DEVELOPMENT OF NEW 'GREEN' METHODOLOGY FOR THE SYNTHESIS OF SUBSTITUTED PHENYLACETIC ACID DERIVATIVES AS PRECURSORS TO ISOFLAVONOIDS AND RELATED COMPOUNDS

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by

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'Chemistry: that most excellent child of intellect and art.'

–Sir Cyril Norman Hinshelwood

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(**433**)

ABBREVIATIONS A1

Solvent Abbreviations

A	=	Acetone
MeCN	=	Acetonitrile
B	=	Benzene
DCM	=	Dichloromethane
Et$_2$O	=	Diethyl ether
DMF	=	Dimethyl formamide
EtOH	=	Ethanol
EtOAc	=	Ethyl Acetate
H	=	Hexane
M	=	Methanol
THF	=	Tetrahydrofuran
T	=	Toluene

Chemical Abbreviations

AcOH	=	Acetic acid
Ac$_2$O	=	Acetic anhydride
AIBN	=	Azobisisobutyronitrile
BuLi	=	Butyllithium
[bmim][BF$_4$]	=	1-Butyl-3-methylimidazolium tetrafluoroborate
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	=	Diethyl azodicarboxylate
DHQD-CLB	=	Dihydroquinidine p-chlorobenzoate
DBQ-CLB	=	Dihydroquinone p-chlorobenzoate
DIAD	=	Diisopropyl azodicarboxylate
DMAP	=	4-Dimethylaminopyridine
DMTSF	=	Dimethyl(methylthio)sulfonium tetrafluoroborate
DMS	=	Dimethyl sulphide

dH$_2$O	=	Distilled water
LDA	=	Lithium diisopropylamide
MOM	=	Methoxymethyl ether
MTPPB	=	Methyltriphenylphosphine bromide
NMM	=	*N*-methyl morpholine
NMMO	=	*N*-methyl morpholine *N*-oxide
PTC	=	Phase transfer catalyst
BQdC	=	Quinidine benzylchloride
BQC	=	Quinine benzylchloride
AgOTf	=	Silver trifluoromethanesulfonate
TTN	=	Thallium trinitrate
PTSA	=	*para*-Toluenesulfonic acid
(Bu)$_3$SnH	=	Tributyltin hydride
Et$_3$N	=	Triethylamine

NMR Abbreviations

s	=	Singlet
d	=	Doublet
dd	=	Doublet of doublets
t	=	Triplet
ddt	=	Doublet of doublets of triplets
m	=	Multiplet
DEPT	=	Distortionless Enhancement by Polarization Transfer
HSQC	=	Heteronuclear Single Quantum Coherence
HMBC	=	Heteronuclear Multiple Bond Correlation
COSY	=	Correlation Spectroscopy
NOESY	=	Nuclear Overhauser Effect Spectroscopy

General Abbreviations

Ar	=	Aromatic
atm.	=	Atmospheric pressure

Bn	=	Benzyl
cat.	=	Catalytic
conc.	=	Concentrated
dil.	=	Diluted
EDG	=	Electron donating group
EWG	=	Electron withdrawing group
FGI	=	Functional group interconversion
HR-MS	=	High resolution mass spectrometry
MS	=	Mass spectrometry
MALDI-TOF	=	Matrix-assisted laser desorption ionization time-of-flight
MW	=	Microwave
Nu	=	Nucleophile
RCM	=	Ring-closing metathesis
w/v	=	Weight per volume

INTRODUCTION 1

The flavonoids represent a group of natural compounds constituting of a C6-C3-C6 carbon skeleton. The two C6 entities, which are joined by the C3 moiety, are aromatic rings, and are usually designated as the A- and B-rings. While some analogues display an acyclic C3 unit, the majority of the flavonoid analogues contain a phenylchroman type structure. Depending on the position where the phenyl substituent (B-ring) is attached to the hetero-atomic ring, the flavonoids are divided into three sub-classes known as flavonoids, isoflavonoids, and neoflavonoids. Flavonoids comprise a 2-phenylchroman skeleton (**1**) whereas isoflavonoids contain a 3-phenylchroman skeleton (**2**) and neoflavonoids a 4-phenylchroman backbone (**3**).

(**1**)
Flavonoid

(**2**)
Isoflavonoid

(**3**)
Neoflavonoid
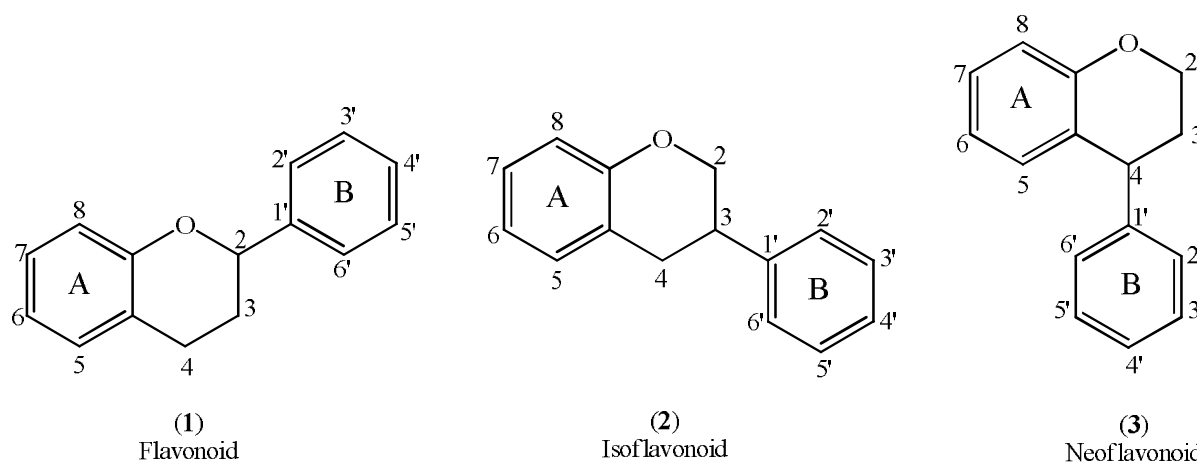
Figure 1.1 Classes of flavonoids

While flavonoids, isoflavonoids and neoflavonoids respectively consist of the above mentioned basic structures, a plethora of substituents on both the aromatic- and heterocyclic rings may lead to a wide variety of compounds being possible. Apart from different levels of hydroxylation of the aromatic rings [phenol (**4**), resorcinol (**5**), phloroglucinol (**6**), pyrogallol (**7**)] and oxidation level of the heterocyclic ring, [flavan (**8**), flavene (**9**), flavanone (**10**), flavone (**11**), flavonol (**12**), dihydroflavonol (**13**)] the naturally occurring flavonoids quite often also display carbohydrate and/or alkyl moieties attached to different positions of the basic C6-C3-C6 skeleton [e.g. genistin (**14**), bidwillon B (**15**), rutin (**16**)].[1,2,3,4,5]

$$\mathbf{4}\ R^1 = R^2 = R^3 = R^4 = R^5 = H$$
$$\mathbf{5}\ R^1 = R^3 = R^4 = R^5 = H,\ R^2 = OH$$
$$\mathbf{6}\ R^1 = R^3 = R^5 = H,\ R^2 = R^4 = OH$$
$$\mathbf{7}\ R^2 = R^3 = R^4 = H,\ R^1 = R^5 = OH$$
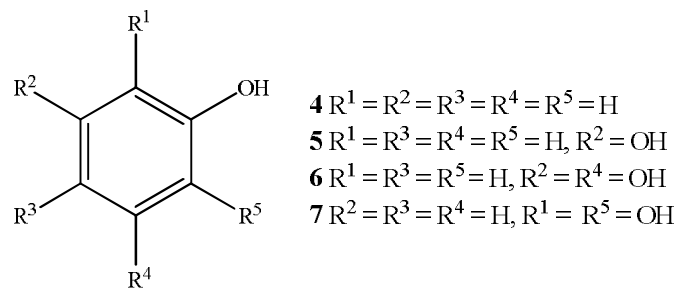
Figure 1.2 Aromatic hydroxylation patterns

(8)

(9)

(10)

(11)

(12)

(13)
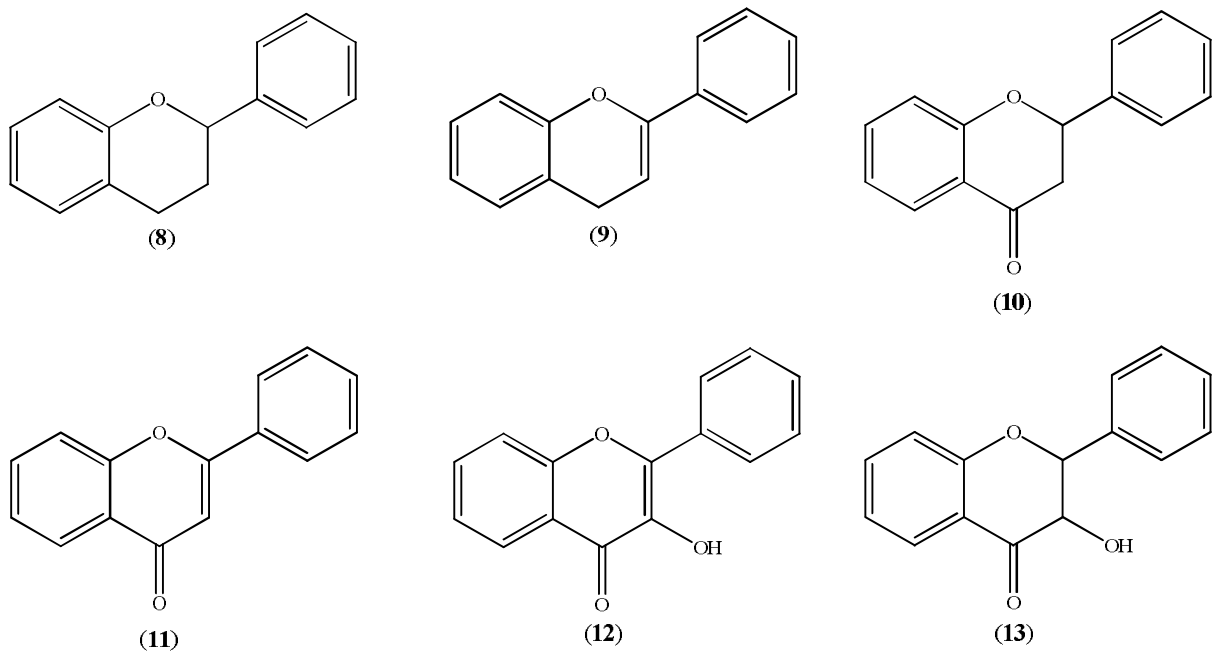
Figure 1.3 Flavonoid oxidation levels
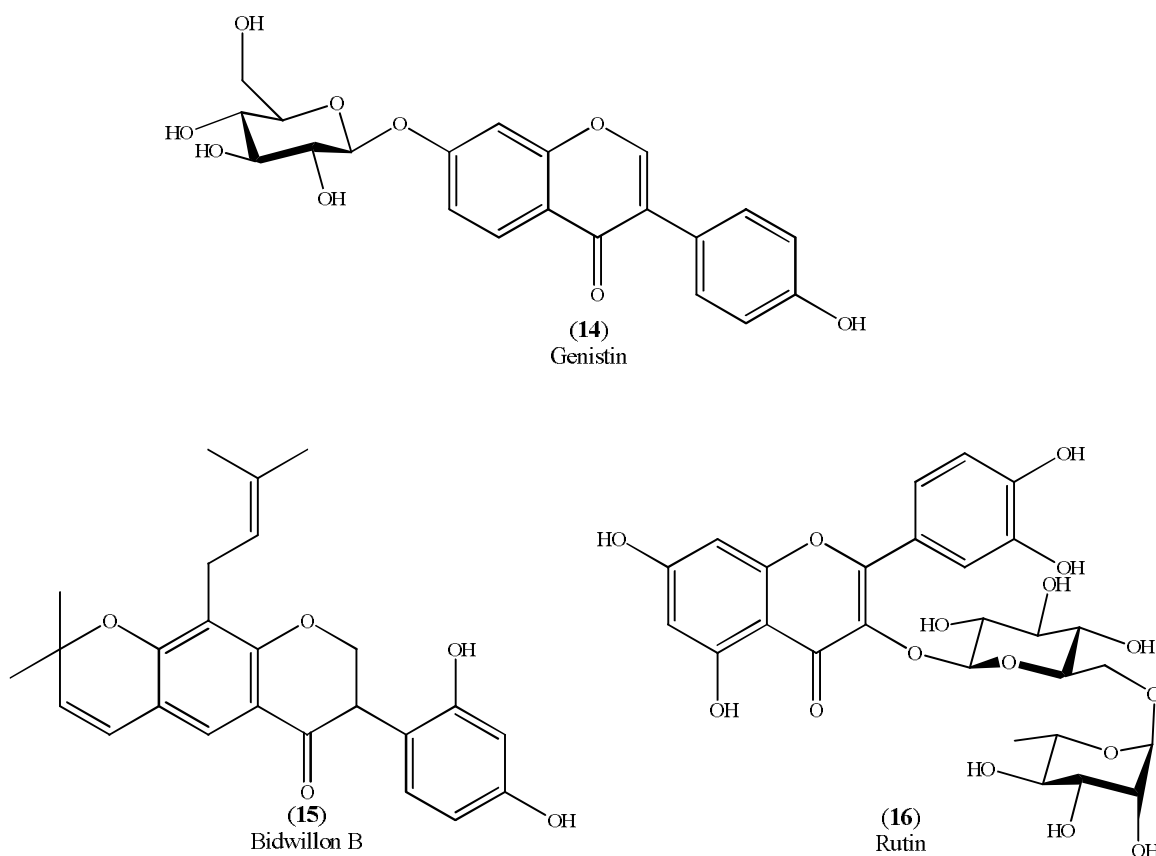
Figure 1.4 Flavonoids with carbohydrate- and/or alkyl groups

Although flavonoids are commonly isolated from plants, little information regarding their quantitative occurrence in food is known. In recent years, however, the biological importance of both flavonoids and isoflavonoids has gained considerable prominence. Various studies indicated an inhibition of oxidative stress and cell propagation, as well as induction of the immune system, apoptosis and detoxification enzymes. These properties are of significant interest as research shows strong evidence toward the modification of the three critical stages in most human cancers (initiation, propagation, progression) by natural dietary compounds, which include the flavonoids.[1,6]

Studies aimed at determining the relationship between the occurrence of cancer and intake of flavonoid rich foods have revealed a strong relationship between cancer prevention and flavonoid intake. An inverse association regarding flavonoid intake to occurrence of breast cancer was observed, especially in postmenopausal women.[1,7]

A gum gathered by bees from various plants, known as propolis, is also known for its biological properties. It has been considered as good adjuvant in the prevention of certain

infectious diseases or treatment thereof. Although the composition of propolis is highly complex and varies due to different phytogeographical areas, the main compounds found in four different Anatolian samples included flavonoids such as quercetin, galangin, naringenin, pinobanksin, chrysin and pinocembrin. These compounds especially proved to have substantial antimicrobial activity against yeasts and Gram-positive bacteria. An investigation toward the aggregatory effect of galangin (**17b**) on bacterial cells of *Staphylococcus aureus* implies that this flavonoid uses the cytoplasmic membrane as target location for its activity. More recently it was reported to display selective and potent activity toward *Cryptococcus gattii* - a pathogenic fungus.[2]

(17a)
Quercetin

(17b)
Galangin

(17c)
Naringenin

(17d)
Pinobanksin

(17e)
Chrysin

(17f)
Pinocembrin
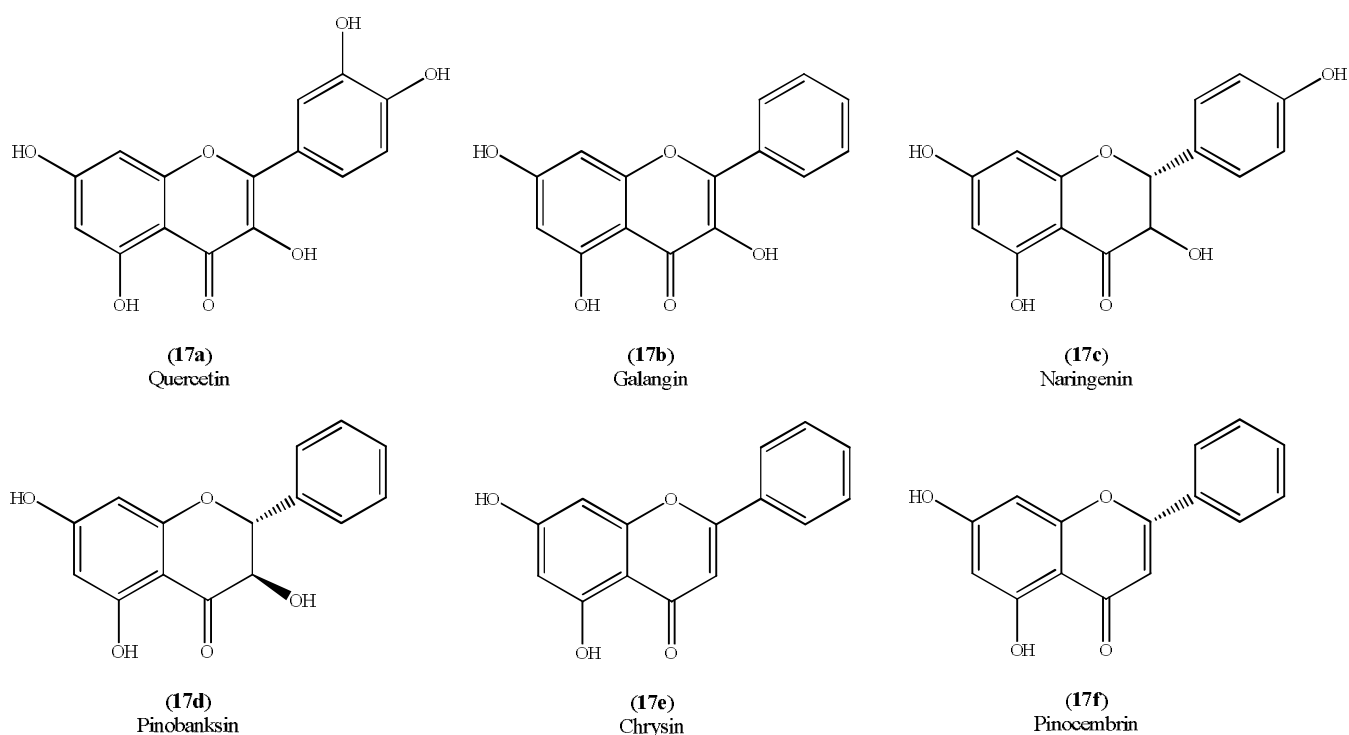
In contrast to the flavonoids, the distribution of isoflavonoids are relatively limited, most likely because of the sporadic occurrence of the isoflavone synthase enzyme, which is only produced by plants when needed.[2] Isoflavonoids are therefore not that widely distributed in the plant kingdom.

Despite their limited distribution, isoflavonoids and especially pterocarpans (**18**) have received immense interest due to their medicinal properties as anti-fungal, anti-bacterial and anti-viral agents as well as their activity as phytoalexins (an insect repellent produced by plants) and potent antitoxins.[8]
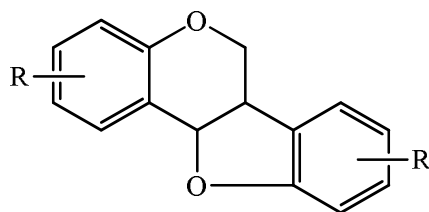
R = O-Alkyl, OH, Alkyl
(**18**)
Pterocarpan

Testing of possible biological properties of these compounds, and their effect on human biochemistry, is an imperative step toward improving human health, thus the synthesis of isoflavonoids has become critical. Regarding the synthesis of isoflavonoids, specifically isoflavones, two major routes are widely utilized: [9]

- Chalcone pathway
- Deoxybenzoin pathway

The chalcone route entails the aldol condensation of a substituted acetophenone (**19**) and benzaldehyde (**20**) to give the desired chalcone (**21**). The next step, however, involves an oxidative rearrangement with Tl(III) salt(s) to form an acetal (**22**), which is then cyclized to the isoflavone (**23**) by exposure to acidic conditions (Scheme 1.1).[9]
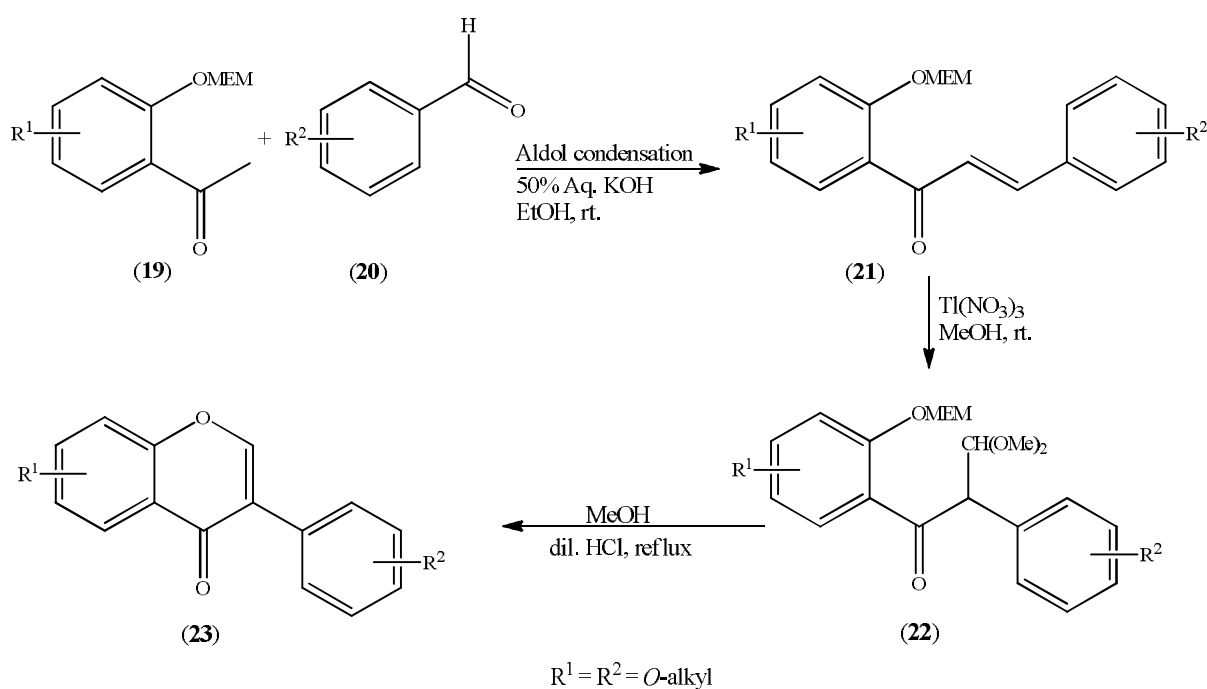
Scheme 1.1 Chalcone pathway for isoflavonoid synthesis

The alternative deoxybenzoin route (Scheme 1.2) has the advantage that it does not require the utilization of poisonous reagents,[9] but it needs the availability of phenylacetic acid derivatives with various substitution patterns. Since these compounds are not always available with substitution patterns displayed by naturally occurring isoflavonoids, this aspect of the deoxybenzoin route limits its applicability and makes the synthesis of these compounds a vital part of this type of preparation.

R = H or OH or O-alkyl or X
X = Halogen
R^1 = OH or O-alkyl
R^2 = OH or O-alkyl
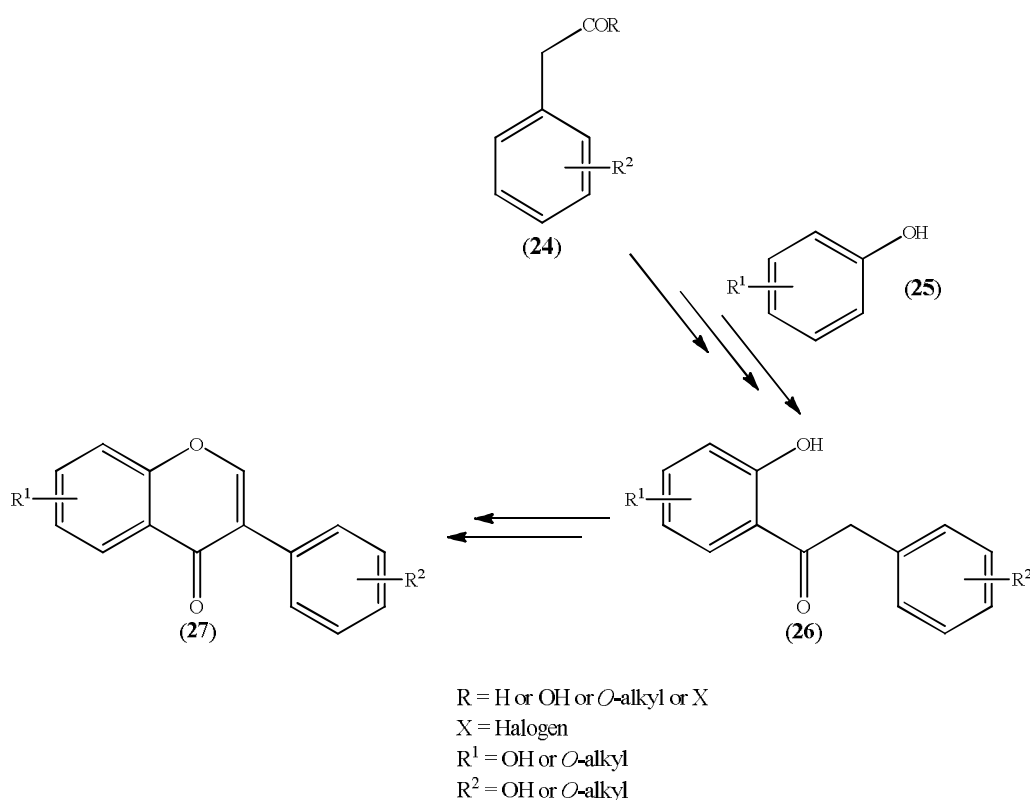
Scheme 1.2 Deoxybenzoin pathway to isoflavonoids

Although substituted phenylacetic acid derivatives are accessible *via* rearrangement of the corresponding acetophenone analogues through the utilization of reactions like the ancient sulphur-based Willgerodt-Kindler reaction,[10,11,12,13] lead(IV)acetate or $Tl(NO_3)_3$ oxidative rearrangements[10,14] and other reactions,[12] most of these methods are also hampered by serious limitations. Application of the Willgerodt-Kindler reaction is, for example, complicated by the requirement of high reaction temperatures and excess quantities of elemental sulphur leading to the formation of large amounts of smelly side products, while yields are also variable.[10,11,12] The methodologies developed by McKillop[10] [$Tl(NO_3)_3$] and Myrboh[15]

[lead(IV)acetate] utilizes toxic heavy metal reagents[16] and are also not always high yielding and compatible with all substitution patterns.

R = H or OH or *O*-alkyl or X
R^1 = OH or *O*-alkyl
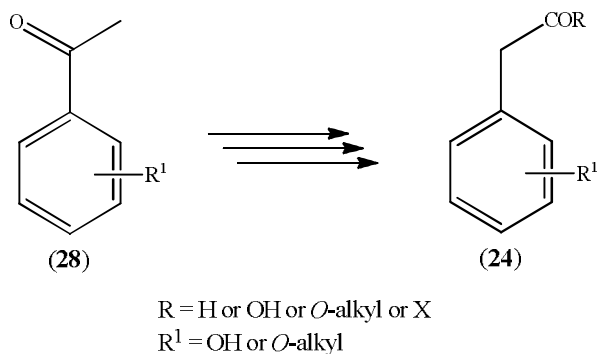
Scheme 1.3 Synthesis of phenylacetic acids as reported in literature[10, 11, 12]

It was therefore envisaged to develop a synthetic route for the preparation of phenylacetic acid derivatives that would be high yielding and environmentally favourable. Since ozonolysis of substituted allylbenzenes has the potential to meet these requirements, this reaction was investigated as methodology for the preparation of phenylacetic acid derivatives. If chiral derivatives of the phenylacetic acids could be made, this protocol would have the added advantage to incorporate stereoselectivity in the synthesis of chiral isoflavonoids.

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ISOFLAVONOID SYNTHESIS 2

2.1 Introduction

The structural variety of isoflavonoids found in natural sources is quite large due to, not only the different oxidation levels present in the basic phenylchroman skeleton, but also the presence of other heterocyclic rings as well as the complexity and number of different substituents on the basic skeleton. The classes of isoflavonoids represented in Figure 2.1.1 are distinguished according to the level of oxygenation and unsaturation present on/in the heterocyclic C-ring and the presence of other heterocyclic rings:

(29)
Isoflavones

(30)
Isoflavanones

(31)
Isoflavenes

(32)
Isoflavans

(18)
Pterocarpans
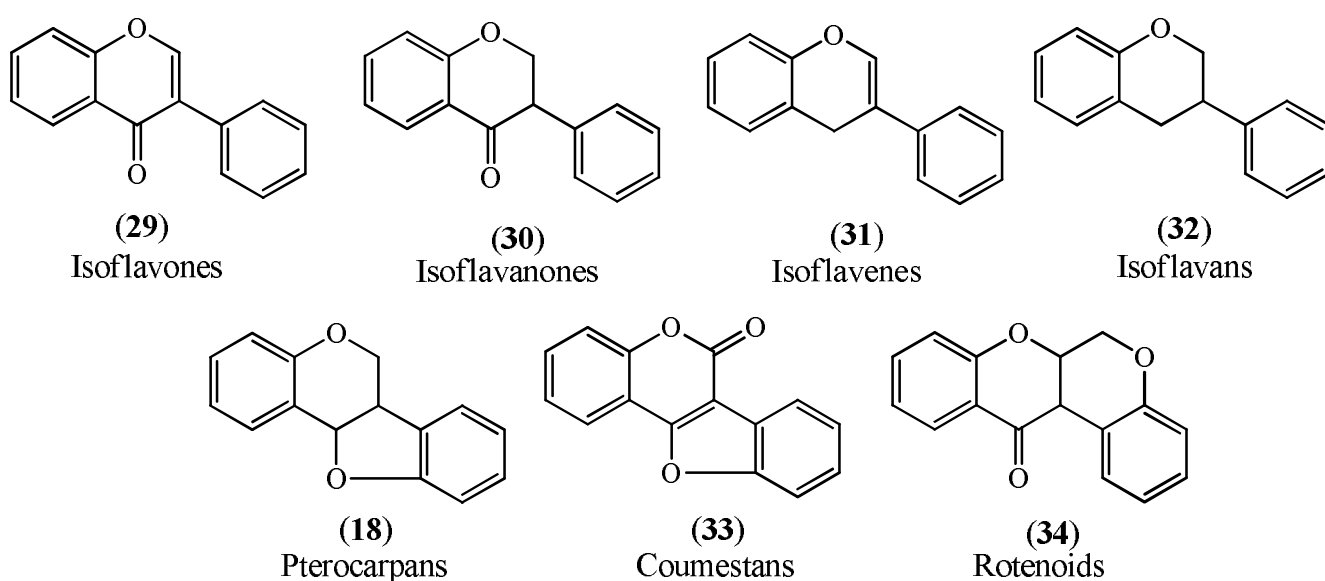
(33)
Coumestans

(34)
Rotenoids

Figure 2.1.1 Classes of isoflavonoids

The development of new methodologies for the synthesis of isoflavonoids is important due to the limited distribution of these compounds in the plant kingdom together with the beneficial health effects they demonstrate, for example the anti-leukemic properties of the isoflavone, genistein (**35**).[1,2,3,4]
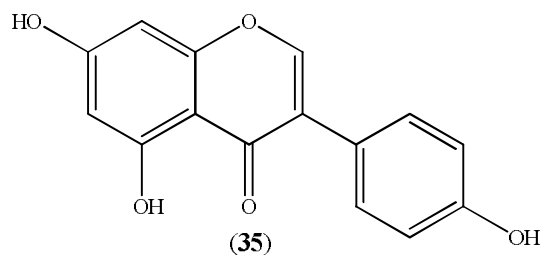
Genistein

2.2 Isoflavones

The synthesis of isoflavones deserve special attention as these compounds often function as key intermediates in the preparation of other isoflavonoids such as isoflavans, isoflavanones and pterocarpans.[5] In recent years, scientific interest towards isoflavones has also increased due to the possible health effects these compounds exhibit. Connections concerning the prevention of osteoporosis and cancer and the effects on cardiovascular diseases have also been made.[2,3,6]

The first synthesis of isoflavones was reported by Baker *et al.*[7] in 1925 where various 2-substituted isoflavones were prepared from 2-hydroxydeoxybenzoins, for e.g. 2,4-dihydroxyphenyl ketone together with acetic anhydride and sodium acetate with subsequent hydrolysis (alkali) yielded 2-hydroxy-7-methylisoflavone (> 90% yield).[6,7,8] Currently the most popular methods for the synthesis of the basic 3-phenylbenzopyrone structure of isoflavones are through the utilization of either a C14 or C15 precursor molecule like a deoxybenzoin (**36**) or chalcone (**37**).[3,4,7,9,10,11,12,13,14] When utilizing a C14 precursor, ring closure of the deoxybenzoin moiety by means of a one-carbon fragment is required, while the utilization of a C15 precursor usually entails oxidative rearrangement.

(**36**)
R = alkyl
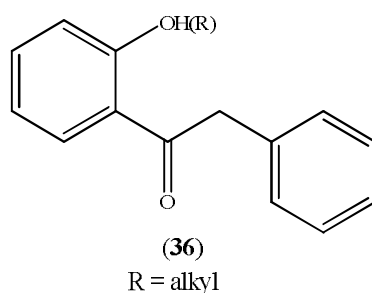
Deoxybenzoin Skeleton

(37) R = alkyl
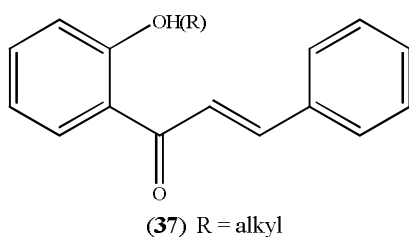
Chalcone Skeleton

Since ring closure of the deoxybenzoin moiety by the addition of a one carbon fragment represents a key step in this synthetic approach, several reagents have been utilized to effect this crucial transformation. Although the application of triethylorthoformate in boiling pyridine-piperidine has found wide application in this regard, it has been unsuccessful for substrates having a phloroglucinol (2,4,6-trihydroxy) substitution pattern on the aromatic ring.[5] Other ring-closing methods include the utilization of zinc cyanide together with hydrogen chloride[5,9] and phosphorus oxychloride with dimethylformamide.[5,9] The application of the latter methods, however, are limited to ketones with resorcinol type oxygenation.[5] Although protection of all hydroxy groups but the one involved in the heterocyclic ring formation was a requirement for the initial application of the ethyl formate/sodium methodology, it was later found that this reagent system could also be applied to deoxybenzoins having free hydroxy groups in the 2-position of both the A- and B-rings (Scheme 2.2.1).[5,13,15] Recently, DMF together with methanesulfonyl chloride and boron trifluoride-etherate was reported to afford excellent yields of isoflavones,[6,9,16,17] while *N*-formylimidazole, formed by reaction of formic acid with *N,N*-carbonyldiimidazole, have also been used as C1 source and afforded the isoflavones in yields of 60–76%.[15,18]


$R^1, R^2 = H$, alkyl, *O*-alkyl
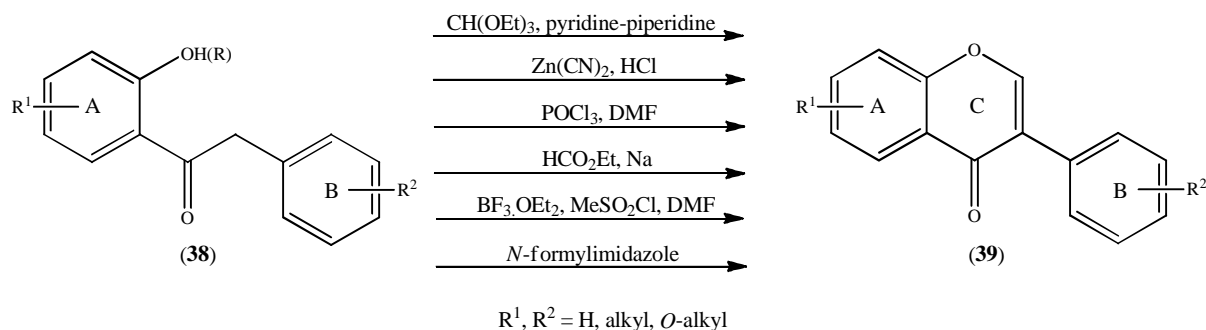
Scheme 2.2.1 Deoxybenzoin ring-closing routes

While the addition of a C1 unit to deoxybenzoins have been achieved in good to excellent yield for quite a number of substrates, the synthesis of these starting materials are not that easy and have been hampered by poor yields and the limited availability of starting materials.[15]

Due to the problems associated with the preparation of deoxybenzoins, methodology centering on the utilization of chalcones as precursors to the formation of isoflavones, have gained popularity in the recent past. The fact that chalcones are readily available *via* condensation of aromatic aldehydes with acetophenones with a wide variety of substitution patterns and that chalcones already contain the required number of non-aromatic carbon atoms, led to investigations into the possible rearrangement of these analogues into isoflavonoids. In this regard it was found that the rearrangement of chalcone epoxides through the action of boron trifluoride as catalyst in fact led to the formation of isoflavones, albeit in poor yields (Scheme 2.2.2).[6,15] Currently the established route towards the synthesis of isoflavones that was developed by Ollis *et al.*,[17] entails treatment of the chalcone precursor with thallium trinitrate (TTN). The oxidative rearrangement induced by the TTN leads to the formation of an acetal intermediate, which, under acidic conditions, cyclizes to give the desired isoflavone.[6,11,17] The synthesis of glycitein (**46**) according to this methodology is shown in Scheme 2.2.3.[6,19]
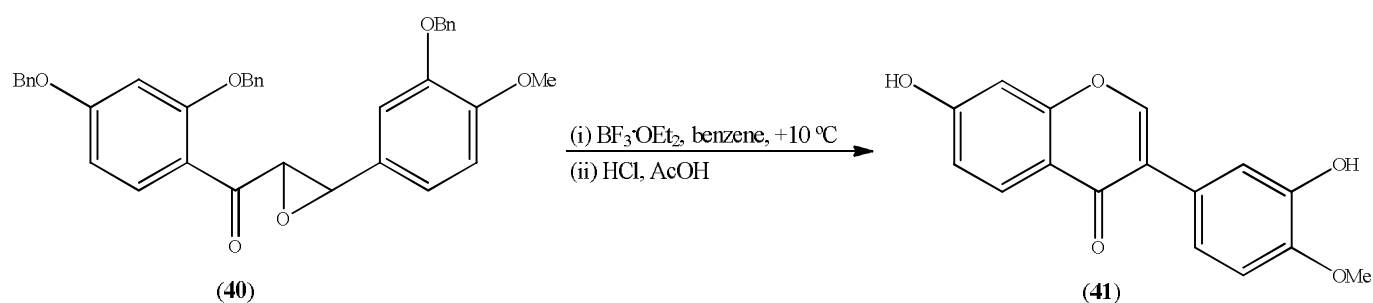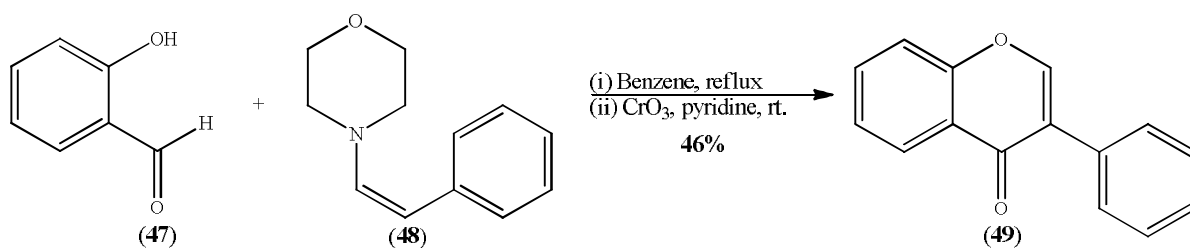

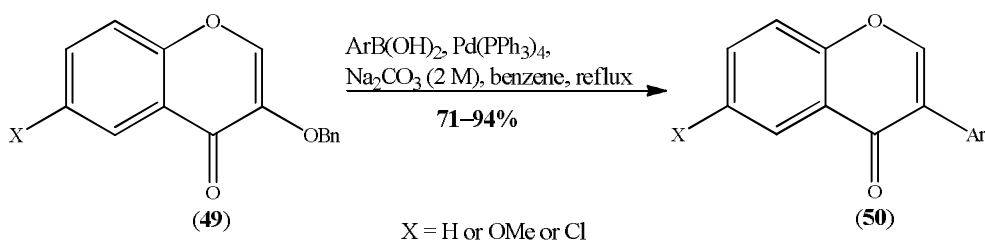**Scheme 2.2.2 Isoflavone from epoxidated chalcones**
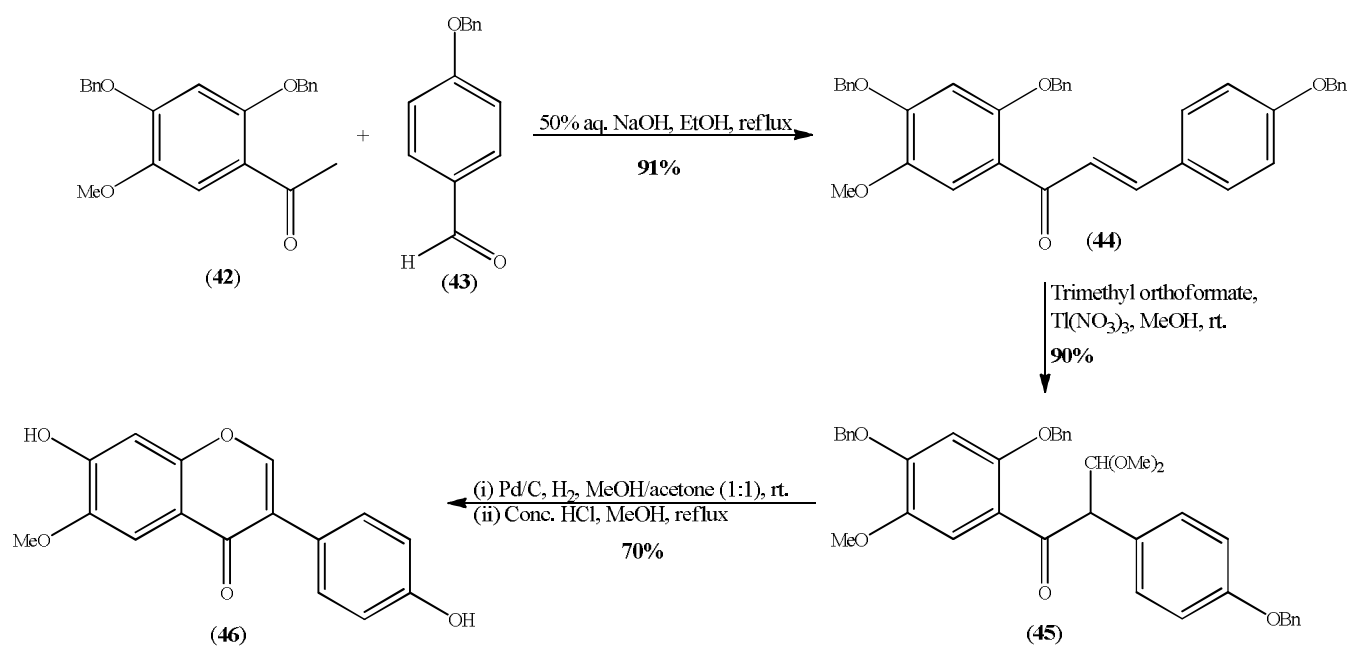
Scheme 2.2.3 Synthesis of glycitein[19]

More recently, isoflavones have been prepared through application of the condensation of enamines with salicylaldehydes as well as the Suzuki cross-coupling reaction (Schemes 2.2.4 and 2.2.5 respectively).[3,20,21]


Scheme 2.2.4 Isoflavone by condensation of enamine[20]

Scheme 2.2.5 Isoflavone *via* Suzuki coupling[21]

2.3 Isoflavanones

Since isoflavanones only differ from the isoflavones w.r.t. the oxidation level of the heterocyclic ring, these compounds are usually synthesized in very much the same manner and as such the synthesis of isoflavanones can be viewed as a trivial exercise. However, since isoflavanones exhibit structural similarities to that of human estrogens and are showing significant physiological activity[22] especially in the case of bidwillon B (**15**) w.r.t. the pathogenic micro-organism, methicillin-resistant *Staphylococcus aureus* (MRSA),[23] the preparation of these analogues have received well deserved attention. Due to their close structural resemblance to isoflavones, the obvious route towards the synthesis of isoflavanones would be through partial reduction of the corresponding isoflavone, which is conveniently achieved by catalytic hydrogenation.[5]
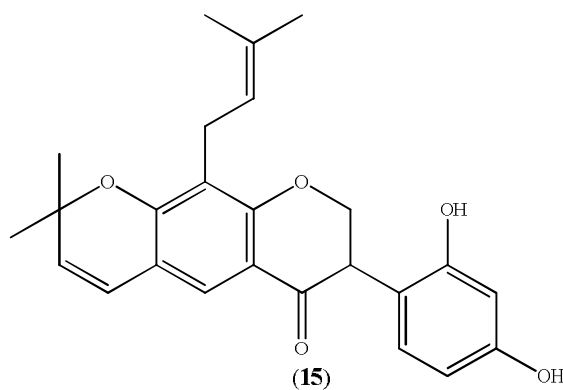

Bidwillon B

Since over reduction to the corresponding isoflavan-4-ol or even isoflavan occurs quite easily during the utilization of catalytic hydrogenation, care must be taken to prevent this side reaction in order to obtain good yields. Farkas *et al.*[24] reported that reduction of isoflavones with 10% Pd/C in acetic acid under carefully monitored conditions gave the desired

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isoflavanone in moderate (45%) yield. Very low selectivity is, however, obtained under these conditions if the substrate does not have any substituent in the 5-position. In this case the solvent may be changed to acetone, but it is done at the cost of an abruptly reduced reaction rate.[25] Alternatively, more selective reducing agents, such as di-isobutylaluminium hydride (DIBAL), may be used, which have led to the preparation of isoflavanones in 50–70% yield.[1,26,27] If the 2'-hydroxy group of isoflavans is protected, DDQ oxidation may be used to transform these compounds into the corresponding isoflavanones.[1,28] Finally, isoflavanones may also be prepared by the reduction of 3-hydroxyisoflavan-4-ones using zinc and acetic acid, but since the substrate is often difficult to prepare, this method is of limited practical value.[5]

Since the synthetic routes described above all go through the isoflavone or similar analogue with limitations as indicated above (paragraph 2.2), methodology analogous to the synthesis of isoflavones from deoxybenzoins was developed, albeit with different C1 moieties. Utilizing methylene iodide (CH_2I_2) as C1 source, under phase transfer conditions in the presence of n-tetrabutylammonium iodide, sodium thiosulphate ($Na_2S_2O_3$) for iodine capture and aqueous base, Singh et $al.$[29] were able to prepare isoflavanones in 60–70% yields through the utilization of this method (Scheme 2.3.1).
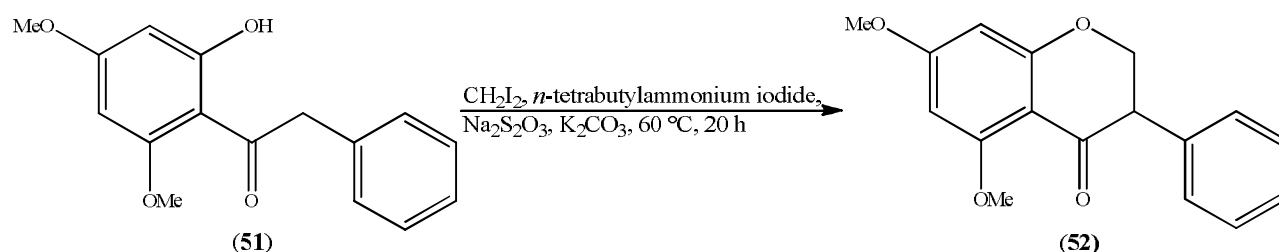
Scheme 2.3.1 Methenylation of deoxybenzoin[29]

Ethoxymethyl chloride ($ClCH_2OEt$) and formaldehyde have also been used as C1 source to obtain α-hydroxymethyl derivatives (**55**), which can then be cyclized to isoflavanones in 50–60% yields (Scheme 2.3.2).[1] This route has the added effect/benefit of in $situ$ protection of the hydroxy groups in the starting deoxybenzoin.
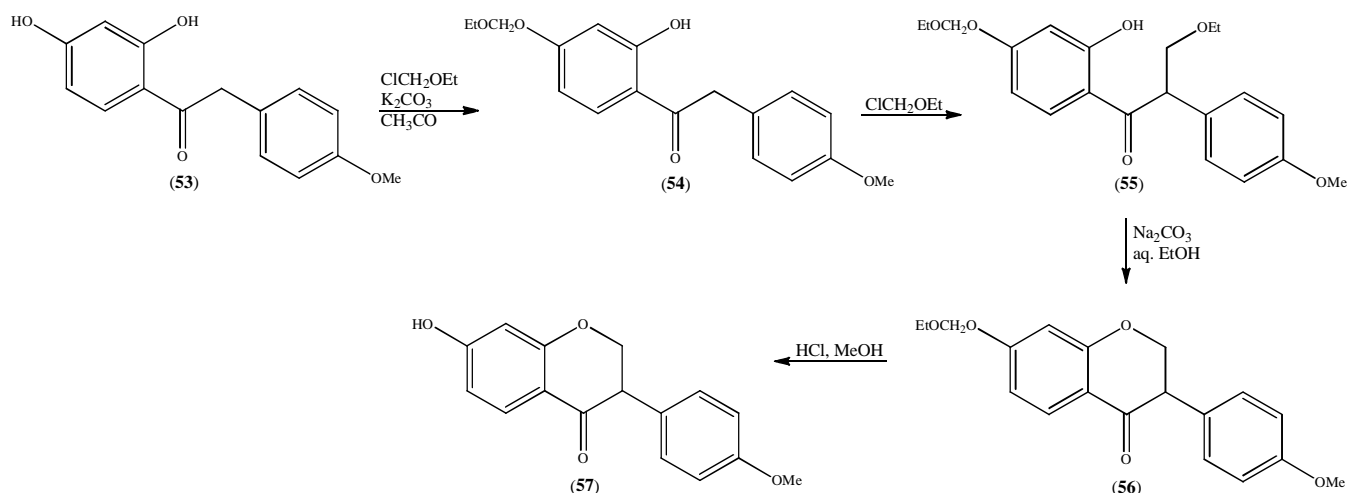
Scheme 2.3.2 Synthesis of dihydroformononetin

As for the isoflavones, this approach is hampered by all the difficulties associated with synthesizing the deoxybenzoin substrate.

2.4 Isoflavans

The isoflavans signify the most reduced form of the isoflavonoids and are normally synthesized by reduction of isoflavones[30] or pterocarpans. (Scheme 2.4.1).[5,15,31]

R = OH, *O*-alkyl or alkyl
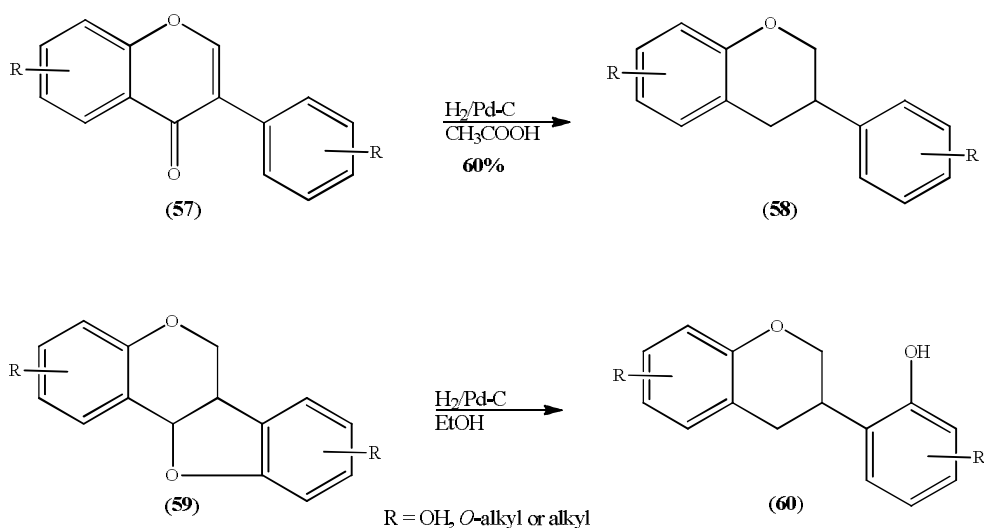
Scheme 2.4.1 Reduction of isoflavone and pterocarpan

However, a large excess of Pd catalyst is required for the reduction of isoflavones[32] and decreasing catalyst quantity or reuse of the catalyst often leads to a mixture of products where

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hydrogenation of the A- or C-rings occur, among others. Moreover, this methodology cannot be applied where unsaturated systems are present in substituents as these moieties may be reduced to the saturated analogues.[33]

Although various synthetic methods to pterocarpans (paragraph 2.6) exist, they are usually not employed as key precursor molecules in the synthesis of isoflavans since various additional steps are required. Consequently isoflavans are rather prepared from isoflavones.[23]
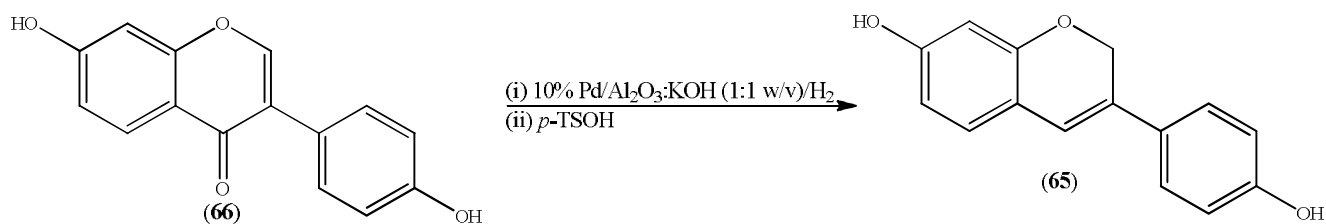
2.5 Isoflavenes

The obvious way for synthesizing isoflavenes would be through reduction of isoflavones (**61**) to the corresponding isoflavan-4-ols (**63**), which could then be subjected to dehydration leading to the isoflav-3-ene (**64**) (Scheme 2.5.1).[34]
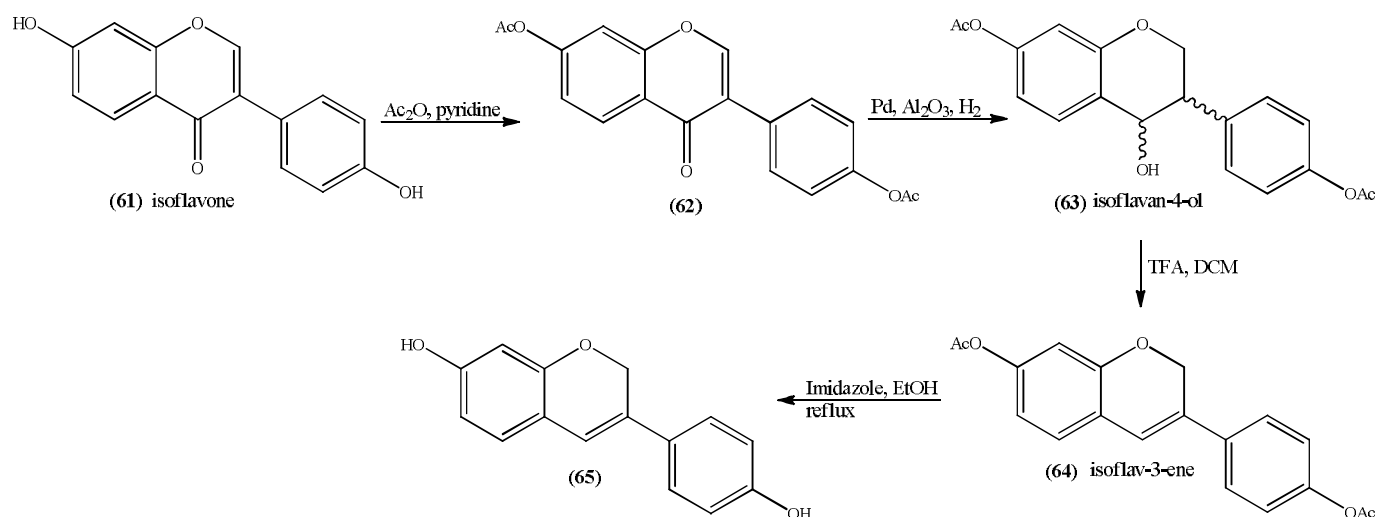
Scheme 2.5.1 Isoflavene synthesis *via* isoflavone: Synthesis of dihydroequol

Application of this method, however, consists of many steps and has the added disadvantage that protection of free hydroxy substituents is required if good yields are to be achieved. Based on isoflavones as starting material, Heaton and Jeoffreys[34] patented a one-pot synthesis for isoflavenes where a basic palladium on alumina catalyst was utilized. Application of this method allowed for the hydrogenation of the isoflavones without protecting the hydroxy substituents on the rings and led to the synthesis of dehydroequol (**65**) from daidzein (**66**) in excellent yield, for example (Scheme 2.5.2).

Scheme 2.5.2 One-pot isoflavene synthesis

In an attempt to reduce the number of steps required for the formation of isoflavenes when isoflavones are used as substrates, Liepa[35] developed a methodology based on the formation and reduction of isoflavylium salts (Scheme 2.5.3). This process, however, is complicated by the fact that the nature of the reducing agent as well as the substitution pattern on the isoflavylium salt determine the outcome of the process w.r.t. the position of the double bond, *i.e.* formation of isoflav-2-ene (**71**) or isoflav-3-ene (**70**). Reduction of 5,7,4'-trihydroxyisoflavylium chloride, for example, predominantly yielded the corresponding isoflav-3-ene when sodium cyanoborohydride (NaBH$_3$CN) is used as reducing agent, whereas 5,7-dihydroxy-4'-methoxyisoflavylium salt (**69**) gave a more or less 1:1 mixture of isoflav-2-ene (**71**) and isoflav-3-ene (**70**) with the same reducing agent (Scheme 2.5.3). While the isoflavylium salt could easily be obtained in this instance by reacting phloroglucinol (**67**) with the arylmalondialdehyde (**68**), this reaction does not represent a general method since the reaction failed when resorcinol was used as phenolic substrate. The process is further complicated by the general unavailability of the appropriate aryl substituted dialdehyde analogue (**68**).[1]

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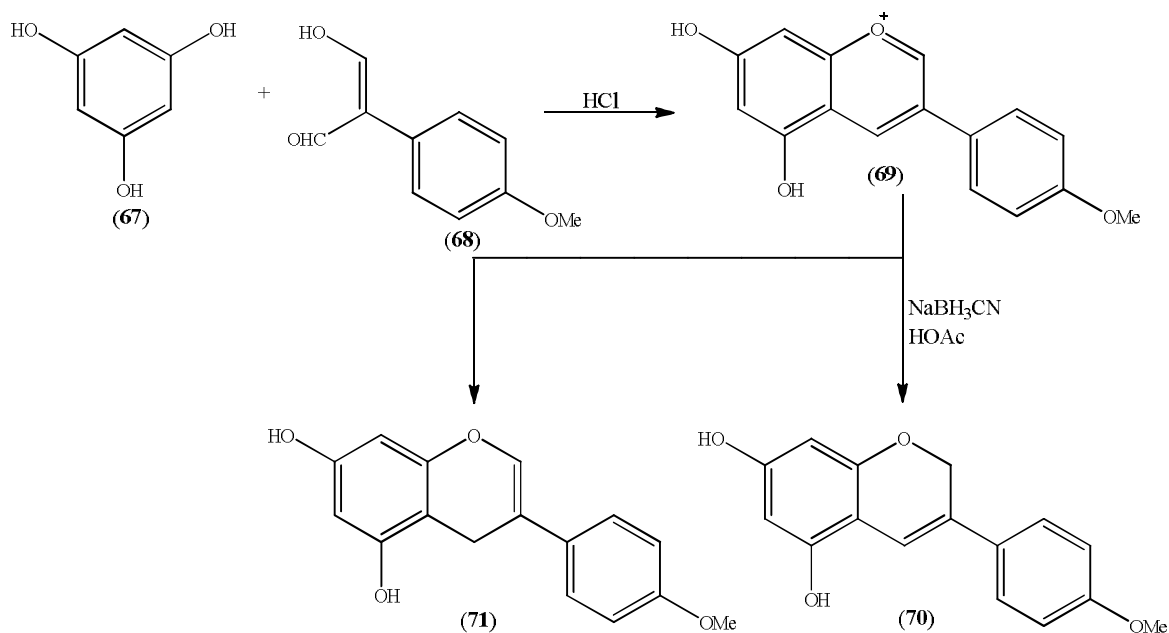
Scheme 2.5.3 Synthesis of isoflavenes through the formation of isoflavylium intermediates

Since the discovery of the Grubbs and other highly efficient catalyst systems, ring-closing metathesis has become a powerful tool in many areas of organic synthesis. In this regard Li *et al.*[36] applied ring-closing metathesis to the synthesis of isoflavenes and were able to obtain the desired product in 82% yield (Scheme 2.5.4).
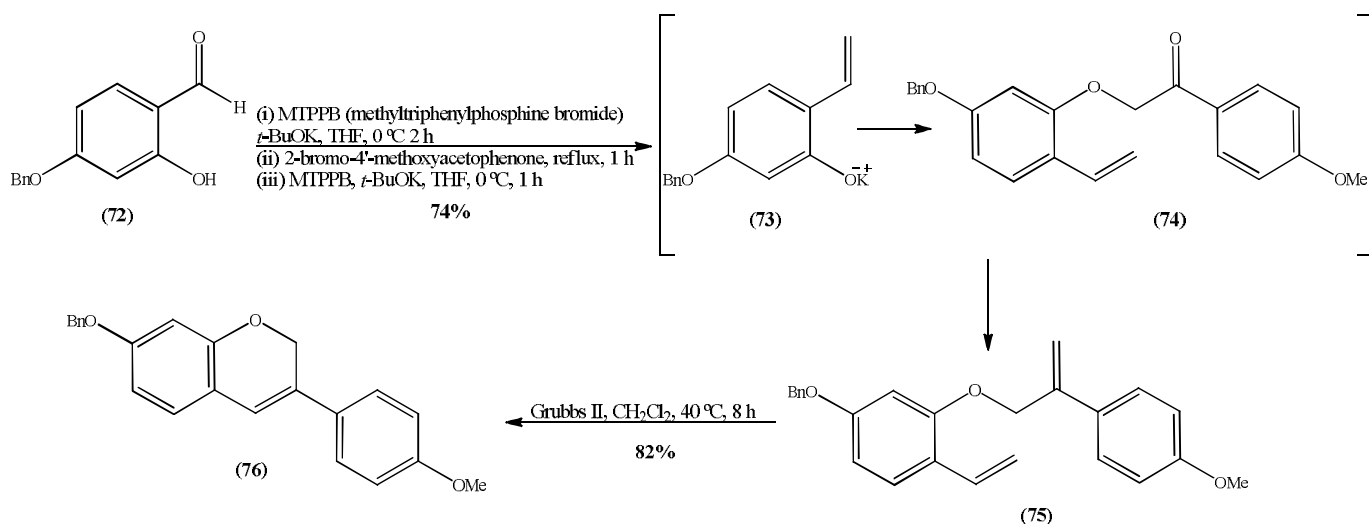
**Scheme 2.5.4 Synthesis of isoflav-3-enes *via* metathesis[36]**

Li *et al.*[36] were able to extend the protocol to the synthesis of some biologically important isoflavonoids like haginin (**77**), daidzein (**66**), formononetin (**79**) and equol (**78**).

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haginin (77) equol (78) daidzein R = H (66) formononetin R = CH₃ (79)
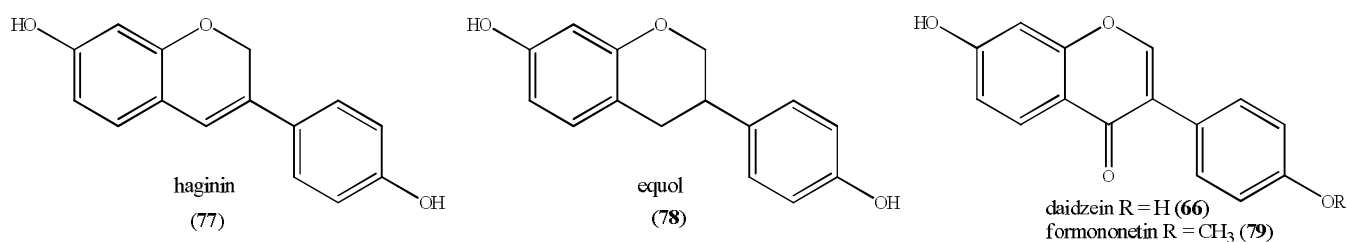
2.6 Pterocarpans

Endeavours toward pterocarpan synthesis include reduction of 2'-hydroxyisoflavones utilizing metal hydrides followed by a mild acid to effect cyclization. Prasad *et al.*[37] reported a one-pot hydrogenative cyclization of an isoflavone (**80**) wherein the utilization of acid is avoided and the necessity of metal hydride is eliminated (Scheme 2.6.1).
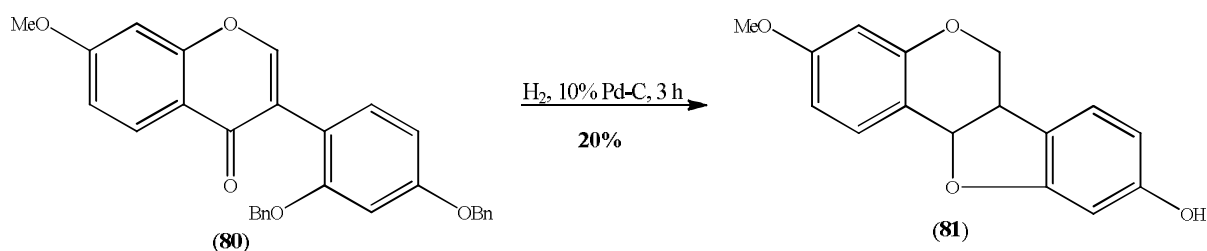
**Scheme 2.6.1 Hydrogenative cyclization of isoflavone to pterocarpan[37]**

Improved yields were reported by Sa e Sant'Anna and co-workers[38] utilizing the Heck oxyarylation, where reaction between 2*H*-chromene (**82**) and 2-chloromercurio-4,5-methylenedioxyphenol (**83**) afforded pterocarpan in 43% yield (Scheme 2.6.2).

$R^1 = R^2 = -OCH_2O-$
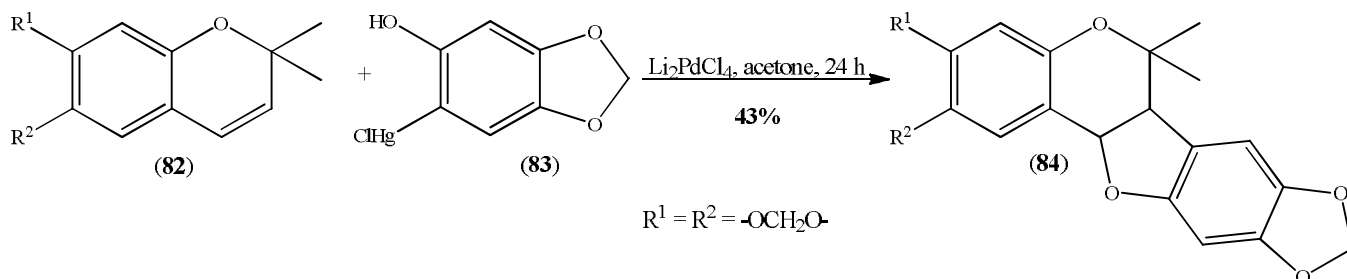
**Scheme 2.6.2 Heck oxyarylation[38]**

This methodology, however, requires the availability of chromenes which cannot be obtained commercially and entails various synthetic steps utilizing phenol as starting material. Moreover, the yield obtained proved to be unsatisfactory even though it was an improvement on the methodology described by Prasad *et al.*[37]

Cycloaddition of 2-alkoxy-1,4-benzoquinones (**86**) with 2*H*-chromenes (**85**) afforded the pterocarpan (**87**) in excellent yield (Scheme 2.6.3) and similar substrates gave yields varying from 10–90%. The methodology does pose the problem of substrate availability once again where several steps are required to obtain the starting materials consisting of various oxygenation patterns for pterocarpan synthesis according to this protocol.[39,40,41]
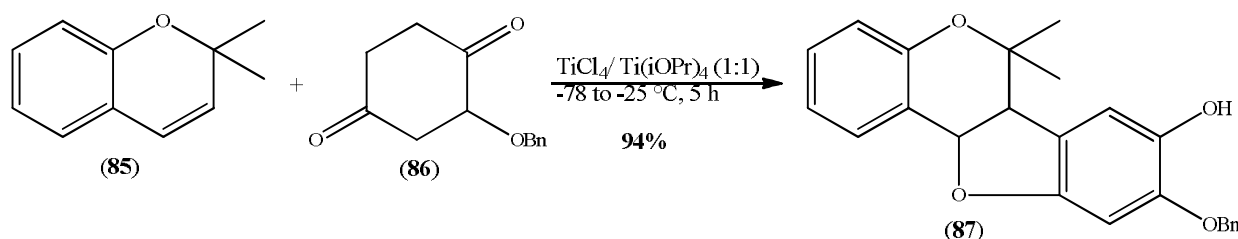
Scheme 2.6.3 Pterocarpan *via* cycloaddition

Recent pterocarpan synthesis was reported by Skouta and Li[42] where annulation of salicylaldehyde (**88**) and phenylacetylene (**89**) followed by treatment with $NaBH_4$ and $BF_3 \cdot OEt_2$ afforded the pterocarpan (**18**) in 91% yield (Scheme 2.6.4). Similarly, 2-chloropterocarpan was obtained in 53% yield.[39,42]
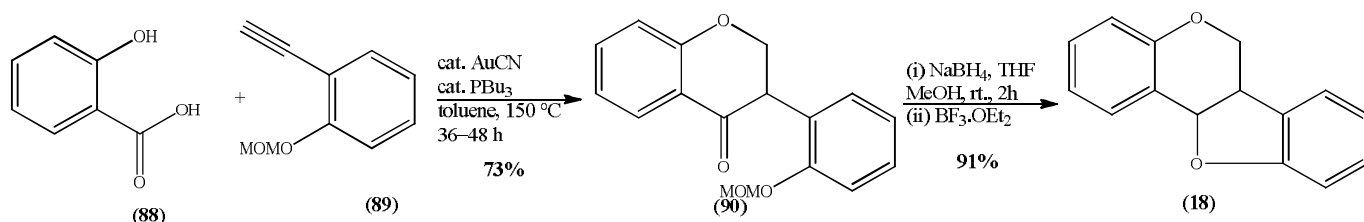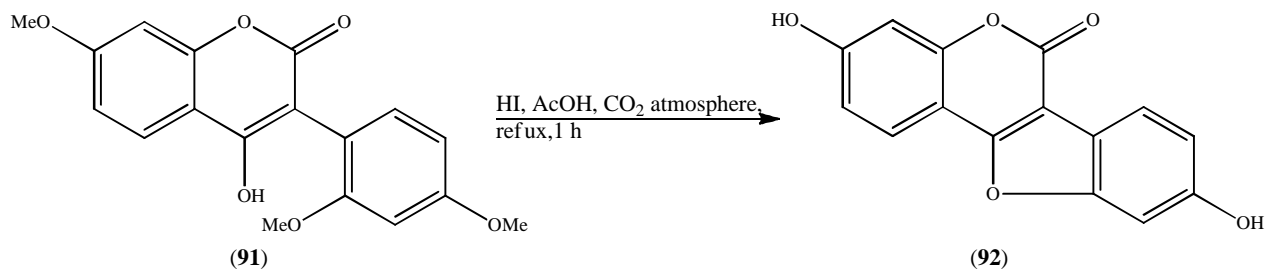

Scheme 2.6.4 Synthesis of pterocarpan *via* gold-catalyzed annulation

2.7 Coumestans

In 1958 Emerson and Bickoff[43] proved that 2'-alkoxy-4-hydroxy-3-phenylcoumarins (**91**) may be cyclized to coumestans (**92**) in the presence of hydroiodic acid (HI) (Scheme 2.7.1).

Even though the desired product was isolated, the yield of the resulting coumestan was not reported.

Scheme 2.7.1 Cyclization of 3-(2,4-dimethoxyphenyl)-4-hydroxy-7-methoxycoumarin[43]

An obvious drawback of this method is that complete dealkylation takes place and subsequent attempts by Farkas and co-workers[25] to circumvent/prevent dealkylation proved to be unsuccessful.

Subsequent studies performed by Wanzlick *et al.*[44] revealed that the coumestan, wedelolactone (**95**), could be formed directly through oxidative coupling of 4-hydroxycoumarins like (**93**) with catechol (**94**) in this way (Scheme 2.7.2).
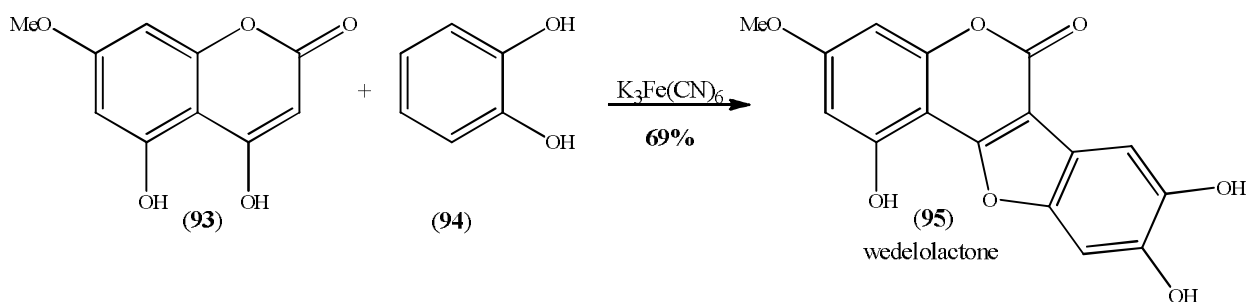
Scheme 2.7.2 Coumestan synthesis by Wanzlick[44]

Other methods include flavalium salt oxidation with H_2O_2 in MeOH followed by heating in acetic acid-hydrochloric acid or oxidation of pterocarpens in air or with chromium trioxide.[5] Even though an array of methods have been applied to the synthesis of coumestans, all of these consisted of multiple steps and/or gave only moderate yields.

A process reported recently involved an intramolecular oxidative annulation of 4-hydroxy-3-phenyl-2*H*-chromen-2-one derivatives (**96**) in the presence of FeCl$_3$. Utilizing this protocol, Tang *et al.*[45] were able to prepare a variety of coumestans from simple readily available starting materials in yields varying from 32–89% (Scheme 2.7.3).
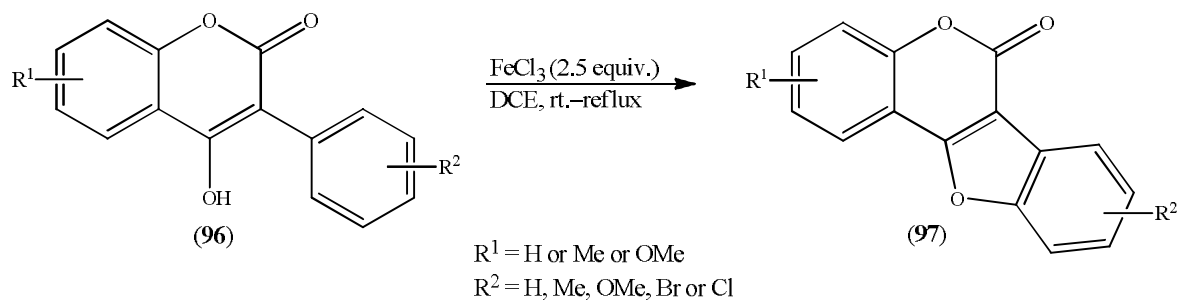
**Scheme 2.7.3 Intramolecular oxidative annulation to coumestans**[45]

Another novel and more efficient two-step route to coumestans consisting of iodocyclization followed by palladium catalyzed carbonylative lactonization has been developed by Yao and co-workers[46] (Scheme 2.7.4). This process afforded the desired products in 31–98% yield.
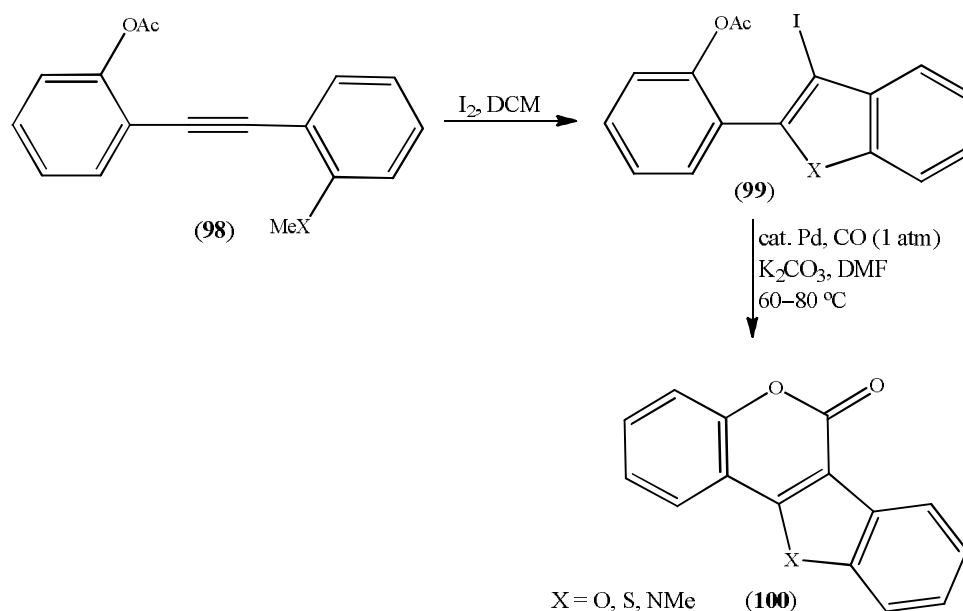
Scheme 2.7.4 Iodolactonization and Pd-catalyzed carbonylative lactonozation[46]

2.8   Rotenoids

In 1960 munduserone (**107**), the simplest naturally occurring rotenoid, was isolated and the structure elucidated. Since then, a number of protocols towards the synthesis of rotenoids have been reported.[47] These processes include the reaction of dimethylsulfoxoniummethylide with 2'-hydroxyisoflavones to form 2-vinyl-coumaran-3-ones which give rise to dehydrorotenoids when heated in pyridine (14% yield),[48] treatment of iodoarylchromene (**101**) with palladium acetate which affords the rotenoid (**102**) in 58% yield (Scheme 2.8.1)[47,49] and reduction of dehydrorotenoids with DIBAL (32% yield).[50]
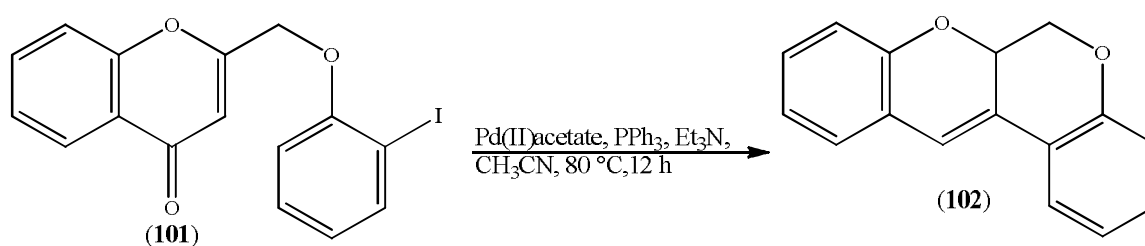
Scheme 2.8.1 Rotenoid synthesis *via* iodoarylchromene

Recently, methodology involving conjugate addition of a lithium carbanion belonging to a protected aromatic cyanohydrin (**103**) (readily available from commercial 2-hydroxy-4-methoxy benzaldehyde) to nitrochromene (**104**) (prepared in one step from 6-hydroxy-3,4-dimethoxy benzaldehyde) was reported to yield (**105**) and even though a mixture of two or three products was usually obtained, these could all be transformed into munduserone by simple chemical conversions (Scheme 2.8.2).[47]
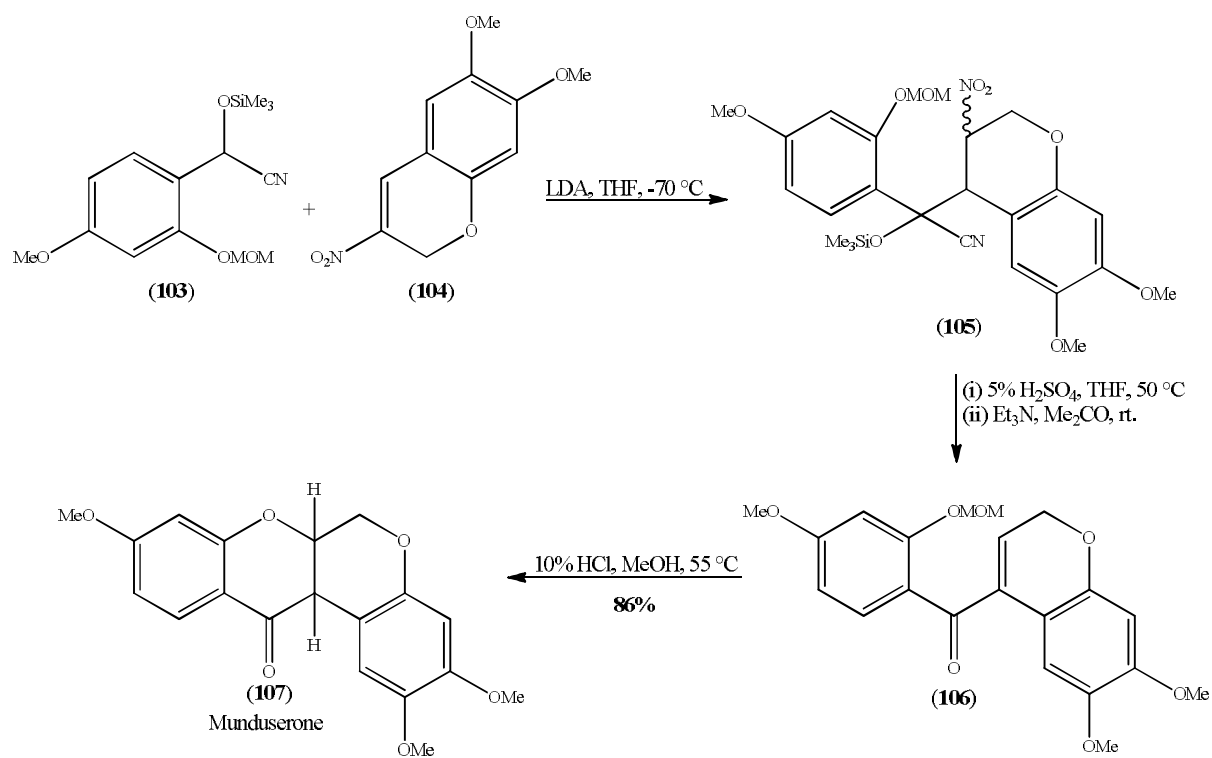
Scheme 2.8.2 Synthesis of munduserone

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ASYMMETRIC SYNTHESIS OF FLAVONOIDS 3

3.1 Introduction

Up to 1965 the concept of asymmetric synthesis existed as only a mechanistic curiosity to the field of science and was not considered to be an important aspect of organic synthesis. This virtually unknown facet of synthesis was transformed in the last *ca.* 40 years by organic chemists into an imperative route to nearly all chiral organic compounds in enantiomeric purity of over 90%.[1]

The need for stereoselective synthesis arose from the realization that the difference between two enantiomers does not merely involve opposite directions in which they rotate plane polarized light, but also the fact that biological macromolecules in living systems, like enzymes, are active towards one enantiomeric form only. It would therefore come as no surprise that two enantiomers of a biologically active chiral substance, such as a drug, would interact differently with a chiral receptor site and thus may lead to completely different effects in living systems.[1]

A tragic example where this phenomenon was ignored, can be found during the 1960's when the drug thalidomide (**108**) was prepared as a racemic mixture and administered as such as a sedative. While both enantiomers showed sedative effects, the (−)-enantiomer also led to foetal abnormalities when taken by pregnant women. Unfortunately, even if the (+)-enantiomer had been synthesized and used in pure form, it would still have had the same awful effect as it was found that the two enantiomers interconvert at physiological conditions.[1,2,3]

(**108**)
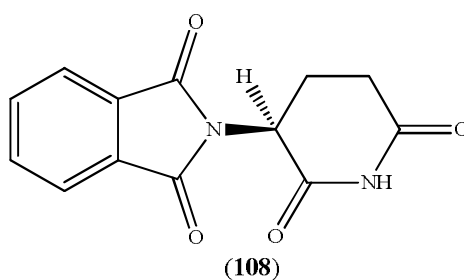
Thalidomide

Another interesting example can be found in the case of DOPA (**109**), used for the treatment of Parkinson's disease, where the active drug, dopamine, is formed from decarboxylation of the prodrug (**109**). Since dopamine is unable to cross the blood to brain barrier to reach the active site, it is useless as such for the treatment of Parkinson's disease and it must be administered as DOPA which can be transported across the blood-brain barrier. In the brain, the enzyme dopamine decarboxylase then decarboxylates only the (−)-enantiomer of DOPA (**109**) to form dopamine. DOPA must therefore be administered as only the (−)-enantiomer seeing that build-up of the (+)-enantiomer may lead to serious effects as the body is not able to metabolise it.[1]

(**109**)
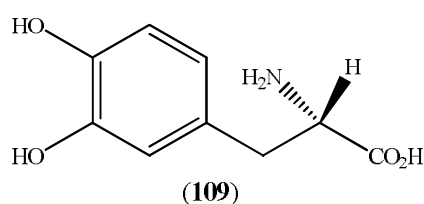
DOPA

Even if the 'unwanted' stereoisomers are inert, it is still desirable to synthesize and use active substances in one pure form, the reason being that inert isomers not only represent a waste of resources but may also cause long-term damage to the environment if not biodegraded rapidly. It is thus common practice today, that when putting a new product to use, all possible stereoisomers are synthesized and evaluated beforehand.[1]

Since many flavonoids and isoflavonoids contain only sp^2 carbon atoms and therefore have no stereogenic centres, the stereoselective synthesis of flavonoids has been neglected for quite some time and has received limited attention from the chemical community. Furthermore, since the major precursors to many chiral flavonoids and isoflavonoids, like chalcones and isoflavones, are planar in nature (*cf.* chapter 2), introducing stereogenicity in an enantioselective way, is very challenging if not impossible. If flavonoids are to be synthesized in an enantiomerically enriched form, methods to convert chalcones or isoflavones into chiral products or methodology that do not go through these substrates are to be developed.

3.2 Asymmetric Epoxidation of Chalcones

Chalcones, considered as key C6-C3-C6 precursors to the synthesis of flavonoids and isoflavonoids, are readily available through base or acid catalyzed aldol condensation between 2'-hydroxyacetophenones (**110**) and benzaldehydes (**111**) as indicated in scheme

3.2.1. [4,5,6] If chalcones (**112**) could therefore be converted into chiral analogues, like epoxides, in high enantiomeric excess (ee), many 'down-stream' flavonoids would become available in optically enriched form.

R = OH, OMe, OBn, OMOM, etc.
MOM = methoxymethyl ether
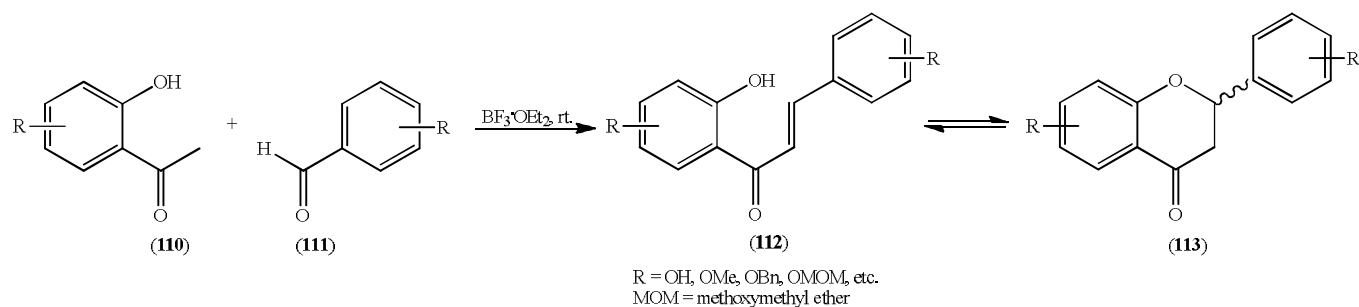
Scheme 3.2.1 Base and acid catalyzed synthesis of chalcones and racemic flavanones

The first attempt at preparing chalcone epoxides in optically enriched form came from Wynberg and Greijdanus[5,7] who utilized quinidine benzylchloride (BQdC) (**115**) and quinine benzylchloride (BQC) (**114**) as chiral phase transfer catalysts (PTC) in a number of 1,4-addition reactions. Utilization of PTC in a Weitz-Scheffer reaction (30% aq. H_2O_2/NaOH/toluene) was done by Helder and co-workers[8] to prepare the first (−)- (**117–122a**) and (+)-*trans*-chalcone epoxides (**117–122b**), respectively, in moderate to high chemical yields (38–92%) but unfortunately very low ee's (25–48%) (Scheme 3.2.2).

BQC
(**114**)

BQdC
(**115**)
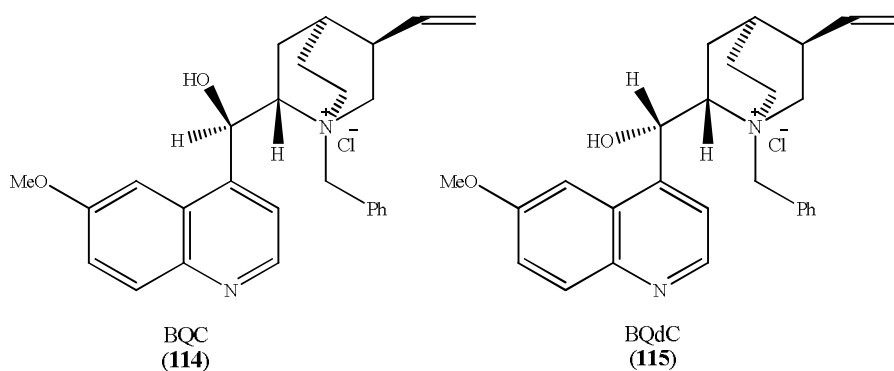
Figure 3.2.1 Phase-transfer catalysts

(-)- and (+)-*trans*-chalcone epoxides:
(**117a/b**) $R^1 = R^2 = R^3 = H$
(**118a/b**) $R^1 = OMe$, $R^2 = R^3 = H$
(**119a**) $R^1 = R^3 = H$, $R^2 = OMe$
(**120a**) $R^1 = R^2 = H$, $R^3 = Cl$
(**121a**) $R^1 = R^2 = H$, $R^3 = NO_2$
(**122a/b**) $R^1 = OMOM$, $R^2 = R^3 = H$

(**116**)

a = configuration shown
b = enantiomer
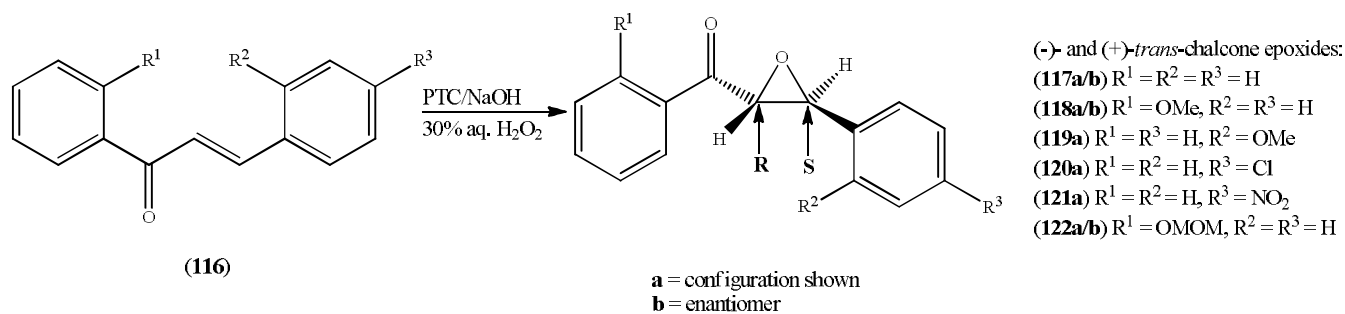
Scheme 3.2.2 **Asymmetric epoxidation of chalcones with PTC**

Due to various unsuccessful attempts to improve the poor ee values obtained with this protocol, investigations involving alternative reaction conditions and catalysts toward improving the enantioselective epoxidation of enones were studied. Limited success was however reached regarding chalcones, especially in the case of substrates with natural product oxygenation patterns.[5]

As a viable alternative to the use of enzymes for asymmetric synthesis, Juliá and co-workers[9] applied synthetic peptides to the asymmetric epoxidation of chalcones. A triphasic system consisting of poly-L- or poly-D-alanine, alkaline hydrogen peroxide and an organic solvent such as toluene or CCl_4 was used to afford chiral chalcone epoxides in 40–92% yield and 14–65% ee.[4,12] Bezuidenhoudt *et al.*[10] extended this protocol to a series of chalcones (**123**) displaying natural product like substitution patterns (Scheme 3.2.3) and obtained the chiral chalcones epoxides in yields and ee's of up to 74% and 84%, respectively. Epoxidation of chalcones with a phloroglucinol-type substitution pattern on the A-ring, did however, prove to afford unsuccessful results and even though the protocol introduced by Juliá and co-workers[9] provided access to chalcone epoxides with natural product type oxygenation patterns in good yield and moderate to high ee's, the continuous addition of oxidant and base required and long reaction times with consequent degradation of the poly-amino acid poses difficulties.[4,5]

(123)

$H_2O_2/NaOH$
Toluene/CCl_4

Poly-L-alanine   Poly-D-alanine

(-)-($\alpha R,\beta S$)-epoxides:
(124) $R^1 = R^2 = R^3 = R^4 = H$
(125) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(126) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(127) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(128) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(129) $R^1 = R^2 = R^3 = R^4 = OMe$
(130) $R^1 = OMOM$, $R^2 = R^3 = H$, $R^4 = OMe$

(+)-($\alpha S, \beta R$)-epoxides:
(131) $R^1 = R^2 = R^3 = R^4 = H$
(132) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(133) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(134) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(135) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(136) $R^1 = R^2 = R^3 = R^4 = OMe$
(137) $R^1 = OMOM$, $R^2 = R^3 = H$, $R^4 = OMe$
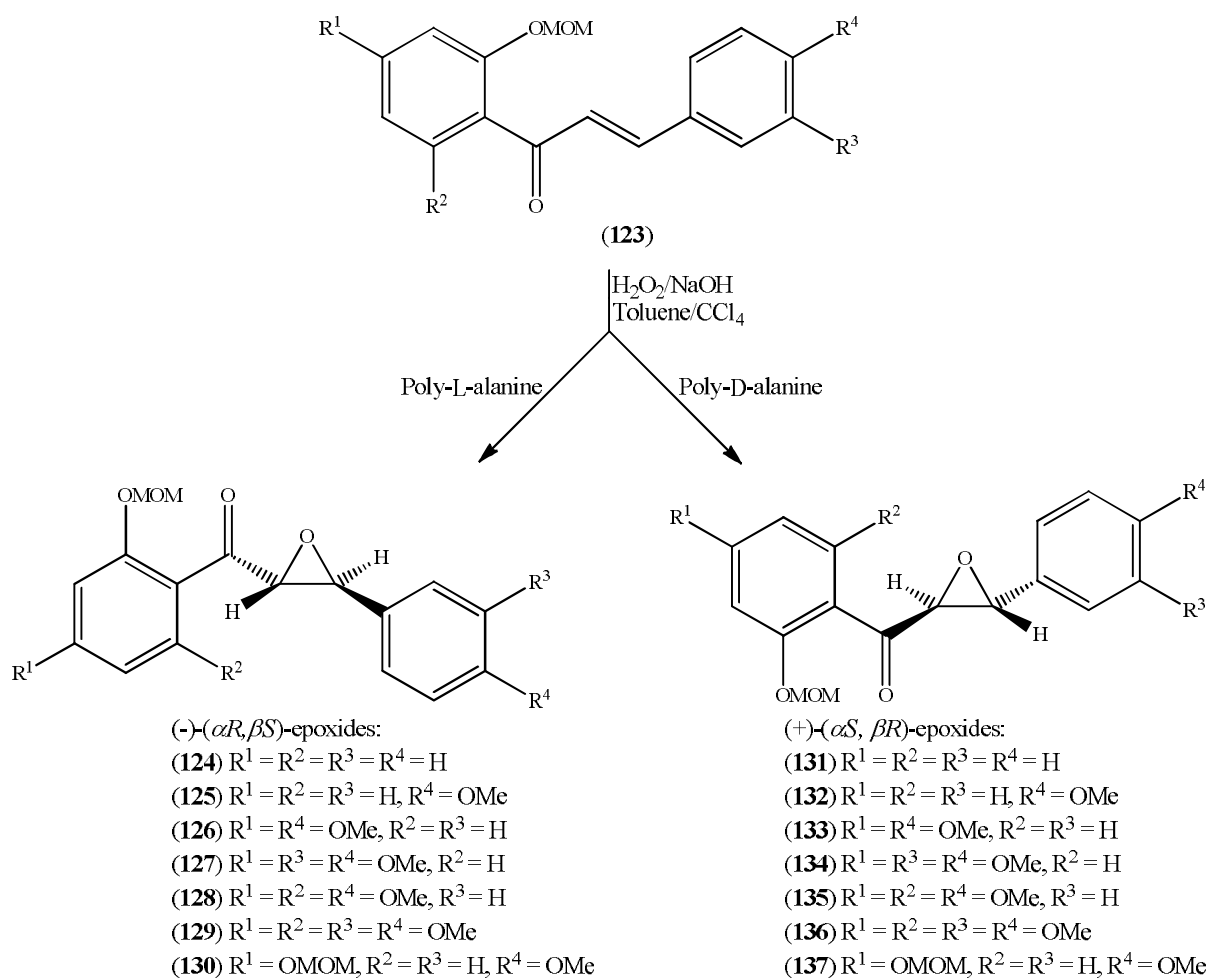
Scheme 3.2.3 Asymmetric epoxidation of chalcones

A satisfactory solution to many of these problems and the best process to date, was reported by Bentley and co-workers.[11]   By using a non-aqueous two-phase system, an immobilized poly-amino acid and non-nucleophilic base in organic solvent, these workers were able to prepare chiral chalcone epoxides in high yields (77 to > 95 %) and ee's (65 to > 95%) (excluding utilization of Hünig's base) and with substantially reduced reaction times.[5,11]

3.3 α- and β-Hydroxydihydrochalcones

α- and β-Hydroxydihydrochalcones make up a rare group of C6-C3-C6 metabolites which apparently share a close biogenetic relationship with α-methyldeoxybenzoins as well as isoflavonoids.[12]

The chiral chalcone epoxides (**124–130**) served as precursor molecules to both the α- and β-hydroxydihydrochalcones *via* either palladium catalyzed hydrogenation (Pd-BaSO$_4$/H$_2$ or Pd-C/H$_2$) to afford the α-hydroxydihydrochalcones (**138–144**) in yields varying from 40% to

92% without any loss in ee or a radical process yielding β-hydroxydihydrochalcones (**145–149**) (yields > 70%) again without any appreciable loss in ee (up to 91%) (Scheme 3.3.1).[5,10,13,14]

(-)-($\alpha R,\beta S$)-epoxides:
(**124**) $R^1 = R^2 = R^3 = R^4 = H$
(**125**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**126**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**127**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**128**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**129**) $R^1 = R^2 = R^3 = R^4 = OMe$
(**130**) $R^1 = OMOM$, $R^2 = R^3 = H$, $R^4 = OMe$

(+)-α-hydroxydihydrochalcones:
(**138**) $R^1 = R^2 = R^3 = R^4 = H$
(**139**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**140**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**141**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**142**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**143**) $R^1 = R^2 = R^3 = R^4 = OMe$
(**144**) $R^1 = OMOM$, $R^2 = R^3 = H$, $R^4 = OMe$

(-)-($\alpha R,\beta S$)-epoxides:
(**125**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**126**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**127**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**128**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**129**) $R^1 = R^2 = R^3 = R^4 = OMe$

(R)-β-hydroxydihydrochalcones:
(**145**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**146**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**147**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**148**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**149**) $R^1 = R^2 = R^3 = R^4 = OMe$

Scheme 3.3.1 Synthesis of α- and β-hydroxydihydrochalcones

3.4 Dihydroflavonols

Various members of the dihydroflavonol family are widely distributed in the plant kingdom and apart from their important biological properties, these compounds may be employed as precursors to the semi-synthesis of proanthocyanidins.[5]

Since cyclization of chalcone epoxides to dihydroflavonols introduces stereoselectivity at C2 and C3, the first syntheses of enantiomerically enriched dihydroflavonols, involved attempts to effect this cyclization without the loss of optical purity. However, initial attempts toward

acid-catalyzed cyclization of the chalcone epoxide to the corresponding optically active dihydroflavonol, were hampered by two major complications *i.e.* isoflavone formation *via* an aroyl migration and racemization of the formed dihydroflavonol.[5]

To circumvent isoflavone formation, Van Rensburg and co-workers[15] developed methodology where the C_β-O bond was cleaved selectively in the presence of tin tetrachloride ($SnCl_4$) and phenylmethanethiol (BnSH) forming the dihydrochalcone intermediates (**150**– **154**). Utilization of a thiophilic Lewis acid such as silver tetrafluoroborate ($AgBF_4$), made deprotection prior to cyclization possible to yield 2,3-*trans*-dihydroflavanols (**155**–**159**) in good yield and for the first time the 2,3-*cis*-analogues albeit in low proportions (**160**–**164**) (Scheme 3.4.1).

(**125**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**126**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**127**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**128**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**129**) $R^1 = R^2 = R^3 = R^4 = OMe$

(**150**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**151**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**152**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**153**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**154**) $R^1 = R^2 = R^3 = R^4 = OMe$

BnSH, $SnCl_4$
DCM, -20 °C
49–86%

$AgBF_4$, DCM, 0 °C

(**160**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**161**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**162**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**163**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**164**) $R^1 = R^2 = R^3 = R^4 = OMe$

61–86% yield, **44–83%** ee

(**155**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**156**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**157**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**158**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**159**) $R^1 = R^2 = R^3 = R^4 = OMe$

+

Scheme 3.4.1 Asymmetric synthesis of dihydroflavanols

3.5 Flavan-3-ols and Flavan-3,4-diols

As flavan-3-ols serve as constituent entities of condensed tannins, these compounds have received considerable interest over the last few years. Additionally these compounds may be employed for the semisynthesis of oligomeric proanthocyanidins where they serve as the nucleophilic entities.[5]

The most common synthesis of flavan-3-ols as well as the closely related flavan-3,4-diols occurs *via* the reduction of dihydroflavonols. While reduction with sodium borohydride (NaBH$_4$) in MeOH affords the 2,3-*trans*-3,4-*trans*-flavan-3,4-diols (**166**), reduction in dioxane as solvent yields the 2,3-*trans*-3,4-*cis*-isomers (**167**) (Scheme 3.5.1).[16]
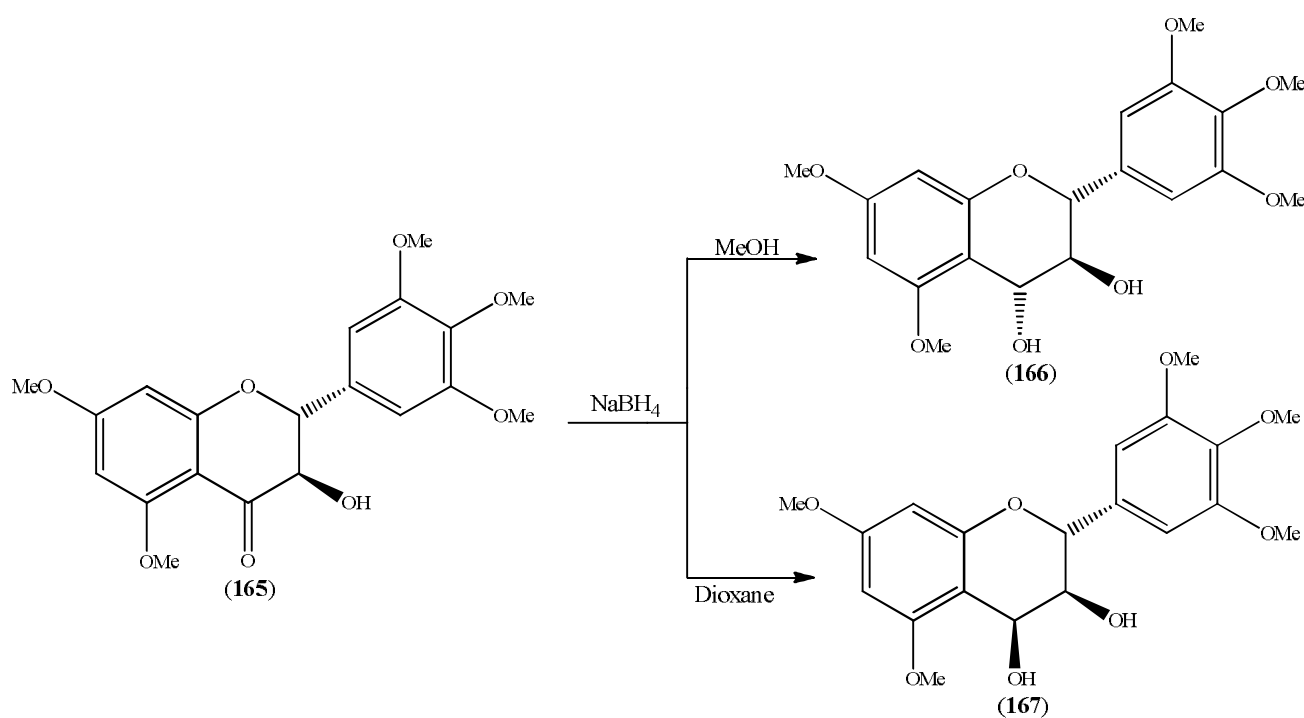
Scheme 3.5.1 Dihydroflavonol reduction

Flavan-3-ols are readily available in high yield (81%) *via* reductive deoxygenation of flavan-3,4-diols in the presence of sodium cyanoborohydride (NaBH$_3$CN) and acetic acid (AcOH).[17,18] These compounds may also be prepared from consecutive reduction of dihydroflavonol with LiAlH$_4$/THF and hydrogenation with Pd/C in dioxane.[5]

However, Van Rensburg and co-workers[19,20] addressed the issue of stereocontrol in the flavan-3-ol at C-2 and C-3 utilizing a concise protocol based on the transformation of *retro*-chalcones into 1,3-diarylpropenes (**173–177**) which are subsequently subjected to enantioselective dihydroxylation to afford poly-oxygenated diarylpropan-1,2-diols (**178–182**) serving, in turn, as chirons for enantiopure flavan-3-ols (**183–192**) (Scheme 3.5.2).

(**123i**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**123ii**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**123iii**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**123iv**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**123v**)
(**123vi**) $R^1 = R^2 = R^3 = R^4 = OMe$

(**168**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**169**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**170**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**171**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**172**) $R^1 = R^2 = R^3 = R^4 = OMe$

(**178a/b**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**179a/b**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**180a/b**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**181a/b**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**182a/b**) $R^1 = R^2 = R^3 = R^4 = OMe$

(**173**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**174**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**175**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**176**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**177**) $R^1 = R^2 = R^3 = R^4 = OMe$

(**183a/b**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**184a/b**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**185a/b**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**186a/b**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**187a/b**) $R^1 = R^2 = R^3 = R^4 = OMe$

a = configuration shown
b = enantiomer

(**188a/b**) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
(**189a/b**) $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
(**190a/b**) $R^1 = R^3 = R^4 = OMe$, $R^2 = H$
(**191a/b**) $R^1 = R^2 = R^4 = OMe$, $R^3 = H$
(**192a/b**) $R^1 = R^2 = R^3 = R^4 = OMe$

Scheme 3.5.2 Synthesis of flavan-3-ols

3.6 Isoflavone epoxides

Lévai and co-workers[21] demonstrated that an efficient reagent for the epoxidation of several substituted isoflavones, is the versatile oxidizing agent, dimethyl dioxirane (DMDO) and subsequently synthesized isoflavone glycoside epoxides in good yield. However, 1:1 diastereomeric mixtures were obtained and it was evident that the chiral sugars (193ai–193aiv) unit did not induce any enantiofacial selectivity during the reactions when DMDO was utilized as oxidant.[4,21] The highly proficient catalysts for the enantioselective epoxidation of olefinic bonds, known as Jacobsen's Mn(III)salen complexes [(R,R)-Mn(III)salen and (S,S)-Mn(II)salen complexes (193b)], together with oxygen donors such as DMDO or sodium hypochlorite (NaOCl) produced, for the very first time, chiral isoflavone epoxides (200–201) in 20 to 92% enantioselectivities (Scheme 3.6.1).

(193ai) $R^1 = OGlAc_4$, $R^2 = R^3 = H$
(193aii) $R^1 = OCbAc_7$, $R^2 = R^3 = H$
(193aiii) $R^1 = OGlAc_4$, $R^2 = R^3 = H$
(193aiv) $R^1 = R^2 = OAc$, $R^3 = OGlAc_4$

GlAc$_4$ = tetra-O-acetyl-β-D-glucosyl
CbAc$_7$ = hepta-O-acetyl-β- cellobiosyl

Chiral sugars

(193b)
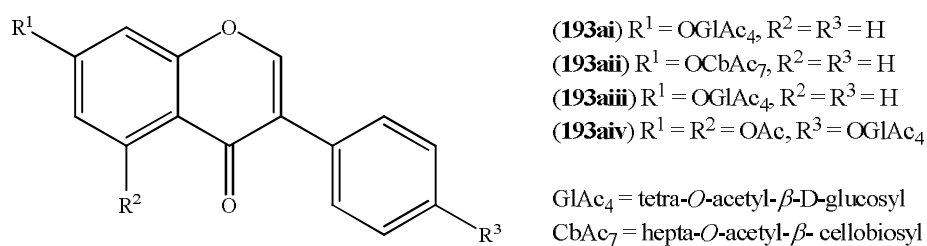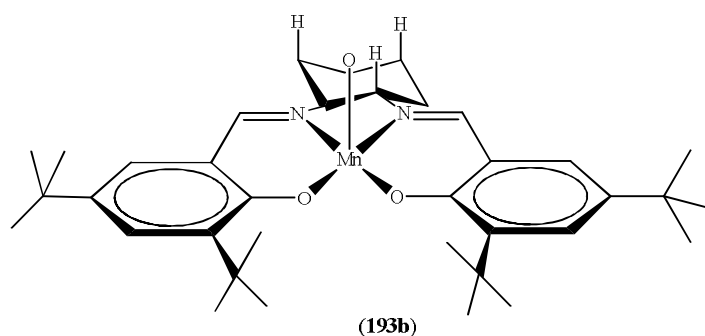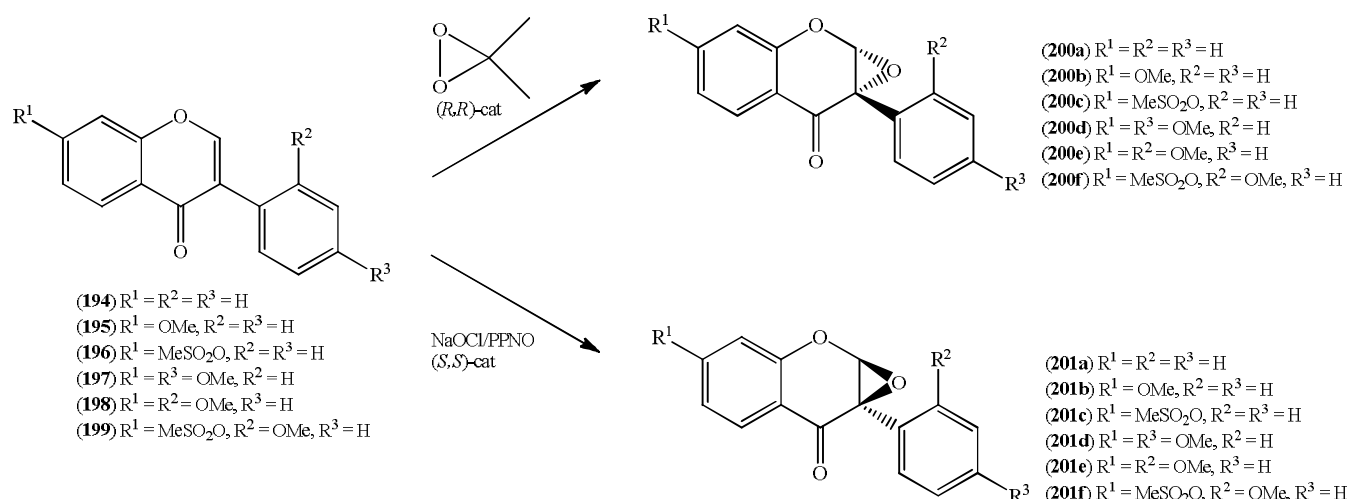
Scheme 3.6.1 (R,R)-cat: (R,R)-N,N'-bis(3,5-t-butylsalicylidene)-1,2-cyclohexanediaminomanganese chloride

(S,S)-cat: (S,S)-N,N'-bis(3,5-t-butylsalicylidene)-1,2-cyclohexanediaminomanganese chloride

PPNO: 4-Phenylpyridine N-oxide

Due to the electron poor character of the double bond to be epoxidized, incomplete conversion of the substrate led to low yields and the problem was addressed by employing NaOCl as oxygen donor together with PPNO as axial ligand. Furthermore, it was found that although the electronic character of the C-7 substituent does not affect the reaction rate and/or enantioselectivity, a methoxy group in the near vicinity of epoxidation in (**199**), enhanced enantiofacial selectivity significantly as the ee increased from 90% to 94%.[21]

3.7 Isoflavanones

The first optically active isoflavanones were synthesized by Vicario et al.[22] through application of a stereocontrolled aldol reaction. This protocol involved an asymmetric aldol reaction between arylacetamides (**202–204**) containing (S,S)-(+)-pseudoephedrine as chiral auxiliary, and formaldehyde (HCOH) to introduce chirality at the C-3 position of the isoflavanone (**211–213**). The A-ring of the isoflavanone to be is subsequently attached to the B-ring fragment through Mitsunobu etherification, while the heterocyclic ring is constructed in the final step by intramolecular Friedel-Crafts acylation (Scheme 3.7.1). Although extremely low temperatures (-105 °C) were a prerequisite, essentially enantiopure isoflavanones (**211–213**) (> 99% ee's) could be prepared in high yields (68–71%) through application of this methodology.[4,22]
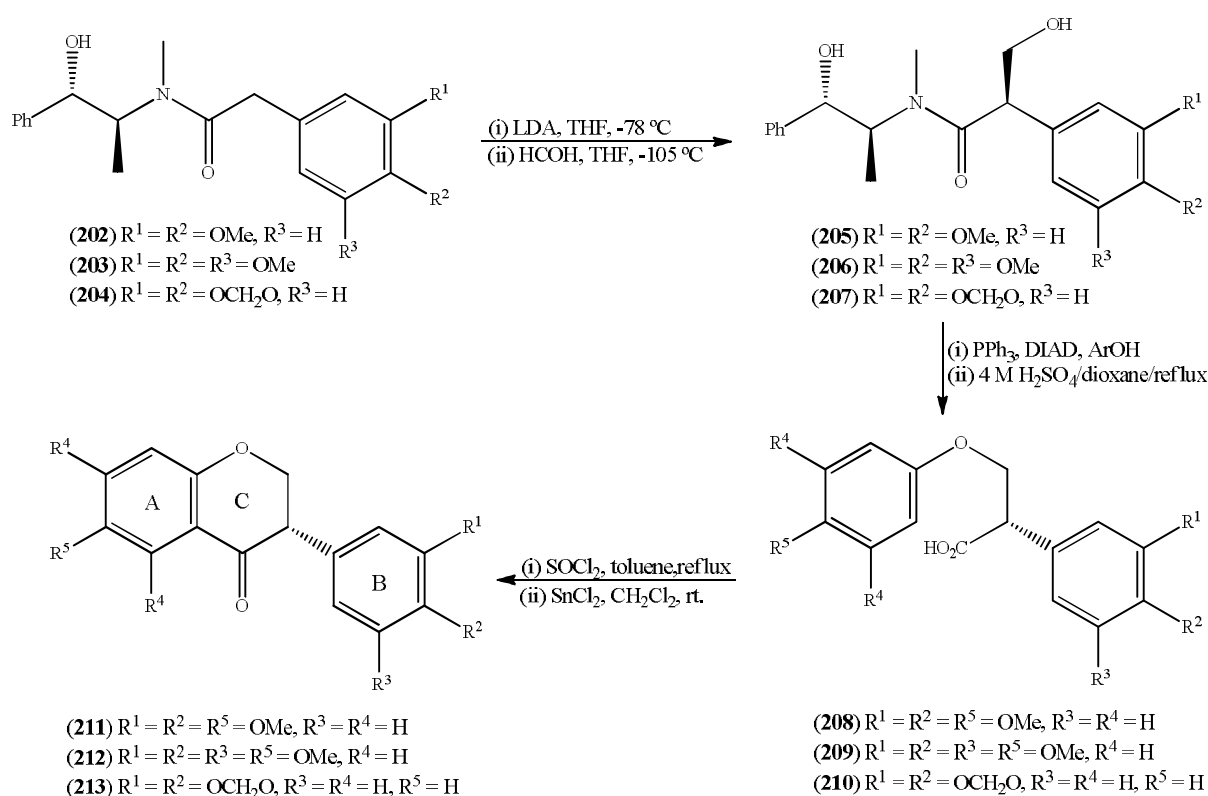
Scheme 3.7.1 Stereoselective synthesis of isoflavanones

3.8 Isoflavans

The first synthetic protocol addressing the issue of stereocontrol at the chiral centre within the isoflavan backbone (at C3), was reported by Versteeg *et al.*[23] and involved the stereoselective α-benzylation of phenylacetic acid derivatives.[24] This was achieved by attaching imidazolidin-2-ones (**215a/b**), as chiral auxiliaries, to the substituted phenyl acetyl chlorides (**216–218**) followed by base catalyzed alkylation with substituted benzyl chlorides or bromides. Removal of the chiral auxiliary *via* lithiumaluminium hydride reduction and cyclization to the isoflavan using Mitsunobu conditions, led to excellent yields (75–92%) and enantiomeric excesses (96–99%) for the final products (**234–239**) (Scheme 3.8.1). Although excellent results were obtained through the application of this methodology, it is complicated by the availability of phenyl acetic acid derivatives displaying substitution patterns found in nature, and the general instability of oxygenated benzyl halide derivatives.

(214a/b)

i

(215a/b)
X = SiMe₃

(216) R¹ = R² = H, R³ = OMe
(217) R¹ = H, R² = R³ = OMe
(218) R¹ = R³ = OMe, R² = H

ii

iii

(219a/b) R¹ = R² = H, R³ = OMe
(220a/b) R¹ = H, R² = R³ = OMe
(221a/b) R¹ = R³ = OMe, R² = H

(222a/b) R¹ = R² = R⁴ = H, R³ = OMe
(223a/b) R¹ = R⁴ = H, R² = R³ = OMe
(224a/b) R¹ = R³ = OMe, R² = R⁴ = H
(225a/b) R¹ = R² = H, R³ = R⁴ = OMe
(226a/b) R¹ = R⁴ = OMe, R² = R³ = H
(227a/b) R¹ = R³ = R⁴ = OMe, R² = H

iv

(214a/b)

v

(234a/b) R¹ = R² = R⁴ = H, R³ = OMe
(235a/b) R¹ = R⁴ = H, R² = R³ = OMe
(236a/b) R¹ = R³ = OMe, R² = R⁴ = H
(237a/b) R¹ = R² = H, R³ = R⁴ = OMe
(238a/b) R¹ = R⁴ = OMe, R² = R³ = H
(239a/b) R¹ = R³ = R⁴ = OMe, R² = H

(228a/b) R¹ = R² = R⁴ = H, R³ = OMe
(229a/b) R¹ = R⁴ = H, R² = R³ = OMe
(230a/b) R¹ = R³ = OMe, R² = R⁴ = H
(231a/b) R¹ = R² = H, R³ = R⁴ = OMe
(232a/b) R¹ = R⁴ = OMe, R² = R³ = H
(233a/b) R¹ = R³ = R⁴ = OMe, R² = H

a = configuration shown
b = enantiomer

i. BuLi, Ph₃CH (catalytic), THF, 0 °C; then Me₃SiCl, -78 °C to rt.; ii. tetrabutylammonium fluoride (TBAF), MeCN, rt.; iii. lithium isopropylcyclohexylamide (LICA), 2-O-Methoxymethylbenzyl bromide, THF–CH₂Cl₂, -40 °C; iv. LiAlH₄/THF or LiBH₄/Et₂O, -24 °C to rt.; v. 3 M HCl, MeOH, reflux, vi. PPh₃, DIAD, THF, rt.

Scheme 3.8.1 Stereoselective synthesis of isoflavans

3.9 Pterocarpans

Although several methodologies for the synthesis of pterocarpans are known, the synthesis of these potent phytoalexins quite often require multi-step processes, which are only applicable to some hydroxylation patterns and with no stereocontrol, what so ever, at C-6a and C-11a of the basic pterocarpan skeleton.[5] As an extension of the isoflavan synthesis protocol, Van Aardt and Ferreira[25,26] reported on an aldol process [instead of α-alkylation (Scheme 3.8.1)] for the stereoselective synthesis of pterocarpans. Unfortunately only control over the relative configuration at the point of junction between the B and C rings of the pterocarpan *i.e.* (6a,11a)-*cis*- (**264**–**267**) and non-natural (6a,11a)-*trans*-pterocarpans (**272**) could be established (Schemes 3.9.1 and 3.9.2).
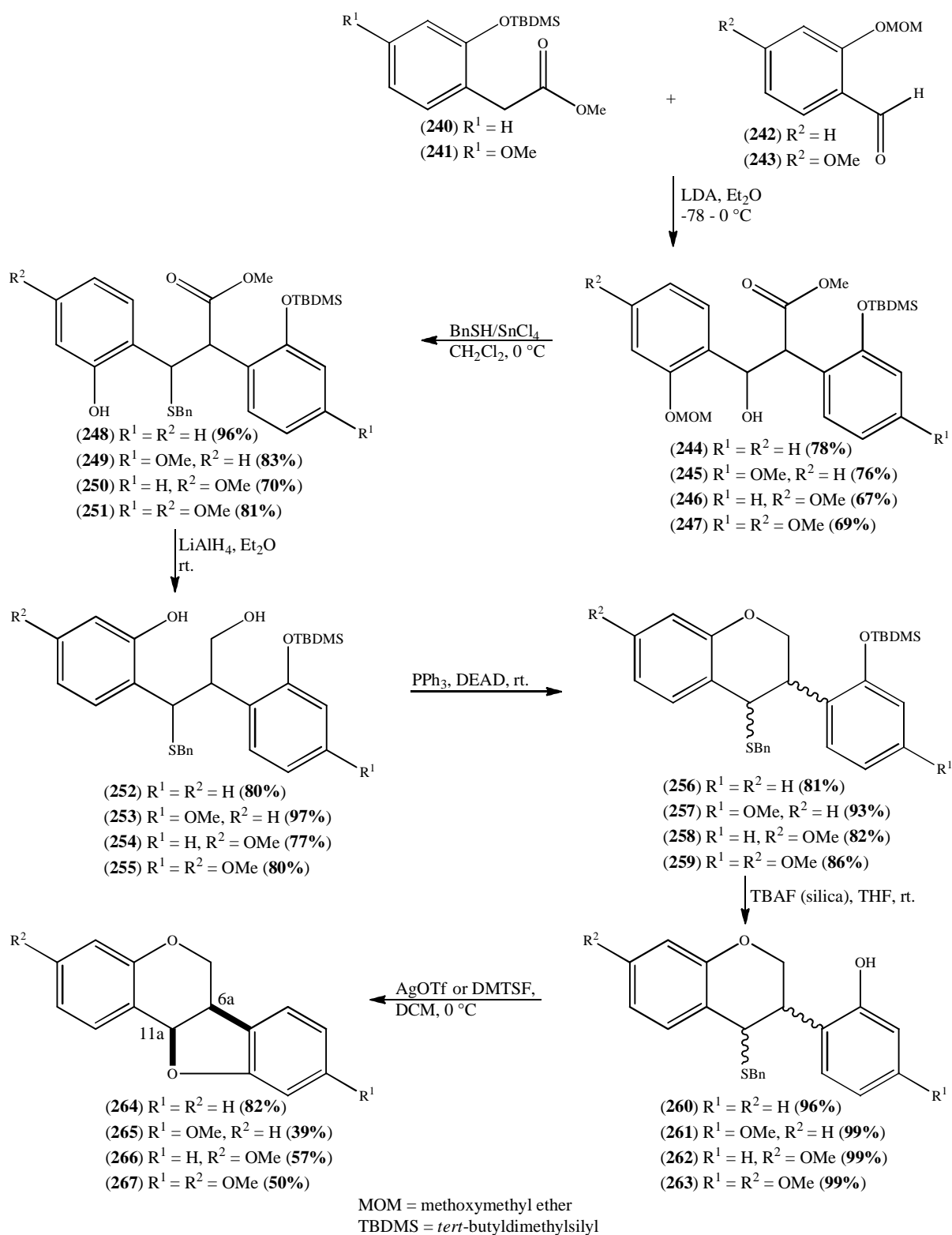
Scheme 3.9.1 Synthesis of pterocarpan precursor molecules

MOM = methoxymethyl ether
TBDMS = *tert*-butyldimethylsilyl
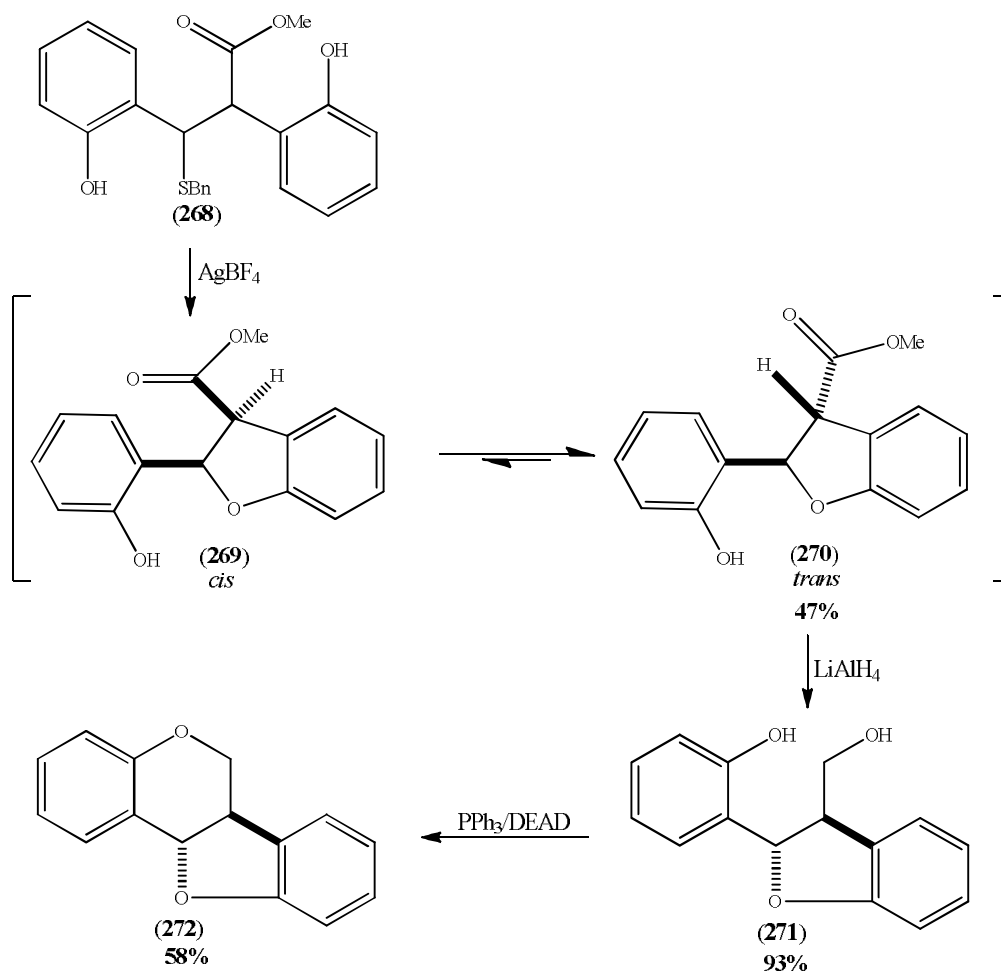
Scheme 3.9.2 Synthesis of *trans*-pterocarpan

Cis- and *trans*-6a-hydroxypterocarpans were now accessible through periodate oxidation of *trans*-4-benzyl-sulfanylisoflavans (**273i**) followed by a thermal elimination to afford the isoflavene (**273**). Sharpless dihydroxylation with osmium tetroxide (OsO$_4$), followed by deprotection and subsequent cyclization afforded both *cis*- and *trans*-6a-hydroxypterocarpans, (**276**) and (**277**) respectively, in essentially enantiopure form.[27]
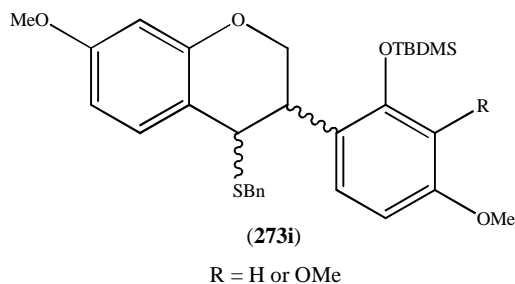
Benzyl-sulfanylisoflavan
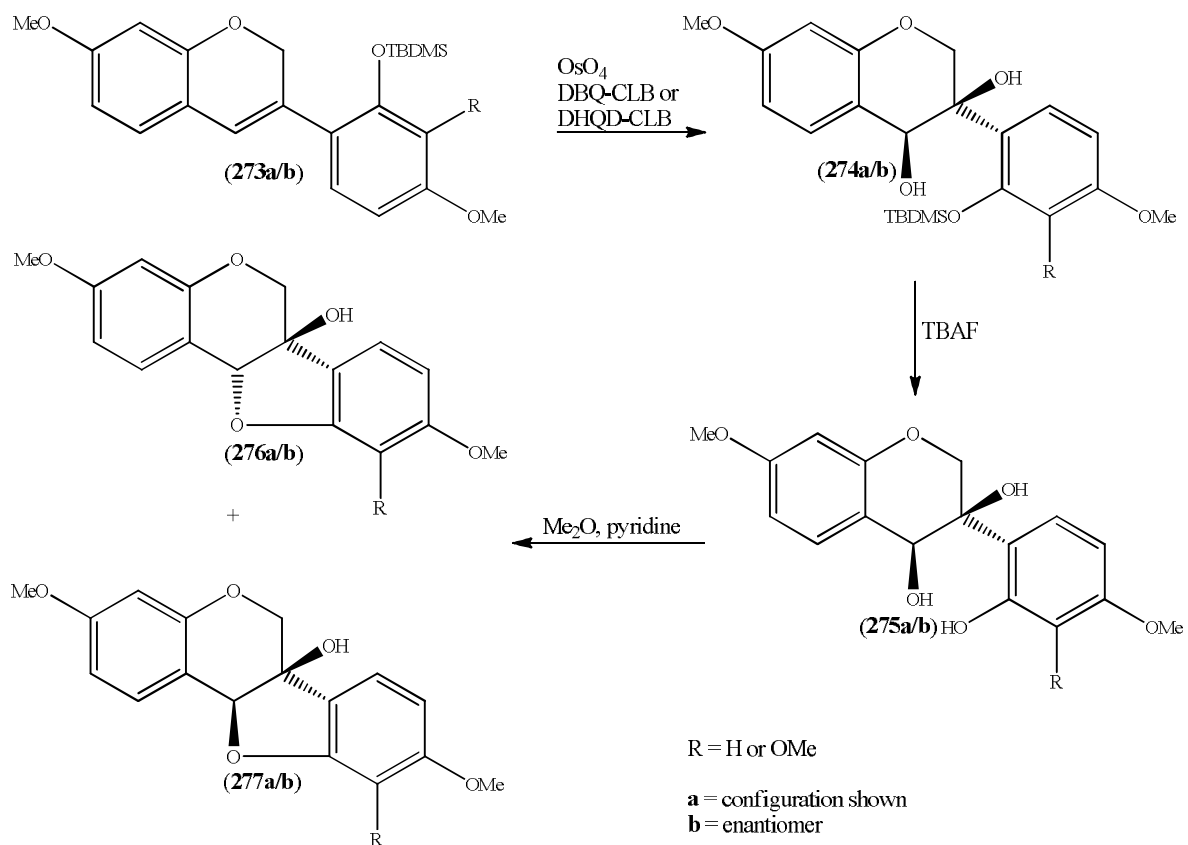
Scheme 3.9.3 Synthesis of 6a-hydroxypterocarpans

(273a/b)

OsO₄
DBQ-CLB or
DHQD-CLB

(274a/b)

TBAF

(275a/b)

Me₂O, pyridine

(276a/b)

+

(277a/b)

R = H or OMe

a = configuration shown
b = enantiomer

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OZONOLYSIS 4

4.1 Introduction

Over the past *ca.* 100 years ozone (O_3) has been used in various reactions and was introduced to the world of chemistry by the 19th century as an efficient oxidizing agent.[1] However, the oxidative cleavage of olefins *via* ozonolysis was already reported in 1840 and the reaction of O_3 with organic compounds was reported by Schönbein as early as 1855.[2]

Even though ozonolysis has come into its own since it was first used and has been established as a powerful tool for chemical transformations in organic chemistry today, it found limited application in earlier days where the use of O_3 was only applied to the synthesis of smaller molecules such as vanillin and its derivatives or sensitive dialdehydes such as adipaldehyde from isoeugenol[3] and cyclohexene,[4] respectively. It was also routinely used for the characterization of natural polymers, lipids and terpenes. Presently, however, O_3 is widely applied in multistep syntheses of steroids and natural products and it has not only been valuable to the synthesis chemist but has also found various applications in academic and industrial environments.[1,4,5]

Although synthesis chemists have several alternative chemical protocols at their disposal, ozonolysis is often the reaction of choice for transforming olefins into carbonyl compounds due to it being a straightforward and, especially in the modern era, absolutely clean.[5] Its utility is, however, often restricted by safety concerns as ozonide intermediates (**278**) and (**279**) are able to spontaneously decompose exothermally, which results in explosions. This often happens after incomplete reduction by mild reducing agents,[6] or if the carbon to oxygen ratio in the product approaches 1:1 i.e., when smaller alkenes are subjected to ozonolysis.

Molozonide/1,2,3-trioxolane   Ozonide/1,2,4-trioxolane

R = H or alkyl
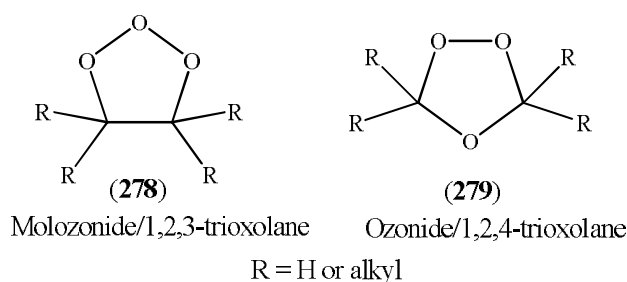
Ozonolysis intermediates[7,8]

Industrial applications of ozonolysis largely centre on treatment of wastewater which is often pre-treated with O_3 before being subjected to a biodegradation process. As phenols and chlorinated phenols are often present in wastewater as micro-pollutants originating from paper bleaching industries, chlorination of wastewater, pesticide production etc., these contaminants are difficult to destroy and biological treatment alone is often unsatisfactory due to low initial concentrations and long degradation times.[9,10,11]

4.2 Ozone

O_3 represents an allotrope of oxygen (O_2) with five canonical (resonance) hybrid structures (**280–284**) as shown in Scheme 4.2.1. Although several proposals regarding the exact nature of bonding within the O_3 molecule have been made, the organic chemist is accustomed to the concept of hybridization and likes to think of the oxygen atoms in O_3 to be sp^2 hybridized with a single π-bond delocalized over the three oxygen atoms.[1]

(280)   **(281)**   **(282)**   **(283)**   **(284)**
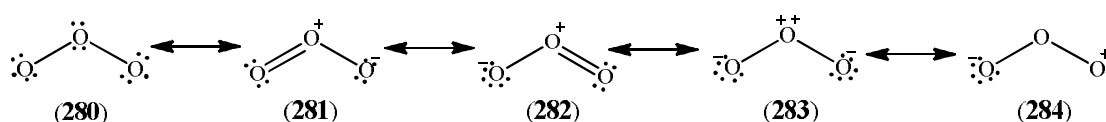
Scheme 4.2.1 Resonance structures of O_3

4.3 Intermediates Involved in Ozonolysis

Due to the dipolar hybrid structures of O_3, it is obvious that it can behave as an electrophile and/or nucleophile and more importantly to ozonolysis, as a 1,3-dipolar entity.[12] The initial interaction between the dipolar O_3 and the olefinic substrate can be viewed as the formation of a π-complex (**286**), which is subsequently transformed into a primary molozonide (**278**). In the case of hindered olefins, the π-complex (**286**) may be transformed into a σ-complex (**287**), which in turn, might give rise to an epoxide (**289**) with the loss of oxygen or it can be transformed into the isomeric molozonide (**288**) (Scheme 4.3.1).[13]
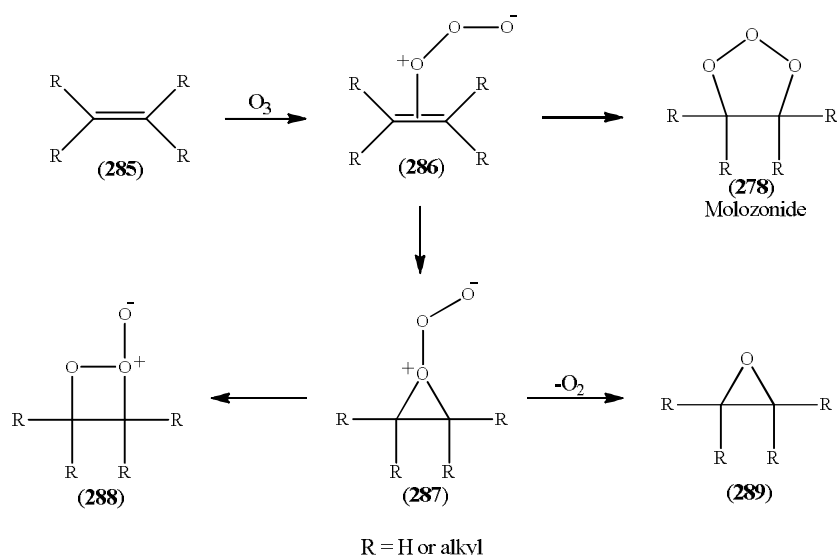
Scheme 4.3.1 Primary intermediates from the reaction of O_3 with alkenes

Subsequent transformation of the molozonide (**278**) according to the accepted Criegee mechanism, involves O-O and C-C bond fragmentation with the formation of a bipolar ion (**290**) and a carbonyl compound (**291**). The final destination of these species is to a large extent influenced by the structure of the substrate and the reaction conditions, but in inert solvents the ozonide (**293**) and/or peroxides like (**294**) and/or (**295**) are usually obtained. In protic solvents like alcohols, water and carboxylic acids, the bipolar intermediate (**290**)/carbonyl oxide (**292**) is stabilized by addition of a solvent molecule giving rise to α-substituted hydroperoxides (Scheme 4.3.2).[13] When unsymmetrical olefins are subjected to ozonolysis, the initially formed molozonide (**278**) may fragment into two different ways leading to two sets of carbonyl compounds (**297**) and (**299**) and zwitterions (**296**) and (**298**), respectively (Scheme 4.3.3). In this instance, the direction of cleavage is governed by the inductive effect of the substituents around the original double bond, *i.e.*, the zwitterion is preferentially formed at the carbon carrying electron-donating groups with the carbonyl compound containing the electron deficient carbon.[13]
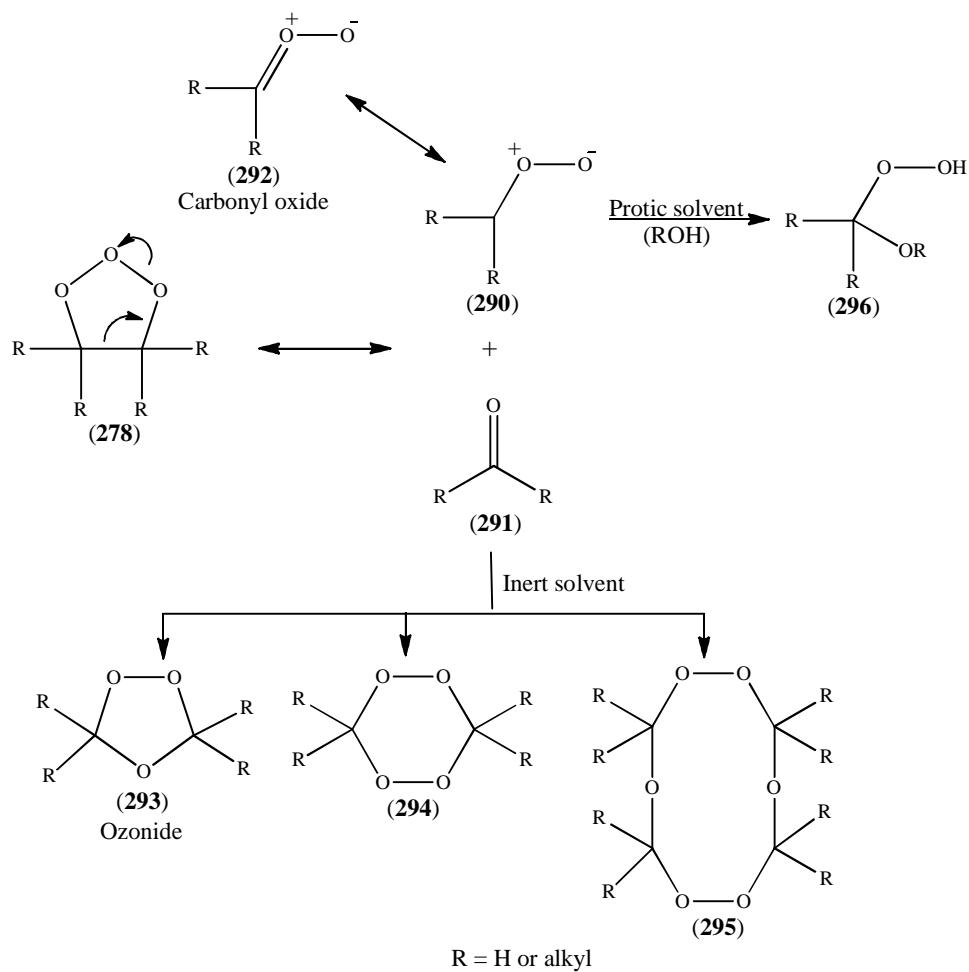
Scheme 4.3.2 Peroxide intermediates of ozonolysis

R = H or alkyl
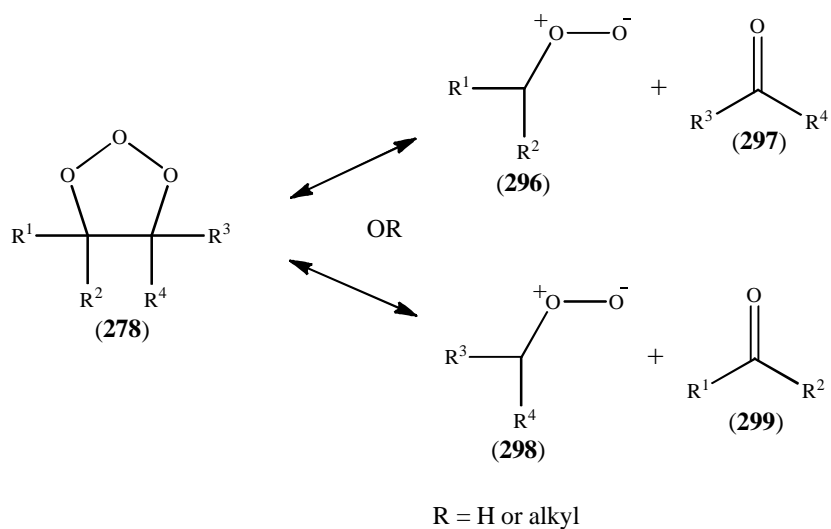
Scheme 4.3.3 Fragmentation of unsymmetrical olefins

Ozonolysis of olefins containing other functional groups may undergo additional reaction(s) between the particular functional group and cationic or anionic part of the zwitterion intermediate(s). This phenomenon is especially observed for carbonyl and hydroxyl functions and is also dependent on the position of the double bond and the reaction conditions.[13]

4.4 Reactions of Ozonides

Since the oxidation state of ozonides can be viewed as intermediate between that of carbonyl compounds and carboxylic acids, the reactions of ozonides can be divided into two classes, *i.e.*, those occurring without a change in the 'overall' oxidation state of the molecule and those involving external oxidants (the so-called oxidative work-up) or reductants (reductive work-up).

