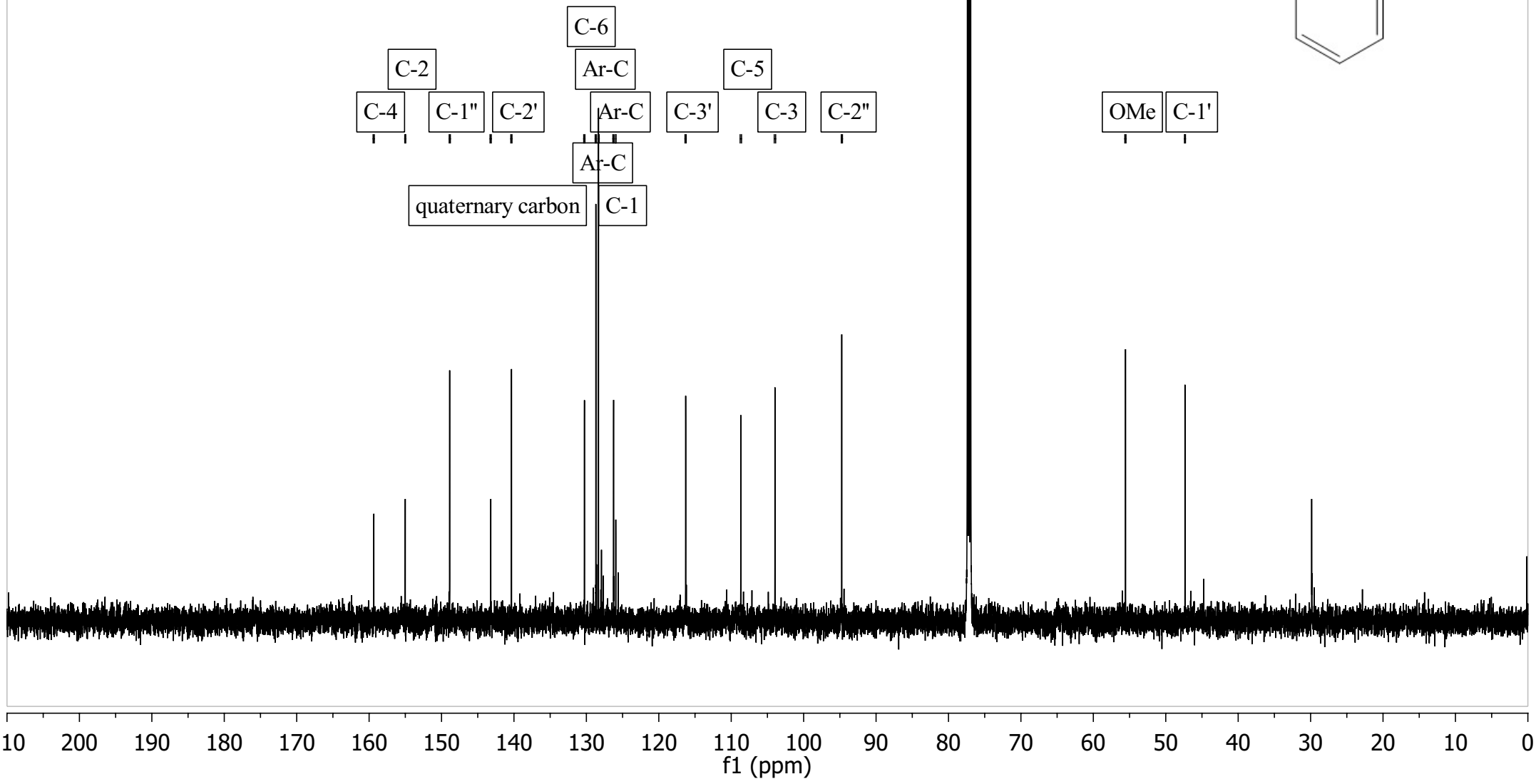


Plate 13c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 4-Methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**)

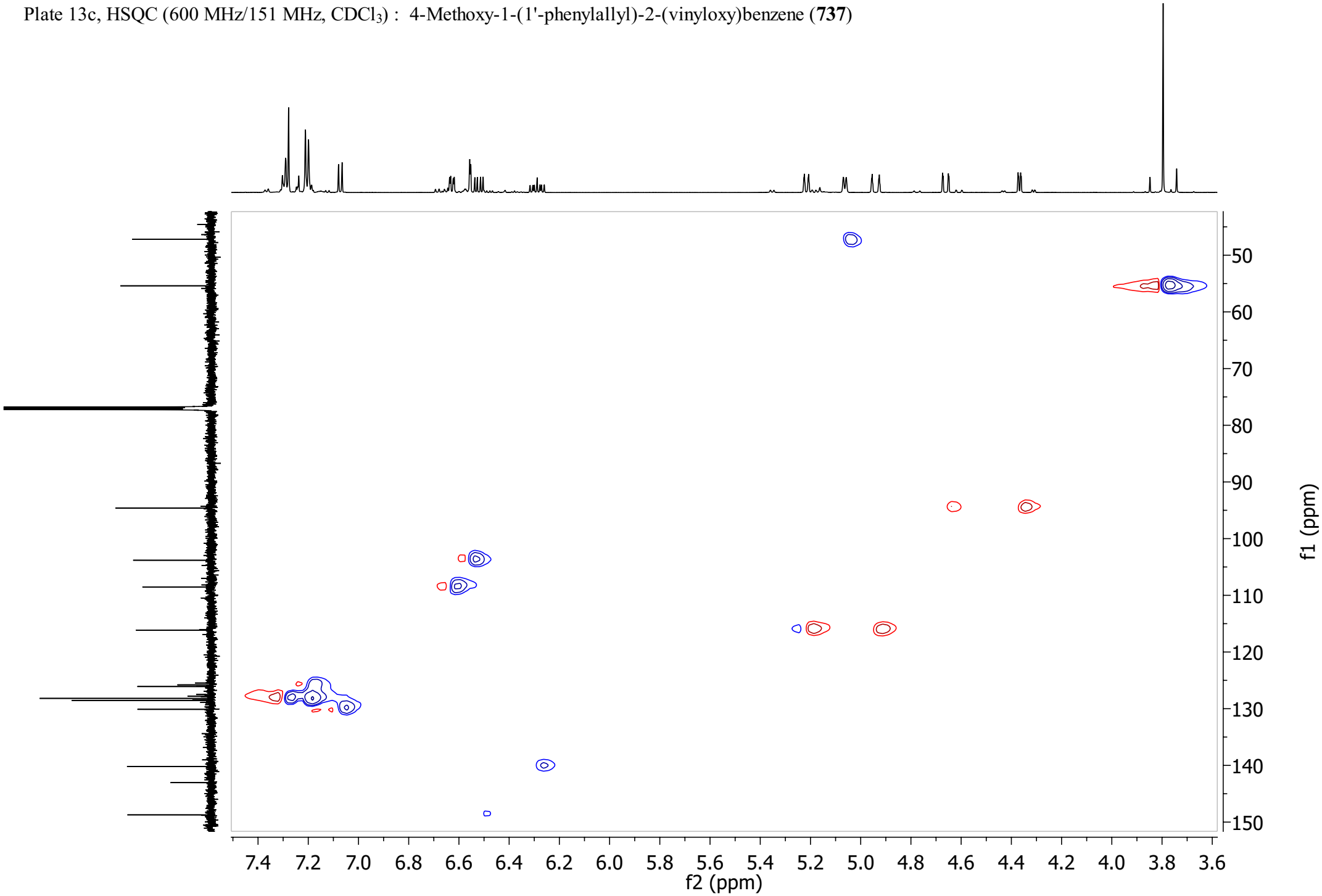


Plate 13d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 4-Methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**)

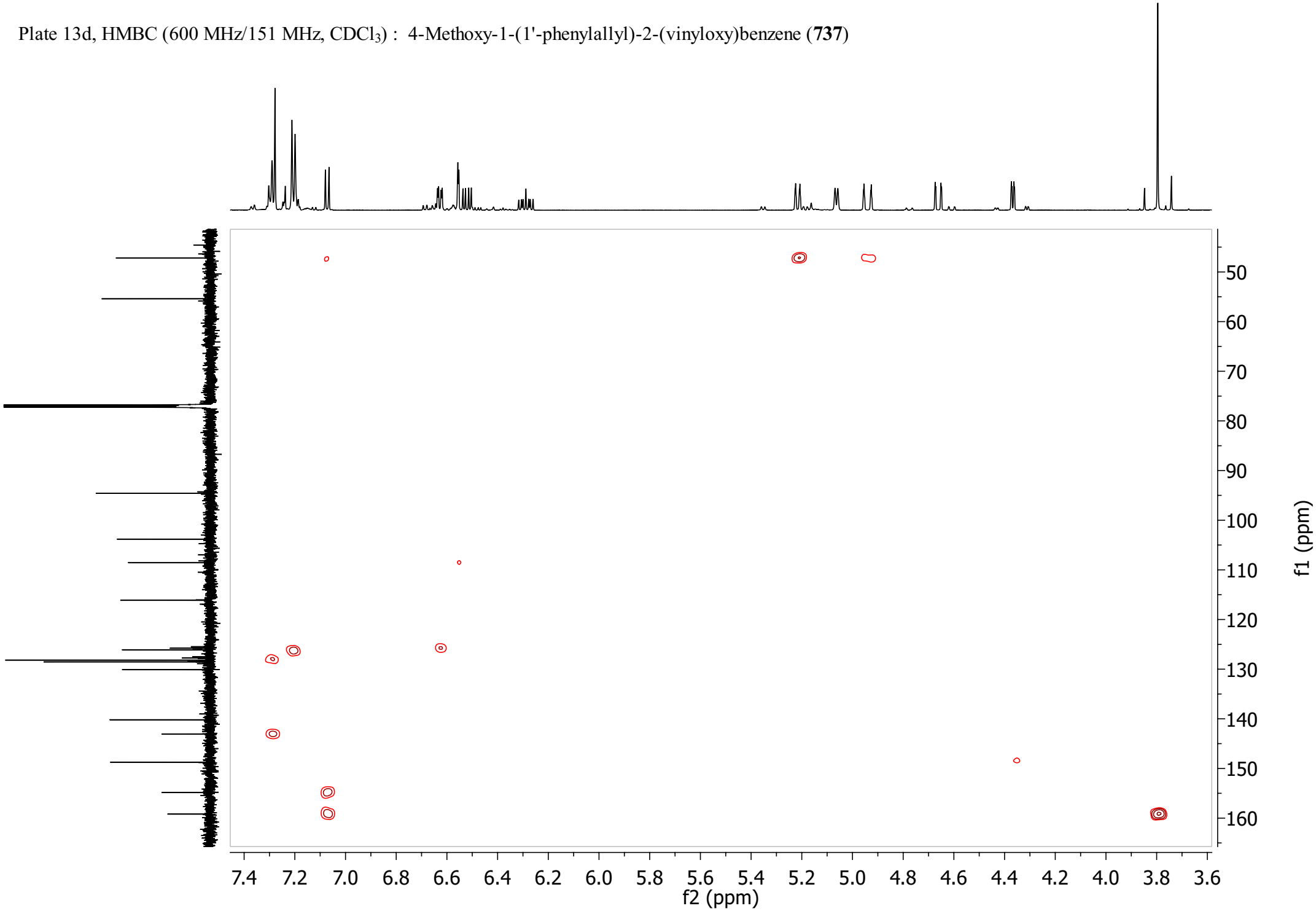
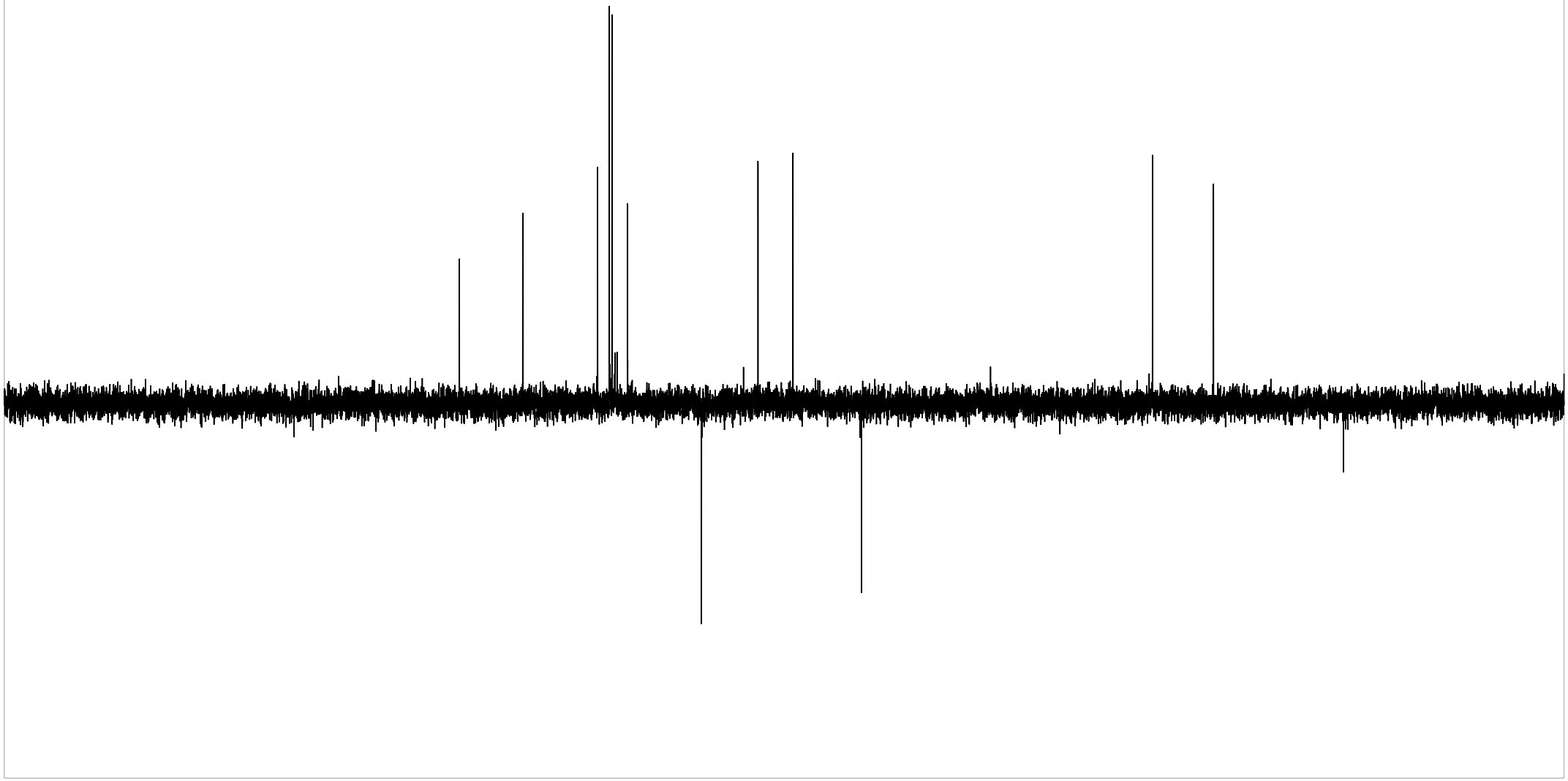


Plate 13e, DEPT (151 MHz, $CDCl_3$) : 4-Methoxy-1-(1'-phenylallyl)-2-(vinyloxy)benzene (**737**)



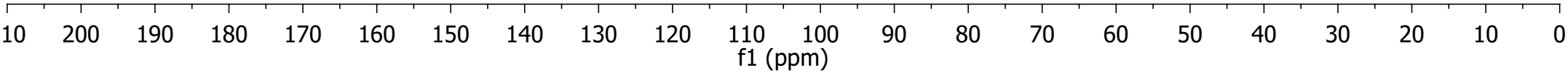
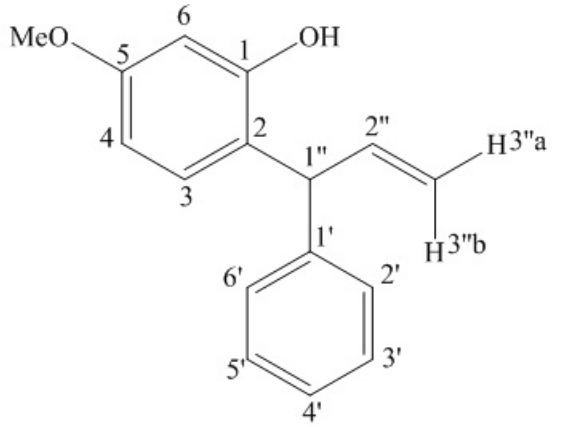


Plate 14a, ^{1}H NMR (600 MHz, $CDCl_3$) : 5-Methoxy-2-(1-phenylallyl)phenol (**732**)

δ 7.35 – 7.32 (2H, dd, H-3' and H-5'), 7.26 – 7.22 (3H, m, Ar-H), 6.95 (1H, d, *J* = 8.5 Hz, H-3), 6.48 (1H, dd, *J* = 8.5, 2.6 Hz, H-4), 6.42 (1H, d, *J* = 2.6 Hz, H-6), 6.33 (1H, ddd, *J* = 17.3, 10.2, 6.5 Hz, H-2''), 5.30 (1H, ddd, *J* = 10.2, 1.5, 1.5 Hz, H-3''b), 5.02 (1H, ddd, *J* = 17.3, 1.5, 1.5 Hz, H-3''a), 4.88 (1H, br. d, *J* = 6.5 Hz, H-1''), 3.78 (3H, s, -OMe)



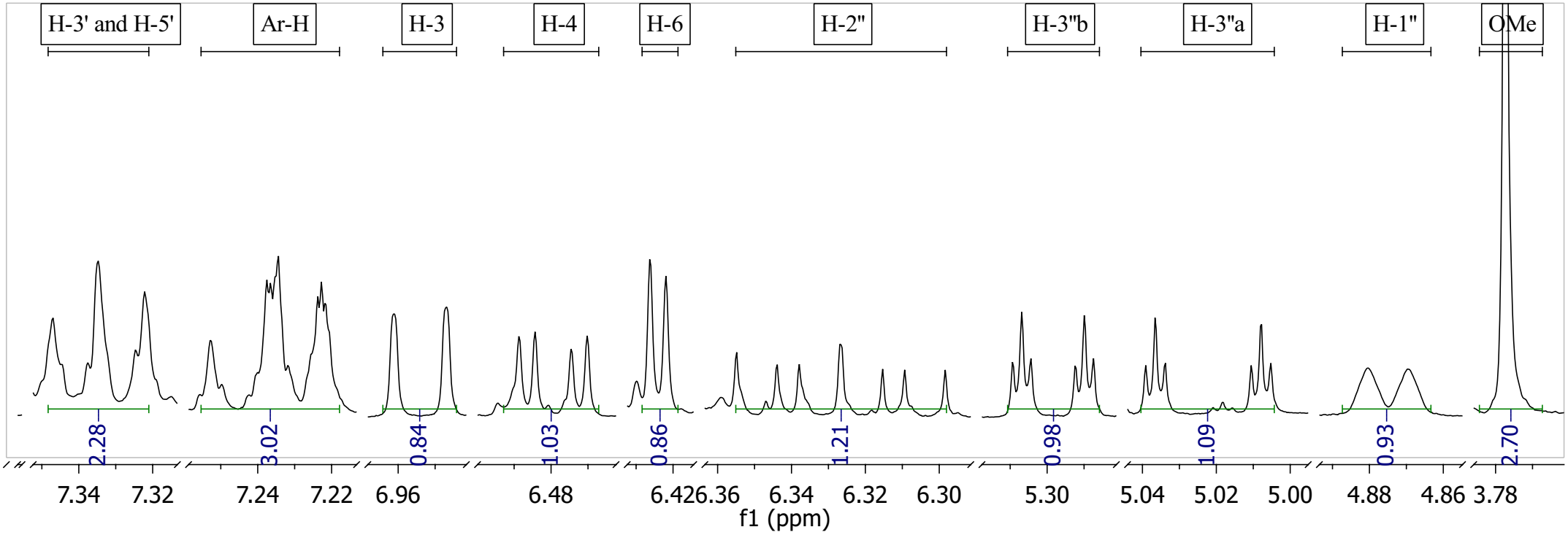
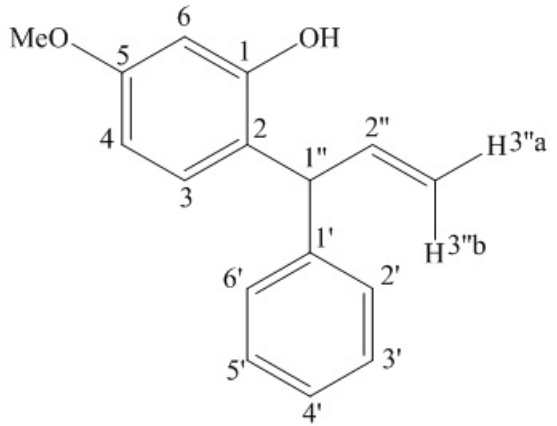


Plate 14b, ^{13}C NMR (151 MHz, $CDCl_3$) : 5-Methoxy-2-(1-phenylallyl)phenol (**732**)

δ 159.80 (C-5), 154.62 (C-1), 139.79 (C-2''), 130.39 (C-3), 128.80 (Ar-C), 126.92 (Ar-C), 126.37 (Ar-C), 117.03 (C-3''), 106.24 (C-4), 102.57 (C-6), 99.72 (C-1'/2), 91.74 (C-1'/2), 55.44 (-O<u>Me</u>), 48.99 (C-1'')



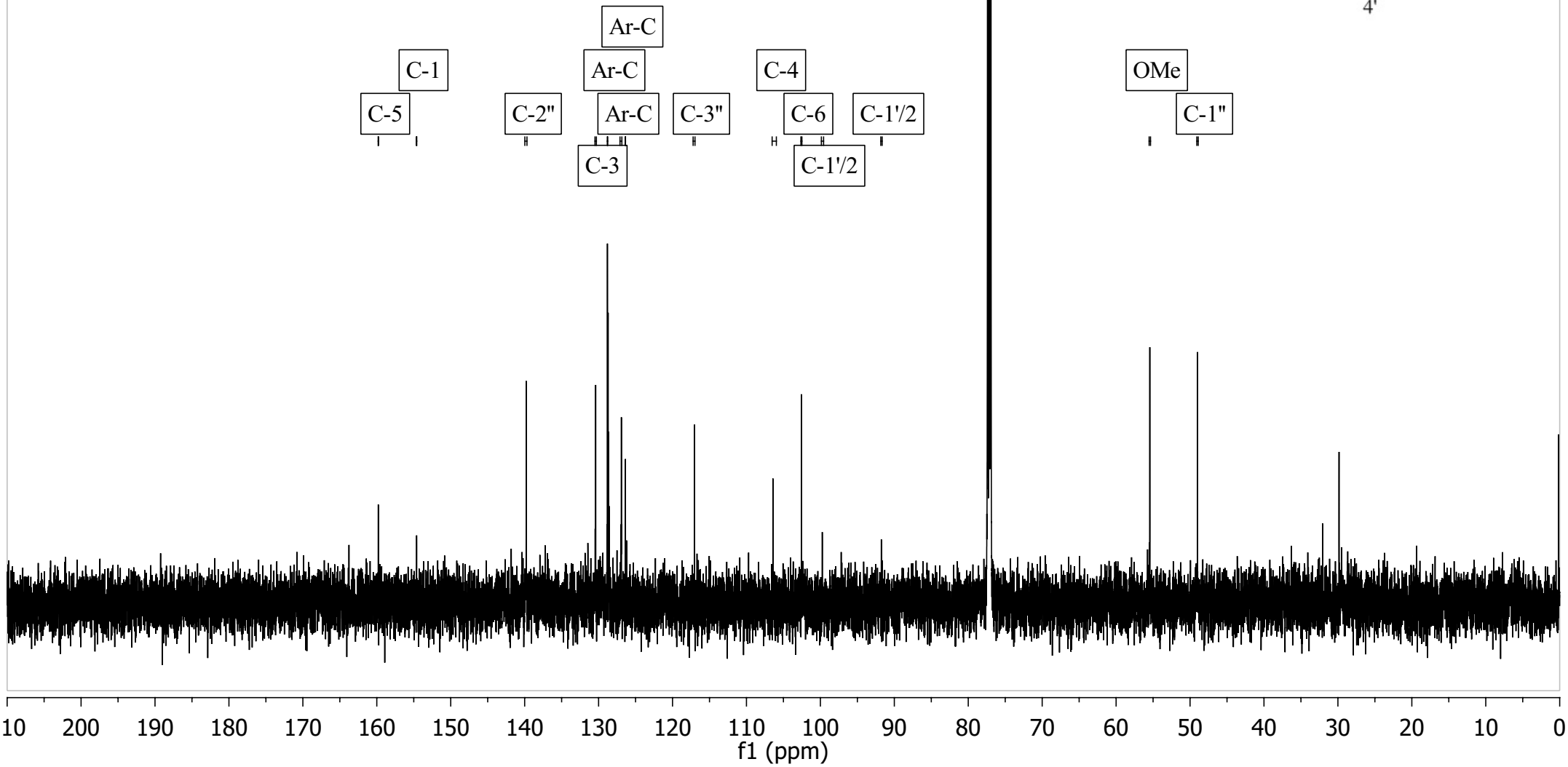


Plate 14c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 5-Methoxy-2-(1-phenylallyl)phenol (**732**)

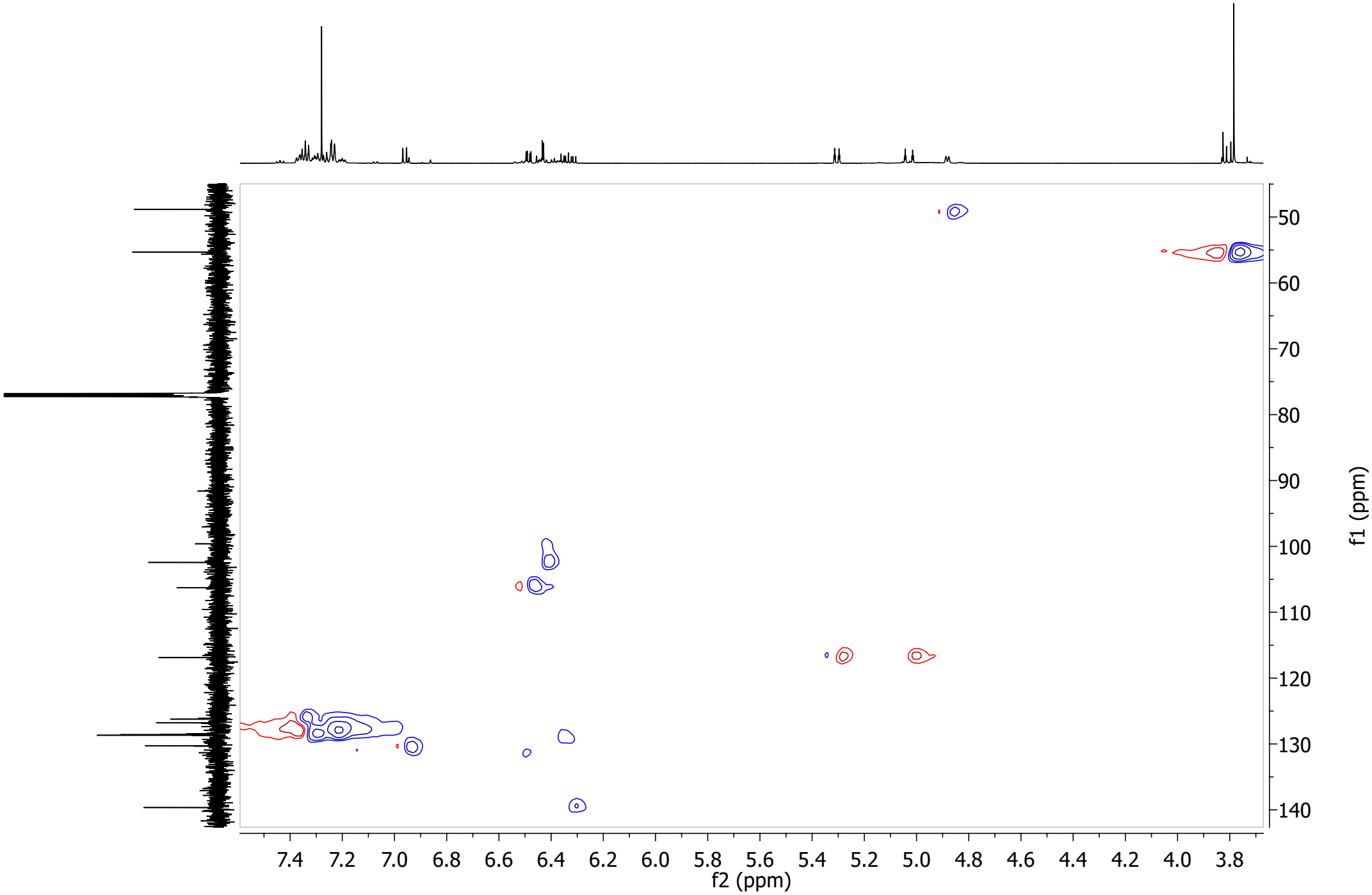


Plate 14d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 5-Methoxy-2-(1-phenylallyl)phenol (**732**)

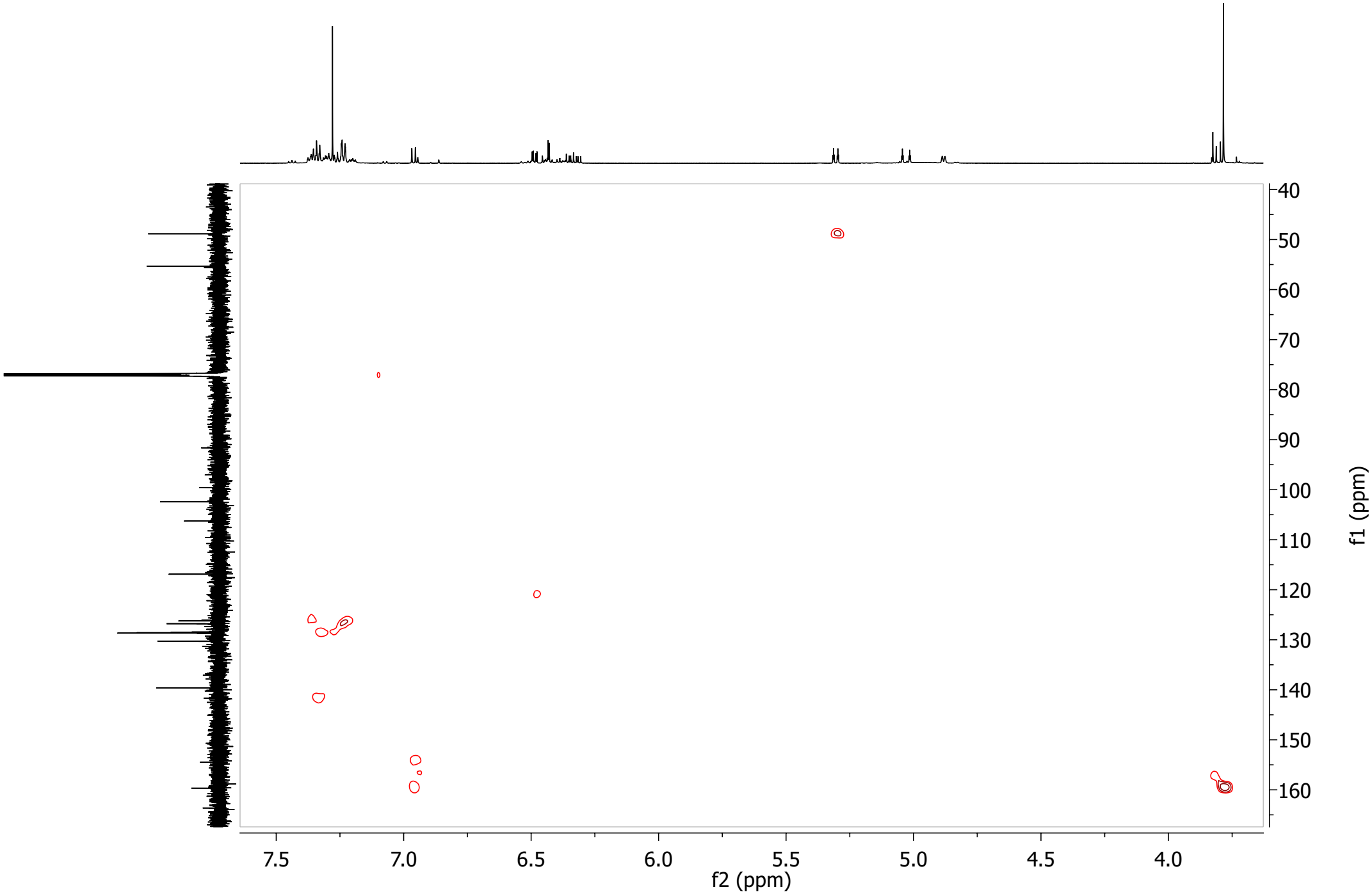


Plate 14e, DEPT (151 MHz, $CDCl_3$) : 5-Methoxy-2-(1-phenylallyl)phenol (**732**)

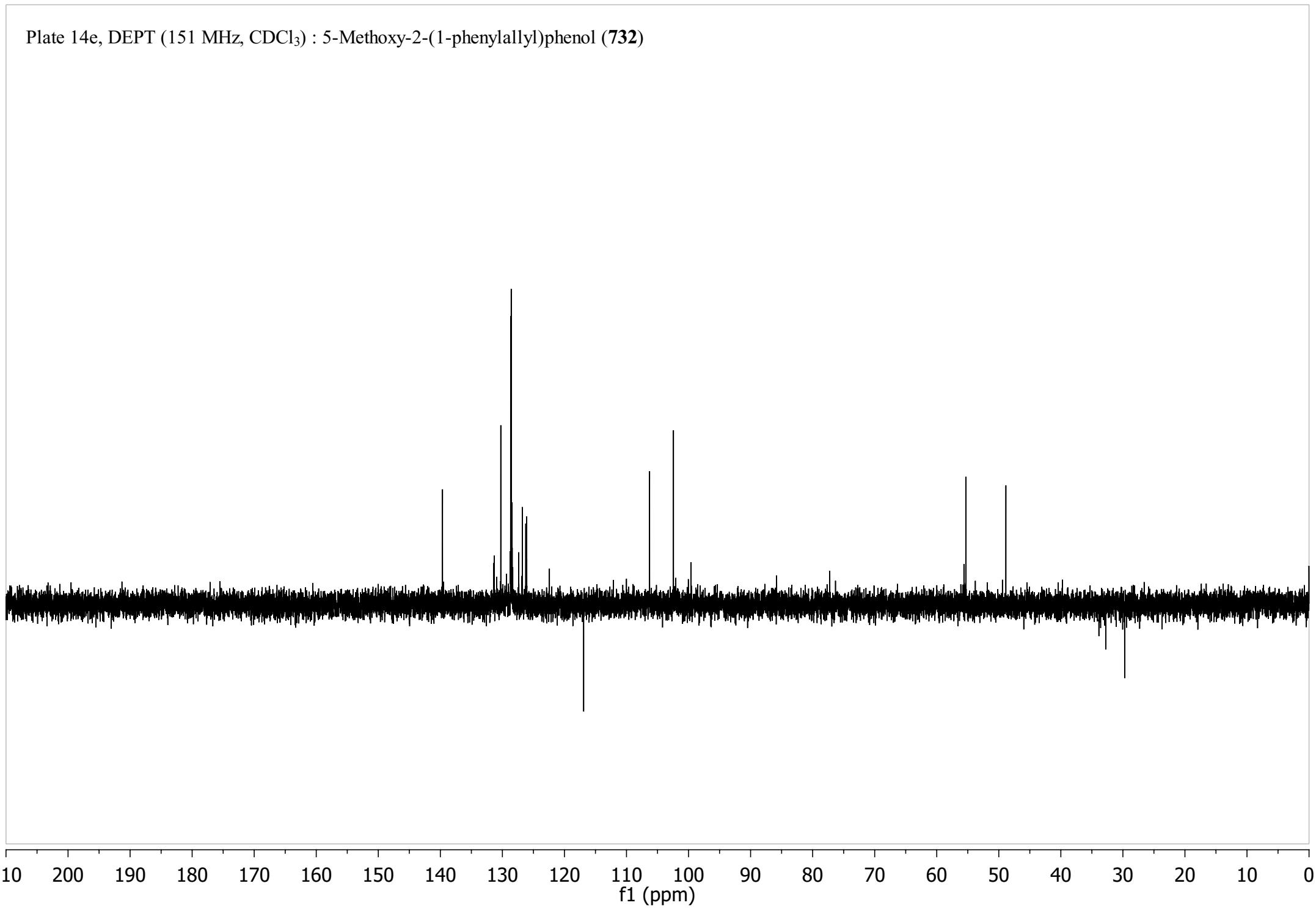
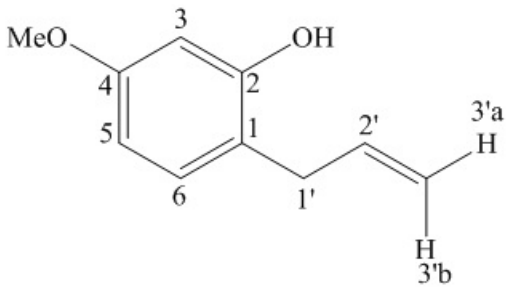
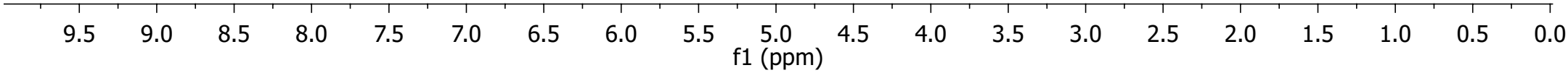


Plate 15a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Allyl-2-hydroxy-4-methoxybenzene (**552**)

δ 7.01 (1H, d, *J* = 8.3 Hz, H-6), 6.47 (1H, dd, *J* = 8.3, 2.5 Hz, H-5), 6.43 (1H, d, *J* = 2.5 Hz, H-3), 6.01 (1H, ddt, *J* = 16.9, 10.4, 6.4 Hz, H-2'), 5.23 (1H, s, -OH), 5.17 – 5.13 (1H, m, H-3'a and H-3'b), 3.76 (3H, s, -OMe), 3.36 (2H, br. d, *J* = 6.4 Hz, H-1')





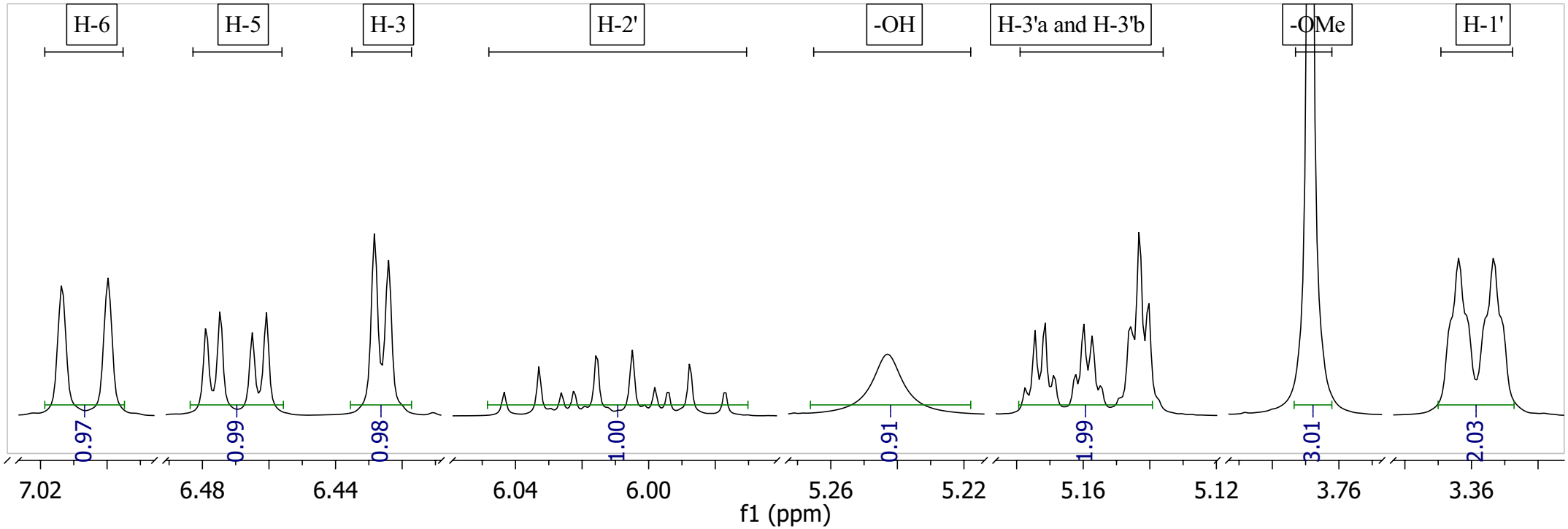
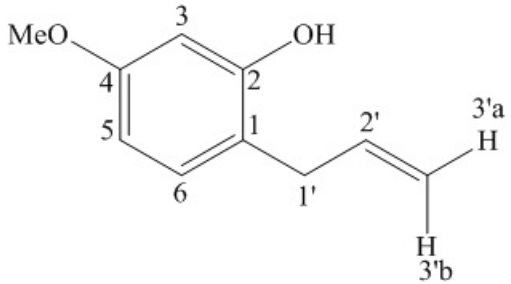


Plate 15b, ^{13}C NMR (151 MHz, $CDCl_3$): 1-Allyl-2-hydroxy-4-methoxybenzene (**552**)

δ 159.65 (C-4), 155.13 (C-2), 136.93 (C-2'), 130.98 (C-6), 117.53 (C-1), 116.36 (C-3'), 106.41 (C-5), 102.12 (C-3), 55.44 (-O<u>Me</u>), 34.64 (C-1')



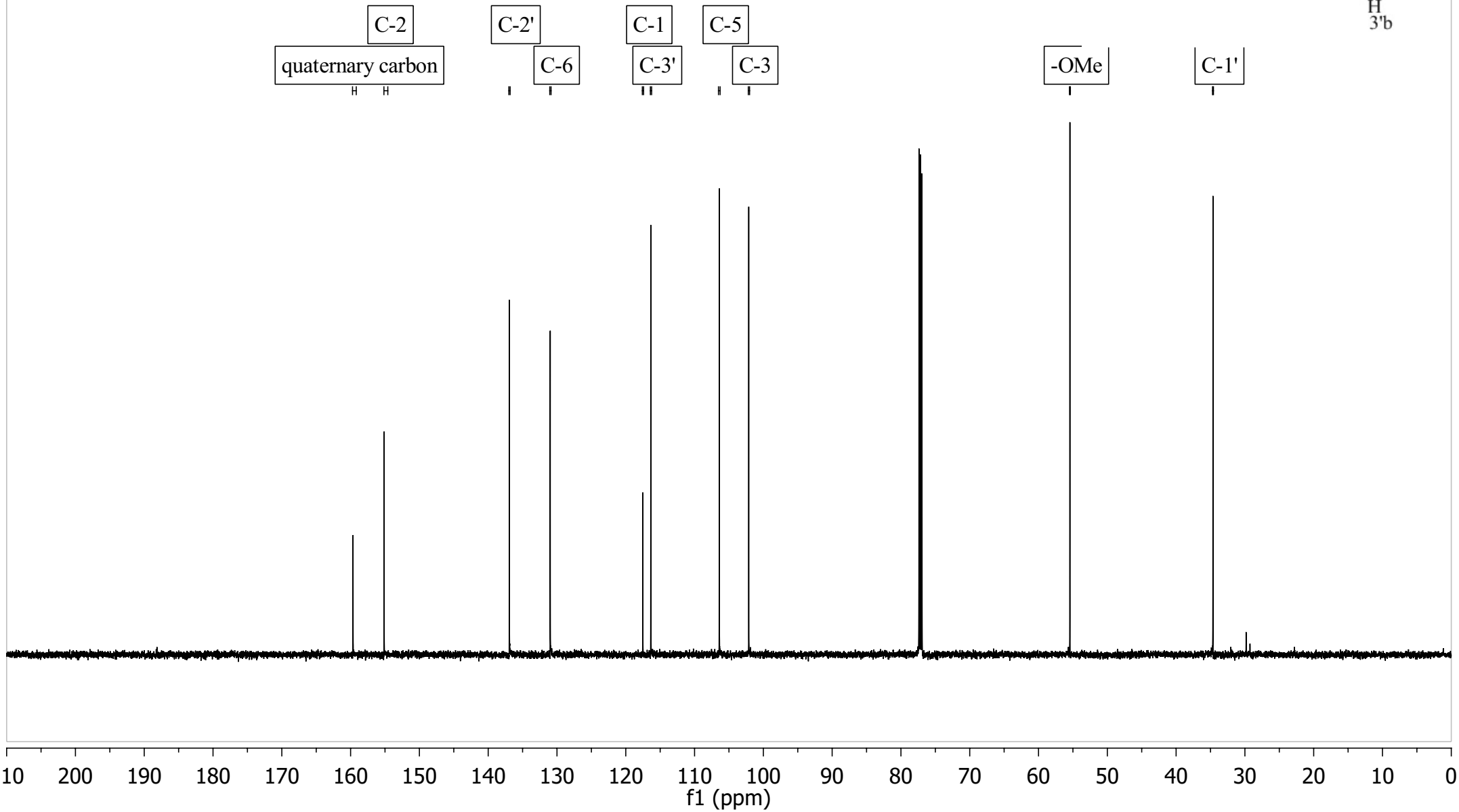


Plate 15c, HSQC (600/151 MHz, $CDCl_3$): 1-Allyl-2-hydroxy-4-methoxybenzene (**552**)

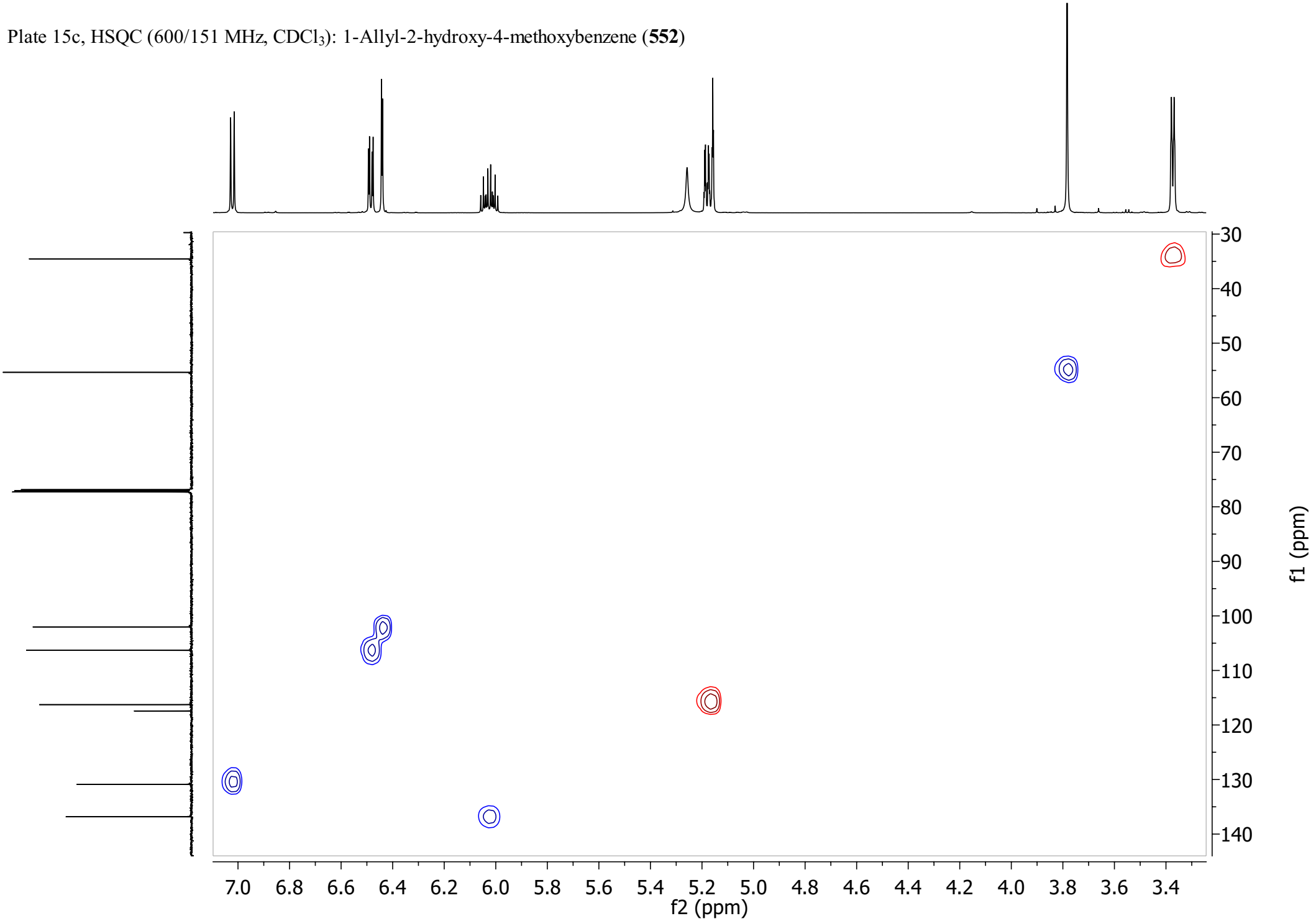


Plate 15d, HMBC (600/151 MHz, $CDCl_3$): 1-Allyl-2-hydroxy-4-methoxybenzene (**552**)

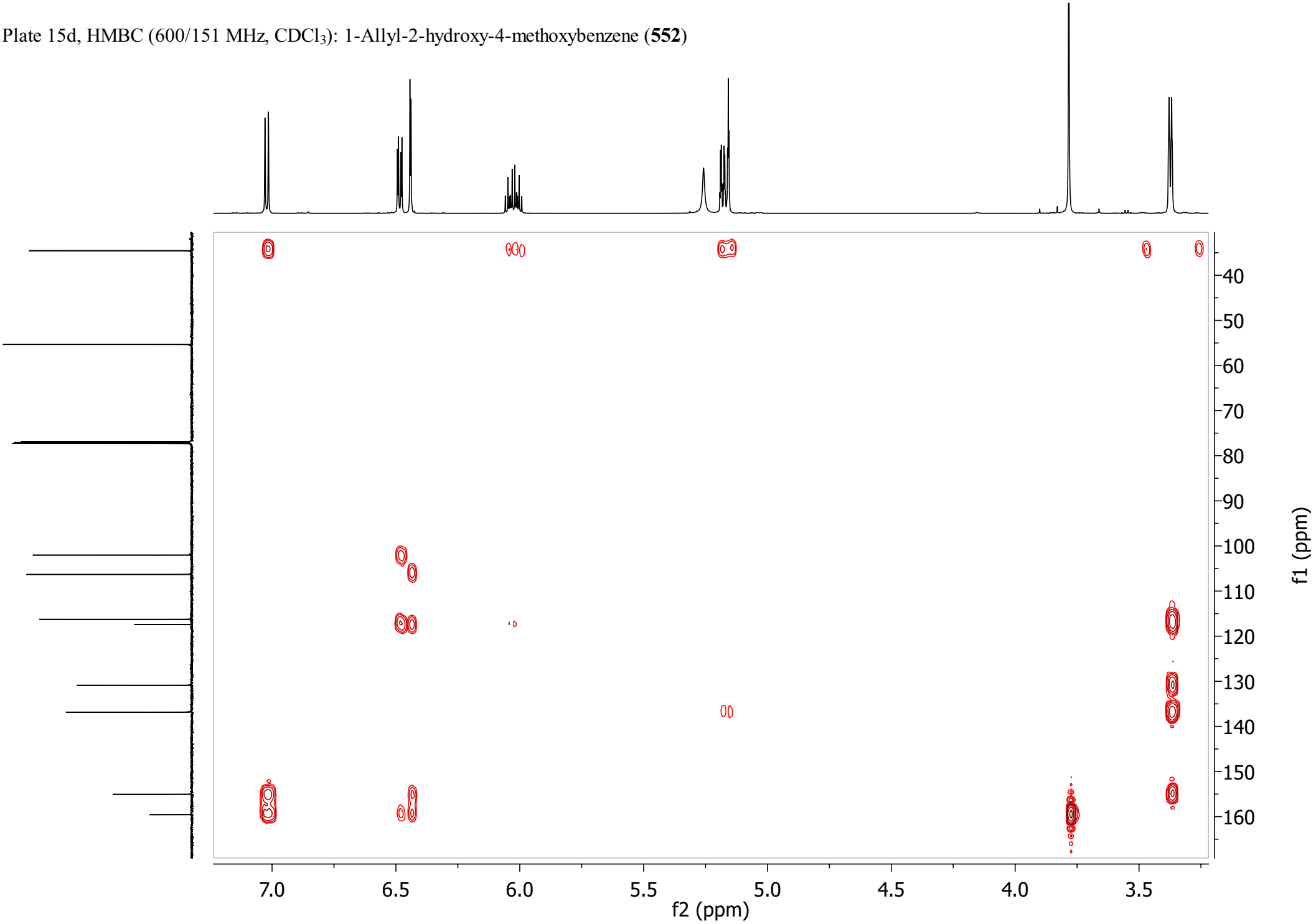


Plate 15e, DEPT (151 MHz, $CDCl_3$): 1-Allyl-2-hydroxy-4-methoxybenzene (**552**)

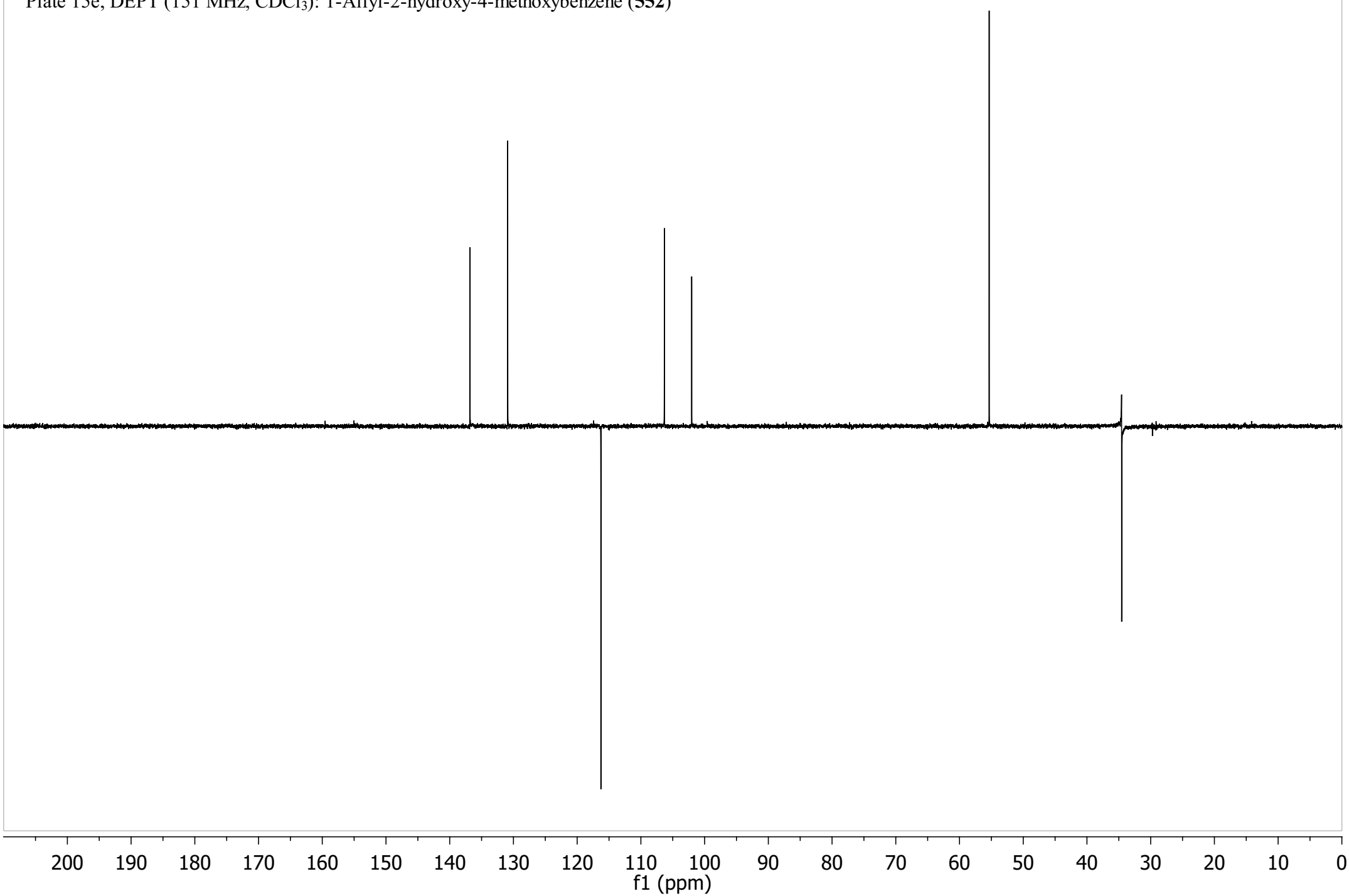


Plate 15f, NOESY (151 MHz, $CDCl_3$): 1-Allyl-2-hydroxy-4-methoxybenzene (**552**)

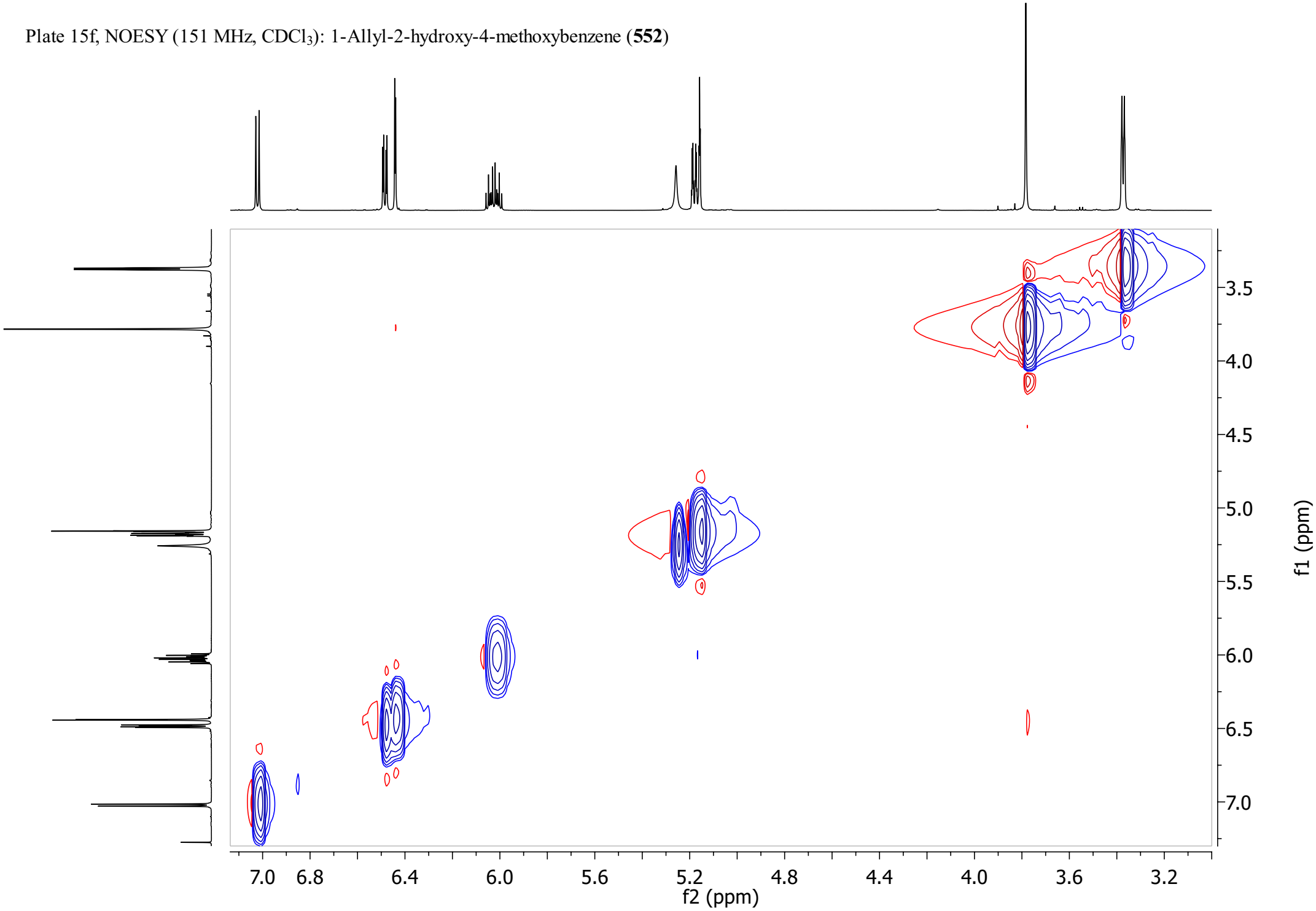
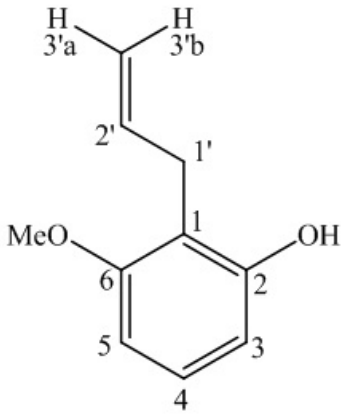


Plate 16a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Allyl-2-hydoxy-6-methoxybenzene (**577**)

δ 7.08 (1H, dd, *J* = 8.6, 8.1 Hz, H-4), 6.51 – 6.50 (2H, m, H-3 and H-5), 5.99 (1H, ddt, *J* = 17.2, 10.1, 6.3 Hz, H-2'), 5.15 (1H, s, -OH), 5.13 – 5.07 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -OMe), 3.48 (2H, ddd, *J* = 6.3, 1.6, 1.6 Hz, H-1')



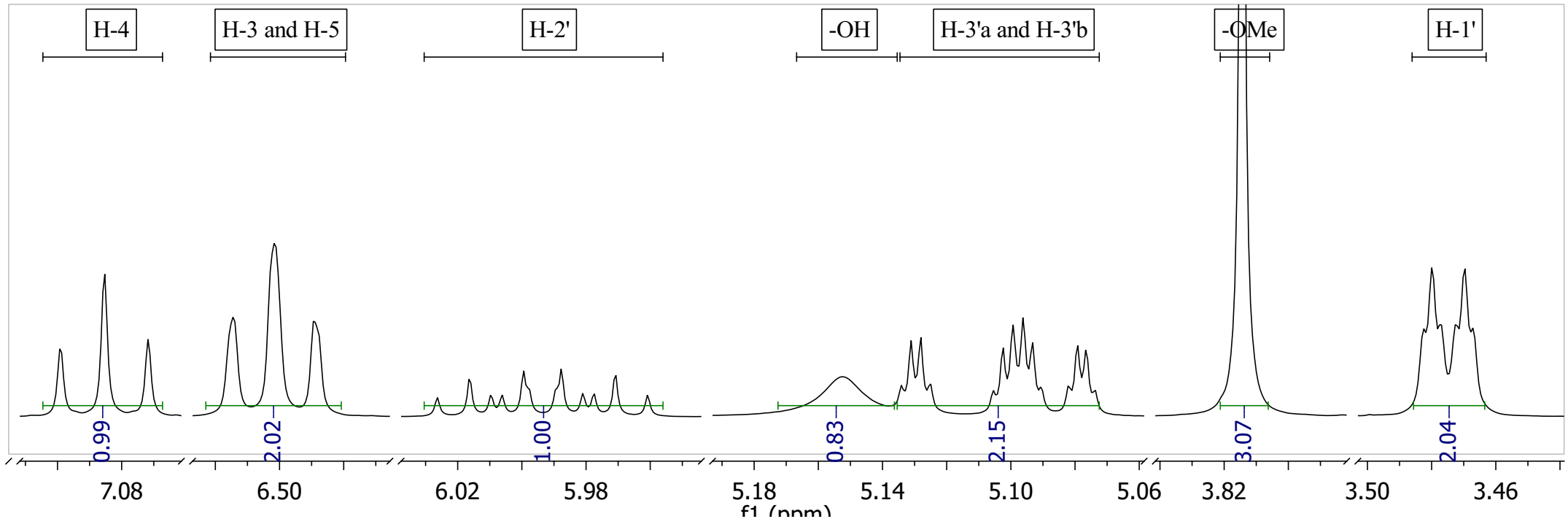
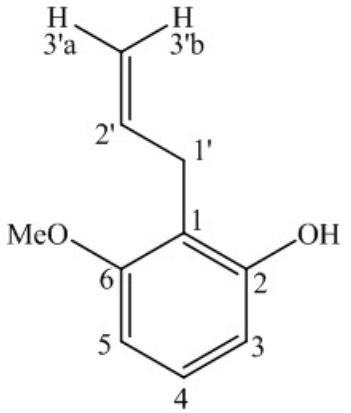


Plate 16b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Allyl-2-hydoxy-6-methoxybenzene (**577**)

δ 158.35 (C-6), 155.28 (C-2), 136.45 (C-2'), 127.66 (C-4), 115.30 (C-3'), 113.73 (C-1), 108.93 (C-3/5), 103.44 (C-3/5), 55.94 (-OMe), 27.47(C-1')



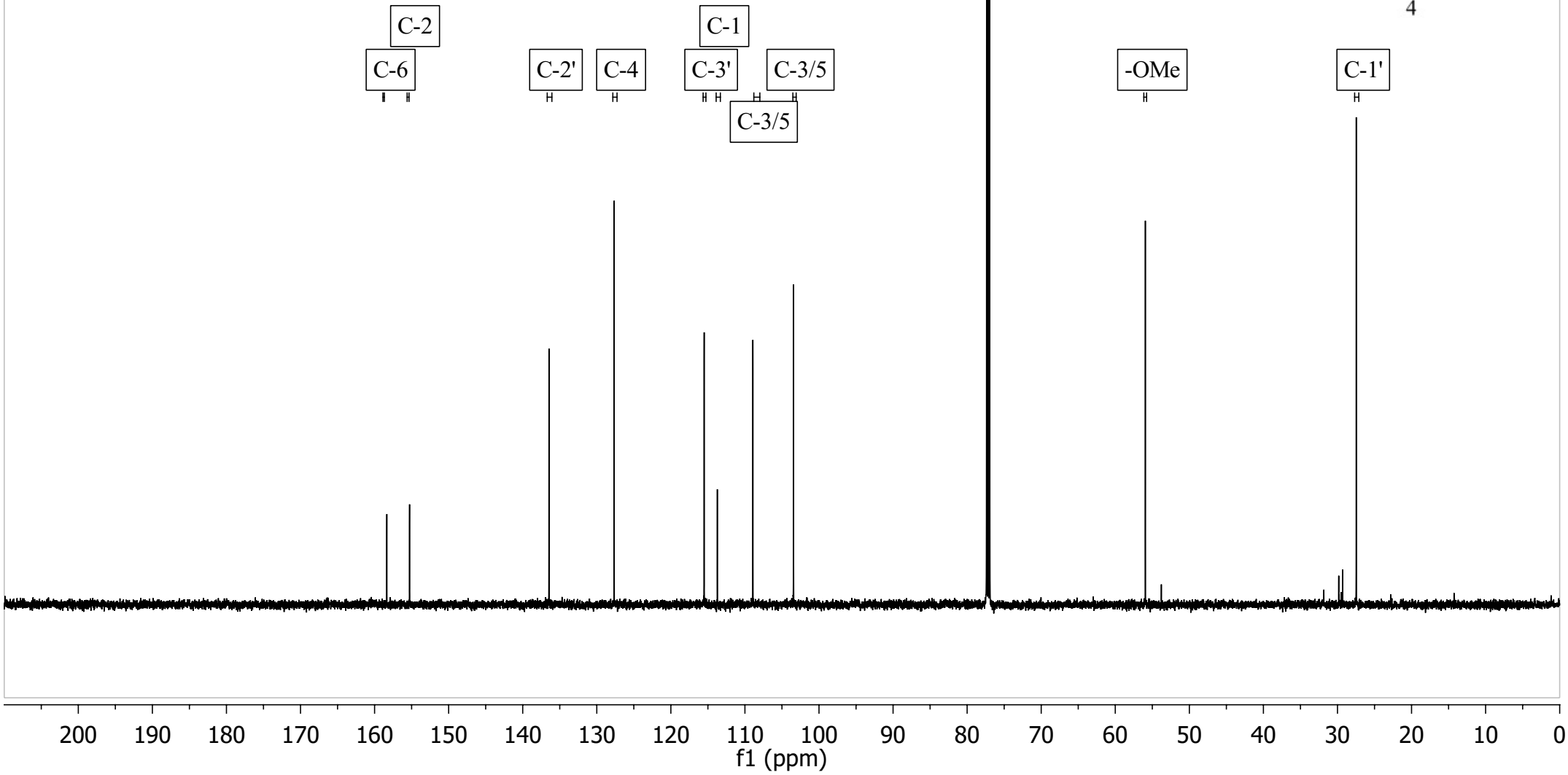


Plate 16c, HSQC (600/151 MHz, $CDCl_3$) : 1-Allyl-2-hydoxy-6-methoxybenzene (**577**)

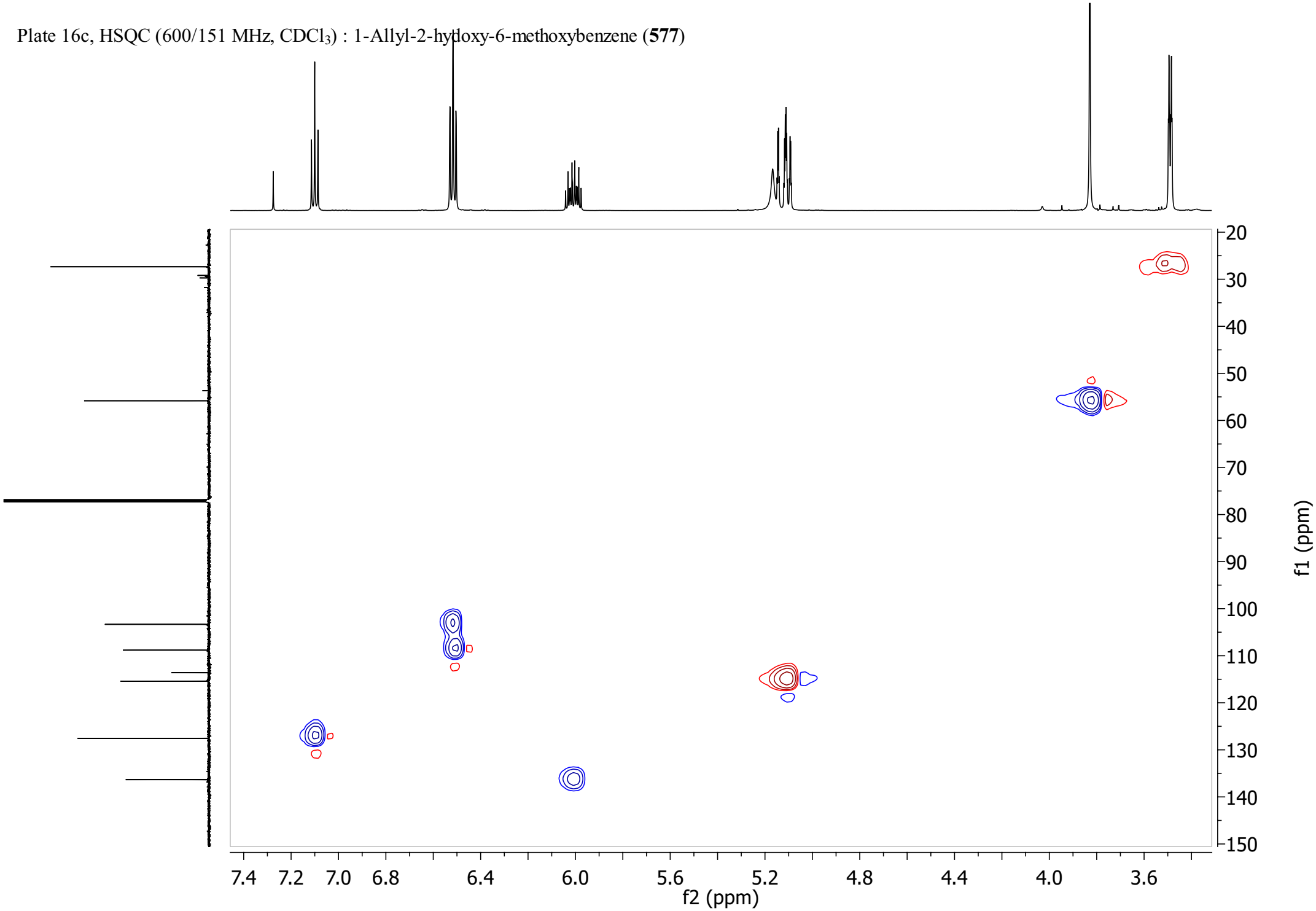


Plate 16d, HMBC (600/151 MHz, $CDCl_3$) : 1-Allyl-2-hydoxy-6-methoxybenzene (**577**)

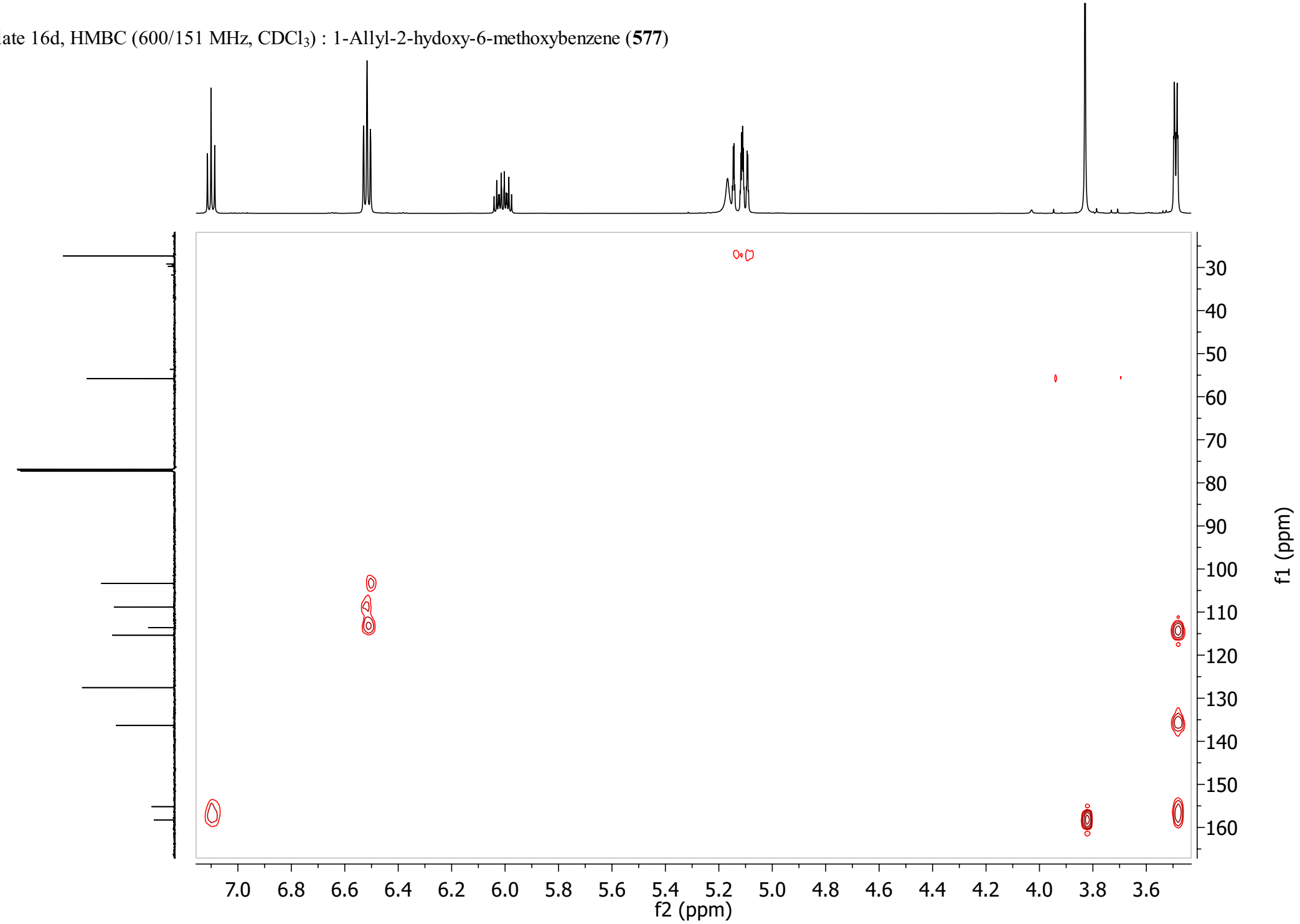
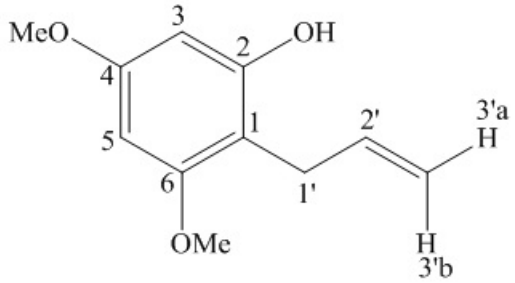


Plate 17a, ^{1}H NMR (600 MHz, $CDCl_3$) : 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**553**)

δ 6.11 (1H, d, *J* = 2.4 Hz, H-3/5), 6.08 (1H, d, *J* = 2.4 Hz, H-3/5), 5.96 (1H, ddt, *J* = 17.3, 10.9, 5.9 Hz, H-2'), 5.25 (1H, s, -OH), 5.13 – 5.07 (2H, m, H-3'a and H-3'b), 3.78 (3H, s, -OMe), 3.76 (3H, s, -OMe), 3.39 (2H, ddd, *J* = 5.9, 1.7, 1.7 Hz, H-1')



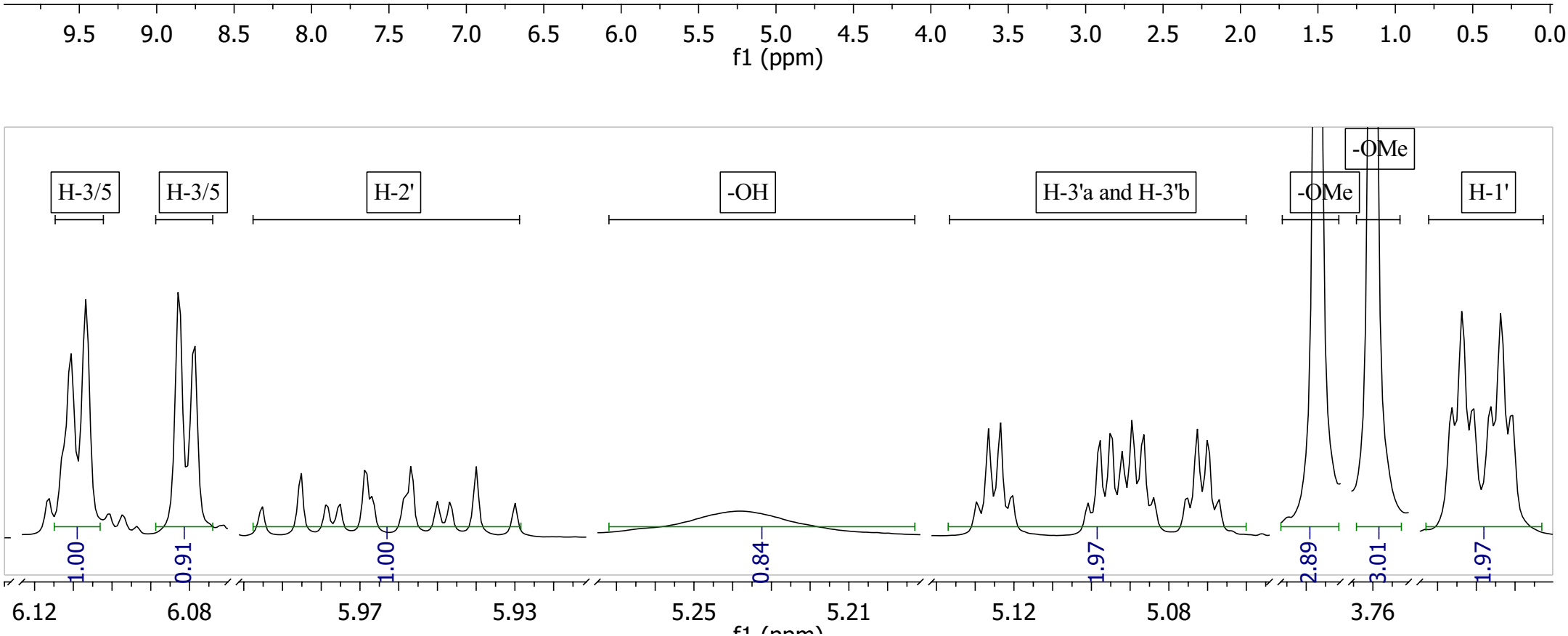
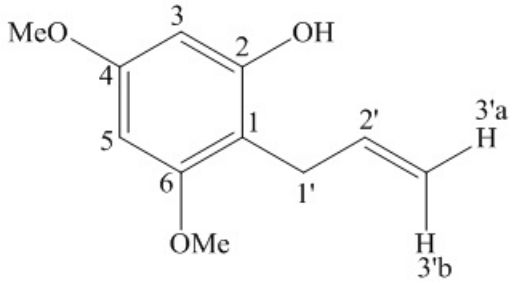


Plate 17b, ^{13}C NMR (151 MHz, $CDCl_3$) : 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**553**)

δ 159.90 (4°-C), 158.69 (4°-C), 155.94 (4°-C), 136.89 (C-2'), 115.41 (C-3'), 105.82 (C-1), 93.88 (C-3/5), 91.67 (C-3/5), 55.93 (-O<u>Me</u>), 55.34 (-O<u>Me</u>), 27.08 (C-1')



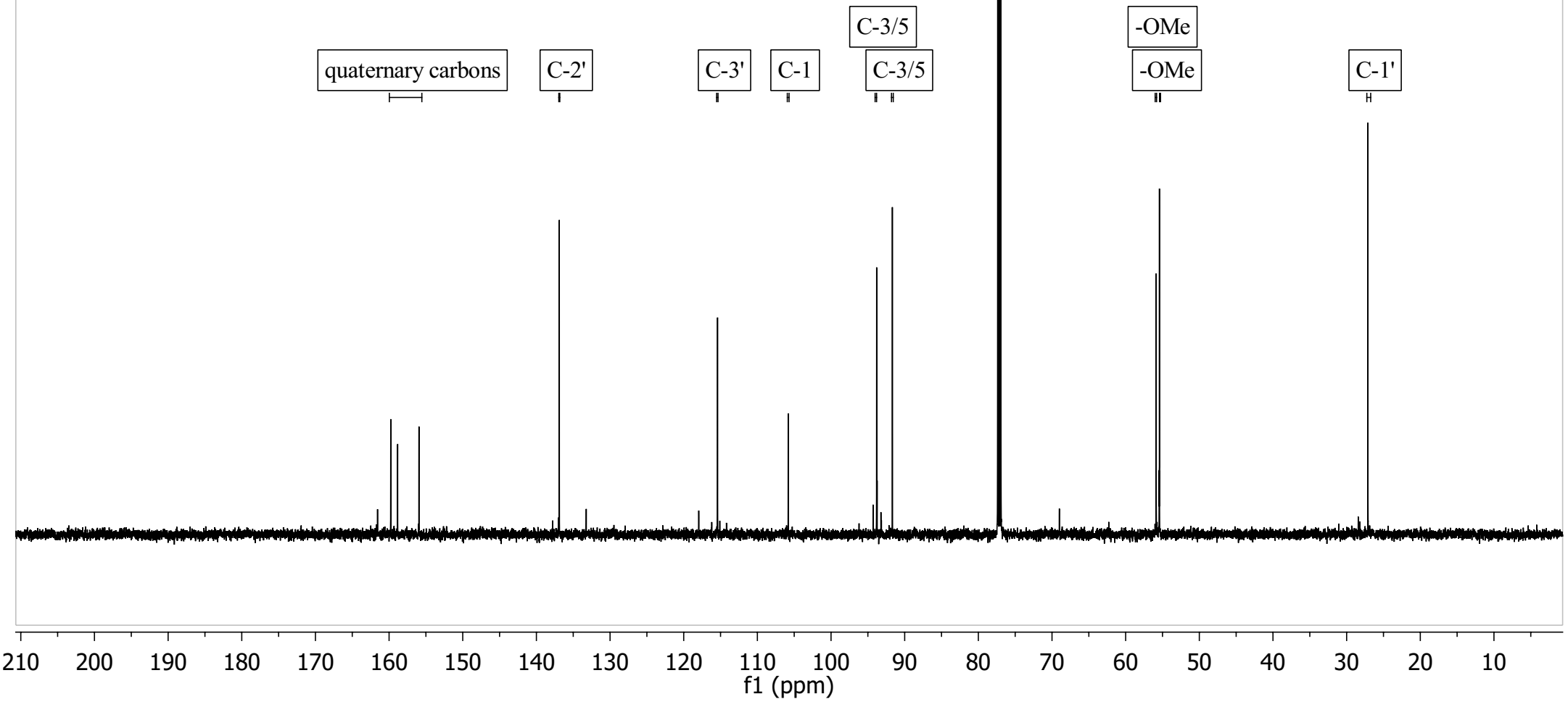


Plate 17c, HSQC (600/151 MHz, $CDCl_3$) : 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**553**)

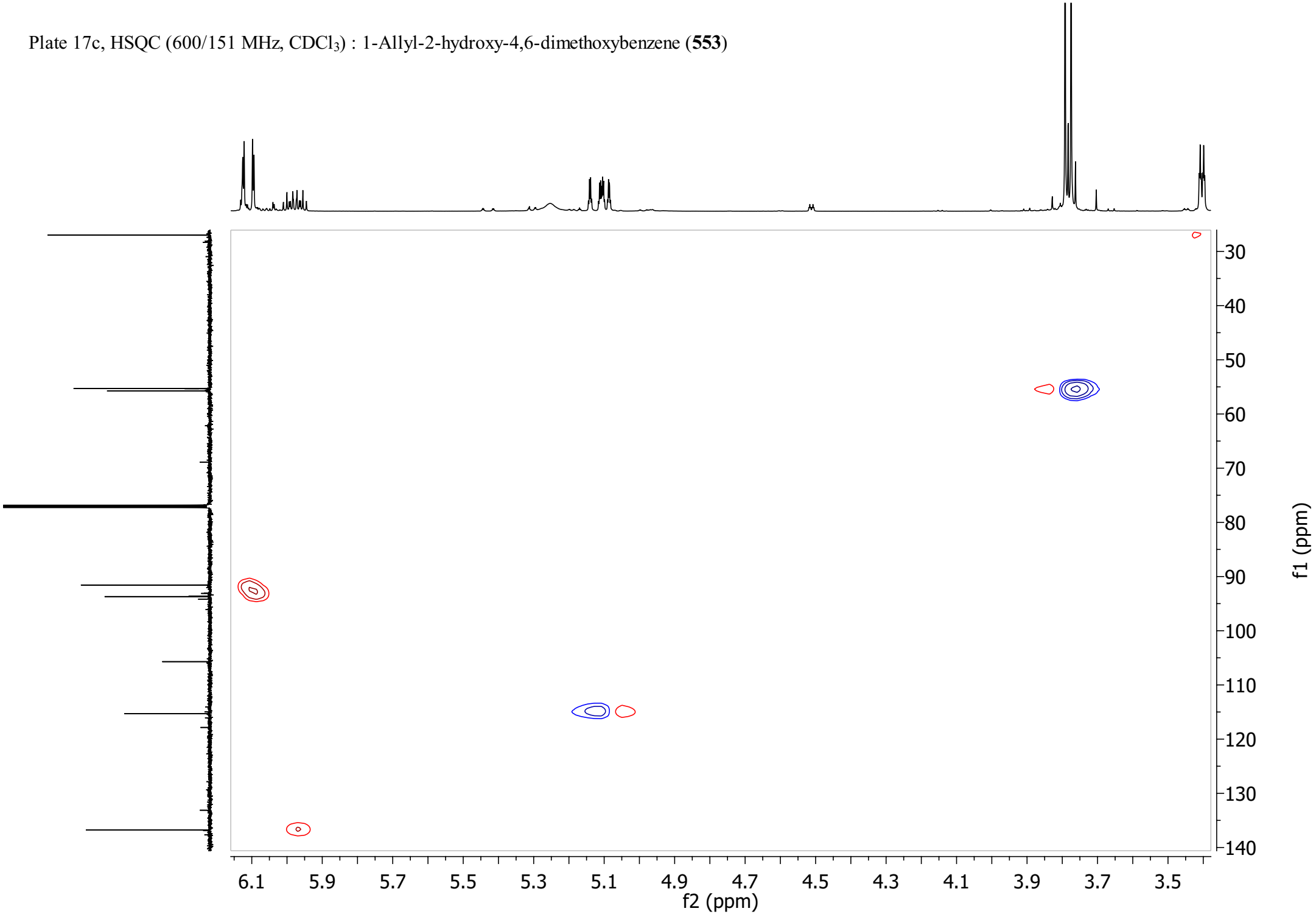
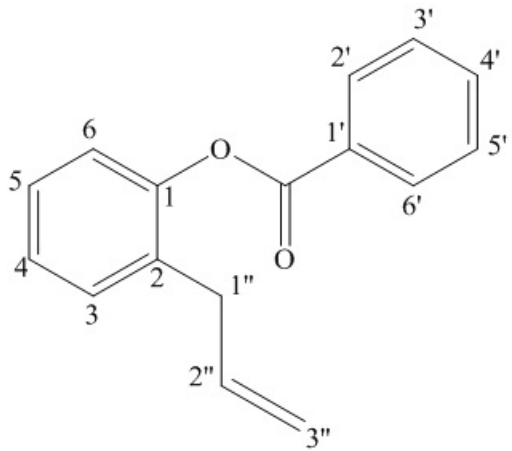
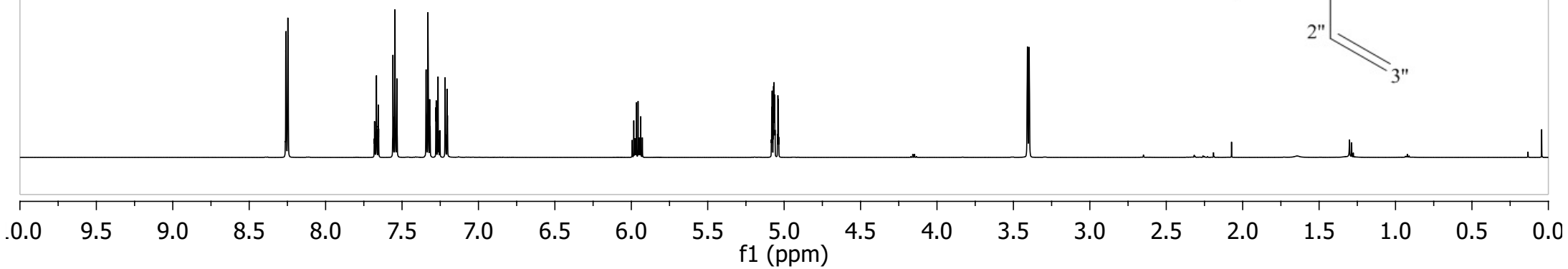


Plate 18a, ^{1}H NMR (600 MHz, $CDCl_3$) : 2-Allylphenylbenzoate (**582**)

δ 8.27 – 8.24 (2H, m, H-2' and H-6'), 7.69 – 7.65 (1H, m, H-4'), 7.56 – 7.53 (2H, m, H-3' and H-5'), 7.35 – 7.31 (2H, m, Ar-H), 7.28 – 7.25 (1H, m, Ar-H), 7.22 – 7.20 (1H, m, Ar-H), 5.96 (1H, ddt, *J* = 16.8, 10.1, 6.6 Hz, H-2''), 5.08 – 5.03 (2H, m, H-3''), 3.40 (2H, br. d, *J* = 6.6 Hz, H-1'')





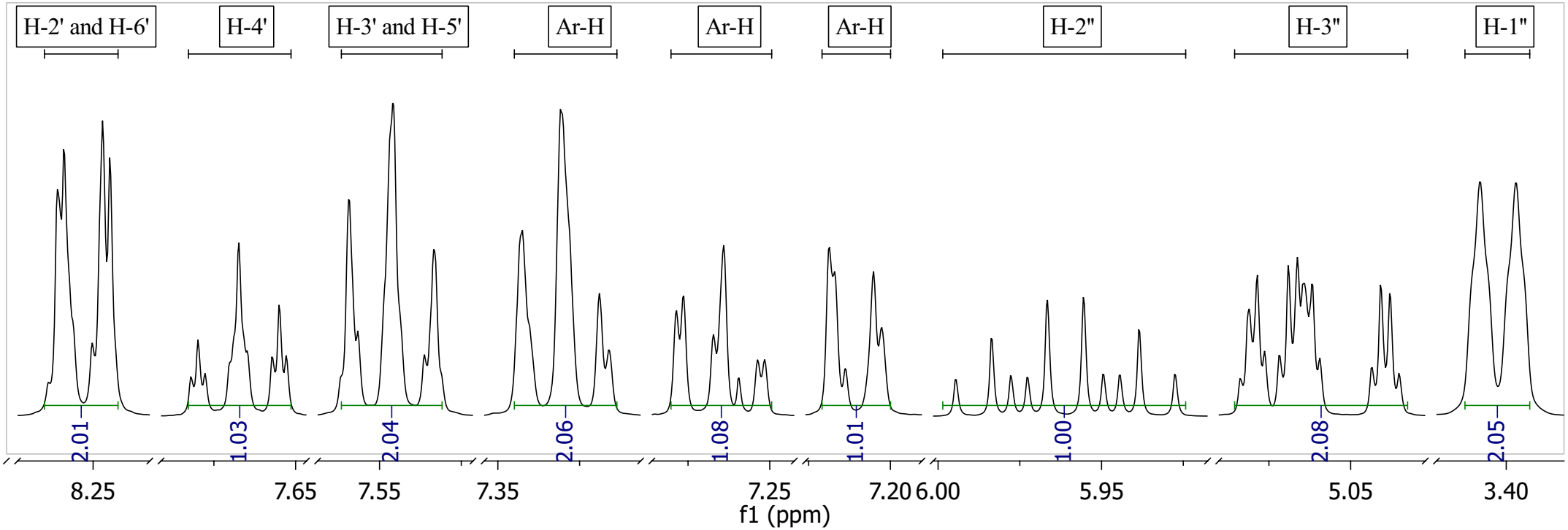
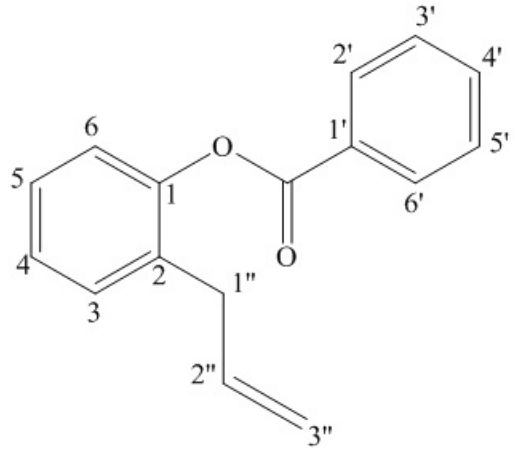


Plate 18b, ^{13}C NMR (151 MHz, $CDCl_3$) : 2-Allylphenylbenzoate (**582**)

δ 165.08 (C=O), 149.22 (C-1), 135.91 (C-2''), 133.70 (C-4'), 132.21 (C-2), 130.51 (Ar-C), 130.26 (C-2' and C-6'), 129.56 (C-1'), 128.72 (C-3' and C-5'), 127.59 (Ar-C), 126.33 (Ar-C), 122.58 (Ar-C), 116.43 (C-3''), 34.79 (C-1'')



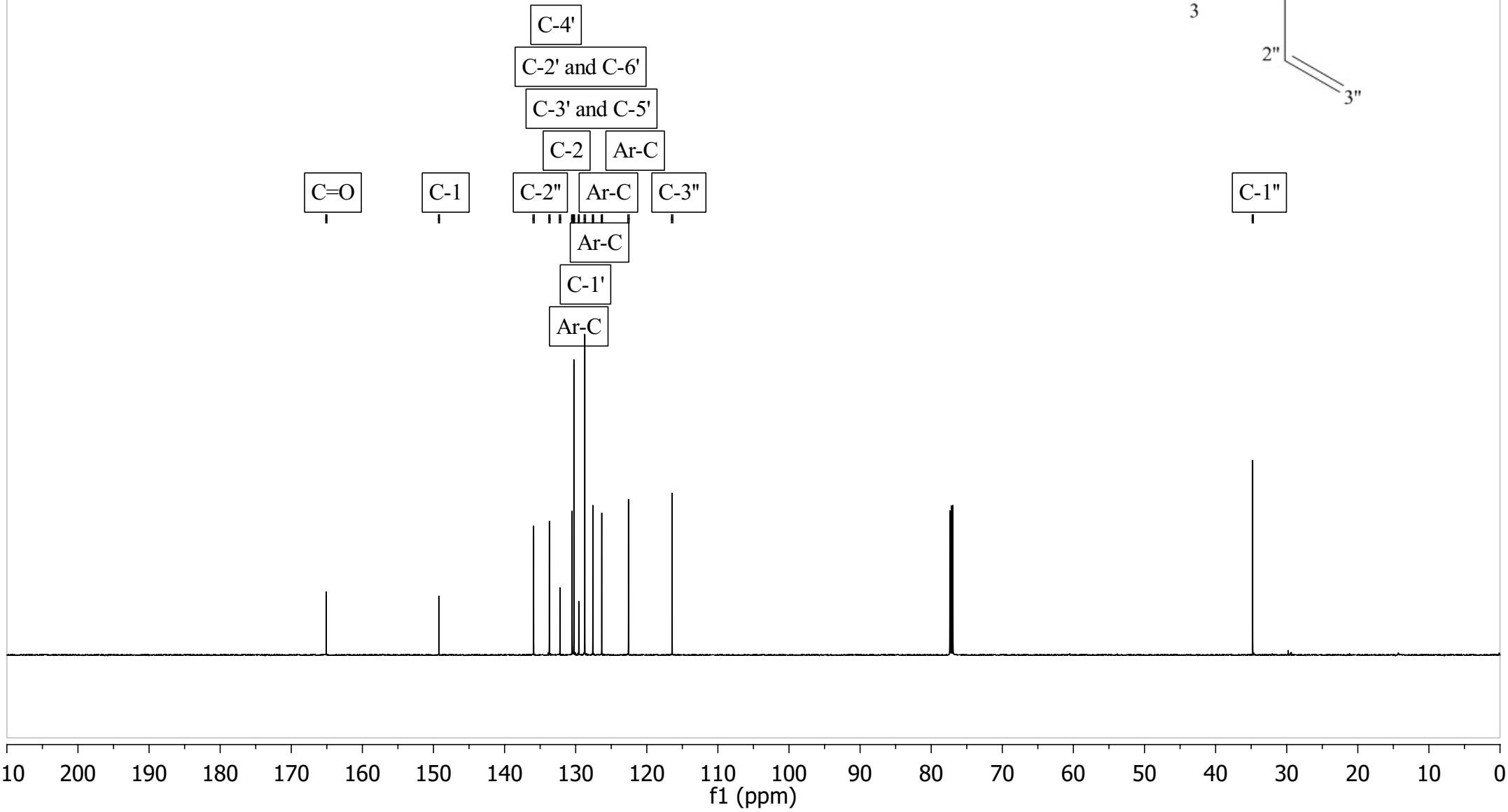


Plate 18c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 2-Allylphenylbenzoate (**582**)

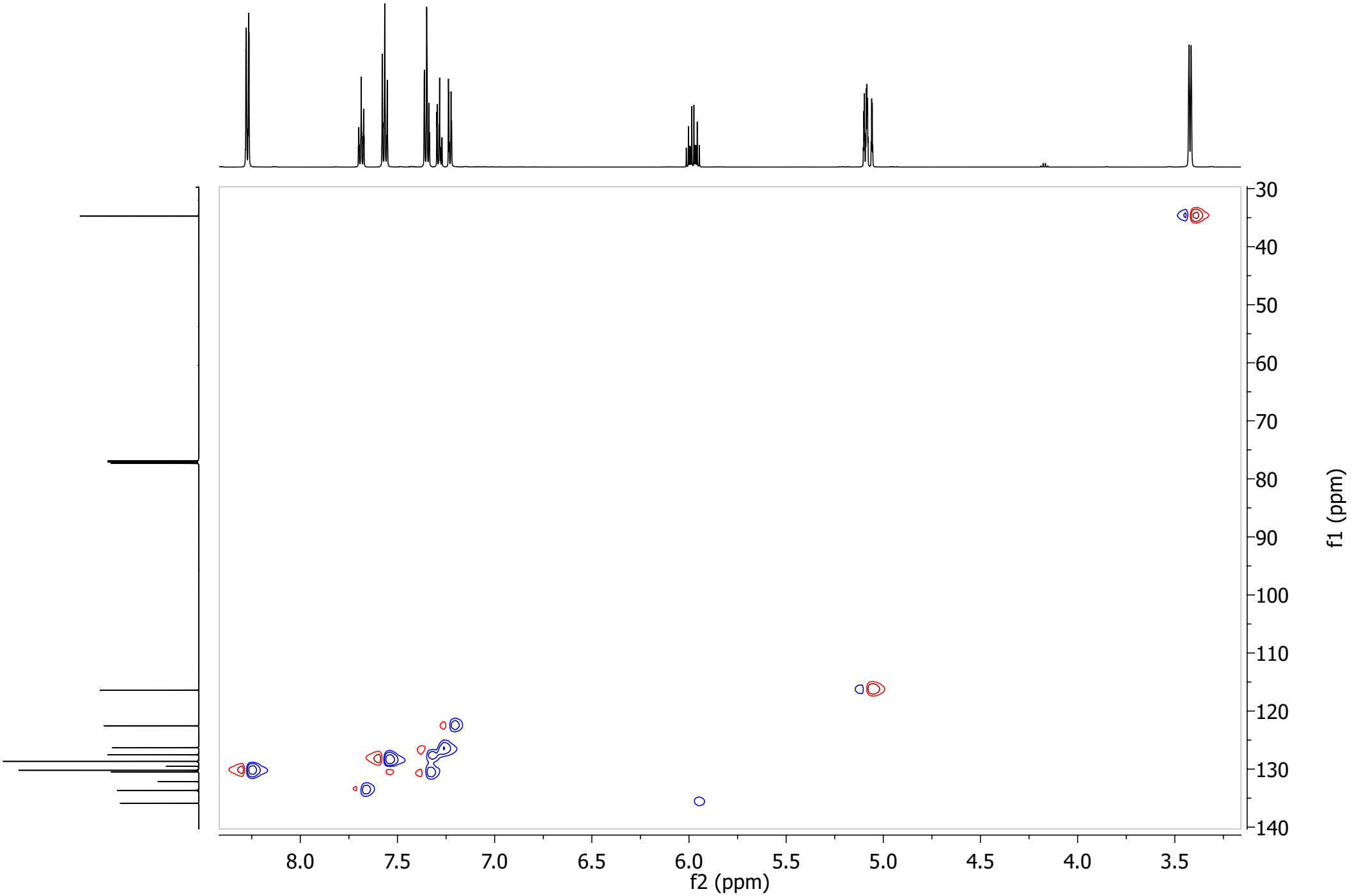


Plate 18d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 2-Allylphenylbenzoate (**582**)

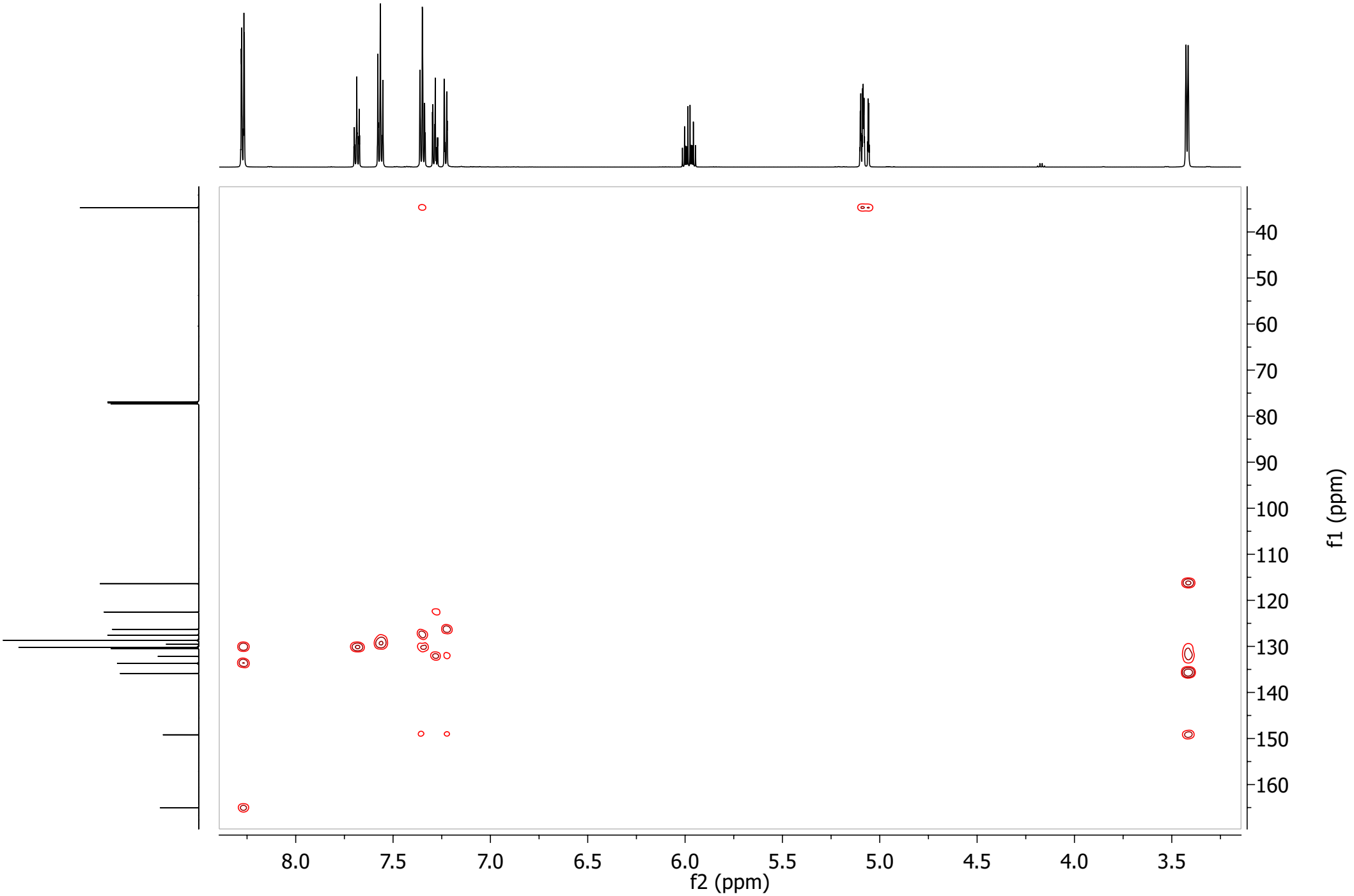


Plate 18e, DEPT (151 MHz, $CDCl_3$) : 2-Allylphenylbenzoate (**582**)

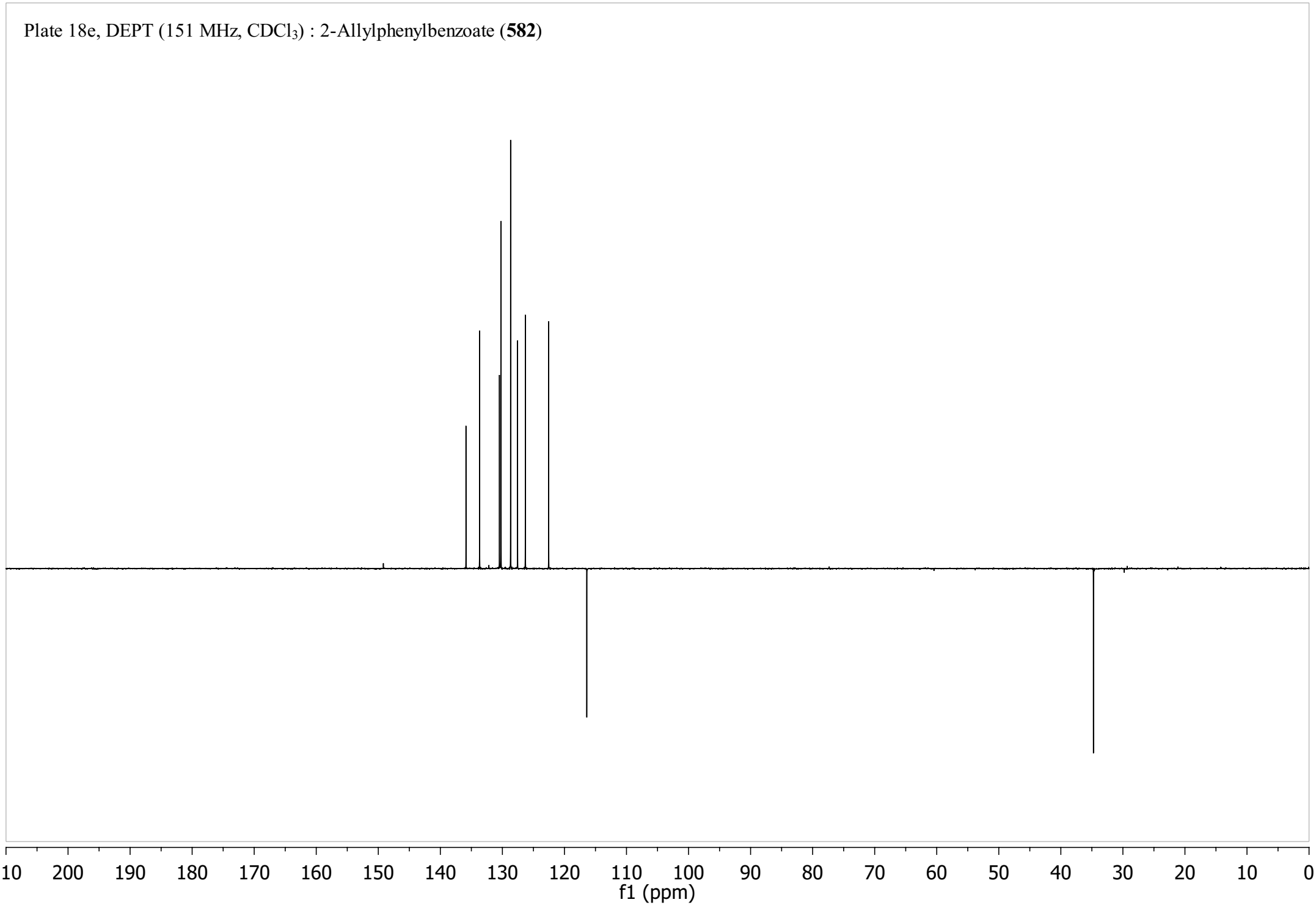
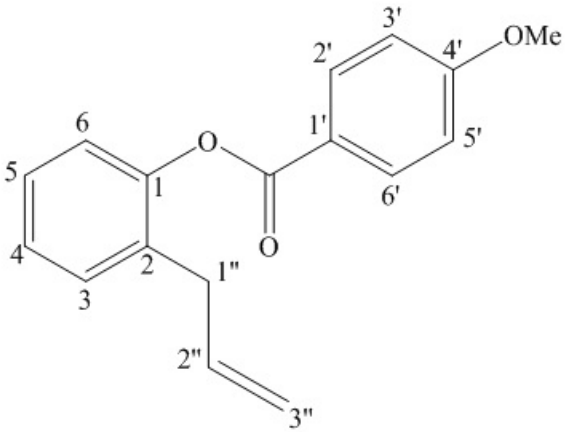
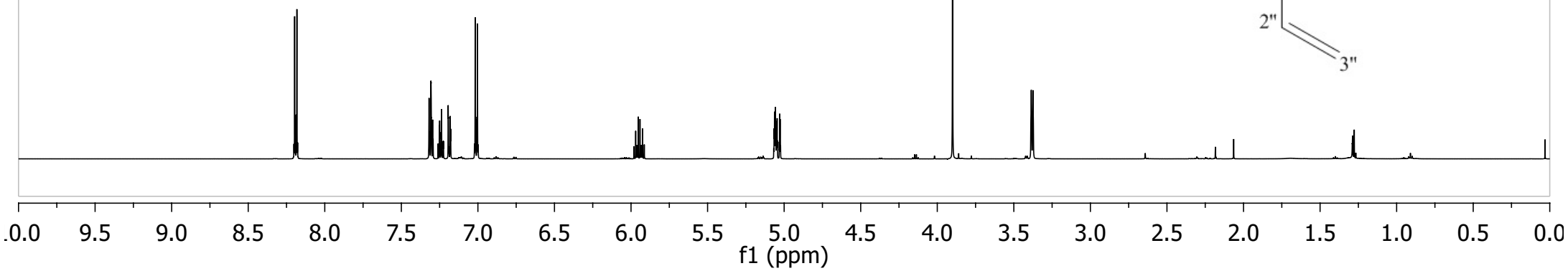


Plate 19a, ^{1}H NMR (600 MHz, $CDCl_3$) : 2-Allylphenyl 4-methoxybenzoate (**583**)

δ 8.19 (2H, d, *J* = 9.3 Hz, H-2' and H-6'), 7.32 – 7.29 (2H, m, Ar-H), 7.25 – 7.22 (1H, m, Ar-H), 7.20 – 7.18 (1H, m, Ar-H), 7.02 – 7.00 (2H, d, *J* = 9.3 Hz, H-3' and H-5'), 5.95 (1H, ddt, *J* = 16.8, 10.2, 6.6 Hz, H-2''), 5.07 – 5.02 (2H, m, H-3''), 3.90 (3H, s, -OMe), 3.38 (2H, br. d, *J* = 6.6 Hz, H-1'')





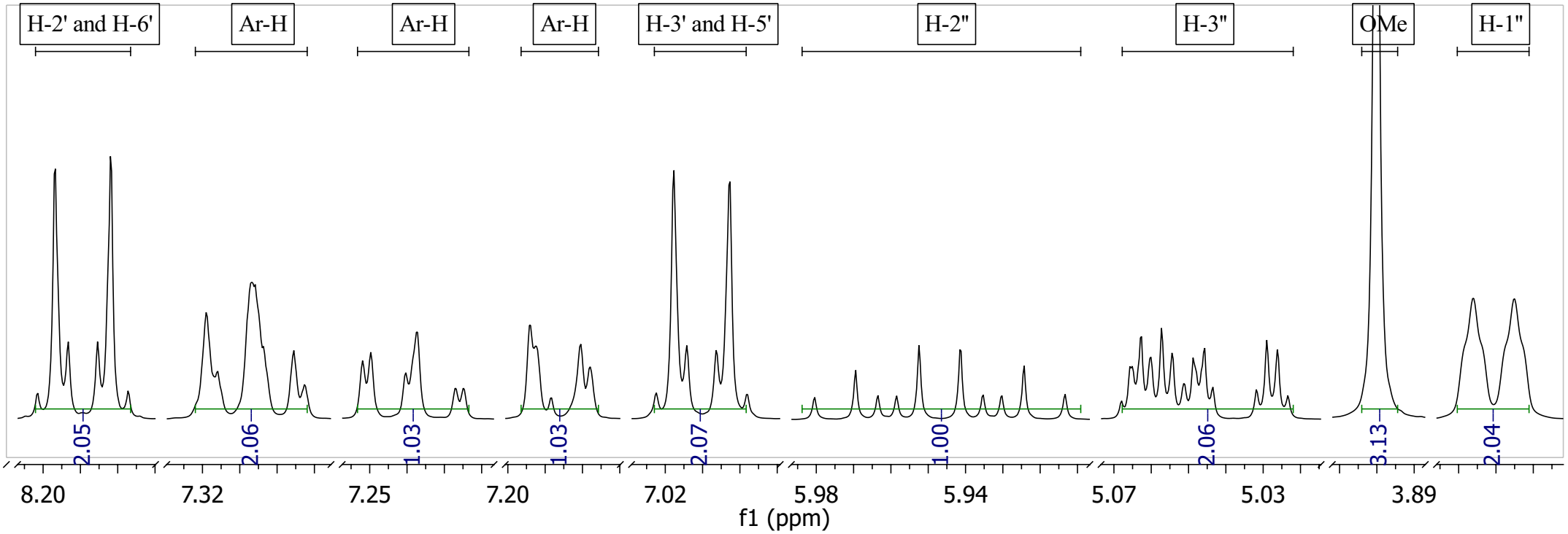
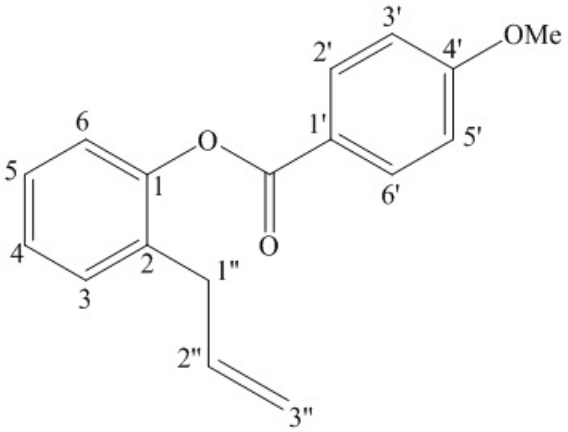


Plate 19b, ^{13}C NMR (151 MHz, $CDCl_3$) : 2-Allylphenyl 4-methoxybenzoate (**583**)

δ 164.80 (C=O), 164.00 (C-4'), 149.32 (C-1), 136.00 (C-2''), 132.36 (C-2' and C-6'), 132.29 (C-2), 130.39 (Ar-C), 127.78 (Ar-C), 126.17 (Ar-C), 122.67 (Ar-C), 121.86 (C-1'), 116.29 (C-3''), 113.98 (C-3' and C-5'), 55.59 (-OMe), 34.80 (C-1'')



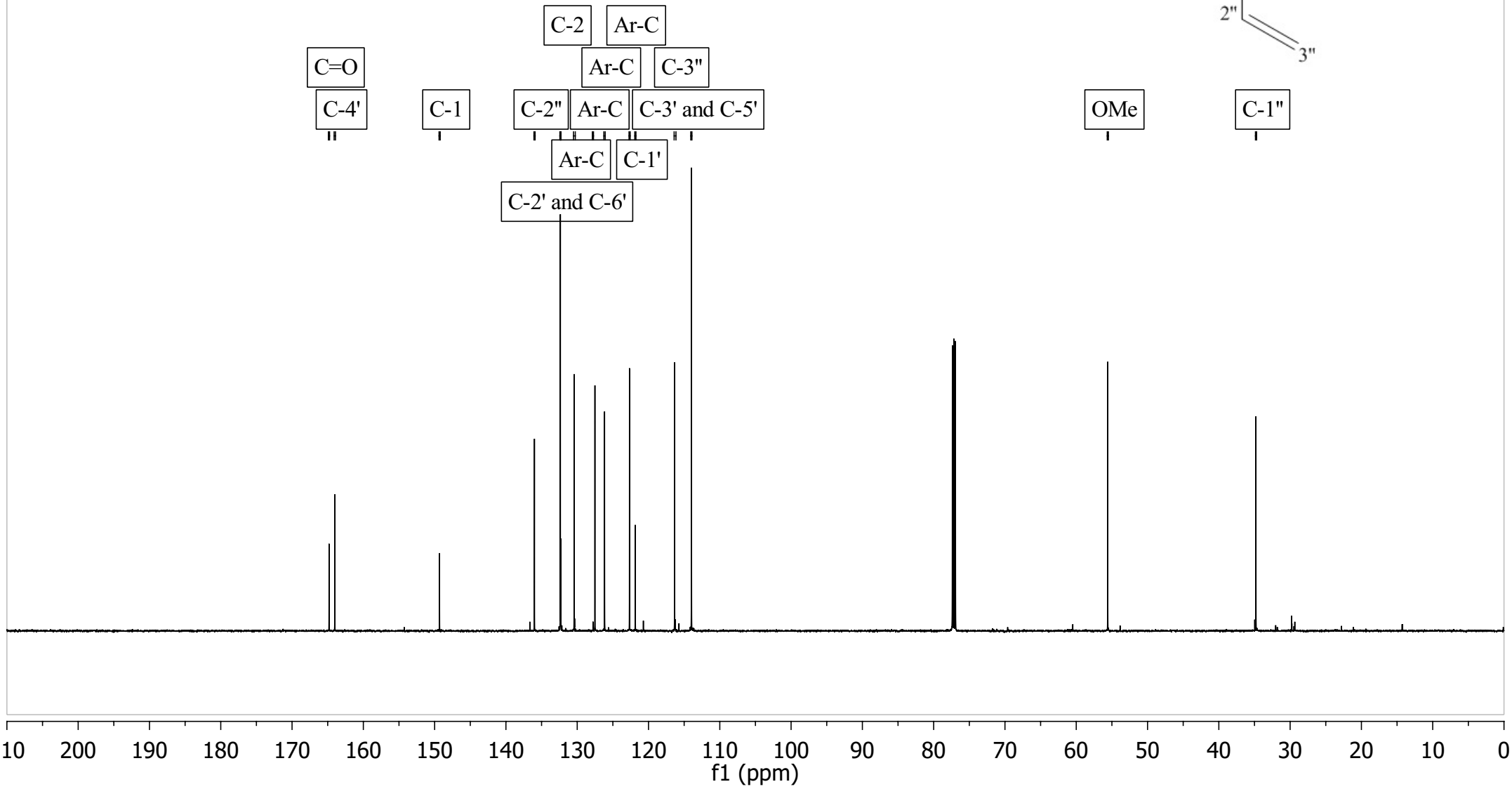


Plate 19c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 2-Allylphenyl 4-methoxybenzoate (**583**)

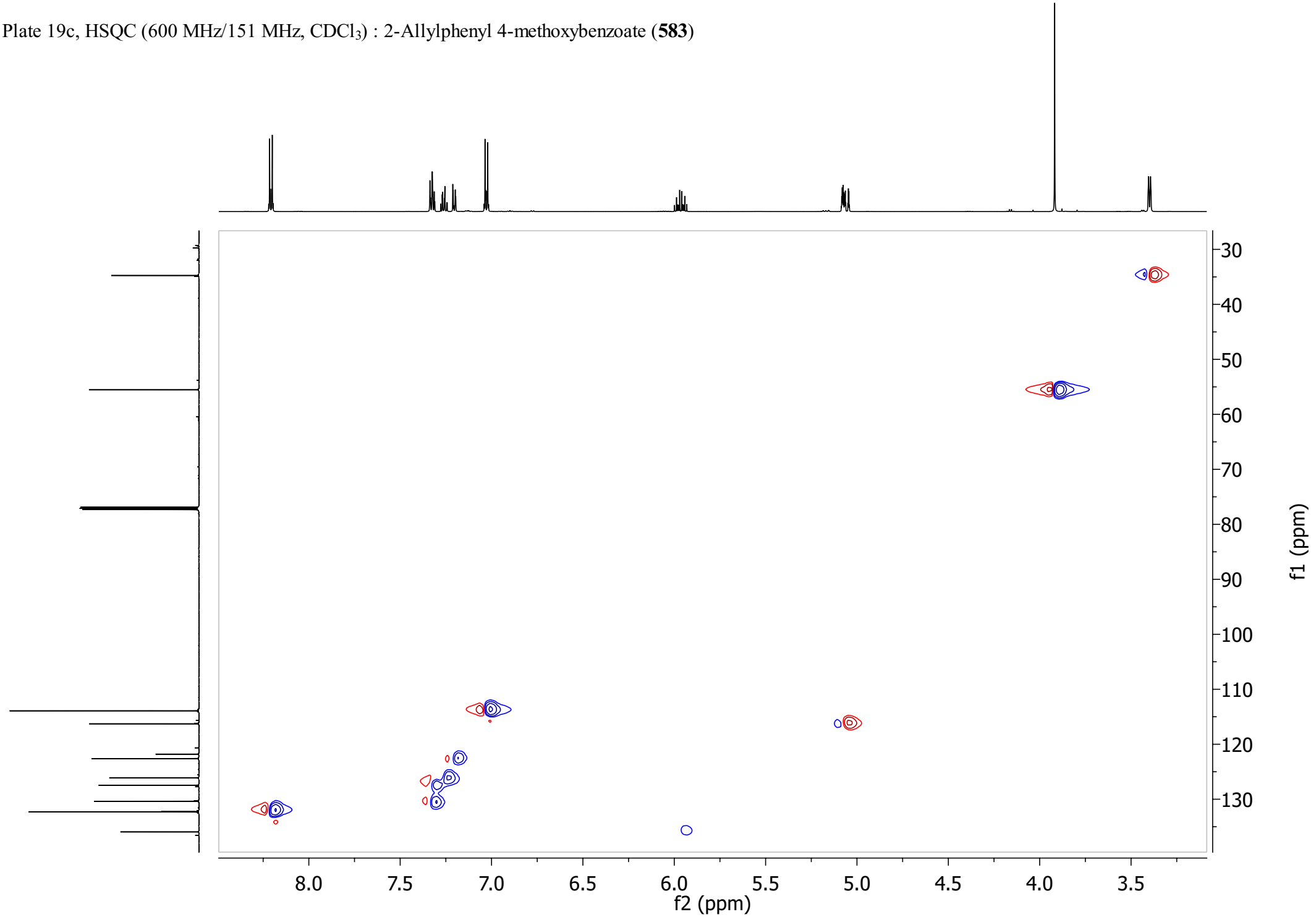


Plate 19d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 2-Allylphenyl 4-methoxybenzoate (**583**)

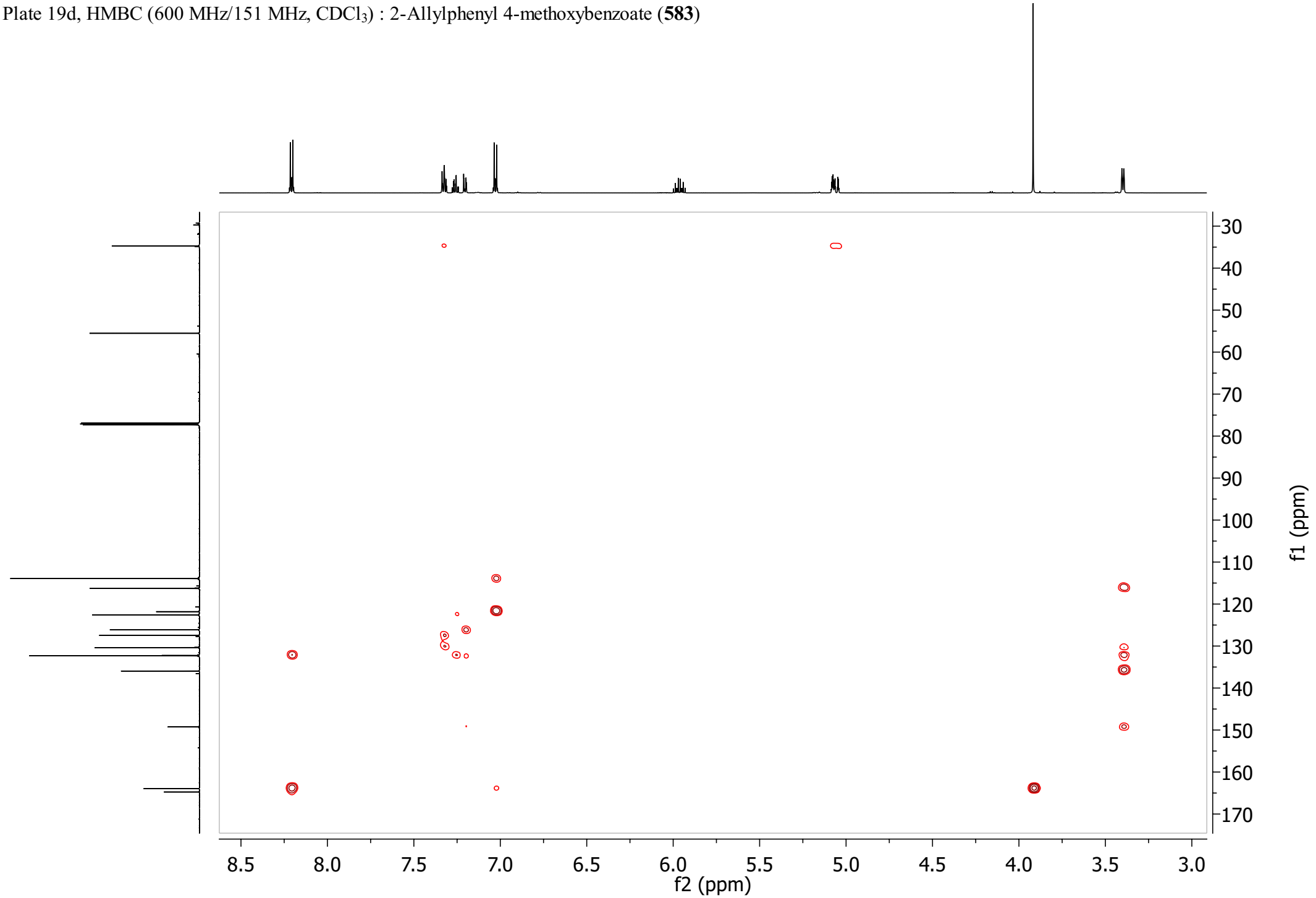


Plate 19e, DEPT (151 MHz, $CDCl_3$) : 2-Allylphenyl 4-methoxybenzoate (**583**)

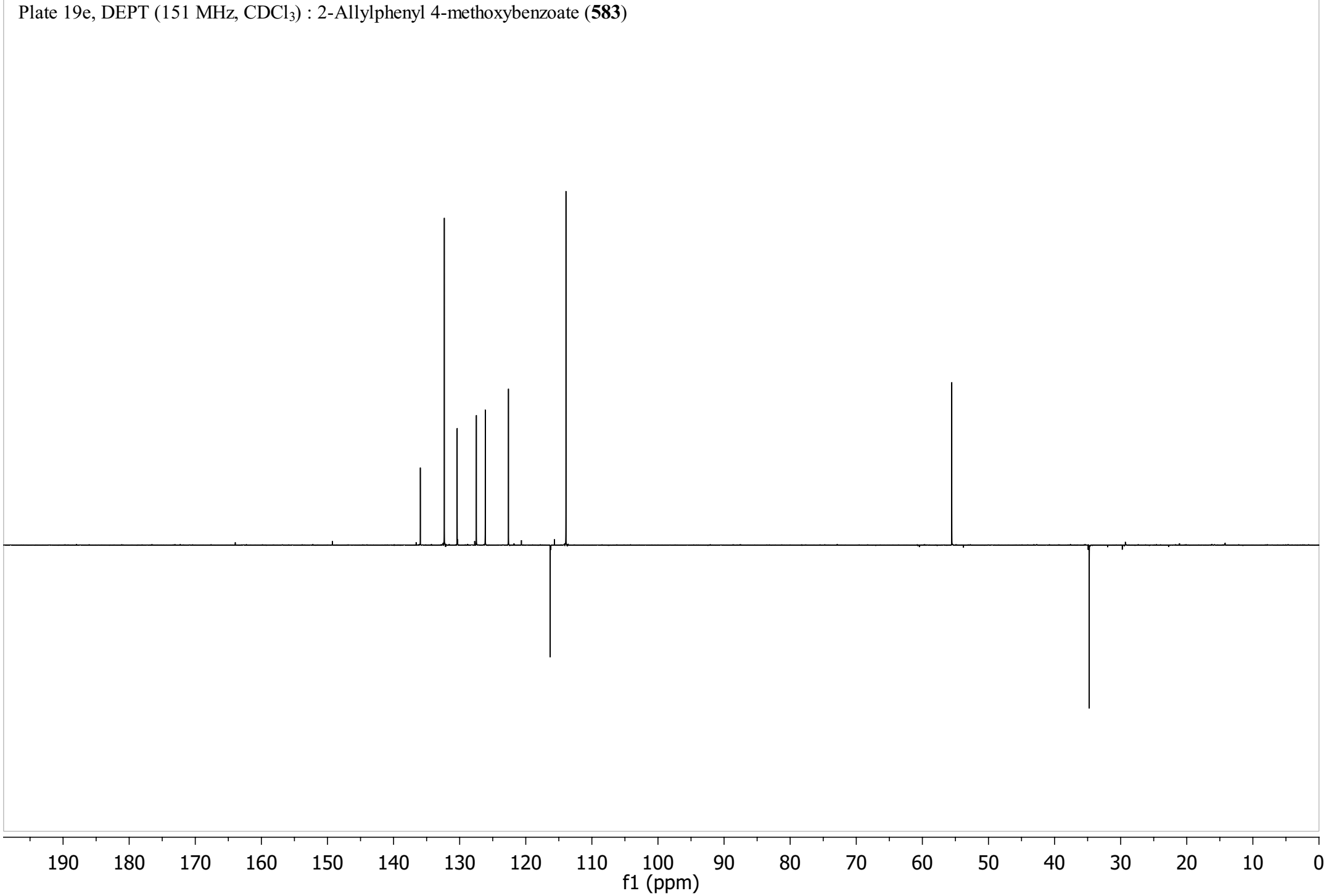
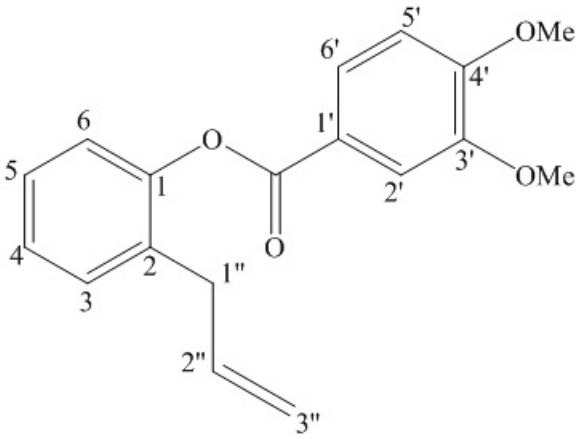
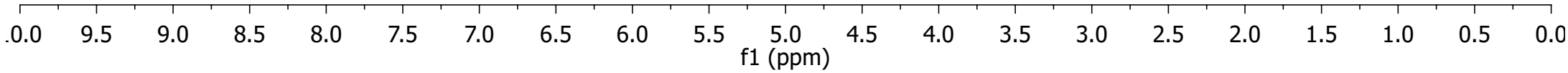


Plate 20a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allylphenyl 3,4-dimethoxybenzoate (**584**)

δ 7.02 (1H, dd, *J* = 8.4, 2.0 Hz, H-6'), 6.85 (1H, d, *J* = 2.0 Hz, H-2'), 6.51 – 6.48 (2H, m, Ar-H), 6.43 – 6.40 (1H, m, Ar-H), 6.40 – 6.38 (1H, m, Ar-H), 6.29 (1H, d, *J* = 8.4 Hz, H-5'), 5.11 (1H, ddt, *J* = 16.7, 10.1, 6.6 Hz, H-2''), 4.22 – 4.16 (2H, m, H-3''), 3.10 (3H, s, -OMe), 3.07 (3H, s, -OMe), 2.54 (2H, br. d, *J* = 6.6 Hz, H-1'')





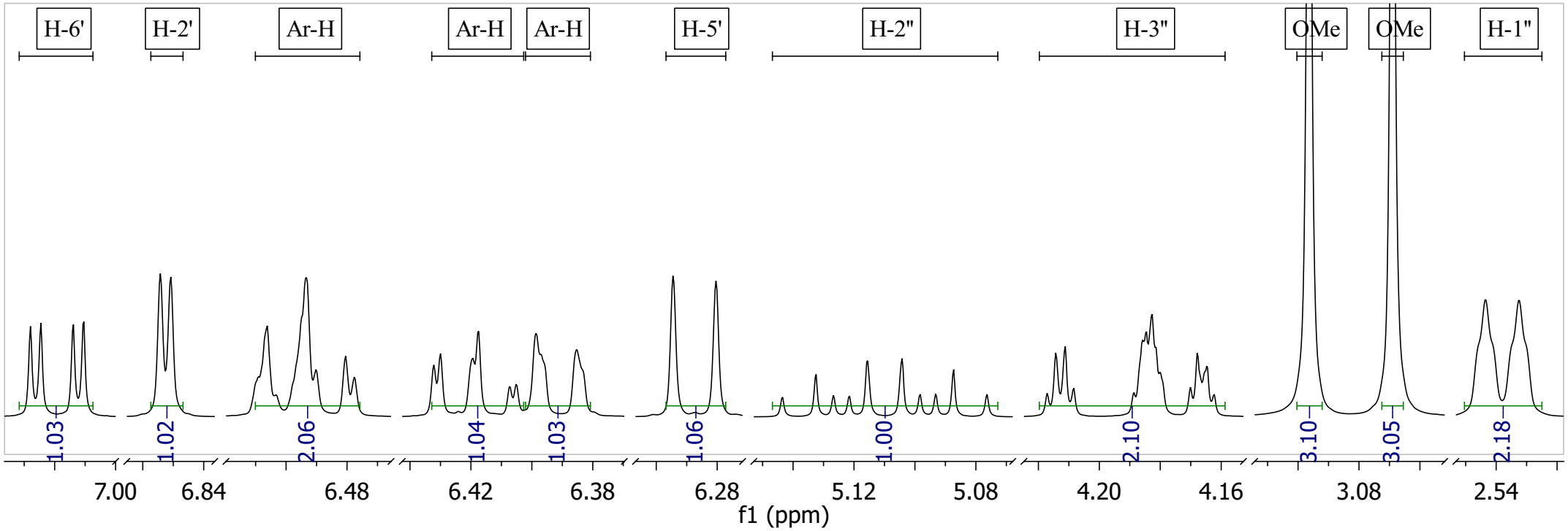
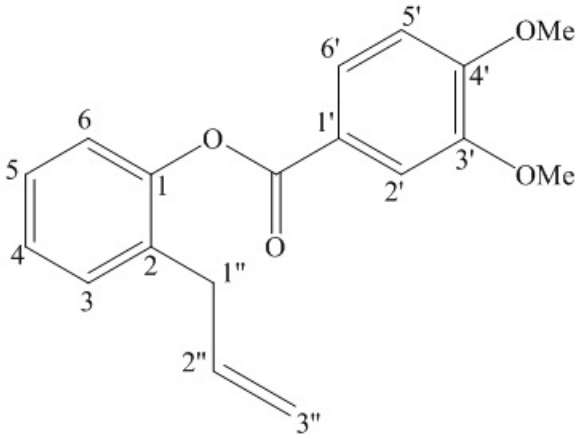
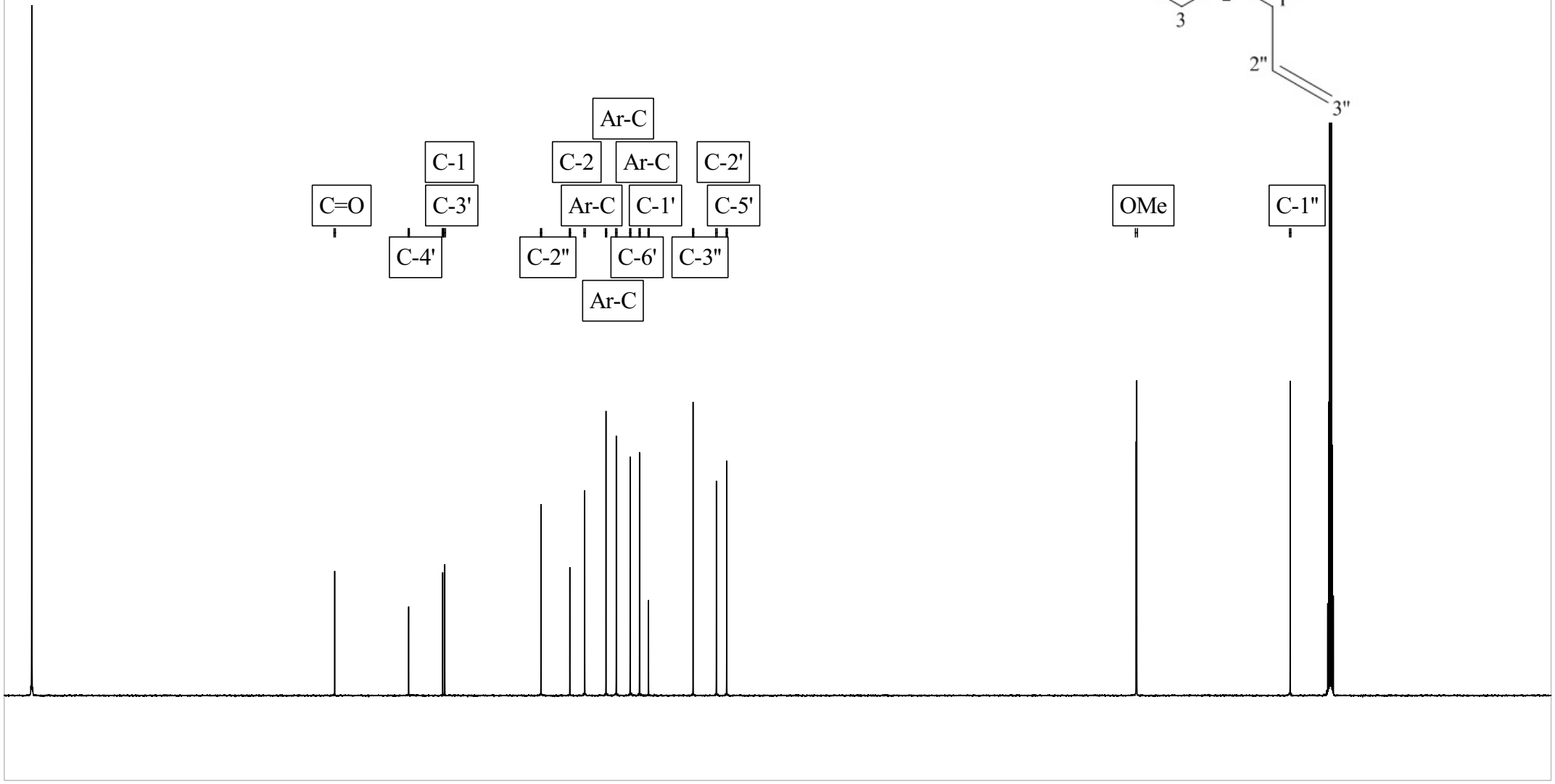


Plate 20b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4-dimethoxybenzoate (**584**)

δ 165.13 (C=O), 155.10 (C-4'), 150.47 (C-1), 150.19 (C-3'), 137.13 (C-2''), 133.22 (C-2), 131.19 (Ar-C), 128.30 (Ar-C), 126.91 (Ar-C), 125.02 (C-6'), 123.75 (Ar-C), 122.53 (C-1'), 116.48 (C-3''), 113.32 (C-2'), 111.92 (C-5'), 56.34 (-OMe), 56.25 (-OMe), 35.42 (C-1'')





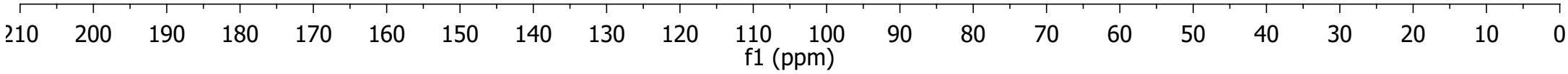


Plate 20c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4-dimethoxybenzoate (**584**)

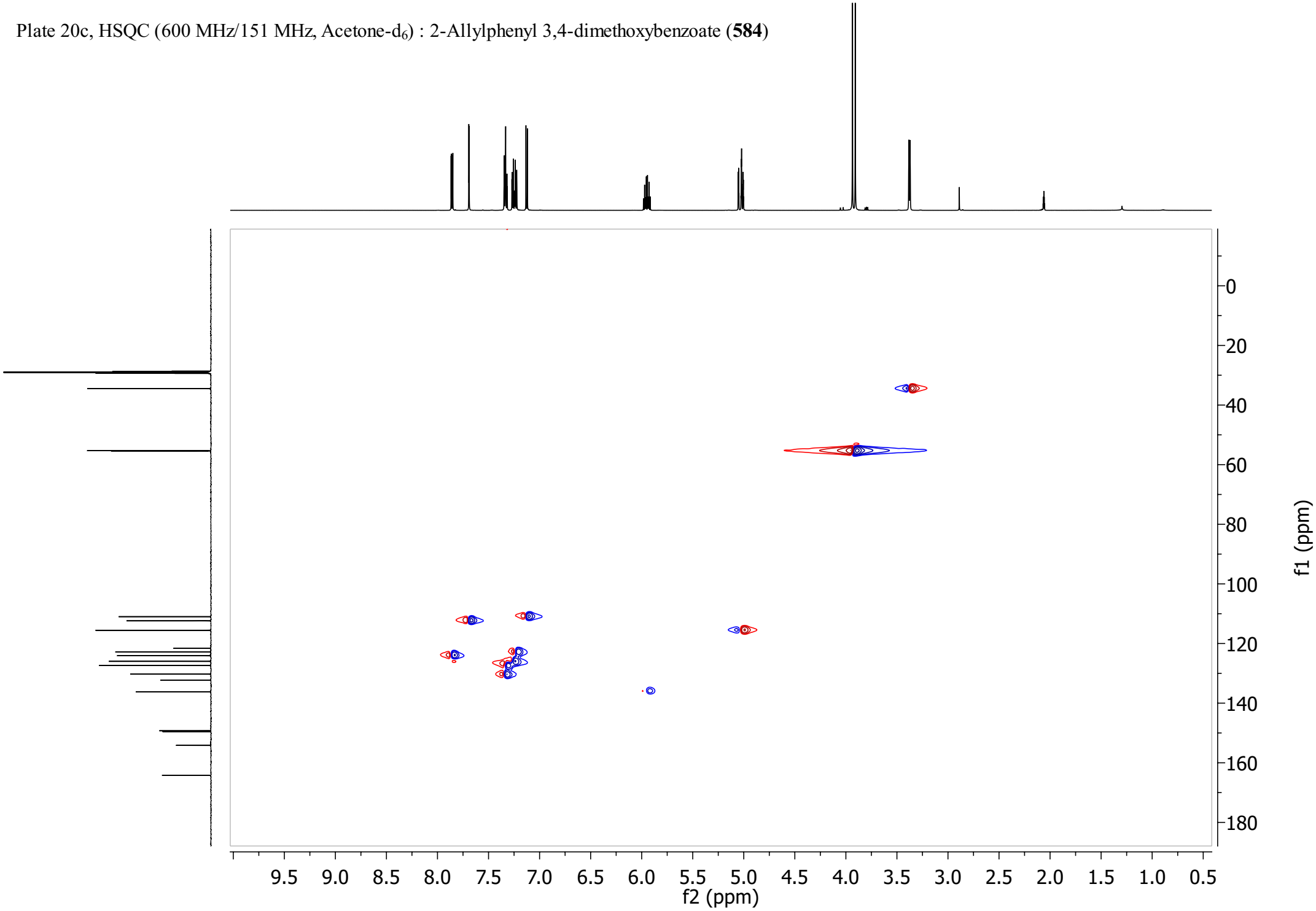


Plate 20d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4-dimethoxybenzoate (**584**)

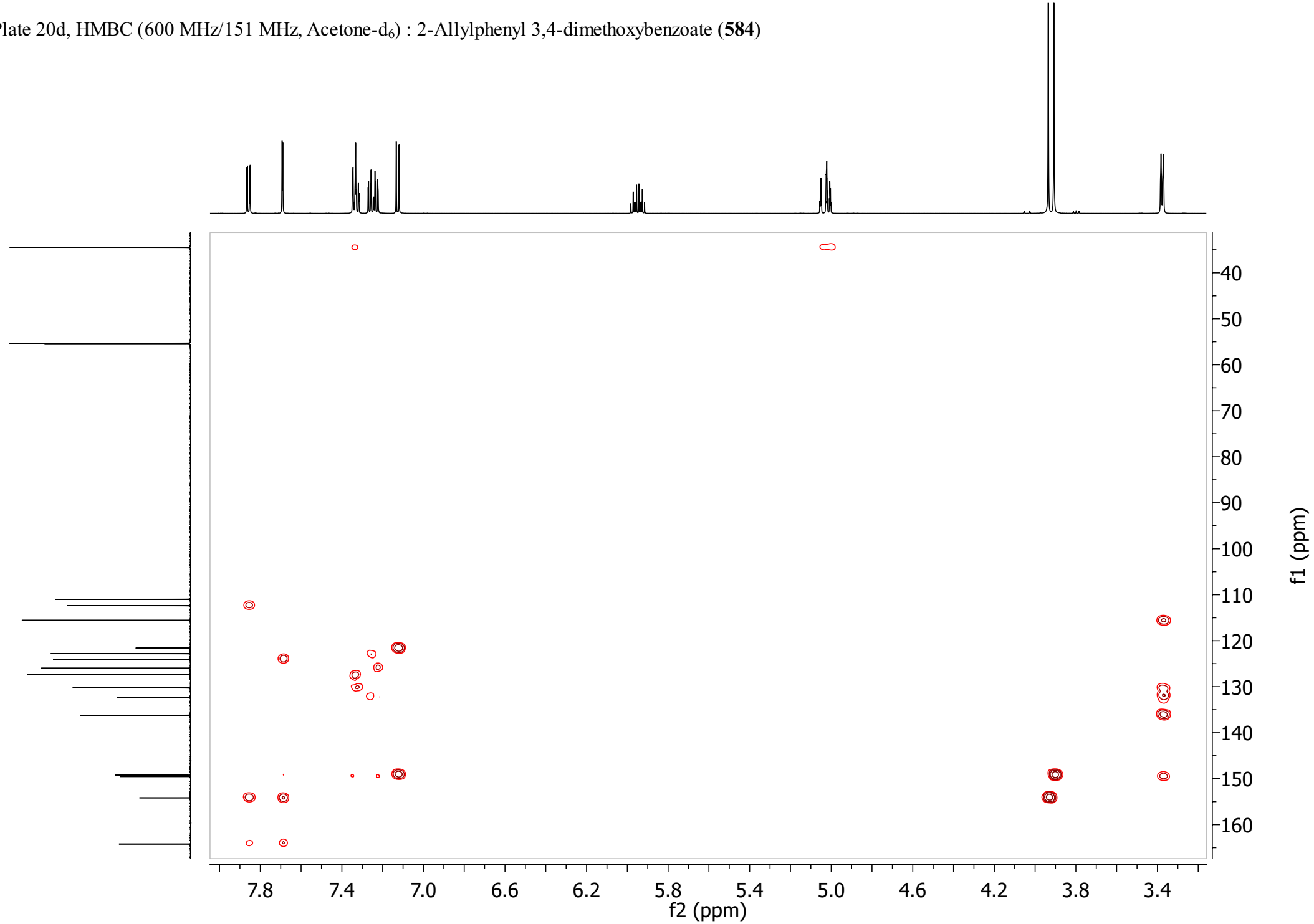


Plate 20e, DEPT (151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4-dimethoxybenzoate (**584**)

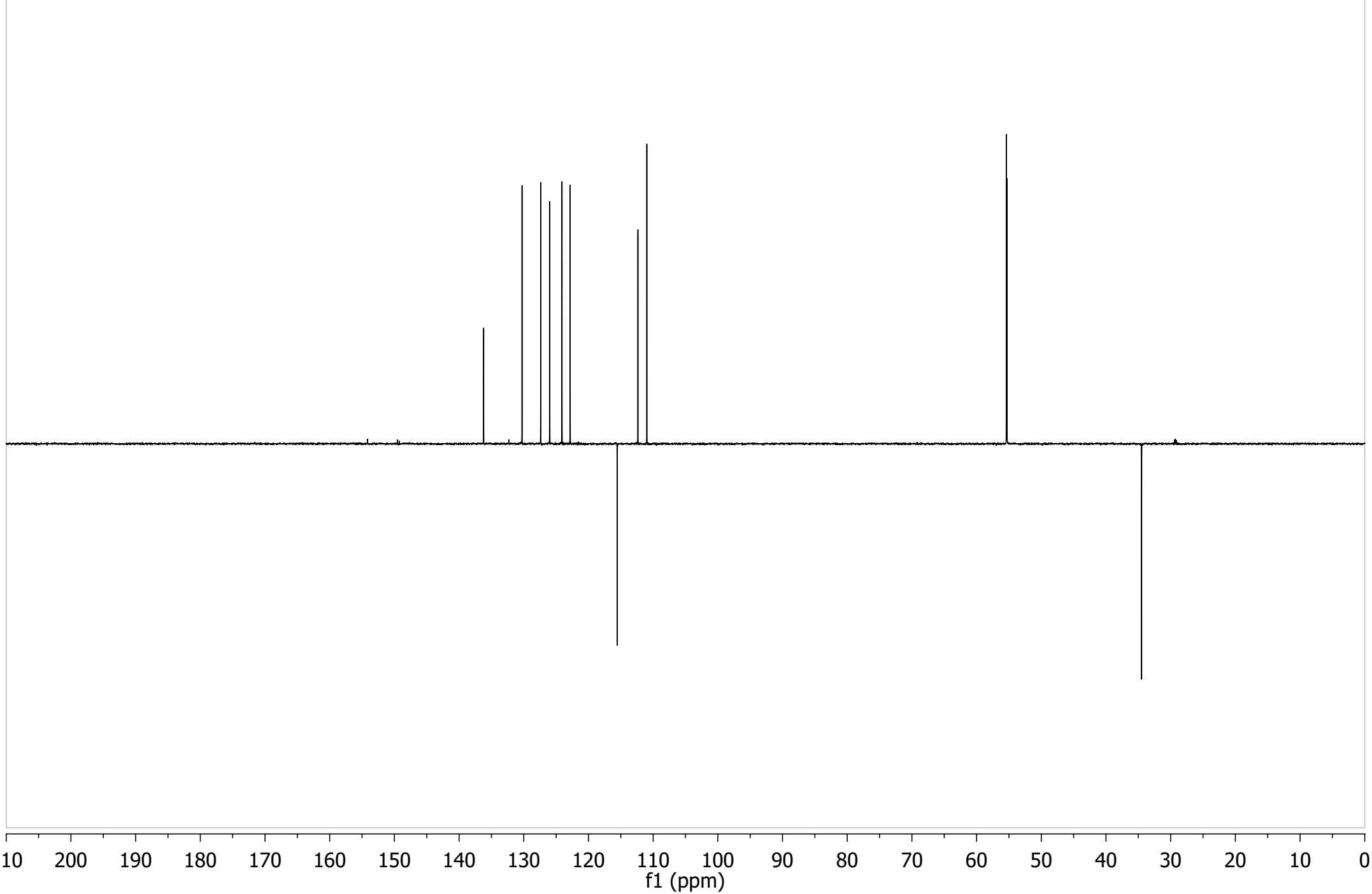
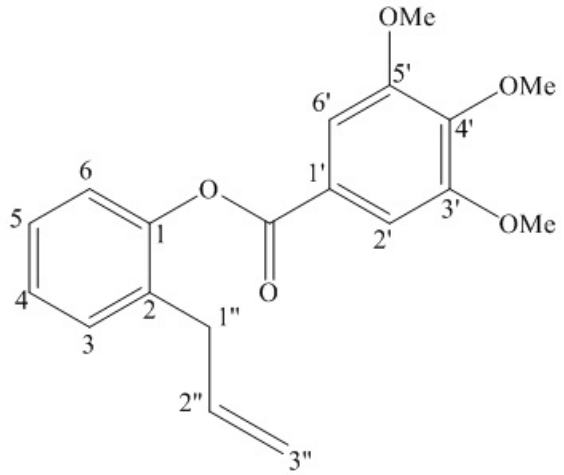
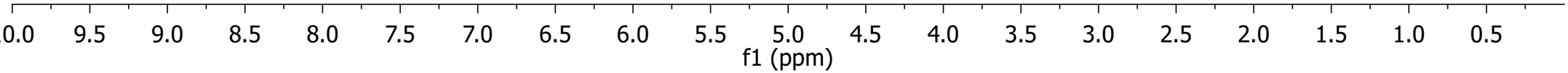


Plate 21a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**)

δ 7.50 (2H, s, H-2' and H-6'), 7.37 – 7.33 (2H, m, Ar-H), 7.29 – 7.26 (1H, m, Ar-H), 7.25 – 7.23 (1H, m, Ar-H), 5.96 (1H, ddt, *J* = 16.7, 10.1, 6.6 Hz, H-2''), 5.04 (2H, m, H-3''), 3.94 (6H, s, -OMe), 3.86 (3H, s, -OMe), 3.39 (2H, br. d, *J* = 6.6 Hz, H-1'')





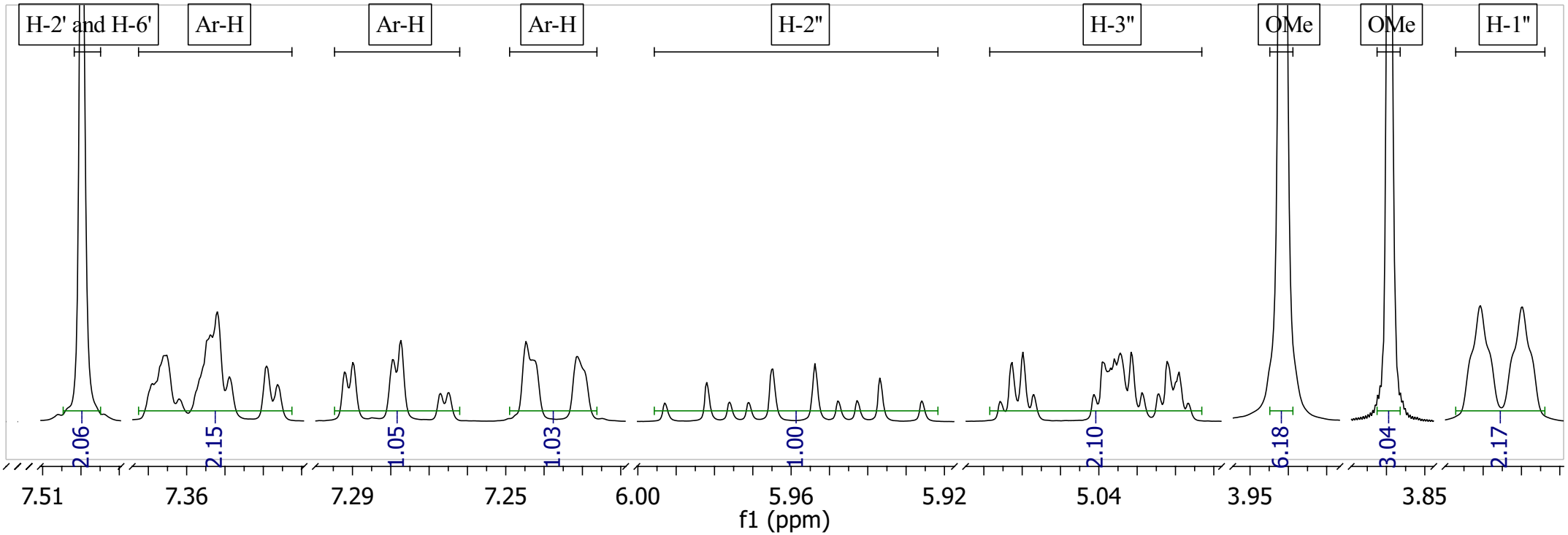
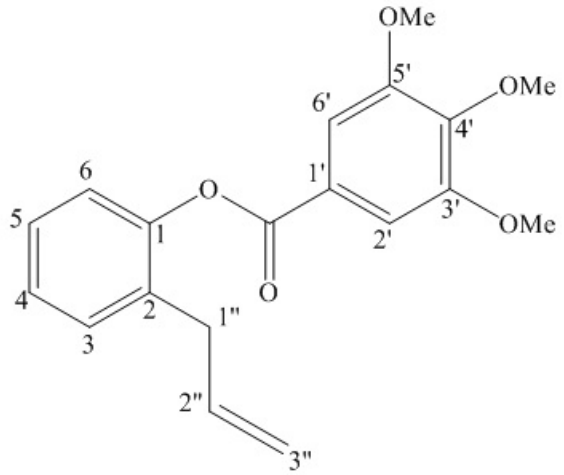
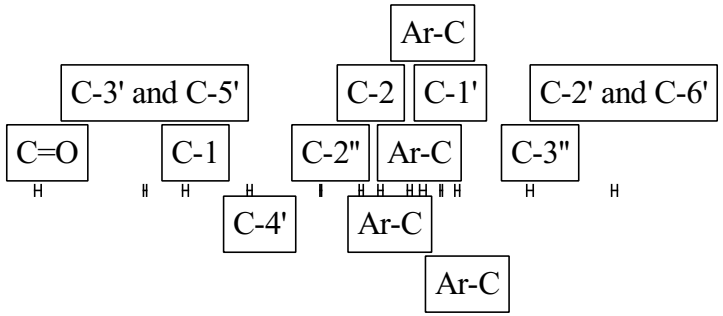
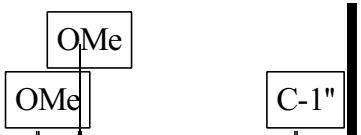


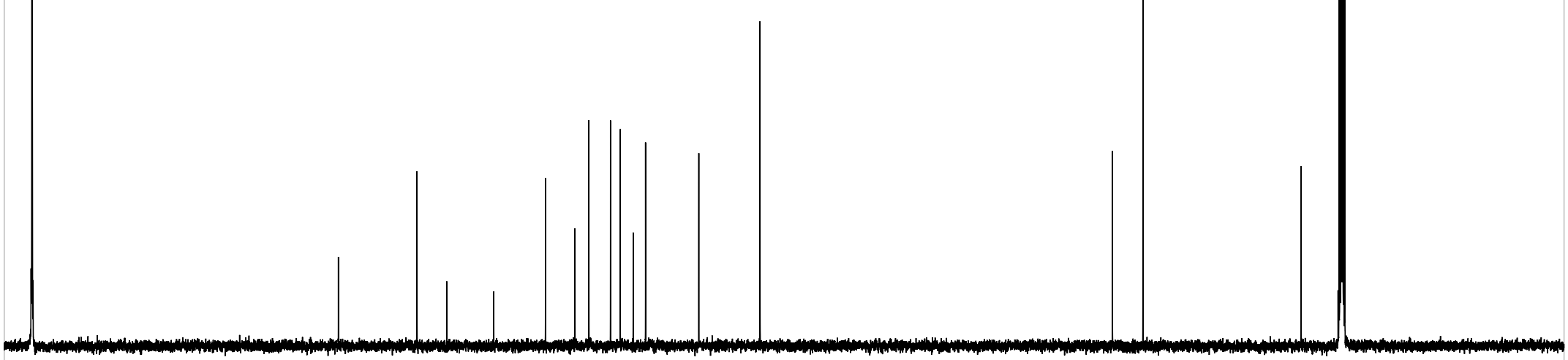
Plate 21b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**)

δ 165.01 (C=O), 154.43 (C-3' and C-5'), 150.42 (C-1), 144.10 (C-4'), 137.13 (C-2''), 133.16 (C-2), 131.29 (Ar-C), 128.38 (Ar-C), 127.07 (Ar-C), 125.32 (C-1'), 123.66 (Ar-C), 116.49 (C-3''), 108.26 (C-2' and C-6'), 60.80 (-OMe), 56.69 (-OMe), 35.41 (C-1'')









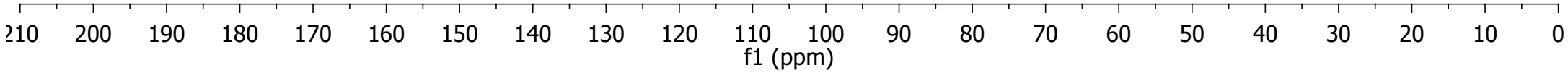


Plate 21b, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**)

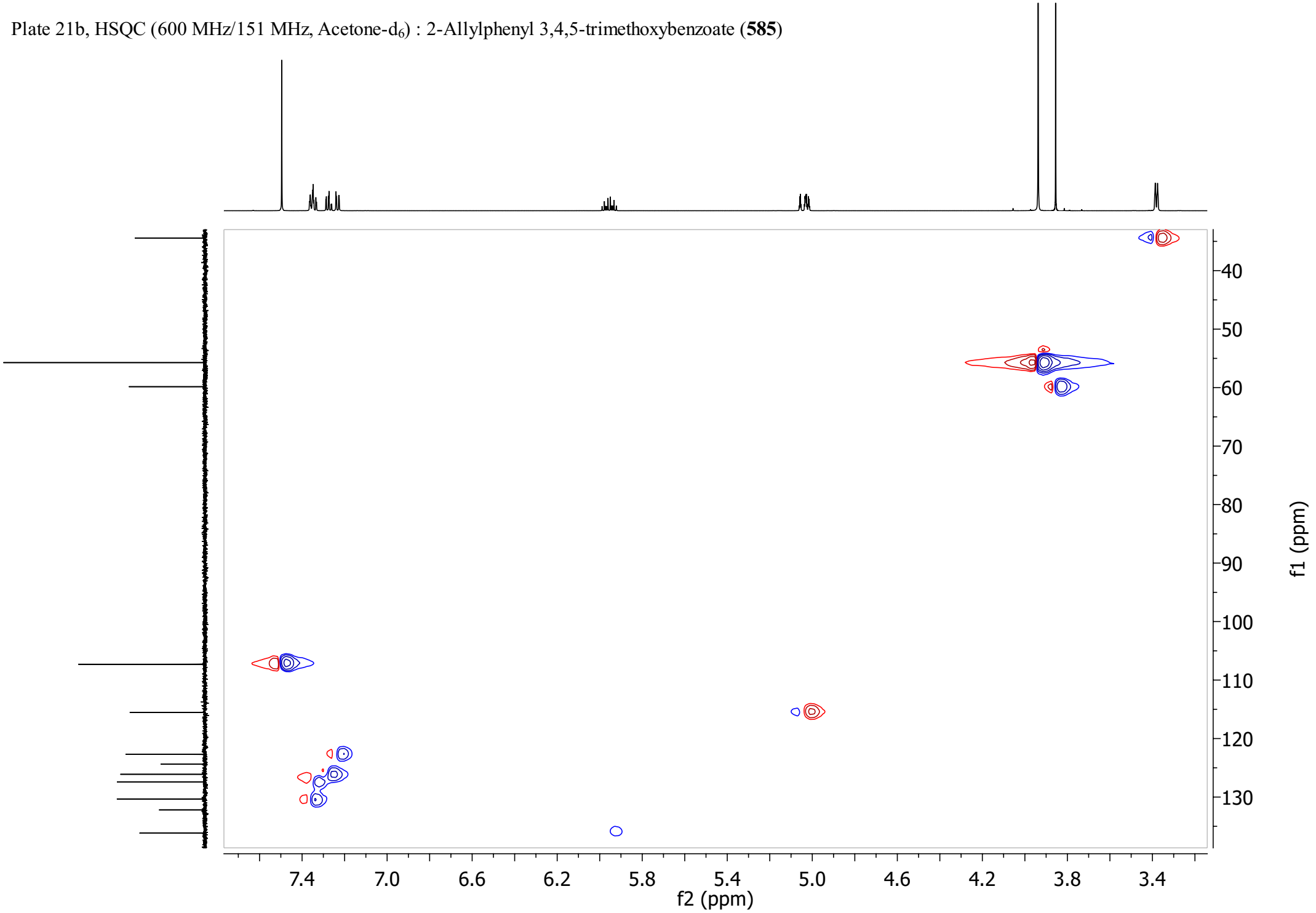


Plate 21d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**)

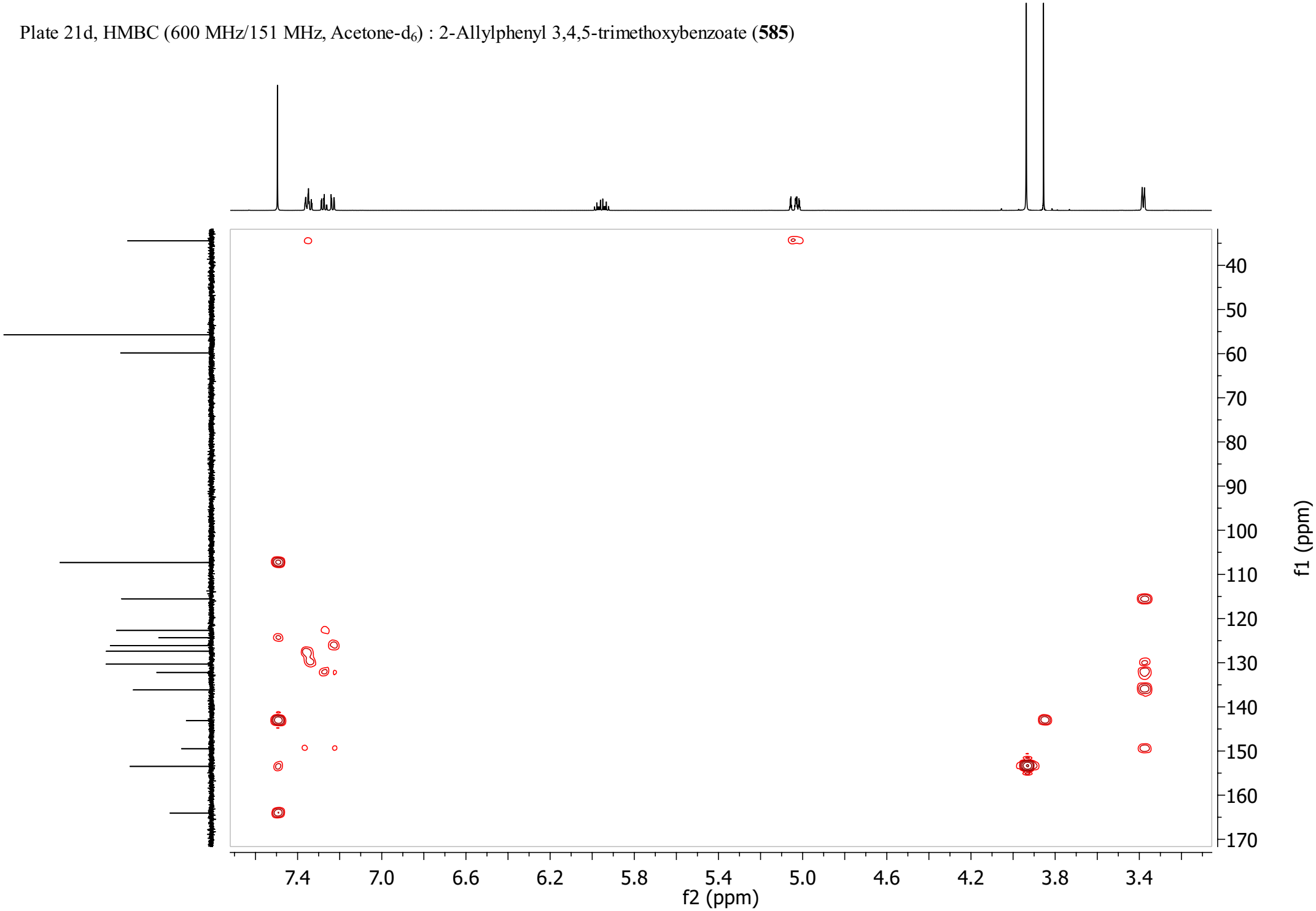


Plate 21e, DEPT (151 MHz, Acetone-d_6) : 2-Allylphenyl 3,4,5-trimethoxybenzoate (**585**)

