PARAMETERS INFLUENCING REGIOSELECTIVITY IN THE PALLADIUM CATALYSED CARBONYLATION OF STILBENES AND RELATED ALKENES

Dissertation submitted in fulfilment of the requirements for the degree

Magister Scientiae

in the

Department of Chemistry

Faculty of Natural and Agricultural Sciences

at the

University of the Free State

Bloemfontein

by

Maretha Serdyn

Supervisor: Prof. B.C.B. Bezuidenhoudt

Co-supervisor: Dr. C. Marais

January 2013

Acknowledgements

I would hereby like to say a word of thanks to:

My supervisor Prof. B.C.B. Bezuidenhoudt for all the friendly guidance, expert advice, support and never ending enthusiastic encouragement through an always open office door. It is a privilege and a pleasure to be your student.

Dr. Charlene Marais, for all her help in teaching me the art of presenting chemistry on paper.

To all the IPC-group members, a special thanks because you are the ones who have to look at the disappointed face returning from the NMR-room or listen to the hopeful arguments in group meetings. While spending nine hours a day with you, you all became more than colleagues but chemistry friends who will always say: "Welcome to organic chemistry" with friendly smiles.

I'd like to say thank you to Johannes, Bernie and Bradley who trained me on various instruments without which this project would not have been possible, always helped with desperate questions and spoke words of encouragement when the sighs could be heard from the lab. to Timbuktu. And of course Tanya who has known me since the start of my life as a chemist, from first year to masters we could always find time for a hysterical laugh whether in disappointing or exciting times.

Thank you to my friends, family and almost in-laws for always understanding when invitation after invitation had to be turned down for the sake of science. I know the chemistry lingo can drive you mad but know that your support and encouragement are greatly appreciated.

To my fiancé and special loved one, Johan, thank you so much for all your patience and reassurance through the years, always telling me to believe that I can and that the mountain I am seeing is actually just a little ant hill. Thank you for taking on amazing adventures with me while exploring the world we live in and for showering me with love and support, love you more.

Thank you to my mom, Lizette, who would bend over backwards to make my life easier and to support me in every step of the way towards whatever I would like to achieve. I would also like to thank my late farther, Naylor, who always said: "In life, always do what you fear most first, everything is down hill from there". You made the best team in teaching me the ways of life.

However this thesis would not be possible without the blessings of our Heavenly Father who holds my hand when it is quivering and carries me when I am tired but also celebrates with me when the sun rises every morning and puts a spring in my step when I know You are in control.

Thank you to the National Research Foundation for funding this M.Sc. research project.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION **1**

1.1. Isoflavonoid classes 1

1.2. Biological activity of isoflavonoids 2

1.3. References 4

CHAPTER 2: ISOFLAVONOID SYNTHESIS **5**

2.1. Isoflavones 5

2.1.1. Deoxybenzoin route 5

2.1.2. Chalcone route 9

2.1.3. More recent methods 12

2.2. Isoflavanones 17

2.3. Isoflavans 21

2.4. Pterocarpans 24

2.4.1. Pterocarpans 24

2.4.2. 6a-Hydroxypterocarpans 28

2.4.3. Pterocarpenes 30

2.5. Rotenoids 30

2.6. Coumestans 37

2.7. References 39

CHAPTER 3: CARBONYLATION OF ALKENES **42**

3.1. Polyketone formation 43

3.2. Hydroformylation 45

3.2.1. Cobalt catalysed hydroformylation 45

3.2.2. Rhodium catalysed hydroformylation 50

3.3. Hydrocarboxylation/Hydroxycarbonylation 56

3.4. Hydroesterification 58

3.5. References 62

CHAPTER 4: RESULTS AND DISCUSSION 66

4.1. Introduction 66

4.2. Synthesis of stilbenes 67

4.2.1. Preparation of methoxy substituted benzyl alcohols 69

4.2.2. Synthesis of phosphonium salts 71

4.2.3. Synthesis of protected aldehydes 75

4.2.4. Stilbenes through application of the Wittig reaction 80

4.2.5. Stilbene preparation through a Perkin-type reaction 85

4.3. Methoxycarbonylation of model substrates 87

4.3.1. Introduction 87

4.3.2. Model substrates 88

4.3.3. Unsubstituted stilbene 90

4.3.4. *Trans-β*-methylstyrene 90

4.3.5. Optimization of conditions and solvent studies with *trans-β*-methylstyrene 92

4.3.6. Methoxycarbonylation of other disubstituted styrenes 96

4.3.7. Influence of ring substituents on methoxycarbonylation of *trans-β*-methylstyrene 97

4.4. Aminocarbonylation/Hydroamidation 103

4.5. Methoxycarbonylation of stilbenes 107

4.6. Methoxycarbonylation with bidentate ligands 109

4.7. Methoxycarbonylation of a non-conjugated alkene 110

4.7.1. Synthesis of 1,3-diphenylprop-1-ene 111

4.7.2. Methoxycarbonylation of 1,3-diphenylprop-1-ene 113

4.8. Conclusions and future work 114

4.9. References 116

CHAPTER 5: EXPERIMENTAL 119

5.1. Chromatography 119

5.1.1. Thin Layer Chromatography (TLC) 119

5.1.2. Preparative Layer Chromatography (PLC) 119

5.1.3. Flash Column Chromatography (FCC) 119

5.1.4. Cyclograph Chromatography (CC) 119

5.2. Spectroscopic and spectrometric methods 120

5.2.1. Nuclear Magnetic Resonance spectroscopy (NMR) 120

5.2.2. Gas spectroscopy (GC) 120

5.2.3. Mass Spectroscopy (MS) 120

5.2.4. Infrared spectroscopy (IR) 121

5.3. Melting Points 121

5.4. Microwave Reactor 121

5.5. Anhydrous Solvents 121

5.6. Standard Procedures 121

5.6.1. Reaction work-up 121

5.6.2. Carbonylation reactions in Parr-reactor 122

5.7. Preparation of methoxysubstituted benzyl alcohols 122

5.7.1. General $NaBH_4$ reduction procedure 122

5.7.1.1. 2,4-Dimethoxybenzyl alcohol (**355**) 122

5.7.1.2. 2,4,6-Trimethoxybenzyl alcohol (**356**) *via* $NaBH_4$ reduction 122

5.7.2. 2,4,6-Trimethoxybenzyl alcohol (**356**) *via* hydrogenation 123

5.8. Synthesis of phosphonium salts 123

5.8.1. General procedure for the synthesis of phosphonium salts from benzyl halides 123

5.8.1.1. Benzyltriphenylphosphonium bromide (**337**) 123

5.8.1.2. 4-Methoxybenzyltriphenylphosphonium chloride (**343**) 124

5.8.1.3. 4-Methoxybenzyl bromide (**349**) 124

5.8.1.4. 4-Methoxybenzyltriphenylphosphonium bromide (**344**) 125

5.8.2. Synthesis of phosphonium salt from benzyl alcohol 125

5.8.2.1. Benzyltriphenylphosphonium trifluoroacetate (**362**) 125

5.8.3. General procedure for the synthesis of benzyl alkyl ethers 126

5.8.3.1. 4-Methoxybenzyl methyl ether (**366**) 126

5.8.3.2. 2-Methoxybenzyl methyl ether (**367**) 126

5.8.4. Synthesis of phosphonium salts through cleavage of benzyl ethers 127

5.8.4.1. 4-Methoxybenzyltriphenylphosphonium bromide (**344**) 127

5.9. Synthesis of protected aldehydes 127

5.9.1. 4-Ethoxymethoxybenzaldehyde (**369**) 127

5.9.2. General procedure for protecting OH-groups with *tert*-butyldiphenylsilyl-chloride 128

5.9.2.1. 4-*Tert*-butyldiphenylsilyloxybenzaldehyde (**371**) 128

5.9.3. General procedure for protecting OH-groups with trifluoromethanesulfonyl chloride 128

5.9.3.1. 4-Trifluoromethanesulfonyloxybenzaldehyde (**382**) 129

5.9.3.2. 2-Trifluoromethanesulfonyloxybenzaldehyde (**383**) 129

5.10. Synthesis of stilbenes *via* the Wittig reaction 129

5.10.1. Utilizing NaH as base 129

5.10.1.1. *Trans*-stilbene (**384**) 129

5.10.1.2. 4-Methoxystilbene (**329**) 130

5.10.2. Utilizing Na-metal as base 130

5.10.2.1. *Trans*-stilbene (**384**) 130

5.10.3. Utilizing BuLi as base 131

5.10.3.1. *Cis*- (385) and *trans*-4-methoxystilbene (**387**) 131

5.10.4. General procedure for utilizing NaOH as base 131

5.10.4.1. *Cis*- (**385**) and *trans*-4-methoxystilbene (**387**) (attempt 1) 132

5.10.4.2. *Cis*- (**385**) and *trans*-4-methoxystilbene (**387**) (attempt 2) 132

5.10.4.3. *Cis*- (**385**) and *trans*-4-methoxystilbene (**387**) (attempt 3) 132

5.10.4.4. *Cis*- (**386**) and *trans*-2-methoxystilbene (**388**) 133

5.10.4.5. *Cis*- (389) and *trans*-4-ethoxymethoxystilbene (**390**) 134

5.11. Synthesis of stilbenes utilizing other methods 135

5.11.1. *Trans*-4-hydroxystilbene (**394**) through deprotection of ethoxymethoxy group 135

5.11.2. *Trans*-4-hydroxystilbene (**394**) with a Perkin-type reaction 135

5.11.3. *Trans*-4'-trifluoromethanesulfonyloxystilbene (**395**) through protection reaction 136

5.12. Methoxycarbonylation of model substrates 136

5.12.1. Methoxycarbonylation of hexene (**397**) 136

5.12.2. Carbonylation of styrene (**313**) 136

5.12.3. Carbonylation of allylbenzene (**398**) 137

5.13. Methoxycarbonylation of *trans*-*β*-methylstyrene (**405**) 137

5.13.1. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH 137

5.13.2. Optimization of the methoxycarbonylation reaction 138

5.13.2.1. Higher catalyst concentration 138

5.13.2.2. $PdCl_2/Al(OTf)_3/PPh_3$ in MeOH 138

5.13.2.3. Model methoxycarbonylation with Diab methodology 138

5.13.2.4. $Pd(OAc)_2$/*p*-TsOH/PPh_3 low temperature 139

5.13.2.5. $Pd(OAc)_2$/*p*-TsOH/PPh_3 medium temperature 139

5.13.2.6. $Pd(OAc)_2$/*p*-TsOH/PPh_3 high temperature 139

5.13.2.7. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH:dioxane 139

5.13.2.8. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH:toluene 140

5.13.2.9. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH:DMA 140

5.13.2.10. $PdCl_2/Al(OTf)_3/PPh_3$ in MeOH:DME 140

5.13.2.11. $PdCl_2/Al(OTf)_3/PPh_3$ in MeOH:THF 140

5.13.2.12. $Pd(OAc)_2$/*p*-TsOH/PPh_3 in MeOH:THF 140

5.13.2.13. $PdCl_2/Al(OTf)_3/PPh_3$ in EtOH 141

5.13.2.14. Optimization of reaction conditions 141

5.14. Methoxycarbonylation of disubstituted styrenes 142

5.14.1. Carbonylation of *α*-methylstyrene (**409**) 142

5.14.2. Carbonylation of 2-methyl-1-phenylprop-1-ene (**411**) 142

5.15. Synthesis of substituted styrenes 143

5.15.1. 1-(4'-Trifluoromethanesulfonyloxyphenyl)propan-1-one (**418**) 143

5.15.2. 1-(4'-Trifluoromethanesulfonyloxyphenyl)propan-1-ol (**419**) 143

5.15.3. General elimination procedure 143

5.15.3.1. *Trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**) 143

5.15.4. 1-(4'-*Tert*-butyldiphenylsilyloxyphenyl)propan-1-one (**424**) 144

5.15.5. 1-(4'-*Tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**) 144

5.15.6. *Trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**) 145

5.16. Methoxycarbonylation of other substituted styrenes 146

5.16.1. Carbonylation of *trans*-anethole (**413**) 146

5.16.2. Carbonylation of 1-(4'-trifluoromethanesulfonyloxyphenyl) prop-1-ene (**420**) 147

5.16.3. Carbonylation of *trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl) prop-1-ene (**426**) 147

5.17. Aminocarbonylation 147

5.17.1. Aniline as nucleophile (attempt 1) 148

5.17.2. Aniline as nucleophile (attempt 2) 148

5.17.3. Aniline as nucleophile (attempt 3) 149

5.17.4. Benzamide as nucleophile 149

5.17.5. Butylamine as nucleophile 149

5.17.6. Piperidine as nucleophile 149

5.18. Methoxycarbonylation of stilbenes 149

5.18.1. Carbonylation of *trans*-stilbene (**384**) in MeOH 149

5.18.2. Carbonylation of *trans*-stilbene (**384**) in MeOH:dioxane (1:1) 150

5.18.3. Carbonylation of *trans*-stilbene in MeOH:THF (**384**) 150

5.18.4. Carbonylation of *cis*-stilbene (**445**) 150

5.18.5. Carbonylation of *trans*-stilbene (**384**) [with p-TsOH and $Al(OTf)_3$] 150

5.18.6. Carbonylation of 2-methoxystilbene (**330**) 150

5.19. Methoxycarbonylation with bidentate ligands 151

5.19.1. BINAP-catalyst system 151

5.19.1.1. Carbonylation of phenyl acetylene (**452**) 151

5.19.1.2. Carbonylation of *trans*-*β*-methylstyrene (**405**) 151

5.19.2. $Pd_2(dba)_3$/DTBPMB-catalyst system 151

5.19.2.1. Carbonylation of 2-octene (**455**) 151

5.19.2.2. Carbonylation of *trans*-*β*-methylstyrene (**405**) 152

5.19.2.3. Carbonylation of *trans*-stilbene (**384**) 152

5.20. Synthesis and methoxycarbonylation of a non-conjugated alkene 152

5.20.1. 1,3-Diphenylpropan-2-ol (**450**) 152

5.20.2 1,3-Diphenylprop-1-ene (**451**) ($CuSO_4$ dehydration) 153

5.20.3. 1,3-Diphenylprop-1-ene (**451**) (*p*-TsOH elimination) 153

5.20.4. *Trans*-1,3-diphenylprop-2-en-1-ol (**453**) 153

5.20.5. 1,3-Diphenylpropan-1-one (**455**) 153

5.20.6. 1,3-Diphenylpropan-1-ol (**454**) 154

5.20.7. 1,3-Diphenylprop-1-ene (**451**) 154

5.20.8 Carbonylation of 1,3-diphenylprop-1-ene (**451**) 155

5.21. References 155

APPENDIX 1 - ABBREVIATIONS

APPENDIX 2 - NMR SPECTRA (^{1}H and ^{13}C)

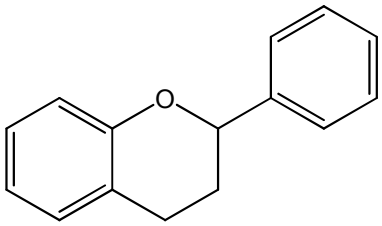
APPENDIX 3 - Two dimensional and supplementary NMR spectra

SUMMARY

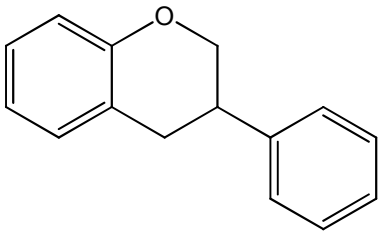
SAMEVATTING

INTRODUCTION 1

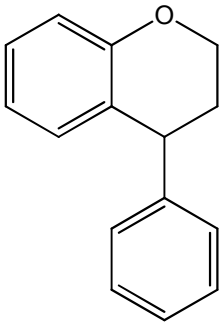
Isoflavonoids have been known for their intense colours and phytoalexin properties since 1975 and became famous in the eighties for their biological activity.[1,2] The isoflavonoids are biogenetically related to the flavonoids, but contain a unique C_6-C_3-C_6 skeleton based on a 3-phenylchroman structure (**2**) whereas flavonoids have a 2-phenylchroman (**1**) and neoflavonoids a 4-phenylchroman skeleton (**3**). Isoflavonoids is a large class of naturally occurring O-heterocycles and have been isolated from the subfamily Papilionoideae of the Leguminosae for over 50 years, leading to the discovery of over 1600 natural products.[1,2,3]



Flavonoid
(**1**)



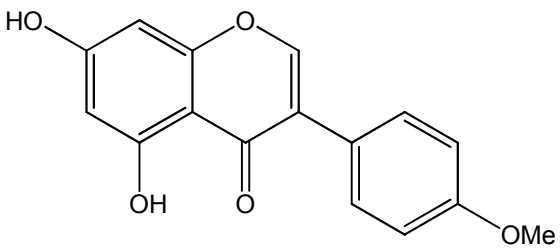
Isoflavonoid
(**2**)



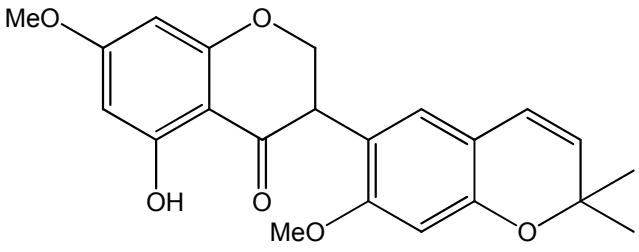
Neoflavonoid
(**3**)

1.1. Isoflavonoid classes

Isoflavonoids can be divided into six classes (Figure 1-1) depending on the level of oxidation and unsaturation present on/in the heterocyclic ring. Hydroxylation, protected and free phenolic, on the A-ring and B-ring may add to structural diversity[4] (**4**) while several compounds displaying secondary heterocyclic rings and/or alkyl substituents[5] (**5**) have also been isolated from natural sources.



Biochanin A
(**4**)



Erypoegin G
(**5**)

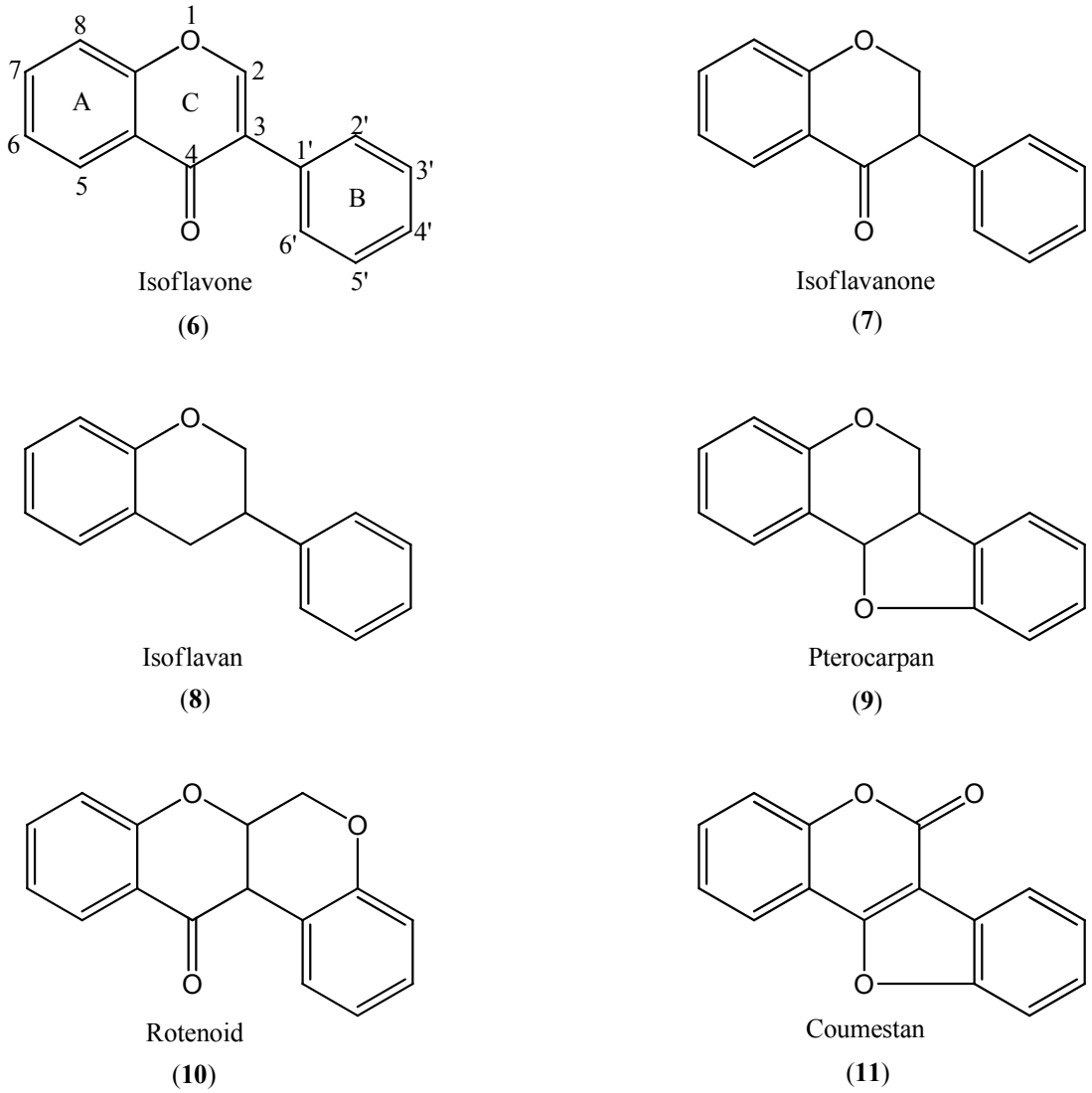
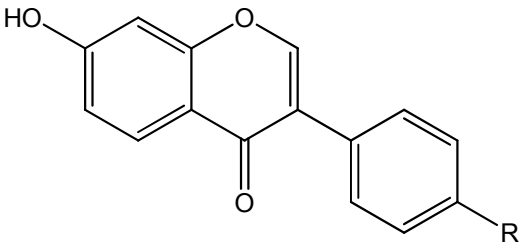


Figure 1-1: Structures of isoflavonoid classes

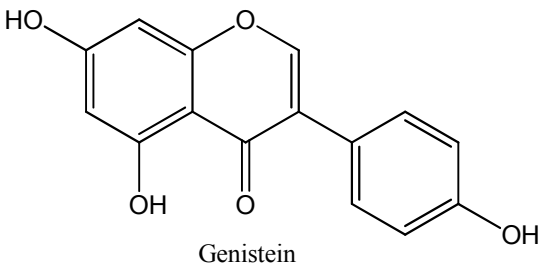
1.2. Biological activity of isoflavonoids

A distinctive feature of isoflavonoids is their estrogenic, insecticidal, piscicidal and anti-microbial properties as opposed to other flavonoids which are mainly innocuous substances.[2,6] Isoflavonoids present in forage legumes, like red and white clover, are weak oestrogens which may cause infertility problems in animals feeding on these plants.[1,3] Epidemiological studies have consistently shown an inverse association between the consumption of fruit and vegetables and the risk of various human cancers.[7] Since 1931 it's been known that soybeans contain high amounts of the isoflavonoids, e.g. daidzein (**12**) and genistein (**14**), which inhibits the growth of breast, prostate and colon cancer and supports the hypothesis that phytoestrogens have anticancer properties.[8,9]

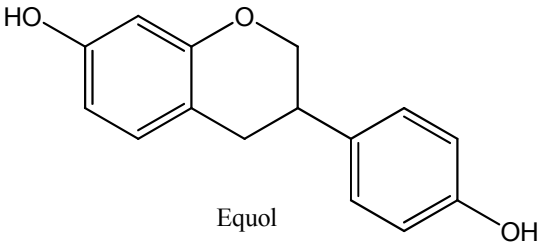
Equol (**15**), a metabolite of daidzein, has attracted a lot of attention for its phytoestrogenic activity and potential use in menopausal hormone replacement therapy as well as in the treatment of breast cancer. Genistein (**14**) which metabolizes into 3'-hydroxy equol (**16**) prevents hormone-related cancer and cardiovascular diseases.[3,10] Isoflavans are also used in the treatment of free radical mediated disorders such as cancer, Alzheimer's, Parkinson's and cardiovascular diseases, due to its antioxidant properties.[10] Plants containing rotenoids (**10**) have been used in tropical Asia, Africa and South America as fish poisons since it decreases oxygen uptake.[3]



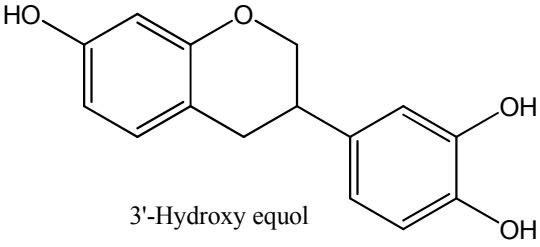
Daidzein (**12**) R = OH
Formononetin (**13**) R = OMe



Genistein
(**14**)



Equol
(**15**)



3'-Hydroxy equol
(**16**)

Since the isoflavonoids are of value, the synthesis of these compounds has been studied extensively for the last 50 years. Unfortunately most of the current synthetic procedures are tedious, use toxic chemicals and/or needs excessive amounts of reagents which generate large quantities of waste, thus polluting the environment. It was therefore decided to investigate the application of recently developed catalytical processes to the synthesis of isoflavonoids. In this regard it is envisaged that a suitable olefinic precursor, like stilbene (**19**), could be transformed by hydroesterification into a C-3 carboxylate containing moiety (**18**) that could be cyclized to produce the heterocyclic C-ring of the isoflavonoid molecule (**17**) (Figure 1-2). Since most isoflavonoids contain only one chiral centre in the heterocyclic ring, an added advantage of the hydroesterification protocol could be the establishment of the desired absolute configuration at this chiral centre during the carbonylation process if a chiral alcohol can be used.

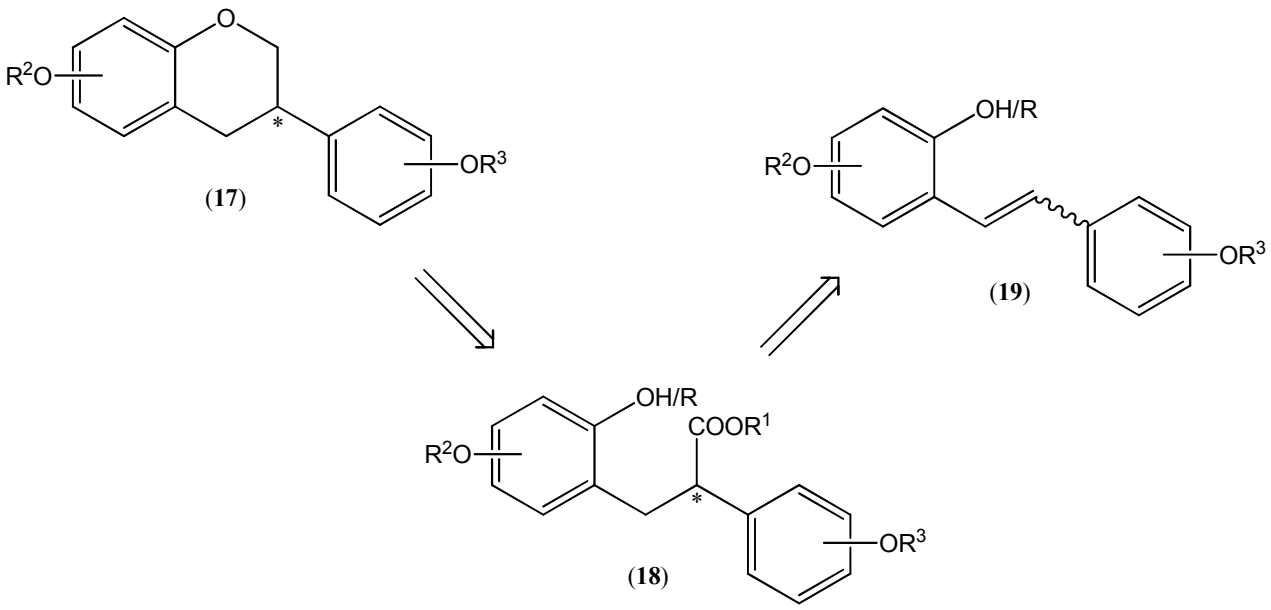


Figure 1-2: Retrosynthetic pathway for isoflavonoid synthesis through carbonylation

1.3. References

(1) Dewick, P. M. In *The Flavonoids - Advances in research*; Harborne, J. B., Ed.; Chapman and Hall Ltd.: London, 1982, pp. 535-632.

(2) Donnelly, D. M. X.; Boland, G. M. *Nat. Prod. Rep.* **1995**, *12*, 321-338.

(3) Wong, E. In *The Flavonoids*; Harborne, J. B.; Mabry, T. J.; Mabry, H., Ed.; Chapman and Hall Ltd.: London, 1975, pp. 741-800.

(4) Benavides, A.; Bassarello, C.; Montoro, P.; Vilegas, W.; Piacente, S.; Pizza, C. *Phytochemistry* **2007**, *68*, 1277-1284.

(5) Tanaka, H.; Oh-Uchi, T.; Etoh, H.; Sako, M.; Sato, M.; Fukai, T.; Tateishi, Y. *Phytochemistry* **2003**, *63*, 597-602.

(6) M. Boland, G.; M. X. Donnelly, D. *Nat. Prod. Rep.* **1998**, *15*, 241-260.

(7) Birt, D. F.; Hendrich, S.; Wang, W. *Pharmacol. Ther.* **2001**, *90*, 157-177.

(8) Coward, L.; Barnes, N. C.; Setchell, K. D. R.; Barnes, S. *J. Agric. Food Chem.* **1993**, *41*, 1961-1967.

(9) Adlercreutz, H. *Environ. Health Perspect.* **1995**, *103*, 103-112.

(10) Gharpure, S. J.; Sathiyanarayanan, A. M.; Jonnalagadda, P. *Tetrahedron Lett.* **2008**, *49*, 2974-2978.

ISOFLAVONOID SYNTHESIS 2

Initially isoflavonoids were isolated from various plant species, but difficulty surrounding the isolation of individual isoflavonoids like low yields, inseparable mixtures, etc., and a desire to study the physiological activities of differently substituted compounds, have led to extensive investigations into the synthesis of monomeric isoflavonoids. The synthesis of isoflavonoids can be divided into two main categories, *i.e.* the preparation of isoflavonoids as racemic mixtures and secondly, the more important stereoselective synthesis of isoflavonoids.

In the beginning of the 21st century a lot of focus was set on the synthesis of biologically important isoflavonoids. Well known isoflavonoids are equol (**15**), known to cause direct growth inhibition of oestrogen-dependent breast cancer and which is currently being studied for prostate cancer and cardiovascular disease therapy, daidzein (**12**) and formononetin (**13**), with diverse biological activities like estrogenic, anti-breast cancer, hormone replacement and cancer chemoprevention.[1,2] Medical applications such as these thus served as impetus to develop viable synthetic pathways towards isoflavonoids.

2.1. Isoflavones

Isoflavones are the most abundant of the natural isoflavonoids and serve as key intermediates for the synthesis of other isoflavonoids like isoflavanones (**7**), isoflavans (**8**) and pterocarpans (**9**).[3,4] The 3-phenylbenzopyrone ring system of isoflavones can be formed through two pathways. The first utilizes either a C_{14} or C_{15} compound of which the former (*i.e.* deoxybenzoins) undergoes ring closure and the latter (*i.e.* chalcones) oxidative transformations. Secondly C_7 and C_8 units can be joined by the enamine acylation methodology.[4]

2.1.1. Deoxybenzoin route

Traditionally, the synthetic approach towards isoflavonoids entailed ring closure of an appropriate deoxybenzoin (**20**) with a suitable C_1 unit. A wide variety of C_1 reagents like triethyl orthoformate, zinc cyanide, dimethylformamide (DMF), ethyl formate, and ethoxallyl chloride were therefore studied in this regard (Figure 2-1).[5,6,7] Unfortunately oxidation patterns and protection of hydroxy groups play a crucial role in the successful application of this approach. With the triethyl orthoformate methodology, for example, the reaction gave a very low yield of 12 % in the case of 2,4,6-trihydroxy substitution on the A-ring,[4,8] while protection is required when sodium or sodium *tert*-butoxide is used as base in the ethyl formate reaction.[3,4,9] Though ethoxallyl chloride showed

no restrictions with respect to substitution pattern on the phenyl ring, it leads to an inconvenient decarboxylation step, which could only be circumvented by executing the reaction in the presence of pyridium hydrochloride.[3,4,10,11] The utilization of modern C_1 moieties[3] *i.e.* *N*-formylimidazole[12] and dimethoxydimethylaminomethane,[13] led to considerable improvements in the application of this methodology with 60-75 % isoflavone yield obtained. The discovery of other C_1 reagents, firstly, 1,3,5-triazine together with BF_3-etherate and secondly, acetic formic anhydride, which requires the presence of acetic anhydride/acetic acid and sodium formate or triethylamine respectively, opened up the possibility of high yielding (up to 90 %) preparations for isoflavones (**21-22**) regardless of free hydroxyl groups and substitution patterns, in a relatively short reaction time (2-3 h) and under mild reaction conditions.[5,14]

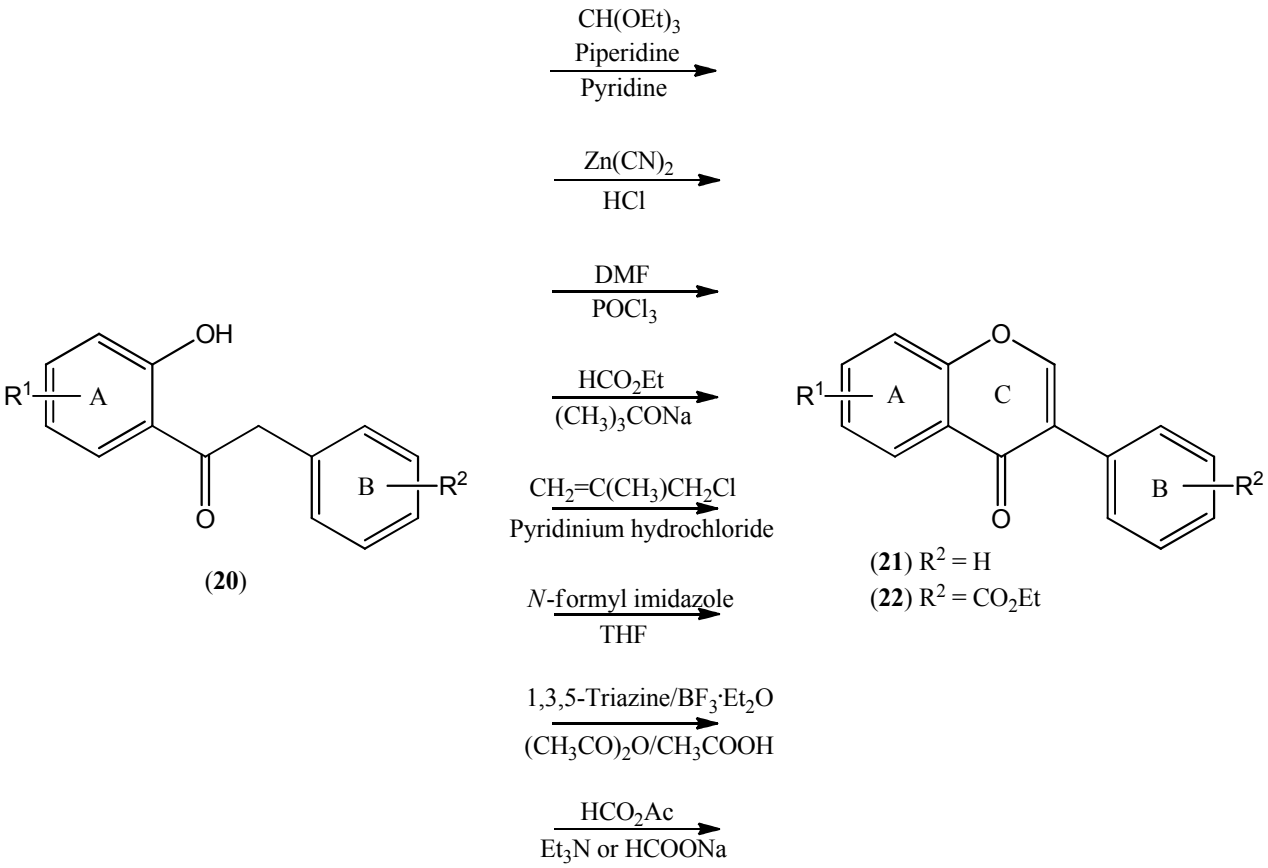
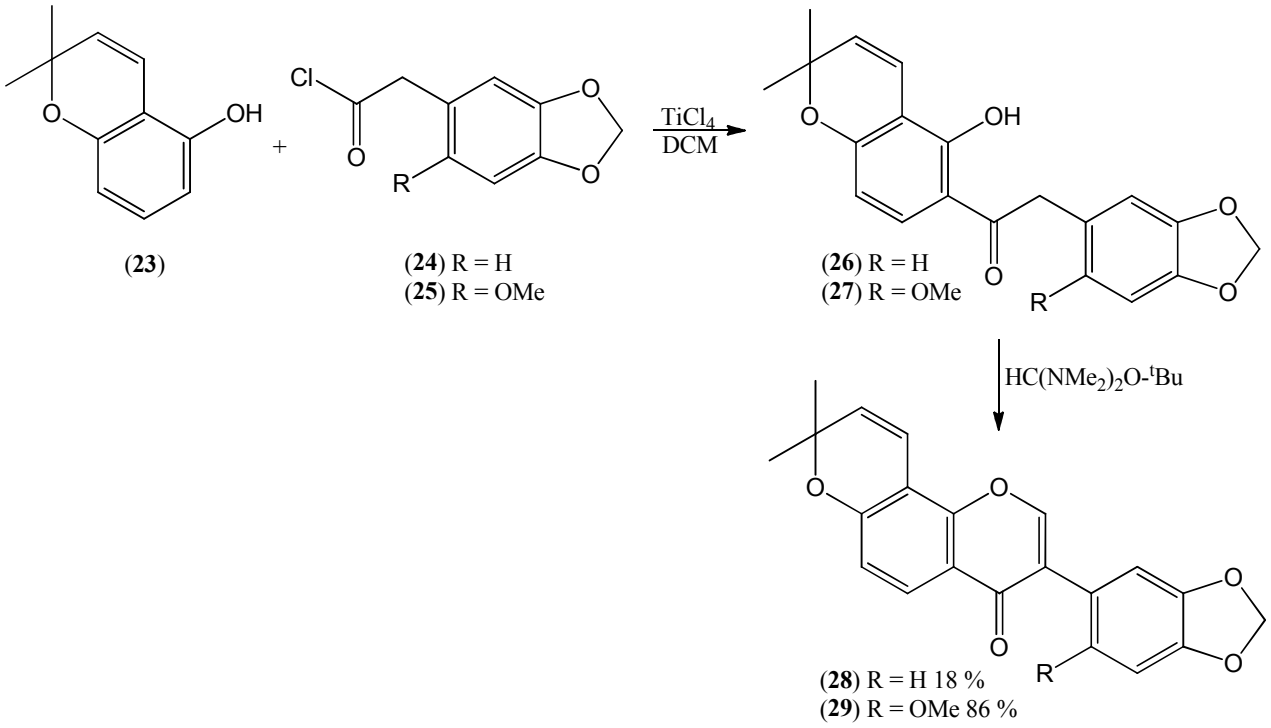


Figure 2-1: Reagents for the ring closing of deoxybenzoins to obtain isoflavones

The Bredereck's reagent, bis(dimethylamino)-*tert*-butoxymethane ($HC(NMe_2)_2O$-^{t}Bu), was discovered in 1987 and forms isoflavones in less than 30 minutes at 90°C without using any solvent. Calopogonium isoflavone B (**28**) and Jamaicin (**29**) was synthesized by subsequent ring closure with $HC(NMe_2)_2O$-^{t}Bu, through the deoxybenzoin intermediate (**26-27**) formed with Friedel-Crafts acylation (Figure 2-2).[10,15]



(**23**)

(**24**) R = H
(**25**) R = OMe

(**26**) R = H
(**27**) R = OMe

(**28**) R = H 18 %
(**29**) R = OMe 86 %

Figure 2-2: Isoflavone synthesis with Brederick's reagent

A serious disadvantage that hampers the application of the deoxybenzoin approach towards the synthesis of isoflavones is found in the availability of substrates with the desired substitution patterns. The synthesis of deoxybenzoin molecules is often complicated by poor yields and starting materials that are not readily available.

In 1991 Wahala and Hase[17] described a Friedel-Crafts type general and direct synthesis of polyhydroxyisoflavones starting from unprotected phenols and arylacetic acids, using BF_3-etherate as both catalyst and solvent. Introduction of the C_1 unit was subsequently achieved by reaction with DMF in the presence of BF_3-etherate and mesyl chloride. Interestingly, the DMF-$MeSO_2Cl$ reaction can be performed in a microwave reactor reducing the reaction time to even less than 2 minutes. An added advantage of this method lies in the fact that protection-deprotection of hydroxy groups are not necessary. This approach was used not only for synthesizing 4',8-dihydroxyisoflavone (**33**) for the first time in free phenolic form but also for the production of numerous natural products in yields ranging from 50-98 % (Figure 2-3).[16,17,18,19]

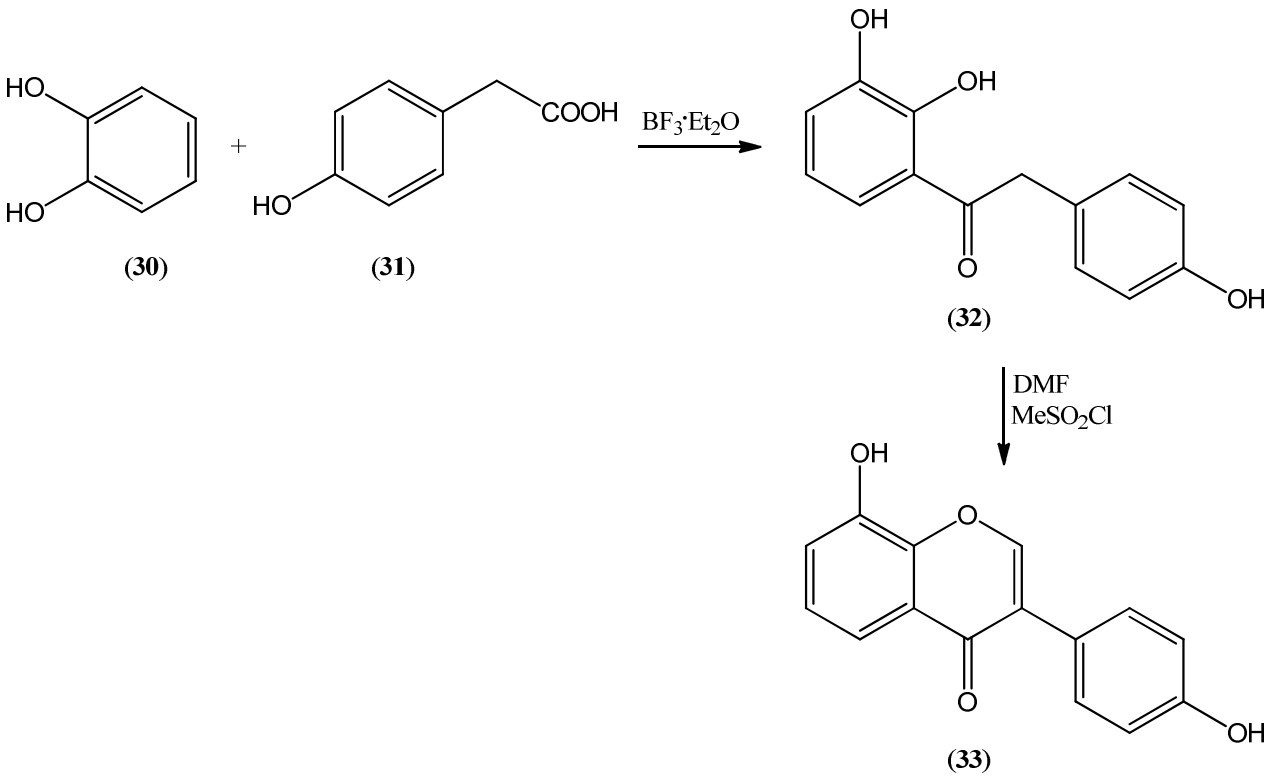


Figure 2-3: Synthesis of 4',8-dihydroxyisoflavone

In a similar approach, 6,7,4'-trimethoxyisoflavone (**41**) and 6,7,3',4'-tetramethoxyisoflavone (**42**) were synthesized using polyphosphoric acid (PPA) as catalyst. In this instance formylation of the methylene was achieved through application of the Vilsmeier-Haack reaction and cyclization by treatment with pyridinium hydrochloride (Figure 2-4).[19]

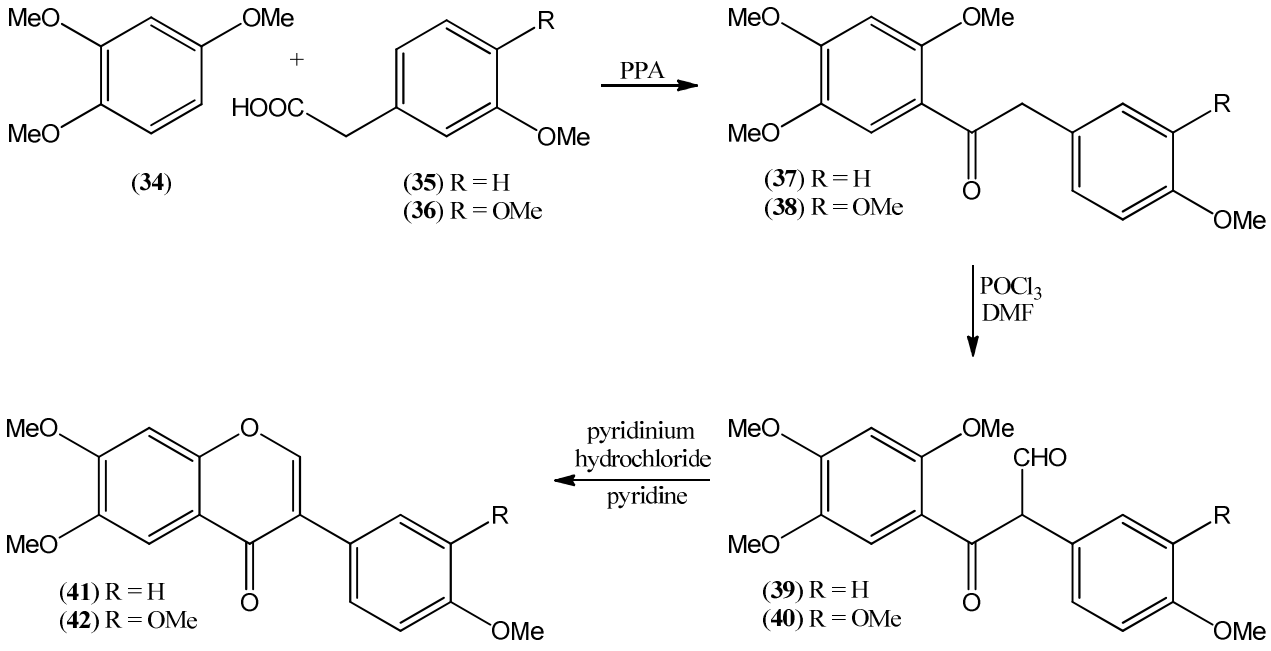


Figure 2-4: Formylation of deoxybenzoins *via* the Vilsmeier-Haack reaction

2.1.2. Chalcone route

Since chalcones are easily prepared through the condensation of acetophenones and aromatic aldehydes, which are readily available in almost all wanted hydroxylation patterns, it is obvious that these compounds would be looked at as possible starting materials for the synthesis of isoflavonoids.[3,10] In the 1960's the first successful attempt at converting a chalcone type substrate into an isoflavone was reported by Grover *et al.*[20] when the 2'-benzyloxychalcone epoxide (**43**) was subjected to Lewis acid catalysed rearrangement and the isoflavone, formononetin (**13**), was obtained in 43 % yield (Figure 2-5).[4,21] Although widely applicable, this method is associated with the disadvantages that an electron-donating group in either the *o*- or *p*-position of the non-migrating phenyl ring (A-ring) is a requirement, together with the poor yields generally obtained.[3,4,5]

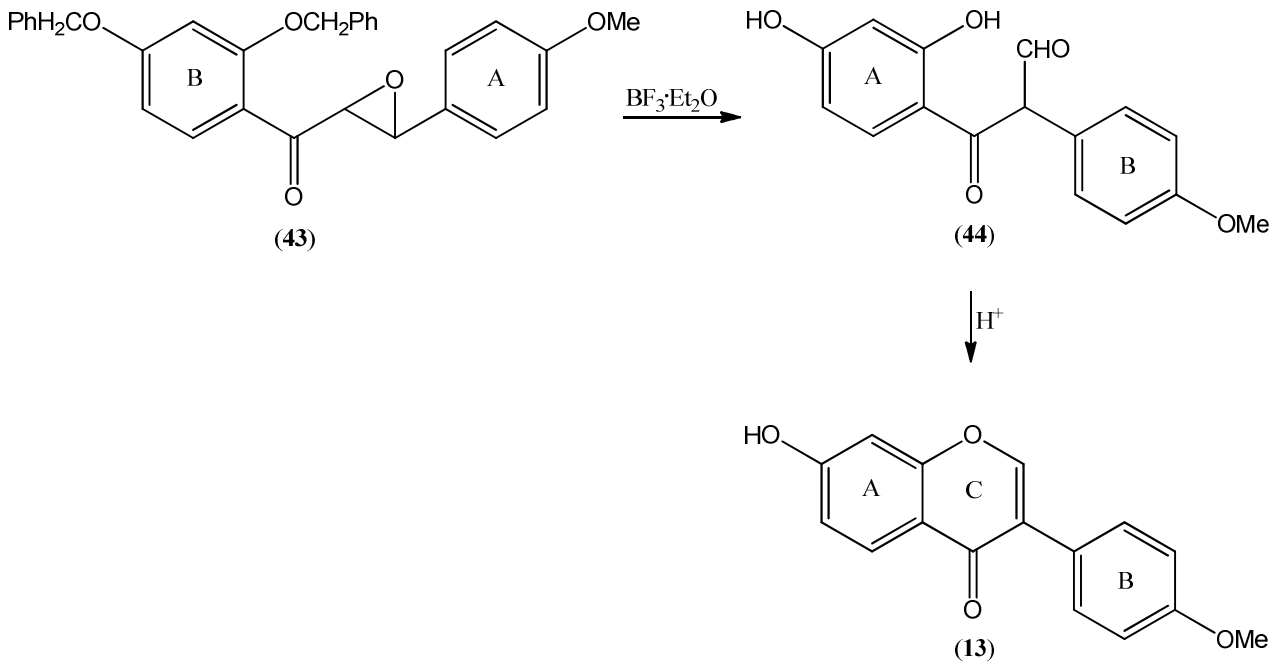


Figure 2-5: Lewis catalysed synthesis of formononetin

A great improvement with respect to this methodology came with the discovery that the same rearrangement could be effected by direct reaction of protected 2'-hydroxychalcones (**45**) with thallium(III) acetate (TTA) in methanol. Although yields were on the low side, this approach permitted the synthesis of isoflavones with sensitive methylenedioxy groups, like milldurone (**47**), and eliminated the epoxidation step from the synthetic sequence towards isoflavones (Figure 2-6).[4,22]

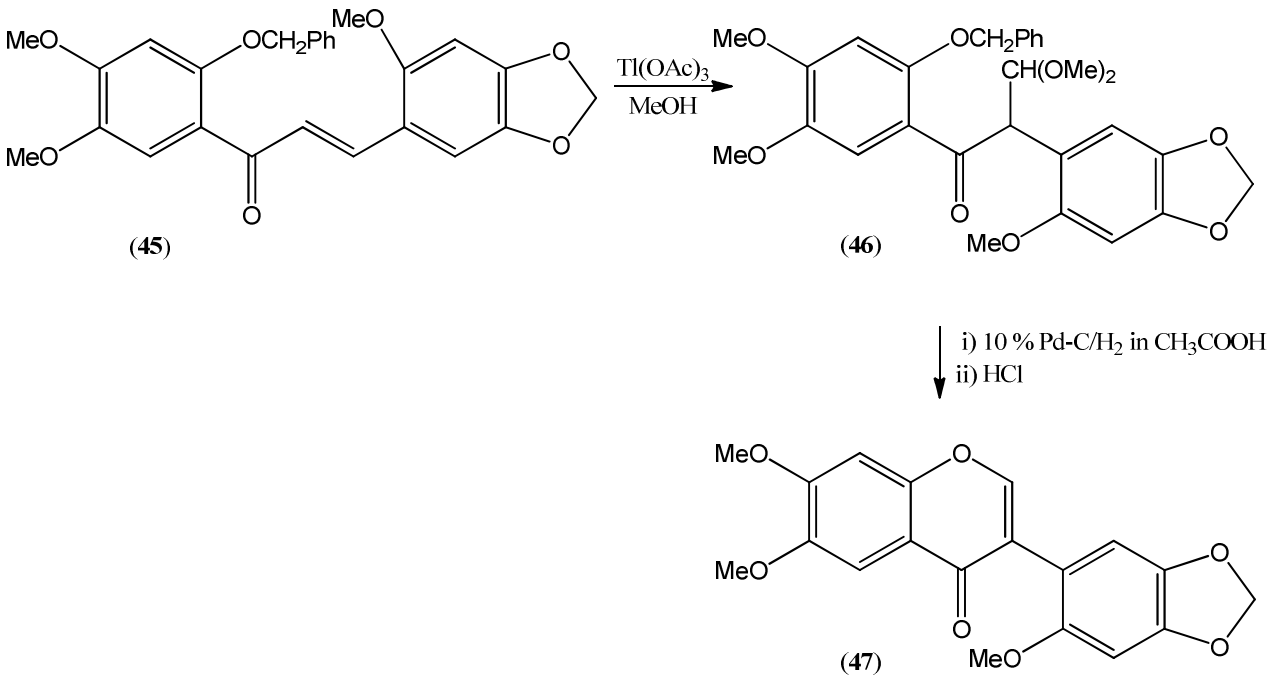


Figure 2-6: Synthesis of milldurone utilizing TTA

Replacing the acetate with the nitrate salt of thallium [thallium(III) nitrate (TTN)] by Farkas *et al.*[23] led to much improved efficiency and lowered the reaction time from up to 100 hours in boiling methanol to a few hours at room temperature with yields of 30-80 % depending on the substitution pattern (Figure 2-7).[4] Even unprotected 2'-hydroxychalcones (**48**) can be smoothly converted by TTN, while this was not possible with the use of thallium(III) acetate. Since the intermediate acetal (**49**) is usually transformed to the isoflavone (**50**) by addition of dilute HCl or base (in the case of acid sensitive substrates) to the methanolic solution of the TTN, this methodology can be regarded as a one-pot transformation of a chalcone into an isoflavone and is currently the preferred methodology for preparation of these compounds.[3,4,19,23]

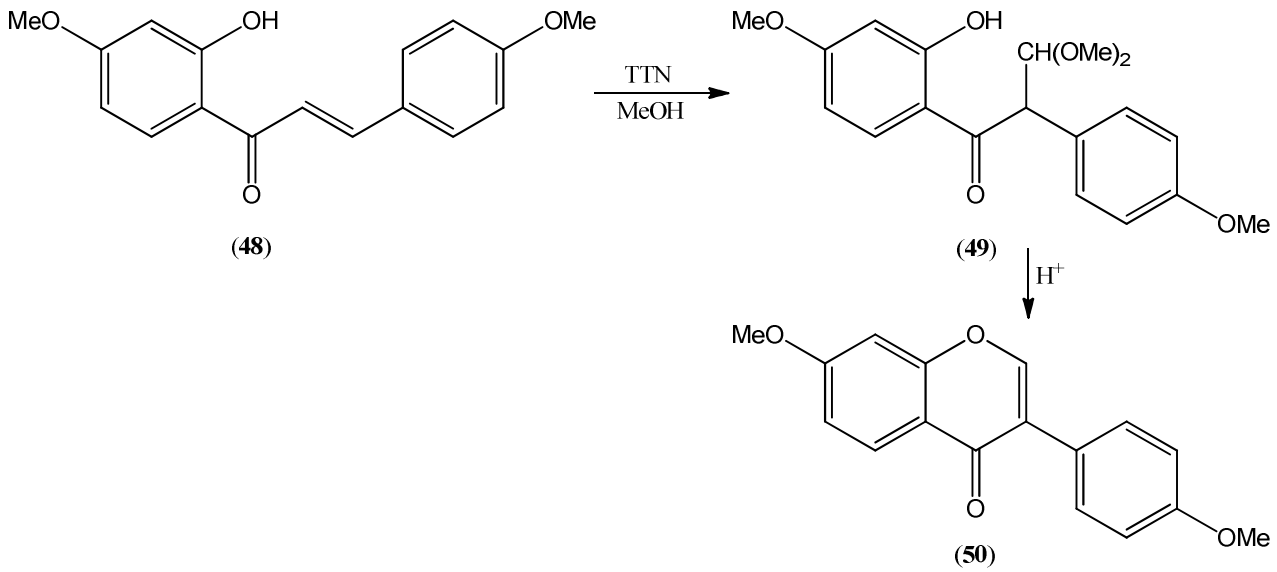


Figure 2-7: Synthesis of isoflavones from 2'-hydroxychalcones with TTN

Unfortunately thallium(III) nitrate can also react with chromene double bonds resulting in ring-contraction products, so chromene rings attached to either the A- or B-ring of the chalcone should either be protected by thiophenol formation or the double bond should be introduced through 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of the corresponding chromane (**54**) after TTN rearrangement (Figure 2-8).[5,10,24] Erythrinin A has been synthesised similarly.[5] Although this protocol works well for the transformation of chalcones into isoflavones, it must be kept in mind that thallium(III) salts are used in stoichiometric quantities in this instance, even though it is highly poisonous.[16]

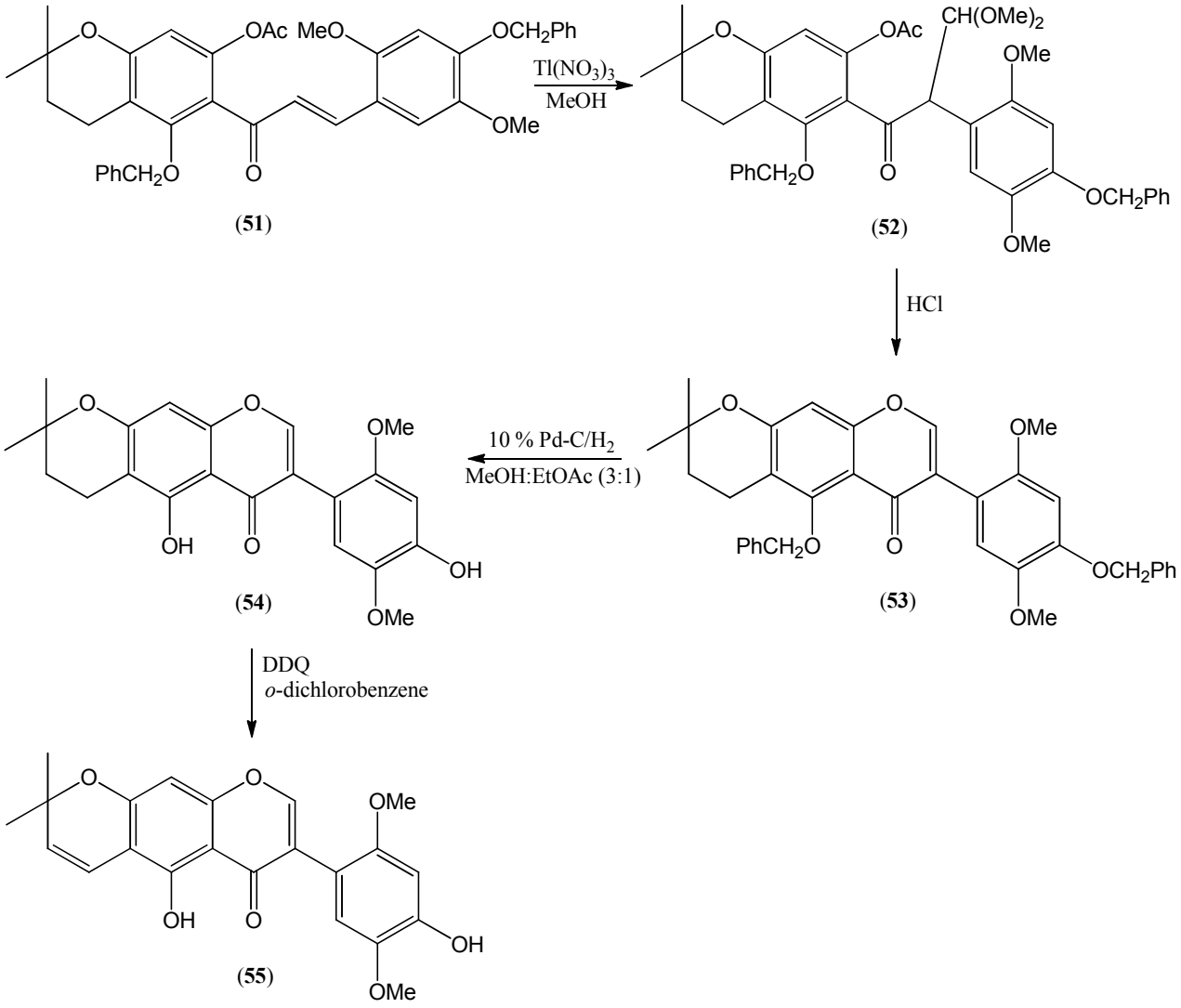
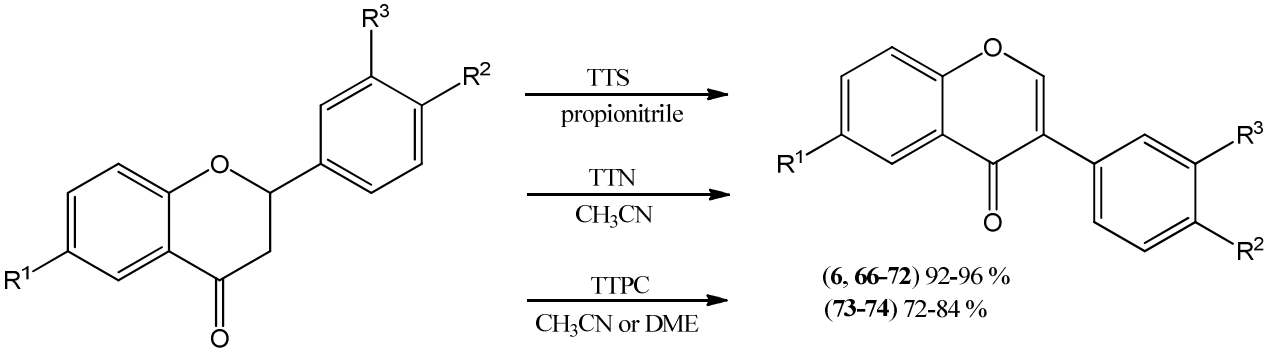


Figure 2-8: Synthesis of elongatin *via* DDQ oxidation

2.1.3. More recent methods

In the early 1990's oxidative rearrangement of flavanones to isoflavones was found to be possible when the former was treated with thallium(III) *p*-tolylsulfonate (TTS), generated *in situ* from thallium(III) acetate and *p*-toluenesulfonic acid (*p*-TsOH) (Figure 2-9). Almost quantitative yields (92-96 %) of isoflavones (**6, 66-72**) were obtained for all substitution patterns except where compounds contained electron-withdrawing groups (e.g. Cl or NO_2) on the B-ring, in which case a mixture of flavone and isoflavone products were formed. When the same reactions were performed with TTN in acetonitrile lower yields were obtained due to the formation of flavone byproducts.[25] This problem was solved by the use of a modified catalyst, thallium(III) perchlorate (TTPC), which gave high yields (72-84 %) of isoflavones (**73-74**) with either electron-withdrawing or electron-donating substituents (Figure 2-9).[10,16]

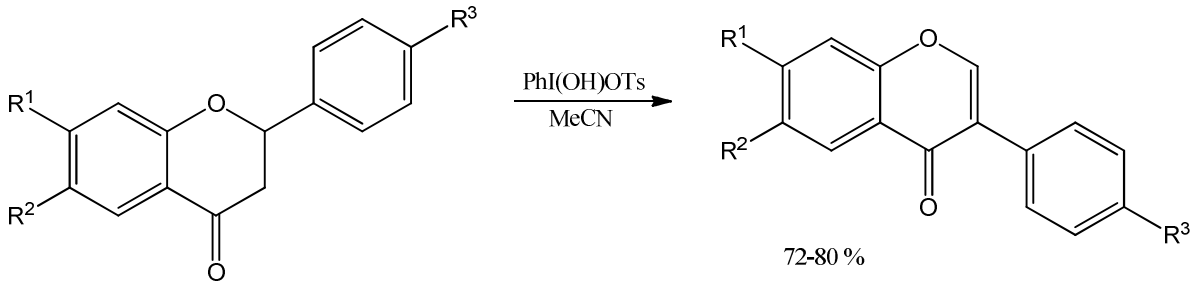


(**56**) $R^1 = R^2 = R^3 = H$
(**57**) $R^1 = R^3 = H$, $R^2 = OMe$
(**58**) $R^1 = R^3 = H$, $R^2 = Me$
(**59**) $R^1 = Cl$, $R^2 = R^3 = H$
(**60**) $R^1 = Cl$, $R^2 = OMe$, $R^3 = H$
(**61**) $R^1 = Cl$, $R^2 = Me$, $R^3 = H$
(**62**) $R^1 = Me$, $R^2 = R^3 = H$
(**63**) $R^1 = Me$, $R^2 = OMe$, $R^3 = H$
(**64**) $R^1 = R^3 = H$, $R^2 = Cl$
(**65**) $R^1 = R^2 = Cl$, $R^3 = H$

(**6**) $R^1 = R^2 = R^3 = H$
(**66**) $R^1 = R^3 = H$, $R^2 = OMe$
(**67**) $R^1 = R^3 = H$, $R^2 = Me$
(**68**) $R^1 = Cl$, $R^2 = R^3 = H$
(**69**) $R^1 = Cl$, $R^2 = OMe$, $R^3 = H$
(**70**) $R^1 = Cl$, $R^2 = Me$, $R^3 = H$
(**71**) $R^1 = Me$, $R^2 = R^3 = H$
(**72**) $R^1 = Me$, $R^2 = OMe$, $R^3 = H$
(**73**) $R^1 = R^3 = H$, $R^2 = Cl$
(**74**) $R^1 = R^2 = Cl$, $R^3 = H$

Figure 2-9: Rearrangement of flavanones to isoflavones utilizing TTS, TTN and TTPC catalysts

Due to the toxicity of thallium(III) salts, Prakash *et al.*[27,28,29] investigated the utilization of hypervalent iodine reagents in the rearrangement of flavonoid substrates to isoflavonoids. In this regard, it was found that flavanones (**56, 57, 59, 75, 76**) could be turned into isoflavones (**6, 66, 68, 77, 78**) in high yields by treatment with iodobenzene diacetate (IBD) or [hydroxyl(tosyloxy)-iodo]benzene (HTIB) (Figure 2-10).[26] The mechanism shows electrophilic attack of the I(III) species on the enol form of the flavanone (**79**) followed by 2,3-aryl migration (Figure 2-11).[10,19,27,28,29] Although this process contains an extra step, *i.e.* flavone formation from the chalcone (compared to the TTN methodology), this step usually represents a mere formality, so the hypervalent iodine methodology can be regarded as a viable alternative to the thallium mediated processes.



(**56**) $R^1 = R^2 = R^3 = H$
(**57**) $R^1 = R^2 = H$, $R^3 = OMe$
(**59**) $R^1 = R^3 = H$, $R^2 = Cl$
(**75**) $R^1 = H$, $R^2 = Cl$, $R^3 = OMe$
(**76**) $R^1 = R^3 = OMe$, $R^2 = H$

(**6**) $R^1 = R^2 = R^3 = H$
(**66**) $R^1 = R^2 = H$, $R^3 = OMe$
(**68**) $R^1 = R^3 = H$, $R^2 = Cl$
(**77**) $R^1 = H$, $R^2 = Cl$, $R^3 = OMe$
(**78**) $R^1 = R^3 = OMe$, $R^2 = H$

Figure 2-10: Rearrangement of flavanones to isoflavones with a hypervalent iodine reagent

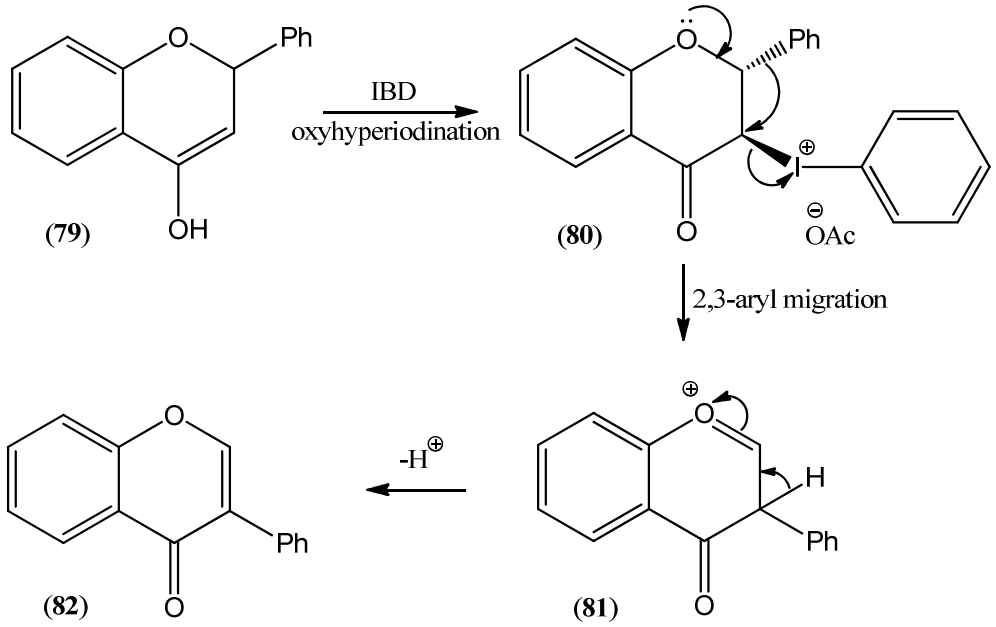


Figure 2-11: Mechanism for the hypervalent iodine rearrangement of isoflavanones to isoflavones

In another attempt to move away from poisonous thallium salts and still have the advantage of relative simple starting materials, Santhosh *et al.*[30] developed a bismuth catalysed process for the direct arylation of substituted chroman-4-one derivatives as a protocol for the synthesis of isoflavones. In the bismuth-catalysed method 3-phenylsulfonylchroman-4-ones (**87-90**) are treated with triphenylbismuth carbonate followed by elimination of the sulfonyl moiety to give the isoflavone (**6, 68, 71, 91**), while reductive removal of the sulphur entity would open up the possibility of direct formation of the corresponding isoflavanone (**7, 92-94**) (Figure 2-12). While

good overall yields were obtained (> 80 %), the applicability of this method is limited by difficulties in the preparation of specifically substituted arylbismuth(V) reagents.[16]

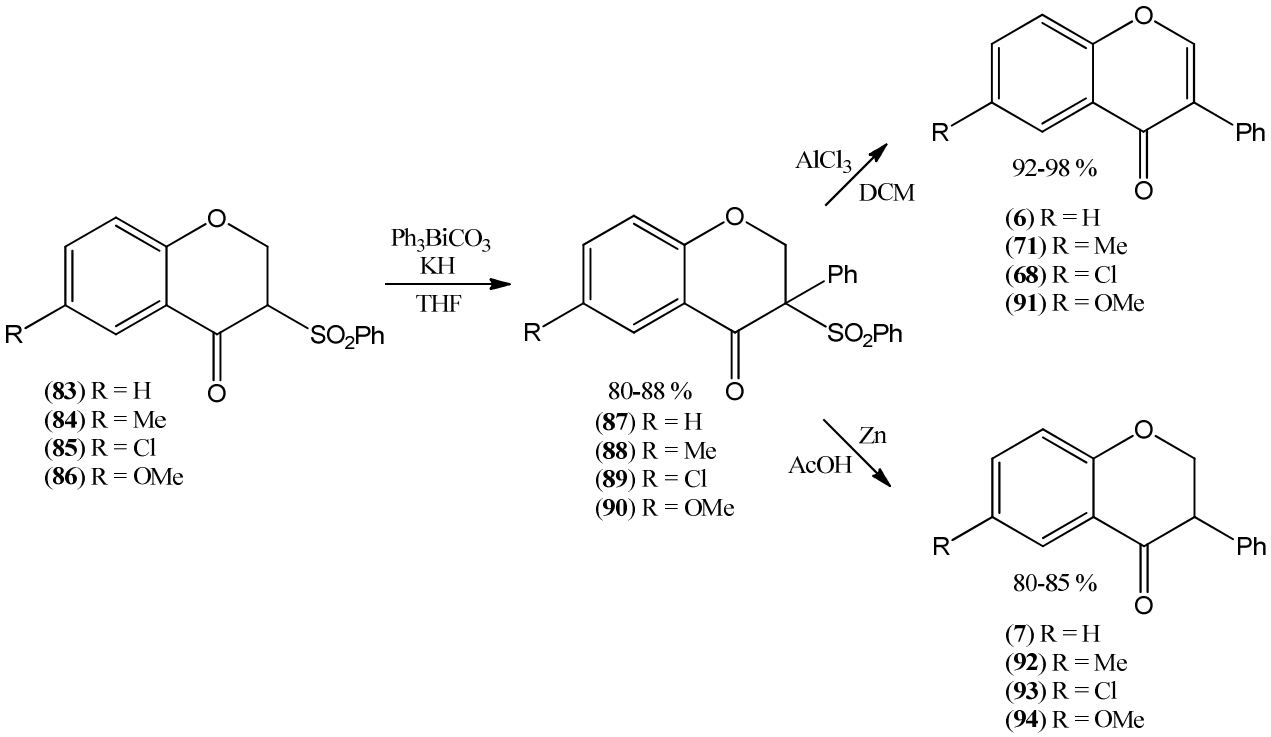


Figure 2-12: Phenylation of chromanones with bismuth(V) reagents

Donelly and co-workers[31,32] improved on the former process with the use of aryllead(IV) reagents that can easily be prepared through direct plumbylation of the corresponding arenes and have been used to synthesize a range of natural isoflavones and isoflavanones in high overall yields (60 % over 3 steps) (Figure 2-13).[16,19] The oxidative deallylation performed with $Pd(OAc)_2$ in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) gives the corresponding isoflavones (**104-106**) in 78-83 % yield, while reductive deallylation with $Pd(OAc)_2$, triphenylphosphine (PPh_3) and triethylammonium formate provides isoflavanones (**107-109**) in quantitative yield.[31,32]

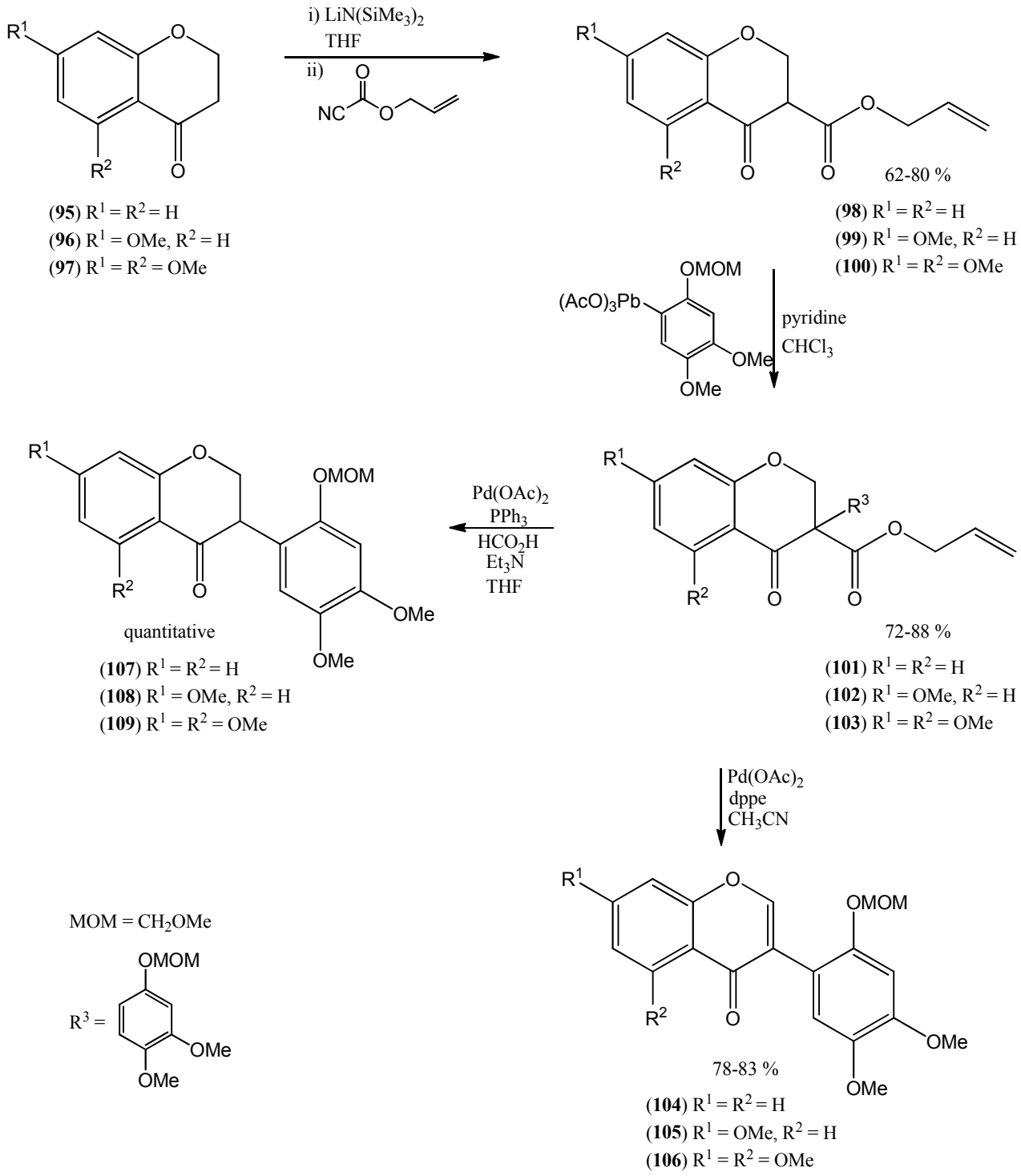


Figure 2-13: Phenylation of chromanones with aryllead(IV) triacetates

The discovery of the Grubbs catalyst induced the use of ring closing metathesis (RCM) in various areas of modern synthetic chemistry hitherto also in the route towards isoflavonoids. It is possible to synthesize isoflavone (**115**) from commercially available 4-(benzyloxy)-2-hydroxy-benzaldehyde (**110 a**) through the appropriate isoflavene (**113**), as shown in Figure 2-14, although

some disadvantages are tedious reaction conditions, expensive reagents, low yields (28 % overall) and multistep sequences.[1]

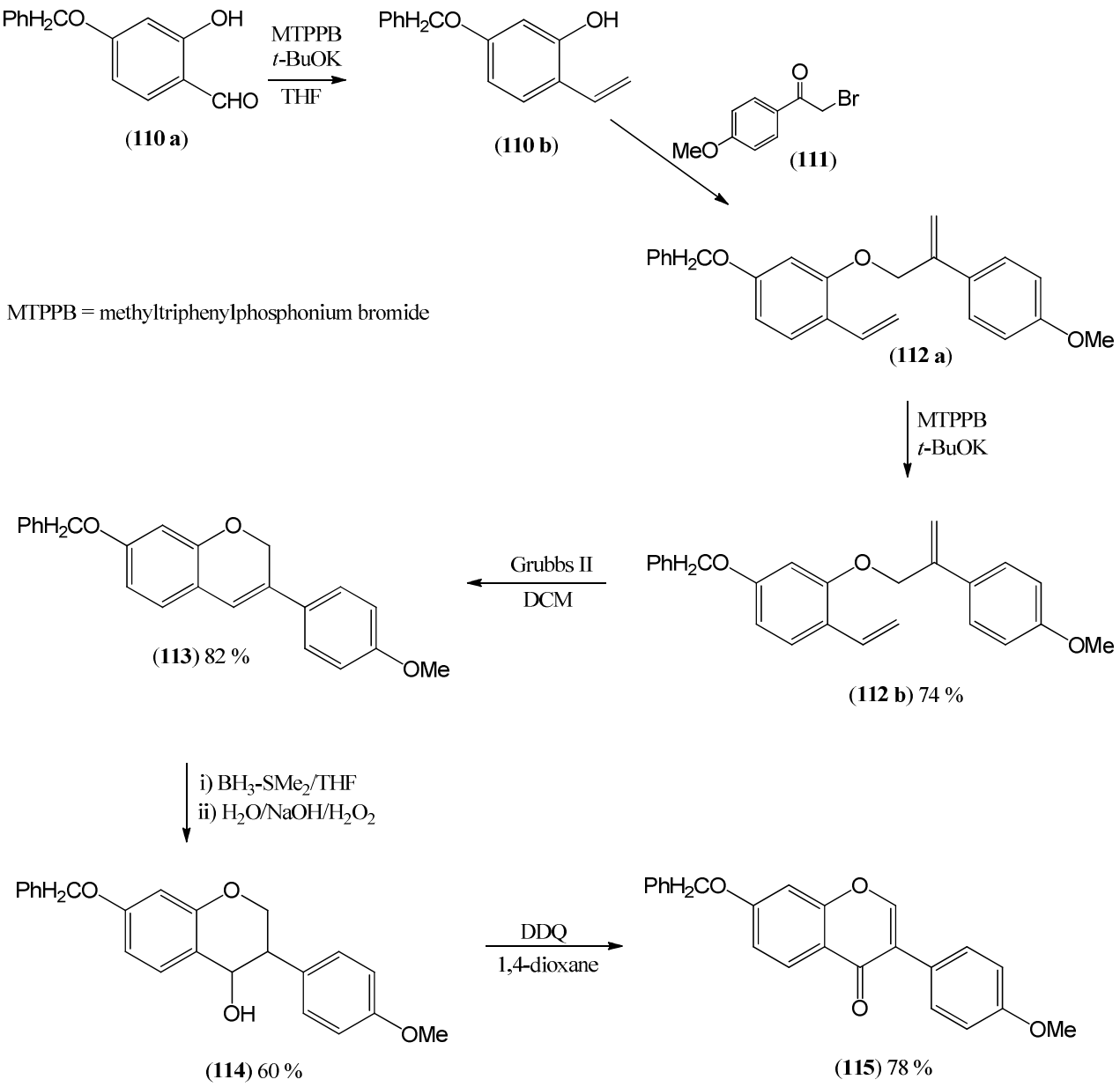


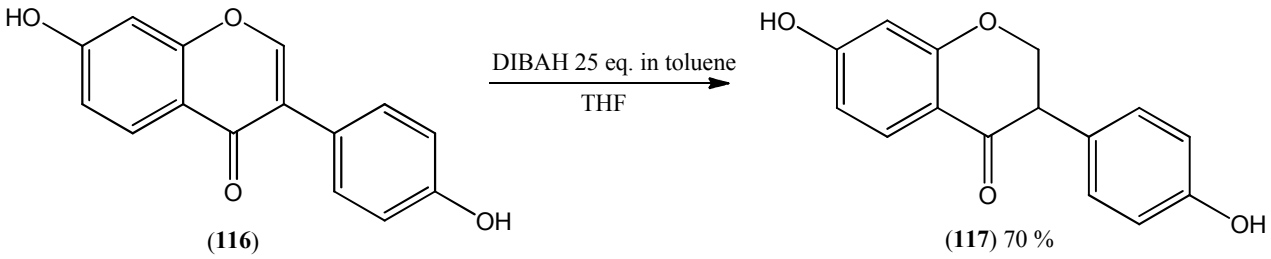
Figure 2-14: Multistep synthesis for isoflavones with the use of Wittig and RCM reactions

2.2. Isoflavanones

Since isoflavanones are a reduced form of isoflavones, these compounds are usually formed by reduction of the corresponding isoflavones through catalytic hydrogenation or by utilizing hydride reducing agents.[3,4] The fact that isoflavanones can easily be over-reduced to isoflavan-4-ols, or even isoflavans, is a complicating factor in the application of the catalytic hydrogenation methodology, but under carefully controlled conditions and persistent reaction progress

monitoring, reasonable yields can be obtained. Utilizing isoflavone acetates instead of free phenolic compounds usually have a beneficial effect on yields.[4]

In the late 1980's catalytic hydrogen-transfer hydrogenation was investigated as an alternative method and several isoflavones were successfully converted into isoflavanones over palladium on carbon refluxed in methanol with ammonium formate as hydrogen source. Although yields were only reasonable (50-60 %), it was found that it could be improved to 90 % if the reactions are performed at room temperature for shorter periods of time rather than at refluxing methanol conditions. When selective hydride reducing reagents, like di-isobutylaluminium hydride (DIBAH) is used, isoflavanones could be obtained in 75-90 % yields with no effect on benzyloxy protecting groups or chromene double bonds.[5,10] It was recently reported that even isoflavones (**116**) containing free phenolic substituents could be reduced in high yield (50-70 %) when an excess of DIBAH is used (Figure 2-15).[33]



(**116**) (**117**) 70 %

Figure 2-15: Isoflavanones through reduction of isoflavones

In a process similar to the synthesis of isoflavones, isoflavanones can also be prepared directly by attaching a C_1 entity to the α-carbon of a phenyl benzyl ketone (deoxybenzoin) followed by cyclization if suitable substrates are available (Figure 2-1). If methyleneiodide (CH_2I_2) is used as C_1 source all free hydroxy groups, except the one needed for ring closure, must be protected.[4,5,10] Yields could be improved to between 60 and 70 % by using a two-phase system with tetra-*n*-butylammonium iodide as phase-transfer catalyst and the addition of sodium thiosulfate which removes the iodine formed. Similar yields (50-60 %) were obtained when ethoxymethyl chloride was utilized, but this reagent has the added advantage that hydroxy groups are protected *in situ* and the protecting group can easily be removed when required at a later stage in the process (Figure 2-16). The highest yield (80 %) was, however, reported when formaldehyde was employed as C_1 source in a two-phase process similar to that described for methylene iodide.[5,10]

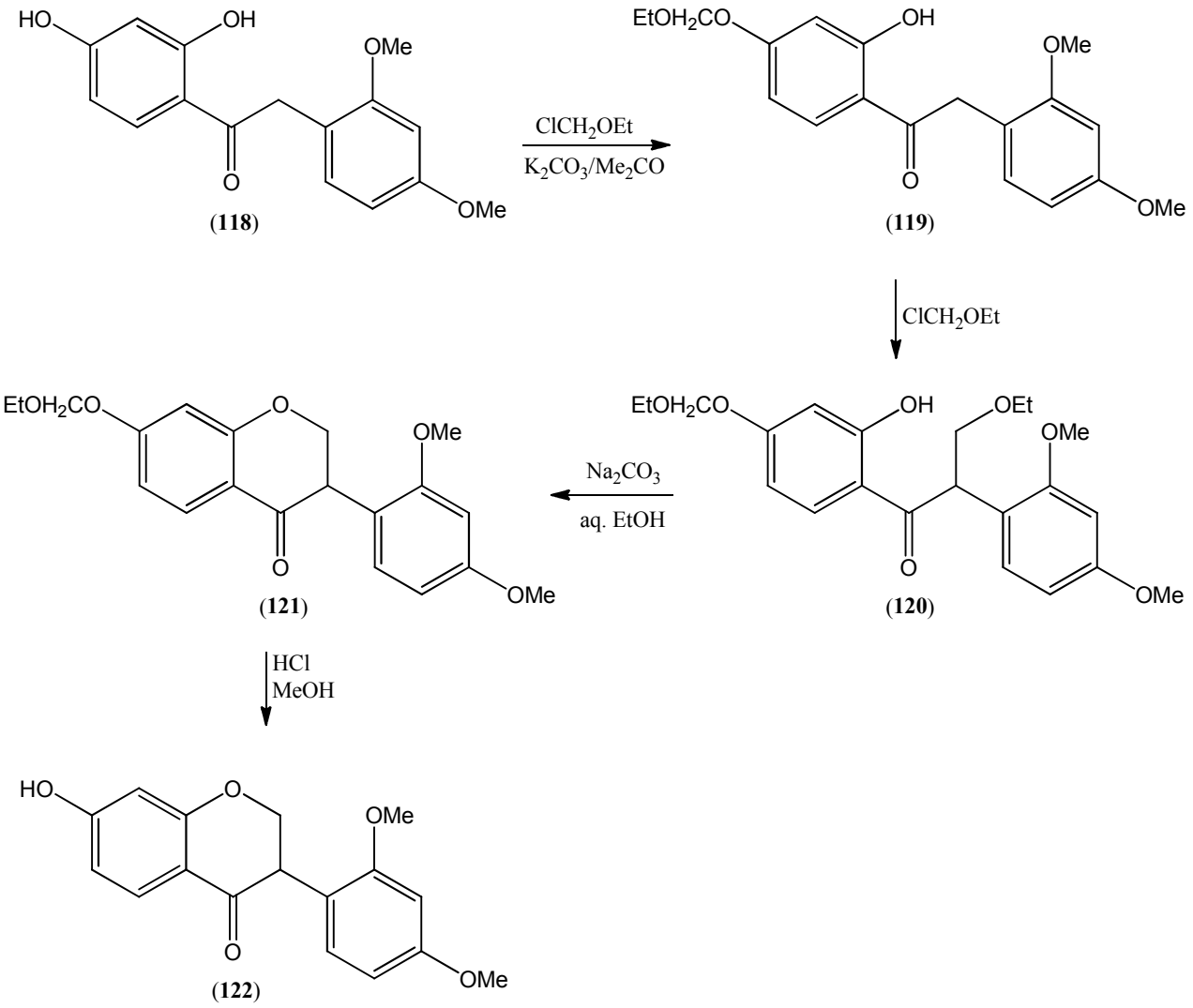


Figure 2-16: Synthesis of sativanone with *in situ* hydroxy group protection

A palladium catalysed Heck reaction with the enol ester of chroman-4-one (**123**), with introduction of the B-ring by an arylmercuric halide (**124**), gave satisfactory yields (60-75 %) of isoflavanones with methoxy substituents in *o*- or *m*-positions on the A-ring as well as a chloro or nitro substituent on the B-ring in various combinations. The synthesis of isoflavanone (**7**) is also successful when the R^1 and R^2 substituents are combinations of methoxy-groups and also when the B-ring is substituted with electron-withdrawing substituents such as chloride (Figure 2-17). The weakness of this reaction is the requirement for toxic arylmercury derivatives and of course the use of expensive palladium acetate in huge amounts.[34]

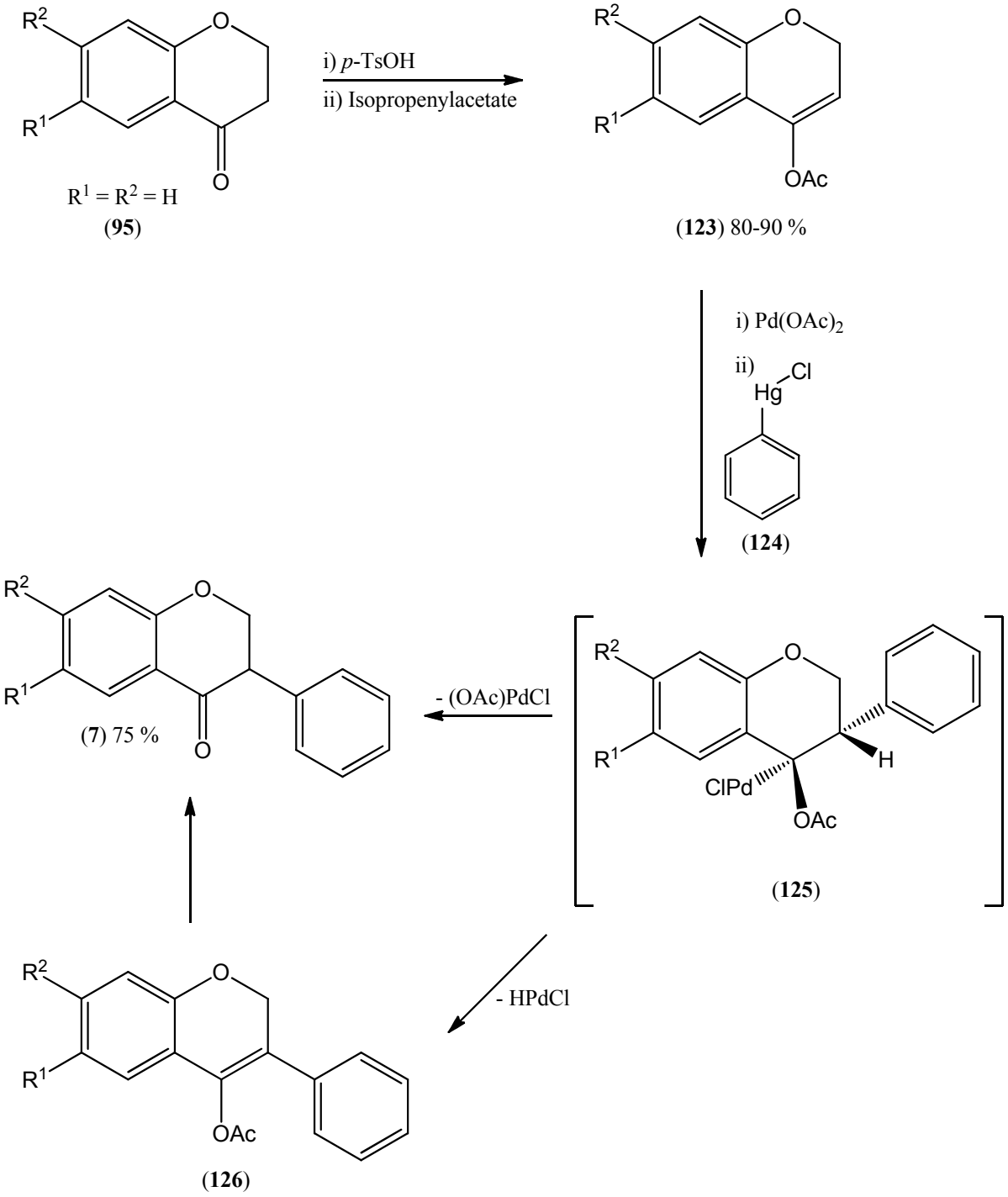


Figure 2-17: Synthesis of isoflavanones by means of the Heck reaction

Using pentaphenylbismuth for the arylation of 3-formyl- or 3-oxalylchroman-4-ones gives high yields of isoflavanones but only in the case of an unsubstituted B-ring since the formyl/oxalyl group is lost otherwise. Good yields of isoflavanone (**7**) can also be obtained in the presence of a $PdCl_2[(o\text{-tolylphosphine})_3]_2$ catalyst if tributyltin enolates of chroman-4-ones (**123**) are arylated with an aryl bromide as shown in Figure 2-18. Substituted isoflavanones can also be prepared in this manner although lower yields are observed.[10,35]

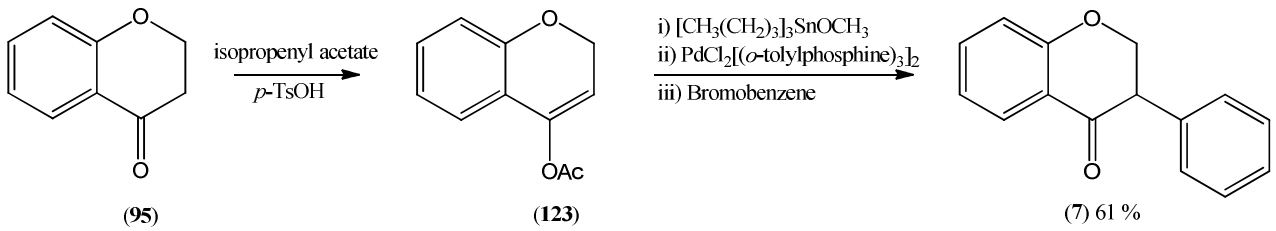


Figure 2-18: Synthesis of isoflavanones with the $PdCl_2[(o\text{-tolylphosphine})_3]_2$ catalyst

As indicated in Paragraph 2.1.3. (*cf.* Figures 2-12 and 2-13), isoflavanones can also be prepared by reacting arylbismuth(V)[16,30] or aryllead(IV)[16,19,31,32] reagents with preformed 3-substituted chromanones.

2.3. Isoflavans

Up to the 1970's isoflavans were almost exclusively prepared by the reduction of isoflavones or isoflavanones, specifically with hydrogenation over palladium on carbon. Hydrogenolysis of the corresponding pterocarpans will also give 2'-hydroxyisoflavans, but since pterocarpans are usually prepared from isoflavones/isoflavanones, this method is of limited applicability.[4]

One of the first attempts at the direct synthesis of isoflavans from simple starting materials came from the Shih group[36] when they reported on the preparation of the prenylated isoflavan (**132**). In a multi-step process that involved Claissen rearrangement of a substituted allyl ether (**129**) followed by hydroboration and finally Mitsunobu-type ether formation/cyclization. These researchers were able to form the isoflavan (**132**) in 75 % yield (Figure 2-19).[10,36]

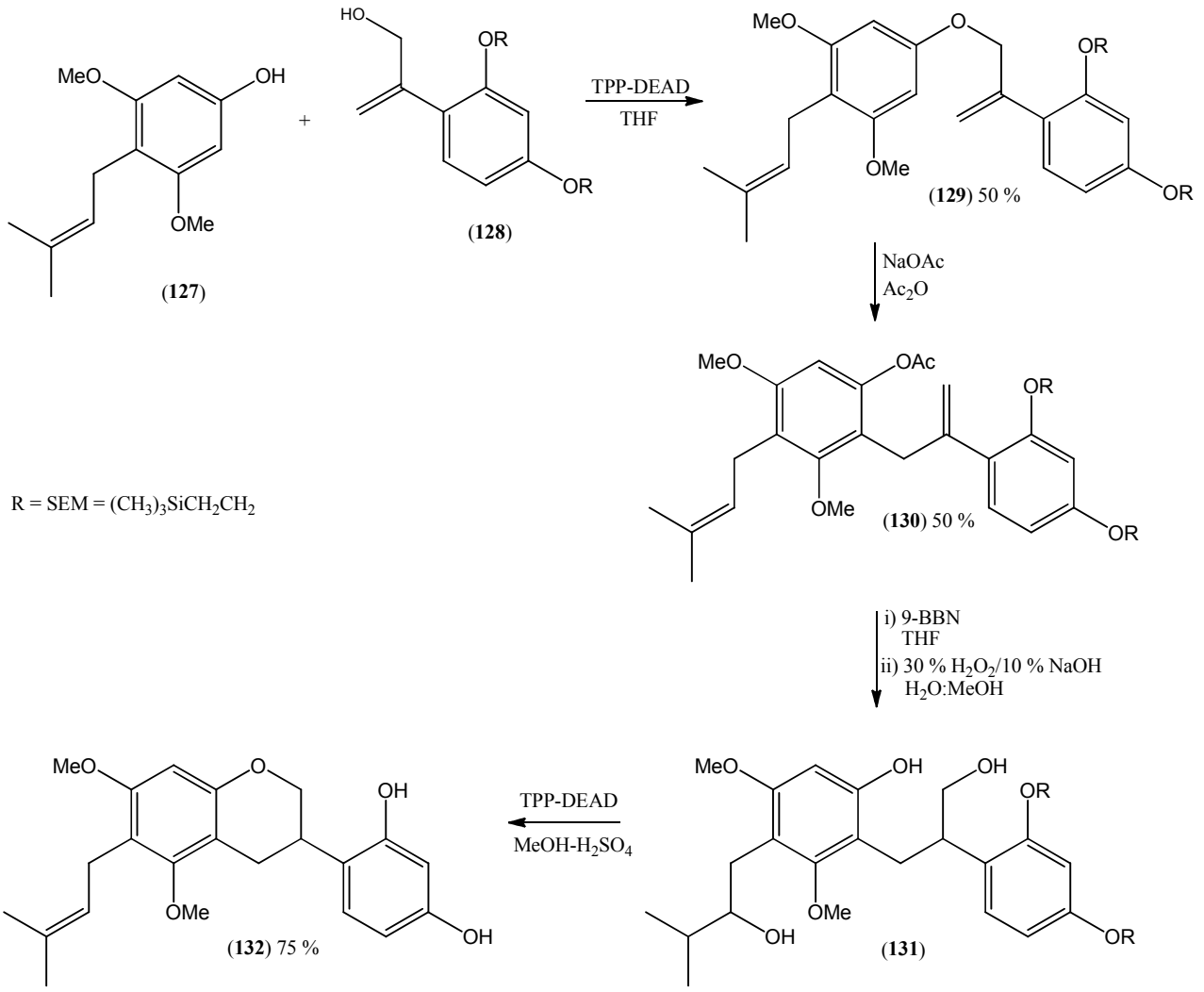
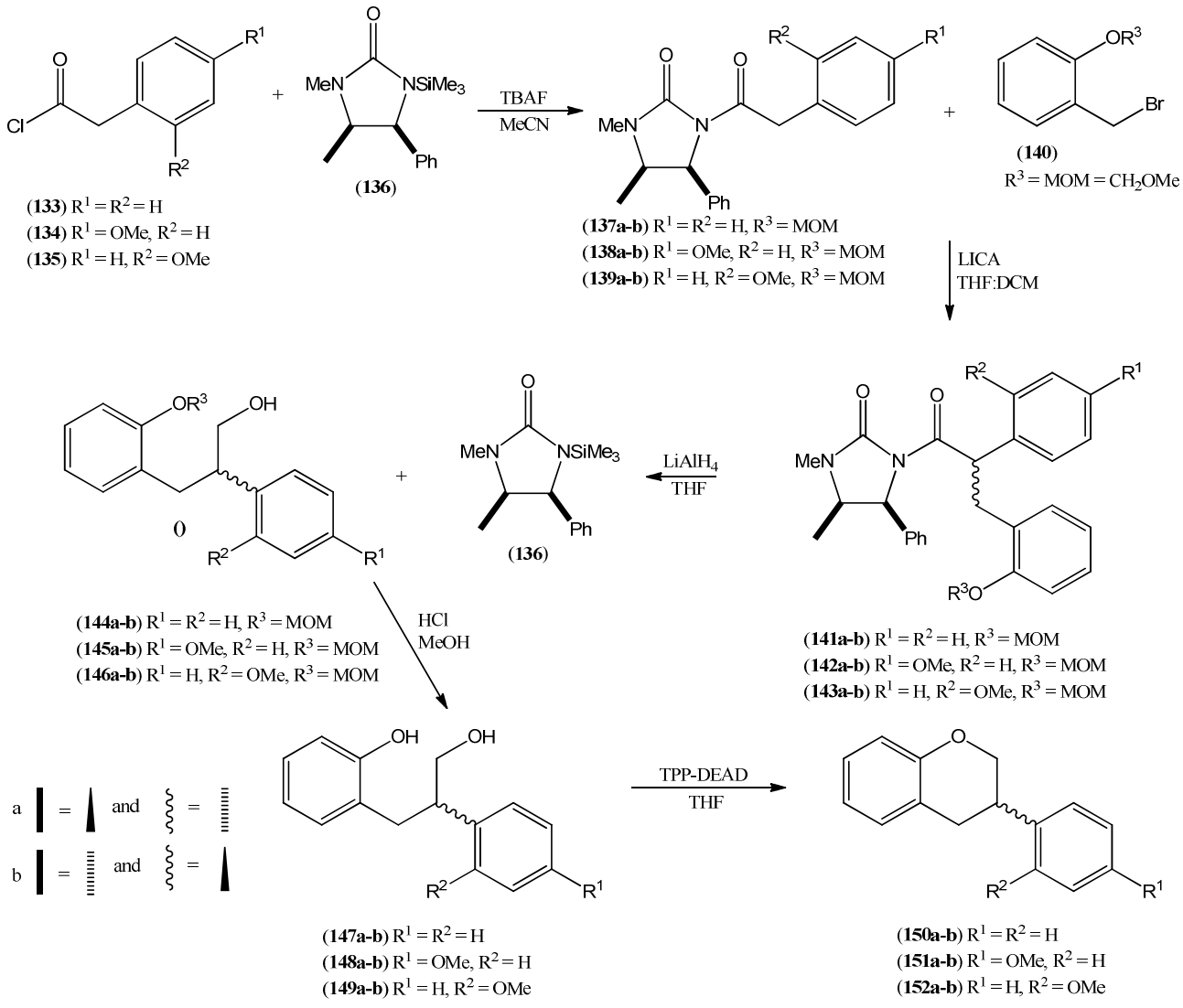


Figure 2-19: Synthesis of isoflavans with the Shih group methodology

Almost all synthetic routes towards the synthesis of isoflavonoids fail to address the issue of stereocontrol at the stereogenic centres, especially the C-3 centre in chiral non-planar isoflavonoids. In 1993 Versteeg and coworkers[37] published the first highly efficient enantioselective synthesis of isoflavans. Based on the α-benzylation of phenylacetates bearing imidazolidinone chiral auxiliaries, these workers were able to form both enantiomers of a range of isoflavans (**150a-152b**) in 48-67 % yields over five steps with 94-99 % enantiomeric excess (ee) (Table 2-1, Figure 2-20).[16,19,38,39,37]

Table 2-1: Yields obtained for the enantioselective synthesis of isoflavans

N-acyl-imidazolidinone (%)	Alkylation product (%)	Propanol (%)	Hydrolysis product (%)	Isoflavan (%)	ee (%)	*R/S*
(**137a**) 91	(**141a**) 90	(**144a**) 84	(**147a**) 97	(**150a**) 92	96	*S*
(**137b**) 90	(**141b**) 86	(**144b**) 77	(**147b**) 98	(**150b**) 87	94	*R*
(**138a**) 75	(**142a**) 84	(**145a**) 89	(**148a**) 94	(**151a**) 85	99	*S*
(**138b**) 80	(**142b**) 92	(**145b**) 85	(**148b**) 85	(**151b**) 80	99	*R*
(**139a**) 72	(**143a**) 88	(**146a**) 90	(**149a**) 85	(**152a**) 73	98	*S*
(**139b**) 73	(**143b**) 90	(**146b**) 76	(**149b**) 95	(**152b**) 75	99	*R*



(**133**) $R^1 = R^2 = H$
(**134**) $R^1 = OMe$, $R^2 = H$
(**135**) $R^1 = H$, $R^2 = OMe$

(**137a-b**) $R^1 = R^2 = H$, $R^3 = MOM$
(**138a-b**) $R^1 = OMe$, $R^2 = H$, $R^3 = MOM$
(**139a-b**) $R^1 = H$, $R^2 = OMe$, $R^3 = MOM$

(**144a-b**) $R^1 = R^2 = H$, $R^3 = MOM$
(**145a-b**) $R^1 = OMe$, $R^2 = H$, $R^3 = MOM$
(**146a-b**) $R^1 = H$, $R^2 = OMe$, $R^3 = MOM$

(**141a-b**) $R^1 = R^2 = H$, $R^3 = MOM$
(**142a-b**) $R^1 = OMe$, $R^2 = H$, $R^3 = MOM$
(**143a-b**) $R^1 = H$, $R^2 = OMe$, $R^3 = MOM$

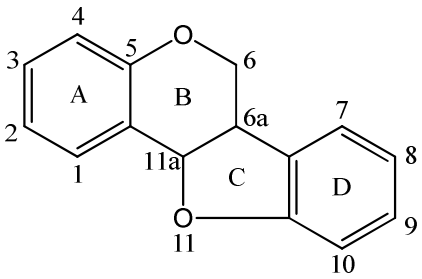
(**147a-b**) $R^1 = R^2 = H$
(**148a-b**) $R^1 = OMe$, $R^2 = H$
(**149a-b**) $R^1 = H$, $R^2 = OMe$

(**150a-b**) $R^1 = R^2 = H$
(**151a-b**) $R^1 = OMe$, $R^2 = H$
(**152a-b**) $R^1 = H$, $R^2 = OMe$

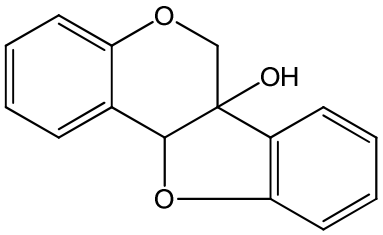
Figure 2-20: Enantioselective synthesis of isoflavans

2.4. Pterocarpans

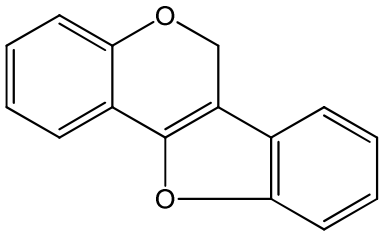
Apart from the isoflavones, the largest groups of natural isoflavonoids are the isoflavans followed by the pterocarpans, which are widely distributed in leguminous plants functioning as phytoalexins.[10] Pterocarpans are identified by a tetracyclic ring system formed by an ether linkage between the C-4 and C-2' positions (isoflavone numbering).[3,16,19] The pterocarpans are subdivided into three categories pterocarpans (**9**), 6a-hydroxypterocarpans (**153**) and pterocarpenes (**154**).[10]



Pterocarpan
(**9**)



6a-Hydroxypterocarpan
(**153**)



Pterocarpene
(**154**)

2.4.1. Pterocarpans

The classical method for the preparation of pterocarpans centres on the reduction of 2'-hydroxyisoflavones. When metal hydrides, like sodium borohydride, is used isoflavanones serve as intermediate products, which are subsequently reduced to isoflavan-4-ols before being cyclized to pterocarpans on treatment with mild acid.[4,10] The utilization of catalytic hydrogenation (over reducing agents) as reduction methodology has the added advantage that benzyl protecting groups are removed at the same time, hitherto a one-pot transformation from benzyloxyisoflavones to hydroxypterocarpans is possible. This process is, however, hampered by the possibility of over reduction to the 2'-hydroxyisoflavans which is inert towards cyclization. The addition of acid to the hydrogenation reaction mixture has been reported as a possible method for preventing over-reduction.[10,19]

Recently, modern metal-catalysed reactions received considerable attention with respect to the direct synthesis of pterocarpans from relative simple starting materials. In this regard, lithium tetrachloropalladate-catalysed Heck arylation of chromenes were used to synthesize naturally occuring pterocarpans like leicocarpin (**157**) (Figure 2-21). It is important to note that the catalyst, in this application, showed preference towards the chromene ring over the dimethylchromene moiety.[10,16,19]

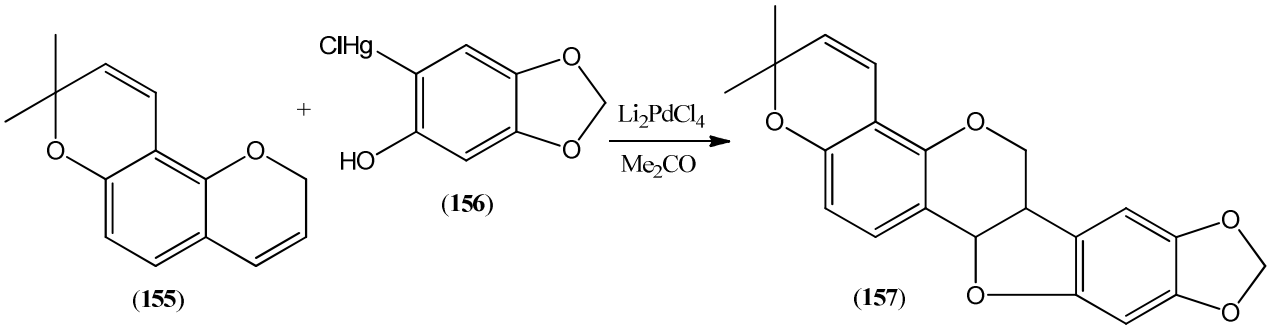


Figure 2-21: Synthesis of leiocarpin

Although not a metal-catalysed reaction, a 1,3-Michael-Claisen annulation reaction has also been reported as an alternative route towards the formation of pterocarpans, like sophorapterocarpan A (**161**) (Figure 2-22), maackianin and anhydropisatin.[10,40]

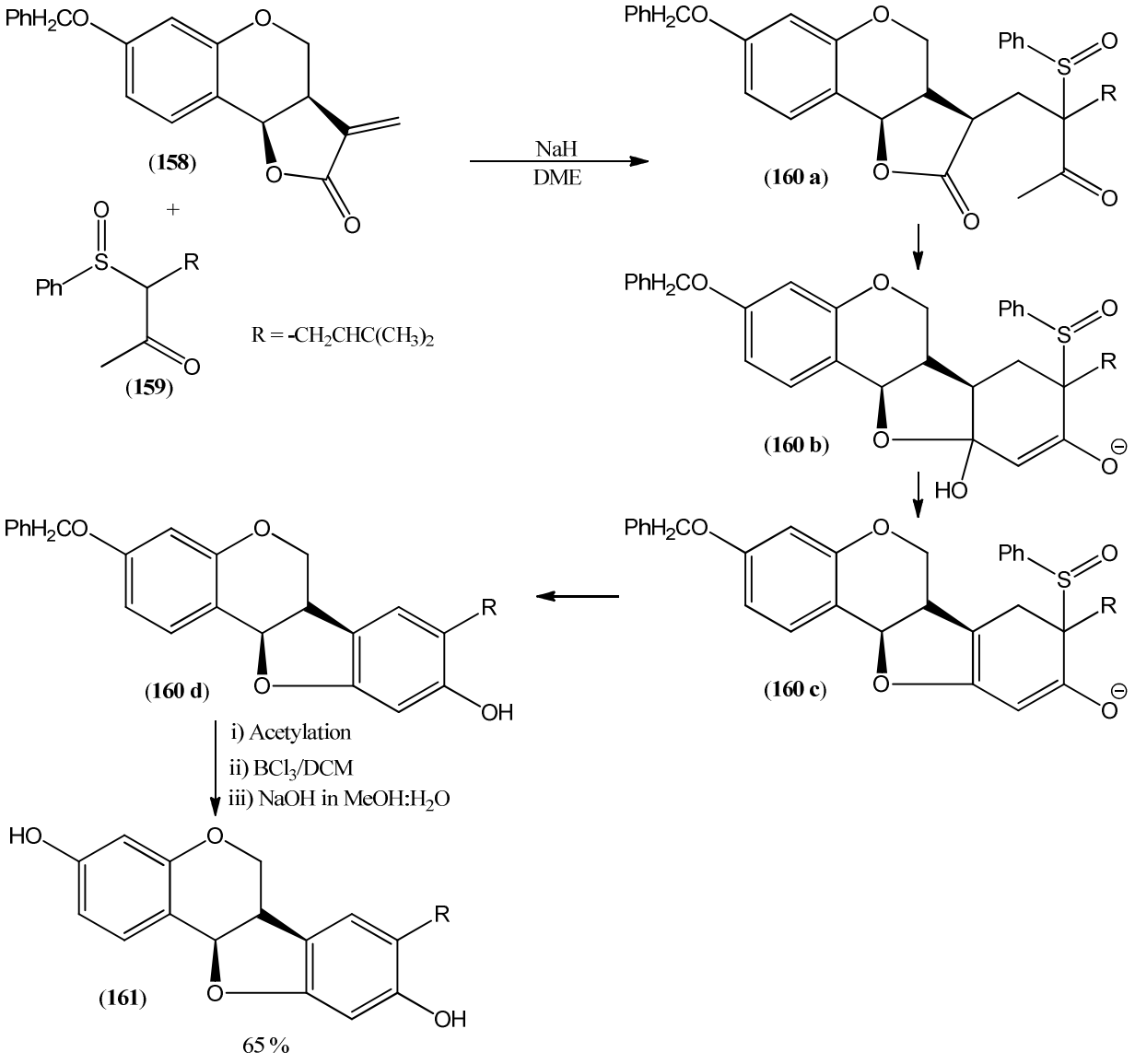


Figure 2-22: Synthesis of sophorapterocarpan A

Cycloaddition of 1,4-benzoquinones (**163**) to chromenes (**162**) catalysed by Lewis acids like titanium(IV) reagents, provides another strategy for the preparation of pterocarpans (**164**) (Figure 2-23).[19] While cyclobutanes may be formed in certain cases, these compounds can easily be rearranged to the pterocarpan in the presence of protic solvents.[10,16] Engler *et al.*[41] then further improved this methodology moving towards the stereoselective synthesis of pterocarpans (**167**) (Figure 2-24).