4.4.1   Fragmentation (Solvolysis) of Ozonides

Reactions of ozonides where the 'overall' oxidation state of the molecules remain unchanged usually involve interaction between a solvent molecule and the ozonide, which essentially depends on the nature of the solvent molecules. The common products of solvolysis, hydrolysis and alcoholysis are also dependent on the acidity of the reaction mixture and usually lead to the formation of carbonyl compounds and carboxylic acids. In the presence of strong solvating solvents like DMSO, DMF and amines, solvolysis of stilbene ozonide (**300**) occurs quickly and quantitatively giving benzaldehyde (**301**) and benzoic acid (**302**) (Scheme 4.4.1.1).[13,14]
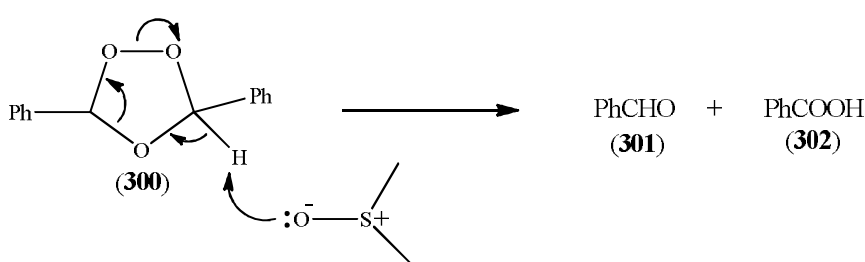
Scheme 4.4.1.1 Solvolysis of stilbene ozonide

Furthermore, ozonolysis in the presence of moist silica gel results in the formation of equal amounts of the aldehyde (or ketone) and carboxylic acid products.[13,15]

Thermal and photochemical fragmentation of ozonides can also be used as a way to form the corresponding carbonyl compound and carboxylic acid from ozonides. Treatment of

cyclooctene (**303**), for example, with O_3 on polyethylene at -79 °C affords the ozonide (**304**), which on warming up to 50 °C leads to aldoacid (**307**) formation in high yield. This process probably proceeds through a biradical mechanism (Scheme 4.4.1.2).[16]
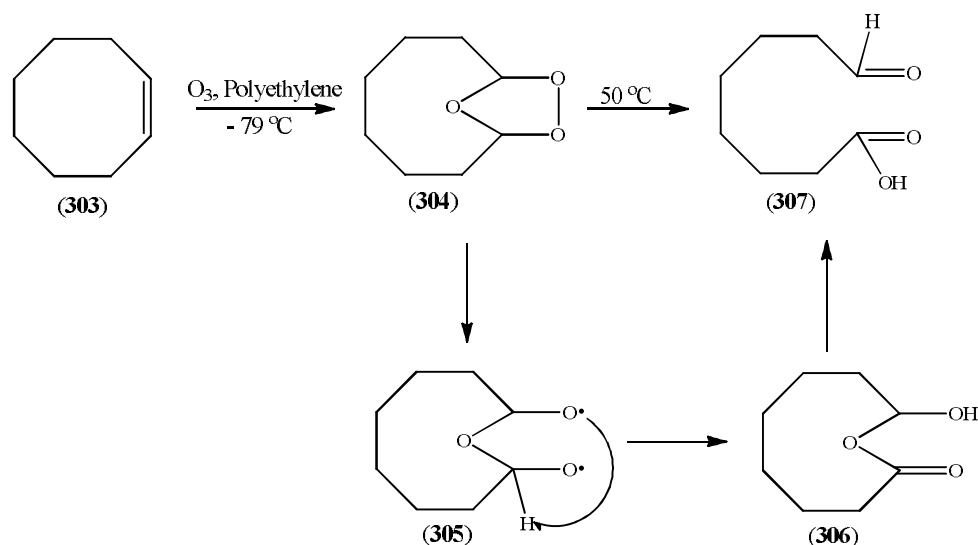
Scheme 4.4.1.2 Ozonolysis of cyclooctene: Biradical mechanism

Solvolysis may also be applied to obtain oxidized or reduced products from the ozonolysis process. In this instance the zwitterion (**290**)/carbonyl oxide (**292**) is formed in the presence of a protic solvent leading to the formation of the α-alkoxyhydroperoxide (**309**) or (**311**), which can subsequently be decomposed to the ester by converting the hydroxyl group of the peroxide into a leaving group by treatment with a base, or an acid or by esterification (Scheme 4.4.1.3).[13]
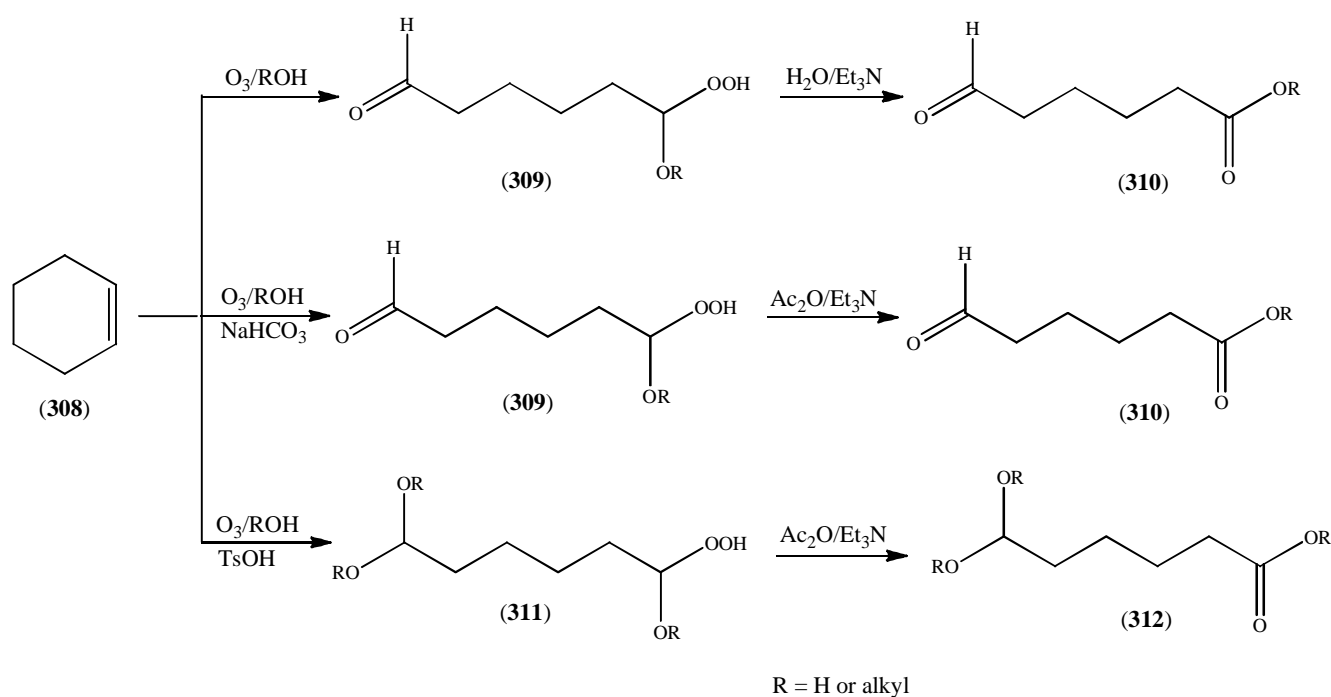
Scheme 4.4.1.3 Solvolysis of *α*-hydroperoxide

Schwartz *et al.*[6] reported a very ingenious 'reductive' ozonolysis protocol where the zwitterion (**290**)/carbonyl oxide (**292**) is formed in the presence of an *N*-oxide nucleophile like the *N*-oxides of *N*-methylmorpholine (**318**), pyridine, or 1,4-diazabicyclo[2.2.2]octane (DABCO). Although the *N*-oxide (**318**) is converted to the corresponding amine (**321**), the process can be viewed as catalytic in the *N*-oxide, since *N*-oxides are easily regenerated by oxidation with O_3. Since this protocol boils down to the generation of carbonyl compounds from alkenes through reaction with only oxygen it can be regarded as an excellent example of an environmentally benign process as only oxygen and electricity is consumed and no waste products (apart from perhaps an alkene fragment) are produced (Scheme 4.4.1.4).[4,6]

R = C$_8$H$_{17}$

(313)

O$_3$/DCM
0 °C

(314)

(315)   +   (316)

(317)

(318)

(319)

O$_3$

(320)   +   O$_2$ +   (321)
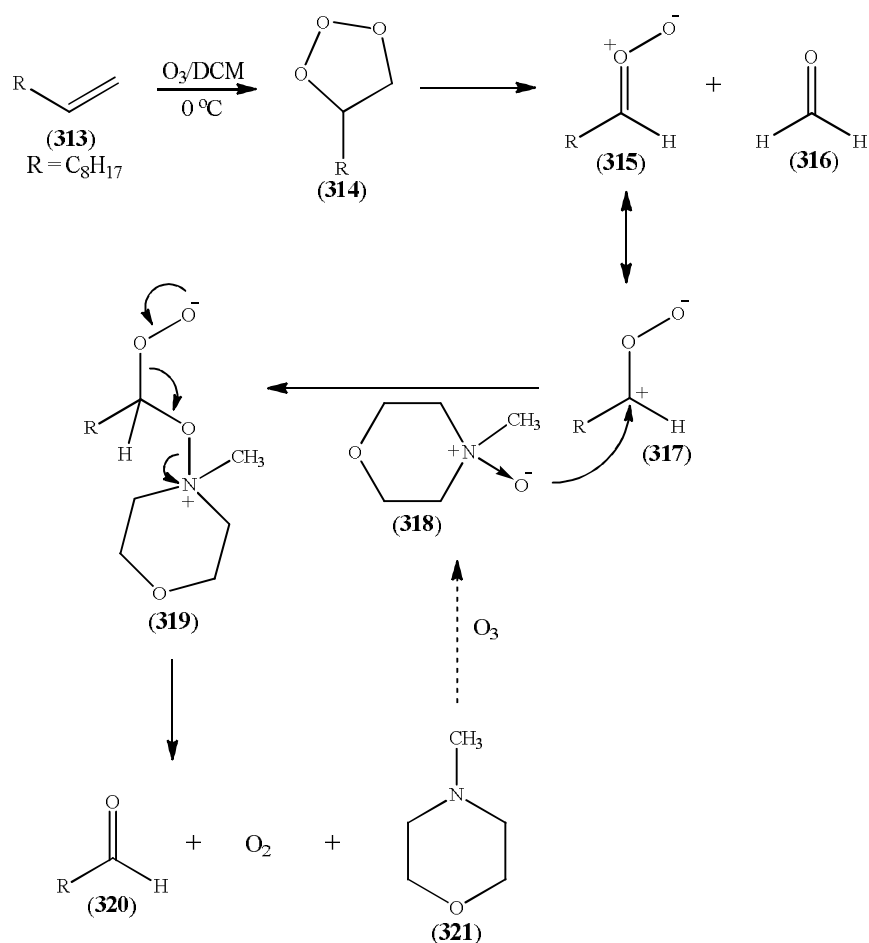
Scheme 4.4.1.4 'Reductive' ozonolysis utilizing *N*-methylmorpholine-*N*-oxide[4,6]

4.4.2   Treatment of Ozonides with Oxidants or Reductants

The use of reductants or oxidants for the transformation of ozonolysis peroxide intermediates (ozonides) into carbonyl compounds is widely used in preparative organic chemistry and has also found application in industrial environments.[5,13,17,18]

Oxidative work-up generally leads to the formation of ketones or carboxylic acids and typical reagents for this purpose includes H$_2$O$_2$, which is often applied in combination with acetic- or formic acid, a suspension of silver oxide (Ag$_2$O) in alkaline solution, chromic acid (H$_2$CrO$_4$) or potassium permanganate (KMnO$_4$).[5,13]
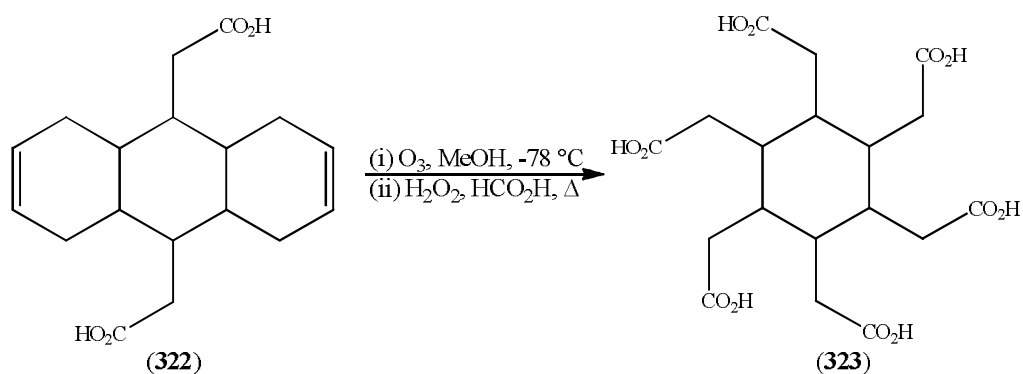
Scheme 4.4.2.1 Oxidative ozonolysis of 9,10-antracenediacetic acid

The addition of selenium dioxide (SeO$_2$) may also be employed in order to not only enhance selectivity, but also accelerate the rate at which the ozonide intermediates are decomposed by H$_2$O$_2$ and in the process provides milder conditions. A simple example is shown in Scheme 4.4.2.2 where dimethyl 3-vinylhexanedioate (**325**) was obtained from 4-vinylcyclohex-1-ene (**324**) *via* ozonolysis using selenium catalyzed decomposition in MeOH. This system provides the possibility of increasing the yield by up to 30% and advances the purity of the resulting aliphatic polycarboxylic acids.[13]
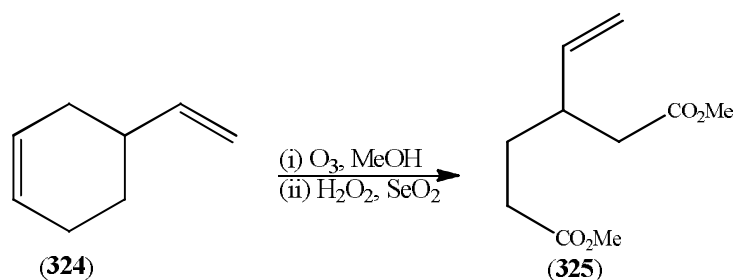
Scheme 4.4.2.2 Ozonolysis of 4-vinylcyclohex-1-ene

Reductive work-up of ozonolysis peroxide intermediates result in the formation of aldehydes (instead of carboxylic acids) and can be accomplished by treating the primary ozonolysis intermediates with reductants like zinc-acetic acid (Zn-AcOH), dimethyl sulphide (DMS), NaBH$_4$, LiAlH$_4$, dialkyl sulphides etc.[5,13,19] Although Zn and AcOH mixtures are often used for reductive work-up after ozonolysis, many substrates are incompatible with the acidic medium and a milder reagent such as Mg-MeOH may be used (Scheme 4.4.2.3).[13,20]
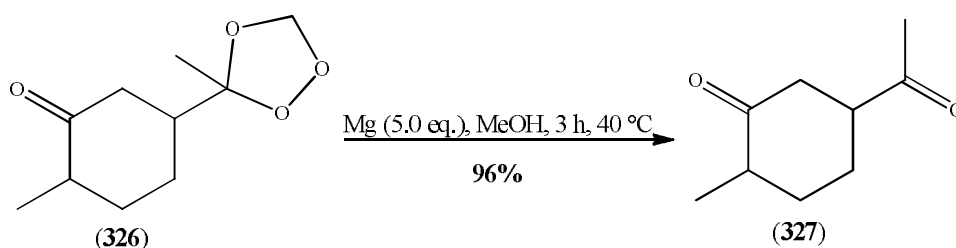
Scheme 4.4.2.3 Mg-MeOH reduction after ozonolysis

In 1966, Pappas and co-workers[18] showed that selective reduction of ozonolysis intermediates to aldehydes or ketones could be accomplished by using DMS as reducing agent. By applying this method they were able to prepare the dialdehyde (**329**) from ozonolysis of naphthalene (**328**) in an isolated yield of 68% (Scheme 4.4.2.4), while it was found that the same protocol could be extended to the cleavage of the ketene dithioacetal (**330**) (Scheme 4.4.2.5).[5,21,22] Reduction of ozonolysis peroxides, e.g., (**332**), utilizing DMS (**333**) has since then become one of the standard reductive work-up methods and can be rationalized by the mechanism given in Scheme 4.4.2.6.
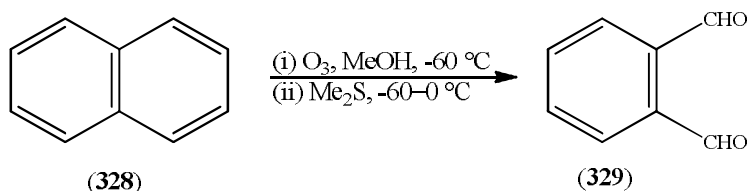
Scheme 4.4.2.4 Ozonolysis of naphthalene
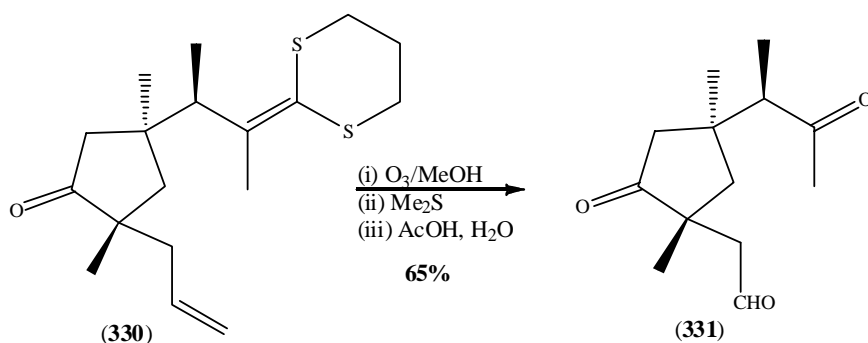
Scheme 4.4.2.5 Ozonolysis of ketene dithioacetal
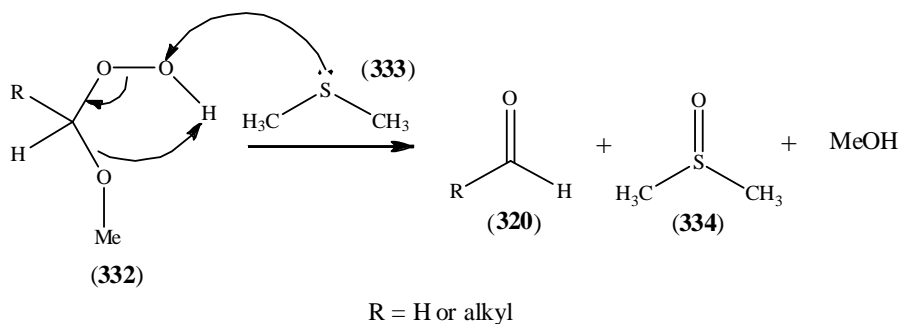
Scheme 4.4.2.6 Reduction of ozonolysis peroxides with DMS

Since it is known that thiourea (**335**) can be oxidized to thiourea *S,S*-dioxide (**336**) by reaction with oxidizing agents ([O]) such as peroxides and peracids (Scheme 4.4.2.7) and one of the primary intermediates in the ozonolysis reaction with MeOH has been established as the *α*-alkoxyhydroperoxide (**332**), this compound has been introduced as alternative reducing agent to replace the odorous DMS (Scheme 4.4.2.8).[13,23]
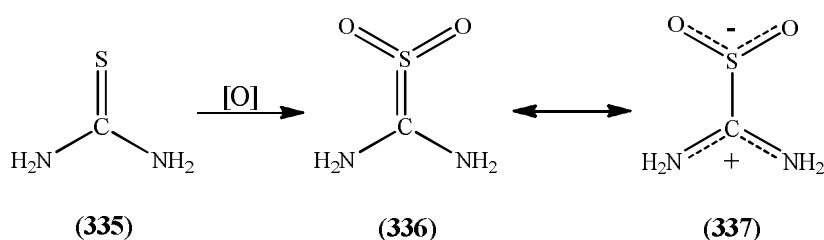
Scheme 4.4.2.7 Peroxide oxidation of thiourea
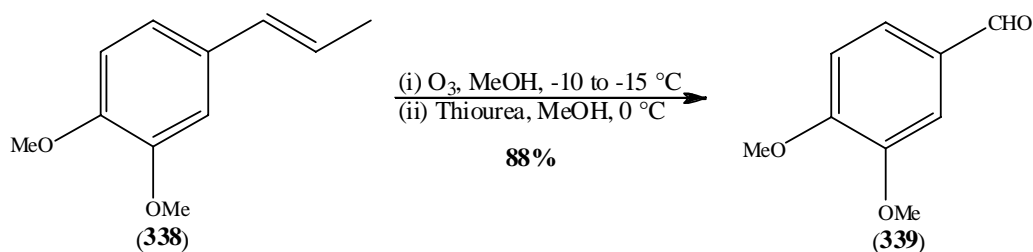
Scheme 4.4.2.8 Reductive work-up after ozonolysis with thiourea

Catalytic hydrogenation of ozonides has also found wide application in the preparation of aldehydes and ketones *via* ozonolysis and has been applied to the synthesis of pheromones

and juvenoids like the sex pheromones of the African Monarch butterfly and the Chinese bean weevil, namely (*E,S*)-3,7-dimethyl-2-octene-1,8-dioic acid (**342**) and (*E,S*)-3,7-dimethyl-2-octene-1,8-diol (**343**) respectively (Scheme 4.4.2.9).[13]
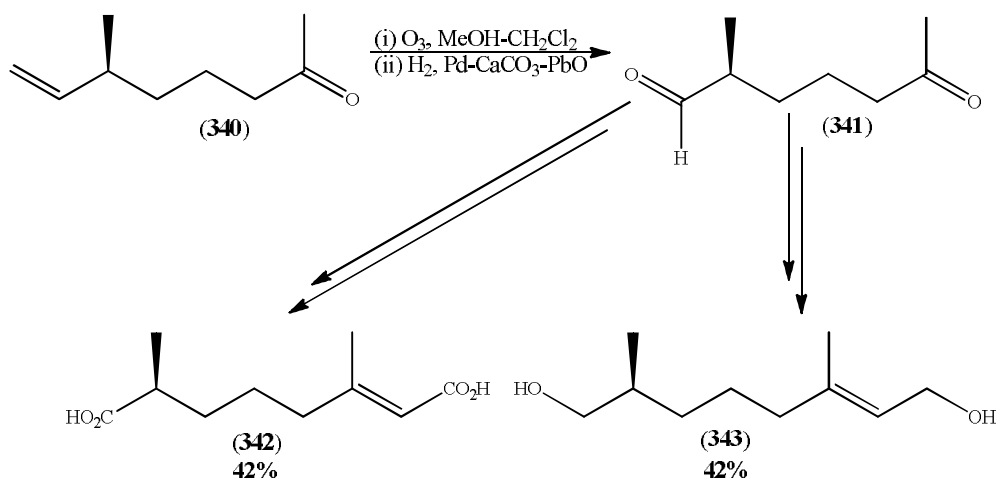
Scheme 4.4.2.9 Ozonolysis and subsequent catalytic hydrogenation

Metal hydrides like LiAlH$_4$ and NaBH$_4$ are also widely used as reductants in the work-up of peroxide intermediate(s) during ozonolysis, but these reagents are associated with the accompanied possible disadvantage of being able to reduce the required aldehyde/ketone to alcohol product (Scheme 4.4.2.10).[13]
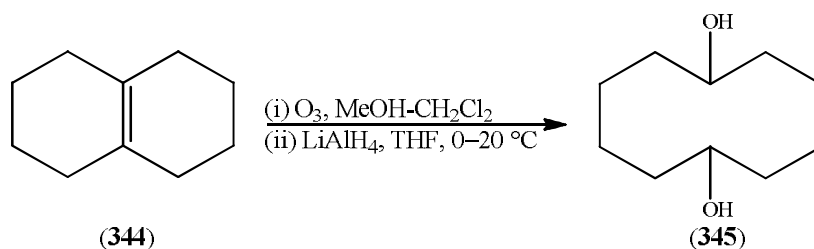
Scheme 4.4.2.10 Reductive work-up with LiAlH$_4$

4.5 Selectivity in Ozonolysis

During the ozonolysis of double bonds, it is important to have careful control over the specific reaction conditions as this might give rise to undesirable side-reactions which may

lead to decreased yields of the wanted product. For example, aldehydes may be oxidised further to peracids and acids or other functional groups present in the substrate may be attacked by O_3 under certain reaction conditions. It may furthermore be desirable to have certain double bonds react over less reactive one's or triple bonds in the same substrate. Since control over the amount of O_3 introduced into the reaction mixture is hard to achieve, the reactivity of multiple (double and triple) bonds towards interaction with O_3 is critical w.r.t. selectivity, while some reaction conditions like temperature or additives might be used in order to achieve the desired result.[13,24]

Since double bonds display increased reactivity towards O_3 over triple bonds, selectivity may be achieved as a result of the inherent properties of the substrate in question. An interesting application of this type of selective oxidative ozonolysis was employed during the design of a synthetic protocol for the pheromone component of the meal beetles, *Cryptolestesferrugineus* and *Oryzaephilusmercator*, namely ferulactone II (**348**). Selective ozonolysis of the enyne (**346**) shown in Scheme 4.5.1 followed by oxidation of the peroxide intermediates using chromic acid, yielded 11-oxo-dodecyne acid (**347**) which could be successfully converted to the target ferrulactone by further transformations.[13,25]
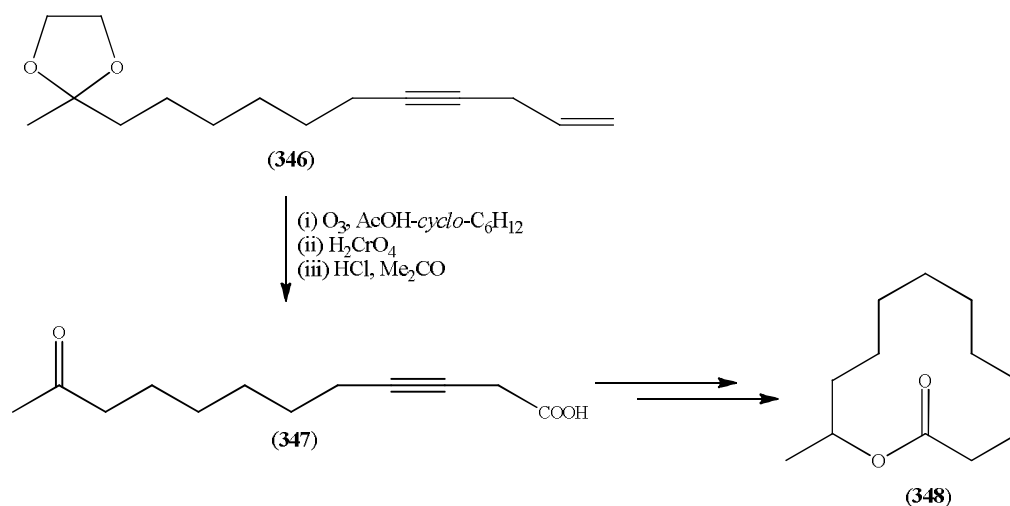
Scheme 4.5.1 Ferrulactone synthesis

Ozonolysis of a double bond in the presence of a triple bond was also carried out by Banfi and Guanti[26] as key step in their synthesis of a methoxy-substituted lactenediyne. An interesting result was obtained when ozonolysis was done on the TBDMS ether of the

silylated alkyne (**349**) shown in Scheme 4.5.2. Even though a certain level of selectivity was observed toward formation of the desired product where ozonation of the double bond only occurred, variable amounts of the side-product resulting from simultaneous ozonation of the triple bond took place. However, better control over the reaction was possible when utilizing the terminal alkyne (**351**) as substrate where the desired alcohol (**352**) was obtained in excellent yield.
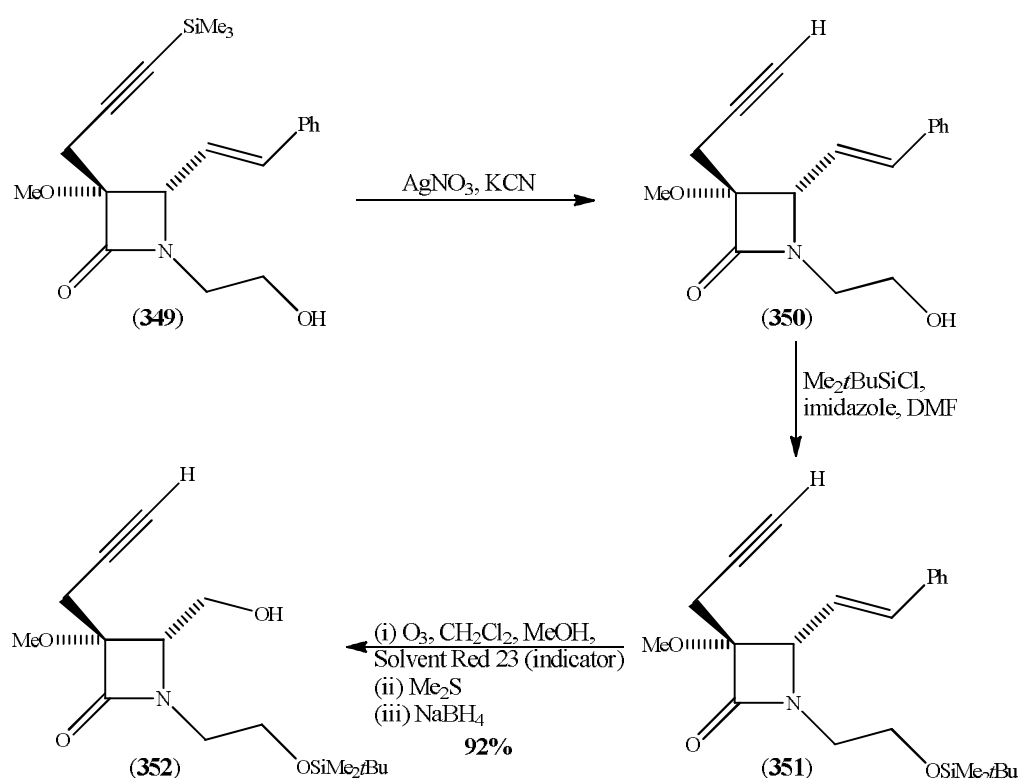
Scheme 4.5.2 Chemoselective ozonolysis

Since more electron rich double bonds also display enhanced reactivity over less electron rich one's, selectivity during ozonolysis may once again be achieved in this regard. Selective oxidative cleavage *via* ozonolysis is demonstrated (Scheme 4.5.3) where the silyloxyalkene (**353**) is converted to lactone (**354**) in 93% yield, leaving the less electron rich vinylic double bond intact.[13,27]
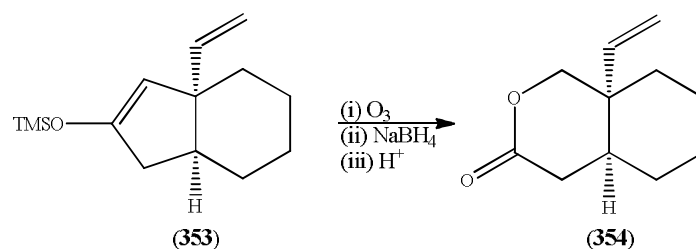
Scheme 4.5.3 A selective ozonolysis with NaBH₄

Aronovitch and co-workers[15] further demonstrated how selectivity may be obtained when comparing the ozonolysis of mono-, di- or trialkyl, or aryl substituted olefins adsorbed on moist silica gel. While the mono- di- and/or trialkyl substituted substrates (1-decene, *cis*-6-dodecene and 1-methylcyclohexene) mainly afforded ozonides, 75–85% (e.g., Scheme 4.5.4), ozonolysis of phenylethylenes (**355i–355iv**) took a different course yielding almost exclusively aromatic ketones or aldehydes (Scheme 4.5.5). The ozonolysis of styrene and its *β*-derivatives (*cis*- and *trans*-stilbene and *trans*-*β*-ethylstyrene) afforded benzaldehyde (**301**) in almost quantitative yield and it was reported that *α*-phenyl-substituted carbonyl oxides, like that of *trans*-stilbene, display exceptional behaviour since their reaction with H_2O rapidly yields hydroxy hydroperoxide (**358**). Apparently, hydrolytic decomposition of the latter yields aromatic aldehyde (**301**) and H_2O_2 (Scheme 4.5.6).
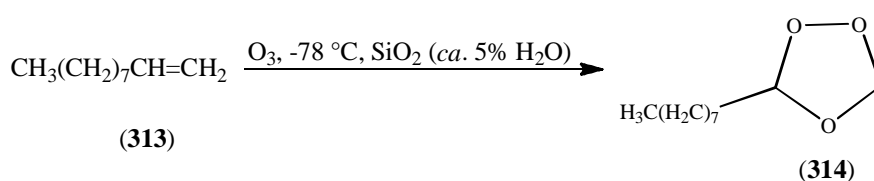
Scheme 4.5.4 Ozonolysis of 1-decene

(**355i**) $R^1 = R^2 = H$
(**355ii**) $R^1 = Ph, R^2 = H$
(**355iii**) $R^1 = H, R^2 = Ph$
(**355iv**) $R^1 = H, R^2 = Et$
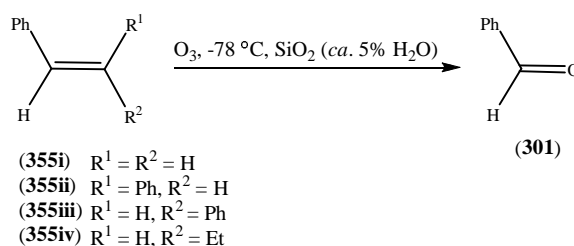
Scheme 4.5.5 Ozonolysis of styrene and its *β*-derivatives
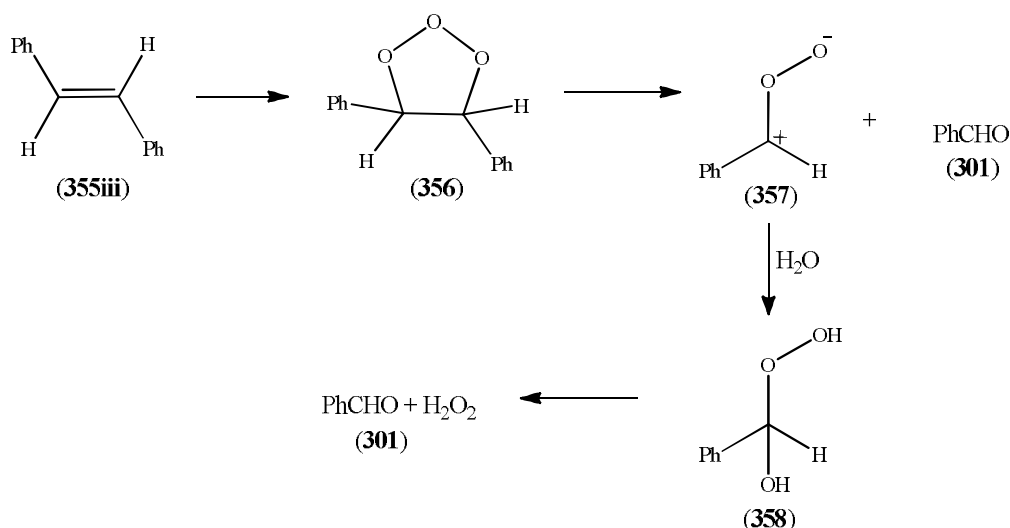
Scheme 4.5.6 Ozonolysis mechanism of *trans*-stilbene with H₂O

It was thus concluded that the intermediate phenyl-substituted zwitterions are far more reactive toward nucleophilic attack of H_2O than that of the mono-, di- or trialkyl substituted carbonyl oxide analogues.[15]

Apart from the inherent properties of substrates that may govern selectivity during ozonolysis, external factors may also be introduced to effect selectivity.

Miura and co-workers[28] reported on the effects of temperature variation on the ozonolysis of indene (**359**) in MeOH where ozonolysis at 20 ℃ afforded a mixture of ozonide isomers (**360**) and (**361**) while lowering the temperature to -70 ℃ afforded the MeOH participated product (**362**) in 78% yield (Scheme 4.5.7).
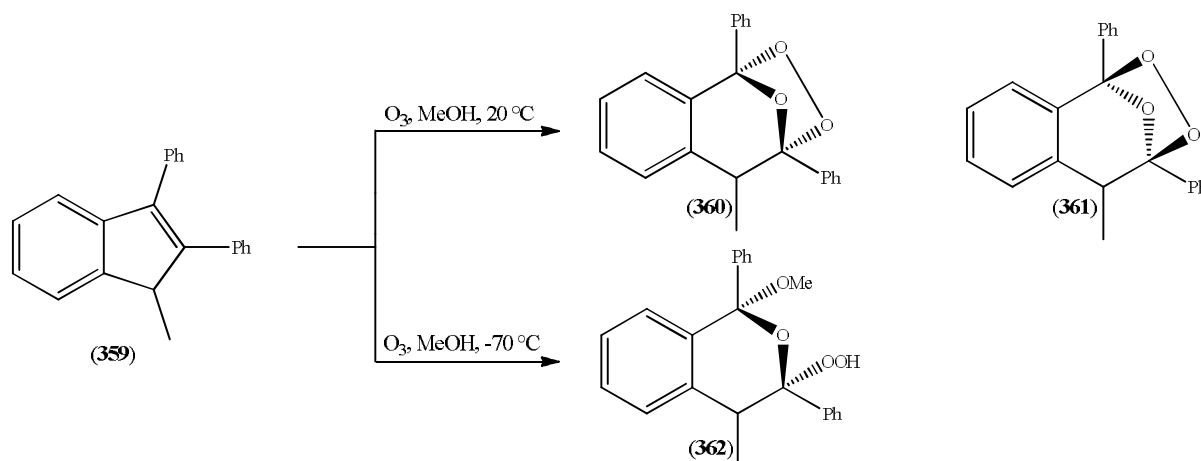
Scheme 4.5.7 Temperature effect on selectivity after ozonolysis

Additives such as boron trifluoride (BF_3) or aluminium chloride ($AlCl_3$) may enhance reactivity during ozonolysis *via* a mechanism much the same as in the familiar Friedel-Crafts reaction, where, with regard to ozonolysis, the Lewis acid may combine with the negatively charged oxygen atom within the O_3 molecule thereby forming a salt-like compound and increased O_3 electrophilicity.[5,24]
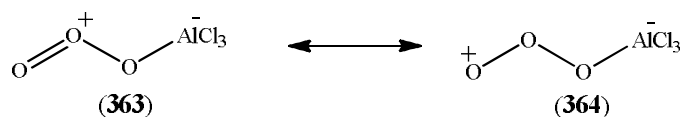
Scheme 4.5.8 Increased O_3 electrophilicity with a Lewis acid

Sixma and co-workers[29] investigated reaction kinetics of ozonolysis and found that the reaction rate increases directly with the increase in $AlCl_3$ concentration during the ozonolysis of benzene.

As an opposite effect, nucleophiles such as pyridine should also react with O_3 but reduce the electrophilic nature of O_3.[24]

(**365**)
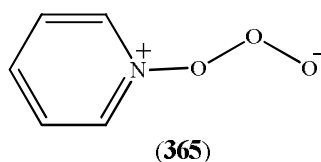
Pyridine-bound O$_3$

According to Slomp and co-workers[24] the interaction of Lewis acids and pyridine with O$_3$ reduces the electrophilicity of O$_3$ and according to their work on the ozonolysis of 4,22-stigmastadien-3-one (**366**), the best selectivity was obtained utilizing a 1:1 ratio of pyridine to substrate and that higher pyridine concentrations actually led to a decrease in yield of the aldehyde product. It was thus proposed that selectivity, in other words, cleavage of only one of the two double bonds in their substrate (Scheme 4.5.9) was obtained as addition of pyridine slowed the ozonolysis to such an extent that differences in electronegativity of the two double bonds became an important factor leading to the regioselective synthesis of desired products in excellent yield.[5,24]
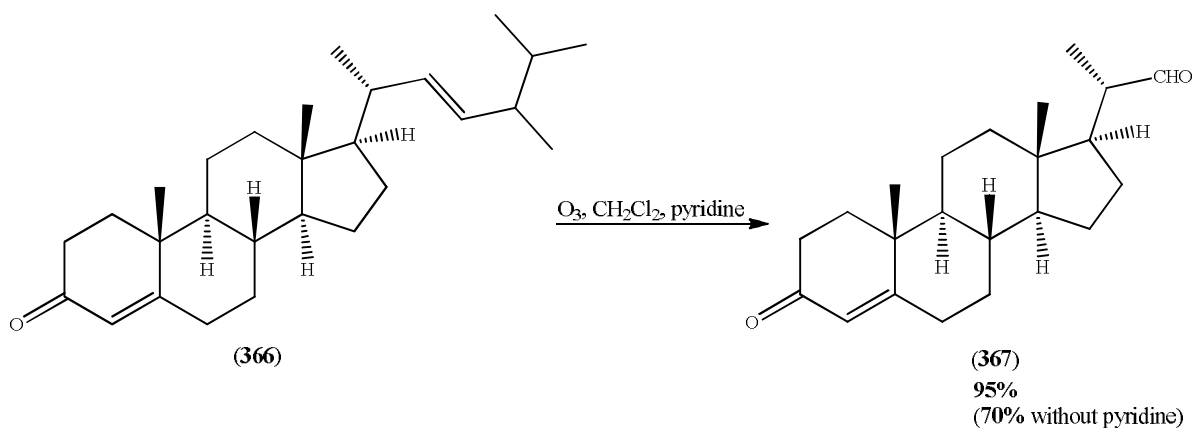
Scheme 4.5.9 Regioselective ozonolysis

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DISCUSSION 5

5.1 Introduction

Similar to that of most natural products, studies directed at the synthesis of flavonoids have emerged from the search for new compounds with beneficial biological properties. As mentioned earlier, flavonoids and isoflavonoids are known to exhibit many important biological properties and are especially promising candidates for, among others, cancer chemoprevention.[1,2]

Metabolic studies are, however, frequently hampered by the inaccessibility of a variety of optically active flavonoids displaying biologically important substitution patterns. While a single process for the synthesis of enantiomerically enriched isoflavonoids have been published (Scheme 5.1.1),[3] this process utilizes phenylacetic acid derivatives (**370**) which are not readily available in all naturally occurring substitution patterns.

(368)
R = H or alkyl
R^1 = H or OH

(369)
R = H or alkyl
R^1 = H or OH
X = O or N

(370)

(371)
R = H or alkyl
X = O or N
Z = CH$_2$Cl or CHO
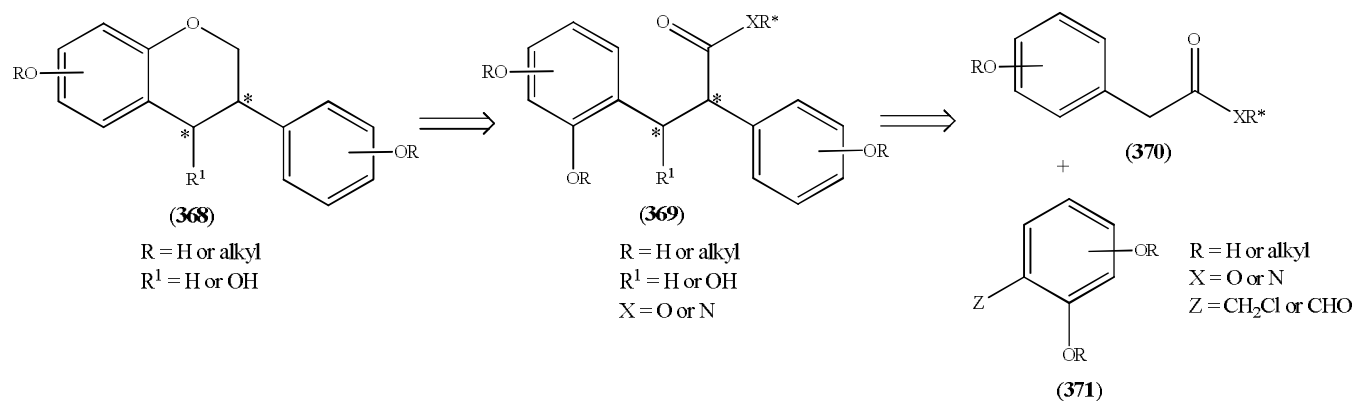
Scheme 5.1.1 Isoflavonoid retrosynthesis[3]

Phenylacetic acid derivatives are accessible *via* rearrangement of acetophenones through a number of routes like (i) the ancient sulphur-based Willgerodt-Kindler reaction (Scheme 5.1.2),[4] (ii) through the use of lead(IV)acetate (Myrboh process) (Scheme 5.1.3),[5] (iii) oxidative rearrangement with Tl(NO$_3$)$_3$ followed by acid treatment (McKillop synthesis) (Scheme 5.1.4),[6] (iv) Grignard reaction (Scheme 5.1.5)[7] or carbonylation reactions utilizing organometallic compounds of palladium, rhodium or cobalt (Scheme 5.1.6)[8,9] and finally (v)

the industrially applied synthesis, which is based on the transformation of benzyl halides to the nitrile analogue with subsequent acid hydrolysis (Scheme 5.1.7).[10]

(372) (373) (374) (321)
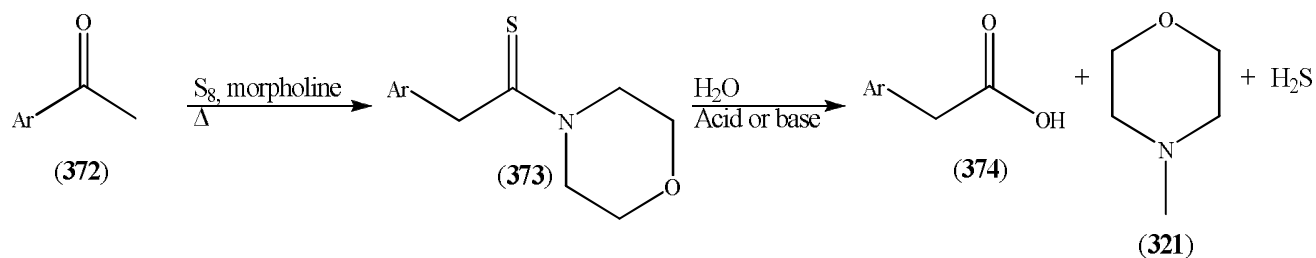
Scheme 5.1.2 Willgerodt-Kindler reaction

(375) (376)
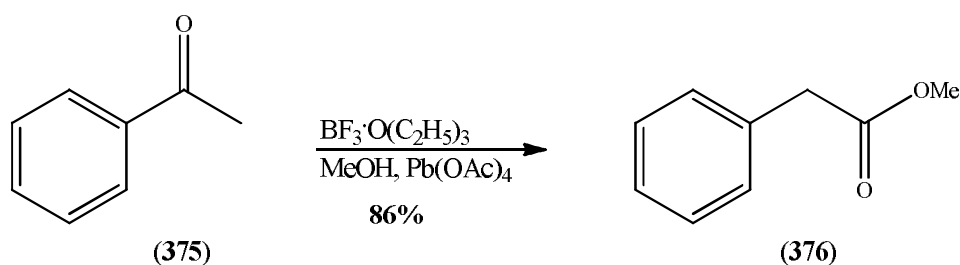
Scheme 5.1.3 Myrboh process

(377) (378)
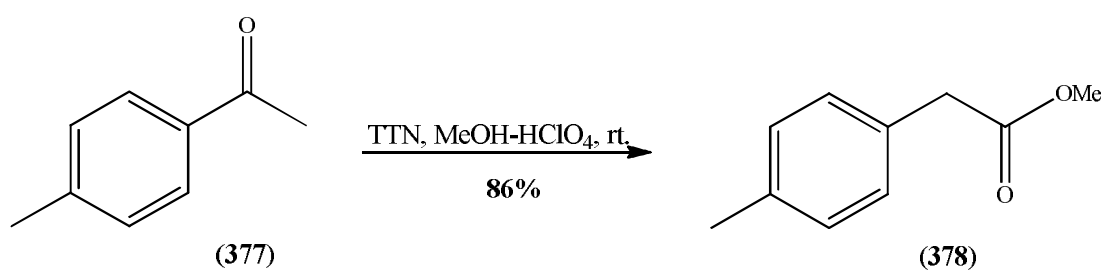
Scheme 5.1.4 TTN oxidative rearrangement (McKillop synthesis)

(379) (380) (381)
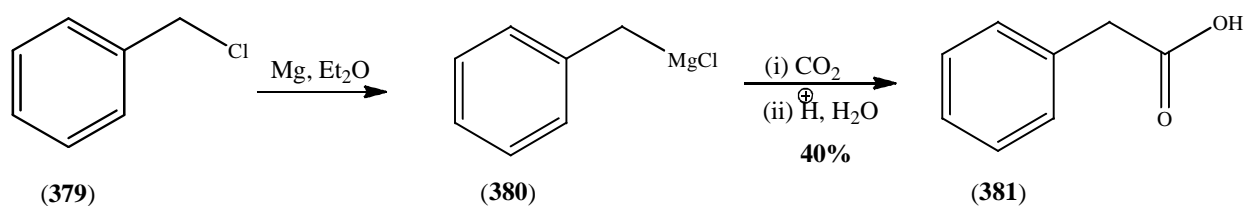
Scheme 5.1.5 Grignard reaction
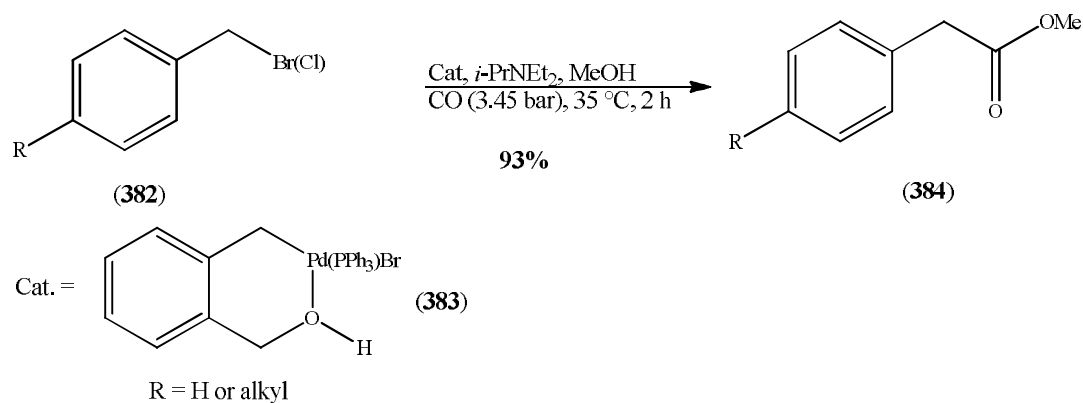
Scheme 5.1.6 Pd-catalyzed carbonylation
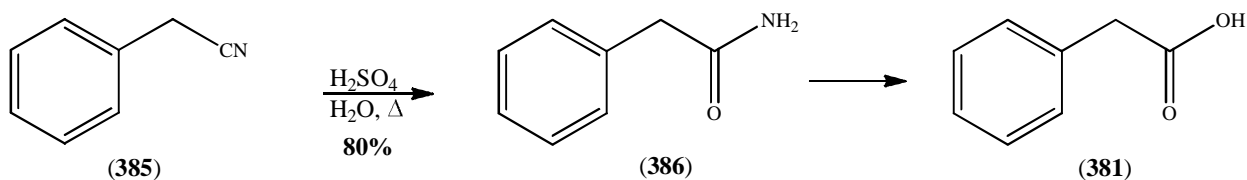
Scheme 5.1.7 Acid hydrolysis of arylmethyl nitriles

Although these methods sometimes lead to the desired phenylacetic acid derivatives in acceptable yields, they are frequently hampered by various limitations. In this regard, the Willgerodt-Kindler reaction is based on the use of excess quantities (1.5 eq.) of elemental sulphur (leading to odourous side products) and high reaction temperatures resulting in variable yields, while the McKillop and Myrboh oxidative rearrangements require poisonous heavy metal reagents such as $Tl(NO_3)_3$ and $Pb(OAc)_4$. Both these methods are also of limited applicability, since substrates with some aromatic substitution patterns (especially amino substituents) lead to virtually no products being formed. Furthermore, acetophenones with highly deactivated aromatic rings may undergo enolization, oxythallation and aryl migration under TTN reaction conditions, leading to low yields and the formation of methoxylated acetophenone derivatives as side products.[5,6]

Carboxylation *via* the Grignard reaction leads to the production of large amounts of waste and are complicated by all the side reactions generally associated with the Grignard reaction, like radical coupling of the alkyl halide leading to dimeric products.[7] Hydrolysis of nitriles suffers from the disadvantage that stoichiometric amounts of acids or bases as well as elevated temperatures are required, while the CN group can easily be substituted by water

present in the acid or base leading to the benzyl alcohol rather than the desired acid.[10] Even though recent methodologies based on carbonylation of benzyl halides (Scheme 5.1.6) are catalytic, highly effective (quantitative yields are obtainable) and executable under moderate temperatures and pressures, all of the methods mentioned above require the availability of benzyl halides as primary starting material.[10] If natural products are to be made, highly oxygenated benzyl halides, which can be difficult to prepare and handle, would be required, which renders this methodology difficult to execute if not unsuitable for the latter application.

Due to the general drive towards the development of more efficient and cleaner methodologies in chemical synthesis and since the existing methods for the preparation of phenylacetic acids are hampered by several problems (*vide supra*), it was decided to embark on a study aimed at the development of alternative methodology for the preparation of phenylacetic acid derivatives that would (i) utilize readily available starting materials (ii) are easily executable with a limited number of process steps, (iii) be environmentally favourable, (iv) high yielding, and (v) compatible with the synthesis of analogues that would display naturally occurring aromatic substitution patterns. All of these could be met by methodology based on the ozonolysis of substituted allylbenzenes, so a study on the ozonolysis of oxygenated allylbenzenes (**387**–**392**) was embarked upon (Scheme 5.1.8).

(387) $R^1 = R^2 = R^3 = R^4 = H, R^5 = OMe$
(388) $R^1 = R^2 = R^4 = R^5 = H, R^3 = OMe$
(389) $R^1 = R^2 = R^4 = H, R^3 = R^5 = OMe$
(390) $R^1 = R^4 = R^5 = H, R^2 = R^3 = OMe$
(391) $R^1 = R^5 = H, R^2 = R^3 = R^4 = OMe$
(392) $R^2 = R^4 = H, R^1 = R^3 = R^5 = OMe$

$R^1, R^2, R^3, R^4, R^5 = H$ or OMe
$R^6 = CHO$ or $COOMe$
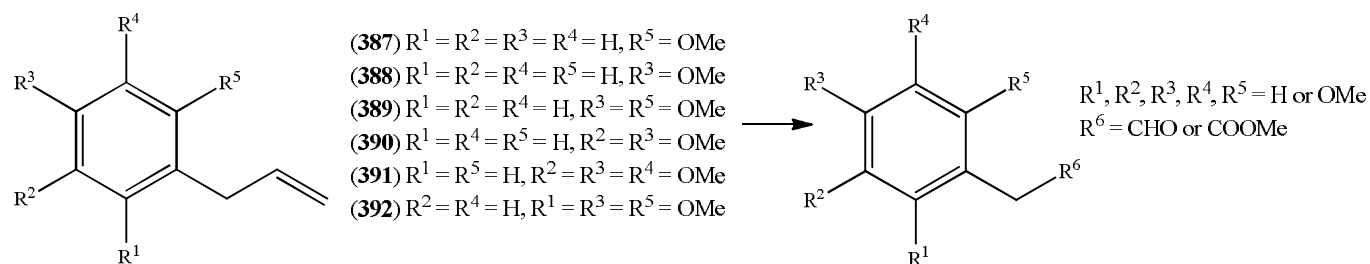
Scheme 5.1.8 Allylbenzene substrates to be subjected to ozonolysis

While some allylbenzenes [(**387**), (**388**), (**390**) and (**391**)] were available commercially either as methoxy derivatives [(**387**) and (**388**)] or in free phenolic form [1-allyl-4-hydroxy-3-methoxybenzene (**390**) and 1-allyl-4-hydroxy-3,5-dimethoxybenzene (**391**)] these just had to be methylated to eliminate any possible effect that free hydroxyl groups might have on the outcome of the ozonolysis reaction. Allylbenzenes with oxygenation in the 2- and 4-

positions (resorcinol-type substitution) and the 2,4,6-analogues (phloroglucinol-type substitution), however, were not commercially available and had to be prepared. In this regard it was envisaged that these compounds could become available through the allylation of 3-methoxyphenol (**393**) and 3,5-dimethoxyphenol (**395**) followed by a [3,3] sigmatropic (Claisen) rearrangement of the 1-allyloxy derivatives (**394**) and (**396**).

5.2 Synthesis of Substituted Allylbenzenes

5.2.1   Allylation of Phenols

The synthesis of the required allylphenols (**403**) and (**404**) was started by subjecting 3-methoxyphenol (**393**) as well as 3,5-dimethoxyphenol (**395**) to the standard Williamson etherification conditions, *i.e.* allyl bromide, K_2CO_3, and dry acetone, and the reaction mixture refluxed for 8 h to obtain the desired products (**394**) and (**396**) in high yields (76% and 80% respectively) (Scheme 5.2.1.1).[11] Although the isolated yields were acceptable, the products (**394**) and (**396**) were accompanied by the UV-inactive diacetone alcohol (4-hydroxy-4-methyl-2-pentanone), originating from aldol condensation of acetone, so the solvent was changed to acetonitrile and the reactions repeated to give the products in quantitative yields without any contamination.
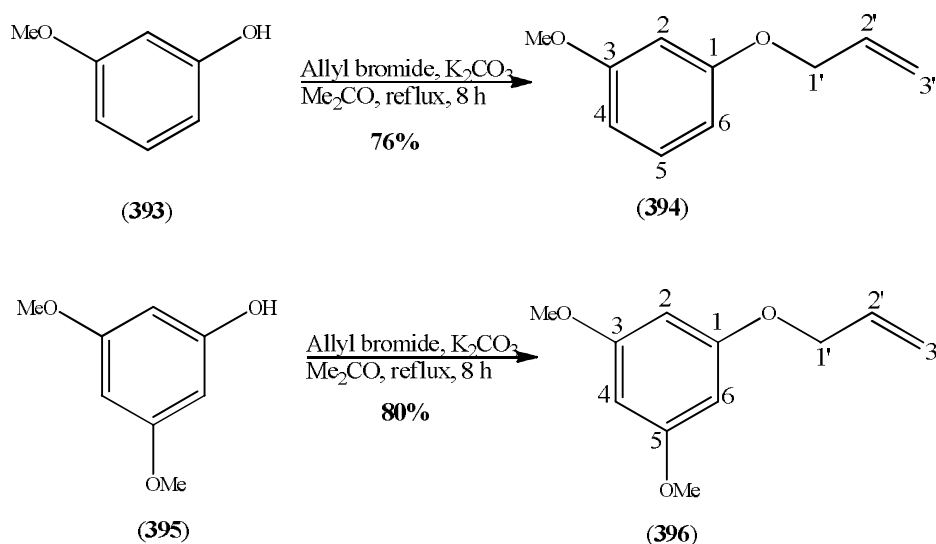
Scheme 5.2.1.1 Allylation of phenols

The structures of 1-allyloxy-3-methoxybenzene (**394**) and 1-allyloxy-3,5-dimethoxybenzene (**396**) were confirmed by ^{1}H NMR (Plate 1a and 2a) where, apart from the expected aromatic resonances, signals from the allylic protons [δ 6.18–6.05 (1H, m, H-2'), 5.46–5.43 (1H, m, H-

3'b), 5.33–5.31 (1H, m, H-3'a), 4.55–4.54 (2H, m, H-1') and 6.08–6.02 (1H, m, H-2'), 5.43–5.40 (1H, m, H-3'b), 5.30–5.28 (1H, m, H-3'a), 4.50–4.49 (2H, m, H-1')] were clearly visible. The structures of the products (**394**) and (**396**) were confirmed by ^{13}C NMR spectroscopy (plates 1b and 2b) and mass spectrometry (EI) where molecular ions at *m/z* 164.15 (M$^+$, 100.00%) and 194.05 (M$^+$, 100.00%), respectively, were found.

5.2.2   Claisen Rearrangement

The Claisen rearrangement may be effected *via* two different methods: (i) a thermal transition, usually the application of reflux conditions in high boiling solvents like *N,N*-dimethylaniline (*ca.* 193 °C) for 5–8 hrs.[12] and/or (ii) with the addition of Lewis-acid catalysts.[13,14]

Initial attempts toward effecting the Claisen rearrangement (Scheme 5.2.2.2) involved 1-allyloxybenzene (**397**) as model substrate and centred on thermal conditions. So, the allyloxybenzene (**397**) was refluxing in *N,N*-dimethylaniline (*ca.* 193 °C) for 8 hours and the desired 1-allyloxy-2-hydroxybenzene (**398**) (^{1}H NMR plate 11a), identical to an authentic sample, obtained, albeit in only 20% yield (Scheme 5.2.2.1).
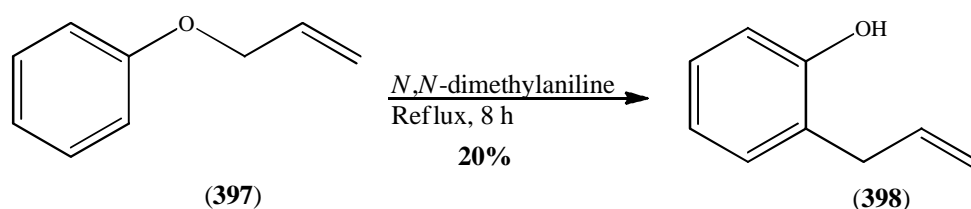
Scheme 5.2.2.1 Standard Claisen Rearrangement

To improve on the yield and work towards an environmentally benign process, it was then decided to apply microwave technology to the Claisen rearrangement. The 3-methoxy- and 3,5-dimethoxybenzene substrates (**394**) and (**396**) were therefore subjected to microwave irradiation (solvent free) with constant cooling to keep the temperature at 200 °C for three intervals of 15 minutes each (power variation 0–200 W depending on reaction temperature) and the products obtained in 88–89% yield (Scheme 5.2.2.3 and 5.2.2.4).

(399)   **(400)**   **(401)**

R = OMe or OH
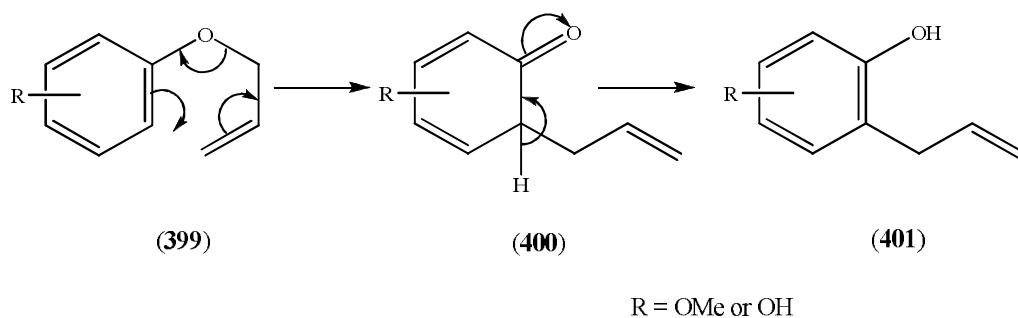
Scheme 5.2.2.2 Claisen rearrangement mechanism

With the application of this method, the allyl moiety of both 1-allyloxy-3-methoxybenzene (**394**) and 1-allyloxy-3,5-dimethoxybenzene (**396**) could be successfully rearranged to the allylbenzenes, as was evident from the proton NMR spectra (plates 12a and 13a) of the products where the methylene resonances (1'-CH_2) moved up-field from *ca.* δ 4.5 to 3.4 ppm. Even though a single *ortho*-allylated product (**403**), indicated by non-equivalent *meta*-coupled doublets (δ 6.11) in the aromatic region of the spectrum was found for 1-allyloxy-3,5-dimethoxybenzene (**396**), reaction of the 3-methoxy analogue (**394**) led to both *ortho*-positions being allylated [formation of the 2-hydroxyallylbenzenes (**404**) and (**405**)] in almost equal quantities (Scheme 5.2.2.4). The ^{1}H NMR spectra (plates 13a and 14a) of the two products (**404**) and (**405**) displayed an ABX system (δ 7.01–6.43) for (**404**) and a dd (δ 7.08) and multiplet (δ 6.51–6.50) for (**405**) in the aromatic region of the spectra, thus confirming the proposed structures for the products. Final confirmation for the structures of all the products came from the ^{13}C NMR spectra (plates 13b and 14b) as well as MS where molecular ions at *m/z* 164.15 (M$^+$ 100.00%) and *m/z* 164.10 (M$^+$ 100.00%) respectively, were observed.

(396)   **(403)**
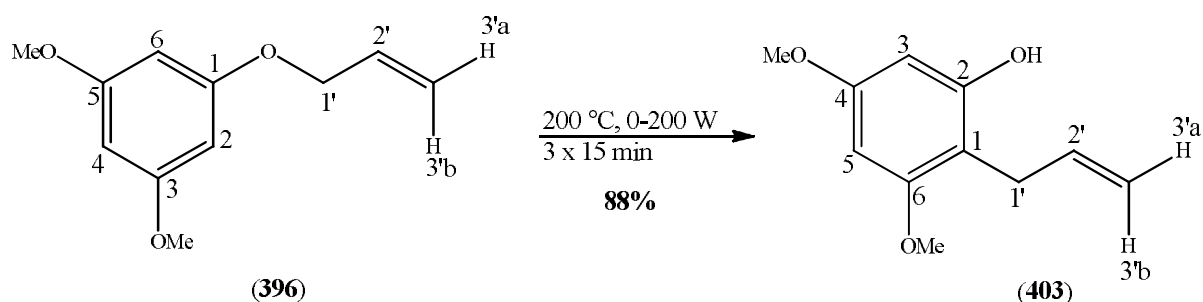
Scheme 5.2.2.3 Claisen rearrangement of 1-allyloxy-3,5-dimethoxybenzene

74
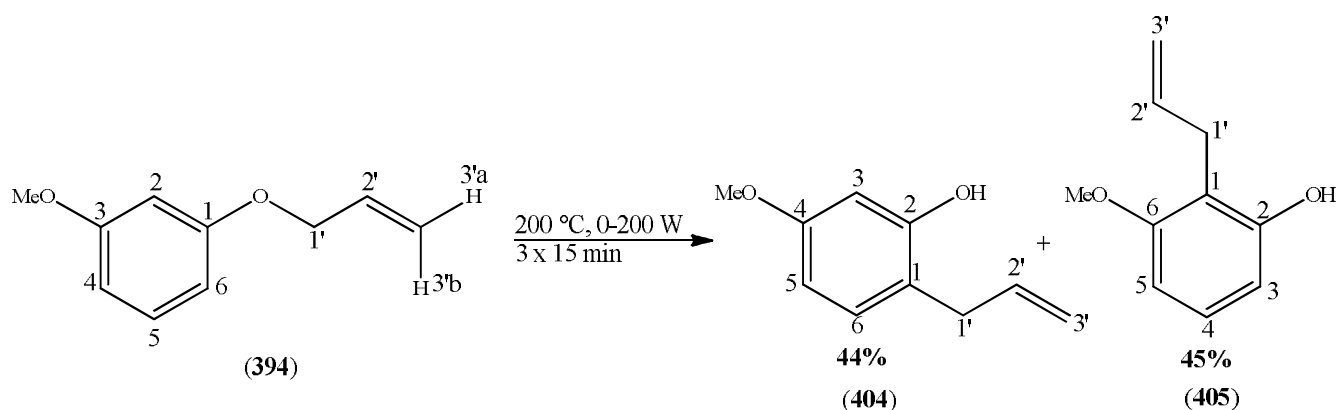
Scheme 5.2.2.4 Claisen rearrangement of 1-allyloxy-3-methoxybenzene

Although chair-like transition states (**406**), which would suggest *meta*-substituents to cause some steric hindrance during the rearrangement, have been proposed for these type of reactions,[15,16] steric hindrance from the methoxy group in the current substrate seems not to play a major role during the rearrangement. It might therefore be concluded that the steric effect of the methoxy group is not quite as significant as was assumed or that the energy from the microwave irradiation is high enough to overcome any steric influence originating from the presence of the methoxy group.

(**406**)
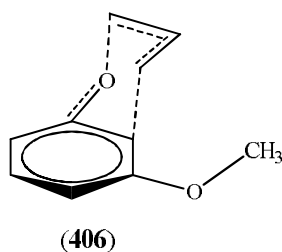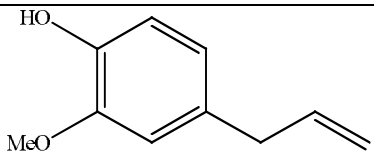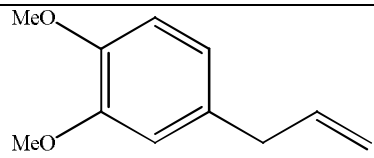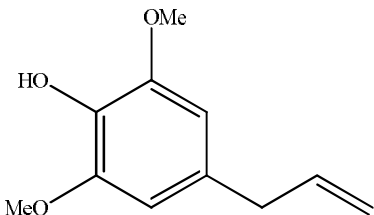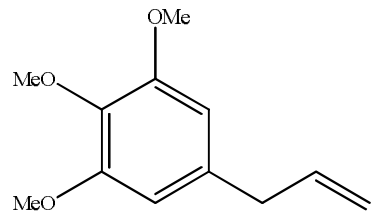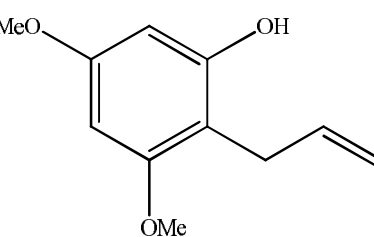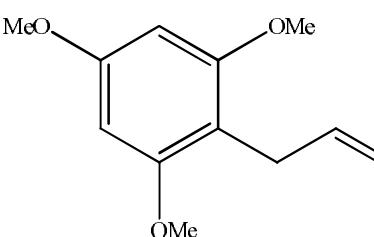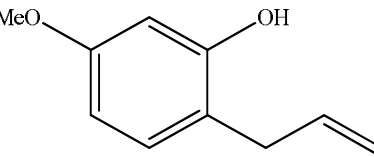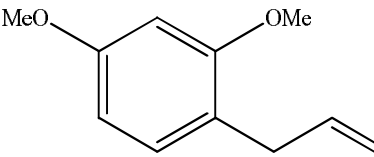
Claisen rearrangement transition state

5.2.3   Methylation of Allylbenzenes

To eliminate all possible negative effects from the free phenolic hydroxyl groups during the subsequent ozonolysis reactions, the allylbenzenes available commercially as well as those prepared, were methylated by application of the standard Williamson ether synthesis methodology. Hydroxyallylbenzenes (**407**), (**408**), (**403**) and (**404**) were therefore subjected to refluxing conditions with MeI in the presence of K_2CO_3 in either Me_2CO or CH_3CN as solvent (Table 5.2.3.1).[11]

Table 5.2.3.1 Methylation of allylbenzenes

Substrate	Solvent	Nr.	Product	Nr.	Isolated yield (%)
	Me₂CO	(**407**)		(**390**)	79
	Me₂CO	(**408**)		(**391**)	77
	CH₃CN	(**403**)		(**392**)	80
	CH₃CN	(**404**)		(**389**)	96

Structures of (**389**)–(**392**) were confirmed by ¹H NMR where an additional methoxy-resonance was observed between 3.80 and 3.87 ppm in the spectra (plates 3a–6a) as well as MS (EI) where the molecular ions were observed at *m/z* 178.10 (M⁺, 100.00%), 178.10 (M⁺, 100.00%), 208.10 (M⁺, 100.00%) and 208.00 (M⁺, 100.00%) for (**389**), (**390**), (**391**) and (**392**) respectively.

5.3 Ozonolysis

With all the envisaged allylbenzenes (**387**)–(**392**) in hand, attention was subsequently turned towards the actual ozonolysis part of the investigation with reductive as well as oxidative work-up. Although the possibility of ring ozonolysis could not be disregarded completely,[17,18,19] successful ozonolysis of a double bond in the presence of an aromatic ring has been reported (e.g. Scheme 5.3.1),[20,21,22,23] so this was not considered as a major complicating factor in the current investigation.
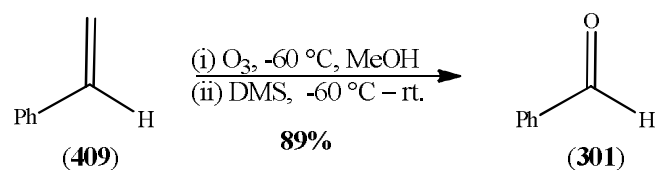
Scheme 5.3.1 Ozonolysis of styrene[21]

Since the direction of the fragmentation of the molozonide (trioxolane) intermediate (**411**) in the Criegee mechanism, is mostly governed by the inductive effect[24] of the substituents surrounding the trioxolane species with the zwitterion being formed at the carbon carrying electron donating groups, this was also not envisaged as a problem in the formation of the desired aldehyde or acid products as the carbonyl fragmentation product (**413**) or (**415**) would involve the non-aromatically substituted carbon atom [$R^1 - R^4 \neq$ Ph in structures (**413**) and (**415**)] (Scheme 5.3.2).
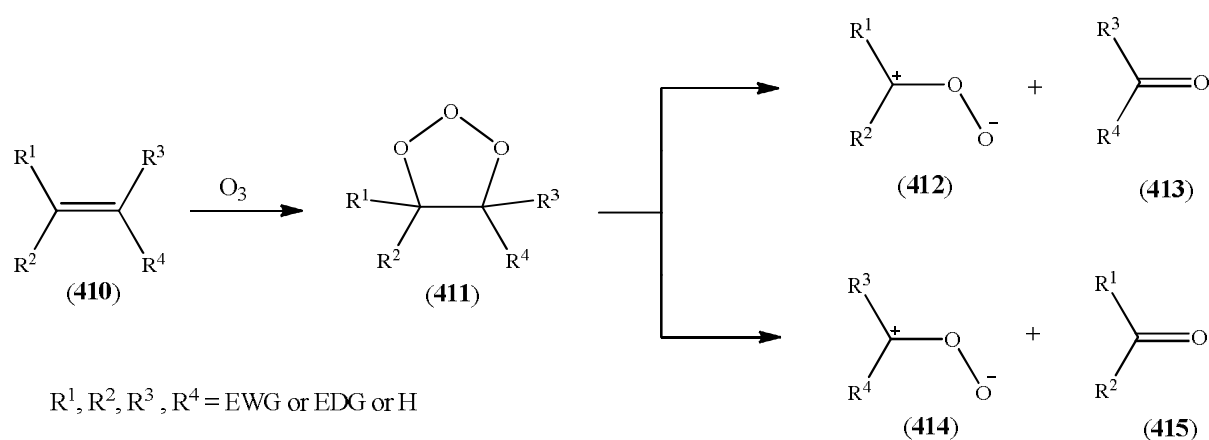
Scheme 5.3.2 Trioxolane fragmentation routes[24]

5.3.1 Ozonolysis with Reductive Work-up

While Zn-AcOH, NaBH$_4$, LiAlH$_4$ has been reported as well-established reducing agents in the reductive work-up of ozonides, substrates are not always compatible with the acidic medium involved in the zinc procedure, while hydride reducing agents may reduce aldehydes and/or ketones to the corresponding alcohol.[24,25,26] Since dimethyl sulphide (DMS) has also been used on a routine basis as reductant of ozonides and found to entail mild reaction

conditions,[21,27] this reagent was selected as reducing agent to start with in the current study and 1-allyl-2-methoxybenzene (**387**) was subjected to O_3 at -78 °C for 30 min. Since DCM had been employed as solvent during various successful ozonolysis reactions, this compound was selected as solvent for starting the investigation.[24,25,28,29,30,31] A mixture of products were, however, obtained with no indication of the desired phenylacetaldehyde being present. Furthermore, identifying any of the products was not possible, due to purification problems and overlapping signals in the ^{1}H NMR spectra.

According to the accepted mechanism for reductive work-up involving DMS (Scheme 5.3.1.1),[24] however, the zwitterion intermediate (**416**) needs to be stabilized for the DMS to complete the reduction, so the reaction conditions were subsequently changed (*cf.* Method B) to utilizing dehydrated MeOH* as solvent instead of the DCM[21] and the reaction repeated. In addition, the reaction time after ozonolysis was also increased from 30 min. to 80 min. to ensure complete conversion of the ozonide to the carbonyl compounds. Only unidentifiable mixtures of products were, however, still obtained.
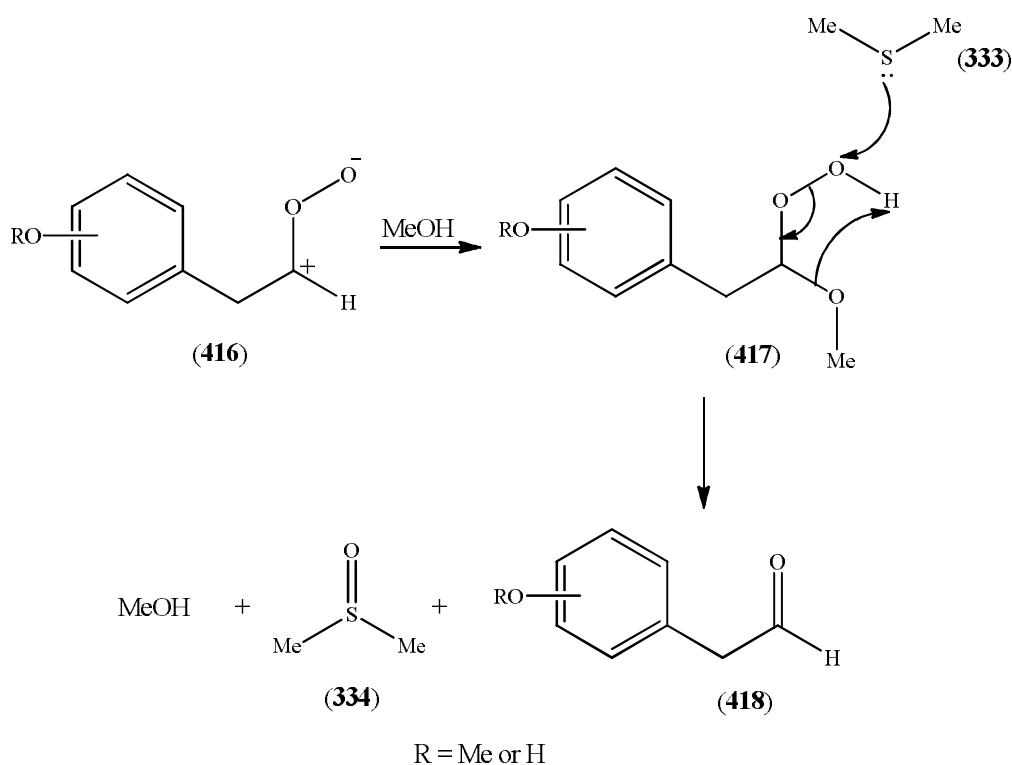
Scheme 5.3.1.1 Ozonolysis with reductive work-up involving DMS[24]

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* MeOH passed though small column of Al_2O_3 (10% v/v)

Since elongated work-up times (after addition of the DMS) did not lead to improved results, it was decided that over-ozonation might be the cause of the failure of the reaction, so this aspect of the reaction was subsequently looked into. While it is generally true that in DCM as solvent the end point of ozonolysis reactions (saturation of the DCM with ozone) is indicated by a colour change in the reaction mixture from colourless to light blue-grey,[32] this colour change was not that easily observed in the case of a methanol medium and over-oxidation may have already occurred by the time the blue colour is observed. Other methods of knowing that the end point of the ozonolysis reaction has been reached were therefore investigated.

While monitoring the precise concentration and flow rate of O_3 into the reaction mixture and keeping it constant, would be very difficult on small-scale reactions (~200–500 mg) and passing the exhaust gas through a potassium iodide solution[33] would be dependent on the efficiency of absorption of O_3 by the reaction mixture, it was decided to rather evaluate the utilization of indicators as method to decide when ozone introduction into the reaction mixture should be stopped.

Several commercially available coloured dyes (Fig. 5.3.1.1) were tested in this regard by Veysoglu and co-workers[34] who dissolved the dyes in DCM, EtOH or MeOH and ozonized the mixtures at -78 ºC until a colourless endpoint was obtained. These workers also stated that oxidation products of the dyes they tested would not affect the course of the reaction or complicate purification procedures. It was therefore decided to utilize Solvent red 23 in the current investigation as this dye is commercially available, provided a sharp end-point and did not show decolouration before completion of the ozonolysis process (as in the case of Solvent red 19) or resistance to ozonolysis (as for solvent red 24 and 27).

(419) 4-(4-Nitrophenylazo)-resorcinol

(420) R = NHC$_2$H$_5$, Solvent red 19
(421) R = OH, Solvent red 23

(422) 4-(Phenylazo)benzoyl chloride

(423) Solvent black 3

(424) R = H, Solvent red 24
(425) R = CH$_3$, Solvent red 27
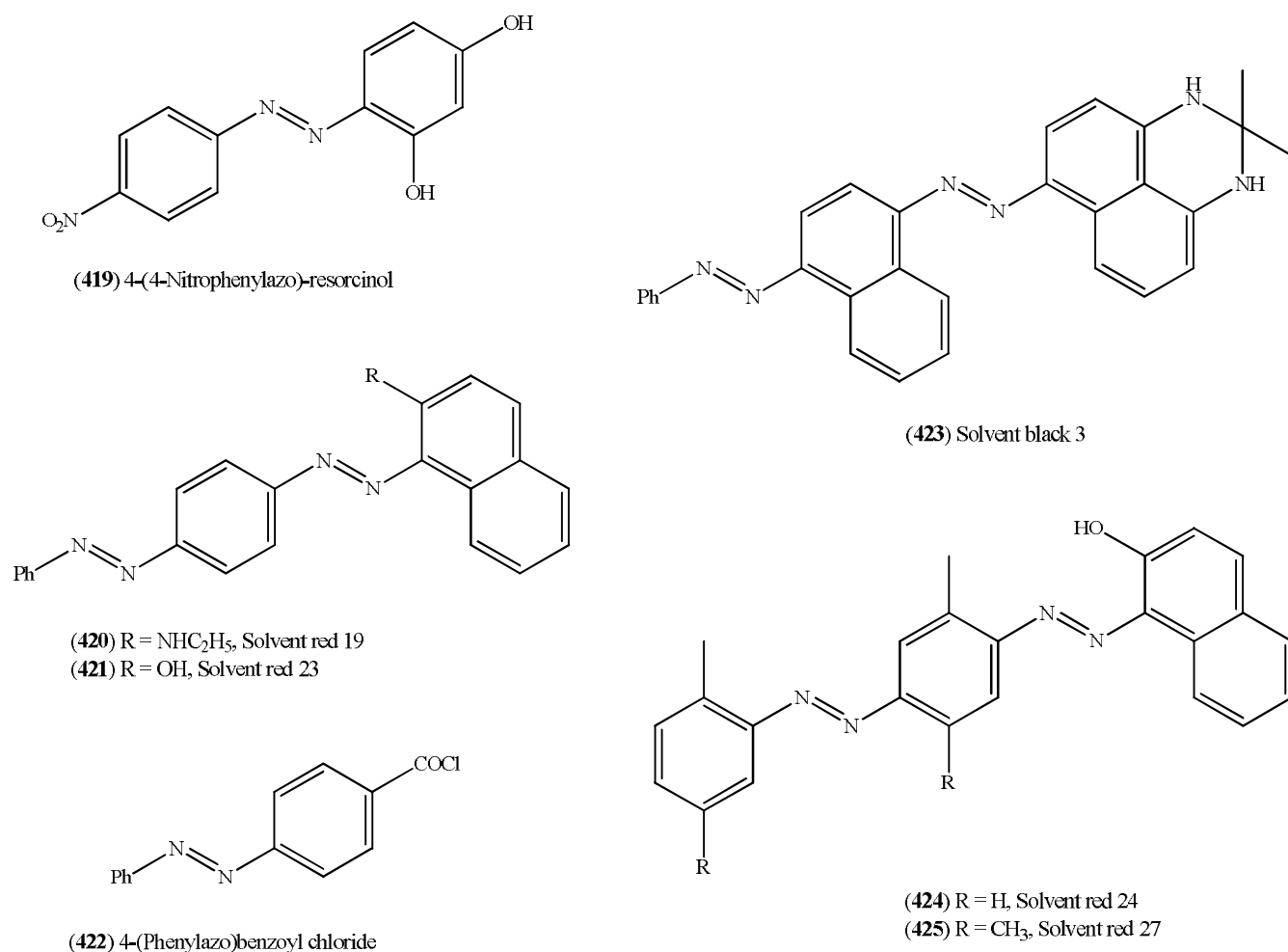
Figure 5.3.1.1 Dyes used as end-point indicators in ozonolysis reactions

To a solution of 1-allyl-2-methoxybenzene (**387**) in dehydrated MeOH† was therefore added *ca.* 0.1 ml of a 0.1% Solvent red 23 solution (just enough to impart a red colour to the reaction mixture) and the mixture exposed to ozone until discolouration of the indicator was completed (20 min.). Subsequent reductive work-up with DMS did not show any indication towards desired product formation (TLC) and a mixture of unidentifiable products were again obtained.

Since Schwartz *et al.*[23,35] reported a so-called 'reductive ozonolysis' *via* fragmentation process entailing reagents such as DMSO, Et$_3$N, and amine oxides like DABCO-*N*-oxide and *N*-methylmorpholine-*N*-oxide (NMMO), this option was subsequently investigated as

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† MeOH passed though small column of Al$_2$O$_3$ (10% v/v)

methodology for the reductive work-up. In this process an unstable peroxyacetal (**426**) is formed by nucleophilic attack of the amine-*N*-oxide on the zwitterion (**416**). The peroxyacetal (**426**) then undergoes decomposition to generate the aldehyde (**418**) and the liberated amine (**321**) which can be re-oxidized by O₃ to regenerate the amine oxide (**318**) (Scheme 5.3.1.2). Although these workers experimented with a series of reagents, NMMO was found to be the best reagent furnishing almost exclusive formation of the aldehyde in high yield (88%), so this compound was evaluated as 'reducing agent' in the following reactions. Since the liberated NMM (**321**) may be re-oxidized by the ozone, this process provides the added advantage of being catalytic in NMMO.
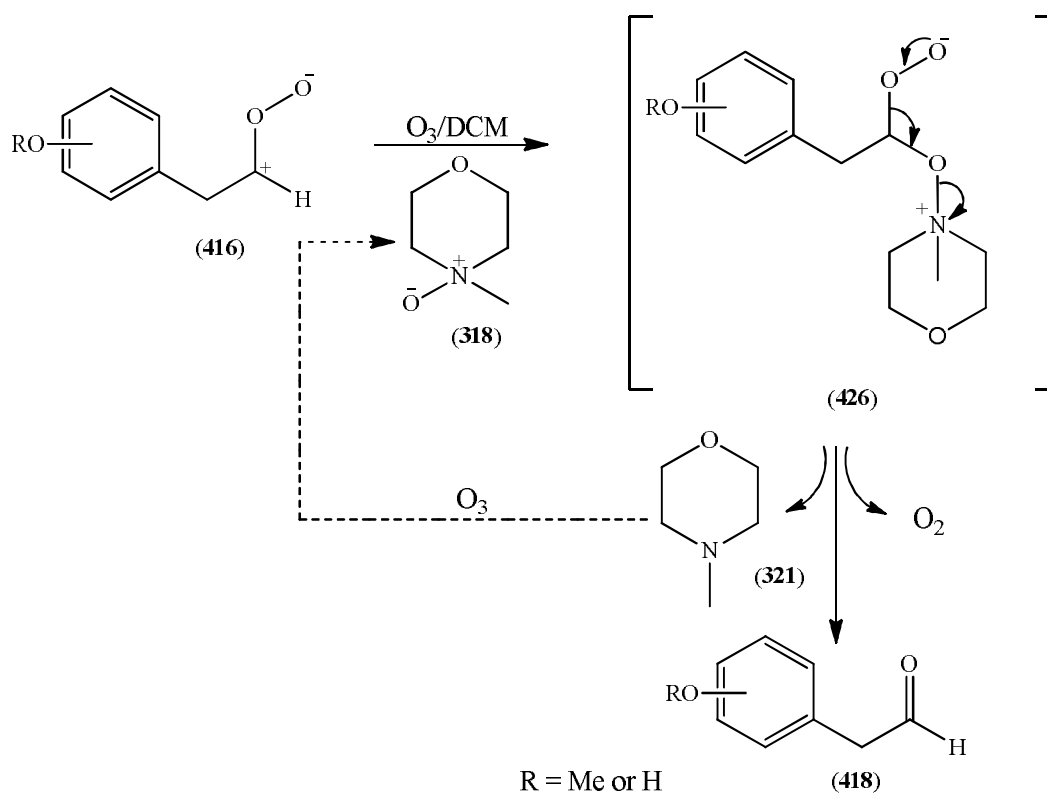
Scheme 5.3.1.2 Ozonolysis with 'reductive work-up' through application of NMMO

The series of substituted allylbenzenes (**387**), (**388**) and (**390**) was therefore subjected to ozonolysis in DCM with the addition of NMMO (3.0 eq.) at 0 °C for (15–30 min.) (*cf*. Method D). With the exception of the reaction of 1-allyl-4-methoxybenzene (**388**), which did not give the desired product but rather 4-methoxybenzaldehyde (**428**), all other substrates again afforded only mixtures of unidentifiable products. Although the desired product in the

case of (**388**) was not formed, the result obtained was encouraging as it indicated that the conditions employed were in fact suitable for ozonolysis of aromatic substrates in the presence of NMMO since the formation of the methoxybenzaldehyde (**428**) could be attributed to a migration of the allylic double bond to the 1'-position of the propene moiety sometime before ozonolysis (Scheme 5.3.1.3). Further impetus towards the successful application of ozonolysis in the formation of substituted phenylacetaldehydes from the corresponding allylbenzenes came from a paper by Branan, Butcher, and Olsen,[27] where it was reported that 4-hydroxy-3-methoxyphenylacetaldehyde (**429**) could in fact be obtained in high yield by ozonolysis of eugenol (**407**) (Scheme 5.3.1.4).
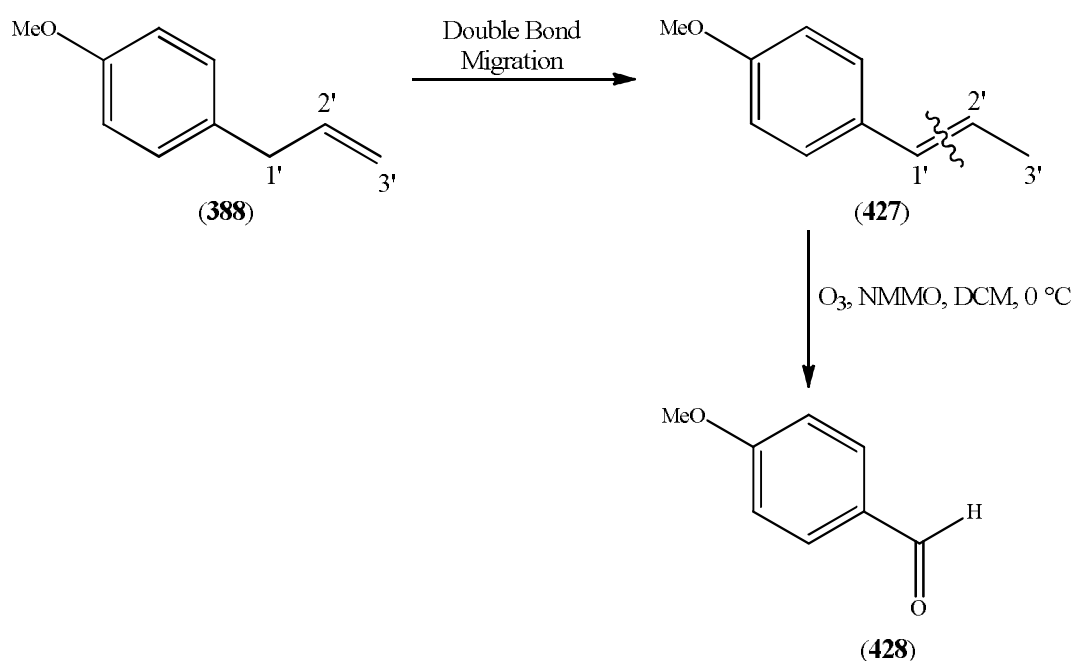
Scheme 5.3.1.3 Allylic double bond migration
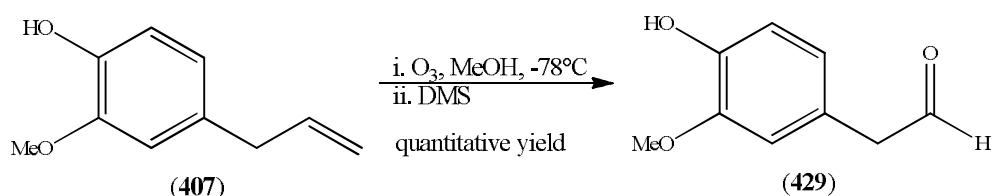
Scheme 5.3.1.4 Phenylacetaldehyde formation by Branan and co-workers[27]

With these positive indications in mind, it was decided that the only cause for the failure of the previous attempts could be destruction of the aromatic rings of the substrates due to too

long exposure of the substrates to ozone. Reactions were therefore repeated, but with the O_3 bubbling time reduced to only 10 min. (*cf*. Method E). When no success was still obtained, the reaction time was reduced even further to between 6 to 8 minutes, which led to the desired products, 2-methoxyphenylacetaldehyde (**430**), 4-methoxyphenylacetaldehyde (**431**) and 3,4-dimethoxyphenylacetaldehyde (**432**), being obtained in 24–88 % yields (Scheme 5.3.1.5).
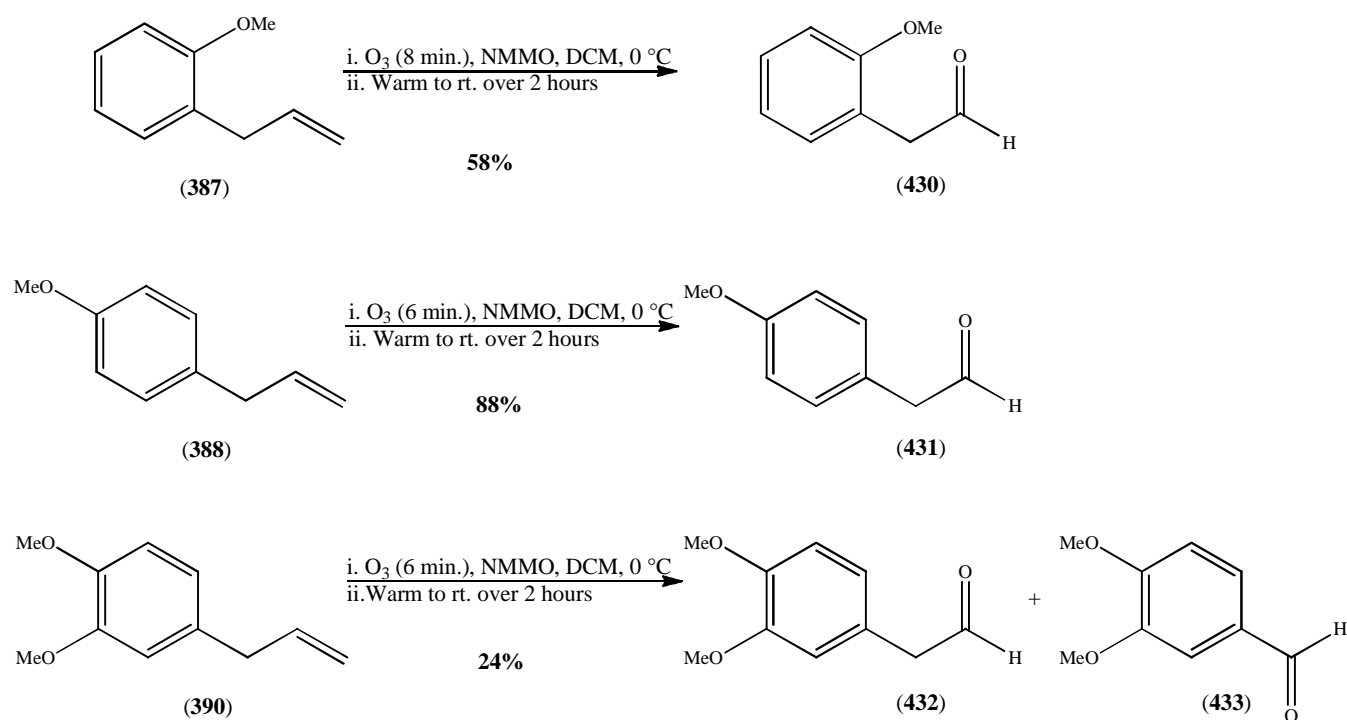
Scheme 5.3.1.5 Preparation of substituted phenylacetaldehydes

The structures of the phenylacetaldehydes (**430**), (**431**) and (**432**) were confirmed by the characteristic aldehyde signal at δ 9.68, 9.89 and 9.72 respectively, together with a CH_2-resonance at δ 3.65, 3.79 and 3.63 respectively in the ^1H NMR spectra (plates 16a, 17a and 18a) of the products. These resonances were accompanied by the expected signals [δ 7.32–7.29 (1H, m, H-4'), 7.16–7.15 (1H, m, H-6'), 6.97–6.94 (1H, m, H-5'), 6.92–6.91 (1H, m, H-3'), for (**430**), δ 7.85 (2H, d, *J* = 8.83 Hz, H-2' and H-6'), 7.01 (2H, d, *J* = 8.83 Hz, H-3' and H-5') for (**431**) and δ 6.86 (2H, d, *J* = 8.11 Hz, H-5'a), 6.77 (2H, dd, *J* = 8.11, 2.04 Hz, H-6'a), 6.70 (2H, d, *J* = 2.04 Hz, H-2'a) for (**432**)] in the aromatic region of the spectra. Final confirmation for the structures of the products came from the ^{13}C NMR spectra (plates 16b,

83

17b and 18b) where apart from the expected aromatic carbon resonances, carbonyl (δ 200.43, 191.26 and 199.93 respectively) and methylene carbon signals [δ 50.30, 55.26 and δ 45.75, respectively) were clearly visible in each of the spectra, as well as GC-MS (EI), which revealed the presence of the expected molecular ions [m/z 150 (M^+, 36.30%), 150.10 (M^+, 15.77%), and 180.05 (M^+, 23.99%) respectively].

While the substituted phenylacetaldehydes (**430**), (**431**) and (**432**) were successfully obtained *via* ozonolysis, the ozonation of 1-allyl-4-hydroxy-3-methoxybenzene (**407**), 1-allyl-3,4,5-trimethoxybenzene (**391**) and 1-allyl-2,4,6-trimethoxybenzene (**392**) furnished complete fragmentation products. Since literature indicated that the aromatic carbons in the *ortho-*, *meta-* or *para*-position to an electron donating group, are nucleophilic and therefore susceptible to attack by O_3,[17,19,36] it could be concluded that single oxygenation of the aromatic ring of the allylbenzene substrate does not lead to O_3 addition directly onto the aromatic ring, provided that the reaction is executed with a short O_3 addition time-span (6–8 min.) and careful monitoring.

To confirm whether the presence of two or more electron donating groups on the aromatic ring would in fact cause O_3 addition to the aromatic double bonds and thus lead to loss of aromaticity, it was decided to embark on an NMR study of the reaction intermediates of the substrates (**391**) and (**392**) that gave no identifiable products during the ozonolysis part of the reaction. In order to get a base case and identify as many of the intermediates indicated in the Criegee mechanism as possible, it was further decided to first identify the intermediate products through an NMR study for one of the substrates that gave the desired product during ozonolysis, 1-allyl-2-methoxybenzene (**387**).

A solution of 1-allyl-2-methoxybenzene (**387**) in DCM was therefore exposed to ozone at -78 ºC for 7 minutes and a aliquot (0.4 ml) of the reaction mixture diluted with an equal volume of deuterated DCM and analyzed by ^{1}H and ^{13}C NMR at increasing temperatures (-50, -20, 0 and 20 ºC) to see if the 1,2,3-trioxolane (**434**) or 1,2,4-trioxolane (**435**) or other intermediates could be identified (Scheme 5.3.1.6).
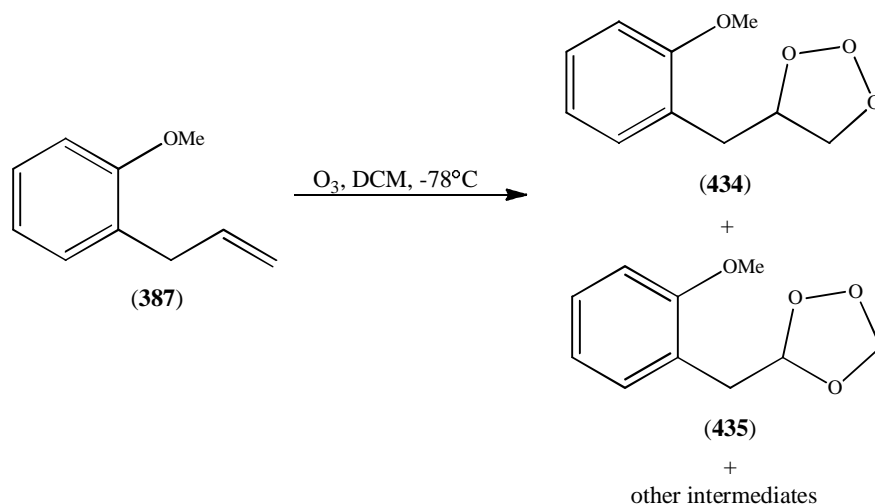
Scheme 5.3.1.6 Possible ozonolysis intermediates

Although complete disappearance of the starting material was evident from the spectra, unambiguous structure elucidation of the intermediate product(s) were not possible due to the complex spin system in the aromatic region and large DCM resonance present in the heterocyclic area of the spectrum. When the solvent suppression technique was applied, no resonances were visible in the heterocyclic region of the spectrum (Fig 5.3.1.2) either.
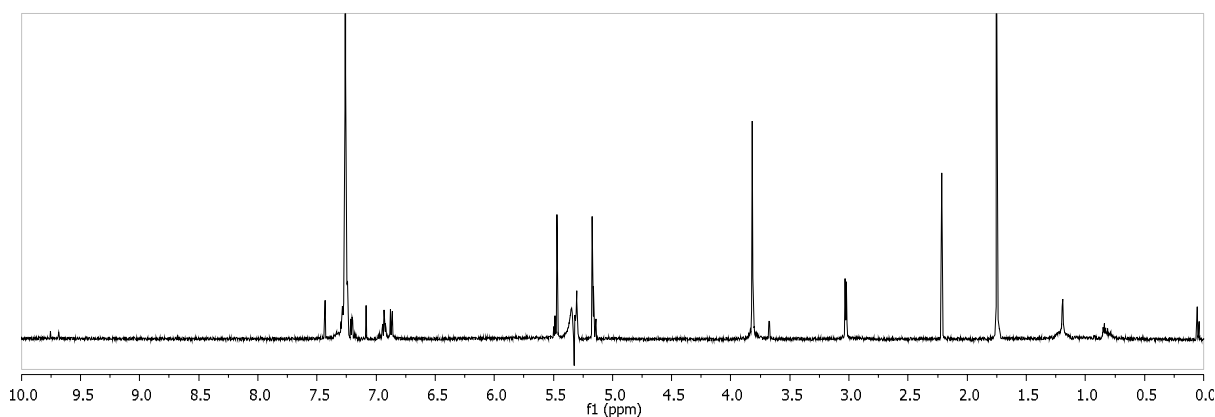
Figure 5.3.1.2 ^{1}H NMR after ozonolysis of 1-allyl-2-methoxybenzene with DCM solvent suppression at -50°C

In order to simplify the aromatic region of the spectrum to be in a position to obtain accurate integrals from the aromatic protons as well as having no interfering solvent signal in the important heterocyclic area of the spectrum, the substrate was changed to the *p*-substituted 1-allyl-4-methoxybenzene (**388**) and the possibility of doing the ozonolysis and subsequent

NMR analysis in deuterated chloroform[37] (instead of DCM) was investigated. Since increasing the temperature by *ca.* 20 ℃ intervals did not result in the appearance or disappearance of any signal in the NMR spectrum of the previous substrate (**387**) it was furthermore decided to only obtain NMR spectra at -50 ℃ and 20 ℃. The reaction was therefore repeated and sampled for NMR analysis as before, but with (**388**) as substrate in deuterated chloroform at -78 $^{\circ}$C. The ^{1}H NMR spectrum (Fig 5.3.1.3) obtained at -50 $^{\circ}$C in CDCl$_3$ revealed an intact aromatic ring with AA'BB' spin system at δ 7.19 (d, J = 8.60 Hz, H-2'a and H-6'a) and δ 6.87 (d, J = 8.60 Hz, H-3'a and H-5'a). Disappearance of all allyl resonances (*ca.* δ 5.92, 5.05, 5.04 and 3.31 ppm) present in the spectrum of the starting material confirmed complete reaction of the starting material, while the integrals for all the non-aromatic resonances (apart from the methoxy group) indicated the presence of 5 protons in the spectrum of the product, *i.e.* two one-proton singlets as well as three one proton doublet of doublets at δ 5.21 (s), 5.06 (s), 5.30 (dd, J = 5.1, 5.1 Hz), 3.01 (dd, J = 14.56, 5.06 Hz) and 2.97 (dd, J = 14.56, 5.06 Hz).
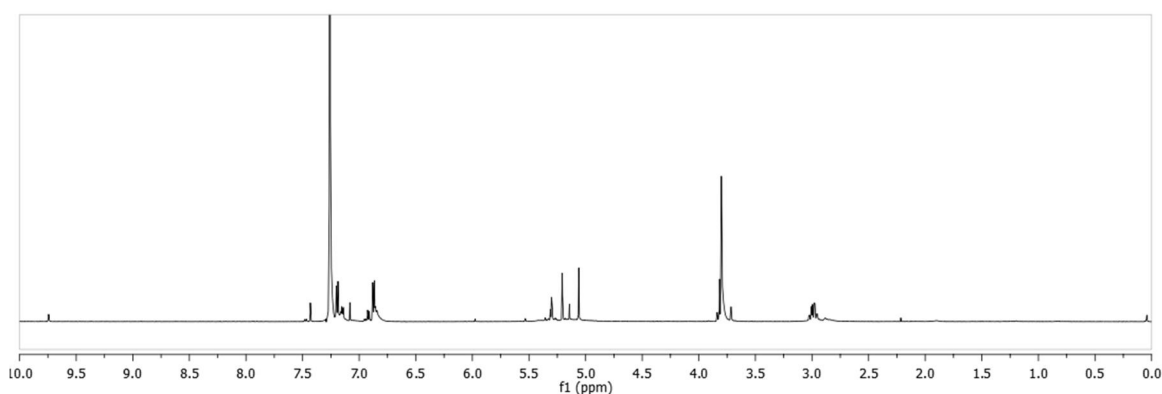
Figure 5.3.1.3 ^{1}H NMR after ozonolysis of 1-allyl-4-methoxybenzene done in CHCl$_3$ at -50ºC
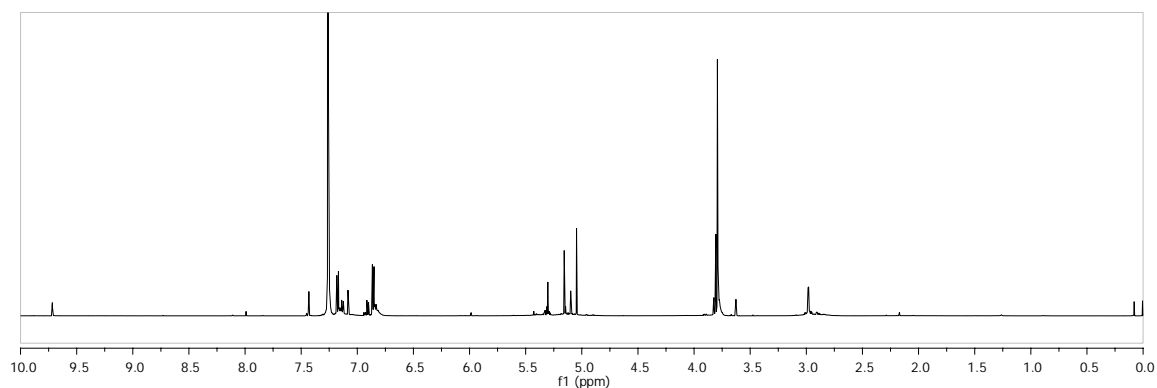
Figure 5.3.1.4 ^{1}H NMR after ozonolysis of 1-allyl-4-methoxybenzene in CHCl$_3$ at rt.

When the spectrum was acquired at room temperature (Fig. 5.3.1.4), only minor changes in chemical shift values and the appearances of the resonances were observed, compared to the intermediate obtained at -50 °C, so it could be concluded that the initially formed intermediate product was relatively stable and did not undergo secondary transformations to a more stable analogue.

Since the chemical shift values of two pairs of doublets of doublets (δ 3.01 and 2.97) were typical of those displayed by benzyl groups and the COSY spectrum (plate 26f) indicated those protons to be coupled to the doublet of doublets at δ 5.30, a partial structure (**436**) could be assigned to the intermediate product from the ozonolysis reaction. The fact that the two pairs of doublets of doublets at δ 3.01 and 2.97 ppm were indeed of a benzylic nature were confirmed by a correlation (observed by HMBC) of both these protons with carbon atoms in the aromatic region [δ 130.85 (C-2'a and C-6'a) and 126.10 (C-1'a)] of the ^{13}C NMR spectrum (plate 26b). Since the ^{1}H NMR spectrum (plate 26a) of the intermediate product contained another two resonances integrating for one proton each, the zwitterion analogue (**440**) could be ruled out as structure of the intermediate product, similarly the 1,2,3-trioxolane (**438**) should display vicinal coupling between the adjacent hydrogen atoms of the oxygen containing ring system. The spectrum of the 1,2,4-trioxolane (**437**), on the other hand, was expected to either display a two-proton singlet (if the residual protons were to be equivalent) or two geminal coupled doublets from the residual two protons. While neither of these options were displayed in the spectrum, a literature investigation revealed the methylene group of 1,2,4-trioxolane to show two singlet resonances in the δ 5.03–5.30 ppm area of the ^{1}H NMR spectrum,[38] so the intermediate product from the ozonolysis reaction could be identified as the 1,2,4-trioxolane and structure (**437**) assigned to it.

(**436**)
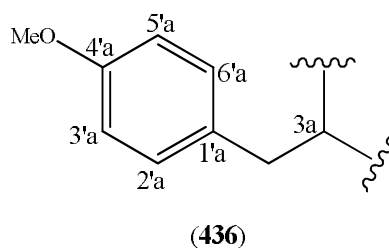
Possible ozonolysis intermediate

Although it could be expected that the methylene protons in the 1,2,4-trioxolane ring should display geminal coupling and thus appear as two doublets, Murray and Williams[39] reported

the coupling constant for those protons to be virtually 0 Hz resulting in the appearance of those resonances as two separate singlets in the ^{1}H NMR spectra of these compounds. Structure (**437**) could therefore be assigned unambiguously to the intermediate product from the reaction.

(**437**)
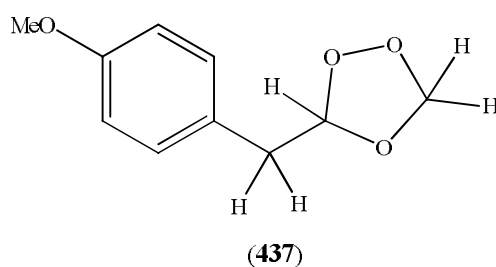
1,2,4-Trioxolane intermediate

The trioxolane (**437**) was accompanied in the reaction mixture by a small quantity of the expected phenylacetaldehyde (**431**) as was evident from the ^{1}H NMR spectra (Figure 5.3.1.3 and 5.3.1.4, plates 26a and 27a) where the presence of the aldehyde triplet resonance at δ 9.74 as well as the corresponding methylene doublet at δ 3.72 ppm (J = 2.17 Hz), were clearly visible. Since no reducing agent was present during the reaction, formation of the aldehyde can only be explained by 'disfavoured' fragmentation of the initially formed 1,2,3-trioxolane (**438**) as indicated in scheme 5.3.1.7. It can therefore be concluded that even though the fragmentation of the trioxolane to zwitterion and carbonyl compound is governed by the methoxy group stabilization of the transition state, the opposite and thus less-favoured fragmentation mechanism also prevail during the reaction, even at -78 ^{o}C.
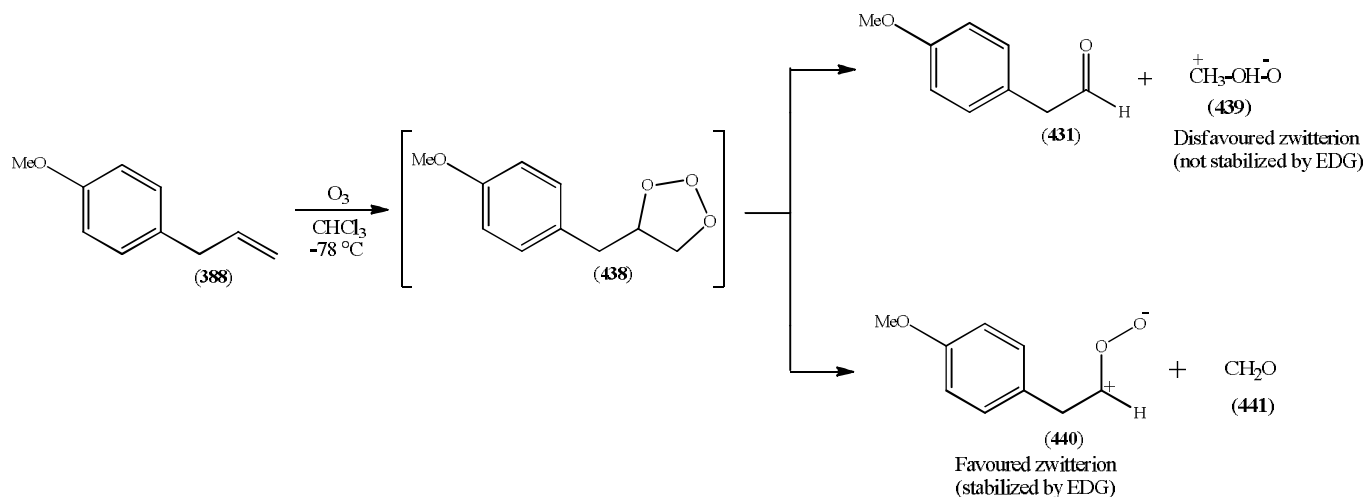
Scheme 5.3.1.7 Routes of zwitterion formation

The observations discussed above provide additional credence to the mechanism proposed by Criegee where it was indicated that the 1,2,3-trioxolane (**438**) undergoes fragmentation to a zwitterion and aldehyde/ketone through heterolytic cleavage of the C-C and O-O bonds. These two fragments are subsequently stabilized by recombination to form the 1,2,4-trioxolane, the destiny of which is then governed by the work-up procedure.[40]

The next mechanistic study centered around the effect of MeOH during the ozonolysis reaction and was aimed at determining whether MeOH indeed acts as a nucleophile for stabilizing the zwitterion (**440**) by transforming it into the peroxide (**442**), a requirement for effective reductive work-up with DMS as well as oxidative work-up (*vide infra*) (Scheme 5.3.1.8).
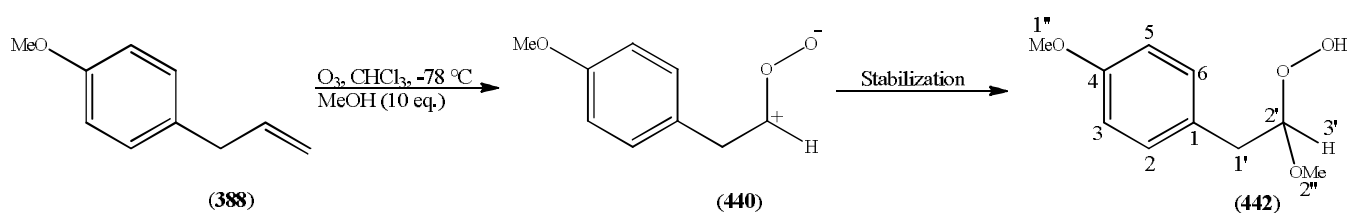
Scheme 5.3.1.8 Zwitterion stabilization with MeOH

1-Allyl-4-methoxybenzene (**388**) was therefore subjected to treatment with ozone in CHCl$_3$ containing 10.0 eq. of MeOH (at -78 $^\circ$C) as executing the reaction in pure methanol could lead to the crucial CH$_2$ resonances of the trioxolane moiety being 'buried' under the solvent

(methanol) resonance (δ 3.49). The ^{1}H NMR spectrum obtained from the reaction mixture, however, still displayed the two singlets (δ 5.21 and 5.06) indicative of 1,2,4-trioxolane formation, while no 'additional' methoxy resonance, apart from the aromatic methoxy and MeOH solvent signals, could be detected.

Finally, attention was turned towards the substrates with higher oxygenation to determine whether failure of product formation could be linked to the work-up procedure or the ozonolysis reaction itself. For this purpose 1-allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) in CHCl$_3$ solution was subjected to ozonolysis at -78 ^{o}C for 7 minutes and the reaction analyzed by proton NMR. To no surprise the NMR spectrum displayed a plethora of peaks over the 2–5 ppm range with no indication of the presence of any aromatic resonances. It could therefore be confirmed that with the current highly oxygenated substrates reaction with ozone occur at the aromatic carbon atoms as has been reported by Goi and co-workers (Scheme 5.3.1.9),[17] Andreev *et al.* (Scheme 5.3.1.10),[18] and Mokrini[19] whom also reported the ozonation of phenol to lead to muconic acid (**446**) and subsequent double bond ozonolysis products.
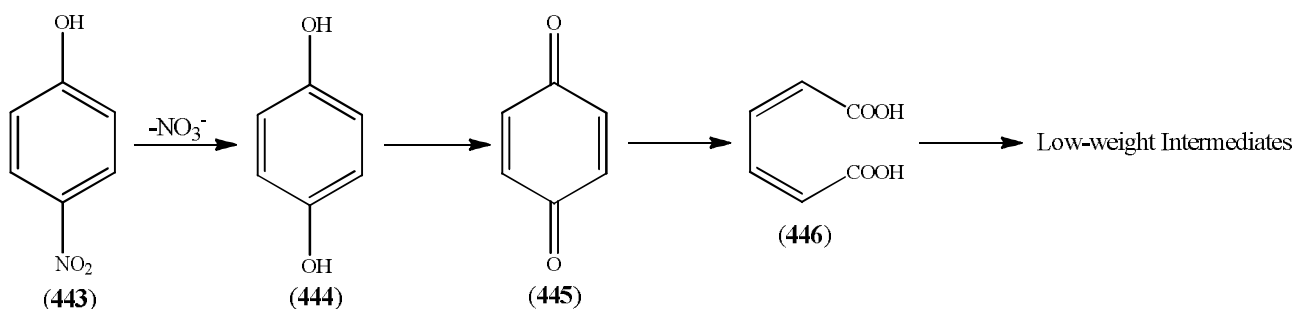
Scheme 5.3.1.9 Degradation of 4-nitrophenol by ozonation[17]
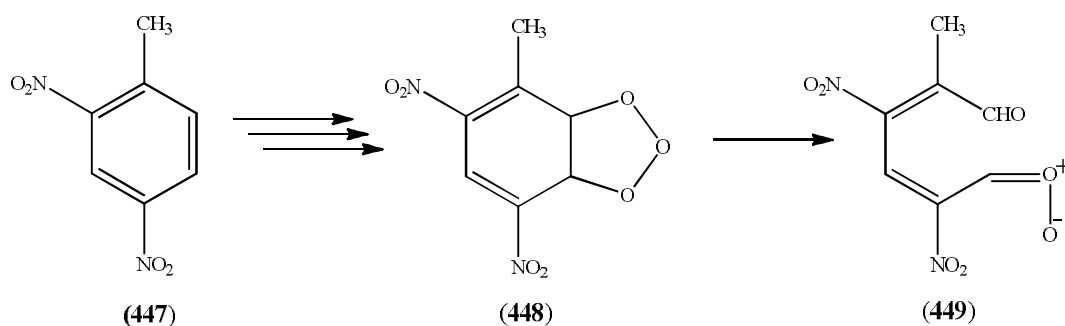
Scheme 5.3.1.10 Ring-opening proposed by the Andreev group[18]

Since the phenylacetaldehyde (**430**) could be obtained during the reaction of 1-allyl-2-methoxybenzene (**387**) in the presence of NMMO (Scheme 5.3.1.5), but not during the reaction with DMS as reducing agent and Solvent Red 23 as indicator (*vide supra*), it must be concluded that the failure of the first reaction (with DMS) could probably be attributed to the allylbenzene being more reactive than the indicator. Oxidation of the aromatic substrate therefore happened before discolouration of the indicator as the reactivity of Solvent Red 23 is rather low on the list of relative reactivities when compared to the other dyes.[34]

As the over oxidation/fragmentation of the aromatic rings in the poly-oxygenated substrates could be attributed to the methoxy groups increasing the nucleophilicity of the carbon atoms to the point where reaction of the ozone was directed at the aromatic rings and not the alkene functionality, it was decided to convert the hydroxyl functions into electron-withdrawing entities. It was therefore envisaged that the influence of every electron-donating (methoxy) group attached to the aromatic ring should be countered by at least one electron-withdrawing group. This idea was tested on 1-allyl-2-hydroxy-4-methoxybenzene (**404**) where the hydroxyl group was protected by reacting it with triflic anhydride in DCM in the presence of DMAP (base) and the protected allylbenzene (**450**) obtained in quantitative yield (Scheme 5.3.1.11).
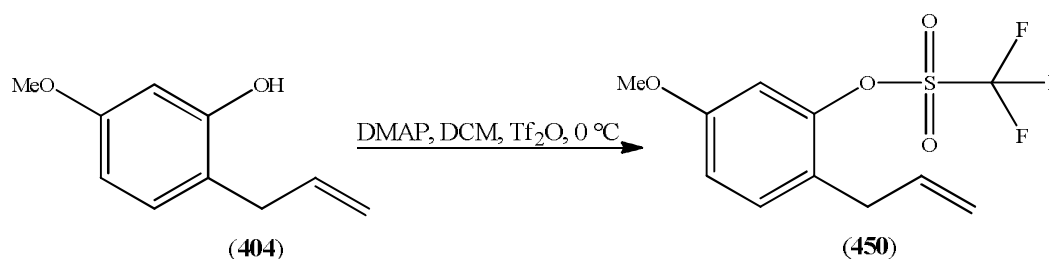
Scheme 5.3.1.11 Hydroxy group protection with an EWG

The structure of 1-allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**) was confirmed by ^{13}C NMR, where the CF_3-group of the triflate could be detected as a quartet at δ 118.59 ppm (plate 7b), and mass spectrometry (EI) indicating the presence if the molecular ion at *m/z* 296.00 (M[+], 64.10%) together with corresponding fragmentation peaks at *m/z* 135 (100.00), 105.05 (28.29), 103.05 (51.87) and 91.05 (28.32).

Reductive ozonolysis of the triflate protected allylbenzene (**450**) using the NMMO methodology described by Schwartz and co-workers,[23,35] however, led to double bond migration sometime before or during the ozonolysis reaction with the consequence of only 4-

methoxy-2-trifluoromethanesulfonyloxybenzaldehyde (**452**) being obtained as product (Scheme 5.3.1.12).
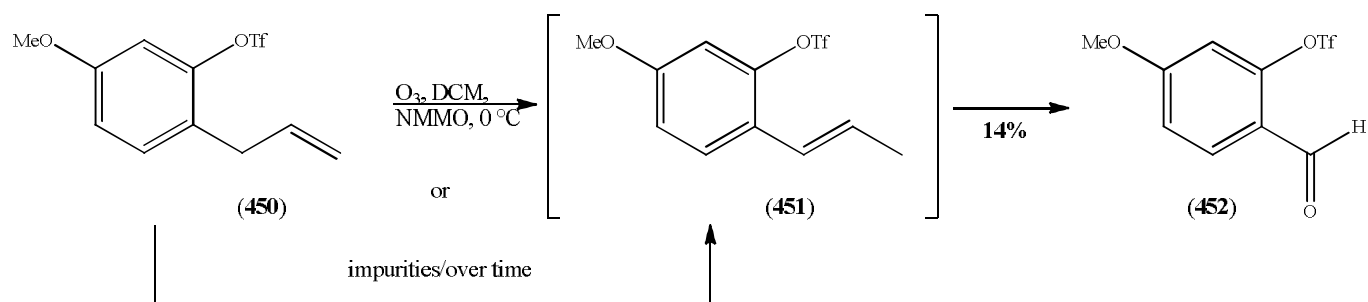
Scheme 5.3.1.12 Reductive ozonolysis of 1-allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene in the presence of NMMO

Since double bond migration could have happened after purification of the starting material or during the reaction (probably due to the basicity of the NMMO) it was decided to use freshly prepared reactant and revert back to DMS as reducing agent (in MeOH). The reaction was therefore repeated leading to the desired product, 2'-trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**), being obtained in 63% yield (Scheme 5.3.1.13).
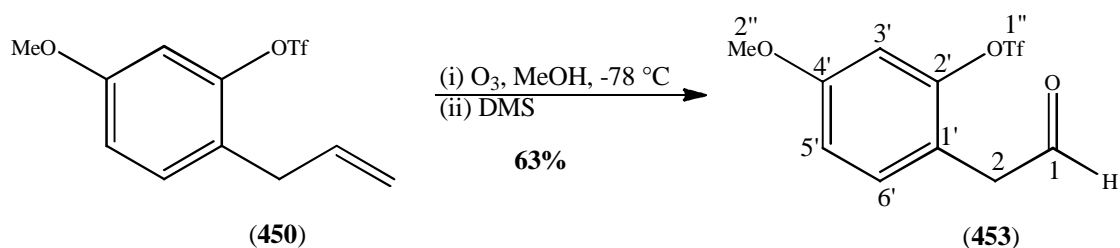
Scheme 5.3.1.13 Reductive ozonolysis of 1-allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene with DMS as reducing agent

The structure of 2'-trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**) was confirmed by ^{1}H NMR (plate 23a) where the distinctive aldehyde triplet signal at δ 9.73 (J = 1.5 Hz) was accompanied by an ABX resonance system at δ 7.21 (d, J = 8.55 Hz, H-6'), 6.93 (dd, J = 8.55, 2.54 Hz, H-5'), 6.88 (d, J = 2.54 Hz, H-3') and a -CH$_2$- signal at δ 3.76 (m)

(Plate 23a). Further confirmation of the structure of (**453**) followed from the ^{13}C NMR spectrum (plate 23b) where the presence of the carbonyl carbon at δ 197.30 (-$\underline{C}$HO), as well as the expected CF_3-quartet (δ 118.42, $J = 316.42$ Hz) were clearly visible. Moreover, mass spectrometry (EI) indicated the presence of a molecular ion at m/z 298 (M$^+$, 2.47%) together with corresponding fragmentation peaks [m/z 269 (100.00%) and 136 (45.14)].

With the ozonolysis of 1-allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**) being successful, attention was subsequently turned towards the other envisaged higher oxygenated analogues. The hydroxyl groups in 1-allyl-4-hydroxy-3-methoxybenzene (**407**), 1-allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) and 1-allyl-2-hydroxy-4,6-dimethoxybenzene (**403**) were therefore protected as triflate esters (Scheme 5.3.1.14) and the products obtained in 82, 71 and 45% yields, respectively. Addition of a triflate group to the substrates was confirmed by ^{13}C NMR where the CF_3-quartet appeared at δ 118.89 (q, $J = 320.51$ Hz), δ 118.05 (q, 320.57 Hz) and δ 118.68 (q, $J = 320.28$ Hz) in the respective spectra (plates 8b, 9b and 10b) of the products. One peak for each of these substrates was also observed at δ -74.70, -76.90 and -76.89 in the ^{19}F NMR spectra (plates 8f, 9f and 10f), while mass spectrometry (EI) further verified the structures to be those expected by displaying molecular ions at m/z 296.10 (32.46%), 326.99 (13.21%) and 326.05 (90.10%) respectively.
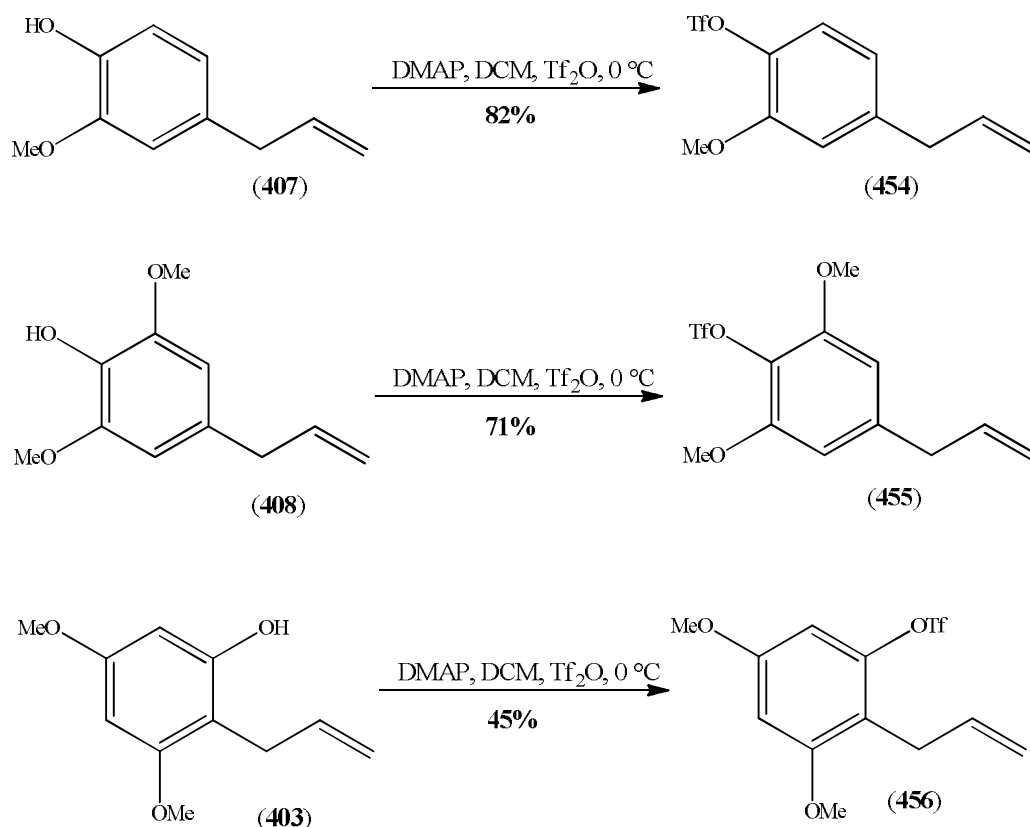
Scheme 5.3.1.14 Hydroxy group protections

Although it was found before that double bond migration could possibly be due to the basicity of the NMMO when utilized during the reductive work-up process, this method was continued with for the highly oxygenated substrates (**454**, **455**, and **456**), since it entailed a more environmentally benign process. For the phloroglucinol-type substrate (**456**), the reaction proved to be successful and the desired phenylacetaldehyde (**457**) was obtained in 71% yield (Scheme 5.3.1.15). The catechol (**454**) and pyrogallol (**455**) substrates, however, only gave the benzaldehydes (**459**) and (**461**) in 33% and 53% yields, respectively. Since the formation of the benzaldehydes are only explicable in terms of a double bond migration before ozonolysis it again points to NMMO being basic enough to induce base catalyzed isomerization of the double bond to the thermodynamically more favourable position in conjugation with the aromatic π-system.
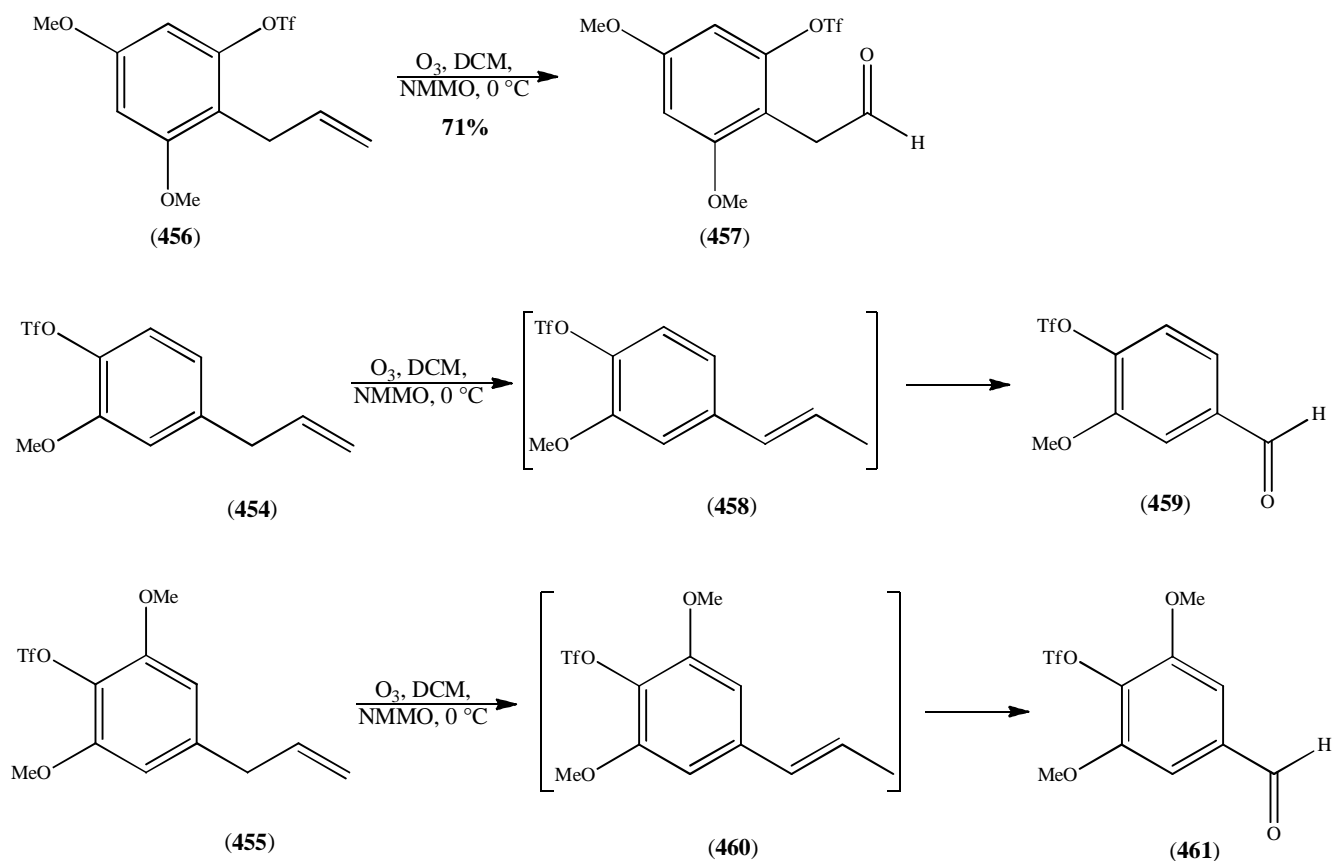
Scheme 5.3.1.15 Ozonolysis of highly oxygenated allylbenzenes in the presence of NMMO

The structure of the phenylacetaldehyde product (**457**) was confirmed by ^{1}H NMR (plate 22a) where the characteristic aldehyde triplet was clearly visible at δ 9.61 (t, J = 1.4 Hz) with the coupled -CH$_2$- protons at δ 3.67 (d, J = 1.4 Hz). ^{13}C NMR (plate 22b) as well as ^{19}F NMR (plate 22f) with resonances at $δ_C$ 118.61 (q, J = 320.19 Hz) and $δ_F$ -76.76 further confirmed that the triflate group stayed intact during the reaction. Moreover, high resolution mass spectrometry indicated the molecular ion Na adduct at *m/z* 351.0131.

The structures of the benzaldehyde products (**459**) and (**461**) obtained from the reactions of allylbenzenes (**454**) and (**455**), respectively, were confirmed by ^{1}H NMR (plates 20a and 21a) where the aldehyde resonances were clearly visible as singlets at δ 10.07 and δ 10.03 for (**459**) and (**461**), respectively, while the spectra also displayed the expected aromatic systems at δ 7.79 (d, J = 1.8 Hz), 7.71 (dd, J = 8.3, 1.8 Hz), and 7.67 (d, J = 8.3 Hz) for (**459**) and at δ 7.44 (s) for product (**461**). Final structural proof for both compounds came from mass spectrometry where molecular ions at *m/z* 284.00 (M$^+$, 60.46%) and 336.9966 (M$^+$ + Na) (HR-MS) were visible. Since strong evidence was now available that the NMMO used

during the reductive work-up process was in fact responsible for double bond migration before the substrate could react with the ozone, ozonolysis of the two triflate-protected substrates (**454**) and (**455**) were repeated with DMS as reducing agent and surprisingly the corresponding 1,2,4-trioxolanes (**462**) and (**463**) were obtained in 32% and 31% yields (Scheme 5.3.1.16). It was concluded that the intermediates (**462**) and (**463**) formed after ozone addition to the exocyclic double bonds are stable enough to not only survive temperatures well above -78 ºC (up to rt.) but also separation on silica. The reason for incomplete reduction happening with (**454**) and (**455**) and not with (**456**) and other less oxygenated substrates, however, cannot be fully explained at this stage and still needs to be investigated. Nonetheless, the wanted intermediates (**462**) and (**463**) essential for reduction to the desired phenylacetaldehydes were obtained successfully (Scheme 5.3.1.16).
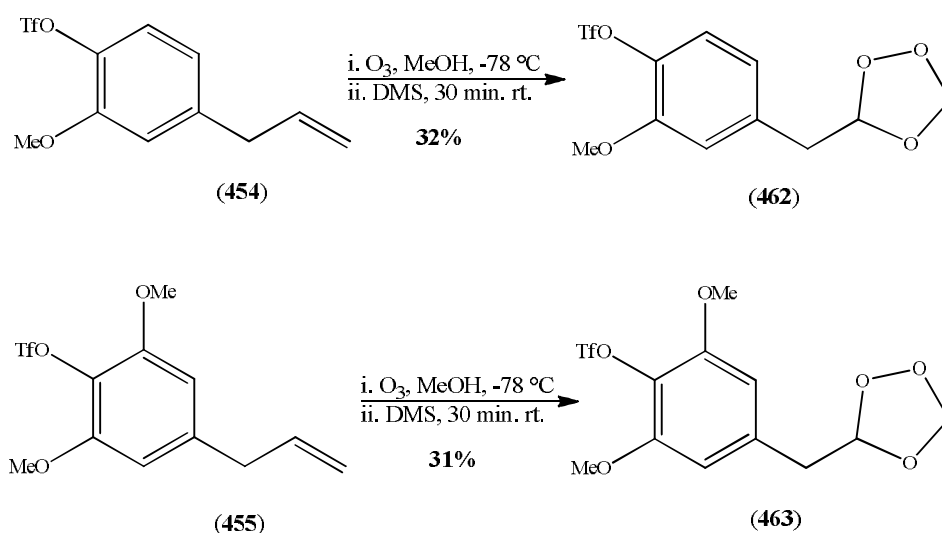
Scheme 5.3.1.16 Ozonolysis of allylbenzenes (454) and (455) with DMS as reductant

The structures of 1,2,4-trioxolanes (**462**) and (**463**) were confirmed by ^{1}H NMR (plates 24a and 25a) where the -CH- trioxolane resonances were clearly visible as triplets at δ 5.36 and δ 5.36 for (**462**) and (**463**), respectively, while the spectra also displayed the expected aromatic systems at δ 7.16 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 1.9 Hz), 6.87 (1H, dd, J = 8.4, 1.9 Hz) and at δ 6.53 (2H, s) and -CH$_2$- signals at δ 3.06 (1H, dd, J = 14.76, 4.83 Hz) and 3.03 (1H, dd, J = 14.76, 4.83 Hz); δ 3.01 (2H, m,) for (**462**) and (**463**), respectively. Two singlets for the endocyclic -CH$_2$- trioxolane moiety was observed at δ 5.16 (1H, s) and 5.07 (1H, s); δ 5.18 (1H, s) and 5.11 (1H, s) for (**462**) and (**463**), respectively. Final structural proof for both

compounds came from mass spectrometry where the molecular ion was indicated at *m/z* 346.43 (M^+, 100.00%) *via* MALDI-TOF and corresponding fragmentation peaks *via* MS (EI) at *m/z* 298.05 (M^+ - OCH_2, 38.80%), 165.10 (M^+ - OTf - OMe, 100.00), 137.10 (98.62) for (**462**) and a fragment of the molecular ion from MALDI-TOF at *m/z* 346.43 (M^+ - OMe, 100.00%) and corresponding fragmentation peaks from MS (EI) at *m/z* 328.05 (M^+ - OCH_2, 19.73%), 195.05 (M^+ - OTf - OMe, 100.00), 167.10 (84.41) for (**463**).

5.3.2   Ozonolysis with Oxidative Work-up

Ozonolysis of allylbenzenes followed by an oxidative work-up procedure provides the availability of a wide range of methyl phenyl acetates. Conversion of the ester group into a chiral auxiliary, which can easily be removed again, ultimately provides a route to the stereoselective synthesis of isoflavonoids (Scheme 5.3.2.1).

R = EDG or EWG

Enantioselective synthesis of isoflavonoids
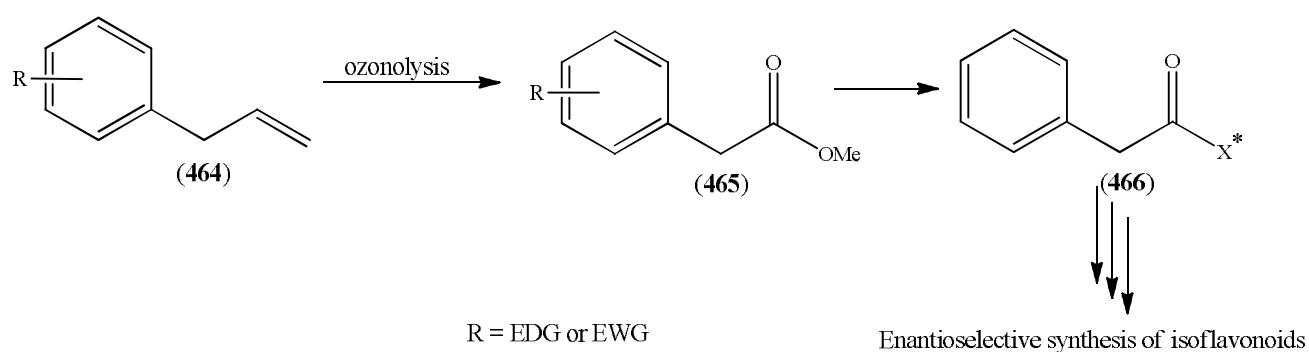
Scheme 5.3.2.1 Enantioselective synthesis of isoflavonoids

The initial approach to ozonolysis followed by oxidative workup would then entail treatment of the *in situ* formed 1,2,4-trioxolane (*cf.* par. 5.3.1) with H_2O_2 which would then afford the desired phenylacetic acid. Since H_2O_2 has been employed quite widely and successfully for the oxidative work-up procedure after ozonolysis to afford carboxylic acids, this was the reagent of choice as starting point.[25,41] Seeing that purification of acids can be difficult, the phenylacetic acid would then directly be subjected to Fischer-Speier esterification with methanol resulting in the methyl phenyl acetate (Scheme 5.3.2.2). Although it was determined in the previous paragraph that highly oxygenated substrates would give ring ozonolysis rather than double bond cleavage, it was thought that the point of reaction during ozonolysis might be dependent on the reaction conditions during treatment with ozone.

Reaction of 1-allyl-2-hydroxybenzene (**398**) with ozone in DCM followed by H_2O_2 treatment at -78 °C and subsequent addition of MeOH and PTSA (cat.), however, resulted in an inseparable mixture, so more recent and efficient methodology was looked into.
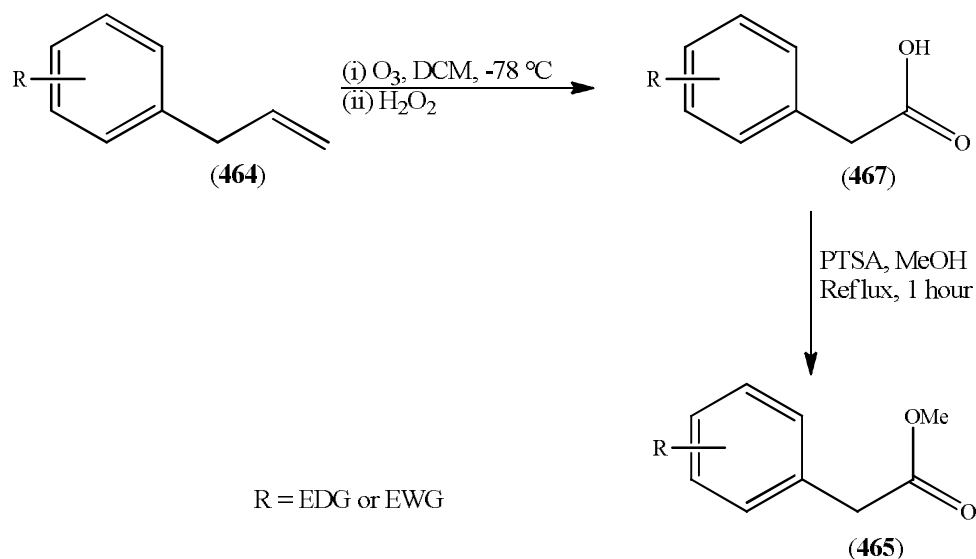
Scheme 5.3.2.2 Proposed ozonolysis followed by oxidative work-up with H_2O_2

Marshall and Garofalo[20] reported on a one-pot synthesis of methyl esters from olefins *via* treatment with ozone in a methanolic $NaOH$-CH_2Cl_2 solution at -78 °C. Their methodology was applied to various allylic- and homoallylic ethers consisting of terminal double bonds and several substrates with internal double bonds (Scheme 5.3.2.3), so this approach was investigated as a second option towards preparing the envisaged phenyl acetate esters.
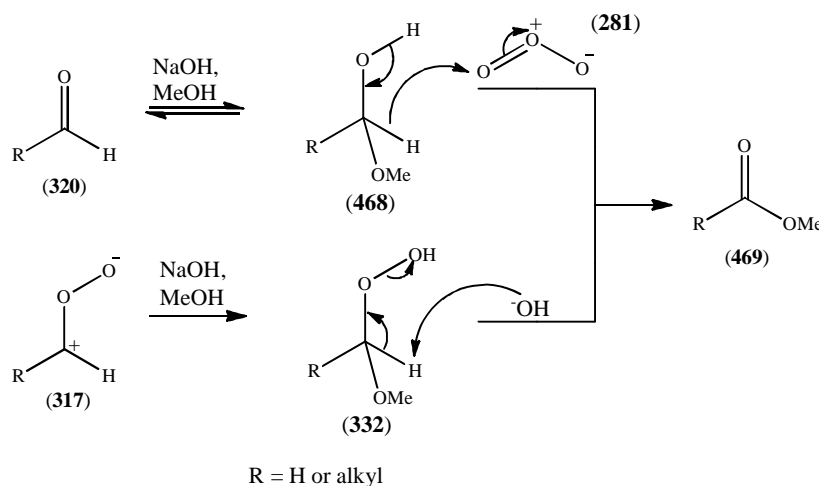
Scheme 5.3.2.3 Methyl ester formation by Marshall and Garofalo[20]

1-Allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) was therefore subjected to ozonolysis in DCM as solvent at -78 °C in the presence of a methanolic NaOH (2.5 M) mixture and a single product with R_f 0.53 (B:A:M; 6:3:1) obtained. ^{1}H NMR analysis (plate 28a) of this product, however, indicated complete absence of any resonances in the aromatic region of the spectrum (δ < 6.00), while a two proton singlet at δ 5.44 ppm was accompanied by a six proton singulet at δ 3.77 ppm as well as multiplets at δ 5.43–5.31, 5.06–5.02, 5.01–4.96 and 2.78–2.72 and a broadened singlet at δ 2.95. Since the resonances from the 2 and 6 protons moved up-field to the alkene region and the methoxy groups and allyl system were still present in the molecule, it was concluded that the aromatic ring was oxidized by the ozone and structure (**470**) proposed for the R_f 0.53 product (B:A:M 6:3:1, v/v). The structure of the dienone (**470**) was confirmed with ^{1}H, ^{13}C and 2D NMR spectra (plates 28a, b, d and e) as well as MALDI-TOF MS analysis where a molecular ion at *m/z* 210.05 (M[+], 100%) was observed. The identical compound was obtained through electrochemical oxidation in MeOH/H_2O/NaHCO$_3$ (Scheme 5.3.2.4) by Iguchi and co-workers.[42]

(**470**)
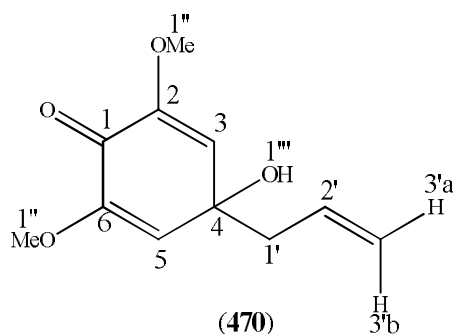
4-Allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone
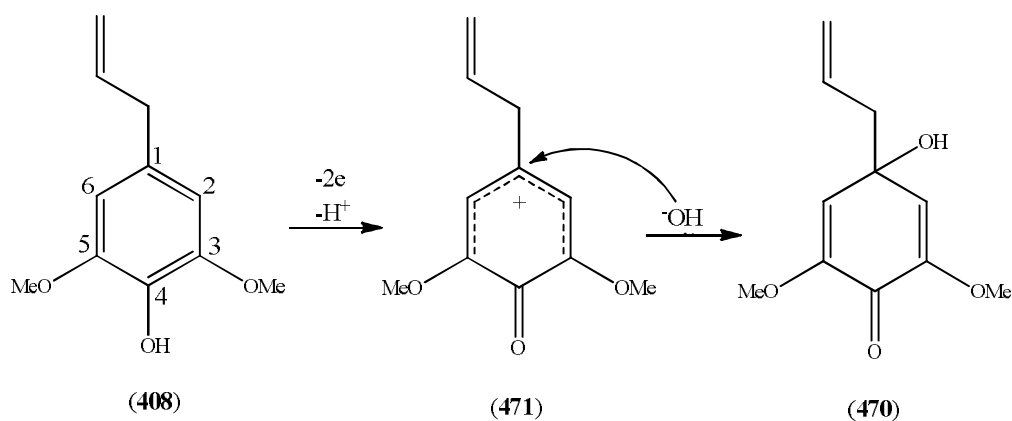
Scheme 5.3.2.4 Formation of 4-allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone[42]
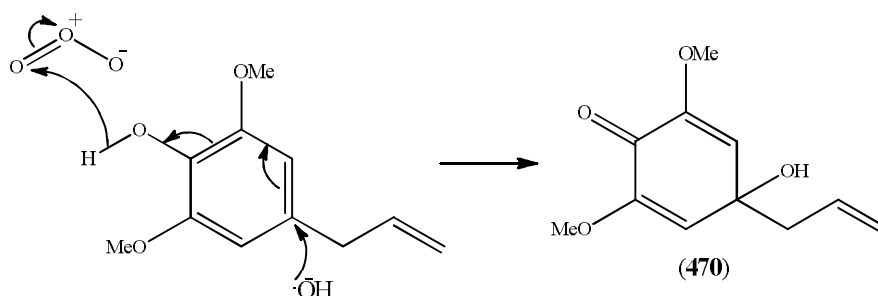
Scheme 5.3.2.5 Proposed mechanism by which (470) is formed during ozonolysis

Since the one-step ozonolysis-oxidative work-up processes proved to be unsuccessful, it was decided to investigate an *in situ* acylation-elimination method as was reported by Helms and Reibig.[22]

During this process, ozonolysis of the substrate is done at -78 °C in dehydrated MeOH[‡] until the reaction mixture turns blue due to excess dissolved O_3. The mixture is subsequently purged with oxygen to remove excess ozone, while it is allowed to warm up to rt. over 2 hours. Careful removal of the solvent under reduced pressure is then followed by an *in situ* acylation and base catalyzed elimination with Ac_2O and Et_3N in DCM over the next 21 hours at rt. Application of this procedure to (**387**), (**388**) and (**472**) led to the successful formation of the desired methyl esters (**480**), (**481**), and (**482**) in 91, 32, and 9% yields respectively (Scheme 5.3.2.6).

[‡] MeOH passed though small column of Al_2O_3 (10% v/v)
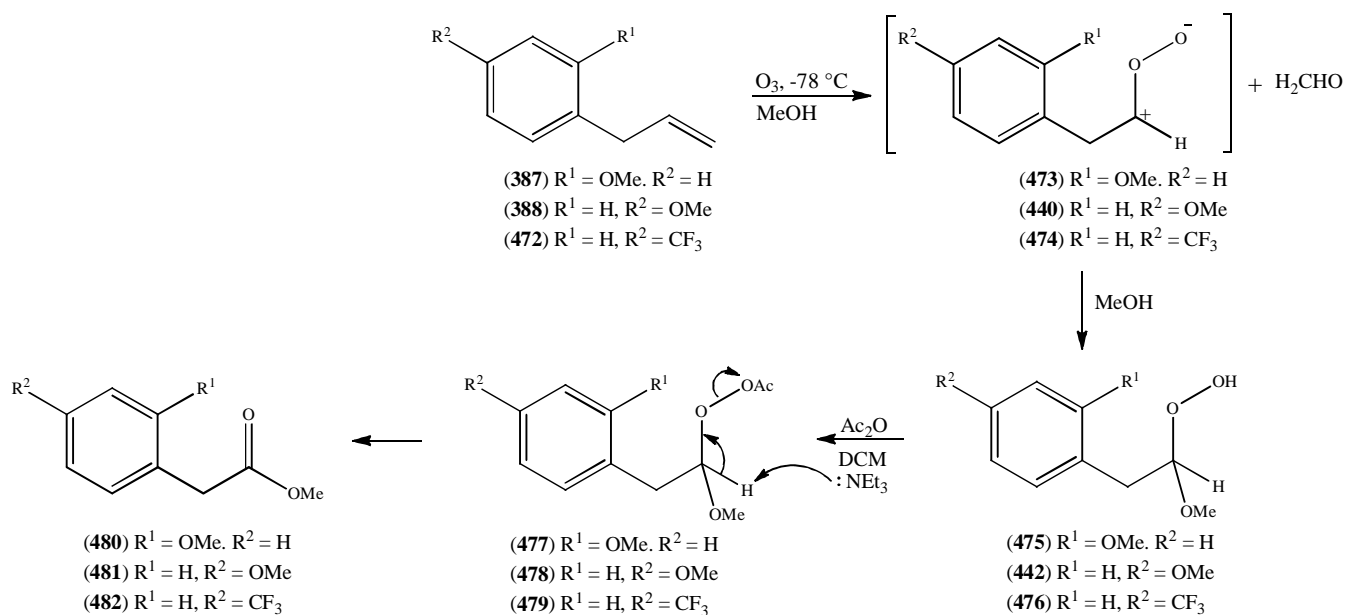
Scheme 5.3.2.6 Oxidative work-up mechanism

The structures of the methyl esters (**480**), (**481**) and (**482**) were elucidated by ^{1}H NMR (plates 29a, 30a and 31a) where the expected aromatic [δ 7.29–7.26 (m), 7.20–7.19 (m), 6.94–6.92 (m) and 6.89–6.88 (m); δ 7.20 (d, J = 8.76 Hz) and 6.86 (d, J = 8.76 Hz); δ 7.59 (d, J = 8.21 Hz) and 7.40 (d, J = 8.21 Hz)], methoxy (δ 3.82 and 3.79) and methylene resonances (δ 3.65, 3.57, and 3.69) were accompanied by the signal from an ester methoxy group at δ 3.70, 3.68, and 3.71, respectively. The structures were confirmed by ^{13}C NMR (plates 29b, 30b and 31b) and MS analysis showing the molecular ions at m/z 180.10 (M$^+$, 47%), m/z 180.05 (M$^+$, 22.99%) and m/z 217.10 (M$^+$, 38%).

Since the 1-allyl-4-methoxybenzene substrate (**388**) also gave better yields during the reductive work-up process (88% *vs.* no product) when compared to the allylbenzene having an electron-withdrawing group attached to the aromatic ring (**472**), it can be concluded that electron-donating groups will stabilize the positive charge on the zwitterion and thus lead to more efficient formation of either the 1,2,4-trioxolane (**437**) or methoxyperoxide (**442**).

When this methodology was applied to the highly oxygenated substrates, 1-allyl-3,4,5-trimethoxybenzene (**391**), 1-allyl-3,4-dimethoxybenzene (**390**) and 1-allyl-2,4,6-trimethoxybenzene (**392**), mixtures of unidentifiable products, similar to what was found during reductive work-up (*cf.* paragraph 5.3.1), were obtained.