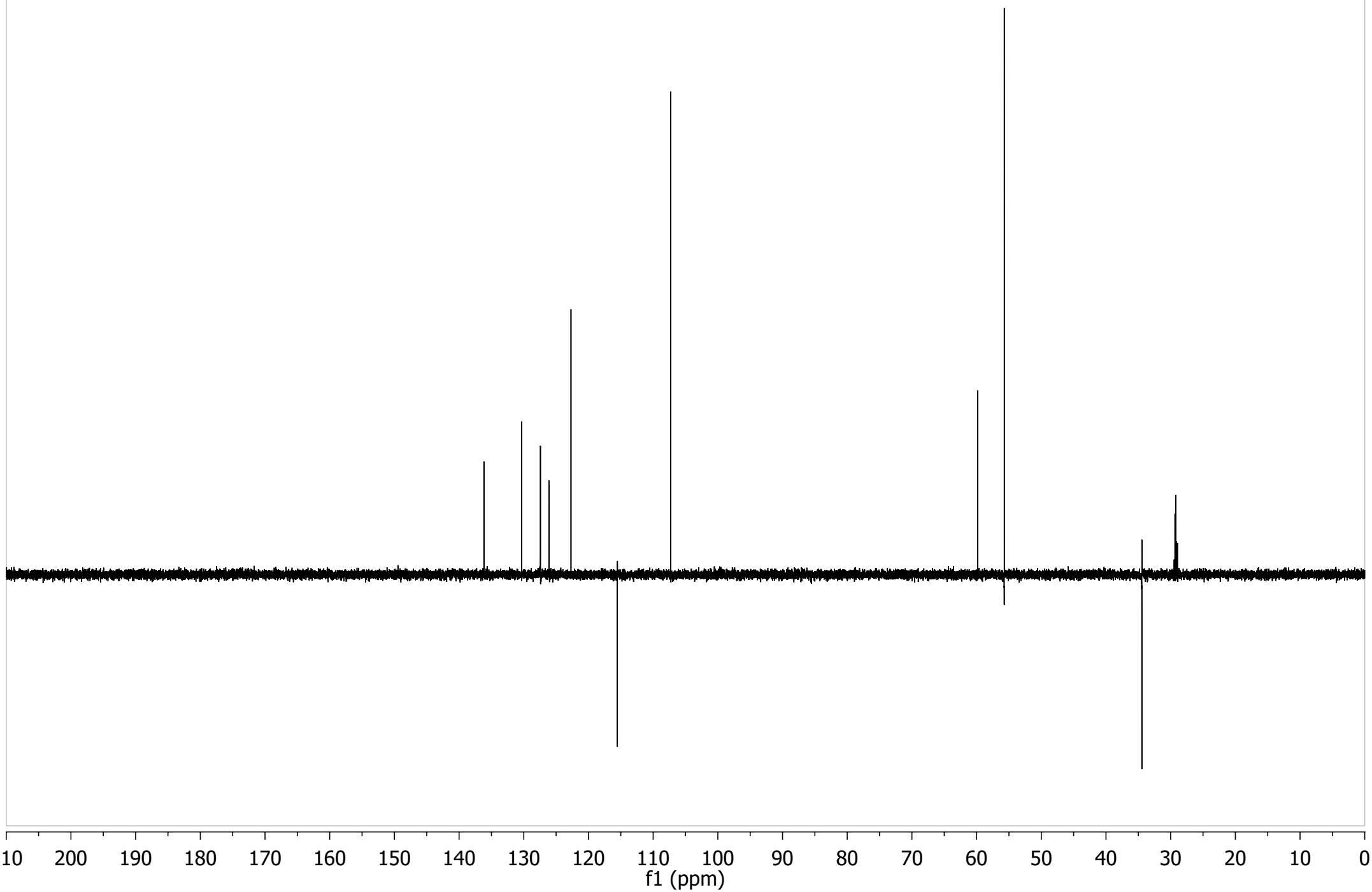
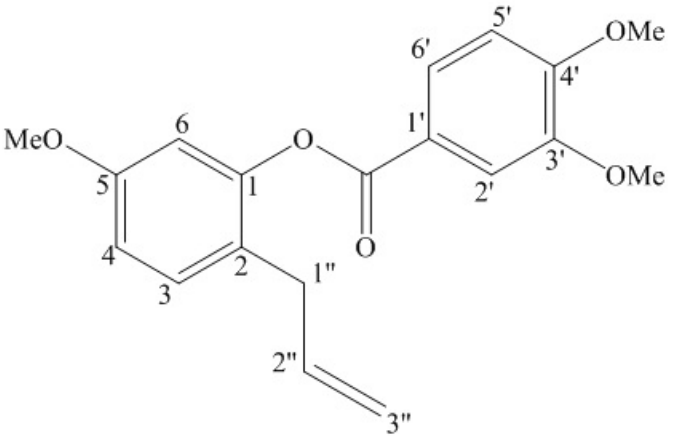
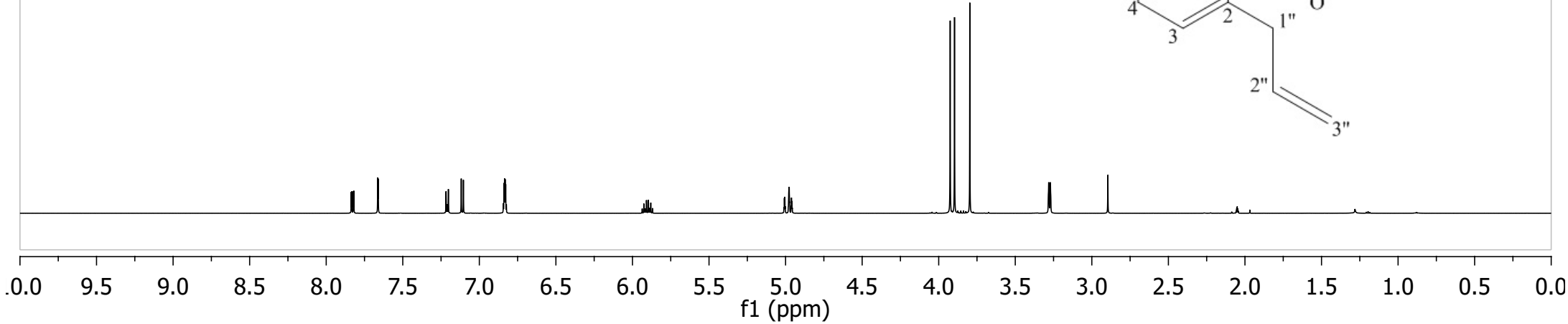


Plate 22a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**)

δ 7.83 (1H, dd, *J* = 8.5, 2.0 Hz, H-6'), 7.66 (1H, d, *J* = 2.0 Hz, H-2'), 7.21 (1H, d, *J* = 9.1 Hz, H-3), 7.11 (1H, d, *J* = 8.5 Hz, H-5'), 6.85 – 6.82 (2H, m, H-4 and H-6), 5.91 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, H-2''), 5.01 – 4.95 (2H, m, H-3''), 3.93 (3H, s, 4'-OMe), 3.90 (3H, s, 3'-OMe), 3.80 (3H, s, 5-OMe), 3.28 (2H, br. d, *J* = 6.6 Hz, H-1'')





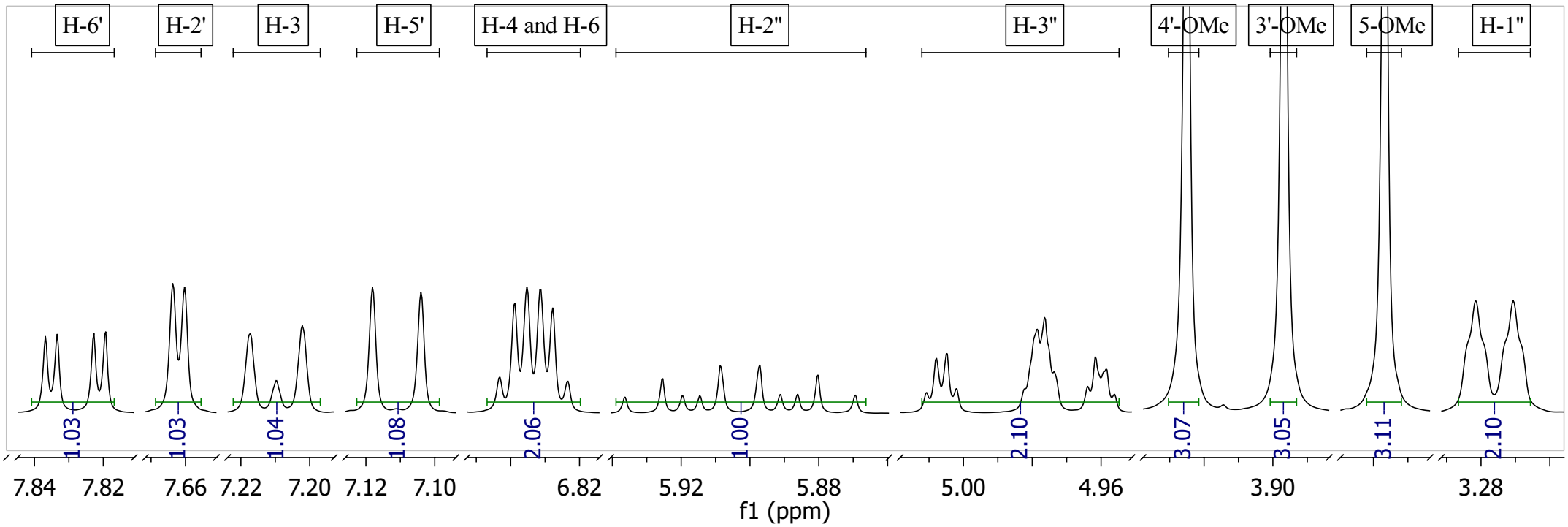
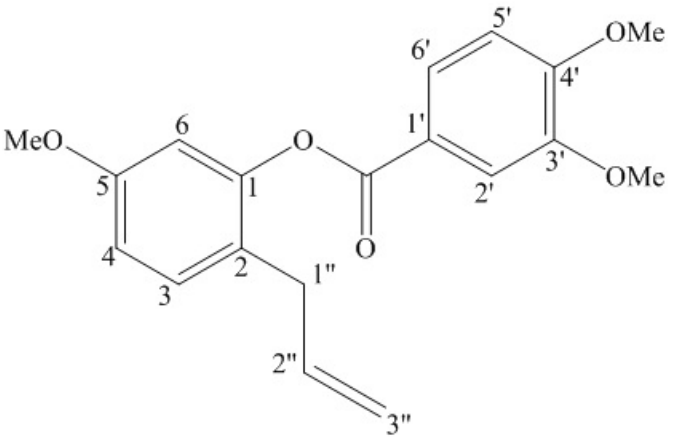


Plate 22b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**)

δ 164.97 (C=O), 159.97 (C-5), 155.03 (C-4'), 151.01 (C-1), 150.11 (C-3'), 137.53 (C-2''), 131.47 (C-3), 124.97 (C-2/6'), 124.89 (C-2/6'), 122.46 (C-1'), 116.00 (C-3''), 113.25 (C-2'), 112.61 (C-4/6), 111.85 (C-5'), 109.44 (C-4/6), 56.27 (-OMe), 56.18 (-OMe) 55.83 (-OMe), 34.73 (C-1'')



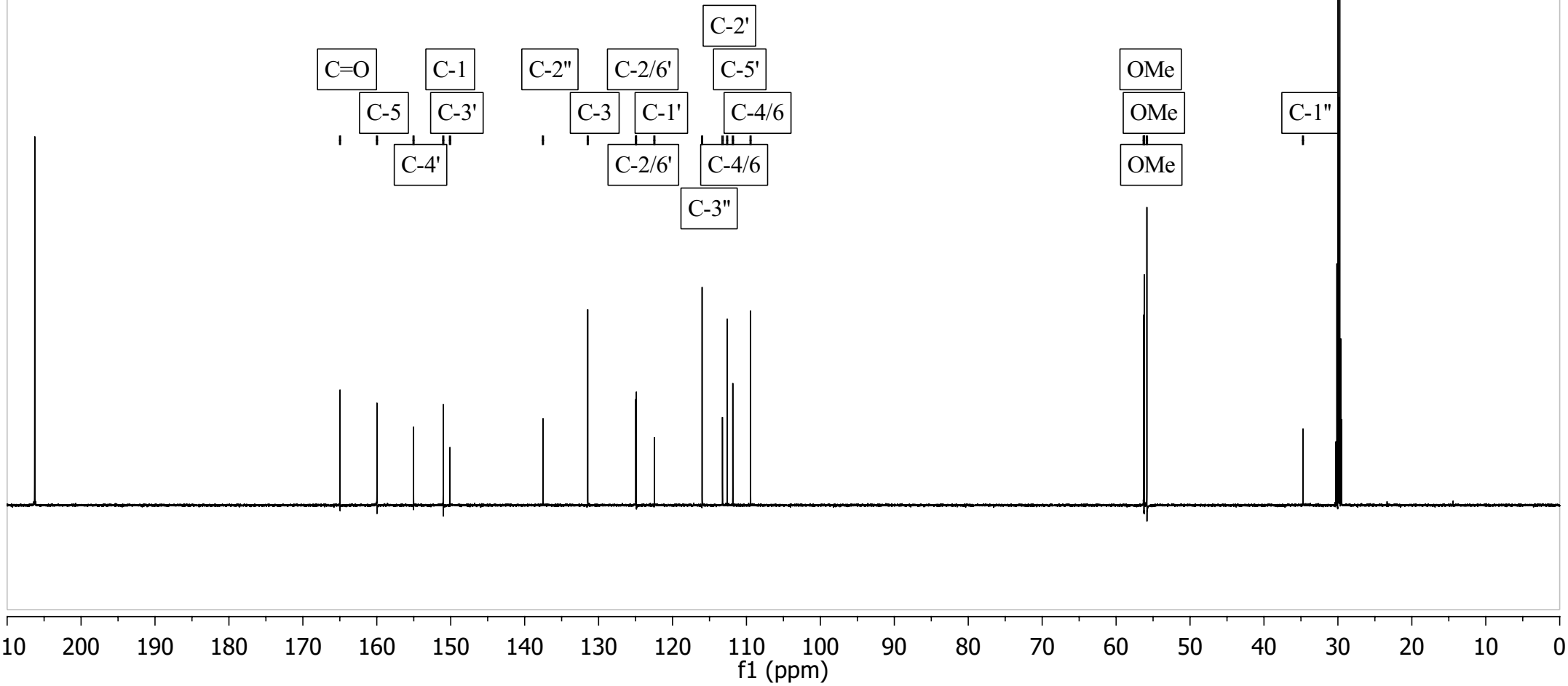


Plate 22c, HSQC (600 MHz151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**)

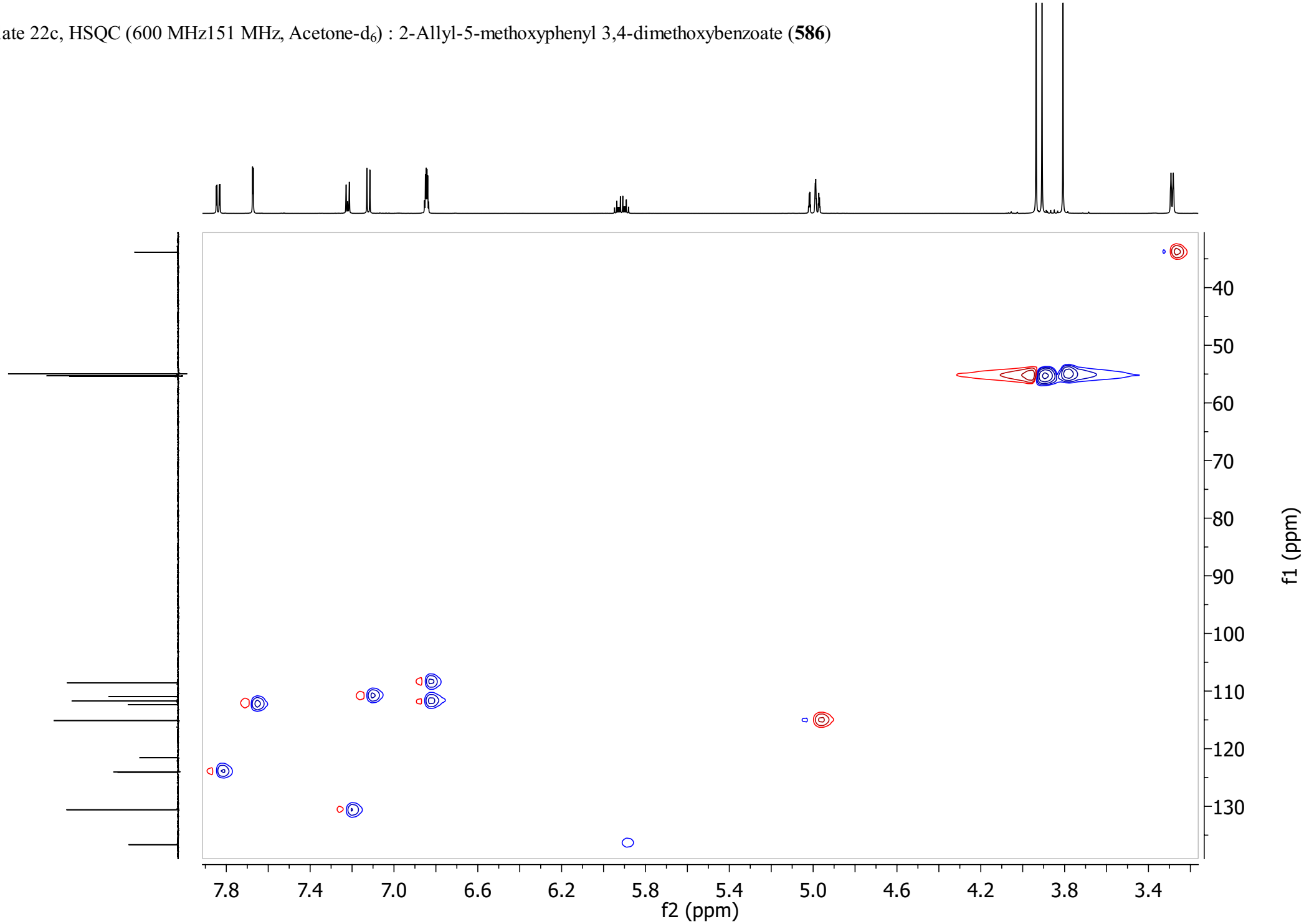


Plate 22d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**)

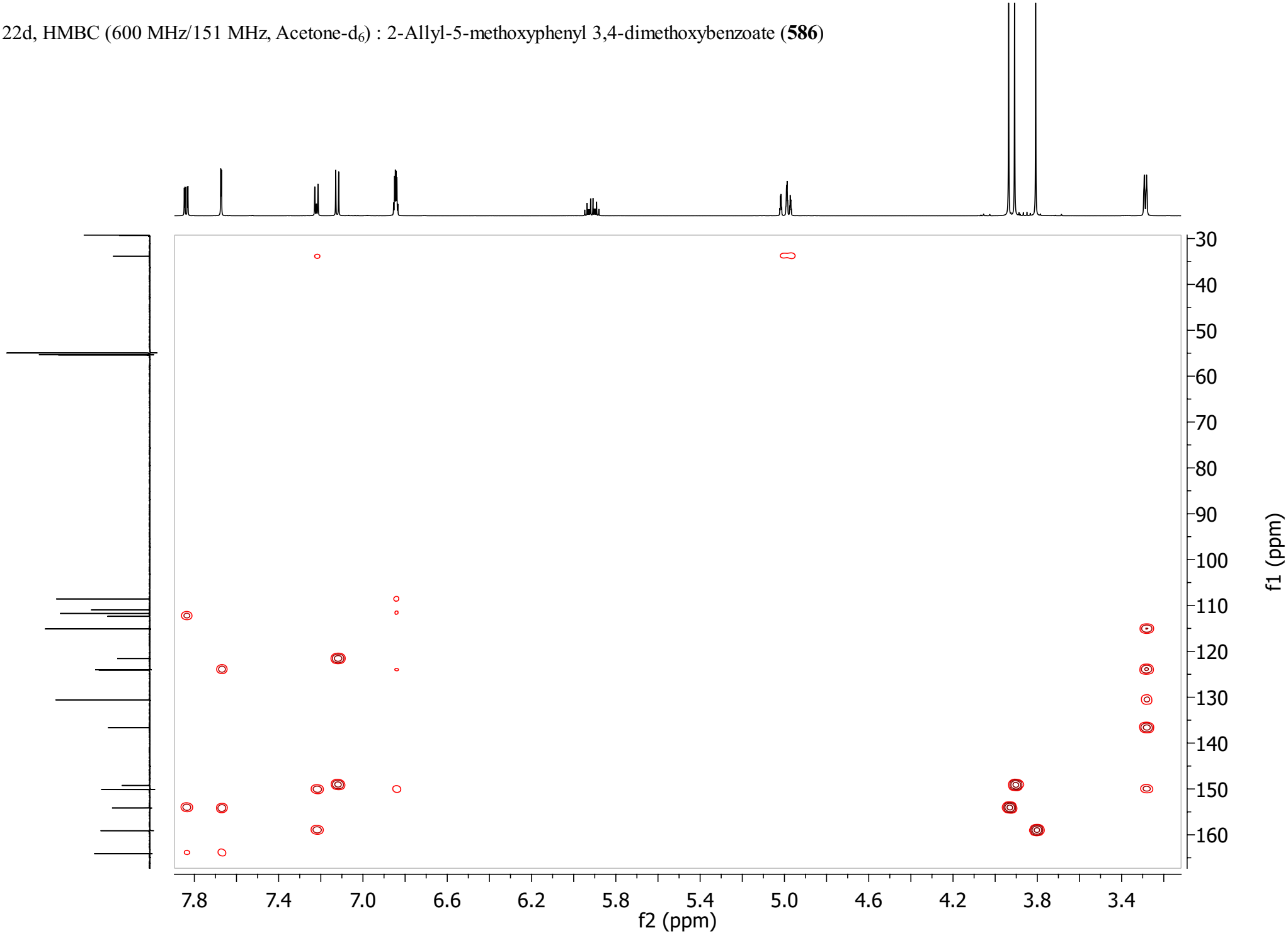
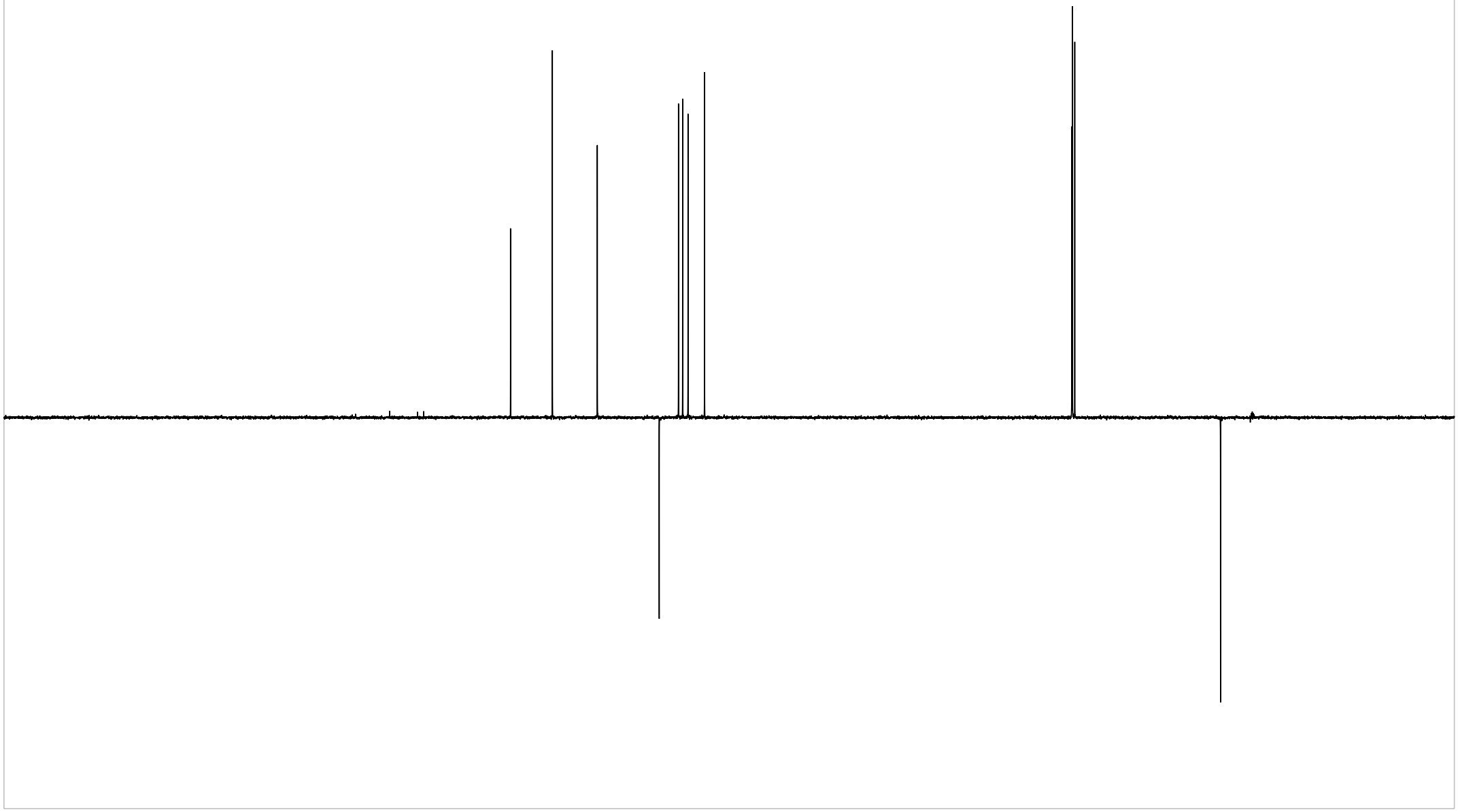


Plate 22e, DEPT (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4-dimethoxybenzoate (**586**)

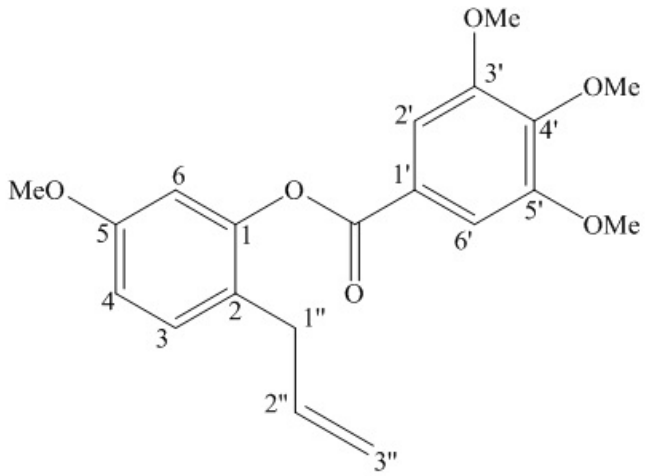


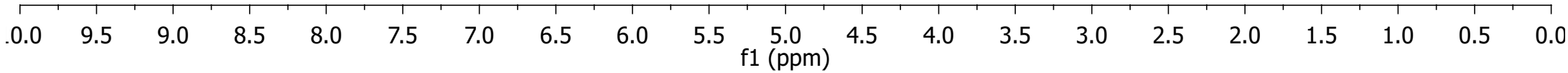
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 23a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**)

δ 7.47 (2H, s, H-2' and H-6'), 7.22 (1H, d, *J* = 8.9 Hz, H-3), 6.86 – 6.83 (2H, m, H-4 and H-6) 5.91 (1H, ddt, *J* = 16.7, 10.1, 6.5 Hz, H-2''), 5.03 – 4.97 (2H, m, H-3''), 3.92 (6H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.28 (2H, br. d, *J* = 6.5 Hz, H-1'')





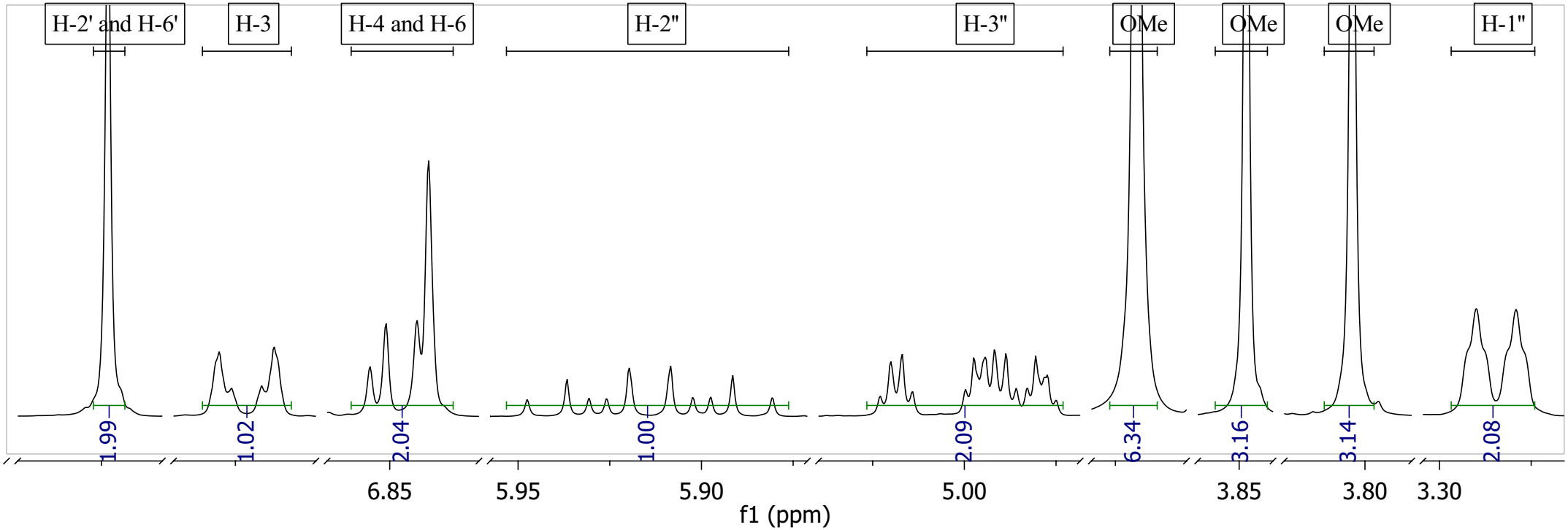
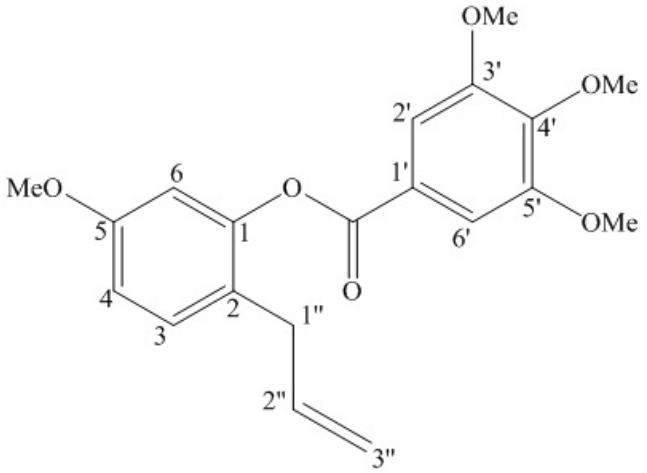


Plate 23b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**)

δ 164.90 (C=O), 160.08 (C-5), 154.39 (C-3' and C-5'), 151.00 (C-1), 144.09 (C-4'), 137.57 (C-2''), 131.62 (C-3), 125.29 (C-2/1'), 124.86 (C-2/1'), 116.10 (C-3''), 112.78 (C-4/6), 109.42 (C-4/6), 108.25 (C-2' and C-6'), 60.83 (-OMe), 56.69 (-OMe), 55.91 (-OMe), 34.79 (C-1'')



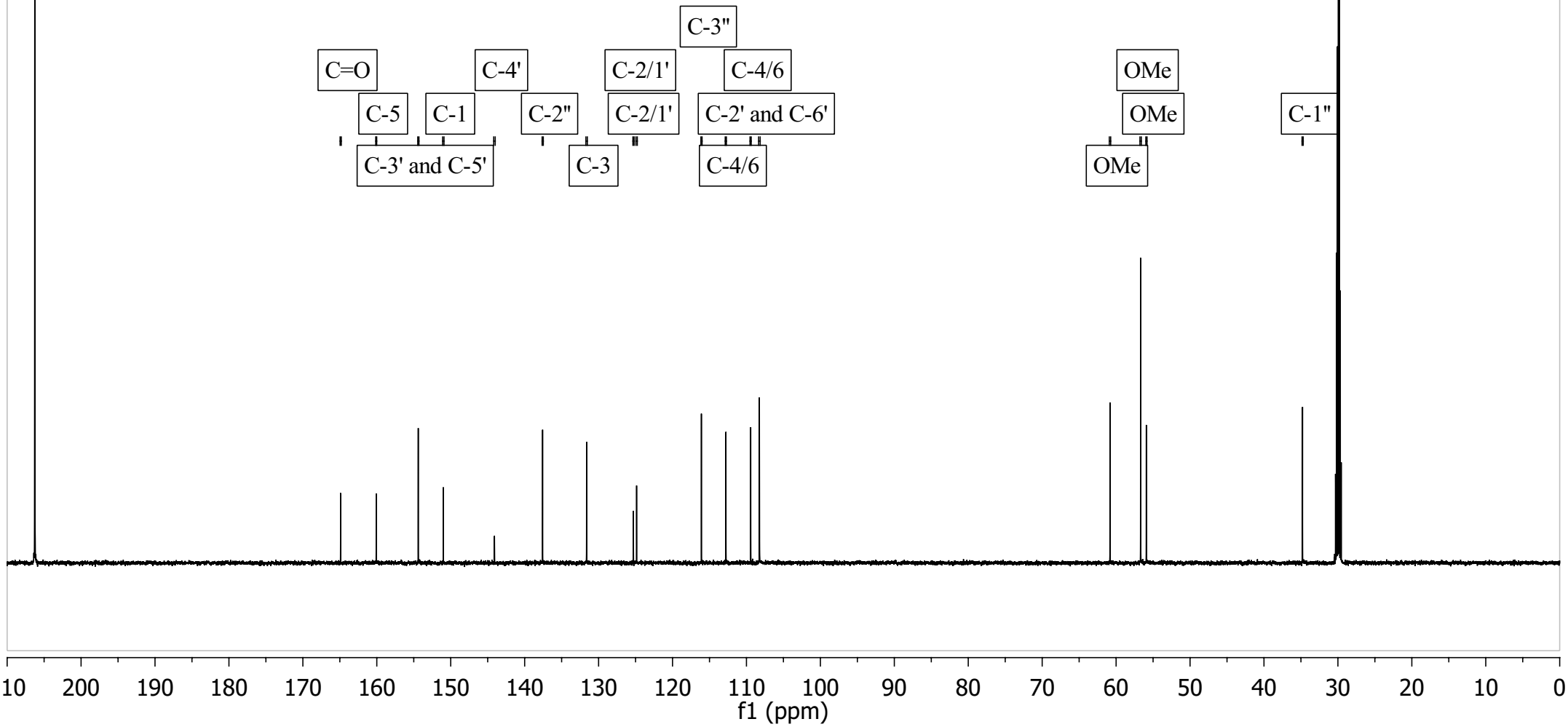


Plate 23c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**)

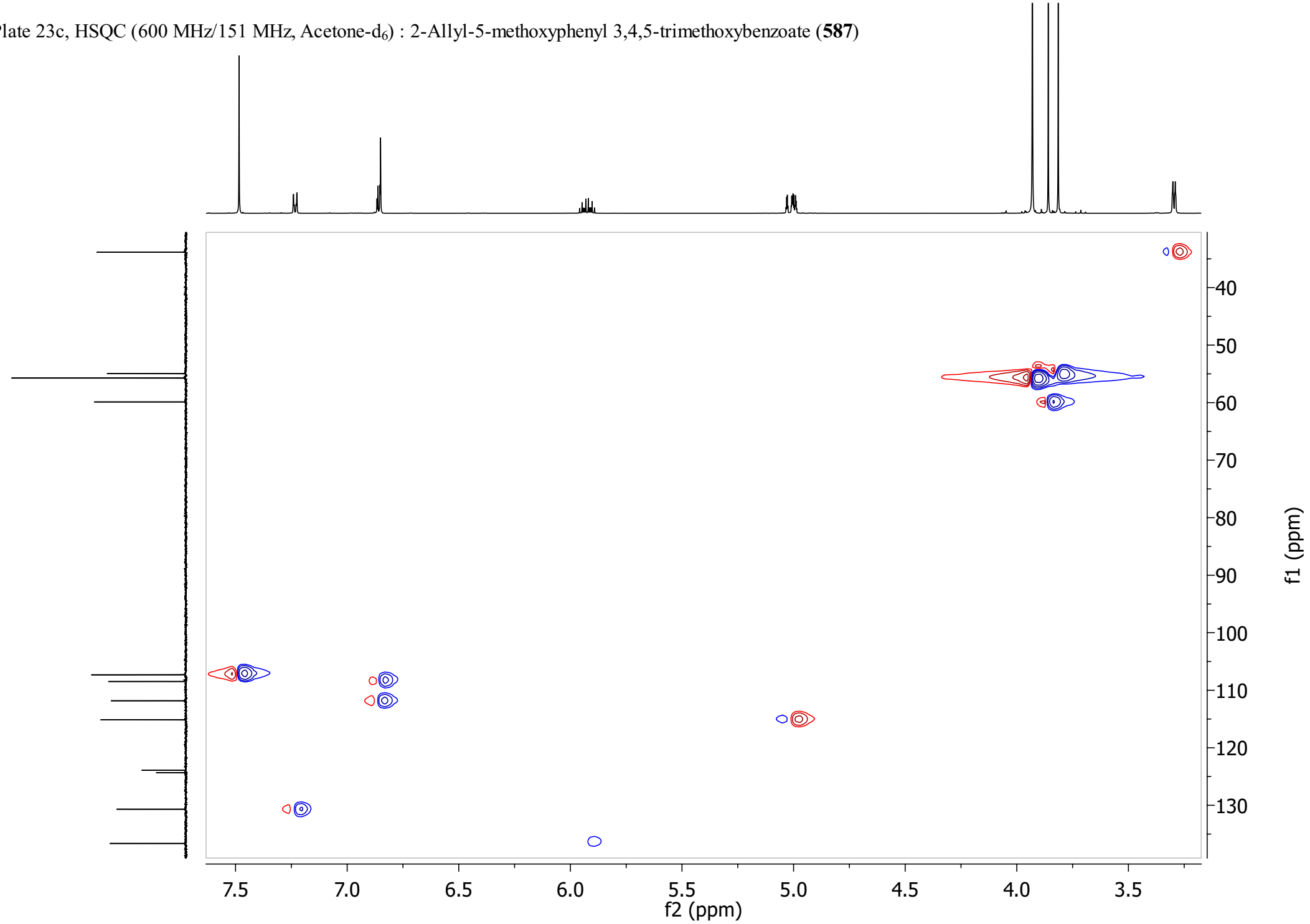


Plate 23d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**)

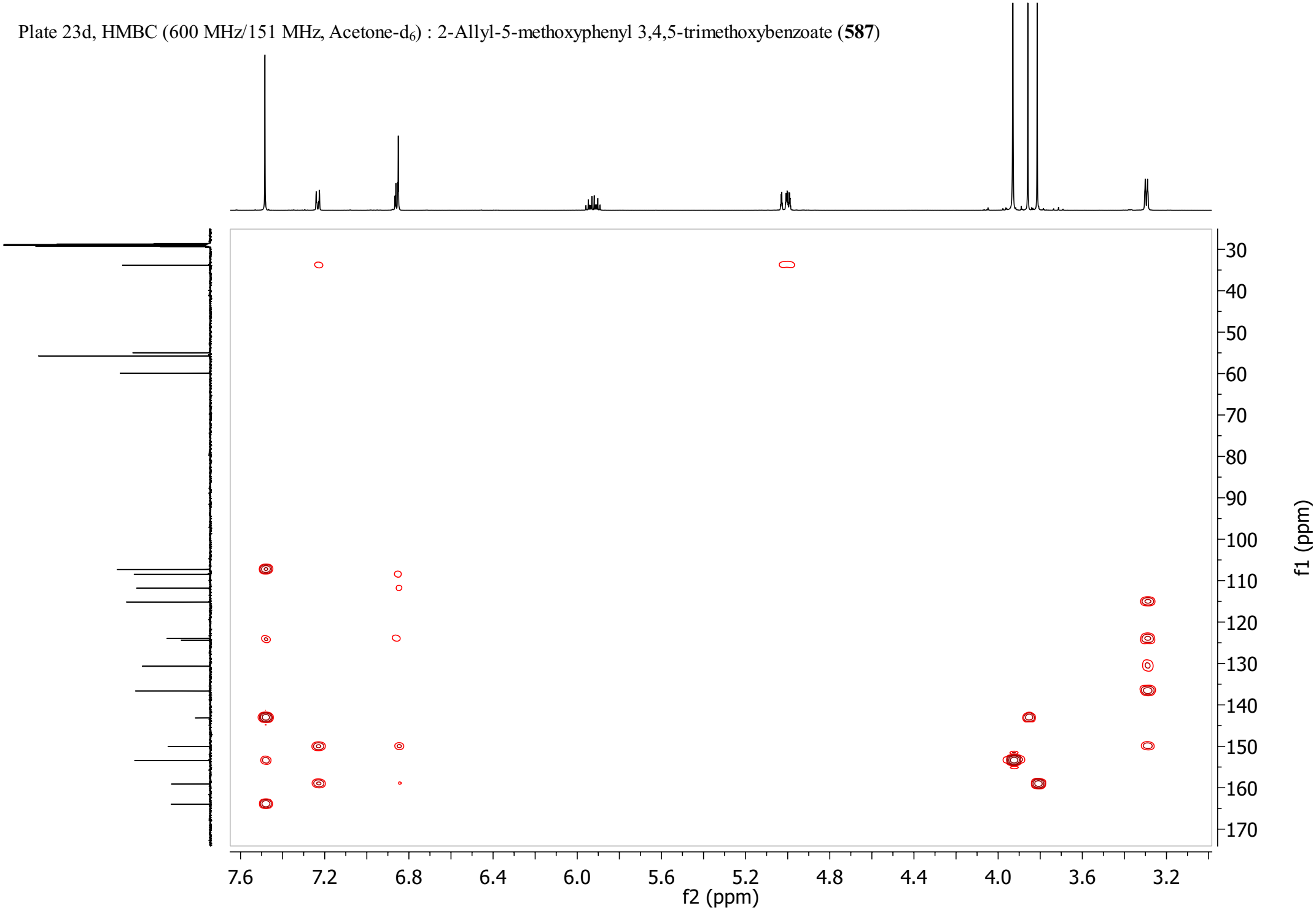


Plate 23e, DEPT (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate (**587**)

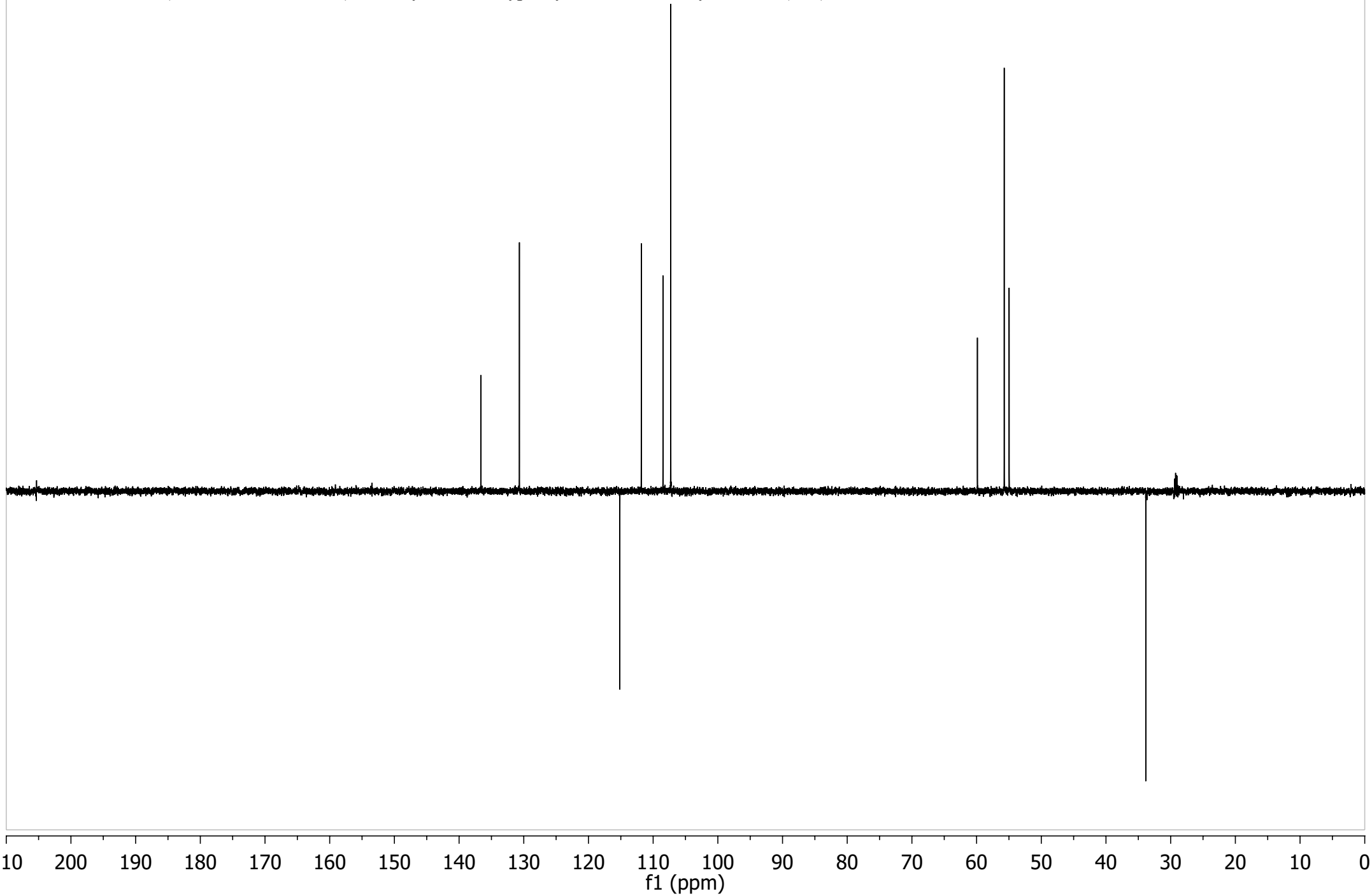
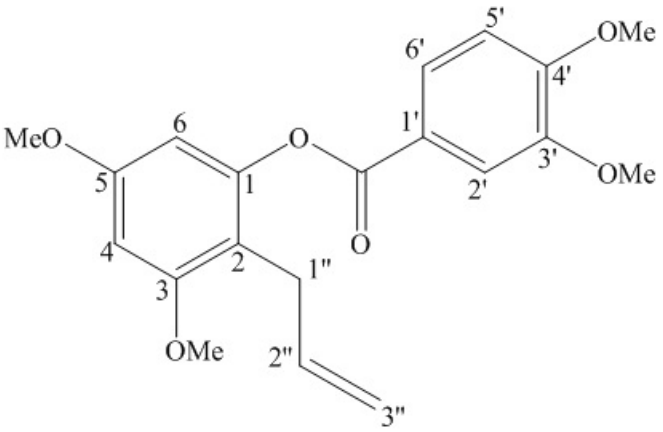


Plate 24a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**)

δ 7.81 (1H, dd, *J* = 8.4, 2.0 Hz, H-6'), 7.64 (1H, d, *J* = 2.0 Hz, H-2'), 7.12 (1H, d, *J* = 8.4 Hz, H-5'), 6.50 (1H, d, *J* = 2.4 Hz, H-4/6), 6.44 (1H, d, *J* = 2.4 Hz, H-4/6), 5.83 (1H, ddt, *J* = 16.4, 10.0, 6.3 Hz, H-2''), 4.90 – 4.83 (2H, m, H-3''), 3.93 (3H, s, -OMe), 3.90 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.25 (2H, br. d, *J* = 6.3 Hz, H-1'')



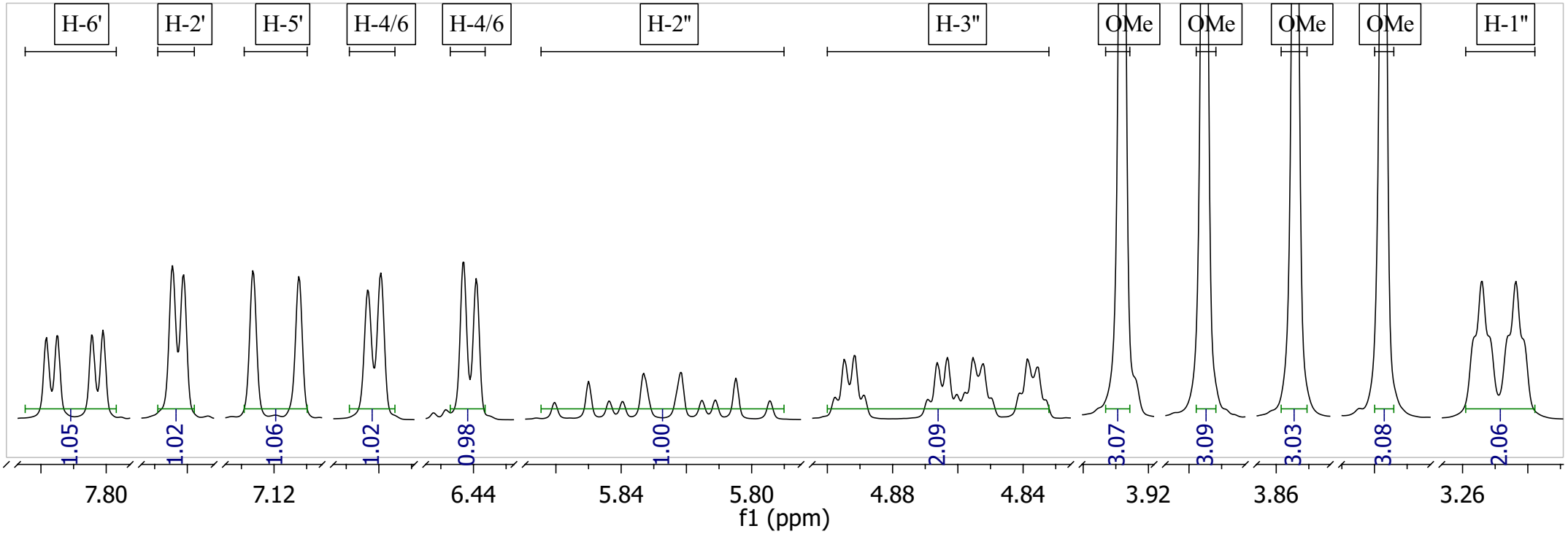
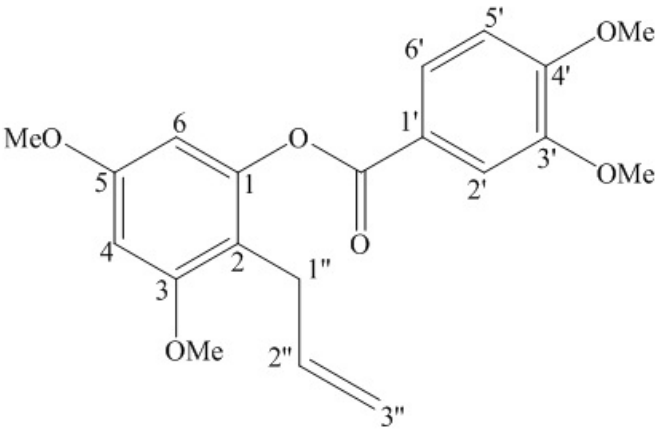


Plate 24b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**)

δ 164.98 (C=O), 160.31 (4º-C), 159.83 (4º-C), 155.06 (4º-C), 151.70 (4º-C), 150.18 (4º-C), 137.27 (C-2''), 124.96 (C-6'), 122.62 (4º-C), 114.91 (C-3''), 113.90 (4º-C), 113.27 (C-2'), 111.92 (C-5'), 100.93 (C-4/6), 97.03 (C-4/6), 56.41 – 55.78 (-OMe), 28.60 (C-1'')



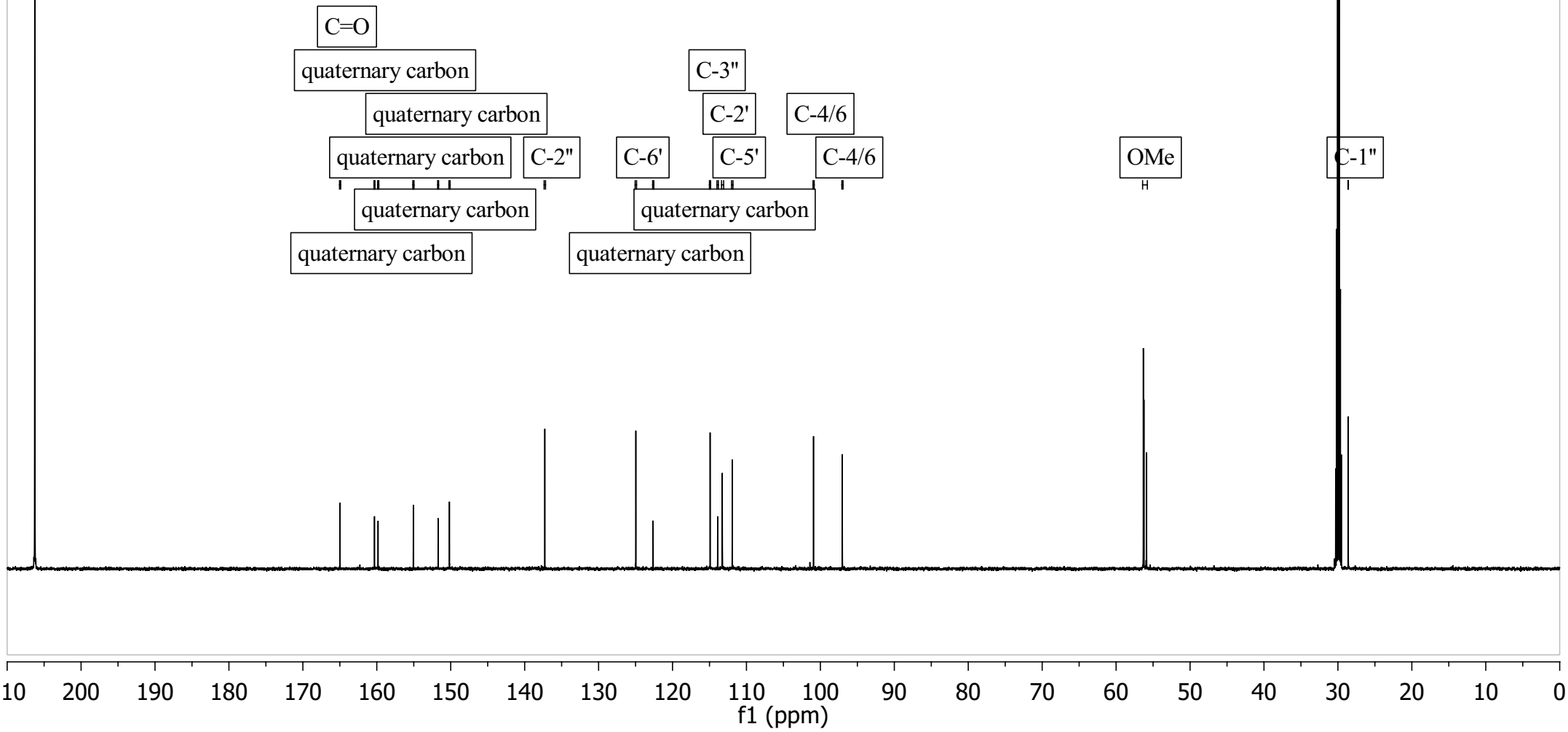


Plate 24c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**)

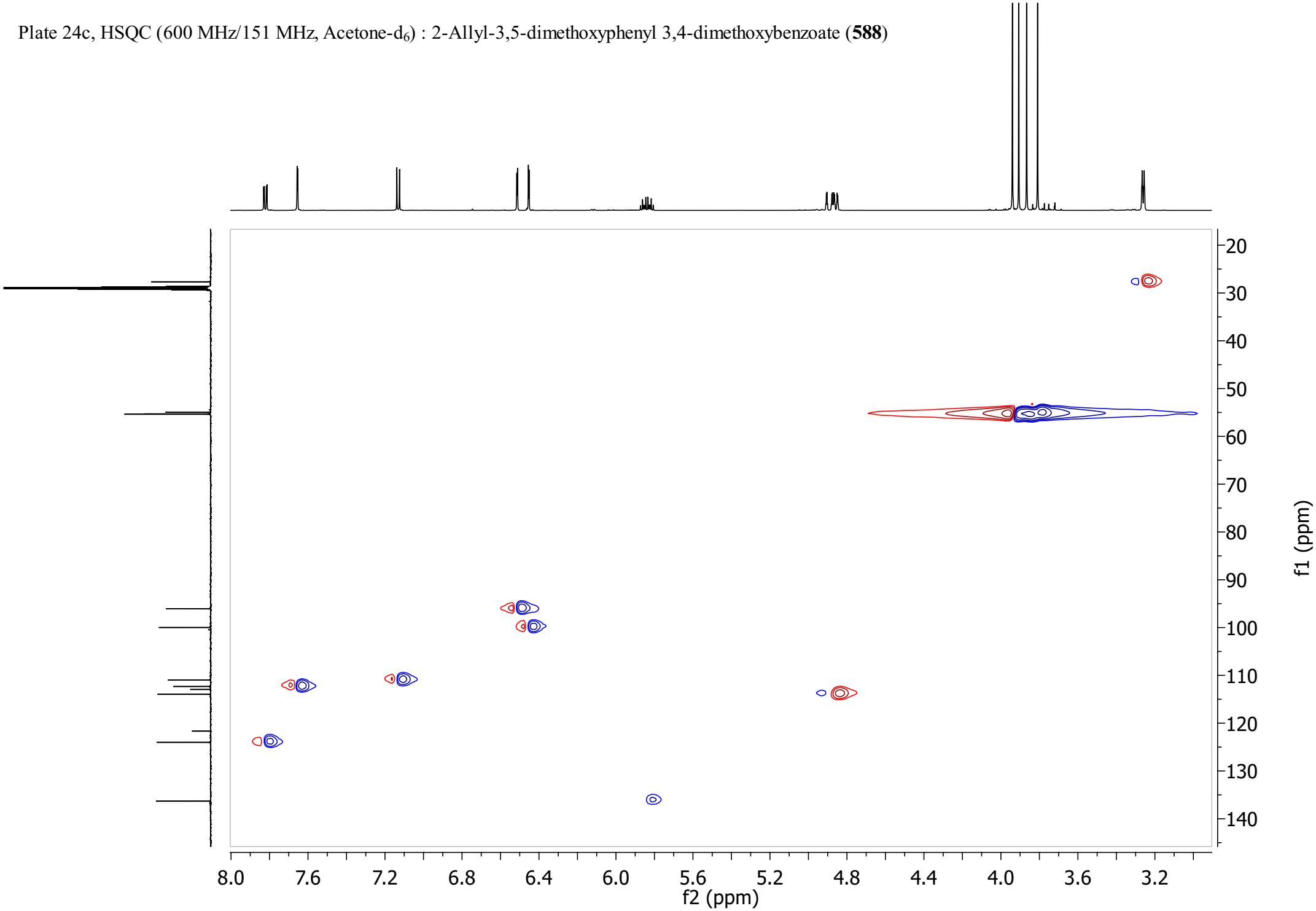


Plate 24d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**)

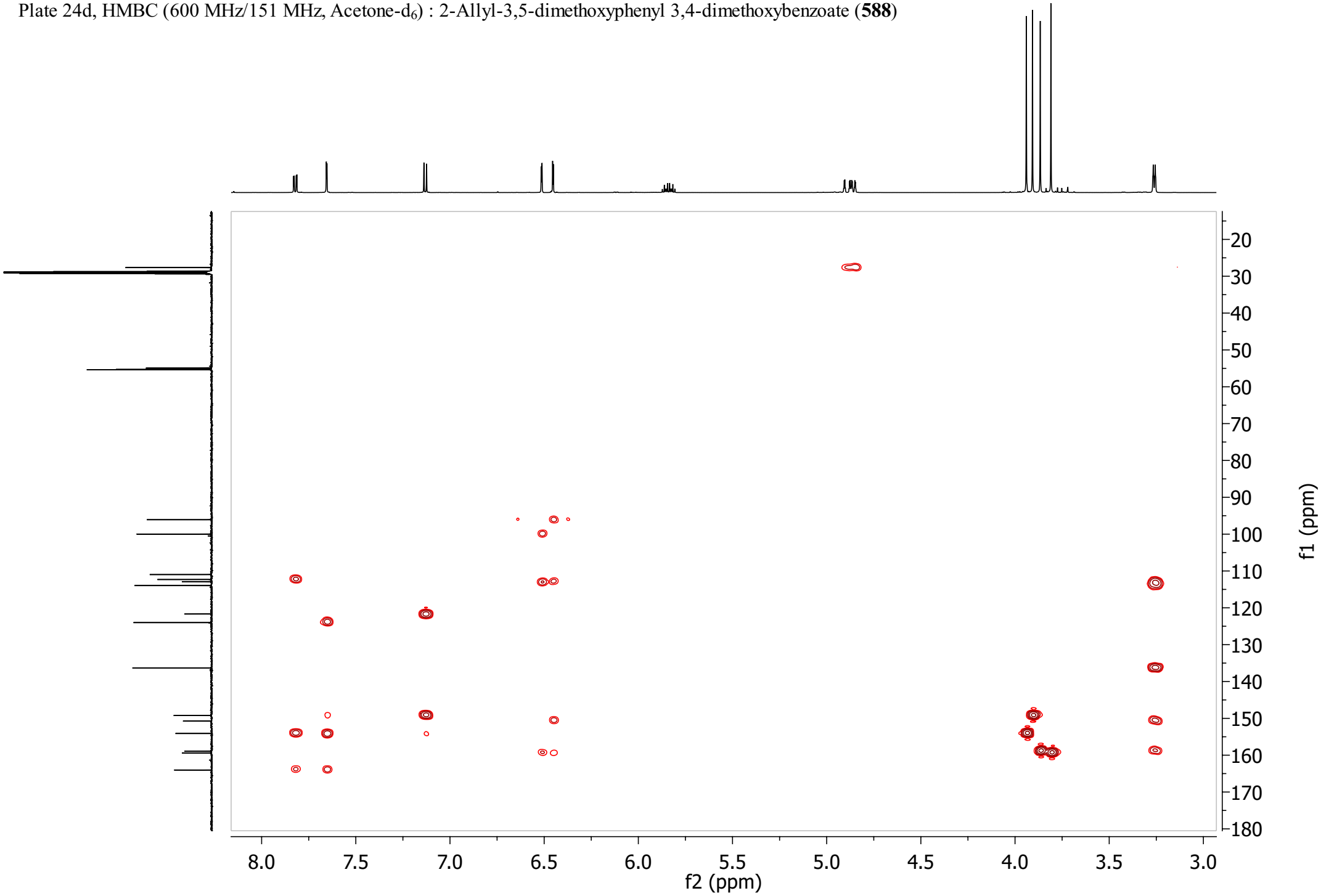


Plate 24e, DEPT (151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate (**588**)

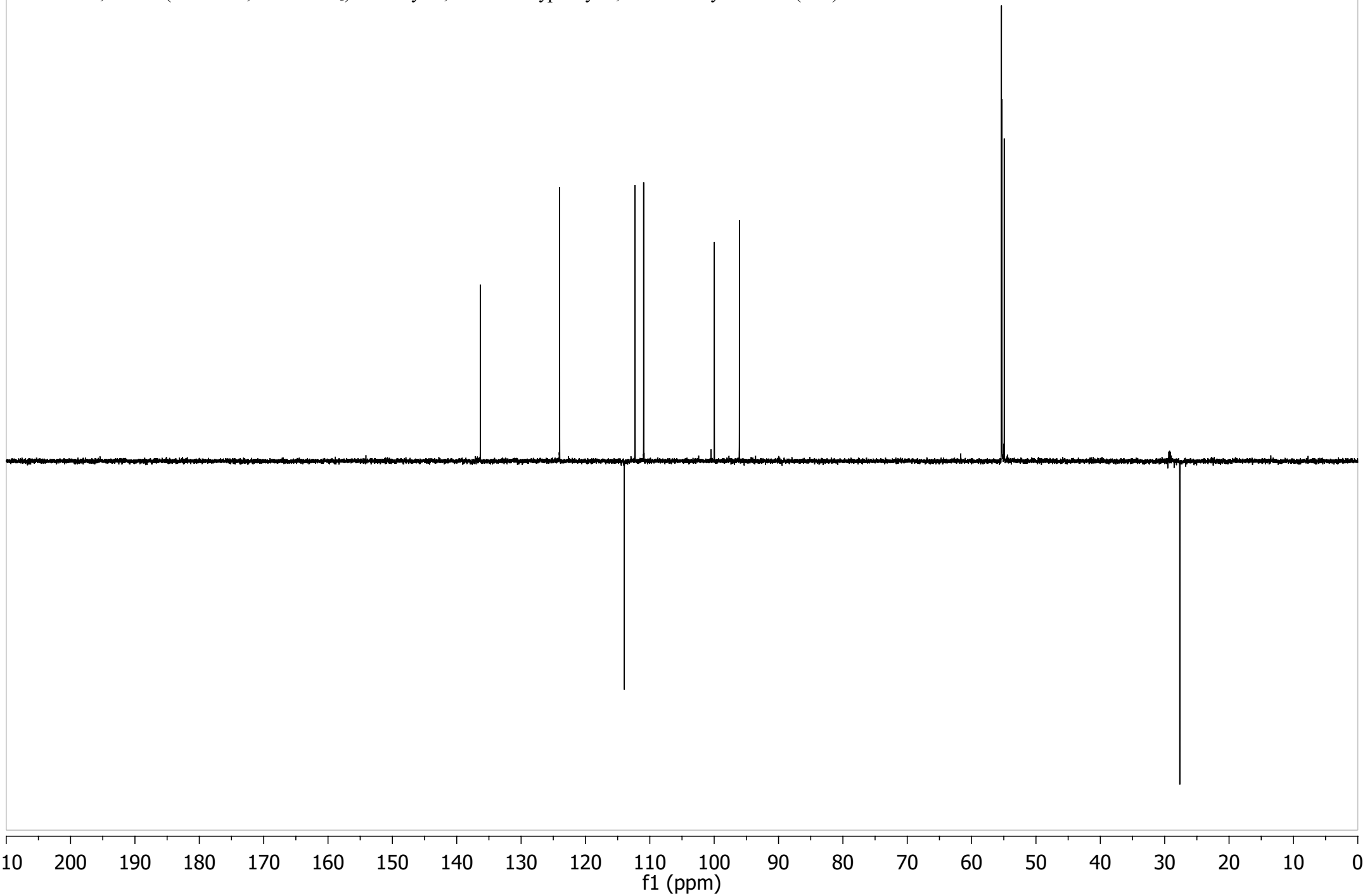
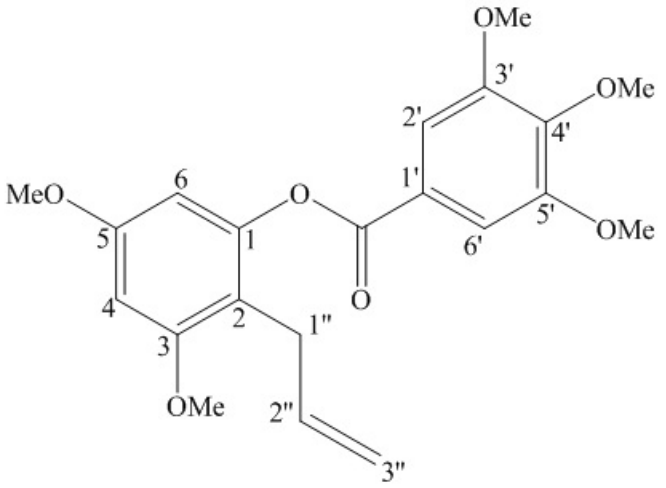
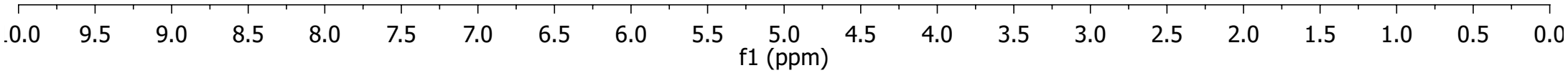


Plate 25a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl-3,4,5-trimethoxybenzoate (**589**)

δ 7.46 (2H, s, H-2' and H-6'), 6.51 (1H, d, *J* = 2.4 Hz, H-4/6), 6.47 (1H, d, *J* = 2.4 Hz, H-4/6), 5.85 (1H, ddt, *J* = 16.3, 10.1, 6.2 Hz, H-2''), 4.93 – 4.87 (2H, m, H-3''), 3.91 (6H, s, -OMe), 3.86 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.27 (2H, br. d, *J* = 6.2 Hz, H-1'')





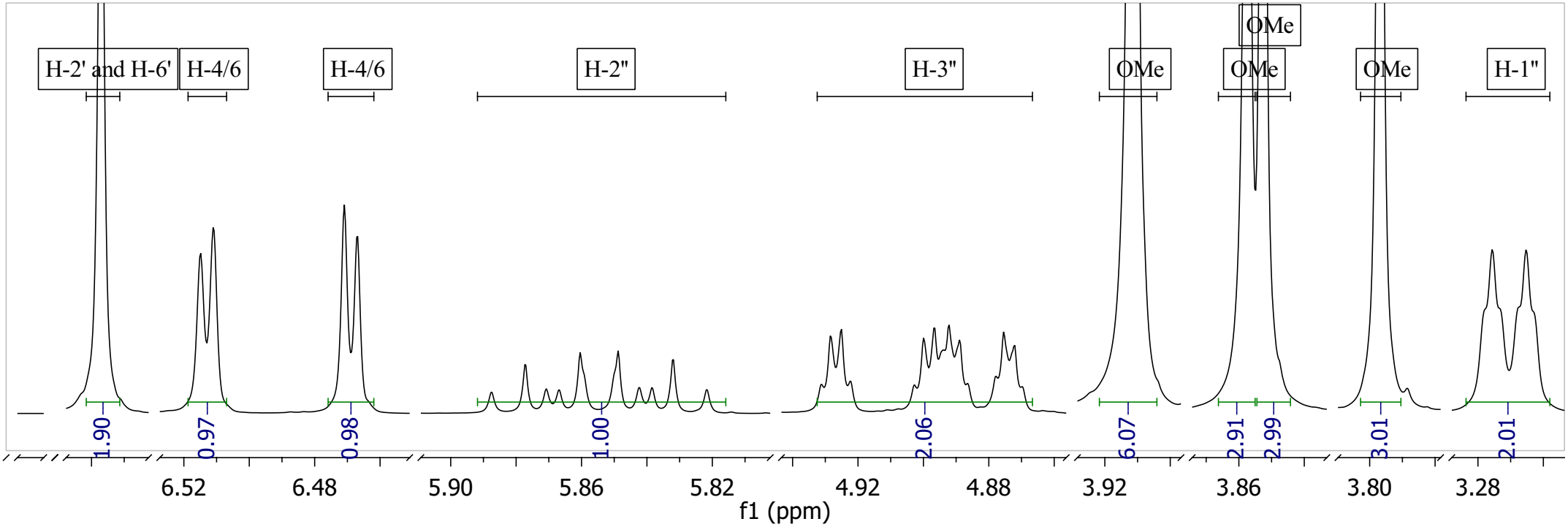
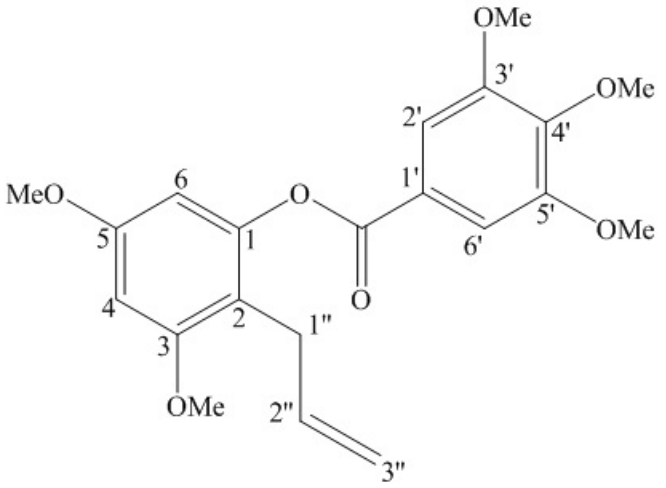


Plate 25b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**589**)

δ 164.82 (C=O), 160.31 (4º-C), 159.81 (4º-C), 154.33 (C-3' and C-5'), 151.60 (4º-C), 143.99 (C-4'), 137.24 (C-2''), 125.32 (4º-C), 114.97 (C-3''), 113.75 (4º-C), 108.14 (C-2' and C-6'), 100.79 (C-4/6), 97.07 (C-4/6), 60.80 (-OMe), 56.63 (-OMe), 56.30 (-OMe), 55.86 (-OMe), 28.56 (C-1'')



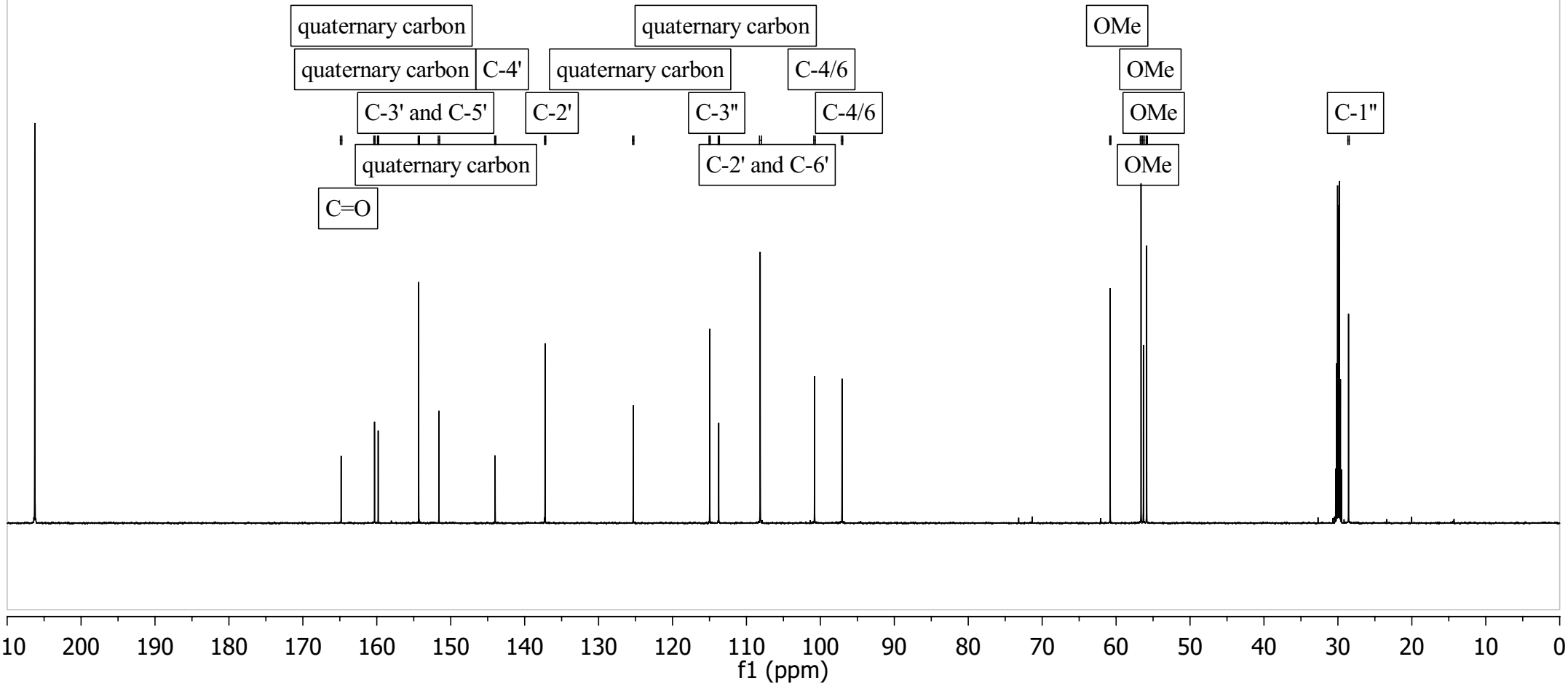


Plate 25c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**589**)

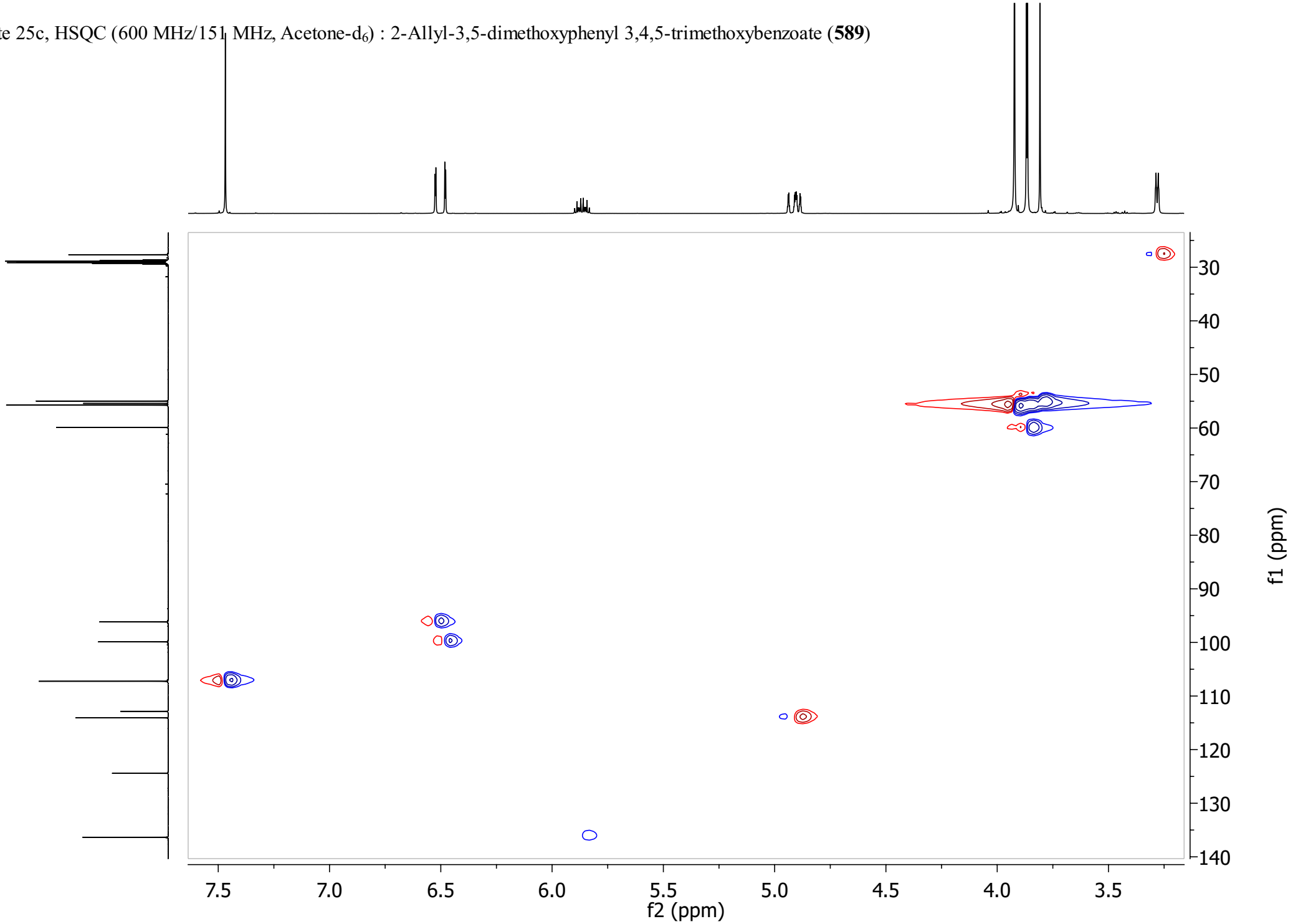


Plate 25d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**589**)

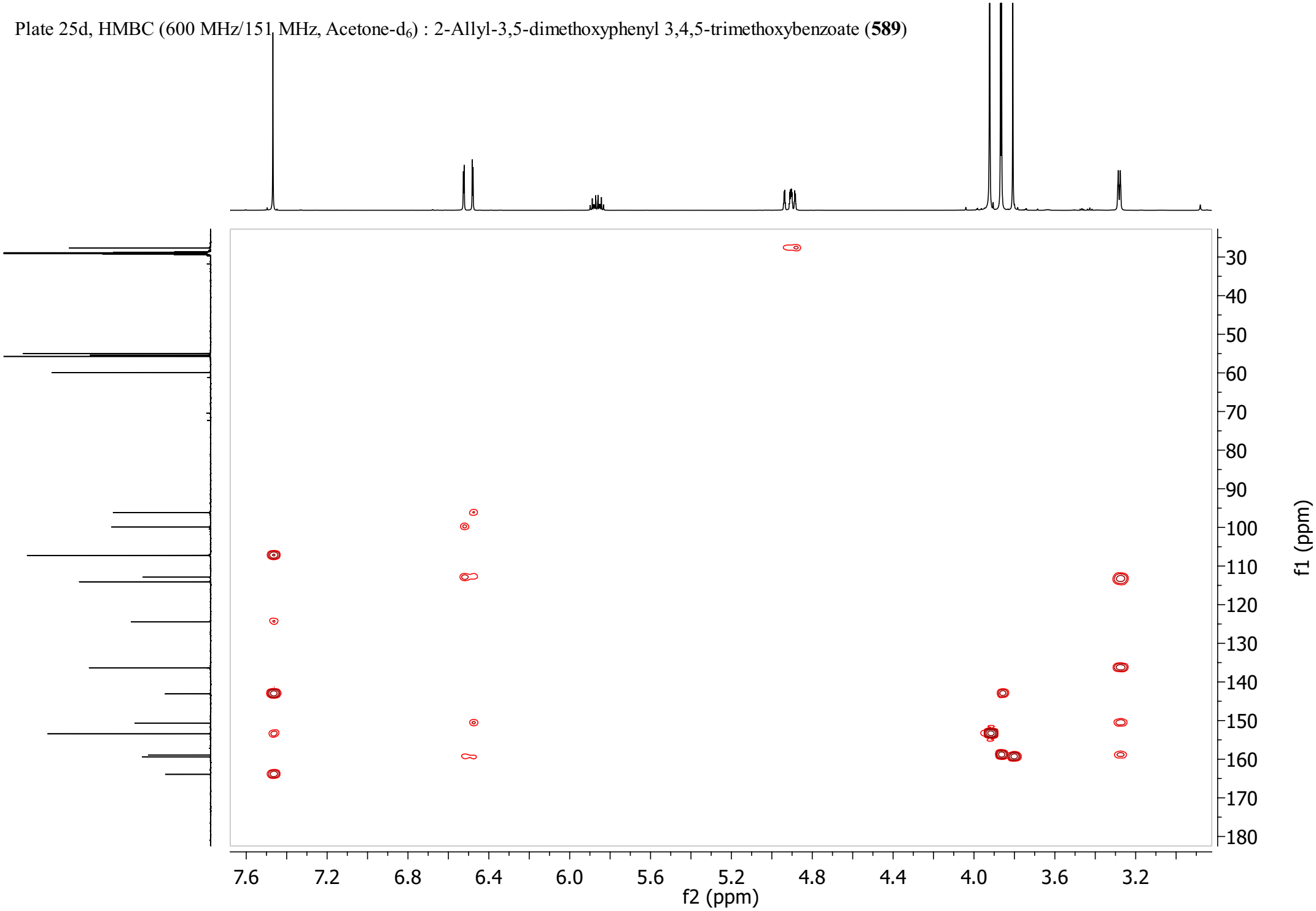


Plate 25e, DEPT (151 MHz, Acetone-d_6) : 2-Allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate (**589**)

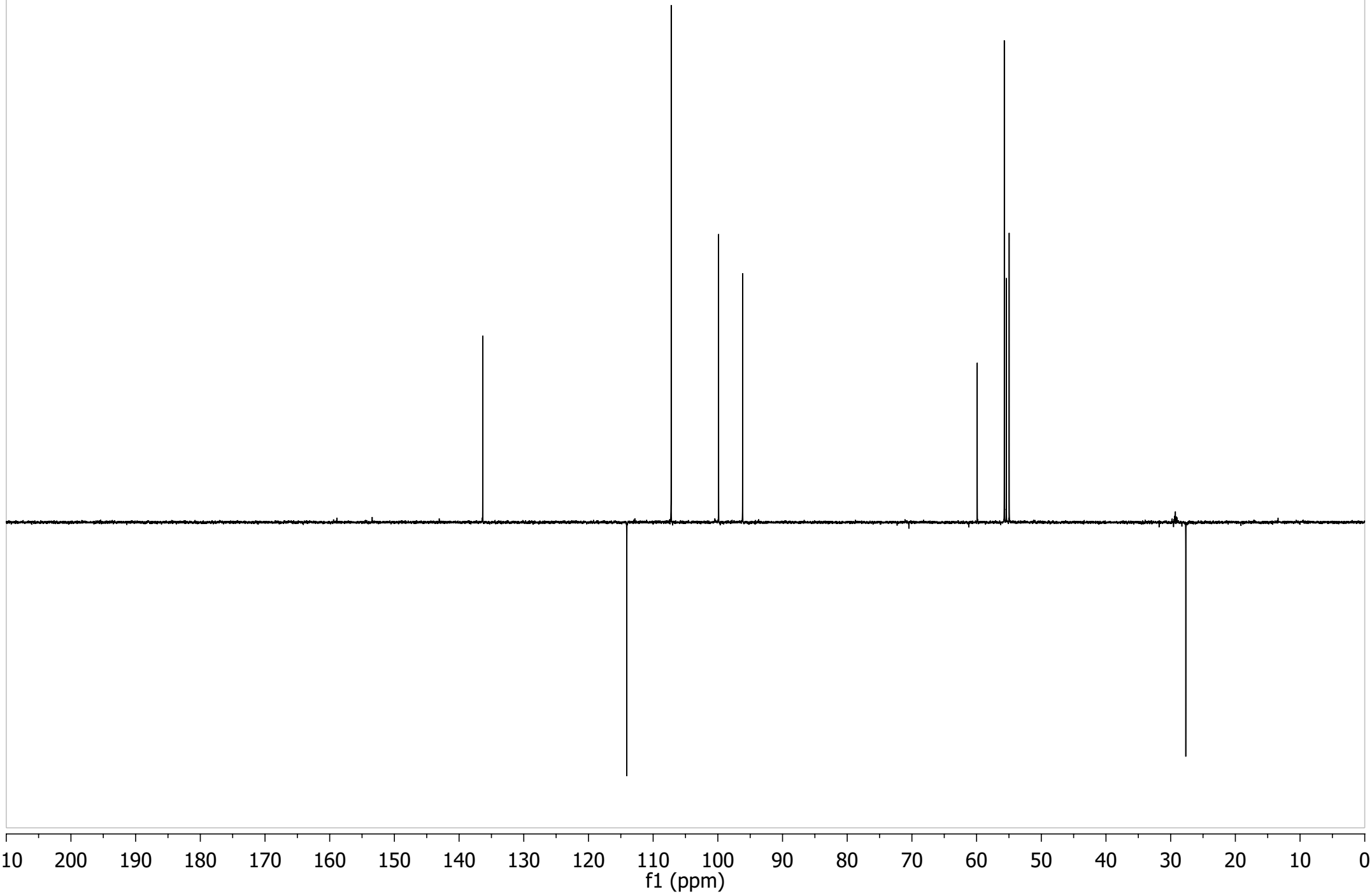
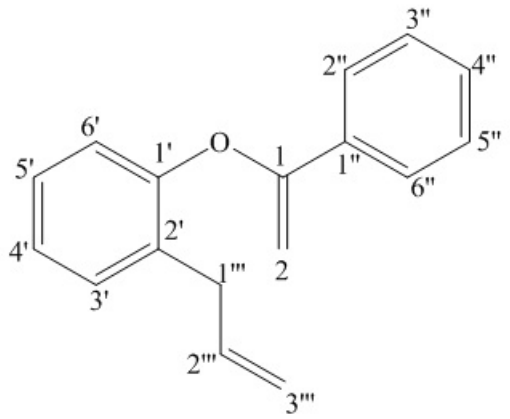
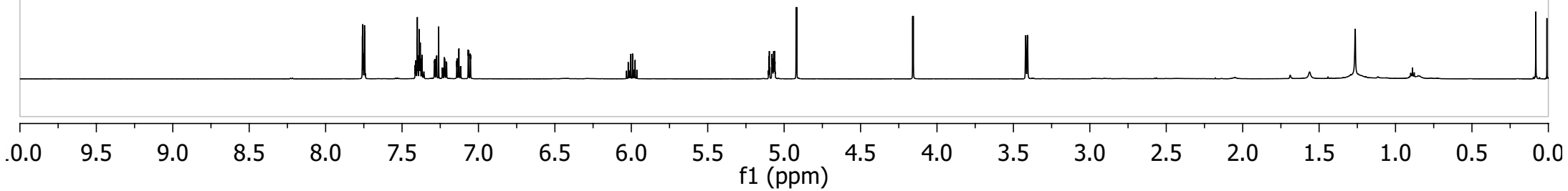


Plate 26a, ^{1}H NMR (600 MHz, $CDCl_3$) : 2-Allyl-1-(1-phenylvinyloxy)benzene (**594**)

δ 7.76 – 7.74 (2H, m, Ar-H), 7.42 – 7.37 (3H, m, Ar-H), 7.28 (1H, dd, *J* = 7.6, 1.6 Hz, H-3'), 7.22 (1H, ddd *J* = 8.0, 8.0, 1.6 Hz, H-5'), 7.13 (1H, ddd, *J* = 8.0, 7.6, 1.3 Hz, H-4'), 7.06 (1H, dd, *J* = 8.0, 1.3 Hz, H-6'), 6.00 (1H, ddt, *J* = 16.9, 10.1, 6.7 Hz, H-2'''), 5.11 – 5.06 (2H, m, H-3'''), 4.92 (1H, d, *J* = 2.6 Hz, H-2), 4.16 (1H, d, *J* = 2.6 Hz, H-2), 3.41 (2H, br. d, *J* = 6.7 Hz, H-1''')





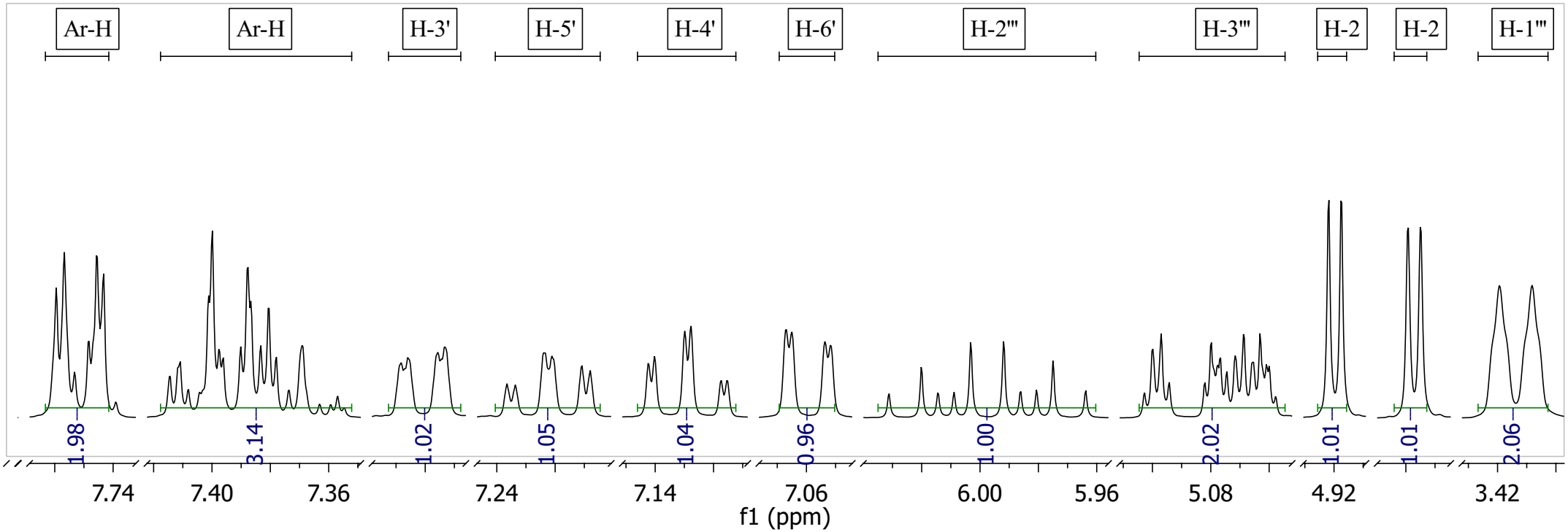
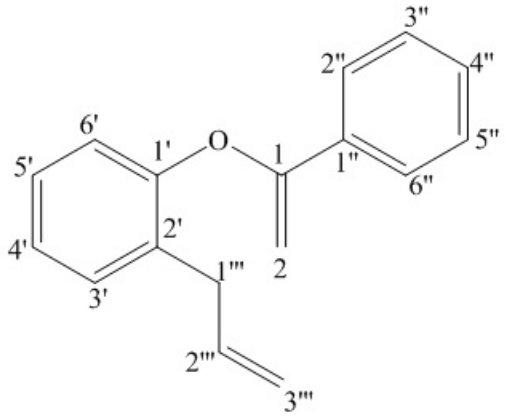


Plate 26b, ^{13}C NMR (151 MHz, $CDCl_3$) : 2-Allyl-1-(1-phenylvinyloxy)benzene (**594**)

δ 159.75 (C-1), 153.32 (C-1'), 136.74 (C-2'''), 135.38 (C-1''), 132.31 (C-2'), 130.55 (C-3'), 128.96 (Ar-C), 128.49 (Ar-C), 127.68 (C-5'), 125.52 (Ar-C), 124.65 (C-4'), 121.18 (C-6'), 116.12 (C-3'''), 89.20 (C-2), 34.24 (C-1''')



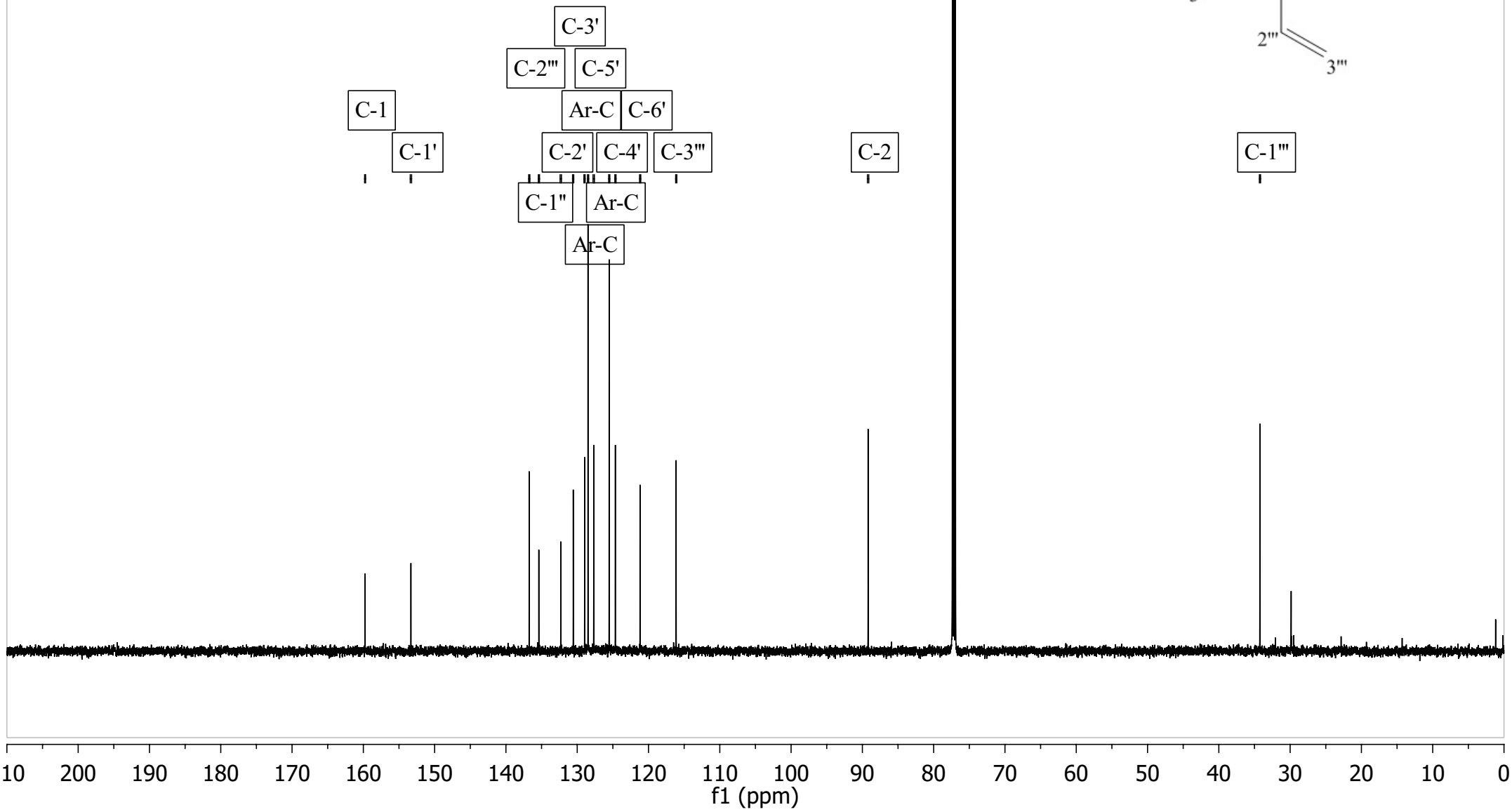


Plate 26c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 2-Allyl-1-(1-phenylvinyloxy)benzene (**594**)

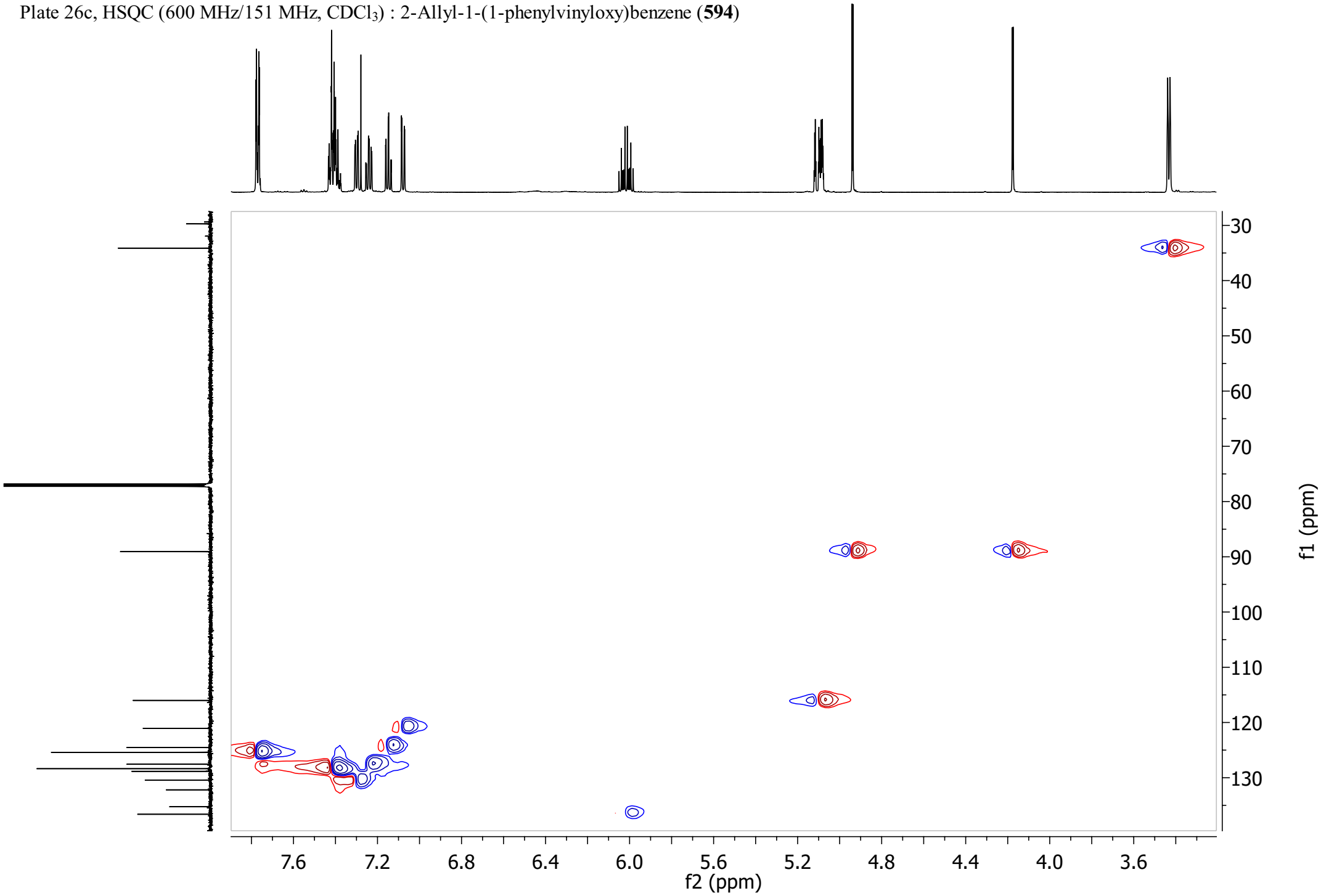


Plate 26d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 2-Allyl-1-(1-phenylvinyloxy)benzene (**594**)

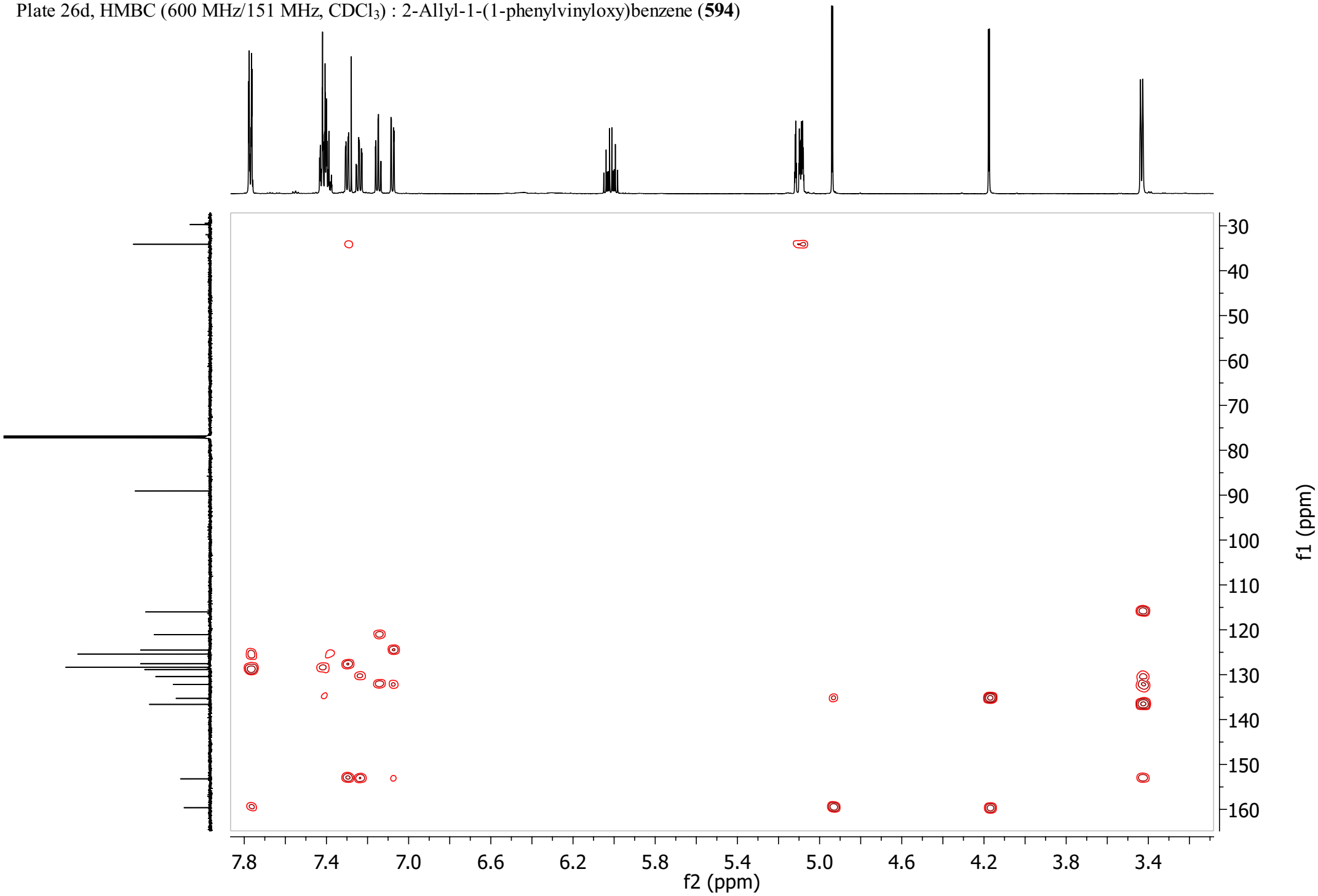


Plate 26e, DEPT (151 MHz, $CDCl_3$) : 2-Allyl-1-(1-phenylvinyloxy)benzene (**594**)

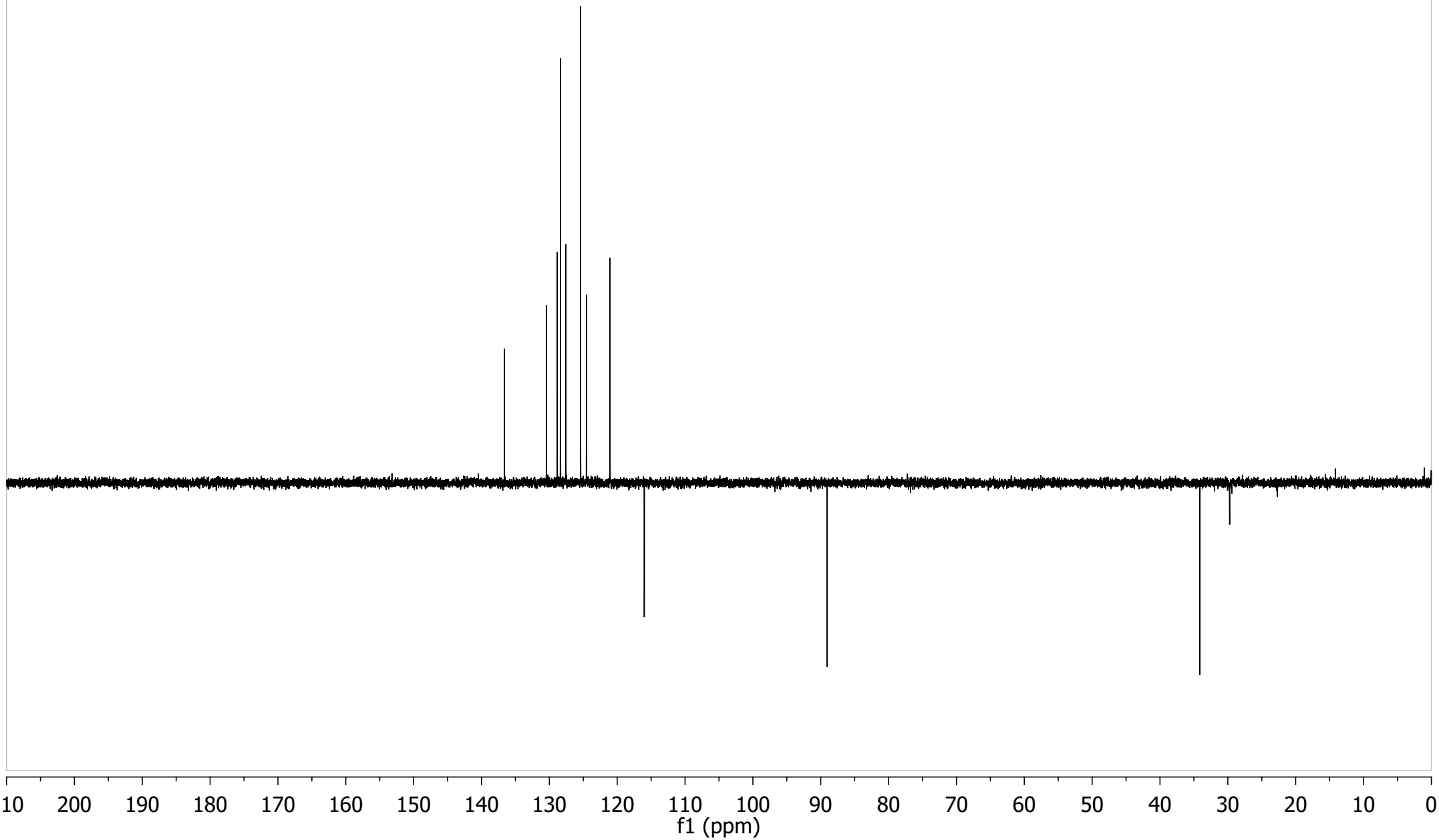
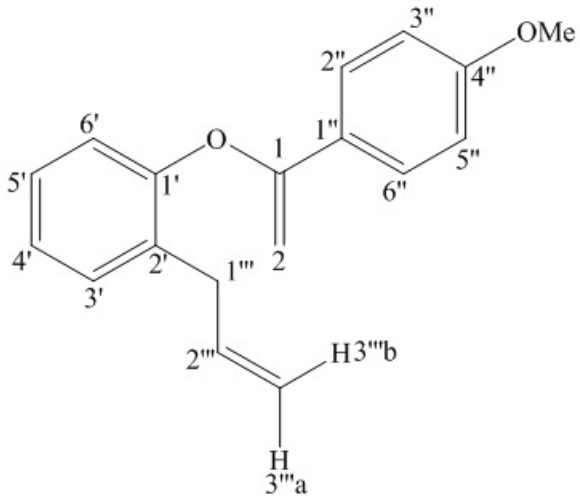
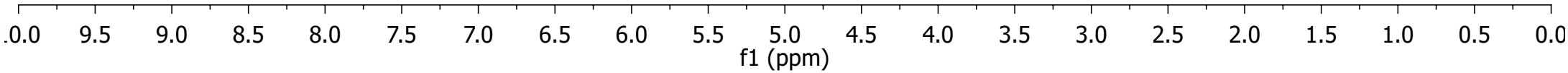


Plate 27a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**)

δ 7.71 (2H, d, *J* = 9.2 Hz, H-2" and H-6"), 7.31 (1H, dd, *J* = 7.6, 1.4 Hz, H-3'), 7.25 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz, H-5'), 7.14 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz, H-4'), 7.05 (1H, dd, *J* = 7.6, 1.4 Hz, H-6'), 6.97 (2H, d, *J* = 9.2 Hz, H-3" and H-5"), 6.00 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05 – 5.01 (1H, m, H-3'''a), 4.91 (1H, d, *J* = 2.5 Hz, H-2), 4.03 (1H, d, *J* = 2.5 Hz, H-2), 3.83 (3H, s, -OMe), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1''')





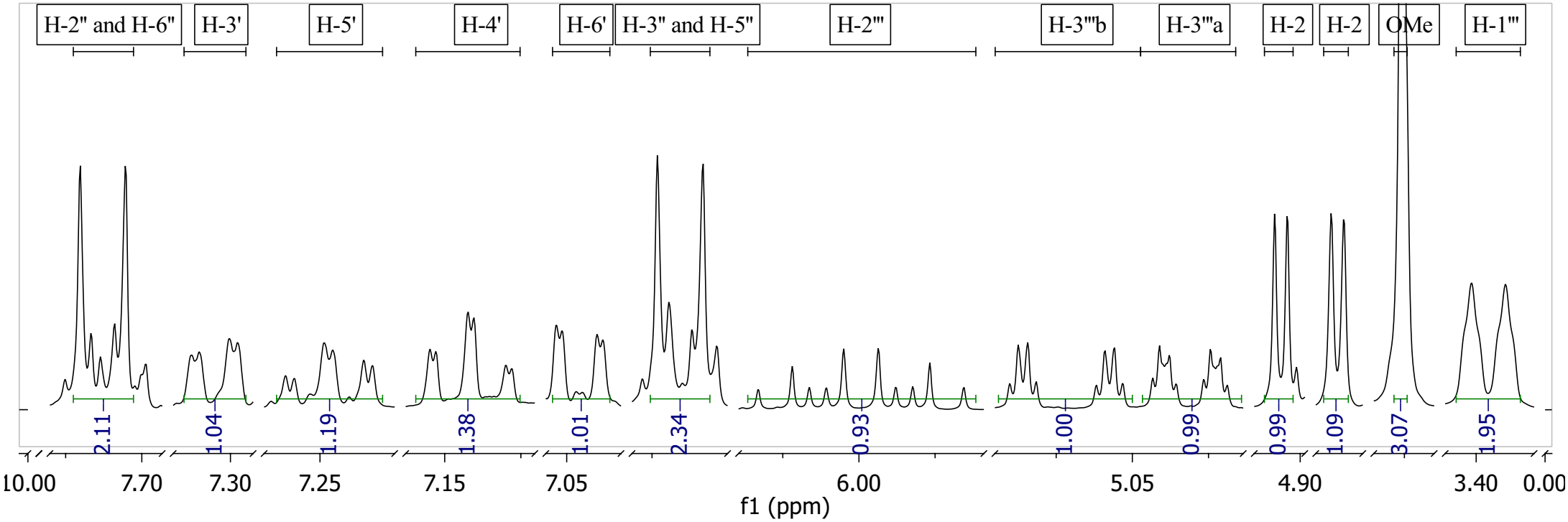
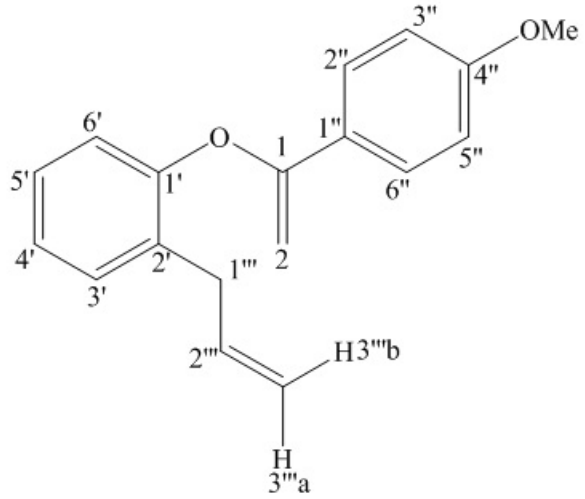


Plate 27b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**)

δ 161.40 (C-4''), 160.42 (4º-C), 154.25 (4º-C), 137.70 (C-2'''), 132.83 (4º-C), 131.42 (C-3'), 128.57 (C-5'), 127.68 (C-2'' and C-6''), 127.29 (C-1''), 125.43 (C-4'), 121.72 (C-6'), 116.29 (C-3'''), 114.63 (C-3'' and C-5''), 88.16 (C-2), 55.72 (-O<u>Me</u>), 34.84 (C-1''')



C-1''
C-2'' and C-6''
quaternary carbon
C-4'
C-3'''
quaternary carbon
C-2'''
C-5'
C-3'' and C-5''
C-2
OMe
C-1'''
C-4''
C-3'
C-6'
quaternary carbon

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Plate 27c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**)

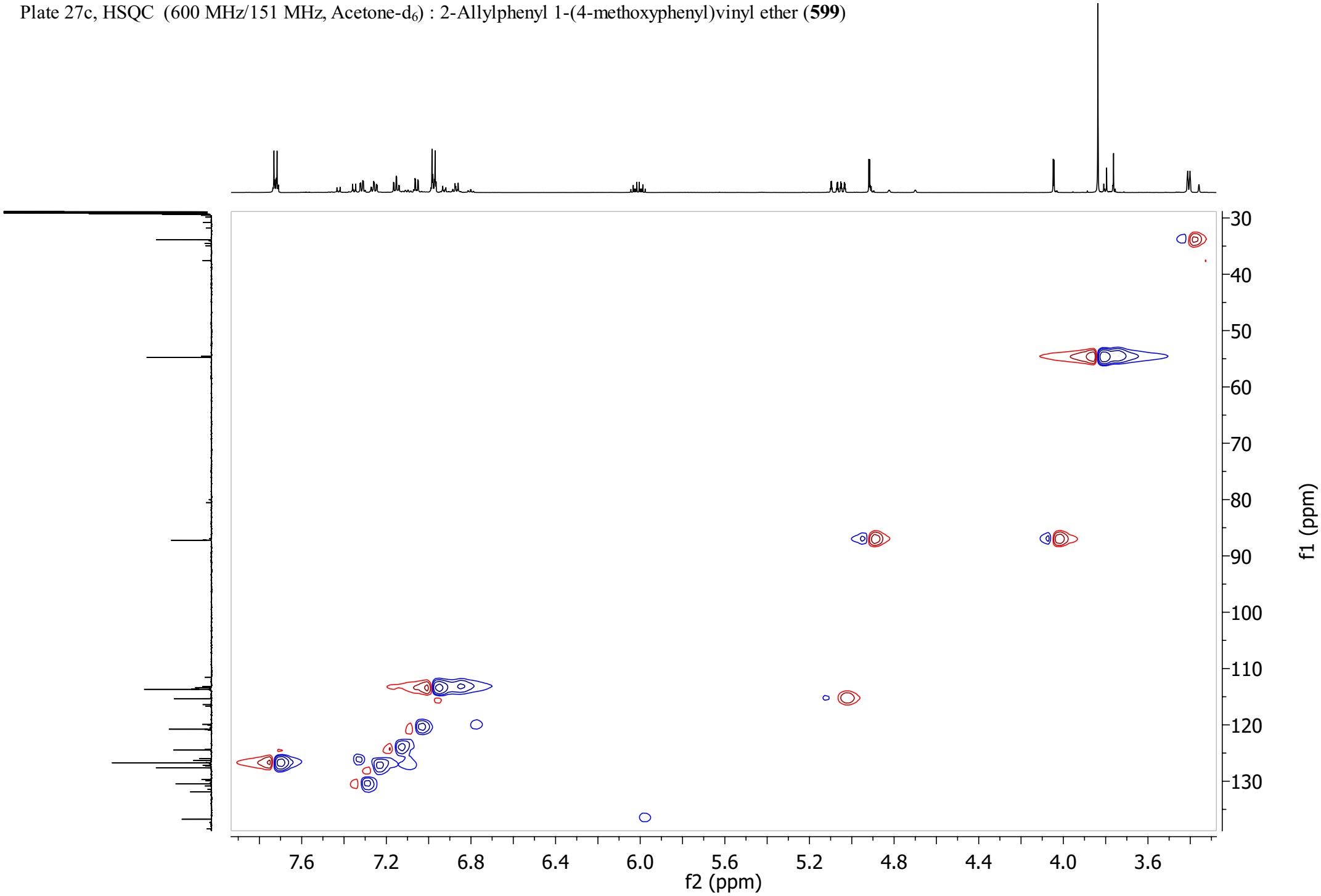


Plate 27d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**)

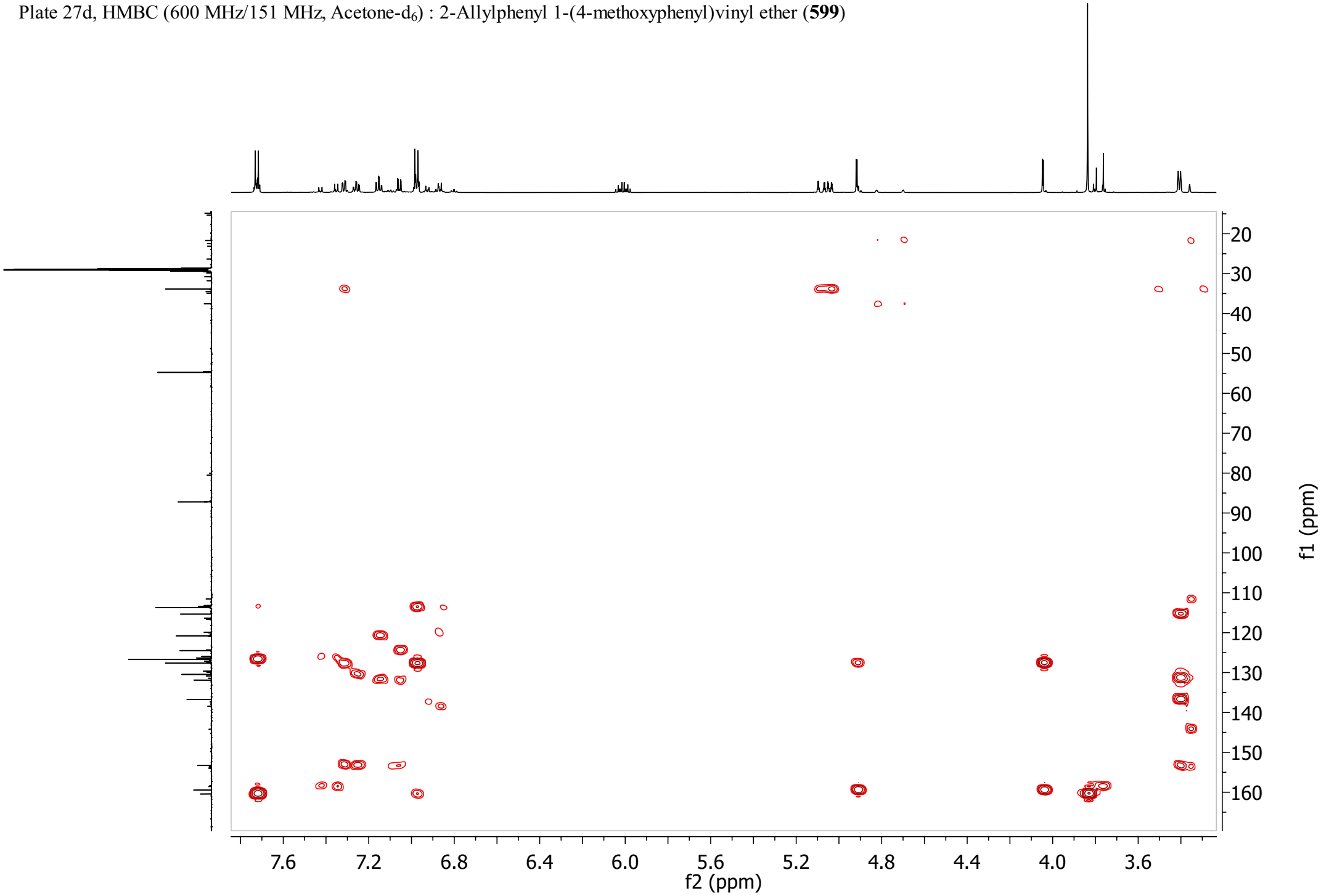


Plate 27e, DEPT (151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(4-methoxyphenyl)vinyl ether (**599**)

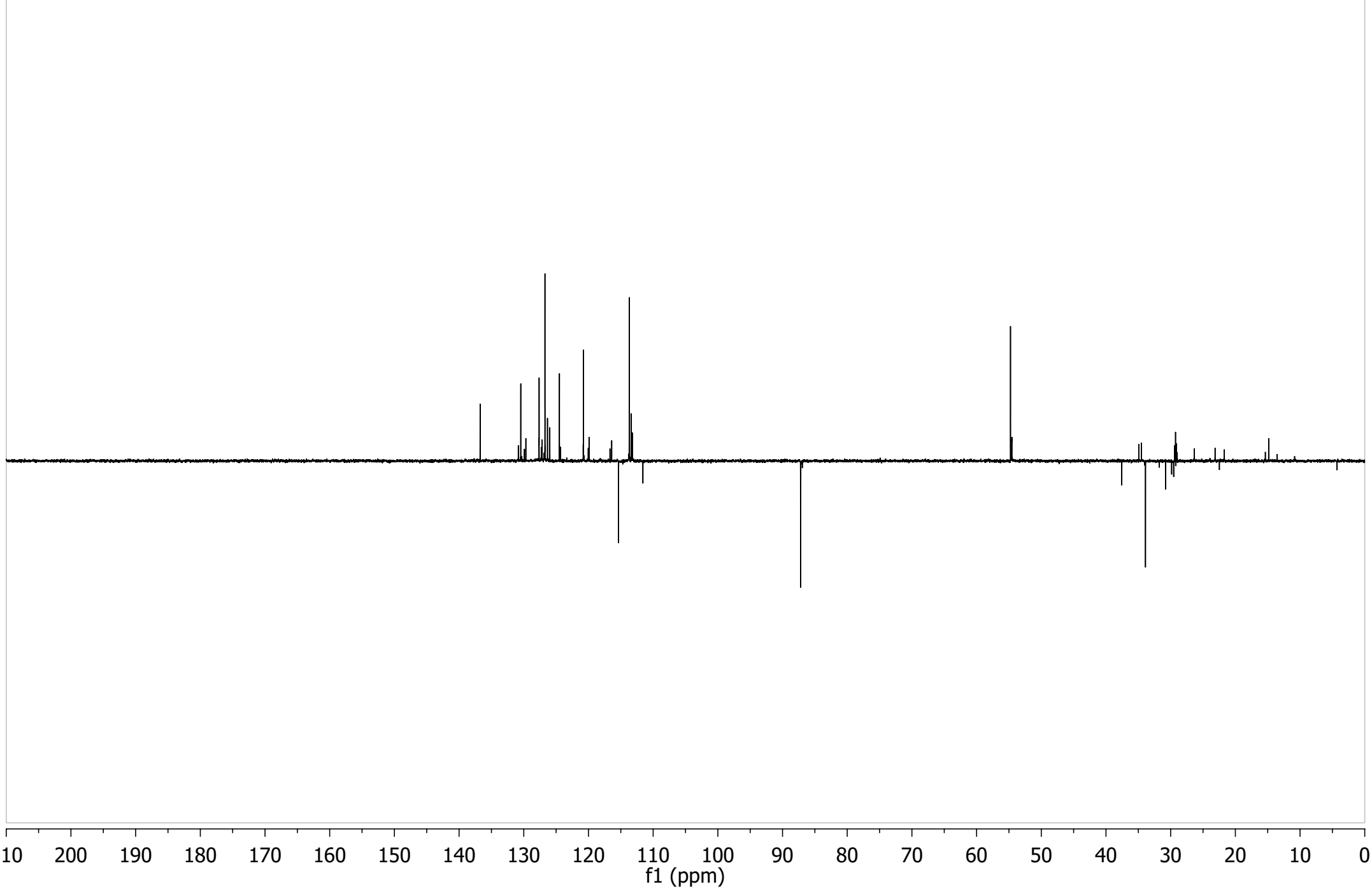
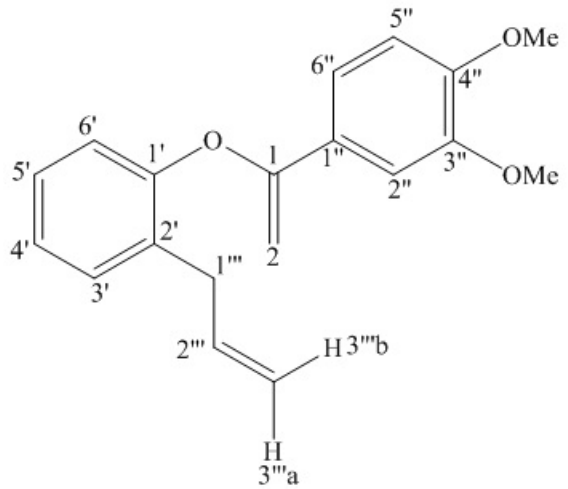
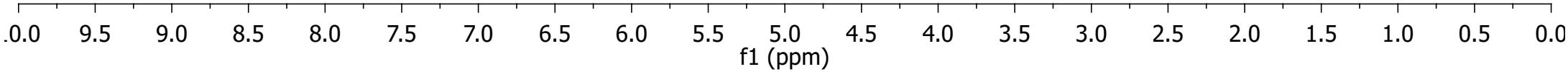


Plate 28a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**)

δ 7.34 – 7.32 (2H, m, H-2" and H-6"), 7.31 (1H, dd, *J* = 7.4, 1.6 Hz, H-3'), 7.25 (1H, ddd, *J* = 8.0, 7.6, 1.6 Hz, H-5'), 7.14 (1H, ddd, *J* = 7.6, 7.4, 1.3 Hz, H-4'), 7.05 (1H, dd, *J* = 8.0, 1.3 Hz, H-6'), 6.97 (1H, d, *J* = 8.7 Hz, H-5"), 6.01 (1H, ddt, *J* = 17.0, 10.0, 6.7 Hz, H-2'''), 5.07 (1H, ddt, *J* = 17.0, 1.7, 1.7 Hz, H-3'''b), 5.05 – 5.02 (1H, m, H-3'''a), 4.95 (1H, d, *J* = 2.5 Hz, H-2), 4.05 (1H, d, *J* = 2.5 Hz, H-2), 3.84 (6H, s, -OMe), 3.40 (2H, br. d, *J* = 6.7 Hz, H-1''')





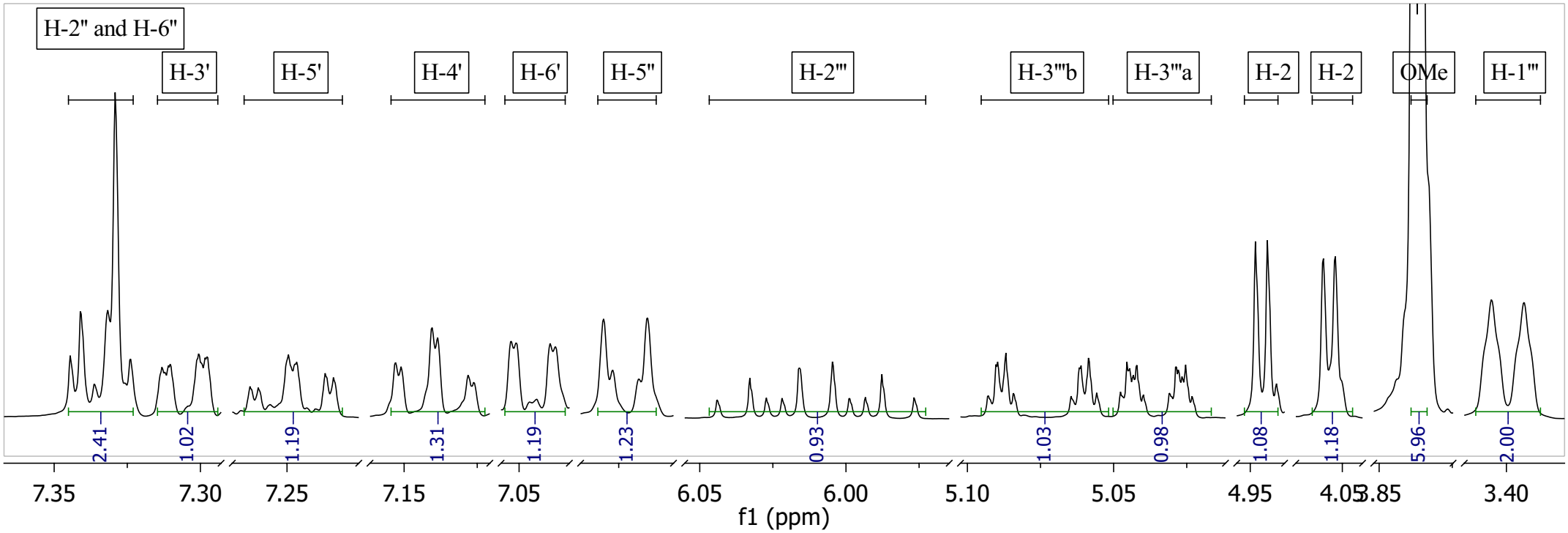
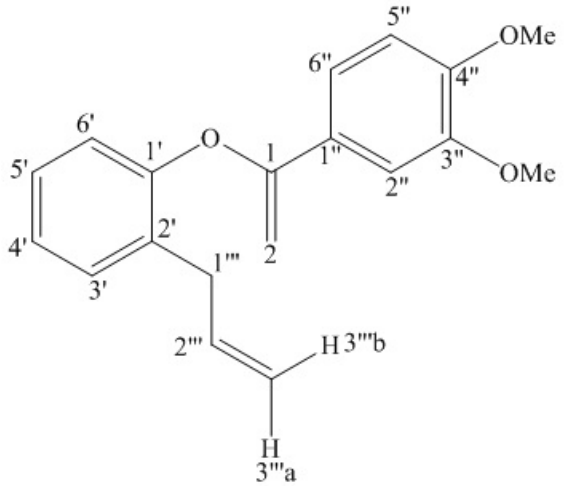


Plate 28b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**)

δ 160.35 (C-1), 154.25 (C-1'), 151.20 (C-3"/4"), 150.11 (C-3"/4"), 137.68 (C-2'"), 132.68 (C-2'), 131.38 (C-3'), 128.77 (C-1"), 128.50 (C-5'), 125.32 (C-4'), 121.58 (C-6'), 119.02 (C-2"/6"), 116.17 (C-3'"), 112.25 (C-5"), 110.02 (C-2"/6"), 88.45 (C-2), 56.08 (-O<u>Me</u>), 34.81 (C-1'")



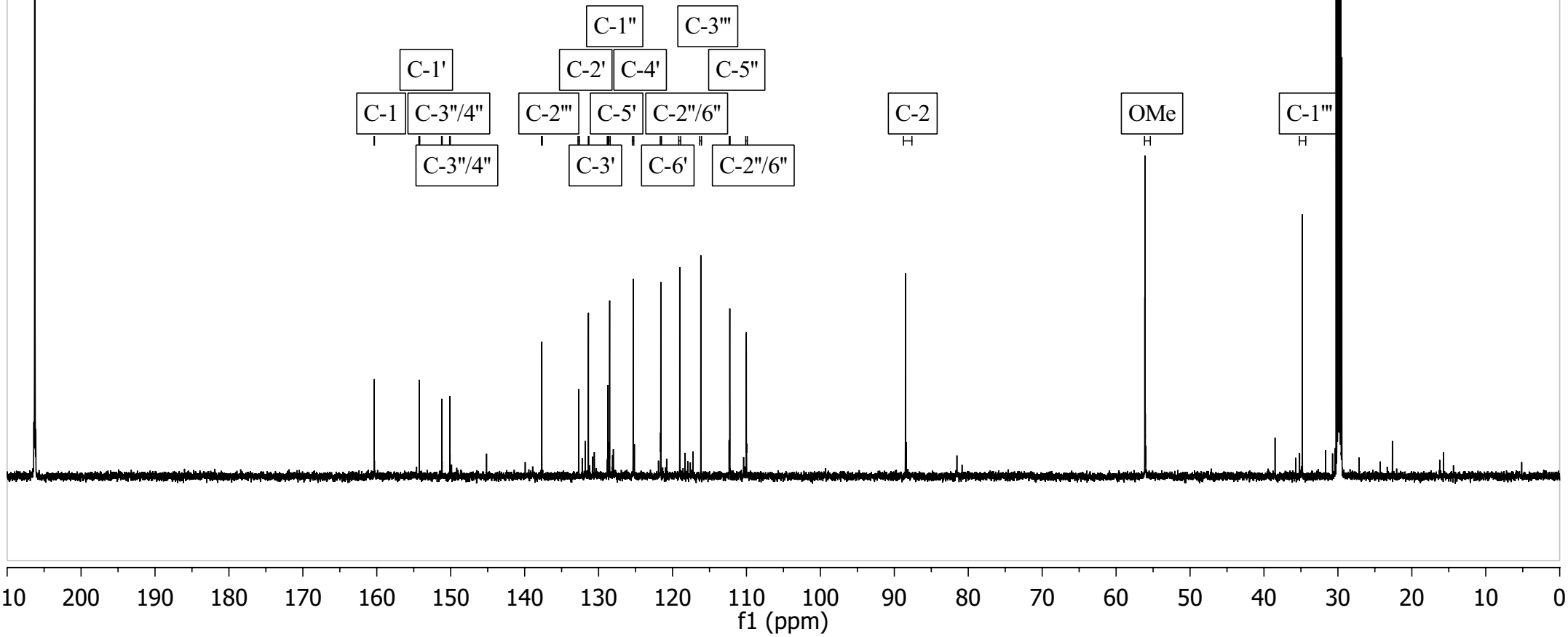


Plate 28c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**)

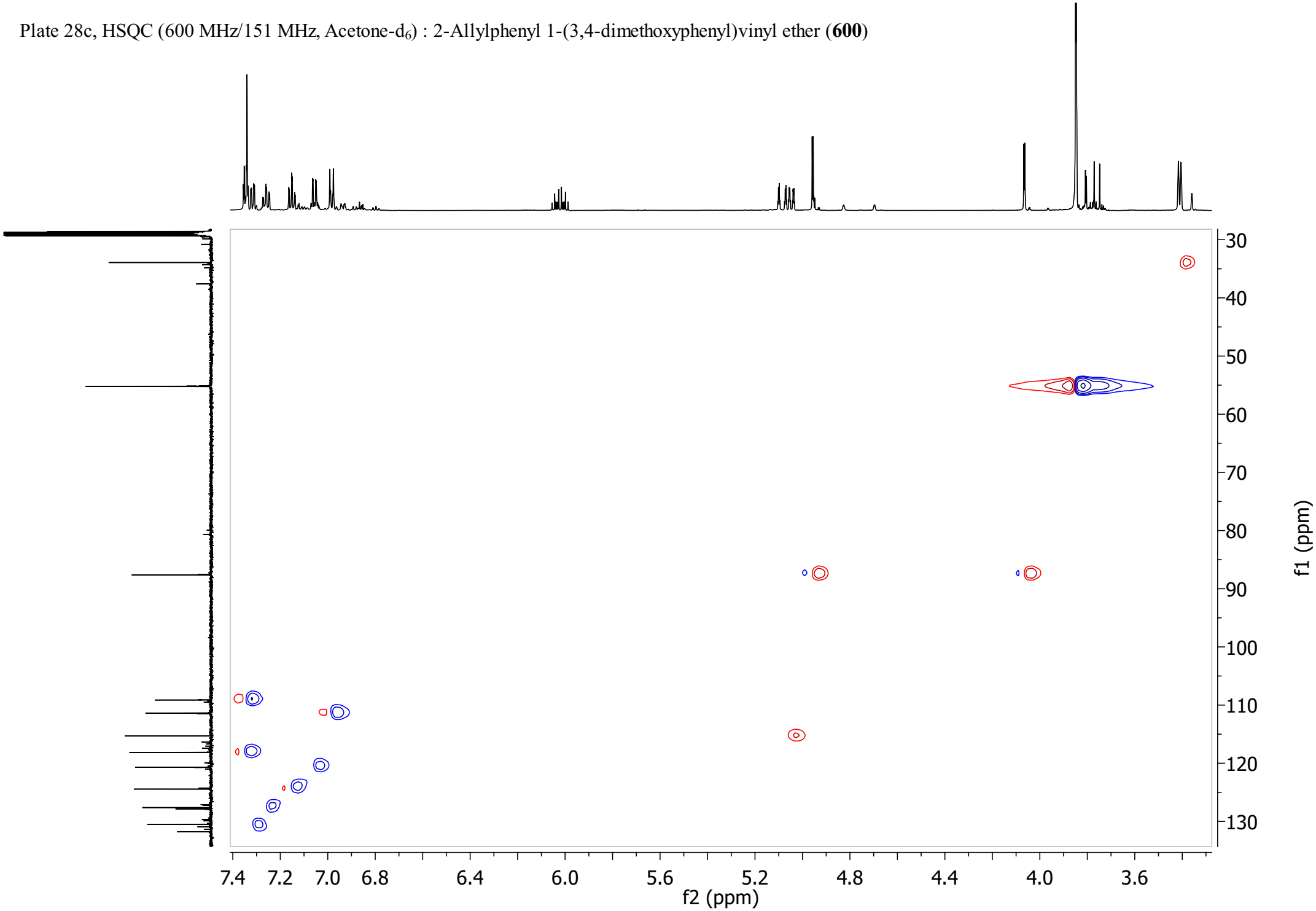


Plate 28d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**)

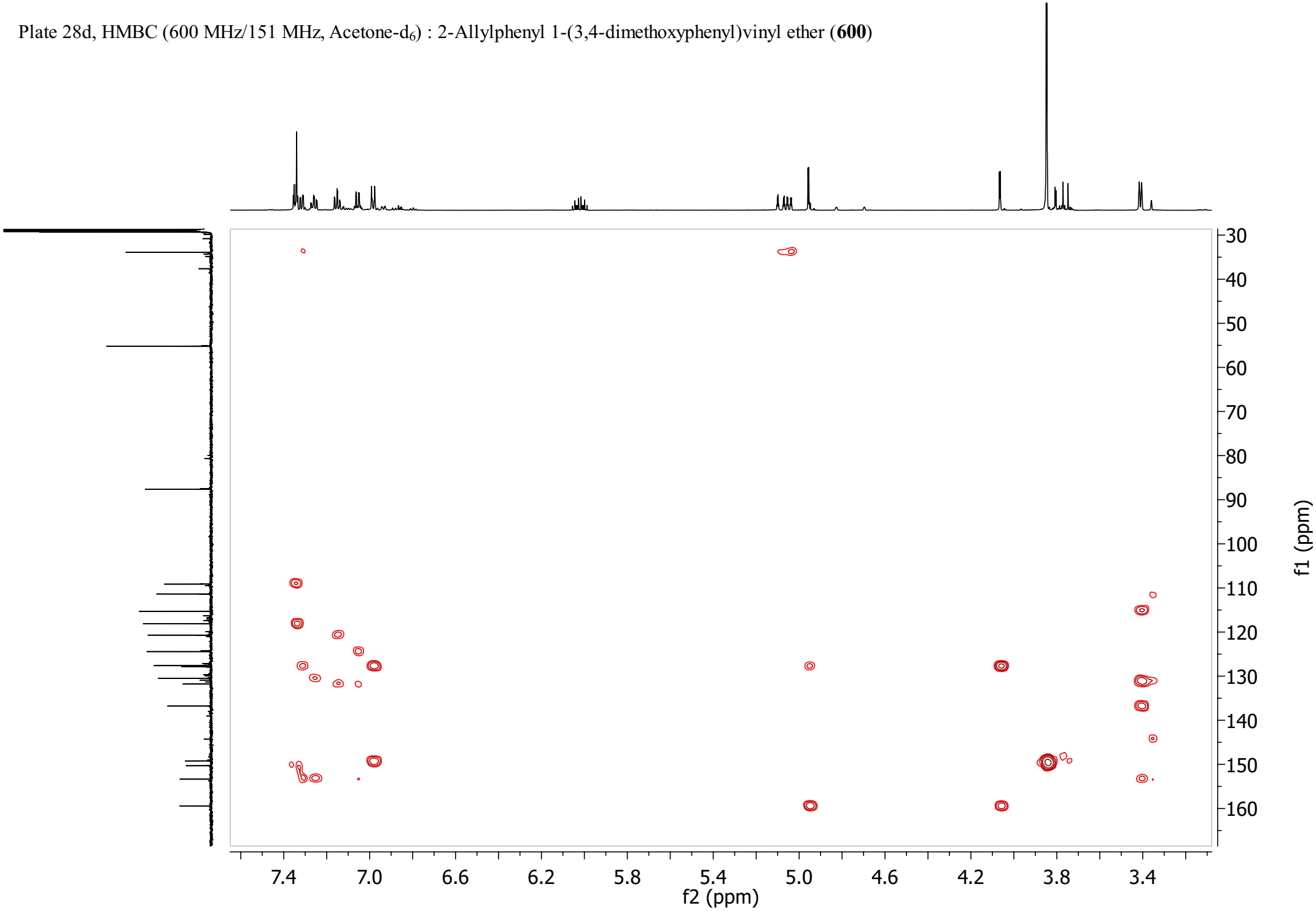


Plate 28e, DEPT (151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**600**)

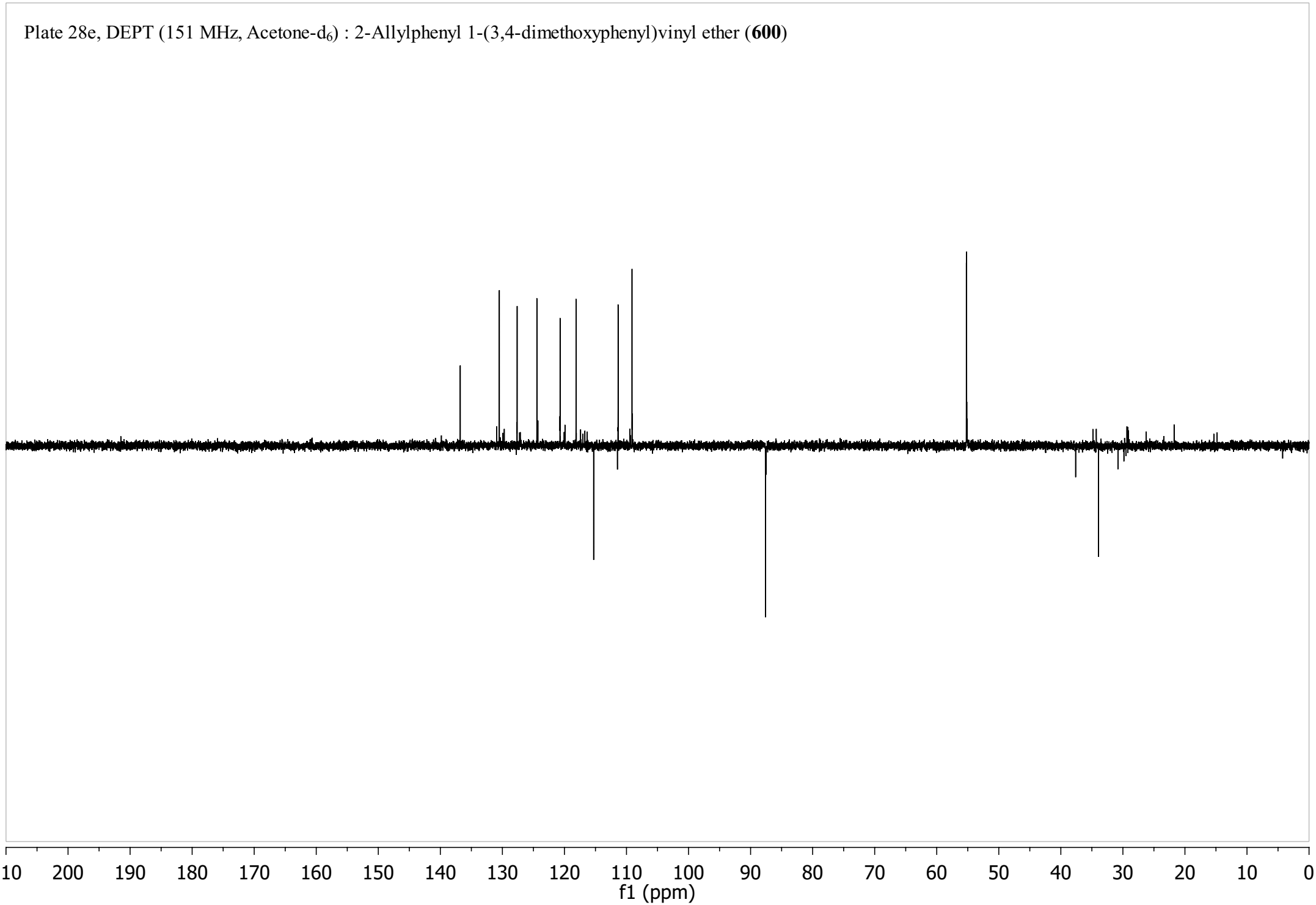
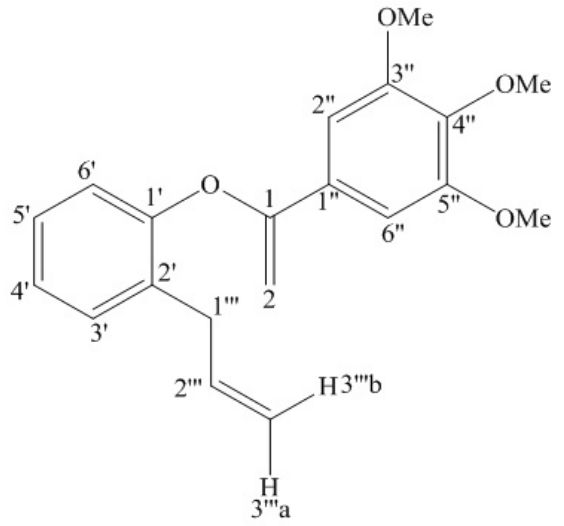
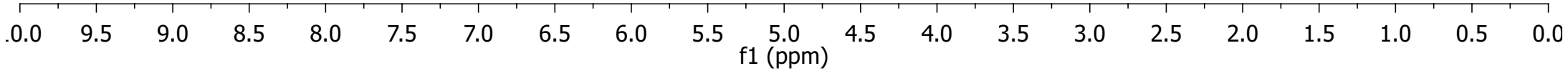


Plate 29a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**)

δ 7.31 (1H, dd, *J* = 7.7, 1.8 Hz, H-3'), 7.26 (1H, ddd, *J* = 8.1, 7.7, 1.8 Hz H-5'), 7.15 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz, H-4'), 7.08 (2H, s, H-2" and H-6"), 7.06 (1H, dd, *J* = 8.1, 1.2 Hz, H-6'), 6.02 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-2'''), 5.08 (1H, ddt, *J* = 17.0, 1.8, 1.8 Hz, H-3'''b), 5.05 (1H, ddt, *J* = 10.1, 1.8, 1.8 Hz, H-3'''a), 5.02 (1H, d, *J* = 2.6 Hz, H-2), 4.11 (1H, d, *J* = 2.6 Hz, H-2), 3.86 (6H, s, -OMe), 3.76 (3H, s, -OMe), 3.41 (1H, br. d, *J* = 6.7 Hz, H-1''')





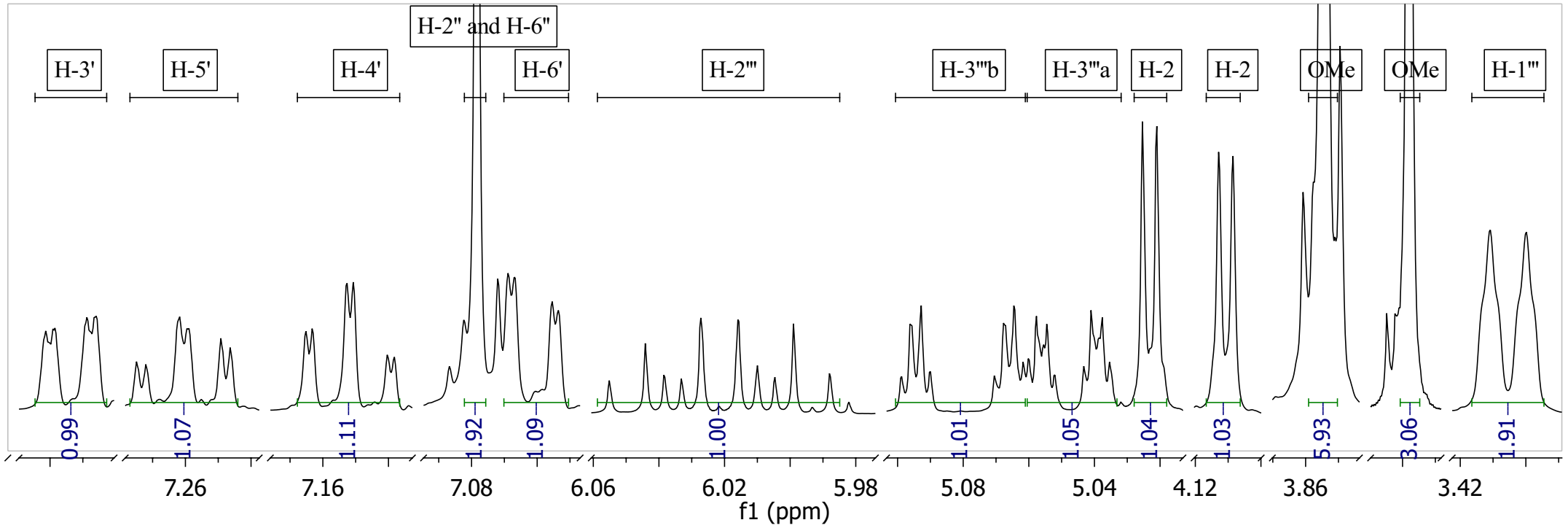
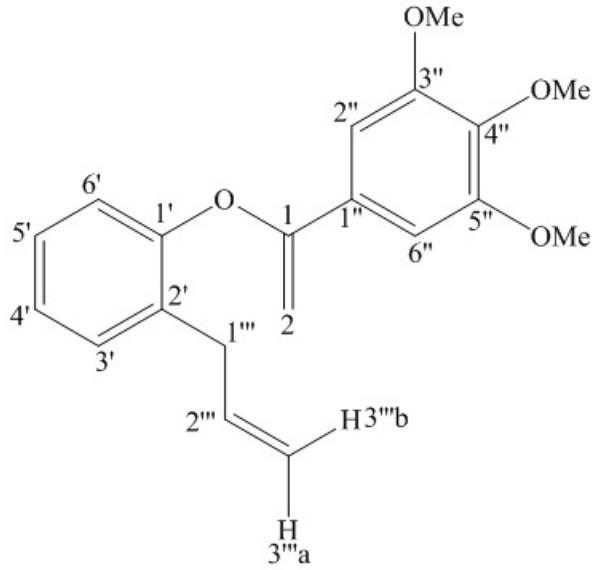


Plate 29b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**)

δ 160.28 (C-1), 154.29 (4º-C), 154.17 (4º-C), 140.09 (4º-C), 137.69 (C-2'''), 132.71 (4º-C), 131.53 (C-1''), 131.51 (C-3'), 128.58 (C-5'), 125.48 (C-4'), 121.68 (C-6'), 116.21 (C-3'''), 103.87 (C-2'' and C-6''), 89.49 (C-2), 60.62 (-OMe), 56.46 (-OMe), 34.87 (C-1''')



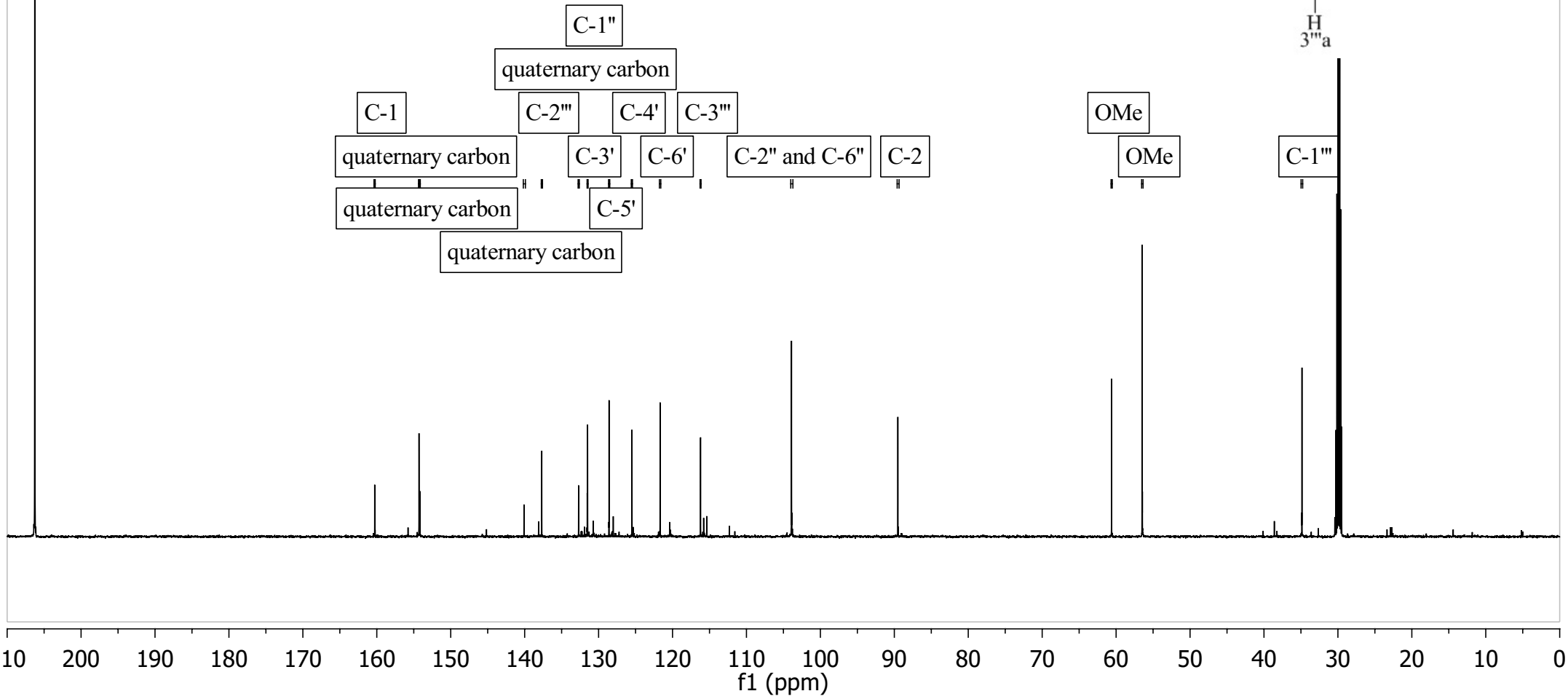


Plate 29c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**)

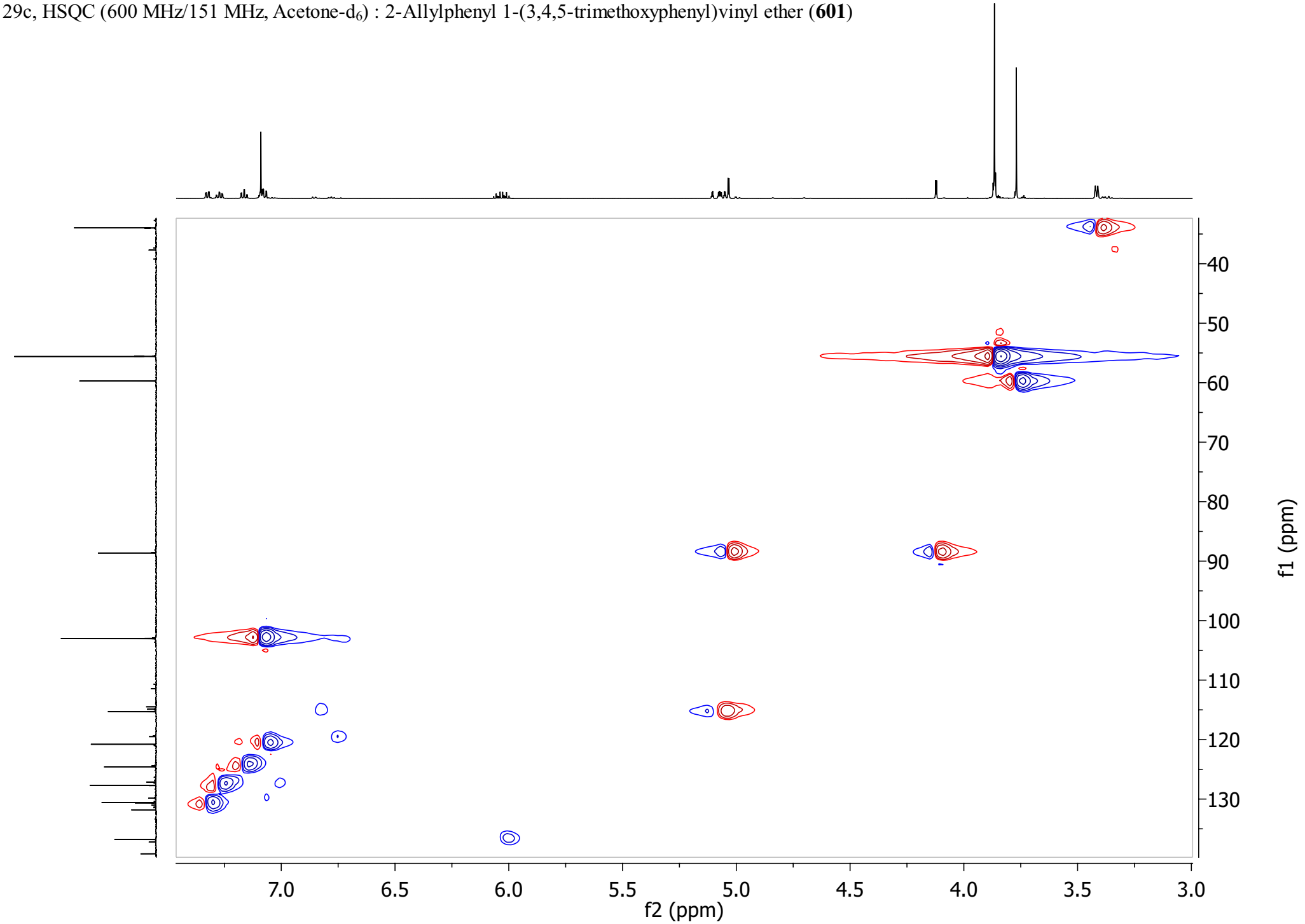


Plate 29d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**)

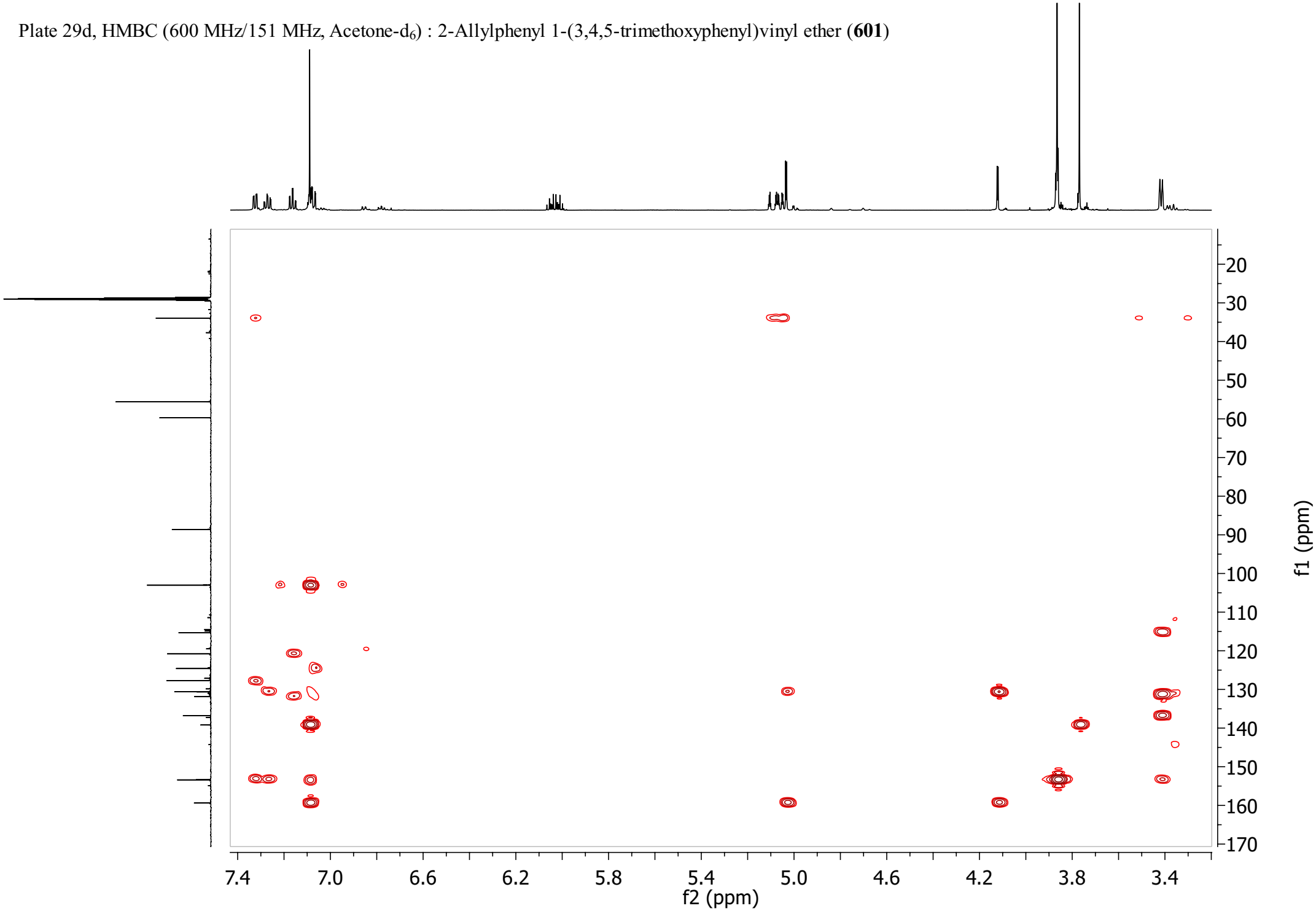


Plate 29e, DEPT (151 MHz, Acetone-d_6) : 2-Allylphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**601**)

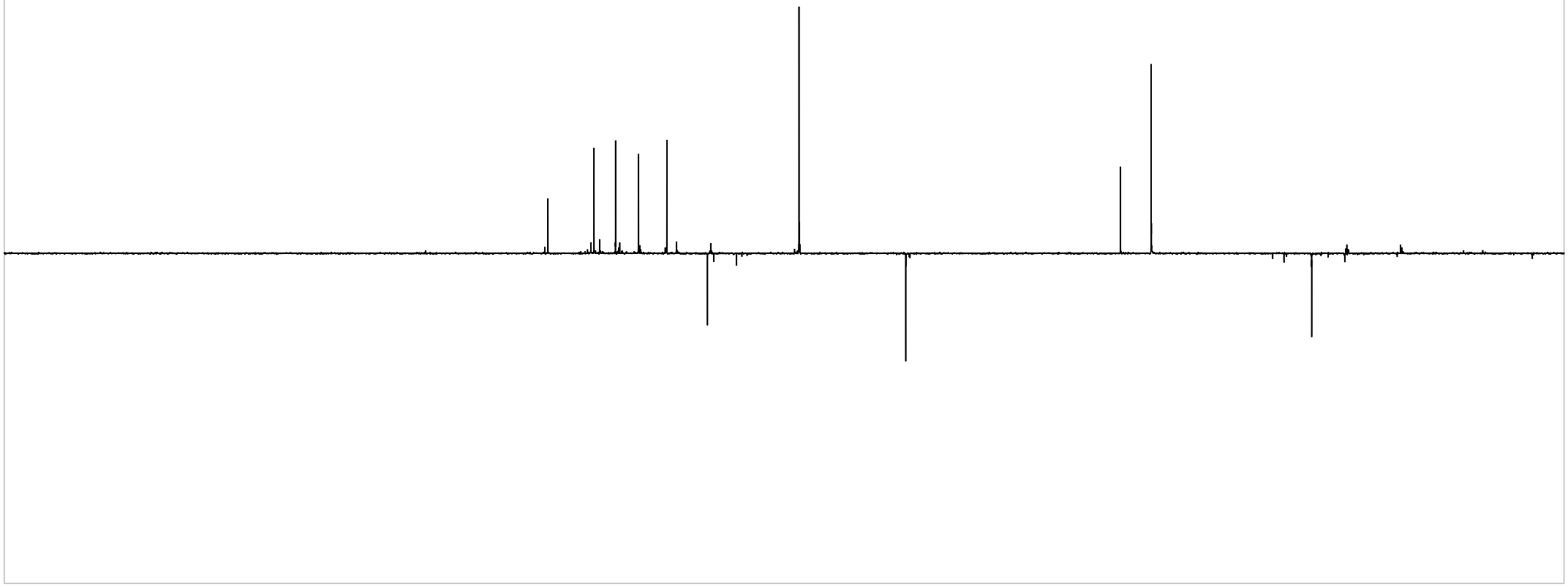
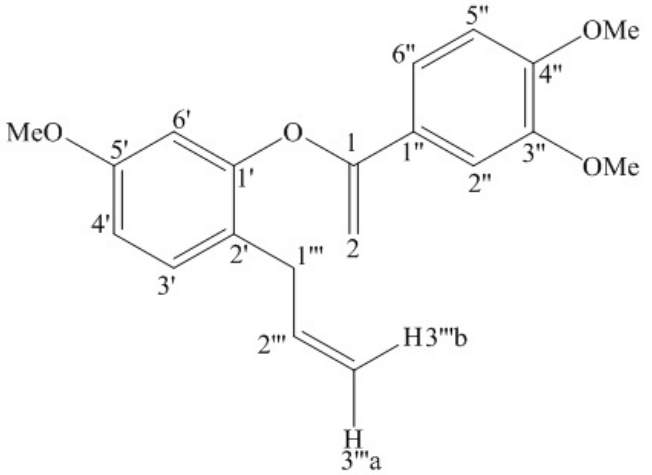


Plate 30a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**)

δ 7.33 – 7.31 (2H, m, H-2" and H-6"), 7.19 (1H, d, *J* = 8.5 Hz, H-3'), 6.96 (1H, d, *J* = 9.0 Hz, H-5"), 6.72 (1H, dd, *J* = 8.5, 2.6 Hz, H-4'), 6.62 (1H, d, *J* = 2.6 Hz, H-6'), 5.98 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H-2'''), 5.07 – 5.03 (1H, m, H-3'''b), 5.03 – 4.99 (1H, m, H-3'''a), 4.97 (1H, d, *J* = 2.4 Hz, H-2), 4.14 (1H, d, *J* = 2.4 Hz, H-2), 3.84 (6H, m, -OMe), 3.75 (3H, s, -OMe), 3.33 (2H, br. d, *J* = 6.6 Hz, H-1''')



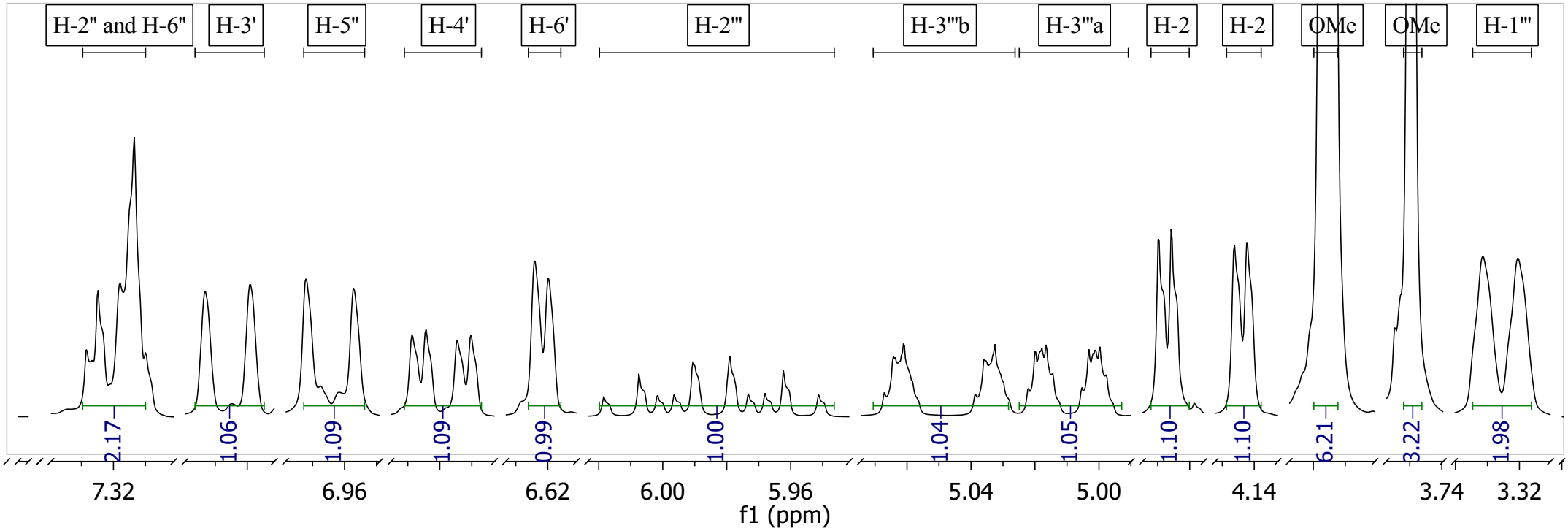
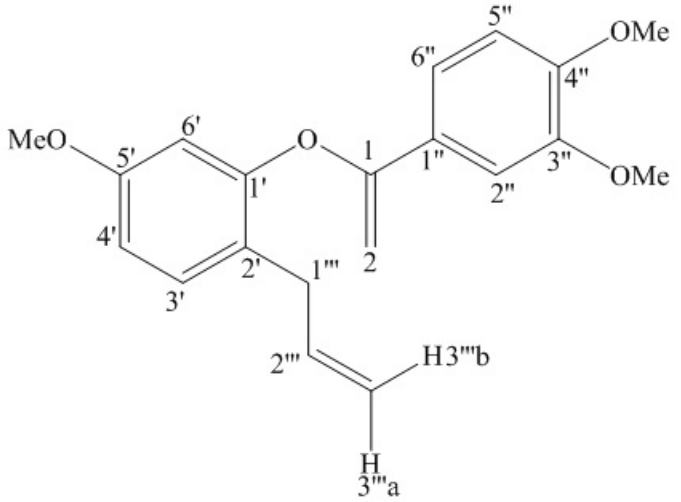