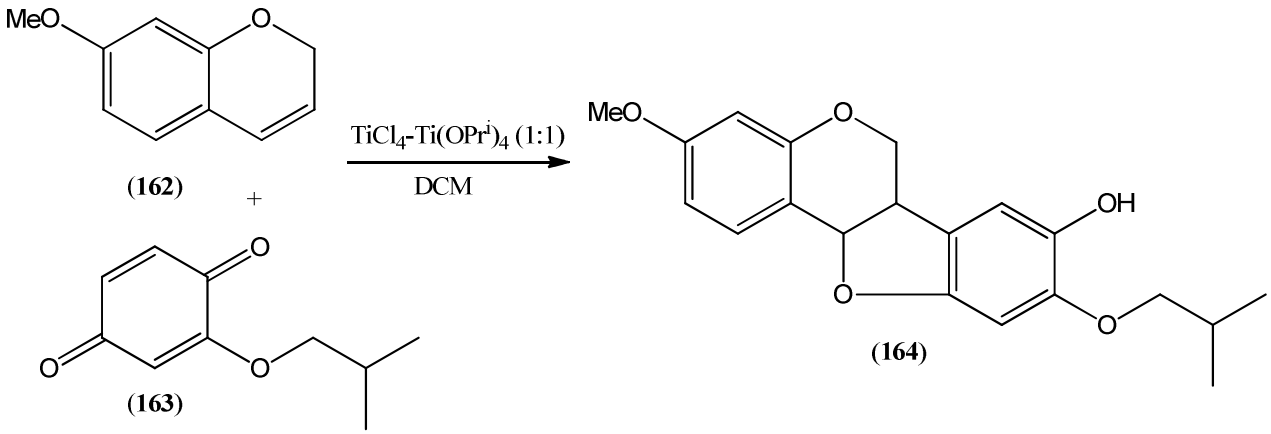


Figure 2-23: Titanium(IV) promoted synthesis of pterocarpans

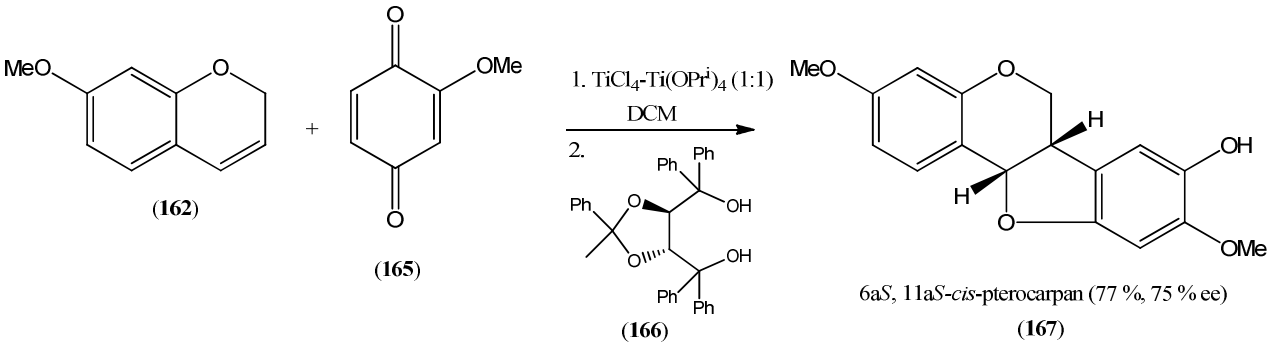


Figure 2-24: Stereoselective synthesis of pterocarpans

The demand for enantiomerically pure pterocarpans prompted Van Aardt *et al.*[42,43] to design a more direct synthetic route that is based on the aldol condensation of phenylacetates (**168**) and benzaldehydes (**169**). Only *cis*-relative stereocontrol could be obtained in good yield (82 %) as displayed in Figure 2-25. The reaction also works when the R^1- and/or R^2-substituents are methoxy groups, though lower yields (39-57 %) are obtained. Although all natural pterocarpans are in the *cis*-configuration (**175**), the next step for the Van Aardt group was to formulate a methodology for the synthesis of *trans*-pterocarpans (**181**) during which a much lower yield was obtained (58 %) (Figure 2-26).[44]

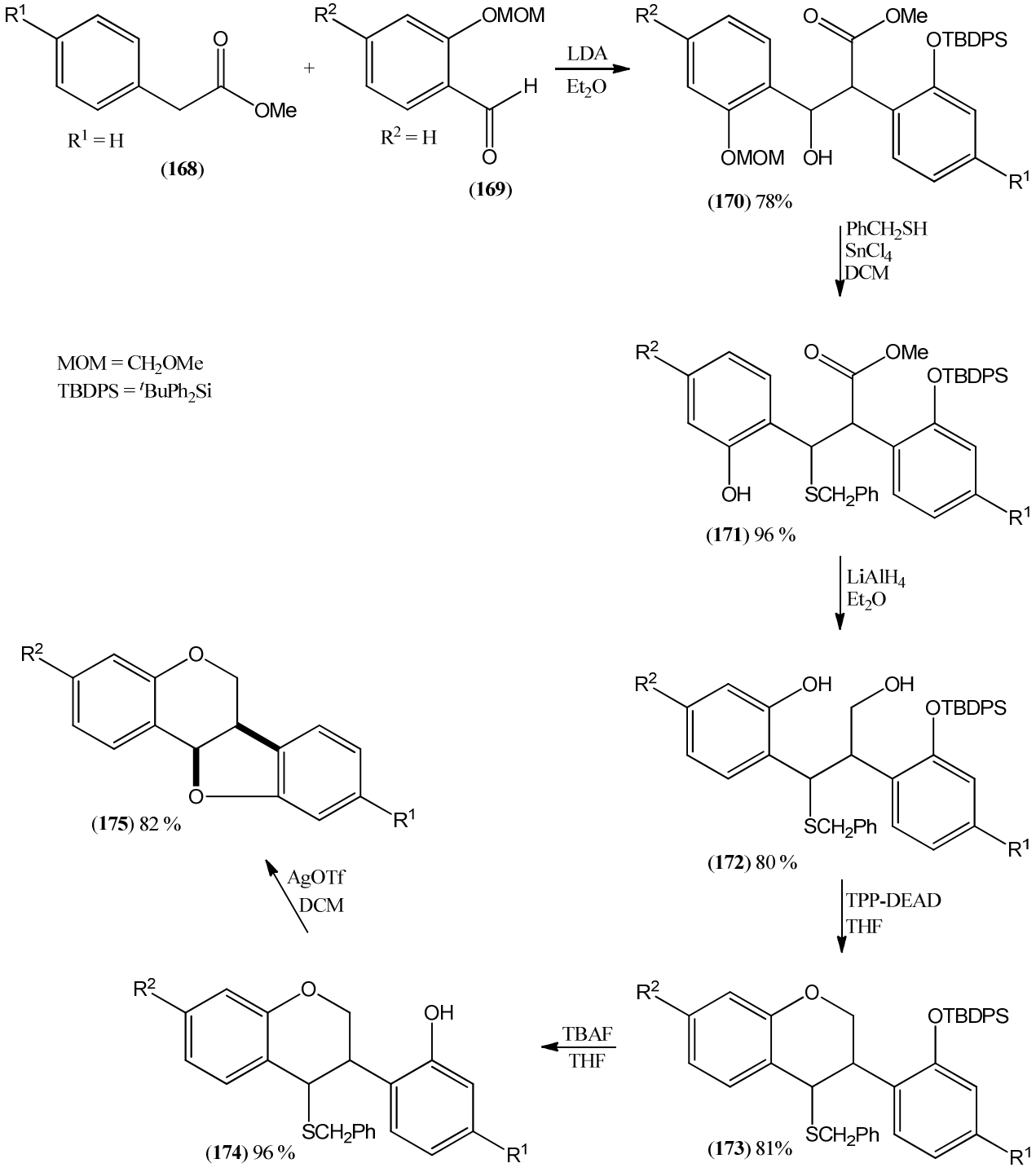


Figure 2-25: Direct synthesis of *cis*-pterocarpan through aldol condensation

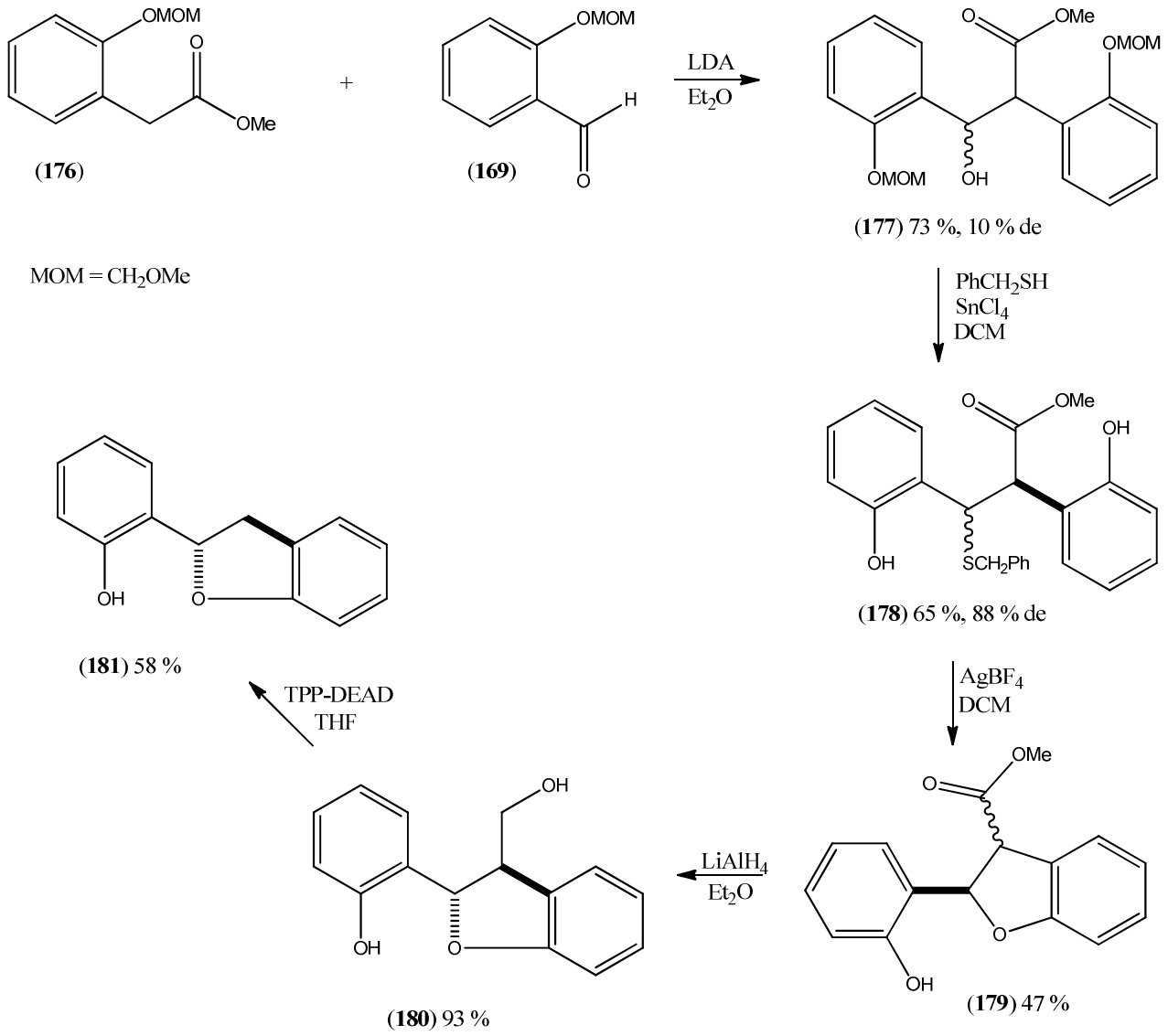


Figure 2-26: Direct synthesis of *trans*-pterocarpan through aldol condensation

2.4.2. 6a-Hydroxypterocarpanes

As indicated in Figure 2-27, 6a-hydroxypterocarpans like the pea phytoalexin, *cis*-pisatin (**187**), are usually prepared from 2'-hydroxyisoflavones (**182**) through borohydride reduction followed by controlled dehydration to isoflav-3-ene (**184**). Osmium(IV)-catalysed dihydroxylation would subsequently lead to the isoflavan-3,4-diol (**185**), which is then converted to the target pterocarpan (**187**) through cyclisation involving the 2'-hydroxy group.[10,45] Interestingly Pinard *et al.*[46] used almost an identical methodology (Figure 2-28) for the enantioselective synthesis of (+)-pisatin (**198**) in good yield (80 %), employing the chiral ligand dihydroquinine *p*-chlorobenzoate (DHQ-CLB) for *R*,*R*-configuration (99 % ee) and dihydroquinidine *p*-chlorobenzoate (DHQD-CLB) to obtain the *S*,*S*-enantiomer (99 % ee).[44]

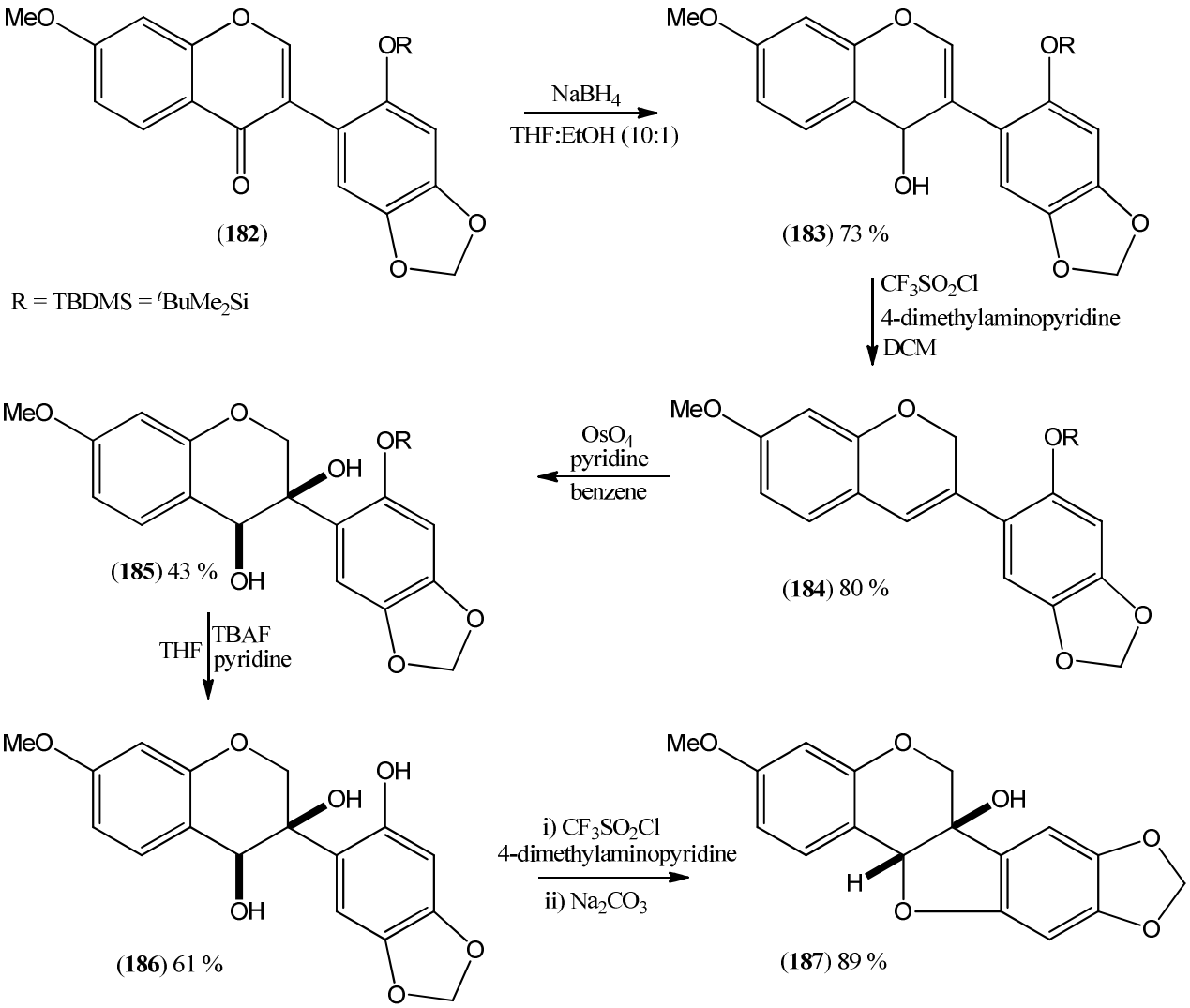


Figure 2-27: Highly diasterioselective synthesis of *cis*-pisatin

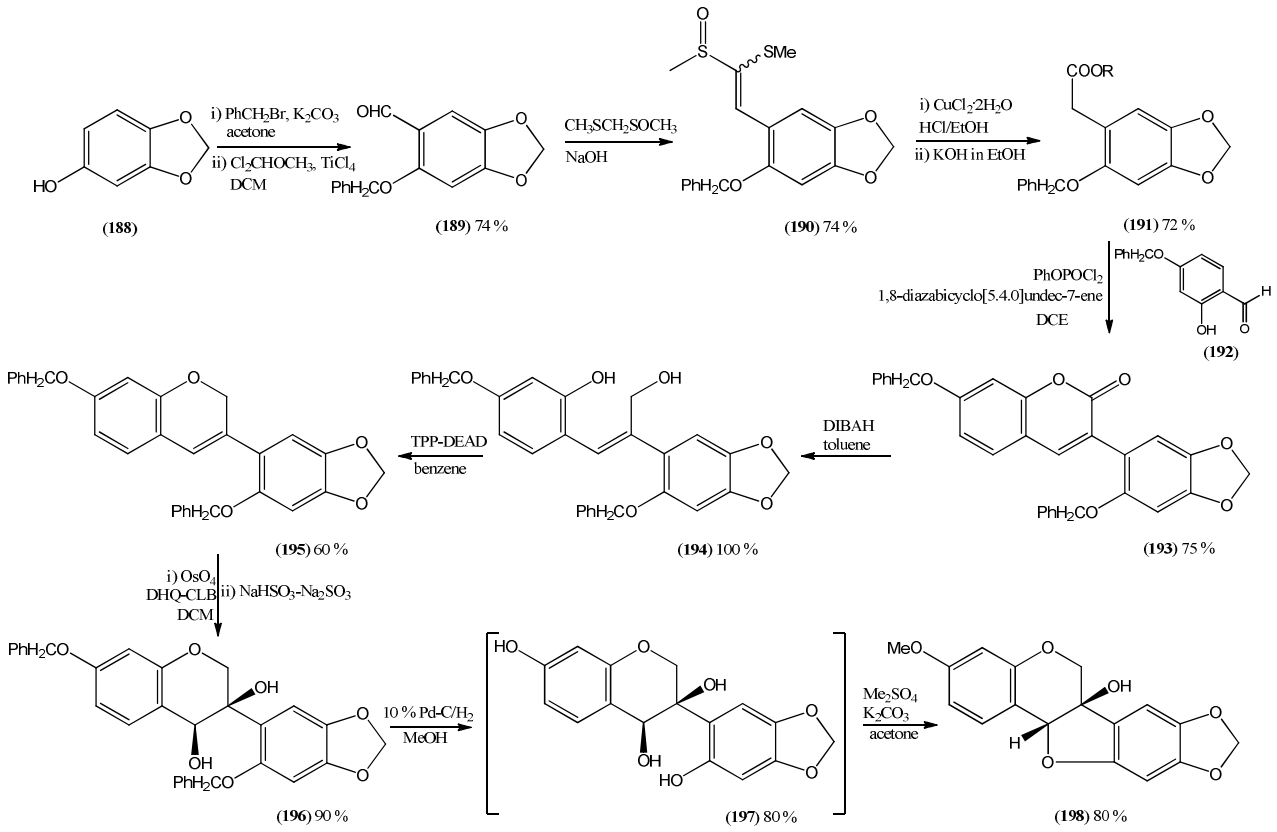


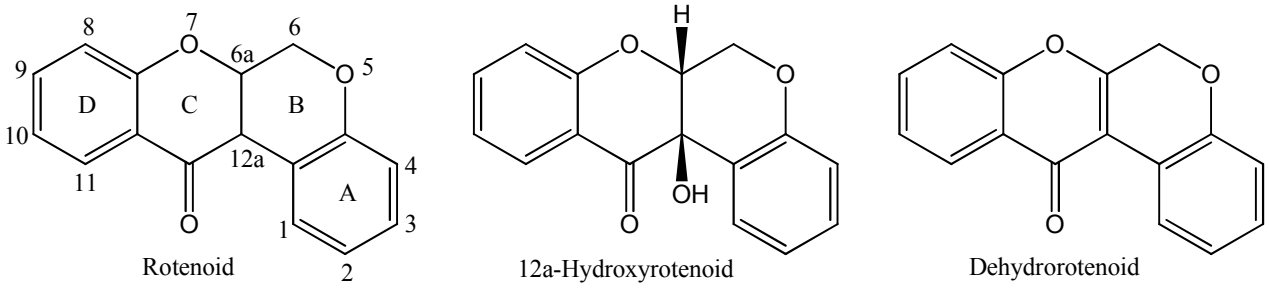
Figure 2-28: Enantiomeric synthesis of 6a*R*, 11a*R*-pisatin

2.4.3. Pterocarpenes

Pterocarpenes are mostly formed by acid catalysed cyclization of 2'-hydroxyisoflavanones. Pterocarpenes are labile in solution and readily oxidized to coumestans even in atmospheric oxygen and this is enhanced by treatment with DDQ.[3,5]

2.5. Rotenoids

The rotenoids are a class of isoflavonoids that can be identified by the presence of an additional heterocyclic ring.[3,10] Known rotenoids almost exclusively contain an isoprenoid substituent and, like pterocarpans, can be classified into three major groups, *i.e.* the rotenoids (**10**), 12a-hydroxyrotenoids (**199**) and dehydrorotenoids (**200**), depending on the level of oxidation present in the heterocyclic rings.[19] Interestingly studies indicate that biological activity of rotenoids depends on the *cis*-B/C ring fusion.[16]



Like the synthesis of isoflavones, one of the first methods towards the preparation of rotenoids comprised the ring closure of prenylated substituted deoxybenzoins. In processes described by Robertson *et al.*[4] and Carson and co-workers,[4] rotenone (**203**) and isorotenone (**206**), were respectively prepared by application of this approach (Figures 2-30 and 2-31). Both groups utilized aldol-type chemistry for the formation of the B-ring of the rotenoid unit as first step in the process, with the Robertson process requiring an additional sodium borohydride reduction followed by reoxidation of the subsequent 4-hydroxy analogue to reach the rotenone skeleton.

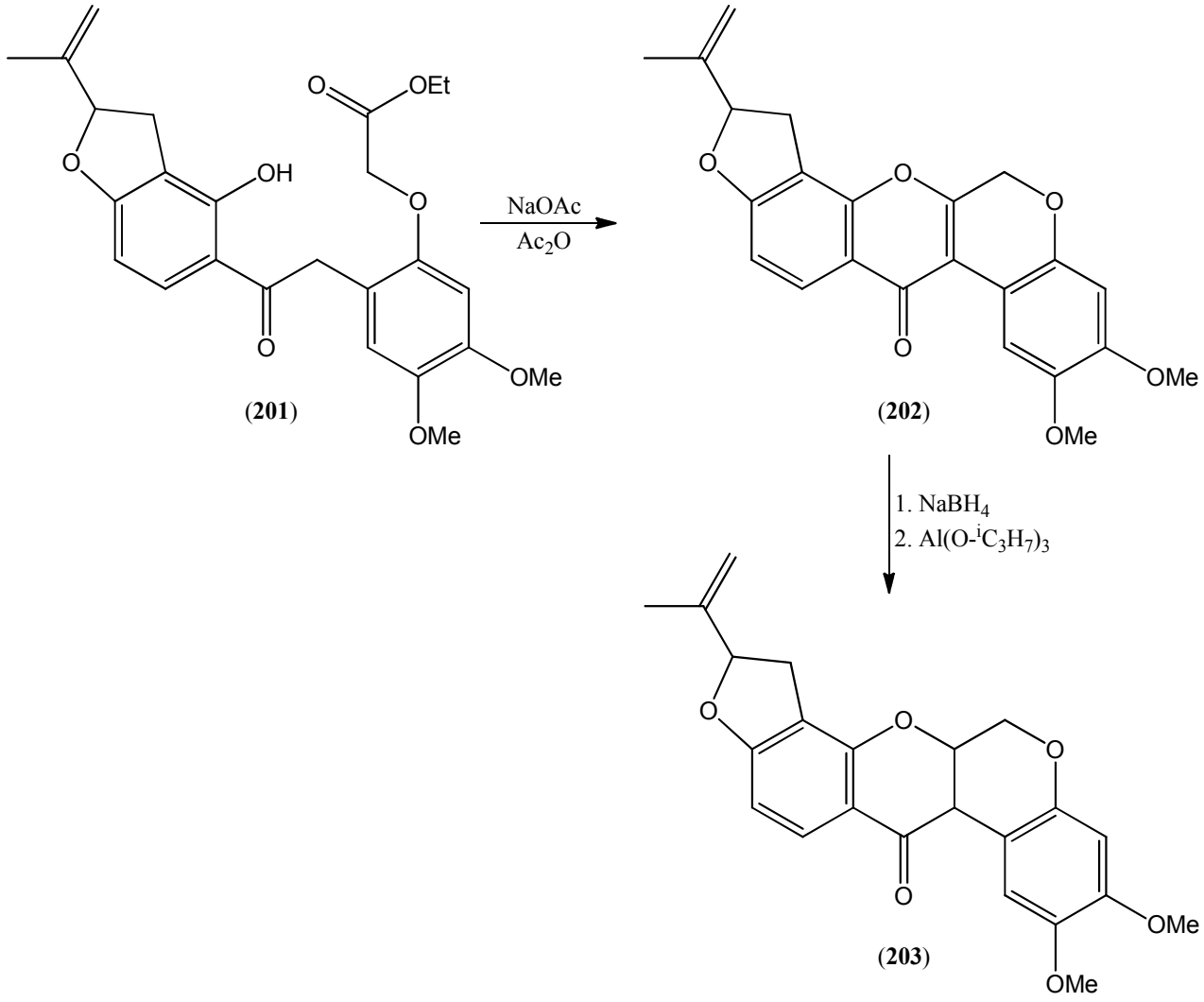


Figure 2-30: Synthesis of (±)-rotenone

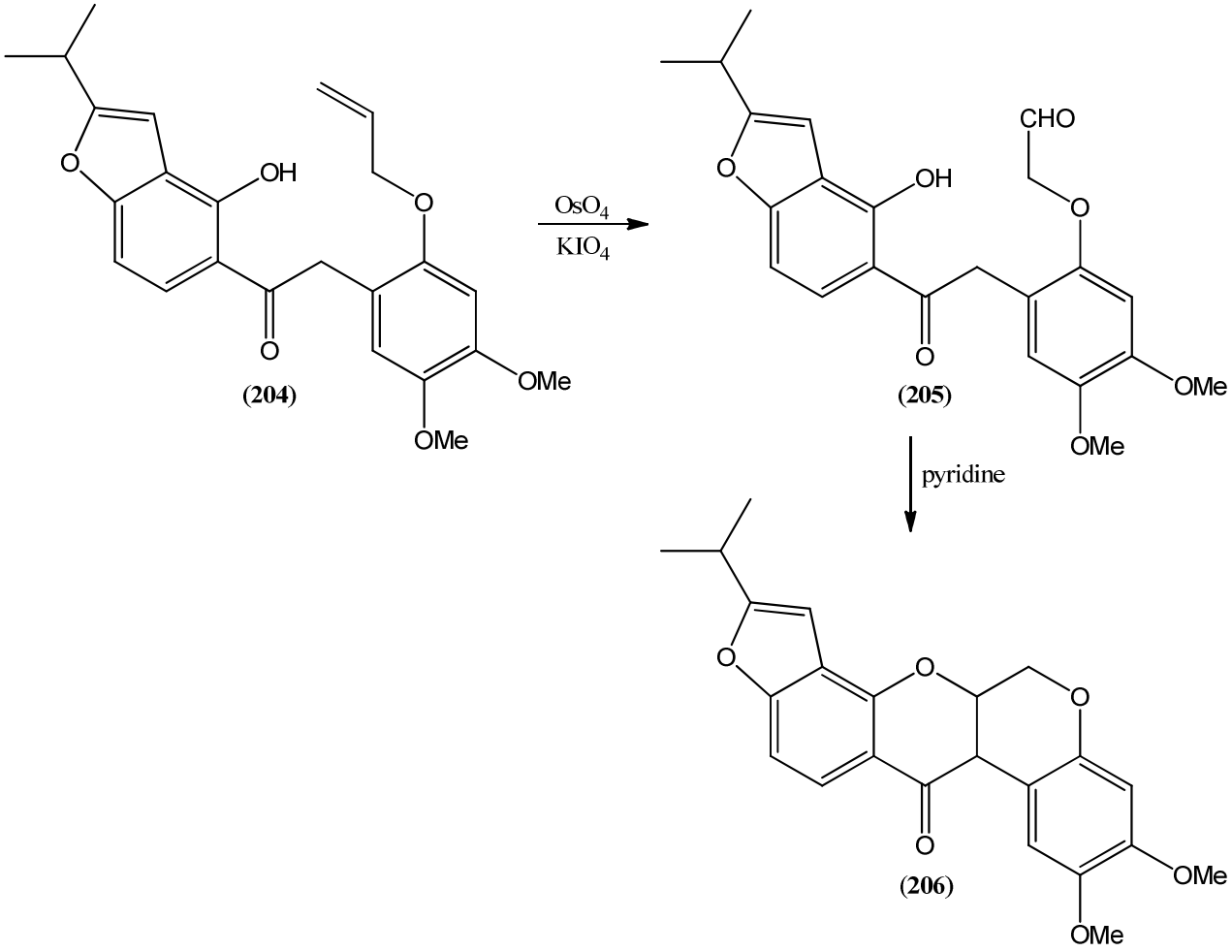


Figure 2-31: Synthesis of (±)-isorotenone

Amos and Whiting[47] utilized the Heck reaction in an approach to form the characteristic rotenoid tetracyclic ring from an aryl iodide which undergoes a palladium acetate catalysed intramolecular reaction. Hydroxylation, oxidation and reduction reactions followed to form munduserone (**211a**) (Figure 2-32). In a similar way a method to synthesize the 12-alcohol was devised *via* an enol acetate using radical cyclization.[10,48]

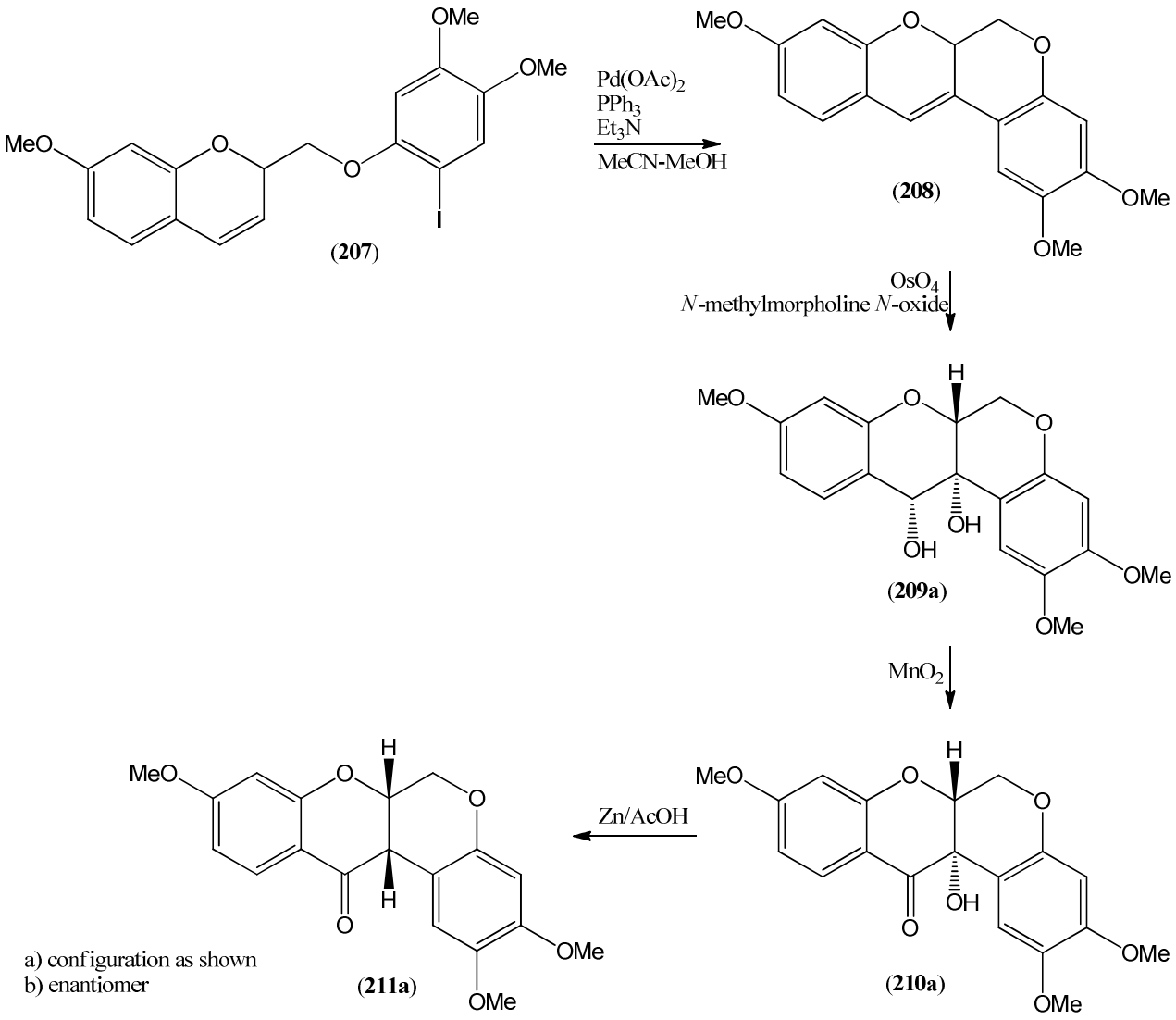


Figure 2-32: Synthesis of a racemic mixture of 6a*S*,12a*S*-munduserone

Omokawa and Yamashita[50] published another pathway to the rotenoid framework in 1972 where an aryloxyacetylide (**213**) reacts with an aromatic aldehyde (**212**) to give an acetylenic intermediate (**214**). The alcohol functional group is then oxidized to a ketone (**215**) using MnO_2 where after the molecule is cyclized to the rotenoid (**217**) *via* a Claisen annulated chromene (**216**) (Figure 2-33).[3] This reaction works well for rotenoids containing an electron rich A-ring, but the Claissen rearrangement step failed in the absence of 2,3-methoxylation.[16,50]

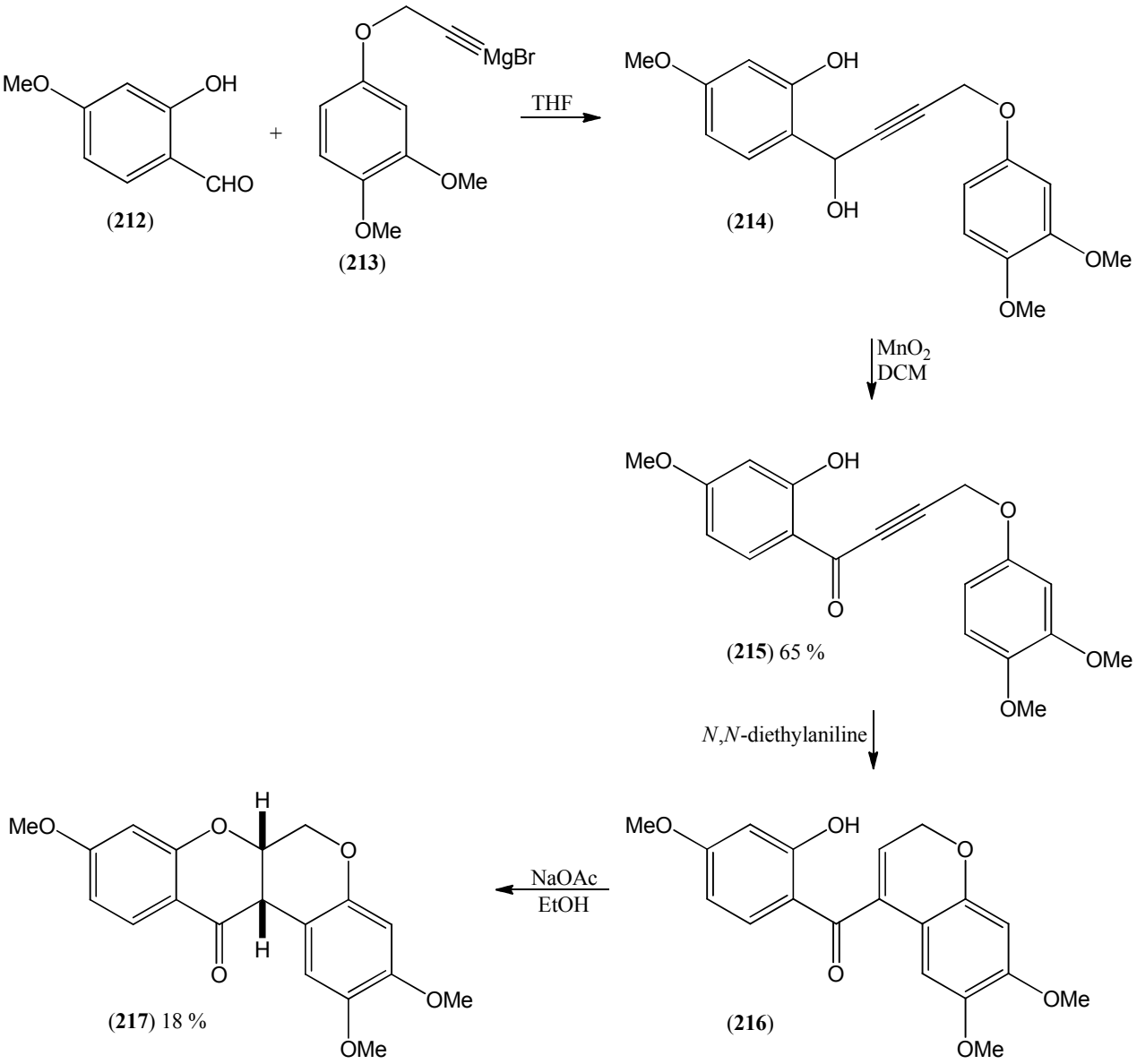


Figure 2-33: Synthesis of (±)-munduserone

An alternative approach was followed by Lai *et al.*[51] who formed rings A and B first through a 4-phenylsulfonyl chroman (**218**) where the sulfonyl group gave the necessary activation for coupling with an acyl chloride (**219**). Ring C is then formed after removal of the sulfonyl group, selective demethylation and dehydrogenation (Figure 2-34).[10]

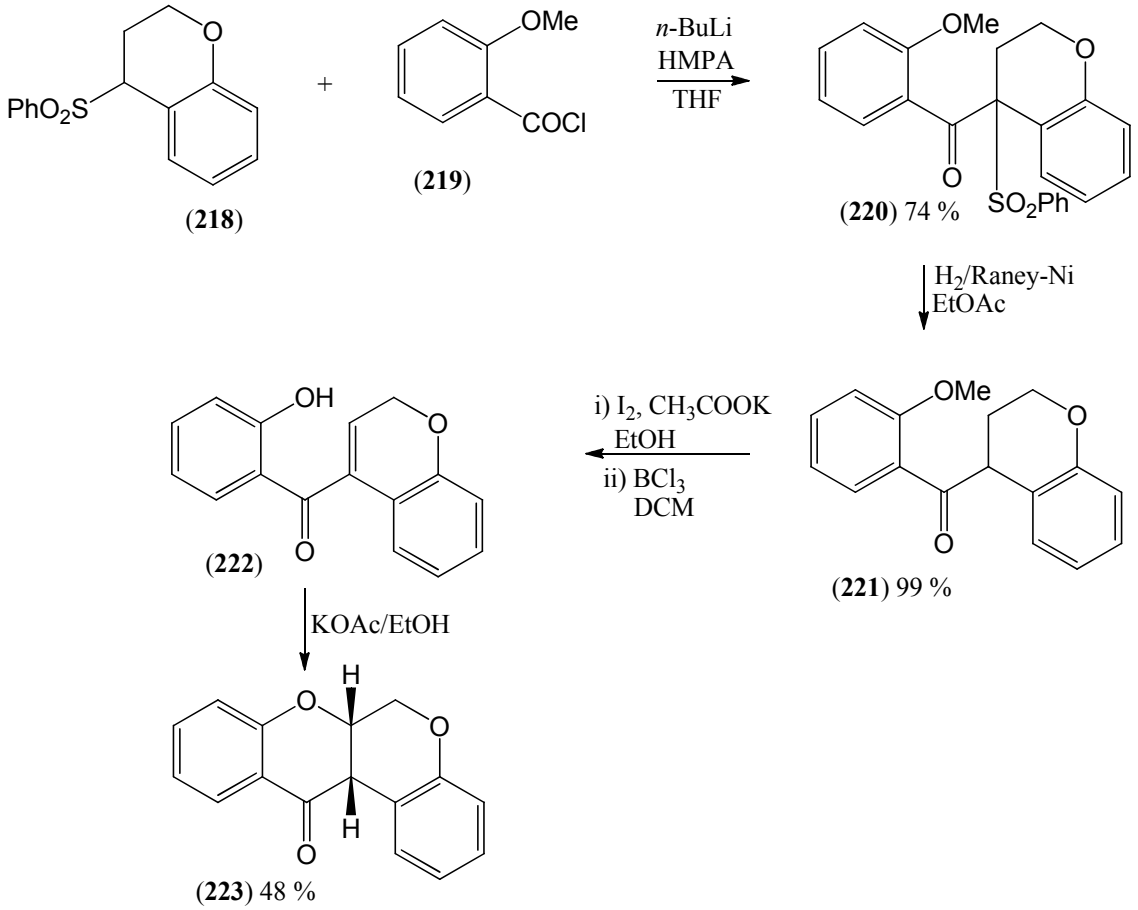


Figure 2-34: Stereoselective synthesis of 6a*S*,12a*S*-rotenoid, an alternative approach

All of the wide variety of discussed strategies involve tedious multi-step pathways from starting materials which are generally not readily available and the synthesis of which often result in low overall yields of rotenoids. In the 1990's a simple four-step synthesis of a 6,6-disubstituted rotenoid from 2'-hydroxyacetophenone was developed. The key step is the lithiation of a 4-bromo-2*H*-chromene (**225**) depicted in Figure 2-35. Deprotection and intramolecular ring closure produced the rotenoid (**229**).[19,52]

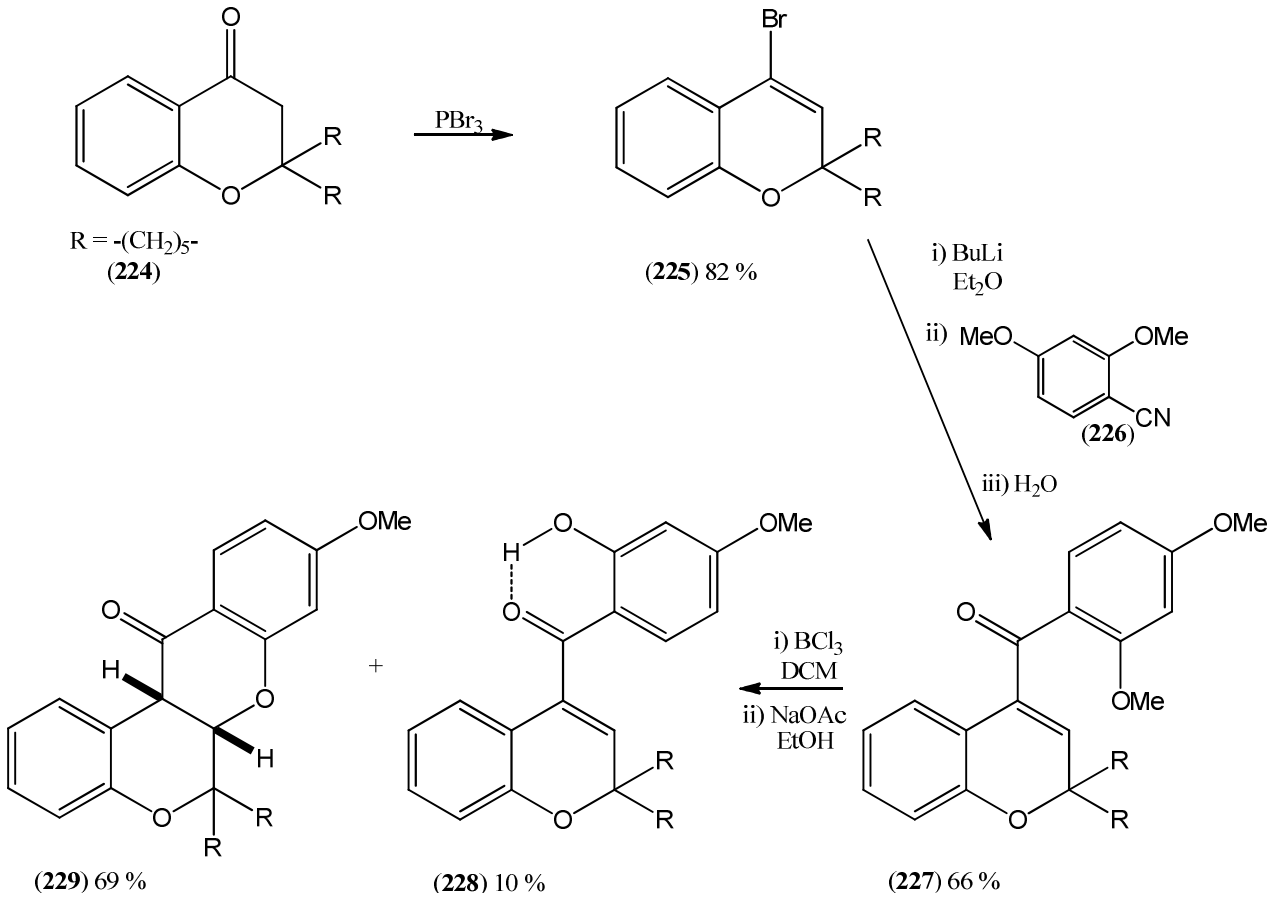


Figure 2-35: Simple 4-step synthesis of substituted rotenoids

Lastly Crombie and co-workers[53,54] reported a more flexible synthesis for general rotenoid structures with special application towards the synthesis of 5-thiorotenoids. The Wadsworth-Emmons reaction between an acetal (**231**) and a phosphate (**230**) is employed, followed by cyclization through a Mukaiyama-aldol-type reaction to give the rotenoid (**235**) as explained in Figure 2-36.[16]

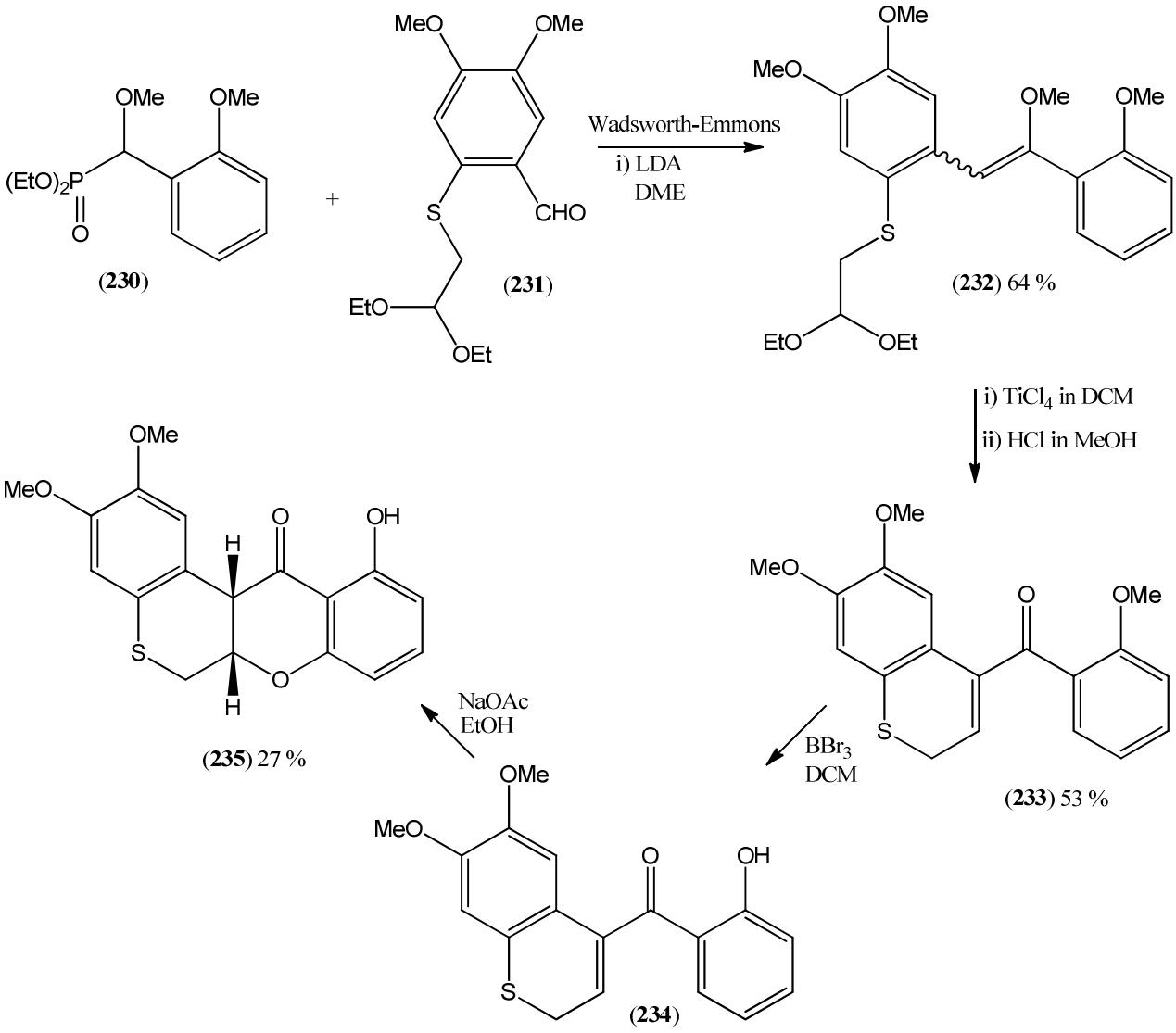


Figure 2-36: Synthesis of 5-thiorotenoids

2.6. Coumestans

Coumestans, representing the fully oxidized version of pterocarpans,[19] were first formed from precursors like pterocarpans, pterocarpenes, 2'-hydroxyisoflav-3-enes and 2'-hydroxy-3-arylcoumarins by DDQ- or lead tetra-acetate-oxidation. An advantage of the mild conditions used is the preservation of possible dihydropyrano substituents.[10] Coumestans can also be formed by the oxidative cyclization of 3-aryl-4-hydroxycoumarins in the presence of a Pd-C catalyst. Although other substrates (*vide supra*) have been utilized in the synthesis of coumestans, the ease of preparation and general availability of 4-hydroxycoumarins led to these compounds being utilized as starting materials in most current synthetic protocols towards the formation of coumestans. For many years, the potassium ferricyanide based coupling of 4-hydroxycoumarins (**236**) with catechol

(**30**) was accepted as the standard method for the synthesis of 8,9-dihydroxycoumestans (**237**). In 1989 it was however found that the enzyme mushroom tyrosinase, in a phosphate buffer could affect the same reaction with coumestan yields of more than 95 % being achieved (Figure 2-37).[10] Similarly, 8,9-dihydroxycoumestans (**237**) could be prepared by electrochemical anodic oxidation in very high product yields (90-95 %).[5]

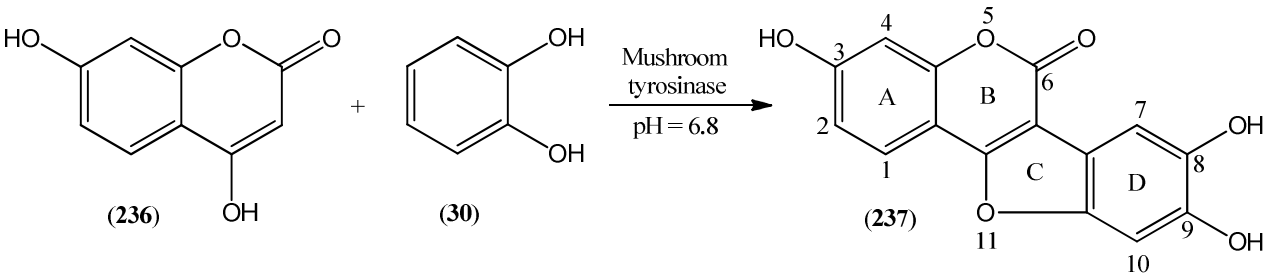


Figure 2-37: Coumestan synthesis through mushroom enzyme coupling

In another 4-hydroxycoumarin based process, developed for the synthesis of naturally occurring coumestans not containing 8,9-dihydroxy substituents, the coumarin is reacted with 2-bromocyclohexanone (**239**) before polyphosphoric acid (PPA) catalysed cyclization and oxidation with DDQ to give the product (**11**) (Figure 2-38).[5,55]

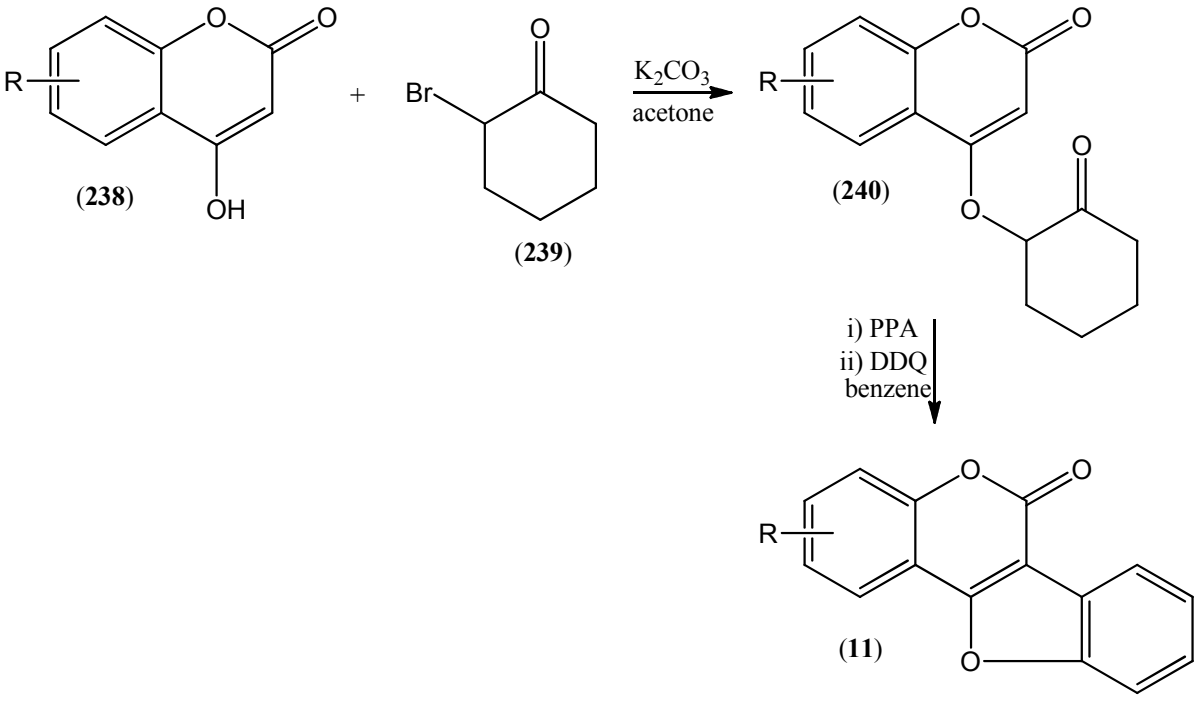


Figure 2-38: Synthesis of A-ring substituted coumestans

Laschober *et al.*[56] devised a process for the preparation of coumestans by utilizing Heck coupling as a way of forming the coumestan C-ring (Figure 2-39). In this interesting process, an iodonium ylide (**243**) is formed through reaction of the 4-hydroxycoumarin (**241**) with a diacetoxy-iodobenzene (**242**). Upon heating, the reactive intermediate (**243**) rearranges to give the 4-aryloxy-3-iodocoumarin (**244**), which serves as the substrate for an intramolecular Heck reaction.[10]

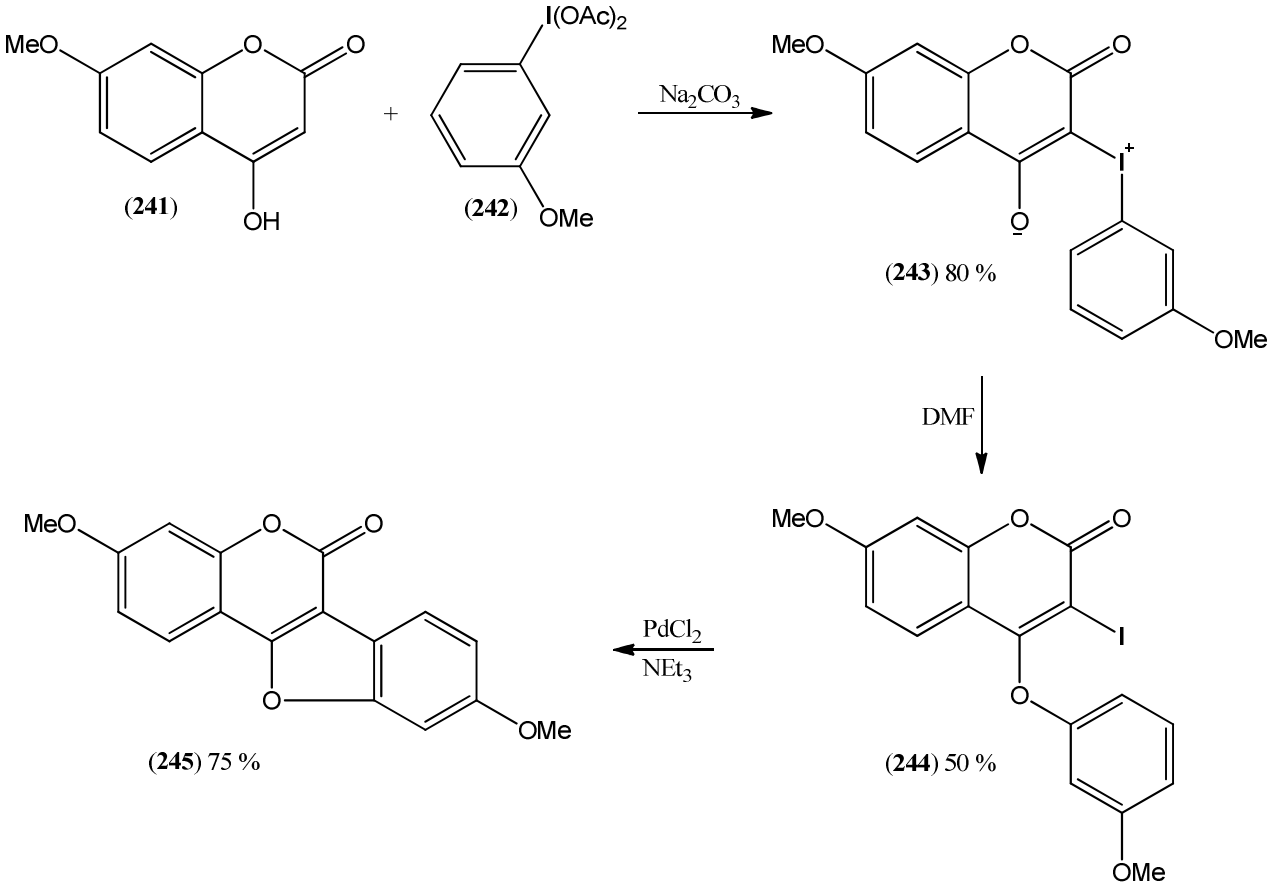


Figure 2-39: Synthesis of di-*O*-methylcoumestrol

2.7. References

(1) Li, S-R.; Chen, P-Y.; Chen, L-Y.; Lo, Y-F.; Tsai, I-L.; Wang, E-C. *Tetrahedron Lett.* **2009**, *50*, 2121-2123.

(2) Takashima, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 5156-5158.

(3) Dewick, P. M. In *The Flavonoids - Advances in research*; Harborne, J. B., Ed.; Chapman and Hall Ltd.: London, 1982, pp. 535-632.

(4) Wong, E. In *The Flavonoids*; Harborne, J. B., Mabry, T. J., Mabry, H., Ed.; Chapman and Hall Ltd.: London, 1975, pp. 743-800.

(5) Dewick, P. M. In *The Flavonoids - Advances in research since 1980*; Harborne, J. B., Ed.; Chapman and Hall Ltd.: London, 1988, pp. 125-204.

(6) Farkas, L. *Chem. Ber.* **1957**, *90*, 2940-2943.

(7) Kagal, S. A.; Madhavan Nair, P.; Venkataraman, K. *Tetrahedron Lett.* **1962**, *3*, 593-597.

(8) Kagal, S. A.; Karmarkar, S. S.; Venkataraman, K. *Proc. Indian Acad. Sci.* **1956**, *44*, 36-41.

(9) Mahal, H. S.; Rai, H. S.; Venkataraman, K. *J. Chem. Soc. (Resumed)* **1934**, 1120.

(10) Dewick, P. M. In *The Flavonoids - Advances in research since 1986*; Harborne, J. B., Ed.; Chapman and Hall Ltd.: London, 1994, pp. 117-232.

(11) Farkas, L.; Gottsegen, A.; Nogradi, M.; Antus, S. *J. Chem. Soc. C* **1971**, 1994-2000.

(12) Krishnamurty, H. G.; Siva Prasad, J. *Tetrahedron Lett.* **1977**, *18*, 3071-3072.

(13) Pelter, A.; Foot, S. *Synthesis* **1976**, *1976*, 326-326.

(14) Jha, H. C.; Zilliken, F.; Breitmaier, E. *Angew. Chem. Int. Ed.* **1981**, *20*, 102-103.

(15) Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972-1979.

(16) Donnelly, D. M. X.; Boland, G. M. *Nat. Prod. Rep.* **1995**, *12*, 321-338.

(17) Wahala, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005-3008.

(18) Chang, Y-C.; Nair, M. G.; Santell, R. C.; Helferich, W. G. *J. Agric. Food Chem.* **1994**, *42*, 1869-1871.

(19) M. Boland, G.; M. X. Donnelly, D. *Nat. Prod. Rep.* **1998**, *15*, 241-260.

(20) Grover, S. K.; Jain, A. C.; Seshadri, T. R. *Indian J. Chem.* **1963**, *1*, 517-520.

(21) Bhrara, S. C.; Jain, A. C.; Seshadri, T. R. *Tetrahedron* **1965**, *21*, 963-967.

(22) Ollis, W. D.; Ormand, K. L.; Redman, B. T.; Roberts, R. J.; Sutherland, I. O. *J. Chem. Soc. C* **1970**, 125-128.

(23) Farkas, L.; Gottsegen, A.; Noagradi, M.; Antus, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 305-312.

(24) Tsukayama, M.; Horie, T.; Iguchi, Y.; Nakayama, M. *Chem. Pharm. Bull.* **1988**, *36*, 592-600.

(25) Khanna, M. S.; Singh, O. V.; Garg, C. P.; Kapoor, R. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2565-2568.

(26) Prakash, O.; Pahuja, S.; Goyal, S.; Sawhney, S. N.; Moriarty, R. M. *Synlett.* **1990**, *1990*, 337-338.

(27) Prakash, O.; Saini, N.; K. Sharma, P. *Heterocycles* **1994**, *38*, 409-431.

(28) Prakash, O.; Tanwar, M. P. *J. Chem. Res. (S)* **1995**, 213.

(29) Prakash, O.; Saini, N.; Sharma, P. K. *Synlett.* **1994**, *1994*, 221-227.

(30) Santhosh, K. C.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1992**, 224-225.

(31) Donnelly, D. M. X.; Finet, J-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1679-1683.

(32) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729-1735.

(33) Salakka, A. K.; Joleka, T. H.; Wahala, K. *Beilstein J. Org. Chem.* **2006**, *2-16*, doi:10.1186/1860-5397-2-16.

(34) Saito, R.; Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1776-1779.

(35) Donnelly, D. M. X.; Finet, J-P.; H. Stenson, P. *Heterocycles* **1989**, *28*, 15-18.

(36) Shih, T. L.; Wyvratt, M. J.; Mrozik, H. *J. Org. Chem.* **1987**, *52*, 2029-2033.

(37) Versteeg, M.; Bezuidenhoudt, B. C. B.; Ferreira, D.; Swart, K. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1317-1318.

(38) Ferreira, D.; Versteeg, M.; Bezuidenhoudt, B. C. B. *Heterocycles* **1993**, *36*, 1743-1746.

(39) Ferreira, D.; Versteeg, M.; Bezuidenhoudt, B. C. B. *Heterocycles* **1998**, *48*, 1373-1380.

(40) Ozaki, Y.; Mochida, K.; Kim, S-W. *J. Chem. Soc., Chem. Commun.* **1988**, 374-375.

(41) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068-5070.

(42) Van Aardt, T. G.; Van Heerden, P. S.; Ferreira, D. *Tetrahedron Lett.* **1998**, *39*, 3881-3884.

(43) Van Aardt, T. G.; Van Rensburg, H.; Ferreira, D. *Tetrahedron* **1999**, *55*, 11773-11786.

(44) Van Aardt, T. G.; Van Rensburg, H.; Ferreira, D. *Tetrahedron* **2001**, *57*, 7113-7126.

(45) Moti, K.; Kisida, H. *Liebigs Ann. Chem.* **1989**, 35-39.

(46) Pinard, E.; Gaudry, M.; Henot, F.; Thellend, A. *Tetrahedron Lett.* **1998**, *39*, 2739-2742.

(47) Amos, P. C.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1987**, 510-511.

(48) Ahmad-Junan, S. A.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1160-1161.

(49) Crombie, L.; Josephs, J. L. *J. Chem. Soc., Perkin Trans. I* **1993**, 2591-2597.

(50) Omokawa, H.; Yamashita, K. *Agr. Biol. Chem.* **1973**, *37*, 1717-1721.

(51) Lai, S. M. F.; Orchison, J. J. A.; Whiting, D. A. *Tetrahedron* **1989**, *45*, 5895-5906.

(52) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. *J. Chem. Soc. Perkin Trans. I* **1994**, 653-657.

(53) Crombie, L.; Josephs, J. L.; Larkin, J.; Weston, J. B. *Chem. Commun.* **1991**, 972-973.

(54) Crombie, L.; Josephs, J. L. *J. Chem. Soc. Perkin Trans. I* **1993**, 2599-2604.

(55) Pal Singh, R.; Singh, D. *Heterocycles* **1985**, *23*, 903-907.

(56) Laschober, R.; Kappe, T. *Synthesis* **1990**, 387-388.

CARBONYLATION OF ALKENES 3

The insertion of a C=O moiety through carbonylation is a major improvement in synthetic organic chemistry since carbon-carbon bond formation represents one of the most fundamental reactions in organic chemistry and carbonyl compounds are regarded as one of the most versatile functional groups for molecular transformations. From *ca*. 1960 the scope and understanding of the carbonylation reaction has grown to the extent that it is now considered as a general technique in synthesis especially due to its tolerance for a wide variety of functional groups.[1,2,3] The three reactions in Figure 3-1 are representative of the three main types of carbonylation reactions, namely hydroformylation (A), hydrocarboxylation (B, Nu = OH), hydroesterification (B, Nu = OR^2) and copolymerization (C) which leads to aldehydes (**247-248**), carboxylic acids (**249**) and (**251**), esters (**250**) and (**252**) and polyketones (**253**), respectively.[4]

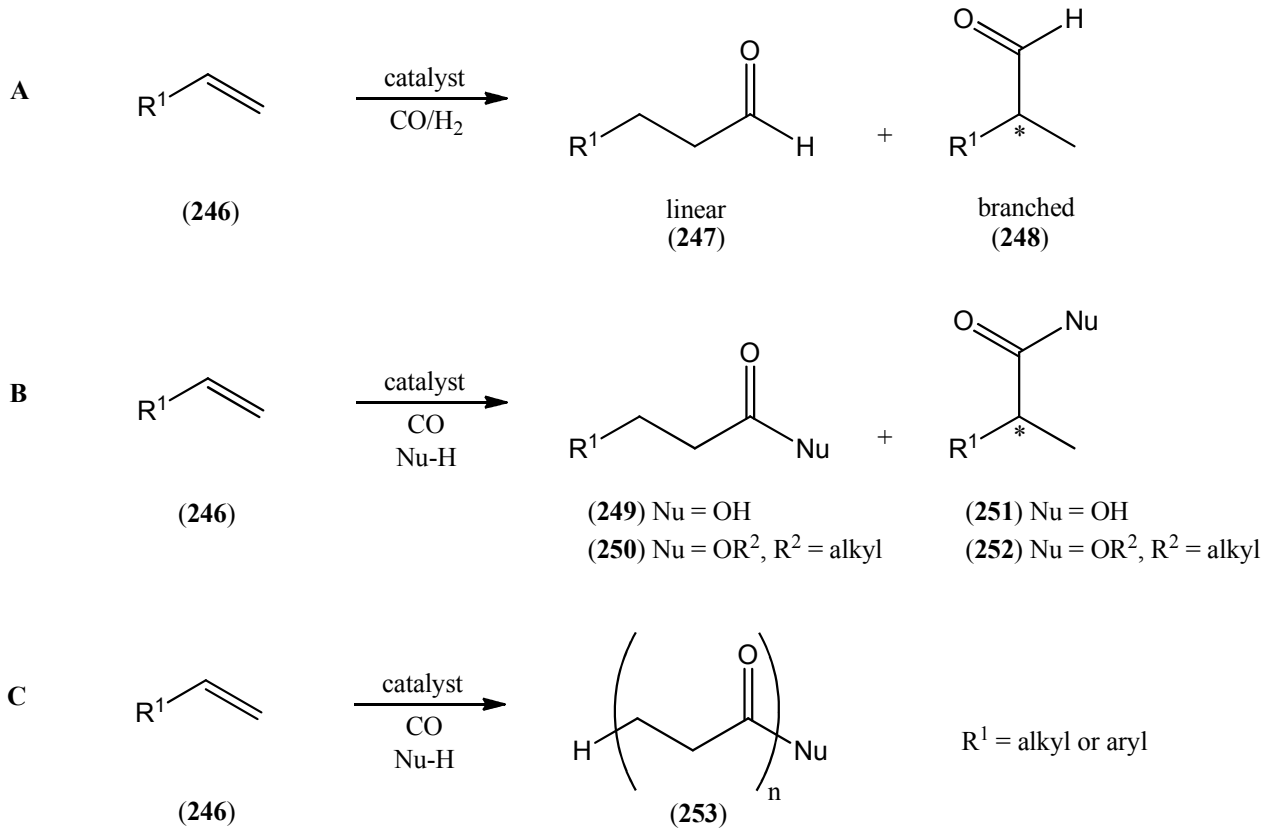


Figure 3-1: Summary of carbonylation reactions

In general, carbonylation catalysts are based on group VIII transition metals like Fe, Ru, Co, Rh, Ir, Ni, Pd and Pt. Among these, Co, Pd and Rh catalysts are the most active, resulting in a range of applications having been investigated. A variety of different substrates like olefins, alkynes, and

reactive aryl, vinyl and alkyl species are susceptible to carbonylation. Furthermore carbonylation of these compounds provide one of the most economical and clean routes to a variety of carboxylic acid derivatives and is therefore of immense industrial importance. The discussion in this chapter will however be limited to the carbonylation of alkenes.[1,2,3]

3.1. Polyketone formation

The first carbonylation reaction was discovered in 1940 by Reppe and Magin when they found that CO and ethene could be copolymerized to give polyketone products.[5] The reaction that was catalysed by $K_2Ni(CN)_4$ in water produced oligomers of ethene and carbon monoxide with low melting points, as well as diethylketone and propionic acid as side products.[5] Thirty years later workers at Shell Development improved the Ni-catalyst by the addition of strong acids like trifluoromethanesulphonic acid (TfOH) and *para*-toluenesulfonic acid (*p*-TsOH) and obtained a polymer of high molecular weight, but unfortunately high catalyst concentrations were still necessary to obtain acceptable yields.[6] In search of better catalysts rhodium carbonyls were experimented with, but these complexes could only produce copolymers with low molecular weights at very low reaction rates.[7] In 1967 Gough[8] disclosed a palladium based catalyst $[Pd(PBu_3)_2Cl_2]$ that yielded polyketone at a catalyst activity of 300 g of polyketone per gram of Pd per hour with the only disadvantage being the requirement of very harsh reaction conditions (250 °C, 2000 bar).[8,9]

The early contributions centred around three basic methods namely free radical initiated, γ-radiation induced and Pd-catalysed $[Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ and $HPd(CN)_3]$ copolymerizations, all of which required harsh reaction conditions (temperatures > 100 °C and pressures from 400 to 1000 bar). Sen *et al.*[10,11] improved the methodology by utilizing $[Pd(CH_3CN)_4](BF_4)_2.nPPh_3$ (n = 1-3) (1) catalysts and managed to obtain high molecular weight polymer of regular alternating ethylene-carbon monoxide units at unusually low reaction temperatures (25 °C) and pressures (25 bar).

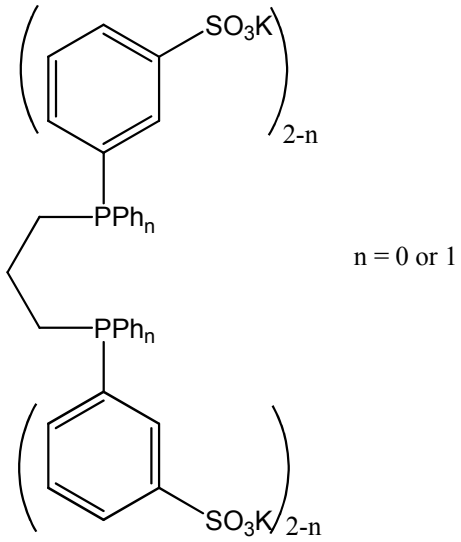
$$n CH_2{=}CH_2 + n CO \xrightarrow{[Pd]} (\text{-}CH_2CH_2CO\text{-})_n \qquad (1)$$

By performing these reactions in alcohols, these workers were able to prepare very long polymer chains (n > 2[7]) with ester functional groups as one terminal unit (2).

$$n CH_2{=}CH_2 + n CO + ROH \xrightarrow{[Pd]} H\text{-}(\text{-}CH_2CH_2CO\text{-})_n\text{-}OR \qquad R = CH_3, CH_2CH_3 \qquad (2)$$

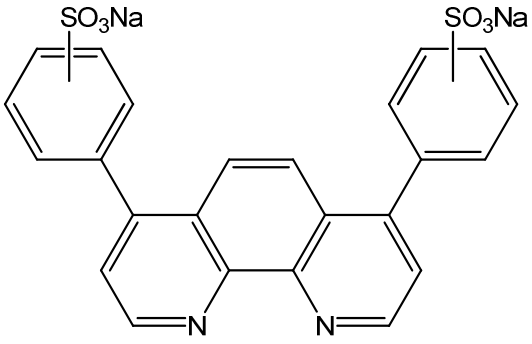
They were also able to show that water soluble palladium(II) compounds such as $[Pd(dppp\text{-}SO_3K)(H_2O)_2](BF_4)_2$ and $[Pd(phenSO_3Na)(H_2O)_2](BF_4)_2$, prepared from the potassium salt of

sulfonated 1,3-bis(diphenylphosphino)propane (dppp) (**254**) and the disodium salt of 4,7-diphenyl-1,10-phenanthrolinedisulfonic acid (phen) (**255**), respectively, gave good catalyst activities (TON's of 470 and 80 respectively in 22 hours) under mild reaction conditions (50 °C as well as CO and ethylene pressures of 35 bar).[12]



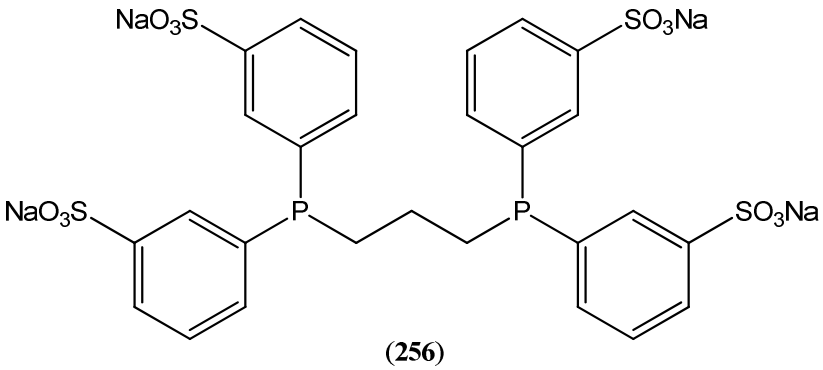
n = 0 or 1

(254)



(255)

By using cationic palladium complexes containing tertiary bidentate phosphine ligands like [$Ph_2P(CH_2)_3PPh_2$] and weakly coordinating anions like sulfonate, Drent and co-workers[9] found a highly reactive system able to produce high molecular weight polyketone products at very high turnover rates [TOF = 6000 gram per gram of Pd per hour] in methanol under relatively mild reaction conditions (90 °C, 45 bar). Similarly Verspui *et al.*[13,14] found the water soluble Pd/S-dppp/*p*-TsOH catalyst system, [S-dppp = 1,3-bis(di(*m*-sodiumsulfonatophenyl)phosphine)-propane (**256**)] to be highly reactive (TOF = 4000 gram of copolymer per gram of Pd per hour).[9]



(256)

The importance of polyketones is found in the fact that these compounds are photo and biodegradable polymers and therefore find application in the automotive industry and in the manufacturing of fibres and packaging materials.

3.2. Hydroformylation

Hydroformylation, also known as the "oxo" reaction, was discovered in 1938 by Otto Roelen and comprises a high temperature metal catalysed reaction of mostly alkenes with synthesis gas ($CO:H_2$ 1:1) to form aldehydes, which may or may not be reduced *in situ* to alcohols.[15] Various transition metals like Rh, Co, Pt, Ru and Pd have been utilized in the hydroformylation reaction but Rh and Co based complexes are currently the commonly used industrial catalysts.[1] Over 9 million tons of oxo-products are produced annually, the majority of which being from the hydroformylation of propene (**257**) (Figure 3-2). Since high carbon number (C_{12-14}) non-branched alcohols are biodegradable and widely used as surfactants, the linear aldehydes produced by hydroformylation of α-olefins (1-alkenes) therefore centres around obtaining high regioselectivity in other words high linear to branched ratios (*l*:*b* also known as *n*:*i*) that would lead to the sought after linear alcohols after hydrogenation. This aspect, as well as minimizing double bond migration in the alkene, plays a pivotal role in catalyst selection during the application of the reaction. The fact that internal olefins are cheaper than the corresponding α-olefins, gave impetus to industrial research projects aimed at converting these low priced starting materials into long-chain linear aldehydes through hydroformylation following isomerization of the internal double bond to the terminal position.[1,16,17,18]

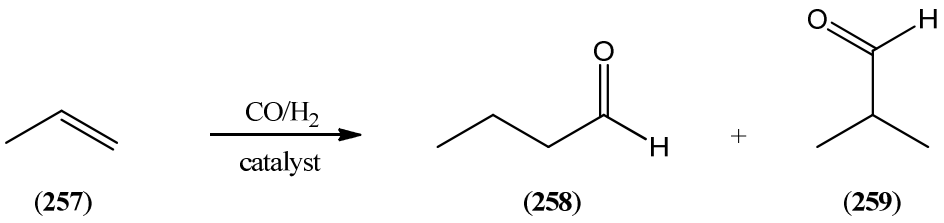


Figure 3-2: Hydroformylation reaction for the formation of *l:b* products

3.2.1. Cobalt catalysed hydroformylation

While the original work by Roelen[15] utilized simple cobalt salts [with formation of $HCo(CO)_4$] as active catalyst in the hydroformylation reaction, the instability of cobalt carbonyls, the harsh reaction conditions with pressures ranging from 200-300 bar and temperatures up to 200 °C led to the Co carbonyl catalysts being modified by the addition of alkyl phosphines. Later generation Co hydroformylation catalysts can therefore be represented by the general formula $H_xM_y(CO)_zL_n$ where M and L represent the Co metal and ligand, respectively. With n = 0 the catalyst is referred to as an *unmodified* cobalt catalyst, while a *modified* Co catalyst will be one where the

coordination sphere of the cobalt metal is changed by at least one ligand other than CO or hydrogen.

Cobalt catalysts are preferred for the hydroformylation of higher alkenes, although some older plants still use Co-catalysis for the hydroformylation of propene. Since common alkene (C_{10-14}) feedstock to hydroformylation plants consists of a mixture of terminal and internal alkenes, many plants still utilize cobalt, because cobalt catalysts have the ability to isomerize internal double bonds to the terminal position resulting in reasonable *l*:*b* ratios (60-70 %).[19,20]

The catalytic cycle for the Co-catalysed hydroformylation reaction has been studied extensively for many decades and although it has been known from 1953 that $HCo(CO)_4$ is the active catalyst, there was a lot of controversy regarding the actual catalytic cycle. Currently the catalytic cycle shown in Figure 3-3 where the $16e^-$ species, $HCo(CO)_3$, is generated by loss of a CO ligand from the $HCo(CO)_4$ resting state, followed by alkene coordination, is generally accepted as the prevailing mechanism. After alkene coordination, hydride transfer occurs to form the alkyl species, (**261**) and (**262**), followed by CO coordination and migratory insertion. Oxidative addition of H_2 and reductive elimination of the aldehyde product (**247**) then leads to the regeneration of the $HCo(CO)_3$ species and completion of the catalytic cycle.[17,19]

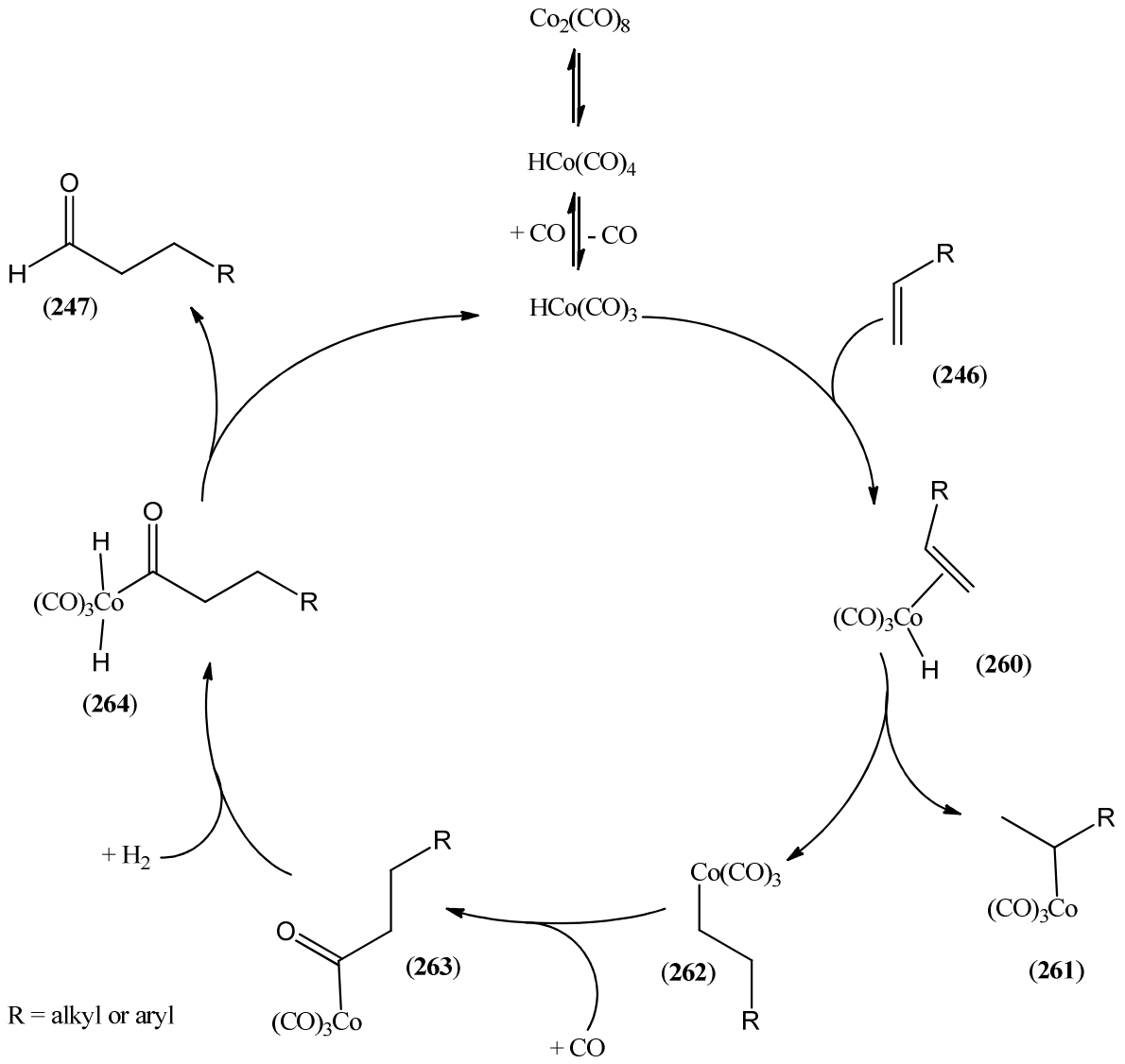


Figure 3-3: Catalytic cycle of Co-catalysed hydroformylation utilizing syngas

In the 1960's Slaugh[21,22,23] found that replacing carbon monoxide on the cobalt with tributylphosphine during the hydroformylation reaction increased the stability of the cobalt catalyst and also gave a better selectivity towards the linear aldehyde. The improved selectivity towards linear aldehydes could be explained by looking at both the steric and electronic effects. The strong donating alkylphosphines retard the dissociation of carbon monoxide by donating electron density onto the metal centre, thus leading to more stable catalysts, but also much slower reactions.[24] It has been noticed that as the metal becomes more electron rich, the catalyst becomes more selective towards the straight chain product, because the more electron rich hydride complexes cause the hydride to become less proton-like with the consequence that the hydrogen is less likely to be added to the carbon having the higher number of hydrogens (anti-Markovnikov addition as shown in Figure 3-4). From a steric point of view, it can be seen that when the

hydrogen is transferred to the alkene carbon bearing the higher number of hydrogen atoms, steric interaction between the bulky phosphine ligand and the alkyl group of the olefin would be less favourable than for anti-Markovnikov addition where little steric interaction would be present as the phosphine ligand is close to the less hindered carbon atom.[24,25]

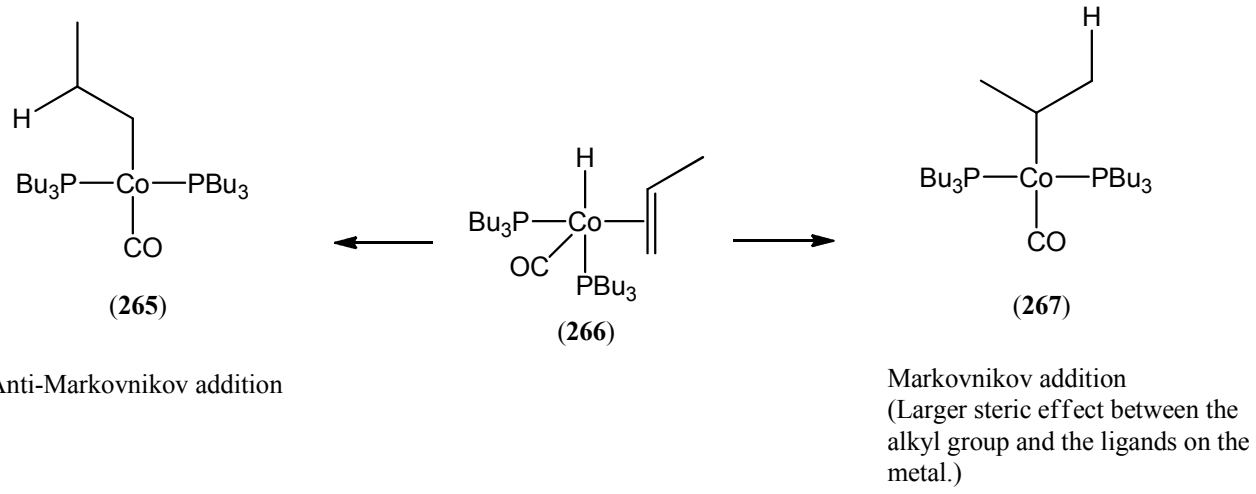


Figure 3-4: Steric effects by phosphine ligand on cobalt-catalysed hydroformylation, anti-Markovnikov

Through experimentation with various phosphine ligands, like Bu_3P, Et_3P, $PhBu_2P$ and Cy_3P, it also became apparent that alkylphosphine ligands, which gave lower reaction rates due to more stable cobalt complexes arising from stronger electron donor properties, form better catalysts than weaker electron donors such as arylphosphine ligands which gave very reactive but unstable cobalt catalysts.[19]

Hydroformylation with modified cobalt catalysts was taken to industrial scale by the Royal Dutch Shell company with the introduction of a series of phobane ligands (**268-269**) (Figure 3-5), which were much more effective than ordinary acyclic trialkylphosphines.[26] Further improvements to the system led to the development of 9-eicosyl-9-phosphabicyclononane (**270-271**), which had the added advantage that the C_{20} chain provided a phosphine with a boiling point much higher than that of most products thus leading to much improved separation processes as well as a catalyst of increased stability.[27] The use of these electron donating ligands resulted in a more stable system operating at lower pressures (25-100 bar), but the phosphine complex is less active than the tetracarbonyl complex, which translates to higher reaction temperatures (170 °C). The result was a significant increase in regioselectivity from 60-70 % formation of the linear aldehyde product to a remarkable 75-90 %.[19,28]

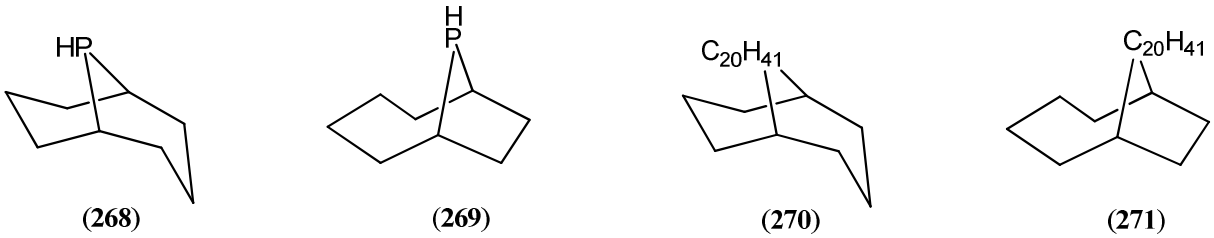


Figure 3-5: Shell's phobane ligands

Another series of bicyclic phosphine ligands related to Shell's phobane ligands were recently developed by Sasol. These compounds, based on the addition of PH_3 to the *R*-enantiomer of the abundant natural product, limonene (**272**), are called *Lim*-ligands (**276**) and (**277**) and also increase the electron density on the phosphorus atom while the steric congestion caused by the ring system raised the electronic parameter of the ligand, which made these ligands better π-acceptors.[29] By using *Lim*-ligands containing different "X" groups in the order of X = Me, OBz, Ph and CN, an increase in the reaction rate was observed. Selectivity towards the linear product, however, decreased as the reaction rate increased.

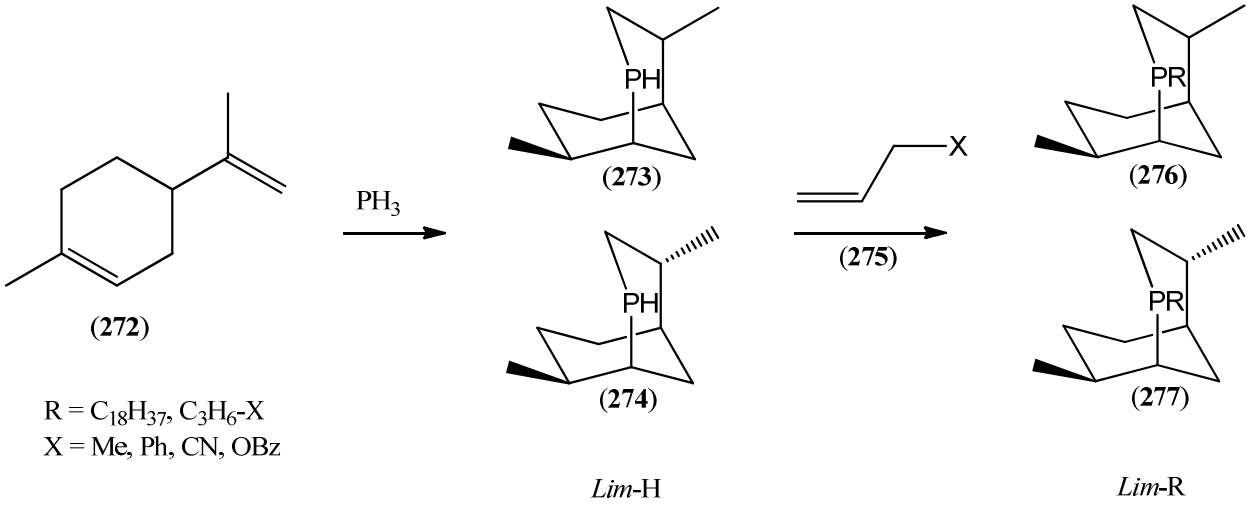


Figure 3-6: *Lim*-ligands developed by Sasol

The same tendency was seen when several other ligands namely bicyclic aliphatic phosphines and diphosphines were developed and experimented with, from which tertiary phosphines [$P(C_3H_6OCH_3)_3$, $P(C_2H_4CO_2CH_3)_3$ and $P(C_2H_4CN)_3$] gave the highest percentage of linear product formation. For a 1:1 ligand:cobalt ratio the results were the same for all of the above mentioned ligands with the percentage of linear products being a comparable 60 % (40 bar H_2, 5 bar CO, 150

°C). When the ligand:cobalt ratio was increased to 10:1, the linearity increased to 90 %, but unfortunately the conversion was extremely low (0.5 % after 3h).[19,28,30]

3.2.2. Rhodium catalysed hydroformylation

Although it was known since 1959 that rhodium is an extremely active catalyst for hydroformylation of alkenes,[31] the pioneers in developing phosphorous ligands for rhodium catalysed hydroformylation were Slaugh, Wilkinson and Pruett. Slaugh[32] and co-workers used a rhodium carbonyl tri-*n*-butylphosphine complex for the hydroformylation of pent-1-ene and obtained a *l*:*b* ratio of 72:28, while Wilkinson *et al.*[33,35,36]discovered triphenylphosphine and trialkylphosphine modified rhodium complexes to act as catalysts in the hydroformylation reaction and showed that arylphosphines (rhodium chloride triphenylphosphine) give a similar *l*:*b* ratio (70:20) which is also comparable to the results of Pruett and co-workers[34] who utilized a phosphite ligand (rhodium carbonyl triphenylphosphite). Compared to the older cobalt catalysts, these complexes offered the advantage of enhanced rates, lower operating temperatures (60-90 °C) and pressures as well as higher selectivity towards straight chain aldehydes. All of these different phosphorous ligands induced the same amount of selectivity towards the linear aldehyde product but while alkylphosphines are the ligand of choice for cobalt catalysts, rhodium alkylphosphine complexes lead to slow hydroformylation reactions and therefore the use of arylphosphines and phosphites became important.[19] The most exciting result from an α-olefin perspective, however turned out to be complete elimination of alkene isomerization and hydrogenation during rhodium based reactions. Because of the milder reaction conditions the rhodium catalysed process became known as the “low pressure oxo” (LPO) process.