Since NMR analysis of the reaction mixture during reductive work-up indicated ozonolysis of the aromatic rings of these compounds to be the cause of the reaction not giving the desired products, it was decided to also subject the triflate analogues (**454**), (**455**) and (**456**) of the highly oxygenated substrates to the ozonolysis reaction with oxidative work-up in order to obtain the ester products. Treatment of methanolic solutions of (**454**), (**455**) and (**456**) with ozone at -78 °C for 2–6 minutes followed by removal of the solvent under reduced pressure and addition of DCM as solvent and Ac$_2$O and Et$_3$N at 0 °C yielded the phenyl acetate esters (**483**), (**484**), and (**485**) in 9, 17 and 65% yields, respectively (Scheme 5.3.2.7). The structures of the methyl esters (**483**), (**484**), and (**485**) were confirmed by the expected aromatic resonances [δ 7.16 (d, J = 8.3 Hz), 6.98 (J = 2.0 Hz), 6.88 (dd, J = 8.3, 2.0 Hz), δ 6.55 (s) and δ 6.46–6.45 (m)] as well as a methylene singlet (δ 3.63, 3.59 and 3.65) and an ester methoxy group at δ 3.72, 3.72 and 3.69 in each of the ^{1}H NMR spectra (plates 32a, 33a and 34a) of the products. Final structural proof for the expected products (**483**), (**484**) and (**485**) came from the ^{13}C NMR spectra (plates 32b, 33b and 34b) as well as MS where molecular ions at m/z 328.15 (M$^+$, 30.21%), 358.05 (M$^+$, 14.64%) and 358.05 (M$^+$, 32.60%) were present, respectively.
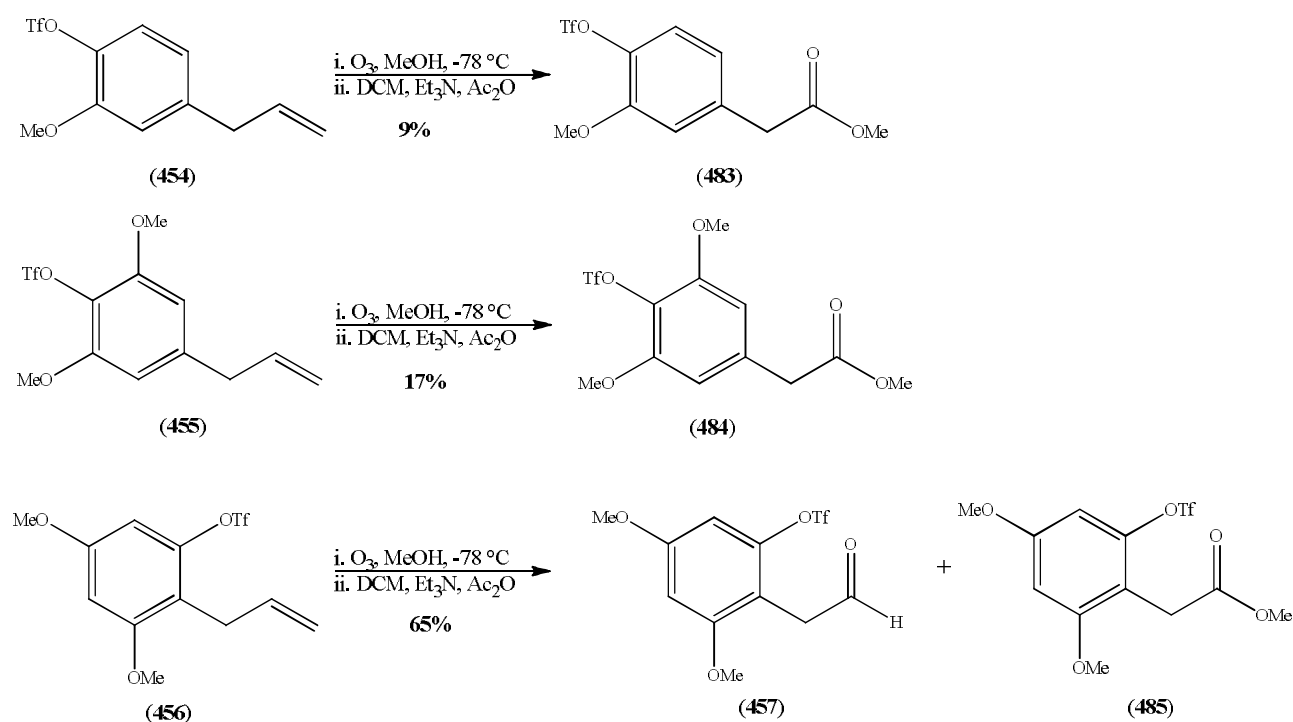
Scheme 5.3.2.7 Ozonolysis with oxidative work-up: i. O$_3$, MeOH, -78ºC, ii. DCM, Ac$_2$O, Et$_3$N, 0ºC, 30 min. followed by stirring at rt. for 21 hours

Together with the desired phenyl acetate ester (**485**), the product mixture of the phloroglucinol triflate analogue (**456**) also contained some phenylacetaldehyde (**457**). The formation of the aldehyde product (**457**) is probably explicable in terms of methanol attack now being directed towards C-5 of the 1,2,3-trioxolane (**486**) instead of C-4 as would be required for formation of the ester products or formation of the 'other' zwittterion [(**487**) *vs.* (**439**)] (Scheme 5.3.2.8). This observation would be in agreement with the Criegee mechanism where it was postulated that the mechanism is mostly governed by the inductive effect of the substituents surrounding the trioxolane species with the zwitterion being formed at the carbon carrying electron donating groups (*cf.* Paragraph 5.3). The phloroglucinol ring of substrate (**456**) could therefore be deemed electron rich enough, when compared to the catechol (**454**) and pyrogallol (**455**) substrates, to direct zwitterion formation towards C-5 and not C-4 as would be required for formation of the phenylacetic acid ester products.
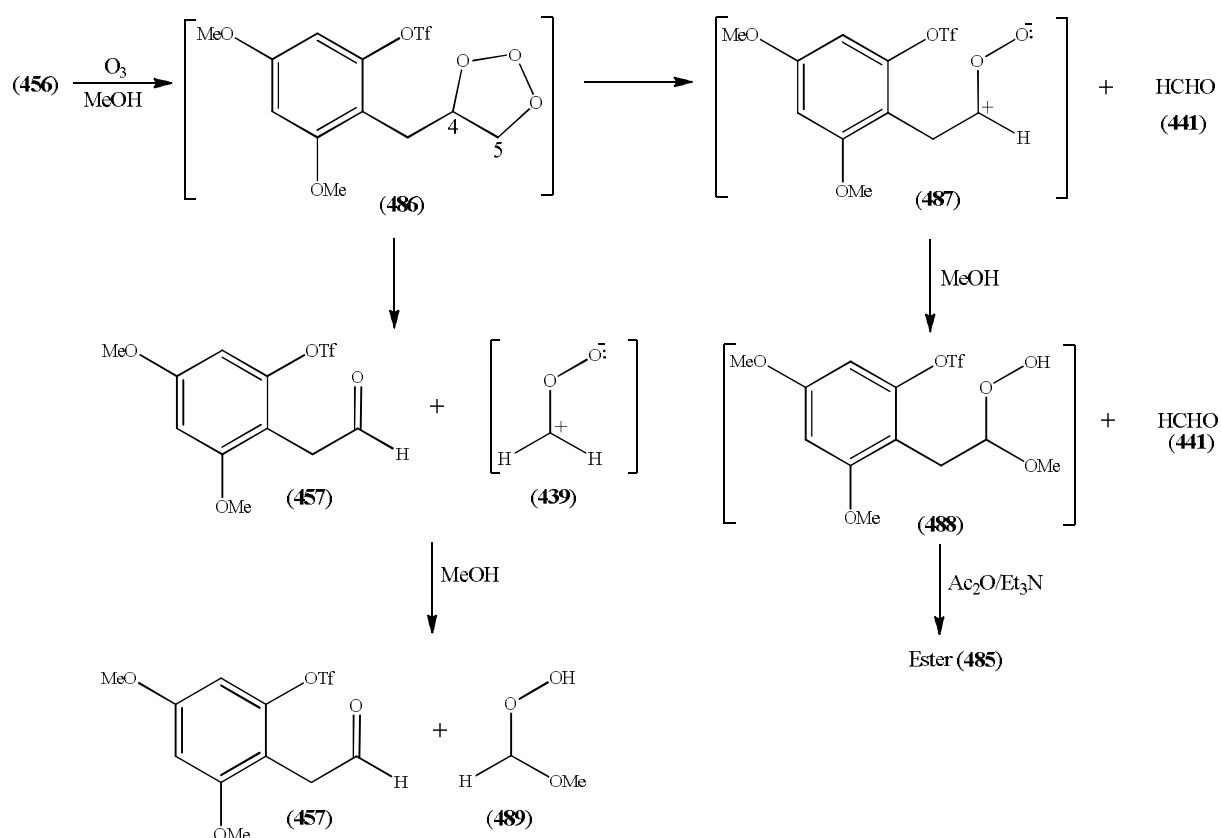
Scheme 5.3.2.8 Fragmentation of phloroglucinol-type substituted 1,2,3-trioxolane

5.4 Ozonolysis with *N*-Nucleophiles

Since the enantioselective process for the synthesis of isoflavonoids described by Versteeg *et al.*[43] (Scheme 5.4.1) was based on the utilization of *N*-based chiral auxiliaries (**215a/b**) and the phenylacetic acid esters prepared *via* ozonolysis would therefore have to be transformed into the amides anyway to be useful in this application, it was decided to investigate the possibility of direct amide formation during ozonolysis. In this regard it was envisaged that if the methanol used in the oxidative work-up could be replaced with a nitrogen nucleophile, it could lead to the direct formation of amide products. If this novel process could be achieved, it would lead to the elimination of at least 4 steps, *i.e.* two steps for transforming the ester into the acid chloride (**216**), one step for preparing the TMS derivative of the imidazolidinone (**215**), and a further step for attaching the imidazolidinone to the phenylacetic acid to form (**219**), from the enantioselective synthesis of isoflavonoids, as described by Versteeg *et al.*[43]
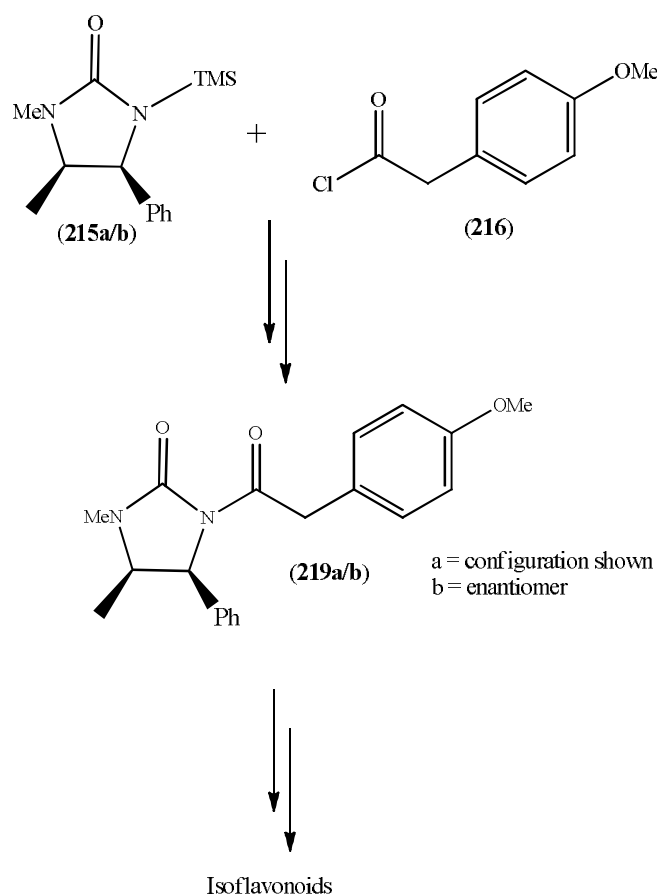
Scheme 5.4.1 Preparation of *N*-phenylacetylimidazolidinone

In order to be able to directly prepare amides through ozonolysis, it was decided to utilize the oxidative work-up methodology as described by Helms and Reibig,[22] but to replace the

MeOH as zwitterion stabilizer by a nitrogen nucleophile (Scheme 5.4.2.). The investigation was therefore started with 1-allyl-4-methoxybenzene (**388**) and aniline (**494**) as nitrogen nucleophile (Scheme 5.4.3).
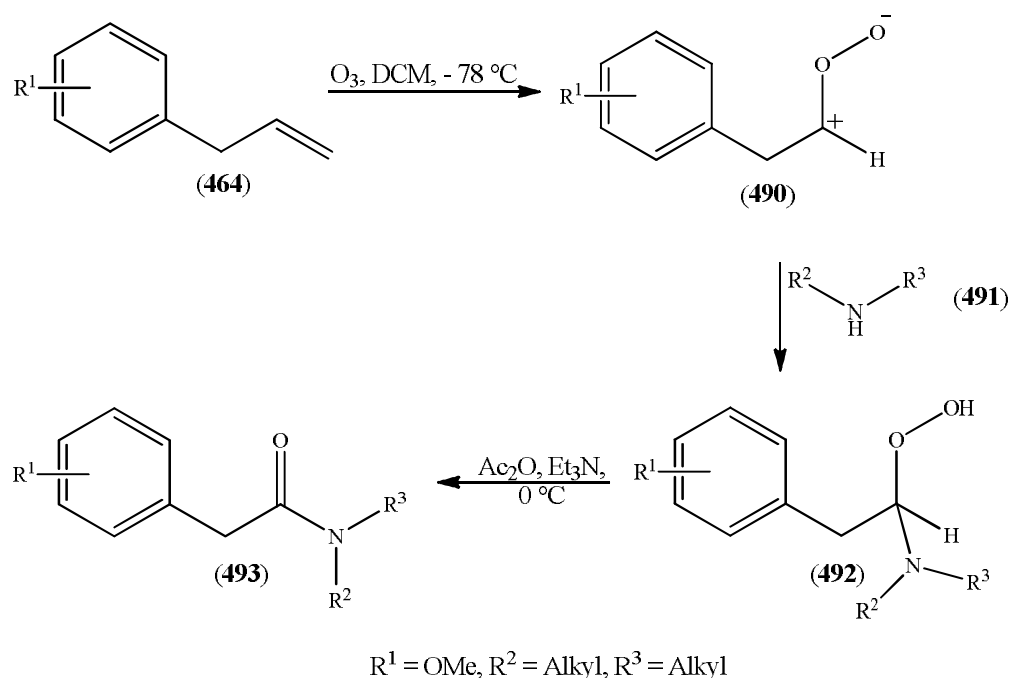
Scheme 5.4.2 Proposed direct preparation of amides *via* ozonolysis in the presence of nitrogen nucleophiles
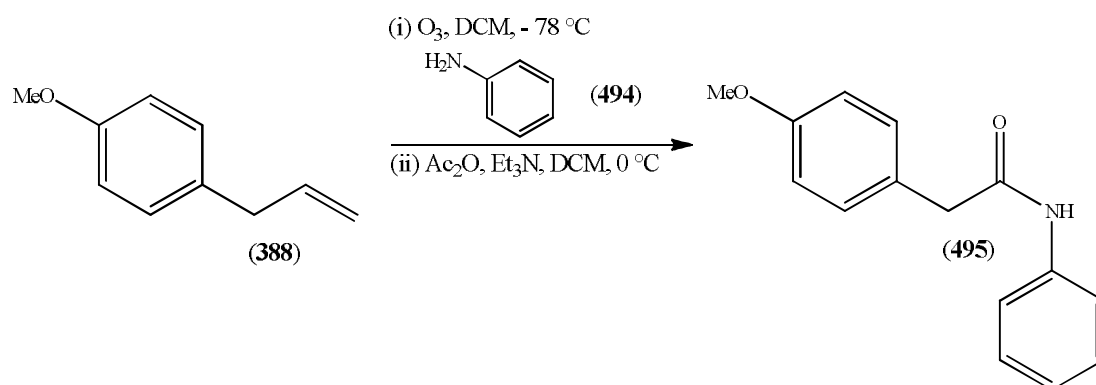
Scheme 5.4.3 Oxidative ozonolysis in the presence of aniline

Unfortunately, only a mixture of unidentifiable products were obtained, but it was soon realized that due to the electron donating properties of the nitrogen atom (*cf*. NMR studies on the ozonolysis reaction described in paragraph 5.3.1), oxidative cleavage of the aniline ring in

the presence of the O_3 could be responsible for the failure of the reaction. The method was therefore adjusted to the bubbling of ozone through the reaction mixture to the point of complete formation of the 1,2,4-trioxolane (**435**) (7–8 minutes) as was identified through the NMR studies described in paragraph 5.3.1 and indicated by a light blue-purple colouration of the DCM. The ozone was substituted by oxygen and the bubbling continued for another 5–15 min. to remove all excess ozone from the reaction mixture before the aniline was added and the stirring continued while the reaction mixture was allowed to reach rt. over 2 hours. The mixture was then cooled back down to 0 °C with subsequent Ac_2O and Et_3N addition for 30 min. where after stirring continued for another 21 hours while the reaction mixture was allowed to reach rt., which led to the desired product (**497**) being obtained in 37% yield (Scheme 5.4.4).
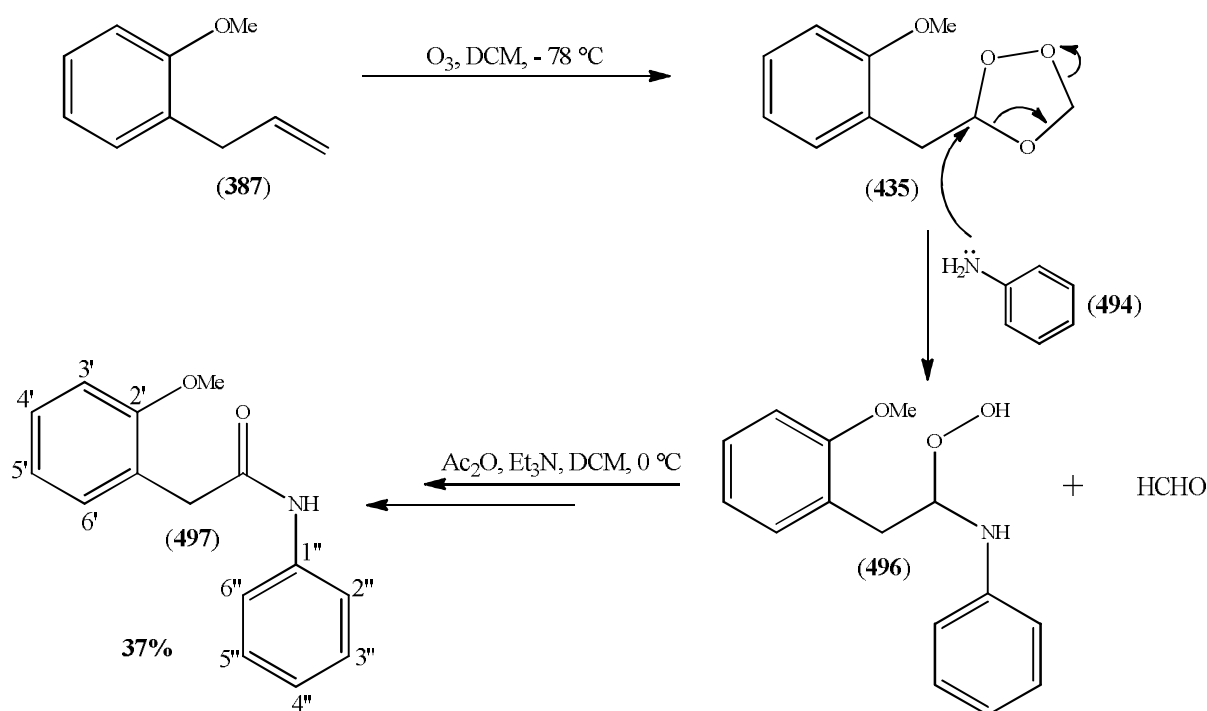
Scheme 5.4.4 Oxidative ozonolysis of 1-allyl-2-methoxybenzene with subsequent aniline addition

The ^{1}H NMR spectrum (plate 35a) of the amide (**497**) clearly displayed a singlet resonance for the -CH_2- group at δ 3.72 (2H, s), as well as aromatic multiplet resonances [δ 7.42–7.27 (6H), 7.07–7.04 (1H), 6.99–6.97 (1H), and 6.96–6.95 (1H)] integrating for 9 protons and the expected methoxy signal at δ 3.94. ^{13}C NMR (plate 35b) as well as mass spectrometry

confirmed the structure of the product (**497**) by displaying aromatic carbon resonances (δ 131.58, 129.23, 129.06, 124.15, 121.57, 119.72, 111.01) and a methylene resonance at δ 40.35 as well as a molecular ion at m/z 241.05 (M^+, 59.02%) together with fragmentation peaks at m/z 148.05 (100.00%), 120.05 (12.60), 91.05 (82.67).

Application of the same methodology to the reaction of 1-allyl-4-methoxybenzene (**388**) with acetamide led to the expected product (**498**) being obtained in 39% yield (Scheme 5.4.5).
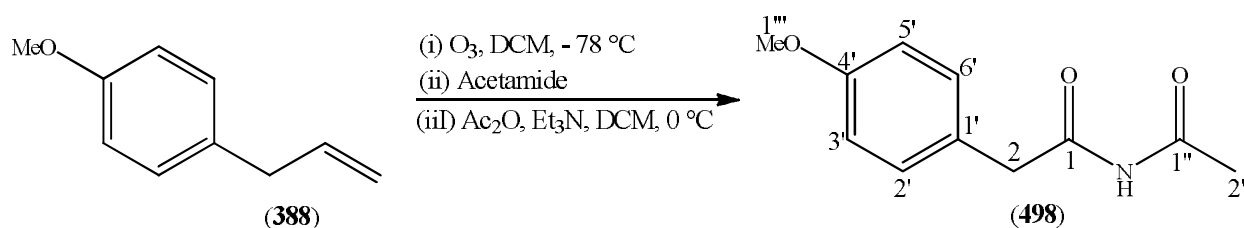
Scheme 5.4.5 Oxidative ozonolysis with acetamide as nucleophile

The structure of the product (**498**) was elucidated *via* ^{1}H NMR (plate 36a) where the two expected doublets for the aromatic protons were observed [δ 7.53 (d, J = 8.78 Hz) and 6.89 (d, J = 8.78 Hz)] as well as the singlet resonance for the methylene group at δ 3.79 (2H, s) and the amide methyl protons at δ 2.26 (3H, s). Mass spectrometry confirmed the structure of the product by displaying the expected molecular ion and fragmentation products at m/z 208.00 (M^+, 4.14%), 177.04 (22.19), 137.10 (100.00), 109.05 (20.85), 77.05 (15.36).

Encouraged by the fact that the nucleophilicity of the nitrogen atom was not reduced by the adjacent carbonyl to the point where it could not to react with the 1,2,4-trioxolane (**437**), the procedure was extended to a reaction between 1-allyl-4-methoxybenzene (**388**) and 2-imidazolidone (**499**) (Scheme 5.4.6), in an attempt to produce the phenylacetic acid imidazolidone derivative (**500**) similar to the chiral imidazolidinone (**215a/b**) utilized by Versteeg *et al.*[43] in their enantioselective synthesis of isoflavans (Scheme 5.4.1). The reaction, however, proved to be unsuccessful and no identifiable product could be isolated from the reaction mixture. Since the acetamide derivative could be prepared in moderate yield and the electronic properties of the imidazole derivative (**499**) should react very similar, failure of the reaction could possibly be due to the fact that the imidazolidinone contains secondary nitrogens which are sterically more hindered. Increasing the temperature of the

reaction between the 1,2,4-trioxolane and the amide nucleophile might overcome this problem and lead to the desired product even in this instance.

(i) O₃, DCM, - 78 °C

(ii) (499)

(iiI) Ac₂O, Et₃N, DCM, 0 °C

(388)   (500)
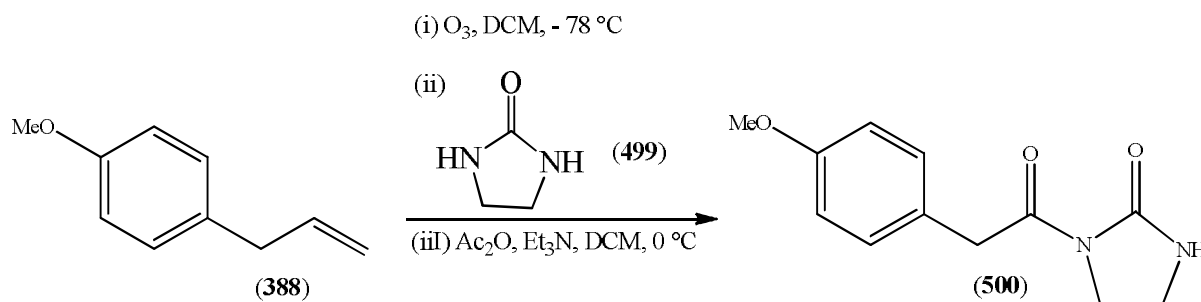
Scheme 5.4.6 Oxidative ozonolysis with 2-imidazolidone as nucleophile

The results obtained during the current investigation, however, gave proof of concept for a successful reaction between the 1,2,4-trioxolane formed as intermediate during ozonolysis of alkenes and nitrogen nucleophiles. More work is needed in order to properly define the scope and limitations of this new reaction and determine the optimum reaction conditions for different nitrogen nucleophiles. These aspects will form the basis of a follow-up study during the Ph.D. study.

5.5 Deoxybenzoin Synthesis

Since deoxybenzoins (**504**) represent another key intermediate in the synthesis of isoflavonoids (Scheme 5.5.1) and it has been shown that phenylacetic acid derivatives can be synthesized in an environmentally benign way, it was decided to investigate the possibility of transforming these compounds into deoxybenzoins through an efficient and generally applicable process. Further impetus for an investigation into better methods for preparing deoxybenzoins came from the fact that polyhydroxy deoxybenzoins received a lot of attention over the last *ca*. 3 decades due to a wide range of biological activities, including anti-cancer activity.[44]
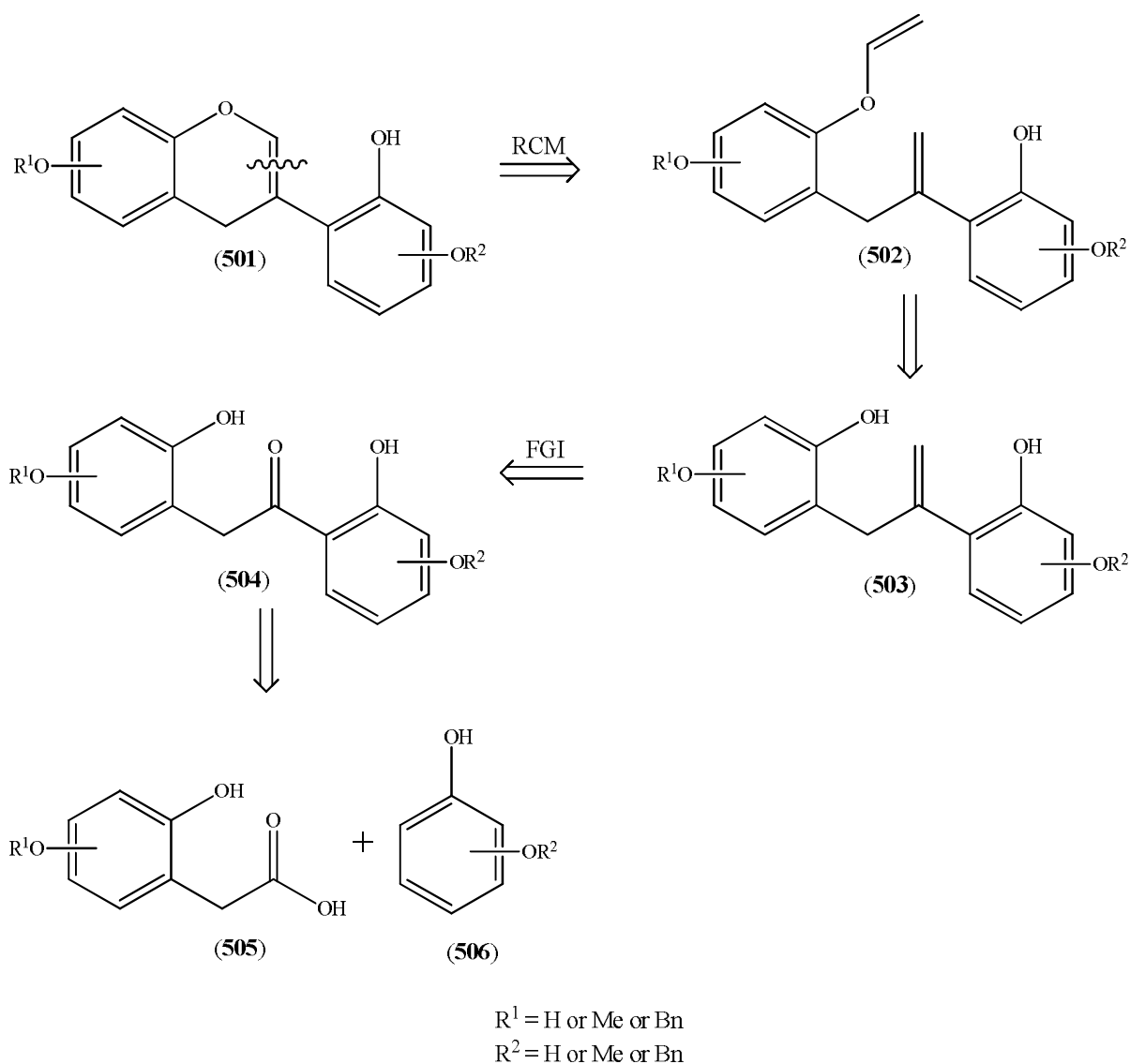
Scheme 5.5.1 Isoflavonoid retrosynthesis

Although several methods for the synthesis of deoxybenzoins have been reported over the last century, these are often tedious multi-step processes that are not generally applicable, like the Hoesch reaction, and also not always high yielding. Since Wähälä and co-workers[44,45] reported methodology for the synthesis of polyhydroxy deoxybenzoins in > 70% yield by reaction of phenylacetic acids with phenolic compounds under microwave conditions utilizing ionic liquids, this process was considered and selected as initial approach towards the preparation of deoxybenzoins during the current investigation. The best yield and conversion obtained by Hakala and Wähälä was for the synthesis of 2,4,4'-trihydroxydeoxybenzoin (**509**) and utilized [bmim][BF$_4$] (**510**) and BF$_3$·OEt$_2$ in a 2:1 relationship (Scheme 5.5.2).[44]
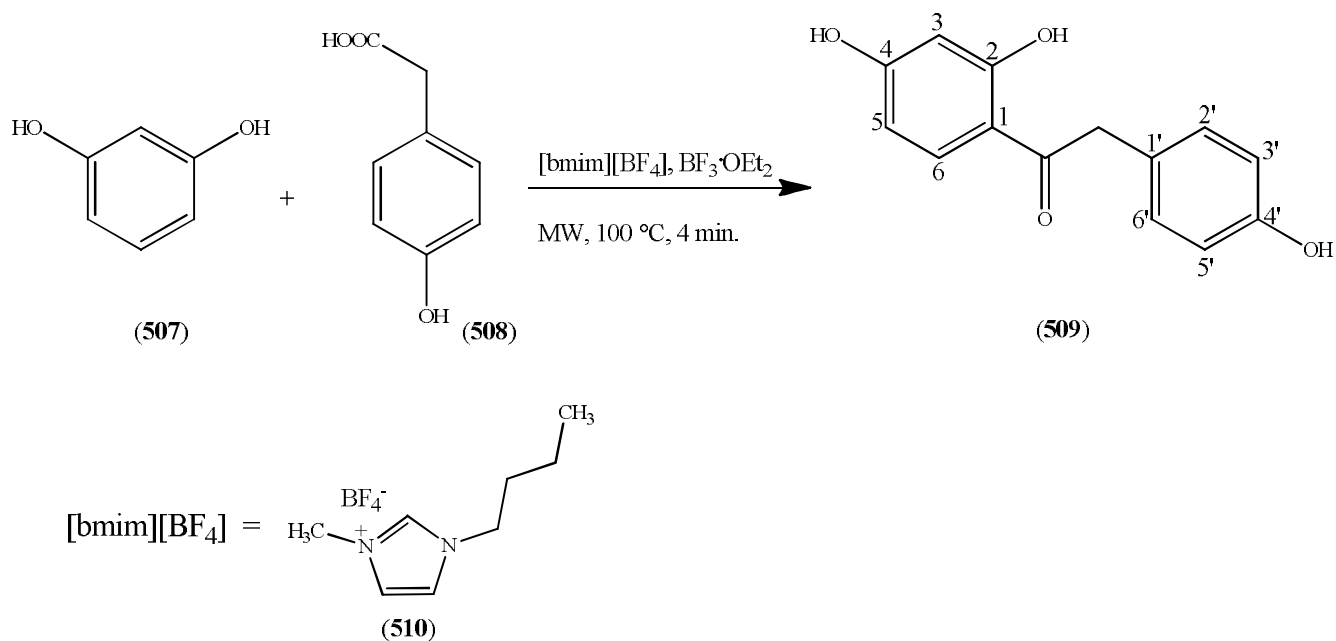
Scheme 5.5.2 Synthesis of 2,4,4'-trihydroxydeoxybenzoin by Hakala and Wähälä[44]

Consequently, these reaction conditions were applied to the preparation of 2,3',4,4'-tetrahydroxydeoxybenzoin (**512**). A solution of 3,4-dihydroxyphenyl acetic acid (**511**) and resorcinol (**507**) was treated with BF₃-etherate under microwave irradiation for 4 minutes (Scheme 5.5.3) to give the expected product (**512**) in 50% yield. The structure of the product was elucidated by ^{1}H NMR (plate 37a) where both aromatic ABX-systems [δ 7.88 (d, J = 8.85 Hz, H-6), 6.79 (d, J = 2.11 Hz, H-2'), 6.73 (d, J = 8.06 Hz, H-5'), 6.63 (dd, J = 8.06, 2.11 Hz, H-6'), 6.39 (dd, J = 8.85, 2.37 Hz, H-5), 6.29 (d, J = 2.37 Hz, H-3)] could be identified together with the α-methylene protons characteristic of deoxybenzoins at δ 4.05 (2H, s) ppm.
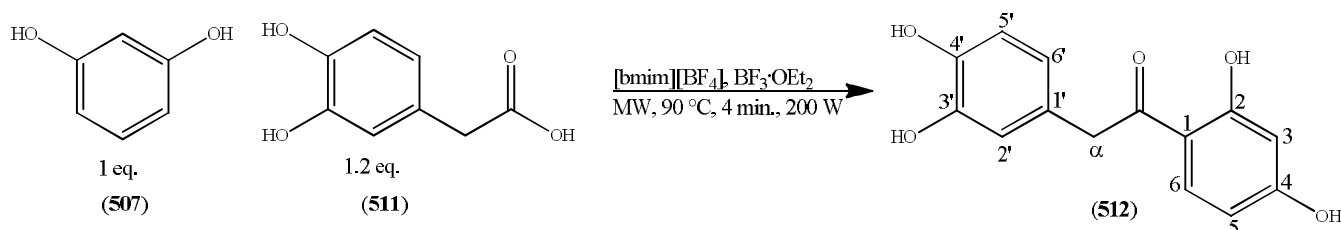
Scheme 5.5.3 2,3',4,4'-Tetrahydroxy deoxybenzoin synthesis

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Following the success of the microwave-assisted synthesis of the tetrahydroxydeoxybenzoin (**512**) the protocol was extended to the reaction of 2,4,6-trimethoxybenzene with phenylacetic acidd, but only 2-hydroxy-4,6-dimethoxydeoxybenzoin (**514**) (Plate 38a) [δ 7.23–7.20 (2H, m), 7.16–7.13 (1H, m), 7.12–7.11 (2H, m), 5.96 (1H, d, J = 2.62 Hz), 5.84 (1H, d, J = 2.62 Hz), 4.23 (2H, s, α-C$\underline{H}_2$), 3.76 (3H, s), 3.72 (3H, s) and MS: m/z 272.05 (M$^+$, 2.29%), 181.00 (M$^+$- CH$_2$Ph, 100.00), (166.00, 5.32) and (138.00, 4.44)] could be isolated from the reaction mixture in 18% yield. The formation of the 2-demethylated product (**514**) is probably explicable in terms of complexation of the *o*-methoxy oxygen to the oxophilic BF$_3$ entity followed by nucleophilic attack on the methyl group by another 2,4,6-trimethoxybenzene or another nucleophilic moiety (Scheme 5.5.4).[46]
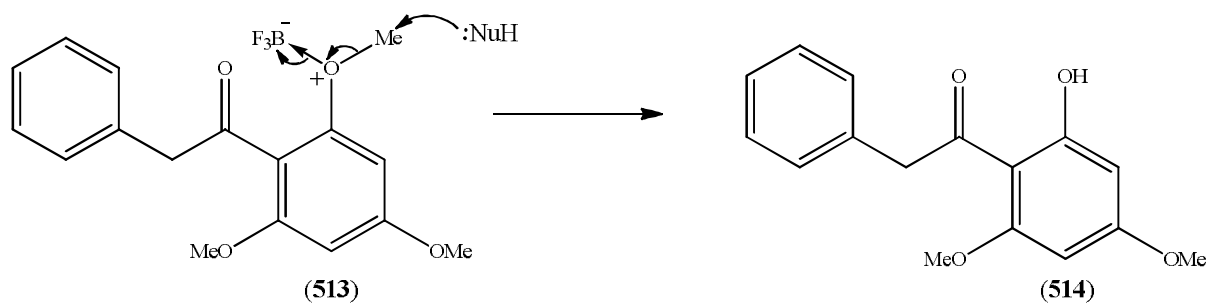
Scheme 5.5.4 Demethylation with BF$_3$·OEt$_2$[43]

Although removal of the -CH$_3$ moiety from the aromatic methoxy group was somewhat unexpected, it was not considered a major stumbling block in the synthetic protocol, as the methyl entity merely served as a protecting group and could easily be replaced for subsequent reactions if required.[46] In order to be able to prepare isoflavonoids according to the retro synthetic protocol in Scheme 5.5.1, a substituted phenol should be reacted with an *ortho*-oxygenated phenylacetic acid, so the synthesis of 2,2'-dihydroxy-4,6-dimethoxydeoxybenzoin (**516**) was subsequently embarked upon (Scheme 5.5.5). Unfortunately not even trace amounts of the desired deoxybenzoin could be isolated or identified.
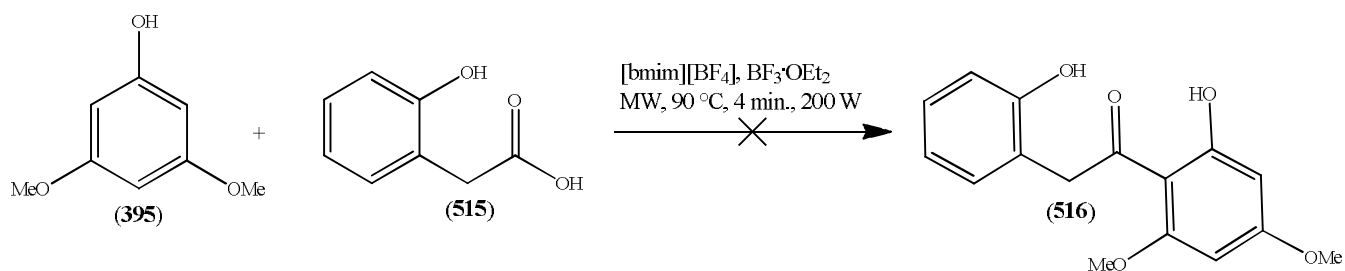
Scheme 5.5.5 Attempted synthesis of 2,2'-dihydroxy-4,6-dimethoxydeoxybenzoin

A deoxybenzoin synthesis utilizing 2-hydroxyphenylacetic acid (**515**) and the sterically less hindered resorcinol (**507**) was attempted next as the steric bulk of the trioxygenated phenol employed was thought to hamper nucleophilic attack on the carboxylate carbon of the phenylacetic acid. Only the phenylacetic acid starting material and unreacted resorcinol could, however, be recovered from the reaction mixture.

Since Wähälä and Hase[45] reported on similar deoxybenzoin preparations utilizing a Friedel-Crafts acylation reaction under $BF_3 \cdot OEt_2$ catalysis (Scheme 5.5.6), this variation of the process was considered for the synthesis of the desired deoxybenzoins. It, however, soon became clear that one of the side reactions reported by these authors, *i.e.* benzofurane formation (Scheme 5.5.7), would limit the applicability of the reaction during the current investigation since a 2'-oxygen function (protected or free hydroxy group) is a prerequisite for final cyclization to the isoflavonoid analogue. Even if the 2'-hydroxy group is protected, the Lewis acid may lead to removal of the protecting group as has been found for the reaction of 1,3,5-trimethoxybenzene in the previous paragraph (Scheme 5.5.4).
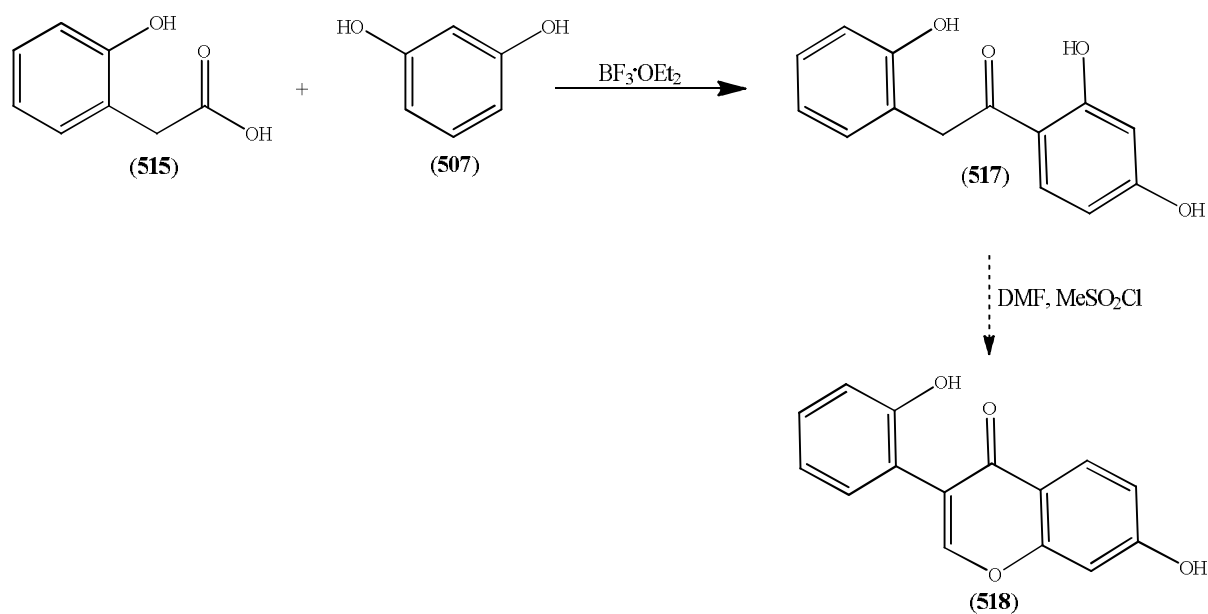
Scheme 5.5.6 Polyhydroxyisoflavone synthesis[45]
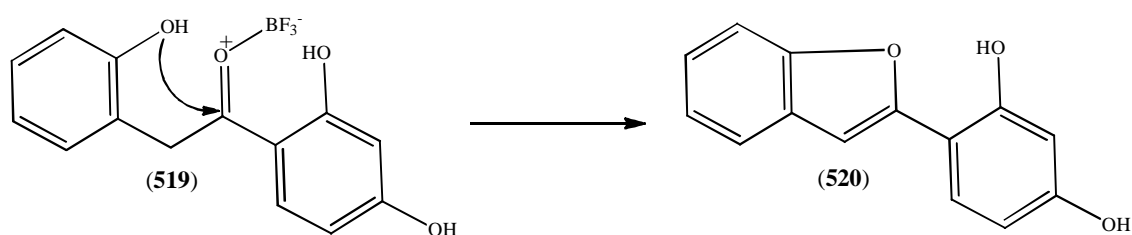
Scheme 5.5.7 Benzofurane formation[45]

Even though the utilization of the recyclable ionic liquid together with microwave irradiation provided an environmentally favourable, fast and effective process for deoxybenzoin synthesis, this methodology had to be abandoned as it proved to be unsuccessful in the synthesis of the desired 2'-hydroxy substituted deoxybenzoins. Furthermore, the yields obtained during the use of this method were not satisfactory.   It was therefore decided to look into the utilization of the Grignard reaction, as indicated in Scheme 5.5.8, as methodology for the preparation of the envisaged deoxybenzoins. Since the methyl ester derivative of the various phenylacetic acids [e.g. methyl 2'-methoxyphenyl acetate (**480**), methyl 4'-methoxyphenyl acetate (**481**), methyl 4'-trifluoromethylphenyl acetate (**482**), methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate (**483**), methyl 4'-

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trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl acetate (**484**) and methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate (**485**)] were available through ozonolysis, these compounds were envisaged as starting material in this process and exposed to the phenylmagnesiumbromide (**521**) as a first attempt. It, however, soon became clear that the intermediate ketone product (**522**) was more reactive than the starting ester. The reaction could not be controlled (even at -78 $^{\circ}$C) to stop at the ketone stage and only indications (MS) of formation of the substituted stilbene (**525**) was found (Scheme 5.5.9).
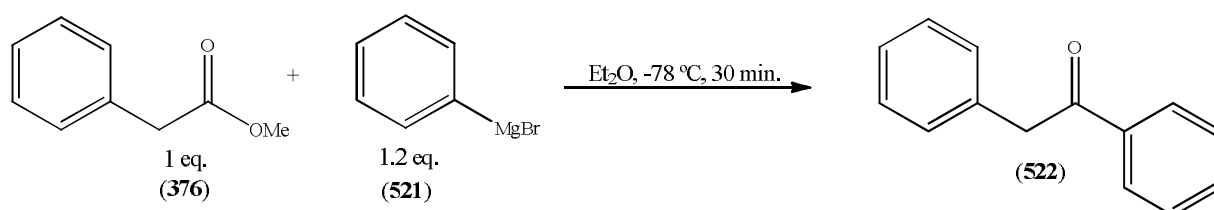
Scheme 5.5.8 Deoxybenzoin synthesis through reaction with PhMgBr
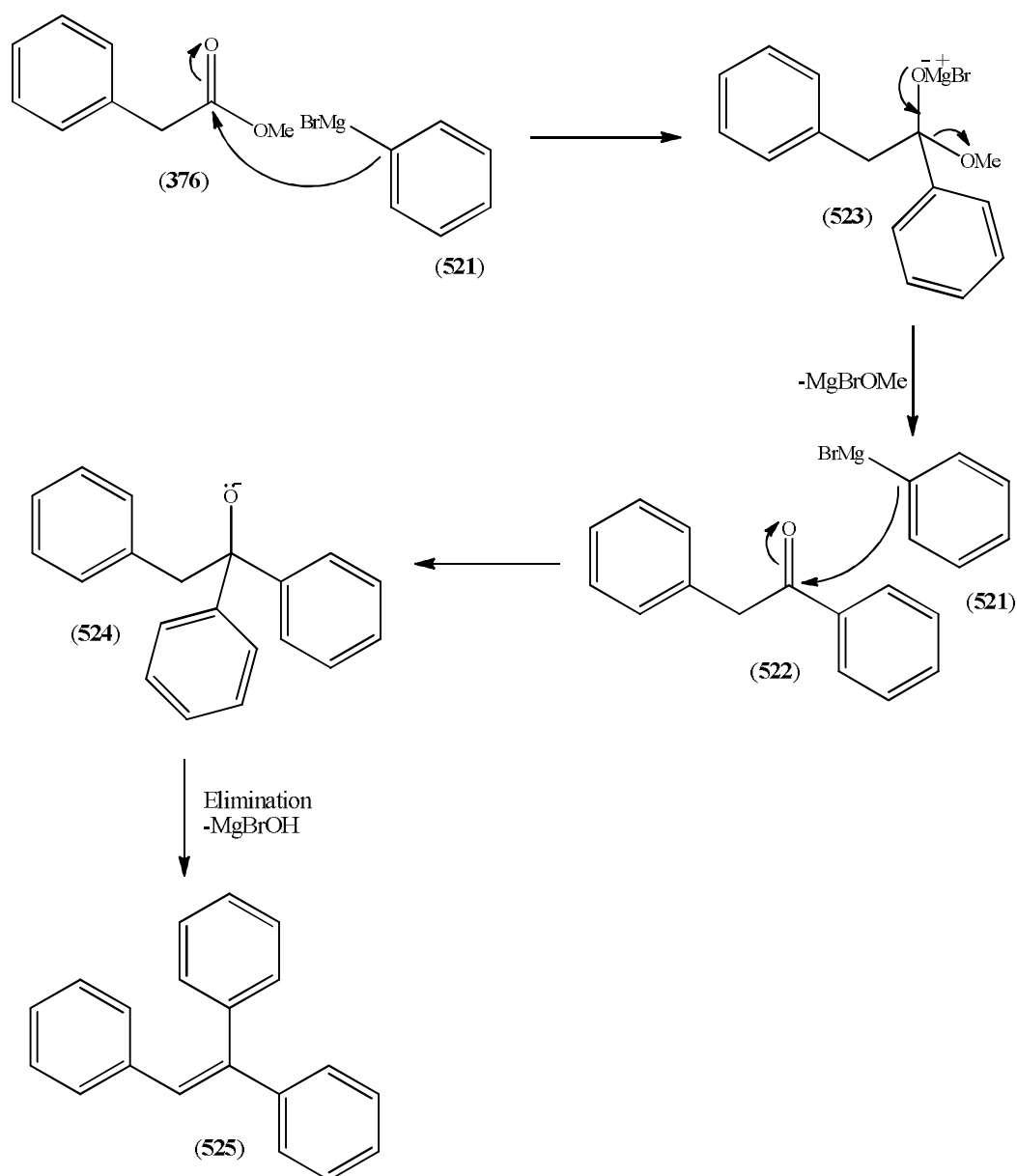
Scheme 5.5.9 Grignard reaction of phenylmagnesiumbromide and methyl phenyl acetate

In an effort to increase the reactivity of the starting material relative to the ketone intermediate, it was subsequently decided to utilize the acid chloride analogue (**526**) as substrate in the Grignard reaction. As model reaction, phenylacetyl chloride (**526**) was therefore reacted with unsubstituted phenylmagnesiumbromide (**521**) in Et$_2$O at rt., but the reaction could again not be prevented from proceeding to the stilbene derivative (**525**). When the reaction was, however, repeated at -78 ^{o}C with 1.2 eq of the Grignard reagent, the desired deoxybenzoin (**522**) could be isolated in 59 % yield (Scheme 5.5.10).
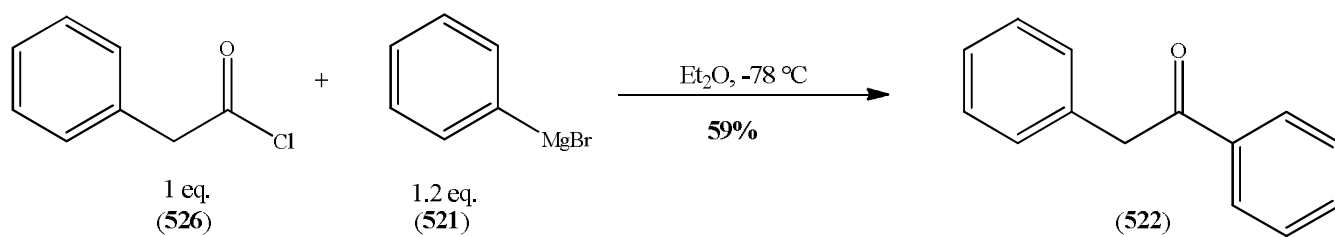
Scheme 5.5.10 Deoxybenzoin synthesis *via* Grignard Reaction at – 78 °C

Although transforming the methyl phenylacetic acid derivatives obtained during ozonolysis into the acid chlorides will add additional steps to the envisaged synthetic protocol, the principle of using an activated phenylacetic acid derivative as substrate in a Grignard reaction for synthesizing deoxybenzoins, have been established and can now be applied with confidence to the synthesis of oxygenated analogues. The possibility of using less reactive equivalents, like thioesters or benzotriazole derivatives that can be prepared in a better way, in the process, will be investigated in a future study.

5.6 Conclusions and Future Work

During the current investigation it has been found that phenylacetaldehydes of various naturally occurring substitution patterns could be prepared from the corresponding allylphenols in moderate to good yields *via* ozonolysis with reductive work-up procedures. While substrates containing two or more electron-donating (methoxy) groups on the aromatic ring had to be deactivated through trifluoromethanesulfonyl (triflate) ester formation to prevent ring ozonolysis with subsequent cleavage of the aromatic ring, those analogues with less activated aromatic rings (one methoxy substituent) only needed protection as methyl ethers provided that exposure to ozone is limited to 6–8 minutes at 0 to -78 °C. The fact that ozone attack was directed at the aromatic ring instead of the exocyclic double bond in the case of the highly oxygenated analogues was confirmed by NMR studies where the presence of the 1,2,4-trioxolane, as proposed in the Criegee mechanism, could be established in the reaction mixture in the cases where the reactions gave the desired product. Furthermore it was found that both DMS and NMMO gave the desired phenylacetaldehydes, but that due to its basicity NMMO caused migration of the double bond leading to benzaldehydes after ozonolysis and reductive workup when applied to substrates with two or more oxygen functions. This side reaction could not be prevented completely even when the triflate derivatives of the starting materials were used.

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The methyl esters of the phenylacetic acids could be prepared by ozonolysis of the allylphenol derivatives combined with oxidative work-up. In this instance a two-step process was required where the intermediate peroxide, formed by reaction of the zwitterion with methanol, had to be acetylated before treatment with Et_3N to give the desired ester product. As for the reductive work-up procedure, highly oxygenated substrates had to be converted into triflates to prevent cleavage of the aromatic ring.

In order to be able to prepare phenylacetamides, as required by the published procedure for the enantioselective synthesis of isoflavonoids, in a one step process from the allylbenzenes, ozonolysis of the allylbenzenes were executed in the presence of aniline, but the aniline was oxidized by the ozone. When the aniline was added after formation of the 1,2,4-trioxolane and the excess ozone removed before addition of the *N*-nucleophile, the desired phenylacetanilide could be obtained in moderate yield. The scope of this novel reaction could be extended to deactivated primary nitrogen nucleophiles, like acetamide, but when the secondary nitrogen nucleophile, 2-imidazolidinone, was used, only a mixture of inseparable products were obtained. The reaction conditions for the imidazolidinone reaction was, however, not optimized, so more work is needed in order to properly define the scope and limitations of this new reaction and to determine the optimum reaction conditions for different nitrogen nucleophiles. These aspects will form the basis of a follow-up study during Ph.D.

The phenylacetic acid esters obtained by ozonolysis could also be transformed into deoxybenzoins, another precursor to isoflavonoids, by activation as the acid chloride and subsequent reaction with a phenyl Grignard reagent. Even though additional steps would be required to transform the ester into an acid chloride, this approach could in principle function as a new general strategy for the synthesis of deoxybenzoins and would be extended to the use of oxygenated analogues in future developments. Furthermore, the possibility of the direct formation of thioesters and/or benzotriazoles during ozonolysis reactions as was demonstrated by the successful preparation of amides, might lead to several process steps being eliminated during the synthesis of deoxybenzoins. The possibility of utilizing the aforementioned derivatives (thioesters and/or benzotriazoles) instead of the acid chlorides during the Grignard reaction will also be looked into during Ph.D. studies.

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EXPERIMENTAL   6

6.1 Chromatography

6.1.1   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.

6.1.2   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 by making use of UV-light (254 nm) after which they were scraped off and the isolated product washed out using acetone or dichloromethane (DCM). All solvent was removed under reduced pressure on a water bath at *ca.* 40 °C.

6.1.3   Flash Column Chromatography (FCC)

A glass column was charged with 100 g of Merck Kieselgel 60 (230–400 mesh) for column chromatography per gram of crude product. Alternatively, FCC was conducted using a SupelcoVersaflash chromatography system utilizing a prepacked VersaPak Silica cartridge (40 mm x 150 mm). Air was disposed of by elution with the appropriate solvent under N_2-pressure (*ca.* 1 bar). The crude mixture was dissolved in a minimum amount of eluent and loaded on top of the column. The purified products were recovered by elution under N_2-pressure with the appropriate solvent system and collected in fractions (*ca.* 20 ml). Clean fractions were combined and the solvent evaporated under reduced pressure at *ca.* 40 ºC. Eluent was prepared v/v.

6.1.4   Cyclograph Chromatography (CC)

Cyclograph™ Centrifugal Chromatography System was used for CC performed on a round glass plate covered with silica of appropriate thickness (2 mm, 4 mm, 6 mm or 8 mm). The crude mixture (300 mg, 600 mg, 1200 mg or 2500 mg) was dissolved in a minimum amount of eluent and applied to the middle of the rotating cyclograph plate. Eluent was passed

through the silica over the rotating plate (flow range: 60–450 ml/min, rotation speed: 700–1480 rpm) and the UV-light fluorescing bands were collected. Clean fractions were combined and the solvent evaporated under reduced pressure at *ca*. 40 ºC.

6.2 Development of Chromatograms with Dip Reagents

6.2.1   Ferrichloride-Perchloric Acid

The reagent was prepared by mixing 35% (v/v) *aq.* perchloric acid (100 ml) and 0.5 M ferrichloride (5 ml). The ferrichloride-perchloric acid solution (10 ml) was diluted with MeOH (90 ml). Thin layer chromatograms (TLC) were dipped in the solution and developed with heat.

6.2.2   Methanol-Sulphuric Acid

The reagent was prepared by mixing 10% (v/v) H_2SO_4 in MeOH. Thin layer chromatograms were dipped in the solution and developed with heat.

6.2.3   Palladium

The reagent was prepared by diluting a 0.02 M palladium chloride solution in 6% (v/v) HCl with MeOH (1:10). Thin layer chromatograms were dipped in the solution and developed a yellow spot for divalent sulphur compounds at rt.

6.3 Anhydrous Solvents[1]

MeCN, MeOH, Et_2O, Me_2CO and DCM were dehydrated by filtering through a small column of activated neutral alumina (10% v/v) prior to use.

Alternatively, Me_2CO was left over dry K_2CO_3 (oven-dried, 24 hours, 170 ºC) for 24 hrs. The solvent was freshly distilled from molecular sieves (4 Å) under Ar prior to use.

N,N-dimethylaniline and DCM (alternative method) was distilled over CaH for 12 hrs. with subsequent fresh distillation under Ar before use.

6.4 Spectroscopic and Spectrometric methods

6.4.1   Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR-spectroscopy was performed on a Bruker AM 300 or 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 2.05 ppm for

$(CD_3)_2CO$, 77.16 ppm for $CDCl_3$ on carbon spectra and 206.26 ppm for $(CD_3)_2CO$ on the δ-scale, 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 (e.g. H_2O) and/or solvent peaks are designated I and S, respectively. Hexafluorobenzene was added as reference for ^{19}F NMR calibrated at a resonance of -164.9 ppm.[3]

6.4.2 Gas-Chromatography (GC)

Gas chromatography was carried out using a Shimadzu GC-17A FID (flame ionization detector) fitted with an HP-5 column (30 m, 0.32 i.d., 0.25 μm film thickness) from J&W Scientific with N_2 as carrier gas.

6.4.3 Mass-Spectroscopy (MS)

Mass spectrometry was performed on a Shimadzu GC-MS QP-2010 gas chromatograph-mass spectrometer by means of electron impact (EI) ionization fitted with a DB-5MS column (30 m, 0.32 i.d., 0.25 μm film thickness) from J&W Scientific with He as carrier gas. 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.

6.5 Melting Points

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

6.6.1 Microwave Irradiation

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

6.6.2 Ozone Generator

Reactions were carried out utilizing an Ozomatic ozone generator making use of O_2 pressure at 0.5 bar and the O_3 flow controlled in g/Nm^3.

6.7 Standard Work-up Procedure

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

6.8 Standard Ether Synthesis[4]

K_2CO_3 (2.0 eq.) was added to a mixture of phenol (1.0 eq.) in dry acetone or CH_3CN. Allylbromide (2.0 eq.) or MeI (2.0 eq.) was added slowly while the mixture heated to reflux. The reaction was followed by TLC and once deemed complete (indicated by disappearance of the phenol), the reaction mixture was allowed to cool and the K_2CO_3 filtered off. The excess allyl bromide or MeI was removed *in vacuo* together with the solvent. Further purification was generally not required.

6.8.1   1-Allyloxy-3-methoxybenzene (**394**)

3-Methoxyphenol (**393**) (4.4 ml, 40.6 mmol, 1.0 eq.), K_2CO_3 (11.93 g, 86.3 mmol, 2.1 eq), CH_3CN (150 ml), allyl bromide (7 ml, 80.9 mmol, 2.0 eq.).
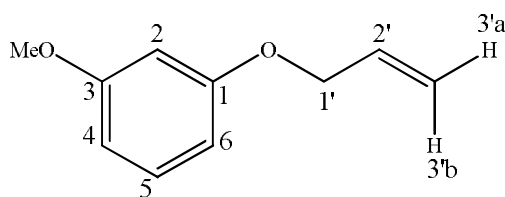
Yielded 1-allyloxy-3-methoxybenzene (**394**) as a bright orange oil. Mass: 6.56 g; quantitative yield. R_f : 0.6 (H:A; 60:40). ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 1a): δ 7.20 (1H, dd, J = 8.17, 8.20 Hz, H-5), 6.56–6.54 (2H, m, H-4 and H-6), 6.53 (1H, dd, J = 2.33, 2.34 Hz, H-2), 6.18–6.05 (1H, m, H-2'), 5.46–5.43 (1H, m, H-3'b), 5.33–5.31 (1H, m, H-3'a), 4.55–4.54 (2H, m, H-1'), 3.81 (3H, s, -O<u>Me</u>). ^{13}C NMR (151 MHz, $CDCl_3$) (plate 1b): 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 (-O<u>Me</u>). MS (EI) *m/z* 164.15 (M$^+$, 100.00%), 149.10 (18.23), 136.15 (14.95), 121.10 (21.94), 94.10 (11.94).

6.8.2   1-Allyloxy-3,5-dimethoxybenzene (**396**)

3,5-Dimethoxyphenol (**395**) (1.02 g, 6.6 mmol, 1.0 eq.), K_2CO_3 (0.85 g, 6.1 mmol, 0.9 eq), CH_3CN (60 ml) allyl bromide (1.1 ml, 13.0 mmol, 2.0 eq.).
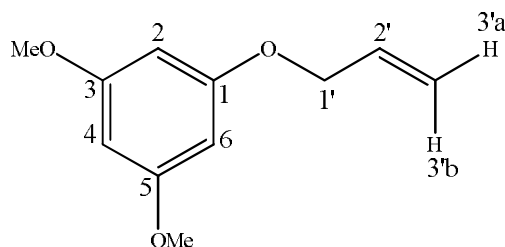
Yielded 1-allyloxy-3,5-dimethoxybenzene (**396**) as a yellow oil. Mass: 1.28 g; quantitative yield. R_f : 0.54 (H:A; 70:30). ^{1}H NMR (600 MHz, $CDCl_3$) (plate 2a): δ 6.11 (2H, d, J = 2.10 Hz, H-2 and H-6), 6.10–6.09 (1H, m, H-4), 6.08–6.02 (1H, m, H-2'), 5.43–5.40 (1H, m, H-3'b), 5.30–5.28 (1H, m, H-3'a), 4.50–4.49 (2H, m, H-1'), 3.77 (6H, s, -O<u>Me</u>). ^{13}C NMR (151 MHz, $CDCl_3$) (plate 2b): 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$\underline{\text{Me}}$). MS (EI) *m/z* 194.05 (M$^+$, 100.00%), 179.00 (16.61), 165.05 (40.28), 151.05 (25.05), 125.05 (71.27).

6.8.3   1-Allyl-3,4-dimethoxybenzene (**390**)

1-Allyl-4-hydroxy-3-methoxybenzene (**407**) (4.7 ml, 30.5 mmol, 1.0 eq.), K_2CO_3 (8.53 g, 61.7 mmol, 2.0 eq.), Me_2CO (120 ml), MeI (3.8 ml, 61.0 mmol, 2.0 eq.).
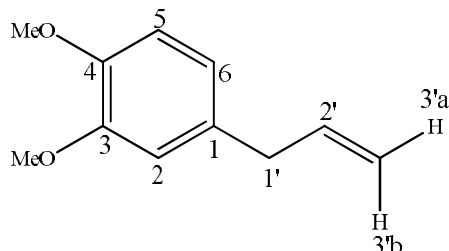
Yielded 1-allyl-3,4-dimethoxybenzene (**390**) as a yellow-orange oil. Mass 4.28 g; 79% yield. R$_f$: 0.66 (H:A; 60:40). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 3a): δ 6.80 (1H, d, *J* = 8.02 Hz, H-5), 6.73 (1H, dd, *J* = 8.02, 1.86 Hz, H-6), 6.71 (1H, d, *J* = 1.86 Hz, H-2), 5.96 (1H, ddt, *J* = 17.02, 10.09, 6.7 Hz, H-2'), 5.10–5.05 (2H, m, H-3'a and H-3'b), 3.87 (3H, s, -O$\underline{\text{Me}}$), 3.86 (3H, s, -O$\underline{\text{Me}}$), 3.34 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 3b): δ 149.00, 147.49, 137.79, 132.74, 120.50, 115.69, 111.98, 111.37, 56.03, 55.89, 39.89.[5] MS (EI) *m/z* 178.10 (M$^+$, 100.00%), 163.05 (34.22), 147.10 (36.87), 91.05 (34.57).

6.8.4   1-Allyl-3,4,5-trimethoxybenzene (**391**)

1-Allyl-4-hydroxy-3,5-dimethoxy-benzene (**408**) (0.9 ml, 5.2 mmol, 1.0 eq.), K_2CO_3 (0.46 g, 3.3 mmol, 0.6 eq.), Me_2CO (60 ml) MeI (0.6 ml, 9.6 mmol, 2.0 eq.).
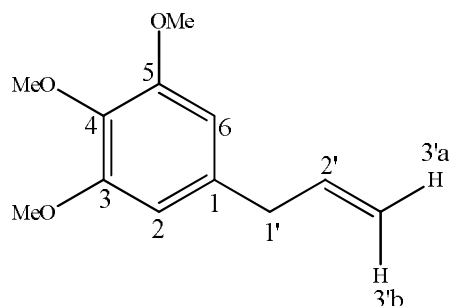
Yielded 1-allyl-3,4,5-trimethoxybenzene (**391**) as an orange oil. Mass: 0.83 g; 77% yield. R$_f$: 0.67 (H:A; 60:40). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 4a): δ 6.41 (2H, s, H-2 and H-6), 5.95 (1H, ddt, *J* = 16.90, 10.04, 6.81 Hz, H-2'), 5.13–5.06 (2H, m, H-3'a and H-3'b), 3.84 (6H, s, -O$\underline{\text{Me}}$), 3.82 (3H, s, -O$\underline{\text{Me}}$), 3.33–3.32 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 4b): δ 153.19 (quaternary carbon), 137.22 (C-2'), 136.29 (quaternary carbon), 135.81 (quaternary carbon), 116.02 (C-3'), 105.41 (C-2 and C-6), 60.86 (-O$\underline{\text{Me}}$), 56.05 (-O$\underline{\text{Me}}$), 40.55 (C-1'). MS (EI) *m/z* 208.10 (M$^+$, 100.00%), 193.10 (50.83), 77.05 (9.11).

6.8.5 1-Allyl-2,4,6-trimethoxybenzene (392)

1-Allyl-6-hydroxy-2,4-dimethoxybenzene (**403**) (2.8 ml, 15.8 mmol, 1.0 eq.), K$_2$CO$_3$ (5.71 g, 41.3 mmol, 7.2 eq.), CH$_3$CN (100 ml), MeI (2.6 ml, 41.8 mmol, 7.3 eq.).
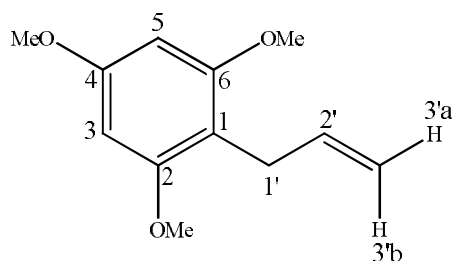
Yielded 1-allyl-2,4,6-trimethoxybenzene (**392**) as a dark orange oil. Mass: 2.62 g; 80% yield. R$_f$: 0.47 (H:A; 60:40). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 5a): δ 6.15 (2H, s, H-3 and H-5), 5.96–5.90 (1H, m, H-2'), 4.97–4.90 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -O$\underline{\text{Me}}$), 3.80 (6H, s, -O$\underline{\text{Me}}$), 3.34–3.33 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 5b): δ 159.76 (quaternary carbon), 158.80 (quaternary carbon), 137.62 (C-2'), 113.69 (C-3'), 109.28 (quaternary carbon), 90.93 (C-3 and C-5), 55.97 (-O$\underline{\text{Me}}$), 55.47 (-O$\underline{\text{Me}}$), 27.04 (C-1'). MS (EI) *m/z* 208.00 (M$^+$, 100.00%), 193.00 (15.15), 179.00 (54.26), 165.10 (14.36), 121.05 (34.44).

6.8.6 1-Allyl-2,4-dimethoxybenzene (389)

1-Allyl-2-hydroxy-4-methoxybenzene (**404**) (0.09, 0.55 mmol, 1.0 eq.), K$_2$CO$_3$ (0.35 g, 2.53 mmol, 4.6 eq.), CH$_3$CN (30 ml), MeI (0.1 ml, 1.61 mmol, 2.9 eq.).
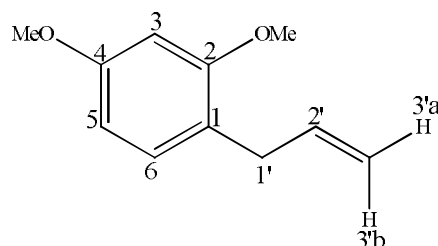
Yielded 1-allyl-2,4-dimethoxybenzene (**389**) as a light yellow oil. Mass: 0.0985 g; 96% yield. R$_f$: 0.39 (H:EtOAc; 95:5). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 6a): δ 7.04 (1H, d, *J* = 8.1 Hz, H-6), 6.46 (1H, d, *J* = 2.4 Hz, H-3), 6.44 (1H, dd, *J* = 8.1, 2.4 Hz, H-5), 5.98 (1H, ddt, *J* = 16.95, 10.22, 6.59 Hz, H-2'), 5.05–5.00 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -O$\underline{\text{Me}}$), 3.80 (3H, s, -O$\underline{\text{Me}}$), 3.33–3.31 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 6b): δ 159.46 (C-2/4), 158.21 (C-2/4), 137.53 (C-2'), 130.08 (C-6), 121.07 (C-1), 115.10 (C-3'), 104.01 (C-3/5), 98.64 (C-3/5), 55.48 (-O$\underline{\text{Me}}$), 33.50 (C-1'). MS (EI) *m/z* 178.10 (M$^+$, 100.00%).

6.9 Standard Phenolic Protection by the Trifluoromethanesulfonyloxy-group

A mixture of phenol (1.0 eq.) and dry DCM (20 ml) was cooled to 0 ºC 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.

6.9.1 1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**)

1-Allyl-2-hydroxy-4-methoxybenzene (**404**) (0.2 g, 1.2 mmol, 1.0 eq.), DCM (20 ml), DMAP (0.18 g, 1.5 mmol, 1.2 eq.), trifluoromethanesulfonic anhydride (0.5 ml, 3.0 mmol, 2.4 eq.).
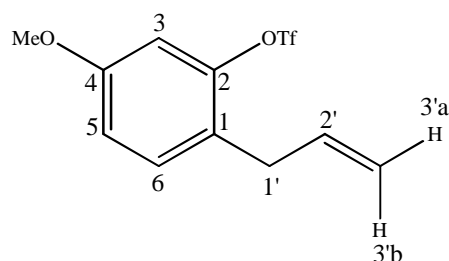
Yielded 1-allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**) as a dark red oil. Mass: 0.35 g; quantitative yield. R_f: 0.69 (H:A; 80:20) . ^{1}H NMR (600 MHz, CDCl$_3$) (plate 7a): δ 7.22 (1H, d, J = 8.57 Hz, H-6), 6.88 (1H, dd, J = 8.57, 2.56 Hz, H-5), 6.82 (1H, d, J = 2.56 Hz H-3), 5.93–5.87 (1H, m, H-2'), 5.14–5.08 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -O$\underline{Me}$), 3.41–3.40 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 7b): δ 159.25 (quaternary carbon), 148.16 (quaternary carbon), 135.22 (C-2'), 131.78 (C-6), 124.43 (quaternary carbon), 118.59 (q, J = 320.10 Hz, -OSO$_2$CF$_3$) 116.95 (C-3'), 115.54 (C-5), 107.34 (C-3), 55.67 (-O$\underline{Me}$), 33.33 (C-1'). MS (EI) m/z 296.00 (M$^+$, 64.10%), 135.10, (100.00), 105.05 (28.29), 103.05 (51.87), 91.05 (28.32).

6.9.2 1-Allyl-4-trifluoromethansulfonyloxy-3-methoxybenzene (**454**)

1-Allyl-4-hydroxy-3-methoxybenzene (**407**) (0.5 ml, 3.1 mmol, 1.0 eq.), DCM (20 ml), DMAP (0.45 g, 3.7 mmol, 1.2 eq.), trifluoromethanesulfonic anhydride (0.6 ml, 3.6 mmol, 1.2 eq.).
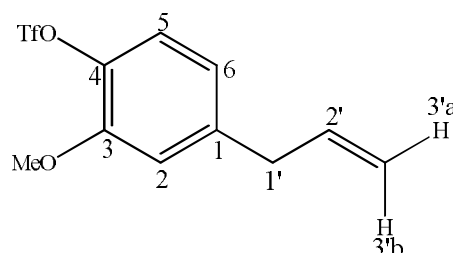
Yielded 1-allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**) as a light yellow oil. Mass: 0.74 g; 82% yield. R_f: 0.62 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 8a): δ 7.13 (1H, d, J = 8.3 Hz, H-5), 6.85 (1H, d, J = 1.9 Hz, H-2), 6.79 (1H, dd, J = 8.3, 1.9 Hz, H-6), 5.94 (1H, ddt, 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, -O$\underline{Me}$), 3.40 (2H, d, J = 6.7 Hz, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 8b): δ 151.30 (C-3), 141.92 (C-4), 137.23 (C-1), 136.42 (C-2'), 122.29 (C-5), 120.93 (C-6), 118.89 (q, J = 320.51 Hz, -OSO$_2$CF$_3$), 116.97 (C-3'), 113.45 (C-2), 56.22 (-O$\underline{Me}$), 40.15 (C-1'). ^{19}F NMR (565 MHz, CDCl$_3$) (plate 8f): δ -74.70 (-OSOC$\underline{F}_3$). MS (EI) m/z 296.10 (M$^+$, 32.46%), 163.10 (100.00), 107.10 (22.88).

6.9.3 1-Allyl-4-trifluoromethansulfonyloxy-3,5-dimethoxybenzene (**455**)

1-Allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) (0.5 ml, 3.1 mmol, 1.0 eq.), DCM (20 ml), DMAP (0.38 g, 3.1 mmol, 1.0 eq.), trifluoromethanesulfonic anhydride (0.5 ml, 3.1 mmol, 1.0 eq.).
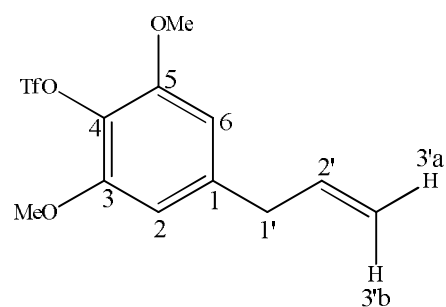
Yielded 1-allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**) as a *beige solid*. Mass: 0.72 g; 71% yield. R_f: 0.43 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 9a): δ 6.45 (2H, s, H-2 and H-6), 5.97–5.90 (1H, m, H-2'), 5.16–5.12 (2H, m, H-3'a and H-3'b), 3.87 (6H, s, -OMe), 3.37 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 9b): δ 152.32 (C-3 and C-5), 141.35 (C-1), 136.36 (C-2'), 126.41 (C-4), 118.05 (q, 320.57 Hz, -OSO$_2$CF$_3$), 117.02 (C-3'), 105.16 (C-2 and C-6), 56.34 (-OMe), 40.77 (C-1'). ^{19}F NMR (565 MHz, CDCl$_3$) (plate 9f): δ -76.90 (-OSOCF$_3$). MS (EI) *m/z* 326.99 (M$^+$, 13.21%), 193.05 (100.00), 133.05 (13.55).

6.9.4 1-Allyl-2-trifluoromethansulfonyloxy-4,6-dimethoxybenzene (**456**)

1-Allyl-6-hydroxy-2,4-dimethoxybenzene (**403**) (0.2 ml, 1.1 mmol, 1.0 eq.), DCM (20 ml), DMAP (0.38 g, 3.1 mmol, 2.8 eq.), trifluoromethanesulfonic anhydride (0.3 ml, 1.8 mmol, 1.6 eq.).
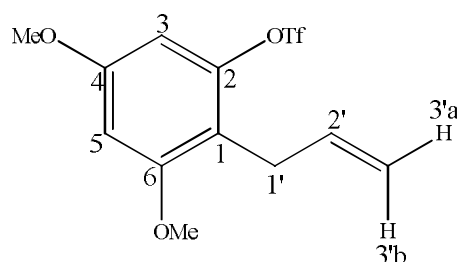
Yielded 1-allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**) as a light yellow oil. Mass: 0.16 g; 45% yield. R_f: 0.57 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 10a): δ 6.45 (1H, d, *J* = 2.3 Hz, H-3/5), 6.42 (1H, d, *J* = 2.3 Hz, H-3/5), 5.91–5.83 (1H, m, H-2'), 5.0–4.97 (2H, m, H-3'a and H-3'b), 3.82 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.39–3.37 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 10b): δ 159.54 (C-4/6), 159.43 (C-4/6) 148.74 (C-1/2), 134.98 (C-2'), 118.68 (q, *J* = 320.28 Hz, -OSO$_2$CF$_3$), 115.54 (C-3'), 114.34 (C-1/2), 98.48 (C-3/5), 98.12 (C-3/5), 56.11 (-OMe), 55.75 (-OMe), 27.89 (C-1'). ^{19}F NMR (565 MHz, CDCl$_3$) (plate 10f): δ -76.89 (-OSOCF$_3$). MS (EI) *m/z* 326.05 (M$^+$, 90.10%), 193.10 (100.00), 163.10 (22.17).

6.10 Standard Claisen Rearrangement

1-Allyloxybenzene was heated to reflux (*ca*. 193 ºC) in *N,N*-dimethylaniline (60 ml) for 8 hours where after the reaction mixture was quenched with cold HCl (40 ml, 32%) and extracted Et$_2$O (3 x 20 ml). The organic phase was washed with dH$_2$O (2 x 20 ml) and the solvent removed in *vacuo*.

6.10.1 1-Allyl-2-hydroxybenzene (**398**)

1-Allyloxybenzene (**397**) (0.40 g, 3.0 mmol, 1.0 eq.).

Yielded 1-allyl-2-hydroxybenzene (**398**) as a light yellow oil.
Mass: 0.08 g, 20% yield. R_f: 0.31 (H:A; 8:2). ^{1}H NMR (300
MHz, CDCl$_3$) (plate 11a): δ 7.28–7.19 (2H, m, Ar-H), 7.06–
7.98 (1H, m, Ar-H), 6.95–6.87 (1H, m, Ar-H), 6.14 (1H, ddt, J = 17.5, 9.6, 6.4 Hz, H-2'),
5.59 (1H, s, -OH), 5.30–5.21 (2H, m, H-3'a and H-3'b), 3.57–3.49 (1H, m, H-1').
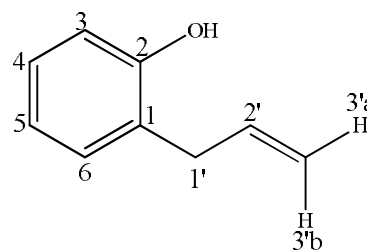
6.11 Standard Microwave Assisted Claisen Rearrangement

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

6.11.1 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**403**)

1-Allyloxy-3,5-dimethoxybenzene (**396**) (0.11 g, 0.6
mmol).

Yielded 1-allyl-2-hydroxy-4,6-dimethoxybenzene (**403**)
as a red-brown amorphous solid. Mass: 0.09 g, 88% yield. R_f: 0.31 (H:EtOAc; 90:10). ^{1}H
NMR (600 MHz, CDCl$_3$) (plate 12a): δ 6.11 (1H, d, J = 2.44 Hz, H-3/5), 6.08 (1H, d, J =
2.44 Hz, H-3/5), 6.00–5.93 (1H, m, H-2'), 5.25 (1H, br.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), 3.40–3.38 (2H, m, H-1'). ^{13}C NMR (151
MHz, CDCl$_3$) (plate 12b): δ 159.90 (quaternary carbon), 158.69 (quaternary carbon), 155.94
(quaternary carbons), 136.89 (C-2'), 115.41 (C-3'), 105.82 (quaternary carbon), 93.88 (C-3/5),
91.67 (C-3/5), 55.93 (-OMe), 55.34 (-OMe), 27.08 (C-1').   MS (EI) m/z 194.10 (M$^+$,
100.00%), 165.05 (39.29), 137.10 (34.91), 91.05 (10.49).
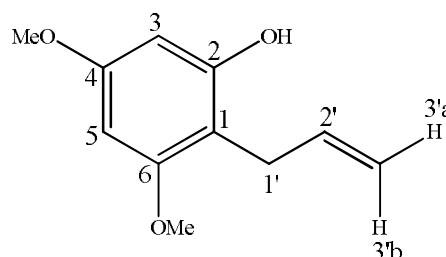
6.11.2 1-Allyl-2-hydroxy-4-methoxybenzene (**404**) and 1-allyl-2-hydroxy-6-methoxybenzene (**405**)

1-Allyloxy-3-methoxybenzene (**394**) (0.50 g, 3.1 mmol).

Yielded 1-allyl-2-hydroxy-4-methoxybenzene (**404**) as a light
yellow oil. Mass: 0.12 g, 44% yield. R_f: 0.54 (H:EtOAc;
90:10). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 13a): δ 7.01 (1H, d,
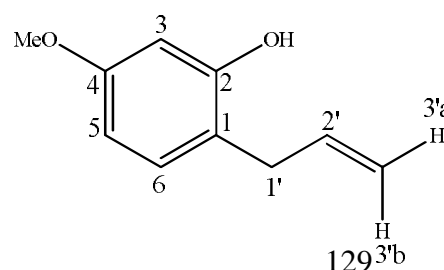
J = 8.33 Hz, H-6), 6.47 (1H, dd, J = 8.33, 2.54 Hz, H-5), 6.43 (1H, d, J = 2.54 Hz, H-3), 6.01 (1H, ddt, J = 16.92, 10.38, 6.36 Hz, H-2'), 5.23 (1H, br.s, -OH), 5.17–5.14 (1H, m, H-3'b), 5.14–5.13 (1H, m, H-3'a), 3.76 (3H, s, -O<u>Me</u>), 3.34–3.35 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 13b): δ 159.65 (quaternary carbon), 155.13 (quaternary carbon), 136.93 (C-2'), 130.98 (C-6), 117.53 (quaternary carbon), 116.36 (C-3'), 106.41 (C-5), 102.12 (C-3), 55.44 (-O<u>Me</u>), 34.64 (C-1'). MS (EI) m/z 164.15 (M$^+$, 100.00%), 149.10 (16.68), 137.10 (36.74), 121.10 (14.14).

Yielded 1-allyl-2-hydoxy-6-methoxybenzene (**405**) as a light yellow oil. Mass: 0.17 g; 45% yield. R$_f$: 0.60 (H:EtOAc; 9:1). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 14a): δ 7.08 (1H, dd, J = 8.10, 8.19 Hz, H-4), 6.51–6.50 (2H, m, H-3 and H-5), 5.99 (1H, ddt, J = 17.19, 10.14, 6.31 Hz, H-2'), 5.15 (1H, br.s, -OH), 5.13–5.07 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -OMe), 3.48–3.47 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 14b): δ 158.35 (C-2/6), 155.28 (C-2/6), 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'). MS (EI) m/z 164.10 (M$^+$, 100.00%), 149.10 (26.72), 135.10 (36.44), 121.10 (26.05), 107.10 (35.85).
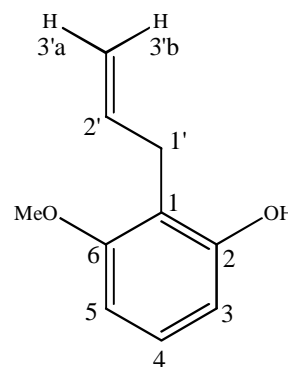
6.12 Ozonolysis: Reductive Work-up

- Method A

O$_3$ was bubbled through a stirred solution of allylbenzene (1.0 eq.) in dry DCM (100 ml) at -78 ℃ for 1 h with a flow rate of 10–200 g/Nm^3 at 0.5 MPa inlet pressure, where after DMS (2.2 eq.) was added slowly. The reaction mixture was left to reach rt. and the solvent removed *in vacuo*. The crude reaction mixture was purified *via* PLC.

6.12.1 <u>Attempted synthesis of 2'-methoxyphenylacetaldehyde (**430**)</u>

1-Allyl-2-methoxybenzene (**387**) (0.25 g, 1.7 mmol, 1.0 eq.), DCM (100 ml), O$_3$ (30 min.), DMS (0.3 ml, 4.1 mmol, 2.4 eq.).

Mixture of unidentifiable products obtained.

- Method B[6]

O$_3$ was bubbled through a stirred solution of allylbenzene (1.0 eq.) in MeOH (100 ml), at a starting temperature of -30 ℃ while gradually lowering the temperature to -78 ℃, at an O$_3$

flow rate of 10–200 g/Nm^3 and 0.5 MPa inlet pressure for 1 hour where after DMS (2.0 eq.) was added slowly. The reaction mixture was then stirred at -10 ºC for 1 h, 0 ºC for 1 h and at rt. for another hour. The product was extracted with petroleum ether and the solvent removed *in vacuo*. The crude reaction mixture was purified *via* PLC.

6.12.2 Attempted synthesis of phenylacetaldehyde

Allylbenzene (0.12 ml, 0.9 mmol, 1.0 eq.), MeOH (60 ml), O$_3$ (1 h), DMS (0.13 ml, 1.8 mmol, 2.0 eq.).

Mixture of unidentifiable products obtained.

- Method C[12,13]

A mixture of allylbenzene (1.0 eq.) in dry MeOH (50 ml) with Solvent Red 23 indicator (0.1% solution in MeOH, *ca.* 0.1 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 colour change from red to colourless) where after the mixture was purged with O$_2$ for 5–15 min. and DMS (2.2 eq.) added slowly. The reaction mixture was left to reach rt. and the solvent removed *in vacuo*. The crude reaction mixture was purified *via* PLC.

6.12.3 Attempted synthesis of 2'-methoxyphenylacetaldehyde (**430**)

1-Allyl-2-methoxybenzene (**387**) (0.2 ml, 1.3 mmol, 1.0 eq.), MeOH (50 ml), DMS (0.26 ml, 3.5 mmol, 2.7 eq.), O$_3$ (29.9–36.5 g/Nm^3, 20 min.).

- Method D[8]

A mixture of allylbenzene (1.0 eq.) and NMMO (3.0 eq.) in dry DCM (50 ml) was cooled to 0 ºC where after a stream of O$_3$ was bubbled through the solution at a flow rate of 10–200 g/Nm^3 and 0.5 MPa inlet pressure until the colour changed from orange to colourless. The reaction mixture was sparged with N$_2$ gas for 3 min. and allowed to warm to rt. where stirring continued for one hour. The crude reaction mixture was concentrated and purified *via* PLC.

6.12.4 Attempted synthesis of 4'-methoxyphenylacetaldehyde (**431**)

1-Allyl-4-methoxybenzene (**388**) (0.5 ml, 3.2 mmol, 1.0 eq.), NMMO (1.19 g, 10.2 mmol, 3.1 eq.), dry DCM (50 ml), O$_3$ (15 min., 51.7–59.4 g/Nm^3).

Yielded 4'-methoxybenzaldehyde (**428**) as a light yellow oil. Mass: 0.36 g; 82% yield. R_f: (H:A; 60:40). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 15a): δ 9.89 (1H, s, -C<u>H</u>O), 7.84 (2H, d, J = 6.77 Hz, H-2' and H-6'), 7.01 (2H, d, J = 6.77 Hz, H-3' and H-5'), 3.90 (3H, s, -O<u>Me</u>). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 15b): δ 191.09 (-<u>C</u>HO), 164.76 (C-4'), 132.16 (C-2' and C-6'), 130.07 (C-1'), 114.46 (C-3' and C-5'), 55.74 (-O<u>Me</u>).
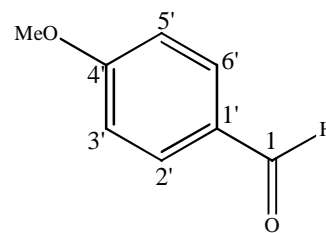
- Method E[8]

A mixture of allylbenzene (1.0 eq.) and NMMO (3.0 eq.) in dry DCM (20 ml) was cooled to 0 ºC where after a stream of O$_3$ was introduced above the solution for 10 min. at a flow rate of 10–200 g/Nm^3 and 0.5 MPa inlet pressure. The reaction mixture was sparged with O$_2$ for 2 min. and allowed to warm to rt. where stirring continued for 2 hrs. The crude reaction mixture was concentrated and purified *via* PLC.

6.12.5   Attempted synthesis of 2'-methoxyphenylacetaldehyde (**430**)

1-Allyl-2-methoxybenzene (**387**) (0.2 ml, 1.3 mmol, 1.0 eq.), NMMO (0.49 g, 4.2 mmol, 3.2 eq.), DCM (20 ml), O$_3$ (90.7–95.0 g/Nm^3, 10 min.).

Mixture of unidentifiable products obtained.

- Method F[10]

To a solution of allylbenzene (1.0 eq.) in dry DCM (50 ml) was added NMMO (3.0 eq.). The reaction mixture was cooled to 0 °C and a stream of O$_3$ with a flow rate of 40–150 g/Nm^3 and 0.5 MPa inlet pressure was introduced above the solution while vigorously stirring for 6–8 min. Subsequently, N$_2$ gas was blown over the solution for 2 min. where after the reaction mixture was allowed to reach rt. Absence of the ozonide was confirmed by TLC and the solvent removed *in vacuo*.

6.12.6   2'-Methoxyphenylacetaldehyde (**430**)

1-Allyl-2-methoxybenzene (**387**) (0.2 ml, 1.3 mmol, 1.0 eq.), DCM (50 ml), NMMO (0.48 g, 4.1 mmol, 3.2 eq.), O$_3$ (34.7–66.8 g/Nm^3, 8 min.).
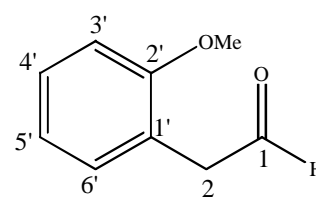
Yielded 2'-methoxyphenylacetaldehyde (**430**) as a yellow oil. Mass: 0.12 g; 58% yield. R_f: 0.41 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 16a): δ

9.68 (1H, t, J = 2.13 Hz, -C$\underline{H}$O), 7.32–7.29 (1H, m, H-4'), 7.16–7.15 (1H, m, H-6'), 6.97–6.94 (1H, m, H-5'), 6.92–6.91 (1H, m, H-3'), 3.83 (3H, s, -O$\underline{Me}$), 3.65 (2H, d, J = 2.13 Hz, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 16b): δ 200.43 (-$\underline{C}$HO), 157.82 (C-2'), 131.42 (C-6'), 129.23 (C-4'), 121.55 (C-1'), 120.85 (C-5'), 110.55 (C-3'), 55.61 (-O$\underline{Me}$), 45.75 (C-2). MS (EI) m/z 150.10 (M$^+$, 36.30%), 121.10 (68.01), 91.05 (100.00), 77.05 (14.23).

6.12.7 4'-Methoxyphenylacetaldehyde (**431**)

1-Allyl-4-methoxybenzene (**388**) (0.2 ml, 1.3 mmol, 1.0 eq.), DCM (50 ml), NMMO (0.48 g, 4.1 mmol, 3.2 eq.), O$_3$ (40.7–45.6 g/Nm^3, 6 min.).
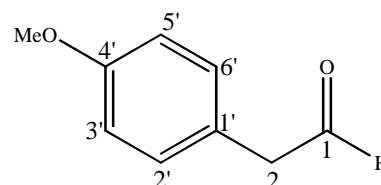
Yielded 4'-methoxyphenylacetaldehyde (**431**) as a yellow oil. Mass: 0.18 g; 88% yield. R$_f$: 0.35 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 17a): δ 9.89 (1H, s, -C$\underline{H}$O), 7.85 (2H, d, J = 8.83 Hz, H-2' and H-6'), 7.01 (2H, d, J = 8.83 Hz, H-3' and H-5'), 3.90 (3H, s, -O$\underline{Me}$), 3.79 (2H, s, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 17b): δ 191.26 (-$\underline{C}$HO), 164.87 (C-4'), 132.11(C-2' and C-6'), 130.80 (C-1'), 114.59 (C-3' and C-5'), 55.69 (-O$\underline{Me}$), 55.26 (C-2). MS (EI) m/z 150.10 (M$^+$, 15.77%), 121.10 (100.00), 77.05 (18.68).

6.12.8 3',4'-Dimethoxyphenylacetaldehyde (**432**) and 3',4'-dimethoxybenzaldehyde (**433**)

1-Allyl-3,4-dimethoxybenzene (**390**) (0.2 ml, 1.2 mmol, 1.0 eq.), DCM (50 ml), NMMO (0.39 g, 3.3 mmol, 2.9 eq.), O$_3$ (29.9–36.5 g/Nm^3, 6 min.).
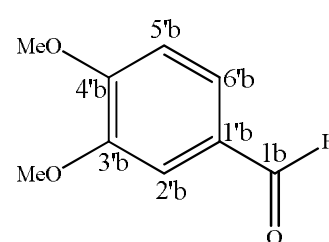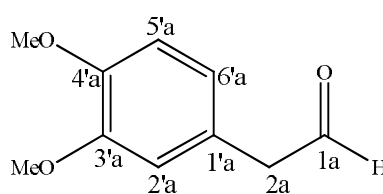
Yielded 3',4'-dimethoxyphenylacetaldehyde (**432**) and 3',4'-dimethoxybenzaldehyde (**433**) as an orange-yellow oil mixture. Mass: 0.05 g; 24% yield. R$_f$: 0.55 (H:A; 60:40). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 18a): δ 9.85 (1H, s, -C$\underline{H}$O[b]), 9.72 (2H, t, J = 2.29 Hz, -C$\underline{H}$O[a]), 7.46 (1H, dd, J = 8.11, 1.86 Hz, H-6'b), 7.41 (1H, d, J = 1.86 Hz, H-2'b), 6.98 (1H, d, J = 8.11 Hz, H-5'b), 6.86 (2H, d, J = 8.11 Hz, H-5'a), 6.77 (2H, dd, J = 8.11, 2.04 Hz, H-6'a), 6.70 (2H, d, J = 2.04 Hz, H-2'a), 3.97 (3H, s, -O$\underline{Me}$ [b]), 3.95 (3H, s, -O$\underline{Me}$ [b]), 3.88–3.87 (12H, m, -OMe [a]), 3.63 (4H, d, J = 2.29 Hz, H-2a). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 18b): δ 199.93 (-$\underline{C}$HO [a]), 191.13 (-$\underline{C}$HO [b]), 154.86 (quaternary carbon), 149.75 (quaternary carbon), 149.58 (quaternary carbon), 148.71 (quaternary carbon), 130.22

(quaternary carbon), 127.14 (C-6'b), 124.06 (quaternary carbon), 122.12 (C-6'a), 112.68 (C-2'a), 111.56 (C-5'a), 110.68 (C-5'b), 108.92 (C-2'b), 56.43 (-OMe), 56.02 (-OMe), 50.30 (C-2a). MS (EI) *m/z* [a] 180.05 (M$^+$, 23.99%), 151.10 (100.00), 107.05 (15.46). MS (EI) *m/z* [b] 166.05 (M$^+$, 100.00%), 151.00 (13.36).

6.12.9 <u>Attempted synthesis of 3',4',5'-trimethoxyphenylacetaldehyde</u>

1-Allyl-3,4,5-trimethoxybenzene (**391**) (0.20 g, 1.0 mmol, 1.0 eq.), DCM (50 ml), NMMO (0.34 g, 2.9 mmol, 3.0 eq.), O$_3$ (40.9–53.6 g/Nm^3, 8 min.).

Mixture of unidentifiable products obtained.

6.12.10 <u>Attempted synthesis of 2',4',6'-trimethoxyphenylacetaldehyde</u>
1-Allyl-2,4,6-trimethoxybenzene (**392**) (0.27 g, 1.3 mmol, 1.0 eq.), DCM (50 ml), NMMO (0.35 g, 3.0 mmol, 2.3 eq.), O$_3$ (47.4–49.2 g/Nm^3, 8 min.).

Mixture of unidentifiable products obtained.

6.12.11 <u>Attempted synthesis of 4'-hydroxy-3',5'-dimethoxyphenylacetaldehyde</u>
1-Allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) (0.18 ml, 1.0 mmol, 1.0 eq.), DCM (50 ml), NMMO (0.37 g, 3.2 mmol, 3.2 eq.), O$_3$ (54.6–56.3 g/Nm^3, 6 min.).

Mixture of unidentifiable products obtained.

6.12.12 <u>Attempted synthesis of 2'-trifluoromethanesulfonyloxy-4'-methoxyphenyl-acetaldehyde (453)</u>
1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**) (0.07 g, 0.2 mmol, 1.0 eq.), DCM (20 ml), NMMO (0.24 g, 2.0 mmol, 8.3 eq.), O$_3$ (88.1–111.2 g/Nm^3, 10 min.).

Yielded 2'-trifluoromethanesulfonyloxy-4'-methoxybenzaldehyde (**452**) as a light yellow oil. Mass: 0.01 g, 14% yield. R$_f$: 0.33 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 19a): δ 10.12 (1H, s, -C<u>H</u>O), 7.94 (1H, d, *J* = 8.71 Hz, H-6'), 7.02 (1H, dd, *J* = 8.71, 2.40 Hz, H-5'), 6.87 (1H, d, *J* = 2.40 Hz, H-3'), 3.92 (3H, s, -O<u>Me</u>) . ^{13}C NMR (151 MHz, CDCl$_3$) (plate 19b): δ 185.49 (-<u>C</u>HO), 165.47 (C-4'), 151.43 (C-1'), 132.40 (C-6'), 121.93 (C-2'), 118.70 (q, *J* = 319.69 Hz, -OSO<u>C</u>F$_3$), 114.35 (C-5'), 108.35 (C-3'), 56.39 (-O<u>Me</u>). ^{19}F NMR (565 MHz, CDCl$_3$) (plate 19f): δ -75.89 (-OSOC<u>F</u>$_3$). MS (EI) *m/z* 283.95 (M$^+$, 100.00%), 151.05 (79.34), 134.05 (26.28), 65.05 (21.02).
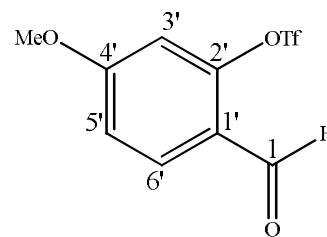
6.12.13 <u>Attempted synthesis of 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl-acetaldehyde (**462**)</u>

1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**) (0.08 g, 0.27 mmol, 1.0 eq.), DCM (20 ml), NMMO (0.11 g, 0.94 mmol, 3.5 eq.), O_3 (88.1–111.2 g/Nm^3, 6 min.).

Yielded 4'-trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**) as a light yellow oil. Mass: 0.03 g, 33% yield. R_f: 0.29 (H:A; 80:20). ^{1}H NMR (600 MHz, CO(CD$_3$)$_2$) (plate 20a): δ 10.07 (1H, s, -C<u>H</u>O), 7.79 (1H, d, J = 1.8 Hz, H-2'), 7.71 (1H, dd, J = 8.3, 1.8 Hz, H-6'), 7.67 (1H, d, J = 8.3 Hz, H-5'), 4.09 (3H, s, -O<u>Me</u>). ^{13}C NMR (151 MHz, CO(CD$_3$)$_2$) (plate 20b): δ 192.03 (-<u>C</u>HO), 153.37 (C-3'), 143.59 (C-4'), 138.83 (C-1'), 124.64 (C-5'/6'), 124.53 (C-5'/6'), 119.00 (q, J = 319.10 Hz, -OSO<u>C</u>F$_3$), 114.16 (C-2'), 57.58 (-O<u>Me</u>). ^{19}F NMR (565 MHz, CDCl$_3$) (plate 20f): δ -77.28 (-OSOC<u>F</u>$_3$). MS (EI) m/z 284.00 (M$^+$, 60.46%), 151.10 (100.00), 95.10 (83.53).
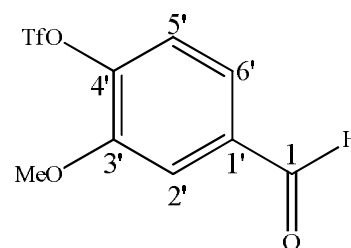
6.12.14 <u>Attempted synthesis of 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl-acetaldehyde (**463**)</u>

1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**) (0.15 g, 0.5 mmol, 1.0 eq.), DCM (20 ml), NMMO (0.21 g, 1.8 mmol, 3.6 eq.), O_3 (88.1–111.2 g/Nm^3, 5 min.).

Yielded 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxy-benzaldehyde (**461**) as a light yellow solid. Mass: 0.07 g, 53% yield. R_f: 0.23 (H:A; 80:20). ^{1}H NMR (600 MHz, CO(CD$_3$)$_2$) (plate 21a): δ 10.03 (1H, s, -C<u>H</u>O), 7.44 (1H, s, H-2' and H-6'), 4.07 (3H, s, -O<u>Me</u>). ^{13}C NMR (151 MHz, CO(CD$_3$)$_2$) (plate 21b): δ 191.72 (-<u>C</u>HO), 153.96 (C-3' and C-5'), 137.64 (C-1'), 132.29 (C-4'), 114.58 (q, J = 319.61 Hz, -OSO<u>C</u>F$_3$), 106.91 (C-2' and C-6'), 57.35 (-O<u>Me</u>). ^{19}F NMR (565 MHz, CO(CD$_3$)$_2$) (plate 21f): δ -74.87 (-OSOC<u>F</u>$_3$). HR-MS (ESI) m/z 336.9966 (M$^+$ + Na).
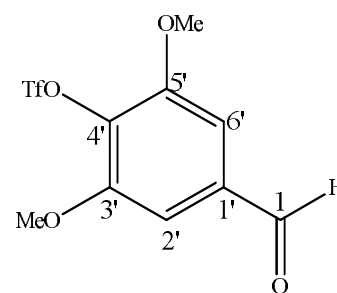
6.12.15 <u>2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)</u>

1-Allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**) (0.21 g, 0.6 mmol, 1.0 eq.), DCM (20 ml), NMMO (0.22 g, 1.9 mmol, 3.1 eq.), O_3 (88.1–111.2 g/Nm^3, 5 min.).
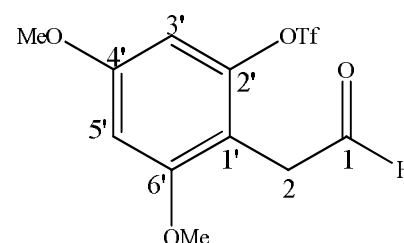
Yielded 2'-trifluoromethanesulfonyloxy-4',6'-

dimethoxyphenylacetaldehyde (**457**) as a *yellow oil*. Mass: 0.15 g, 71% yield. R_f : 0.34 (H:A; 80:20). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 22a): δ 9.61 (1H, t, J = 1.4 Hz, -C<u>H</u>O), 6.49 (1H, d, J = 2.3 Hz, H-3'/5'), 6.48 (1H, d, J = 2.3 Hz, H-3'/5'), 3.82 (3H, s, -O<u>Me</u>), 3.81 (3H, s, -O<u>Me</u>), 3.67 (2H, d, J = 1.4 Hz, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 22b): δ 198.13 (-<u>C</u>HO), 160.70 (C-4'/6'), 159.61 (C-4'/6'), 148.89 (C-2'), 118.61 (q, J = 320.19 Hz, -OSO<u>C</u>F$_3$), 107.67 (C-1'), 98.64 (C-3'/5'), 98.43 (C-3'/5'), 56.20 (-O<u>Me</u>), 55.86 (-O<u>Me</u>), 38.71 (C-2). ^{19}F NMR (565 MHz, CDCl$_3$) (plate 22f): δ -76.76 (-OSOC<u>F</u>$_3$). HR-MS (ESI) *m/z* 351.0131 (M$^+$ + Na).

- Method G

To a stirred solution of allylbenzene (1.0 eq.) in dry MeOH (30 ml), O$_3$ was bubbled at -78 ℃ for 1–5 min. (resulting in a blue reaction mixture) at a flow rate of 10–200 g/Nm^3 and 0.5 MPa inlet pressure, where after DMS (1.0 eq.) was added slowly. The reaction mixture was allowed to reach rt. The product was extracted with Et$_2$O (40 ml) and saturated NaHCO$_3$ solution (40 ml x 2) with subsequent washing of the organic phase with dH$_2$O (40 ml). The crude reaction mixture was purified *via* PLC.

6.12.16 2'-Trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**)

1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**) (0.08 g, 0.3 mmol, 1.0 eq.), MeOH (20 ml), O$_3$ (62.4–73.9 g/Nm^3, 3 min.), DMS (0.1 ml, 1.4 mmol, 5.3 eq.).
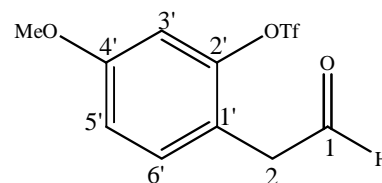
Yielded 2'-trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**) as a light yellow oil. Mass: 0.05 g, 63% yield. R_f : 0.51 (H:EtOAc; 90:10). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 23a): δ 9.73 (1H, t, J = 1.5 Hz, -C<u>H</u>O), 7.21 (1H, d, J = 8.55 Hz, H-6'), 6.93 (1H, dd, J = 8.55, 2.54 Hz, H-5'), 6.88 (1H, d, J = 2.54 Hz, H-3'), 3.83 (3H, s, -O<u>Me</u>), 3.76 (2H, m, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 23b): δ 197.30 (-<u>C</u>HO), 160.23 (C-2'/4'), 148.46 (C-2'/4'), 132.76 (C-6'), 118.42 (q, J = 316.42 Hz, -OSO$_2$<u>C</u>F$_3$), 117.05 (C-1'), 114.46 (C-5'), 107.86 (C-3'), 55.76 (-OMe), 43.99 (C-2). MS (EI) *m/z* 298.90 (M$^+$, 2.47%), 268.95 (100.00), 136.05 (45.14).

6.12.17 <u>3-(4'-Trifluoromethanesulfonyloxy-3'-methoxybenzyl)-1,2,4-trioxolane (**462**)</u>

1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**) (0.19 g, 0.6 mmol, 1.0 eq.), MeOH (30 ml), O_3 (90.0–93.2 g/Nm^3, 4 min.), DMS (0.1 ml, 1.4 mmol, 2.3 eq.).
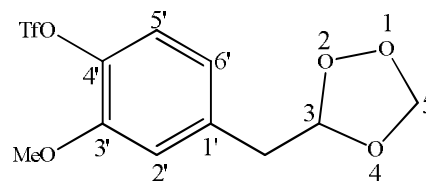
Yielded 3-(4'-trifluoromethanesulfonyloxy-3'-methoxybenzyl)-1,2,4-trioxolane (**462**) as a colourless oil. Mass: 0.07 g, 32% yield. R_f: 0.27 (H:EtOAc:Et$_3$N; 90:10:1). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 24a): δ 7.16 (1H, d, J = 8.4 Hz, H-5'), 6.94 (1H, d, J = 1.9 Hz, H-2'), 6.87 (1H, dd, J = 8.4, 1.9 Hz, H-6'), 5.36 (1H, t, J = 4.9 Hz, H-3), 5.16 (1H, s, H-5), 5.07 (1H, s, H-5), 3.91 (3H, s, -O<u>Me</u>), 3.06 (1H, dd, J = 14.76, 4.83 Hz, -C<u>H</u>$_2$-), 3.03 (1H, dd, J = 14.76, 4.83 Hz, -C<u>H</u>$_2$-). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 24b): δ 151.34 (C-3'), 137.95 (C-1'), 136.28 (C-4'), 122.43–122.19 (C-5' and C-6'), 119.90 (-O<u>Tf</u>), 114.70 (C-2'), 102.99 (C-3), 94.35 (C-5), 56.30 (-O<u>Me</u>), 38.41 (-<u>C</u>H$_2$-). MALDI-TOF m/z 346.43 (M$^+$, 100.00%). MS (EI) m/z 298.05 (M$^+$ - OCH$_2$, 38.80%), 165.10 (M$^+$ - OTf - OMe, 100.00), 137.10 (98.62).

6.12.18 <u>3-(4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzyl)-1,2,4-trioxolane (**463**)</u>

1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**) (0.26 g, 0.8 mmol, 1.0 eq.), MeOH (30 ml), O_3 (90.0–93.2 g/Nm^3, 4 min.), DMS (0.1 ml, 1.4 mmol, 1.8 eq.).
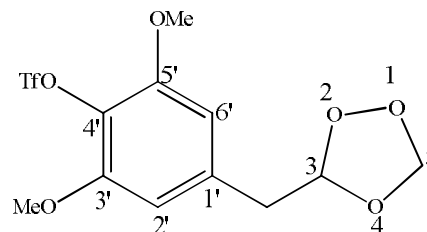
Yielded 3-(4'-trifluoromethanesulfonyloxy-3',5'-dimethoxybenzyl)-1,2,4-trioxolane (**463**) as a colourless oil. Mass: 0.09 g, 32% yield. R_f: 0.17 (H:EtOAc:Et$_3$N; 90:10:1). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 25a): δ 6.53 (2H, s, H-2' and H-6'), 5.36 (1H, t, J = 4.9 Hz, H-3), 5.18 (1H, s, H-5), 5.11 (1H, s, H-5), 3.89 (6H, s, -O<u>Me</u>), 3.01 (2H, m, -C<u>H</u>$_2$-). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 25b): δ 152.34 (C-3' and C-5'), 135.72 (C-1'/4'), 127.09 (C-1'/4'), 119.81 (-O<u>Tf</u>), 106.29 (C-2' and C-6'), 103.05 (C-3), 94.32 (C-5), 56.42 (-O<u>Me</u>), 39.05 (-<u>C</u>H$_2$-). MALDI-TOF m/z 346.43 (M$^+$ - OMe, 100.00%). MS (EI) m/z 328.05 (M$^+$ - OCH$_2$, 19.73%), 195.05 (M$^+$ - OTf - OMe, 100.00), 167.10 (84.41).

6.13 Mechanistic NMR Studies: Ozonolysis

- Study A

A solution of 1-allyl-4-methoxybenzene (**388**) (0.2 ml, 1.4 mmol, 1.0 eq.) in CHCl$_3$ was cooled to -78 °C where after 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 until it had acquired a blue colour. The reaction mixture was purged with oxygen for 5 min. NMR analyses (-50 °C and 20 °C) were conducted on an aliquot of reaction mixture (0.4 ml) in CDCl$_3$ (0.4 ml) prepared at -78 °C.

Yielded 3-(4'-methoxybenzyl)-1,2,4-trioxolane (**437**)

3-(4'-methoxybenzyl)-1,2,4-trioxolane

+

4'-methoxyphenylacetaldehyde

^{1}H NMR (600 MHz, CDCl$_3$, -50 °C) (plate 26a): δ 7.19 (2H, d, J = 8.60 Hz, H-2'a and H-6'a), 6.87 (2H, d, J = 8.60 Hz, H-3'a and H-5'a), 5.30 (1H, dd, J = 5.1, 5.1 Hz, H-3a), 5.21 (1H, s, H-5a), 5.06 (1H, s, H-5a), 3.80 (3H, s, -OMe), 3.01 (1H, dd, J = 14.56, 5.06 Hz , -C$\underline{H}_2$-), 2.97 (1H, dd, J = 14.56, 5.06 Hz, -C$\underline{H}_2$-).^{13}C NMR (151 MHz, CDCl$_3$, -50 °C) (plate 26b): δ 158.19 (C-4'a), 130.85 (C-2'a and C-6'a), 126.10 (C-1'a), 113.69 (C-3'a and C-5'a), 103.60 (C-3a), 94.28 (C-5a), 55.34 (-O$\underline{Me}$), 37.05 (-$\underline{C}$H$_2$-).
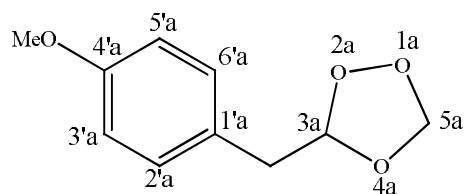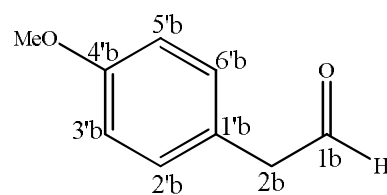
and 4'-methoxyphenylacetaldehyde (**431**)

^{1}H NMR (600 MHz, CDCl$_3$, -50 °C) (plate 26a): δ 9.74 (1H, t, J = 2.17 Hz, -C$\underline{H}$O), 7.15 (2H, d, J = 8.44 Hz, H-2'b and H-6'b), 6.92 (2H, d, J = 8.44 Hz, H-3'b and H-5'b), 3.82 (3H, s, -O$\underline{Me}$), 3.72 (2H, d, J = 2.17 Hz, H-2b).

- Study B

A mixture of 1-allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) (0.2 ml, 1.01 mmol, 1.0 eq.) in CHCl$_3$ was cooled to -78 °C where after 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 until it had acquired a blue colour. The reaction mixture was purged with oxygen for 5 min. NMR analyses (-50 °C and 20 °C) were conducted on an aliquot of reaction mixture (0.4 ml) in CDCl$_3$ (0.4 ml) prepared at -78 °C.

A mixture of unidentifiable products was obtained.

6.14 Ozonolysis: Oxidative workup

- Method A

A mixture of allylbenzene (1.0 eq.) and dry DCM (100 ml) was cooled to -78 °C. 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 solution for 30 min. where after the reaction mixture was thoroughly purged with N_2 gas. 30% H_2O_2 (excess) was added and the reaction mixture allowed to warm to rt. MeOH (100 ml) and PTSA (catalytic) were added with subsequent reflux for 1 h. The product was extracted into EtOAc (100 ml x 3) with an aq. NaHCO$_3$ solution (50 ml) where after the organic layer was washed with dH$_2$O (50 ml x 2). The organic phase was concentrated with subsequent PLC purification.

6.14.1 Attempted synthesis of methyl 2'-hydroxyphenyl acetate
1-Allyl-2-hydroxybenzene (**398**) (0.22 g, 1.6 mmol, 1.0 eq), DCM (100 ml), O_3 (30 min.), H_2O_2 (0.2 ml, 6.5 mmol, 4.1 eq.), MeOH (100 ml), PTSA (0.01 g, 0.1 mmol, 0.1 eq.).

Mixture of unidentifiable products obtained.

- Method B[11]

A mixture of allylbenzene (1.0 eq.) in DCM (15 ml) and methanolic NaOH (40 ml, 2.5 M) was cooled to -78 ºC where after a stream of O_3 with a flow rate of 10–200 g/Nm^3 and 0.5 MPa inlet pressure was passed through the reaction mixture until the initially yellow colour changed to blue and a yellow precipitate had formed. The reaction mixture was diluted with dH$_2$O and Et$_2$O, allowed to reach rt. and extracted into Et$_2$O. The organic layer was dried and the solvent removed under reduced pressure.

6.14.2 Attempted synthesis of methyl 4'-hydroxy-3',5'-dimethoxyphenyl acetate
1-Allyl-4-hydroxy-3,5-dimethoxybenzene (**408**) (0.18 ml, 1.0 mmol, 1.0 eq.), DCM (15 ml), methanolic NaOH (40 ml).

Yielded 4-allyl-4-hydroxy-2,6-dimethoxycyclohexan-2,5-dienone (**470**) as a yellow-orange oil. Mass: 0.13 g, 57% yield. R$_f$: 0.53 (B:A:M; 60:30:10). ^{1}H NMR (300 MHz, CDCl$_3$) (plate 28a): δ 5.44 (2H, s, H-3 and
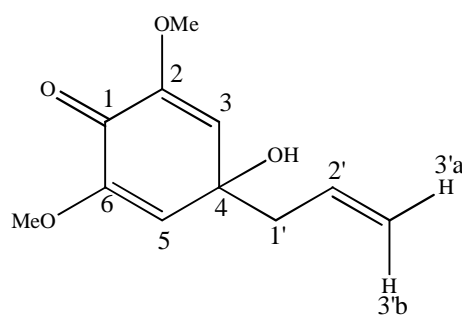
H-5), 5.43–5.31 (1H, m, H-2'), 5.06–5.02 (1H, m, H-3'b), 5.01–4.96 (1H, m, H-3'a), 3.77 (6H, s, -OMe), 2.95 (1H, s, -OH), 2.78–2.72 (2H, m, H-1'). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 28b): δ 187.22 (C-1), 170.62 (C-2 and C-6), 130.60 (C-2'), 119.17 (C-3'), 101.04 (C-3 and C-5), 72.70 (C-4), 56.13 (-OMe), 42.51 (C-1'). MALDI-TOF m/z 210.05 (M$^+$, 100.00%).

- Method C^{12}

A mixture of allylbenzene (1.0 eq.) in dry MeOH (50 ml) was cooled to -78 ºC under Ar. A stream O$_3$ of 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 reaction mixture) where after the mixture was purged with O$_2$ for 5–15 minutes. The reaction mixture was allowed to warm to rt. over 2 hrs. where after the solvent was removed *in vacuo*. The crude reaction material was then dissolved in dry DCM (30 ml) and cooled to 0 ºC with subsequent addition of Et$_3$N (2.0 eq.) and Ac$_2$O (8.0 eq.). The reaction mixture was stirred at 0 ºC for 30 min. and then for 21 hrs. at rt. MeOH (2.5 ml) was added and the reaction mixture stirred for 10–20 min. with subsequent addition of Et$_2$O (40 ml). The product was extracted into Et$_2$O with a saturated aq. NaHCO$_3$ solution (40 ml x 2) and washed with dH$_2$O (40 ml x 1). The organic phase was dried over Na$_2$SO$_4$ and the solvent removed under reduced pressure. The product was purified *via* PLC.

6.14.3 Methyl 2'-methoxyphenyl acetate (**480**)

1-Allyl-2-methoxybenzene (**387**) (0.21 ml, 1.4 mmol, 1.0 eq.), dry MeOH (50 ml), O$_3$ (14.7–15.5 g/Nm^3, 11 min.), dry DCM (20 ml), Ac$_2$O (1.02 ml, 11.0 mmol, 8.0 eq.), Et$_3$N (0.38 ml, 2.7 mmol, 2.0 eq).
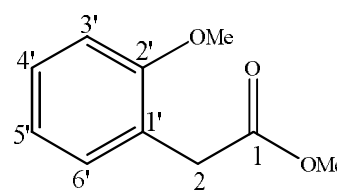
Yielded methyl 2'-methoxyphenyl acetate (**480**) as a light yellow oil. Mass: 0.22 g, 91% yield. R$_f$: 0.59 (B:A:MeOH; 60:30:10). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 29a): δ 7.29–7.26 (1H, m, H-4'), 7.20–7.19 (1H, m, H-6'), 6.94–6.92 (1H, m, H-5'), 6.89–6.88 (1H, m, H-3'), 3.82 (3H, s, -O<u>Me</u>), 3.70 (3H, s, -COO<u>Me</u>), 3.65 (2H, s, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 29b): δ 172.42 (C-1), 157.58 (C-2'), 130.95 (C-6'), 128.67 (C-4'), 123.07 (C-1'), 120.59 (C-5'), 110.56 (C-3'), 55.52 (-O<u>Me</u>), 51.98 (-COO<u>Me</u>), 35.83 (C-2). MS m/z 180.10 (M$^+$, 46.86%), 148.10 (12.44), 121.10 (100.00), 91.10 (83.99).

6.14.4 Methyl 4'-methoxyphenyl acetate (**481**)

1-Allyl-4-methoxybenzene (**388**) (0.21 ml, 1.4 mmol, 1.0 eq.), dry MeOH (50 ml), O_3 (63.0–72.5 g/Nm^3, 5 min.), dry DCM (20 ml), Ac_2O (1.5 ml, 15.9 mmol, 11.4 eq.), Et_3N (1 ml, 7.2 mmol, 5.1 eq.).
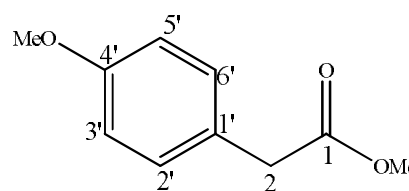
Yielded methyl 4'-methoxyphenyl acetate (**481**) as an orange oil. Mass: 0.07 g, 32% yield. R_f : 0.49 (H:A; 70:30). ^{1}H NMR (300 MHz, CDCl$_3$) (plate 30a): δ 7.20 (2H, d, J = 8.76 Hz, H-2' and H-6'), 6.86 (2H, d, J = 8.76 Hz, H-3' and H-5'), 3.79 (3H, s, -O$\underline{Me}$), 3.68 (3H, s, -COO$\underline{Me}$), 3.57 (2H, s, H-2). MS (EI) m/z 180.05 (M$^+$, 22.99%), 121.10 (100.00), 77.05 (9.36).

6.14.5 Methyl 4'-trifluoromethylphenyl acetate (**482**)

1-Allyl-4-trifluoromethylbenzene (**472**) (0.2 ml, 1.2 mmol, 1.0 eq.), dry MeOH (50 ml), O_3 (56.3–56.4 g/Nm^3, 15 min.), dry DCM (20 ml), Ac_2O (0.8 ml, 8.5 mmol, 7.1 eq.), Et_3N (0.3 ml, 2.2 mmol, 1.8 eq).
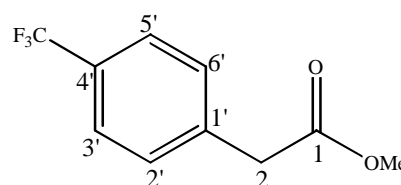
Yielded methyl 4'-trifluoromethylphenyl acetate (**482**) as an orange oil. Mass: 0.02 g, 9% yield. R_f : 0.66 (H:A; 60:40). ^{1}H NMR (300 MHz, CDCl$_3$) (plate 31a): δ 7.59 (2H, d, J = 8.21 Hz, H-3' and H-5'), 7.40 (2H, d, J = 8.21 Hz, H-2' and H-6'), 3.71 (3H, s, -COO$\underline{Me}$), 3.69 (2H, s, H-2). MS (EI) m/z 217.10 (M$^+$, 37.85%), 160.10 (100.00), 145.10 (16.26).

6.14.6 Attempted synthesis of methyl 3',4',5'-trimethoxyphenyl acetate

1-Allyl-3,4,5-trimethoxybenzene (**391**) (0.2 g, 1.0 mmol, 1.0 eq.), dry MeOH (50 ml), O_3 (35.2–42.2 g/Nm^3, 10 min.), dry DCM (20 ml), Ac_2O (2 ml, 21.2 mmol, 22.1 eq.), Et_3N (4 ml, 28.7 mmol, 29.8 eq.).

Mixture of unidentifiable products obtained.

6.14.7 Attempted synthesis of methyl 2',4',6'-trimethoxyphenyl acetate

1-Allyl-2,4,6-trimethoxybenzene (**392**) (0.50 g, 2.4 mmol, 1.0 eq.), dry MeOH (50 ml), O_3 (49.8–51.0 g/Nm^3, 20 min.), dry DCM (20 ml), Ac_2O (2 ml, 21.2 mmol, 8.8 eq.), Et_3N (4 ml, 28.7 mmol, 12.0 eq).

Mixture of unidentifiable products obtained.

6.14.8 Methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate (**483**)

1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxy benzene (**454**) (0.21 g, 0.71 mmol, 1.0 eq.), dry MeOH (30 ml), O_3 (67.4–72.5 g/Nm^3, 4 min.), dry DCM (20 ml), Ac_2O (0.51 ml, 5.4 mmol, 7.6 eq.), Et_3N (0.2 ml, 1.43 mmol, 2.0 eq).
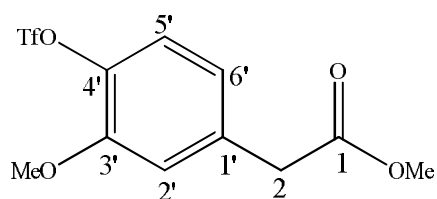
Yielded methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate (**483**) as a yellow oil. Mass: 0.02 g, 9% yield. R_f : 0.14 (H:EtOAc:Et$_3$N; 90:10:1). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 32a): δ 7.16 (1H, d, J = 8.3 Hz, H-5'), 6.98 (1H, d, J = 2.0 Hz, H-2'), 6.88 (1H, dd, J = 8.3, 2.0 Hz, H-6'), 3.91 (3H, s, -O$\underline{Me}$), 3.72 (3H, s, -COO$\underline{Me}$), 3.63 (2H, s, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 32b): δ 171.38 (C-1), 151.41 (C-3'), 137.99 (C-1'), 135.57 (C-4'), 122.52 (C-5'), 121.83 (C-6'), 117.78 (q, J = 319.92 Hz, -OSO$_2$CF$_3$), 114.30 (C-2'), 56.33 (-O$\underline{Me}$), 52.43 (-COO$\underline{Me}$), 41.01 (C-2). MS m/z 328.15 (M$^+$, 30.21%), 195.10 (100.00), 135.10 (16.47).

6.14.9 Methyl 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl acetate (**484**)

1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxy benzene (**455**) (0.11 g, 0.34 mmol, 1.0 eq.), dry MeOH (30 ml), O_3 (84.3–92.5 g/Nm^3, 2 min.), dry DCM (20 ml), Ac_2O (0.46 ml, 4.88 mmol, 14.3 eq.), Et_3N (0.17 ml, 1.2 mmol, 3.5 eq).
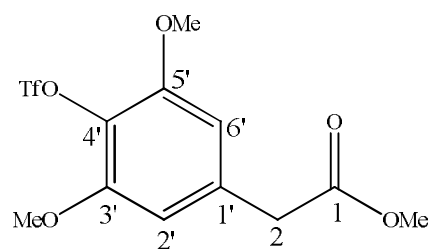
Yielded methyl 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl acetate (**484**) as a yellow oil. Mass: 0.02 g, 17% yield. R_f : 0.11 (H:EtOAc:Et$_3$N; 90:10:1). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 33a): δ 6.55 (2H, s, H-2' and H-6'), 3.88 (6H, s, -O$\underline{Me}$), 3.72 (3H, s, -COO$\underline{Me}$), 3.59 (2H, s, H-2). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 33b): δ 171.37 (C-1), 152.43 (C-3' and C-5'), 134.94 (C-1'), 127.19 (C-4'), 118.93 (q, J = 320.19 Hz, -OSO$_2$$\underline{C}F_3$), 106.10 (C-2' and C-6'), 56.43 (-O$\underline{Me}$), 52.46 (-COO$\underline{Me}$), 41.65 (C-2). MS m/z 358.05 (M$^+$, 14.64%), 225.00 (100.00), 148.05 (17.68).

6.14.10 Methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate (485) and 2'- trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (457)

1-Allyl-4,6-dimethoxy-2-trifluoromethanesulfonyloxybenzene (456) (0.19 g, 0.58 mmol, 1.0 eq.), dry MeOH (30 ml), O_3 (79.2–80.4 g/Nm^3, 6 min.), dry DCM (20 ml), Ac_2O (0.46 ml, 4.88 mmol, 8.4 eq.), Et_3N (0.17 ml, 1.2 mmol, 2.1 eq).

Yielded methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate (485) and 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (457) as a yellow oil mixture. Mass: 0.13 g, 65% yield. R_f : 0.34 (H:A; 70:30). ^{1}H NMR (600 MHz, CDCl$_3$) (plate 34a): δ 9.61 (2H, t, J = 1.4 Hz, -CHO), 6.49 (2H, d, J = 2.3 Hz, H-3'b/5'b), 6.48 (2H, d, J = 2.3 Hz, H-3'b/5'b), 6.46–6.45 (7H, m, H-3'a/5'a), 3.82 (6H, s, -OMe[b]), 3.82 (10H, s, -OMe[a]), 3.81 (6H, s, -OMe[b]), 3.81 (10H, s, -OMe[a]), 3.69 (10H, s,-COOMe), 3.67 (4H, d, J = 1.4 Hz, H-2b), 3.65 (7H, s, H-2a). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 34b): δ 198.16 (-CHO), 170.97–148.90 (quaternary carbons), 129.94 (q, J = 320.19 Hz, -OSO$_2$CF$_3$), 119.68 (q, J = 320.19 Hz, -OSO$_2$CF$_3$), 109.27–108.24 (quaternary carbons), 98.40 (C-3'a, C-5'a, C-3'b and C-5'b), 56.23–55.63 (-OMe), 52.24 (-COOMe), 38.74 (C-2b), 29.26 (C-2a). MS m/z [a] 358.05 (M$^+$, 32.60%), 299.00 (100.00), 138.10 (23.07). MS m/z [b] 328.05 (M$^+$, 22.29%), 299.00 (100.00), 138.10 (37.27).
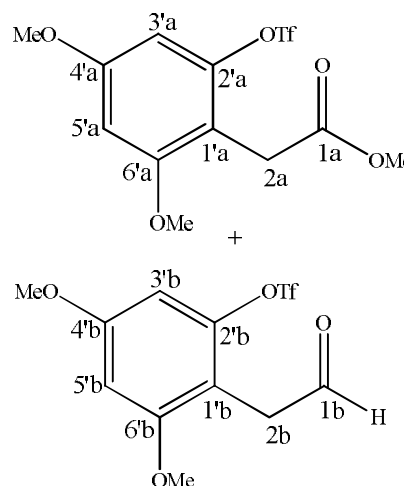
6.15 Ozonolysis: Oxidative Work-up with *N*-nucleophiles

- Method A[12]

A mixture of allylbenzene (1.0 eq.) and the nitrogen-nucleophile (2.0 eq.) in dry DCM (50 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 passed through the reaction mixture (until a colour change to blue or colourless was observed) where after the reaction mixture was purged with O_2 for 5–15 min. The reaction mixture was allowed to warm to rt. and stirred for 2 hrs. where after it was cooled again 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 hrs. at rt. MeOH (2.5–20 ml) was then added and the mixture stirred for 10–20 min. with subsequent addition of Et_2O (40 ml). The product was extracted into Et_2O with a saturated aq. NaHCO$_3$ solution (40 ml x 2)

and washed with dH_2O (40 ml x 1). The organic phase was dried and the solvent removed under reduced pressure. The product was purified *via* PLC.

6.15.1 Attempted synthesis of *N*-phenyl 2-(4'-methoxyphenyl)acetamide (**497**)

1-Allyl-4-methoxybenzene (**388**) (0.5 ml, 3.4 mmol, 1.0 eq.), aniline (0.61 ml, 6.7 mmol, 2.0 eq.) dry DCM (50 ml), O_3 (101.9–104.1 g/Nm^3, 5 min.), Ac_2O (2 ml, 21.2 mmol, 6.3 eq.), Et_3N (4 ml, 28.7 mmol, 8.5 eq).

Mixture of unidentifiable products obtained.

- Method B[12]

Allylbenzene (1.0 eq.) in dry DCM (50 ml) was cooled to -78 ℃ under Ar. A stream O_3 of with a flow rate of 10–200 g/Nm^3 and 0.5 MPa inlet pressure was bubbled through the reaction mixture (until a colour change to blue was observed) where after the reaction mixture was purged with O_2 for 5–15 minutes and the nitrogen nucleophile (2.0 eq.) added. The reaction mixture was allowed to warm to rt. and stirred for 2 hrs. where after it was cooled again to 0 ℃ with subsequent addition of Et_3N (2.0 eq.) and Ac_2O (8.0 eq.). The reaction mixture was stirred at 0 ℃ for 30 min. and then for 21 hrs. at rt. MeOH (2.5–20 ml) was then added and the mixture stirred for a further 10–20 min. followed by subsequent addition of Et_2O (40 ml). The product was extracted into Et_2O with a saturated aq. $NaHCO_3$ solution (40 ml x 2) and washed with dH_2O (40 ml x 1). The organic phase was dried and the solvent removed under reduced pressure. The product was purified *via* PLC.

6.15.2 2-(2'-Methoxyphenyl)-*N*-phenylacetamide (**497**)

1-Allyl-2-methoxybenzene (**387**) (0.2 ml, 1.3 mmol, 1.0 eq.), dry DCM (50 ml), O_3 (76.8–84.2 g/Nm^3, 8 min.), aniline (**494**) (0.2 ml, 2.2 mmol, 1.7 eq.) Ac_2O (2 ml, 21.2 mmol, 16.4 eq.), Et_3N (4 ml, 28.7 mmol, 22.1 eq).
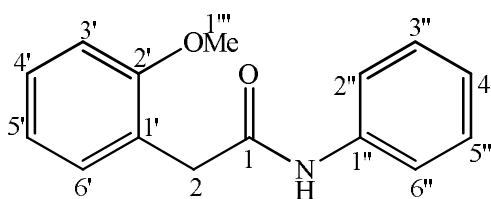
Yielded 2-(2'-methoxyphenyl)-*N*-phenylacetamide (**497**) as a yellow oil. Mass: 0.12 g, 37% yield. R_f : 0.68 (H:A:MeOH; 70:20:10). ^{1}H NMR (600 MHz, $CDCl_3$) (plate 35a): δ 7.42–7.27 (6H, m, Ar-H), 7.07–7.04 (1H, m, H-4'), 6.99–6.97 (1H, m, H-5'), 6.96–6.95 (1H, m, H-3'), 3.94 (3H, s, -O<u>Me</u>), 3.72 (2H, s, H-2). ^{13}C NMR (151 MHz, $CDCl_3$) (plate 35b): δ 169.52 (quaternary carbon), 156.99 (C-2'), 138.19 (quaternary carbon), 131.58 (Ar.-C), 129.23 (Ar.-C), 129.06 (Ar-C), 124.15 (C-4'), 123.40 (quaternary carbon), 121.57 (C-5'),

119.72 (Ar-C), 111.01 (C-3'), 55.72 (-O$\underline{Me}$), 40.35 (C-2). MS (EI) m/z 241.05 (M$^+$, 59.02%), 148.05 (100.00), 120.05 (12.60), 91.05 (82.67).

6.15.3 *N*-acetyl 2-(4'-methoxyphenyl)acetamide (**498**)

1-Allyl-4-methoxybenzene (**388**) (0.4 ml, 2.7 mmol, 1.0 eq.), dry DCM (20 ml), O$_3$ (86.4–87.5 g/Nm^3, 8 min.), acetamide (0.20 g, 3.4 mmol, 1.3 eq.) Ac$_2$O (2 ml, 21.2 mmol, 6.1 eq.), Et$_3$N (4 ml, 28.7 mmol, 10.6 eq).
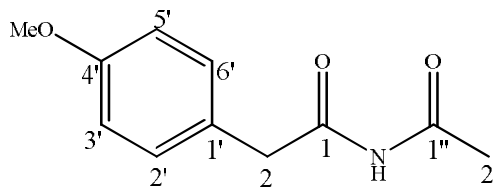
Yielded *N*-acetyl-2-(4'-methoxyphenyl)acetamide (**498**) as a yellow oil. Mass: 0.22 g, 39% yield. R$_f$: 0.55 (H:A:MeOH; 70:20:10). ^{1}H NMR (300 MHz, CDCl$_3$) (plate 36a): δ 7.53 (2H, d, J = 8.78 Hz, H-2' and H-6'), 6.89 (2H, d, J = 8.78 Hz, H-3' and H-5'), 3.81 (3H, s, -O$\underline{Me}$), 3.79 (2H, s, H-2), 2.26 (3H, s, H-2"). MS (EI) m/z 208.00 (M$^+$, 4.14%), 177.04 (22.19), 137.10 (100.00), 109.05 (20.85), 77.05 (15.36).

6.16 Deoxybenzoin Synthesis

- Method A[14]

To a dry 25 ml microwave reactor vial was added dry phenol (1.0 eq.), dry phenyl acetic acid (1.2 eq), [bmim][BF$_4$] (2.0 eq.) and BF$_3$·OEt$_2$ (1.0 eq.). The reaction mixture was irradiated at 90°C for 4 min. with constant cooling where after it was poured into water (40 ml) and extracted into EtOAc (3 x 40 ml). The EtOAc layer was then washed with dH$_2$O (3 x 40 ml), dried and the solvent removed *in vacuo*.

6.16.1 2,3',4,4'-Tetrahydroxy deoxybenzoin (**512**)

3,4-Dihydroxy phenyl acetic acid (**511**) (0.16 g, 1.0 mmol, 1.0 eq.), resorcinol (**507**) (0.14 g, 1.3 mmol, 1.3 eq.), BF$_3$·OEt$_2$ (0.13 ml, 0.70 mmol, 0.7 eq.)
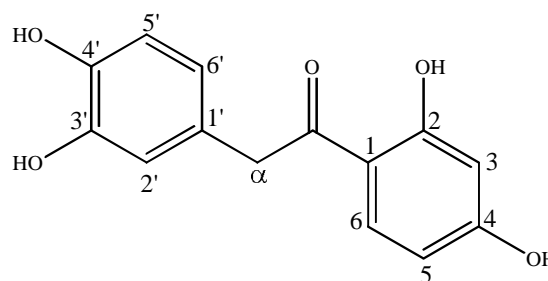
Yielded 2,3',4,4'-tetrahydroxy deoxybenzoin (**512**) as a light brown solid. Mass: 0.13 g, 50% yield. R$_f$: 0.18 (B:A:MeOH; 8:1:1). ^{1}H NMR (600 MHz, (CD$_3$)$_2$CO) (plate 37a): δ 7.88 (1H, d, J = 8.85 Hz, H-6), 6.79 (1H, d, J = 2.11 Hz, H-2'), 6.73 (1H, d, J = 8.06 Hz, H-5'), 6.63 (1H, dd, J = 8.06, 2.11 Hz, H-6'), 6.39 (1H, dd, J = 8.85, 2.37 Hz, H-5), 6.29 (1H, d, J = 2.37 Hz, H-3), 4.05 (2H, s, α-C$\underline{H_2}$). ^{13}C

NMR (151 MHz, (CD$_3$)$_2$CO) (plate 37b): δ 203.32 (-CO), 166.23 (C-2), 165.24 (C-4), 145.46 (C-3'/4'), 144.37 (C-3'/4'), 133.91 (C-6), 127.05 (C-1'), 121.03 (C-6''), 116.65 (C-2'), 115.67 (C-5'), 112.84 (C-1), 108.37 (C-5), 103.11 (C-3), 44.09 (α-CH$_2$).

6.16.2 Attempted synthesis of 2,4,6-trimethoxy deoxybenzoin

1,3,5-Trimethoxyphenol (0.20 g, 1.2 mmol, 1.0 eq.), phenyl acetic acid (**515**) (0.14 g, 1.0 mmol, 0.9 eq.), [bmim][BF$_4$] (0.4 ml, 2.1 mmol, 1.8 eq.), BF$_3$·OEt$_2$ (0.1 ml, 0.8 mmol, 0.7 eq.).
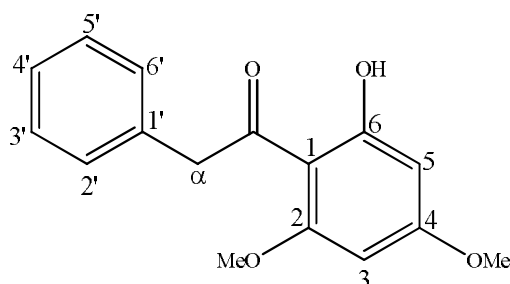
Yielded 6-hydroxy-2,4-dimethoxy deoxybenzoin (**514**) as light orange needles. Mass: 0.05 g, 18% yield. R$_f$: 0.53 (H:EtOAc; 90:10). ^{1}H NMR (300 MHz, CDCl$_3$) (plate 38a): δ 7.23–7.20 (2H, m, H-3' and H-5'), 7.16–7.13 (1H, m, H-4'), 7.12–7.11 (2H, m, H-2' and H-6'), 5.96 (1H, d, J = 2.62 Hz, H-3/5), 5.84 (1H, d, J = 2.62 Hz, H-3/5), 4.23 (2H, s, α -CH2), 3.76 (3H, s, -OMe), 3.72 (3H, s, -OMe). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 38b): δ 202.67 (-CO), 167.78 (C-6), 166.19 (C-2/4), 162.56 (C-2/4), 135.43 (C-1'), 129.47 (C-2' and C-6'), 128.21 (C-3' and C-5'), 126.47 (C-4'), 105.50 (C-1), 93.60 (C-3/5), 90.74 (C-3/5), 55.42 (-OMe), 50.19 (α-CH$_2$). MS (EI) *m/z* 272.05 (M$^+$, 2.29%), 181.00 (M$^+$- CH$_2$Ph, 100.00), (166.00, 5.32), (138.00, 4.44).

- Method B

Phenyl acetyl chloride (1.0 eq.) was dissolved in dry Et$_2$O (20 ml) and cooled to -78 ºC where after phenylmagnesiumbromide (3.0 M in Et$_2$O, 1.2 eq.) was also dissolved in dry Et$_2$O (20 ml) and added to the phenyl acetyl chloride in a drop-wise manner over 30 min. After completion of the addition, stirring was continued for another 30 min. at -78 ºC. Crushed ice (50 ml) and HCl (50 ml, 32% v/v) was added to the reaction mixture and the product extracted into EtOAc (50 ml x 3). The organic phase was dried over Na$_2$SO$_4$ and the solvent removed under reduced pressure. The crude reaction material was purified *via* PLC.

6.16.3 Deoxybenzoin (**522**)

Phenyl acetyl chloride (**526**) (0.4 ml, 3.0 mmol, 1.0 eq.), phenylmagnesiumbromide (**521**) (1.3 ml, 3.9 mmol, 1.3 eq.).
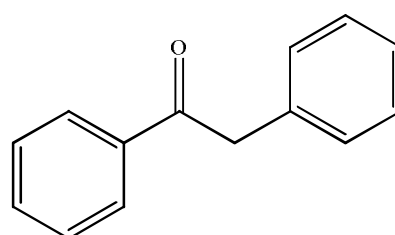
Yielded deoxybenzoin (**522**) as a white solid. Mass: 0.37 g, 59% yield. R_f: 0.68 (Hexane). ^{1}H NMR (300 MHz, CD$_3$OD) (plate 39a): δ 7.45–7.39 (5H, m, Ar.-H), 7.25–7.10 (5H, m, Ar.-H), 4.74 (2H, s, α-C$\underline{H}_2$). ^{13}C NMR (151 MHz, CDCl$_3$) (plate 39b): δ 197.80 (-$\underline{C}$=O), 136.70 (Ar-C), 134.65 (Ar-C), 133.31 (Ar-C), 129.60 (Ar-C), 128.75 (Ar-C), 127.03 (Ar-C), 45.63 (-$\underline{C}$H$_2$-).

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Plate 1a; ¹H NMR [CDCl₃]: 1-Allyloxy-3-methoxybenzene (**394**)
δ 7.20 (1H, dd, *J* = 8.17, 8.20 Hz, H-5), 6.56–6.54 (2H, m, H-4 and H-6), 6.53 (1H, dd, *J* = 2.33, 2.34 Hz, H-2), 6.18–6.05 (1H, m, H-2'), 5.46–5.43 (1H, m, H-3'b), 5.33–5.31 (1H, m, H-3'a), 4.55–4.54 (2H, m, H-1'), 3.81 (3H, s, -OMe).
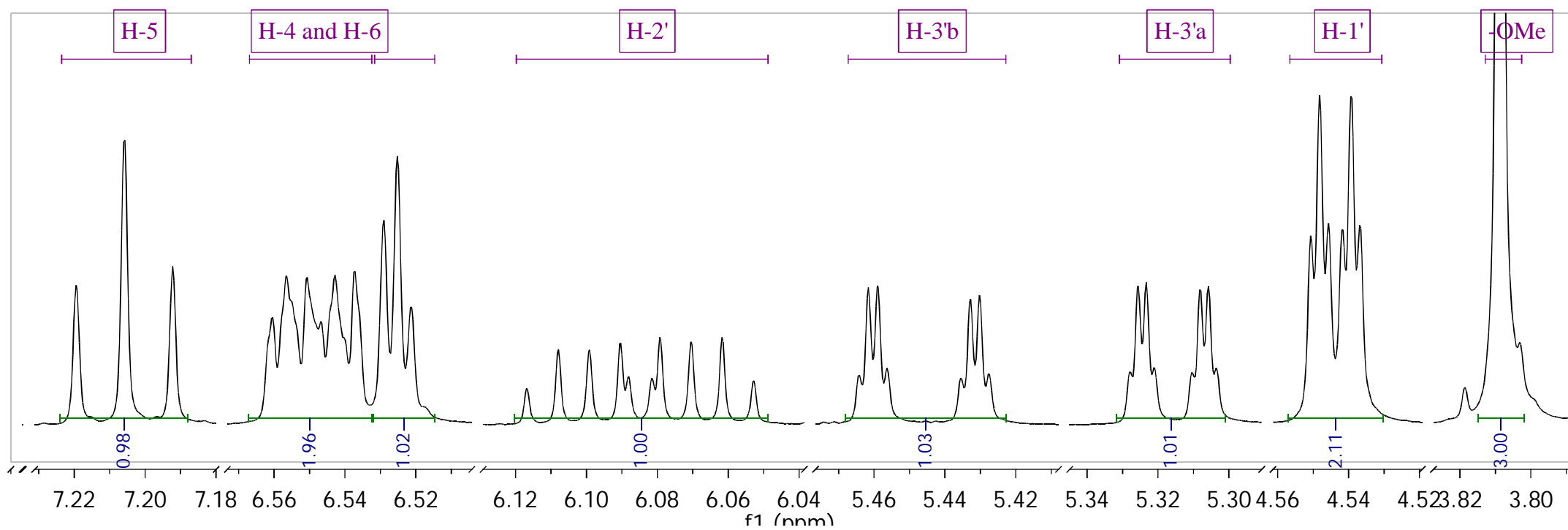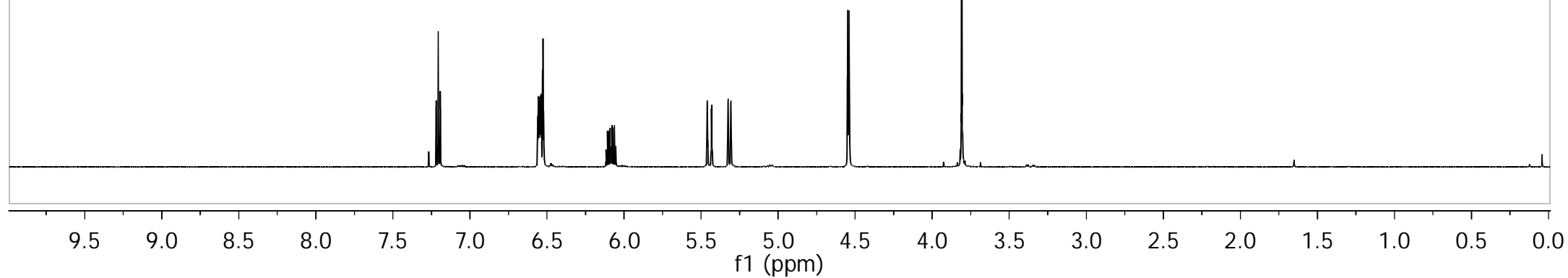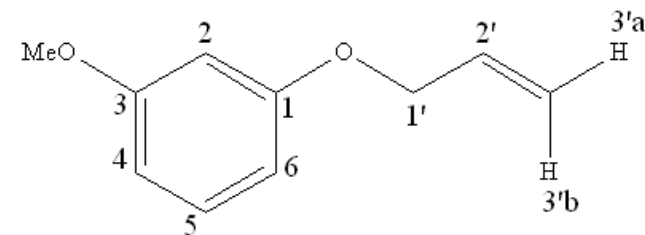
Plate 1b; ^{13}C NMR [CDCl$_3$]: 1-Allyloxy-3-methoxybenzene (**394**)
δ 160.91 (C-1/3), 159.94 (C-1/3), 133.36 (C-2'), 129.95 (C-5), 117.75 (C-3'), 106.95 (C-4/6), 106.51 (C-4/6), 101.31 (C-2), 68.89 (C-1'), 55.32 (-OMe).
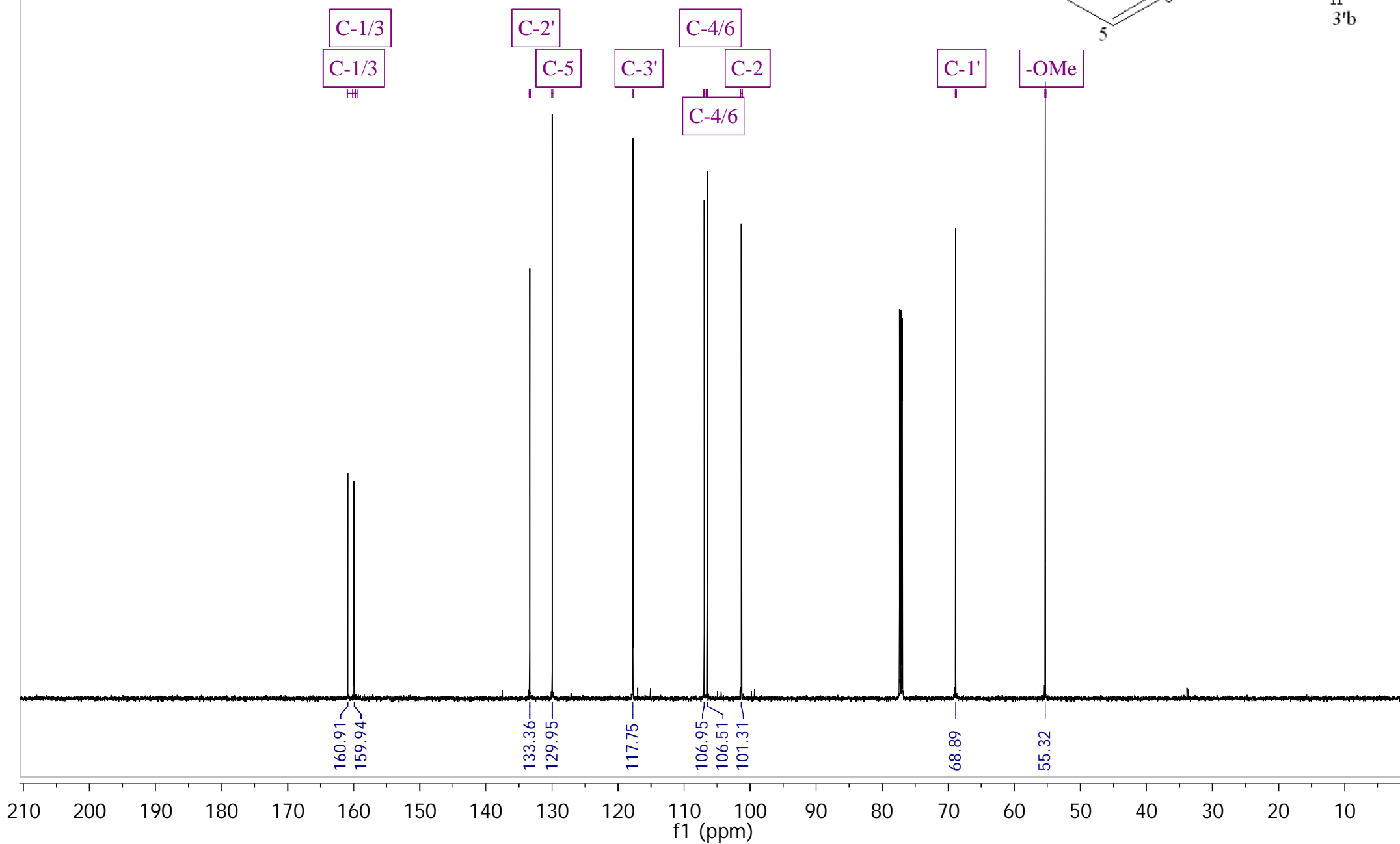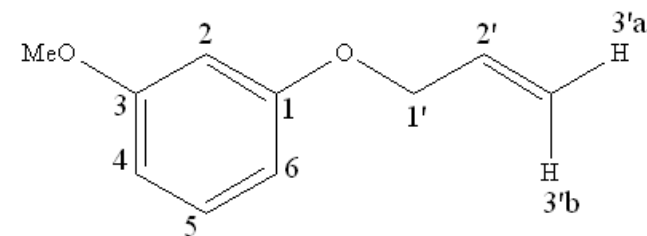
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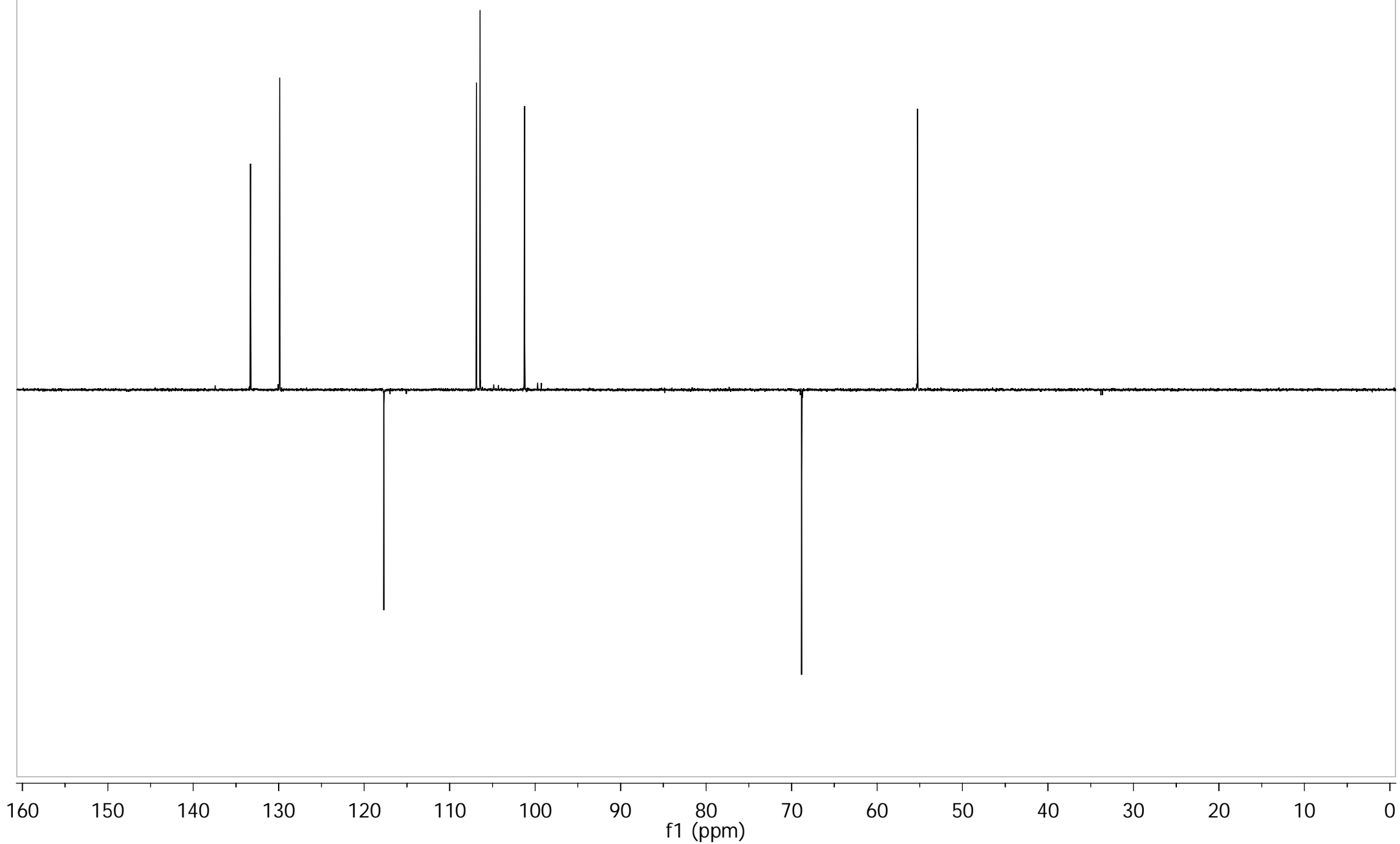
Plate 1d; HSQC [CDCl₃]: 1-Allyloxy-3-methoxybenzene (**394**)
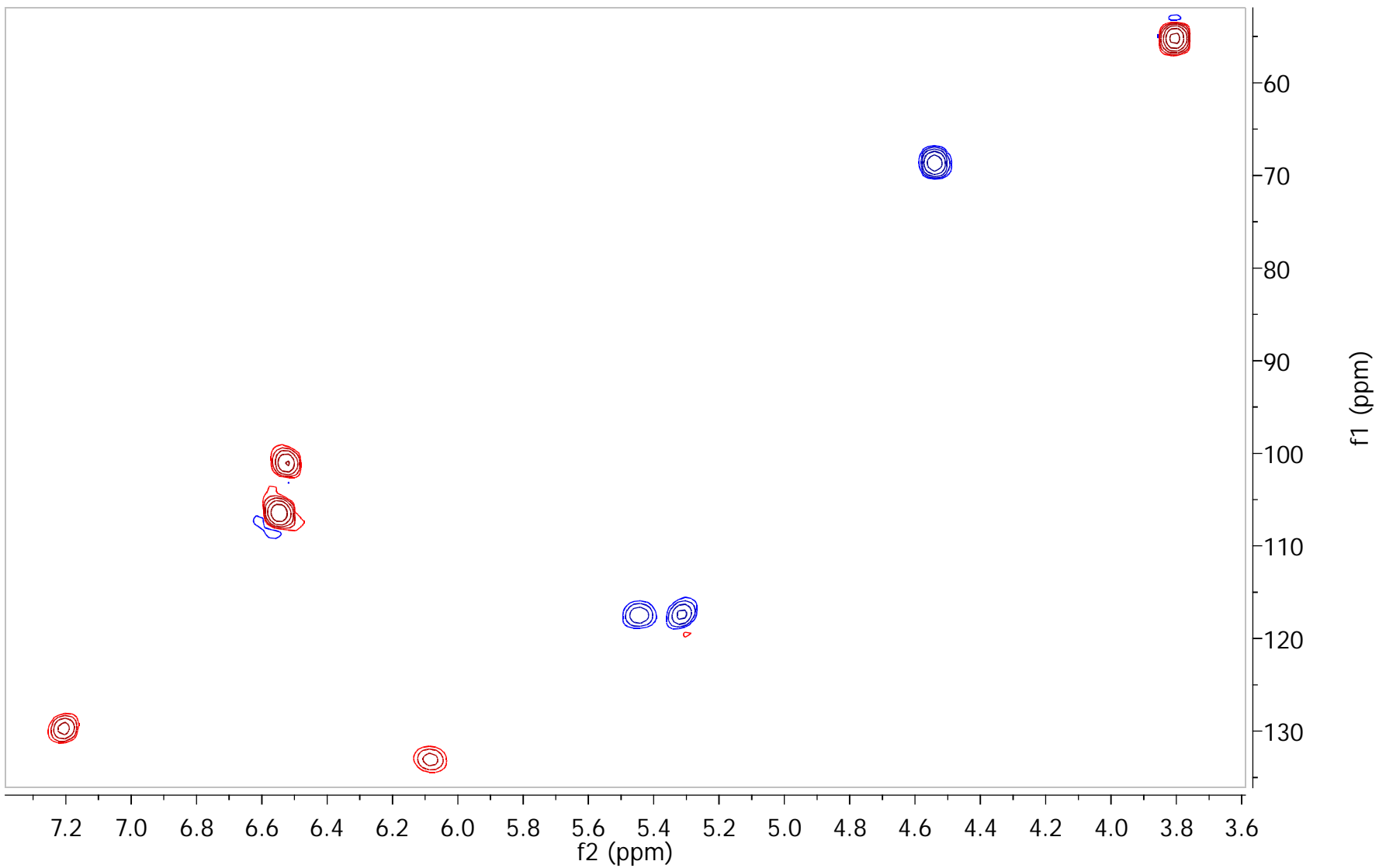
Plate 1e; HMBC [CDCl₃]: 1-Allyloxy-3-methoxybenzene (**394**)
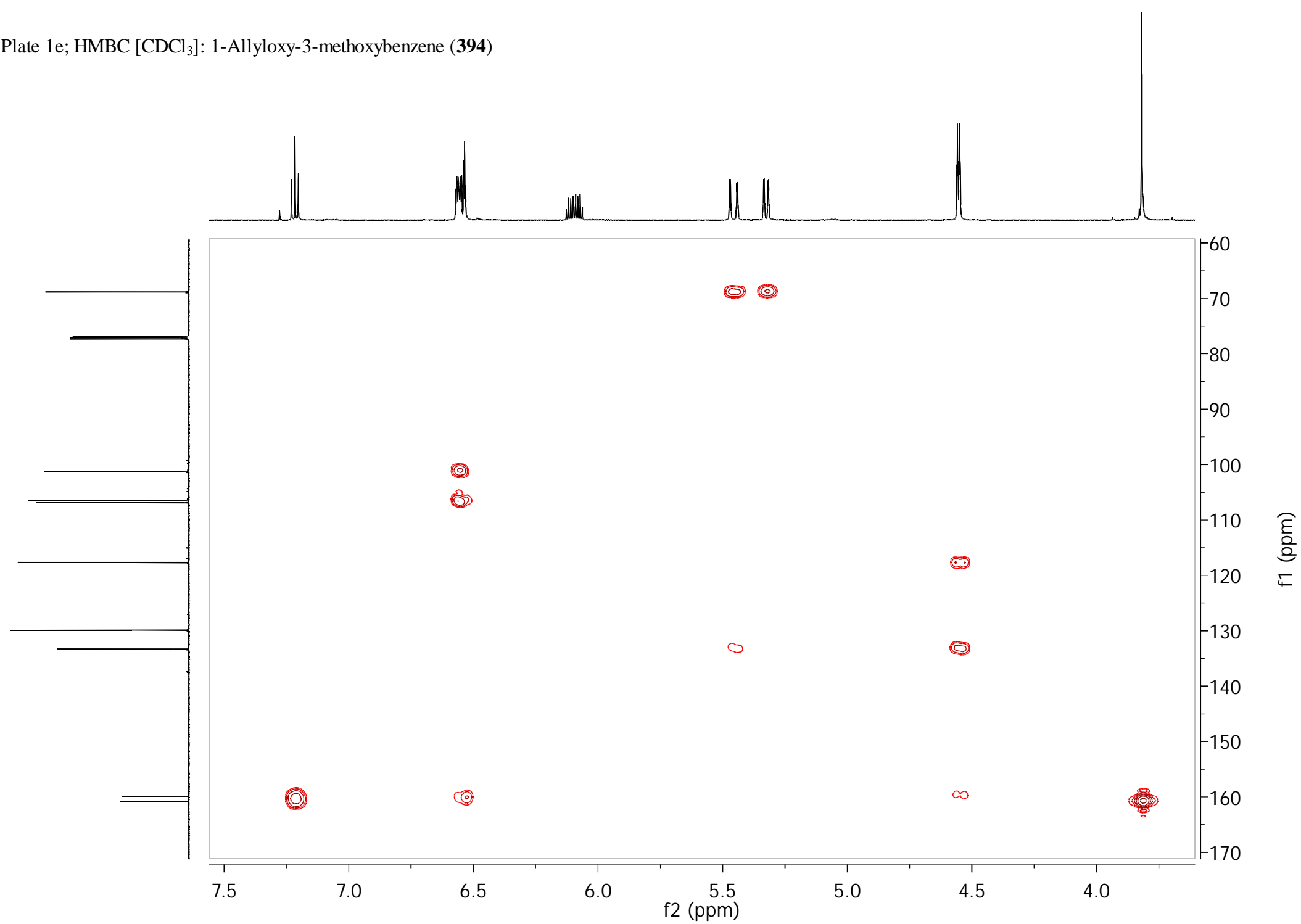
Plate 2a; ^{1}H NMR [CDCl$_3$]: 1-Allyloxy-3,5-dimethoxybenzene (**396**)

δ 6.11 (2H, d, *J* = 2.10 Hz, H-2 and H-6), 6.10–6.09 (1H, m, H-4), 6.08–6.02 (1H, m, H-2'), 5.43–5.40 (1H, m, H-3'b), 5.30–5.28 (1H, m, H-3'a), 4.50–4.49 (2H, m, H-1'), 3.77 (6H, s, -OMe).

H-2 and H-6   H-2'   H-3'b   H-3'a   H-1'   -OMe

Plate 2b; ^{13}C NMR [CDCl$_3$]: 1-Allyloxy-3,5-dimethoxybenzene (**396**)
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).