Plate 30b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**)

δ 160.44 (4º-C), 160.22 (4º-C), 155.14 (4º-C), 151.39 (4º-C), 150.31 (4º-C), 138.27 (C-2'''), 131.91 (C-3'), 128.91 (4º-C), 124.46 (4º-C), 119.24 (C-2''/6''), 115.89 (C-3'''), 112.49 (C-5''), 110.82 (C-4'), 110.28 (C-2''/6''), 107.40 (C-6'), 89.19 (C-2), 56.28 (-OMe), 55.84 (-OMe), 34.32 (C-1''')



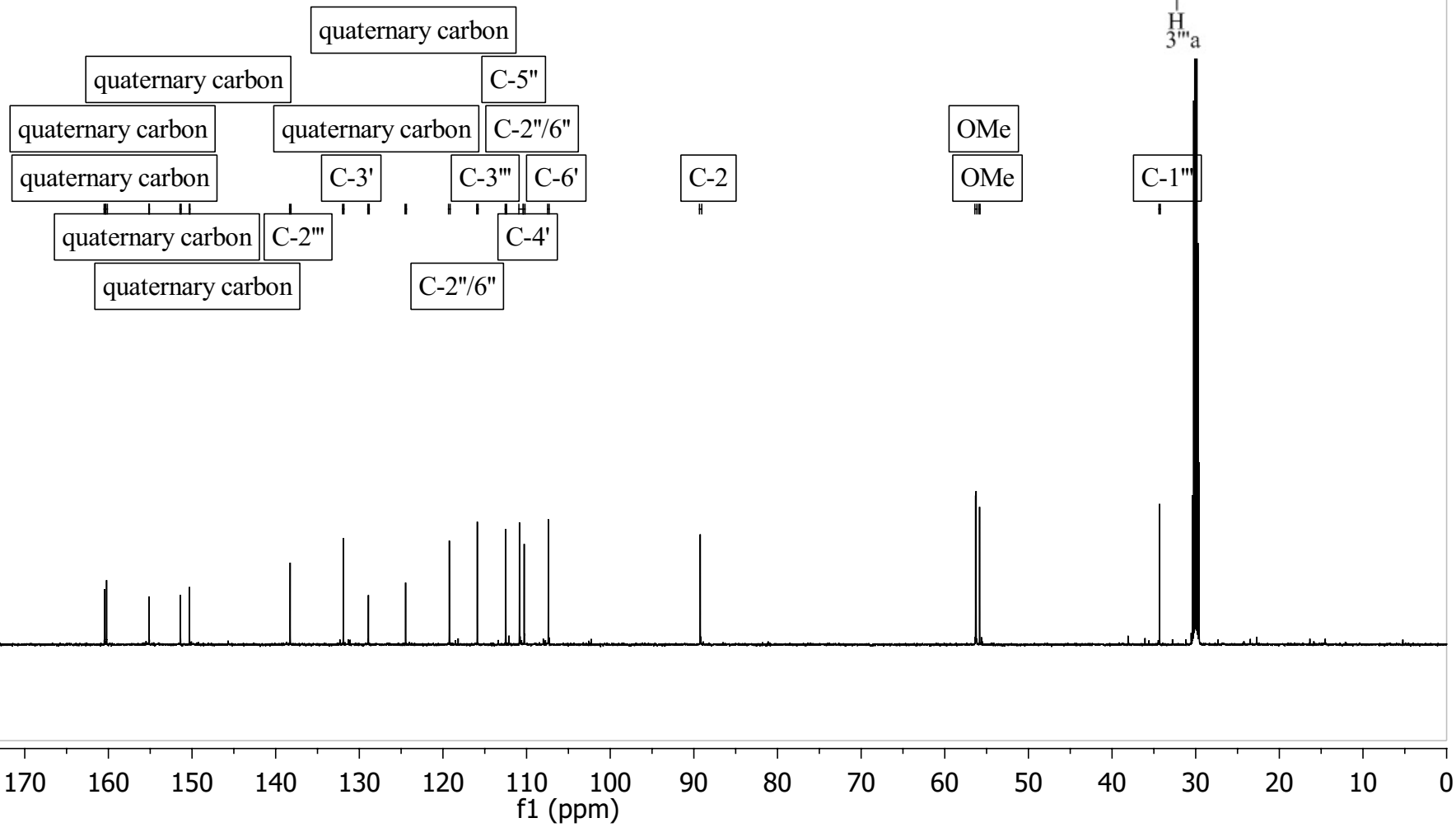


Plate 30c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**)

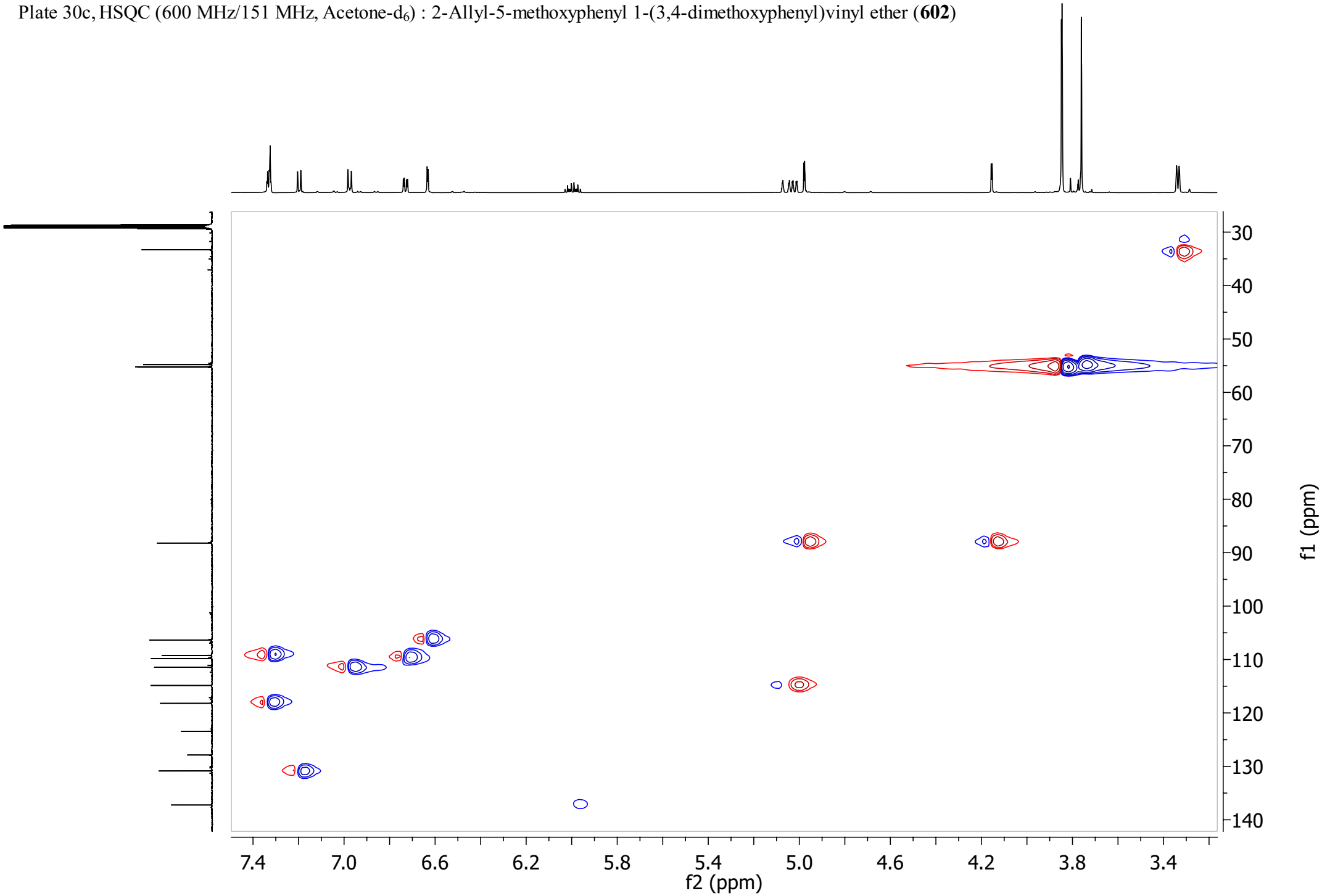


Plate 30d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**)

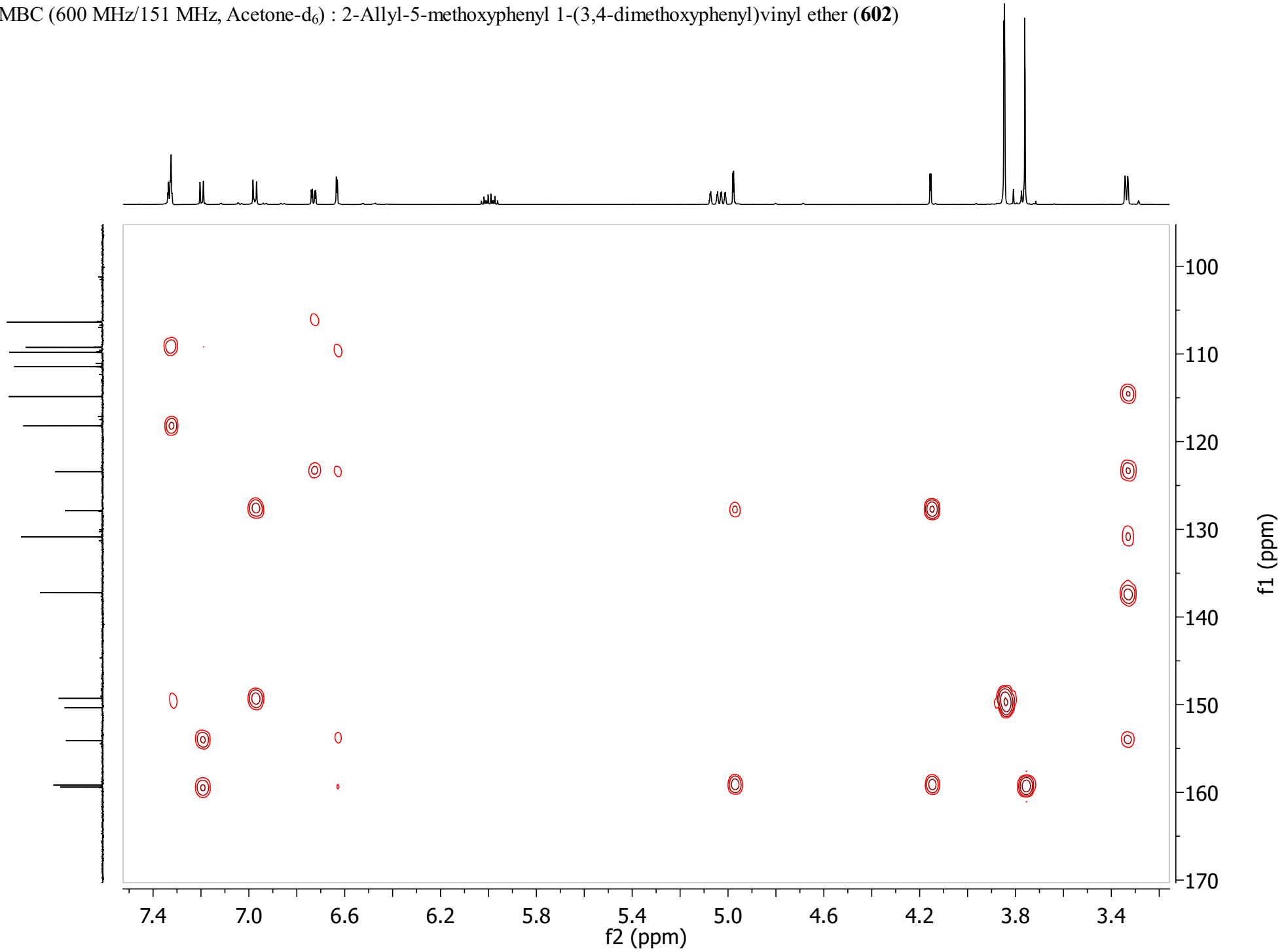


Plate 30e, DEPT (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4-dimethoxyphenyl)vinyl ether (**602**)

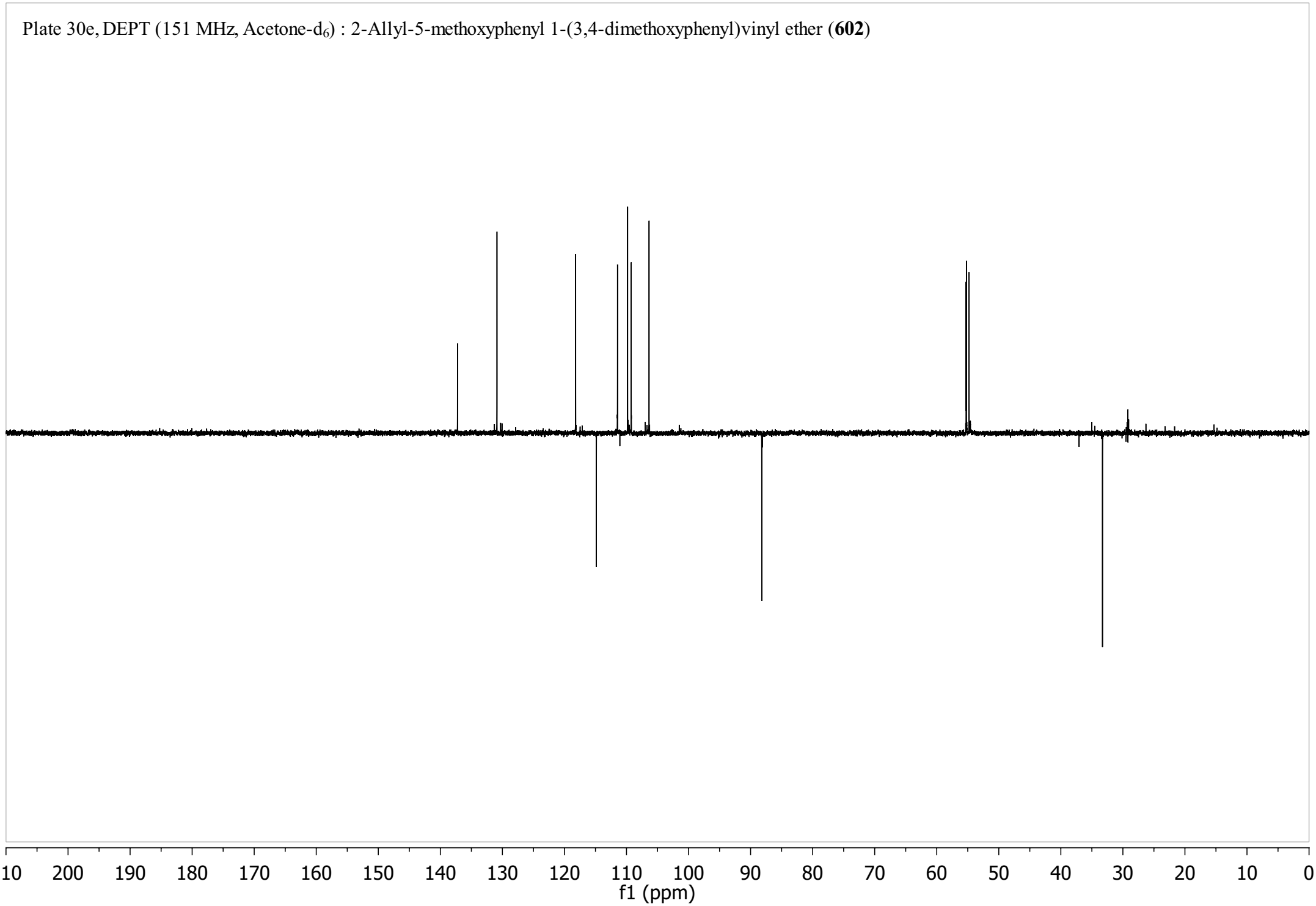
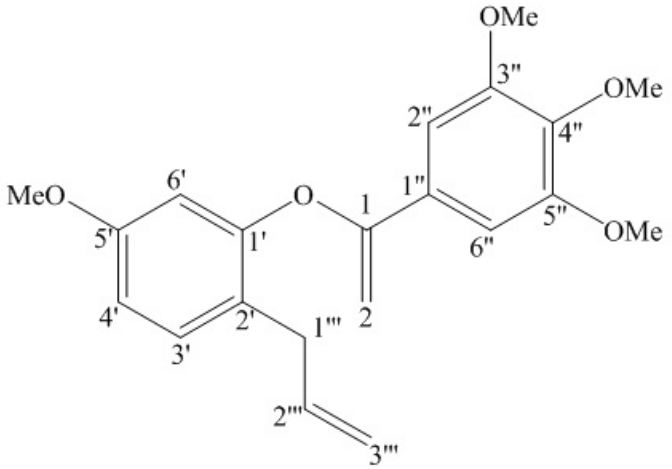
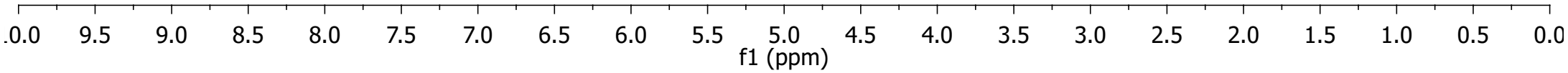


Plate 31a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-Allyl-5 methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**)

δ 7.20 (1H, d, *J* = 8.5 Hz, H-3'), 7.06 (2H, s, H-2" and H-6"), 6.74 (1H, dd, *J* = 8.5, 2.6 Hz, H-4'), 6.63 (1H, d, *J* = 2.6 Hz, H-6'), 5.99 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H-2'''), 5.07 – 5.00 (2H, m, H-3'''), 5.04 (1H, d, *J* = 2.6 Hz, H-2), 4.18 (1H, d, *J* = 2.6 Hz, H-2), 3.86 (6H, s, -OMe), 3.76 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.32 (2H, br. d, *J* = 6.6 Hz, H-1''')





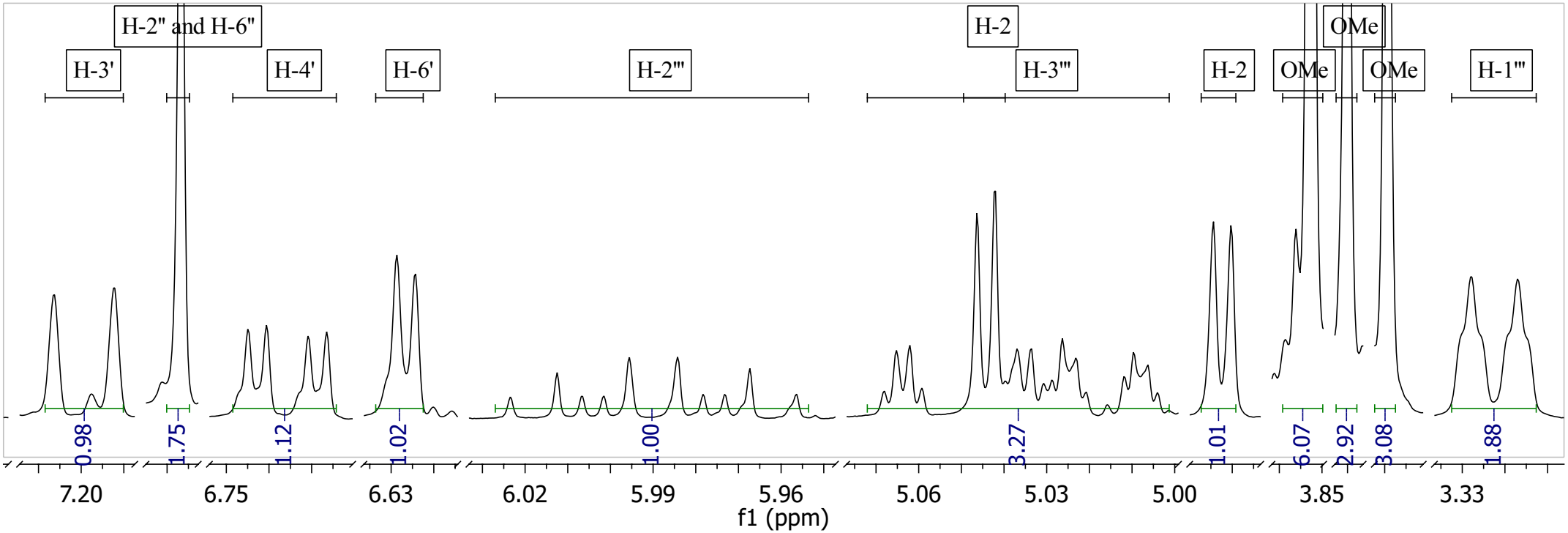
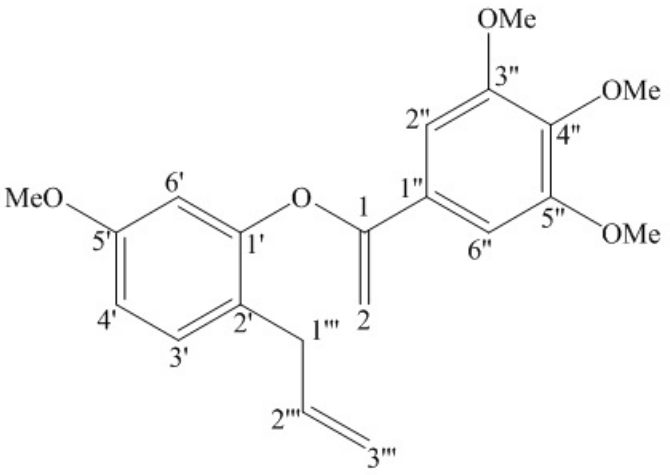


Plate 31b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**)

δ 160.42 (4º-C), 160.08 (4º-C), 154.98 (4º-C), 154.39 (C-3'' and C-5''), 140.10 (4º-C), 138.22 (C-2'''), 131.96 (C-3'), 131.58 (4º-C), 124.39 (4º-C), 115.85 (C-3'''), 110.95 (C-4'), 107.41 (C-6'), 104.02 (C-2'' and C-6''), 90.15 (C-2), 60.68 (-O<u>Me</u>), 56.57 (-O<u>Me</u>), 55.80 (-O<u>Me</u>), 34.30 (C-1''')



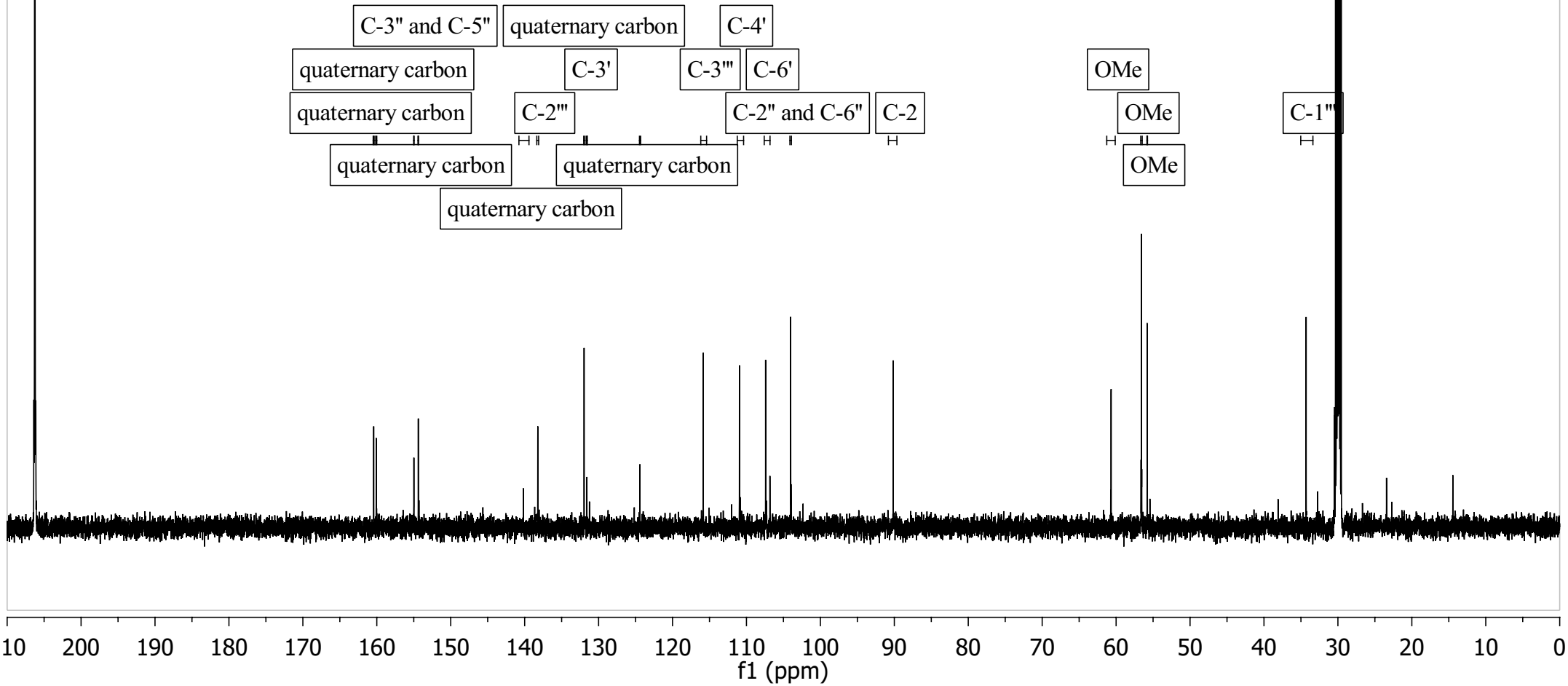


Plate 31c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**)

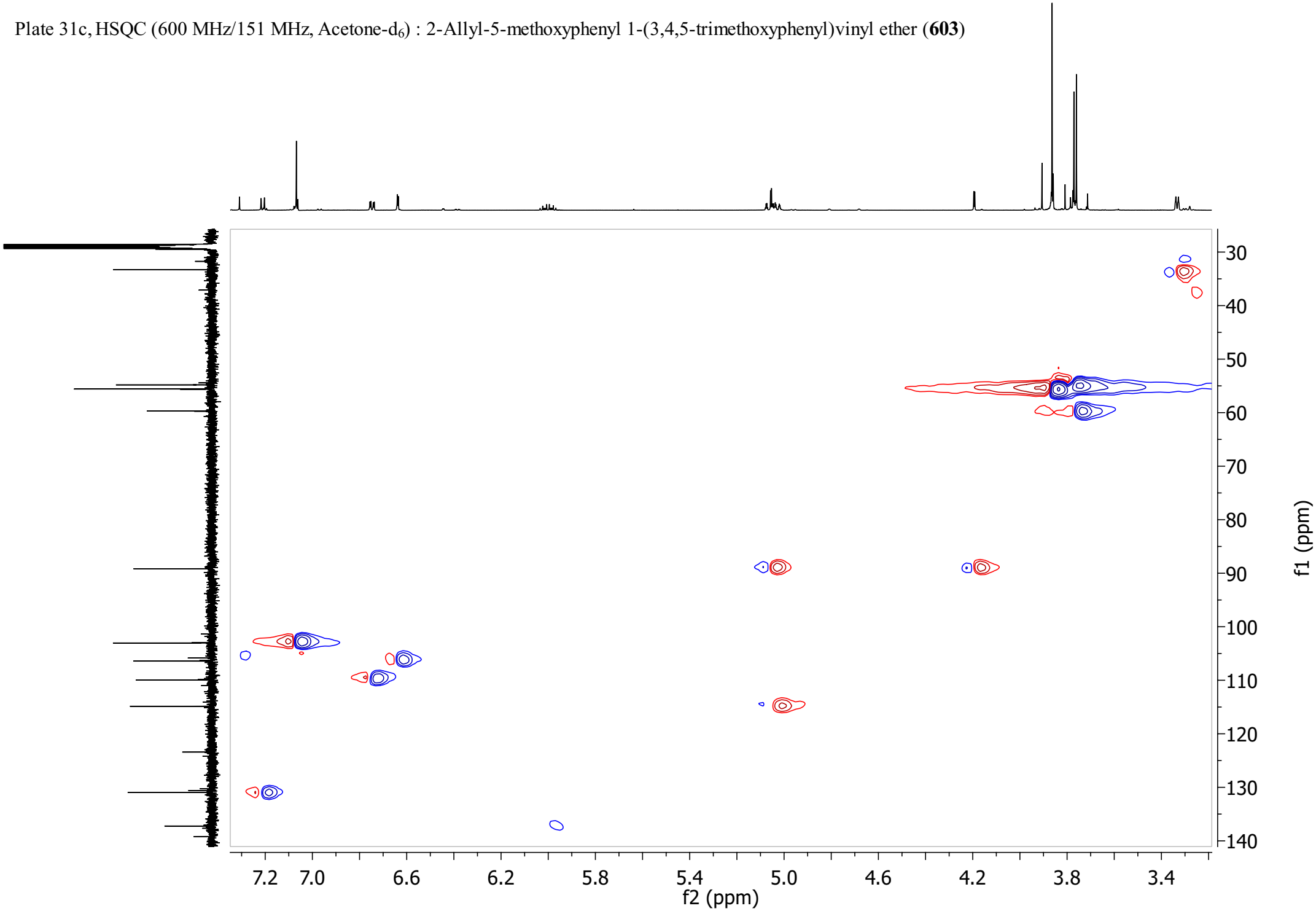


Plate 31d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**)

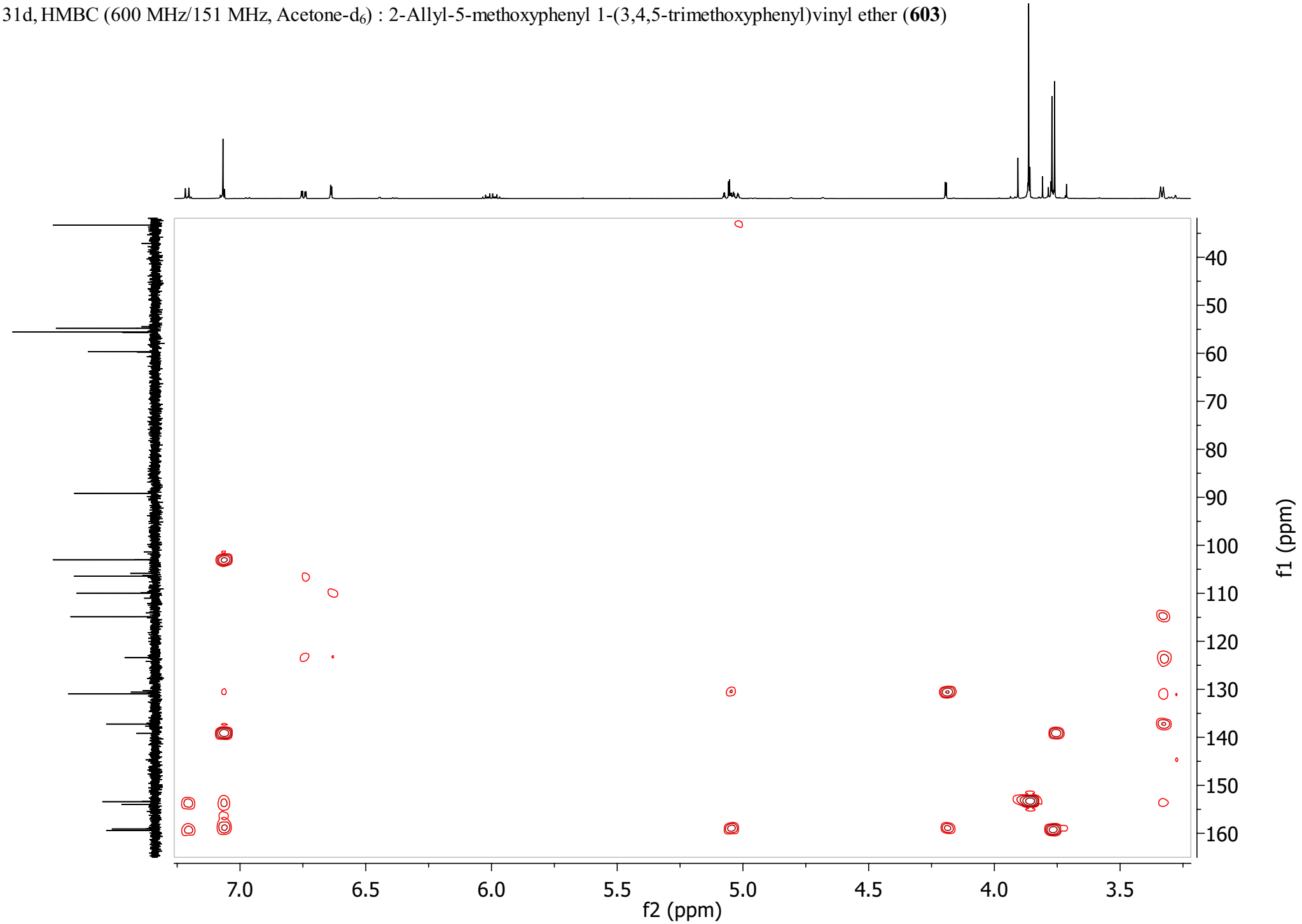
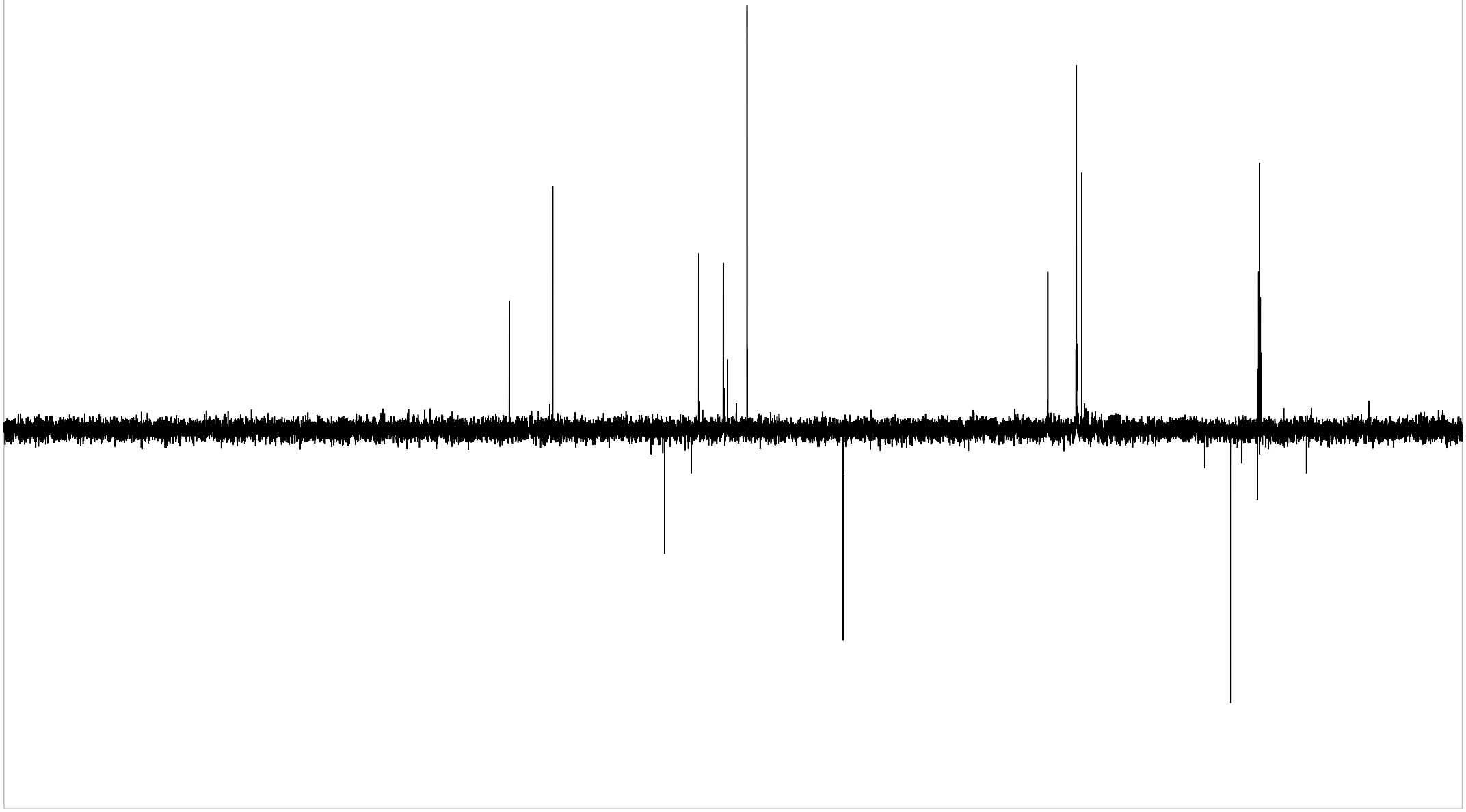


Plate 31e, DEPT (151 MHz, Acetone-d_6) : 2-Allyl-5-methoxyphenyl 1-(3,4,5-trimethoxyphenyl)vinyl ether (**603**)



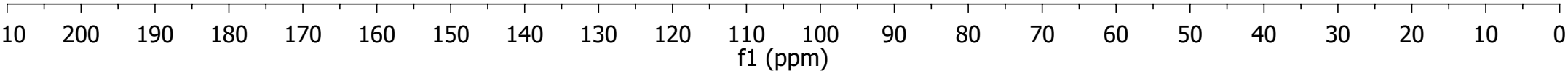
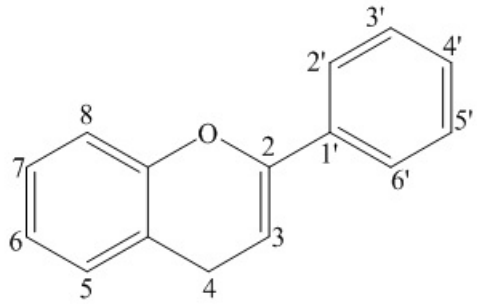
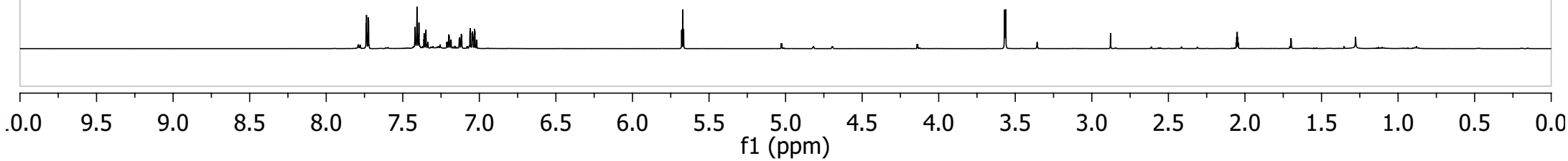


Plate 32a, ^{1}H NMR (600 MHz, Acetone-d_6) : Flav-2-ene (**608**)

δ 7.74 – 7.72 (2H, m, H-2' and H-6'), 7.42 – 7.39 (2H, m, H-3' and H-5'), 7.36 – 7.33 (1H, m, H-4'), 7.21 – 7.18 (1H, m, H-7), 7.12 (1H, br. d, *J* = 7.5 Hz, H-5), 7.05 (1H, dd, *J* = 8.1, 1.1 Hz, H-8) 7.03 (1H, ddd, *J* = 8.1, 7.5, 1.1 Hz, H-6), 5.67 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.57 (2H, br. d, *J* = 3.9 Hz, H-4)





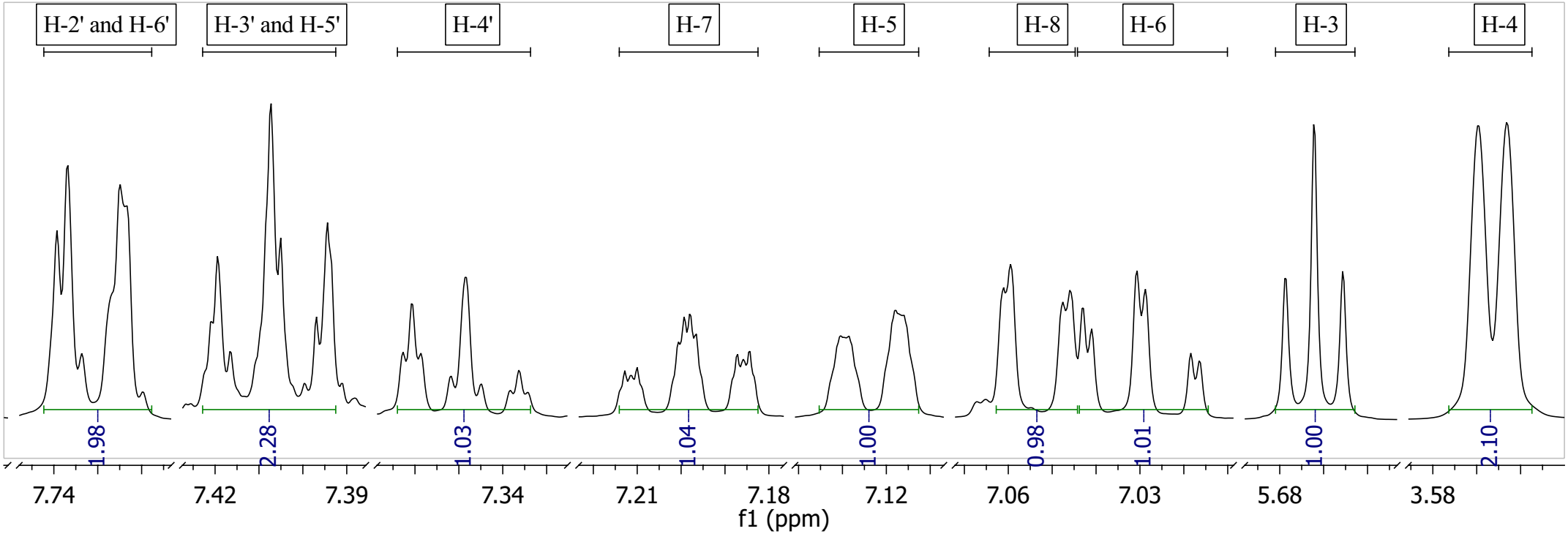
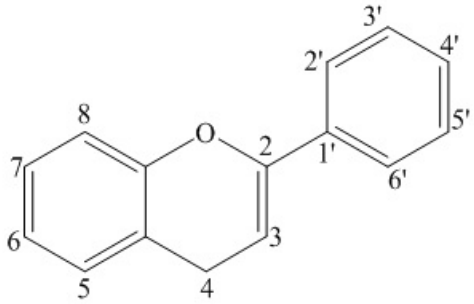


Plate 32b, ^{13}C NMR (151 MHz, Acetone-d_6) : Flav-2-ene (**608**)

δ 152.82 (4º-C), 149.66 (4º-C), 135.33 (4º-C), 130.04 (C-5), 129.31 (C-3' and C-5'), 129.27 (C-4'), 128.54 (C-7), 125.24 (C-2' and C-6'), 124.40 (C-6), 120.72 (4º-C), 117.36 (C-8), 97.55 (C-3), 24.93 (C-4)



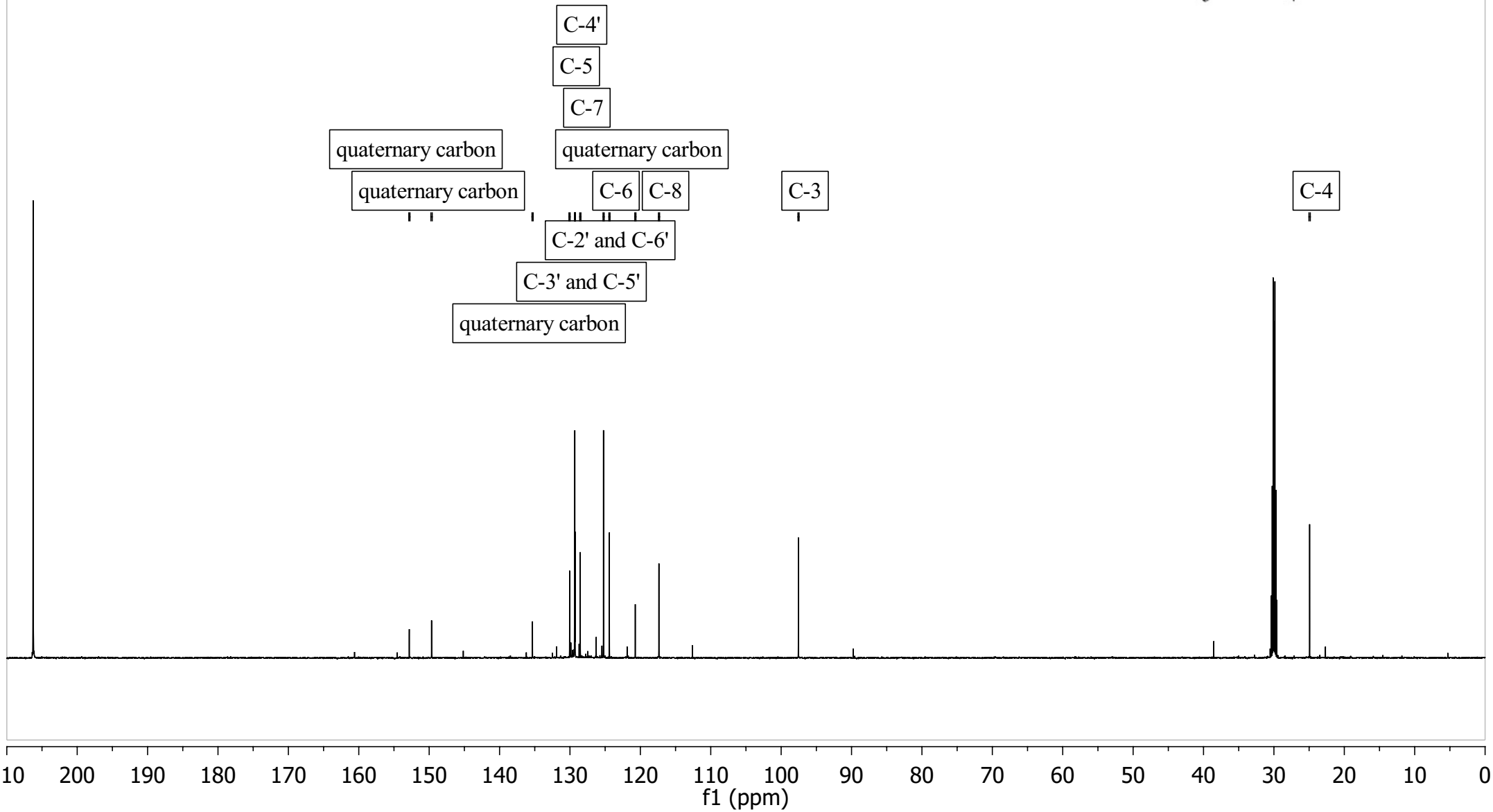


Plate 32c, HSQC (600 MHz/151 MHz, Acetone-$_{d6}$) : Flav-2-ene (**608**)

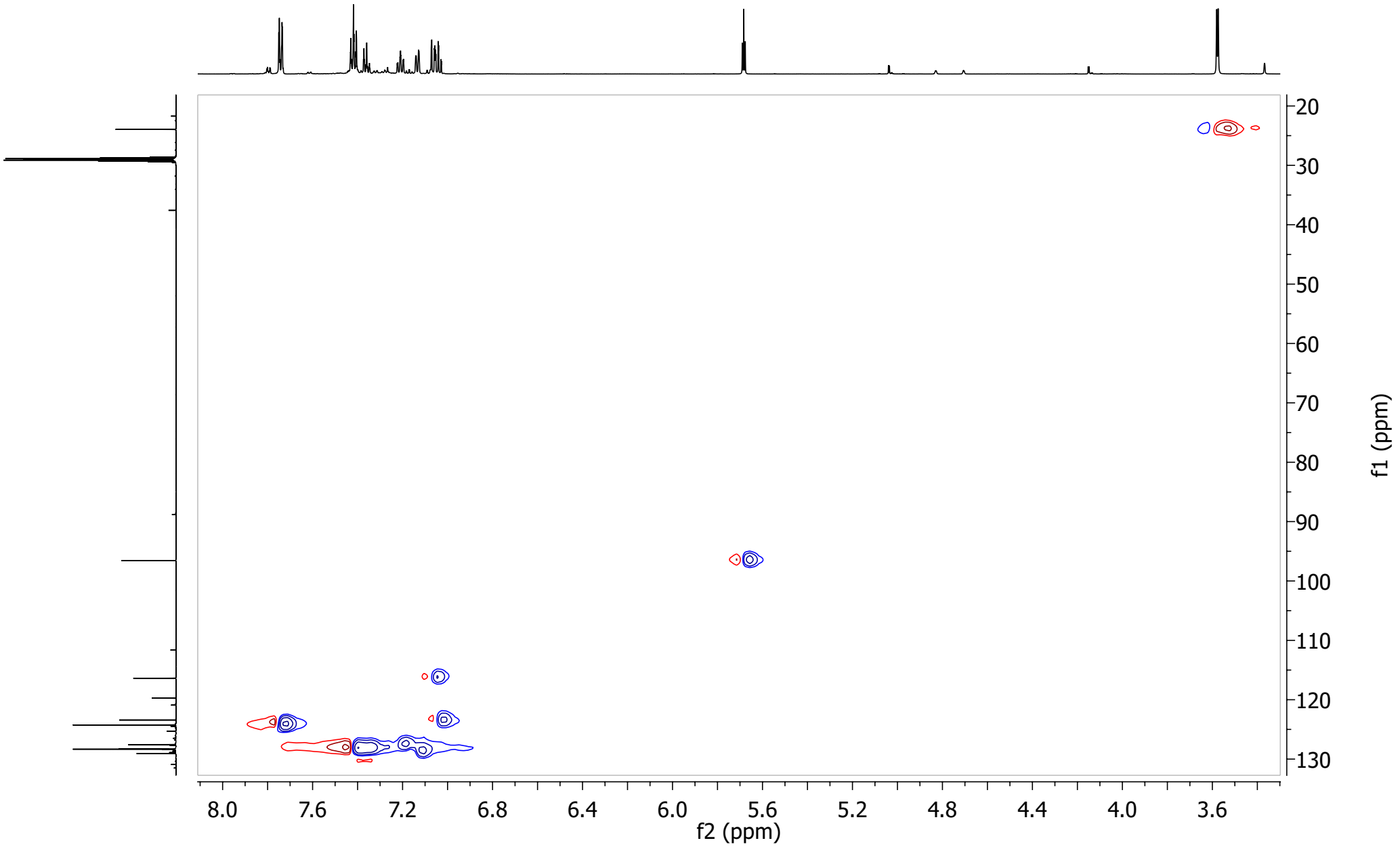


Plate 32d, HMBC (600 MHz/151 MHz, Acetone-d_6) : Flav-2-ene (**608**)

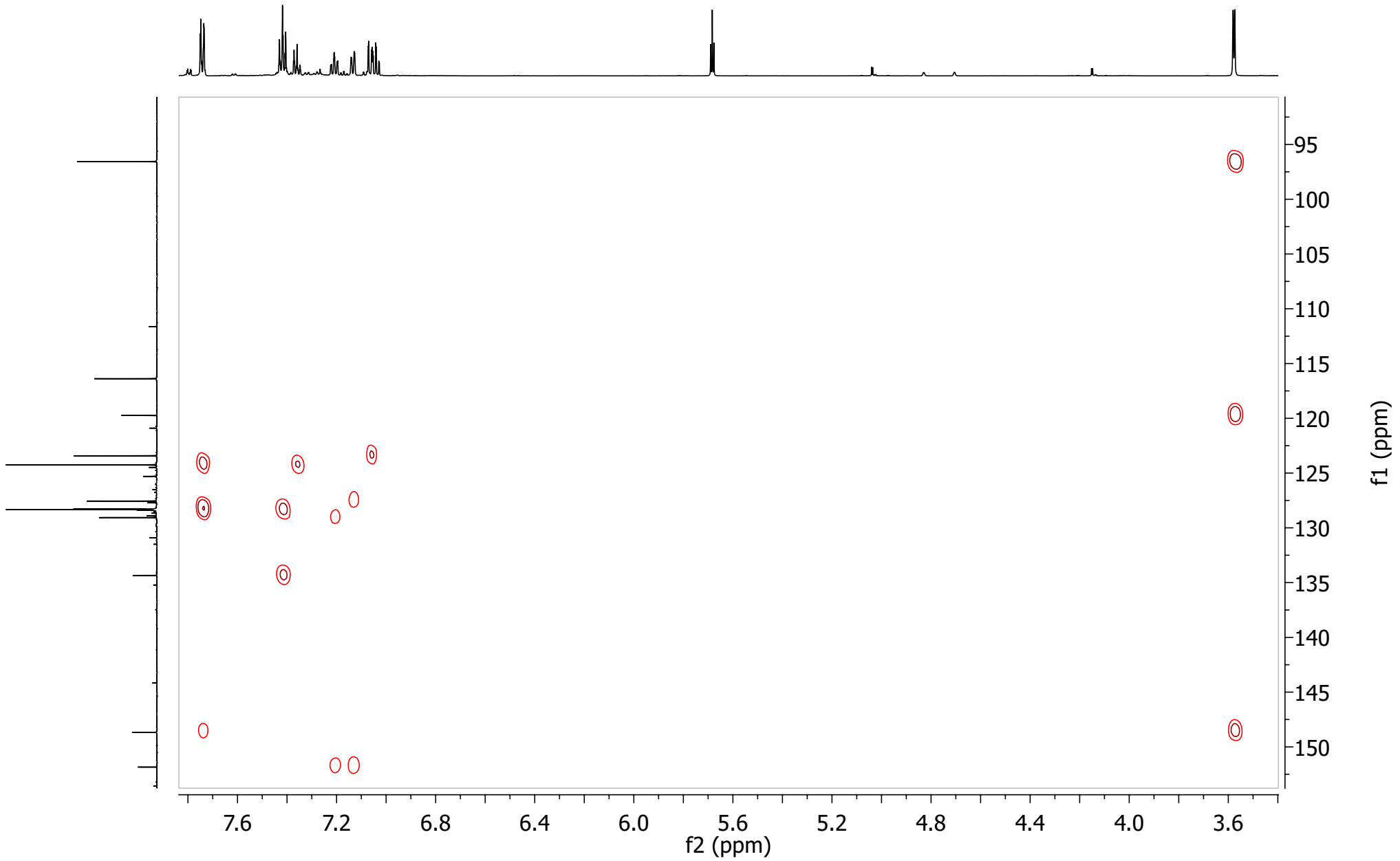


Plate 32e, DEPT (151 MHz, Acetone-d_6) : Flav-2-ene (**608**)

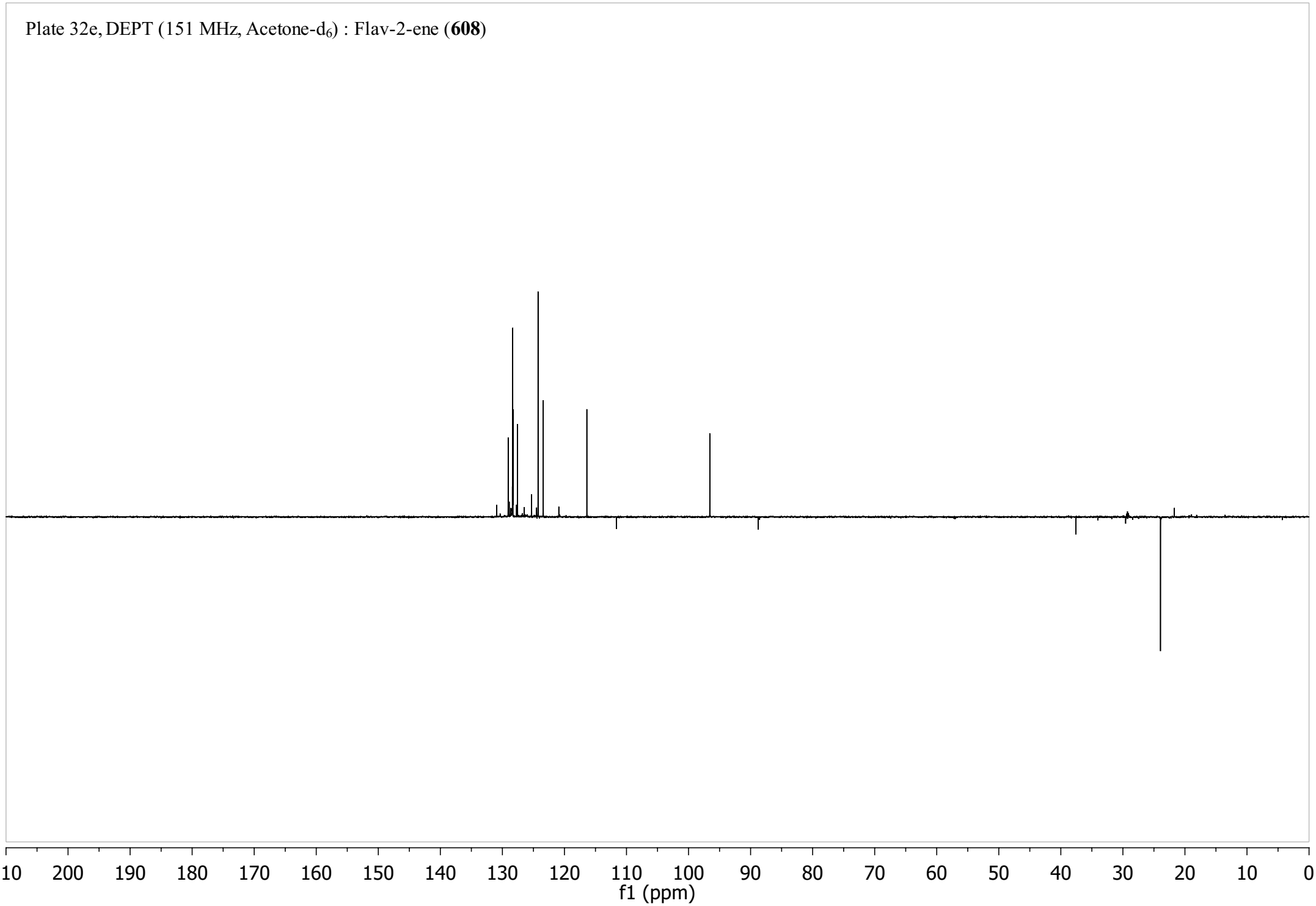
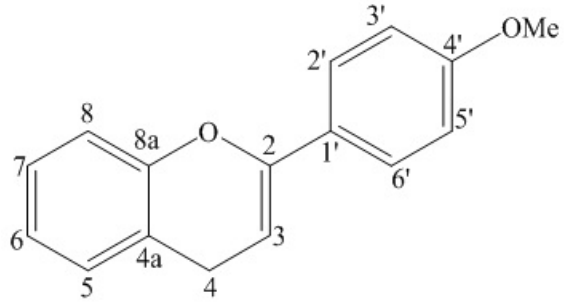
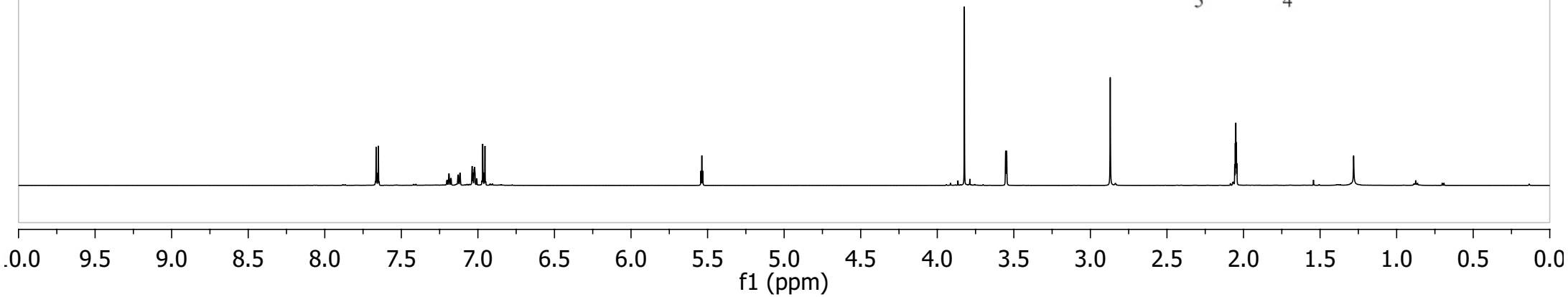


Plate 33a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4'-Methoxyflav-2-ene (**613**)

δ 7.66 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.20 – 7.19 (1H, m, H-7), 7.13 – 7.11 (1H, br. d, *J* = 7.2 Hz, H-5), 7.04 – 7.00 (2H, m, H-6 and H-8), 6.96 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 5.54 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.82 (3H, s, -OMe), 3.55 (2H, br. d, *J* = 3.9 Hz, H-4)





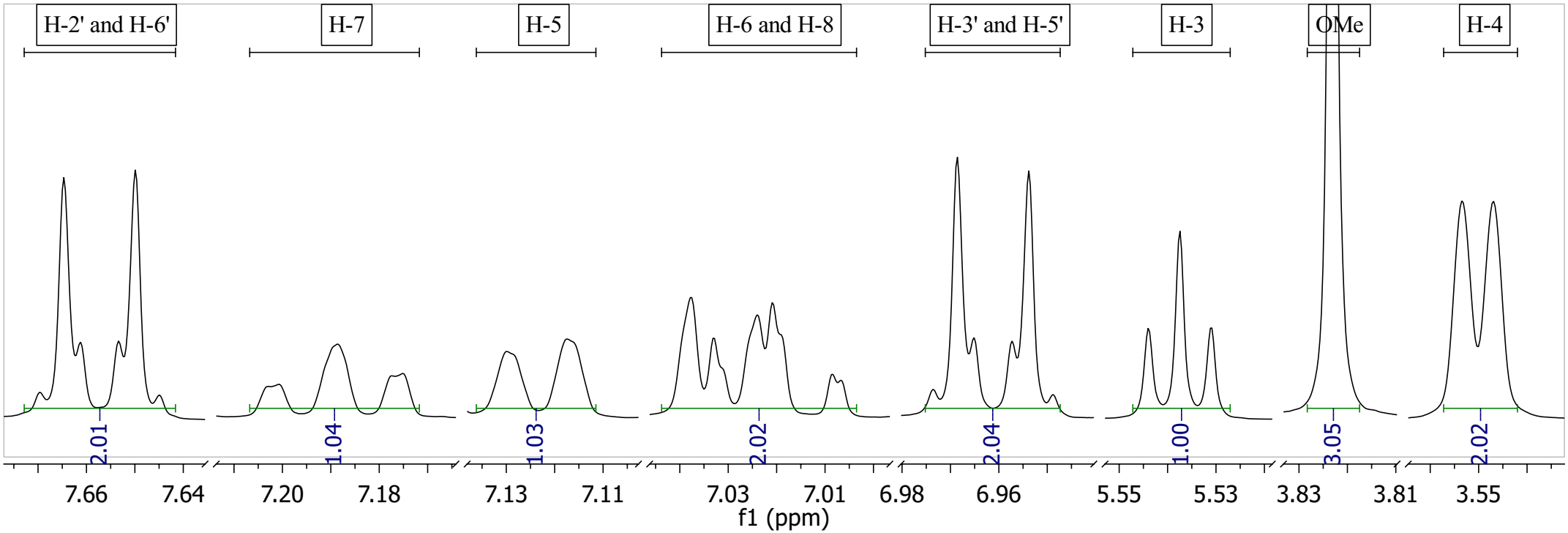
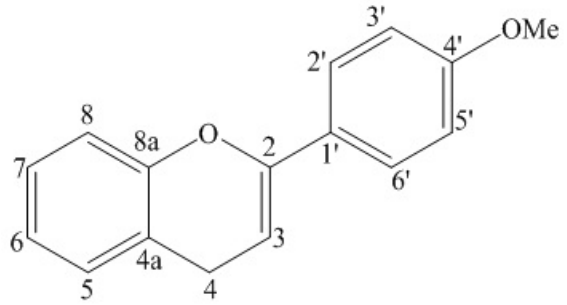
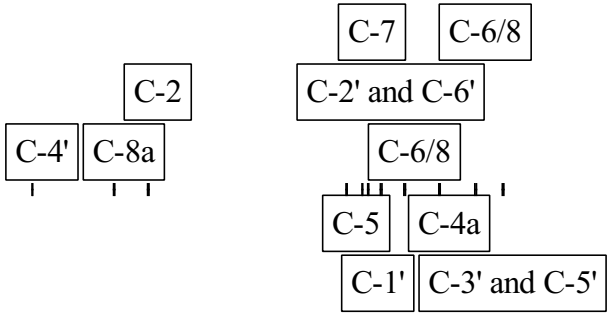


Plate 33b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4'-Methoxyflav-2-ene (**613**)

δ 160.91 (C-4'), 152.85 (C-8a), 149.51 (C-2), 129.97 (C-5), 128.42 (C-7), 127.85 (C-1'), 126.58 (C-2' and C-6'), 124.24 (C-6/8), 120.82 (C-4a), 117.27 (C-6/8), 114.57 (C-3' and C-5'), 95.49 (C-3), 55.65 (-OMe), 24.81 (C-4)





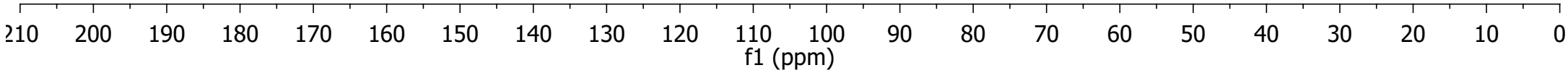


Plate 33c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 4'-Methoxyflav-2-ene (**613**)

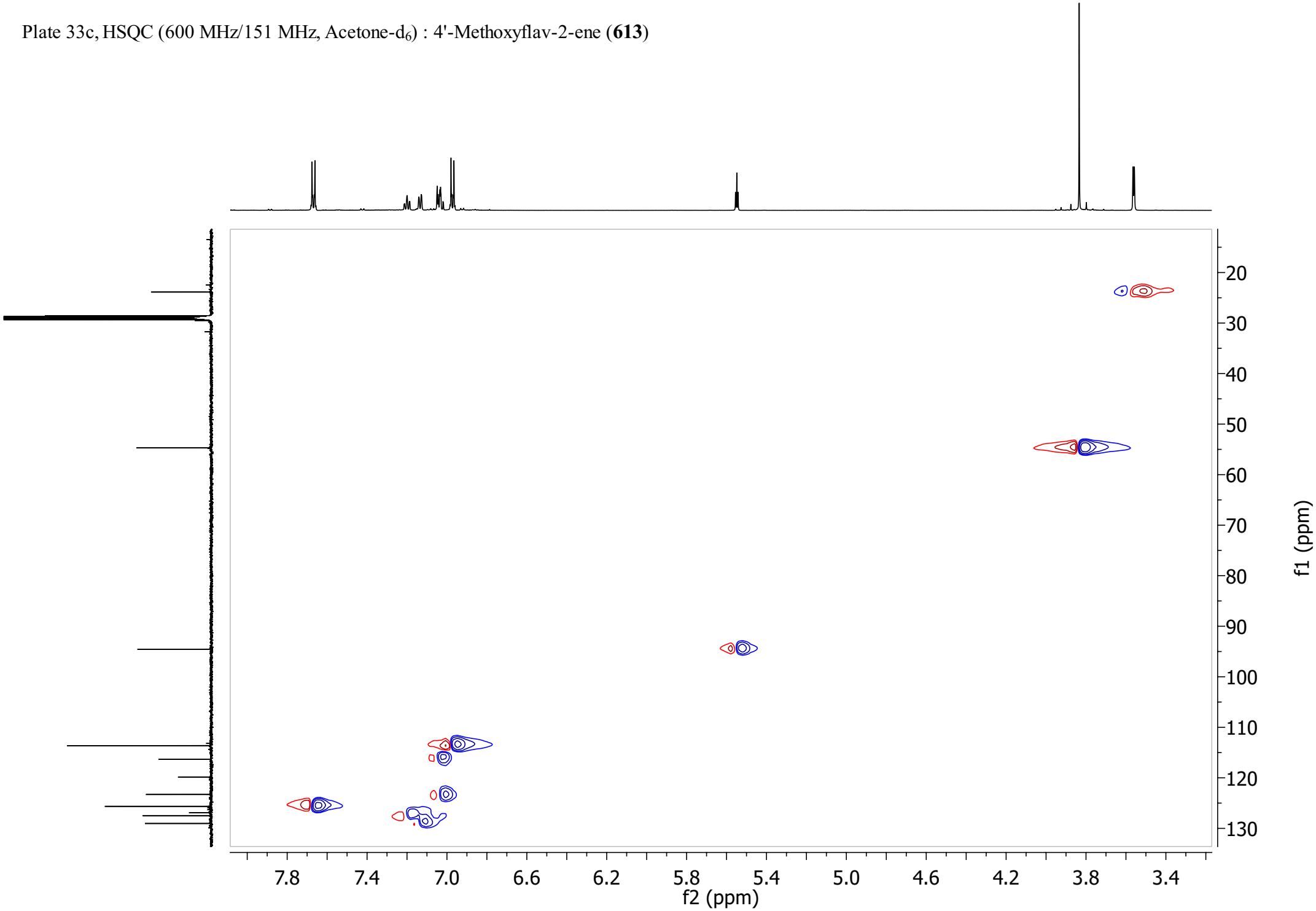


Plate 33d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 4'-Methoxyflav-2-ene (**613**)

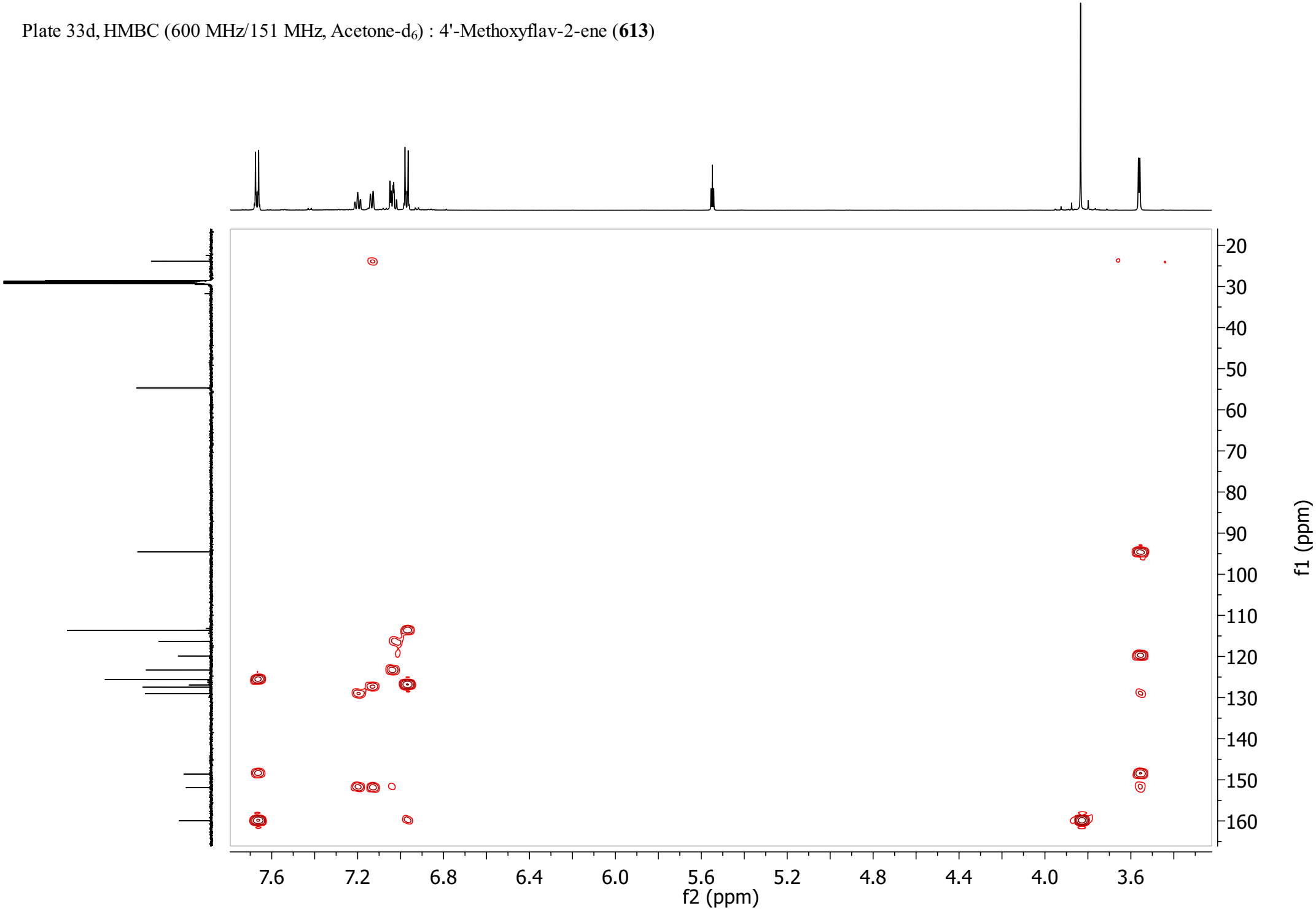


Plate 33e, DEPT (151 MHz, Acetone-d_6) : 4'-Methoxyflav-2-ene (**613**)

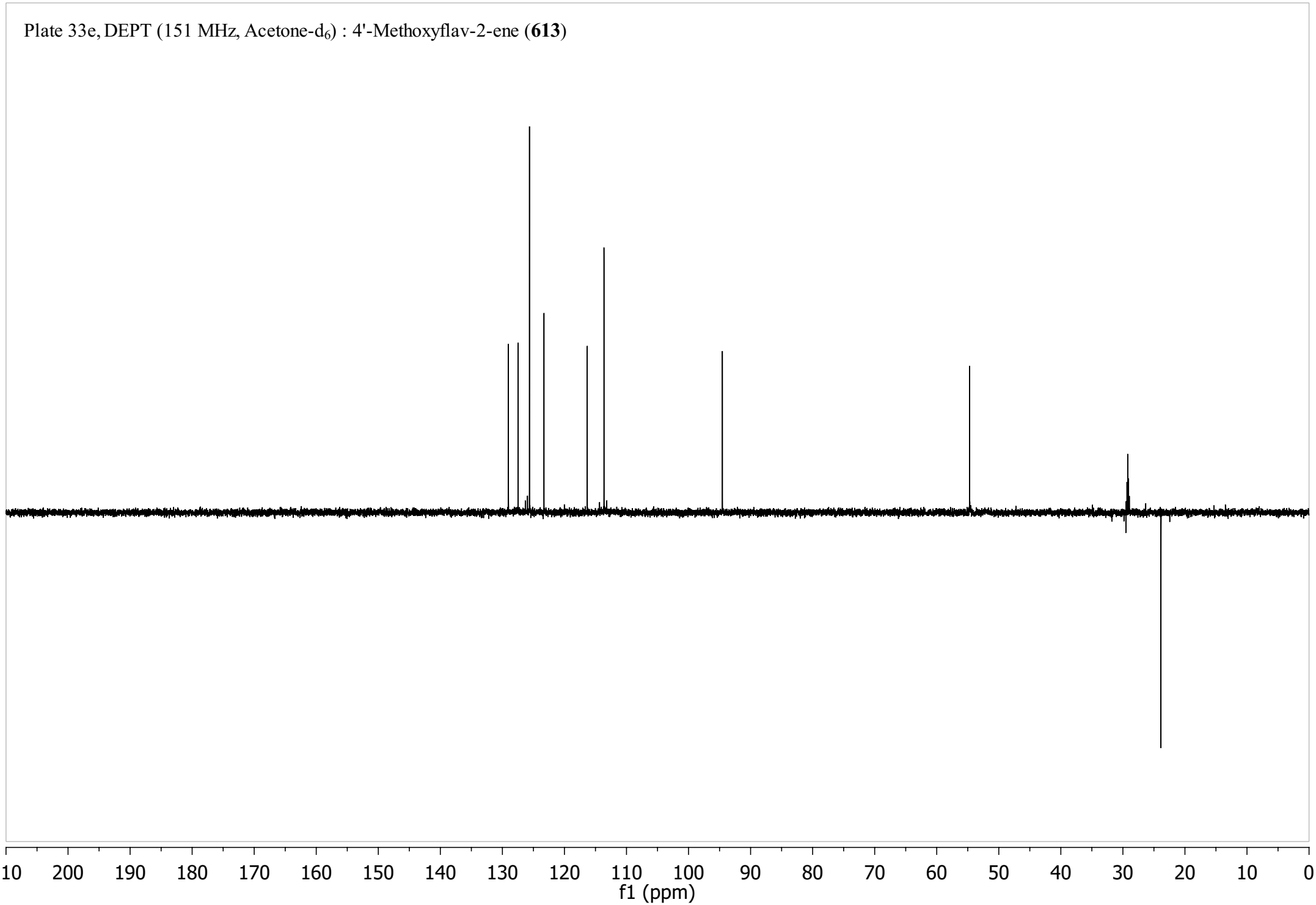
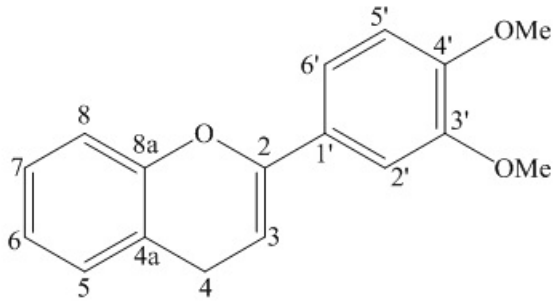
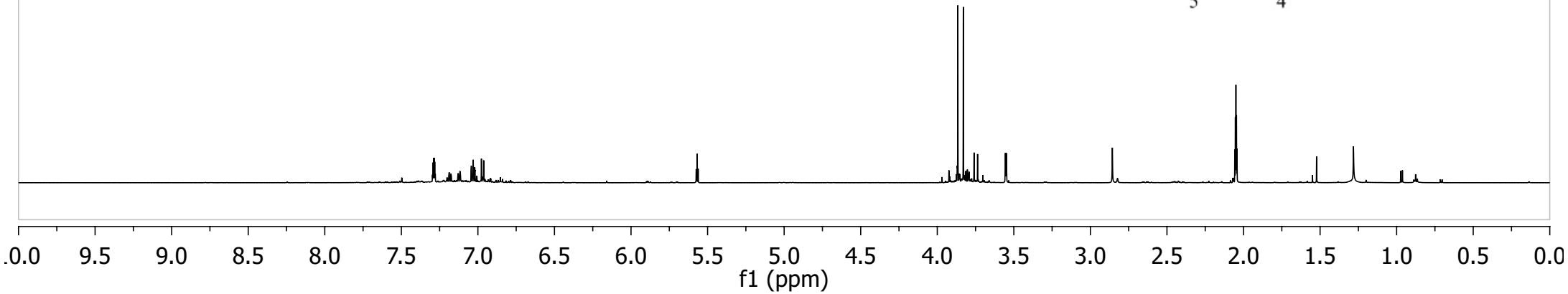


Plate 34a, ^{1}H NMR (600 MHz, Acetone-d_6) : 3',4'-Dimethoxyflav-2-ene (**614**)

δ 7.30 – 7.28 (2H, m, H-2' and H-6'), 7.20 – 7.17 (1H, m, H-7), 7.12 (1H, br. d, *J* = 8.0 Hz, H-5), 7.05 – 7.03 (1H, m, H-6), 7.01(1H, dd, *J* = 7.5, 1.2 Hz, H-8), 6.97 (1H, d, *J* = 8.9 Hz, H-5'), 5.57 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.87 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.55 (2H, br. d, *J* = 3.9 Hz, H-4)





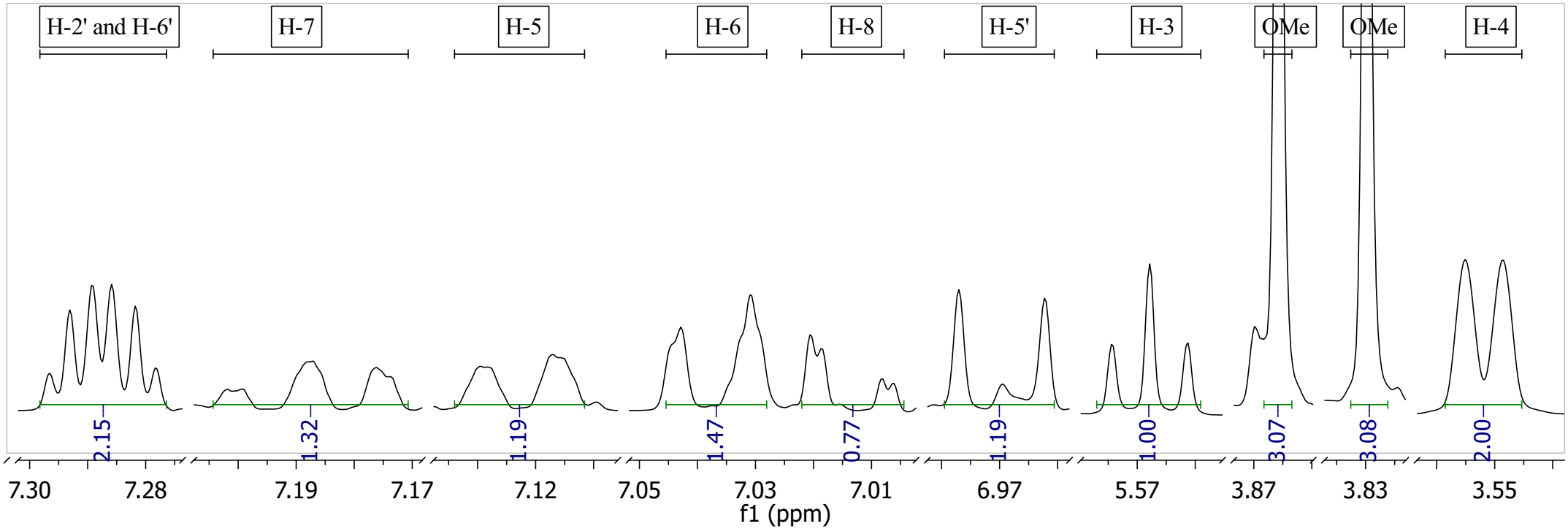
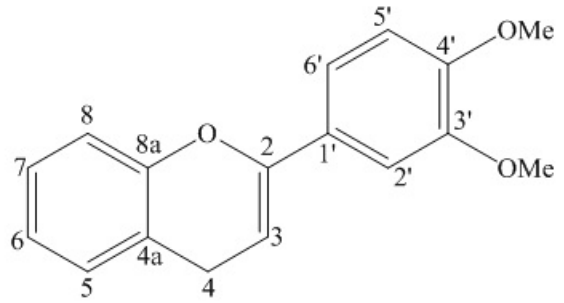


Plate 34b, ^{13}C NMR (151 MHz, Acetone-d_6) : 3',4'-Dimethoxyflav-2-ene (**614**)

δ 152.93 (C-8a), 150.90 (C-3'/4'), 150.28 (C-3'/4'), 149.65 (C-2), 130.01 (C-5), 128.45 (C-7), 128.26 (C-1'), 124.29 (C-8), 120.88 (C-4a), 118.07 (C-2'/6'), 117.35 (C-6), 112.47 (C-5'), 109.38 (C-2'/6'), 95.85 (C-3), 56.27 (-OMe), 56.20 (-OMe), 24.91 (C-4)



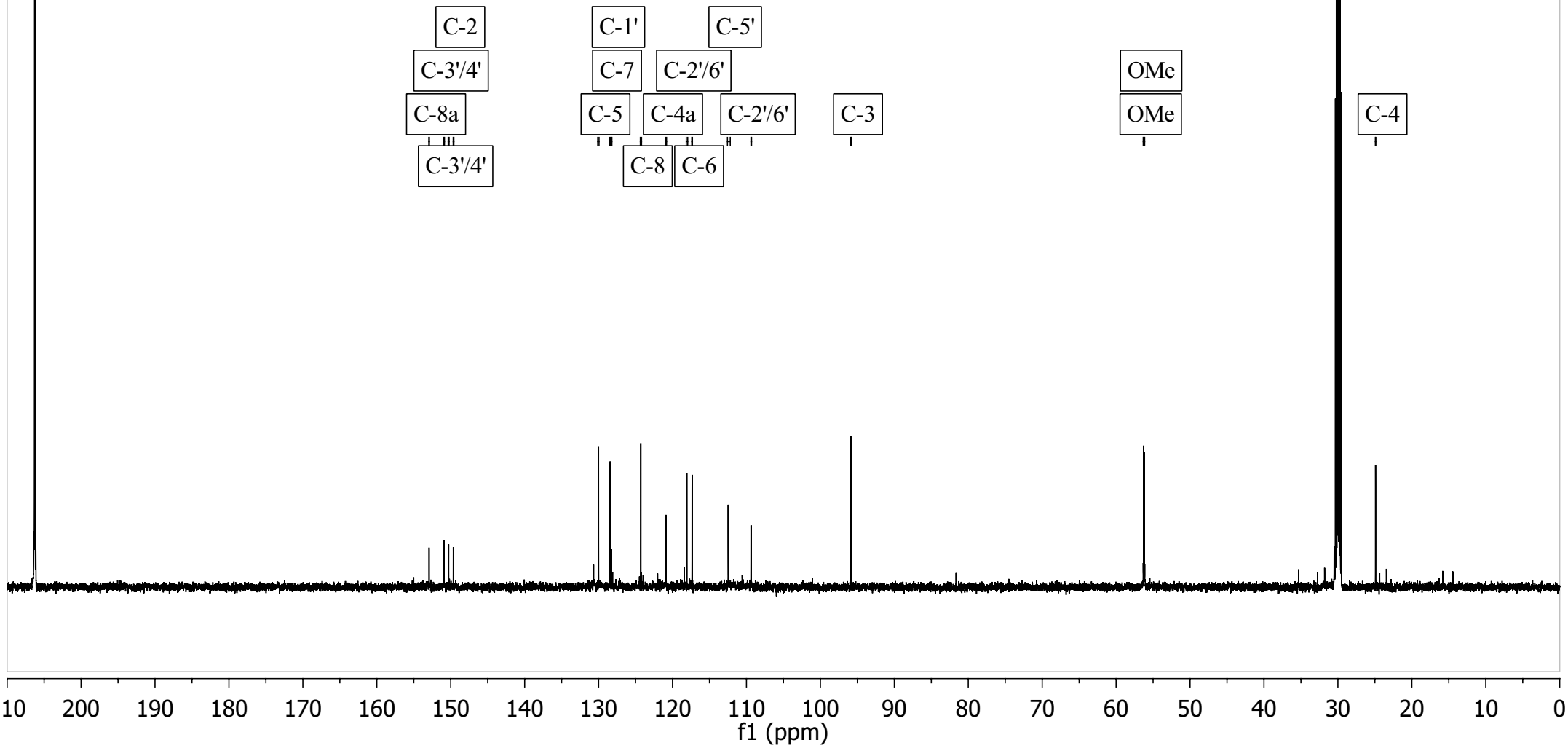


Plate 34c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 3',4'-Dimethoxyflav-2-ene (**614**)

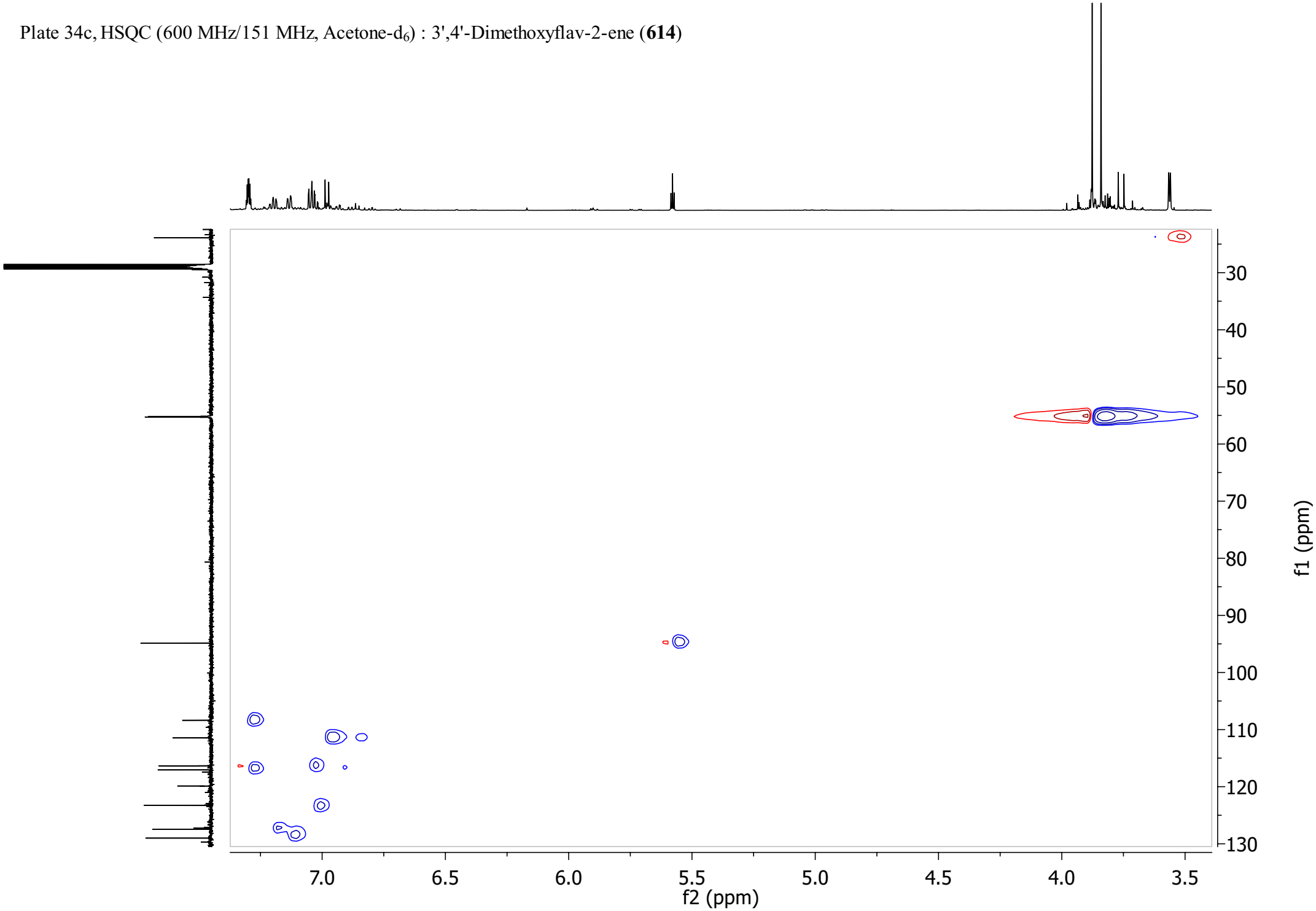


Plate 34d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 3',4'-Dimethoxyflav-2-ene (**614**)

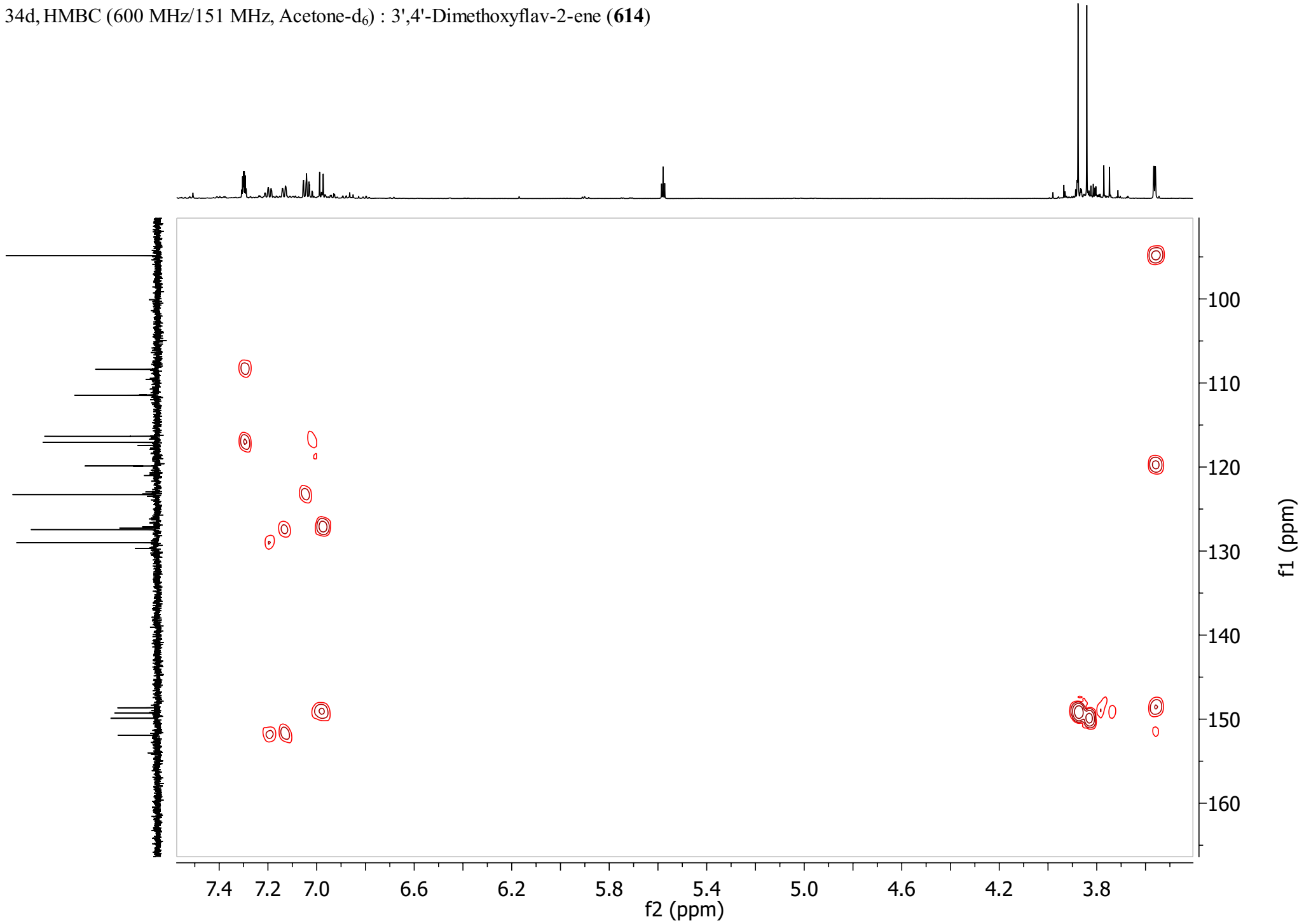


Plate 34e, DEPT (151 MHz, Acetone-d_6) : 3',4'-Dimethoxyflav-2-ene (**614**)

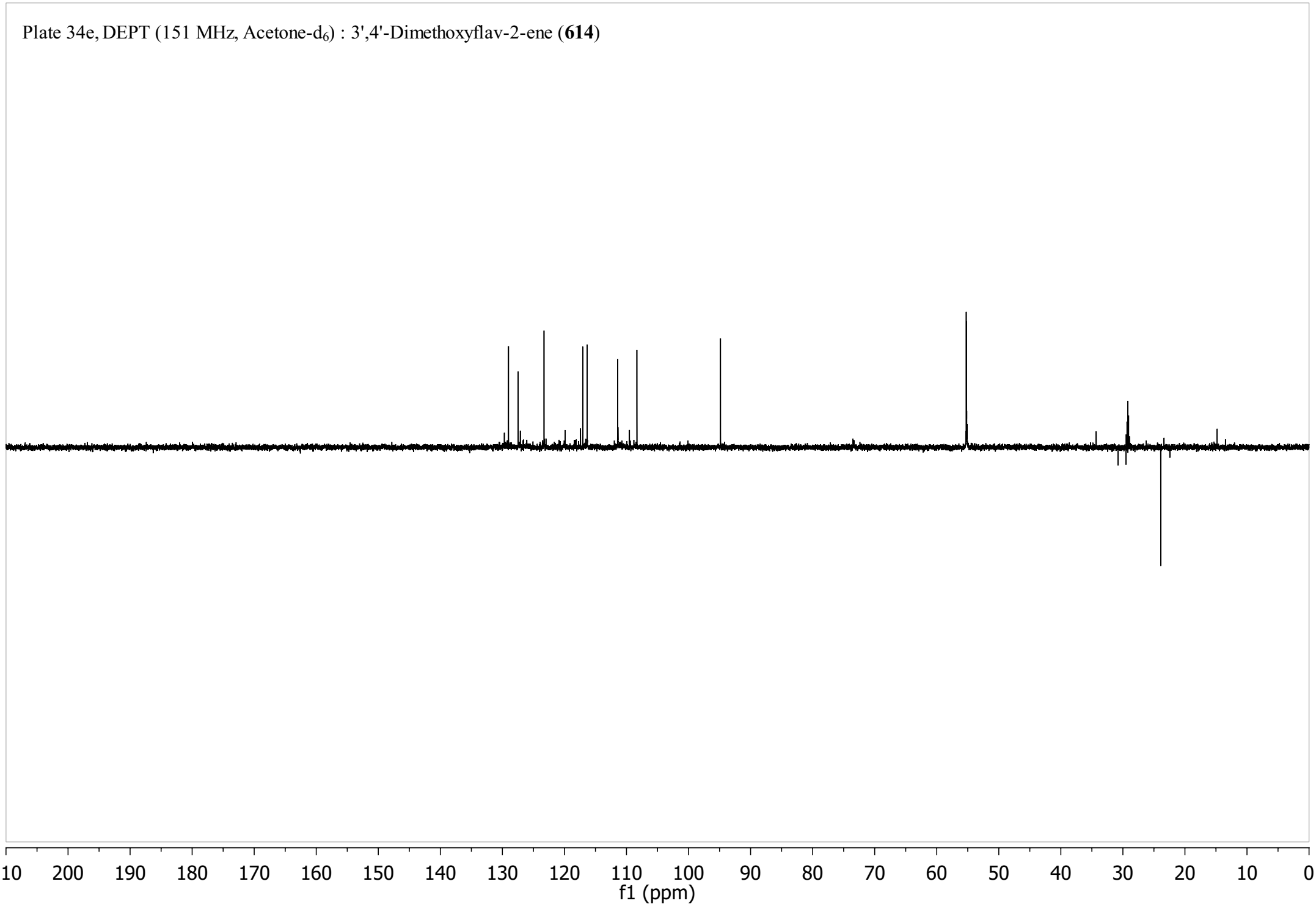
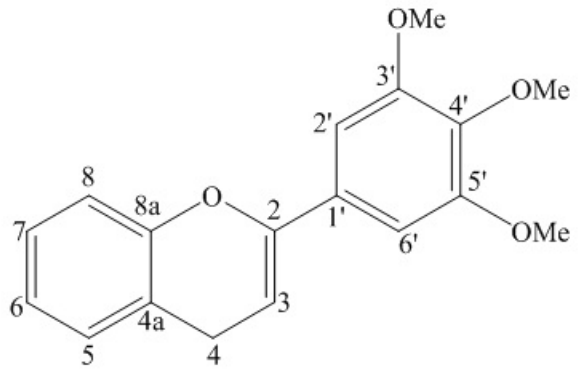
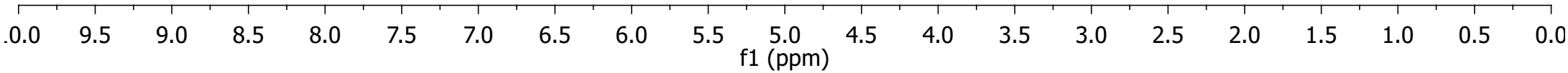


Plate 35a, ^{1}H NMR (600 MHz, Acetone-d_6) : 3',4',5'-Trimethoxyflav-2-ene (**615**)

δ 7.21 – 7.18 (1H, m, H-7), 7.14 – 7.12 (1H, m, H-5), 7.06 – 7.02 (4H, m, H-6, H-8, H-2' and H-6'), 5.66 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.88 (6H, s, -OMe), 3.75 (3H, s, -OMe), 3.57 (2H, br. d, *J* = 3.9 Hz, H-4)





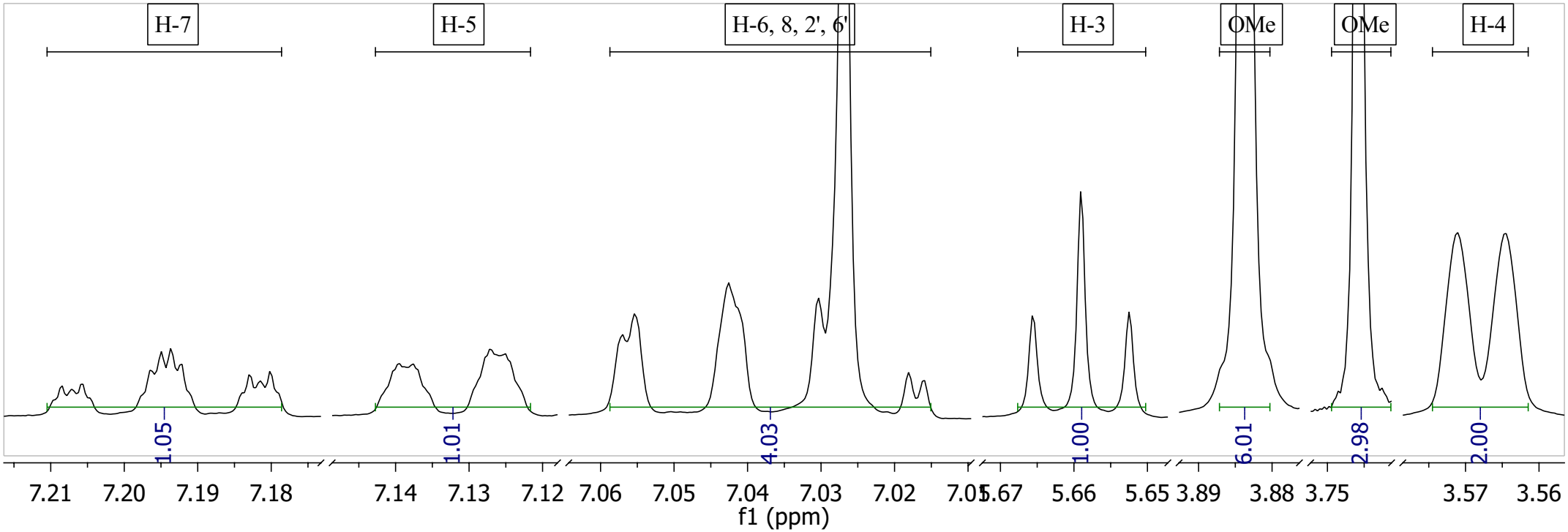
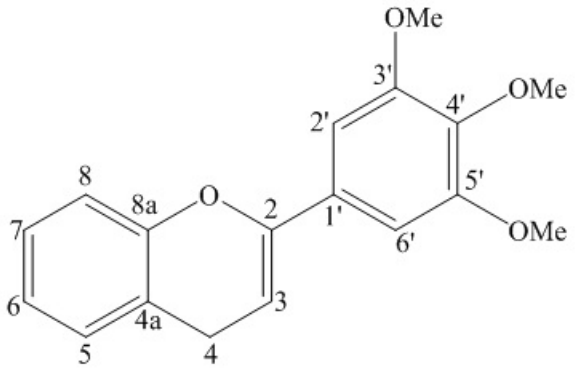
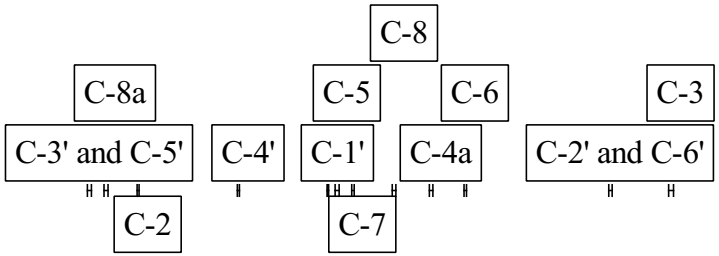


Plate 35b, ^{13}C NMR (151 MHz, Acetone-d_6) : 3',4',5'-Trimethoxyflav-2-ene (**615**)

δ 154.41 (C-3' and C-5'), 152.84 (C-8a), 149.61 (C-2), 139.74 (C-4'), 130.94 (C-1'), 130.01 (C-5), 128.48 (C-7), 124.38 (C-8), 120.75 (C-4a), 117.40 (C-6), 103.12 (C-2' and C-6'), 97.15 (C-3), 60.68 (-O<u>Me</u>), 56.58 (-O<u>Me</u>), 24.92 (C-4)





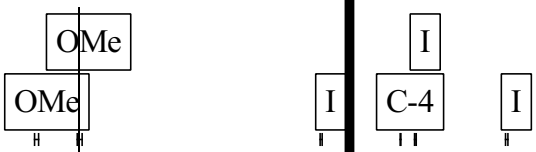


Plate 35c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 3',4',5'-Trimethoxyflav-2-ene (**615**)

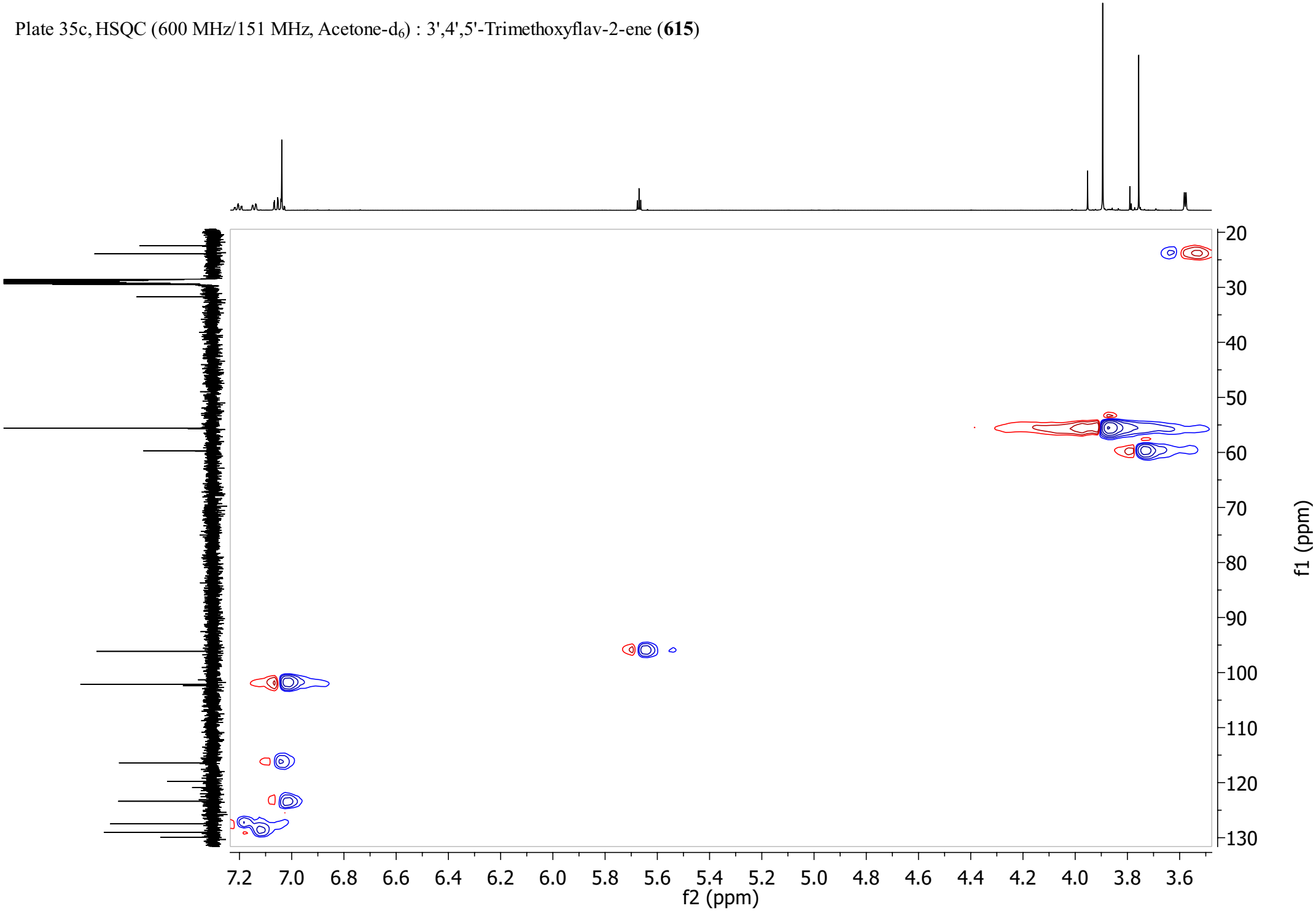


Plate 35d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 3',4',5'-Trimethoxyflav-2-ene (**615**)

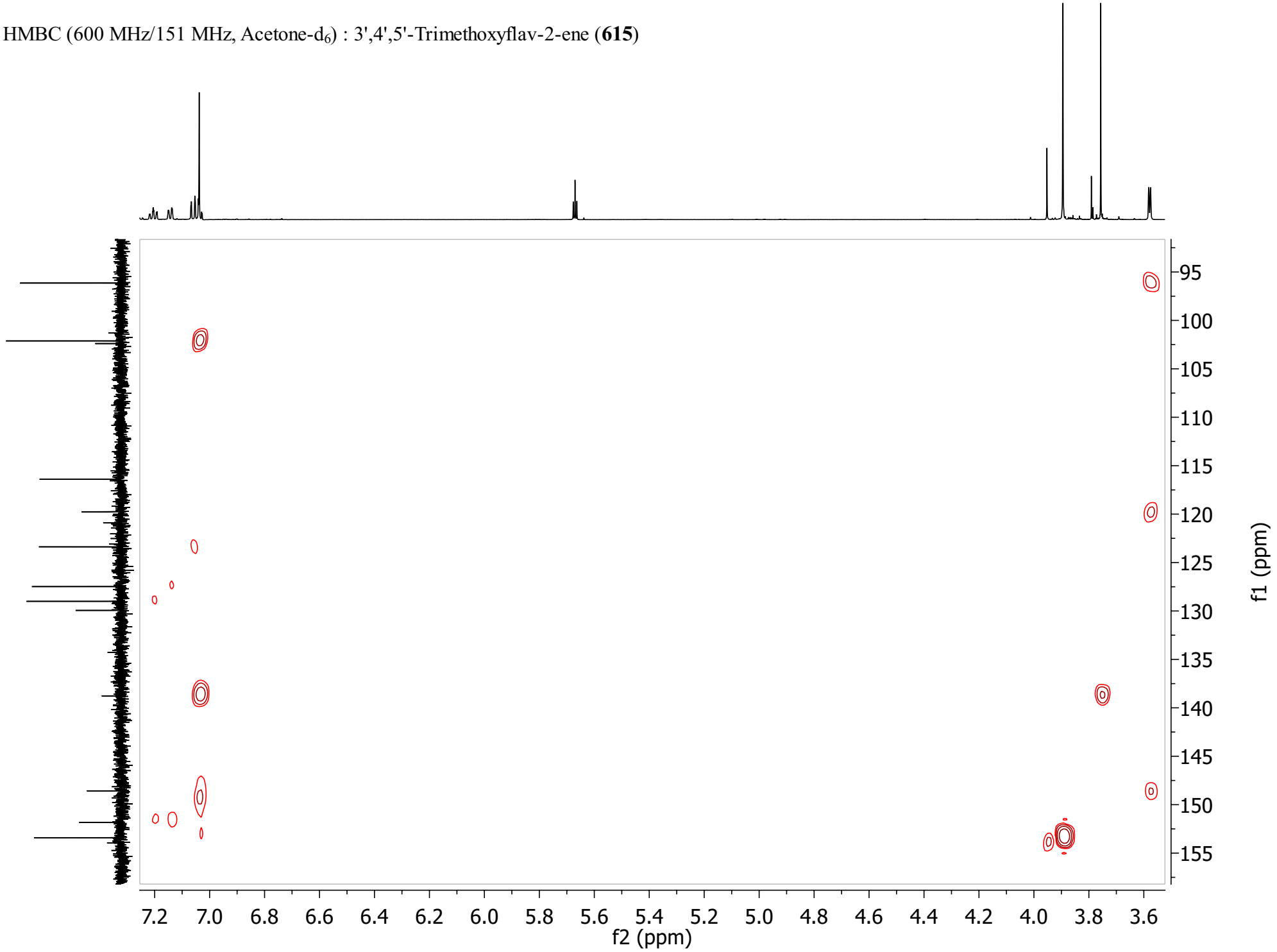


Plate 35e, DEPT (151 MHz, Acetone-d_6) : 3',4',5'-Trimethoxyflav-2-ene (**615**)

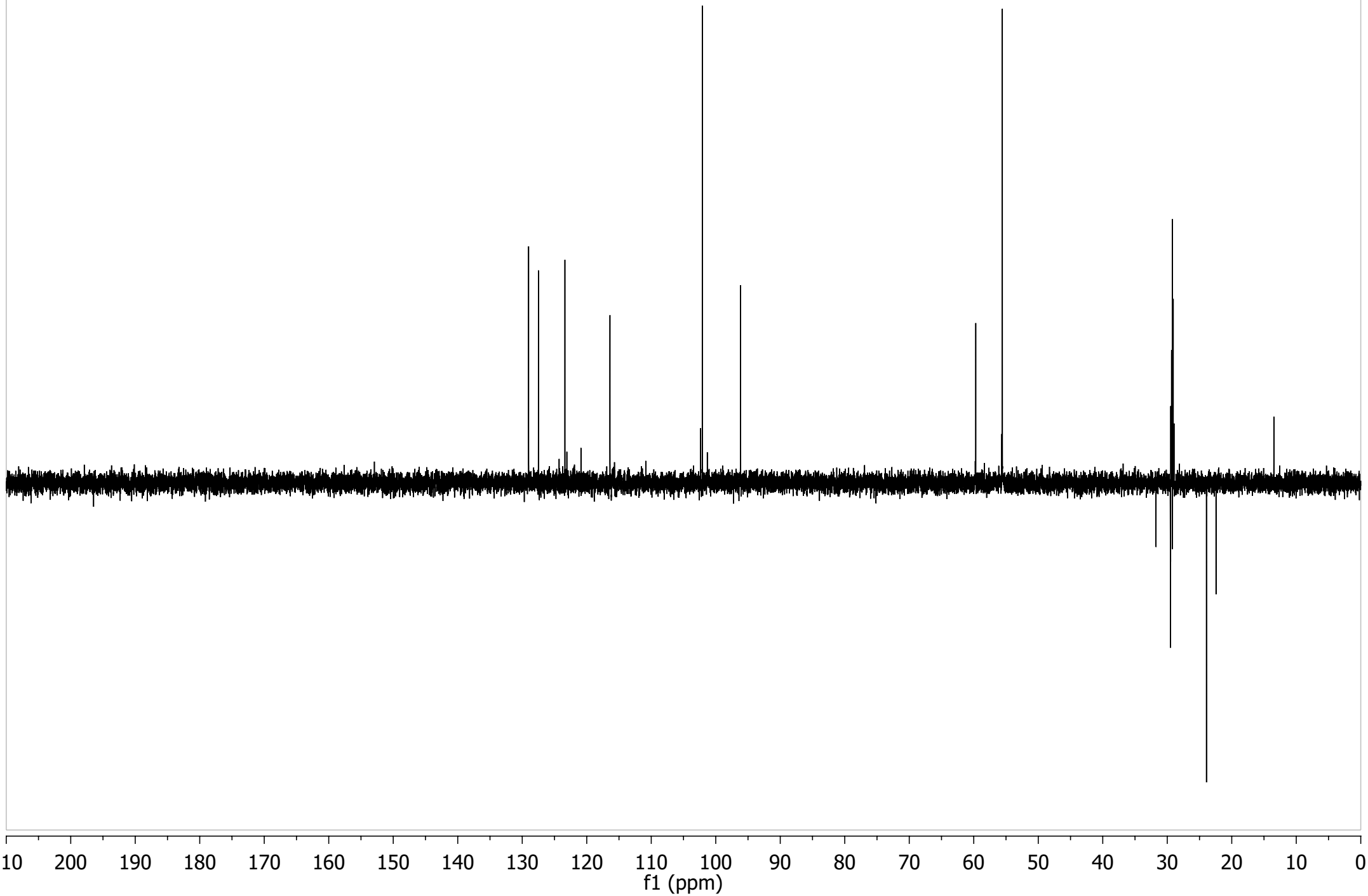
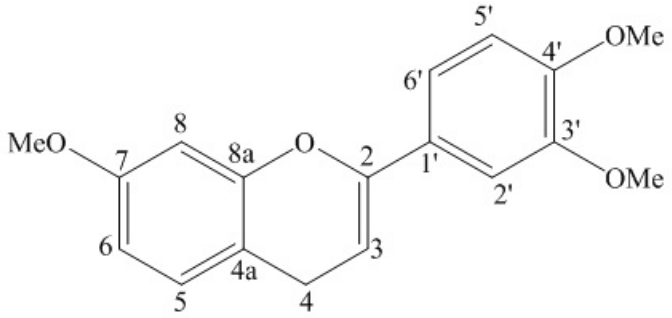
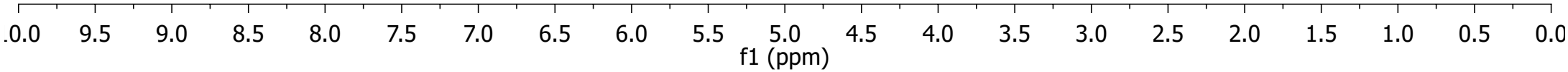


Plate 36a, ^{1}H NMR (600 MHz, Acetone-d_6) : 3',4',7-Trimethoxyflav-2-ene (**616**)

δ 7.29 – 7.27 (2H, m, H-2' and H-6'), 7.03 – 7.01 (1H, m, H-5), 6.97 (1H, d, *J* = 8.7 Hz, H-5'), 6.64 – 6.61 (2H, m, H-6 and H-8), 5.57 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.86 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.48 (2H, br. d, *J* = 3.9 Hz, H-4)





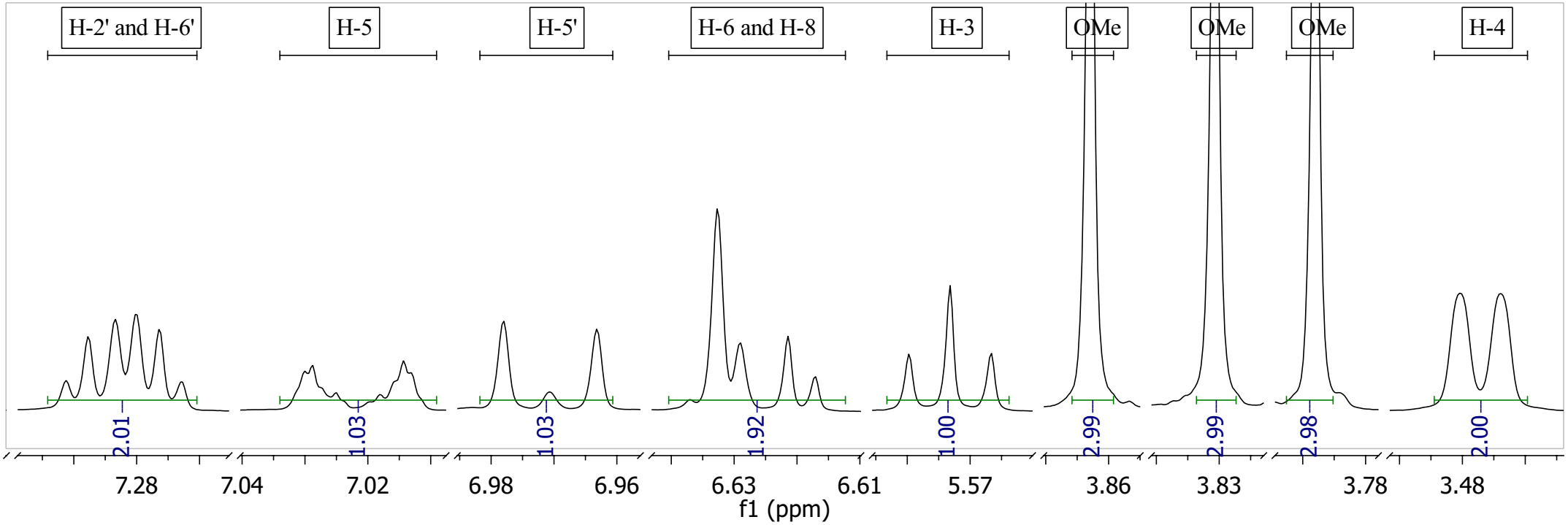
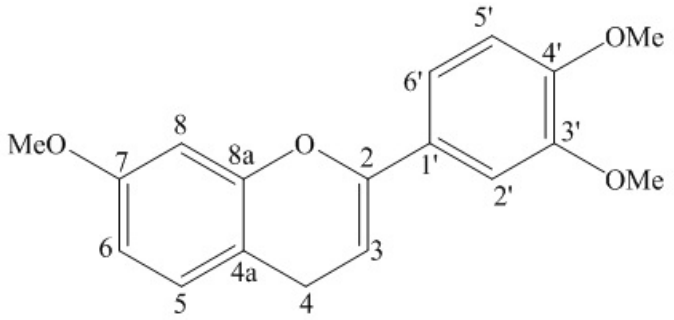


Plate 36b, ^{13}C NMR (151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyflav-2-ene (**616**)

δ 160.37 (C-7), 153.48 (C-8a), 150.85 (C-4'), 150.25 (C-3'), 149.36 (C-2), 130.44 (C-5), 128.24 (C-1'), 118.03 (C-2'/6'), 112.54 (C-4a), 112.40 (C-5'), 110.81 (C-6/8), 109.35 (C-2'/6'), 102.44 (C-6/8), 96.21 (C-3), 56.25 (-O<u>Me</u>), 56.17 (-O<u>Me</u>), 55.77 (-O<u>Me</u>), 24.27 (C-4)



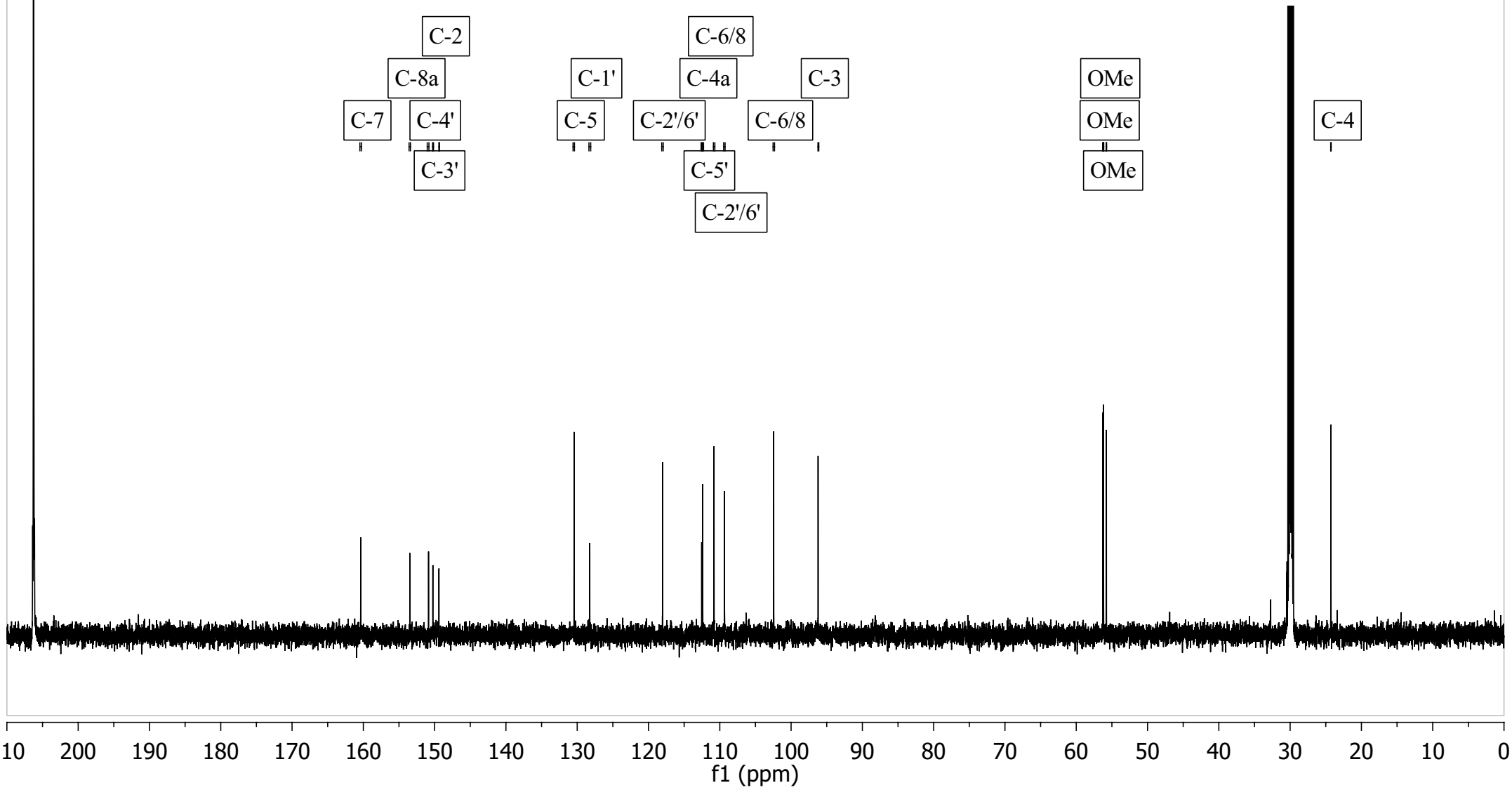


Plate 36c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyflav-2-ene (**616**)

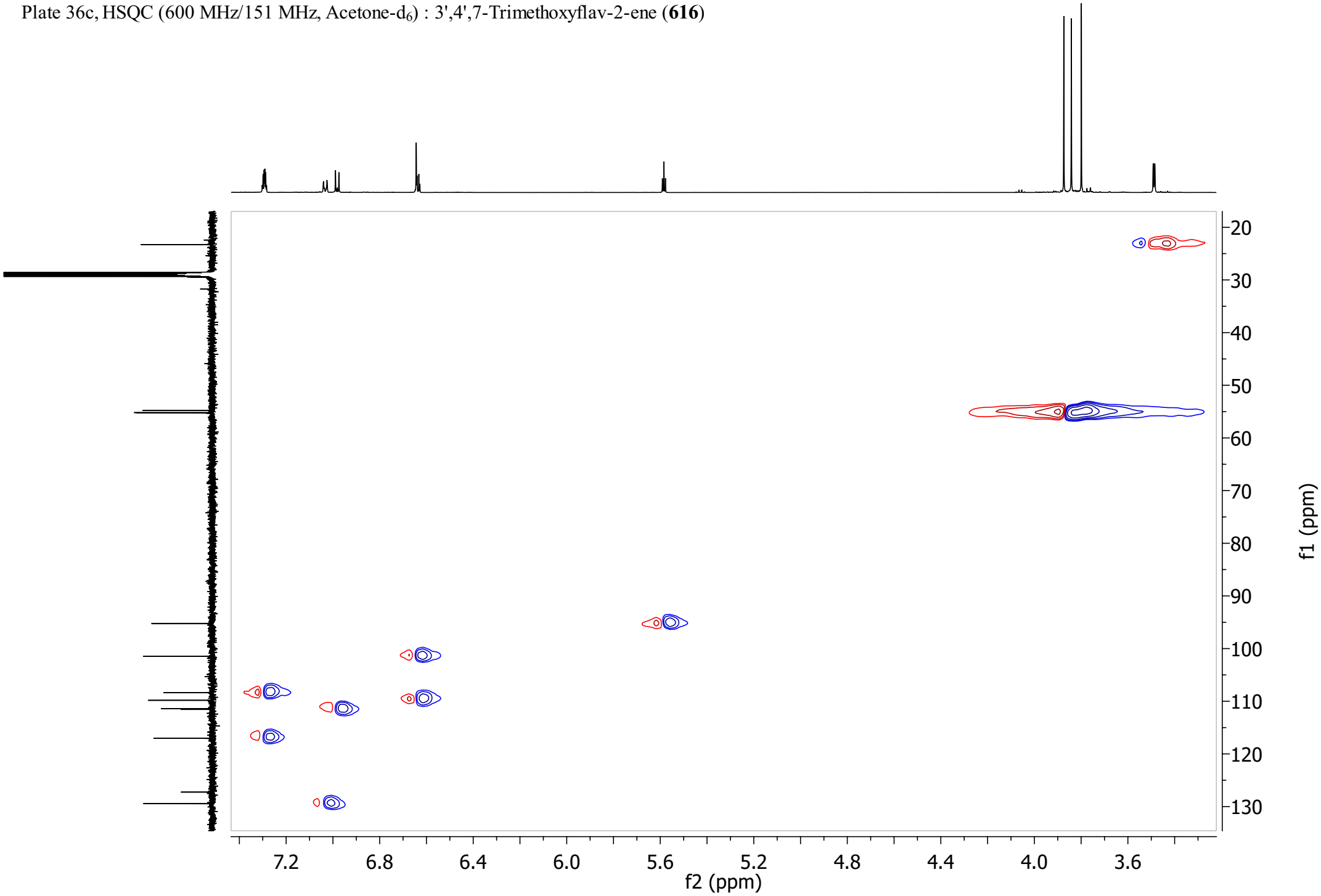


Plate 36d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyflav-2-ene (**616**)

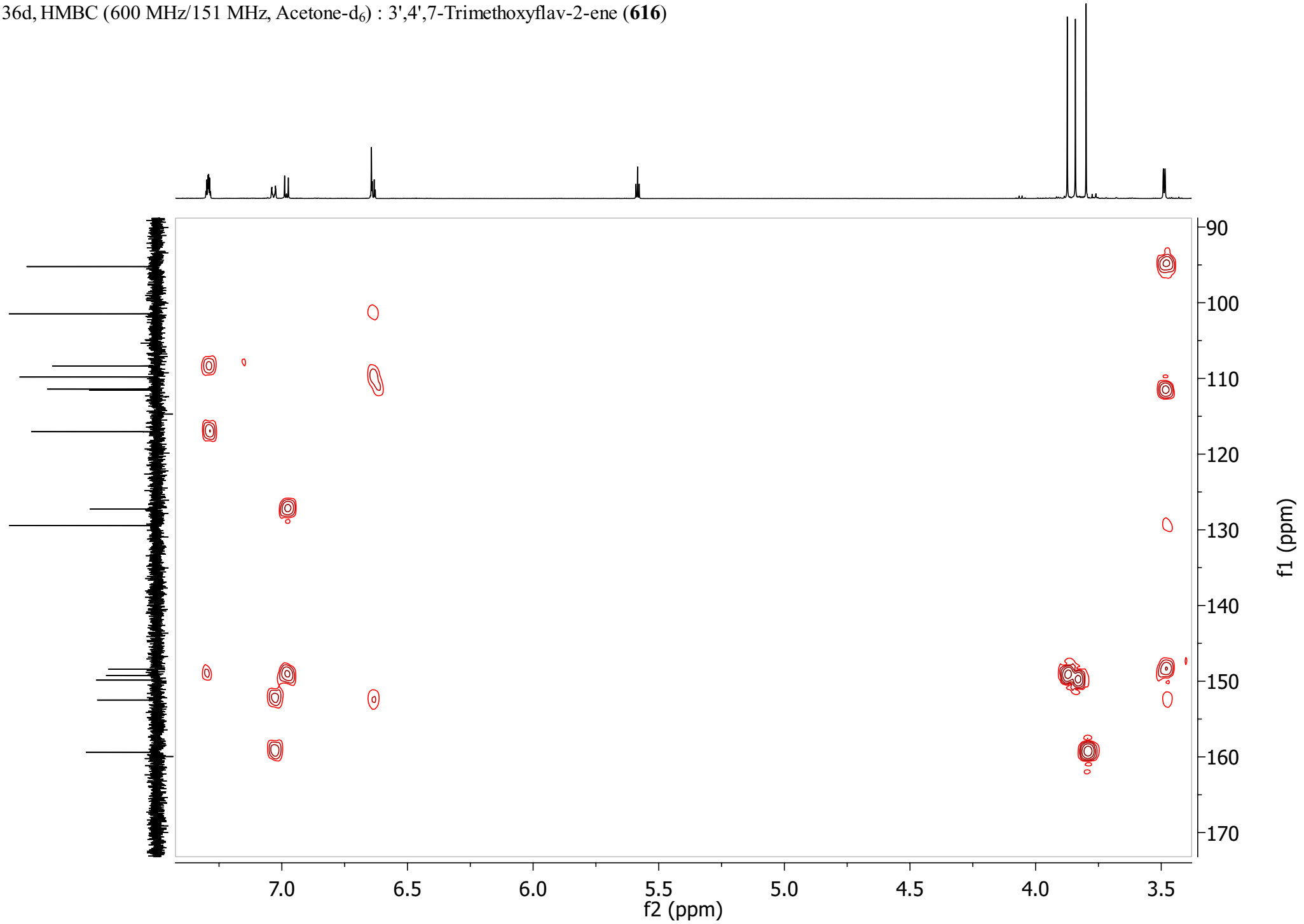
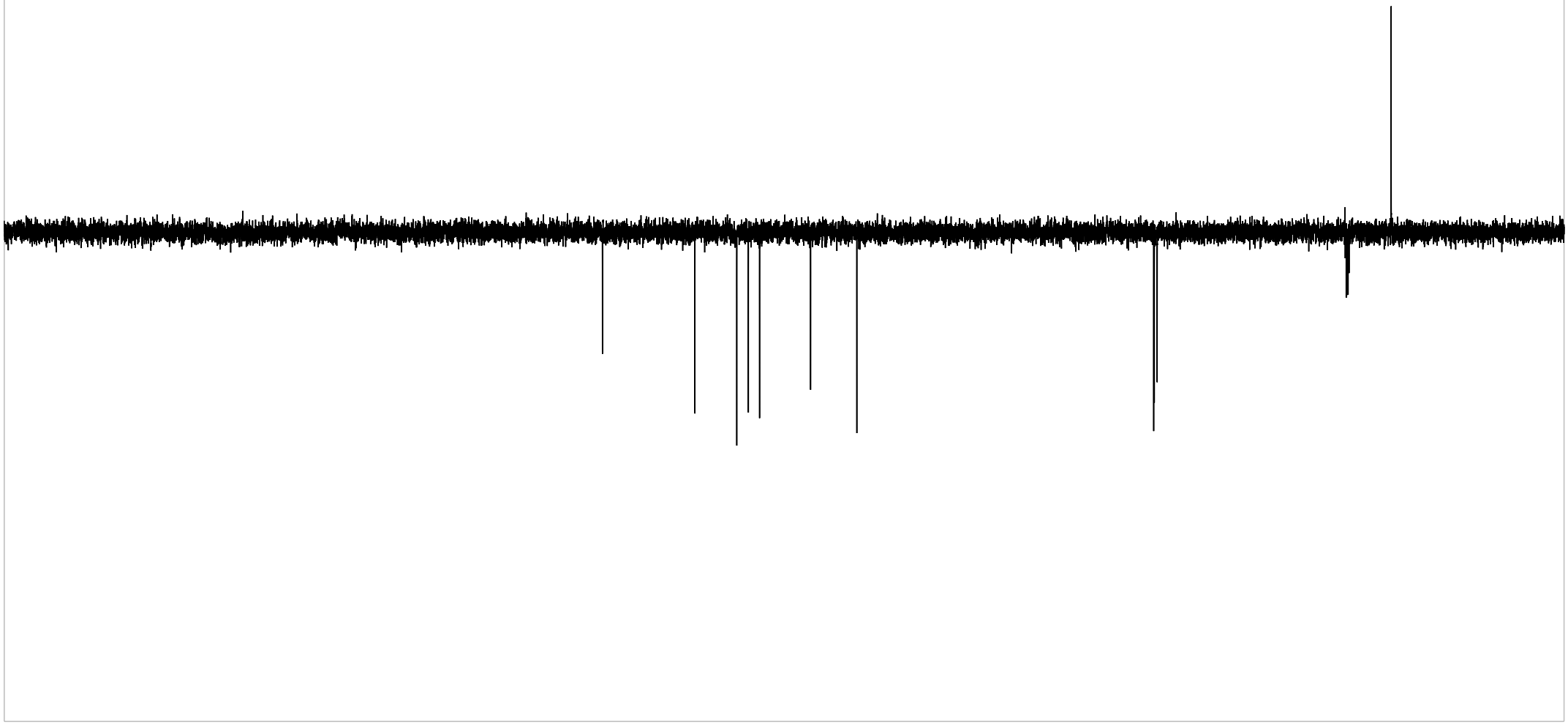


Plate 36e, DEPT (151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyflav-2-ene (**616**)

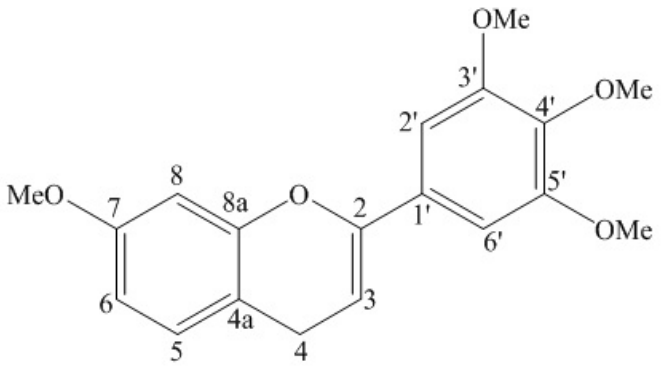


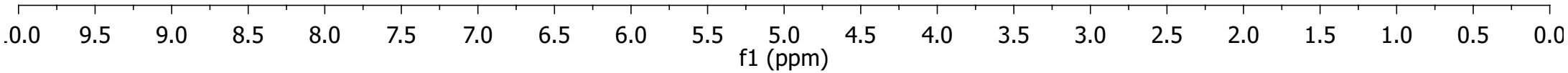
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 37a, ^{1}H NMR (600 MHz, Acetone-d_6) : 3',4',5',7-Tetramethoxyflav-2-ene (**617**)

δ 7.03 (1H, d, *J* = 8.3 Hz, H-5), 7.02 (2H, s, H-2' and H-6'), 6.65 (1H, d, *J* = 2.5 Hz, H-8), 6.63 (1H, dd, *J* = 8.3, 2.5 Hz, H-6), 5.65 (1H, dd, *J* = 3.9, 3.9 Hz, H-3), 3.88 (3H, s, -OMe), 3.78 (3H, s, -OMe), 3.75 (3H, s, -OMe), 3.48 (2H, br. d, *J* = 3.9 Hz, H-4)





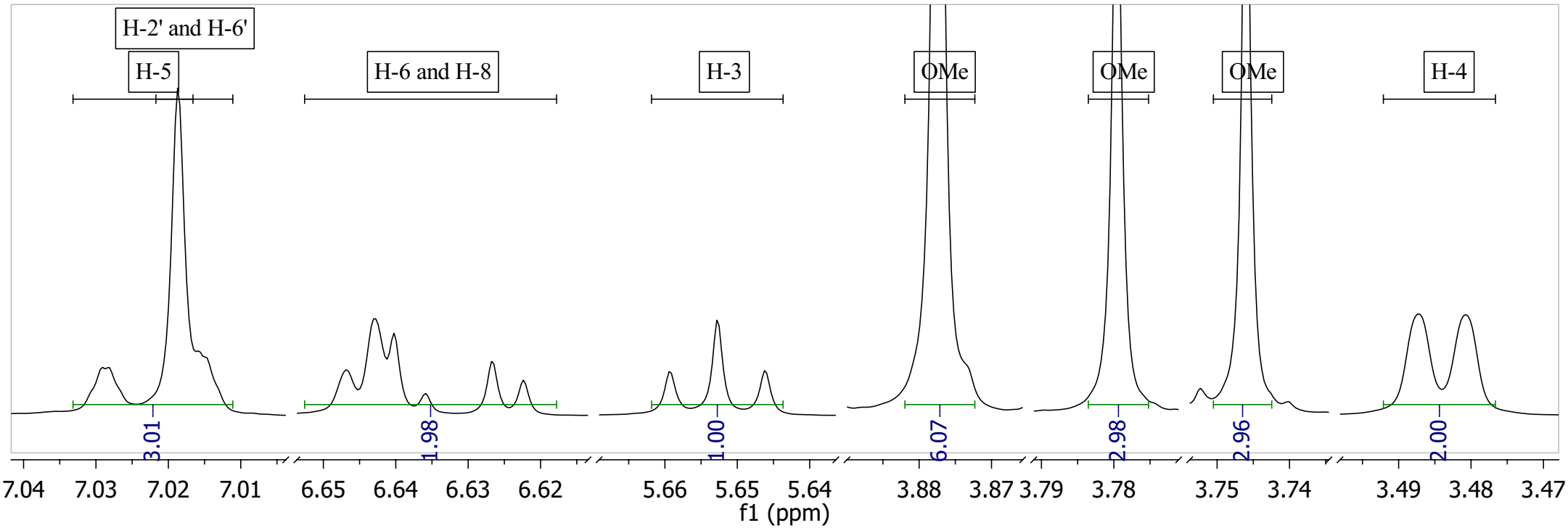
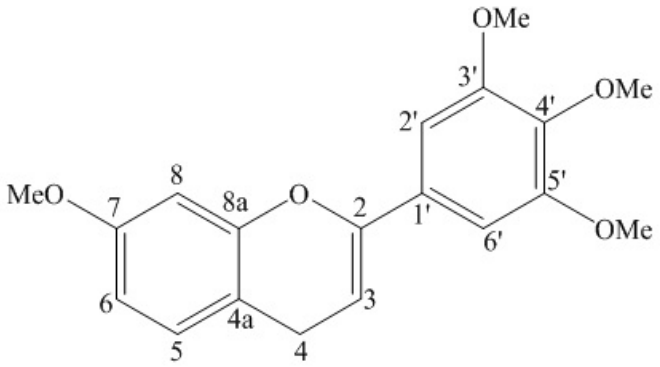


Plate 37b, ^{13}C NMR (151 MHz, Acetone-d_6) : 3',4',5',7-Tetramethoxyflav-2-ene (**617**)

δ 160.27 (C-4'/7), 154.28 (C-3' and C-5'), 153.29 (C-8a), 149.22 (C-2), 139.62 (C-4'/7), 130.84 (C-1'), 130.34 (C-5), 112.32 (C-4a), 110.75 (C-6), 103.01 (C-2' and C-6'), 102.42 (C-8), 97.42 (C-3), 60.59 (-OMe), 56.48 (-OMe), 55.68 (-OMe), 24.20 (C-4)



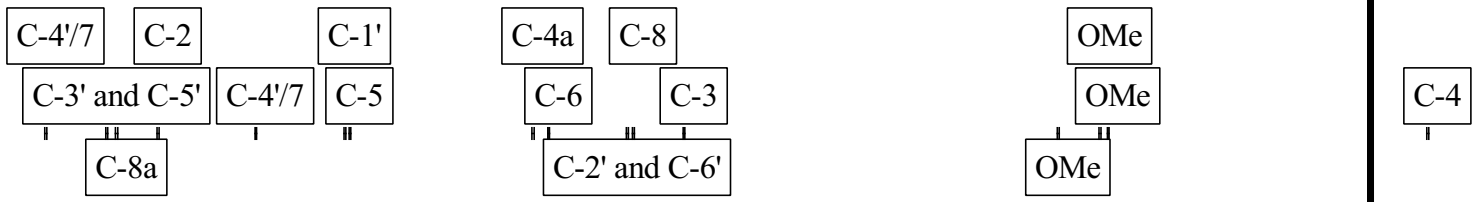


Plate 37c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 3',4',5',7-Tetramethoxyflav-2-ene (**617**)

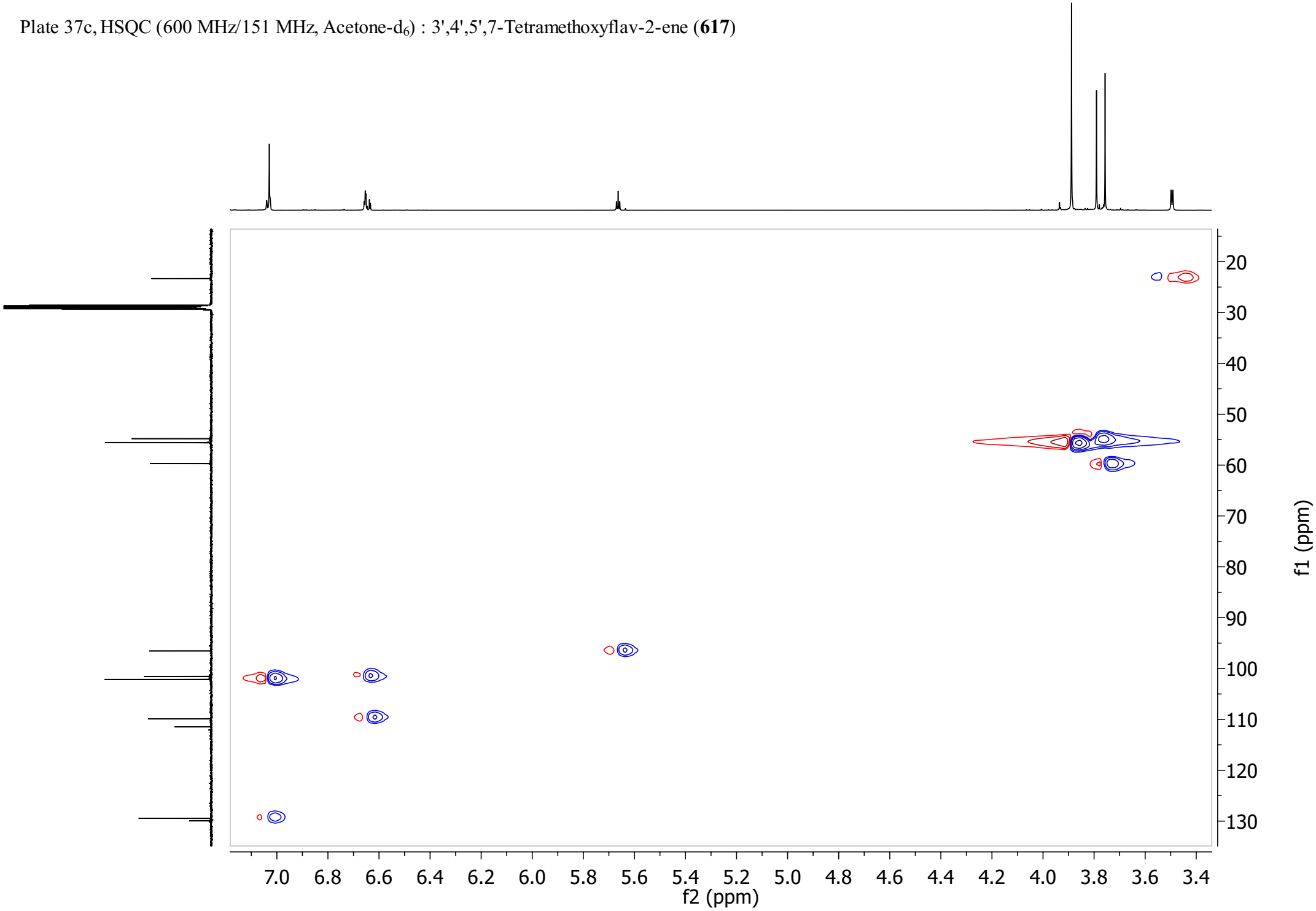


Plate 37d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 3',4',5',7-Tetramethoxyflav-2-ene (**617**)

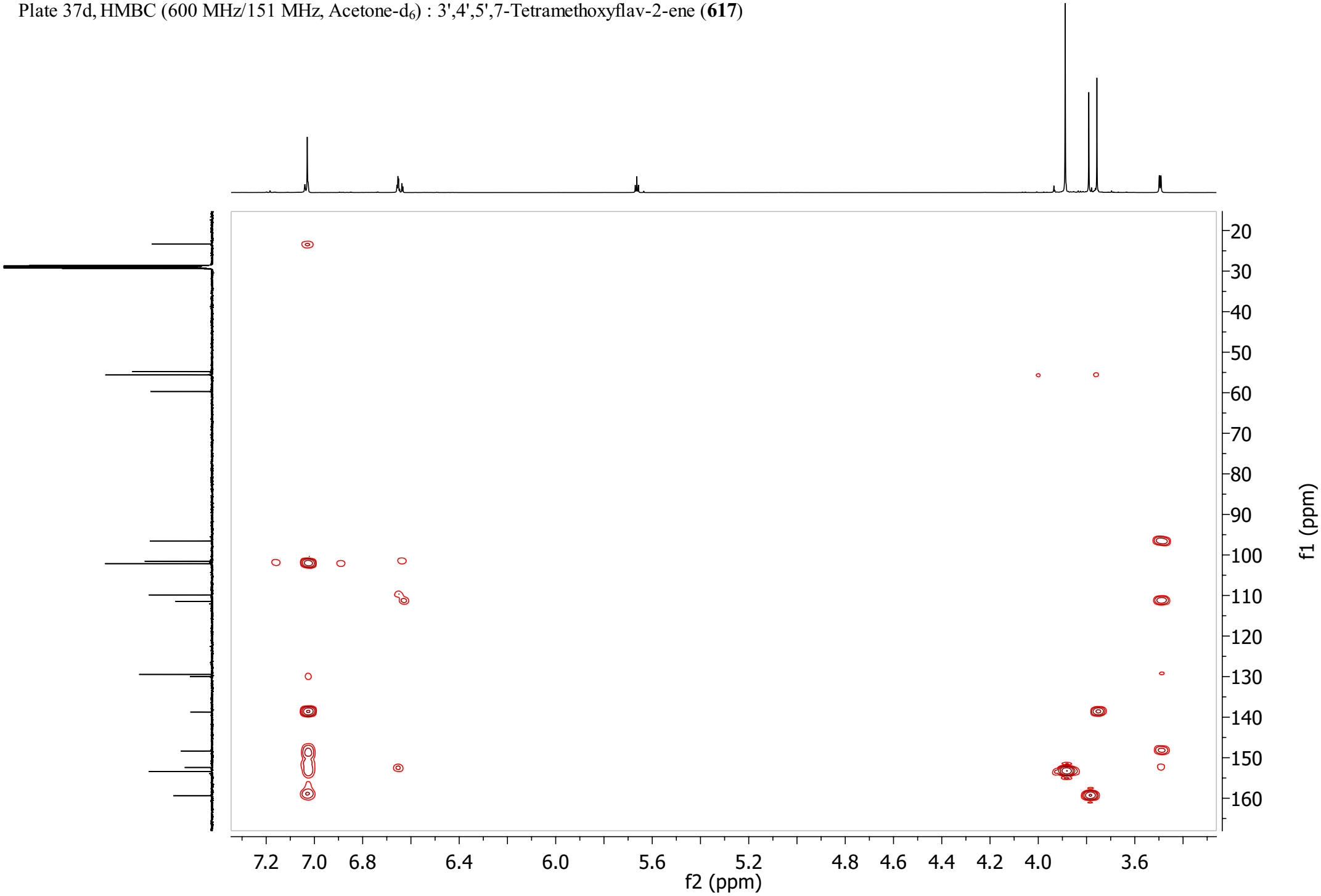


Plate 37e, DEPT (151 MHz, Acetone-d_6) : 3',4',5',7-Tetramethoxyflav-2-ene (**617**)

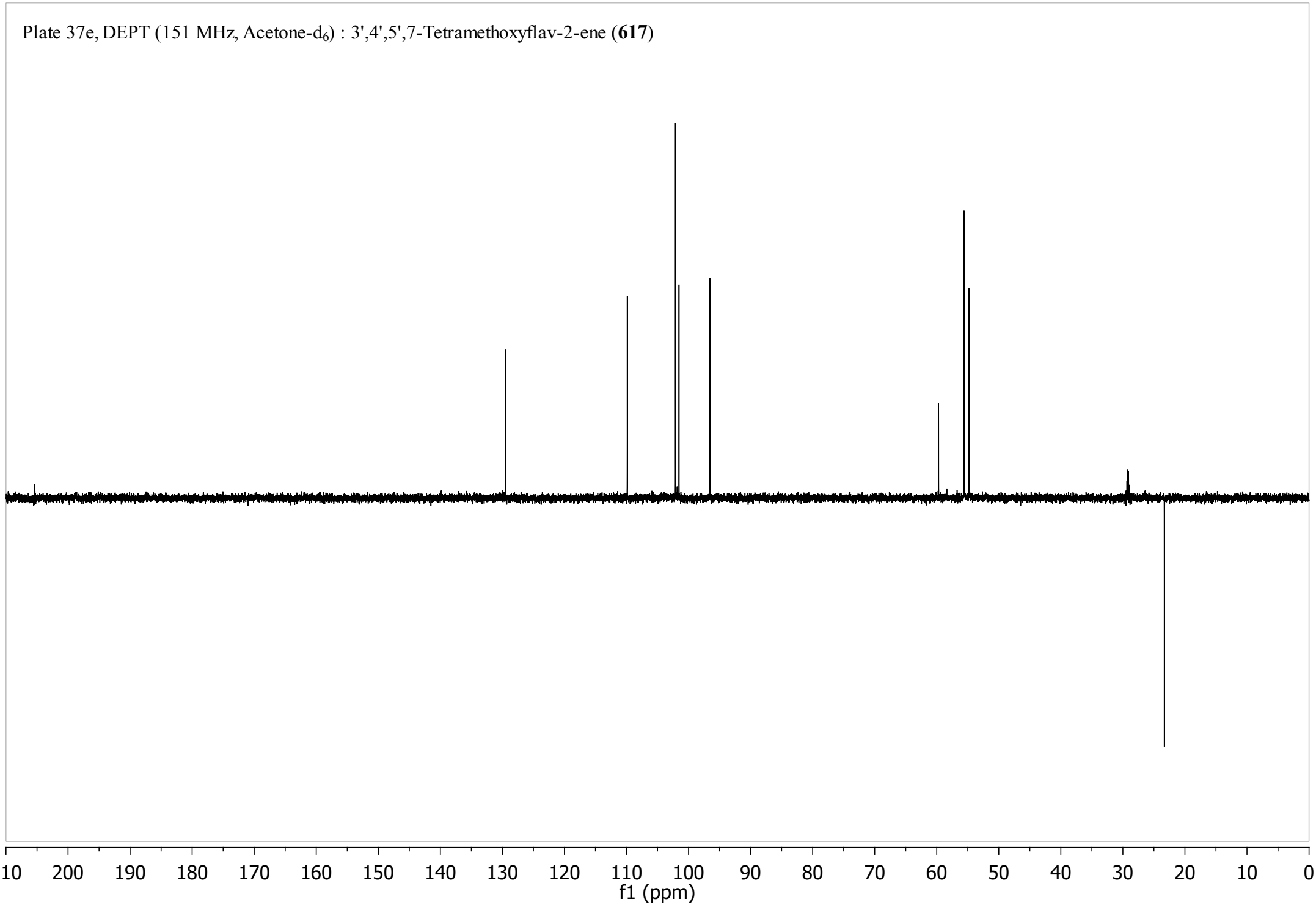
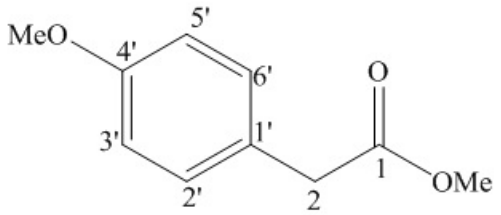


Plate 38a, ^{1}H NMR (300 MHz, $CDCl_3$) : Methyl 4-methoxyphenyl acetate (**670**)

δ 7.20 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.86 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 3.79 (3H, s, -OMe), 3.68 (3H, s, -COOMe), 3.57 (2H, s, H-2)



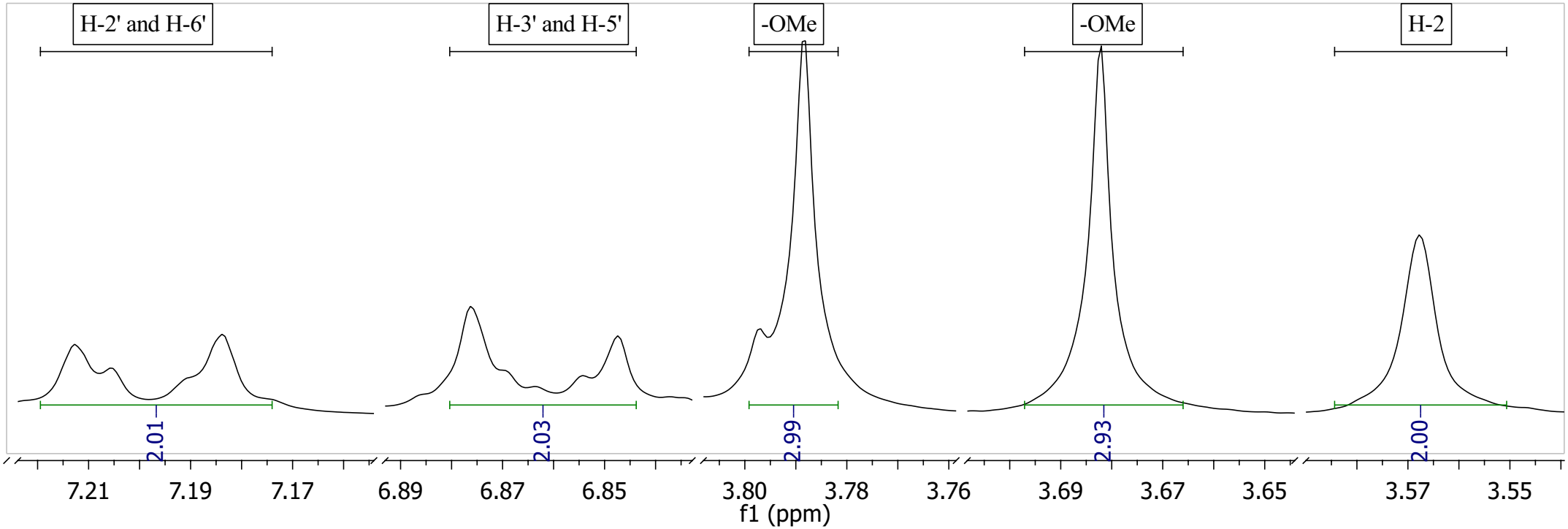
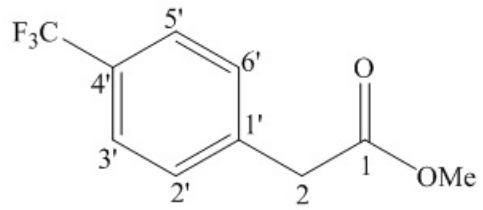
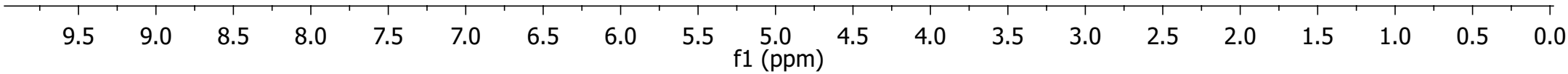


Plate 39a, ^{1}H NMR (300 MHz, $CDCl_3$) : Methyl 4-trifluoromethylphenyl acetate (**671**)

δ 7.59 (2H, d, *J* = 8.2 Hz, H-3' and H-5'), 7.40 (2H, d, *J* = 8.2 Hz, H-2' and H-6'), 3.71 (3H, s, -COOMe), 3.69 (2H, s, H-2)





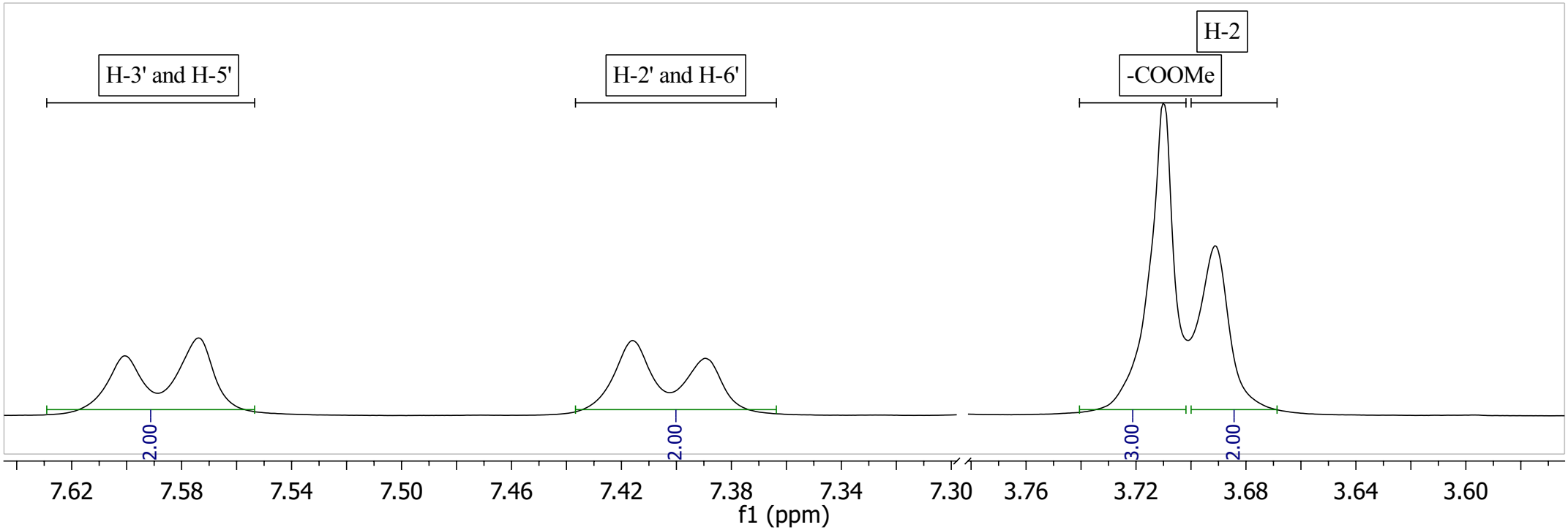
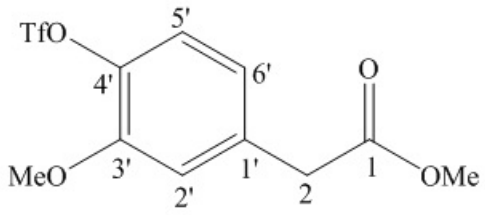


Plate 40a, ^{1}H NMR (600 MHz, $CDCl_3$) : Methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate (**672**)

δ 7.16 (1H, d, *J* = 8.3 Hz, H-5'), 6.98 (1H, d, *J* = 2.0 Hz, H-2'), 6.88 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 3.91 (3H, s, -OMe), 3.72 (3H, s, -COOMe), 3.63 (2H, s, H-2)



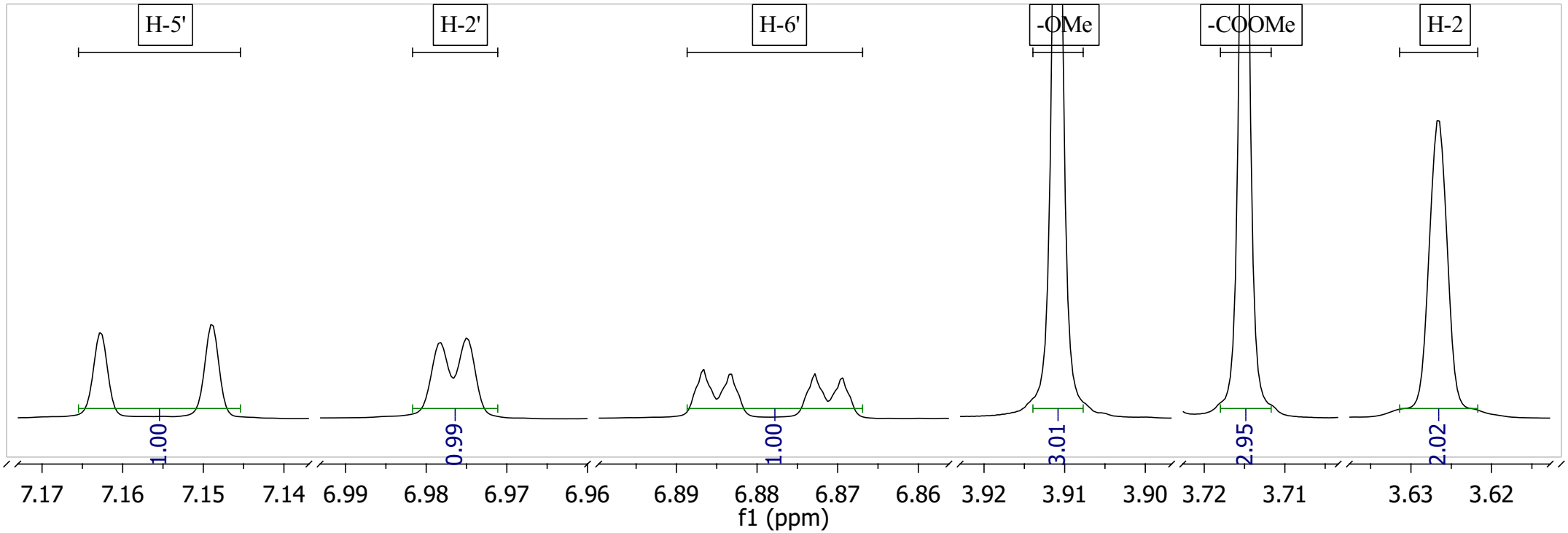
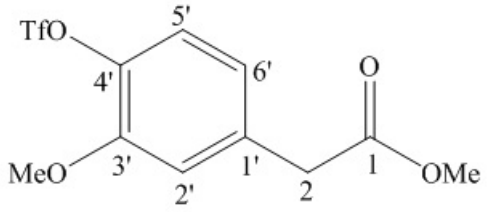
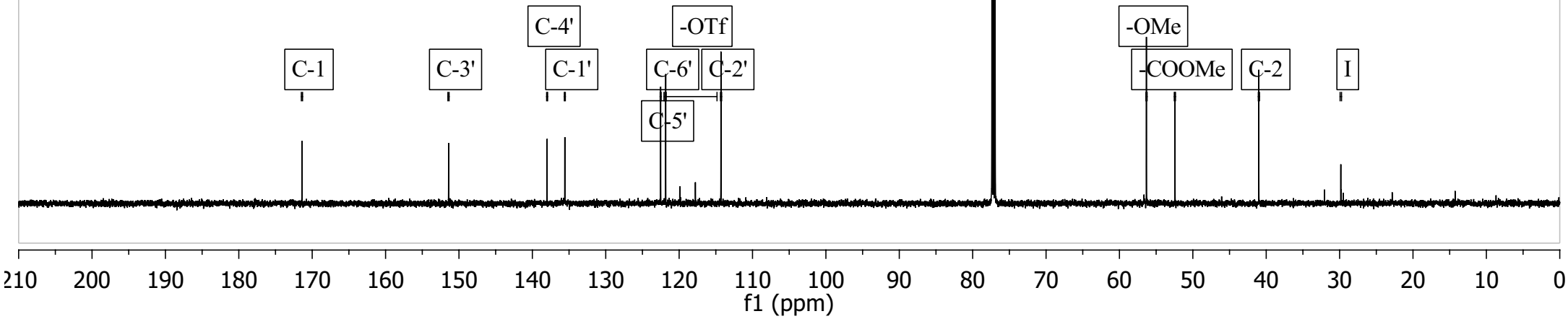


Plate 40b, ^{13}C NMR (151 MHz, $CDCl_3$) : Methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate (**672**)

δ 171.38 (C-1), 151.41 (C-3'), 137.99 (C-4'), 135.57 (C-1'), 122.52 (C-5'), 121.83 (C-6'), 117.78 (q, *J* = 319.9 Hz, -$OSO_2\underline{C}F_3$), 114.30 (C-2'), 56.33 (-O<u>Me</u>), 52.43 (-COO<u>Me</u>), 41.01 (C-2)





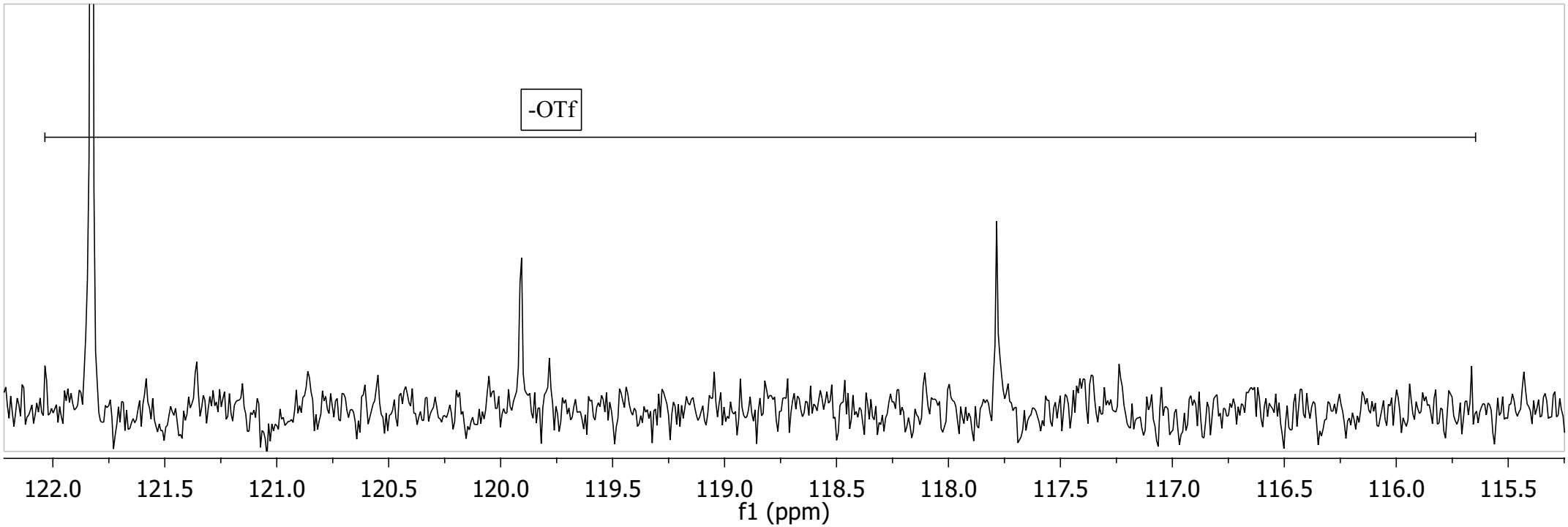


Plate 40c, HSQC (600 MHz/151 MHz, $CDCl_3$) : Methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate (**672**)