The accepted catalytic cycle for Rh-catalysed hydroformylation was proposed by Heck[37] in 1969 (Figure 3-7) and is based on the common starting complex $RhH(PPh_3)_3CO$ (**279**). The most important steps are dissociation of one ligand to form a square planar intermediate (**280**) that would allow for ethene association which is followed by migratory insertion to form a square planar alkyl complex (**282**). This intermediate can either undergo β-hydride elimination leading to isomerization (low CO pressure) or react with CO (temperatures below 70 °C, CO pressure above 10 bar) to form the trigonal bypiramidal complex (**283**). A second migratory insertion subsequently forms the acyl complex (**284**), which can either react with H_2 to form the aldehyde product (**286**) or with CO to form a coordinatively saturated acyl intermediate (**285**). Note that the trigonal bypiramidal intermediates (**278**, **281**, **283**, **285**) can either exist in the ee-form where both phosphine ligands are in equatorial positions or in the ae-form where one ligand is in apical position and the other one in an equatorial position, though all the structures in Figure 3-7 are in

the ee-form. Likewise the square planar intermediates (**280**, **282**, **284**) can exist in either the *cis* or *trans* configuration, but all the structures in Figure 3-7 are displayed in the *trans* form.[4,19]

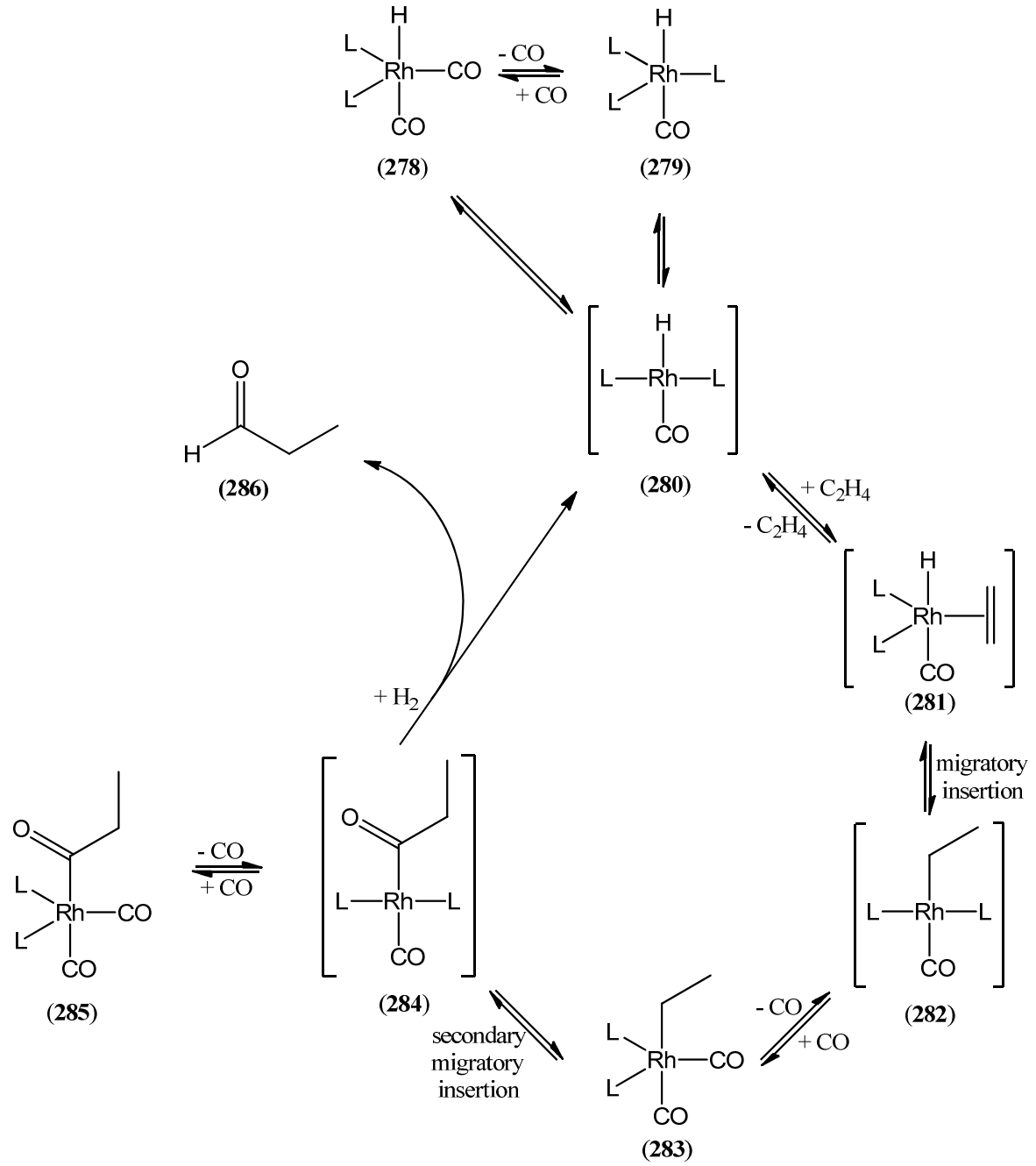
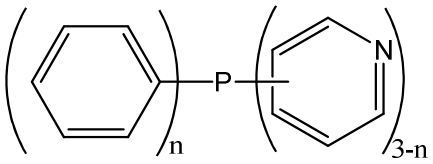


Figure 3-7: Catalytic cycle for Rh-catalysed hydroformylation, where L = PPh_3

The steric and electronic properties of phosphine ligands were first studied by Tolman *et al.*[24,25] and inspired numerous subsequent studies aimed at defining and understanding these effects in transition metal catalyst complexes, since it has a huge influence on the rate and selectivity of specifically the hydroformylation reaction.[19,38] Steric and electronic effects are not easily distinguished and a systematic study is impeded by the variety of complexes involved in various

stages of the reaction as well as the wide variety of reaction conditions experimented with, nevertheless a few rules of thumb can be depicted.[19,38]

Electron-donating ligands, such as alkylphosphines, lead to slower catalysis and as a result higher temperatures are required, but it has been shown that triethylphosphine gives turnover numbers of 700 for 1-hexene (120 °C and 40 bar) and very high turnover numbers for ethene. This exception can be explained by the reaction following a different mechanism involving a secondary solvent-dependent hydrogenation to form the corresponding alcohol instead of the aldehyde.[39] Arylphosphines containing electron-withdrawing substituents give a faster catalytic reaction than triphenylphosphine. This was confirmed by Van Leeuwen *et al.*[40] through the synthesis of pyridylphosphines (**287**), (**288**) and (**289**) that doubled the TOF values obtained with triphenylphosphine for the hydroformylation of 1-octene. Phosphites can occasionally give faster catalysis than phosphines, but without exception dibenzophospholes, which are more electron-withdrawing then diphenylphosphino groups, leads to faster catalysis. In explanation it can be said that electron-withdrawing ligands leads to a decrease of the back-donation to carbon monoxide and thus to weaker bonding of carbonyls as well as the acceleration of alkene complexation. The oxidative addition step is slightly slowed down when electron-withdrawing ligands are used and migratory insertions are not significantly influenced by the electronic properties of the ligand.[19]

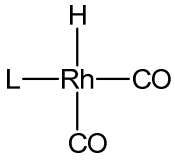


(**287**) 4-pyridyl, n = 2
(**288**) 3-pyridyl, n = 2
(**289**) 3-pyridyl, n = 1

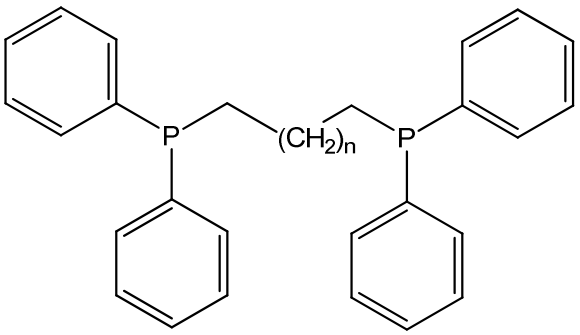
Steric effects are very important in phosphine- and phosphite-modified rhodium-catalysed hydroformylation of alkenes and although there is great controversy in the literature regarding kinetic studies, it is agreed upon that the rate of hydroformylation falls with increasing steric hindrance in the ligand and the substrate and at the same time the *l*:*b* ratio rises.[41] More sterically demanding ligands will favour the formation of species containing less phosphorous ligands and therefore more CO ligands. A high proportion of CO ligands will lead to an electron poor rhodium species and thus enhanced CO dissociation.[19] It is known that the reactivity of hydroformylation catalysts decrease with the degree of olefin substitution from the most reactive 1-alkenes to substituted 1-alkenes followed by the least reactive internal alkenes. During ligand modification studies some trends have been discovered and gives a hint towards a solution to this problem. Strong and small σ-donor ligands retard or even inhibits the hydroformylation reaction, while π-acceptor ligands, such as phosphites and especially bulky phosphites, leads to more active

hydroformylation catalysts. As phosphites are labile towards hydrolysis and degradation, research are being done to develop other π-acceptor ligands and although phosphabenzenes seems to be a promising candidate, further research will be necessary.[41,42]

The most abundantly used phosphorous ligand for the modification of Rh-catalysts is specifically triphenylphosphine (PPh_3) which gives high regioselectivity, for example for the hydroformylation of 1-alkenes the linear aldehyde is obtained in between 70 and 96 % yield. Regioselectivity is influenced by the number of phosphines coordinated to rhodium, along with the stereochemistry at rhodium. At high and moderate PPh_3 concentrations the resting state of the catalyst is (**279**) and a mixture of (**278**) in ae and ee form, respectively. Both of these species lead to (**280**) which gives high *l*:*b* ratios (20:1). At moderate and low PPh_3 concentrations the square planar intermediate (**290**) is formed, containing only one phosphine ligand leading to a decrease in *l*:*b* ratios (4:1).[19] The use of diphosphines such as dppe (**291**) and dppp (**292**) gives modest linear-branched ratios (3:1) and since their putative intermediate (**280**) must exist in *cis* structure, the conclusion can be drawn that the species leading to high linearity is the *trans* species (**280**) while the *cis* structure of (**280**) and both species of (**290**) lead to low *l*:*b* ratios.[19]

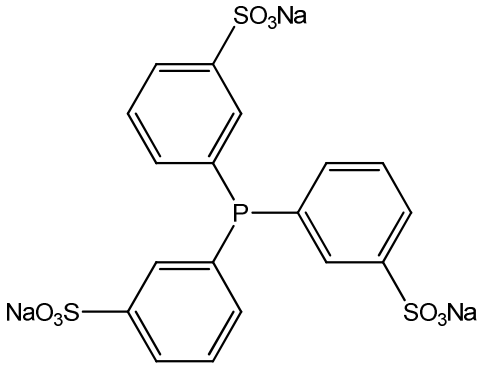


(**290**)

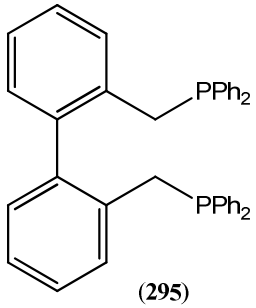


(**291**) n = 0
(**292**) n = 1
(**293**) n = 2

Industrially, triphenylphosphine is used extensively as ligand in LPO hydroformylation reactions. For example Dow Chemicals is using this process to convert propylene into butanal with a linear selectivity of 92 % and a TOF of *ca*. 300. Several other ligands have, however, also found application in the production of commercially important aldehydes. In this regard, Ruhrchemie (now Celanese) commercialized a two-phase process utilizing 3,3',3''-phosphinidynetris-(benzenesulfonic acid)trisodium salt (tppts) (**294**) as ligand for the production of butanal from propene in very high selectivity (92 %). The Rh-catalyst in this instance resides in the water-phase, while the butanal and propene are dissolved in an organic solvent. Vigorous mixing is therefore required in order to obtain decent conversion.[19]

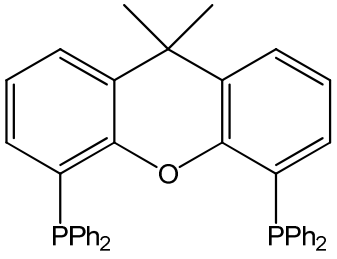


(**294**)

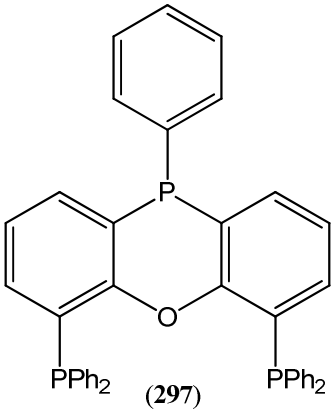


(**295**)

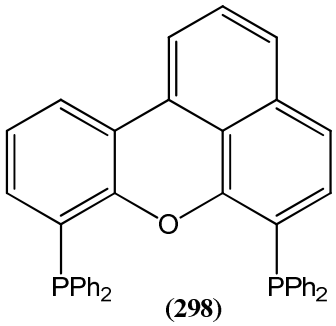
While it is generally true that diphosphine ligands, like dppe (**291**) and dppp (**292**), make better catalysts than their monomeric counterparts (e.g. PPh_3), because less ligand is required to prevent the palladium metal from precipitating out, catalysts prepared from these ligands gave poor performance for linear products in the hydroformylation reaction. The BISBI (**295**) diphosphine ligand, developed by Eastman Chemicals for their propene hydroformylation process, however, were capable of producing very high *l*:*b* ratios of 30:1.[19,43] This methodology was improved by using dibenzophosphole groups instead of diphenylphosphino groups which increased the *l*:*b* ratio to a remarkable 288:1.[19,44] Careful analysis of the results obtained with different diphosphine ligands and comparing *l*:*b* ratios of different ligands led to the idea that the linearity of the products is, to a large extent, dependant on the bite angle of the ligand when attached to palladium. This observation led to the development of a series of xanthene based ligands (e.g. xantphos (**296**), phosxantphos (**297**), benzoxantphos (**298**), nixantphos (**299**) and thizantphos (**300**)), the so-called xantphos ligands, which have tunable wide bite angles and gave *l*:*b* ratios of 8.5-69, albeit at the cost of catalyst activity (TOF's of only 37-340).[19,45,46]



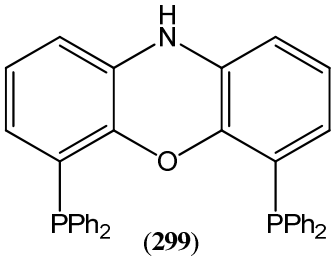
(**296**)



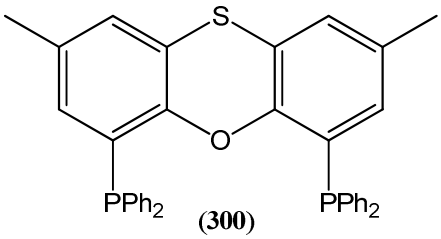
(**297**)



(**298**)

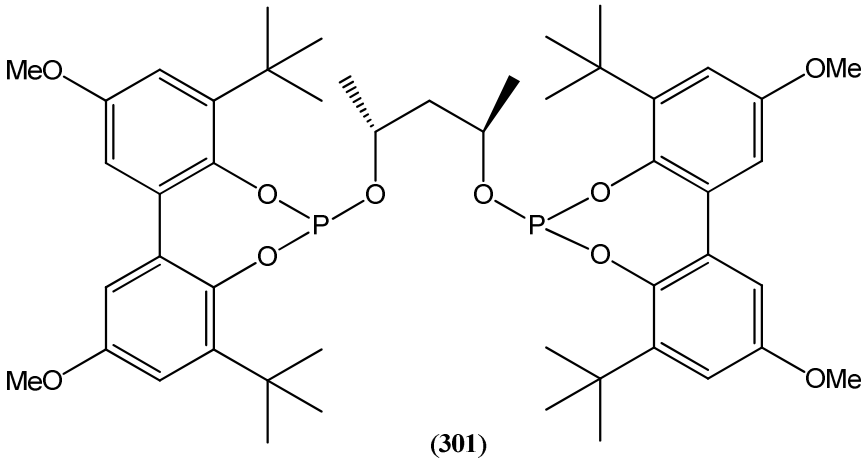


(**299**)

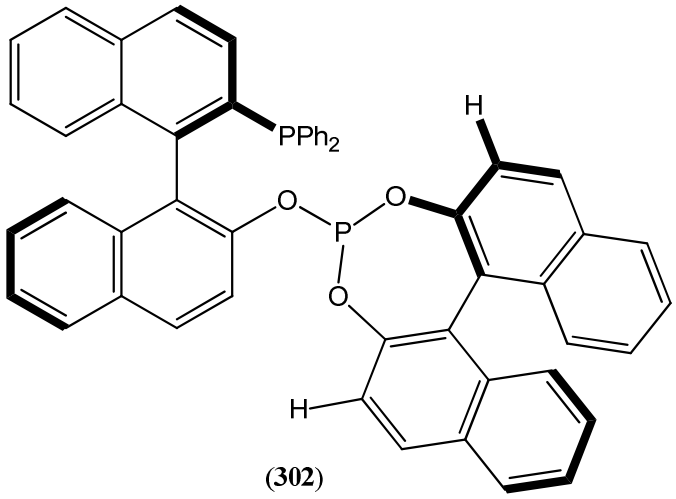


(**300**)

While asymmetric hydroformylation of alkenes is important for the synthesis of chiral aldehydes as intermediates in drug synthesis, enantiomeric excesses obtained using rhodium diphosphine catalysts were disappointingly low for many years and it was only when chiral diphosphite ligands were introduced that acceptable ee's were obtained. In this regard Babin and Whiteker (at Union Carbide) reported ee's of up to 90 % during the hydroformylation of a series of alkenes with a bulky chiral diphosphite catalyst, (isoBHA-P)$_2$-2R,4R-pentanediol (**301**), prepared from homochiral (2*R*,4*R*)-pentane-2,4-diol.[47,48] Currently, the C_1-symmetrical phosphine-phosphite ligand, (*R*,*S*)-BINAPHOS (**302**), developed by Takaya and Nozaki, can be regarded as the best ligand for asymmetric hydroformylation reactions with more than 90 % ee's being obtainable for a wide variety of prochiral both functionalised and internal alkenes.[19,49,50,51,52,53]



(**301**)



(**302**)

3.3. Hydrocarboxylation/Hydroxycarbonylation

The first catalytic hydroxycarbonylation process was discovered by Reppe[2,3] and converted acetylene, CO and water to acrylic acid with the use of $Ni(CO)_4$ as catalyst. This process for the production of acrylic acid required harsh reaction conditions (200-300 °C, 10-1000 bar), but was nevertheless commercialized in several countries until the oxidation of propene, a cheaper feedstock, was developed and implemented. The severe conditions required in the Reppe hydroxycarbonylation process directed research towards the development of improved catalysts leading to experimenting with a variety of transition metals like Co, Pd, Rh and Ir.[3] During the 1980's, Hoffman *et al.*[54] reported $Co_2(CO)_8$ to be a very efficient catalyst for the hydroxycarbonylation of olefins to carboxylic acids. While the catalyst showed high selectivity towards the linear products, which could be enhanced by the addition of pyridine, higher olefins such as 1-octene and 1-dodecene required severe operating conditions (160 °C, 200 bar).[3]

In the early 1990's Alper and co-workers[55,56] reported the first palladium based hydroxycarbonylation catalyst, [$Pd(OAc)_2$/dppb/PPh_3], which was used in combination with an acid promoter (formic or oxalic acid) and led to the regioselective formation of linear carboxylic acids (**304**) (> 75 % linearity) from a number of mono- and di-substituted olefins (**303**). While only mild reaction conditions [150 °C, 6.8 atm CO (Figure 3-8)] were required, the acid was formed through a complete different catalytic cycle (Figure 3-9). Control of the product regioselectivity depended on the effective bulk of the substituent (R in Figure 3-9) so only the linear acid was formed during reactions of sterically hindered alkenes.[56]

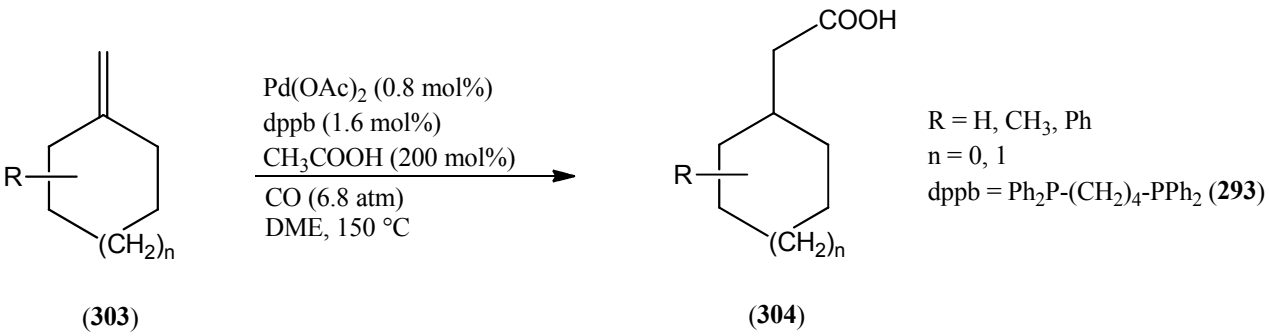


Figure 3-8: Alper's hydroxycarbonylation reaction with acetic acid

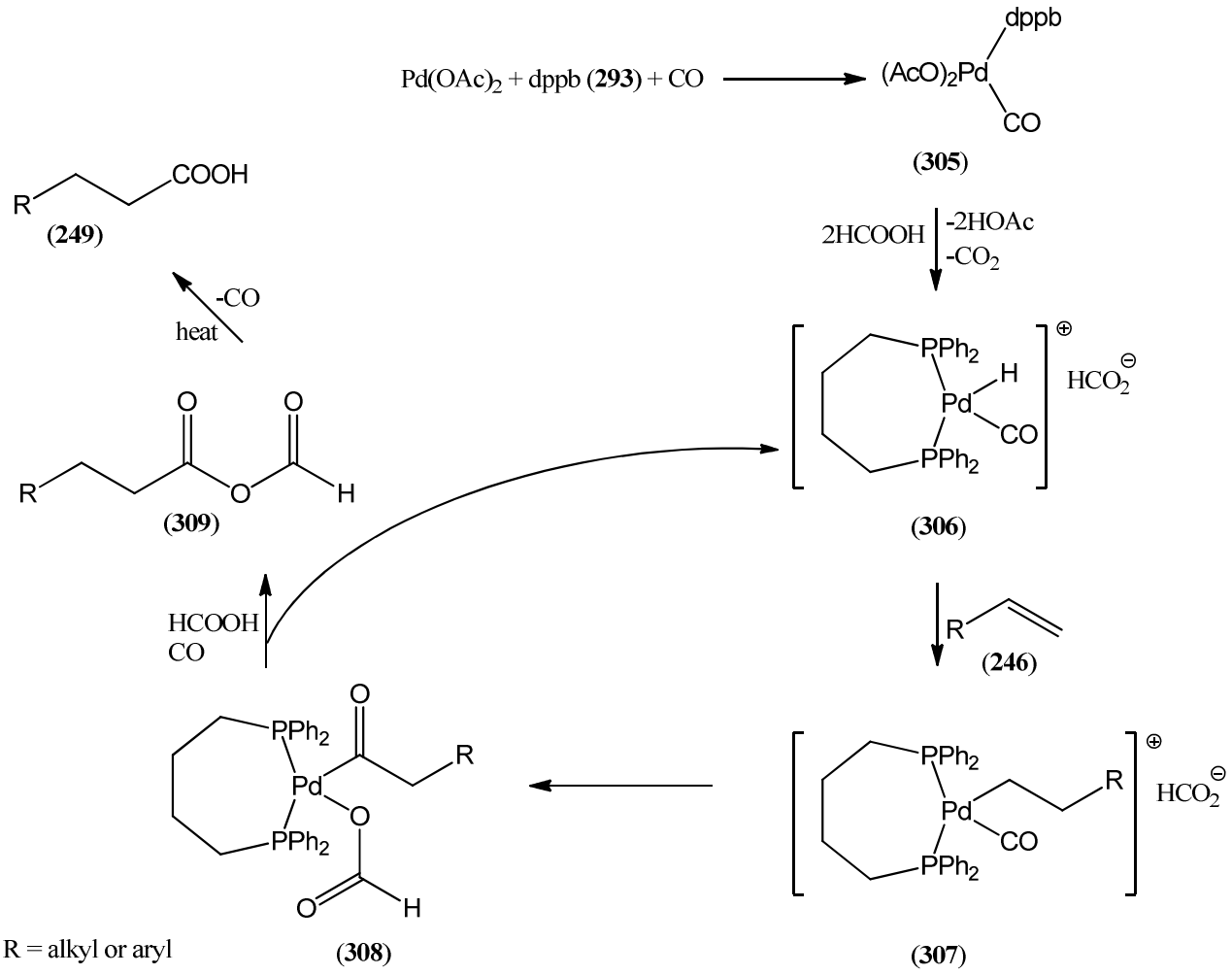


Figure 3-9: Alper's mechanism for hydroxycarbonylation with acetic acid

Through the utilization of a PdCl-PPh_3 catalyst system together with *p*-TsOH as acid promotor, Seayad and co-workers[57] were able to change the regioselectivity in favour of the branched acids. When these workers performed their reactions in the presence of the Lewis acid, LiCl,

hydroxycarbonylation of various vinyl aromatics (**310**) at moderate reaction conditions (115 °C, 54 bar) gave the branched acids (**311**) in excellent regioselectivity (up to 99.8 %) with high TOF (2250 h^{-1}) (Figure 3-10).[57]

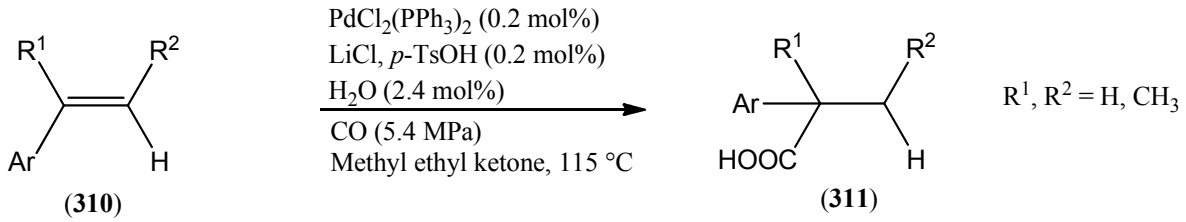
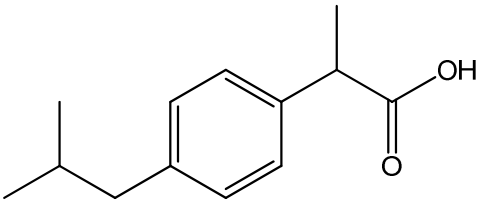


Figure 3-10: Seyad's hydroxycarbonylation reaction with LiCl, *p*-TsOH as acid promotor

Regioselectivity for the linear product can also be increased by the addition of a co-catalyst, such as $SnCl_2$ or $Co_2(CO)_8$, but the addition of co-catalysts unfortunately often decreases the rate of the reaction.[58] Consiglio[59] studied the influence of the structure of the Pd-ligand on the regioselectivity and proved that monophosphines (e.g. PPh_3) lead predominantly to the formation of the branched product, while diphosphines [e.g. DIOP (**323**)] produce the straight chain product instead. Unfortunately bidentate ligands are much more expensive and not as easily prepared as monodentate ligands.

3.4. Hydroesterification

Due to the close relationship between hydroxycarbonylation and hydroesterification many of the catalysts discussed in the previous paragraph can also be used for hydroesterification reactions and the knowledge gained regarding regioselectivity and ligand properties also applies to hydroesterification. Since carbonylation of vinyl aromatics or 1-arylethenes may lead to the formation of 2-arylpropanoic acid derivatives like ibuprofen (**312**), the focus of this paragraph will be on the hydroesterification of vinyl aromatic compounds.[58,60]



(**312**)

As mentioned above, it was found that monophosphines like PPh_3 favour the formation of branched esters, while linearity is achieved through the utilization of bidentate phosphine systems, but for hydroesterification an additional correlation was found between P-Pd-P bite angle and selectivity towards linear products. At P-Pd-P bite angles of 114° high conversions and almost

exclusively linear products have been found.[19,60] Consequently in a study about the ethoxycarbonylation of styrene (**313**) with [$PdCl_2\{Ph_2P(CH_2)_nPPh_2\}$] (n = 1-6, 10) palladium catalysts, Sugi and Bando[61] found that for n = 3,4,5 diphosphine complexes predominate and the linear 3-phenylpropionate (**314**) was formed in significant amounts. However, monophosphine complexes are formed when n = 1, 6, 10 which results in the formation of 2-phenylpropionate (**315**) instead. Surprisingly dppe (n = 2) (**291**) gave no conversion to products whatsoever. The highest selectivity (99.5 %) was obtained for the branched ester (**315**) using PBu_3 as ligand.[58,61]

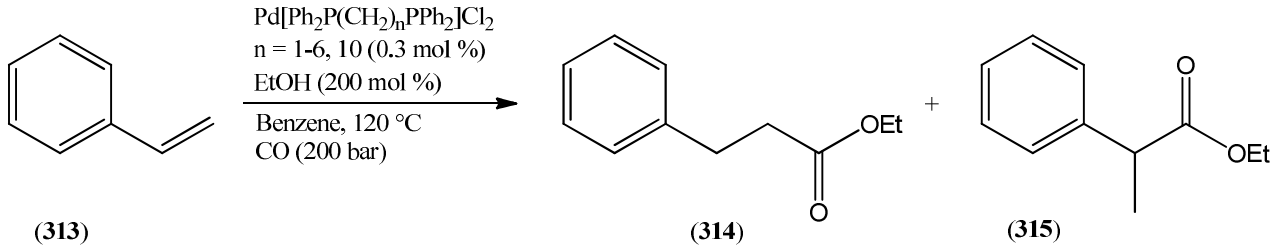


Figure 3-11: Ethoxycarbonylation of styrene

The effect of various acid co-catalysts on the rate of the methoxycarbonylation reaction of ethene has been studied in detail by Shell[9] and *p*-TsOH was found to be the most active, closely followed by triflic acid. The choice of acid is very important since it determines the type of counterion available for the cationic palladium species. Strongly coordinating anions will reduce the rate of the kinetically significant addition of CO to ethene, while weakly coordinating or even non-coordinating anions (like methanesulfonate or toluenesulfonate) will allow for facile coordination of these compounds to the metal and thus relatively high reaction rates.[62] A major disadvantage of the utilization of these strong acids, however, is the rapid alkylation and removal of the phosphine ligands, which lead to unstable palladium species and subsequent metal plating.[9,62] In an effort to circumvent this problem, Ferreira *et al.*[62] reported on the usage of bis(salicylato)boric acid, also known as borosalicylic acid (BSA), as an alternative acid promoter for the palladium catalysed methoxycarbonylation of ethylene with triphenylphosphine as ligand. Although reactions done with methanesulfonic acid (MSA) gave the highest turnover frequency (TOF = 2130 h^{-1}) and trifluoroacetic acid (TFA) the lowest (TOF = 572 h^{-1}), BSA was found to be a very effective acid co-catalyst with a TOF of 1020 h^{-1} with the added advantage of 99 % PPh_3 remaining in solution, which proves significantly less alkylation compared to the mere 28 % PPh_3 remaining when MSA is used.[62]

Other efforts to prevent phosphine removal by alkylation centred around the utilization of Lewis acids as co-catalysts. Williams and co-workers[63] performed a detailed study on the usage of

aluminum trifluoromethanesulfonate [$Al(OTf)_3$], as acid promoter and found that with various ratios of Pd:ligand:Lewis acid:styrene, conversion of 95 % or more were possible for the methoxycarbonylation of styrene (**313**). In a comparison between the different acid promoters, $Al(OTf)_3$ (conversion = 62 %, TOF = 3700 h^{-1}), *p*-TsOH (conversion = 39 %, TOF = 2300 h^{-1}) and triflic acid (conversion = 42 %, TOF = 2500 h^{-1}), $Al(OTf)_3$ was found to be superior and resulted in the highest conversions and TOF values being observed.[63]

The mechanism of the alkoxycarbonylation reaction has been a point of controversy ever since the discovery of this reaction. In the early 90's two proposals (Figure 3-12) regarding the prevailing catalytic cycle were postulated and received some support from the broad scientific community. Catalytic cycle A, the so-called palladium-hydride mechanism, starts with the formation of a palladium-hydride complex (**316**). The olefin then inserts into the Pd-H bond to form a Pd-alkyl intermediate (**317**), which undergoes migratory insertion of CO to produce the Pd-acyl species (**318**) that eventually forms the ester (**319**) and a second Pd-H upon alcoholysis. Catalytic cycle B, known as the alkoxycarbonyl mechanism, on the other hand, starts with an alkoxy-palladium complex (**320**). Ligand exchange followed by CO insertion then leads to the carbomethoxy intermediate (**321**), which is transformed into the alkoxycarbonyl-palladium species (**322**) *via* olefin insertion, before alcoholysis finally gives the ester product (**319**).[58,64,65,66] By focussing on the methoxycarbonylation of ethene, Eastham and co-workers[67] were able to provide unambiguous spectroscopic evidence for all the intermediates in the palladium hydride cycle thus confirming catalytic cycle A (Figure 3-12) to be the correct mechanism for the alkoxycarbonylation reaction.

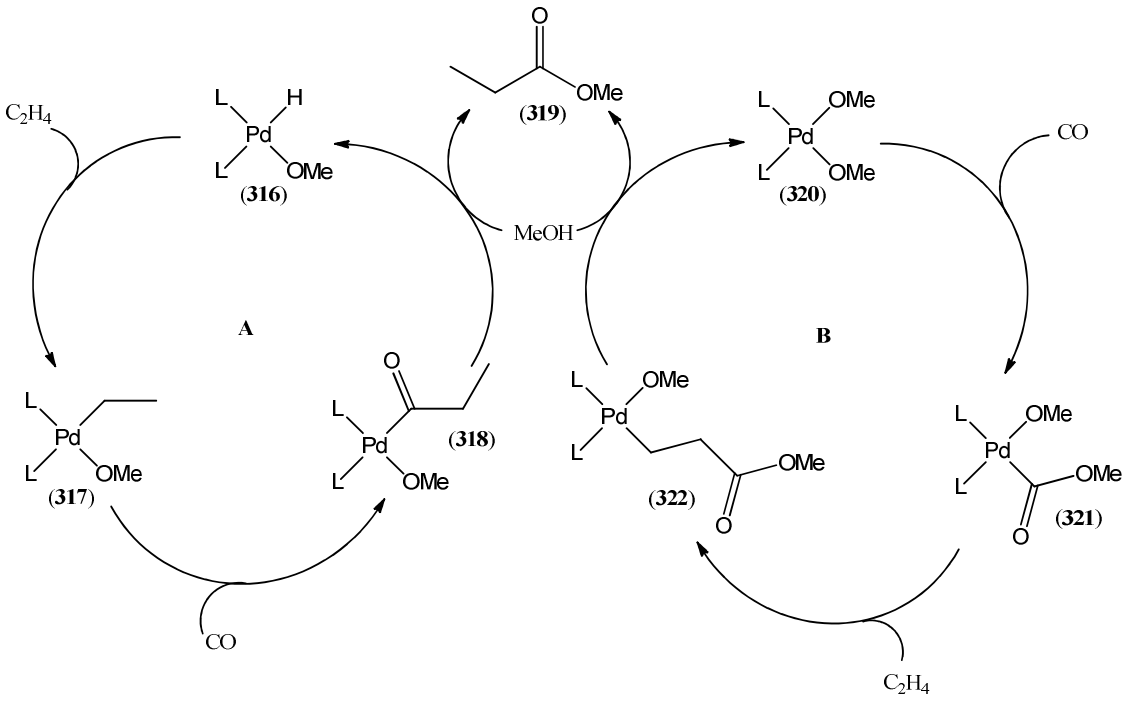
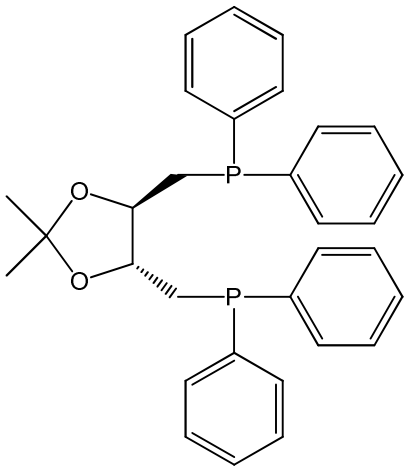


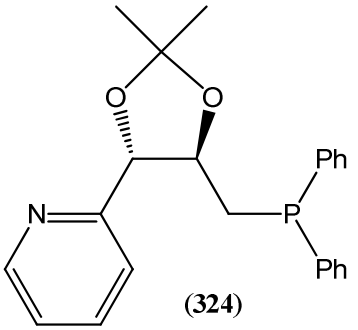
Figure 3-12: Catalytic cycle for Pd-catalysed hydroesterification

One of the first reports describing the asymmetric hydroxy- and alkoxycarbonylation of vinylarenes, with chiral diphosphine ligands, appeared in the 1970's.[59,68,69] By utilizing a Pd/DIOP (**323**) system, Consiglio and co-workers[59,69,70] found that both the alcohol and substrate components have an influence on the selectivity of this type of reaction. For example with *α*-methylstyrene as substrate the ee of the reaction ranges from 3 % to 20 % when the alcohol is changed from methanol to *tert*-butanol, while for styrene a dramatic decrease in ee (from 10 % to 2 %) was observed for the ethoxycarbonylation reaction.[70] The reaction rate was also greatly enhanced when co-solvents like THF or benzene was used. The greatest effect on the enantioselectivity of the reaction, however, came from CO pressure resulting in an increase in ee values from 3 % to 50 % when the pressure was increased from 50 atm to 700 atm.[71]

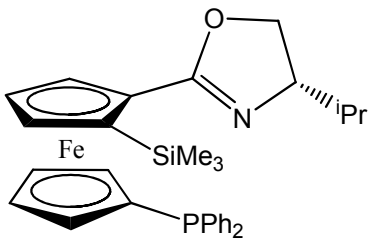


(**323**)

In an effort to improve on the enantioselectivities obtained by Consiglio *et al.*,[59,69,70] Chelucci and co-workers[72] investigated the utilization of the hemilabile mixed bidentate pyridine-phosphine ligands (**324**) in the ethoxycarbonylation of styrene and found total selectivity towards the branched ester with very low ee's of 20% under conditions of 100 °C and 105 atm CO pressure. Chan *et al.*[73] reported on the application of P-N ferrocenyl phosphine-oxazoline ligands (**325**) together with a $PdCl_2/CuCl_2$/*p*-TsOH catalyst system for the hydroesterification of styrene (**313**). Catalysts based on these ligands gave low ee values (< 63 %).

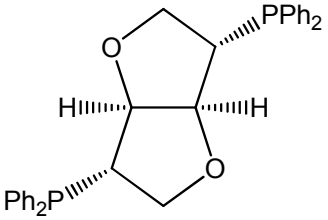


(**324**)

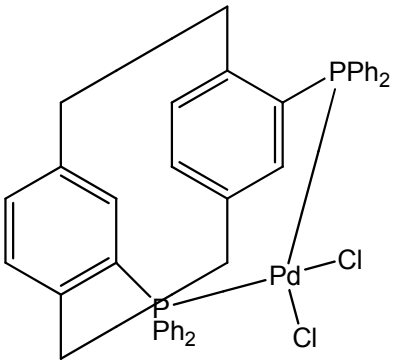


(**325**)

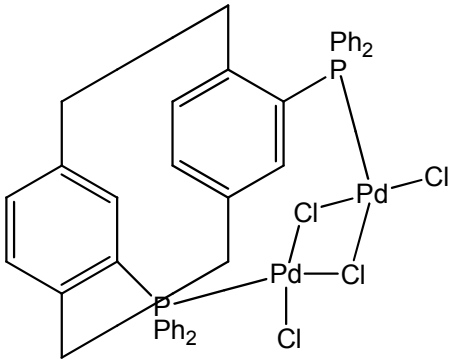
The best results obtained to date came from Zhou *et al.*[74] who reported the utilization of a chiral diphosphine (DDPPI) system (**326**) which gave 99 % regioselectivity to the branched ester and enantioselectivities of up to 98 % in the $PdCl_2$-$CuCl_2$ catalysed methoxycarbonylation of styrene under mild reaction conditions (80 °C, 50 atm). These authors also described the methoxycarbonylation of norbornene with a $Pd(OAc)_2$/DDPPI/*p*-TsOH catalyst system and reported an ee of 92 % at moderate reaction conditions (120 °C, 50 atm). Similarly Konrad *et al.*[75] reported on an enantioselective process for the methoxycarbonylation of styrene under very low temperature conditions (25 °C, 30 bar). Precatalysts known as dimetallic halides derived from chiral bridging diphosphines (**327**) and (**328**) were used to obtain ee values of 91%.



(**326**)



(**327**)



(**328**)

3.5. References

(1) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17-85.

(2) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435-3456.

(3) Sarkar, B. R.; Chaudhari, R. V. *Catal. Surv. Asia* **2005**, *9*, 193-205.

(4) Nozaki, K. *The Chemical Record* **2005**, *5*, 376-384.

(5) Reppe, W.; Magin, A. U.S. Patent 2,577,208, 1948.

(6) Shryne, T. M.; Holler, H. V. U.S. Patent 3,984,388, 1975.

(7) Iwashita, Y.; Sakuraba, M. *Tetrahedron Lett.* **1971**, *12*, 2409-2412.

(8) Gough, A. G.B. Patent 1,081,304(A), 1967

(9) Drent, E.; Budzelaar, H. M. *Chem. Rev.* **1996**, *96*, 663-681.

(10) Lai, T. W.; Sen, A. *Organometallics* **1984**, *3*, 866-870.

(11) Sen, A.; Lai, T. W. *J. Am. Chem. Soc.* **1982**, *104*, 3520-3522.

(12) Jiang, Z.; Sen, A. *Macromolecules* **1994**, *27*, 7215-7216.

(13) Verspui, G.; Schanssema, F.; Sheldon, R. A. *Appl. Catal., A* **2000**, *198*, 5-11.

(14) Verspui, G.; Schanssema, F.; Sheldon, R. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 804-806.

(15) Roelen, O. British Patent 2,327,066, 1939

(16) Beller, M.; Zimmermann, B.; Geissler, H. *Chem. Eur. J.* **1999**, *5*, 1301-1305.

(17) Hebrard, F.; Kalck, P. *Chem. Rev.* **2009**, *109*, 4272-4282.

(18) Gual, A.; Godard, C.; Castillón, S.; Claver, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1135-1146.

(19) Van Leewen, P. W. N. M. *Homogeneous Catalysis - Understanding the Art*; Kluwer Academic Publishers: London, 2004, pp. 109-122, 239-263.

(20) Pruett, R. L. *J. Chem. Educ.* **1986**, *63*, 196-198.

(21) Slaugh, L. H.; Mullineaux, R. D. *J. Organomet. Chem.* **1968**, *13*, 469-477.

(22) Slaugh, L. H.; Mullineaux, R. D. US Patent 3,239,569, 1963.

(23) Slaugh, L. H.; Mullineaux, R. D. US Patent 3,239,570, 1963.

(24) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2956-2965.

(25) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953-2956.

(26) Johnson, T. H. US Patent 4,584,411, 1985.

(27) Van Winkle, J.L.; Morris, R. C.; Mason, R. F. US Patent 3,420,898, 1965.

(28) Dubois, R. A.; Garrou, P. E. *Organometallics* **1986**, *5*, 466-473.

(29) Steynberg, J. P.; Govender, K.; Steynberg, J. P. WO Patent WO 02/14248 A2, 2001

(30) Rosi, L.; Bini, A.; Frediani, P.; Bianchi, M.; Salvini, A. *J. Mol. Catal. A: Chem.* **1996**, *112*, 367-383.

(31) Hughes, V. L. US Patent 2,880,241, 1959.

(32) Slaugh, L. H.; Mullineaux, R. D. US Patent 3,239,566, 1963.

(33) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Chem. Commun.* **1965**, 131-132.

(34) Pruett, R. L.; Smith, J. A. *J. Org. Chem.* **1969**, *34*, 327-330.

(35) Evans, D.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 3133-3142.

(36) Evans, D.; Yagupsky, G.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 2660-2665.

(37) Heck, R. F. *Acc. Chem. Res.* **1969**, *2*, 10-16.

(38) Palo, D. R.; Erkey, C. *Organometallics* **2000**, *19*, 81-86.

(39) MacDougall, J. K.; Simpson, M. C.; Green, M. J.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans.* **1996**, 1161-1172.

(40) Buhling, A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Mol. Catal. A: Chem.* **1995**, *98*, 69-80.

(41) Van Rooy, A. *J. Organomet. Chem.* **1996**, *507*, 69-73.

(42) Breit, B.; Winde, R.; Mackewitz, T.; Paciello, R.; Harms, K. *Chem. Eur. J.* **2001**, *7*, 3106-3121.

(43) Devon, T. J.; Phillips, G. W.; Puckettte, T. A.; Stavinoha, J. L.; Vanderbilt, J. J. US Patent 5,332,846, 1993.

(44) Devon, T. J.; Phillips, G. W.; Puckettte, T. A.; Stavinoha, J. L.; Vanderbilt, J. J. US Patent 4,694,109, 1986.

(45) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081-3089.

(46) Van der Veen, L. A.; Keeven, P. H.; Schoemaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 872-883.

(47) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1995**, 409-417.

(48) Babin, J. E.; Whiteker, G. T. WO Patent WO/1993/003839, 1992.

(49) Sakai, N.; Nozaki, K.; Mashima, K.; Takaya, H. *Tetrahedron: Asymmetry* **1992**, *3*, 583-586.

(50) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033-7034.

(51) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395-396.

(52) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun.* **1996**, 155-156.

(53) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285-4292.

(54) Hofmann, P.; Kosswig, K.; Schaefer, W. *Ind. Eng. Chem. Prod. Res. Dev.* **1980**, *19*, 330-334.

(55) Ali, B. E.; Alper, H. *J. Mol. Catal.* **1992**, *77*, 7-13.

(56) Ali, B. E.; Alper, H. *J. Org. Chem.* **1993**, *58*, 3595-3596.

(57) Seayad, A.; Jayasree, S.; Chaudhari, R. V. *Org. Lett.* **1999**, *1*, 459-462.

(58) Del Rio, I.; Claver, C.; Van Leewen, P. W. N. M. *Eur. J. Inorg. Chem.* **2001**, 2719-2738.

(59) Consiglio, G. *J. Organomet. Chem.* **1977**, *132*, C26-C28.

(60) Guiu, E.; Caporali, M.; Muñoz, B.; Müller, C.; Lutz, M.; Spek, A. L.; Claver, C.; van Leeuwen, P. W. N. M. *Organometallics* **2006**, *25*, 3102-3104.

(61) Sugi, Y.; Bando, K. *Chem. Lett.* **1976**, 727-730.

(62) Ferreira, A. C.; Crous, R.; Bennie, L.; Meij, A. M. M.; Blann, K.; Bezuidenhoudt, B. C. B.; Young, D. A.; Green, M. J.; Roodt, A. *Angew. Chem.* **2007**, *119*, 2323-2325.

(63) Williams, D. B. G.; Shaw, M. L.; Green, M. J.; Holzapfel, C. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 560-563.

(64) Cavinato, G.; Facchetti, S.; Toniolo, L. *J. Mol. Catal. A: Chem.* **2010**, *333*, 180-185.

(65) Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 250-252.

(66) Kalck, P.; Urrutigoïty, M.; Dechy-Cabaret, O. In *Catalytic Carbonylation Reactions*; Beller, M., Ed.; Springer: Berlin Heidelberg, 2006; Vol. 18, pp. 97-123.

(67) Eastham, G. R.; Tooze, R. P.; Heaton, B. T.; Iggo, J. A.; Whyman, R.; Zacchini, S. *Chem. Commun.* **2000**, 609-610.

(68) Godard, C.; Muñoz, B. K.; Ruiz, A.; Claver, C. *Dalton Trans.* **2008**, 853-860.

(69) Consiglio, G. *Helv. Chim. Acta* **1976**, *59*, 124-126.

(70) Consiglio, G. *Chimia* **1973**, *27*, 477-478.

(71) Consiglio, G.; Pino, P. *Chimia* **1976**, *30*, 193.

(72) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Basoli, C.; Marchetti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 885-895.

(73) Wang, L.; Kwok, W. H.; Chan, A. S. C.; Tu, T.; Hou, X.; Dai, L. *Tetrahedron: Asymmetry* **2003**, *14*, 2291-2295.

(74) Zhou, H.; Hou, J.; Cheng, J.; Lu, S.; Fu, H.; Wang, H. *J. Organomet. Chem.* **1997**, *543*, 227-228.

(75) Konrad, T. M.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9197-9200.

RESULTS & DISCUSSION 4

4.1. Introduction

As indicated in chapter one, flavonoids and isoflavonoids are an important group of natural products that should be freely available in enantiomerically pure form with all possible substitution patterns in order to be able to study the effect of differences in substitution on the physiological properties of the different compounds. Although numerous methodologies towards the synthesis of isoflavonoids have been developed and reported, none of these are catalytic in nature, does not produce excessive amounts of waste, and are capable of delivering the products in enantiomerically pure form.

In order to address the above mentioned shortfalls in the existing methodologies with respect to isoflavonoid synthesis, it was decided to embark on a strategy for the synthesis of isoflavonoids that would be catalytic in nature as well as allow for the possibility of producing the final products in optically enriched form. Although the traditional route towards the synthesis of isoflavonoids usually goes through the chalcone intermediate, this methodology does not allow for stereochemical control during the key aroyl migration step (*cf.* Paragraph 2.1.2.). A process consisting of an easily accessible starting material that could be converted into isoflavonoids by means of a stereoselective catalytic process, as depicted in Figure 4-1, would therefore make an important contribution to this field of natural product synthesis.

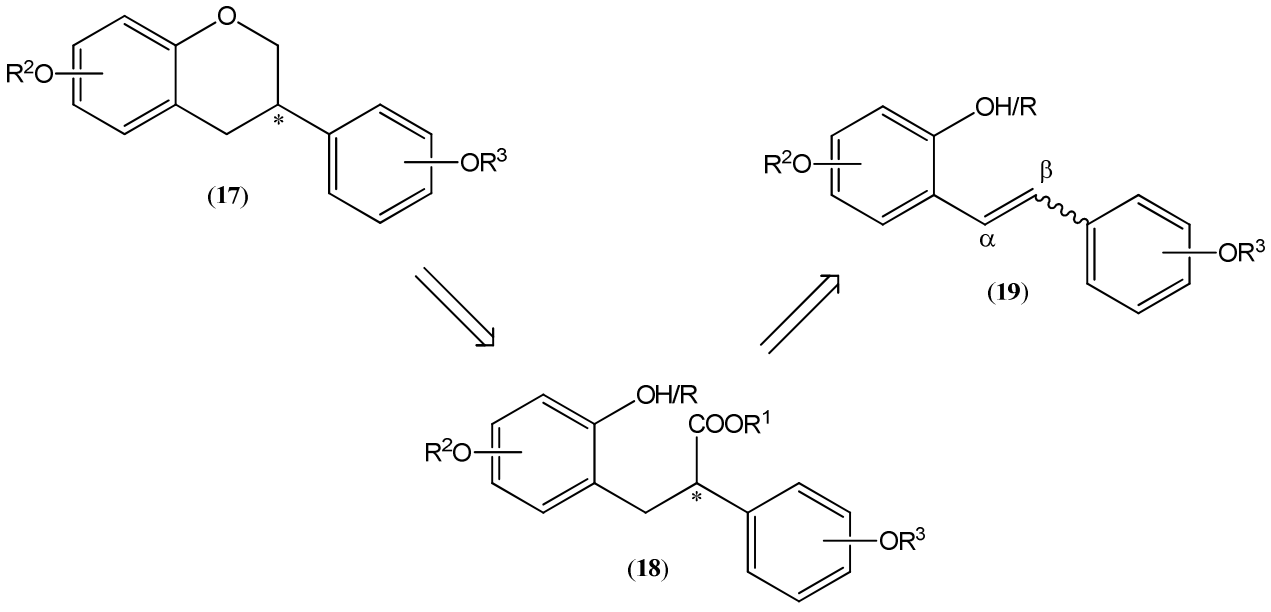
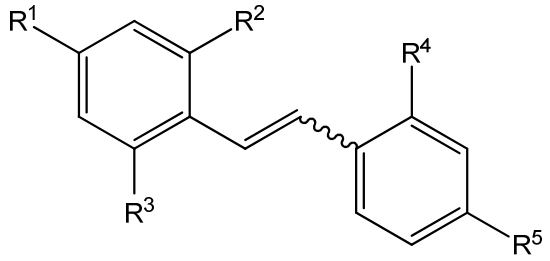


Figure 4-1: Catalytic isoflavonoid retrosynthesis

While stilbenes would be readily accessible in a number of substitution patterns by, for example, application of the Wittig reaction, the next step in the envisaged synthetic protocol, *i.e.* introduction of the third carbon to become part of the heterocyclic C-ring of the isoflavonoid skeleton, could be achieved catalytically by application of either hydroformylation or hydroesterification (alkoxycarbonylation). Since hydroesterification would, apart from chiral induction through a chiral element in the catalyst system, also allow for introducing chirality into the resulting propanoid moiety by executing the reaction in the presence of a chiral alcohol, this approach was selected as methodology to be looked into during the current investigation. Before the issue of stereoselectivity could, however, be addressed, the effect of the substitution pattern on the regioselectivity towards the desired double bond carbon (the one that would allow cyclization in the final step of the isoflavonoid synthesis) of the stilbene starting material during the hydroesterification reaction, had to be determined.

In order to investigate the possible effect that substituents on the two aromatic rings of the stilbenes might have on the direction of CO addition to the double bond, a series of stilbenes containing electron-withdrawing groups (EWG) on one ring and electron-donating groups (EDG) on the other ring had to be synthesized as starting point in the study.

The initial objective therefore was to prepare a range of stilbene molecules containing EDG in the *para* (**329**), *orto* (**330**) and *para* and *orto* (**331**) positions of one aromatic ring and EWG in the *para* (**333**) and *orto* (**334**) positions of the other aromatic ring. A Stilbene with a free hydroxy substituent in the *para* position (**335**) was also to be synthesized in order to study the effect that a *p*-OMe *vs.* a *p*-OH substituent would have on the outcome of the reaction.



(**329**) $R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H$
(**330**) $R^2 = OMe, R^1 = R^3 = R^4 = R^5 = H$
(**331**) $R^1 = R^2 = OMe, R^3 = R^4 = R^5 = H$
(**332**) $R^1 = R^2 = R^3 = OMe, R^4 = R^5 = H$
(**333**) $R^5 = OTf, R^1 = R^2 = R^3 = R^4 = H$
(**334**) $R^4 = OTf, R^1 = R^2 = R^3 = R^5 = H$
(**335**) $R^1 = OH, R^2 = R^3 = R^4 = R^5 = H$

4.2. Synthesis of Stilbenes

Since the Wittig reaction represents one of the best methods for the synthesis of alkenes and requires the reaction of, in this instance, an aldehyde with a phosphonium salt (Figure 4-2), this approach was considered as methodology for the preparation of the envisaged stilbenes.

Furthermore, since aldehydes displaying a wide variety of substitution patterns are readily available commercially, these compounds could be used directly in the synthesis of stilbenes while the desired phosphonium salt and ylide could be prepared from an aldehyde through reduction followed by activation of the benzyl alcohol moiety and treatment with triphenylphosphine (PPh_3) (Figure 4-3). This protocol was therefore selected for preparation of the envisaged stilbenes to be utilized as starting materials in the current investigation. It would furthermore be advantageous to have the EWG on the aldehyde molecule rather than on the phosphonium salt, since this would increase the electrophilicity of the aldehyde carbon and thus have an accelerating effect on the reaction. Placement of the methoxy substituents (EDG) on the phosphonium salt would, on the other hand, increase the nucleophilicity of the phosphorous atom.

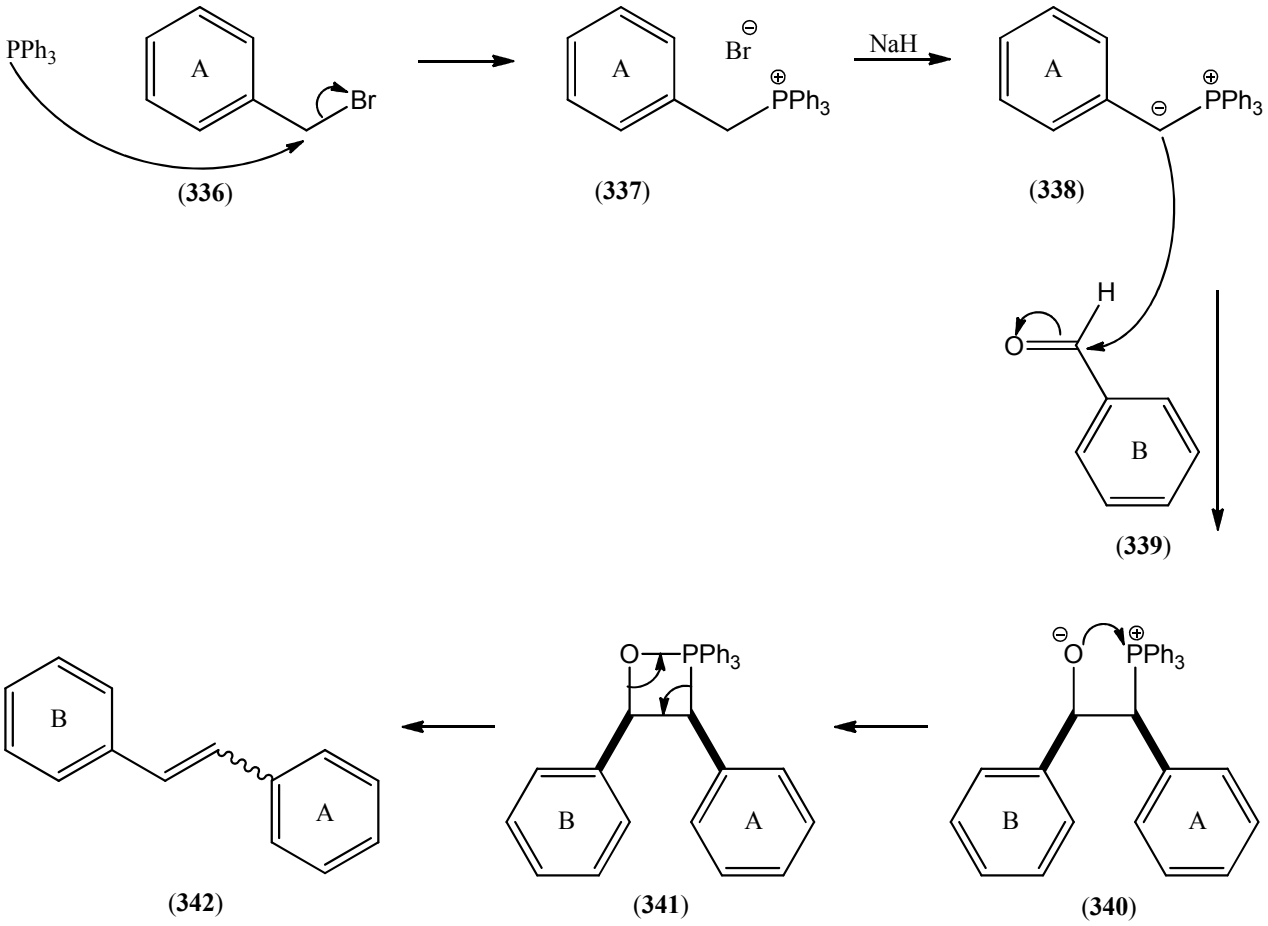
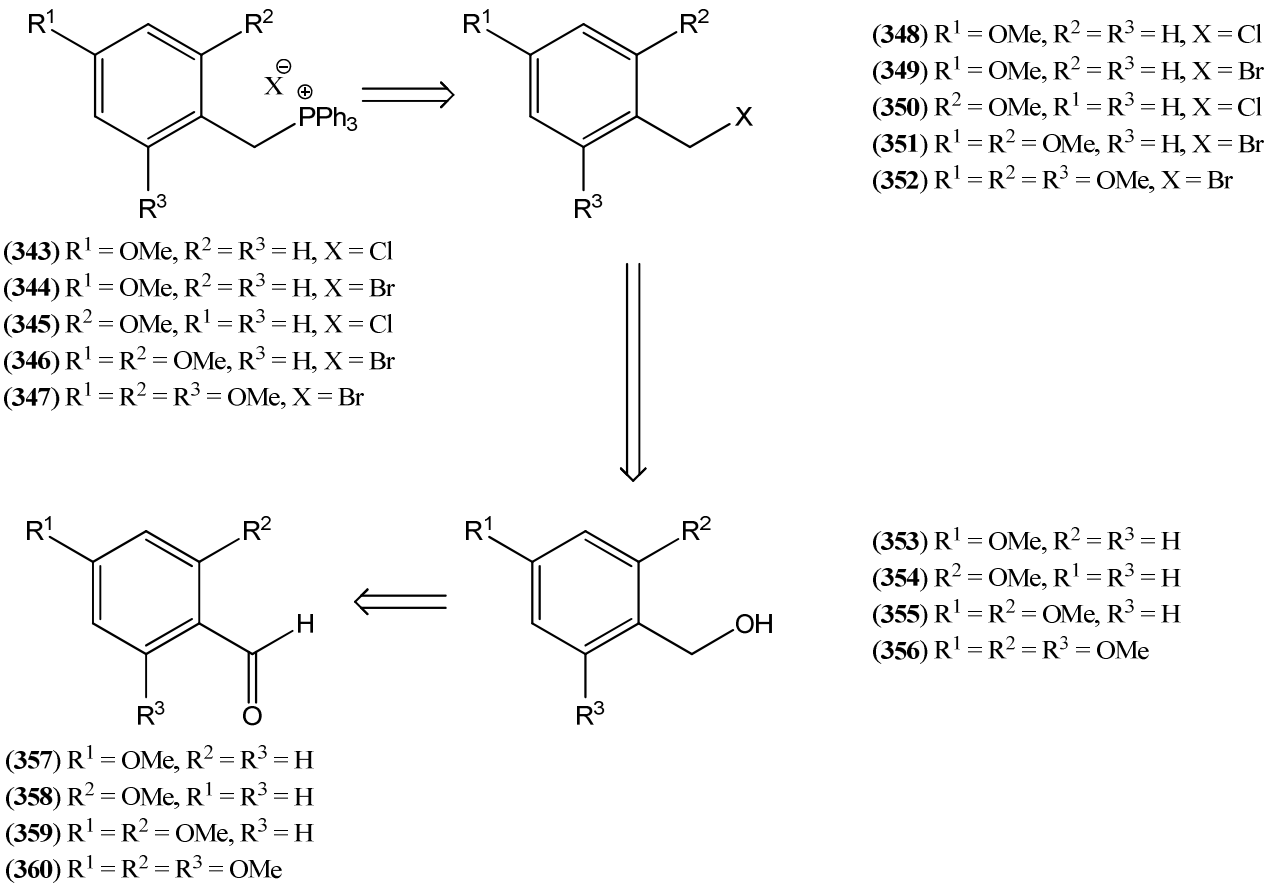


Figure 4-2: Wittig reaction mechanism



(**343**) R^1 = OMe, R^2 = R^3 = H, X = Cl
(**344**) R^1 = OMe, R^2 = R^3 = H, X = Br
(**345**) R^2 = OMe, R^1 = R^3 = H, X = Cl
(**346**) R^1 = R^2 = OMe, R^3 = H, X = Br
(**347**) R^1 = R^2 = R^3 = OMe, X = Br

(**348**) R^1 = OMe, R^2 = R^3 = H, X = Cl
(**349**) R^1 = OMe, R^2 = R^3 = H, X = Br
(**350**) R^2 = OMe, R^1 = R^3 = H, X = Cl
(**351**) R^1 = R^2 = OMe, R^3 = H, X = Br
(**352**) R^1 = R^2 = R^3 = OMe, X = Br

(**353**) R^1 = OMe, R^2 = R^3 = H
(**354**) R^2 = OMe, R^1 = R^3 = H
(**355**) R^1 = R^2 = OMe, R^3 = H
(**356**) R^1 = R^2 = R^3 = OMe

(**357**) R^1 = OMe, R^2 = R^3 = H
(**358**) R^2 = OMe, R^1 = R^3 = H
(**359**) R^1 = R^2 = OMe, R^3 = H
(**360**) R^1 = R^2 = R^3 = OMe

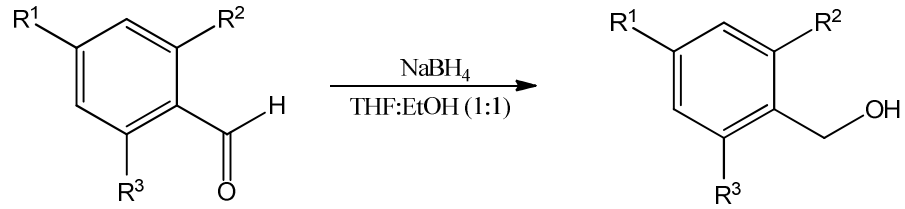
Figure 4-3: Retrosynthesis of phosphonium salts from aldehydes

While some benzyl halides (*p*- and *o*-methoxybenzyl chloride) are available commercially and can readily be reacted with triphenylphosphine, to give the required phosphonium salts, highly oxygenated analogues, like 2,4-dimethoxybenzyl chloride (**351**), have to be prepared from either the corresponding alcohol or aldehyde for use during the Wittig reaction. Preparation of these oxygenated benzyl alcohols/benzyl halides were therefore the first step to receive attention during the investigation.

4.2.1. Preparation of methoxy substituted benzyl alcohols

In order to prepare the required benzyl alcohols the first substrate, 2,4-dimethoxybenzaldehyde (**359**), was therefore treated with $NaBH_4$ in THF:MeOH (1:1) to afford the corresponding benzyl alcohol (**355**) in high yield (Table 4-1). Although this molecule can be obtained commercially, the reaction was nevertheless performed in order to validate the reaction process and assure that future reactions could be executed successfully. Reduction of the 2,4,6-trisubstituted benzaldehyde (**360**) with $NaBH_4$, however, only gave trace amounts of the alcohol (**356**), probably due to steric hindrance caused by the 6-methoxy group and/or the decreased electrophilicity of the carbonyl

carbon arising from the number of electron donating methoxy substituents present in the molecule. Changing the protocol to catalytic hydrogenation (5 % Pd on C in acetone under atmospheric pressure), however, led to the desired alcohol (**356**) being formed in 32 % yield (reaction time of 3 days) (Figure 4-4).



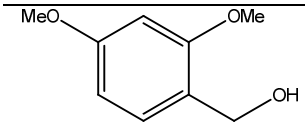
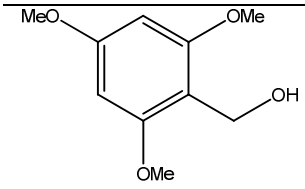
(**359**) $R^1 = R^2 = OMe$, $R^3 = H$
(**360**) $R^1 = R^2 = R^3 = OMe$

(**355**) $R^1 = R^2 = OMe$, $R^3 = H$ (93 %)
(**356**) $R^1 = R^2 = R^3 = OMe$ (trace)

Figure 4-4: Benzyl alcohol preparation through reduction with $NaBH_4$

Apart from the expected aromatic resonances, the ^1H NMR spectrum (Plate 1a) of 2,4-dimethoxybenzyl alcohol (**355**) also exhibited the methylene group as a broadened singlet at δ 4.59 ppm, while the 2,4,6-trimethoxy analogue (**356**) (Plate 2a) displayed the corresponding protons as a doublet at δ 4.69 ppm (J = 6.51 Hz) (Table 4-1) due to coupling to the OH-proton. This phenomenon, where coupling between an OH and adjacent protons is sometimes observed [e.g. 2,4,6-trimethoxybenzyl alcohol (**356**)] and sometimes not [e.g. 2,4-dimethoxybenzyl alcohol (**355**)] is well documented.[1,2] The structures of benzyl alcohols (**355**) and (**356**) were confirmed by ^{13}C NMR (Plate 1b and 2b, respectively) where all the expected carbon resonances were observed, as well as MS analysis that showed molecular ions at *m/z* 168 (M^+, 100 %) and 198 (M^+, 90 %), respectively.

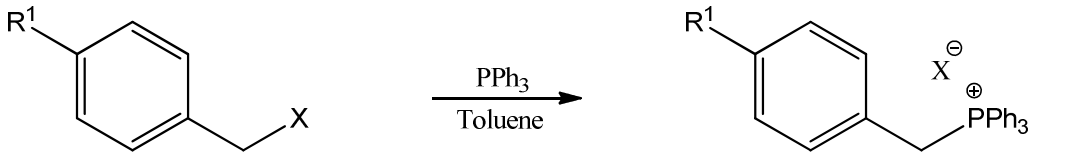
Table 4-1: Characteristic NMR resonances of methoxy substituted benzyl alcohols

Structure	Reducing agent	Yield (%)	Chemical shift and coupling constant -CH_2-		
			δ_H (ppm)	J (Hz)	δ_C (ppm)
	$NaBH_4$	93	4.59	-	61.54
	H_2 (5 % Pd/C)	32	4.69	6.51	54.44

4.2.2. Synthesis of phosphonium salts

- **From benzyl halides**

Before the synthesis of all of the benzyl halides were attempted, it was decided to first investigate the most economical method for the synthesis of the phosphonium salts and for these reactions the commercially available unsubstituted benzyl bromide (**336**) was used as substrate. Reaction of benzyl bromide with triphenylphosphine in toluene[3] gave the desired benzyltriphenylphosphonium bromide (**337**), as a white powder in an excellent yield of 98 % (Figure 4-5). The ^{1}H NMR spectrum (Plate 3a) of the product (**337**) displayed the methylene protons at δ 5.28 ppm as a doublet of doublets with a relatively big coupling constant (J = 14.33 Hz) caused by phosphorous coupling, as well as all the expected aromatic signals. Noteworthy, in the ^{13}C NMR spectrum (Plate 3b) of the phosphonium salt (**337**) all the carbon resonances appeared as doublets with coupling constants ranging from 2.21 Hz for C-4' to 85.99 Hz for C-1' (carbon directly bonded to the phosphorous atom) due to phosphorous coupling. The structure of the product was finally confirmed by melting point (m.p.) determination 295-297 °C (lit.[4] 296-297 °C) and MALDI-TOF mass analysis [*m/z* 353.164 (M^+ -Br)].



(**336**) R^1 = H, X = Br
(**348**) R^1 = OMe, X = Cl

(**337**) R^1 = H, X = Br (98 %)
(**343**) R^1 = OMe, X = Cl (76 %)

Figure 4-5: Synthesis of phosphonium salts from benzyl halides

Following the same procedure, the oxygenated analogue, 4-methoxybenzyl triphenylphosphonium chloride (**343**), could be synthesized from commercially available 4-methoxybenzyl chloride (**348**) in good yield (76 %) (Figure 4-5). The characteristic methylene protons appeared as a doublet at δ 5.33 ppm (J = 13.79 Hz) in the ^{1}H NMR spectrum (Plate 4a) of the product (**343**) while phosphorous coupling was again observed in the ^{13}C NMR spectrum (Plate 4b), resulting in a range of doublets. Melting point (*cf.* Paragraph 5.8.1.2.) determination confirmed the product structure.

With all uncertainty with regards to the preparation of the phosphonium salt taken care of, attention was subsequently turned towards synthesizing the oxygenated phosphonium salts having

methoxy groups in the 2-, 2,4-, and 2,4,6-positions. Although 2-methoxybenzyl chloride (**350**) is commercially available, 2,4-dimethoxy- (**351**) and 2,4,6-trimethoxybenzyl bromide (**352**) had to be prepared from the previously synthesized alcohols (**355**) and (**356**) (*cf.* Paragraph 4.2.1.). According to a procedure reported by Versteeg *et al.*[5], this could be achieved under acid-free conditions in a one-pot process by transforming the alcohol into its tosyl ester and treating the intermediate with lithium bromide and 2,6-lutidine in THF. As a model reaction, commercially available 4-methoxybenzyl alcohol (**353**) was therefore reacted with *p*-toluenesulfonic anhydride (Ts_2O) and lithium bromide in dry THF containing 2,6-lutidine to give the 4-methoxybenzyl bromide (**349**), which was found to be unstable and therefore treated as is with triphenylphosphine in toluene to form the 4-methoxybenzyltriphenylphosphonium bromide (**344**) (Figure 4-6) in 45 % yield (over two steps). Similar to the spectrum of triphenylphosphonium bromide (**337**), the ^{1}H NMR spectrum (Plate 5a) of 4-methoxytriphenylphosphonium bromide (**344**) exhibited the typical ^{1}H-^{31}P coupled doublet at δ 5.17 ppm (J = 13.68 Hz) integrating for the two methylene protons, while the ^{13}C NMR spectrum (Plate 5b) also showed all the carbon resonances as doublets. MALDI-TOF mass analysis [*m/z* 383.157 (M^+ -Br)] revealed the presence of the molecular ion and the determined m.p. (234-235 °C) corresponded well with the literature value[6] of 234-235 °C, thus confirming the structure of (**344**).

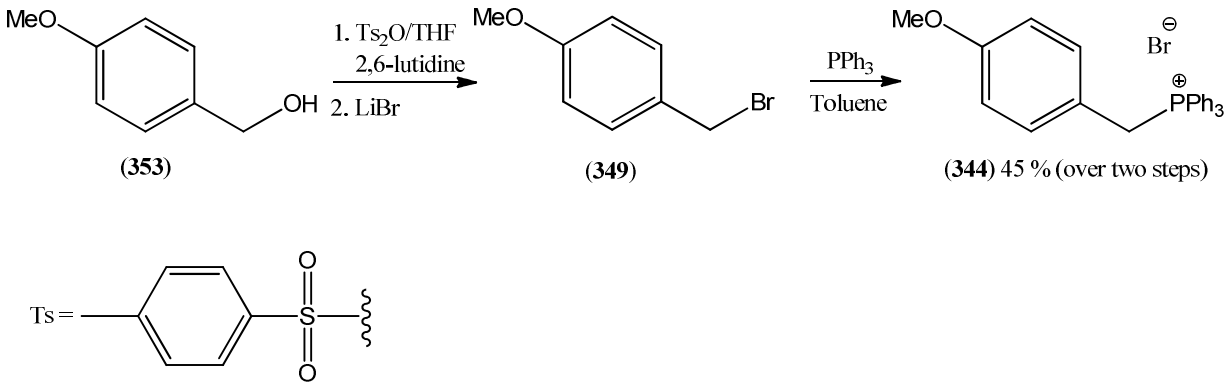
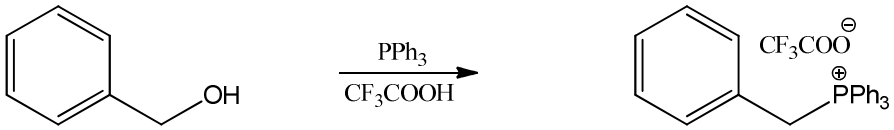


Figure 4-6: Synthesis of 4-methoxybenzyltriphenylphosphonium bromide

Although the oxygenated benzyl halides and corresponding phosphonium salts could be prepared in moderate yields (45 %) it was realized that if the level of oxygenation on the aromatic ring of the alcohols were to be increased, the benzyl halides will become increasingly unstable, more difficult to handle, and therefore probably result in unacceptably low yields, so more attention was paid to this aspect of the methodology.

- **From alcohols as trifluoroacetate salts**

Since Lee and Kim[7] reported that phosphonium salts could be prepared directly from alcohols through the *in situ* generation of trifluoroacetates, this protocol was subsequently evaluated for the synthesis of the required phosphonium salts. Benzyl alcohol (**361**) was thus treated with triphenylphosphine in trifluoroacetic acid (TFA) at 60 °C (Figure 4-7) and the salt (**362**) isolated as a faint yellow precipitate in very low yield (10 %) in contrast to the reported 93 % yield.[7] Although the reaction was repeated with fresh TFA the yield could not be improved. The ^{1}H NMR spectrum (Plate 6a) of the trifluoroacetate salt (**362**) showed the typical methylene doublet (^{1}H-^{31}P coupling) at δ 4.97 ppm with coupling constant of 14.39 Hz as well as the expected resonances from the aromatic protons. All signals in the ^{13}C NMR spectrum (Plate 6b) of the product were also present as doublets due to ^{31}P-coupling. A carbonyl carbon resonance at δ 160.96 ppm confirmed the presence of the trifluoroacetate anion and even though the expected characteristic quartet resonance of the CF_3-group was not observed, final confirmation of the product structure came from the ^{31}P as well as ^{19}F NMR spectra (Plates 6g and 6h, respectively) where phosphorous and fluoride resonances were clearly visible at δ_P 23.16 and δ_F -78.00 ppm, respectively.



(**361**) (**362**) 10 %

Figure 4-7: Synthesis of benzyltriphenylphosphonium trifluoroacetate

Although the yield of the benzyltriphenylphosphonium trifluoroacetate (**362**) from the last reaction was low, it was decided to extend the reaction to 4-methoxybenzyl alcohol in the hope that the more reactive alcohol might lead to better yields. No product could, however, be obtained from this reaction.

- **Through the cleavage of benzyl ethers**

Due to the unsatisfactory results obtained with the direct conversion of benzyl alcohols to phosphonium salts through reaction with PPh_3 and TFA, other methods that would circumvent the handling of oxygenated benzyl halides, were perused. In this regard, Ramanathan and Hou[8] reported a procedure for the deprotection of benzyl ethers that leads to the formation of phosphonium salts as product. In this protocol the alkyl benzyl ether is treated with triphenylphosphine hydrobromide (PPh_3·HBr) which gives rise to the benzyltriphenyl-

phosphonium bromide and deprotected alcohol when primary and secondary alcohols were used in the formation of the alkyl benzyl ethers (**363**) (Figure 4-8).

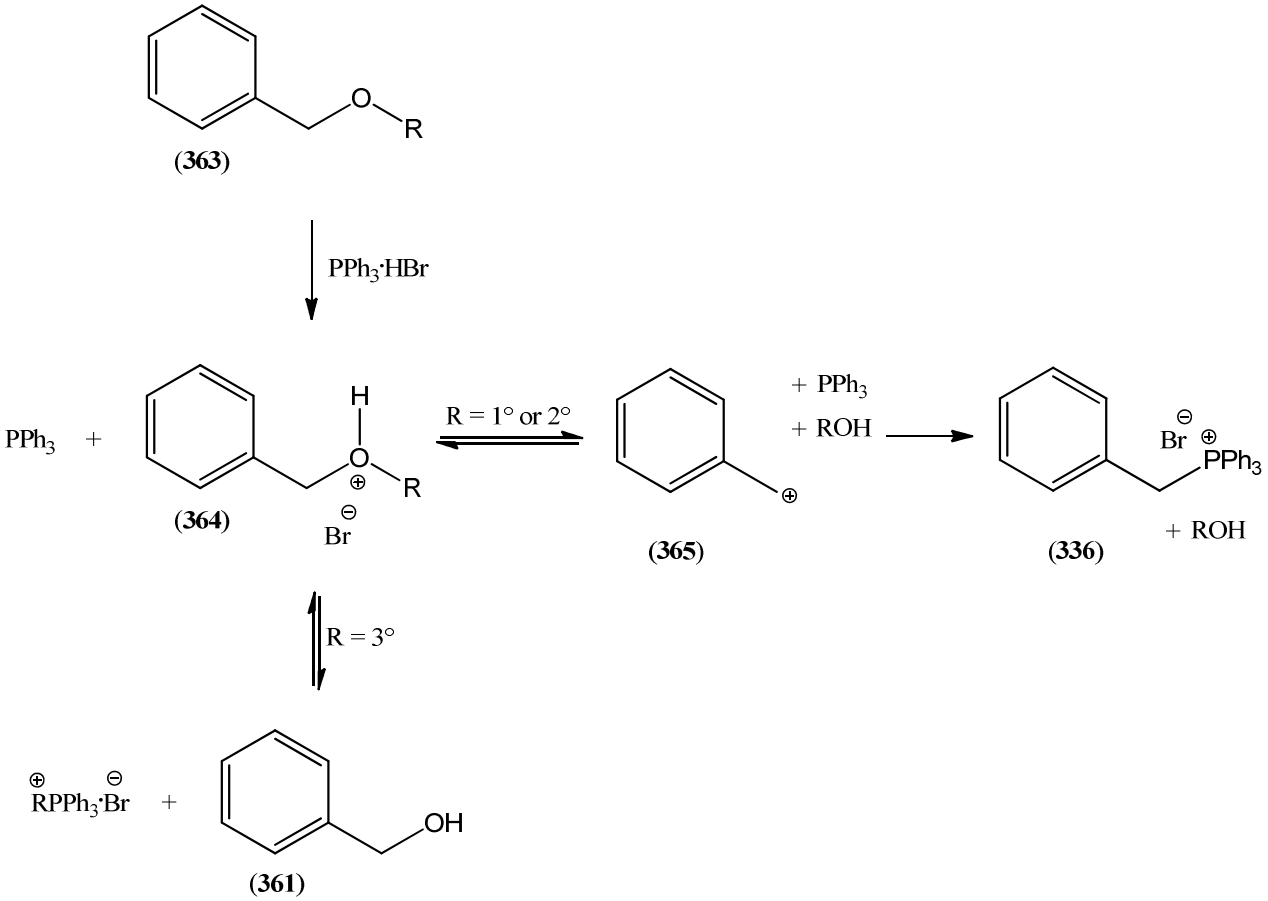
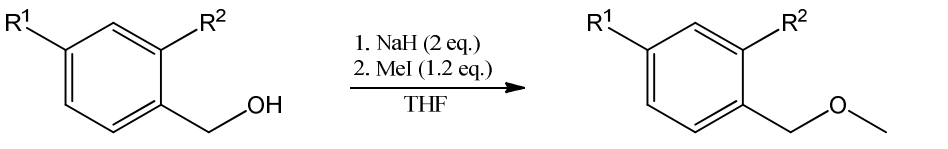


Figure 4-8: Mechanism of phosphonium salt formation through debenzylation of alkyl benzyl ethers

Two benzyl methyl ethers, (**366**) and (**367**), were therefore prepared by the methylation (Figure 4-9, Table 4-2) of the corresponding benzyl alcohols, (**353**) and (**354**). The 4-methoxy analogue (**366**) was subsequently submitted to treatment with PPh_3·HBr in acetonitrile to obtain the insoluble phosphonium salt, 4-methoxybenzylphosphonium bromide (**344**), after filtration, identical to the salt obtained from the reaction with benzyl alcohol (*vide supra*), in 38 % yield (Figure 4-10).

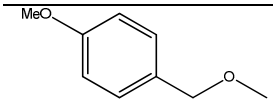
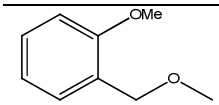


(**353**) R^1 = OMe, R^2 = H
(**354**) R^1 = H, R^2 = OMe

(**366**) R^1 = OMe, R^2 = H (quantitative)
(**367**) R^1 = H, R^2 = OMe (68 %)

Figure 4-9: Methylation of methoxy substituted benzyl alcohols

Table 4-2: Characteristic NMR resonances of methoxy substituted benzyl ethers synthesized

Structure	Chemical shifts					
	-CH_2OMe		-PhOMe		-CH_2-	
	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)
	3.35	57.87	3.79	55.31	4.38	74.43
	3.44	58.43	3.85	55.43	4.52	69.66

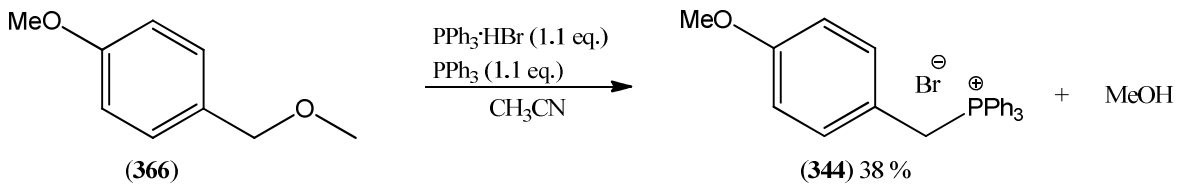


Figure 4-10: Synthesis of 4-methoxytriphenylphosphonium bromide through PPh_3·HBr debenzylation

In conclusion, it was found that the reaction of a benzyl halide with triphenylphosphine in toluene gave the best yield for unsubstituted phosphonium salts (98 %), while methoxy substituted salts could be prepared most economically from the corresponding methoxy substituted benzyl alcohol through bromination (*cf.* Figure 4-6) even though a yield of only 45 % was obtained. Due to the difficulties experienced in obtaining the phosphonium salts of oxygenated aromatic substrates in good yields, it was decided to also investigate the option of rather having methoxy substitutes on the aldehyde than the phosphonium salt (*cf.* Paragraph 4.2.4.) in subsequent Wittig reactions.

4.2.3. Synthesis of protected aldehydes

- **Aldehydes with electron-donating groups**

Since the Wittig reaction relies on a strong base to deprotonate the methylene group of the phosphonium salt to form the ylide, and the hydrogen of a free hydroxy group is more acidic than a methylene proton, 4-hydroxybenzaldehydes had to be protected with an easily removable protecting group if hydroxystilbenes were to be prepared successfully.

4-Hydroxybenzaldehyde (**368**) was therefore protected with chloromethyl ethyl ether in DCM (Figure 4-11) and the product, 4-ethoxymethoxybenzaldehyde (**369**), obtained as a colourless liquid in 71 % yield. The ^{1}H NMR spectrum (Plate 9a) of the product (**369**) showed the methylene proton resonance as a singlet at δ 5.24 ppm and the typical ethoxy peaks as a quartet and triplet at

δ 3.69 and δ 1.16 ppm (J = 7.06 Hz), respectively. Full characterization by ^{13}C NMR (Plate 9b) and MS analysis [*m/z* 180 (M^+, 15 %)] confirmed the product structure.

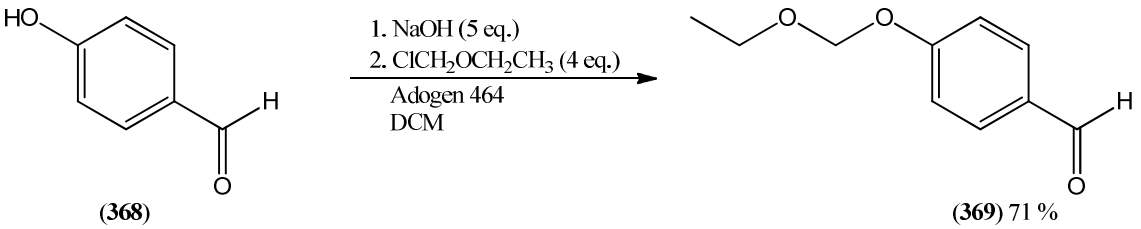


Figure 4-11: Protection of 4-hydroxybenzaldehyde with chloromethyl ethyl ether

Although deprotection of the envisaged 4-ethoxymethoxystilbene should easily be achievable by refluxing the substrate in methanol and concentrated sulphuric acid, these reaction conditions have the potential of causing unwanted reactions of the double bond and in the process destroy the stilbene moiety, so an alternative protecting group, namely *tert*-butyldiphenylsilyloxy (OTBDPS), which can easily be removed by NH_4F, was also investigated. Hydroxybenzaldehyde (**368**) was therefore also reacted with *tert*-butylchlorodiphenylsilane (**370**) and imidazole in DMF to give the crude 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**) (Figure 4-12).

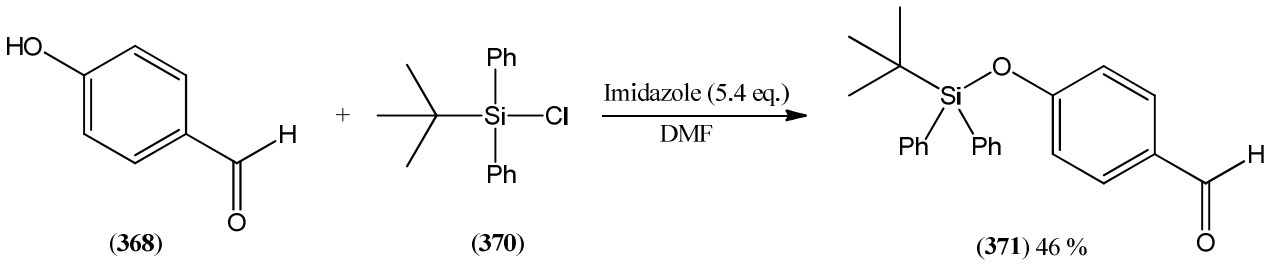


Figure 4-12: Protection of 4-hydroxybenzaldehyde by *tert*-butylchlorodiphenylsilane

After extraction into ethyl acetate the product (**371**) was, however, found to be contaminated with *tert*-butylhydroxydiphenylsilane, so it was decided to simplify the chromatographic separation procedure by adding an excess of NaH to deprotonate the silanol which would then stick to the baseline during PLC purification. Subsequent ^1H NMR analysis of the product obtained after chromatography, however, showed no signal resembling an aldehyde proton. This implied that the NaH added caused an additional reaction with the desired aldehyde product (**371**) as well, which might be explicable by assuming that this was one of the rare occasions where NaH reacted as a base as well as a nucleophile.[9] To test this theory, *p*-anisaldehyde (**357**) (0.45 ml, 3.699 mmol) was dissolved in dry THF (4 ml) and NaH (0.178 g, 7.421 mmol, 2 eq.) added. Stirring the

reaction mixture at room temperature for 4 hours followed by addition of (wet) ethyl acetate and removal of the solvents by distillation under reduced pressure resulted in a mixture of products in a 5:2:1 ratio. The first product was identified by ^{1}H NMR (Plate 11) as anisyl acetate (**374**) [δ 7.24-7.22 (2H, m, H-Ar), 6.83-6.82 (2H, m, H-Ar), 4.98 (2H, s, -CH_2-), 3.70 (3H, s, -OMe), 1.99 (3H, s, -CH_3)], the second product as ethyl methoxycinnamate (**376**) [δ 7.60 (0.3H, d, *J* = 15.94 Hz, -CH-), 7.39 (0.6H, d, *J* = 8.72 Hz, H-Ar), 6.85-6.83 (0.6H, m, H-Ar), 6.27 (0.3 H, d, *J* = 15.94 Hz, -CH-), 4.20 (0.6H, q, *J* = 7.14 Hz, -CH_2-), 3.72 (0.9H, s, -OMe), 1.27 (0.9H, t, *J* = 7.14 Hz, -CH_3)] and the third one as ethyl *p*-methoxybenzoate (**379**) [δ 7.95 (0.4H, d, *J* = 8.92 Hz, H-Ar), 6.83-6.82 (0.6H, m, H-Ar), 4.28 (0.4H, q, *J* = 7.13 Hz, -CH_2-), 3.74 (0.7H, s, -OMe), 1.32 (0.7H, t, *J* = 7.13 Hz, -CH_3)]. MS analysis of the three products showed molecular ions at *m/z* 207 (M^+, 33 %), 180 (M^+, 39 %) and 180 (M^+, 17 %), respectively, which confirmed the structures as that of anisyl acetate (**374**), ethyl methoxycinnamate (**376**) and ethyl *p*-methoxybenzoate (**379**). The formation of anisyl acetate (**374**) is probably explicable in terms of nucleophilic attack of the hydride ion on anisaldehyde (**357**) followed by a transesterification reaction between the formed benzylate anion (**372**) and the added ethyl acetate. The ethoxide ion (**377**) liberated through this transesterification reaction might subsequently have reacted with an aldehyde molecule leading to the hemiacetal (**378**), which could then be oxidized (by air) to the benzoyl ester (**379**), therefore explaining the formation of ethyl *p*-methoxybenzoate (**379**). Finally, the formation of ethyl methoxycinnamate (**376**) can be explained in terms of an aldol-type reaction between anisaldehyde (**357**) and the anion of ethyl acetate (**375**), which might have been formed by deprotonation of the added ethyl acetate (Figure 4-13). Apart from anisyl acetate (**374**), the formation of the other two products can probably be explained by taking into account that the base was not completely destroyed before the ethyl acetate was removed by vacuum distillation during the work-up process.

The reaction between 4-hydroxybenzaldehyde (**368**) and *tert*-butylchlorodiphenylsilane (**370**) was therefore repeated and the pure product (**371**) obtained in 46 % yield after repetitive FCC and PLC (H:A 8:2) purifications. The ^{1}H NMR spectrum (Plate 10a) of 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**) showed the 9 protons, characteristic of the *tert*-butyldiphenylsilyloxy group, resonating as a singlet at δ 1.12 ppm, together with the expected amount of aromatic protons [δ 7.72-7.70 (4H, m, H-2' and H-6'), 7.65 (2H, d, *J* = 8.59 Hz, H-2 and H-6), 7.47-7.44 (2H, m, H-4'), 7.40-7.38 (4H, m, H-3' and H-5'), 6.87 (2H, d, *J* = 8.59 Hz, H-3 and H-5)]. The structure was finally confirmed by ^{13}C NMR (Plate 10b) and TOF-MS-ES which displayed a molecular ion at *m/z* 383.1441 (M^+ +Na) in positive mode.

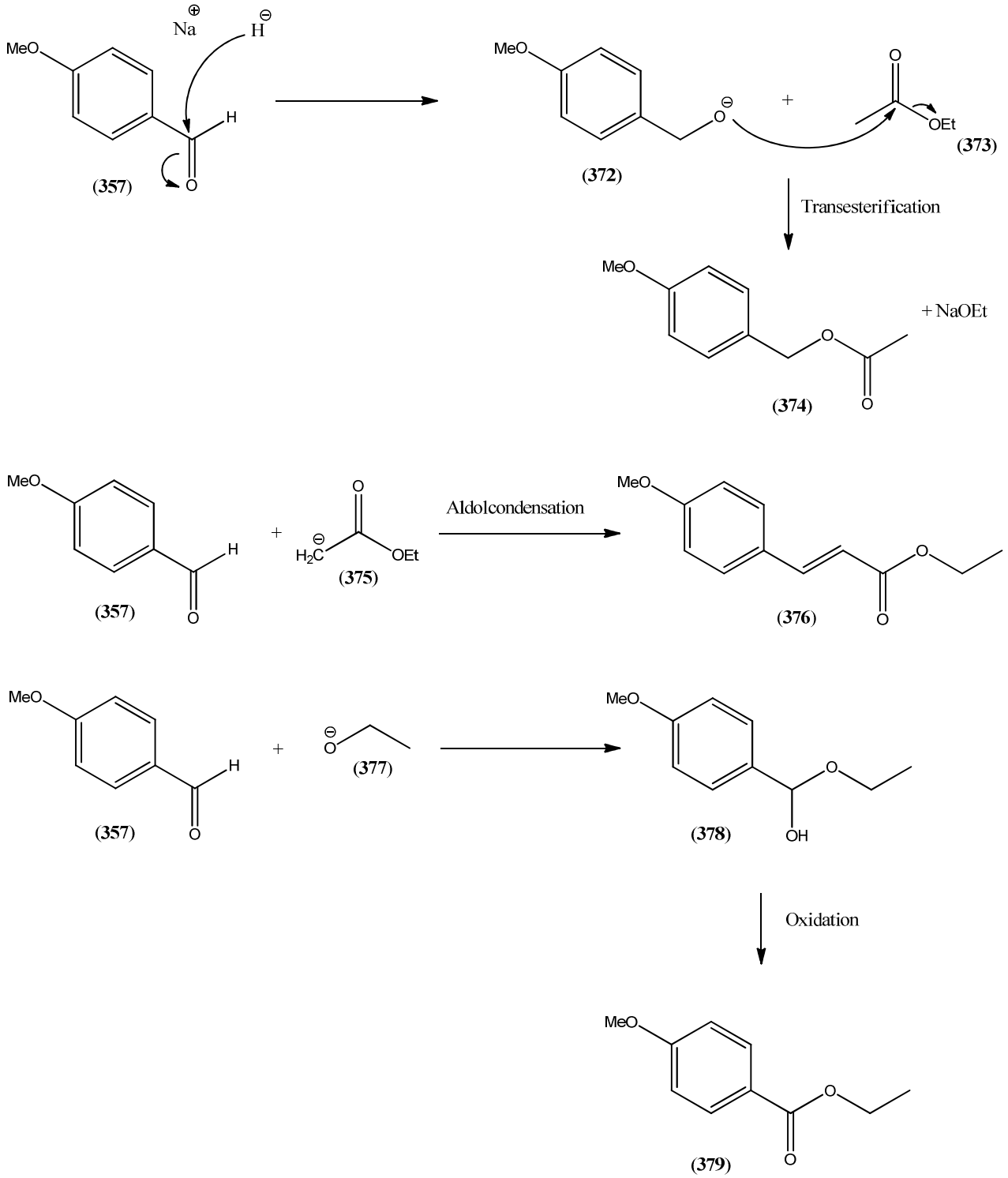
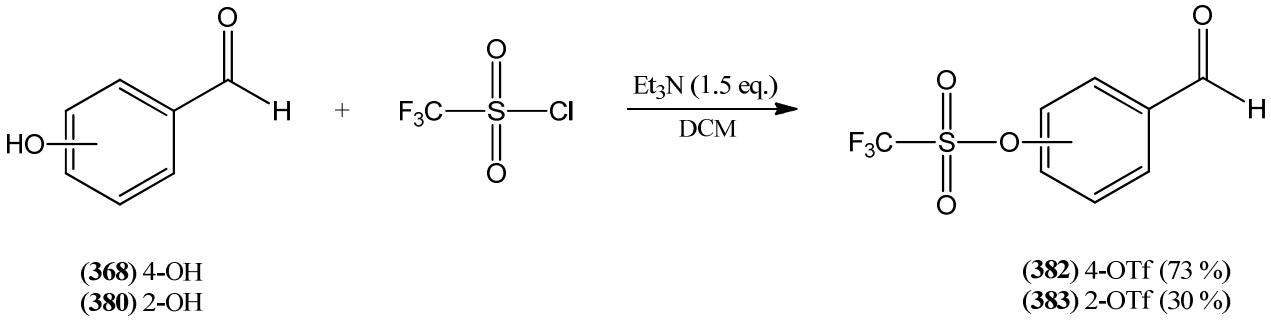


Figure 4-13: Formation of anisyl acetate, ethyl methoxycinnamate and ethyl *p*-methoxybenzoate during the treatment of anisaldehyde with NaH.

- **Aldehydes with electron-withdrawing groups**

In order to be able to prepare the stilbenes containing electron-withdrawing groups attached to one of the aromatic rings (*cf.* Paragraph 4.1), it was decided to have the electron-withdrawing group on the electrophilic reagent, *i.e.* aldehyde, so 2- and 4-hydroxybenzaldehydes, (**380**) and (**368**), also

had to be protected with a trifluoromethanesulfonyloxy (triflate) group. Treatment of these aldehydes, (**368**) and (**380**), with trifluoromethanesulfonyl chloride and triethyl amine in DCM (Figure 4-14) led to the formation of the protected aldehydes (**382**) and (**383**) as light yellow oils in 73 % and 30 % yield, respectively. The low yield obtained for (**383**) can probably be ascribed to steric interaction between the aldehyde function and the incoming triflate group.



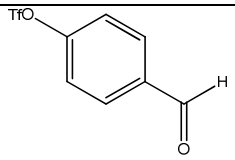
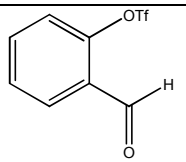
(**368**) 4-OH
(**380**) 2-OH

(**382**) 4-OTf (73 %)
(**383**) 2-OTf (30 %)

Figure 4-14: Synthesis of benzaldehydes with trifluoromethanesulfonyloxy substituents

In the characterization of (**382**) and (**383**) with ^{1}H (Plate 12a and 13a) and ^{13}C NMR (Plate 12b and 13b) analysis all the expected resonances were observed including the characteristic CF_3-carbon resonating as a quartet at δ 118.78 (J = 320.90 Hz) and δ 118.77 ppm (J = 320.65 Hz), respectively. The presence of a fluorine atom was also confirmed by ^{19}F NMR analysis which showed singlets at δ -75.81 (Plate 12f) and δ -75.94 ppm (Plate 13e) for (**382**) and (**383**), respectively (Table 4-3). Mass spectra of (**382**) and (**383**) displayed molecular ions at *m/z* 254 (M^+, 76 % and 17 %), thus confirming the structures of the products.

Table 4-3: Characteristic NMR resonances of trifluoromethanesulfonyloxybenzaldehydes synthesized

Structure	Chemical shifts and coupling constant (-CF_3)		
	δ_C (ppm)	J (Hz)	δ_F (ppm)
	118.87	320.90	-75.81
	118.77	320.65	-75.94

4.2.4. Stilbenes through application of the Wittig reaction

With all the envisaged starting materials in hand, attention was subsequently turned towards formation of the stilbenes themselves and it was decided to optimize reaction conditions with the commercially available starting materials before extending the reaction to more demanding substrates. Thus triphenylphosphonium bromide (**337**) and benzaldehyde (**339**) were subjected to the conventional Wittig reaction conditions (sodium hydride, dry THF, 4 hours) and *trans*-stilbene (**384**) was obtained as a white powder in only 17 % yield (Figure 4-15).

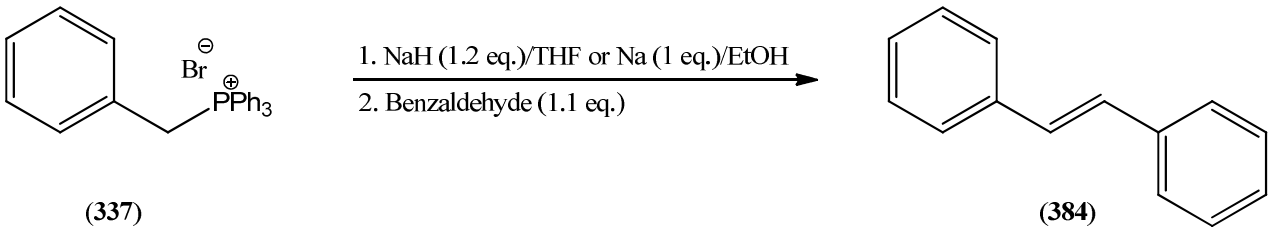


Figure 4-15: Synthesis of stilbenes through Wittig reaction with NaH/Na as base

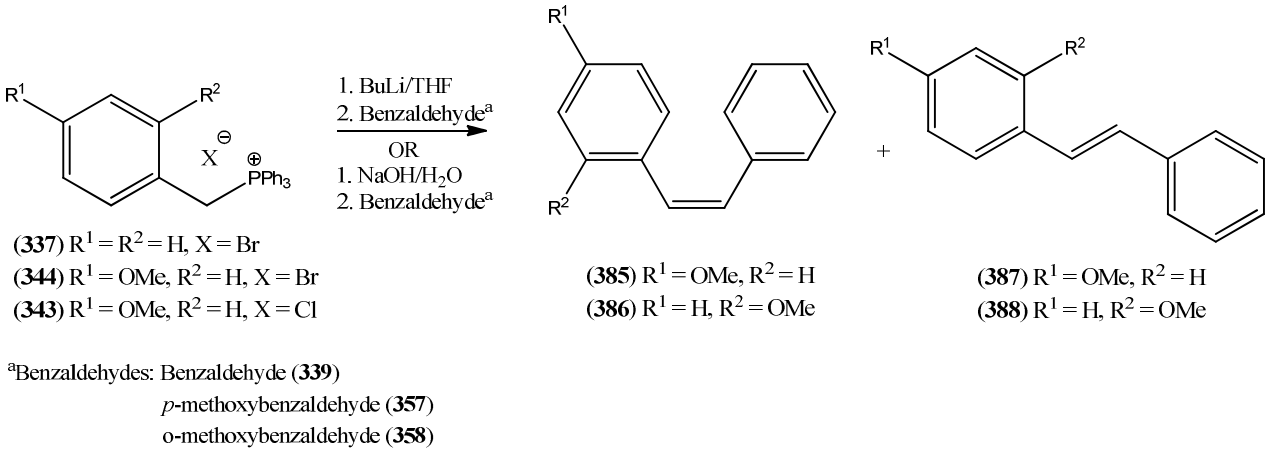
The indentity of the product (**384**) was confirmed by ^{1}H NMR (Plate 14a) where the two vinyl protons were clearly visible as a singlet at δ 7.14 ppm, due to a plane of symmetry through the double bond in the molecule. The structure was confirmed by ^{13}C NMR (Plate 14b) analysis. Since the unacceptably low yield could probably be explained by incomplete deprotonation of the phosphonium salt before addition of the aldehyde due to insufficient quantities of NaH and/or a too short period of time allowed for the deprotonation to reach completion, it was decided to evaluate other bases in order to find a method better suited towards the preparation of stilbenes.

When sodium metal in anhydrous ethanol was used as base and stirring continued for 15 minutes before addition of benzaldehyde (**339**), an even lower yield of *trans*-stilbene (**384**) (14 %) was obtained.

- **Stilbenes with electron-donating substituents**

Since *p*-anisaldehyde (**357**) is commercially available and methoxy substituted benzyl halides (for preparation of the phosphonium salts) are difficult to prepare and handle, it was decided to attempt the synthesis of the first oxygenated stilbene, 4-methoxystilbene (**385/387**), by reaction of *p*-anisaldehyde (**357**) with unsubstituted benzyltriphenylphosphonium bromide (**337**) (Figure 4-16). Treatment of a THF solution of the phosphonium bromide (**337**) with NaH followed by addition of *p*-anisaldehyde (**357**), however, led to no stilbene-like product being formed. As it was possible

that the failure of the reaction could be due to the reduced electrophilicity of the carbonyl carbon in anisaldehyde, the reaction was repeated, but with reagents reversed, *i.e.* reaction of benzaldehyde (**339**) with the methoxylated phosphonium salt (**344**). In an attempt to improve on the low yield (17 %) obtained during the preparation of the unsubstituted stilbene (**384**), it was also decided to change to butyl lithium (BuLi) as base for the deprotonation and to assure that enough base is added by using a standardized (titration with pentanol using triphenylmethane as indicator) BuLi solution. This procedure led to the desired *cis*- (**385**) and *trans*-4-methoxystilbenes (**387**) being formed in 33 % yield and a 5:1 ratio of the two isomers (Figure 4-16). A two fold increase in yield when compared to the previous preparation of unsubstituted *trans*-stilbene (**384**) utilizing NaH (*vide supra*). Column chromatography gave pure *cis*-4-methoxystilbene (**385**), showing the characteristic α and β proton resonances as doublets at δ 6.53 and δ 6.50 ppm (J = 12.22 Hz) in the ^{1}H NMR spectrum (Plate 15a), as well as pure *trans*-4-methoxystilbene (**387**) with the corresponding α and β proton peaks at δ 7.10 and δ 7.01 ppm (d, J = 16.31 Hz) displaying the bigger coupling constant associated with the vinyl protons of *trans*-stilbenes[10] in the ^{1}H NMR spectrum (Plate 16a) (Table 4-4).



(**337**) $R^1 = R^2 = H$, X = Br
(**344**) R^1 = OMe, $R^2 = H$, X = Br
(**343**) R^1 = OMe, $R^2 = H$, X = Cl

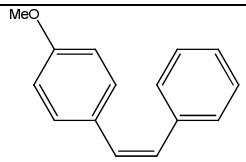
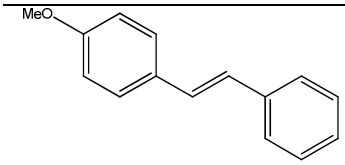
(**385**) R^1 = OMe, $R^2 = H$
(**386**) $R^1 = H$, R^2 = OMe

(**387**) R^1 = OMe, $R^2 = H$
(**388**) $R^1 = H$, R^2 = OMe

[a]Benzaldehydes: Benzaldehyde (**339**)
p-methoxybenzaldehyde (**357**)
o-methoxybenzaldehyde (**358**)

Figure 4-16: Synthesis of stilbenes through Wittig reaction

Table 4-4: NMR resonances of the vinyl protons of *cis*- and *trans*-4-methoxystilbene

Stilbene	*α*-proton		*β*-proton		
	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	*J* (Hz)
	6.53	129.88	6.50	128.87	12.22
	7.10	128.32	7.01	126.72	16.31

In an effort to improve on the yields of stilbene formation and to utilize more environmentally friendly methodology, it was decided to investigate the process reported by McNulty and Das[11] for the synthesis of the oxygenated stilbenes. Benzyltriphenylphosphonium bromide (**337**) was therefore dissolved in a small amount of water to prepare a 1.5-2.5 M solution of the substrate. Hereafter solid NaOH (4 eq.) was added and the mixture stirred for a few minutes resulting in a colour change from colourless to milky yellow, indicating complete formation of the ylide. Subsequent addition of *p*-anisaldehyde (**357**) at room temperature followed by heating the mixture to 70 °C for 3 hours led to the formation of the desired *cis*- and *trans*-4-methoxystilbenes (**385**) and (**387**), which were isolated in 55 % combined yield and a 1:1 ratio (Figure 4-16). NMR and MS data confirmed the products, (**385**) and (**387**), to be identical to those obtained previously (*vide supra*).

Interestingly, performing the same reaction with the substrates reversed, *i.e.* reacting 4-methoxybenzyltriphenylphosphonium chloride (**343**) and benzaldehyde (**339**), led to only 28 % yield of the 4-methoxystilbenes (**329**) being obtained (*cf.* Paragraph 5.7.5.5.). This observation stood in direct contrast to what was found for the conventional Wittig reaction discussed previously, where the reaction gave a higher yield when the methoxy substituent was on the phosphonium salt reagent rather than on the aldehyde.

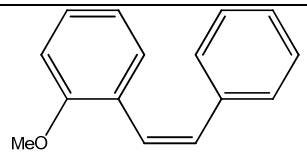
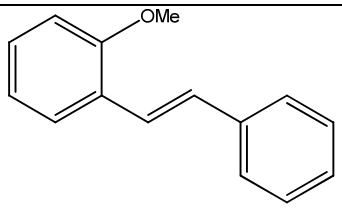
Since it was postulated by McNulty and Das[11] that the reaction is driven by a phase transfer process where the stilbene precipitates out, and it could be envisaged that the aldehyde would be present in the organic phase, while the phosphonium salt would be water soluble, it was decided to investigate the possibility of further increases in yield by the addition of a phase transfer catalyst to the reaction mixture. The reaction was therefore repeated under the same conditions as previously

in the presence of tetrabutylammonium bromide (10 mol %), but this modification to the procedure actually resulted in the yield decreasing to only 24 %.

Although yields from the reaction could not be improved beyond the average 55 % (and it was still better than what was obtained with the standard Wittig conditions), it must be pointed out that the commercially available *p*-anisaldehyde (**357**) and benzyltriphenylphosphonium bromide (**337**) (available in 98 % yield from benzyl bromide and PPh_3) could be used as starting materials, which eliminated the need for the time consuming preparation and handling of oxygenated benzyl halides in the synthesis of all the oxygenated stilbenes. It was therefore decided to extend the application of the McNulty and Das[11] methodology to the preparation of 2-methoxystilbene (**386/388**) to establish what the effect of a methoxy substituent next to the aldehyde function would be on both yield and *cis*-*trans* selectivity.

Subjecting 2-methoxybenzaldehyde (**358**) to the conditions mentioned above (basic solution of benzyltriphenylphosphonium bromide (**337**) in water) led to the isolation of the desired product as a mixture of *cis*- and *trans*-isomers, (**386**) and (**388**), in 53 % yield and 2:1 ratio. Column chromatography gave pure *cis*-2-methoxystilbene (**386**), displaying the characteristic α and β proton resonances as doublets (J = 12.26 Hz) at δ 6.69 and δ 6.63 ppm in the ^{1}H NMR spectrum (Plate 17a). The ^{13}C NMR spectrum (Plate 17b) showed all the expected carbon resonances of the product (**386**) and the structure was finally confirmed by MS analysis where a molecular ion at *m/z* 210 (M^+, 100 %) could be detected. A pure sample (without any *cis*-isomer contamination) of *trans*-2-methoxystilbene (**388**) could not be obtained by FCC, but the proton NMR spectrum (Plate 18) of the mixture clearly indicated the presence of the *trans*-isomer (**388**) by displaying the characteristic vinyl doublet resonances at δ 7.48 and δ 7.11 ppm (J = 16.48 Hz) (Table 4-5).

Table 4-5: NMR resonances of the vinyl protons of *cis*- and *trans*-2-methoxystilbene

Stilbene	α		β		J (Hz)
	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	
	6.69	125.92	6.63	-	12.26
	7.48	-	7.11	-	16.48

In order to complement the series of stilbenes carrying electron-donating groups on one aromatic ring with an analogue that contains a strongly activated ring, it was decided to also prepare 4-hydroxystilbene (**335**), which could also be converted into an analogue containing an electron-withdrawing group by reacting it with trifluoromethanesulfonyl chloride.

4-Ethoxymethoxyaldehyde (**369**) (*cf.* Paragraph 4.2.3.) was therefore reacted with benzyltriphenyl-phosphonium bromide (**337**) utilizing the aqueous NaOH procedure (Figure 4-17) and the product again obtained as a mixture of *cis*- and *trans*-isomers, (**389**) and (**390**), in 55 % yield and a 1:1 ratio. The ^{1}H NMR spectra (Plate 19a and 20a) of the pure *cis*- and *trans* products (**389**) and (**390**) are summarized in Table 4-6 and confirmed the products to be the expected *cis*- (**389**) and *trans*-4-ethoxymethoxystilbenes (**390**); the structures of which were also proved by ^{13}C NMR (Plate 19b and 20b) and MS analysis.

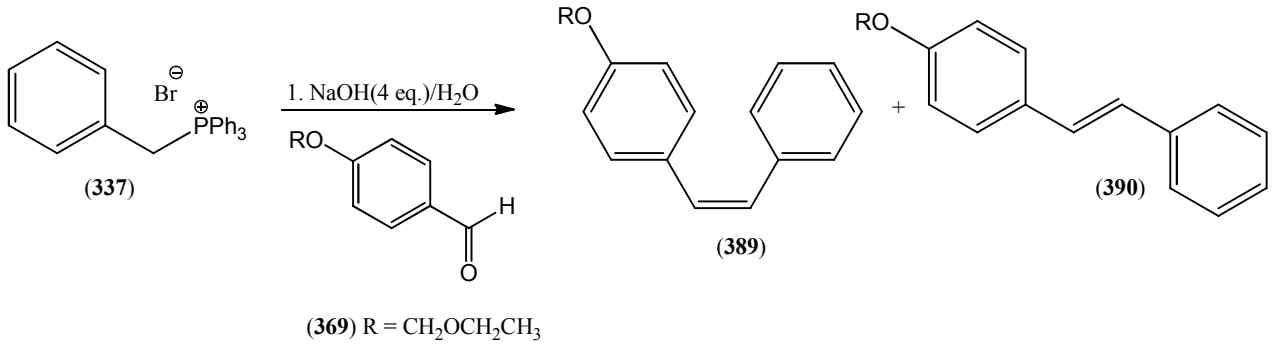


Figure 4-17: Synthesis of 4-ethoxymethoxystilbene

Table 4-6: Characteristic ^{1}H and ^{13}C NMR resonances of 4-ethoxymethoxystilbene

Isomer	*Cis* (**389**)			*Trans* (**390**)		
H/C	δ_H (ppm)	δ_C (ppm)	*J* (Hz)	δ_H (ppm)	δ_C (ppm)	*J* (Hz)
-CH- (α)	6.52	129.80 or 129.13	-	7.07	128.26	16.32
-CH- (β)	6.52	129.80 or 129.13	-	6.99	127.13	16.32
-OCH_2O- (s)	5.19	93.22	-	5.24	93.24	-
-OCH_2- (q)	3.71	64.36	7.05	3.74	64.42	7.08
-CH_3 (t)	1.21	15.23	7.05	1.23	15.26	7.08

Deprotection of a mixture of the 4-ethoxymethoxystilbene isomers (**389**) and (**390**) was achieved by dissolving the protected stilbenes in MeOH and stirring the mixture in the presence of a

catalytic amount of concentrated sulphuric acid for 2 hours to give only *trans*-4-hydroxystilbene (**394**) in quantitative yield due to acid catalysed *cis-trans* isomerization. The ^{1}H NMR spectrum (Plate 21a) of *trans*-4-hydroxystilbene (**394**) showed the characteristic doublets for H-*α* and H-*β* at δ 6.15 and δ 6.03 ppm, respectively, (J = 16.40 Hz) as well as all the expected aromatic protons, while the ^{13}C NMR spectrum (Plate 21b) displayed all the expected carbon peaks. The structure of the product was finally confirmed by m.p. (183-186 °C) correlation with the literature value (lit.[12] m.p. 185-187 °C) and MS analysis where a molecular ion at *m/z* 196 (M^{+}, 100 %) was observed.

4.2.5. Stilbene preparation through a Perkin-type reaction

Since Sinha[13] *et al.* reported a one-pot preparation of stilbenes by reacting hydroxybenzaldehydes with phenylacetic acids under microwave activation conditions, it was decided to investigate application of this methodology to the synthesis of the required stilbenes in an effort to obtain improved yields. While Sinha[13] *et al.* were able to obtain stilbenes in 41-71 % yield for certain substrates, they also found that a hydroxy substituent in the *ortho* or *para* position of either the benzaldehyde or the phenylacetic acid is required for the reaction to proceed well, while an EWG (e.g. Cl) and EDG (e.g. OMe) in the *meta* position of either starting material, enhances the reactivity of the substrates even further. In order to explain these results, Sinha and co-workers[13] postulated the reaction to follow a mechanism as presented in Figure 4-18.

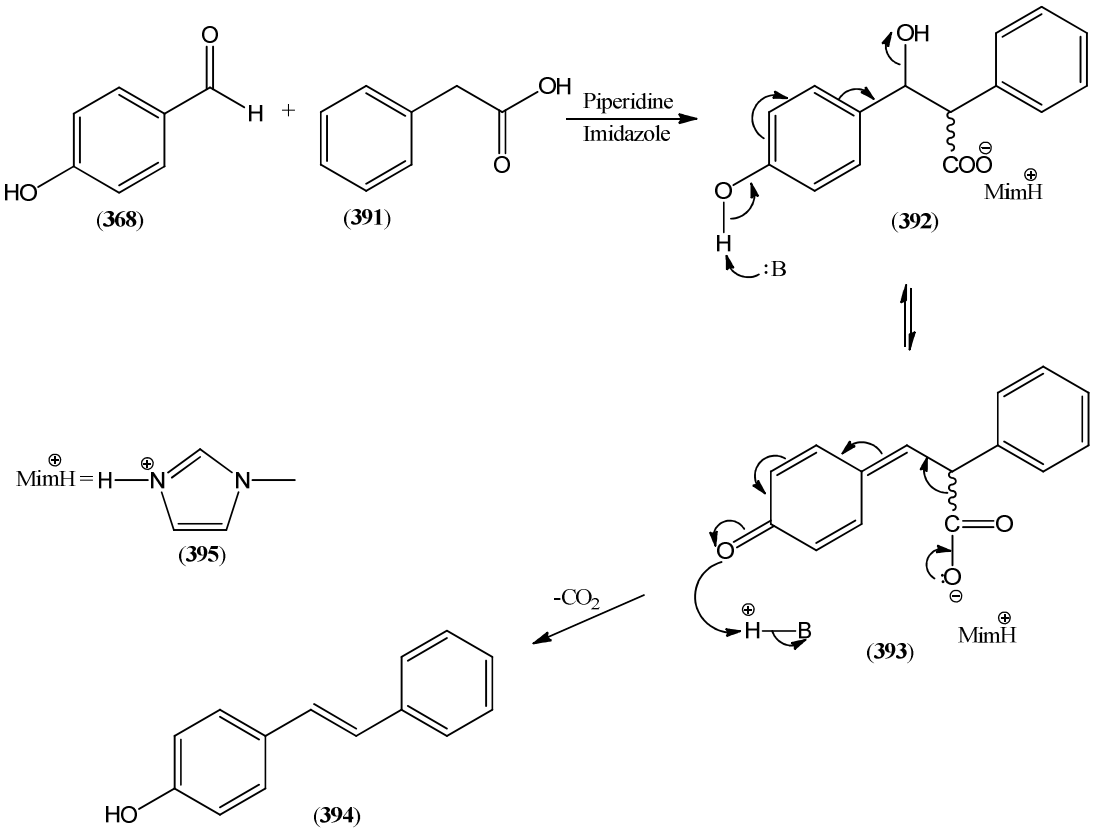


Figure 4-18: Postulated mechanism for the Perkin reaction as proposed by Sinha[13]

Since various substitution patterns for hydroxybenzaldehydes and phenylacetic acids are available commercially, the Sinha[13] methodology was anticipated to represent an economical route towards the synthesis of hydroxystilbenes and was subsequently investigated as an alternative methodology for the preparation of these compounds. Phenylacetic acid (**391**) in PEG-400 was therefore reacted with *p*-hydroxybenzaldehyde (**368**) in the presence of piperidine and imidazole under microwave irradiation (Figure 4-19) and *trans*-4-hydroxystilbene (**394**), identical to the product obtained in the previous section (*cf.* Paragraph 4.2.4.), was formed in 42 % yield after 10 minutes. Since the one-pot microwave procedure allowed vastly reduced reaction times, gave a slightly higher yield than the previous protection-deprotection method (39 % over 3 steps) (*cf.* Paragraph 4.2.4.) and required no intermediate purification processes, it can be regarded as the method of choice for the synthesis of hydroxylated stilbenes.

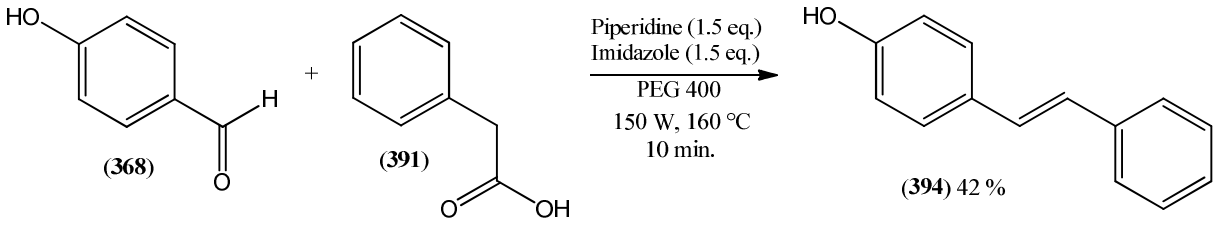


Figure 4-19: Synthesis of 4-hydroxystilbene in one-pot microwave reaction

- **Stilbene with electron-withdrawing substituent**

With the 4-hydroxystilbene (**394**) in hand, it was decided to use this compound as starting material for the synthesis of the stilbenes containing electron-withdrawing groups on one of the aromatic rings. 4-Trifluoromethanesulfonyloxystilbene (**395**) was therefore prepared by treating *trans*-4-hydroxystilbene (**394**) with trifluoromethanesulfonyl chloride (**381**) (1.1 eq.) and triethyl amine (1.5 eq.) in DCM and the product (**395**) was isolated in good yield (54 %) after aqueous work-up (Figure 4-20). The ^{1}H NMR spectrum (Plate 22a) of the product (**395**) contained the vinyl proton resonances associated with *trans*-stilbenes [δ 7.10 and δ 7.08 ppm (d, J = 16.38 Hz)], as well as a deshielded aromatic AA'BB' system [δ 7.53 and δ 7.25 ppm (d, J = 8.76 Hz)] indicative of an electron-withdrawing substituent in the *para*-position of the aromatic ring. The structure of the product (**395**) was confirmed by ^{13}C NMR where the spectrum (Plate 22b) showed the CF_3-carbon resonance at δ 118.90 ppm as a quartet with a large coupling constant (320.86 Hz) as well as a molecular ion at *m/z* 328 (M^+, 45 %) in the mass spectrum.

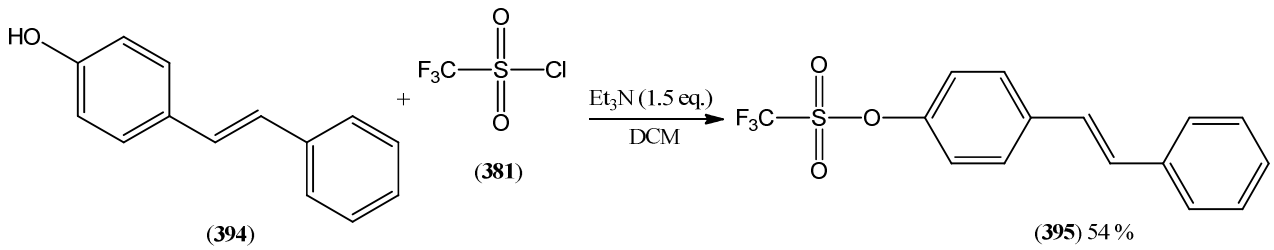


Figure 4-20: Synthesis of 4'-trifluoromethanesulfonyloxystilbene

4.3. Methoxycarbonylation of model substrates

4.3.1. Introduction

Although not all of the stilbenes envisaged for the current investigation had been prepared, it was decided to start with the methoxycarbonylation reactions in order to find the appropriate catalyst system and reaction conditions applicable to the methoxycarbonylation of stilbenes, which has not been attempted before. This would also allow for a preliminary assessment of the possibility of regioselective control through differences in the electronic properties of the two aromatic rings attached to the stilbene double bond.