C-1

C-3 and C-5

C-2'

C-3'

C-2 and C-6

C-4

C-1'

-OMe

161.59
160.58

133.26

117.91

93.71
93.20

68.98

55.44

f1 (ppm)
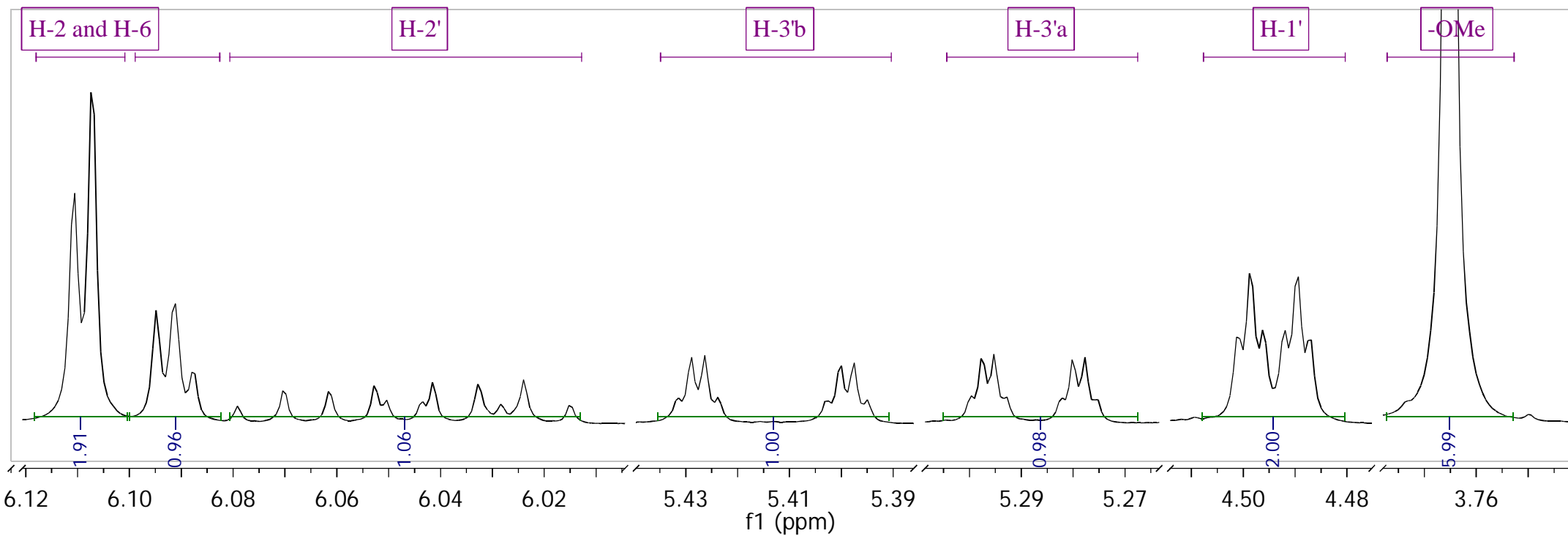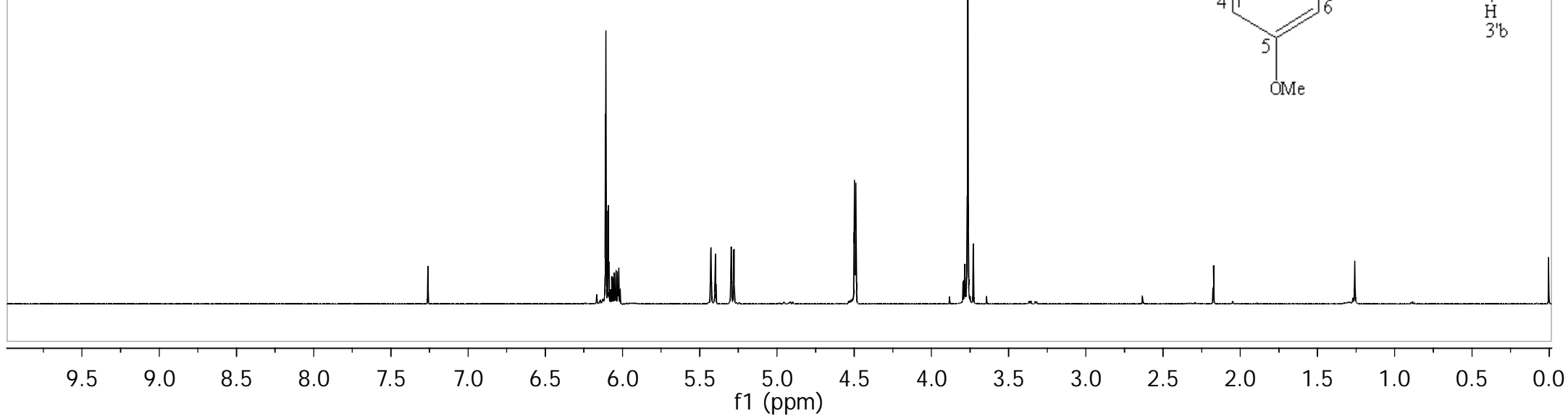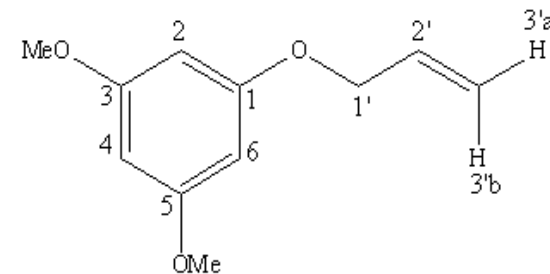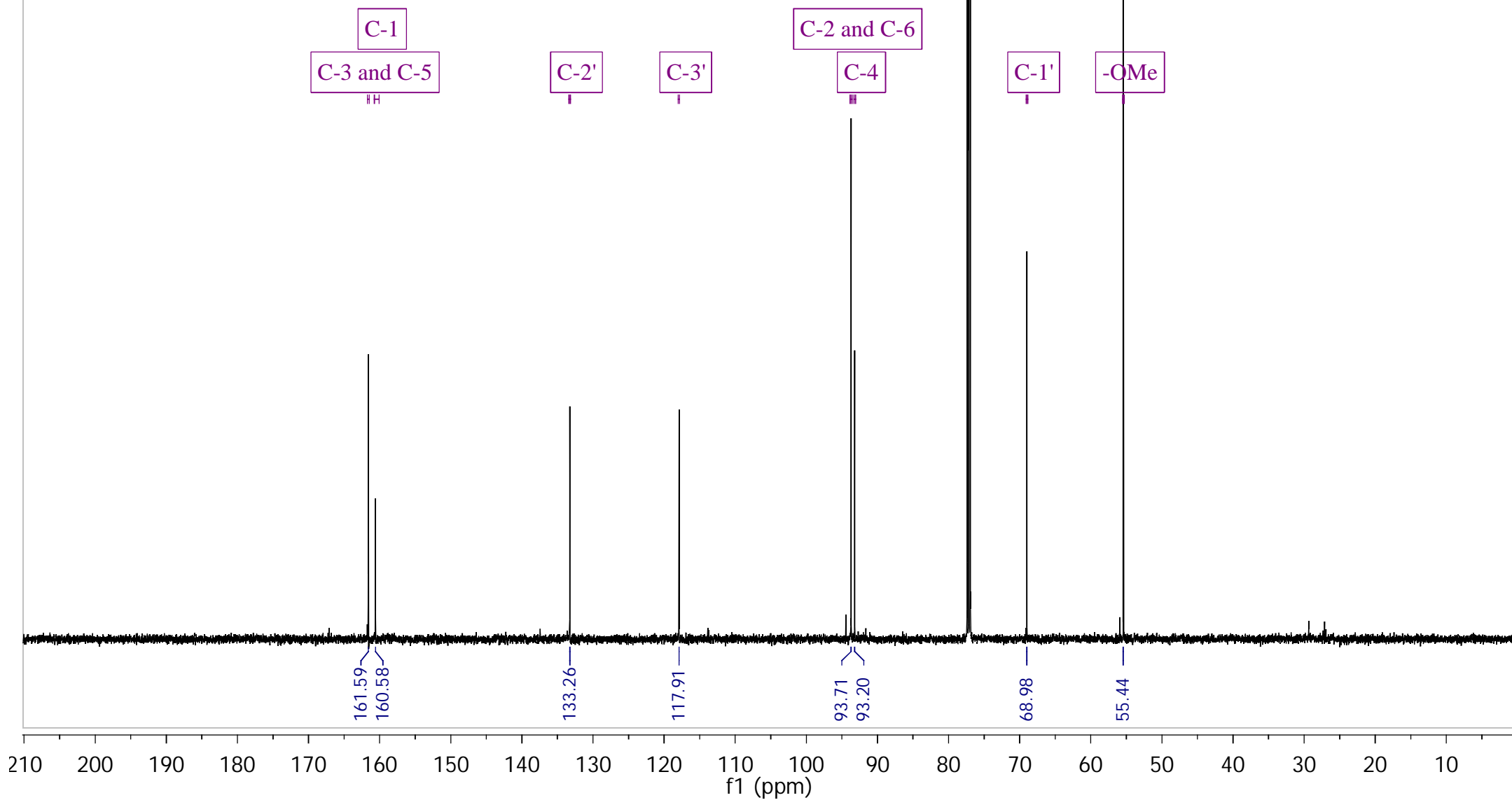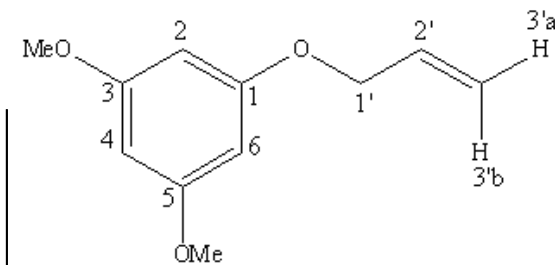
Plate 2c; HSQC [CDCl$_3$]: 1-Allyloxy-3,5-dimethoxybenzene (**396**)
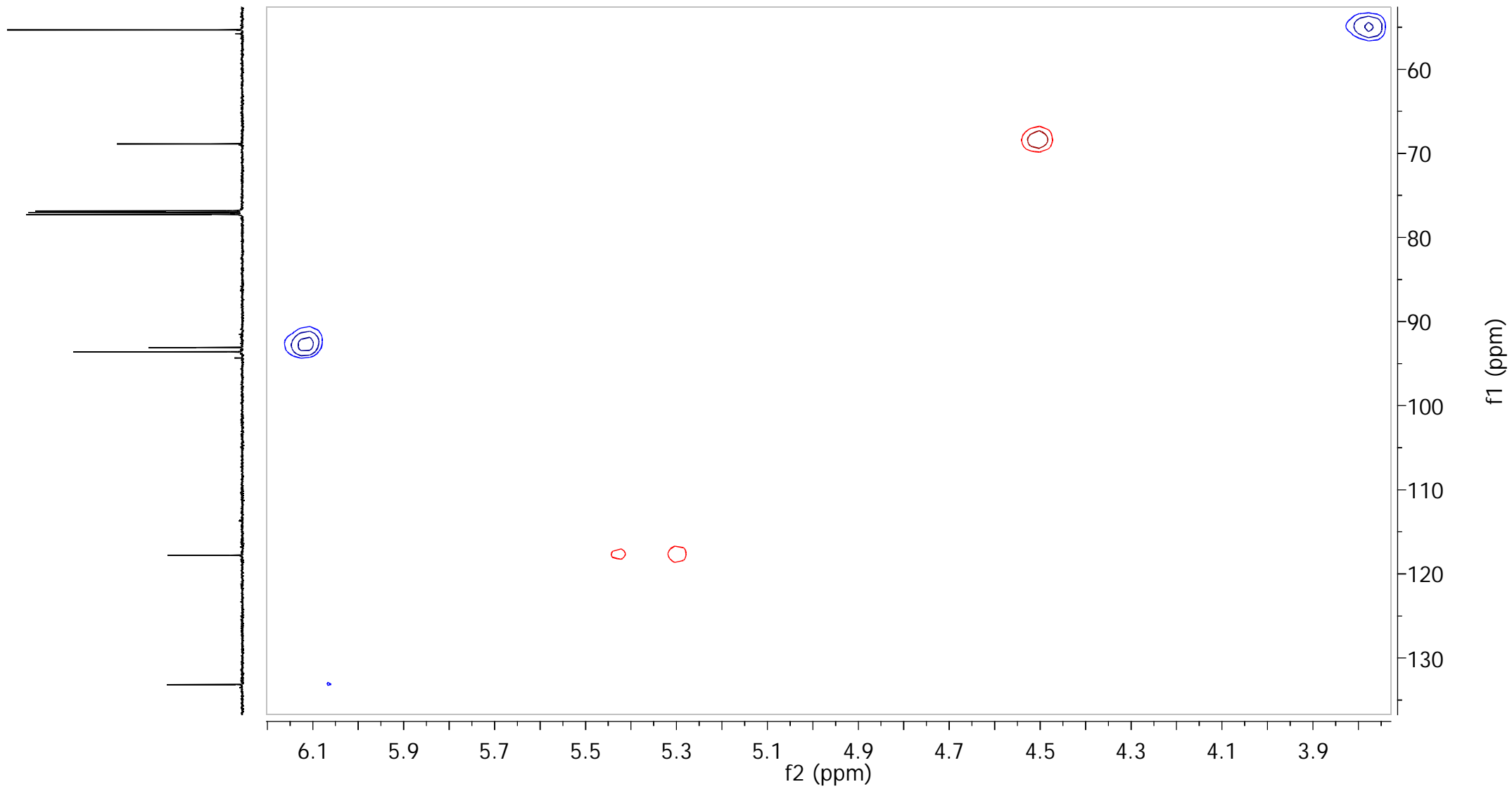
Plate 3a; ¹H NMR [CDCl₃]: 1-Allyl-3,4-dimethoxybenzene (**390**)
δ 6.80 (1H, d, J = 8.02 Hz, H-5), 6.73 (1H, dd, J = 8.02, 1.86 Hz, H-6), 6.71 (1H, d, J = 1.86 Hz, H-2), 5.96 (1H, ddt, J = 17.02, 10.09, 6.7 Hz, H-2'), 5.10–5.05 (2H, m, H-3'a and H-3'b), 3.87 (3H, s, -OMe), 3.86 (3H, s, -OMe), 3.34 (2H, m, H-1').
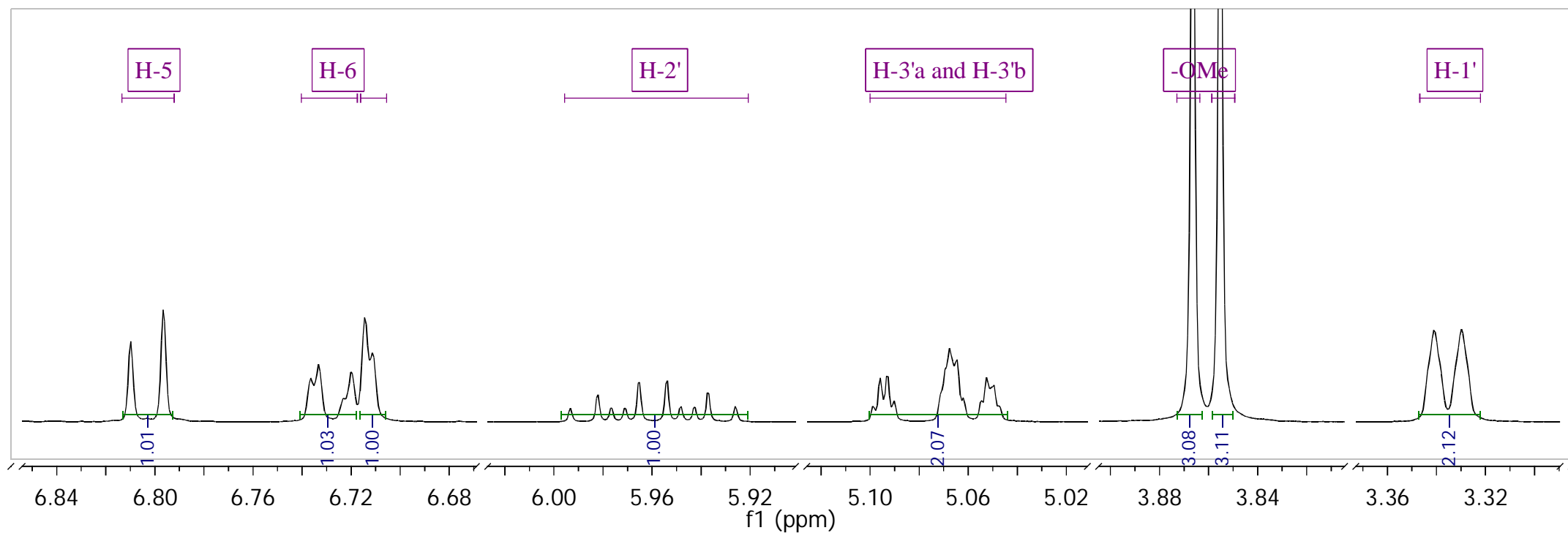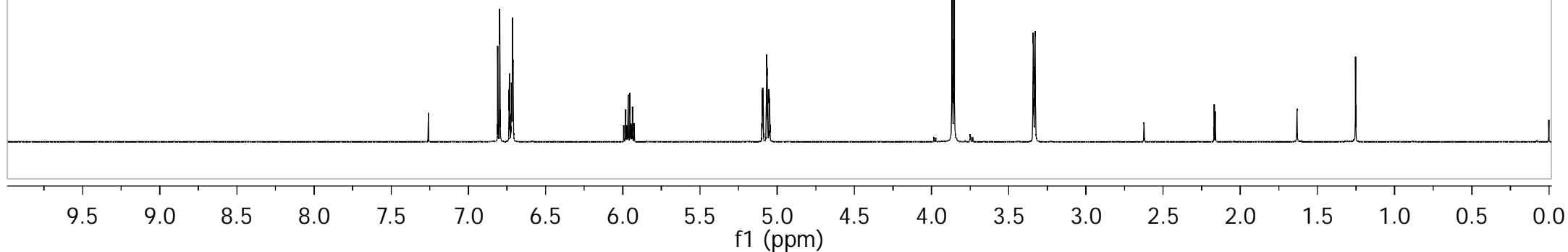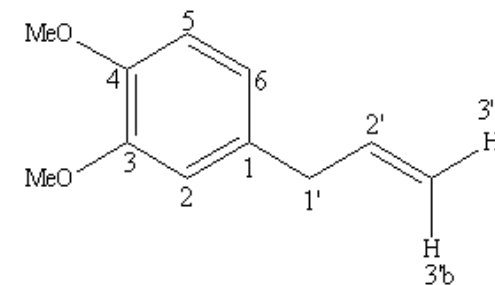
Plate 3b; ¹³C NMR [CDCl₃]: 1-Allyl-3,4-dimethoxybenzene (**390**)
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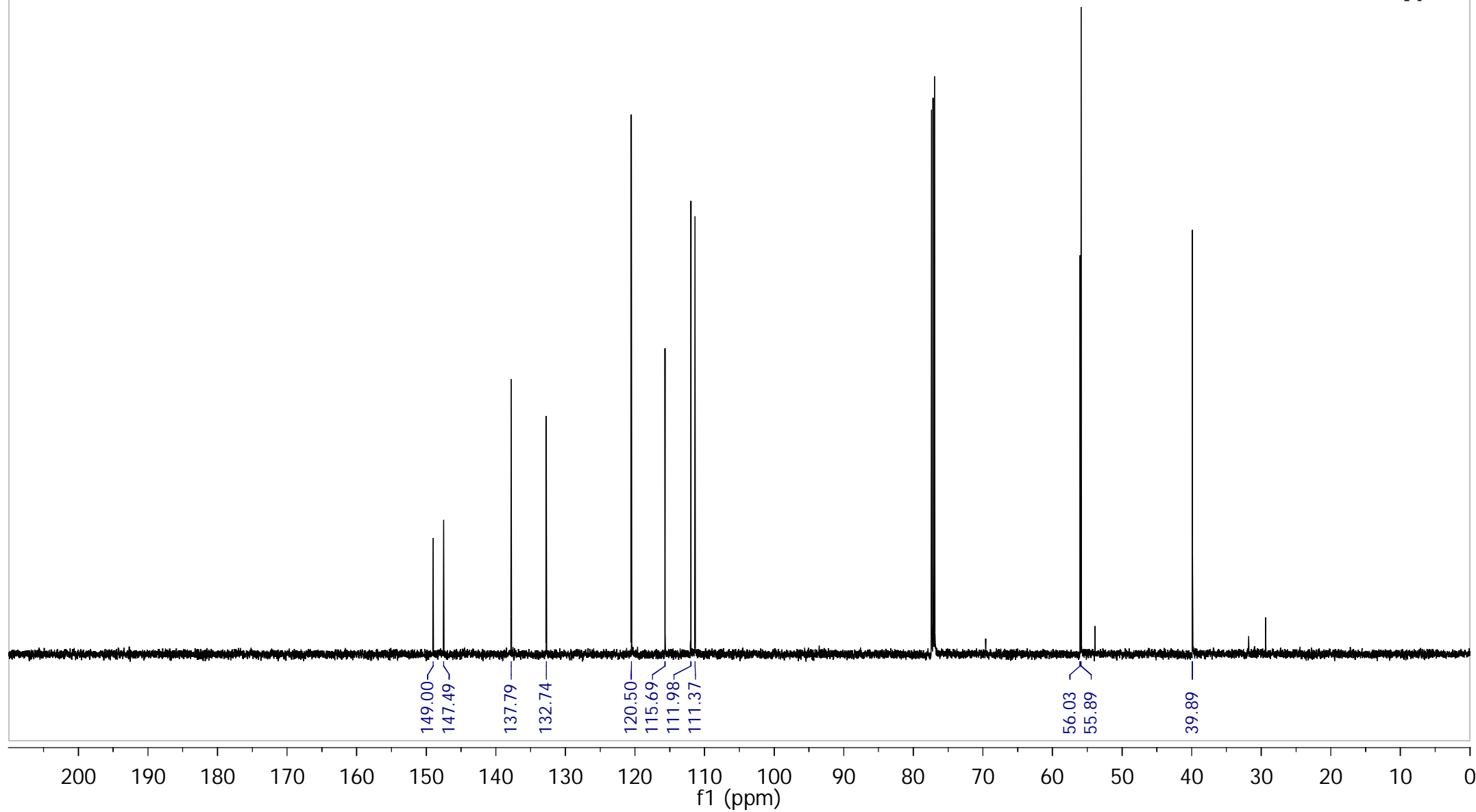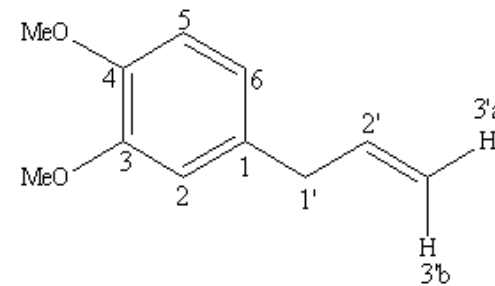
Plate 4a; ^{1}H NMR [CDCl$_3$]: 1-Allyl-3,4,5-trimethoxybenzene (**391**)

δ 6.41 (2H, s, H-2 and H-6), 5.95 (1H, ddt, J = 16.90, 10.04, 6.81 Hz, H-2'), 5.13–5.06 (2H, m, H-3'a and H-3'b), 3.84 (6H, s, -OMe), 3.82 (3H, s, -OMe), 3.33–3.32 (2H, m, H-1').
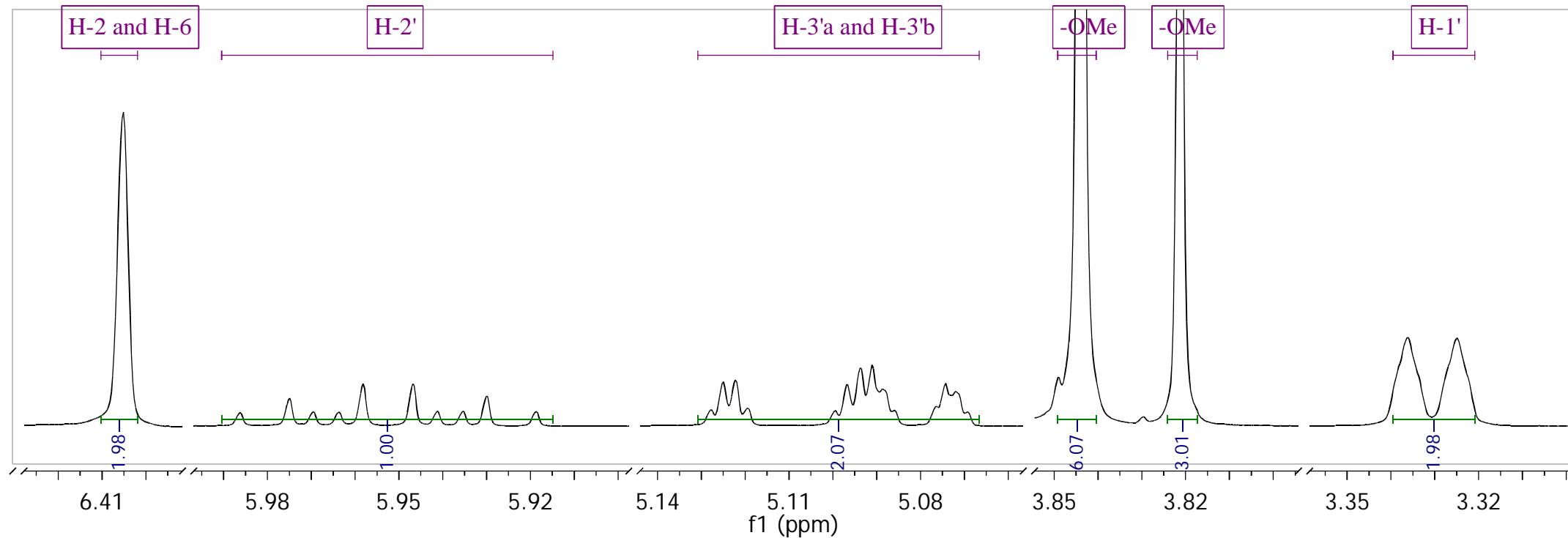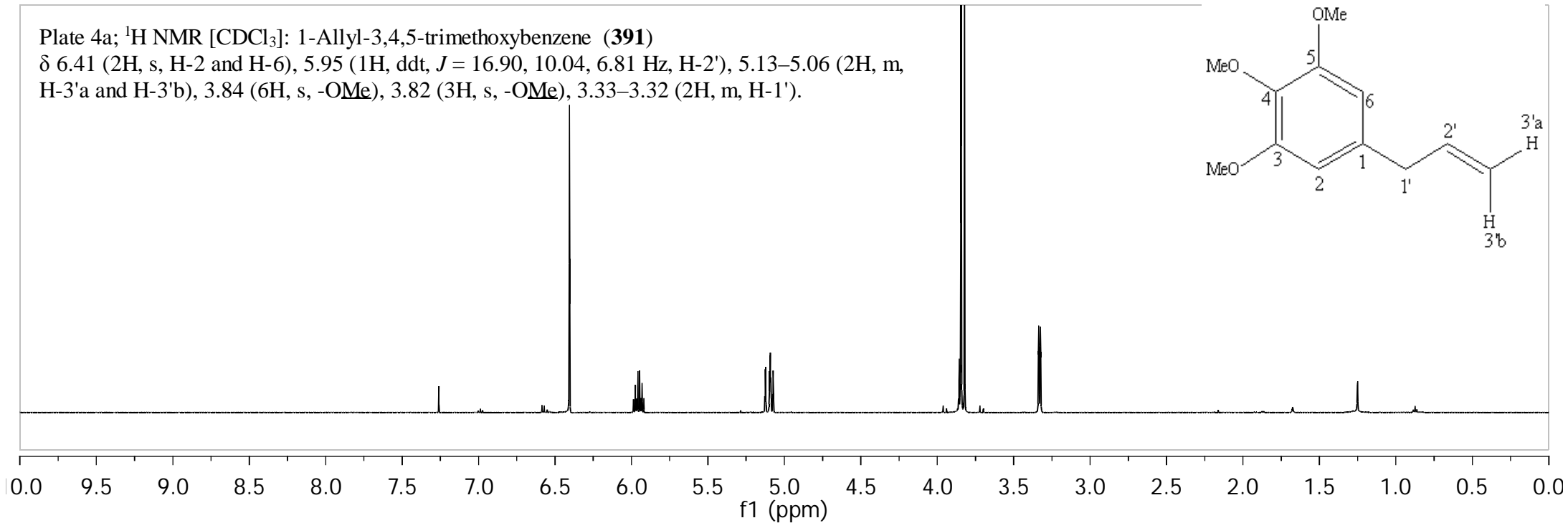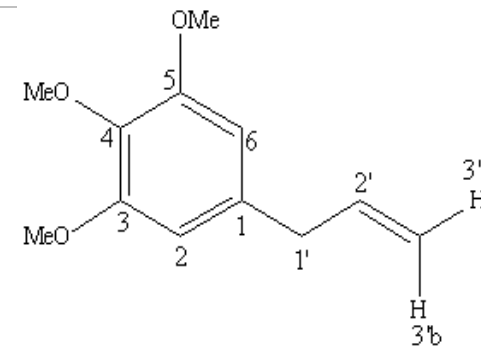
Plate 4b; ^{13}C NMR [CDCl$_3$] : 1-Allyl-3,4,5-trimethoxybenzene (**391**)
δ 153.19 (quaternary carbon), 137.22 (C-2'), 136.29 (quaternary carbon), 135.81 (quaternary carbon), 116.02 (C-3'), 105.41 (C-2 and C-6), 60.86 (-OMe), 56.05 (-OMe), 40.55 (C-1').
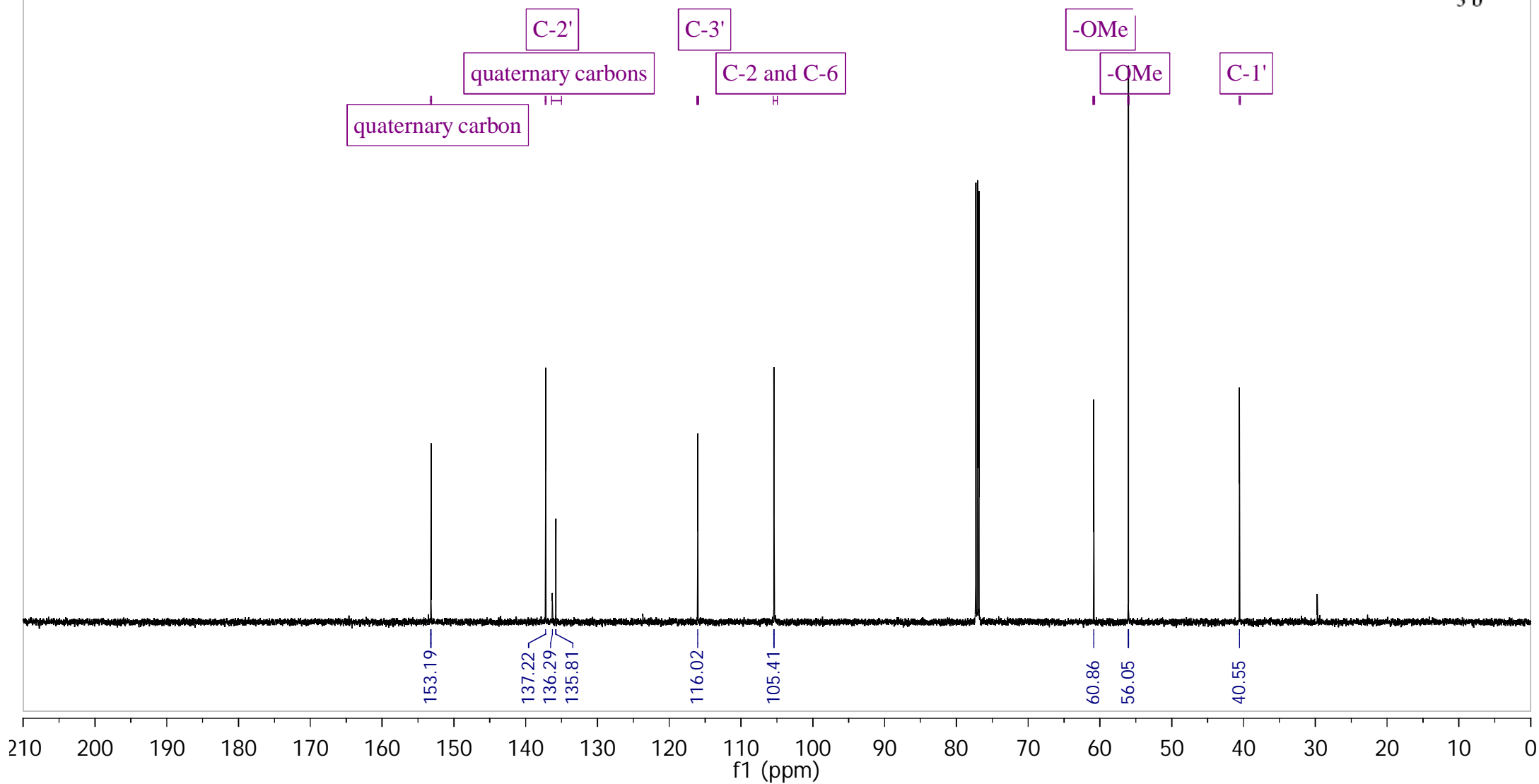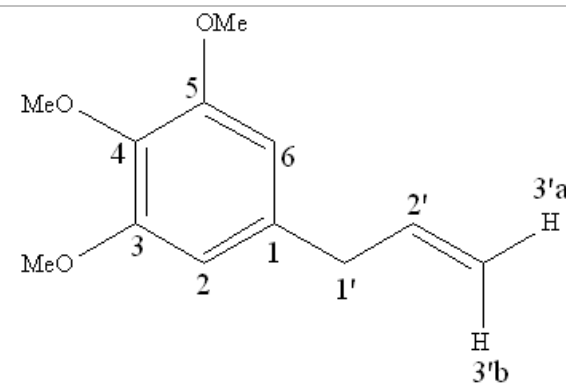
Plate 4c; DEPT [CDCl$_3$]: 1-Allyl-3,4,5-trimethoxybenzene (**391**)
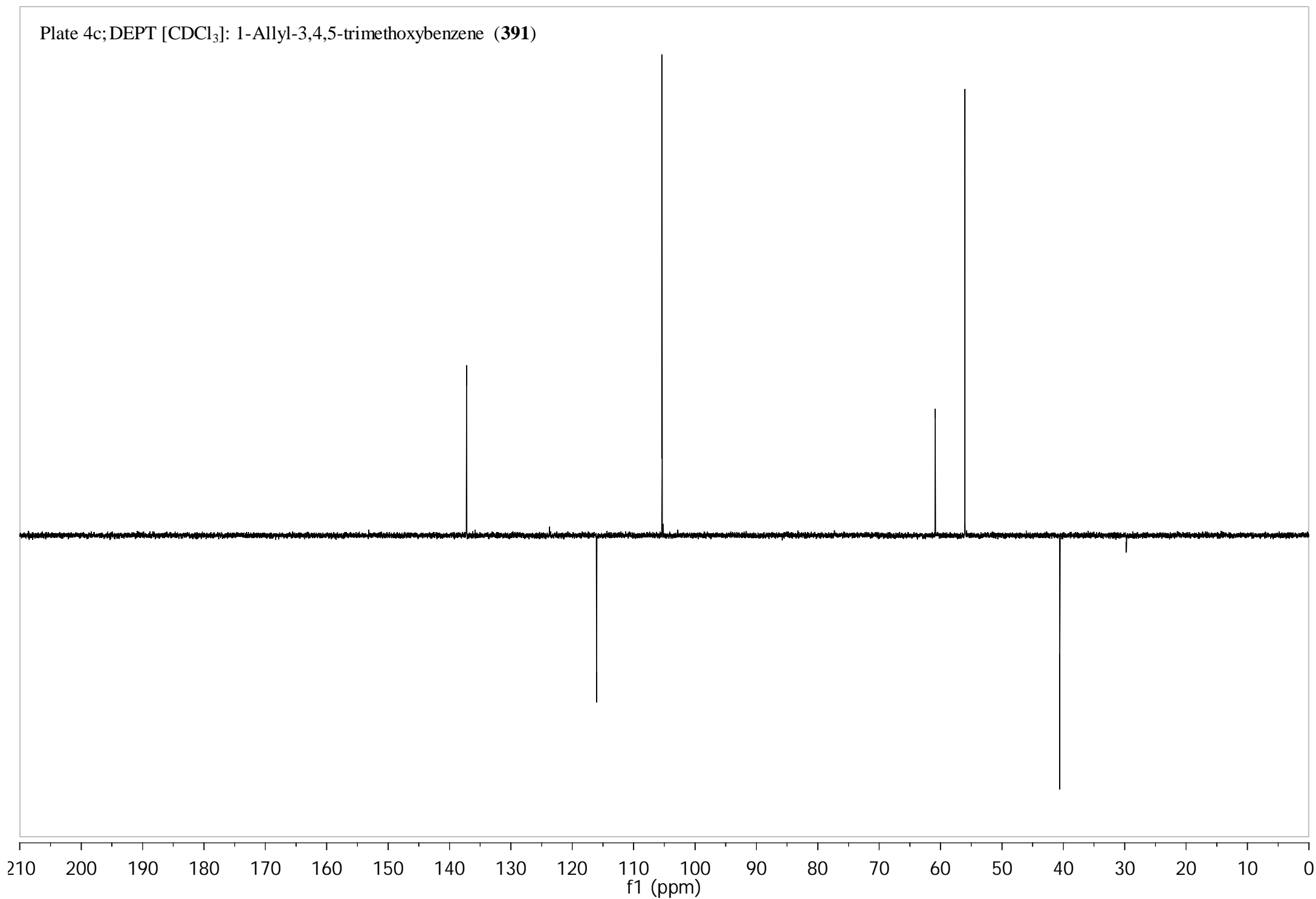
Plate 4d; HSQC [CDCl$_3$]: 1-Allyl-3,4,5-trimethoxybenzene (**391**)
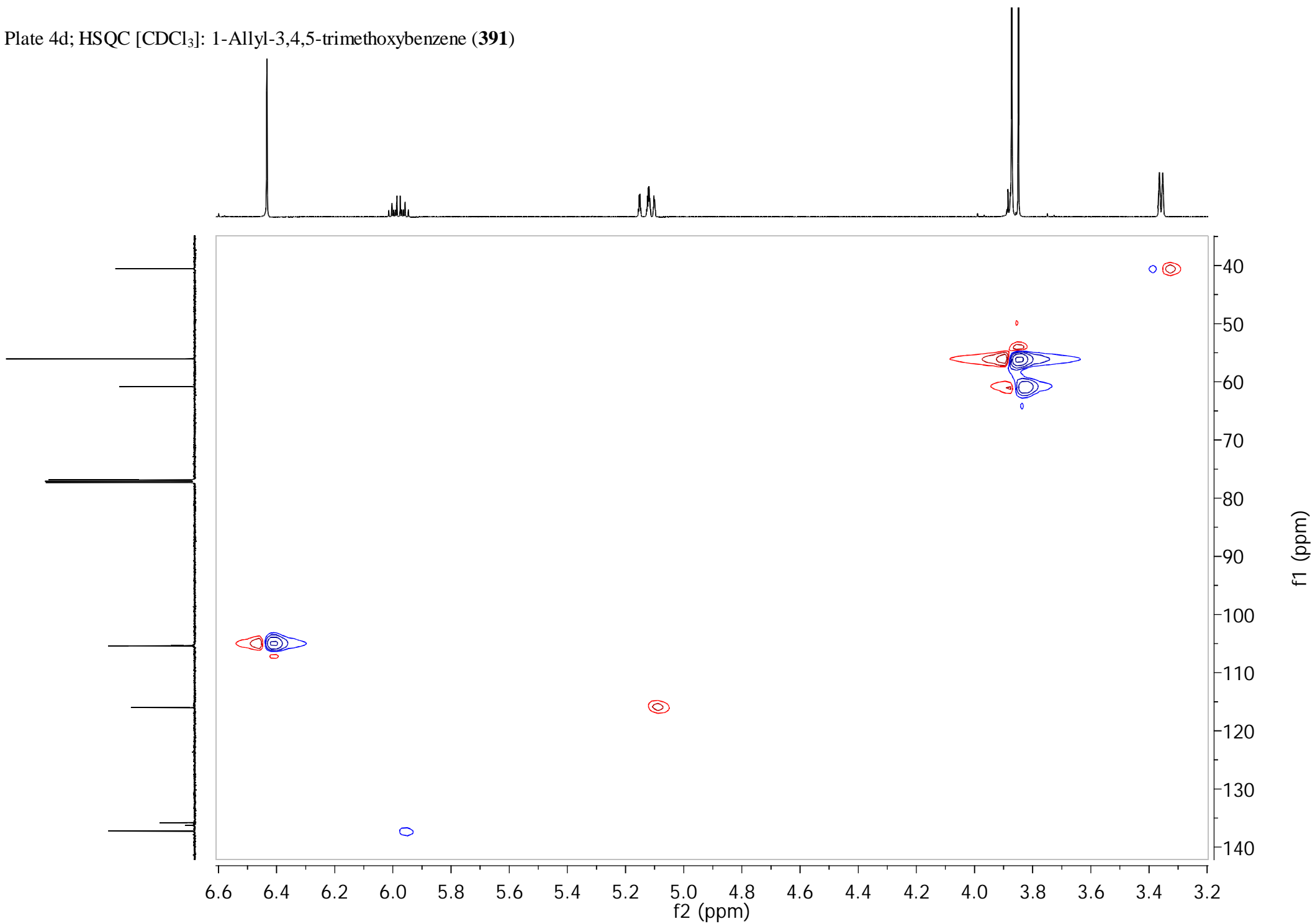
Plate 4e; HMBC [CDCl$_3$]: 1-Allyl-3,4,5-trimethoxybenzene (**391**)
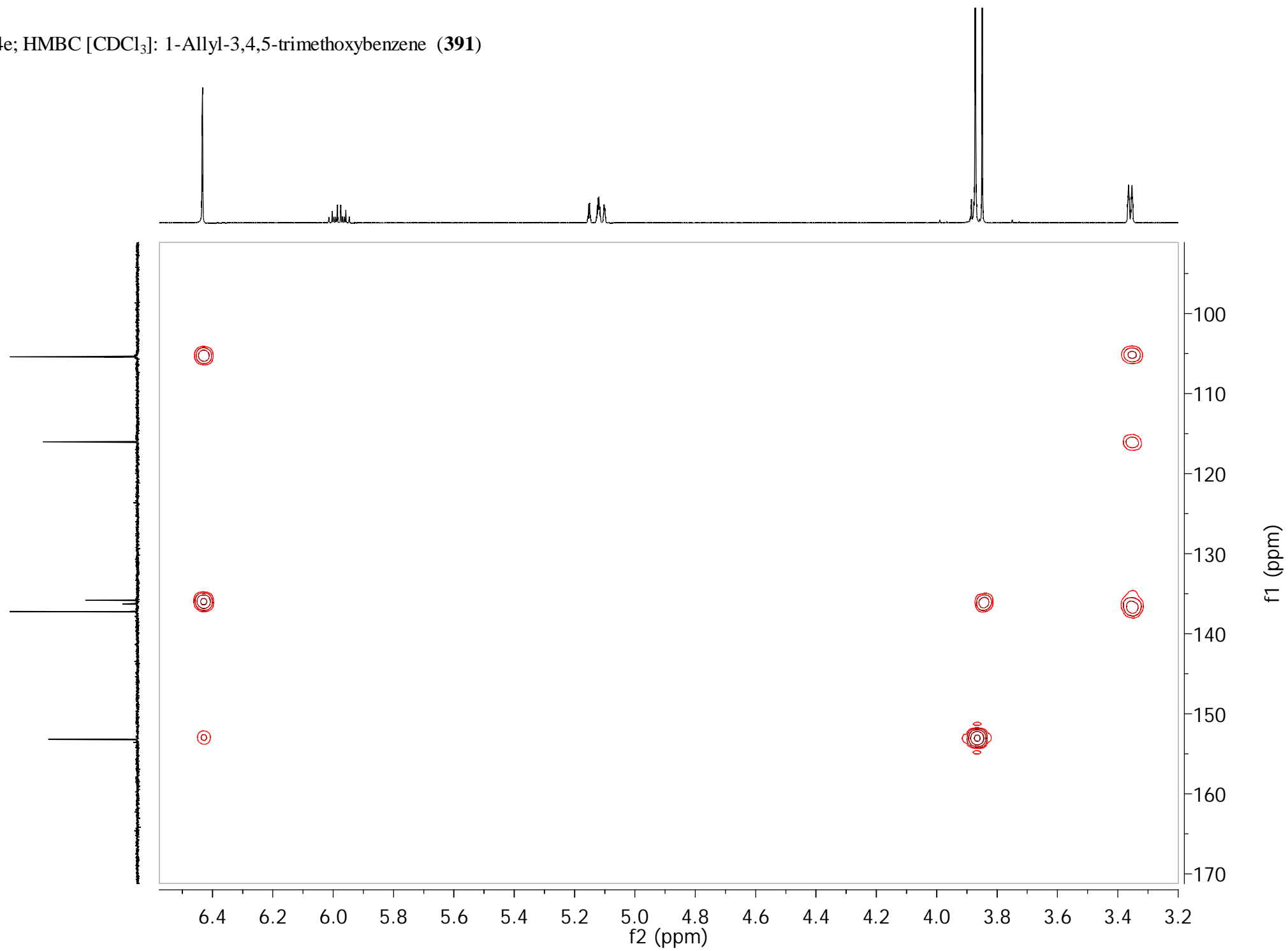
Plate 5a ^{1}H NMR [CDCl$_3$]: 1-Allyl-2,4,6-trimethoxybenzene (**392**)
δ 6.15 (2H, s, H-3 and H-5), 5.96–5.90 (1H, m, H-2'), 4.97–4.90 (2H, m, H-3'a and H-3'b), 3.81
(3H, s, -O$\underline{\text{Me}}$), 3.80 (6H, s, -O$\underline{\text{Me}}$), 3.34–3.33 (2H, m, H-1').
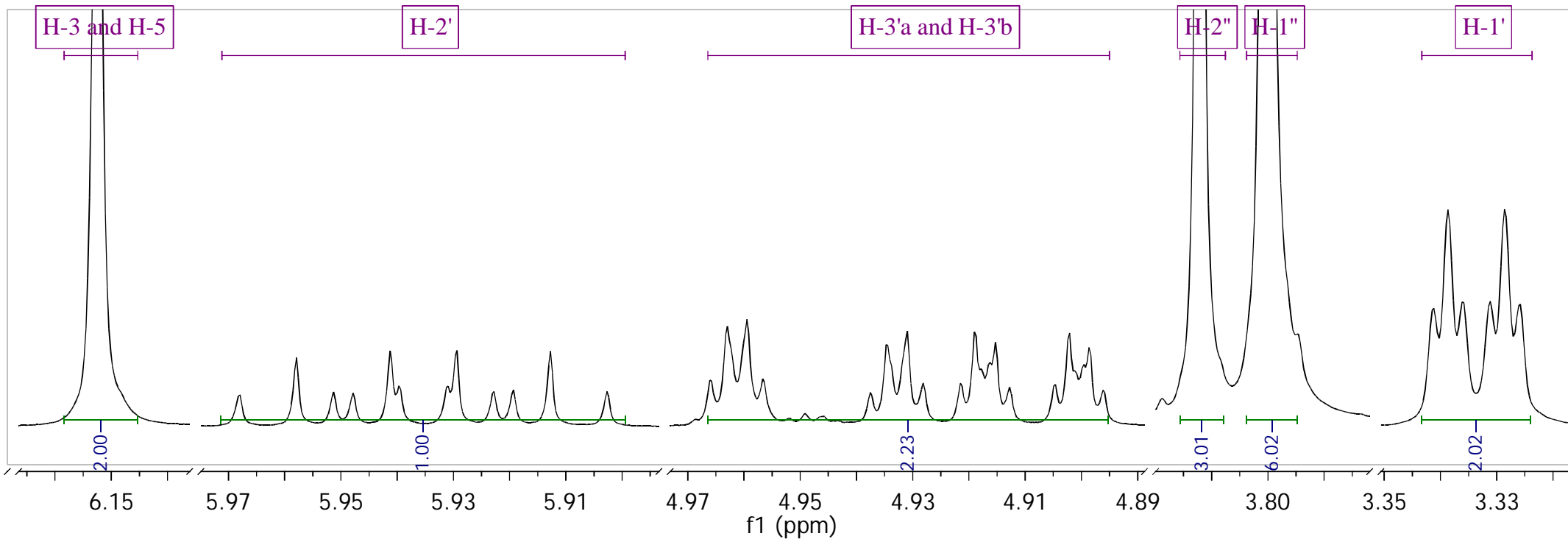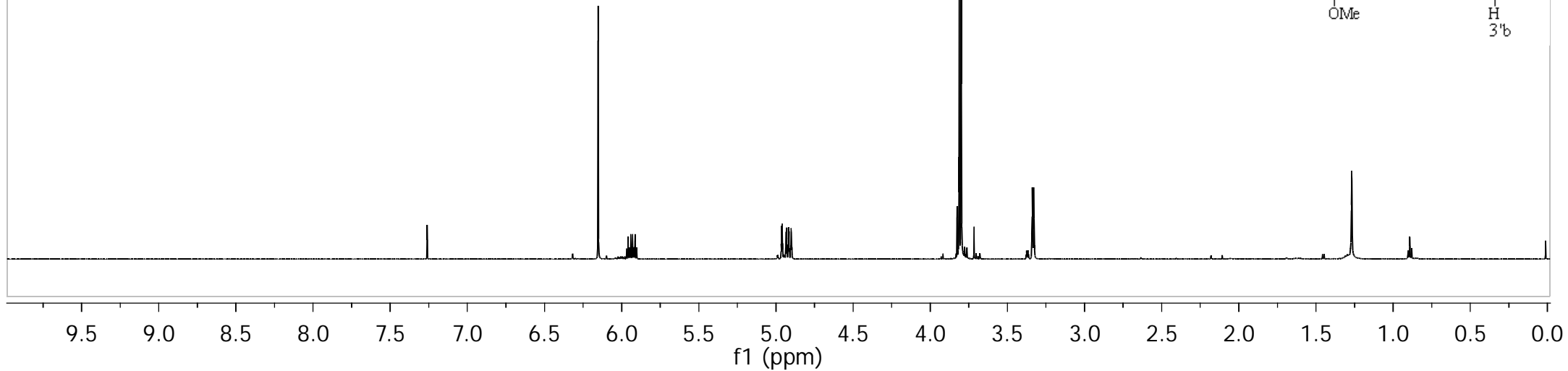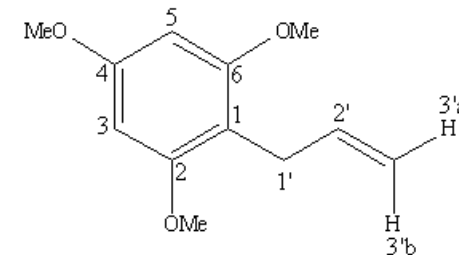
Plate 5b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-2,4,6-trimethoxybenzene (**392**)
δ 159.76 (quaternary carbon), 158.80 (quaternary carbon), 137.62 (C-2'), 113.69 (C-3'), 109.28 (quaternary carbon), 90.93 (C-3 and C-5), 55.97 (-OMe), 55.47 (-OMe), 27.04 (C-1').
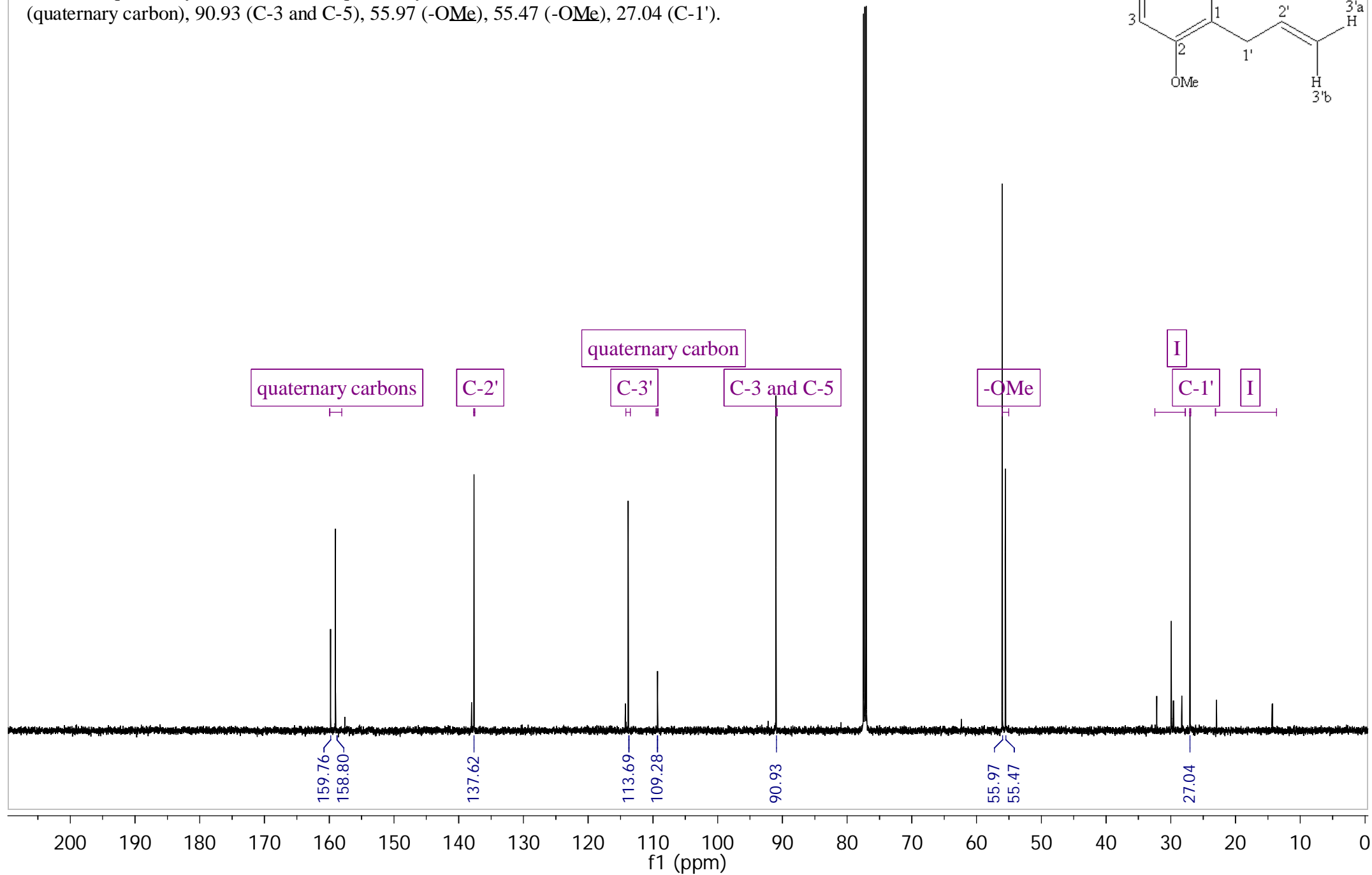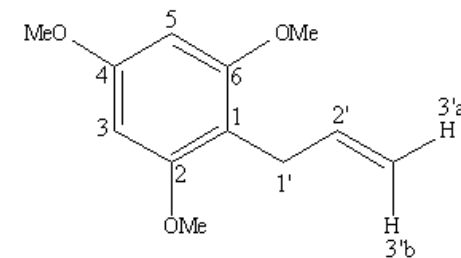
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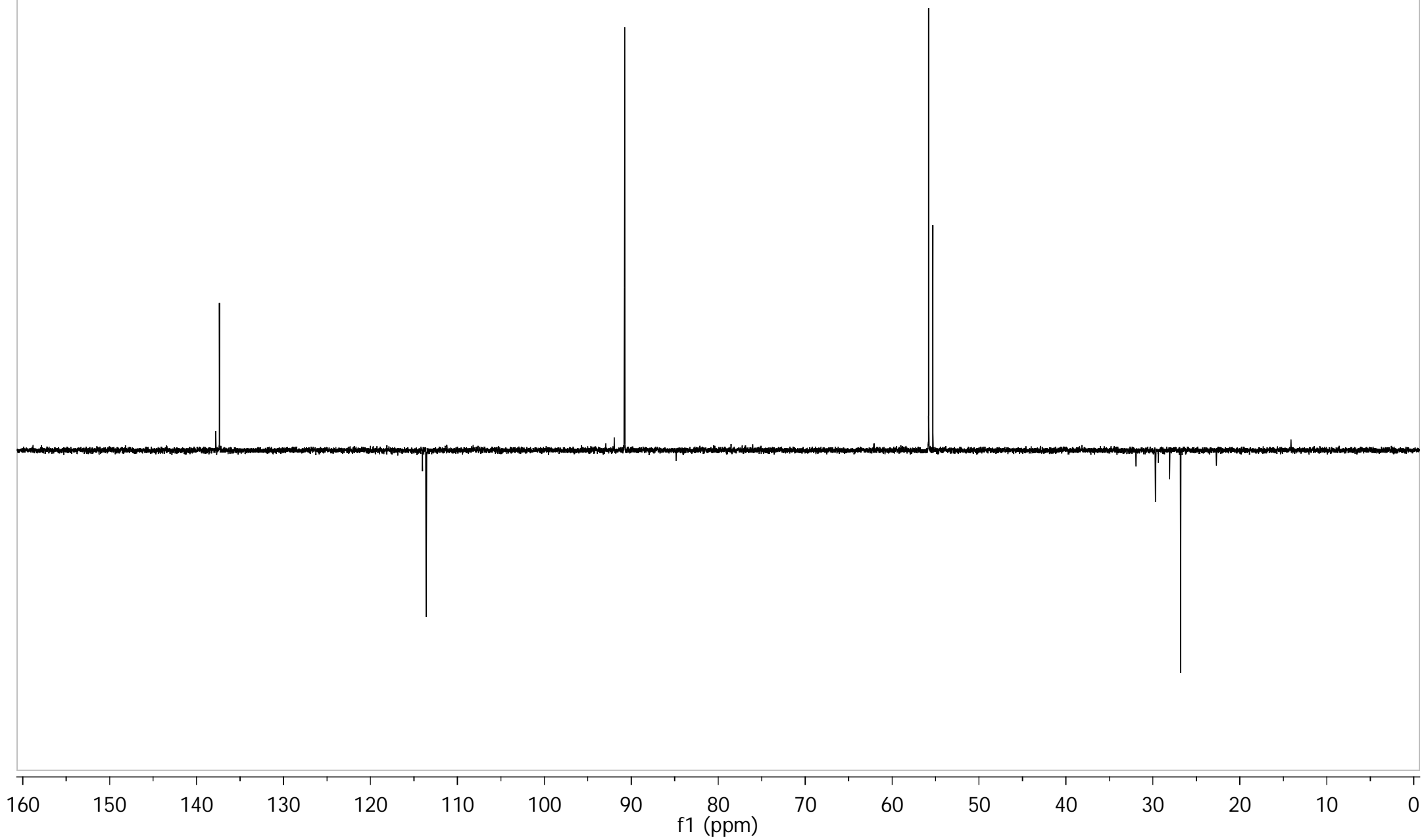
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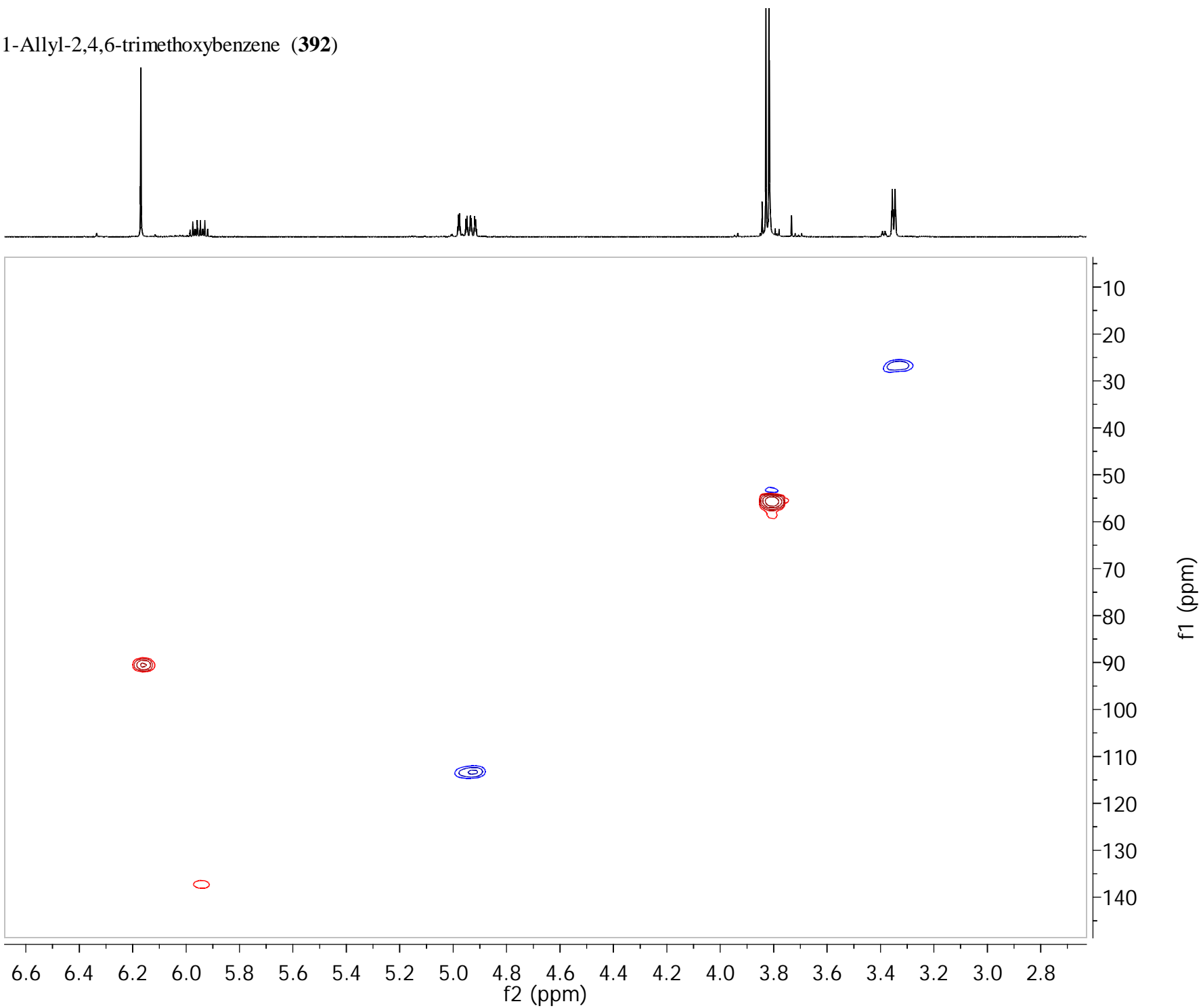
Plate 5e; HMBC [CDCl₃]: 1-Allyl-2,4,6-trimethoxybenzene (**392**)
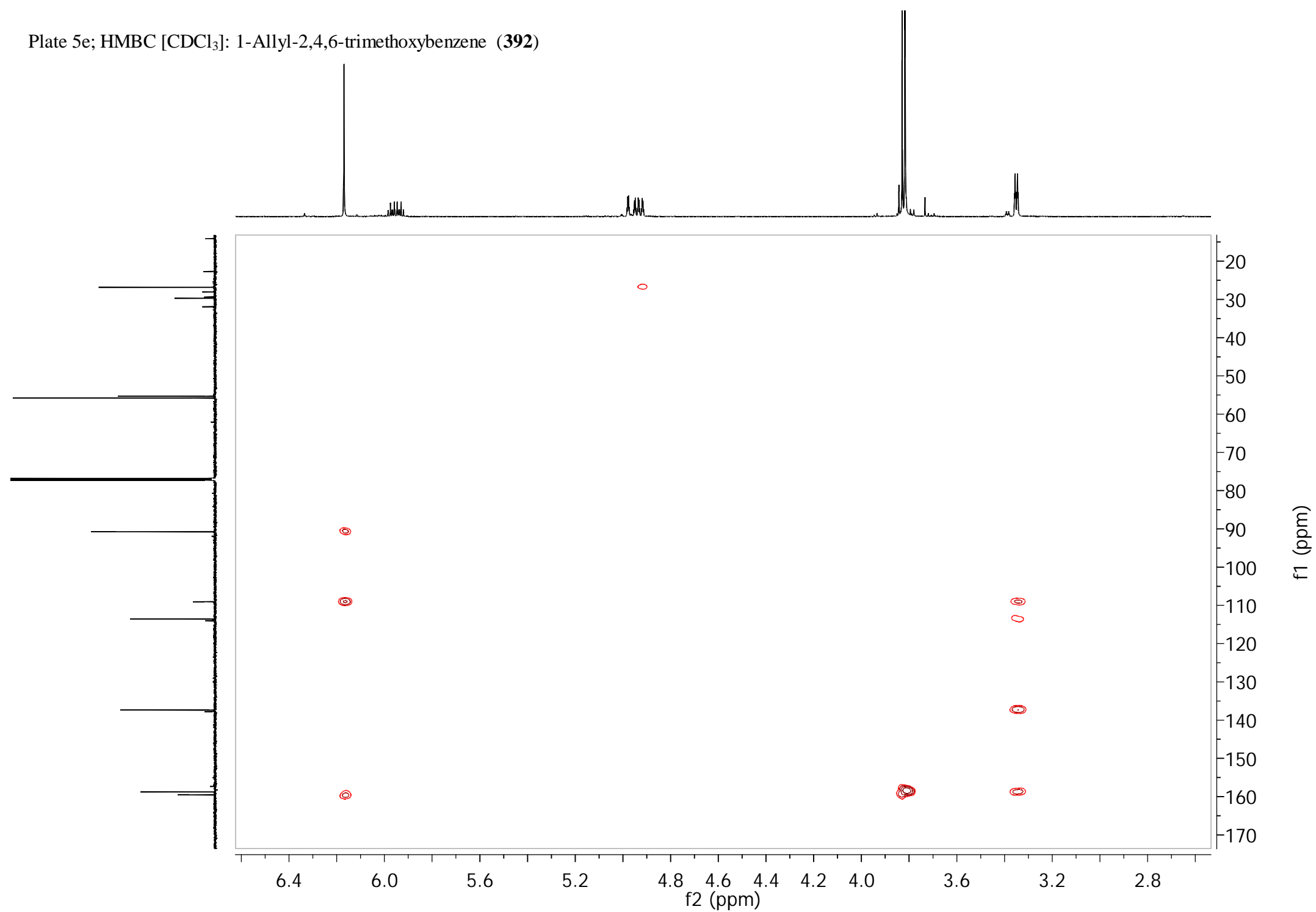
Plate 6a; ^{1}H NMR [CDCl$_3$]: 1-Allyl-2,4-dimethoxybenzene (**389**)
δ 7.04 (1H, d, J = 8.1 Hz, H-6), 6.46 (1H, d, J = 2.4 Hz, H-3), 6.44 (1H, dd, J = 8.1, 2.4 Hz, H-5), 5.98 (1H, ddt, J = 16.95, 10.22, 6.59 Hz, H-2'), 5.05–5.00 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.33–3.31 (2H, m, H-1').
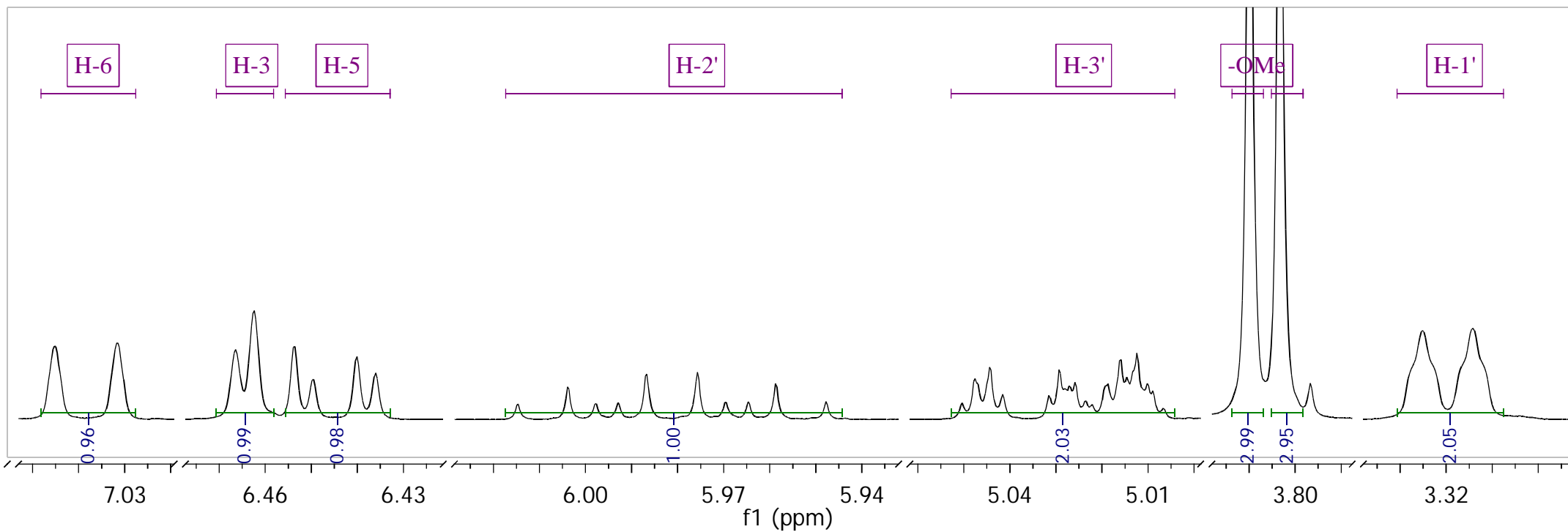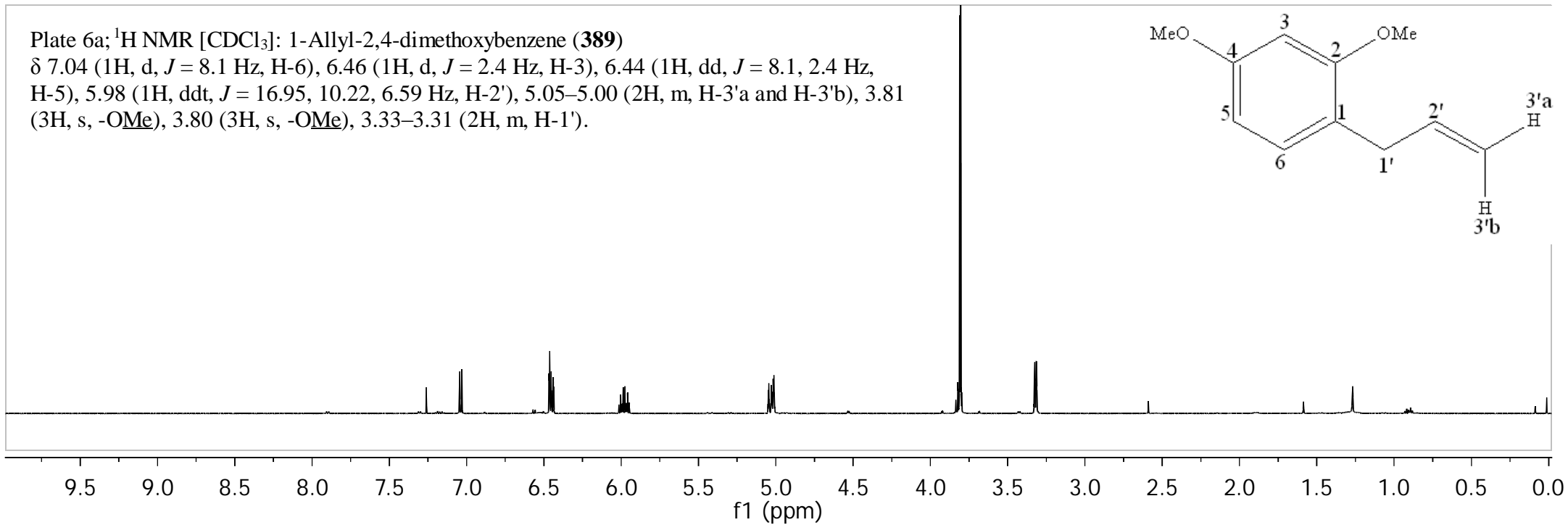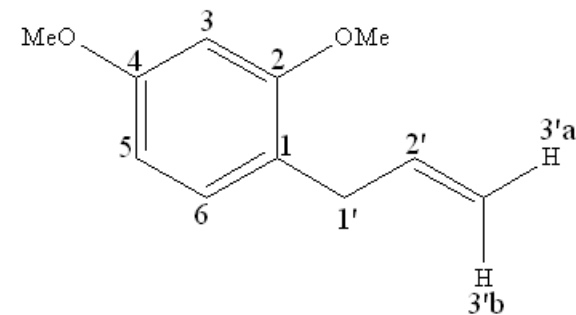
Plate 6b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-2,4-dimethoxybenzene (**389**)
δ 159.46 (C-2/4), 158.21 (C-2/4), 137.53 (C-2'), 130.08 (C-6), 121.07 (C-1), 115.10 (C-3'), 104.01 (C-3/5), 98.64 (C-3/5), 55.48 (-OMe), 33.50 (C-1').
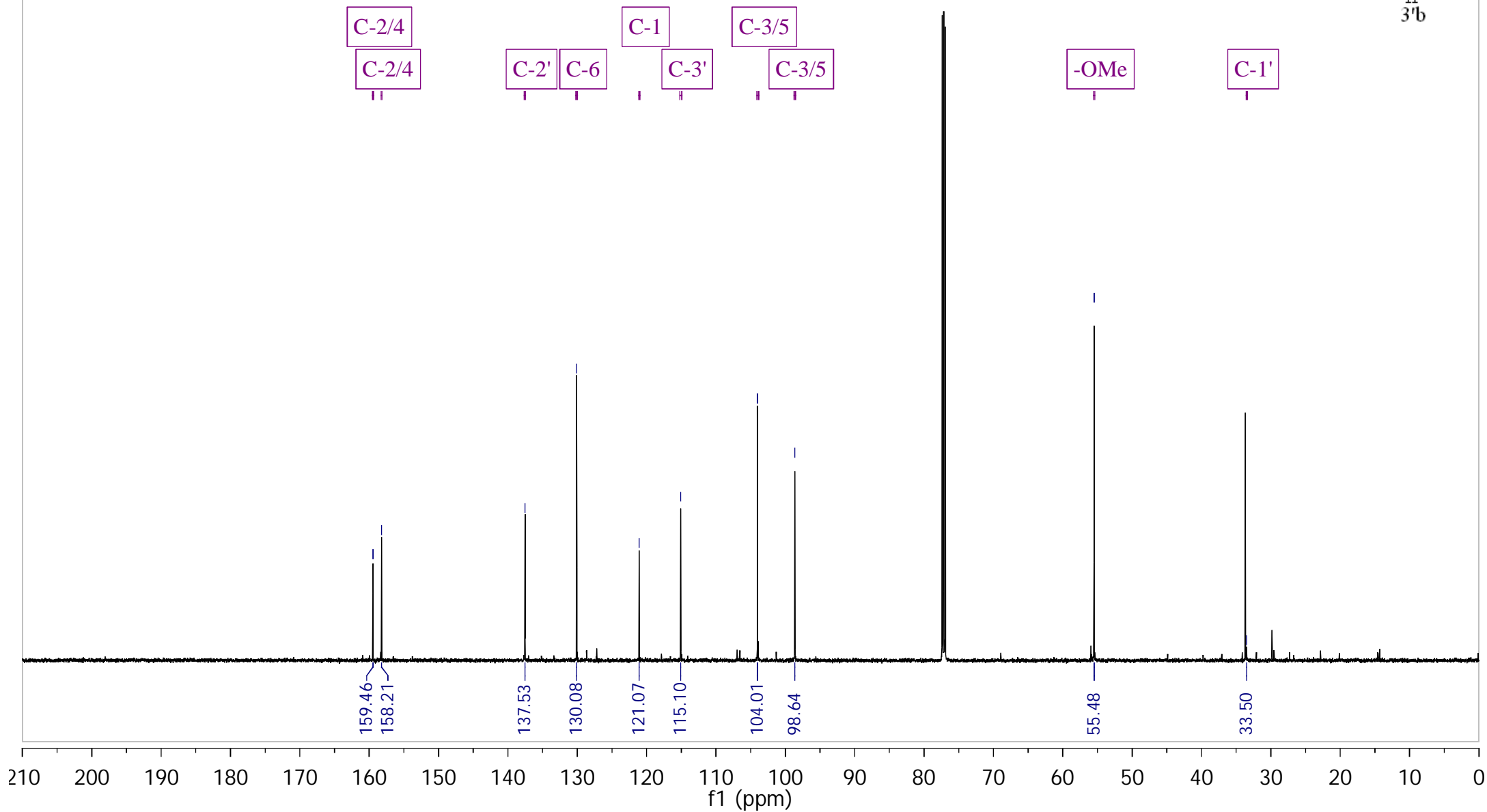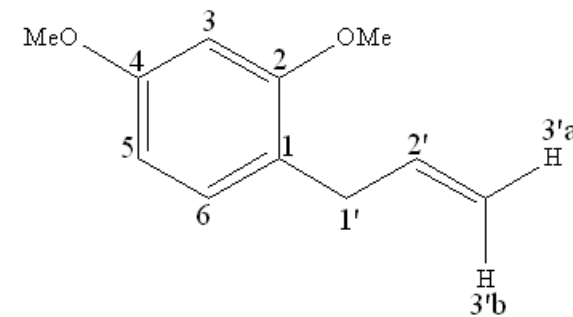
Plate 6c; DEPT [CDCl$_3$]: 1-Allyl-2,4-dimethoxybenzene (**389**)
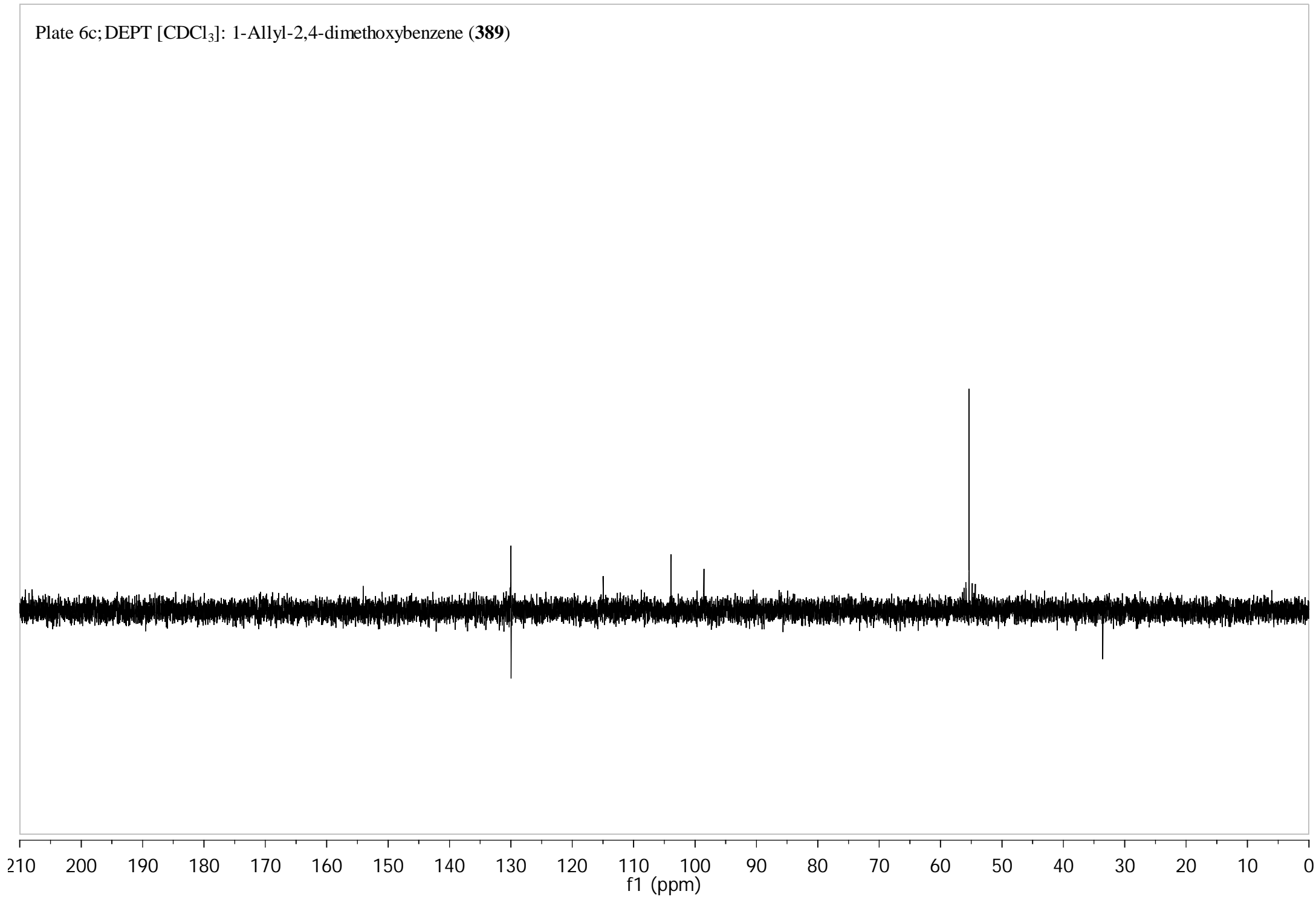
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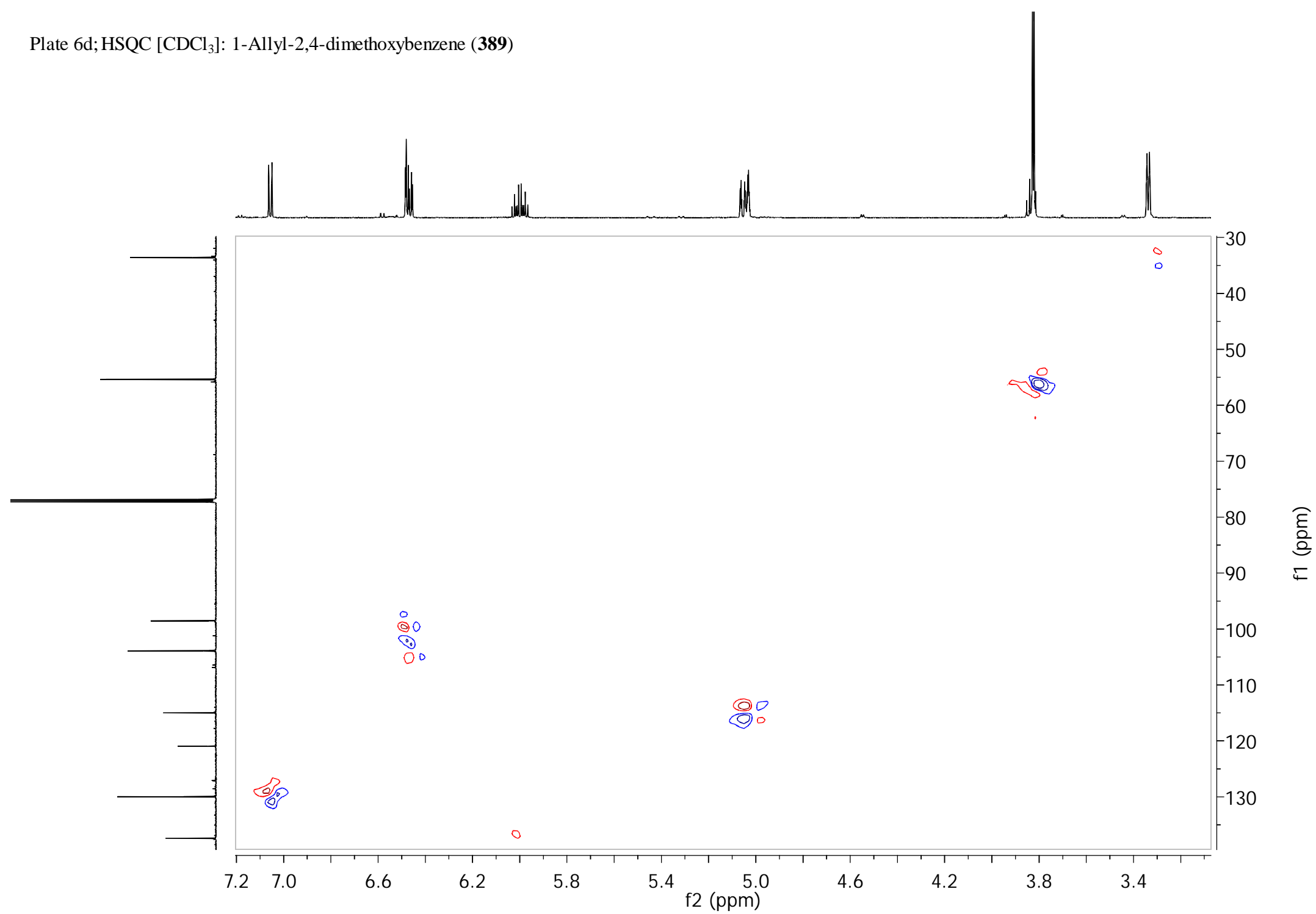
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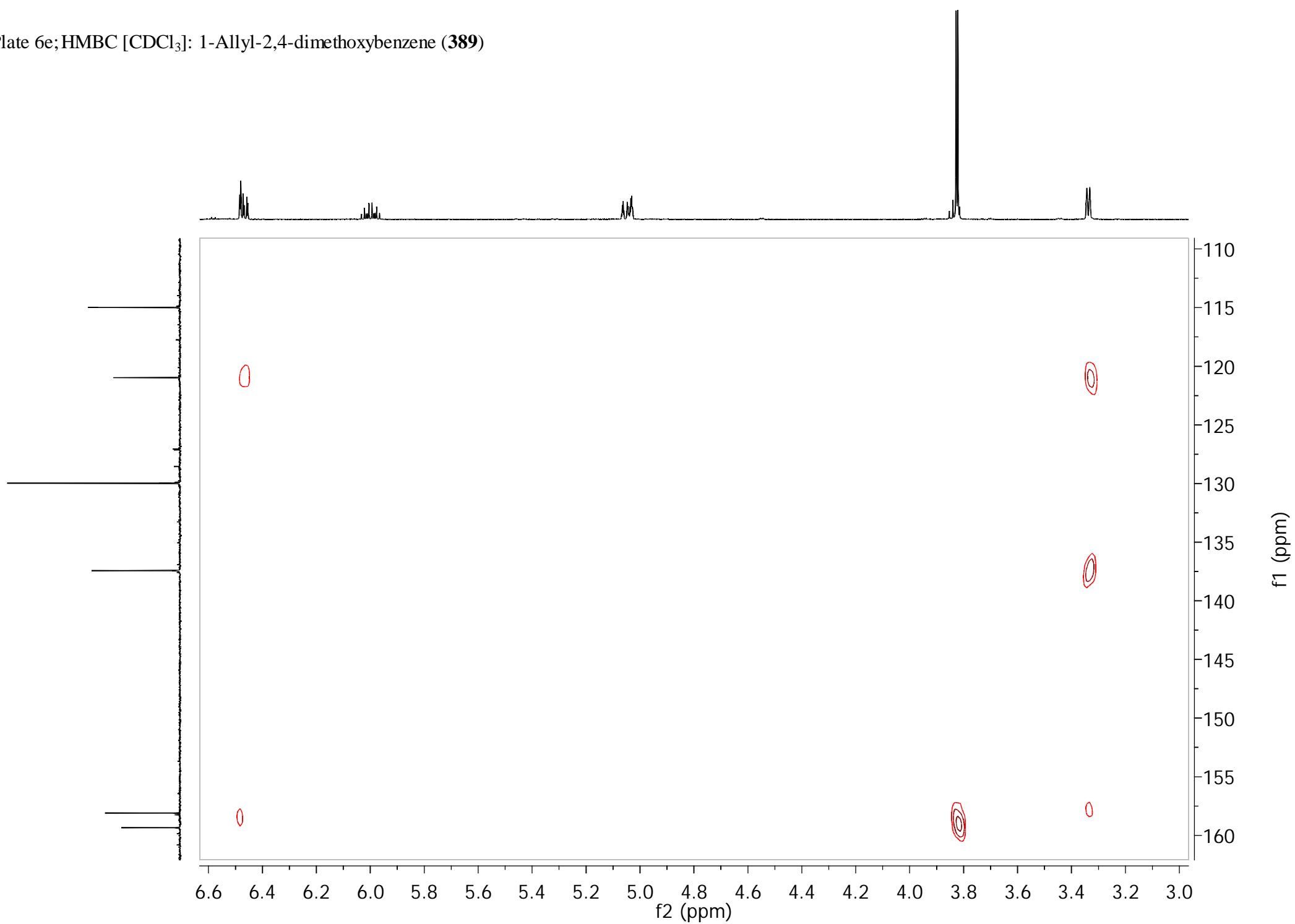
Plate 7a; ¹H NMR [CDCl₃]: 1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**)
δ 7.22 (1H, d, *J* = 8.57 Hz, H-6), 6.88 (1H, dd, *J* = 8.57, 2.56 Hz, H-5), 6.82 (1H, d, *J* = 2.56 Hz H-3), 5.93–5.87 (1H, m, H-2'), 5.14–5.08 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -OMe), 3.41–3.40 (2H, m, H-1').
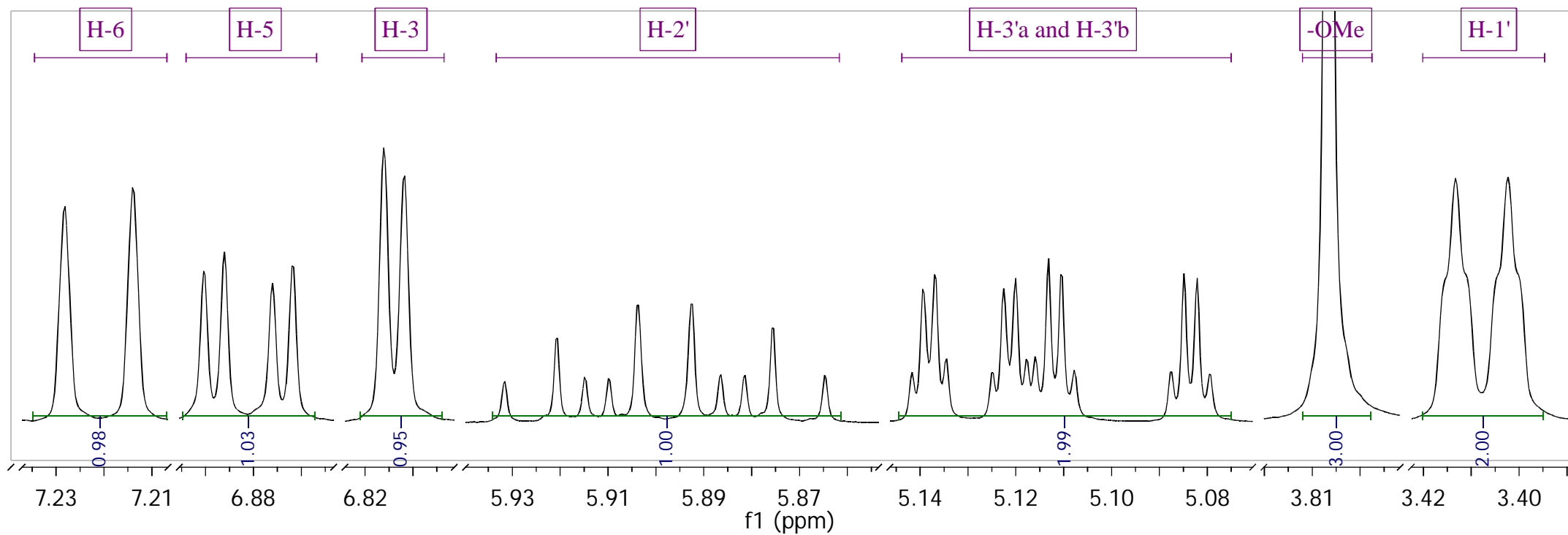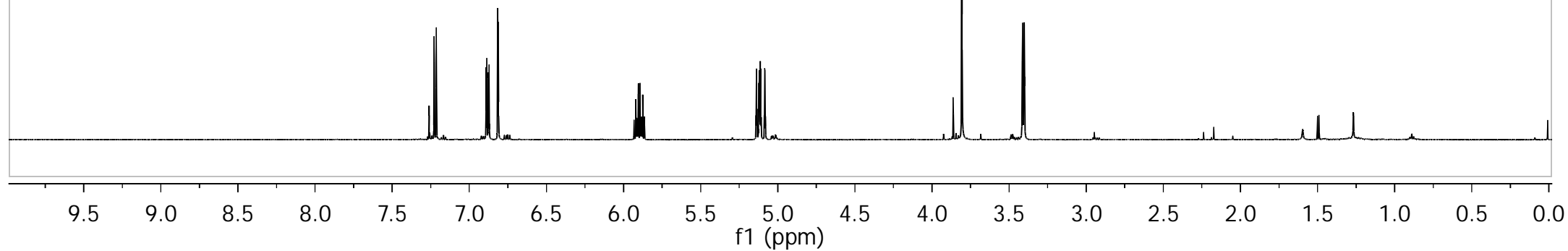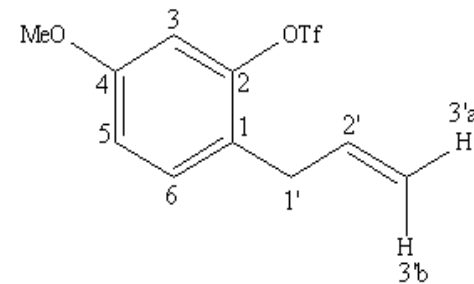
Plate 7b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene (**450**)
δ 159.25 (quaternary carbon), 148.16 (quaternary carbon), 135.22 (C-2'), 131.78 (C-6), 124.43 (quaternary carbon), 118.59 (q, J = 320.10 Hz, -OSO$_2$C̲F$_3$) 116.95 (C-3'), 115.54 (C-5), 107.34 (C-3), 55.67 (-OM̲e), 33.33 (C-1').
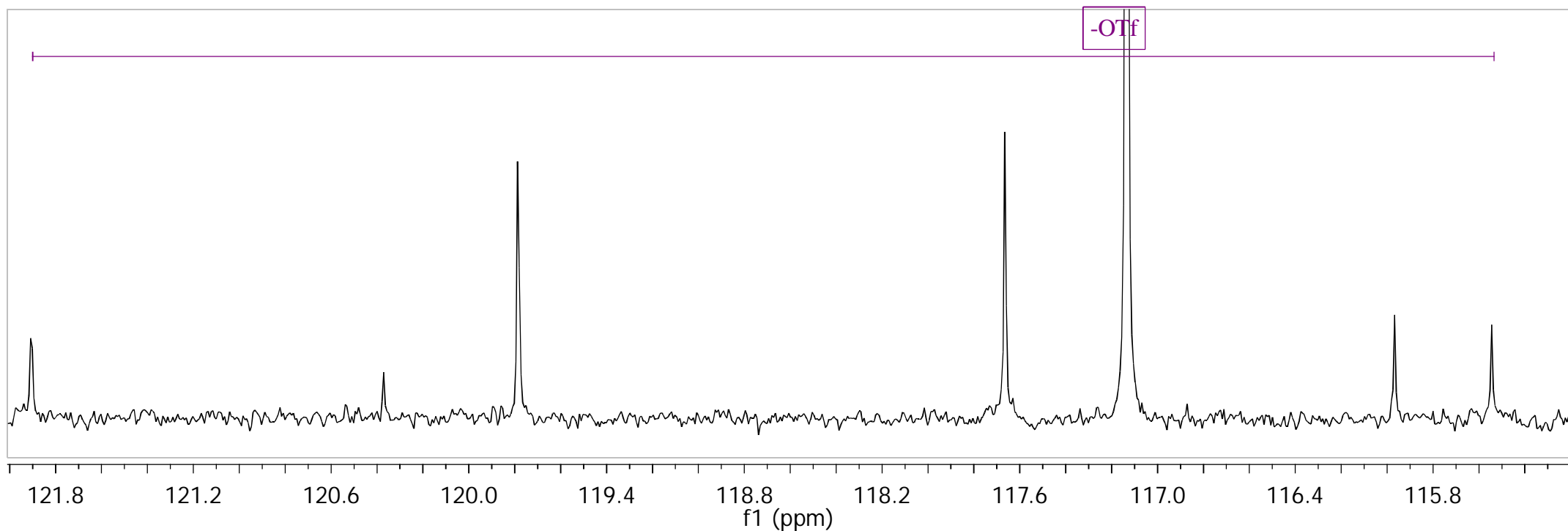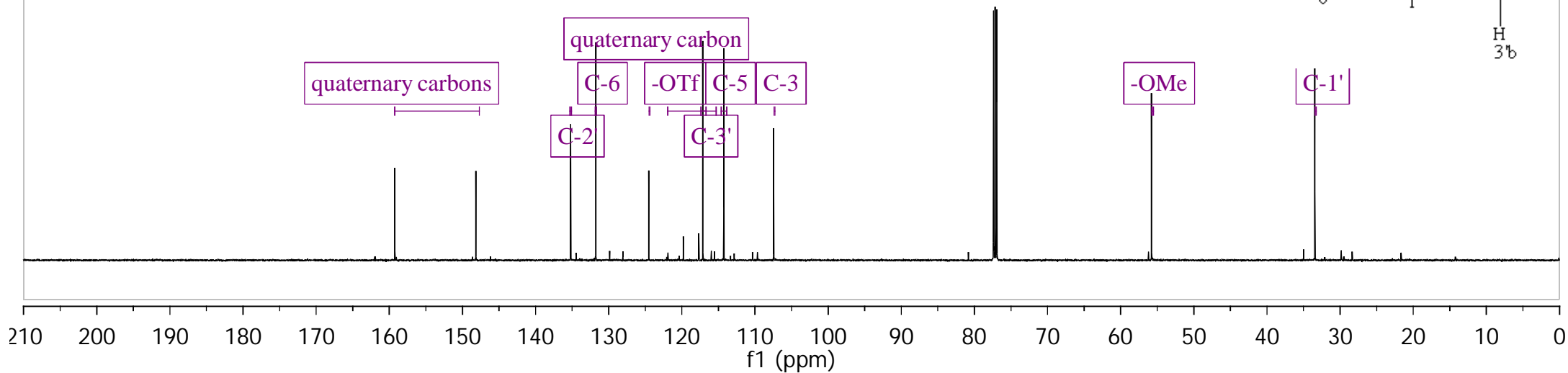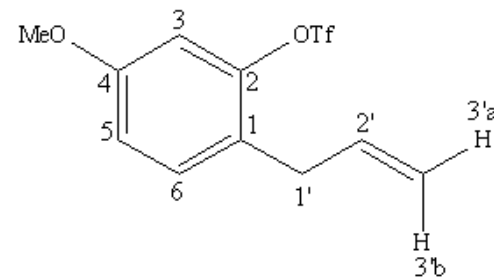
Plate 7c; DEPT [CDCl₃]: 1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene
(**450**)
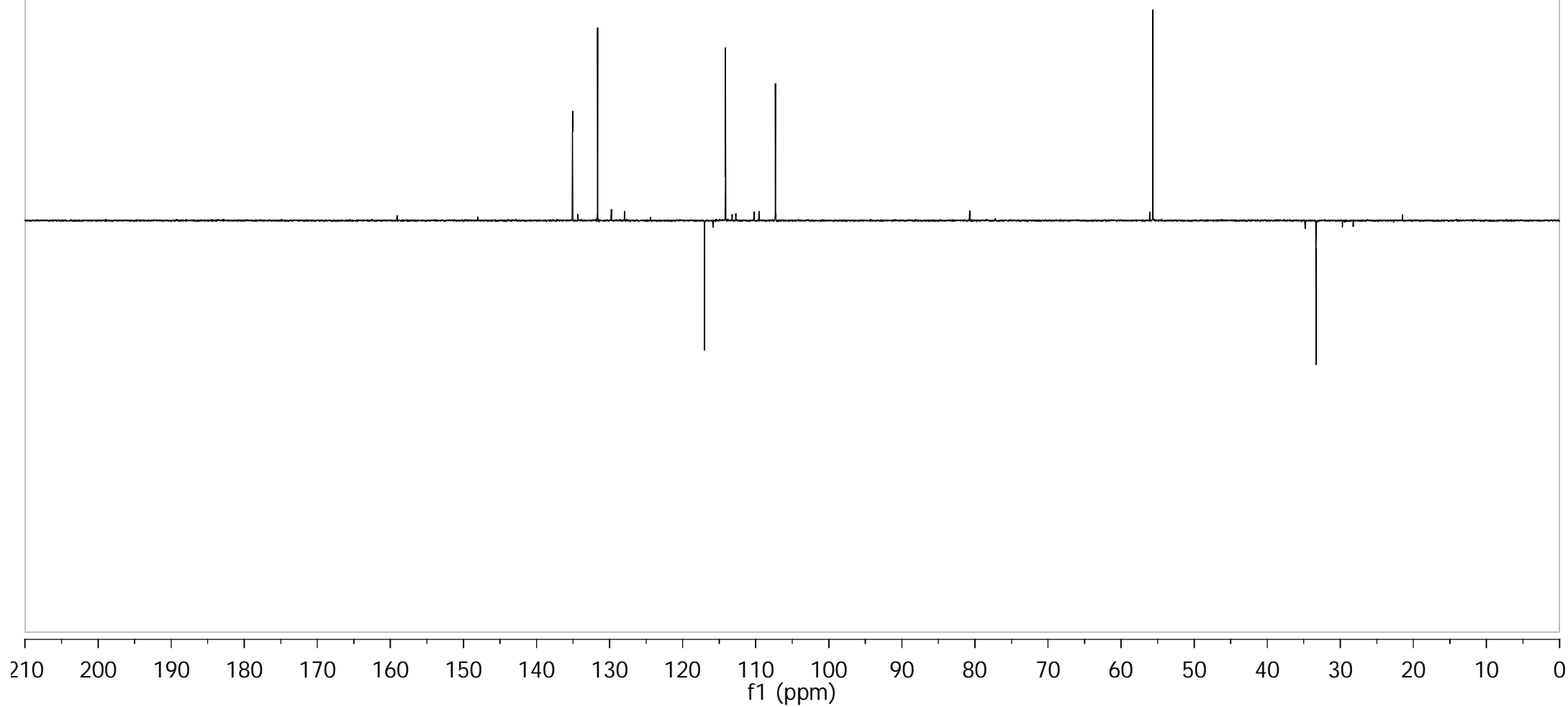
Plate 7d; HSQC [CDCl$_3$]:1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene
(**450**)
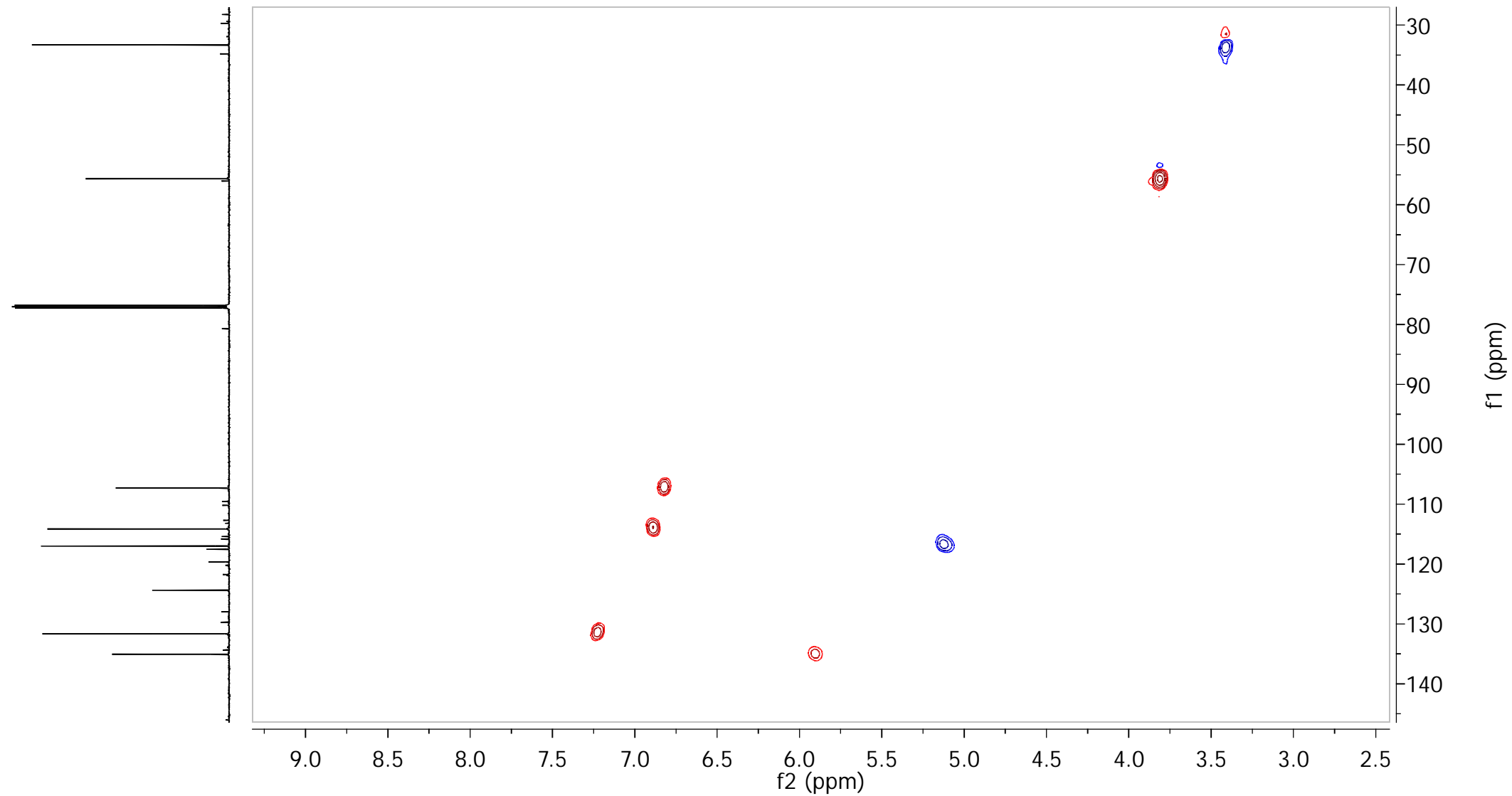
Plate 7e; HMBC [CDCl3]:1-Allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene
(**450**)
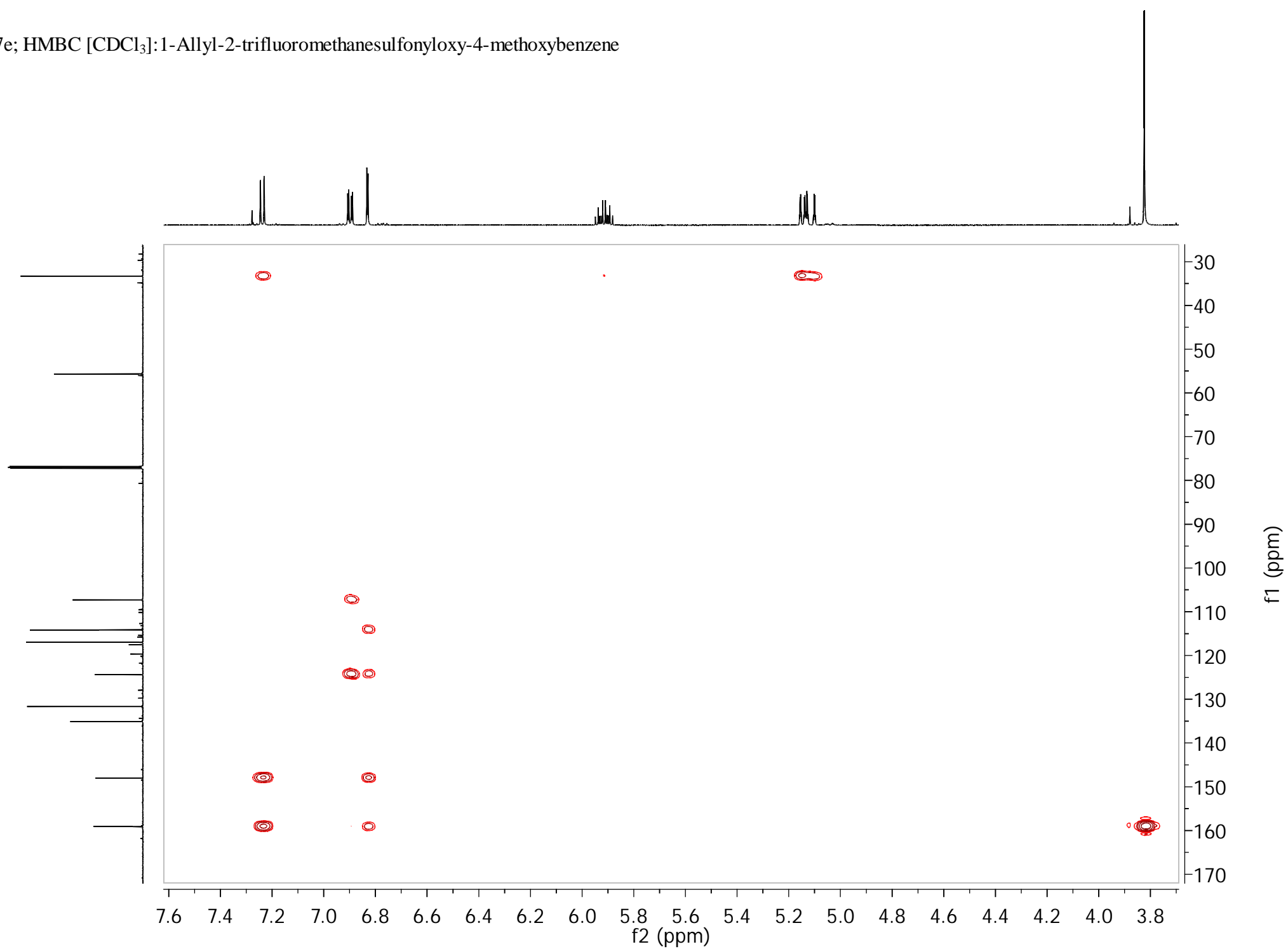
Plate 8a; ¹H NMR [CDCl₃]: 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**)
δ 7.13 (1H, d, J = 8.3 Hz, H-5), 6.85 (1H, d, J = 1.9 Hz, H-2), 6.79 (1H, dd, J = 8.3, 1.9 Hz, H-6), 5.94 (1H, ddt, J = 17.1, 10.5, 6.7 Hz, H-2'), 5.14–5.10 (2H, m, H-3'a and H-3'b), 3.90 (3H, s, -O<u>Me</u>), 3.40 (2H, d, J = 6.7 Hz, H-1').
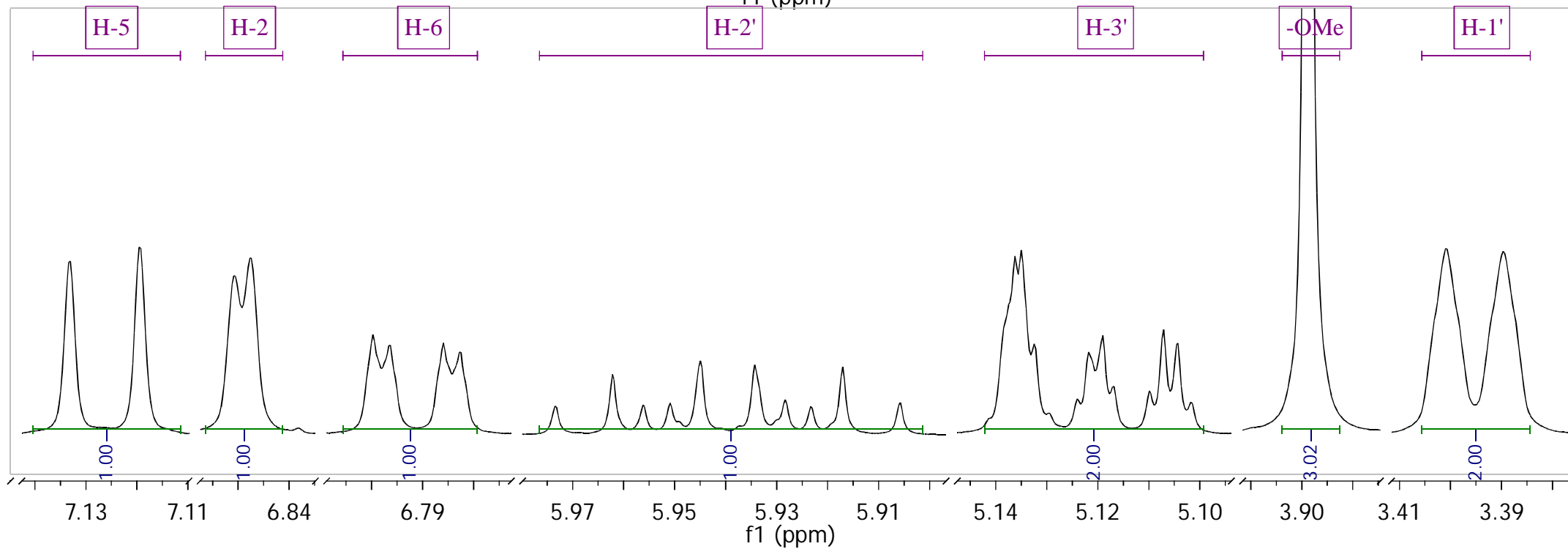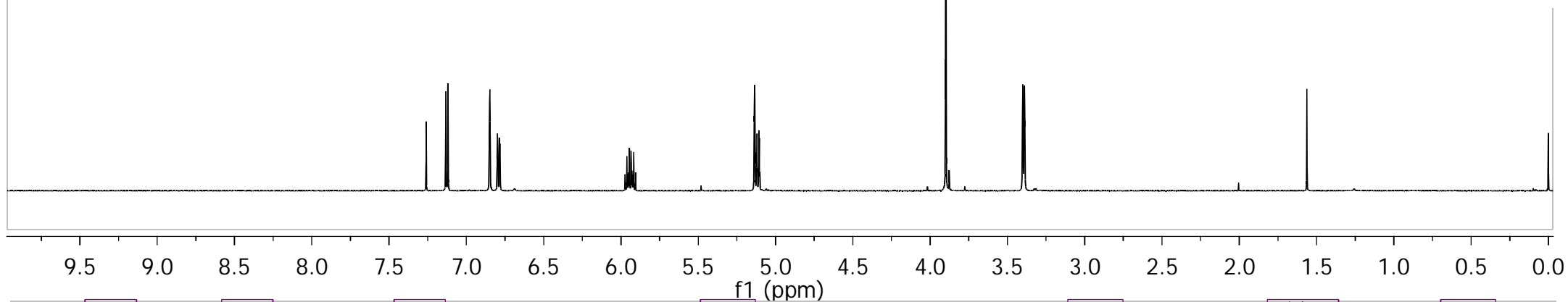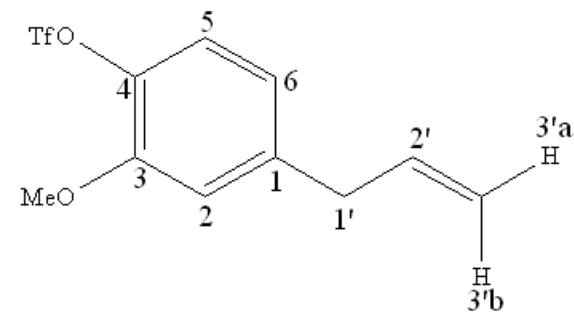
Plate 8b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**)
δ 151.30 (C-3), 141.92 (C-4), 137.23 (C-1), 136.42 (C-2'), 122.29 (C-5), 120.93 (C-6), 118.89 (q, J = 320.51 Hz, -OSO$_2$CF$_3$), 116.97 (C-3'), 113.45 (C-2), 56.22 (-OMe), 40.15 (C-1').
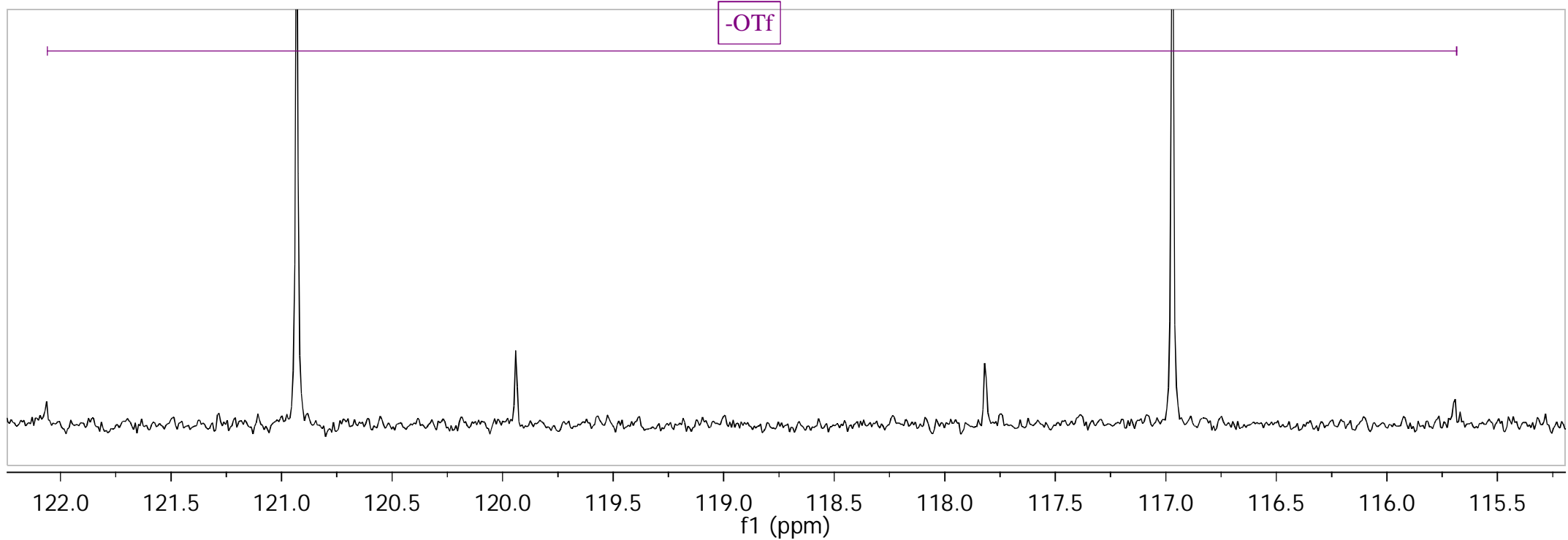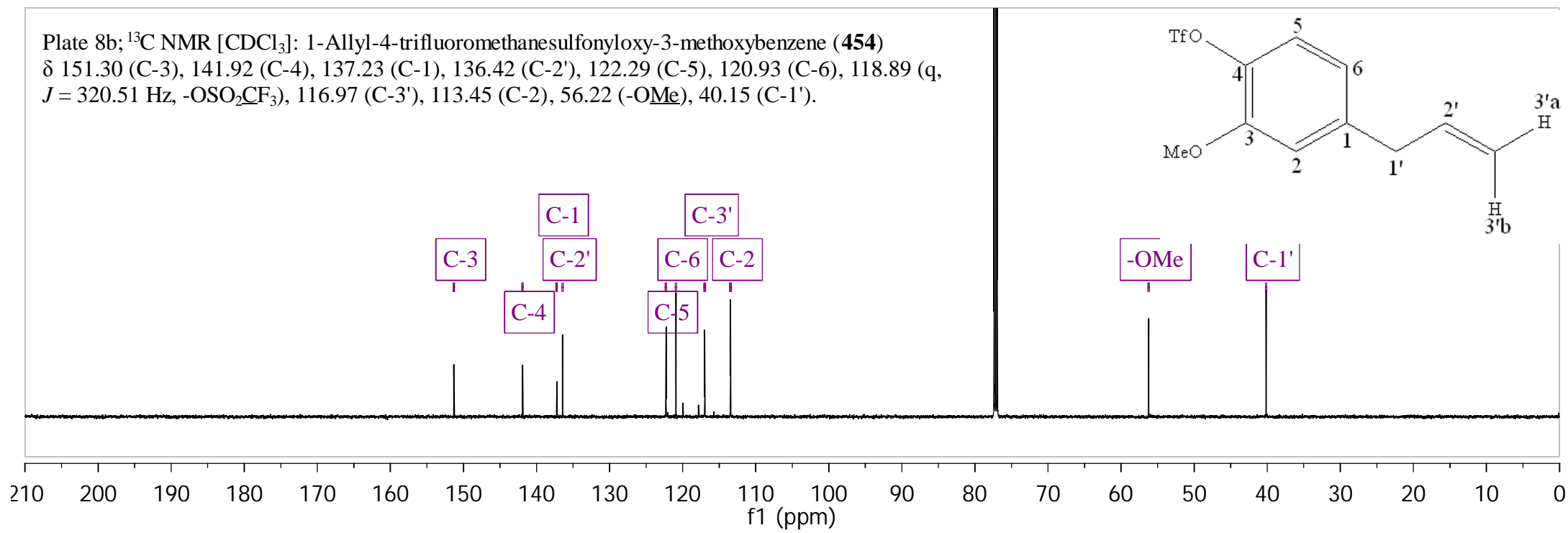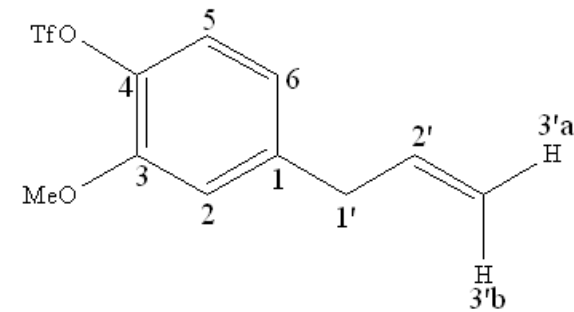
Plate 8c; DEPT [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**)
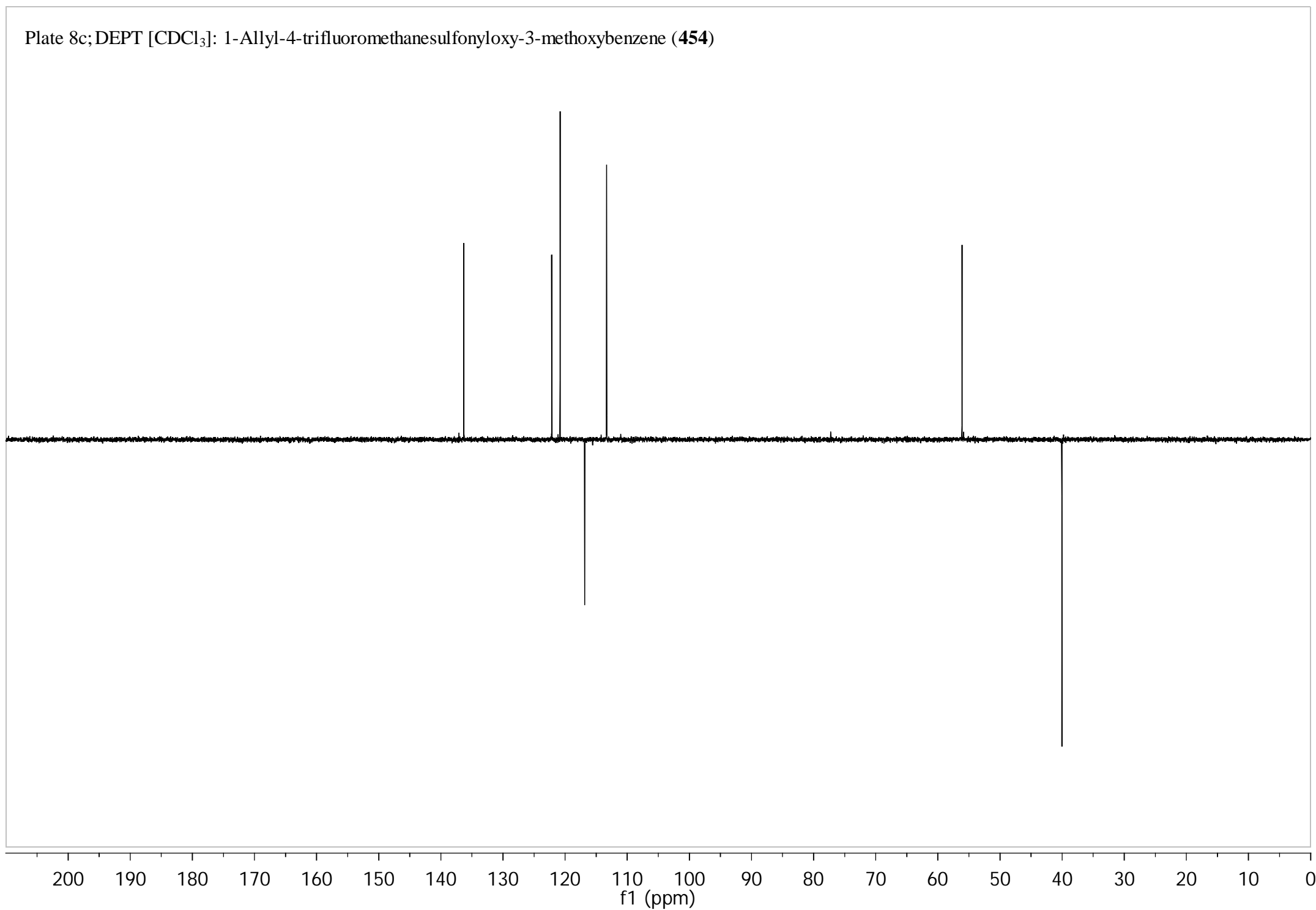
Plate 8d; HSQC [CDCl₃]: 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**)
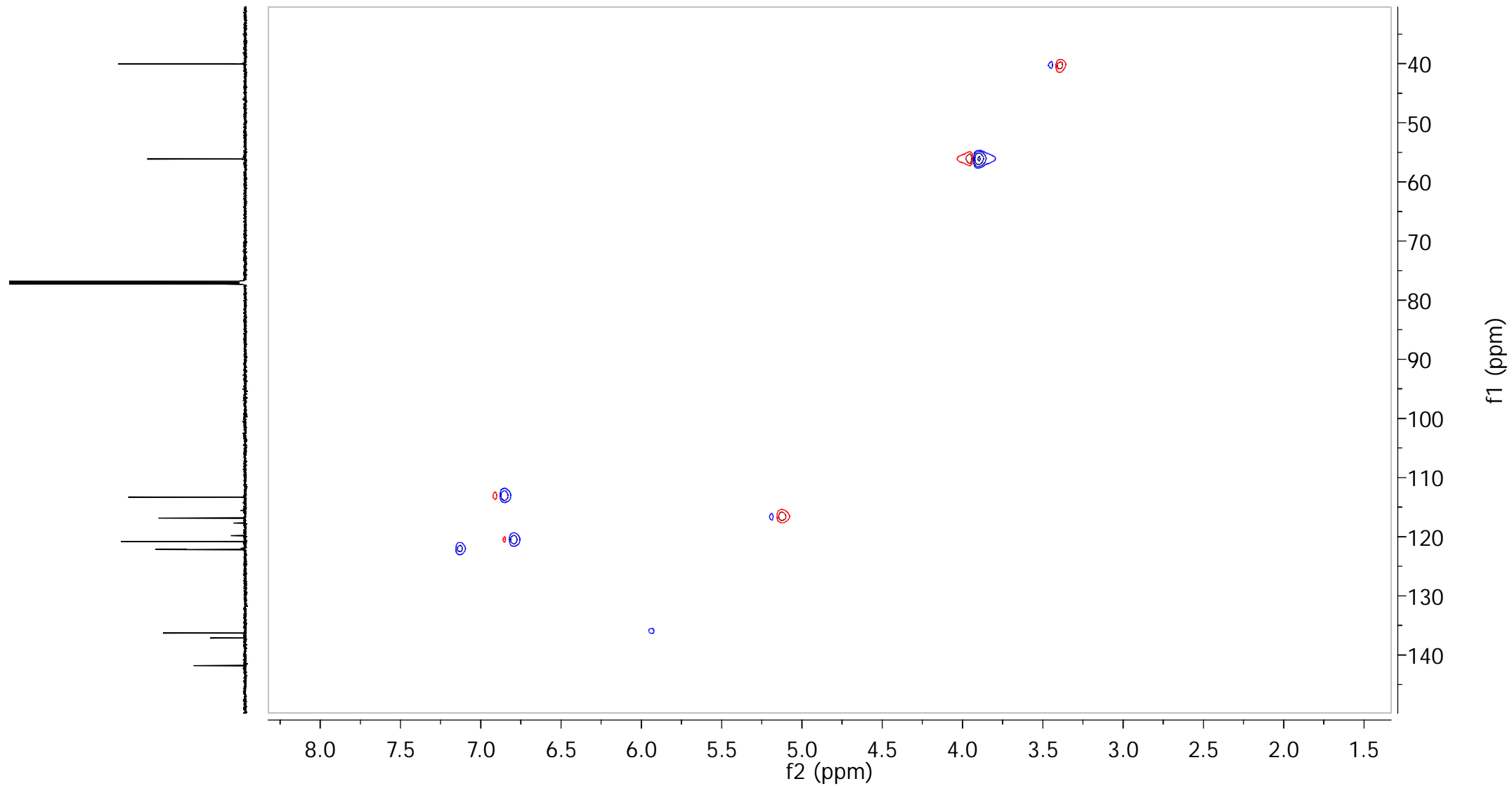
Plate 8e; HMBC [CDCl₃]: 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**)
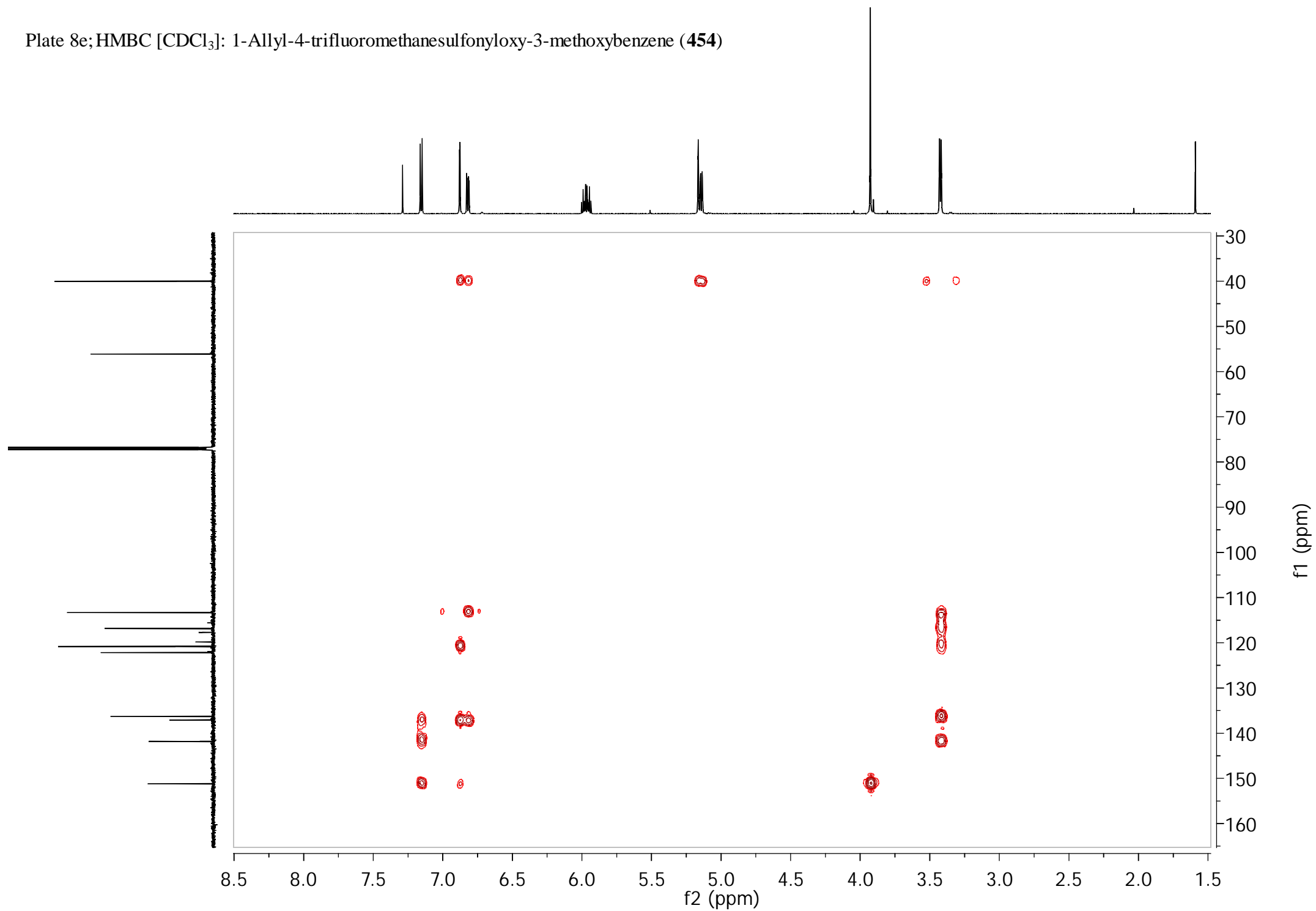
Plate 8f; ^{19}F [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene (**454**)
δ -74.70 (-OSOC$\underline{F}_3$)

-OTf
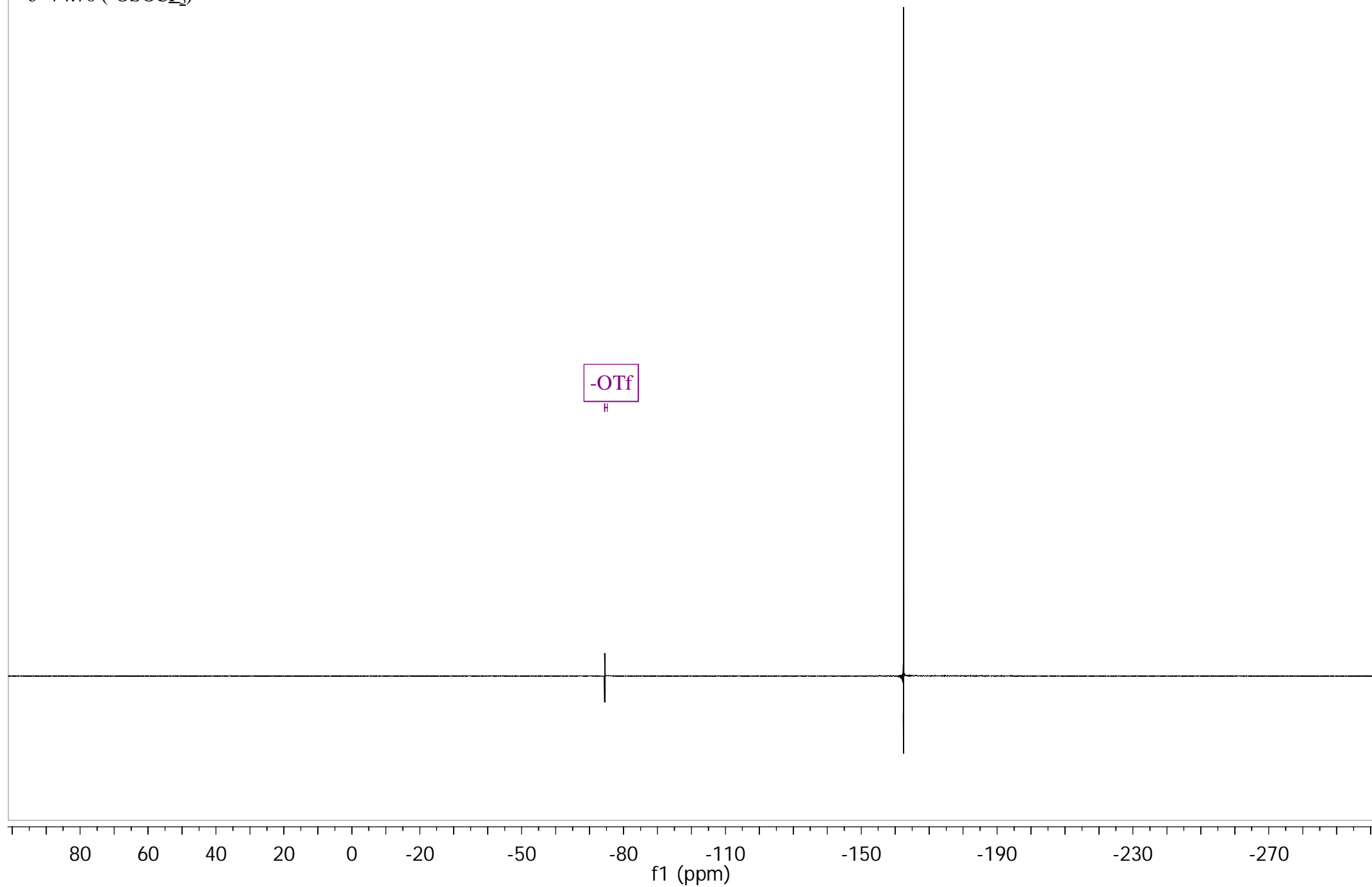
Plate 9a; ^{1}H NMR [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene
(**455**)
δ 6.45 (2H, s, H-2 and H-6), 5.97–5.90 (1H, m, H-2'), 5.16–5.12 (2H, m, H-3'a and H-3'b),
3.87 (6H, s, -OMe), 3.37 (2H, m, H-1').
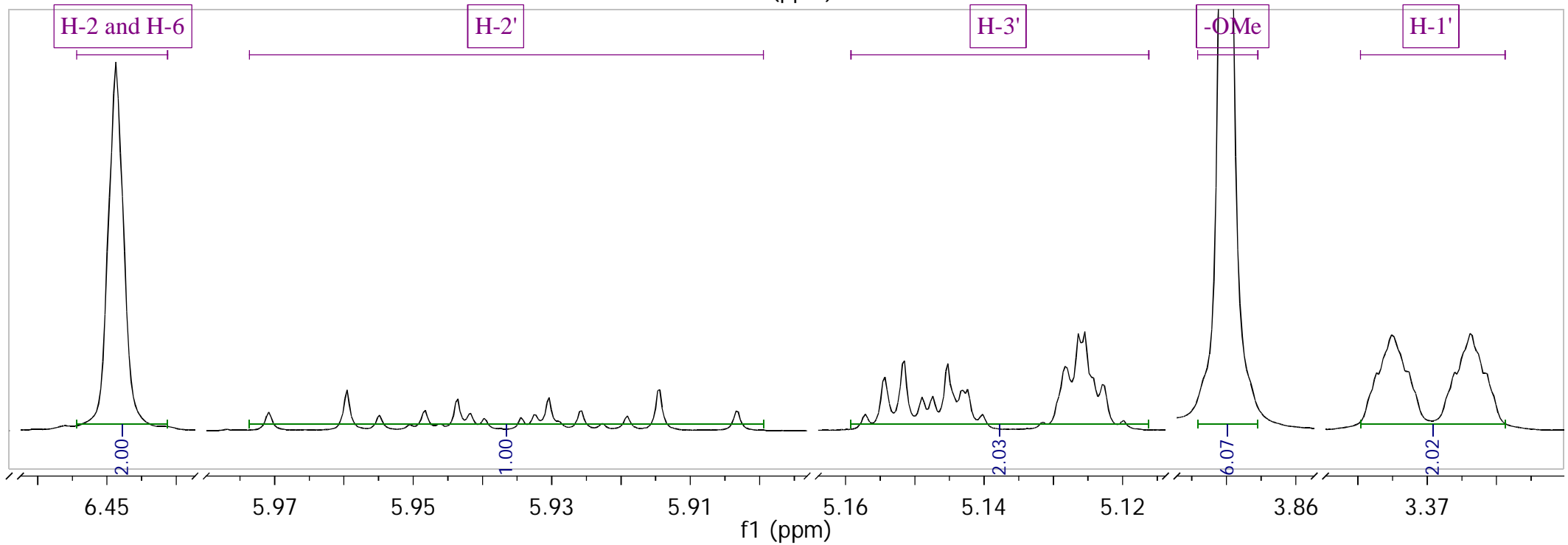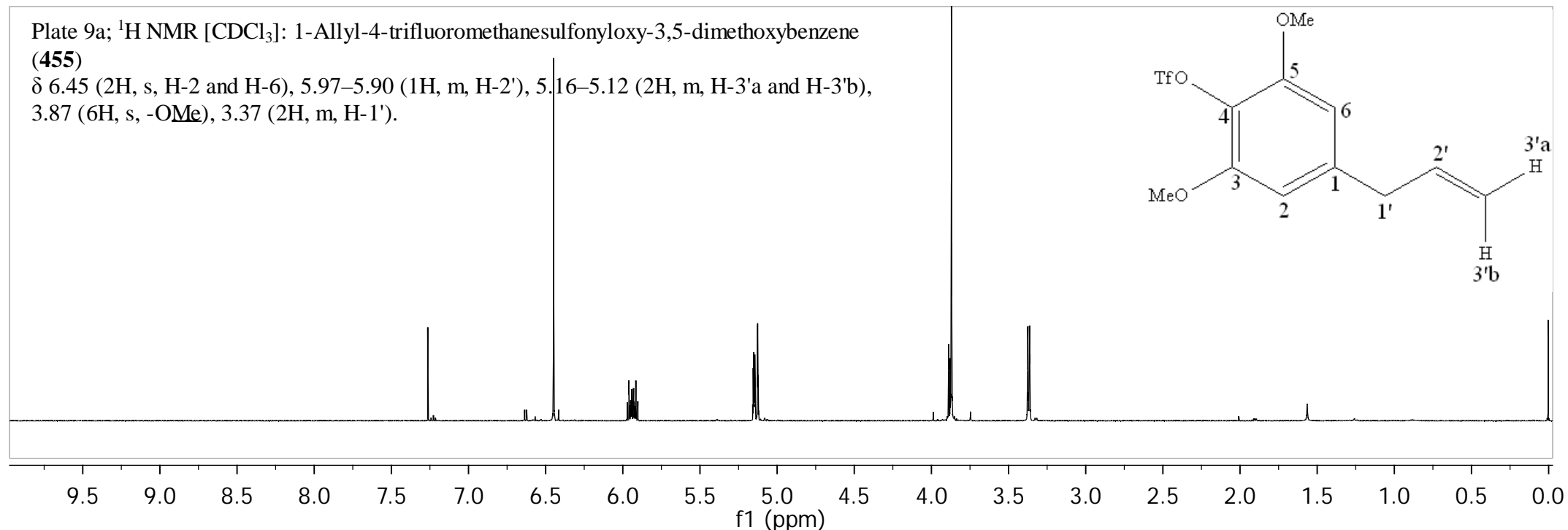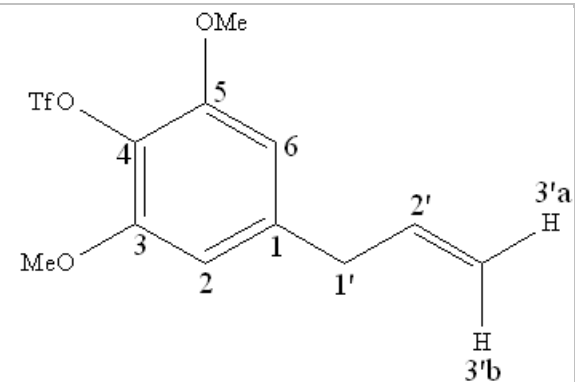
Plate 9b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**)
δ 152.32 (C-3 and C-5), 141.35 (C-1), 136.36 (C-2'), 126.41 (C-4), 118.05 (q, 320.57 Hz, -OSO$_2$CF$_3$),
117.02 (C-3'), 105.16 (C-2 and C-6), 56.34 (-OMe), 40.77 (C-1').
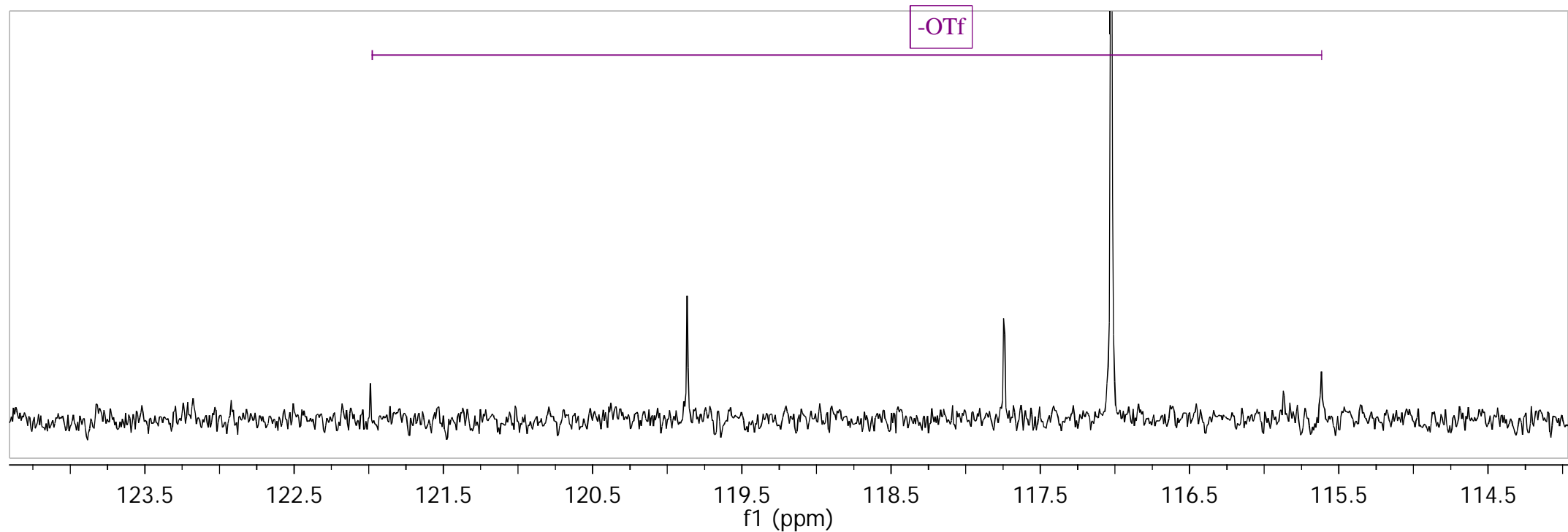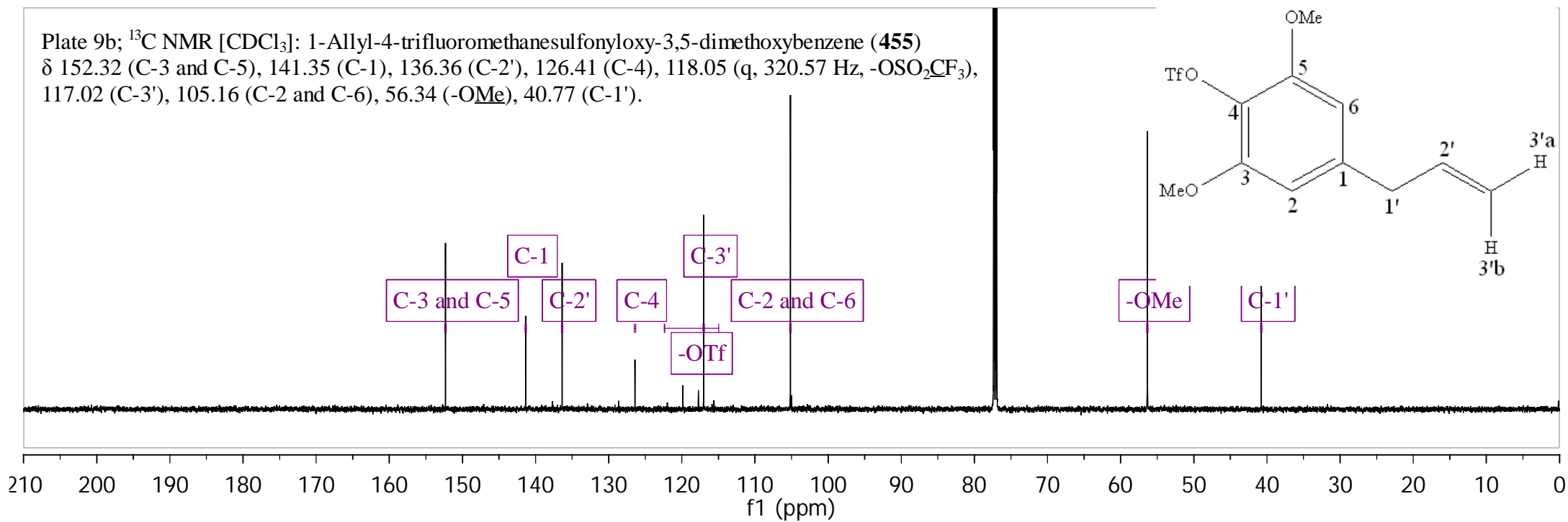
Plate 9c; ^{13}C NMR [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**)
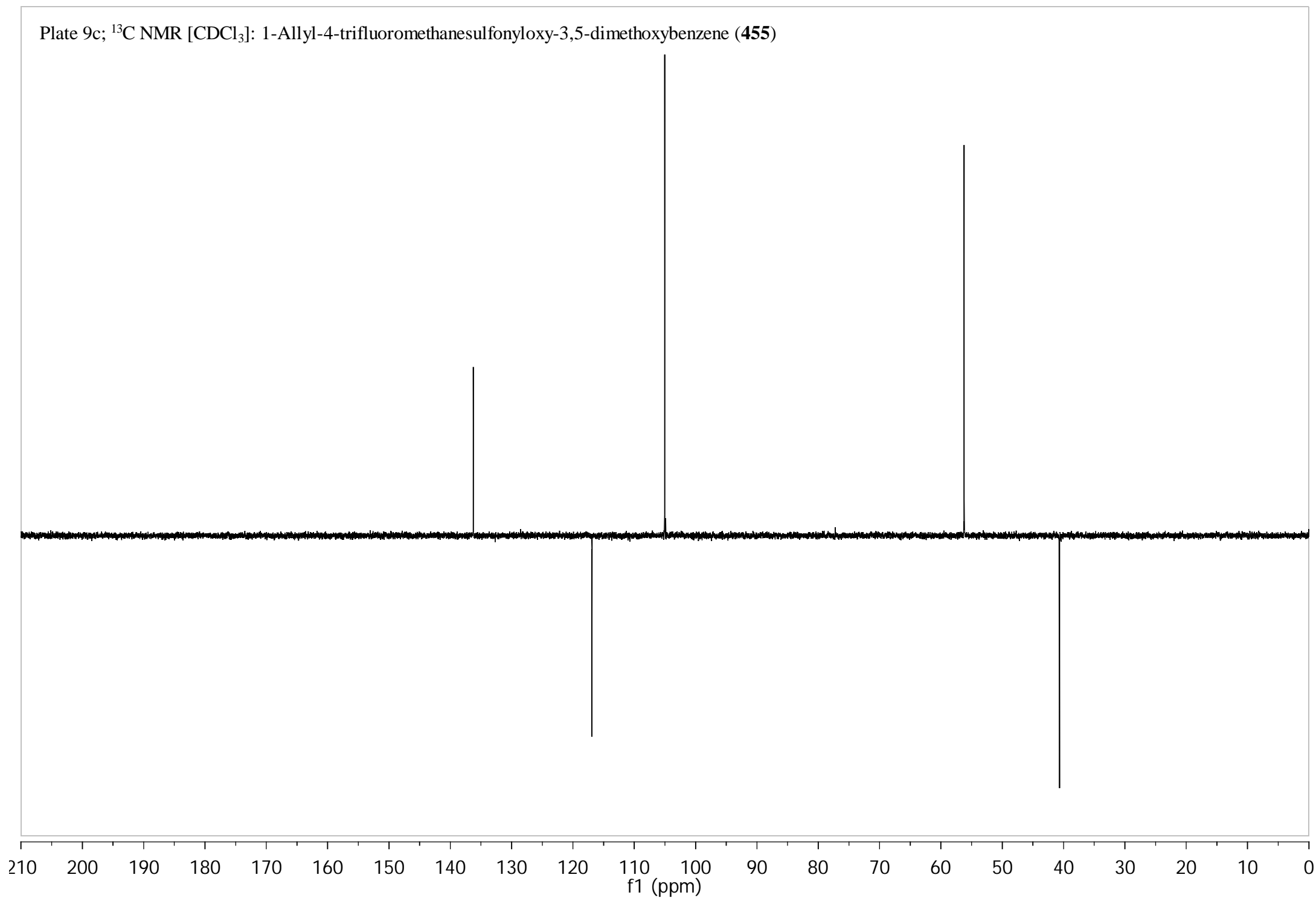
Plate 9d; HSQC [CDCl₃]: 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**)
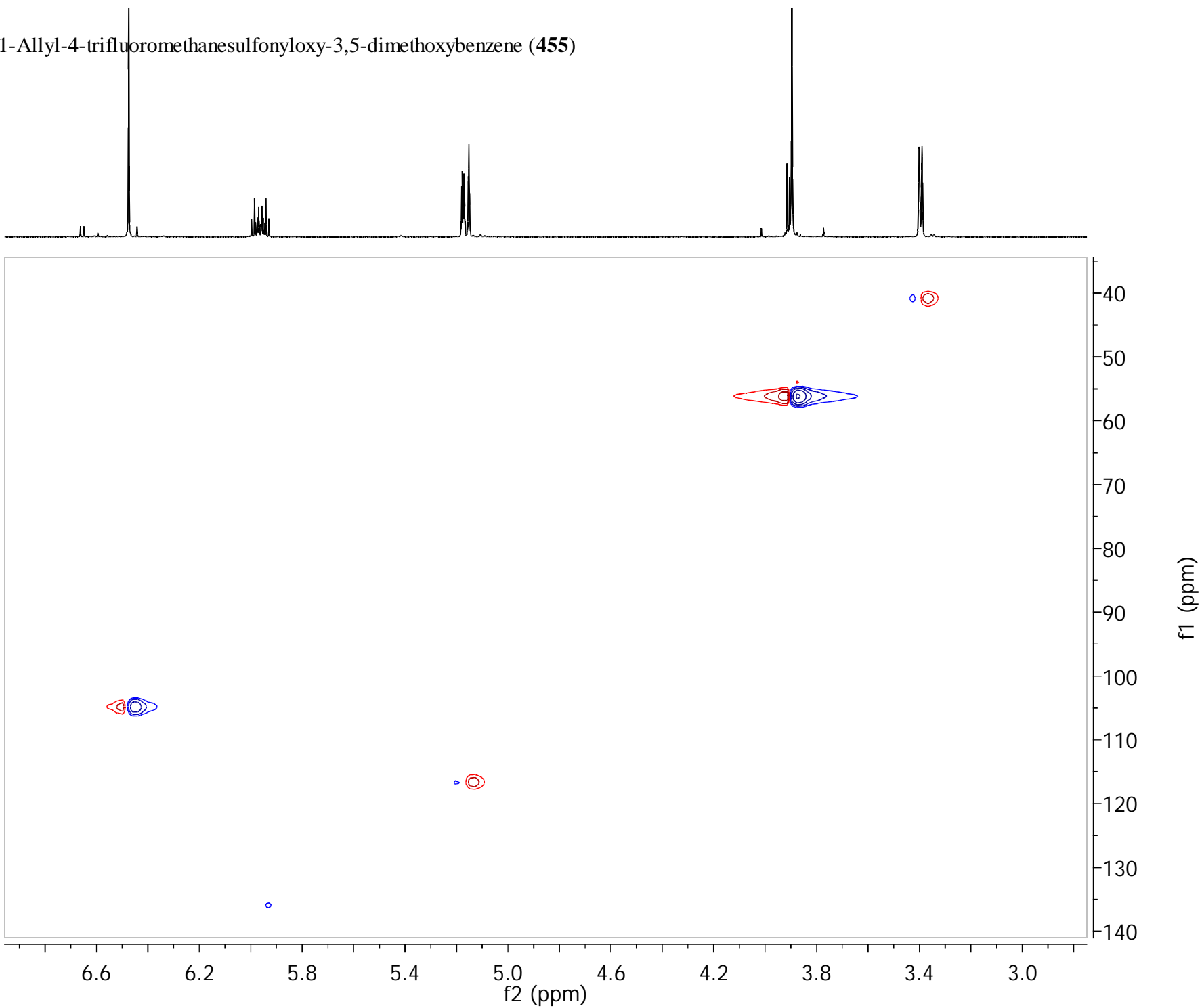
Plate 9e; HMBC [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**)
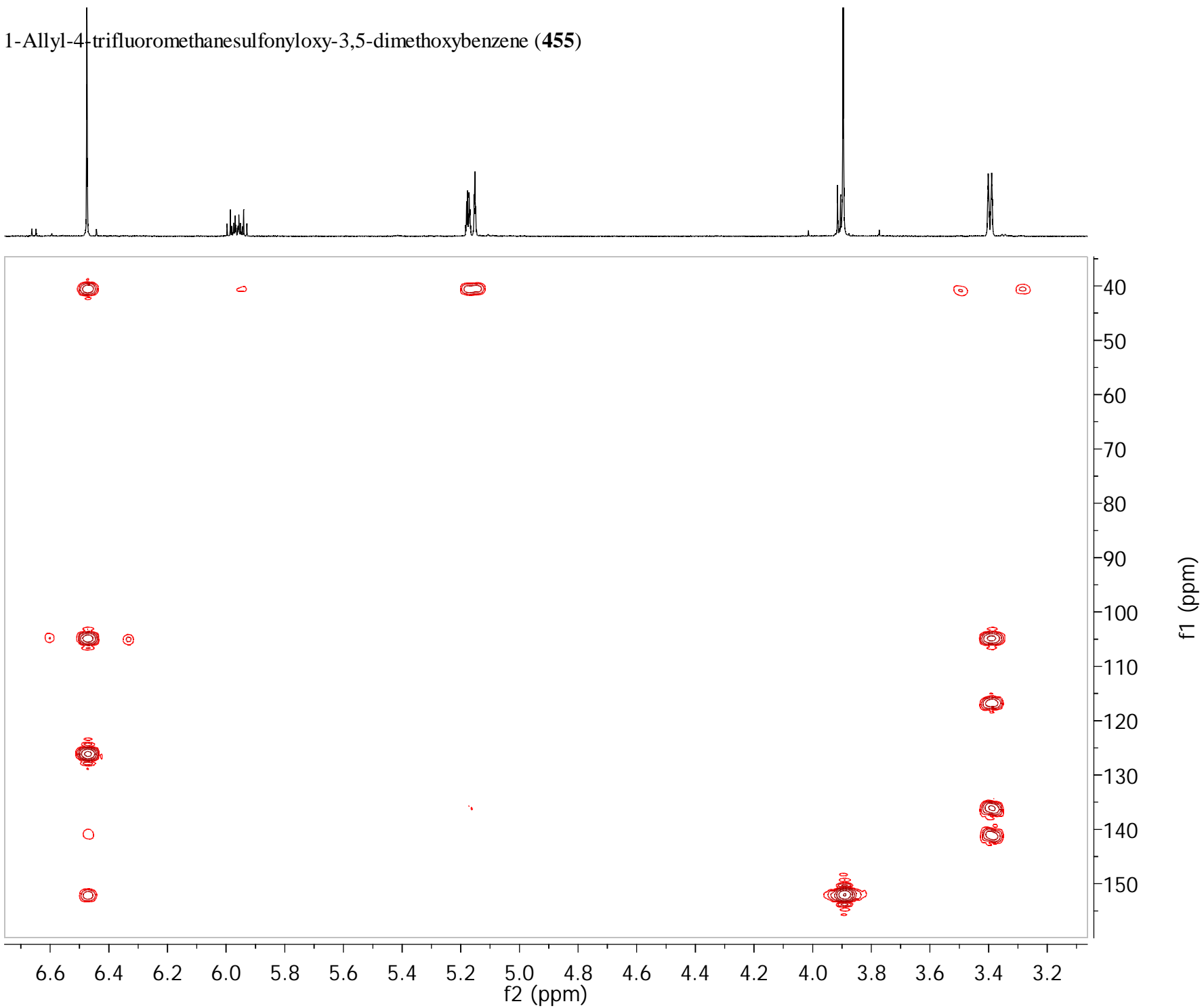
Plate 9f; ^{19}F NMR [CDCl$_3$]: 1-Allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene (**455**)
δ -76.90 (-OSOC$\underline{F}_3$)