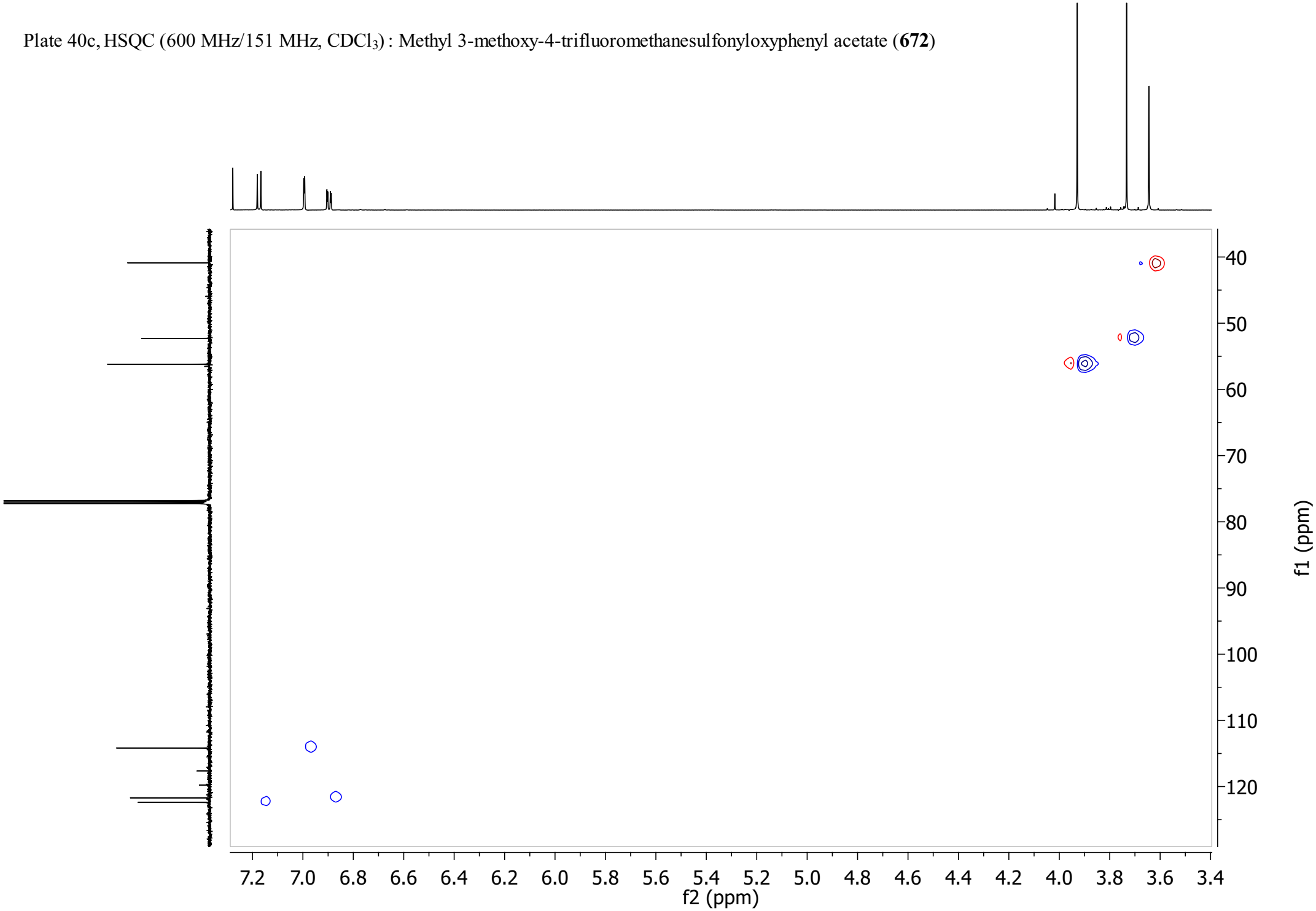


Plate 40d, HMBC (600 MHz/151 MHz, $CDCl_3$) : Methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate (**672**)

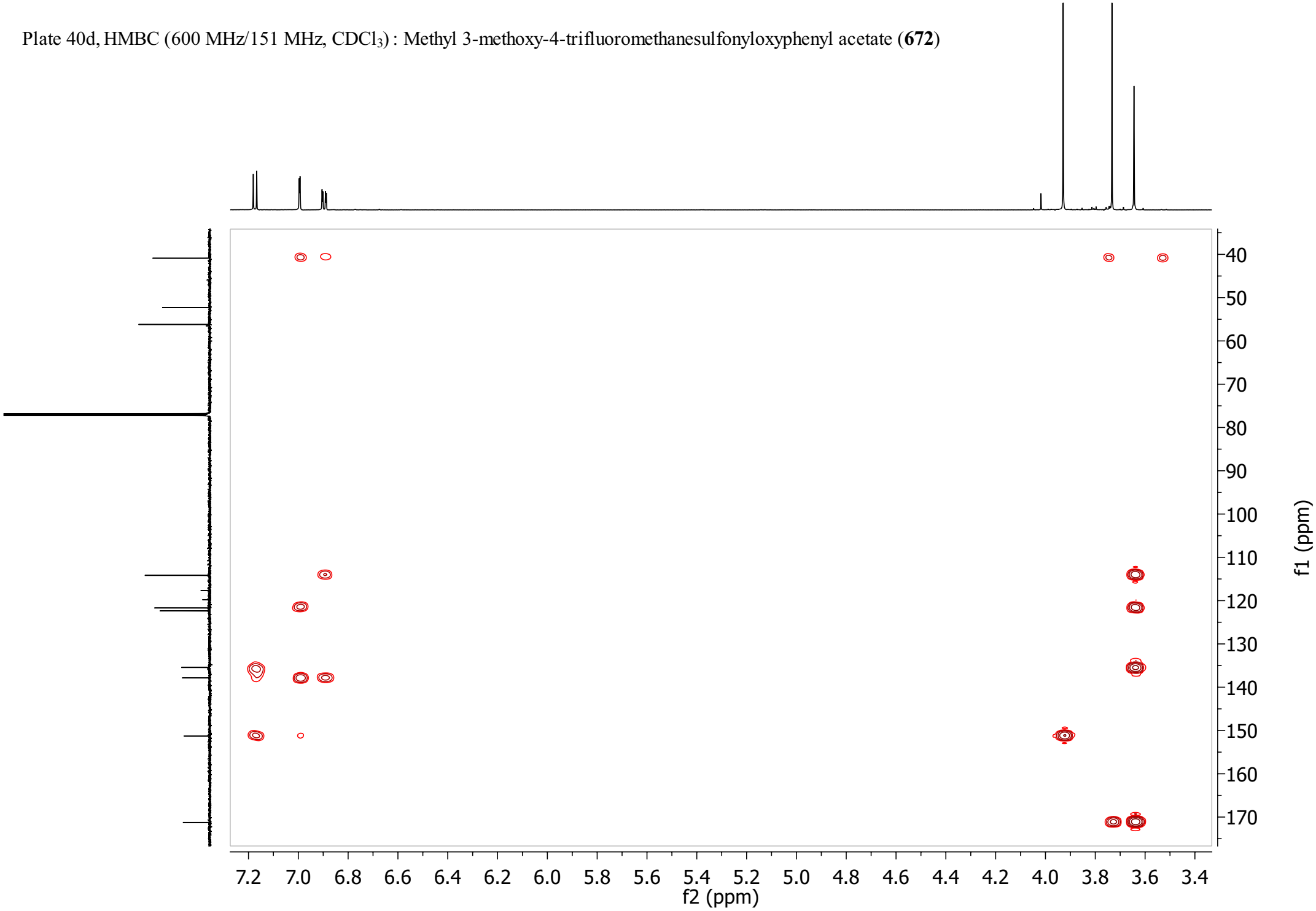
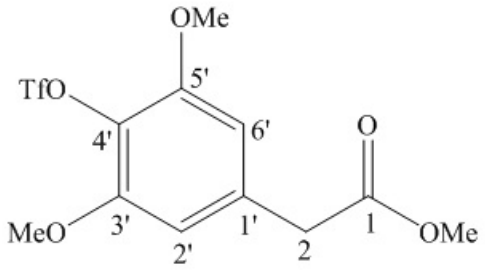
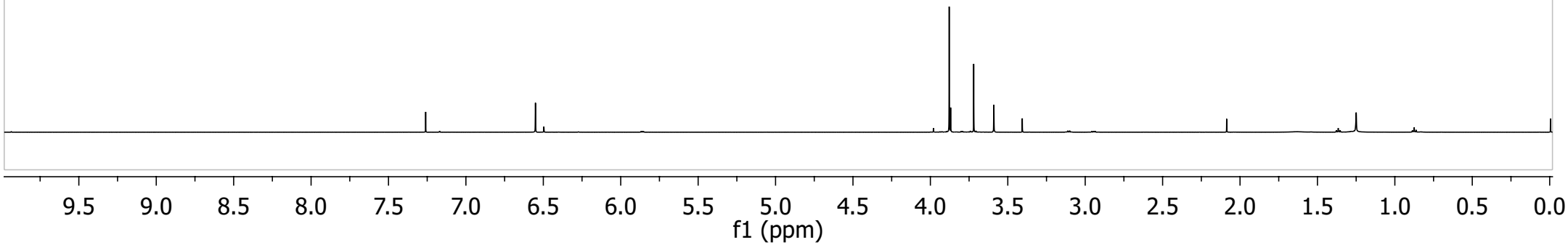


Plate 41a, ^{1}H NMR (600 MHz, $CDCl_3$) : Methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate (**673**)

δ 6.55 (2H, s, H-2' and H-6'), 3.88 (6H, s, -O<u>Me</u>), 3.72 (3H, s, -COO<u>Me</u>), 3.59 (2H, s, H-2)





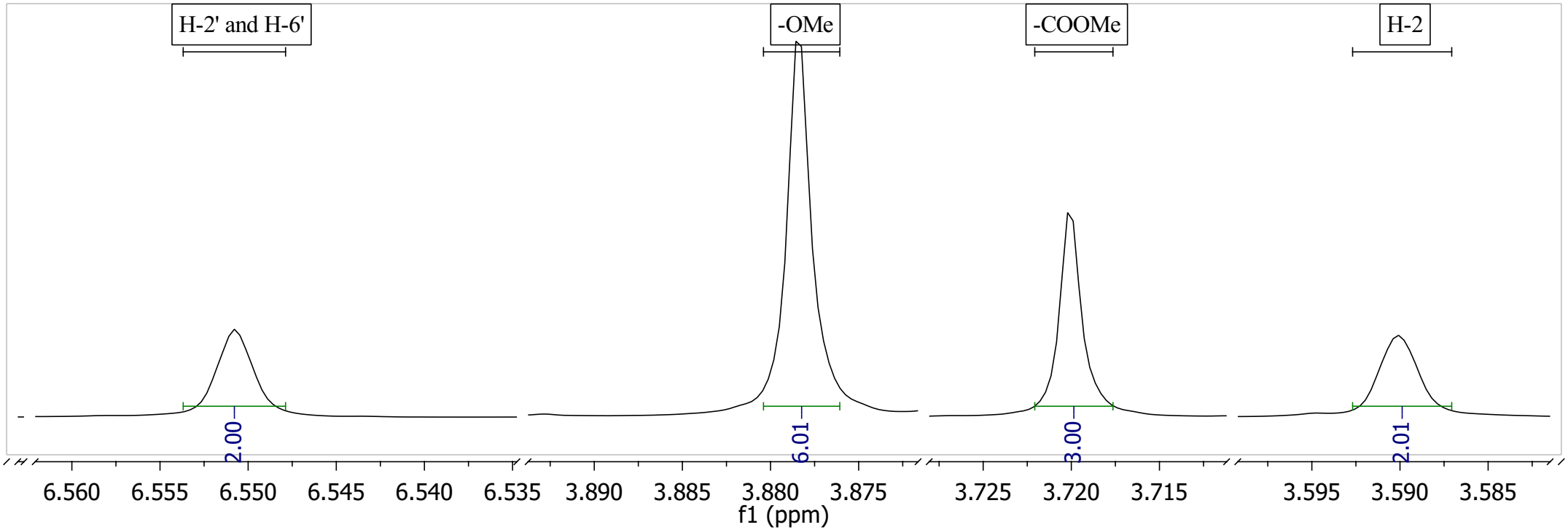
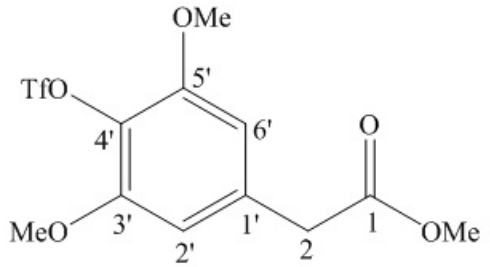
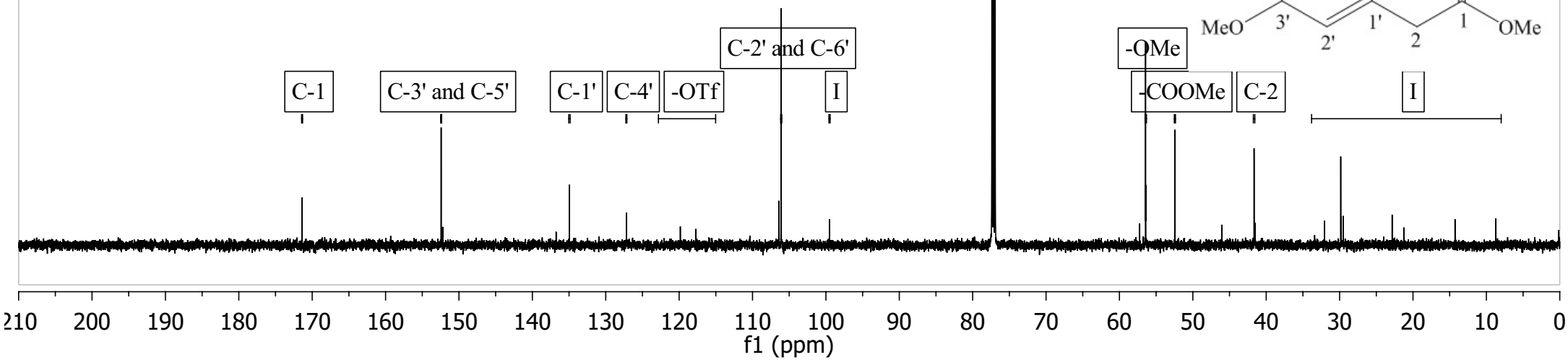


Plate 41b, ^{13}C NMR (151 MHz, $CDCl_3$) : Methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate (**673**)

δ 171.37 (C-1), 152.43 (C-3' and C-5'), 134.94 (C-1'), 127.19 (C-4'), 118.93 (q, J = 320.2 Hz, -$OSO_2\underline{C}F_3$), 106.10 (C-2' and C-6'), 56.43 (-O<u>Me</u>), 52.46 (-COO<u>Me</u>), 41.65 (C-2)





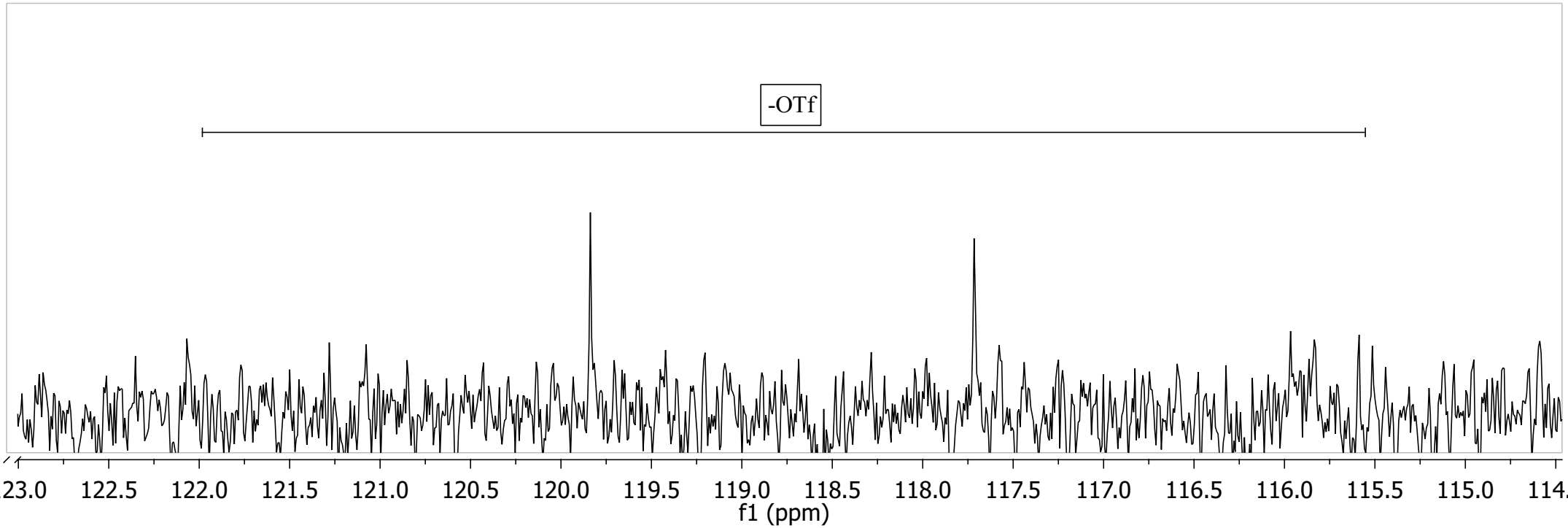


Plate 41c, HSQC (600 MHz/151 MHz, $CDCl_3$) : Methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate (**673**)

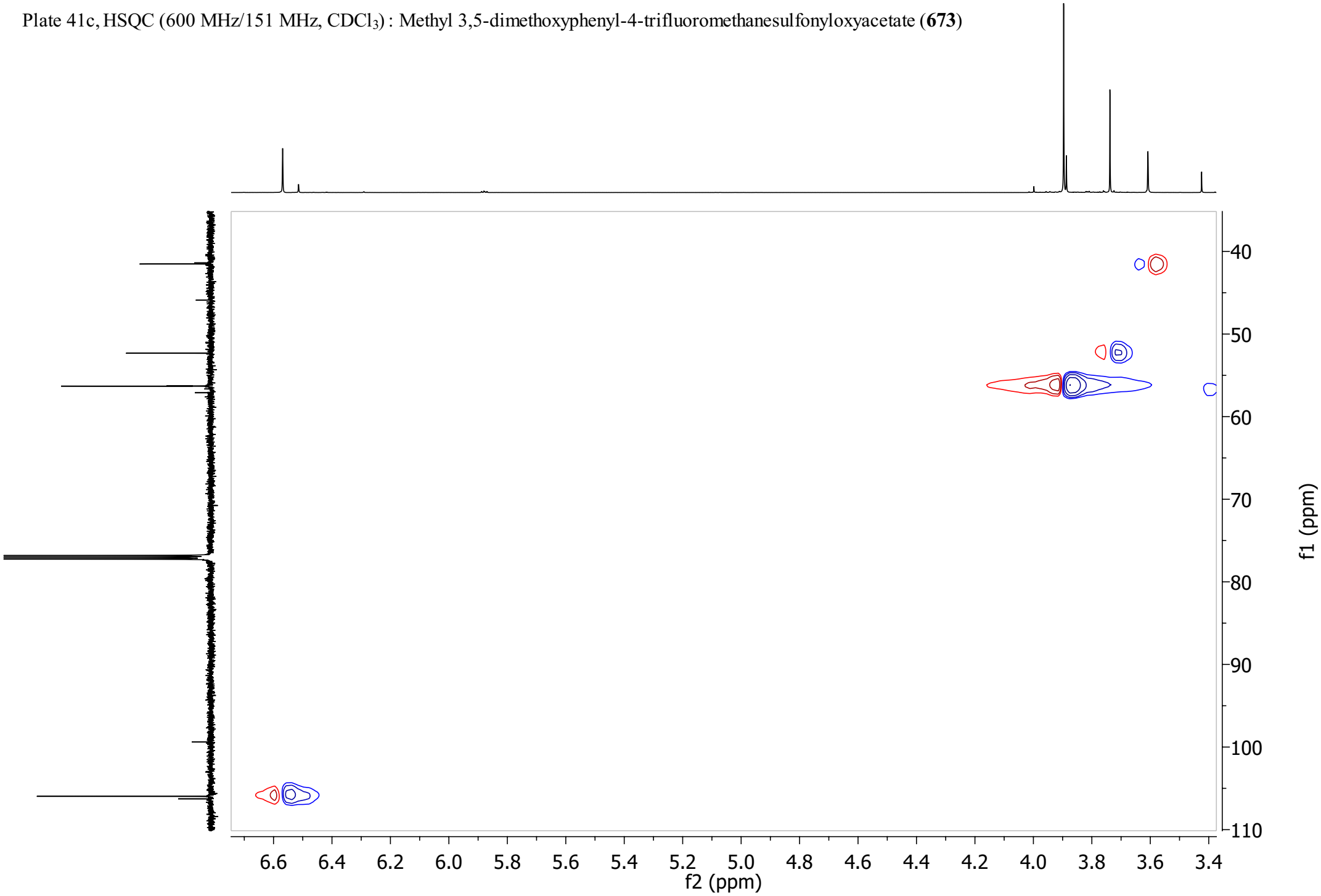


Plate 41d, HMBC (600 MHz/151 MHz, $CDCl_3$) : Methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate (**673**)

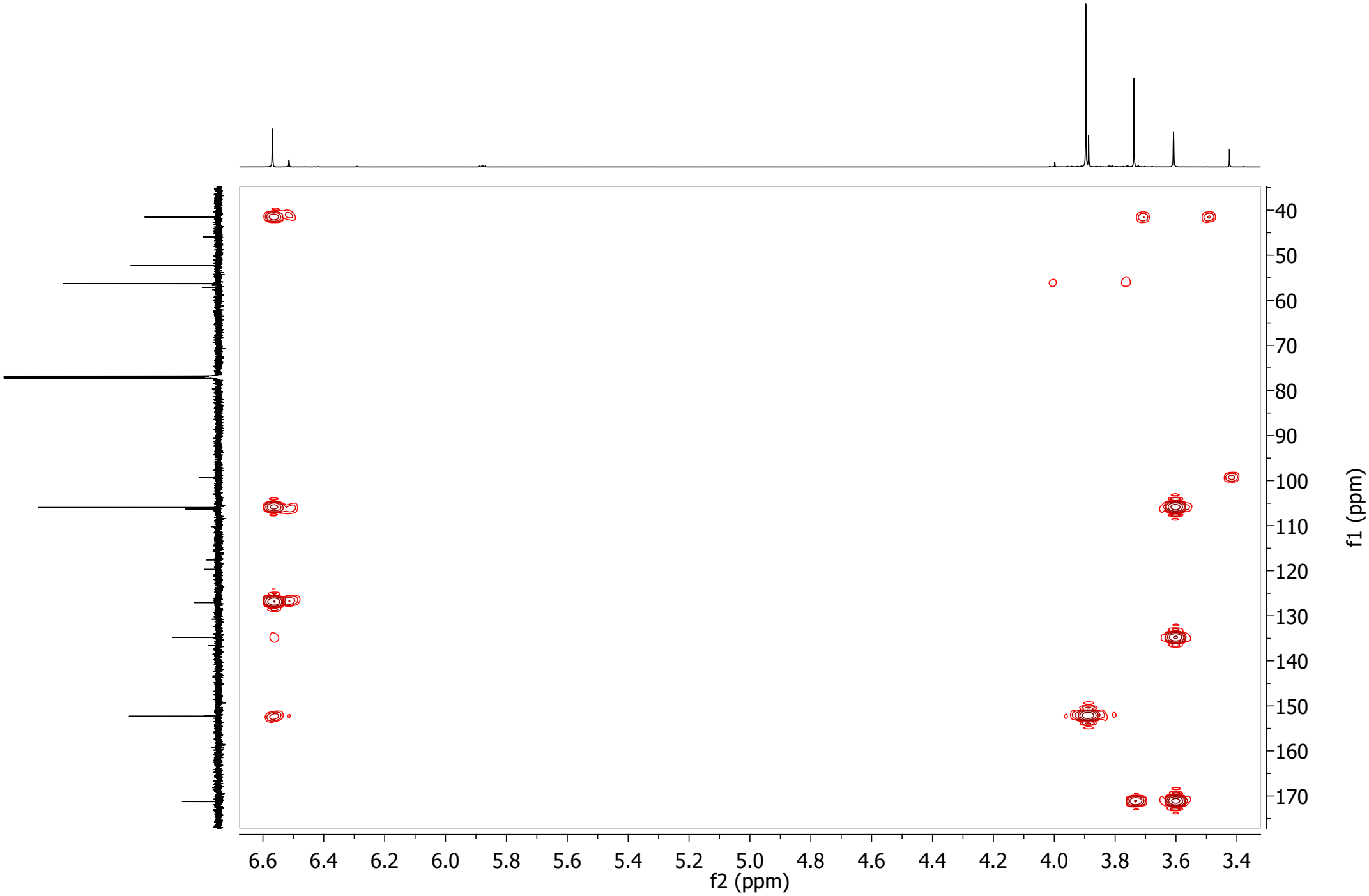
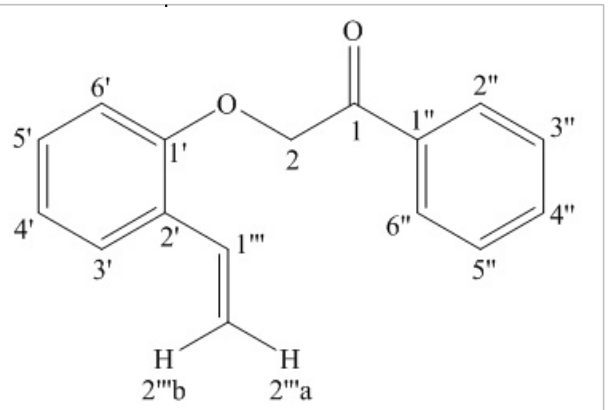
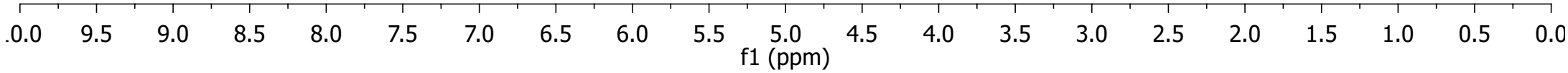


Plate 42a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-Phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**)

δ 8.10 – 8.08 (2H, m, H-2'' and H-6''), 7.70 – 7.67 (1H, m, H-4''), 7.59 – 7.55 (2H, m, H-3'' and H-5''), 7.54 (1H, dd, *J* = 7.7, 1.7 Hz, H-3'), 7.23 – 7.20 (1H, m, H-5'), 7.16 (1H, dd, *J* = 17.8, 11.3 Hz, H-1'''), 7.00 (1H, dd, *J* = 8.3, 1.0 Hz, H-6'), 6.97 – 6.93 (1H, m, H-4'), 5.88 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.57 (2H, s, H-2), 5.25 (1H, dd, *J* = 11.3, 1.6 Hz, H-2'''a)





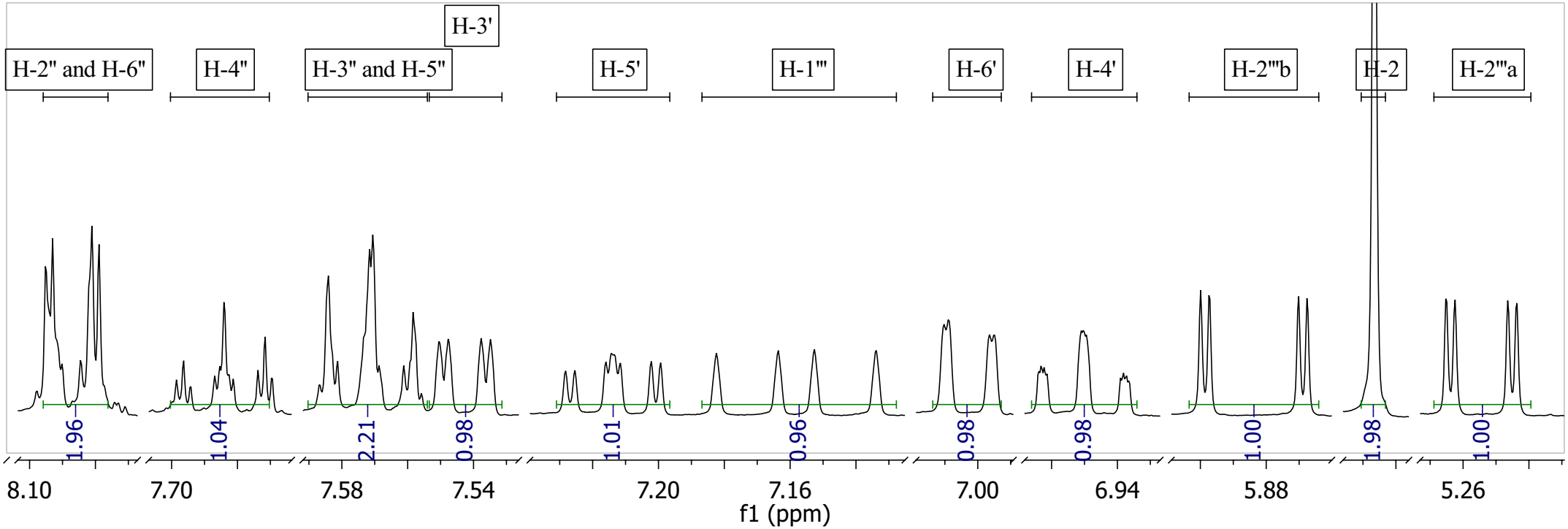
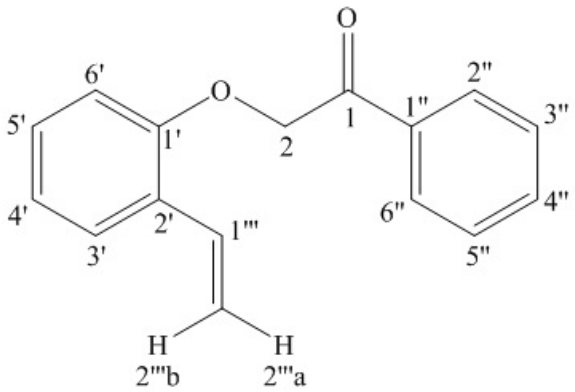


Plate 42b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-Phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**)

δ 194.76 (C-1), 156.45 (C-1'), 135.84 (C-1''), 134.48 (C-4''), 132.65 (C-1'''), 129.70 (C-5'), 129.66 (C-3'' and C-5''), 128.81 (C-2'' and C-6''), 127.56 (C-2'), 127.36 (C-3'), 121.95 (C-4'), 114.82 (C-2'''), 113.31 (C-6'), 71.49 (C-2)



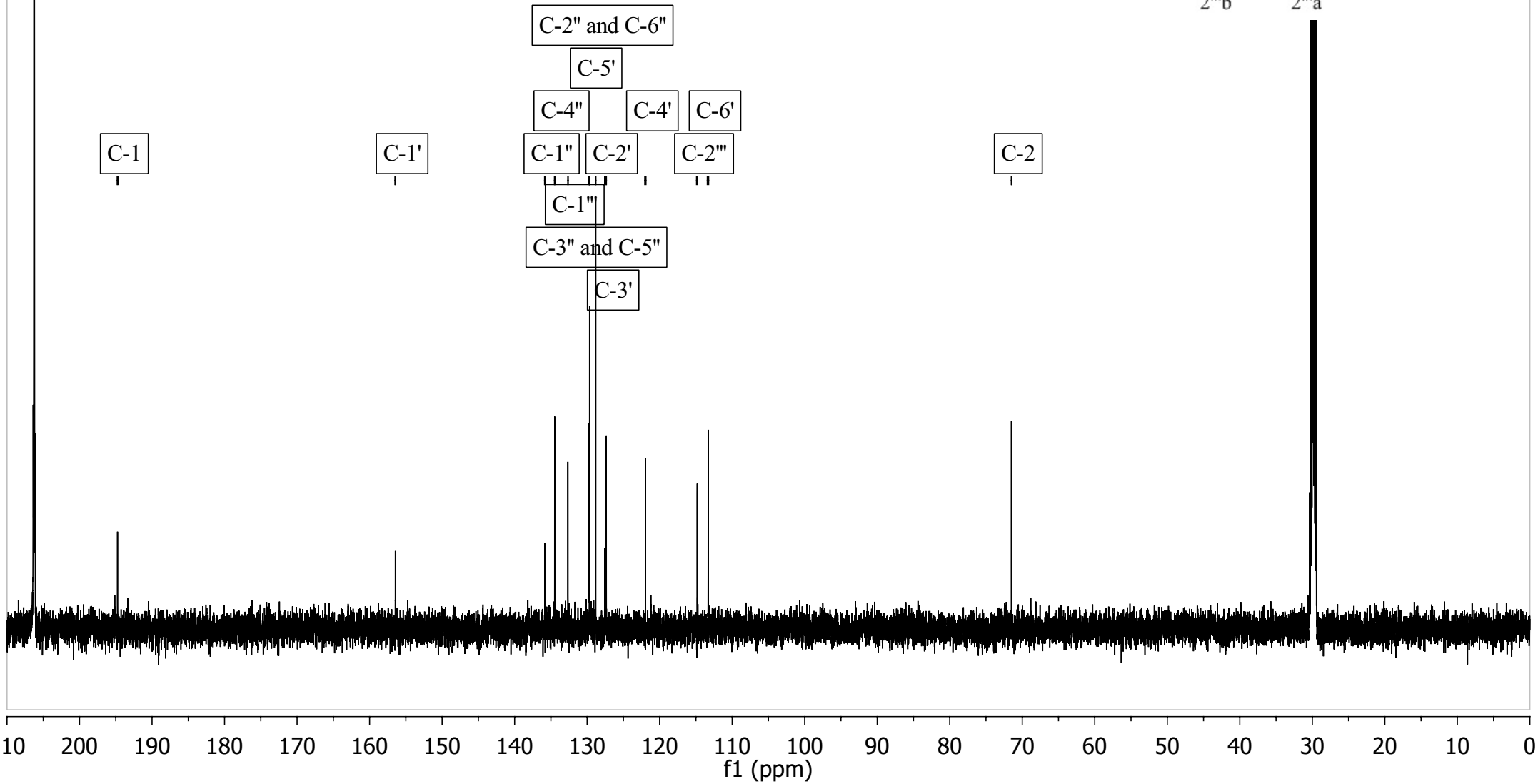


Plate 42c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1-Phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**)

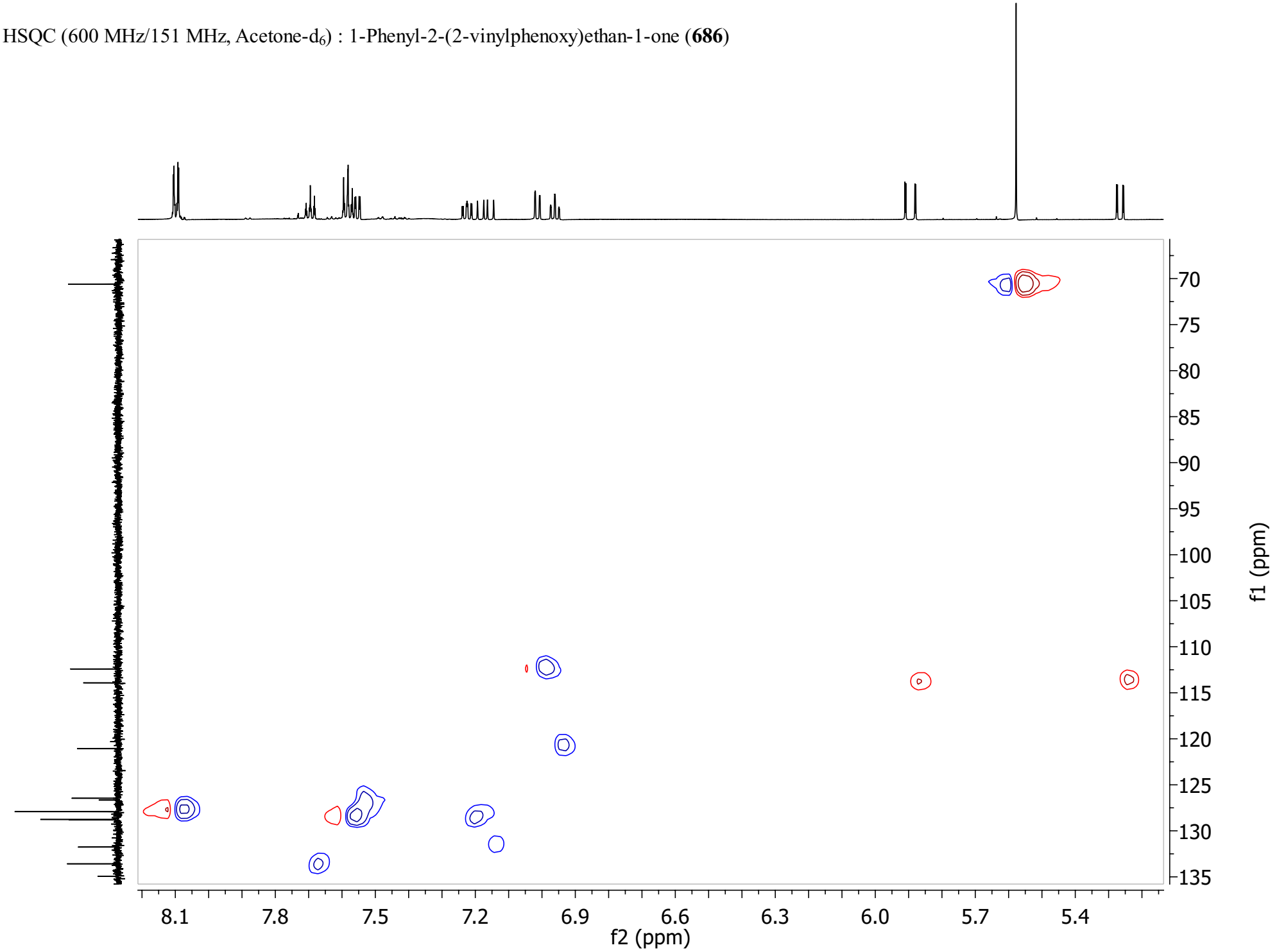


Plate 42d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1-Phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**)

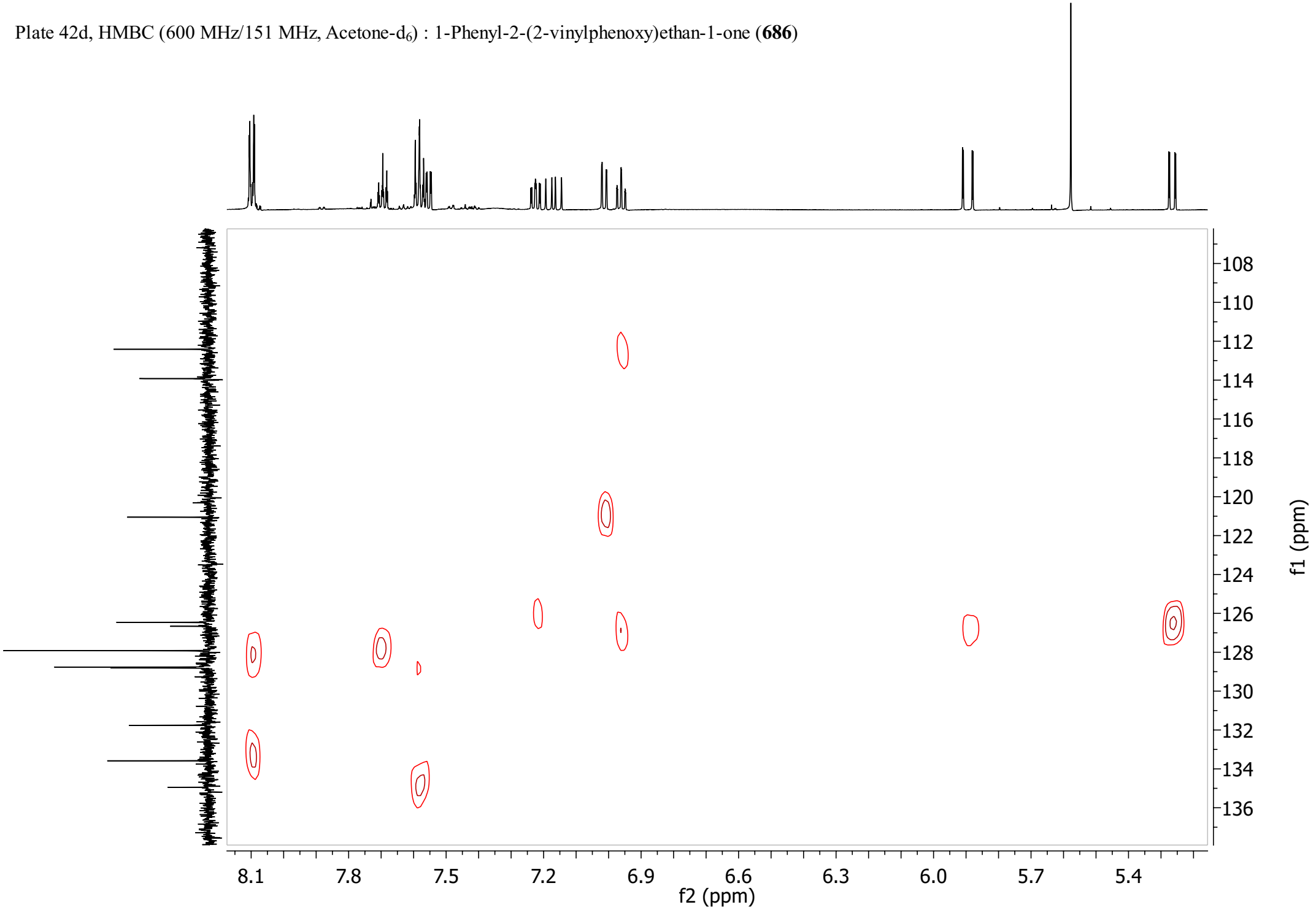


Plate 42e, DEPT (151 MHz, Acetone-d_6) : 1-Phenyl-2-(2-vinylphenoxy)ethan-1-one (**686**)

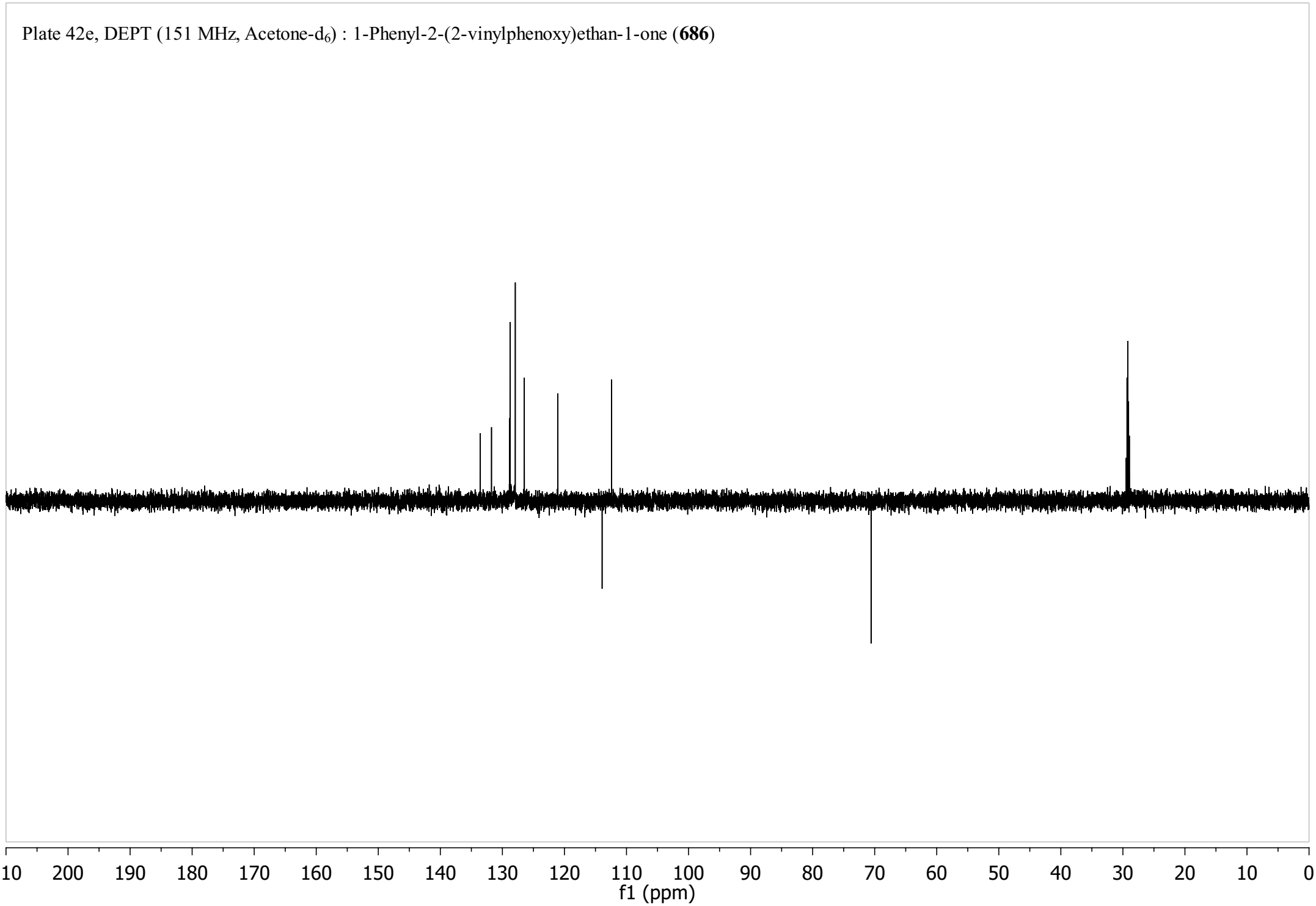
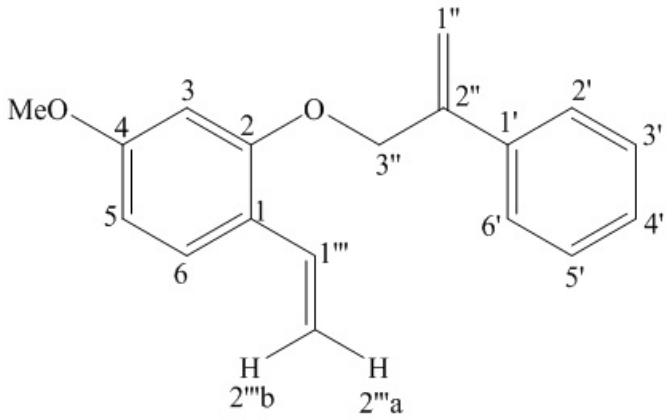
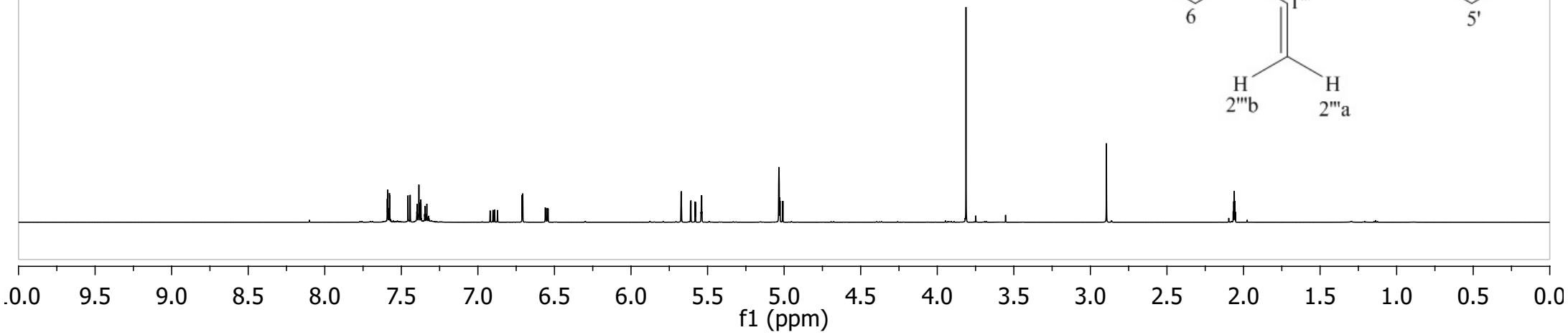


Plate 43a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**689**)

δ 7.60 – 7.57 (2H, m, H-2' and H-6'), 7.45 (1H, d, *J* = 8.4 Hz, H-6), 7.40 – 7.37 (2H, m, H-3' and H-5'), 7.35 – 7.31 (1H, m, H-4'), 6.90 (1H, dd, *J* = 17.8, 11.2 Hz, H-1'''), 6.71 (1H, d, *J* = 2.4 Hz, H-3), 6.55 (1H, dd, *J* = 8.4, 2.4 Hz, H-5), 5.68 – 5.67 (1H, m, H-1''), 5.60 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.55 – 5.53 (1H, m, H-1''), 5.03 (2H, br. s H-3''), 5.02 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a), 3.81 (3H, s, -OMe)





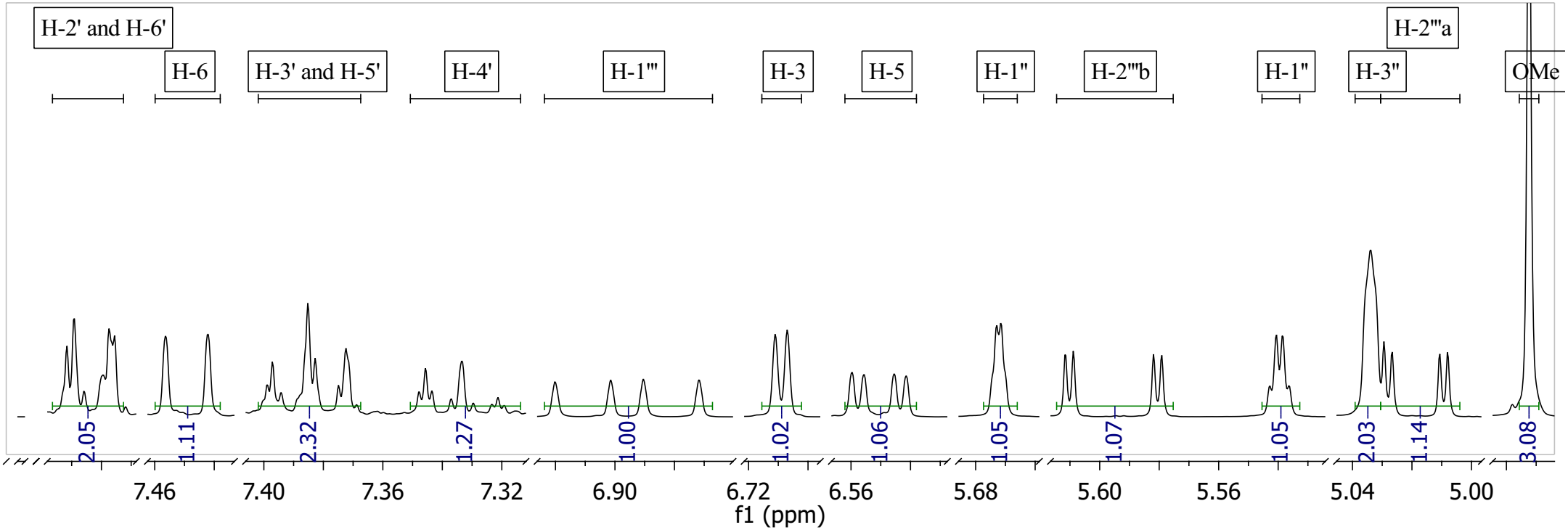
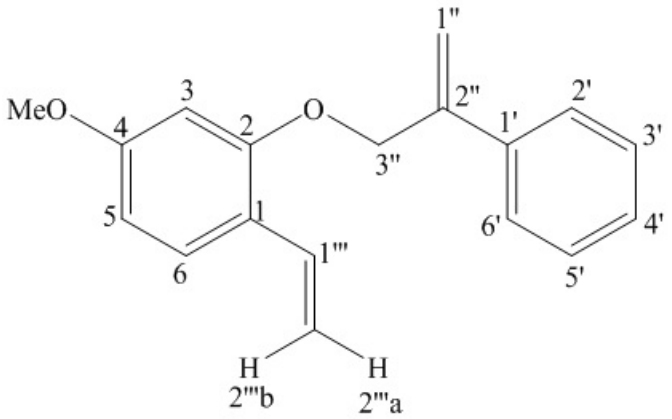
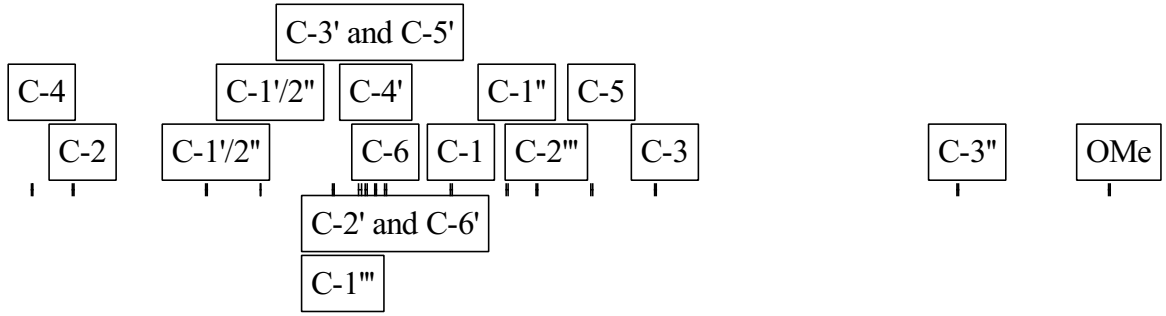


Plate 43b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**689**)

δ 161.62 (C-4), 157.60 (C-2), 144.47 (C-1'/2"), 139.14 (C-1'/2"), 131.98 (C-1'"), 129.32 (C-3' and C-5'), 128.73 (C-4'), 127.79 (C-6), 126.82 (C-2' and C-6'), 120.35 (C-1), 114.85 (C-1"), 111.94 (C-2'"), 106.52 (C-5), 100.27 (C-3), 70.50 (C-3"), 55.57 (-O<u>Me</u>)





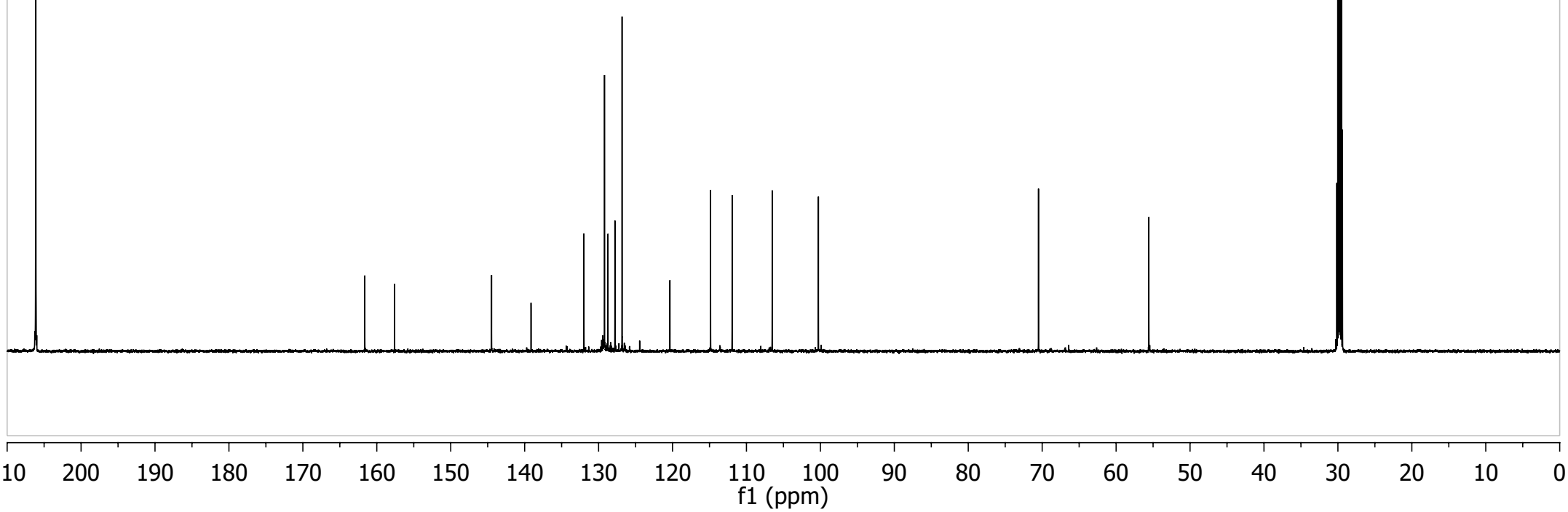


Plate 45c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**)

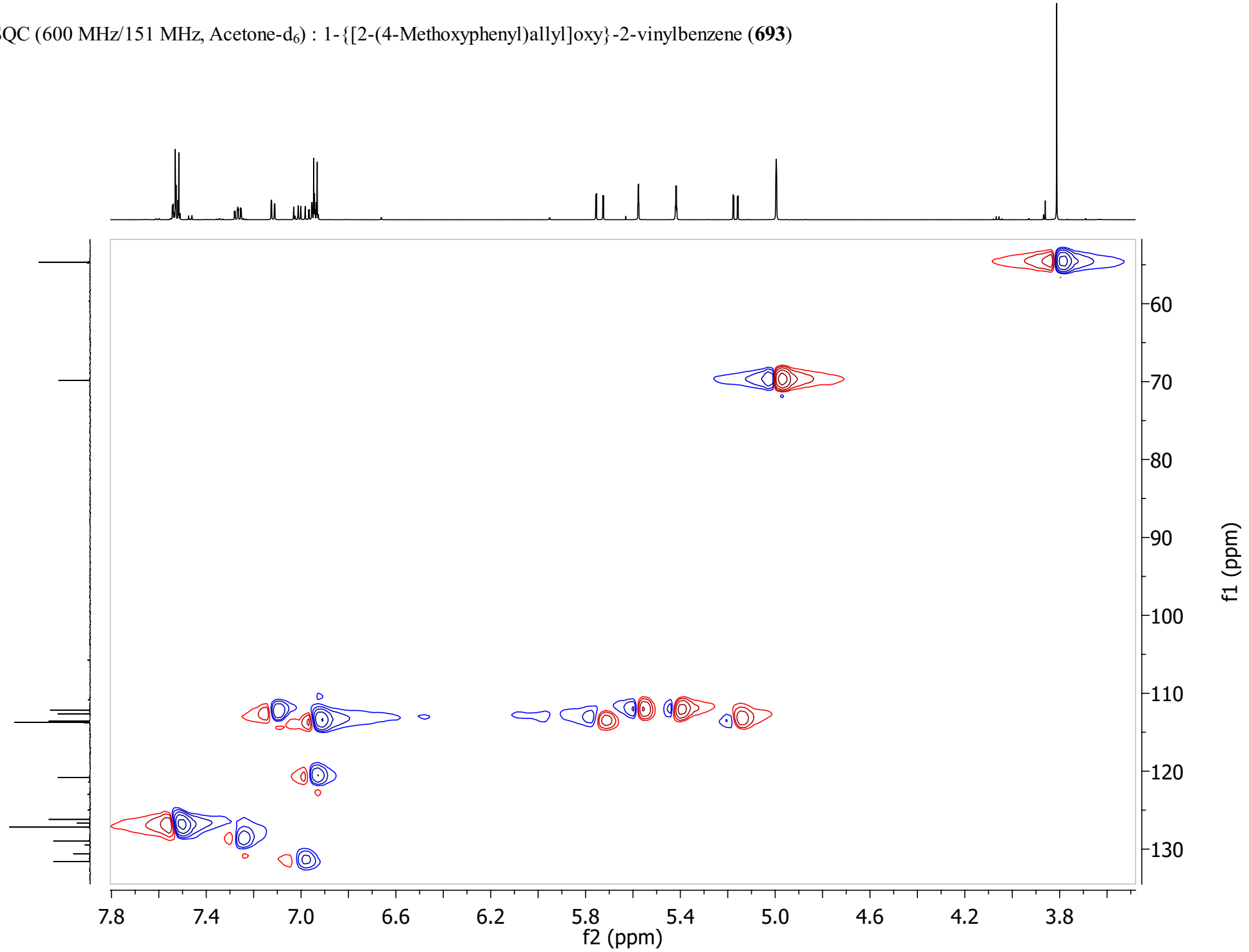


Plate 43d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**689**)

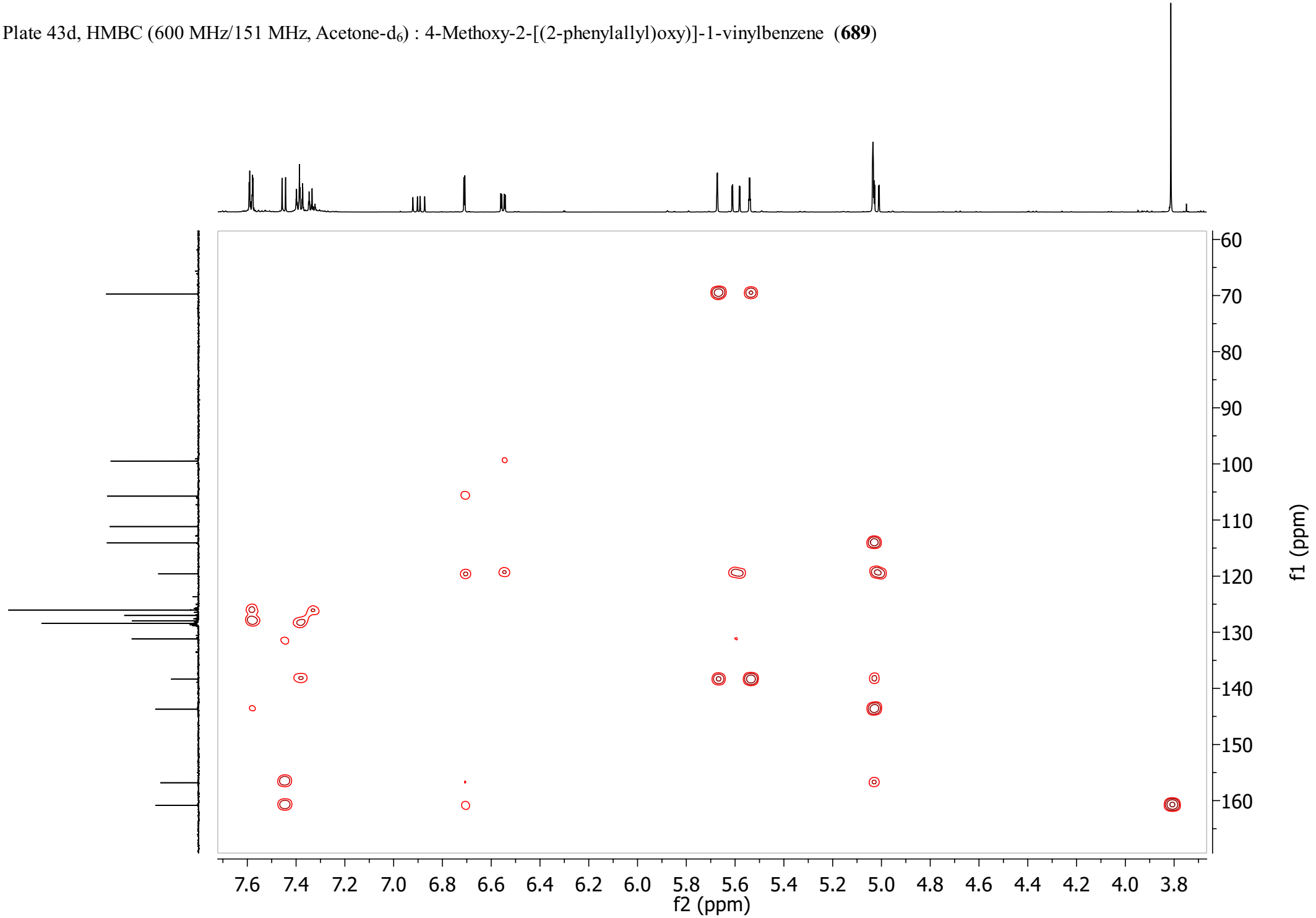


Plate 43e, DEPT (151 MHz, Acetone-d_6) : 4-Methoxy-2-[(2-phenylallyl)oxy)]-1-vinylbenzene (**689**)

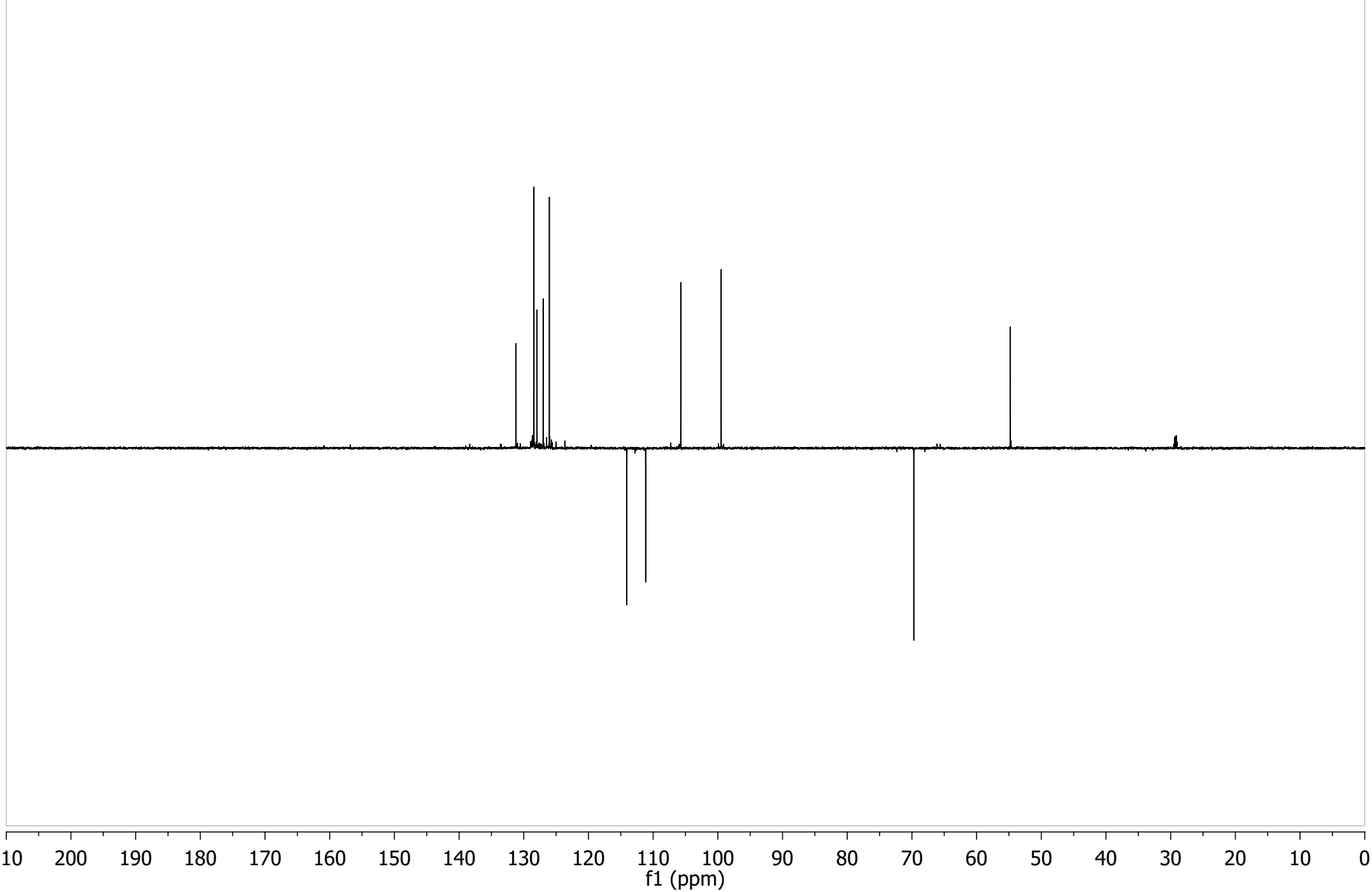
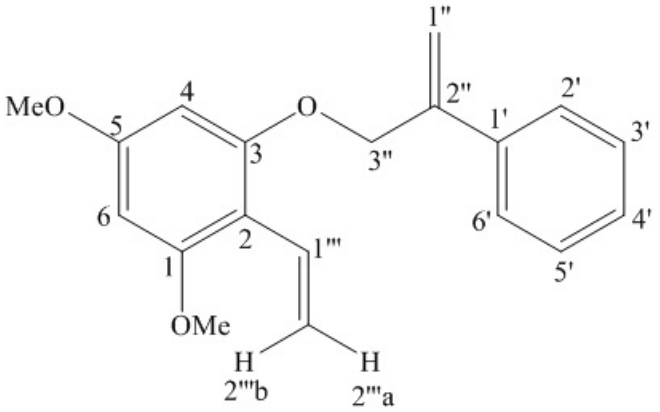
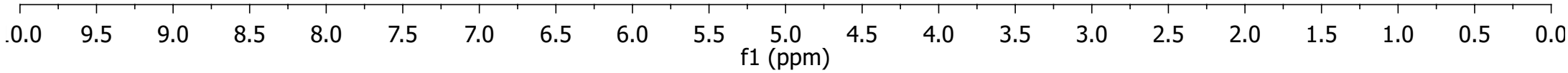


Plate 44a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**)

δ 7.57 – 7.54 (2H, m, H-2' and H-6'), 7.38 – 7.35 (2H, m, H-3' and H-5'), 7.33 – 7.30 (1H, m, H-4'), 6.86 (1H, dd, *J* = 17.9, 12.0 Hz, H-1'''), 6.39 (1H, d, *J* = 2.3 Hz, H-4), 6.26 (1H, d, *J* = 2.3 Hz, H-6), 5.87 (1H, dd, *J* = 17.9, 3.0 Hz, H-2'''b), 5.66 – 5.64 (1H, m, H-1''), 5.53 – 5.52 (1H, m, H-1''), 5.10 (1H, dd, *J* = 12.0, 3.0 Hz, H-2'''a), 5.01 (2H, br. s, H-3''), 3.82 (3H, s, -OMe), 3.81 (3H, s, -OMe)





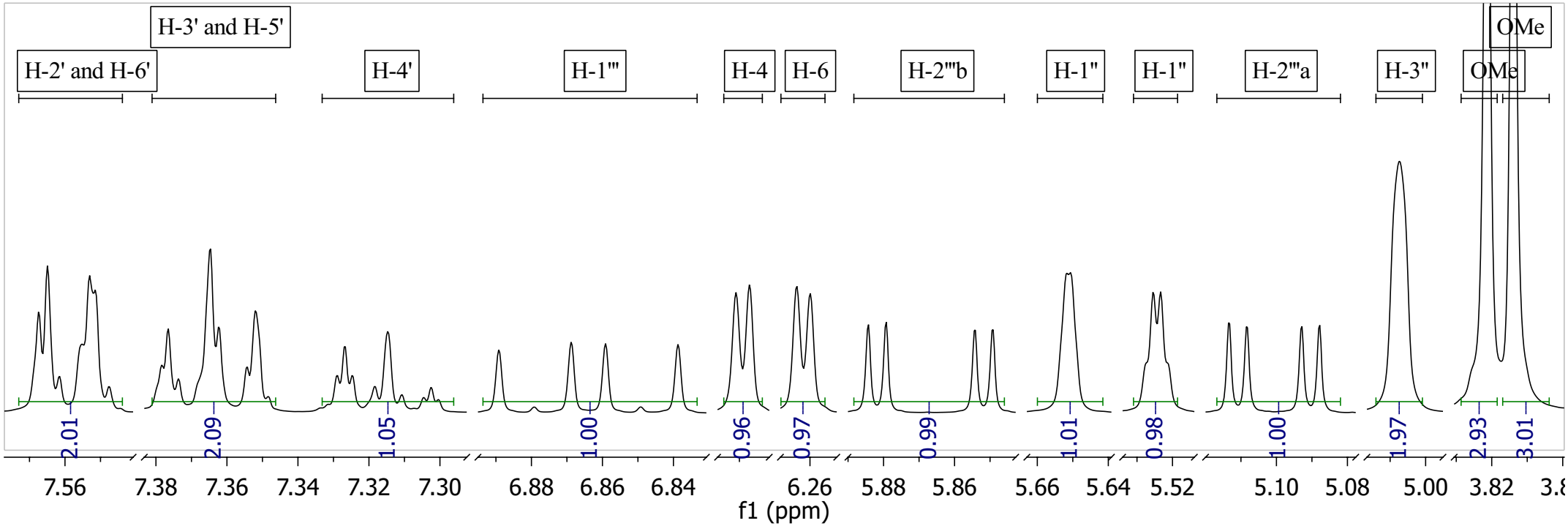
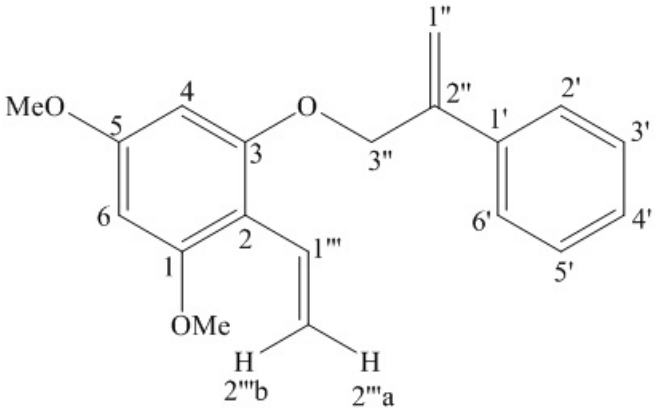


Plate 44b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**)

δ 161.29 (C-1), 160.48 (C-5), 159.20 (C-3), 144.50 (C-2''), 139.16 (C-1'), 129.18 (C-3' and C-5'), 128.76 (C-4'), 127.91 (C-1'''), 126.78 (C-2' and C-6'), 115.71 (C-2'''), 115.07 (C-1''), 108.80 (C-2), 92.67 (C-4), 91.76 (C-6), 70.84 (C-3''), 55.90 (-OMe), 55.53 (-OMe)



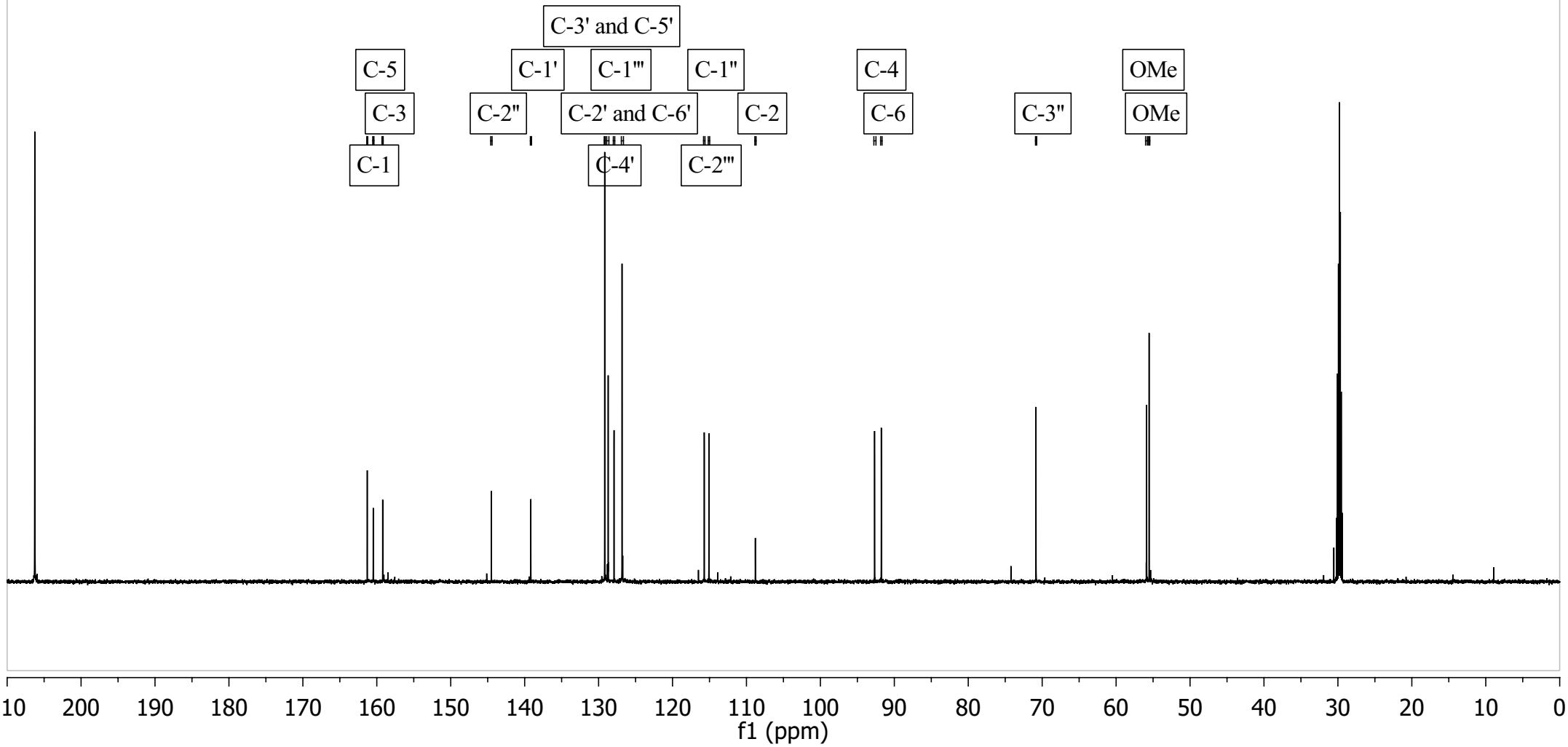


Plate 44c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**)

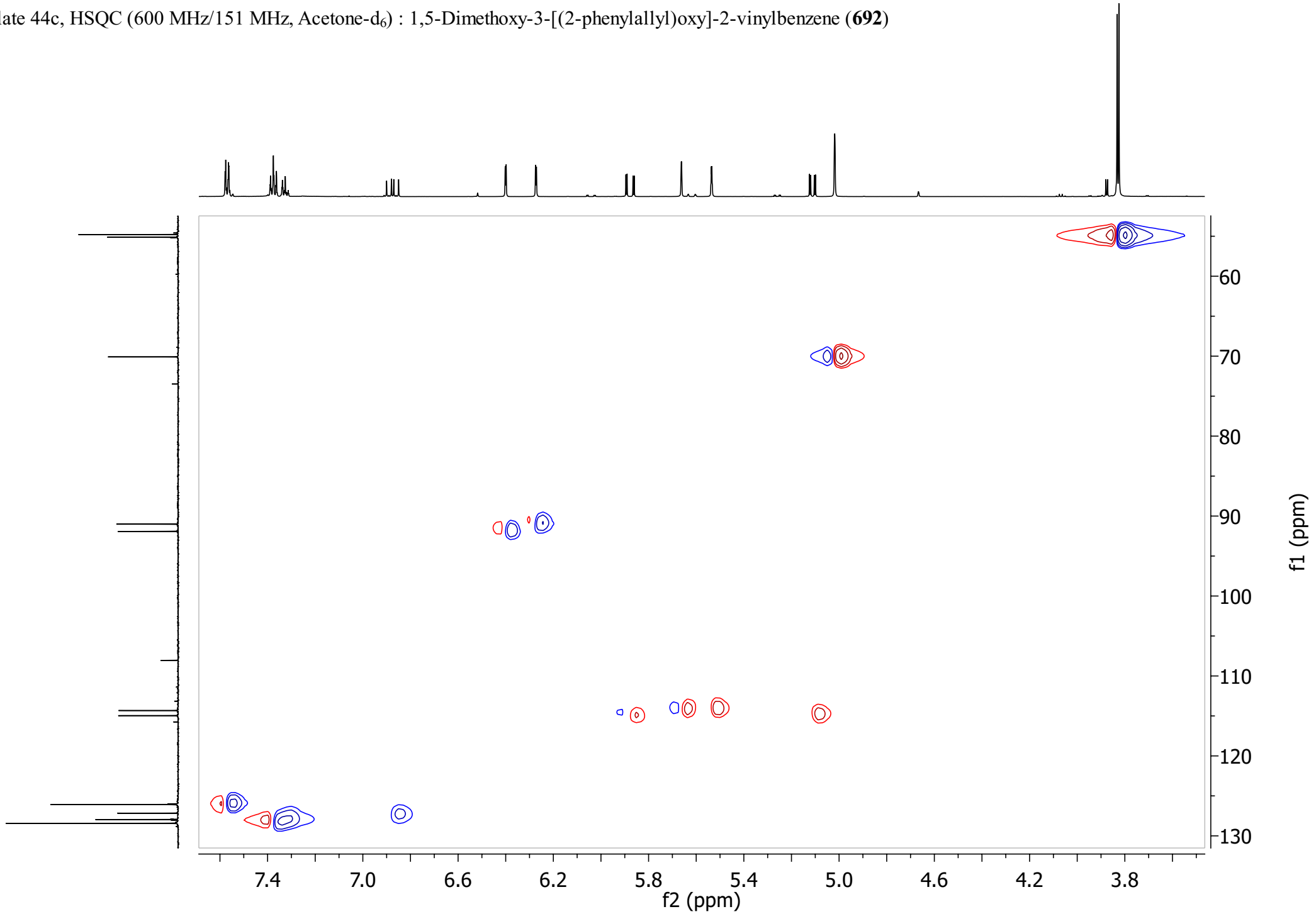


Plate 44d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**)

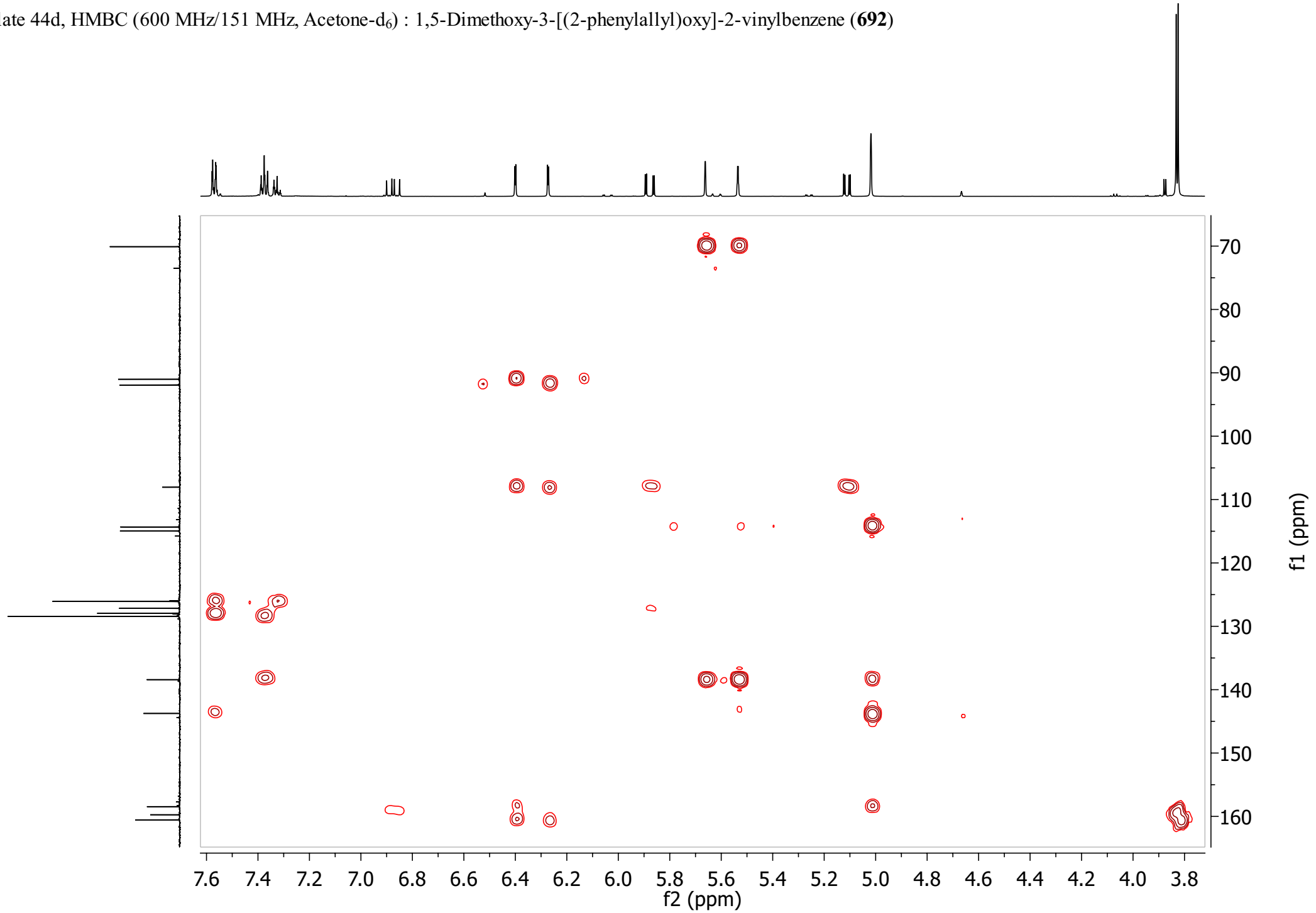


Plate 44e, DEPT (151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene (**692**)

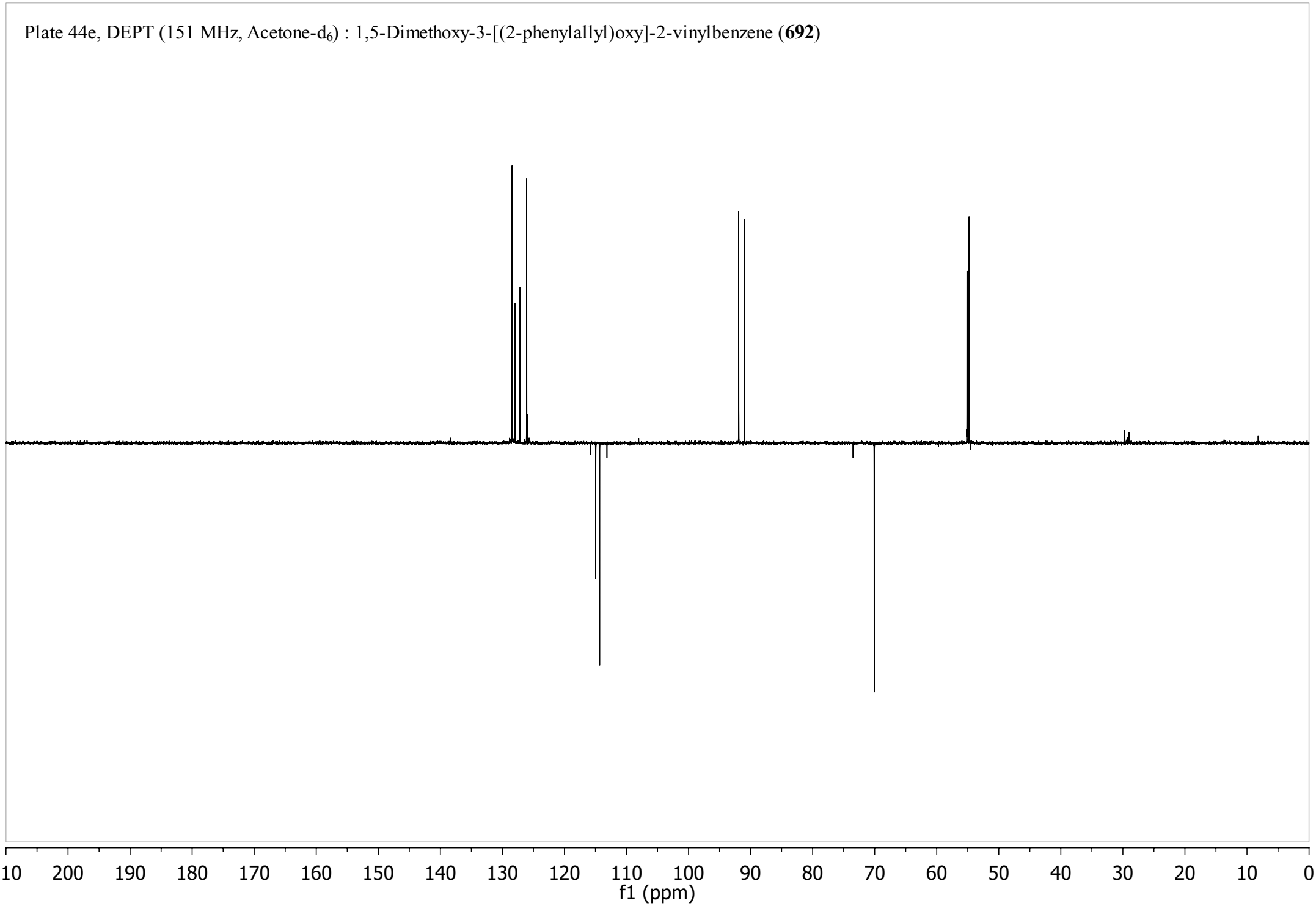
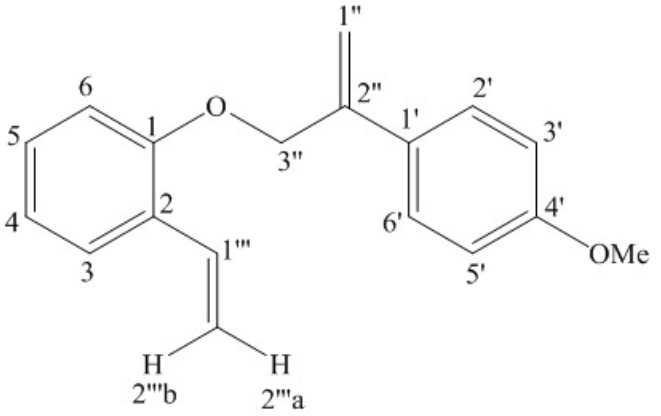
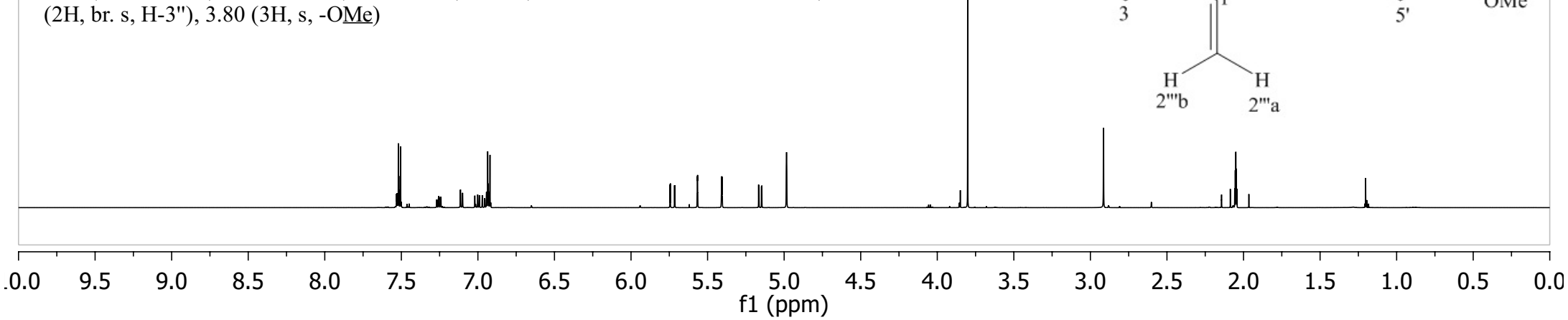


Plate 45a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**)

δ 7.54 – 7.50 (1H, m, H-3), 7.51 (2H, d, *J* = 9.0, H-2' and H-6'), 7.27 – 7.24 (1H, m, H-5), 7.11 (1H, dd, *J* = 8.3, 1.0 Hz, H-6), 7.00 (1H, dd, *J* = 17.8, 11.2 Hz, H-1'''), 6.96 – 6.94 (1H, m, H-4), 6.93 (2H, d, *J* = 9.0, H-3' and H-5'), 5.73 (1H, dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.57 – 5.56 (1H, m, H-1''), 5.41 – 5.40 (1H, m, H-1''), 5.16 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a), 4.98 (2H, br. s, H-3''), 3.80 (3H, s, -OMe)





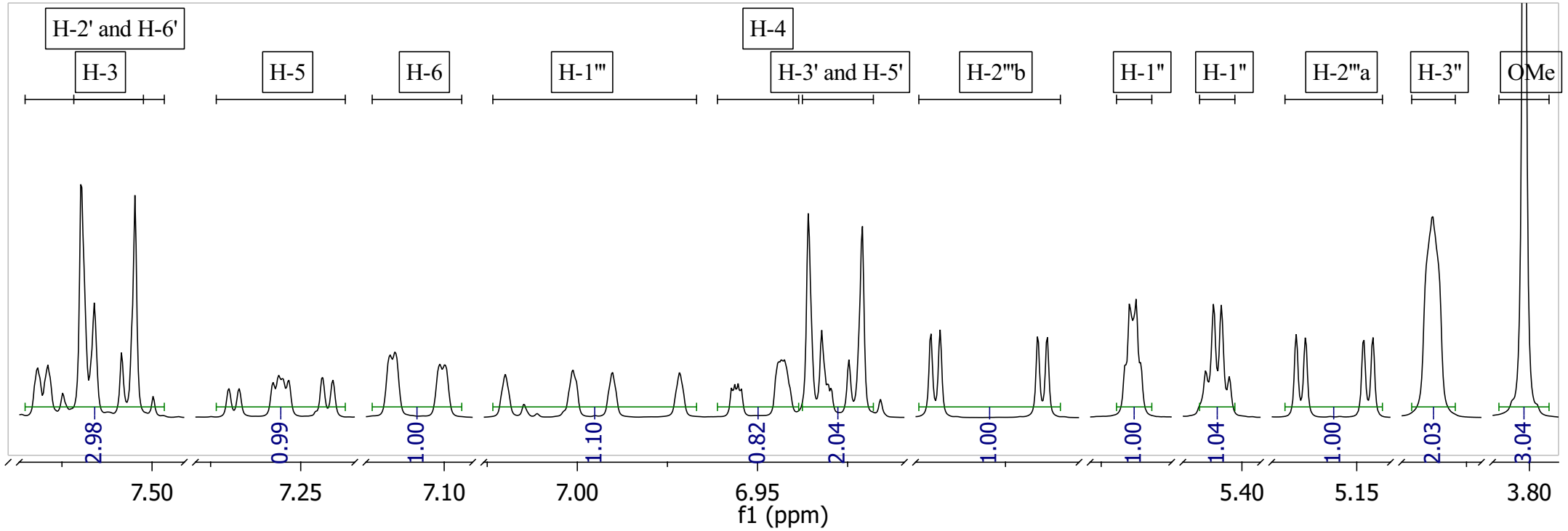
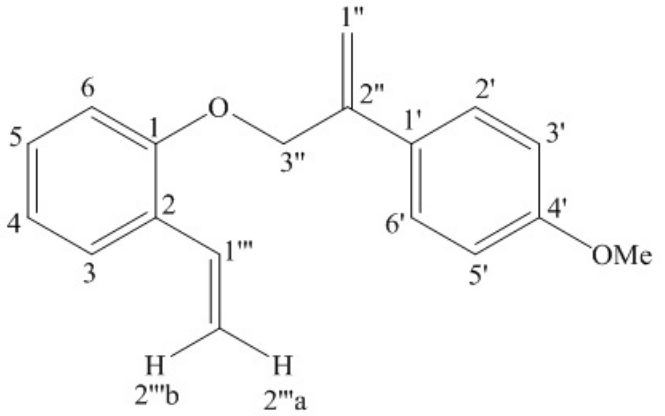


Plate 45b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**)

δ 160.56 (C-4'), 156.65 (C-1), 143.82 (C-2''), 132.44 (C-1'''), 131.45 (C-1'), 129.81 (C-5), 128.03 (C-2' and C-6'), 127.52 (C-2), 127.04 (C-3), 121.65 (C-4), 114.60 (C-3' and C-5'), 114.42 (C-2'''), 113.48 (C-6), 113.03 (C-1''), 70.68 (C-3''), 55.56 (-O<u>Me</u>)



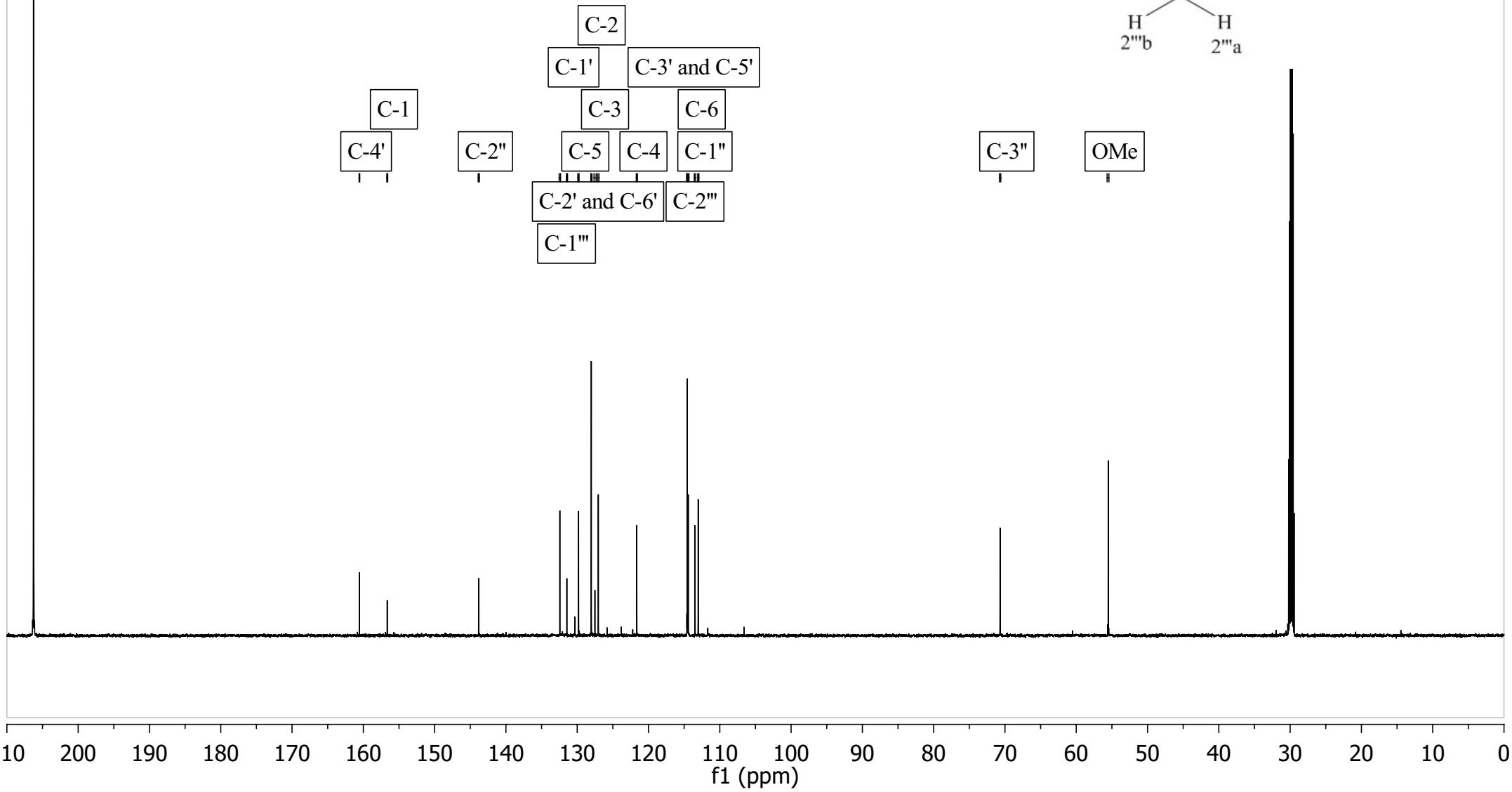


Plate 45c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1-((2-(4-Methoxyphenyl)allyl)oxy)-2-vinylbenzene (**693**)

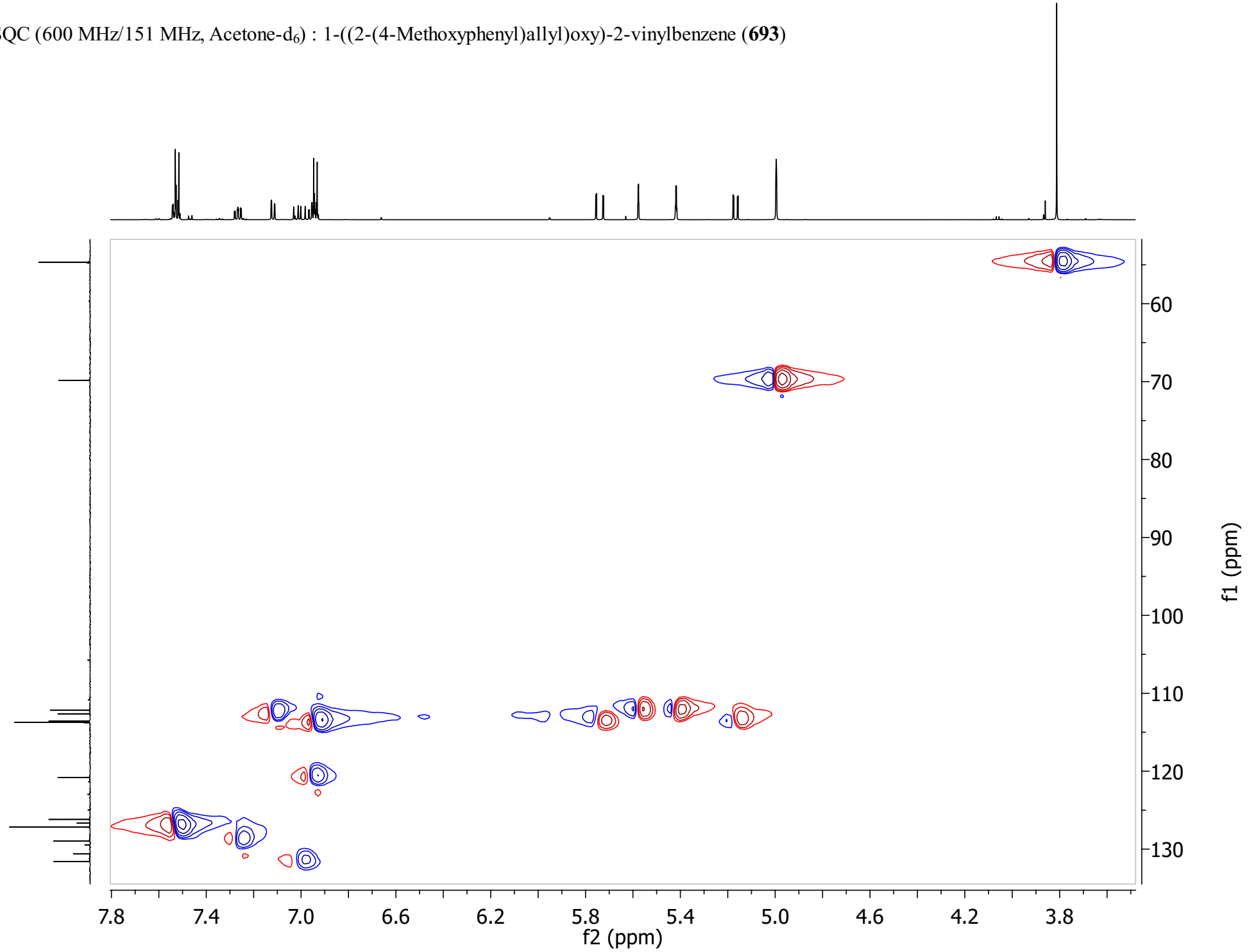


Plate 45d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**)

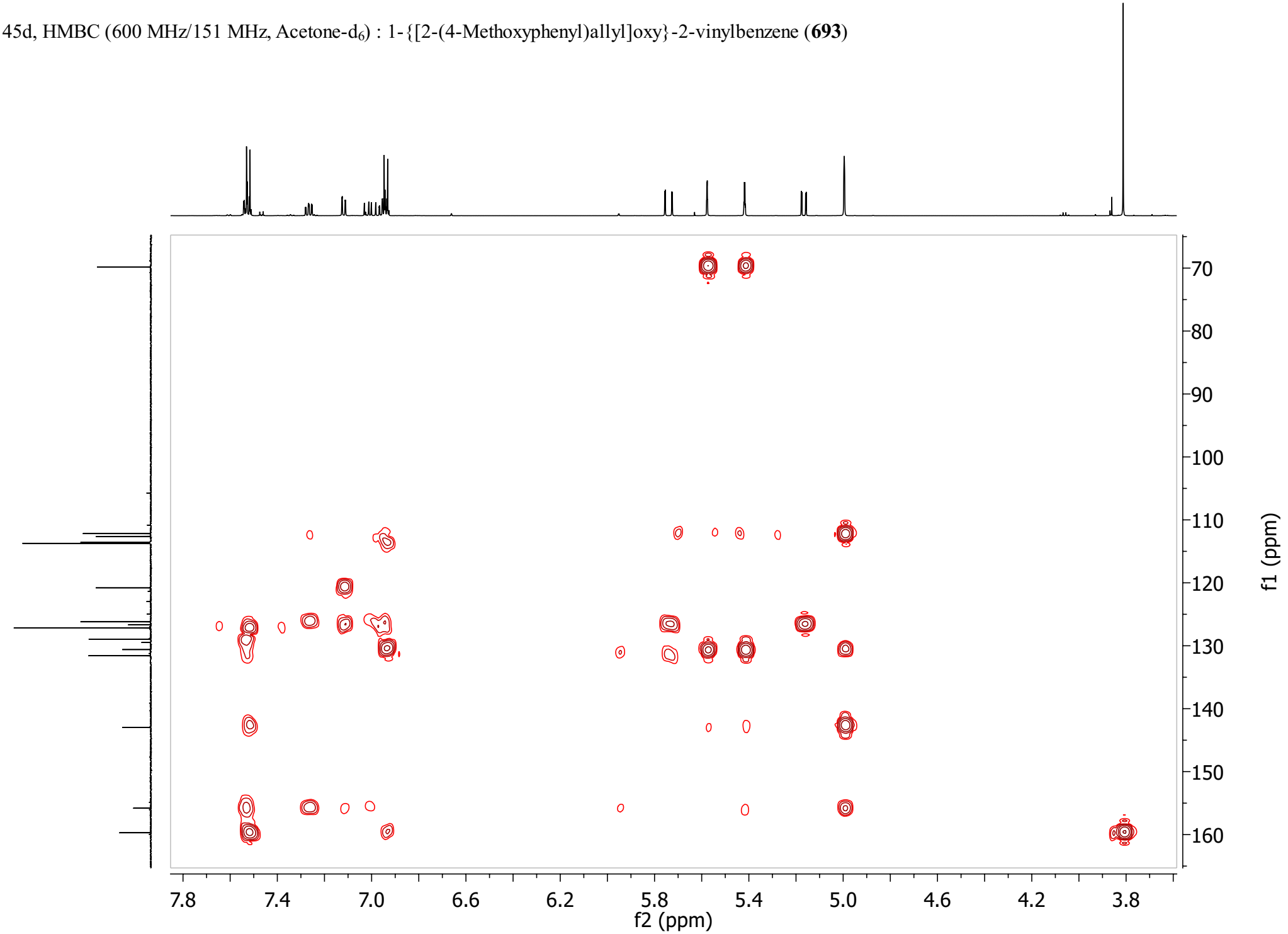
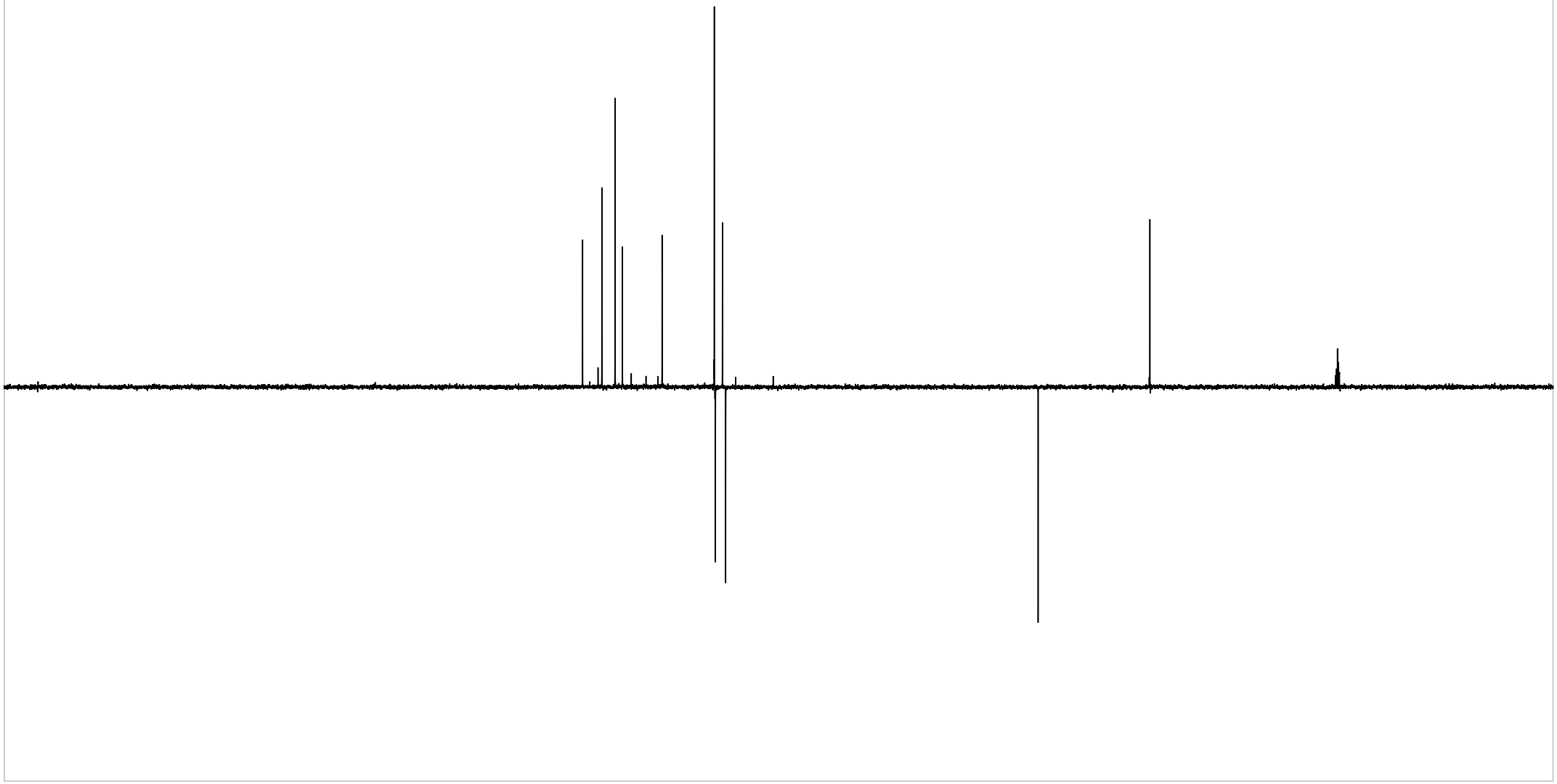


Plate 45e, DEPT (151 MHz, Acetone-d_6) : 1-{[2-(4-Methoxyphenyl)allyl]oxy}-2-vinylbenzene (**693**)

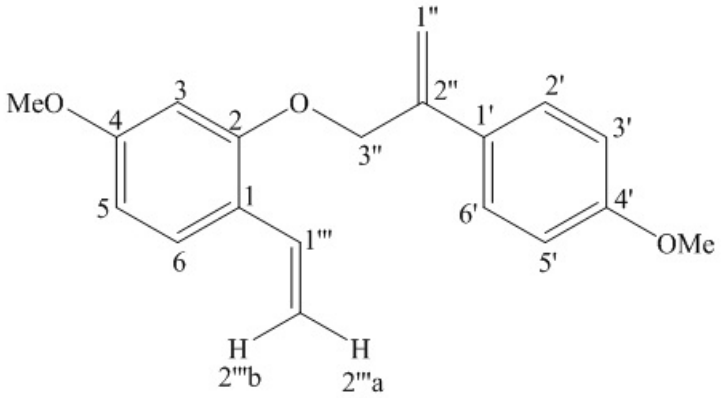


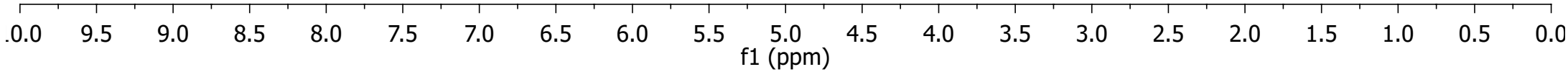
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 46a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**)

δ 7.51 (2H, d, *J* = 8.5 Hz, H-2' and H-6'), 7.45 (1H, d, *J* = 8.5 Hz, H-6), 6.96 – 6.90 (1H, m, H-1'''), 6.92 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 6.69 (1H, d, *J* = 2.4 Hz, H-3), 6.54 (1H, dd, *J* = 8.5, 2.4 Hz, H-5), 5.61 (dd, *J* = 17.8, 1.6 Hz, H-2'''b), 5.58 (1H, br. s H-1''), 5.43 – 5.42 (1H, m, H-1''), 5.04 (1H, dd, *J* = 11.2, 1.6 Hz, H-2'''a), 4.97 (2H, br. s, H-3''), 3.79 (3H, s, -OMe), 3.78 (3H, s, -OMe)





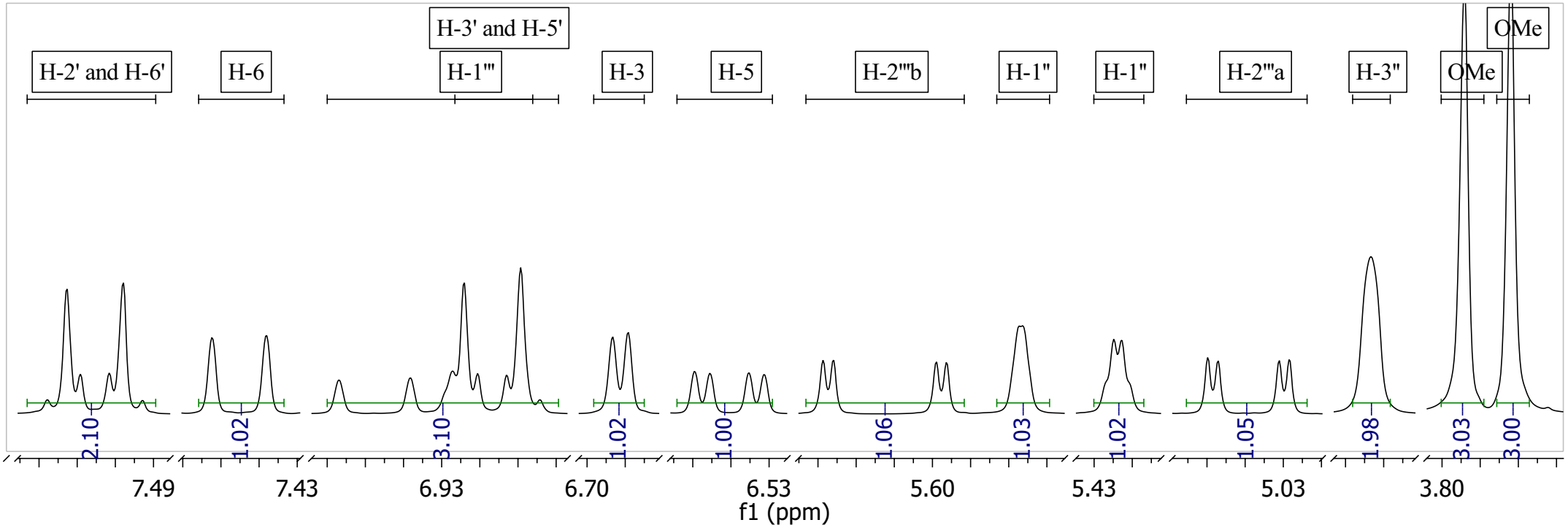
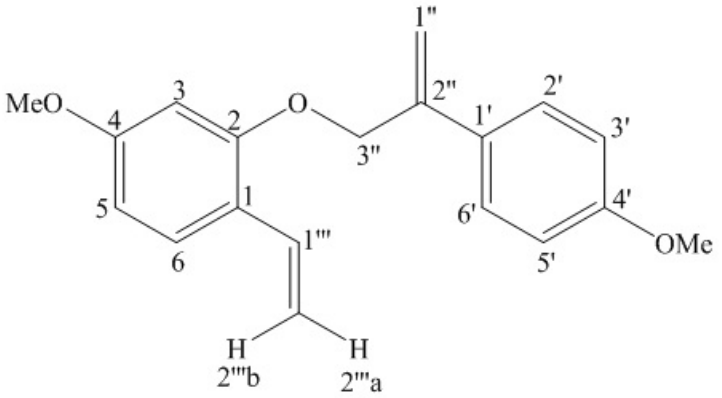


Plate 46b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**)

δ 161.56 (C-4), 160.42 (C-4'), 157.61 (C-2), 143.60 (C-2''), 131.99 (C-1'''), 131.29 (C-1'), 128.08 (C-2' and C-6'), 127.93 (C-6), 120.35 (C-1), 114.49 (C-3' and C-5'), 113.07 (C-1''), 111.99 (C-2'''), 106.36 (C-5), 100.28 (C-3), 70.61 (C-3''), 55.56 (-O<u>Me</u>), 55.43 (-O<u>Me</u>)



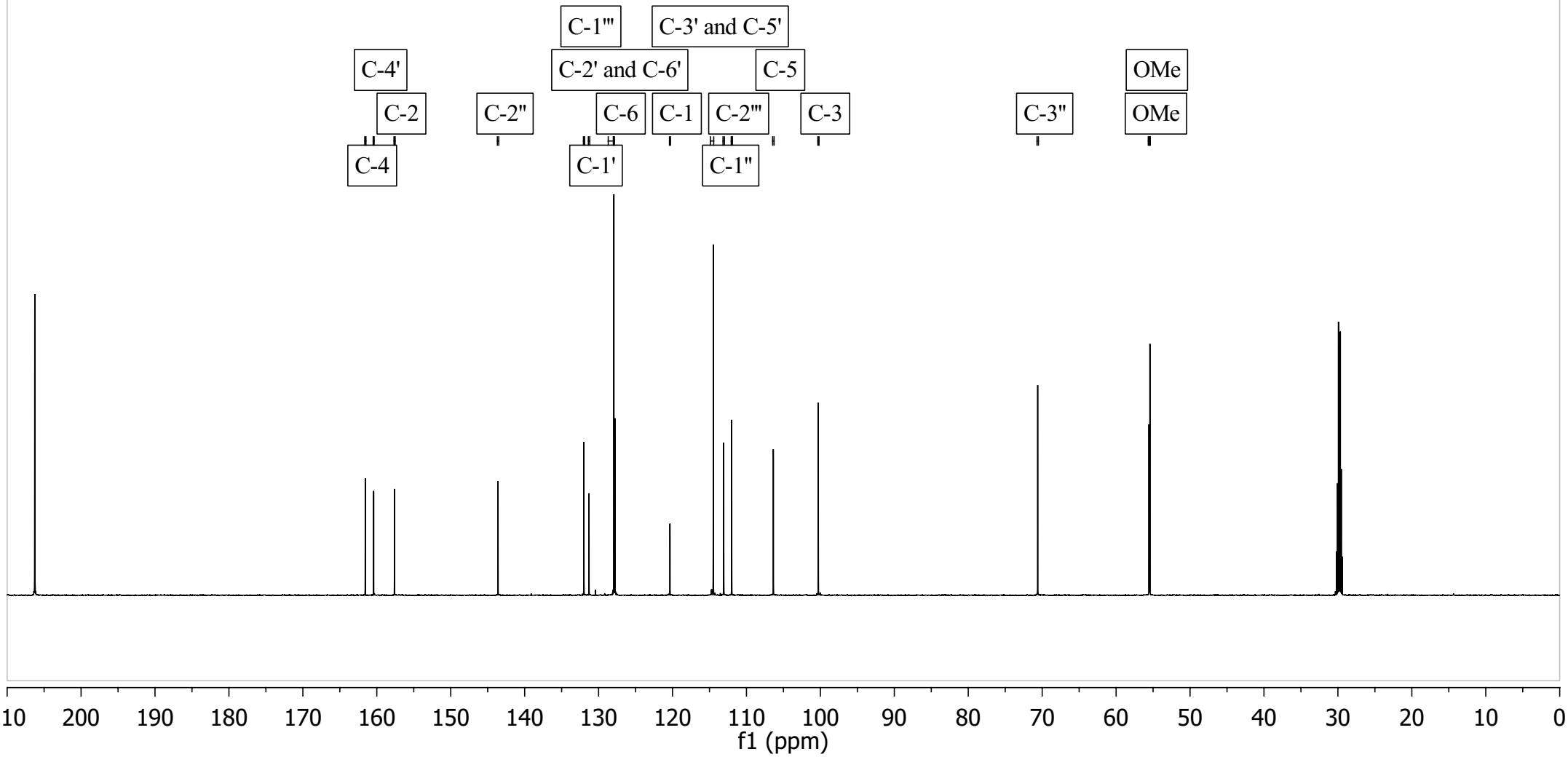


Plate 46c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**)

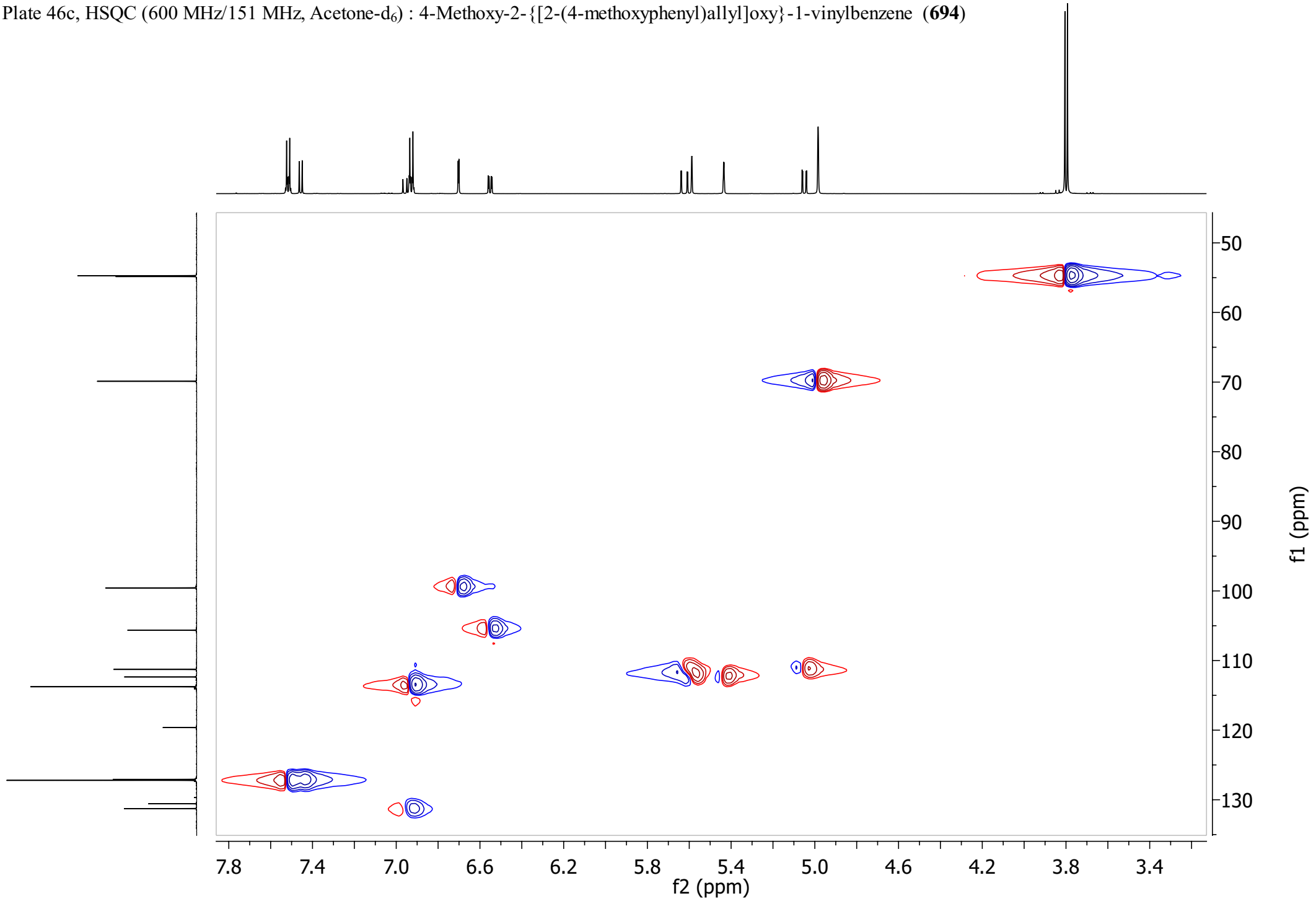


Plate 46d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**)

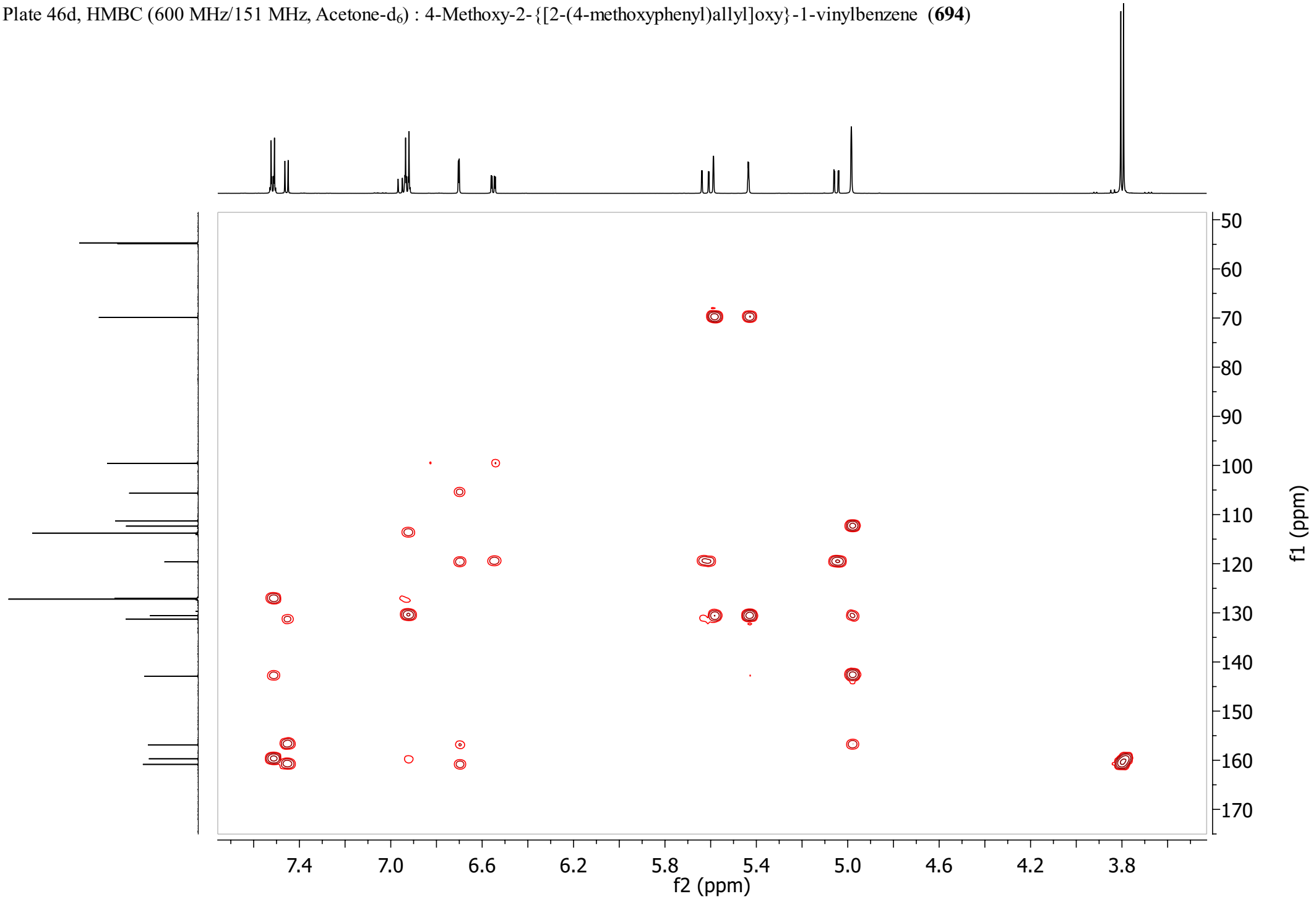


Plate 46e, DEPT (151 MHz, Acetone-d_6) :4-Methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene (**694**)

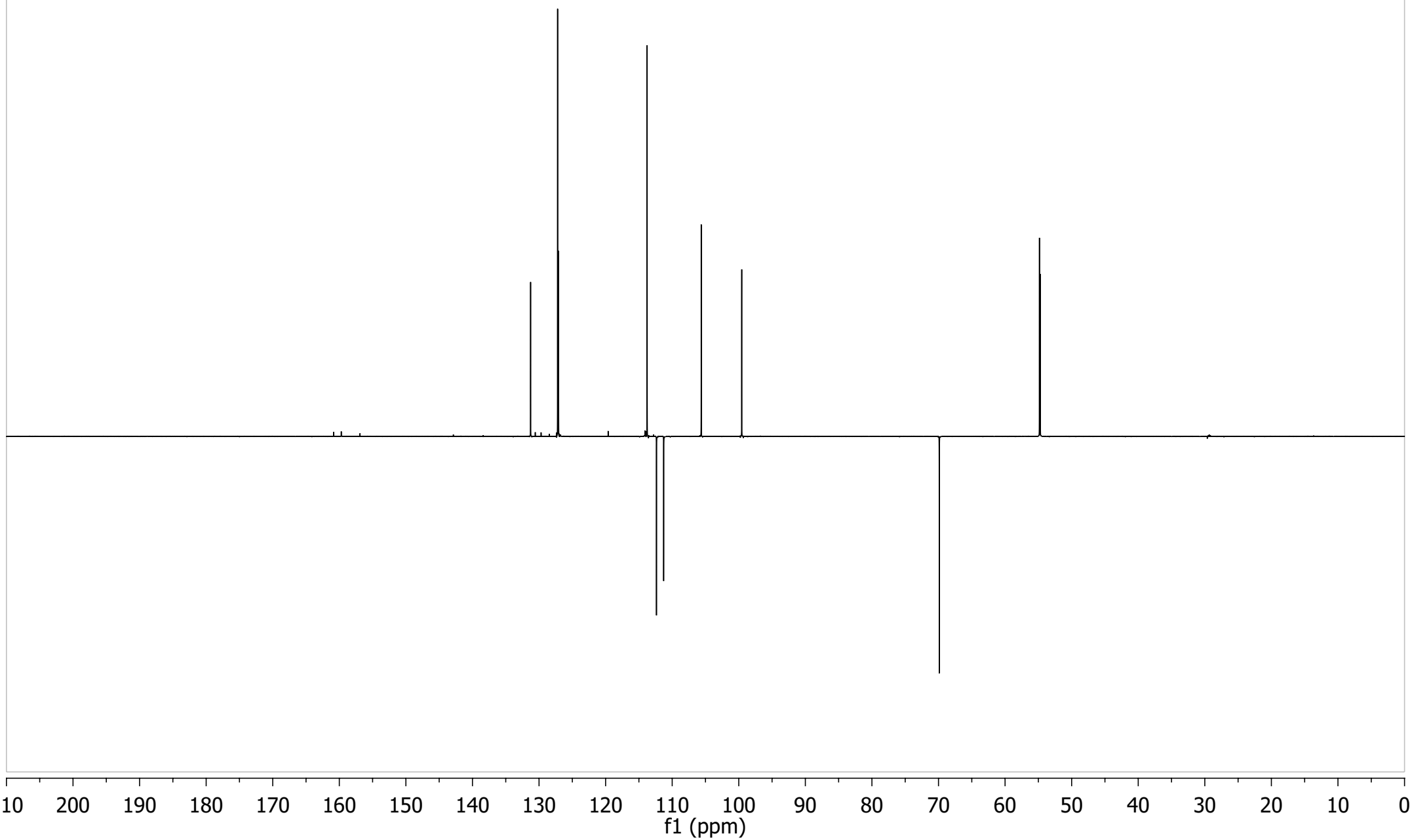
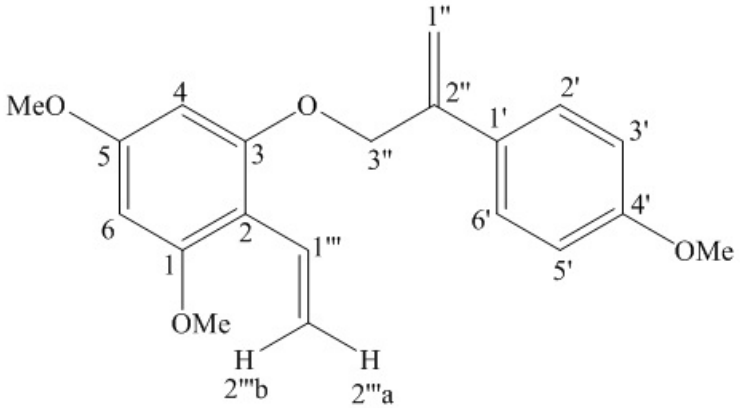


Plate 47a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**)

δ 7.51 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.93 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.85 (1H, dd, *J* = 18.0, 12.3 Hz, H-1'''), 6.39 (1H, d, *J* = 2.3 Hz, H-4/6), 6.27 (1H, d, *J* = 2.3 Hz, H-4/6), 5.86 (1H, dd, *J* = 18.0, 3.0 Hz, H-2'''b), 5.57 (1H, br. s H-1''), 5.43 – 5.41 (1H, m, H-1''), 5.09 (1H, dd, *J* = 12.3, 3.0 Hz, H-2'''a), 4.99 (2H, br. s, H-3''), 3.84 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.81 (3H, s, -OMe)



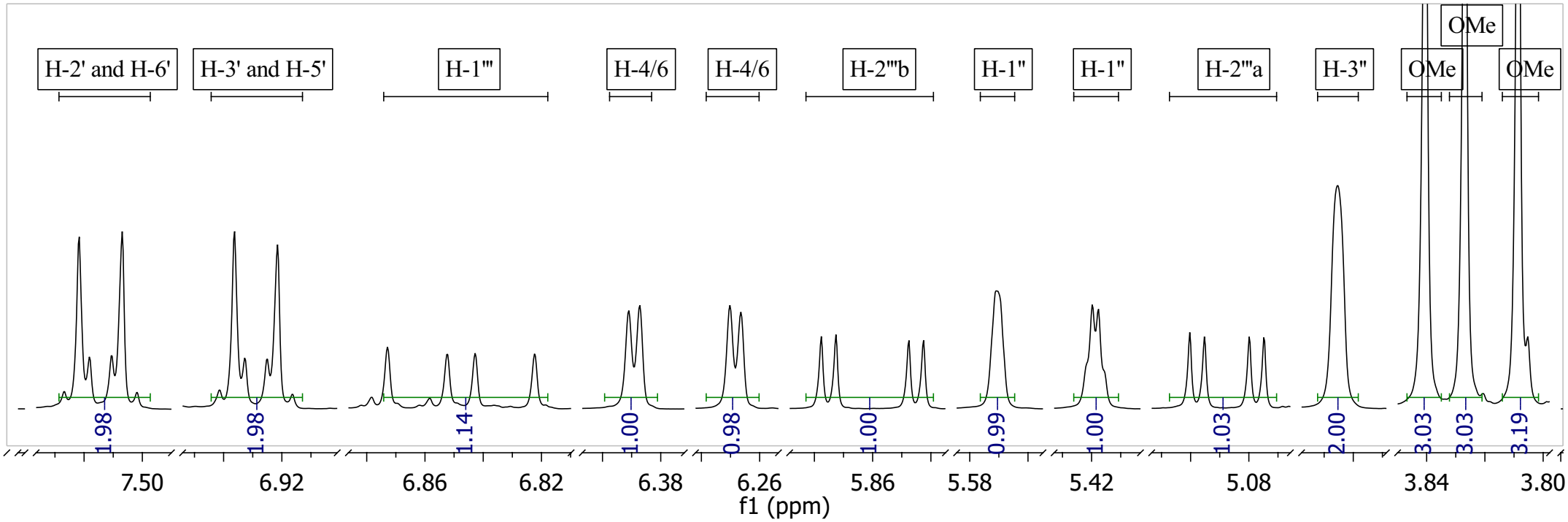
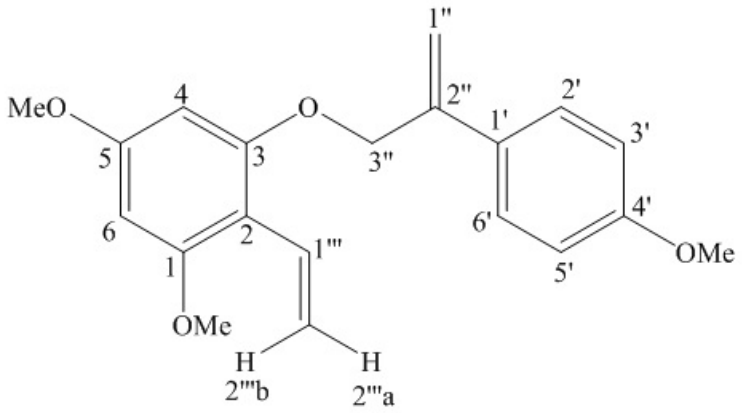


Plate 47b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**)

δ 161.50 (C-5), 160.68 (C-1/4'), 160.67 (C-1/4'), 159.46 (C-3), 144.04 (C-2''), 131.63 (C-1'), 128.18 (C-2' and C-6'), 128.11 (C-1'''), 115.81 (C-2'''), 114.64 (C-3' and C-5'), 113.41 (C-1''), 108.97 (C-2), 92.86 (C-4/6), 91.92 (C-4/6), 71.18 (C-3''), 56.05 (-OMe), 55.70 (-OMe), 55.62 (-OMe)



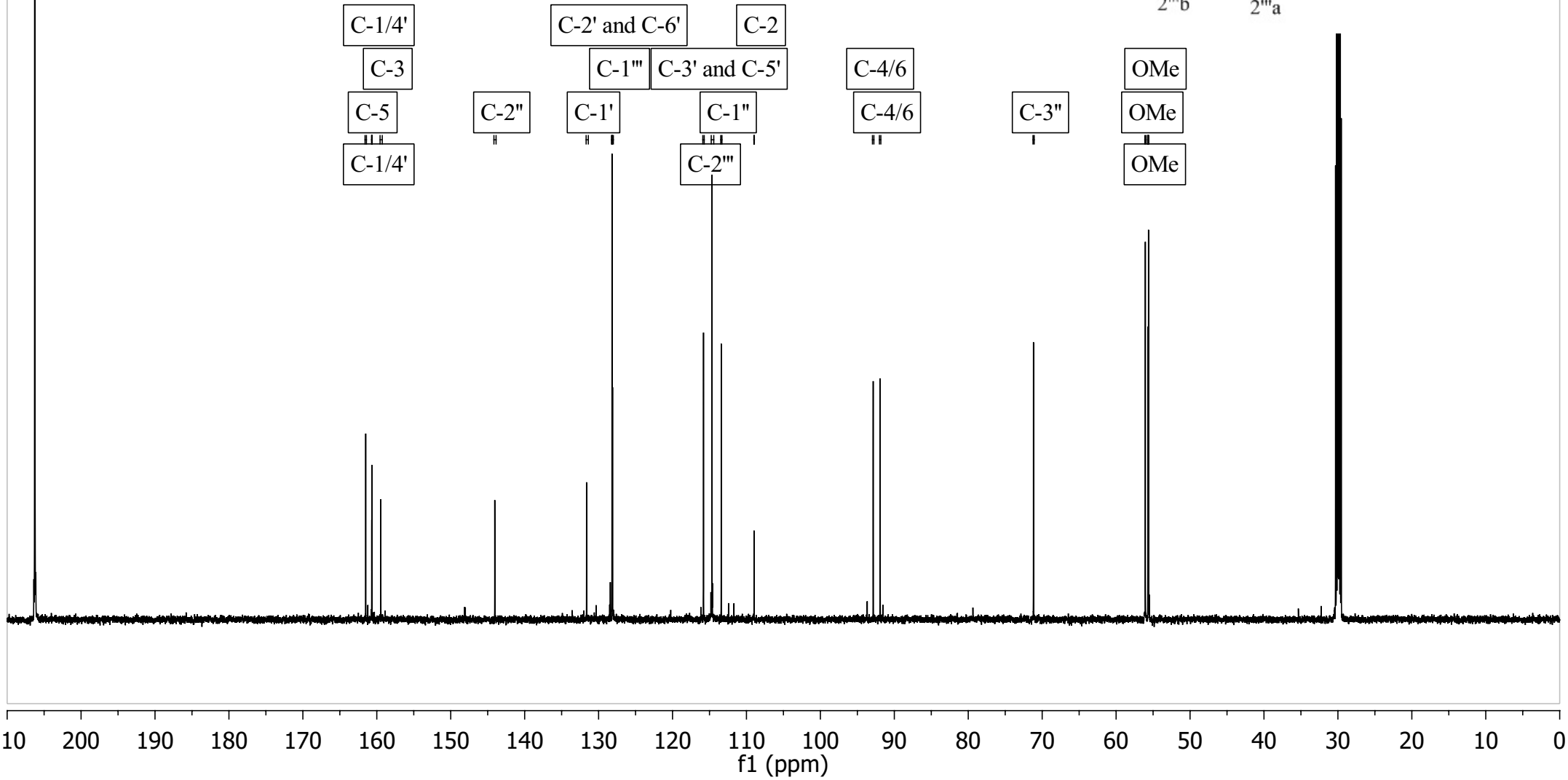


Plate 47c, HSQC (600/151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**)

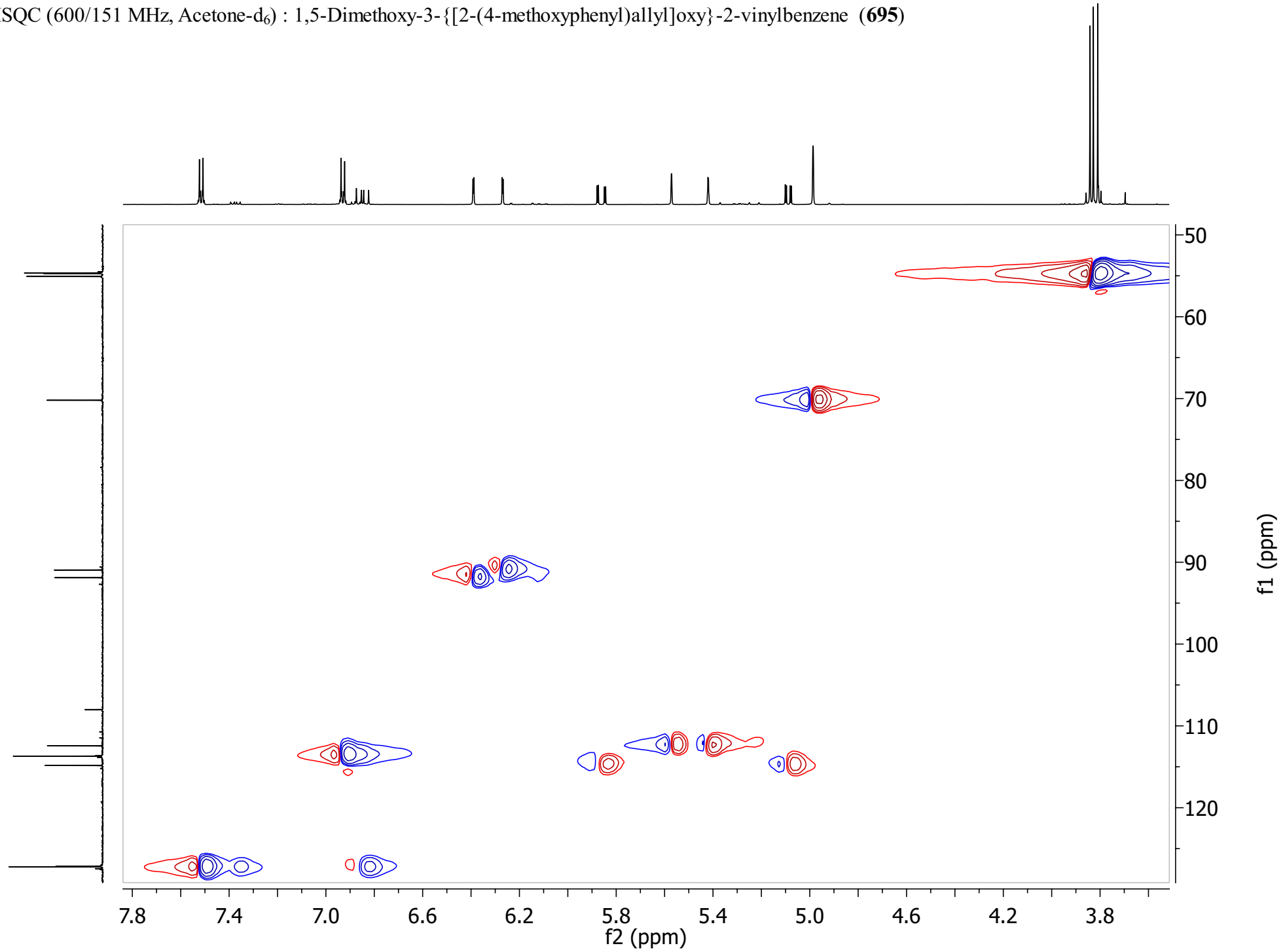


Plate 47d, HMBC (600/151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**)

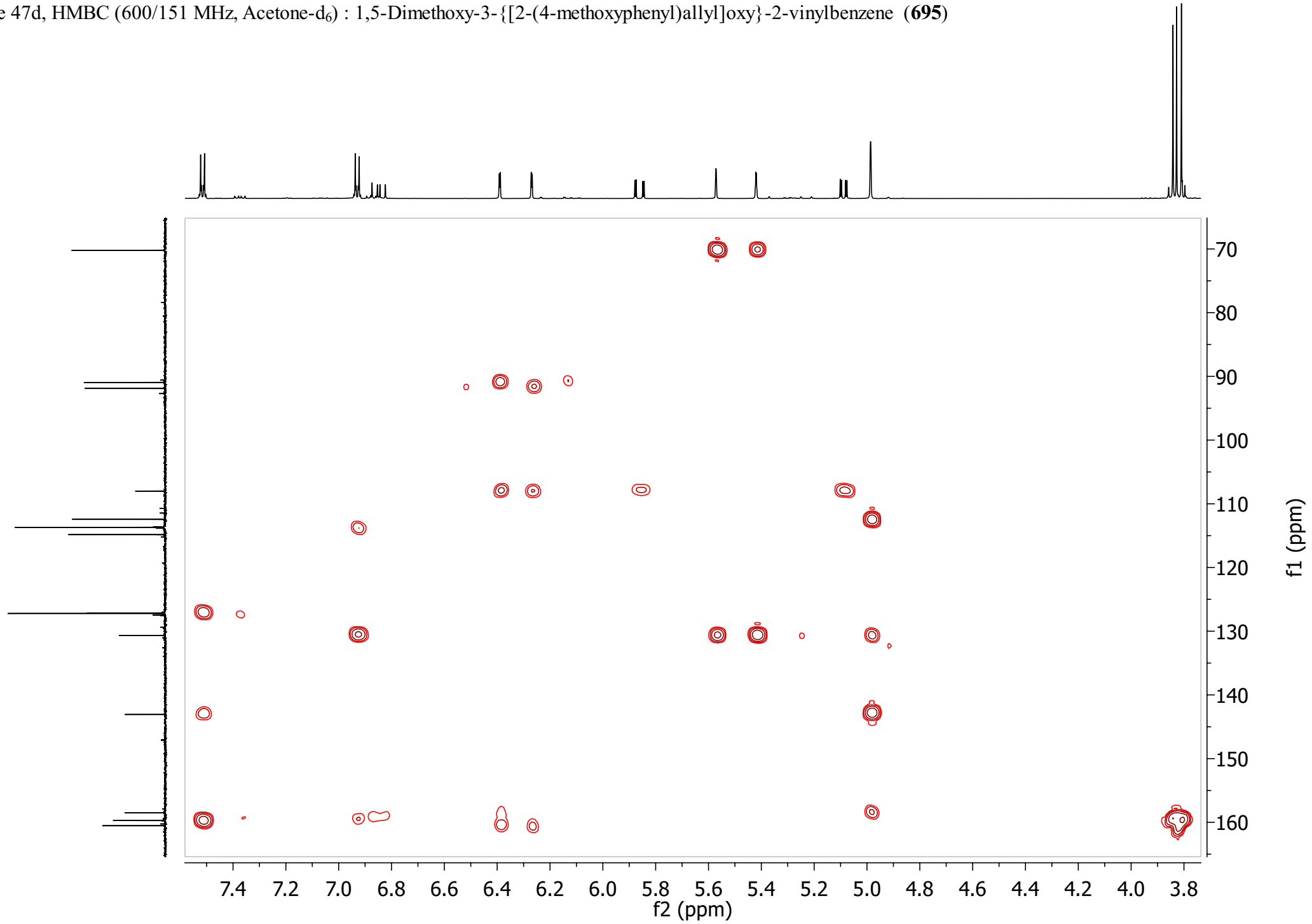


Plate 47e, DEPT (151 MHz, Acetone-d_6) : 1,5-Dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene (**695**)

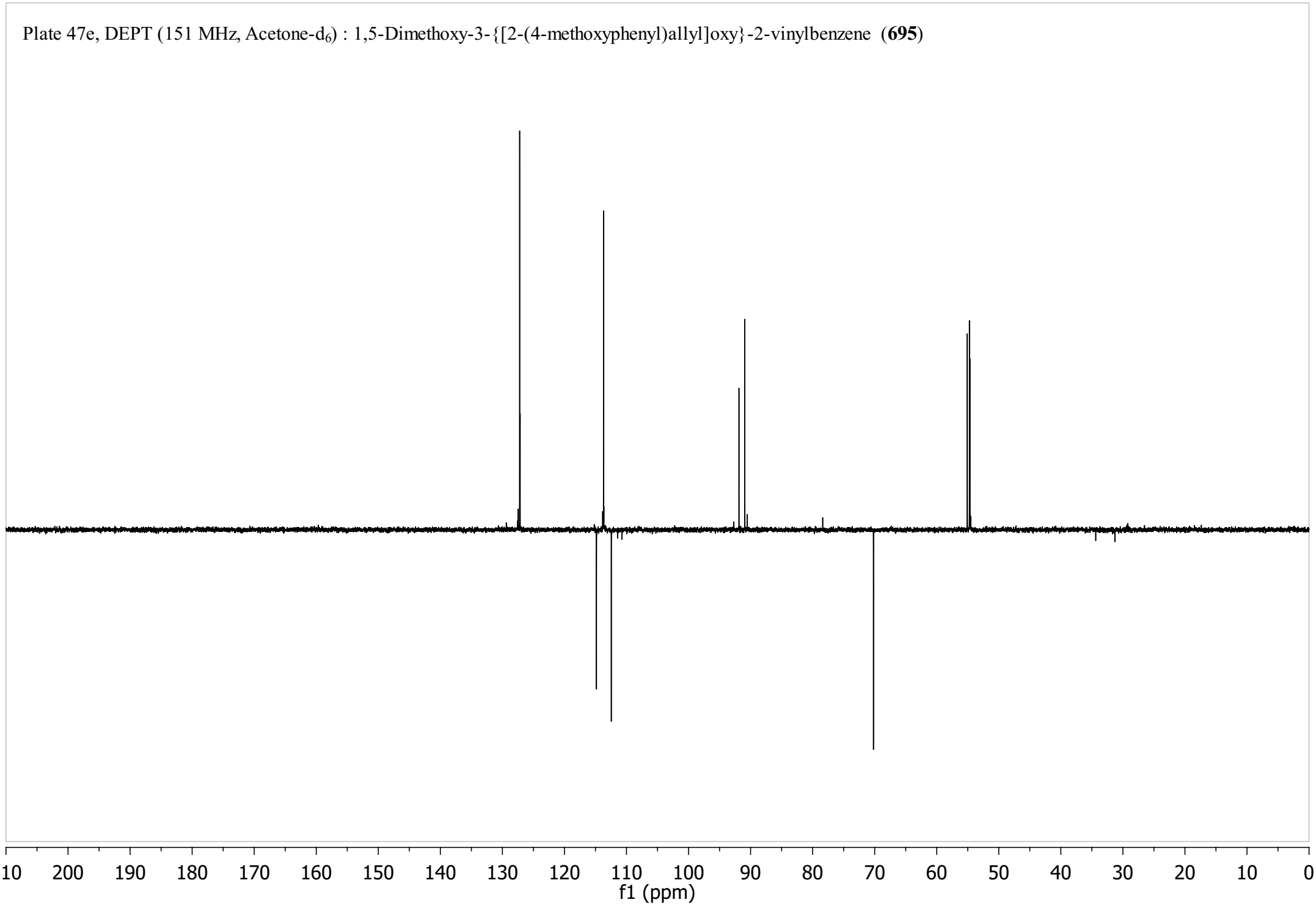
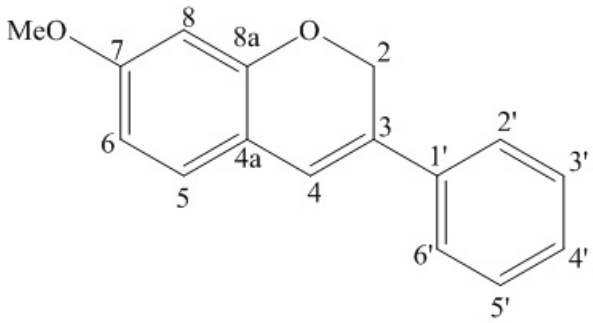
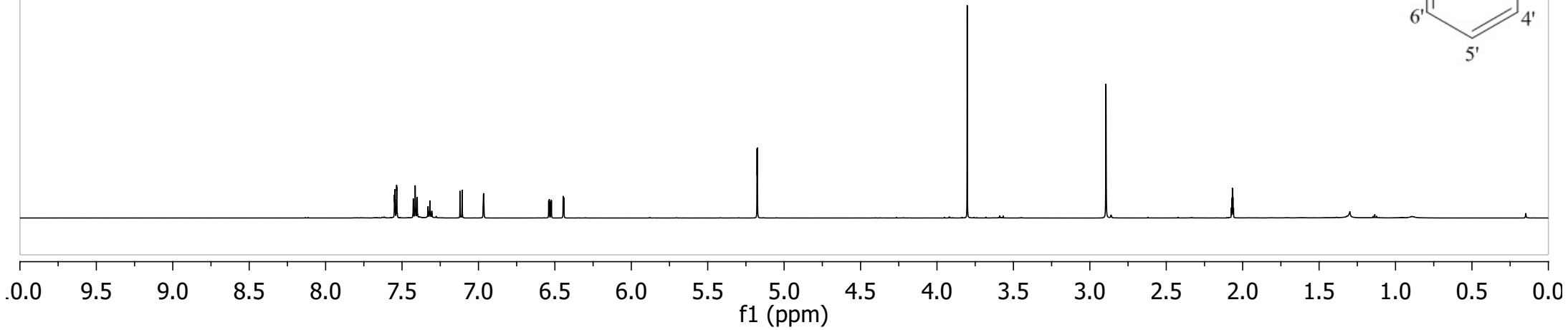


Plate 48a, ^{1}H NMR (600 MHz, Acetone-d_6) : 7-Methoxyisoflav-3-ene (**696**)

δ 7.55 – 7.53 (2H, m, H-2' and H-6'), 7.43 – 7.40 (2H, m, H-3' and H-5'), 7.33 – 7.31 (1H, m, H-4'), 7.11 (1H, d, *J* = 8.3 Hz, H-5), 6.97 (1H, br. s, H-4), 6.53 (1H, dd, *J* = 8.3, 2.4 Hz, H-6), 6.44 (1H, d, *J* = 2.4 Hz, H-8), 5.18 (1H, s, H-2), 5.17 (1H, s, H-2), 3.80 (3H, s, -OMe)





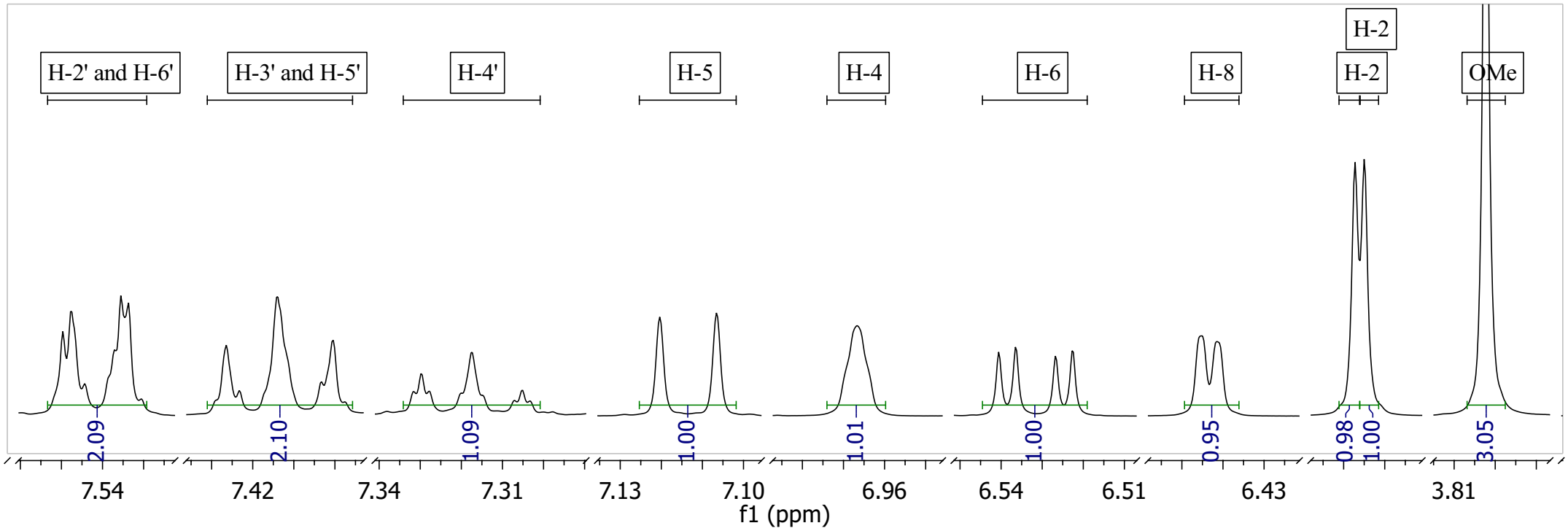
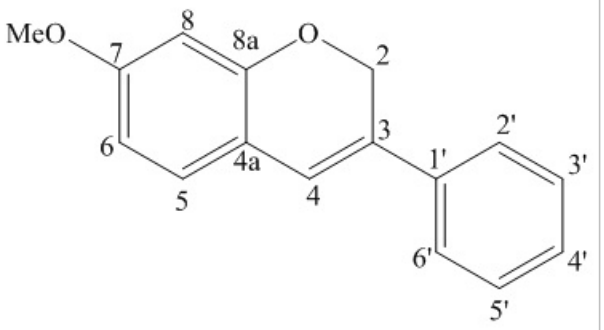
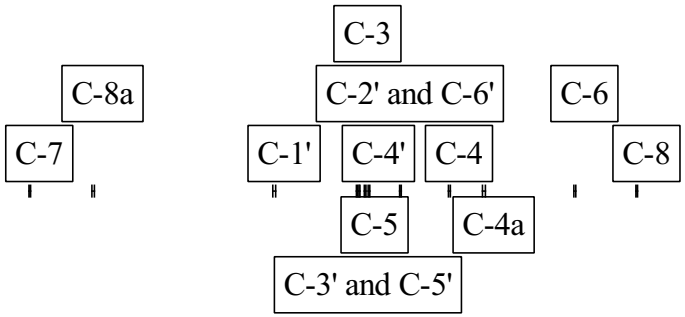


Plate 48b, ^{13}C NMR (151 MHz, Acetone-d_6) : 7-Methoxyisoflav-3-ene (**696**)

δ 161.86 (C-7), 155.64 (C-8a), 137.76 (C-1'), 129.55 (C-3), 129.50 (C-3' and C-5'), 128.85 (C-5), 128.47 (C-4'), 125.37 (C-2' and C-6'), 120.54 (C-4), 117.13 (C-4a), 108.19 (C-6), 102.08 (C-8), 67.67 (C-2), 55.72 (-OMe)





C-2

OMe

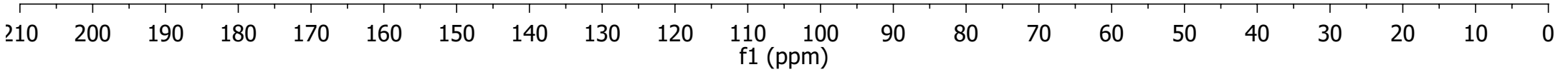


Plate 48c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 7-Methoxyisoflav-3-ene (**696**)

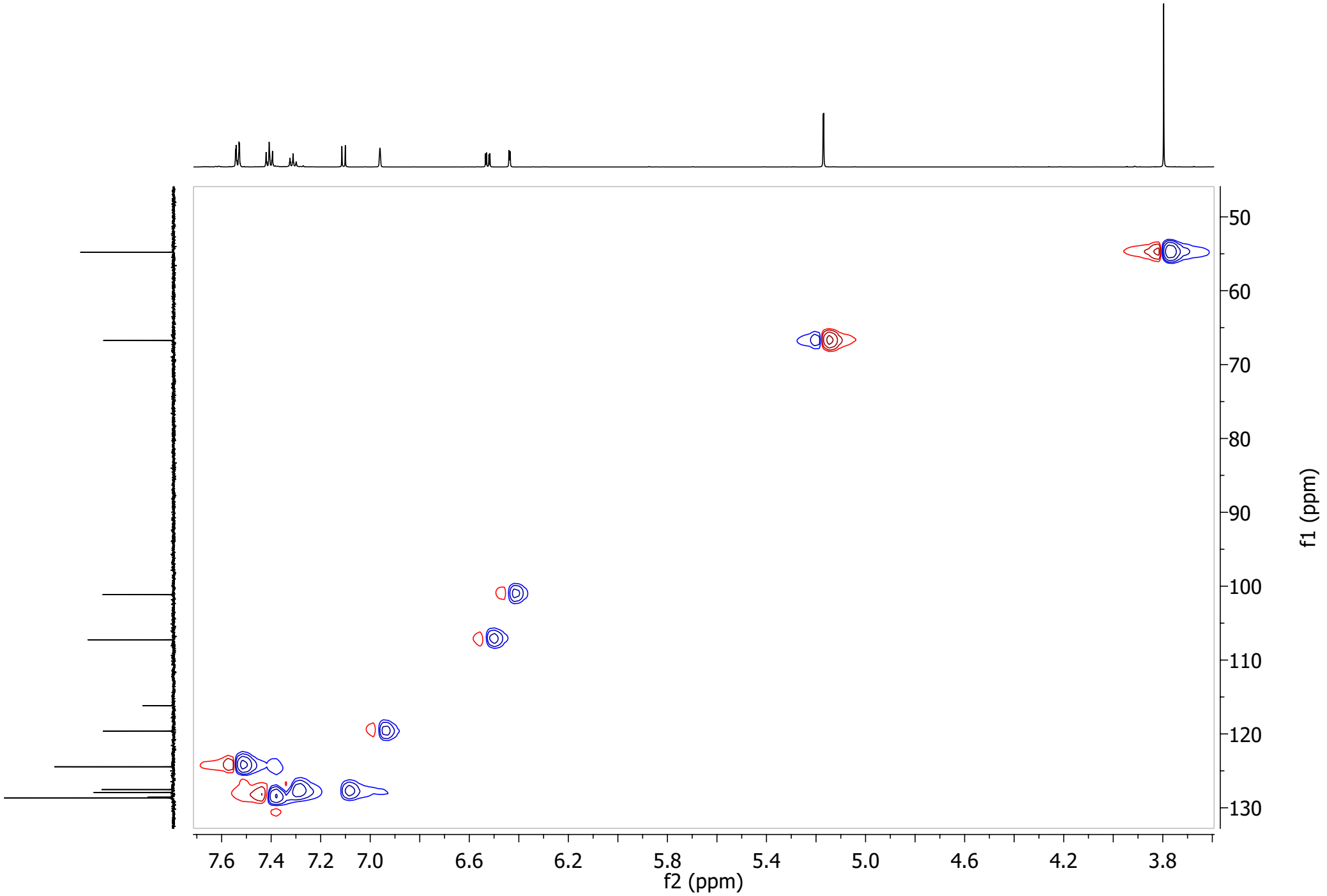


Plate 48d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 7-Methoxyisoflav-3-ene (**696**)

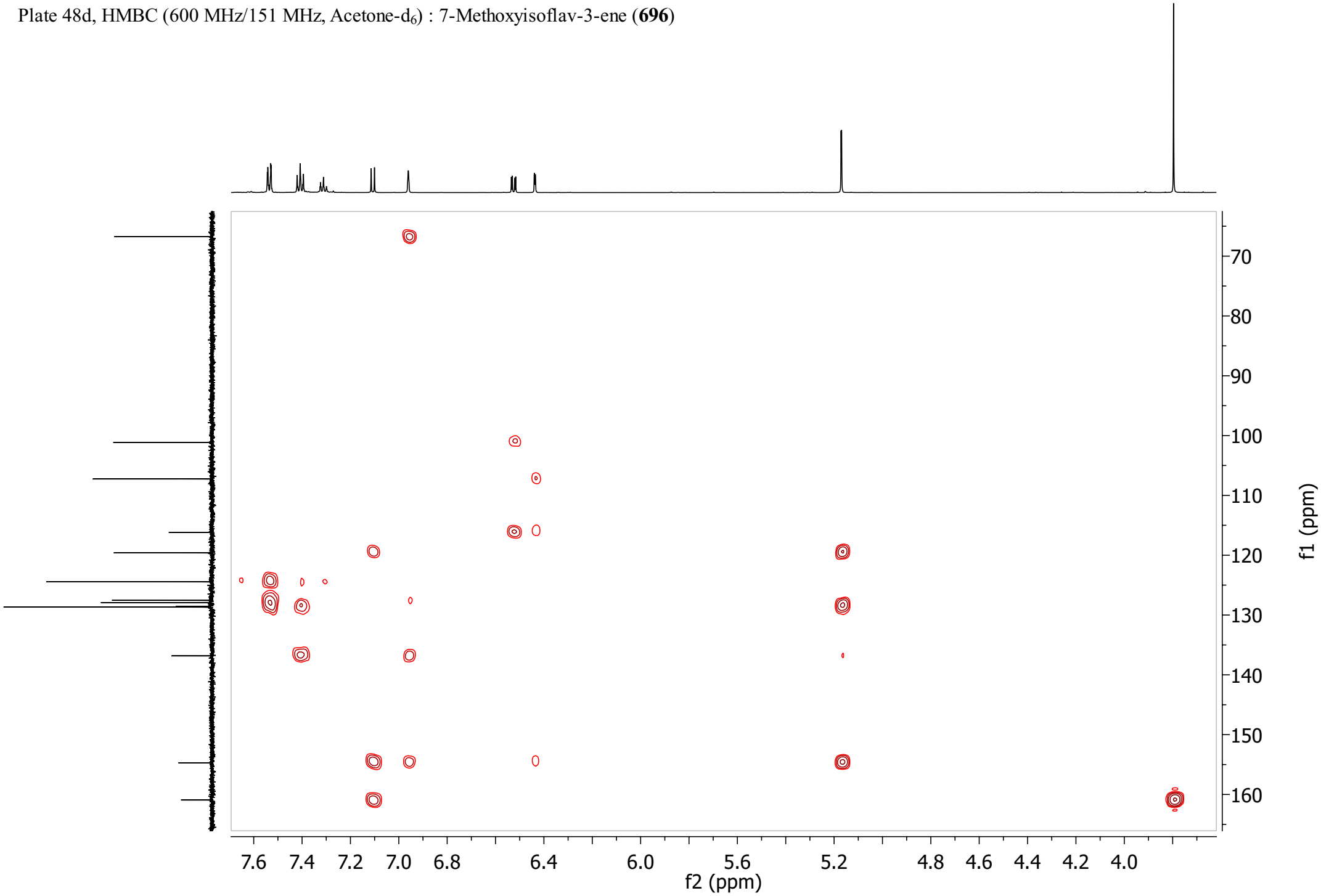


Plate 48e, DEPT (151 MHz, Acetone-d_6) : 7-Methoxyisoflav-3-ene (**696**)

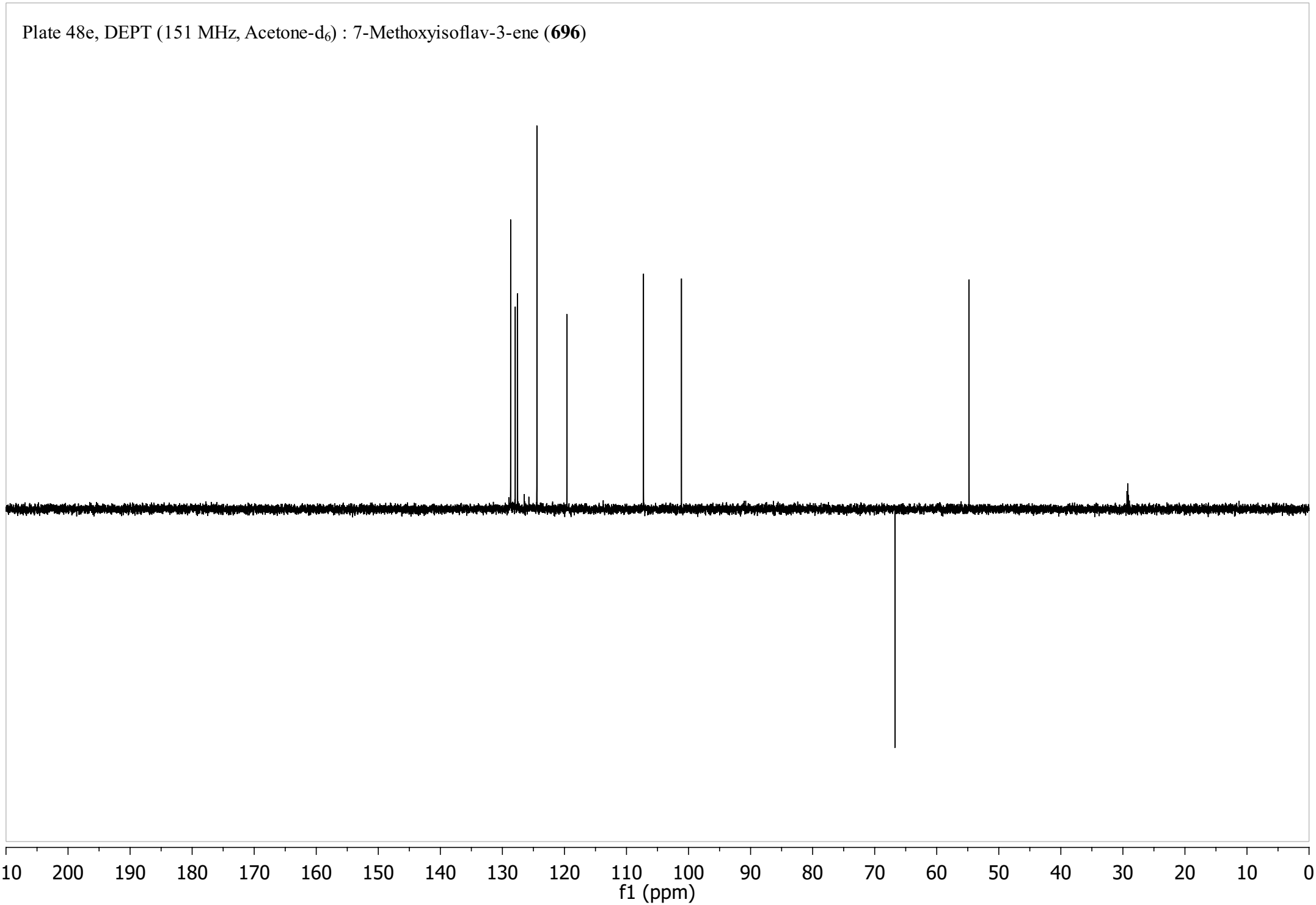
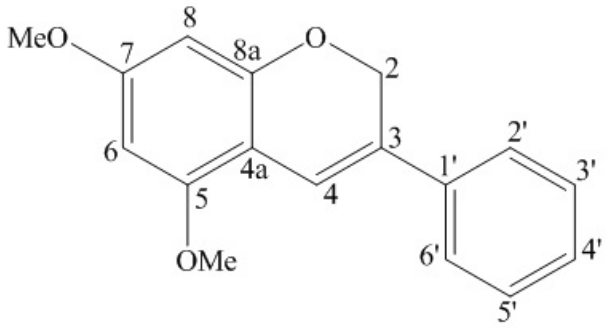
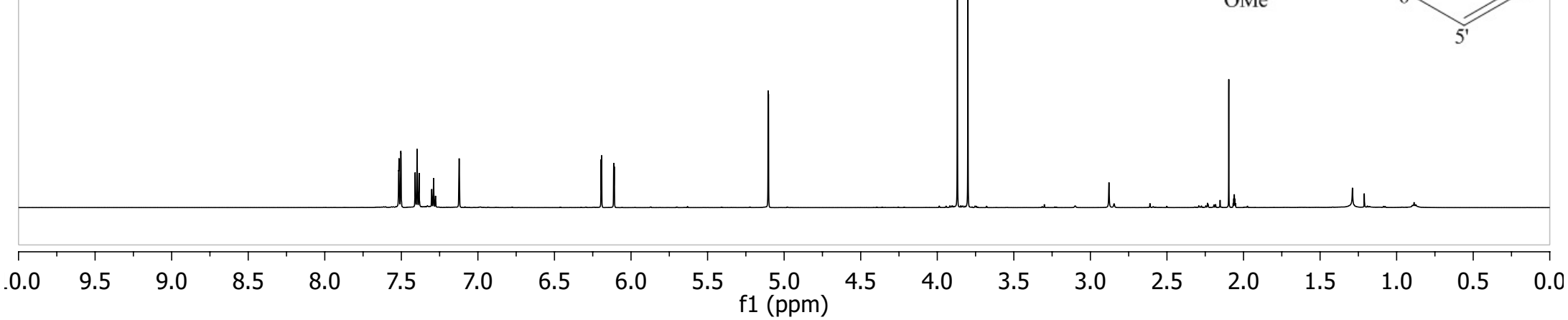