While two catalyst systems, *i.e.* i) $Co_2(CO)_8$ and ii) palladium salts [$PdCl_2$ or $Pd(OAc)_2$] together with a phosphine ligand and an acid promoter, have been utilized in the hydroesterification of alkenes (*cf.* Paragraphs 3.3 and 3.4), the former system involves high temperatures and pressures and would therefore probably not be conducive to obtaining high regioselectivities towards one of the two possible esters if the reaction pathway is to be governed by small differences in the electronic properties around the stilbene double bond. Since the platinum group metals usually requires moderate conditions with respect to temperature and pressures during reactions, palladium salts [$PdCl_2$ or $Pd(OAc)_2$] together with a phosphine ligand, to keep the palladium in solution, were therefore selected to be evaluated in the current investigation. In contrast to hydroformylation, hydroesterification reactions involving palladium salts also require the presence of an acid co-catalyst or promoter, usually a Bronsted acid, like *p*-TsOH, $MeSO_3H$, BSA or TFA.[14,15] While a catalytic cycle for the hydroesterification reaction has been proposed and the existence of all the intermediates proven by Eastham and co-workers[16] (*cf.* Figure 3-6), this mechanism does not account for the requirement of an acid promoter/co-catalyst and should therefore probably be amended to the cycle given in Figure 4-21, where the acid assists in the formation of the Pd-hydride species (**316**) through oxidative addition of the acid activated methanol to the solvated palladium metal. Although all of the mentioned Bronsted acids (*vide*

supra) are capable of producing the ester products in acceptable yields, the utilization of these reagents in conjunction with less reactive di- or trisubstituted alkene substrates lead to methylation of the phosphine ligand and therefore requires constant addition of phosphine in order to prevent palladium metal "fall out" or reduction causing Pd(0) precipitation leading to incomplete reactions. In order to prevent this unwanted side reaction from occurring, Williams *et al.*[15] described the utilization of Lewis acids, like $Al(OTf)_3$, as acid promoter in hydroesterification reactions, so it was decided to utilize the Williams system, *i.e.* $Pd(OAc)_2/Al(OTf)_3/PPh_3$, as starting catalyst during the current investigation.[17,18]

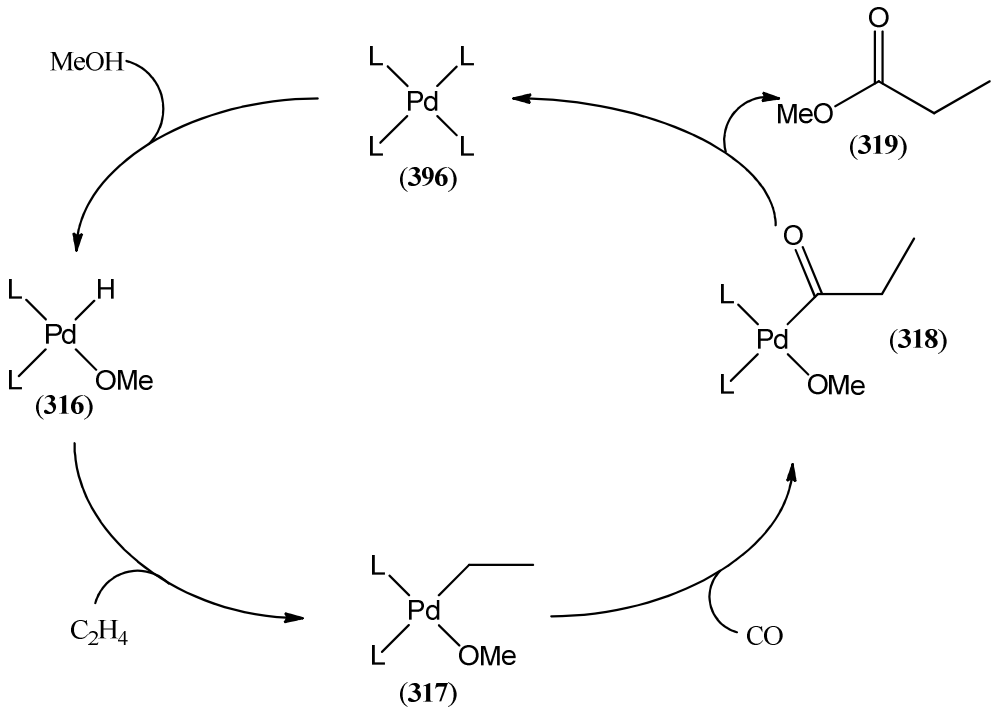


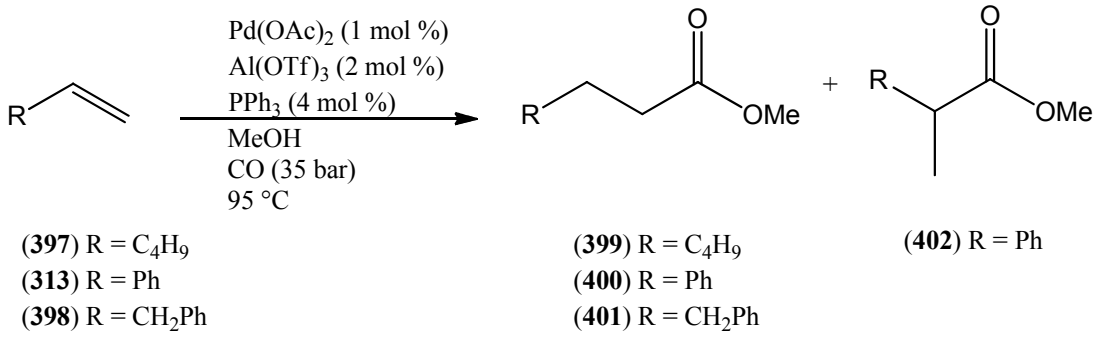
Figure 4-21: Methoxycarbonylation mechanism showing the possible function of an acid co-catalyst

4.3.2. Model substrates

As the Williams catalyst system was tested extensively on acyclic aliphatic alkenes, it was decided to start the investigation with simple alkenes like hexene (**397**) and then extend the substrates to aromatic analogues like styrene (**313**) and allylbenzene (**398**) before attempting any stilbenes.

The first methoxycarbonylation reaction was therefore performed on hexene (**397**) at 95 °C and 35 bar CO pressure with the reaction being monitored by GCMS (Figure 4-22). After 4 hours a 70 % conversion of hexene (**397**) to methyl heptanoate (**399**), the desired product, was observed, but the GCMS chromatogram, however, also showed an 8 % peak that was identified as triphenylphosphine oxide ($OPPh_3$) whereas no PPh_3 could be detected. This observation pointed

towards PPh_3 being oxidized to $OPPh_3$ and indicates possible metal plating [Pd(0) 'fall-out'] during the reaction, which was somewhat disturbing, but as the conversion was acceptable it was decided to continue with the methoxycarbonylation of styrene, which showed a remarkable 99 % conversion to methyl 3-phenylpropanoate (**400**) and methyl 2-phenylpropanoate (**402**) in a 3:1 ratio after only one hour (Figure 4-22). Probably due to the shorter reaction time, only 1 % of $OPPh_3$ formation was detected by GCMS analysis.



(**397**) R = C_4H_9
(**313**) R = Ph
(**398**) R = CH_2Ph

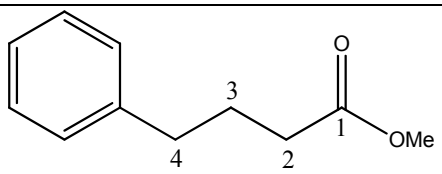
(**399**) R = C_4H_9
(**400**) R = Ph
(**401**) R = CH_2Ph

(**402**) R = Ph

Figure 4-22: Methoxycarbonylation of hexene, styrene and allylbenzene

Methoxycarbonylation of allylbenzene (**398**) (Figure 4-22) led almost exclusively to the formation of methyl 4-phenylbutanoate (**401**) in 57 % conversion (22 hours). The product was purified by FCC (H:T:A 4:4:2) and characterized by NMR spectroscopy where two triplet resonances were observed at δ 2.66 and δ 2.34 ppm in the ^1H NMR spectrum (Plate 23a). These signals together with a pentet at δ 1.97 ppm and a methoxy resonance at δ 3.67 ppm indicated the structure of the product to be methyl 4-phenylbutanoate (**401**) and not the branched isomer methyl 2-benzylpropanoate (Table 4-7). The structure of the product (**401**) was confirmed by the ^{13}C NMR spectrum (Plate 23b), which displayed all expected resonances, as well as mass analysis which showed a molecular ion at *m/z* 178 (M^+, 33 %) and fragmentation peaks at *m/z* 147 (33 %), 146 (42 %), 104 (96 %) and 91 (76 %).

Table 4-7: Most important ^{1}H and ^{13}C NMR resonances of methyl 4-phenylbutanoate

Structure			
H/C	δ_H (ppm)	δ_C (ppm)	J (Hz)
2 (t)	2.34	35.13	7.56
3 (p)	1.97	26.50	7.56
4 (t)	2.66	33.39	7.56
OMe (s)	3.67	51.54	-

4.3.3. Unsubstituted stilbene

The next step in the investigation was to use the same methodology for the methoxycarbonylation of *trans*-stilbene (**384**), but unfortunately no product formation was observed upon GCMS analysis. Since the solubility of *trans*-stilbene (**384**) in methanol was rather limited, this was identified as a possible cause for the failure of the reaction, so the reaction was repeated in MeOH:dioxane (1:1), a solvent system known for its solvating properties in cases where the substrate does not dissolve in pure methanol.[19] Disappointingly, no product could be detected (GCMS) yet again.

Due to the failure of the methoxycarbonylation of stilbene and the fact that the reaction conditions were not optimized for aromatic substrates, it was decided to revert back to model reactions in order to optimize reaction conditions and find a solvent capable of properly dissolving stilbenes. Since the only structural difference between *trans*-*β*-methylstyrene (**405**) and *trans*-stilbene (**384**) would be that the former contains a methyl group where stilbene would have a phenyl substituent, it was anticipated that *trans*-*β*-methylstyrene (**405**) would be an appropriate model substrate to be utilized in this respect.

4.3.4. *Trans*-*β*-methylstyrene

Methoxycarbonylation of *trans*-*β*-methylstyrene (**405**) under the conditions used for hexene (**397**), styrene (**313**) and allylbenzene (**398**) (*cf.* Paragraph 4.3.2.) gave 46 % conversion and led to the formation of a mixture of methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) in 26 % overall yield and a 3:2:1 ratio (Figure 4-23).

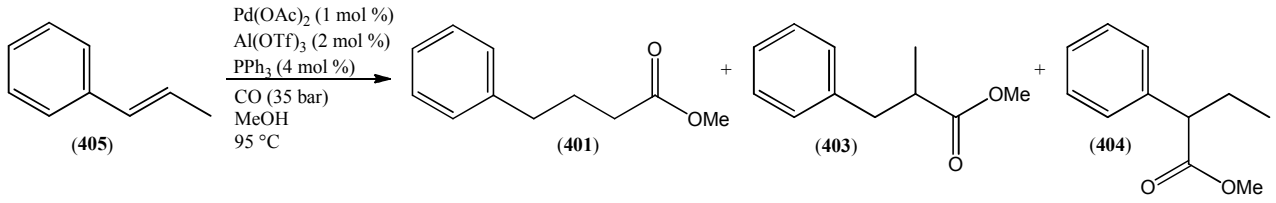
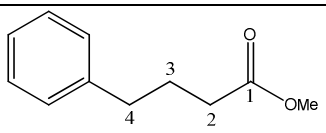
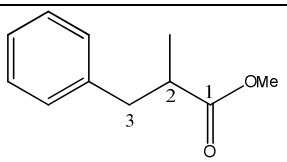
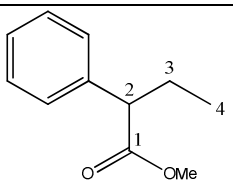


Figure 4-23: Methoxycarbonylation of *trans*-*β*-methylstyrene over a palladium acetate catalyst system

The major product, methyl 4-phenylbutanoate (**401**), isolated through FCC (H:A 8:2), was found to be identical to the compound obtained during the methoxycarbonylation of allylbenzene (**398**) (*vide supra*). Unfortunately all the other fractions contained a mixture of all three products, but the structures of methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) could be unravelled by careful analysis of the ^{1}H NMR spectrum (Plate 24a) of the mixture.

Table 4-8: Comparison of the ^{1}H NMR resonances of methyl 4-phenylbutanoate, methyl 2-methyl-3-phenylpropanoate and methyl 2-phenylbutanoate

Proton						
	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)
2	2.34	t, 7.56	2.76-2.71	m	3.46	t, 7.71
3	1.96	p, 7.56	3.03	dd, 6.83 and 13.56	2.13-2.08	m
3b	-	-	2.65	dd, 6.83 and 13.56	1.82-1.78	m
4	2.65	t, 7.56	-	-	0.92	t, 7.43
-OMe	3.67	s	3.64 (s)	s	3.66	s
2-CH_3	-	-	1.15 (d)	d, 6.90	-	-

The formation of methyl 4-phenylbutanoate (**401**), the major product, can possibly be explained in terms of the ability of the palladium catalyst to isomerize an internal double bond to the terminal position. There would then be two substrates available for methoxycarbonylation in this reaction *i.e. trans*-*β*-methylstyrene (**405**) and allylbenzene (**398**). The former may lead to methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) as products, while allylbenzene (**398**), may give methyl 4-phenylbutanoate (**401**) and methyl 2-methyl-3-phenylpropanoate (**403**).

Although the product from isomerization, methyl 4-phenylbutanoate (**401**), was found to be the main product from the reaction, this was of no concern at this stage of the investigation as isomerization would have no effect when stilbene substrates would be submitted to the methoxycarbonylation reaction.

4.3.5. Optimization of conditions and solvent studies with *trans-β*-methylstyrene

- **Catalyst and catalyst concentration**

Although $Pd(OAc)_2$ was used by Williams *et al.*[15] and the quantity of the catalyst relative to the substrate kept more or less the same, the first attempt at improving the reaction conditions with respect to the aromatic substrates involved increasing the palladium concentration. Thus the quantity of $Pd(OAc)_2$ was increased from *ca.* 10 mg (in 7 ml solvent) to 20 mg and the amounts of $Al(OTf)_3$ and PPh_3 adjusted accordingly (*cf.* Paragraph 5.13.2.1.) when the reaction was repeated, the conversion of *trans-β*-methylstyrene (**405**) to the three products (**401**), (**403**) and (**404**) was increased from 46 % to 51 % (after 22 hours). Since a higher concentration of Pd-catalyst would result in a higher degree of isomerization of the double bond to the terminal position, formation of the linear product (**401**) was also enhanced during this reaction (ratio 7:2:1 *vs.* 3:2:1 for the previous reaction).

Since PPh_3 depletion due to oxidation to triphenylphosphine oxide ($OPPh_3$), detected (GCMS) during the previous reactions, will cause the formation of Pd(0) and thus metal plating with decreased catalyst activity, the solution was degassed meticulously with ultra-high purity argon and the reactor flushed several times with the same argon. Despite this, the oxidation of PPh_3, could still not be completely eliminated, so it was decided to add an additional 4 mol % PPh_3 to the reaction mixture after 4 hours in all the subsequent methoxycarbonylation reactions.

The next attempt to increase the conversion and reaction rate of the methoxycarbonylation reaction was to replace $Pd(OAc)_2$ with $PdCl_2$ which usually has higher reactivity. Switching from $Pd(OAc)_2$ to $PdCl_2$ and adding PPh_3 after 4 hours of reaction time resulted in the conversion of *trans-β*-methylstyrene (**405**), to the three products found before, methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**), to increase significantly from 51 % to 90 % (reaction time 22 hours), while the ratio between the different products remained more or less constant at 6:2:1.

Diab *et al.*[20] published a methoxycarbonylation reaction which utilized a different acid promoter/co-catalyst namely *p*-TsOH at much lower pressures and temperatures. This process seemed very attractive, since milder reaction conditions are known to improve selectivity, so the

methoxycarbonylation of styrene (**313**) was repeated (*cf.* Paragraph 4.3.2.) utilizing the $Pd(OAc)_2$/*p*-TsOH/PPh_3 catalyst system and lowering of the temperature and pressure to 25 °C and 10 bar, respectively (Figure 4-24). This led to a conversion of 99 % after 24 hours, which was in good correlation with the published results.[20] Very poor conversion (2 %) was, however, obtained when the same catalyst system and reaction conditions were used for the methoxycarbonylation of *trans*-*β*-methylstyrene (**405**). Increasing the pressure to 25 and 35 bar and the temperature to 50 and 95 °C resulted in an improved conversion of 79 %, but it was nevertheless not as good as what was found with the $PdCl_2/Al(OTf)_3/PPh_3$ system, so it was concluded that $PdCl_2/Al(OTf)_3/PPh_3$ is the system of choice for the methoxycarbonylation of *trans*-*β*-methylstyrene (**405**).

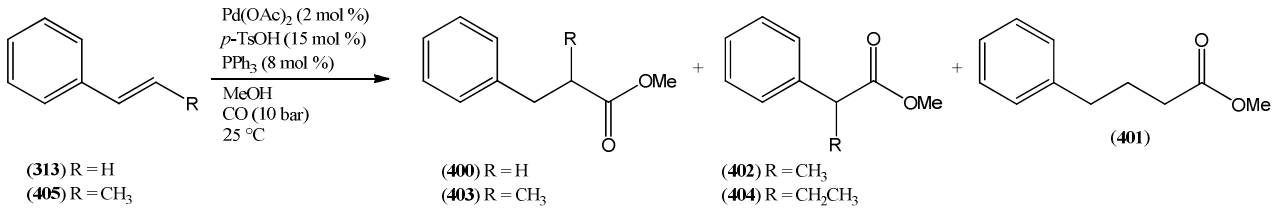


Figure 4-24: Methoxycarbonylation of styrene and *trans*-*β*-methylstyrene utilizing Diab[20] methodology

- **Solvents**

With the solubility of *trans*-stilbene (**384**) in MeOH being problematic, it was decided to investigate the methoxycarbonylation of *trans*-*β*-methylstyrene (**405**) (under the conditions shown in Figure 4-23) in alternative solvents that would dissolve *trans*-stilbene (**384**) and that could possibly be used in the methoxycarbonylation of stilbenes. Since methanol also served as reagent during the methoxycarbonylation reaction, only solvent systems that included some methanol were considered and combinations of some less polar solvents together with methanol were evaluated (Table 4-9).

Table 4-9: Solvent systems tested for methoxycarbonylation of *trans*-*β*-methylstyrene

Entry	Catalyst system	Solvent system (ratio)	Conversion (%)
1	$PdCl_2/Al(OTf)_3/PPh_3$	MeOH	90
2	$Pd(OAc)_2/Al(OTf)_3/PPh_3$	MeOH:Dioxane (1:1)	1
3	$PdCl_2/Al(OTf)_3/PPh_3$	MeOH:Toluene (6:4)	34
4	$PdCl_2/Al(OTf)_3/PPh_3$	MeOH:DMA* (6:4)	n.d.
5	$PdCl_2/Al(OTf)_3/PPh_3$	MeOH:DME** (1:1)	60
6	$PdCl_2/Al(OTf)_3/PPh_3$	MeOH:THF (1:1)	61
7	$Pd(OAc)_2$/*p*-TsOH/PPh_3	MeOH:THF (1:1)	38

* DMA = *N*,*N*-dimethylacetamide, **DME = 1,2-dimethoxyethane

From the results in Table 4-9 it is clear that MeOH:THF (1:1) is the best solvent system to use for methoxycarbonylation reactions of MeOH insoluble substrates, even though the conversion decreased from 90 % in pure MeOH to 61 % (in MeOH:THF 1:1). The reduction in yield with the methanol-ether solvent systems (MeOH:DME and MeOH:THF) is probably due to the lower methanol concentration.

Since the alcohol used in the esterification would not have any effect in the eventual utilization of the prepared esters with respect to the synthesis of isoflavonoids, and it was felt that a less polar solvent might be better for dissolving stilbenes, it was decided to also investigate the hydroesterification of *trans-β*-methylstyrene (**405**) in ethanol rather than methanol (Figure 4-25). A good conversion of 80 % (compared to 90 % for MeOH) to the three ester analogues found before, *i.e.* ethyl 4-phenylbutanoate (**406**), ethyl 2-methyl-3-phenylpropanoate (**407**) and ethyl 2-phenylbutanoate (**408**), in a 6:3:1 ratio was obtained. Purification by FCC (H:A 8:2) gave the three products, (**406**), (**407**) and (**408**), (R_f = 0.68), as a mixture in which the structures of the individual products could be completely elucidated by ^{1}H NMR (Plate 25a) (Table 4-10), IR [ν_{max} (CO) 1735 cm^{-1}] and MS analysis [*m/z* 192 (M^+, 33 %)].

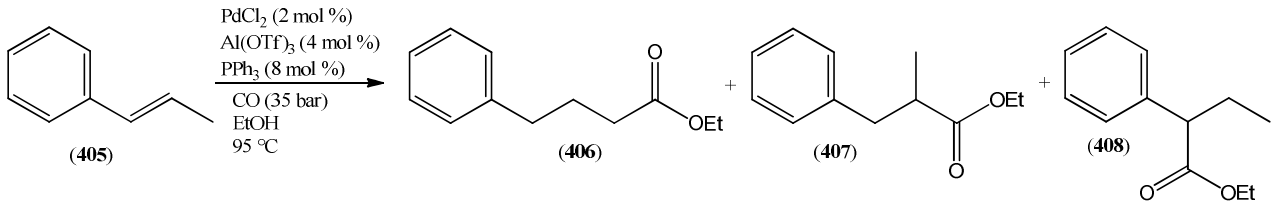
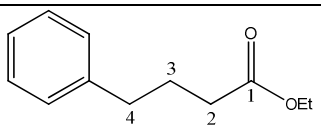
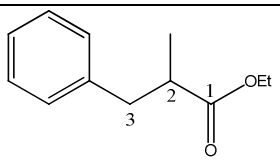
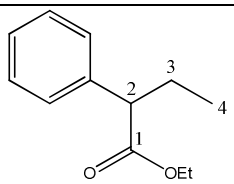


Figure 4-25: Ethoxycarbonylation of *trans-β*-methylstyrene

Table 4-10: ^{1}H NMR resonances of ethyl 4-phenylbutanoate, ethyl 2-methyl-3-phenylpropanoate and ethyl 2-phenylbutanoate

Proton						
	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)
2	2.35	t, 7.57	2.79-2.73	m	3.48	t, 7.71
3	2.00	p, 7.57	3.06	dd, 6.83 and 13.20	2.18-2.10	m
3b			2.72	dd, 7.07 and 13.20	1.88-1.79	m
4	2.68	t, 7.57	-	-	0.94	t, 7.37
-OCH_2-	4.16	q, 7.14	4.12	q, 7.15	4.12	q, 7.13
-$OCH_2\underline{CH_3}$	1.28	t, 7.14	1.22	t, 7.15	1.24	t, 7.13
2-Me	-	-	1.19	d, 6.86	-	-

- **Optimization of reaction conditions**

Although Williams *et al.*[15] published optimized conditions for the methoxycarbonylation reaction with their $Pd(OAc)_2/Al(OTf)_3/PPh_3$ catalyst system, these results were reported for aliphatic substrates, so the optimum conditions for the methoxycarbonylation of analogues with the double bond in conjugation with an aromatic ring, was the next step to be investigated. *Trans-β*-methylstyrene (**405**), was therefore subjected to the methoxycarbonylation reaction over the Pd-catalyst system [$PdCl_2/Al(OTf)_3/PPh_3$] in MeOH at different temperatures (55 to 105 °C) and pressures (15 to 35 bar) (Table 4-11).

Table 4-11: Methoxycarbonylation of *trans-β*-methylstyrene at different temperatures and pressures

Entry	Pressure CO (bar)	Temperature (°C)	Conversion (%)
1	35	105	88
2	35	95	90
3	35	75	80
4	35	55	44
5	25	95	83
6	15	95	84

As is evident from Table 4-11 the highest conversion (90 %) was reached at 95 °C (entry 2) although increasing the temperature to 105 °C only had a marginal effect on the reaction. Varying CO pressure had an even less dramatic effect and a decrease from 35 to 15 bar in pressure (entries 2, 5 and 6, Table 4-11) only led to conversion values declining slightly from 90 to 83 %. The optimum reaction conditions of temperature and pressure for conjugated substrates were therefore determined to be the same as those found by the Williams group[15] for aliphatic compounds, *i.e.* 35 bar and 95 °C. These conditions were therefore used for all subsequent methoxycarbonylation reactions.

4.3.6. Methoxycarbonylation of other disubstituted styrenes

Although *trans-β*-methylstyrene (**405**) is structurally closely related to stilbene and therefore of particular importance to the current study, it was decided to broaden the scope of the current investigation and also study the effect of the position of branching as well as a higher degree of branching on the methoxycarbonylation of substrates with double bonds in conjugation with aromatic rings.

α-Methylstyrene (**409**) and 2-methyl-1-phenylprop-1-ene (**411**) were therefore subjected to methoxycarbonylation under the conditions optimized for *trans-β*-methylstyrene (**405**) (Figure 4-26) and the products, methyl 3-phenylbutanoate (**410**) and methyl 3-methyl-4-phenylbutanoate (**412**) obtained in 38 and 22 % yields, respectively. The two products, (**410**) and (**412**), were characterized by ^{1}H NMR where, apart from the expected aromatic resonances [δ 7.29-7.26 (2H, m, H-3' and H-5'), 7.21-7.17 (3H, m, H-2', H-4' and H-6') and δ 7.29-7.27 (2H, m, H-3' and H-5'), 7.21-7.18 (1H, m, H-4'), 7.17-7.15 (2H, m, H-2' and H-6')], the spectra (Plate 26a and 27a) contained methoxy signals at δ 3.59 and 3.65 ppm, respectively, as well as doublets from methyl groups at δ 1.29 (J = 7.00 Hz) and 0.94 ppm (J = 6.58 Hz), respectively. The spectrum of methyl 3-phenylbutanoate (**410**) (Plate 26a) further displayed resonances from a single methylene function [δ 2.61 (1H, dd, J = 15.20, 6.91 Hz, H-2a or H-2b) and 2.54 (1H, dd, J = 15.20, 8.23 Hz, H-2a or H-2b)], while that of methyl 3-methyl-4-phenylbutanoate (**412**) contained signals (Plate 27a) arising from four methylene protons [δ 2.62 (1H, dd, J = 13.45, 6.76 Hz, H-4a or H-4b), 2.51 (1H, dd, J = 13.45, 7.44 Hz, H-4a or H-4b), 2.34 (1H, dd, J = 14.66, 5.76 Hz, H-2a or H-2b), 2.14 (1H, dd, J = 14.66, 7.87 Hz, H-2a or H-2b)]. The ^{13}C NMR spectra (Plate 26b and 27b) of the two products, (**410**) and (**412**), showed the characteristic C=O resonance at δ 172.82 and 173.67 ppm, respectively as well as all the other expected carbon signals. The structures of the two products were confirmed by MS where molecular ions at *m/z* 178 (M^+, 24 %) and *m/z* 192 (M^+, 14 %), respectively, were clearly visible.

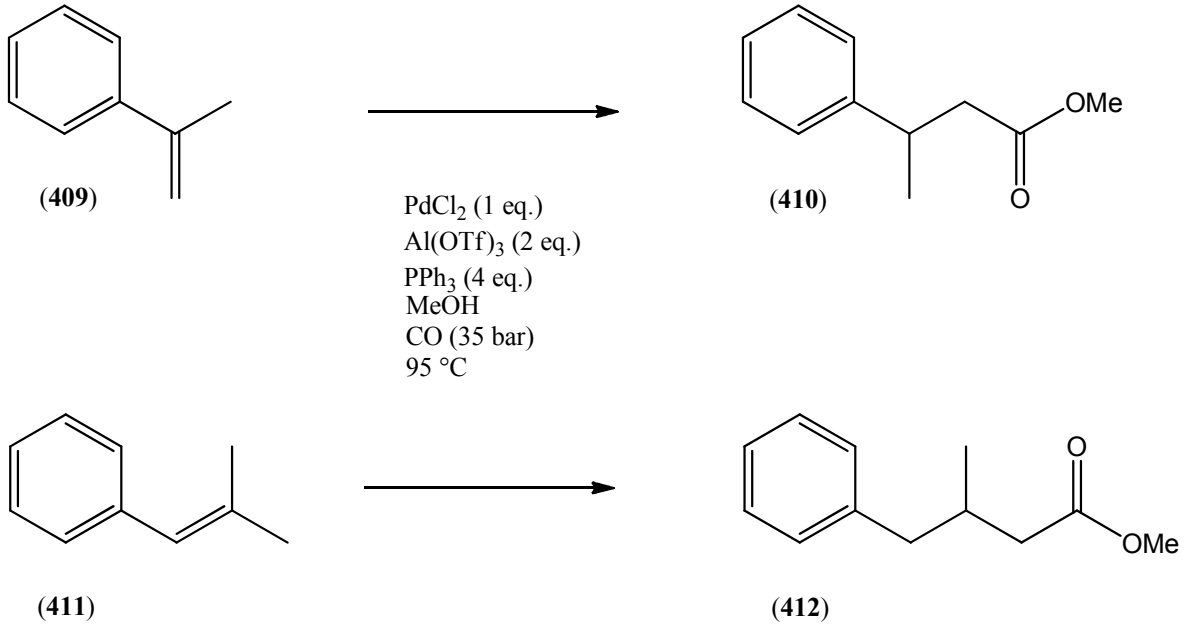


Figure 4-26: Methoxycarbonylation of *α*-methylstyrene and 2-methyl-1-phenylprop-1-ene

Similar to what was found for *trans*-*β*-methylstyrene (**405**), the formation of methyl 3-methyl-4-phenylbutanoate (**412**) during the methoxycarbonylation of 2-methyl-1-phenylprop-1-ene (**411**) can be explained by palladium catalyzed migration of the double bond to the sterically least hindered *α*-position before the actual carbonylation reaction occurred. After isomerisation of the double bond of 2-methyl-1-phenylprop-1-ene (**411**), both substrates, (**409**) and (**411**), would contain a 1,1-disubstituted alkene moiety, which despite being *α*-olefinic in nature gave conversions (38 and 22 %, respectively) far lower than what was found for *trans*-*β*-methylstyrene (**405**) (90 %). It can therefore be concluded that a 1,1-disubstituted double bond is sterically far more demanding with respect to hydroesterification reactions than a 1,2-disubstituted double bond.

4.3.7. Influence of ring substituents on methoxycarbonylation of *trans*-*β*-methylstyrene

Since the original idea of influencing the direction of methoxycarbonylation by electronic effects would involve the addition of EDGs, like methoxy or other oxygenated substituents, to one ring of the stilbene and EWGs to the other ring (*cf.* Paragraph 4.1), it was decided at this point to also investigate whether the presence of a methoxy group would have any enhancing effect on the reactivity of the substrate when compared to *trans*-*β*-methylstyrene (**405**). *Trans*-anethole (**413**), the *p*-methoxy equivalent of *trans*-*β*-methylstyrene (**405**), was therefore subjected to methoxycarbonylation under the conditions optimized for *trans*-*β*-methylstyrene (**405**) (Figure 4-27).

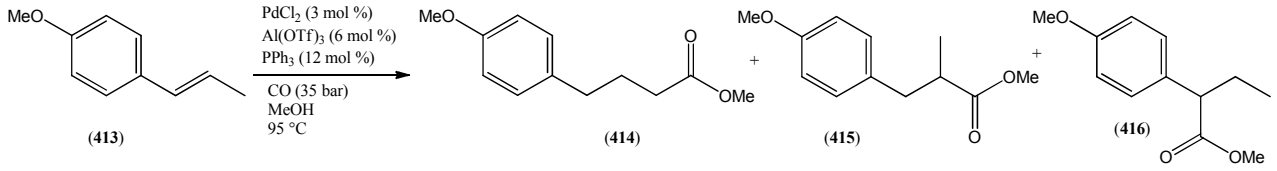
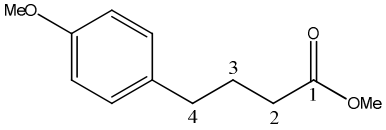
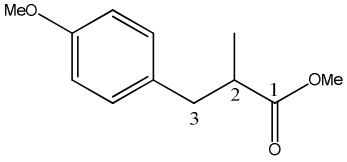
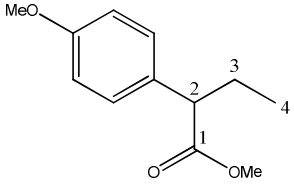


Figure 4-27: Methoxycarbonylation of *trans*-anethole

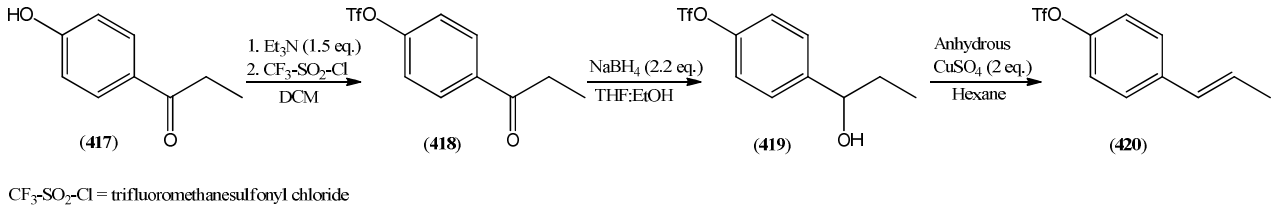
In agreement with the results obtained for *trans*-*β*-methylstyrene (**405**), this substrate (**413**) also gave three products, *i.e.* methyl 4-(4'-methoxyphenyl)butanoate (**414**), methyl 2-methyl-3-(4'-methoxyphenyl)propanoate (**415**) and methyl 2-(4'-methoxyphenyl)butanoate (**416**), albeit in much lower yield (only 21 % *vs.* 90 % for *trans*-*β*-methylstyrene). Purification by FCC (H:T:A 4:4:2) gave the three products, (**414**), (**415**) and (**416**) (R_f = 0.70), as a mixture in which the structures of the individual products could be completely elucidated by ^{1}H NMR (Plate 28a, Table 4-12) and MS analysis [*m/z* 208 (M^+, 26 %), 208 (M^+, 11 %) and 208 (M^+, 21 %), respectively].

Table 4-12: ^{1}H NMR resonances of methyl 4-(4'-methoxyphenyl)butanoate, methyl 2-methyl-3-(4'-methoxyphenyl)propanoate and methyl 2-(4'-methoxyphenyl)butanoate

Proton						
	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)
2	2.32	t, 7.54	2.72-2.66	m	3.40	t, 7.71
3	1.92	p, 7.54	2.96	dd, 6.93 and 13.53	2.09-2.03	m
3a/b			2.62	dd, 7.68 and 13.53	1.80-1.73	m
4	2.59	t, 7.54	-	-	0.87	t, 7.36
Ph-OMe	3.79	s	3.79	s	3.79	s
CO-OMe	3.66	s	3.64	s	3.65	s
2-Me	-	-	1.14	d, 6.92	-	-

While it was expected that a change in the electronic environment of the double bond in the substrate would have an effect on the reactivity of the functional group, it was suspected that a more electron rich double bond would lead to enhanced reaction rates, so the decrease in conversion came as a surprise. In order to validate the result that electron-donating substituents

would in fact lead to less reactive substrates, it was decided to subject an equivalent substrate having an electron-withdrawing substituent to the methoxycarbonylation reaction. Since *trans*-*β*-methylstyrene containing a *p*-hydroxy substituent, that could be converted to an analogue with an electron deficient aromatic ring, like a triflate ester, was not available commercially, this compound had to be prepared and it was envisaged that it could be prepared by esterification followed by reductive elimination of the benzylic hydroxy group from readily available *p*-hydroxypropiophenone (**417**). *p*-Hydroxypropiophenone (**417**) was therefore reacted with trifluoromethanesulfonyl chloride and triethylamine in DCM at room temperature and the crude product was used directly in the subsequent $NaBH_4$ reduction, followed by $CuSO_4$ catalysed elimination of water, which led to the desired product, 1-(4'-trifluoromethanesulfonyloxyphenyl)-prop-1-ene (**420**), in 16 % overall yield (Figure 4-28).

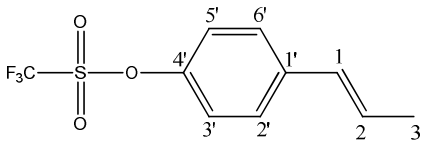


CF_3-SO_2-Cl = trifluoromethanesulfonyl chloride

Figure 4-28: Synthesis of *trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene

The structure of the product, *trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**), was confirmed by ^{1}H NMR (plate 29a) analysis which showed the characteristic vinyl protons at δ 6.39 and 6.27 ppm (J = 15.76 Hz) together with the methyl resonance at δ 1.90 ppm. The presence of the triflate group in the product (**420**) was confirmed by the characteristic CF_3-quartet resonance at δ 118.90 ppm (J = 320.94 Hz) in the ^{13}C NMR (Plate 29b) spectrum (Table 4-13). The molecular ion observed at *m/z* 267.0298 (M^+) by TOF-MS-AP analysis in positive mode was also indicative of the product (**420**) structure.

Table 4-13: Important ^{1}H and ^{13}C NMR resonances in the spectra of *trans*-1-(4'-trifluoromethane-sulfonyloxyphenyl)prop-1-ene

Structure			
H/C	δ_H (ppm)	*J* (Hz)	δ_C (ppm) *J* (Hz)
1	6.39	dd, 1.65 and 15.76	129.37
2	6.27	dq, 6.59 and 15.76	128.27
3	1.90	dd, 1.65 and 6.59	18.60
$-CF_3$	-	q, 320.94	118.90

The subsequent methoxycarbonylation of *trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**) in THF:MeOH (1:1) indeed gave an improved conversion of 31 % (Figure 4-29) when compared to the reaction of *trans*-anethole (**413**).

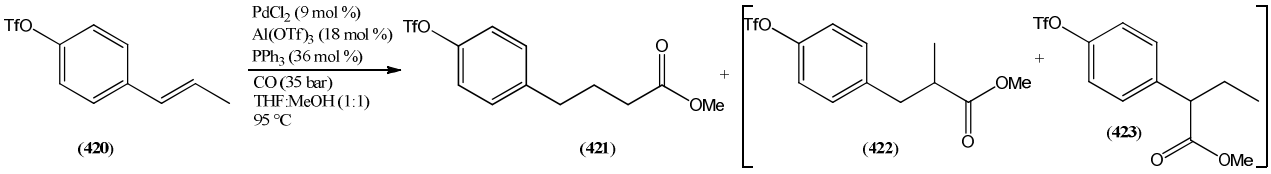


Figure 4-29: Methoxycarbonylation of *trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene

Although three products *i.e.* methyl 4-(4'-trifluoromethanesulfonyloxyphenyl)butanoate (**421**), methyl 2-methyl-3-(4'-trifluoromethanesulfonyloxyphenyl)propanoate (**422**) and methyl 2-(4'-trifluoromethanesulfonyloxyphenyl)butanoate (**423**), were expected from the reaction, preparative TLC purification (H:T 1:1) of the reaction mixture led to the isolation of methyl 4-(4'-trifluoromethanesulfonyloxyphenyl)butanoate (**421**), with only traces of the other two isomers being present. The structure of the product was confirmed by ^{1}H NMR (Plate 30a) where the spectrum showed the characteristic two methylene groups as triplets, at δ 2.68 (*J* = 7.55 Hz), 2.34 (*J* = 7.55 Hz) and the other methylene group as a pentet at δ 1.96 ppm (*J* = 7.55 Hz) together with the expected methoxy signal (δ 3.67 ppm) and aromatic resonances (δ 7.26 and 7.19 ppm). The presence of the triflate group as well as the ester carbonyl group was confirmed by resonances at δ 118.88 (q, *J* = 320.9 Hz) and 173.78 ppm, respectively, in the ^{13}C NMR spectrum (Plate 30b), while the presence of the ester carbonyl was also evident from a distinctive C=O absorbance at 1714 cm^{-1} in the IR spectrum. MS analysis revealed a molecular ion at *m/z* 326 (M^{+}, 11 %) to

finally establish the structure of the product as methyl 4-(4'-trifluoromethanesulfonyloxyphenyl)-butanoate (**421**).

While an improvement in conversion was observed for the methoxycarbonylation of the deactivated substrate (**420**), it was still lower than the value found for *trans*-*β*-methylstyrene (**405**) itself (90 %), so the results from the activation/deactivation study were still inconclusive and it was not absolutely clear what the effect of activation or deactivation is. Since a decrease in conversion was also found for 2-methoxystilbene (*cf.* Paragraph 4.5.) when compared to unsubstituted stilbene (*cf.* Paragraph 4.5.) the idea arose that the methoxy substituent itself, rather than the activating effect it has on the reactivity of the substrate, might be cause of the decline in conversion. In order to assess this possibility, the methoxycarbonylation of *trans*-*β*-methylstyrene (**405**) in methanol as solvent, was repeated in the presence of anisole (methoxybenzene) (1:1 ratio of *trans*-*β*-methylstyrene:anisole). Since only trace amounts of products (*vs.* 90 %) were observed by GCMS analysis, it could be concluded that, despite the fact that methoxycarbonylation reactions have been reported in ether solvents (*cf.* Table 4-9), an aromatic methoxy substituent has an inhibiting effect on the methoxycarbonylation reaction, probably through complexation/ interaction of the methoxy group with the palladium catalyst. This theory was supported by research done by the Williams group[21] who found that an ether moiety near the reactive double bond causes a decrease in methoxycarbonylation conversion values, this effect diminishes as the ether moiety is moved farther away from the double bond. In an attempt to determine whether this in fact is the case and to investigate the real effect of an electron-donating substituent on the reaction, it was decided to subject a substrate with a bulky silylether substituent, in irder to prevent any complexation of palladium to the ether oxygen function, to the methoxycarbonylation reaction.

By repeating the reaction sequence for the preparation of the triflate substituted *trans*-*β*-methylstyrene (**405**) on *p*-hydroxypropiophenone (**417**), the silylated styrene (**426**) was obtained in a good overall yield of 48 % (Figure 4-30).

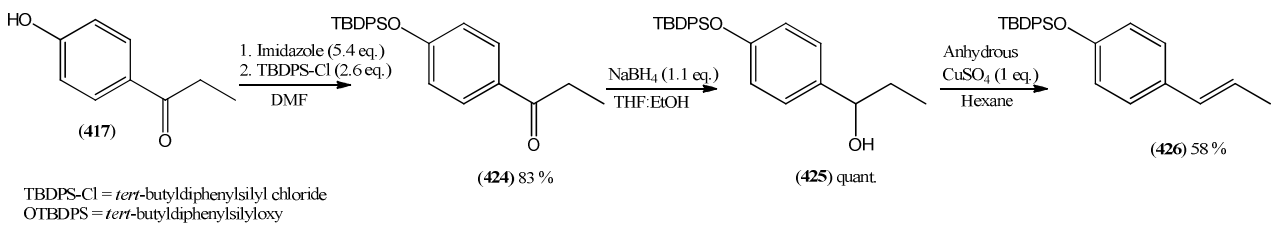
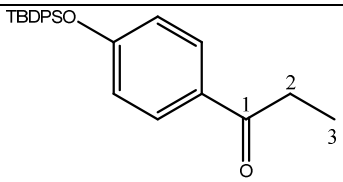
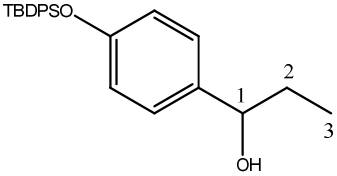
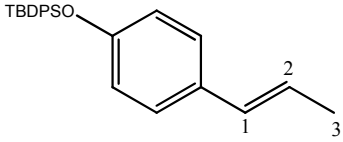


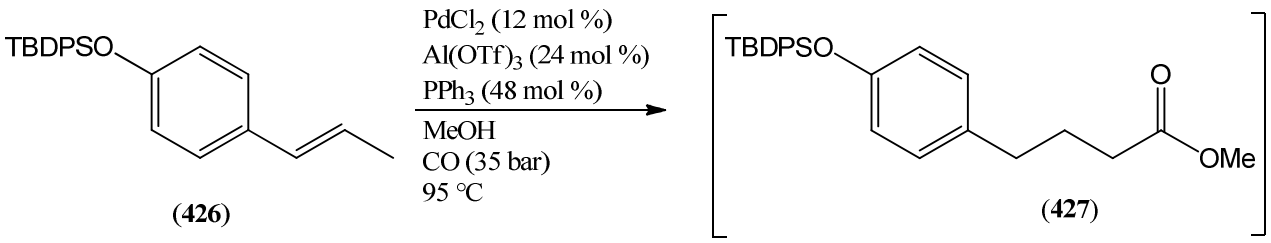
Figure 4-30: Synthesis of *trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene

The structures of the intermediates (**424**) and (**425**) and the final product (**426**) were confirmed by ^{1}H (plate 31a, 32a and 33a) and ^{13}C NMR (plate 31b, 32b and 33b) spectroscopy (Table 4-14), as well as MS analysis where the molecular ions were observed at *m/z* 390 (M^+, 2 %), 413.1913 (M^+ +Na) and 395.1810 (M^+), respectively.

Table 4-14: Significant ^{1}H and ^{13}C NMR resonances in the spectra of 1-(4'-*t*-butyldiphenylsilyloxy-phenyl)propan-1-one, 1-(4'-*t*-butyldiphenylsilyloxyphenyl)propan-1-ol and *trans*-1-(4'-*t*-butyldiphenyl-silyloxyphenyl)prop-1-ene

						
H/C	δ_H (ppm) (*J*)	δ_C (ppm)	δ_H (ppm) (*J*)	δ_C (ppm)	δ_H (ppm) (*J*)	δ_C (ppm)
Plate nr	31a	31b	32a	32b	33a	33b
1	-	199.78	4.46, (t, 6.67 Hz)	75.68	6.29 (dd, 15.70 and 1.64 Hz)	130.53
2 2b	2.88, (q, 7.27 Hz)	31.49	1.81-1.74 (m) 1.71-1.64 (m)	31.72	6.05 (dd, 15.70 and 6.64 Hz)	123.60
3	1.16 (t, 7.27 Hz)	8.50	0.86 (t, 7.42 Hz)	10.31	1.83 (dd, 6.64 and 1.64 Hz)	18.53
$-(CH_3)_3$	1.10 (s)	26.52	1.14 (s)	26.57	1.12 (s)	26.64
$-\underline{C}(CH_3)_3$	-	19.58	-	19.57	-	19.59

Since *trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**) did not dissolve in pure methanol, the methoxycarbonylation in this instance was performed in MeOH:toluene (5:1) (Figure 4-31), but only *ca.* 5 % conversion to what looked like methyl 4-(4'-*tert*-butyldiphenyl-silyloxyphenyl)butanoate (**427**) was found.



(426) **(427)**

OTBDPS = *tert*-butyldiphenylsilyloxy

Figure 4-31: Methoxycarbonylation of 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene

Although methoxycarbonylation reactions in mixed solvent systems containing only a fraction of methanol in general gave lower yields than pure MeOH, (*cf.* Table 4-9), the fact that almost no product was found for the reaction of silylated *trans*-*β*-methylstyrene (**405**) can be viewed as an indication that oxygenation on the aromatic ring indeed leads to deactivation of the double bond with respect to palladium catalysed hydroesterification reactions of conjugated alkene systems. It can thus be concluded that an electron-withdrawing substituent on the aromatic ring, such as triflate, indeed have a positive effect on the methoxycarbonylation reaction when compared to oxygen containing electron-donating substituents [31 % conversion for (**420**) *vs.* 5 % for (**426**)]. Although exciting yields were not obtained with the methoxycarbonylation of oxygenated substrates, it must be taken into account that the conditions were not optimized for those substrates, so it was decided to continue with the investigation and come back to this aspect of the technology at a later stage.

4.4. Aminocarbonylation/Hydroamidation

Since chiral induction during the enantioselective synthesis of isoflavonoids have been achieved through utilization of amide chiral auxiliaries, like 2-imidazolidinones (**136**)[22] (*cf.* Figure 2-13), it was at this point decided to investigate the possibility of transforming an alkene into an amide in a one-step reaction and avoid amidation of the ester functionality that would be available through hydroesterification (alkoxycarbonylation). If a chiral amide type reagent could be used during the functionalization of the stilbene substrate, this would, on top of a chiral catalyst system, open up another avenue for chiral induction during the enantioselective synthesis of isoflavonoids (Figure 4-32).

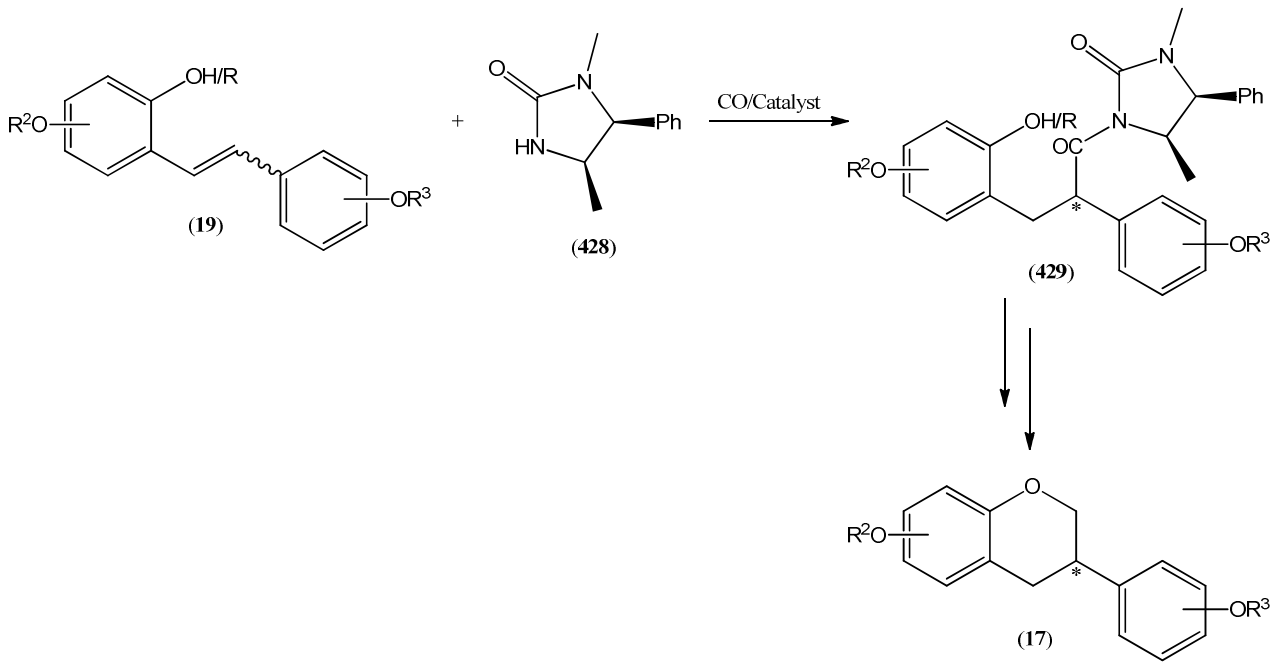


Figure 4-32: Possible enantioselective synthesis of isoflavonoids

Although the term hydroamidation is widely reported on in literature,[23,24,25,26,27,28,29,30] it usually refers to a reaction where an amide is attached to an alkene/alkyne through its nitrogen or carbon atom and the CO-moiety in the product comes inherently from the amide substrate and is not introduced through a carbonylation process (Figure 4-33).

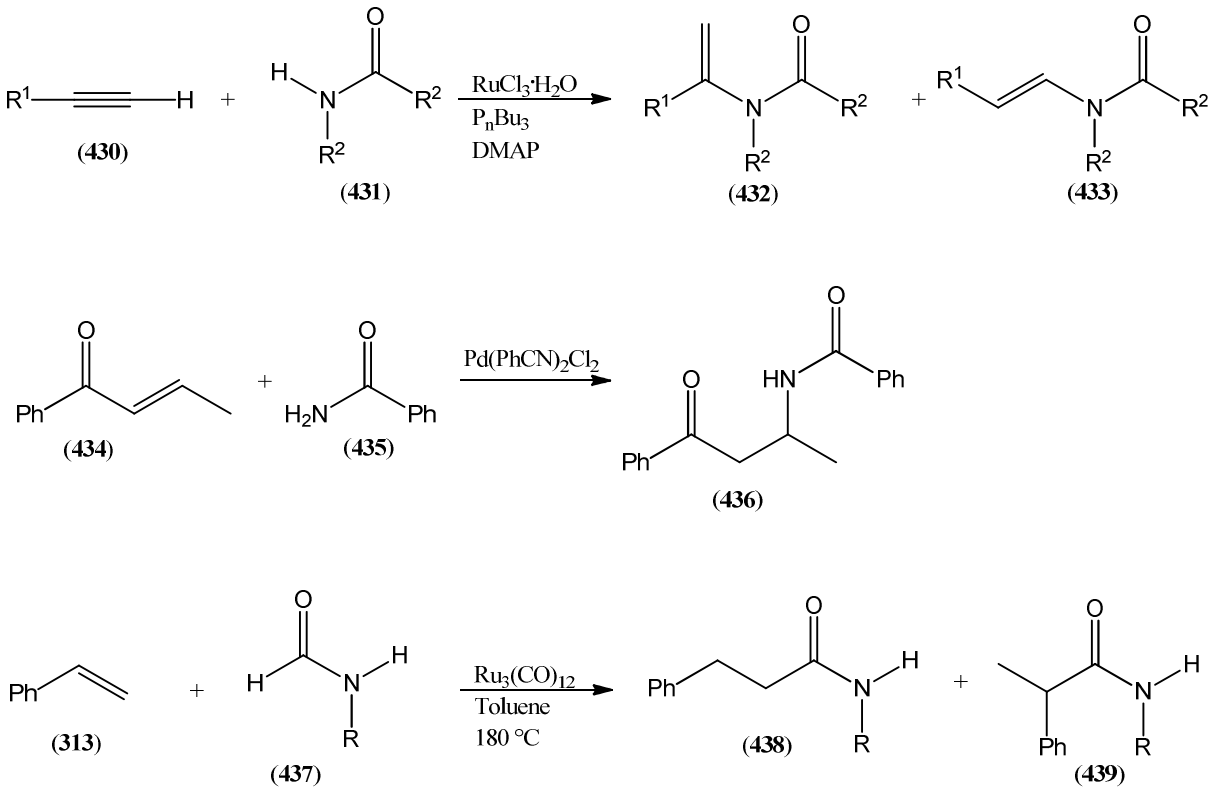


Figure 4-33: Examples of hydroamidation reactions reported in literature

While the idea of aminocarbonylation (hydroamidation) where an amine could be used as nucleophile during a 'hydroesterification type' reaction seems logical, literature revealed only one instance where a ruthenium catalyzed aminocarbonylation ('true' hydroamidation) reaction has been reported on (Figure 4-34).[31]

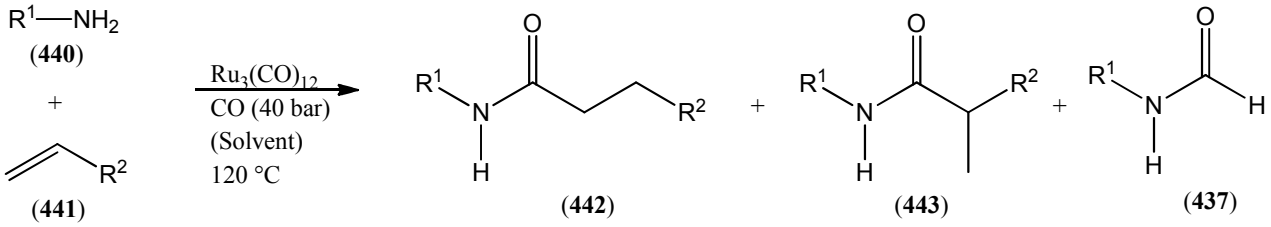


Figure 4-34: Example of the only aminocarbonylation reaction reported in literature

Trans-*β*-methylstyrene (**405**) was therefore subjected to the methoxycarbonylation conditions developed previously, but in an inert solvent (THF) containing aniline as model nucleophile. Since the acid/Lewis acid co-catalyst usually present during hydroesterification reactions could, in principle, react with and deactivate the nitrogen nucleophile (aniline), the $Al(OTf)_3$ was omitted in the first attempt. No product formation could, however, be detected (GCMS), even after 22 hours of reaction time. Acknowledging the important role of an acid promoter in the hydroesterification process where it is involved in the activation of the alcohol towards oxidative addition (*cf.* Paragraph 4.3.1.), a second attempt followed in which $Al(OTf)_3$ was added to the reaction mixture (Figure 4-35) and 53 % conversion to *N*,2-diphenylbutanamide (**444A**) and 2-methyl-*N*,3-diphenylpropanamide (**444B**) in a 6:1 ratio, which were isolated as a mixture of isomers after FCC purification (H:T:A 4:4:2), was obtained (Figure 4-35).

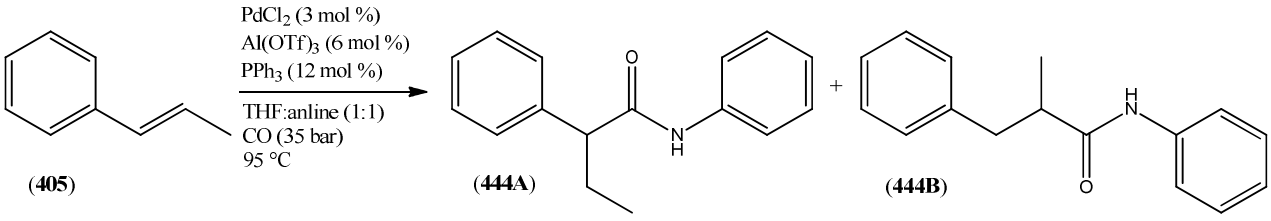
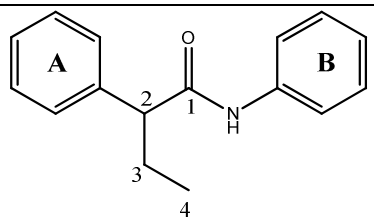
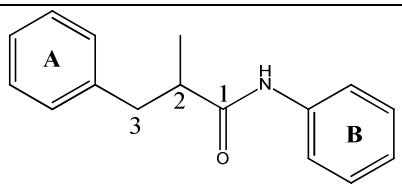


Figure 4-35: Aminocarbonylation of *trans*-*β*-methylstyrene

The structures of *N*,2-diphenylbutanamide (**444A**) and 2-methyl-*N*,3-diphenylpropanamide (**444B**) was confirmed by ^{1}H (Plate 34a) and ^{13}C (Plate 34c) NMR spectroscopy of the mixture of isomers (Table 4-15) as well as IR spectroscopy [ν_{max} (C=O) = 1654 cm^{-1}] and GCMS analysis which displayed the molecular ions at *m/z* 239 (M^+, 30 %) and 239 (M^+, 31 %), respectively.

Table 4-15: ^{1}H and ^{13}C NMR resonances of *N*,2-diphenylbutanamide and 2-methyl-*N*,3-diphenylpropanamide

Structure						
H/C	δ_H (ppm), (#H)	*J* (Hz)	δ_C (ppm)	δ_H (ppm), (#H)	*J* (Hz)	δ_C (ppm)
1	-	-	171.87			174.06
2	3.40 (1H)	t, 7.55	56.25	2.63-2.57 (0.15H)	m	-
3a/b 3a/b	2.31-2.23 (1H) 1.90-1.83 (1H)	m m	26.53	3.03 (0.15H) 2.76 (0.15H)	8.52 and 13.55 6.33 and 13.55	-
4	0.92 (3H)	t, 7.38	12.47	-	-	-
2-CH_3	-	-	-	1.28 (0.5H)	d, 6.79	-

While the possibility of ring-B being attached the other way around leading to a ketone-amine molecule (with C=O resonating at δ 197.5 ppm)[32] could not be ignored, the chemical shift on the ^{13}C NMR spectrum of a similar amide C=O moiety, that of *N*,2-diphenylacetamide, is reported in literature[33] as 169.3 ppm which does not differ significantly from the δ 171.87 ppm where the C=O peak of our product (**444A**) resonates. Another argument in favour of the amide structure came from the IR spectrum where the C=O group in *N*,2-diphenylacetamide absorbs at 1655 cm^{-1} (according to literature[33]), while the C=O absorbance of product (**444A**) was detected at 1654 cm^{-1}. These facts indeed confirmed *N*,2-diphenylbutanamide (**444A**) to be the major product from the reaction.

Encouraged by the success of the first palladium catalysed aminocarbonylation reaction, the issue of the high aniline concentration used during the reaction was subsequently addressed. Lowering the *trans*-*β*-methylstyrene:aniline ratio from 1:9 to 1:5, however, resulted in a considerable drop in conversion from 53 % to 15 %. In order to determine the scope and limitations of the new reaction and move closer to the type of reagents visualized as substrates in the enantioselective synthesis of isoflavonoids (*vide supra*), benzamide was subjected to the reaction as the second substrate to be evaluated. Unfortunately, due to the insolubility of benzamide in THF, the ratio of *trans*-*β*-

methylstyrene:benzamide could not be increased beyond 1:3, with the consequence that no product formation could be detected by GCMS analysis. Although the failure of the benzamide reaction could probably be ascribed to solubility issues, it could also be due to the decreased nucleophilicity of the N-atom in the substrate, so *n*-butylamine and piperidine were selected as the next two substrates to be exposed to the new palladium catalysed aminocarbonylation reaction. No product formation could, however, be detected by GCMS, so it became clear that a considerable amount of additional research is needed to come to a full understanding of this novel reaction and fully develop it into viable methodology in Organic synthesis. Attention was therefore reverted back to the original goal of the investigation, *i.e.* the development of methoxycarbonylation methodology for the synthesis of isoflavonoids and thus the methoxycarbonylation of stilbenes.

4.5. Methoxycarbonylation of stilbenes

Due to the fact that the solubility of *trans*-stilbene (**384**) in methanol and even ethanol appeared to be rather low and the low conversion obtained with this substrate (*cf.* Paragraph 4.3.3.) could possibly be ascribed to this aspect, it was decided to continue the investigation on the methoxycarbonylation of stilbenes by subjecting *cis*-stilbene (**445**), a liquid at room temperature, to the optimized methoxycarbonylation conditions [$PdCl_2$/$Al(OTf)_3$/PPh_3 catalyst system, CO (35 bar), 95 °C] in methanol. Only isomerization to *trans*-stilbene was however, observed. Since it was found during the solvent studies with *trans*-*β*-methylstyrene (**405**) that acceptable methoxycarbonylation reactions could also be performed in methanol-THF mixtures and it was determined that a 1:1 solution of MeOH:THF would completely dissolve *trans*-stilbene, the reactions with both *trans*- (**384**) and *cis*-stilbene (**445**) were repeated in this solvent system (Figure 4-36). Although a yellow reaction mixture, indicating high Pd-catalyst concentration and no Pd(0) 'fall-out', was observed during both reactions, disappointingly low conversions of only 1 and 4 %, respectively, were obtained.

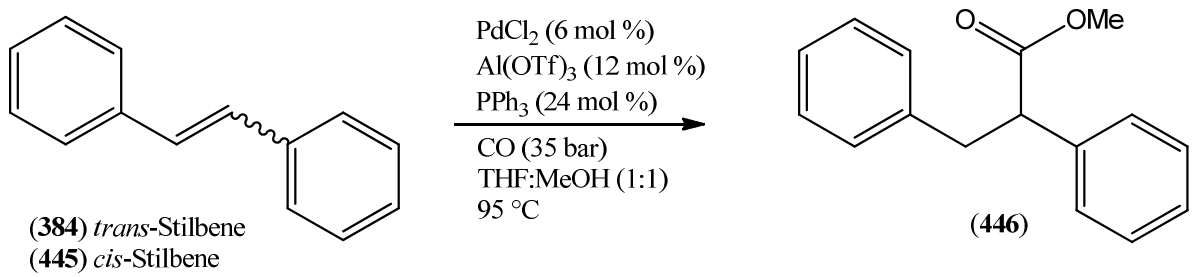


Figure 4-36: Methoxy carbonylation of stilbene

Since Williams *et al.*[21] reported a combination of a Lewis acid and a Bronsted acid, as activator/co-catalyst, to be beneficial to the hydroesterification reaction, this option was investigated as last resort to obtain decent yields and conversions during the methoxycarbonylation of stilbenes. The reaction of *trans*-stilbene (**384**), as described in Figure 4-36, was therefore repeated with the addition of *p*-TsOH (12 mol %) as well as $Al(OTf)_3$ (12 mol %) to the reaction mixture, but this change in co-catalyst also led to no improvement in conversion and yield.

As it was, at this point, clear that the utilization of mixed solvent systems has a detrimental effect on conversions, and methoxy substituted stilbenes would be more polar and thus more soluble in methanol than their unsubstituted counterparts, it was decided to switch to the methoxy analogues, e.g. (**330**), in subsequent reactions. Mono-methoxylated stilbenes like (**330**) are also oils, which would assist in proper mixing with the solvent when compared to the unsubstituted equivalents. This led to the methoxycarbonylation of 2-methoxystilbene (**330**) (Figure 4-37), but only 3 % conversion to what looked like methyl 3-(2'-methoxyphenyl)-2-phenylpropanoate (**447**) and methyl 2-(2'-methoxyphenyl)-3-phenylpropanoate (**448**) was found upon GCMS analysis of the reaction mixture.

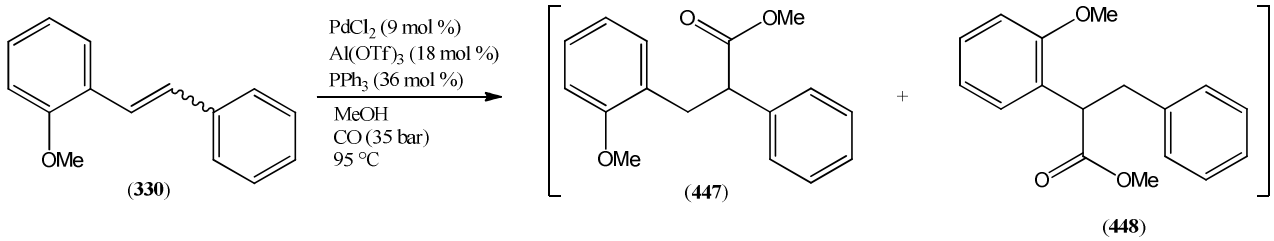


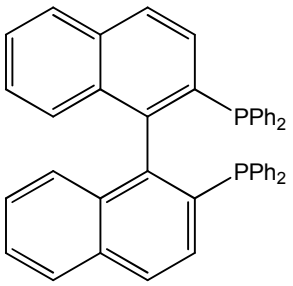
Figure 4-37: Methoxycarbonylation of methoxy substituted stilbenes

Although other activating substituents on the aromatic rings, like silyl ethers, could be introduced and evaluated to see if the conversion could not be improved, the model reactions performed on *trans*-*β*-methylstyrene (**405**) already indicated the conversion for methoxy substituted substrates to be very similar to that of the silyl ether analogues (21 % *vs.* 5 %; *cf.* Paragraph 4.3.7.), so it was doubtful if this would be a solution to the problem. Furthermore, since the basic idea for utilizing methoxycarbonylation as a way of synthesizing isoflavonoids was based on the difference in reactivity between an activated and a deactivated aromatic ring and triflate substituted aromatic compounds also did not give yields as high as the unsubstituted analogues, it was at this stage decided that the overall conversion for stilbene substrates were too low and that more efficient catalysts and conditions should first be found for stilbene substrates. Since the model substrate, *trans*-*β*-methylstyrene (**405**), gave acceptable conversions, it was concluded that the problem with

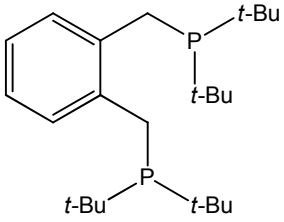
the methoxycarbonylation of stilbenes must be related to the inherent steric and/or electronic properties of these substrates. While it is generally accepted that the steric bulk of a phenyl ring can be considered to be almost the same as that of a methyl group and the only difference between *trans*-*β*-methylstyrene (**405**) and *trans*-stilbene (**384**) would be in that respect, it seemed unlikely that the cause of the differences in reactivity between these two substrates could be originating in the steric aspect of the stilbene structure. It was nevertheless decided to investigate the utilization of sterically less demanding catalysts, like those based on bidentate ligands, in the methoxycarbonylation of stilbenes.

4.6. Methoxycarbonylation with bidentate ligands

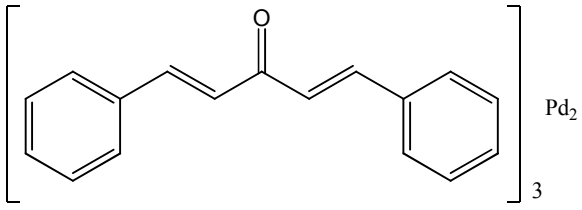
Since bidentate ligands are known for having a higher reactivity than their monodentate counterparts[34] especially towards the hydroesterification of sterically more demanding substrates like branched alkenes, it was decided to evaluate two of the more promising examples of bidentate ligands in the methoxycarbonylation of stilbenes. In this regard, Williams and co-workers[35] reported excellent conversions and yields for the methoxycarbonylation of alkynes like phenylacetylene, with a BINAP (**449**) containing catalyst system [$Pd(OAc)_2$/$Al(OTf)_3$/BINAP], while Cole-Hamilton *et al.*[36] described the utilization of 1,2-bis-(di-*tert*-butylphosphinomethyl)-benzene (DTBPMB) (**450**) together with tris-(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (**451**) as catalyst for the methoxycarbonylation of sterically hindered substrates like 4-methyl-2-pentene and compounds containing internal double bonds, like 4-octene.



(**449**)



(**450**)



(**451**)

In order to verify the published methodology, methoxycarbonylation of phenylacetylene (**452**) with the BINAP containing catalyst system was embarked upon as starting point and the products, methyl 3-phenylprop-2-enoate (**453**) and methyl 2-phenylprop-2-enoate (**454**), identical to those described in literature, obtained in 45 % yield (71 % conversion) and 8:1 ratio after 24 hours of reaction time (Figure 4-38). With the execution of the technology established, *trans*-*β*-methylstyrene (**405**) was subjected to the same reaction conditions and the expected products, methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-

phenylbutanoate (**404**), obtained in a 13:3:1 ratio, albeit in a low yield of only 18 %. Since this yield was considerably lower than what was reachable with the monodentate PPh_3 ligand, the reaction sequence was not extended to *trans*-stilbene, but it was decided to rather evaluate the Cole-Hamilton[36] methodology in the methoxycarbonylation of the envisaged aromatic substrates.

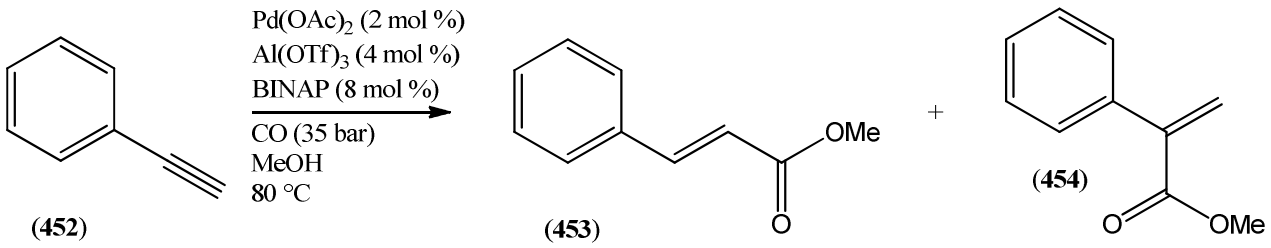


Figure 4-38: Methoxycarbonylation of phenylacetylene over BINAP containing catalyst system

Methoxycarbonylation of 2-octene (**455**) under the catalyst system and conditions as described by the Cole-Hamilton group[36] subsequently led to a 59 % conversion of the starting material to the expected products (Figure 4-39), so the reaction was extended to *trans*-*β*-methylstyrene (**405**). Although a good conversion of 49 % to methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) in a 45:3:1 ratio was found for the model substrate, no product formation could again be detected for the reaction of *trans*-stilbene (**384**) under the same reaction conditions.

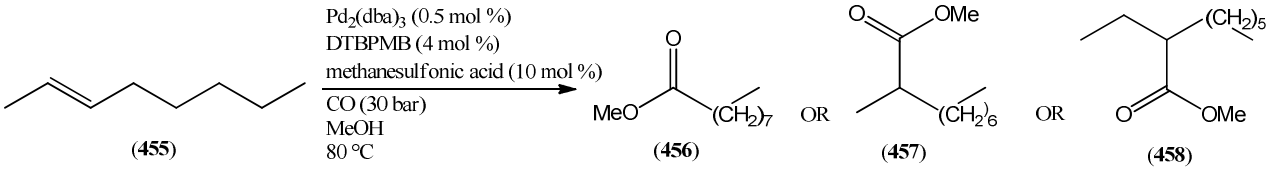


Figure 4-39: Methoxycarbonylation of 2-octene

4.7. Methoxycarbonylation of a non-conjugated alkene

Since strong evidence existed at this point that the difficulties experienced with the methoxycarbonylation of stilbenes were not associated with steric crowding, it was felt that the origin of the low conversions found for stilbene substrates might be in the fact that the double bond is in conjugation with both aromatic rings. In order to determine whether the low conversions and yields experienced could in fact be ascribed to the conjugated system, it was decided to alter the structure of the stilbene by introducing an additional methylene group between the double bond and one of the aromatic rings and thus break the effect of conjugation with minimal

alteration to the steric bulk of the substrate. 1,3-Diphenylprop-1-ene (**451**) was therefore synthesized and subjected to the methoxycarbonylation reaction.

4.7.1. Synthesis of 1,3-diphenylprop-1-ene

Since diphenylacetone (**459**) is commercially available and can easily be reduced to the corresponding alcohol and dehydrated to form the desired alkene product (**451**), this strategy was chosen for the preparation of the required 1,3-diphenylprop-1-ene (**451**) (Figure 4-40).

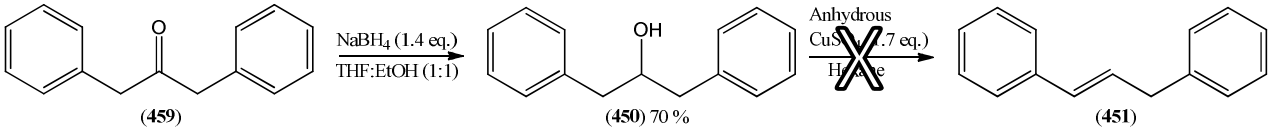


Figure 4-40: Proposed synthesis of 1,3-diphenylprop-1-ene *via* reduction of diphenylacetone

While the $NaBH_4$ reduction of diphenylacetone (**459**) went smoothly and led to the formation of the desired 1,3-diphenylpropan-2-ol (**450**) in 70 % yield, the second step of the envisaged process *i.e.* $CuSO_4$ catalysed dehydration, could not be achieved successfully (Figure 4-40).

The ^1H NMR spectrum (Plate 35a) of the propan-2-ol (**450**) displayed an interesting phenomenon regarding the resonances from the methylene protons. Although H-1 and H-3 were expected to be equivalent and only display coupling to H-2, signals from these protons appeared as two doublets of doublets at δ 2.82 (J = 13.67 and 4.66 Hz) and δ 2.72 ppm (J = 13.67 and 8.19 Hz), respectively. The difference in coupling constants towards H-2 (4.66 and 8.19 Hz) shows that these protons are diastereotopic and can therefore not be chemically equivalent. All the other proton and carbon resonances in the ^1H and ^{13}C NMR spectra (Plate 35a and 35b) were in agreement with the proposed structure which was confirmed by a molecular ion of *m/z* 212 (M^+, 100 %) in the mass spectrum.

Since it was felt that the conditions for water elimination was too mild, a second attempt at this reaction centred around the utilization of the more general conditions of *p*-TsOH in DCM, but this also did not lead to any alkene product, so it was realized that the elimination of the secondary hydroxy function might be more challenging than expected. Although the plethora of other reagents and conditions available for this reaction could have been evaluated, the risk of acid catalysed side reactions, *i.e.* oligomerization of the initially formed alkene, led to a decision to rather change the starting material to the also commercially available chalcone (**452**) that would contain a benzylic hydroxy group to be eliminated in the final step (Figure 4-41).

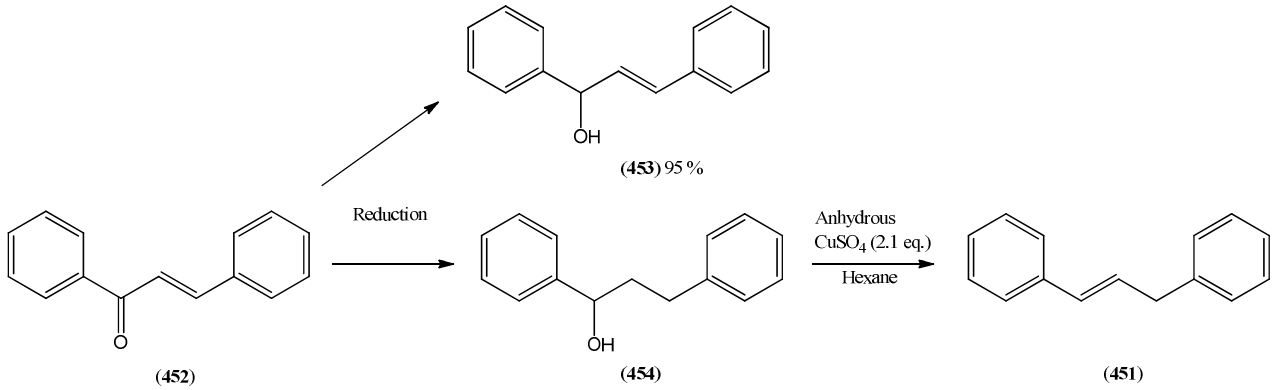


Figure 4-41: Chalcone based route towards 1,3-diphenylprop-1-ene

$NaBH_4$ reduction of a solution of the chalcone in THF:EtOH (1:1), the reagent system known for 1,4-reductions,[37] however, in this instance led to the direct reduction of the carbonyl group with the formation of the unsaturated alcohol, 1,3-diphenylprop-2-en-1-ol (**453**) [^{1}H and ^{13}C NMR spectra (Plate 36a and 36b, respectively)] in 95 % yield. Changing the reduction process to catalytic hydrogenation over 5 % Pd on carbon in ethanol, on the other hand led to the saturated ketone (**455**) [^{1}H and ^{13}C NMR spectra (Plate 37a and 37b, respectively)] being formed in 63 % yield (Figure 4-42). Although increasing the reaction time could probably have solved the problem, over-reduction to the propane remained a threat in this method, so it was decided to rather opt for a two-step process and use $NaBH_4$ as reducing agent for transforming the ketone (**455**) into the desired unsaturated alcohol (**454**). In this instance $NaBH_4$ reduction led to the formation of the desired 1,3-diphenylpropan-1-ol (**454**) [^{1}H and ^{13}C NMR spectra (plate 38a and 38b, respectively)] in 86 % yield (Figure 4-42).

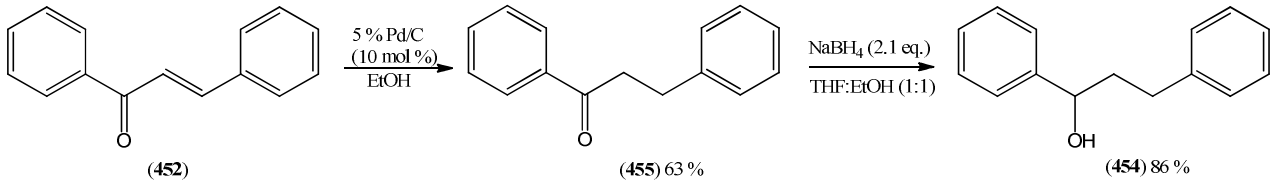


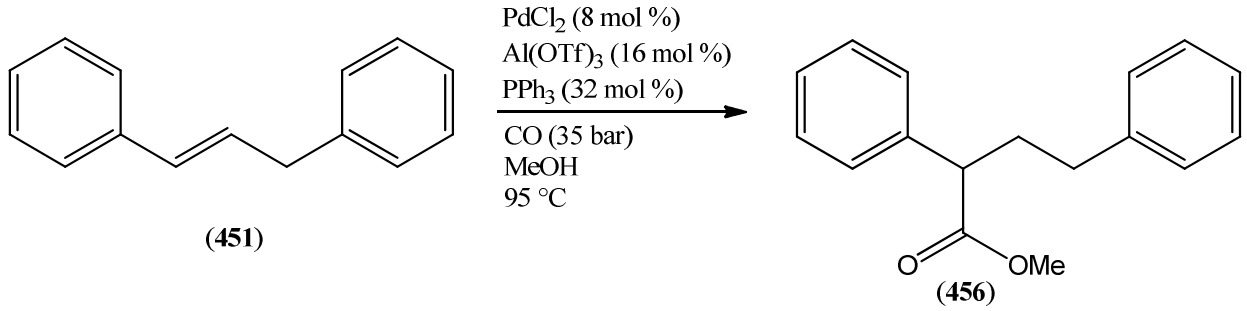
Figure 4-42: Formation of 1,3-diphenylpropan-1-ol

$CuSO_4$ mediated dehydration of the diphenylpropan-1-ol (**454**) now proceeded smoothly and gave the desired propene (**451**) in 35 % yield. The product was characterized by ^{1}H (Plate 39a) and ^{13}C (Plate 39b) NMR where the vinylic protons appeared as a broad doublet at δ 6.44 ppm (J = 15.75 Hz) and a doublet of triplets at δ 6.34 ppm (J = 15.75, 6.82 Hz). The methylene function was observed at δ 3.53 ppm (J = 6.82 Hz), while the carbon spectrum displayed resonances from the

vinyl system and methylene group at δ 131.19, 129.34 and 39.47 ppm, respectively. The structure of 1,3-diphenylprop-1-ene (**451**) was finally confirmed by MS analysis which indicated the molecular ion at *m/z* 194 (M^+, 100 %).

4.7.2. Methoxycarbonylation of 1,3-diphenylprop-1-ene

With the envisaged 1,3-diphenylprop-1-ene (**451**) in hand, attention was subsequently turned towards methoxycarbonylation of this compound. The substrate (**451**) was therefore subjected to the optimized methoxycarbonylation reaction conditions as determined for *trans*-*β*-methylstyrene (**405**) and methyl 2,4-diphenylbutanoate (**456**) obtained as an orange oil in 27 % yield after FCC (H:A 8:2) purification (Figure 4-43).



(451) **(456)**

Figure 4-43: Methoxycarbonylation of 1,3-diphenylprop-1-ene

The structure of methyl 2,4-diphenylbutanoate (**456**) (R_f 0.54) was confirmed by ^{1}H NMR (Plate 40a) where resonances from the methoxy group and a 4 substituted C-2 branched butanoate function were clearly visible [δ_H 3.63 (3H, s, -OMe), 3.56 (1H, t, *J* = 7.65 Hz, H-2), 2.56 (2H, t, *J* = 7.76 Hz, H-4), 2.44-2.38 (1H, m, H-3a or H-3b) and 2.13-2.07 (1H, m, H-3a or H-3b)]. Final structural proof came from the ^{13}C NMR spectrum (Plate 40b) where the C=O resonance was observed at δ 174.40 ppm, as well as mass spectral analysis which indicated the molecular ion at *m/z* 254 (M^+, 2 %).

While it was found that the carboxylate moiety in this reaction is preferentially attached to the carbon next to the aromatic ring of the 1,3-diphenylprop-1-ene (**451**) substrate *vs.* formation of the linear product (**401**), *i.e.* carboxylate group at the 3rd carbon from the aromatic ring, as major isomer during the methoxycarbonylation of *trans*-*β*-methylstyrene (**405**) (*cf.* Figure 4-23), it must be kept in mind that the migration of the double bond in the case of the 1,3-diphenylpropene (**451**) would lead to a product identical to that formed from the starting material. The fact that the 2,4-diphenylbutanoate (**456**) is formed as the only product, can therefore not be taken as an indication of the absence of isomerization during this reaction. The formation of only 2,4-diphenylbutanoate

(**456**) also points towards a mechanism for the reaction where the hydride from the palladium is preferentially transferred to the least stable carbocation intermediate during the migratory insertion step where the alkene is attached to the metal (*cf.* Figure 4-21).

Finally, the fact that a moderate conversion (37 %) was obtained during the reaction in this instance *vs.* less than 4 % for the stilbene equivalents, (**384**) and (**445**), confirms that the electronic structure of stilbenes, where the double bond is in conjugation with the two aromatic rings, is the major cause of the poor methoxycarbonylation reactions observed for these compounds.

4.8. Conclusions and Future Work

While several methods for the preparation of oxygenated benzyltriphenylphosphonium salts, required for the preparation of stilbenes, have been evaluated, only conversion of the benzyl halides by reaction with PPh_3 led to formation of the corresponding phosphonium salts in acceptable yields (76-98 %). This methodology was, however, hampered by difficulties in the handling of the oxygenated benzyl halides, which led to average overall yields for the phosphonium salts of only 45 % being found. Application of the standard Wittig reaction conditions (BuLi/THF) to the preparation of oxygenated stilbenes gave the expected products in only *ca.* 30 % yield. Although switching to an organic-aqueous biphasic solvent system (aldehyde and *aq.* NaOH) led to improved yields (53 and 55 %, respectively) being obtained for the oxygenated stilbenes, *ortho*- and *para*-methoxystilbenes, this was still not acceptable, so the preparation of 4-hydroxystilbene was attempted through a microwave assisted Perkin-type reaction between *p*-hydroxybenzaldehyde and phenylacetic acid in PEG-400. Although an average yield of only 42 % could be achieved, this process proved to be the method of choice for the preparation of oxygenated stilbenes, since neither protection of hydroxy groups on the acid and/or aldehyde starting material is required. Furthermore reaction times are only 10 minutes and the process has the added advantage of it being an environmentally more favourable procedure compared to the Wittig reaction.

Methoxycarbonylation of *trans*-*β*-methylstyrene, as model substrate for stilbenes, led to the conclusion that the generally accepted optimum conditions of 35 bar and 95 ^{o}C, determined for the methoxycarbonylation aliphatic alkenes, are also applicable to alkenes where the double bond happens to be in conjugation with an aromatic ring. $PdCl_2$ [together with $Al(OTf)_3$] was, furthermore, found to be a more reactive catalyst than $Pd(OAc)_2$ in the methoxycarbonylation of substituted styrene-type substrates, while MeOH-THF (1:1) proved to be the best alternative solvent system (to methanol) for reactions involving less polar substrates. Methoxycarbonylation

reactions performed on *α*-methylstyrene and 2-methyl-1-phenylprop-1-ene confirmed this palladium catalysed reaction also to be very sensitive to the steric environment around the double bond, while it was also determined by subjecting *trans*-anethole [1-(4'-methoxyphenyl)-1-propene] and 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene to the reaction conditions that an aromatic methoxy group has an extremely prominent inhibiting effect on the reaction. Substituting methanol with aniline in an inert solvent (THF) during the carbonylation reaction led to the first ever palladium catalysed aminocarbonylation reaction being obtained. While the reaction could not be extended to include other nitrogen nucleophiles at this stage, it must be kept in mind that the reaction conditions were not optimised for an aminocarbonylation reaction, so more work is needed in order to determine the full scope and limitations of this novel process in which amides can be prepared from alkenes in a single step.

While the methoxycarbonylation of several stilbenes were attempted, these substrates proved to be almost un-reactive towards the catalyst system and conditions found to be effective for substituted styrene-like substrates. It was furthermore determined that the lack of reactivity observed for stilbenes could be attributed to the double bond being in conjugation with two aromatic rings, since 1,3-diphenylprop-1-ene, an alkene in which this fully conjugated system has been broken, did not show reactivity properties similar to stilbenes.

Although the ultimate objective of the investigation, *i.e.* development of stilbene-based catalytic methodology for the synthesis of isoflavonoids could not be reached, valuable new information as to the properties of styrene-like substrates with respect to the palladium catalysed methoxycarbonylation reaction was obtained. Since alkynes are known to be more reactive than alkenes with respect to hydroesterification reactions and 1,2-diphenylethyne has been utilized successfully as substrate in methoxycarbonylation reactions, the basic idea of using a C-14 unit as building block in a catalytic process for the synthesis of isoflavonoids could be amended to include this new approach (Scheme Figure 4-44). If an enantioselective process for the reduction of the double bond in intermediate (**458**) could be found, this method could still be adapted to also allow for the enantioselective synthesis of isoflavonoids in a fully catalytic process as was envisaged at the start of this investigation. Catalytic methodology for the preparation of oxygenated alkyne substrates, as well as hydroesterification and reduction of the intermediate alkene analogues (**458**) will therefore form the basis of the candidate's Ph.D. studies. This study will be complemented by a full investigation into the newly discovered palladium catalysed aminocarbonylation reaction.

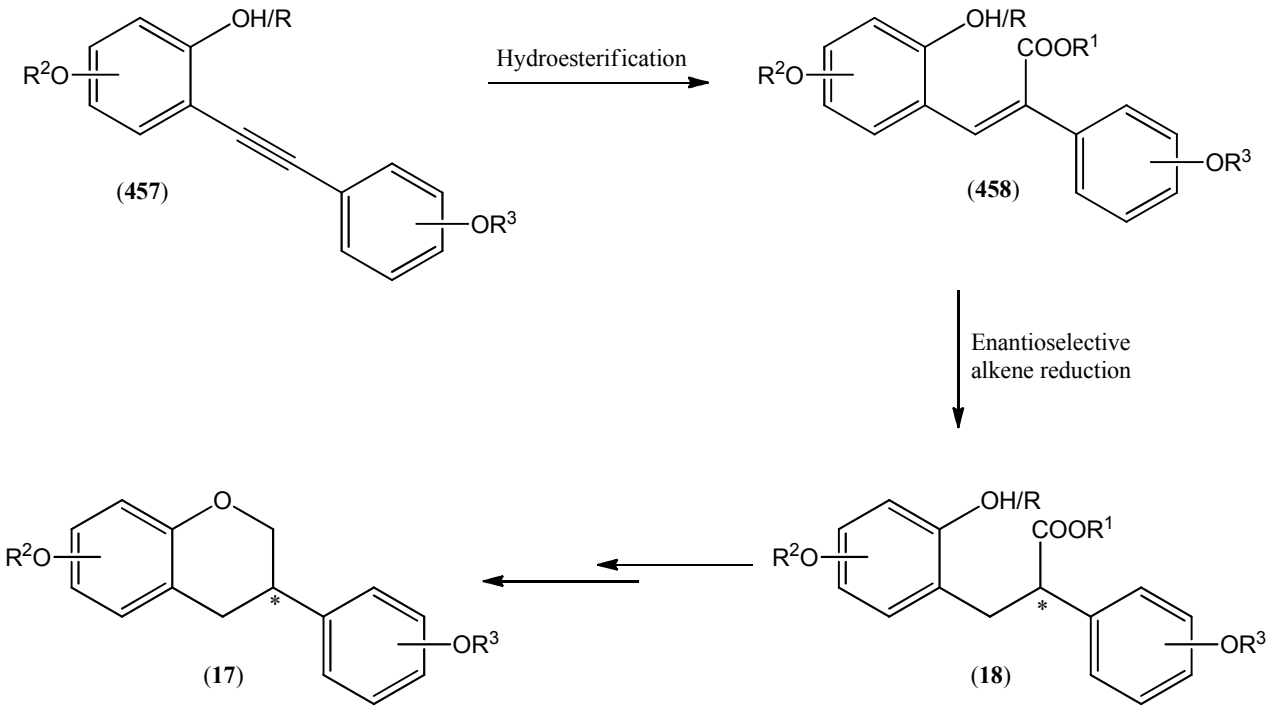


Figure 4-44: Enantioselective synthesis of isoflavonoids *via* alkyne methoxycarbonylation

4.9. References

(1) Morales-Serna, J.; García-Ríos, E.; Bernal, J.; Paleo, E.; Gaviño, R.; Cárdenas, J. *Synthesis* **2011**, *2011*, 1375-1382.

(2) Moiseev, D. V.; James, B. R.; Hu, T. Q. *Inorg. Chem.* **2006**, *45*, 10338-10346.

(3) Mende, V. E. M.Sc. thesis, University of the Free State, Bloemfontein, 2010.

(4) Cvengros, J.; Toma, S.; Marque, S.; Loupy, A. *Can. J. Chem.* **2004**, *82*, 1365-1371.

(5) Versteeg, M. Ph.D. thesis, University of the Free State, Bloemfontein, 1996.

(6) Zhang, W.; Go, M. L. *Eur. J. Med. Chem.* **2007**, *42*, 841-850.

(7) Lee, K. Y.; Kim, J. N. *Bull. Kor. Chem. Soc.* **2000**, *21*, 763-764.

(8) Ramanathan, M.; Hou, D.-R. *Tetrahedron Lett.* **2010**, *51*, 6143-6145.

(9) Aksenov, A. V.; Magedov, I. V.; Smushkevich, Y. I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 759.

(10) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2001; p. 258-274.

(11) McNulty, J.; Das, P. *Eur. J. Org. Chem.* **2009**, *2009*, 4031-4035.

(12) Sharma, A.; Kumar, R.; Sharma, N.; Kumar, V.; Sinha, A. K. *Adv. Synth. Cat.* **2008**, *350*, 2910-2920.

(13) Sinha, A. K.; Kumar, V.; Sharma, A.; Sharma, A.; Kumar, R. *Tetrahedron* **2007**, *63*, 11070-11077.

(14) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435-3456.

(15) Williams, D. B. G.; Shaw, M. L.; Green, M. J.; Holzapfel, C. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 560-563.

(16) Eastham, G. R.; Tooze, R. P.; Heaton, B. T.; Iggo, J. A.; Whyman, R.; Zacchini, S. *Chem. Commun.* **2000**, 609-610.

(17) Drent, E.; Budzelaar, H. M. *Chem. Rev.* **1996**, *96*, 663-681.

(18) Ferreira, A. C.; Crous, R.; Bennie, L.; Meij, A. M. M.; Blann, K.; Bezuidenhoudt, B. C. B.; Young, D. A.; Green, M. J.; Roodt, A. *Angew. Chem.* **2007**, *119*, 2323-2325.

(19) Bezuidenhoudt, B. C. B. Ph.D. thesis, University of the Free State, Bloemfontein, 1985

(20) Diab, L.; Gouygou, M.; Manoury, E.; Kalck, P.; Urrutigoïty, M. *Tetrahedron Lett.* **2008**, *49*, 5186-5189.

(21) Personal communication with Williams, D.B.G.; University of Johannesburg, South Africa.

(22) Versteeg, M.; Bezuidenhoudt, B. C. B.; Ferreira, D.; Swart, K. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1317-1318.

(23) Tsuchikawa, H.; Maekawa, Y.; Katsumura, S. *Org. Lett.* **2012**, *14*, 2326-2329.

(24) Miyazaki, Y.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Chem. Lett.* **2012**, *41*, 298-300.

(25) Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2094-2098.

(26) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070-5071.

(27) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687-2690.

(28) Goossen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4042-4045.

(29) Takasu, K.; Nishida, N.; Ihara, M. *Synlett.* **2004**, 1844-1846.

(30) Nath, D. C. D.; Fellows, C. M.; Kobayashi, T.; Hayashi, T. *Aust. J. Chem.* **2006**, *59*, 218-224.

(31) Tsuji, Y.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1986**, *309*, 333-344.

(32) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987-5990.

(33) Nordstrom, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.

(34) Van Leewen, P. W. N. M. *Homogeneous Catalysis - Understanding the Art*; Kluwer Academic Publishers: London, 2004, p. 109-122, 239-263.

(35) Williams, D. B. G.; Shaw, M. L.; Hughes, T. *Organometallics* **2011**, 4968-4973.

(36) Rodriguez, C. J.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun.* **2004**, 1720-1721.

(37) Van Tonder, J. H. University of the Free State: Bloemfontein, 2008.

EXPERIMENTAL 5

5.1. Chromatography

5.1.1. Thin Layer Chromatography (TLC)

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

5.1.2. Preparative Layer Chromatography (PLC)

PLC was conducted on glass plates (20 cm x 20 cm) coated with a layer (1 mm) of Merck Kieselgel 60 PF_{254} that had been air-dried overnight at room temperature. Eluent was prepared v/v. Crude mixture (15-20 mg) was applied per plate and after development, in the appropriate solvent system, the plates were air-dried in a fume hood. Bands were distinguished by making use of UV light (254 nm) after which the bands were scraped off and the isolated product washed out using acetone or dichloromethane. The solvent was then removed under reduced pressure on a water bath at *ca.* 40 °C.

5.1.3. Flash Column Chromatography (FCC)

FCC was conducted on 100 g of Merck Kieselgel 60 (230-400 mesh) per gram of crude mixture in a glass column. The silica was suspended in the appropriate eluent and packed into a glass column under N_2 pressure (*ca*. 1 bar). The crude mixture was dissolved in a minimum amount of eluent and applied at the top of the column. In the case of low solubility the crude mixture was adsorbed on a minimum amount of silica and loaded on top of the column. The purified products were recovered by elution under N_2 pressure and collected in fractions (*ca.* 10 ml). Clean fractions were combined and concentrated under reduced pressure at *ca*. 40 °C.

5.1.4. Cyclograph Chromatography (CC)

CycloGraph™ Centrifugal Chromatography System was used for CC performed on a round glass plate coated with silica of different thicknesses (2 mm, 4 mm, 6mm 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 in the middle of the rotating cyclograph plate and the UV-light (254 nm)

fluorescing bands were eluted while rotating (700 rpm - 1480 rpm). Clean fractions were combined and concentrated under reduced pressure at *ca*. 40 °C.

5.2. Spectroscopic and Spectrometric Methods

5.2.1. Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR-spectroscopy experiments were performed on a Bruker AM 300 or Bruker AM 600 FT-spectrometer at 293 K, with deuterochloroform ($CDCl_3$) as solvent, unless otherwise specified. Chemical shifts are reported in parts per million (ppm) with the solvent residual peak at 7.26 ppm for proton spectra and 77.16 ppm for carbon spectra on the δ-scale, whereas coupling constants are given in Hz.[1] Standard references added for ^{31}P and ^{19}F NMR experiments are phosphoric acid and hexafluorobenzene which resonates at 0.00 ppm and -164.9 ppm, respectively. The chemical impurity resonating as a singlet at 1.56 ppm in proton spectra is identified as moisture according to Gottlieb *et al*.[1]

5.2.2. Gas Spectroscopy

Gas chromatography was used to follow the methoxycarbonylation reactions utilizing a Shimadzu GC-17A flame induced detector (FID) fitted with a HP-5 column (30 m, 0.32 mm i.d., 0.25 μm film thickness) from Agilent Technologies with nitrogen as carrier gas.

5.2.3. Mass Spectroscopy

Mass spectrometry of compounds and reaction mixtures were performed by means of electron impact (EI) ionization making use of a Shimadzu GC-MS QP-2010 gas chromatograph-mass spectrometer fitted with a DB-5 MS column (30 m, 0.32 mm i.d., 0.25 μm film thickness). Mass spectrometry of certain compounds were performed by means of Matrix Assisted Laser Desorption/Ionization Time-Of-Flight (MALDI-TOF) MS making use of a Bruker Microflex LRF20 either in positive or negative mode with the minimum laser power required to observe signals.

Products formed during methoxycarbonylation reactions were identified using the above mentioned Shimadzu GC-MS QP-2010 instrument utilizing N_2 as carrier gas in linear velocity (27.5 $cm.s^{-1}$) flow control mode. Injections were made in the split mode at 250 °C. The initial column temperature (70 °C) was increased at 5 $°C.min^{-1}$ to 150 °C, kept constant for 2 minutes, followed by further ramping at 7 $°C.min^{-1}$ to 250 °C, holding for 10 minutes. The

retention times (R_T) and conversion values reported were observed using this temperature program.

5.2.4. Infrared Spectroscopy

Fourier transform infrared (FTIR) measurement was performed using a Bruker Tensor 27 IR spectrometer and Pike MIRacle ATR, running OPUS software (Version 1.1).

5.3. Melting Points

Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP 3) apparatus and are uncorrected.

5.4. Microwave Reactor

Microwave irradiated reactions were performed in a CEM® Corporation Discover SP microwave reactor utilizing the dynamic method (variable power). The reaction mixture was irradiated with microwaves to 160 °C (maximum 150 W) for 10 minutes, unless stated the contrary.

5.5. Anhydrous Solvents

Toluene and THF were dried by refluxing over Na under Ar for 12 hours with subsequent fresh distillation under Ar prior to use. Hexane, acetone, CH_3CN, and DCM were dried by filtering through a syringe column of activated neutral aluminium oxide (10 % m/v).[2] Et_3N was dried over potassium hydroxide under Ar atmosphere.

5.6. Standard Procedures

5.6.1. Reaction work-up

Unless specified otherwise, water was added to the reaction mixture and the aqueous phase extracted with EtOAc or Et_2O. The organic layers were combined and washed with water, dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* at *ca*. 40 °C. Subsequent purification afforded the product.

5.6.2. Carbonylation reactions in Parr-reactor

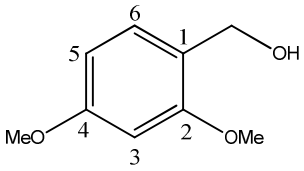
The substrate and catalyst system, (e.g. $Pd(OAc)_2$:$Al(OTf)_3$:PPh_3 1:2:4), were dissolved in the specified solvent, added to the Parr reactor and degassed with CO (x5). The reaction was performed at 95 °C under 35 bar of CO pressure, unless stated otherwise.[19] Aliquots of reaction mixture were analysed by GCMS and conversion values determined. The work-up procedure involved the evaporation of the solvent used and removal of the Pd(0) precipitate if present by filtration.

5.7. Preparation of methoxy substituted benzyl alcohols

5.7.1. General $NaBH_4$ reduction procedure[3]

$NaBH_4$ (1 eq.) was dissolved in THF:EtOH (1:1, 50 ml) and the aldehyde/ketone (1 eq.) added, where after the reaction mixture was stirred at room temperature for 20-60 minutes. After completion of the reaction, followed by TLC, the THF:EtOH solvent mixture was removed under reduced pressure and the residue was washed with acetone (3 x 20 ml), followed by the standard work-up procedure (*cf.* Paragraph 5.6).

5.7.1.1. 2,4-Dimethoxybenzyl alcohol (355)[3]



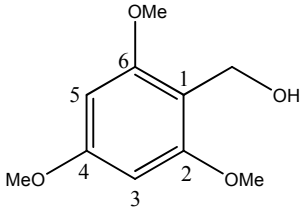
$NaBH_4$ (0.46 g, 12.04 mmol, 1 eq.) and 2,4-dimethoxybenzaldehyde (**359**) (2.00 g, 12.08 mmol) gave the crude mixture which was purified with CC (H:A 8:2) to yield the benzyl alcohol (**355**) (1.89 g, 93 %) as a yellow oil. R_f 0.14 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 1a) δ_H ppm 7.16 (1H, d, J = 8.07 Hz, H-6), 6.45 (1H, d, J = 2.34 Hz, H-3), 6.43 (1H, dd, J = 8.07, 2.34 Hz, H-5), 4.59 (2H, br s, -CH_2-), 3.81 (3H, s, 2-OMe), 3.79 (3H, s, 4-OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 1b) δ_C ppm 160.69 (C-4), 158.60 (C-2), 129.73 (C-6), 121.80 (C-1), 103.84 (C-5), 98.58 (C-3), 61.54 (-CH_2-), 55.43 (2-OMe or 4-OMe), 55.33 (2-OMe or 4-OMe); MS (EI) *m/z* 168 (M^+, 100 %), 167 (65 %), 151 (74 %), 137 (44 %), 121 (36 %).

5.7.1.2. 2,4,6-Trimethoxybenzyl alcohol (356) *via* $NaBH_4$ reduction[3]

$NaBH_4$ (0.39 g, 10.27 mmol, 1 eq.) and 2,4,6-trimethoxybenzaldehyde (**360**) (2.01 g, 10.23 mmol) did not form any product after 4 hours so an additional amount of $NaBH_4$ (0.78 g,

20.51 mmol, 2 eq.) was added. After another 3 hours no product was observed and therefore the reaction mixture was refluxed overnight. No product was detected by TLC.

5.7.2. 2,4,6-Trimethoxybenzyl alcohol (356) *via* hydrogenation[3]



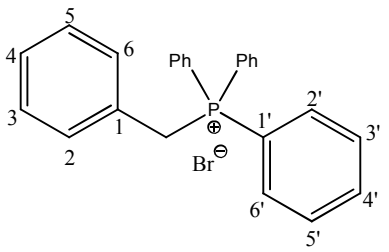
2,4,6-Dimethoxybenzaldehyde (**360**) (2.00 g, 10.19 mmol) was dissolved in acetone (100 ml) and 5 % Pd/C (0.20 g, 10 mol %) was added. The reaction mixture was stirred at room temperature under atmospheric H_2 pressure for 3 days. The crude reaction mixture was then filtered through celite and the acetone removed under reduced pressure. The oil obtained was purified with CC (H:A 8:2) to give the benzyl alcohol (**356**) (0.65 g, 32 %) as a light yellow oil. R_f 0.06 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 2a) δ_H ppm 6.12 (2H, s, H-3 and H-5), 4.69 (2H, d, J = 6.51 Hz, -CH_2-), 3.81 (6H, s, 2-OMe and 6-OMe), 3.80 (3H, s, 4-OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 2b) δ_C ppm 161.12 (C-4), 159.27 (C-2 and C-6), 109.94 (C-1), 90.54 (C-3 and C-5), 55.78 (2-OMe and 6-OMe), 55.44 (4-OMe), 54.44 (-CH_2-); MS (EI) *m/z* 198 (M^+, 90 %), 197 (81 %), 181 (100 %), 167 (22 %), 136 (24 %).

5.8. Synthesis of phosphonium salts

5.8.1. General procedure for the synthesis of phosphonium salts from benzyl halides[4]

Benzyl halide (1 eq.) was added drop-wise to a solution of PPh_3 (1.2 eq.) in dry toluene (20 ml) at room temperature, where after the reaction mixture was refluxed for 2 hours while being monitored to completion by TLC. After completion, the reaction mixture was cooled to room temperature. Acetonitrile was added to induce precipitation and recrystallization of the latter from Et_2O gave the pure product.

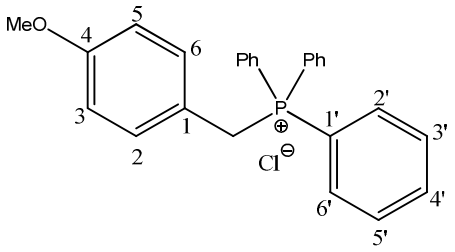
5.8.1.1. Benzyltriphenylphosphonium bromide (337)[4]



Starting materials, benzylbromide (**336**) (2.10 ml, 17.66 mmol) and PPh_3 (5.52 g, 21.06 mmol, 1.2 eq.) yielded phosphonium salt (**337**) (7.51 g, 98 %) as fine white crystals: m.p. 295.2-296.5 °C (lit.[5] m.p. 296-297 °C); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 3a) δ_H ppm 7.74-7.72 (3H, m, H-4'), 7.68-7.65 (6H, m, H-2' and H-6'), 7.61-7.57 (6H, m, H-3' and H-5'), 7.20-7.16 (1H, m, H-4), 7.09-7.06 (2H, m, H-3 and H-5), 7.05-7.03 (2H, m, H-2 and H-6), 5.28 (2H, br d, J_{PH} = 14.33 Hz, -CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 3b) δ_C ppm 135.08 (d, J_{PC} = 2.21 Hz, C-4'),

134.37 (d, J_{PC} = 9.78 Hz, C-2' and C-6'), 131.48 (d, J_{PC} = 5.32 Hz, C-2 and C-6), 130.21 (d, J_{PC} = 12.52 Hz, C-3' and C-5'), 128.87 (d, J_{PC} = 2.74 Hz, C-3 and C-5), 128.47 (d, J_{PC} = 3.53 Hz, C-4), 127.08 (d, J_{PC} = 8.47 Hz, C-1), 117.69 (d, J_{PC} = 85.99 Hz, C-1'), 30.86 (d, J_{PC} = 47.10 Hz, -CH_2-); ^{31}P NMR (151 MHz, $CDCl_3$) (Plate 3h) δ_P ppm 23.33 (s, -PPh_3); MS (MALDI-TOF, positive mode) *m/z* 353.164 (M^+ -Br).

5.8.1.2. 4-Methoxybenzyltriphenylphosphonium chloride (**343**)[4]

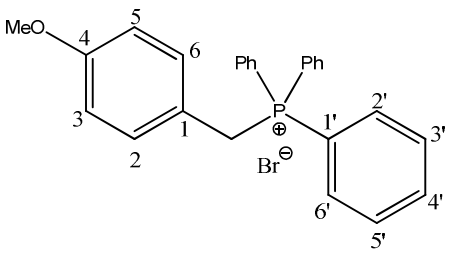


Starting materials 4-methoxybenzyl chloride (**348**) (0.87 ml, 6.42 mmol) and PPh_3 (1.85 g, 7.04 mmol, 1.1 eq.) yielded phosphonium salt (**343**) (2.05 g, 76 %) as fine white crystals: m.p. 234.8-235.7 °C (lit.[6] m.p. 241-243 °C); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 4a) δ_H ppm 7.76-7.69 (9H, m, H-2', H-4' and H-6'), 7.63-7.60 (6H, m, H-3' and H-5'), 6.99 (2H, dd, *J* = 8.82, 2.57 Hz, H-2 and H-6), 6.63 (2H, br d, *J* = 8.82 Hz, H-3 and H-5), 5.33 (2H, d, J_{PH} = 13.79 Hz, -CH_2-), 3.70 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 4b) δ_C ppm 159.56 (d, J_{PC} = 2.85 Hz, C-4), 134.88 (d, J_{PC} = 2.63 Hz, C-4'), 134.39 (d, J_{PC} = 9.69 Hz, C-2' and C-6'), 132.70 (d, J_{PC} = 5.52 Hz, C-2 and C-6), 130.12 (d, J_{PC} = 12.34 Hz, C-3' and C-5'), 118.67 (d, J_{PC} = 8.40 Hz, C-1), 118.03 (d, J_{PC} = 85.05 Hz, C-1'), 114.22 (d, J_{PC} = 3.01 Hz, C-3 and C-5), 55.24 (s, -OMe), 29.94 (d, J_{PC} = 46.04 Hz, -CH_2-).

5.8.1.3. 4-Methoxybenzyl bromide (**349**)[4]

4-Methoxybenzyl alcohol (**353**) (1.50 g, 10.85 mmol), LiBr (1.89 g, 21.73 mmol, 2 eq.) and 2,6-lutidine (2.50 ml, 21.47 mmol, 2 eq.) were dissolved in dry THF (10 ml) and stirred at 0 °C. Methanesulfonic anhydride (2.12 g, 12.18 mmol, 1.1 eq.) was added and the reaction mixture was stirred at 0 °C for 2 hours and was thereafter allowed to warm to room temperature and stirring continued overnight. Pentane (5 ml) was added to precipitate the salts formed. The salts were filtered off and all solvent removed *in vacuo* to give a yellow-brown oil as product (**349**) which was used immediately in the preparation of 4-methoxybenzyl-triphenylphosphonium bromide (**344**).

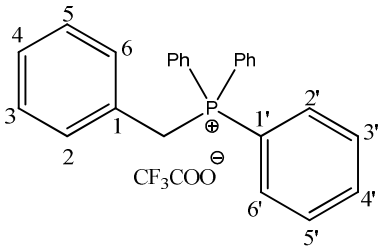
5.8.1.4. 4-Methoxybenzyltriphenylphosphonium bromide (344)[4]



Starting materials 4-methoxybenzyl bromide (**349**) (~ 2 g) and PPh_3 (3.12 g, 11.94 mmol, ~1.2 eq.) yielded phosphonium salt (**344**) (2.24 g, 45 % calculated over two steps) as fine white crystals: m.p. 233.8-235.0 °C (lit.[7] m.p. 234-235 °C); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 5a) δ_H ppm 7.75-7.71 (3H, m, H-4'), 7.67-7.64 (6H, m, H-2' and H-6'), 7.61-7.57 (6H, m, H-3' and H-5'), 6.95 (2H, dd, J = 8.81, 2.54 Hz, H-2 and H-6), 6.59 (2H, br d, J = 8.81 Hz, H-3 and H-5), 5.17 (2H, d, J_{PH} = 13.68 Hz, -CH_2-), 3.67 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 5b) δ_C ppm 159.6 (d, J_{PC} = 2.9 Hz, C-4), 135.00 (d, J_{PC} = 2.54 Hz, C-4'), 134.35 (d, J_{PC} = 9.69 Hz, C-2' and C-6'), 132.63 (d, J_{PC} = 5.45 Hz, C-2 and C-6), 130.16 (d, J_{PC} = 12.48 Hz, C-3' and C-5'), 118.39 (d, J_{PC} = 9.12 Hz, C-1), 117.77 (d, J_{PC} = 85.30 Hz, C-1'), 114.23 (d, J_{PC} = 3.40 Hz, C-3 and C-5), 55.25 (s, -OMe), 30.11 (d, J_{PC} = 46.96 Hz, -CH_2-); ^{31}P NMR (151 MHz, $CDCl_3$) (Plate 5g) δ_P ppm 22.47 (s, -PPh_3); MS (MALDI-TOF, positive mode) *m/z* 383.157 (M^+ -Br).