-OTf

f1 (ppm)
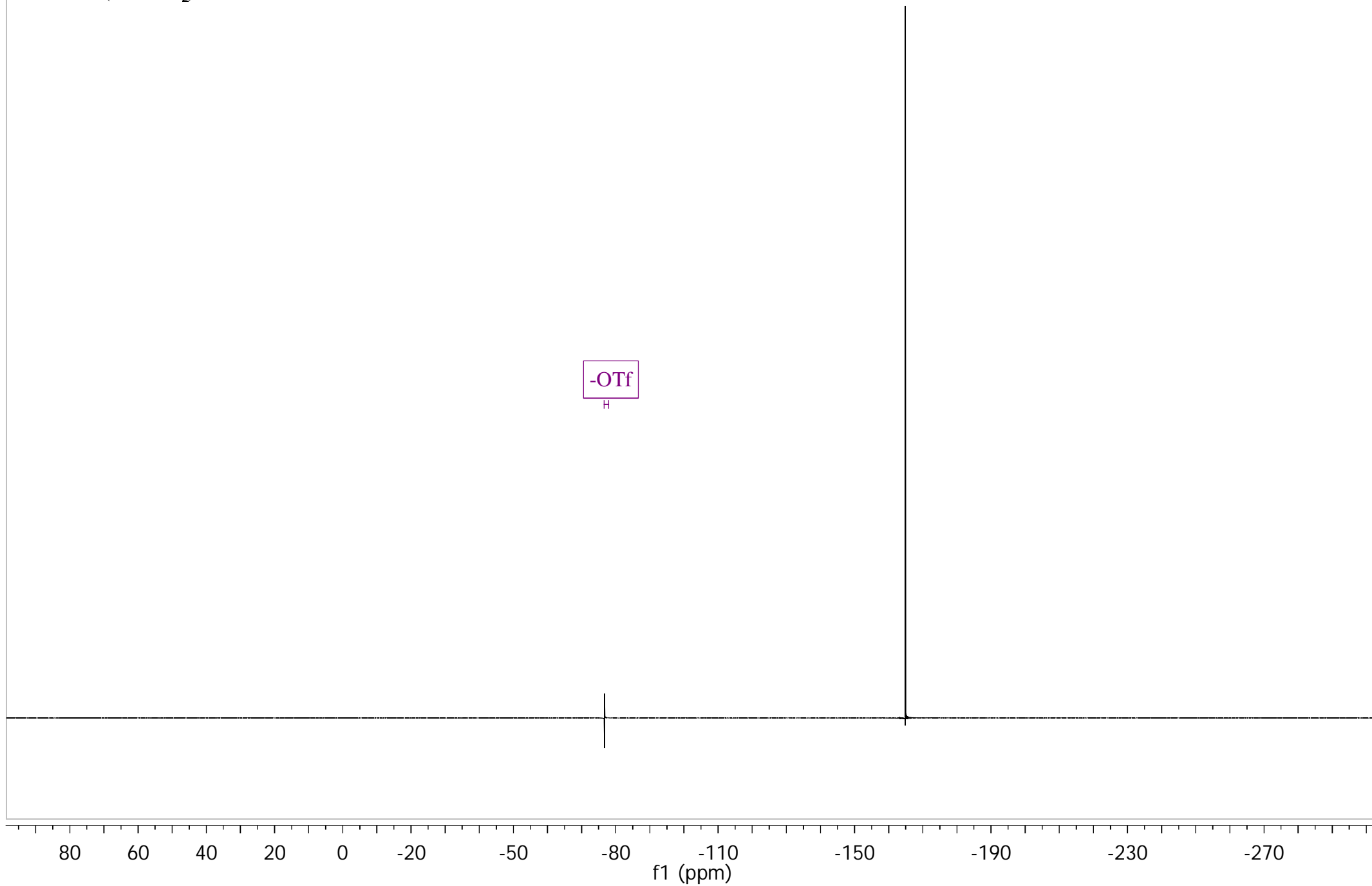
Plate 10a; [^1]H NMR [CDCl₃]: 1-Allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**)
δ 6.45 (1H, d, *J* = 2.3 Hz, H-3/5), 6.42 (1H, d, *J* = 2.3 Hz, H-3/5), 5.91–5.83 (1H, m, H-2'), 5.0–4.97 (2H, m, H-3'a and H-3'b), 3.82 (3H, s, -OMe), 3.80 (3H, s, -OMe), 3.39–3.37 (2H, m, H-1').
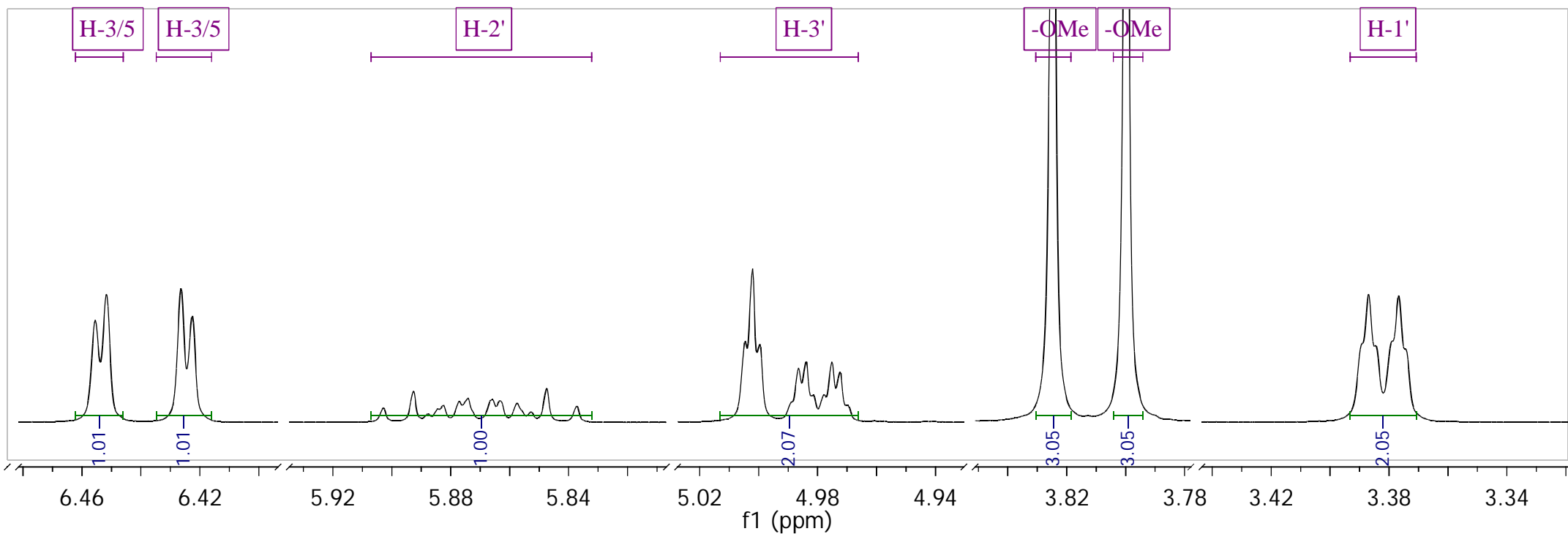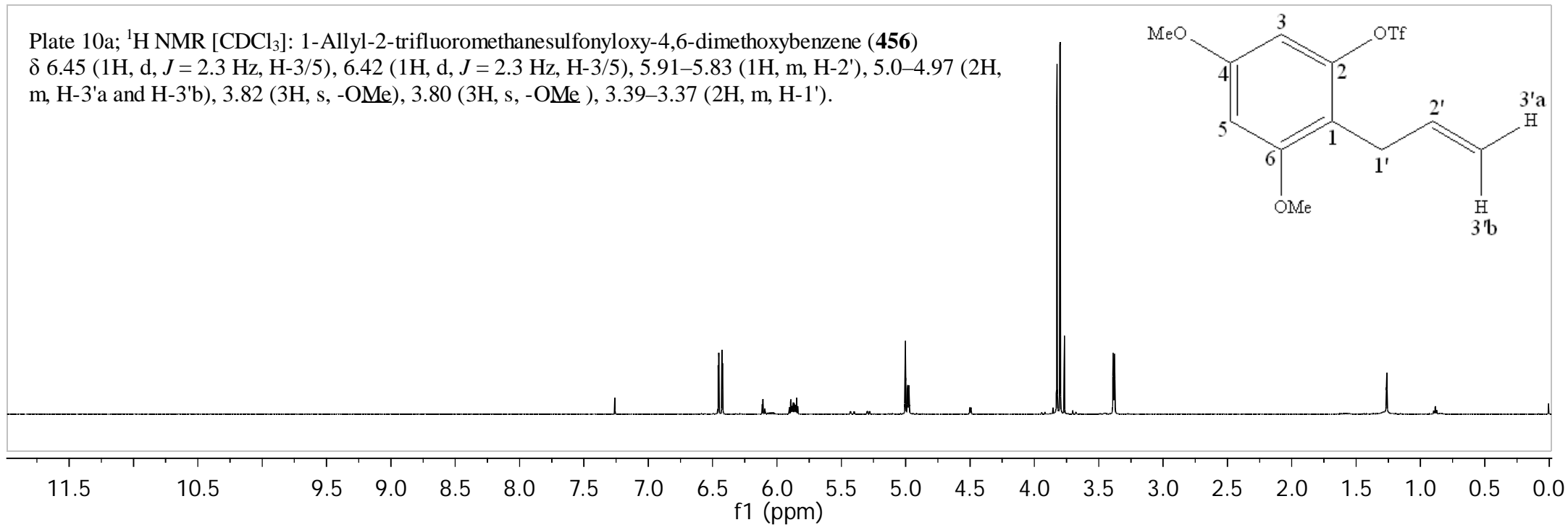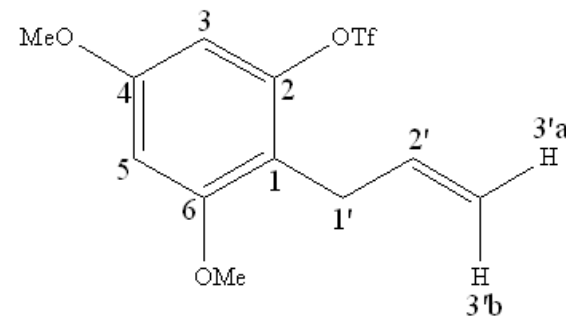
Plate 10b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**)
δ 159.54 (C-4/6), 159.43 (C-4/6) 148.74 (C-1/2), 134.98 (C-2'), 118.68 (q, J = 320.28 Hz, -OSO$_2$CF$_3$), 115.54 (C-3'), 114.34 (C-1/2), 98.48 (C-3/5), 98.12 (C-3/5), 56.11 (-OMe), 55.75 (-OMe), 27.89 (C-1').
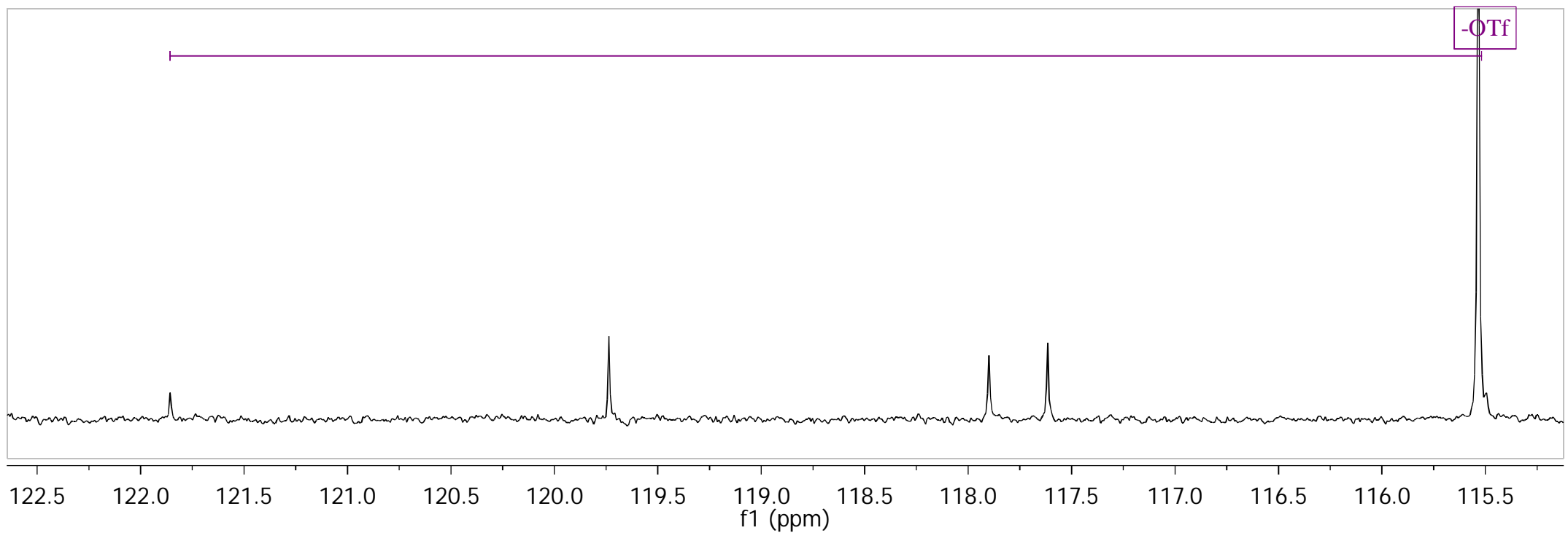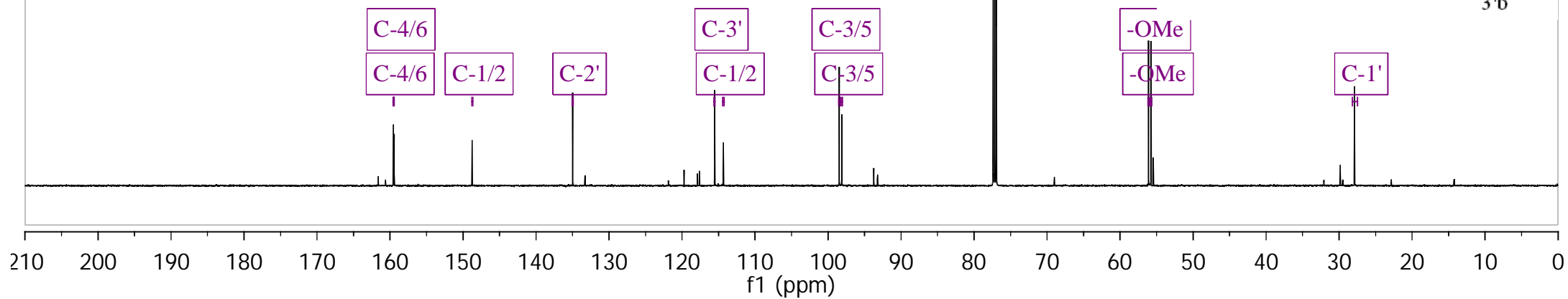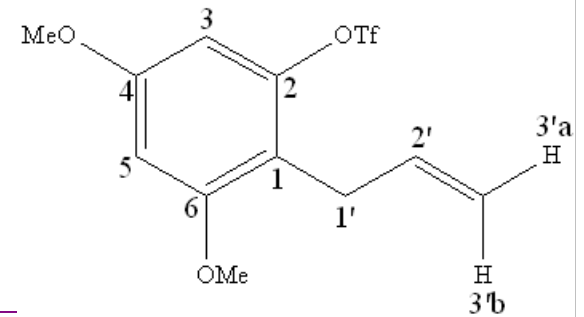
Plate 10c; DEPT [CDCl$_3$]: 1-Allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**)
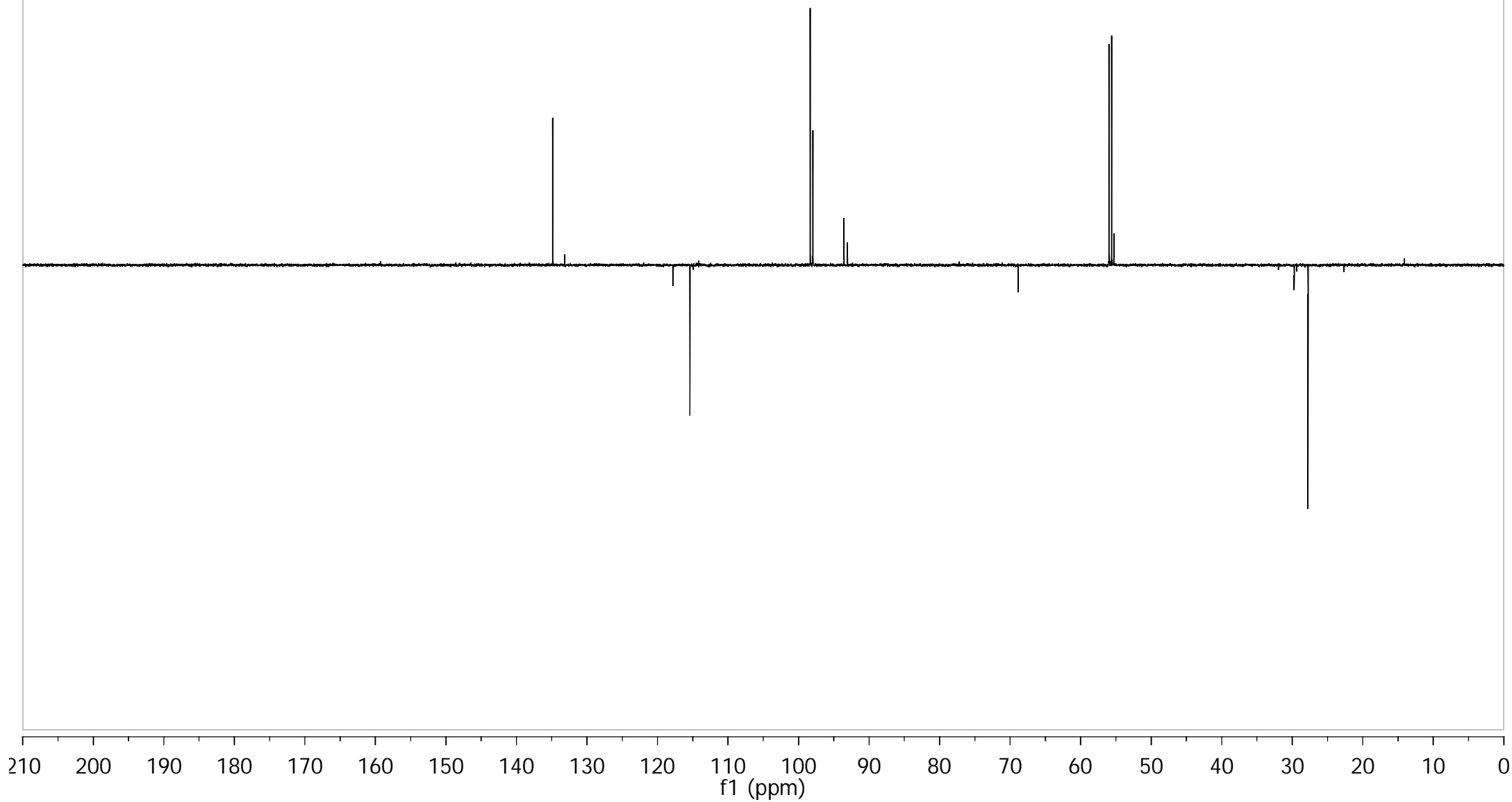
Plate 10d; HSQC [CDCl$_3$]: 1-Allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**)
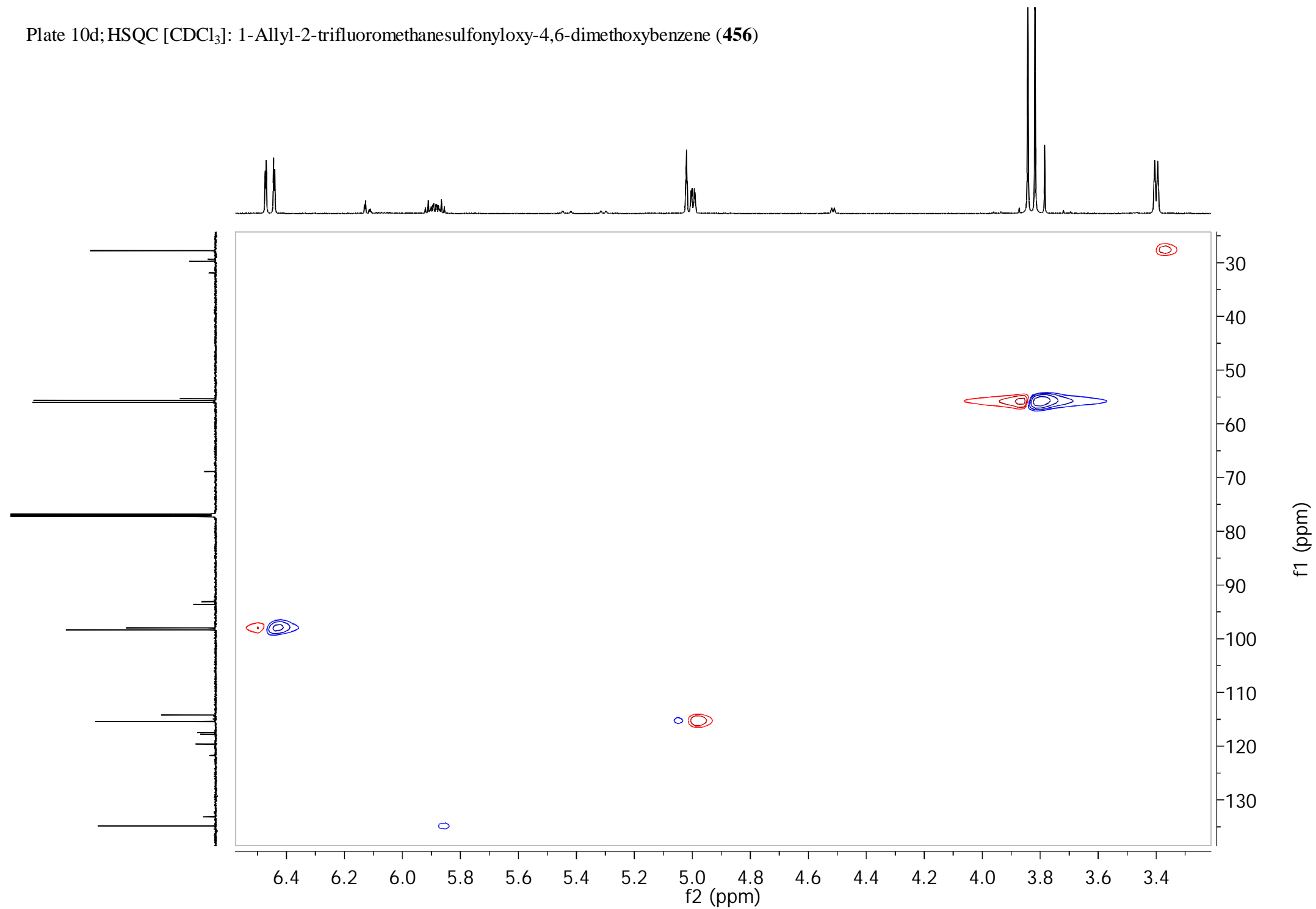
Plate 10e; HMBC [CDCl$_3$]: 1-Allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene (**456**)
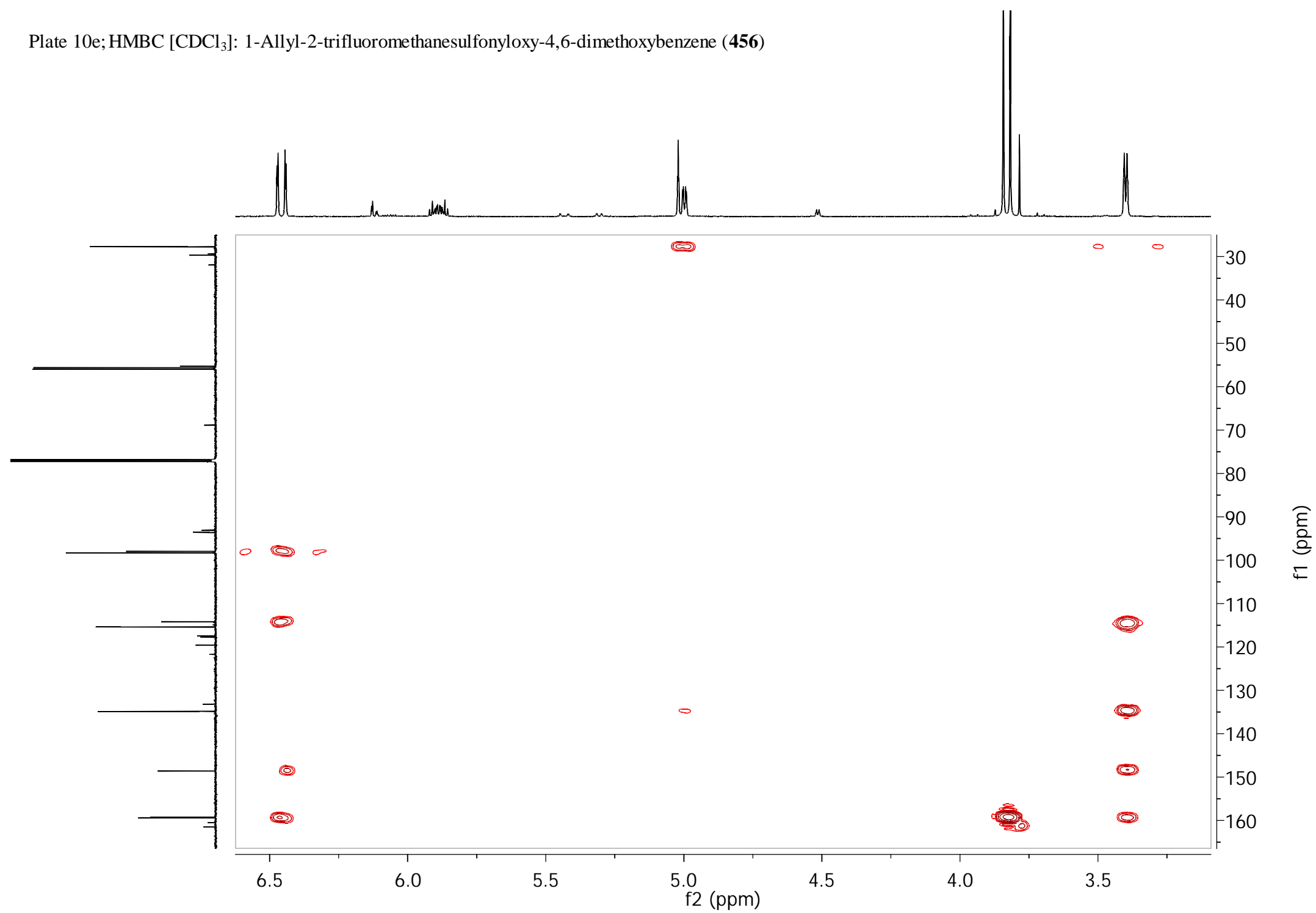
Plate 11a; ¹H NMR [CDCl₃]: 1-Allyl-2-hydroxybenzene (**398**)
δ 7.28–7.19 (2H, m, Ar-H), 7.06–7.98 (1H, m, Ar-H), 6.95–6.87 (1H, m, Ar-H), 6.14 (1H, ddt, J = 17.5, 9.6, 6.4 Hz, H-2'), 5.59 (1H, s, -OH), 5.30–5.21 (2H, m, H-3'a and H-3'b), 3.57–3.49 (1H, m, H-1').
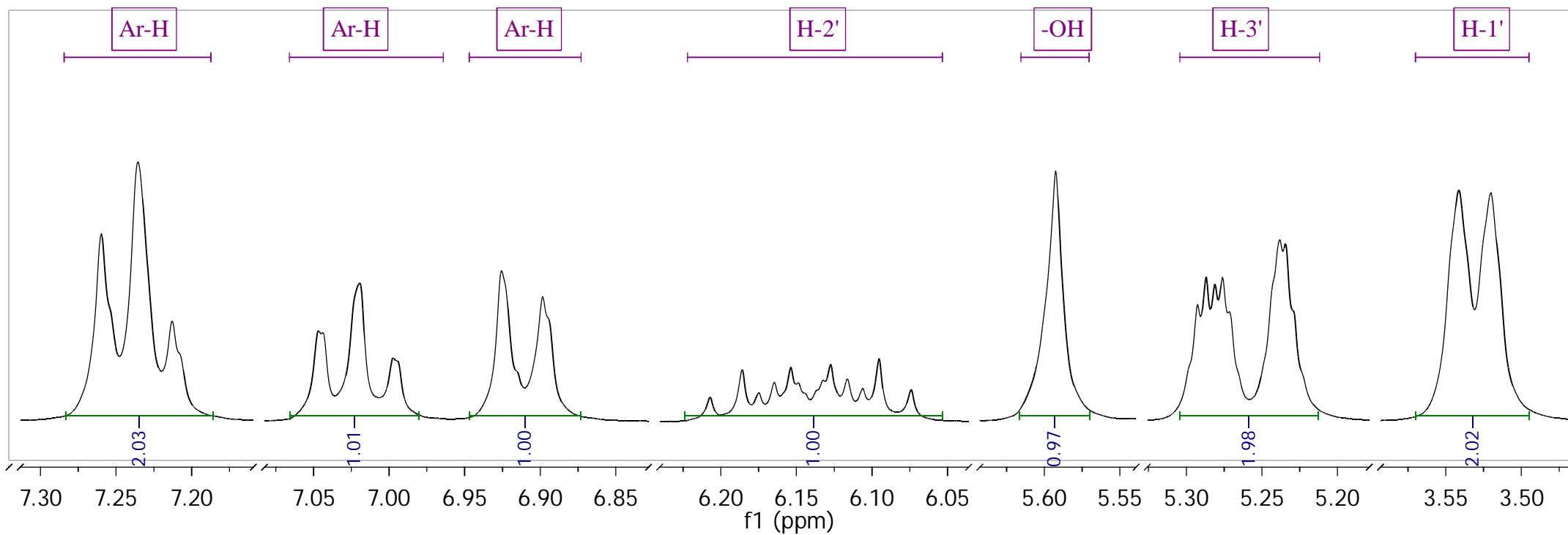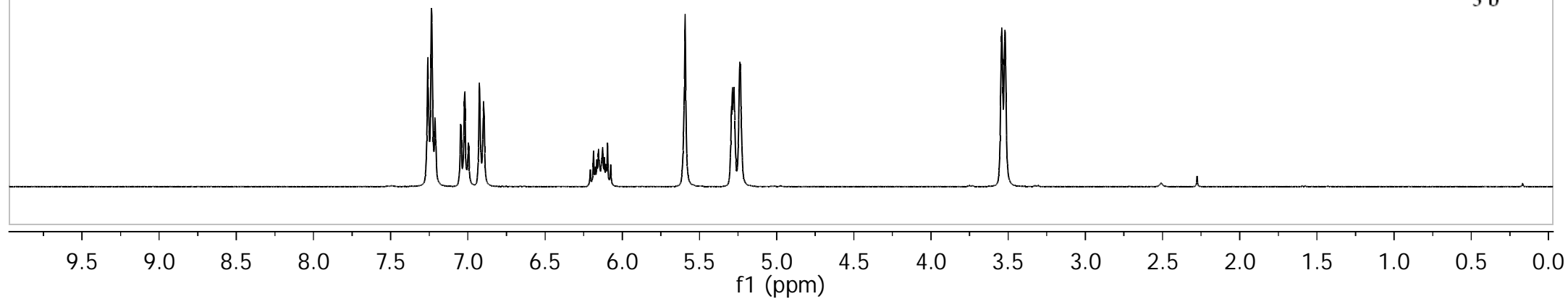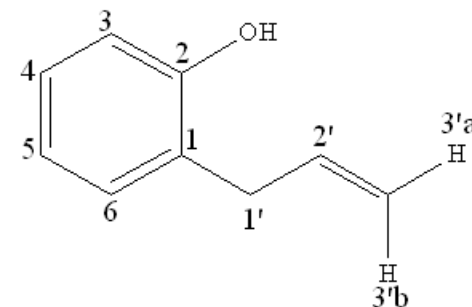
Plate 12a; ^{1}H NMR [CDCl$_3$]: 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**403**)
δ 6.11 (1H, d, J = 2.44 Hz, H-3/5), 6.08 (1H, d, J = 2.44 Hz, H-3/5), 6.00–5.93 (1H, m, H-2'), 5.25 (1H, br.s, -OH), 5.13–5.07 (2H, m, H-3'a and H-3'b), 3.78 (3H, s, -OMe), 3.76 (3H, s, -OMe), 3.40–3.38 (2H, m, H-1').
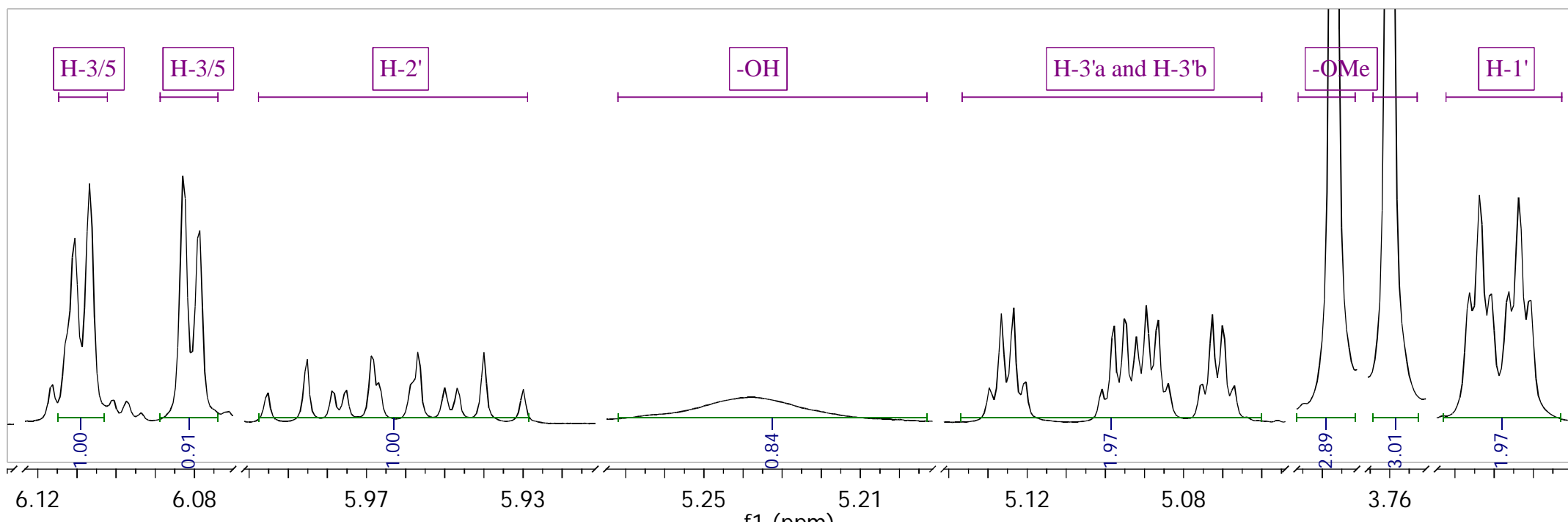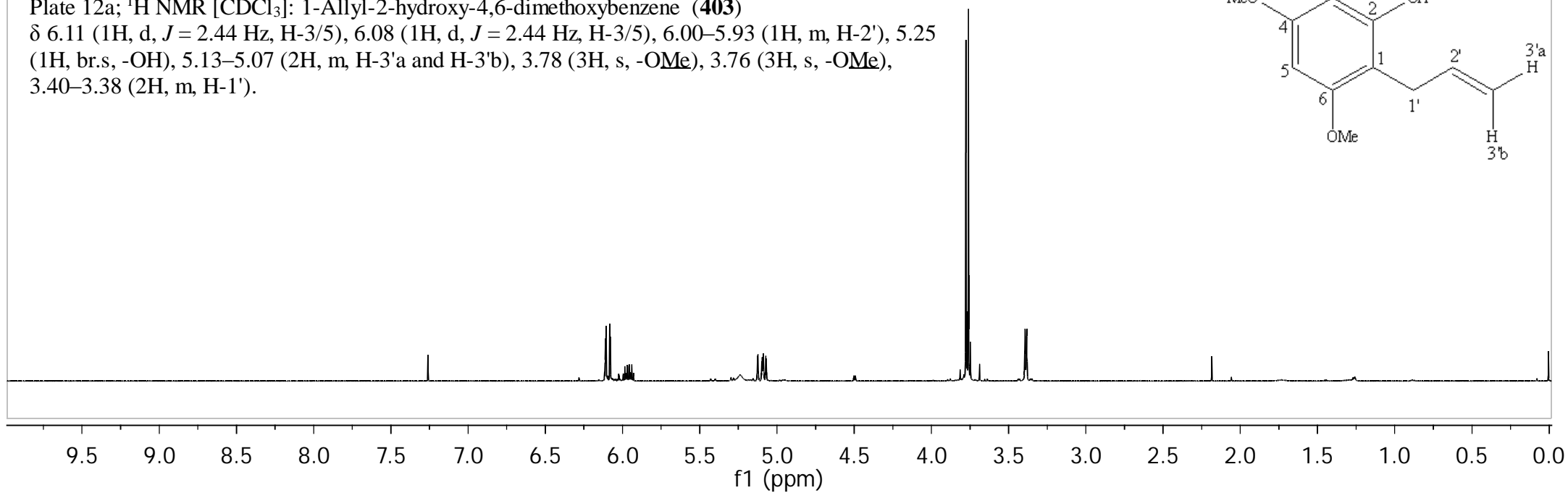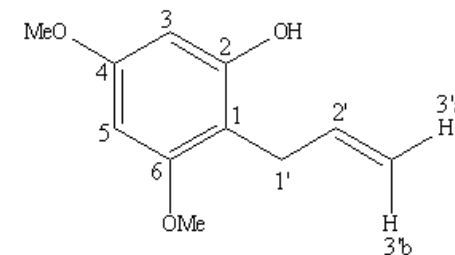
Plate 12b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-2-hydroxy-4,6-dimethoxybenzene (**403**)
δ 159.90 (quaternary carbon), 158.69 (quaternary carbon), 155.94 (quaternary carbons), 136.89 (C-2'), 115.41 (C-3'), 105.82 (quaternary carbon), 93.88 (C-3/5), 91.67 (C-3/5), 55.93 (-OMe), 55.34 (-OMe), 27.08 (C-1').
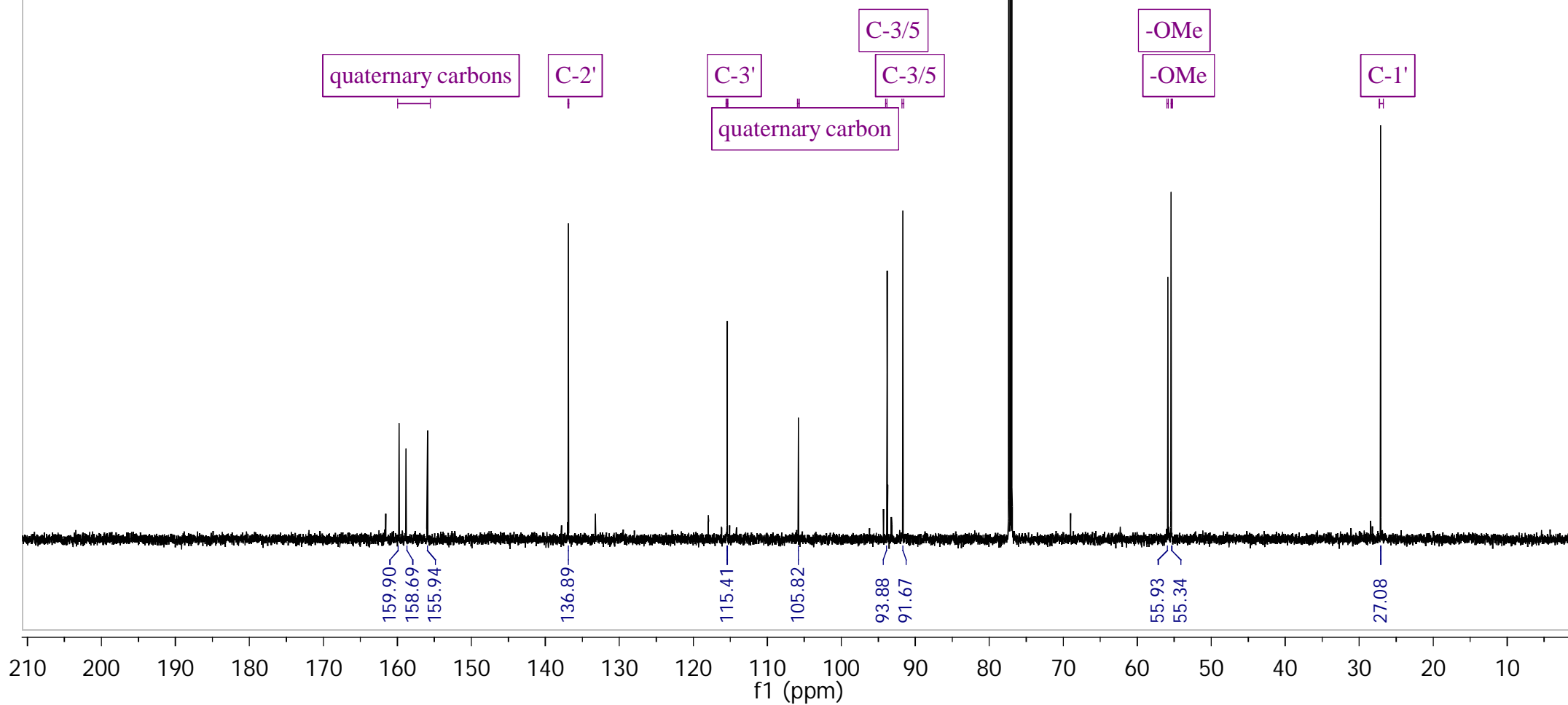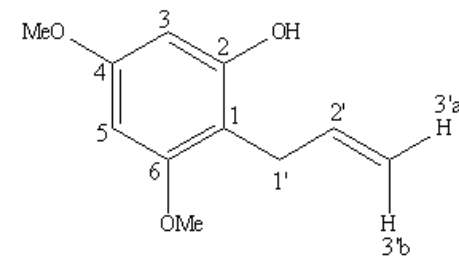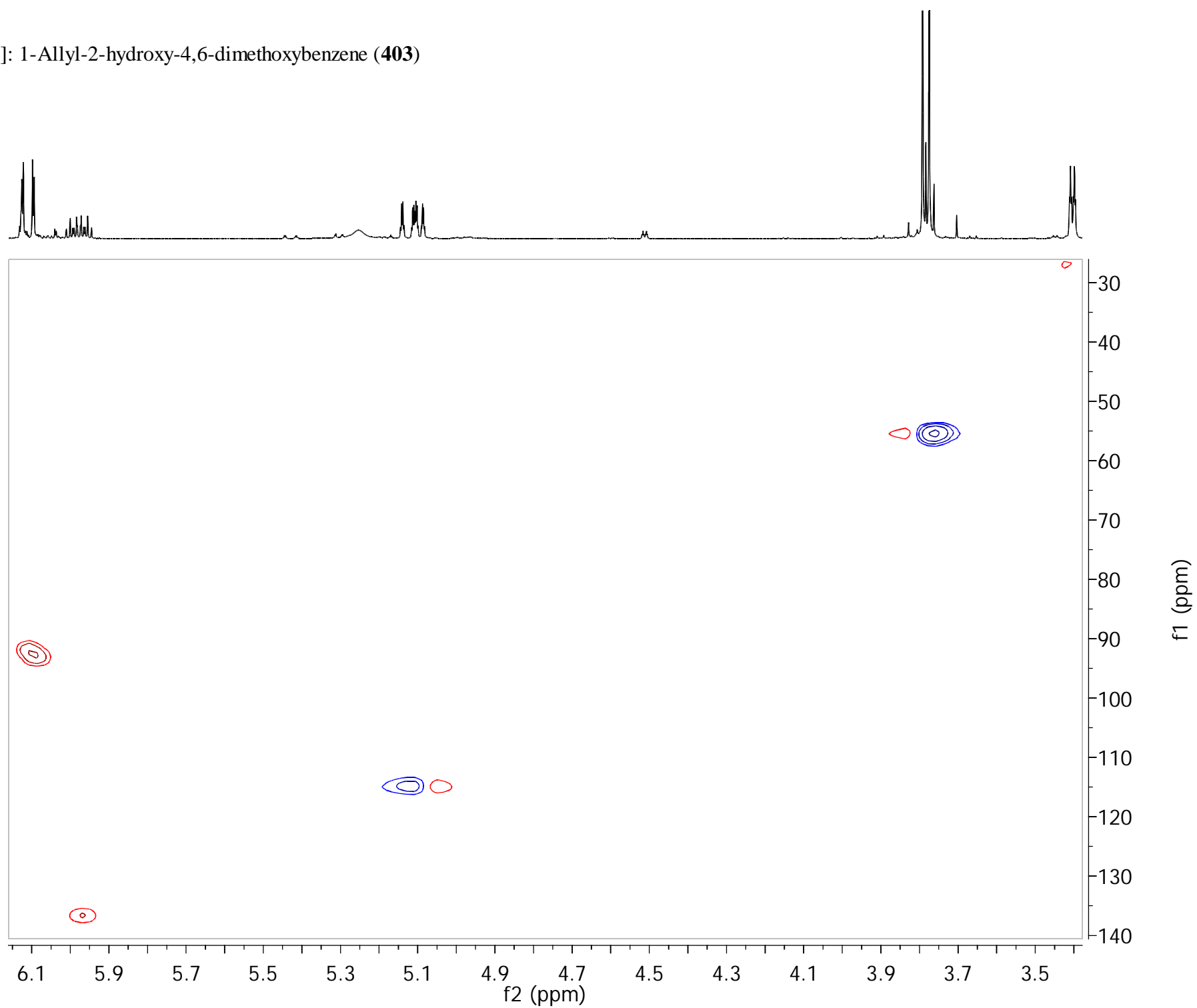
Plate 12d; NOESY [CDCl$_3$]: 1-Allyl-2-hydroxy-4,6-dimethoxybenzene
(**403**)
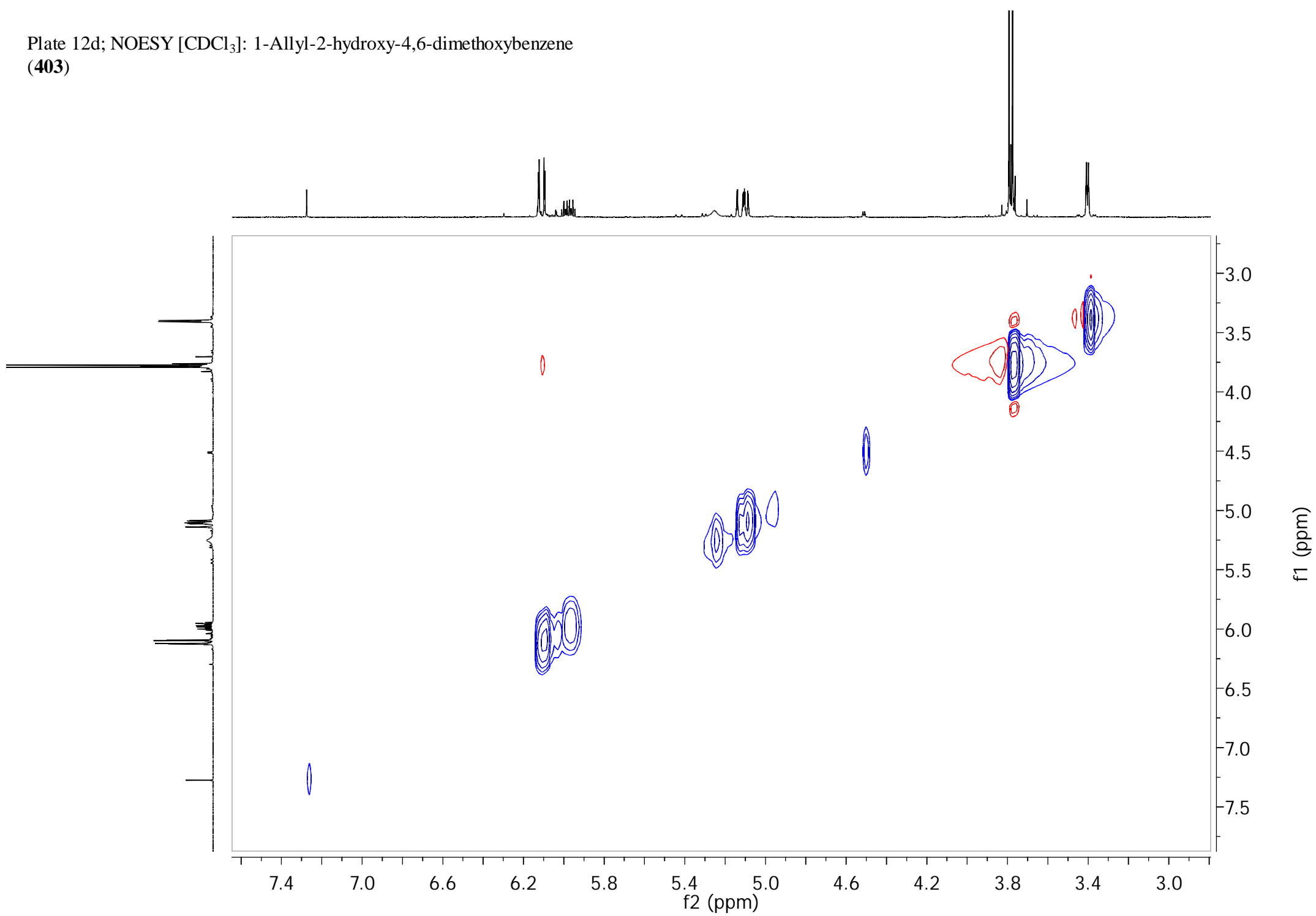
Plate 13a; ¹H NMR [CDCl₃]: 1-Allyl-2-hydroxy-4-methoxybenzene (**404**)
δ 7.01 (1H, d, J = 8.33 Hz, H-6), 6.47 (1H, dd, J = 8.33, 2.54 Hz, H-5), 6.43 (1H, d, J = 2.54 Hz, H-3), 6.01 (1H, ddt, J = 16.92, 10.38, 6.36 Hz, H-2'), 5.23 (1H, br.s, -OH), 5.17–5.14 (1H, m, H-3'b), 5.14–5.13 (1H, m, H-3'a), 3.76 (3H, s, -OMe), 3.34–3.35 (2H, m, H-1').
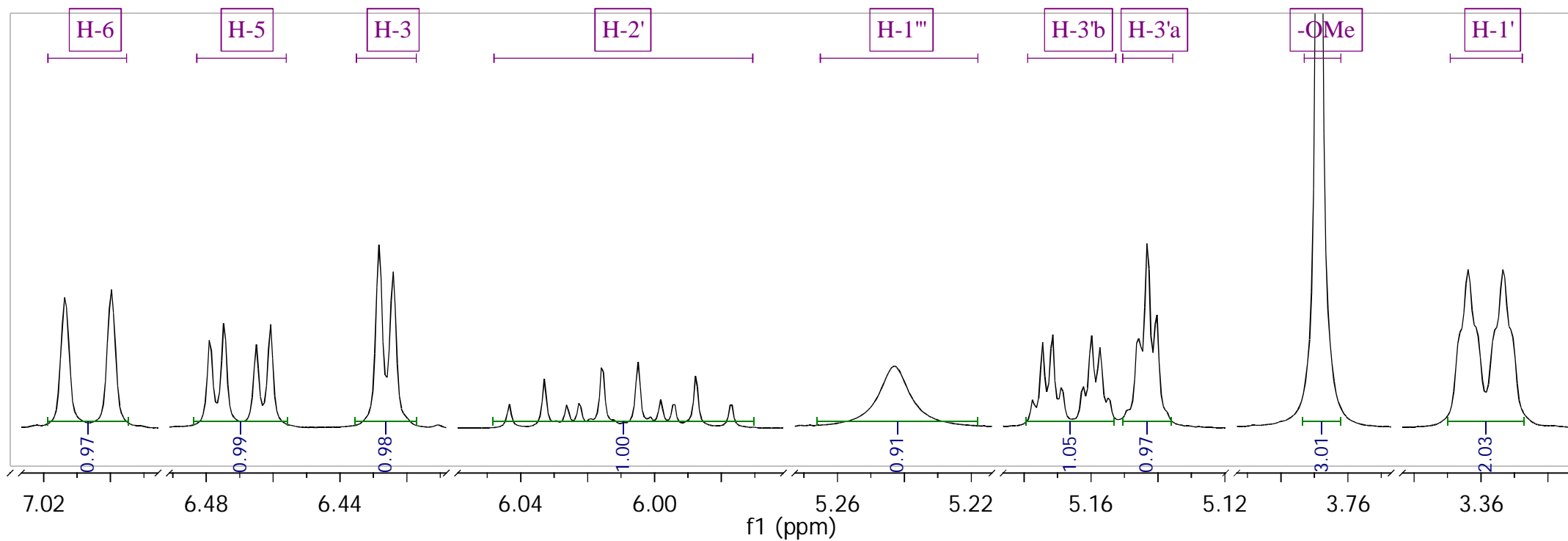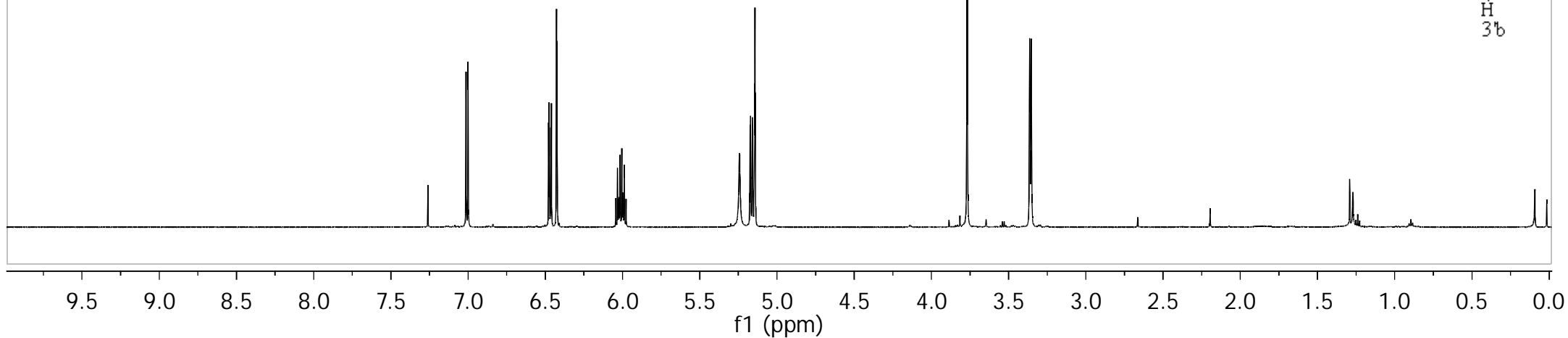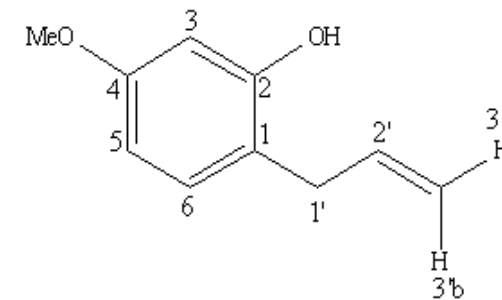
Plate 13b; ¹³C NMR [CDCl₃]: 1-Allyl-2-hydroxy-4-methoxybenzene (**404**)
δ 159.65 (quaternary carbon), 155.13 (quaternary carbon), 136.93 (C-2'), 130.98 (C-6), 117.53 (quaternary carbon), 116.36 (C-3'), 106.41 (C-5), 102.12 (C-3), 55.44 (-OMe), 34.64 (C-1').
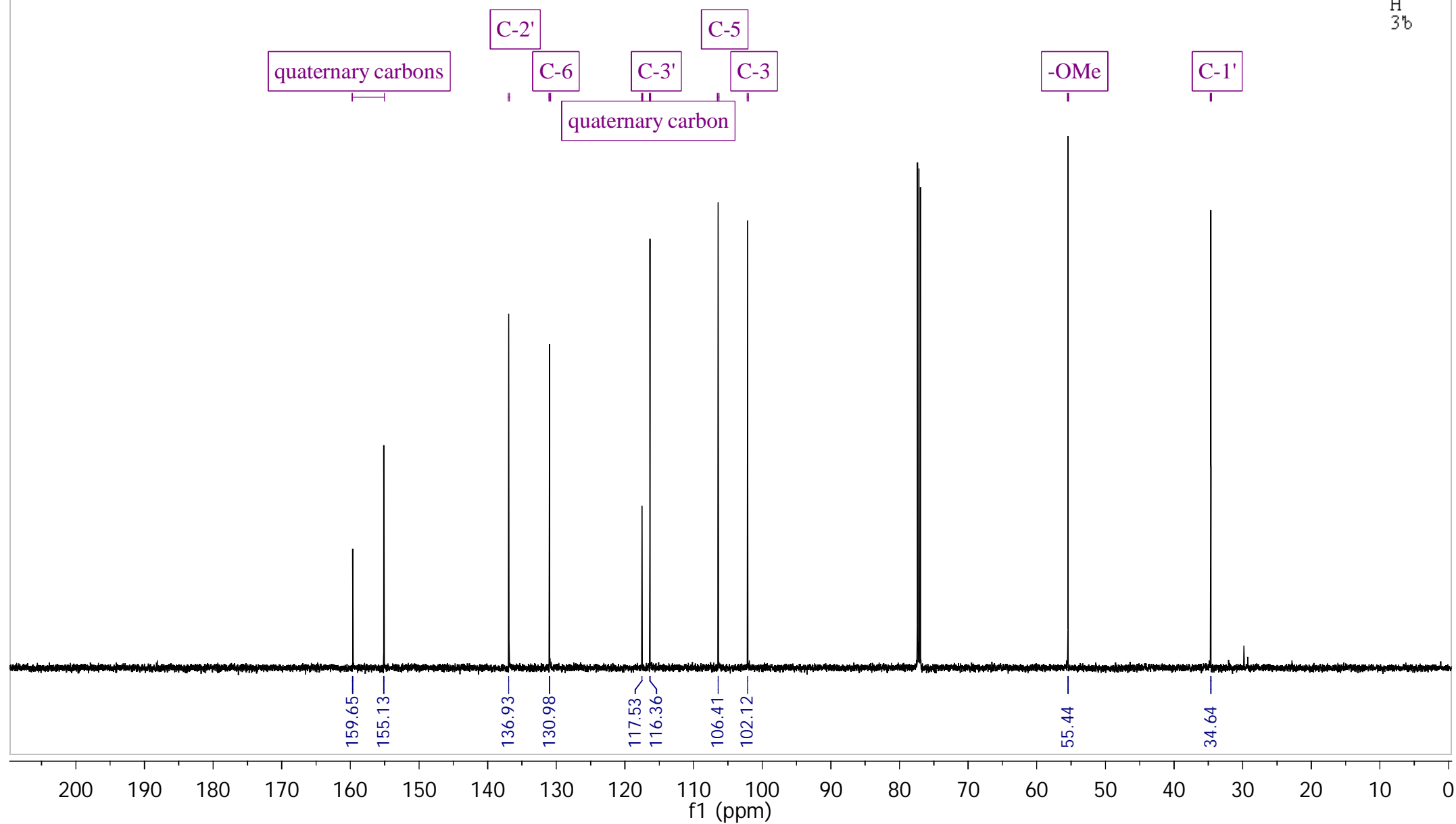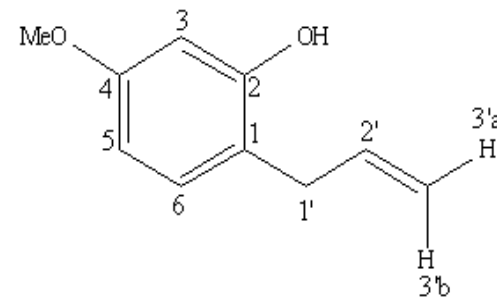
Plate 13c; DEPT [CDCl$_3$]: 1-Allyl-2-hydroxy-4-methoxybenzene (**404**)
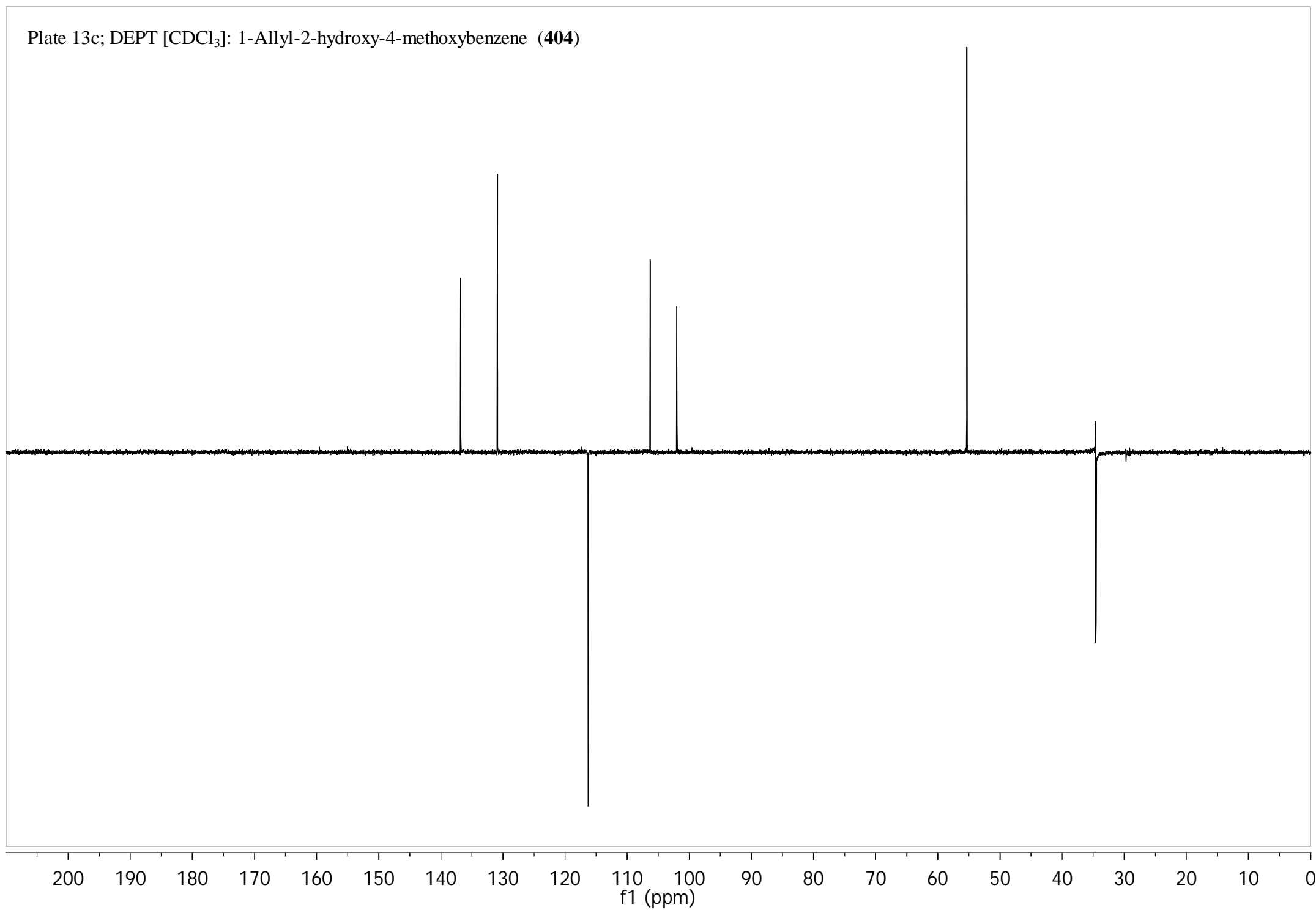
Plate 13d; HSQC [CDCl$_3$]: 1-Allyl-2-hydroxy-4-methoxybenzene (**404**)
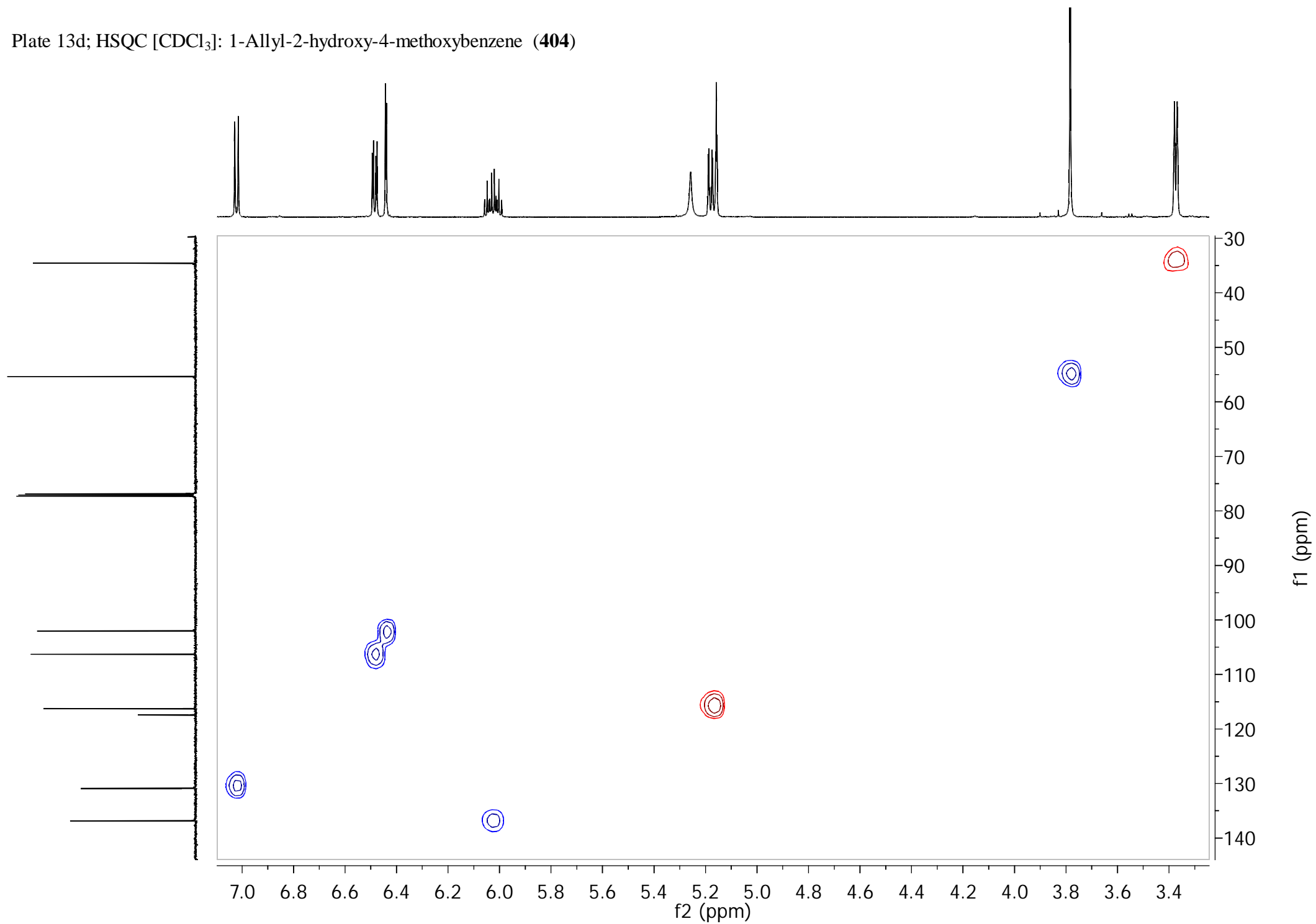
Plate 13e; HMBC [CDCl₃]: 1-Allyl-2-hydroxy-4-methoxybenzene (**404**)
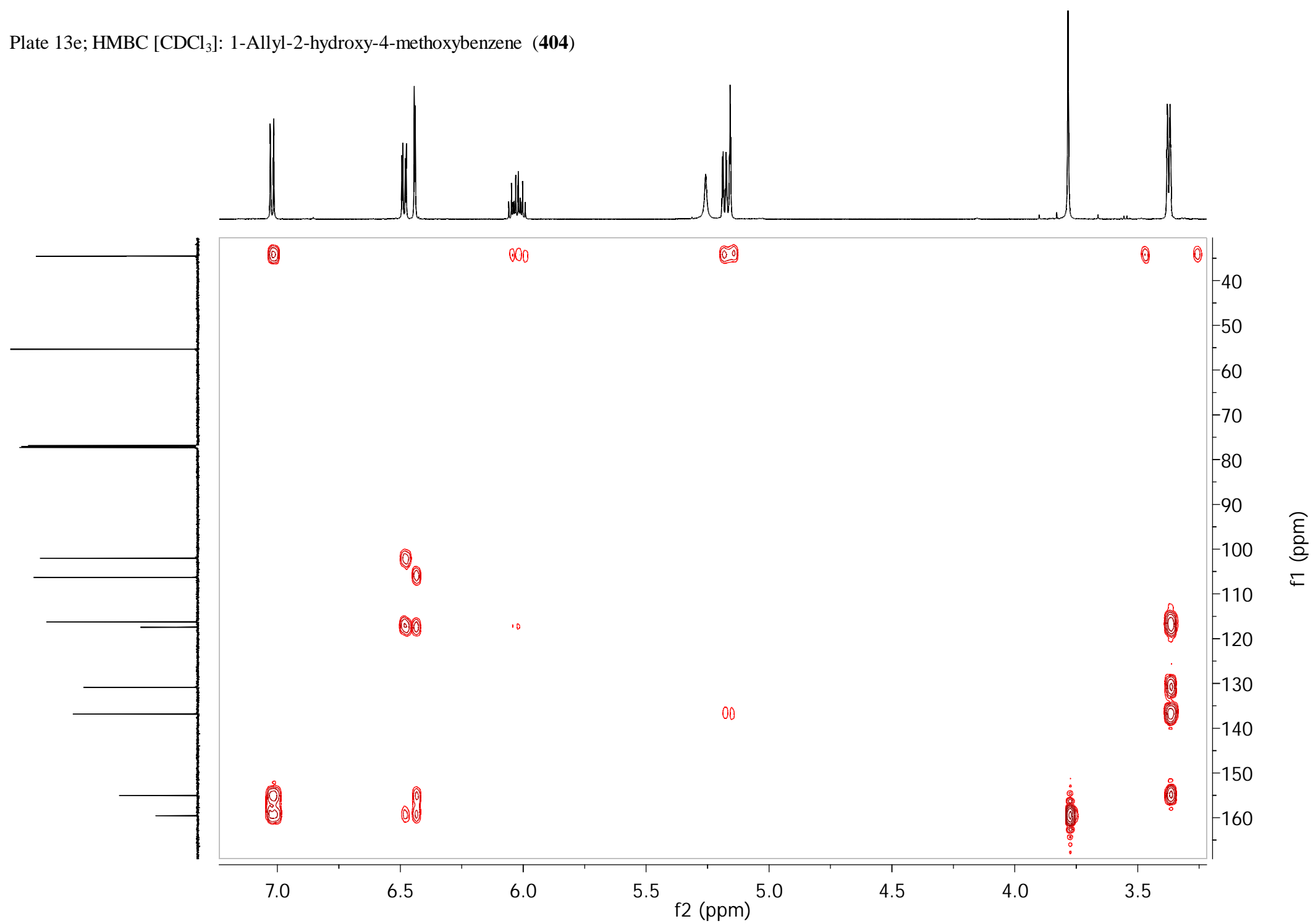
Plate 13f; NOESY [CDCl₃]: 1-Allyl-2-hydroxy-4-methoxybenzene (**404**)
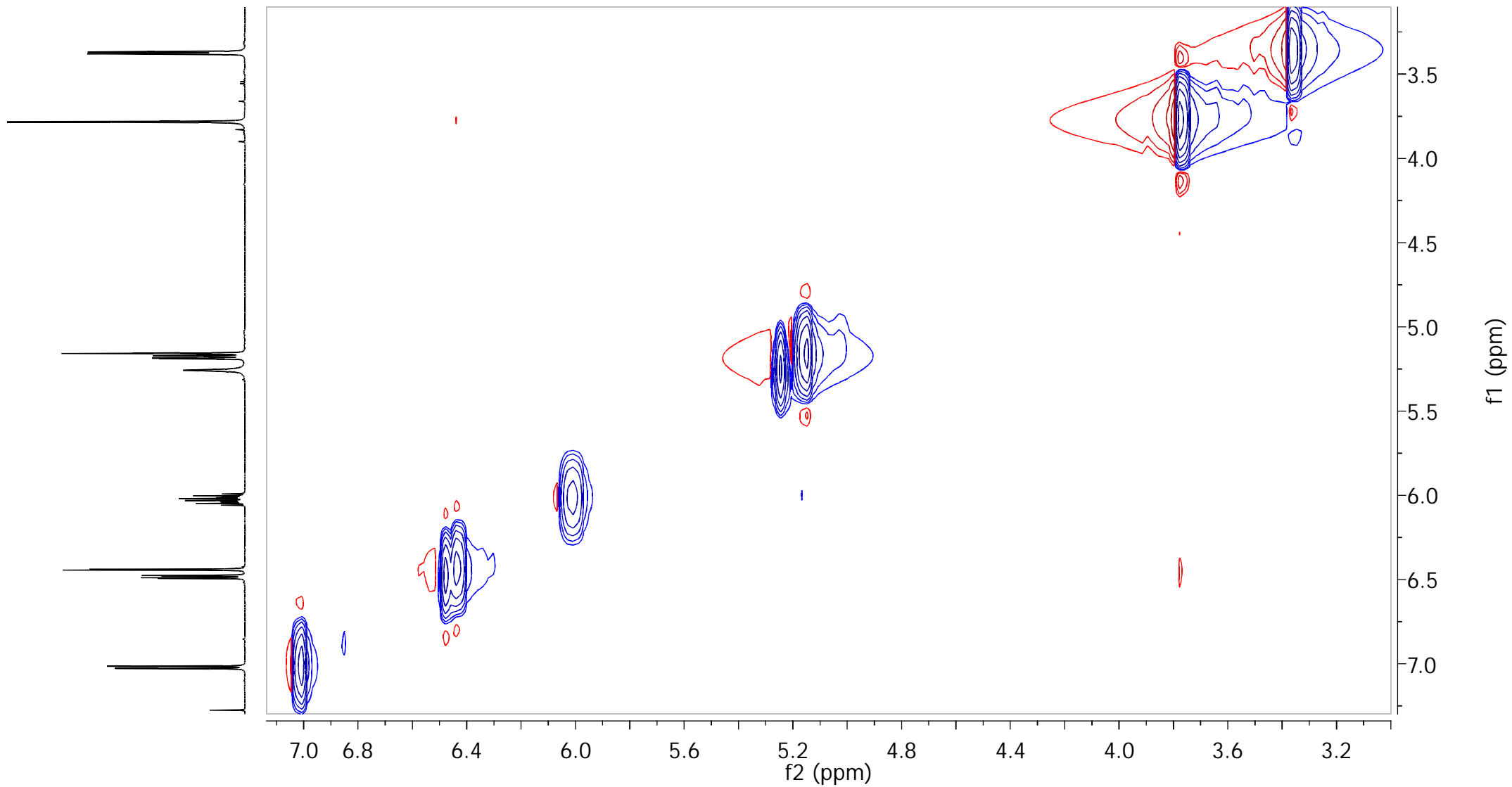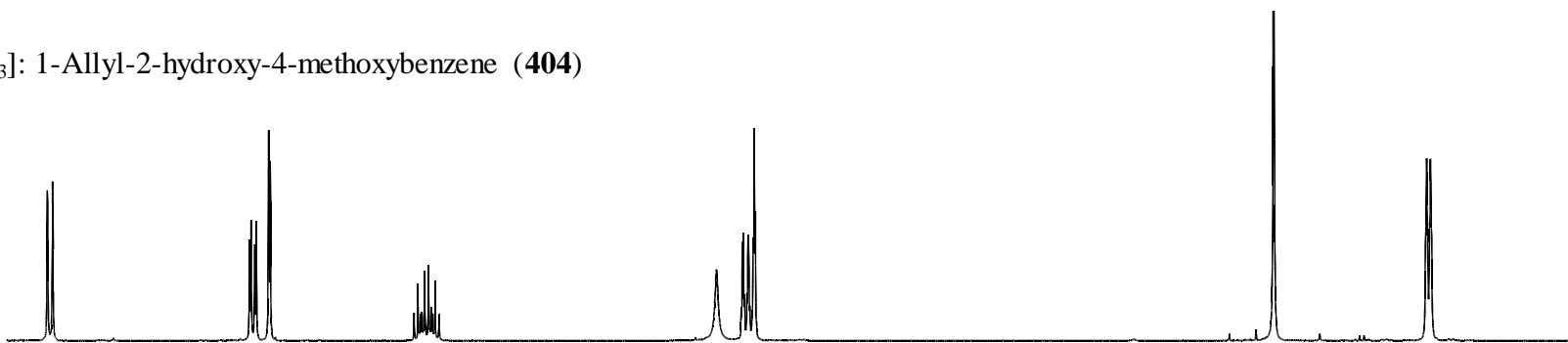
Plate 14a; ^{1}H NMR [CDCl$_3$]: 1-Allyl-2-hydoxy-6-methoxybenzene (**405**)
δ 7.08 (1H, dd, *J* = 8.10, 8.19 Hz, H-4), 6.51–6.50 (2H, m, H-3 and H-5), 5.99 (1H, ddt, *J* = 17.19, 10.14, 6.31 Hz, H-2'), 5.15 (1H, br.s, -OH), 5.13–5.07 (2H, m, H-3'a and H-3'b), 3.81 (3H, s, -OMe), 3.48–3.47 (2H, m, H-1').

H-4

H-5 and H-3

H-2'

-OH

H-3'a and H-3'b

-OMe

H-1'

0.99   2.02   1.00   0.83   2.15   3.07   2.04

7.08   6.50   6.02   5.98   5.18   5.14   5.10   5.06   3.82   3.50   3.46

f1 (ppm)
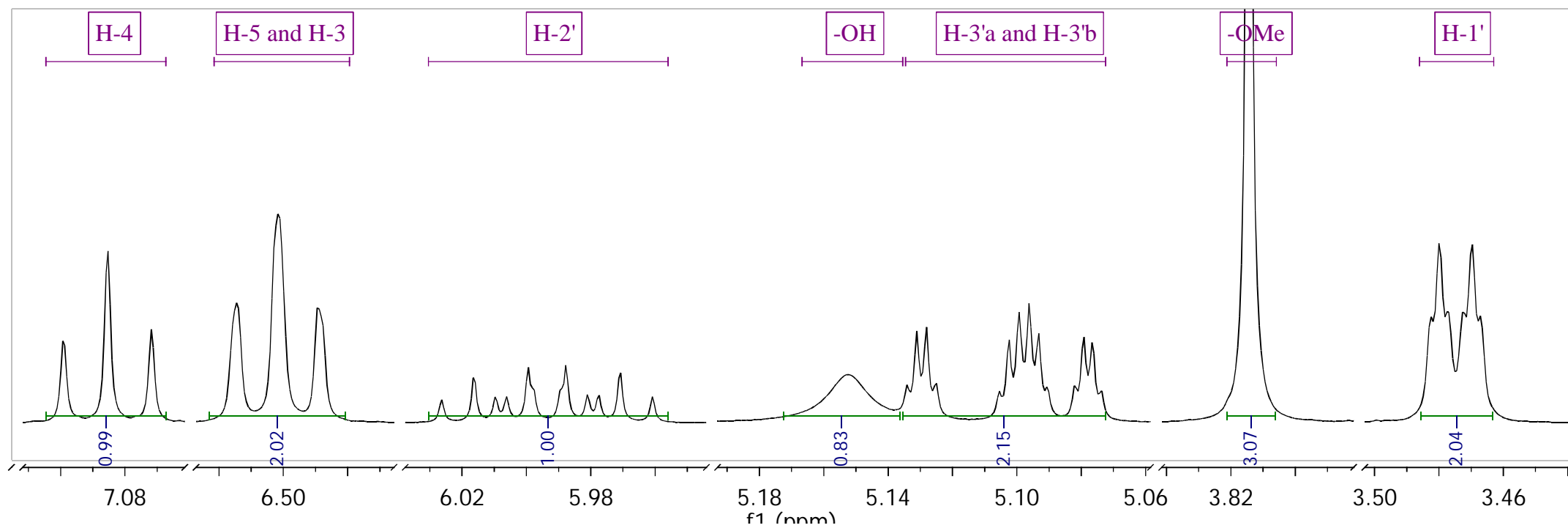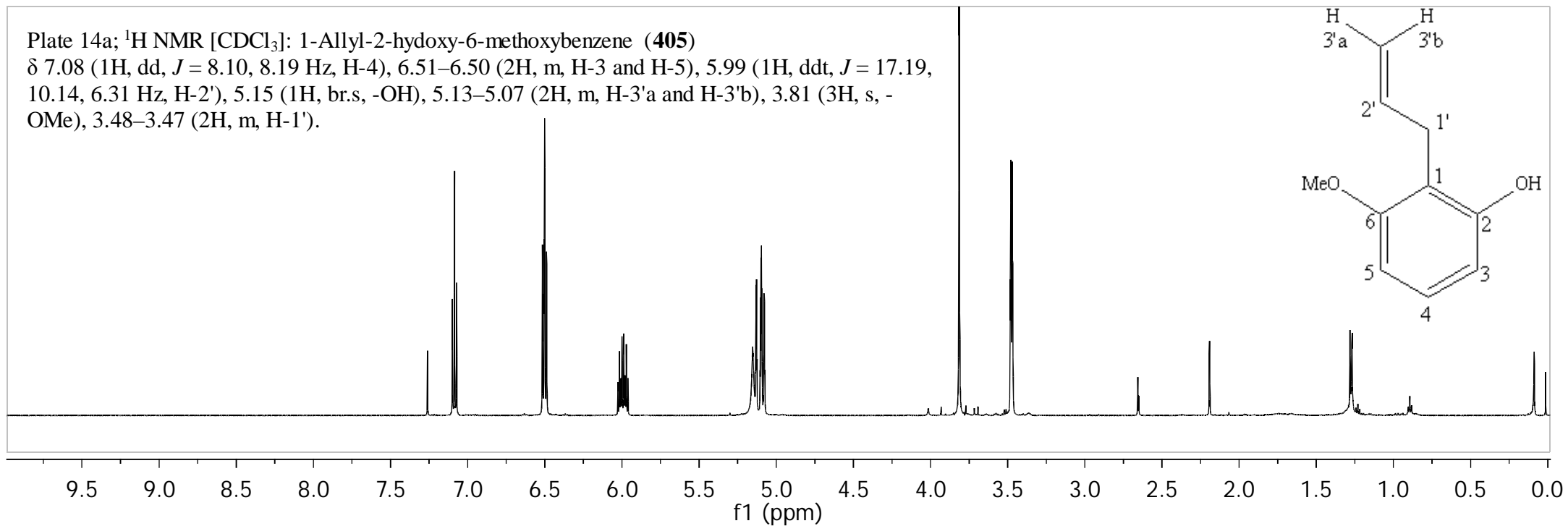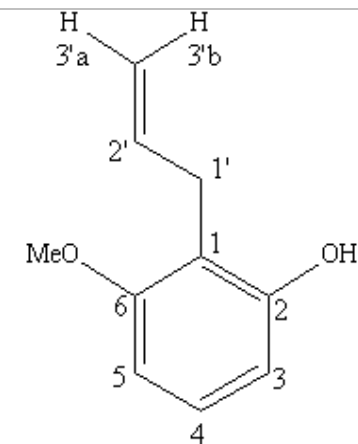
Plate 14b; ^{13}C NMR [CDCl$_3$]: 1-Allyl-2-hydoxy-6-methoxybenzene (**405**)
δ 158.35 (C-2/6), 155.28 (C-2/6), 136.45 (C-2'), 127.66 (C-4), 115.30 (C-3'), 113.73 (C-1),
108.93 (C-3/5), 103.44 (C-3/5), 55.94 (-OMe), 27.47(C-1').
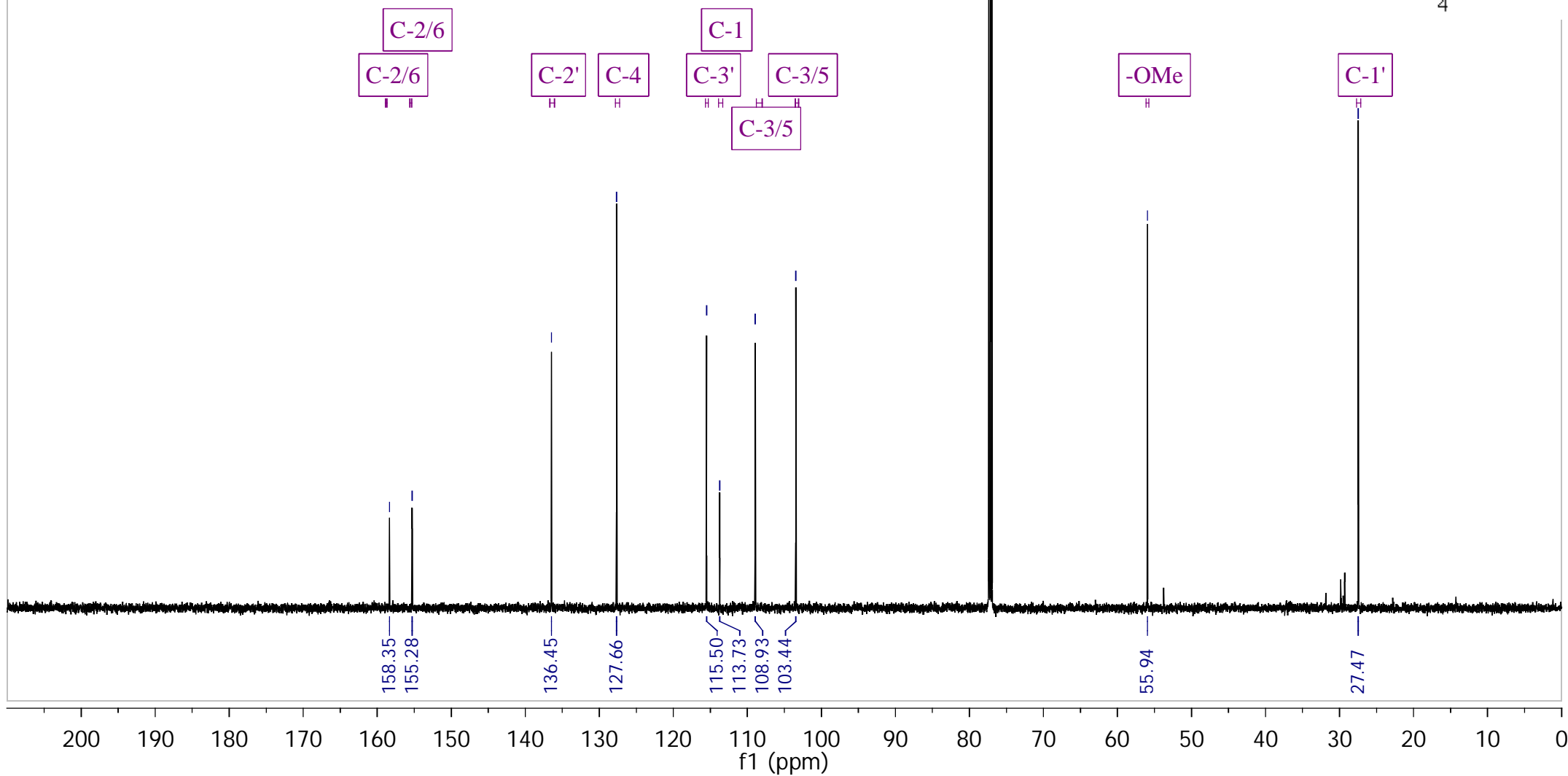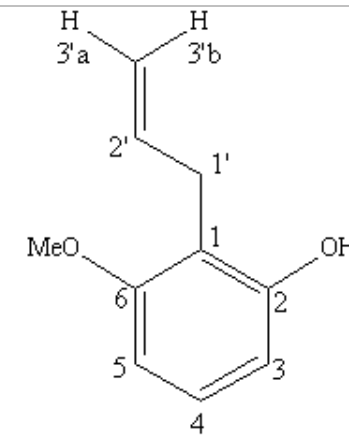
Plate 14c; DEPT [CDCl₃]: 1-Allyl-2-hydoxy-6-methoxybenzene (**405**)
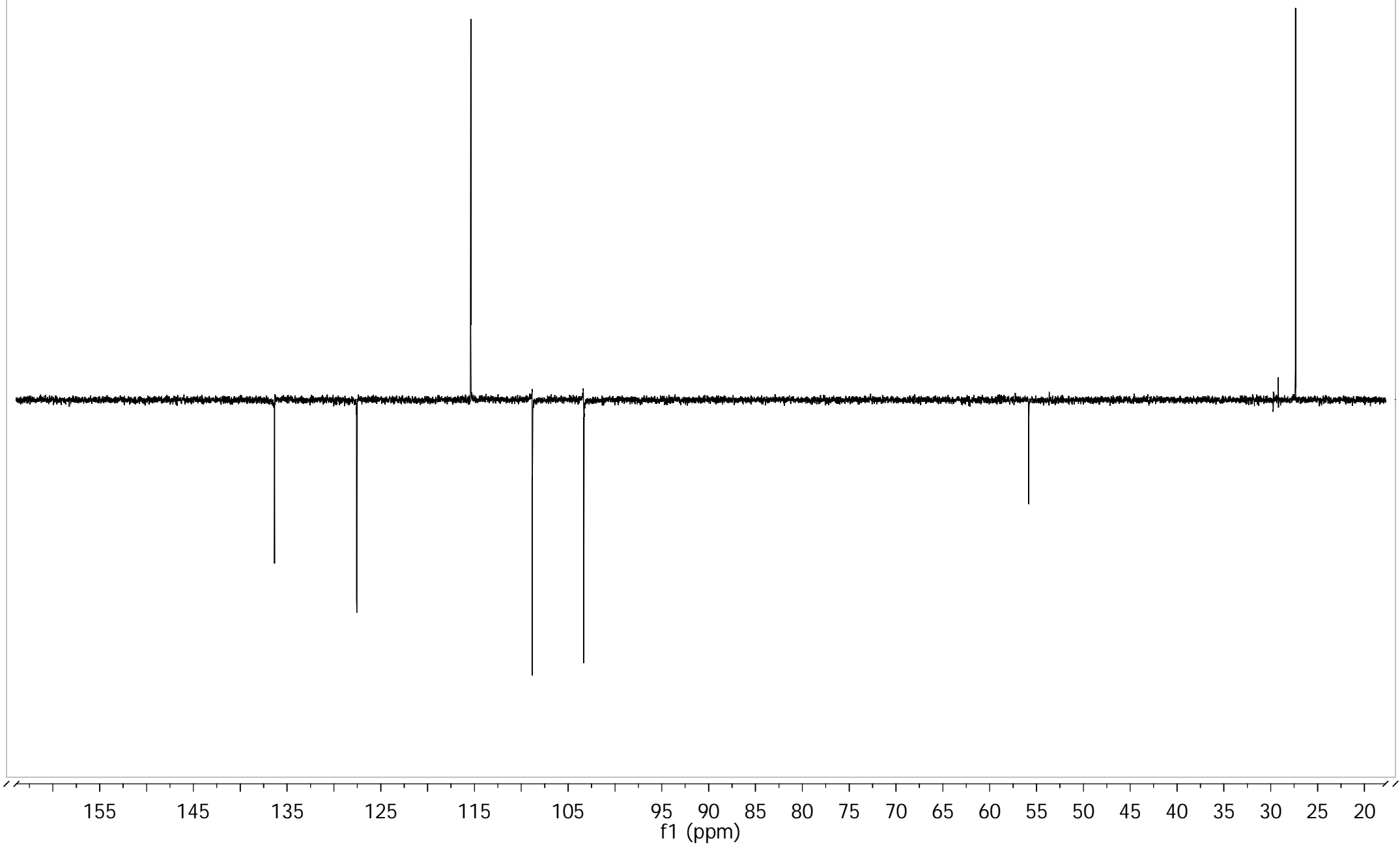
Plate 14d; HSQC [CDCl₃]: 1-Allyl-2-hydoxy-6-methoxybenzene (**405**)
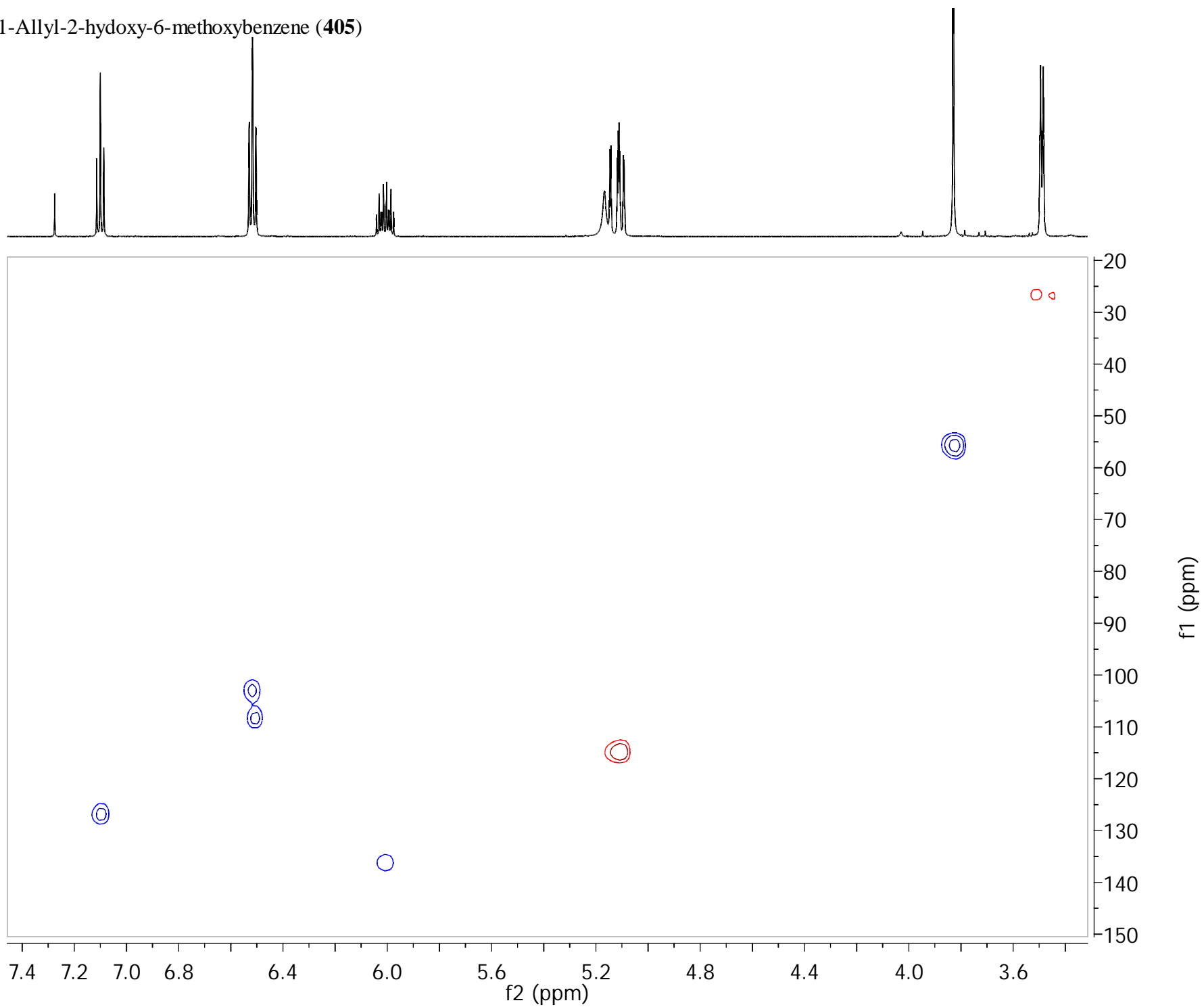
Plate 14e; HMBC [CDCl$_3$]: 1-Allyl-2-hydoxy-6-methoxybenzene (**405**)
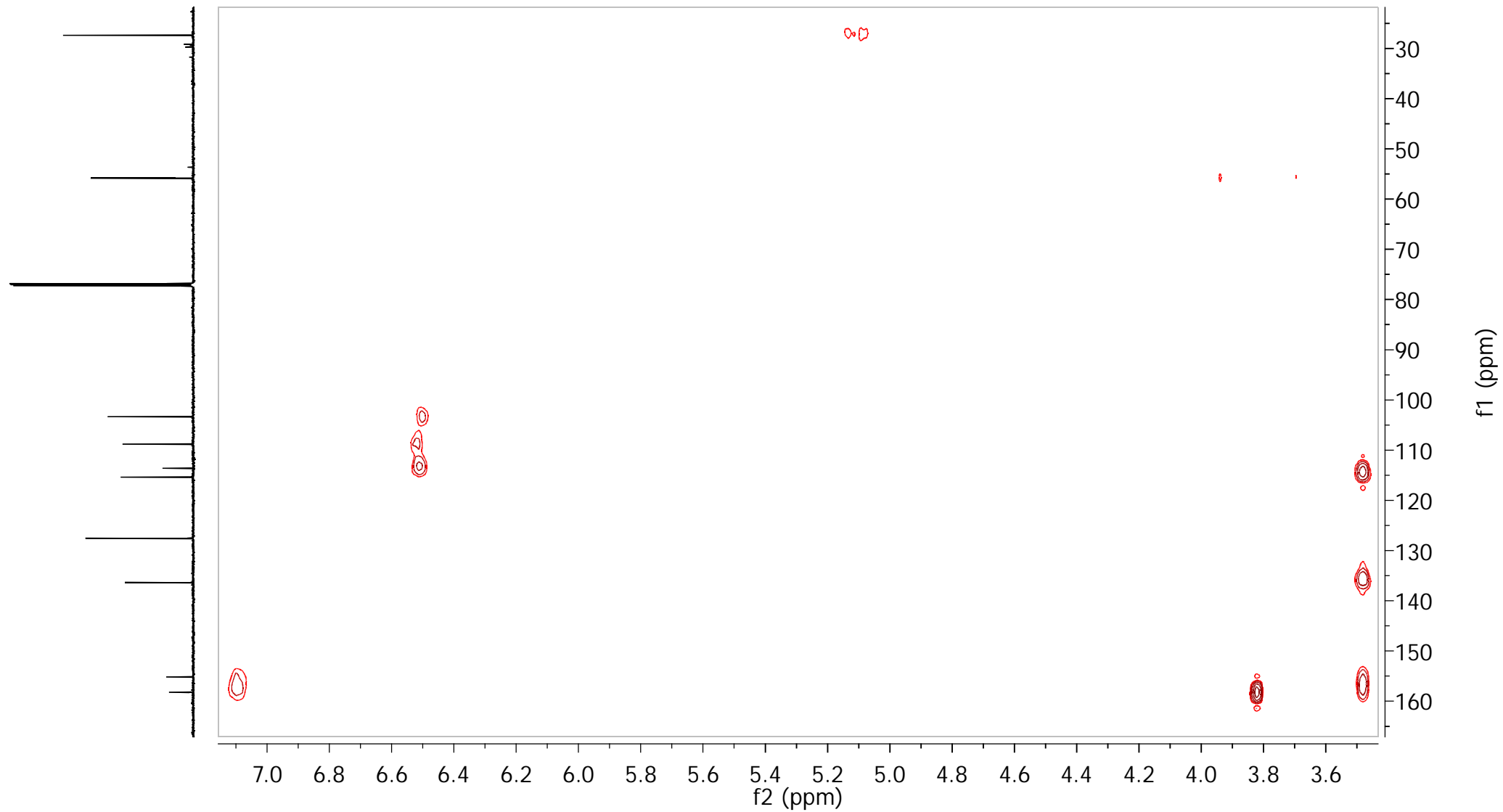
Plate 15a; ^{1}H NMR [CDCl$_3$]: 4-Methoxybenzaldehyde (**431**)

δ 9.89 (1H, s, -C**H**O), 7.84 (2H, d, J = 6.77 Hz, H-2' and H-6'), 7.01 (2H, d, J = 6.77 Hz, H-3' and H-5'), 3.90 (3H, s, -O**M**e).

-CHO

H-2' and H-6'

H-3' and H-5'

-OMe

f1 (ppm)

0.97   2.00   2.08   3.00
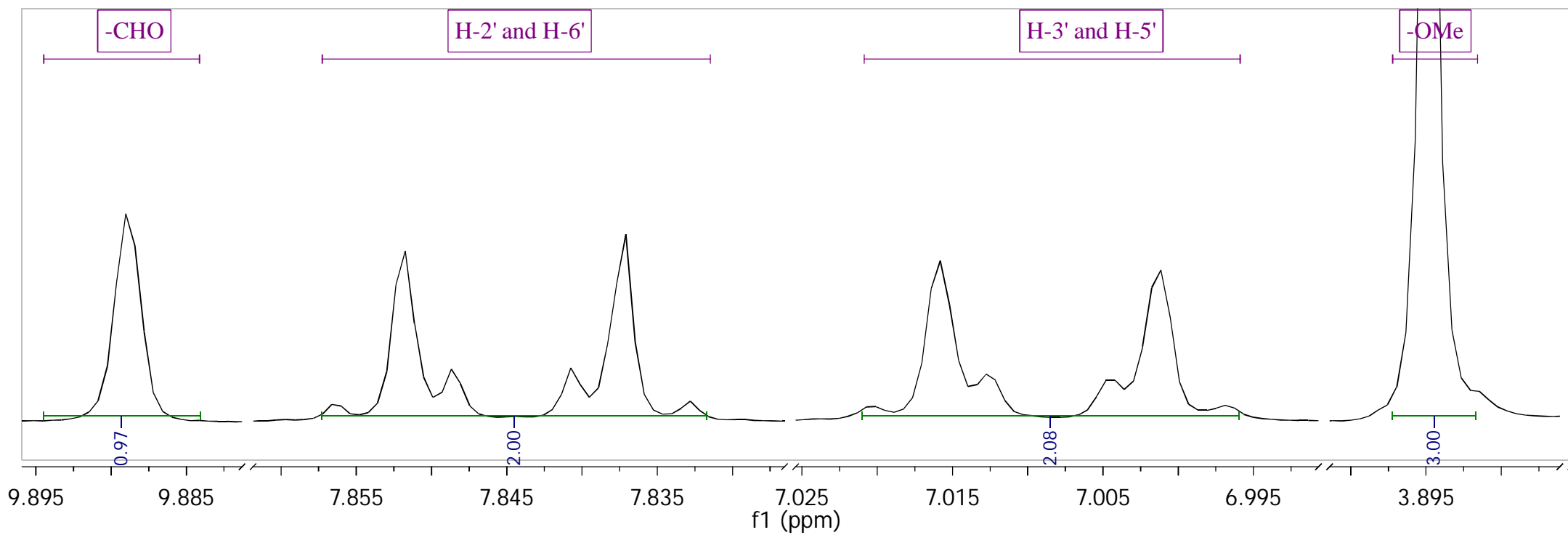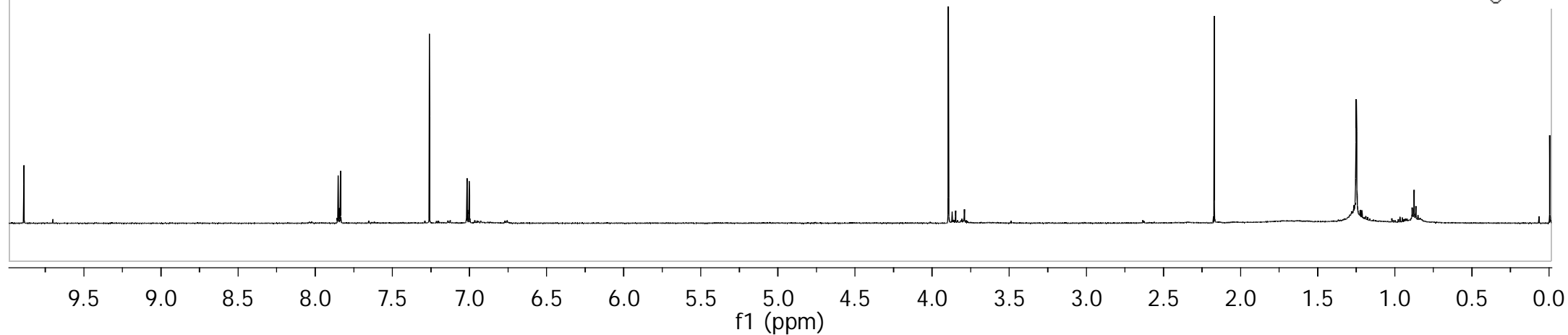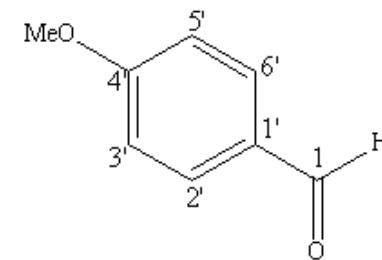
Plate 15b; ^{13}C NMR [CDCl$_3$]: 4-Methoxy benzaldehyde (**431**)
δ 191.09 (-CHO), 164.76 (C-4'), 132.16 (C-2' and C-6'), 130.07 (C-1'), 114.46 (C-3' and C-5'),
55.74 (-OMe).
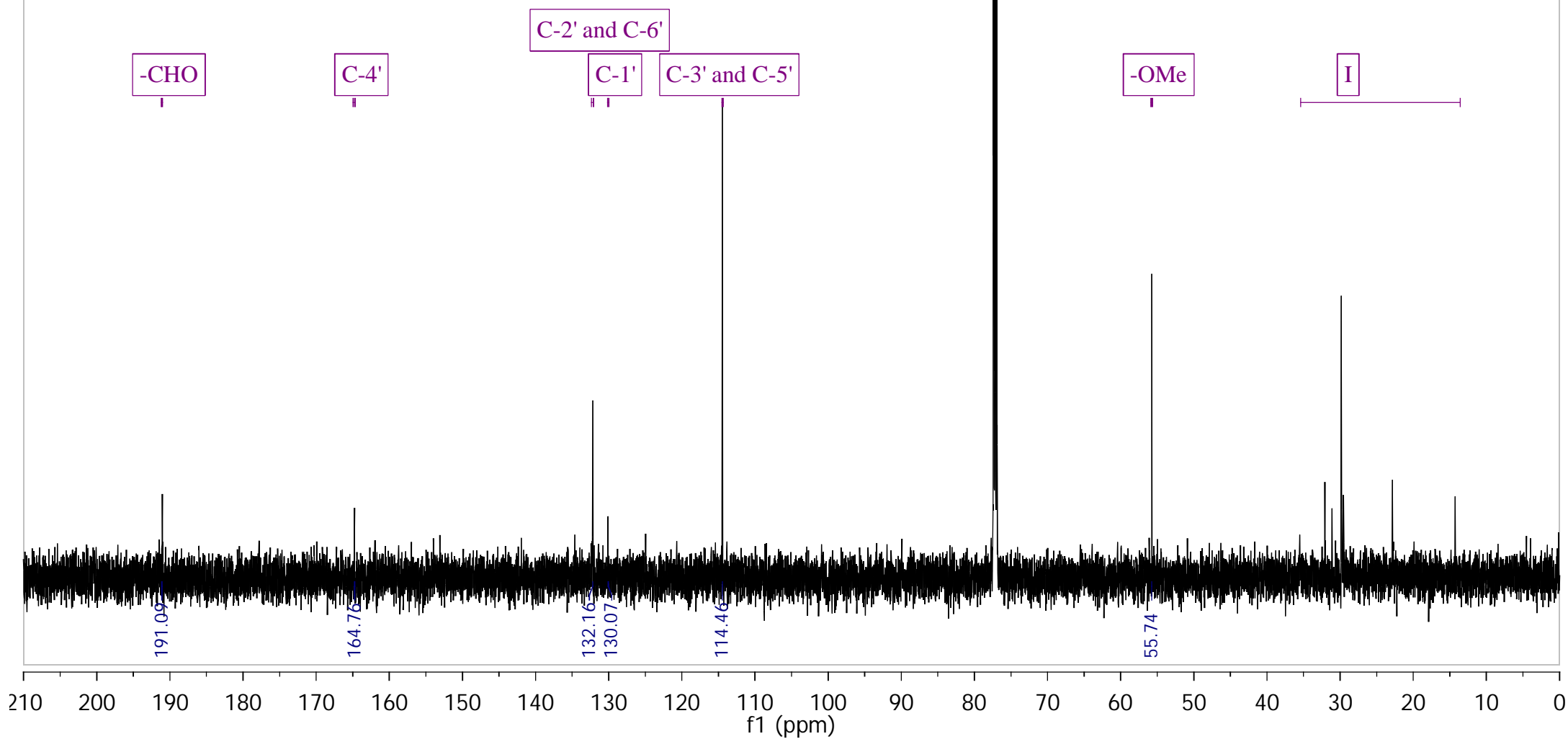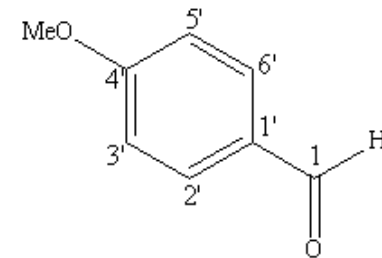
Plate 15c; DEPT [CDCl$_3$]: 4-Methoxybenzaldehyde (**431**)
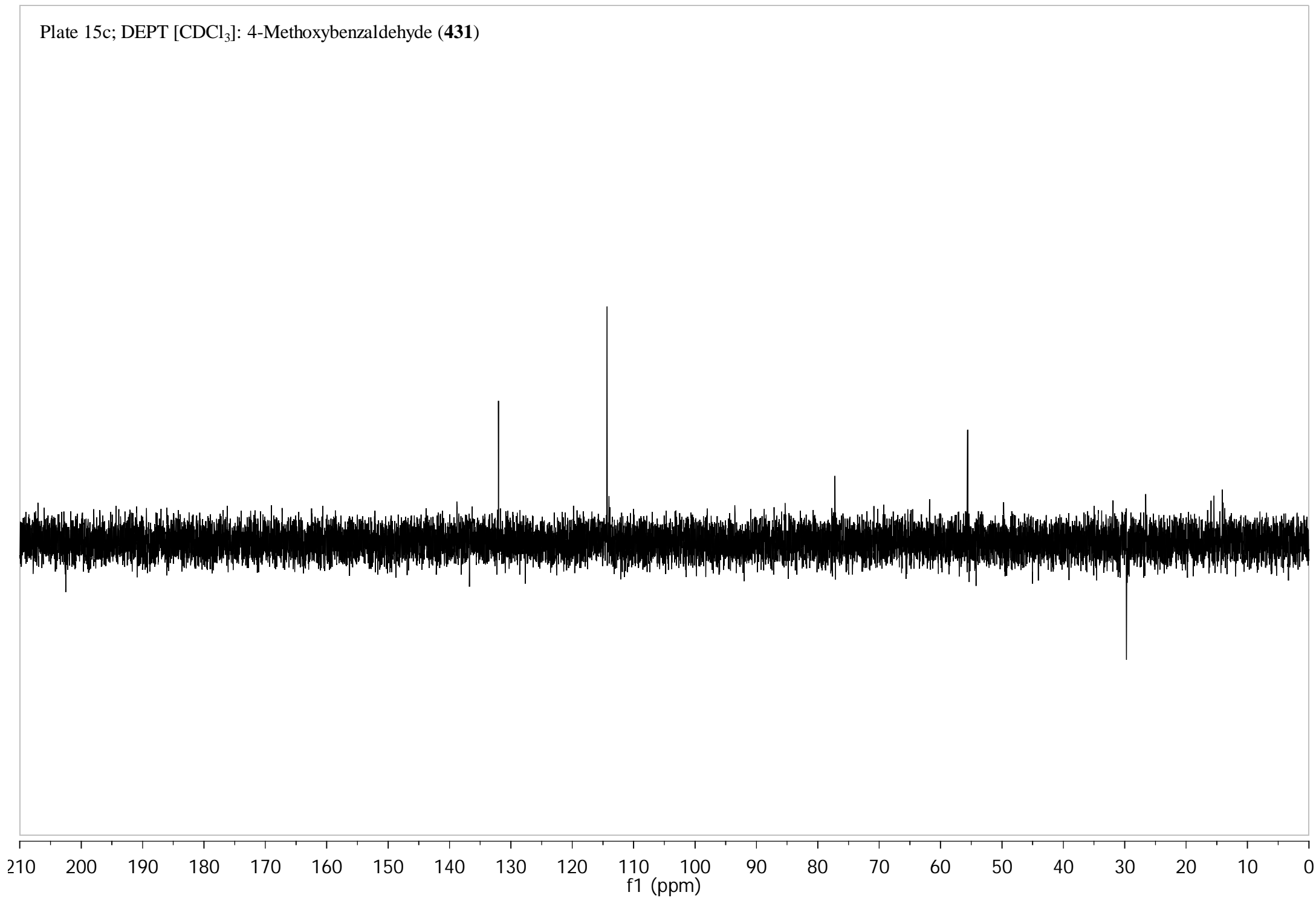
Plate 15d; HSQC [CDCl$_3$]: 4-Methoxybenzaldehyde (**431**)
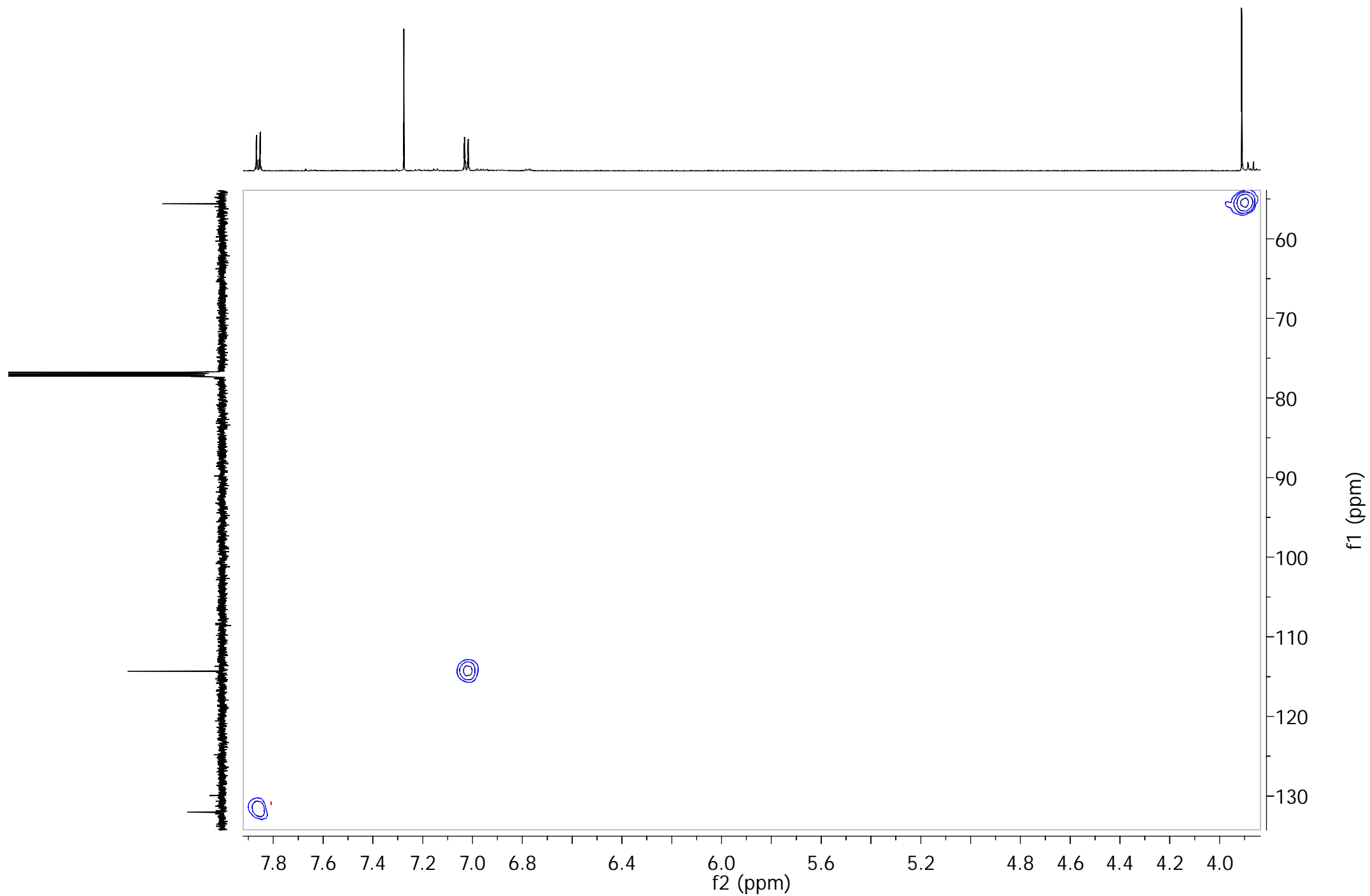
Plate 15e; HMBC [CDCl$_3$]: 4-Methoxybenzaldehyde (**431**)
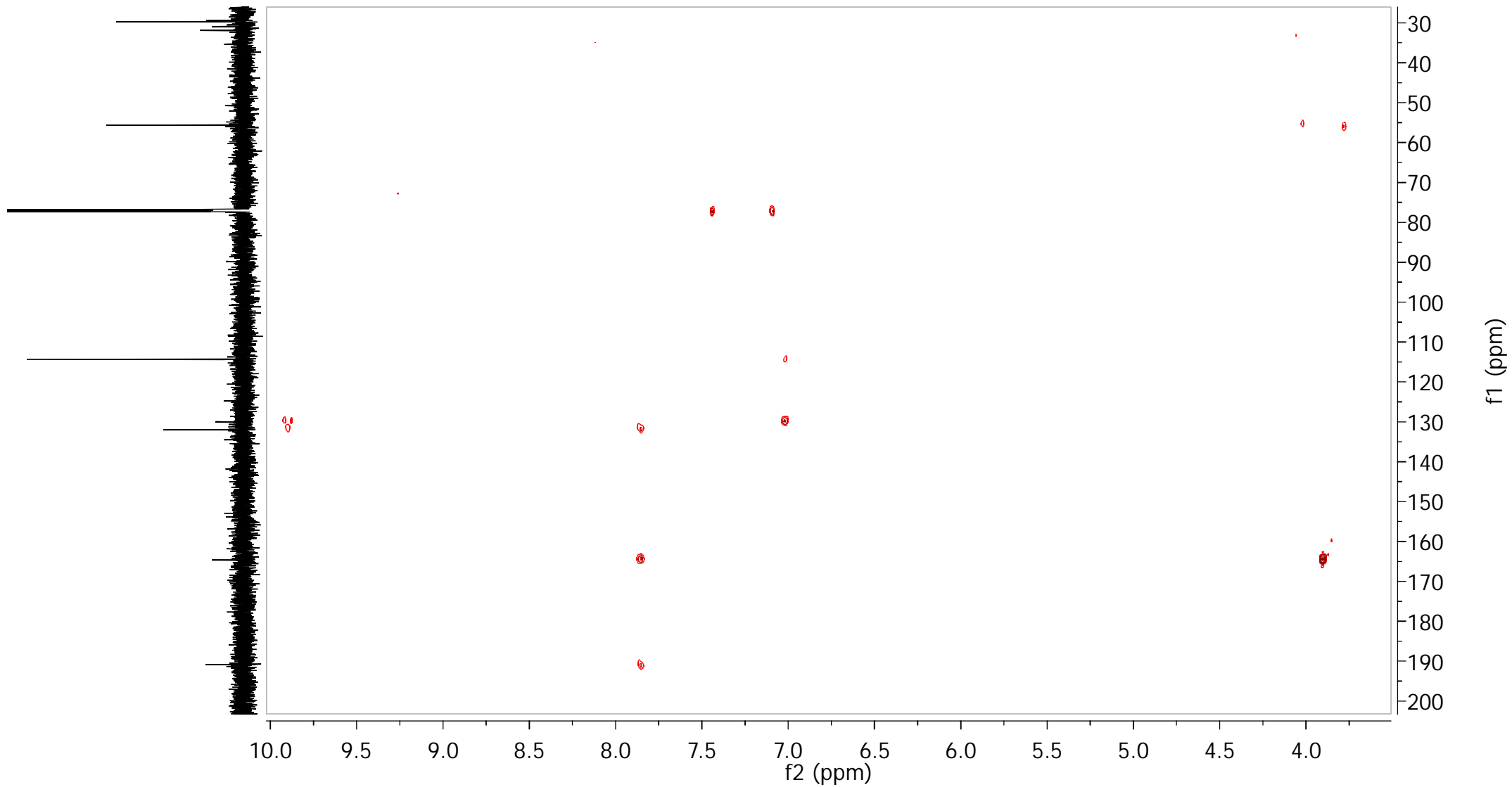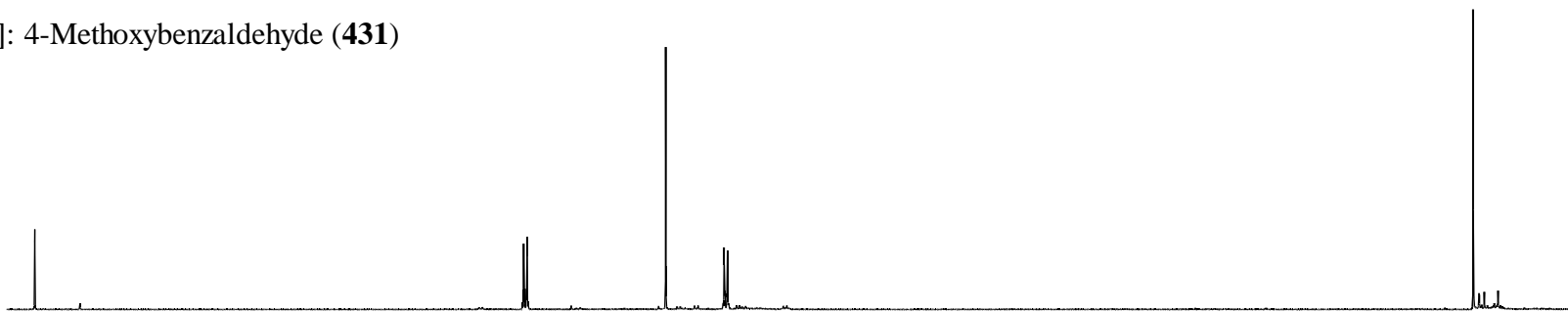
Plate 16a; ^{1}H NMR [CDCl$_3$]: 2'-Methoxyphenylacetaldehyde (**430**)
δ 9.68 (1H, t, J = 2.13 Hz, -CHO), 7.32–7.29 (1H, m, H-4'), 7.16–7.15 (1H, m, H-6'), 6.97–6.94 (1H, m, H-5'), 6.92–6.91 (1H, m, H-3'), 3.83 (3H, s, -OMe), 3.65 (2H, d, J = 2.13 Hz, H-2).
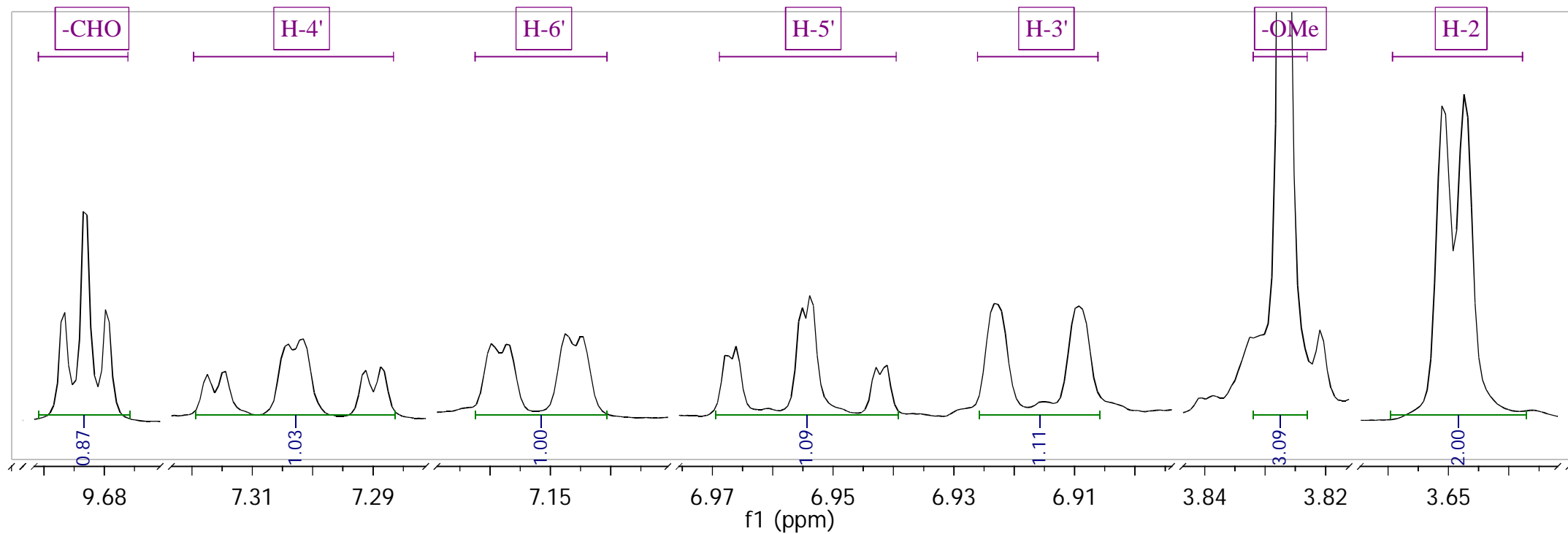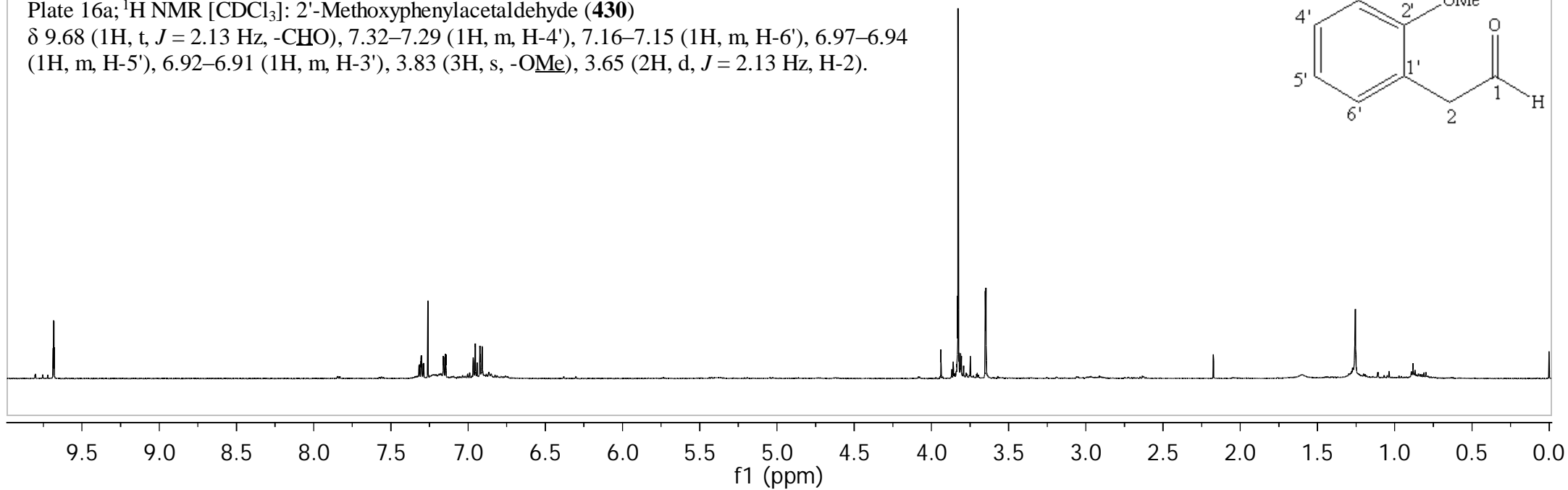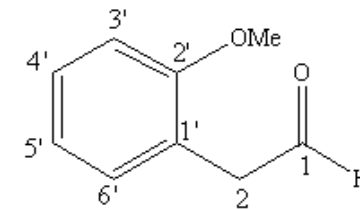
Plate 16b; ^{13}C NMR [CDCl$_3$]: 2'-Methoxyphenylacetaldehyde (**430**)
δ 200.43 (-CHO), 157.82 (C-2'), 131.42 (C-6'), 129.23 (C-4'), 121.55 (C-1'), 120.85 (C-5'), 110.55 (C-3'), 55.61 (-OMe), 45.75 (C-2).

-CHO C-2' C-6' C-1' C-4' C-5' C-3' -OMe C-2 I

200.43   157.82   131.42   129.23   121.55   120.85   110.55   55.61   45.75   29.73

f1 (ppm)
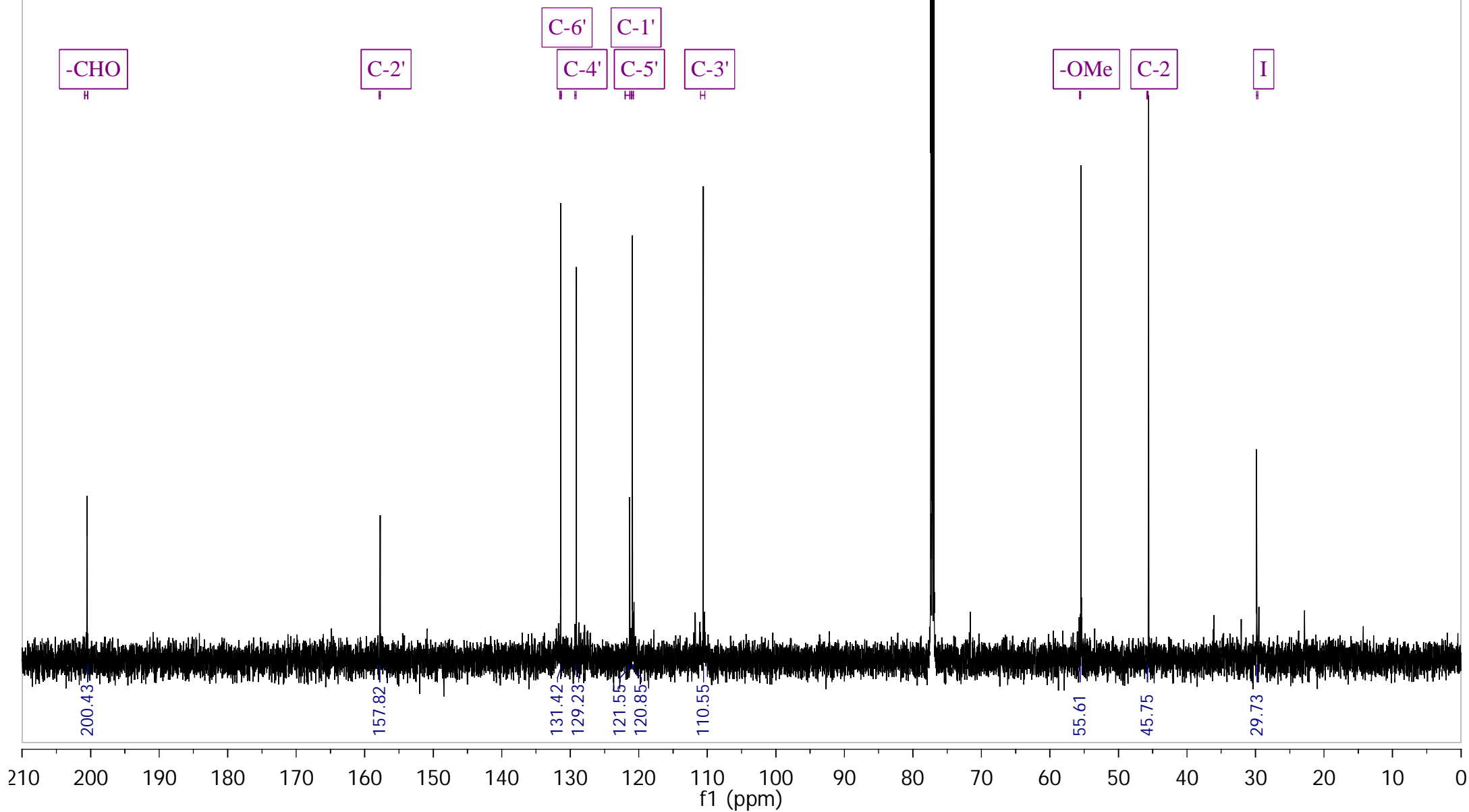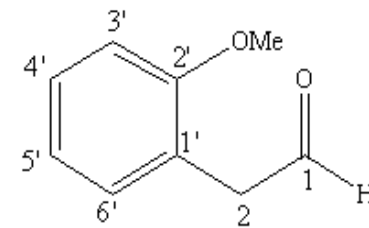
Plate 16c; DEPT [CDCl₃]: 2'-Methoxyphenylacetaldehyde (**430**)
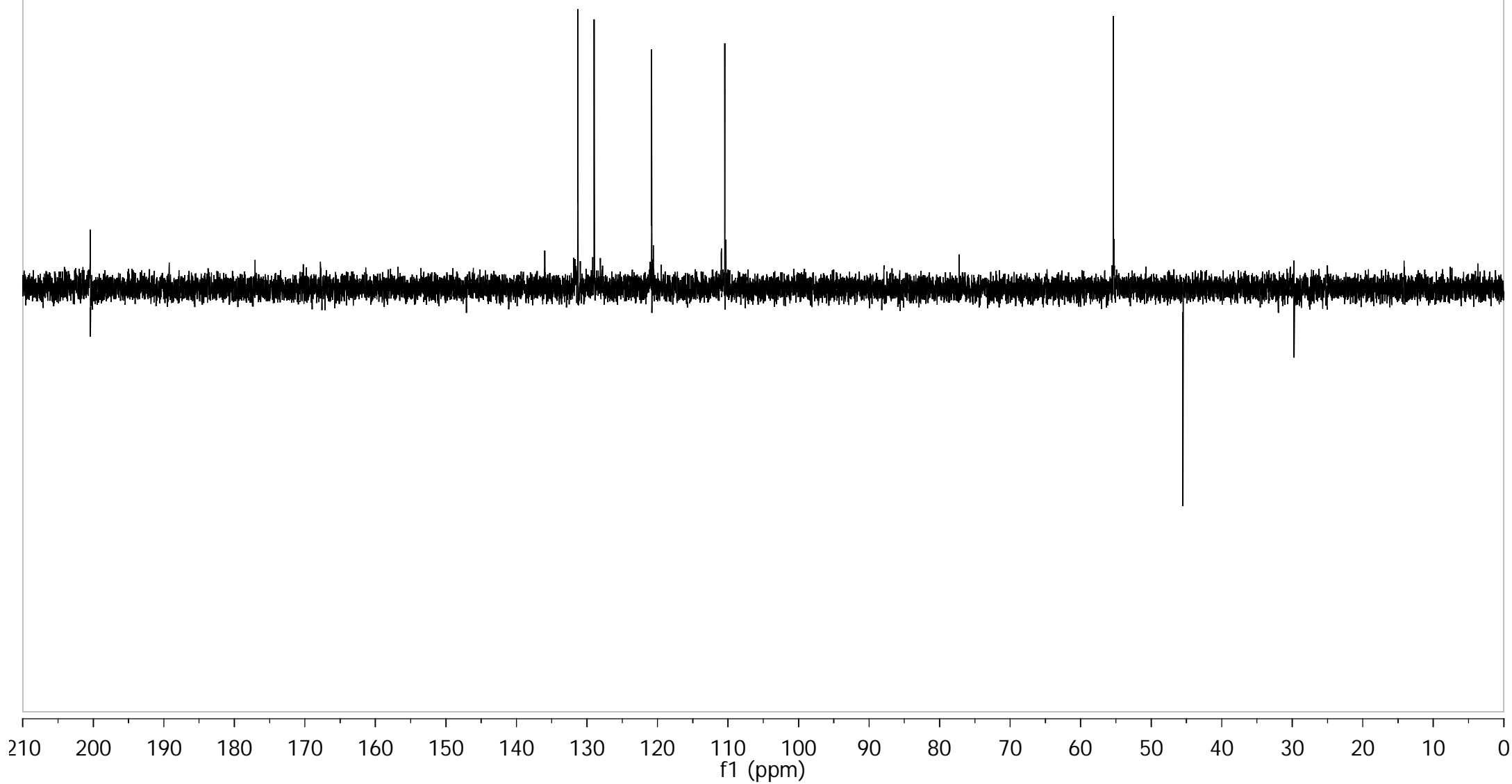
Plate 16d; HSQC [CDCl$_3$]: 2'-Methoxyphenylacetaldehyde (**430**)
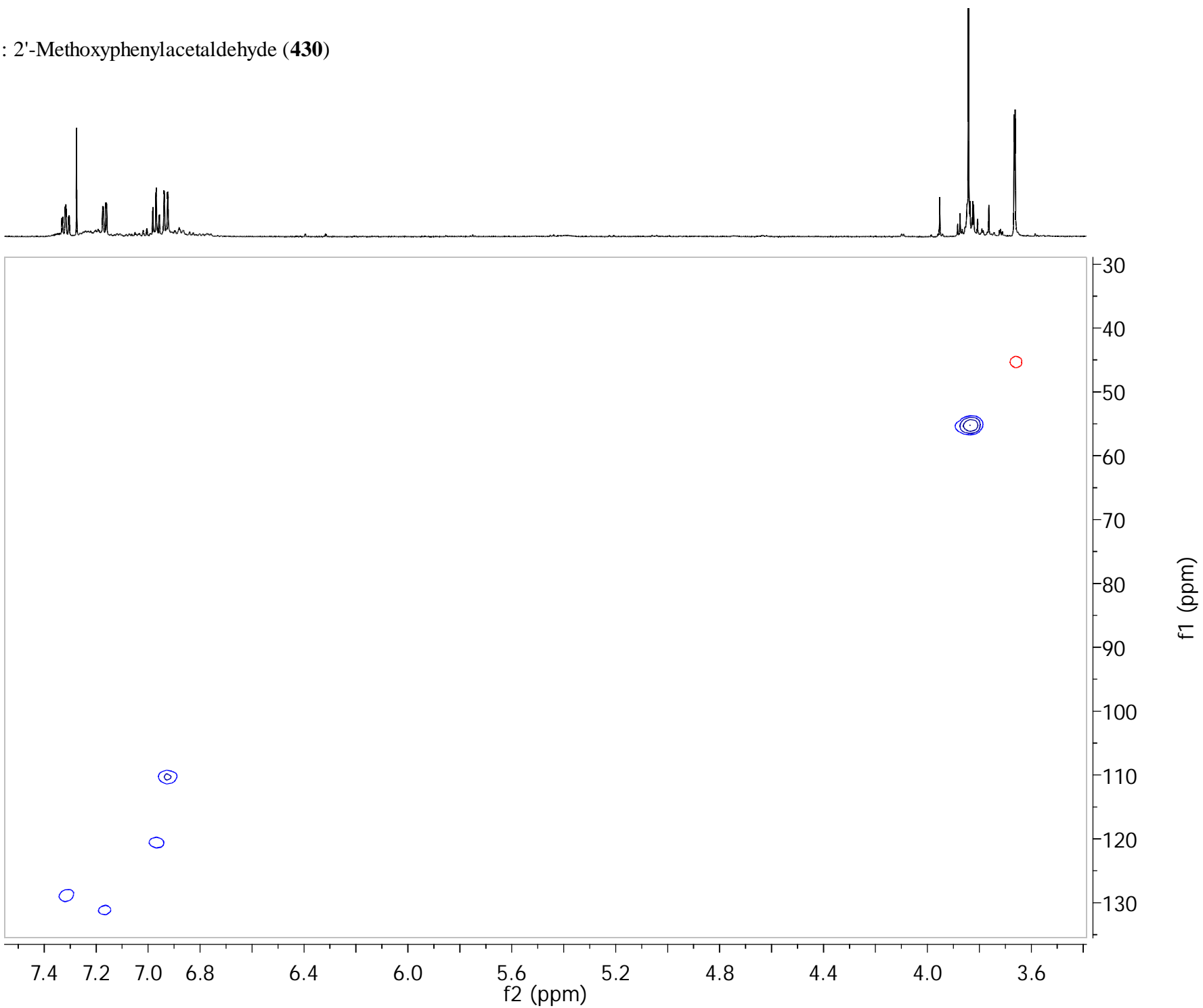
Plate 16e; HMBC [CDCl₃]: 2'-Methoxyphenylacetaldehyde
(**430**)
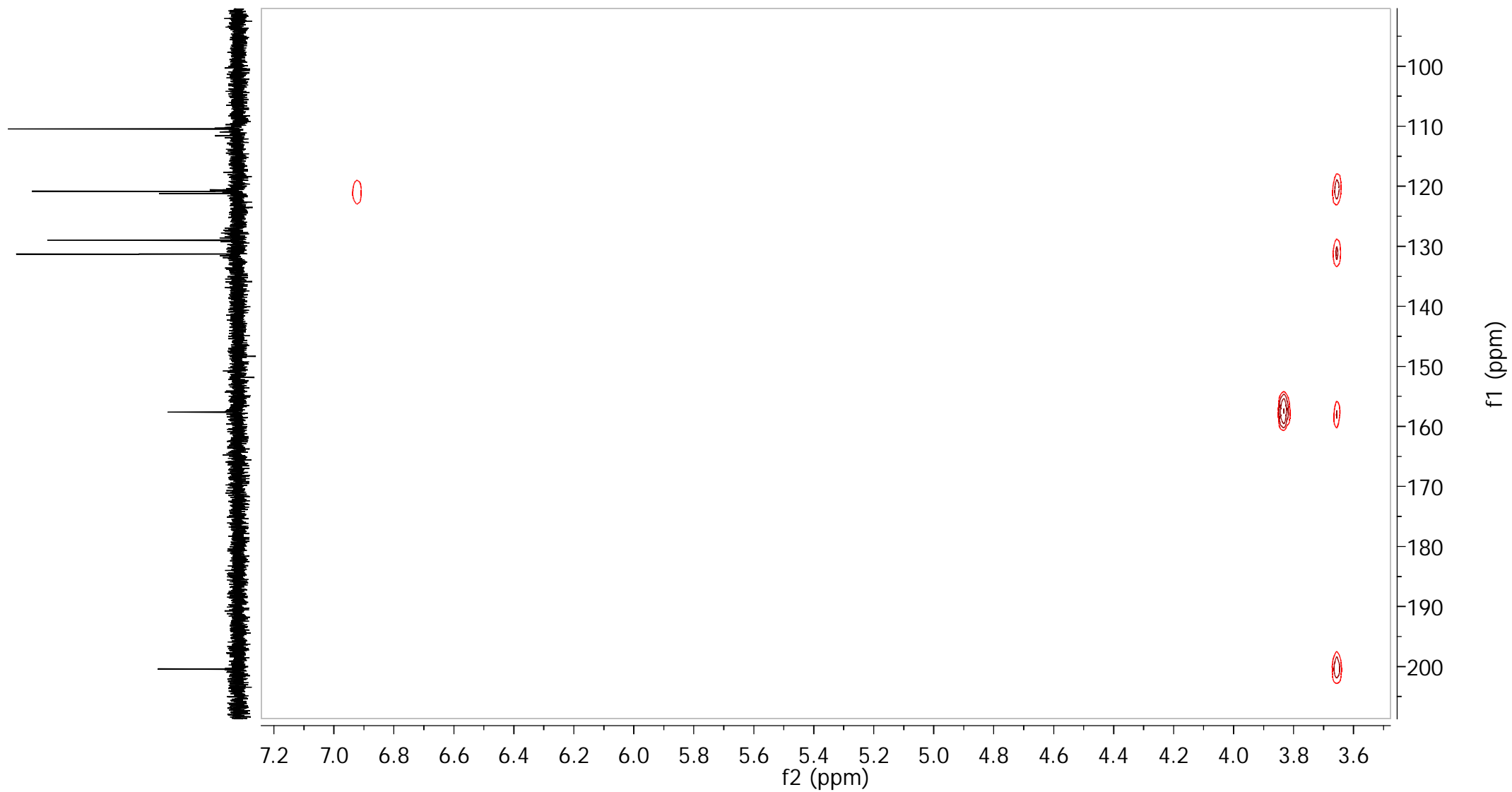
Plate 17a; ^{1}H NMR [CDCl$_3$]: 4'-Methoxyphenylacetaldehyde (**431**)