Plate 49a, ^{1}H NMR (600 MHz, Acetone-d_6) : 5,7-Dimethoxyisoflav-3-ene (**712**)

δ 7.52 – 7.49 (2H, m, H-2' and H-6'), 7.42 – 7.38 (2H, m, H-3' and H-5'), 7.31 – 7.27 (1H, m, H-4'), 7.12 (1H, br. s, H-4), 6.19 (1H, d, *J* = 2.2 Hz, H-6/8), 6.11 (1H, d, *J* = 2.2 Hz, H-6/8), 5.10 (1H, s, H-2), 5.10 (1H, s, H-2), 3.87 (3H, s, -OMe), 3.80 (3H, s, -OMe))





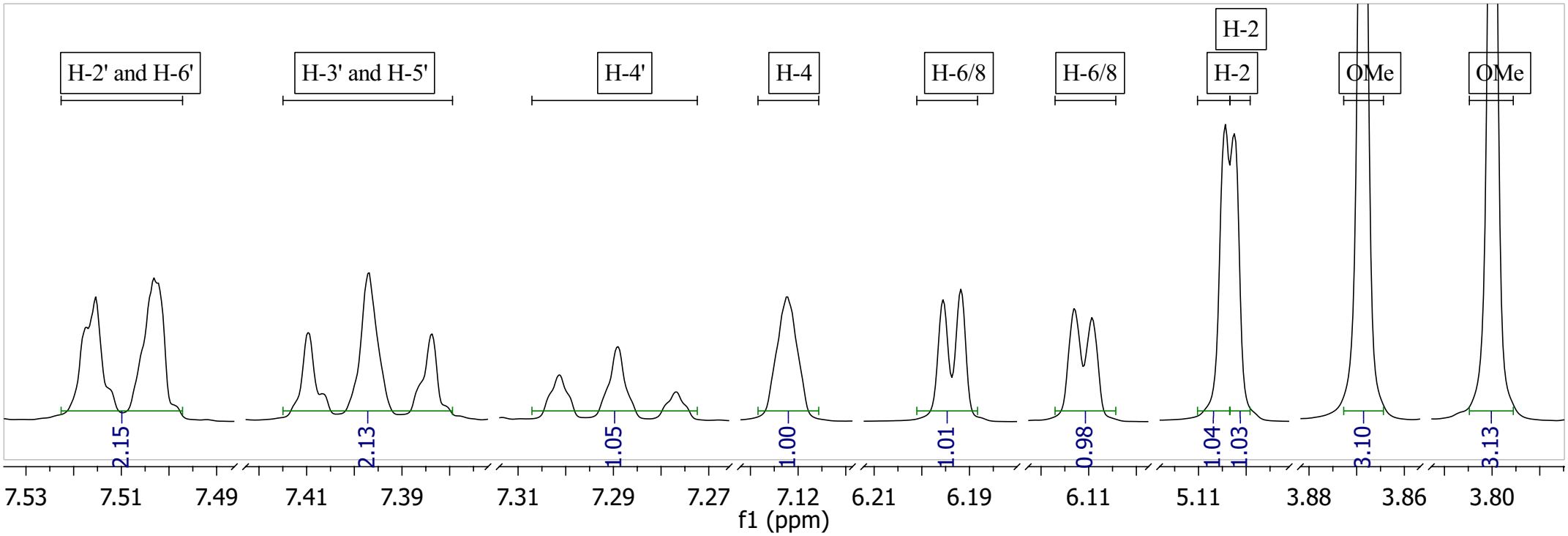
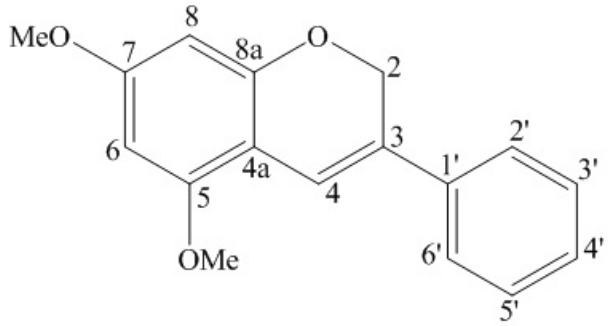


Plate 49b, ^{13}C NMR (151 MHz, Acetone-d_6) : 5,7-Dimethoxyisoflav-3-ene (**712**)

δ 162.48 (C-5/7), 157.69 (C-5/7), 156.23 (C-8a), 138.18 (C-1'), 129.62 (C-3' and C-5'), 128.20 (C-4'), 127.48 (C-3), 125.33 (C-2' and C-6'), 115.56 (C-4), 106.62 (C-4a), 94.37 (C-6/8), 92.71 (C-6/8), 67.53 (C-2), 56.14 (-O<u>Me</u>), 55.79 (-O<u>Me</u>)



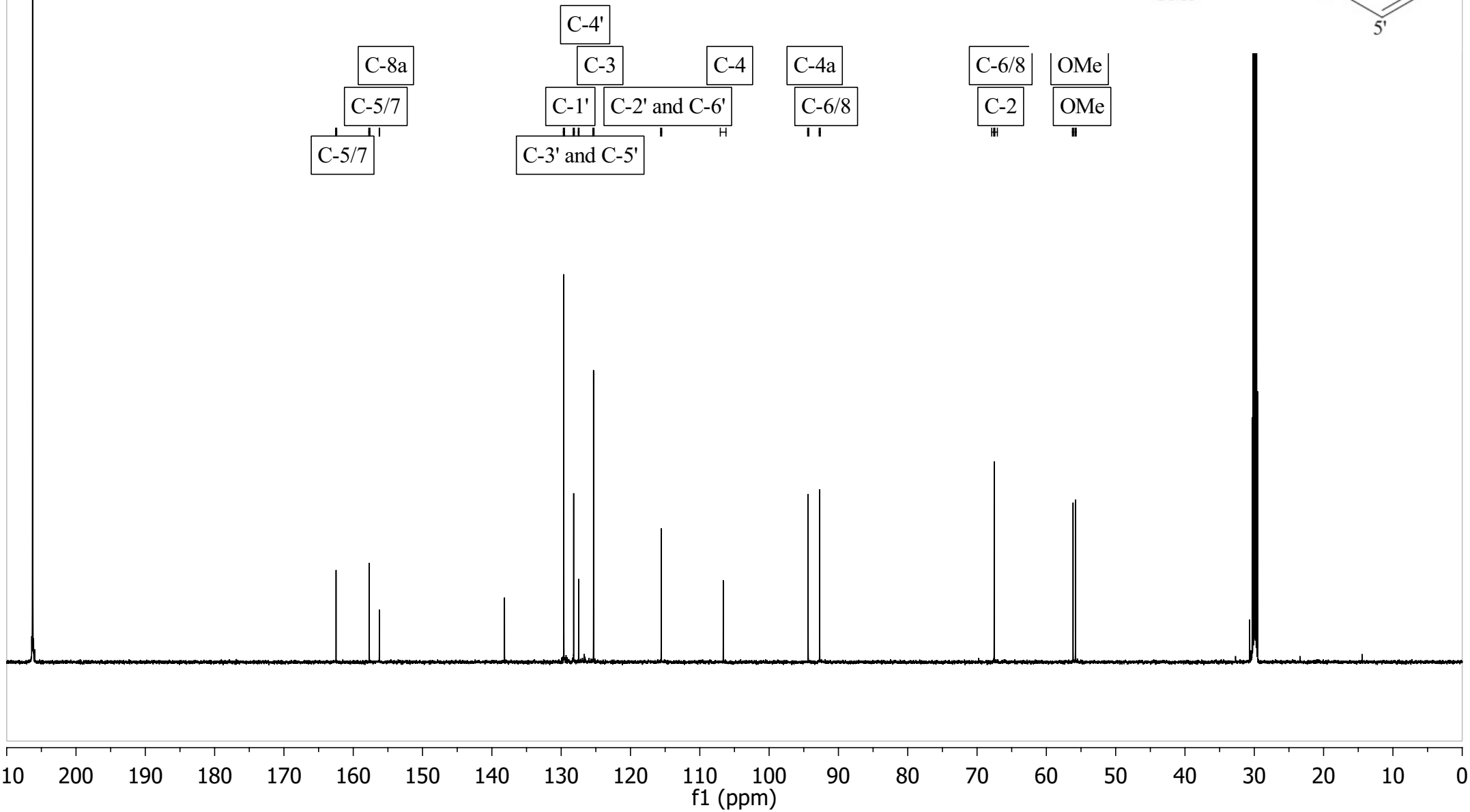


Plate 49c, HSQC (600/151 MHz, Acetone-d_6) : 5,7-Dimethoxyisoflav-3-ene (**712**)

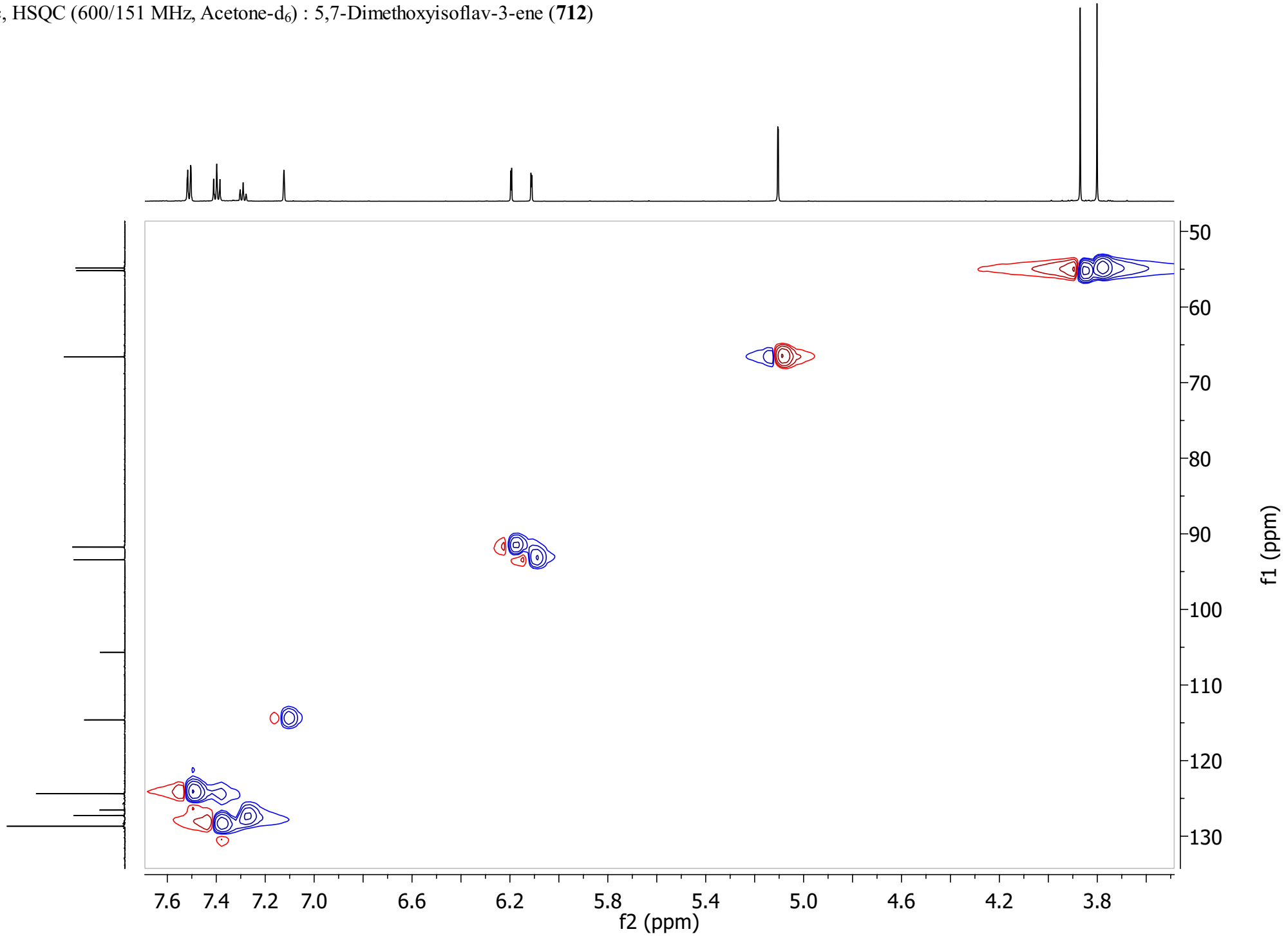


Plate 49d, HMBC (600/151 MHz, Acetone-d_6) : 5,7-Dimethoxyisoflav-3-ene (**712**)

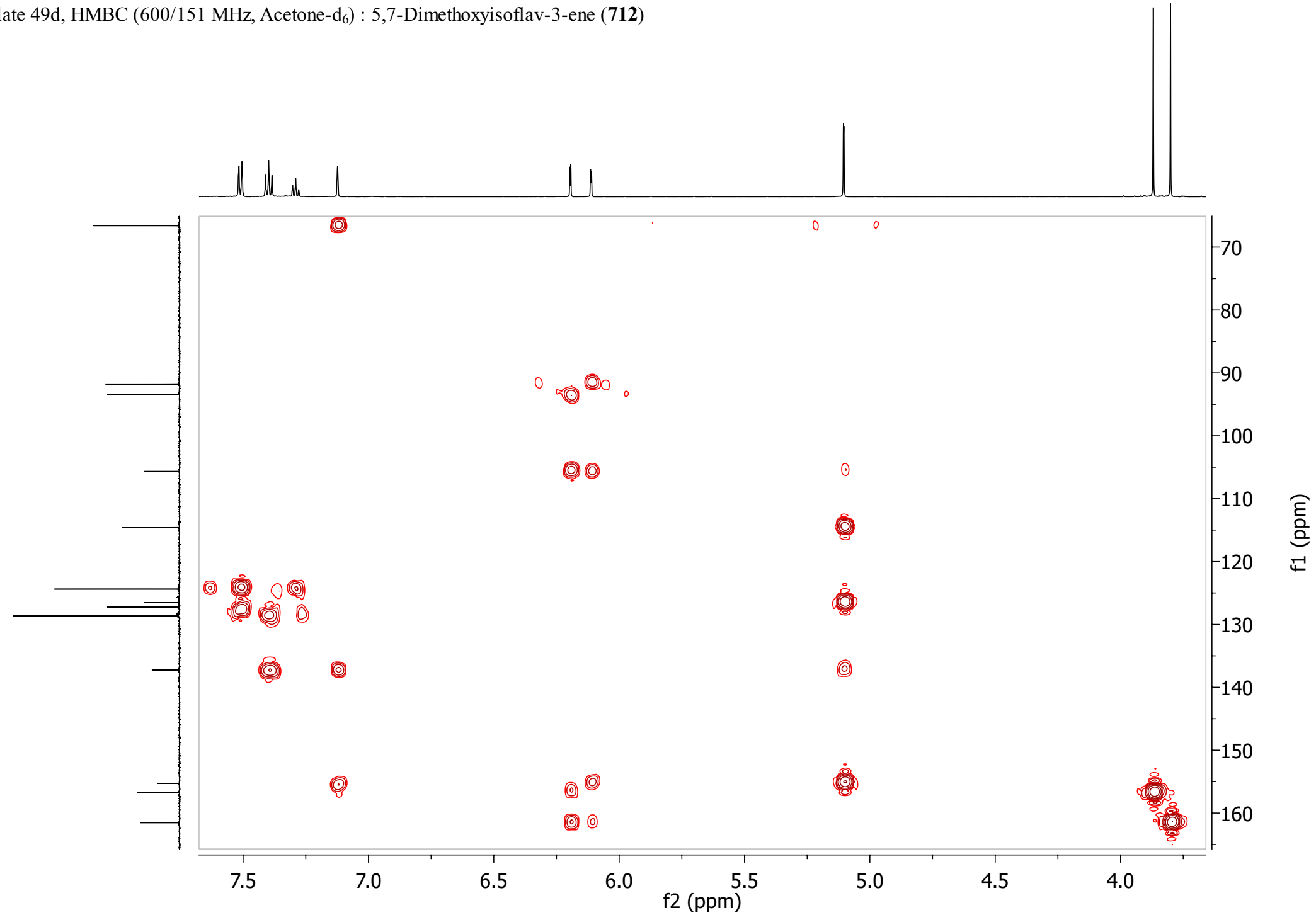


Plate 49e, DEPT (151 MHz, Acetone-d_6) : 5,7-Dimethoxyisoflav-3-ene (**712**)

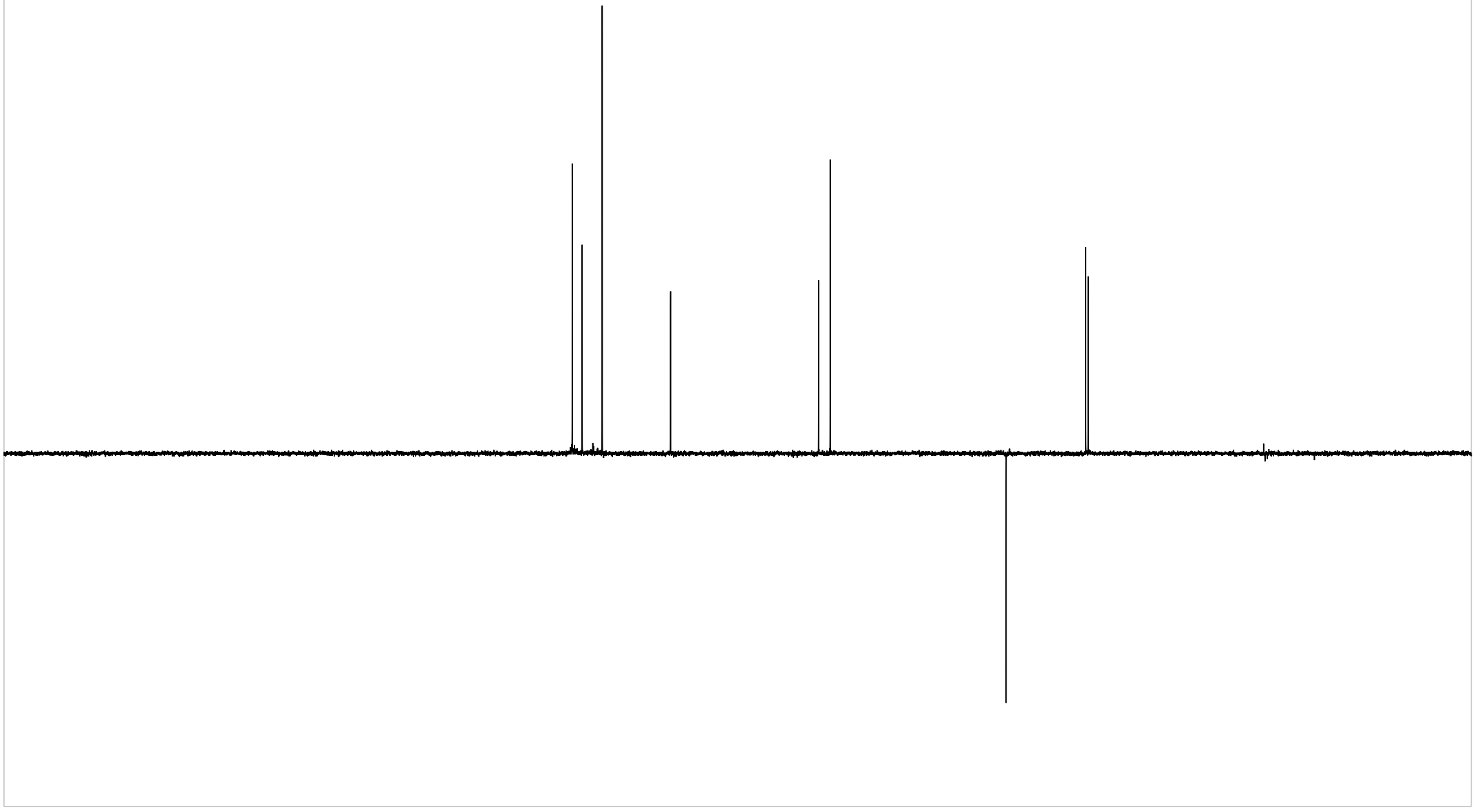
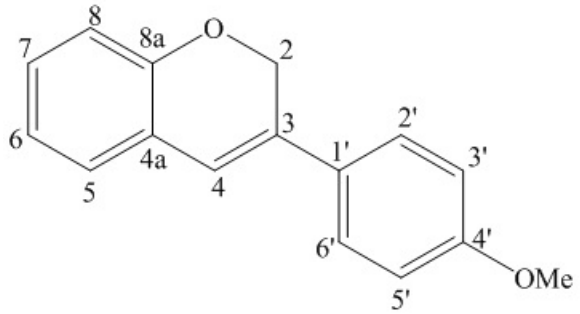


Plate 50a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4'-Methoxyisoflav-3-ene (**697**)

δ 7.50 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.13 (1H, dd, *J* = 7.4, 1.6 Hz, H-5), 7.11 (1H, ddd, *J* = 8.0, 7.7, 1.6 Hz, H-7), 6.97 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.90 (1H, ddd, *J* = 7.7, 7.4, 1.2 Hz, H-6), 6.87 (1H, br. s, H-4), 6.80 (1H, br. d, *J* = 8.0 Hz, H-8), 5.15 (1H, s, H-2), 5.14 (1H, s, H-2), 3.82 (3H, s, -OMe)



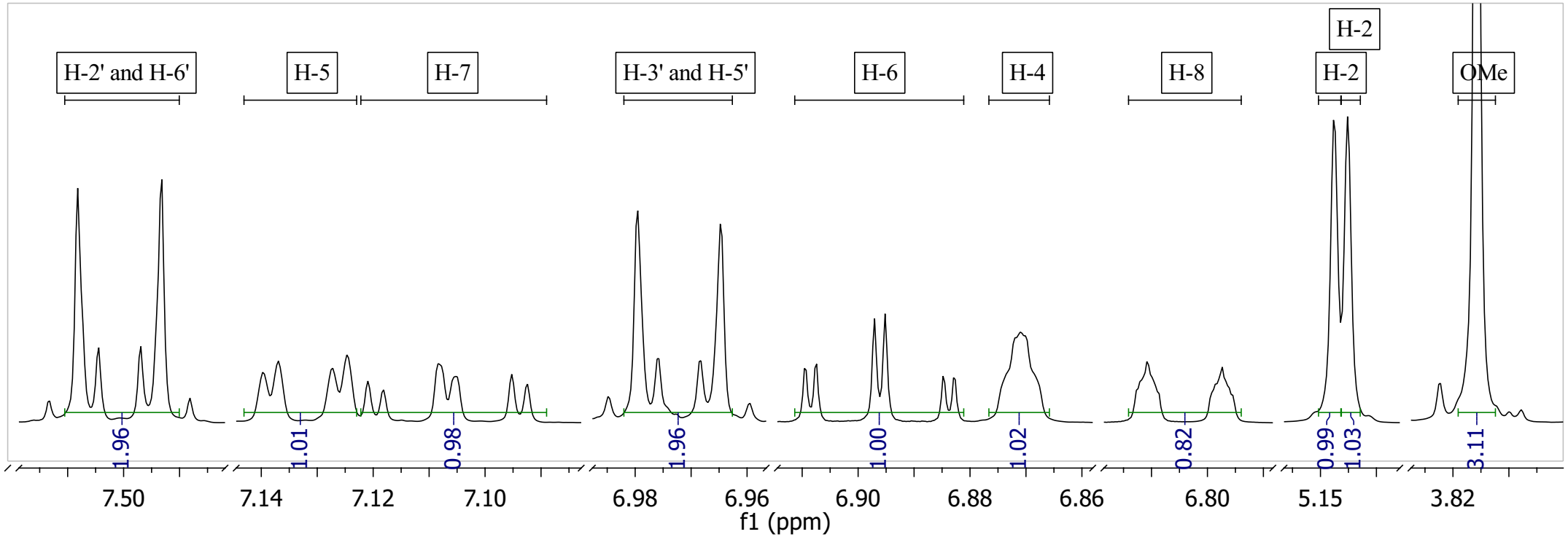
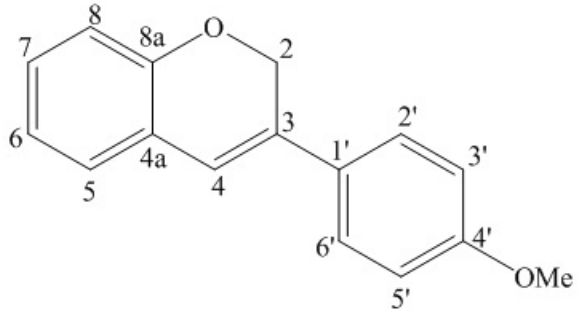


Plate 50b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4'-Methoxyisoflav-3-ene (**697**)

δ 160.67 (C-4'), 154.02 (C-8a), 132.42 (C-3), 129.74 (C-1'), 129.39 (C-5/7), 127.69 (C-5/7), 126.90 (C-2' and C-6'), 124.20 (C-4a), 122.32 (C-6), 118.65 (C-4), 115.97 (C-8), 114.97 (C-3' and C-5'), 67.53 (C-2), 55.61 (-OMe)



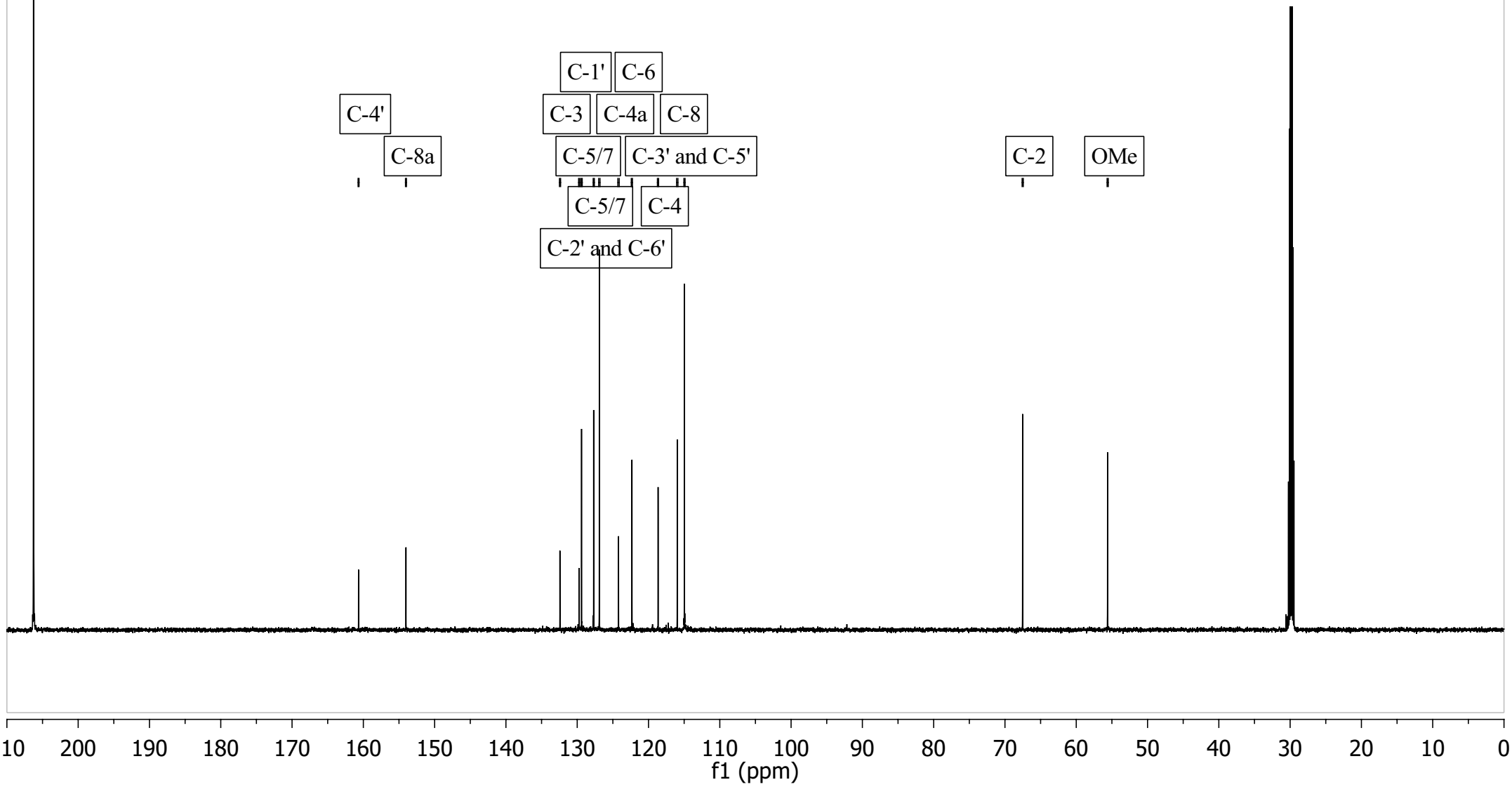


Plate 50c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 4'-Methoxyisoflav-3-ene (**697**)

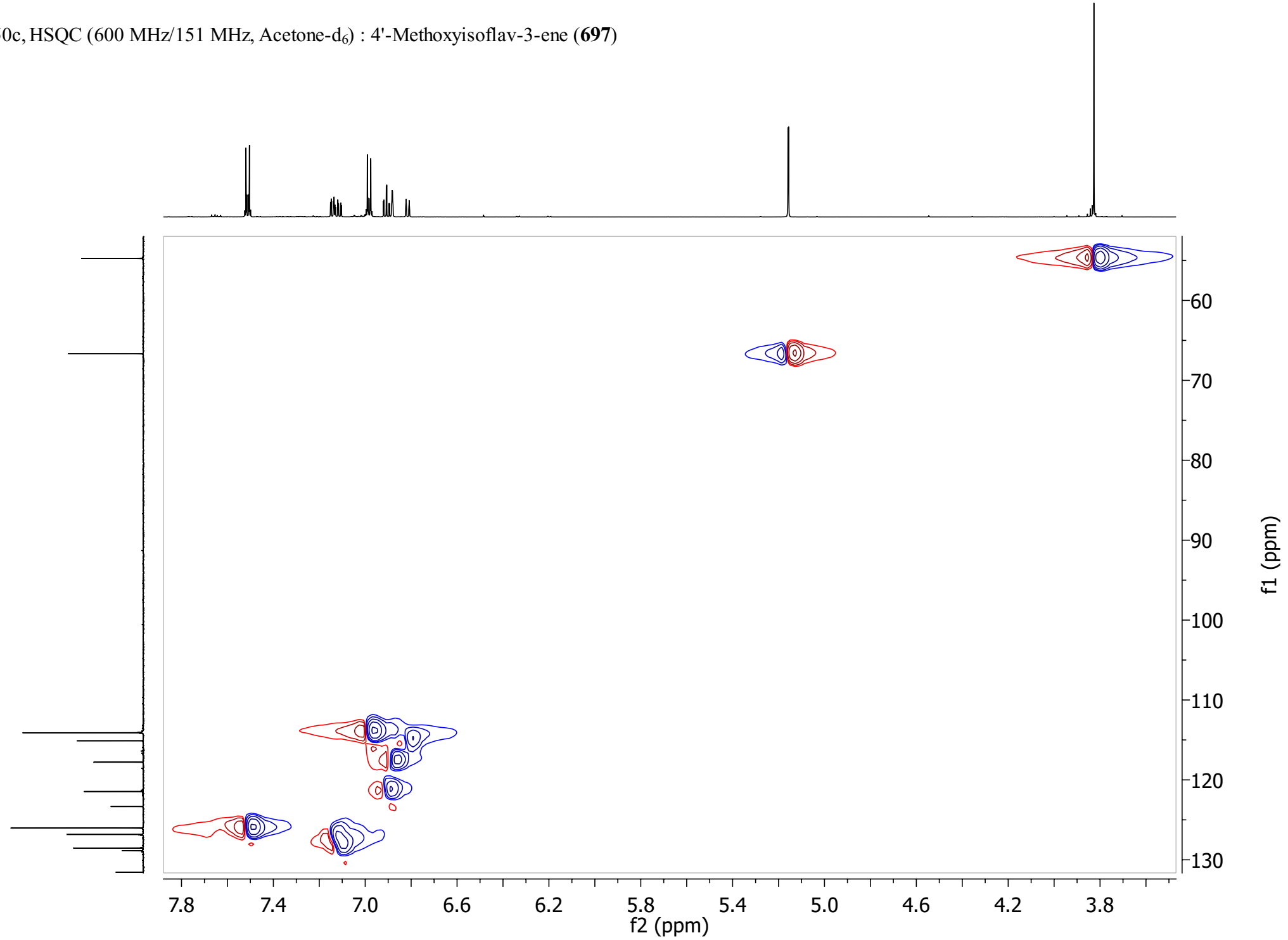


Plate 50d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 4'-Methoxyisoflav-3-ene (**697**)

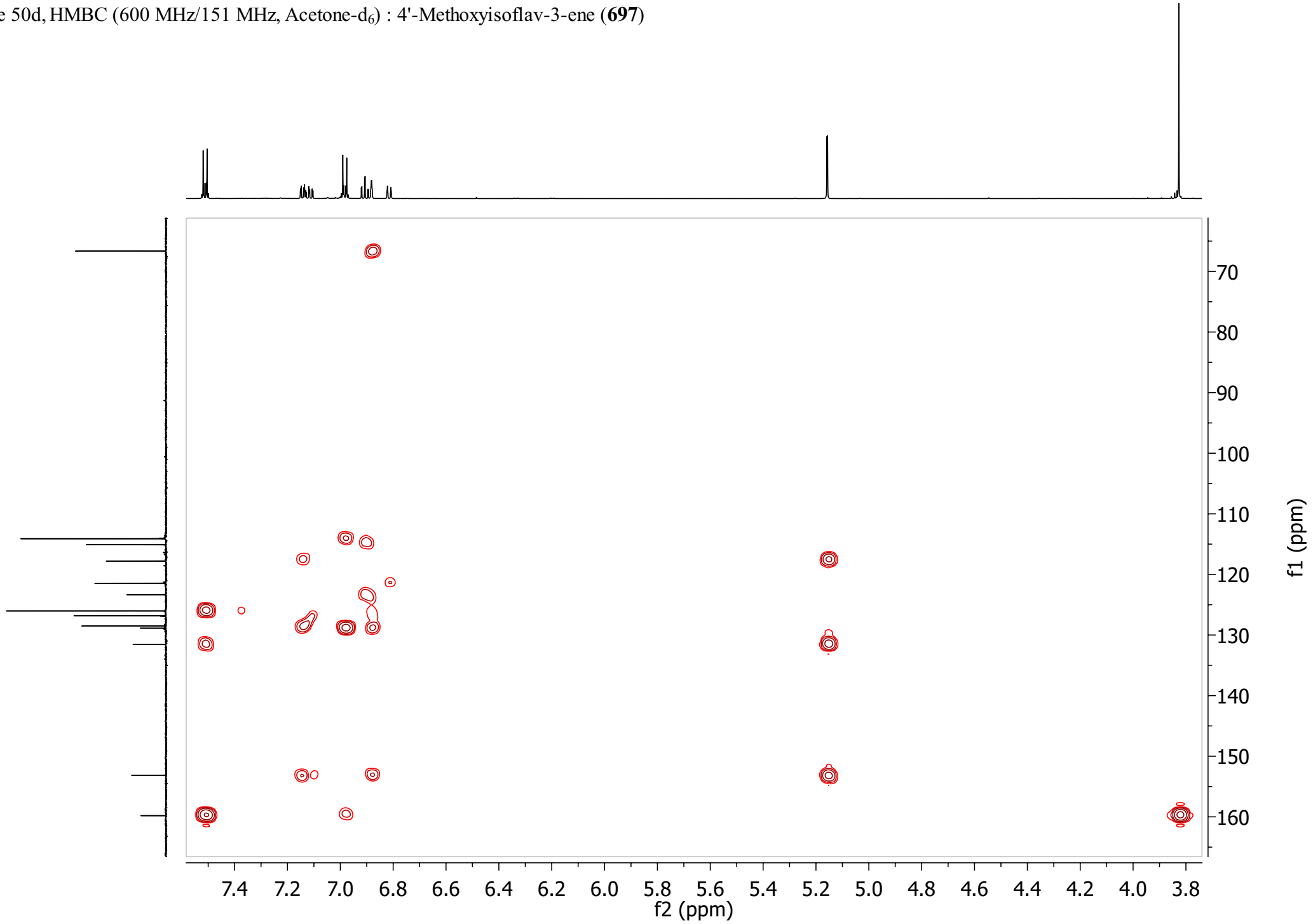


Plate 50e, DEPT (151 MHz, Acetone-d_6) : 4'-Methoxyisoflav-3-ene (**697**)

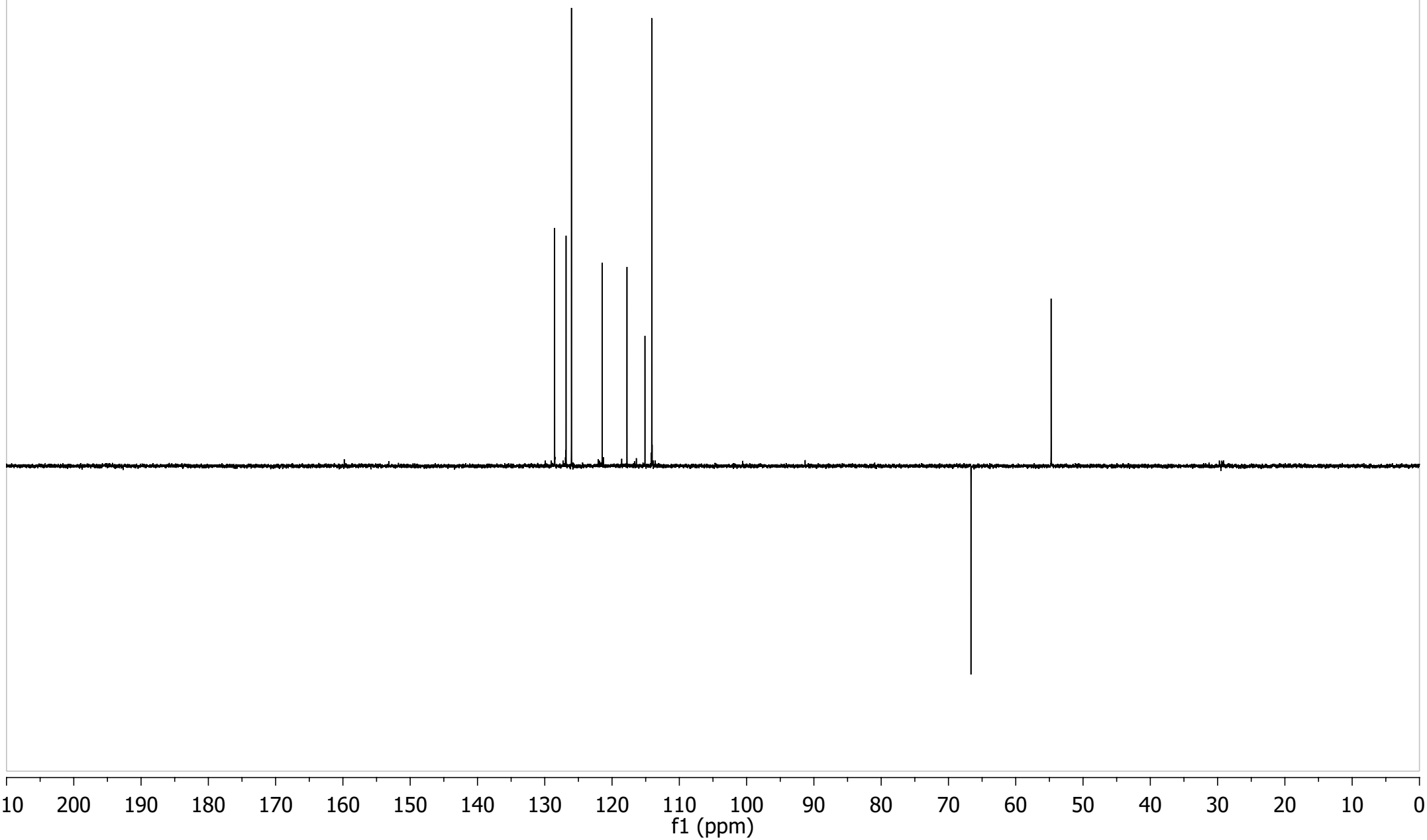
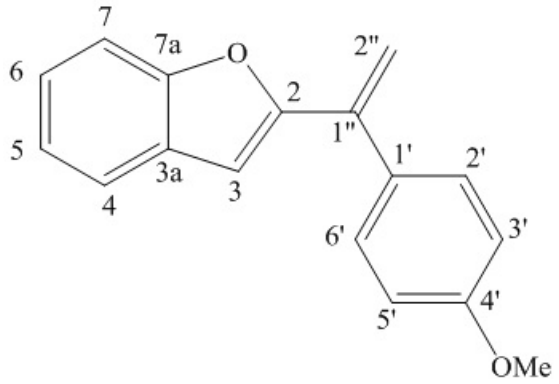
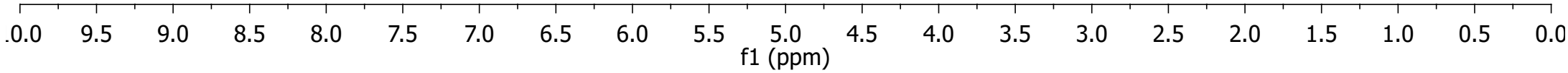


Plate 51a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-[1-(4-Methoxyphenyl)vinyl]benzofuran (**701**)

δ 7.60 – 7.58 (1H, m, H-4), 7.54 – 7.52 (1H, m, H-7), 7.46 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 7.35 – 7.32 (1H, m, H-6), 7.25 – 7.22 (1H, m H-5), 6.94 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 6.66 (1H, br. s, H-3), 5.94 (1H, br. d, *J* = 1.0 Hz, H-2''), 5.41 (1H, br. d, *J* = 1.0 Hz, H-2''), 3.85 (3H, s, OMe)





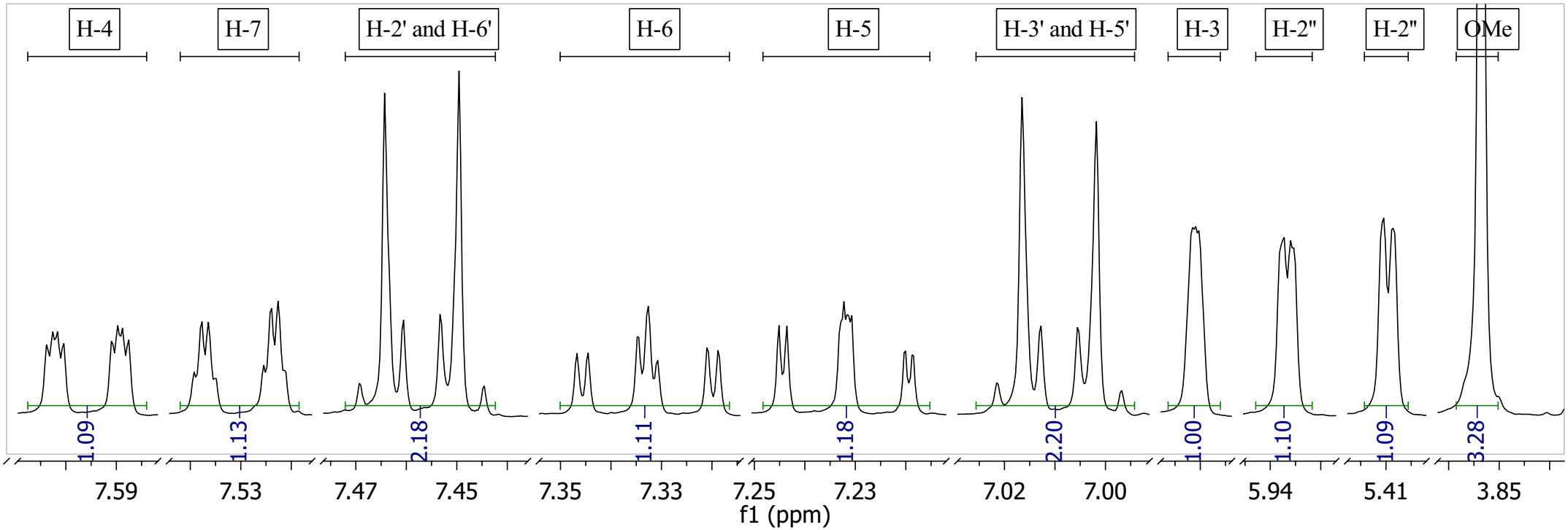
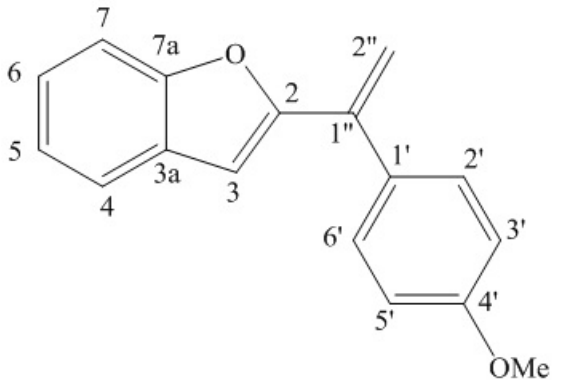


Plate 51b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-[1-(4-Methoxyphenyl)vinyl]benzofuran (**701**)

δ 160.87 (C-4'), 156.92 (C-2), 155.76 (C-7a), 140.01 (C-1''), 132.10 (C-1'), 130.35 (C-2' and C-6'), 129.79 (C-3a), 125.84 (C-6), 123.85 (C-5), 122.23 (C-4), 114.65 (C-3' and C-5'), 114.49 (C-2''), 111.70 (C-7), 106.60 (C-3), 55.62 (OMe)



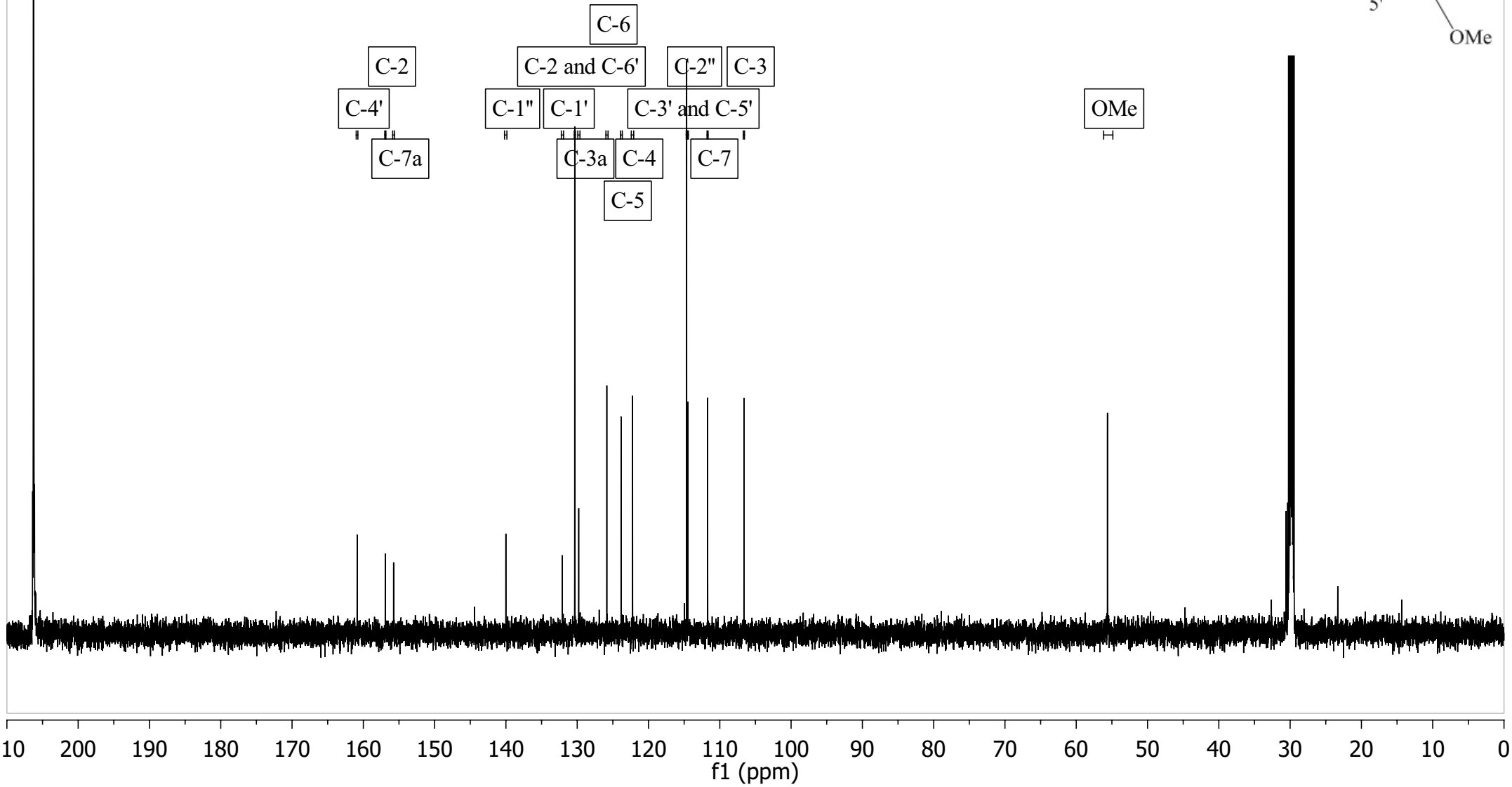


Plate 51c, HSQC (600 MHz/151 MHz, Acetone-d_6) :2-[1-(4-Methoxyphenyl)vinyl]benzofuran (**701**)

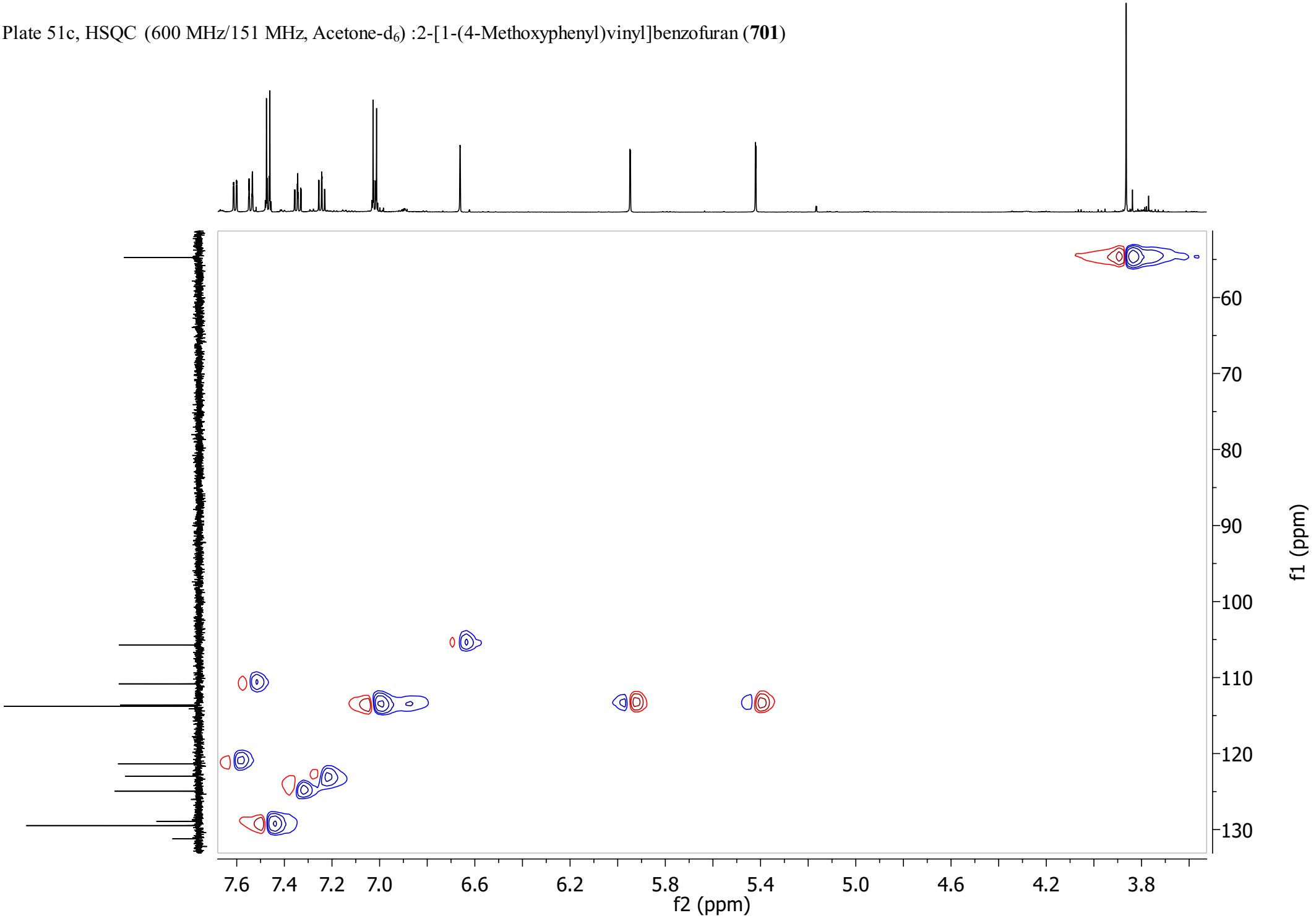


Plate 51d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-[1-(4-Methoxyphenyl)vinyl]benzofuran (**701**)

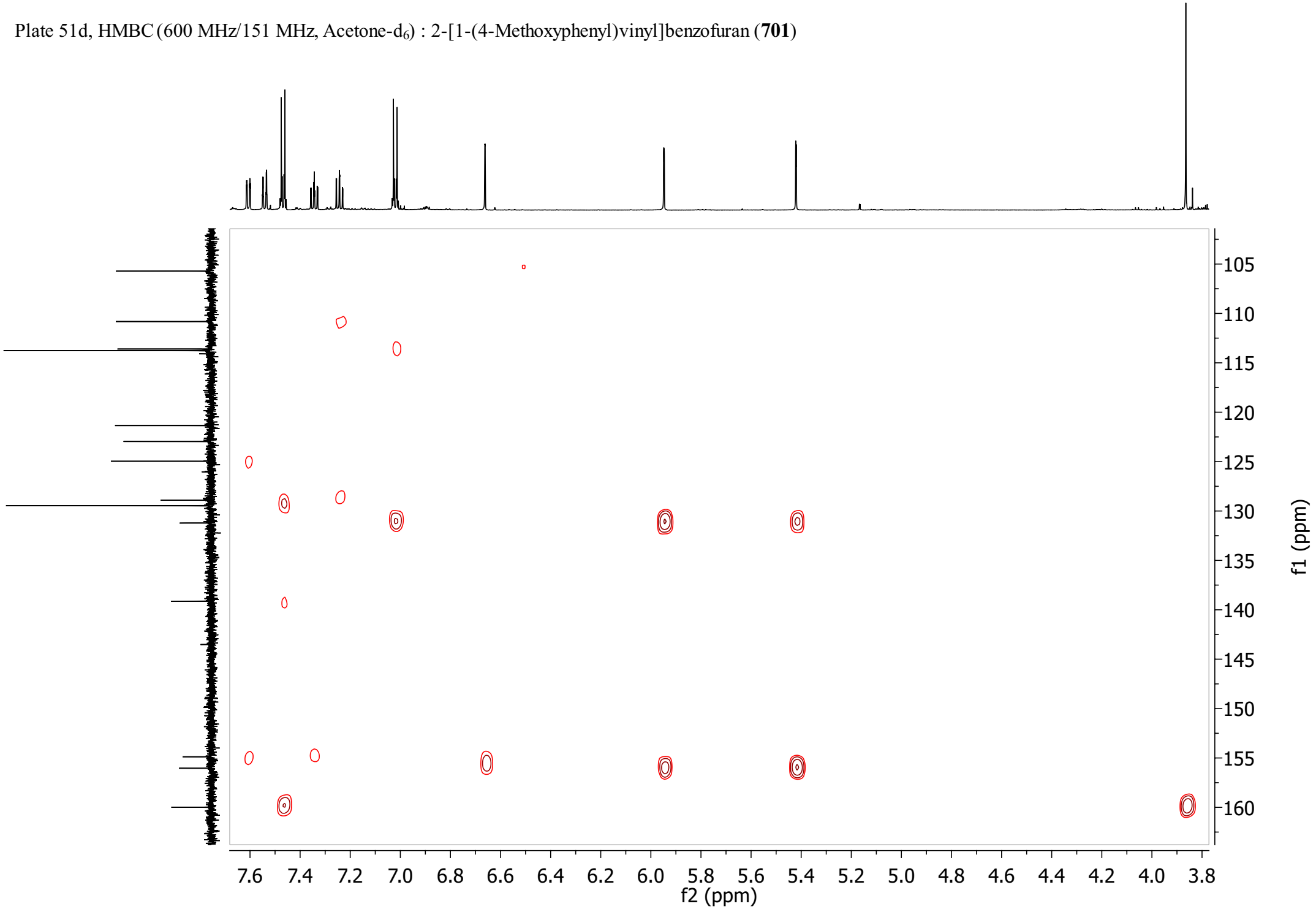


Plate 51e, DEPT (151 MHz, Acetone-d_6) : 2-[1-(4-Methoxyphenyl)vinyl]benzofuran (**701**)

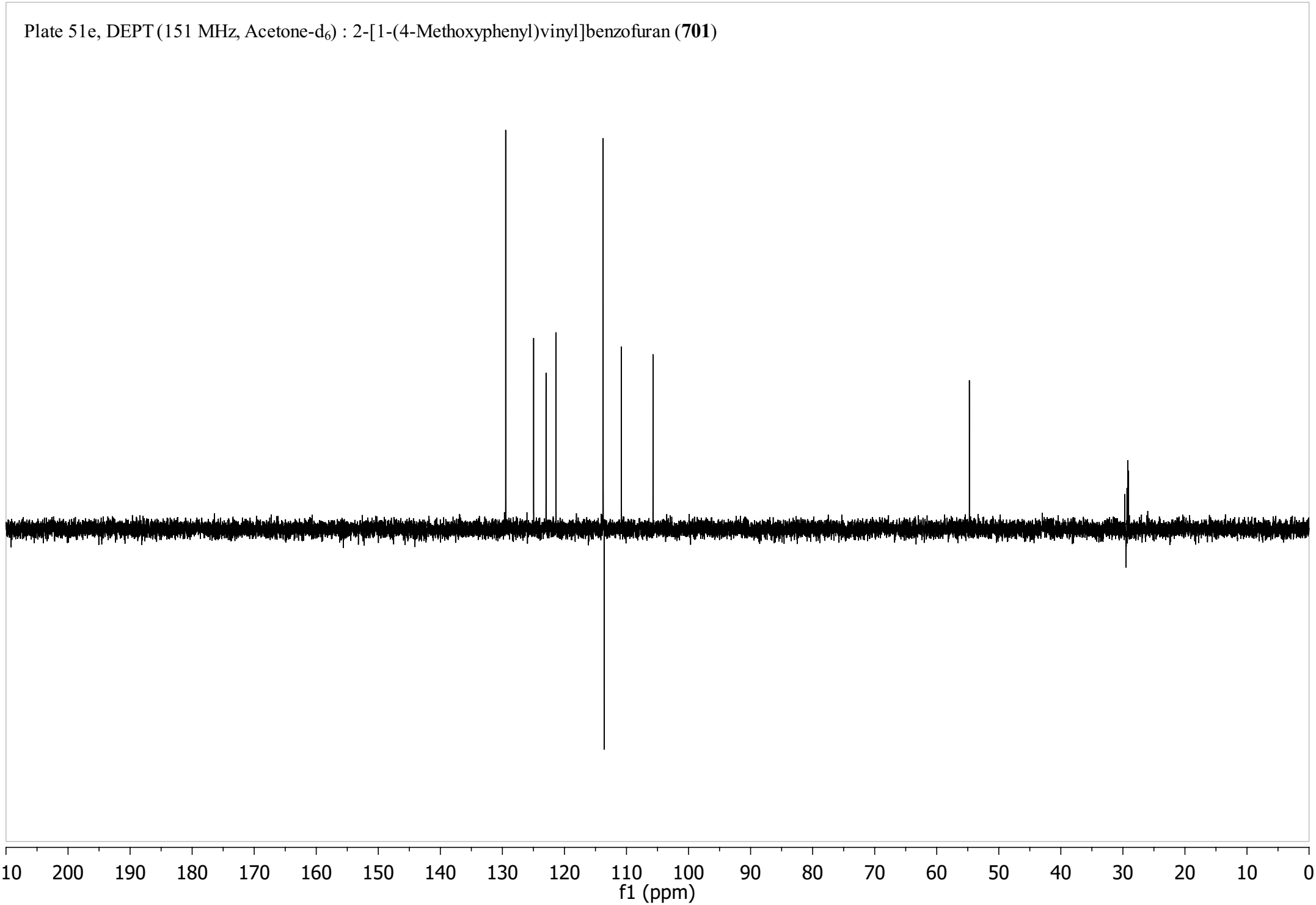


Plate 51f, NOESY (600 MHz, Acetone-d_6) : 2-(1-(4-Methoxyphenyl)vinyl)benzofuran (**701**)

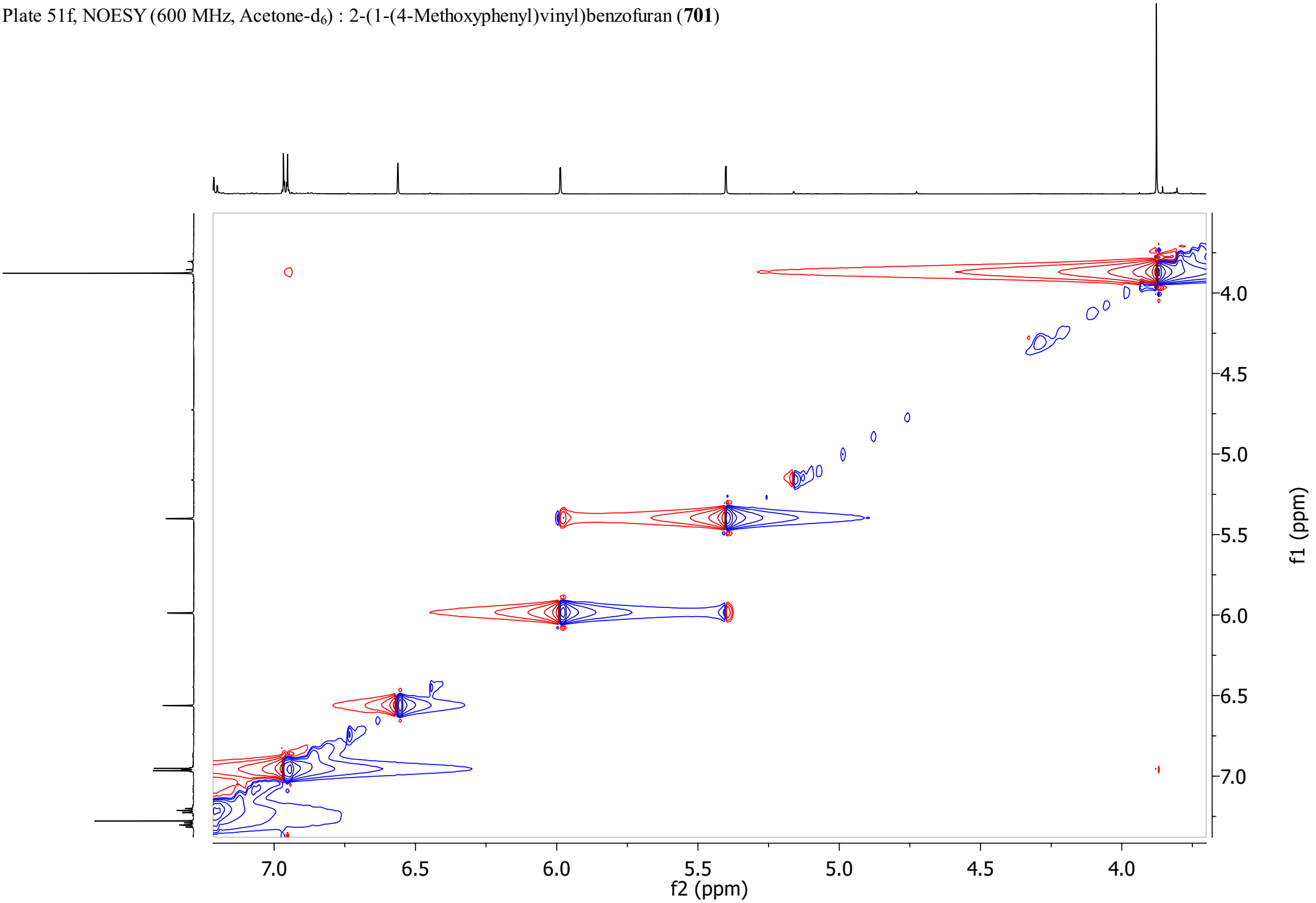
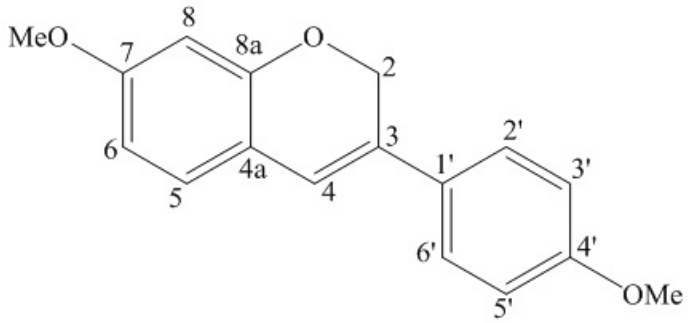
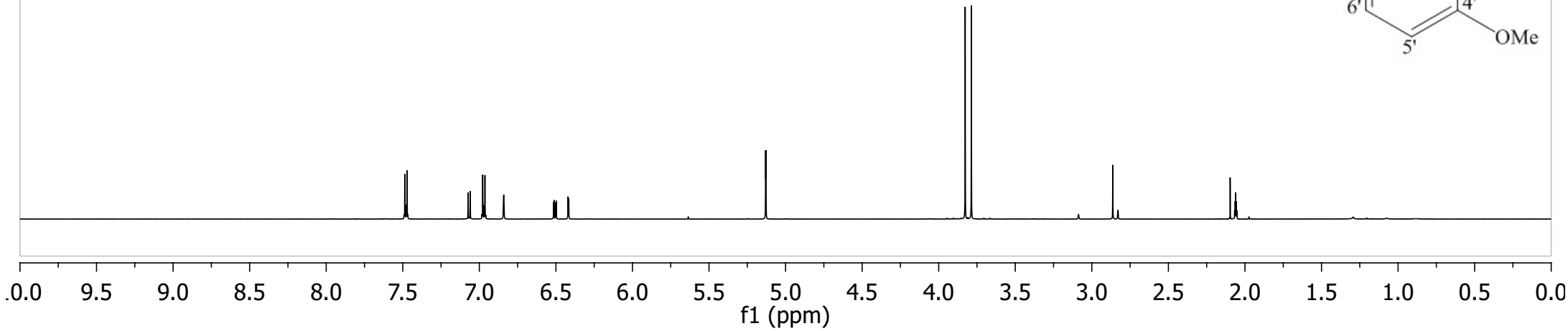


Plate 52a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4',7-Dimethoxyisoflav-3-ene (**698**)

δ 7.48 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.07 (1H, d, *J* = 8.3 Hz, H-5), 6.97 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.84 (1H, br. s, H-4), 6.51 (1H, dd, *J* = 8.3, 2.5 Hz, H-6), 6.42 (1H, d, *J* = 2.5 Hz, H-8), 5.13 (1H, br. s, H-2), 5.13 (1H, br. s, H-2), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe)





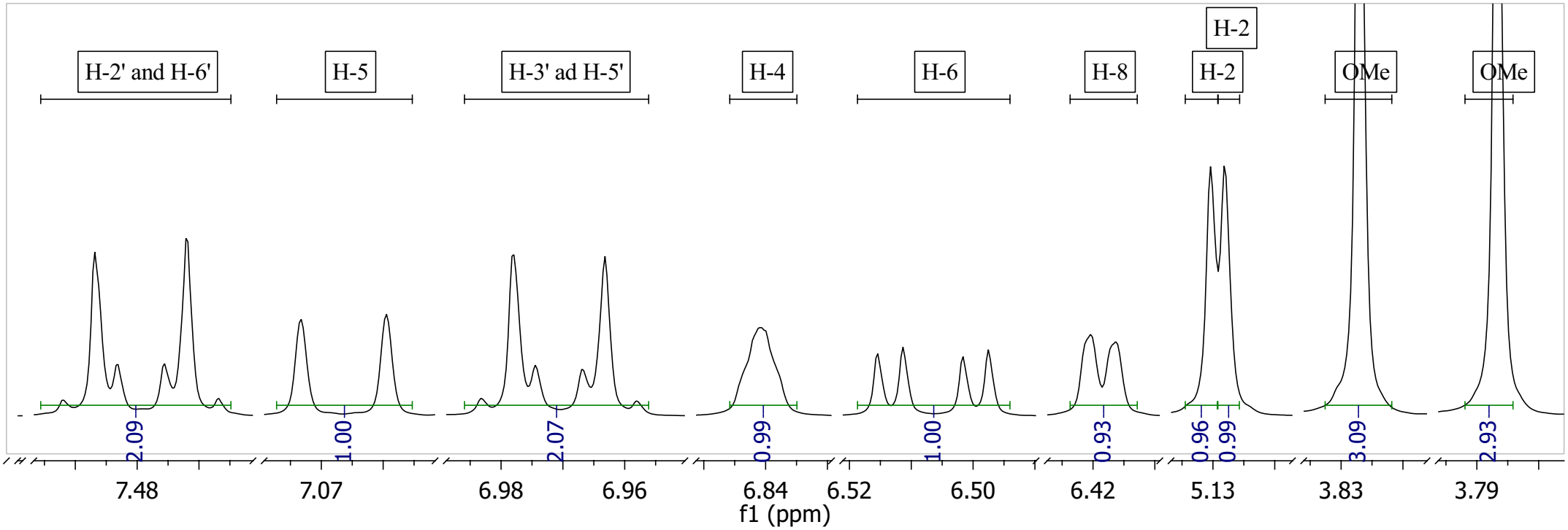
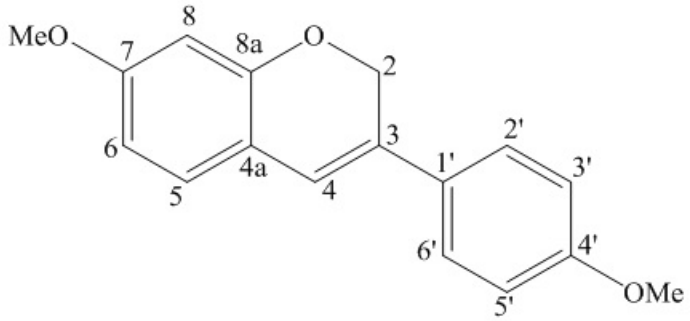


Plate 52b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4',7-Dimethoxyisoflav-3-ene (**698**)

δ 161.55 (C-7), 160.44 (C-4'), 155.38 (C-8a), 130.18 (C-1'), 129.35 (C-3), 128.49 (C-5), 126.70 (C-2' and C-6'), 118.61 (C-4), 117.40 (C-4a), 115.02 (C-3' and C-5'), 108.09 (C-6), 102.09 (C-8), 67.73 (C-2), 55.72 (-OMe), 55.67 (-OMe)



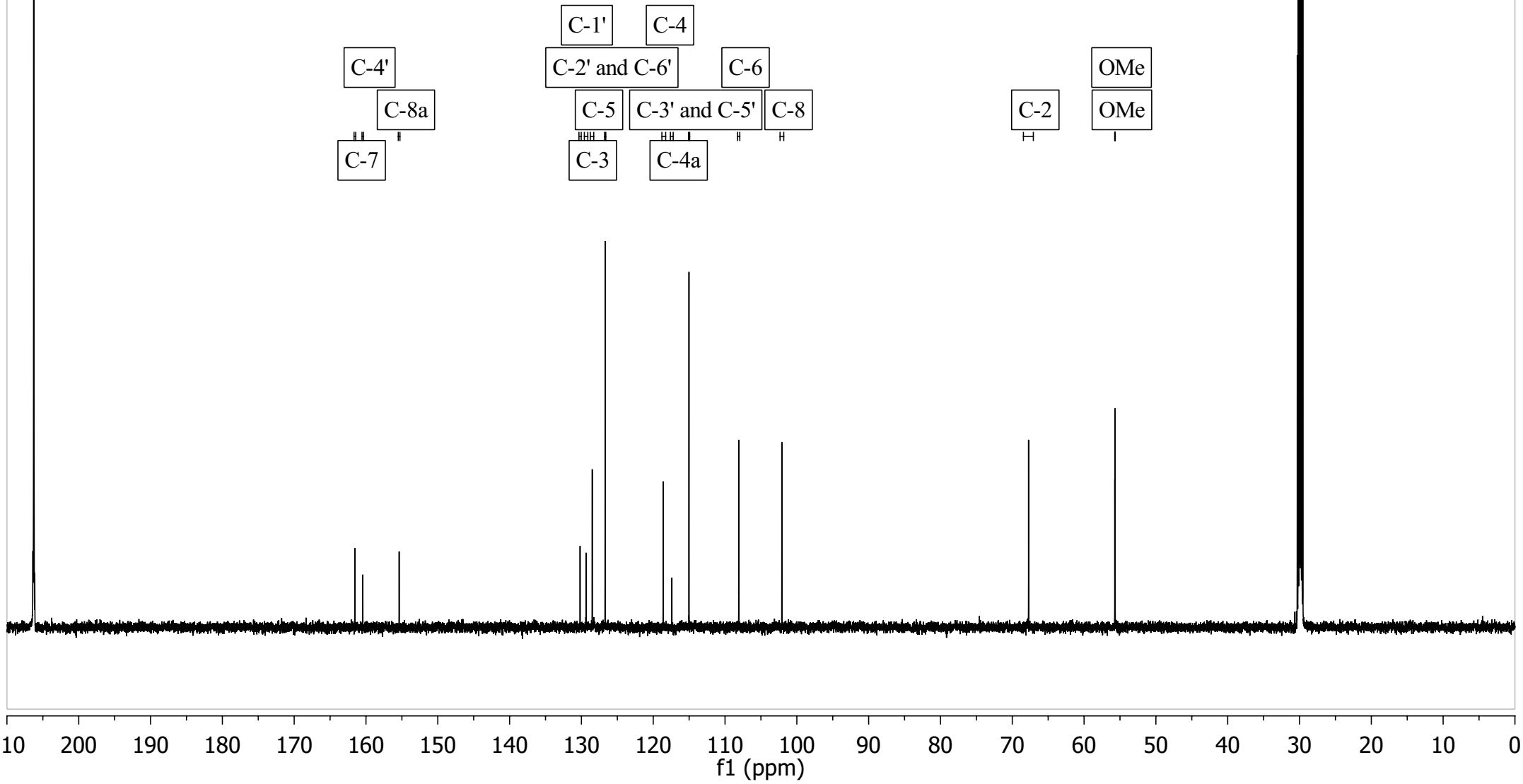


Plate 52c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 4',7-Dimethoxyisoflav-3-ene (**698**)

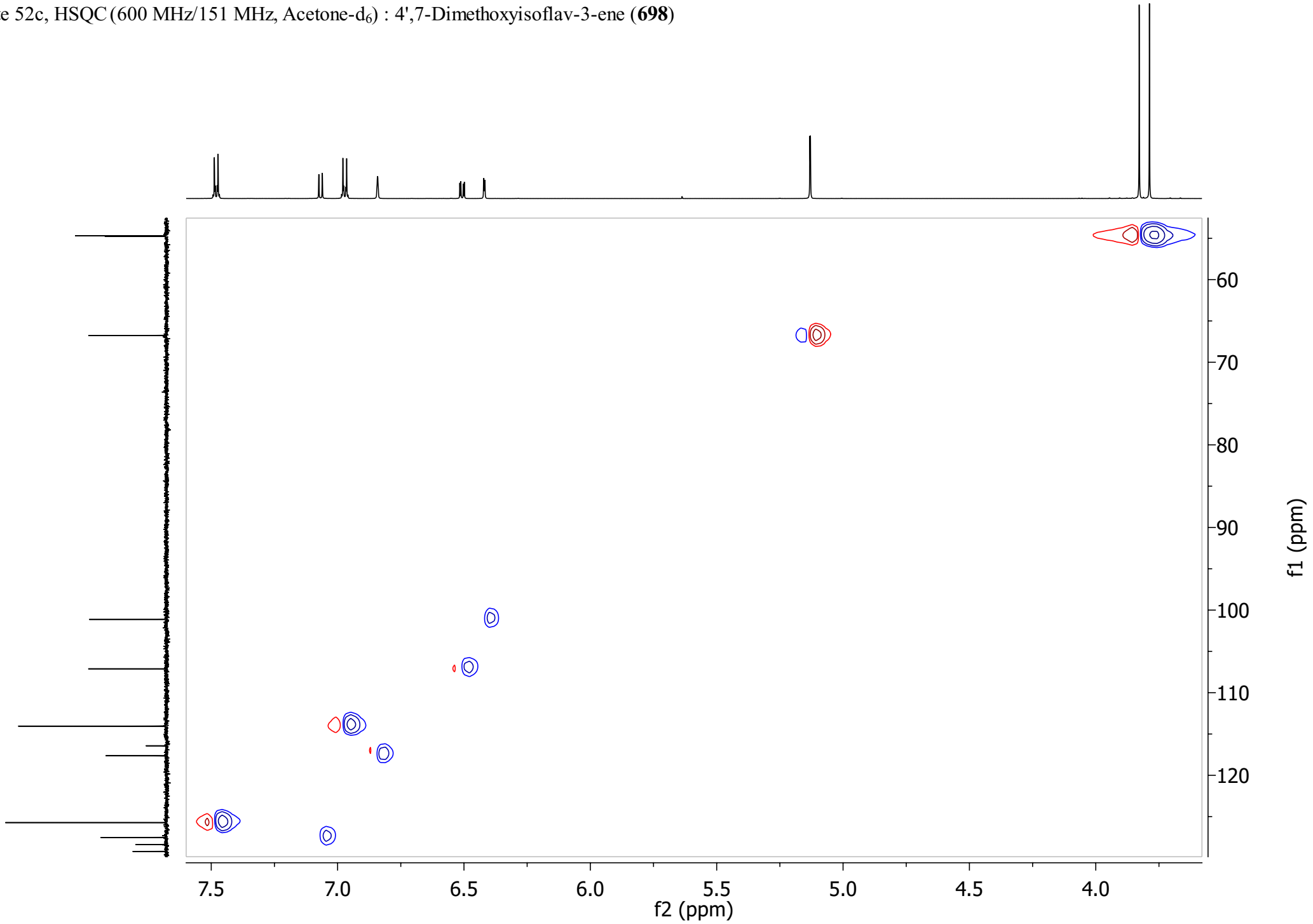


Plate 52d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 4',7-Dimethoxyisoflav-3-ene (**698**)

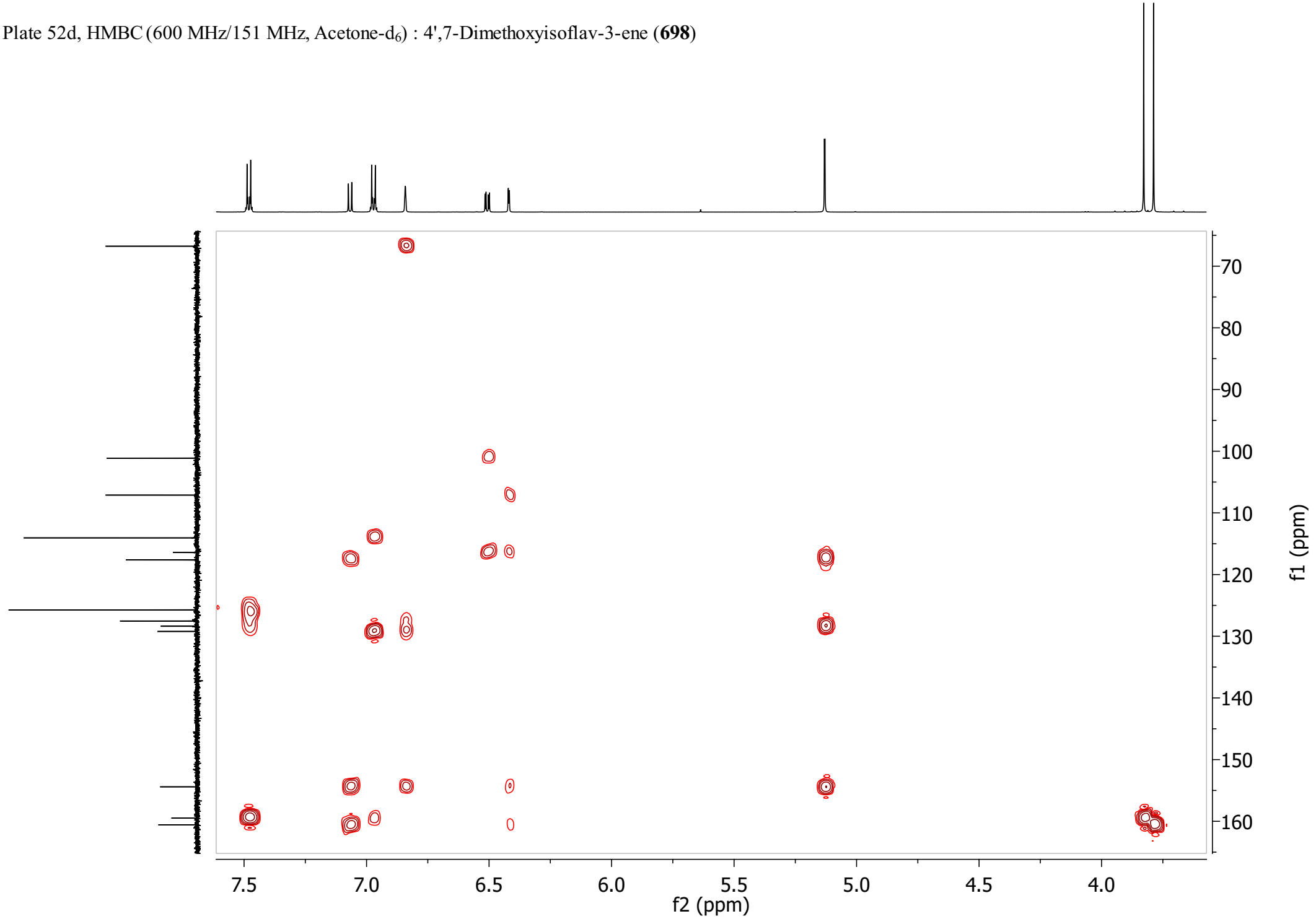
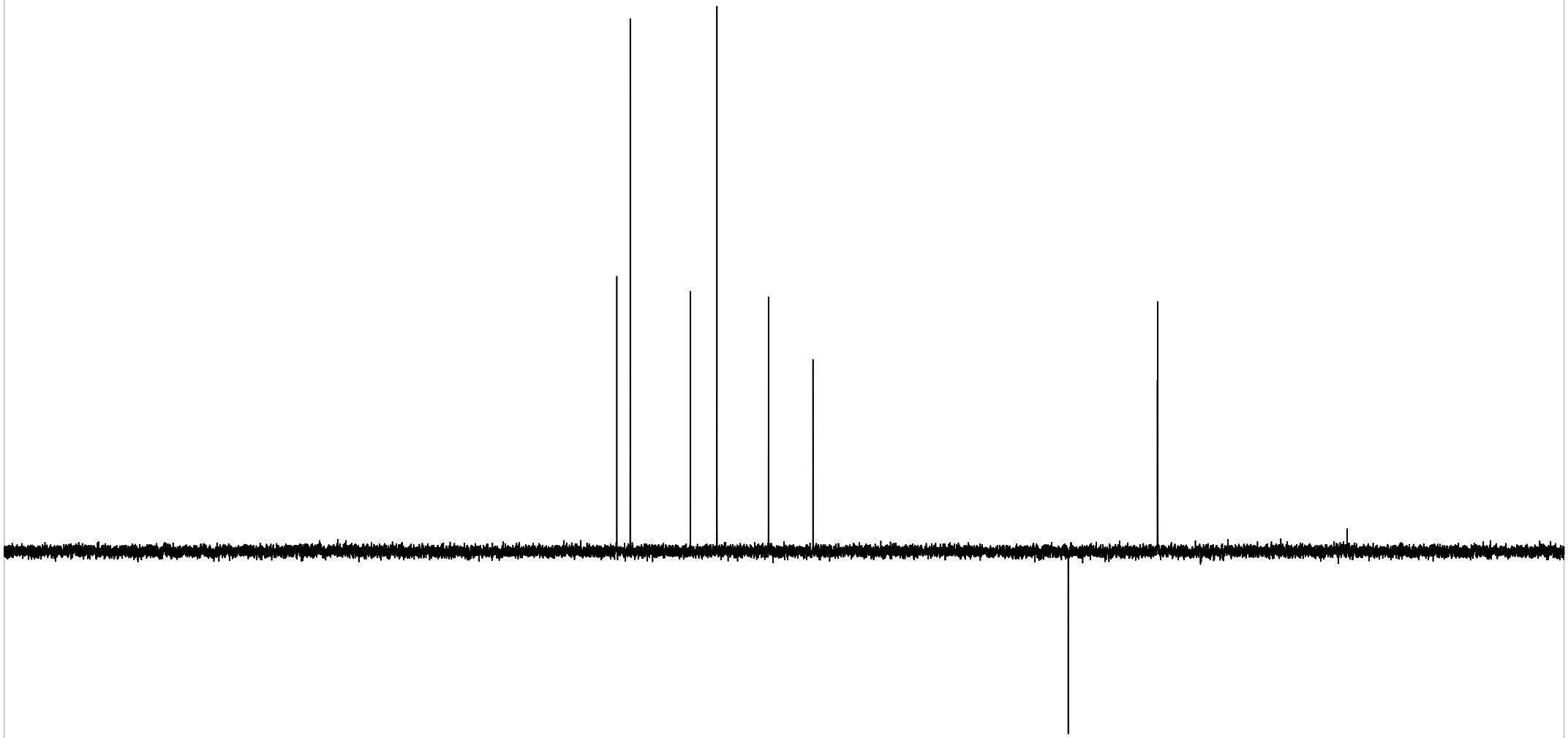


Plate 52e, DEPT (151 MHz, Acetone-d_6) : 4',7-Dimethoxyisoflav-3-ene (**698**)

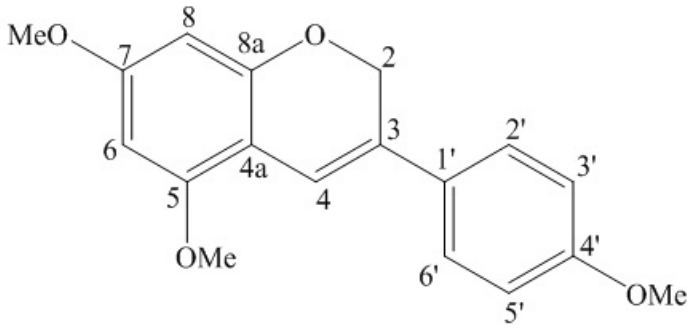


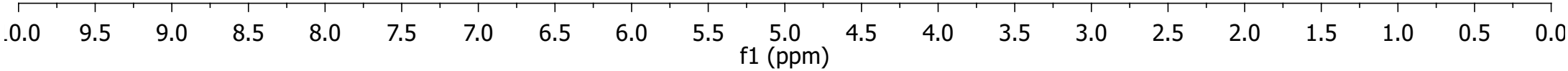
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 53a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4',5,7-Trimethoxyisoflav-3-ene (**713**)

δ 7.46 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.01 – 6.99 (1H, m, H-4), 6.97 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.18 (1H, d, *J* = 2.2 Hz, H-6), 6.09 (1H, dd, *J* = 2.2, 0.5 Hz, H-8), 5.07 (1H, s, H-2), 5.07 (1H, s, H-2), 3.86 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.79 (3H, s, -OMe)





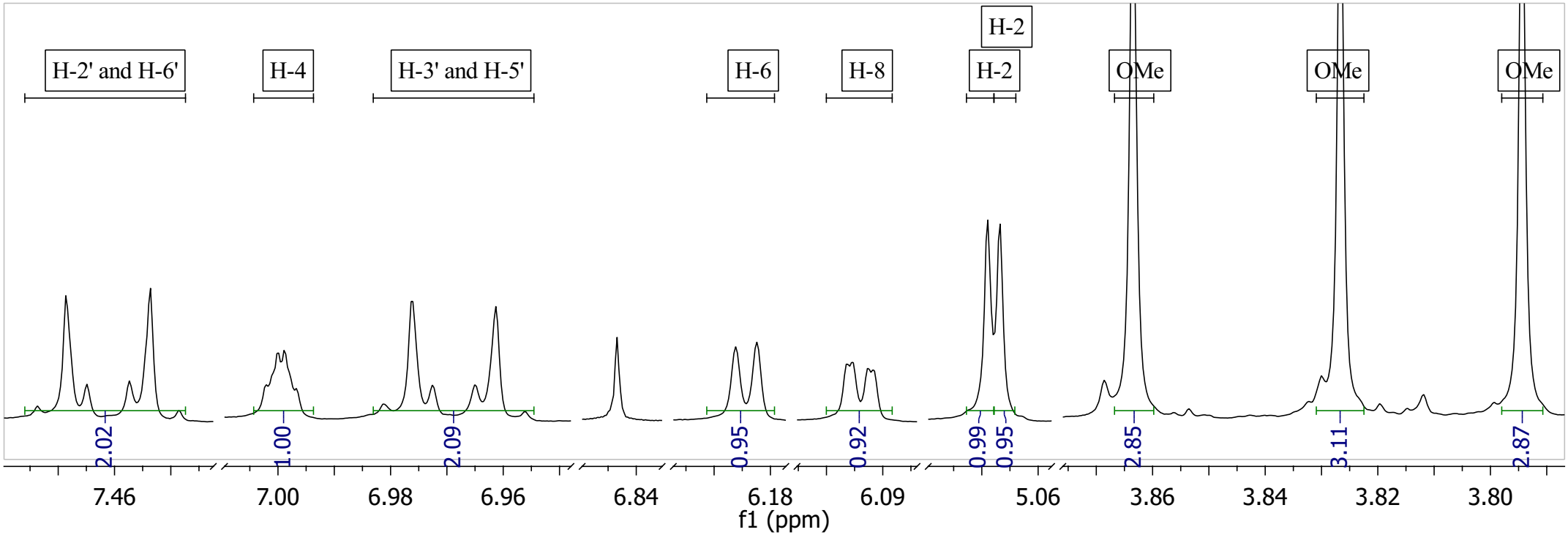
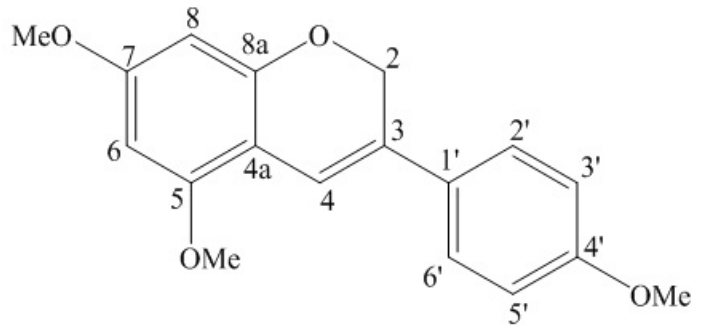


Plate 53b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyisoflav-3-ene (**713**)

δ 162.00 (C-5/7), 160.15 (C-4'), 157.36 (C-5/7), 155.83 (C-8a), 130.55 (C-1'), 127.16 (C-3), 126.54 (C-2' and C-6'), 114.91 (C-3' and C-5'), 113.51 (C-4), 106.71 (C-4a), 94.30 (C-8), 92.58 (C-6), 67.50 (C-2), 56.04 (-OMe), 55.69 (-OMe), 55.56 (-OMe)



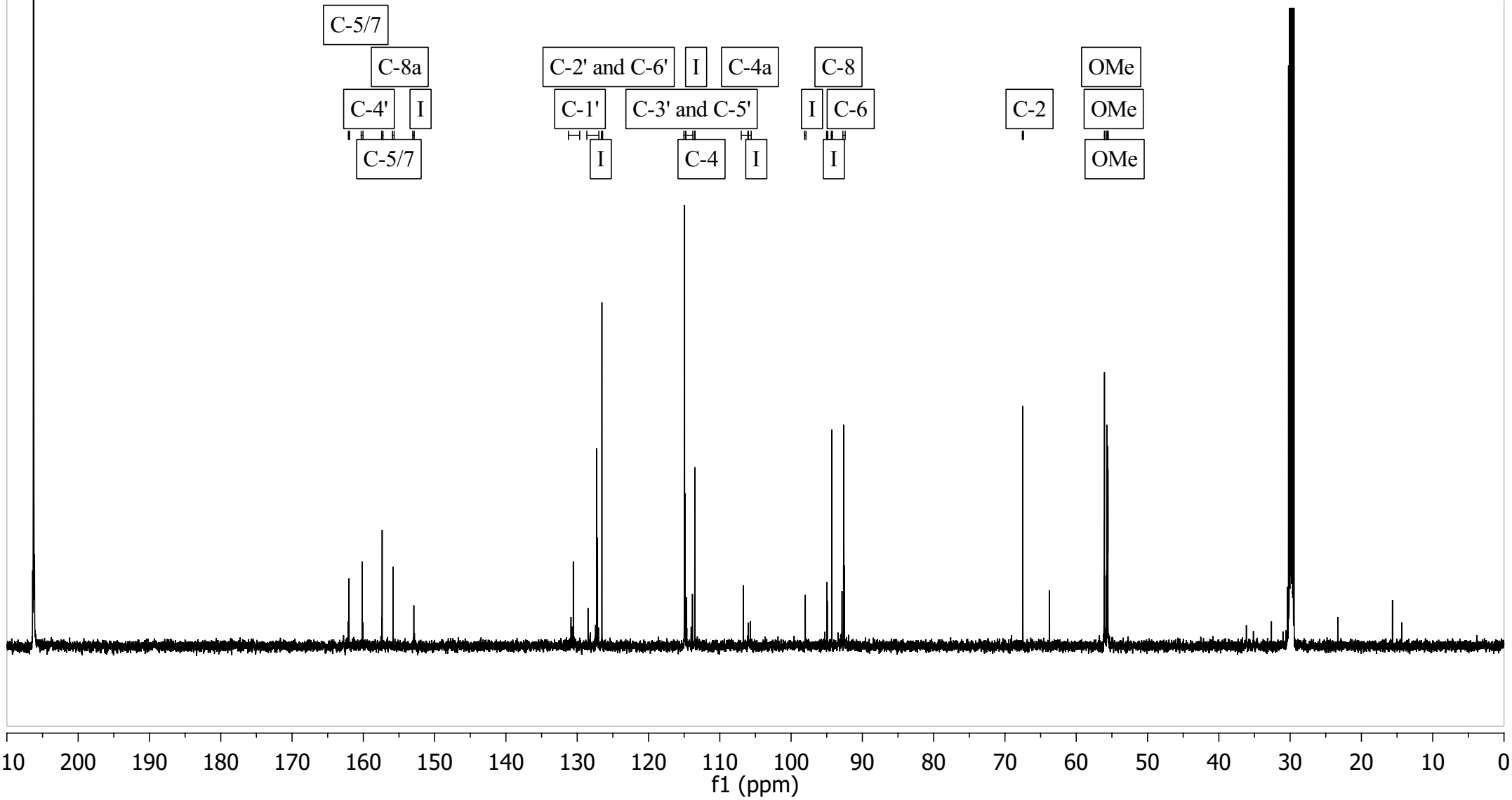


Plate 53c, HSQC (600/151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyisoflav-3-ene (**713**)

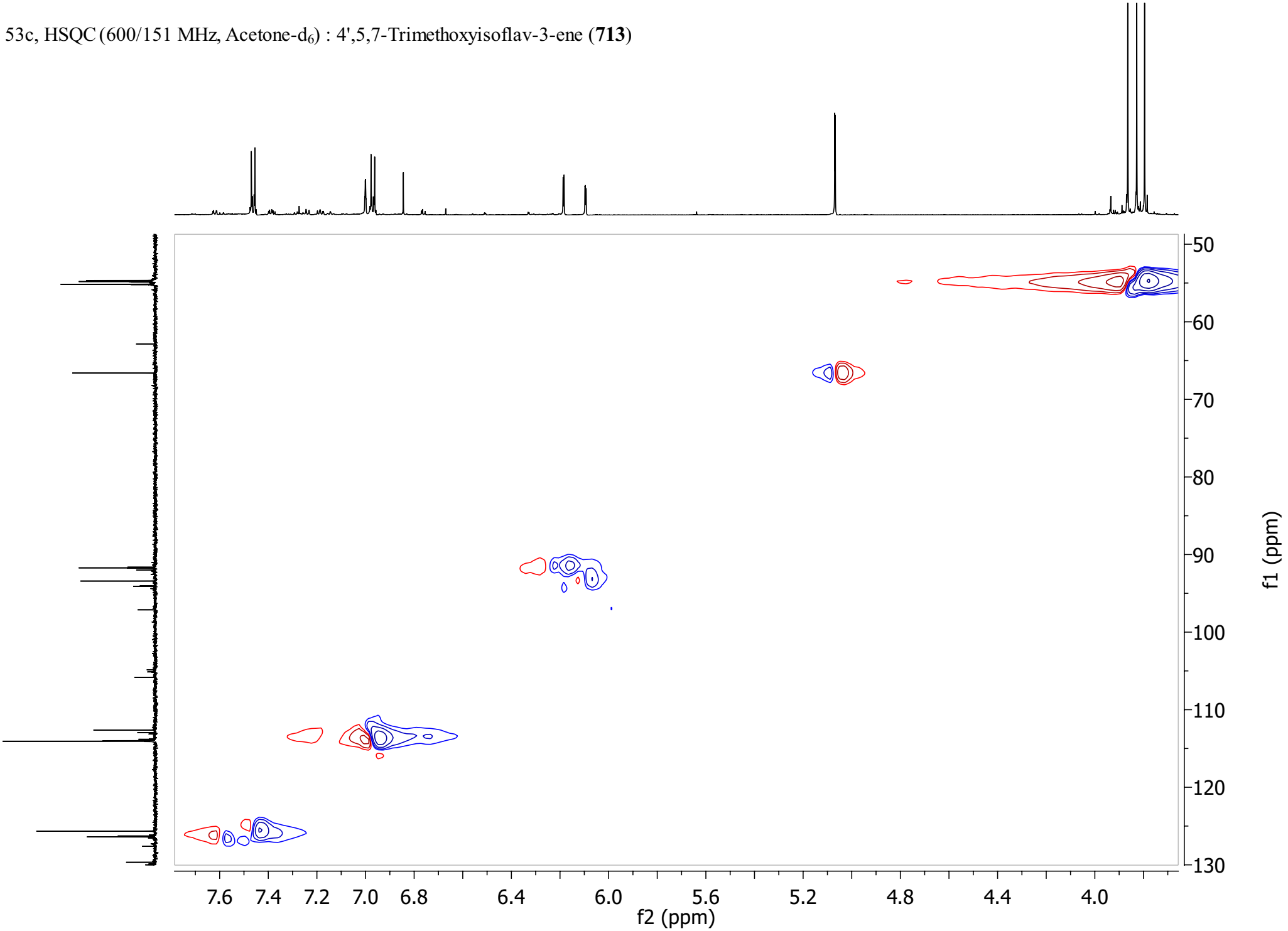


Plate 53d, HMBC (600/151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyisoflav-3-ene (**713**)

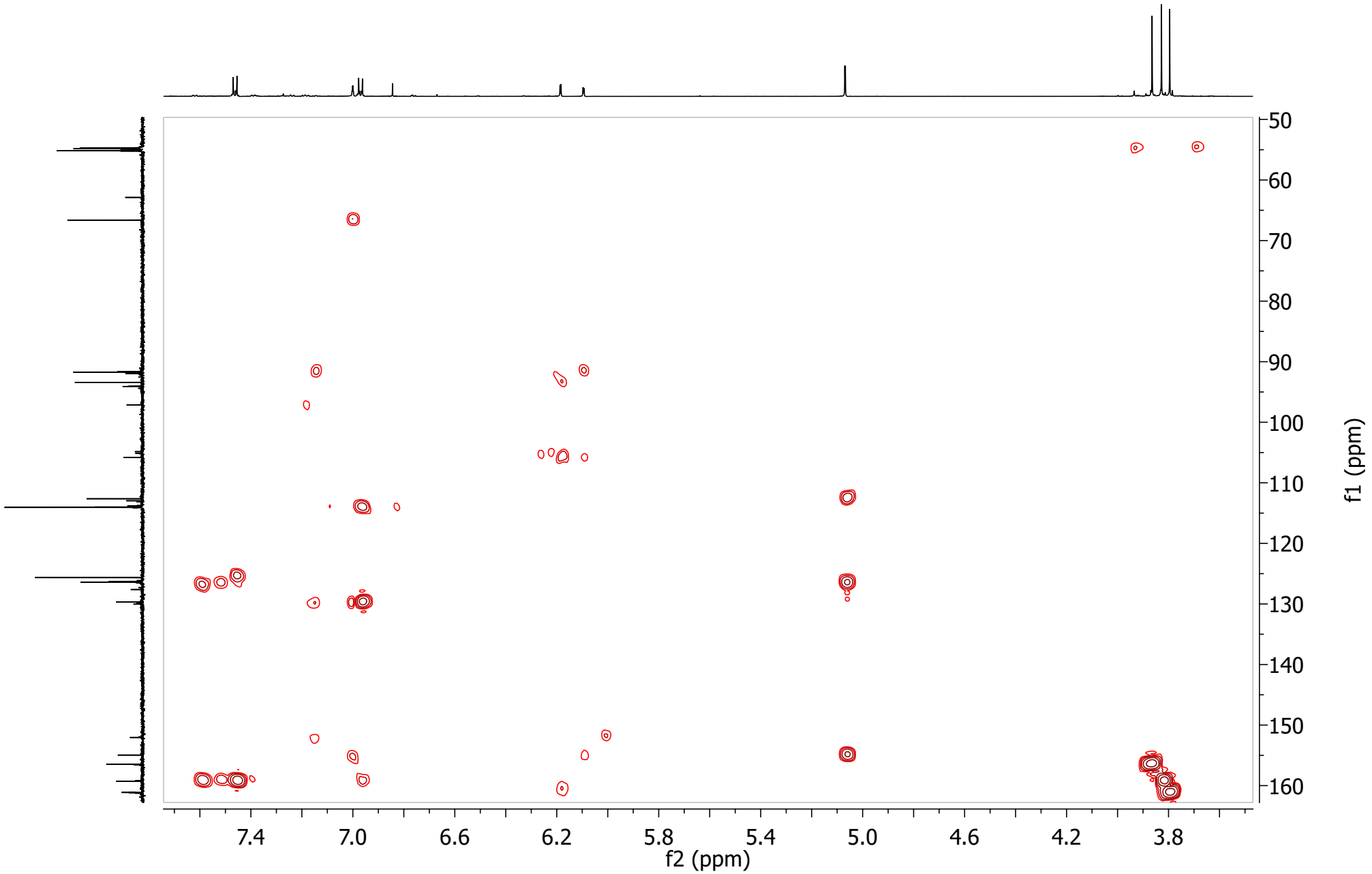


Plate 53e, DEPT (151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyisoflav-3-ene (**713**)

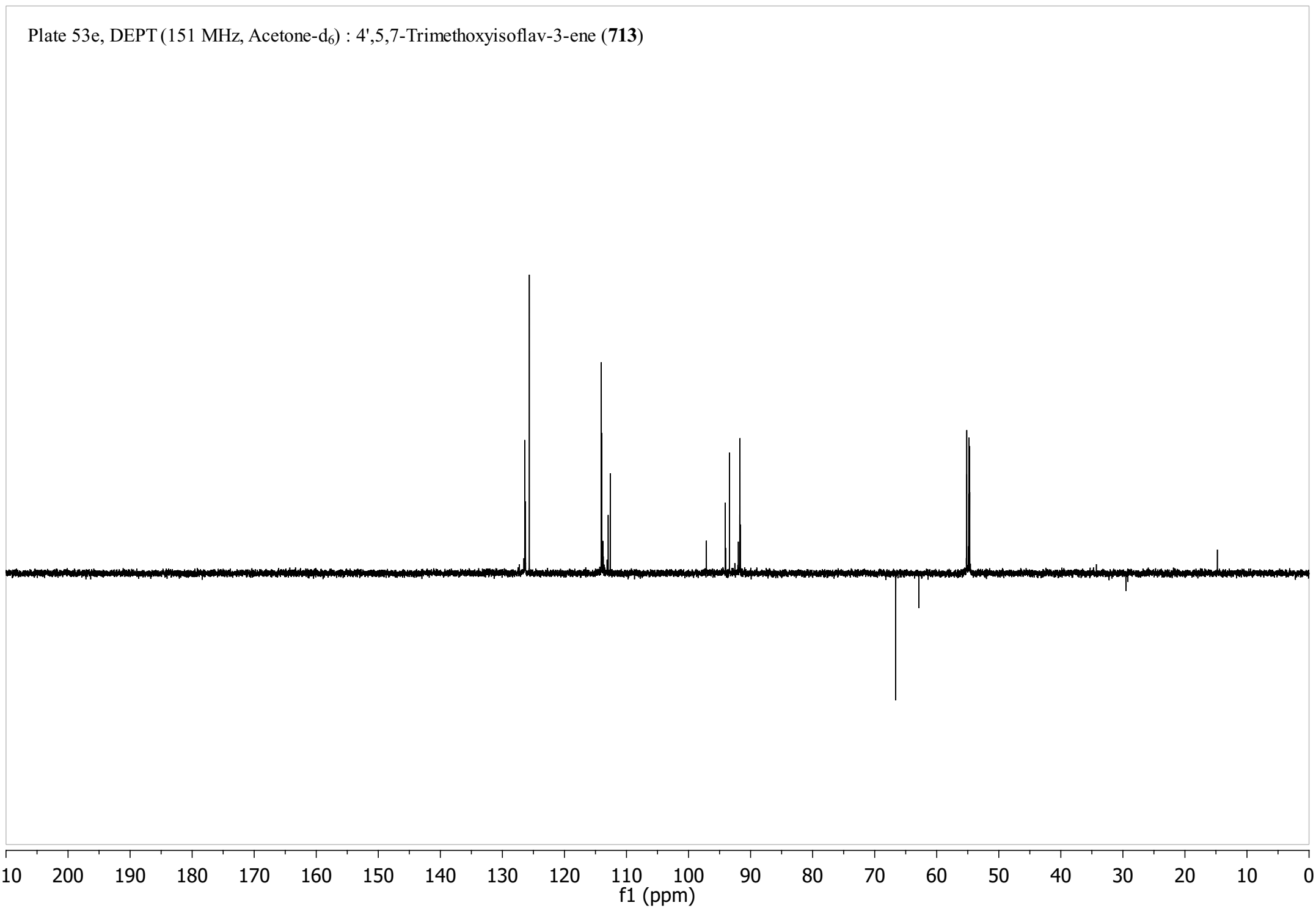
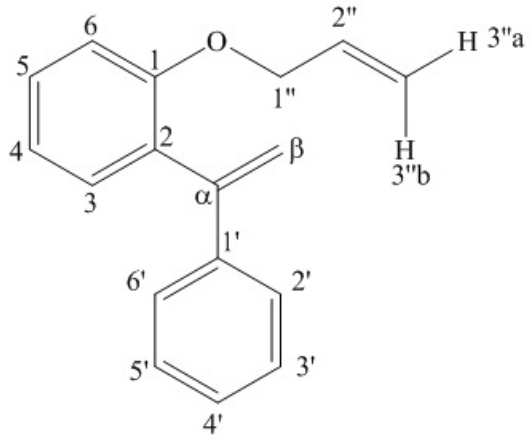
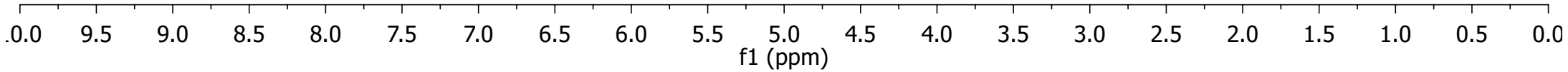


Plate 54a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**)

δ 7.36 – 7.32 (1H, m, H-5), 7.31 – 7.28 (4H, m, H-2', 6', 3' and 5'), 7.28 – 7.23 (2H, m, H-3 and H-4'), 7.03 – 7.00 (2H, m, H-4 and H-6), 5.70 (1H, d, *J* = 1.5 Hz, H-β), 5.67 (1H, ddt, *J* = 17.3, 10.6, 4.8 Hz, H-2''), 5.28 (1H, d, *J* = 1.5 Hz, H-β), 5.03 (1H, ddt, *J* = 17.3, 1.8, 1.8 Hz, H-3''b), 4.98 (1H, ddt, *J* = 10.6, 1.8, 1.8 Hz, H-3''a), 4.39 (2H, ddd, *J* = 4.8, 1.8, 1.8 Hz, H-1'')





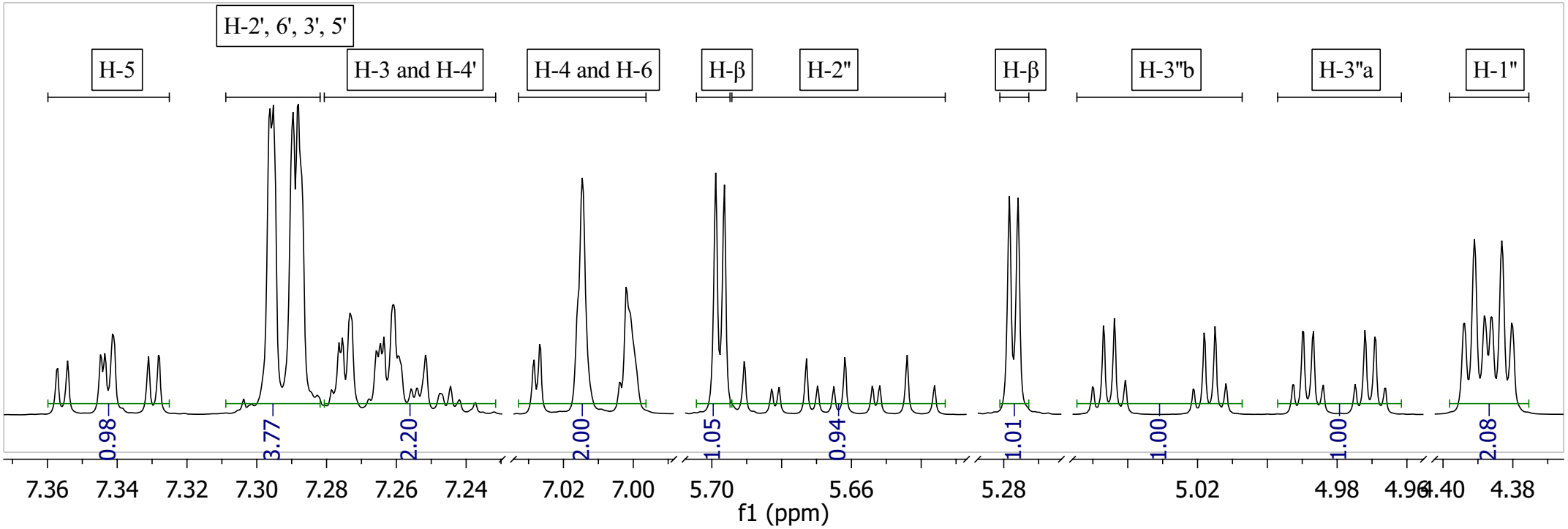
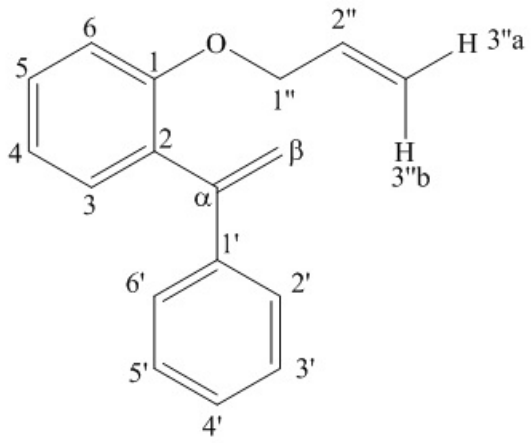


Plate 54b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**)

δ 157.03 (C-1), 148.78 (C-α), 142.35 (C-1'), 134.29 (C-2''), 132.20 (C-2), 131.93 (C-3), 130.06 (C-4'), 128.89 (C-2' and C-6'), 128.13 (C-5), 127.20 (C-3' and C-5'), 121.64 (C-4), 116.42 (C-3''), 115.54 (C-β), 113.62 (C-6), 69.33 (C-1'')



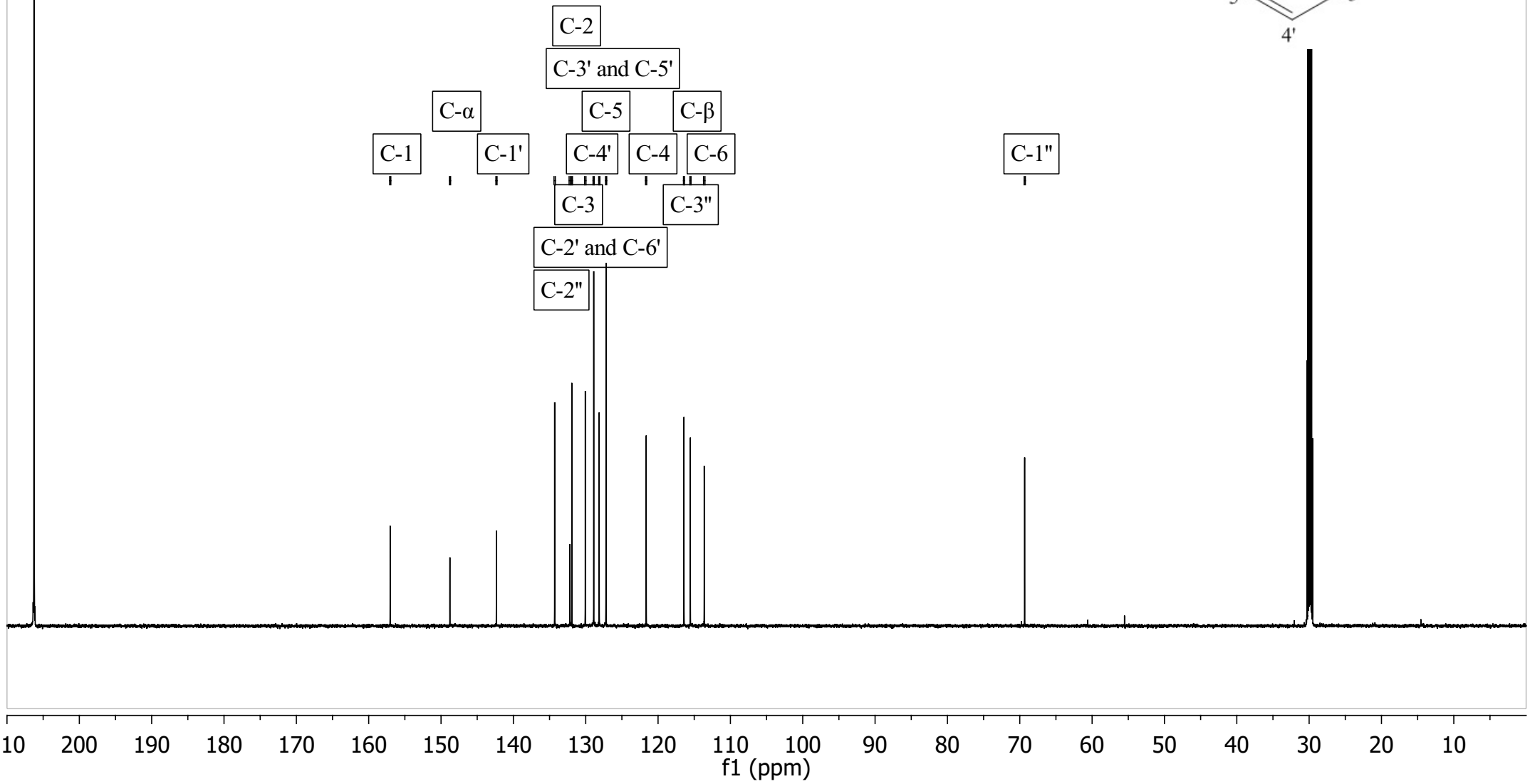


Plate 54c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**)

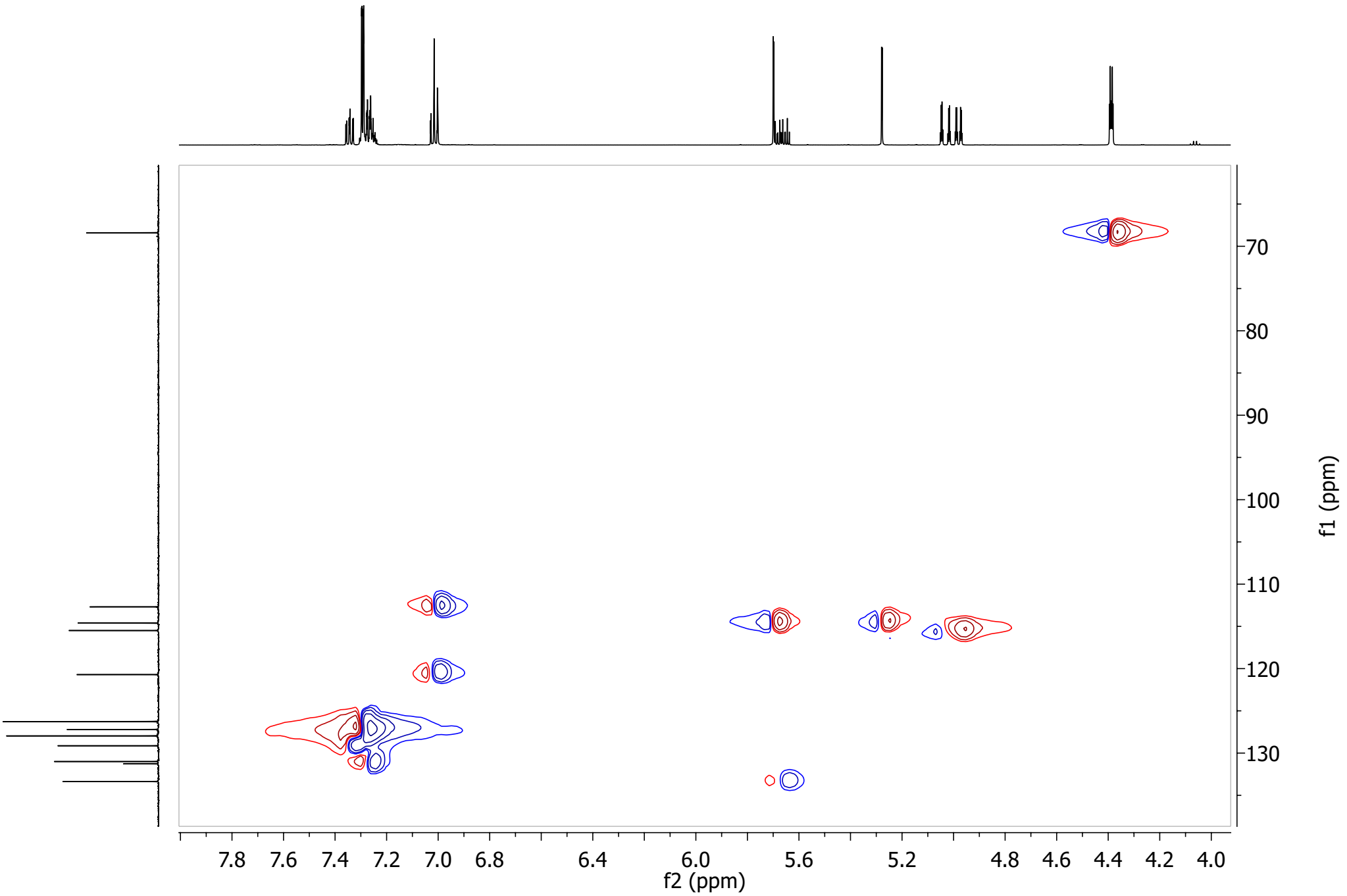


Plate 54d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**)

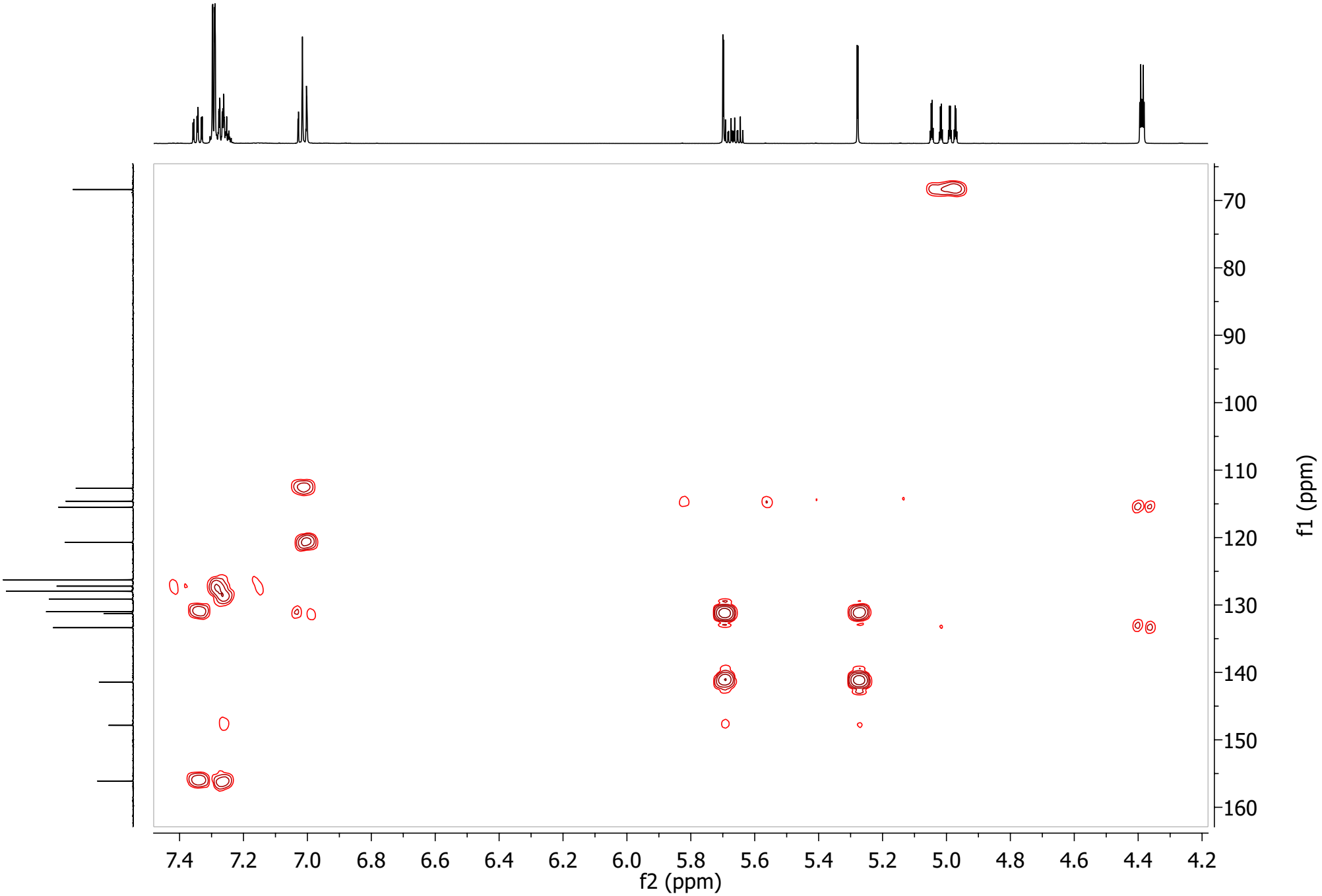


Plate 54e, DEPT (151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-(1-phenylvinyl)benzene (**740**)

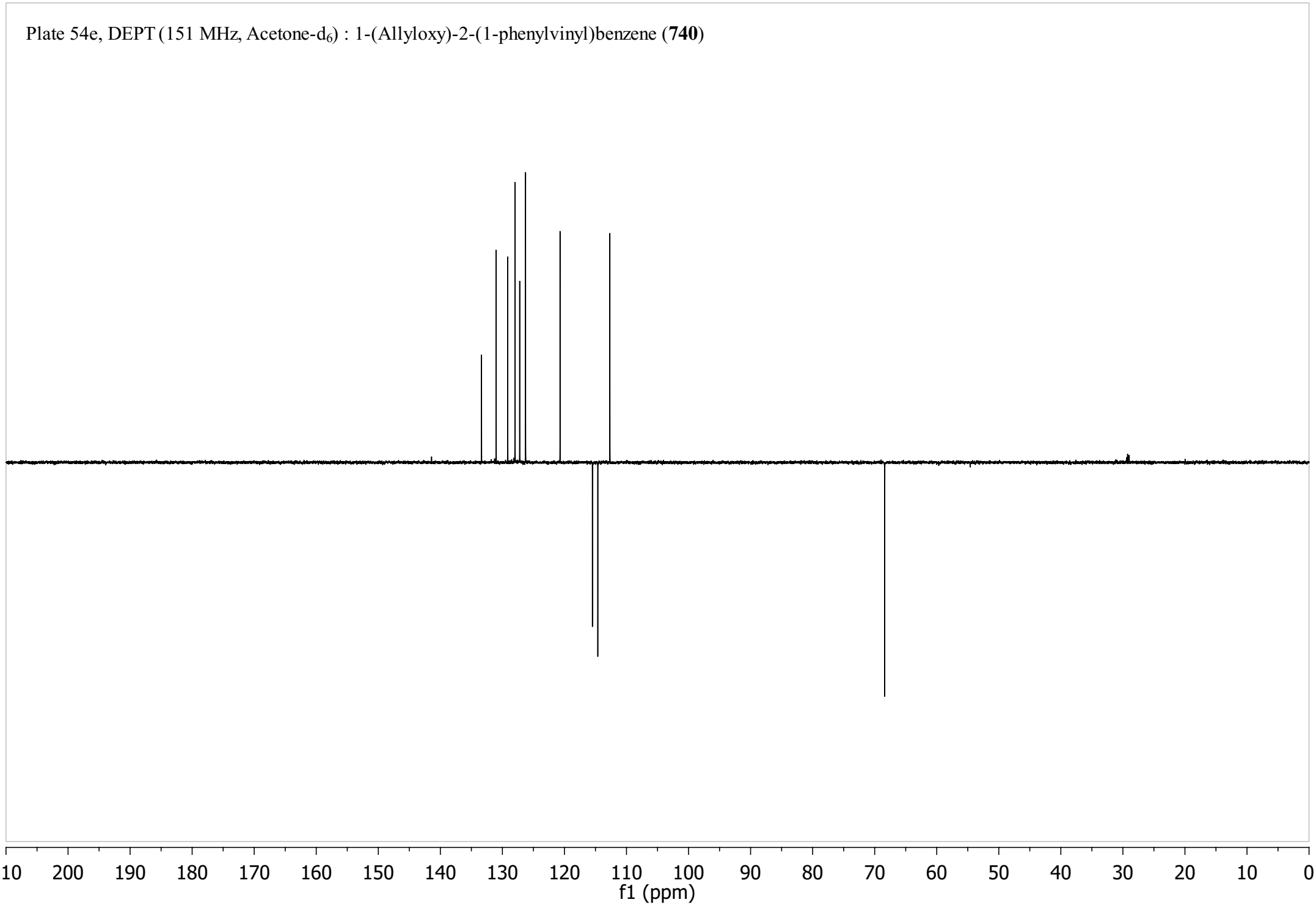
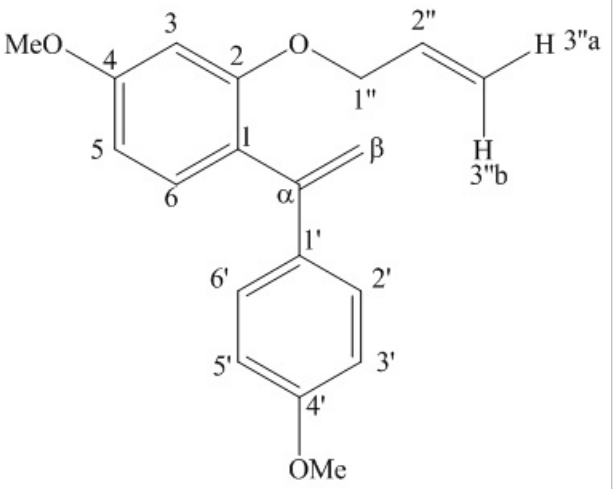
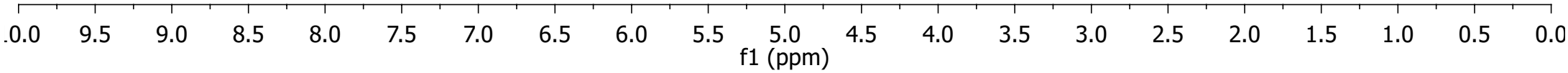


Plate 55a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**)

δ 7.22 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.14 (1H, d, *J* = 9.2 Hz, H-6), 6.85 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.57 (1H, dd, *J* = 9.2, 2.3 Hz, H-5), 6.57 (1H, d, *J* = 2.3 Hz, H-3), 5.72 (1H, ddt, *J* = 17.3, 10.7, 4.7 Hz, H-2''), 5.54 (1H, d, *J* = 1.7 Hz, H-β), 5.12 (1H, d, *J* = 1.7 Hz, H-β), 5.07 (1H, ddt, *J* = 17.3, 1.9, 1.9 Hz, H-3''b), 5.01 (1H, ddt, *J* = 10.7, 1.9, 1.9 Hz, H-3''a), 4.40 (1H, ddd, *J* = 4.7, 1.9, 1.9 Hz, H-1''), 3.82 (3H, s, -OMe), 3.78 (3H, s, -OMe)





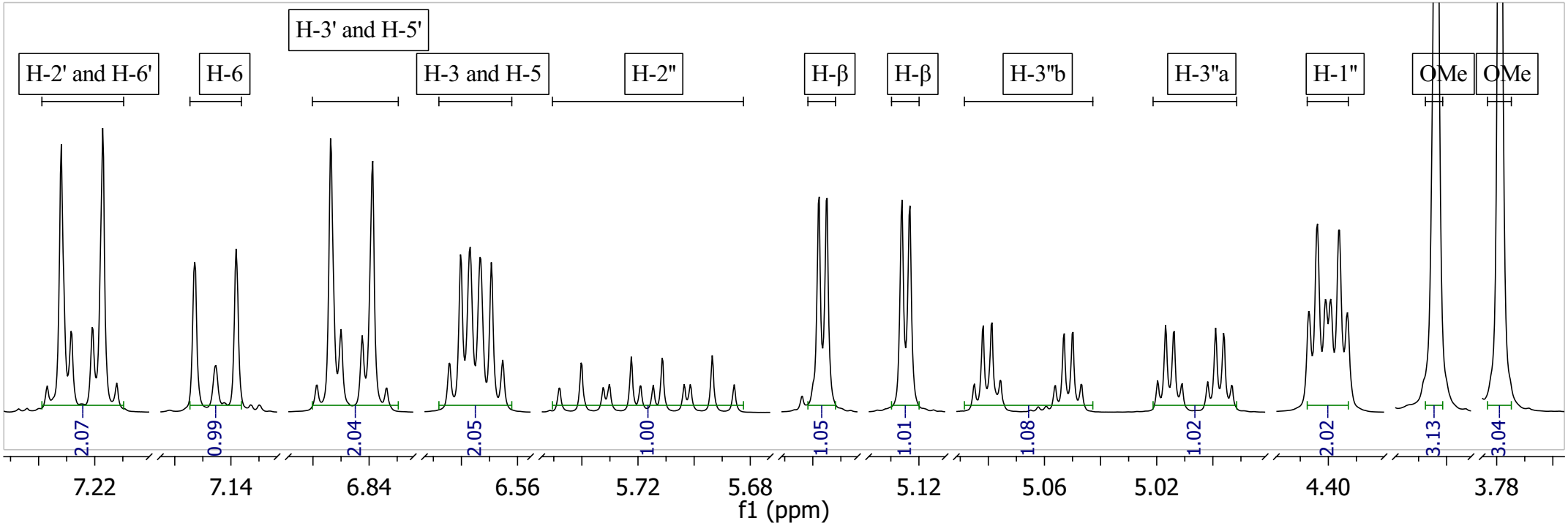
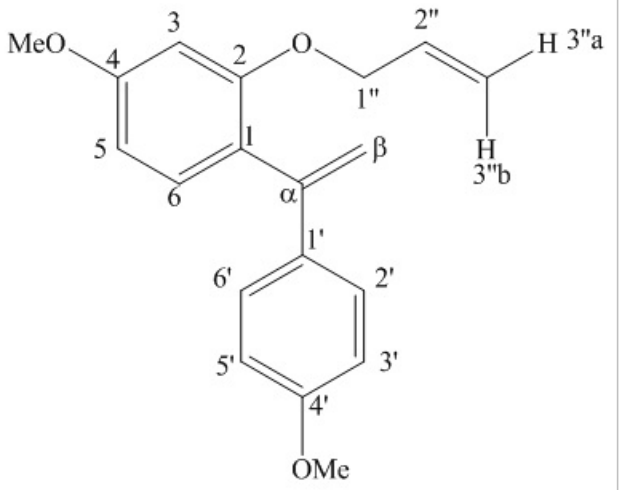


Plate 55b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**)

δ 161.76 (C-4), 160.19 (C-4'), 158.04 (C-2), 147.85 (C-α), 135.23 (C-1'), 134.33 (C-2''), 132.39 (C-6), 128.41 (C-2' and C-6'), 125.00 (C-1), 116.47 (C-3''), 114.19 (C-3' and C-5'), 113.34 (C-β), 105.78 (C-3/5), 100.91 (C-3/5), 69.36 (C-1''), 55.71 (-O<u>Me</u>), 55.58 (-O<u>Me</u>)



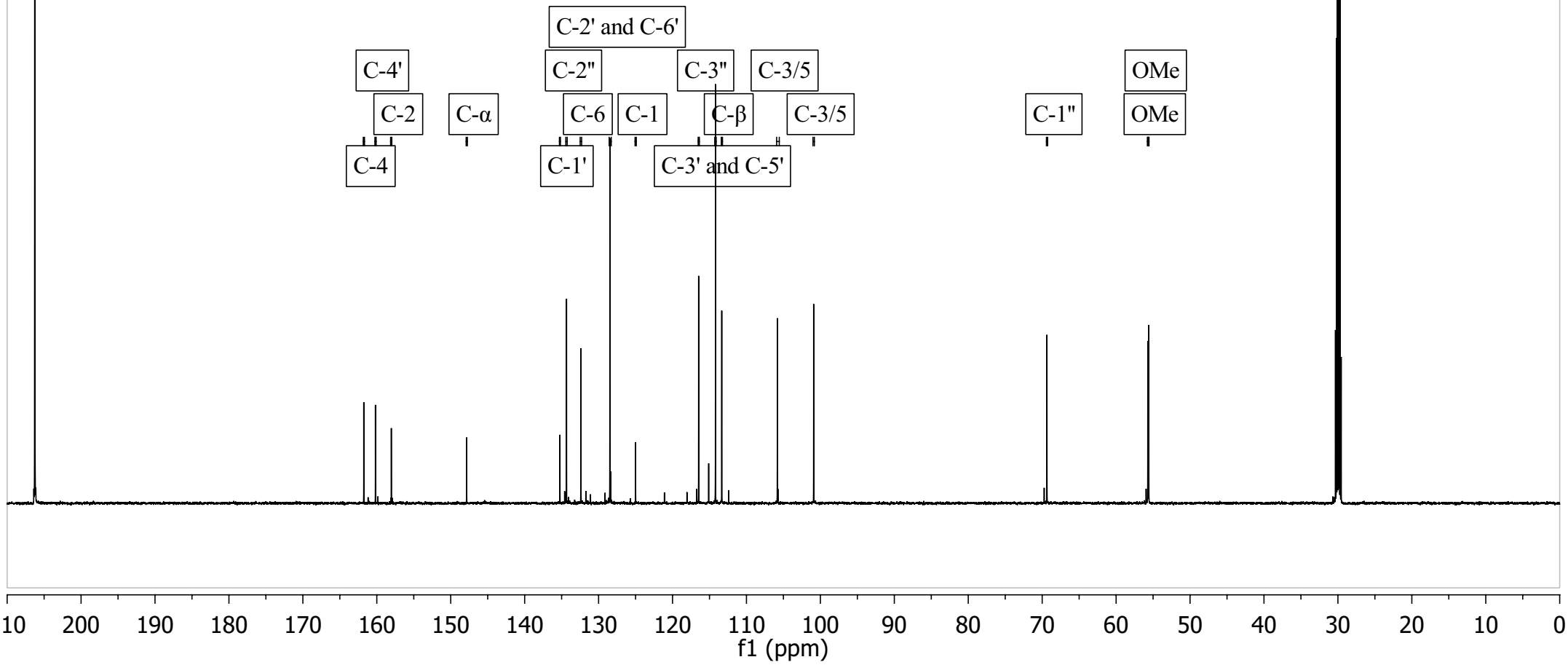


Plate 55c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**)

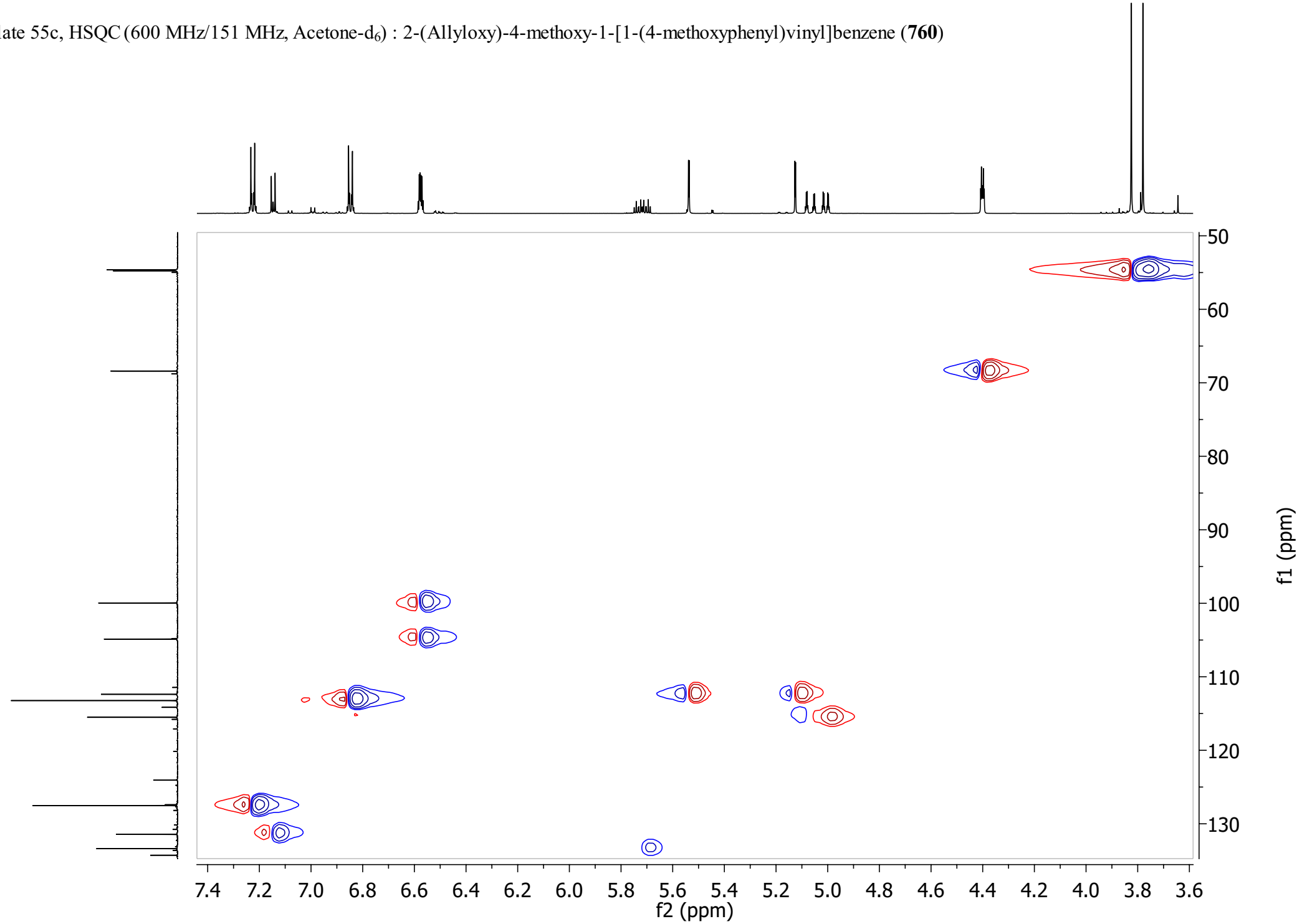


Plate 55d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**)

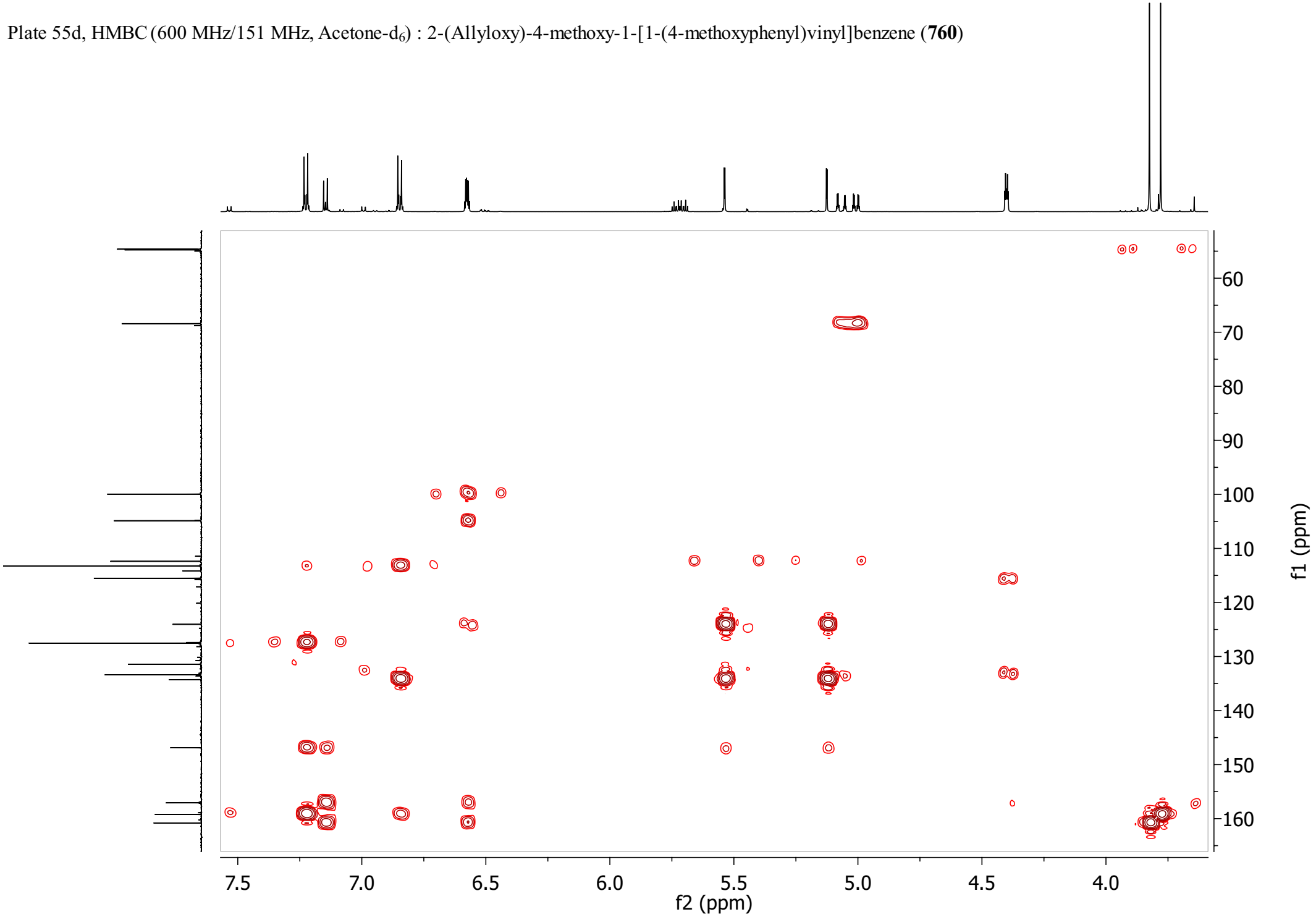


Plate 55e, DEPT (151 MHz, Acetone-d_6) : 2-(Allyloxy)-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]benzene (**760**)

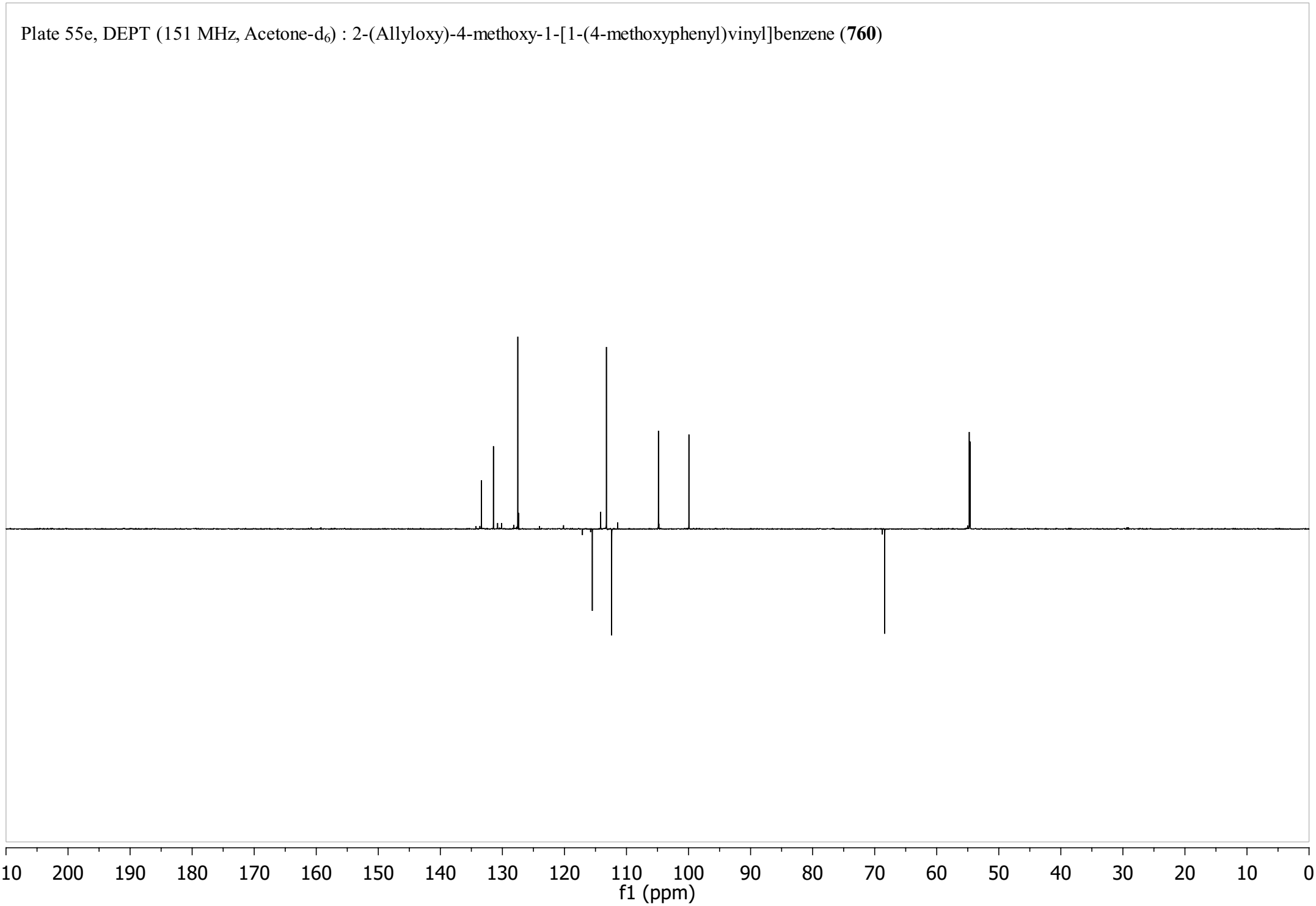
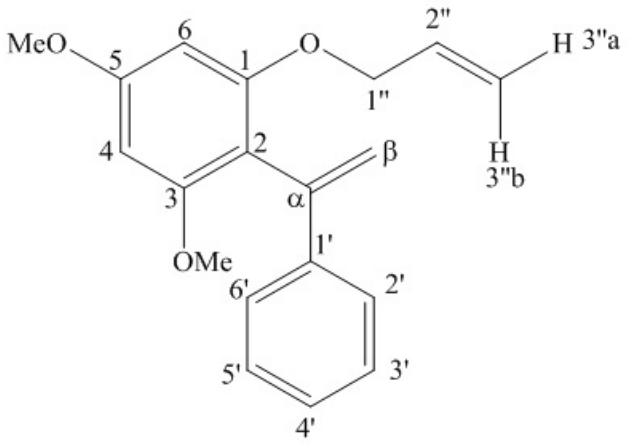
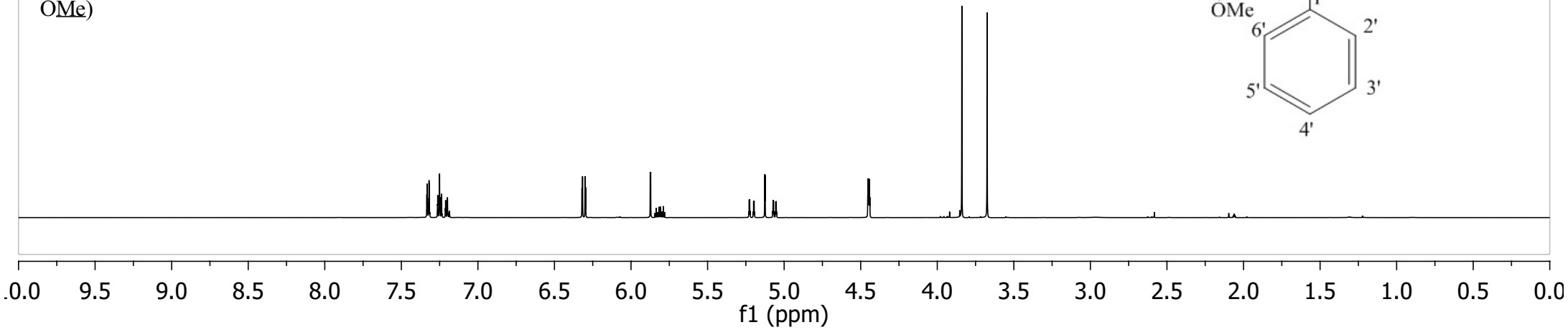


Plate 56a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**)

δ 7.34 – 7.31 (2H, m, H-2' and H-6'), 7.27 – 7.23 (2H, m, H-3' and H-5'), 7.22 – 7.18 (1H, m, H-4'), 6.32 (1H, d, *J* = 2.2 Hz, H-4/6), 6.30 (1H, d, *J* = 2.2 Hz, H-4/6), 5.87 (1H, d, *J* = 1.7 Hz, H-β), 5.81 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, H-2''), 5.22 (1H, ddt, *J* = 17.3, 1.7, 1.7 Hz, H-3''b), 5.13 (1H, d, *J* = 1.7 Hz, H-β), 5.06 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3''a), 4.45 (2H, ddd, *J* = 4.7, 1.7, 1.7 Hz, H-1''), 3.84 (3H, s, -OMe), 3.67 (3H, s, -OMe)





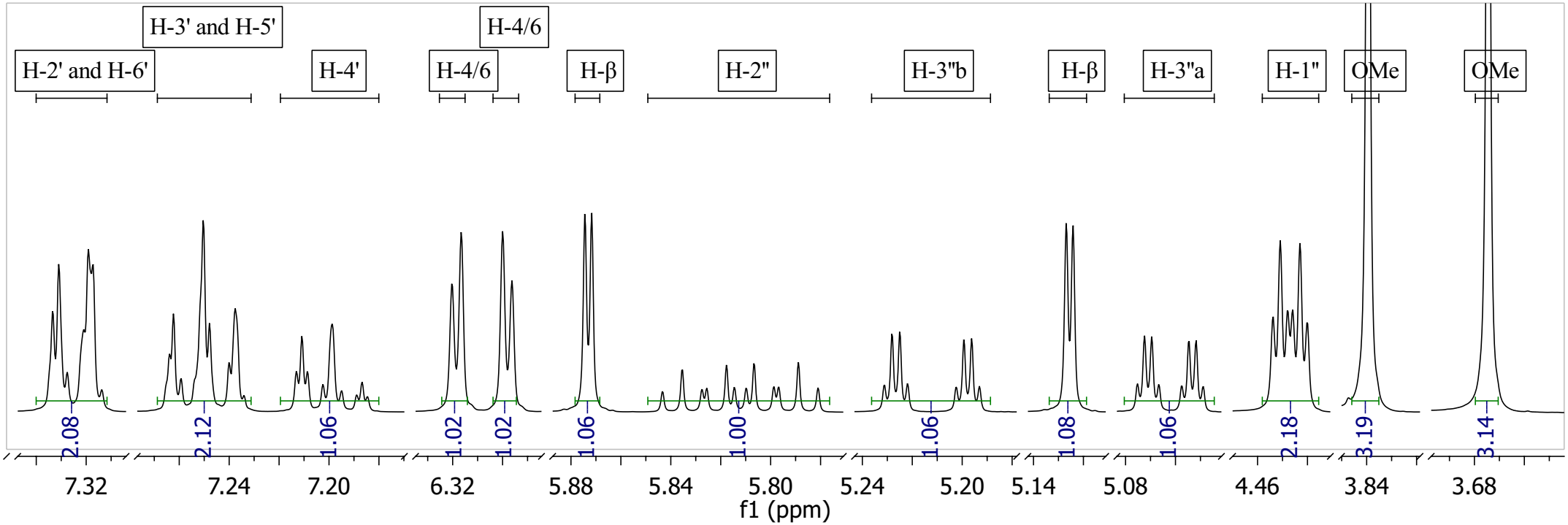
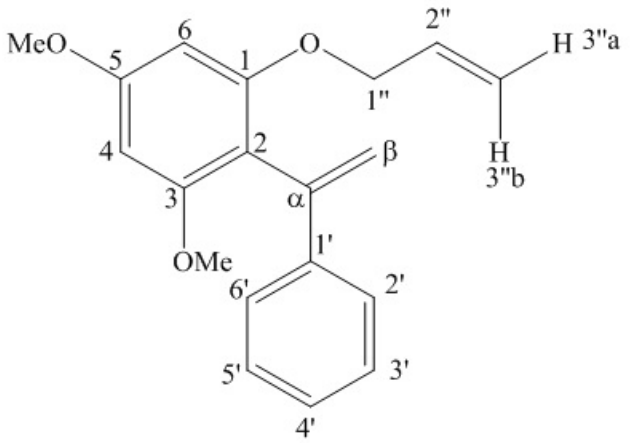


Plate 56b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**)

δ 161.79 (C-3/5), 159.77 (C-3/5), 158.52 (C-1), 142.48 (C-1'), 142.35 (C-α), 134.57 (C-2''), 128.76 (C-3' and C-5'), 127.73 (C-4'), 126.71 (C-2' and C-6'), 116.53 (C-3'' and C-β), 113.26 (C-2), 93.00 (C-4/6), 92.00 (C-4/6), 69.56 (C-1''), 56.11 (-OMe), 55.67 (-OMe)



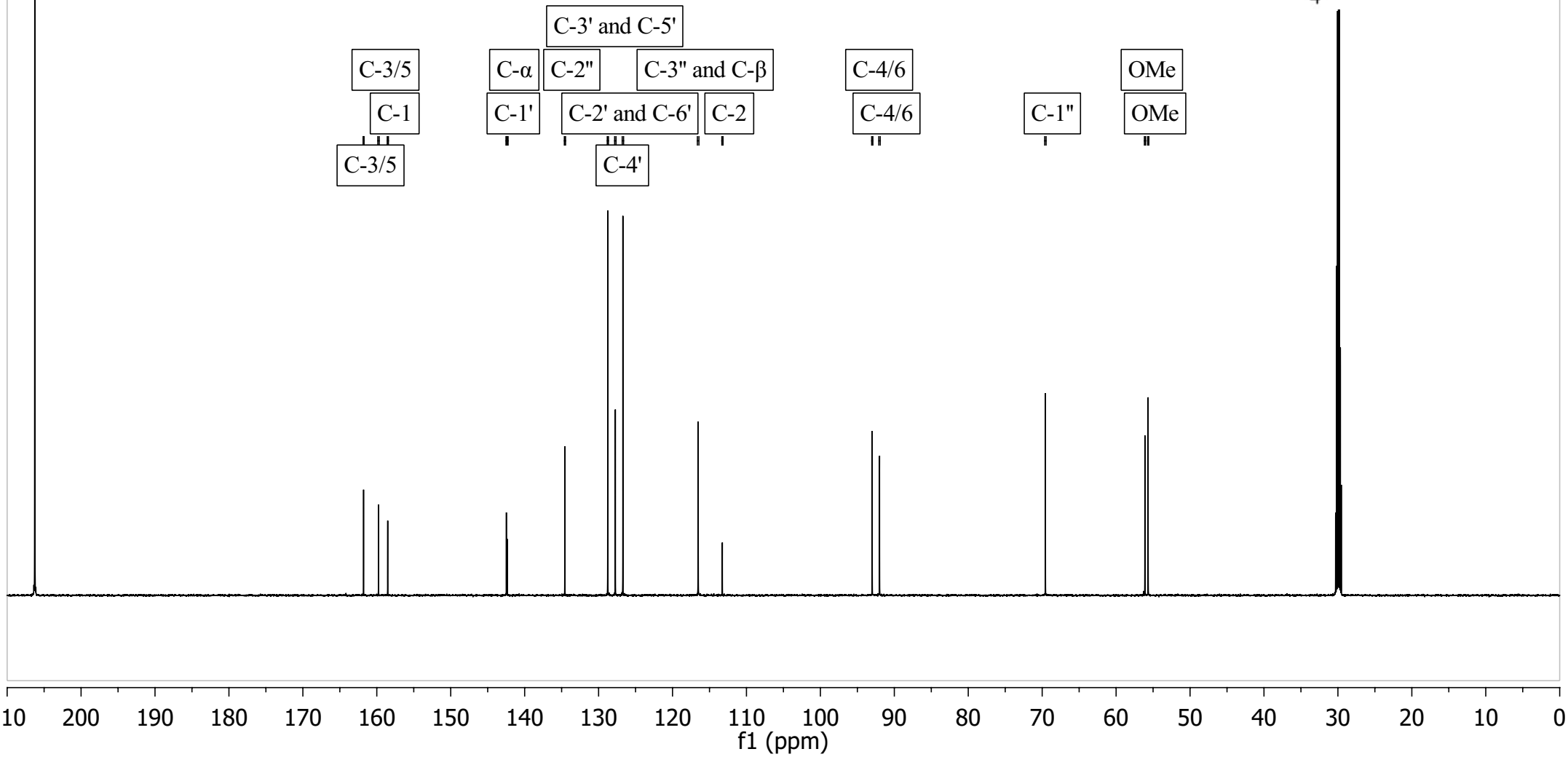


Plate 56c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**)

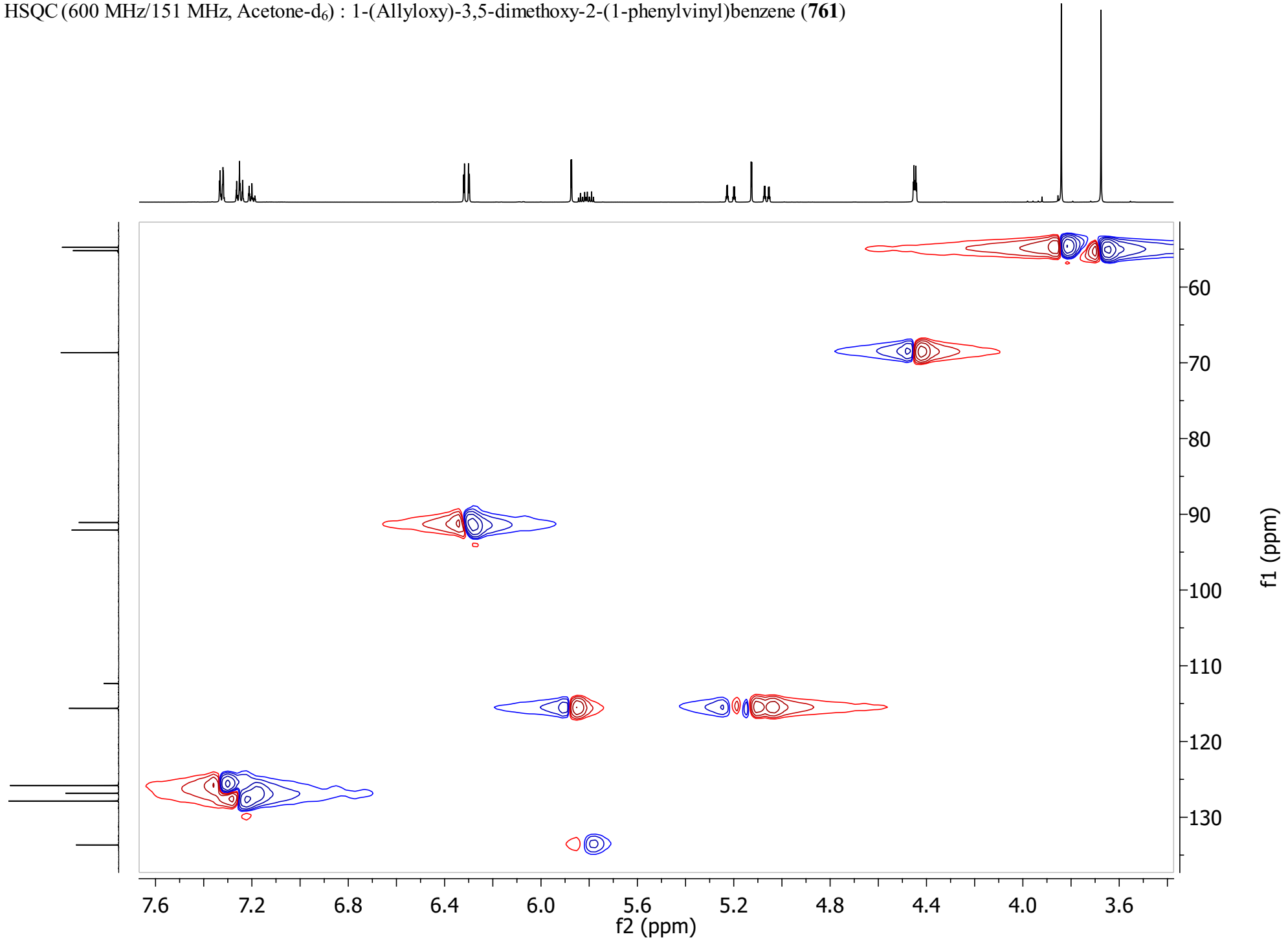


Plate 56d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**)

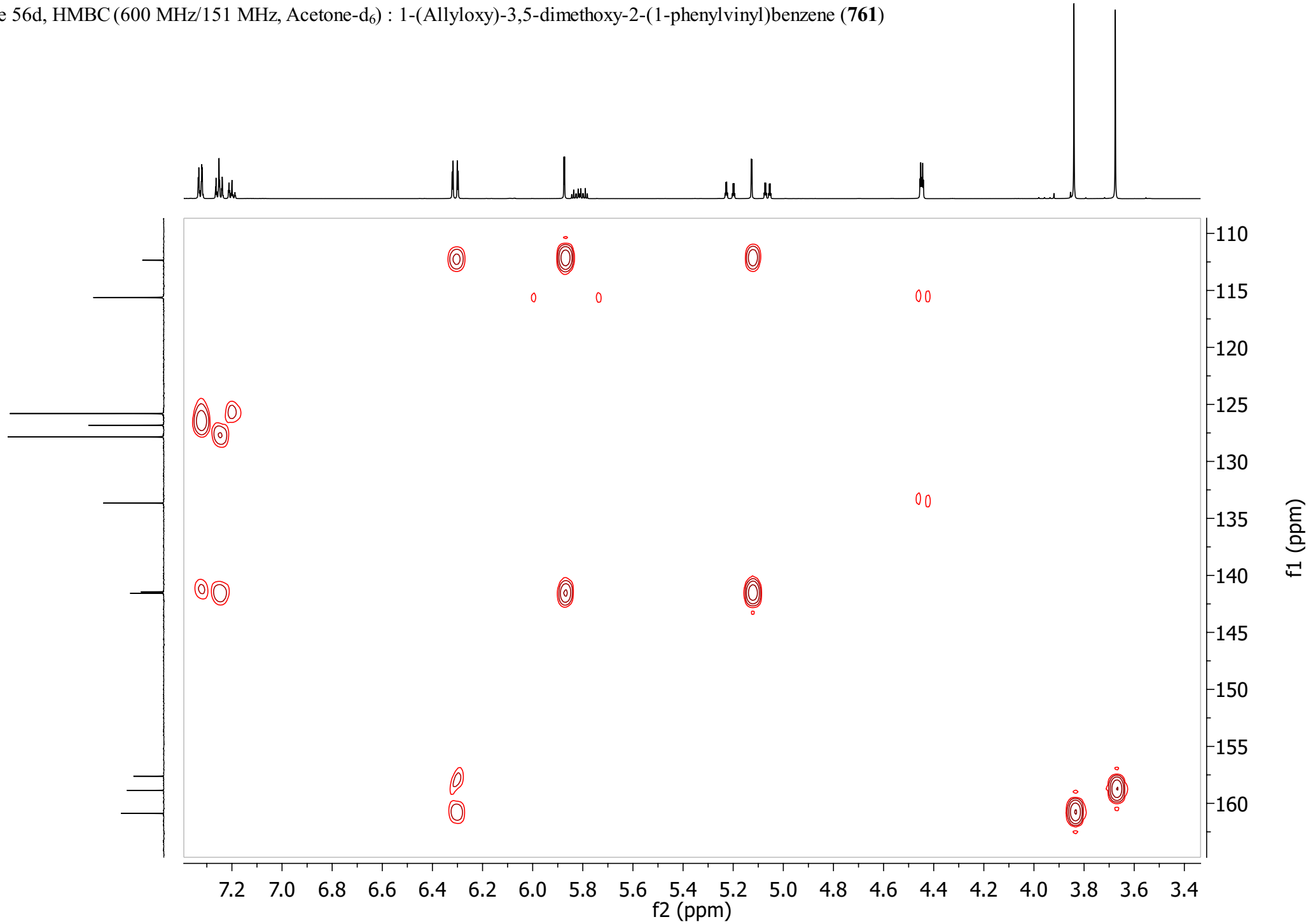


Plate 56e, DEPT (151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-(1-phenylvinyl)benzene (**761**)