5.8.2. Synthesis of phosphonium salt from benzyl alcohol

5.8.2.1. Benzyltriphenylphosphonium trifluoroacetate (362)[8]



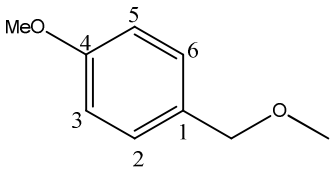
Benzyl alcohol (**361**) (1.10 ml, 10.63 mmol), PPh_3 (2.90 g, 11.08 mmol, 1 eq.) and trifluoroacetic acid (5 ml) were stirred overnight at 60 °C. The reaction mixture was cooled to room temperature and cold H_2O was added where after the phosphonium salt (**362**) was extracted into DCM and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure an orange oil remained. Recrystalization from Et_2O afforded the phosphonium salt (**362**) as *faint yellow crystals* (0.50 g, 10 %): m.p. 181.3-182.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 6a) δ_H ppm 7.77-7.73 (1H, m, H-4'), 7.62-7.56 (12H, m, H-2', H-3', H-5' and H-6'), 7.21 (1H, m, H-4), 7.10 (2H, m, H-3 and H-5), 6.92 (2H, m, H-2 and H-6), 4.97 (2H, d, J_{PH} = 14.39 Hz, -CH_2-); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 6b) δ_C ppm 160.96 (d, J_{PC} = 32.94 Hz, C=O), 135.21 (d, J_{PC} = 2.54 Hz, C-4'), 134.18 (d, J_{PC} = 9.71 Hz, C-2' and C-6'), 131.29 (d, J_{PC} = 5.47 Hz, C-2 and C-6), 130.29 (d, J_{PC} = 12.50 Hz, C-3' and C-5'), 129.04 (d, J_{PC} = 3.44 Hz, C-3 and C-5), 128.65 (d, J_{PC} = 3.71 Hz, C-4), 127.07 (d, J_{PC} = 8.39 Hz, C-1), 117.66 (d, J_{PC} = 85.81 Hz, C-1'), 30.35 (d, J_{PC} = 47.54 Hz, -CH_2-); ^{31}P NMR (121 MHz, $CDCl_3$) (Plate 6g) δ_P ppm 23.16 (s,

-PPh_3); ^{19}F NMR (565 MHz, $CDCl_3$) (Plate 6h) δ_F ppm -78.00 (s, -CF_3); MS (MALDI-TOF, positive mode) *m/z* 353.180 (M^+ -CF_3COO), (negative mode) *m/z* 112.867 (CF_3COO^-).

5.8.3. General procedure for the synthesis of benzyl alkyl ethers[9]

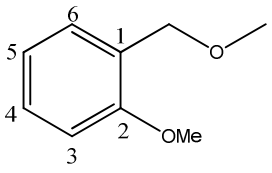
Benzyl alcohol (1 eq.) was dissolved in dry THF (5 ml). NaH (2 eq.) was added and the reaction mixture was stirred at 50 °C for 3 hours. The reaction mixture was cooled down to 0 °C, methyl iodide (1.2 eq.) was added and the reaction mixture was stirred at 25 °C for 30 minutes. After completion of the reaction, Et_2O (20 ml) was added and the reaction mixture filtered through celite. The solvent was removed under vacuum to give the crude product mixture.

5.8.3.1. 4-Methoxybenzyl methyl ether (**366**)[9]



Reagents 4-methoxybenzyl alcohol (**353**) (1.00 g, 7.25 mmol), NaH (0.35 g, 14.72 mmol, 2 eq.) and methyl iodide (0.55 ml, 8.84 mmol, 1.2 eq.) gave pure 4-methoxybenzyl methyl ether (**366**) (1.10 g) in quantitative yield as a yellow oil. R_f 0.62 (H:A 8:2); ^1H NMR (600 MHz, $CDCl_3$) (Plate 7a) δ_H ppm 7.26 (2H, d, *J* = 8.67 Hz, H-2 and H-6), 6.88 (2H, d, *J* = 8.67 Hz, H-3, H-5), 4.38 (2H, s, -CH_2-), 3.79 (3H, s, -Ph<u>OMe</u>), 3.35 (3H, s, -CH_2<u>OMe</u>); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 7b) δ_C ppm 159.30 (C-4), 130.36 (C-1), 129.45 (C-2 and C-6), 113.85 (C-3, C-5), 74.43 (-CH_2-), 57.87 (-CH_2<u>OMe</u>), 55.31 (-Ph<u>OMe</u>); MS (EI) *m/z* 152 (M^+, 48 %), 151 (24 %), 122 (14 %), 121 (100 %), 77 (18 %).

5.8.3.2. 2-Methoxybenzyl methyl ether (**367**)[9]



Starting materials 2-methoxybenzyl alcohol (**354**) (0.75 g, 5.40 mmol), NaH (0.28 g, 12.21 mmol, 2.2 eq.) and methyl iodide (0.43 ml, 6.91 mmol, 1.3 eq.) gave pure 2-methoxybenzyl methyl ether (**354**) (0.55 g, 68 %) as a yellow oil. R_f 0.62 (H:A 8:2); ^1H NMR (600 MHz, $CDCl_3$) (Plate 8a) δ_H ppm 7.38-7.36 (1H, m, H-6), 7.30-7.27 (1H, m, H-4), 6.98-6.96 (1H, m, H-5), 6.89-6.88 (1H, m, H-3), 4.52 (2H, s, -CH_2-), 3.85 (3H, s, -Ph<u>OMe</u>), 3.44 (1H, s, -CH_2<u>OMe</u>); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 8b) δ_C ppm 157.29 (C-2), 129.20 (C-6), 128.85 (C-4), 126.55 (C-1), 120.48 (C-5), 110.29 (C-3), 69.66 (-CH_2-), 58.43 (-CH_2<u>OMe</u>), 55.43 (-Ph<u>OMe</u>); MS (EI) *m/z* 152 (M^+, 79 %), 151 (20 %), 137 (26 %), 121 (100 %), 91 (93 %).

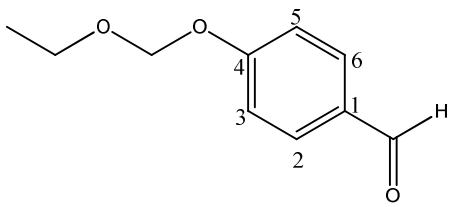
5.8.4. Synthesis of phosphonium salts through cleavage of benzyl ethers

5.8.4.1. 4-Methoxybenzyltriphenylphosphonium bromide (**344**)[10]

4-Methoxybenzyl methyl ether (**366**) (0.51 g, 3.32 mmol), PPh_3 (0.95 g, 3.61 mmol, 1.1 eq.) and PPh_3.HBr (1.24 g, 3.62 mmol, 1.1 eq.) were dissolved in dry CH_3CN (3.5 ml). The reaction mixture was irradiated with microwaves (*cf.* Paragraph 5.4.) to 100 °C (maximum 100 W) for 30 minutes while stirring. The reaction mixture was cooled down and recrystallization from Et_2O gave the phosphonium salt (**344**) as fine white crystals (0.59 g, 38 %), identical to the product characterized in Paragraph 5.8.1.4.

5.9. Synthesis of protected aldehydes

5.9.1. 4-Ethoxymethoxybenzaldehyde (**369**)[11]

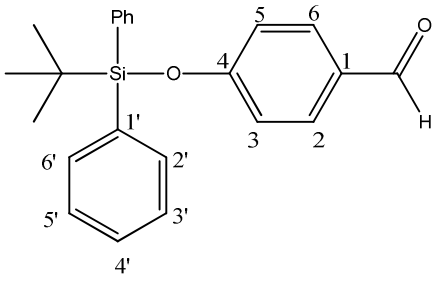


4-Hydroxybenzaldehyde (**368**) (1.51 g, 12.34 mmol) was dissolved in DCM (8 ml) and a previously prepared solution of Adogen 464 (0.84 g) in DCM was added to the reaction mixture. NaOH (5.0 M, 12.30 ml, 61.50 mmol, 5 eq.) was added and reaction mixture was stirred vigorously for 45 minutes at room temperature. Chloromethyl ethyl ether (5.00 ml, 54.77 mmol, 4 eq.) was added and reaction mixture was stirred for 24 hours. After completion, followed by TLC, H_2O (20 ml) was added and the product extracted into DCM. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude reaction mixture which was purified by FCC (H:EtOAc 8:2) to obtain 4-ethoxymethoxybenzaldehyde (**369**) (1.57 g, 71 %) as a colourless amorphous solid. R_f 0.46 (H:EtOAc 8:2); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 9a) δ_H ppm 9.83 (1H, s, -CHO), 7.78 (2H, d, J = 8.62 Hz, H-2 and H-6), 7.09 (2H, d, J = 8.62 Hz, H-3 and H-5), 5.24 (2H, s, -OCH_2O-), 3.68 (2H, q, J = 7.06 Hz, -OCH_2-), 1.16 (3H, t, J = 7.06 Hz, -CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 9b) δ_C ppm 190.84 (-CHO), 162.37 (C-4), 131.91 (C-2 and C-6), 130.58 (C-1), 116.23 (C-3 and C-5), 92.79 (-OCH_2O-), 64.70 (-OCH_2-), 15.04 (-CH_3); MS (EI) *m/z* 180 (M^+, 15 %), 121 (38 %), 65 (11 %), 59 (100 %).

5.9.2. General procedure for protecting OH-groups with *tert*-butyldiphenylsilyl chloride[12]

Hydroxylated molecule (1 eq.) and imidazole (5.4 eq.) were dissolved in dry DMF (20 ml) while stirring. *Tert*-butyldiphenylsilyl chloride (2.6 eq.) was separately dissolved in dry DMF (10 ml) and added slowly to the reaction mixture. The reaction mixture was stirred for 5 hours and the reaction thereafter quenched with cold H_2O. The crude product was extracted into Et_2O and the organic layers combined, washed with cold HCl (3.0 M), H_2O and aq. $NaHCO_3$ (sat.) consecutively and dried with anhydrous Na_2SO_4.

5.9.2.1. 4-*Tert*-butyldiphenylsilyloxybenzaldehyde (**371**)[12]

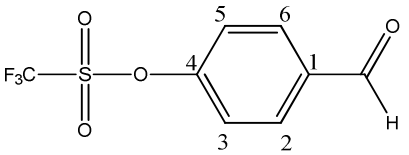


4-Hydroxybenzaldehyde (**368**) (1.99 g, 16.31 mmol), imidazole (6.10 g, 9.01 mmol, 5.5 eq.) and *tert*-butyldiphenylsilyl chloride (10.70 ml, 41.15 mmol, 2.5 eq.) gave the crude product mixture which was separated with FCC (H:A 8:2). Fractions with R_f 0.51 were combined to obtain 1-(4'-tertbutyldiphenylsilyloxy-phenyl)propan-1-one (**371**) (2.71 g, 46 %) as *light yellow needles*. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 10a) δ_H ppm 9.82 (1H, s, -CHO), 7.72-7.70 (4H, m, H-2' and H-6'), 7.65 (2H, d, J = 8.59 Hz, H-2 and H-6), 7.47-7.44 (2H, m, H-4'), 7.40-7.38 (4H, m, H-3' and H-5'), 6.87 (2H, d, J = 8.59 Hz, H-3 and H-5), 1.12 [9H, s, -$(CH_3)_3$]; ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 10b) δ_C ppm 191.01 (-CHO), 161.31 (C-4), 135.49 (C-2' and C-6'), 132.01 (C-1'), 131.82 (C-2 and C-6), 130.37 (C-4'), 130.32 (C-1), 128.09 (C-3' and C-5'), 120.39 (C-3 and C-5), 26.47 [-$(CH_3)_3$], 19.57 [C-$(CH_3)_3$]; MS (TOF-MS-ES, positive mode) *m/z* 383.1441 (M^+ +Na).

5.9.3. General procedure for protecting OH-groups with trifluoromethanesulfonyl chloride[4]

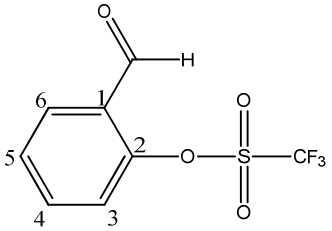
Hydroxylated molecule (1 eq.) was dissolved in dry DCM (3 ml) and dry Et_3N (1.5 eq.) was added. The reaction mixture was stirred at room temperature for 45 minutes where after trifluoromethanesulfonyl chloride (1.1 eq.) was added and stirring continued overnight. The reaction mixture was diluted with DCM, $NaHCO_3$ (saturated *aq.*) added and the product extracted into DCM. The DCM was dried over anhydrous Na_2SO_4 and removed under vacuum.

5.9.3.1. 4-Trifluoromethanesulfonyloxybenzaldehyde (382)[4]



4-Hydroxybenzaldehyde (**368**) (1.00 g, 8.22 mmol), EtN_3 (1.70 ml, 12.20 mmol, 1.5 eq.) and trifluoromethanesulfonyl chloride (0.97 ml, 9.17 mmol, 1.1 eq.) gave the triflate derivative (**382**) (1.53 g, 73 %) as a light yellow oil with R_f 0.50 (H:A 8:2). ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 12a) δ_H ppm 10.03 (1H, s, -CHO), 7.99 (2H, d, *J* = 8.73 Hz, H-2 and H-6), 7.45 (2H, d, *J* = 8.73 Hz, H-3 and H-5); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 12b) δ_C ppm 190.27 (-CHO), 153.31 (C-4), 136.02 (C-1), 131.86 (C-2 and C-6), 122.36 (C-3 and C-5), 118.78 (q, *J* = 320.90 Hz, $-CF_3$); (Plate 12f) ^{19}F NMR (565 MHz, $CDCl_3$) δ_F ppm -75.81 (s, $-CF_3$); MS (EI) *m/z* 254 (M^+, 76 %), 189 (100 %), 161 (22 %), 95 (37 %), 69 (52 %).

5.9.3.2. 2-Trifluoromethanesulfonyloxybenzaldehyde (383)[4]

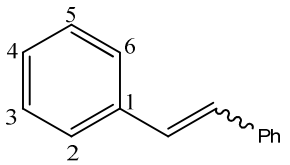


2-Hydroxybenzaldehyde (**380**) (0.87 ml, 8.16 mmol), EtN_3 (1.70 ml, 12.34 mmol, 1.5 eq.) and trifluoromethanesulfonyl chloride (0.95 ml, 8.98 mmol, 1.1 eq.) gave the triflate derivative (**383**) (0.63 g, 30 %) as a light yellow oil with R_f 0.61 (H:A 8:2). ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 13a) δ_H ppm 10.27 (1H, s, -CHO), 8.01-7.98 (1H, m, H-6), 7.73-7.70 (1H, m, H-4), 7.57-7.54 (1H, m, H-5), 7.42-7.40 (1H, m, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 13b) δ_C ppm 186.65 (-CHO), 149.96 (C-2), 136.00 (C-4), 131.01 (C-6), 129.05 (C-5), 128.63 (C-1), 122.59 (C-3), 118.77 (q, *J* = 320.65 Hz, $-CF_3$); ^{19}F NMR (565 MHz, $CDCl_3$) (Plate 13e) δ_F ppm -75.94 (s, $-CF_3$); MS (EI) *m/z* 254 (M^+, 17 %), 189 (36 %), 162 (7 %), 121 (60 %), 120 (86 %).

5.10. Synthesis of stilbenes *via* the Wittig reaction

5.10.1. Utilizing NaH as base

5.10.1.1. *Trans*-stilbene (384)[4]



Benzyltriphenylphosphonium salt (**337**) (1.02 g, 2.35 mmol) was dissolved in dry THF (60 ml) and cooled to 0 °C. NaH (0.07 g, 2.88 mmol, 1.2 eq.) was added and the reaction mixture stirred for 2 hours after which benzaldehyde (**339**) (0.28 ml, 2.74 mmol, 1.1 eq.) was added at 0 °C. The reaction mixture was stirred at 0 °C for 40 minutes, warmed to room

temperature and stirring continued overnight. After completion the reaction mixture was passed through a short column of silica to remove unreacted salts using DCM as eluent after which all solvent was removed under reduced pressure. Crystallization from DCM gave *trans*-stilbene (**384**) (0.42 g, 17 %) as shiny white crystals: m.p. 124.5-125.1 °C (lit.[13] m.p. 124-125 °C); R_f 0.57 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 14a) δ_H ppm 7.56-7.54 (4H, m, H-2 and H-6), 7.40-7.38 (4H, m, H-3 and H-5), 7.30-7.28 (2H, m, H-4), 7.14 (2H, s, H-*α* and H-*β*); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 14b) δ_C ppm 137.35 (C-1), 128.72 (C-*α* and C-*β*), 128.69 (C-3 and C-5), 127.63 (C-4), 126.53 (C-2 and C-6).

5.10.1.2. 4-Methoxystilbene (329)[4]

Benzyltriphenylphosphonium bromide (**337**) (1.00 g, 2.32 mmol) was dissolved in dry THF. The reaction mixture was cooled to 0 °C to add NaH (0.07 g, 2.91 mmol, 1.2 eq.) and the reaction mixture was stirred for two hours. 4-Methoxybenzaldehyde (**357**) (0.25 ml, 2.06 mmol, 0.9 eq.) was then added at 0 °C and the reaction mixture stirred at this temperature for 30 minutes before warming to room temperature and stirring overnight. Only trace amounts of 4-methoxystilbene **()** was detected.

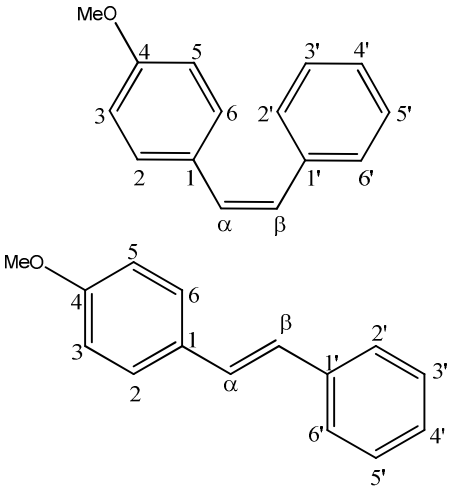
5.10.2. Utilizing Na-metal as base

5.10.2.1. *Trans*-stilbene (384)[14]

Benzyltriphenylphosphonium bromide (**337**) (1.05 g, 2.42 mmol) was dissolved in dry EtOH (6 ml), a small piece of sodium metal was added and reaction mixture stirred for 15 minutes. Benzaldehyde (**339**) (0.23 ml, 2.27 mmol, 0.9 eq.) was added and reaction mixture stirred for 10 minutes where after it was cooled in an ice bath. The precipitate formed was filtered off and the filtrate concentrated under reduced pressure to give the crude mixture which was purified by PLC (H:A 8:2); *trans*-stilbene (**384**) was obtained (0.02 g, 14 %) as a white powder, identical to the product characterized in Paragraph 5.10.1.1.

5.10.3. Utilizing BuLi as base

5.10.3.1. *Cis*- (385) and *trans*-4-methoxystilbene (387)[4]



4-Methoxybenzyltriphenylphosphonium bromide (**344**) (1.00 g, 2.16 mmol) was dissolved in dry THF (60 ml) and cooled to 0 °C. BuLi (4.00 ml, 2.56 mmol, 1.2 eq.) was added and the reaction mixture stirred for 2 hours. The reaction mixture was cooled to 0 °C, benzaldehyde (**339**) (0.25 ml, 2.46 mmol, 1.1 eq.) added and the reaction mixture stirred for another hour at 0 °C where after it was allowed to warm to room temperature and stirred overnight. The reaction mixture was then passed through a short column of silica with DCM as eluent. DCM was removed under reduced pressure and the dark orange crude mixture was purified with FCC (H:A 8:2) to give *cis*-4-methoxystilbene (**385**) (0.08 g, 18 %) as a light yellow oil with R_f 0.59; ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 15a) δ_H ppm 7.28-7.26 (2H, m, H-2'and H-6'), 7.24-7.21 (2H, m, H-3'and H-5'), 7.19-7.16 (3H, m, H-2, H-6 and H-4'), 6.75 (2H, d, *J* = 8.77 Hz, H-3 and H-5), 6.53 (1H, d, *J* = 12.22 Hz, H-*α*), 6.50 (1H, d, *J* = 12.22 Hz, H-*β*), 3.77 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 15b) δ_C ppm 158.77 (C-4), 137.73 (C-1'), 130.27 (C-2 and C-6), 129.88 (C-*α*), 129.76 (C-1), 128.93 (C-2' and C-6'), 128.87 (C-*β*), 128.35 (C-3' and C-5'), 127.02 (C-4'), 113.69 (C-3 and C-5), 55.30 (-OMe); MS (EI) *m/z* 210 (M^+, 100 %), 211 (17 %), 209 (18 %), 195 (21 %), 179 (16 %) as well as *trans*-4-methoxystilbene (**387**) (0.07 g, 15 %) as a yellow precipitate with R_f 0.51; ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 16a) δ_H ppm 7.53-7.52 (2H, d, *J* = 7.45 Hz, H-2' and H-6'), 7.49 (2H, d, *J* = 8.68 Hz, H-2 and H-6), 7.39-7.36 (2H, dd, *J* = 7.84, 7.45 Hz, H-3' and H-5'), 7.28-7.25 (1H, m, H-4'), 7.10 (1H, d, *J* = 16.31 Hz, H-*α*), 7.01 (1H, d, *J* = 16.31 Hz, H-*β*), 6.93 (2H, d, *J* = 8.68 Hz, H-3 and H-5), 3.86 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 16b) δ_C ppm 159.41 (C-4), 137.76 (C-1'), 130.25 (C-1), 128.77 (C-3' and C-5'), 128.32 (C-*α*), 127.84 (C-2 and C-6), 127.34 (C-4'), 126.72 (C-*β*), 126.38 (C-2' and C-6'), 114.25 (C-3 and C-5), 55.45 (-OMe); MS (EI) *m/z* 210 (M^+, 100 %), 211 (27 %), 209 (21 %), 195 (25 %), 167 (19 %).

5.10.4. General procedure for utilizing NaOH as base[15]

A solution (C = 1.5, 2.0 or 2.5 M) of the phosphonium salt (1 eq.) was prepared in H_2O where after NaOH (4 eq.) was slowly added at room temperature and the reaction mixture stirred for

2-3 minutes, followed by aldehyde (0.9 eq.) addition, the reaction mixture was stirred for 4 hours at 70 °C. The reaction mixture was subsequently cooled down, H_2O (15 ml) added and the mixture stirred for about 5 minutes. The precipitate was filtered off, washed with H_2O and dissolved in ethyl acetate.

5.10.4.1. *Cis*- (**385**) and *trans*-4-methoxystilbene (**387**)[15] (attempt 1)

Benzyltriphenylphosphonium bromide (**337**) (0.50 g, 1.16 mmol) in H_2O (0.46 ml) (C = 2.5 M), NaOH (0.19 g, 4.65 mmol, 4 eq.) and 4-methoxybenzaldehyde (**357**) (0.13 ml, 1.07 mmol, 0.9 eq.) gave the crude product mixture which was separated by FCC (H:A 8:2). A mixture of *cis*- (**385**) and *trans*-4-methoxystilbene (**387**) (0.12 g, 55 %) was obtained in a 1:1 ratio. Complete characterization is as described in Paragraph 5.10.3.1.

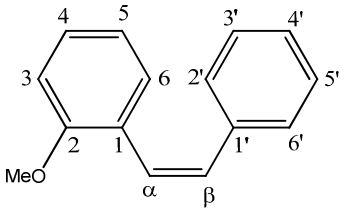
5.10.4.2. *Cis*- (**385**) and *trans*-4-methoxystilbene (**387**)[15] (attempt 2)

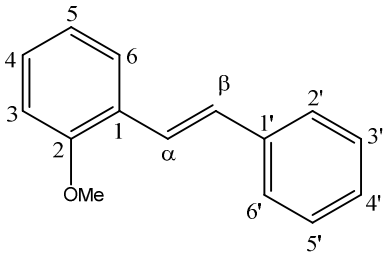
4-Methoxybenzyltriphenylphosphonium chloride (**343**) (0.20 g, 0.48 mmol) in H_2O (0.20 ml) (C = 2.5 M), NaOH (0.08 g, 2.00 mmol, 4.2 eq.) and benzaldehyde (**339**) (0.05 ml, 0.41 mmol, 0.8 eq.) gave the crude product mixture which was separated by PLC (H:A 8:2) to obtain a mixture of *cis*- (**385**) (0.013 g, 16 %) and *trans*-isomers (**387**) (0.010 g, 12 %) in a 1:1 ratio. Complete characterization is as described in Paragraph 5.10.3.1.

5.10.4.3. *Cis*- (**385**) and *trans*-4-methoxystilbene (**387**)[15] (attempt 3)

Benzyltriphenylphosphonium bromide (**337**) (0.80 g, 1.86 mmol) in H_2O (0.90 ml) (C = 2.0 M), tetrabutylammonium bromide (0.06 g, 0.20 mmol, 10 mol %) and NaOH (0.30 g, 7.40 mmol, 4 eq.) was added together at room temperature and the reaction mixture stirred for 2-3 minutes. 4-Methoxybenzaldehyde (**357**) (0.21 ml, 1.73 mmol, 0.9 eq.) was added and reaction mixture stirred overnight at 70 °C. After cooling the reaction down to room temperature, H_2O (10 ml) was added. The precipitate formed was filtered off, washed with H_2O and dissolved in ethyl acetate. The crude reaction mixture was separated with PLC (H:A 8:2) and gave a mixture of *cis*- (**385**) and *trans*-4-methoxystilbene (**387**) (0.09 g, 24 %). Complete characterization is as described in Paragraph 5.10.3.1.

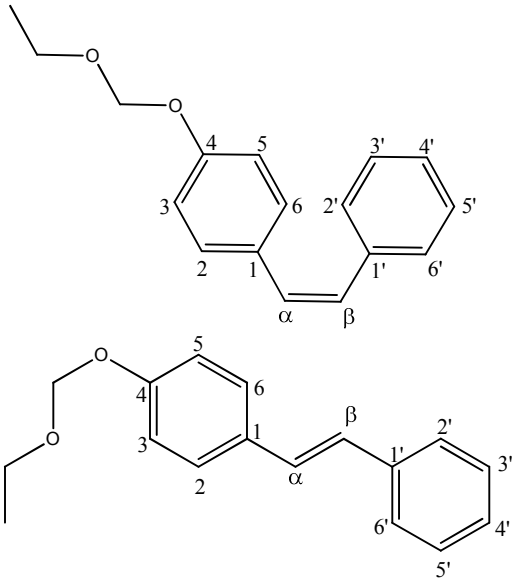
5.10.4.4. *Cis*- (**386**) and *trans*-2-methoxystilbene (**388**)[15]





Benzyltriphenylphosphonium bromide (**337**) (2.00 g, 4.62 mmol) in H_2O (2.30 ml) (C = 2.0 M), NaOH (0.74 g, 18.49 mmol, 4 eq.) and 2-methoxybenzaldehyde (**358**) (0.50 ml, 4.14 mmol, 0.9 eq.) gave the crude product mixture which was separated with FCC (H:A 8:2). A mixture of *cis*- (**386**) and *trans*-2-methoxystilbene (**388**) (0.37 g, 53 %) in a 3:1 ratio was obtained with R_f values of 0.63 and 0.56, respectively. Further purification by PLC (H:A 8:2) gave *cis*-2-methoxystilbene (**386**) as a colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 17a) δ_H ppm 7.24-7.13 (7H, m, H-4, H-6, H-2', H-3', H-4', H-5' and H-6'), 6.90-6.88 (1H, m, H-3), 6.76-6.74 (1H, m, H-5), 6.69 (1H, d, *J* = 12.26 Hz, H-*α*), 6.63 (1H, d, *J* = 12.26 Hz, H-*β*), 3.82 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 17b) δ_C ppm 157.30 (C-2), 137.43 (C-1'), 130.36, 130.23, 128.97, 128.72, 128.16, 127.04, 126.31 (C-1), 125.92 (C-*α*), 120.33 (C-5), 110.76 (C-3), 55.57 (OMe); MS (EI) *m/z* 210 (M^+, 100 %), 179 (19 %), 167 (29 %), 165 (50 %), 152 (33 %) as well as a mixture of *cis*- (**386**) and *trans*-2-methoxystilbene (**388**); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 18) δ_H ppm 7.60-7.59 [0.4H, m, H-Ar, (**388**)], 7.54-7.53 [0.8H, m, H-Ar, (**388**)], 7.48 [0.4H, d, *J* = 16.48 Hz, H-*α*, (**388**)], 7.36-7.33 [0.8H, m, H-Ar, (**388**)], 7.26-7.13 [7.8H, m, H-Ar, (**386**) and (**388**)], 7.11 [0.4H, d, *J* = 16.48 Hz, H-*β*, (**388**)], 6.98-6.95 [0.4H, m, H-Ar, (**388**)], 6.91-6.90 [0.2H, m, H-Ar (**388**)], 6.90-6.88 [1H, m, H-3, (**386**)], 6.76-6.74 [1H, m, H-5, (**386**)], 6.69 [1H, d, *J* = 12.26 Hz, H-*α*, (**386**)], 6.63 [1H, d, *J* = 12.26 Hz, H-*β*, (**386**)], 3.88, [1.2H, s, -OMe, (**388**)], 3.82 [3H, s, -OMe, (**386**)].

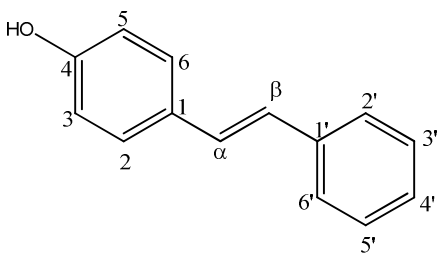
5.10.4.5. *Cis*- (**389**) and *trans*-4-ethoxymethoxystilbene (**390**)[15]



Benzyltriphenylphosphonium bromide (**337**) (1.22 g, 2.81 mmol) in H_2O (0.90 ml) (C = 1.5 M), NaOH (0.45 g, 11.21 mmol, 4 eq.) and 4-ethoxymethoxybenzaldehyde (**369**) (0.49 g, 2.70 mmol) gave the crude product mixture which was purified with FCC (H:A 8:2). A mixture of *cis*- (**389**) and *trans*-4-ethoxymethoxystilbene (**390**) (0.38 g, 55 %) in ratio 1:1 was obtained with R_f values of 0.65 and 0.51, respectively. Further purification gave *cis*-4-ethoxymethoxy-stilbene (**389**) as a *colourless amorphous solid*;) ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 19a) δ_H ppm 7.28-7.26 (2H, m, H-2' and H-6'), 7.24-7.22 (2H, m, H-3' and H-5'), 7.19-7.16 (3H, m, H-2, H-6 and H-4'), 6.88 (2H, d, *J* = 8.77 Hz, H-3 and H-5), 6.52 (2H, s, H-*α* and H-*β*), 5.19 (2H, s, -OCH_2O-), 3.71 (2H, q, *J* = 7.05 Hz, -OCH_2-), 1.21 (3H, t, *J* = 7.05 Hz, -CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 19b) δ_C ppm 156.60 (C-4), 137.64 (C-1'), 130.81 (C-1), 130.23 (C-2 and C-6), 129.80 (C-*α* or C-*β*), 129.13 (C-*α* or C-*β*), 128.92 (C-2' and C-6'), 128.36 (C-3' and C-5'), 127.06 (C-4'), 116.01 (C-3 and C-5), 93.22 (-OCH_2O-), 64.36 (-OCH_2-), 15.23 (-CH_3); MS (EI) *m/z* 254 (M^+, 80 %), 224 (54 %), 196 (43 %), 195 (31 %), 167 (21 %) and *trans*-4-ethoxymethoxystilbene (**390**) as a *colourless amorphous solid*; ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 20a) δ_H ppm 7.50-7.48 (2H, m, H-2' and H-6'), 7.45 (2H, d, *J* = 8.68 Hz, H-2 and H-6), 7.36-7.33 (2H, m, H-3' and H-5'), 7.25-7.22 (1H, m, H-4'), 7.07 (1H, d, *J* = 16.32 Hz, H-*α*), 7.04 (2H, d, *J* = 8.68 Hz, H-3 and H-5), 6.99 (1H, d, *J* = 16.32 Hz, H-*β*), 5.24 (2H, s, -OCH_2O-), 3.74 (2H, q, *J* = 7.08 Hz, -OCH_2-), 1.23 (3H, t, *J* = 7.08 Hz, -CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 20b) δ_C ppm 157.18 (C-4), 137.70 (C-1'), 131.26 (C-1), 128.78 (C-3' and C-5'), 128.26 (C-*α*), 127.79 (C-2 and C-6), 127.42 (C-4'), 127.13 (C-*β*), 126.43 (C-2' and C-6'), 116.54 (C-3 and C-5), 93.24 (-OCH_2O-), 64.42 (-OCH_2-), 15.26 (-CH_3); MS (EI) *m/z* 254 (M^+, 79 %), 255 (15 %), 224 (45 %), 196 (40 %), 195 (27 %).

5.11. Synthesis of stilbenes utilizing other methods

5.11.1. *Trans*-4-hydroxystilbene (394) through deprotection of ethoxymethoxy groups

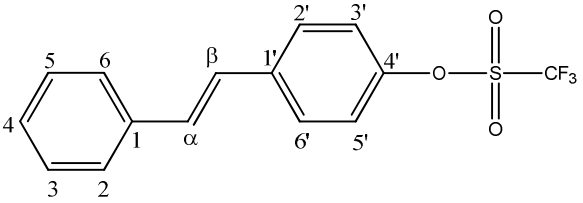


4-Methoxyethoxystilbene (**389**) and (**390**) (2.02 g, 7.94 mmol) was dissolved in MeOH (3 ml). H_2SO_4 (0.2 ml) was added and reaction mixture stirred at room temperature for 2 hours. After completion of the reaction, the standard extraction procedure was followed. Solvent and possible byproducts were removed under reduced pressure to give *trans*-4-hydroxystilbene (**394**) in quantitative yield. Further purification by PLC (H:A 8:2) gave *trans*-4-hydroxystilbene (**394**) as a white solid: m.p. 183.3-185.5 °C (lit.[16] m.p. 185-187 °C); R_f 0.30 (H:A 8:2); ^{1}H NMR (600 MHz, $(CD_3)_2CO$) (Plate 21a) δ_H ppm 6.53-6.52 (2H, m, H-2' and H-6'), 6.44 (2H, d, *J* = 8.54 Hz, H-2 and H-6), 6.33-6.31 (2H, m, H-3' and H-5'), 6.21-6.19 (1H, m, H-4'), 6.15 (1H, d, *J* = 16.40 Hz, H-*α*), 6.03 (1H, d, *J* = 16.40 Hz, H-*β*), 5.83 (2H, d, *J* = 8.54 Hz, H-3 and H-5); ^{13}C NMR (151 MHz, $(CD_3)_2CO$) (Plate 21b) δ_C ppm 158.01 (C-4), 138.51 (C-1'), 129.47 (C-1), 129.12 (C-3' and C-5'), 129.02 (C-*α*), 128.39 (C-2 and C-6), 127.47 (C-4'), 126.62 (C-2' and C-6'), 126.01 (C-*β*), 116.09 (C-3 and C-5); MS (EI) *m/z* 196 (M^+, 100 %), 197 (15 %), 195 (36 %), 181 (18 %), 177 (28 %).

5.11.2. *Trans*-4-hydroxystilbene (394)[17] with a Perkin-type reaction

4-Hydroxybenzaldehyde (**394**) (0.81 g, 6.60 mmol), phenylacetic acid (**391**) (1.01 g, 7.45 mmol, 1.1 eq.), piperidine (0.97 ml, 9.83 mmol, 1.5 eq.) and imidazole (0.67 g, 9.82 mmol, 1.5 eq.) were dissolved in PEG-400 (5 ml). After irradiation (*cf.* Paragraph 5.4.), the reaction mixture was allowed to cool to room temperature, acidified with diluted HCl (3 M) to a pH of 5 (indicator strip) and the product extracted into ethylacetate. The organic layers were combined and washed with both H_2O and *aq.* $NaHCO_3$, followed by drying over anhydrous Na_2SO_4. The product (**394**) was concentrated *in vacuo* and purified with FCC (H:A 6:4). Fractions with an R_f of 0.68 were combined to give *trans*-4-hydroxystilbene (**394**) (0.54 g, 42 %) as characterized in Paragraph 5.11.1.

5.11.3. *Trans*-4'-trifluoromethanesulfonyloxystilbene (395)[4] through protection reaction



4-Hydroxystilbene (**394**) (0.34 g, 1.74 mmol), EtN_3 (0.36 ml, 2.58 mmol, 1.5 eq.) and trifluoromethanesulfonyl chloride (0.20 ml, 1.89 mmol, 1.1 eq.) reacted as described in Paragraph 5.9.3. and gave the crude reaction mixture which was purified with FCC to obtain 4'-trifluoromethanesulfonyloxystilbene (**395**) (0.31 g, 54 %) as a *white powder*. Melting point 76.7-78.2 °C; R_f 0.64 (H:A 8:2); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 22a) δ_H ppm 7.53 (2H, d, *J* = 8.76 Hz, H-2' and H-6'), 7.51-7.50 (2H, m, H-2 and H-6), 7.38-7.36 (2H, m, H-3 and H-5), 7.30-7.28 (1H, m, H-4), 7.25 (2H, d, *J* = 8.76 Hz, H-3' and H-5'), 7.10 (1H, d, *J* = 16.38 Hz, H-*α*), 7.08 (1H, d, *J* = 16.38 Hz, H-*β*); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 22b) δ_C ppm 148.72 (C-4'), 137.92 (C-1'), 136.73 (C-1), 130.86 (C-*α*), 128.93 (C-3 and C-5), 128.37 (C-4), 128.10 (C-2' and C-6'), 126.83 (C-2 and C-6), 126.63 (C-*β*), 121.73 (C-3' and C-5'), 118.90 (q, *J* = 320.86 Hz, -CF_3); MS (EI) *m/z* 328 (M^+, 45 %), 195 (100 %), 167 (55 %), 166 (20 %), 165 (61 %).

5.12. Methoxycarbonylation of model substrates

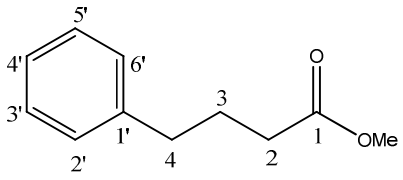
5.12.1. Methoxycarbonylation of hexene (397)[19]

$Pd(OAc)_2$ (0.011 g, 0.049 mmol, 1 mol %), $Al(OTf)_3$ (0.046 g, 0.097 mmol, 2 mol %), PPh_3 (0.050 g, 0.191 mmol, 4 mol %) and hexene (**397**) (0.60 ml, 4.80 mmol) were dissolved in MeOH (10.8 ml). Conversion (4 h, 70 %) to heptanoate (**399**) [R_T 8.84 min., *m/z* = 113 (M^+, 15 %)] was observed with GCMS analysis.

5.12.2. Carbonylation of styrene (313)[19]

$Pd(OAc)_2$ (0.010 g, 0.045 mmol, 1 mol %), $Al(OTf)_3$ (0.041 g, 0.086 mmol, 2 mol %), PPh_3 (0.046 g, 0.173 mmol, 4 mol %) and styrene (**313**) (0.50 ml, 4.35 mmol) were dissolved in MeOH (9 ml). Conversion (1 h, 100 %) to methyl 3-phenylpropanoate (**400**) [R_T 13.06 min., *m/z* = 164 (M^+, 24 %)] and methyl 2-phenylpropanoate (**402**) [R_T 12.04 min., *m/z* = 164 (M^+, 38 %)] in a 3:1 ratio were observed with GCMS analysis.

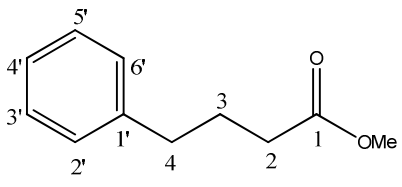
5.12.3. Carbonylation of allylbenzene (398)[19]

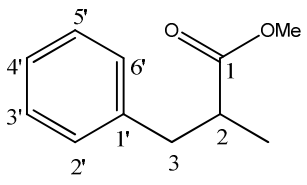


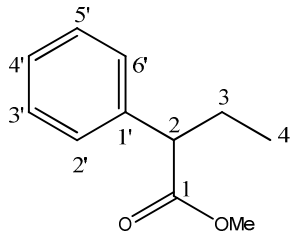
$Pd(OAc)_2$ (0.011 g, 0.049 mmol, 1 mol %), $Al(OTf)_3$ (0.045 g, 0.095 mmol, 2 mol %), PPh_3 (0.049 g, 0.187 mmol, 4 mol %) and allylbenzene (**398**) (0.45 ml, 3.02 mmol) were dissolved in MeOH (6 ml). The crude reaction mixture was purified with PLC (H:T:A 4:4:2) and the band with R_f 0.73 was identified as methyl 4-phenylbutanoate (**401**), a light yellow amorphous solid with ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 23a) δ_H ppm 7.31-7.28 (2H, m, H-3' and H-5'), 7.21-7.18 (3H, m, H-2', H-4' and H-6'), 3.67 (3H, s, -OMe), 2.66 (2H, t, J = 7.56 Hz, H-4), 2.34 (2H, t, J = 7.56 Hz, H-2), 1.97 (2H, p, J = 7.56 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 23b) δ_C ppm 174.00 (C-1), 141.38 (C-1'), 128.51 (C-2', C-6' or C-3', C-5'), 128.40 (C-2', C-6' or C-3', C-5'), 126.01 (C-4'), 51.54 (-OMe), 35.13 (C-4), 33.39 (C-2), 26.50 (C-3); IR (C=O) 1739 cm^{-1}; MS (EI) *m/z* 178 (M^+, 37 %), 147 (36 %), 146 (44 %), 105 (42 %), 104 (100 %).

5.13. Methoxycarbonylation of *trans-β*-methylstyrene (405)

5.13.1. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH[19]







$Pd(OAc)_2$ (0.010 g, 0.045 mmol, 1 mol %), $Al(OTf)_3$ (0.043 g, 0.091 mmol, 2 mol %), PPh_3 (0.049 g, 0.185 mmol, 4 mol %) and *trans-β*-methylstyrene (**405**) (0.60 ml, 4.63 mmol) were dissolved in MeOH (10.8 ml). Conversion (22 h, 46 %) to methyl 4-phenylbutanoate (**401**) [R_T 14.58 min., *m/z* = 178 (M^+, 18 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 13.38 min., *m/z* = 178 (M^+, 18 %)] and methyl 2-phenylbutanoate (**404**) [R_T 13.08 min., *m/z* = 178 (M^+, 33 %)] in relationship 3:2:1. The reaction mixture was purified with FCC (H:A 8:2) and the major product, methyl 4-phenylbutanoate (**401**), was isolated, identical in structure to the product previously characterized (*cf.* Paragraph 5.12.3). Fractions with R_f 0.57 were combined to give an inseparable mixture of methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) (0.37 g, 49 %) as a light yellow oil with ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 24a) δ_H 7.31-7.26 [2.9H, m, H-Ar, (**401**) (**403**) (**404**)], 7.21-7.16 [3.7H, m, H-

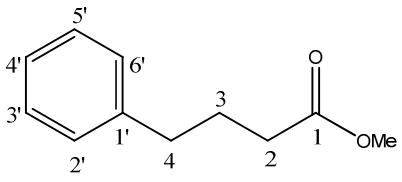
Ar, (**401**) (**403**) (**404**)], 3.67 [3H, s, -OMe, (**401**)], 3.66 [0.3H, s, -OMe, (**404**)], 3.64 [0.6H, s, -OMe, (**403**)], 3.46 [0.1H, t, *J* = 7.71 Hz, H-2, (**404**)], 3.03 [0.2H, dd, *J* = 6.83 and 13.56 Hz, H-3a/b, (**403**)], 2.76-2.71 [0.2H, m, H-2, (**403**)], 2.65 [0.4H, dd, *J* = 6.83 and 13.56 Hz, H-3a/b, (**403**)], 2.65 [2H, t, *J* = 7.56 Hz, H-4, (**401**)] 2.34 [2H, t, *J* = 7.56 Hz, H-2, (**401**)], 2.13-2.08 [0.1H, m, H-3a/b, (**404**)], 1.96 [2H, p, *J* = 7.56 Hz, H-3, (**401**)], 1.82-1.78 [0.1H, m, H-3a/b, (**404**)], 1.15 [3H, d, *J* = 6.9 Hz, 2-CH_3, (**403**)], 0.92 [0.3H, t, *J* = 7.43 Hz, H-4, (**404**)].

5.13.2. Optimization of the methoxycarbonylation reaction

5.13.2.1. Higher catalyst concentration

$Pd(OAc)_2$ (0.021 g, 0.094 mmol, 2 mol %), $Al(OTf)_3$ (0.086 g, 0.181 mmol, 4 mol %), PPh_3 (0.097 g, 0.370 mmol, 8 mol %) and *trans-β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml). Conversion (22 h, 51 %) to methyl 4-phenylbutanoate (**401**) [R_T 16.69 min., *m/z* = 178 (M^+, 15 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.40 min., *m/z* = 178 (M^+, 14 %)] and methyl 2-phenylbutanoate (**404**) [R_T 13.87 min., *m/z* = 178 (M^+, 32 %)] in relationship 7:2:1, identical to products previously characterized (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.2. $PdCl_2/Al(OTf)_3/PPh_3$ in MeOH



$PdCl_2$ (0.021 g, 0.118 mmol, 3 mol %), $Al(OTf)_3$ (0.108 g, 0.228 mmol, 6 mol %), PPh_3 (0.118 g, 0.450 mmol, 12 mol %) and *trans-β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml), an additional amount of PPh_3 (0.120 g, 0.458 mmol, 4 eq.) were added after 4 h of reaction time. Conversion (22 h, 90 %) to methyl 4-phenylbutanoate (**401**) [R_T 16.65 min., *m/z* = 178 (M^+, 15 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.38 min., *m/z* = 178 (M^+, 14 %)] and methyl 2-phenylbutanoate (**404**) [R_T 13.86 min., *m/z* = 178 (M^+, 35 %)] in relationship 7:2:1, identical to products previously characterized (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.3. Model methoxycarbonylation with Diab methodology[20]

$Pd(OAc)_2$ (0.022 g, 0.098 mmol, 2 mol %), *p*-TsOH (0.140 g, 0.736 mmol, 15 mol %), PPh_3 (0.101 g, 0.385 mmol, 8 mol %) and styrene (**313**) (0.55 ml, 4.78 mmol) were dissolved in MeOH (7 ml). Reaction was performed at 25 °C and under CO (10 bar) pressure. Conversion

(24 h, 99%) was found to methyl 3-phenylpropanoate (**400**) [R_T 12.00 min., *m/z* = 164 (M^+, 23 %)] with GCMS analysis.

5.13.2.4. $Pd(OAc)_2$/*p*-TsOH/PPh_3 low temperature[20]

$Pd(OAc)_2$ (0.019 g, 0.085 mmol, 2 mol %), *p*-TsOH (0.121 g, 0.636 mmol, 15 mol %), PPh_3 (0.090 g, 0.343 mmol, 8 mol %) and *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml). Reaction was performed at 25 °C and under CO (10 bar) pressure. Conversion (24 h, 2 %) to methyl 4-phenylbutanoate (**401**) [R_T 13.86 min., *m/z* = 178 (M^+, 11 %)] was observed with GCMS analysis (*cf.* Paragraph 5.12.3.).

5.13.2.5. $Pd(OAc)_2$/*p*-TsOH/PPh_3 medium temperature[20]

$Pd(OAc)_2$ (0.019 g, 0.085 mmol, 2 mol %), *p*-TsOH (0.121 g, 0.636 mmol, 15 mol %), PPh_3 (0.090 g, 0.343 mmol, 8 mol %) and *trans*-*β*-methylstyrene (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml). Reaction was performed at 50 °C and under CO (25 bar) pressure. Conversion (24 h, 50 %) to methyl 4-phenylbutanoate (**401**) [R_T 13.88 min., *m/z* = 178 (M^+, 15 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.40 min., *m/z* = 178 (M^+, 14 %)] and methyl 2-phenylbutanoate (**404**) [R_T 16.63 min., *m/z* = 178 (M^+, 33 %)] in a ratio of 5:4:1, identical to previously characterized products (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.6. $Pd(OAc)_2$/*p*-TsOH/PPh_3 high temperature[20]

$Pd(OAc)_2$ (0.019 g, 0.085 mmol, 2 mol %), *p*-TsOH (0.121 g, 0.636 mmol, 15 mol %), PPh_3 (0.089 g, 0.339 mmol, 8 mol %) and *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml). Reaction was performed at 95 °C and under CO (35 bar) pressure. Conversion (22 h, 79 %) to methyl 4-phenylbutanoate (**401**) [R_T 16.59 min., *m/z* = 178 (M^+, 32 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.37 min., *m/z* = 178 (M^+, 14 %)] and methyl 2-phenylbutanoate (**404**) [R_T 13.86 min., *m/z* = 178 (M^+, 15 %)] in a ratio of 4:2:1, (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.7. $Pd(OAc)_2$/$Al(OTf)_3$/PPh_3 in MeOH:dioxane

$Pd(OAc)_2$ (0.010 g, 0.045 mmol, 1 mol %), $Al(OTf)_3$ (0.042 g, 0.089 mmol, 2 mol %), PPh_3 (0.047 g, 0.179 mmol, 4 mol %) and *trans*-*β*-methylstyrene (**405**) (0.58 ml, 4.47 mmol) were dissolved in MeOH:dioxane (1:1, 10 ml). Conversion (22 h, 0.5 %) with GCMS analysis.

5.13.2.8. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH:toluene

$Pd(OAc)_2$ (0.010 g, 0.045 mmol, 1 mol %), $Al(OTf)_3$ (0.042 g, 0.089 mmol, 2 mol %), PPh_3 (0.047 g, 0.179 mmol, 4 mol %) and *trans*-*β*-methylstyrene (**405**) (0.58 ml, 4.47 mmol) were dissolved in MeOH:Toluene (6:4, 10 ml). Conversion (22 h, 34 %) to methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) in relationship 2:2:1, identical to previously characterized products (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.9. $Pd(OAc)_2/Al(OTf)_3/PPh_3$ in MeOH:DMA

$Pd(OAc)_2$ (0.010 g, 0.045 mmol, 1 mol %), $Al(OTf)_3$ (0.042 g, 0.089 mmol, 2 mol %), PPh_3 (0.047 g, 0.179 mmol, 4 mol %) and *trans*-*β*-methylstyrene (**405**) (0.58 ml, 4.47 mmol) were dissolved in MeOH:DMA (6:4, 10 ml). No products were detected with GCMS analysis.

5.13.2.10. $PdCl_2/Al(OTf)_3/PPh_3$ in MeOH:DME

$PdCl_2$ (0.020 g, 0.114 mmol, 2 mol %), $Al(OTf)_3$ (0.108 g, 0.228 mmol, 4 mol %), PPh_3 (0.119 g, 0.453 mmol, 8 mol %) and *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH:DME (1:1, 7 ml). Conversion (22 h, 60 %) to methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) in relationship 5:2:1, (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.11. $PdCl_2/Al(OTf)_3/PPh_3$ in MeOH:THF

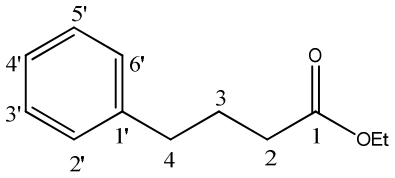
$PdCl_2$ (0.020 g, 0.114 mmol, 2 mol %), $Al(OTf)_3$ (0.107 g, 0.226 mmol, 4 mol %), PPh_3 (0.119 g, 0.453 mmol, 8 mol %) and *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH:THF (1:1, 7 ml). Conversion (22 h, 61 %) to methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**) in a 5:3:1 ratio, (*cf.* Paragraphs 5.12.3. and 5.12.6.).

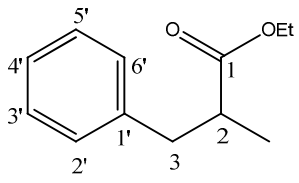
5.13.2.12. $Pd(OAc)_2$/*p*-TsOH/PPh_3 in MeOH:THF

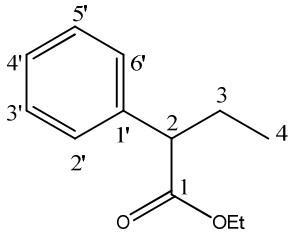
$Pd(OAc)_2$ (0.019 g, 0.085 mmol, 2 mol %), *p*-TsOH (0.121 g, 0.636 mmol, 15 mol %), PPh_3 (0.089 g, 0.339 mmol, 8 mol %) and *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in MeOH:THF (7 ml, 1:1). Reaction was performed at 95 °C and under CO (35 bar) pressure. Conversion (24 h, 38 %) to methyl 4-phenylbutanoate (**401**) [R_T 16.66 min., *m/z* = 178 (M^+, 14 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.40 min., *m/z* = 178 (M^+,

14 %)] and methyl 2-phenylbutanoate (**404**) [R_T 13.88 min., *m/z* = 178 (M^+, 34 %)] in a ratio of 4:2:1, (*cf.* Paragraphs 5.12.3. and 5.12.6.).

5.13.2.13. $PdCl_2/Al(OTf)_3/PPh_3$ in EtOH







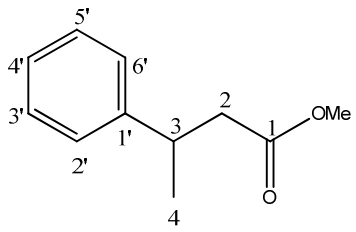
$PdCl_2$ (0.020 g, 0.113 mmol, 2 mol %), $Al(OTf)_3$ (0.108 g, 0.228 mmol, 4 mol %), PPh_3 (0.119 g, 0.454 mmol, 8 mol %) and *trans-β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) were dissolved in EtOH (10 ml). Conversion (24 h, 80 %) to ethyl 4-phenylbutanoate (**406**) [R_T 18.94 min., *m/z* = 192 (M^+, 11 %)], ethyl 2-methyl-3-phenylpropanoate (**407**) [R_T 16.16 min., *m/z* = 192 (M^+, 15 %)] and ethyl 2-phenylbutanoate (**408**) [R_T 15.41 min., *m/z* = 192 (M^+, 33 %)] in relationship 6:3:1. The reaction mixture was separated with FCC (H:A 8:2) and fractions with R_f 0.68 were combined to give a mixture of ethyl 4-phenylbutanoate (**406**), ethyl 2-methyl-3-phenylpropanoate (**407**) and ethyl 2-phenylbutanoate (**408**) (0.44 g, 54 %) as a yellow oil with ^1H NMR (600 MHz, $CDCl_3$) (Plate 25a) δ_H ppm 7.35-7.29 [2.8H, m, H-Ar, (**406**) (**407**) (**408**)], 7.24-7.20 [3.7H, m, H-Ar, (**406**) (**407**) (**408**)], 4.16 [2H, q, *J* = 7.14 Hz, -OCH_2-, (**406**)], 4.12 [0.3H, q, *J* = 7.13 Hz, -OCH_2- (**408**)], 4.12 [0.6H, q, *J* = 7.15 Hz, -OCH_2- (**407**)], 3.48 [0.1H, t, *J* = 7.71 Hz, H-2, (**408**)], 3.06 [0.3H, dd, *J* = 6.83 and 13.20 Hz, H-3a/b, (**407**)], 2.79-2.73 [0.3H, m, H-2, (**407**)], 2.72 [0.3H, dd, *J* = 7.07 and 13.20 Hz, H-3a/b, (**407**)], 2.68 [2H, t, *J* = 7.57 Hz, H-4, (**406**)], 2.35 [2H, t, *J* = 7.57 Hz, H-2, (**406**)], 2.18-2.10 [0.1H, m, H-3a/b, (**408**)], 2.00 [2H, p, *J* = 7.57 Hz, H-3, (**406**)], 1.88-1.79 [0.1H, m, H-3a/b, (**408**)], 1.28 [3H, t, *J* = 7.14 Hz, -$OCH_2\underline{CH_3}$, (**406**)], 1.24 [0.3H, t, *J* = 7.13 Hz, -$OCH_2\underline{CH_3}$, (**408**)], 1.22 [0.9H, t, *J* = 7.15 Hz, -$OCH_2\underline{CH_3}$ (**407**)], 1.19 [0.9H, d, *J* = 6.86 Hz, 2-CH_3 (**407**)], 0.94 (0.3H, t, *J* = 7.37 Hz, H-4, (**408**)]; IR (FT) (C=O) 1735 cm^{-1}.

5.13.2.14. Optimization of reaction conditions

Catalyst system, $PdCl_2/Al(OTf)_3/PPh_3$ in a 1:2:4 ratio, and *trans-β*-methylstyrene (0.55 ml, 4.24 mmol, 37 eq.) were dissolved in MeOH (7 ml), added to the Parr reactor and degassed with CO (x5). The reaction conditions (CO pressure and temperature) were as stated in Table 4-11. After 4 hours, more PPh_3 (12 mol %) was added. Aliquots of reaction mixture were analysed by GCMS and conversion values determined.

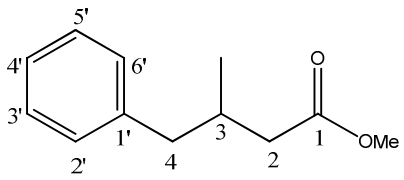
5.14. Methoxycarbonylation of disubstituted styrenes

5.14.1. Carbonylation of *α*-methylstyrene (409)



$PdCl_2$ (0.020 g, 0.113 mmol, 3 mol %), $Al(OTf)_3$ (0.109 g, 0.230 mmol, 6 mol %), PPh_3 (0.120 g, 0.458 mmol, 12 mol %) and *α*-methylstyrene (**409**) (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml). Conversion (22 h, 38 %) to methyl 3-phenylbutanoate (**410**) (R_T 14.56 min.). The reaction mixture was separated with FCC (H:T:A 80:17:3) and fractions with R_f 0.57 were combined to give methyl 3-phenylbutanoate (**410**) (0.18 g, 25 %) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 26a) δ_H ppm 7.29-7.26 (2H, m, H-3' and H-5'), 7.21-7.17 (3H, m, H-2', H-4' and H-6'), 3.59 (3H, s, -OMe), 3.30-3.24 (1H, m, H-3), 2.61 (1H, dd, *J* = 15.20, 6.91 Hz, H-2a or H-2b), 2.54 (1H, dd, *J* = 15.20, 8.23 Hz, H-2a or H-2b), 1.29 (3H, d, *J* = 7.0 Hz, H-4); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 26b) δ_C ppm 172.82 (C-1), 145.71 (C-1'), 128.53 (C-3' and C-5'), 126.73 (C-2' and C-6'), 126.44 (C-4'), 51.47 (-OMe), 42.72 (C-2), 36.45 (C-3), 21.79 (C-4); IR (FT) 1740 (C=O) cm^{-1}; MS (EI) *m/z* 178 (M^+, 24 %), 121 (14 %), 118 (72 %), 105 (100 %), 77 (18 %).

5.14.2. Carbonylation of 2-methyl-1-phenylprop-1-ene (411)



$PdCl_2$ (0.020 g, 0.113 mmol, 3 mol %), $Al(OTf)_3$ (0.107 g, 0.226 mmol, 6 mol %), PPh_3 (0.119 g, 0.454 mmol, 12 mol %) and 2-methyl-1-phenylpropene (**411**) (0.55 ml, 4.24 mmol) were dissolved in MeOH (7 ml). Conversion (22 h, 22 %) to methyl 3-methyl-4-phenylbutanoate (**412**) (R_T 17.53 min) according to GCMS analysis. The reaction mixture was separated with PLC (H:A 6:4) and the band with R_f 0.85 were scraped off to give methyl 3-methyl-4-phenylbutanoate (**412**) (0.04 g, 6 %) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 27a) δ_H ppm 7.29-7.27 (2H, m, H-3' and H-5'), 7.21-7.18 (1H, m, H-4'), 7.17-7.15 (2H, m, H-2' and H-6'), 3.65 (3H, s, -OMe), 2.62 (1H, dd, *J* = 13.45, 6.76 Hz, H-4a or H-4b), 2.51 (1H, dd, *J* = 13.45, 7.44 Hz, H-4a or H-4b), 2.34 (1H, dd, *J* = 14.66, 5.76 Hz, H-2a or H-2b), 2.31-2.25 (1H, m, H-3), 2.14 (1H, dd, *J* = 14.66, 7.87 Hz, H-2a or H-2b), 0.94 (3H, d, *J* = 6.58 Hz, 3-CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 27b) δ_C ppm 173.67 (C-1), 140.36 (C-1'), 129.35 (C-2' and C-6'), 128.39 (C-3' and C-

5'), 126.17 (C-4'), 51.55 (-OMe), 43.16 (C-4), 41.02 (C-2), 32.41 (C-3), 19.79 (3-CH_3); MS (EI) *m/z* 192 (M^+, 14 %), 161 (13 %), 118 (100 %), 117 (30 %), 91 (65 %).

5.15. Synthesis of substituted styrenes

5.15.1. 1-(4'-Trifluoromethanesulfonyloxyphenyl)propan-1-one (418)[4]

Utilizing the procedure described in Paragraph 5.9.3., 4-hydroxypropiophenone (**417**) (2.01 g, 13.38 mmol), EtN_3 (2.80 ml, 20.09 mmol, 1.5 eq.) and trifluoromethanesulfonyl chloride (1.55 ml, 14.65 mmol, 1.1 eq.) gave 1-(4'-trifluoromethanesulfonyloxyphenyl)propan-1-one (**418**) which was used directly in the reduction reaction to give 1-(4'-trifluoromethane-sulfonyloxyphenyl)propan-1-ol (**419**).

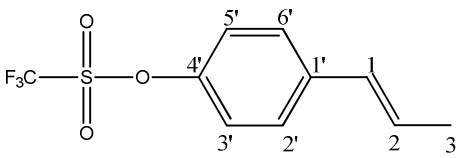
5.15.2. 1-(4'-Trifluoromethanesulfonyloxyphenyl)propan-1-ol (419)[3]

As described in Paragraph 5.7.1. $NaBH_4$ (1.12 g, 29.56 mmol, 2.2 eq.) and 1-(4'-trifluoromethanesulfonyloxyphenyl)propan-1-one (**418**) (~3.8 g, 13.46 mmol) were reacted to give the crude product which was used directly in the dehydration reaction to synthesize 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**).

5.15.3. General elimination procedure[18]

The alcohol (1 eq.) was dissolved in dry hexane (40 ml) and anhydrous $CuSO_4$ (2 eq.) added. The reaction mixture was refluxed overnight where after the standard work-up procedure was followed with an extraction into hexane. The solvent was concentrated under reduced pressure and the crude product purified further.

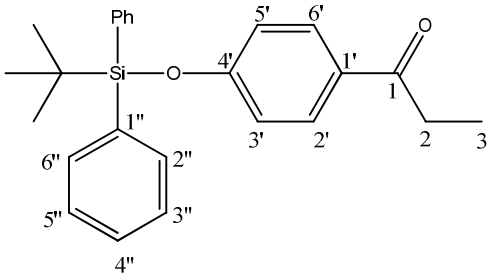
5.15.3.1. *Trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (420)[18]



1-(4'-Trifluoromethanesulfonyloxyphenyl)propan-1-ol (**419**) (~ 3.83 g, 13.47 mmol) and $CuSO_4$ (4.34 g, 27.18 mmol, 2 eq.) gave the crude product which was purified by FCC (H:A 8:2) and fractions with an R_f of 0.70 were combined to obtain *trans*-1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**) (0.56 g, 16 %) as a *light yellow oil*. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 29a) δ_H ppm 7.37 (2H, d, J = 8.80 Hz, H-2' and H-6'), 7.19 (2H, d, J = 8.80 Hz, H-3' and H-5'), 6.39 (1H, br dd, J = 15.76, 1.65 Hz, H-1), 6.27 (1H, dq, J = 15.76, 6.59 Hz, H-2), 1.90 (3H, dd, J = 6.59, 1.65 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 29b) δ_C ppm 148.29 (C-4'), 138.51 (C-1'), 129.37 (C-1),

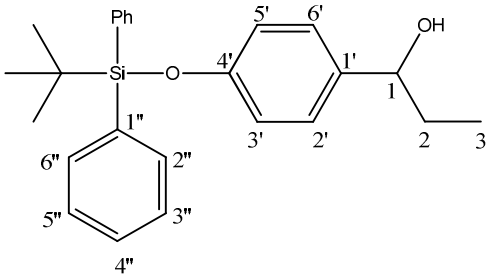
128.27 (C-2), 127.43 (C-2' and C-6'), 121.47 (C-3' and C-5'), 118.90 (q, J = 320.94 Hz, -CF_3), 18.60 (C-3); MS (TOF-MS-AP, positive mode) *m/z* 267.0298 (M^+).

5.15.4. 1-(4'-*Tert*-butyldiphenylsilyloxyphenyl)propan-1-one (424)[12]



As portrayed in Paragraph 5.9.2. 4'-hydroxypropiophenone (**417**) (1.50 g, 10.00 mmol), imidazole (3.41 g, 54.07 mmol, 5.4 eq.) and *tert*-butyldiphenylsilyl chloride (4.50 ml, 3.92 g, 25.98 mmol, 2.6 eq.) gave a crude product mixture which was purified with FCC (H:EtOAc 95:5). Fractions with R_f 0.27 were combined to afford 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one (**424**) (1.94 g, 83 %) as colourless needle crystals with m.p. 66.9-68.2. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 31a) δ_H ppm 7.75 (2H, d, J = 8.77 Hz, H-2' and H-6'), 7.70 (4H, dd, J = 7.04, 1.31 Hz, H-2" and H-6"), 7.46-7.43 (2H, m, H-4"), 7.38 (4H, dd, J = 7.58, 7.04 Hz, H-3" and H-5"), 6.79 (2H, d, J = 8.77 Hz, H-3' and H-5'), 2.88 (q, J = 7.27 Hz, H-2), 1.16 (t, J = 7.27 Hz, H-3), 1.10 [9H, s, -$(CH_3)_3$]; ^{13}C NMR (151 MHz, $CDCl_3$) δ_C ppm 199.78 (C-1), 159.94 (C-4'), 135.53 (C-2" and C-6"), 132.30 (C-1"), 130.51 (C-1'), 130.24 (C-4"), 130.00 (C-2' and C-6'), 128.05 (C-3" and C-5"), 119.74 (C-3' and C-5'), 31.49 (C-2), 26.52 [-$(CH_3)_3$], 19.58 [C-$(CH_3)_3$], 8.50 (C-3); MS (EI) *m/z* 390 (M^+, 2 %), 332 (100 %), 334 (32 %), 257 (61 %), 221 (21 %).

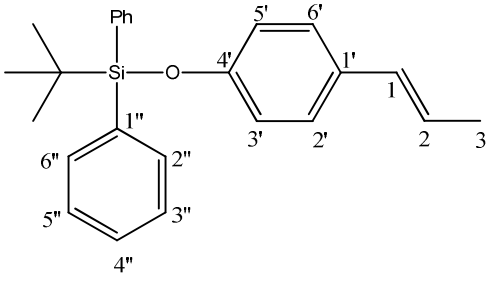
5.15.5. 1-(4'-*Tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (425)[3]



Utilizing the reduction procedure described in Paragraph 5.7.1 $NaBH_4$ (0.20 g, 5.39 mmol, 2.2 eq.) and 1-phenyl-4'-*tert*-butyldiphenylsilyloxypropanone (0.93 g, 2.40 mmol) gave the crude product which was purified with PLC (H:EtOAc 95:5) to obtain 1-(4'-*tert*-butyldiphenylsilyloxy-phenyl)propan-1-ol (**425**) in quantitative yield as a *colourless oil* with R_f 0.32. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 32a) δ_H ppm 7.76-7.74 (4H, m, H-2" and H-6"), 7.46-7.43 (2H, m, H-4"), 7.40-7.37 (4H, m, H-3" and H-5"), 7.08 (2H, d, J = 8.39 Hz, H-2' and H-6'), 6.77 (2H, d, J = 8.39 Hz, H-3' and H-5'), 4.46 (1H, t, J = 6.67 Hz, H-1), 1.81-1.74 (1H, m, H-2a or H-2b), 1.71-1.64 (1H, m, H-2a or H-2b), 1.14 [9H, s, -$(CH_3)_3$], 0.86 (3H, t, J = 7.42 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 32b) δ_C ppm 155.00 (C-4'), 137.07 (C-1'), 135.56 (C-2" and C-6"), 132.97 (C-1"), 129.92 (C-4"), 127.80 (C-3" and C-5"), 127.00 (C-2' and C-6'), 119.58 (C-3' and C-5'),

75.68 (C-1), 31.72 (C-2), 26.57 [-$(CH_3)_3$], 19.57 [C-$(CH_3)_3$], 10.31 (C-3); MS (TOF-MS-ES, positive mode) *m/z* 413.1913 (M^+ +Na).

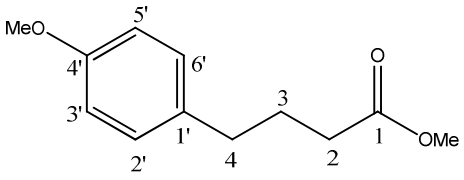
5.15.6. *Trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (426)[18]

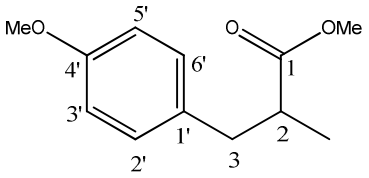


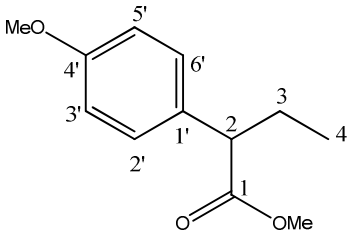
Following the elimination procedure shown in Paragraph 5.15.3. *trans*-1-(4'-*tert*-butyldiphenyl-silyloxyphenyl)-propanol (**425**) (0.68 g, 1.74 mmol) and $CuSO_4$ (0.96 g, 6.01 mmol, 3.5 eq.) gave the crude product mixture which was purified with FCC (H:A 8:2). Fractions with R_f 0.76 were combined to obtain 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**) (0.617 g, 95 %) as a *bright yellow oil*. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 33a) δ_H ppm 7.76-7.73 (4H, m, H-2" and H-6"), 7.46-7.43 (2H, m, H-4"), 7.40-7.37 (4H, m, H-3" and H-5"), 7.09 (2H, d, *J* = 8.64 Hz, H-2' and H-6'), 6.72 (2H, d, *J* = 8.64 Hz, H-3' and H-5'), 6.29 (1H, dd, *J* = 15.70, 1.64 Hz, H-1), 6.05 (1H, dd, *J* = 15.70, 6.64 Hz, H-2), 1.83 (1H, dd, *J* = 6.64, 1.64 Hz, H-3), 1.12 [9H, s, -$(CH_3)_3$]; ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 33b) δ_C ppm 154.70 (C-4'), 135.64 (C-2" and C-6"), 133.09 (C-1"), 131.12 (C-1'), 130.53 (C-1), 129.95 (C-4"), 127.89 (C-3" and C-5"), 126.75 (C-2' and C-6'), 123.60 (C-2), 119.81 (C-3' and C-5'), 26.64 [-$(CH_3)_3$], 19.59 [C-$CH_3)_3$], 18.53 (C-3); MS (TOF-MS-ES, positive mode) *m/z* 395.1810 (M^+).

5.16. Methoxycarbonylation of other substituted styrenes

5.16.1. Carbonylation of *trans*-anethole (413)

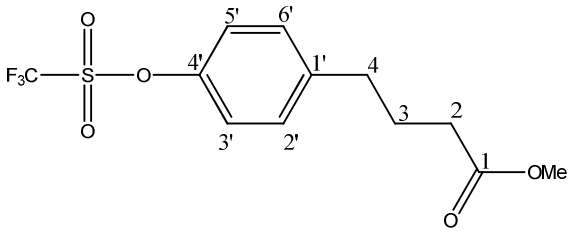






$PdCl_2$ (0.021 g, 0.118 mmol, 3 mol %), $Al(OTf)_3$ (0.110 g, 0.232 mmol, 6 mol %), PPh_3 (0.120 g, 0.458 mmol, 12 mol %) and *trans*-anethole (**413**) (0.51 ml, 3.40 mmol) were dissolved in MeOH (10 ml). Conversion (22 h, 21 %) to methyl 4-(4'-methoxyphenyl)butanoate (**414**) [R_T 23.79 min., *m/z* = 208 (M^+, 26 %)], methyl 2-methyl-3-(4'-methoxyphenyl)propanoate (**415**) [R_T 22.72 min., *m/z* = 208 (M^+, 11 %)] and methyl 2-(4'-methoxyphenyl)butanoate (**416**) [R_T 22.47 min., *m/z* = 208 (M^+, 21 %)] in a 2:1:1 ratio. The reaction mixture was separated with FCC (H:T:A 4:4:2) and fractions with R_f 0.70 were combined to give a mixture of the three products, (**414**), (**415**) and (**416**), as a light yellow oil with ^1H NMR (600 MHz, $CDCl_3$) (Plate 28a) δ_H ppm 7.22 [0.4H, d, *J* = 8.67 Hz, H-2' and H-6', (**416**)], 7.10 [2H, d, *J* = 8.51 Hz, H-2' and H-6', (**414**)], 7.08 [0.8H, d, *J* = 8.46 Hz, H-2' and H-6', (**415**)], 6.86 [0.4H, d, *J* = 8.67 Hz, H-3' and H-5', (**416**)], 6.83 [2H, d, *J* = 8.51 Hz, H-3' and H-5', (**414**)], 6.82 [0.8H, d, *J* = 8.46 Hz, H-3' and H-5', (**415**)], 3.79 [4.8H, s, -PhOMe, (**414**), (**415**), (**416**)], 3.66 [3H, s, -COOMe, (**414**)], 3.65 [0.6H, s, -COOMe, (**416**)], 3.64 [1.2H, s, -COOMe, (**415**)], 3.40 [0.2H, t, *J* = 7.71 Hz, H-2, (**416**)], 2.96 [0.4H, dd, *J* = 6.93 and 13.53 Hz, H-3a/b (**415**)], 2.72-2.66 [0.4H, m, H-2 (**415**)], 2.62 [0.4H, dd, *J* = 7.68 and 13.53 Hz, H-3a/b, (B)], 2.59 [2H, t, *J* = 7.54 Hz, H-4, (**414**)], 2.32 [2H, t, *J* = 7.54 Hz, H-2, (**414**)], 2.09-2.03 [0.2H, m, H-3a/b (**416**)], 1.92 [2H, p, *J* = 7.54 Hz, H-3, (**414**)], 1.80-1.73 (0.2H, m, H-3a/b (**416**)], 1.14 [1.2H, d, *J* = 6.92 Hz, 2-CH_3, (**415**)], 0.87 [0.6H, t, *J* = 7.36 Hz, H-4 (**416**)].

5.16.2. Carbonylation of 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (420)



$PdCl_2$ (0.020 g, 0.113 mmol, 9 mol %), $Al(OTf)_3$ (0.108 g, 0.228 mmol, 18 mol %), PPh_3 (0.120 g, 0.458 mmol, 36 mol %) and 4'-trifluoromethane-sulfonyloxy-1-phenylpropene (**420**) (0.396 g, 1.214 mmol) were dissolved in MeOH (7 ml). Conversion (22 h, 31 %) to methyl 4-(4'-trifluoromethanesulfonyloxyphenyl)-butanoate (**421**) [R_T 24.21 min., *m/z* = 326 (M^+, 22 %)], methyl 2-methyl-3-(4'-trifluoro-methanesulfonyloxyphenyl)-propanoate (**422**) [R_T 22.02 min., *m/z* = 326 (M^+, 18 %)] and methyl 2-(4'-trifluoromethane-sulfonyloxyphenyl)butanoate (**423**) [R_T 21.37 min., *m/z* = 326 (M^+, 22 %)] in a 10:4:1 ratio. Separation with PLC (H:T 1:1) gave methyl 4-(4'-trifluoro-methanesulfonyloxyphenyl)butanoate (**421**) (0.02 g, 4 %) as a light yellow oil with R_f 0.78; ^1H NMR (600 MHz, $CDCl_3$) (Plate 30a) δ_H ppm 7.26 (2H, d, *J* = 8.64 Hz, H-3' and H-5'), 7.19 (2H, d, *J* = 8.64 Hz, H-2' and H-6'), 3.67 (3H, s, -OMe), 2.68 (2H, t, *J* = 7.55 Hz, H-4), 2.34 (2H, t, *J* = 7.55 Hz, H-2), 1.96 (2H, p, *J* = 7.55 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 30b) δ_C ppm 173.78 (C-1), 148.05 (C-4'), 142.13 (C-1'), 130.31 (C-3' and C-5'), 121.36 (C-2' and C-6'), 118.88 (q, *J* = 320.87 Hz, $-CF_3$), 51.76 (-OMe), 34.56 (C-4), 33.34 (C-2), 26.38 (C-3); IR (FT) 1741 (C=O) cm^{-1}; MS (EI) *m/z* 326 (M^+, 11 %), 295 (16 %), 252 (23 %), 133 (19 %), 119 (22 %).

5.16.3. Carbonylation of *trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (426)

$PdCl_2$ (0.020 g, 0.116 mmol, 12 mol %), $Al(OTf)_3$ (0.107 g, 0.226 mmol, 24 mol %), PPh_3 (0.118 g, 0.450 mmol, 48 mol %) and *trans*-1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**) (0.330 g, 0.887 mmol) were dissolved in MeOH:Toluene (5:1, 12 ml). The reaction mixture was separated with PLC (H:A 8:2) to give only a trace amount of product.

5.17. Aminocarbonylation of *trans*-*β*-methylstyrene (405)

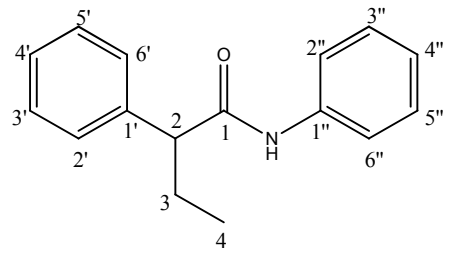
$PdCl_2$ (1 eq.), $Al(OTf)_3$ (2 eq.), PPh_3 (4 eq.), substrate and nitrogen containing nucleophile were dissolved in the specified solvent, added to the Parr reactor vessel and degassed with CO (x5). The reaction was performed at 95 °C under 35 bar of CO pressure, unless stated otherwise. Samples of reaction mixture were analysed on GCMS and reported conversion

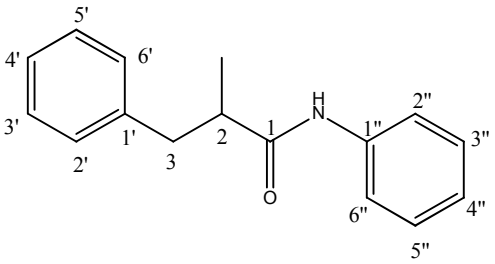
values were determined. After completion the reaction mixture was dissolved in EtOAc and diluted HCl was added (pH 5) where after the standard work-up procedure was followed.

5.17.1. Aniline as nucleophile (attempt 1)

$PdCl_2$ (0.020 g, 0.113 mmol, 3 mol %), PPh_3 (0.119 g, 0.454 mmol, 12 mol %), *trans-β*-methylstyrene (0.55 ml, 4.24 mmol) and aniline (3.50 ml, 38.41 mmol, 9 eq.) were dissolved in THF (3.5 ml). Conversion (22 h, 6 %) to *N*-phenyl 4-phenylbutanamide [R_T 30.51 min., *m/z* = 239 (M^+, 30 %)] was detected (GCMS).

5.17.2. Aniline as nucleophile (attempt 2)





$PdCl_2$ (0.020 g, 0.113 mmol, 3 mol %), $Al(OTf)_3$ (0.108, 0.228 mmol, 6 mol %), PPh_3 (0.120 g, 0.458 mmol, 12 mol %), *trans-β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) and aniline (3.5 ml, 38.41 mmol, 9 eq.) were dissolved in THF (3.5 ml). Conversion (22 h, 53 %) to *N*,2-diphenylbutanamide (**444A**) [R_T 30.55 min., *m/z* = 239 (M^+, 30%)] and 2-methyl-*N*,3-diphenylpropanamide (**444B**) [R_T 30.84 min., *m/z* = 239 (M^+, 31 %)] in a ratio of 6:1. Separation with FCC (H:T:A 4:4:2) gave a mixture of *N*,2-diphenylbutanamide (**444A**) and 2-methyl-*N*,3-diphenylpropan-amide (**444B**) as a light yellow amorphous solid: m.p. 75.5-77.9 °C (lit.[21] m.p. 95-96 °C); R_f 0.54 (H:T:A 4:4:2); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 34a) δ_H ppm 7.44-7.43 [2H, m, H-Ar, (**444A**) (**444B**)], 7.35-7.36 [4H, m, H-Ar, (**444A**) (**444B**)], 7.32-7.14 [6H, m, H-Ar, (**444A**) (**444B**)], 7.07-7.05 [1H, m, H-Ar, (**444A**) (**444B**)], 3.40 [1H, t, *J* = 7.55 Hz, H-2, (**444A**)], 3.03 [0.15H, dd, *J* = 8.52, 13.55 Hz, H-3a/b, (**444B**)], 2.76 [0.15H, dd, *J* = 6.33, 13.55 Hz, H-3a/b, (**444B**)], 2.63-2.57 [0.15H, m, H-2, (**444B**)] 2.31-2.23 [1H, m, H-3a/b, (**444A**)], 1.90-1.83 [1H, m, H-3a/b, (**444A**)], 1.28 [0.5H, d, *J* = 6.79 Hz, 2-CH_3, (**444B**)] 0.92 [3H, t, *J* = 7.38 Hz, H-4, (**444A**)]; ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 34c) δ_C ppm 174.06 [C-1, (**444B**)], 171.87 (C-1), 139.63 (C-1'), 137.99 (C-1''), 129.12, 129.03, 128.18, 127.62, 124.35, 119.88, 56.25 (C-2), 26.53 (C-3), 12.47 (C-4); IR 1654 cm^{-1}.

5.17.3. Aniline as nucleophile (attempt 3)

$PdCl_2$ (0.020 g, 0.113 mmol, 3 mol %), $Al(OTf)_3$ (0.108, 0.228 mmol, 6 mol %), PPh_3 (0.119 g, 0.454 mmol, 10 mol %), *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) and aniline (2.00 ml, 21.95 mmol, 5 eq.) were dissolved in THF (5 ml). Conversion (22 h, 15 %) to N,2-diphenylbutanamide [R_T 30.49 min., *m/z* = 239 (M^+, 31 %)] and 2-methyl-N,3-diphenylpropanamide [R_T 30.79 min., *m/z* = 239 (M^+, 35 %)] in a 3:1 ratio, as previously characterized (*cf.* Paragraph 5.17.2.).

5.17.4. Benzamide as nucleophile

$PdCl_2$ (0.021 g, 0.118 mmol, 3 mol %), $Al(OTf)_3$ (0.110, 0.232 mmol, 6 mol %), PPh_3 (0.119 g, 0.454 mmol, 12 mol %), *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) and benzamide (1.40 g, 11.56 mmol, 3 eq.) were dissolved in THF (9 ml). No product formation was detected with GCMS analysis.

5.17.5. Butylamine as nucleophile

$PdCl_2$ (0.020 g, 0.113 mmol, 3 mol %), $Al(OTf)_3$ (0.109, 0.230 mmol, 6 mol %), PPh_3 (0.119 g, 0.454 mmol, 12 mol %), *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) and butylamine (3.80 ml, 38.45 mmol, 9 eq.) were dissolved in THF (3.2 ml). No product formation was detected with GCMS analysis.

5.17.6. Piperidine as nucleophile

$PdCl_2$ (0.021 g, 0.118 mmol, 3 mol %), $Al(OTf)_3$ (0.109, 0.230 mmol, 6 mol %), PPh_3 (0.119 g, 0.454 mmol, 12 mol %), *trans*-*β*-methylstyrene (**405**) (0.55 ml, 4.24 mmol) and piperidine (3.80 ml, 38.47 mmol, 9 eq.) were dissolved in THF (7 ml). No product formation was detected with GCMS analysis.

5.18. Methoxycarbonylation of stilbenes

5.18.1. Carbonylation of *trans*-stilbene (384) in MeOH[19]

$Pd(OAc)_2$ (0.011 g, 0.049 mmol, 2 mol %), $Al(OTf)_3$ (0.047 g, 0.099 mmol, 4 mol %), PPh_3 (0.053 g, 0.200 mmol, 8 mol %) and *trans*-stilbene (**384**) (0.402 g, 2.23 mmol) were dissolved in MeOH (6 ml). No product was detected with GCMS analysis.

5.18.2. Carbonylation of *trans*-stilbene (384)[19] in MeOH:dioxane (1:1)

$Pd(OAc)_2$ (0.010 g, 0.045 mmol, 1 mol %), $Al(OTf)_3$ (0.045 g, 0.095 mmol, 2 mol %), PPh_3 (0.046 g, 0.177 mmol, 4 mol %) and *trans*-stilbene (**384**) (0.802 g, 4.45 mmol) were dissolved in MeOH:Dioxane (1:1, 18 ml). No product was detected with GCMS analysis.

5.18.3. Carbonylation of *trans*-stilbene (384) in MeOH:THF

$PdCl_2$ (0.020 g, 0.113 mmol, 6 mol %), $Al(OTf)_3$ (0.109 g, 0.230 mmol, 12 mol %), PPh_3 (0.119 g, 0.455 mmol, 24 mol %) and *trans*-stilbene (**384**) (0.305 g, 1.694 mmol) were dissolved in MeOH:THF (1:1, 7 ml). Conversion (22 h, 1 %) to methyl 2,3-diphenylpropanoate [R_T 26.46 min., *m/z* = 240 (M^+, 17 %)] was observed with GCMS analysis.

5.18.4. Carbonylation of *cis*-stilbene (445)

$PdCl_2$ (0.020 g, 0.113 mmol, 6 mol %), $Al(OTf)_3$ (0.108 g, 0.228 mmol, 12 mol %), PPh_3 (0.119 g, 0.455 mmol, 24 mol %) and *cis*-stilbene (**445**) (0.4 ml, 2.25 mmol) were dissolved in MeOH:THF (1:1, 7 ml). Conversion (22 h, 4 %) to methyl 2,3- diphenylpropanoate [R_T 26.46 min., *m/z* = 240 (M^+, 17 %)] was observed with GCMS analysis.

5.18.5. Carbonylation of *trans*-stilbene (384) [with *p*-TsOH and $Al(OTf)_3$]

$PdCl_2$ (0.021 g, 0.118 mmol, 6 mol %), $Al(OTf)_3$ (0.108 g, 0.228 mmol, 12 mol %), PPh_3 (0.119 g, 0.455 mmol, 24 mol %), PTSA (0.045 g, 0.235 mmol, 12 mol %) and *trans*-stilbene (**384**) (0.309 g, 1.717 mmol) were dissolved in MeOH:THF (1:1, 7 ml). No product formation was observed with GCMS analysis.

5.18.6. Carbonylation of 2-methoxystilbene (330)

$PdCl_2$ (0.020 g, 0.113 mmol, 9 mol %), $Al(OTf)_3$ (0.107 g, 0.226 mmol, 18 mol %), PPh_3 (0.118 g, 0.451 mmol, 36 mol %) and 2-methoxystilbene (**330**) (0.257 g, 1.223 mmol) were dissolved in MeOH (9 ml). Conversion (22 h, 3 %) to methyl 3-(4'-methoxyphenyl)-2-phenylpropanoate (**447**) and methyl 2-(4'-methoxyphenyl)-3-phenylpropanoate (**448**) the one with R_T 27.4 min., *m/z* = 270 (M^+, 39 %), 179 (100 %), 151 (54 %), 121 (20 %), 108 (40 %) and the other with R_T 28.3 min., *m/z* = 270 (M^+, 14 %), 179 (67 %), 151 (40 %), 121 (100 %), 91 (21 %) was observed with GCMS analysis.

5.19. Methoxycarbonylation with bidentate ligands

5.19.1. BINAP-catalyst system[22]

The substrate and catalyst system, $Pd(OAc)_2$:$Al(OTf)_3$:BINAP 1:2:4, were dissolved in the specified solvent, added to the Parr reactor vessel and degassed with CO (x5). The reaction was performed at 80 °C under 35 bar of CO pressure, unless stated otherwise. Samples of reaction mixture were analysed on GCMS to determine the conversion values.

5.19.1.1. Carbonylation of phenyl acetylene (452)[22]

$Pd(OAc)_2$ (0.011 g, 0.049 mmol, 2 mol %), $Al(OTf)_3$ (0.044 g, 0.093 mmol, 4 mol %), BINAP (0.115 g, 0.185 mmol, 8 mol %) and phenyl acetylene (**452**) (0.25 ml, 2.28 mmol) were dissolved in MeOH (7 ml). Conversion (24 h, 64 %) to methyl 3-phenylprop-2-enoate (**453**) [R_T 13.46 min., *m/z* = 162 (M^+, 54 %)] and methyl 2-phenylprop-2-enoate (**454**) [R_T 16.58 min., *m/z* = 162 (M^+, 57 %)] in a 63:1 ratio.

5.19.1.2. Carbonylation of *trans-β*-methylstyrene (405)[22]

$Pd(OAc)_2$ (0.020 g, 0.089 mmol, 4 mol %), $Al(OTf)_3$ (0.086 g, 0.181 mmol, 8 mol %), BINAP (0.223 g, 0.337 mmol, 16 mol %) and *trans-β*-methylstyrene (**405**) (0.25 ml, 2.28 mmol) were dissolved in MeOH (7 ml). Conversion (24 h, 18 %) to methyl 4-phenylbutanoate (**401**) [R_T 16.49 min., *m/z* = 178 (M^+, 17 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.25 min., *m/z* = 178 (M^+, 16 %)] and methyl 2-phenylbutanoate (**404**) [R_T 13.73 min., *m/z* = 178 (M^+, 36 %)] in relationship 13:3:1.

5.19.2. $Pd_2(dba)_3$/DTBPMB-catalyst system[23]

The substrate and catalyst system, $Pd_2(dba)_3$:methane sulfonic acid:DTBPMB 1:23:10, were dissolved in the specified solvent, added to the Parr reactor vessel and degassed with CO (x5). The reaction was performed at 80 °C under 30 bar of CO pressure, unless stated otherwise. Samples of reaction mixture were analysed on GCMS and reported conversion values were determined.

5.19.2.1. Carbonylation of 2-octene (455)[23]

$Pd_2(dba)_3$ (0.025 g, 0.027 mmol, 0.5 mol %), methane sulfonic acid (0.04 ml, 0.62 mmol, 10 mol %), DTBPMB (0.112 g, 0.284 mmol, 4 mol %), and 2-octene (**455**) (1.00 ml, 6.40 mmol)

were dissolved in MeOH (8 ml). Conversion (24 h, 59 %) to nonanoate (**456**) (**457**) (**458**) [R_T 12.16 min., *m/z* = 172 (M^+, 2 %)] was observed.

5.19.2.2. Carbonylation of *trans*-*β*-methylstyrene (405)[23]

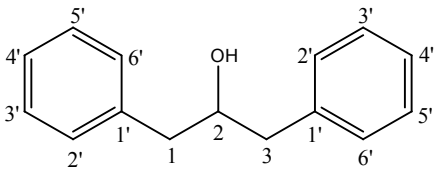
$Pd_2(dba)_3$ (0.024 g, 0.026 mmol, 0.4 mol %), methane sulfonic acid (0.04 ml, 0.62 mmol, 8 mol %), DTBPMB (0.107 g, 0.272 mmol, 4 mol %), and *trans*-*β*-methylstyrene (**405**) (1.00 ml, 7.71 mmol) were dissolved in MeOH (8 ml). Conversion (24 h, 49 %) to methyl 4-phenylbutanoate (**401**) [R_T 16.87 min., *m/z* = 178 (M^+, 18 %)], methyl 2-methyl-3-phenylpropanoate (**403**) [R_T 14.57 min., *m/z* = 178 (M^+, 17 %)] and methyl 2-phenylbutanoate (**404**) [R_T 14.05 min., *m/z* = 178 (M^+, 36 %)] in relationship 45:3:1.

5.19.2.3. Carbonylation of *trans*-stilbene (384)[23]

$Pd_2(dba)_3$ (0.025 g, 0.027 mmol, 2 mol %), methane sulfonic acid (0.04 ml, 0.62 mmol, 37 mol %), DTBPMB (0.114 g, 0.289 mmol, 17 mol %), and *trans*-stilbene (**384**) (0.303 g, 1.683 mmol, 62 eq.) were dissolved in MeOH:THF (7 ml, 1:1). No product was detected with GCMS analysis.

5.20. Synthesis and methoxycarbonylation of a non-conjugated alkene

5.20.1. 1,3-Diphenylpropan-2-ol (450)[3]



Following the procedure described in Paragraph 5.7.1. $NaBH_4$ (0.38 g, 9.99 mmol, 1.4 eq.) and 1,3-diphenylpropan-2-one (**459**) (1.50 g, 7.14 mmol) gave the crude reaction mixture which was purified with FCC (H:A 8:2). Fractions with R_f 0.38 was combined and concentrated *in vacuo* to obtain 1,3-diphenylpropan-2-ol (**450**) (1.06 g, 70 %) as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 35a) δ_H ppm 7.30-7.28 (4H, m, H-3' and H-5'), 7.22-7.20 (6H, m, H-2', H-4' and H-6'), 4.04-4.00 (1H, m, H-2), 2.82 (2H, dd, *J* = 13.67, 4.66 Hz, H-1 or H-3), 2.72 (2H, dd, *J* = 13.67, 8.19 Hz, H-1 or H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 35b) δ_C ppm 138.56 (C-1'), 129.51 (C-2' and C-6'), 128.60 (C-3' and C-5'), 126.55 (C-4'), 73.66 (C-2), 43.43 (C-1 and C-3); MS (EI) *m/z* 212 (M^+, 100 %), 122 (75 %), 121 (12 %), 92 (64 %), 91 (19 %).

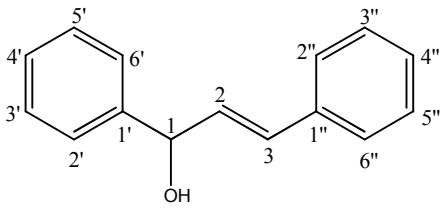
5.20.2. 1,3-Diphenylprop-1-ene (451)[18] (through $CuSO_4$ dehydration)

1,3-Diphenylpropan-2-ol (**450**) (~1.52 g, 7.16 mmol) and $CuSO_4$ (1.90 g, 11.91 mmol, 1.7 eq.): no product formation was detected.

5.20.3. 1,3-Diphenylprop-1-ene (451) (*p*-TsOH elimination)

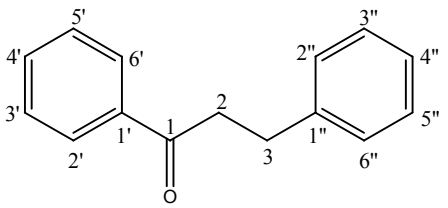
1,3-Diphenylpropan-2-ol (**450**) (0.51 g, 2.39 mmol) was dissolved in dry DCM (40 ml), *p*-toluenesulfonic acid (0.07 g, 0.39 mmol, 0.2 eq.) was added and reaction mixture was refluxed for 1 hour. No product formation was observed. More *p*-toluenesulfonic acid (0.07 g, 0.32 mmol, 0.2 eq.) was added. No product was detected after 5 hours of reflux.

5.20.4. *Trans*-1,3-diphenylprop-2-en-1-ol (453)[3]



Chalcone (**452**) (1.00 g, 4.81 mmol) was dissolved in THF:EtOH (1:1, 20 ml). $NaBH_4$ (0.23 g, 5.95 mmol, 1.2 eq.) was added and the reaction mixture stirred at room temperature overnight. After completion of the reaction, the THF:EtOH solvent mixture was removed under reduced pressure and the residue was washed with acetone (3 x 20 ml), where after the standard work-up procedure was followed. The product, *trans*-1,3-diphenylprop-2-en-1-ol (**453**) (0.96 g, 95 %), was obtained as a light yellow oil with R_f 0.27 (H:A 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) (Plate 36a) δ_H ppm 7.43-7.42 (2H, m, H-2" and H-6"), 7.39-7.35 (4H, m, H-2', H-3', H-5' and H-6'), 7.31-7.28 (3H, m, Ar-H) 7.25-7.22 (1H, m, Ar-H) 6.68 (1H, d, J = 15.86 Hz, H-3), 6.38 (1H, dd, J = 15.86, 6.55 Hz, H-2), 5.37 (1H, d, J = 6.55 Hz, H-1); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 36b) δ_C ppm 142.87 (C-1'), 136.63 (C-1"), 131.62 (C-2), 130.67 (C-3), 128.76, 128.70, 127.94, 127.92, 126.74, 126.48, 75.26 (C-1); MS (EI) *m/z* 210 (M^+, 34 %), 107 (15 %), 105 (100 %), 77 (48 %), 91 (15%).

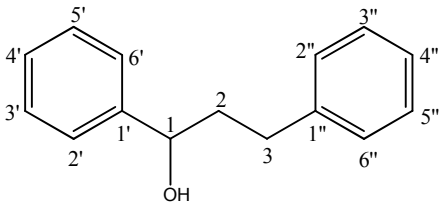
5.20.5. 1,3-diphenylpropan-1-one (455)[3]



Chalcone (**452**) (2.01 g, 9.64 mmol) was dissolved in EtOH (30 ml) and 5 percent Pd/C (0.20 g, 10 mol%) was added. The reaction mixture was stirred at room temperature under atmospheric H_2 pressure for 3 hours. The crude reaction mixture was filtered through celite and concentrated under reduced pressure to give the crude product which was purified by PLC (H:A 8:2). The band with R_f

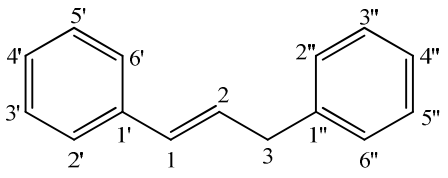
0.56 gave 1,3-diphenylpropan-1-one (**455**) (1.28 g, 63 %) as a white crystalline solid: m.p. 71.1-71.7 °C (lit.[24] 70-72 °C); ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 37a) δ_H ppm 7.97-7.95 (2H, m, H-2' and H-6'), 7.56-7.53 (1H, m, H-4'), 7.46-7.43 (2H, m, H-3' and H-5'), 7.31-7.29 (2H, m, H-3" and H-5"), 7.26-7.25 (2H, m, H-2" and H-6"), 7.22-7.19 (1H, m, H-4"), 3.30 (2H, t, *J* = 7.75 Hz, H-2), 3.07 (2H, t, *J* = 7.75 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 37b) δ_C ppm 199.36 (C-1), 141.41 (C-1"), 136.96 (C-1'), 133.19 (C-4'), 128.72, 128.65, 128.55, 128.16 (C-2' and C-6'), 126.26 (C-4"), 40.57 (C-2), 30.24 (C-3); MS (EI) *m/z* 210 (M^+, 36 %), 105 (100 %), 77 (44 %), 51 (13 %), 91 (11 %).

5.20.6. 1,3-Diphenylpropan-1-ol (454)[3]



Dihydrochalcone (**455**) (1.73 g, 8.24 mmol) was dissolved in THF:EtOH (1:1, 50 ml) and $NaBH_4$ (0.65 g, 17.03 mmol, 2 eq.) was added. After completion of the reaction, THF:EtOH solvent mixture was removed under reduced pressure and washed with acetone (3 x 20 ml) where after the standard work-up procedure was followed. The crude product mixture was purified with FCC (H:EtOAc 8:2) and fractions with R_f 0.41 were combined to give 1,3-diphenylpropan-1-ol (**454**) (1.51 g, 86 %) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 38a) δ_H ppm 7.34-7.30 (4H, m, Ar-H), 7.27-7.25 (3H, m, Ar-H), 7.18-7.16 (3H, m, Ar-H), 4.64 (1H, br t, *J* = 6.57 Hz, H-1), 2.74-2.69 (1H, m, H-3a or H-3b), 2.66-2.61 (1H, m, H-3a or H-3b), 2.13-2.07 (2H, m, -OH and H-2a or H-2b), 2.03-1.97 (1H, m, H-2a or H-2b); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 38c) δ_C ppm 144.66 (C-1'), 141.88 (C-1"), 128.60, 128.54, 128.49, 127.73, 126.04 (C-2' and C-6'), 125.95, 73.94 (C-1), 40.54 (C-2), 32.14 (C-3); MS (EI) *m/z* 212 (M^+, 9 %), 194 (50 %), 107 (100 %), 91 (27 %), 92 (21 %).

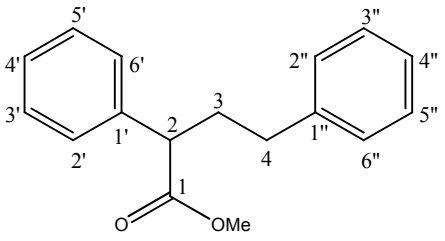
5.20.7. 1,3-Diphenylprop-1-ene (451)[18]



1,3-Diphenylpropan-1-ol (**454**) (1.43 g, 6.76 mmol) and $CuSO_4$ (2.29 g, 14.34 mmol, 2.1 eq.) gave the crude product which was purified by FCC (H). Fractions with R_f 0.57 were combined to obtain 1,3-diphenylprop-1-ene (**451**) (0.46 g, 35 %) as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 39a) δ_H ppm 7.35-7.34 (2H, m, H-2' and H-6'), 7.31-7.26 (4H, m, H-3', H-5', H-3" and H-5"), 7.24-7.23 (2H, m, H-2" and H-6"), 7.22-7.17 (2H, m, H-'4 and H-4"), 6.44 (1H, br d, *J* = 15.75 Hz, H-1), 6.34 (1H, dt, *J* = 15.75, 6.82 Hz, H-2), 3.53 (2H, br d, *J* = 6.82 Hz, H-3); ^{13}C NMR (151

MHz, $CDCl_3$) (Plate 39b) δ_C ppm 140.28 (C-1''), 137.59 (C-1'), 131.19 (C-1), 129.34 (C-2), 128.80 (C-2'' and C-6''), 128.62 (C-3', C-5', C-3'' and C-5''), 127.23 (C-4' or C-4''), 126.31 (C-4' or C-4''), 126.25 (C-2' and C-6'), 39.47 (C-3); MS (EI) *m/z* 194 (M^+, 100 %), 193 (53 %), 178 (38 %), 116 (49 %), 115 (80 %).

5.20.8. Carbonylation of 1,3-diphenylprop-1-ene (451)



$PdCl_2$ (0.021 g, 0.118 mmol, 8 mol %), $Al(OTf)_3$ (0.109 g, 0.230 mmol, 16 mol %), PPh_3 (0.119 g, 0.454 mmol, 32 mol %) and 1,3-diphenylpropene (**451**) (0.28 g, 1.44 mmol, 12 eq.) were dissolved in THF:MeOH (7 ml, 1:1). Conversion (22 h, 37 %) to methyl 2,4-diphenylbutanoate (**456**) [R_T 29.03 min., *m/z* = 254 (M^+, 2 %)]. The reaction mixture was separated with FCC (H:A 8:2) to obtain methyl 2,4-diphenylbutanoate (**456**) (0.05 g, 14 %) as an orange oil with R_f 0.54; ^{1}H NMR (600 MHz, $CDCl_3$) (Plate 40a) δ_H ppm 7.33-7.24 (7H, m, H-Ar), 7.19-7.16 (1H, m, H-Ar), 7.15-7.13 (2H, m, H-2'' and H-6''), 3.63 (3H, s, -OMe), 3.56 (1H, t, *J* = 7.65 Hz, H-2), 2.56 (2H, t, *J* = 7.76 Hz, H-4), 2.44-2.38 (1H, m, H-3a or H-3b), 2.13-2.07 (1H, m, H-3a or H-3b); ^{13}C NMR (151 MHz, $CDCl_3$) (Plate 40b) δ_C ppm 174.40 (C-1), 141.36 (C-1''), 138.94 (C-1'), 128.80, 128.57, 128.50, 128.11, 127.44, 126.11, 52.09 (-OMe), 50.90 (C-2), 35.01 (C-3), 33.64 (C-4); IR (FT) 1736 (C=O) cm^{-1}; MS (EI) *m/z* 254 (M^+, 2 %), 150 (100 %), 151 (10 %), 118 (35 %), 91 (49 %).

5.21. References

(1) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

(2) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351-8354.

(3) Van Tonder, J. H. Ph.D. thesis, University of the Free State, Bloemfontein, 2008.

(4) Mende, V. E. M.Sc. thesis, University of the Free State, Bloemfontein, 2010.

(5) Cvengros, J.; Toma, S.; Marque, S.; Loupy, A. *Canadian Journal of Chemistry* **2004**, *82*, 1365-1371.

(6) Ketcham, R.; Jambotkar, D.; Martinelli, L. *J. Org. Chem.* **1962**, 4666-4667.

(7) Zhang, W.; Go, M. L. *Eur. J. Med. Chem.* **2007**, *42*, 841-850.

(8) Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2000**, *21*, 763-764.

(9) Blagg, J.; Davies, S. G.; Holman, N. J.; Laughton, C. A.; Mobbs, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1581-1589.

(10) Ramanathan, M.; Hou, D.-R. *Tetrahedron Lett.* **2010**, *51*, 6143-6145.

(11) Kuo, C. M.Sc. thesis, University of the Free State, Bloemfontein, 2008.

(12) Marshallsay, G. J.; Bryce, M. R. *J. Org. Chem.* **1994**, *59*, 6847-6849.

(13) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018-5020.

(14) Grabarnick, M.; Zamir, S. *Org. Process Res. Dev.* **2003**, *7*, 237-243.

(15) McNulty, J.; Das, P. *Eur. J. Org. Chem.* **2009**, *2009*, 4031-4035.

(16) Sharma, A.; Kumar, R.; Sharma, N.; Kumar, V.; Sinha, A. K. *Adv. Synth. Cat.* **2008**, *350*, 2910-2920.

(17) Sinha, A. K.; Kumar, V.; Sharma, A.; Sharma, A.; Kumar, R. *Tetrahedron* **2007**, *63*, 11070-11077.

(18) Van Tonder, B. M.Sc. thesis, University of the Free State, Bloemfontein, 2008.

(19) Williams, D. B. G.; Shaw, M. L.; Green, M. J.; Holzapfel, C. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 560-563.

(20) Diab, L.; Gouygou, M.; Manoury, E.; Kalck, P.; Urrutigoïty, M. *Tetrahedron Lett.* **2008**, *49*, 5186-5189.

(21) Comerford, J. W.; Clark, J. H.; Macquarrie, D. J.; Breeden, S. W. *Chem. Commun.* **2009**, 2562-2564.

(22) Williams, D. B. G.; Shaw, M. L.; Hughes, T. *Organometallics* **2011**, 4968-4973.

(23) Rodriguez, C. J.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun.* **2004**, 1720-1721.

(24) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554-3557.