δ 9.89 (1H, s, -C<u>H</u>O), 7.85 (2H, d, *J* = 8.83 Hz, H-2' and H-6'), 7.01 (2H, d, *J* = 8.83 Hz, H-3' and H-5'),
3.90 (3H, s, -O<u>Me</u>), 3.79 (2H, s, H-2)
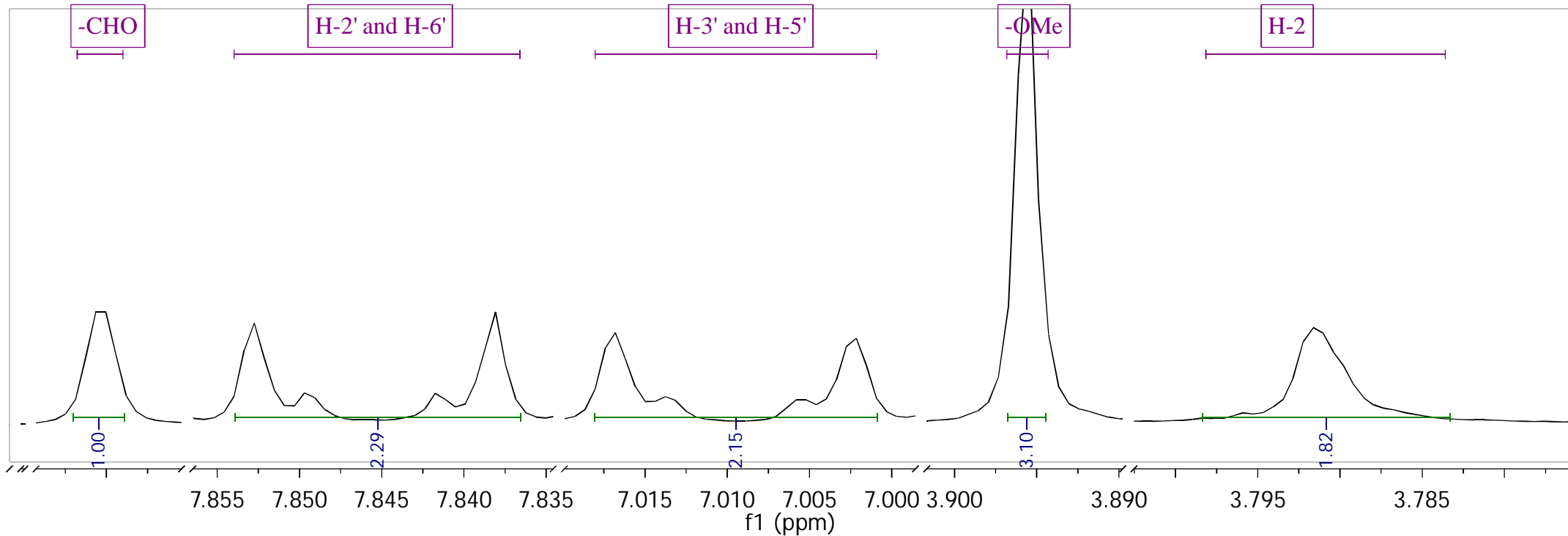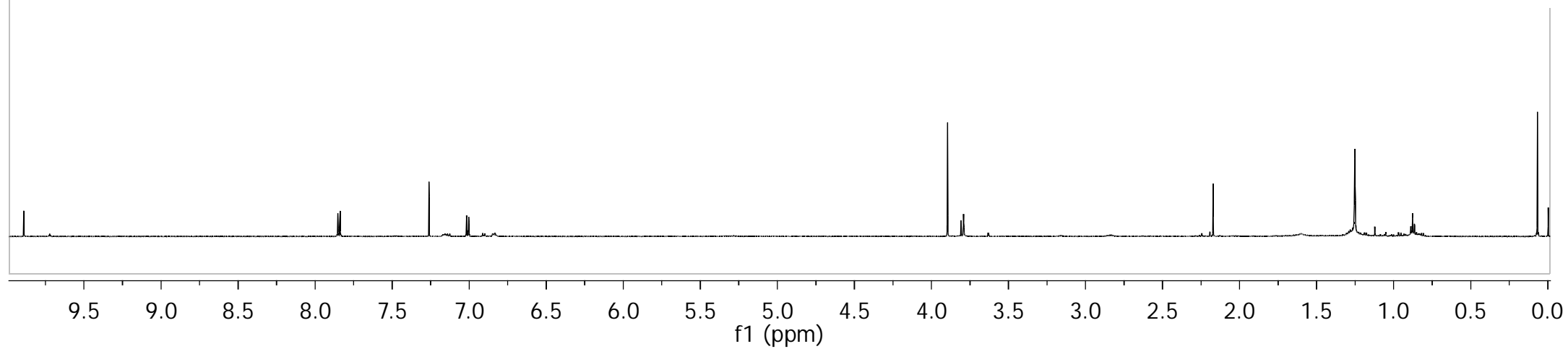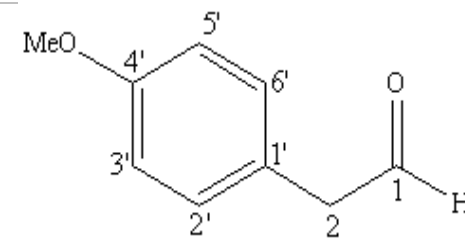
Plate 17b; ^{13}C NMR [CDCl$_3$]: 4'-Methoxyphenylacetaldehyde (**431**)
δ 191.26 (-CHO), 164.87 (C-4'), 132.11(C-2' and C-6'), 130.80 (C-1'), 114.59 (C-3' and C-5'),
55.69 (-OMe), 55.26 (C-2).
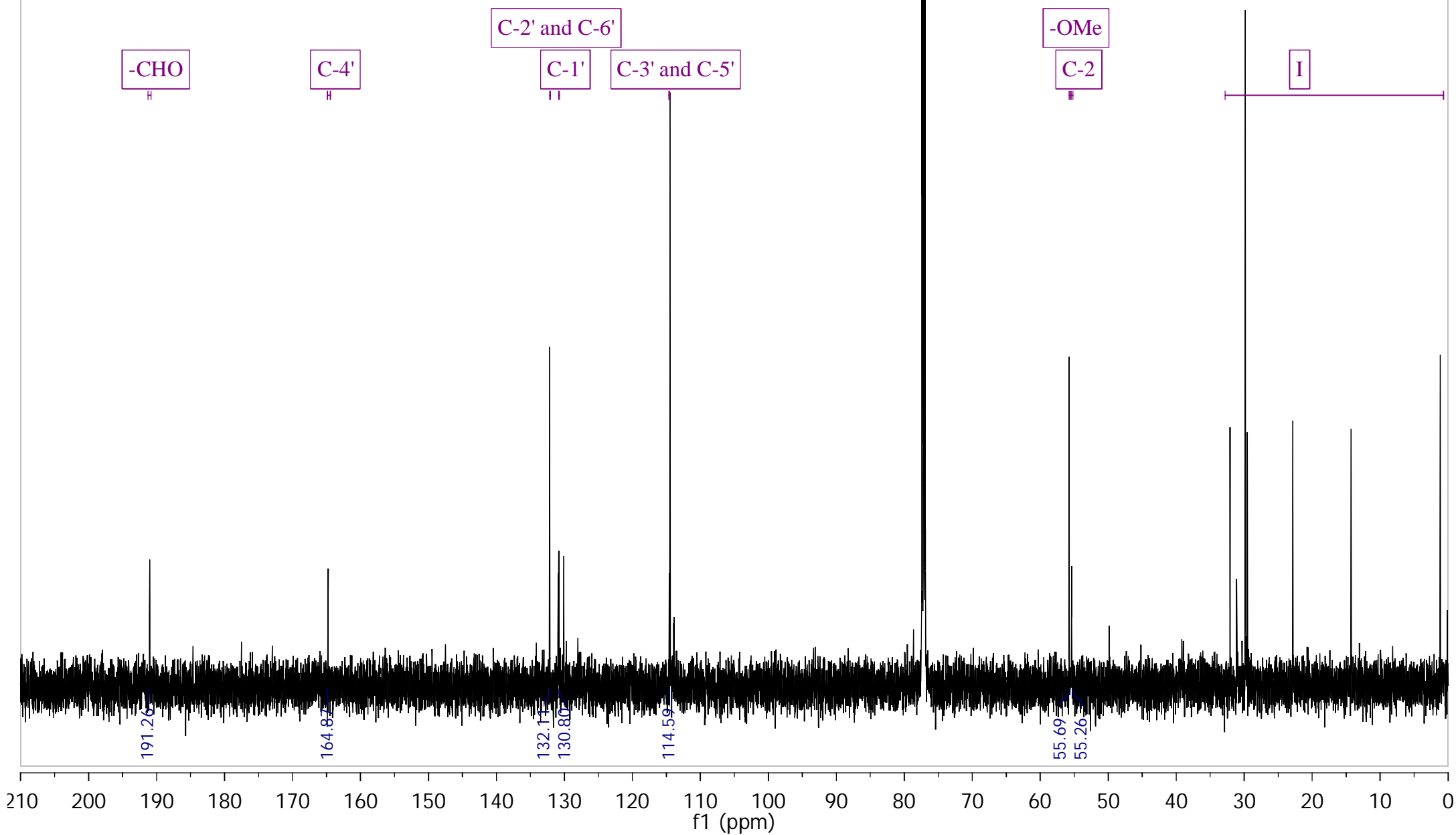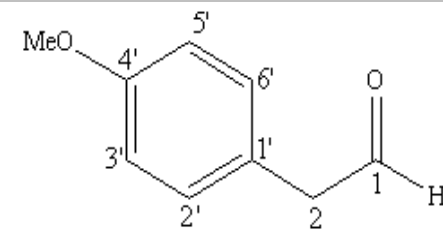
Plate 17c; DEPT [CDCl₃]: 4'-Methoxyphenylacetaldehyde (**431**)
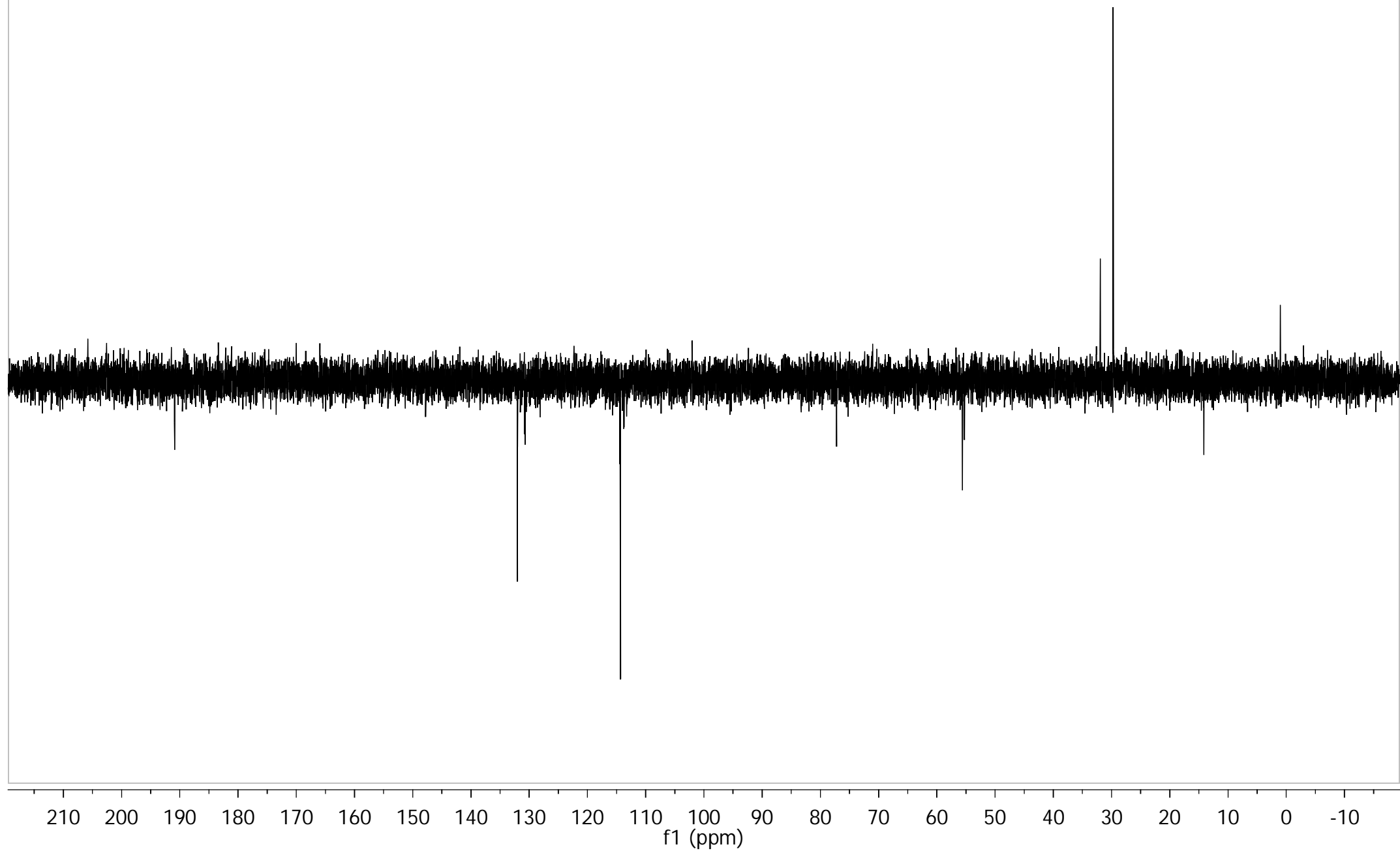
Plate 17d; HSQC [CDCl$_3$]: 4'-Methoxyphenylacetaldehyde (**431**)
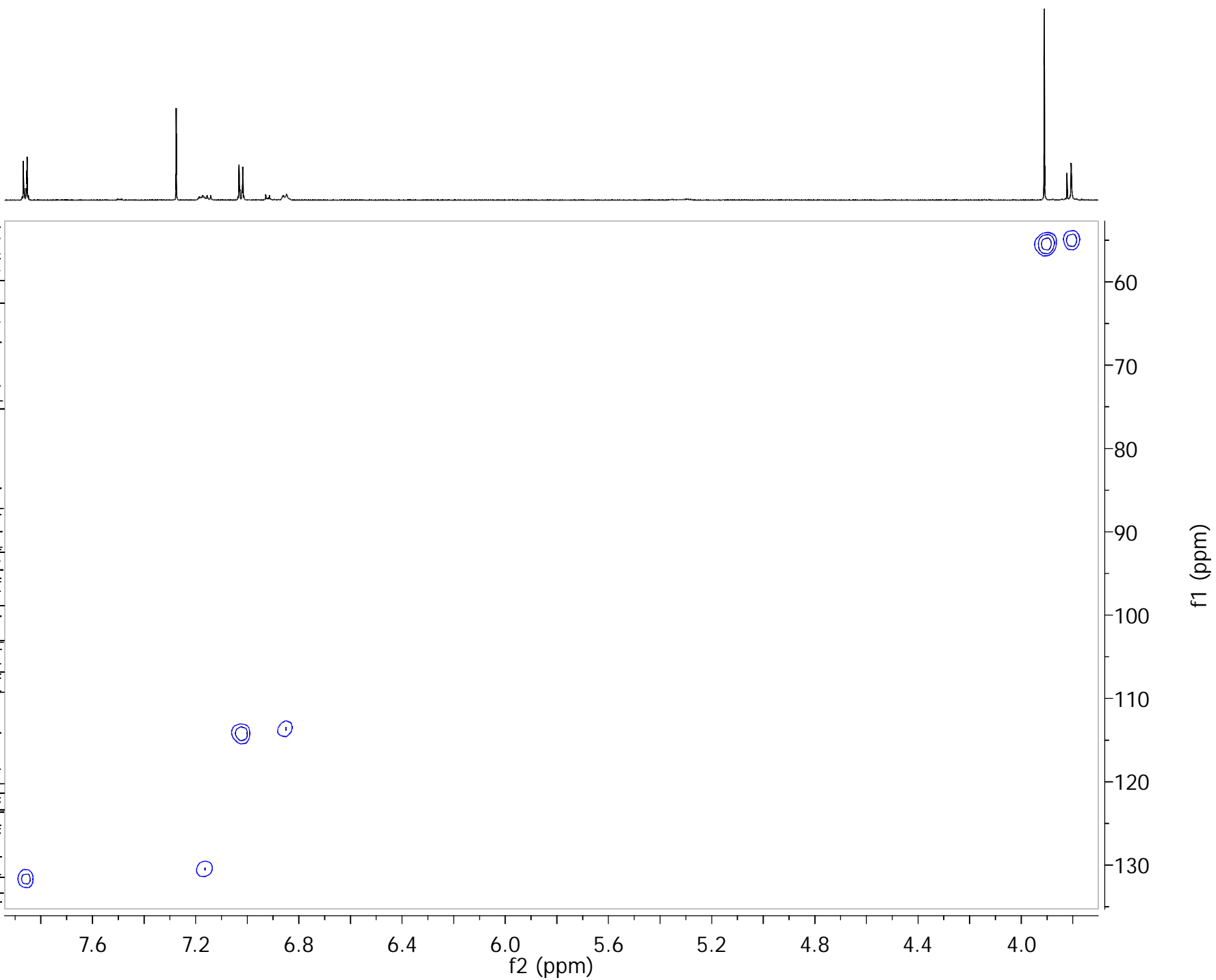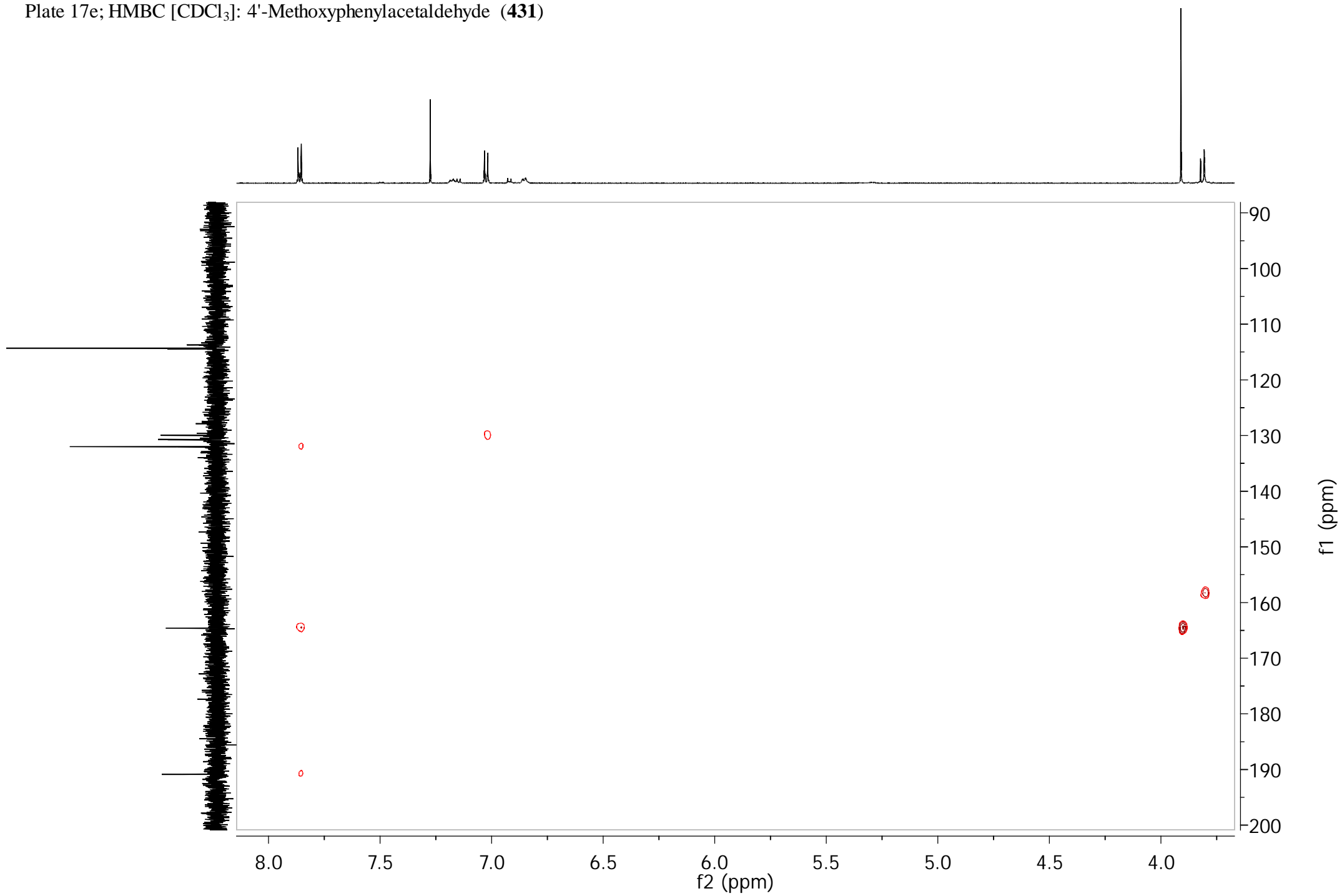
Plate 18a; ^{1}H NMR [CDCl$_3$]: 3',4'-Dimethoxyphenylacetaldehyde (**432**) and 3',4'-Dimethoxybenzaldehyde (**433**)

δ 9.85 (1H, s, -CHO[b]), 9.72 (2H, t, J = 2.29 Hz, -CHO[a]), 7.46 (1H, dd, J = 8.11, 1.86 Hz, H-6'b), 7.41 (1H, d, J = 1.86 Hz, H-2'b), 6.98 (1H, d, J = 8.11 Hz, H-5'b), 6.86 (2H, d, J = 8.11 Hz, H-5'a), 6.77 (2H, dd, J = 8.11, 2.04 Hz, H-6'a), 6.70 (2H, d, J = 2.04 Hz, H-2'a), 3.97 (3H, s, -OMe [b]), 3.95 (3H, s, -OMe [b]), 3.88–3.87 (12H, m, -OMe [a]), 3.63 (4H, d, J = 2.29 Hz, H-2a).
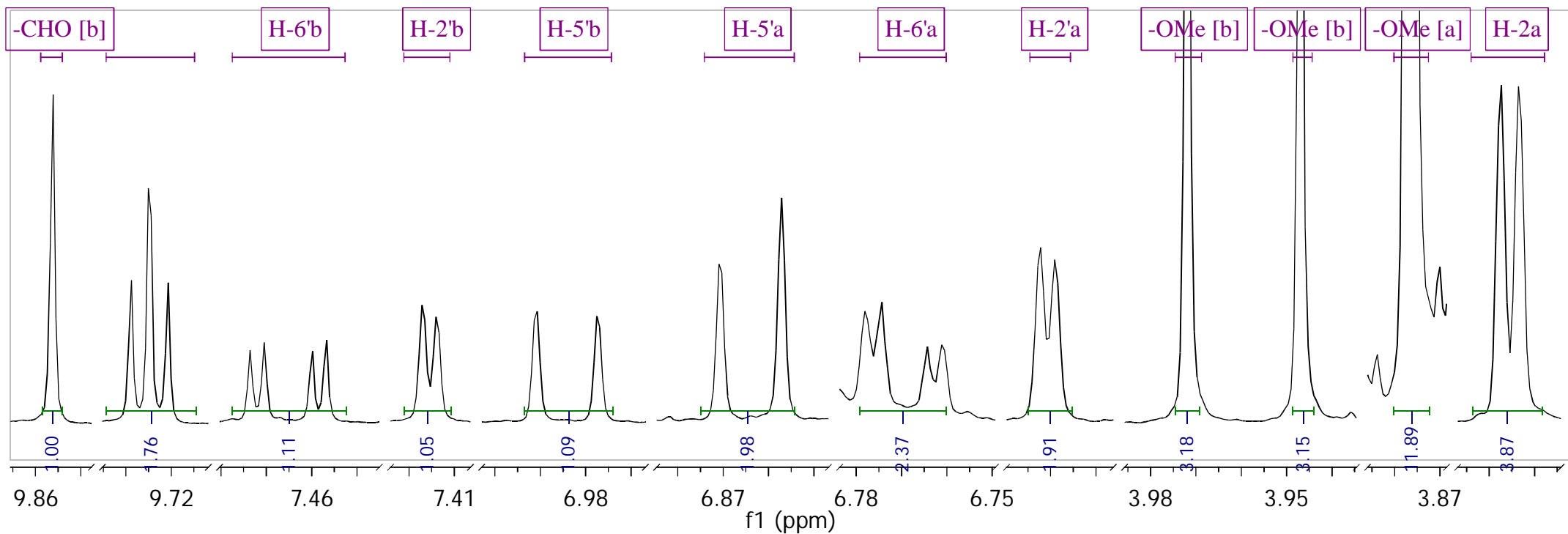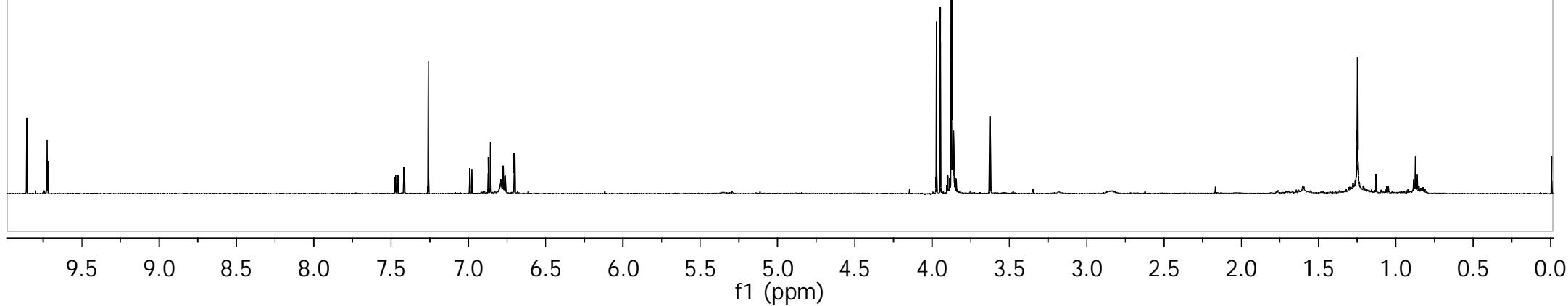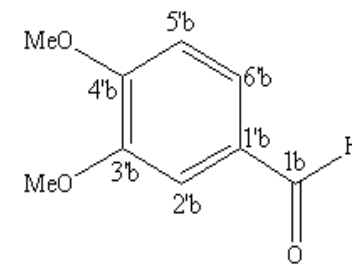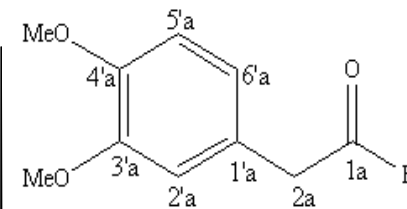
Plate 18b; ^{13}C NMR [CDCl$_3$]: 3',4'-Dimethoxyphenylacetaldehyde (**432**) and 3',4'-Dimethoxybenzaldehyde (**433**)

δ 199.93 (-CHO [a]), 191.13 (-CHO [b]), 154.86 (quaternary carbon), 149.75 (quaternary carbon), 149.58 (quaternary carbon), 148.71 (quaternary carbon), 130.22 (quaternary carbon), 127.14 (C-6'b 124.06 (quaternary carbon), 122.12 (C-6'a), 112.68 (C-2'a), 111.56 (C-5'a), 110.68 (C-5'b), 108.92 (C-2'b), 56.43 (-OMe), 56.02 (-OMe), 50.30 (C-2a).
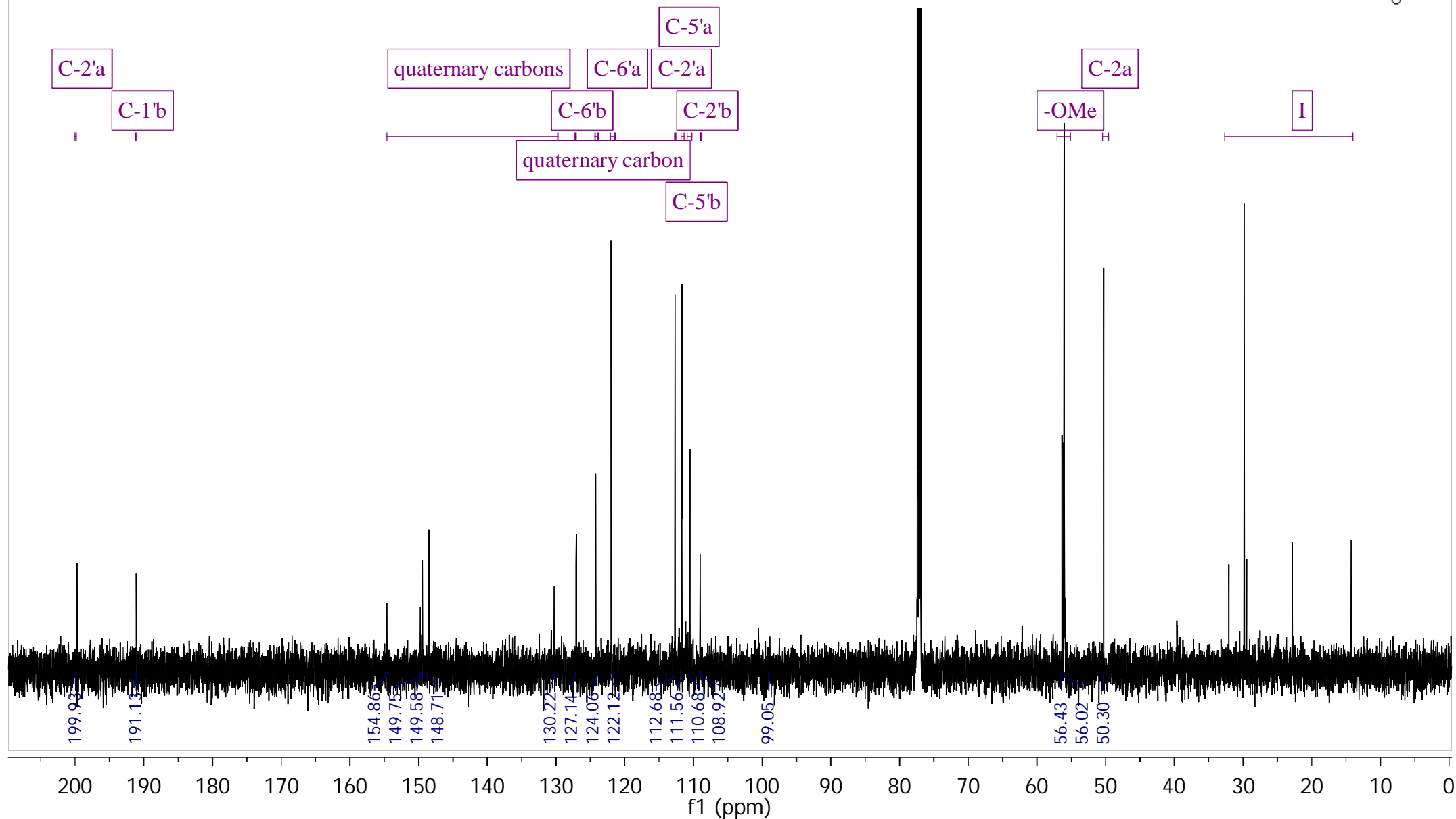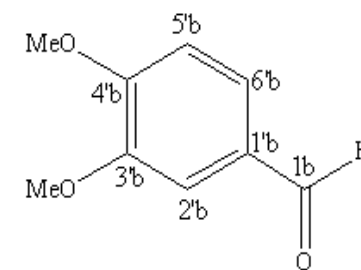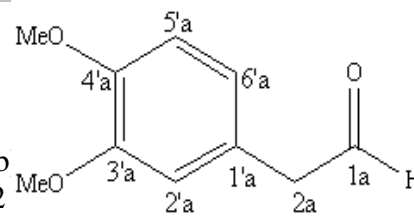
Plate 18c: DEPT [CDCl$_3$]: 3',4'-Dimethoxyphenylacetaldehyde (**432**) and 3',4'-Dimethoxybenzaldehyde (**433**)
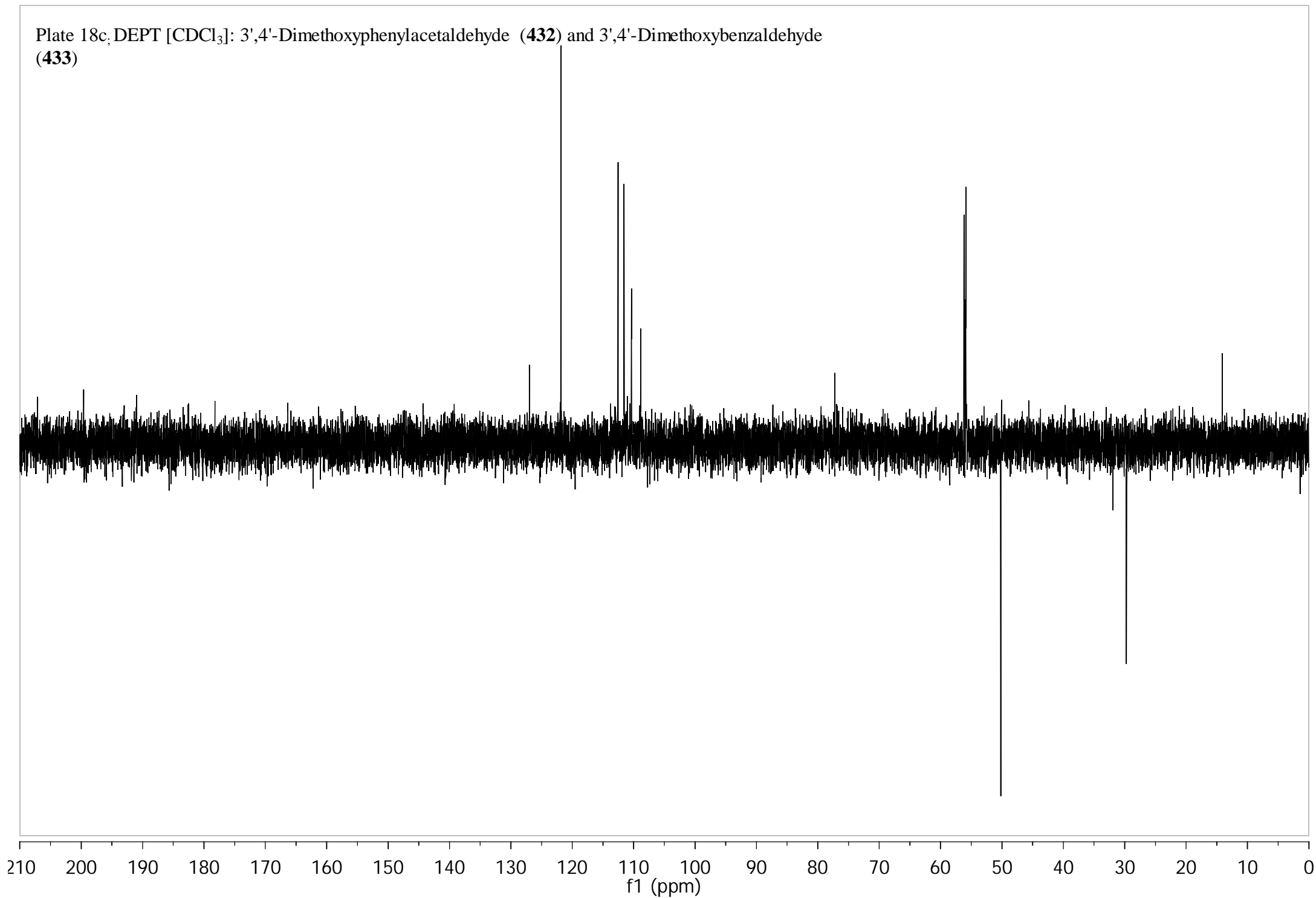
Plate 18d; HSQC [CDCl₃]: 3',4'-Dimethoxyphenylacetaldehyde (**432**) and 3',4'-Dimethoxybenzaldehyde (**433**)
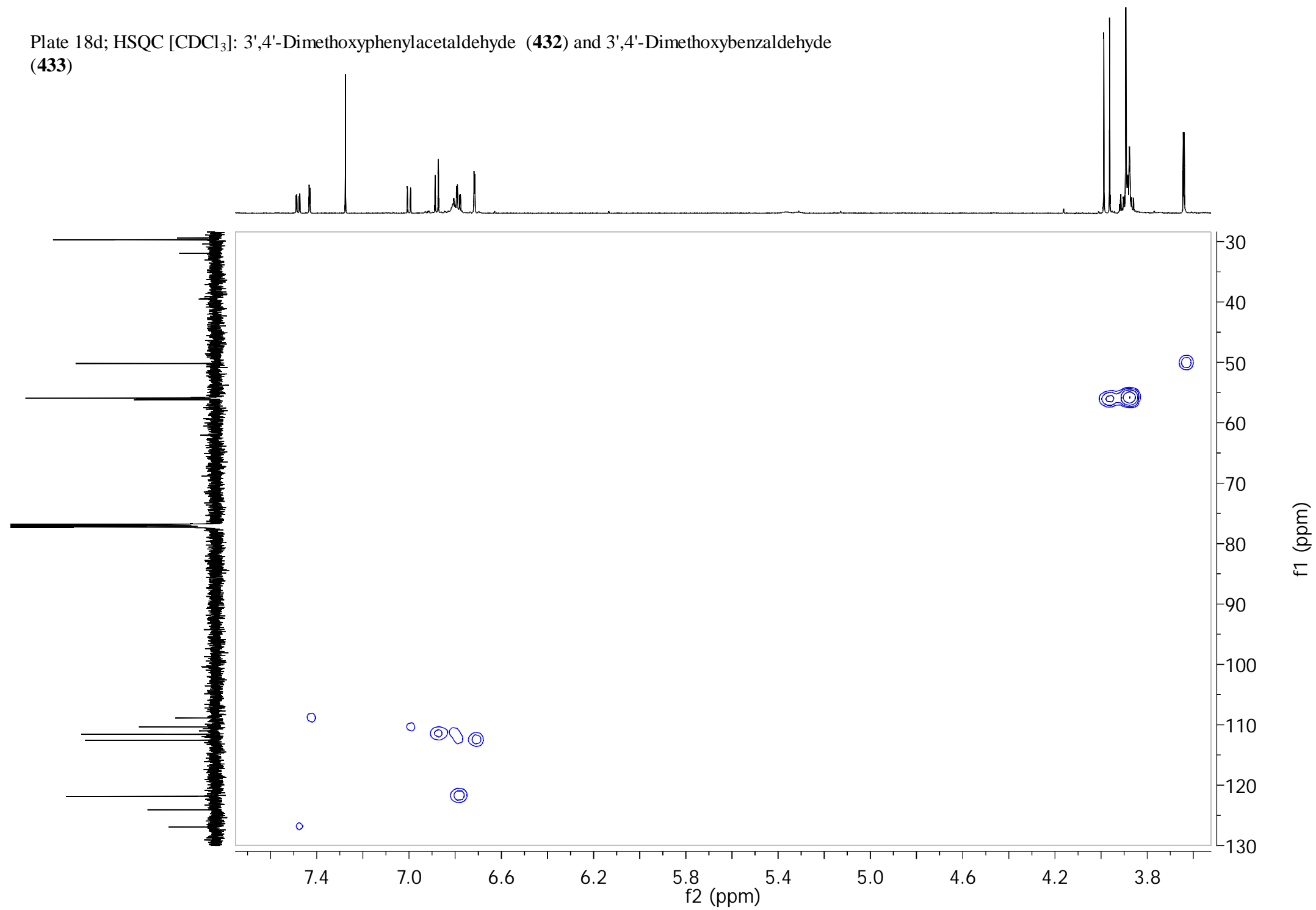
Plate 18e; HMBC [CDCl$_3$]: 3',4'-Dimethoxyphenylacetaldehyde (**432**) and 3',4'-Dimethoxybenzaldehyde (**433**)
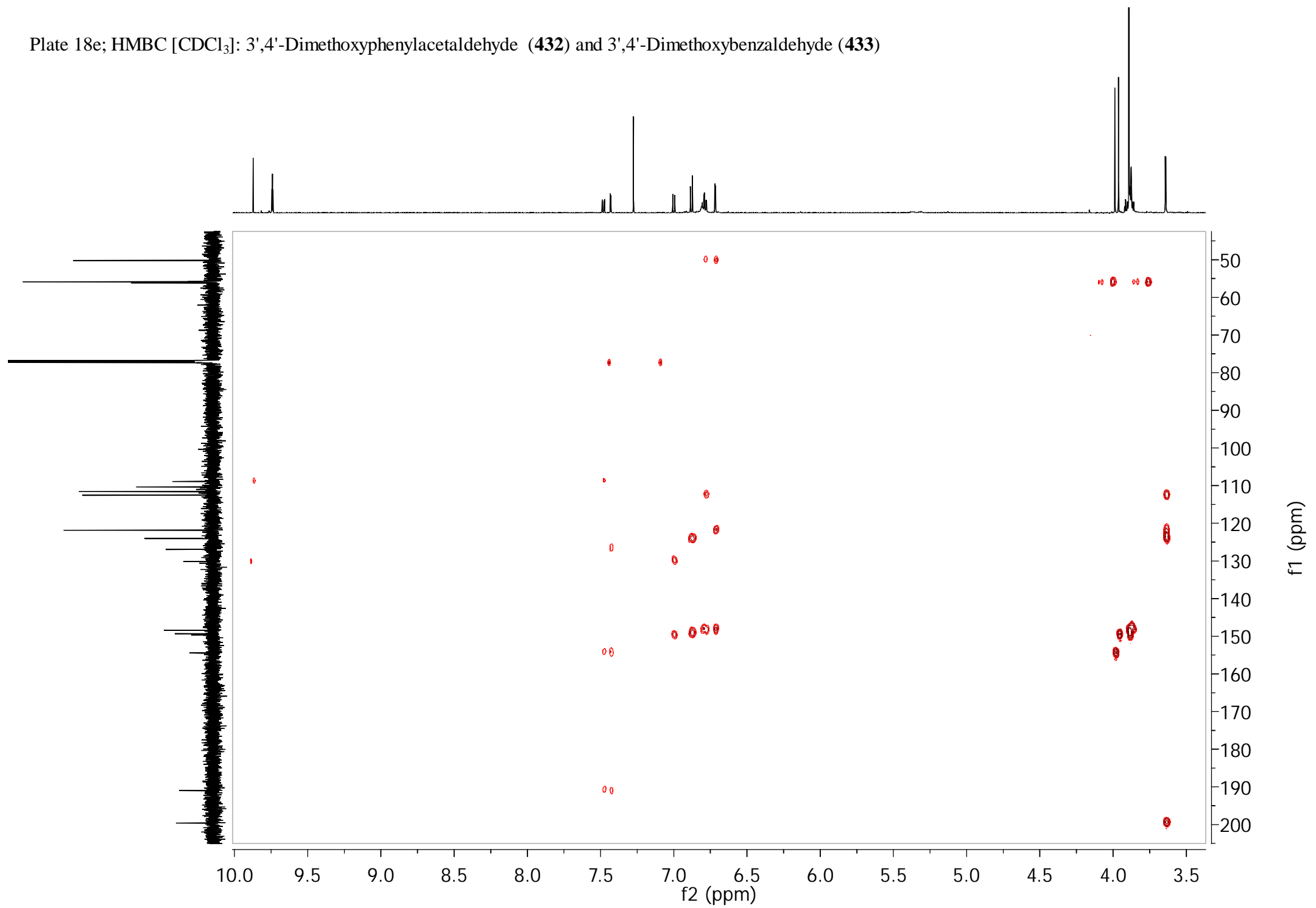
Plate 19a; ¹H NMR [CDCl₃]: 2'-Trifluoromethanesulfonyloxy-4'-methoxybenzaldehyde (**452**)
δ 10.12 (1H, s, -C$\underline{H}$O), 7.94 (1H, d, J = 8.71 Hz, H-6'), 7.02 (1H, dd, J = 8.71, 2.40 Hz, H-5'), 6.87 (1H, d, J = 2.40 Hz, H-3'), 3.92 (3H, s, -O$\underline{Me}$).
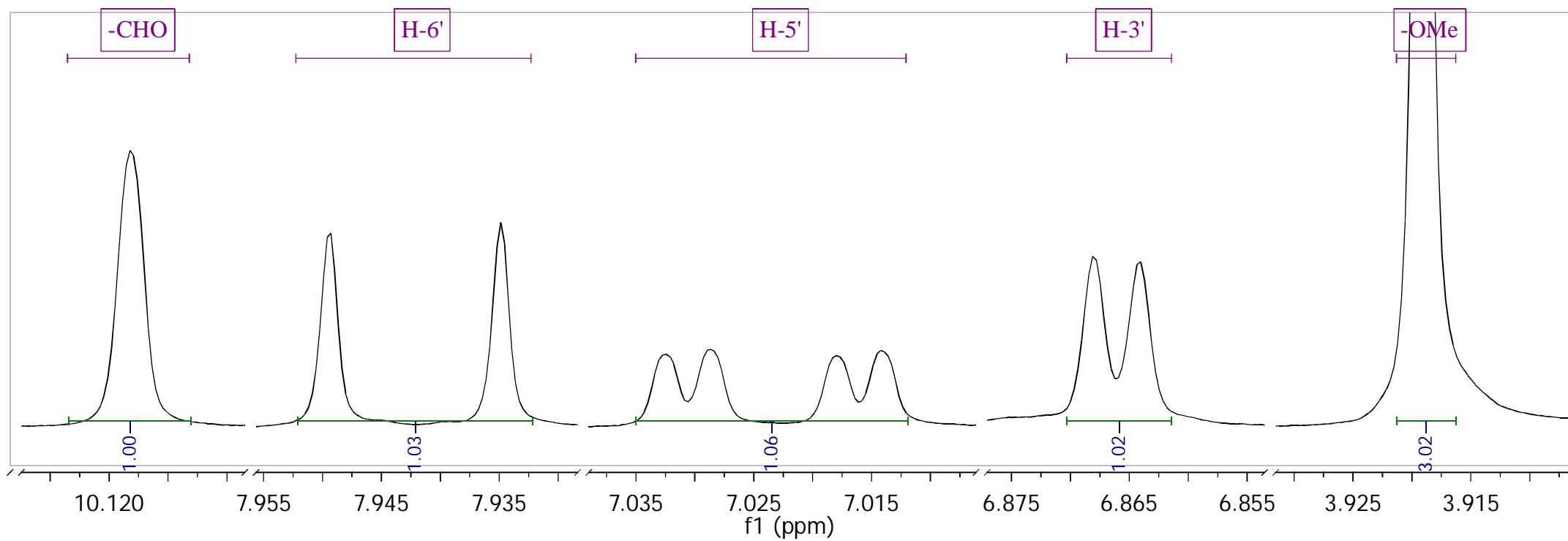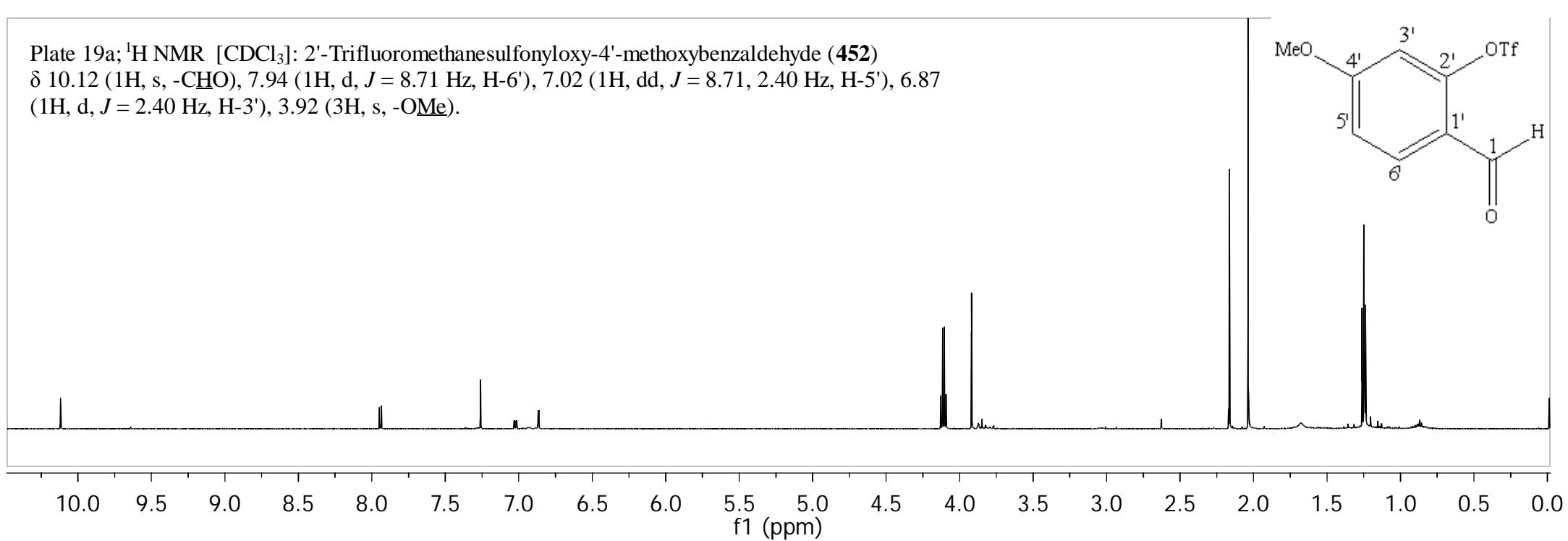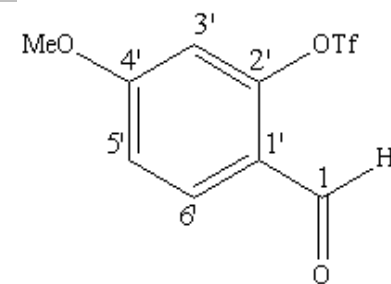
Plate 19b; ^{13}C NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxybenzaldehyde (**452**)
δ 185.49 (-CHO), 165.47 (C-4'), 151.43 (C-1'), 132.40 (C-6'), 121.93 (C-2'), 118.70 (q, J = 319.69 Hz, -OSO$\underline{C}$F$_3$), 114.35 (C-5'), 108.35 (C-3'), 56.39 (-O$\underline{Me}$).
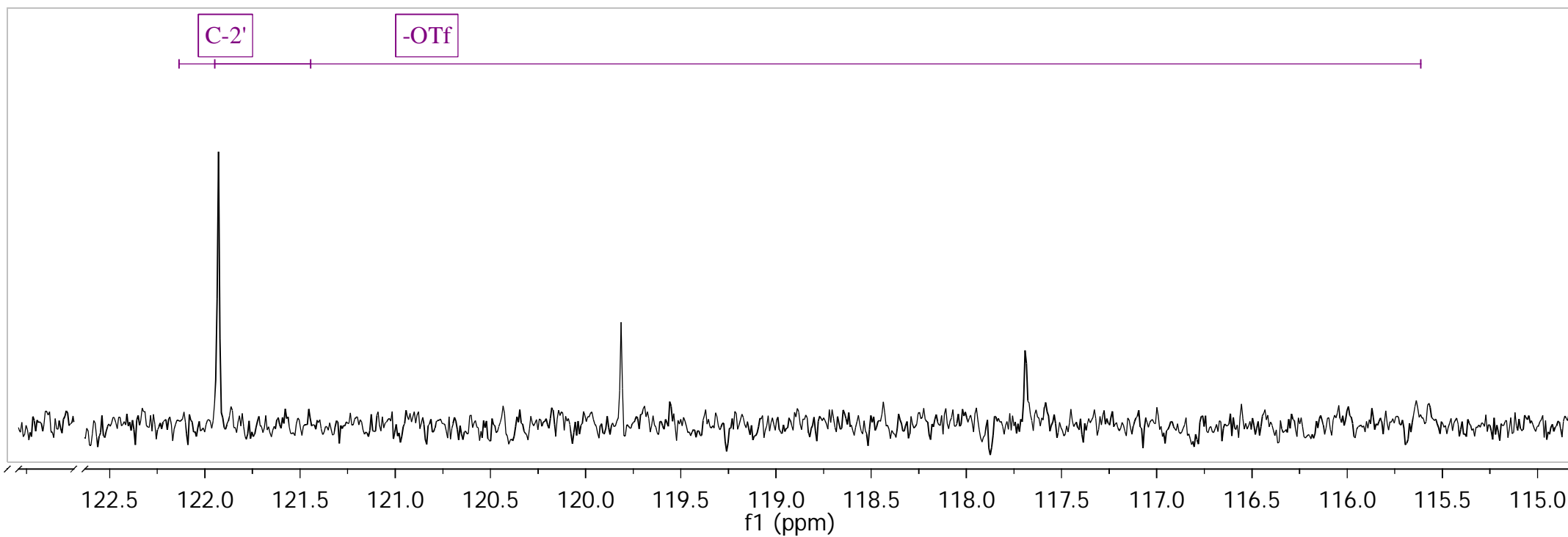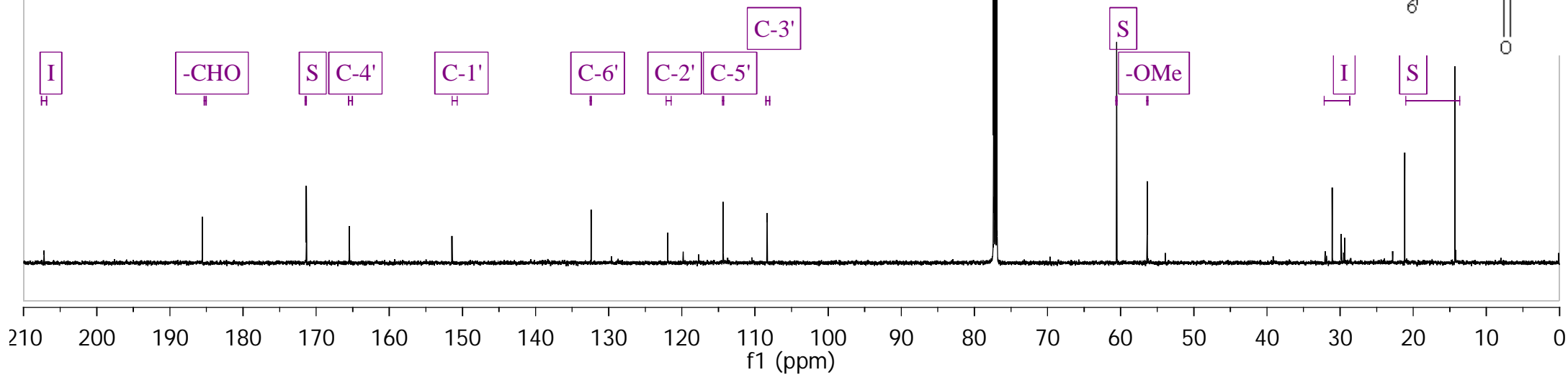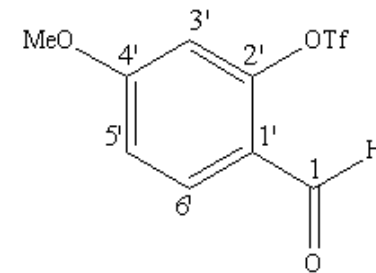
Plate 19c; DEPT [CDCl$_3$] : 2'-Trifluoromethanesulfonyloxy-4'-methoxybenzaldehyde
(**452**)
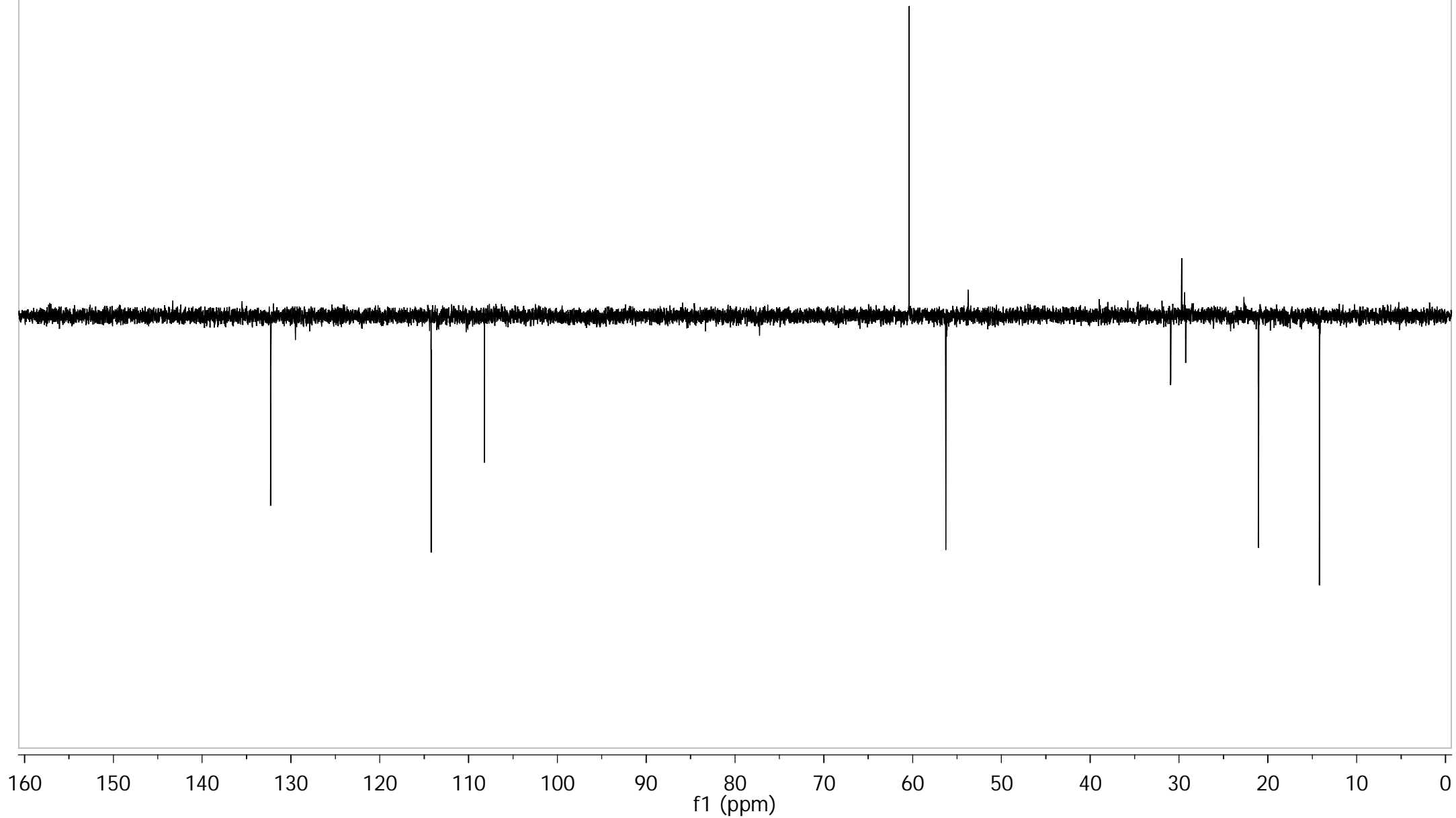
Plate 19d; HSQC [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxybenzaldehyde
(**452**)
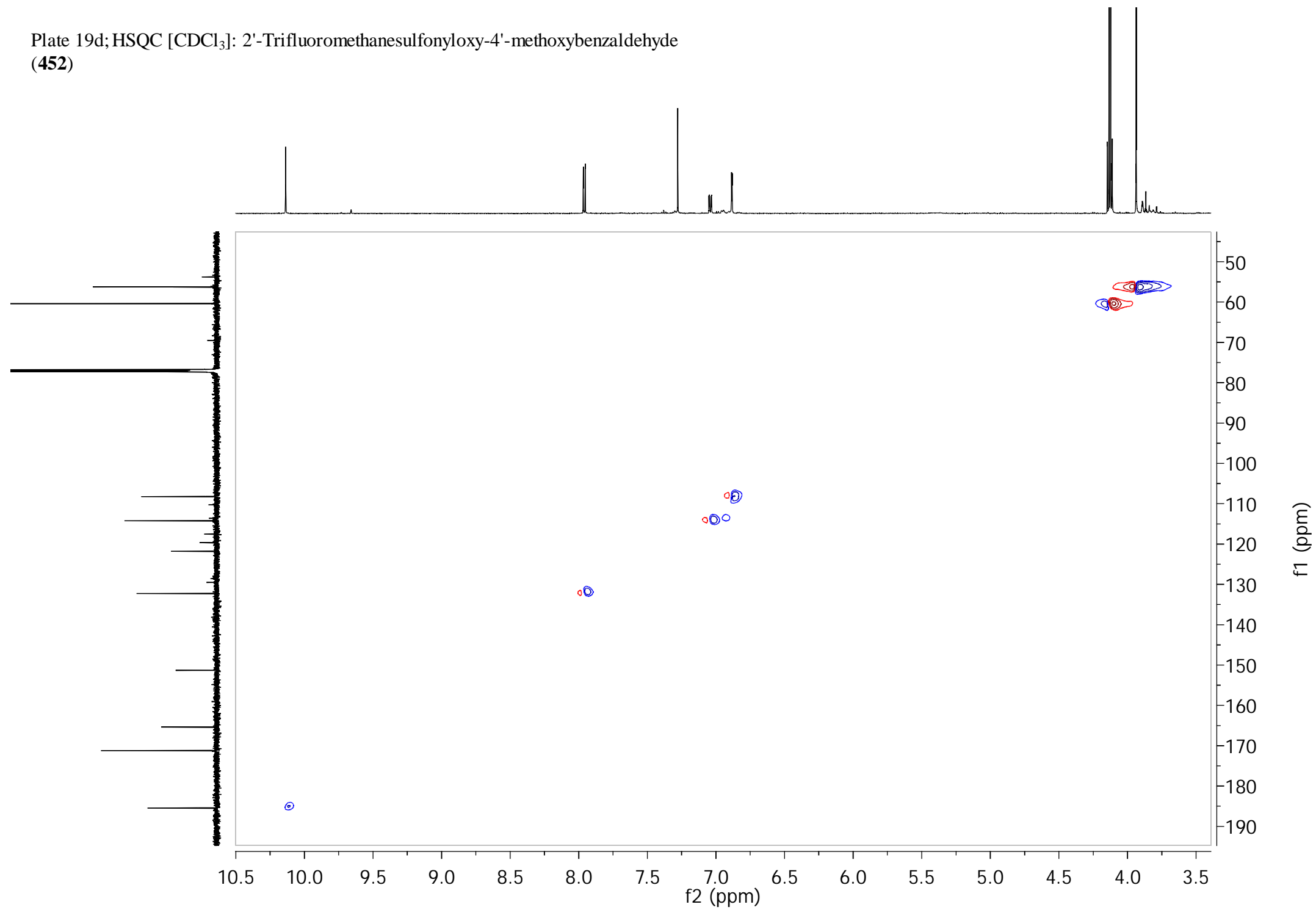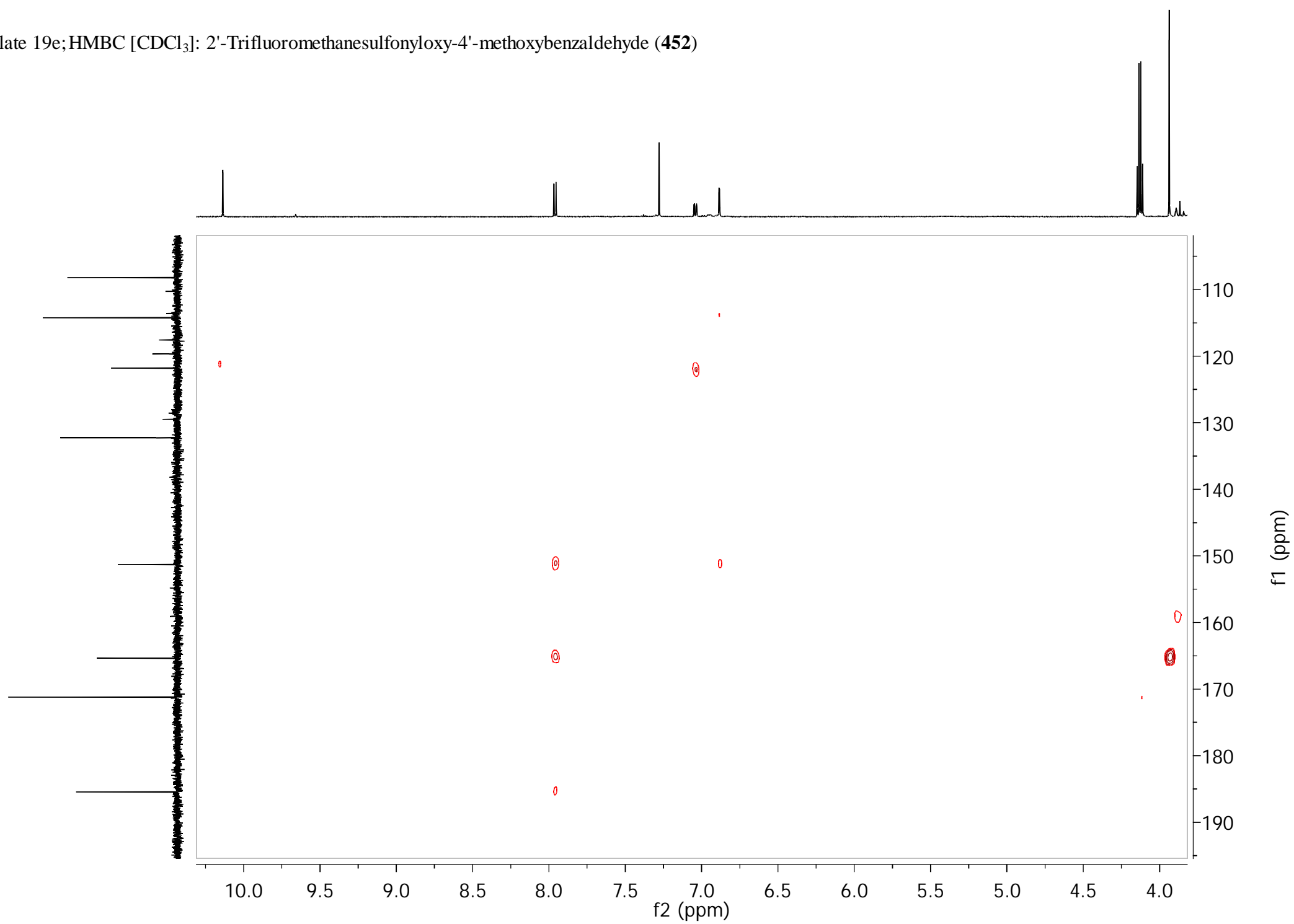
Plate 19f; ^{19}F NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxybenzaldehyde (**452**)
δ -75.89 (-OSOC$\underline{F}_3$)

-OTf
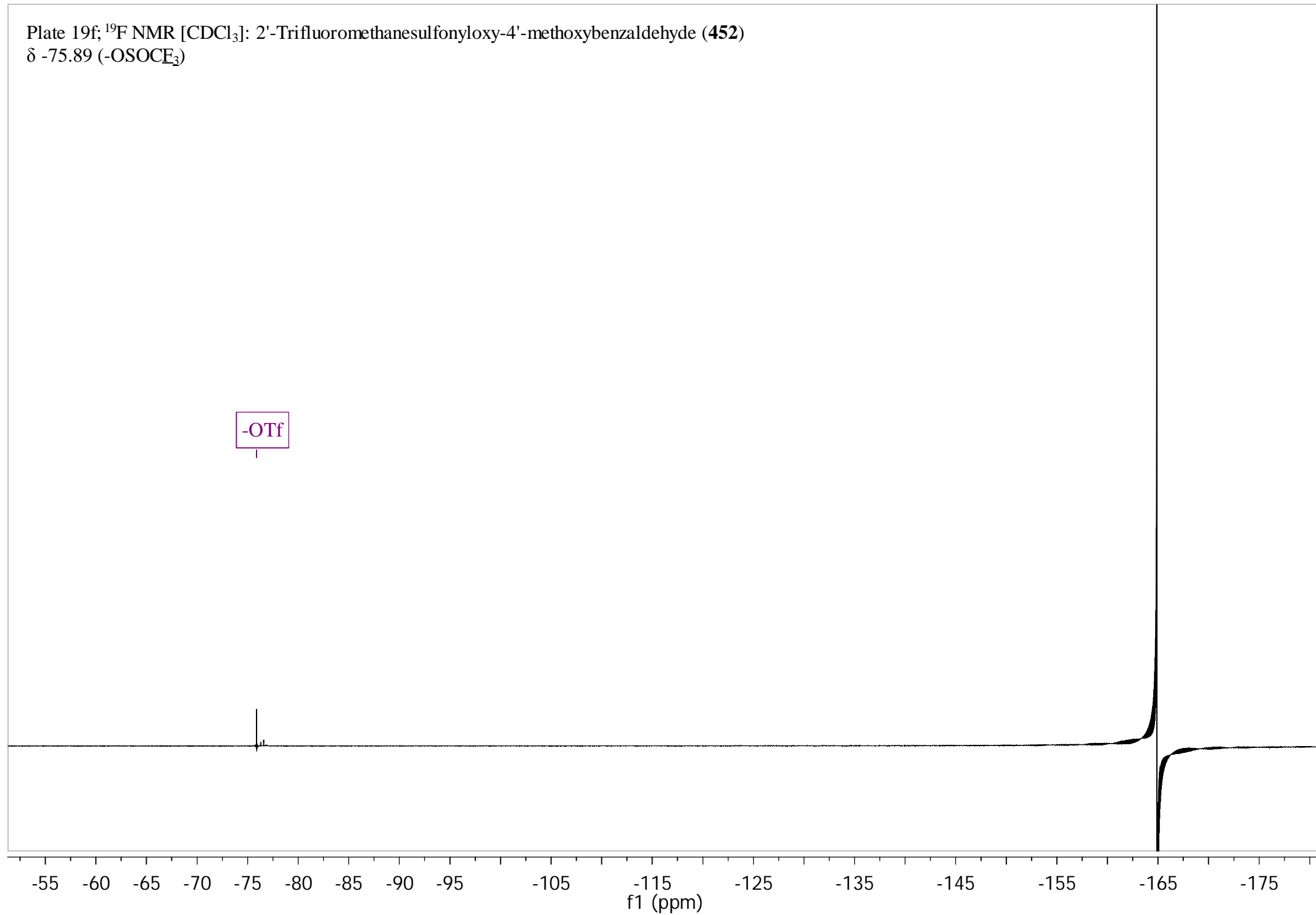
Plate 20a; ^{1}H NMR [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**)
δ 10.07 (1H, s, -C<u>H</u>O), 7.79 (1H, d, *J* = 1.8 Hz, H-2'), 7.71 (1H, dd, *J* = 8.3, 1.8 Hz, H-6'), 7.67
(1H, d, *J* = 8.3 Hz, H-5'), 4.09 (3H, s, -O<u>Me</u>).
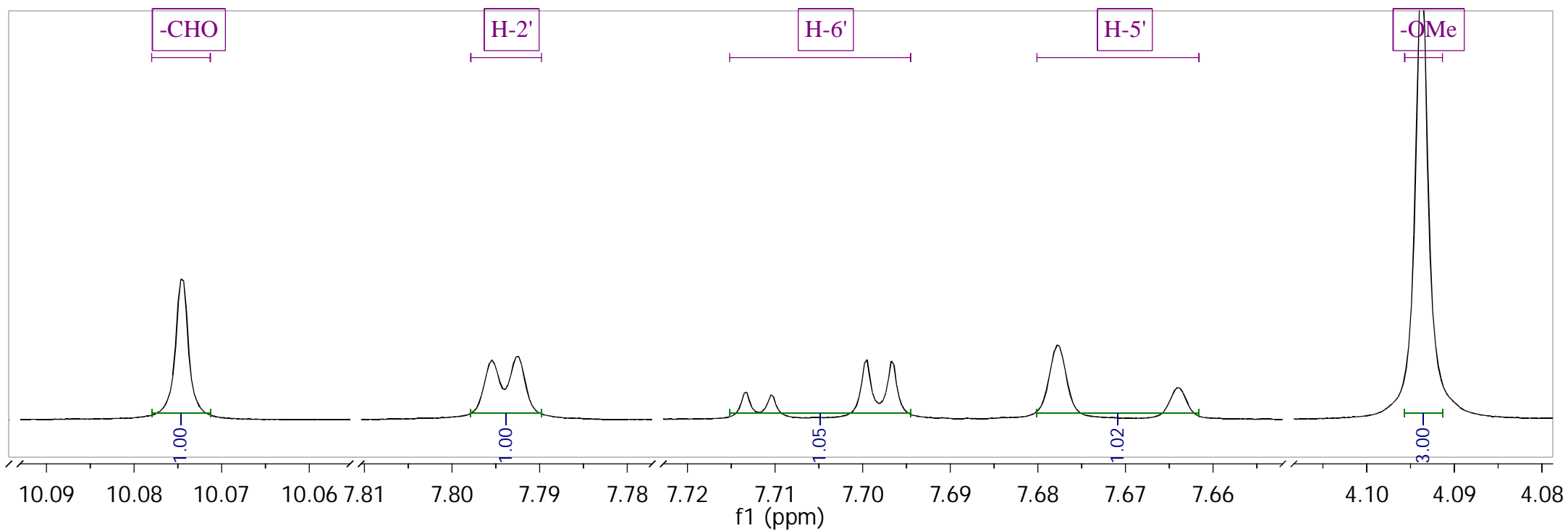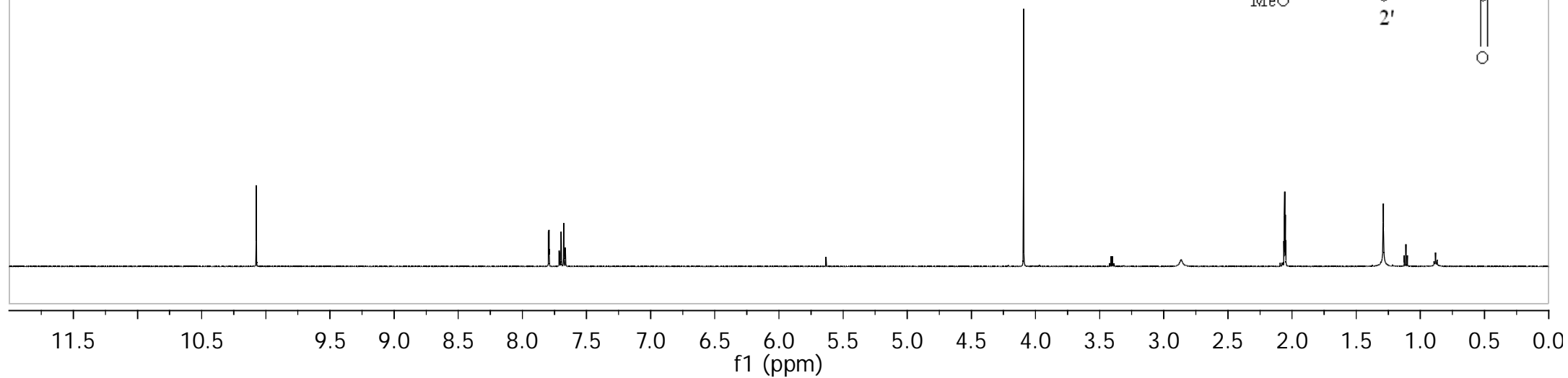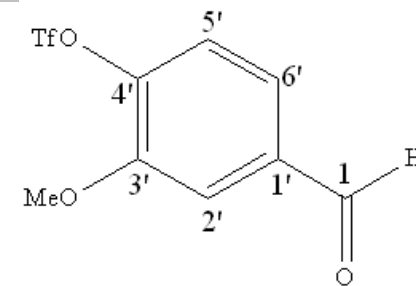
Plate 20b; ^{13}C NMR [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**)
δ 192.03 (-CHO), 153.37 (C-3'), 143.59 (C-4'), 138.83 (C-1'), 124.64 (C-5'/6'), 124.53 (C-5'/6'), 119.00 (q, J = 319.10 Hz, -OSOCF$_3$), 114.16 (C-2'), 57.58 (-OMe).
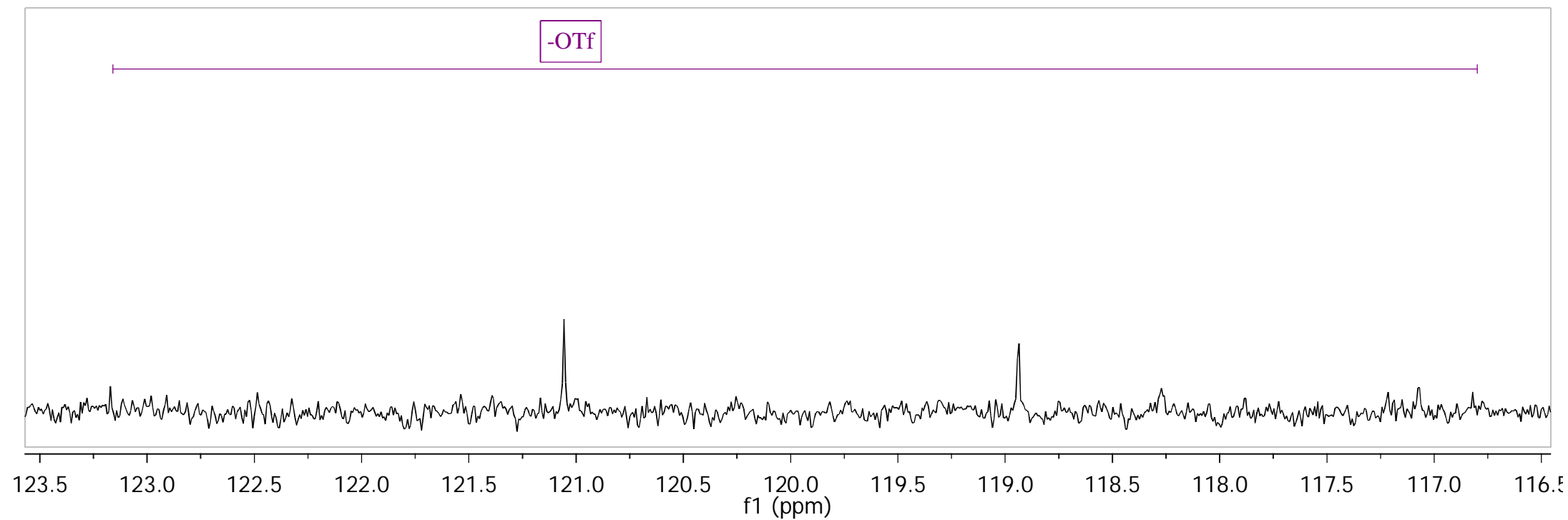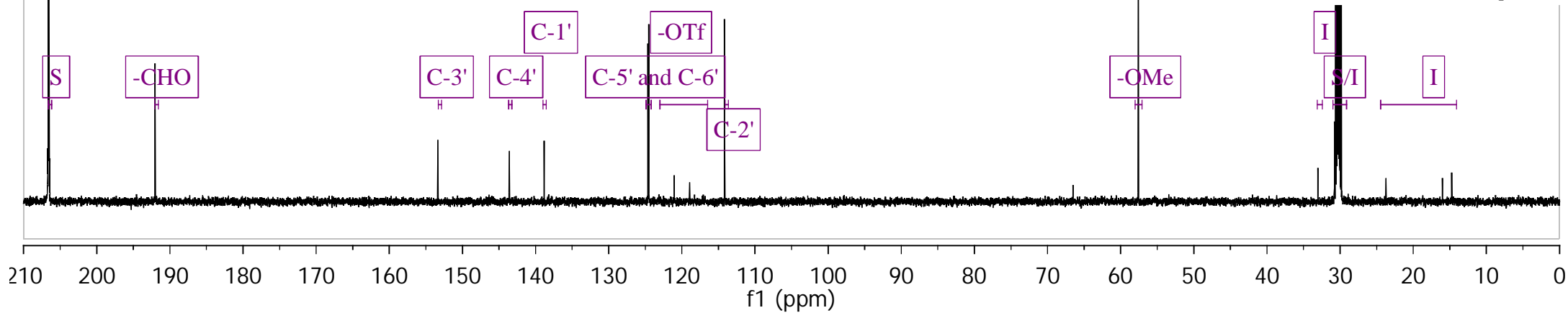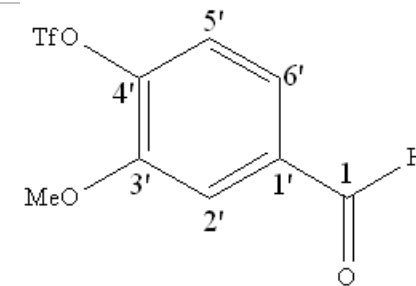
Plate 20c; DEPT [CO(CD₃)₂]: 4'-Trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**)
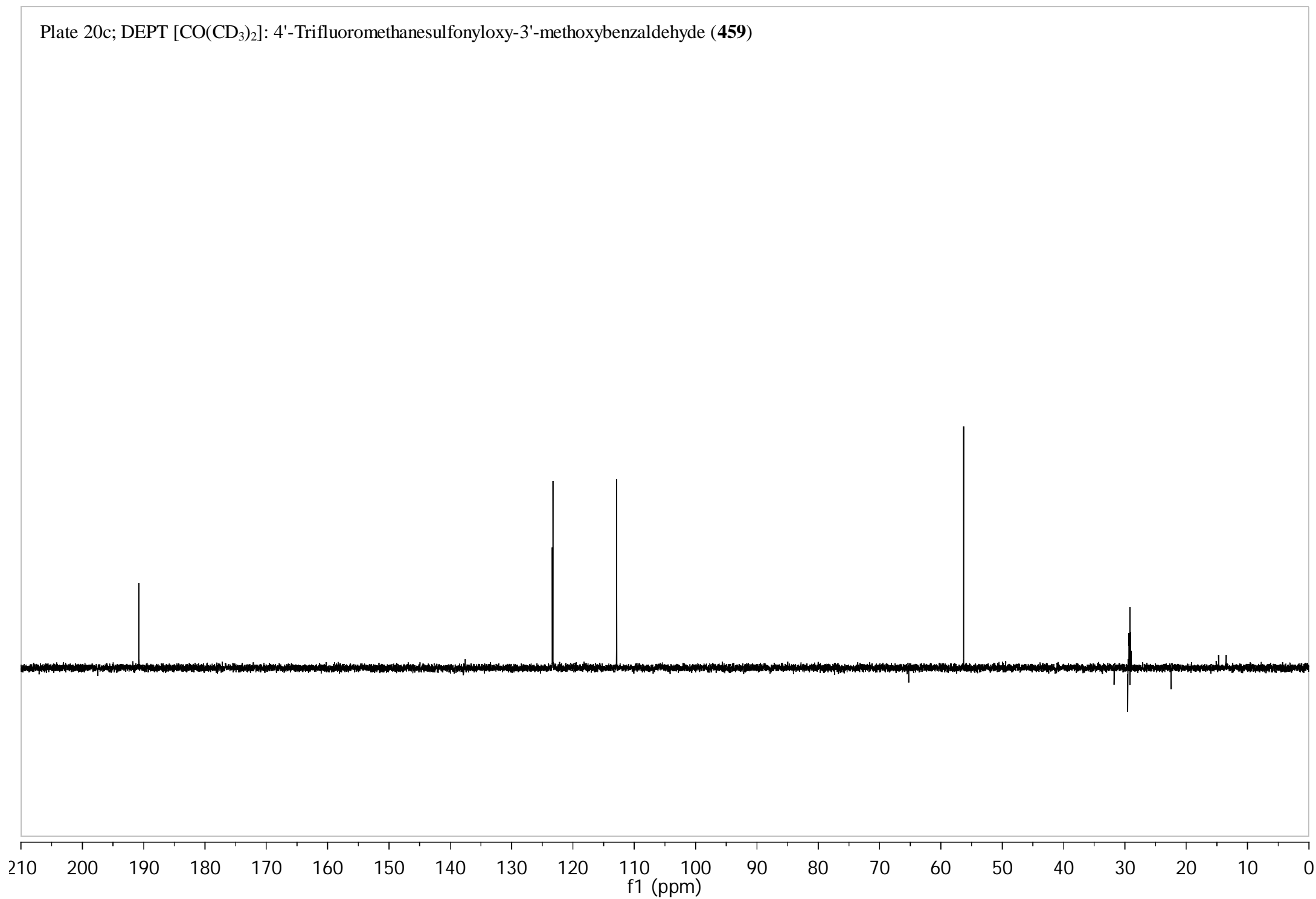
Plate 20d; HSQC [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**)
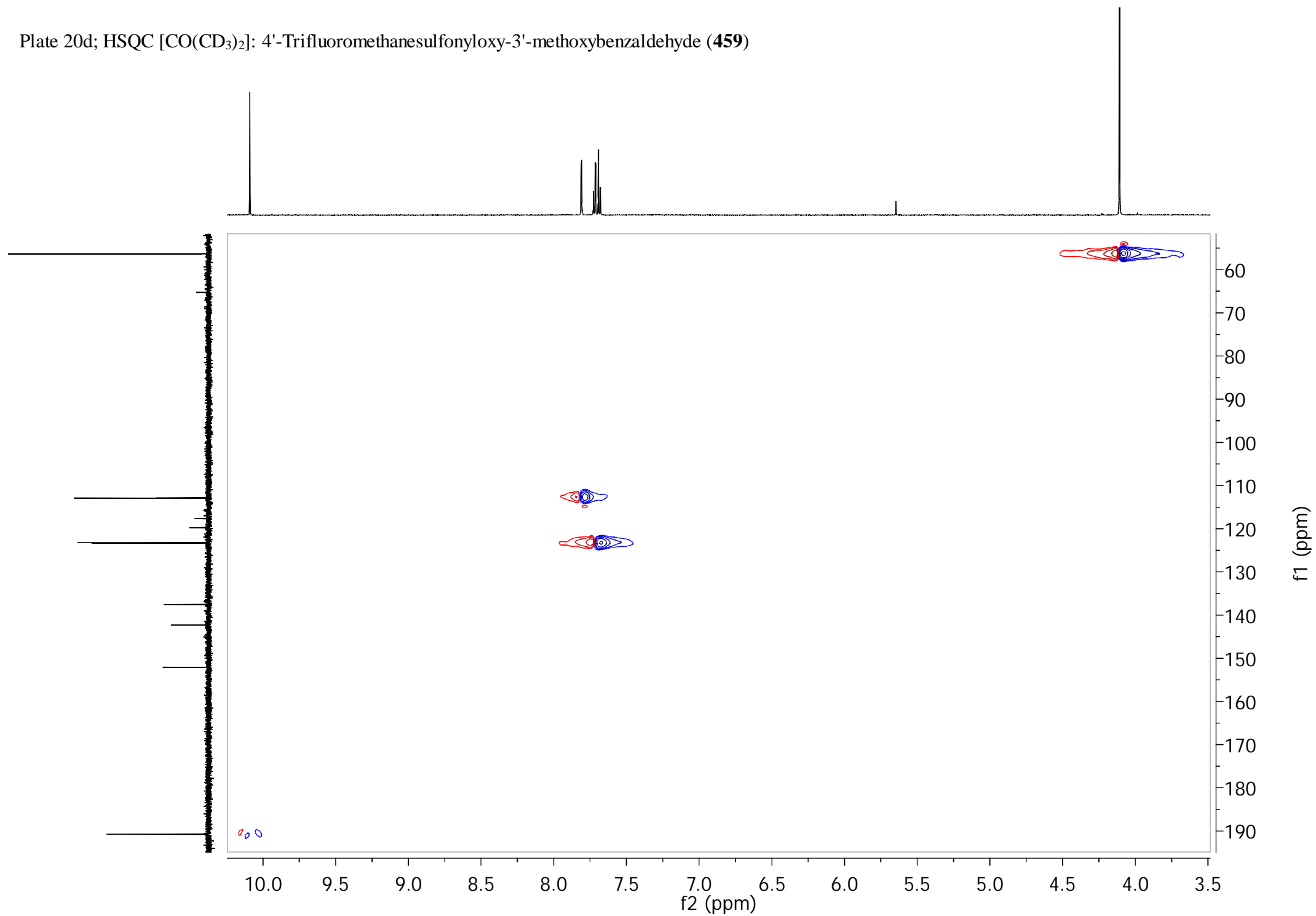
Plate 20e; HMBC [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**)
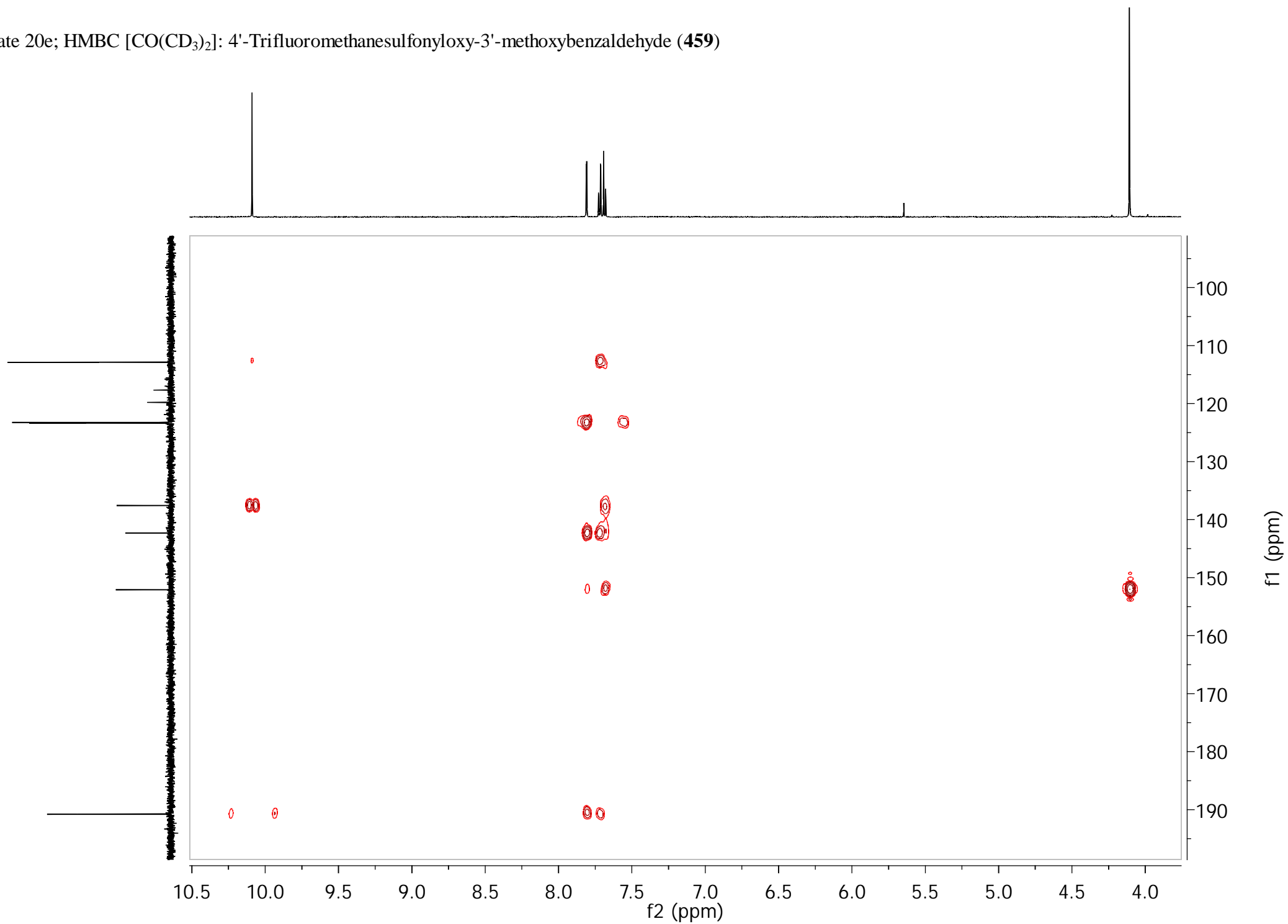
Plate 20f; ^{19}F [CDCl$_3$]: 4'-Trifluoromethanesulfonyloxy-3'-methoxybenzaldehyde (**459**)
δ -77.28 (-OSOC$\underline{F}_3$)

-OTf

f1 (ppm)
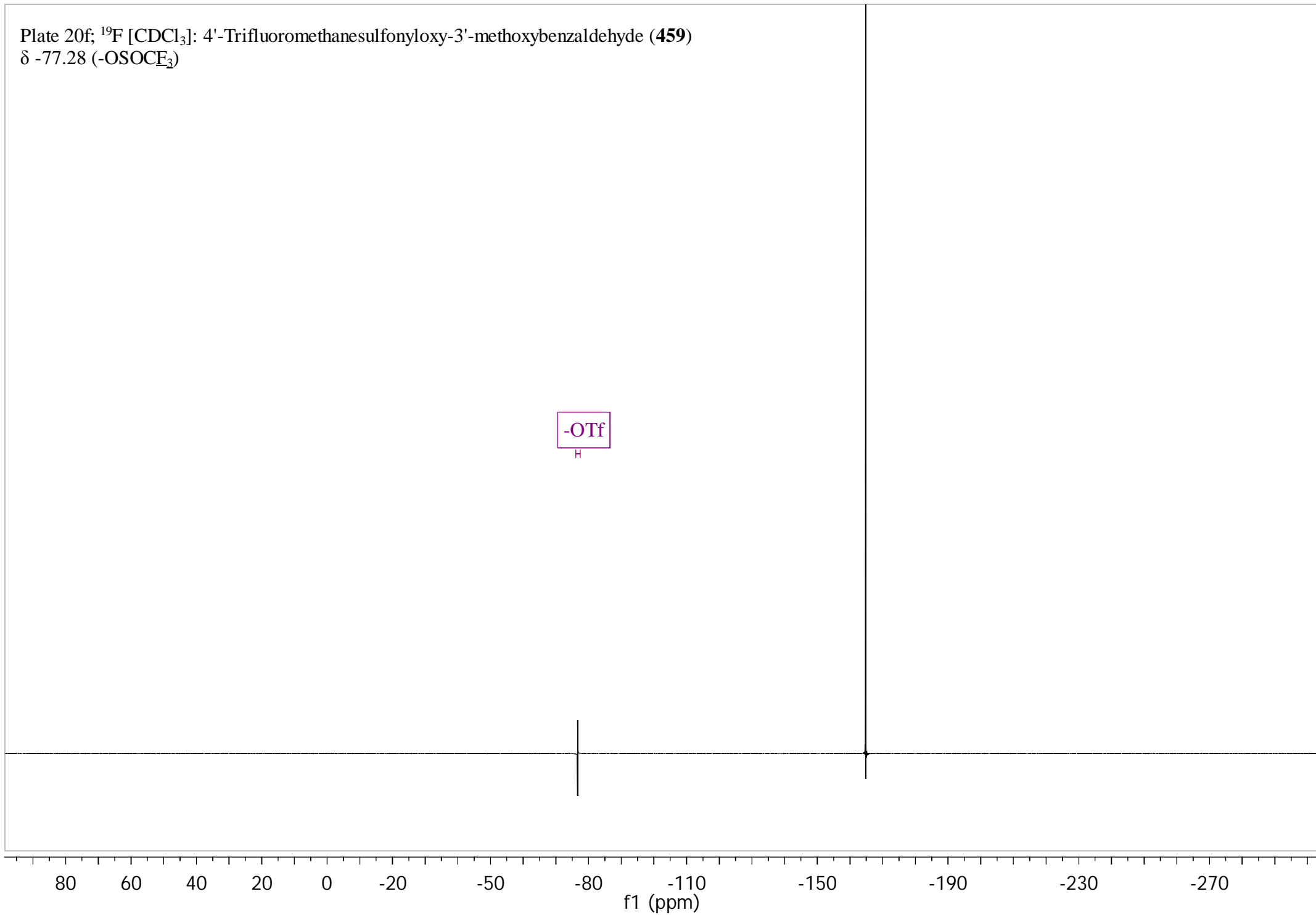
Plate 21a; ^{1}H NMR [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzaldehyde (**461**)
δ 10.03 (1H, s, -C<u>H</u>O), 7.44 (1H, s, H-2' and H-6'), 4.07 (3H, s, -O<u>Me</u>).

-CHO

H-2' and H-6'

-OMe
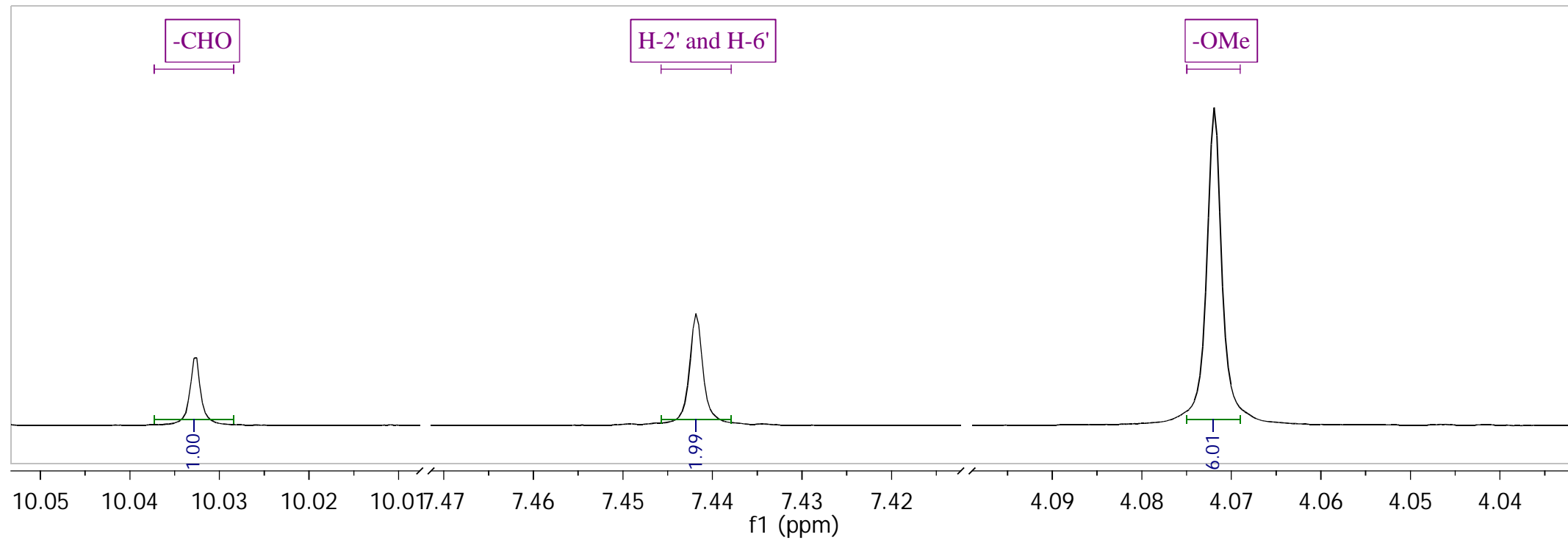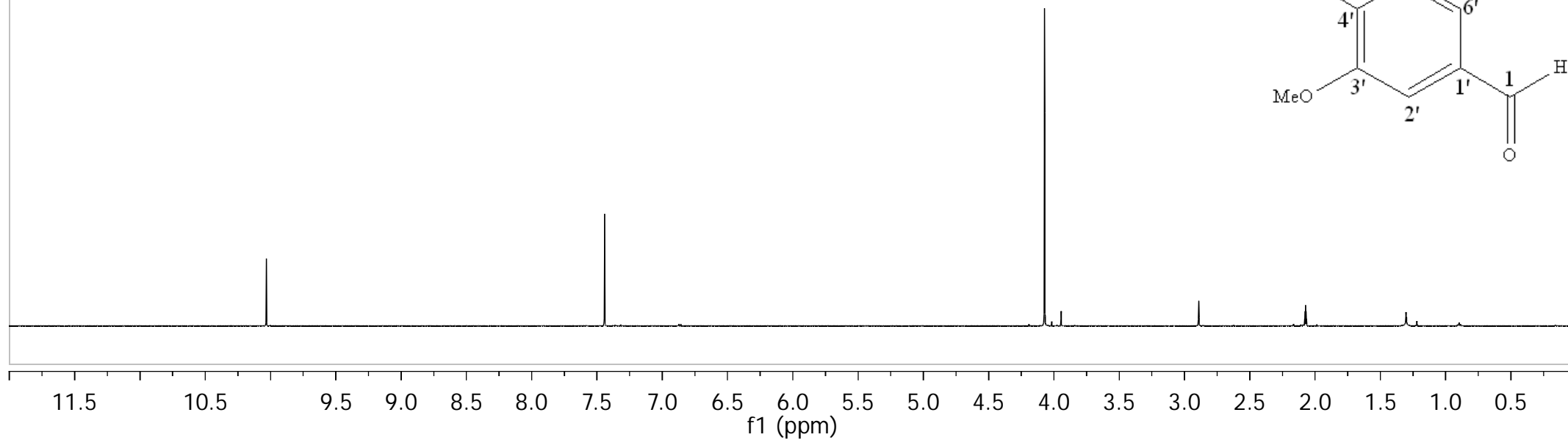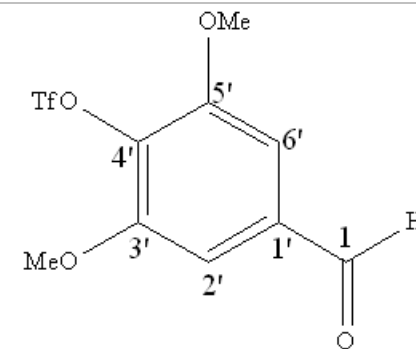
Plate 21b; ^{13}C NMR [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzaldehyde (**461**)
δ 191.72 (-$\underline{C}$HO), 153.96 (C-3' and C-5'), 137.64 (C-1'), 132.29 (C-4'), 114.58 (q, J = 319.61 Hz, -OSO$\underline{C}$F$_3$), 106.91 (C-2' and C-6'), 57.35 (-O$\underline{Me}$).
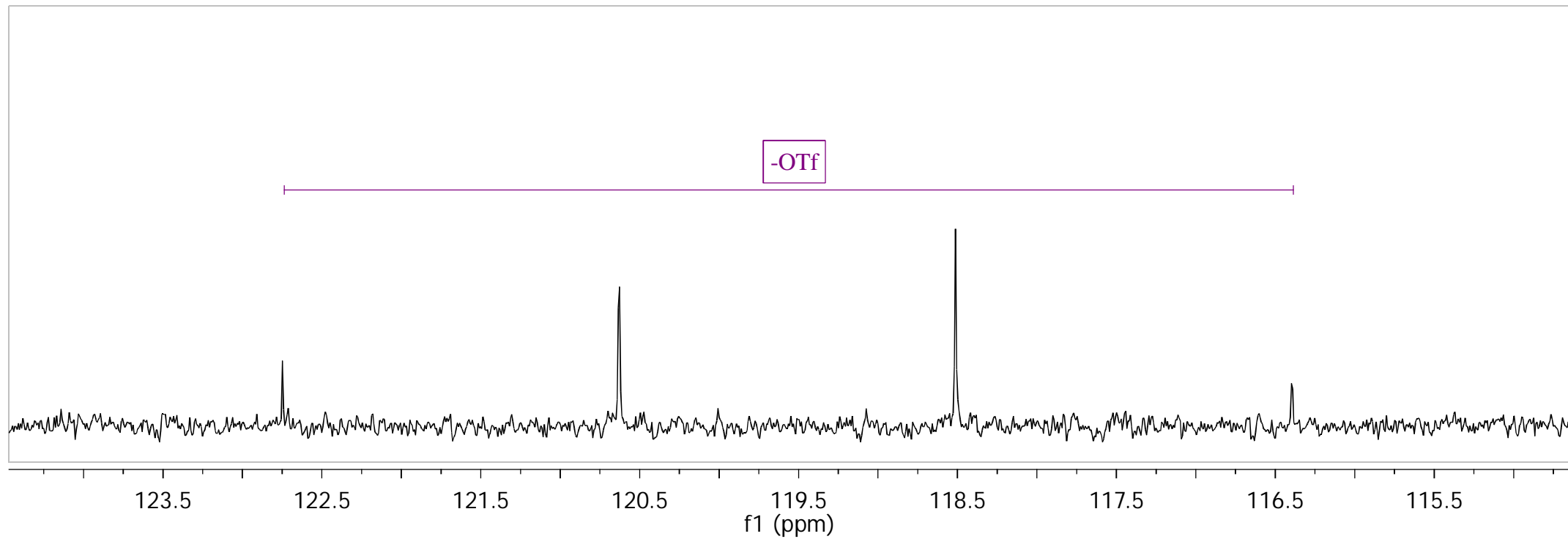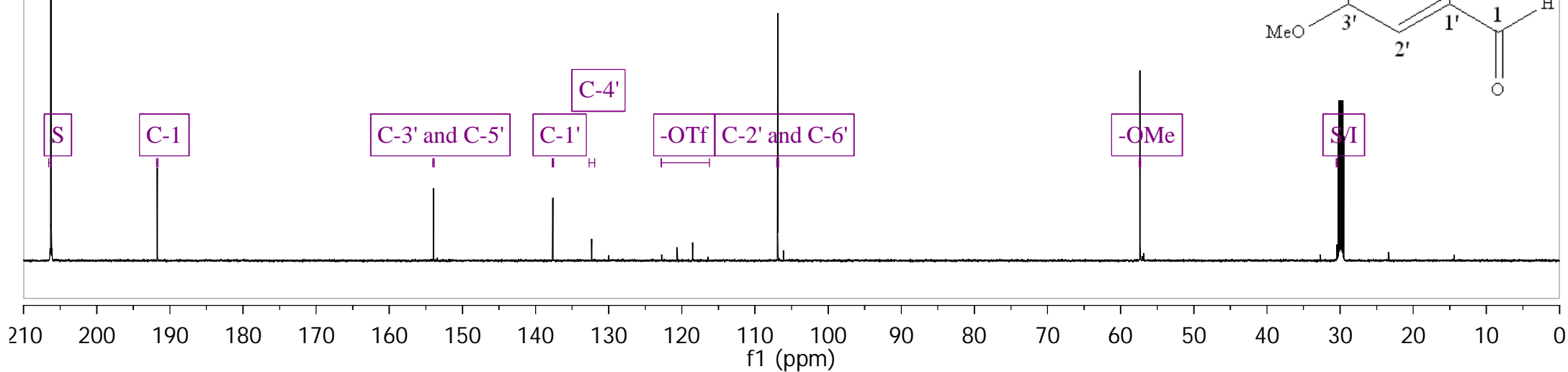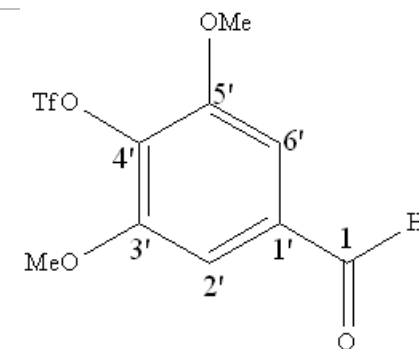
Plate 21c; DEPT [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzaldehyde (**461**)
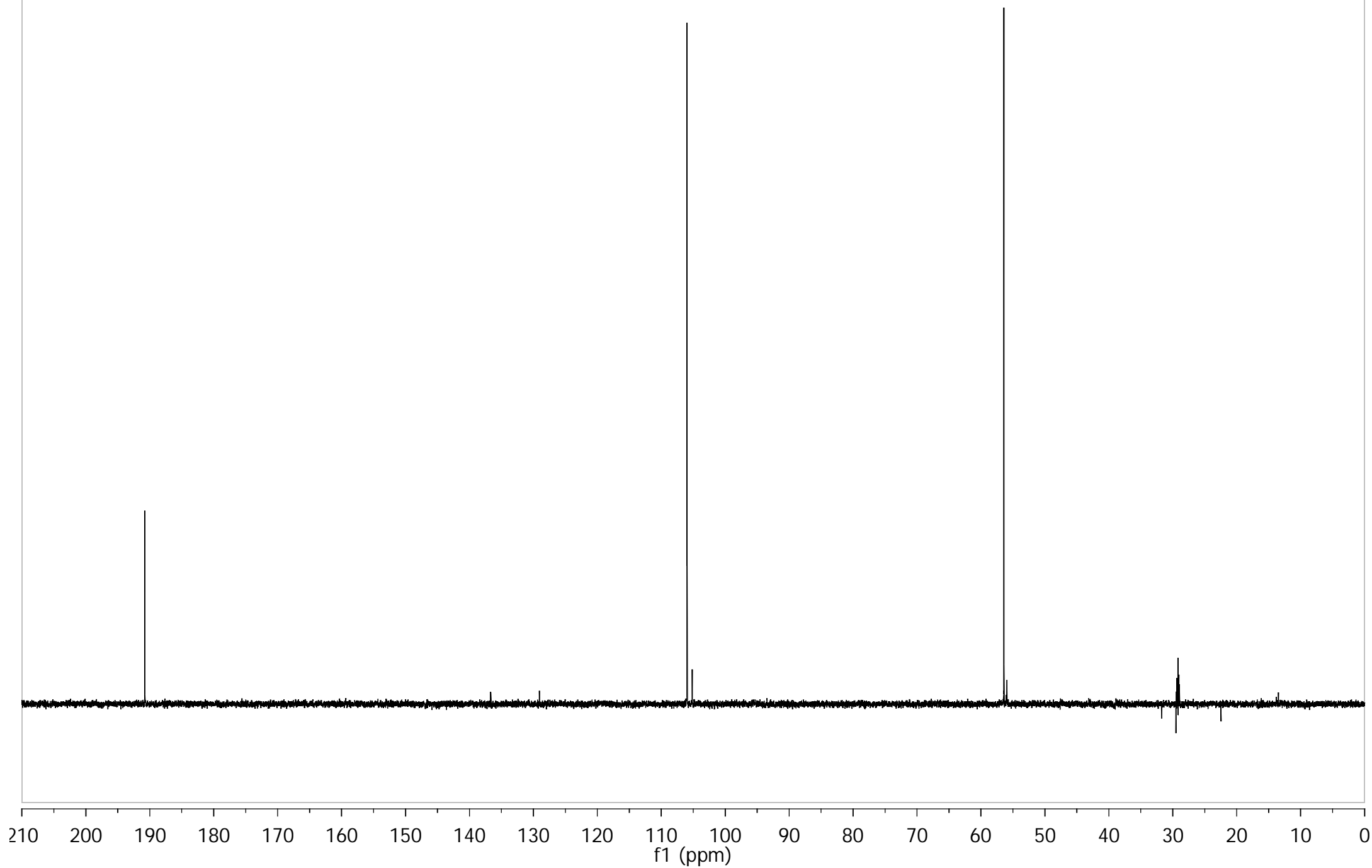
Plate 21d; HSQC [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzaldehyde (**461**)
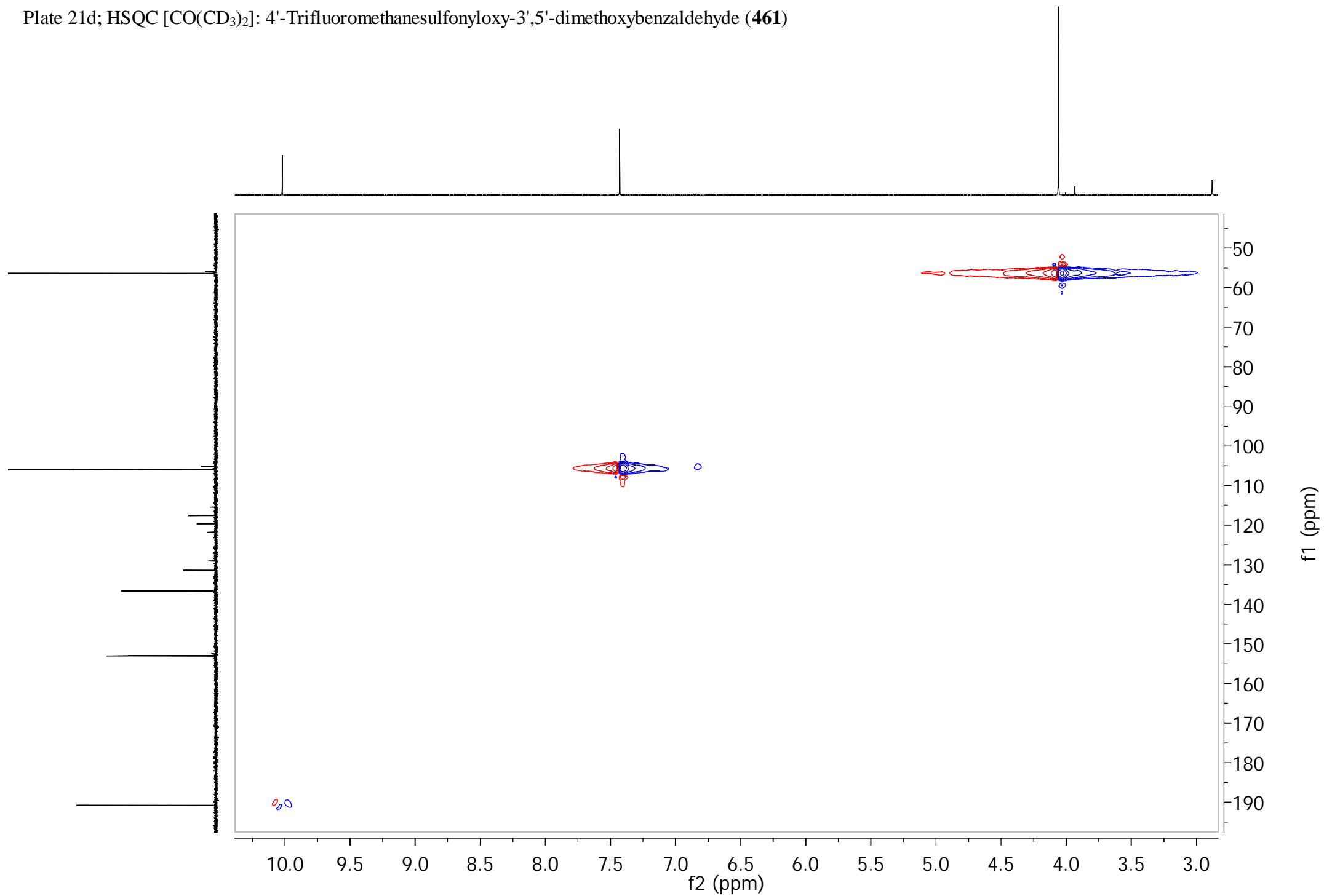
Plate 21e; HMBC [CO(CD₃)₂]: 4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzaldehyde (**461**)
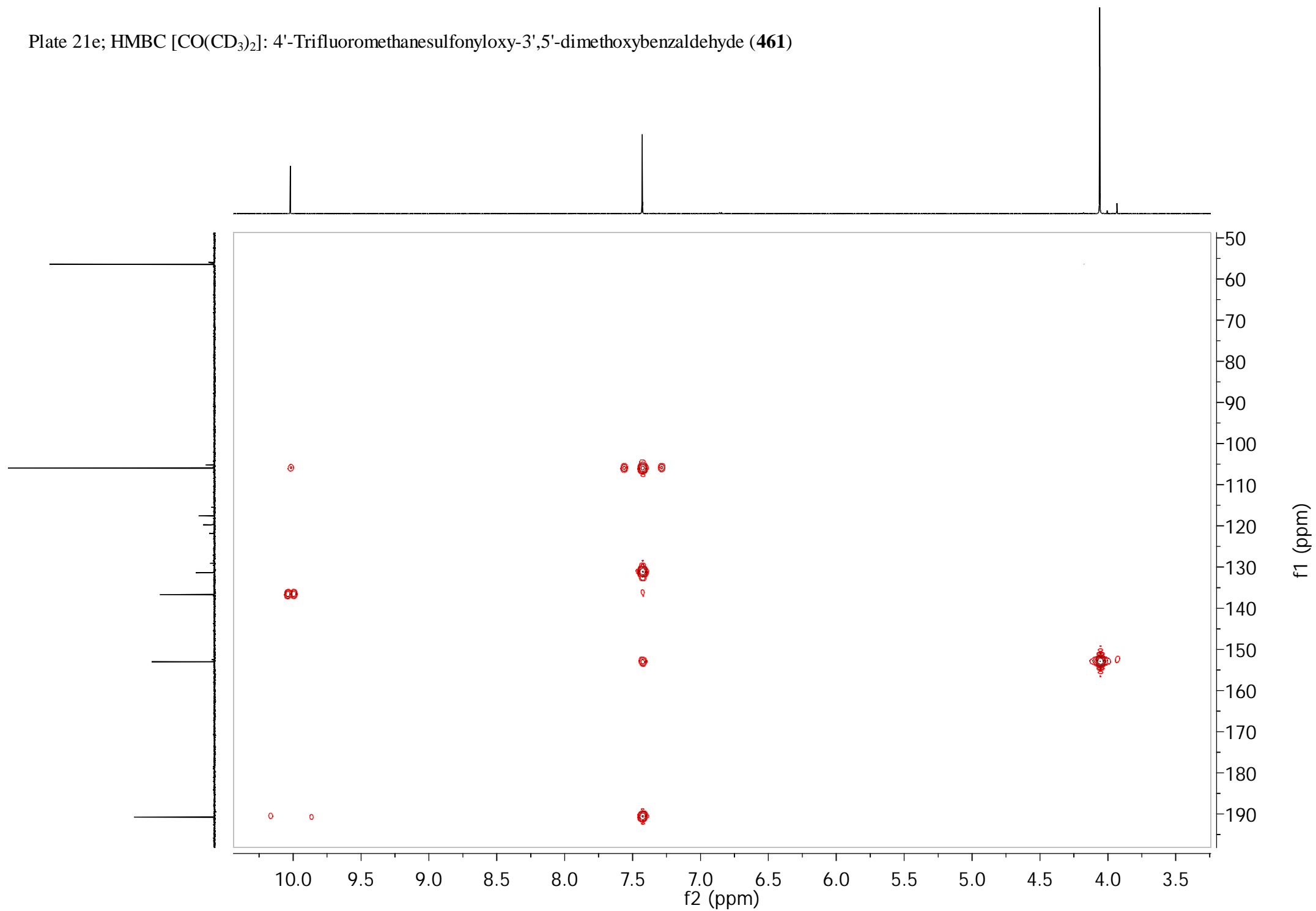
Plate 21f; ^{19}F NMR [CO(CD$_3$)$_2$]: 4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzaldehyde
(**461**)
δ -74.87 (-OSOCF$_3$).

-OTf
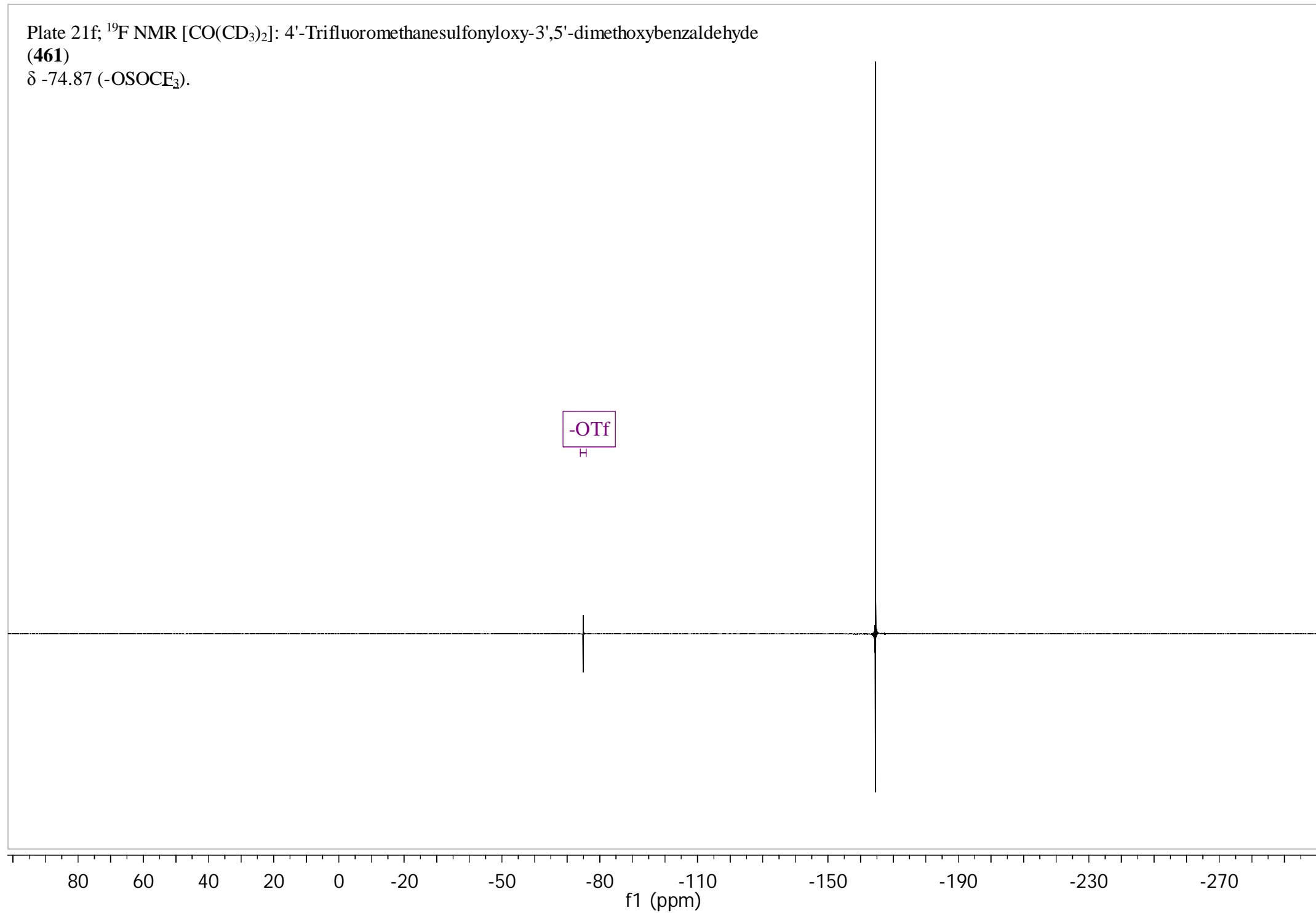
Plate 22a; ^{1}H NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
δ 9.61 (1H, t, J = 1.4 Hz, -C$\underline{H}$O), 6.49 (1H, d, J = 2.3 Hz, H-3'/5'), 6.48 (1H, d, J = 2.3 Hz, H-3'/5'),
3.82 (3H, s, -O$\underline{Me}$), 3.81 (3H, s, -O$\underline{Me}$), 3.67 (2H, d, J = 1.4 Hz, H-2).
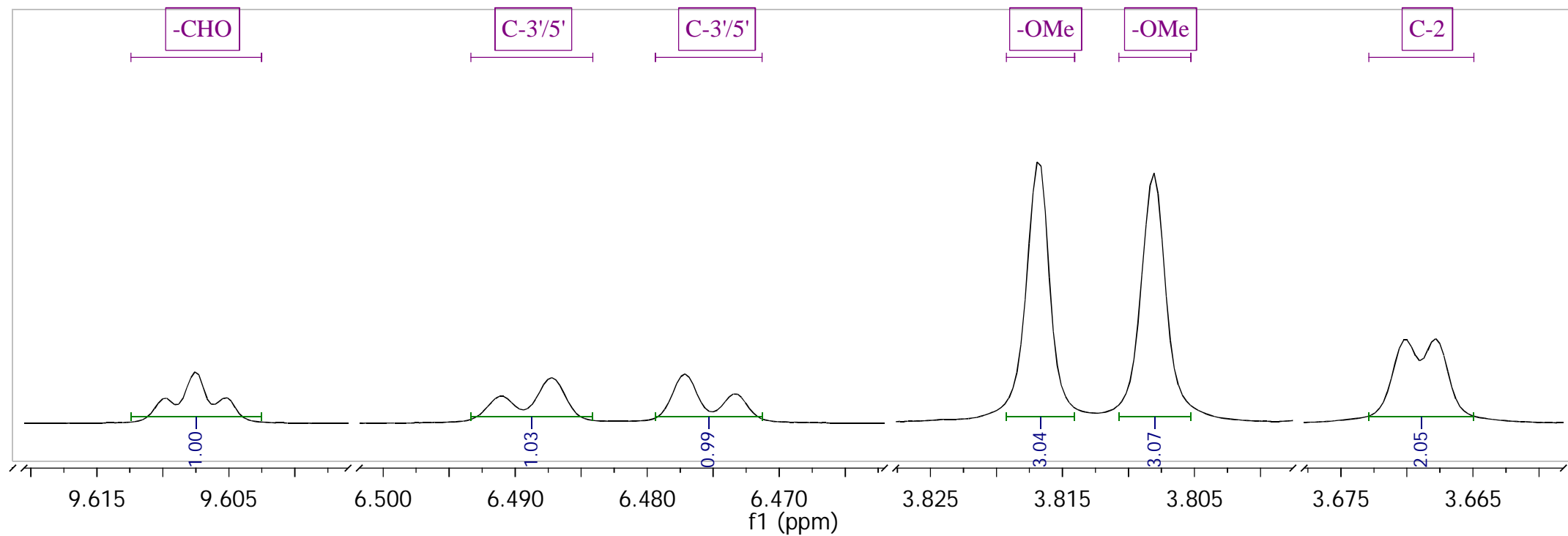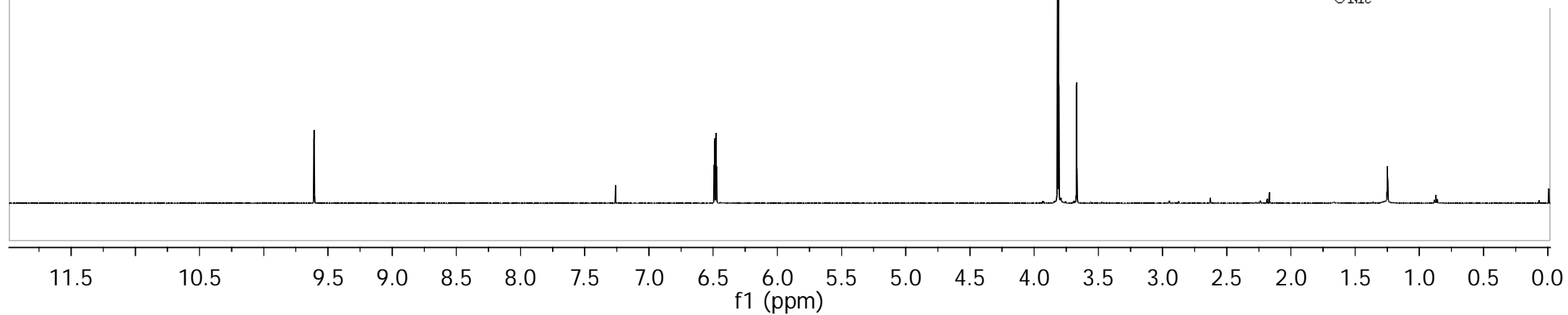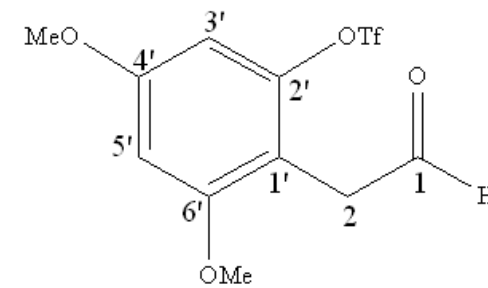
Plate 22b; ^{13}C NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
δ 198.13 (-$\underline{C}$HO), 160.70 (C-4'/6'), 159.61 (C-4'/6'), 148.89 (C-2'), 118.61 (q, J = 320.19 Hz, -OSO$\underline{C}$F$_3$), 107.67 (C-1'), 98.64 (C-3'/5'), 98.43 (C-3'/5'), 56.20 (-O$\underline{Me}$), 55.86 (-O$\underline{Me}$), 38.71 (C-2).
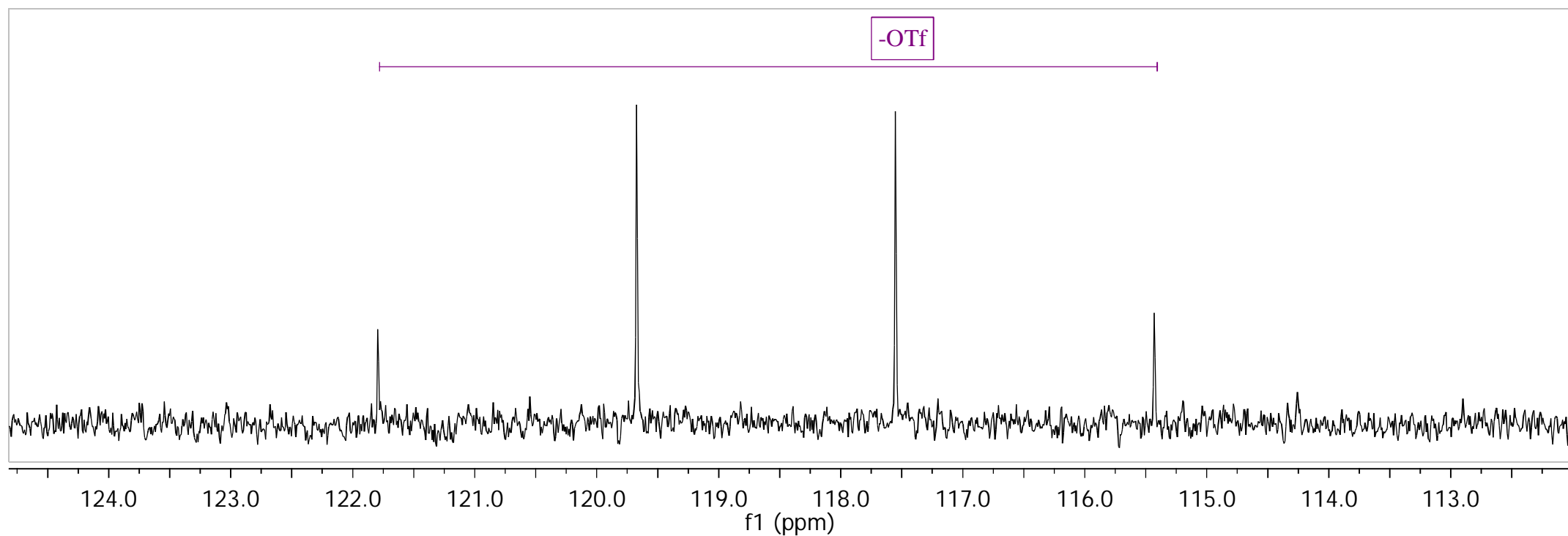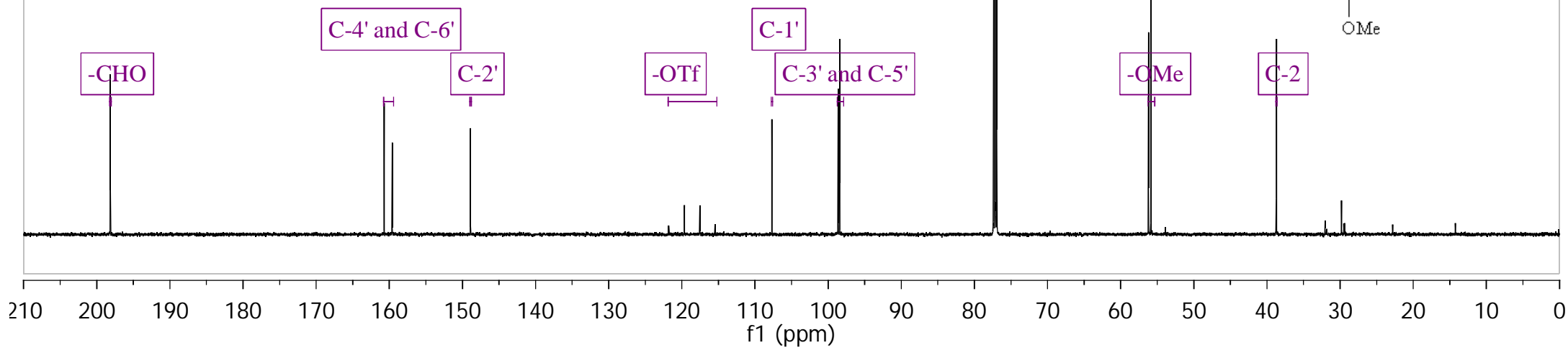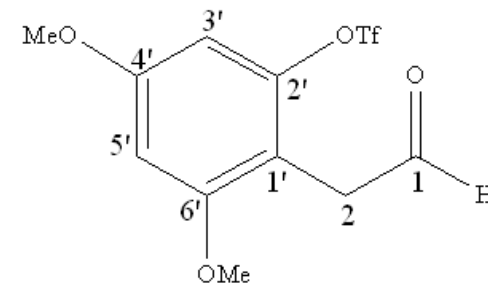
Plate 22c; DEPT [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
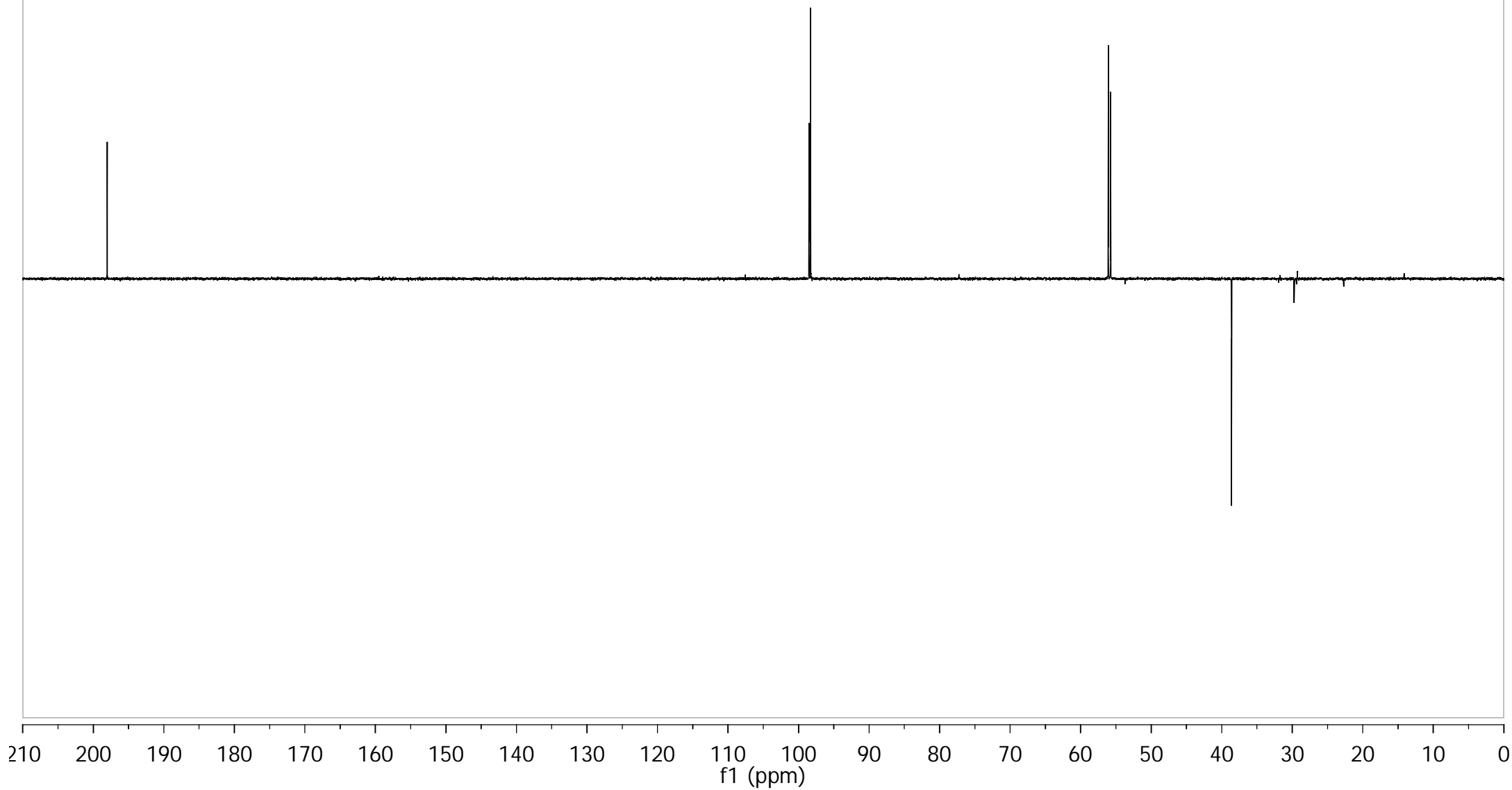
Plate 22d; HSQC [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
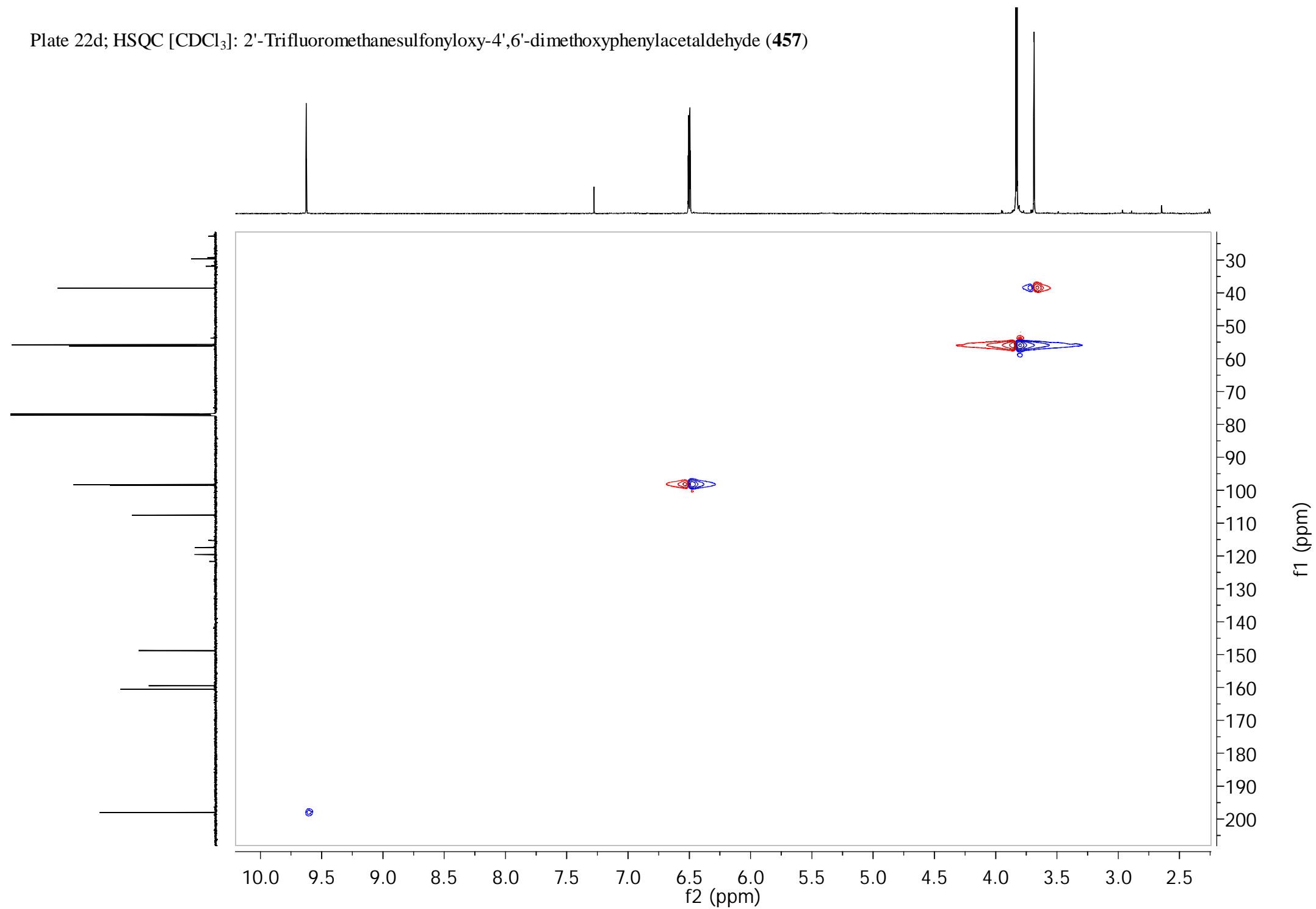
Plate 22e; HMBC [CDCl₃]: 2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
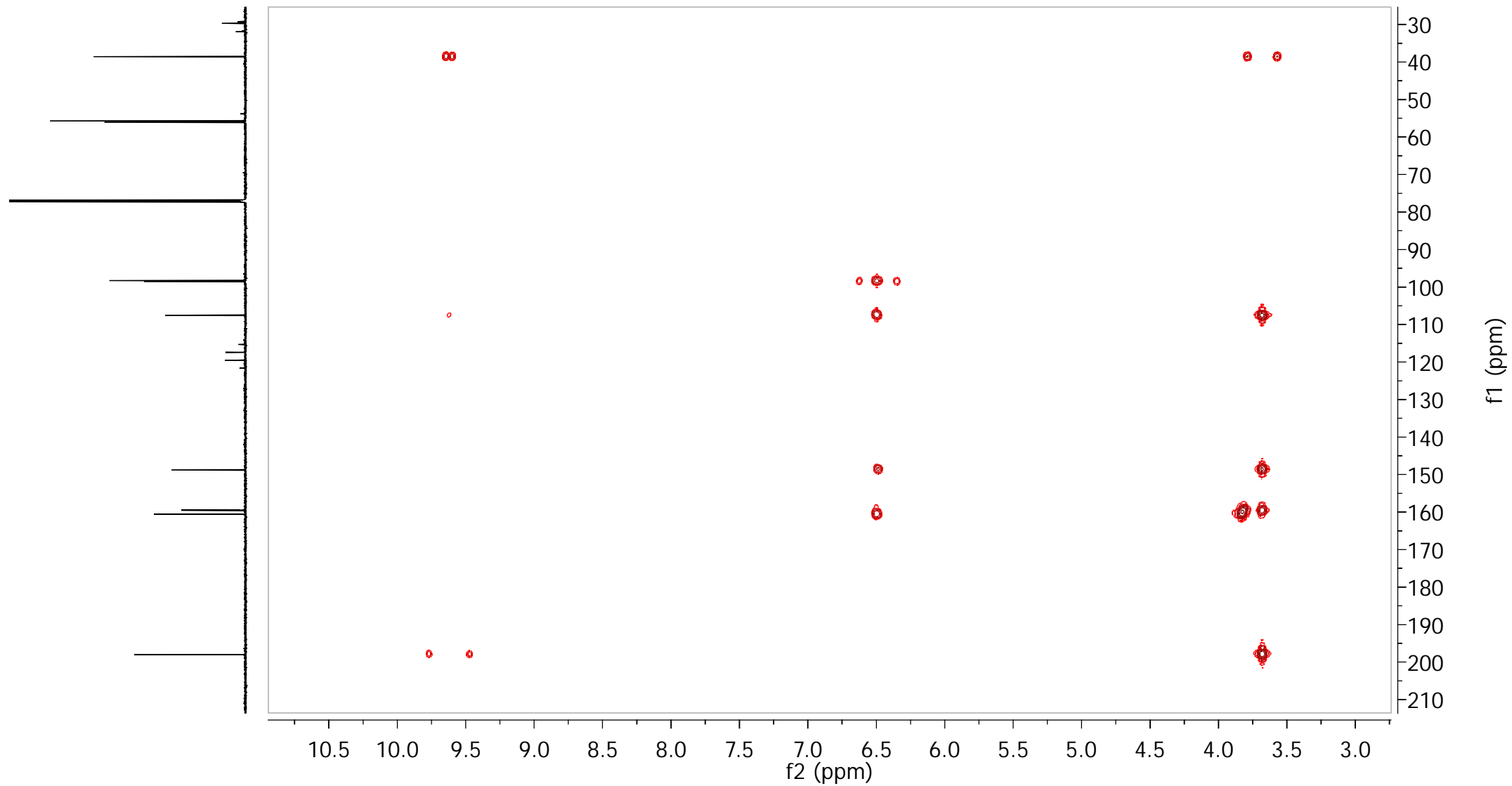
Plate 22f; ^{19}F NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde
(**457**)
δ -76.76 (-OSOC<u>F</u>$_3$).

-OTf

f1 (ppm)
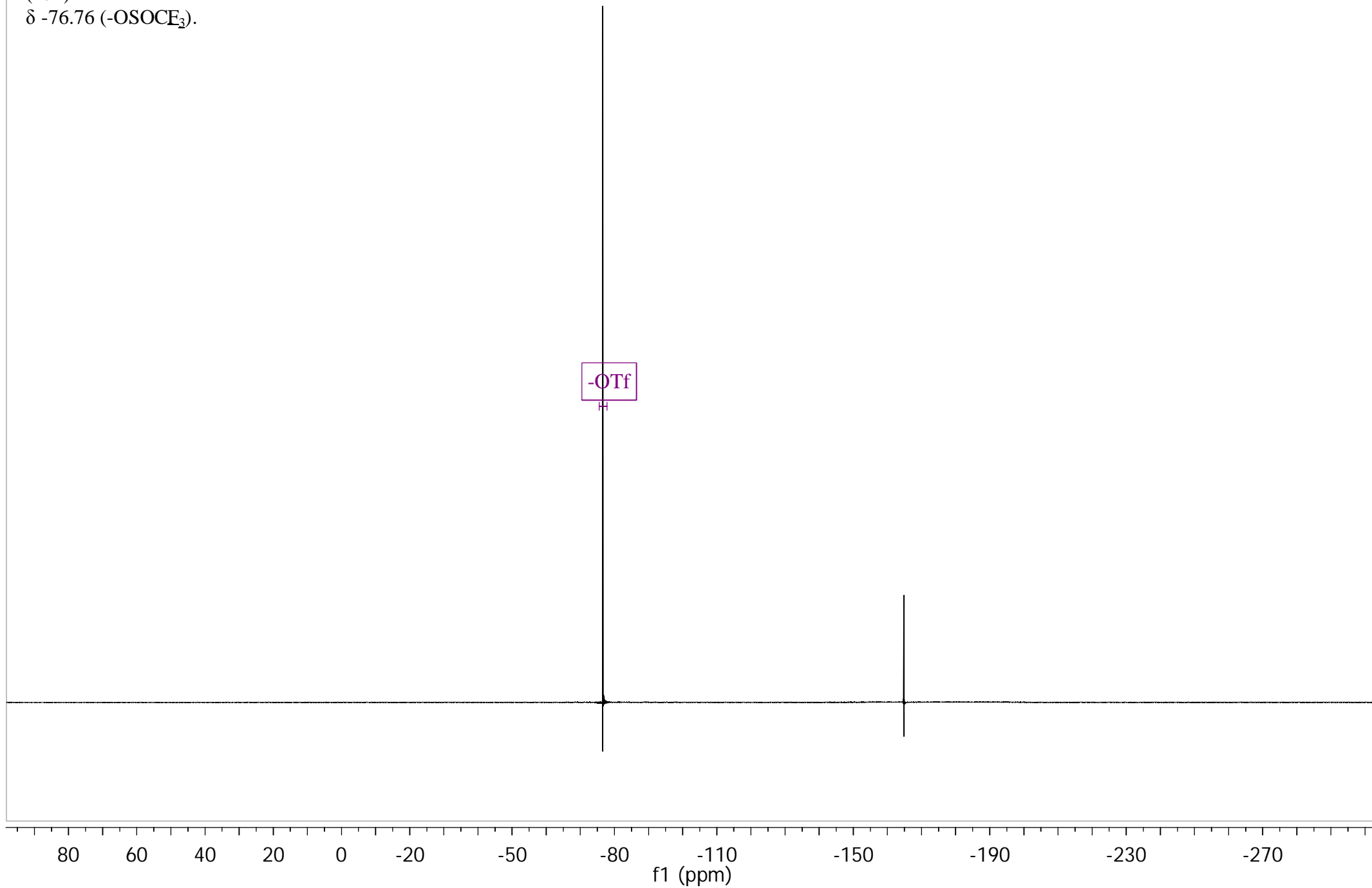
Plate 23a; ^{1}H NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde **(453)**
δ 9.73 (1H, t, J = 1.5 Hz, -CHO), 7.21 (1H, d, J = 8.55 Hz, H-6'), 6.93 (1H, dd, J = 8.55, 2.54 Hz, H-5'), 6.88 (1H, d, J = 2.54 Hz, H-3'), 3.83 (3H, s, -OMe), 3.76 (2H, m, H-2).