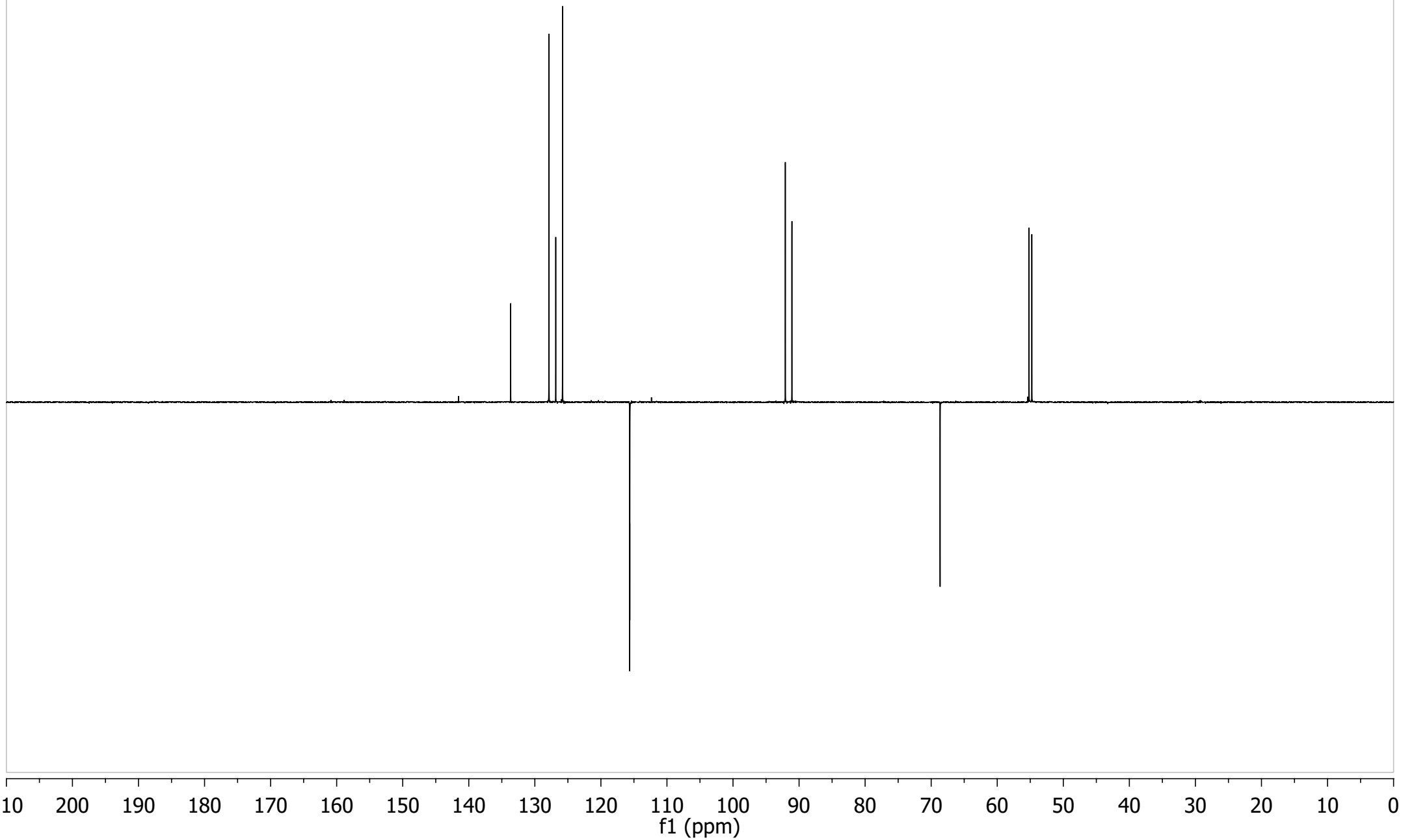
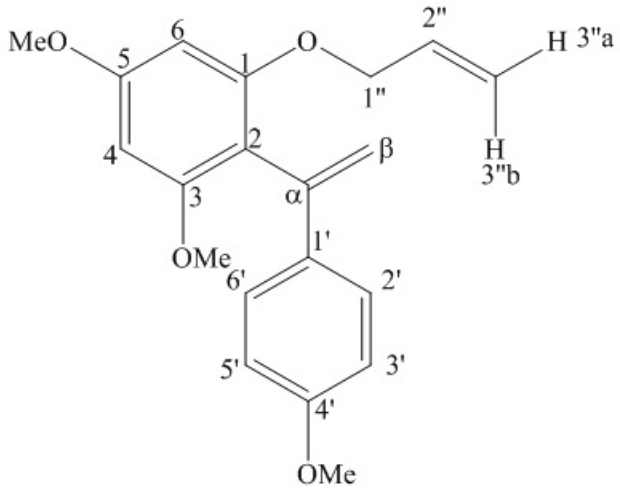
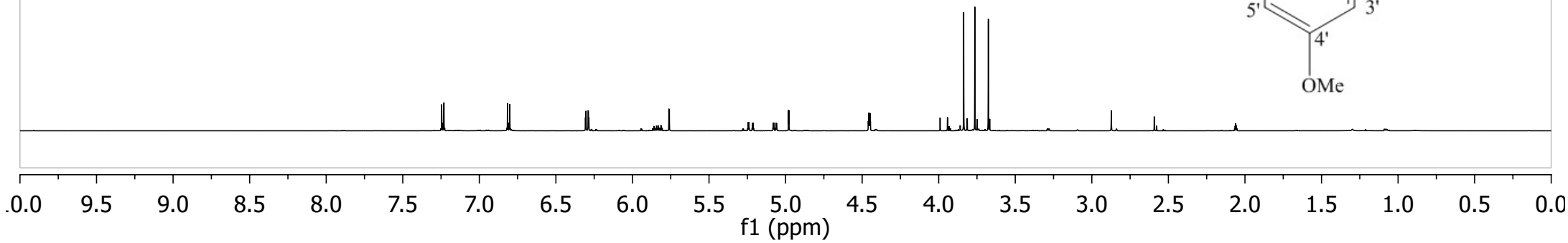


Plate 57a, ^{1}H NMR (600 MHz, Acetone-d_6) :1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**)

δ 7.24 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 6.81 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.30 (1H, d, *J* = 2.2 Hz, H-4/6), 6.29 (1H, d, *J* = 2.2 Hz, H-4/6), 5.84 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, H-2''), 5.76 (1H, d, *J* = 1.6 Hz, H-β), 5.23 (1H, ddt, *J* = 17.3, 1.8, 1.8 Hz, H-3''b), 5.07 (1H, ddt, *J* = 10.6, 1.8, 1.8 Hz, H-3''a), 4.98 (1H, d, *J* = 1.6 Hz, H-β), 4.45 (2H, ddd, *J* = 4.7, 1.8, 1.8 Hz, H-1''), 3.84 (3H, s, -OMe), 3.76 (3H, s, -OMe), 3.68 (3H, s, -OMe)





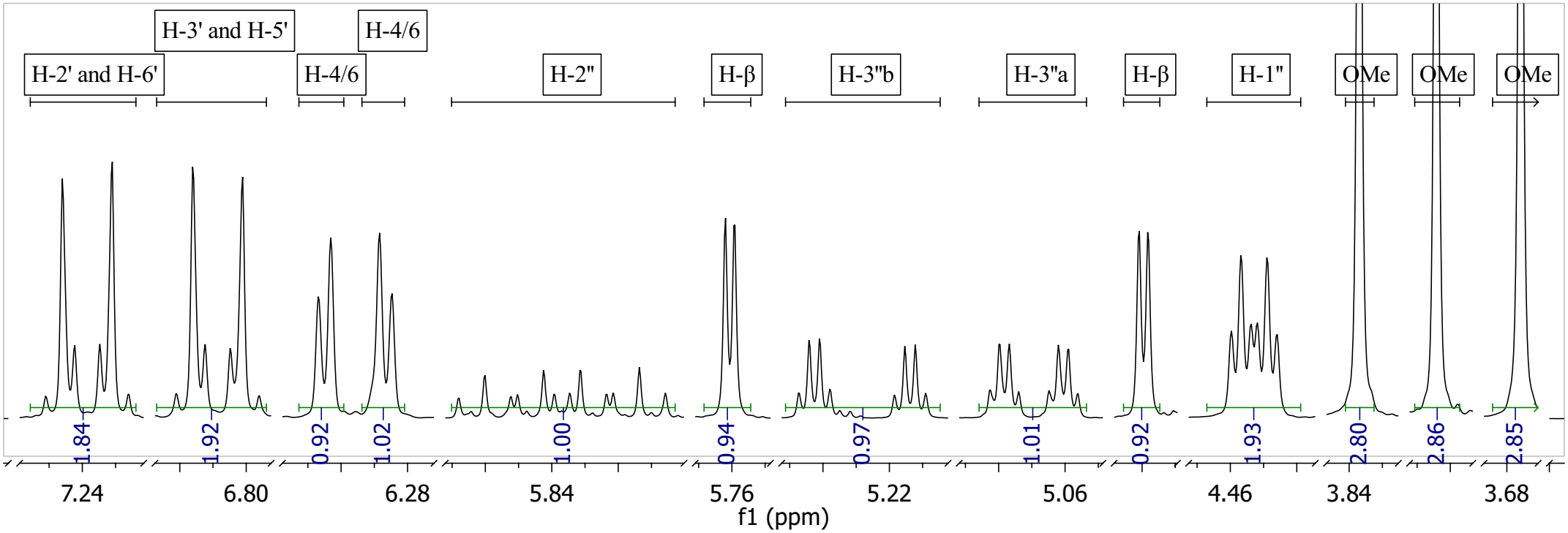
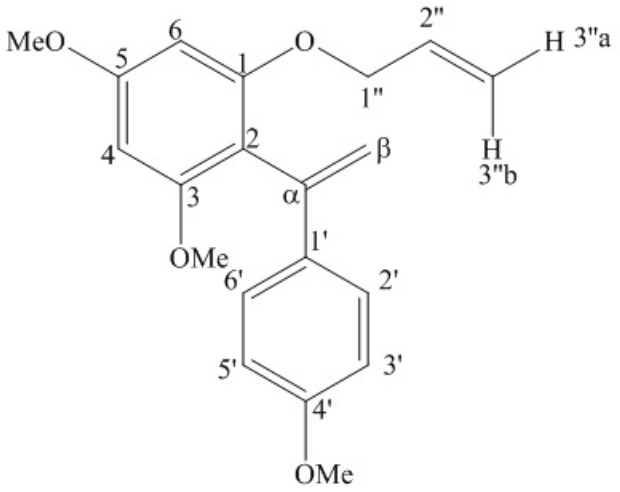


Plate 57b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**)

δ 161.69 (C-3/5), 159.92 (C-3/5/4'), 159.74 (C-3/5/4'), 158.50 (C-1), 141.76 (C-α), 134.83 (C-1'), 134.66 (C-2''), 127.86 (C-2' and C-6'), 116.47 (C-3''), 114.44 (C-β), 114.10 (C-3' and C-5'), 113.59 (C-2), 93.02 (C-4/6), 92.07 (C-4/6), 69.64 (C-1''), 56.11 (-OMe), 55.66 (-OMe), 55.49 (-OMe)



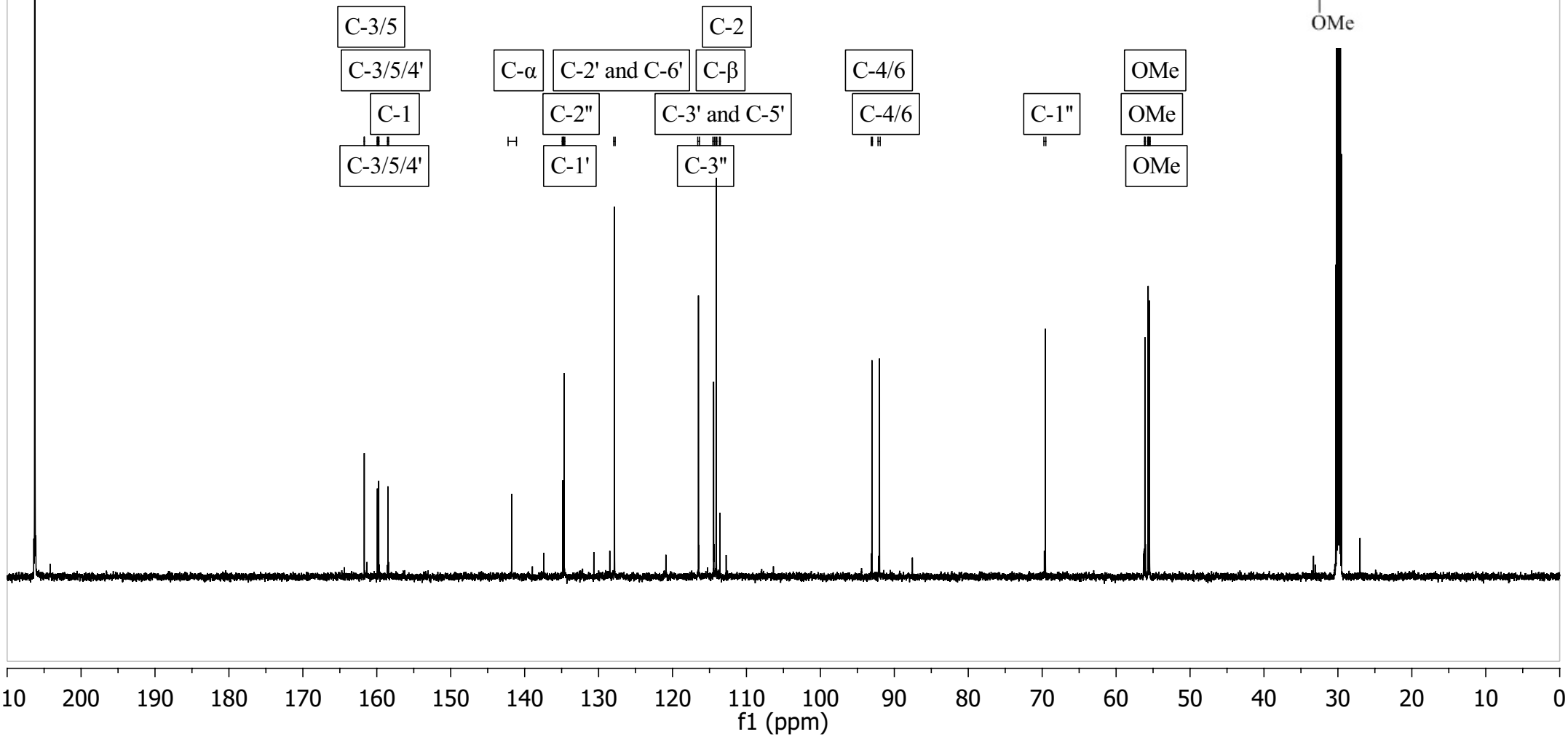


Plate 57c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**)

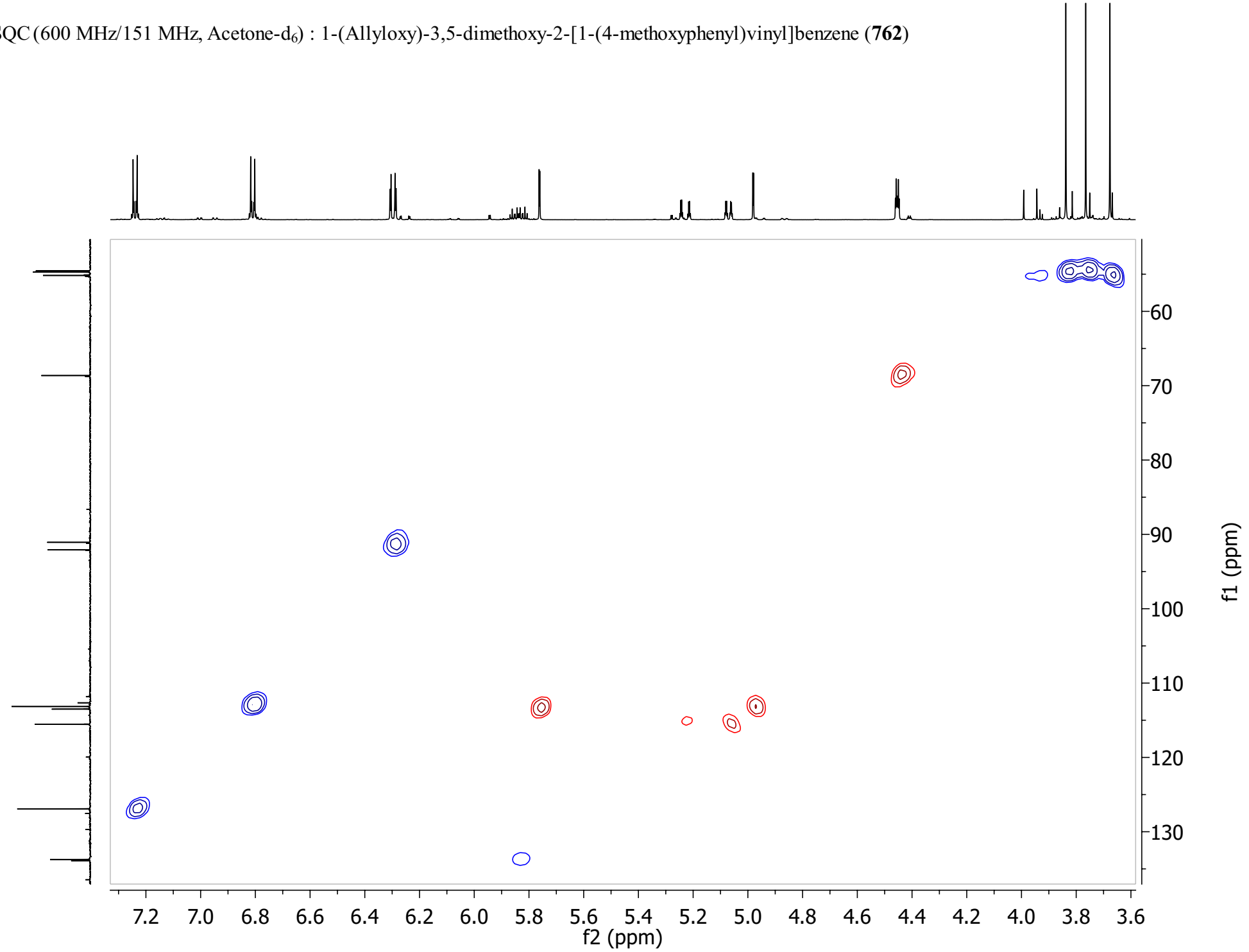


Plate 57d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**)

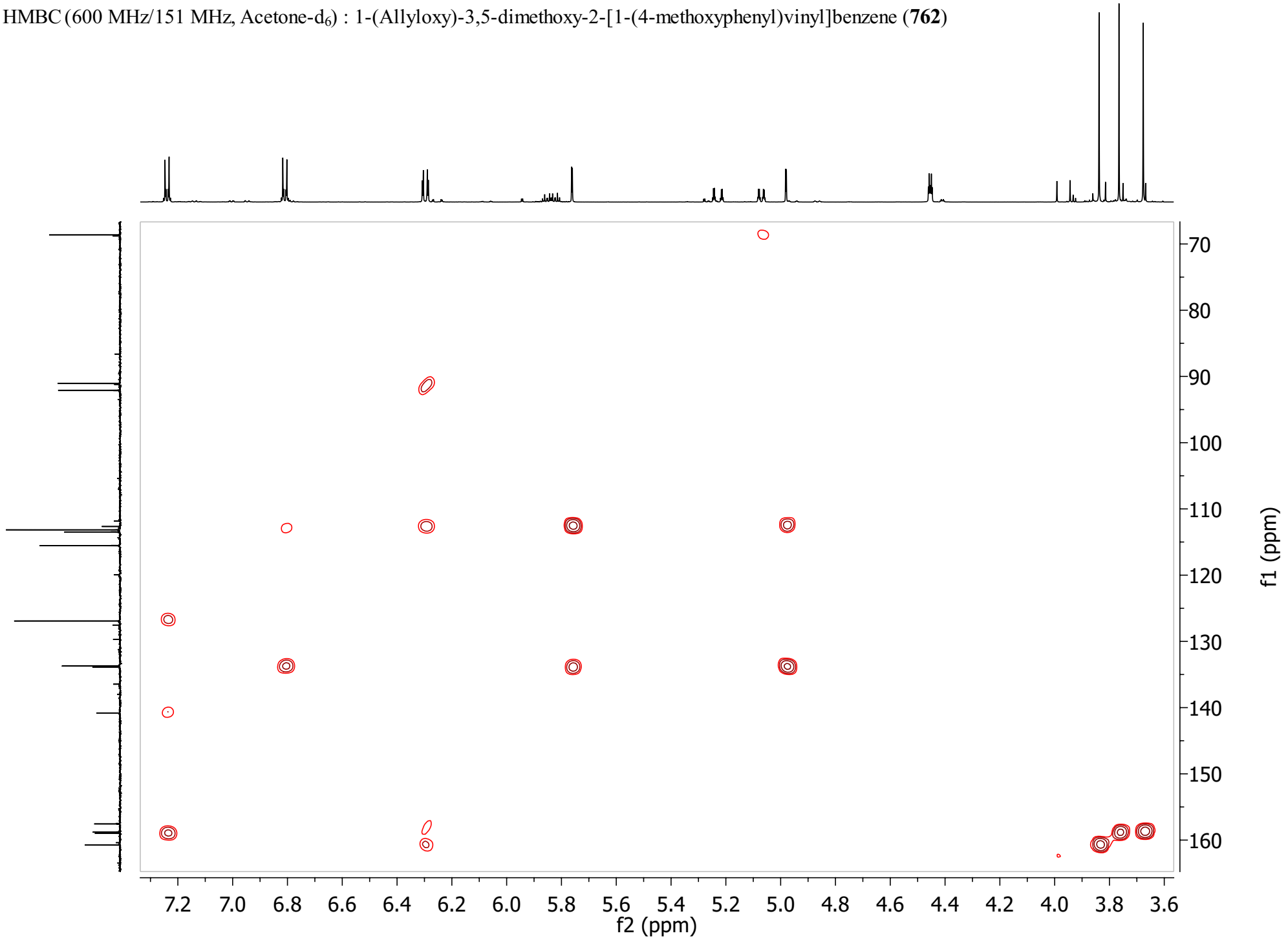


Plate 57e, DEPT (151 MHz, Acetone-d_6) : 1-(Allyloxy)-3,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**762**)

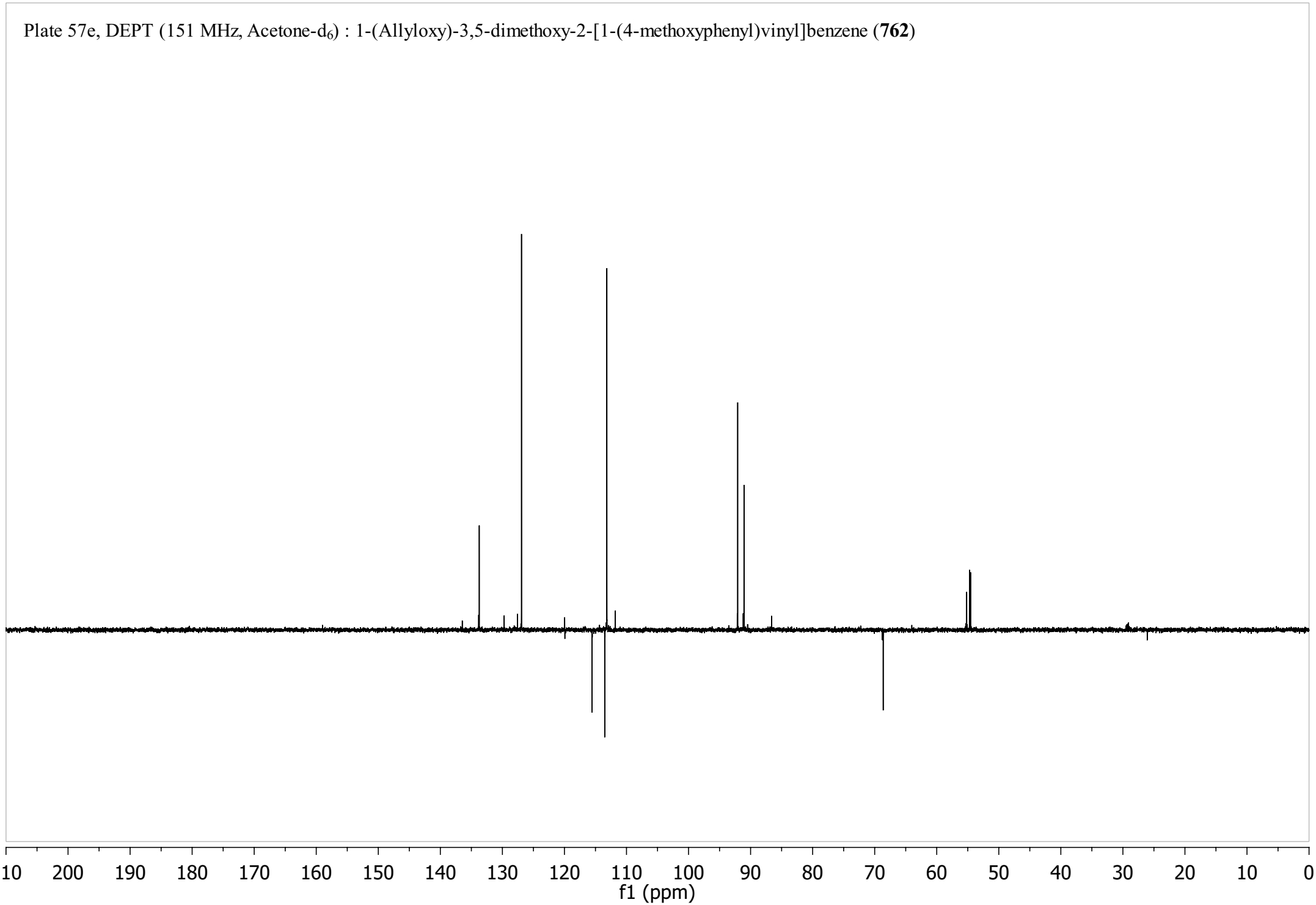
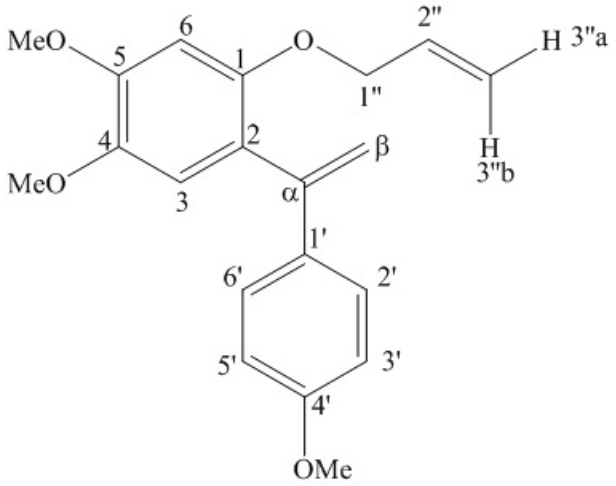
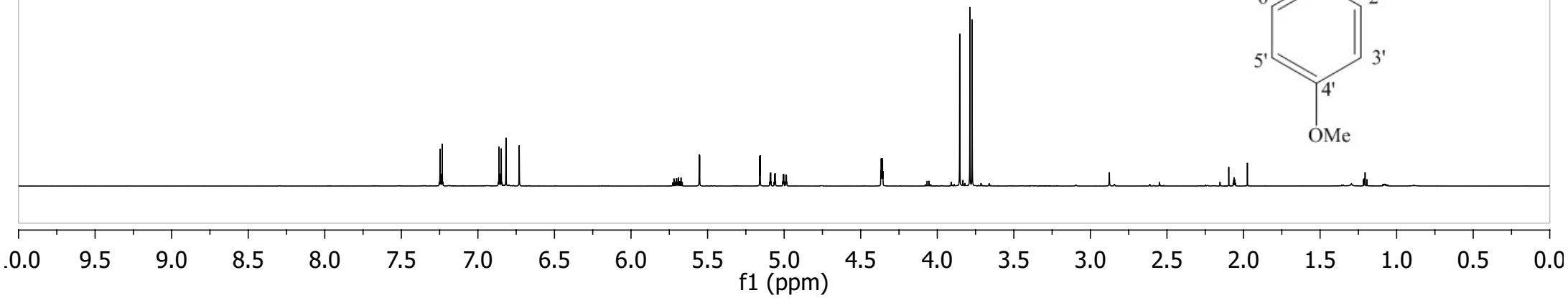


Plate 58a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**)

δ 7.24 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.85 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.82 (1H, s, H-3/6), 6.73 (1H, s, H-3/6), 5.70 (1H, ddt, *J* = 17.2, 10.7, 5.0 Hz, H-2"), 5.55 (1H, d, *J* = 1.6 Hz, H-β), 5.16 (1H, d, *J* = 1.6 Hz, H-β), 5.08 (1H, ddt, *J* = 17.2, 1.8, 1.8 Hz, H-3"b), 5.00 (1H, ddt, *J* = 10.7, 1.8, 1.8 Hz, H-3"a), 4.36 (2H, ddd, *J* = 5.0, 1.8, 1.8 Hz, H-1"), 3.85 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.77 (3H, s, -OMe)





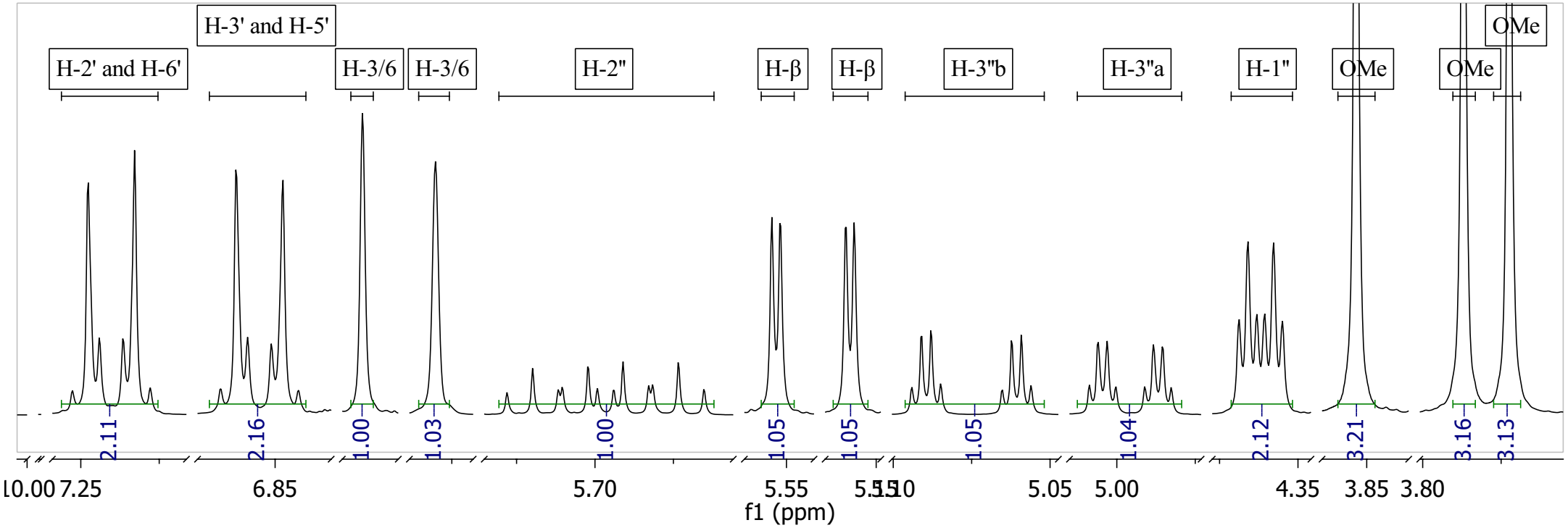
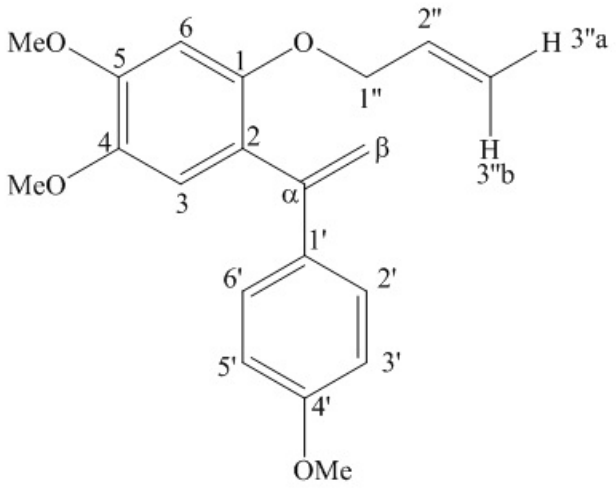


Plate 58b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**)

δ 160.22 (C-4'), 151.46 (C-4/5), 150.88 (C-1), 147.77 (C-α), 144.53 (C-4/5), 135.14 (C-1'), 134.89 (C-2''), 128.57 (C-2' and C-6'), 124.18 (C-2), 116.61 (C-3/6), 116.45 (C-3''), 114.19 (C-3' and C-5'), 113.55 (C-β), 101.51 (C-3/6), 70.78 (C-1''), 57.01 (-O<u>Me</u>), 56.40 (-O<u>Me</u>), 55.58 (-O<u>Me</u>)



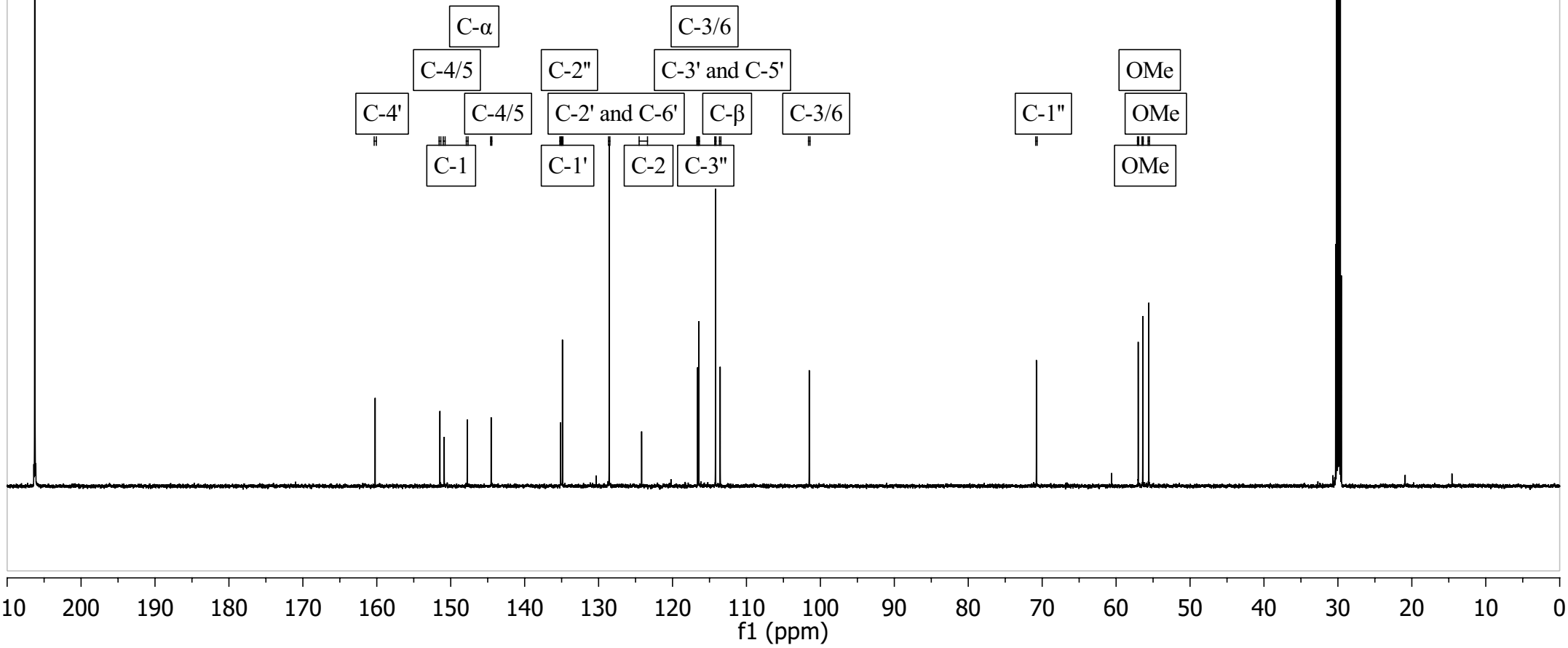


Plate 58c, HSQC (600 MHz/151 MHz, Acetone-d_6) :1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**)

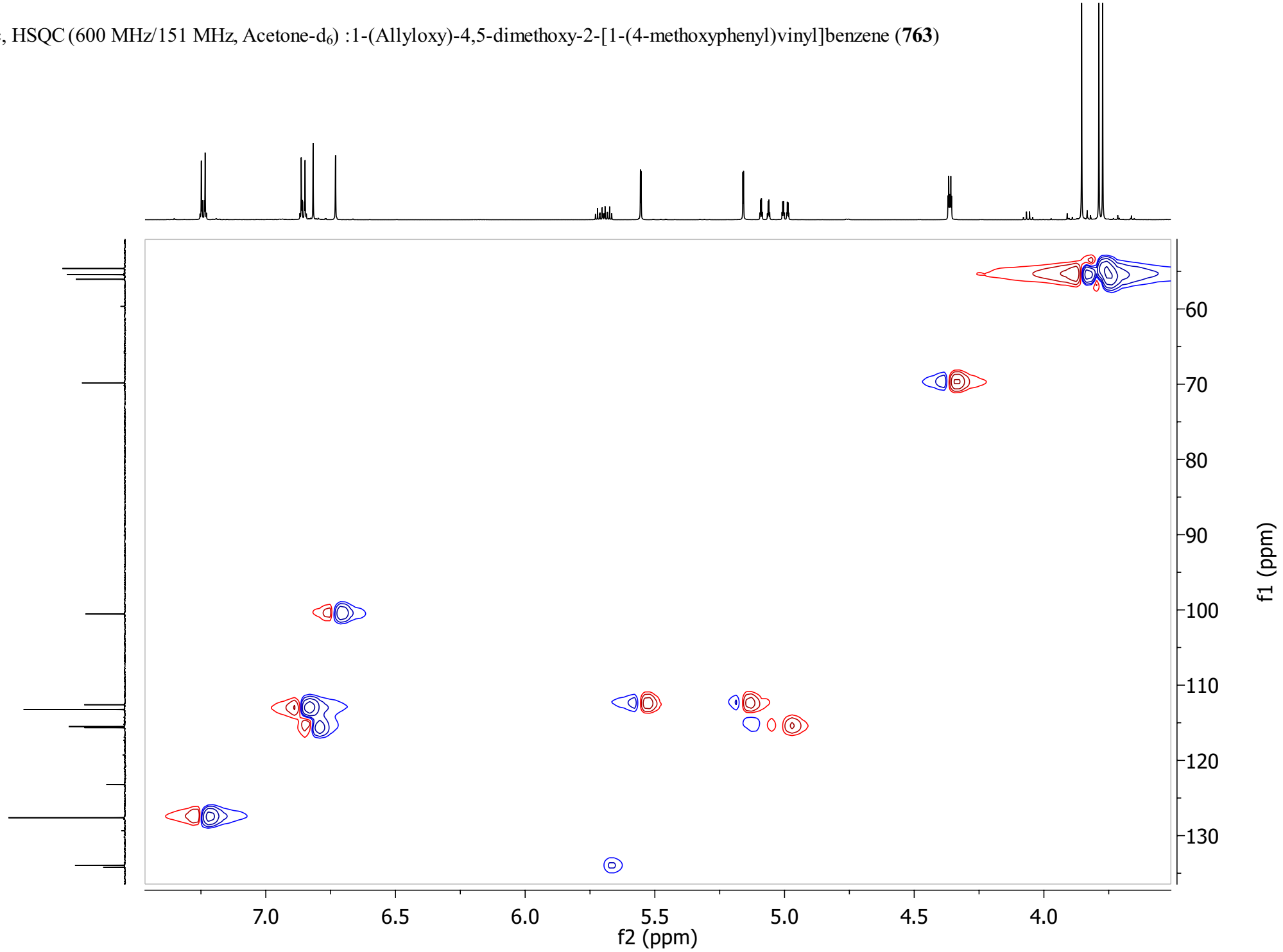


Plate 58d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**)

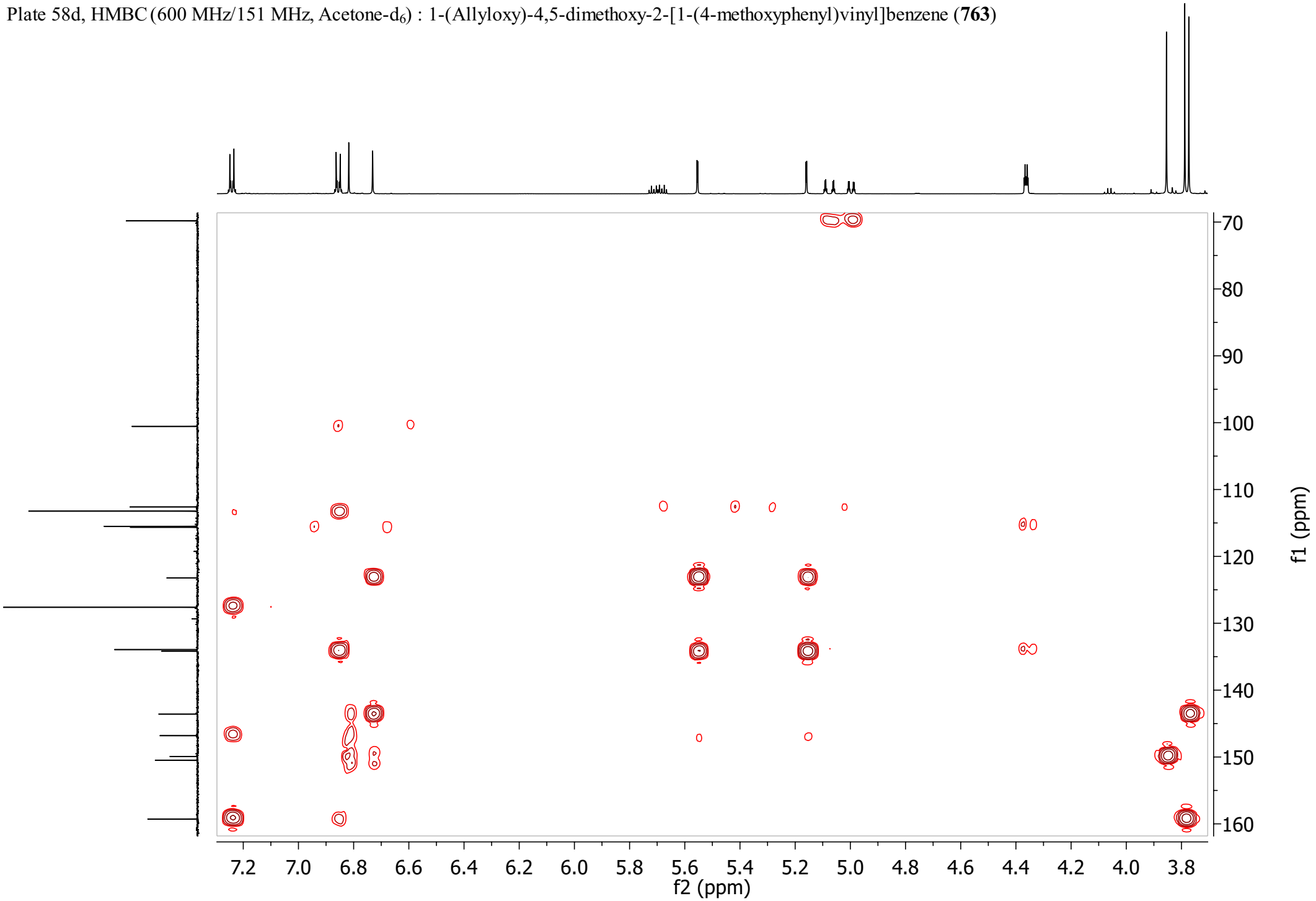
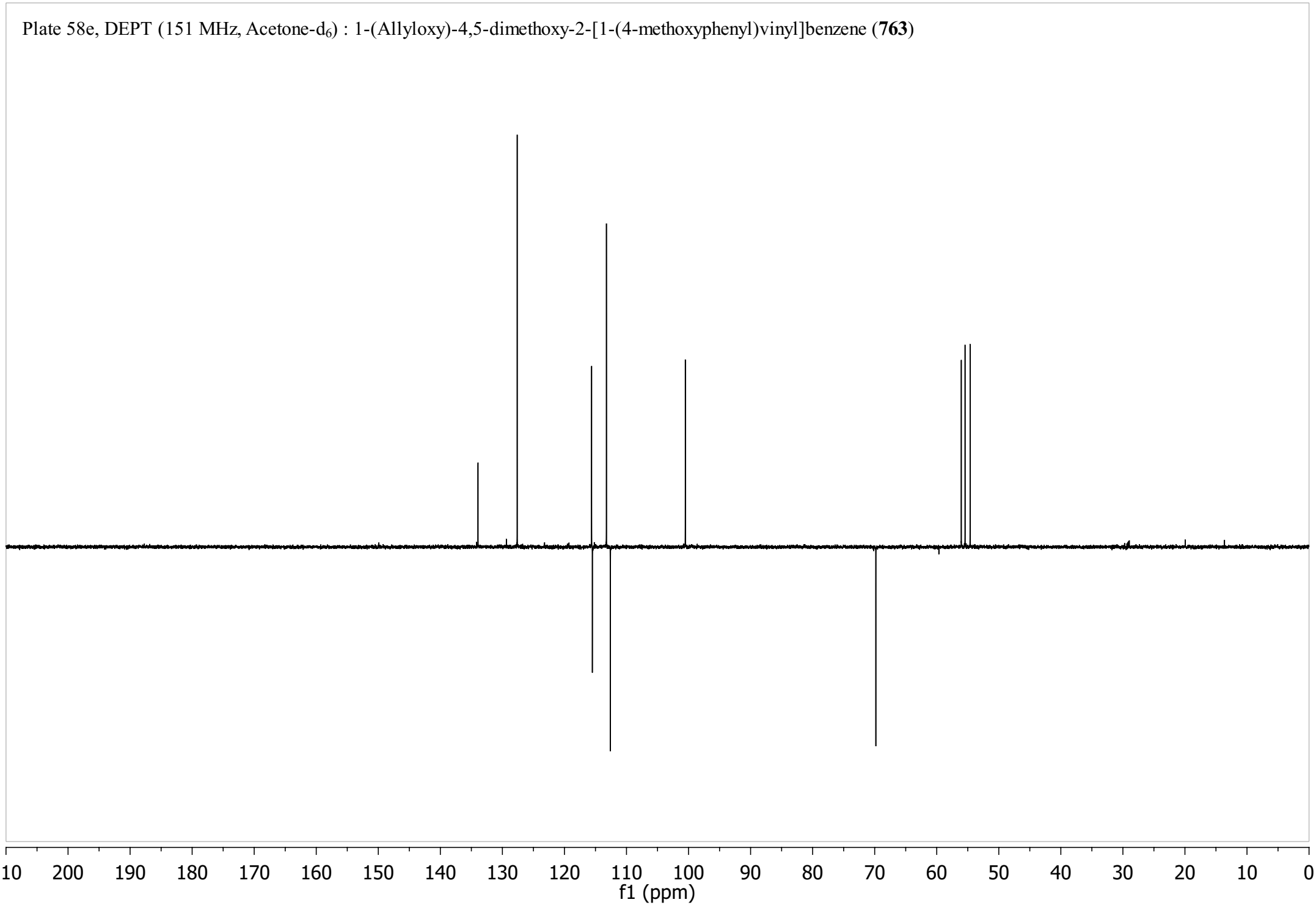


Plate 58e, DEPT (151 MHz, Acetone-d_6) : 1-(Allyloxy)-4,5-dimethoxy-2-[1-(4-methoxyphenyl)vinyl]benzene (**763**)



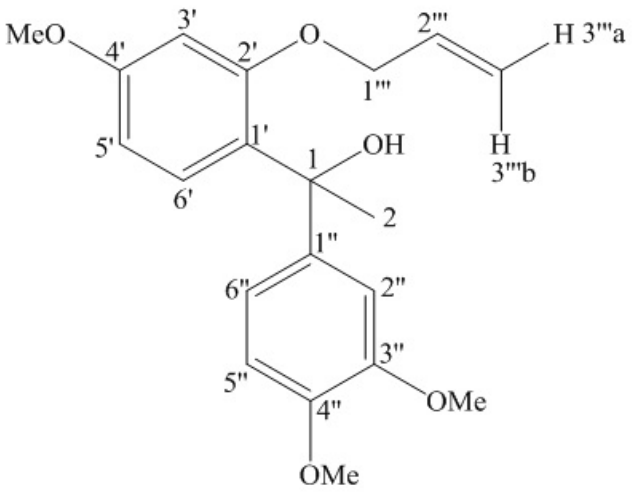
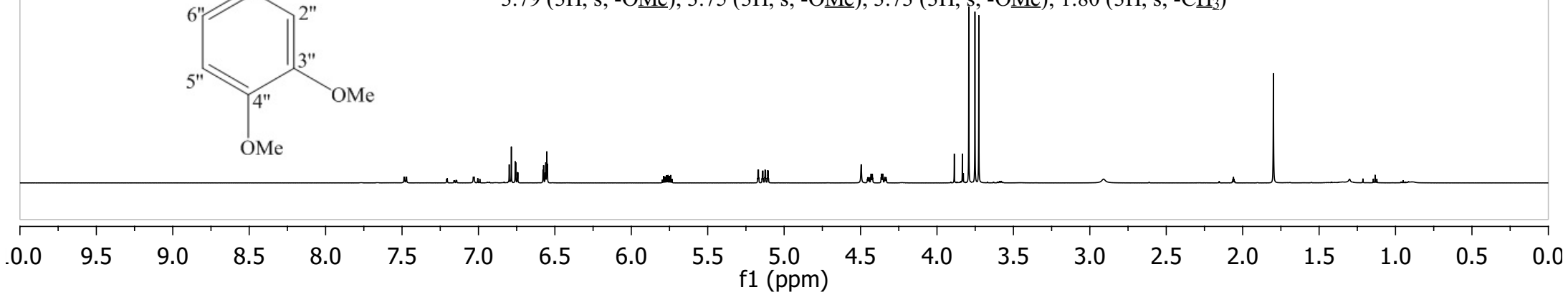


Plate 59a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**)

δ 7.48 (1H, d, *J* = 8.4 Hz, H-6'), 7.03 (1H, d, *J* = 2.1 Hz, H-2''), 6.79 (1H, d, *J* = 8.4 Hz, H-5''), 6.75 (1H, dd, *J* = 8.4, 2.1 Hz, H-6''), 6.56 (H, dd, *J* = 8.4, 2.5 Hz, H-5'), 6.55 (1H, d, *J* = 2.5 Hz, H-3'), 5.76 (1H, ddt, *J* = 17.3, 10.4, 5.1 Hz, H-2'''), 5.15 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, H-3'''b), 5.11 (1H, ddt, *J* = 10.4, 1.5, 1.5 Hz, H-3'''a), 4.50 (1H, s, -O<u>H</u>), 4.44 (1H, ddd, *J* = 13.0, 5.1, 1.5 Hz, H-1'''a), 4.35 (1H, ddd, *J* = 13.0, 5.1, 1.5 Hz, H-1'''b), 3.79 (3H, s, -O<u>Me</u>), 3.75 (3H, s, -O<u>Me</u>), 3.73 (3H, s, -O<u>Me</u>), 1.80 (3H, s, -C<u>H$_3$</u>)



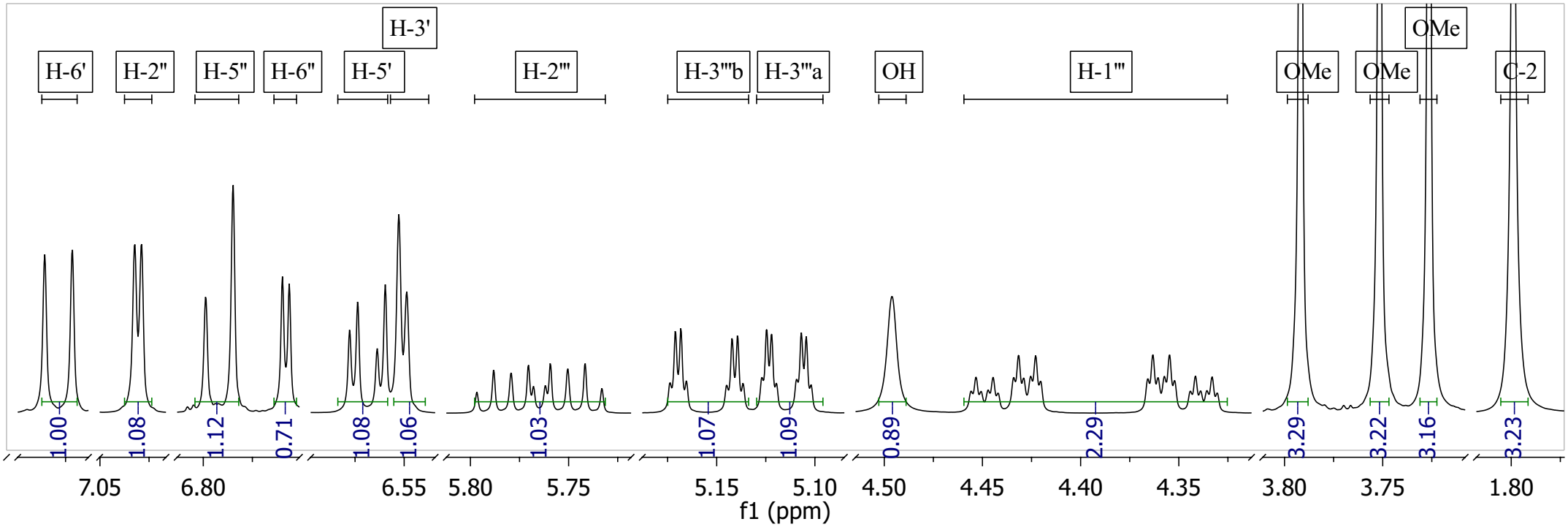
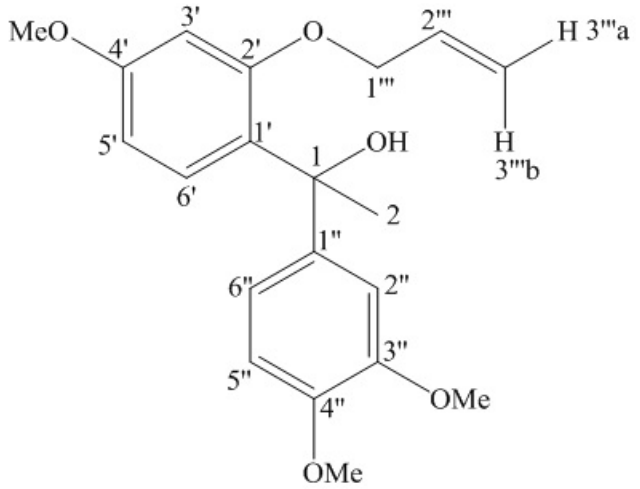


Plate 59b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**)

δ 160.96 (C-4'), 157.67 (C-2'), 149.57 (C-3''), 148.77 (C-4''), 143.81 (C-1''), 134.14 (C-2'''), 129.82 (C-1'), 128.16 (C-6'), 118.51 (C-6''), 117.51 (C-3'''), 112.01 (C-5''), 110.93 (C-2''), 105.21 (C-5'), 101.57 (C-3'), 75.70 (C-1), 69.80 (C-1'''), 56.13 (-O<u>Me</u>), 56.08 (-O<u>Me</u>), 55.58 (-O<u>Me</u>), 30.35 (-<u>C</u>H_3)



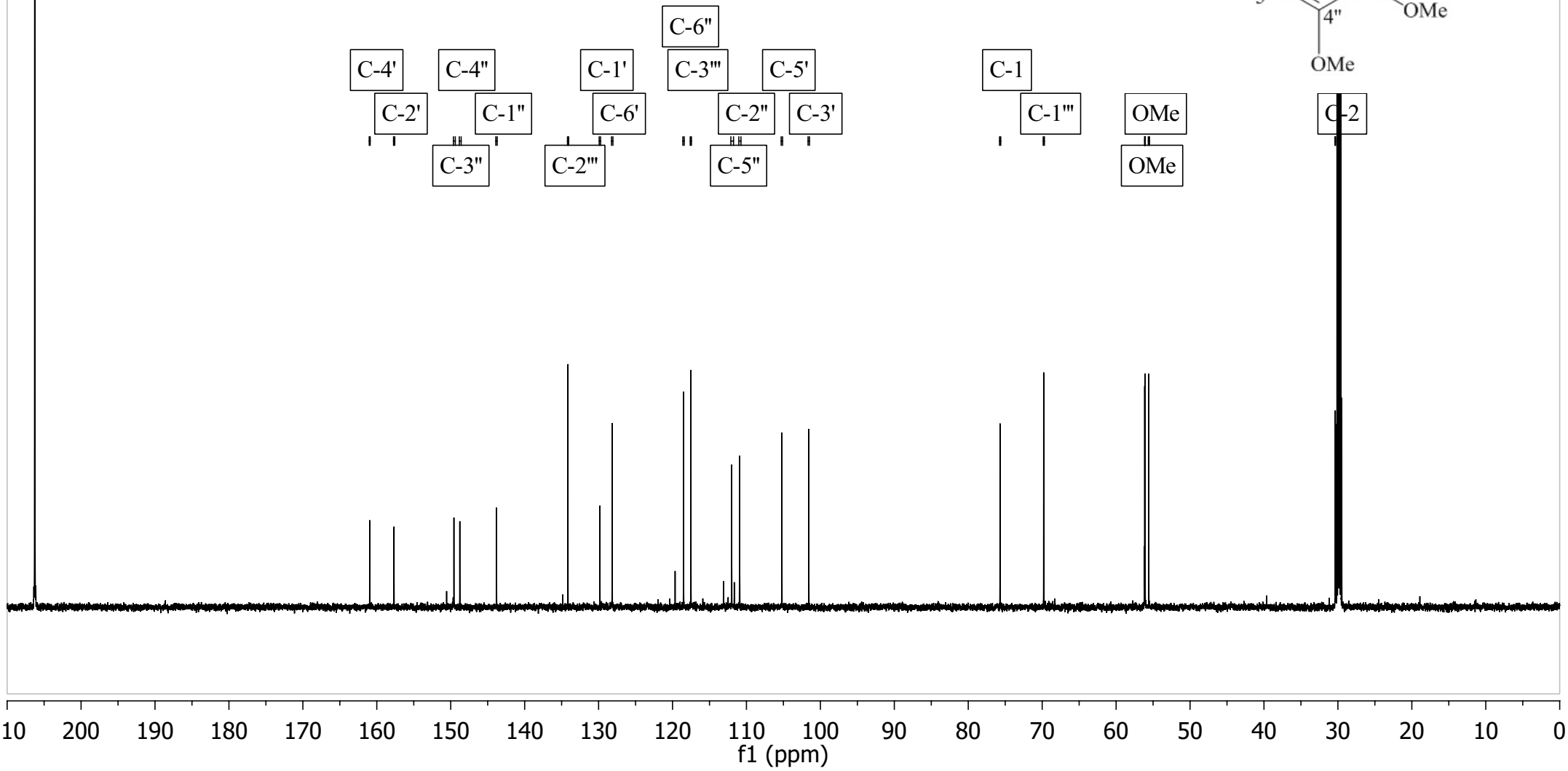


Plate 59c, HSQC (600/151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**)

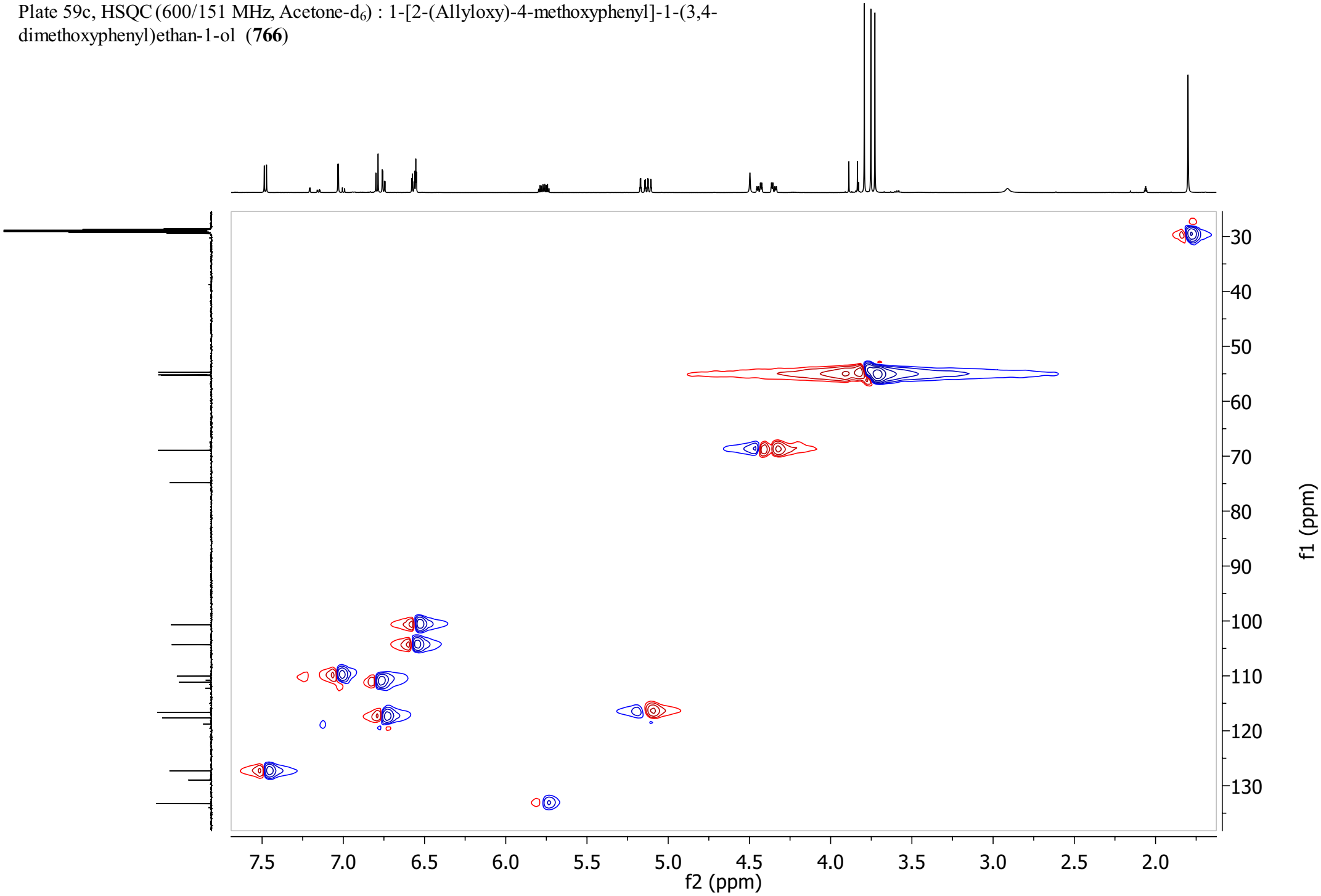


Plate 59d, HMBC (600/151 MHz, Acetone-d_6 :1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**)

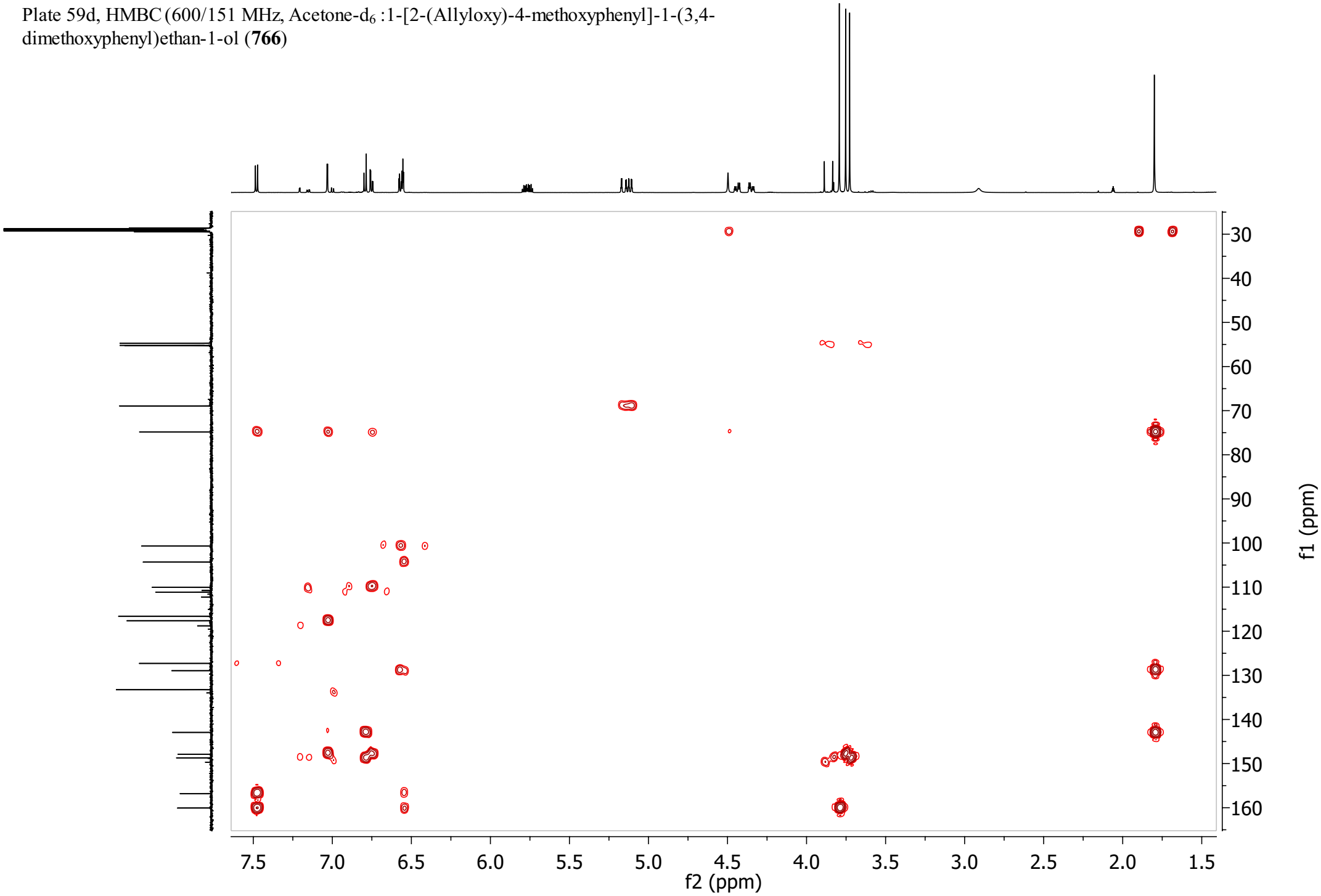
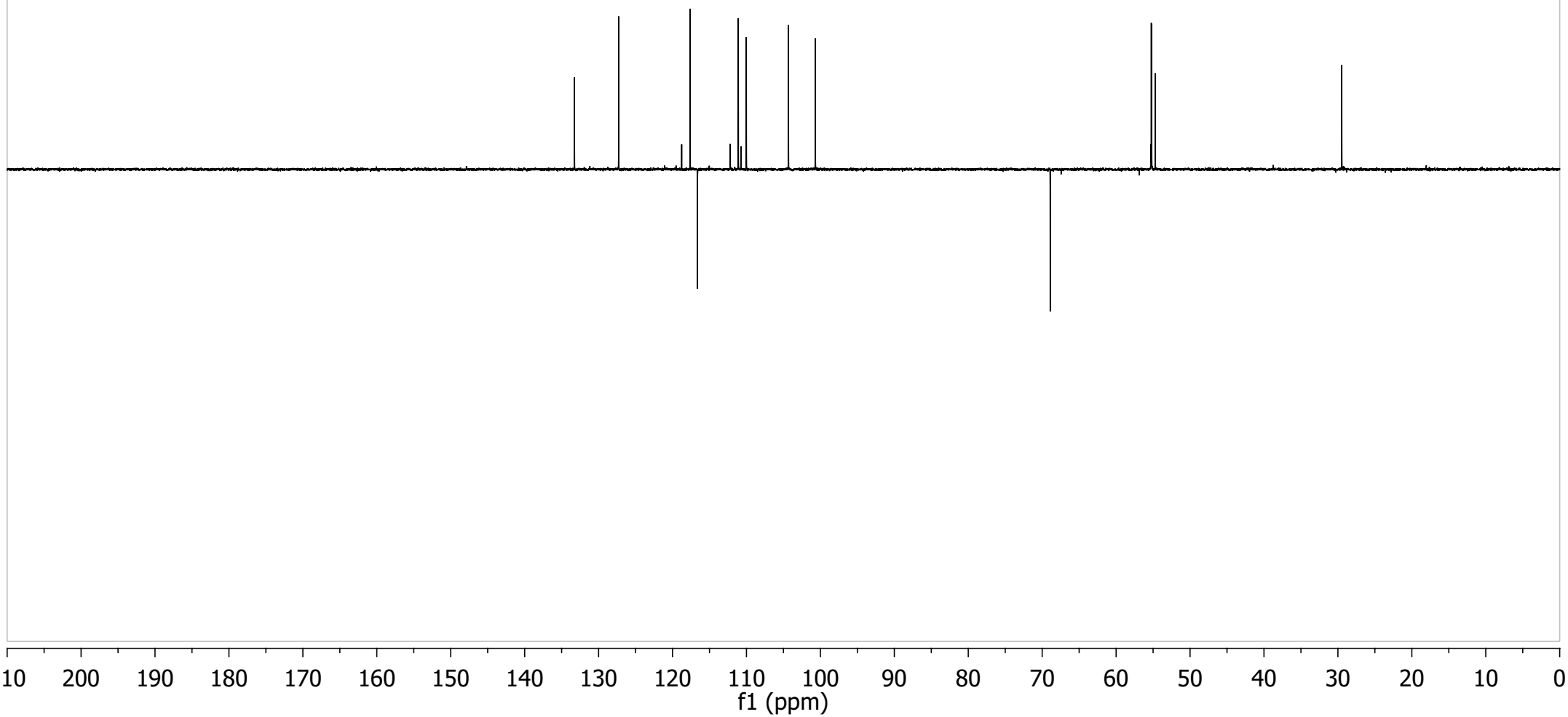


Plate 59e, DEPT (151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4-methoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**766**)



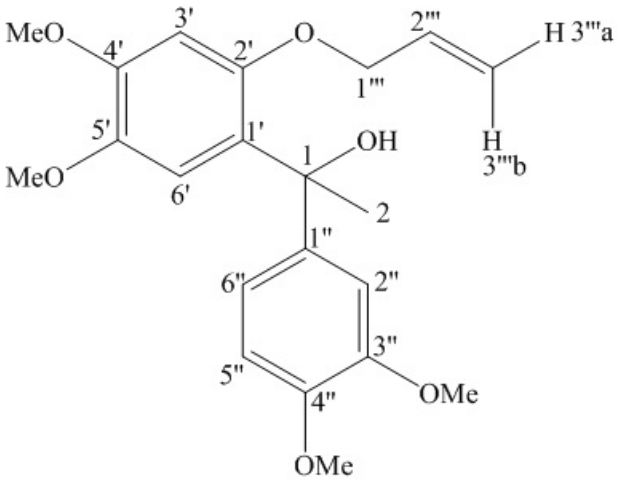
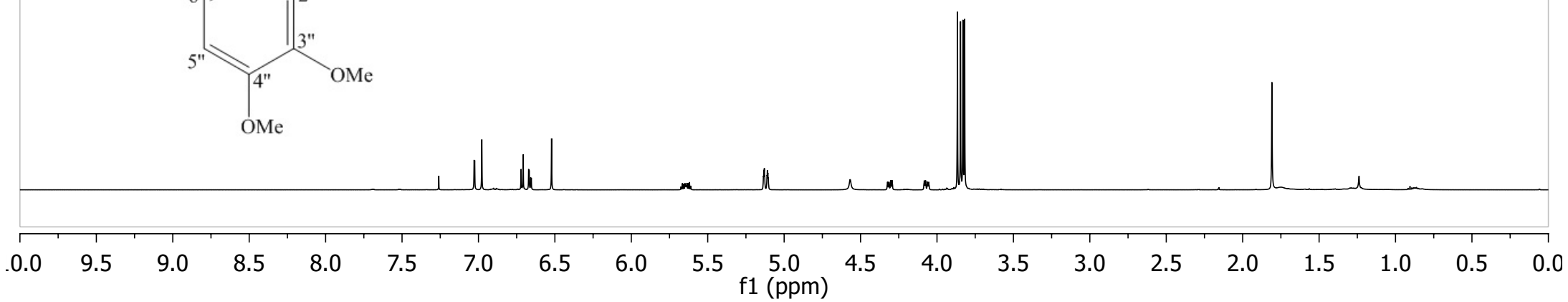


Plate 60a, ^{1}H NMR (600 MHz, Acetone-d_6) :1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**)

δ 7.03 (1H, d, *J* = 2.0 Hz, H-2''), 6.98 (1H, s, H-6'), 6.71 (1H, d, *J* = 8.4 Hz, H-5''), 6.66 (1H, dd, *J* = 8.4, 2.0 Hz, H-6''), 6.52 (1H, s, H-3'), 5.68 – 5.61 (1H, m, H-2'''), 5.15 – 5.10 (2H, m, 3'''a and 3'''b), 4.57 (1H, s, -O<u>H</u>), 4.31 (1H, br. dd, *J* = 12.5, 5.7 Hz, H-1'''a), 4.07 (1H, br. dd, *J* = 12.5, 5.7 Hz, H-1'''b), 3.87 (3H, s, -O<u>Me</u>), 3.85 (3H, s, -O<u>Me</u>), 3.83 (3H, s, -O<u>Me</u>), 3.82 (3H, s, -O<u>Me</u>), 1.81 (3H, s, -C<u>H</u>$_3$)



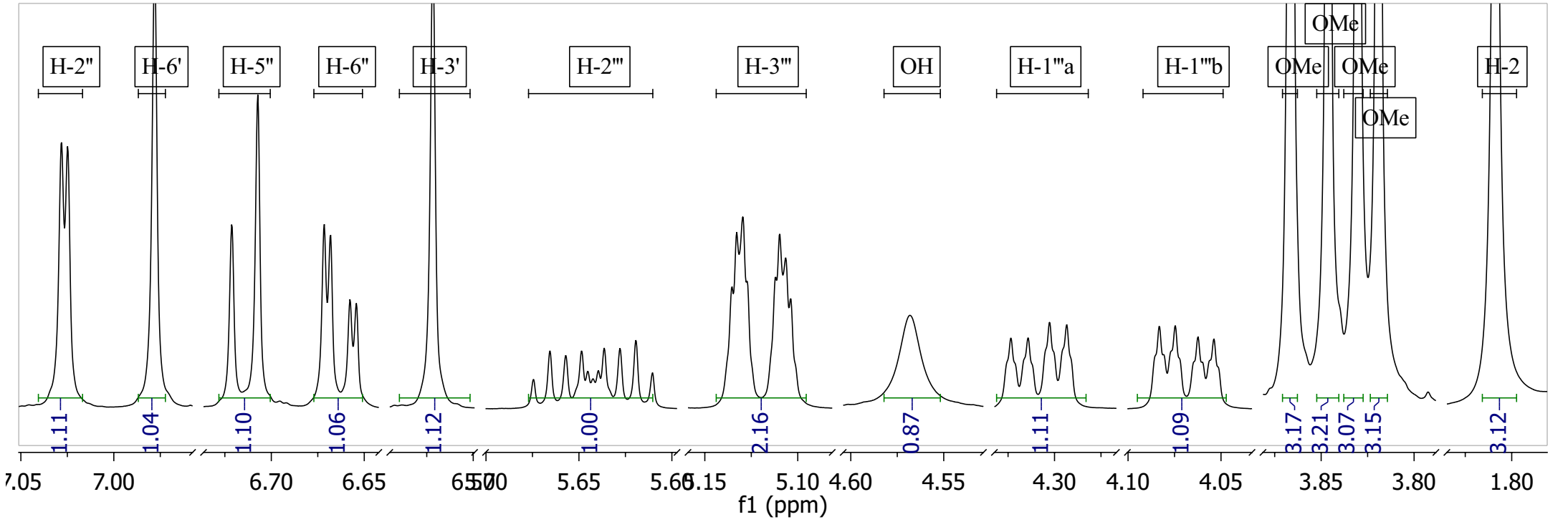


Plate 60b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**)

δ 150.49 (C-2'), 148.91 (C-4'/4''), 148.44 (C-3'), 147.53 (C-4'/4''), 142.98 (C-5'), 142.95 (C-1''), 132.87 (C-2'''), 128.15 (C-1'), 117.92 (C-3'''), 117.30 (C-6''), 111.73 (C-6'), 110.40 (C-5''), 108.74 (C-2''), 100.55 (C-3'), 75.91 (C-1), 70.82 (C-1'''), 56.94 (-O<u>Me</u>), 56.19 (-O<u>Me</u>), 55.97 (-O<u>Me</u>), 55.94 (-O<u>Me</u>), 30.36 (-<u>C</u>H_3)

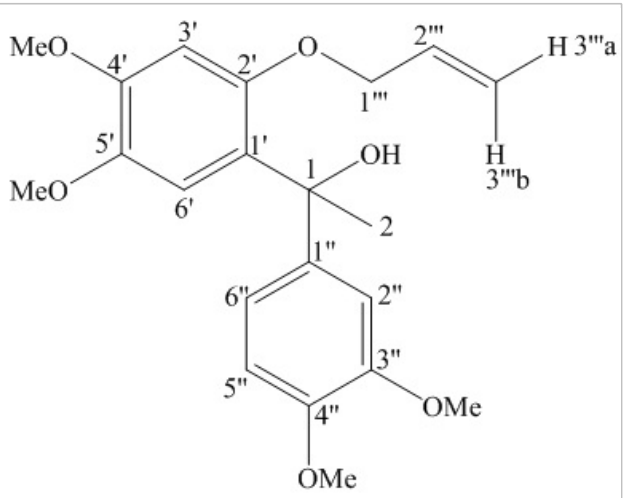


Plate 60c, HSQC (600/151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**)

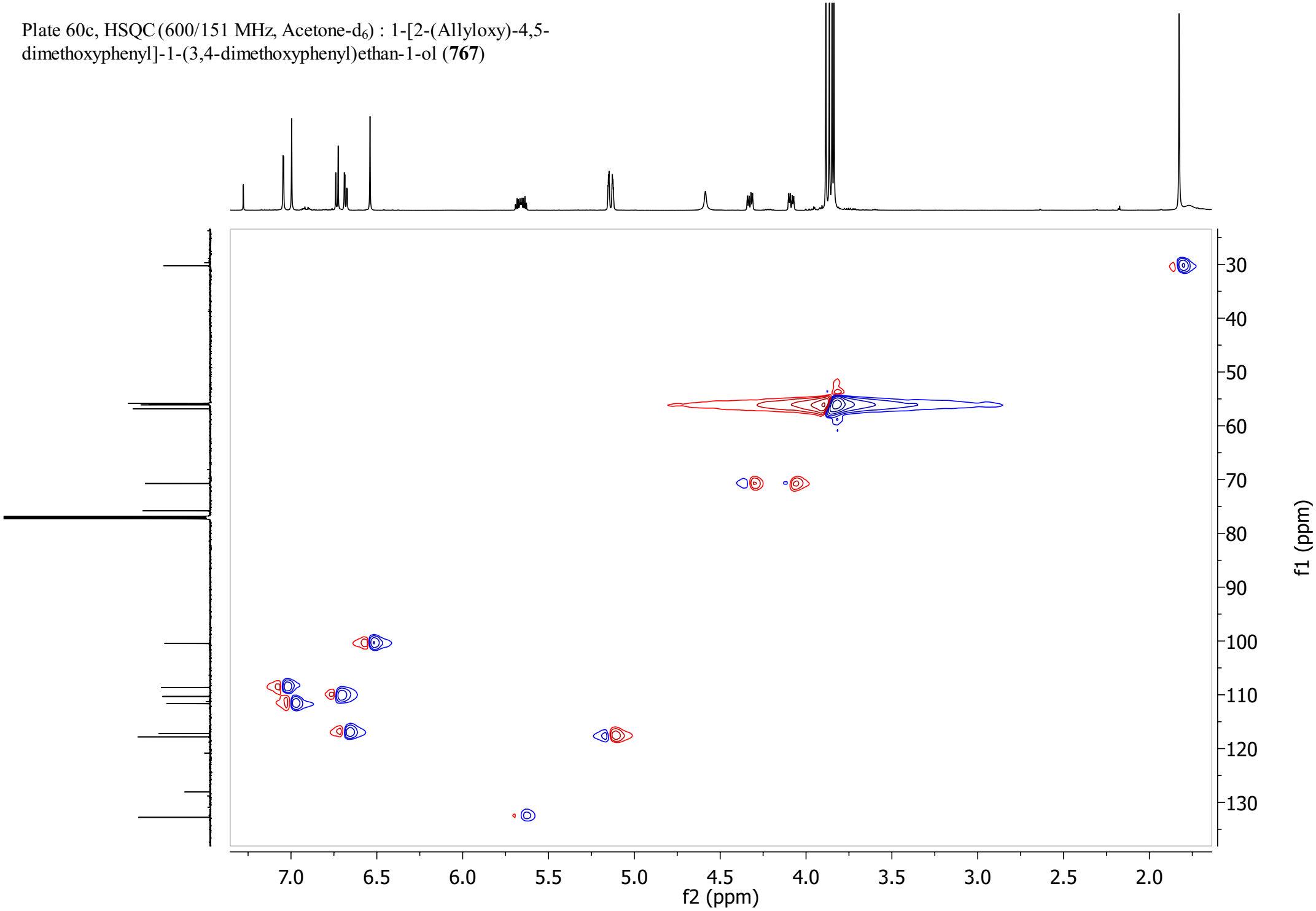


Plate 60d, HMBC (600/151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**)

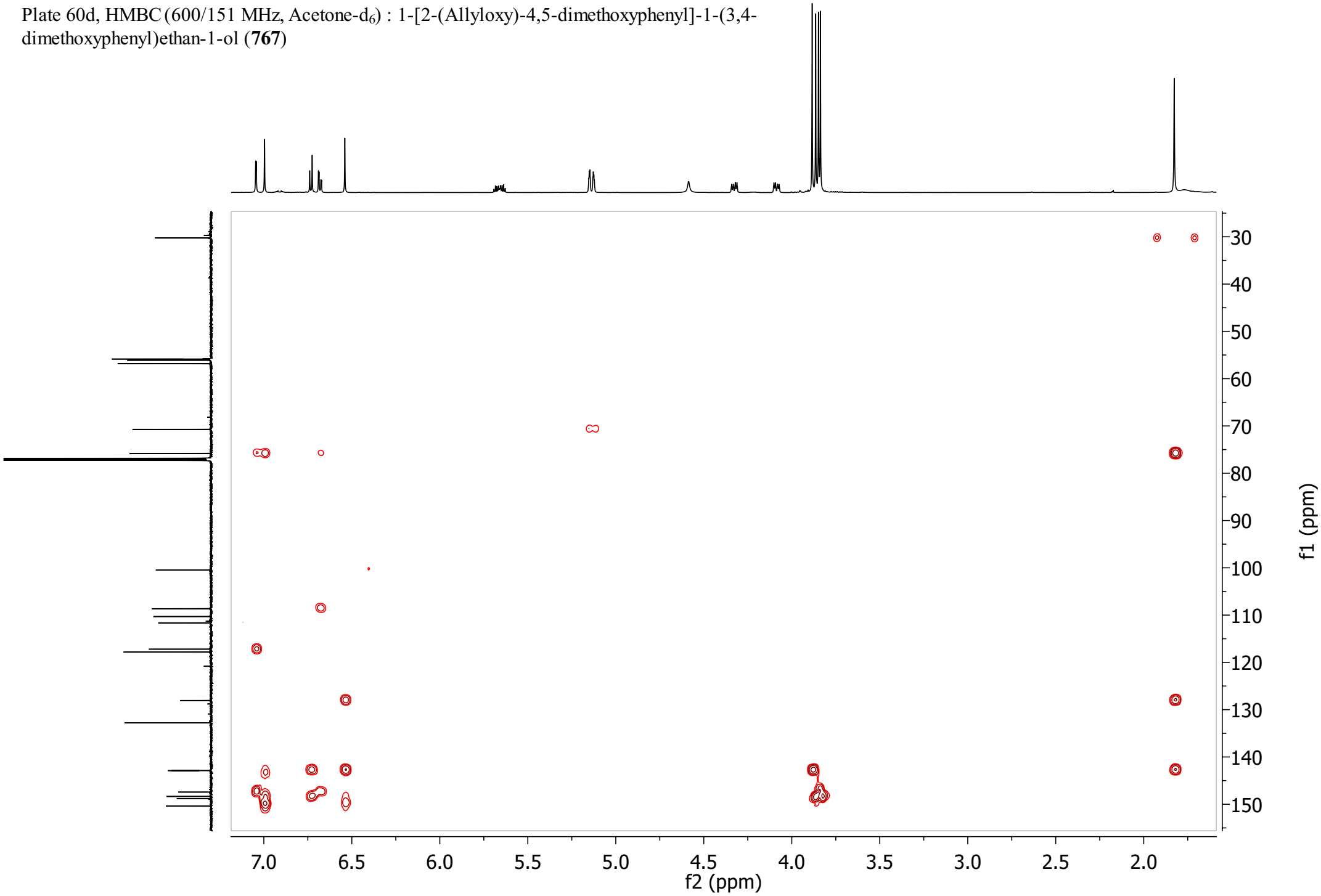


Plate 60e, DEPT (151 MHz, Acetone-d_6) : 1-[2-(Allyloxy)-4,5-dimethoxyphenyl]-1-(3,4-dimethoxyphenyl)ethan-1-ol (**767**)

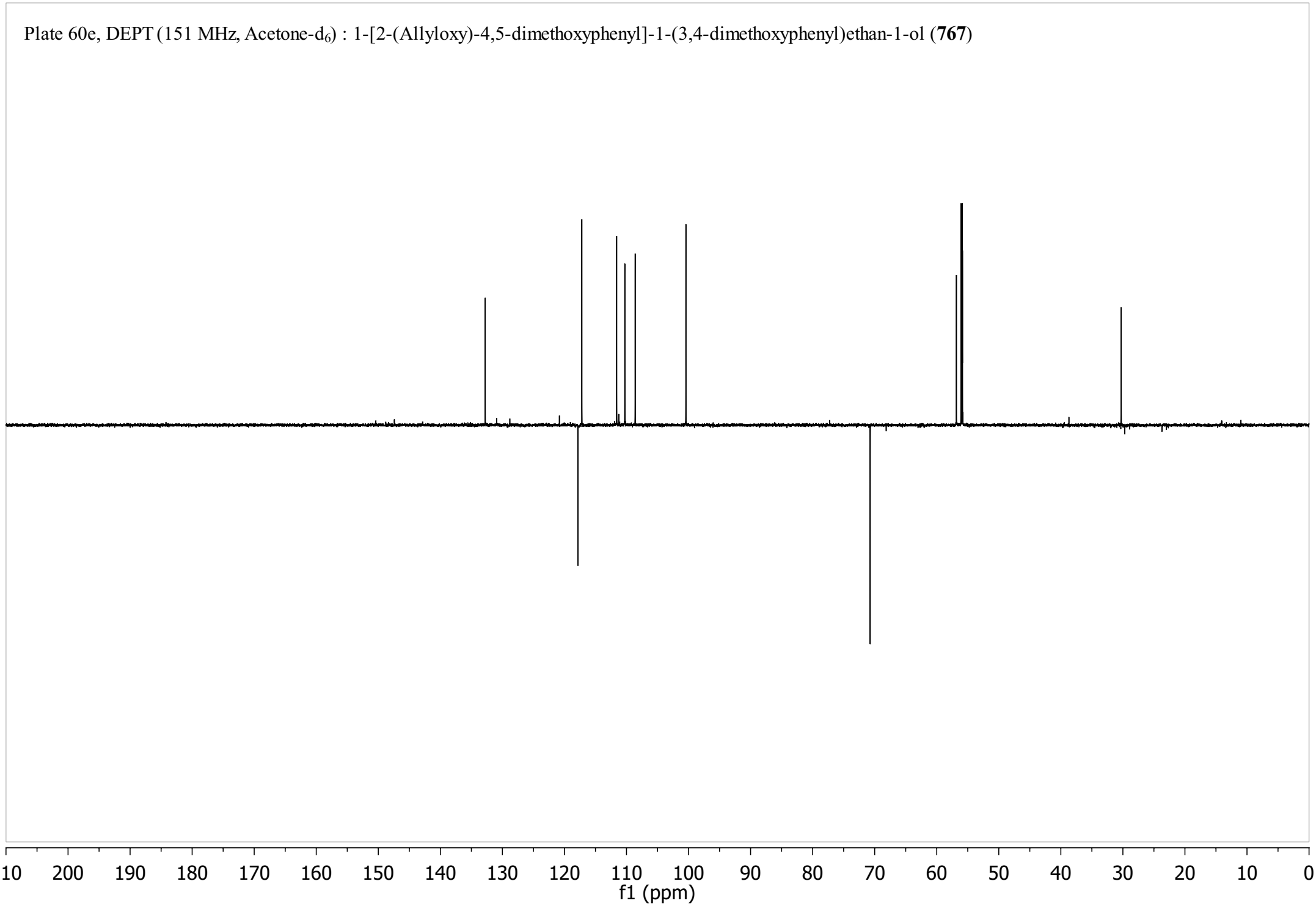
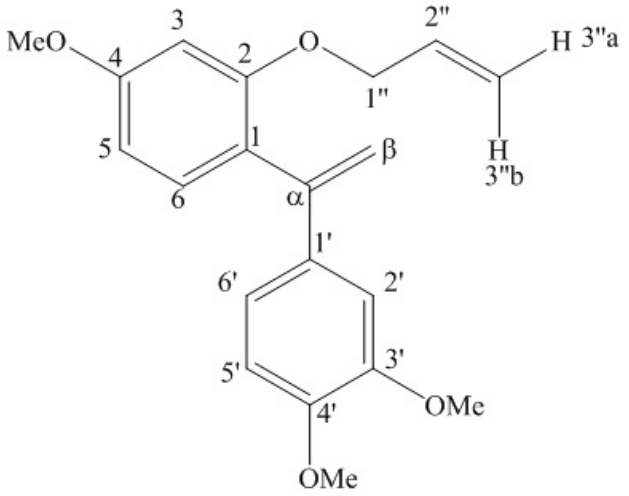
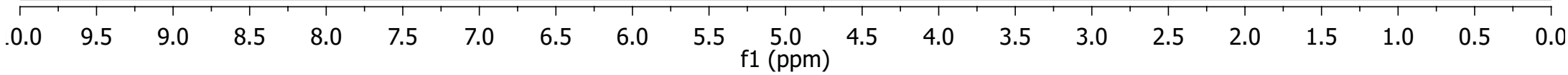


Plate 61a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**)

δ 7.15 (1H, d, *J* = 8.7 Hz, H-6), 6.95 (1H, d, *J* = 2.0 Hz, H-2'), 6.84 (1H, d, *J* = 8.3 Hz, H-5'), 6.77 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 6.59 – 6.56 (2H, m, H-3 and H-5), 5.77 – 5.70 (1H, m, H-2"), 5.56 (1H, d, *J* = 1.6 Hz, H-β), 5.14 (1H, d, *J* = 1.6 Hz, H-β), 5.08 (1H, br. d, *J* = 17.3, 1.7 Hz, H-3"b), 5.02 (1H, br. d, *J* = 10.5, 1.7 Hz, H-3"a), 4.43 – 4.40 (2H, m, H-1"), 3.82 (3H, s, -OMe), 3.79 (3H, s, -OMe), 3.75 (3H, s, -OMe)





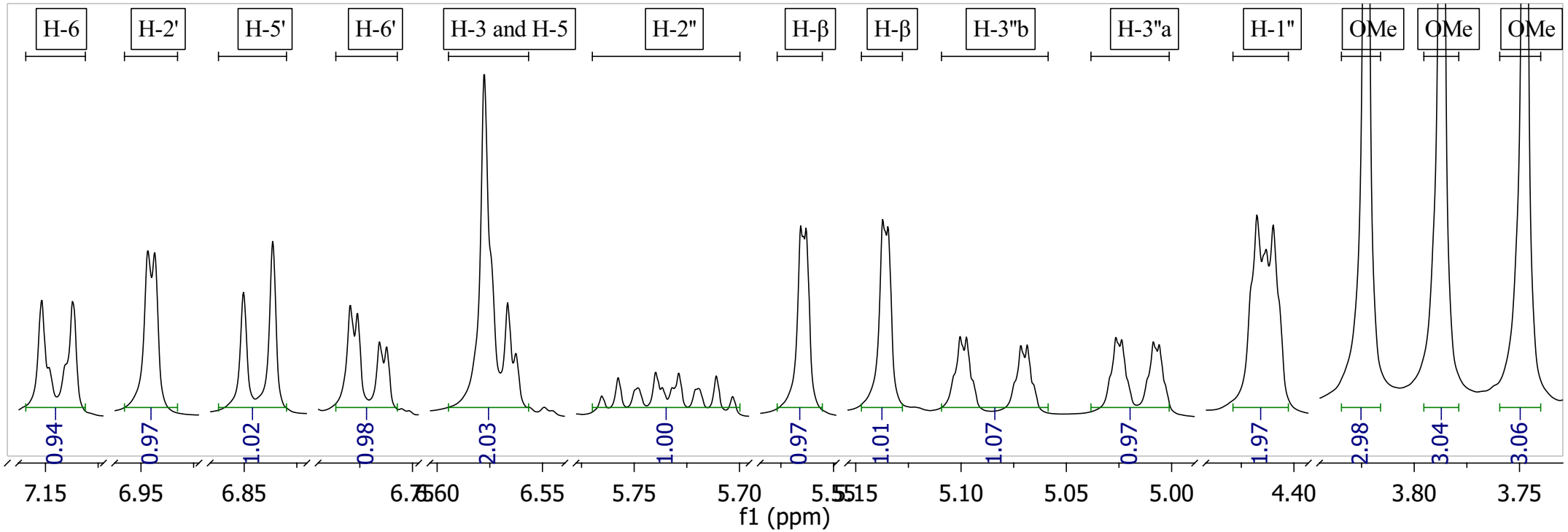
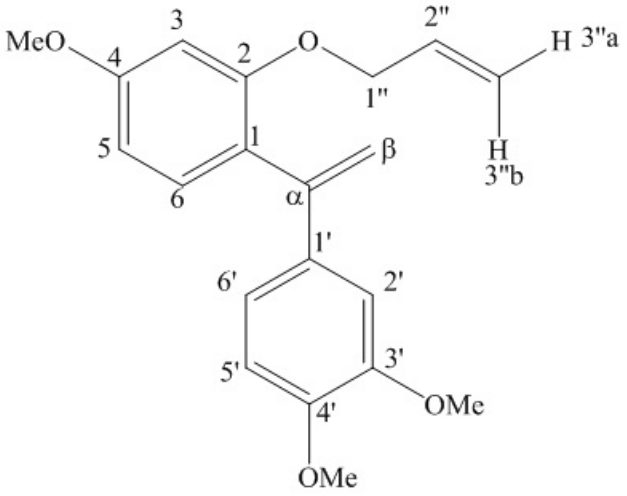


Plate 61b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**)

δ 161.63 (C-4), 157.97 (C-2), 149.99 (C-3'/4'), 149.88 (C-3'/4'), 147.92 (C-α), 135.61 (C-1'), 134.25 (C-2''), 132.30 (C-6), 124.85 (C-1), 120.06 (C-6'), 116.35 (C-3''), 113.48 (C-β), 112.18 (C-5'), 111.42 (C-2'), 105.69 (C-5), 100.80 (C-3), 69.27 (C-1''), 56.08 (-OMe), 56.07 (-OMe), 55.59 (-OMe)



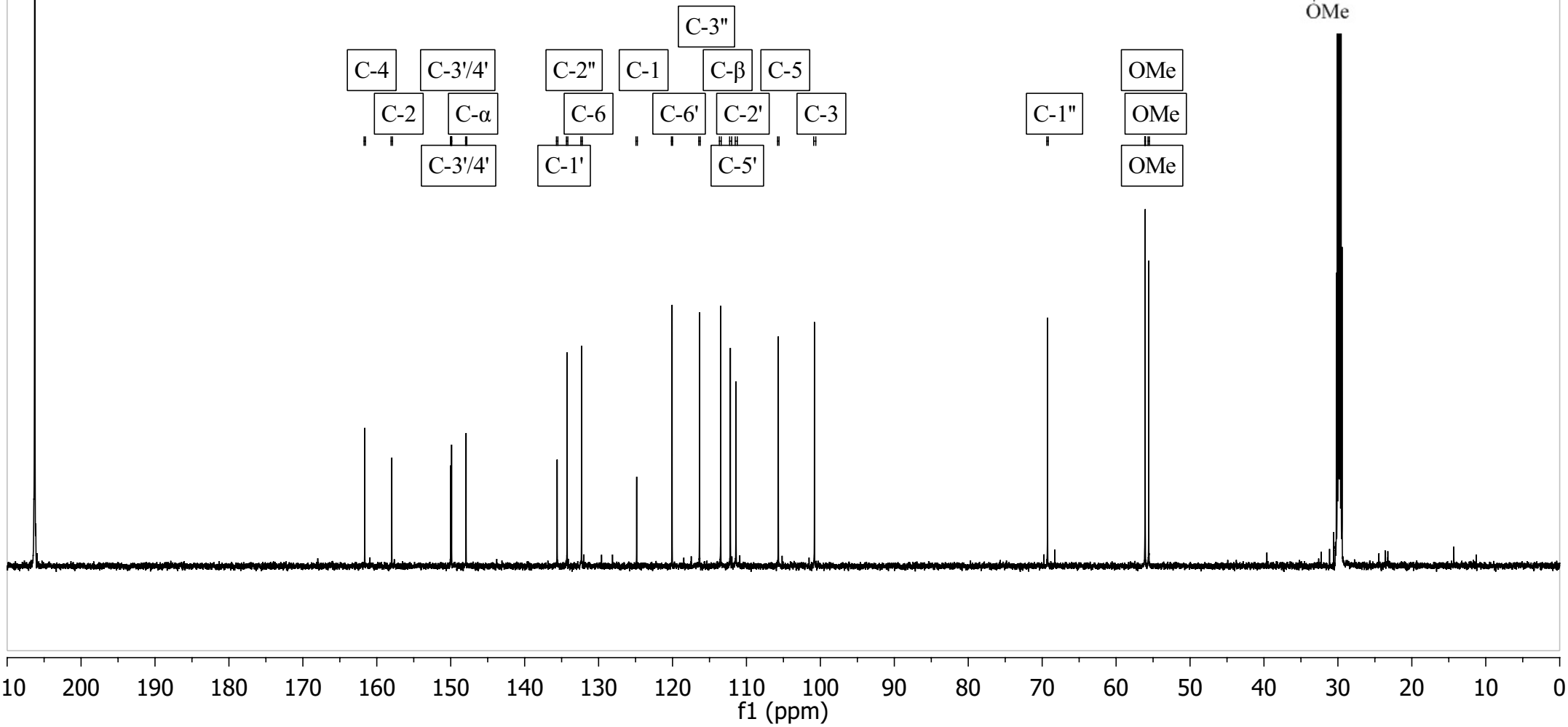


Plate 61c, HSQC (600/151 MHz, Acetone-d_6) : 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**)

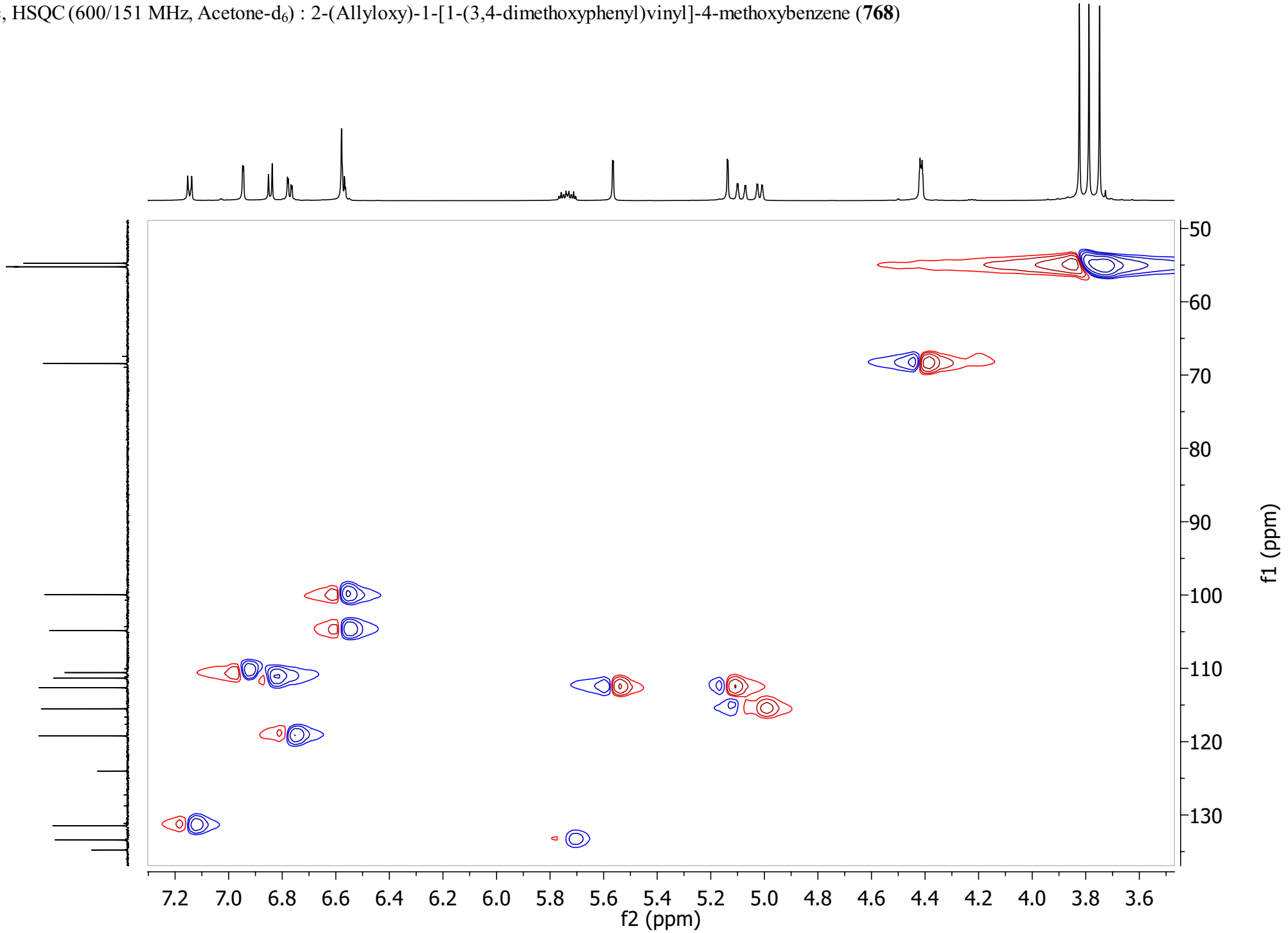


Plate 61d, HMBC (600/151 MHz, Acetone-d_6) : 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**)

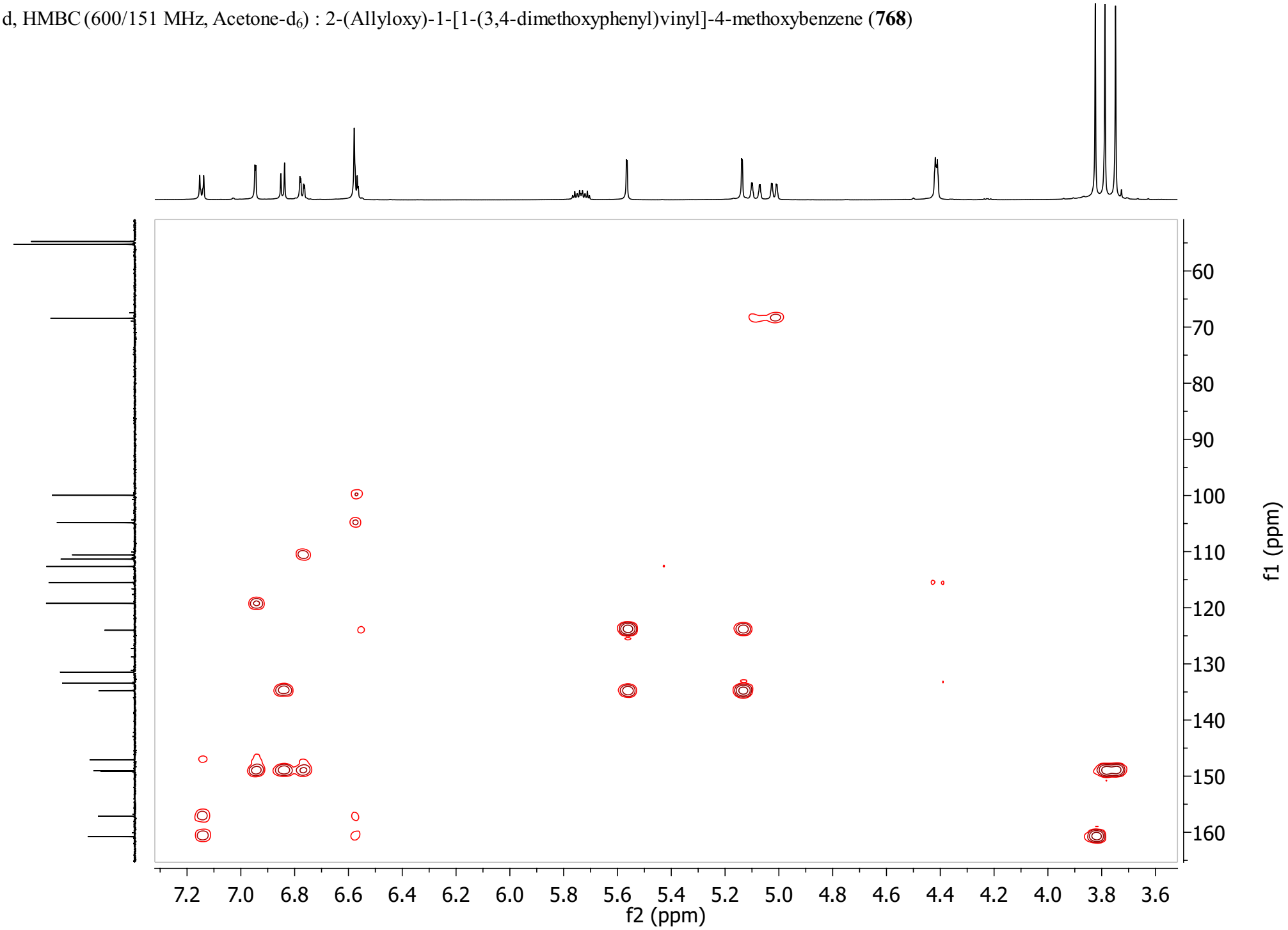
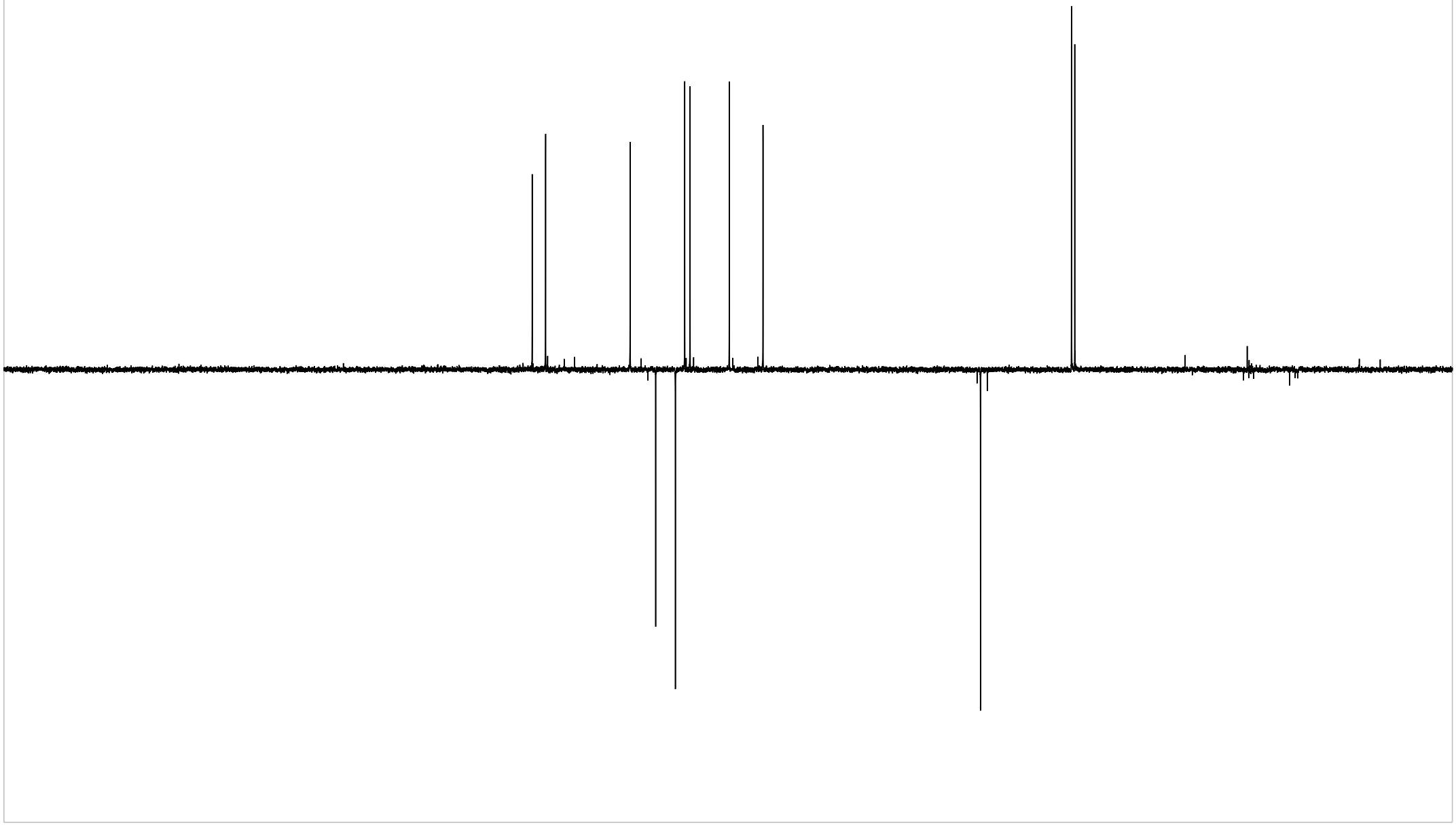


Plate 61e, DEPT (151 MHz, Acetone-d_6) : 2-(Allyloxy)-1-[1-(3,4-dimethoxyphenyl)vinyl]-4-methoxybenzene (**768**)

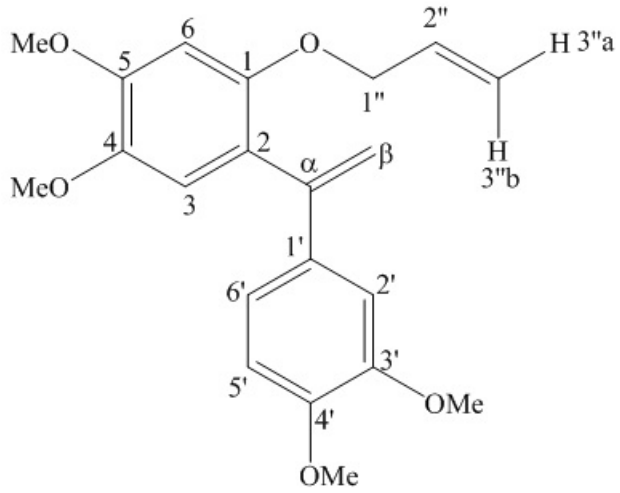


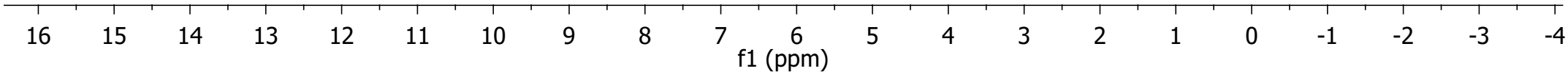
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 62a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**)

δ 6.96 (1H, d, *J* = 2.1 Hz, H-2'), 6.86 (1H, d, *J* = 8.4 Hz, H-5'), 6.81 (1H, s, H-3/6), 6.79 (1H, dd, *J* = 8.4, 2.1 Hz, H-6'), 6.74 (1H, s, H-3/6), 5.72 (1H, ddt, *J* = 17.3, 10.6, 4.9 Hz, H-2''), 5.58 (1H, d, *J* = 1.6 Hz, H-β), 5.17 (1H, d, *J* = 1.6 Hz, H-β), 5.09 (1H, ddt, *J* = 17.3, 1.7, 1.7 Hz, H-3''b), 5.01 (1H, ddt, *J* = 10.6, 1.7, 1.7 Hz, H-3''a), 4.38 (2H, ddd, *J* = 4.9, 1.7, 1.7 Hz, H-1''), 3.85 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.77 (3H, s, -OMe), 3.76 (3H, s, -OMe)





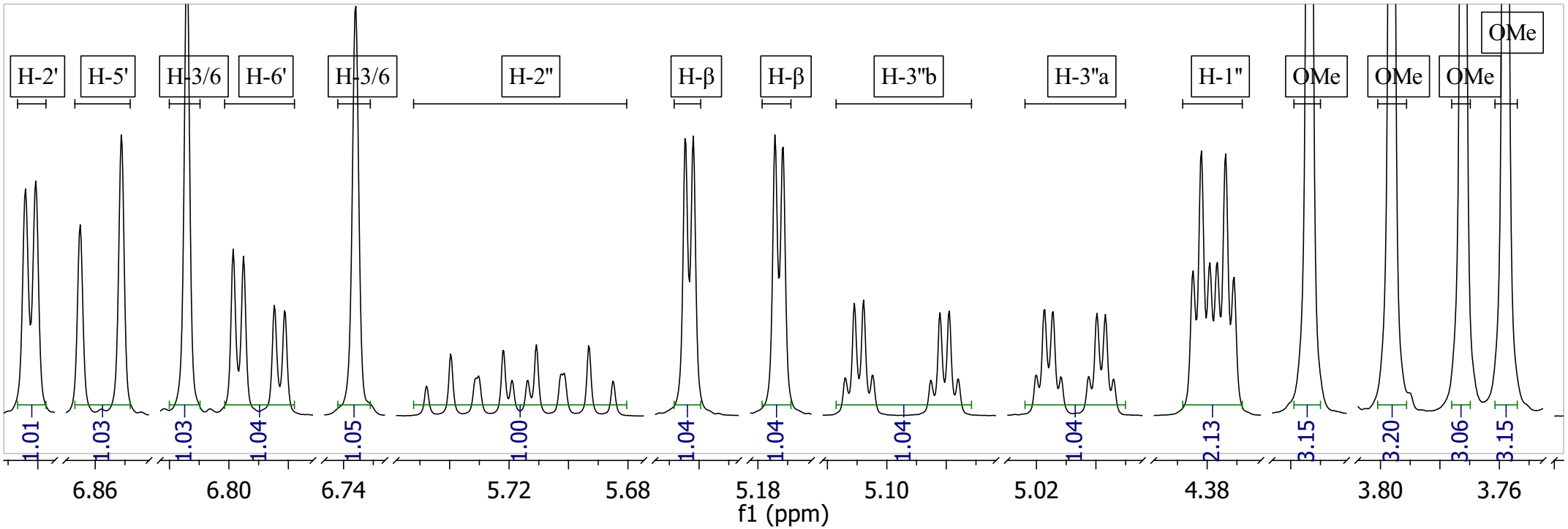
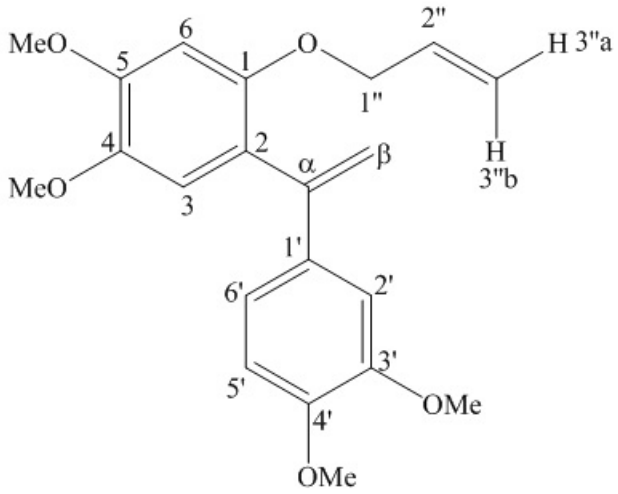


Plate 62b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**)

δ 151.56 (4°-C), 150.89 (4°-C), 150.18 (4°-C), 150.03 (4°-C), 147.94 (C-α), 144.52 (C-4), 135.66 (C-1'), 134.95 (C-2''), 124.17 (C-2), 120.31 (C-6'), 116.64 (C-3/6), 116.46 (C-3''), 113.84 (C-β), 112.31 (C-5'), 111.65 (C-2'), 101.55 (C-3/6), 70.85 (C-1''), 57.02 (-OMe), 56.39 (-OMe), 56.22 (-OMe), 56.19 (-OMe)



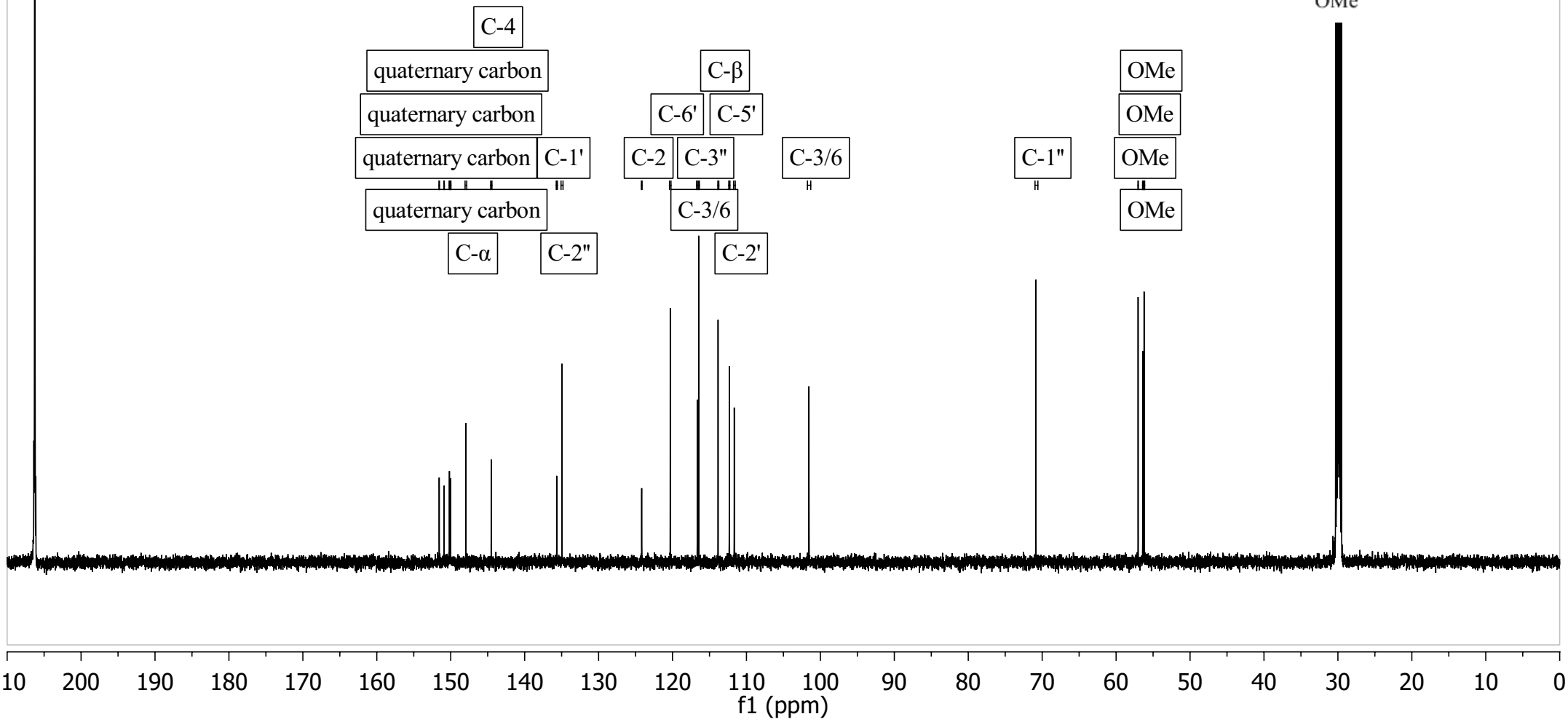


Plate 62c, HSQC (600/151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**)

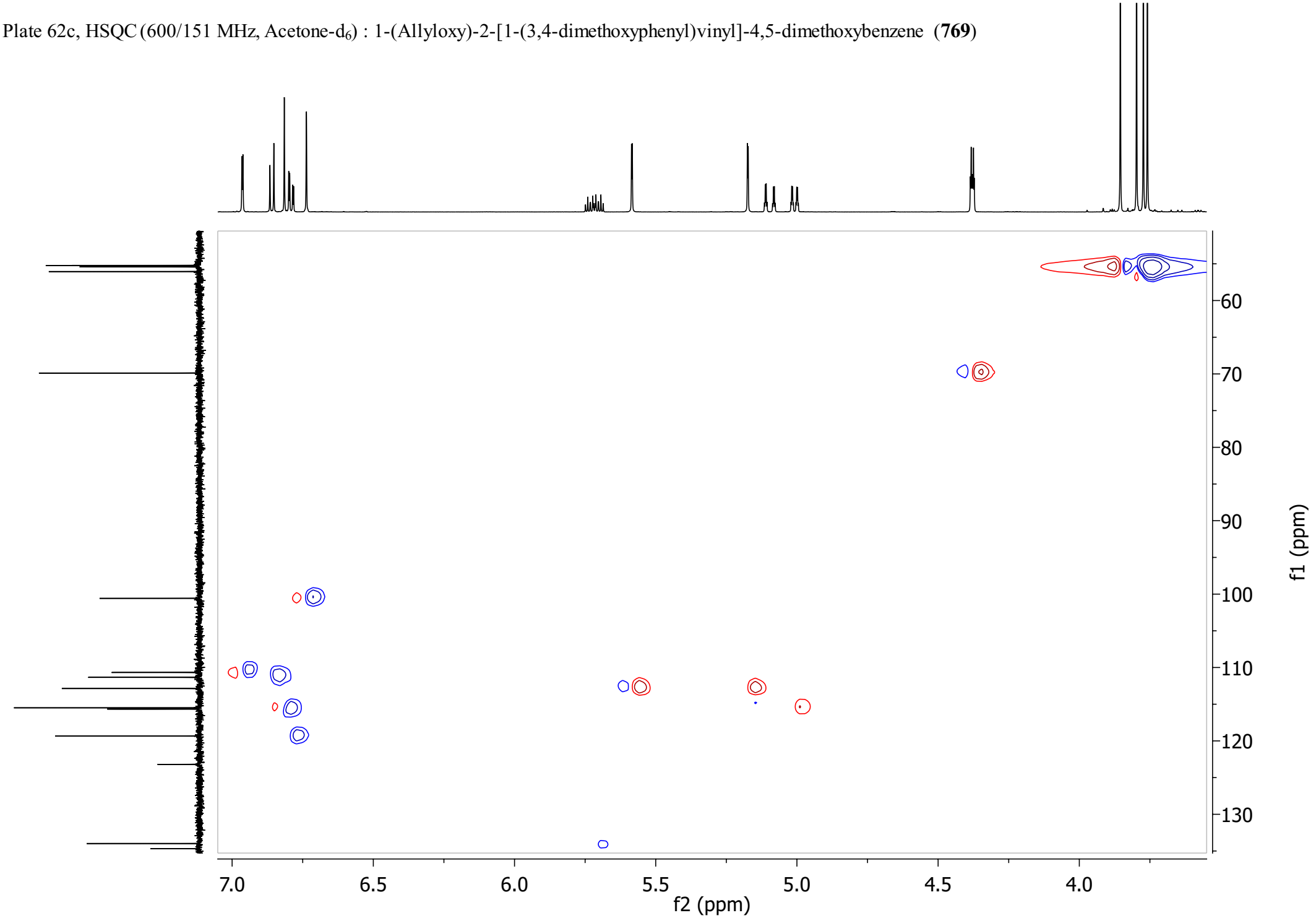


Plate 62d, HMBC (600/151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**)

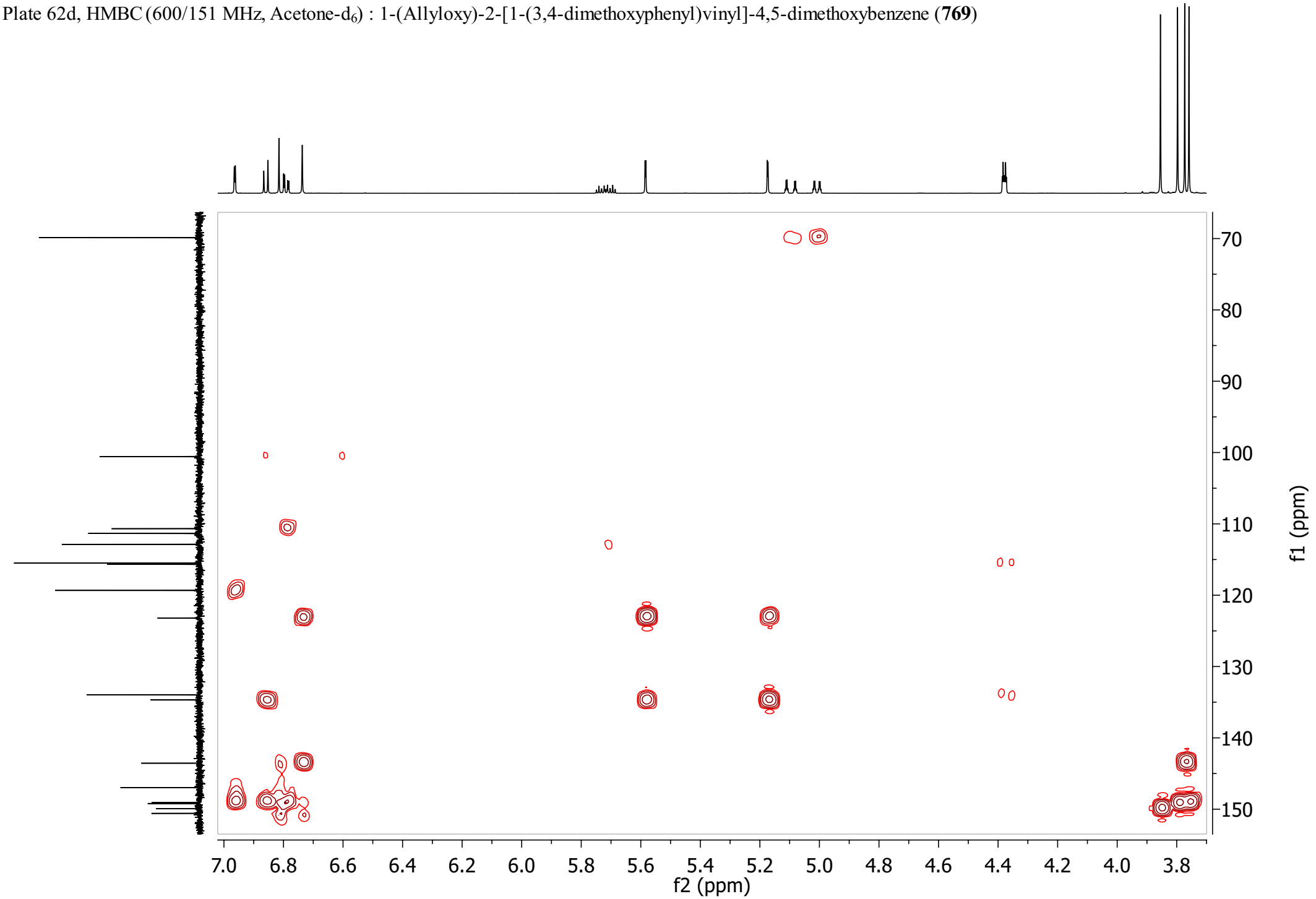
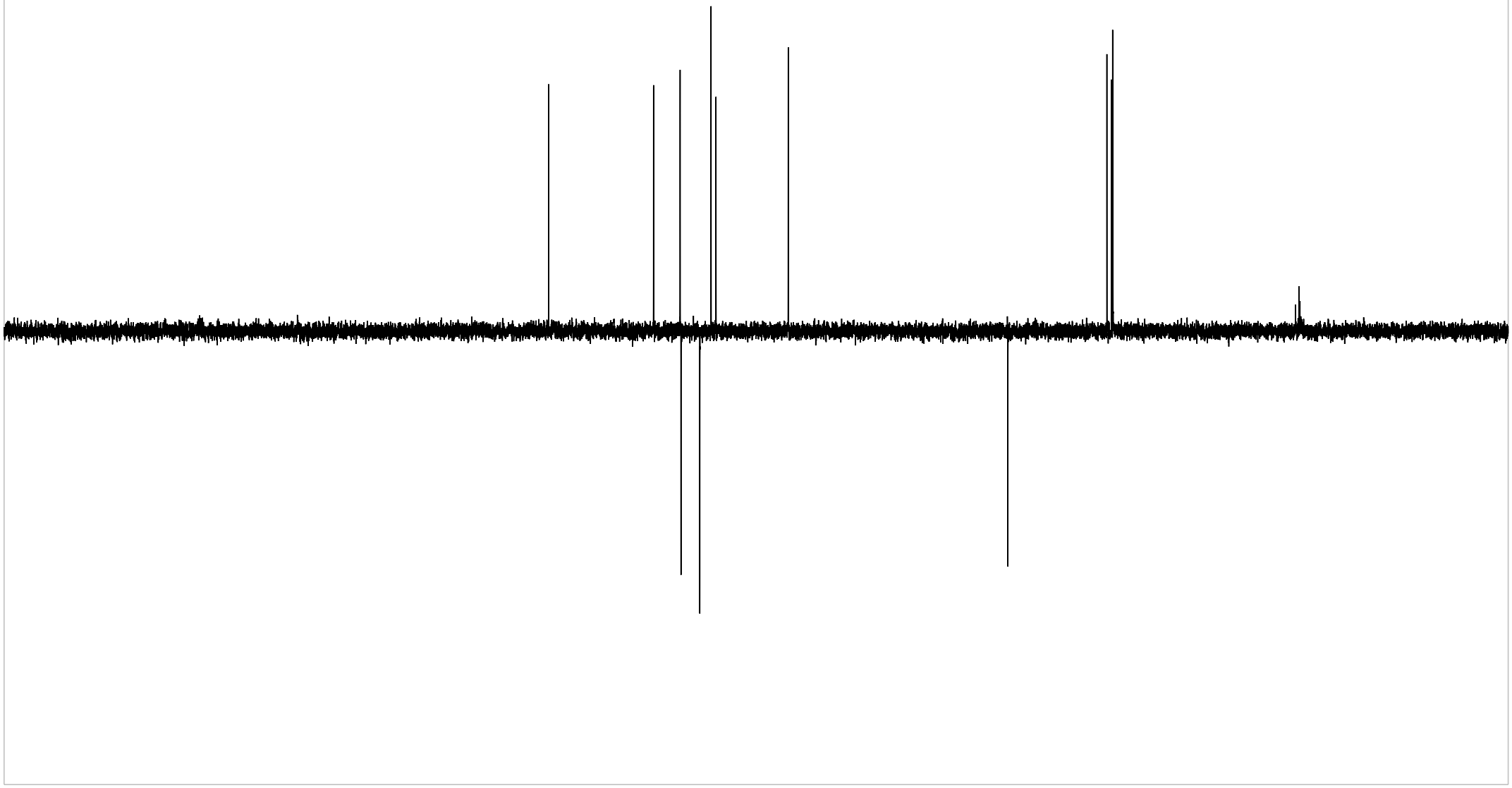


Plate 62e, DEPT (151 MHz, Acetone-d_6) : 1-(Allyloxy)-2-[1-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxybenzene (**769**)

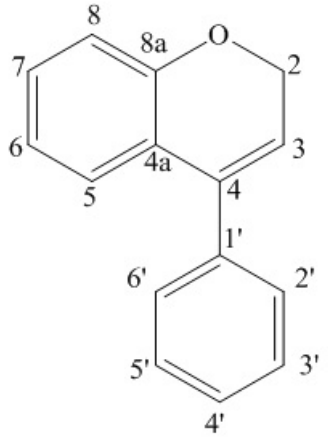


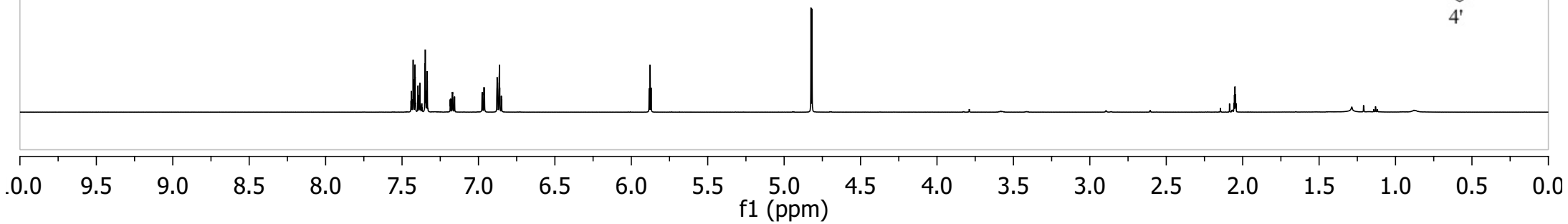
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 63a, ^{1}H NMR (600 MHz, Acetone-d_6) : Neoflav-3-ene (**741**)

δ 7.45 – 7.41 (2H, m, H-2' and H-6') , 7.40 – 7.37 (1H, m, H-4'), 7.36 – 7.33 (2H, m, H-3' and H-5'), 7.19 – 7.15 (1H, m, H-7), 6.97 (1H, dd, *J* = 7.6, 1.6 Hz, H-5), 6.88 – 6.85 (2H, m, H-6 and H-8), 5.88 (1H, t, *J* = 4.0 Hz, H-3), 4.82 (2H, d, *J* = 4.0 Hz, H-2)





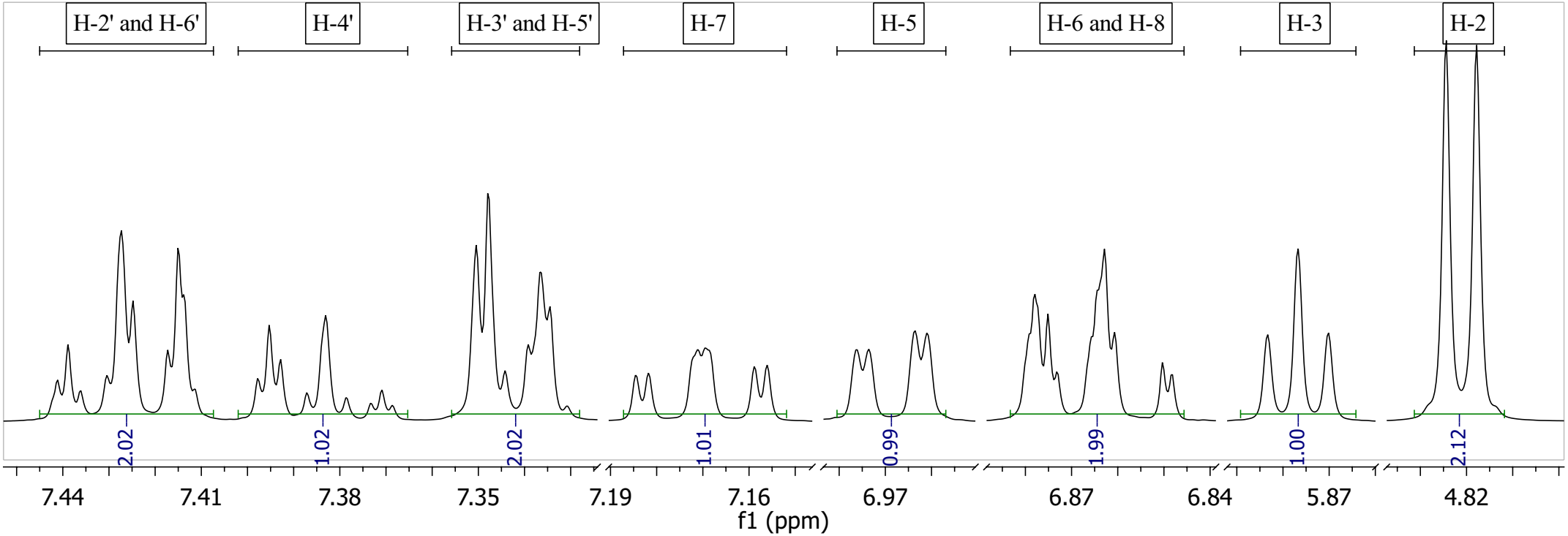
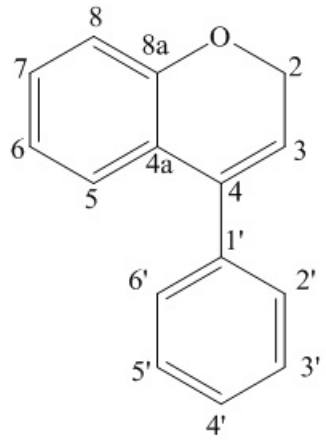


Plate 63b, ^{13}C NMR (151 MHz, Acetone-d_6) : Neoflav-3-ene (**741**)

δ 155.96 (C-8a), 139.24 (C-1'), 137.68 (C-4), 130.23 (C-7), 129.45 (C-4'), 129.43 (C-3' and C-5'), 128.80 (C-2' and C-6'), 126.50 (C-5), 124.54 (C-4a), 122.04 (C-3/6), 121.57 (C-3/6), 117.10 (C-8), 65.89 (C-2)



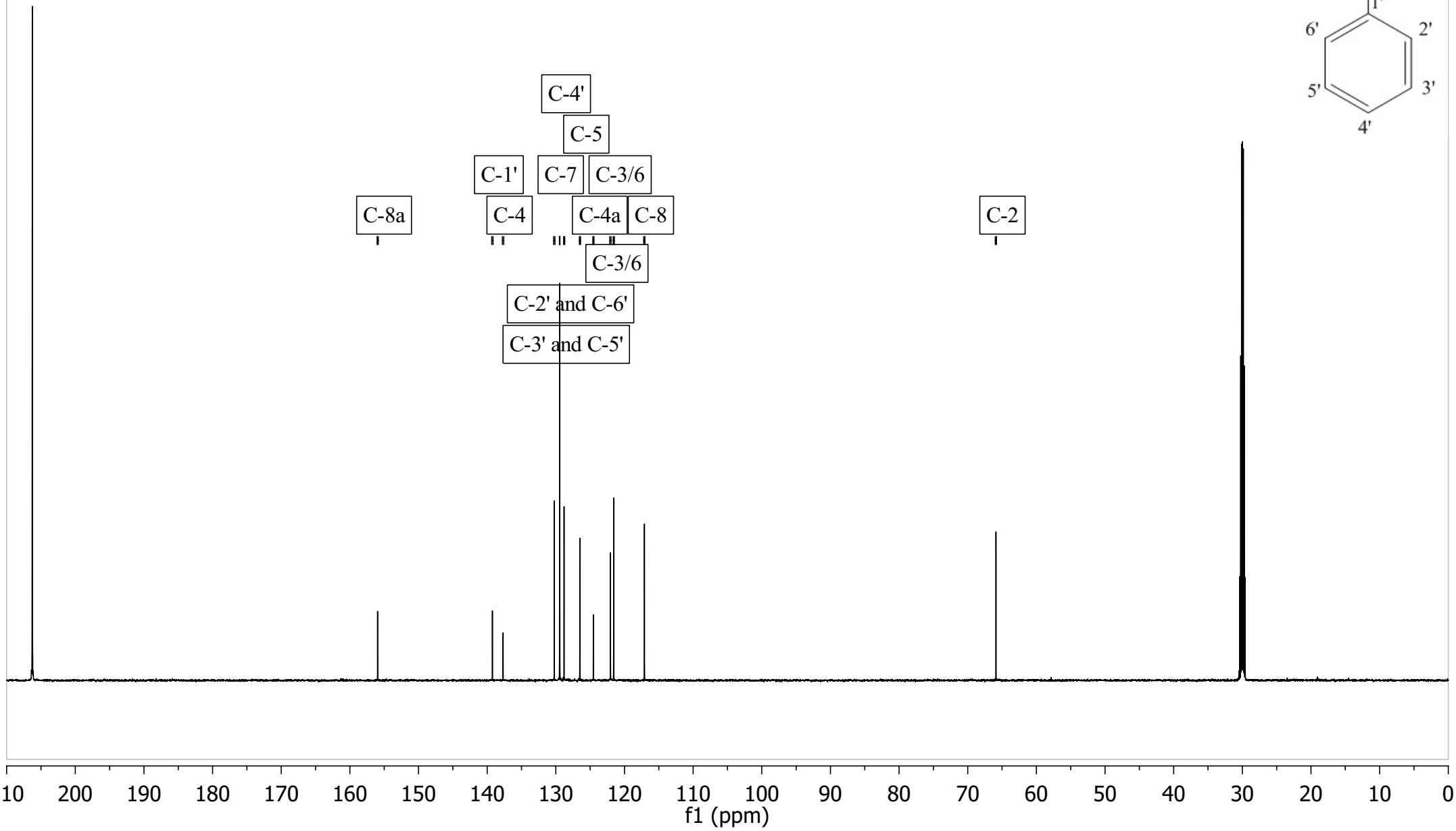


Plate 63c, HSQC (600 MHz/151 MHz, Acetone-d_6) : Neoflav-3-ene (**741**)

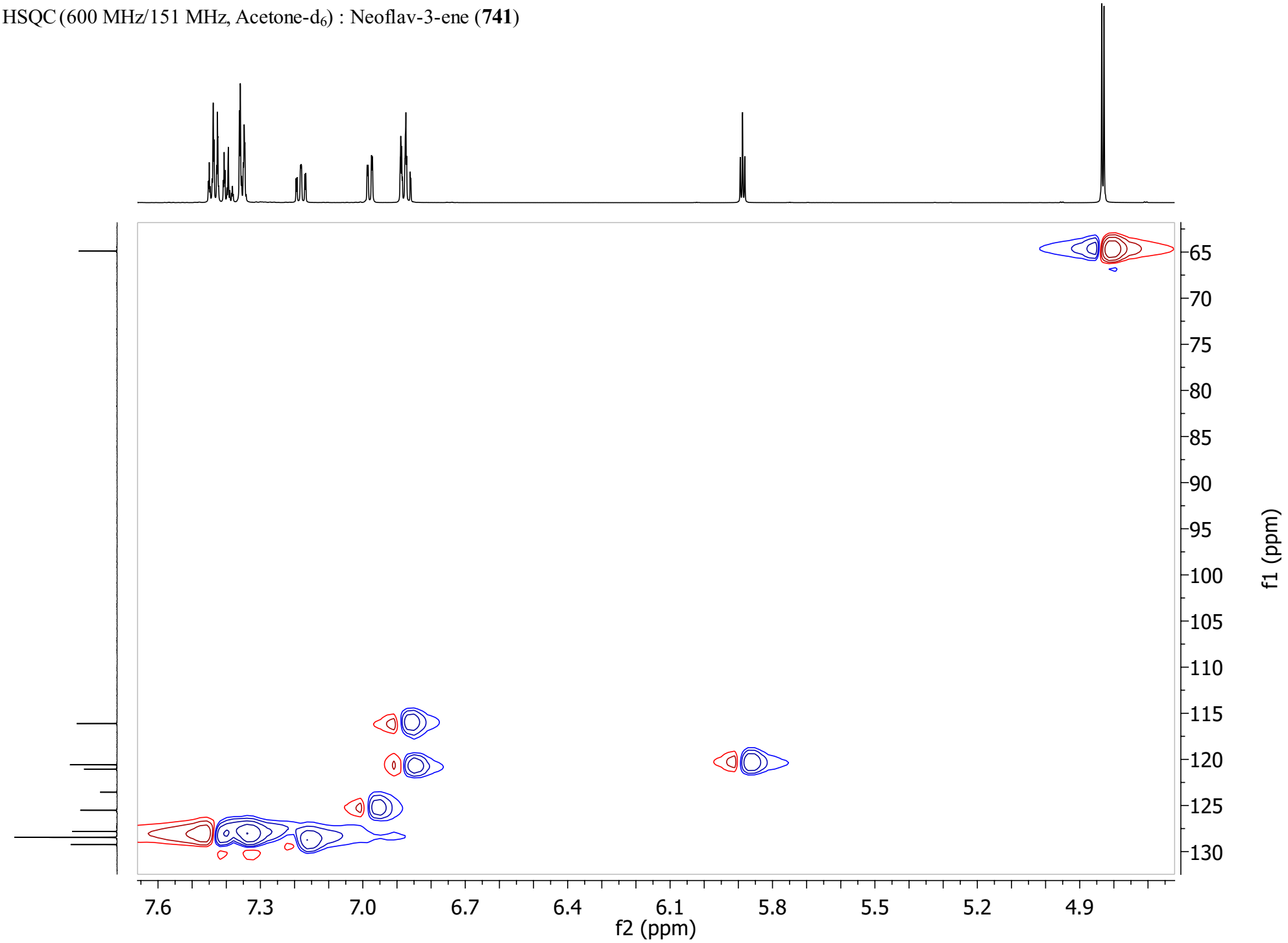


Plate 63d, HMBC (600 MHz/151 MHz, Acetone-d_6) : Neoflav-3-ene (**741**)

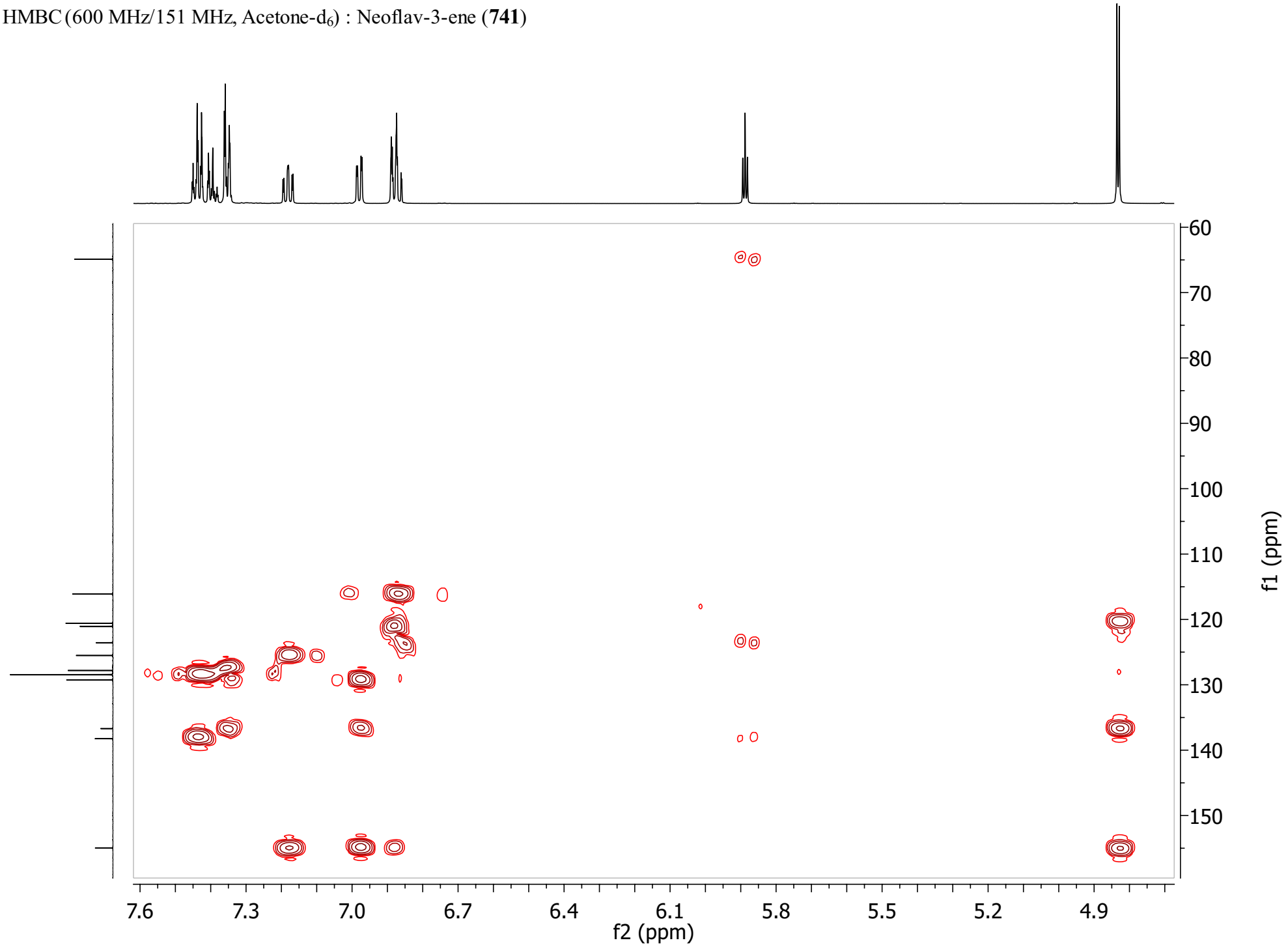


Plate 63e, DEPT (151 MHz, Acetone-d_6) : Neoflav-3-ene (**741**)

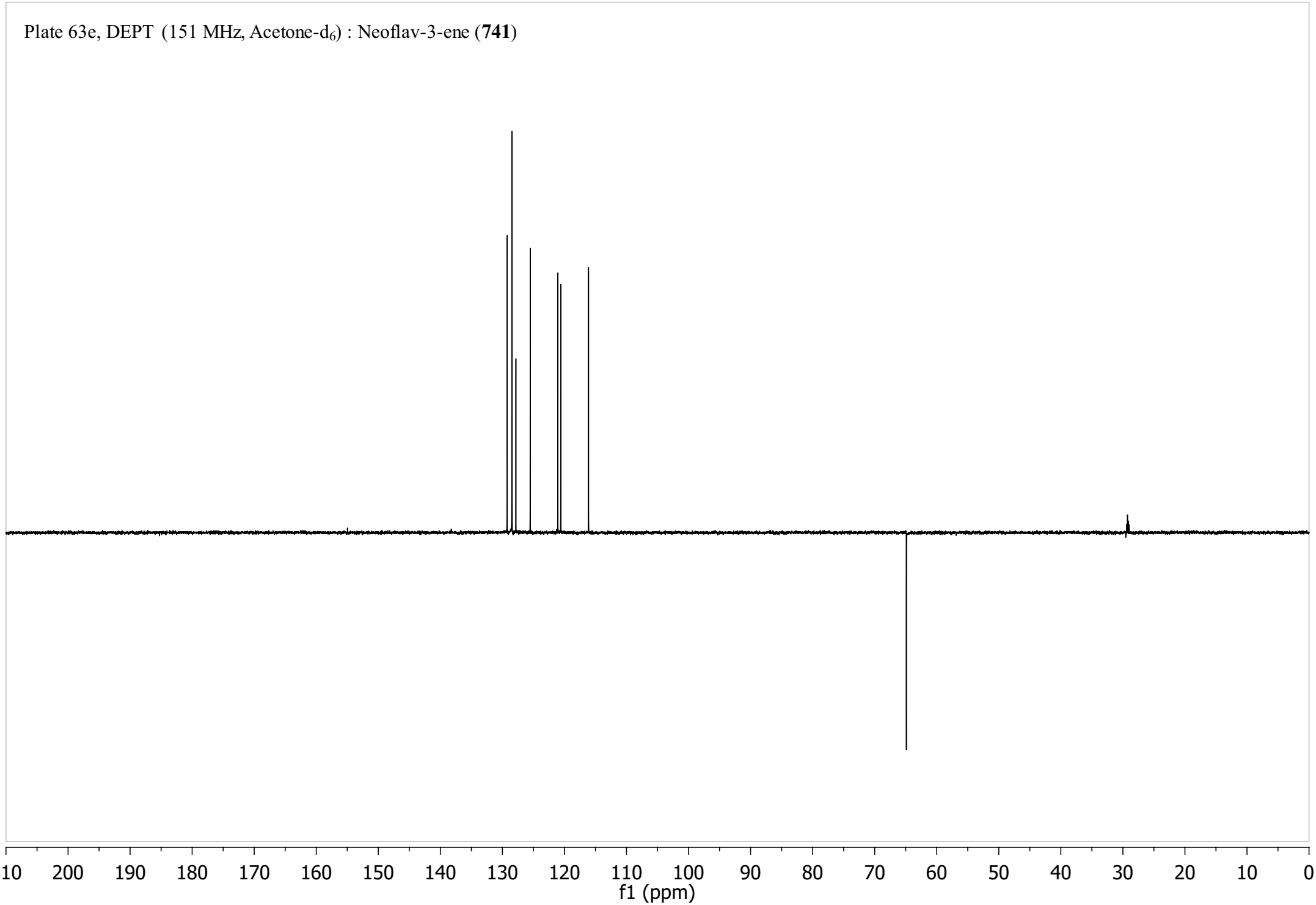
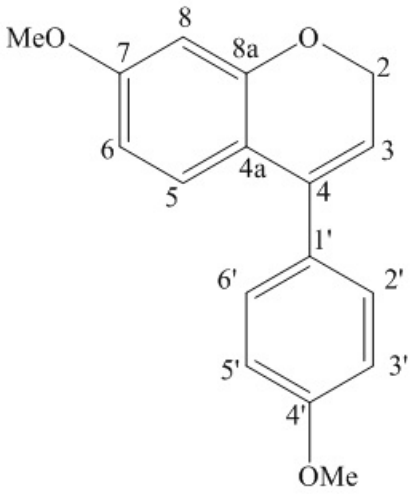
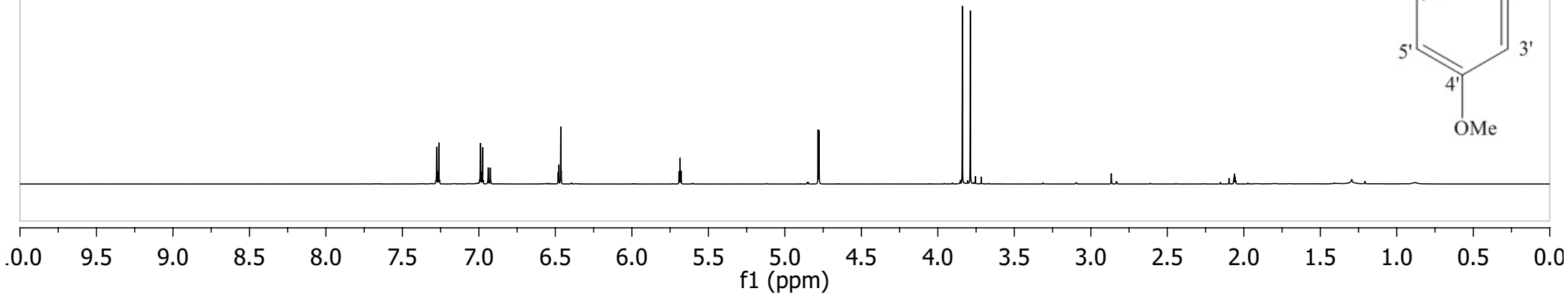


Plate 64a, ^{1}H NMR (600 MHz, Acetone--d_6) : 4',7-Dimethoxyneoflav-3-ene (**770**)

δ 7.27 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.98 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.93 (1H, d, *J* = 8.0 Hz, H-5), 6.49 – 6.46 (2H, m, H-6 and H-8), 5.68 (1H, t, *J* = 4.0 Hz, H-3), 4.78 (2H, d, *J* = 4.0 Hz, H-2), 3.84 (-OMe), 3.79 (-OMe)





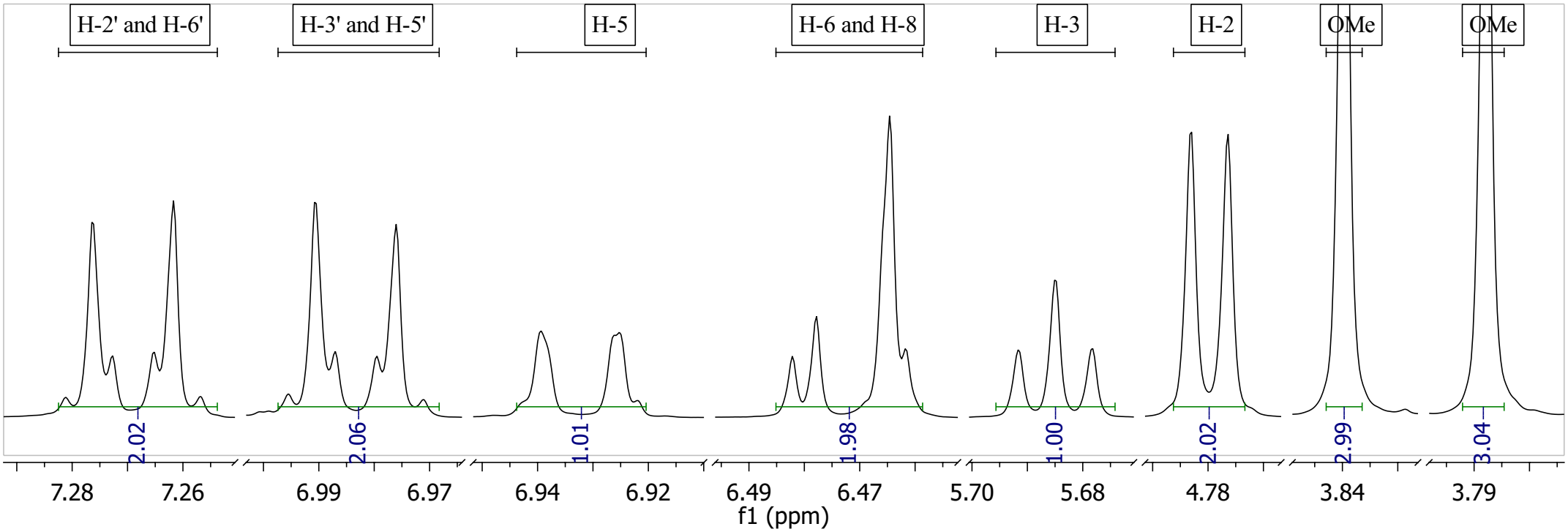
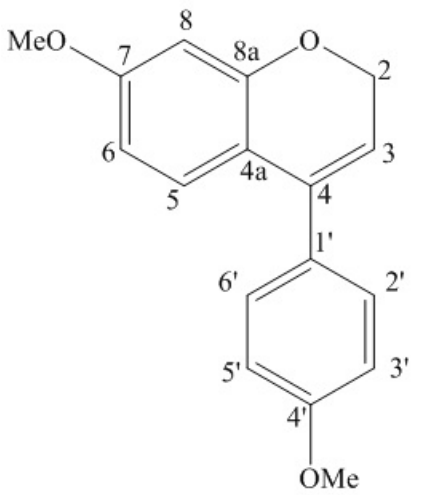


Plate 64b, ^{13}C NMR (151 MHz, Acetone--d_6) : 4',7-Dimethoxyneoflav-3-ene (**770**)

δ 161.72 (C-7), 160.48 (C-4'), 157.37 (C-8a), 137.22 (C-4), 131.63 (C-1'), 130.49 (C-2' and C-6'), 127.44 (C-5), 117.85 (C-4a), 117.49 (C-3), 114.73 (C-3' and C-5'), 107.63 (C-6/8), 102.77 (C-6/8), 66.10 (C-2), 55.73 (-OMe), 55.66 (-OMe)



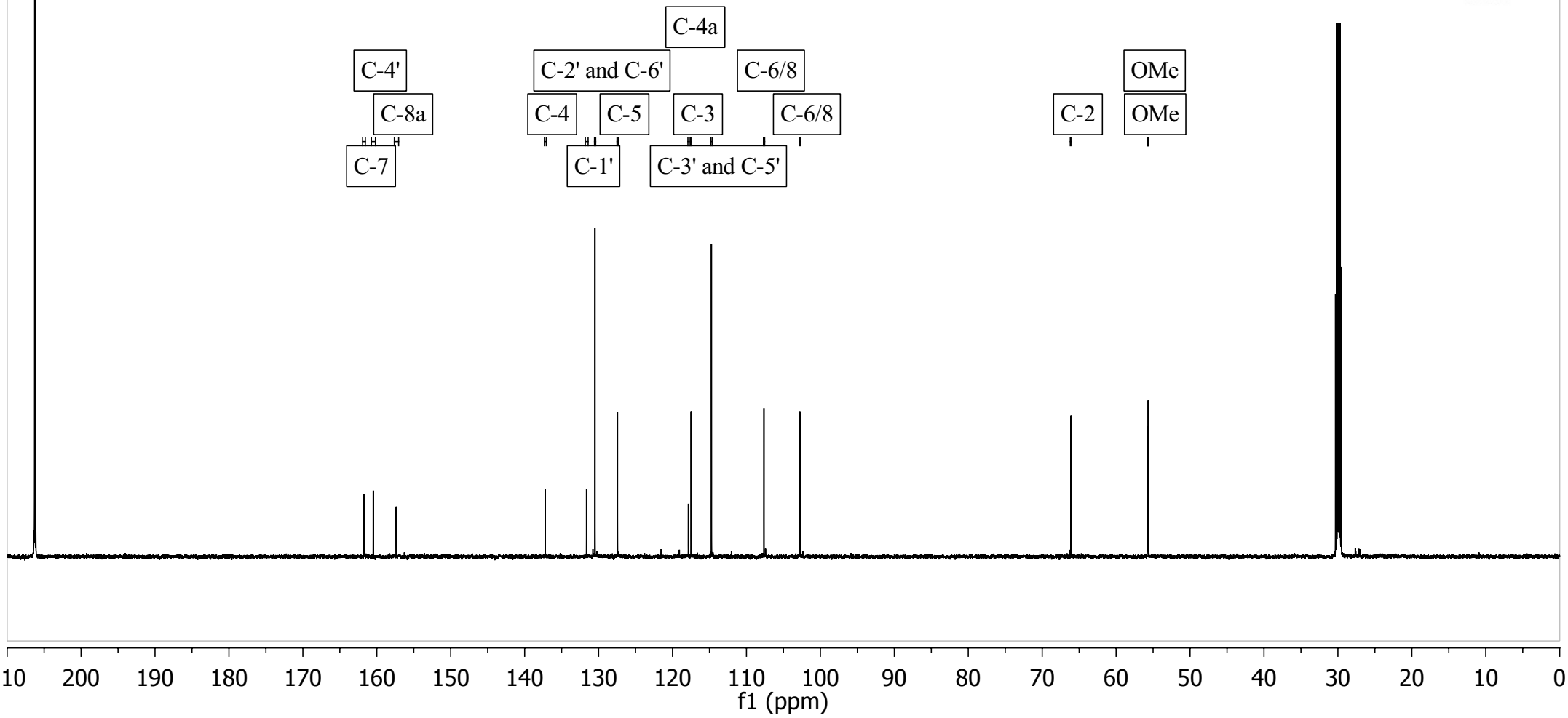


Plate 64c, HSQC (600/151 MHz, Acetone-d_6) : 4',7-Dimethoxyneoflav-3-ene (**770**)

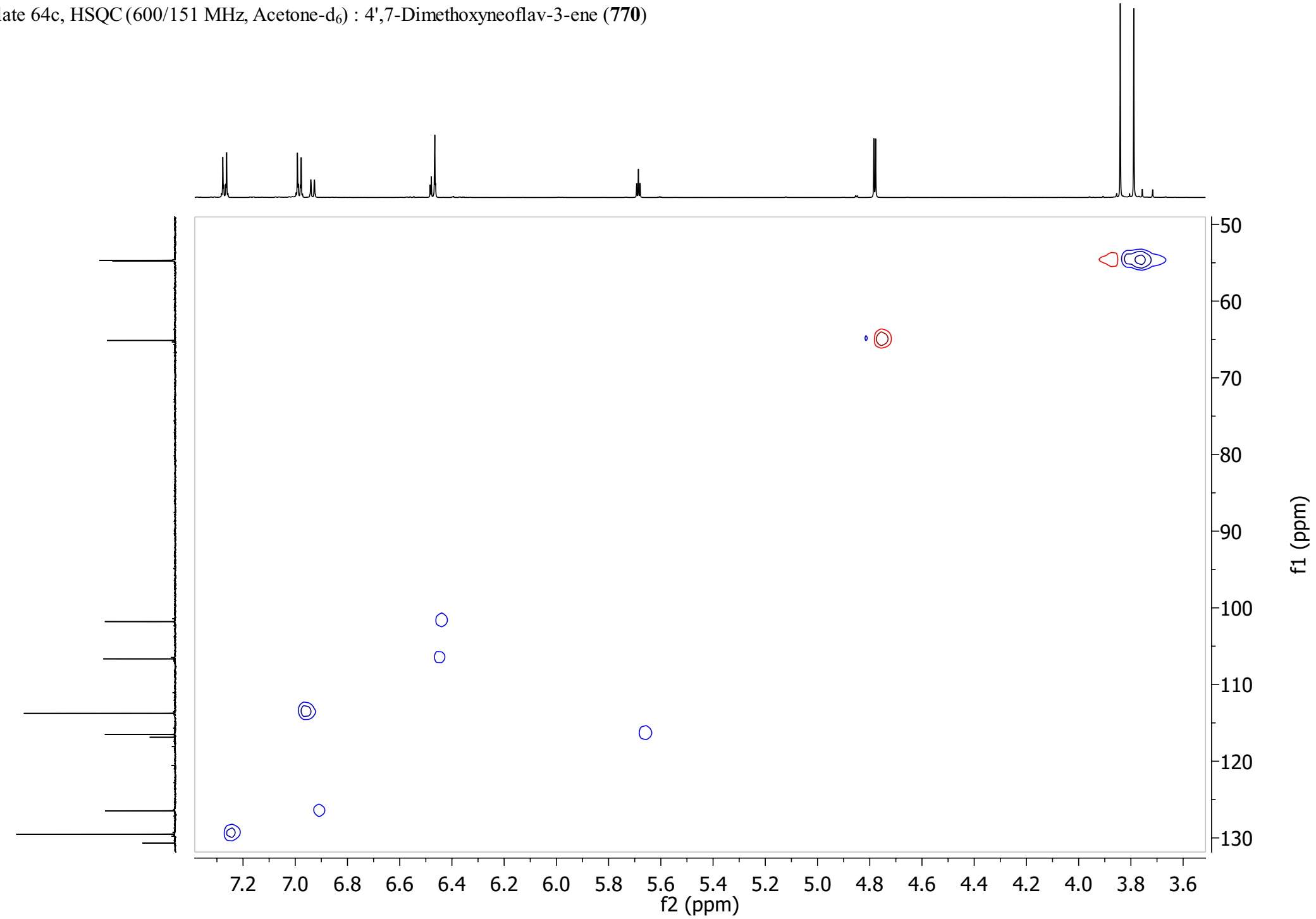


Plate 64d, HMBC (600/151 MHz, Acetone--d_6) : 4',7-Dimethoxyneoflav-3-ene (**770**)

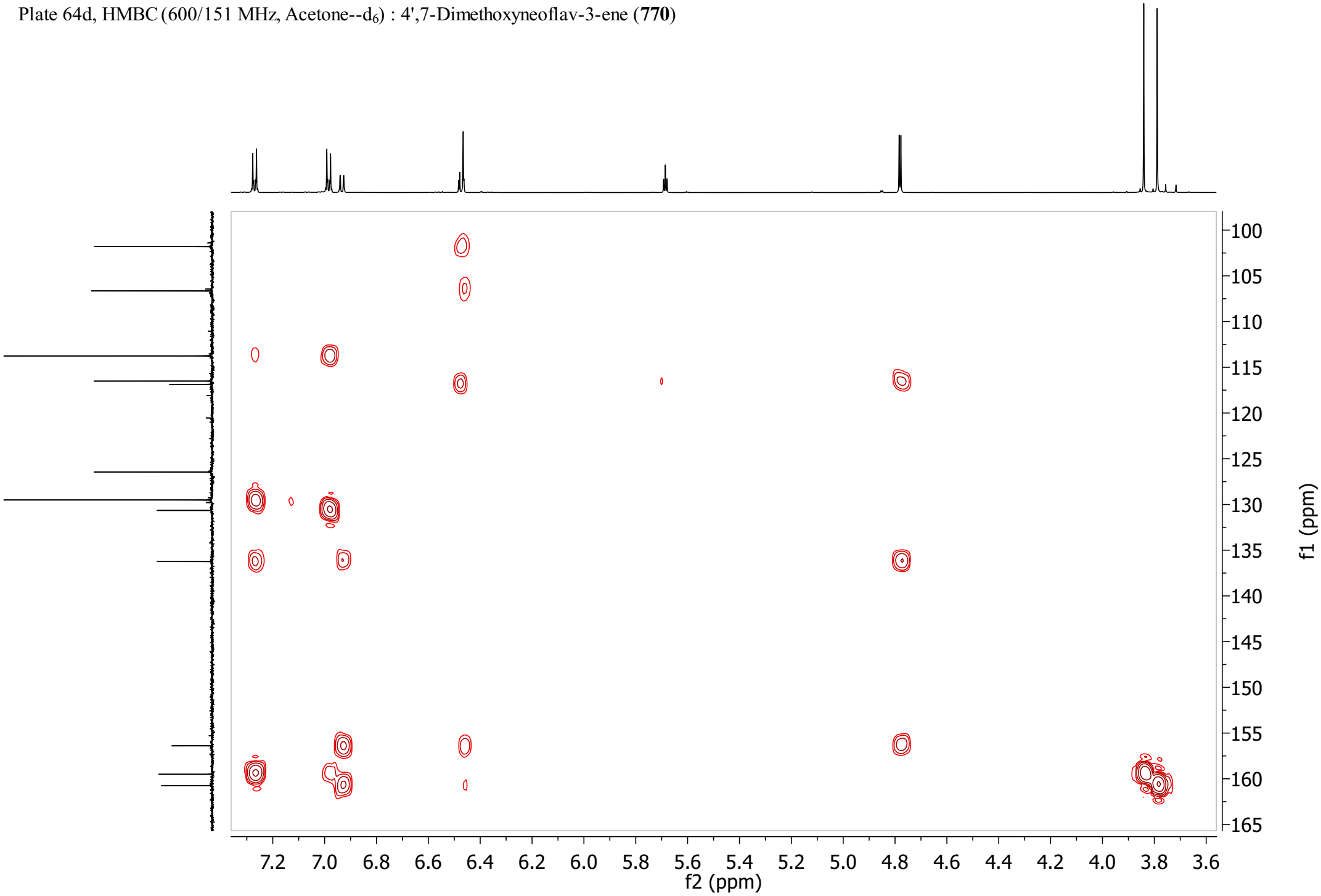
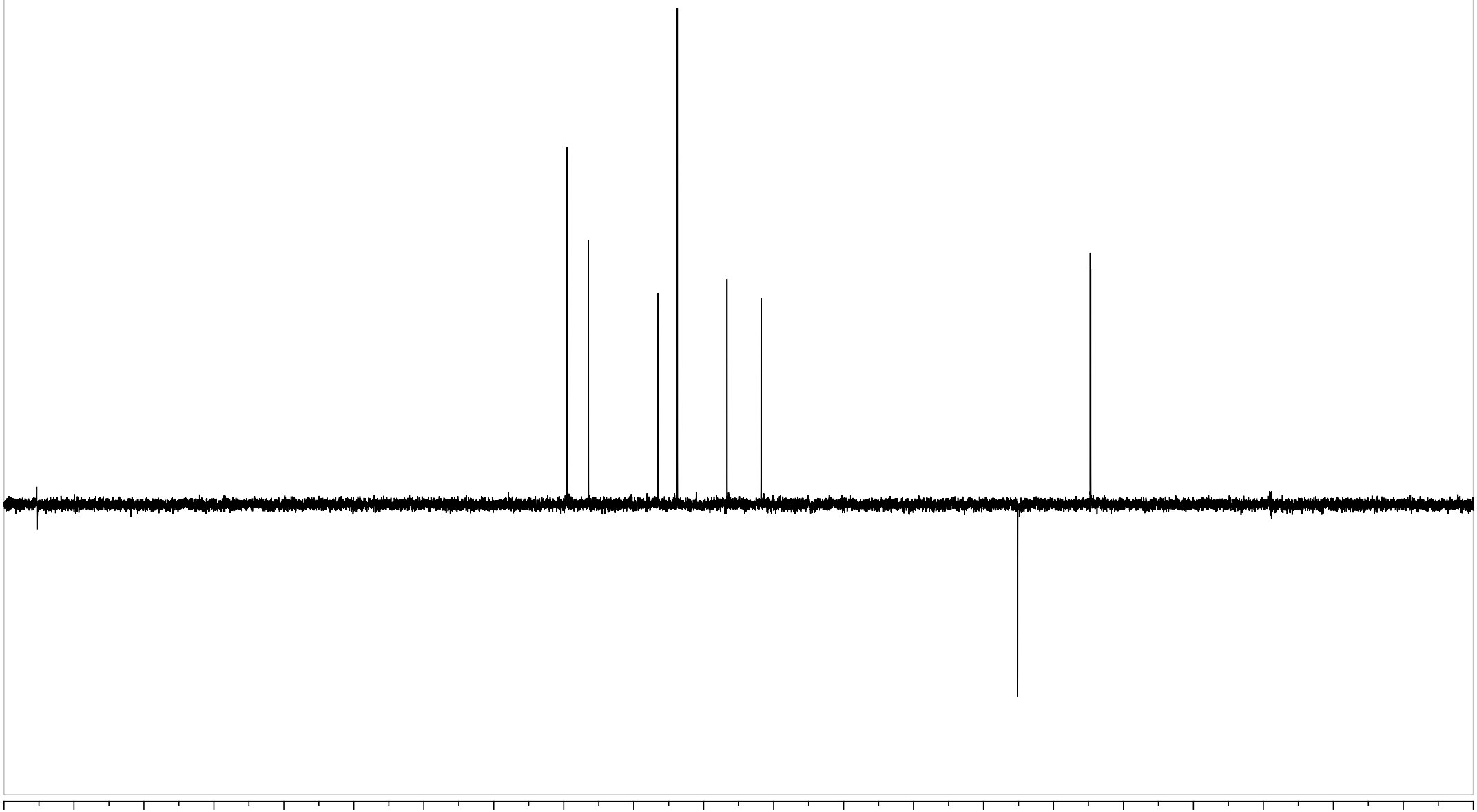