APPENDIX 1 - ABBREVIATIONS

➢ NMR Abbreviations

DEPT	=	Distortionless Enhancement by Polarization Transfer
HSQC	=	Heteronuclear Single Quantum Correlation
HMBC	=	Heteronuclear Multiple Bond Correlation
s	=	singlet
d	=	doublet
dd	=	doublet of doublets
dq	=	doublet of quartets
m	=	multiplet
p	=	pentet
J	=	Coupling constant
δ	=	Chemical shift

➢ Solvent Abbreviations

A	=	Acetone
DCM	=	Dichloromethane
DMF	=	Dimethylformamide
DME	=	Dimethylether
Et_2O	=	Diethyl ether
Et_3N	=	Triethyl amine
EtOAc	=	Ethyl acetate

EtOH	=	Ethanol
H	=	Hexane
MeOH	=	Methanol
PEG	=	Polyethylene glycol
T	=	Toluene
THF	=	Tetrahydrofuran

➢ Chemical Abbreviations

$Al(OTf)_3$	=	Aluminum trifluoromethanesulfonyl
9-BBN	=	9-Borabicyclo[3.3.1]nonane
BINAP	=	*R*-(1,1′-Binaphthalene-2,2′-diyl) bis(diphenylphosphine)
BuLi	=	Butyl lithium
^{t}BuOK	=	Potassium *tert*-butixide
BSA	=	Borosalicylic acid
DBU	=	1,8-Diazabicycloundec-7-ene
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAH	=	Di-isobutylaluminium hydride
DHQ-CLB	=	Dihydroquinine *p*-chlorobenzoate
DHQD-CLB	=	Dihydro-quinidine *p*-chlorobenzoate
DPPB	=	1,4-Bis(diphenylphosphino)butane
DPPE	=	1,2-Bis(diphenylphosphino)ethane
DPPP	=	1,3-Bis(diphenylphosphino)propane
DTBPMB	=	1,2-Bis-(di-*tert*-butylphosphinomethyl)benzene
HMPA	=	Hexamethylphosphoramide

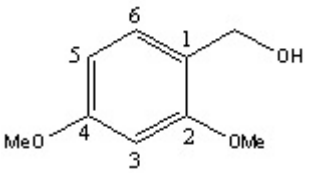
HTIB-MeOH	=	[Hydroxyl(tosyloxy)iodo]benzene
IBD-H_2SO_4-MeOH	=	Iodobenzene diacetate
LDA	=	Lithium diisopropylamine
LICA	=	Lithium isopropylcyclohexylamine
MSA	=	Methanesulfonic acid
Pd/C	=	Palladium on carbon
$Pd_2(DBA)_3$	=	Palladium(II) dibenzylidene acetone
Phen	=	4,7-diphenyl-1,10-phenanthrolinedisulfonic acid
PPA	=	Polyphosphoric acid
PPh_3	=	Triphenylphosphine
PPh_3.HBr	=	Triphenylphosphine hydrobromide
p-TsOH	=	*p*-toluenesulfonic acid
S-DPPP	=	1,3-bis(di(*m*-sodiumsulfonatophenyl)phosphine) propane
TBAF	=	tetra-*n*-butylammonium fluoride
TBDPS	=	*tert*-butyldiphenylsilyl
TfOH	=	trifluoromethanesulfonic acid
TFA	=	trifluoroacetic acid
TPP-DEAD	=	Triphenylphosphine-diethyl azodicarboxylate
TPPTS	=	3,3',3''-phosphinidynetris-(benzenesulfonic acid)-trisodium salt
TTA	=	Thallium(III) acetate
TTN	=	Thallium(III) nitrate
TTPC	=	Thallium(III) perchlorate

TTS	=	Thallium(III) *p*-tolylsulfonate
Ts_2O	=	*p*-Toluenesulphonic anhydride

APPENDIX 2 & 3

NMR SPECTRA

Plate 1a - ^{1}H NMR [$CDCl_3$]: 2,4-dimethoxybenzyl alcohol (**355**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 8.07 Hz, H-6), 6.45 (1H, d, *J* = 2.34 Hz, H-3), 6.43 (1H, dd, *J* = 8.07, 2.34 Hz, H-5), 4.59 (2H, s, -CH_2-), 3.81 (3H, s, 2-OMe), 3.79 (3H, s, 4-OMe)

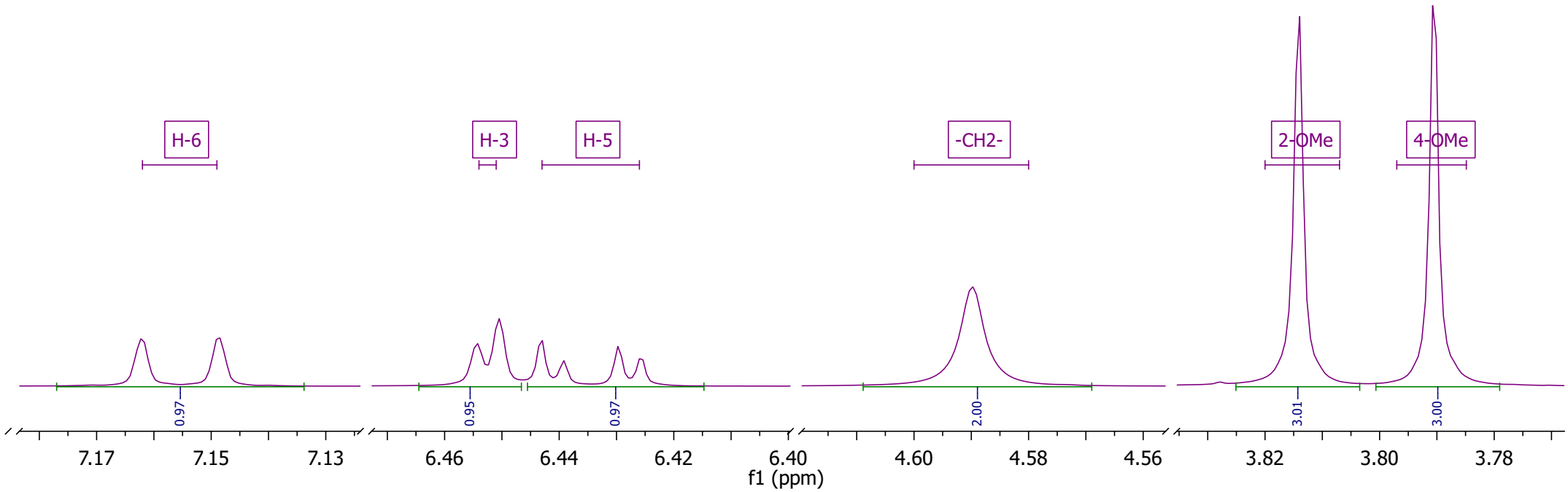
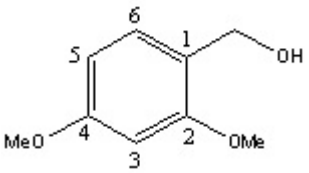
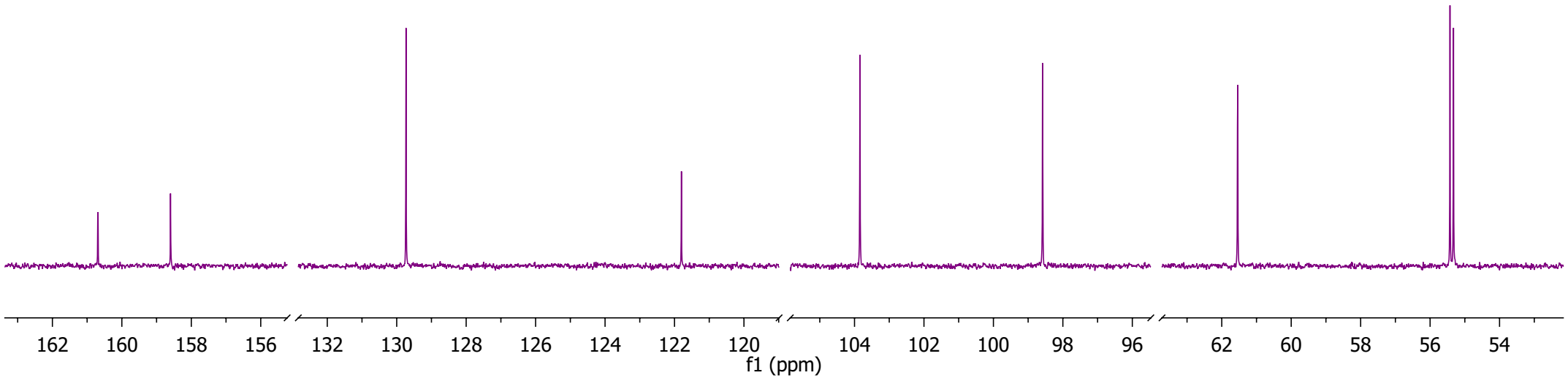


Plate 1b - ^{13}C NMR [$CDCl_3$]: 2,4-dimethoxybenzyl alcohol (**355**)





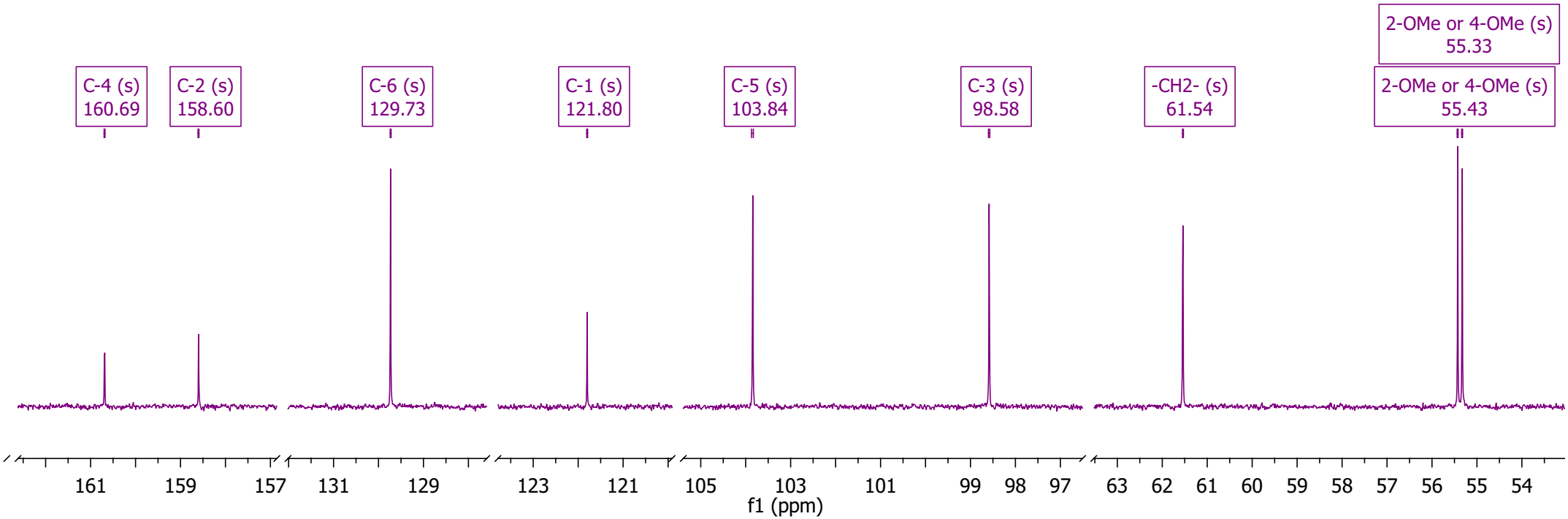


Plate 1c - DEPT [$CDCl_3$]: 2,4-dimethoxybenzyl alcohol (**355**)

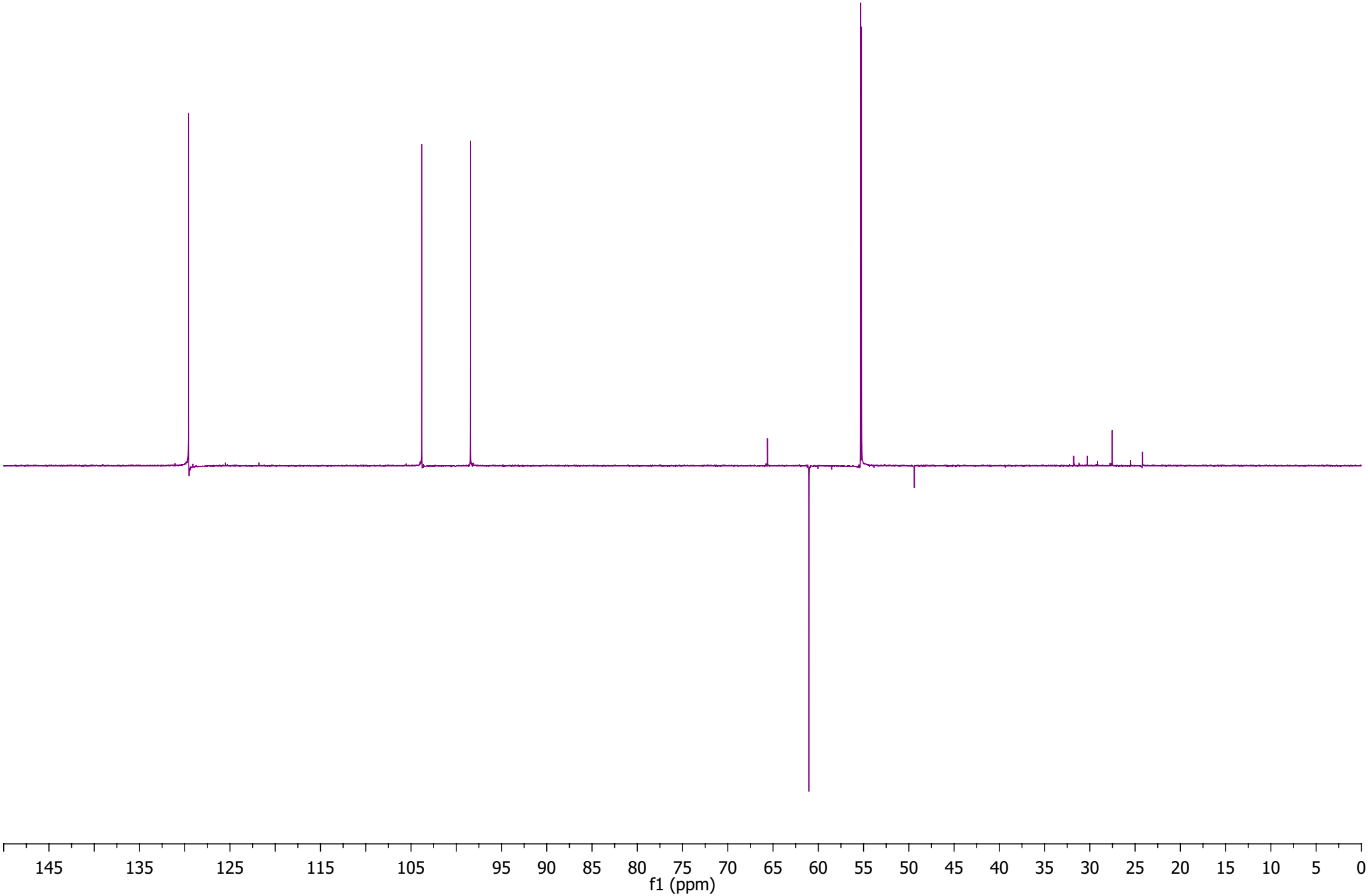


Plate 1d - HSQC [$CDCl_3$]: 2,4-dimethoxybenzyl alcohol (**355**)

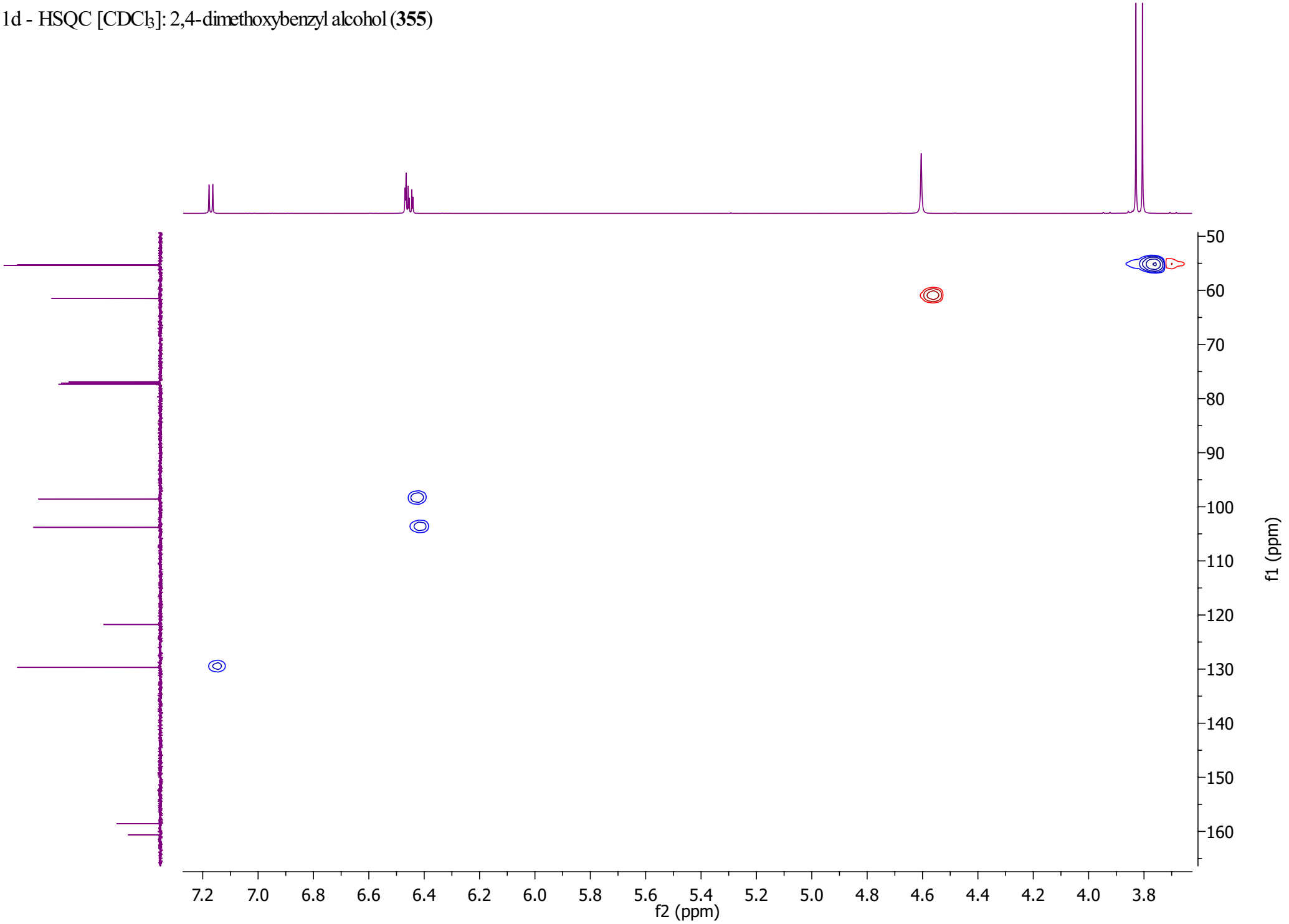


Plate 1e - HMBC [$CDCl_3$]: 2,4-dimethoxybenzyl alcohol (**355**)

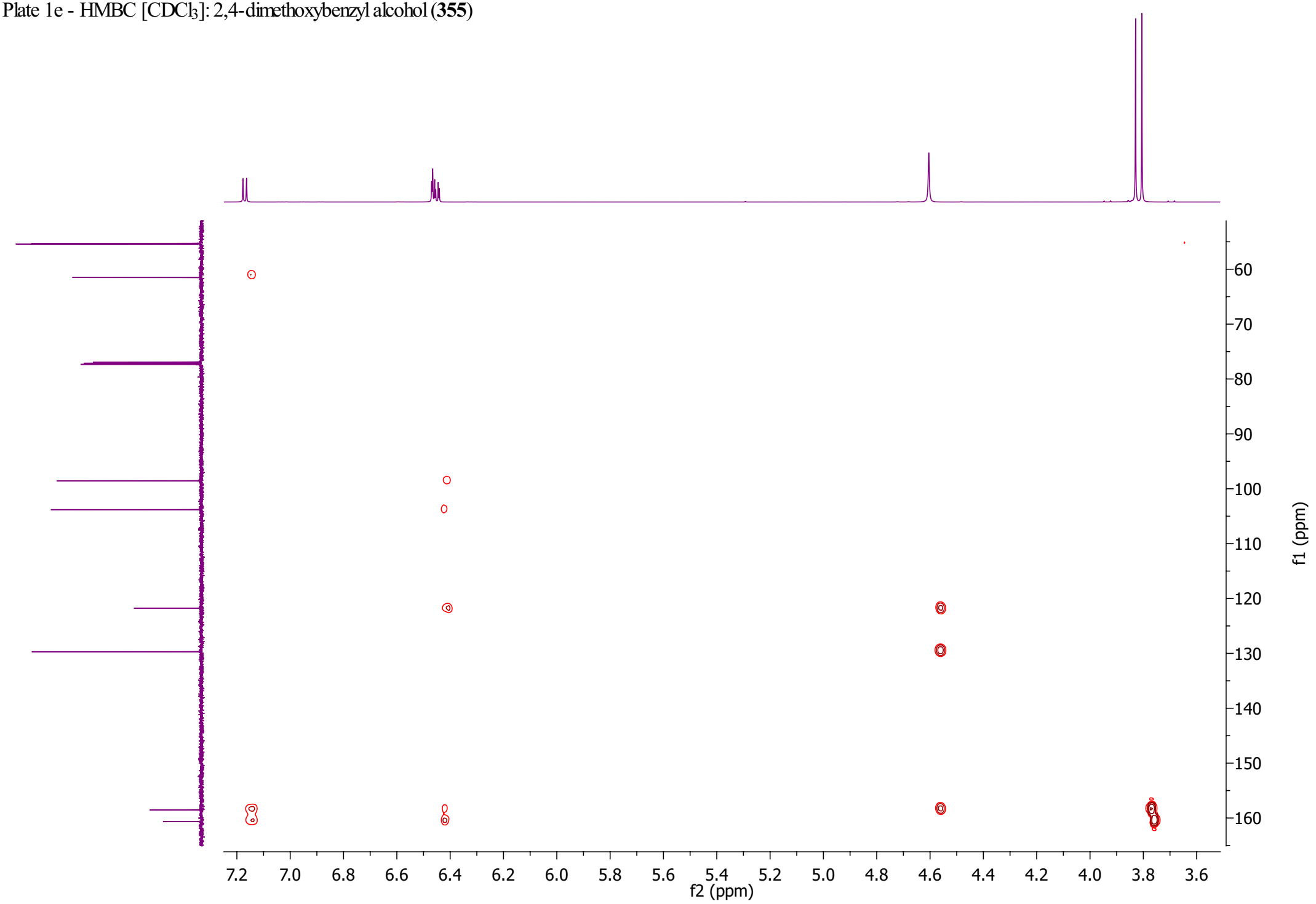
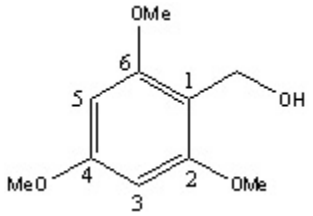


Plate 2a - ^{1}H NMR [$CDCl_3$]: 2,4,6-trimethoxybenzyl alcohol (**356**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.12 (2H, s, H-3 and H-5), 4.69 (2H, d, J = 6.51 Hz, -CH_2-), 3.81 (6H, s, 2-OMe and 6-OMe), 3.80 (3H, s, 4-OMe)

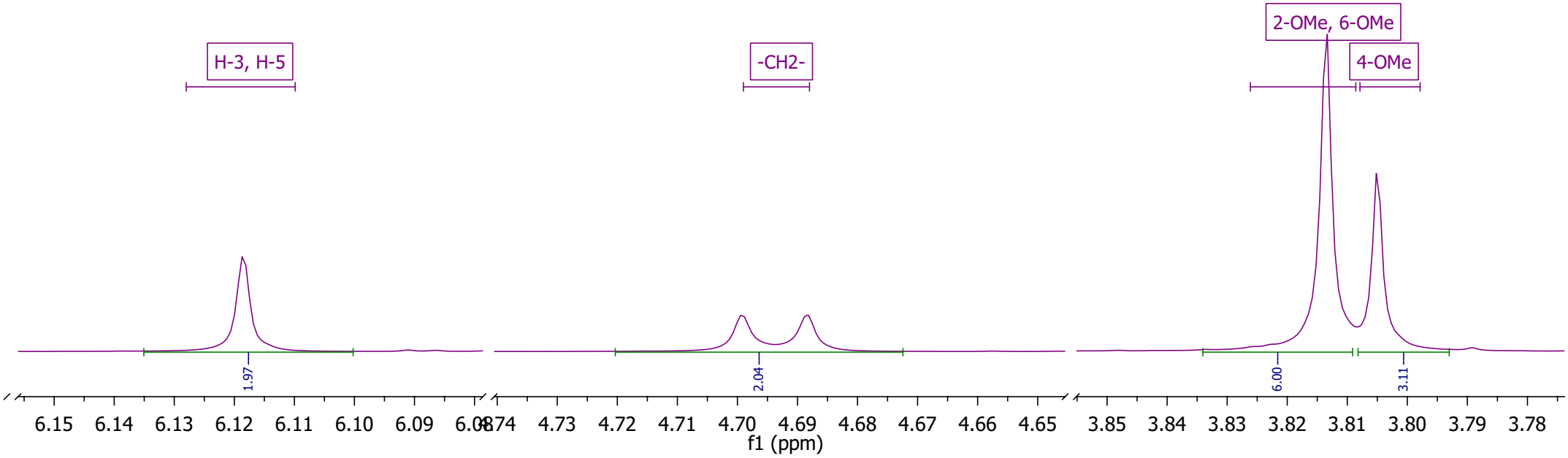
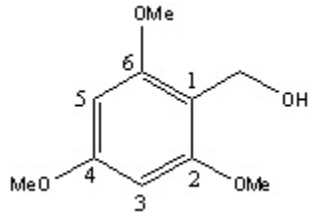


Plate 2b - ^{13}C NMR [$CDCl_3$]: 2,4,6-trimethoxybenzyl alcohol (**356**)



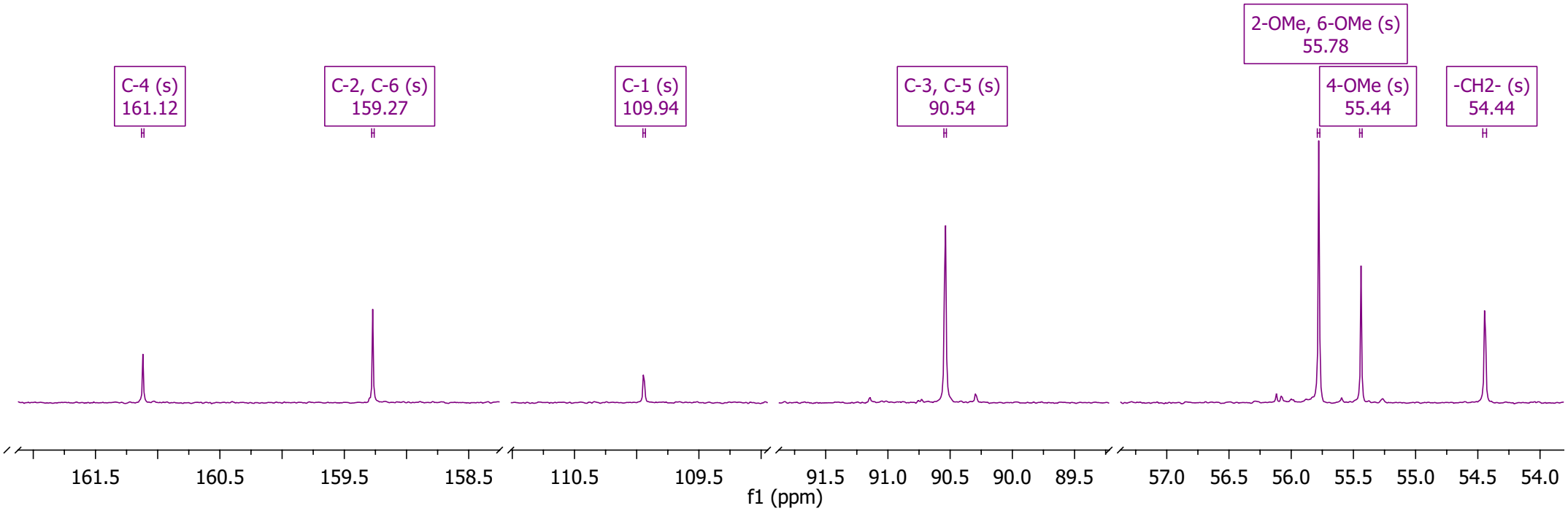


Plate 2c - DEPT [$CDCl_3$]: 2,4,6-trimethoxybenzyl alcohol (**356**)

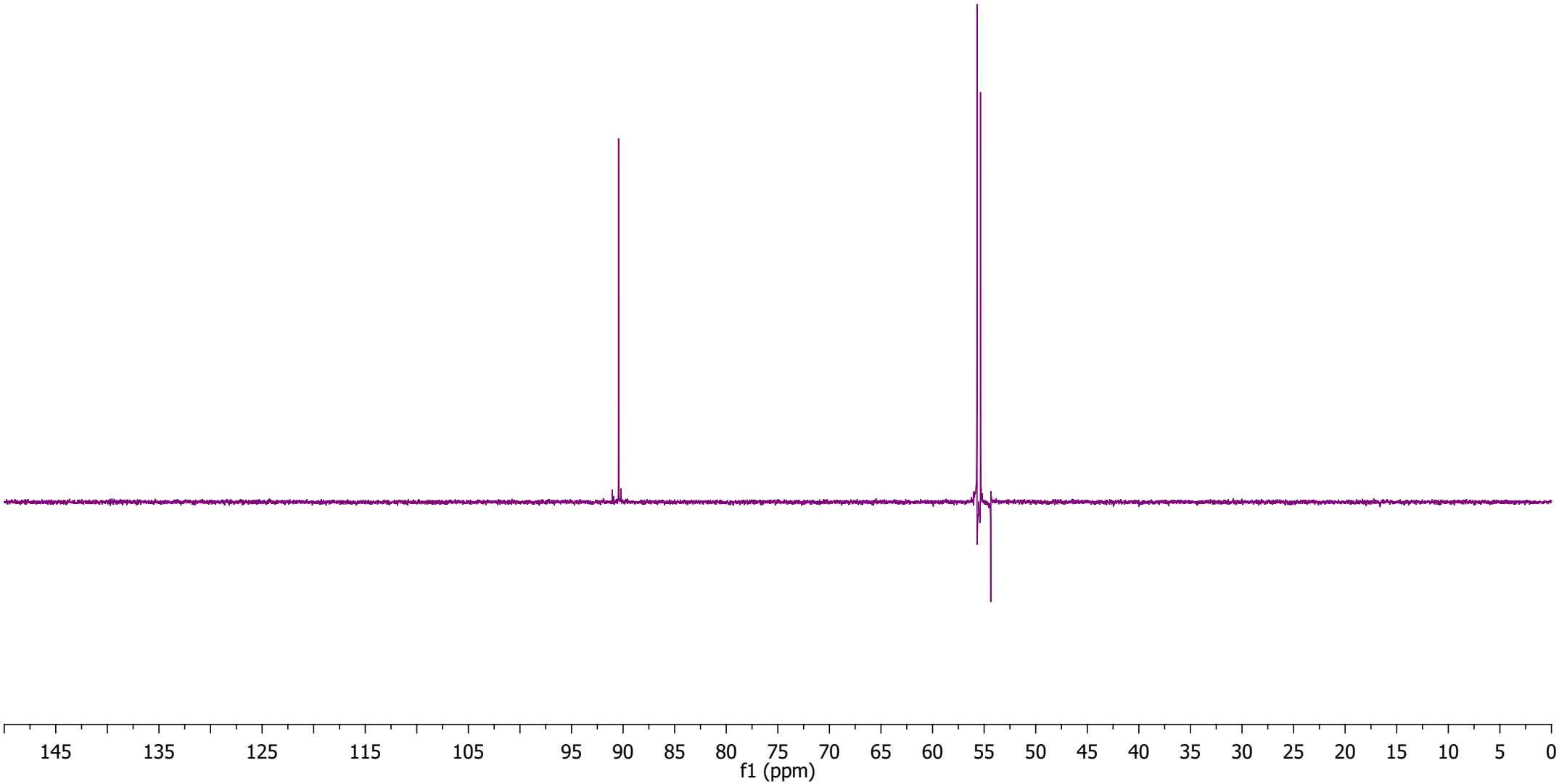


Plate 2d - HSQC [$CDCl_3$]: 2,4,6-trimethoxybenzyl alcohol (**356**)

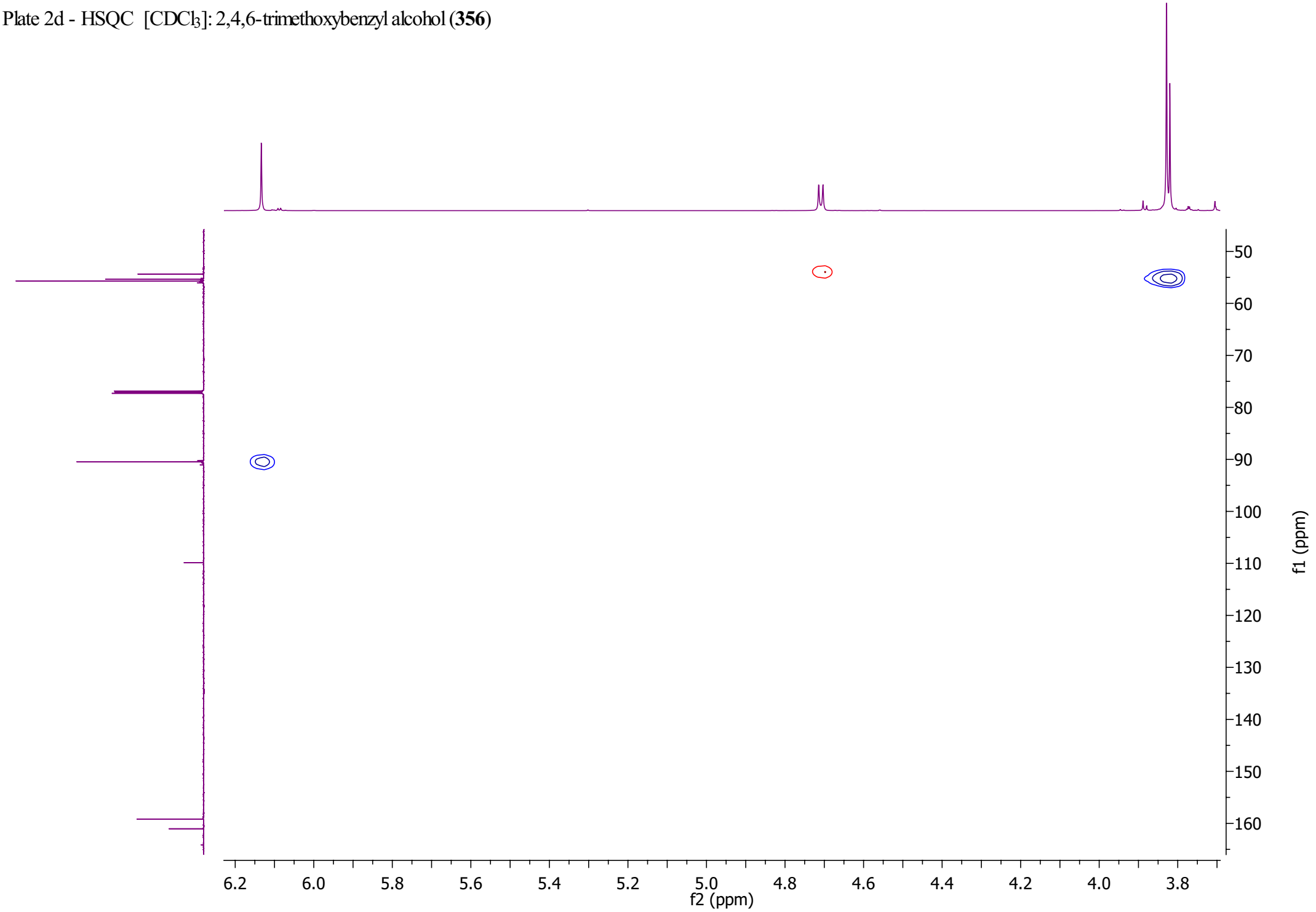


Plate 2e - HMBC [$CDCl_3$]: 2,4,6-trimethoxybenzyl alcohol (**356**)

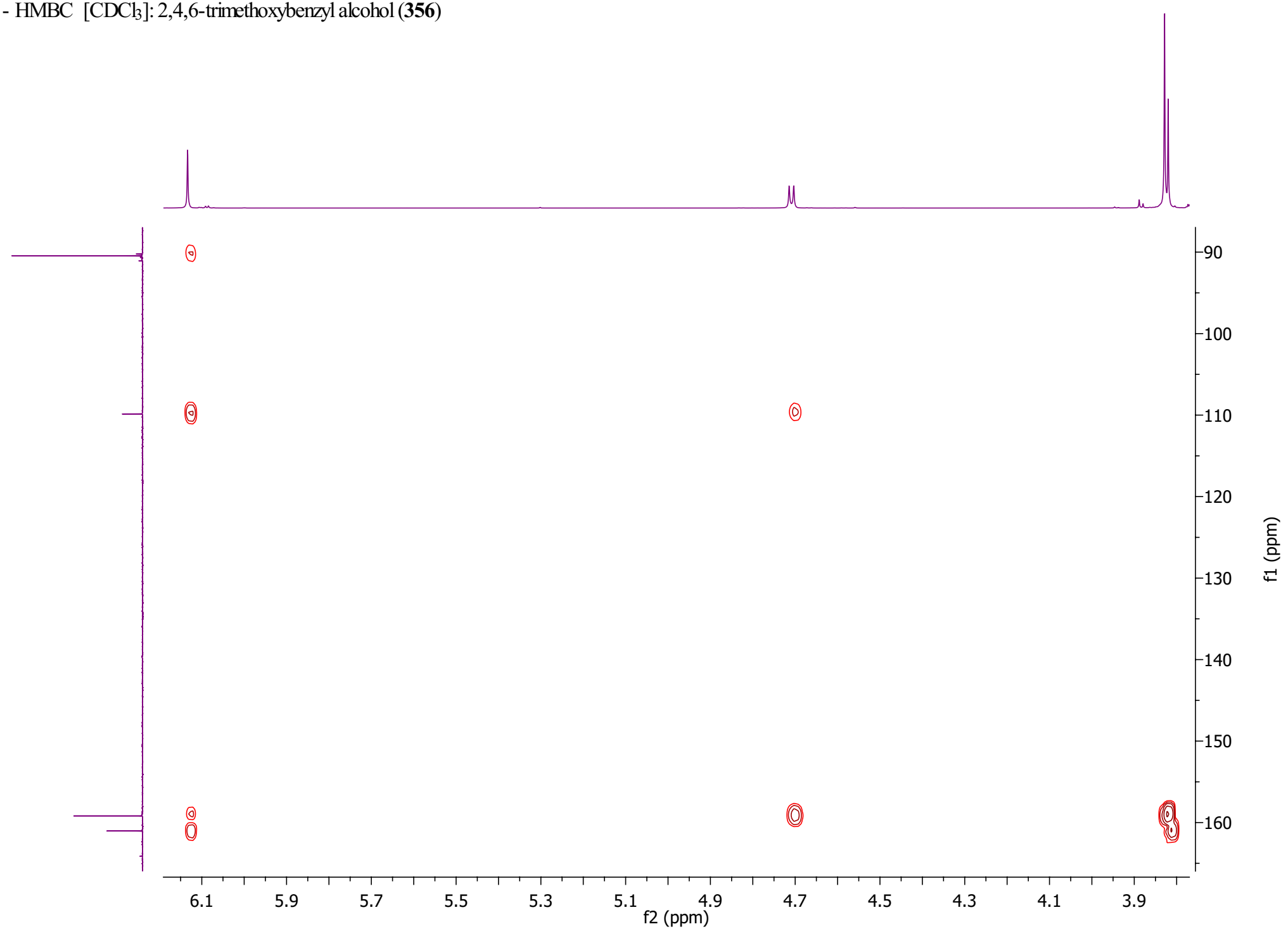
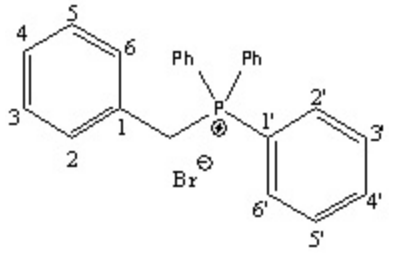
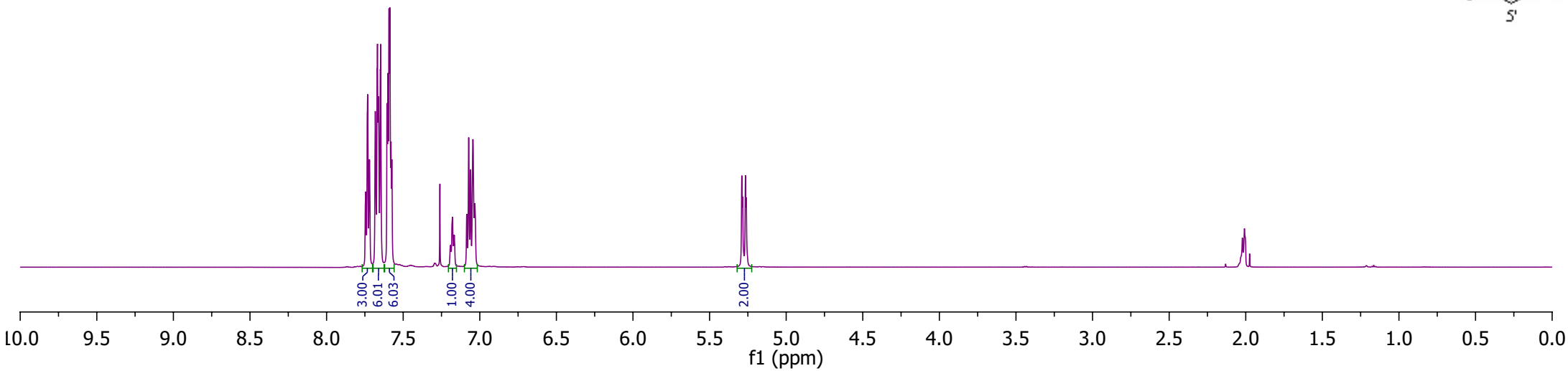


Plate 3a - ^{1}H NMR [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74-7.72 (3H, m, H-4'), 7.68-7.65 (6H, m, H-2' and H-6'), 7.61-7.57 (6H, m, H-3' and H-5'), 7.20-7.16 (1H, m, H-4), 7.09-7.06 (2H, m, H-3 and H-5), 7.05-7.03 (2H, m, H-2 and H-6), 5.28 (2H, br d, J = 14.33, -CH_2-)

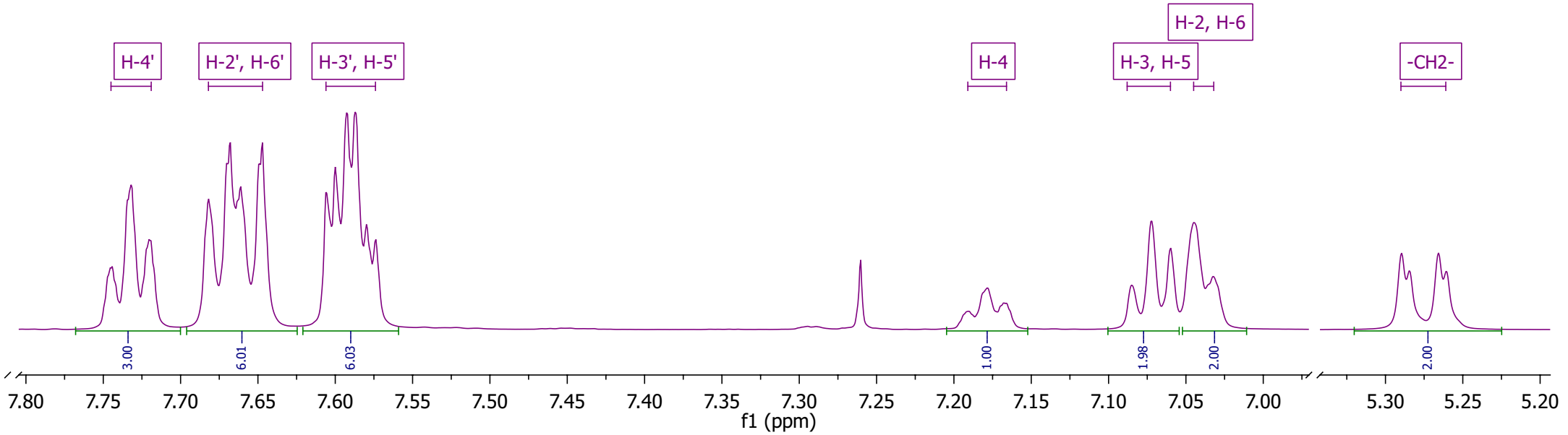
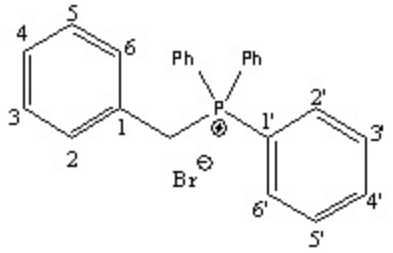


Plate 3b - ^{13}C NMR [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)



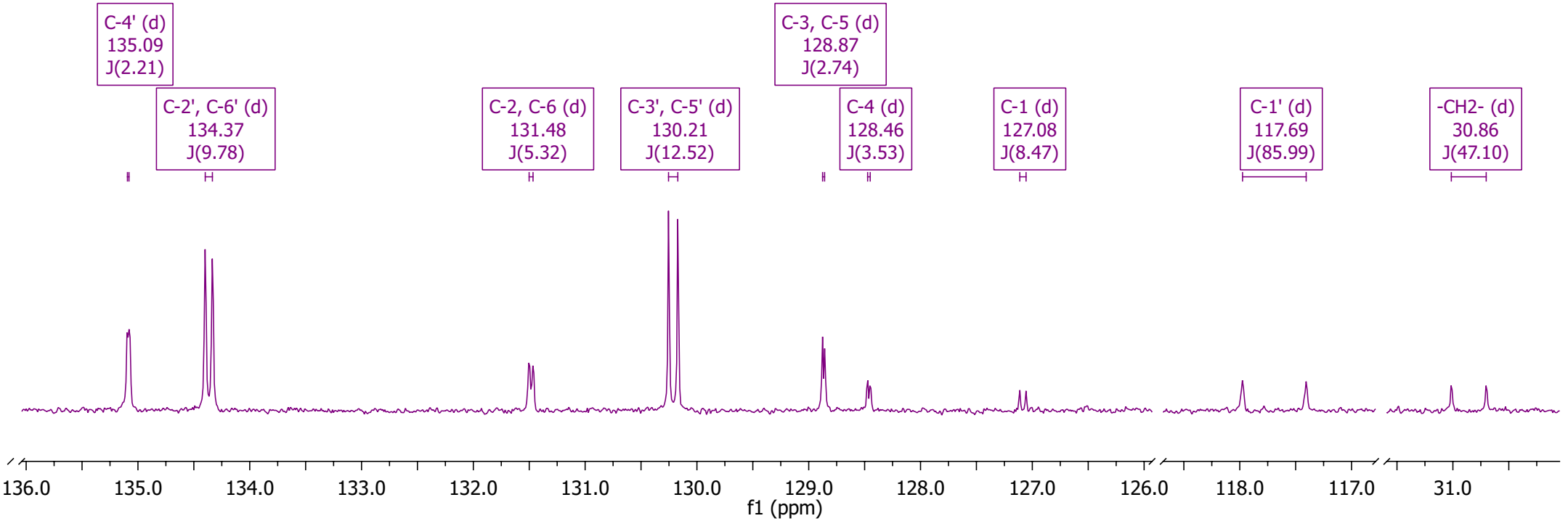


Plate 3c - DEPT [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)

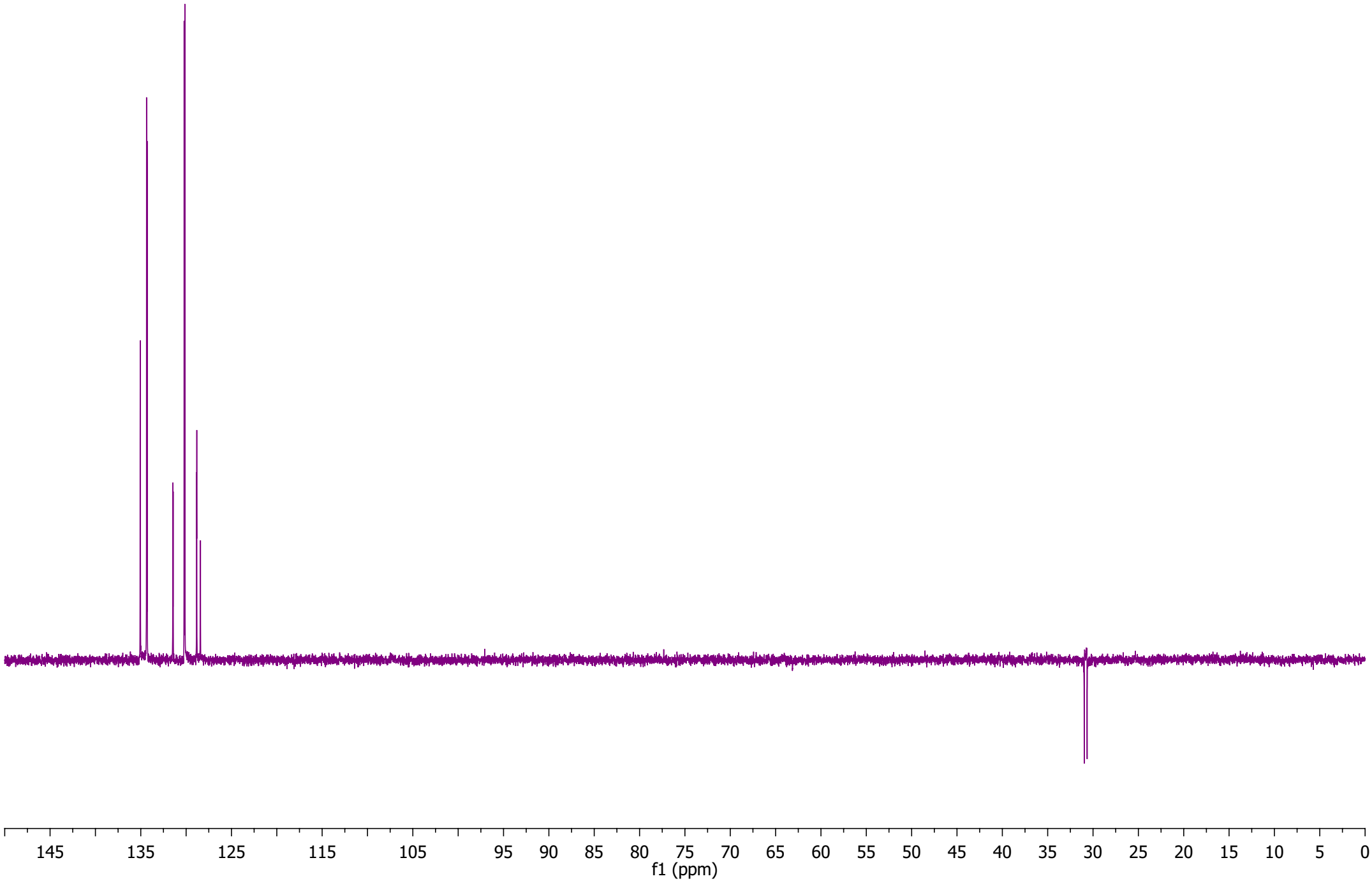


Plate 3d - HSQC [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)

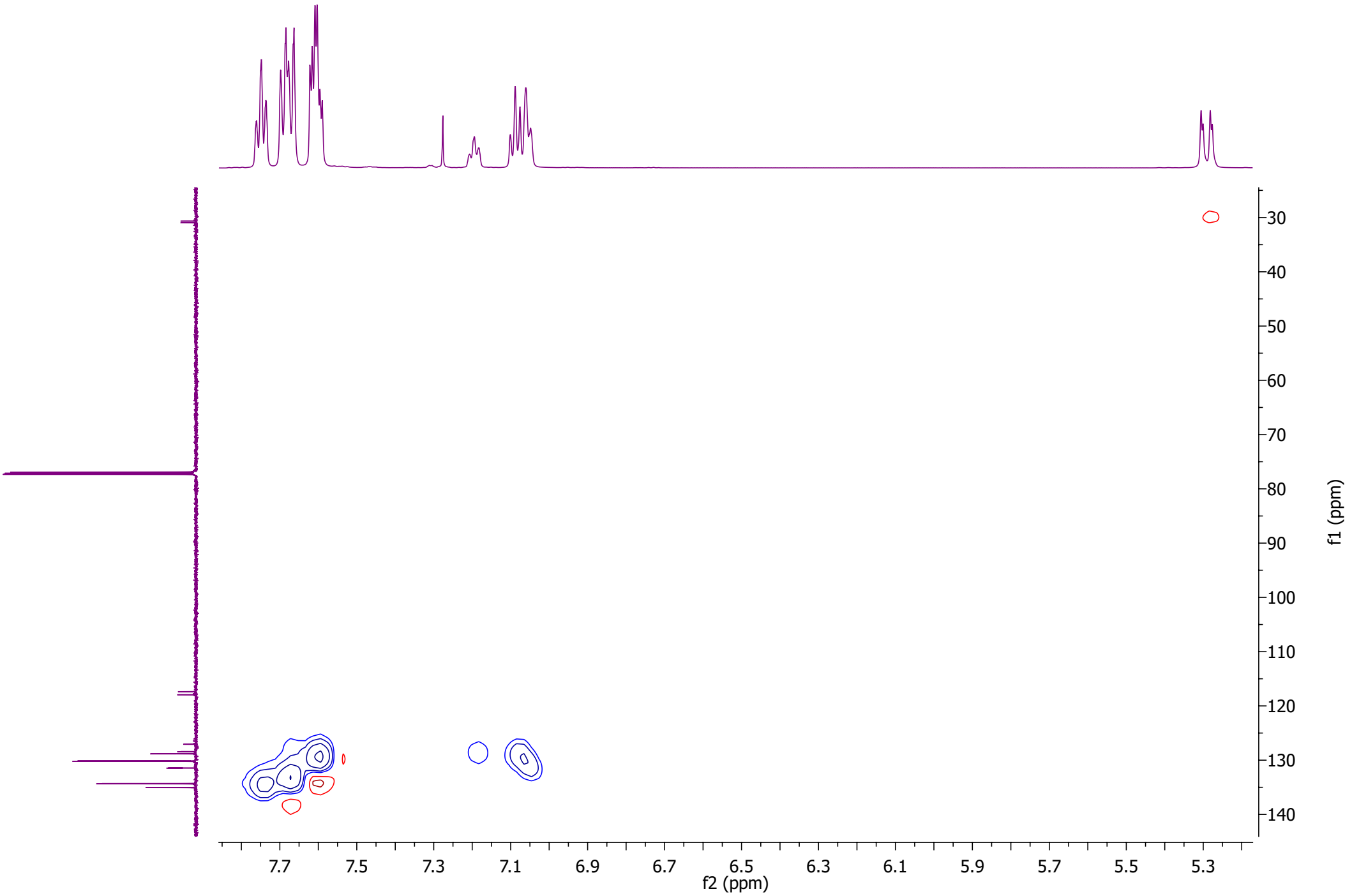


Plate 3e - HSQC (expansion) [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)

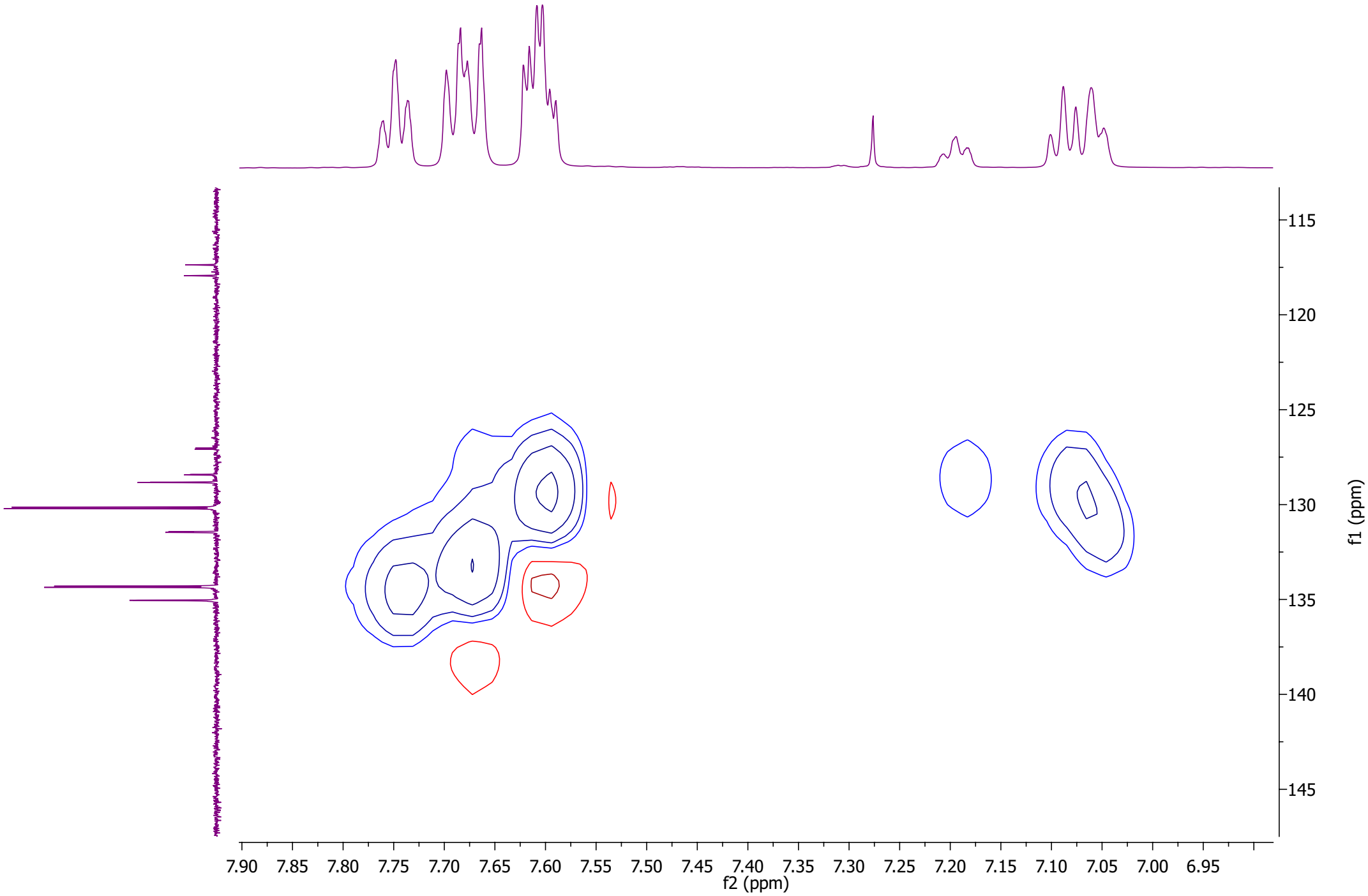


Plate 3f - HMBC [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)

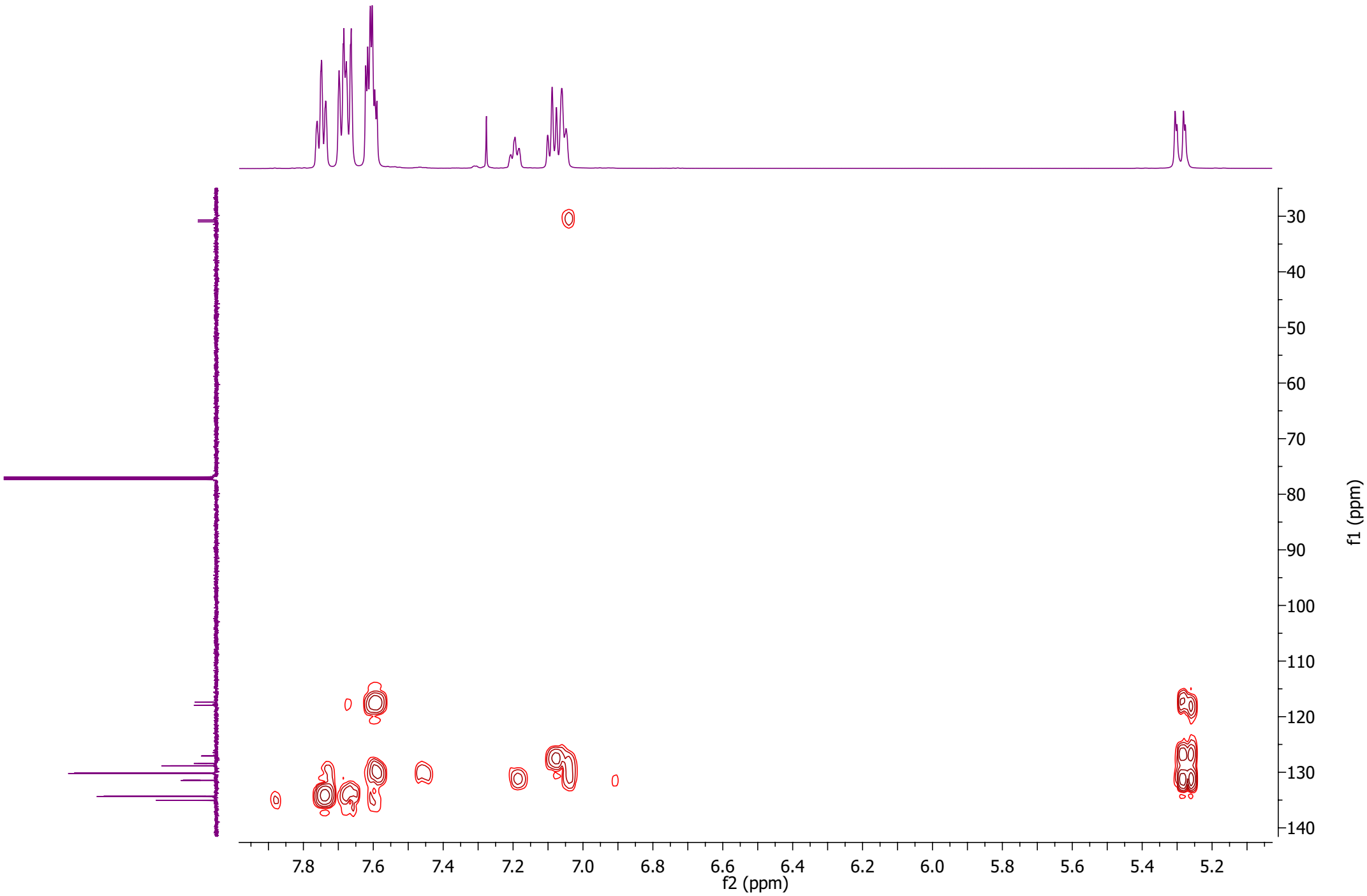


Plate 3g - HMBC (expansion) [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)

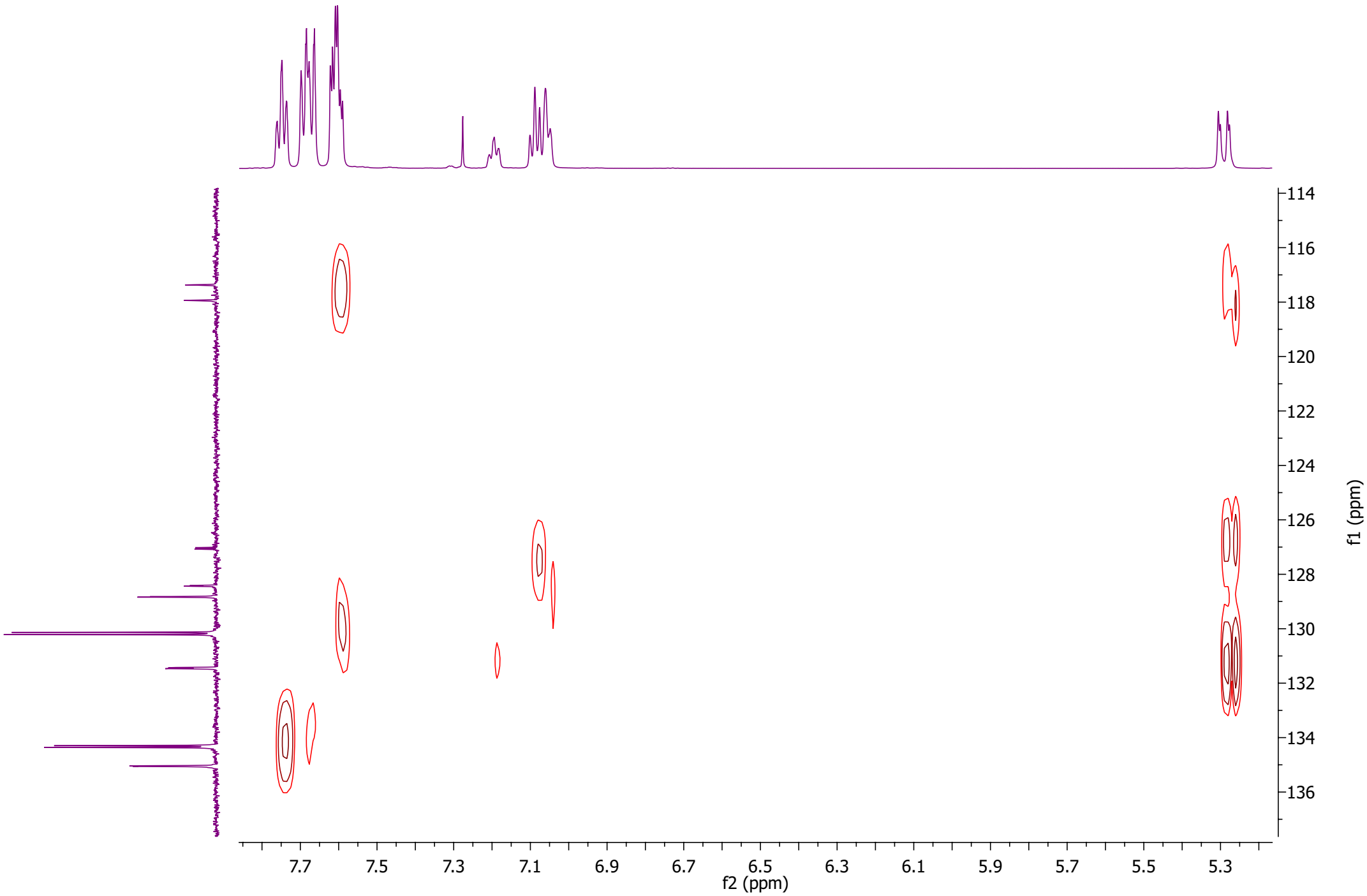


Plate 3h - ^{31}P NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**337**)

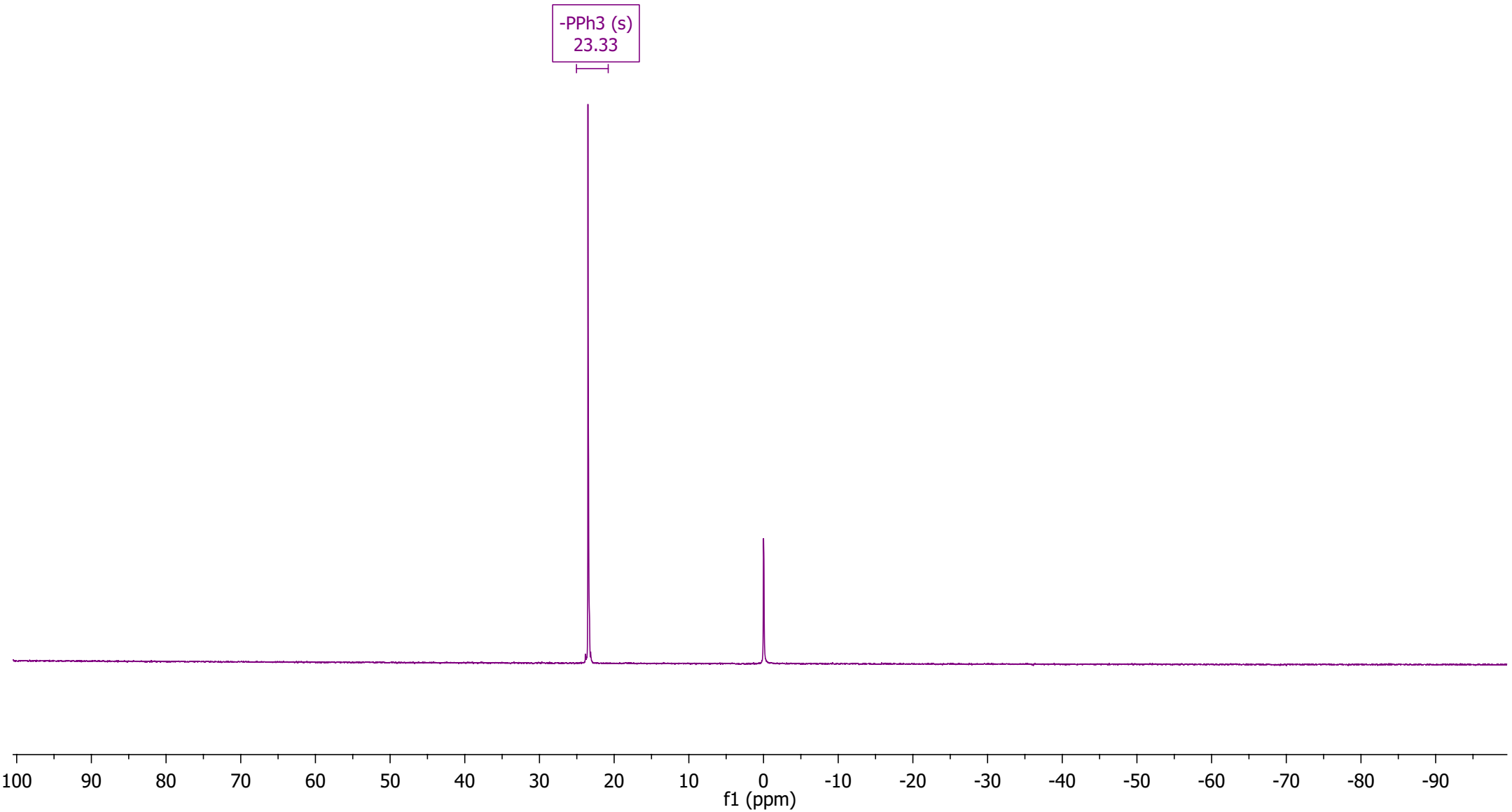


Plate 3i - HMBC H-P [$CDCl_3$]: benzyltriphenylphosphonium bromide (**337**)

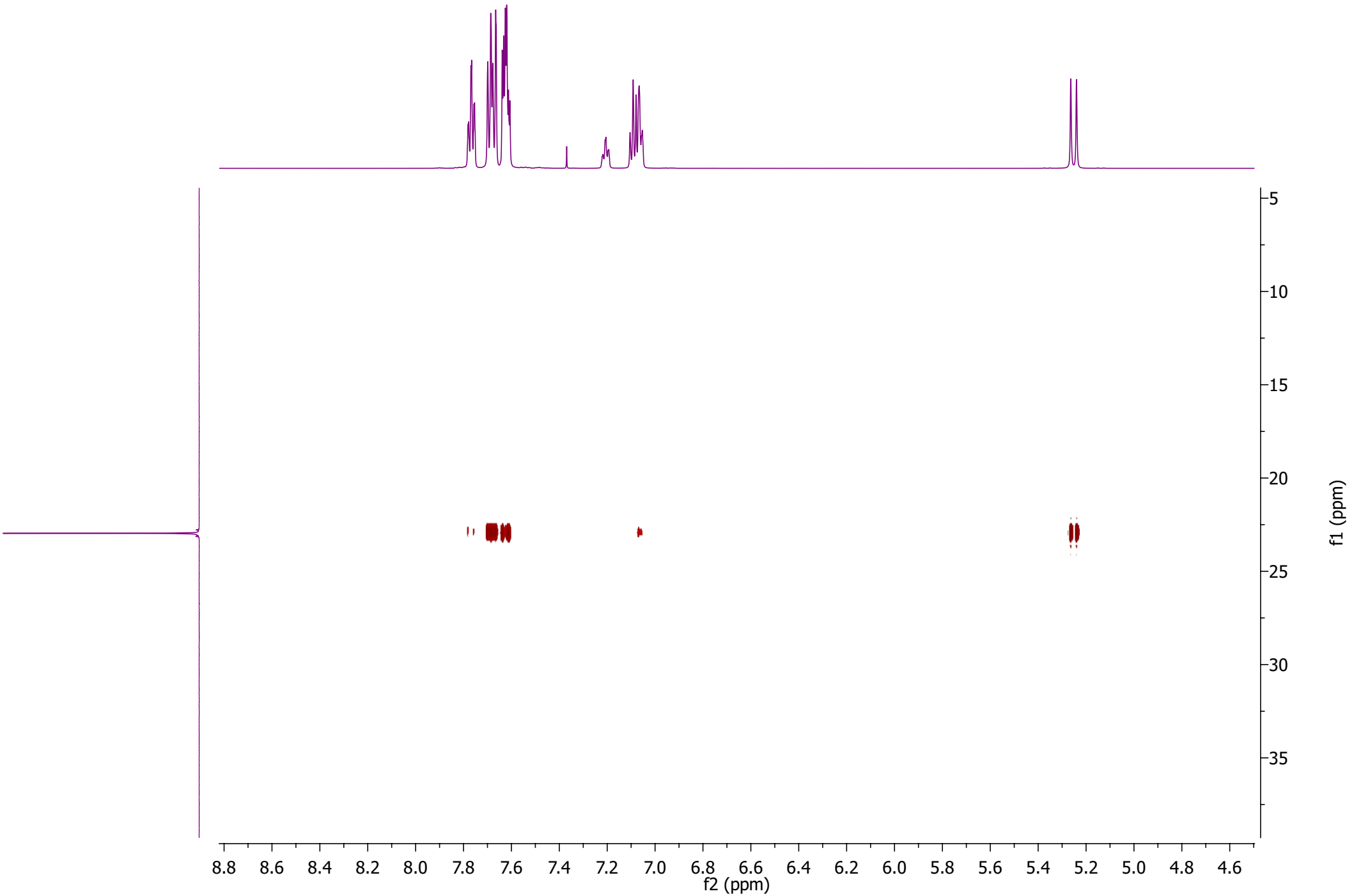
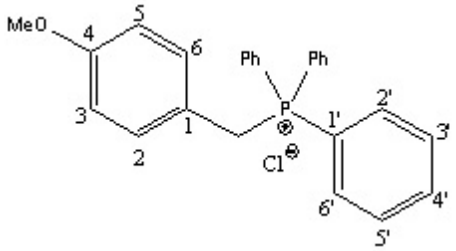


Plate 4a - ^{1}H NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.69 (9H, m, H-2', H-4' and H-6'), 7.63-7.60 (6H, m, H-3' and H-5'), 6.99 (2H, dd, *J* = 8.82, 2.57 Hz, H-2 and H-6), 6.63 (2H, d, *J* = 8.82 Hz, H-3 and H-5), 5.33 (2H, d, *J* = 13.79 Hz, -CH_2-), 3.70 (3H, s, -OMe)

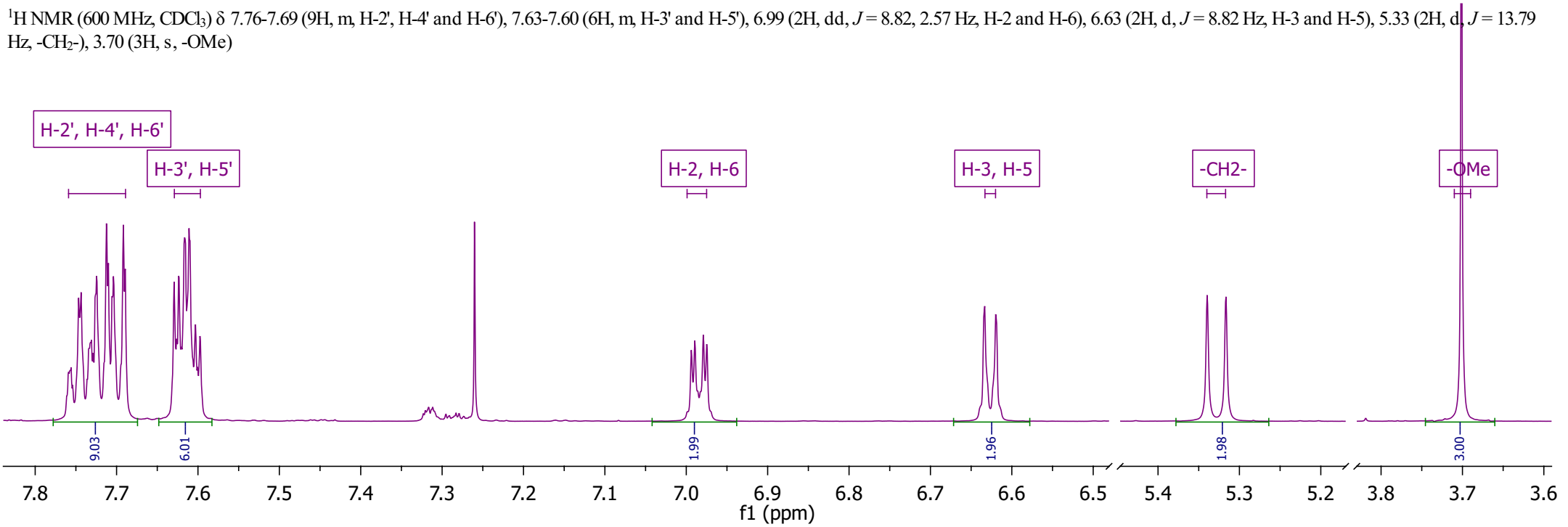
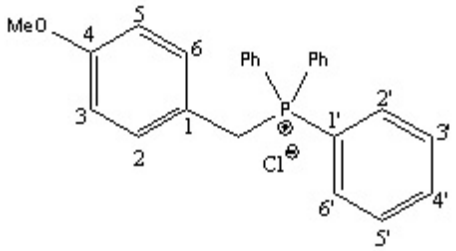


Plate 4b - ^{13}C NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)



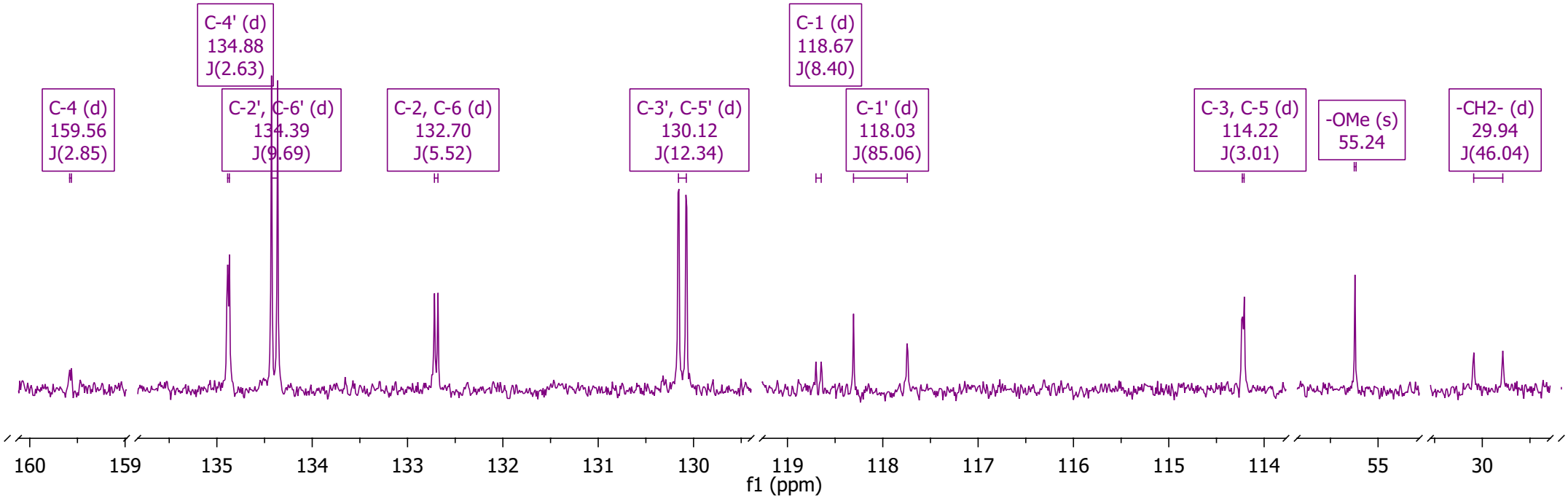


Plate 4c - DEPT NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)

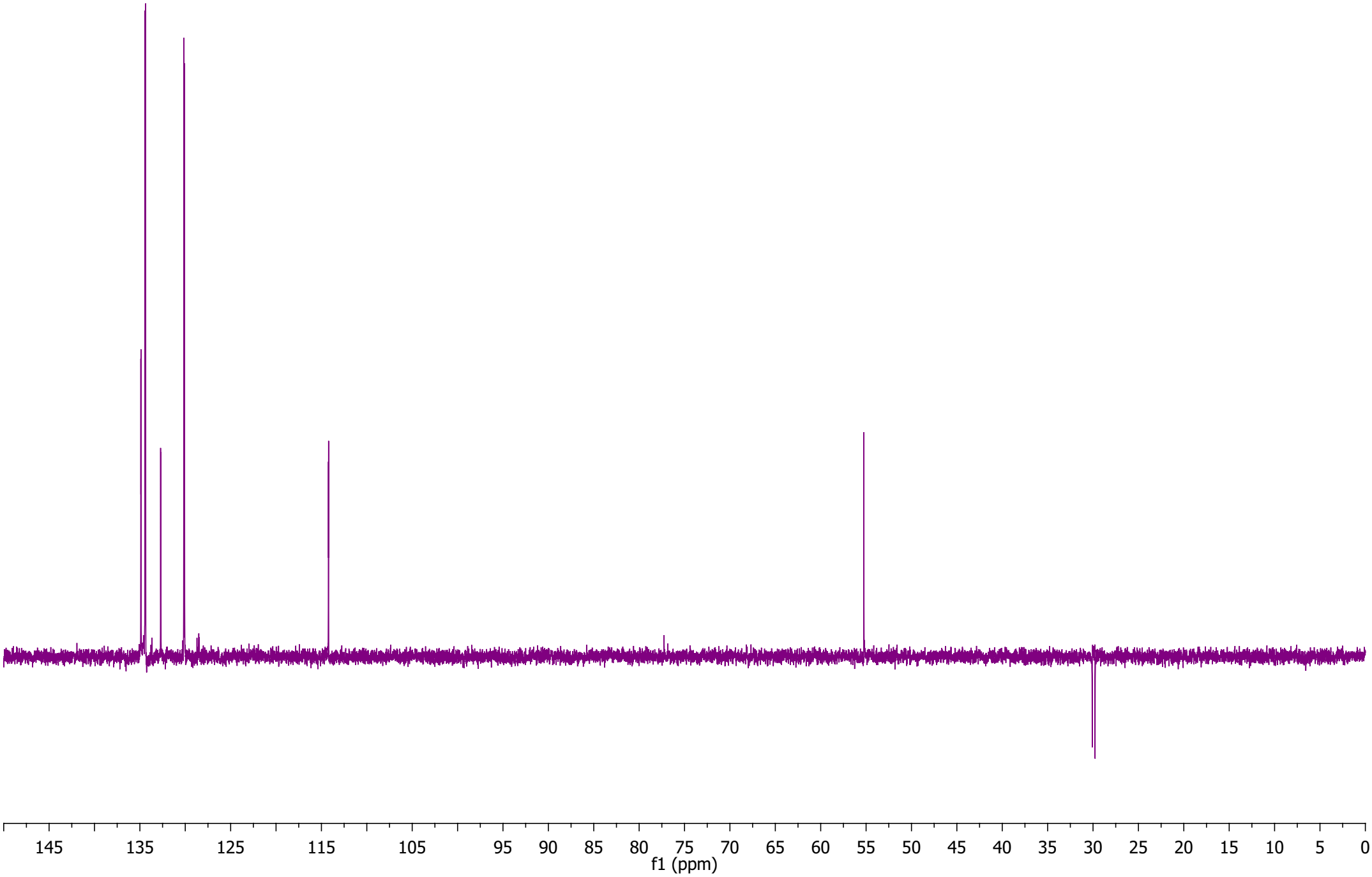


Plate 4d - HSQC NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)

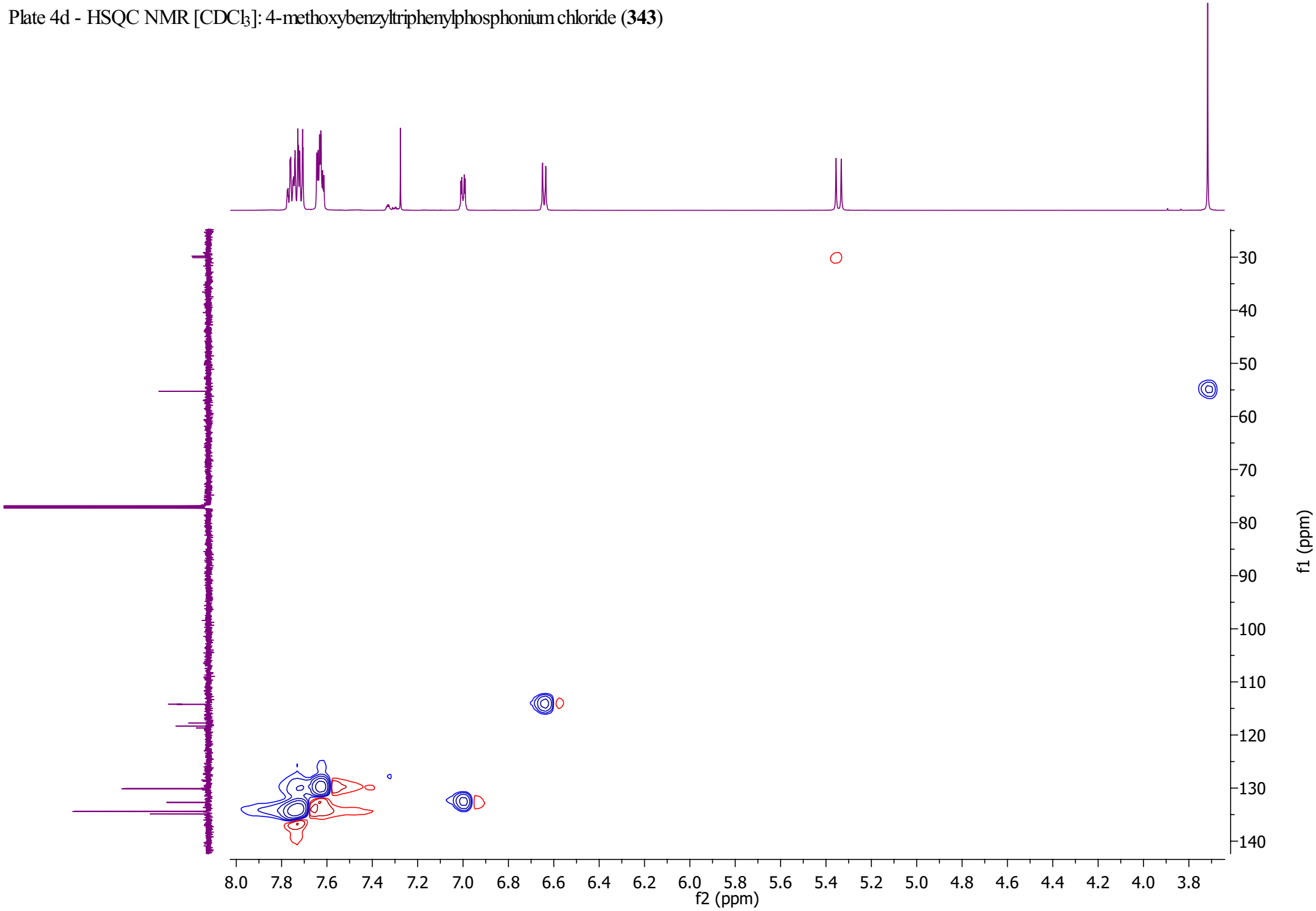


Plate 4e - HSQC (expansion) NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)

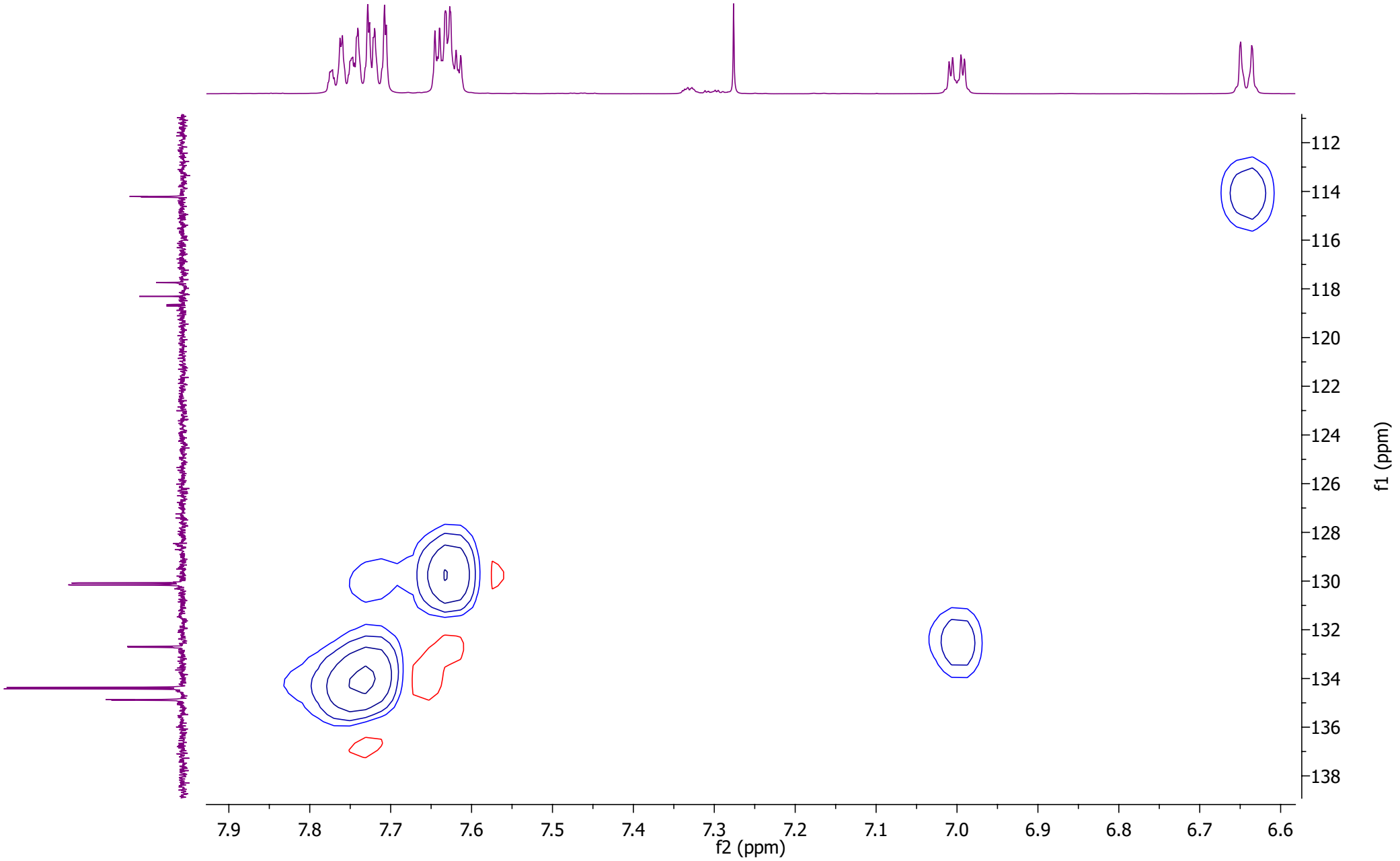


Plate 4f - HMBC NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)

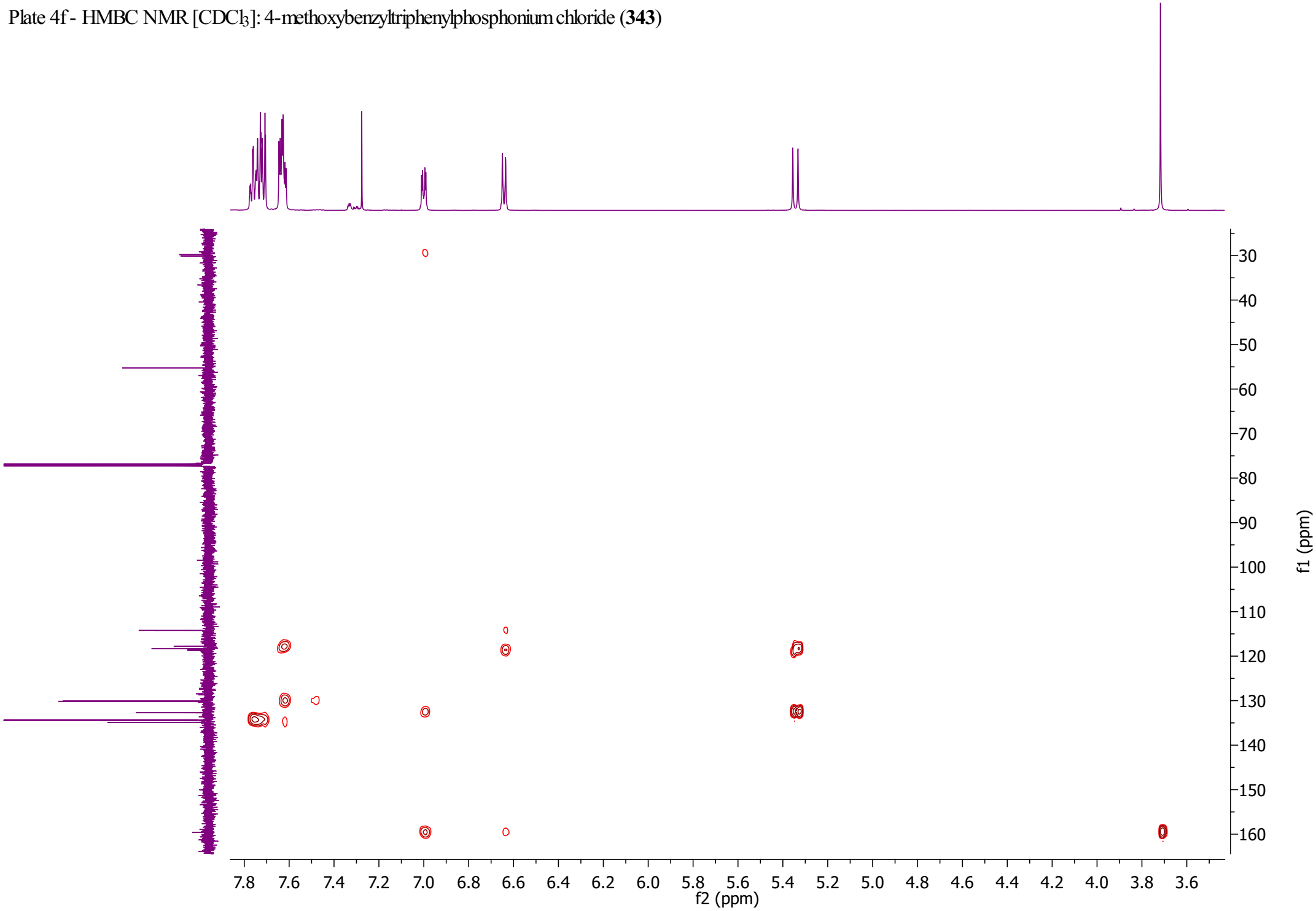


Plate 4g - HMBC(expansion) NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium chloride (**343**)

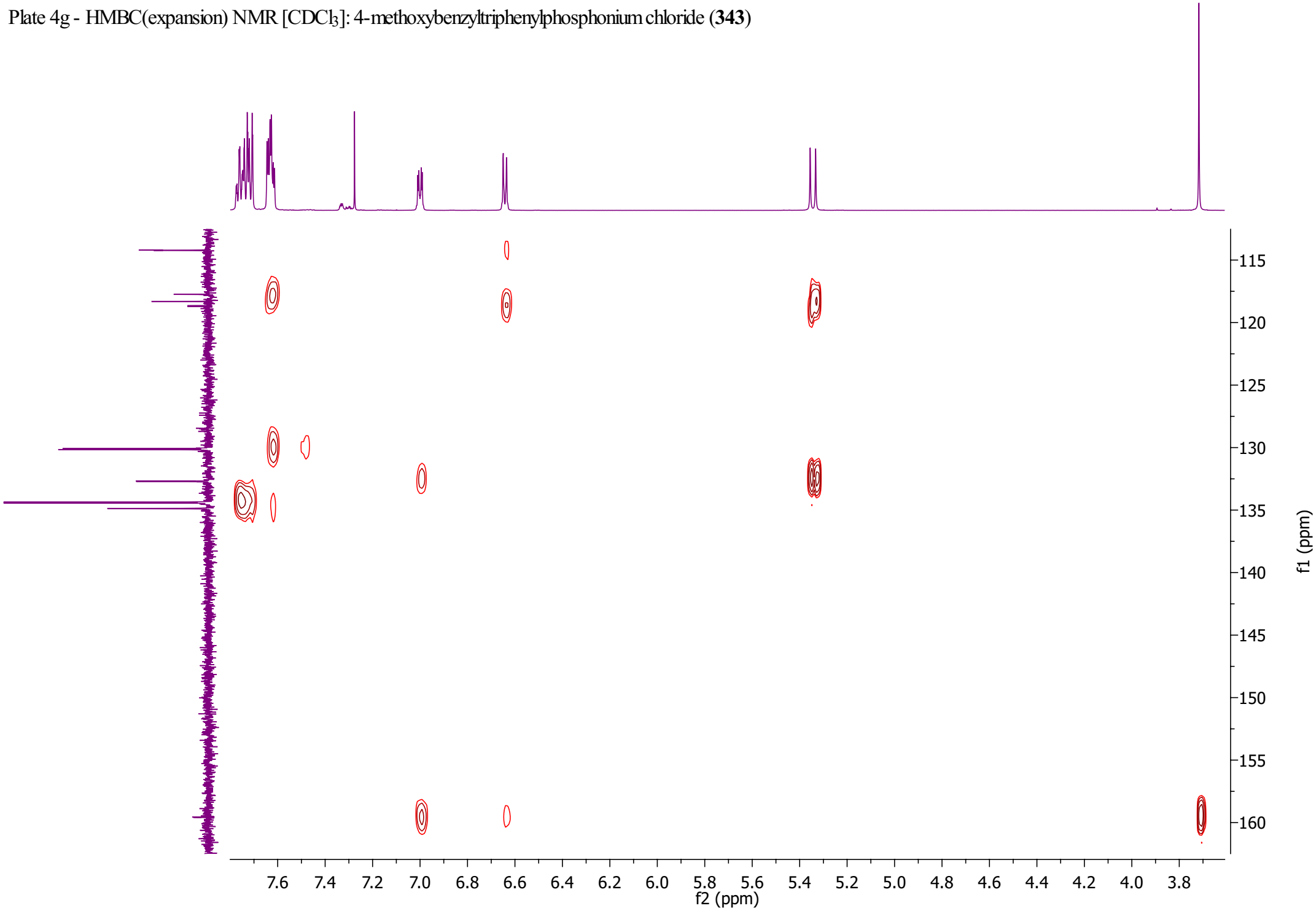
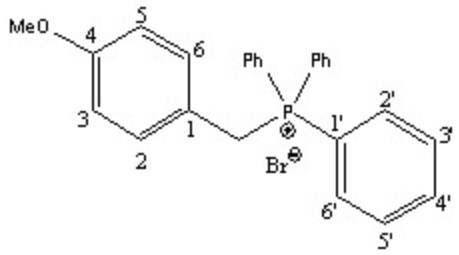


Plate 5a - ^{1}H NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75-7.71 (3H, m, H-4'), 7.67-7.64 (6H, m, H-2' and H-6'), 7.61-7.57 (6H, m, H-3' and H-5'), 6.95 (2H, dd, *J* = 8.81, 2.54 Hz, H-2 and H-6), 6.59 (2H, d, *J* = 8.81 Hz, H-3 and H-5), 5.17 (2H, d, *J* = 13.68 Hz, -CH_2-), 3.67 (3H, s, -OMe)

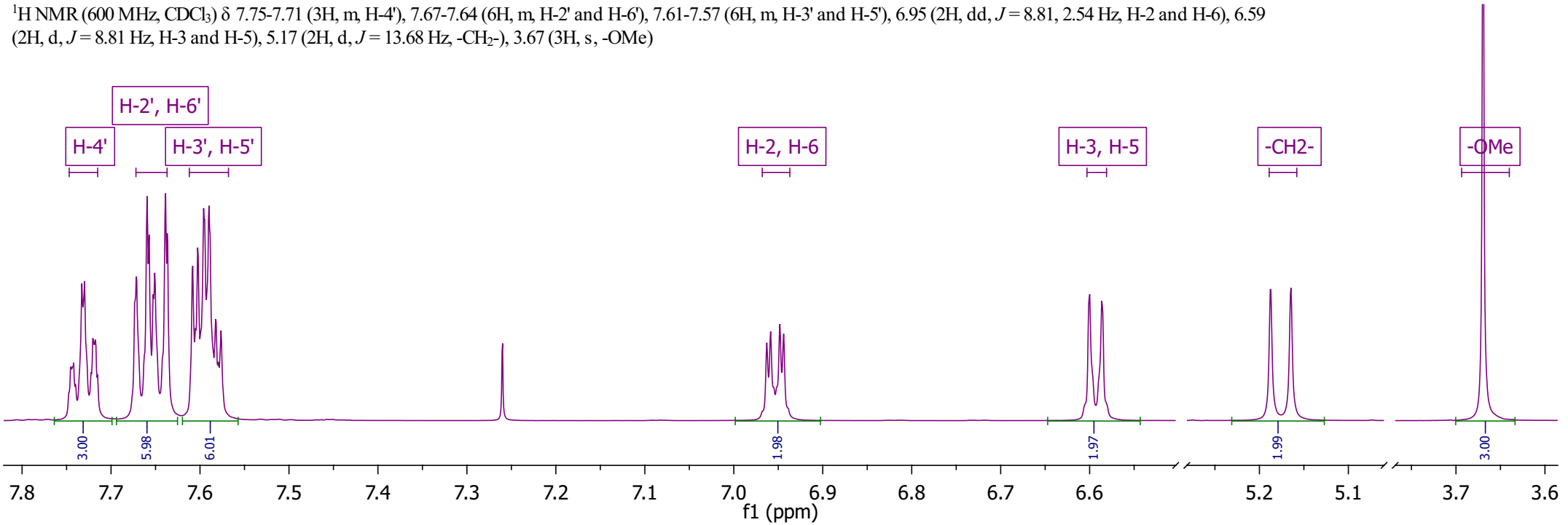
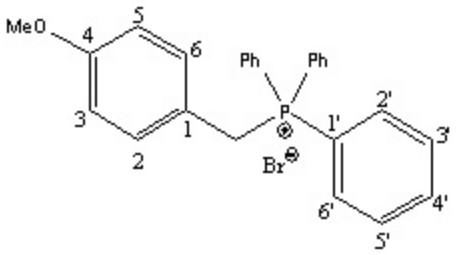


Plate 5b - ^{13}C NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)



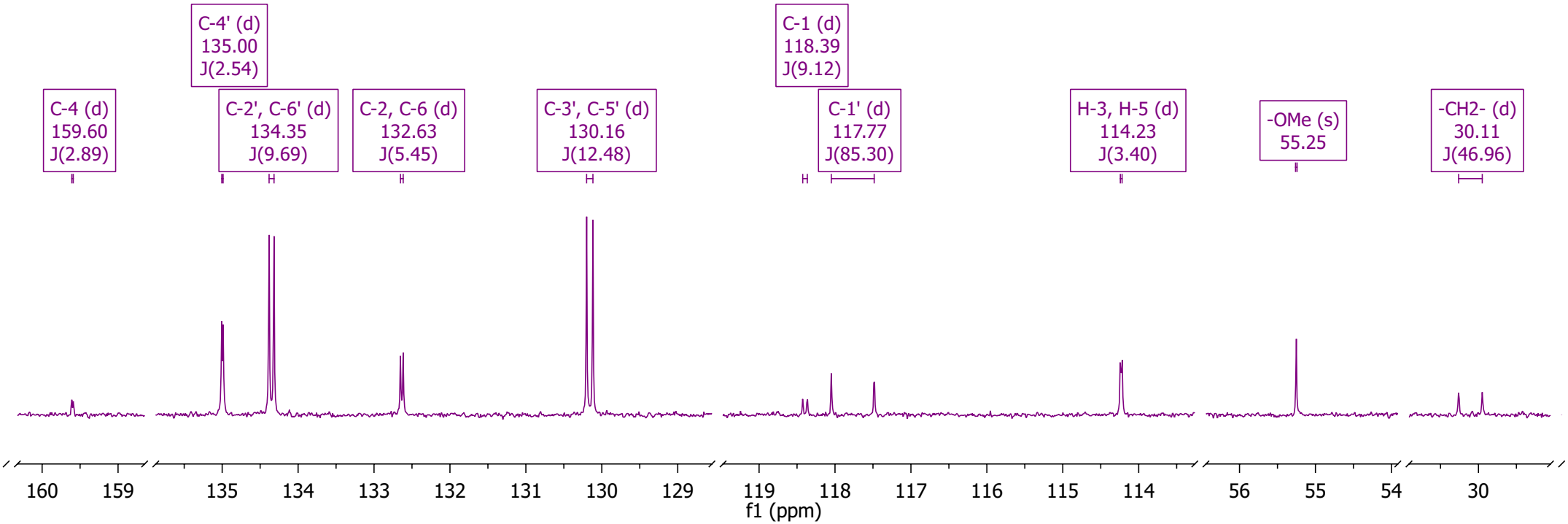


Plate 5c - DEPT NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)

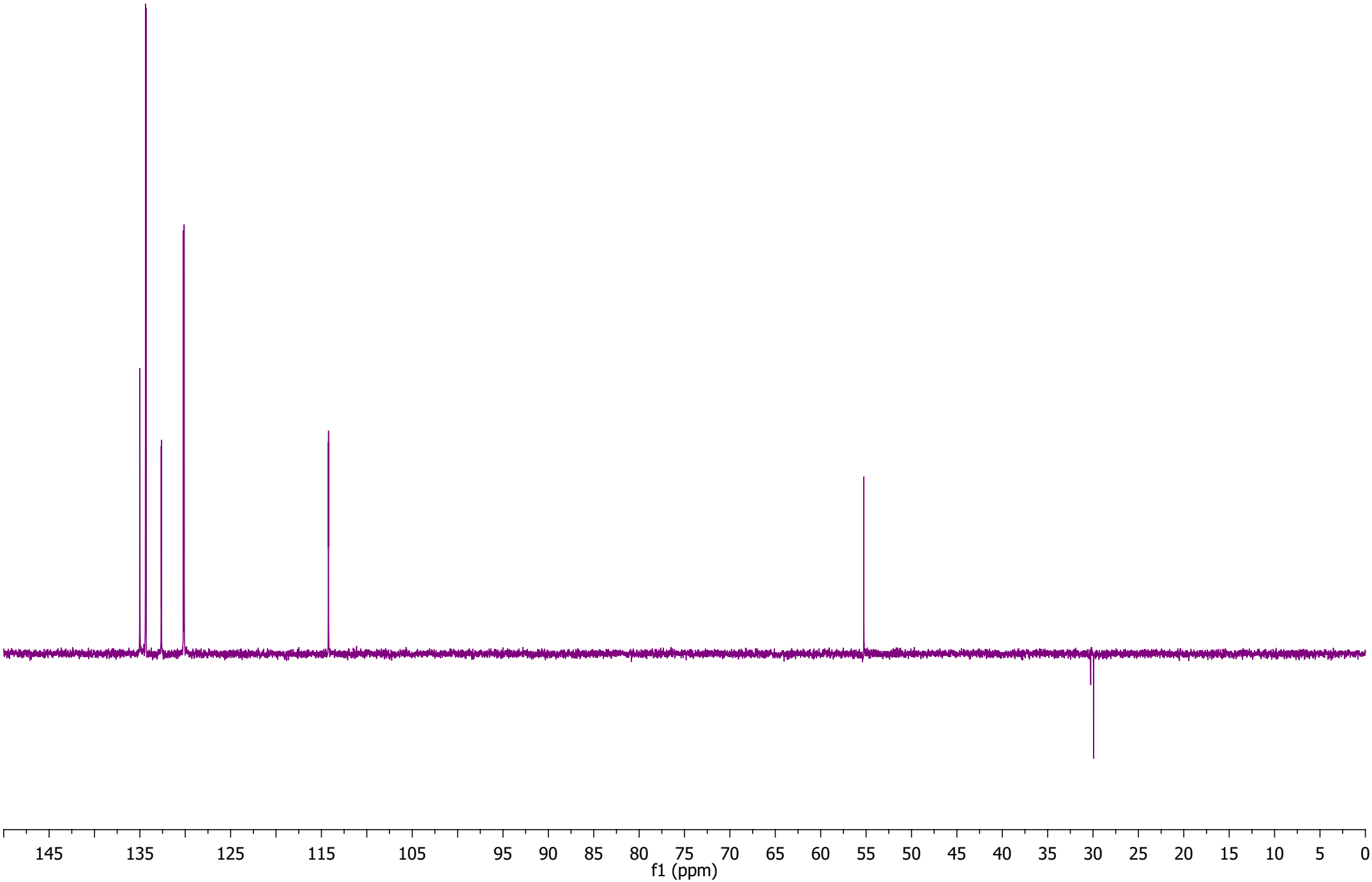


Plate 5d - HSQC [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)

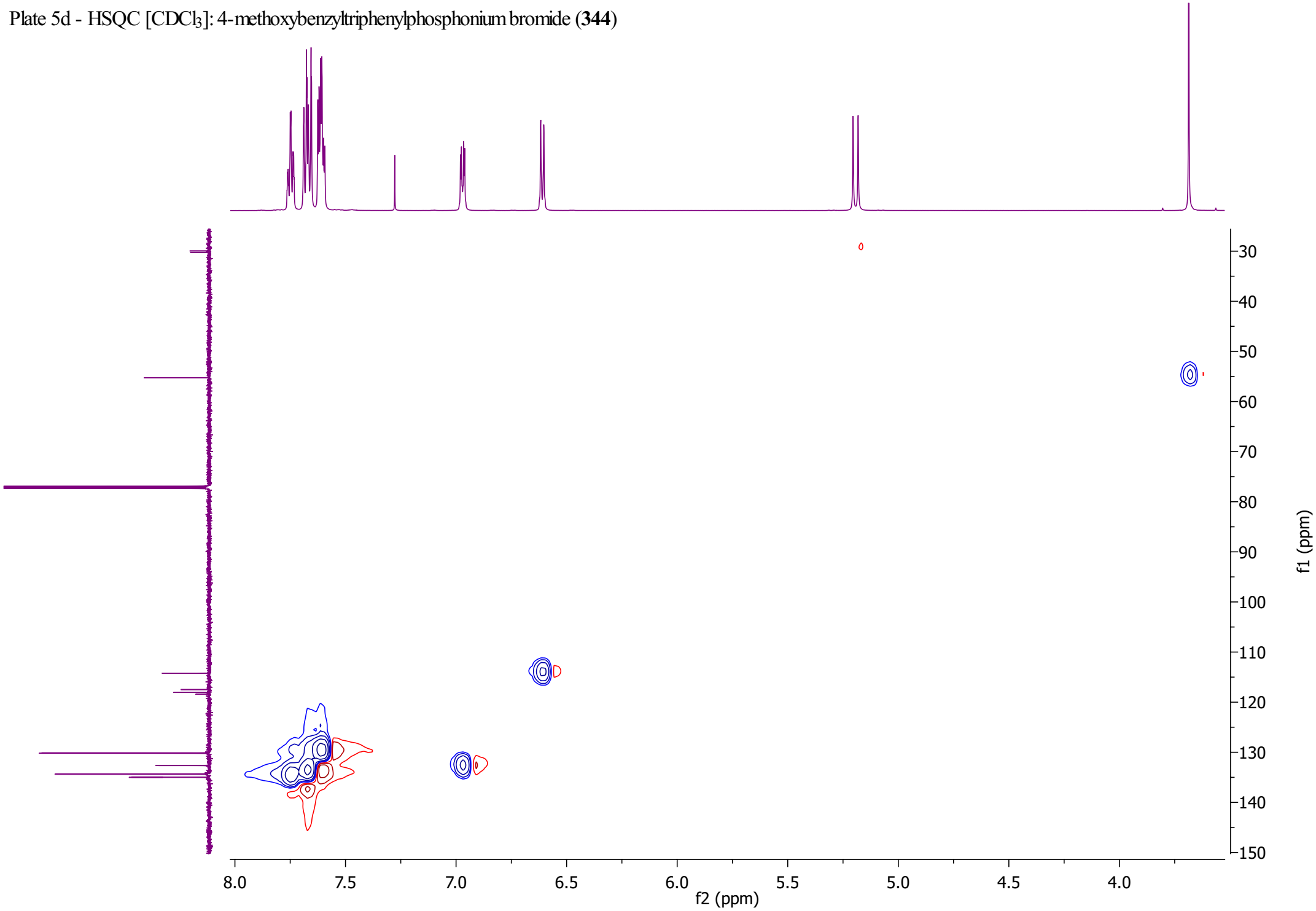


Plate 5e - HSQC (expansion) [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)

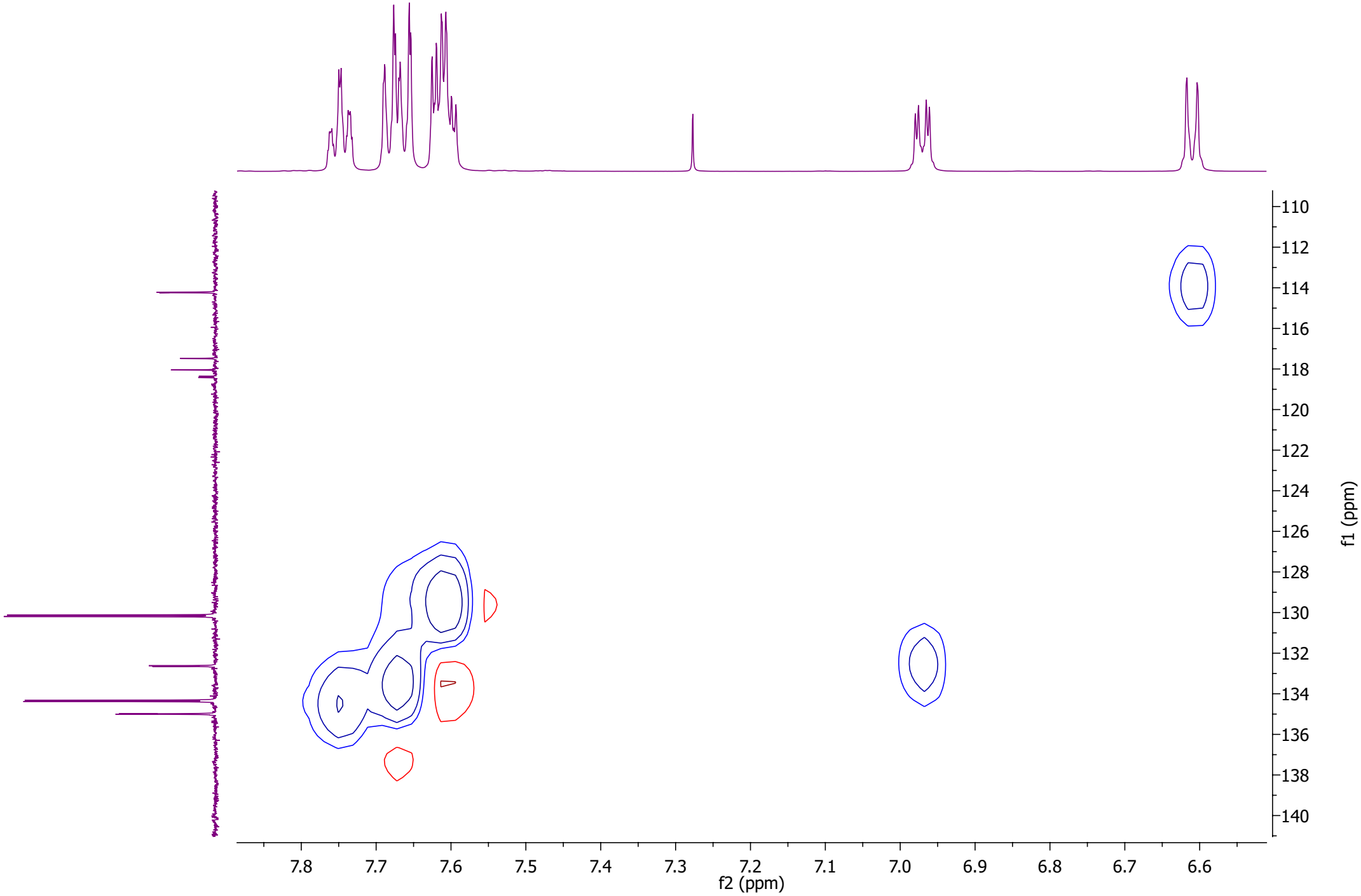


Plate 5f - HMBC NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)