-CHO   H-6'   H-5'   H-3'   -OMe   H-2

1.00   1.06   1.14   1.07   3.03   2.04
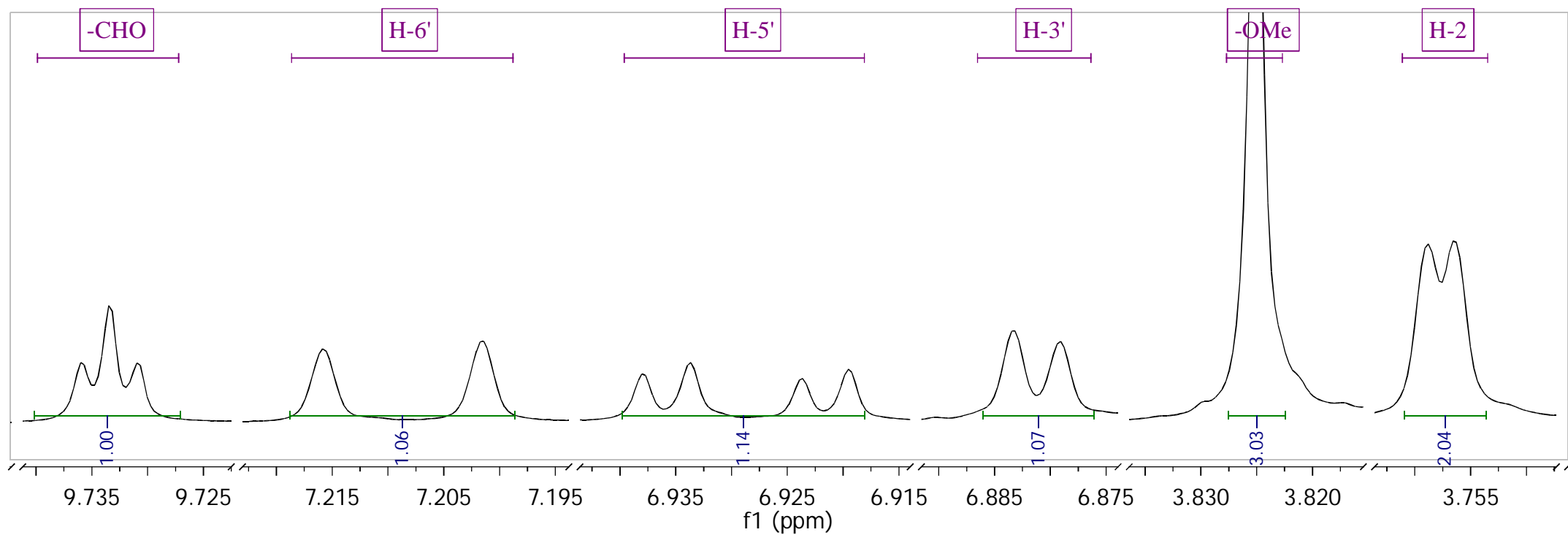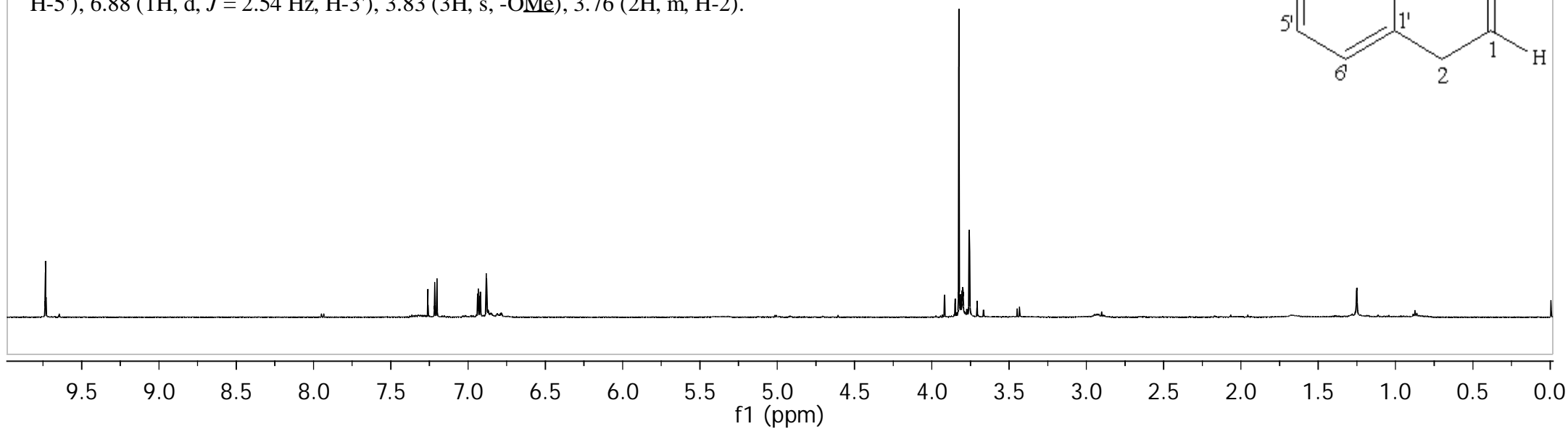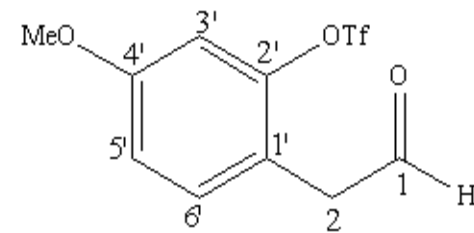
Plate 23b; ^{13}C NMR [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**) δ 197.30 (-CHO), 160.23 (C-2'/4'), 148.46 (C-2'/4'), 132.76 (C-6'), 118.42 (q, J = 316.42 Hz, -OSO$_2$CF$_3$), 117.05 (C-1'), 114.46 (C-5'), 107.86 (C-3'), 55.76 (-OMe), 43.99 (C-2).
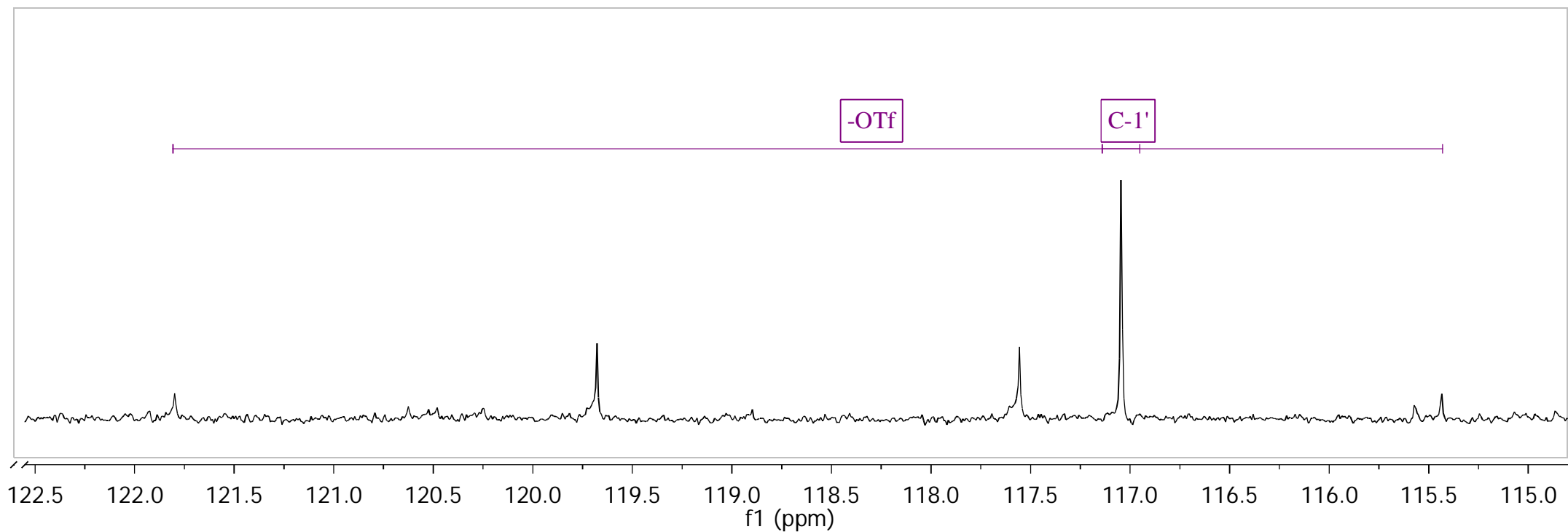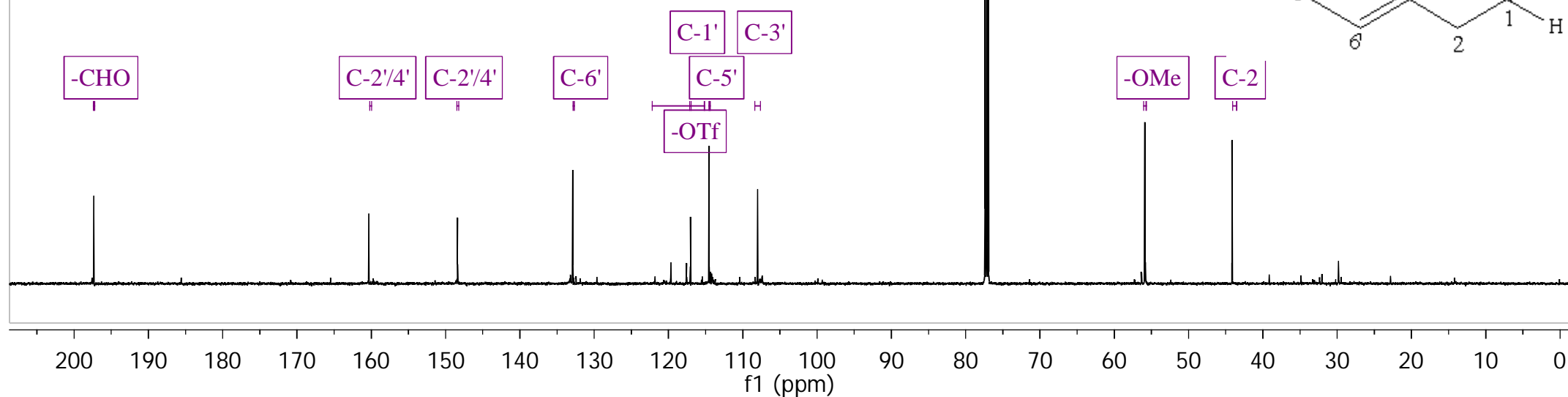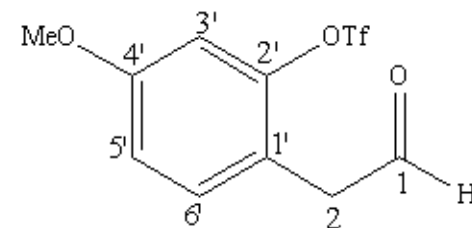
Plate 23c; DEPT [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**)
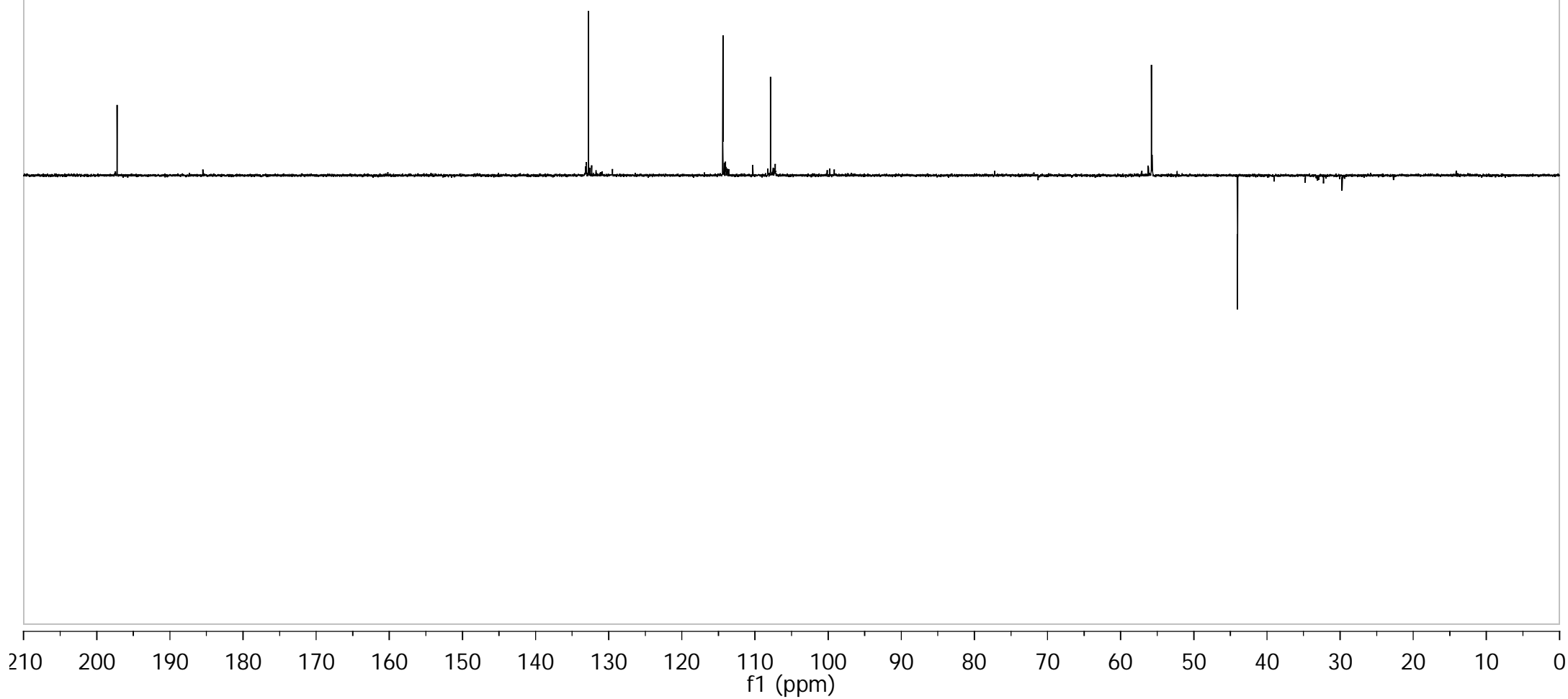
Plate 23d; HSQC [CDCl₃]: 2'-Trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**)
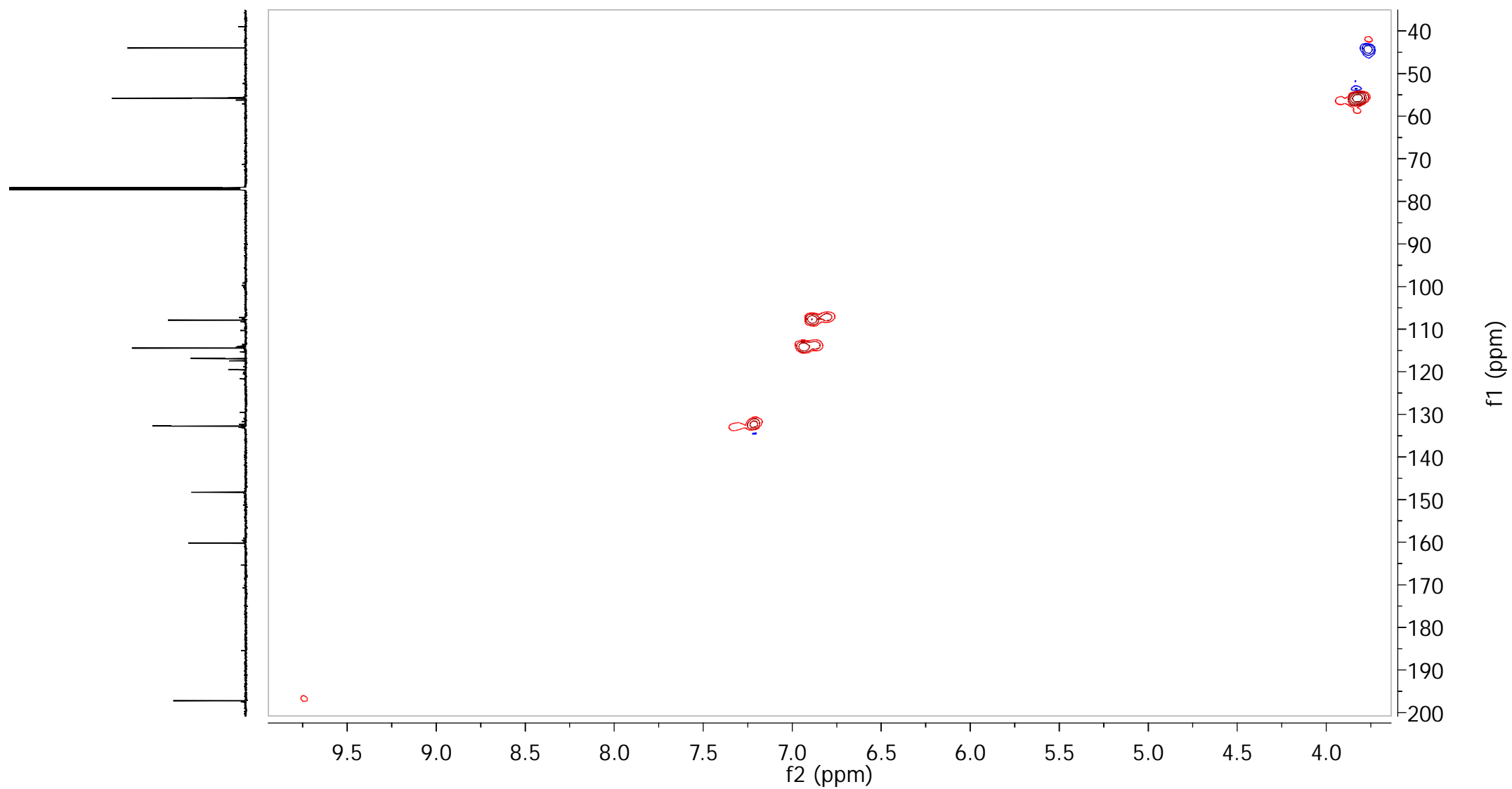
Plate 23e; HMBC [CDCl$_3$]: 2'-Trifluoromethanesulfonyloxy-4'-methoxyphenylacetaldehyde (**453**)
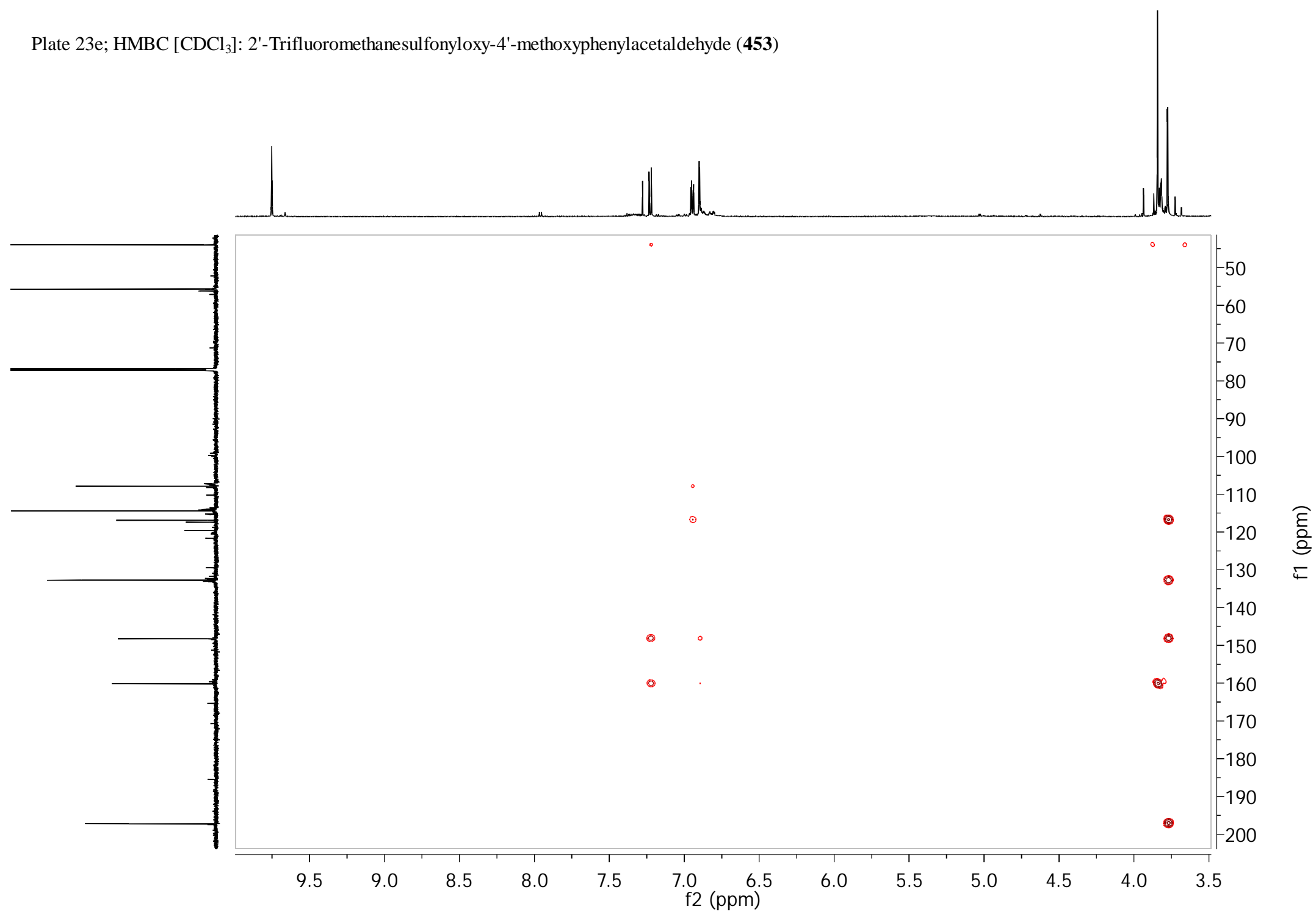
Plate 24a; ¹H NMR [CDCl₃]: 3-(4'-Trifluoromethanesulfonyloxy-3'-methoxybenzyl)-1,2,4-trioxolane (**462**)
δ 7.16 (1H, d, J = 8.4 Hz, H-5'), 6.94 (1H, d, J = 1.9 Hz, H-2'), 6.87 (1H, dd, J = 8.4, 1.9 Hz, H-6'), 5.36 (1H, t, J = 4.9 Hz, H-3), 5.16 (1H, s, H-5), 5.07 (1H, s, H-5), 3.91 (3H, s, -OMe), 3.06 (1H, dd, J = 14.76, 4.83 Hz, -CH₂-), 3.03 (1H, dd, J = 14.76, 4.83 Hz, -CH₂-)
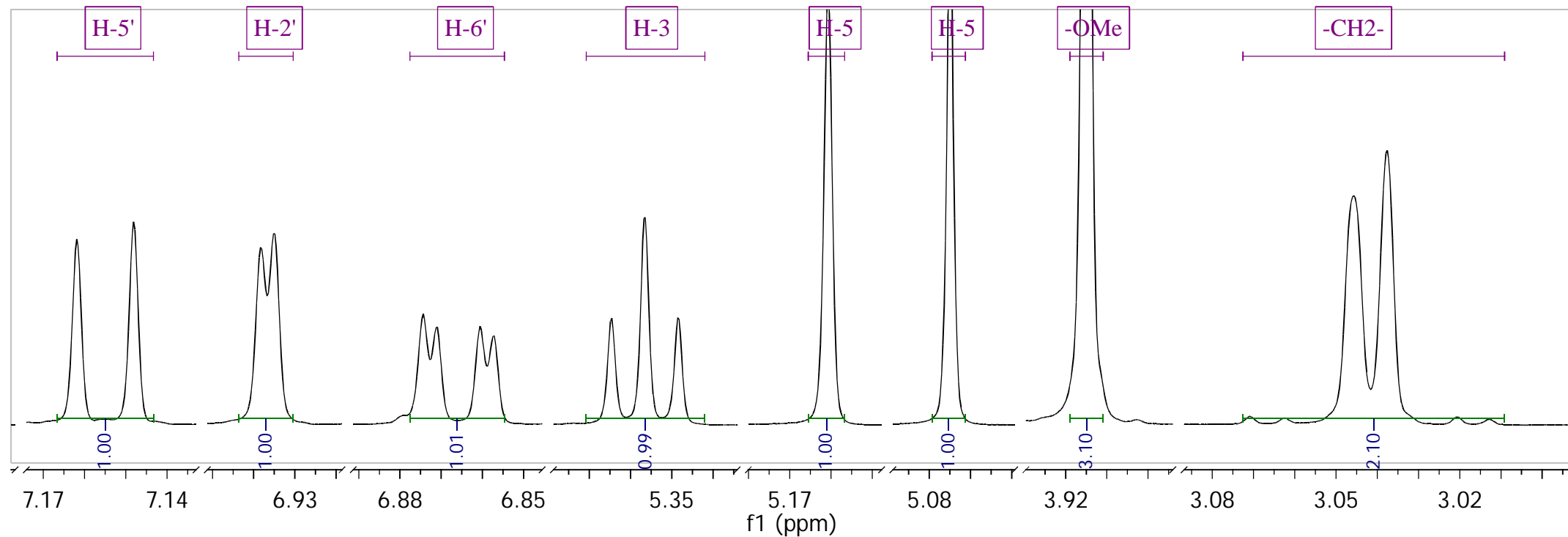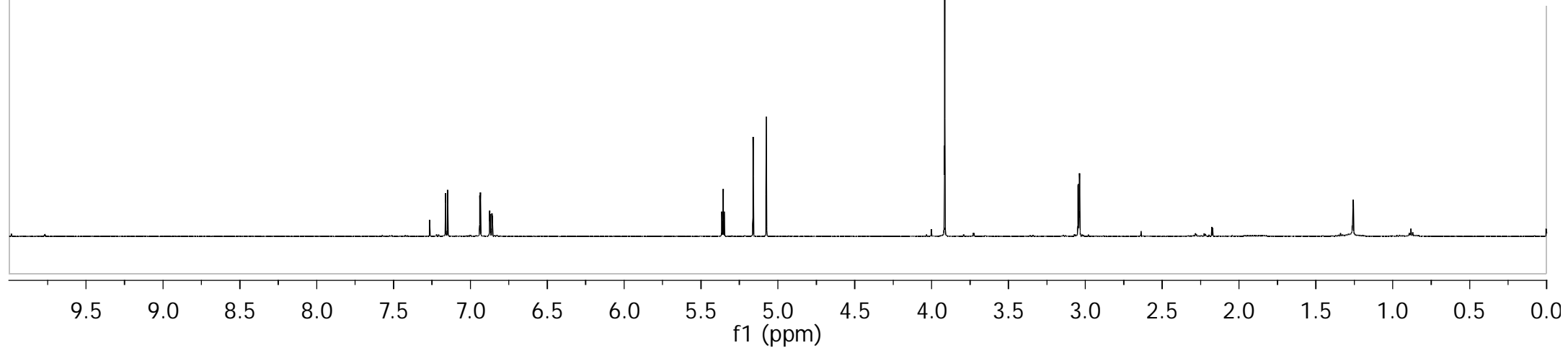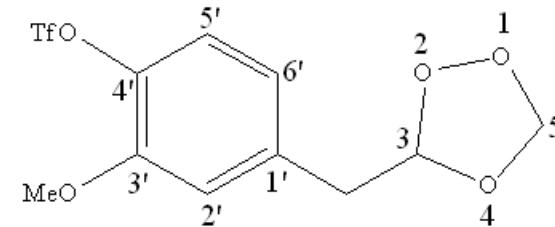
Plate 24b; ^{13}C NMR [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3'-methoxybenzyl)-1,2,4-trioxolane (**462**)
δ 151.34 (C-3'), 137.95 (C-1'), 136.28 (C-4'), 122.43–122.19 (C-5' and C-6'), 119.90 (-O<u>T</u>f), 114.70 (C-2'),
102.99 (C-3), 94.35 (C-5), 56.30 (-O<u>Me</u>), 38.41 (-<u>C</u>H$_2$-).
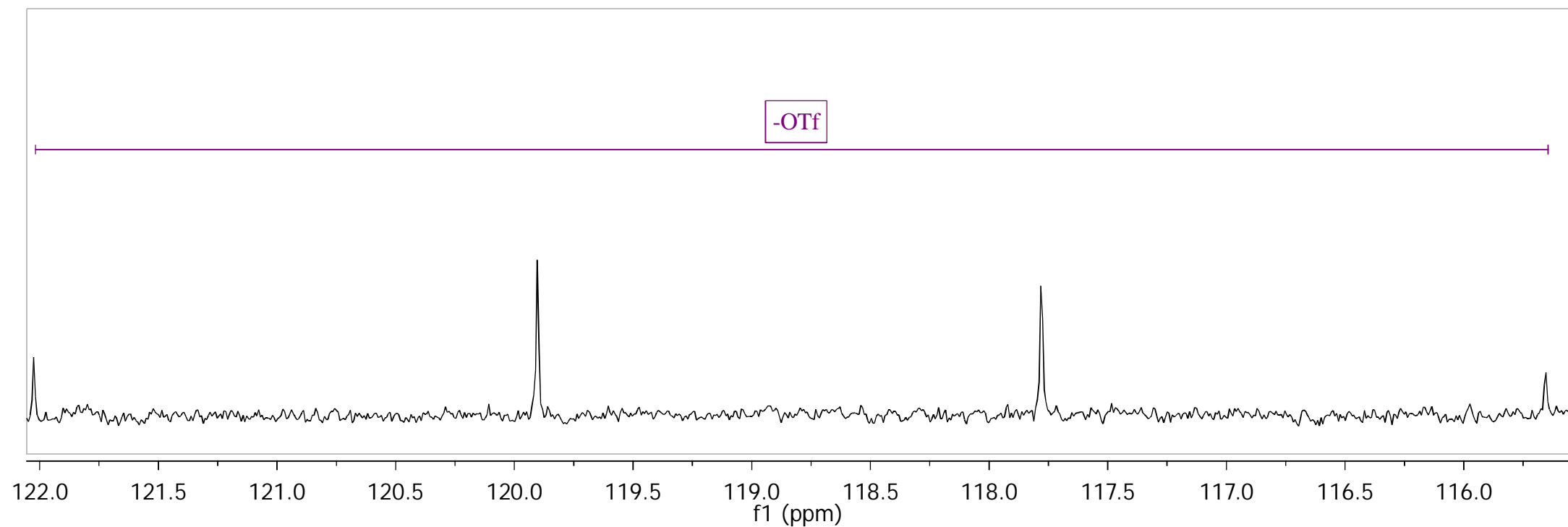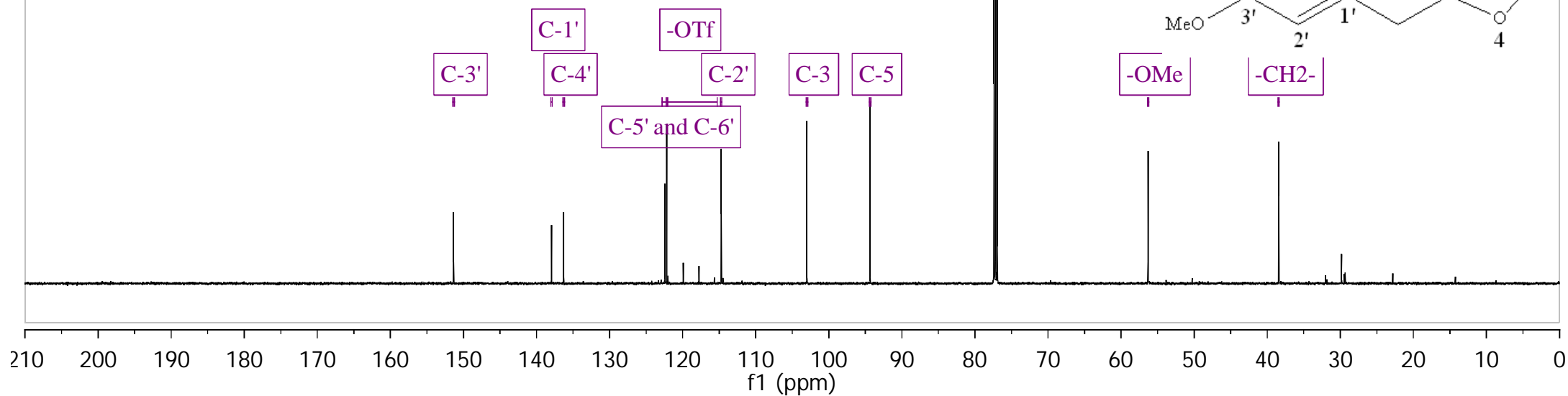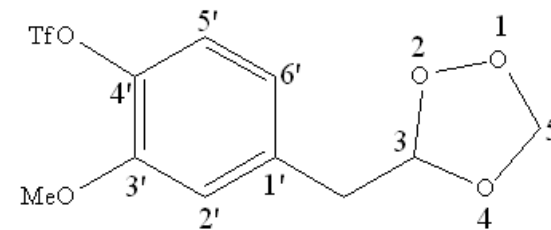
Plate 24c; HSQC [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3'-methoxybenzyl)-1,2,4-trioxolane (**462**)
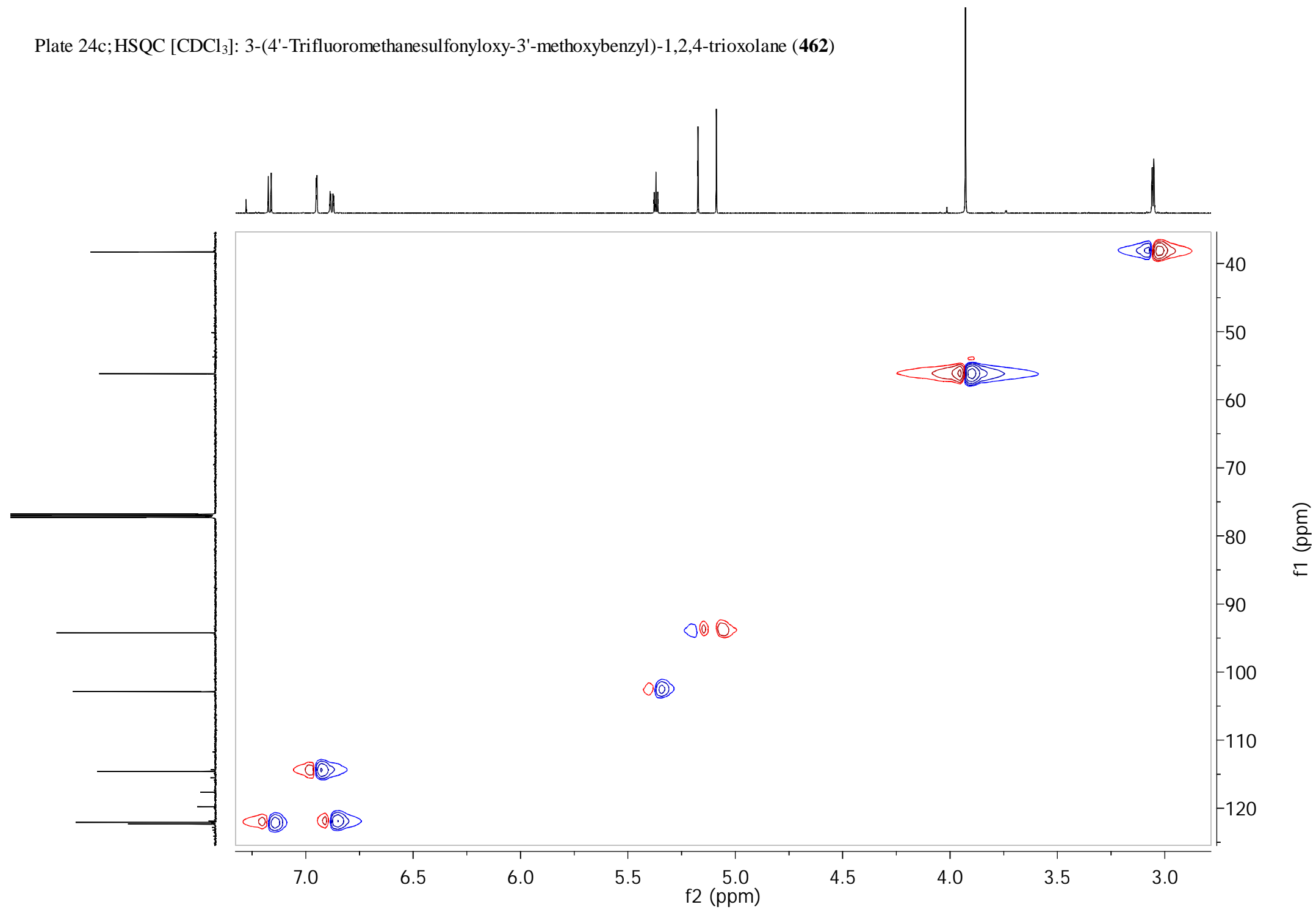
Plate 24d; HMBC [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3'-methoxybenzyl)-1,2,4-trioxolane (**462**)
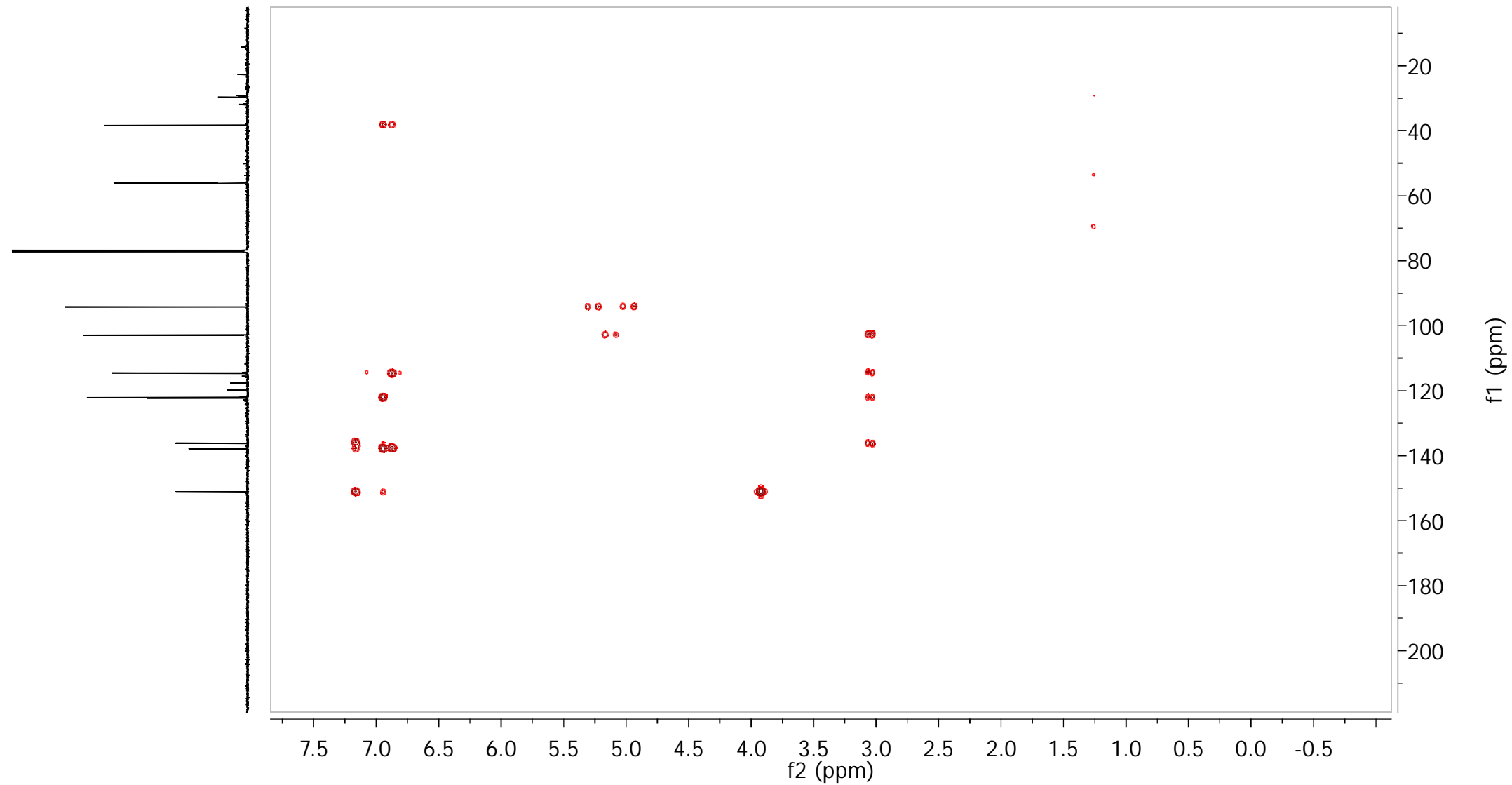
Plate 25a; ^{1}H NMR [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzyl)-1,2,4-trioxolane (**463**)
δ 6.53 (2H, s, H-2' and H-6'), 5.36 (1H, t, *J* = 4.9 Hz, H-3), 5.18 (1H, s, H-5), 5.11 (1H, s, H-5), 3.89 (6H, s, -O$\underline{\text{Me}}$),
3.01 (2H, m, -C$\underline{\text{H}}_2$-)

H-2' and H-6'   H-3   H-5   H-5   OMe   -CH2-
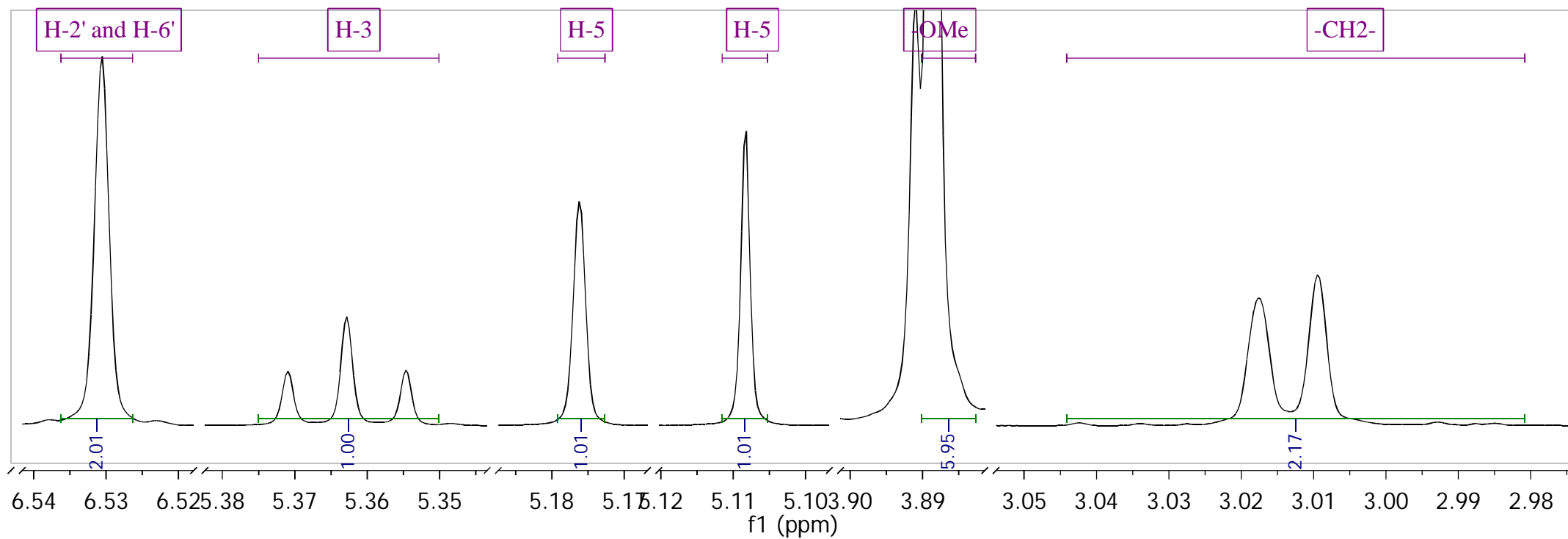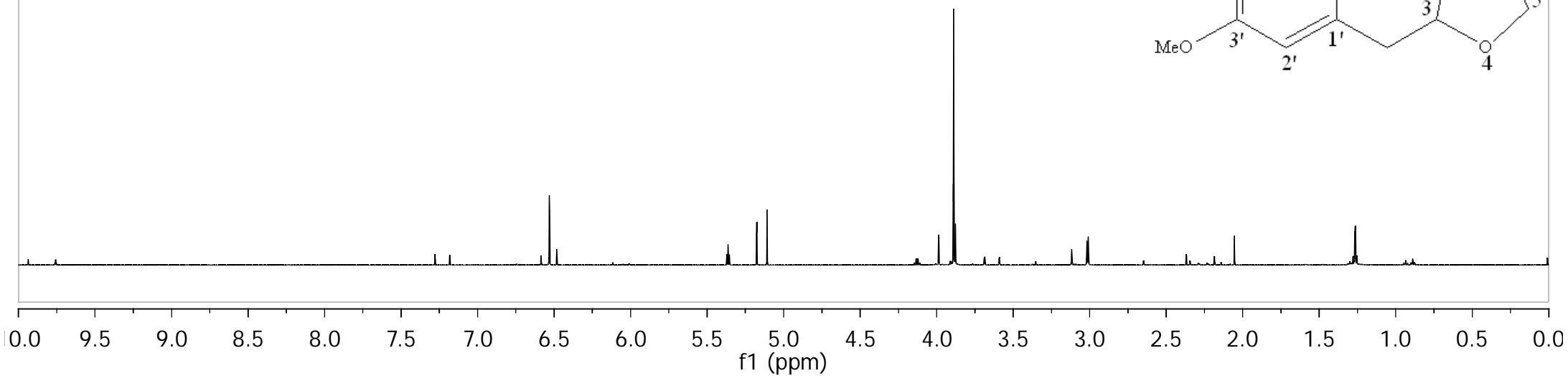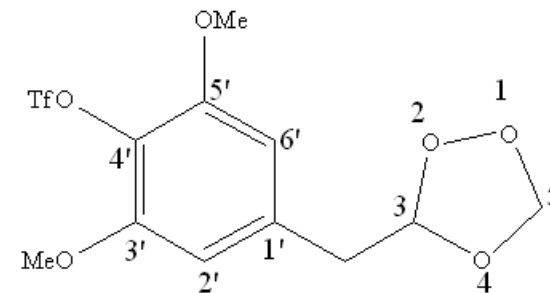
Plate 25b; ^{13}C NMR [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzyl)-1,2,4-trioxolane
(**463**)
δ 152.34 (C-3' and C-5'), 135.72 (C-1'/4'), 127.09 (C-1'/4'), 119.81 (-OTf), 106.29 (C-2' and C-6'), 103.05 (C-3), 94.32 (C-5), 56.42 (-OMe), 39.05 (-CH$_2$-)
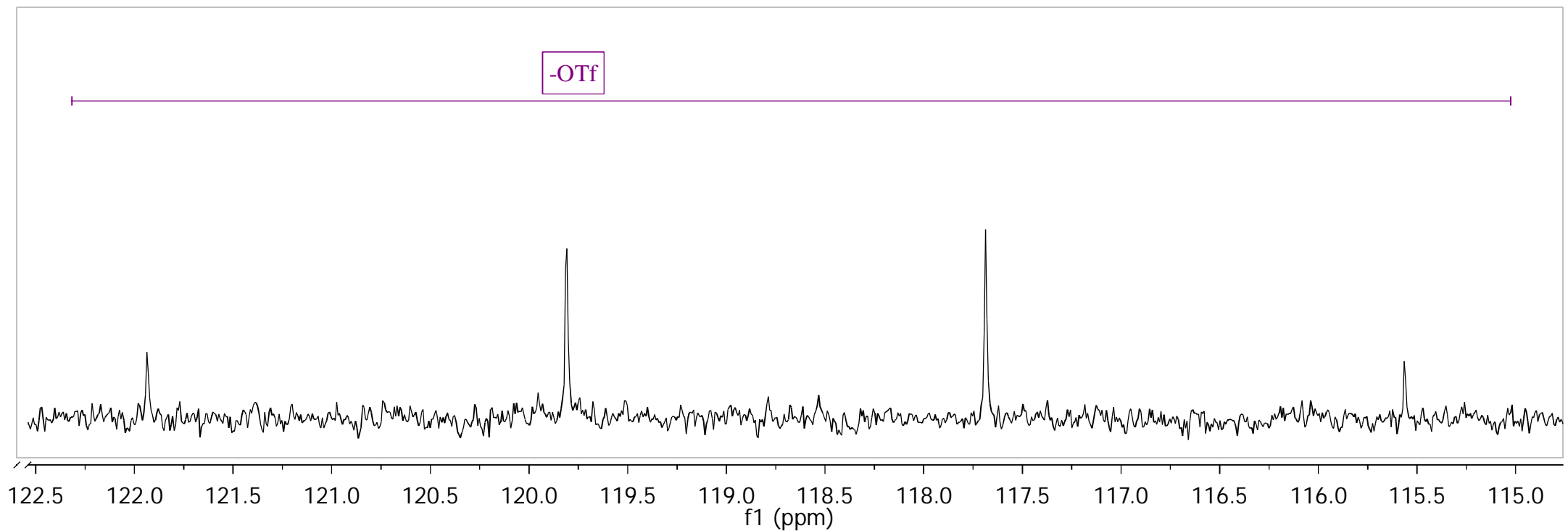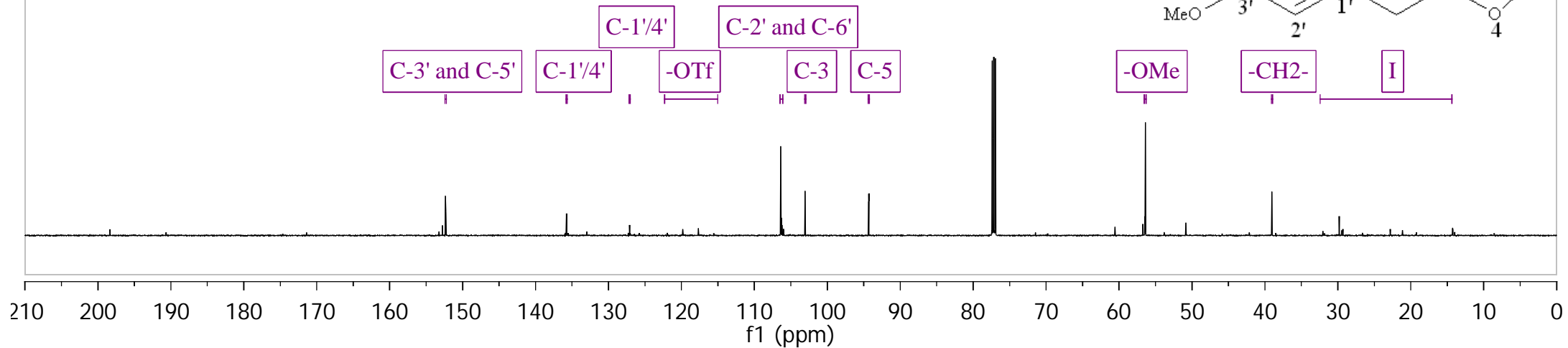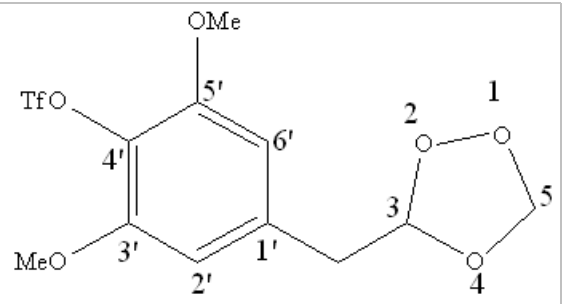
Plate 25c; HSQC [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzyl)-1,2,4-trioxolane (**463**)
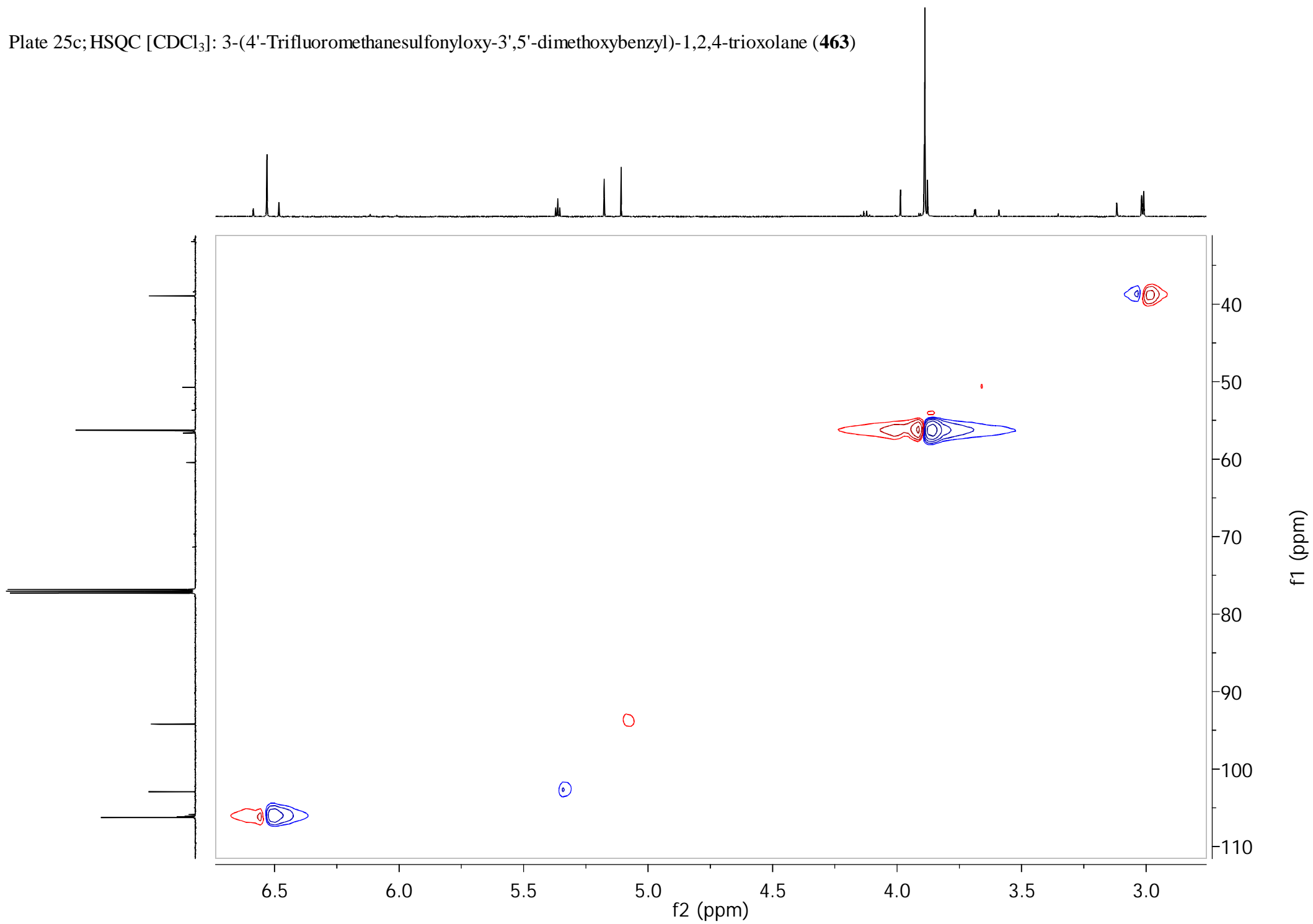
Plate 25d; HMBC [CDCl$_3$]: 3-(4'-Trifluoromethanesulfonyloxy-3',5'-dimethoxybenzyl)-1,2,4-trioxolane (**463**)
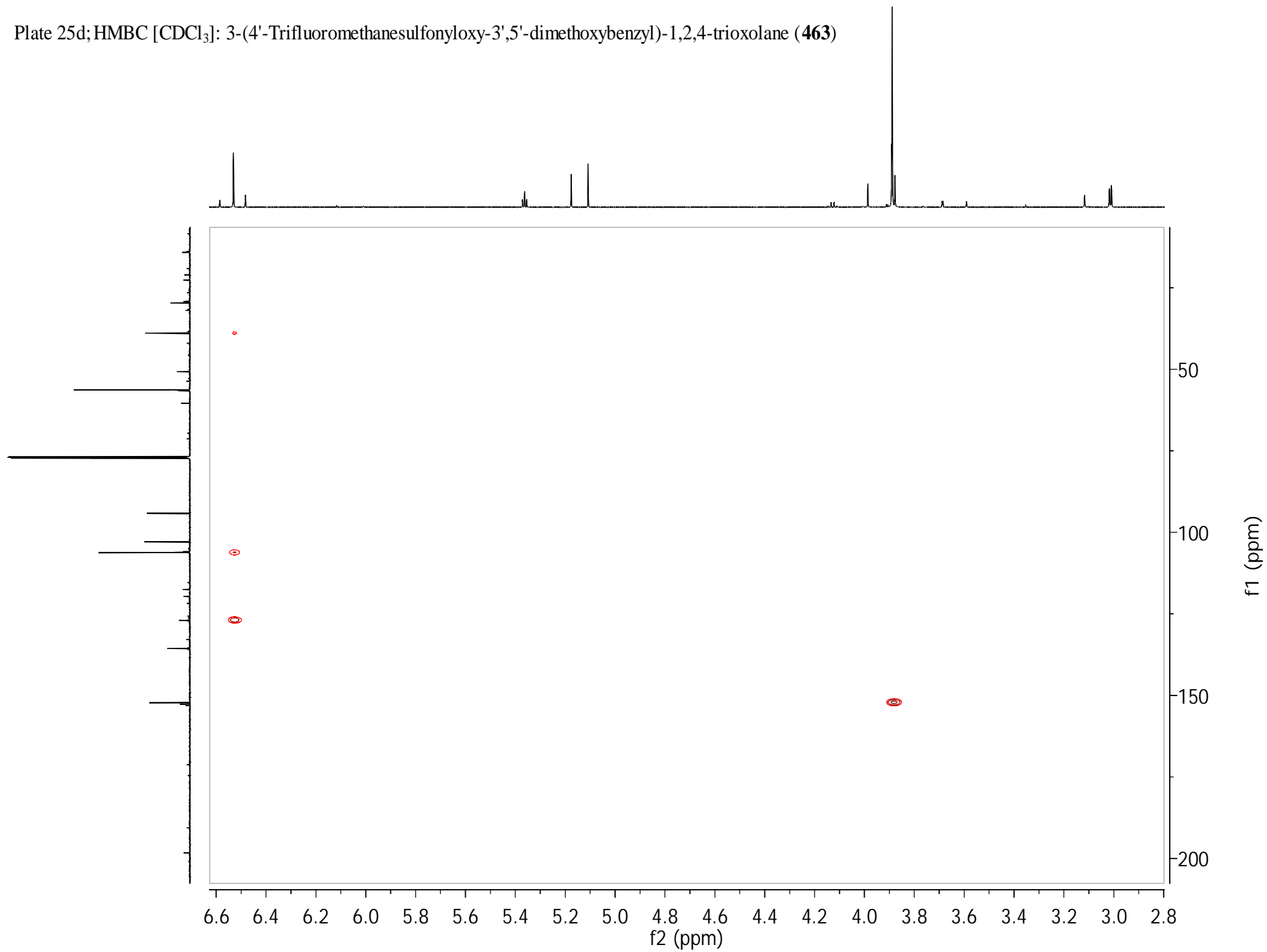
Plate 26a; ^{1}H NMR [CDCl$_3$, -50 °C]:

3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**) δ 7.19 (2H, d, J = 8.60 Hz, H-2'a and H-6'a), 6.87 (2H, d, J = 8.60 Hz, H-3'a and H-5'a), 5.30 (1H, dd, J = 5.1, 5.1 Hz, H-3a), 5.21 (1H, s, H-5a), 5.06 (1H, s, H-5a), 3.80 (3H, s, -OMe), 3.01 (1H, dd, J = 14.56, 5.06 Hz , -CH$_2$-), 2.97 (1H, dd, J = 14.56, 5.06 Hz, -CH$_2$-).

4'-Methoxyphenylacetaldehyde (**431**) δ 9.74 (1H, t, J = 2.17 Hz, -CHO), 7.15 (2H, d, J = 8.44 Hz, H-2'b and H-6'b), 6.92 (2H, d, J = 8.44 Hz, H-3'b and H-5'b), 3.82 (3H, s, -OMe), 3.72 (2H, d, J = 2.17 Hz, H-2b).

3-(4'-methoxybenzyl)-1,2,4-trioxolane

+
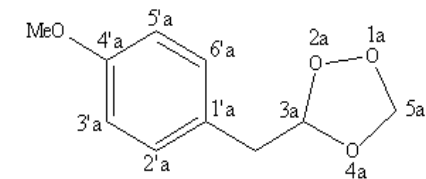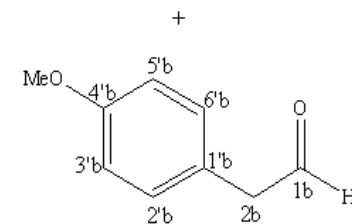
4'-methoxyphenylacetaldehyde
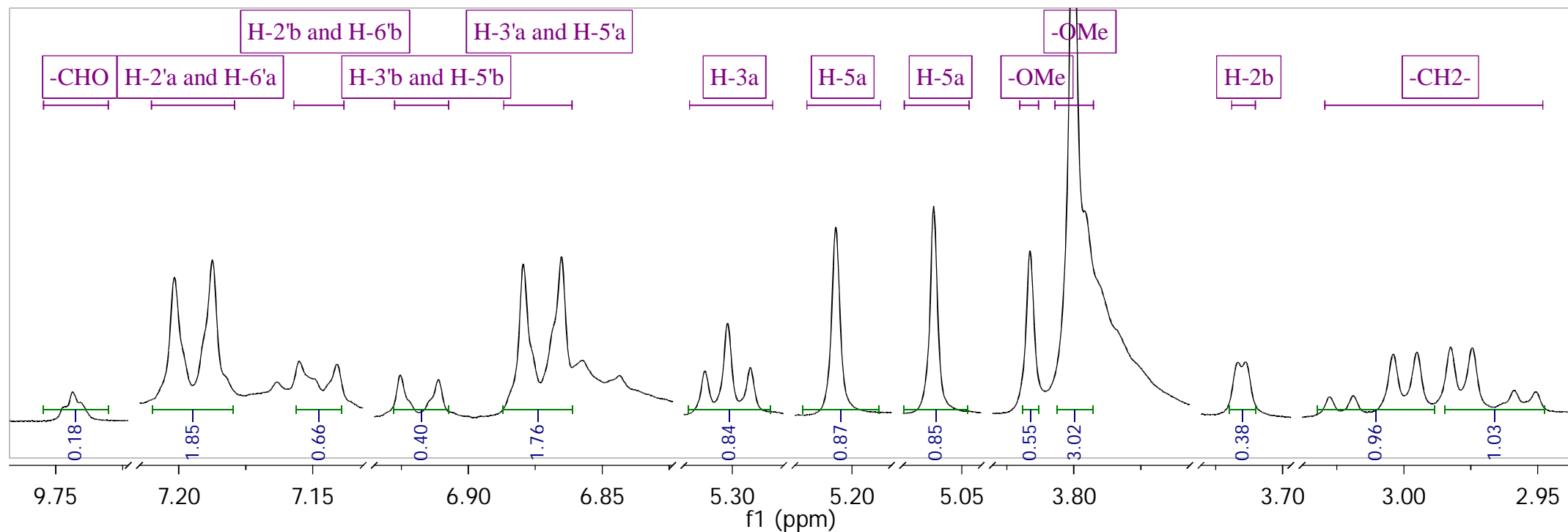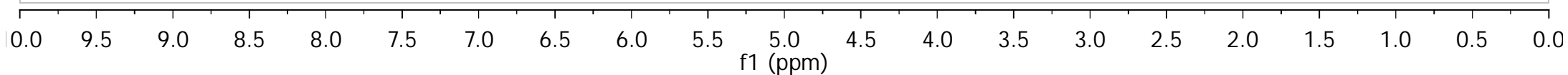
Plate 26b; ^{13}C NMR [CDCl$_3$, -50 °C]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
δ 158.19 (C-4'a), 130.85 (C-2'a and C-6'a), 126.10 (C-1'a), 113.69 (C-3'a and C-5'a), 103.60 (C-3a), 94.28 (C-5a), 55.34 (-O$\underline{Me}$), 37.05 (-$\underline{CH}_2$-).
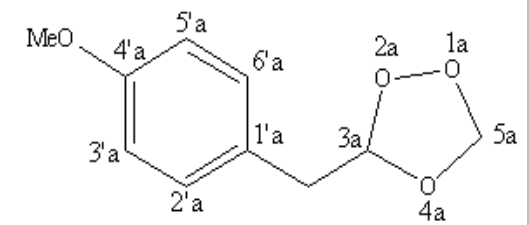
3-(4'-methoxybenzyl)-1,2,4-trioxolane
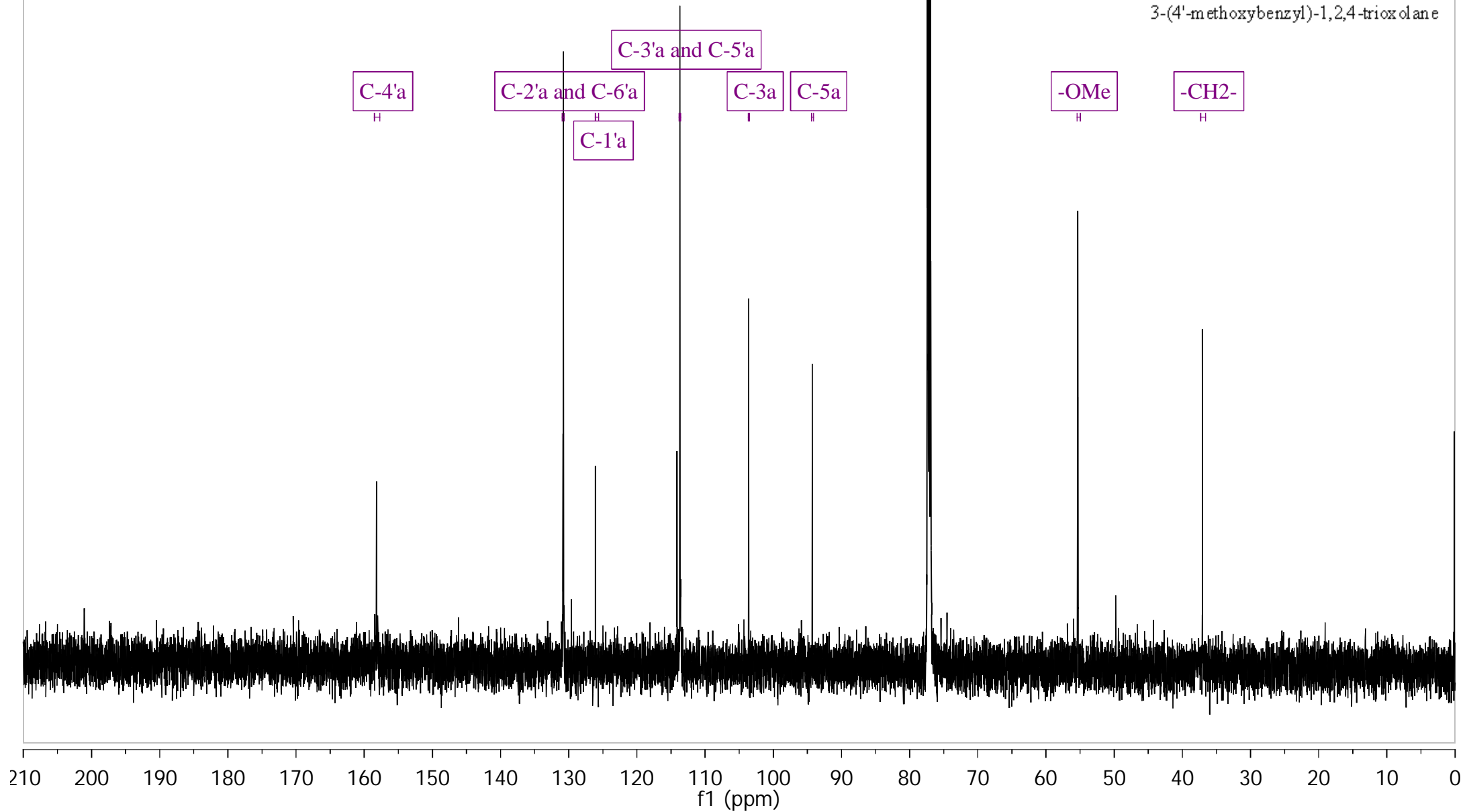
Plate 26c, DEPT [CDCl$_3$, - 50 °C]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
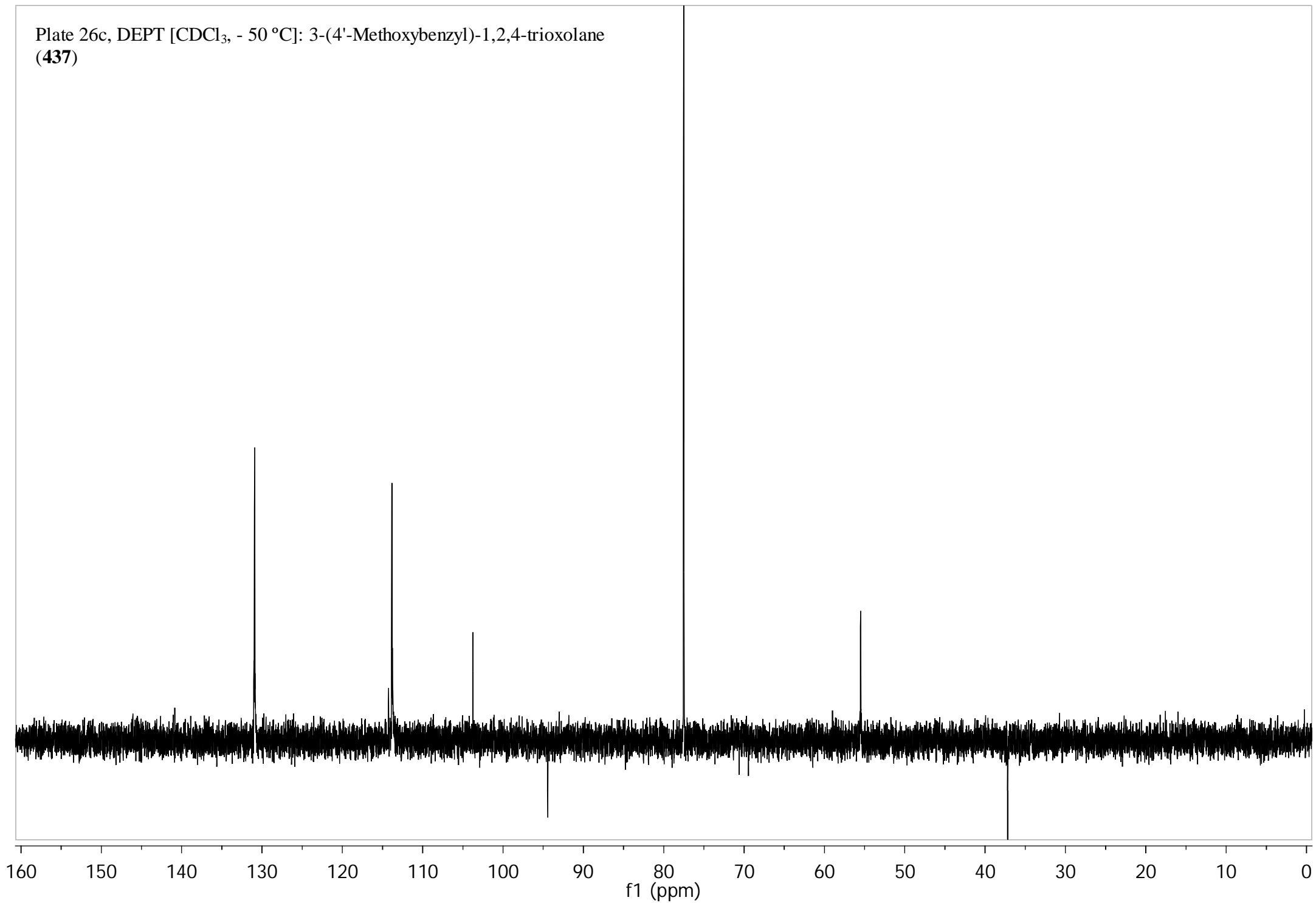
Plate 26d, HSQC [CDCl$_3$, - 50 ºC]:
3-(4'-Methoxybenzyl)-1,2,4-
trioxolane (**437**)
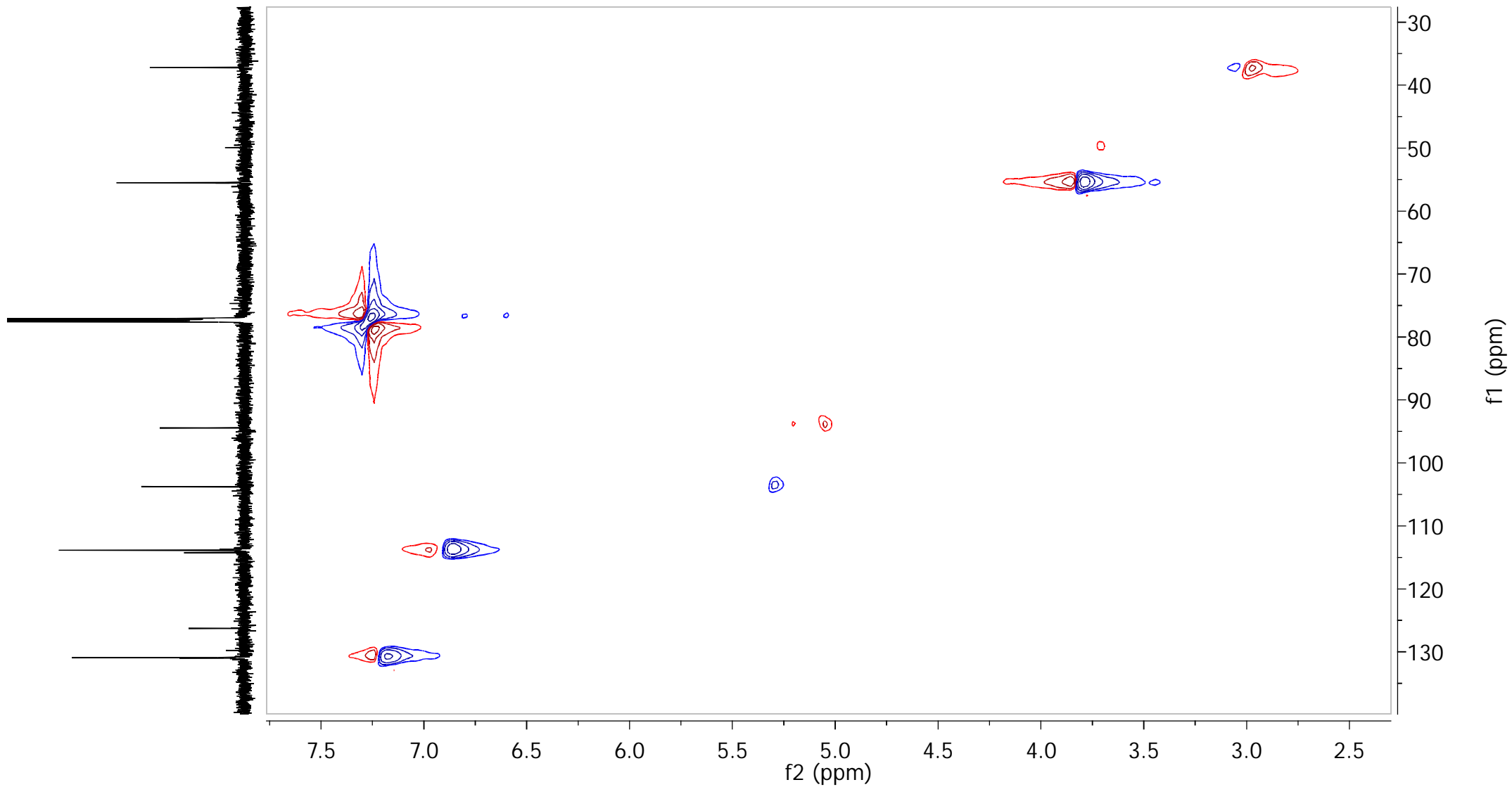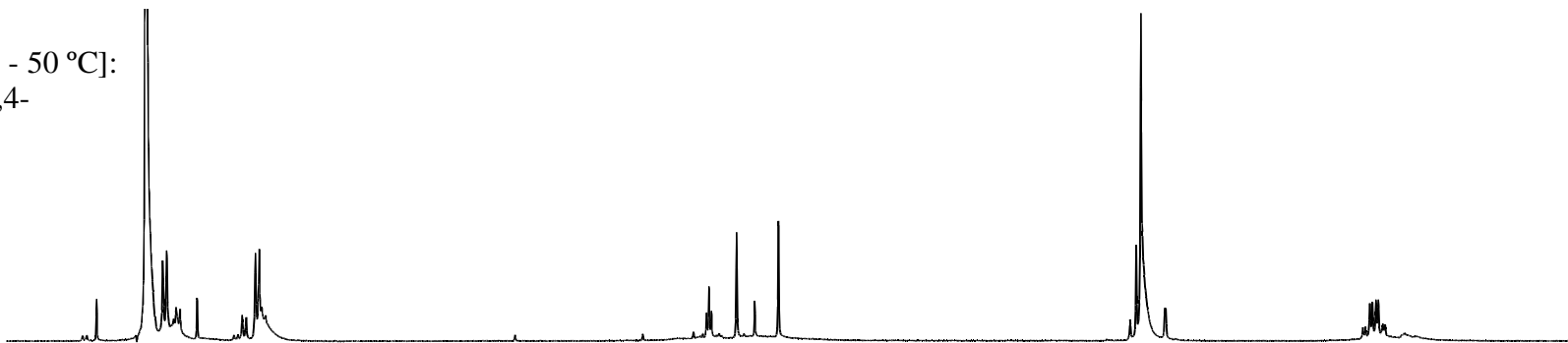
Plate 26e, HMBC [CDCl$_3$, - 50 ºC]:
3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
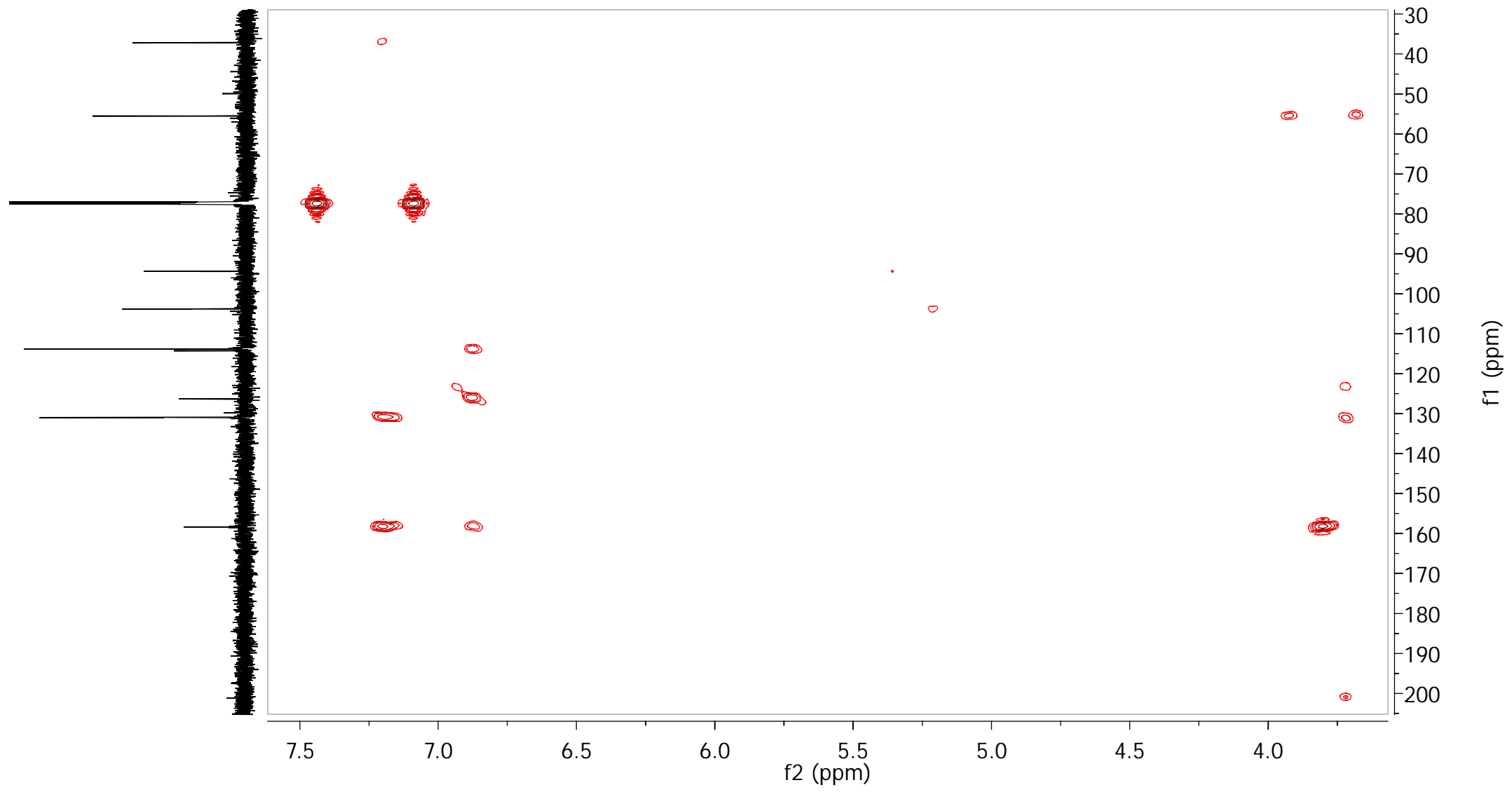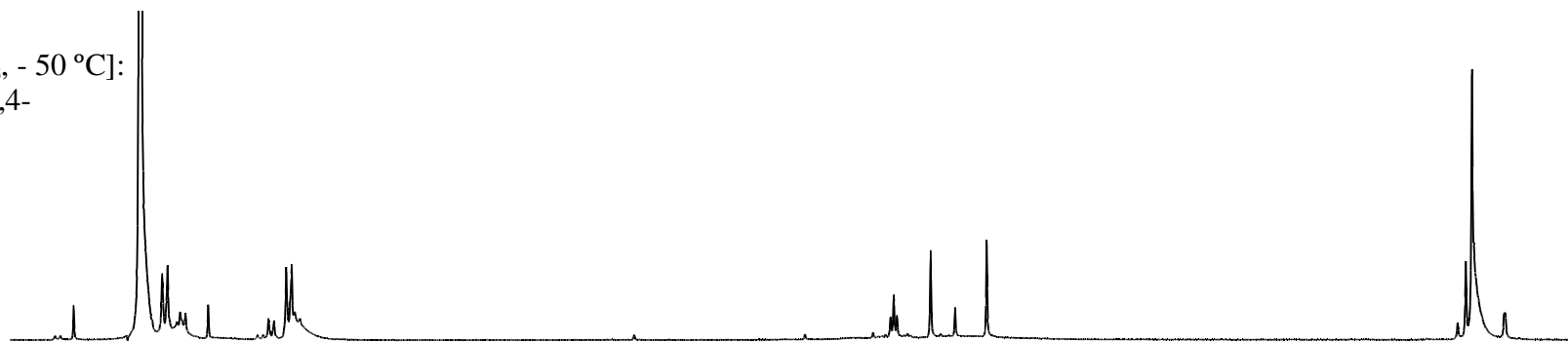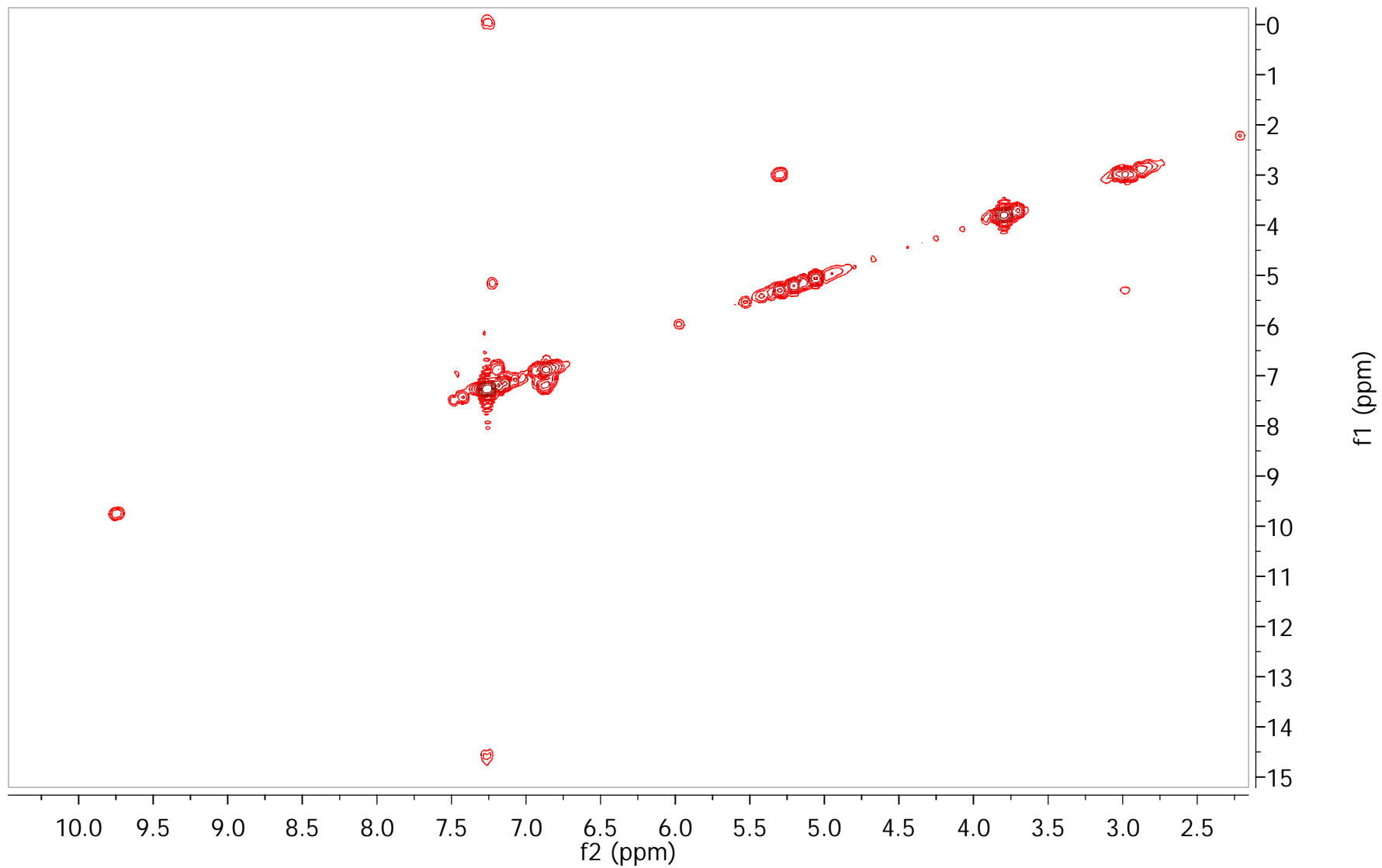
Plate 27a ¹H NMR [CDCl₃, 20 °C]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**) and 4'-methoxyphenylacetaldehyde (**431**)

3-(4'-methoxybenzyl)-1,2,4-trioxolane

+
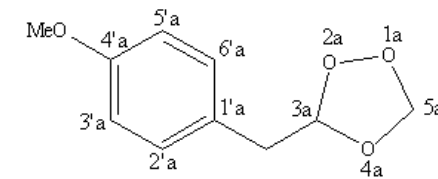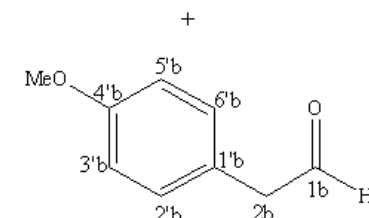
4'-methoxyphenylacetaldehyde
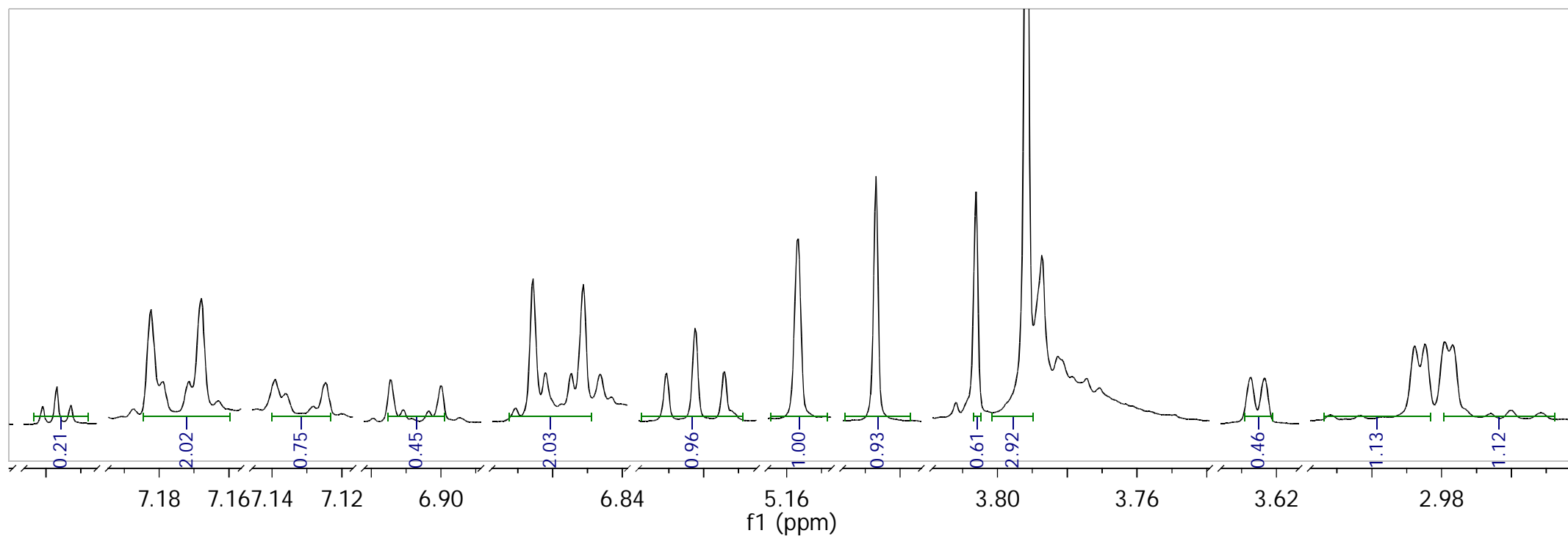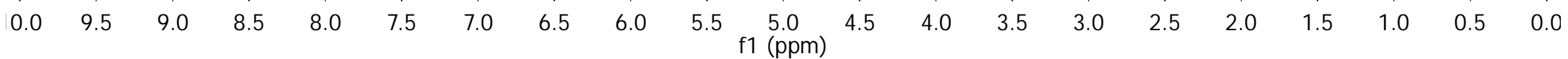
Plate 27b; ^{13}C NMR [CDCl$_3$, 20 °C]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
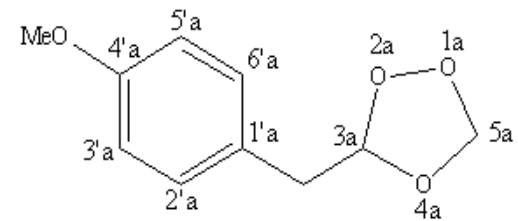
3-(4'-methoxybenzyl)-1,2,4-trioxolane
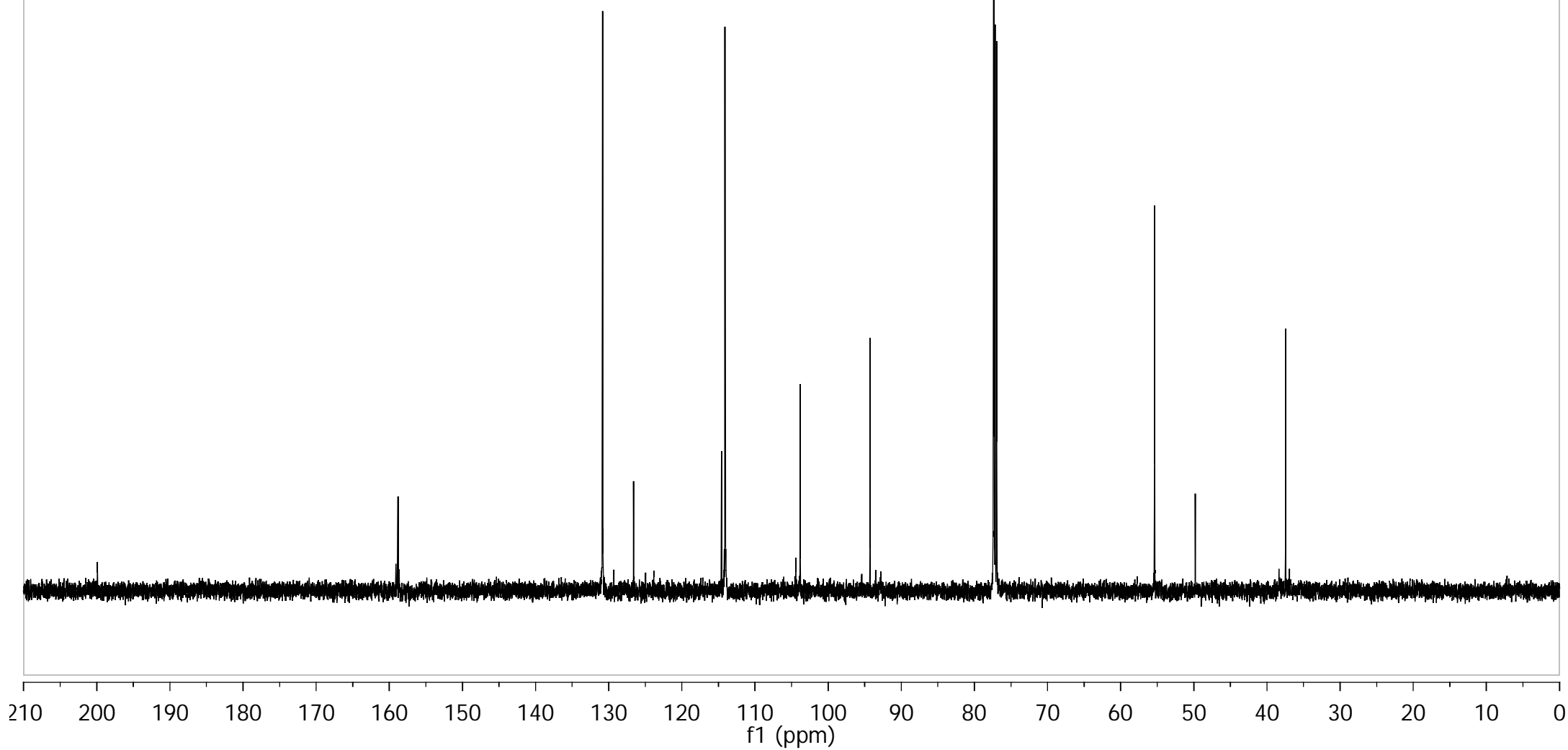
Plate 27c; DEPT [CDCl₃, 20 ℃]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
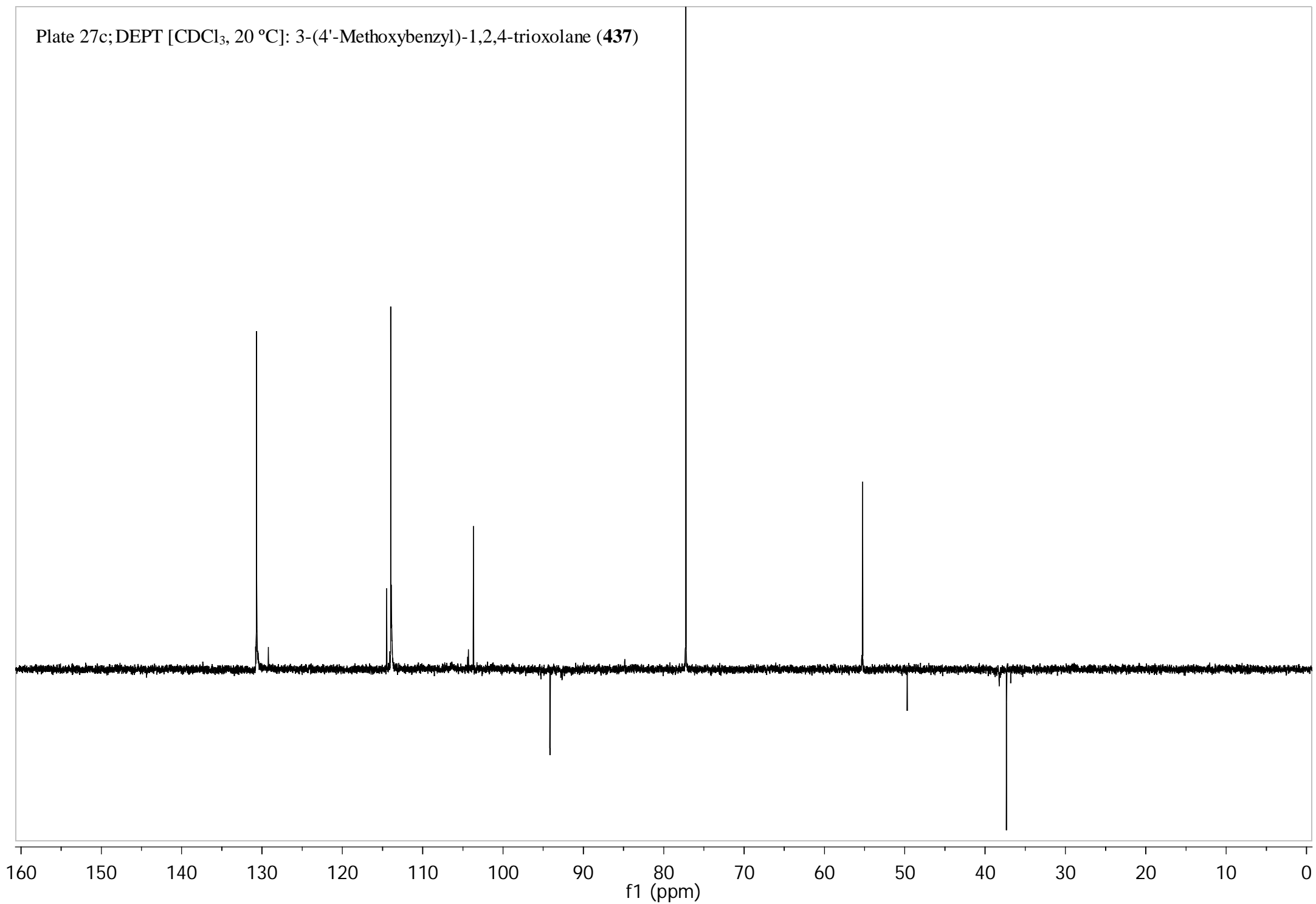
Plate 27d; HSQC [CDCl₃, 20 °C]:
3-(4'-Methoxybenzyl)-1,2,4-trioxolane (437)
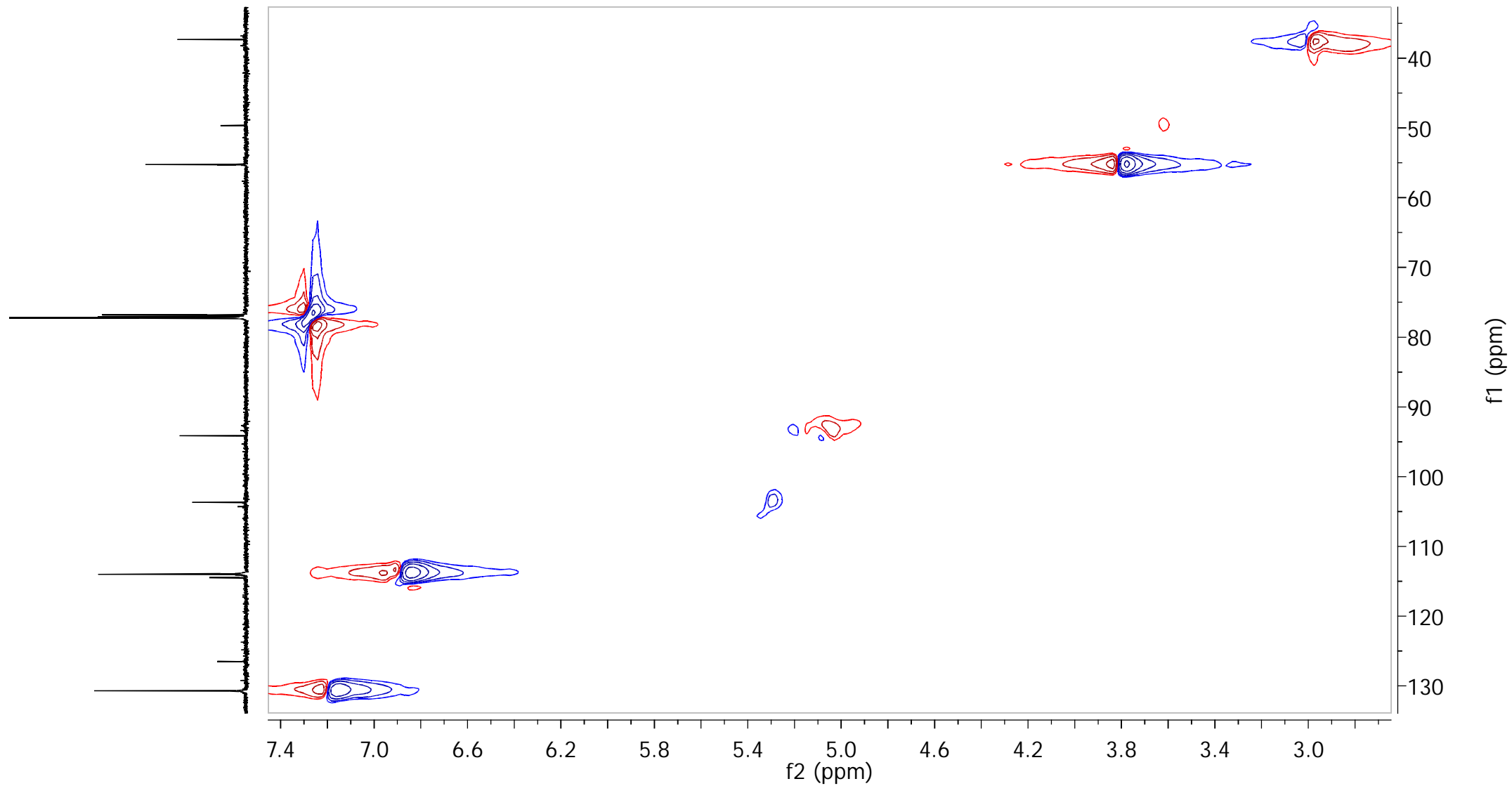
Plate 27e; HMBC [CDCl$_3$, 20 °C]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
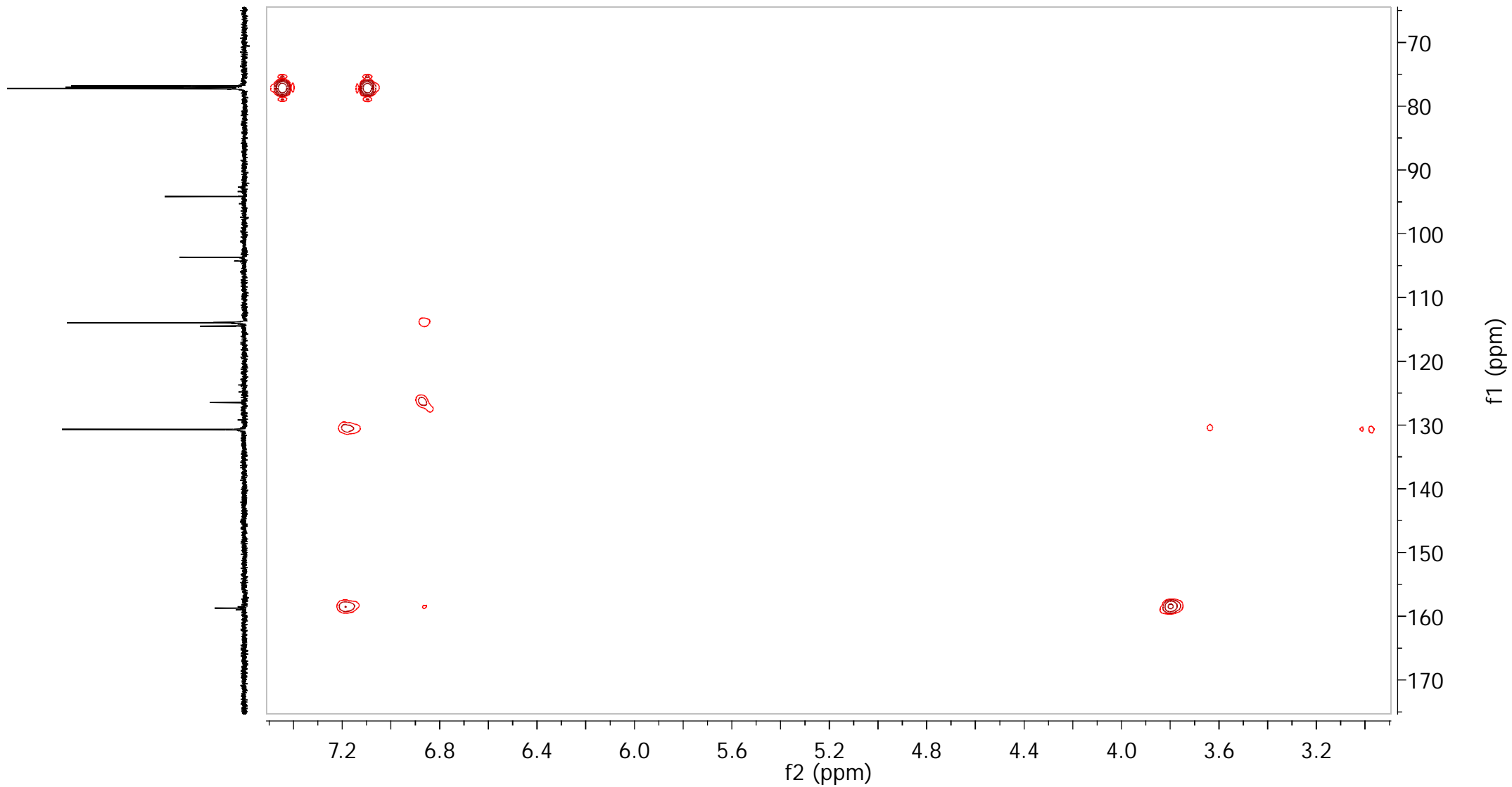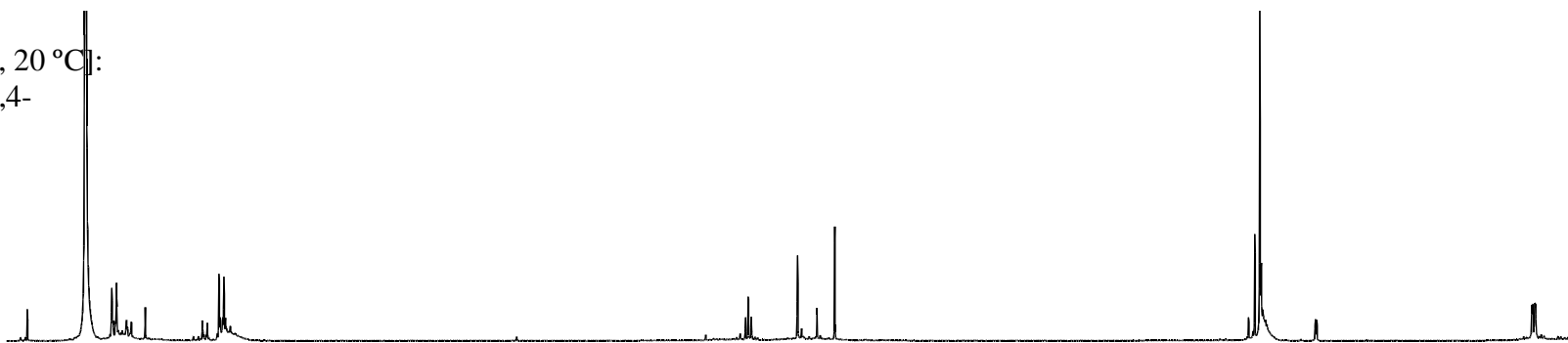
Plate 27f; COSY [CDCl$_3$, 20 °C]: 3-(4'-Methoxybenzyl)-1,2,4-trioxolane (**437**)
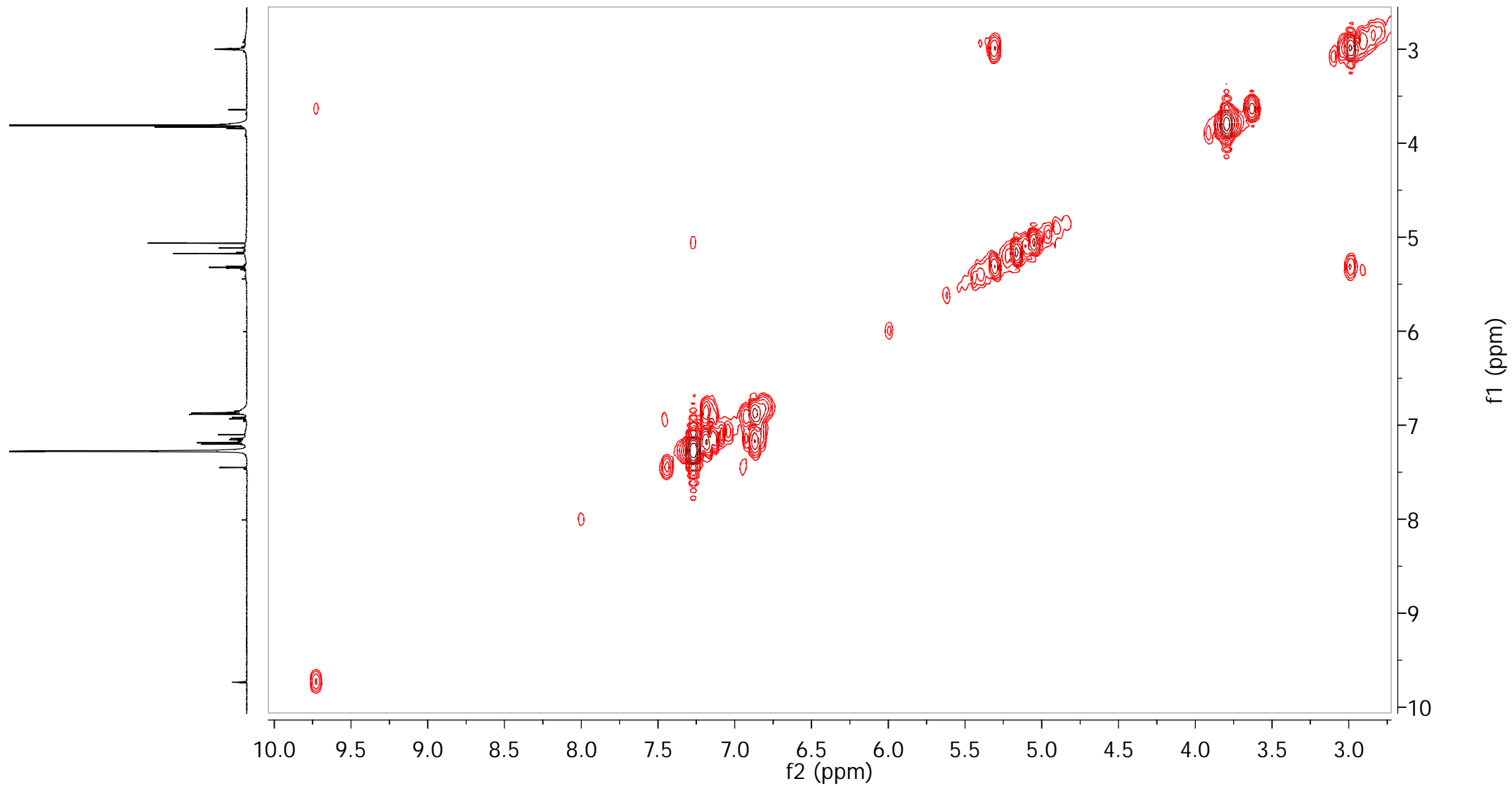
Plate 28a; ^{1}H NMR [CDCl$_3$]: 4-Allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone (**470**)
δ 5.44 (2H, s, H-3 and H-5), 5.43–5.31 (1H, m, H-2'), 5.06–5.02 (1H, m, H-3'b), 5.01–4.96 (1H, m, H-3'a), 3.77 (6H, s, -O**Me**), 2.95 (1H, s, -OH), 2.78–2.72 (2H, m, H-1').
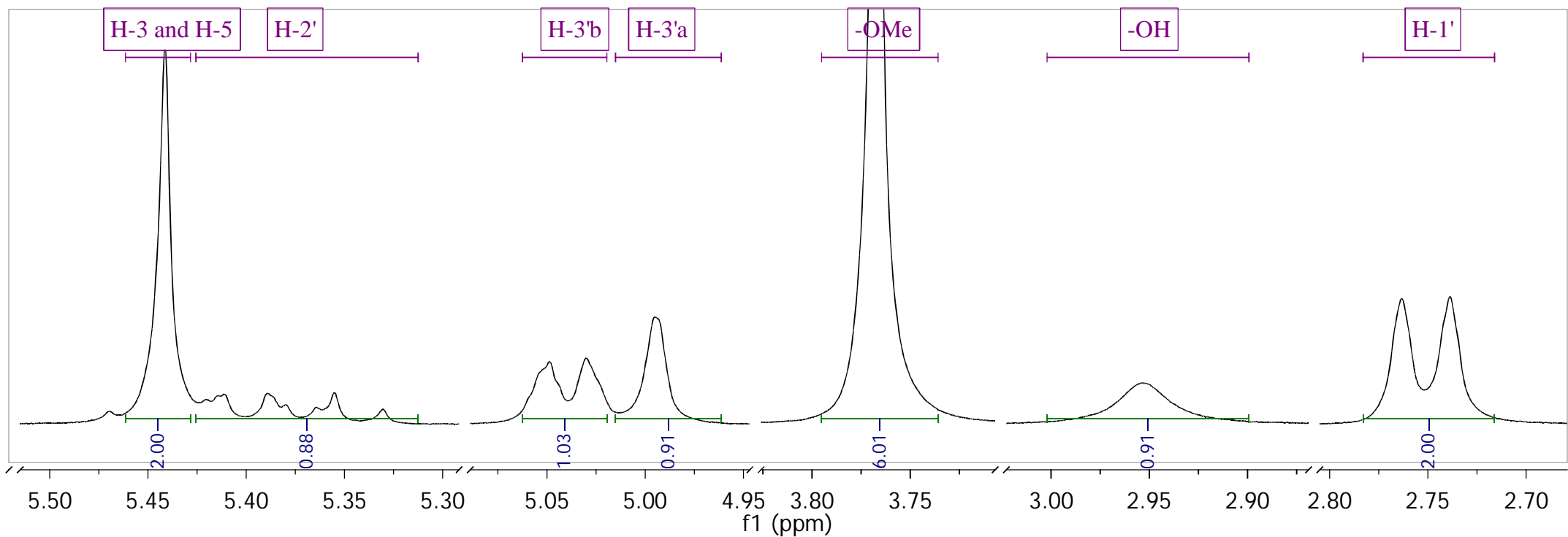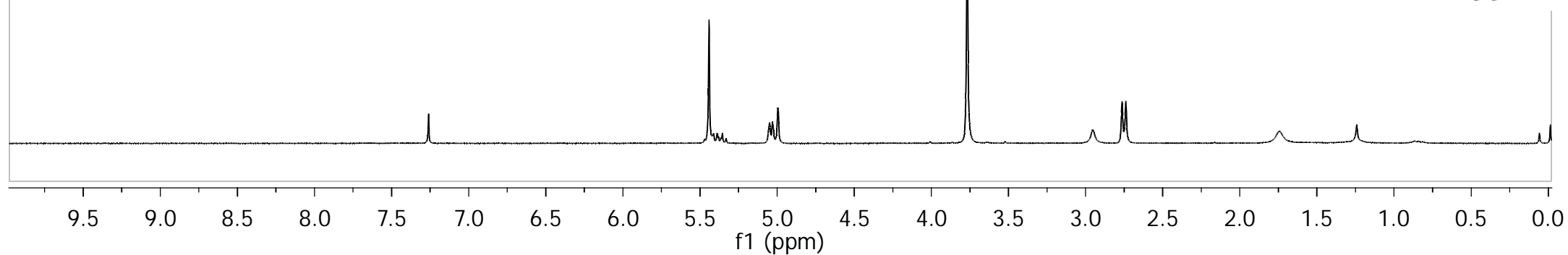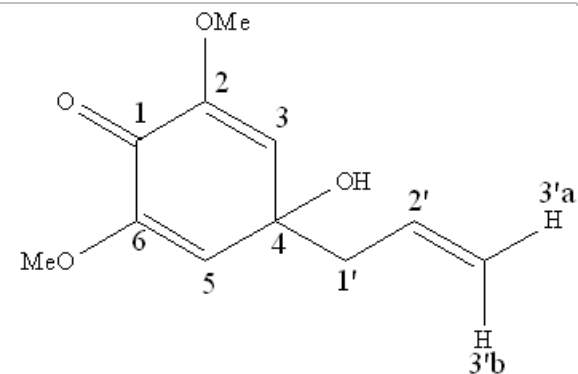
Plate 28b; ^{13}C NMR [CDCl$_3$]: 4-Allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone (**470**)
δ 187.22 (C-1), 170.62 (C-2 and C-6), 130.60 (C-2'), 119.17 (C-3'), 101.04 (C-3 and C-5),
72.70 (C-4), 56.13 (-O<u>Me</u>), 42.51 (C-1').

I | C-1 | C-2 and C-6 | C-2' | C-3' | C-3 and C-5 | C-4 | -OMe | C-1' | I

187.22   170.62   130.60   119.17   101.04   72.70   56.13   42.51

f1 (ppm)
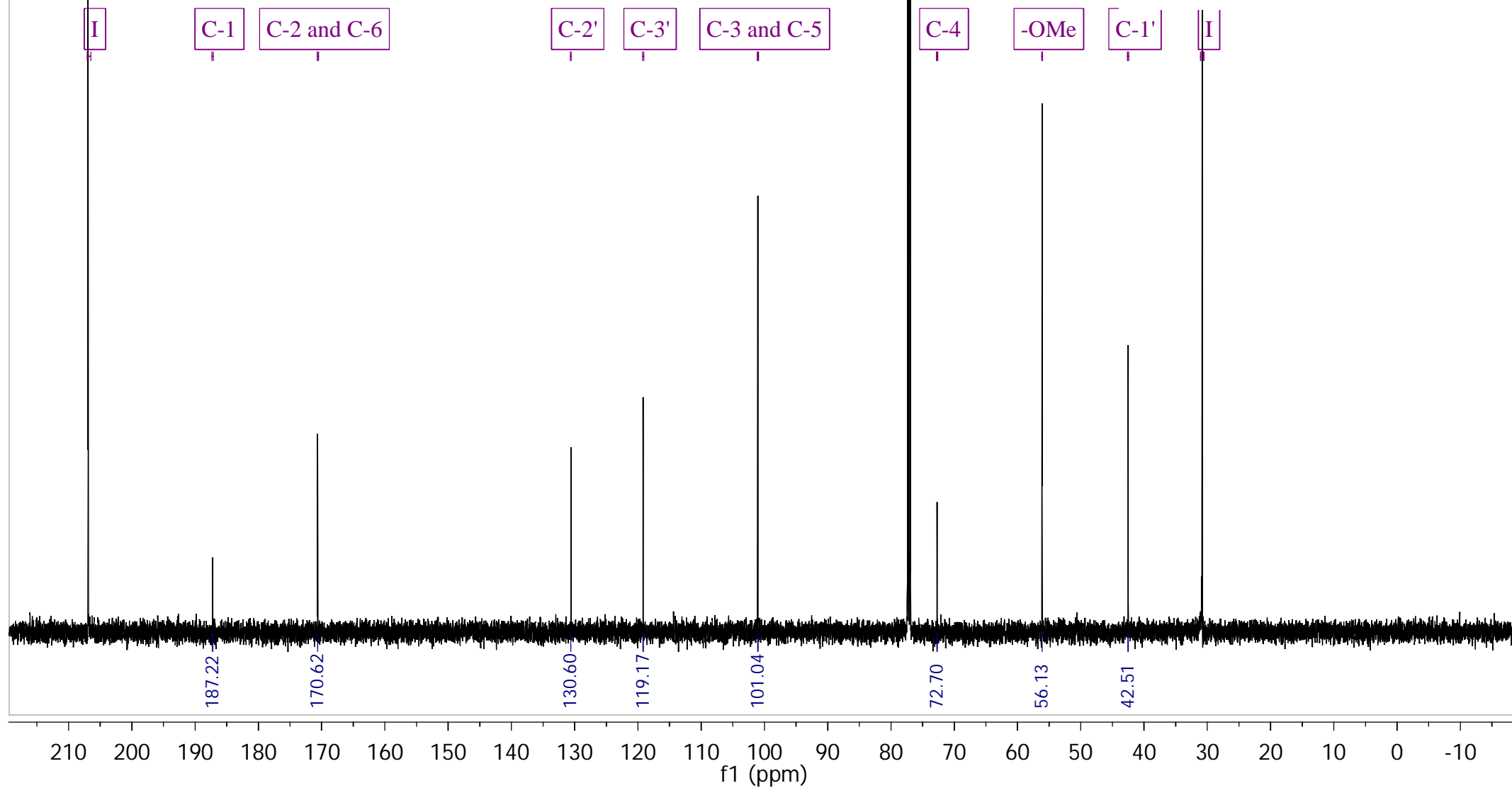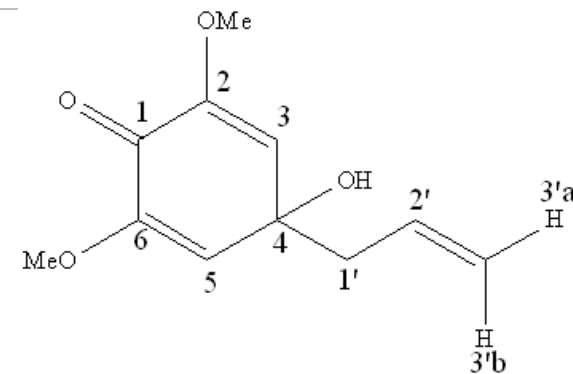
Plate 28c; DEPT [CDCl$_3$]: 4-Allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone (**470**)
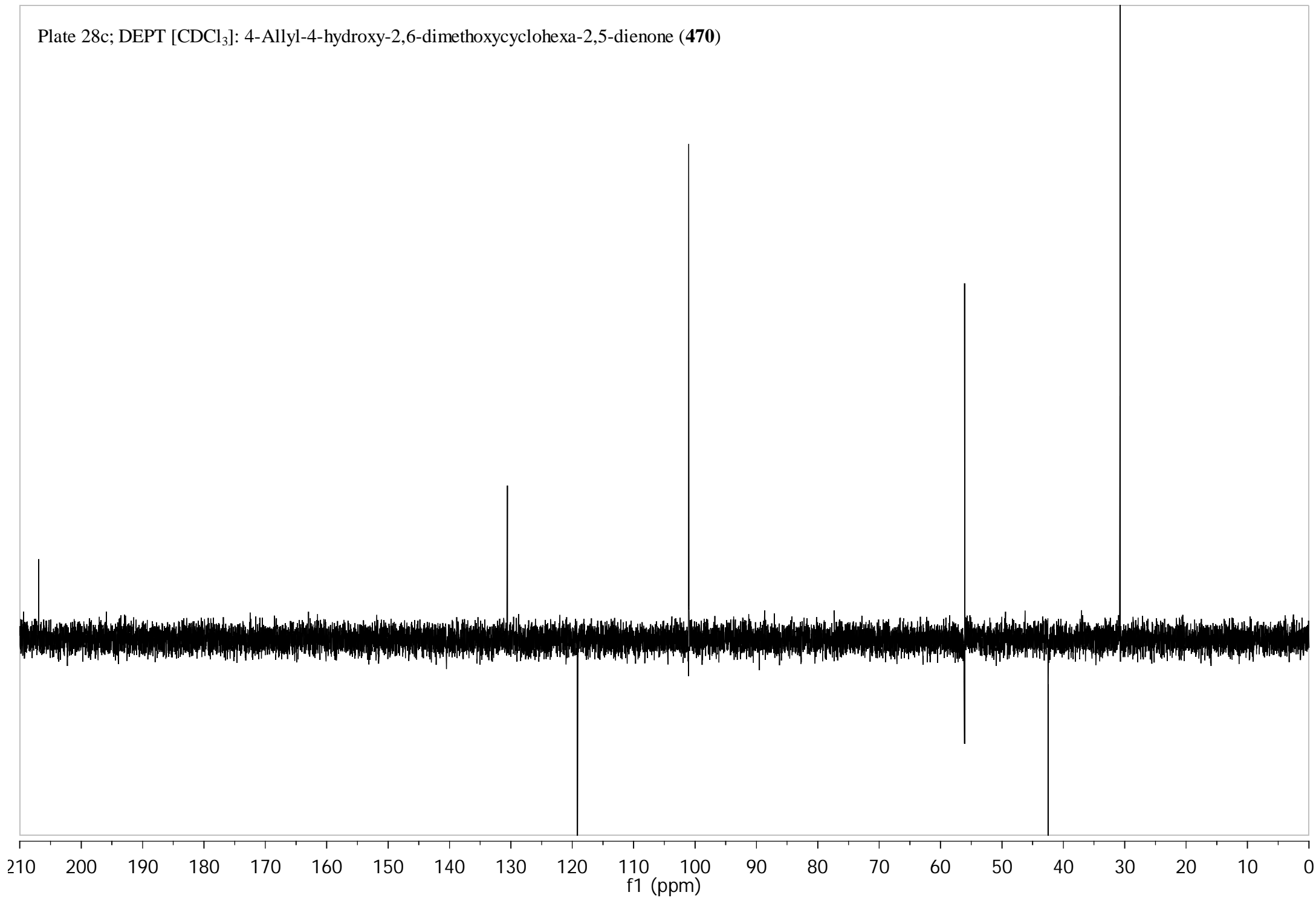
Plate 28d; HSQC [CDCl$_3$]: 4-Allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone (**470**)
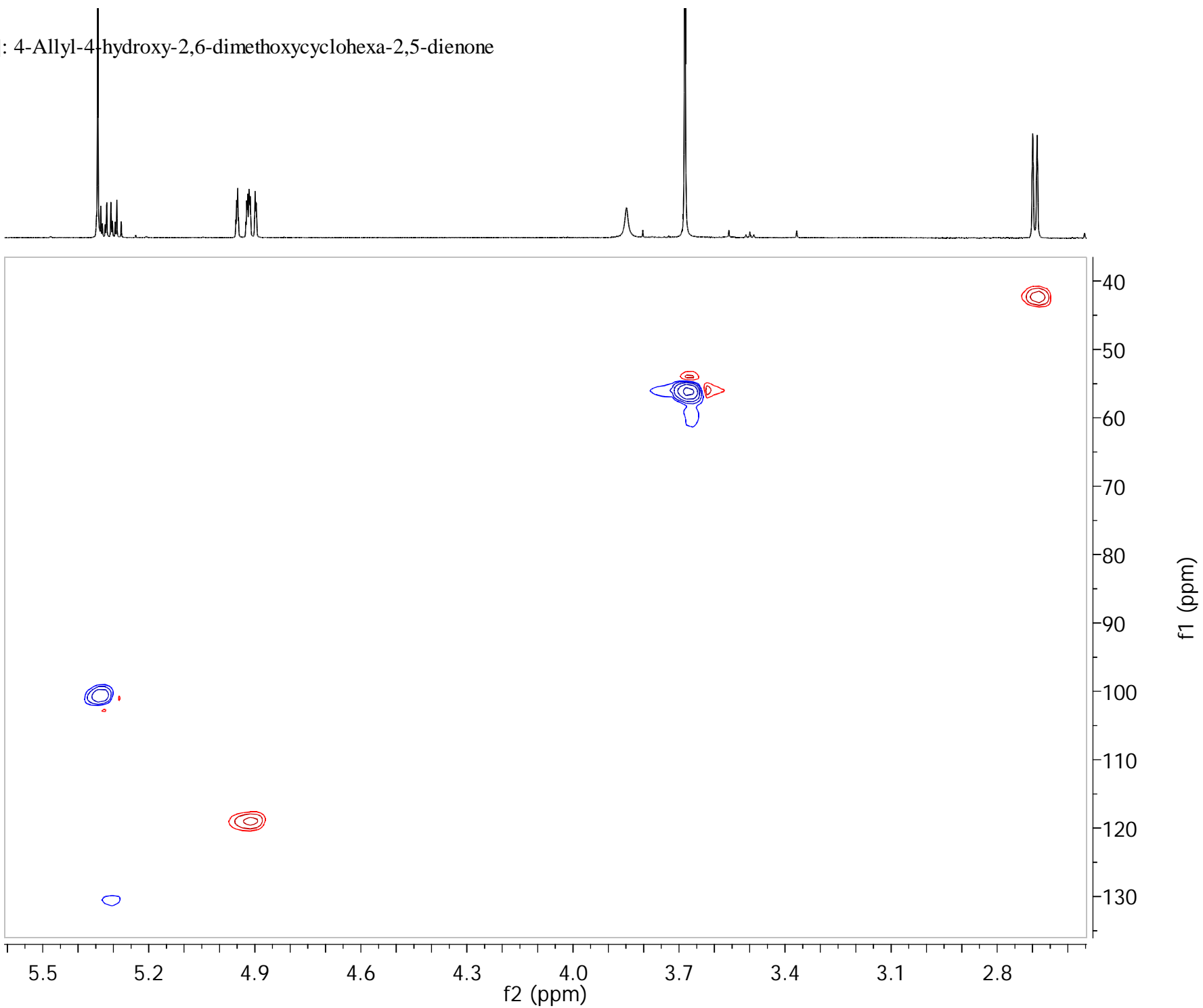
Plate 28e; HMBC [CDCl$_3$]: 4-Allyl-4-hydroxy-2,6-dimethoxycyclohexa-2,5-dienone (**470**)
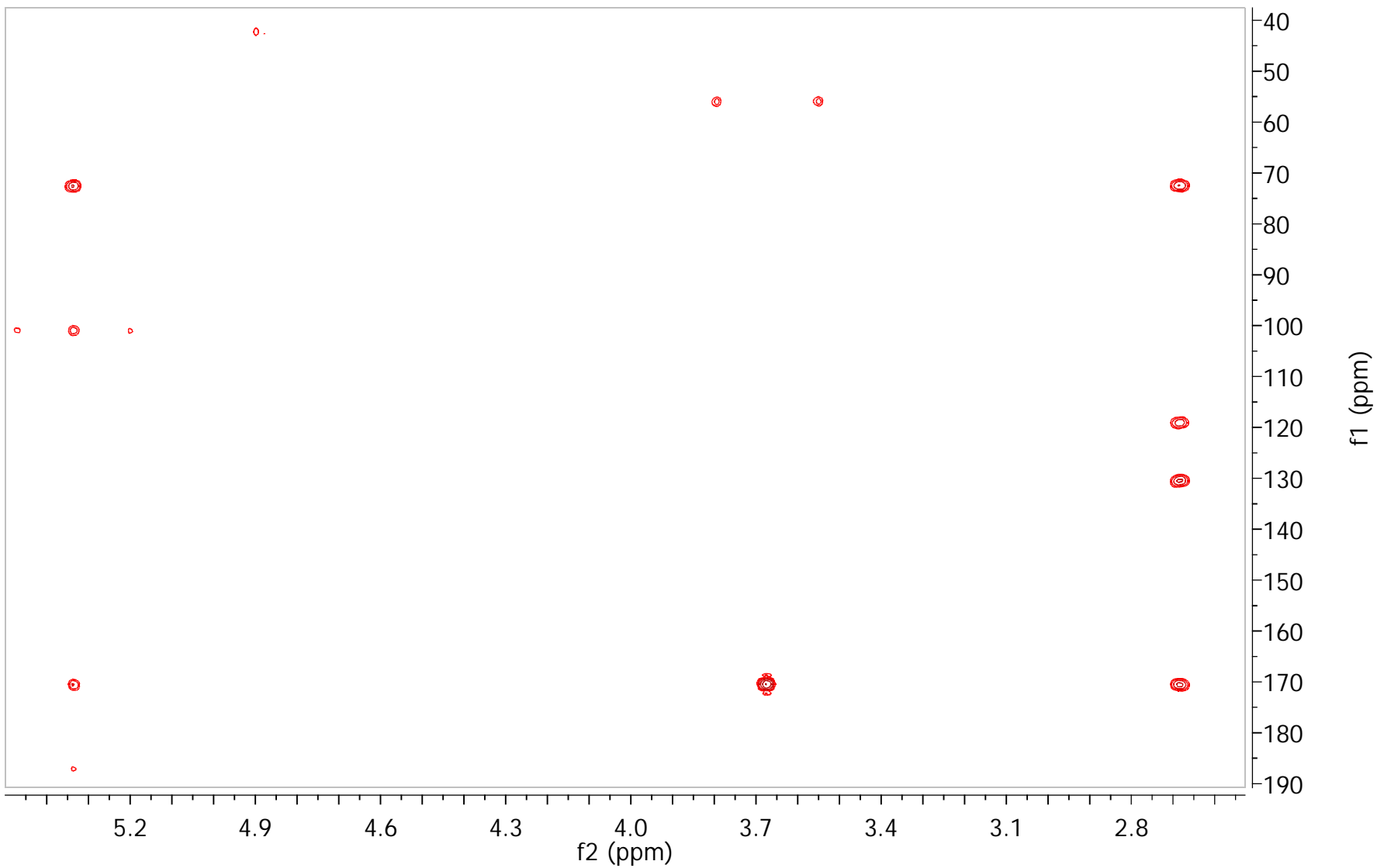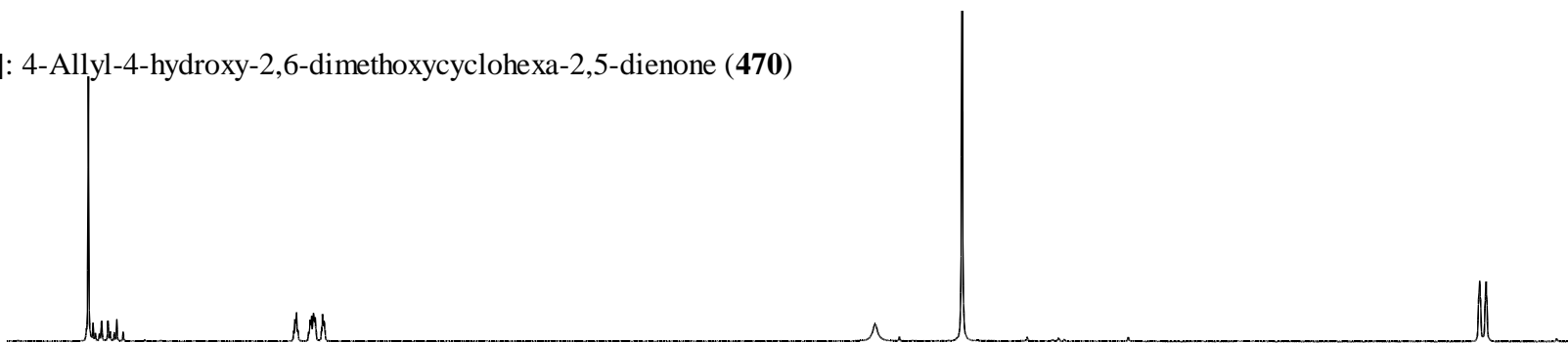
Plate 29a; ¹H NMR [CDCl₃]: Methyl 2'-methoxyphenyl acetate (**480**)
δ 7.29–7.26 (1H, m, H-4'), 7.20–7.19 (1H, m, H-6'), 6.94–6.92 (1H, m, H-5'), 6.89–6.88 (1H, m, H-3'), 3.82 (3H, s, -OMe), 3.70 (3H, s, -COOMe), 3.65 (2H, s, H-2).
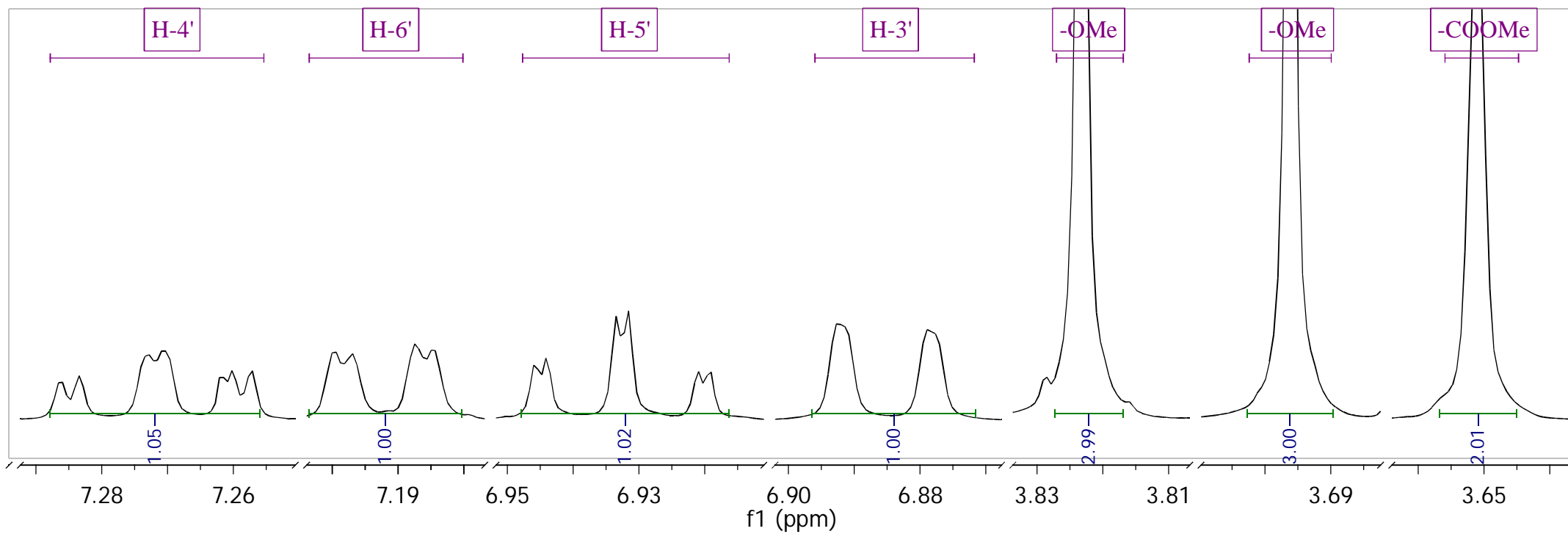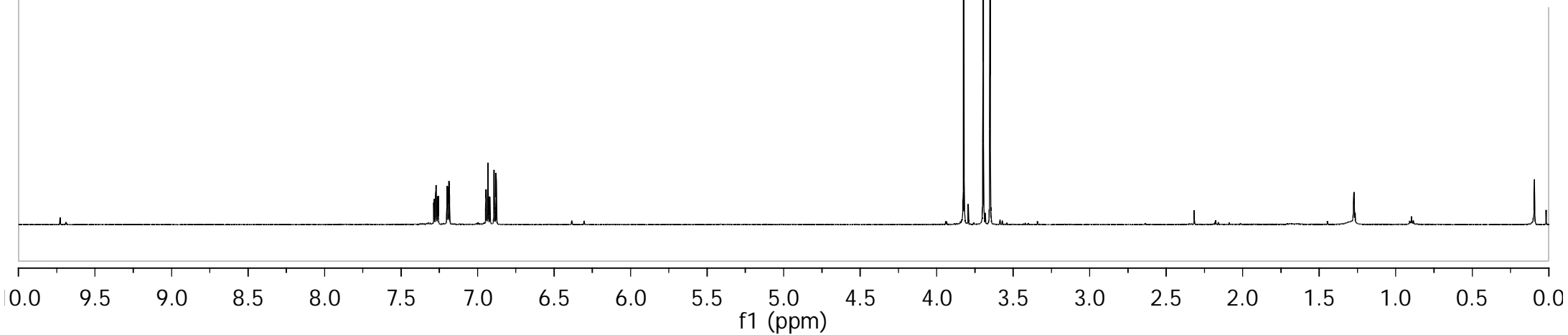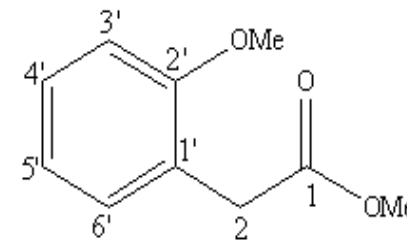
Plate 29b; ^{13}C NMR [CDCl$_3$]: Methyl 2'-methoxyphenyl acetate (**480**)
δ 172.42 (C-1), 157.58 (C-2'), 130.95 (C-6'), 128.67 (C-4'), 123.07 (C-1'), 120.59 (C-5'), 110.56
(C-3'), 55.52 (-OMe), 51.98 (-COOMe), 35.83 (C-2).
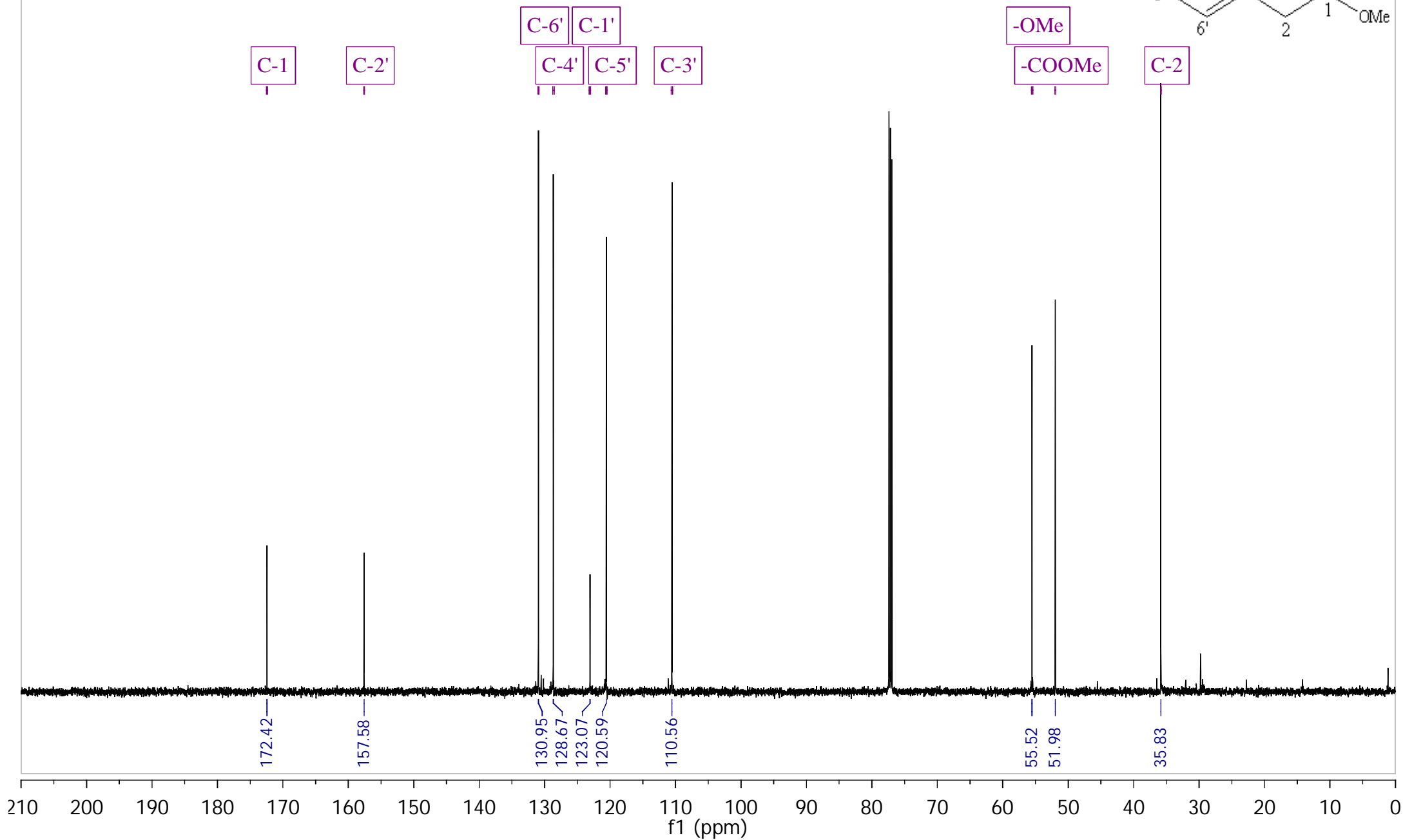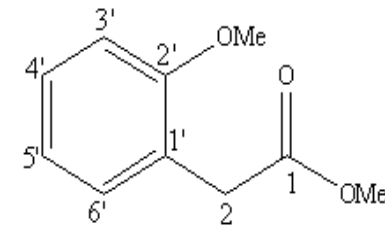
Plate 29c; HSQC [CDCl₃]: Methyl 2'-methoxyphenyl acetate (**480**)
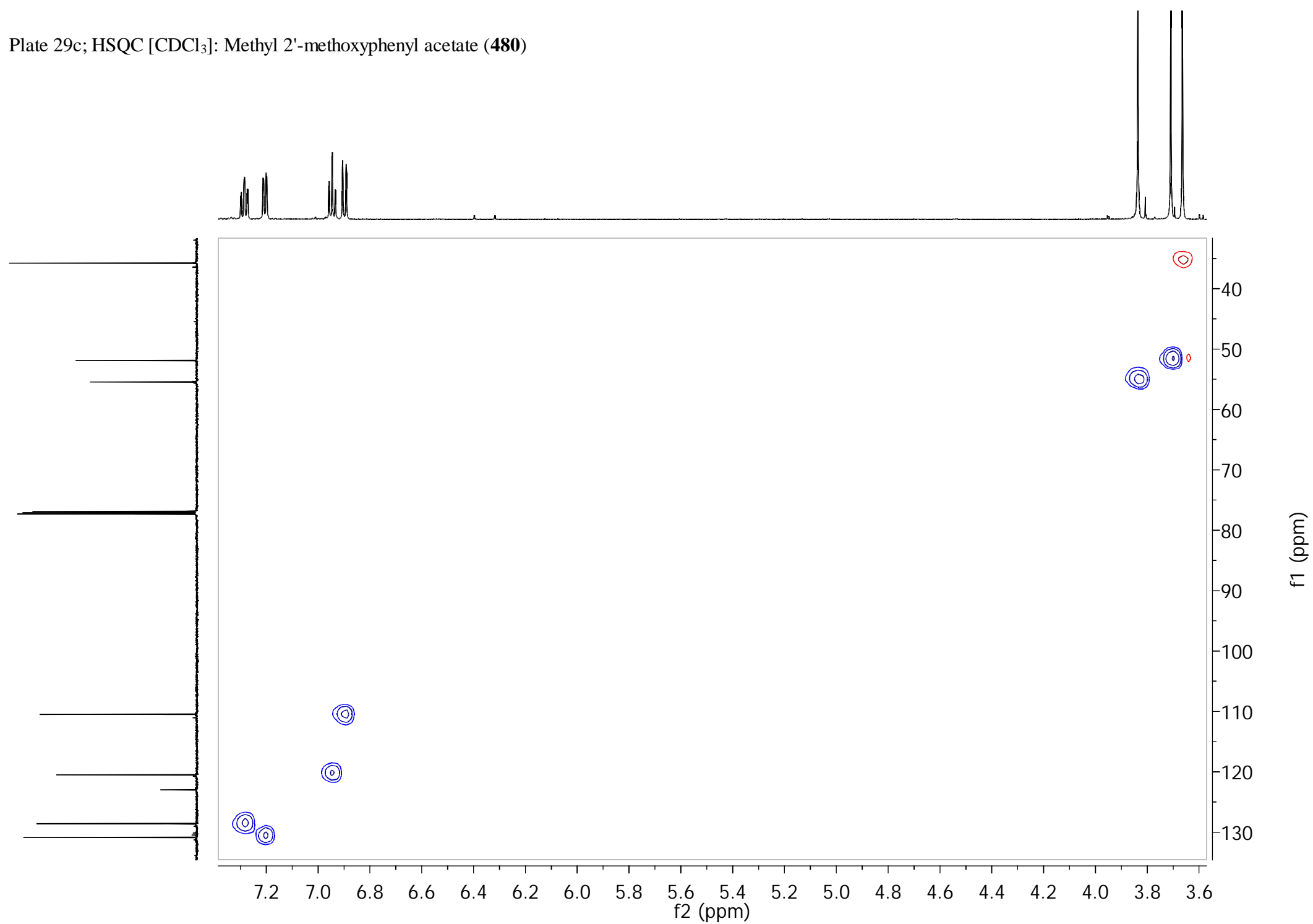
Plate 29d; HMBC [CDCl$_3$]: Methyl 2'-methoxyphenyl acetate (**480**)
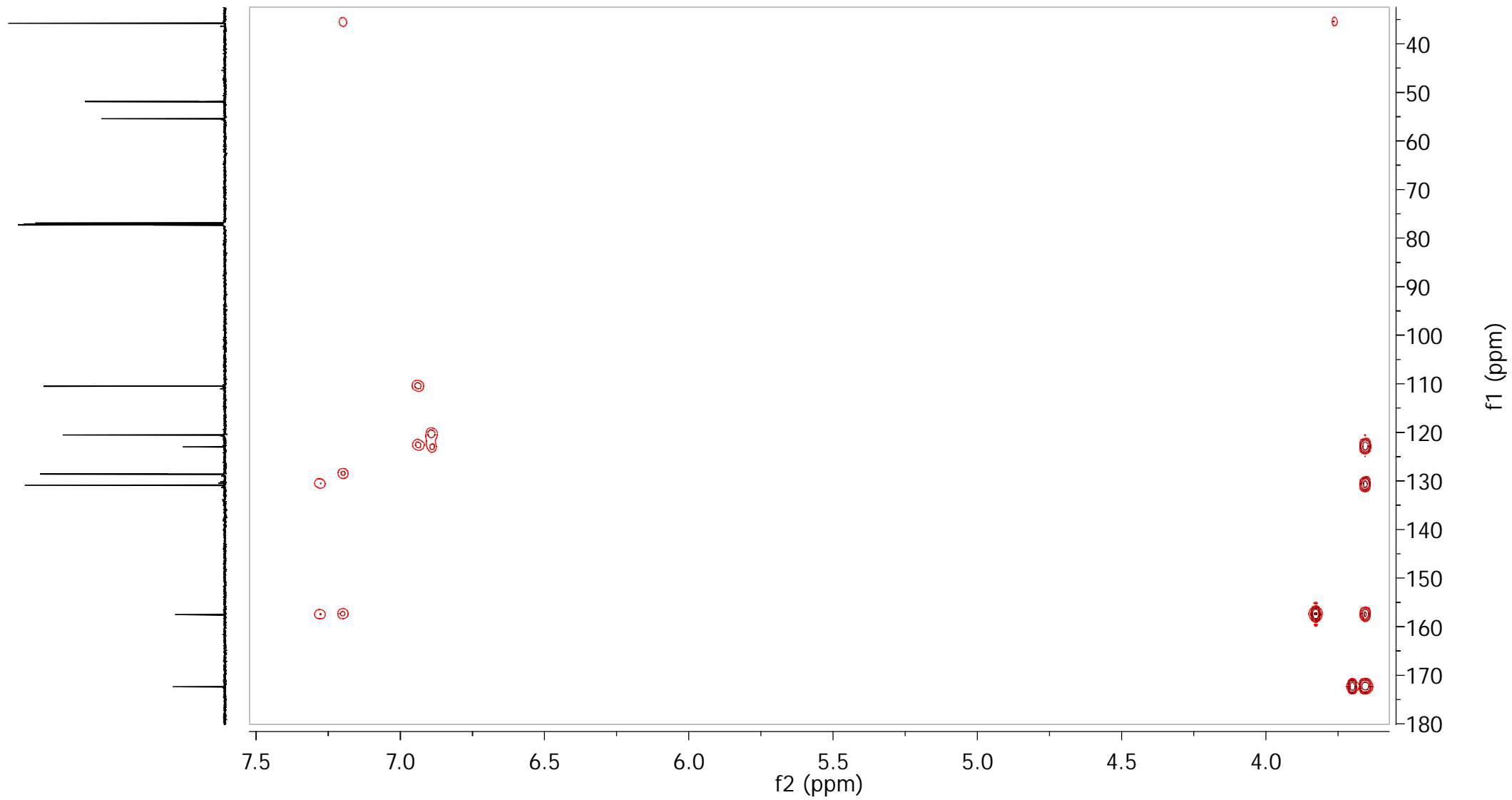
Plate 30a; ¹H NMR [CDCl₃]: Methyl 4'-methoxyphenyl acetate (**481**)
δ 7.20 (2H, d, *J* = 8.76 Hz, H-2' and H-6'), 6.86 (2H, d, *J* = 8.76 Hz, H-3' and H-5'),
3.79 (3H, s, -OMe), 3.68 (3H, s, -COOMe), 3.57 (2H, s, H-2).
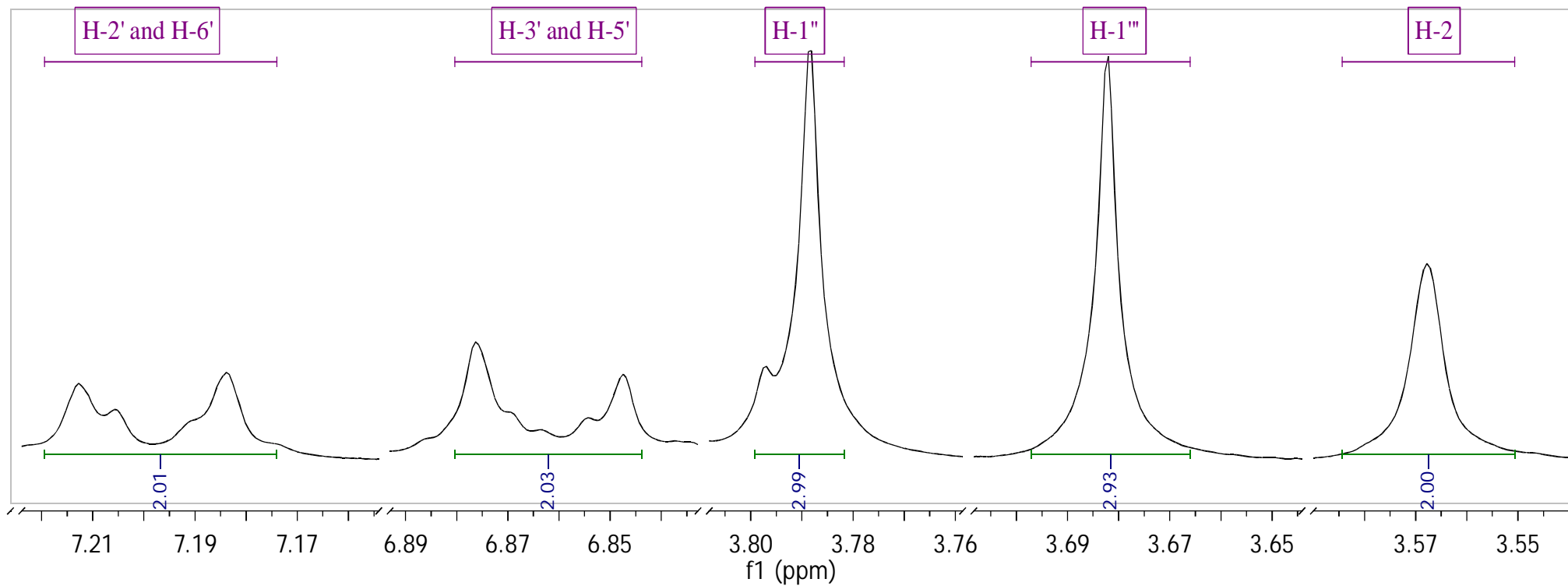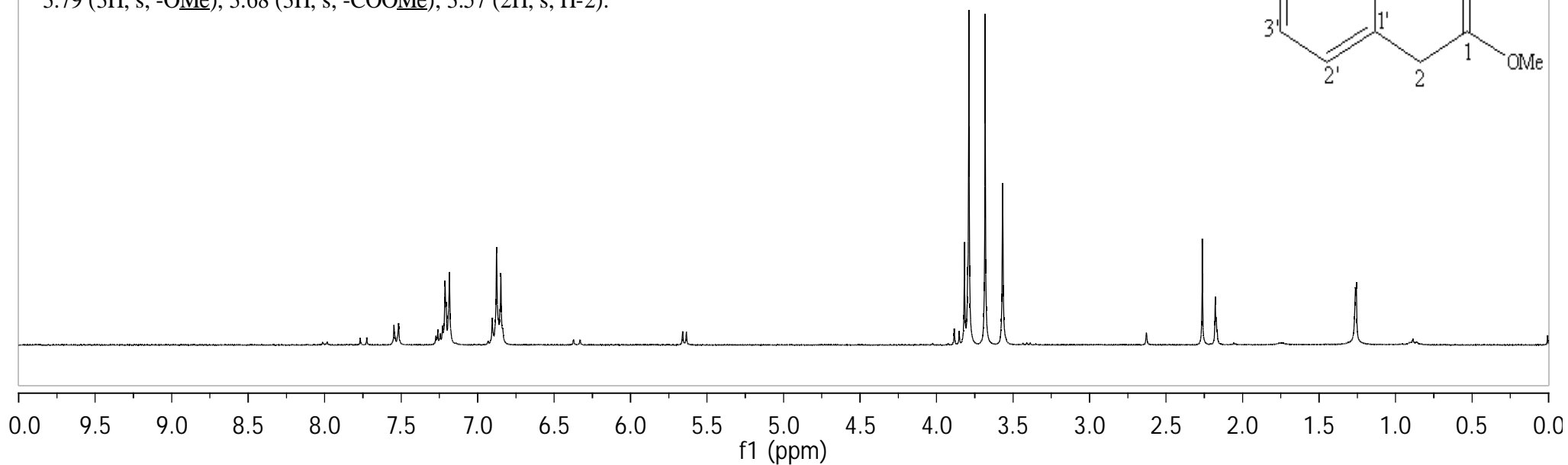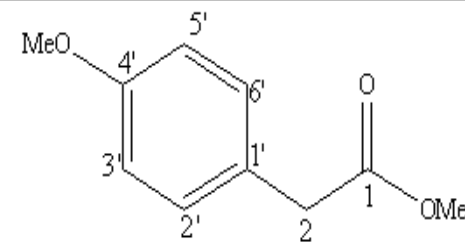
Plate 31a; ^{1}H NMR [CDCl$_3$]: Methyl 4'-trifluoromethylphenyl acetate (**482**)
δ 7.59 (2H, d, J = 8.21 Hz, H-3' and H-5'), 7.40 (2H, d, J = 8.21 Hz, H-2' and H-6'),
3.71 (3H, s, -COOMe), 3.69 (2H, s, H-2).