Plate 64e, DEPT (151 MHz, Acetone--d_6) : 4',7-Dimethoxyneoflav-3-ene (**770**)

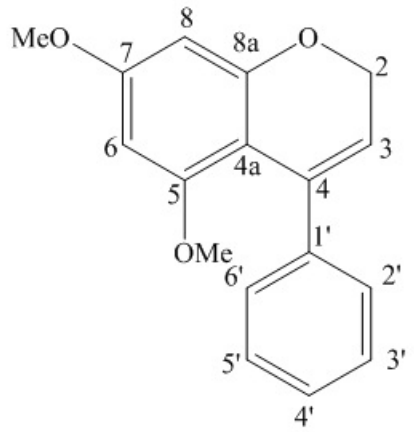


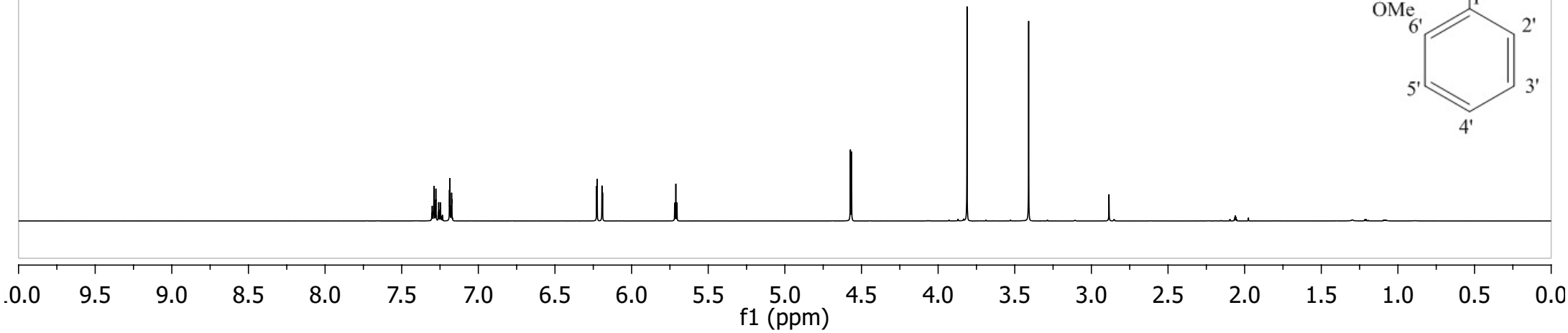
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 65a, ^{1}H NMR (600 MHz, Acetone-d_6) : 5,7-Dimethoxyneoflav-3-ene (**771**)

δ 7.31 – 7.27 (2H, m, H-3' and H-5'), 7.27 – 7.23 (1H, m, H-4'), 7.19 – 7.17 (2H, m, H-2' and H-6'), 6.23 (1H, d, *J* = 2.4 Hz, H-6/8), 6.19 (1H, d, *J* = 2.4 Hz, H-6/8), 5.71 (1H, t, *J* = 4.7 Hz, H-3), 4.57 (2H, d, *J* = 4.7 Hz, H-2), 3.81 (-OMe), 3.41 (-OMe)





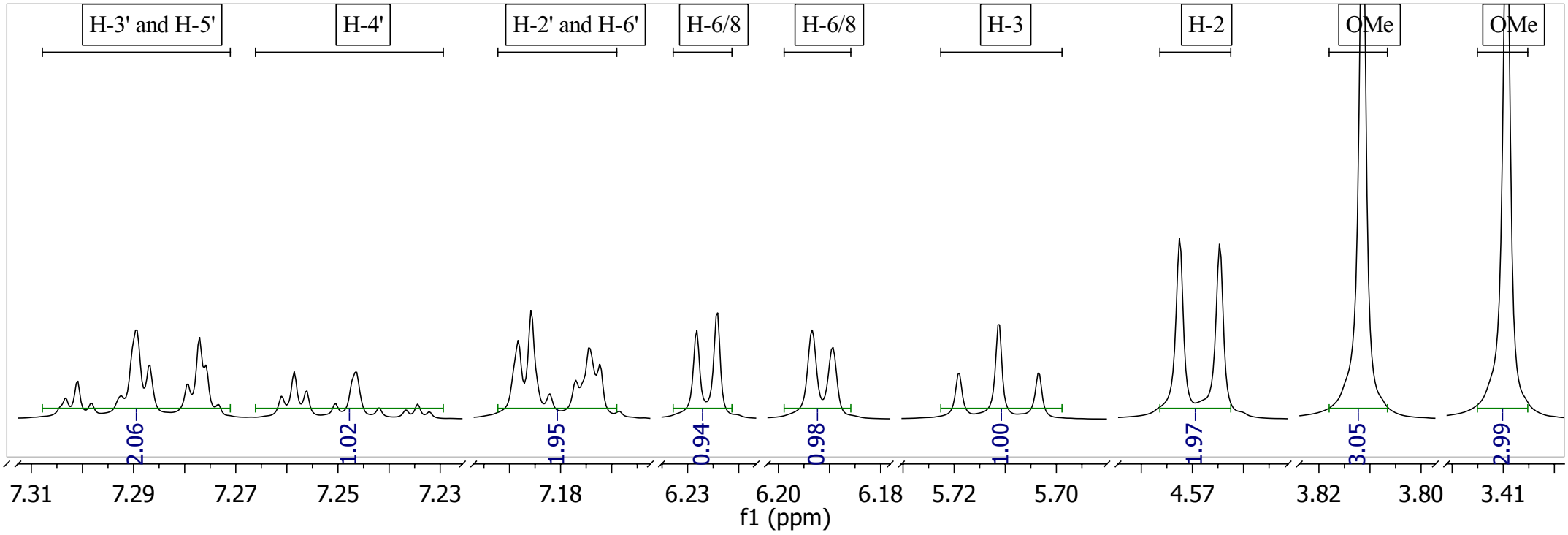
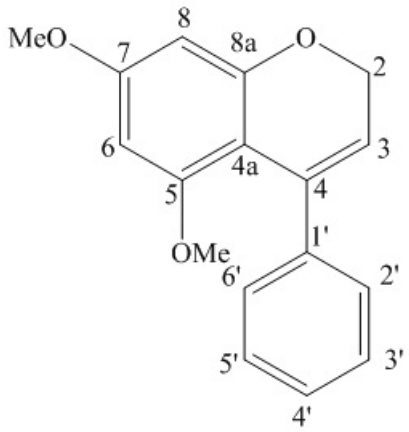


Plate 65b, ^{13}C NMR (151 MHz, Acetone-d_6) : 5,7-Dimethoxyneoflav-3-ene (**771**)

δ 162.51 (C-7), 159.22 (C-8a), 158.63 (C-5), 142.02 (C-1'), 137.47 (C-4), 128.25 (Ar-C), 127.78 (Ar-C), 127.39 (C-4'), 118.65 (C-3), 107.45 (C-4a), 94.98 (C-6/8), 94.02 (C-6/8), 65.38 (C-2), 55.73 (-OMe), 55.50 (-OMe)



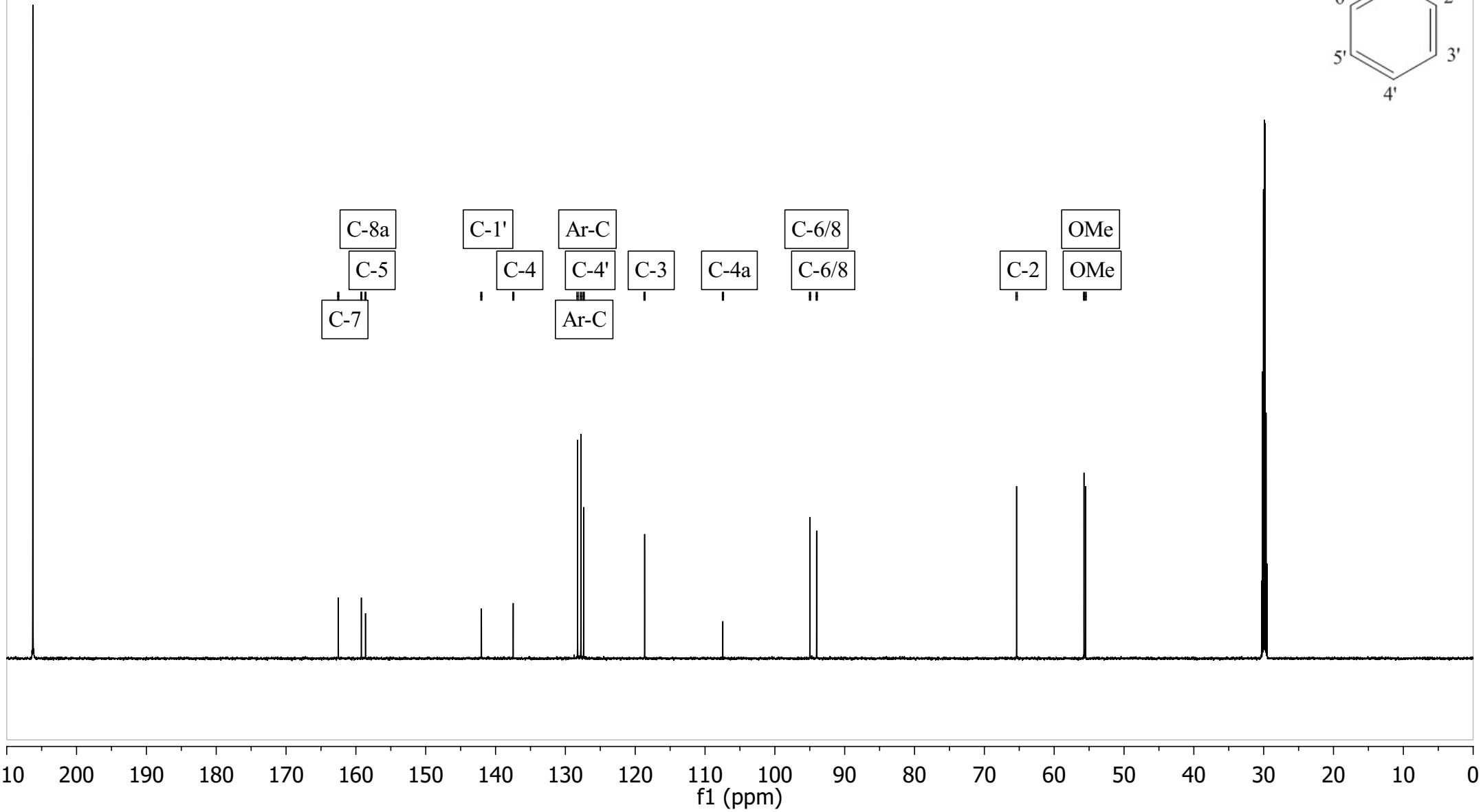


Plate 65c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 5,7-Dimethoxyneoflav-3-ene (**771**)

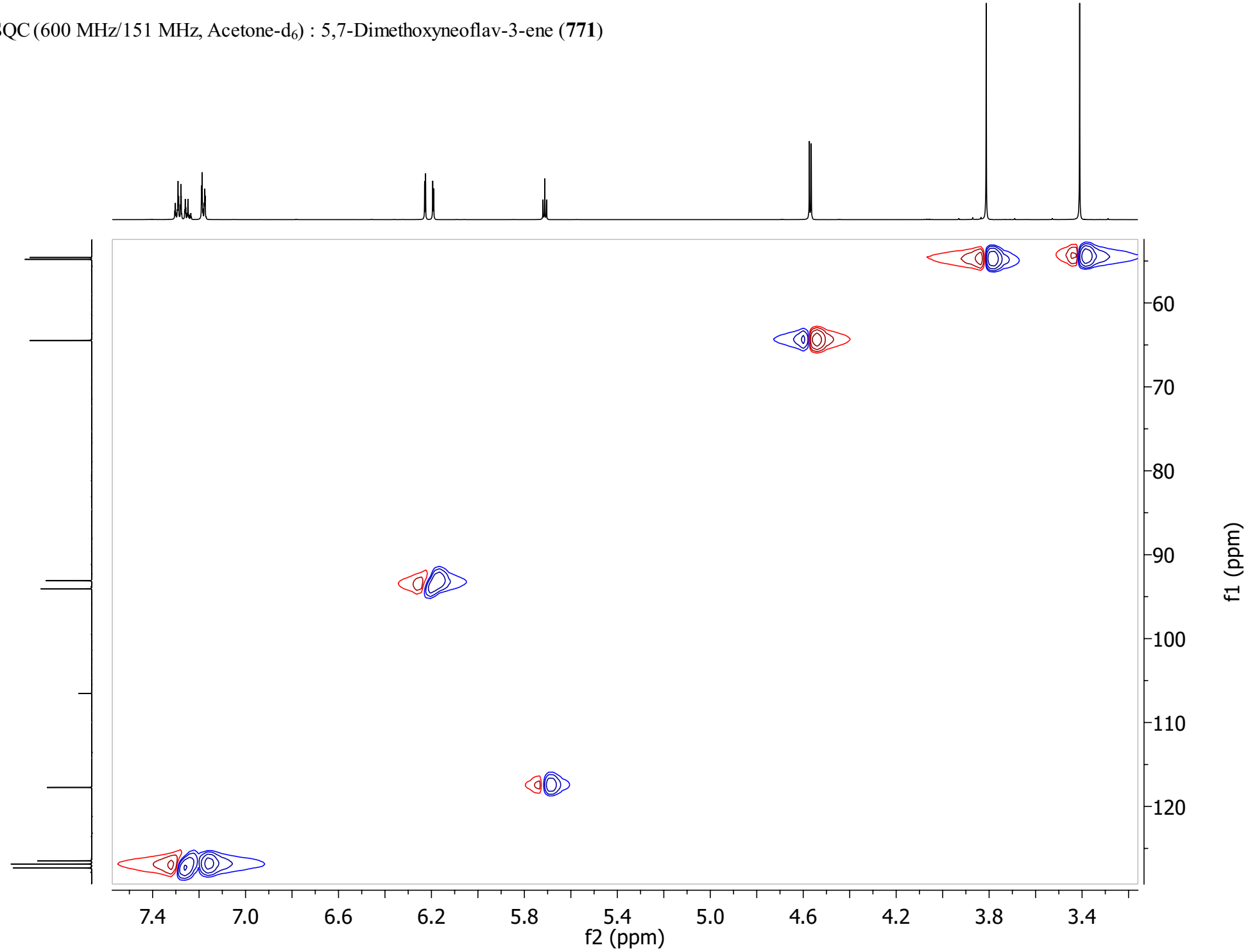


Plate 65d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 5,7-Dimethoxyneoflav-3-ene (**771**)

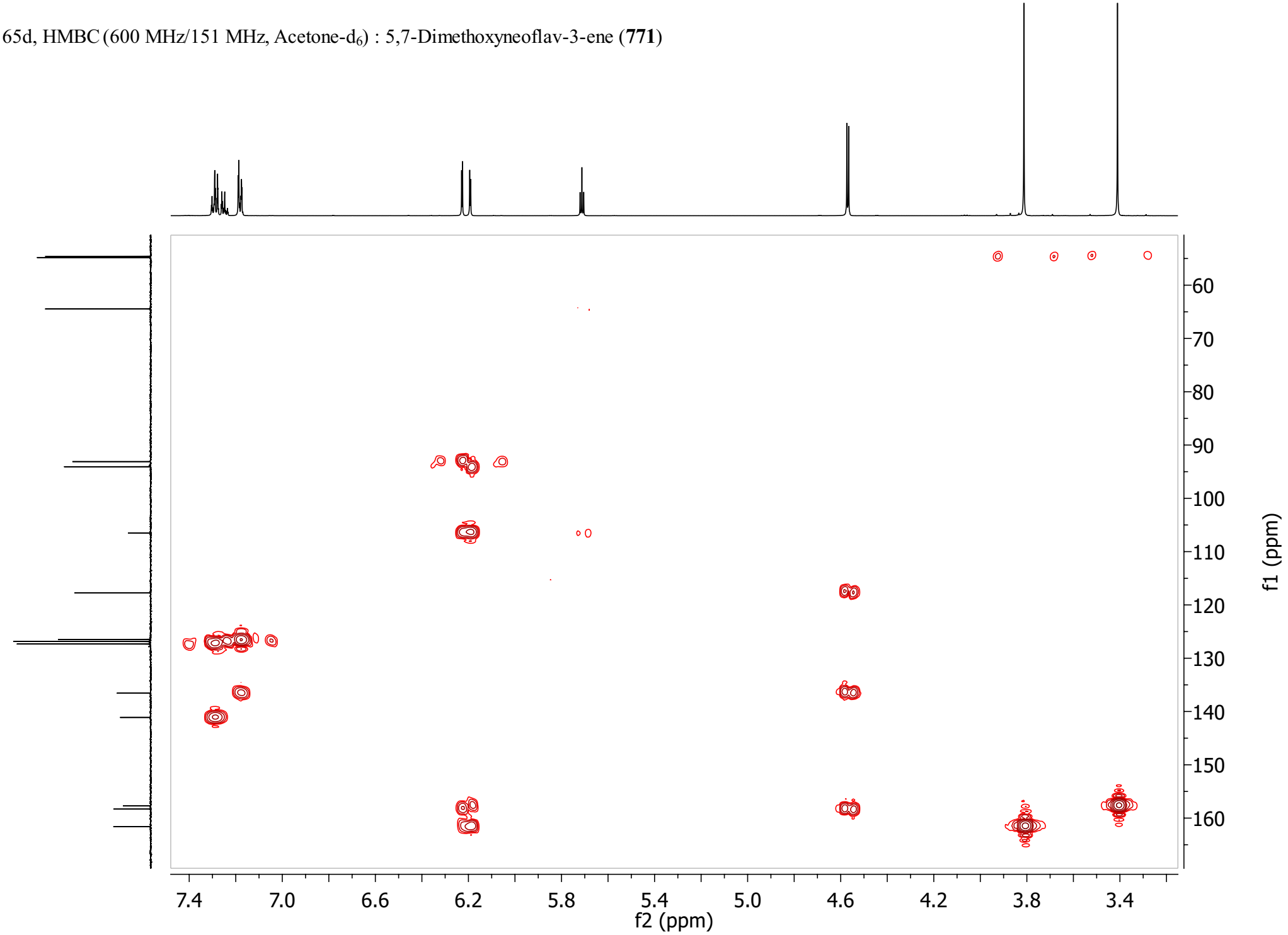


Plate 65e, DEPT (151 MHz, Acetone-d_6) : 5,7-Dimethoxyneoflav-3-ene (**771**)

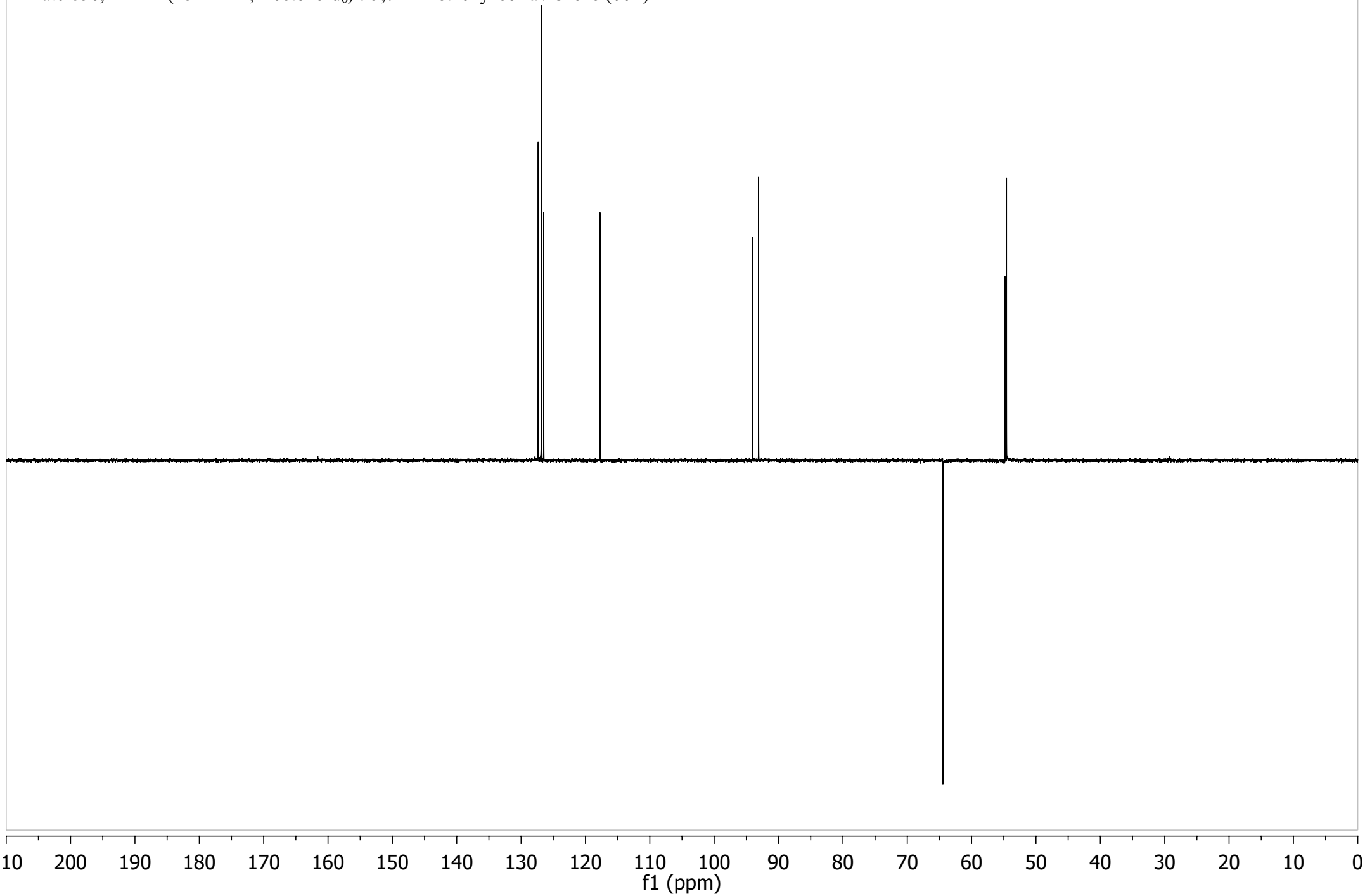
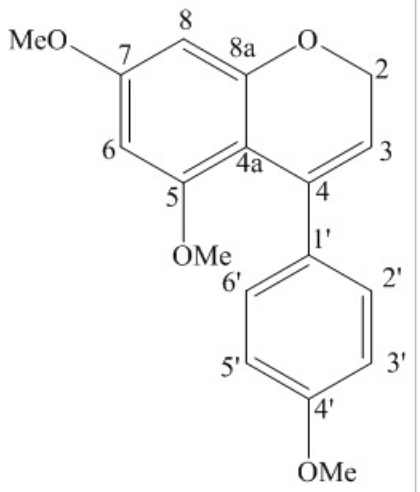
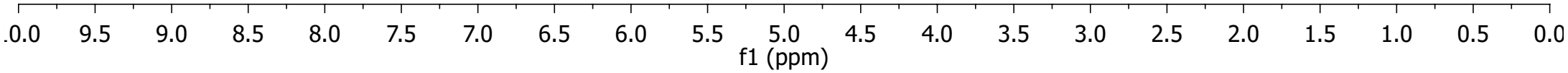


Plate 66a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4',5,7-Trimethoxyneoflav-3-ene (**772**)

δ 7.11 (2H, d, *J* = 8.8, H-2' and H-6'), 6.86 (2H, d, *J* = 8.8, H-3' and H-5'), 6.21 (1H, d, *J* = 2.4 Hz, H-6), 6.19 (1H, d, *J* = 2.4 Hz, H-8), 5.67 (1H, t, *J* = 4.7 Hz, H-3), 4.54 (2H, d, *J* = 4.7 Hz, H-2), 3.81 (3H, s, -OMe), 3.81 (3H, s, -OMe), 3.45 (3H, s, -OMe))





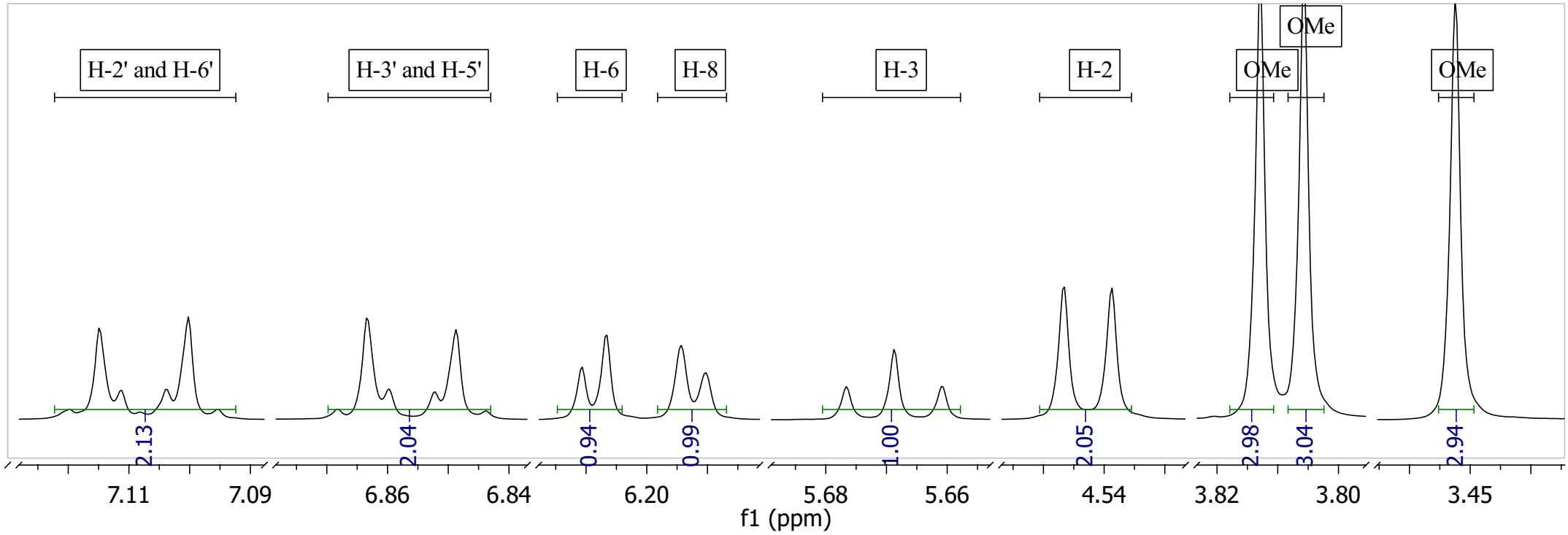
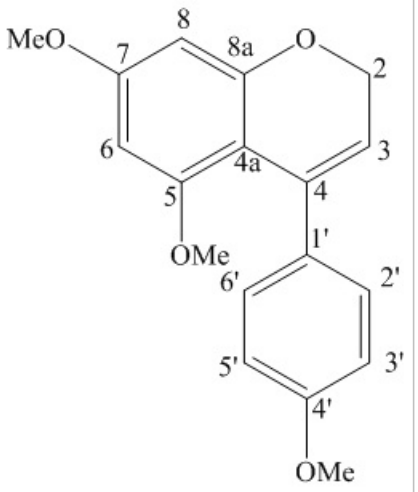


Plate 66b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyneoflav-3-ene (**772**)

δ 162.48 (C-7), 159.71 (C-5), 159.40 (C-4'), 158.78 (C-8a), 137.10 (C-4), 134.30 (C-1'), 128.93 (C-2' and C-6'), 117.62 (C-3), 113.67 (C-3' and C-5'), 107.62 (C-4a), 95.01 (C-6/8), 94.09 (C-6/8), 65.42 (C-2), 55.76 (-OMe), 55.64 (-OMe), 55.53 (-OMe)



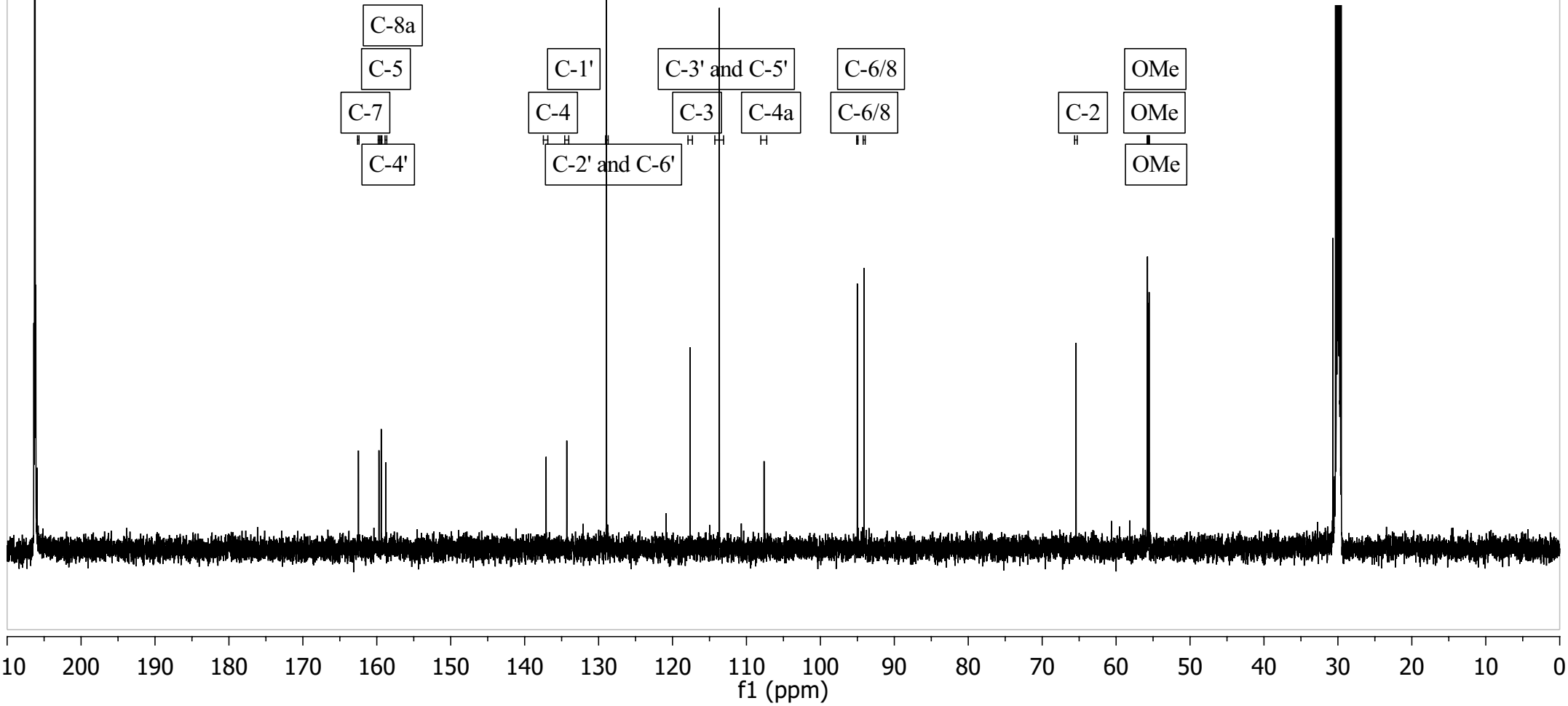


Plate 66c, HSQC (600/151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyneoflav-3-ene (**772**)

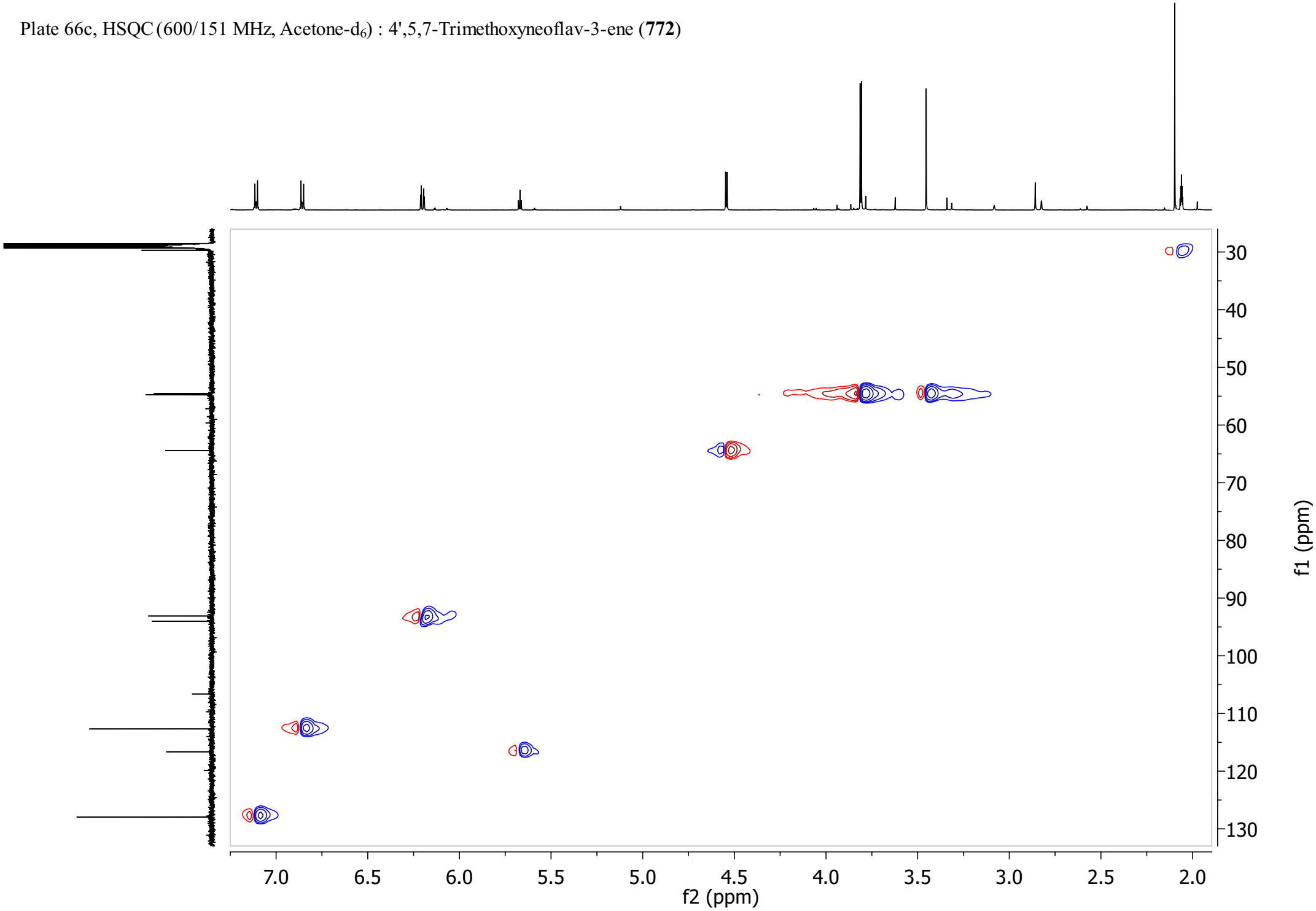


Plate 66d, HMBC (600/151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyneoflav-3-ene (**772**)

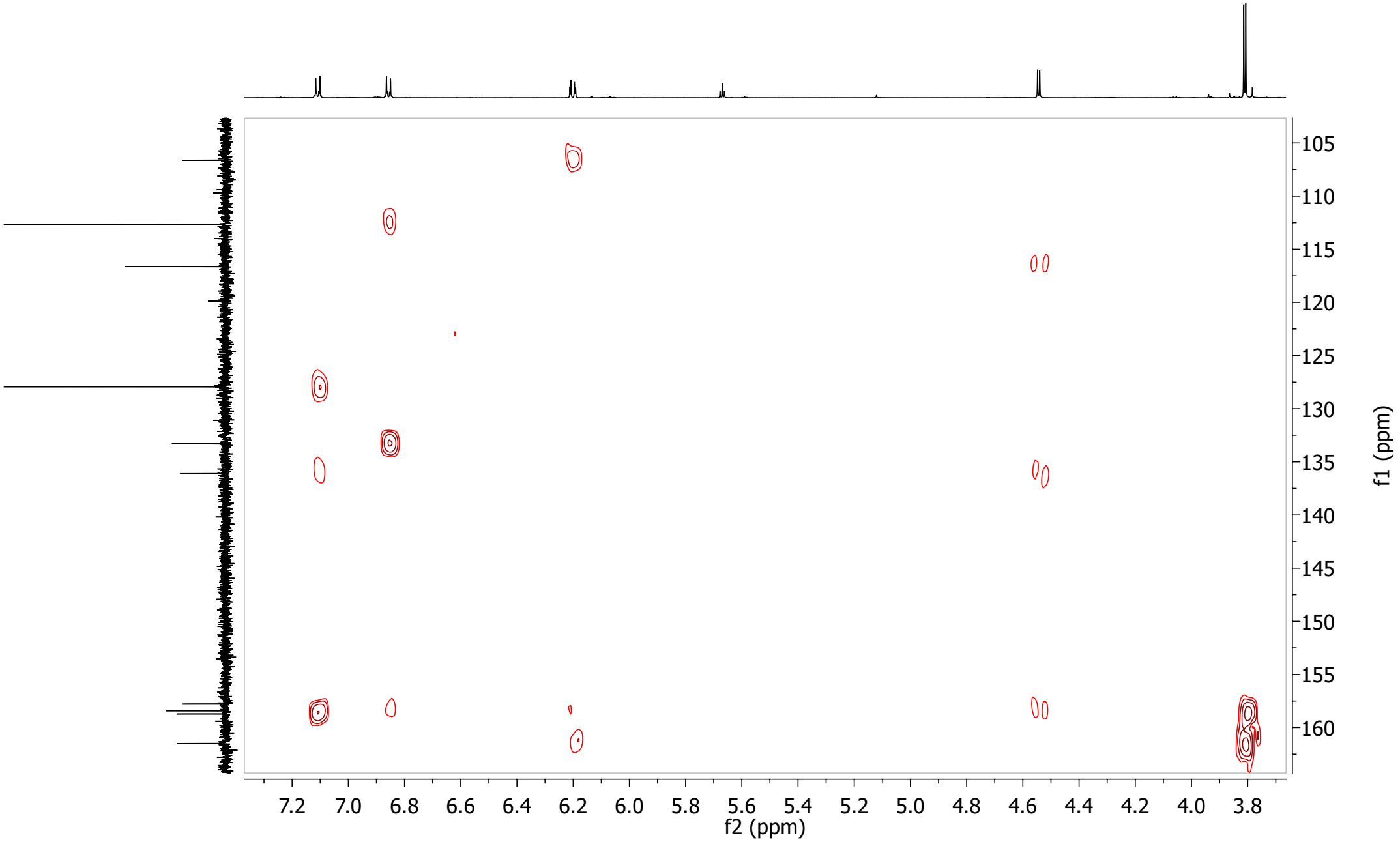
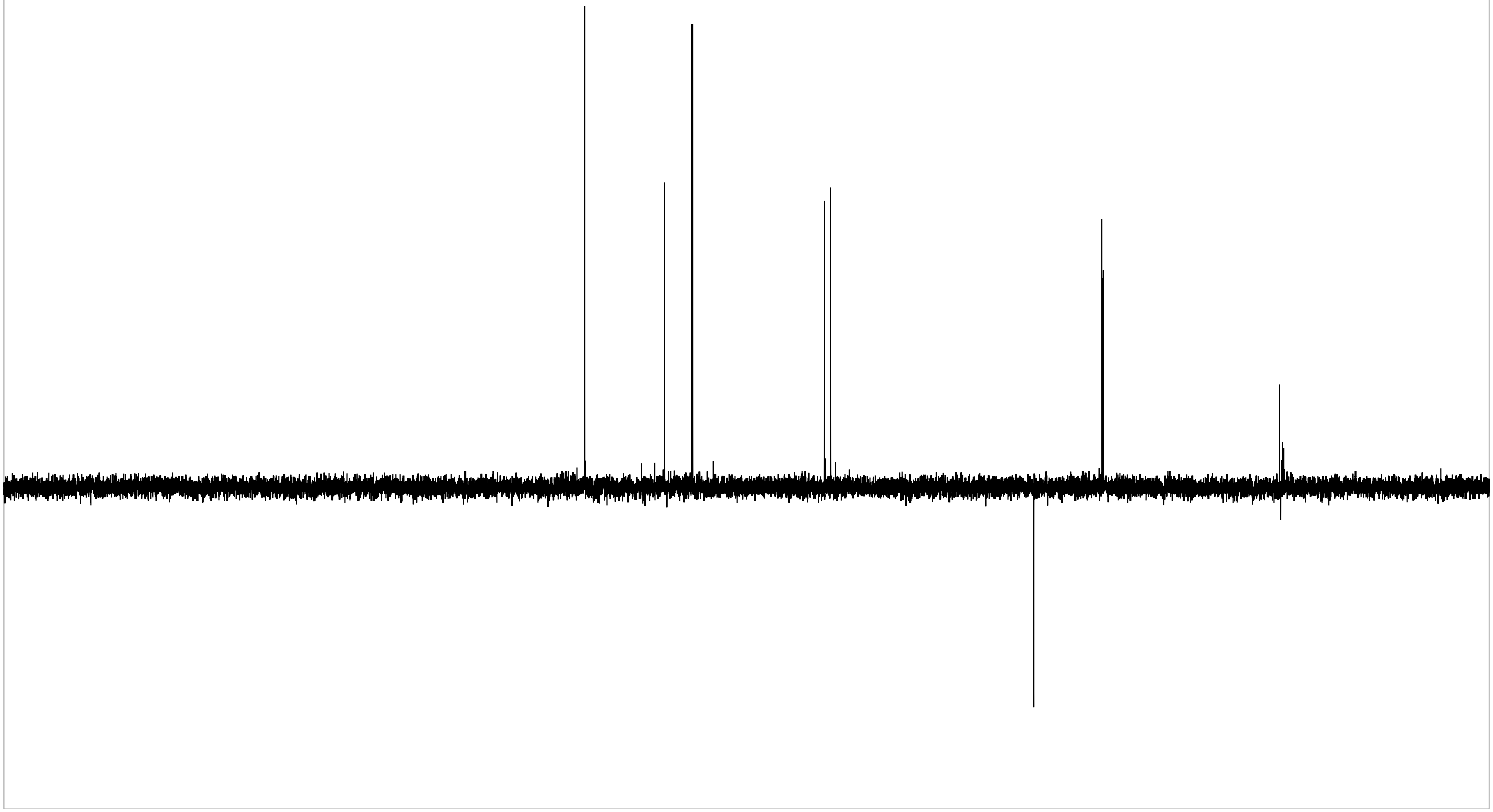


Plate 66e, DEPT (151 MHz, Acetone-d_6) : 4',5,7-Trimethoxyneoflav-3-ene (**772**)

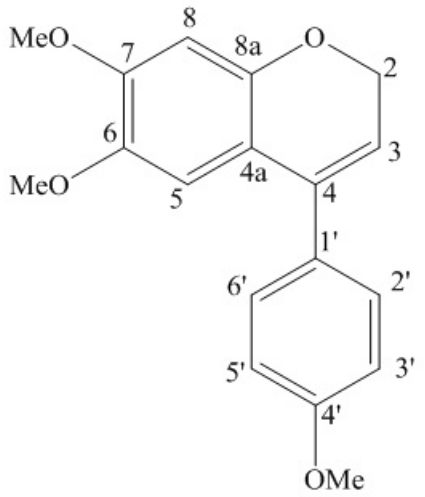


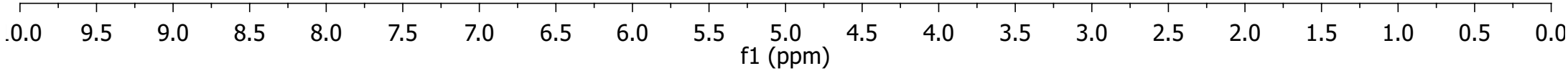
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 67a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4',6,7-Trimethoxyneoflav-3-ene (**773**)

δ 7.31 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 7.00 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 6.61 (1H, s, H-5), 6.56 (1H, s, H-8), 5.72 (1H, t, *J* = 4.1 Hz, H-3), 4.72 (2H, d, *J* = 4.1 Hz, H-2), 3.85 (3H, s, -OMe), 3.83 (3H, s, -OMe), 3.62 (3H, s, -OMe)





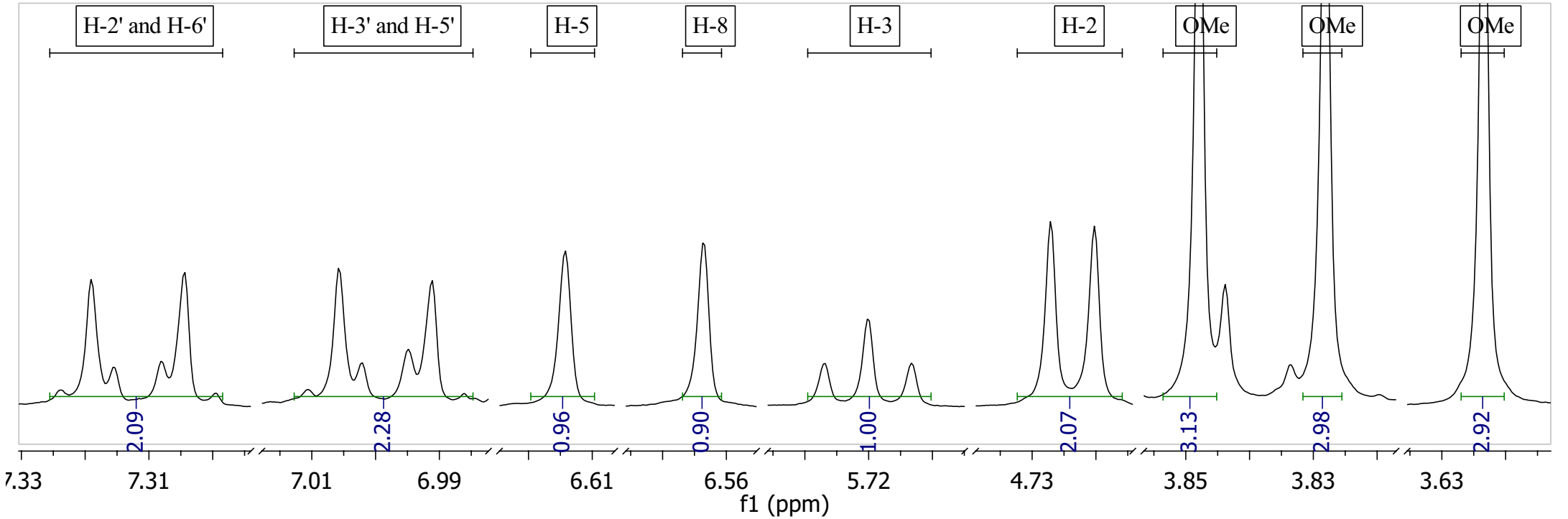
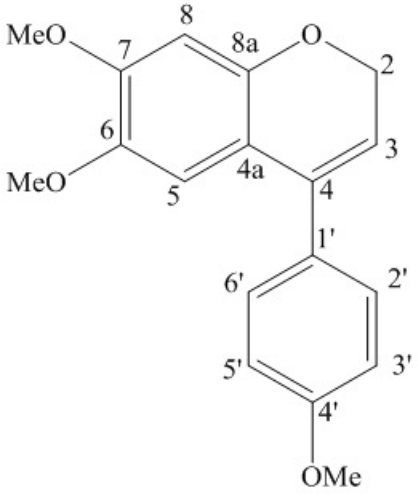
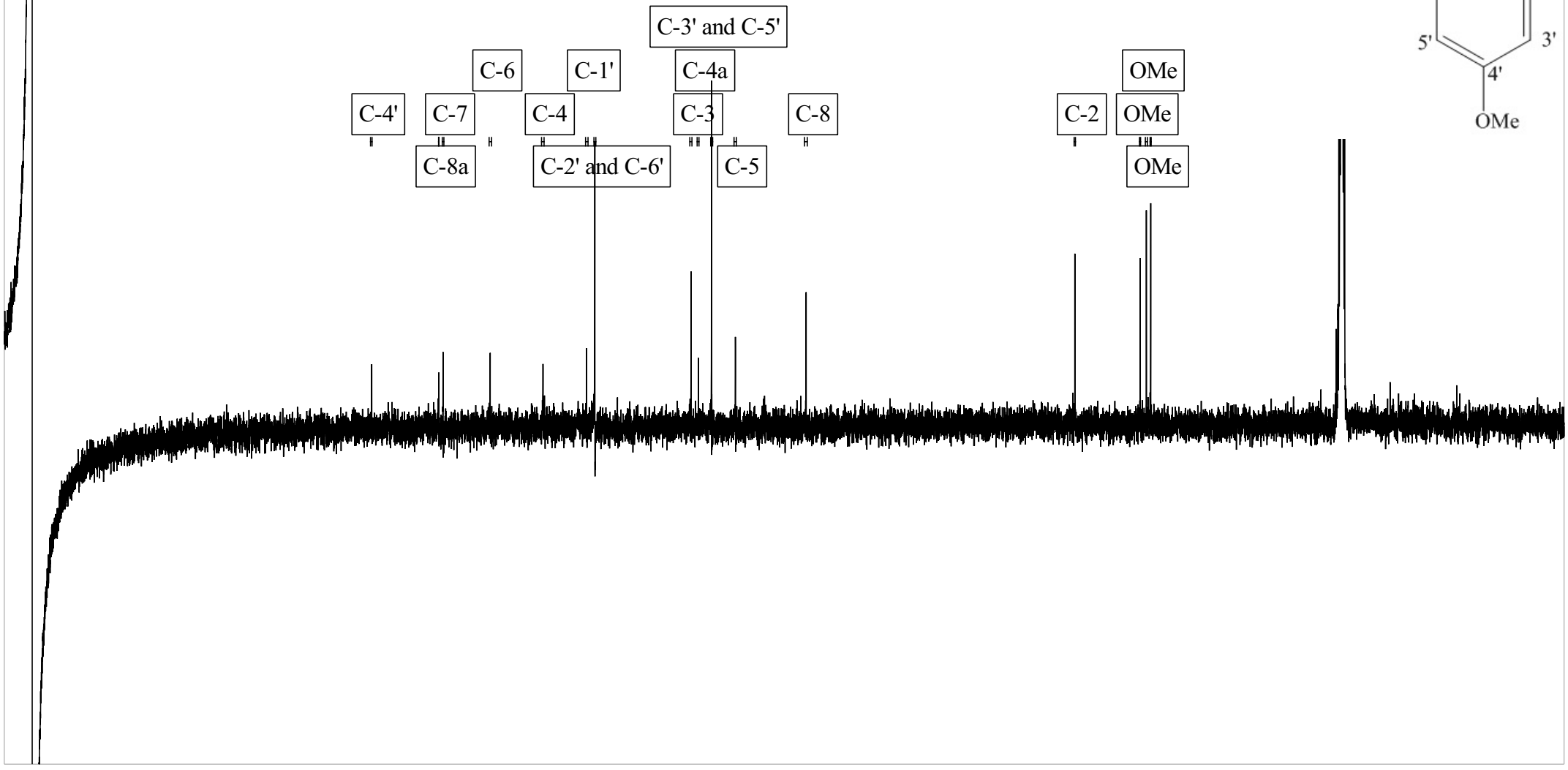


Plate 67b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4',6,7-Trimethoxyneoflav-3-ene (**773**)

δ 160.58 (C-4'), 151.50 (C-8a), 150.92 (C-7), 144.55 (C-6), 137.49 (C-4), 131.57 (C-1'), 130.49 (C-2' and C-6'), 117.53 (C-3), 116.59 (C-4a), 114.78 (C-3' and C-5'), 111.59 (C-5), 102.04 (C-8), 65.86 (C-2), 57.06 (-OMe), 56.24 (-OMe), 55.65 (-OMe)





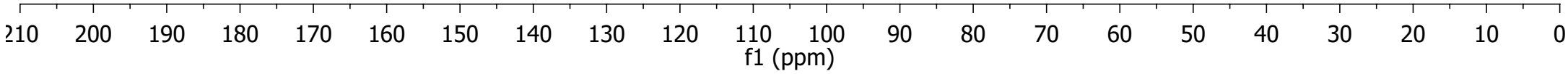


Plate 67c, HSQC (600/151 MHz, Acetone-d_6) : 4',6,7-Trimethoxyneoflav-3-ene (**773**)

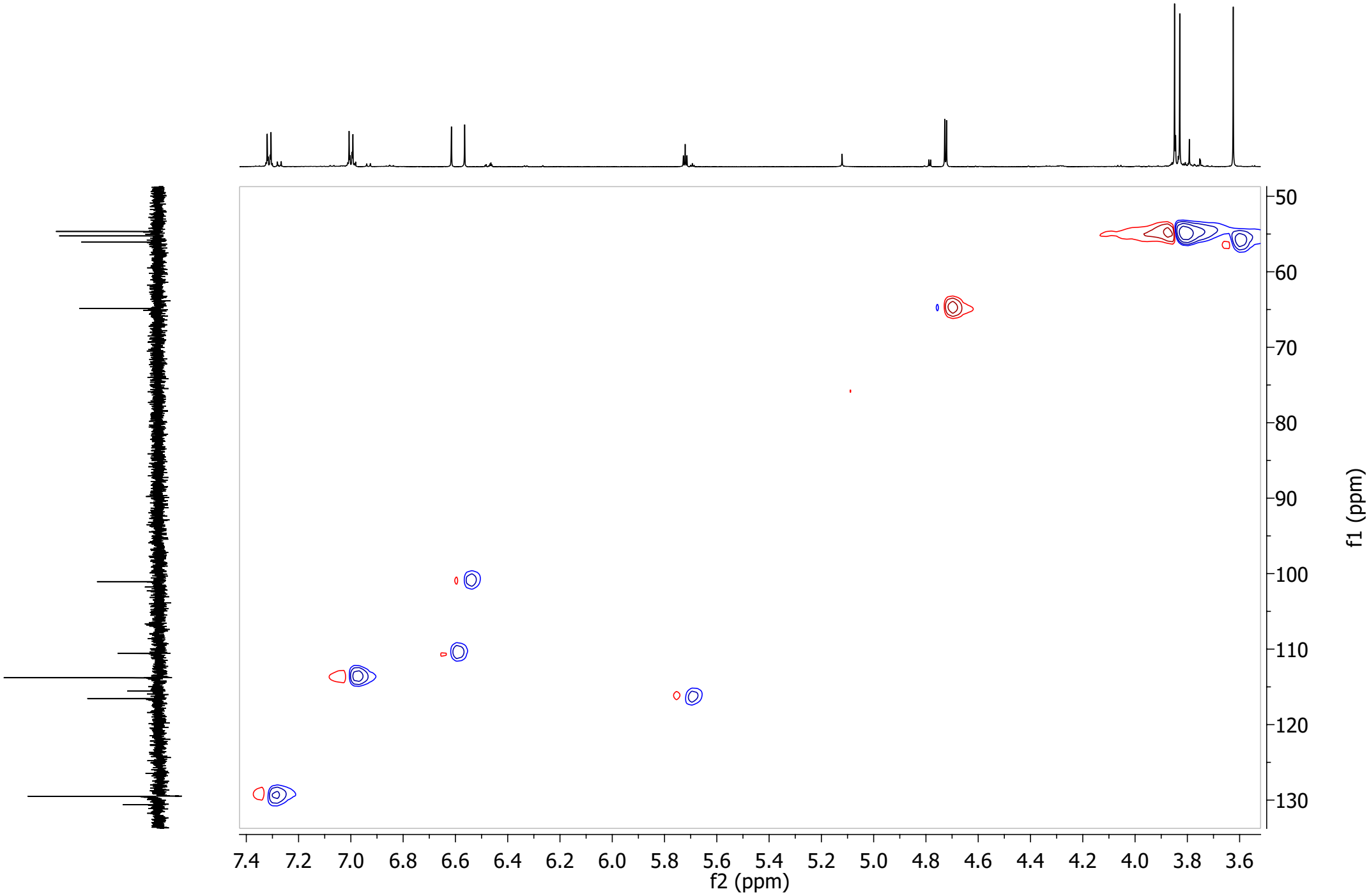


Plate 67d, HMBC (600/151 MHz, Acetone-d_6) : 4',6,7-Trimethoxyneoflav-3-ene (**773**)

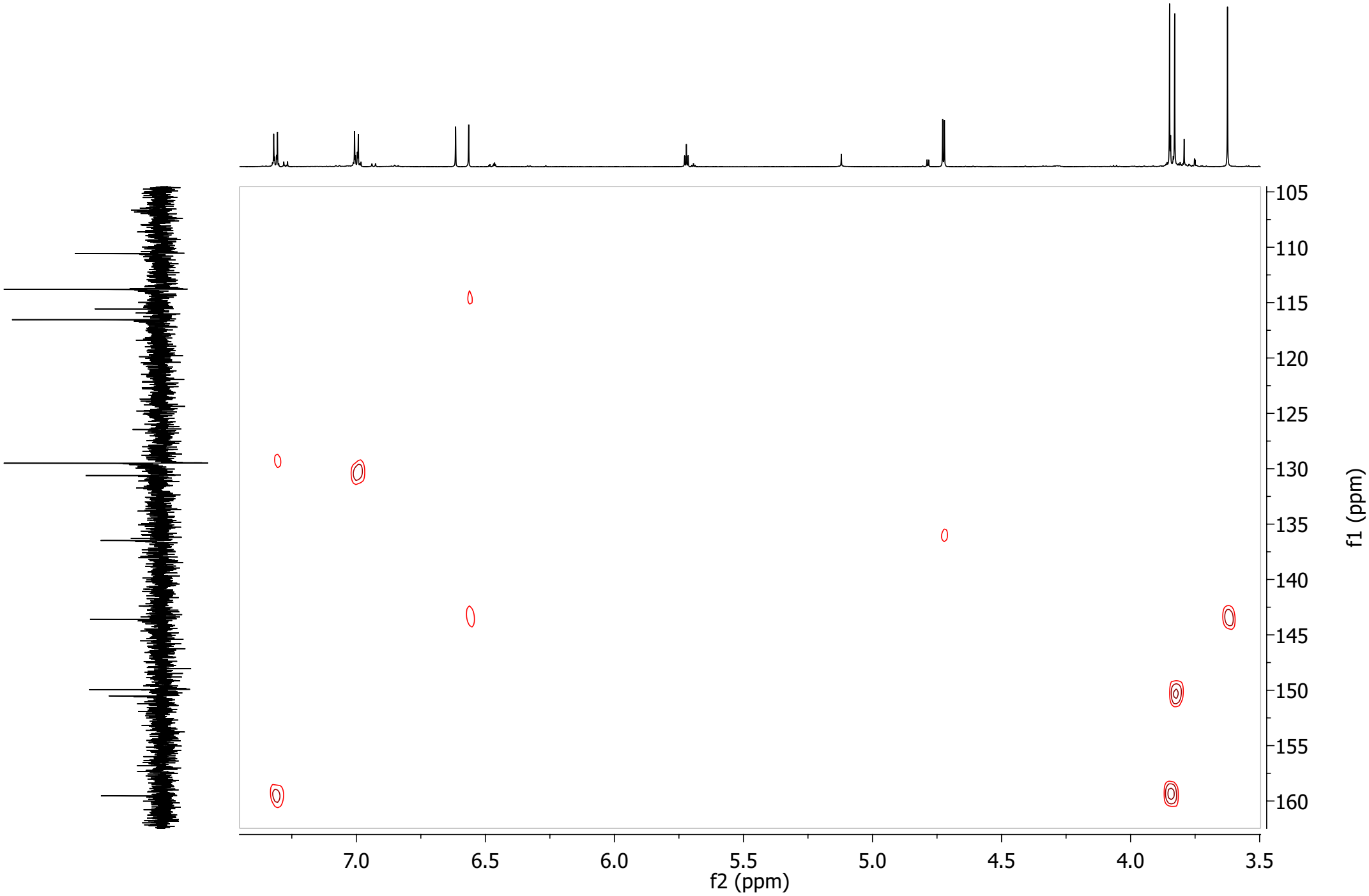
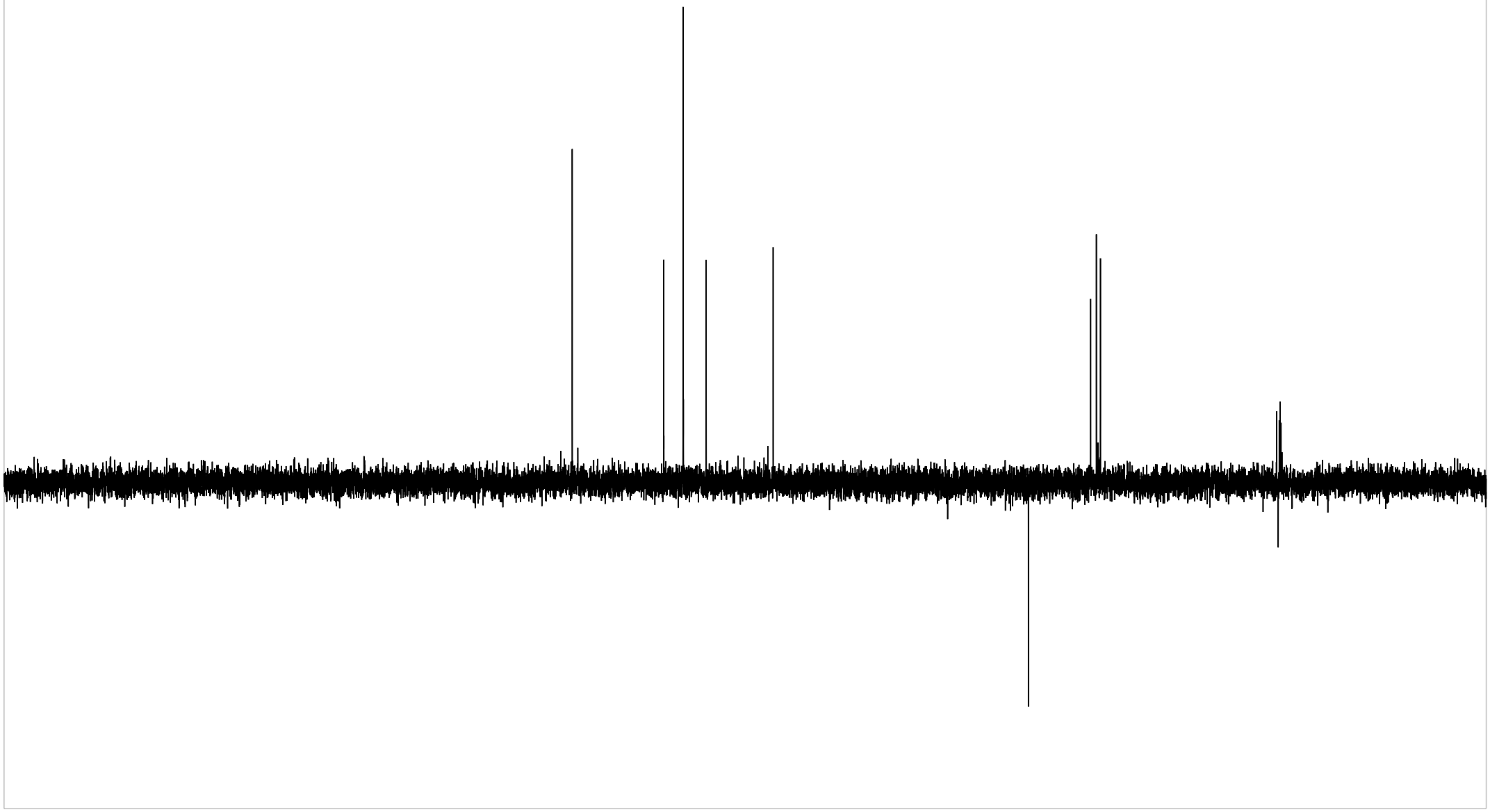


Plate 67e, DEPT (151 MHz, Acetone-d_6) : 4',6,7-Trimethoxyneoflav-3-ene (**773**)

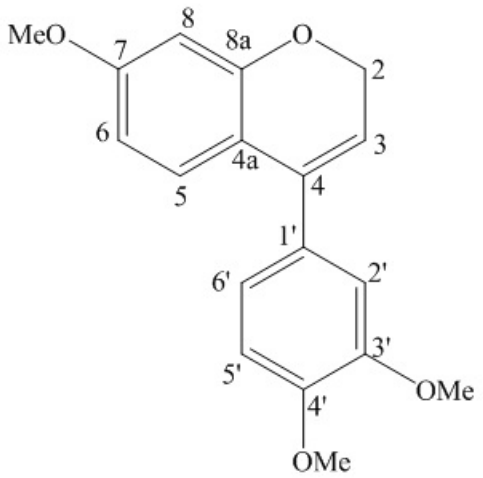


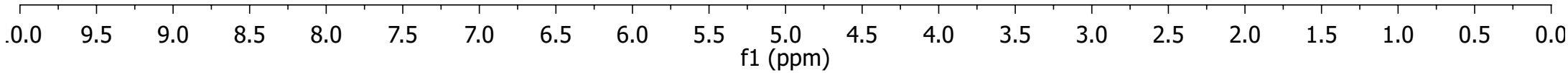
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 68a, ^{1}H NMR (600 MHz, Acetone-d_6) : 3',4',7-Trimethoxyneoflav-3-ene (**774**)

δ 6.99 (2H, d, *J* = 8.3 Hz, H-5 and H-5'), 6.90 (1H, d, *J* = 2.0 Hz, H-2'), 6.88 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 6.48 (1H, dd, *J* = 8.3, 2.5 Hz, H-6), 6.46 (1H, d, *J* = 2.5 Hz, H-8), 5.72 (1H, t, *J* = 4.0 Hz, H-3), 4.78 (2H, d, *J* = 4.0 Hz, H-2), 3.85 (3H, s, -OMe), 3.82 (3H, s, -OMe), 3.79 (3H, s, -OMe)





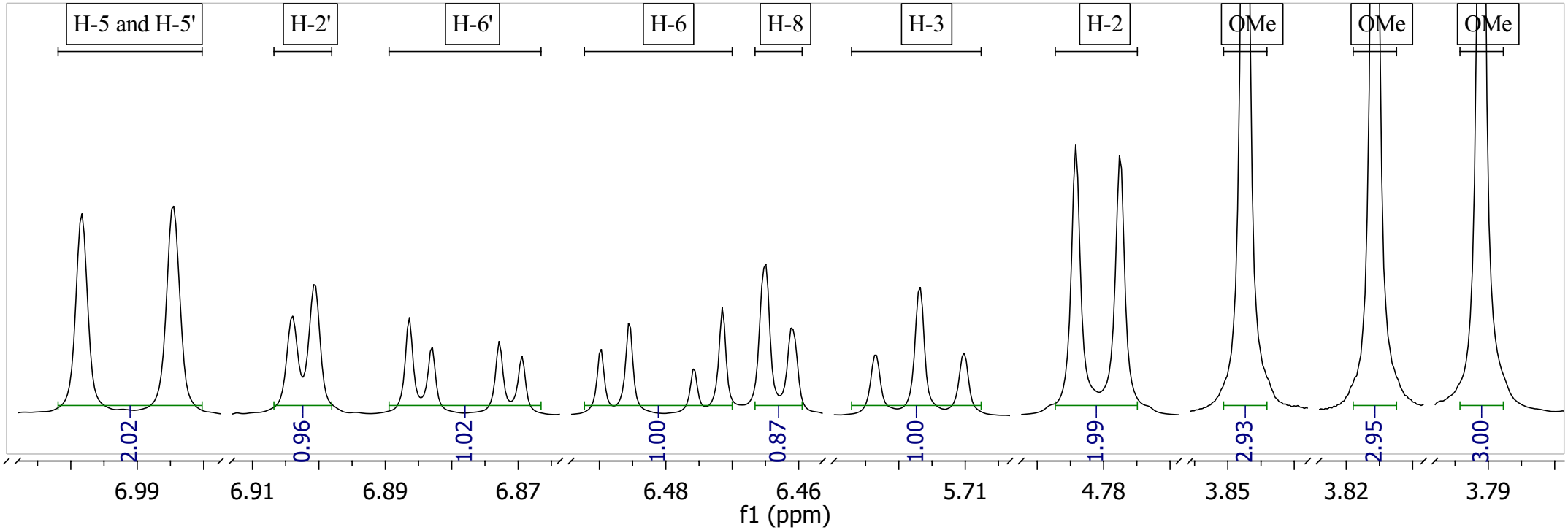
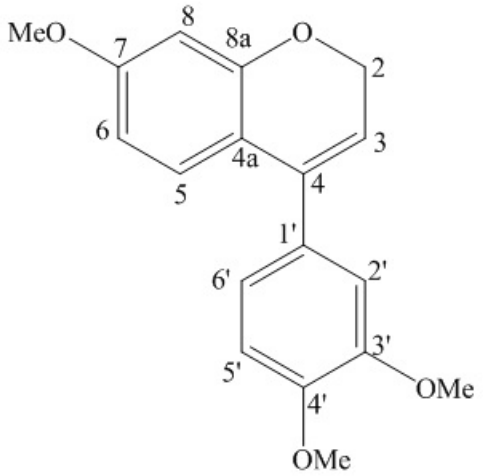
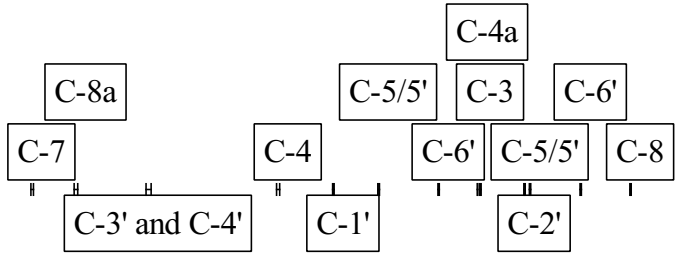


Plate 68b, ^{13}C NMR (151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyneoflav-3-ene (**774**)

δ 161.65 (C-7), 157.31 (C-8a), 150.19 (C-3' and C-4'), 137.40 (C-4), 131.97 (C-1'), 127.52 (C-5/5'), 121.60 (C-6'), 117.77 (C-4a), 117.48 (C-3), 113.14 (C-2'), 112.60 (C-5/5'), 107.61 (C-6'), 102.70 (C-8), 66.06 (C-2), 56.12 (-O<u>Me</u>), 56.10 (-O<u>Me</u>), 55.68 (-O<u>Me</u>)





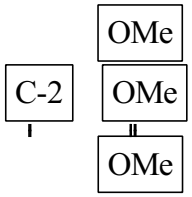


Plate 68c, HSQC (600/151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyneoflav-3-ene (**774**)

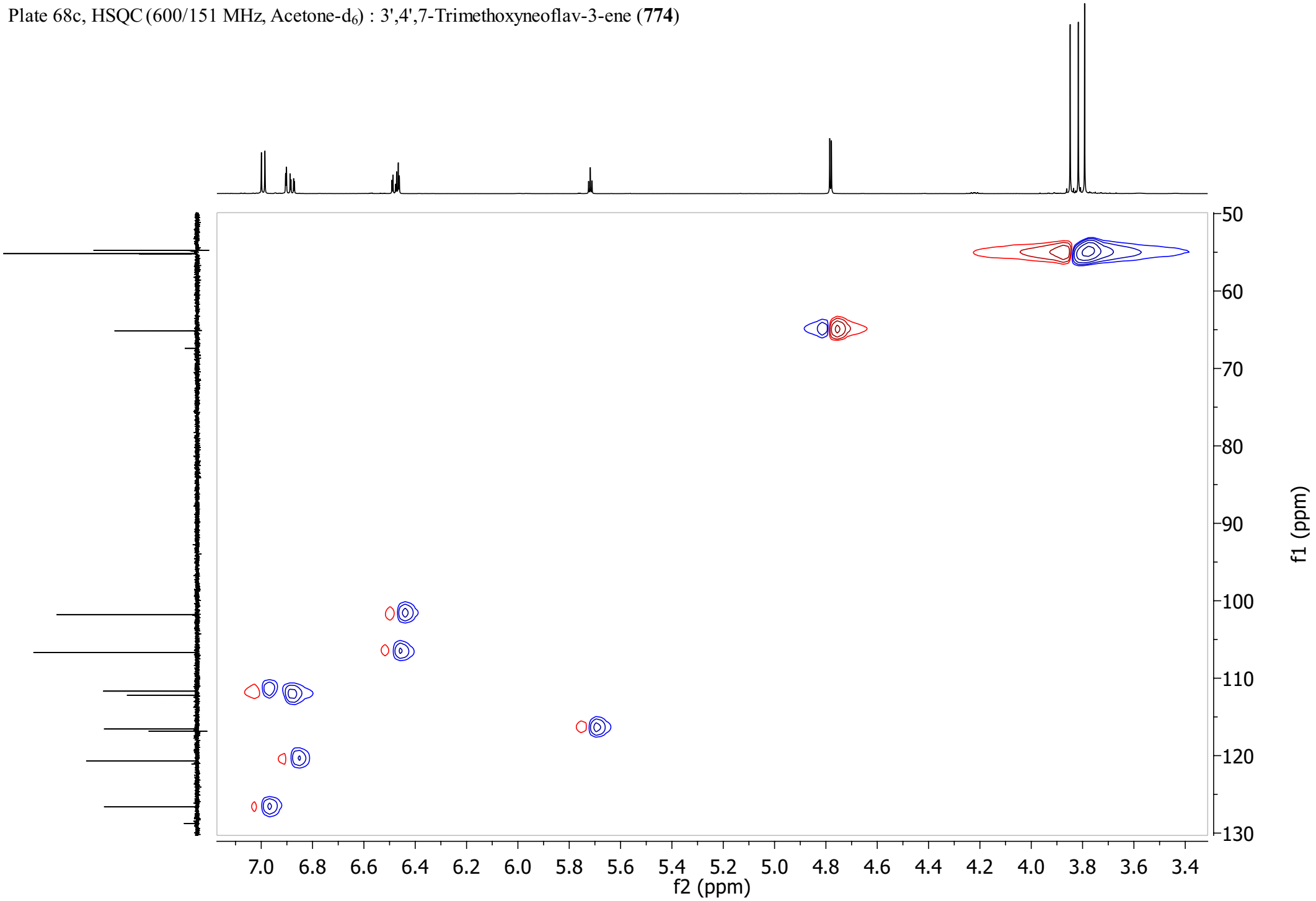


Plate 68d, HMBC (600/151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyneoflav-3-ene (**774**)

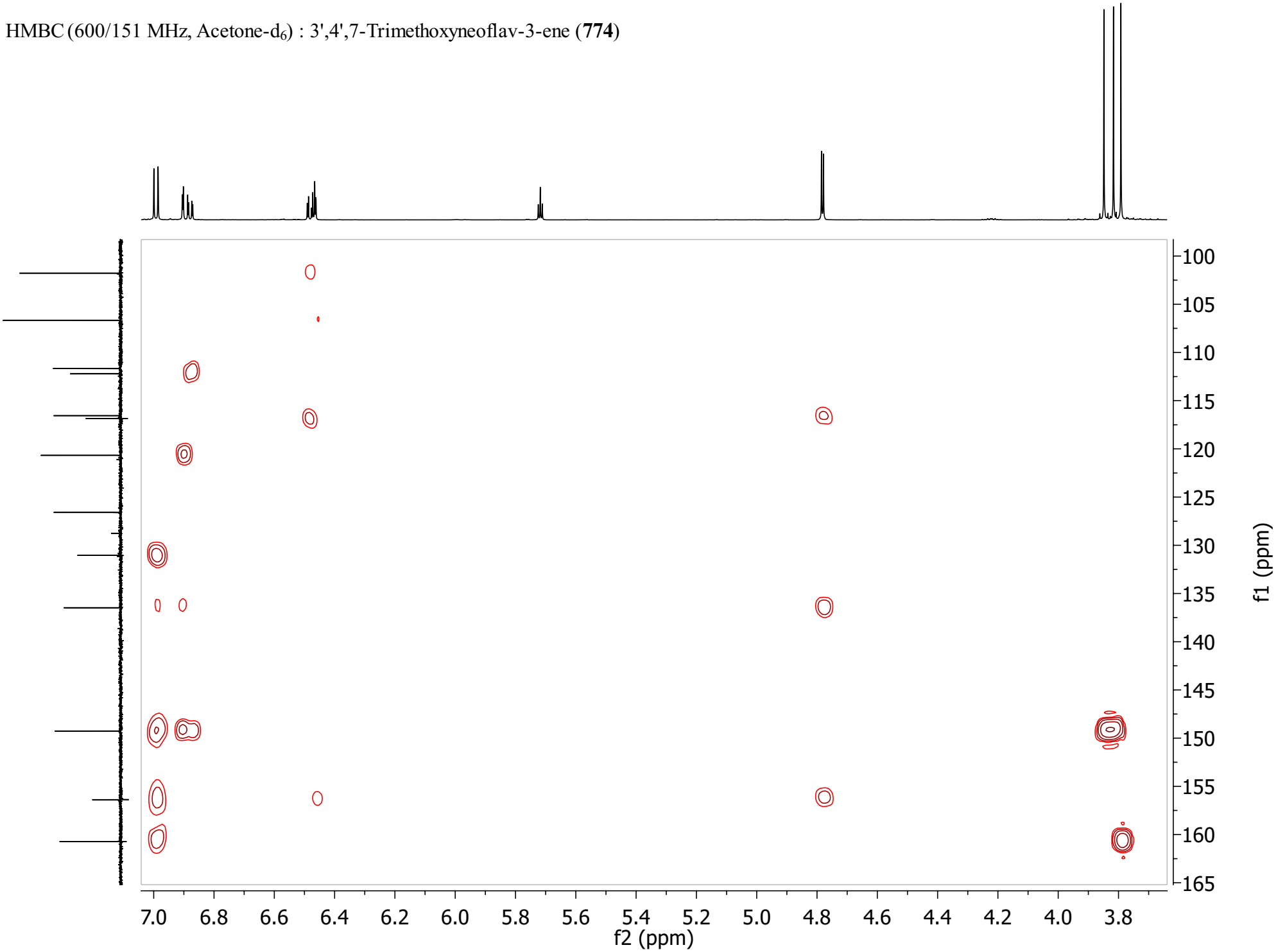
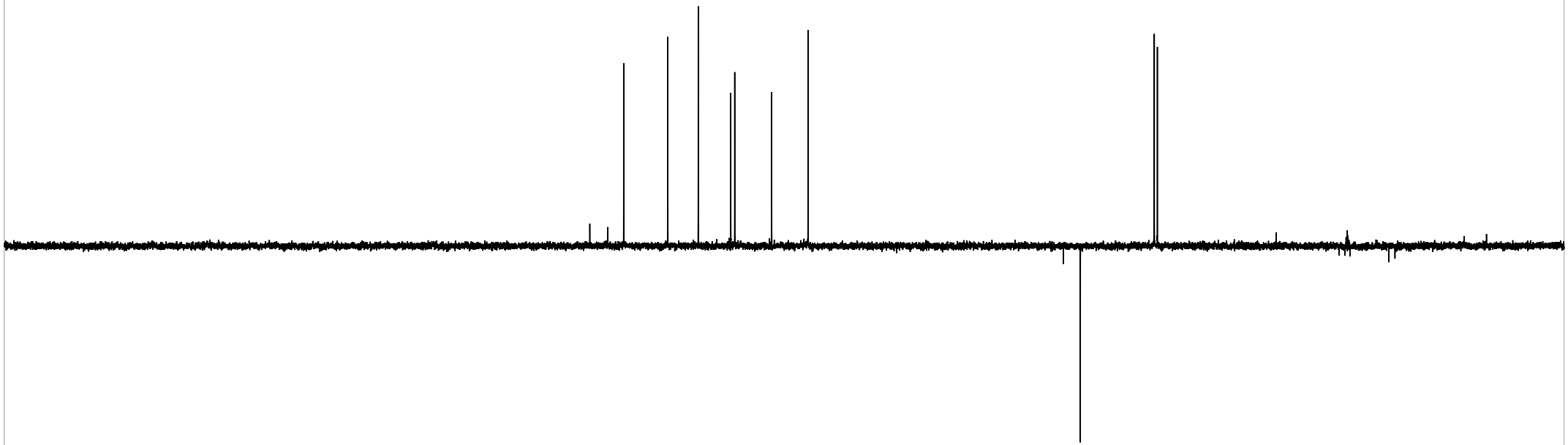


Plate 68e, DEPT (151 MHz, Acetone-d_6) : 3',4',7-Trimethoxyneoflav-3-ene (**774**)

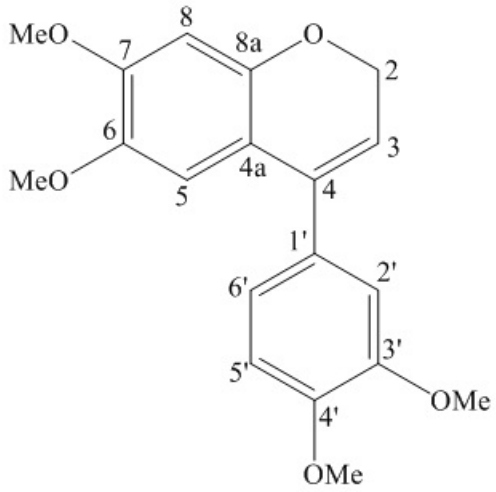


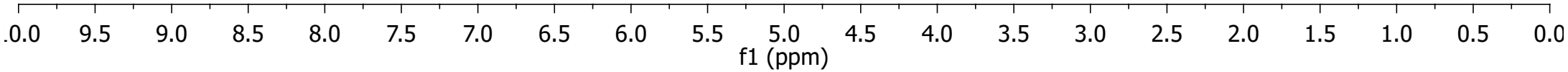
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 69a, ^{1}H NMR (600 MHz, Acetone-d_6) : 3',4',6,7-Tetramethoxyneoflav-3-ene (**775**)

δ 7.01 (1H, d, *J* = 8.7 Hz, H-5'), 6.94 – 6.91 (2H, m, H-2' and H-6'), 6.67 (1H, s, H-5), 6.57 (1H, s, H-8), 5.75 (1H, t, *J* = 4.1 Hz, H-3), 4.72 (2H, d, *J* = 4.1 Hz, H-2), 3.85 (3H, s, -OMe), 3.83 (6H, s, -OMe), 3.64 (3H, s, -OMe)





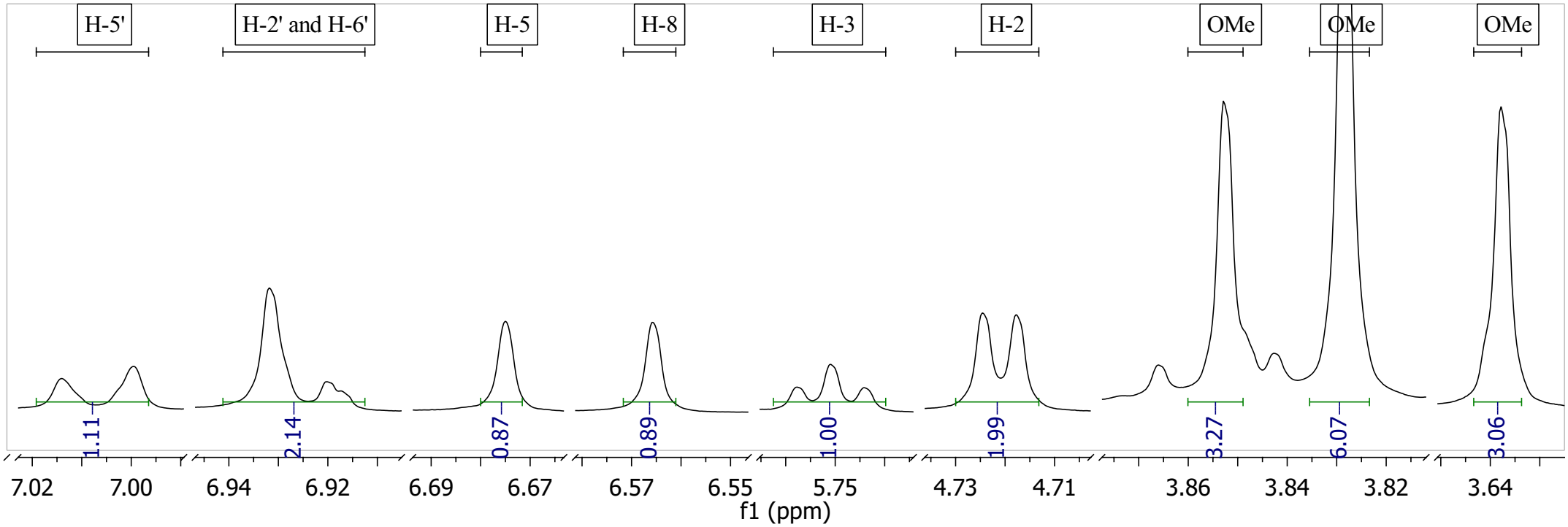
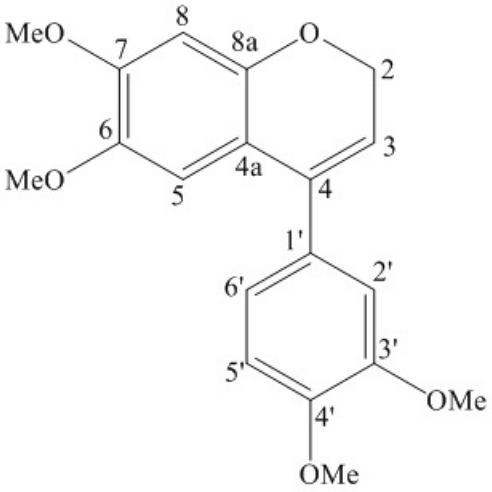


Plate 69b, ^{13}C NMR (151 MHz, Acetone-d_6) : 3',4',6,7-Tetramethoxyneoflav-3-ene (**775**)

δ 151.33 (C-8a), 150.79 (C-7), 150.19 (C-3'/4'), 150.14 (C-3'/4'), 144.50 (C-6), 137.62 (C-4), 131.88 (C-1'), 121.57 (C-2'/6'), 117.51 (C-3), 116.41 (C-4a), 112.95 (C-2'/6'), 112.59 (C-5'), 111.34 (C-5), 101.93 (C-8), 65.79 (C-2), 56.92 (-OMe), 56.16 (-OMe), 56.10 (-OMe), 56.06 (-OMe)



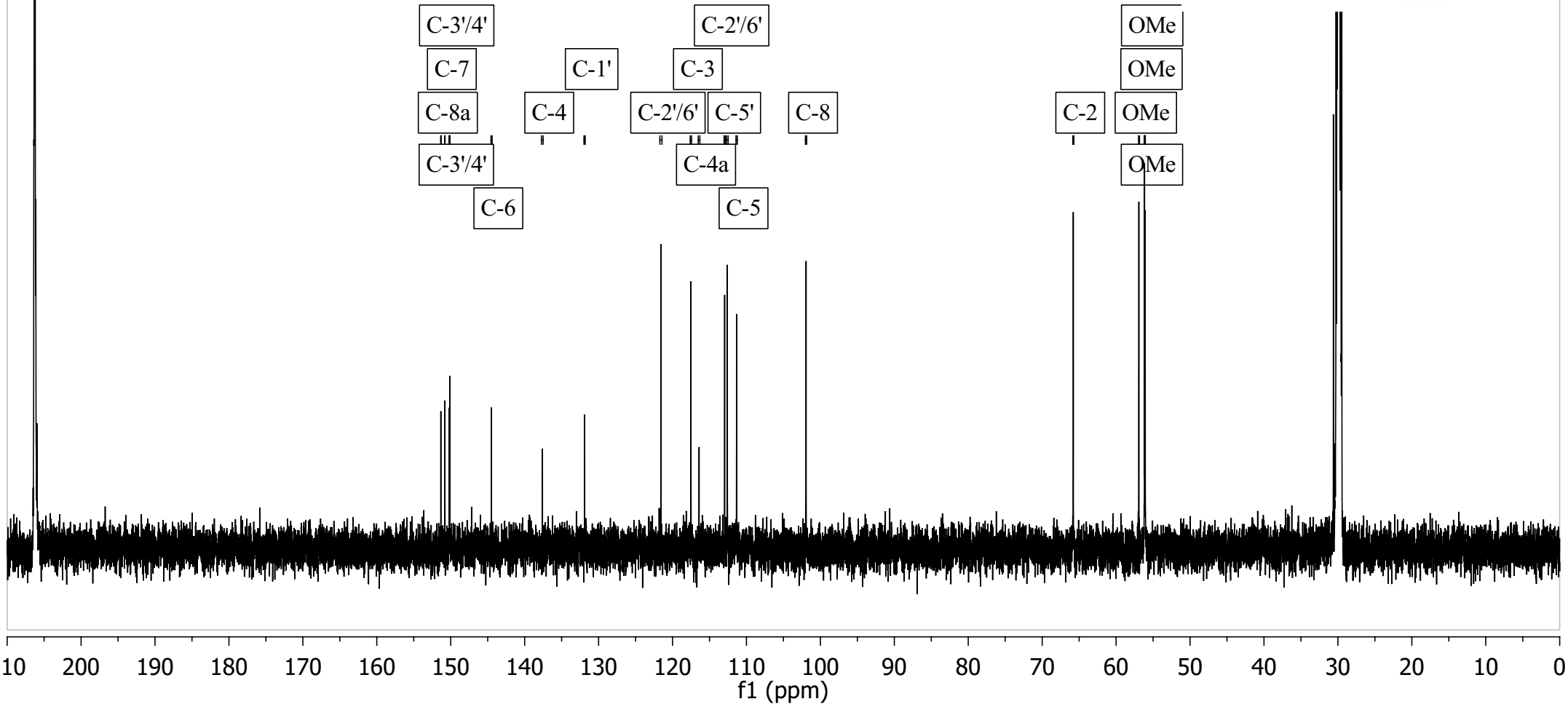


Plate 69c, HSQC (600/151 MHz, Acetone-d_6) : 3',4',6,7-Tetramethoxyneoflav-3-ene (**775**)

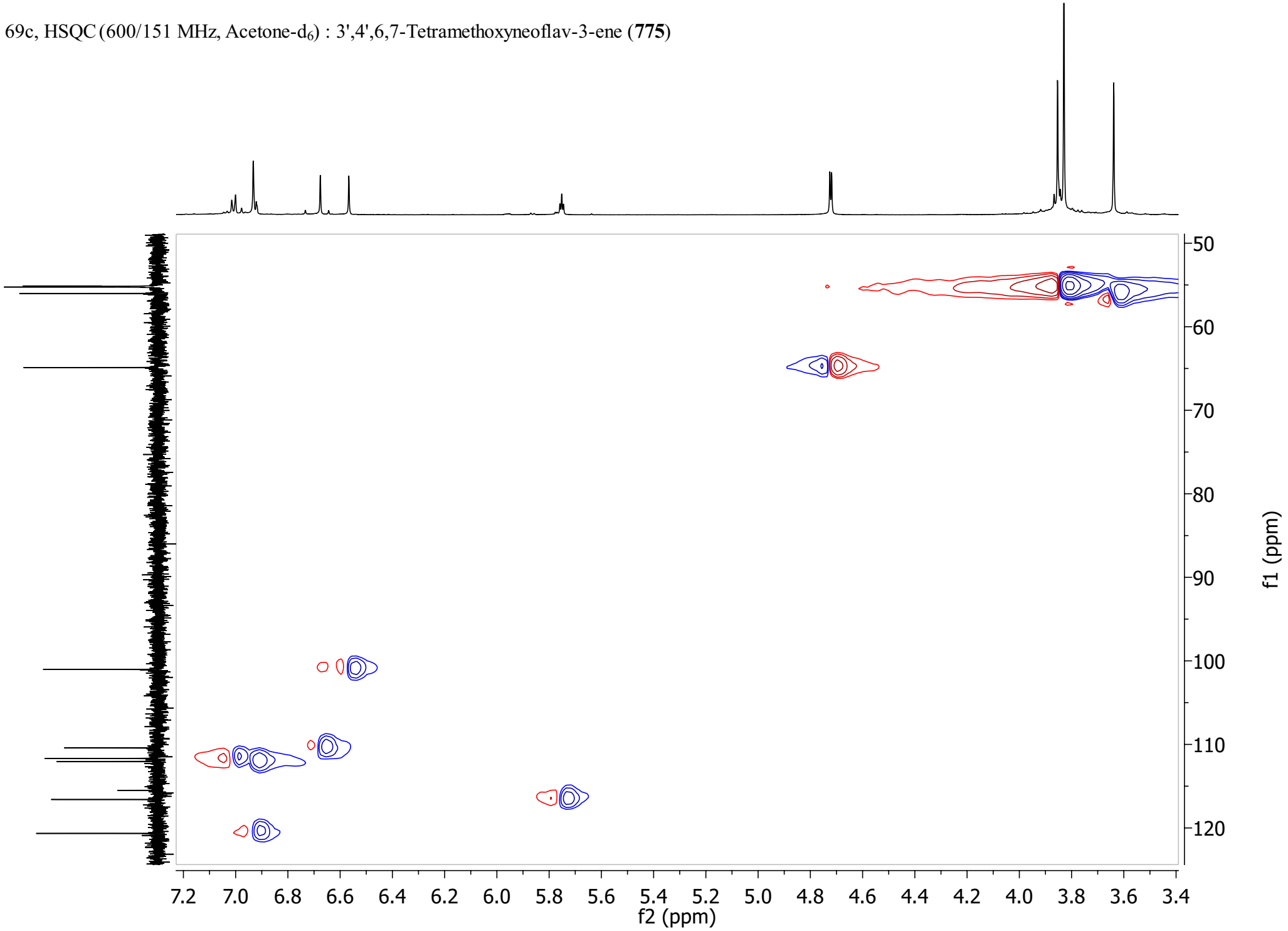


Plate 69d, HMBC (600/151 MHz, Acetone-d_6) : 3',4',6,7-Tetramethoxyneoflav-3-ene (**775**)

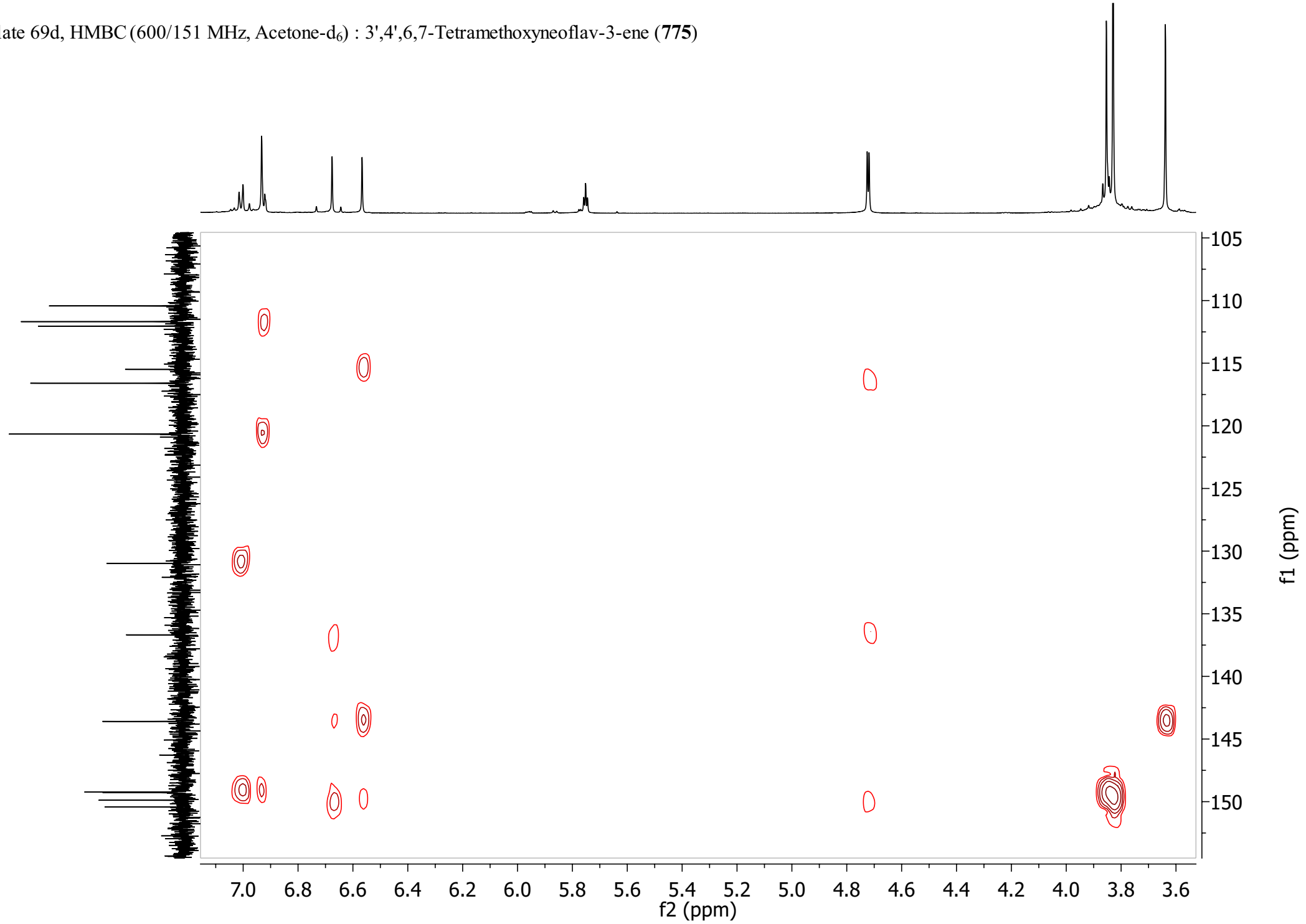


Plate 69e, DEPT (151 MHz, Acetone-d_6) : 3',4',6,7-Tetramethoxyneoflav-3-ene (**775**)

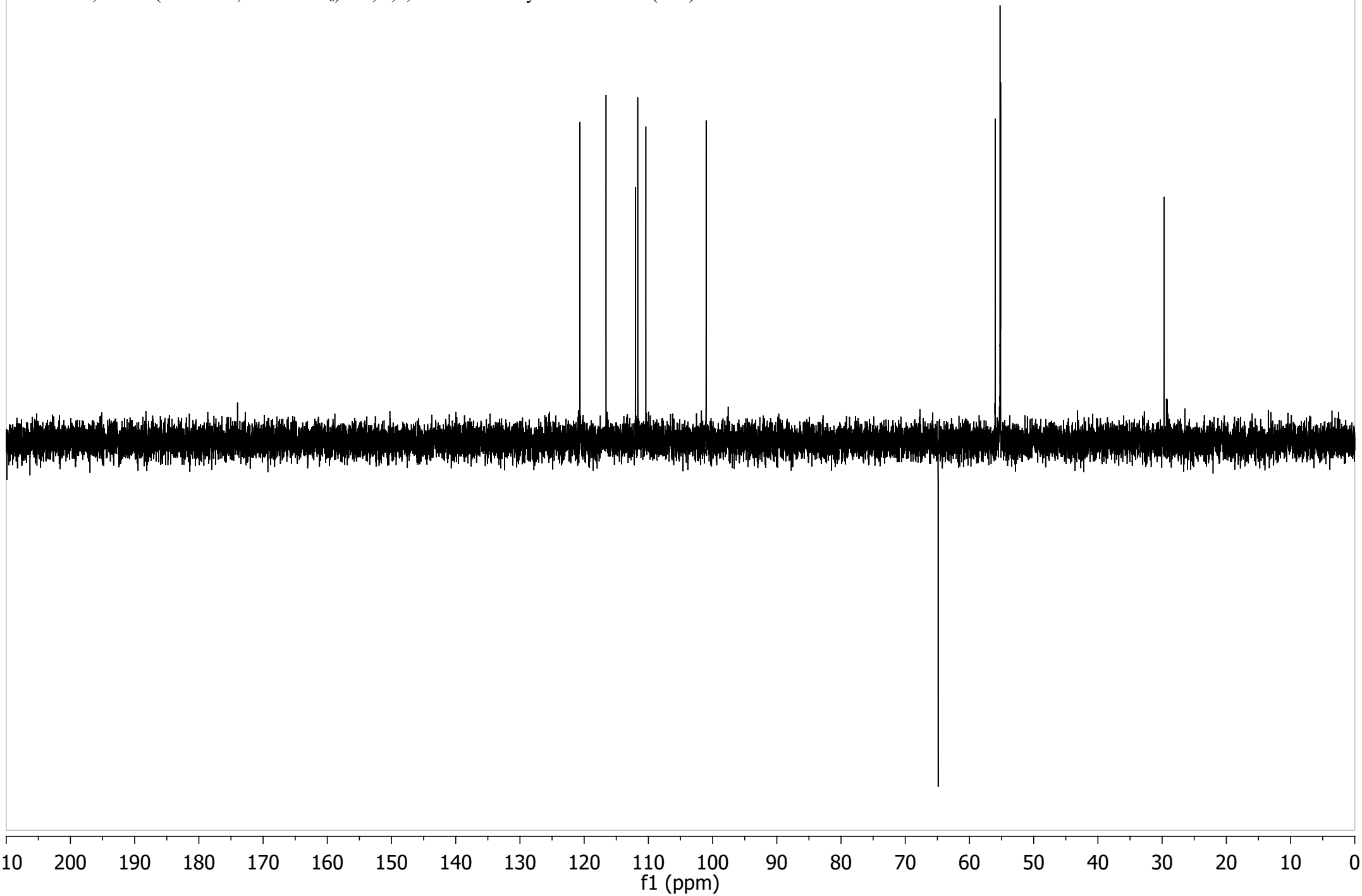
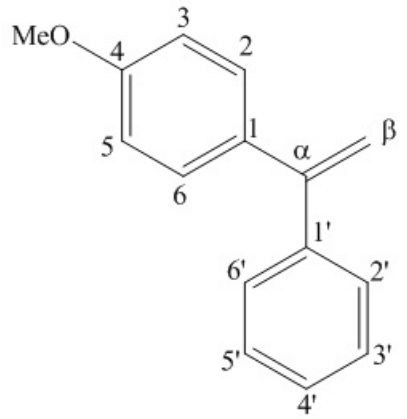


Plate 70a, ^{1}H NMR (600 MHz, $CDCl_3$) : 4-Methoxy-α-phenylstyrene (**789**)

δ 7.37 – 7.31 (5H, m, Ar-H), 7.29 (2H, d, *J* = 8.8 Hz, H-2 and H-6), 6.88 (2H, d, *J* = 8.8 Hz, H-3 and H-5), 5.41 (1H, d, *J* = 1.2 Hz, H-β), 5.37 (1H, d, *J* = 1.2 Hz, H-β), 3.82 (3H, s, -OMe)



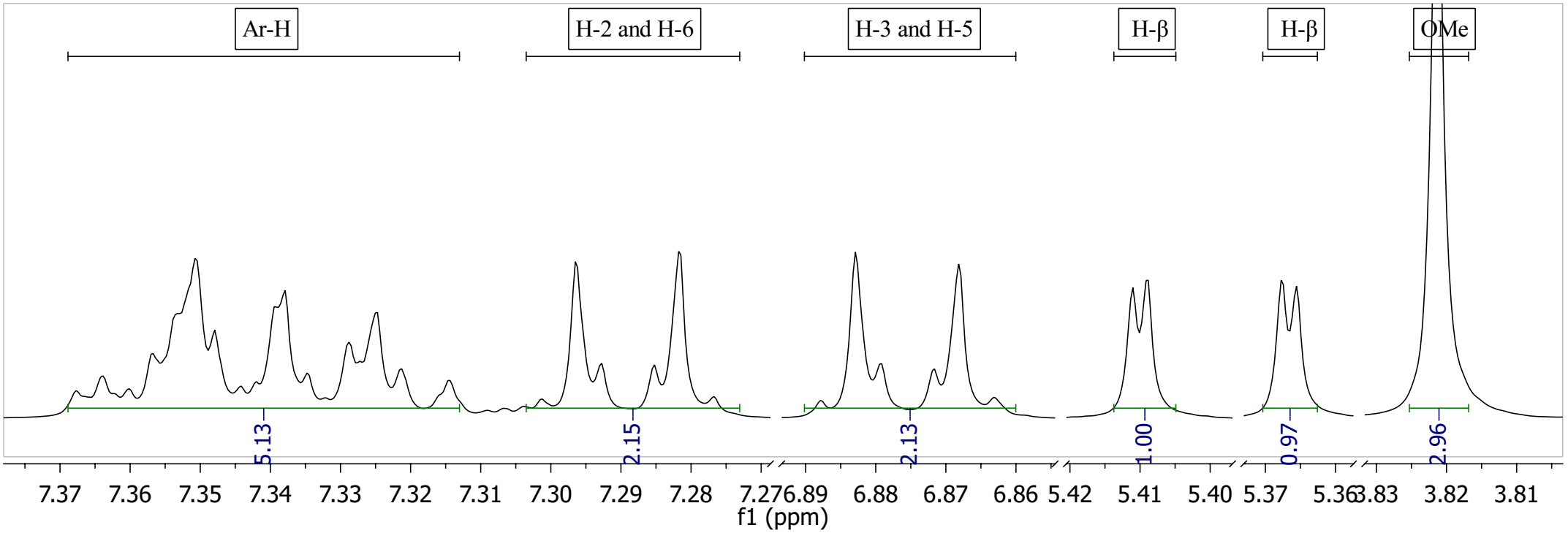
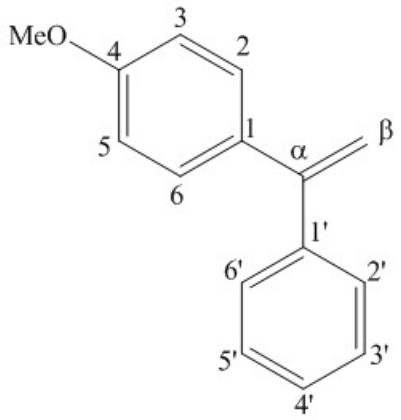


Plate 70b, ^{13}C NMR (151 MHz, $CDCl_3$) : 4-Methoxy-α-phenylstyrene (**789**)

δ 159.37 (C-4), 149.55 (C-α), 141.84 (C-1'), 133.99 (C-1), 129.43 (C-2 and C-6), 128.35 (Ar-C), 128.17 (Ar-C), 127.70 (C-4'), 113.56 (C-3 and C-5), 112.97 (C-β), 55.29 (-O<u>Me</u>)



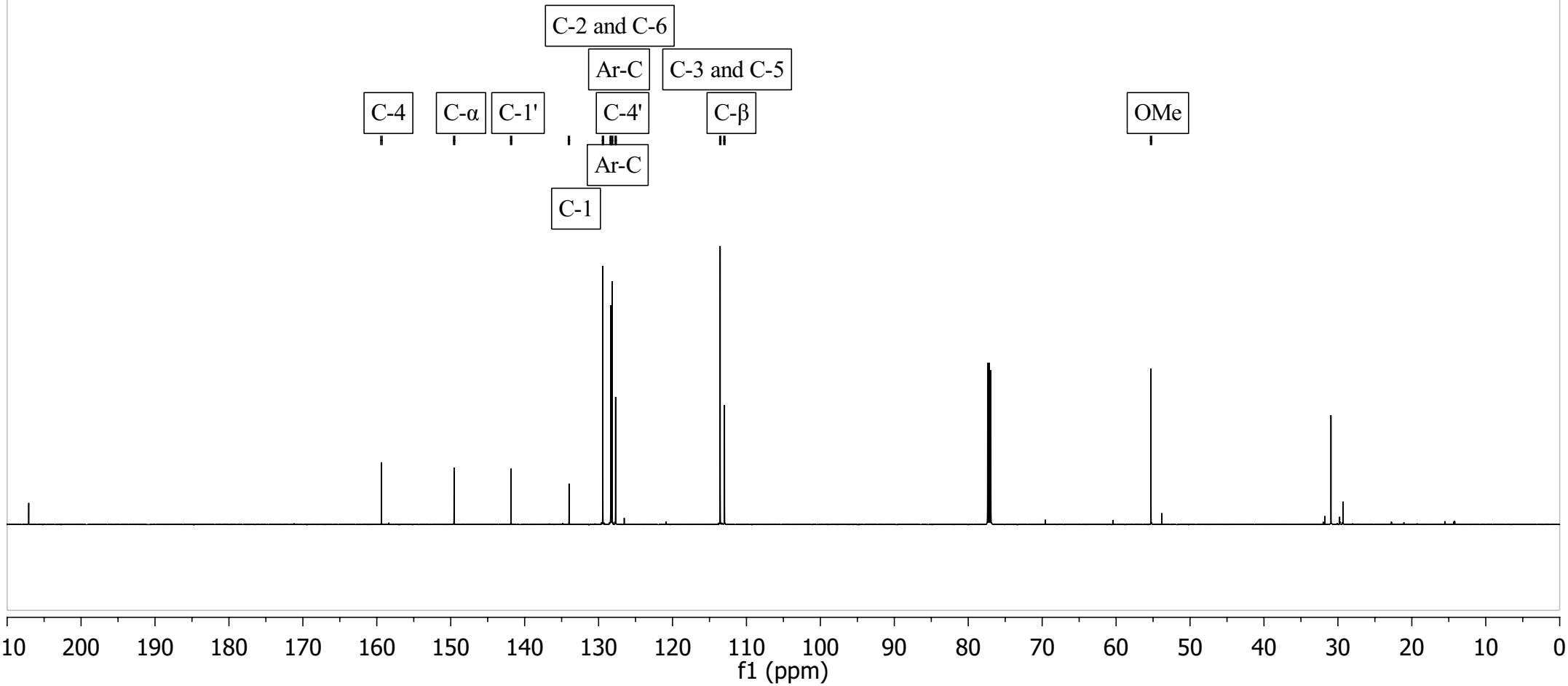


Plate 70c, HSQC (600 MHz/151 MHz, $CDCl_3$) : 4-Methoxy-α-phenylstyrene (**789**)

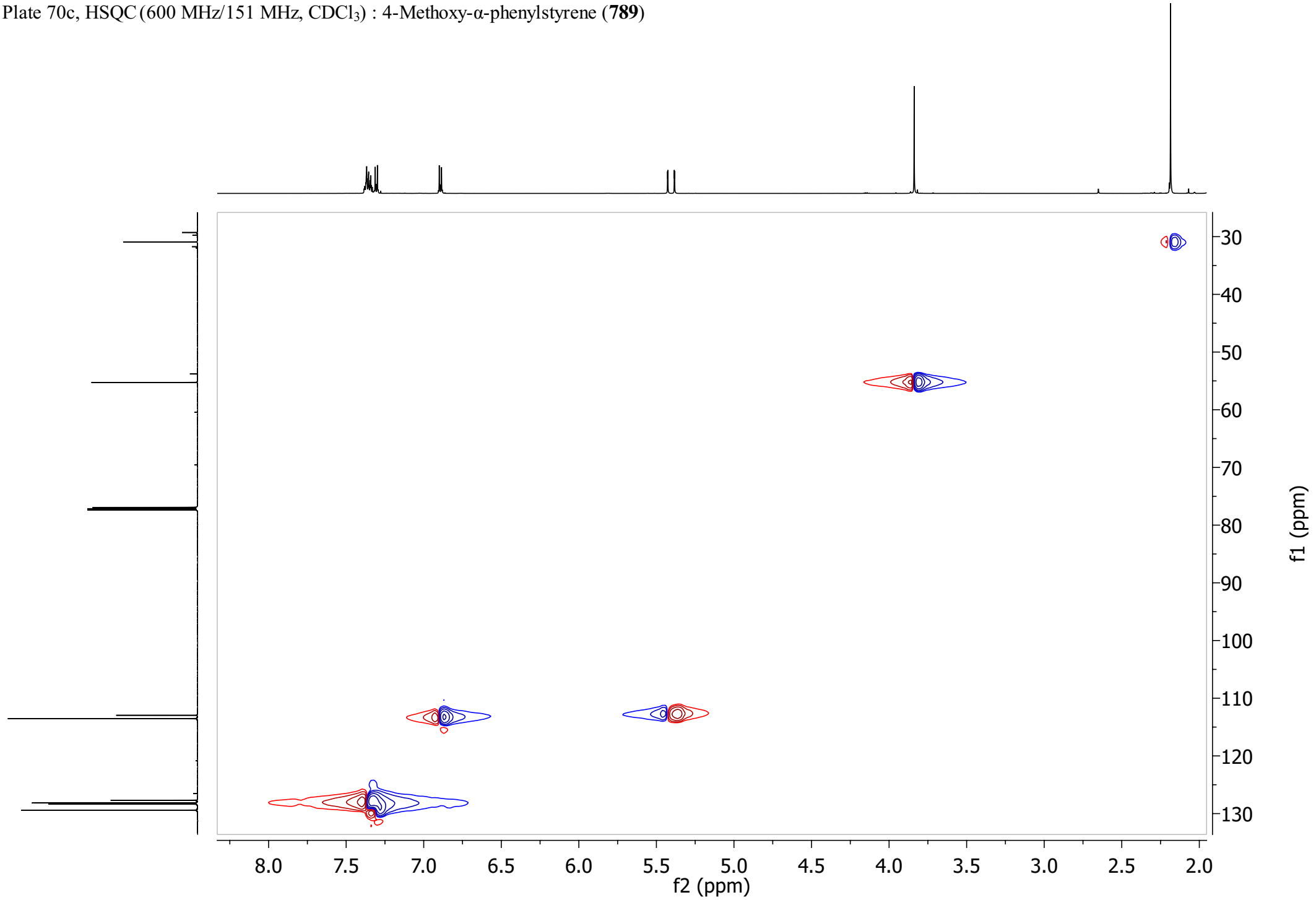


Plate 70d, HMBC (600 MHz/151 MHz, $CDCl_3$) : 4-Methoxy-α-phenylstyrene (**789**)

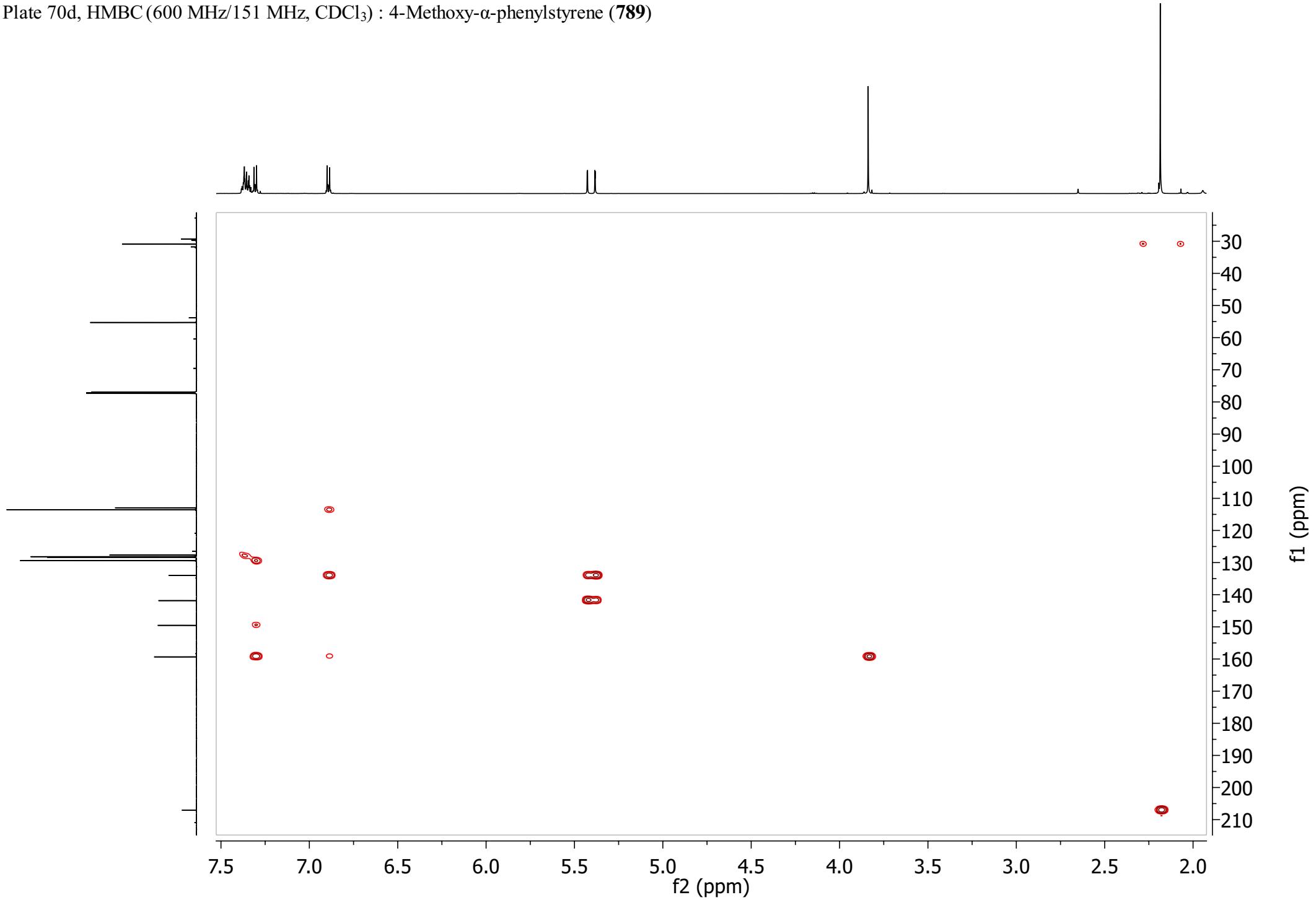
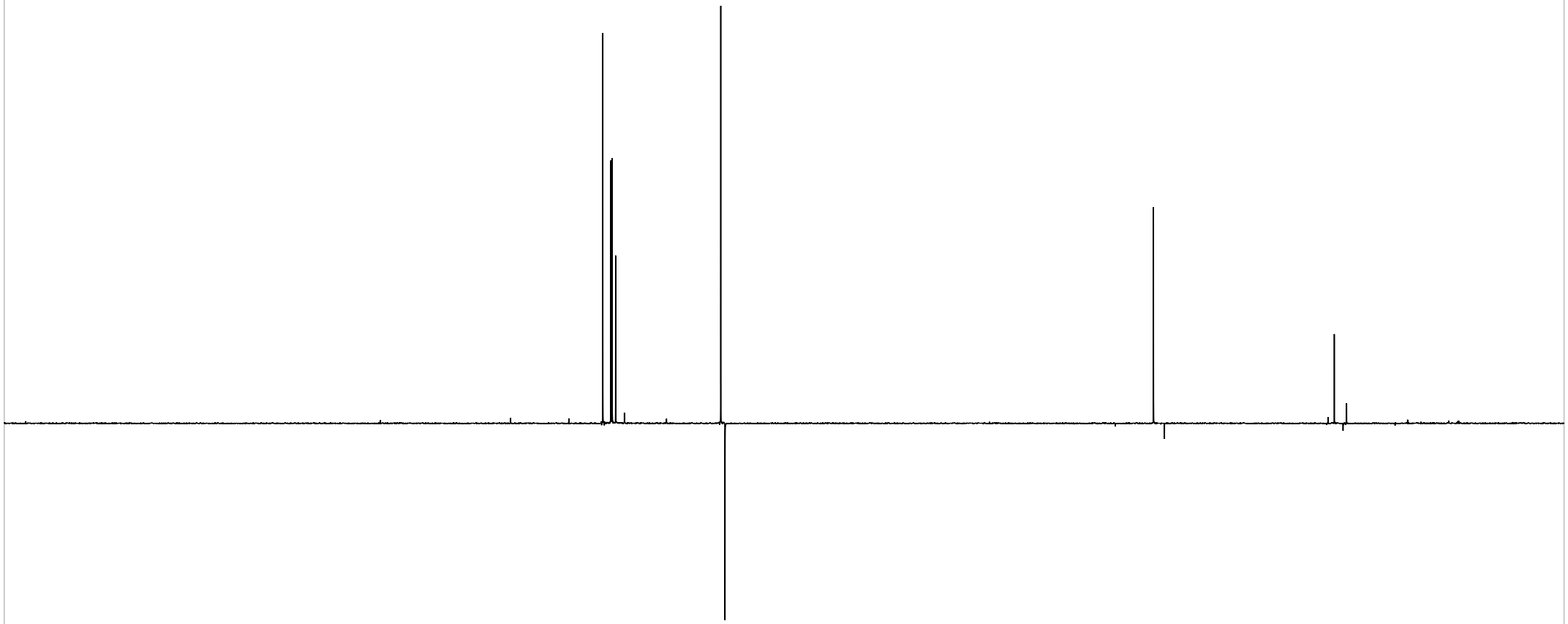


Plate 70e, DEPT (151 MHz, $CDCl_3$) : 4-Methoxy-α-phenylstyrene (**789**)



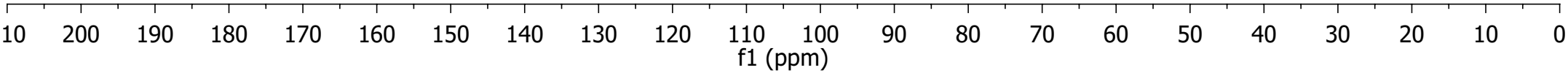
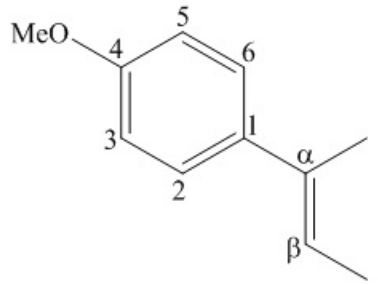
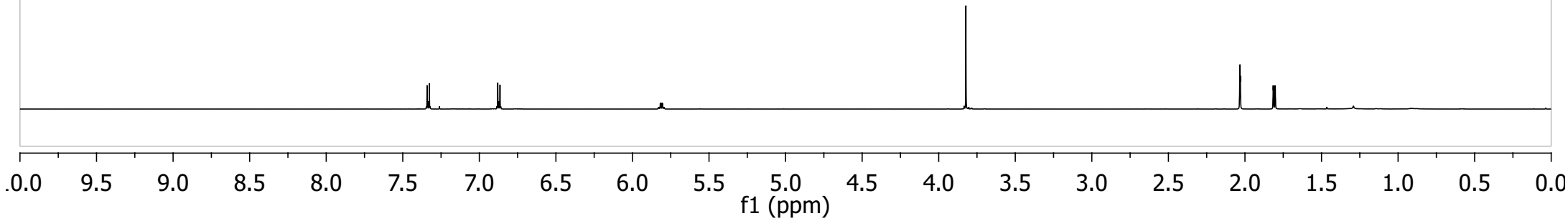


Plate 71a, ^{1}H NMR (600 MHz, $CDCl_3$) : (*E*)-4-Methoxy-α,β-dimethylstyrene (**790**)

δ 7.33 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 6.87 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 5.81 (1H, qq, *J* = 6.8, 1.3 Hz, H-β), 3.82 (3H, s, -OMe), 2.04 – 2.02 (3H, m, α-CH_3), 1.82 – 1.80 (3H, m, β-CH_3)





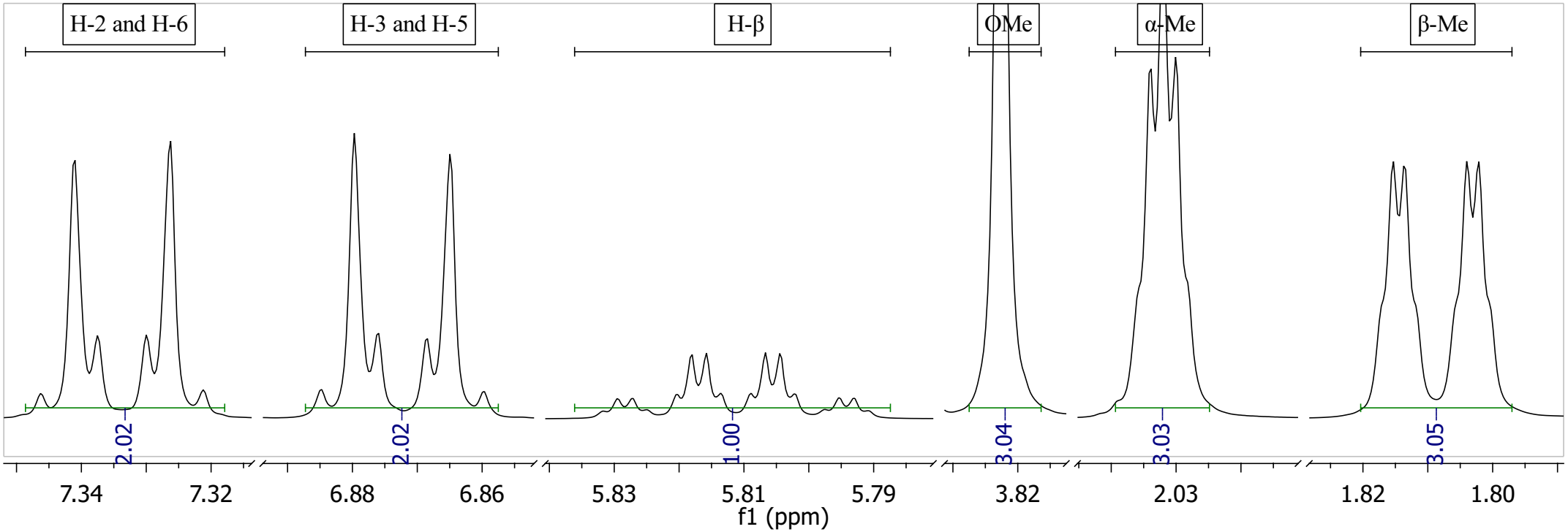
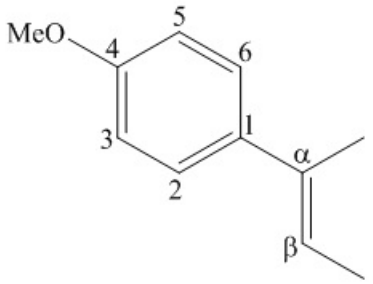


Plate 71b, ^{13}C NMR (151 MHz, $CDCl_3$) : (*E*)-4-Methoxy-α,β-dimethylstyrene (**790**)

δ 158.44 (C-4), 136.75 (C-1), 134.93 (C-α), 126.61 (C-2 and C-6), 120.95 (C-β), 113.55 (C-3 and C-5), 55.34 (-O<u>Me</u>), 15.63 (α-<u>C</u>H_3), 14.40 (β-<u>C</u>H_3)



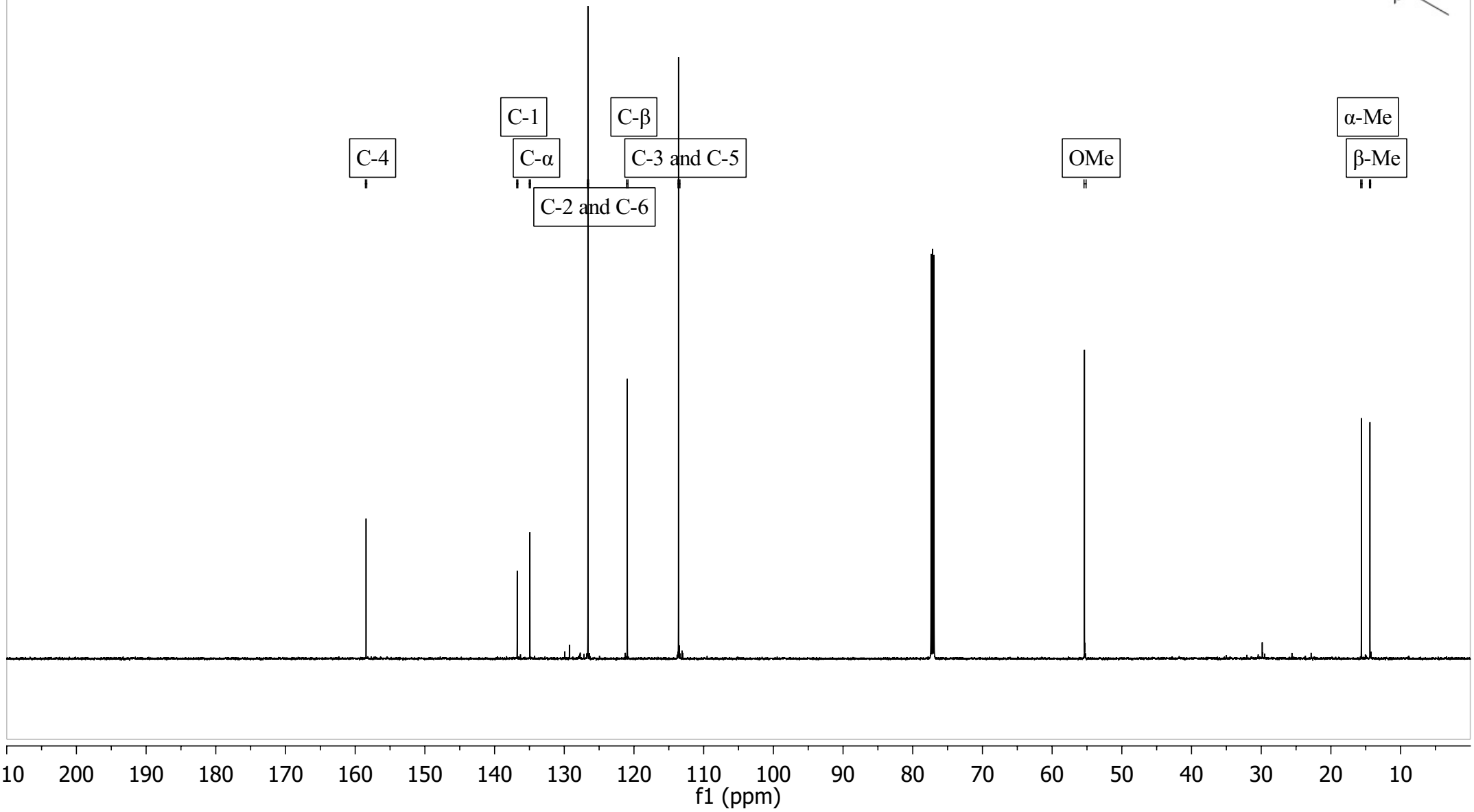


Plate 71c, HSQC (600 MHz/151 MHz, $CDCl_3$) : (*E*)-4-Methoxy-α,β-dimethylstyrene (**790**)

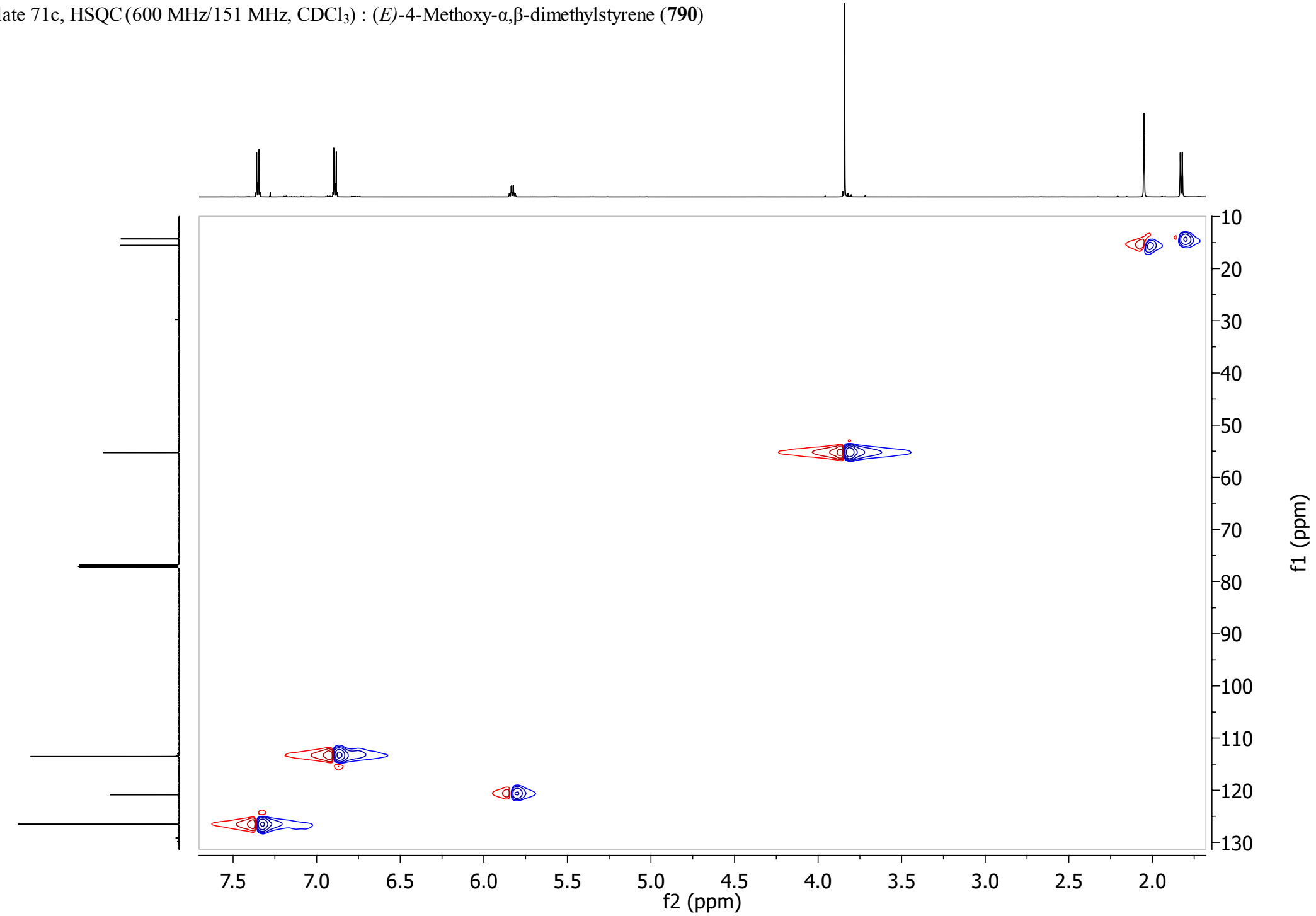


Plate 71d, HMBC (600 MHz/151 MHz, $CDCl_3$) : (*E*)-4-Methoxy-α,β-dimethylstyrene (**790**)

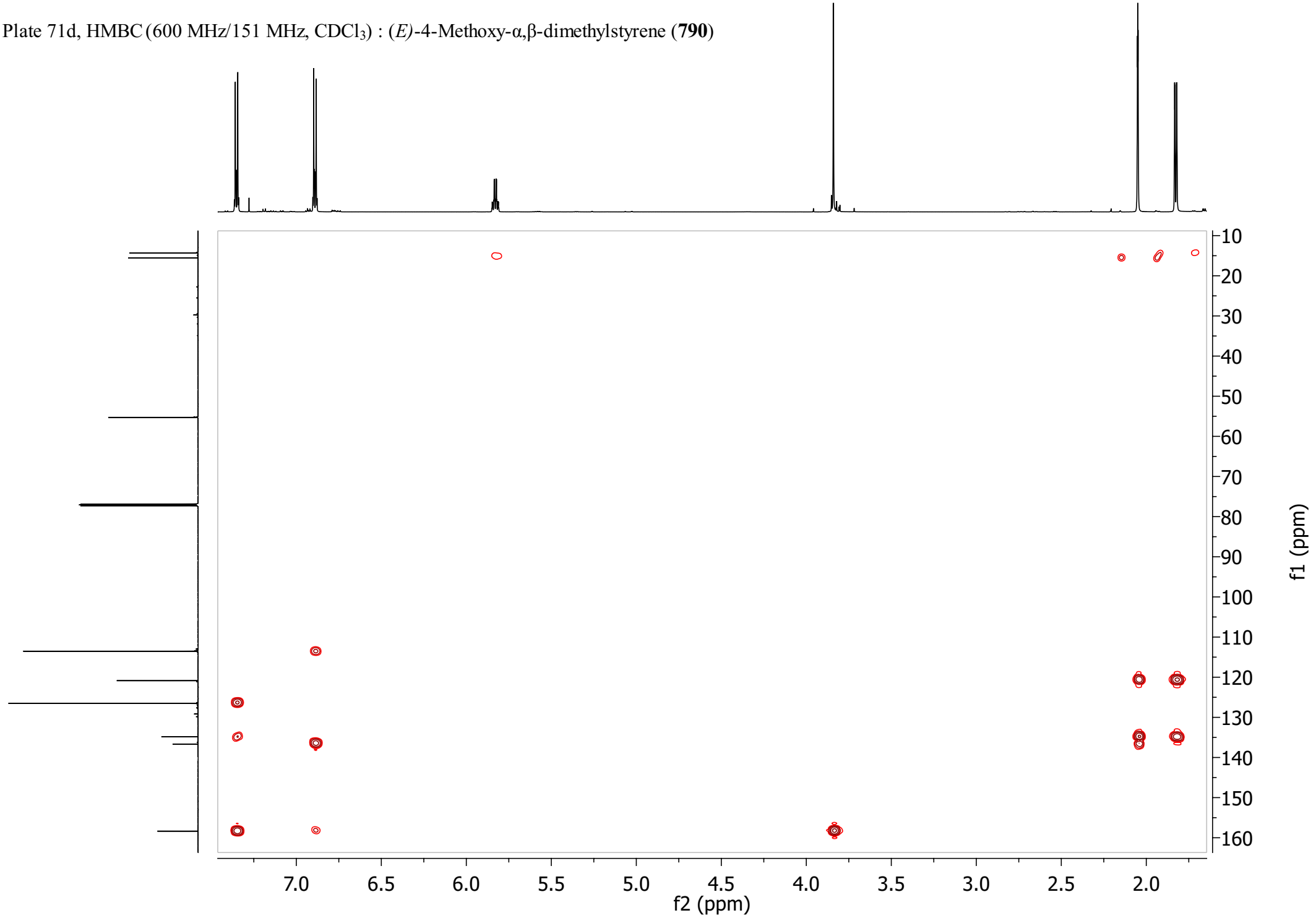


Plate 71e, DEPT (151 MHz, $CDCl_3$) : (*E)*-4-Methoxy-α,β-dimethylstyrene (**790**)

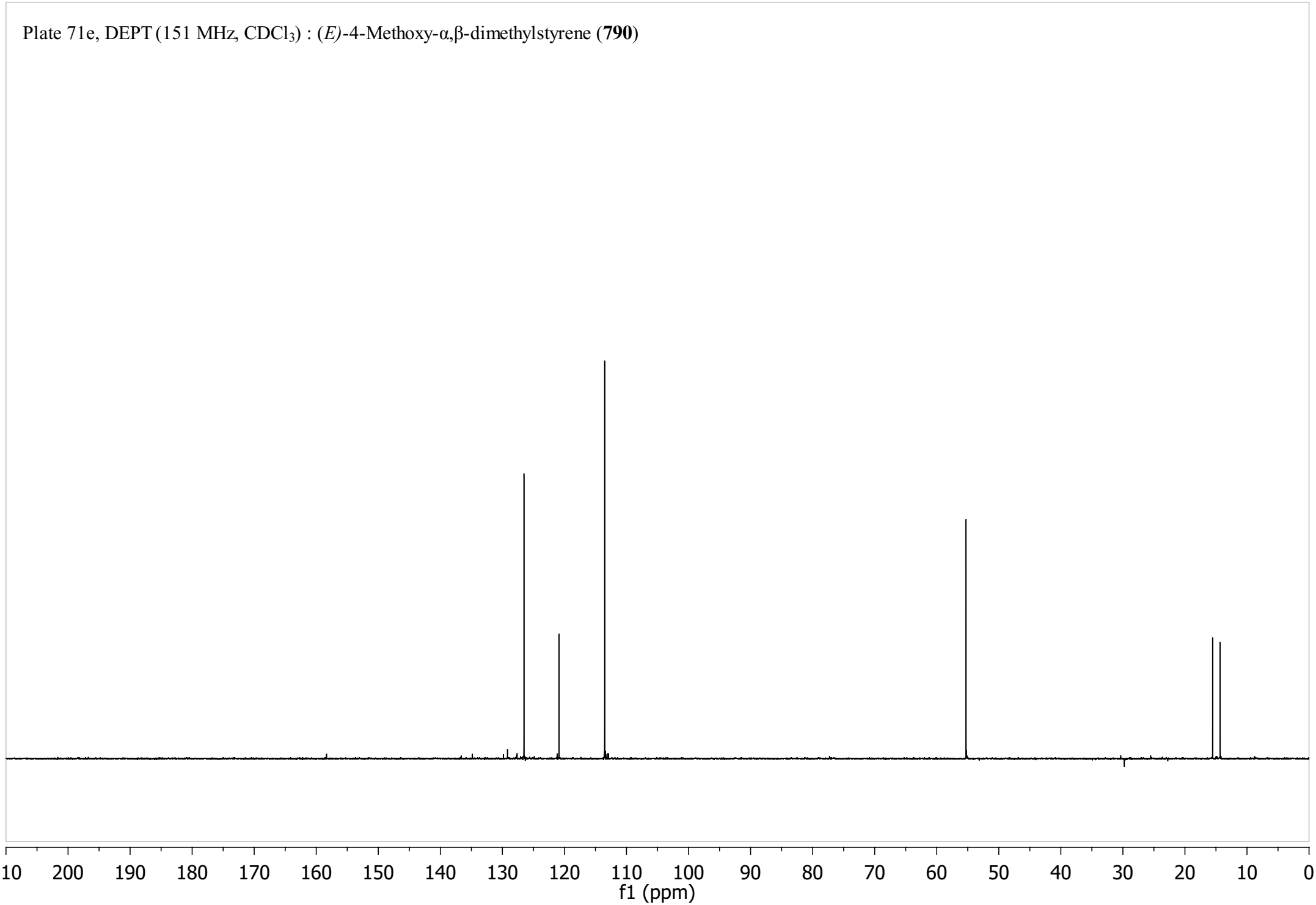
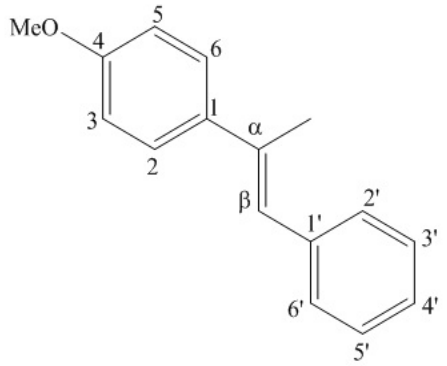
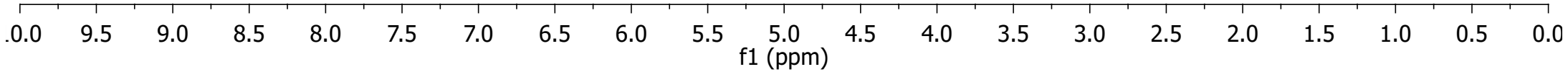


Plate 72a, ^{1}H NMR (600 MHz, Acetone-d_6) : (*E*)-4-Methoxy-α-methyl-β-phenylstyrene (**791**)

δ 7.52 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 7.40 – 7.36 (4H, m, Ar-H), 7.26 – 7.22 (1H, m, Ar-H), 6.94 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 6.85 – 6.83 (1H, m, H-β), 3.81 (3H, s, -OMe), 2.24 (3H, d, *J* = 1.3 Hz, -CH_3)





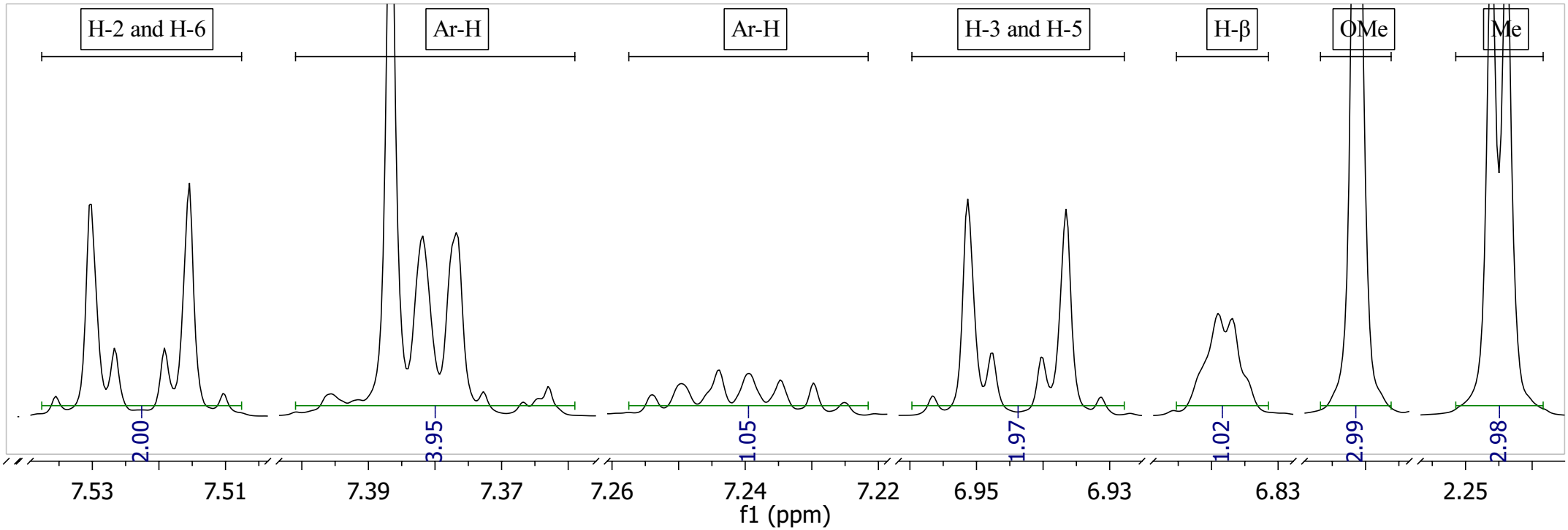
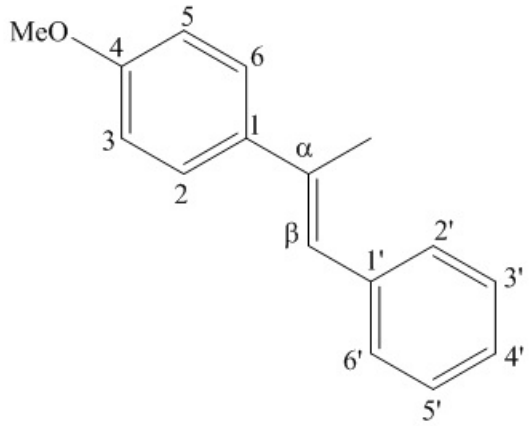


Plate 72b, ^{13}C NMR (151 MHz, Acetone-d_6) : (*E*)-4-Methoxy-α-methyl-β-phenylstyrene (**791**)

δ 160.22 (C-4), 139.55 (C-1'), 137.57 (C-α), 136.99 (C-1), 130.08 (Ar-C), 129.11 (Ar-C), 127.95 (C-2 and C-6), 127.23 (C-4'), 126.88 (C-β), 114.62 (C-3 and C-5), 55.60 (-O<u>Me</u>), 17.68 (-<u>C</u>H_3)



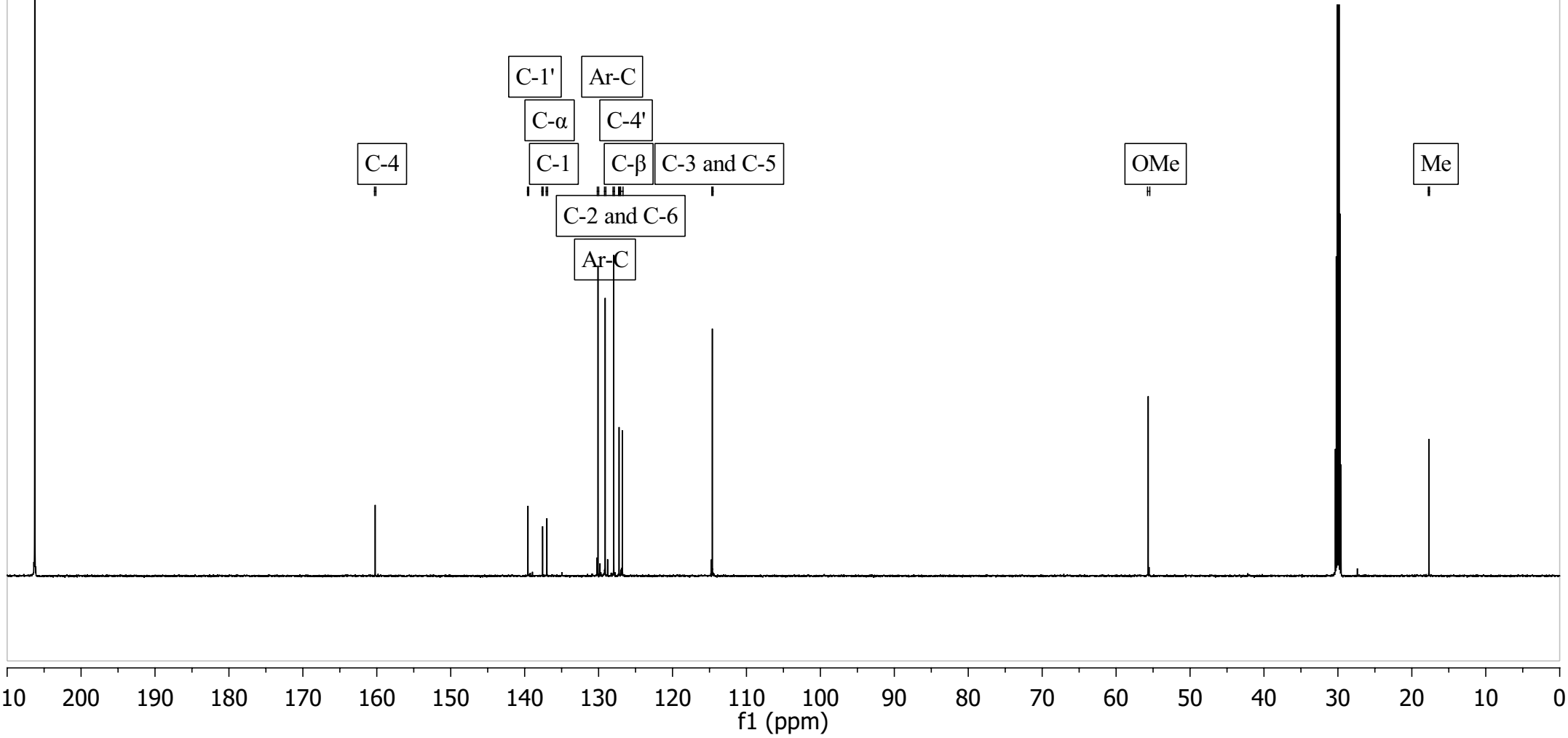


Plate 72c, HSQC (600 MHz/151 MHz, Acetone-d_6) : (*E*)-4-Methoxy-α-methyl-β-phenylstyrene (**791**)

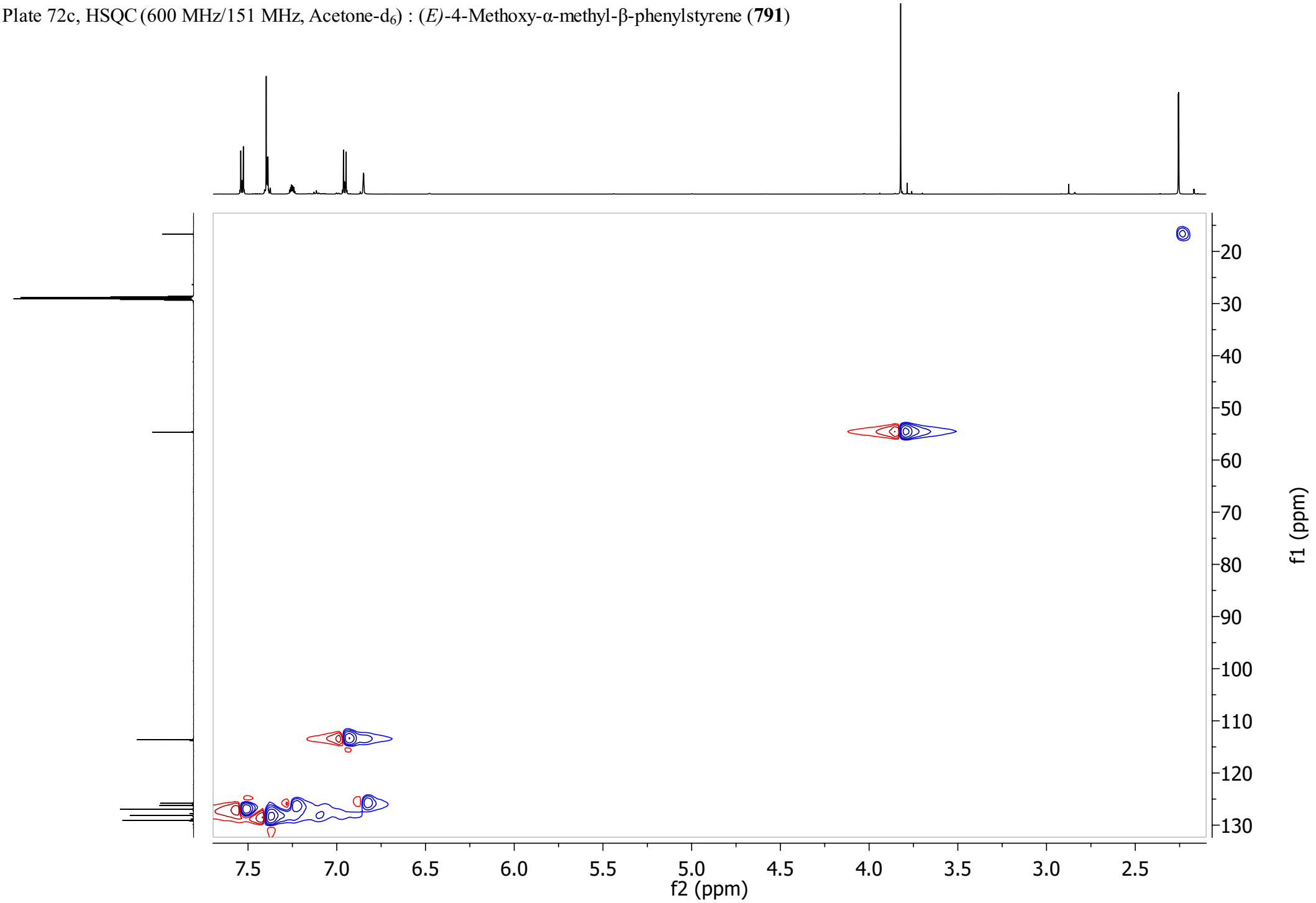


Plate 72d, HMBC (600 MHz/151 Mhz, Acetone-d_6) : (*E*)-4-Methoxy-α-methyl-β-phenylstyrene (**791**)

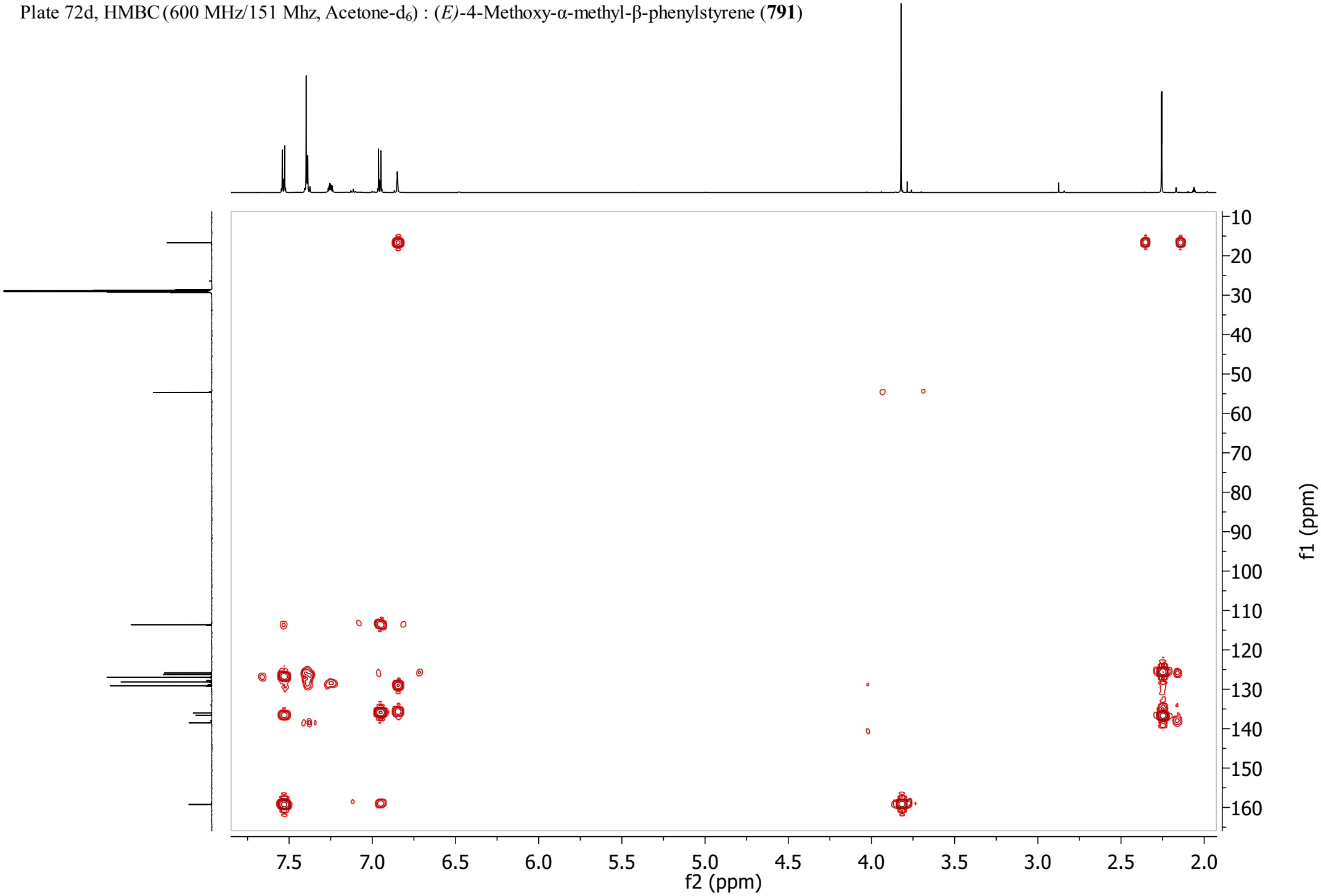


Plate 72e, DEPT (151 MHz, Acetone-d_6) : (*E*)-4-Methoxy-α-methyl-β-phenylstyrene (**791**)

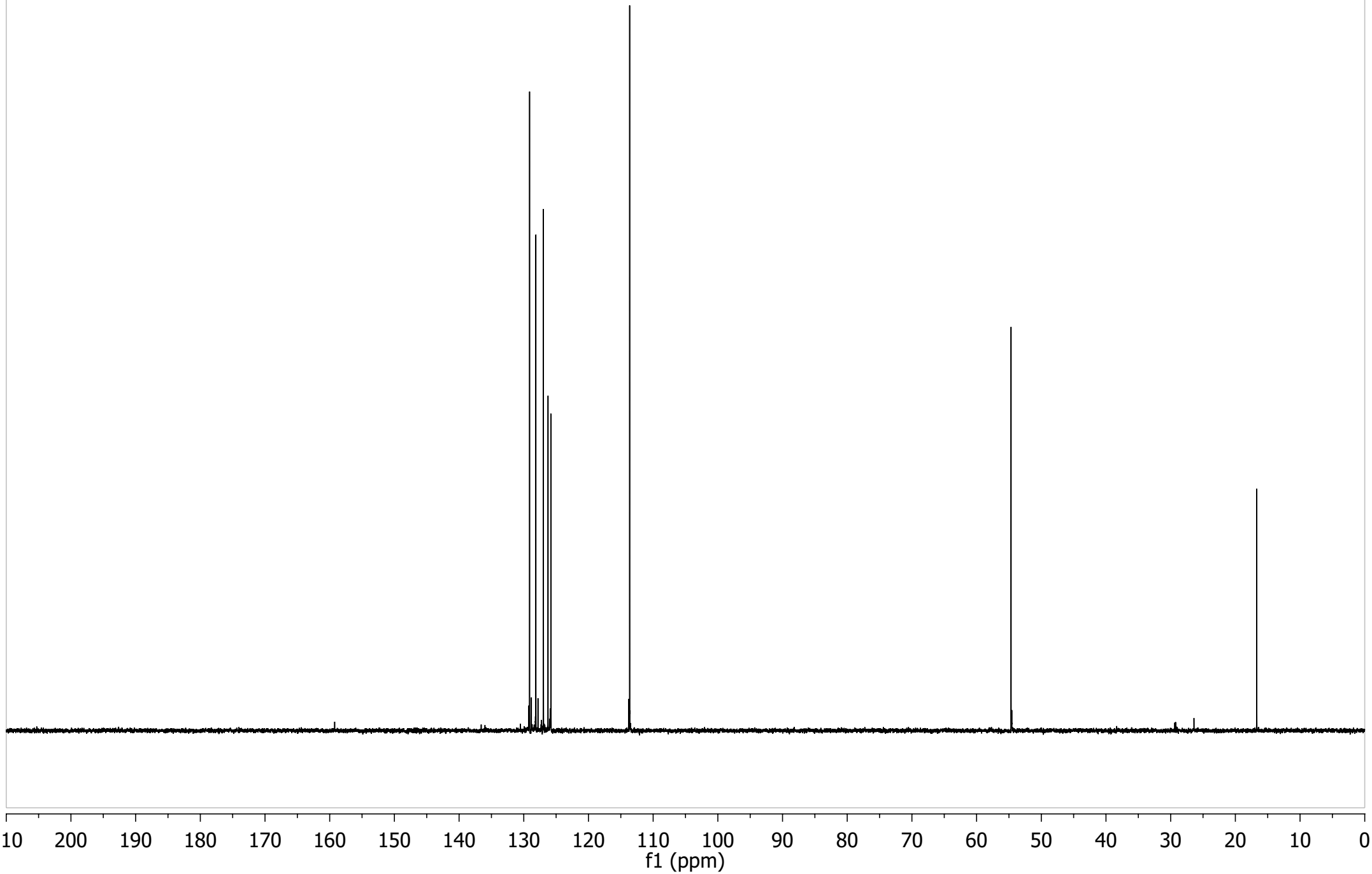
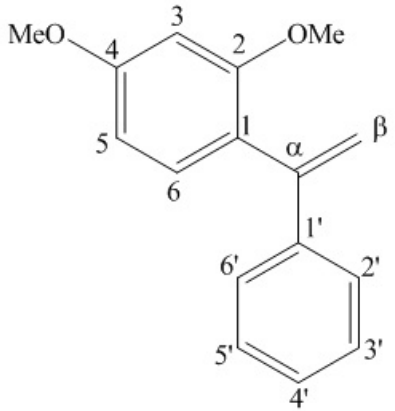
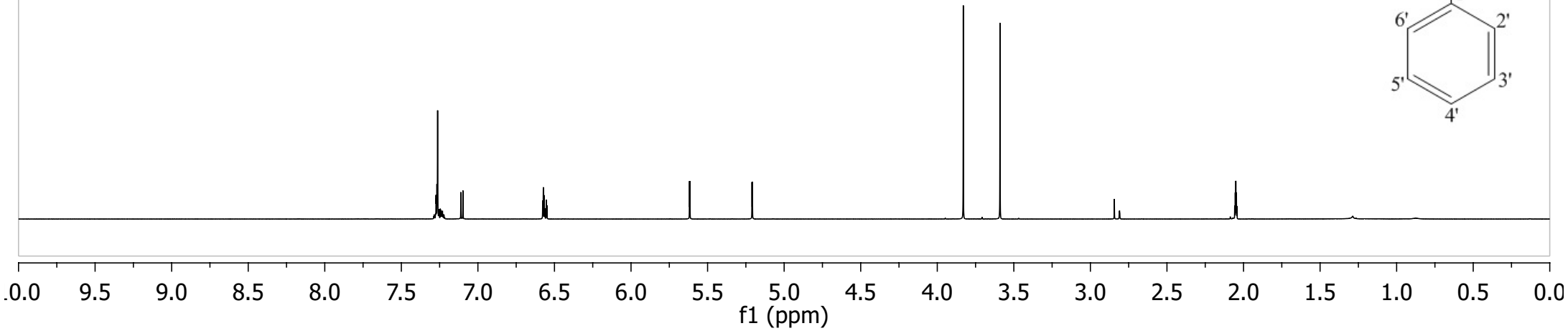


Plate 73a, ^{1}H NMR (600 MHz, Acetone-d_6) : 2,4-Dimethoxy-α-phenylstyrene (**792**)

δ 7.28 – 7.21 (5H, m, Ar-H), 7.10 (1H, d, *J* = 8.1 Hz, H-6), 6.57 (1H, d, *J* = 2.4 Hz, H-3), 6.56 (1H, dd, *J* = 8.1, 2.4 Hz, H-5), 5.62 (1H, d, *J* = 1.6 Hz, H-β), 5.21 (1H, d, *J* = 1.6 Hz, H-β), 3.83 (3H, s, -OMe), 3.59 (3H, s, -OMe)





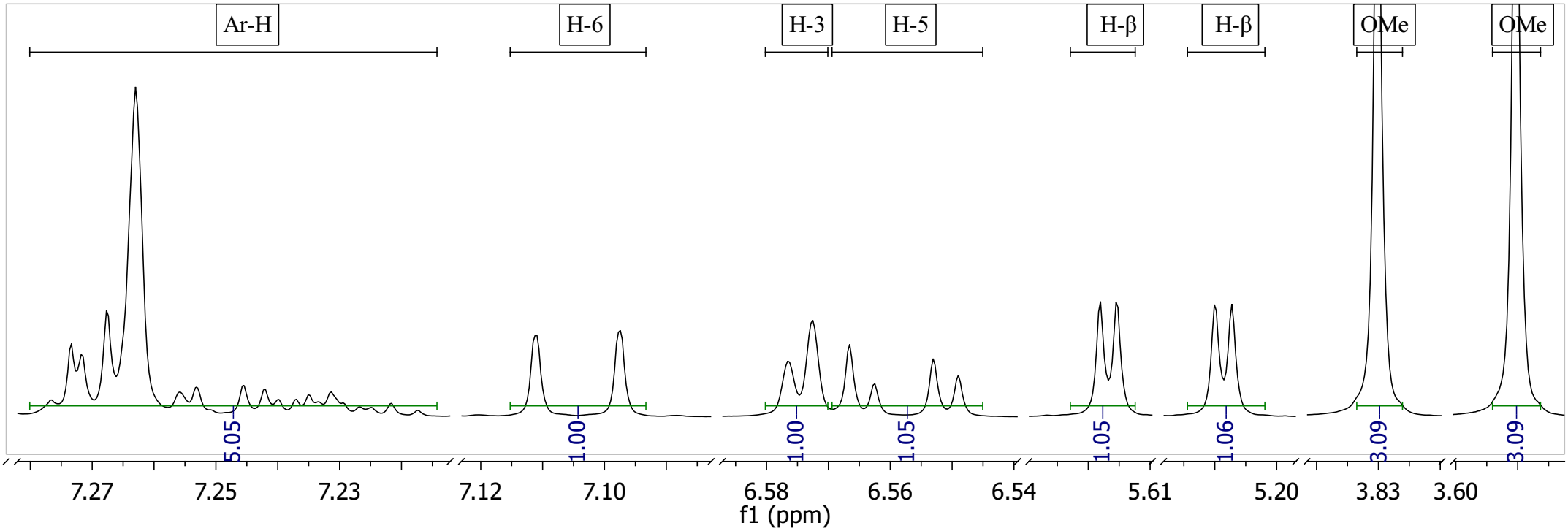
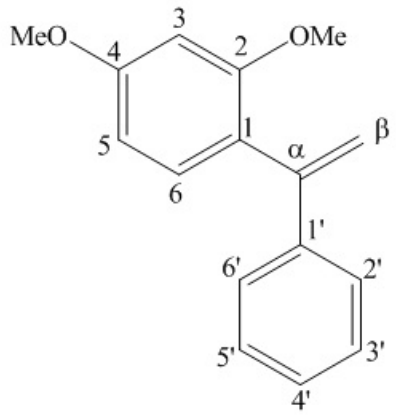


Plate 73b, ^{13}C NMR (151 MHz, Acetone-d_6) : 2,4-Dimethoxy-α-phenylstyrene (**792**)

δ 162.00 (C-4), 159.25 (C-2), 148.27 (C-α), 142.70 (C-1'), 132.39 (C-6), 128.89 (Ar-C), 128.03 (C-4'), 127.28 (Ar-C), 124.44 (C-1), 115.13 (C-β), 105.55 (C-5), 99.73 (C-3), 55.83 (-O<u>Me</u>), 55.75 (-O<u>Me</u>)



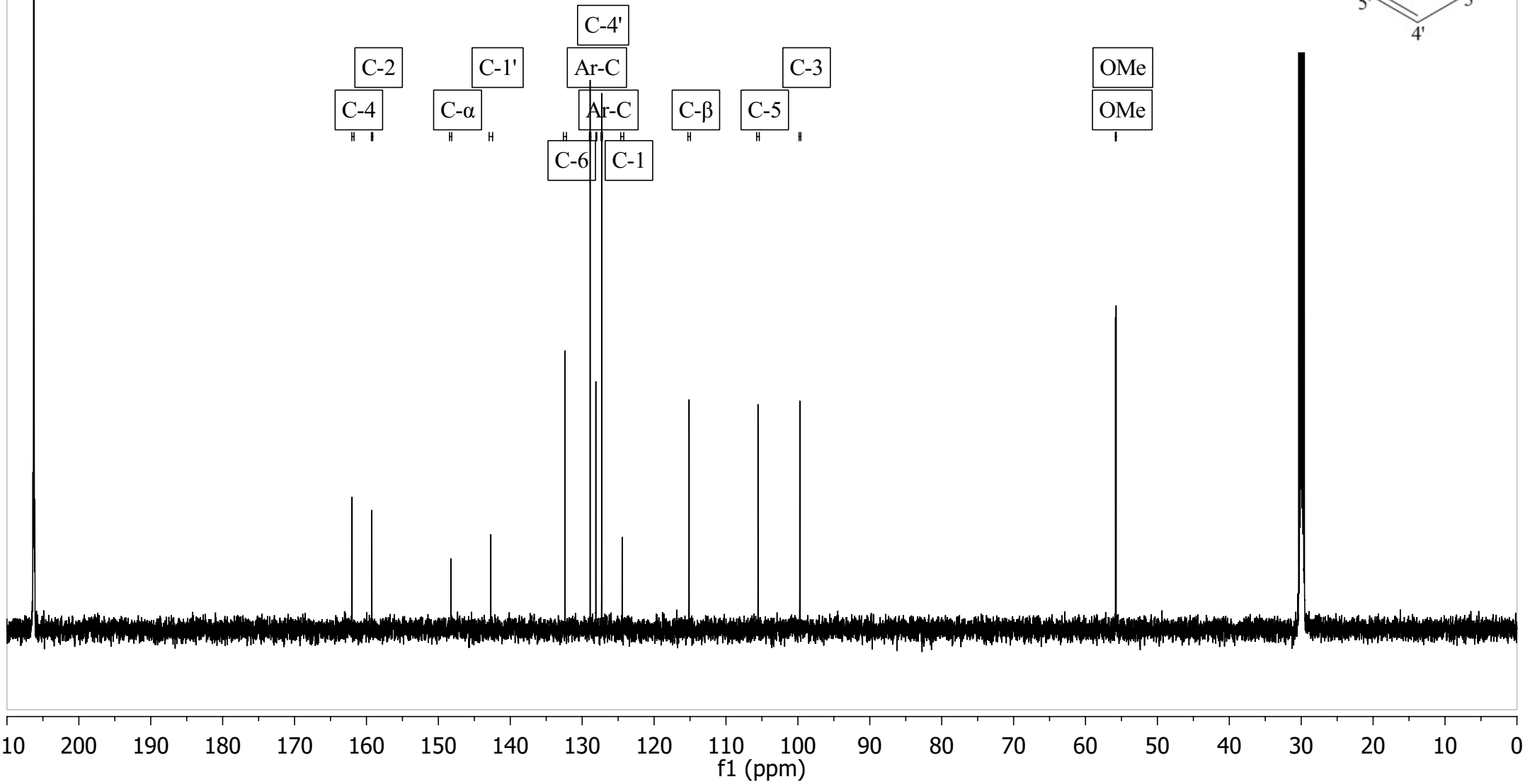


Plate 73c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 2,4-Dimethoxy-α-phenylstyrene (**792**)