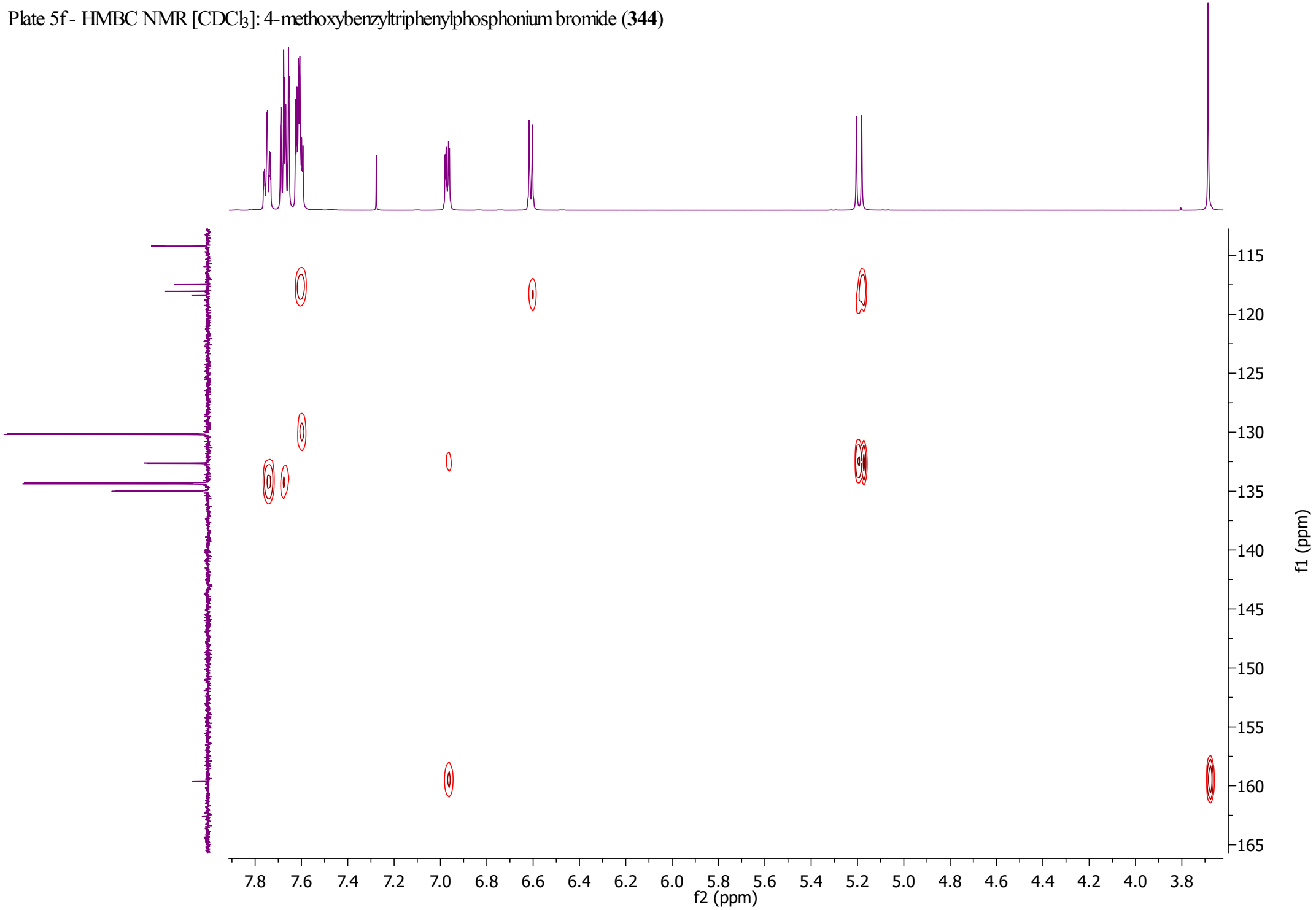


Plate 5g - ^{31}P NMR [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)

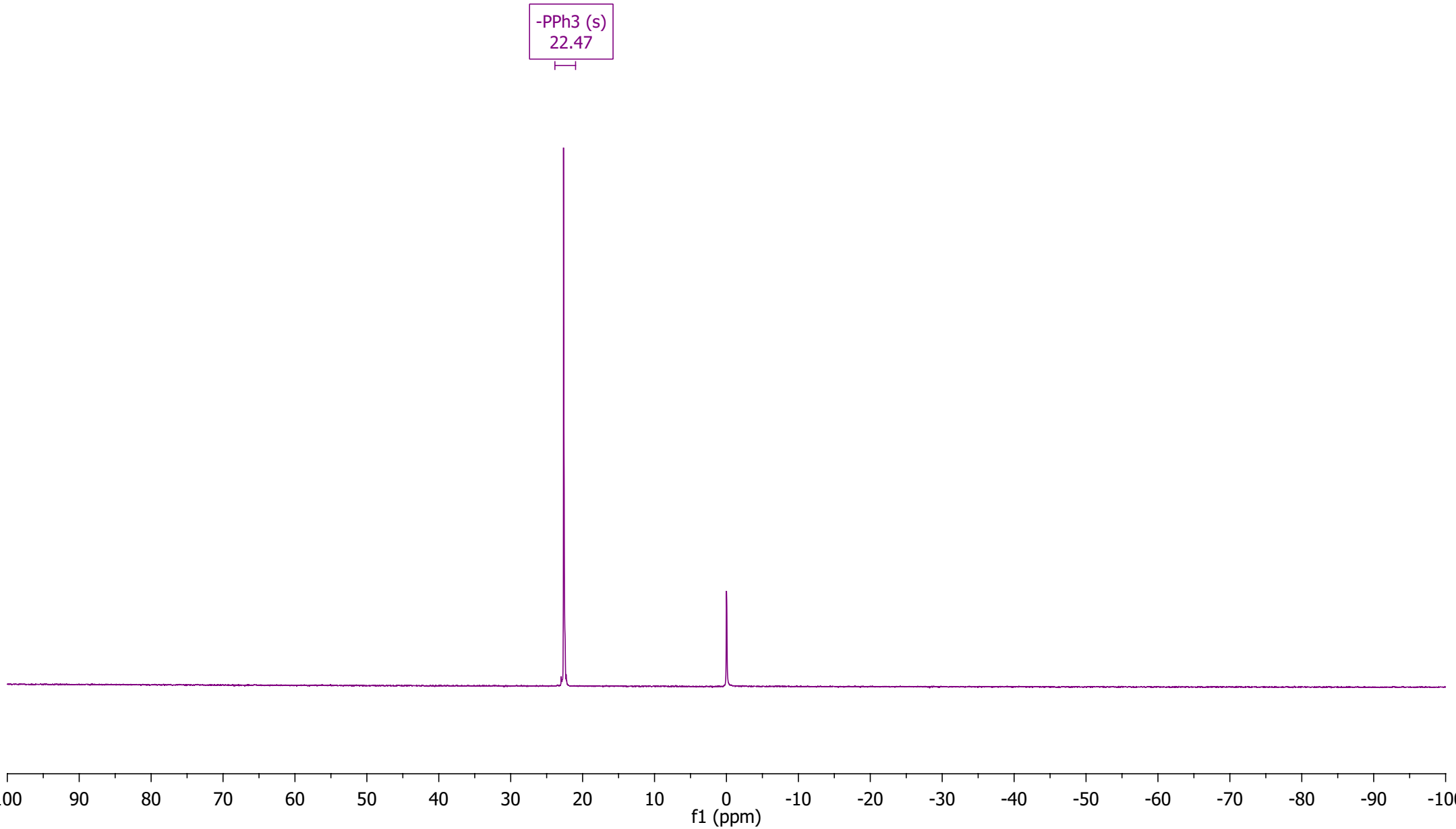


Plate 5h - HMBC (H-P) [$CDCl_3$]: 4-methoxybenzyltriphenylphosphonium bromide (**344**)

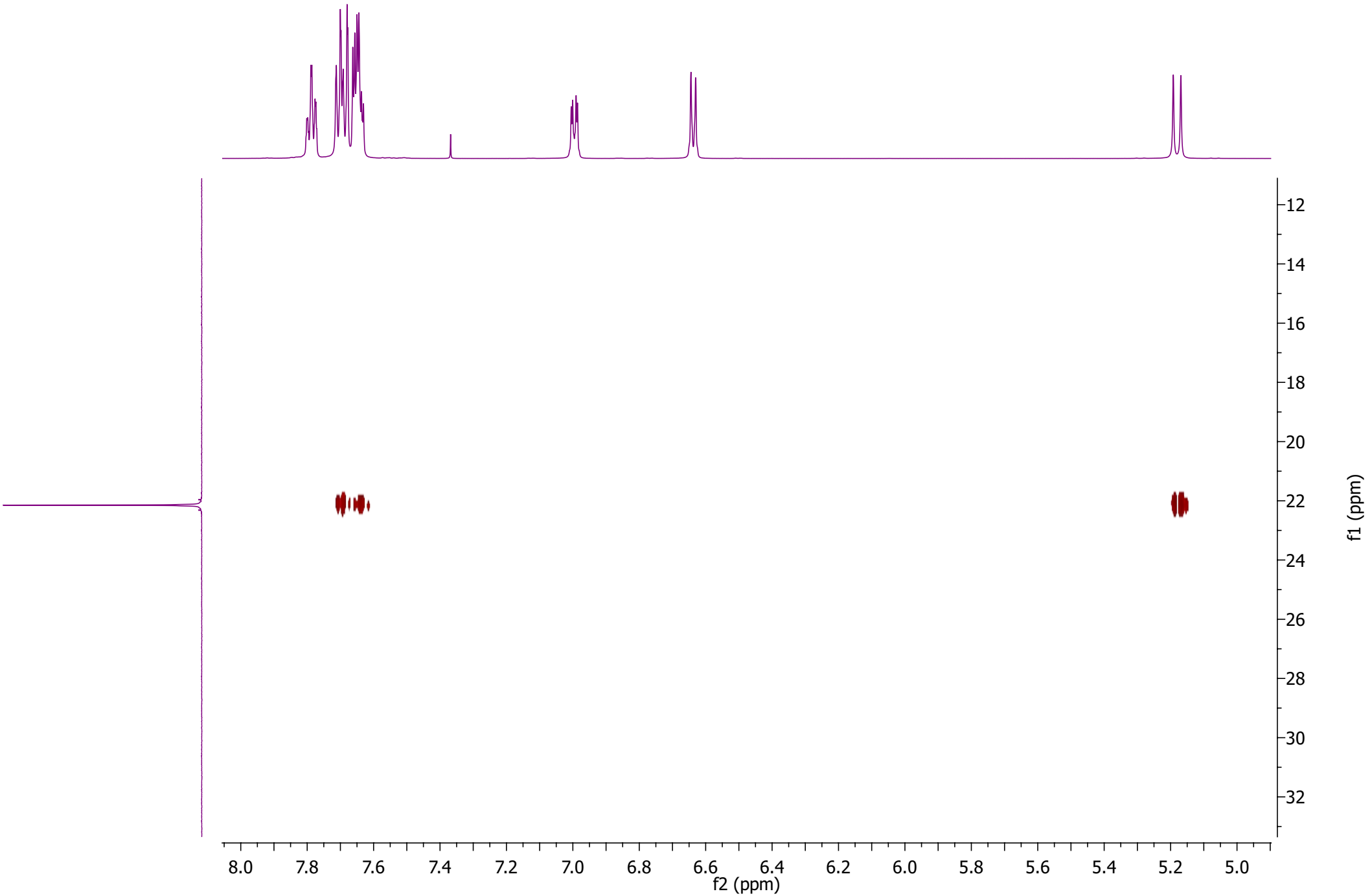
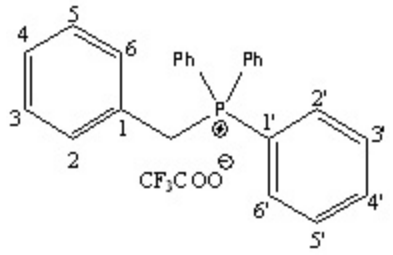


Plate 6a - ^{1}H NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 – 7.73 (1H, m, H-4'), 7.62 – 7.56 (12H, m, H-2', H-3', H-5' and H-6'), 7.21 (1H, m, H-4), 7.10 (2H, m, H-3 and H-5), 6.92 (2H, m, H-2 and H-6), 4.97 (2H, d, *J* = 14.39 Hz, -CH_2-)

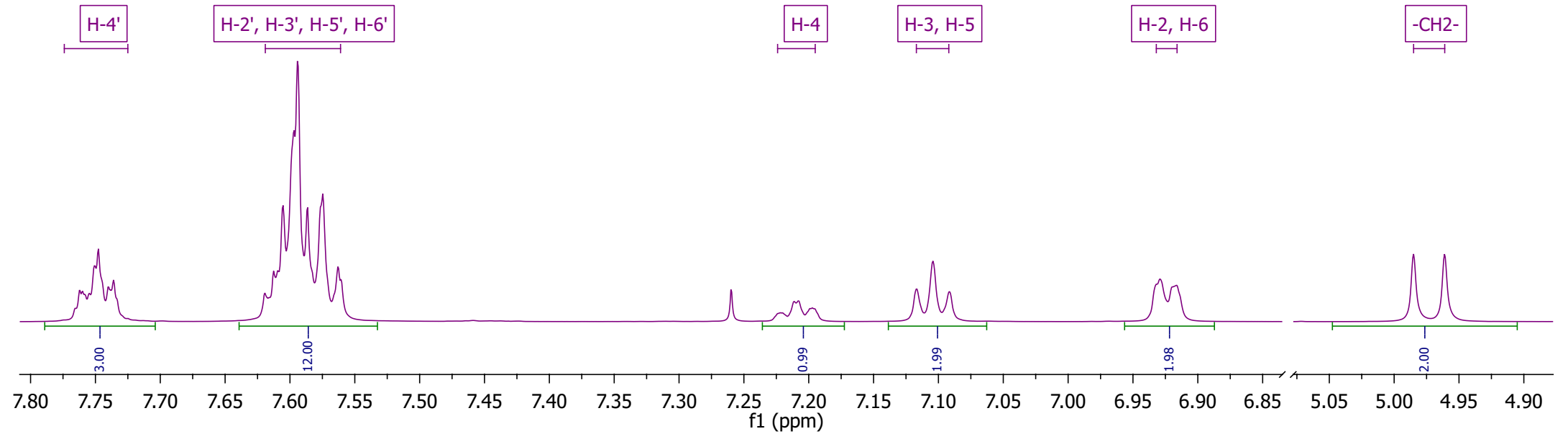
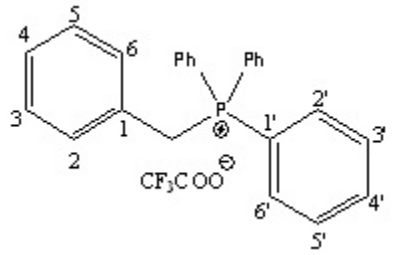


Plate 6b - ^{13}C NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)



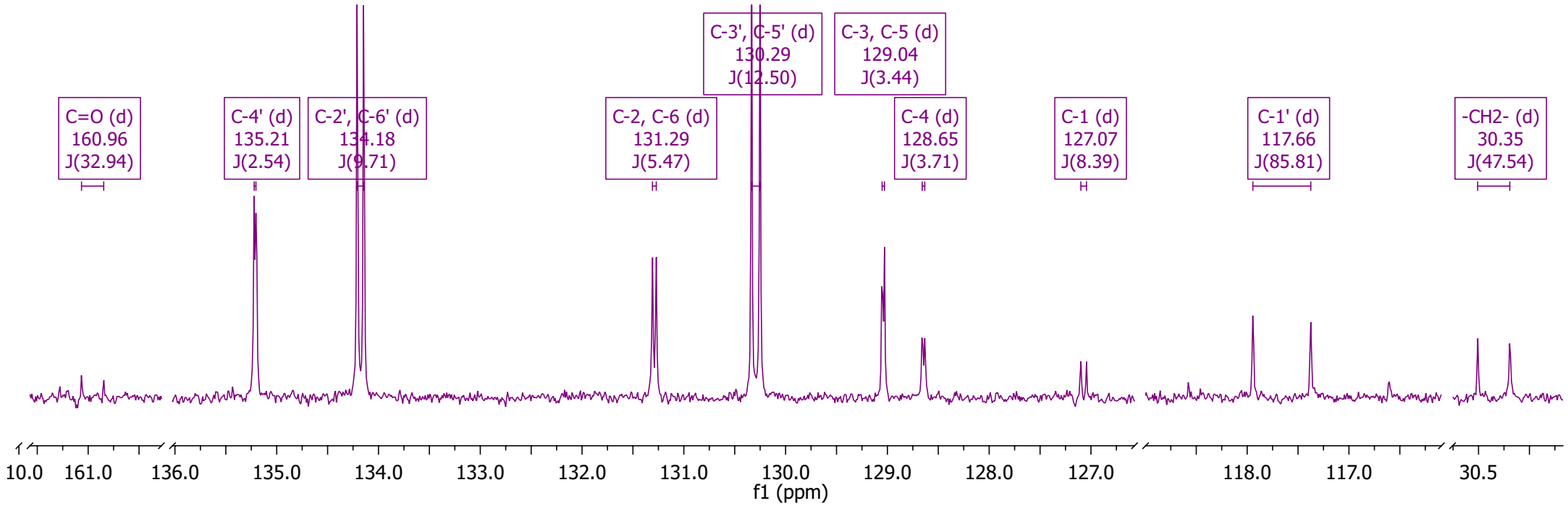


Plate 6c - DEPT NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)

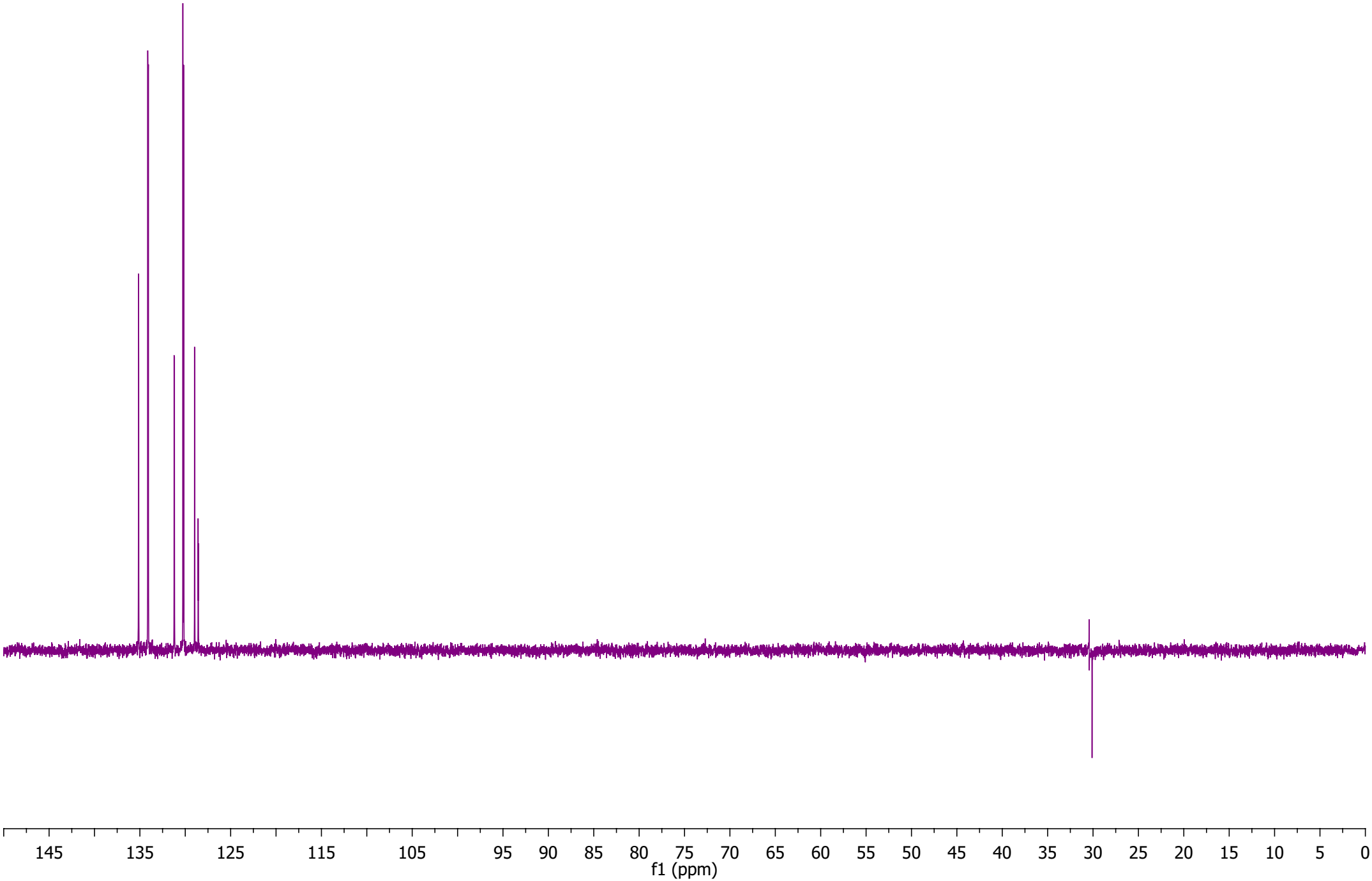


Plate 6d - HSQC NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)

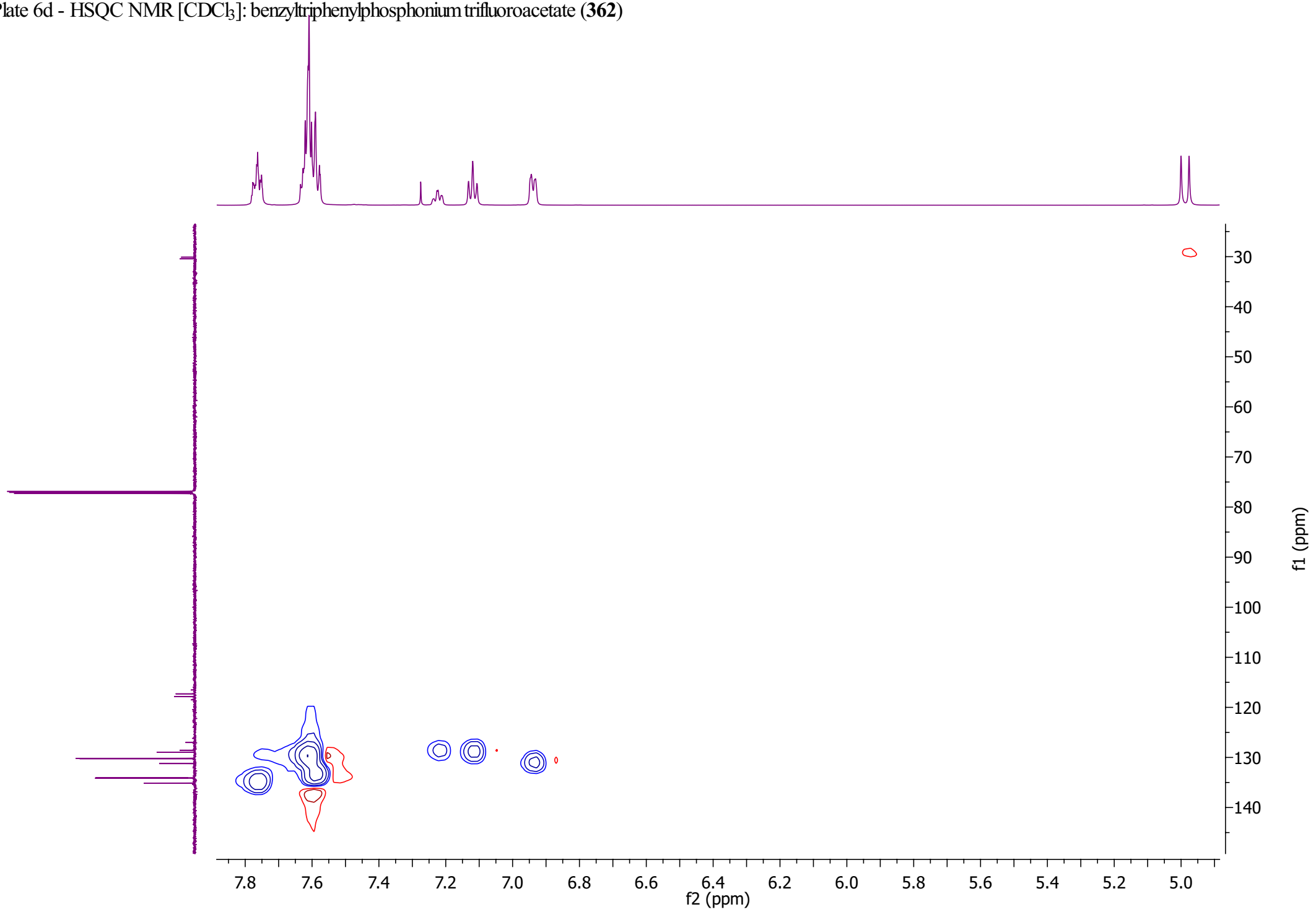


Plate 6e - HSQC (expansion) NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)

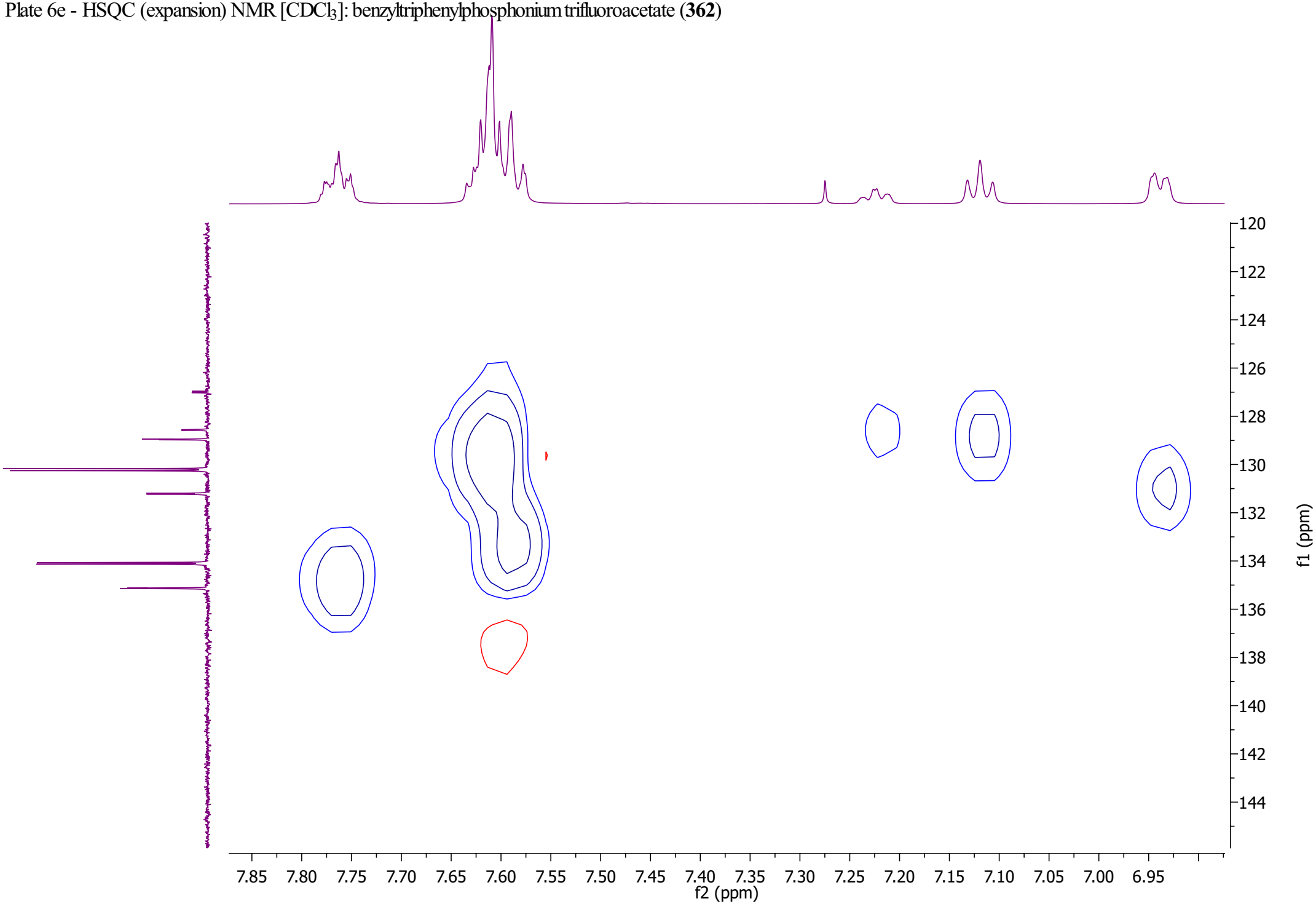


Plate 6f - HMBC NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)

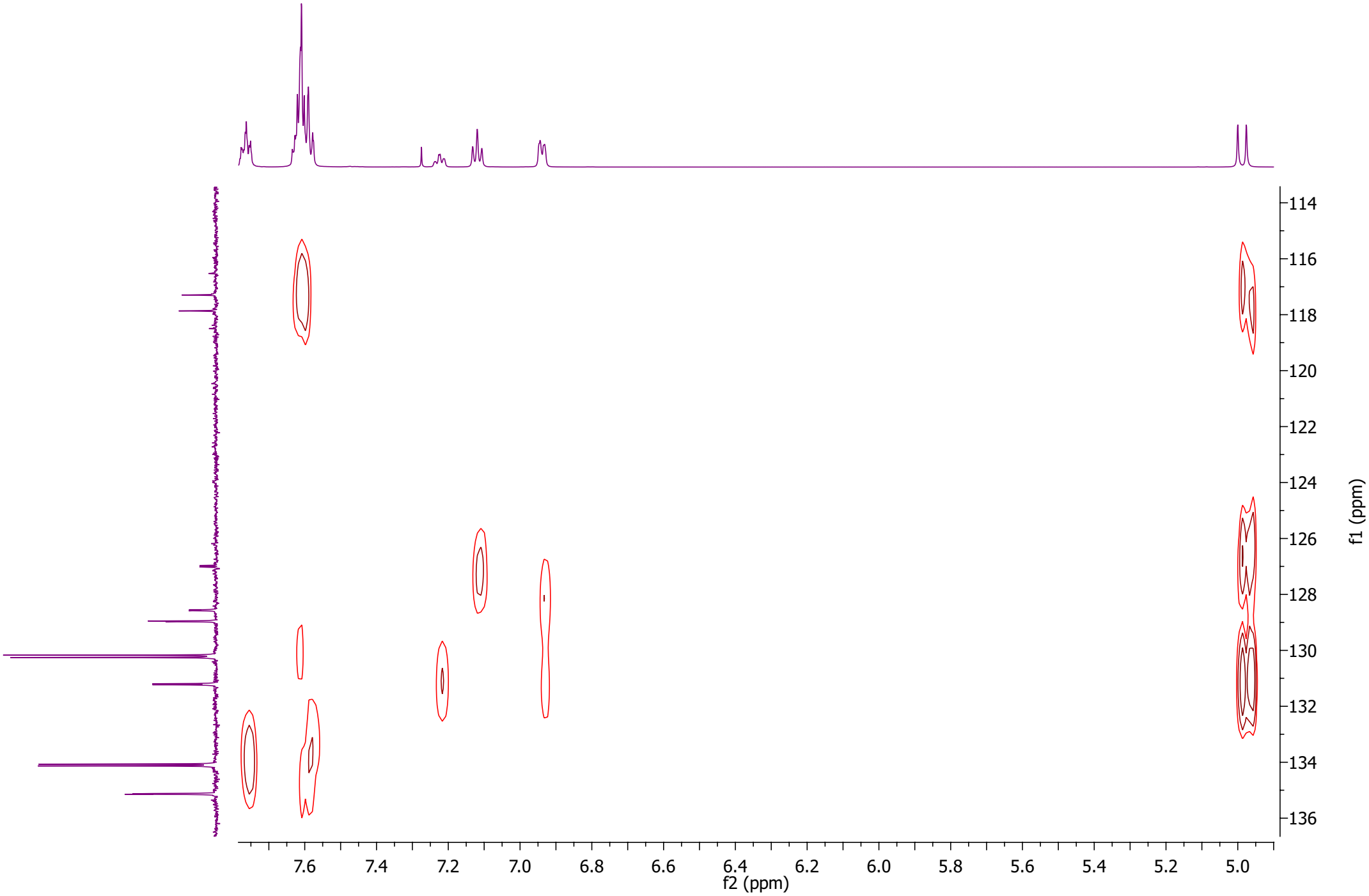


Plate 6g - ^{31}P NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)

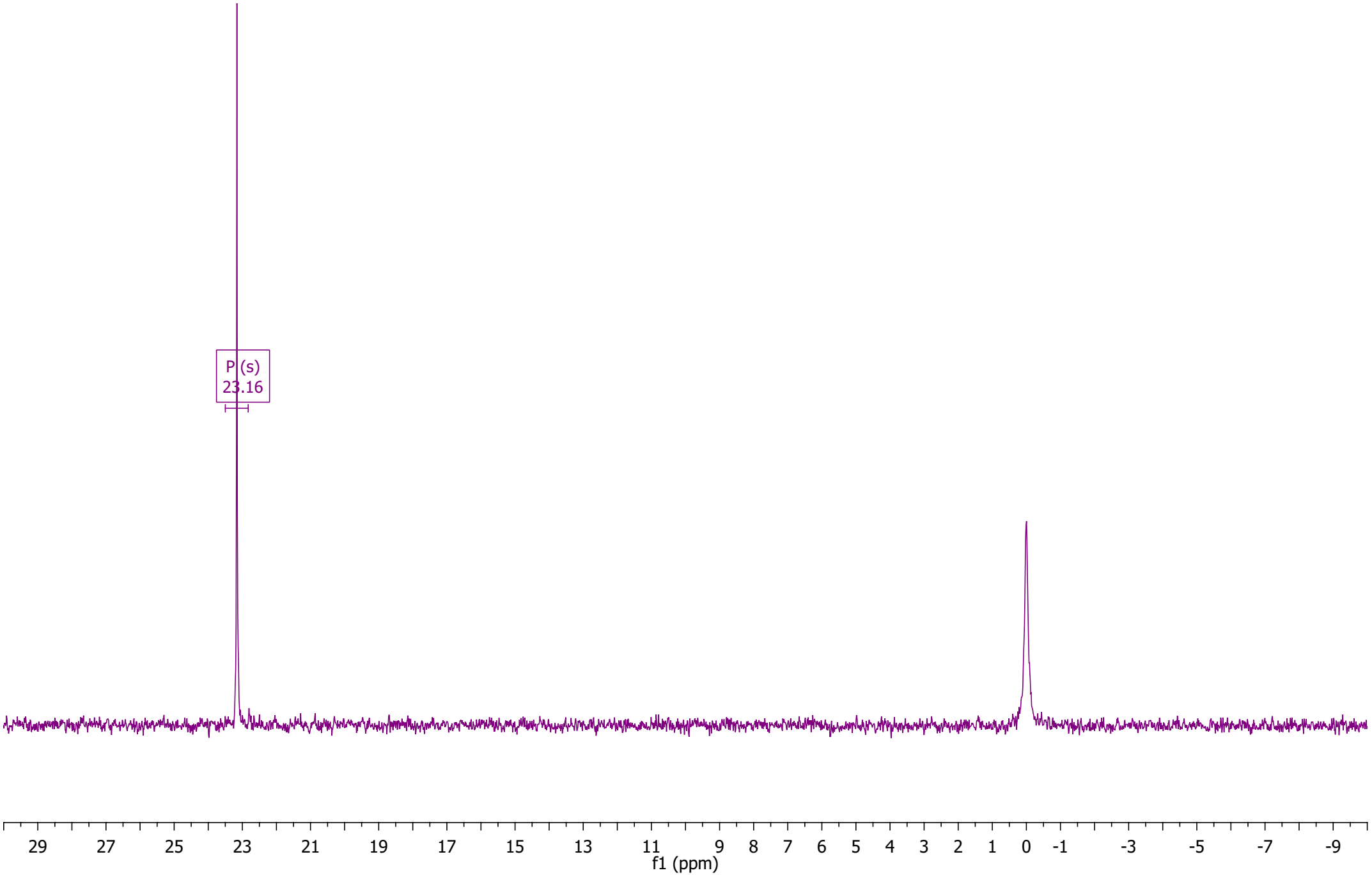


Plate 6h - ^{19}F NMR [$CDCl_3$]: benzyltriphenylphosphonium trifluoroacetate (**362**)

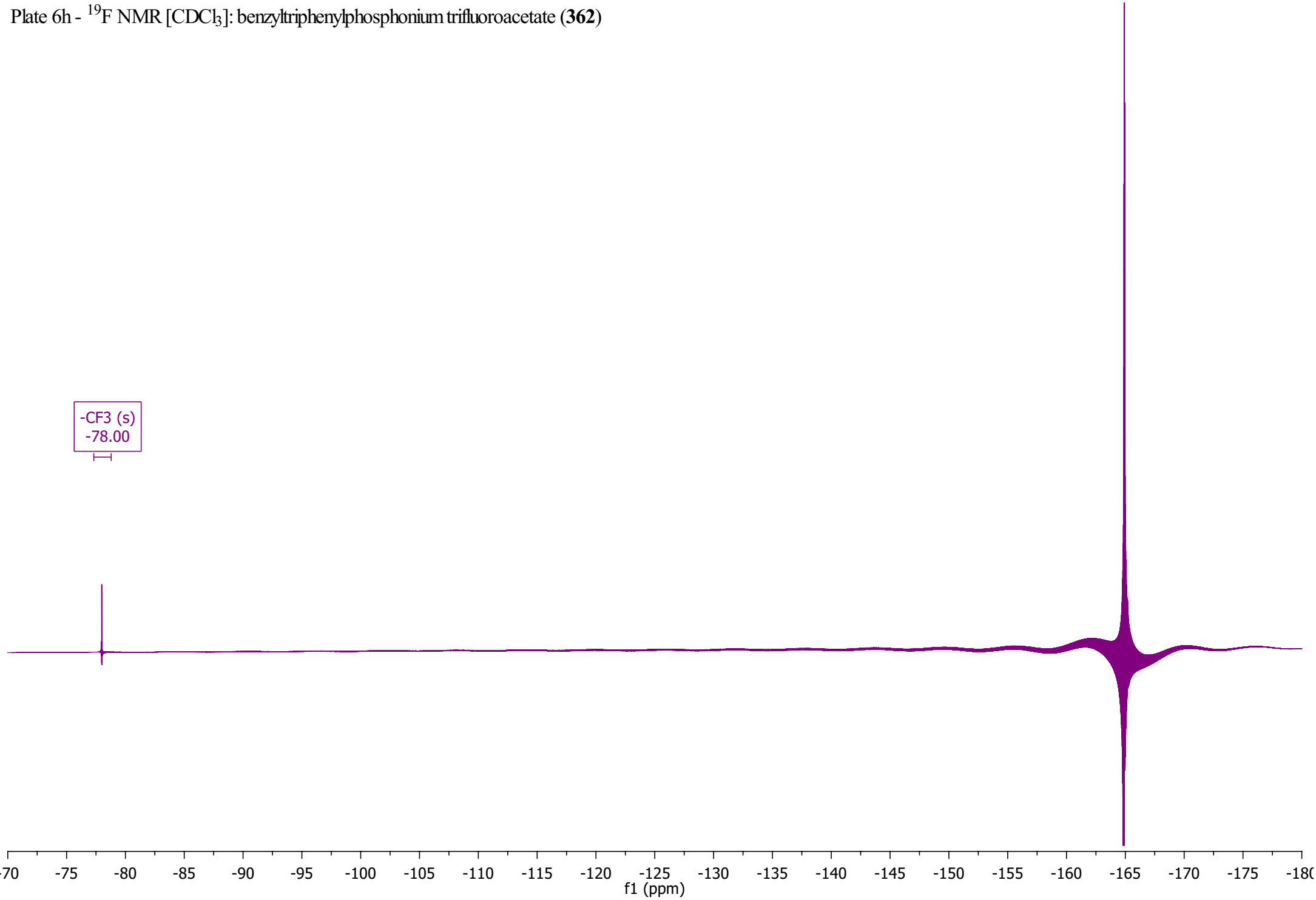
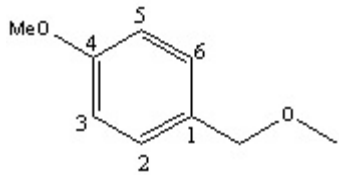


Plate 7a - ^{1}H NMR [$CDCl_3$]: 4-methoxybenzyl methyl ether (**366**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.7 Hz, H-2 and H-6), 6.88 (2H, d, J = 8.7 Hz, H-3, H-5), 4.38 (2H, s, CH_2-), 3.79 (3H, s, -PhOMe), 3.35 (3H, s, -CH_2OMe)

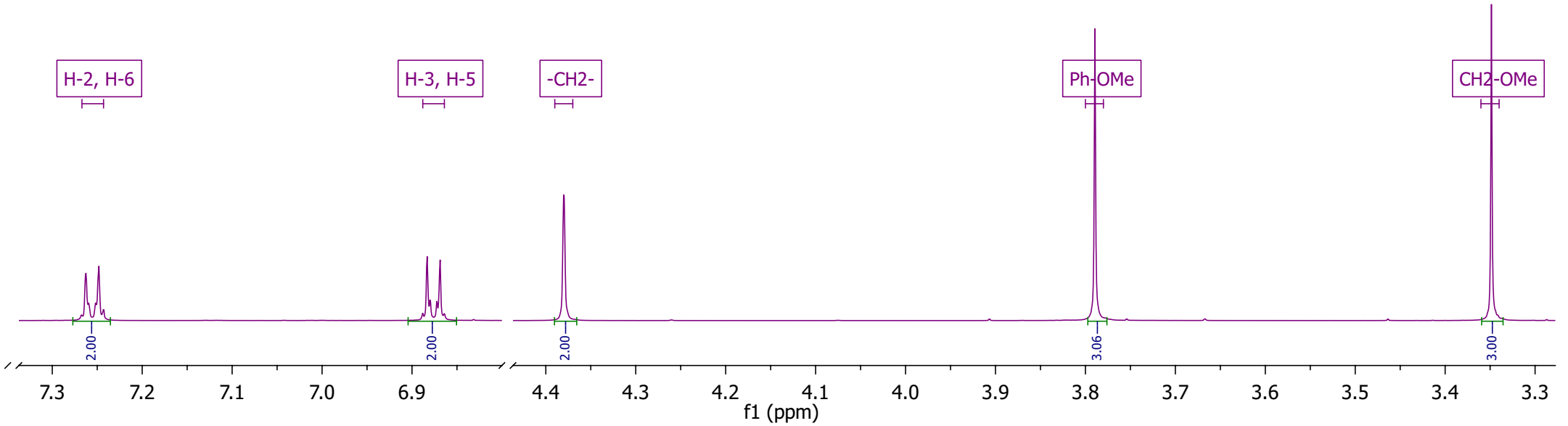
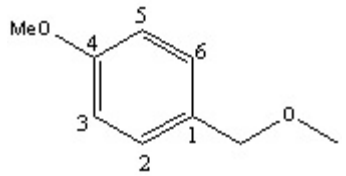


Plate 7b - ^{13}C NMR [$CDCl_3$]: 4-methoxybenzyl methyl ether (**366**)



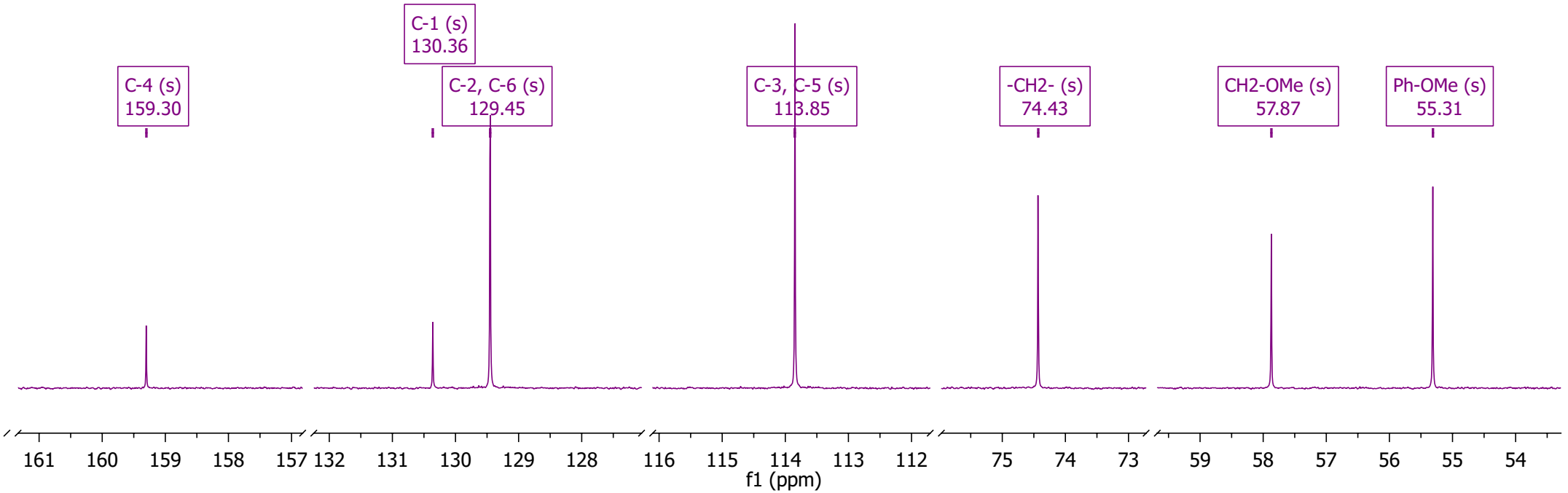


Plate 7c - HSQC NMR [$CDCl_3$]: 4-methoxybenzyl methyl ether (**366**)

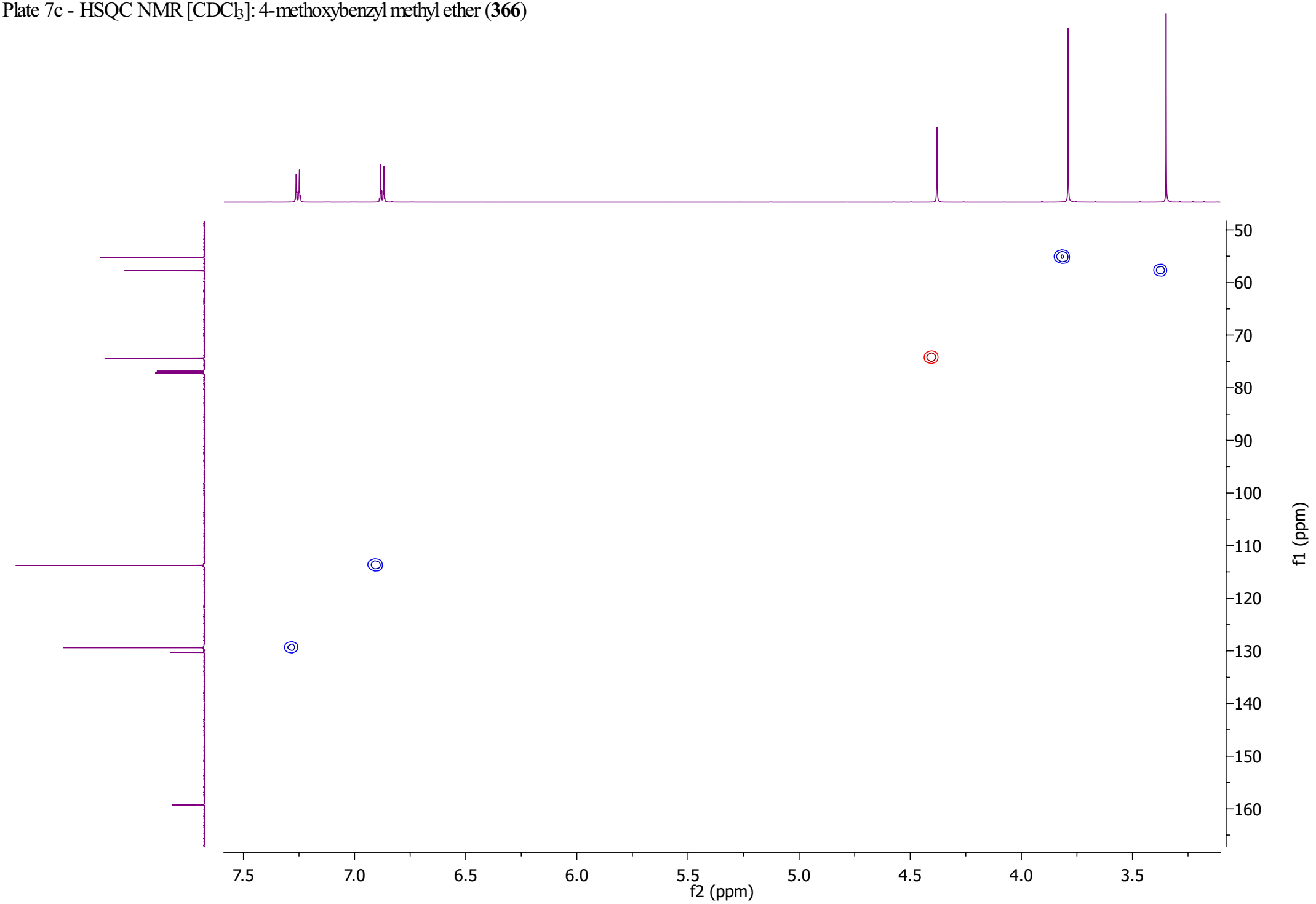


Plate 7d - HMBC NMR [$CDCl_3$]: 4-methoxybenzyl methyl ether (**366**)

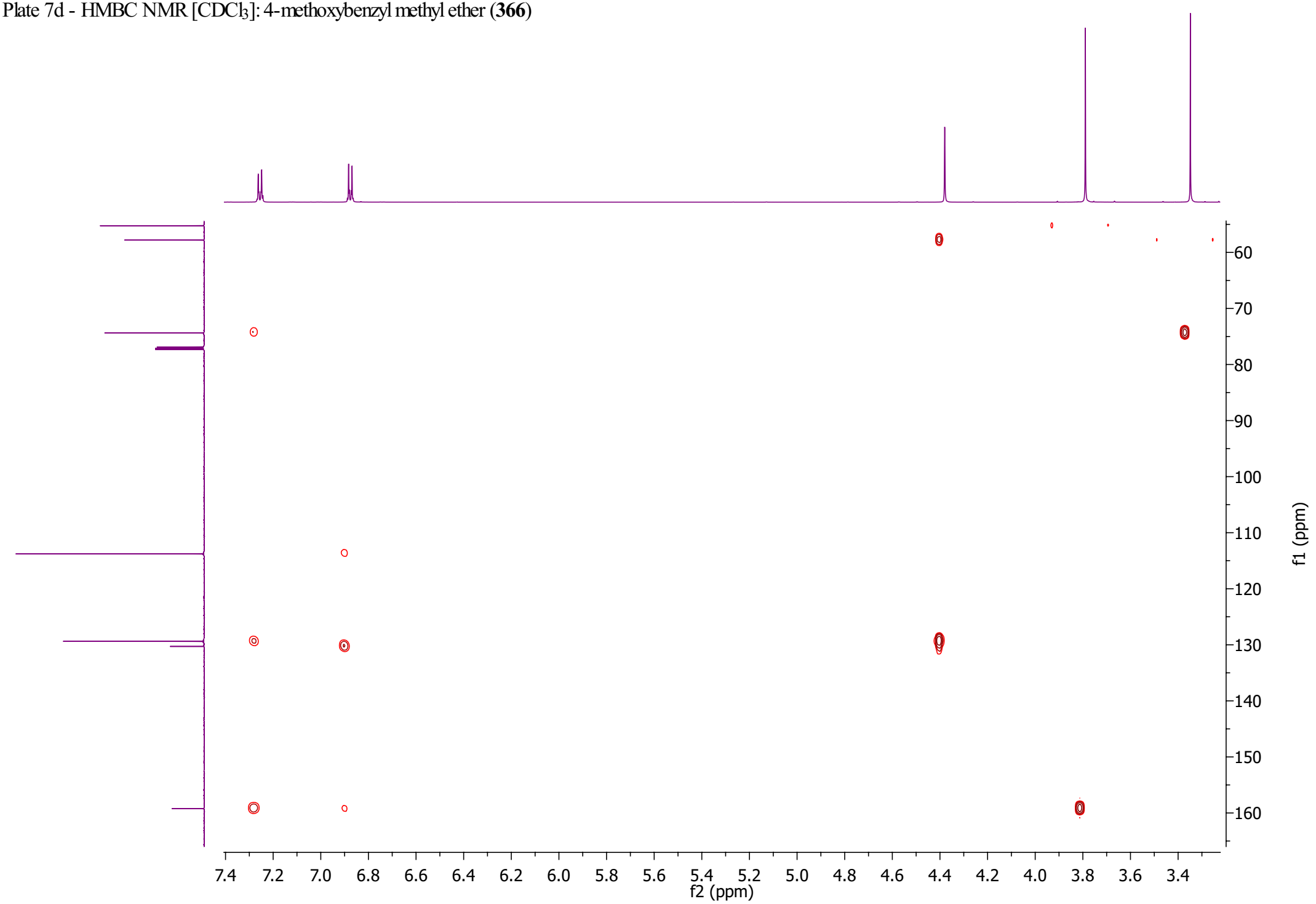
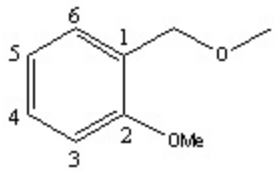


Plate 8a - ^{1}H NMR [$CDCl_3$]: 2-methoxybenzyl methyl ether (**367**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.36 (1H, m, H-6), 7.30-7.27 (1H, m, H-4), 6.98-6.96 (1H, m, H-5), 6.89-6.88 (1H, m, H-3), 4.52 (2H, s, -CH_2-), 3.85 (3H, s, -PhOMe), 3.44 (1H, s, -CH_2OMe)

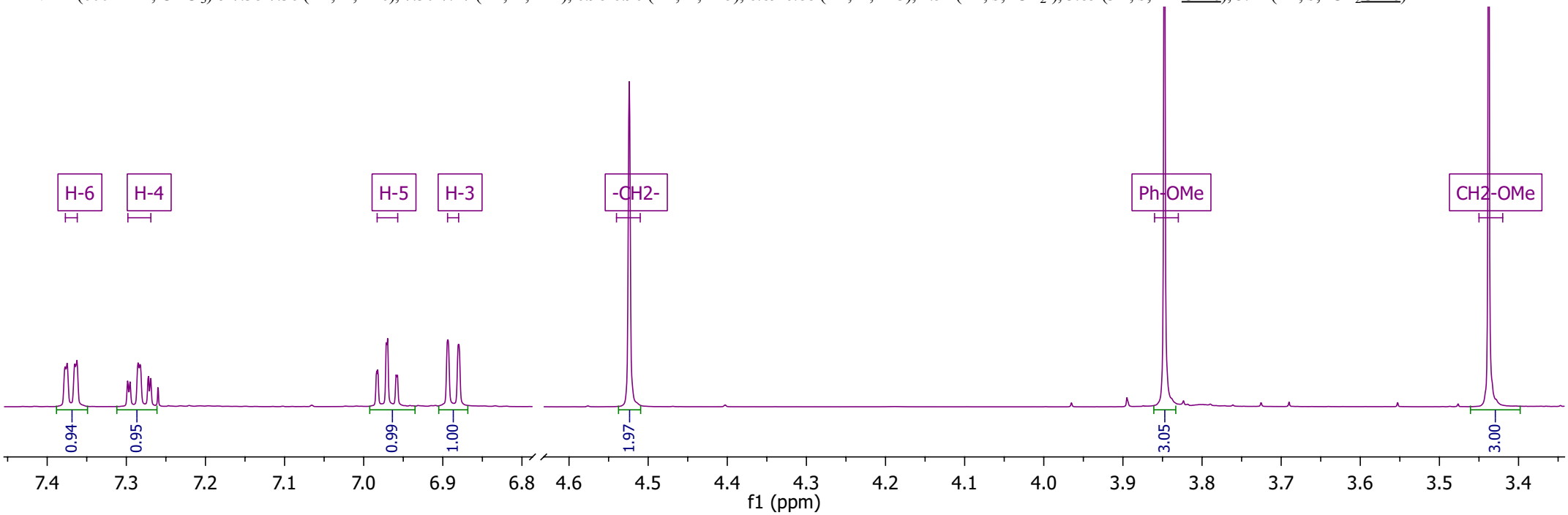
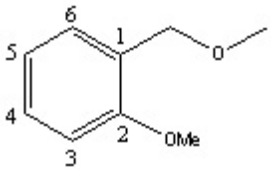


Plate 8b - ^{13}C NMR [$CDCl_3$]: 2-methoxybenzyl methyl ether (**367**)



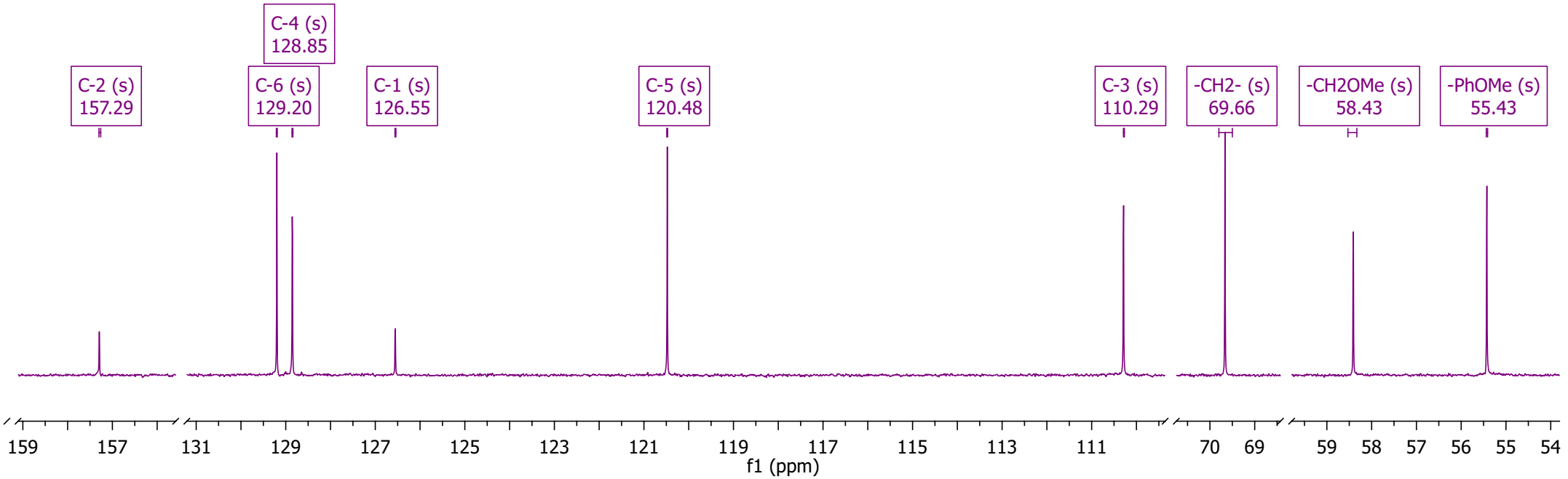


Plate 8c - DEPT [$CDCl_3$]: 2-methoxybenzyl methyl ether (**367**)

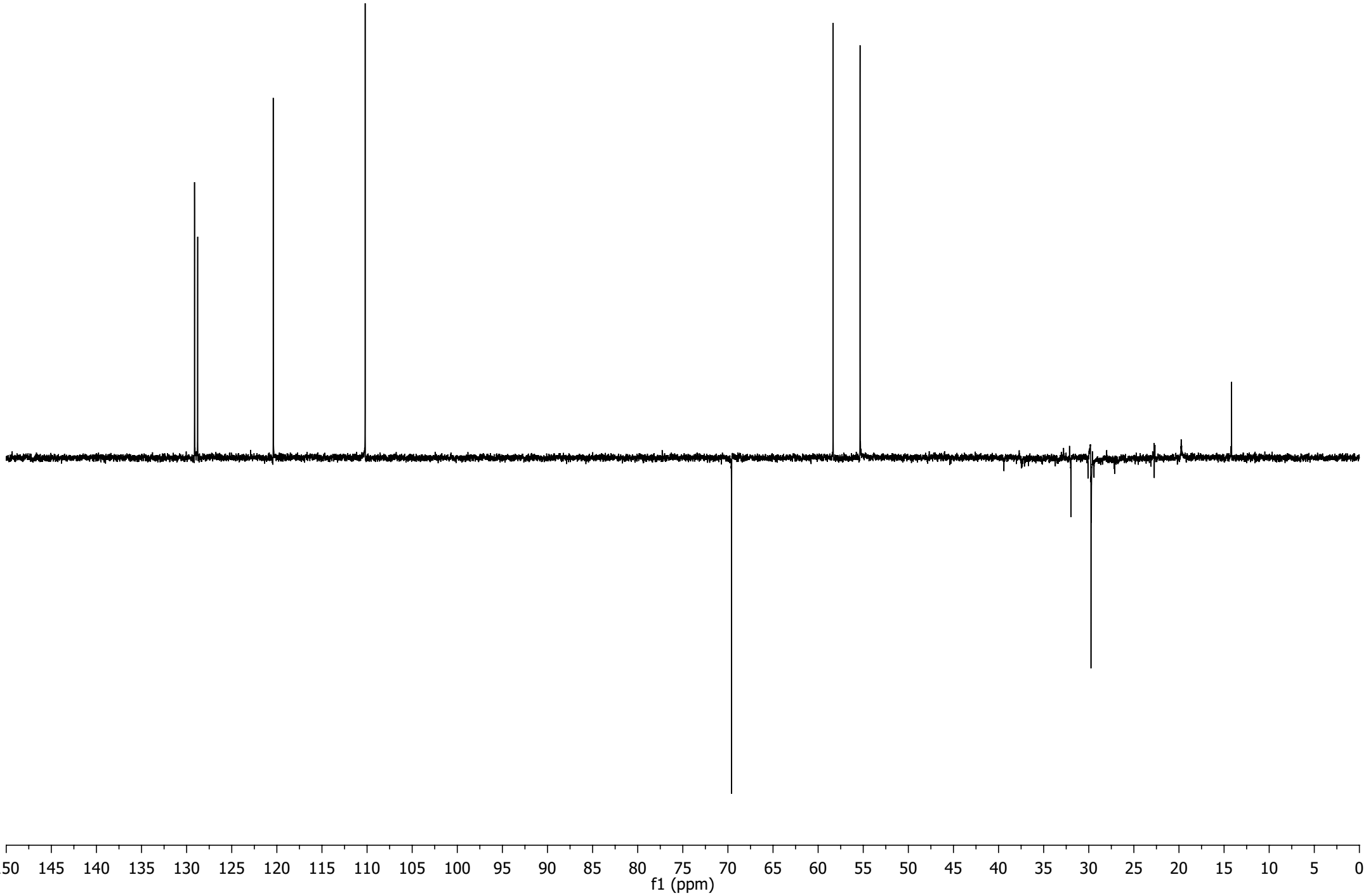


Plate 8d - HSQC [$CDCl_3$]: 2-methoxybenzyl methyl ether (**367**)

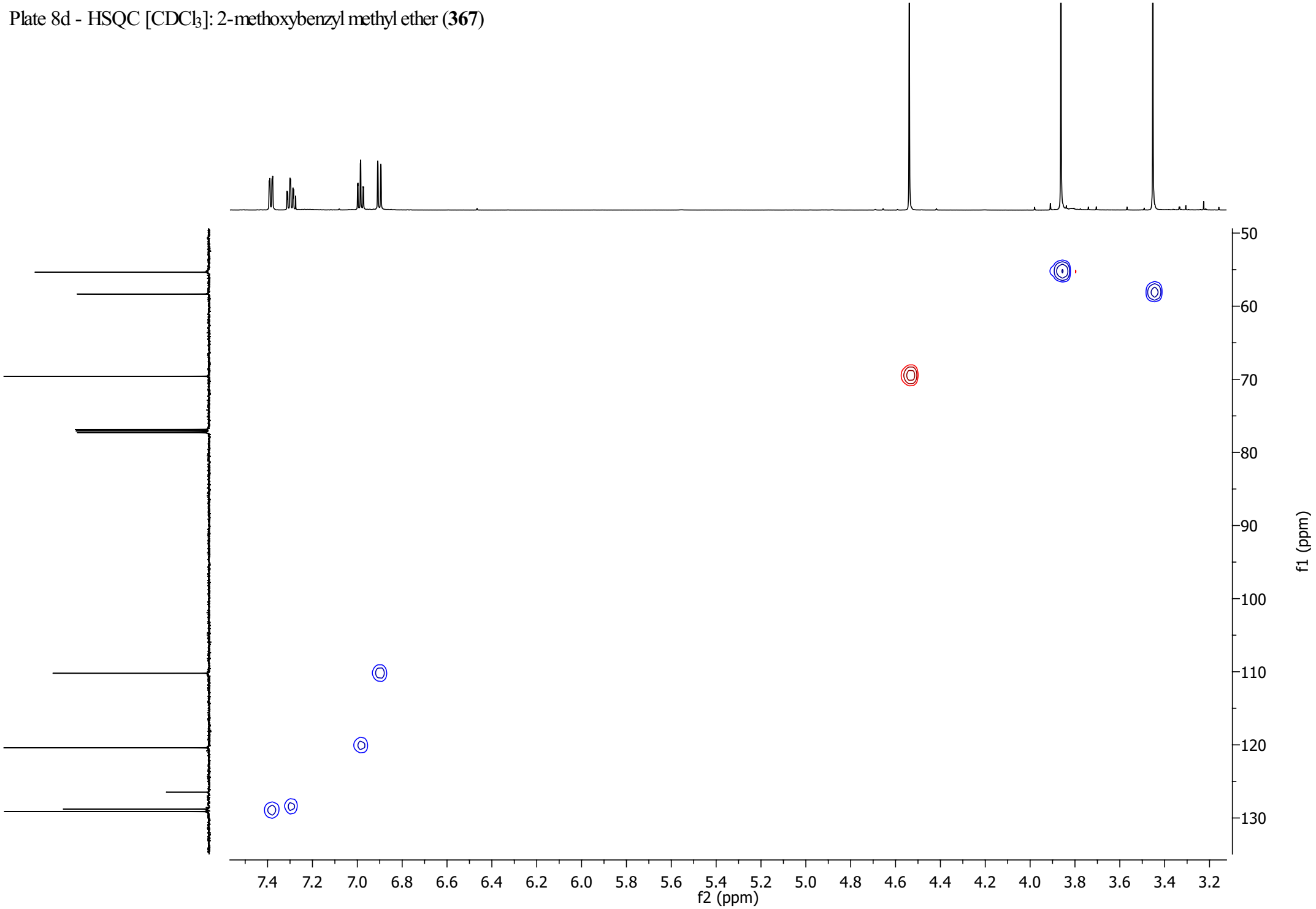


Plate 8e - HMBC [$CDCl_3$]: 2-methoxybenzyl methyl ether (**367**)

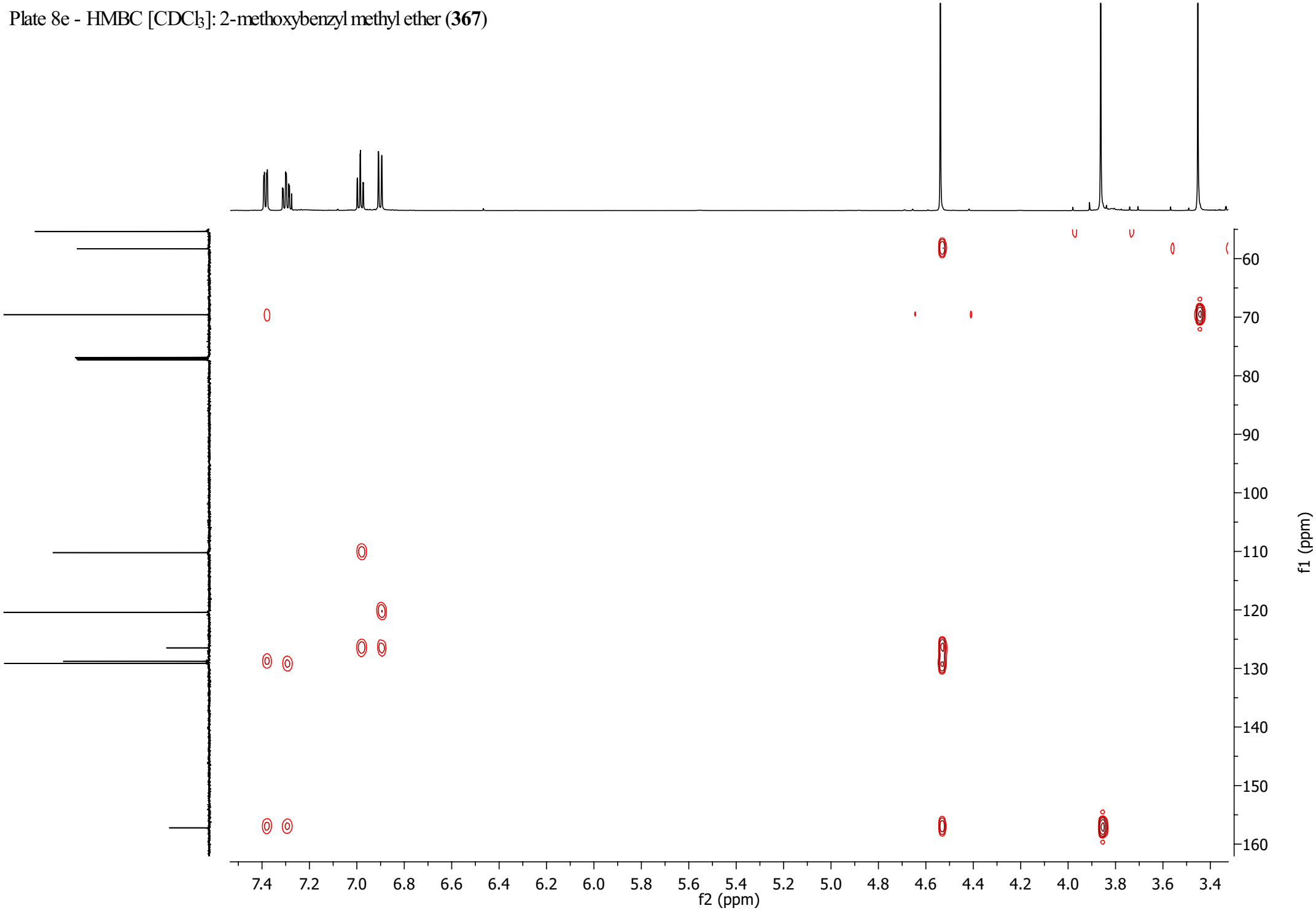
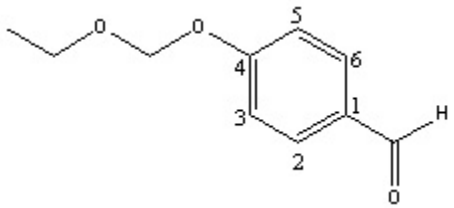
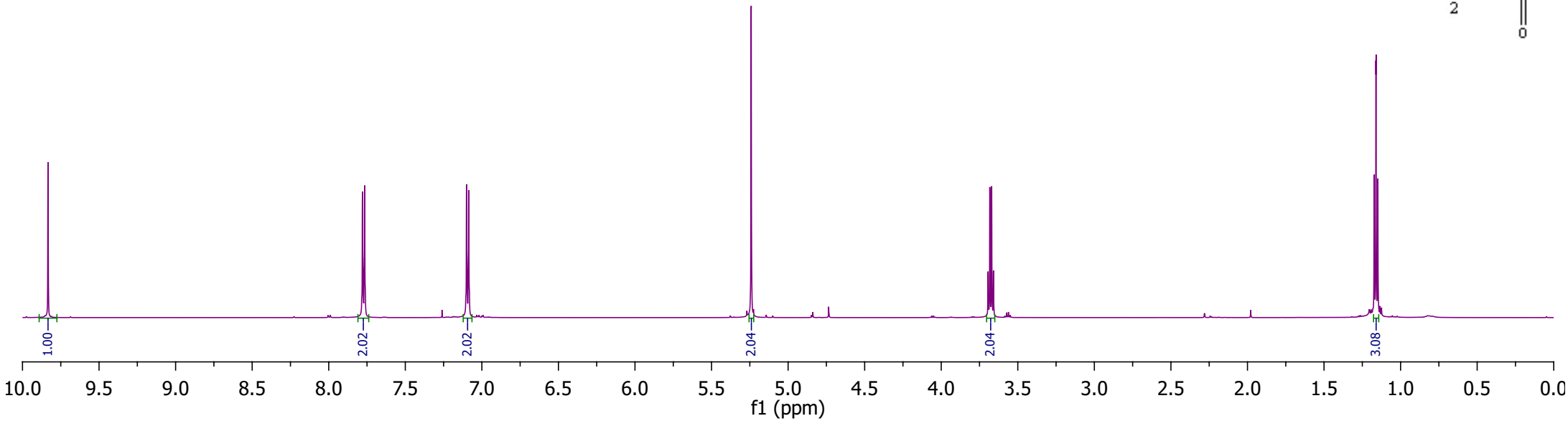


Plate 9a - ^{1}H NMR [$CDCl_3$]: 4-ethoxymethoxybenzaldehyde (**369**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (1H, s, -CHO), 7.78 (2H, d, *J* = 8.62 Hz, H-2 and H-6), 7.09 (2H, d, *J* = 8.62 Hz, H-3 and H-5), 5.24 (2H, s, -OCH_2O-), 3.68 (2H, q, *J* = 7.06 Hz, -OCH_2-), 1.16 (3H, t, *J* = 7.06 Hz, -CH_3).

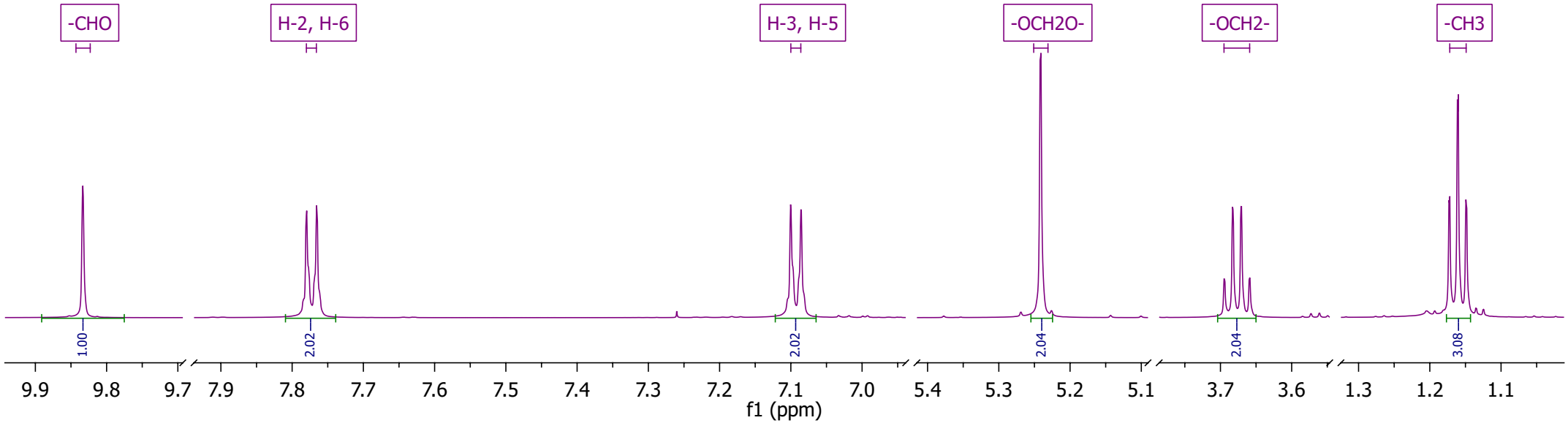
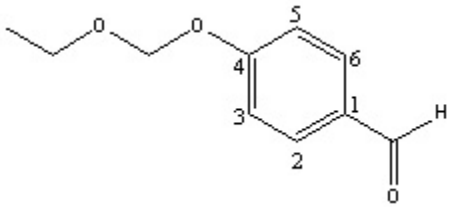


Plate 9b - ^{13}C NMR [$CDCl_3$]: 4-ethoxymethoxybenzaldehyde (**369**)



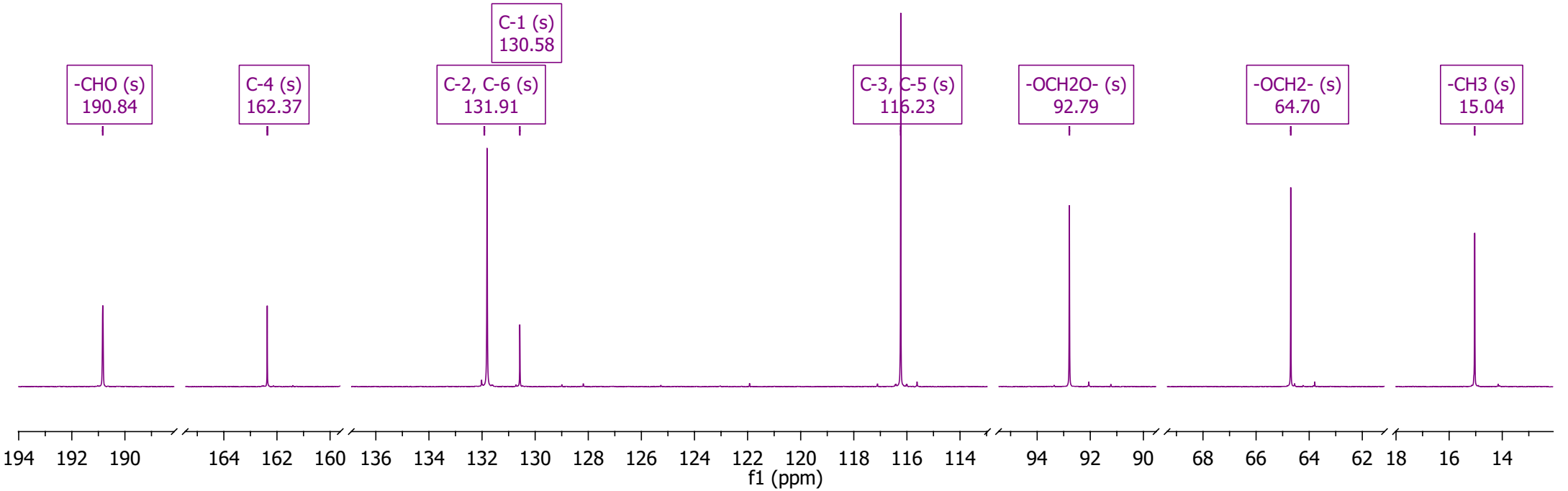


Plate 9c - DEPT [$CDCl_3$]: 4-ethoxymethoxybenzaldehyde (**369**)

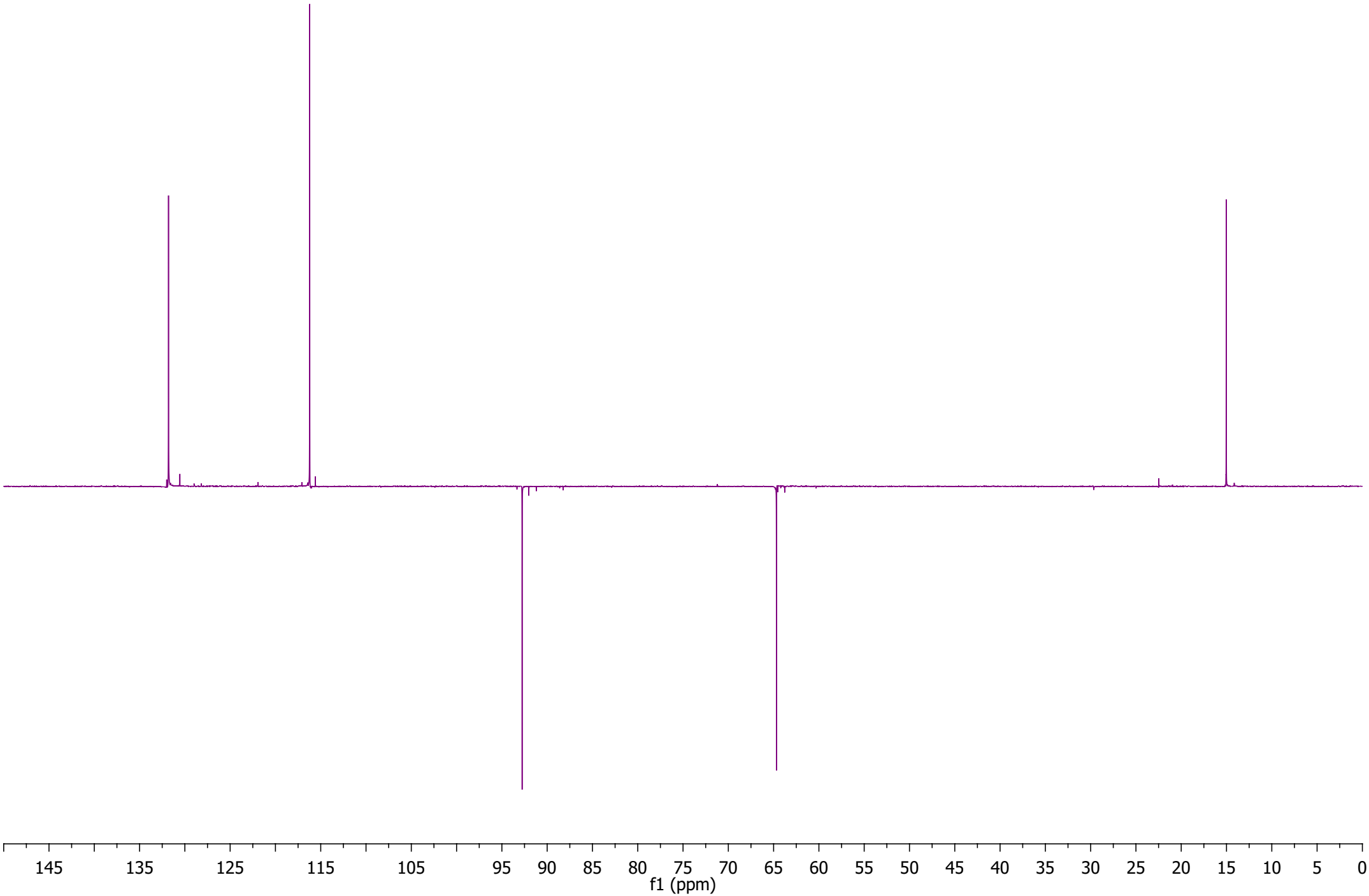


Plate 9d - HSQC [$CDCl_3$]: 4-ethoxymethoxybenzaldehyde (**369**)

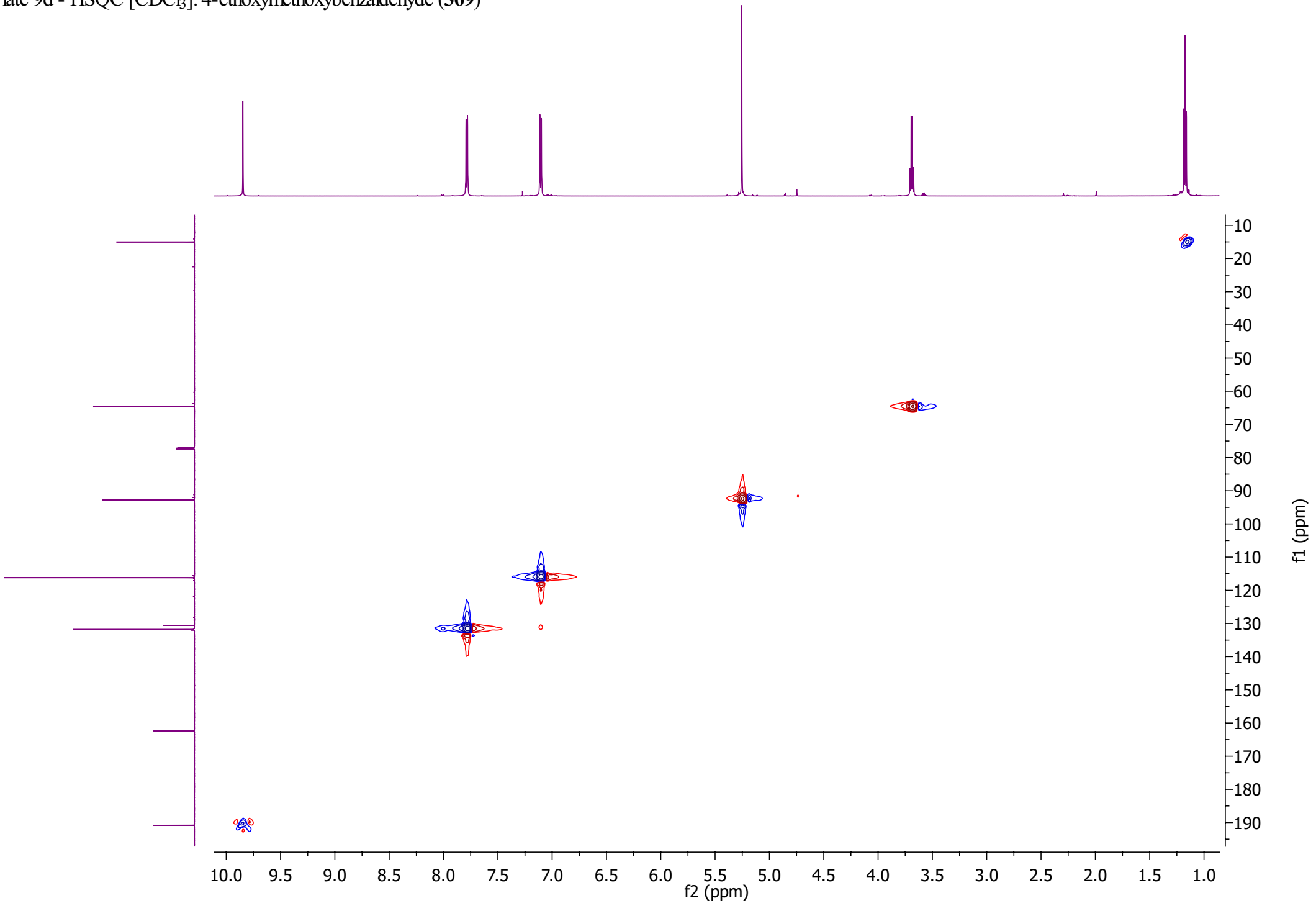


Plate 9e - HMBC [$CDCl_3$]: 4-ethoxymethoxybenzaldehyde (**369**)

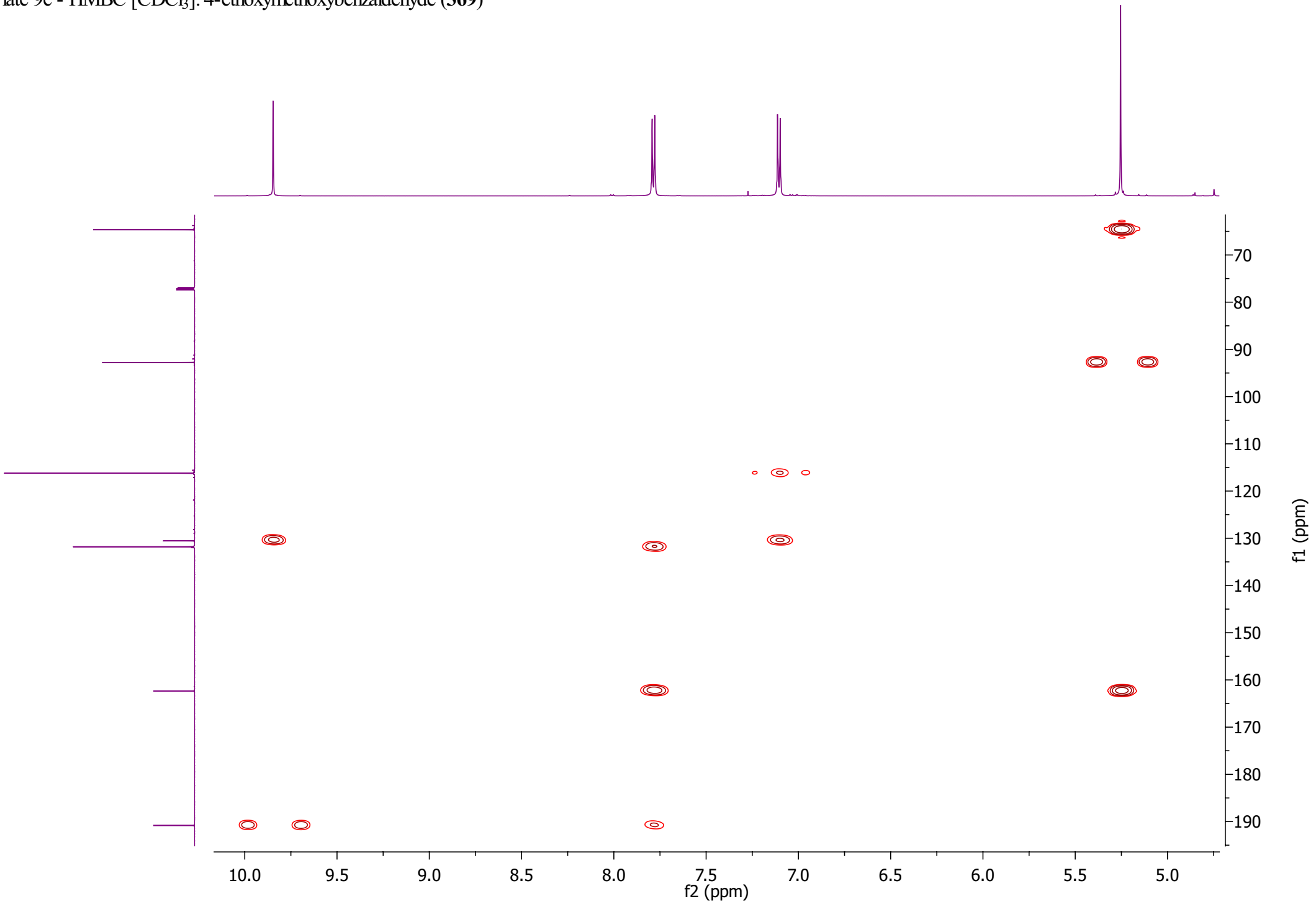
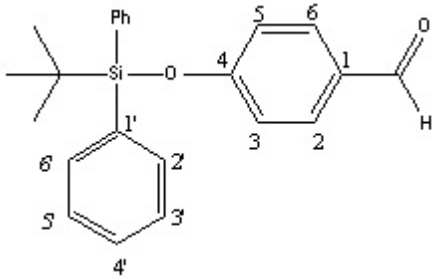


Plate 10a - ^{1}H NMR [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)



^{1}H NMR (600 MHz, $CDCl_3$) δ9.82 (1H, s, -CHO), 7.72-7.70 (4H, m, H-2' and H-6'), 7.65 (2H, d, *J* = 8.59 Hz, H-2 and H-6), 7.47-7.44 (2H, m, H-4'), 7.40-7.38 (4H, m, H-3' and H-5'), 6.87 (2H, d, *J* = 8.59 Hz, H-3 and H-5), 1.12 [9H, s, -$(CH_3)_3$]

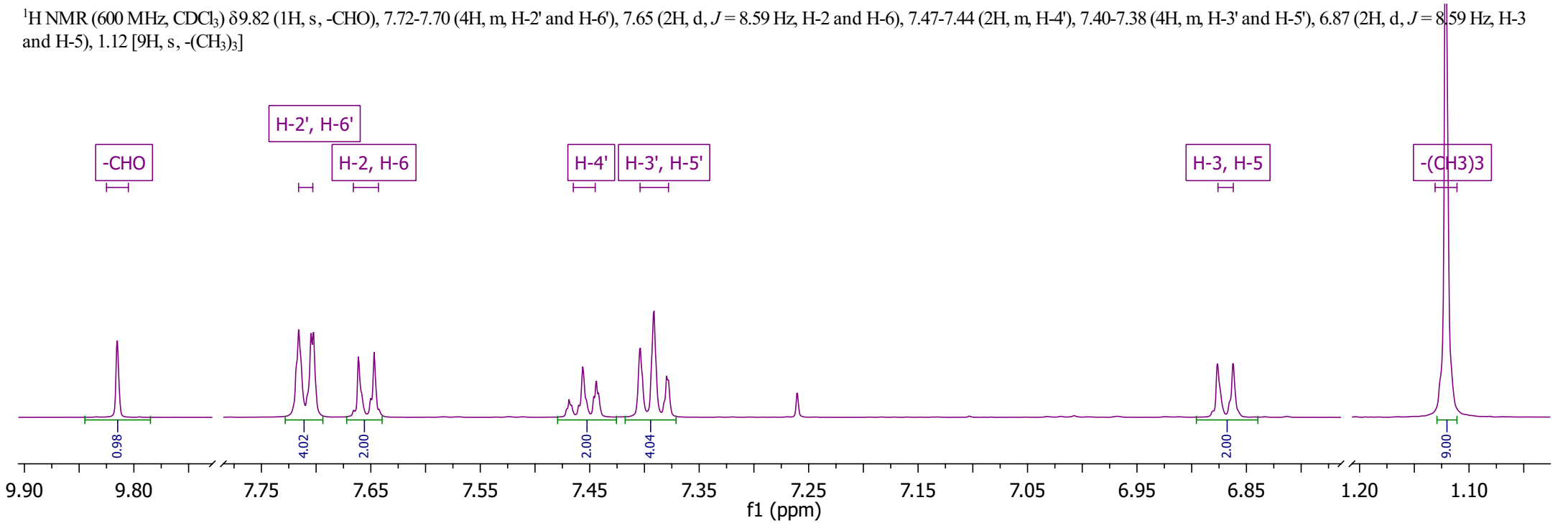
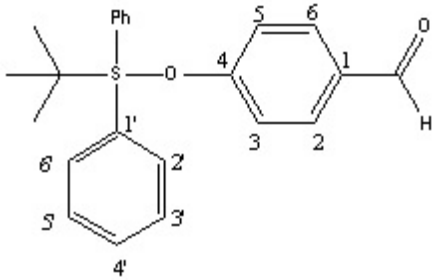


Plate 10b - ^{13}C NMR [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)



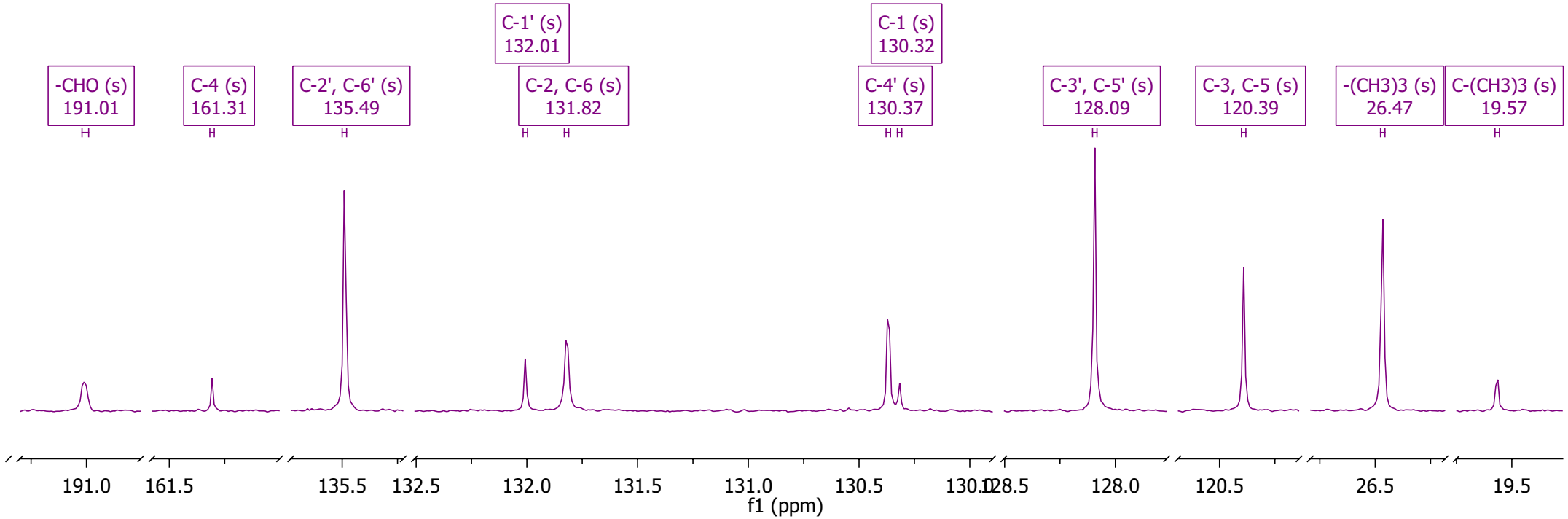


Plate 10c - DEPT [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)

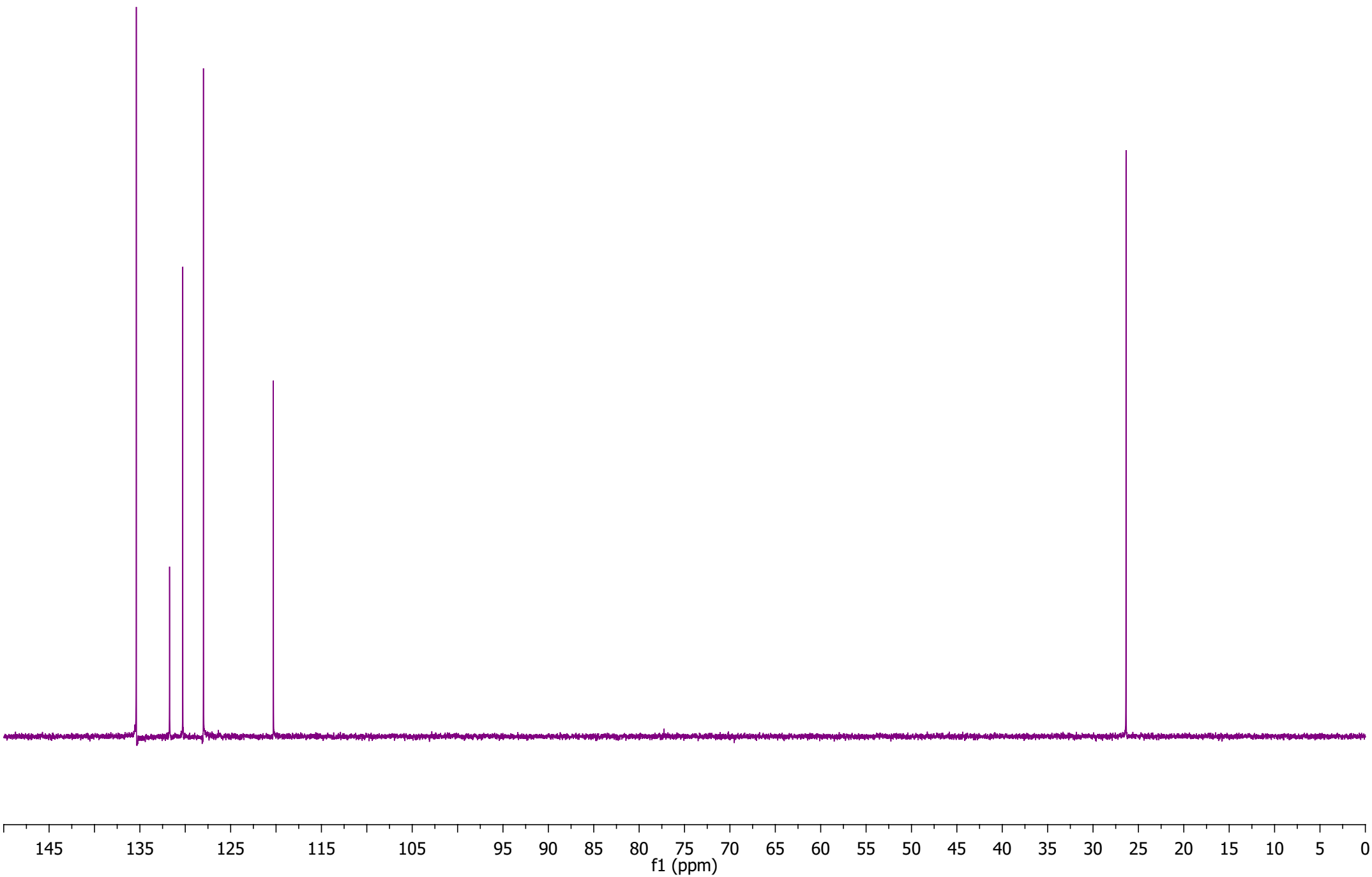


Plate 10d - HSQC [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)

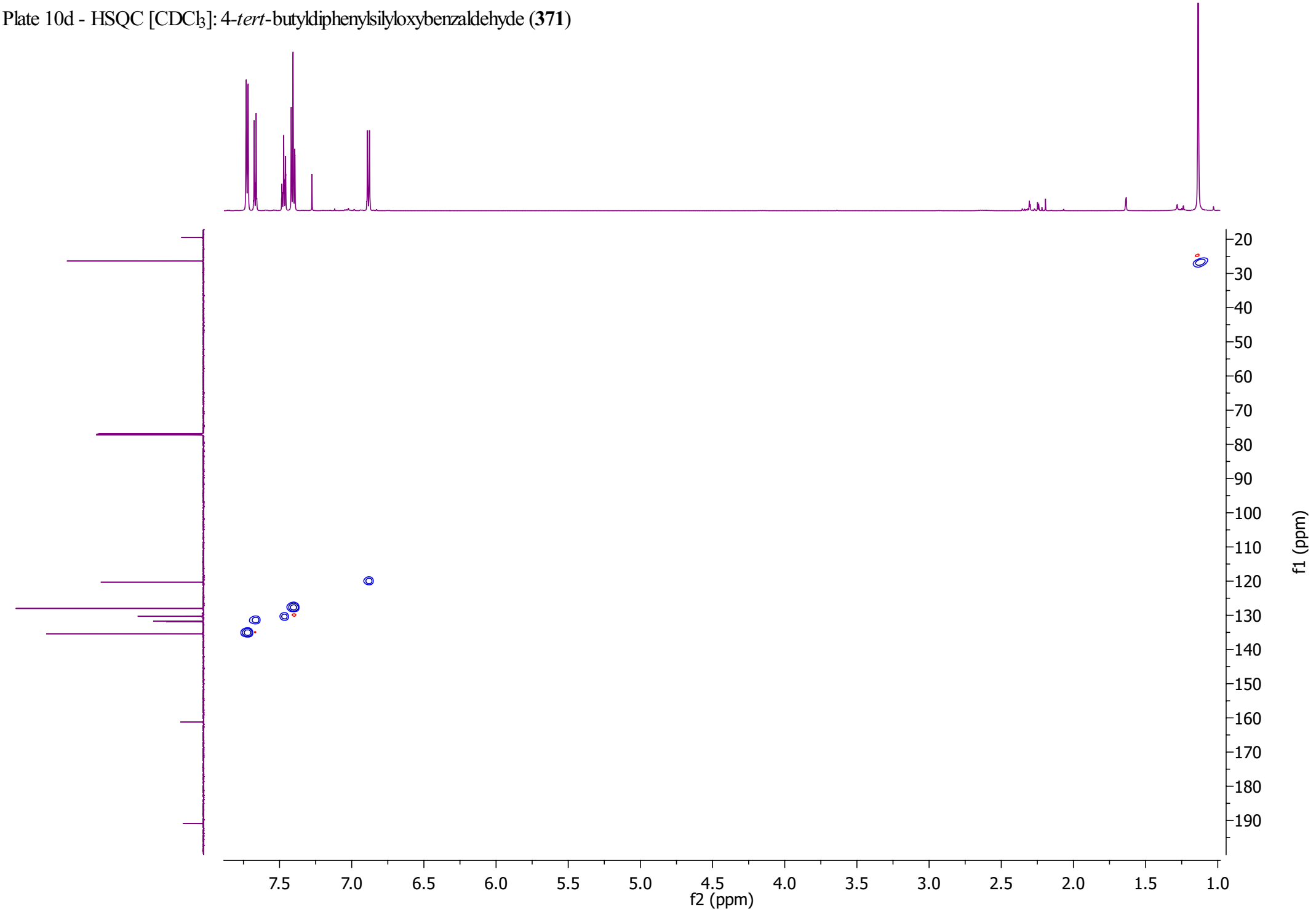


Plate 10e - HSQC (expansion) [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)

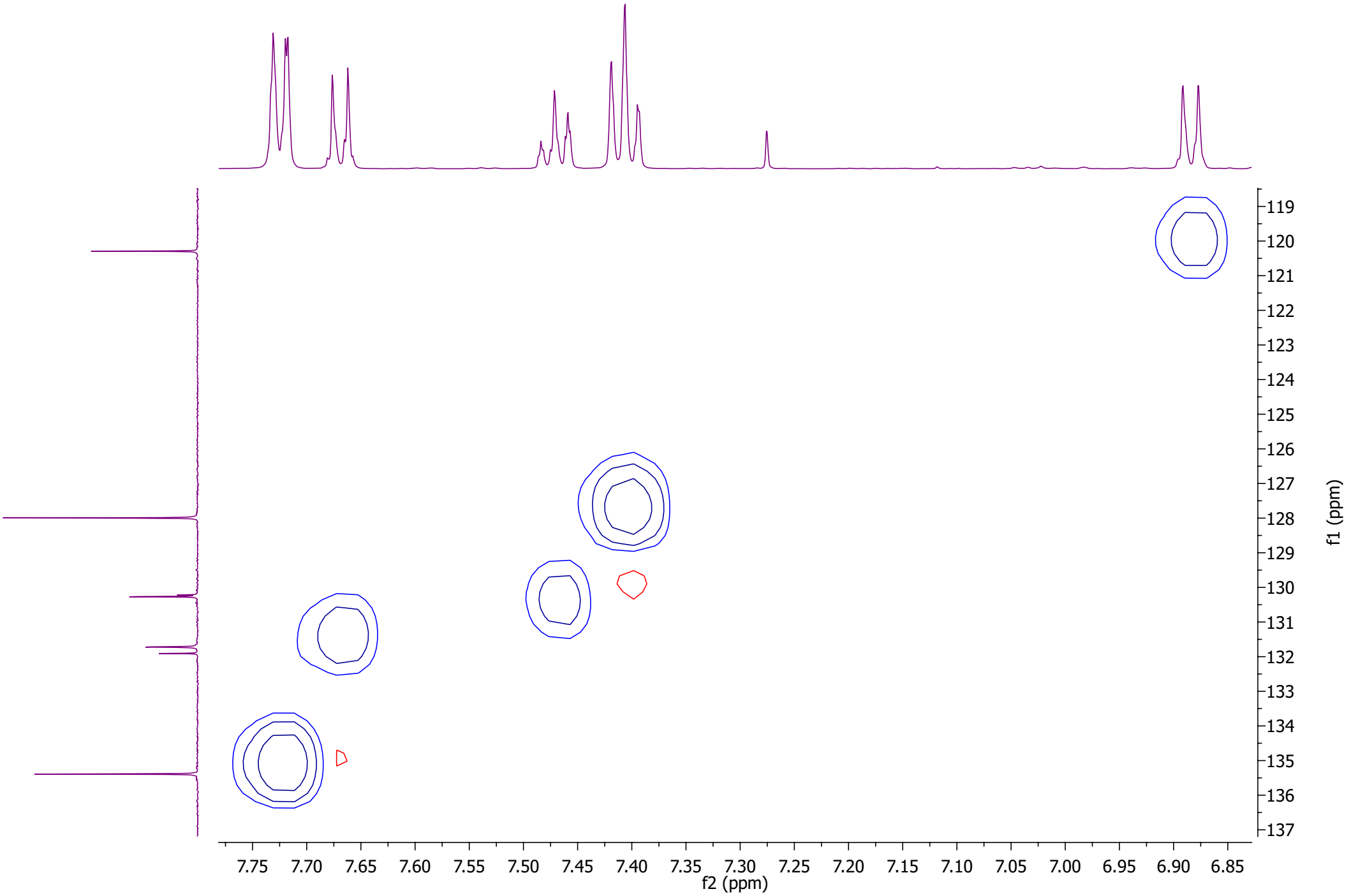


Plate 10f - HMBC [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)

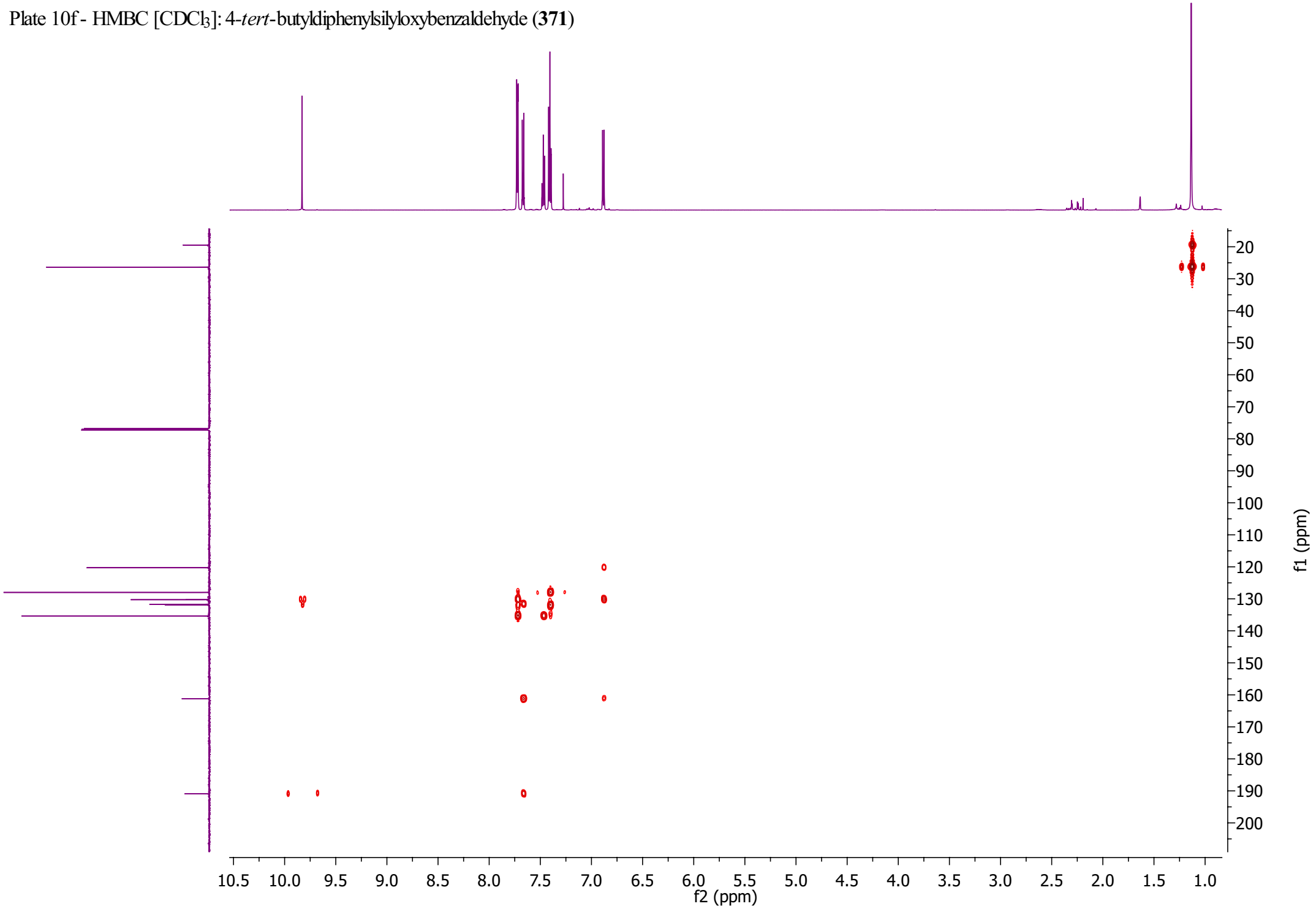


Plate 10g - HMBC (expansion) [$CDCl_3$]: 4-*tert*-butyldiphenylsilyloxybenzaldehyde (**371**)