H-3' and H-5'

H-2' and H-6'
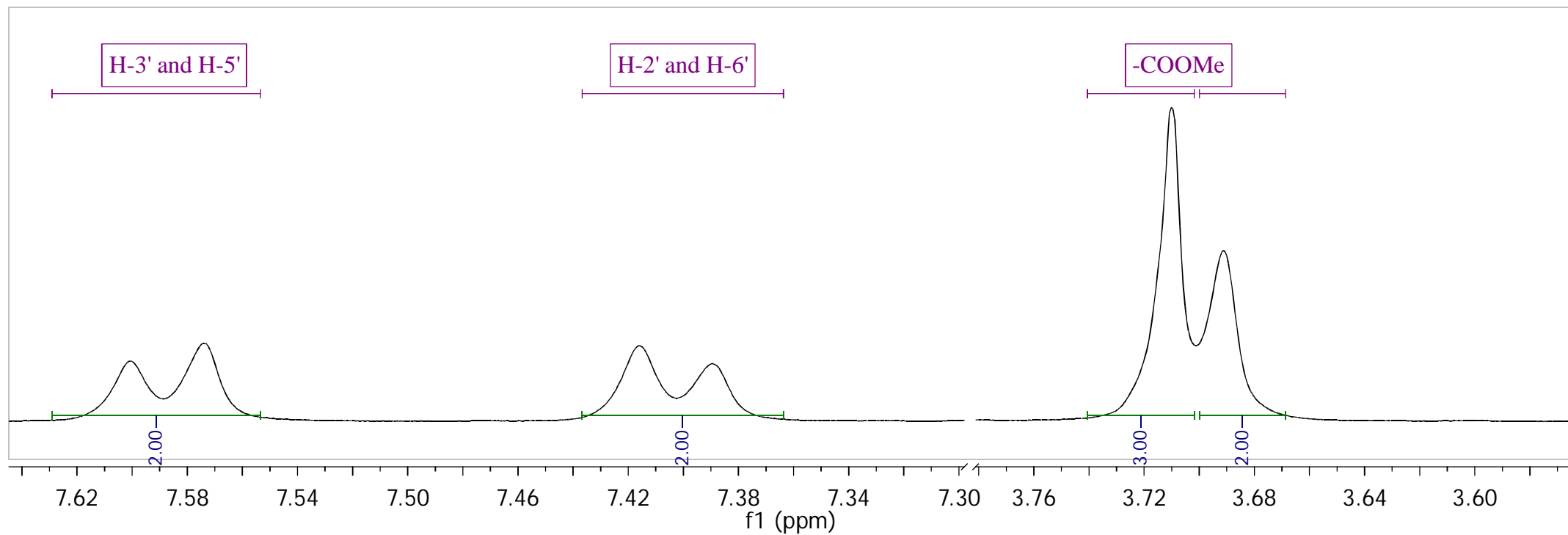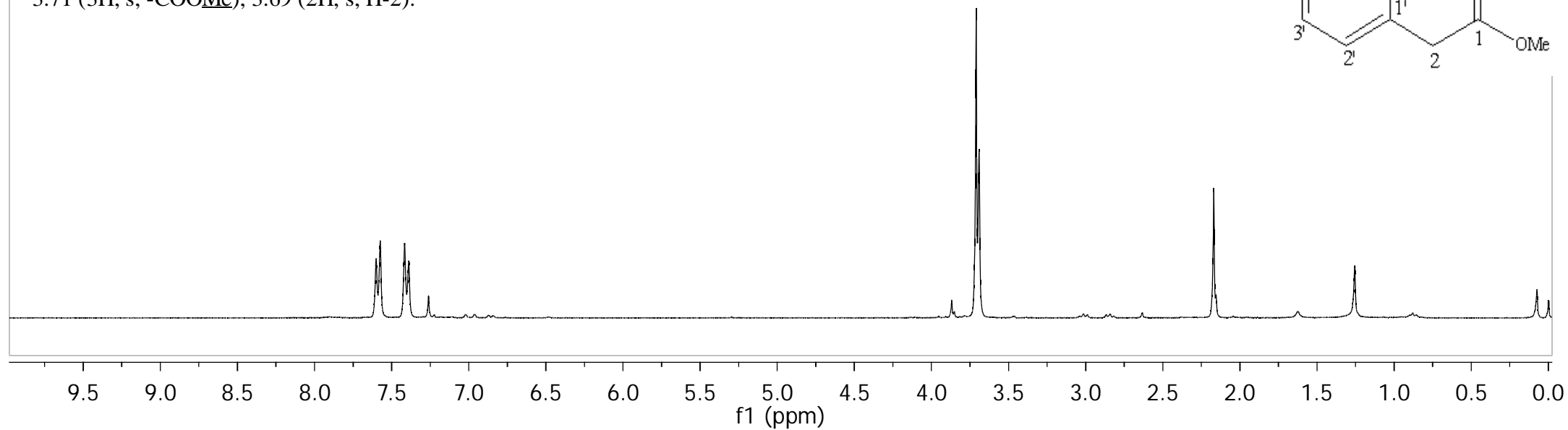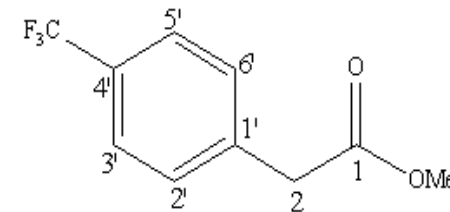
-COOMe

Plate 32a; ^{1}H NMR [CDCl$_3$]: Methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate

(**483**)

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).
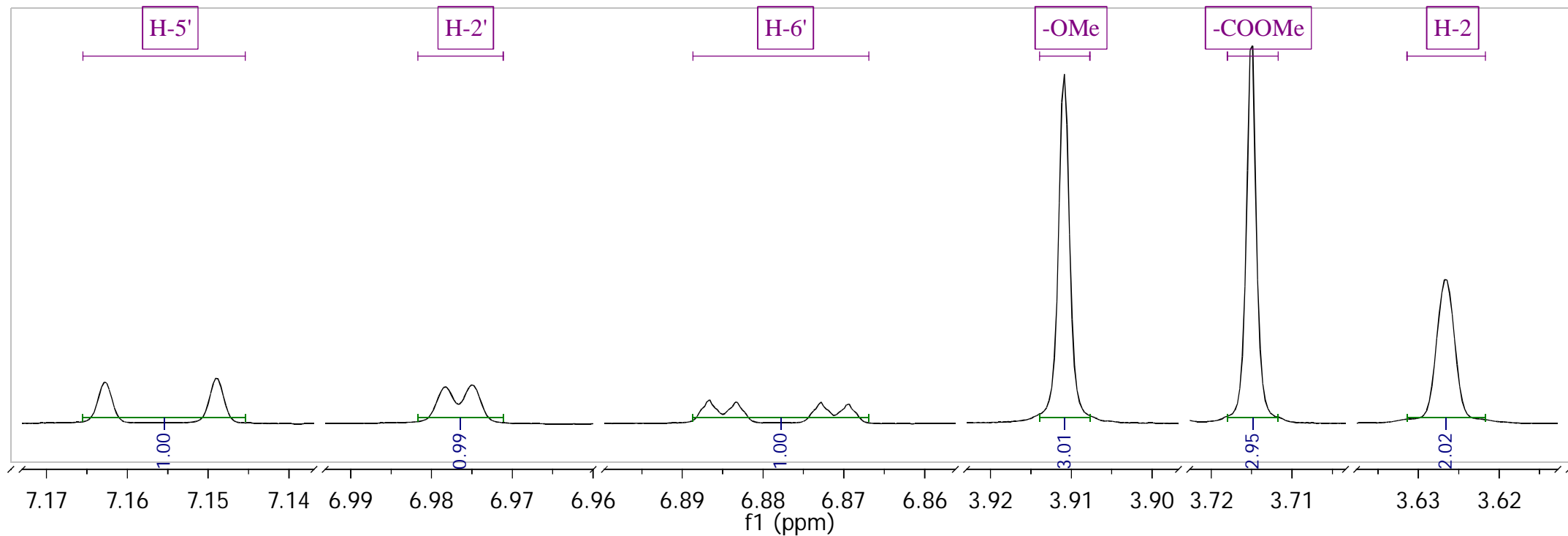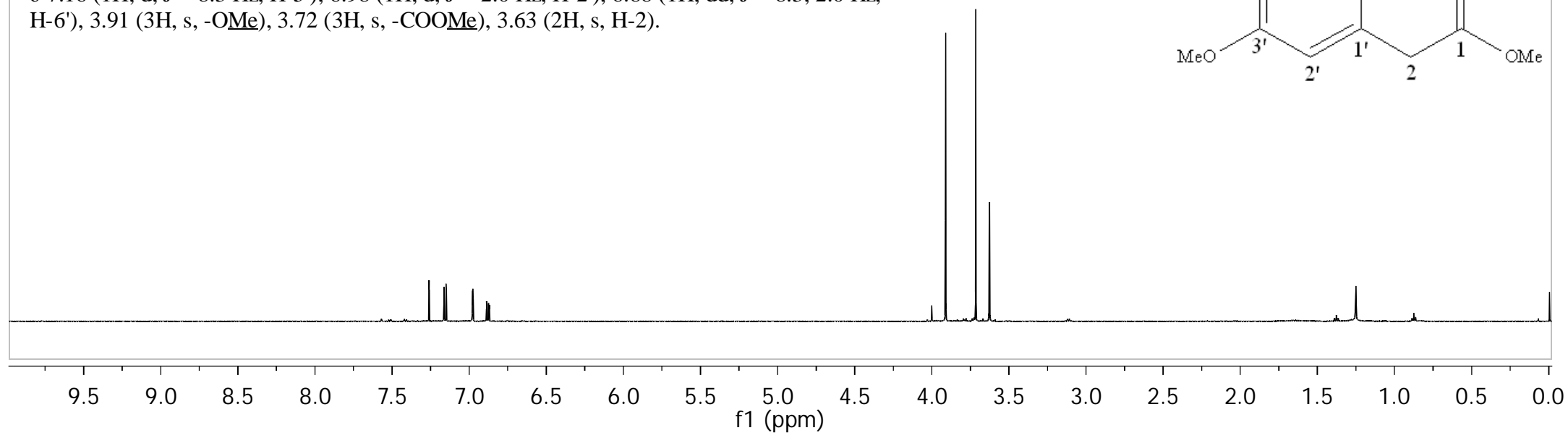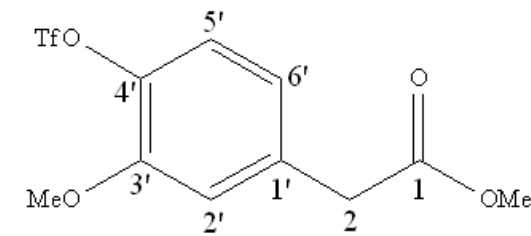
Plate 32b; ^{13}C NMR [CDCl$_3$]: Methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate (**483**)
δ 171.38 (C-1), 151.41 (C-3'), 137.99 (C-1'), 135.57 (C-4'), 122.52 (C-5'), 121.83 (C-6'), 117.78
(q, J = 319.92 Hz, -OSO$_2$CF$_3$), 114.30 (C-2'), 56.33 (-OMe), 52.43 (-COOMe), 41.01 (C-2).
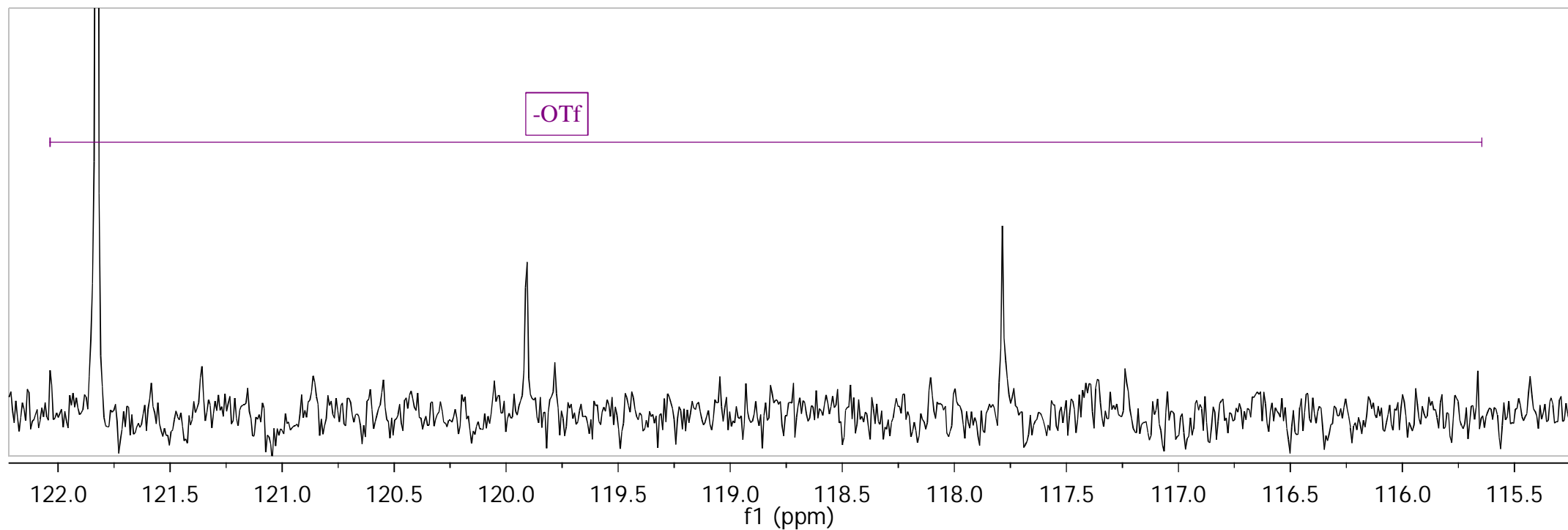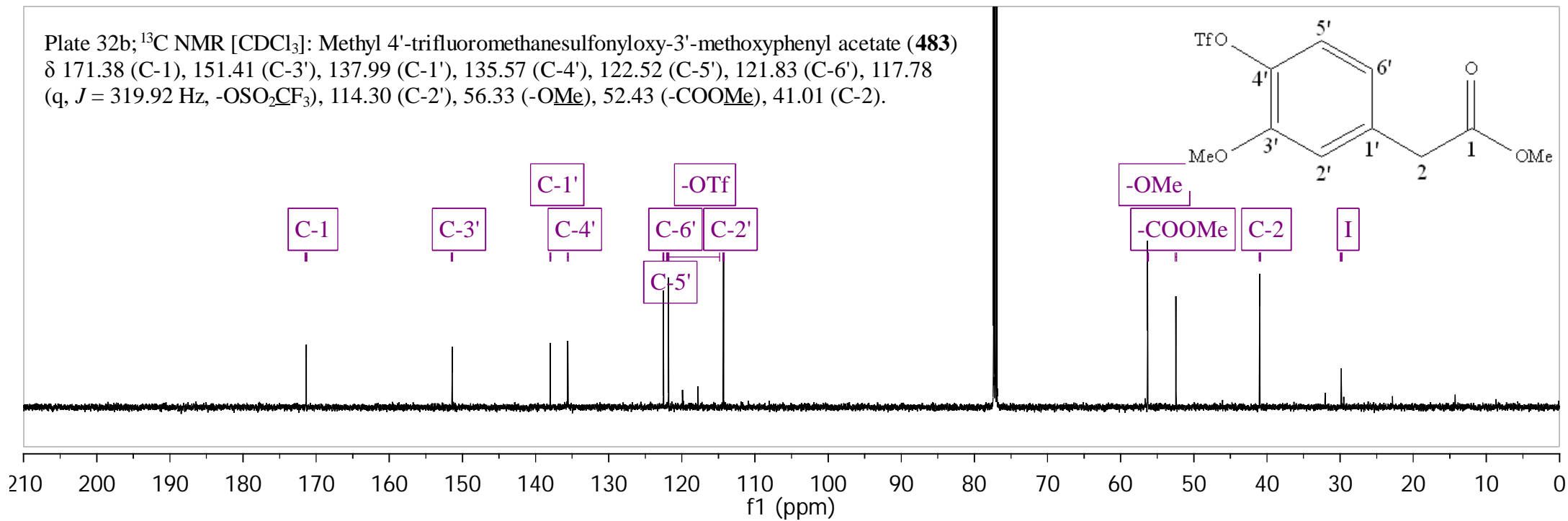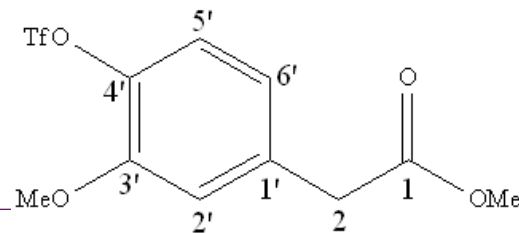
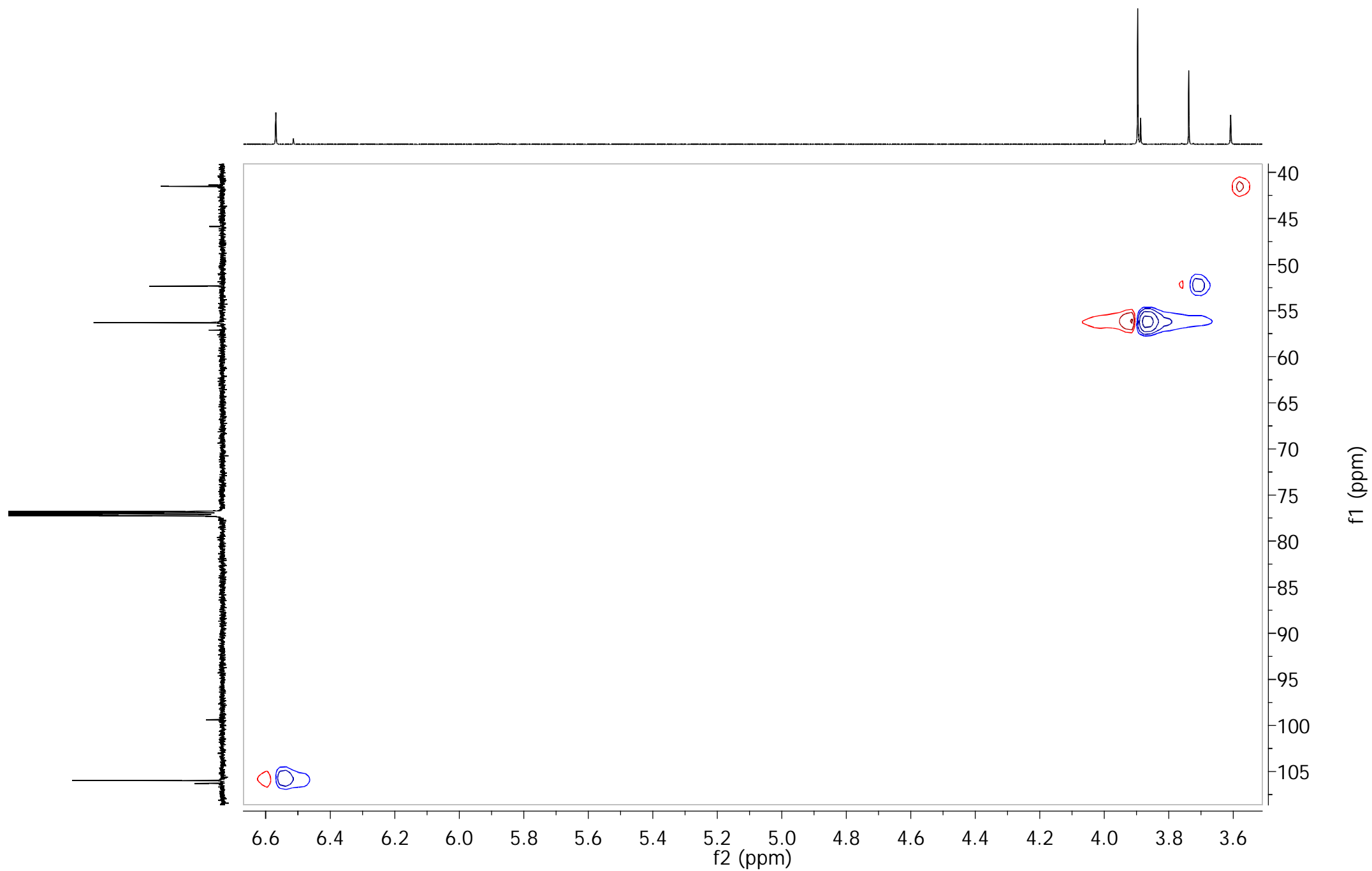Plate 32c; HSQC [CDCl$_3$]: Methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate (**483**)
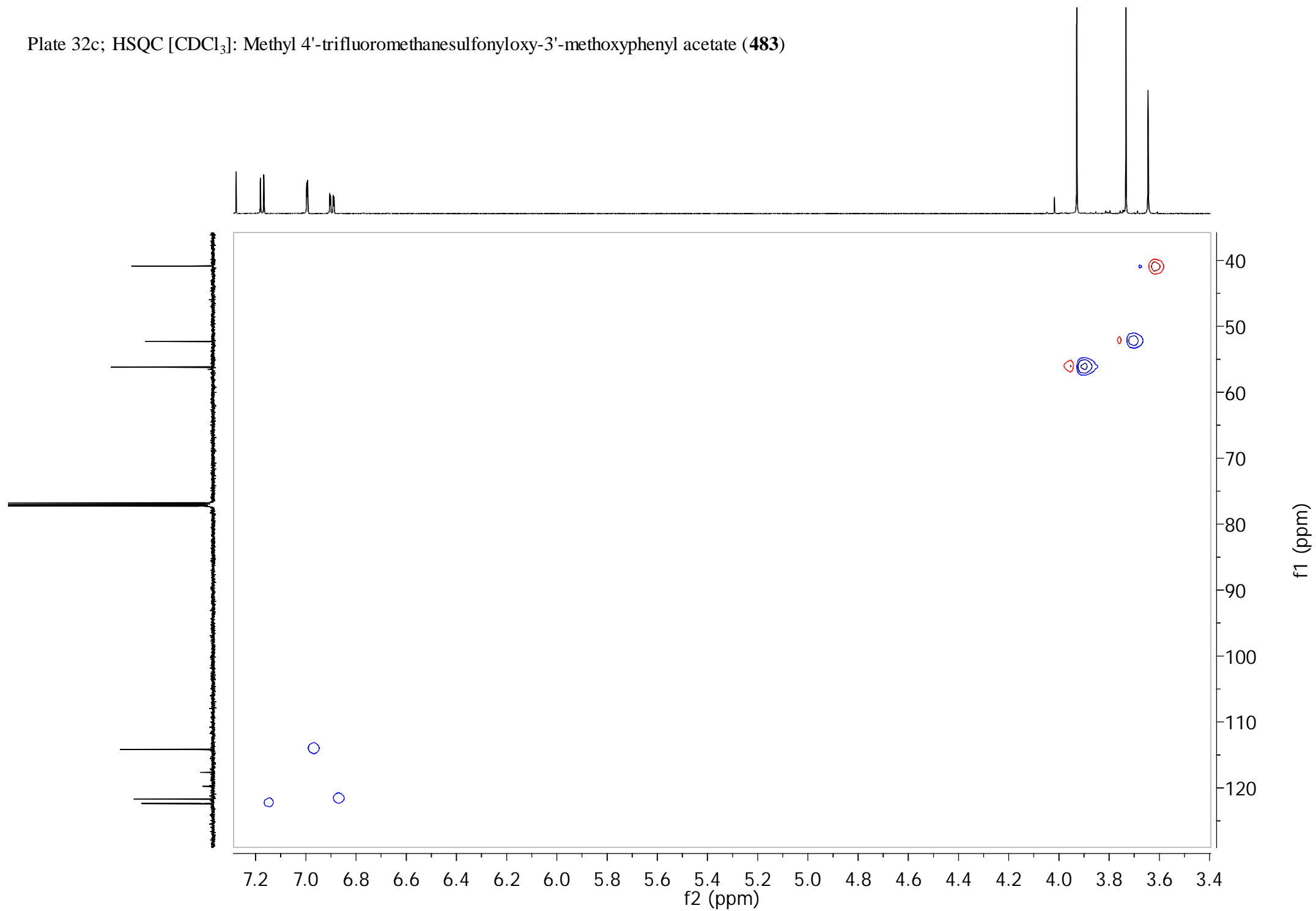
Plate 32d; HMBC [CDCl$_3$]: Methyl 4'-trifluoromethanesulfonyloxy-3'-methoxyphenyl acetate (**483**)
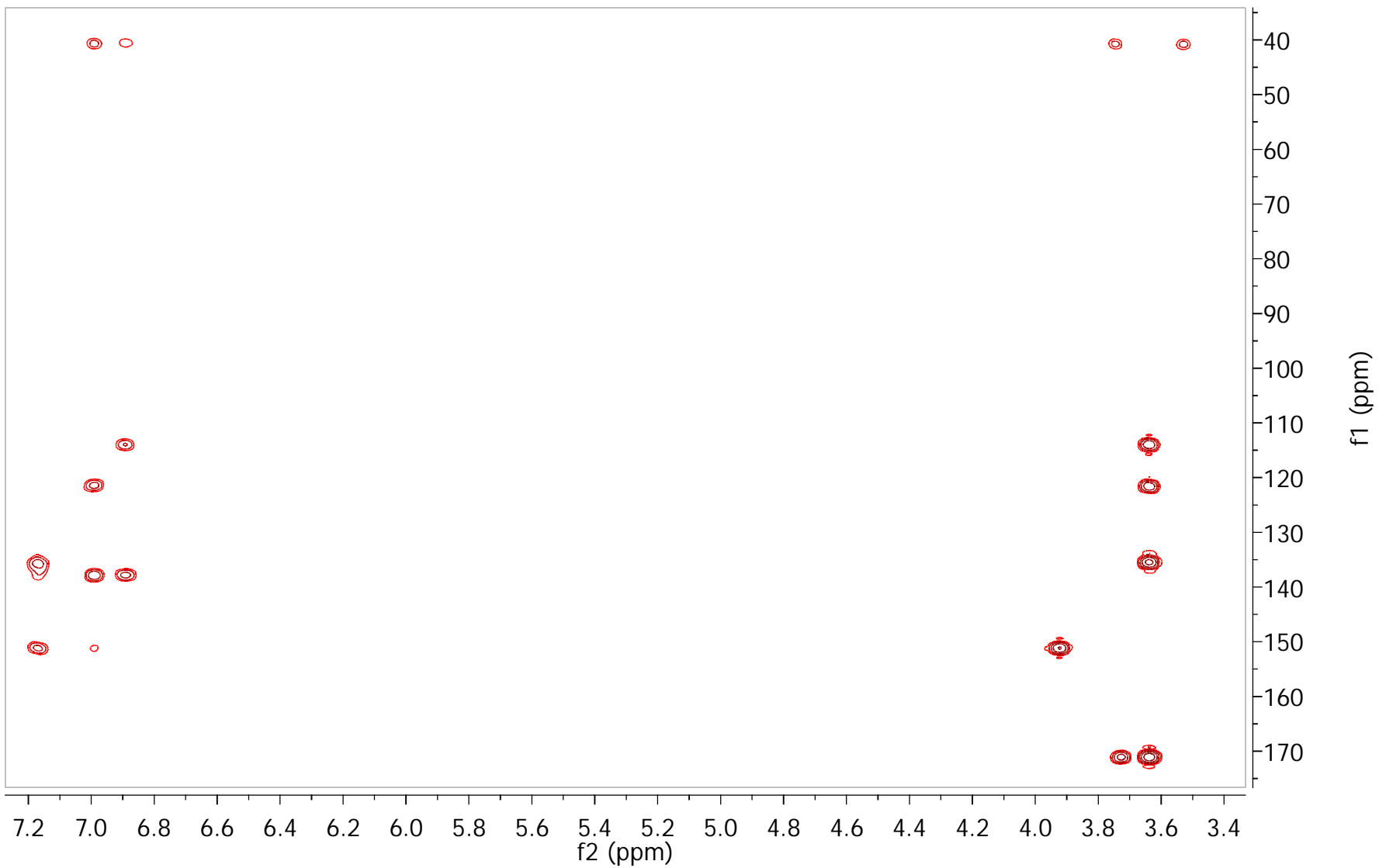
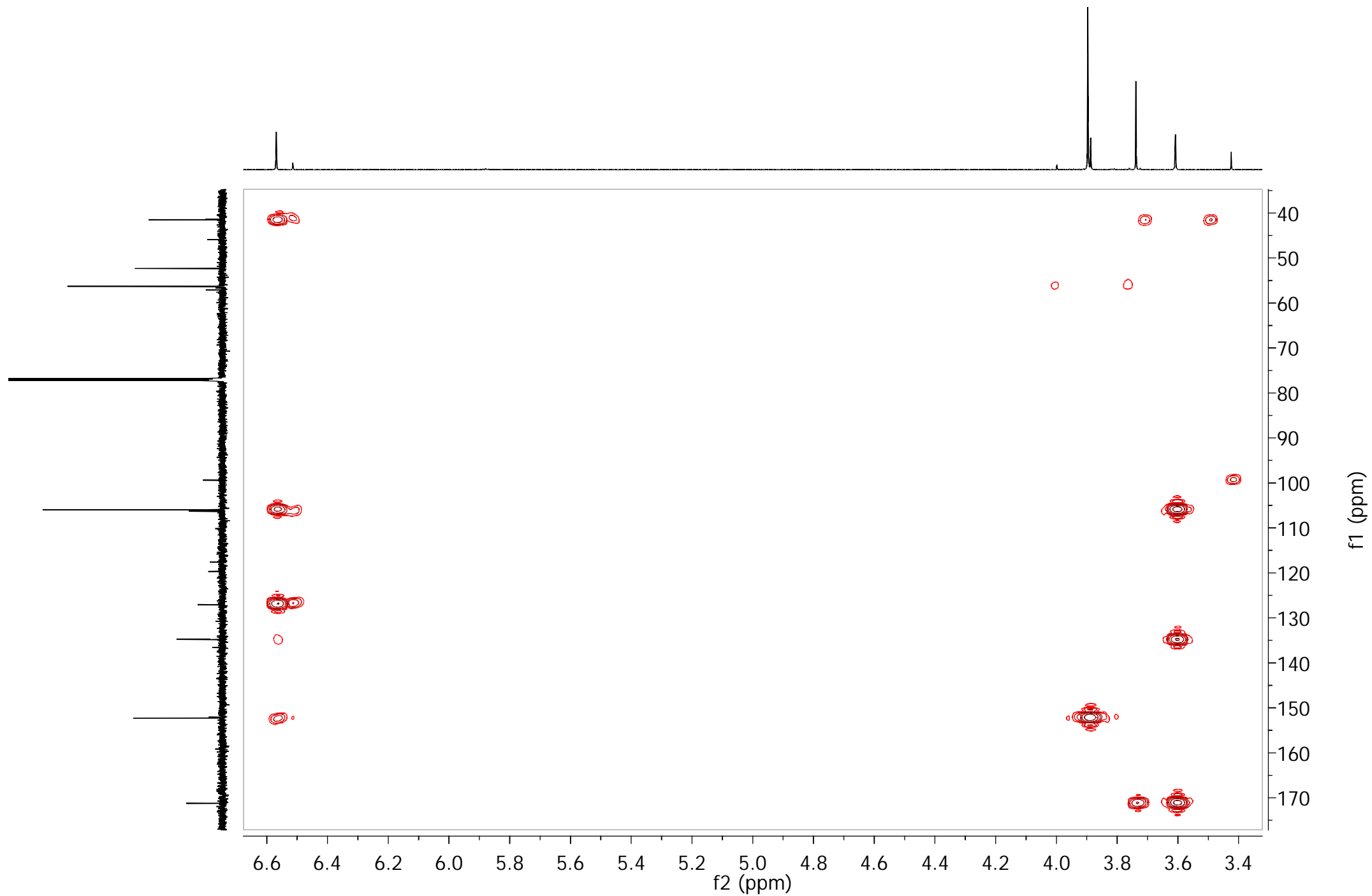Plate 33a; ^{1}H NMR [CDCl$_3$]: Methyl 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl acetate (**484**)
δ 6.55 (2H, s, H-2' and H-6'), 3.88 (6H, s, -O<u>Me</u>), 3.72 (3H, s, -COO<u>Me</u>), 3.59 (2H, s, H-2).
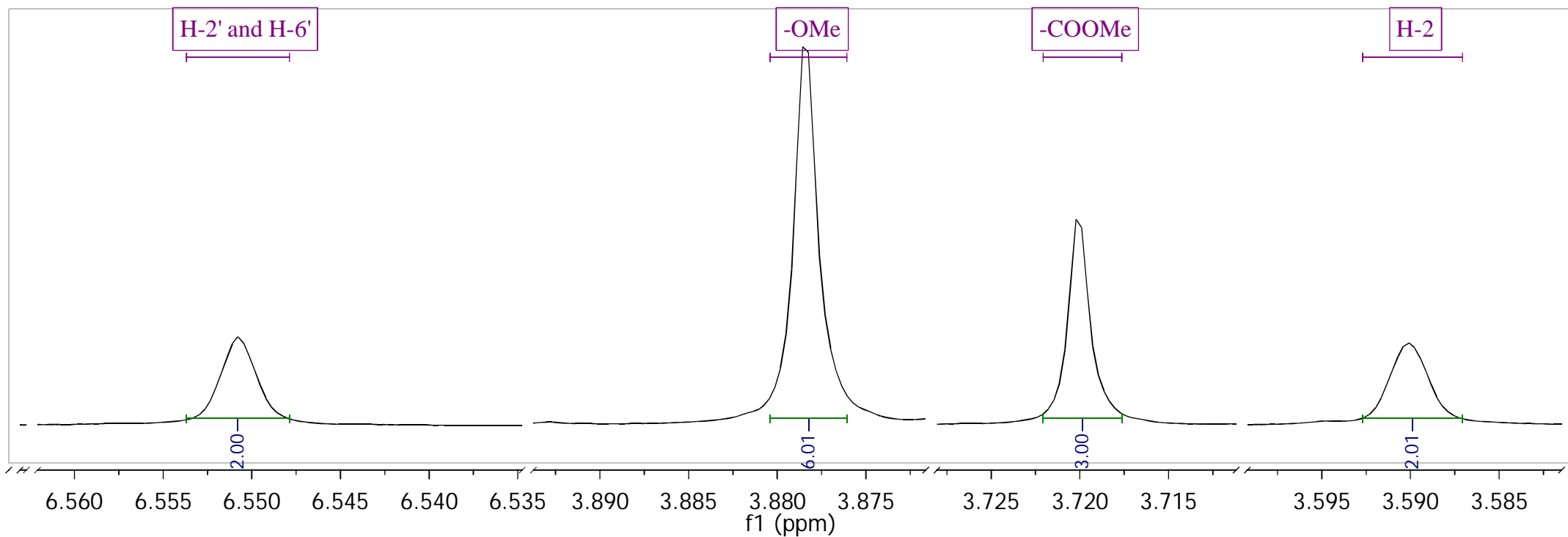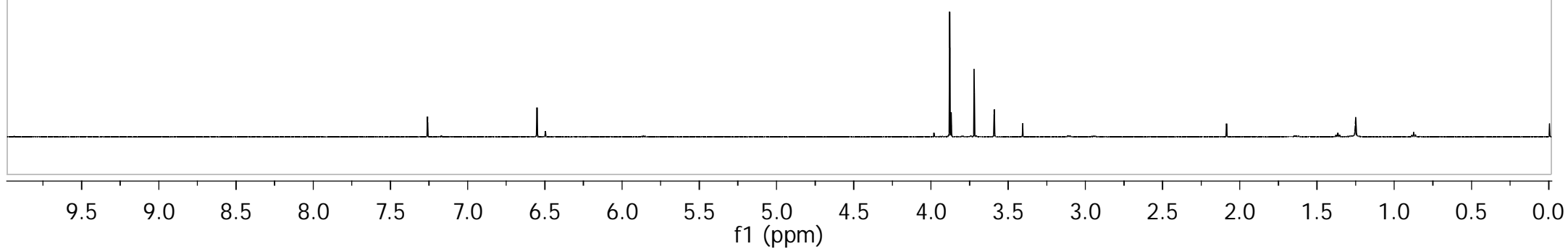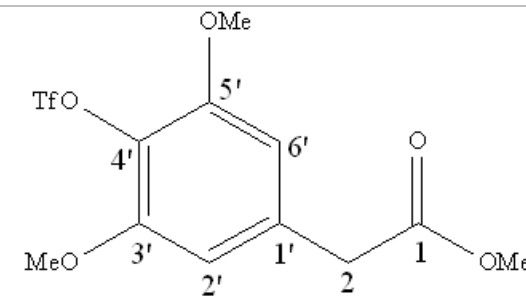
Plate 33b; ^{13}C NMR [CDCl$_3$]: methyl 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl acetate
(**484**)
δ 171.37 (C-1), 152.43 (C-3' and C-5'), 134.94 (C-1'), 127.19 (C-4'), 118.93 (q, J = 320.19 Hz, -OSO$_2$CF$_3$), 106.10 (C-2' and C-6'), 56.43 (-OMe), 52.46 (-COOMe), 41.65 (C-2).
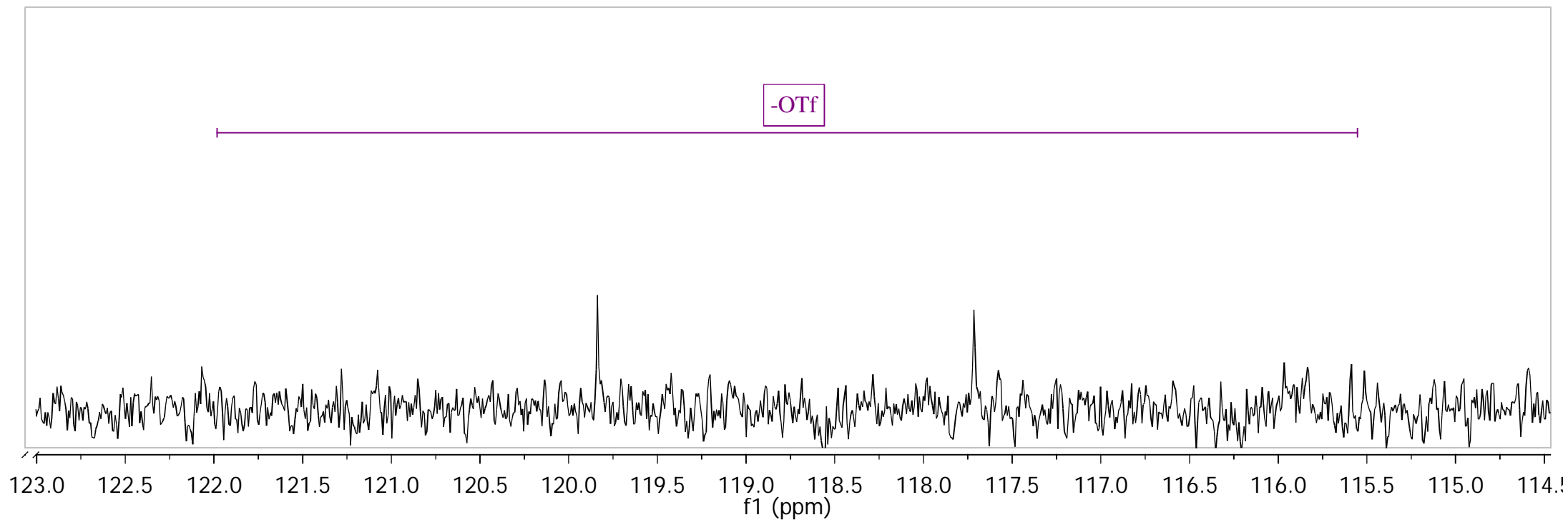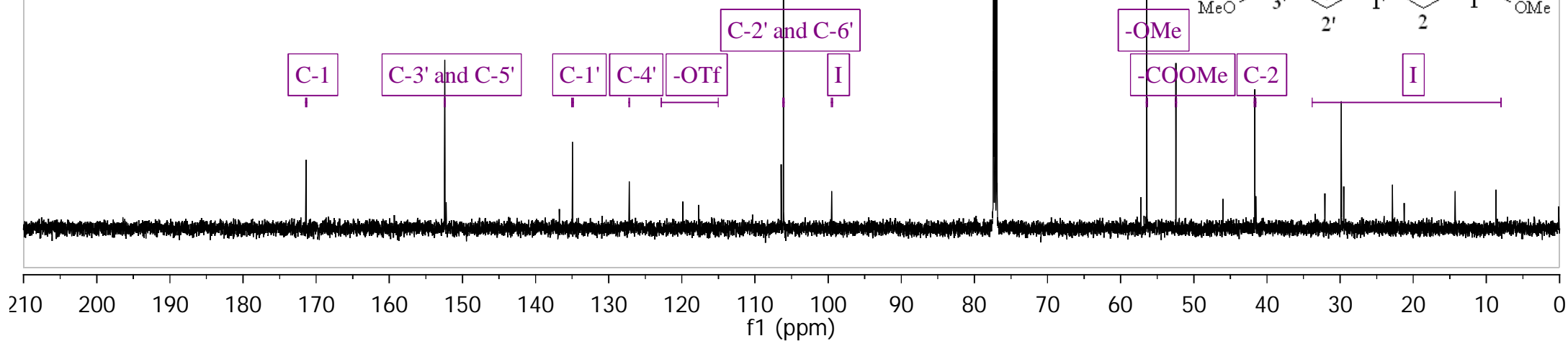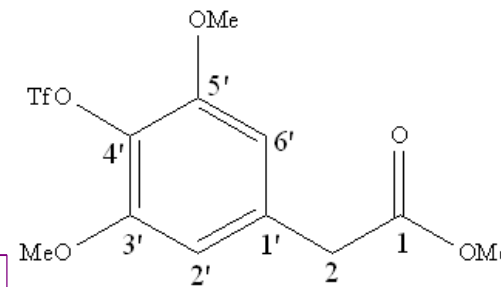
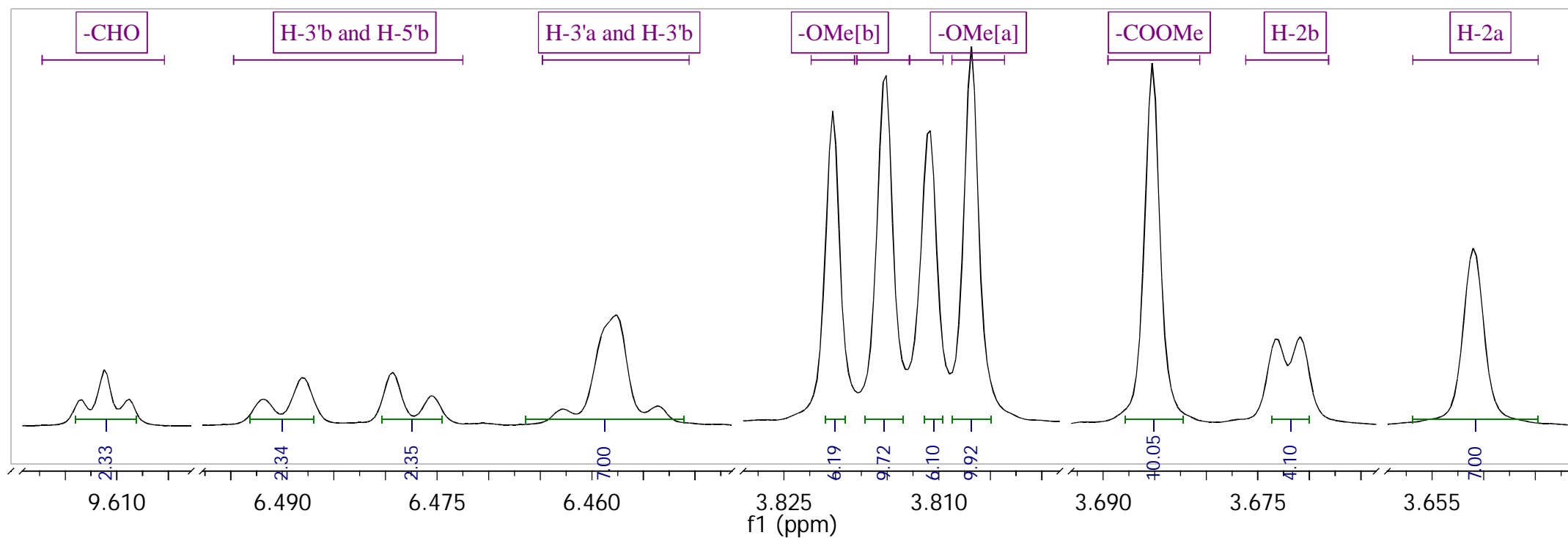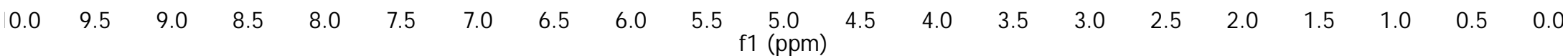Plate 33d; HMBC [CDCl$_3$]: Methyl 4'-trifluoromethanesulfonyloxy-3',5'-dimethoxyphenyl acetate (**484**)
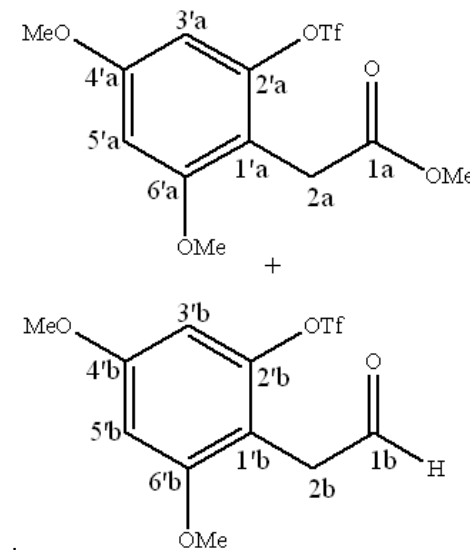
Plate 34a; ¹H NMR [CDCl₃]: Methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate (**485**) and 2'- trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
δ 9.61 (2H, t, *J* = 1.4 Hz, -C<u>H</u>O), 6.49 (2H, d, *J* = 2.3 Hz, H-3'b/5'b), 6.48 (2H, d, *J* = 2.3 Hz, H-3'b/5'b), 6.46–6.45 (7H, m, H-3'a/5'a), 3.82 (6H, s, -O<u>Me</u>[b]), 3.82 (10H, s, -O<u>Me</u>[a]), 3.81 (6H, s, -O<u>Me</u>[b]), 3.81 (10H, s, -O<u>Me</u>[a]), 3.69 (10H, s,-COO<u>Me</u>), 3.67 (4H, d, *J* = 1.4 Hz, H-2b), 3.65 (7H, s, H-2a)

Plate 34b; ^{13}C NMR [CDCl$_3$]: Methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate
(**485**) and 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
δ 198.16 (-CHO), 170.97–148.90 (quaternary carbons), 129.94 (q, J = 320.19 Hz, -OSO$_2$CF$_3$), 119.68
(q, J = 320.19 Hz, -OSO$_2$CF$_3$), 109.27–108.24 (quaternary carbons), 98.40 (C-3'a, C-5'a, C-3'b and
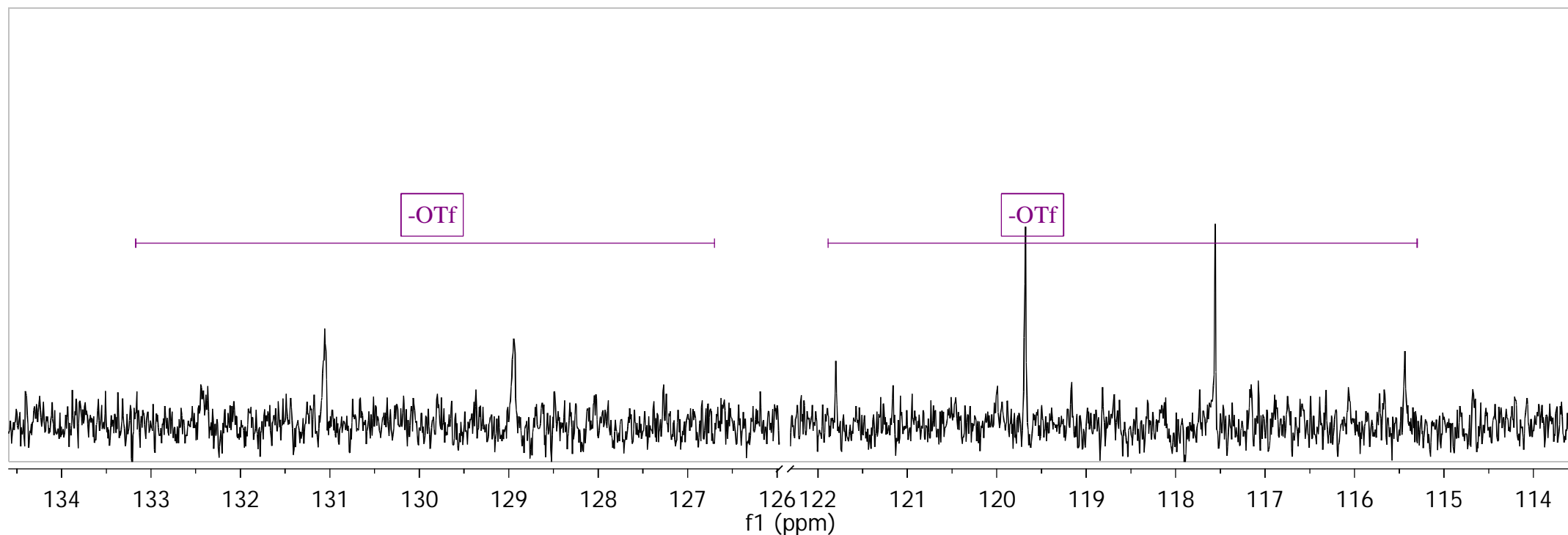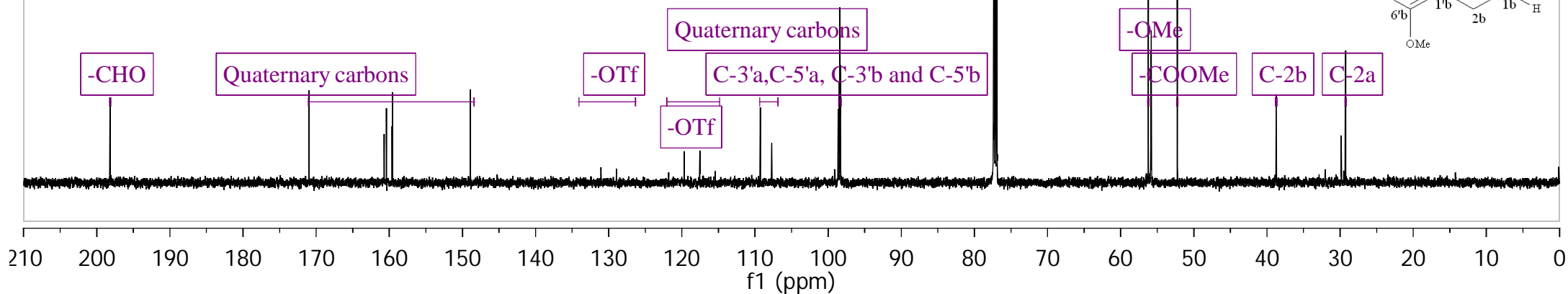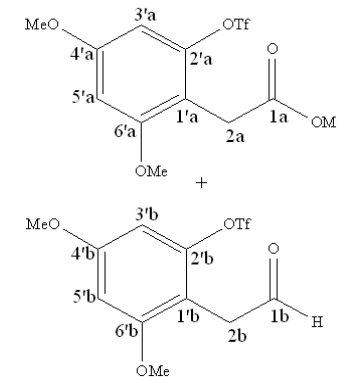C-5'b), 56.23–55.63 (-OMe), 52.24 (-COOMe), 38.74 (C-2b), 29.26 (C-2a).

Plate 34c; HSQC [CDCl$_3$]: Methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate (**485**) and
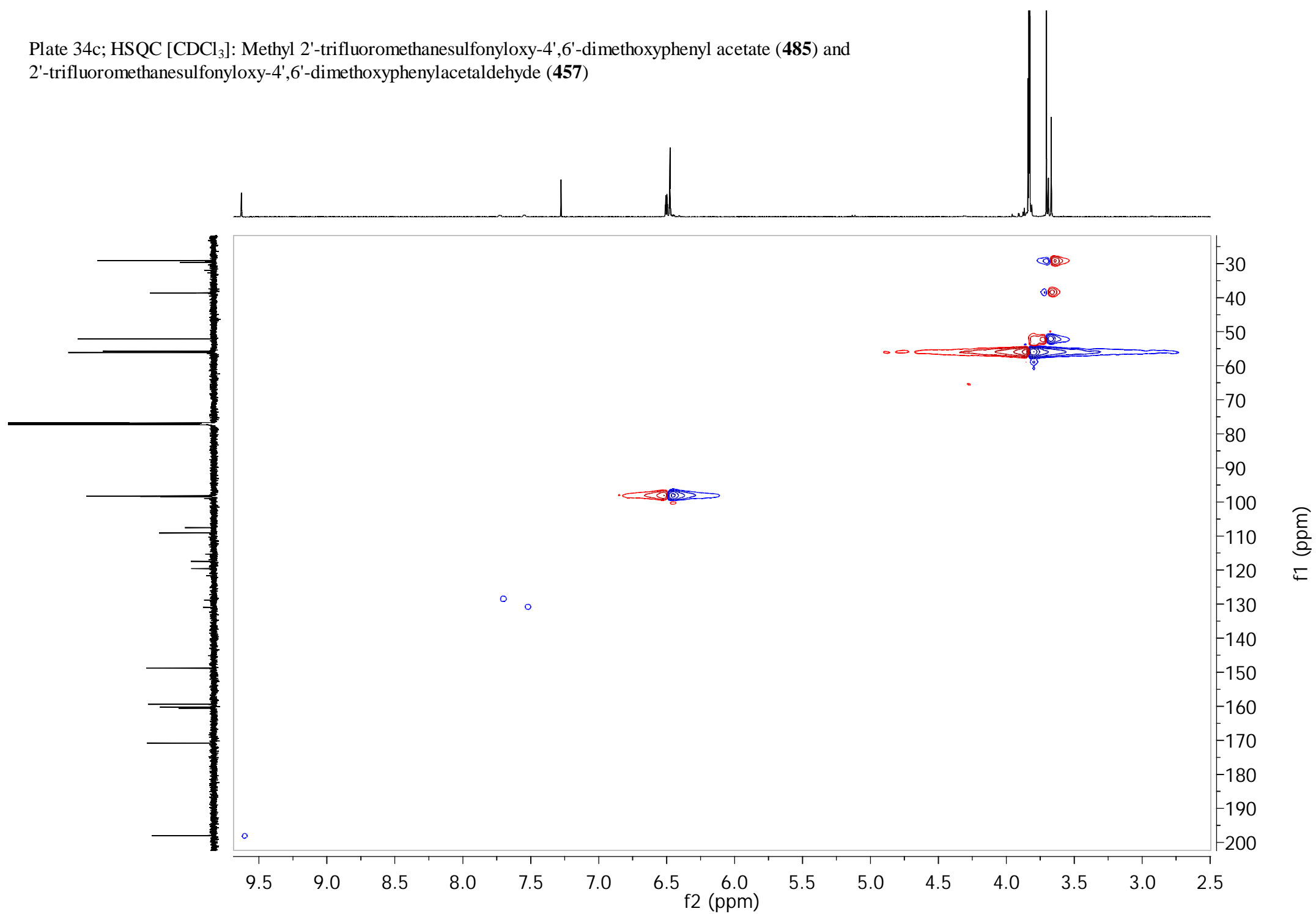2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)

Plate 34d; HMBC [CDCl$_3$]: Methyl 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenyl acetate
(**485**) and 2'-trifluoromethanesulfonyloxy-4',6'-dimethoxyphenylacetaldehyde (**457**)
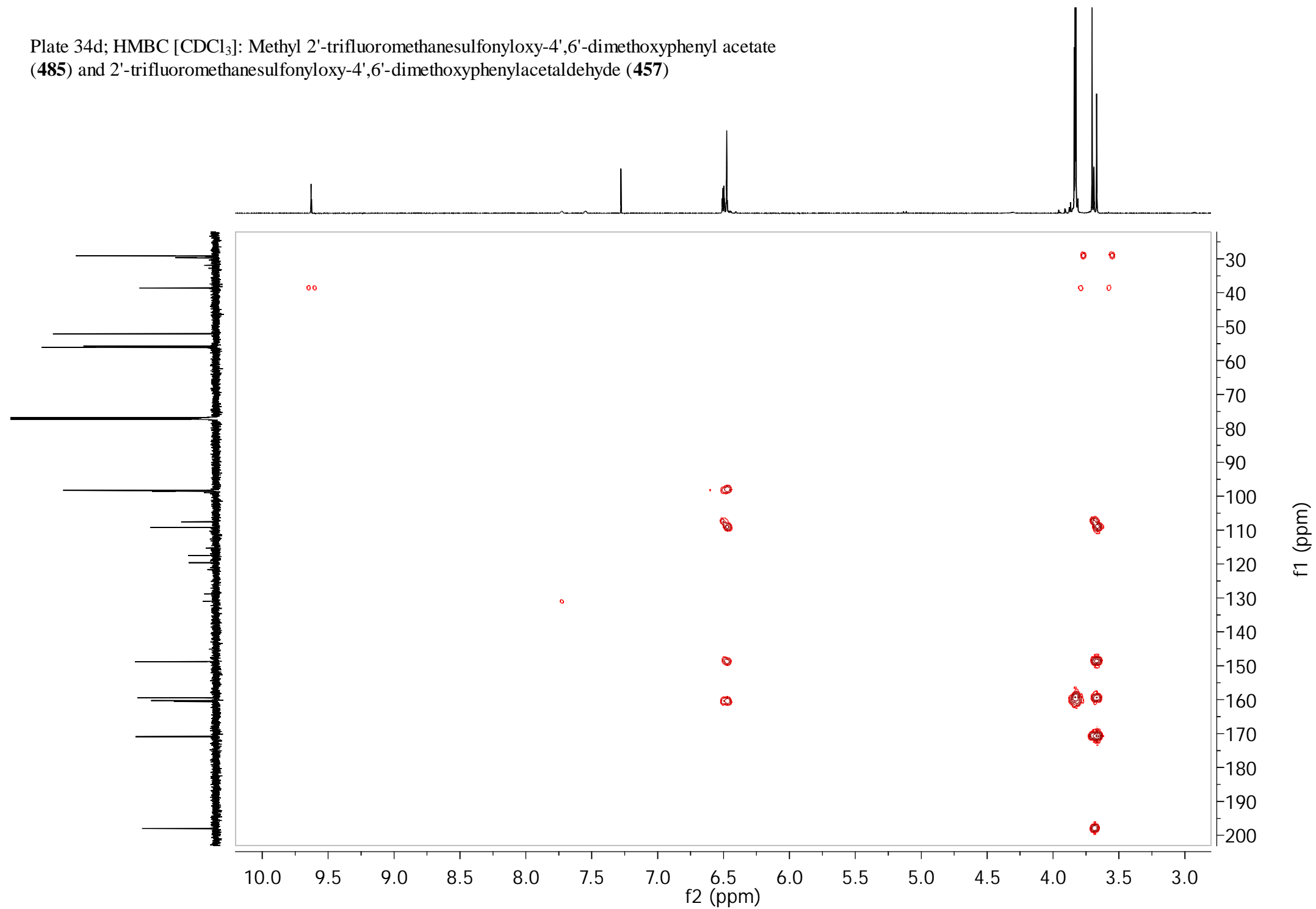
Plate 35a; ^{1}H NMR [CDCl$_3$]:
2-(2'-Methoxyphenyl)-*N*-
phenylacetamide (**497**)
δ 7.42–7.27 (6H, m, Ar-H), 7.07–7.04
(1H, m, H-4'), 6.99–6.97 (1H, m, H-5'),
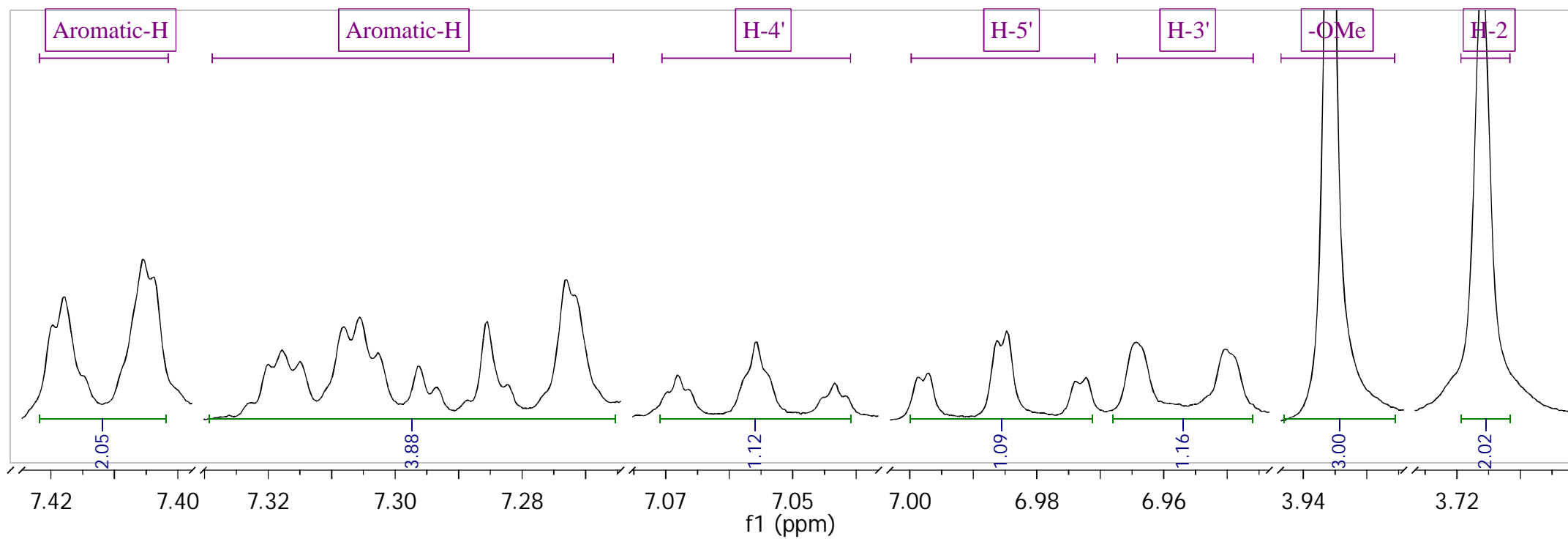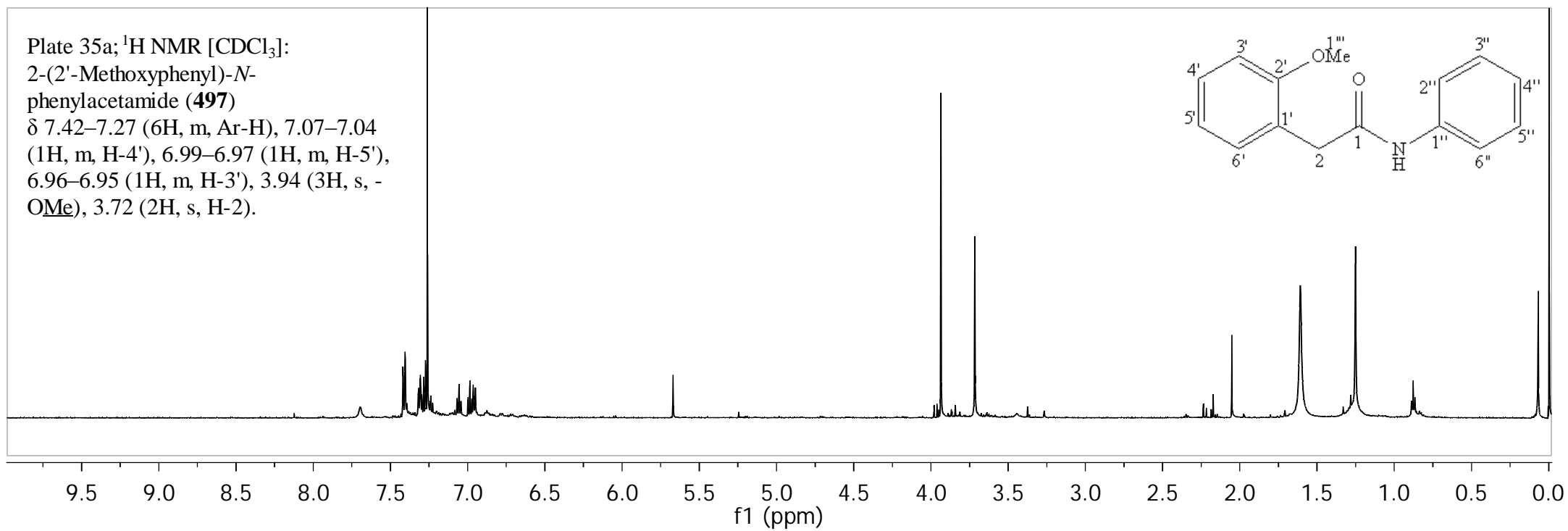6.96–6.95 (1H, m, H-3'), 3.94 (3H, s, -
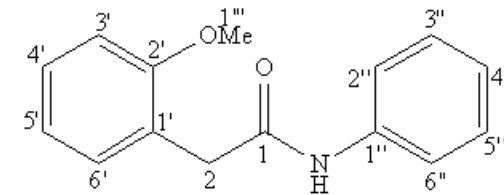O<u>Me</u>), 3.72 (2H, s, H-2).

Aromatic-H | Aromatic-H | H-4' | H-5' | H-3' | -OMe | H-2

2.05 | 3.88 | 1.12 | 1.09 | 1.16 | 3.00 | 2.02

Plate 35b; ^{13}C NMR [CDCl$_3$]: 2-(2'-Methoxyphenyl)-*N*-phenylacetamide (**497**)
δ 169.52 (quaternary carbon), 156.99 (C-2'), 138.19 (quaternary carbon), 131.58 (Ar.-C), 129.23 (Ar.-C), 129.06 (Ar-C), 124.15 (C-4'), 123.40 (quaternary carbon), 121.57 (C-5'), 119.72 (Ar-C), 111.01 (C-3'), 55.72 (-O<u>Me</u>), 40.35 (C-2)
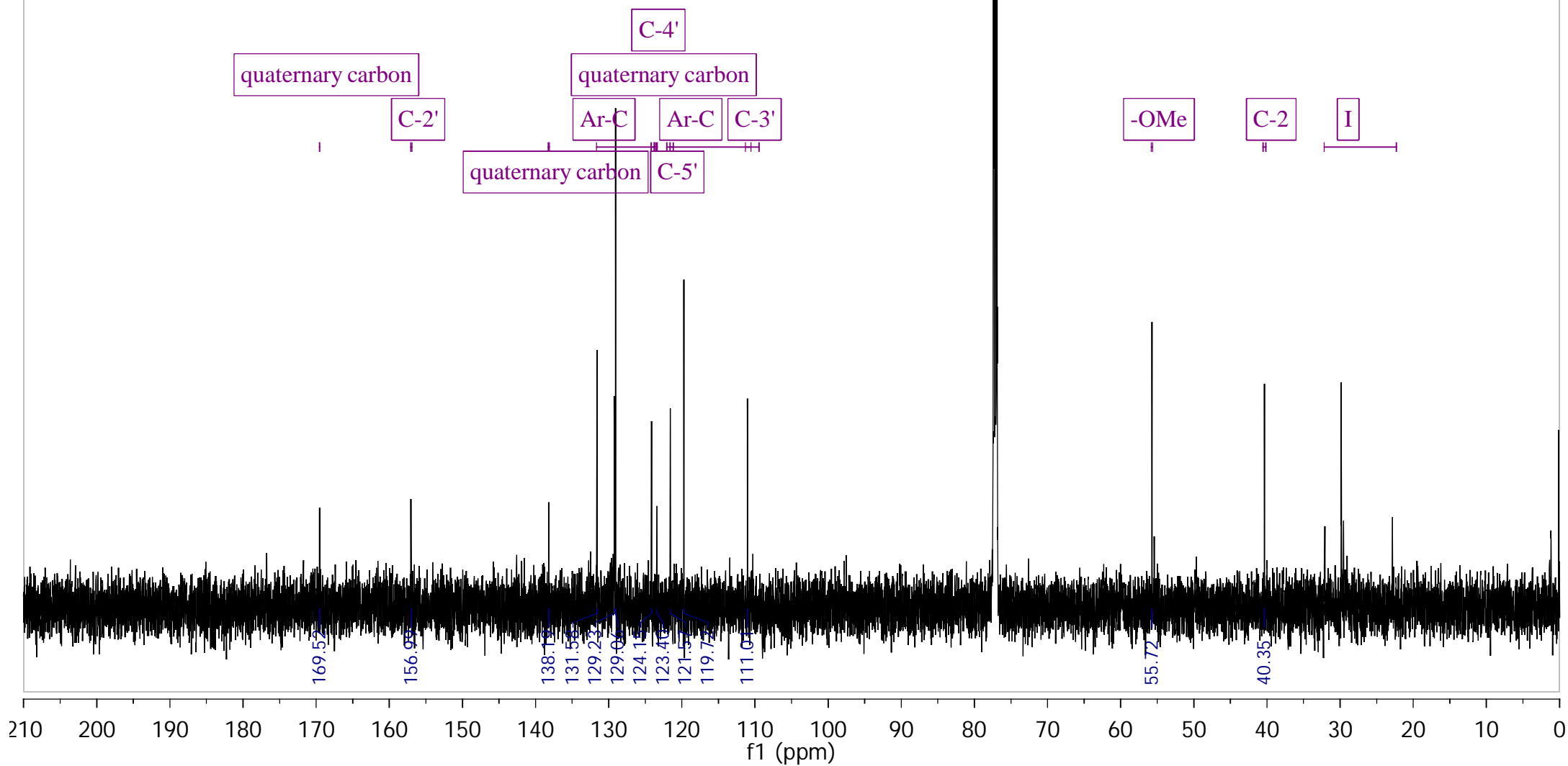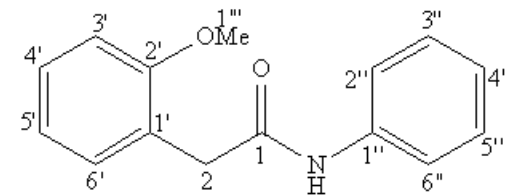
Plate 35c; DEPT [CDCl$_3$]: 2-(2'-Methoxyphenyl)-*N*-phenylacetamide (**497**)
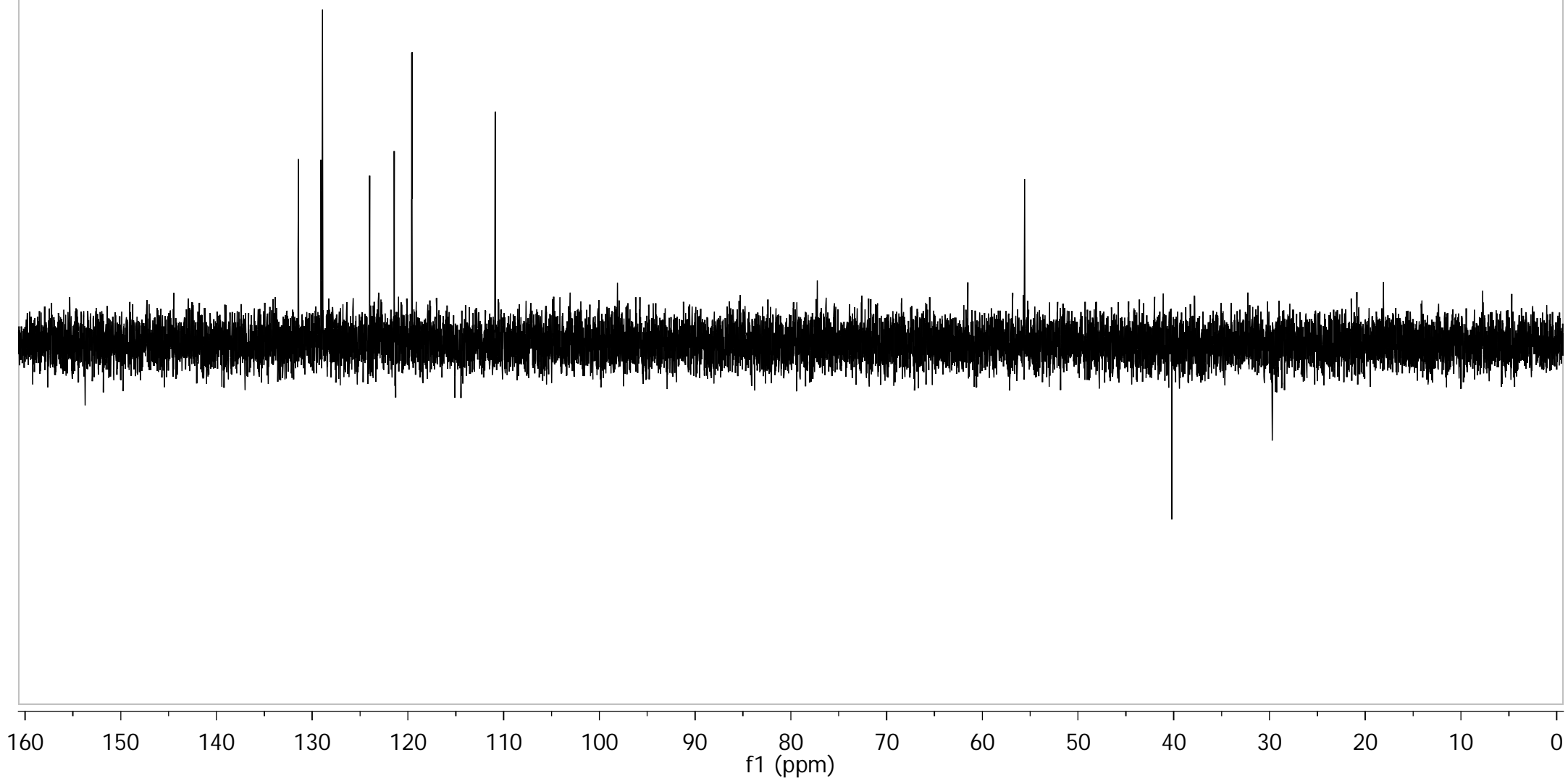
Plate 35d; HSQC [CDCl₃]:
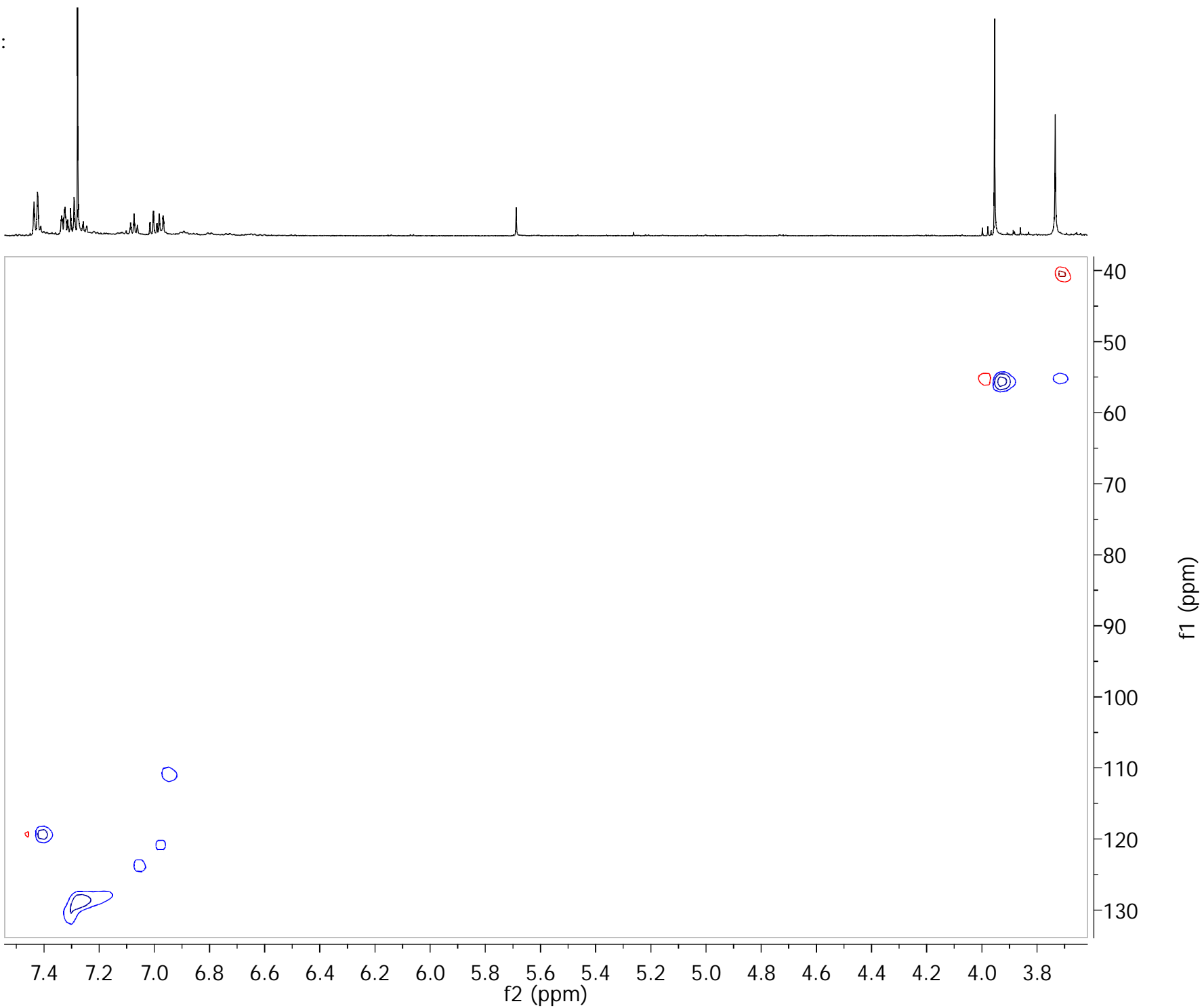2-(2'-Methoxyphenyl)-*N*-phenylacetamide (**497**)

Plate 35e; HMBC [CDCl₃]:
2-(2'-Methoxyphenyl)-*N*-phenylacetamide (**497**)
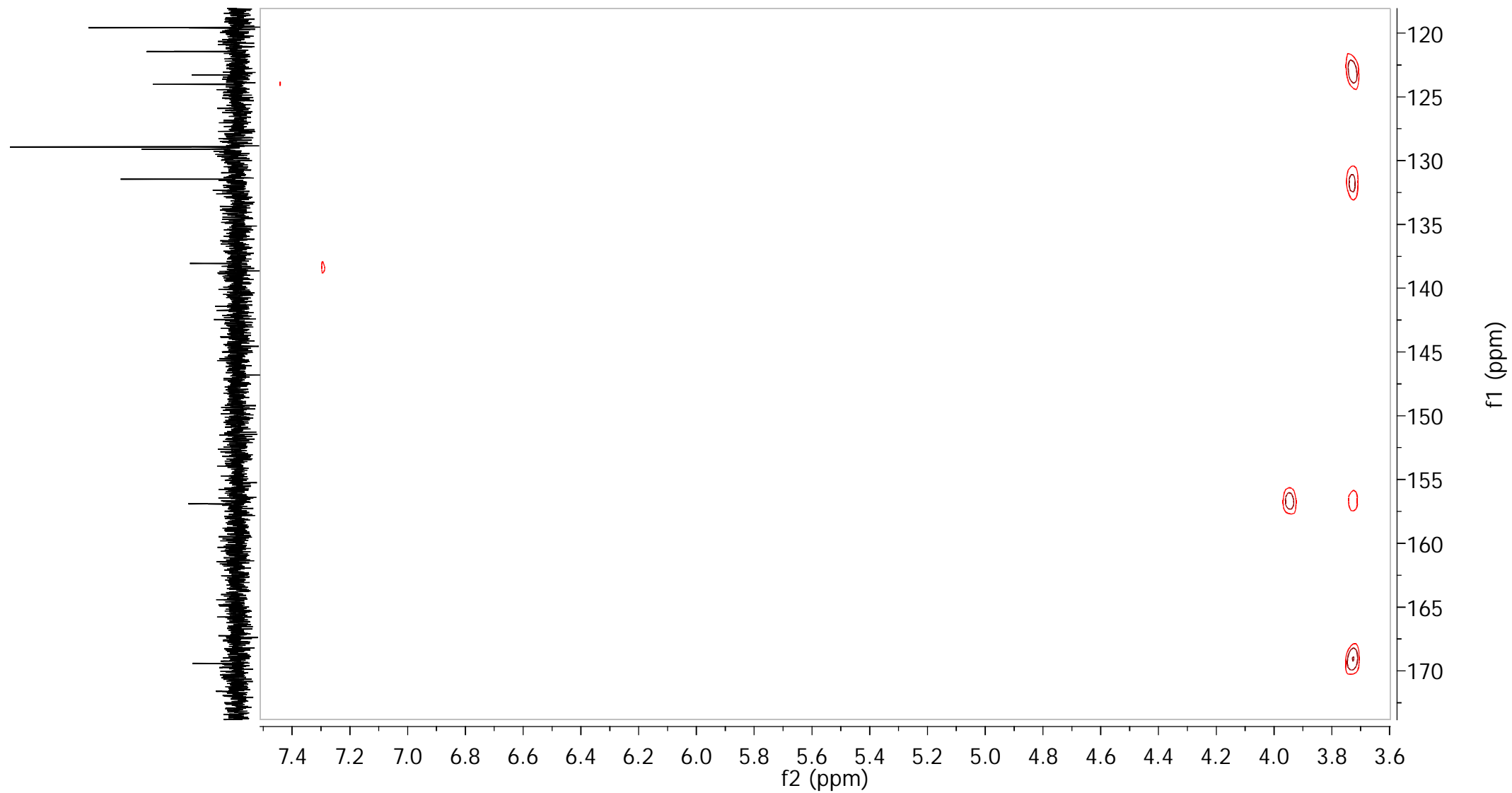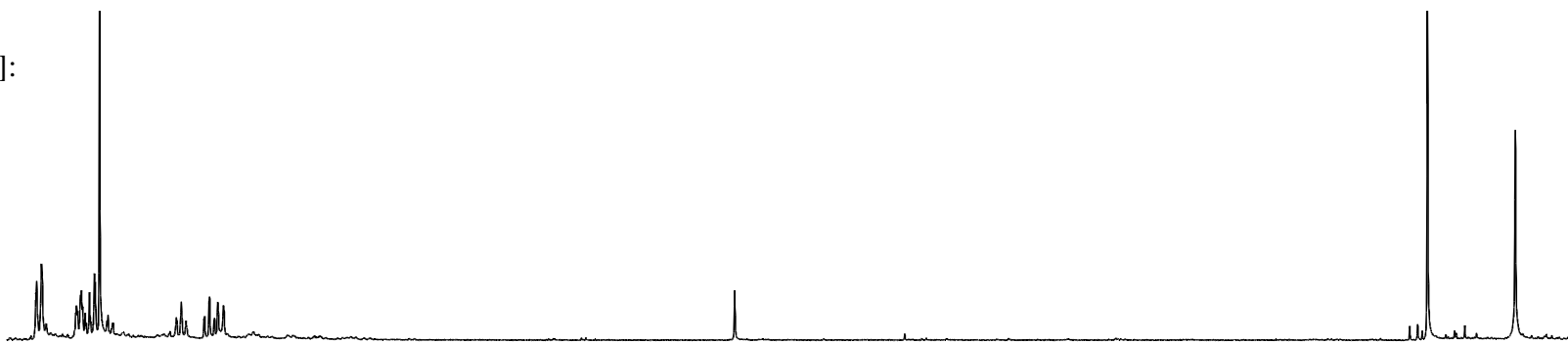
Plate 36a; ¹H NMR [CDCl₃]: *N*-acetyl-2-(4'-methoxyphenyl)acetamide (**498**)
δ 7.53 (2H, d, *J* = 8.78 Hz, H-2' and H-6'), 6.89 (2H, d, , *J* = 8.78 Hz, H-3' and H-5'), 3.81
(3H, s, -O<u>Me</u>), 3.79 (2H, s, H-2), 2.26 (3H, s, H-2")
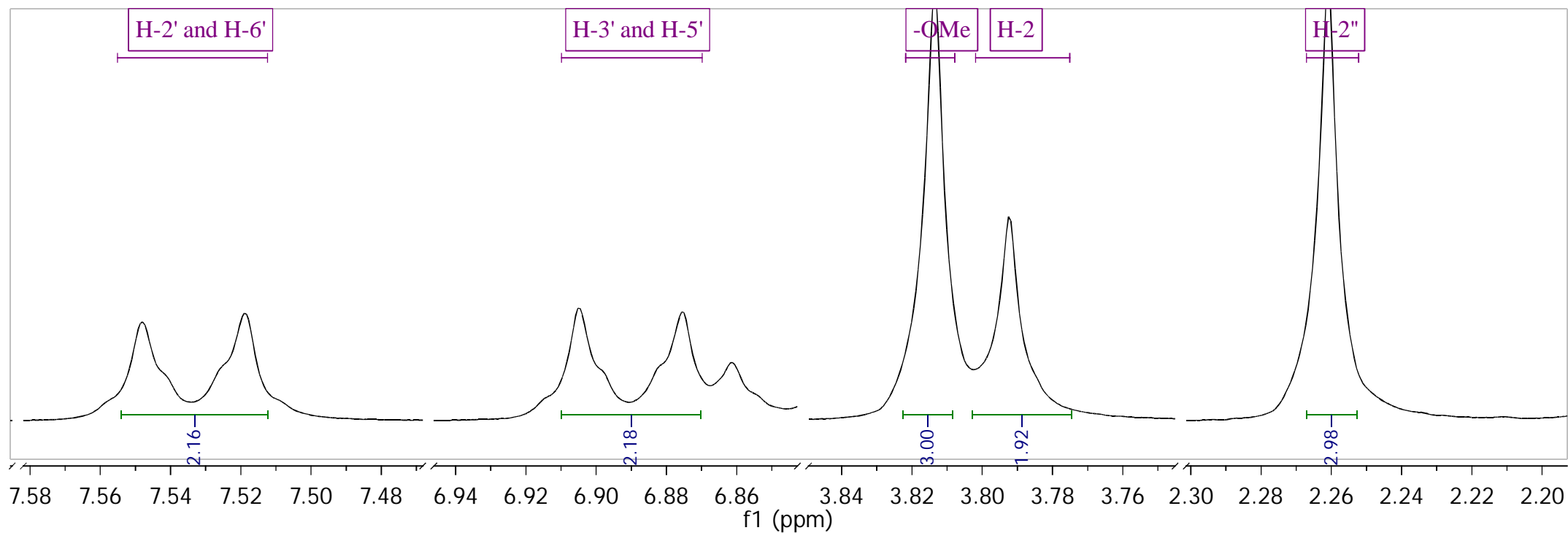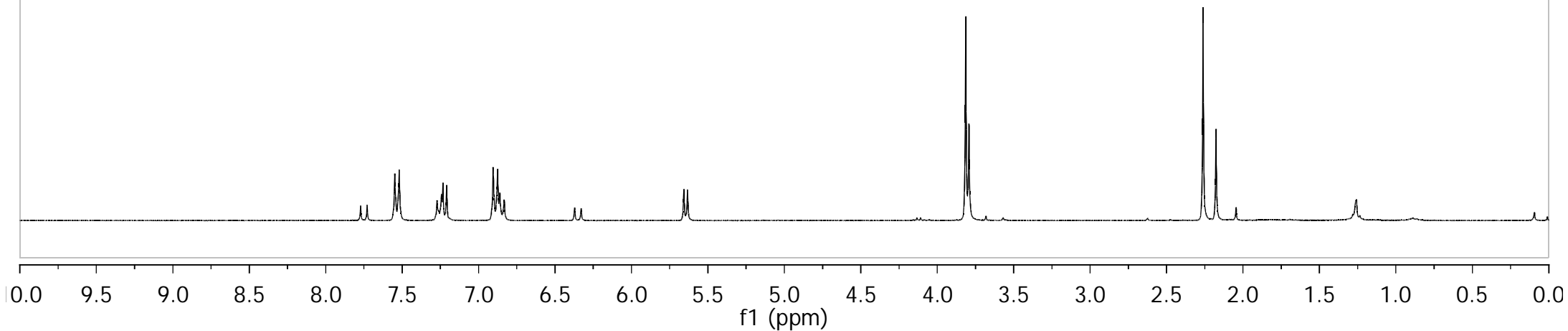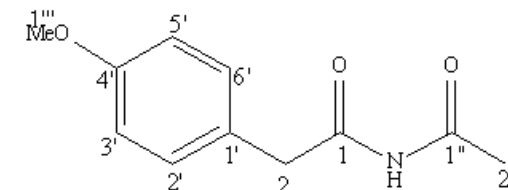
Plate 37a; ^{1}H NMR [(CD$_3$)$_2$CO]: 2,3',4,4'-Tetrahydroxy deoxybenzoin (**512**)
δ 7.88 (1H, d, J = 8.85 Hz, H-6), 6.79 (1H, d, J = 2.11 Hz, H-2'), 6.73 (1H, d, J = 8.06 Hz, H-5'), 6.63
(1H, dd, J = 8.06, 2.11 Hz, H-6'), 6.39 (1H, dd, J = 8.85, 2.37 Hz, H-5), 6.29 (1H, d, J = 2.37 Hz, H-3),
4.05 (2H, s, α-CH$_2$)
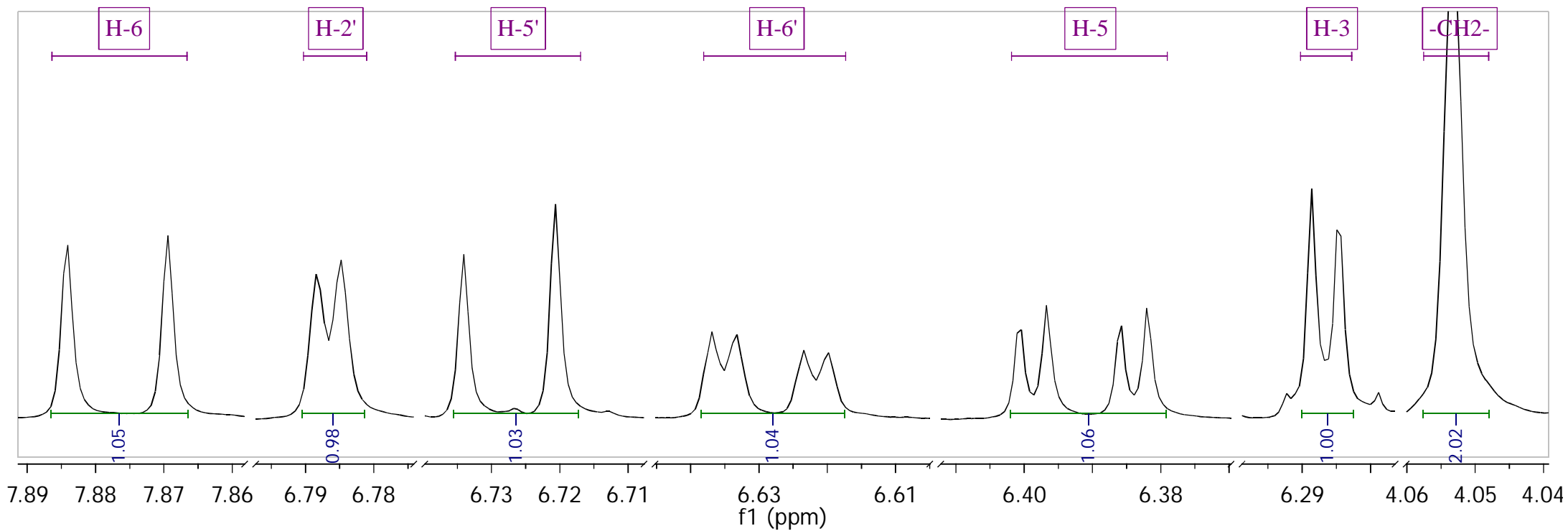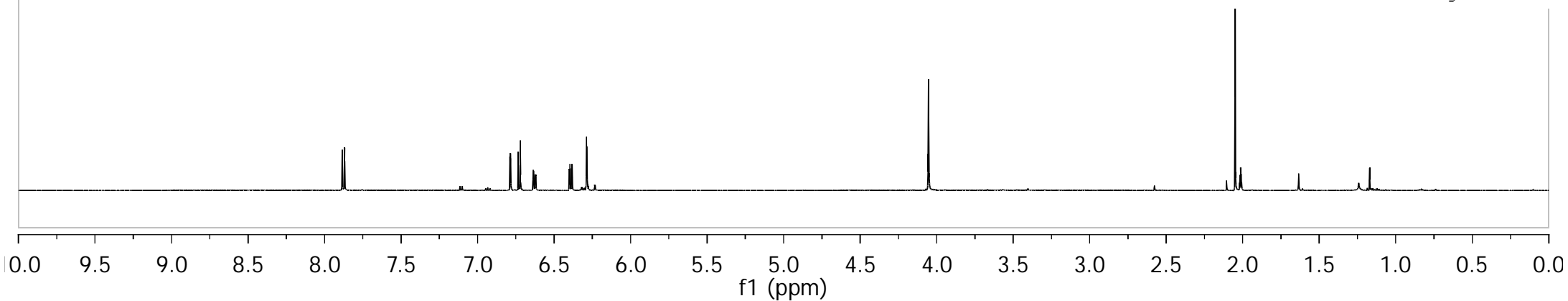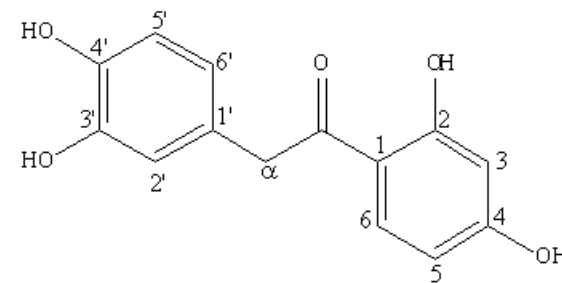
Plate 37b; ^{13}C NMR [(CD$_3$)$_2$CO]: 2,3',4,4'-Tetrahydroxy deoxybenzoin (**512**)
δ 203.32 (-CO), 166.23 (C-2), 165.24 (C-4), 145.46 (C-3'/4'), 144.37 (C-3'/4'), 133.91 (C-6), 127.05 (C-1'),
121.03 (C-6''), 116.65 (C-2'), 115.67 (C-5'), 112.84 (C-1), 108.37 (C-5), 103.11 (C-3), 44.09 (α-CH$_2$).
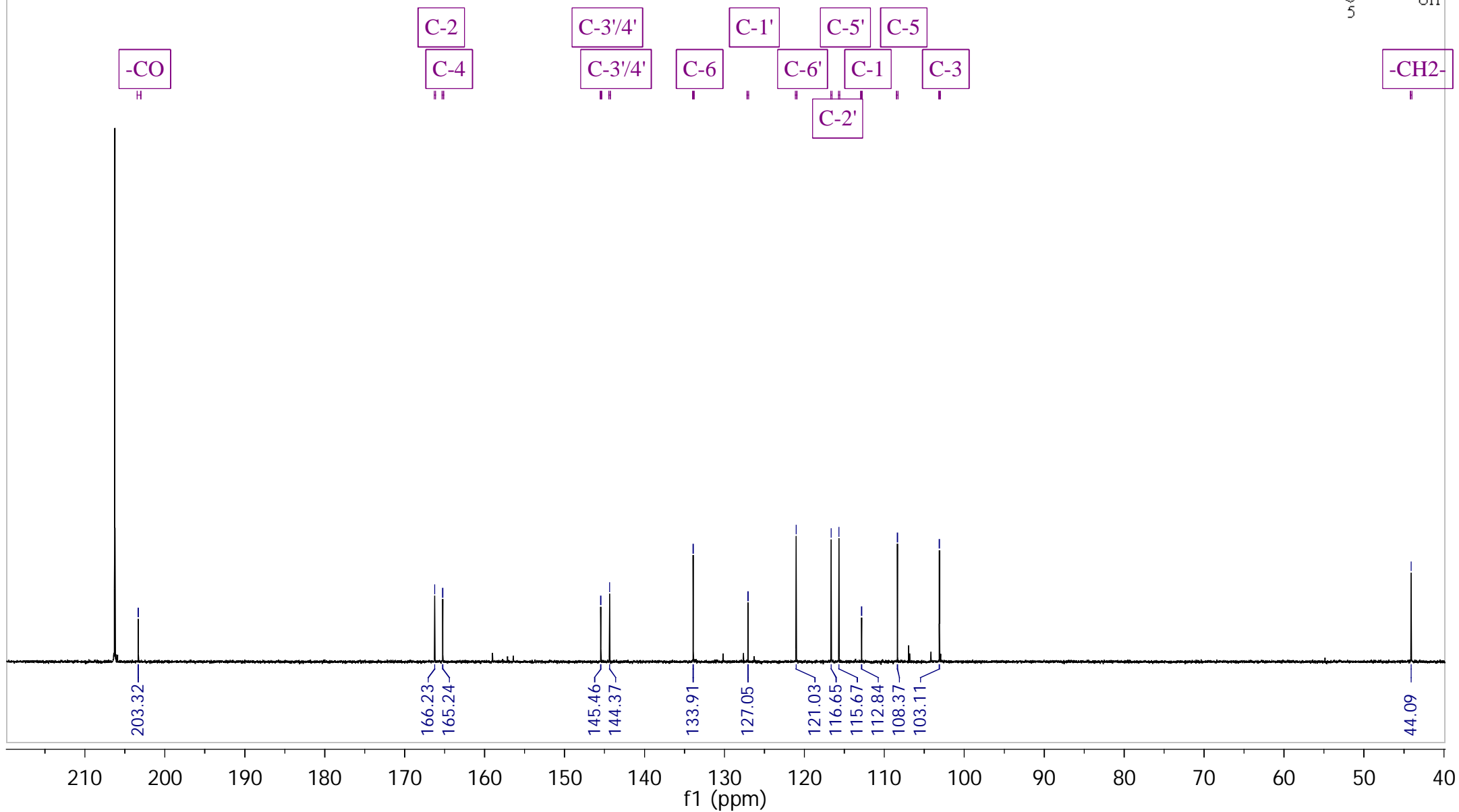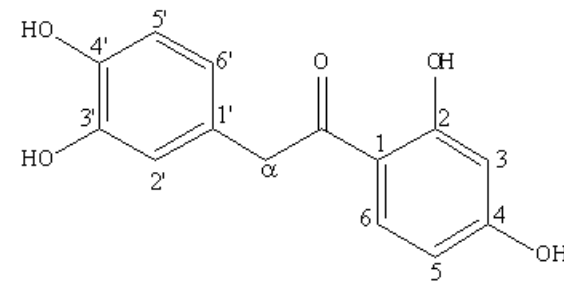
Plate 37c; DEPT [(CD$_3$)$_2$CO]: 2,3',4,4'-Tetrahydroxy deoxybenzoin (**512**)
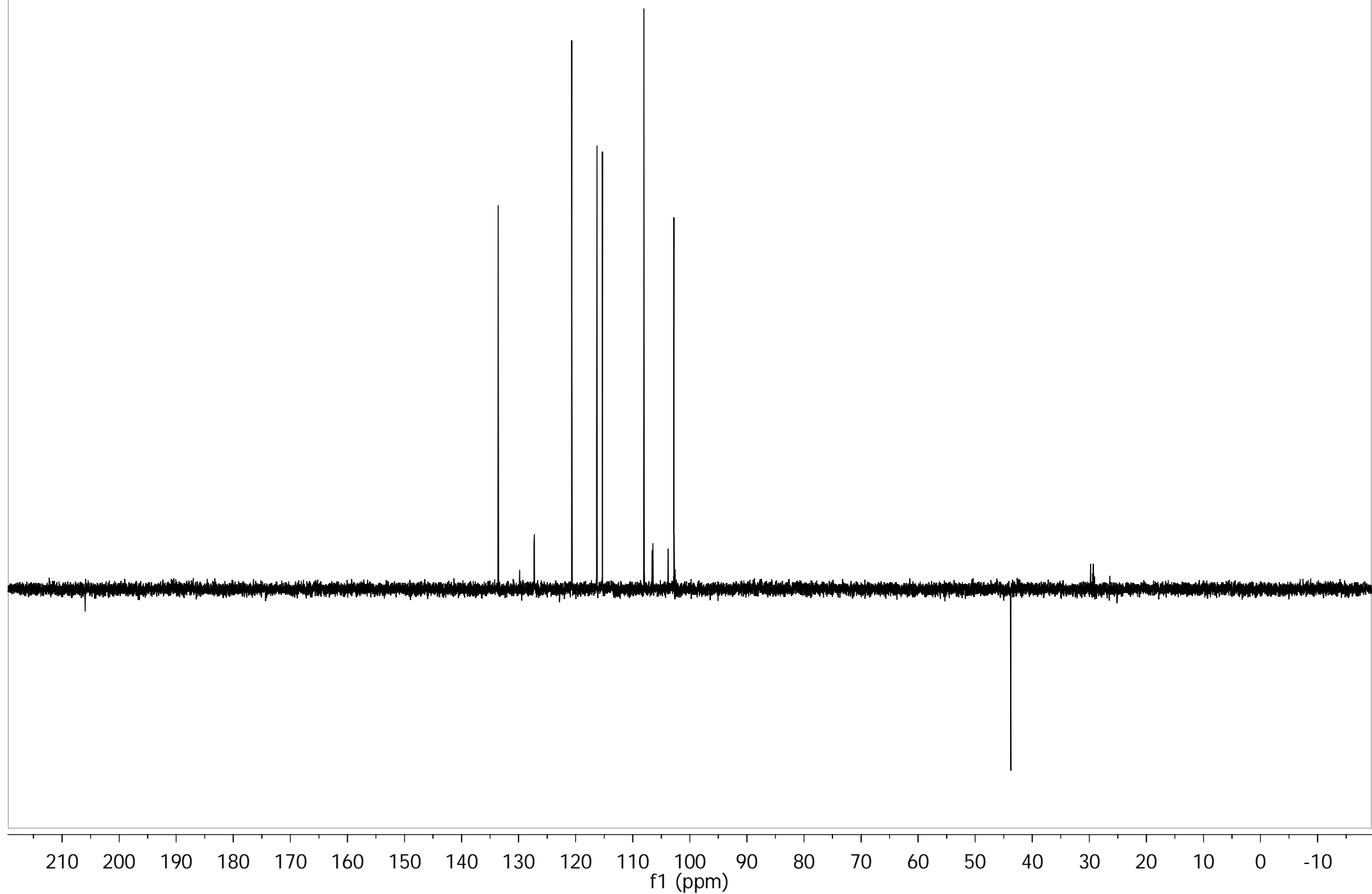
Plate 37d; HSQC [(CD$_3$)$_2$CO]: 2,3',4,4'-Tetrahydroxy deoxybenzoin (**512**)
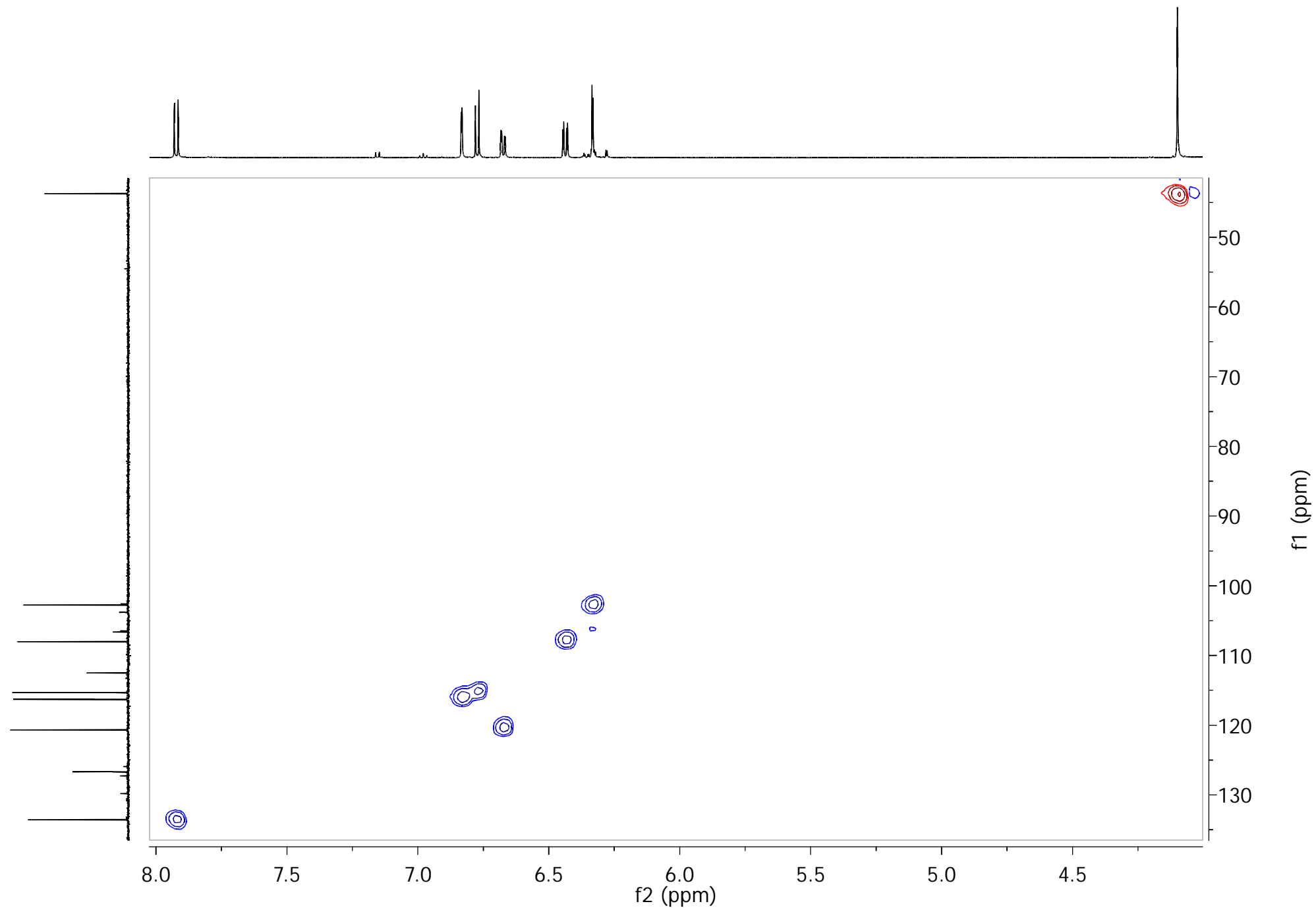
Plate 37e; HMBC [(CD$_3$)$_2$CO]: 2,3',4,4'-Tetrahydroxy deoxybenzoin (**512**)
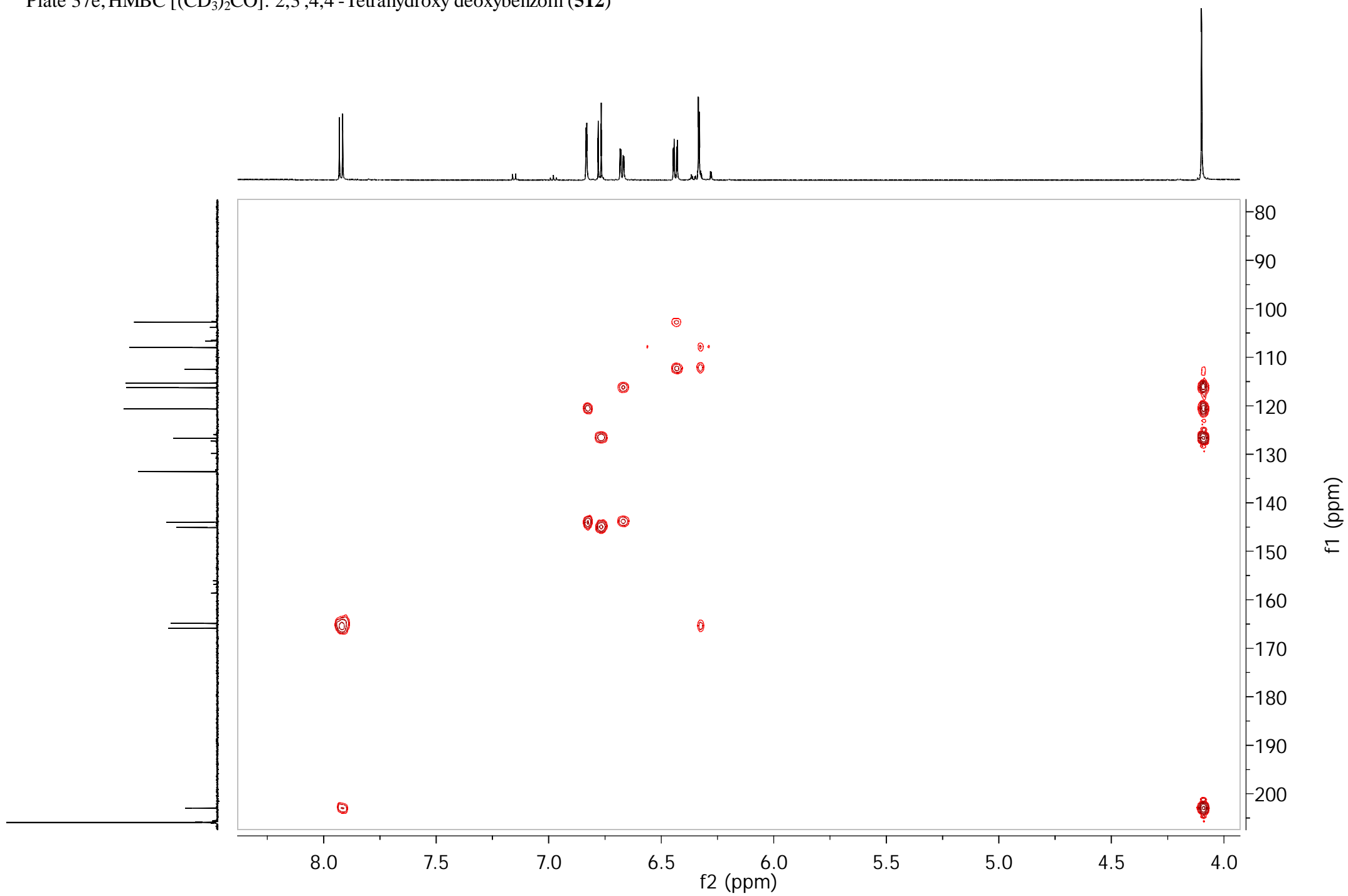
Plate 38a; ¹H NMR [CDCl₃]: 6-Hydroxy-2,4-dimethoxy deoxybenzoin (**514**)

δ 7.23–7.20 (2H, m, H-3' and H-5'), 7.16–7.13 (1H, m, H-4'), 7.12–7.11 (2H, m, H-2' and H-6'), 5.96 (1H, d, J = 2.62 Hz, H-3/5), 5.84 (1H, d, J = 2.62 Hz, H-3/5), 4.23 (2H, s, α-CH₂), 3.76 (3H, s, -OMe), 3.72 (3H, s, -OMe)
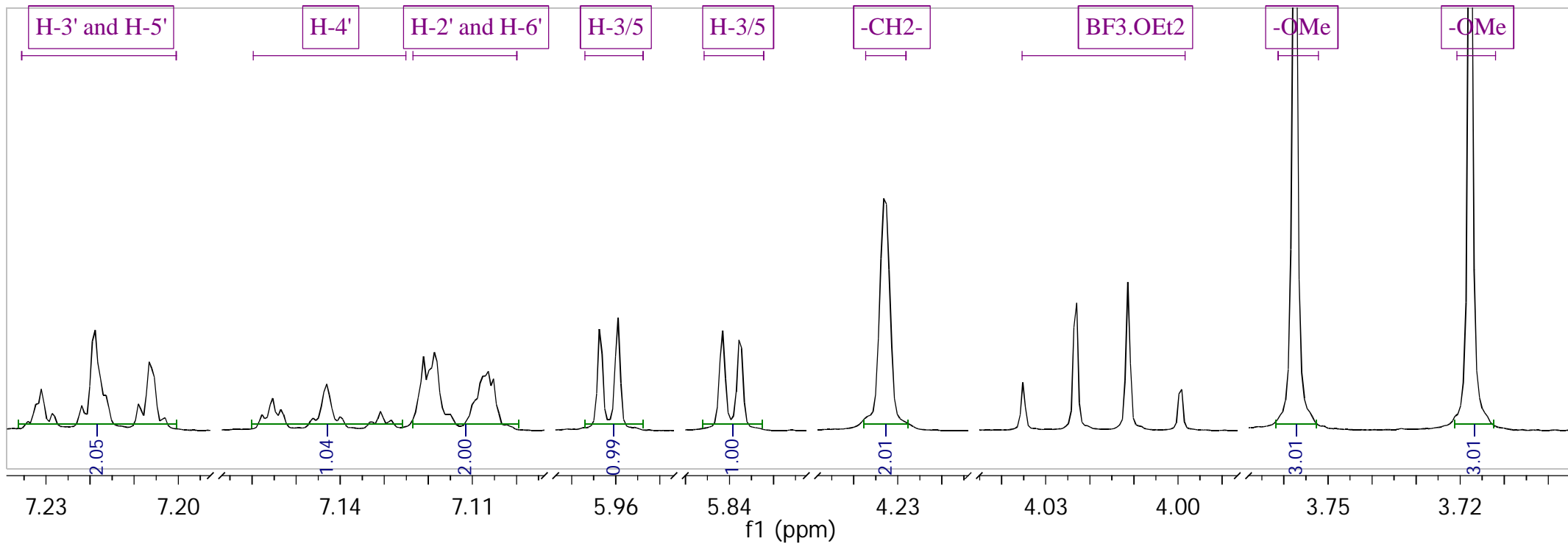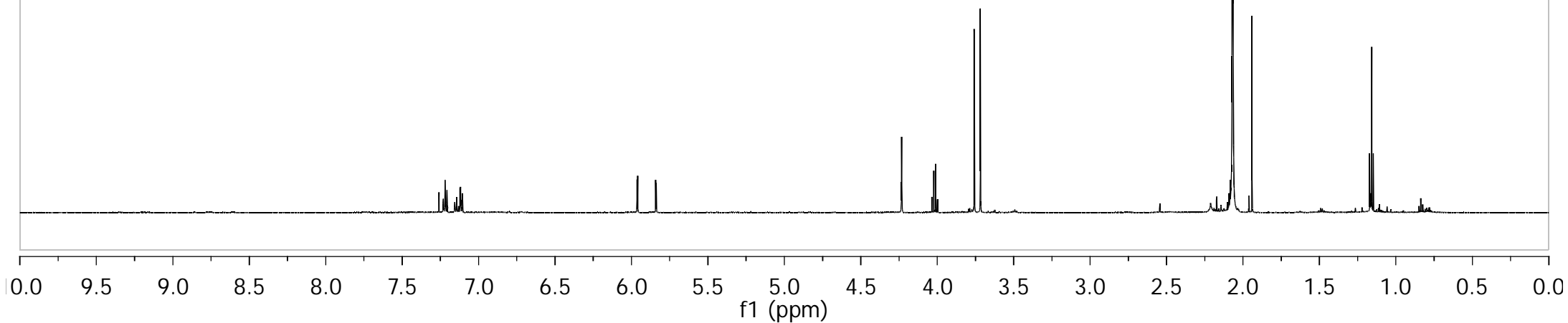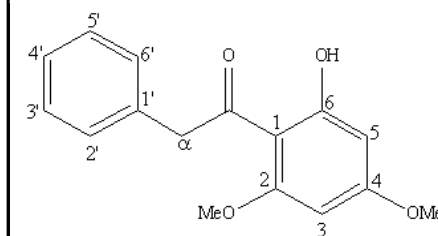
Plate 38b; ^{13}C NMR [CDCl$_3$]: 6-Hydroxy-2,4-dimethoxy deoxybenzoin (**514**)
δ 202.67 (-CO), 167.78 (C-6), 166.19 (C-2/4), 162.56 (C-2/4), 135.43 (C-1'), 129.47 (C-2' and C-6'), 128.21
(C-3' and C-5'), 126.47 (C-4'), 105.50 (C-1), 93.60 (C-3/5), 90.74 (C-3/5), 55.42 (-OMe), 50.19 (α-CH$_2$)

Peak labels: I, -CO, C-6, C-2 and C-4, I, C-3' and C-5', C-1', C-4', C-2' and C-6', C-1, C-3/5, C-3/5, -OMe, I, -CH2-, I

Chemical shift values: 206.86, 202.67, 170.99, 167.78, 166.19, 162.56, 135.43, 129.47, 128.21, 126.47, 105.50, 93.60, 90.74, 60.24, 55.42, 50.19

f1 (ppm)
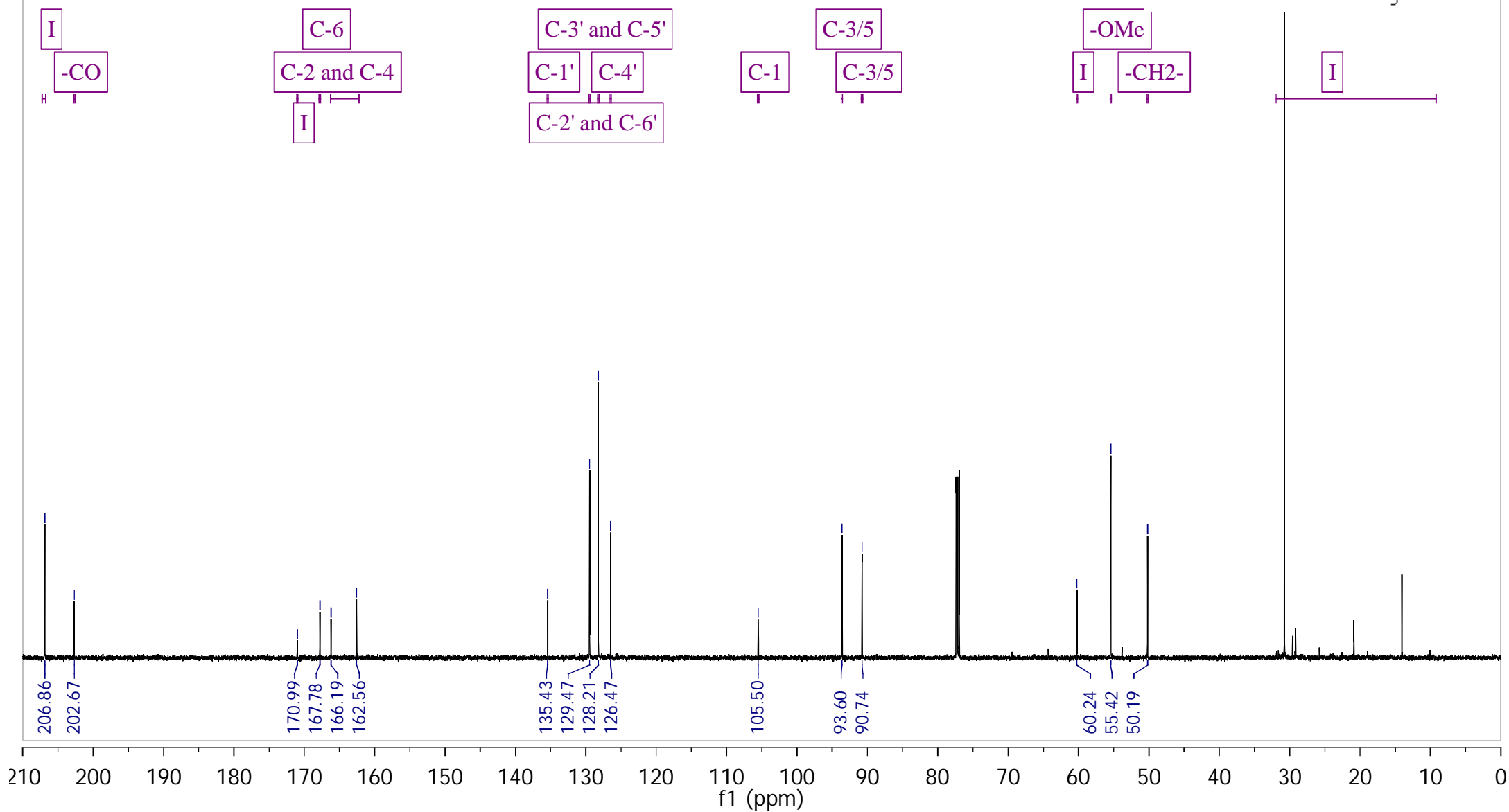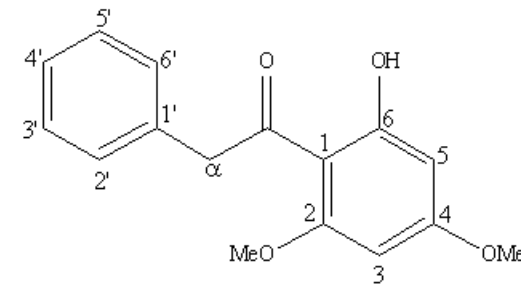
Plate 38c; DEPT [CDCl$_3$]: 6-Hydroxy-2,4-dimethoxy deoxybenzoin (**514**)
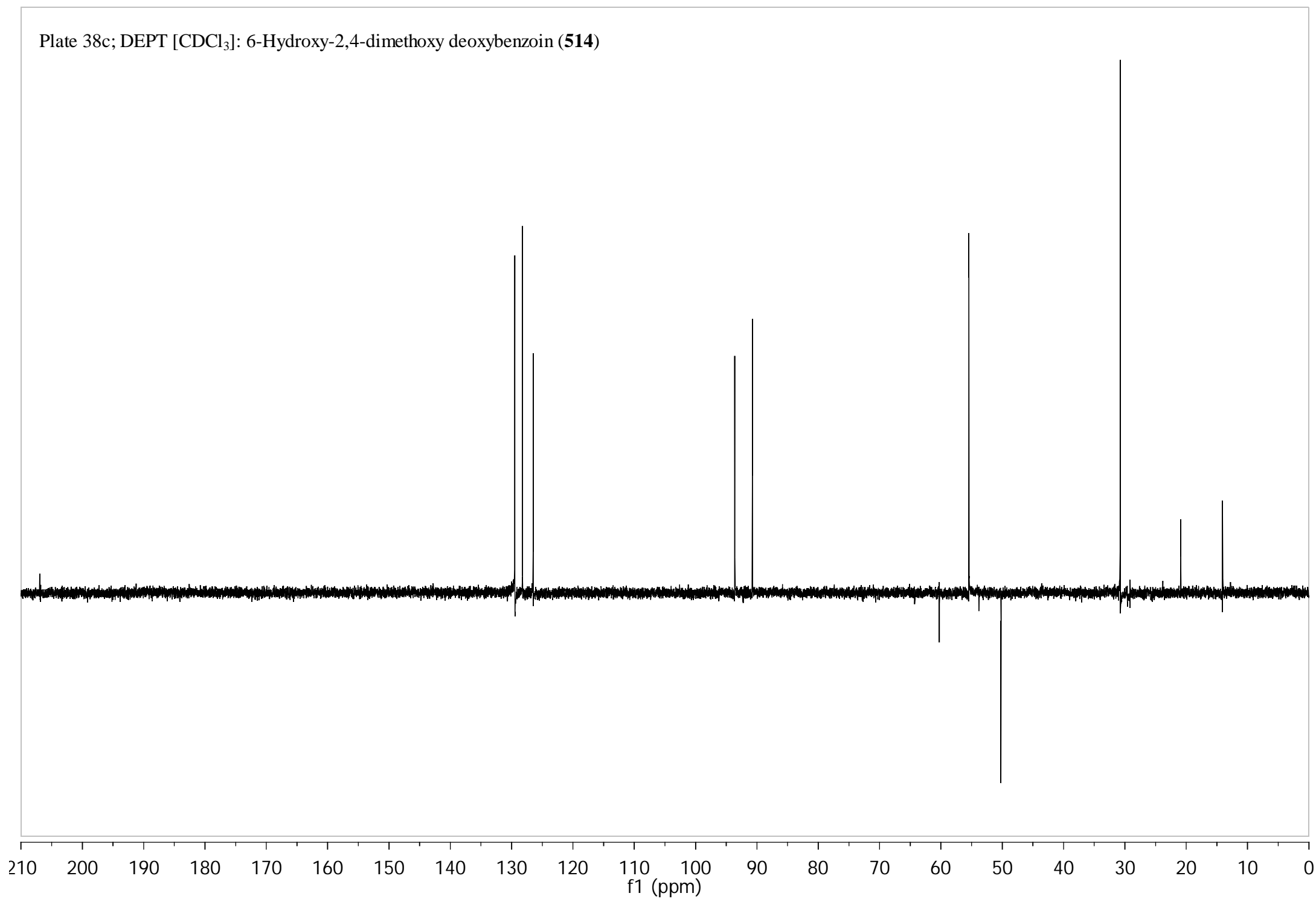
Plate 38d; HSQC [CDCl$_3$]: 6-Hydroxy-2,4-dimethoxy deoxybenzoin (**514**)
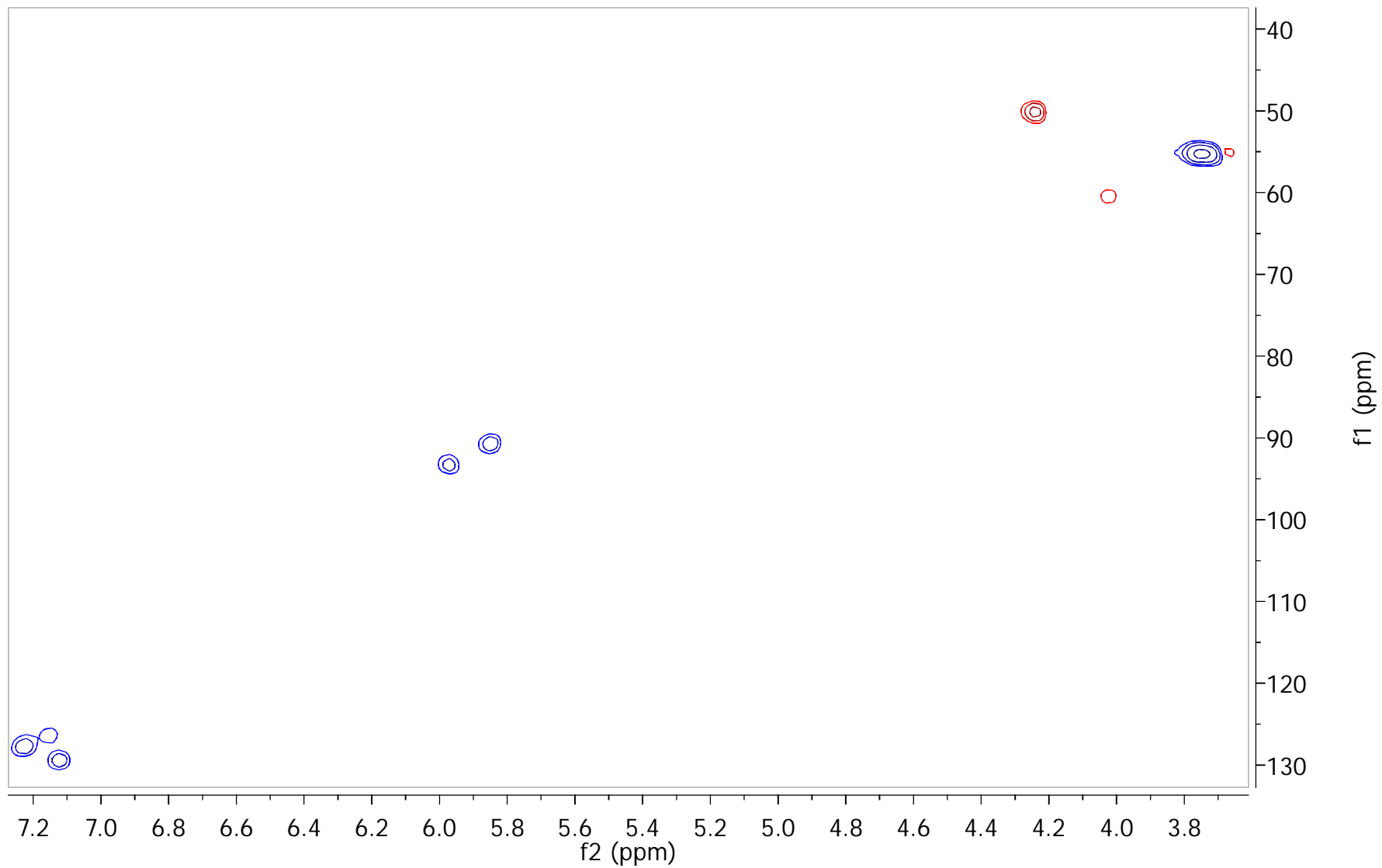
Plate 38e; HMBC [CDCl$_3$]: 6-Hydroxy-2,4-dimethoxy deoxybenzoin (**514**)
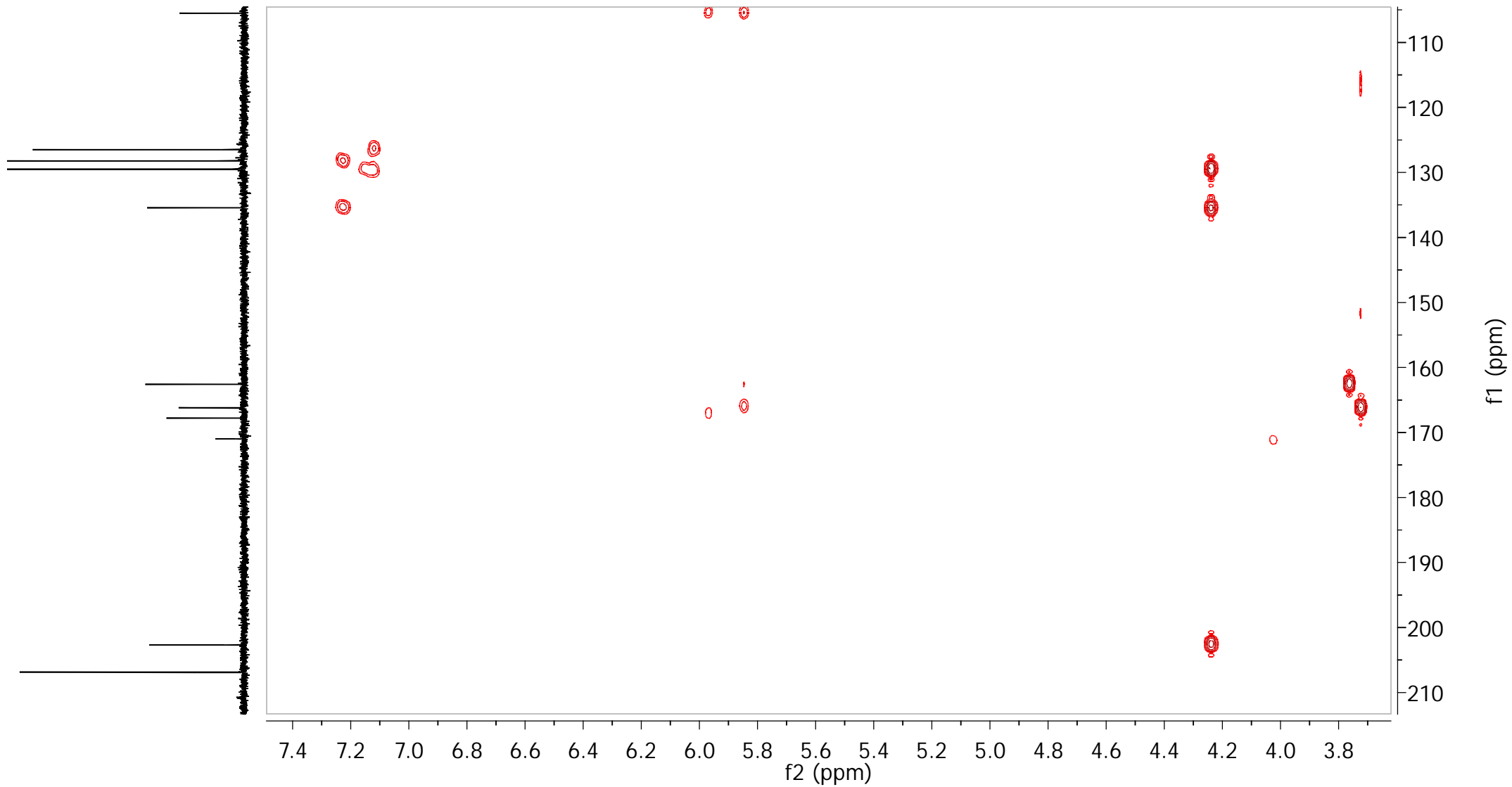
Plate 39a; ¹H NMR [CD₃OD]: Deoxybenzoin (**522**)
δ 7.45–7.39 (5H, m, Ar.-H), 7.25–7.10 (5H, m, Ar.-H), 4.74 (2H, s, α-CH₂)
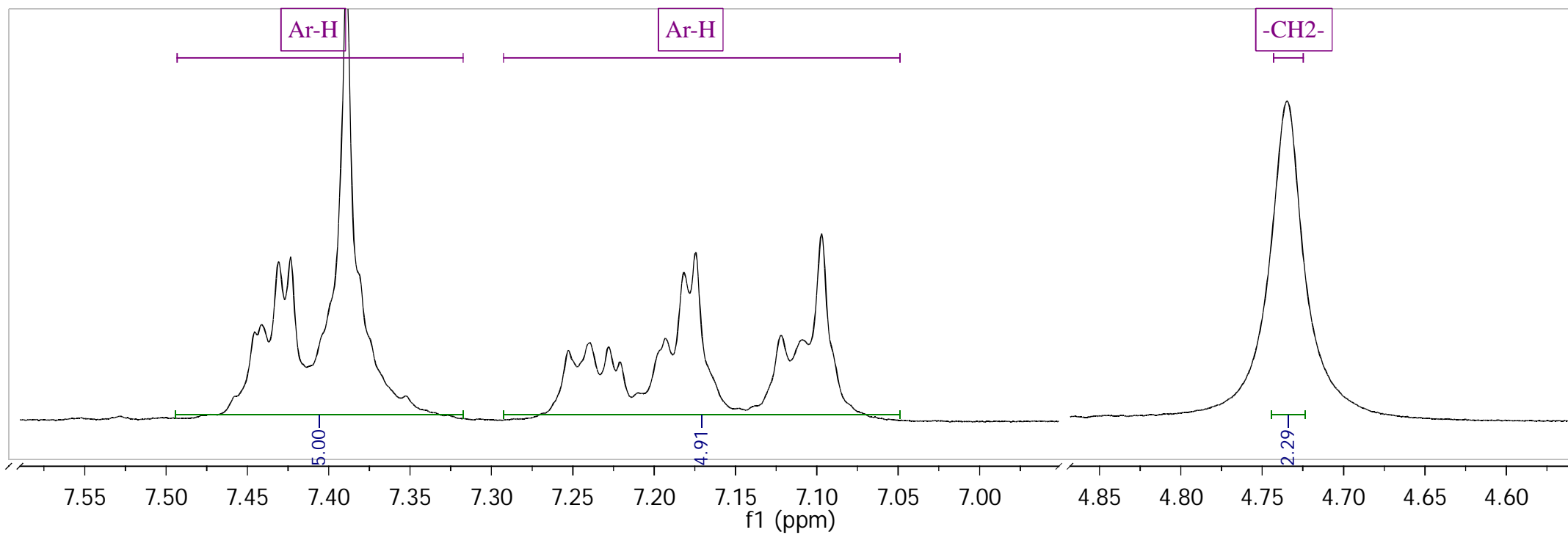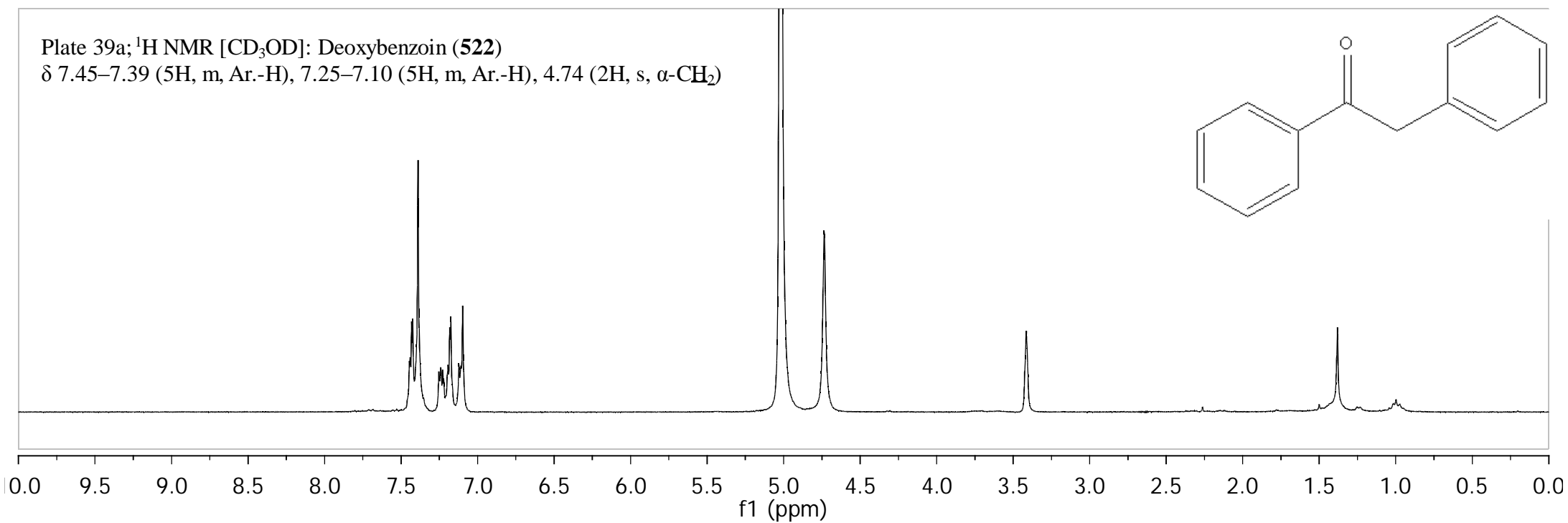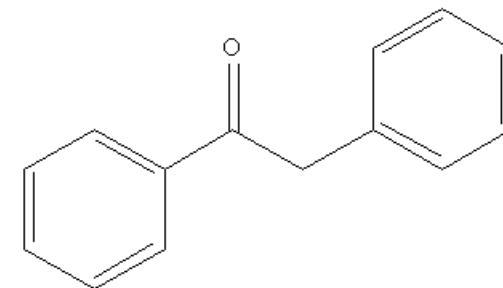
Plate 39b; ^{13}C NMR [CDCl$_3$]: Deoxybenzoin (**522**)
δ 197.80 (-$\underline{C}$=O), 136.70 (Ar-C), 134.65 (Ar-C), 133.31 (Ar-C), 129.60 (Ar-C), 128.75 (Ar-C), 127.03 (Ar-C), 45.63 (-$\underline{C}$H$_2$-).

-C=O

Ar-C

-CH2-

197.80

136.70
134.65
133.31
129.60
128.75
127.03

45.63

f1 (ppm)
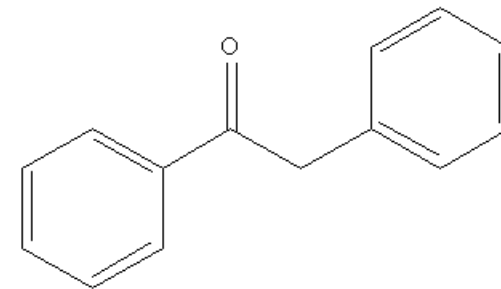
Plate 39c; DEPT [CDCl₃]: Deoxybenzoin (**522**)
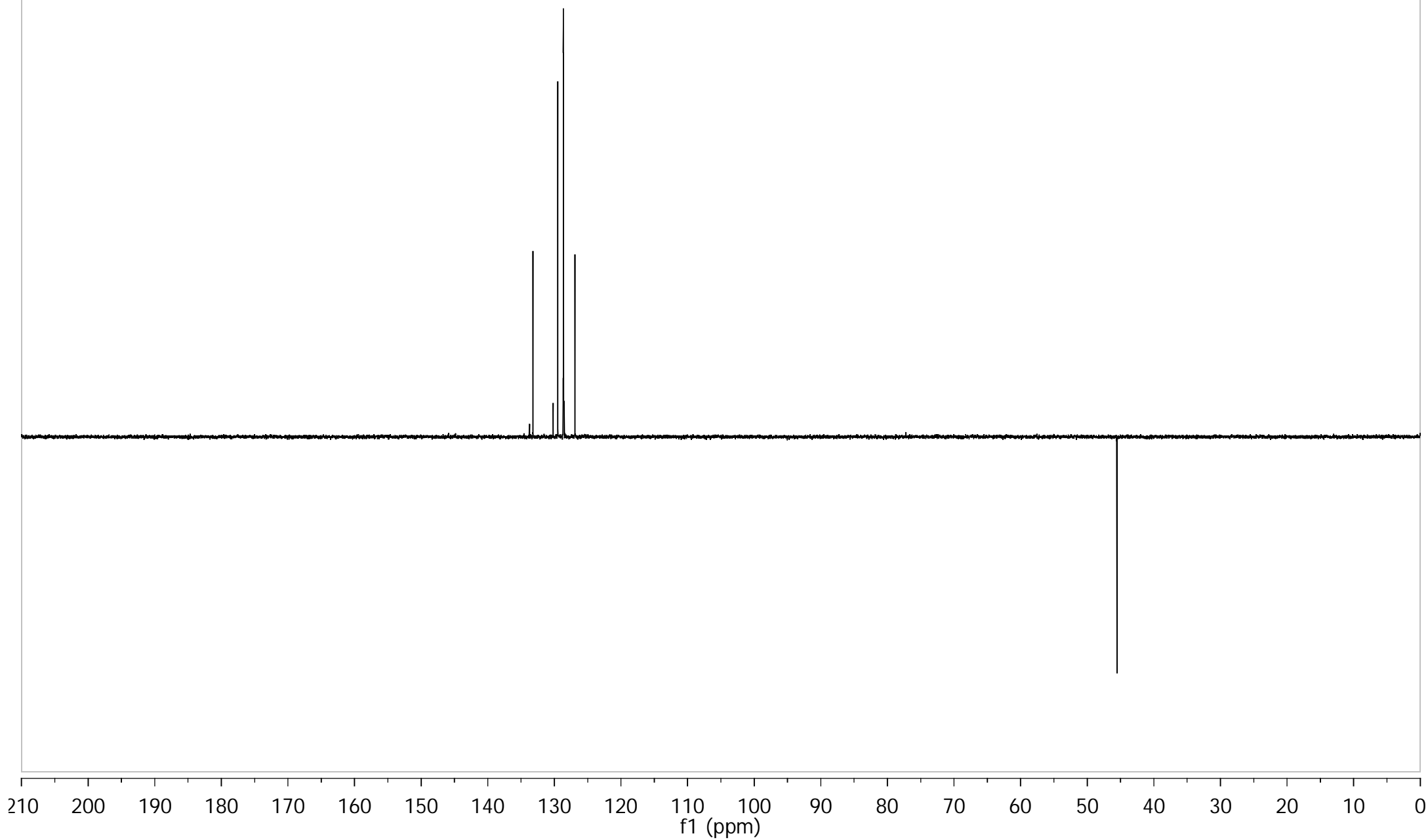
Plate 39d; HSQC [CDCl$_3$]: Deoxybenzoin (**522**)
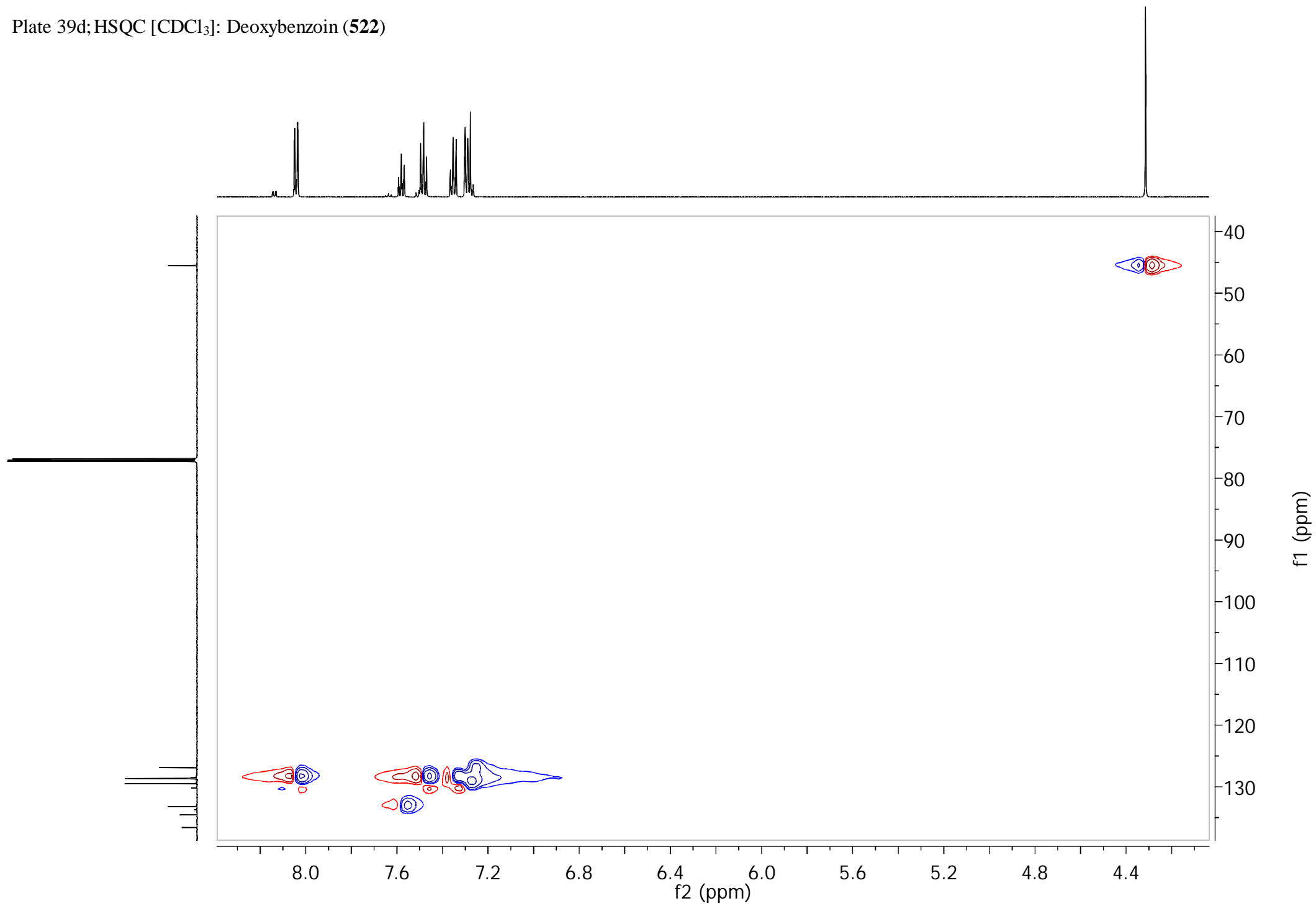
Plate 39e; HMBC [CDCl$_3$]: Deoxybenzoin (**522**)
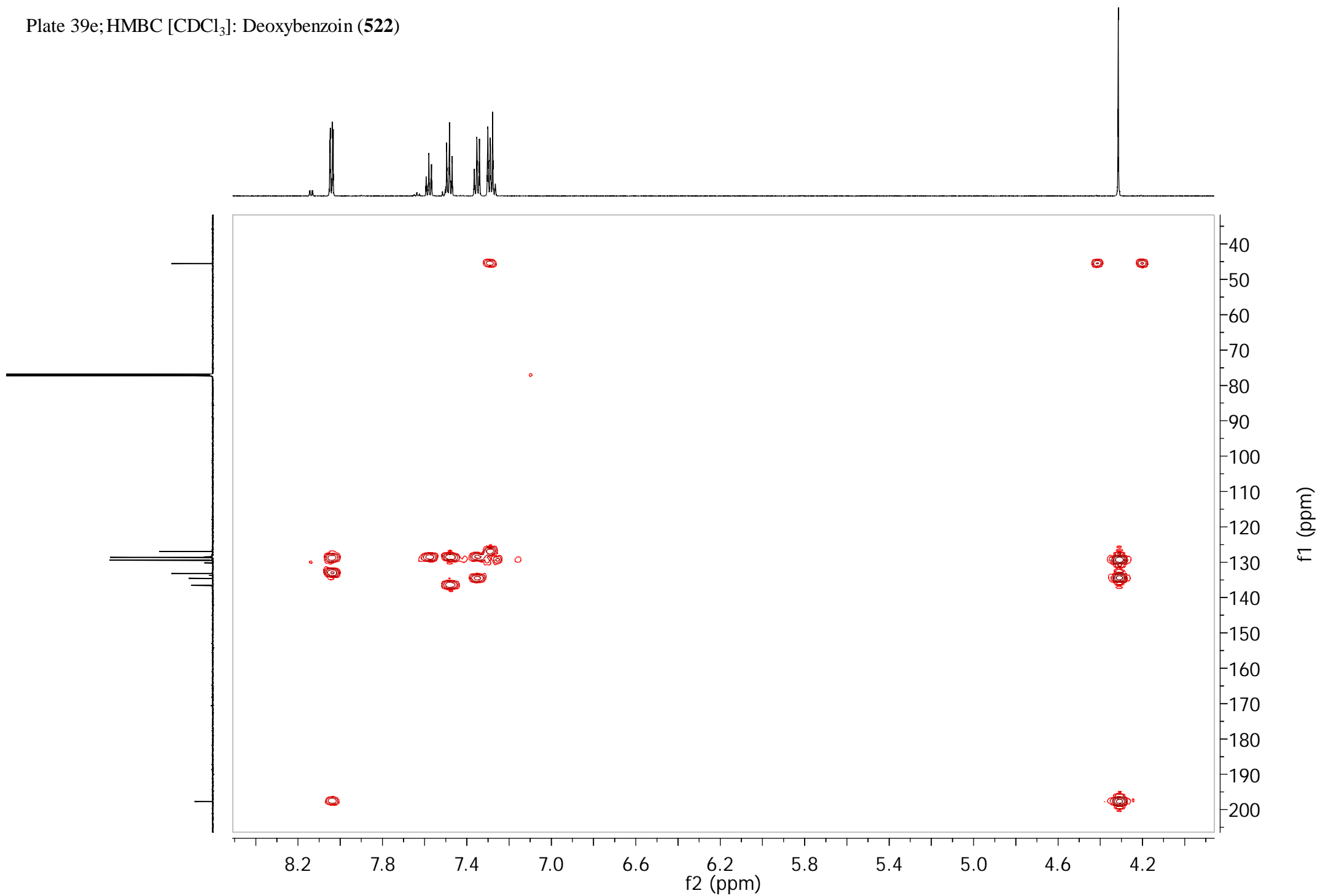
Summary

Flavonoids and isoflavonoids are known to exhibit many important physiological properties and are especially promising candidates for cancer chemoprevention. Similar to most natural products, studies directed at the synthesis of flavonoids have, therefore, emerged from the search for new compounds with beneficial biological properties. Metabolic studies related to flavonoids are, however, frequently hampered by the inaccessibility of a variety of optically active compounds. While a single method for the synthesis of enantiomerically enriched isoflavonoids has been published, this process utilizes phenylacetic acid derivatives which are not always readily available in all naturally occurring substitution patterns. Even though the synthesis of phenylacetic acids are possible *via* a number of routes, these are based on ancient low yielding chemical processes utilizing harsh reaction conditions, stoichiometric quantities of reagents and in many cases, poisonous heavy metals like lead and thallium.
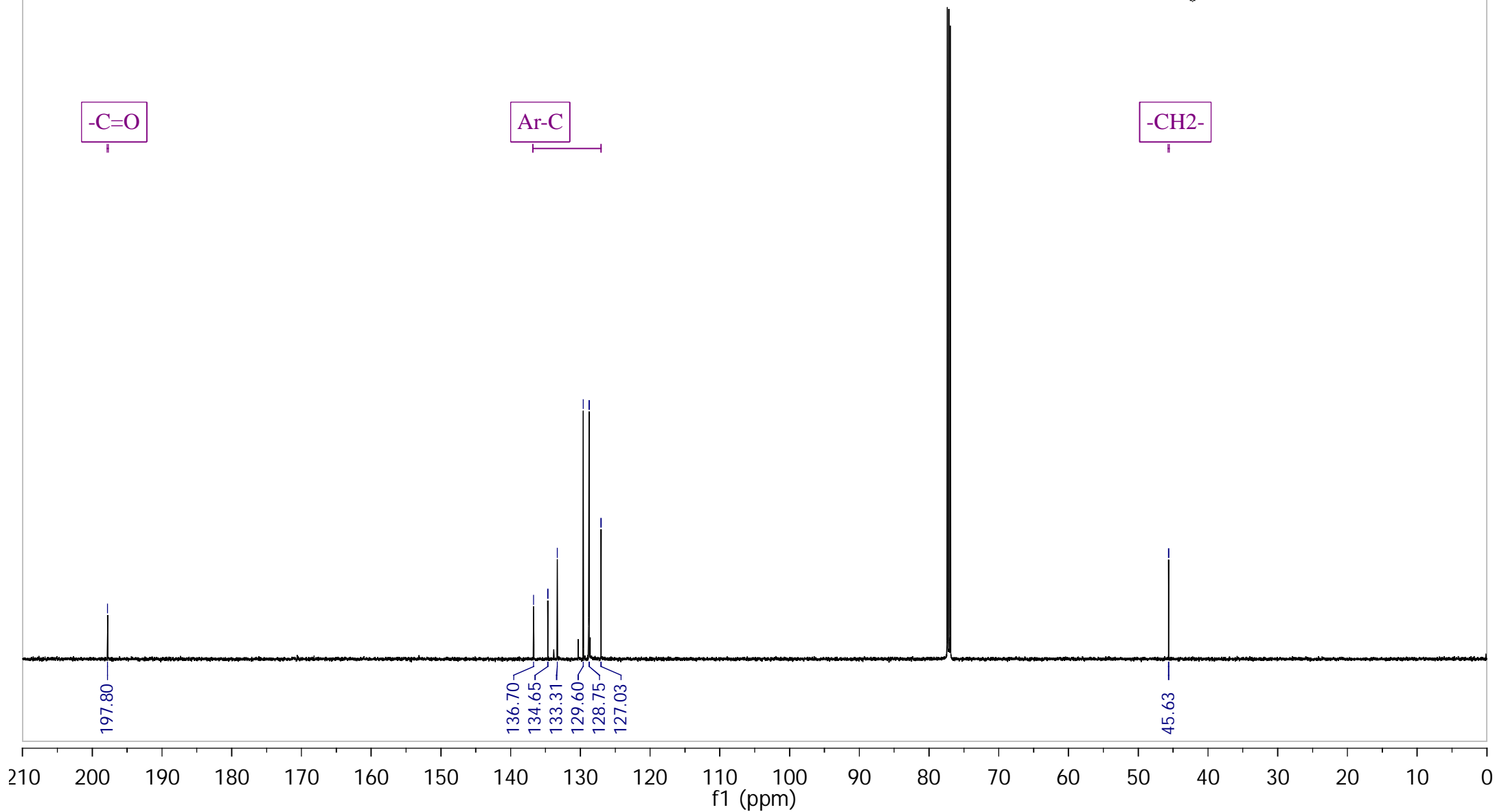
In order to address the availability of phenylacetic acid derivatives of variable substitution patterns, the current study was aimed at the development of methodology for the synthesis of phenylacetic acid derivatives that would be high yielding, environmentally benign, have a limited number of process steps, and are applicable to all naturally occurring flavonoid substitution patterns. In this regard it was envisaged that ozonolysis of substituted allylbenzenes would comply with all of the stated criteria and was therefore investigated as methodology for the synthesis of phenylacetic acid derivatives that could serve as building blocks during isoflavonoid preparations.

Since substituted allylbenzenes of all oxygenation patterns are not available commercially, the allylic moiety was introduced into the required phenols by means of a allyl phenyl ether intermediate, through utilization of Williamson ether synthesis (allyl bromide; K_2CO_3, refluxing CH_3CN) followed by Claisen rearrangement of the neat allyl phenyl ethers, allyl 3-methoxyphenyl ether and allyl 3,5-dimethoxyphenyl ether, under microwave irradiation (at 200 ℃ in 15 min. intervals and 0–200 W variable power) to obtain the desired allylphenols, 1-allyl-2-hydroxy-4-methoxybenzene and 1-allyl-2-hydroxy-4,6-dimethoxy-benzene, in 44 and 88 % yield, respectively. Apart from the desired allylphenol, Claisen rearrangement of allyl 3-methoxyphenyl ether, however, also led to the formation of 1-allyl-2-hydroxy-6-methoxybenzene in 45% yield, indicating a lack of selectivity towards the formation of the sterically less hindered product under the prevailing reaction conditions. Since free phenolic substituents on the aromatic rings of the envisaged substrates might have a negative effect

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during ozonolysis reactions, the commercially available allylphenols as well as the two substrates prepared by allylation and Claisen rearrangement (*vide supra*) were subjected to methylation (MeI; K_2CO_3; refluxing acetone or acetonitrile) and the respective fully methylated analogues, 1-allyl-3,4-dimethoxybenzene, 1-allyl-2,4-dimethoxybenzene, 1-allyl-2,4,6-trimethoxy-benzene, and 1-allyl-3,4,5-trimethoxybenzene, obtained in 79, 96, 80, and 77% yield, respectively.

Ozonolysis [O_3 (6–8 min.), DCM, 0 °C] with reductive work-up [N-methylmorpholine-N-oxide (NMMO)] of 1-allyl-2-methoxybenzene, 1-allyl-4-methoxybenzene, and 1-allyl-3,4-dimethoxybenzene afforded the corresponding phenylacetaldehydes in 58, 88 and 15% yield, respectively. Ozonolysis of the highly oxygenated substrates, 1-allyl-2-hydroxy-4-methoxybenzene, 1-allyl-2,4,6-trimethoxybenzene, and 1-allyl-3,4,5-trimethoxybenzene, however, only led to cleavage of the aromatic ring and formation of unidentifiable product mixtures. Cleavage of the aromatic rings of these substrates was confirmed by ^{1}H NMR analysis of the reaction mixture [O_3 (6–8 min.), $CDCl_3$, -78 °C] where the formation of the 1,2,4-trioxolane intermediate could be detected for the substrates that gave the desired phenylacetaldehydes but not for the highly oxygenated analogues.

In order to reduce electron density on the aromatic ring of the highly oxygenated substrates and prevent ring ozonolysis in this way, the free hydroxy function on each substrate was changed into a trifluoromethanesulfonyl ester and the subtrates, 1-allyl-2-trifluoromethanesulfonyloxy-4-methoxybenzene, 1-allyl-4-trifluoromethanesulfonyloxy-3-methoxybenzene, 1-allyl-4-trifluoromethanesulfonyloxy-3,5-dimethoxybenzene, and 1-allyl-2-trifluoromethanesulfonyloxy-4,6-dimethoxybenzene submitted to ozonation with NMMO work-up again. While the phloroglucinol based sulfonyl ester gave the desired phenylacetaldehyde in 71% yield, the other three substrates furnished NMMO induced double bond migration with the subsequent formation of the benzaldehyde equivalent products. When the ozonation reaction was repeated on the resorcinol, catechol and pyrogallol trifluoromethanesulphonyl esters, with replacement of the NMMO with dimethyl sulphide (DMS) as reductant, the desired phenylacetaldehydes or trioxolanes were, however, obtained in 63, 32 and 31% yield, respectively.

Ozonolysis with oxidative work-up [(i) O_3/MeOH; (ii) Ac_2O-Et_3N] applied to the monomethoxy substrates, 1-allyl-2-methoxybenzene and 1-allyl-4-methoxybenzene, afforded the desired methyl phenylacetates in 91 and 32% yield, respectively. Similar to what was

found for the reductive work-up procedure, the higher oxygenated substrates had to be converted to their respective triflates before ozonolysis of the allylic double bond could be effected successfully and the phenylacetic acid esters, methyl 4-trifluoro-methanesulfonyloxy-3-methoxyphenyl acetate, methyl 4-trifluoromethanesulfonyloxy-3,5-dimethoxyphenyl acetate, and methyl 2-trifluoromethanesulfonyloxy-4,6-dimethoxyphenyl acetate obtained in 9, 17 and 65% yield, respectively.

Since the published process for the stereoselective synthesis of isoflavonoids would require the phenyl acetates prepared through ozonolysis to be transformed into the corresponding amides, the possibility of direct formation of the nitrogen derivatives, like anilides, during the ozonolysis reaction was subsequently investigated. While first attempts at having the aniline present during the ozonolysis reaction only led to nitrogen oxidation, the process was amended to addition of the nitrogen nucleophile after formation of the 1,2,4-trioxolane, which resulted in the desired 2-methoxyphenylacetanilide being formed in 37% yield. The scope of this novel reaction was subsequently extended to the reaction of 1-allyl-4-methoxybenzene with acetamide leading to the product being obtained in 39% yield. While this reaction gave indications that deactivated nitrogen nucleophiles could also be used in this process, the reaction with 2-imidazolidinone, a secondary amide, did not succeed indicating that the new reaction still needs to be optimized to be useful in the enantioselective synthesis of isoflavonoids.

Finally, it was shown during the current study that the phenylacetic acid derivatives prepared *via* ozonolysis could be transformed into deoxybenzoins, another isoflavonoid precursor, through formation of the acid chloride followed by reaction with a phenyl Grignard reagent. Thus phenylacetyl chloride could be reacted successfully with phenylmagnesiumbromide at -78 $^{\circ}$C in diethyl ether to give the deoxybenzoin in almost 60% yield.

Keywords

Isoflavonoids, Claisen rearrangement, allylbenzene, ozonolysis, 1,2,4-trioxolane, phenylacetaldehyde, methyl phenylacetate, phenylacetanilide, phenylacetamide, deoxybenzoin.

Opsomming

Flavonoïede en isoflavonoïede beskik oor 'n wye verskeidenheid belangrike biologiese eienskappe waaronder belowende eienskappe t.o.v. kanker voorkoming. Soortgelyk aan die studie van die meeste ander natuurprodukte, het flavonoïedchemie sy oorsprong te danke aan die soeke na nuwe verbindings met voordelige biologiese eienskappe. Metabolise studies met flavonoïede word egter dikwels belemmer deur die ontoegangklikheid van substrate met verskillende substitusiepatrone in opties aktiewe vorm en slegs 'n enkele proses vir die sintese van enantiomeries verrykte isoflavonoïede het tot dusver die lig gesien. Aangesien hierdie proses op fenielasynsuurderivate berus, is dit dus noodsaaklik dat hiedie tipe verbindings met alle moontlike natuurlike substitusie patrone beskikbaar moet wees. Hoewel sommige fenielasynsure en derivate kommersieël beskikbaar is, is dit nie die geval vir verbindings van alle substitusiepatrone nie en moet verskeie van hierdie verbindings, wanneer benodig, berei word. Alhoewel metodes vir die sintese van fenielasynsure wel bestaan, is baie hiervan op antieke chemiese prosesse waarin drastiese reaksie kondisies, stoigiometriese hoeveelhede reagense en giftige swaarmetale gebruik word, gebaseer en is baie metodes nie geskik vir die bereiding van substrate met hoë vlakke van oksigenering nie.

Ten einde die beskikbaarheid van fenielasynsure van alle moontlike substitusie patrone aan te spreek en 'n omgewingsvriendelike proses met beperkte aantal prosesstappe vir die sintese van hierdie groep verbindings daar te stel, is 'n ondersoek na die osonolise van gesubstitueerde allielbensene as metodiek vir die sintese van fenielasynsuurderivate aangepak.

Aangesien allielbensene met alle moontlike substitusie patrone nie kommersieël beskikbaar is nie, is besluit om die allielgroep aan die fenielring te heg d.m.v. Williamson etersintese (allielbromied, K_2CO_3, kokende CH_3CN) gevolg deur Claisen-herrangskikking van die gevormde allielfenieleters. Die allielfenieleters, alliel-3-metoksifenieleter en alliel-3,5-dimetoksifenieleter, is dus onder oplosmiddelvrye toestande aan mikrogolf bestraling blootgestel (200 ^{o}C, 15 min. intervalle, 0–200 W veranderlike krag) om die allielbensene, 1-alliel-2-hidroksi-4-metoksibenseen en 1-alliel-2-hidroksi-4,6-dimetkosibenseen in 44 en 88% opbrengs onderskeidelik, op te lewer. Benewens die verlangde allielfenol, het die Claisen-herrangskikking van alliel-3-metoksifenieleter ook tot die vorming van die ongunstige isomeer, 1-alliel-2-hidroksi-6-metkosibenseen, in 45% opbrengs gelei, sodat afgelei kon word dat geen regioselektiwiteit onder die toestande waarby die reaksie uitgevoer is, moontlik is

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nie. Weens die feit dat vry-fenoliese hidroksigroepe tydens die osonolise proses tot ongewenste newereaksies kon lei, is die hidroksifunksies van die bereide allielbensene asook dié van die kommersieël beskikbare analoë deur metilering (MeI, K_2CO_3, kokende asetoon of asetonitriel) beskerm en is die volledig gemetileerde verbindings, 1-alliel-3,4-dimetoksibenseen, 1-alliel-2,4-dimetoksibenseen, 1-alliel-2,4,6-trimetoksibenseen en 1-alliel-3,4,5-trimetoksibenseen in onderskeidelik 79, 96, 80 en 77% opbrengs, daargestel.

Osonolise [O_3 (6–8 min), dichlorometaan, 0^oC] met daaropvolgende reduktiewe opwerk [N-metiel-morfolien-N-oksied (NMMO)] van 1-alliel-2-metoksibenseen, 1-alliel-4-metoksibenseen en 1-alliel-3,4-dimetoksibenseen het dan ook die ooreenstemmende feniel-asetaldehiede, in onderskeidelik 58, 88 en 15% opbrengs, gelewer. Reaksie van die hoogs geoksigeneerde substrate, 1-alliel-2-hidroksi-4-dimetoksibenseen, 1-alliel-2,4,6-trimetoksi-benseen en 1-alliel-3,4,5-trimetoksibenseen, het egter as gevolg van osonolise van die aromatiese ring se dubbelbindings slegs tot 'n mengsel van onidentifiseerbare produkte gelei. Hierdie waarneming is m.b.v. ^{1}H KMR bevestig waar die vorming van die 1,2,4-trioksolaan tussenproduk waargeneem kon word tydens osonolise [O_3 (6–8 min), $CHCl_3$, -78 ^{o}C] van die substrate wat die verlange produkte gelewer het, maar nie tydens osonolise van die hoogs geoksigeneerde uitgangstowwe nie.

Ten einde die elektronrykheid van die aromatiese ringe, van die resorsinol, katesjol, floroglusinol en pirogallol substrate, wat moontlik die oorsaak van die mislukking van die osonolise reaksies kon wees, te verminder, is een van die OH-funksies van elk van hierdie uitgangstowwe as trifluorometaansulfonielester beskerm en die reaksies op 1-alliel-2-trifluorometaansulfonieloksi-4-metoksibenseen, 1-alliel-4-trifluorometaansulfonieloksi-3-metoksibenseen, 1-alliel-4-trifluorometaansulfonielloksi-3,5-dimetokibenseen en 1-alliel-2-trifluorometaansulfonieloksi-4,6-dimetoksibenseen met NMMO opwerk, herhaal. Die floroglusinol gebaseerde triflaatester het dan ook die verlangde fenielasetaldehied in 71 % opbrengs gelewer, maar die ander substrate het slegs die bensaldehiedanaloë as produkte, gelewer. Hierdie verskynsel kan waarskynlik aan basis gekataliseerde dubbelbindingsmigrasie, weens die teenwoordigheid van die NMMO, toegeskryf word. Herhaling van die osonolise reaksies met DMS as reduktant het dan ook hierdie feit bevestig, aangesien die gesogte fenielasetaldehiede of trioksolane in 63, 32 en 31% opbrengs uit die reaksies verkry kon word.

Osonolise gevolg deur oksidatiewe opwerk [(i) O_3/MeOH; (ii) Ac_2O-Et_3N] van die monometoksi-allielbensene, 1-alliel-2-metoksibenseen en 1-alliel-4-metoksibenseen, het die ooreenstemmende metielfenielasetate in 91 en 32 % opbrengs onderskeidelik, gelewer. Soortgelyk aan wat vir die reduktiewe opwerk proses gevind is, moes die hoër geoksigeneerde subtrate ook as die monotriflaatesters beskerm word ten einde suksesvolle osonolise moontlik te maak en kon die verlangde produkte, metiel-4-trifluoro-metaansulfonieloksi-3-metoksifenielasetaat, metiel-4-trifluorometaansulfonieloksi-3,5-di-metoksifenielasetaat en metiel-2-trifluorometaansulfonieloksi-4,6-dimetoksifenielasetaat, op hierdie wyse in 9, 17 en 65% opbrengs onderskeidelik, berei word.

Aangesien die gepubliseerde proses vir die enantioselektiewe sintese van isoflavonoïede vereis dat die fenielasetate, wat d.m.v. osonolise verkry word, na die amiede omgeskakel moet word, is besluit om 'n ondersoek na die moontlikheid om die allielbenseensubstrate tydens osonolise direk na amiede om te skakel, in te stel. Aanvanklike pogings waarin anilien tydens die osonolisereaksie by die substraat en oplosmiddel gevoeg is, het egter slegs tot oksidasie van die anilien gelei, maar nadat die proses gewysig is om na vorming van die 1,2,4-trioksolaan die oortollige osoon te verwyder voordat die anilien bygevoeg is, het dit daartoe gelei dat die verlangde produk, 2-metoksifenielasetanilied in 37% opbrengs verkry kon word. 'n Uitbreiding van hierdie proses na die reaksie van 1-alliel-4-metoksibenseen met asetamied waartydens die produk in 39% opbrengs verkry is, het voorts getoon dat gedeaktiveerde stikstof nukleofiele ook tydens die nuwe unieke reaksie gebruik kan word. Die benutting van 2-imidasolidinone, 'n sekondêre stikstof nukleofiel, het egter nie tot die vorming van enige bruikbare produk gelei nie, waardeur aangetoon is dat heelwat navorsingswerk nog benodig word ten einde die volle omvang van hierdie nuwe reaksie te bepaal en dit vir die enantioselektiewe sintese isoflavonoïede bruikbaar te maak.

Laastens is dit ook tydens die huidige ondersoek aangetoon dat die fenielasynsuur derivate wat d.m.v. osonolise gevorm word, ook na deoksibenzoïene, 'n ander belangrike isoflavonoïed-voorloper, omgeskakel kan word. In hierdie verband is ongesubstitueerde deoksibenzoïen in ongeveer 60% opbrengs berei deur die reaksie van fenielasetielchloried met fenielmagnesiumbromied by -78 ^{o}C.

Sleutelwoorde

Isoflavonoïede, Claisen-herrangskikking, allielbenseen, osonolise, 1,2,4-trioksolaan, fenielasetaldehied, metielfenielasetaat, fenielasetanilied, fenielasetamied, deoksiebenzoïen.