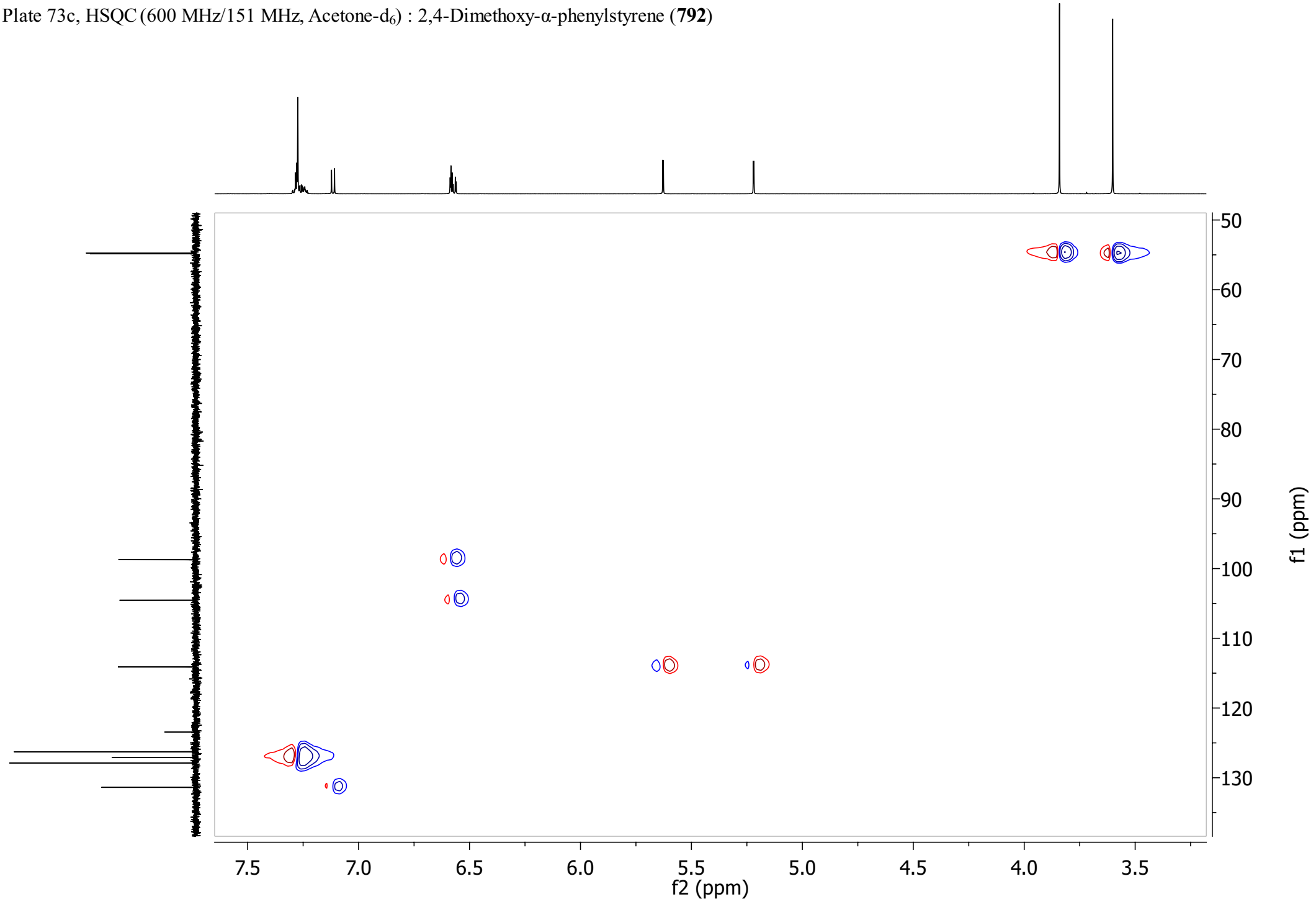


Plate 73d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 2,4-Dimethoxy-α-phenylstyrene (**792**)

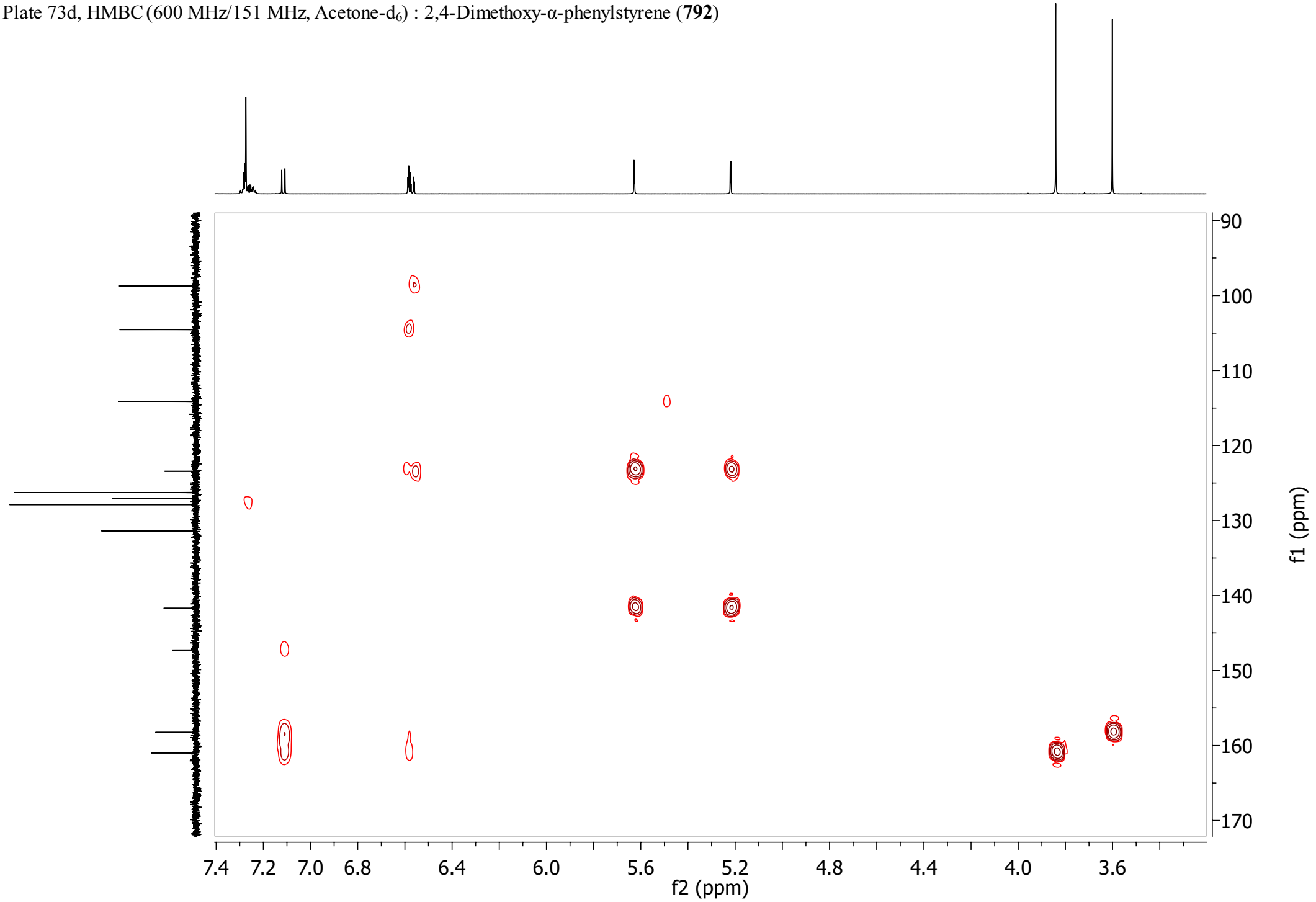


Plate 73e, DEPT (151 MHz, Acetone-d_6) : 2,4-Dimethoxy-α-phenylstyrene (**792**)

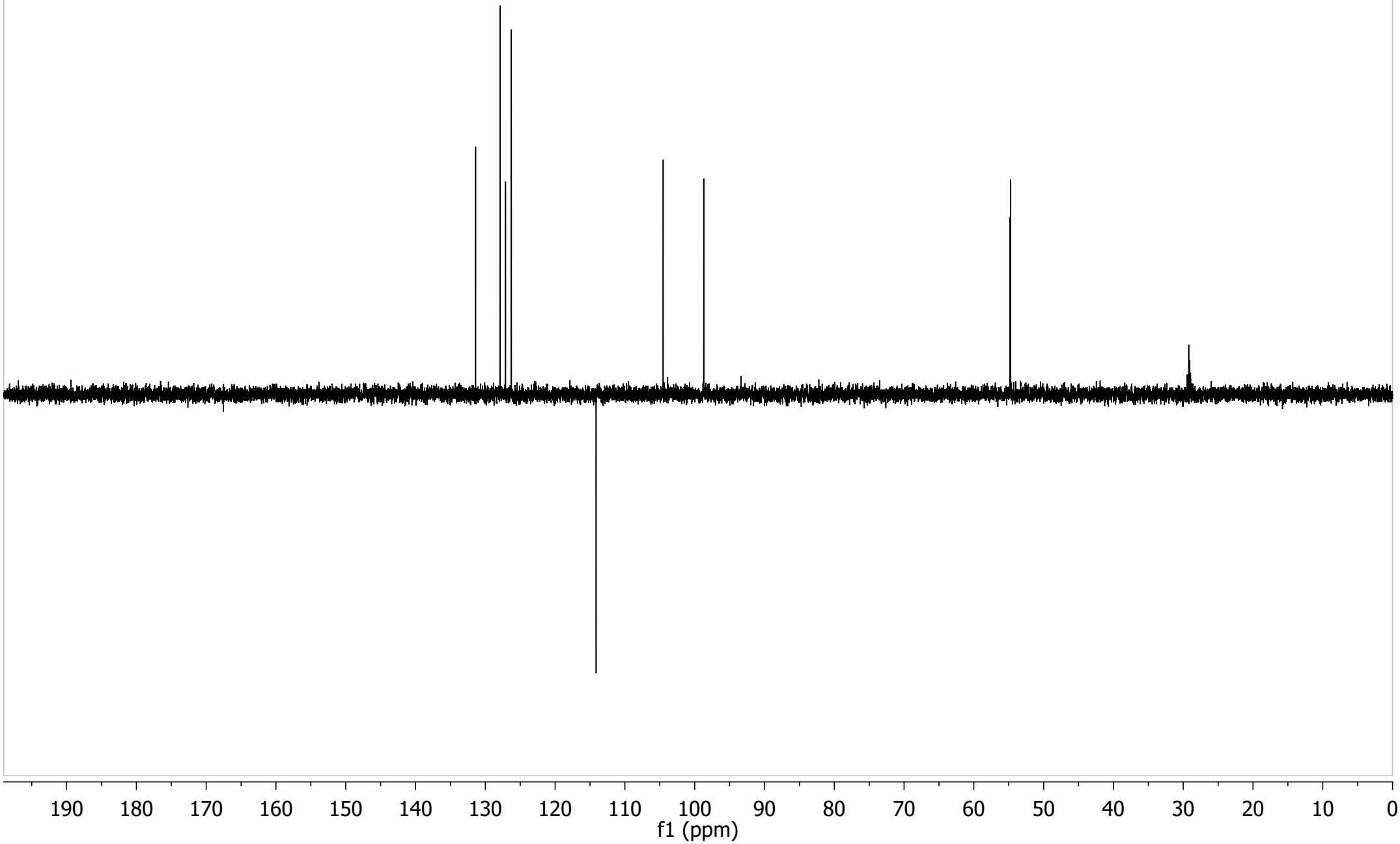
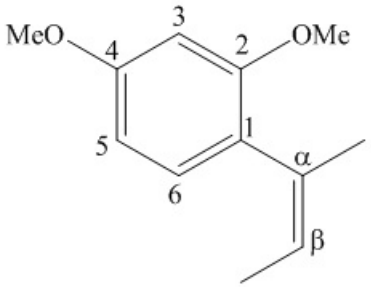
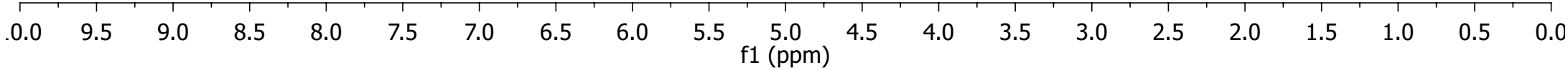


Plate 74a, ^{1}H NMR (600 MHz, $CDCl_3$) : (*Z*)-2,4-Dimethoxy-α,β-dimethylstyrene (**793**)

δ 7.06 (1H, d, *J* = 8.2 Hz, H-6), 6.48 (1H, d, *J* = 2.4 Hz, H-3), 6.46 (1H, dd, *J* = 8.2, 2.4 Hz, H-5), 5.55 (1H, qq, *J* = 6.7, 1.3 Hz, H-β), 3.83 (6H, s, -OMe), 2.00 – 1.98 (3H, m, α-CH_3), 1.80 – 1.78 (3H, m, β-CH_3)





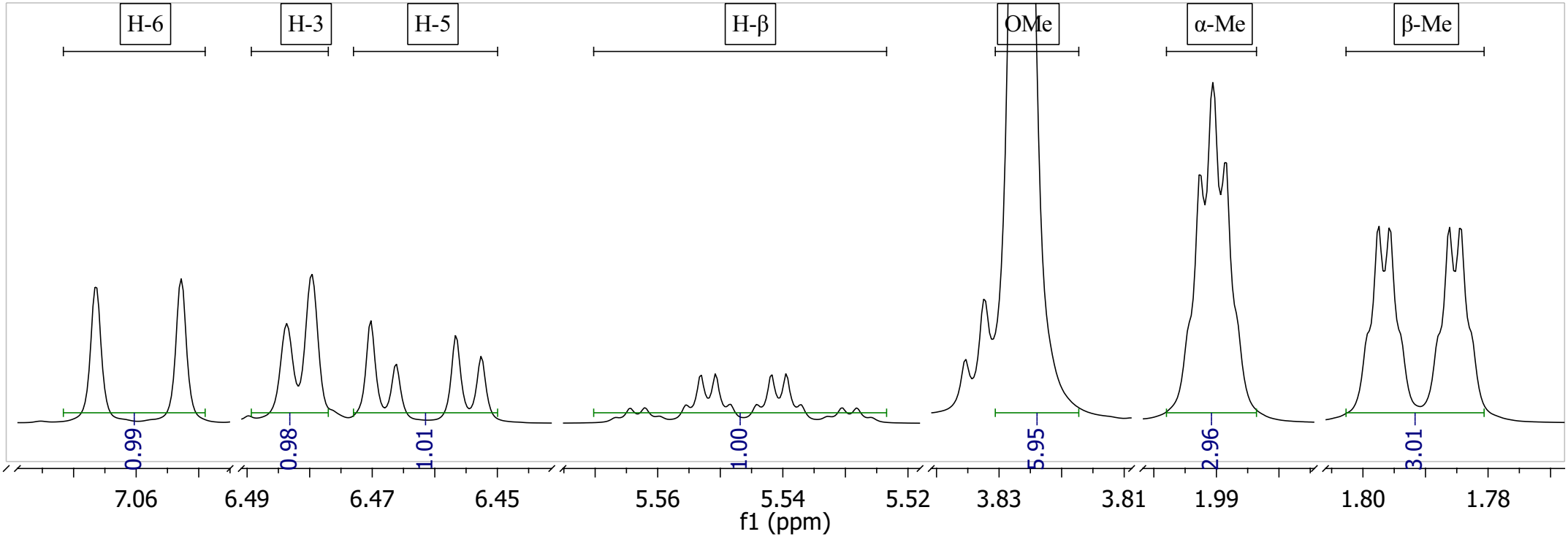
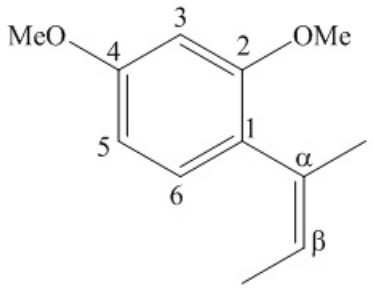


Plate 74b, ^{13}C NMR (151 MHz, $CDCl_3$) : (*Z*)-2,4-Dimethoxy-α,β-dimethylstyrene (**793**)

δ 159.75 (C-4), 157.60 (C-2), 135.32 (C-α), 129.98 (C-6), 128.06 (C-1), 123.46 (C-β), 103.92 (C-5), 98.67 (C-3), 55.44 (-O<u>Me</u>), 16.98 (α-<u>C</u>H_3), 14.03 (β-<u>C</u>H_3)



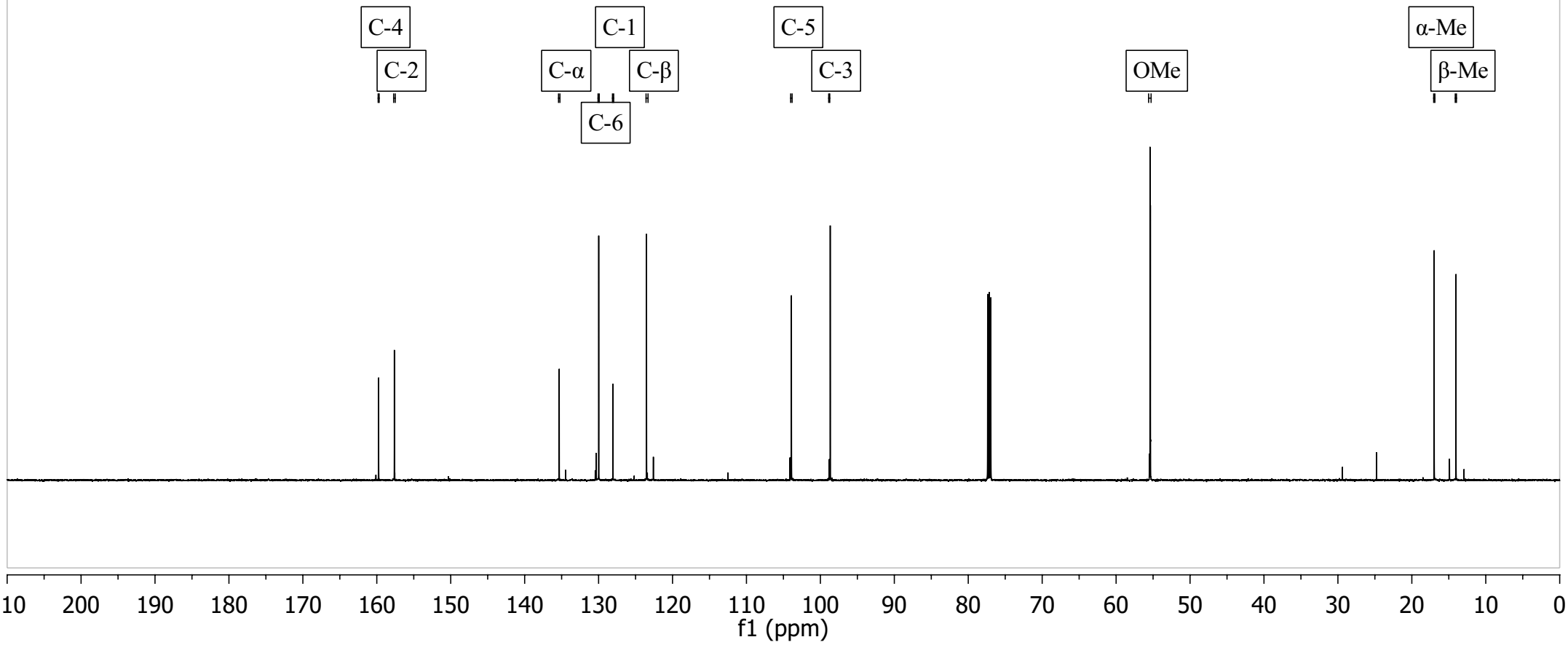


Plate 74c, HSQC (600 MHz/151 MHz, $CDCl_3$) : (*Z*)-2,4-Dimethoxy-α,β-dimethylstyrene (**793**)

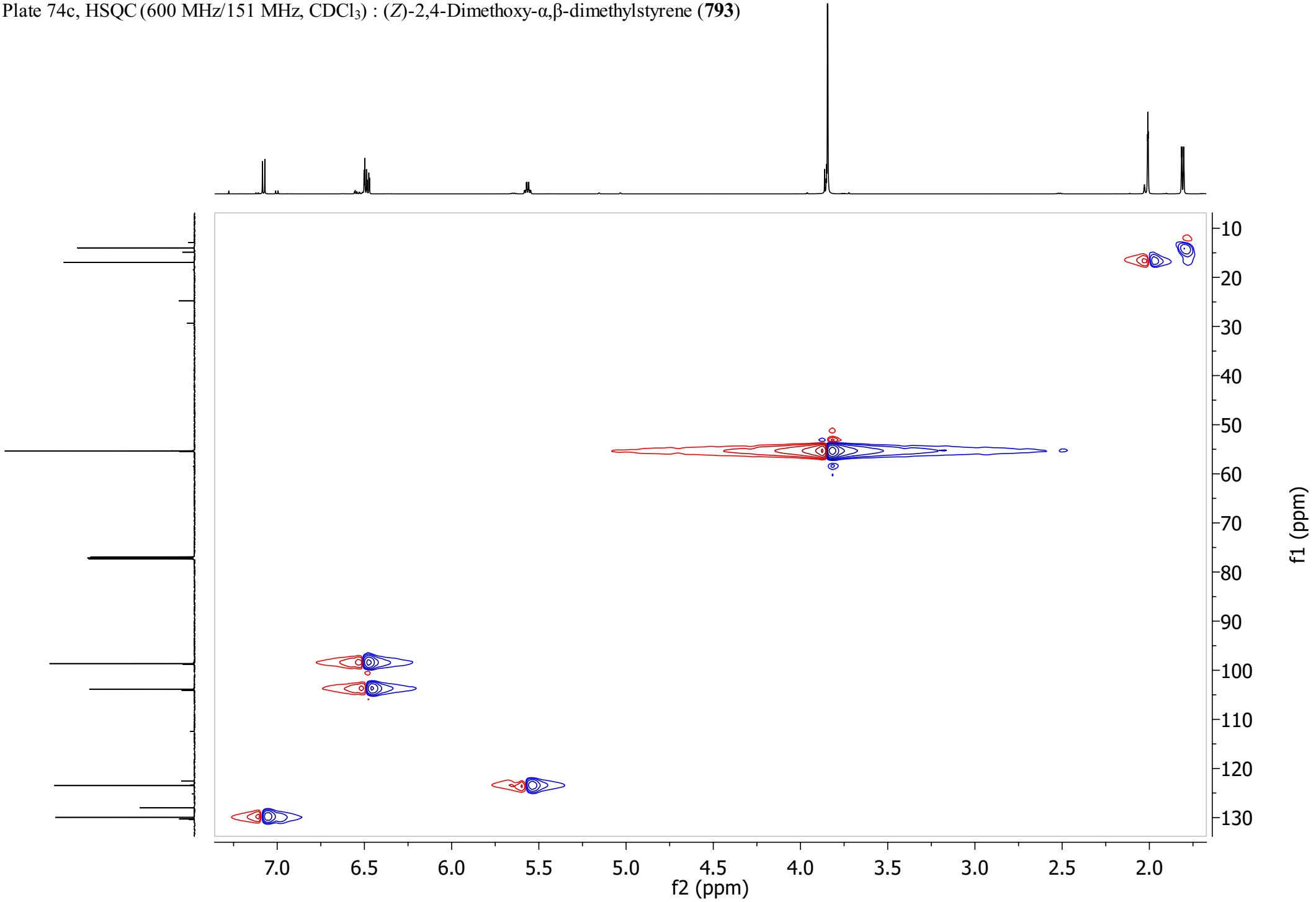


Plate 74d, HMBC (600 MHz/151 MHz, $CDCl_3$) : (*Z*)-2,4-Dimethoxy-α,β-dimethylstyrene (**793**)

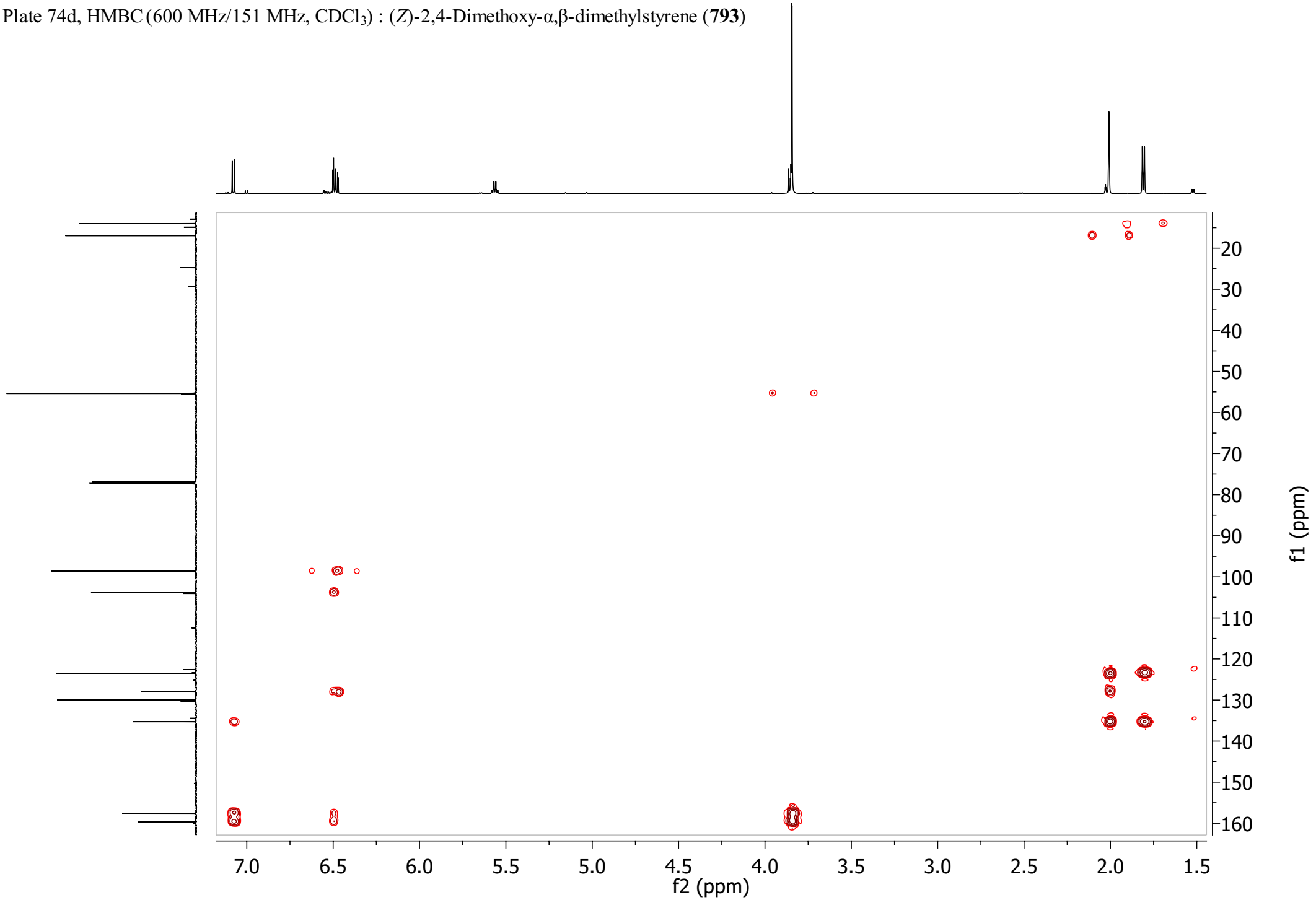


Plate 74e, DEPT (151 MHz, $CDCl_3$) : (*Z*)-2,4-Dimethoxy-α,β-dimethylstyrene (**793**)

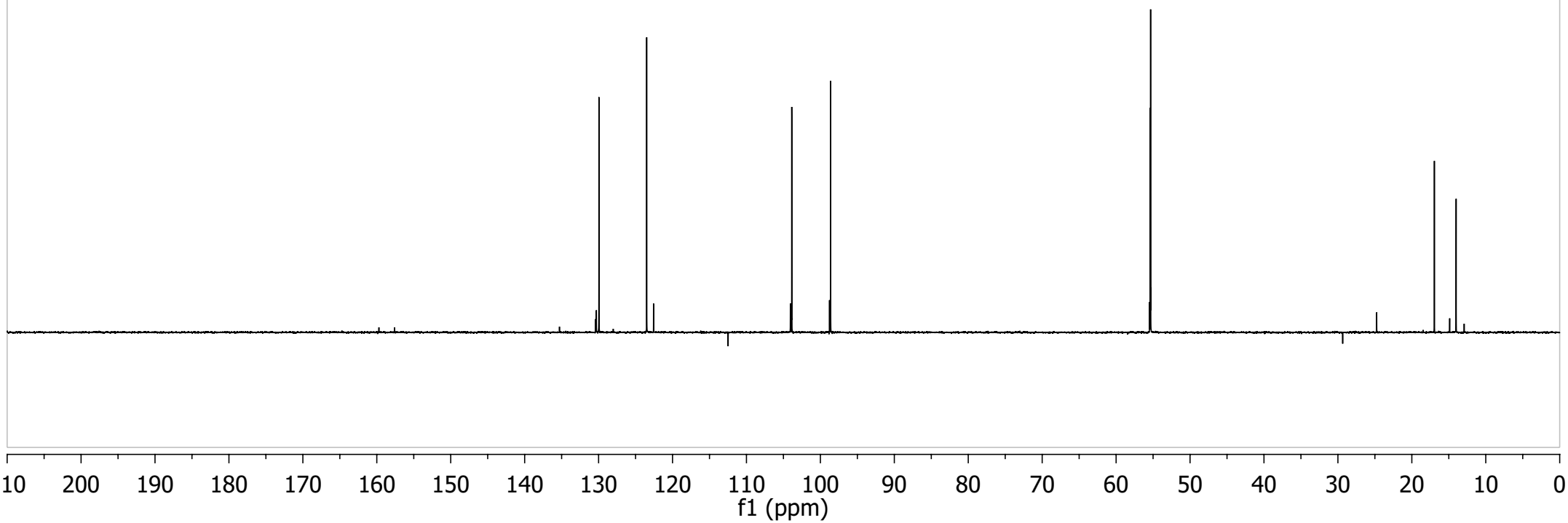
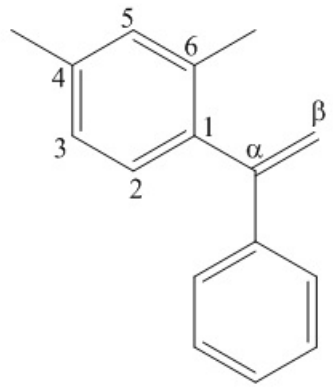
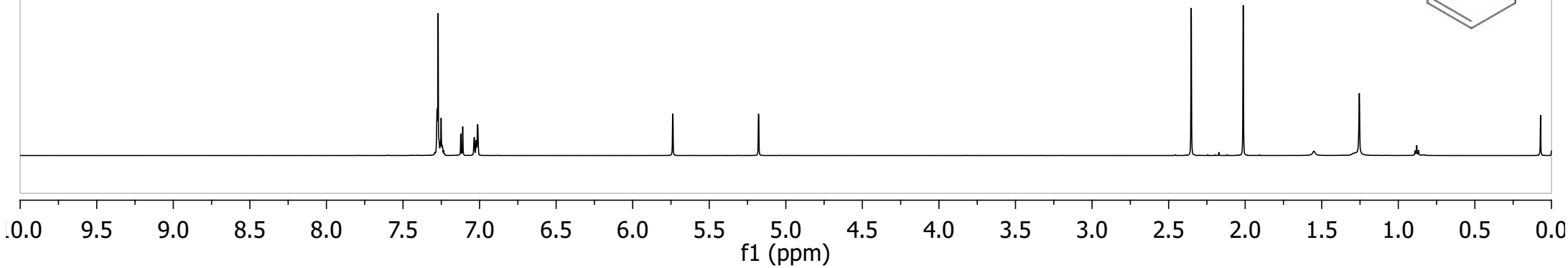


Plate 75a, ^{1}H NMR (600 MHz, $CDCl_3$) : 2,4-Dimethyl-α-phenylstyrene (**794**)

δ 7.28 – 7.24 (5H, m, Ar-H), 7.12 (1H, d, *J* = 7.6 Hz, H-2), 7.04 – 7.00 (2H, m, H-3 and H-5), 5.75 – 5.73 (1H, m, H-β), 5.19 – 5.17 (1H, m, H-β), 2.35 (3H, s, -C<u>H</u>$_3$), 2.01 (3H, s, -C<u>H</u>$_3$)





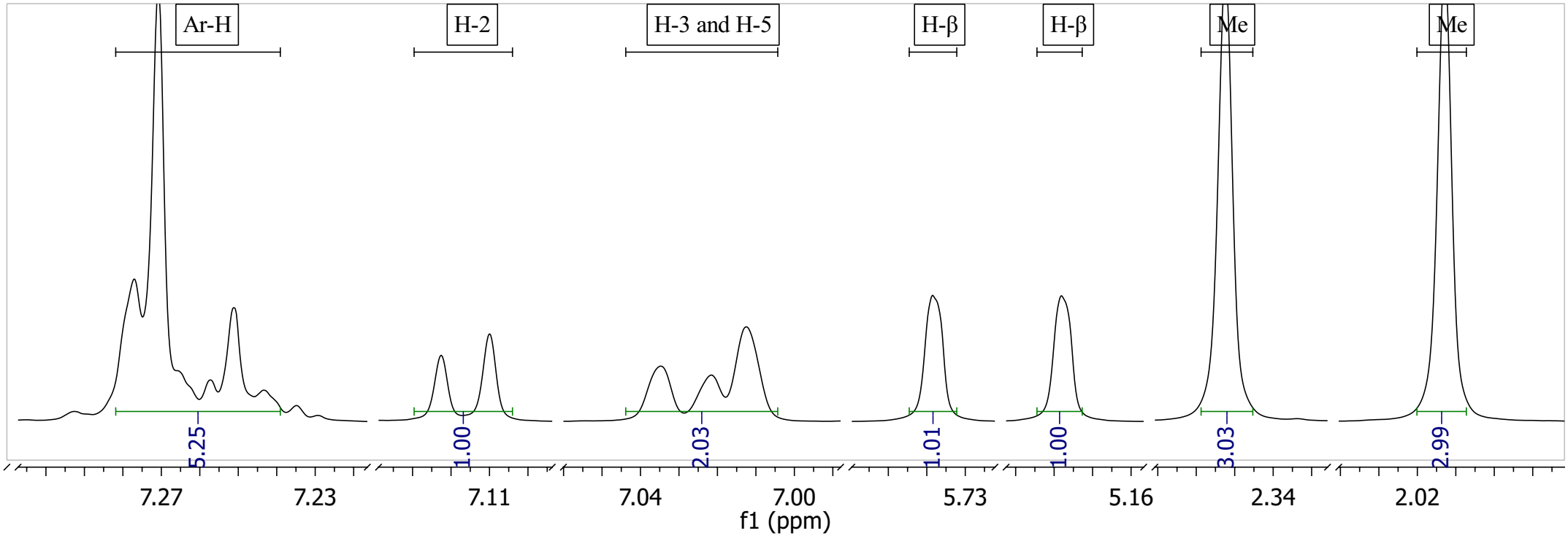
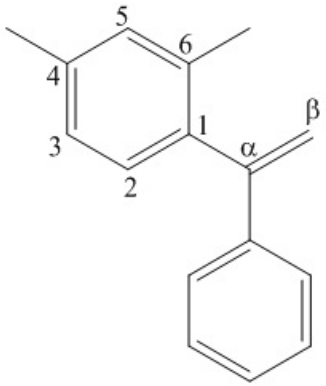


Plate 75b, ^{13}C NMR (151 MHz, $CDCl_3$) : 2,4-Dimethyl-α-phenylstyrene (**794**)

δ 149.52 (4°-C), 140.97 (4°-C), 138.89 (4°-C), 137.28 (C-4/6), 136.10 (C-4/6), 131.03 (C-3/5), 130.12 (C-2), 128.43 (Ar-C), 127.63 (Ar-C), 126.65 (Ar-C), 126.46 (C-3/5), 114.93 (C-β), 21.26 (-$\underline{C}H_3$), 20.20 (-$\underline{C}H_3$)



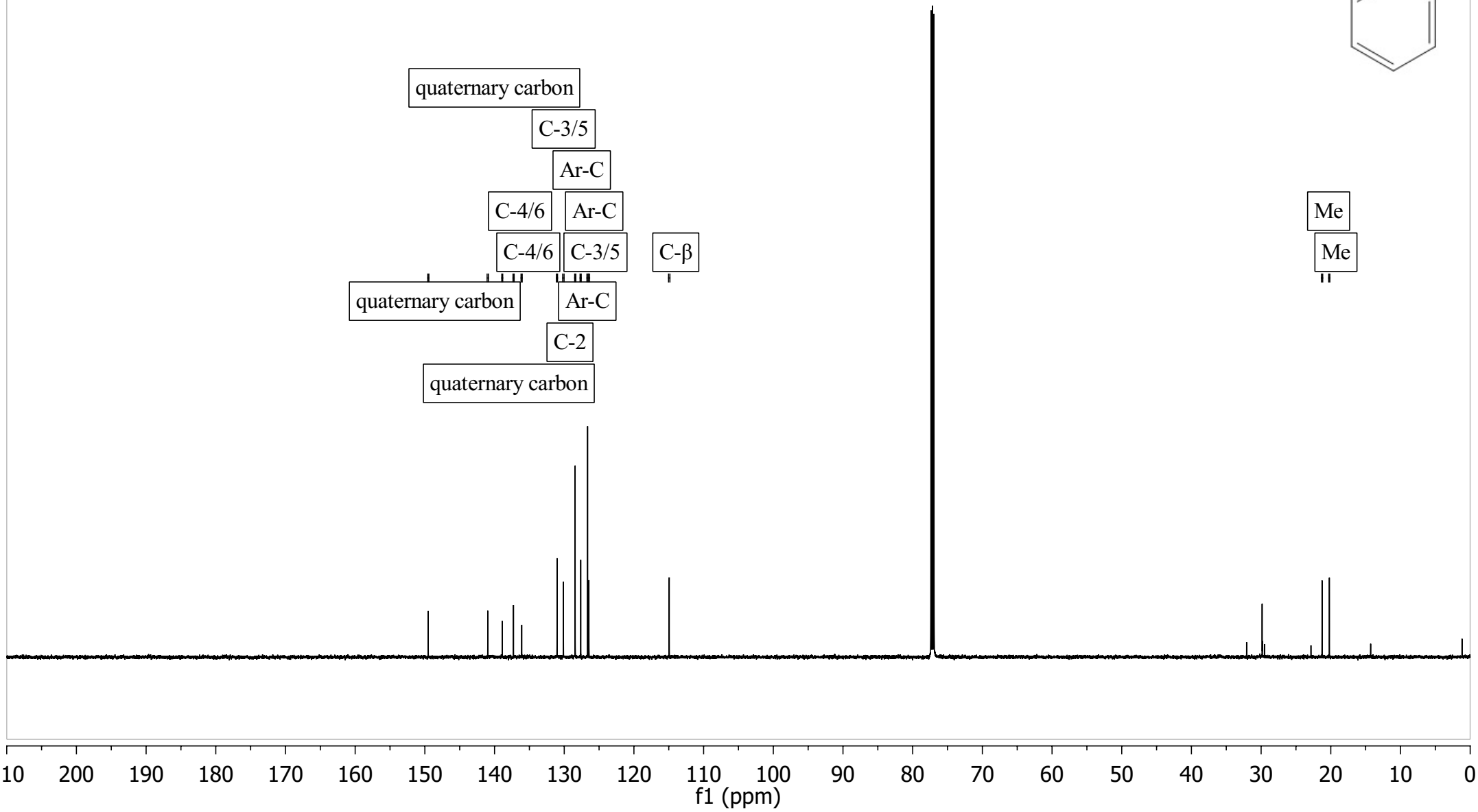


Plate 75c, HSQC (600/151 MHz, $CDCl_3$) : 2,4-Dimethyl-α-phenylstyrene (**794**)

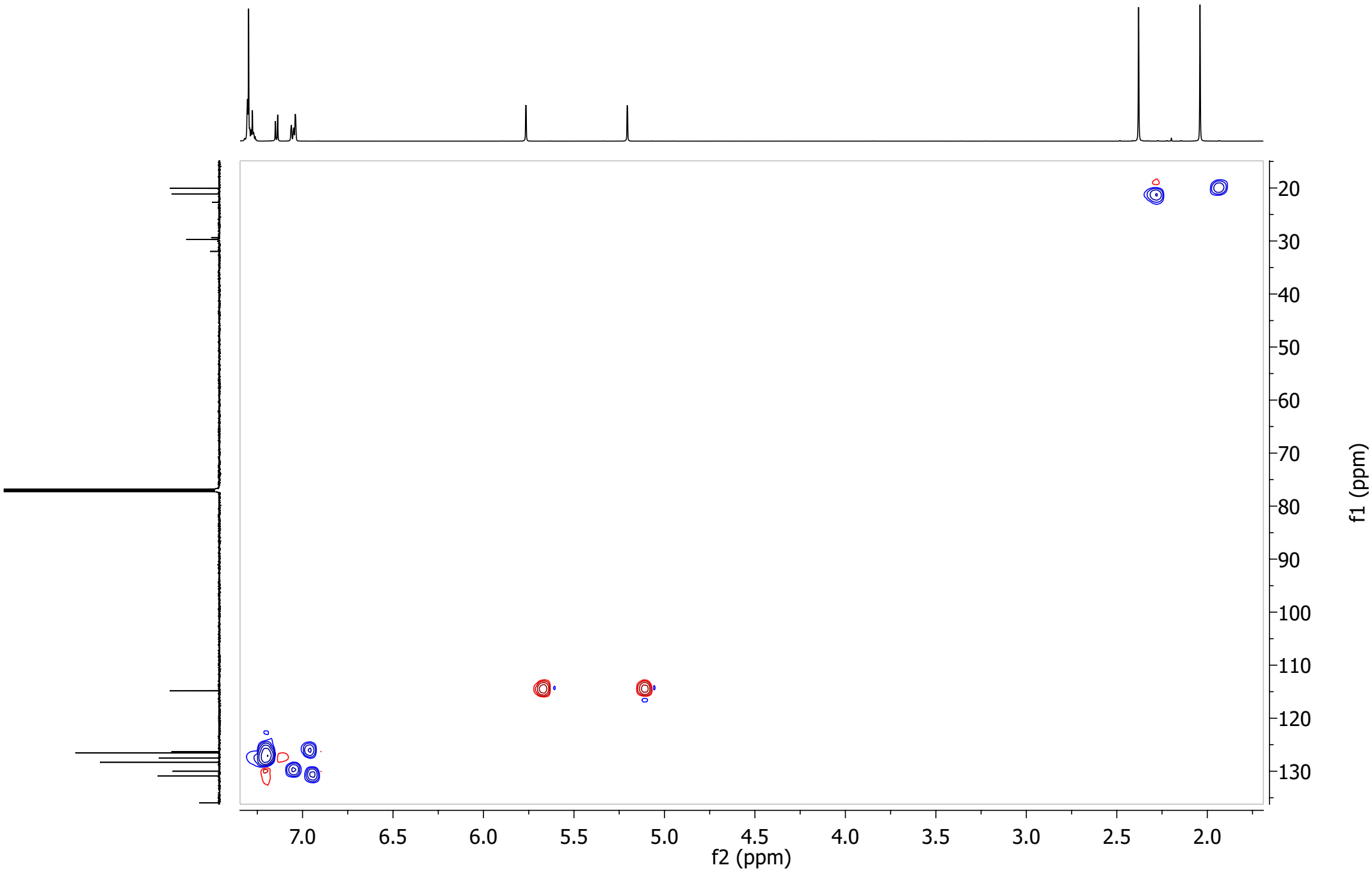


Plate 75d, HMBC (600/151 MHz, $CDCl_3$) : 2,4-Dimethyl-α-phenylstyrene (**794**)

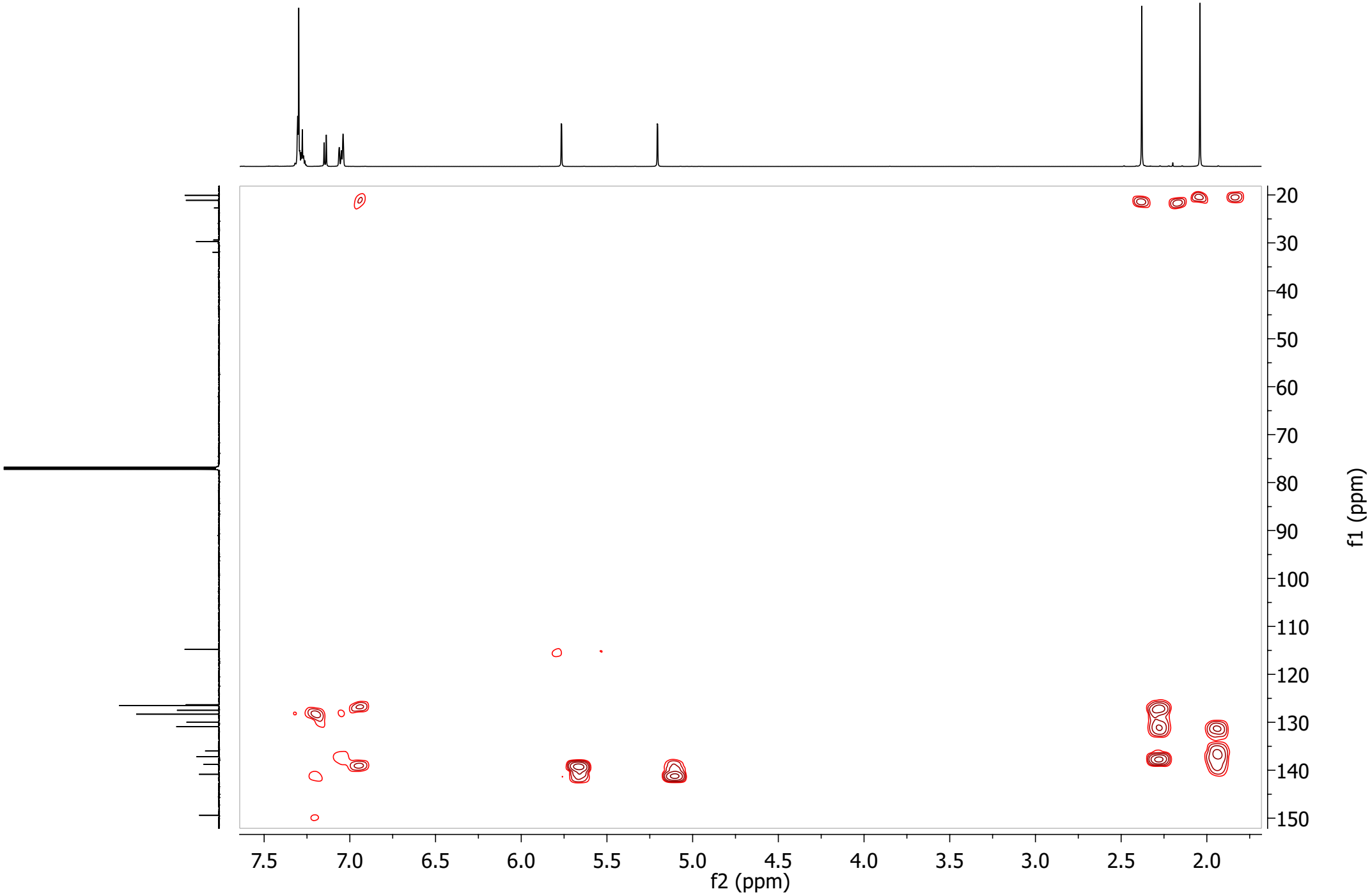


Plate 75e, DEPT (151 MHz, $CDCl_3$) : 2,4-Dimethyl-α-phenylstyrene (**794**)

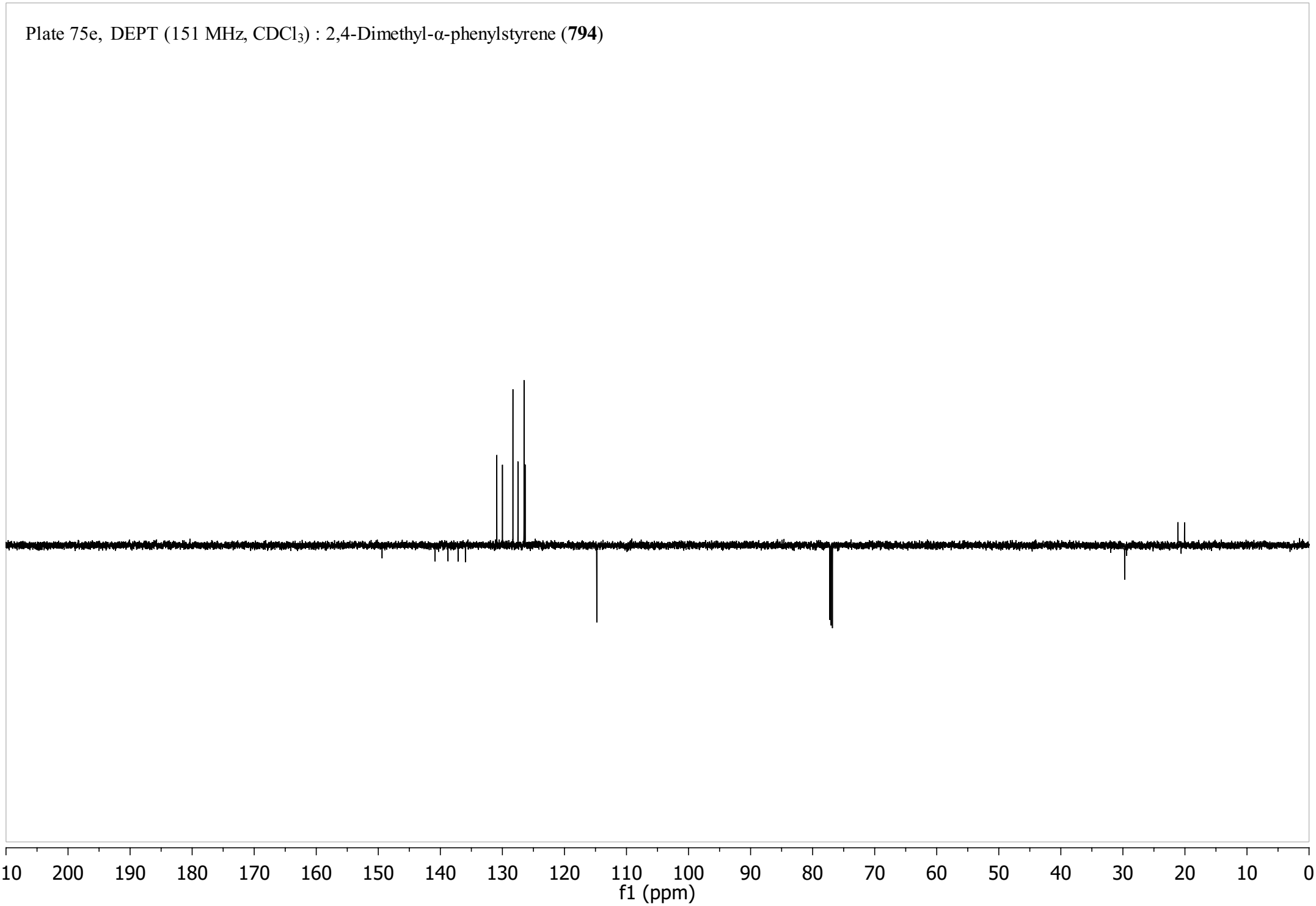
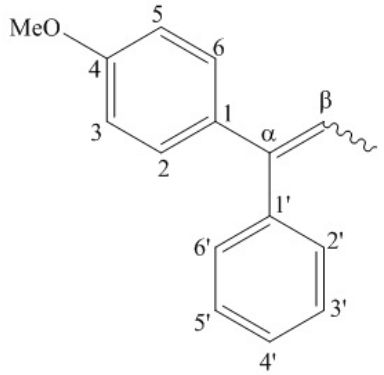
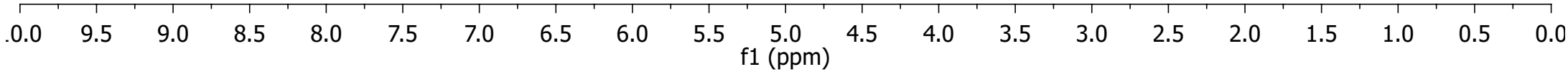


Plate 76a, ^{1}H NMR (600 MHz, Acetone-d_6) : 4-Methoxy-α-phenyl-β-methylstyrene (**804**)

δ 7.42 – 7.38 (2H, m, H-3' and H-5' (*E*)), 7.34 – 7.29 (1H, m, H-4' (*E*)), 7.28 – 7.24 (2H, m, Ar-H (*Z*)), 7.23 – 7.19 (3H, m, Ar-H (*Z*)), 7.17 – 7.15 (2H, m, H-2' and H-6' (*E*)), 7.12 (2H, d, *J* = 8.8 Hz, H-2 and H-6 (*E*)), 7.09 (2H, d, *J* = 8.7 Hz, H-2 and H-6 (*Z*)), 6.96 (2H, d, *J* = 8.8 Hz, H-3 and H-5 (*Z*)), 6.83 (2H, d, *J* = 8.7 Hz, H-3 and H-5 (*E*)), 6.14 (1H, q, *J* = 7.0 Hz, H-β (*Z*)), 6.10 (1H, q, *J* = 7.0 Hz, H-β (*E*)), 3.81 (3H, s, -OMe (*Z*)), 3.76 (3H, s, -OMe (*E*)), 1.74 (3H, d, *J* = 7.0 Hz, -CH_3 (*Z*)), 1.70 (3H, d, *J* = 7.0 Hz, -CH_3 (*E*))





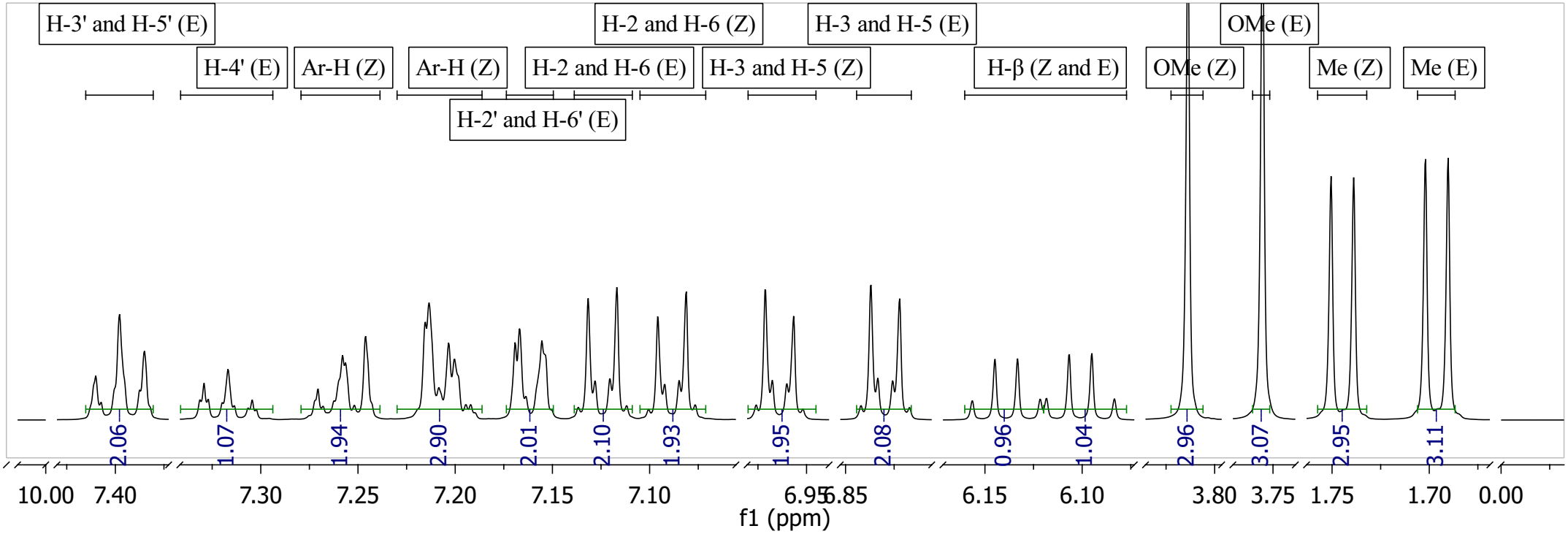
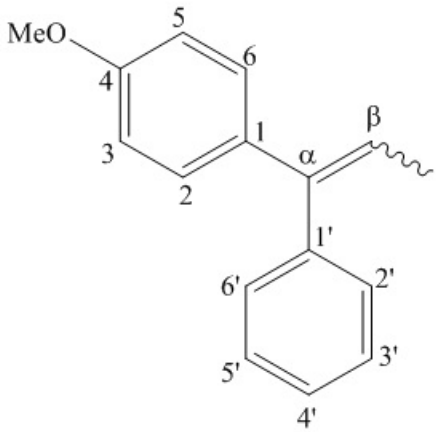


Plate 76b, ^{13}C NMR (151 MHz, Acetone-d_6) : 4-Methoxy-α-phenyl-β-methylstyrene (**804**)

δ 159.87 (C-4 (*E*/*Z*)), 159.77 (C-4 (*E*/*Z*)), 144.33 (C-1' (*Z*)), 143.21 (C-α (*E*/*Z*)), 143.05 (C-α (*E*/*Z*)), 141.30 (C-1' (*E*)), 136.40 (C-1 (*E*)), 133.00 (C-1 (*Z*)), 132.01 (Ar-C), 130.82 (Ar-C), 129.19 (Ar-C), 129.08 (Ar-C), 129.02 (Ar-C), 128.10 (Ar-C), 127.84 (Ar-C), 127.67 (Ar-C), 124.32 (C-β (*E*/*Z*)), 122.74 (C-β (*E*/*Z*)), 114.58 (C-3 and C-5 (*E*/*Z*)), 114.43 (C-3 and C-5 (*E*/*Z*)), 55.62 (-O<u>Me</u> (*E* and *Z*)), 16.07 (-<u>C</u>H$_3$ (*E*/*Z*)), 15.92 (-<u>C</u>H$_3$ (*E*/*Z*))



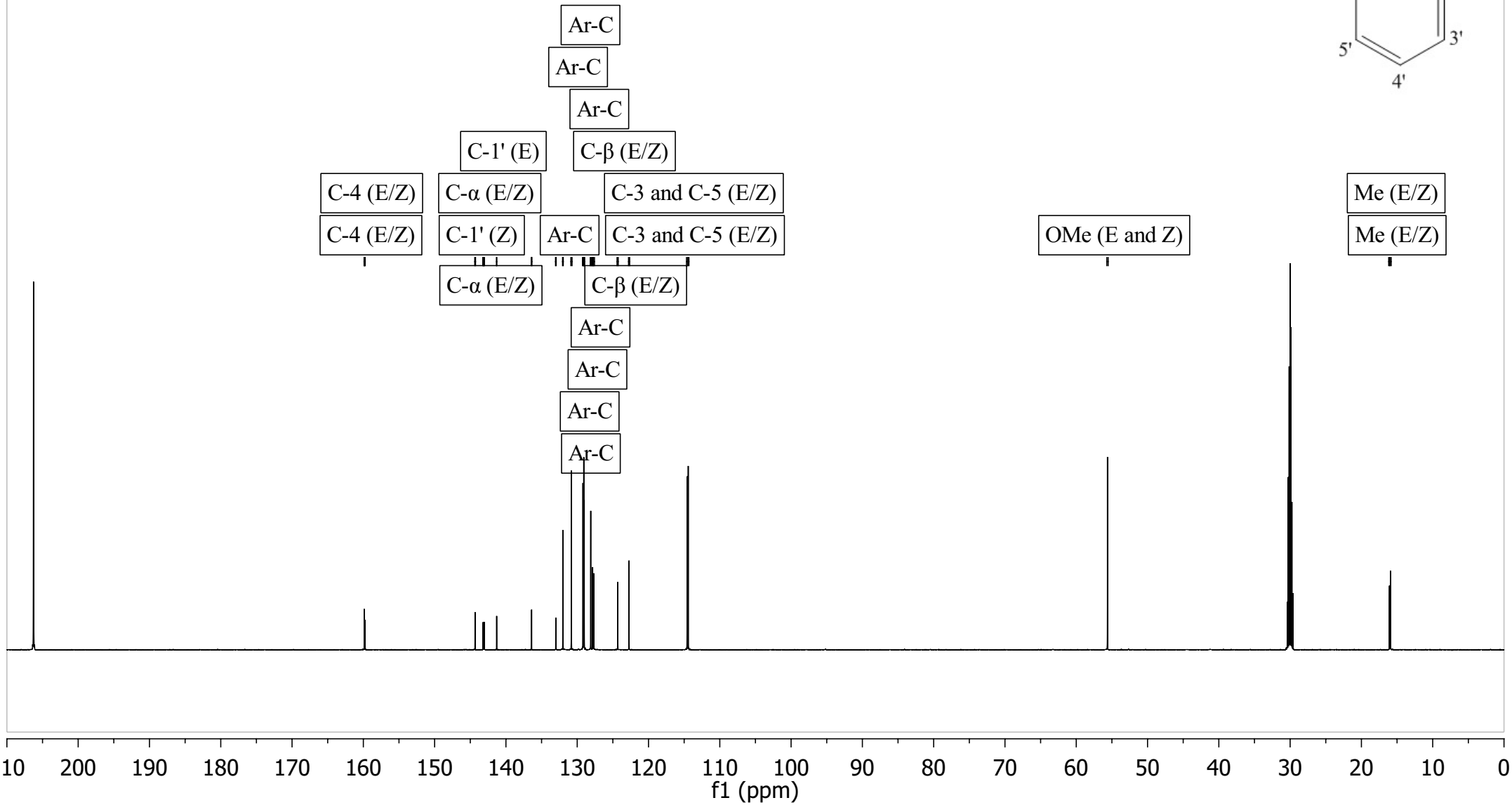


Plate 76c, HSQC (600/151 MHz, Acetone-d_6) : 4-Methoxy-α-phenyl-β-methylstyrene (**804**)

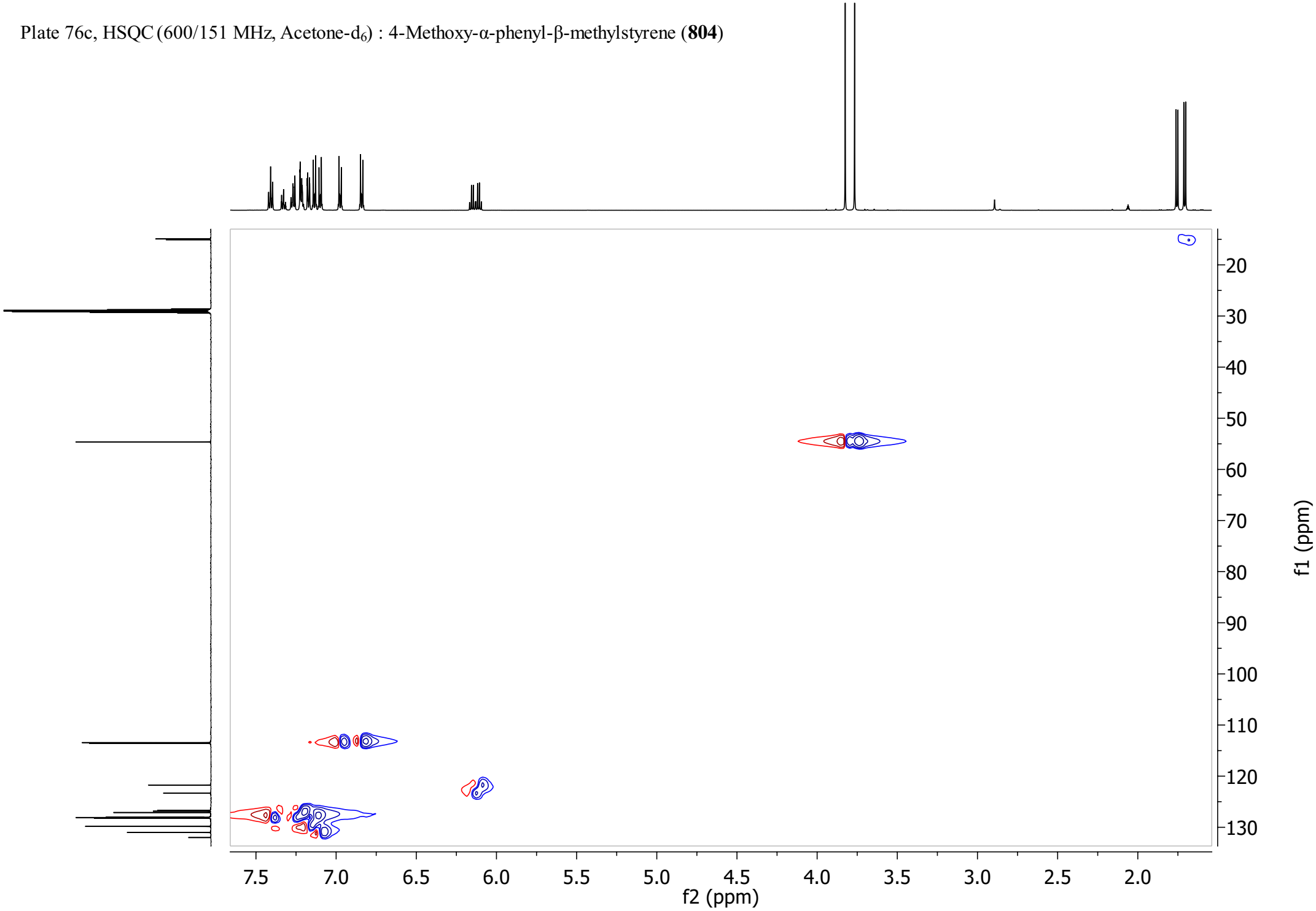


Plate 76d, HMBC (600/151 MHz, Acetone-d_6) : 4-Methoxy-α-phenyl-β-methylstyrene (**804**)

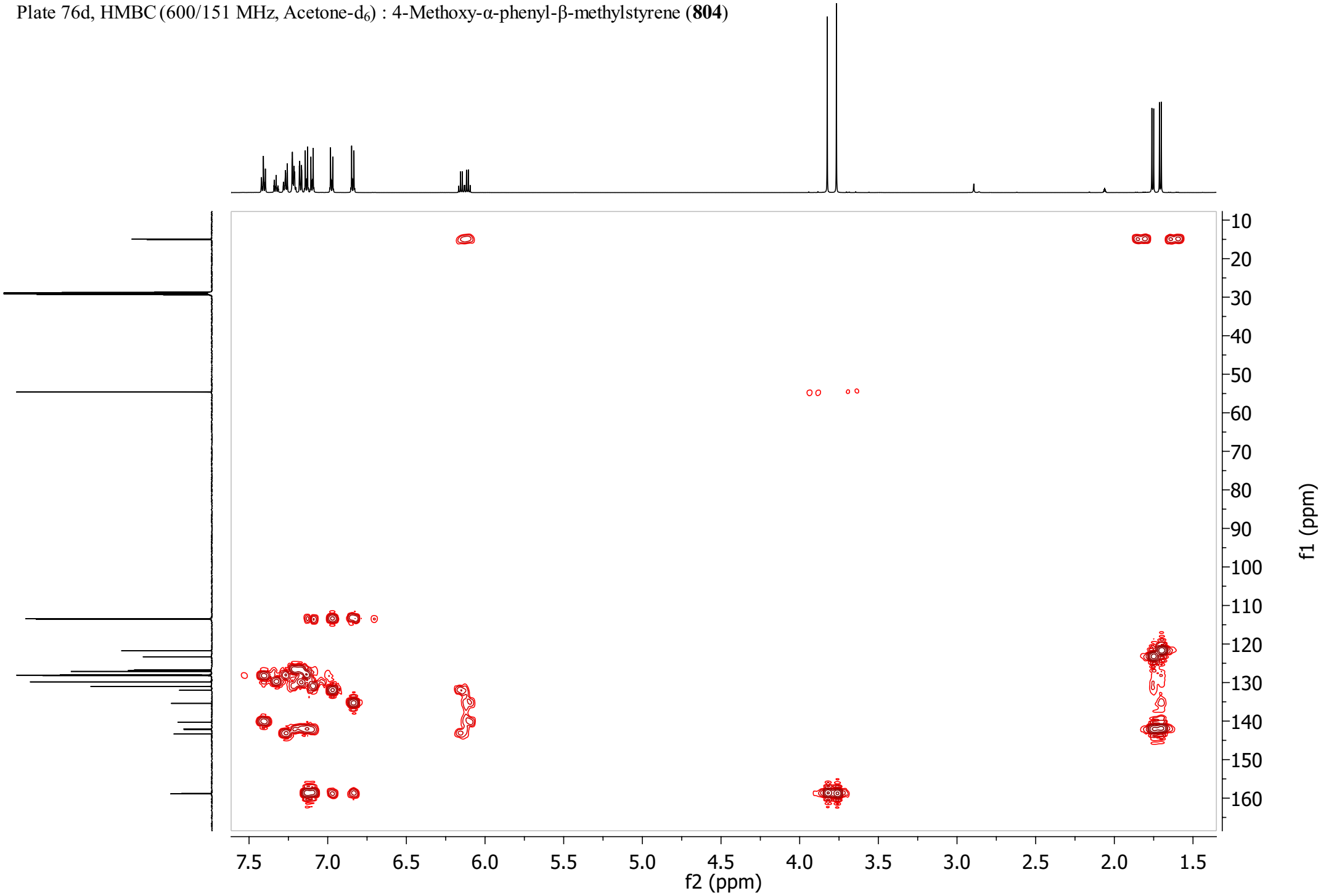


Plate 76e, DEPT (151 MHz, Acetone-d_6) : 4-Methoxy-α-phenyl-β-methylstyrene (**804**)

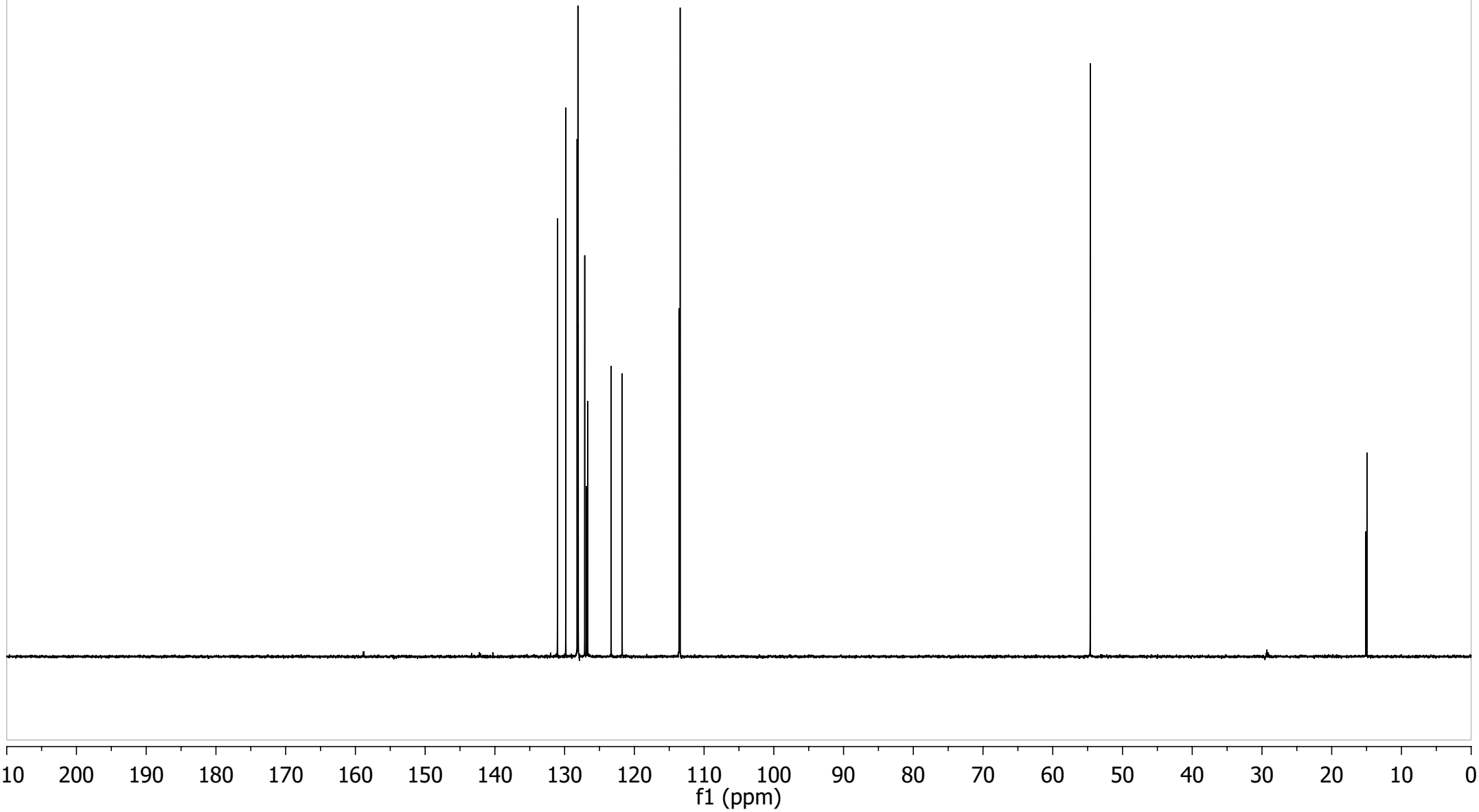


Plate 76f, NOESY (151 MHz, Acetone-d_6) : 4-Methoxy-α-phenyl-β-methylstyrene (**804**)

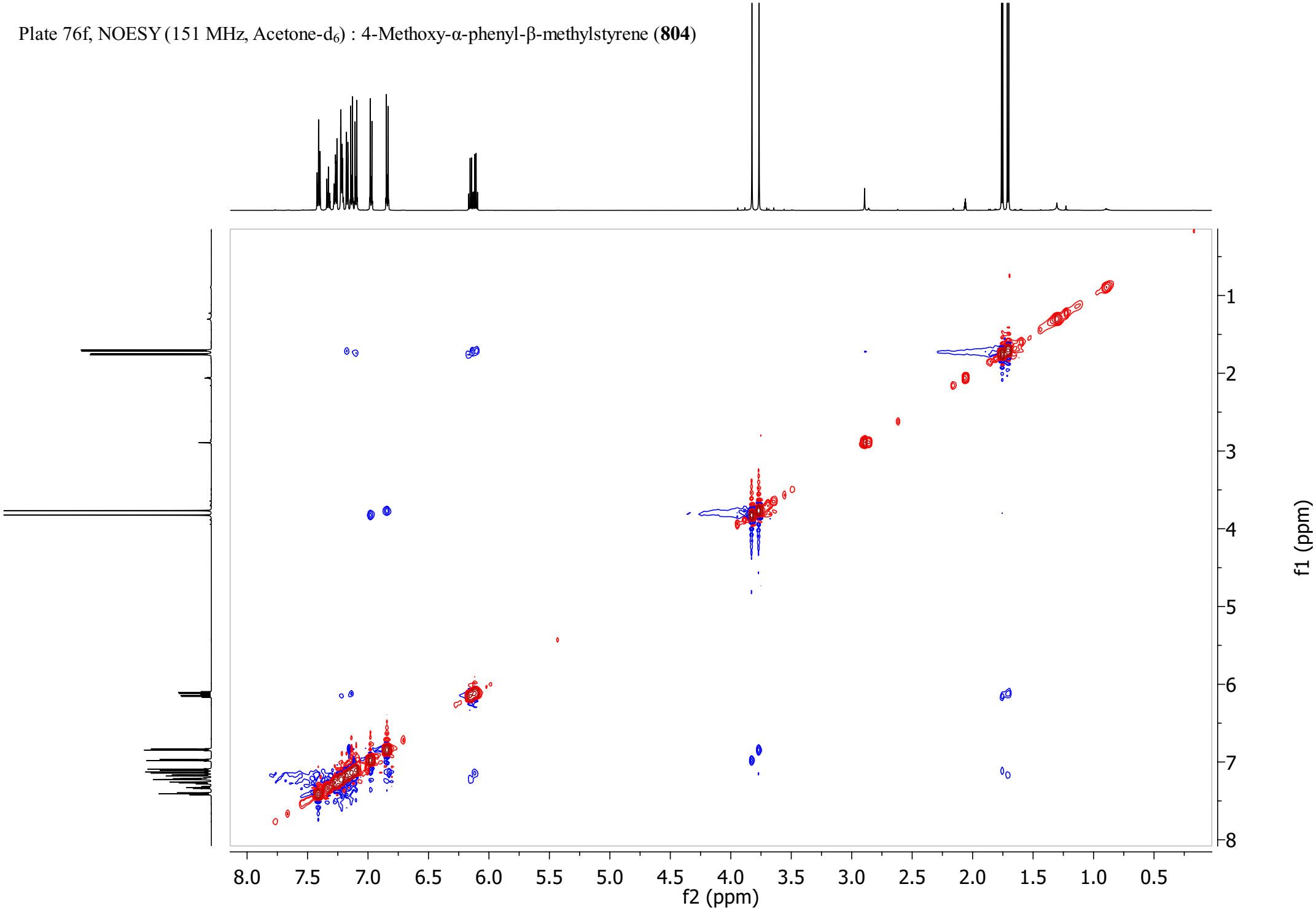
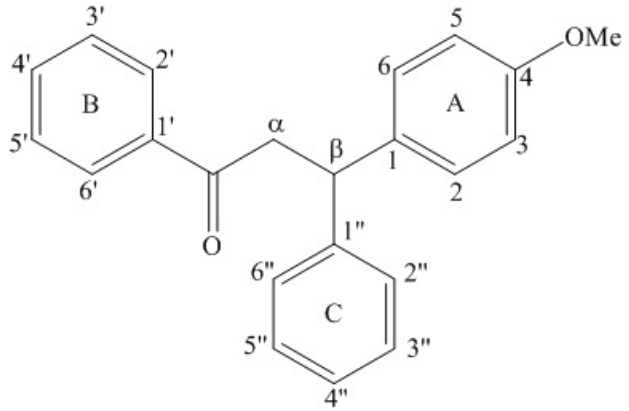
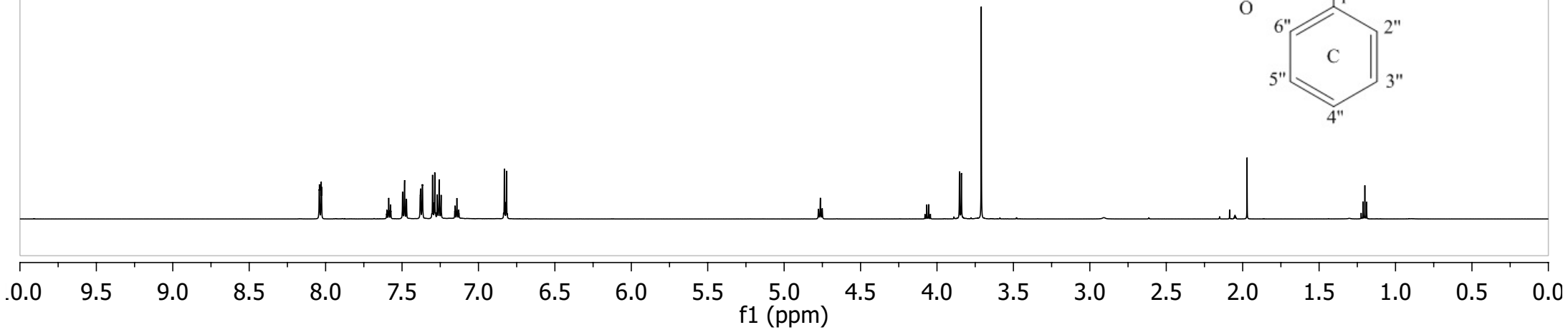


Plate 77a, ^{1}H NMR (600 MHz, Acetone-d_6) : β-Phenyl-4-methoxydihydrochalcone (**805**)

δ 8.05 – 8.02 (2H, m, H-2' and H-6'), 7.60 – 7.57 (1H, m, H-4'), 7.50 – 7.46 (2H, m, H-3' and H-5'), 7.39 – 7.36 (2H, m, H-2'' and H-6''), 7.29 (2H, d, *J* = 8.8, H-2 and H-6), 7.27 – 7.24 (2H, m, H-3'' and H-5''), 7.17 – 7.12 (1H, m, H-4''), 6.82 (2H, d, *J* = 8.8, H-3 and H-5), 4.76 (1H, t, *J* = 7.3 Hz, H-β), 3.84 (2H, d, *J* = 7.3 Hz, H-α), 3.71 (3H, s, -OMe)





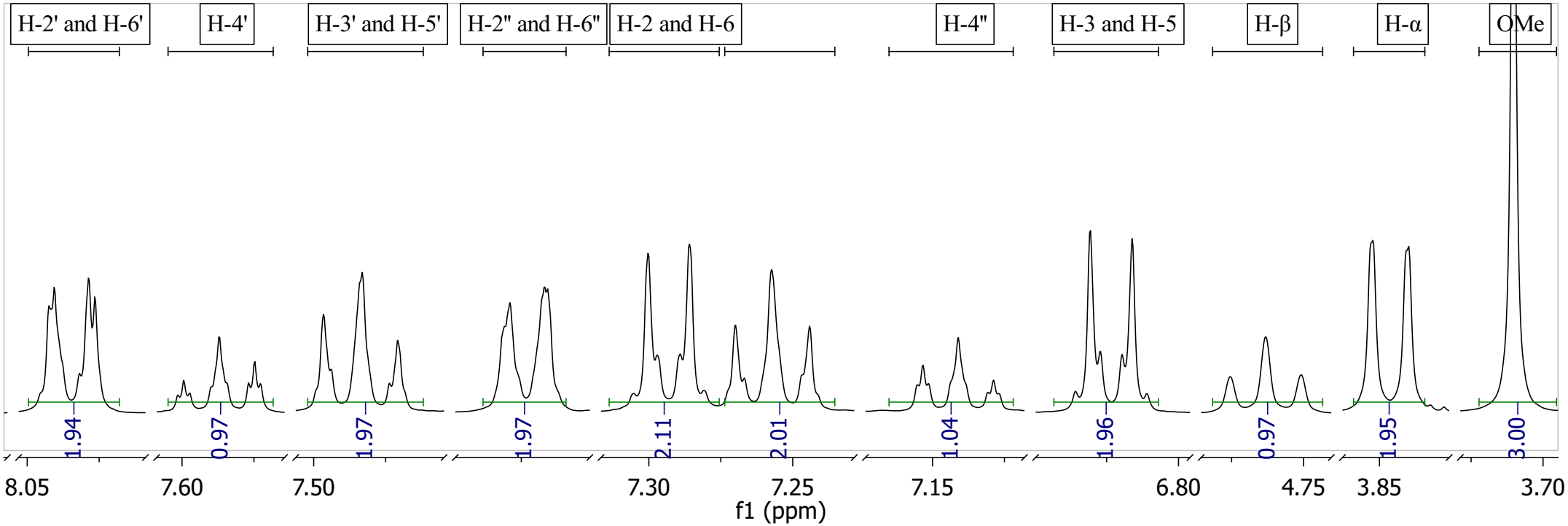
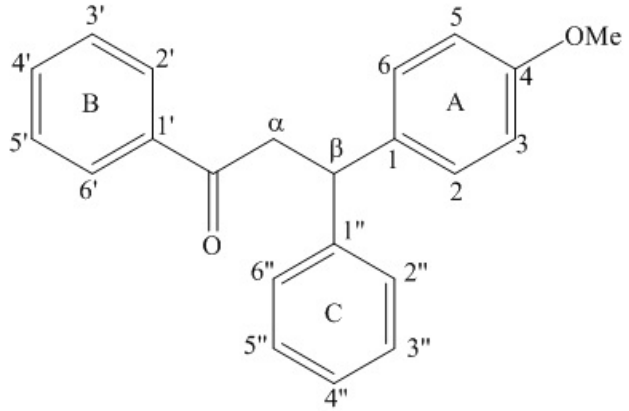


Plate 77b, ^{13}C NMR (151 MHz, Acetone-d_6) : β-Phenyl-4-methoxydihydrochalcone (**805**)

δ 198.39 (C=O), 159.07 (C-4), 146.16 (C-1''), 138.27 (C-1'), 137.68 (C-1), 133.81 (C-4'), 129.71 (Ar-C), 129.49 (Ar-C), 129.23 (Ar-C), 128.92 (Ar-C), 128.70 (Ar-C), 126.90 (C-4''), 114.60 (C-3 and C-5), 55.45 (-OMe), 46.28 (C-β), 45.02 (C-α)



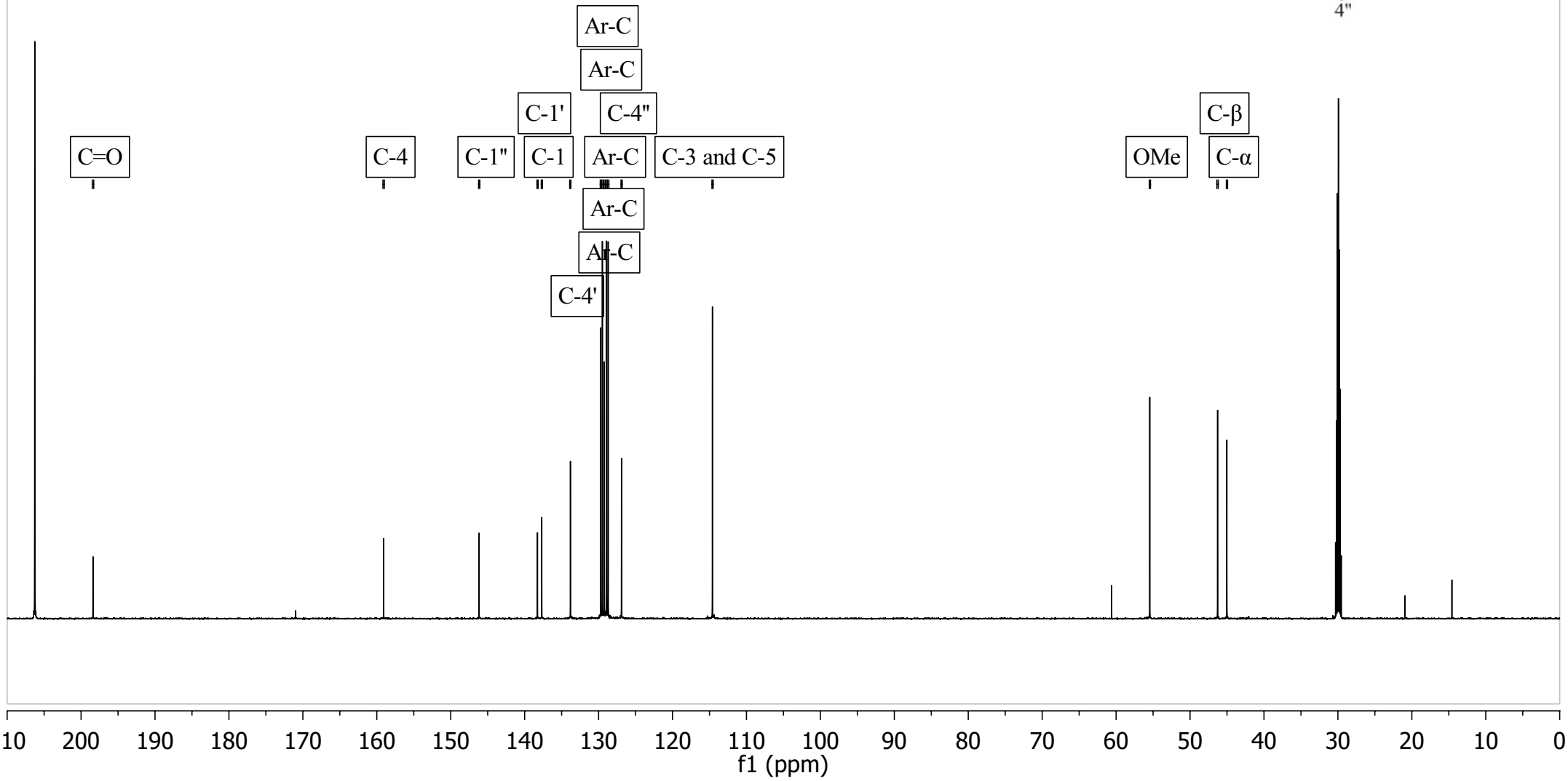


Plate 77c, HSQC (600 MHz/151 MHz, Acetone-d_6) : β-Phenyl-4-methoxydihydrochalcone (**805**)

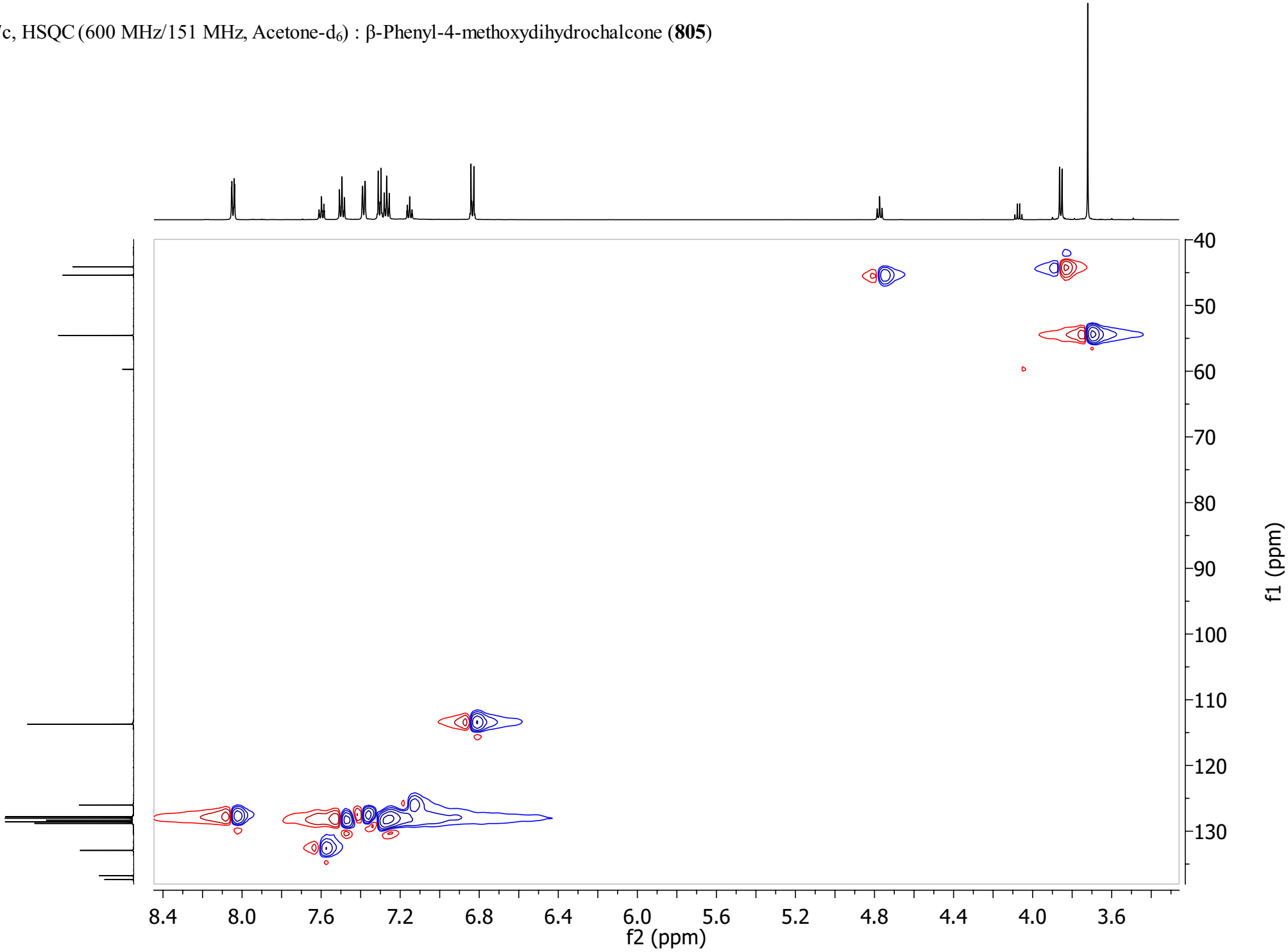


Plate 77d, HMBC (600 MHz/151 MHz, Acetone-d_6) : β-Phenyl-4-methoxydihydrochalcone (**805**)

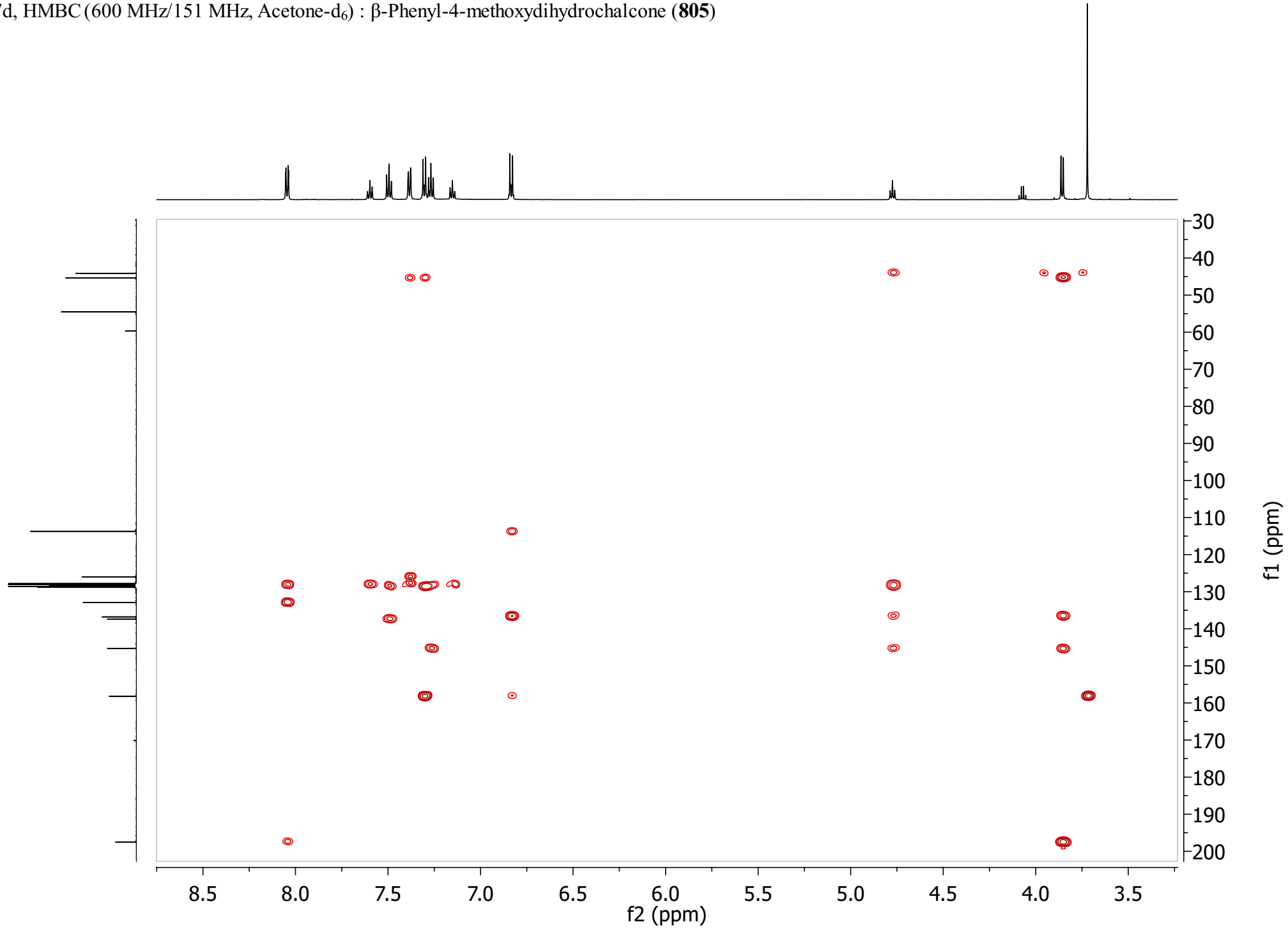
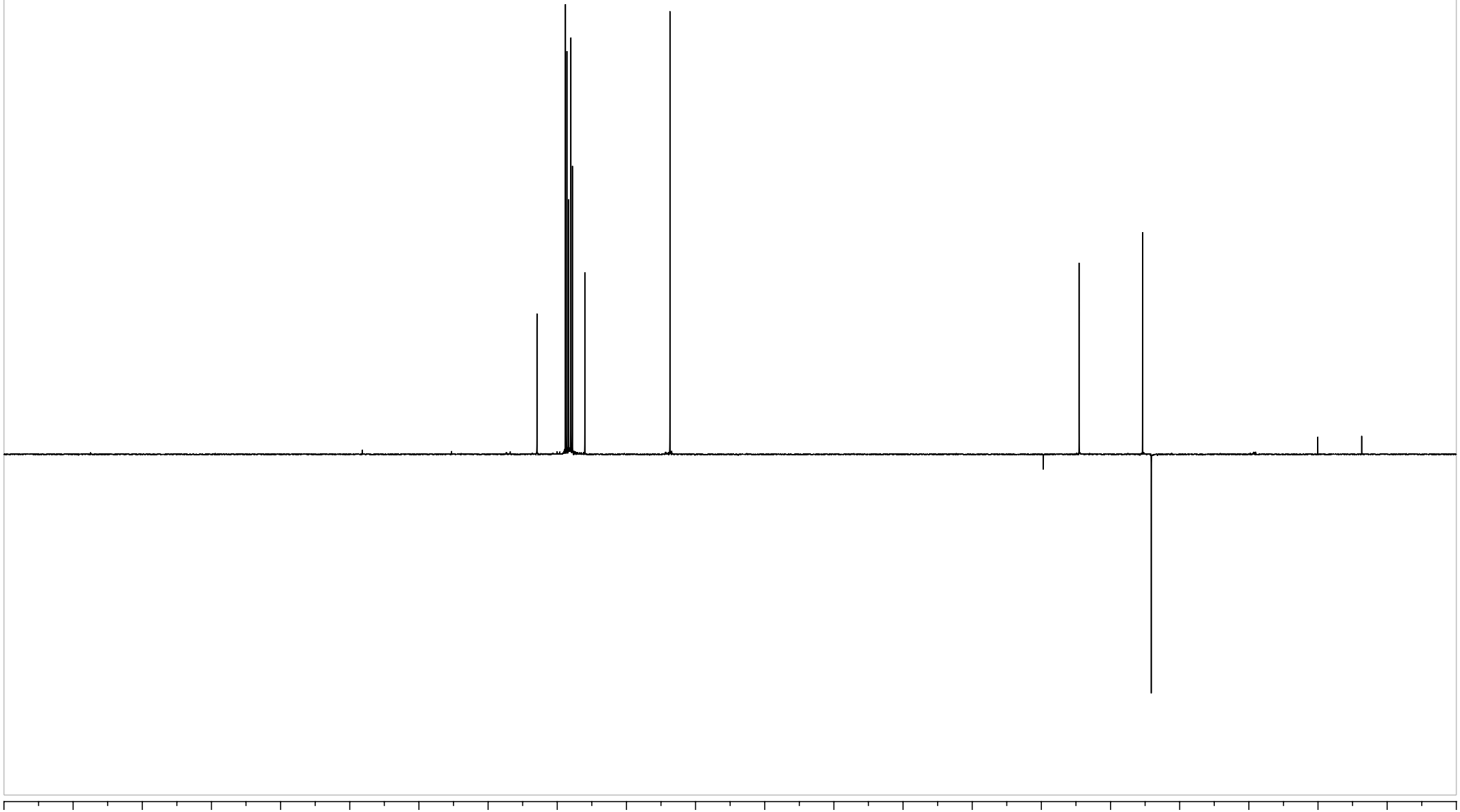


Plate 77e, DEPT (151 MHz, Acetone-d_6) : β-Phenyl-4-methoxydihydrochalcone (**805**)

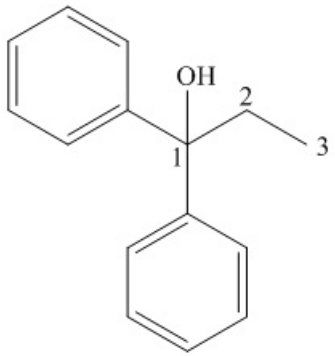


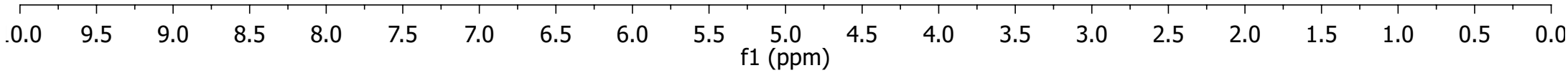
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

Plate 78a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1,1-Diphenylpropanol (**756**)

δ 7.51 – 7.49 (4H, m, Ar-H), 7.29 – 7.26 (4H, m, Ar-H), 7.18 – 7.15 (2H, m, Ar-H), 4.37 (1H, s, -OH), 2.35 (2H, q, *J* = 7.3 Hz, H-2), 0.86 (3H, t, *J* = 7.3 Hz, H-3)





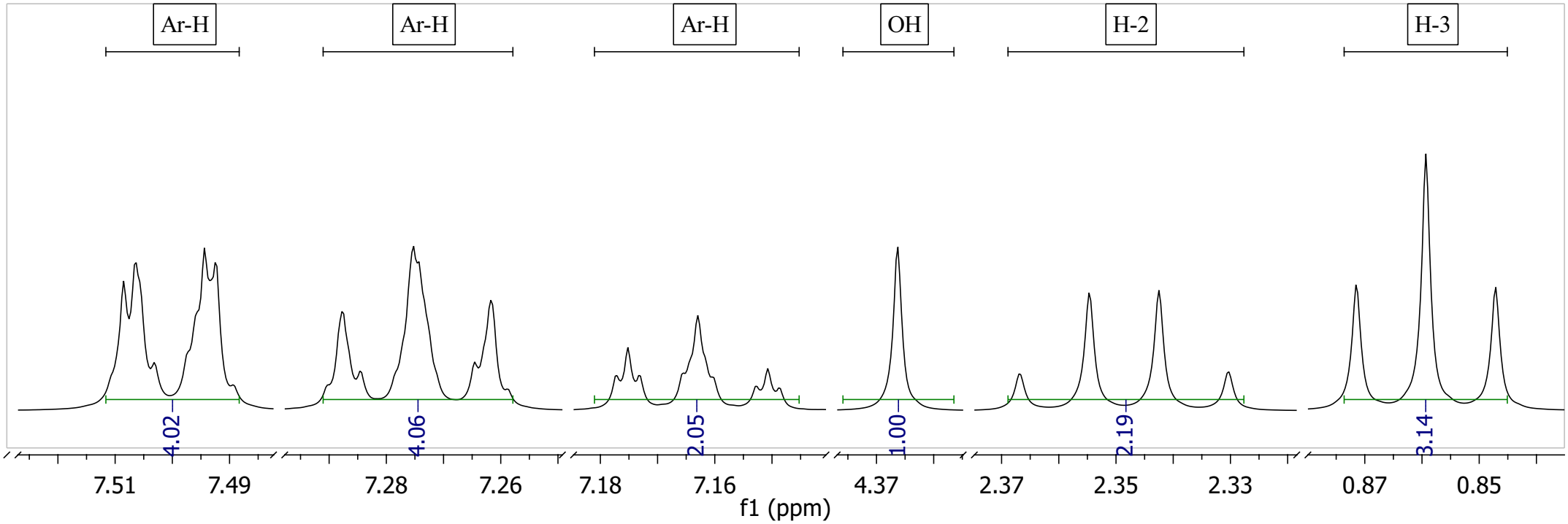
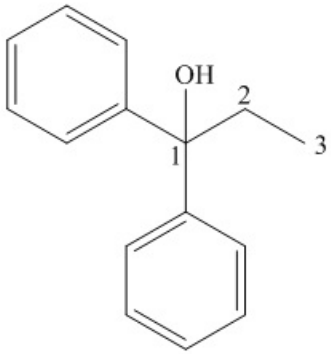


Plate 78b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1,1-Diphenylpropanol (**756**)

δ 149.20 (4°-C), 128.64 (Ar-C), 127.03 (Ar-C), 78.23 (4°-C), 35.05 (C-2), 8.56 (C-3)



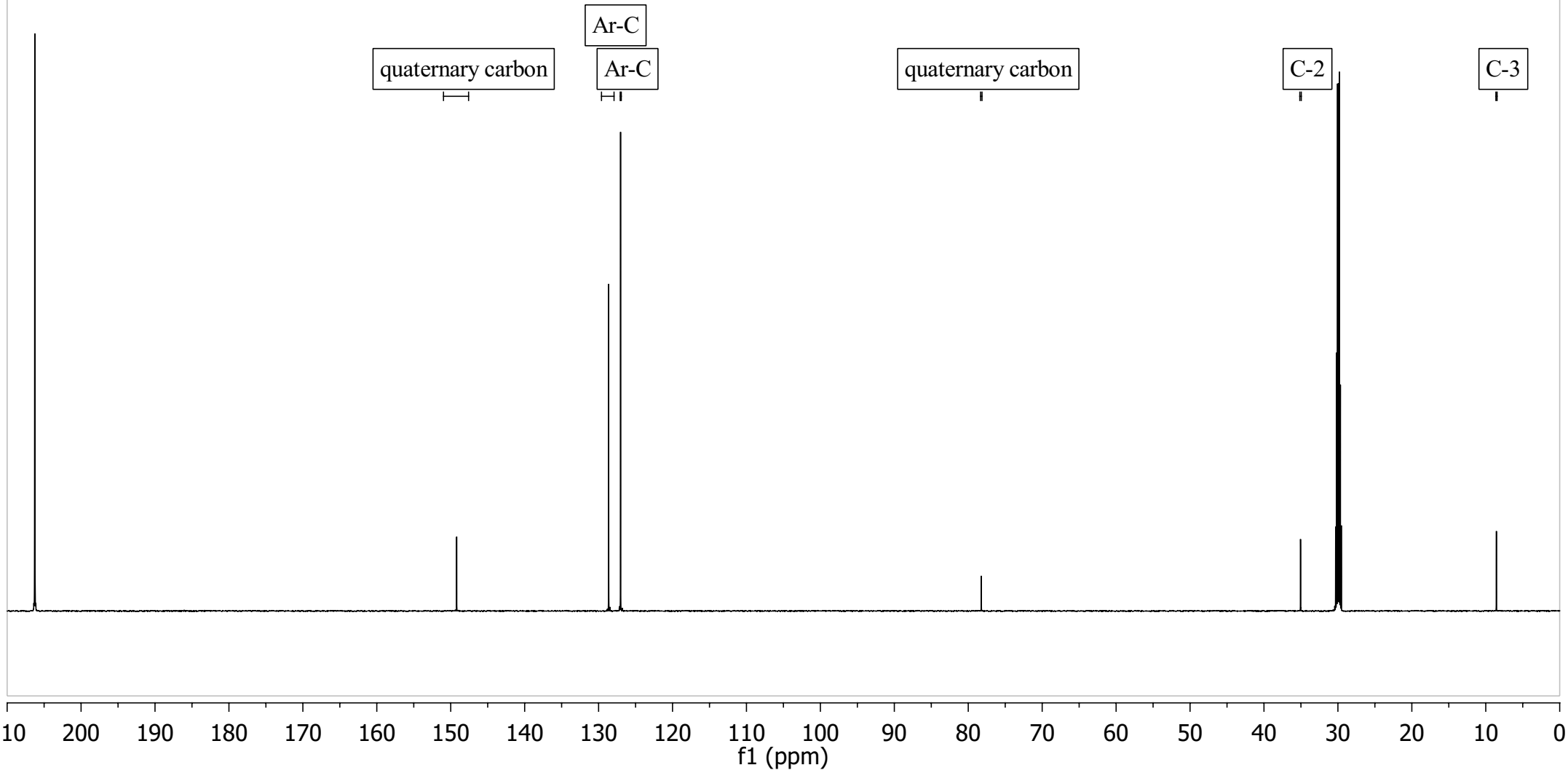


Plate 78c, HSQC (600 MHz/151 MHz, Acetone-d_6) : 1,1-Diphenylpropanol (**756**)

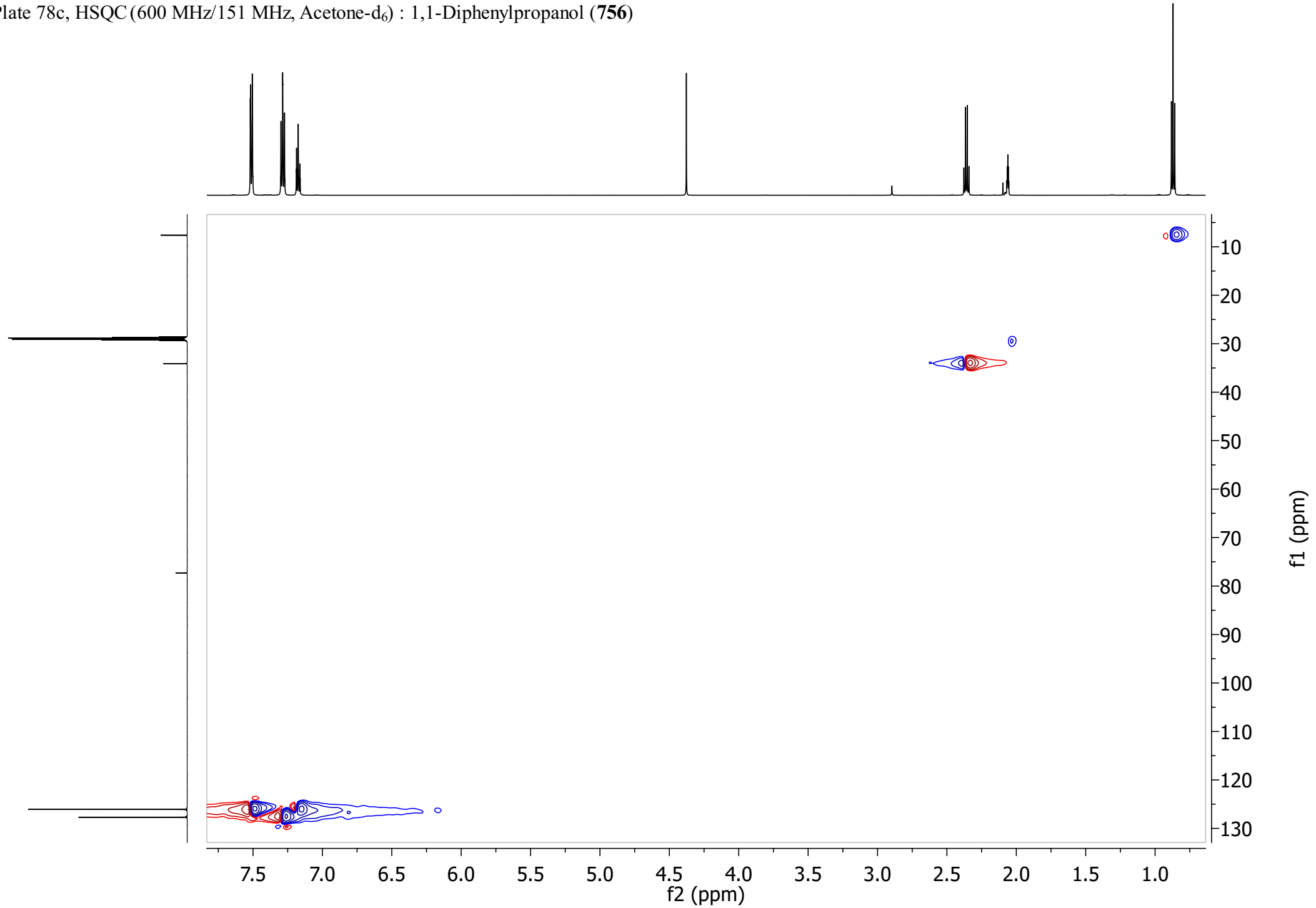


Plate 78d, HMBC (600 MHz/151 MHz, Acetone-d_6) : 1,1-Diphenylpropanol (**756**)

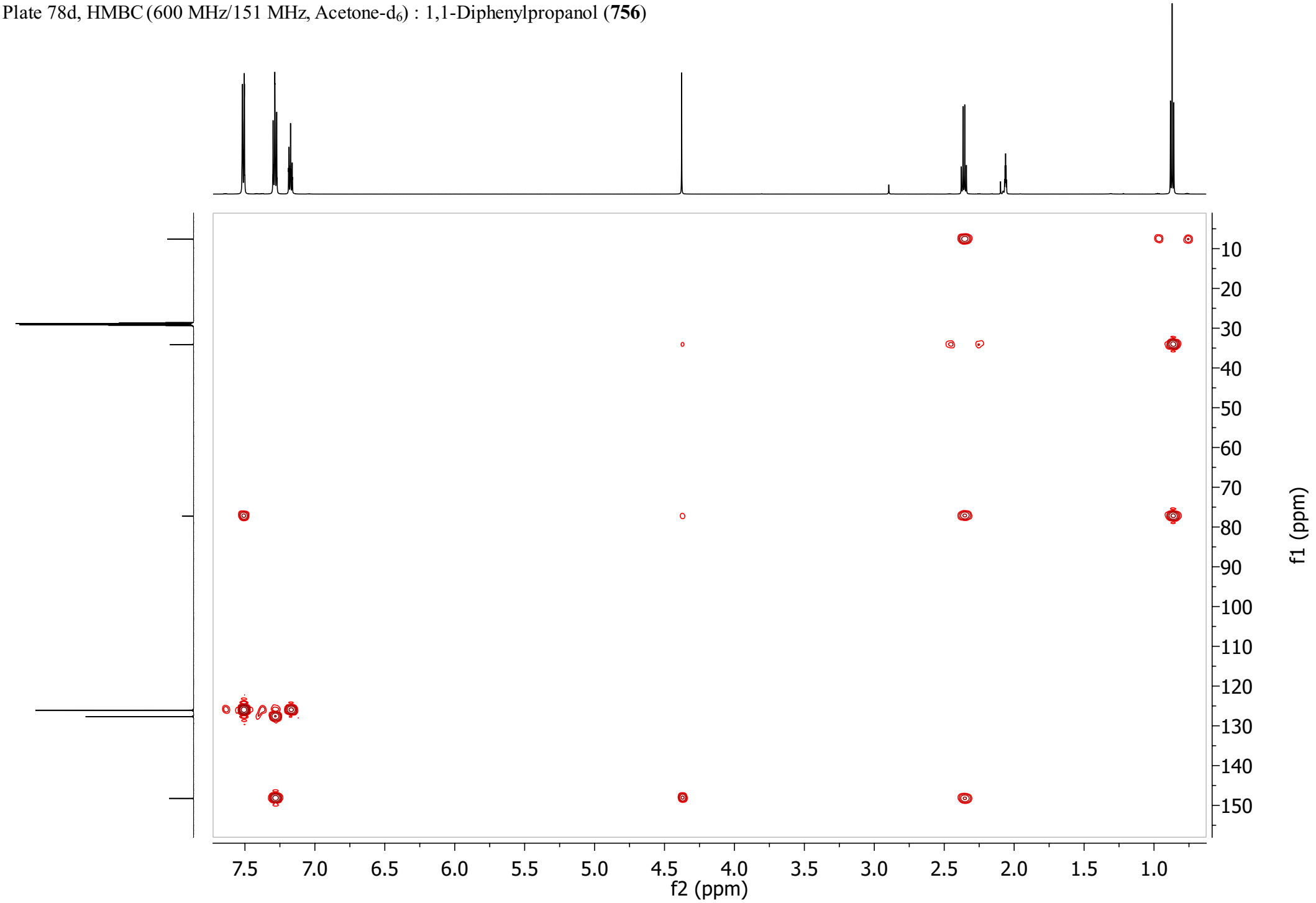


Plate 78e, DEPT (151 MHz, Acetone-d_6) : 1,1-Diphenylpropanol (**756**)

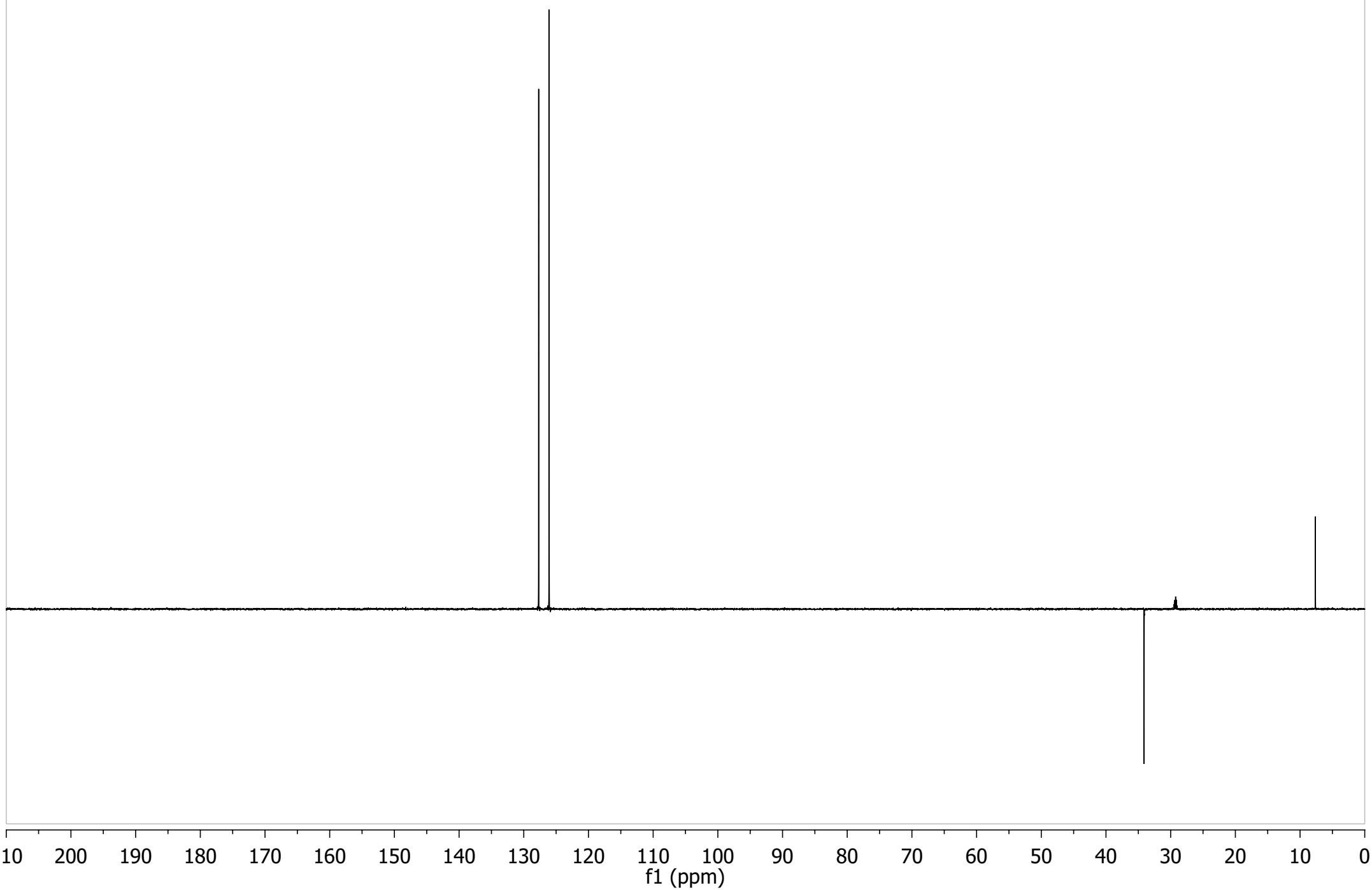
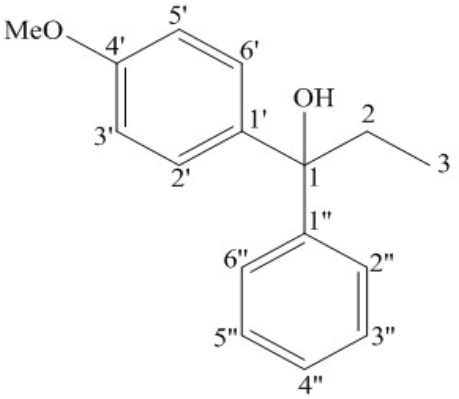
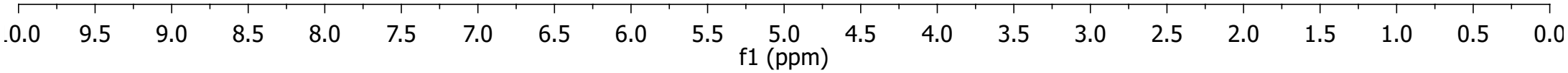


Plate 79a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**806**)

δ 7.49 (2H, dd, *J* = 8.3, 1.0 Hz, H-2" and H-6"), 7.41 (2H, d, *J* = 9.1 Hz, H-2' and H-6'), 7.30 – 7.26 (2H, m, H-3" and H-5"), 7.19 – 7.14 (1H, m, H-4"), 6.85 (2H, d, *J* = 9.1 Hz, H-3' and H-5'), 4.28 (1H, s, OH), 3.74 (3H, s, -OMe), 2.33 (2H, q, *J* = 7.3 Hz, H-2), 0.87 (1H, t, *J* = 7.3 Hz, H-3)





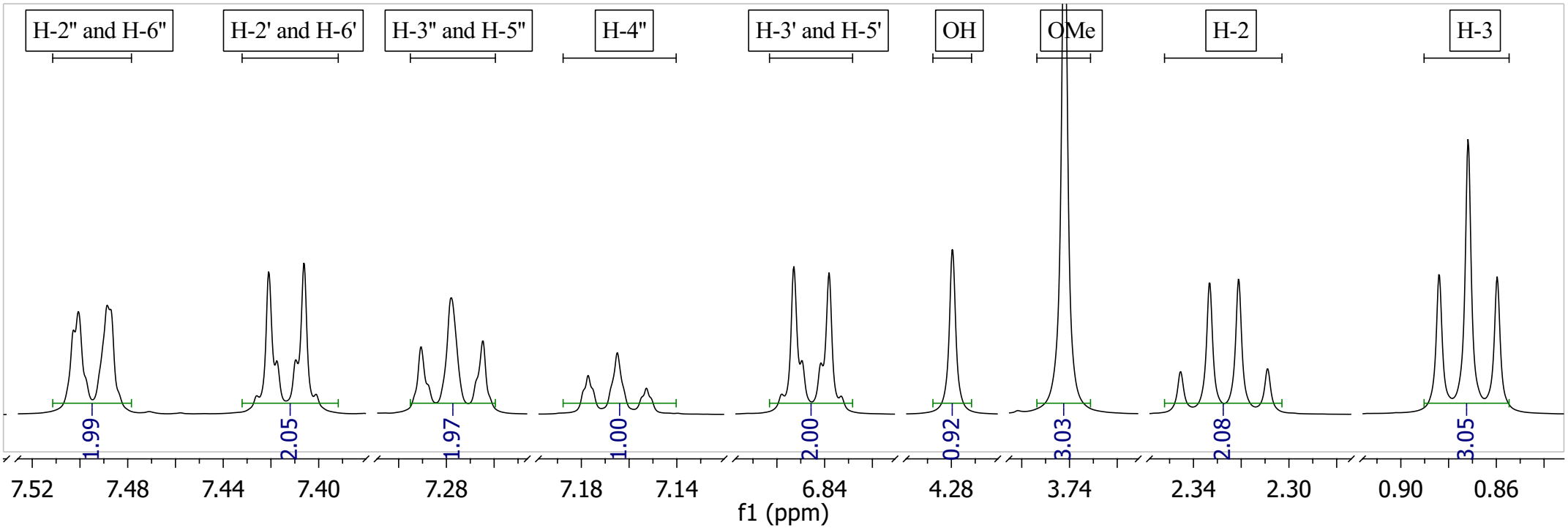
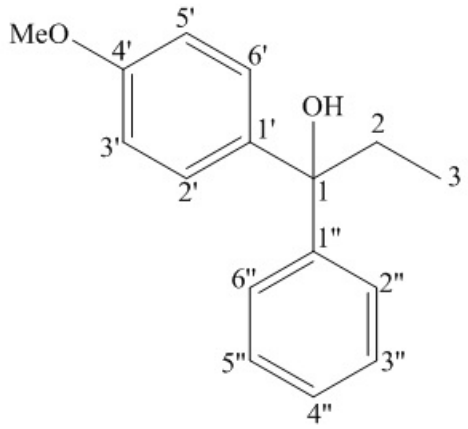


Plate 79b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**806**)

δ 158.91 (C-4'), 149.24 (C-1''), 141.15 (C-1'), 128.40 (C-3'' and C-5''), 128.04 (C-2' and C-6'), 126.81 (C-2'' and C-6''), 126.73 (C-4''), 113.75 (C-3' and C-5'), 77.76 (C-1), 55.29 (-OMe), 35.04 (C-2), 8.49 (C-3)



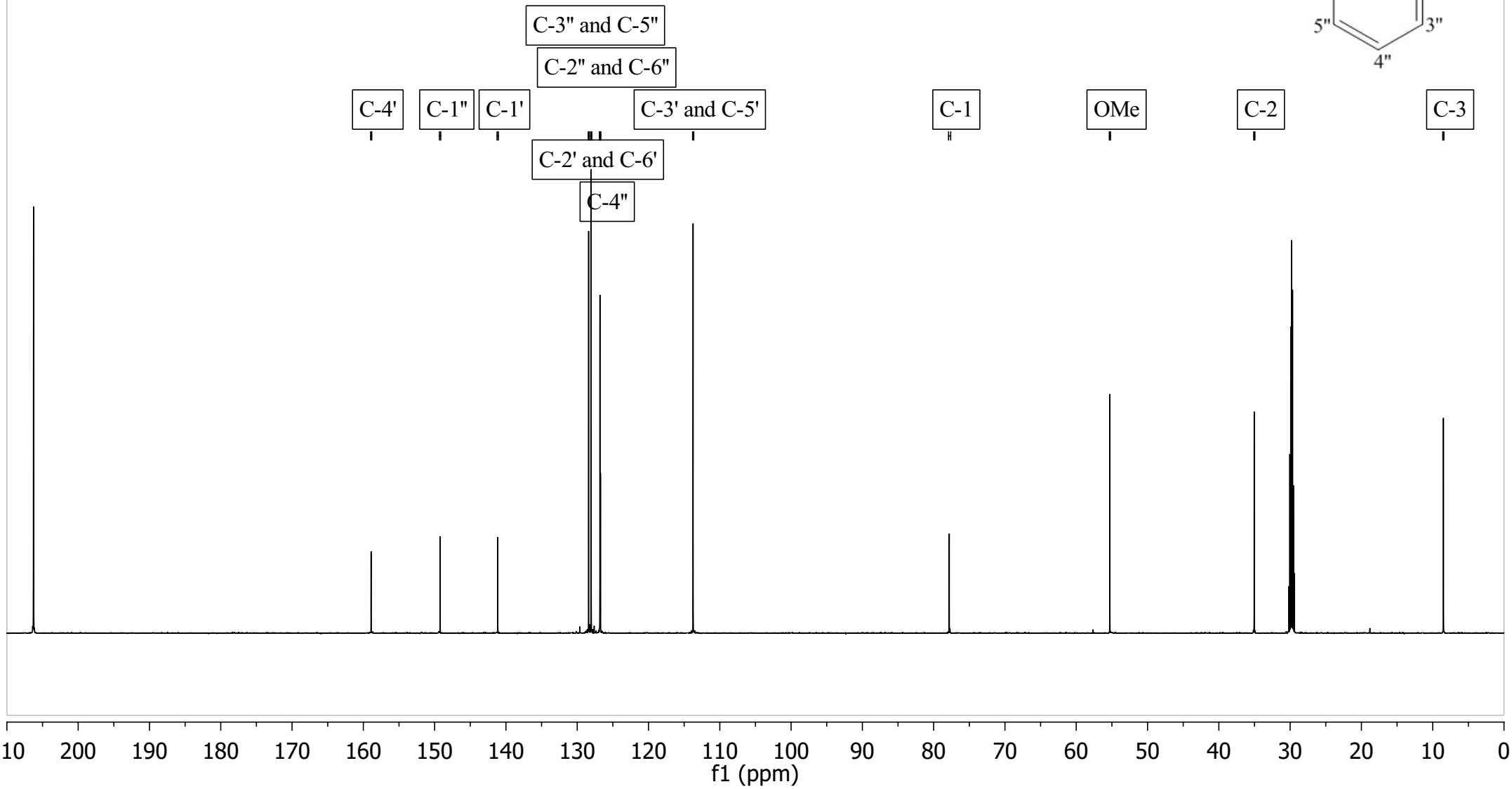


Plate 79c, HSQC (600/151 MHz, Acetone-d_6) : 1-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**806**)

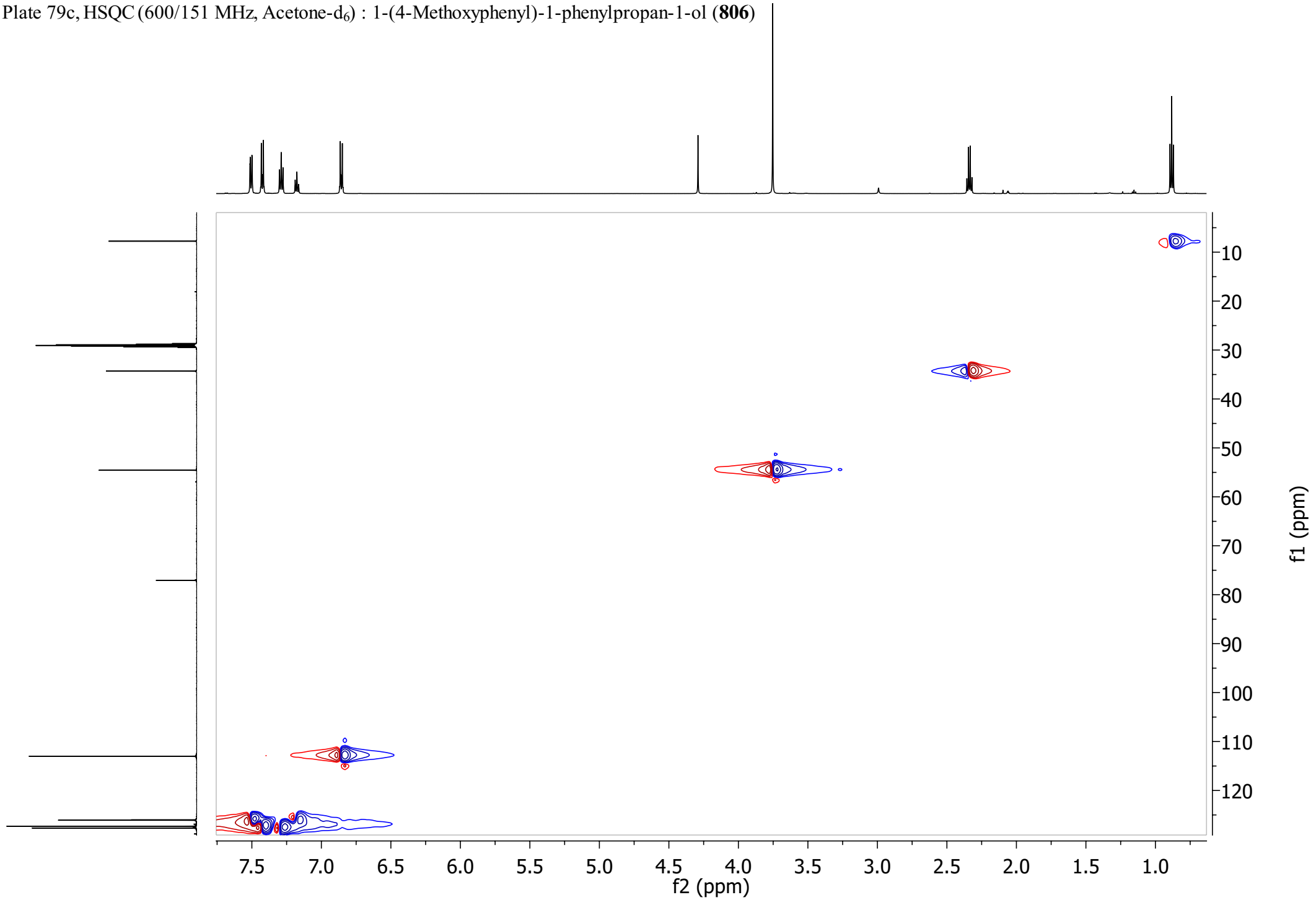


Plate 79d, HMBC (600/151 MHz, Acetone-d_6) : 1-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**806**)

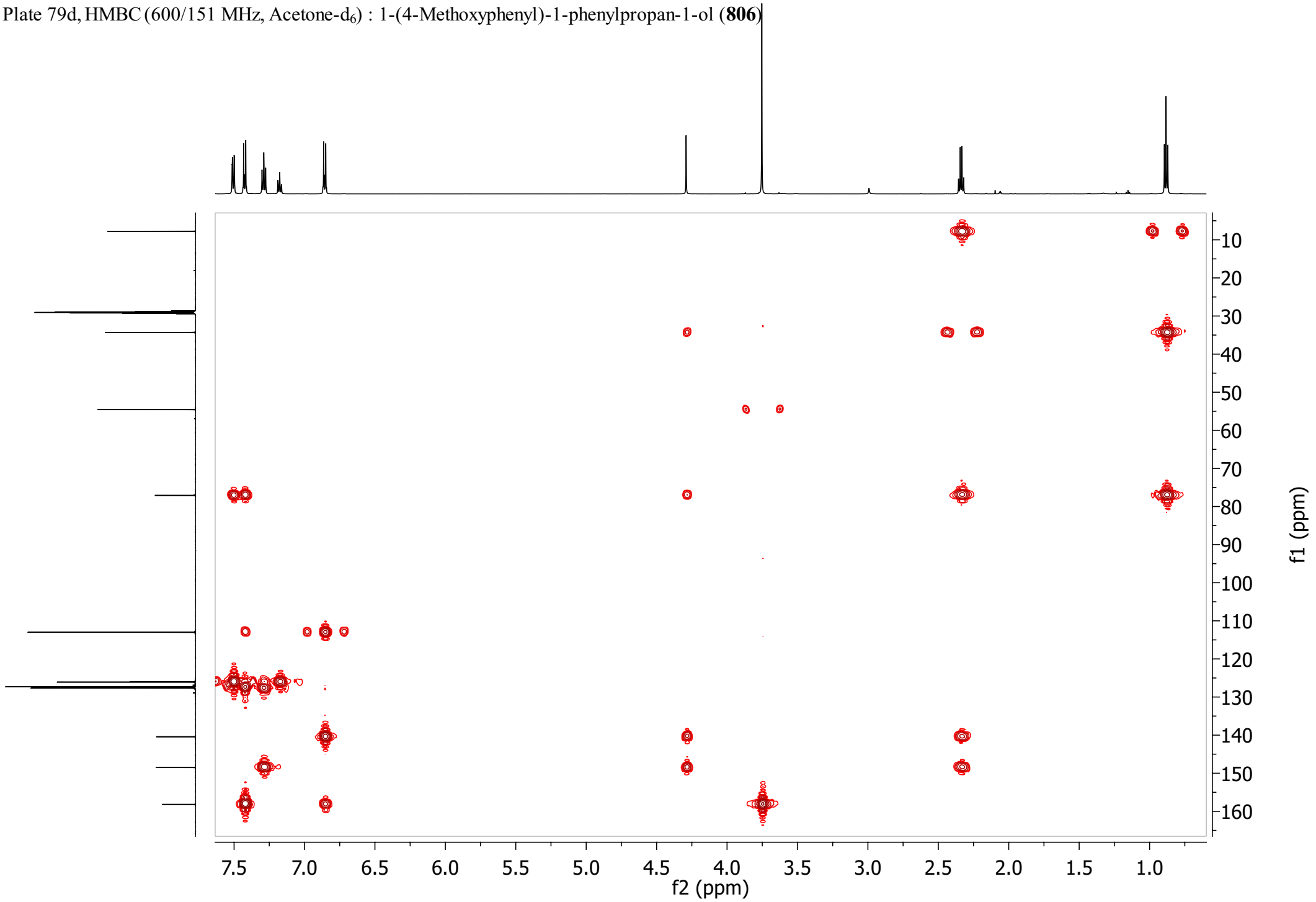


Plate 79e, DEPT (151 MHz, Acetone-d_6) : 1-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**806**)

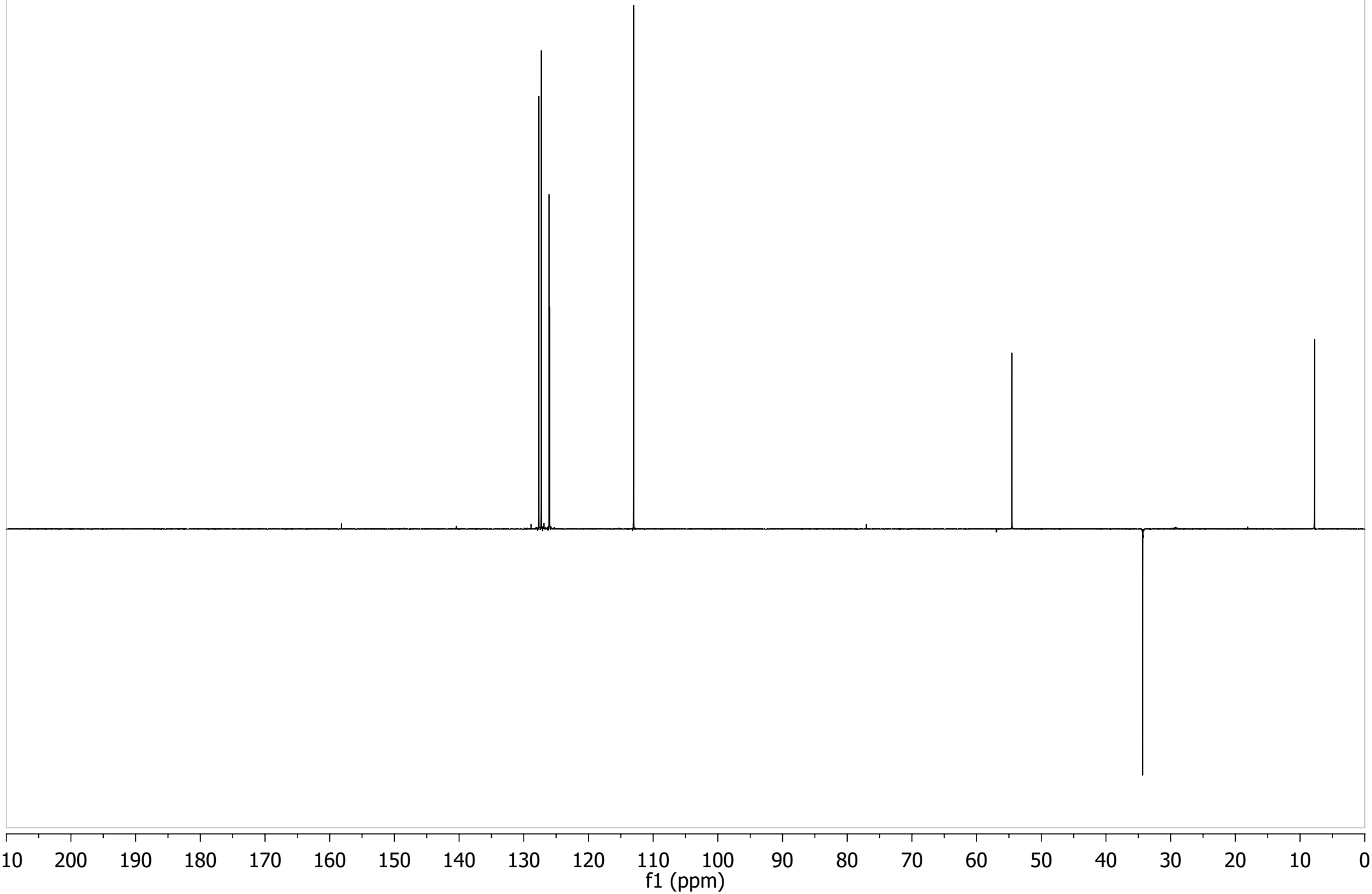
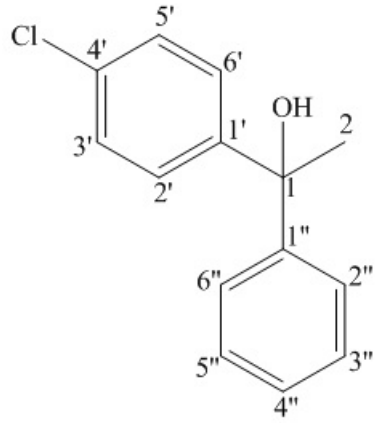
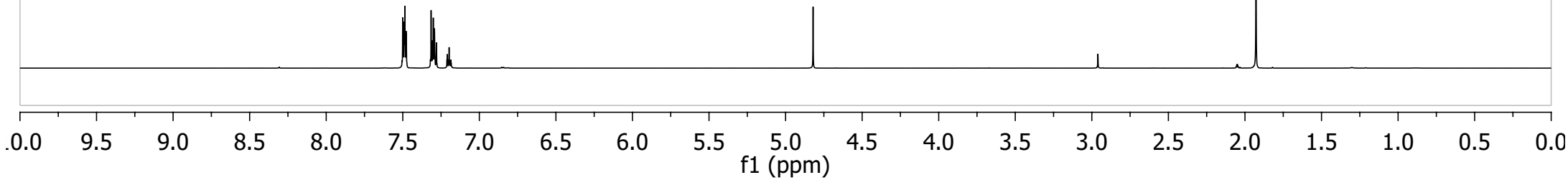


Plate 80a, ^{1}H NMR (600 MHz, Acetone-d_6) : 1-(4-Chlorophenyl)-1-phenylethan-1-ol (**795**)

δ 7.51 – 7.47 (4H, m, Ar-H), 7.32 – 7.27 (4H, m, Ar-H), 7.21 – 7.18 (1H, m, H-4''), 4.82 (1H, s, -OH), 1.93 (3H, s, H-2)





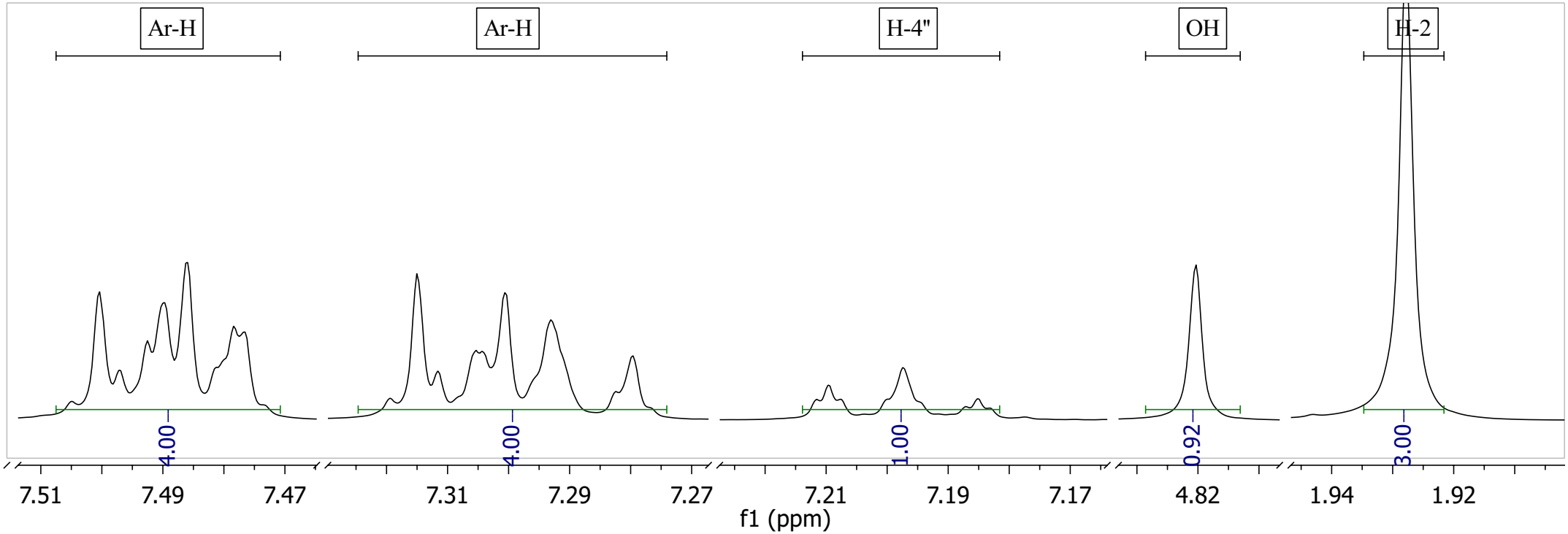
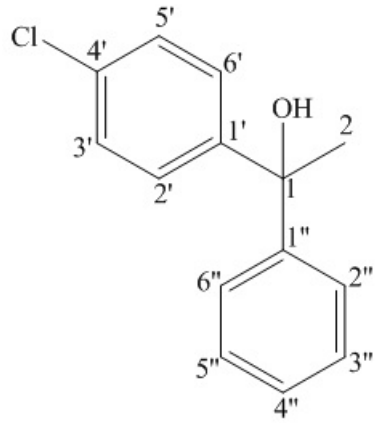
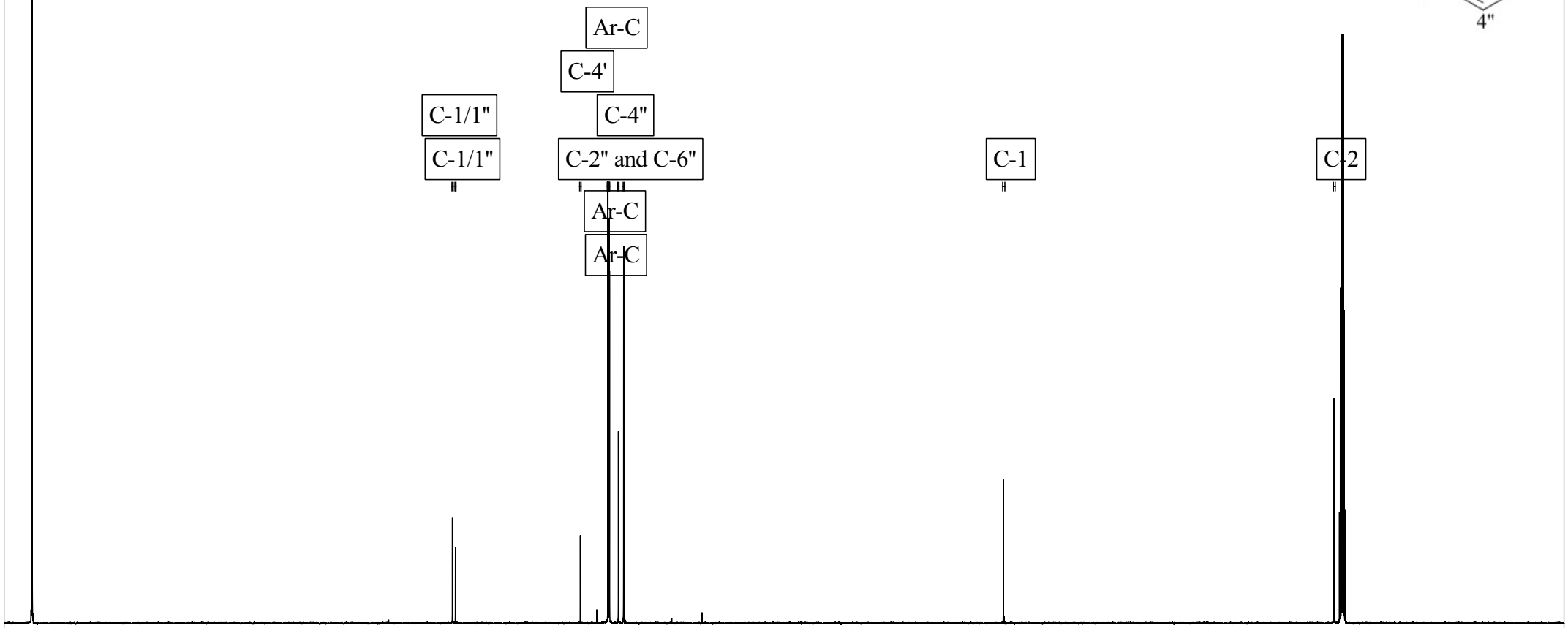


Plate 80b, ^{13}C NMR (151 MHz, Acetone-d_6) : 1-(4-Chlorophenyl)-1-phenylethan-1-ol (**795**)

δ 149.66 (C-1'/1''), 149.25 (C-1'/1''), 132.44 (C-4'), 128.73 (Ar-C), 128.58 (Ar-C), 128.51 (Ar-C), 127.31 (C-4''), 126.61 (C-2'' and C-6''), 75.43 (C-1), 30.93 (C-2)





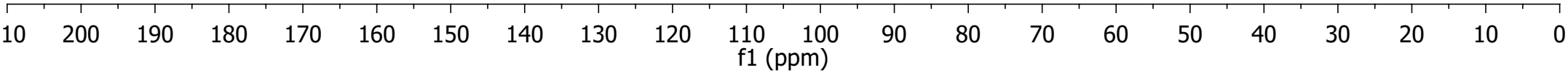


Plate 80c, HSQC (600/151 MHz, Acetone-d_6) : 1-(4-Chlorophenyl)-1-phenylethan-1-ol (**795**)

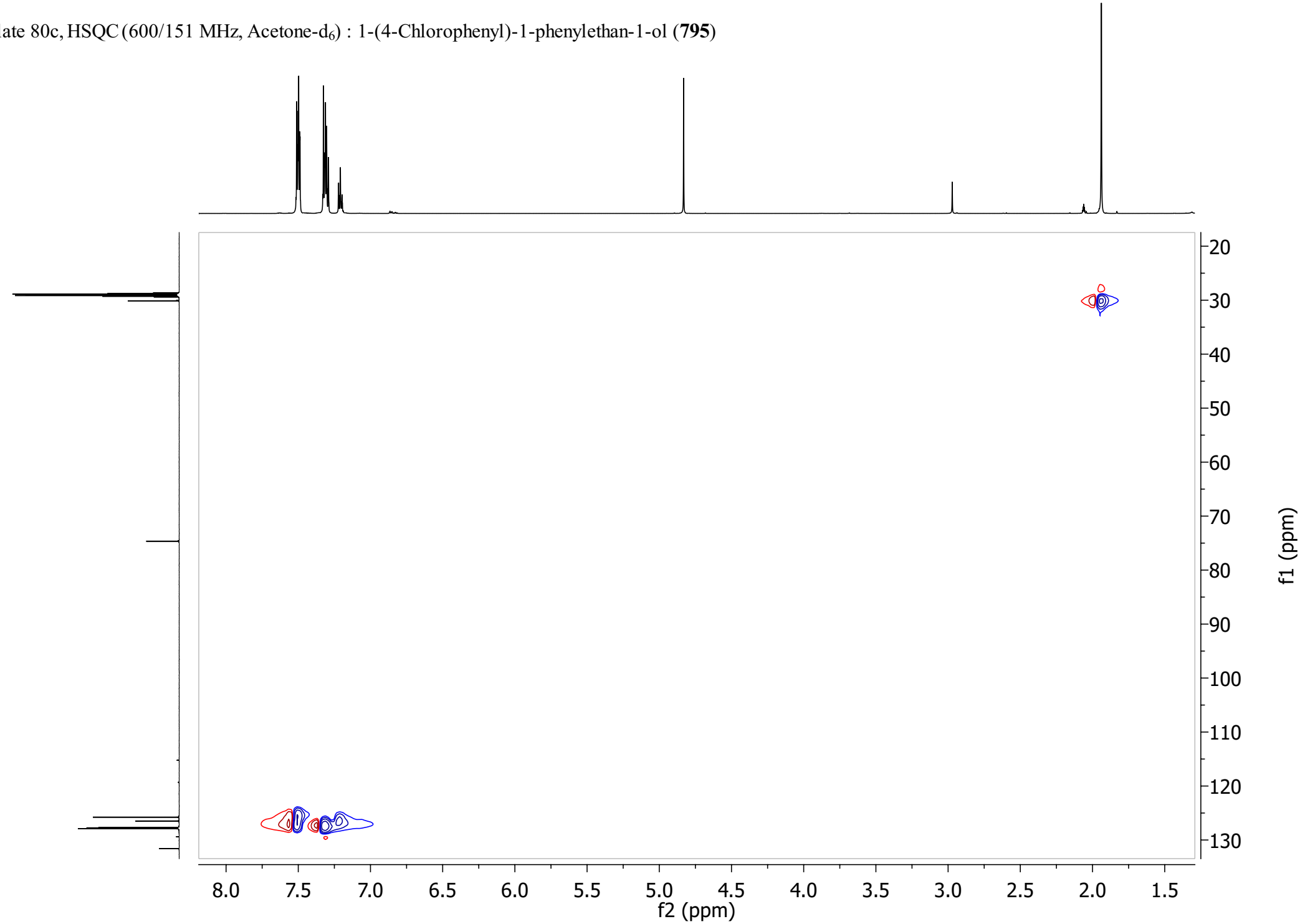


Plate 80d, HMBC (600/151 MHz, Acetone-d_6) : 1-(4-Chlorophenyl)-1-phenylethan-1-ol (**795**)

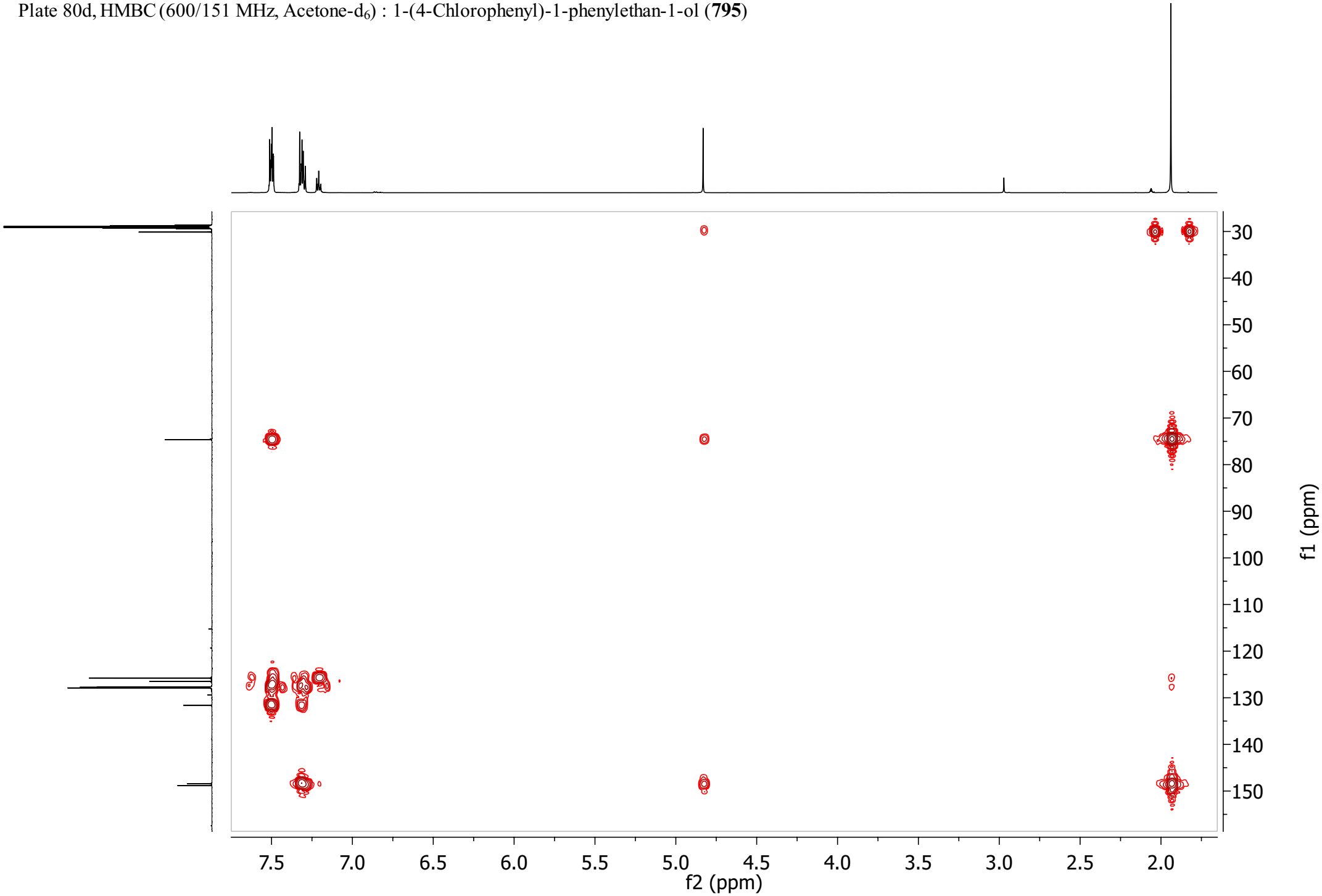
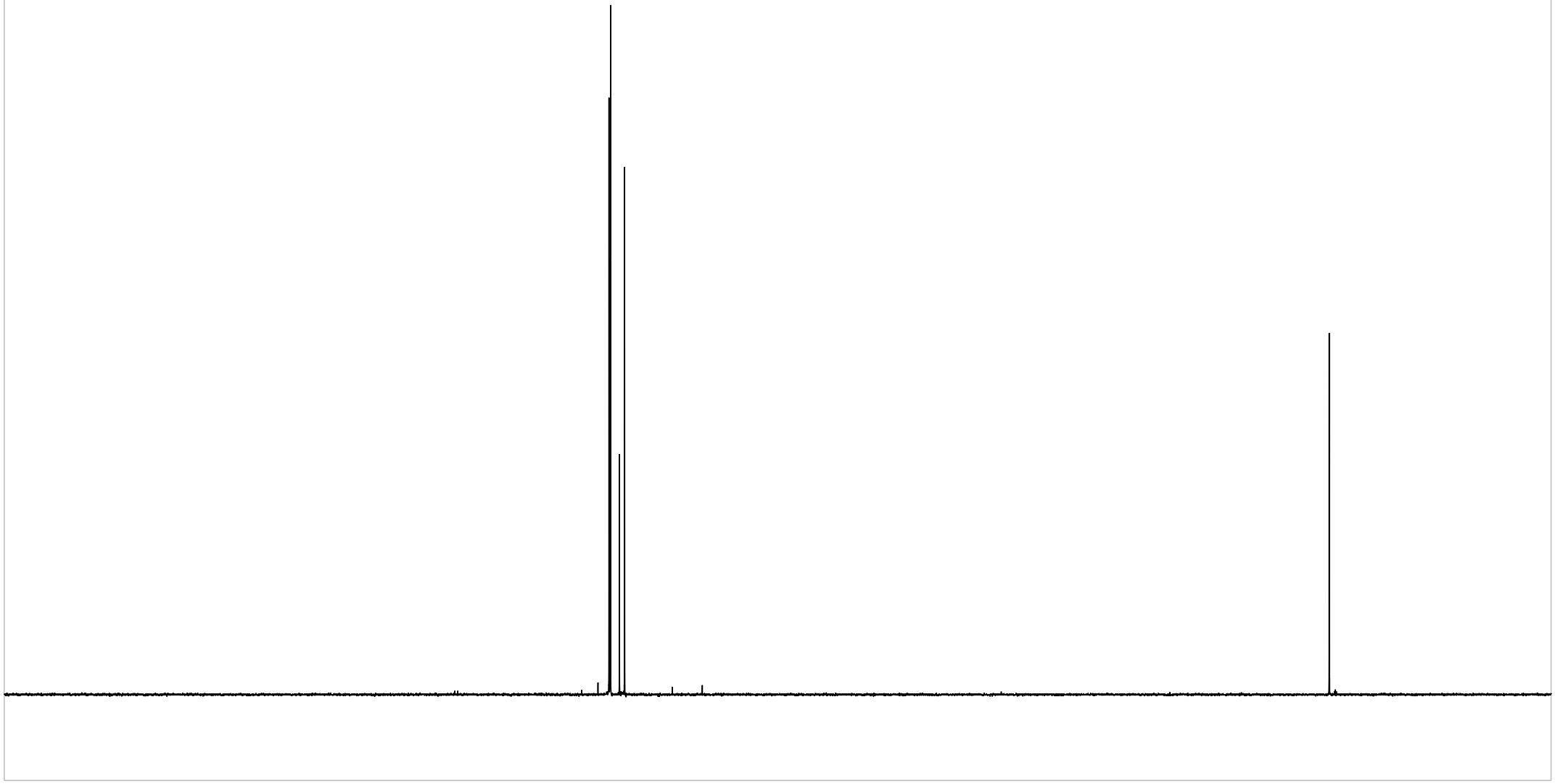


Plate 80e, DEPT (151 MHz, Acetone-d_6) : 1-(4-Chlorophenyl)-1-phenylethan-1-ol (**795**)



Summary

Although the physiological activity of flavonoids stimulated investigations into more efficient synthetic methods for the preparation of these compounds, many of these routes entail multiple steps and require the utilization of stoichiometric and often poisonous reagents. Known methodologies are also hampered by difficulties around the isolation of the desired product and often lead to inseparable mixtures, low yields, and tedious synthetic processes. To circumvent these problems and to bring the synthesis of flavonoids in line with modern synthetic methodologies, it was decided to embark on a process of preparing the different classes of flavonoids through the application of a catalytic process, like ring closing metathesis (RCM), as key step in the methodology. Developing this methodology would have the added advantage that all the different classes of flavonoids would be reachable from readily available starting materials and the application of basically a single catalytic reaction in the final process step.

For entry into the first class of flavonoids, i.e. compounds with a 2-phenylchromane skeleton, the preparation of flav-2-enes were investigated as key intermediate. In this regard, allyl phenyl ethers, prepared *via* Williamson etherification [K_2CO_3 (2.0 e.q), CH_3CN, reflux], were subjected to Claisen rearrangement in a neat microwave assisted process to obtain the substituted allyl benzenes, 1-allyl-2-hydroxy-4-methoxybenzene and 1-allyl-2-hydroxy-4,6-dimethoxybenzene, in 44% and 88% yields, respectively. Subsequent esterification of the allyl phenols with substituted benzoyl chlorides [aq. NaOH (2.0 M, 40.0 mL) or 4-dimethylaminopyridine (0.2 eq.), dry pyridine (1.0 eq.), dichloromethane, reflux] afforded a series of the benzoates, i.e. 2-allylphenyl benzoate, 2-allylphenyl 4-methoxybenzoate, 2-allylphenyl 3,4-dimethoxybenzoate, 2-allylphenyl 3,4,5-trimethoxybenzoate, 2-allyl-5-methoxyphenyl 3,4-dimethoxybenzoate, 2-allyl-5-methoxyphenyl 3,4,5-trimethoxybenzoate, 2-allyl-3,5-dimethoxyphenyl 3,4-dimethoxybenzoate and 2-allyl-3,5-dimethoxyphenyl 3,4,5-trimethoxybenzoate in 68 – 98% yield. During methylenation of these esters through utilisation of the Tebbe reagent, it was found that the reaction is largely dependent on the concentration of the substrate, as well as reaction time and temperature. High yields (71 – 94%) were obtained with an increase in concentration of the ester and a brief period at elevated temperature (80 – 90°C). While a series of substituted diaryl vinyl ethers could be prepared, methylenation of substrates containing a phloroglucinol-type substitution pattern on what was to become the A-ring of the flavonoid failed. Ring closing metathesis of all the

vinyl ethers in hand under standard metathesis conditions [Grubbs II, dichloromethane, reflux] led to the formation of flav-2-ene, 4'-methoxyflav-2-ene, 3',4'-dimethoxyflav-2-ene, 3',4',5'-trimethoxyflav-2-ene, 3',4',7-trimethoxyflav-2-ene and 3',4',5',7-tetramethoxyflav-2-ene in 41 – 96% yields. Attempts at the epoxidation of flav-2-ene with *m*-CPBA with and without a base ($NaHCO_3$), did not yield any of the desired product.

Construction of the isoflavonoid nucleus was first attempted through preparation of the isoflav-2-ene analogue *via* the deoxybenzoin intermediate, which could be prepared by phenylmagnesium bromide addition to the corresponding phenyl acetate. Although the phenyl acetates (methyl 4-methoxyphenyl acetate, methyl 4-trifluoromethylphenyl acetate, methyl 3-methoxy-4-trifluoromethanesulfonyloxyphenyl acetate and methyl 3,5-dimethoxyphenyl-4-trifluoromethanesulfonyloxyacetate) could be prepared in excellent yields (80 – 99%) *via* ozonolysis of the substituted allyl benzenes, the transformation of these compounds into the required deoxybenzoins was hampered by the inability (even at temperatures as low as -78 °C) to stop the reaction of the Grignard reagent with the substrate at the ketone stage. The methodology for the preparation of isoflavenes was therefore adapted to the synthesis of the isoflav-3-ene analogues, which could be constructed through a one-pot reaction of the substituted benzaldehyde with substituted α-bromoacetophenones followed by Wittig reaction with methyltriphenylphosphonium bromide to afford vinyl benzene intermediates, 4-methoxy-2-[(2-phenylallyl)oxy]-1-vinylbenzene, 1,5-dimethoxy-3-[(2-phenylallyl)oxy]-2-vinylbenzene, 1-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene, 4-methoxy-2-{[2-(4-methoxyphenyl)allyl]oxy}-1-vinylbenzene and 1,5-dimethoxy-3-{[2-(4-methoxyphenyl)allyl]oxy}-2-vinylbenzene, in 61 – 89% yield. Subsequent ring closing metathesis of the 7- and/or 4' substituted vinyl benzenes proceeded smoothly over Grubbs II catalyst in refluxing DCM and gave the isoflav-3-enes, (7-methoxyisoflav-3-ene, 4'-methoxyisoflav-3-ene and 4',7-dimethoxyisoflav-3-ene) in 57% to quantitative yields. RCM of the vinyl benzenes with a phloroglucinol-type substitution pattern, however, required elevated temperatures (refluxing toluene) and/or the addition of 1,4-benzoquinone in order to form the isoflav-3-enes, 5,7-dimethoxyisoflav-3-ene and 4',5,7-trimethoxyisoflav-3-ene, in decent yields (67 and 65%, respectively). Subsequent epoxidation of 7-methoxyisoflav-3-ene with *m*-CPBA and $NaHCO_3$ in dichloromethane again failed to give any of the desired isoflavene epoxide.

Although the neoflavonoid nucleus could be reached through Claisen rearrangement of 1-cinnamyloxybenzenes followed by vinylation of the phenolic hydroxy entity or Wittig

mediated methylenation of 2-allyloxybenzophenones, followed by ring closing metathesis, this methodology was not viewed as being appropriate for application to oxygenated substrates as a number of process steps would be required to obtain oxygenated starting materials. It was therefore decided to follow a process where the appropriate acetophenones would be converted into the substituted styrenes by a Grignard reaction-dehydration process. Since electron-rich acetophenones are notorious for being lousy substrates in Grignard reactions the addition of aluminium triflate to the reaction mixture to enhance the reactivity of the reactant was investigated and it was found that the addition of $Al(OTf)_3$ to the reaction mixture had a significant effect on the reaction of 4-methoxyphenylmagnesium bromide and 2-allyloxy-4-methoxyacetophenone. Not only did the presence of the Lewis acid increase the reaction rate, but it also led to the direct formation of the substituted styrene in 66% yield. Extending this reaction to the addition of phenylmagnesium bromide to 2-allyloxy-4,6-dimethoxyacetophenone and the addition of 4-methoxyphenylmagnesium bromide to 2-allyloxy-4,6-dimethoxyacetophenone and 2-allyloxy-4,5-dimethoxyacetophenone gave the substituted styrene products in moderate to high yields (52 – 94%). When 3,4-dimethoxyphenylmagnesium bromide was utilised in reactions with 2-allyloxy-4-methoxyacetophenone and 2-allyloxy-4,5-dimethoxyacetophenone, however, the analogous alcohols were obtained in 50% and 4% yields, respectively. When employing standard Grignard conditions (THF, -60 °C) i.e. without $Al(OTf)_3$ activation, the tertiary alcohol products could be obtained 60% and 80% yields, respectively. Subsequent $CuSO_4$-mediated dehydration of the alcohols yielded the desired styrenes (75% and 65%, respectively). Ring closing metathesis of all the styrene intermediates in hand proceeded smoothly and yielded the series of neoflav-3-enes, (4',7-dimethoxyneoflav-3-ene, 5,7-dimethoxyneoflav-3-ene, 4',5,7-trimethoxyneoflav-3-ene, 4',6,7-trimethoxyneoflav-3-ene, 3',4',7-trimethoxyneoflav-3-ene and 3',4',6,7-tetramethoxyneoflav-3-ene) in excellent yields (67% – quant.).

Since it was shown that aluminium triflate had an enhancing effect on the addition of Grignard reagents to the acetophenones required for the synthesis of neoflavenes and that the styrenes could be obtained in a one-step process, it was decided to explore the scope of this novel process towards other ketones. During this investigation it was determined that the addition of Grignard reagents like phenylmagnesium bromide, benzylmagnesium bromide and ethylmagnesium bromide, to electron-rich ketones, i.e. 4-methoxyacetophenone, 2,4-dimethoxyacetophenone, 2,4-dimethoxypropiophenone and 4-chromanone, led to the formation of respective alkenes in 46 – 97% yields, while no product formation was observed

for the less activated substrates like 4-chloroacetophenone and α-tetralone. It was furthermore observed that for the reaction of 4-methoxyacetophenone with ethyl - and benzylmagnesium bromide only the *E*-isomers of the product was formed, while only the *Z*-isomer was obtained during the addition of ethylmagnesium bromide to 2,4-dimethoxyacetophenone. The reaction of 2,4-dimethoxypropiophenone with phenylmagnesium bromide, on the other hand, yielded both geometric isomers in a 1:1 ratio. The stereoselectivity found during the reactions of 4-methoxy- and 2,4-dimethoxyacetophenone with ethyl - and benzylmagnesium bromide is probably explicable in terms of an E2 elimination process involving the preferred sterically less hindered gauche conformation of the transition state. Extending the reaction to the addition of phenylmagnesium bromide to α,β -unsaturated systems, like chalcone, indicated $Al(OTf)_3$ to also have an activating effect in this regard, albeit to a marginal extent, since only an 8% increase in the yield of the 1,4-addition product was observed. Finally, indications were also found that $Al(OTf)_3$ may also be utilized in catalytic quantities for this reaction when *p*-methoxy-1-phenylstyrene could be prepared in 82% yield by utilising $Al(OTf)_3$ in 10 mol%; thus rendering the new methodology the first Grignard based Lewis acid catalysed process for the direct synthesis of alkenes.

Key words

Ring closing metathesis, flavonoid, Claisen rearrangement, Tebbe, Grubbs II, isoflavonoid, Wittig, neoflavonoid, aluminium triflate, elimination.