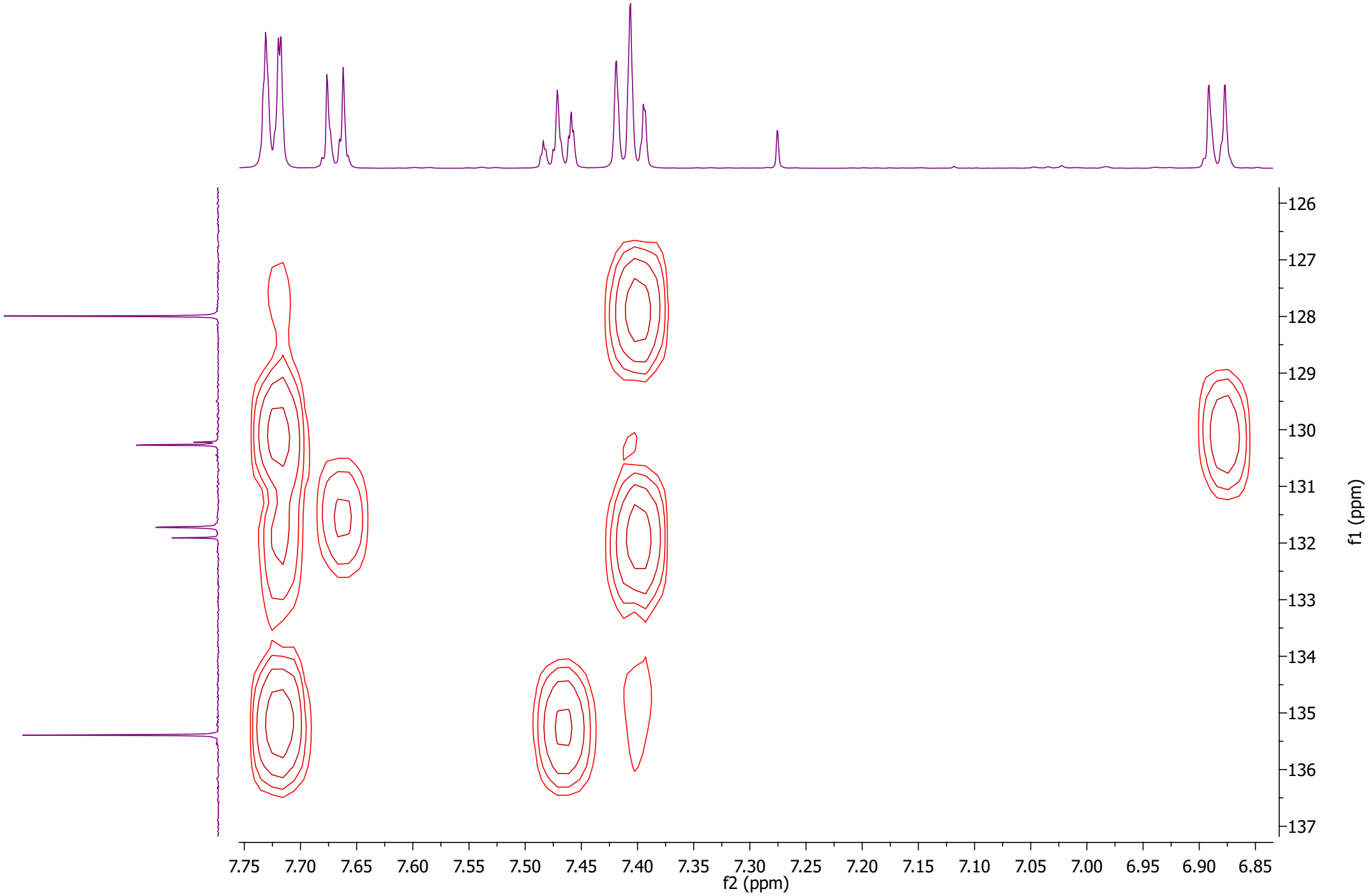
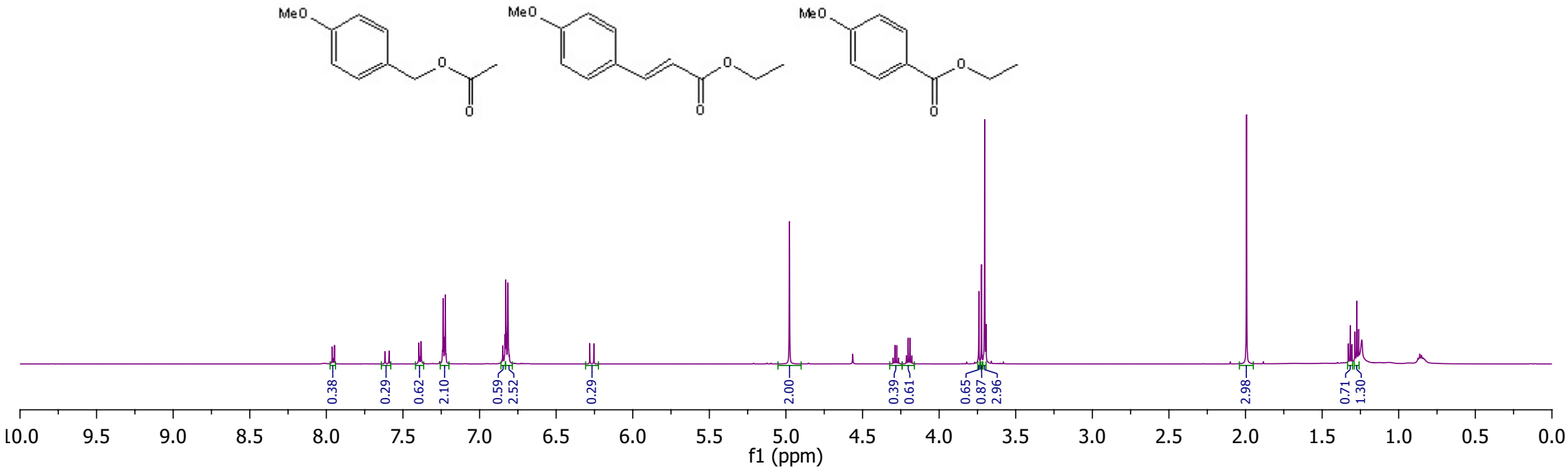


Plate 11 - ^{1}H NMR [$CDCl_3$]: anisyl acetate (**374**), ethyl methoxycinnamate (**376**) and ethyl *p*-methoxybenzoate (**379**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 [0.3H, d, J = 8.92 Hz, H-Ar, (**379**)], 7.60 [0.3H, d, J = 15.94 Hz, -CH-, (**376**)], 7.39 [0.6H, d, J = 8.72 Hz, H-Ar, (**376**)], 7.24-7.22 [2H, m, H-Ar, (**374**)], 6.85-6.83 [0.6H, m, H-Ar, (**376**)], 6.83-6.82 [2H, m, H-Ar, (**374**) and (**379**)], 6.27 [0.3 H, d, J = 15.94 Hz, -CH-, (**376**)], 4.98 [2H, s, $-CH_2-$, (**374**)], 4.28 [0.3H, q, J = 7.13 Hz, $-CH_2-$, (**379**)], 4.20 [0.6H, q, J = 7.14 Hz, $-CH_2-$, (**376**)], 3.74 [0.6H, s, -OMe, (**379**)], 3.72 [0.9H, s, -OMe, (**376**)], 3.70 [3H, s, -OMe, (**374**)], 1.99 [3H, s, $-CH_3$, (**374**)], 1.32 [0.6H, t, J = 7.13 Hz, $-CH_3$, (**379**)], 1.27 [0.9H, t, J = 7.14 Hz, $-CH_3$, (**376**)]

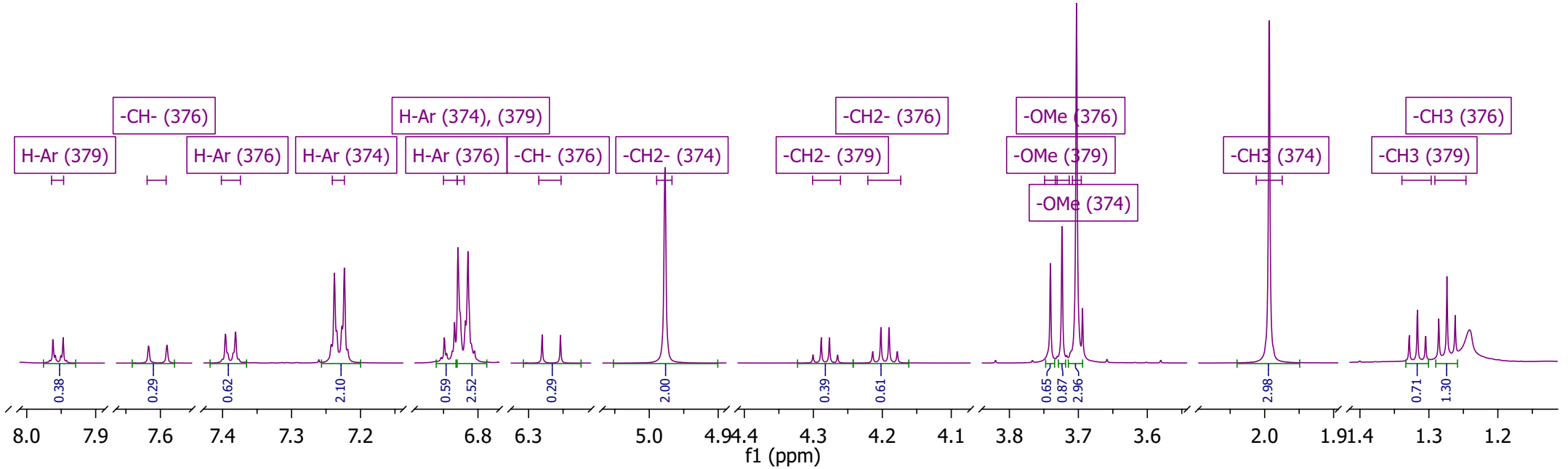
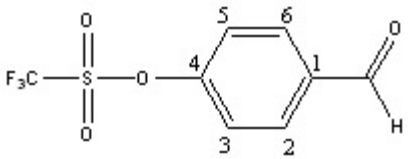
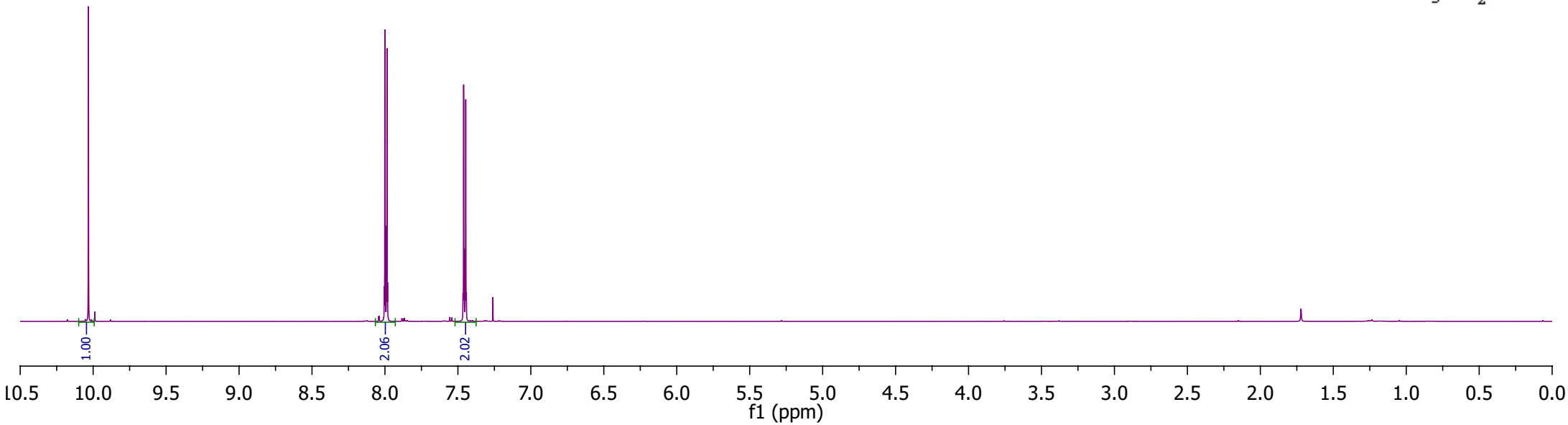


Plate 12a - ^{1}H NMR [$CDCl_3$]: 4-trifluromethanesulfonyloxybenzaldehyde (**382**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 10.03 (1H, s, -CHO), 7.99 (2H, d, J = 8.73 Hz, H-2 and H-6), 7.45 (2H, d, J = 8.73 Hz, H-3 and H-5)

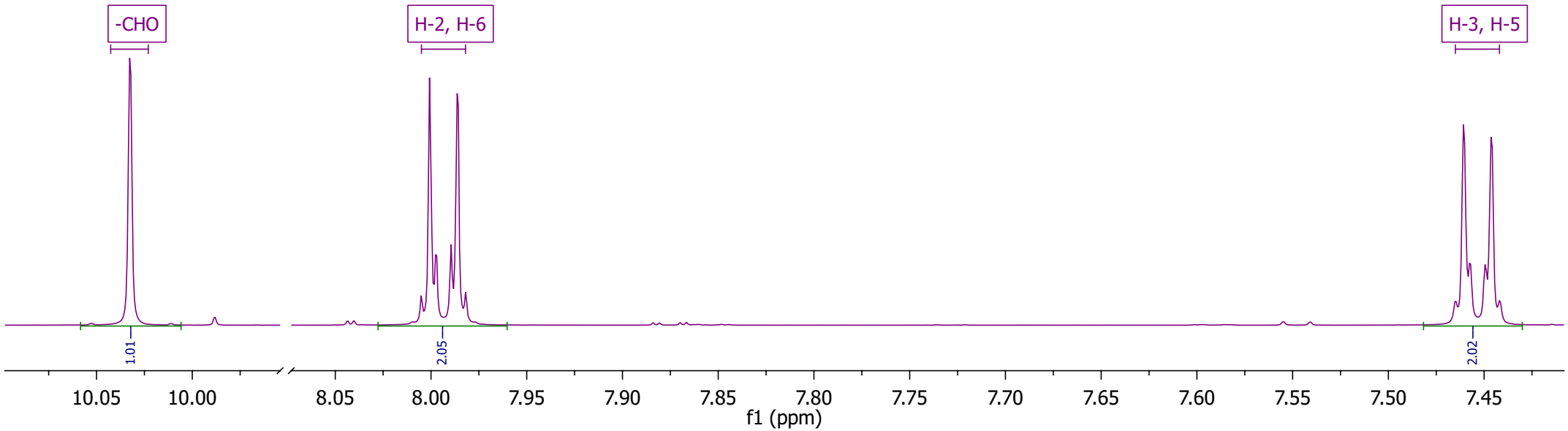
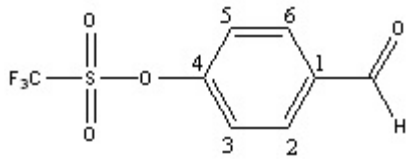
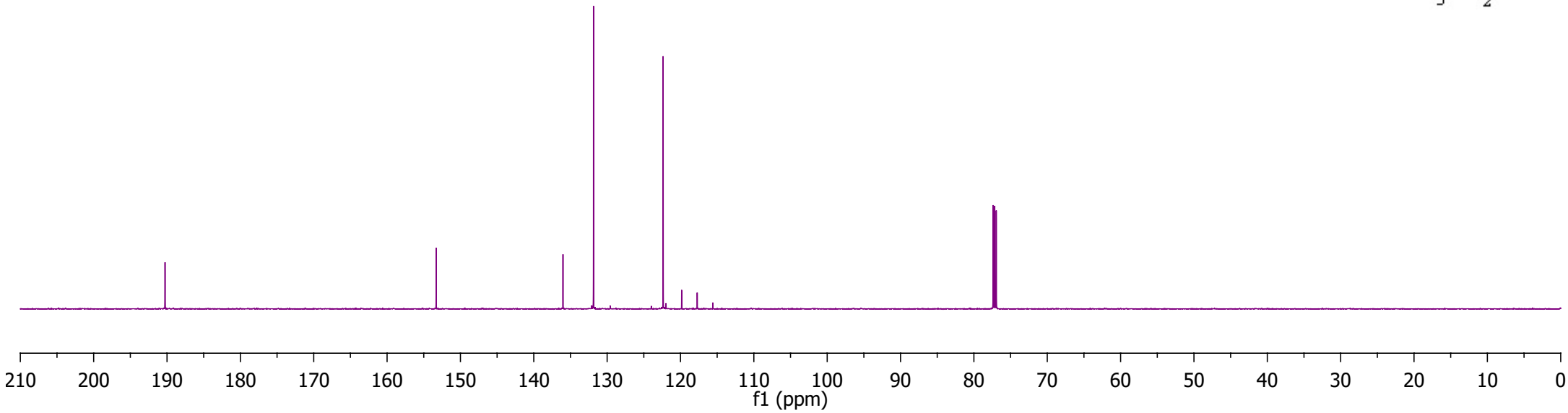


Plate 12b - ^{13}C NMR [$CDCl_3$]: 4-trifluromethanesulfonyloxybenzaldehyde (**382**)





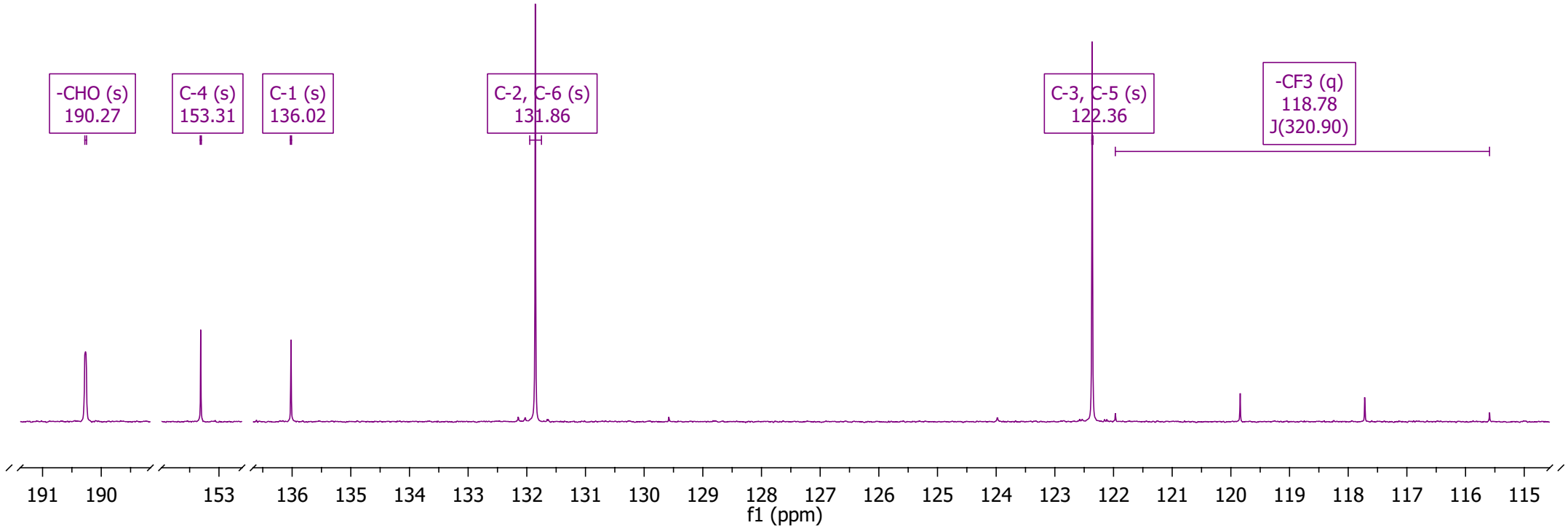


Plate 13c - DEPT [$CDCl_3$]: 4-trifluromethanesulfonyloxybenzaldehyde (**382**)

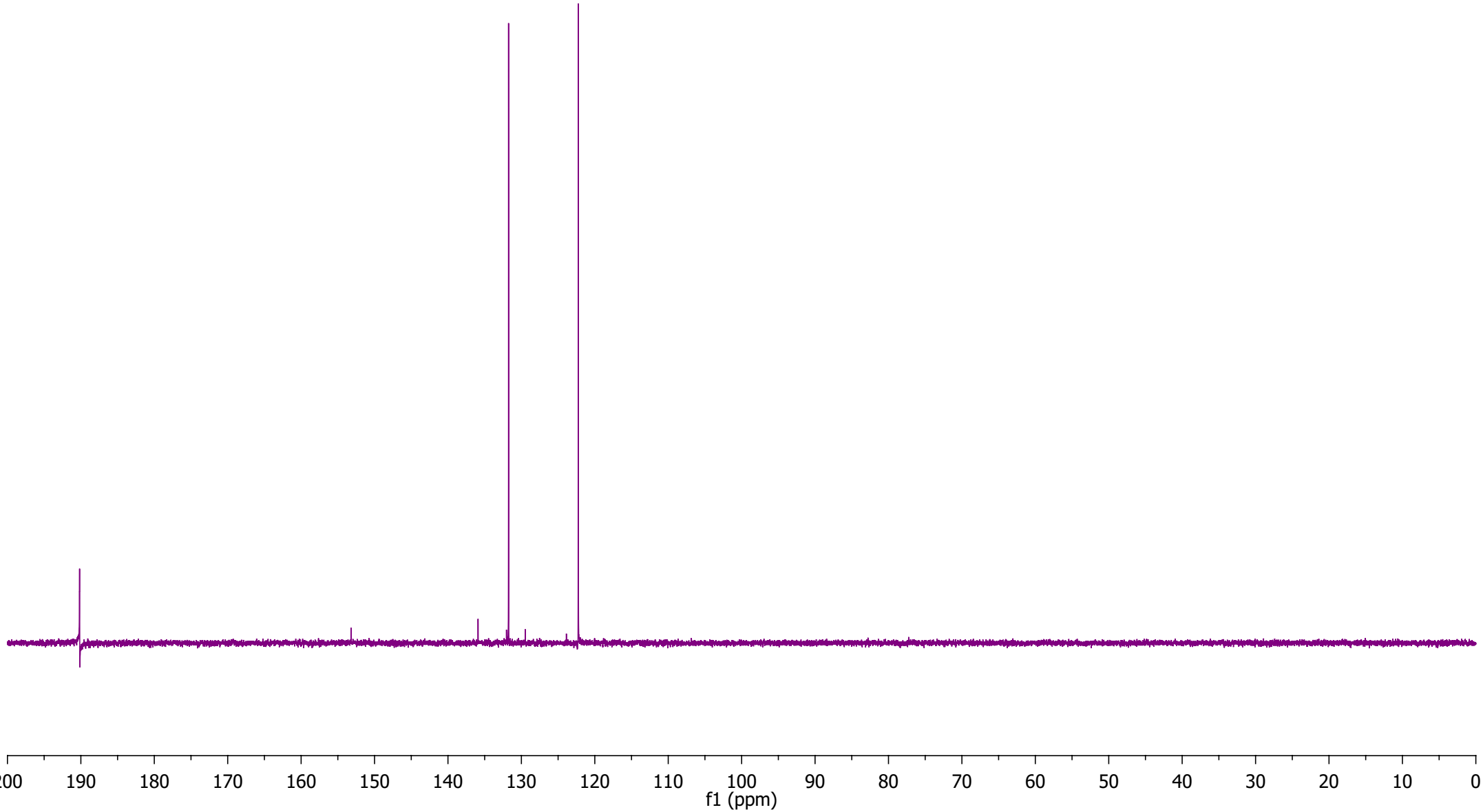


Plate 12d - HSQC [$CDCl_3$]: 4-trifluromethanesulfonyloxybenzaldehyde (**382**)

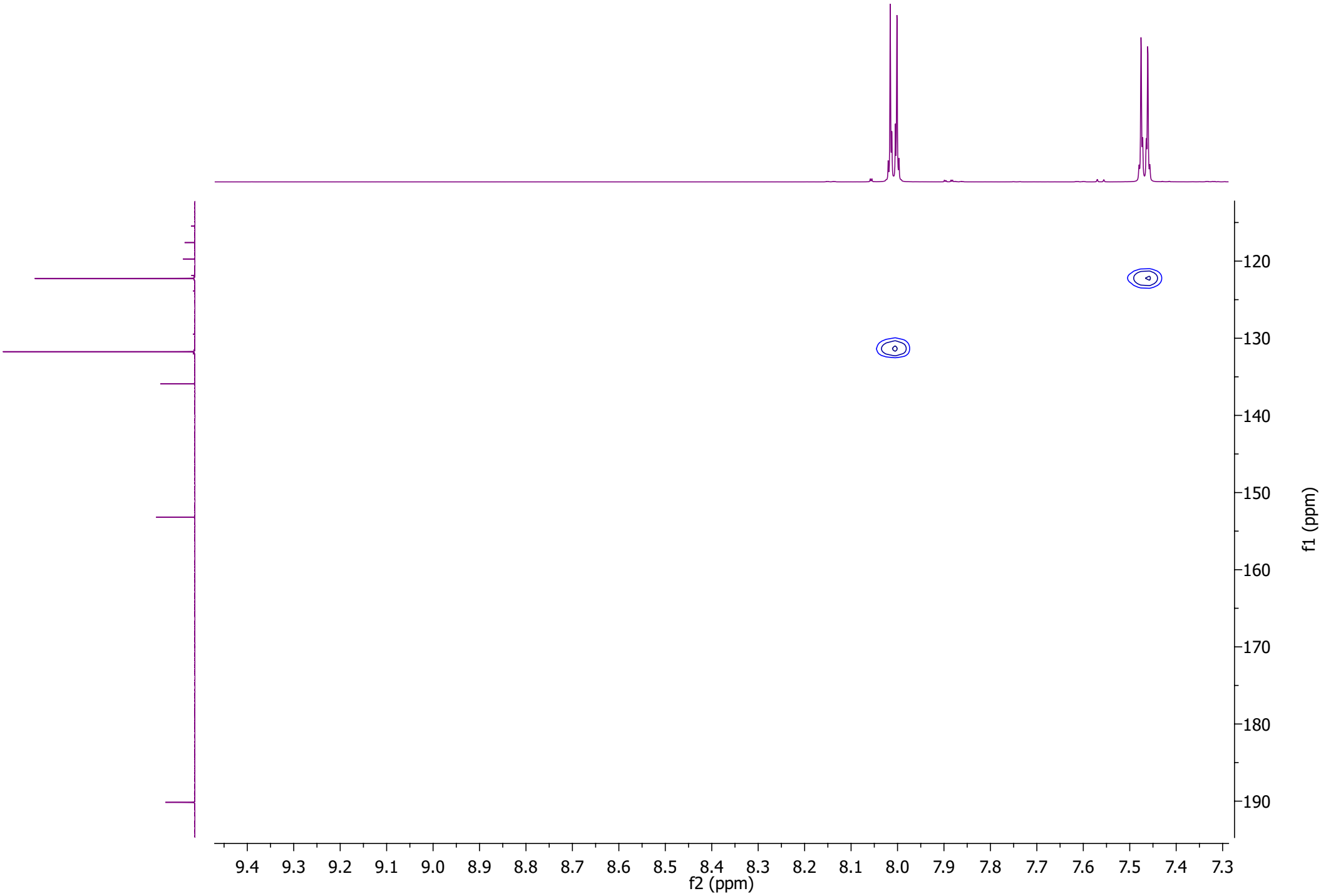


Plate 12e - HMBC [$CDCl_3$]: 4-trifluromethanesulfonyloxybenzaldehyde (**382**)

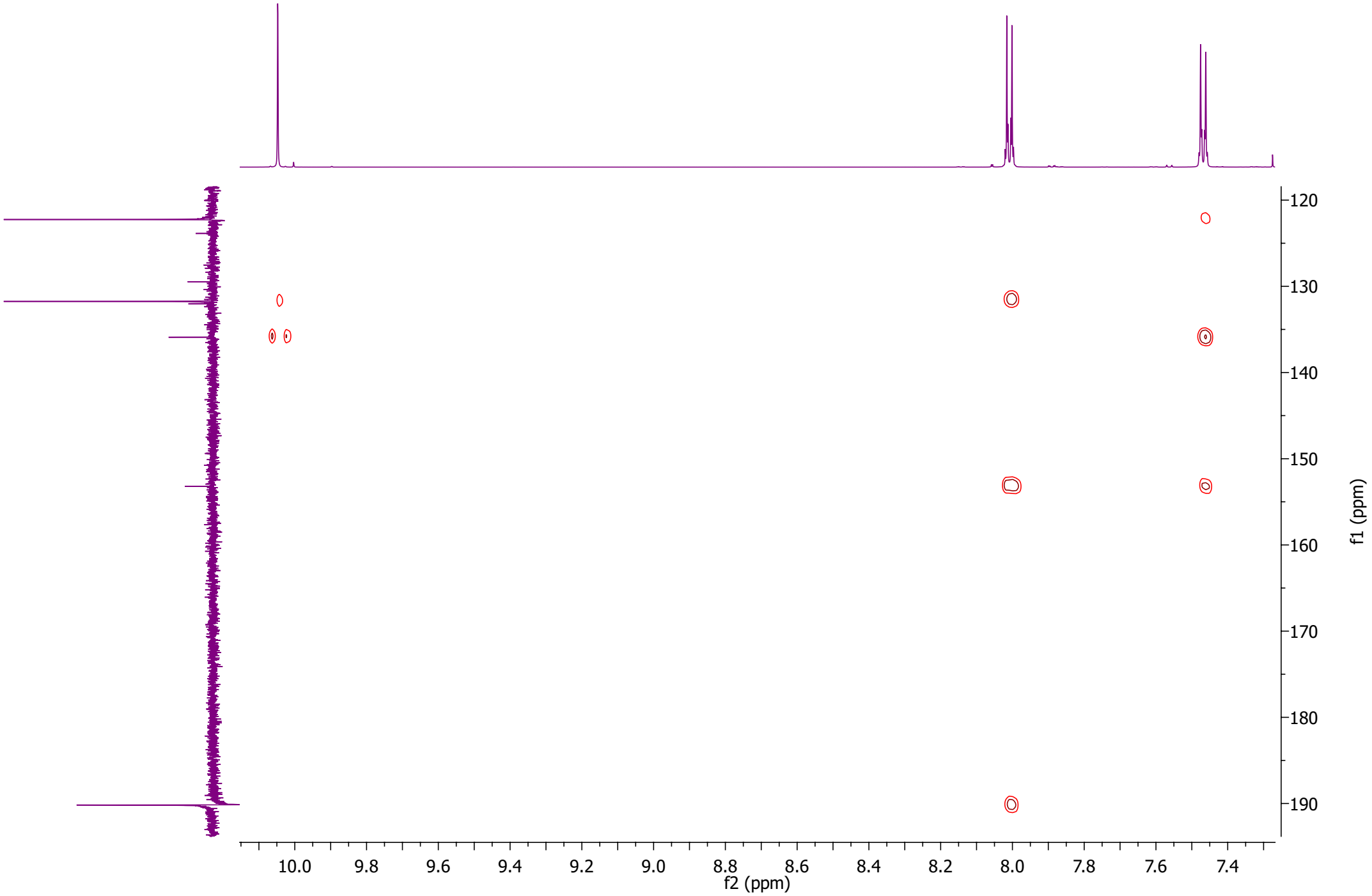


Plate 12f - ^{19}F NMR [$CDCl_3$]: 4-trifluromethanesulfonyloxybenzaldehyde (**382**)

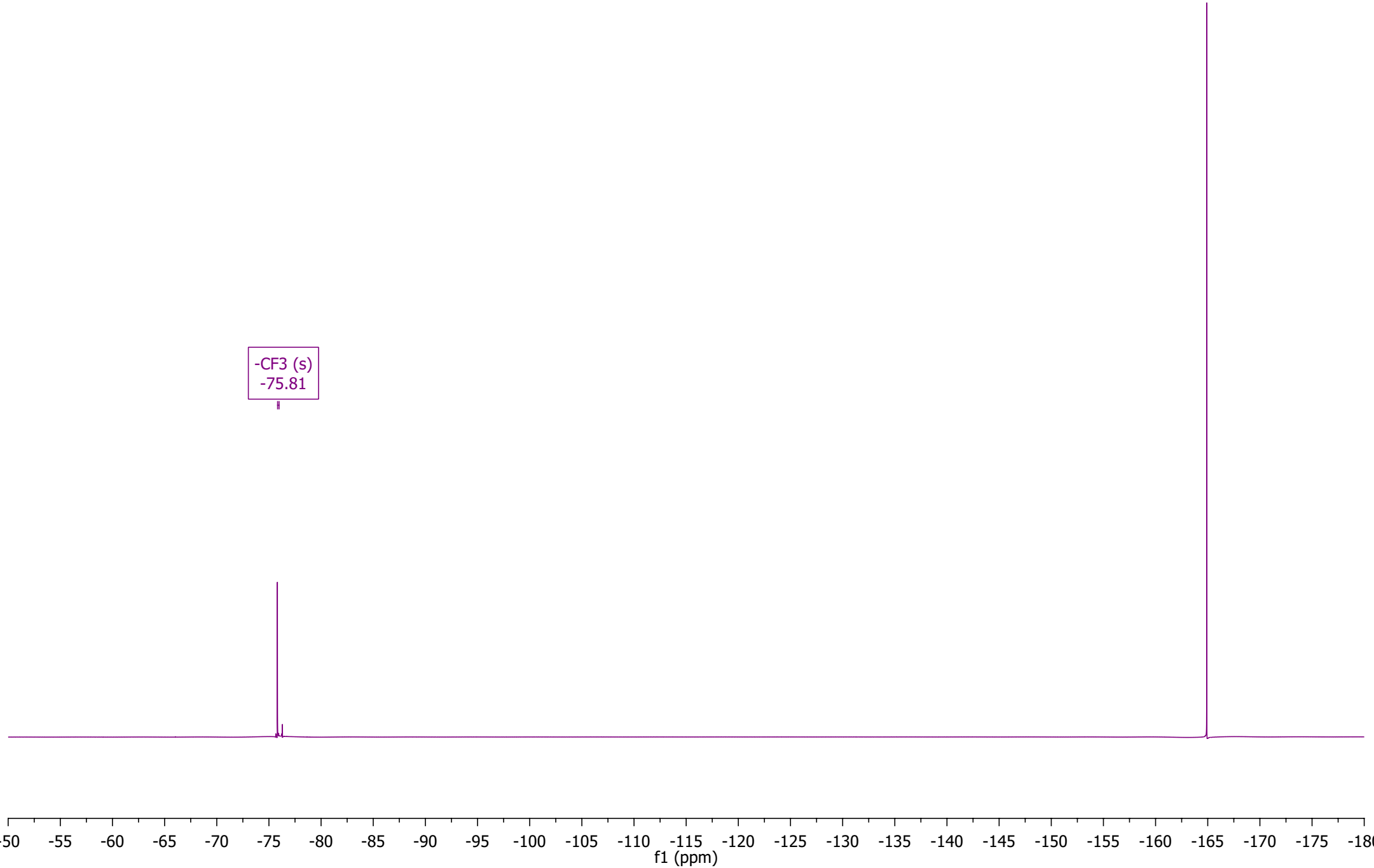
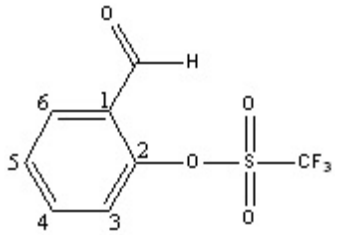
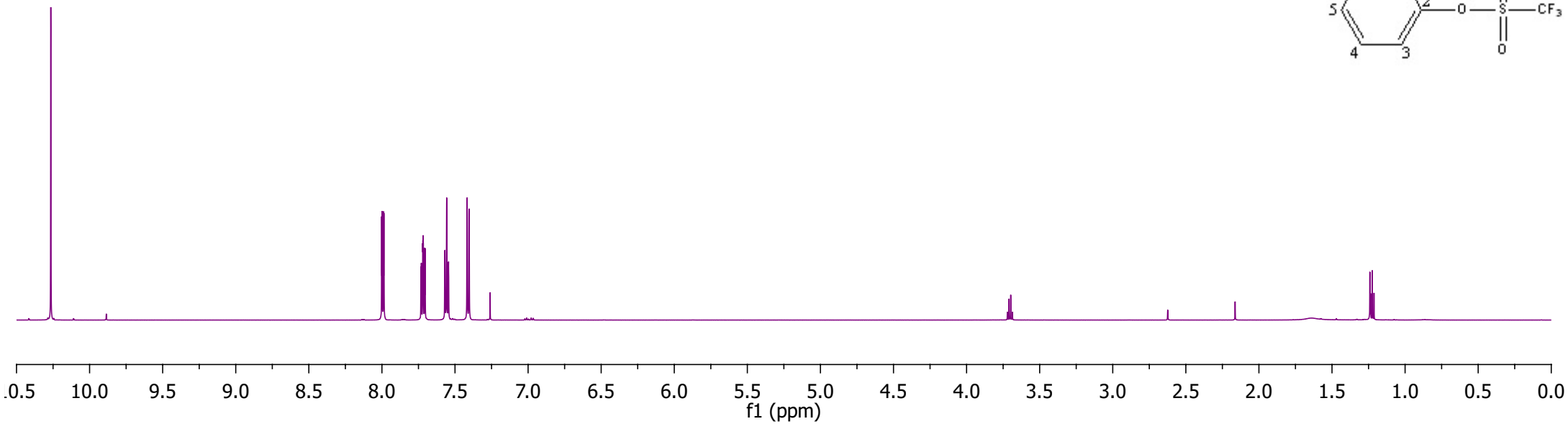


Plate 13a - ^{1}H NMR [$CDCl_3$]: 2-trifluromethanesulfonyloxybenzaldehyde (**383**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 10.27 (1H, s, -CHO), 8.01-7.98 (1H, m, H-6), 7.73-7.70 (1H, m, H-4), 7.57-7.54 (1H, m, H-5), 7.42-7.40 (1H, m, H-3)

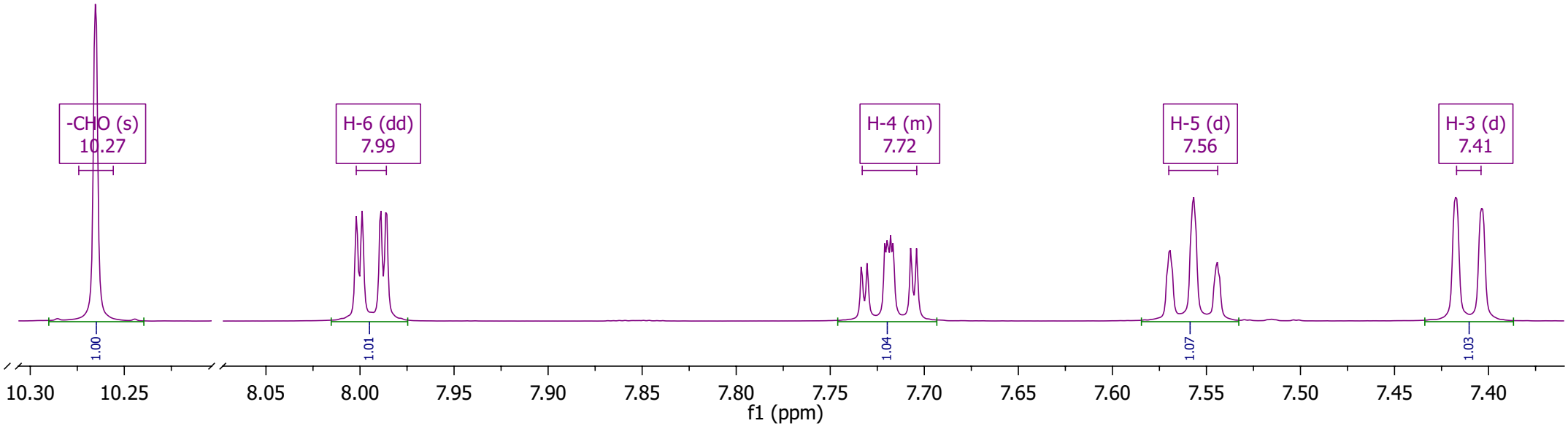
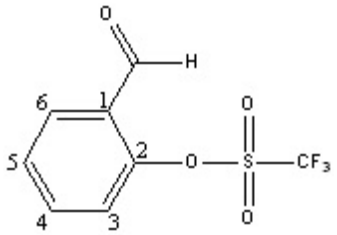


Plate 13b - ^{13}C NMR [$CDCl_3$]: 2-trifluromethanesulfonyloxybenzaldehyde (**383**)



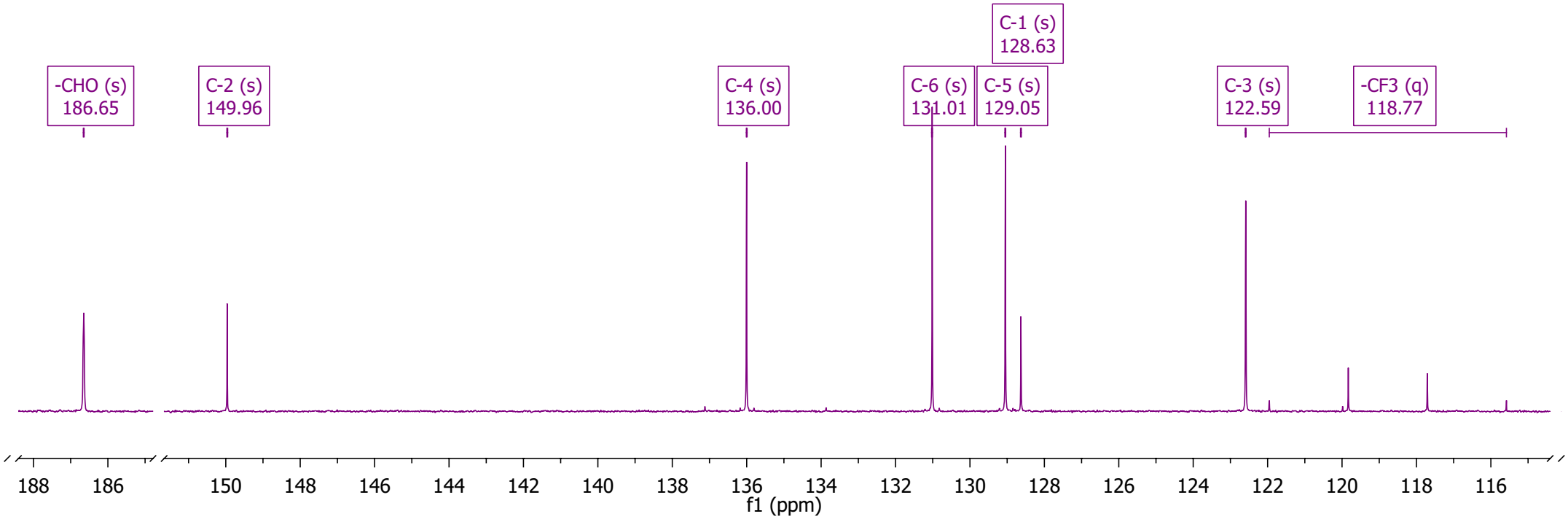


Plate 13c - HSQC NMR [$CDCl_3$]: 2-trifluromethanesulfonyloxybenzaldehyde (**383**)

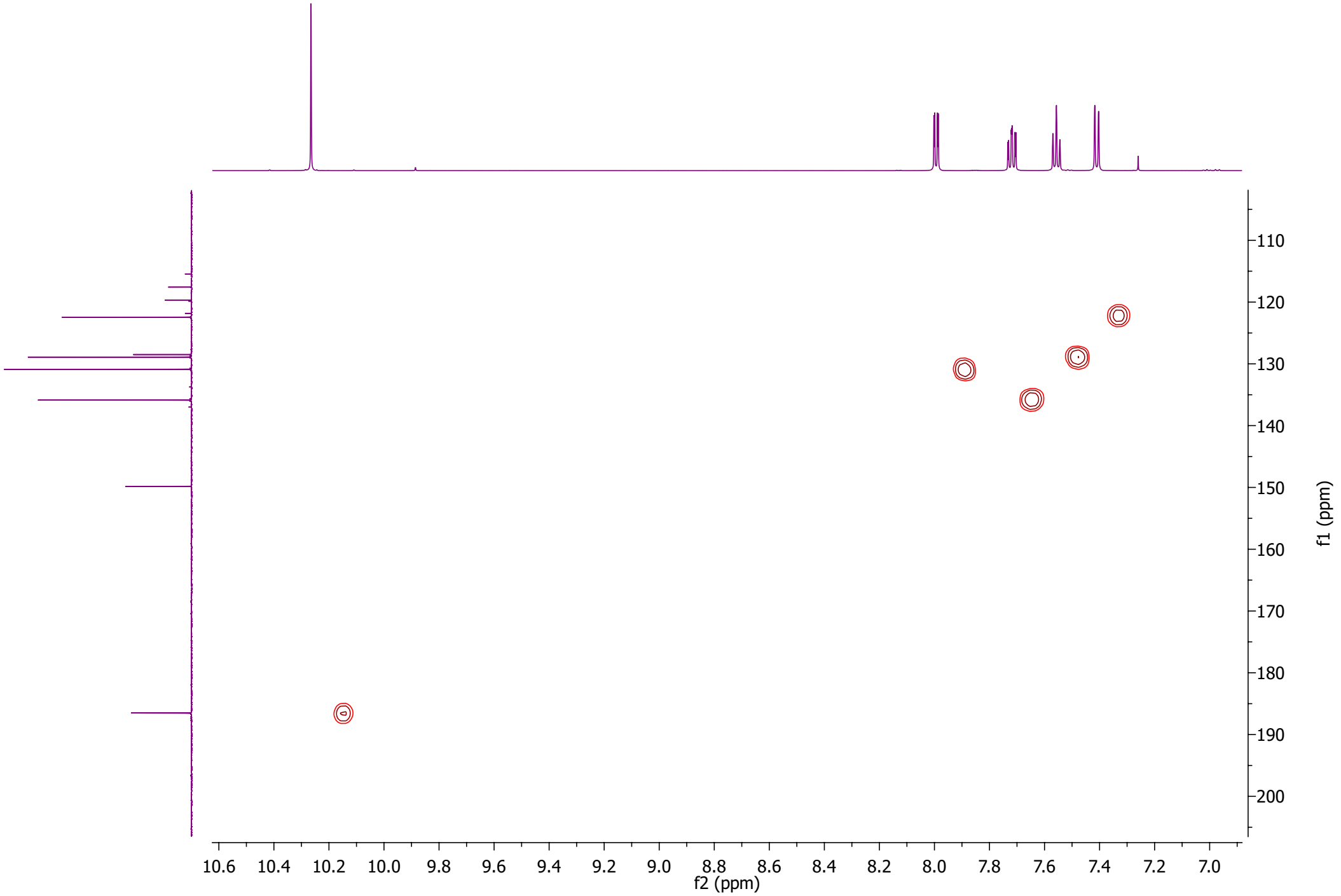


Plate 13d - HMBC [$CDCl_3$]: 2-trifluromethanesulfonyloxybenzaldehyde (**383**)

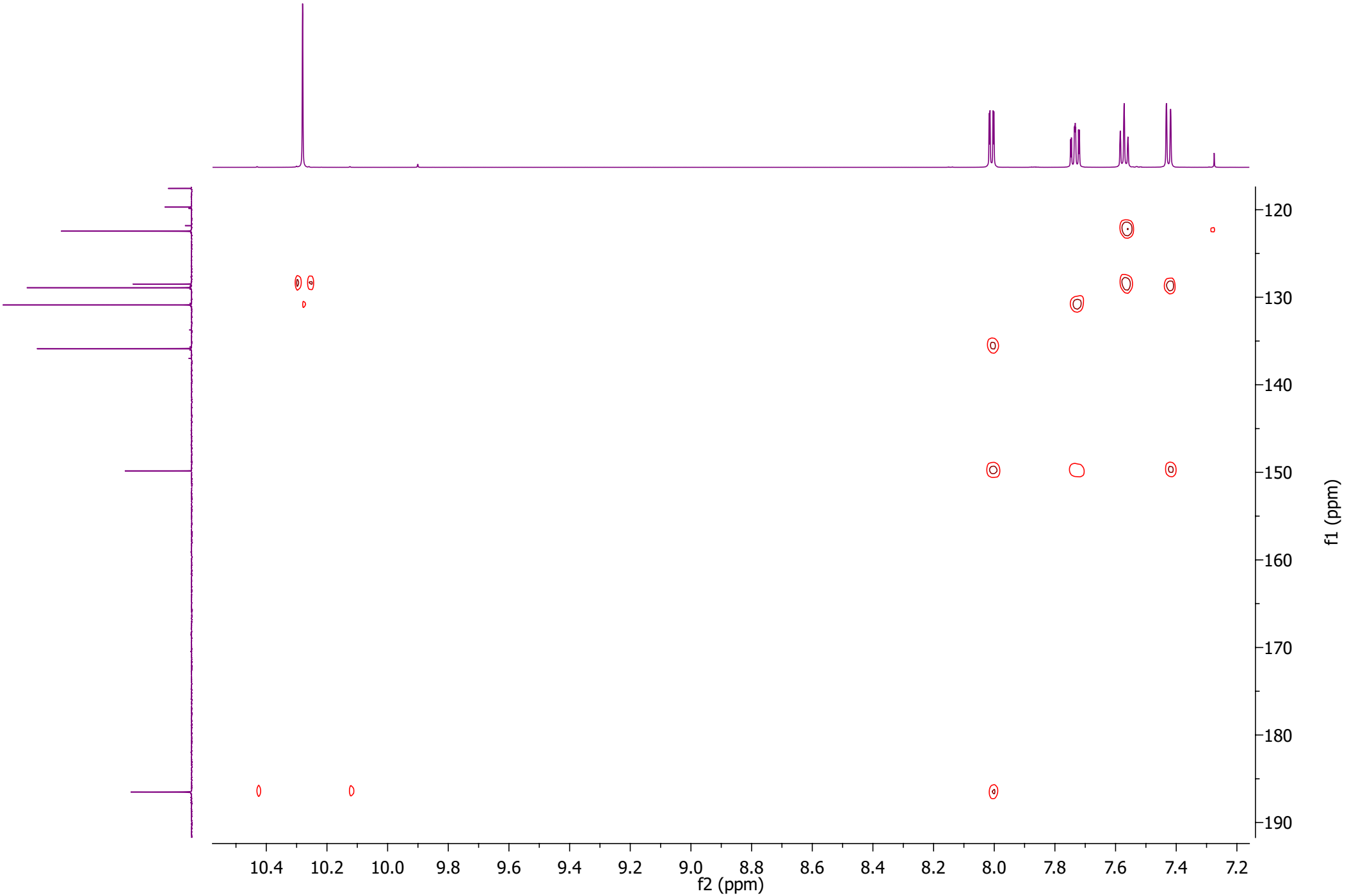


Plate 13e - ^{19}F NMR [$CDCl_3$]: 2-trifluromethanesulfonyloxybenzaldehyde (**383**)

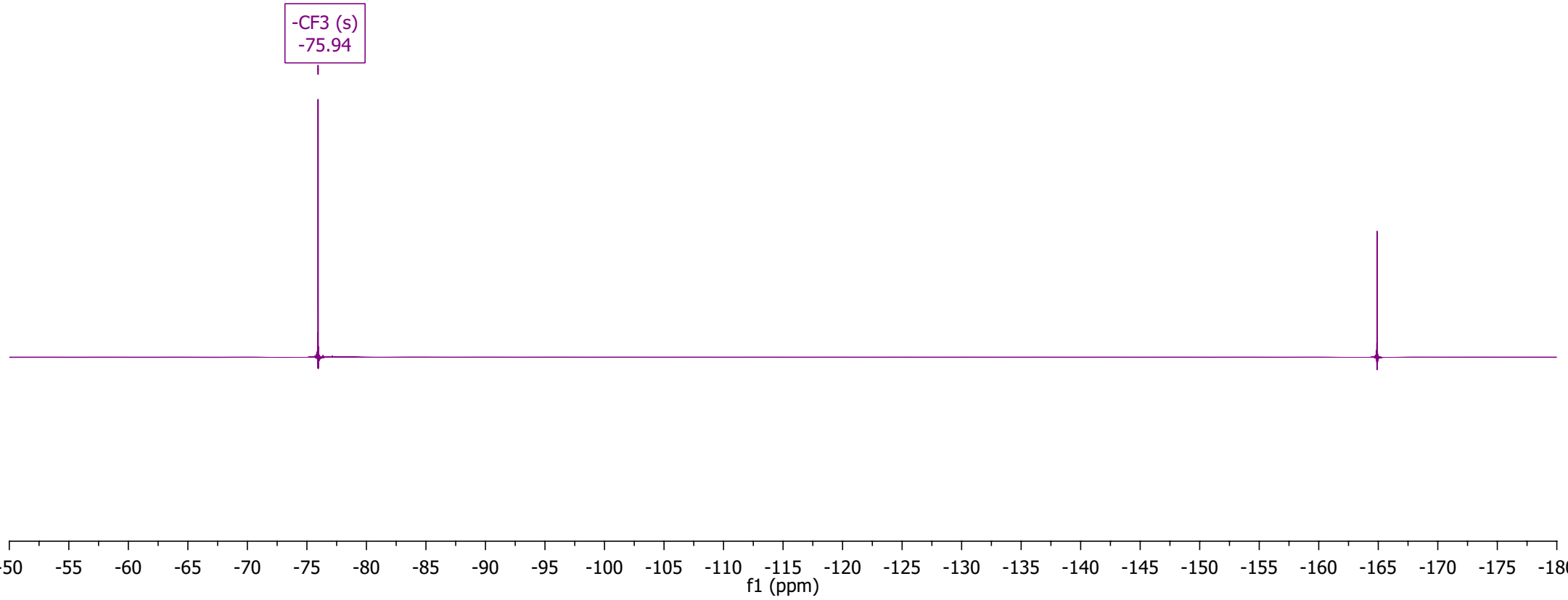
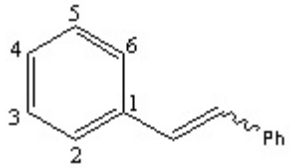
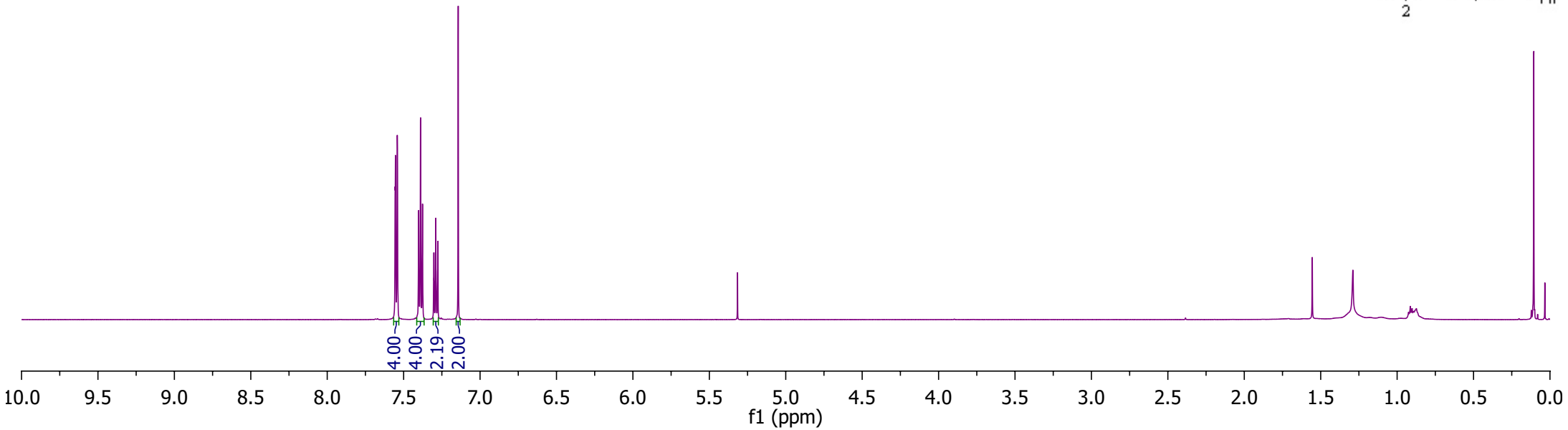


Plate 14a - ^{1}H NMR [$CDCl_3$]: *trans*-stilbene (**384**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56-7.54 (4H, m, H-2 and H-6), 7.40-7.38 (4H, m, H-3 and H-5), 7.30-7.28 (2H, m, H-4), 7.14 (2H, s, H-*α* and H-*β*)

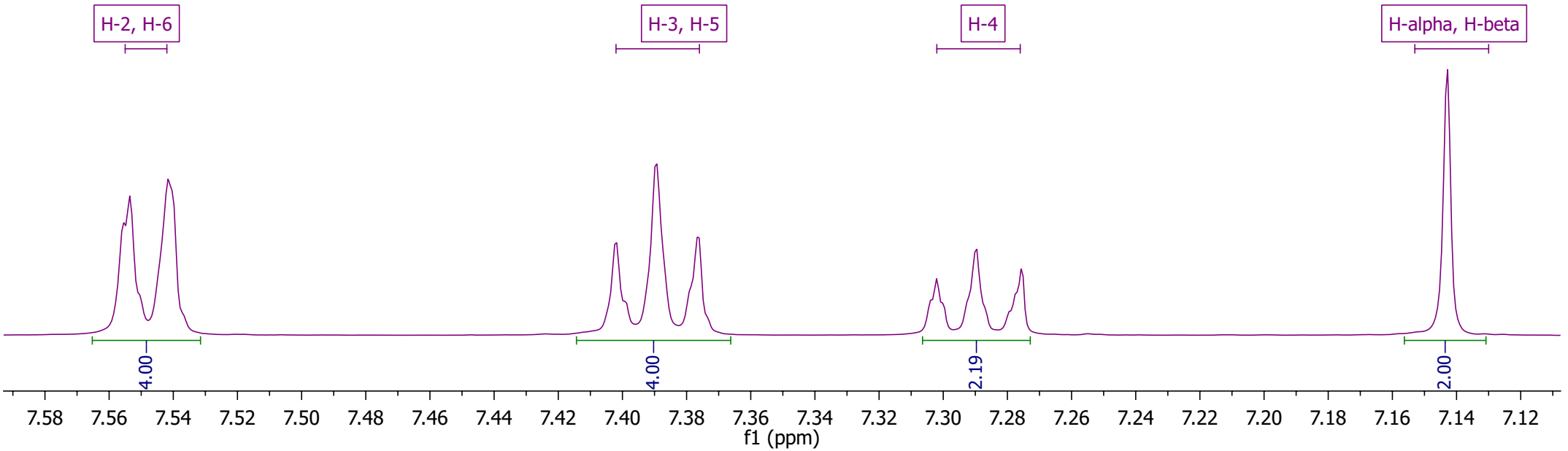
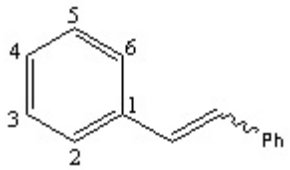


Plate 14b - ^{13}C NMR [$CDCl_3$]: *trans*-stilbene (**384**)



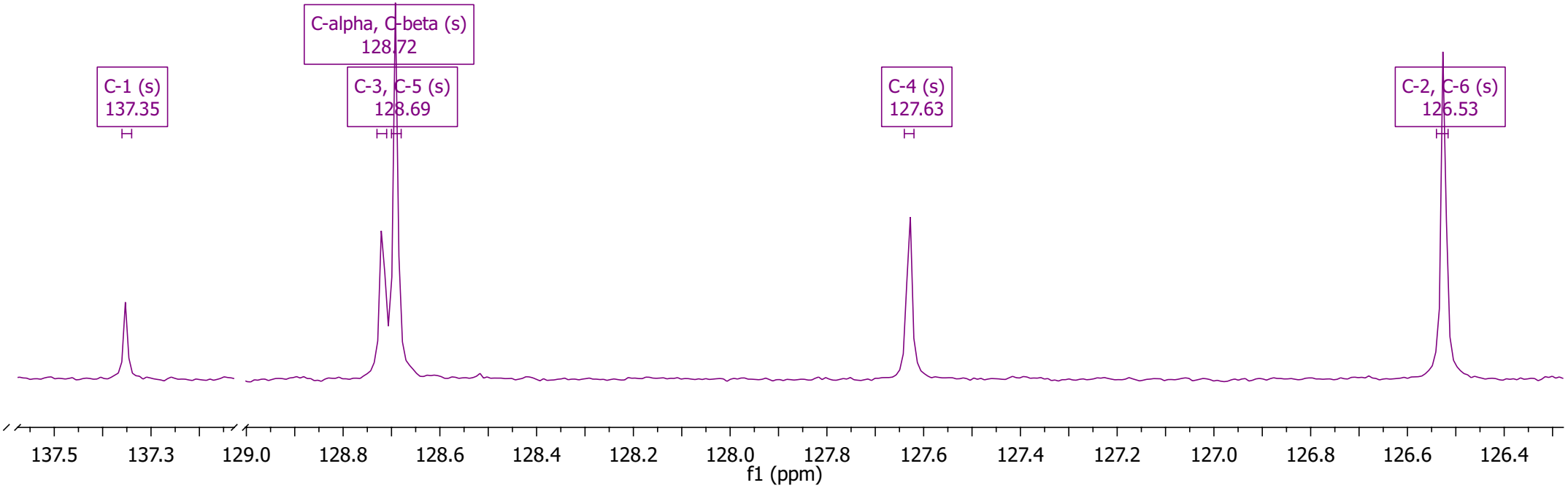


Plate 14c - HSQC [$CDCl_3$]: *trans*-stilbene (**384**)

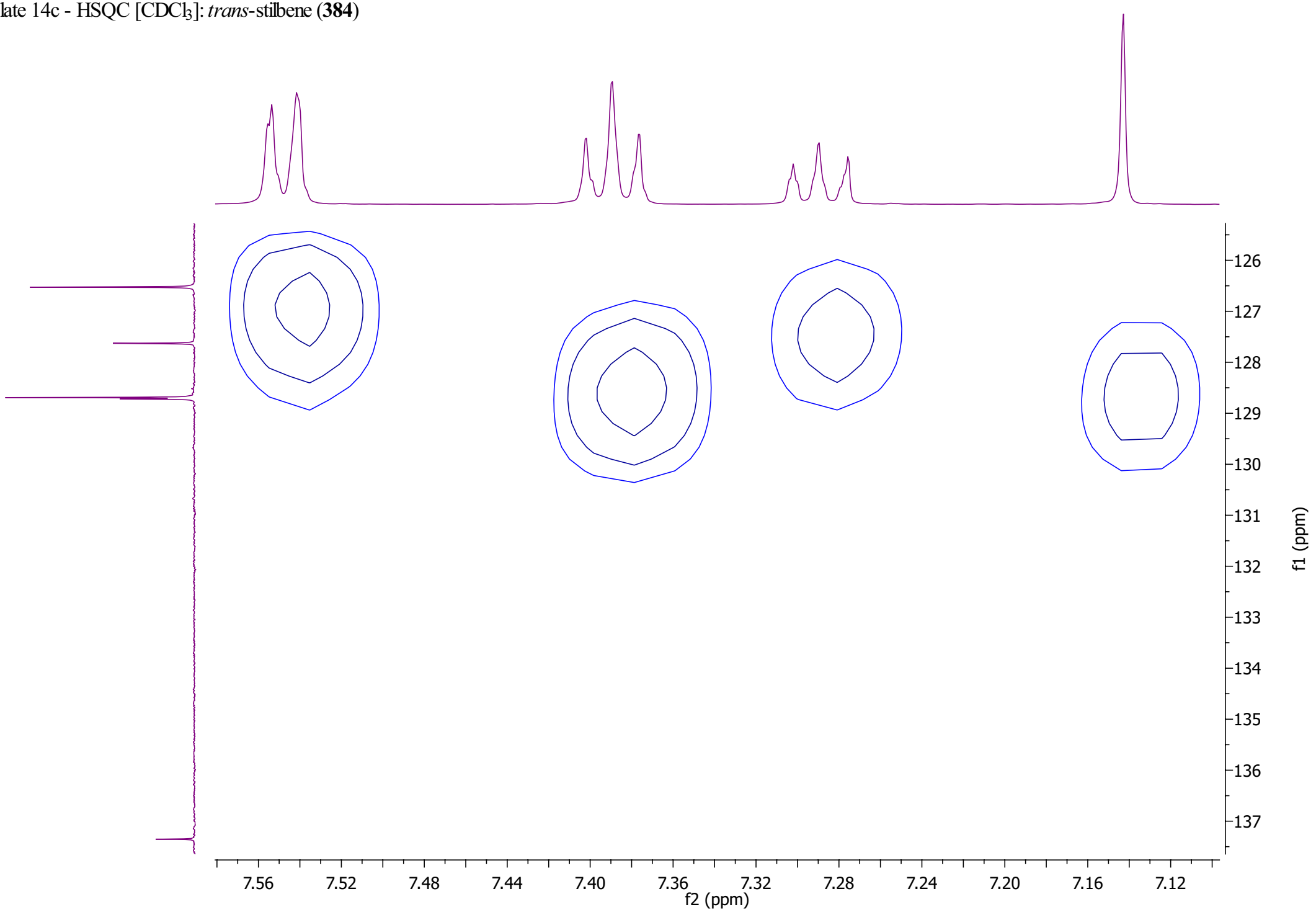
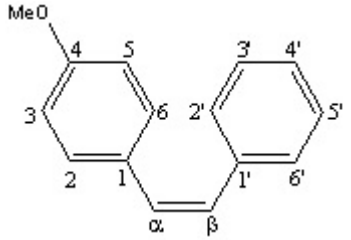


Plate 15a - ^{1}H NMR [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)



NMR (600 MHz,) δ 7.28-7.26 (2H, m, H-2'and H-6'), 7.24-7.21 (2H, m, H-3'and H-5'), 7.19-7.16 (3H, m, H-2, H-6 and H-4'), 6.75 (2H, d, *J* = 8.77 Hz, H-3 and H-5), 6.53 (1H, d, *J* = 12.22 Hz, H-*α*), 6.50 (1H, d, *J* = 12.22 Hz, H-*β*), 3.77 (3H, s, OMe)

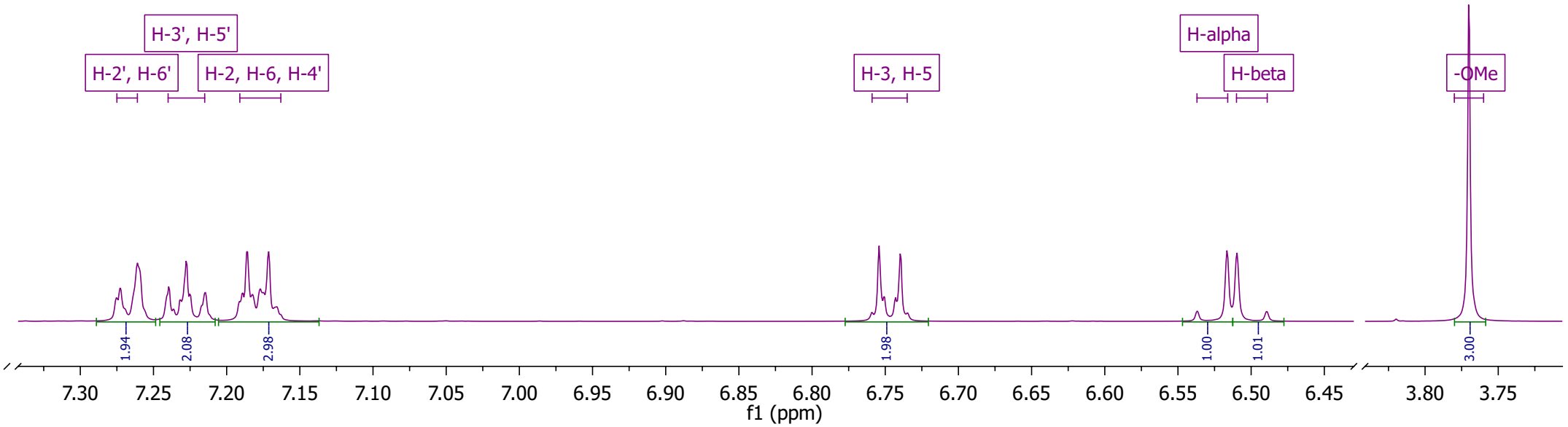
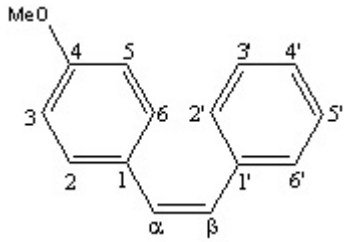
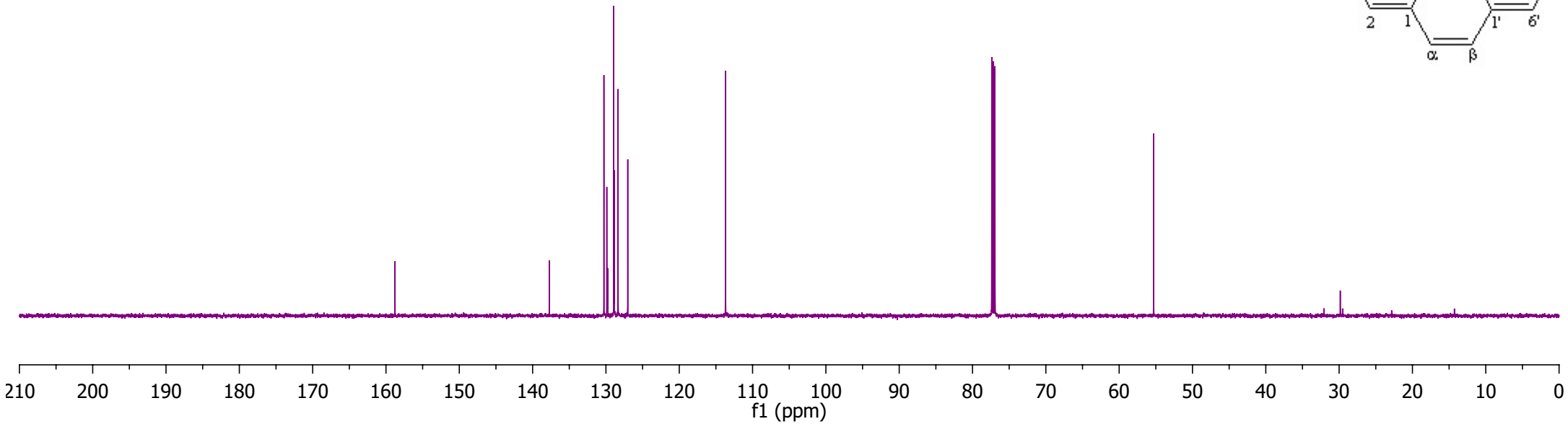


Plate 15b - ^{13}C NMR [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)





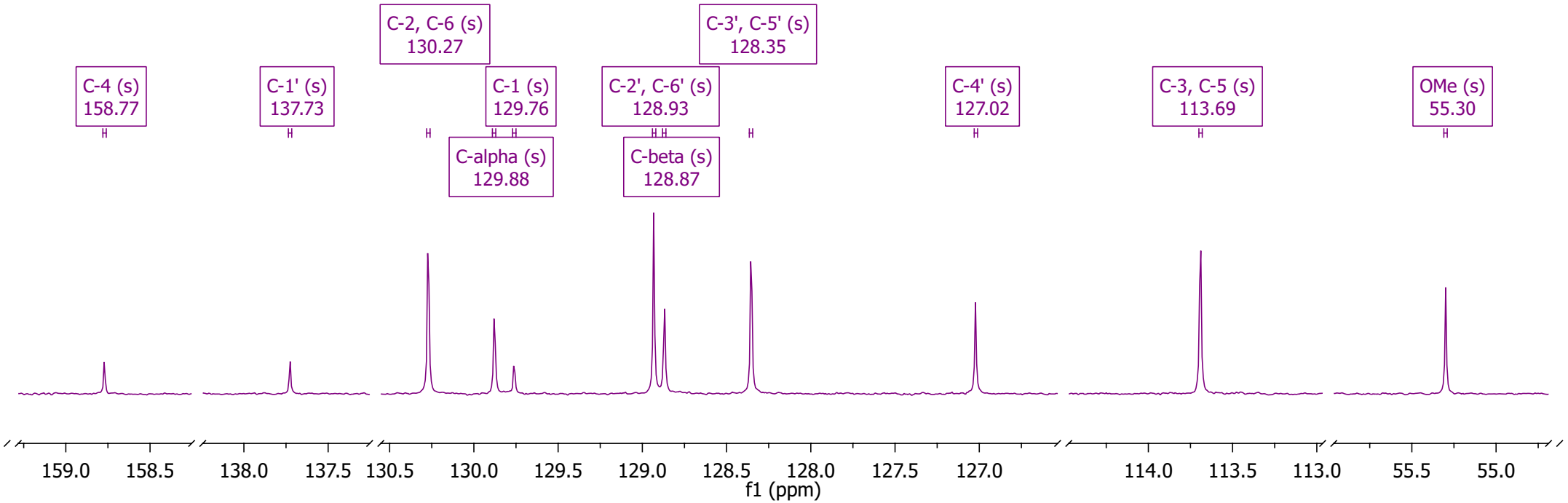


Plate 15c - DEPT [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)

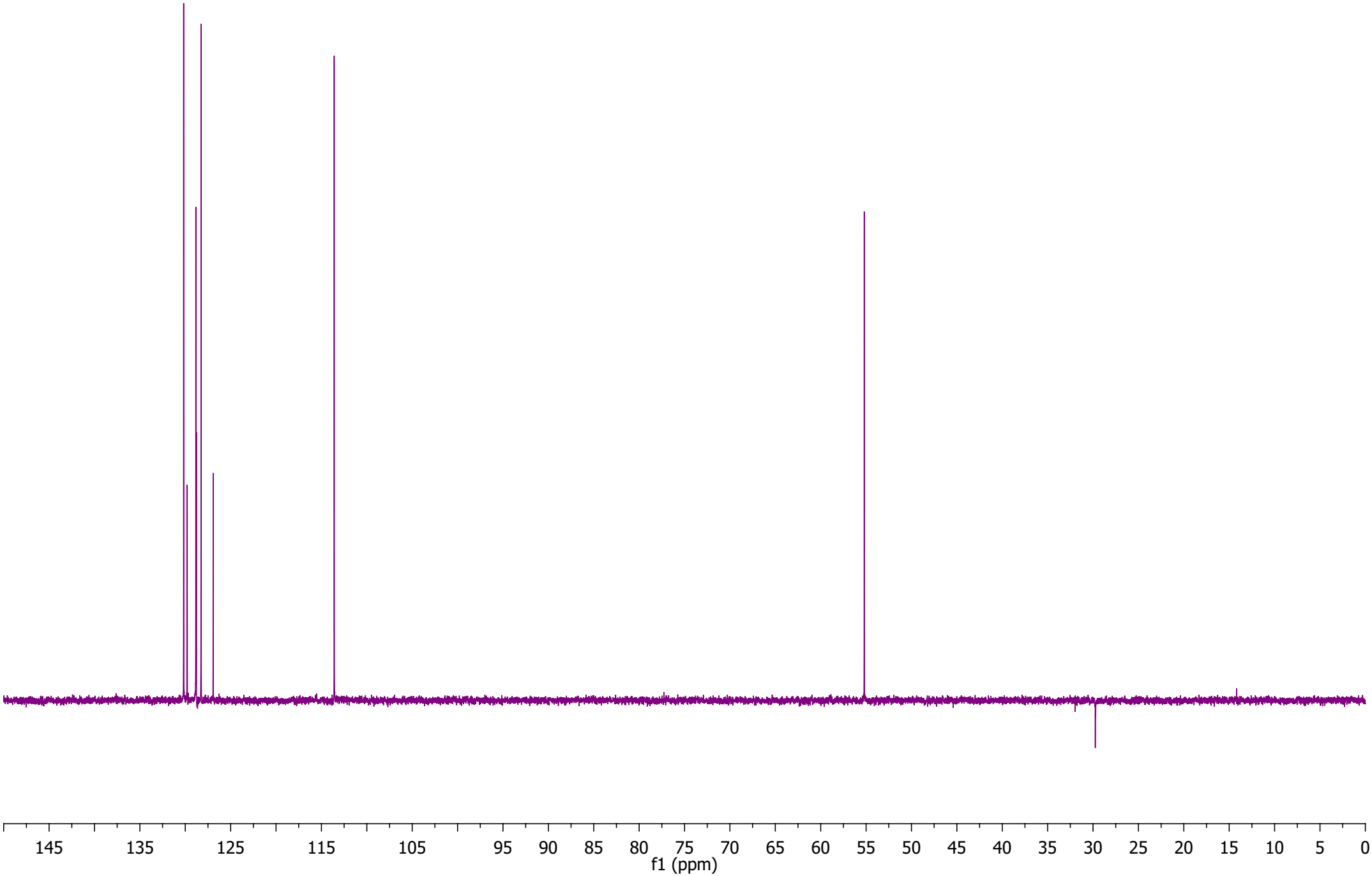


Plate 15d - HSQC [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)

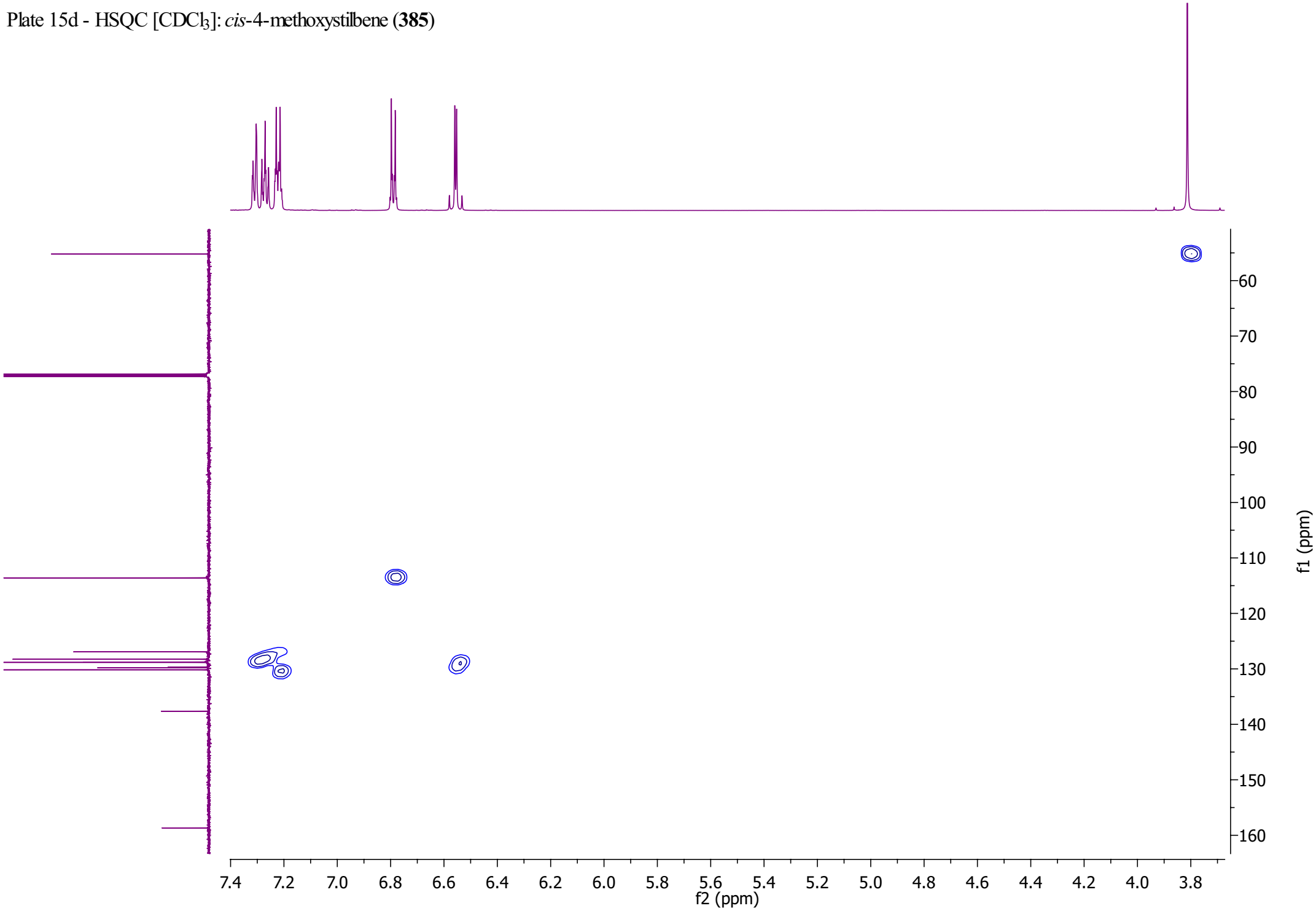


Plate 15e - HSQC (expansion) [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)

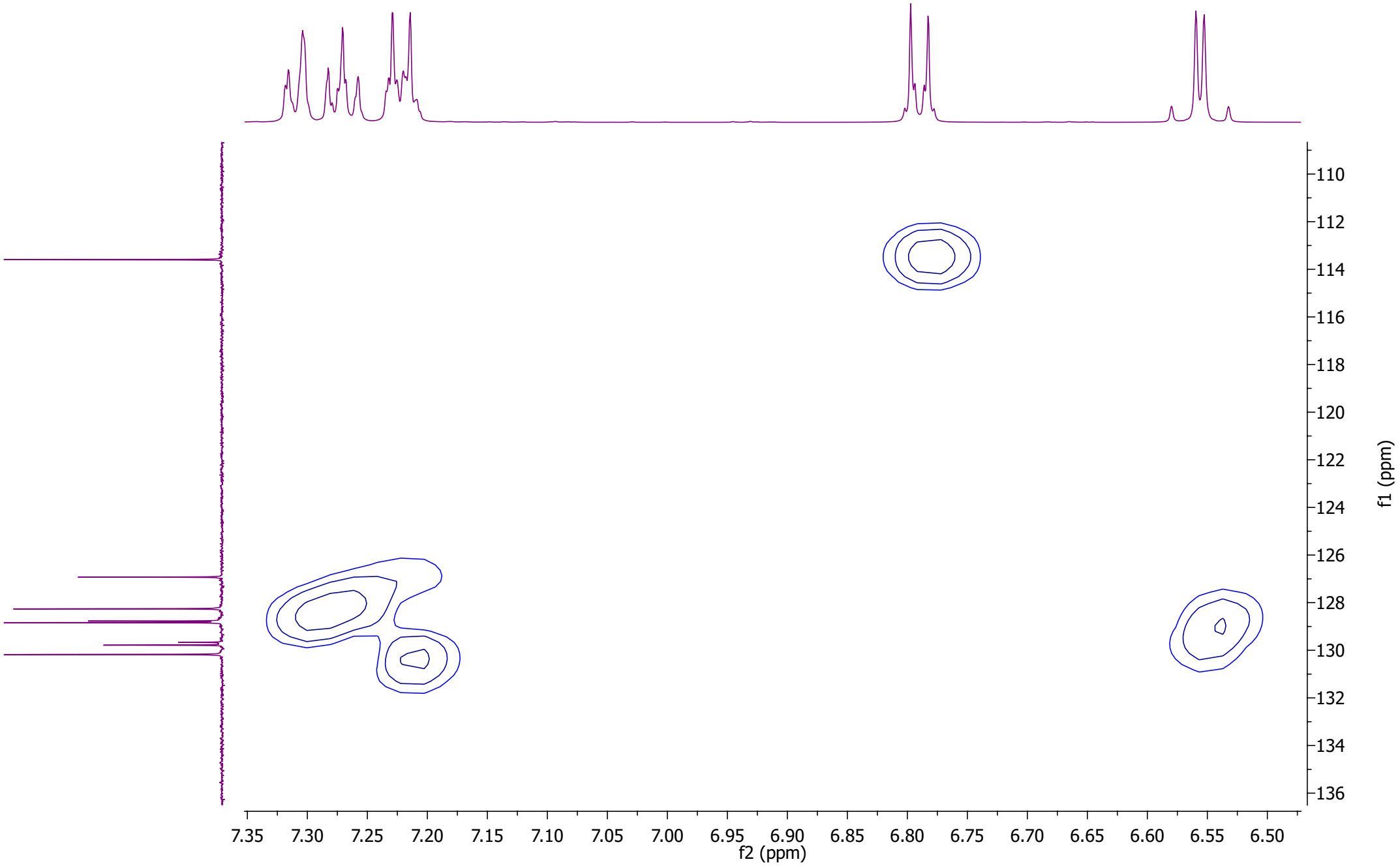


Plate 15f - HMBC [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)

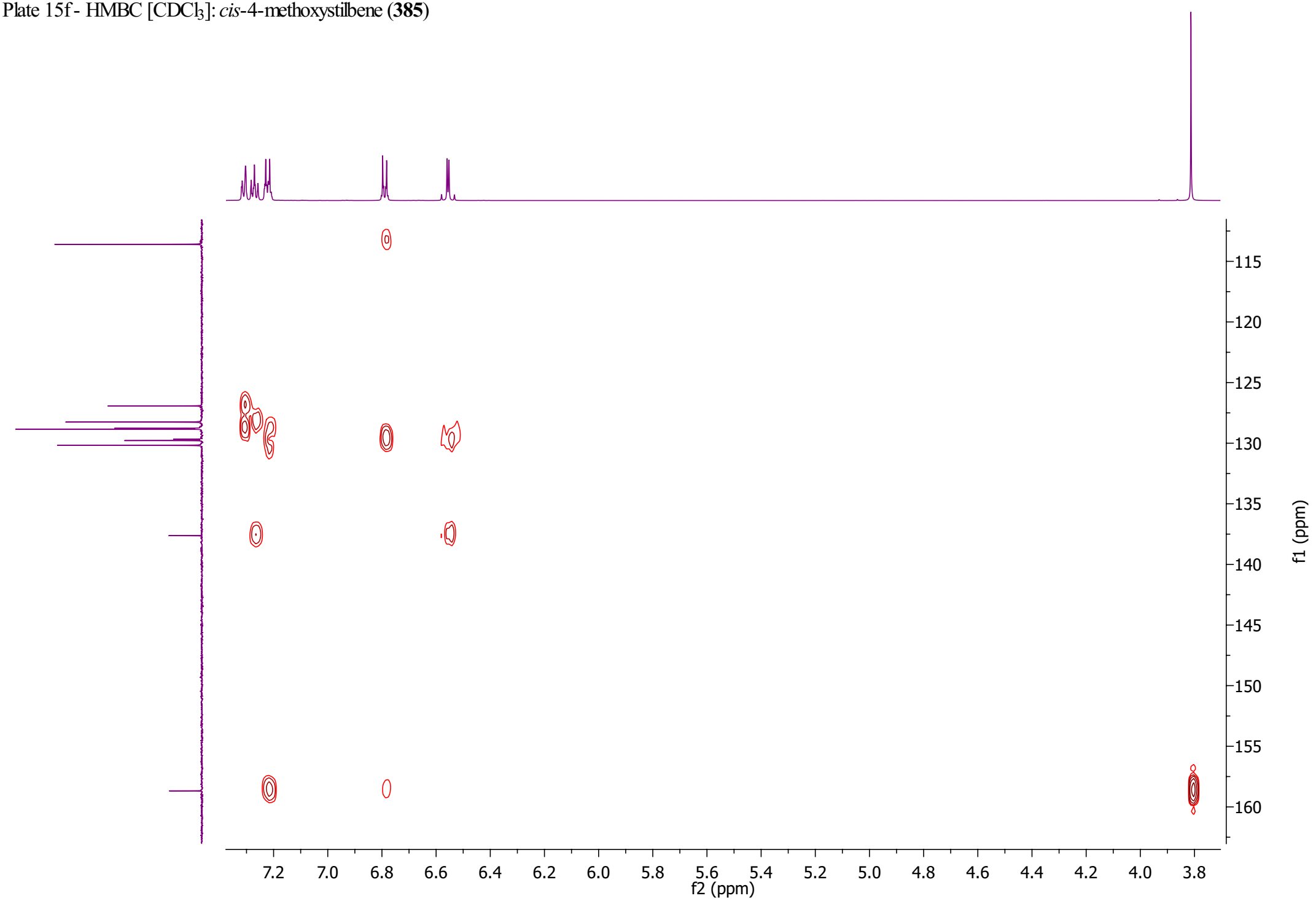


Plate 15g - HMBC (expansion) [$CDCl_3$]: *cis*-4-methoxystilbene (**385**)

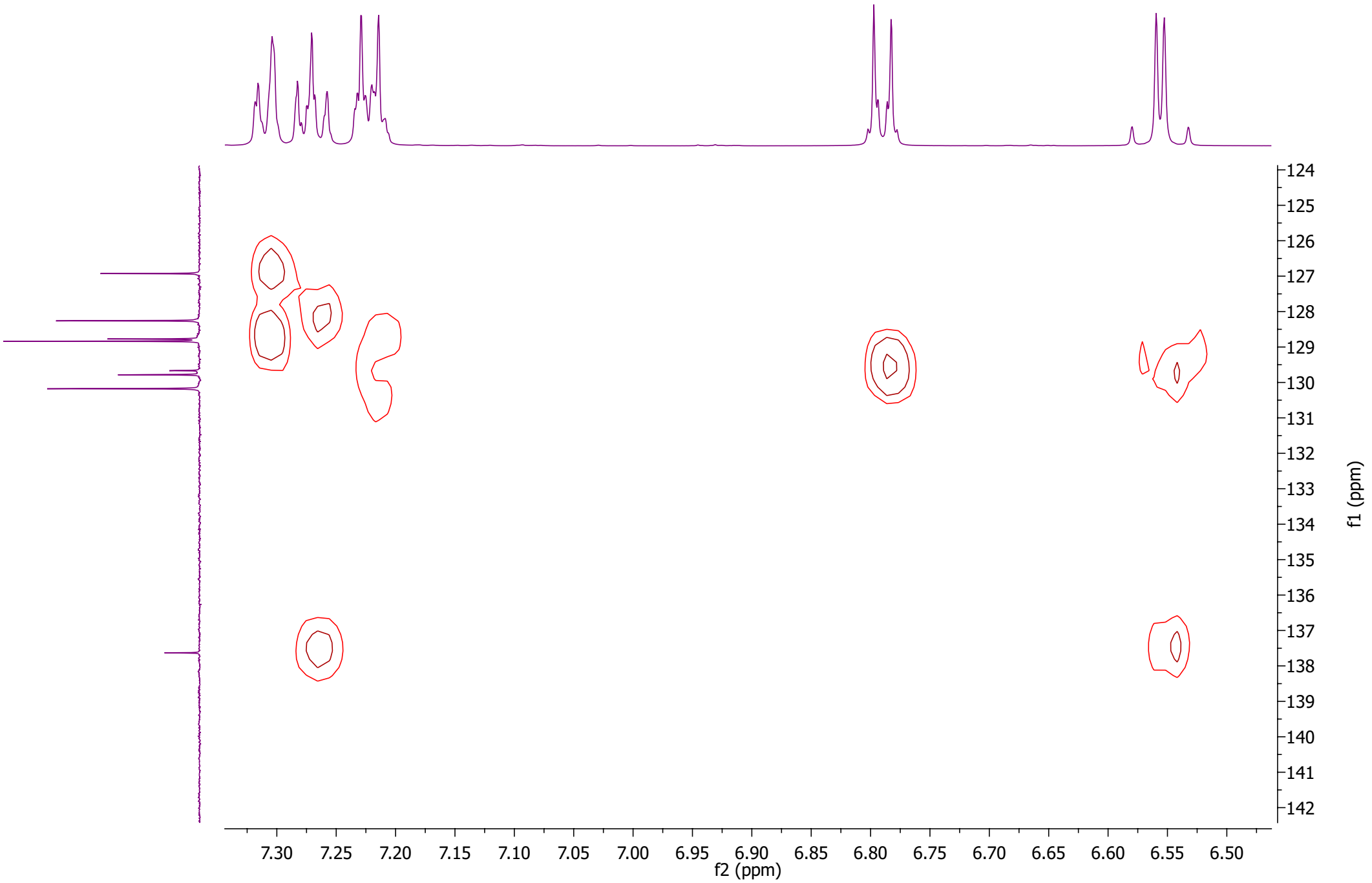
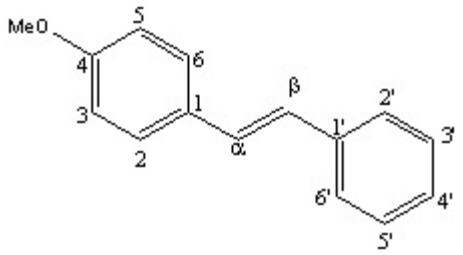


Plate 16a - ^{1}H NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53-7.52 (2H, m, H-2' and H-6'), 7.49 (2H, d, *J* = 8.68 Hz, H-2 and H-6), 7.39-7.36 (2H, m, H-3' and H-5'), 7.28-7.25 (1H, m, H-4'), 7.10 (1H, d, *J* = 16.31 Hz, H-*α*), 7.01 (1H, d, *J* = 16.31 Hz, H-*β*), 6.93 (2H, d, *J* = 8.68 Hz, H-3 and H-5), 3.86 (3H, s, -OMe)

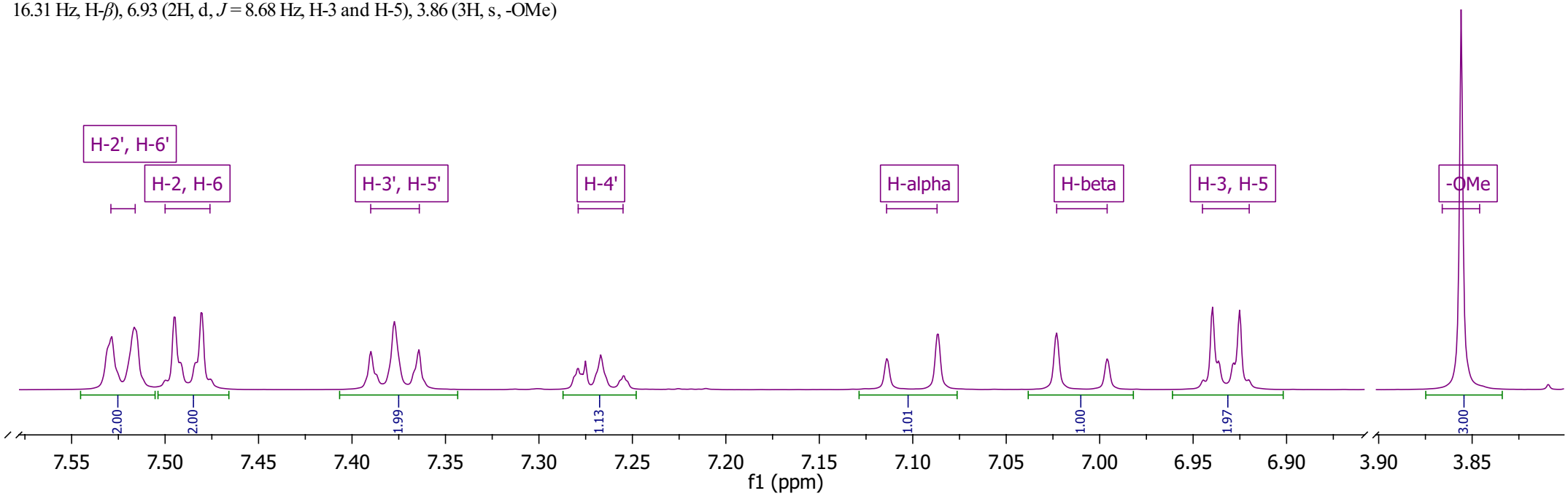
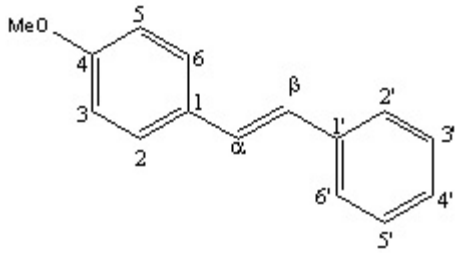


Plate 16b - ^{13}C NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)



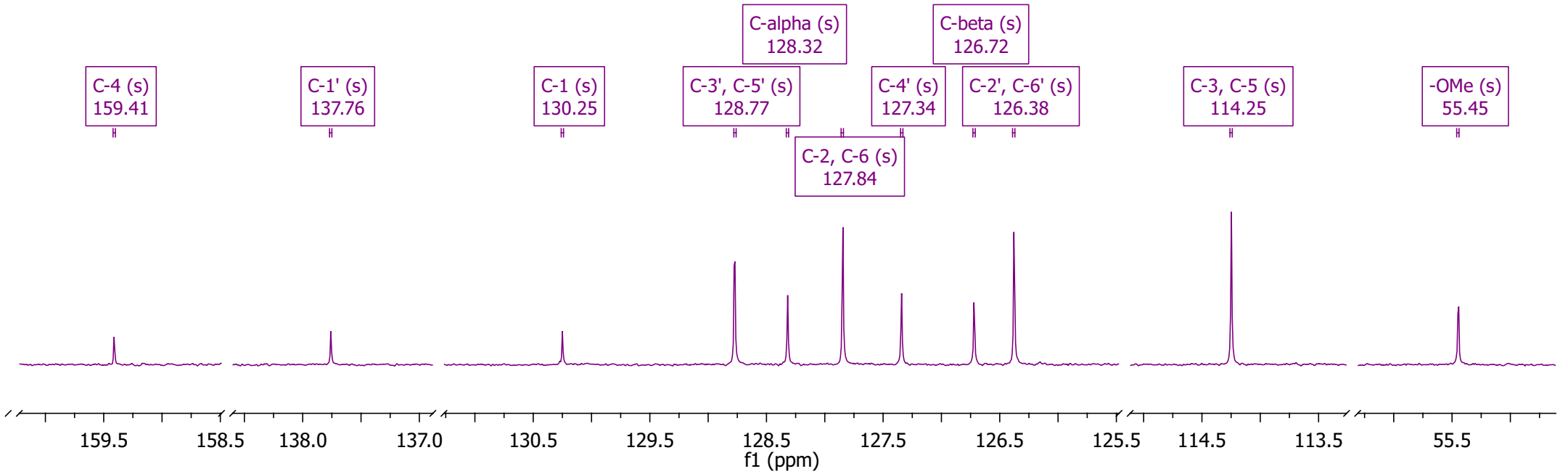


Plate 16c - DEPT NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)

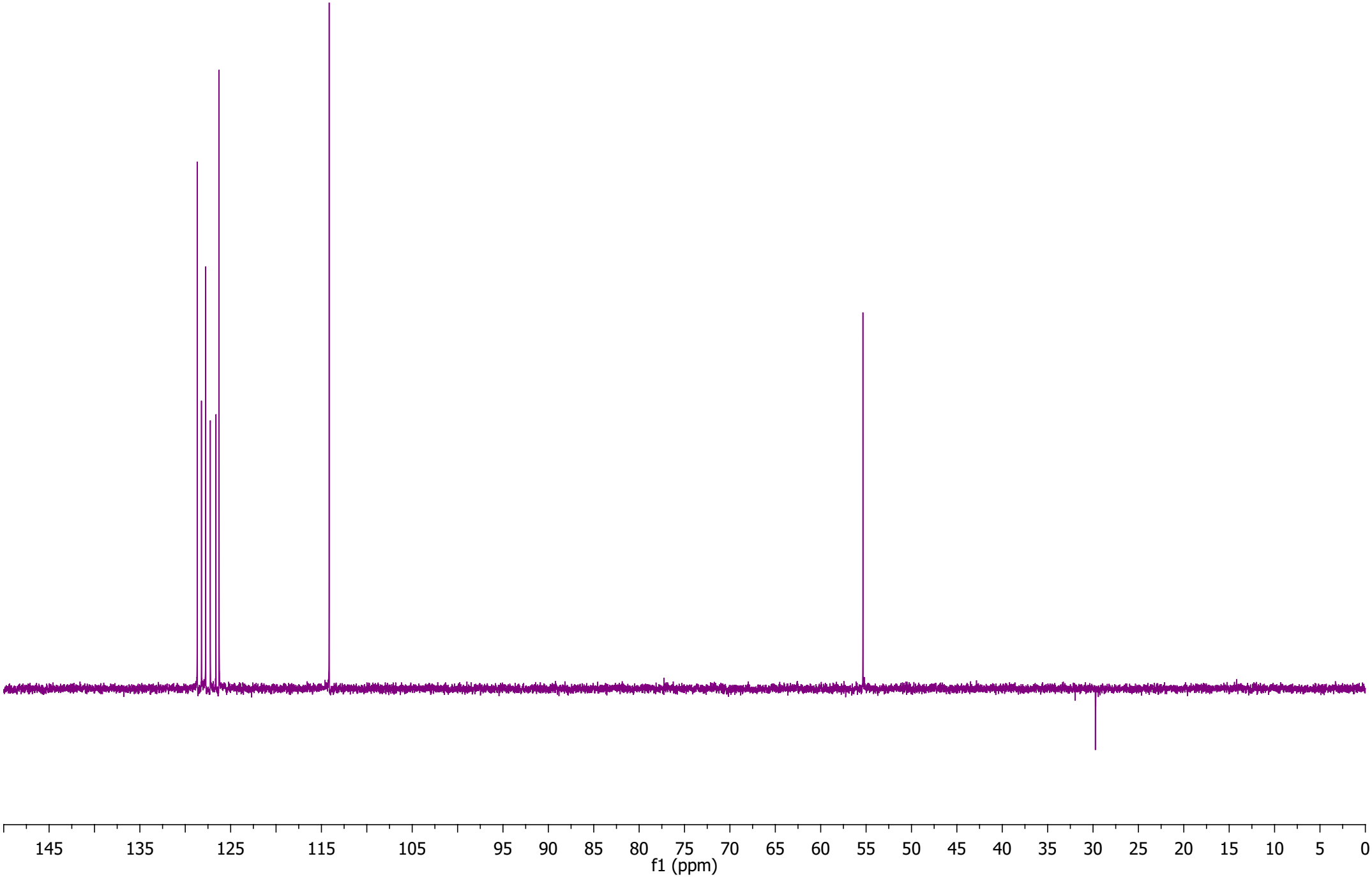


Plate 16d - HSQC NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)

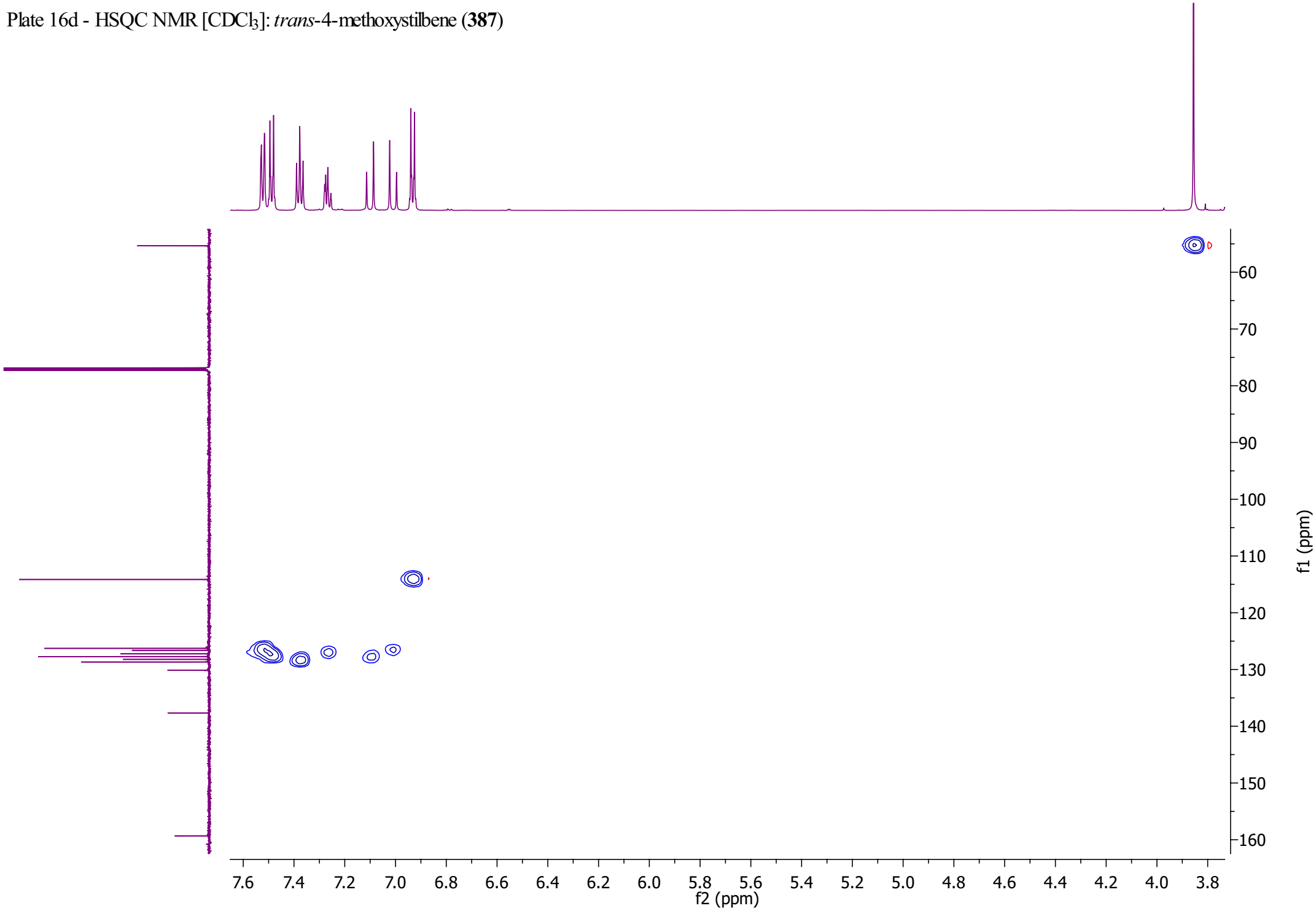


Plate 16e - HSQC (expnsion) NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)

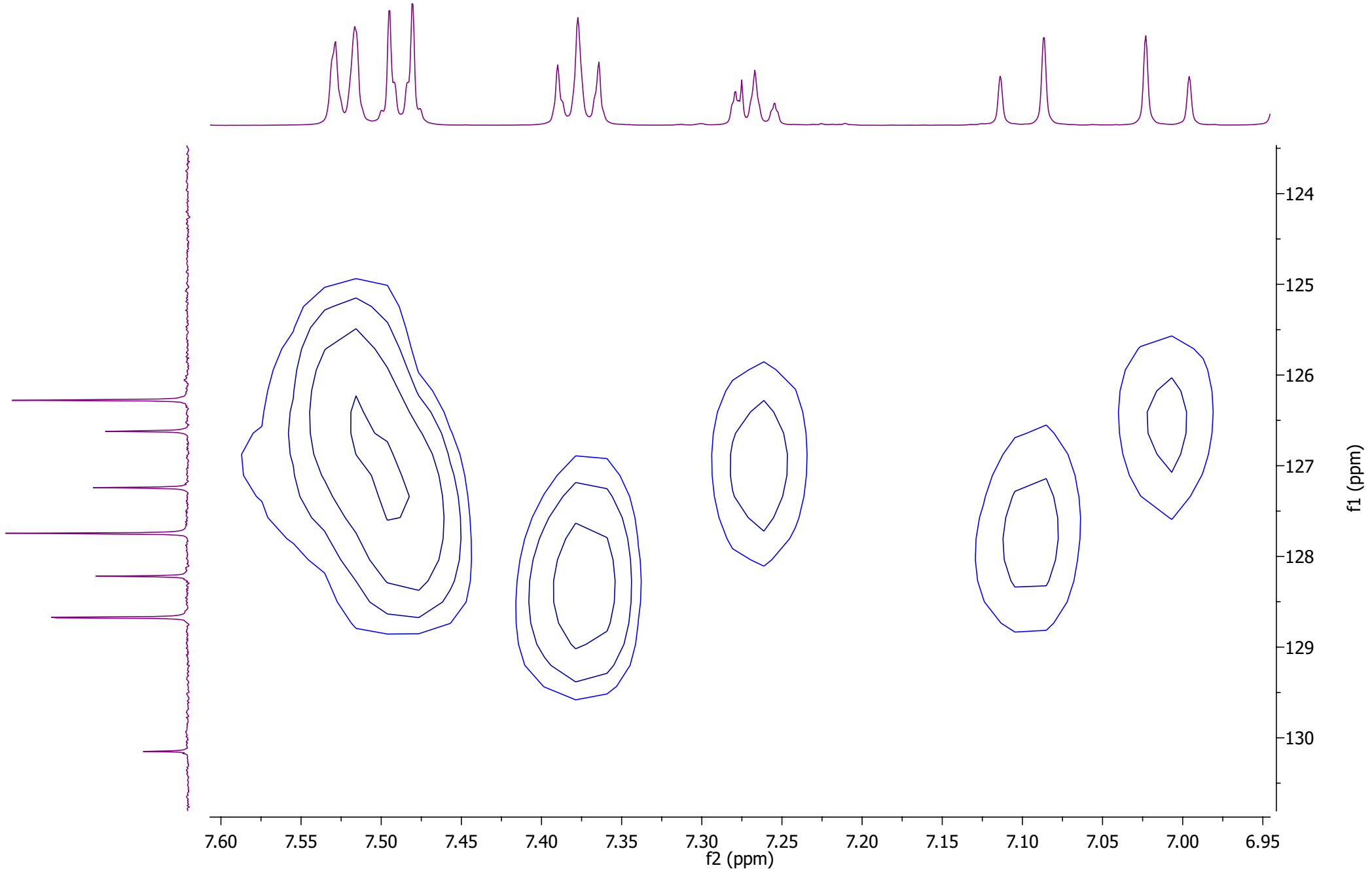


Plate 16f - HMBC NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)

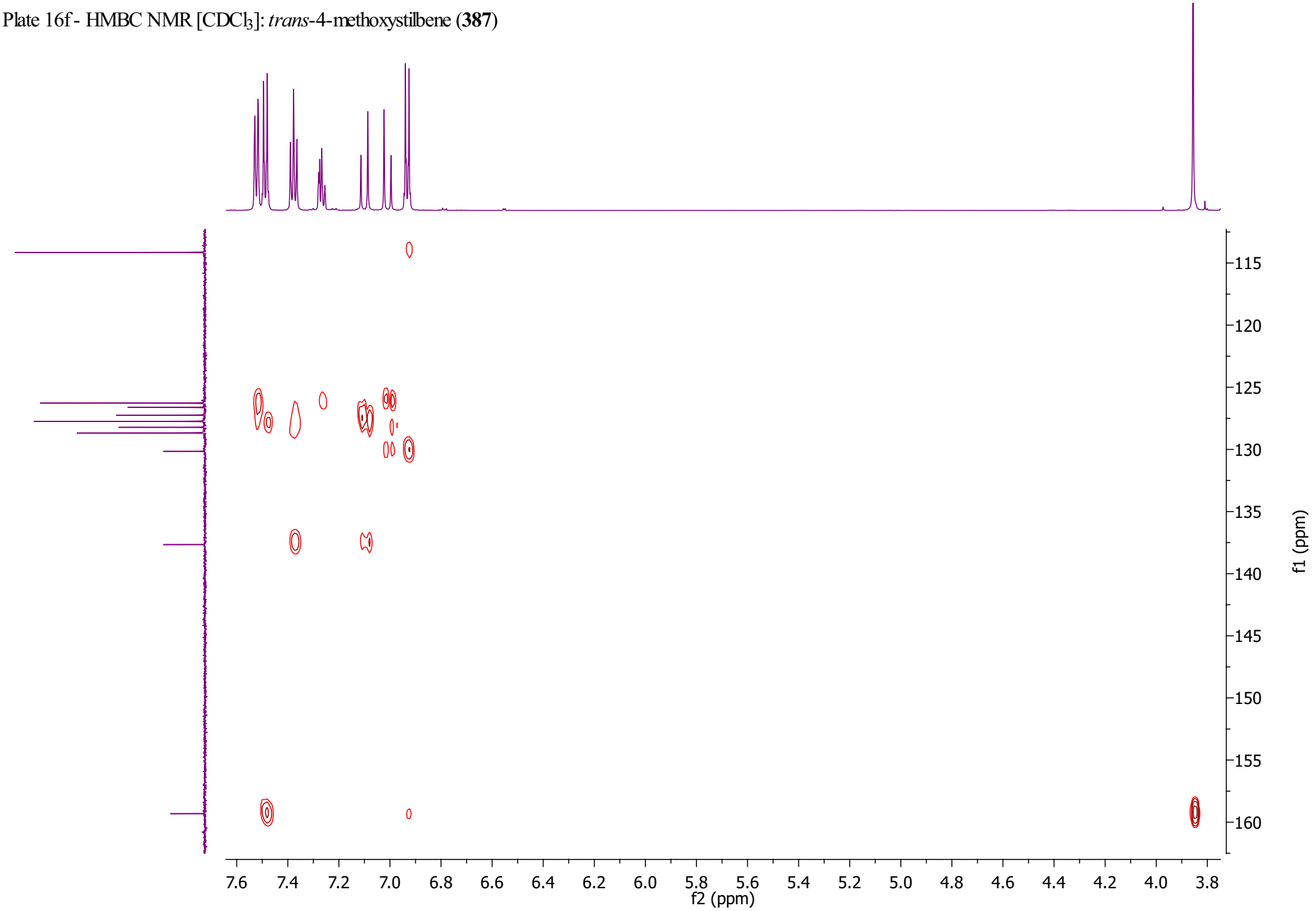
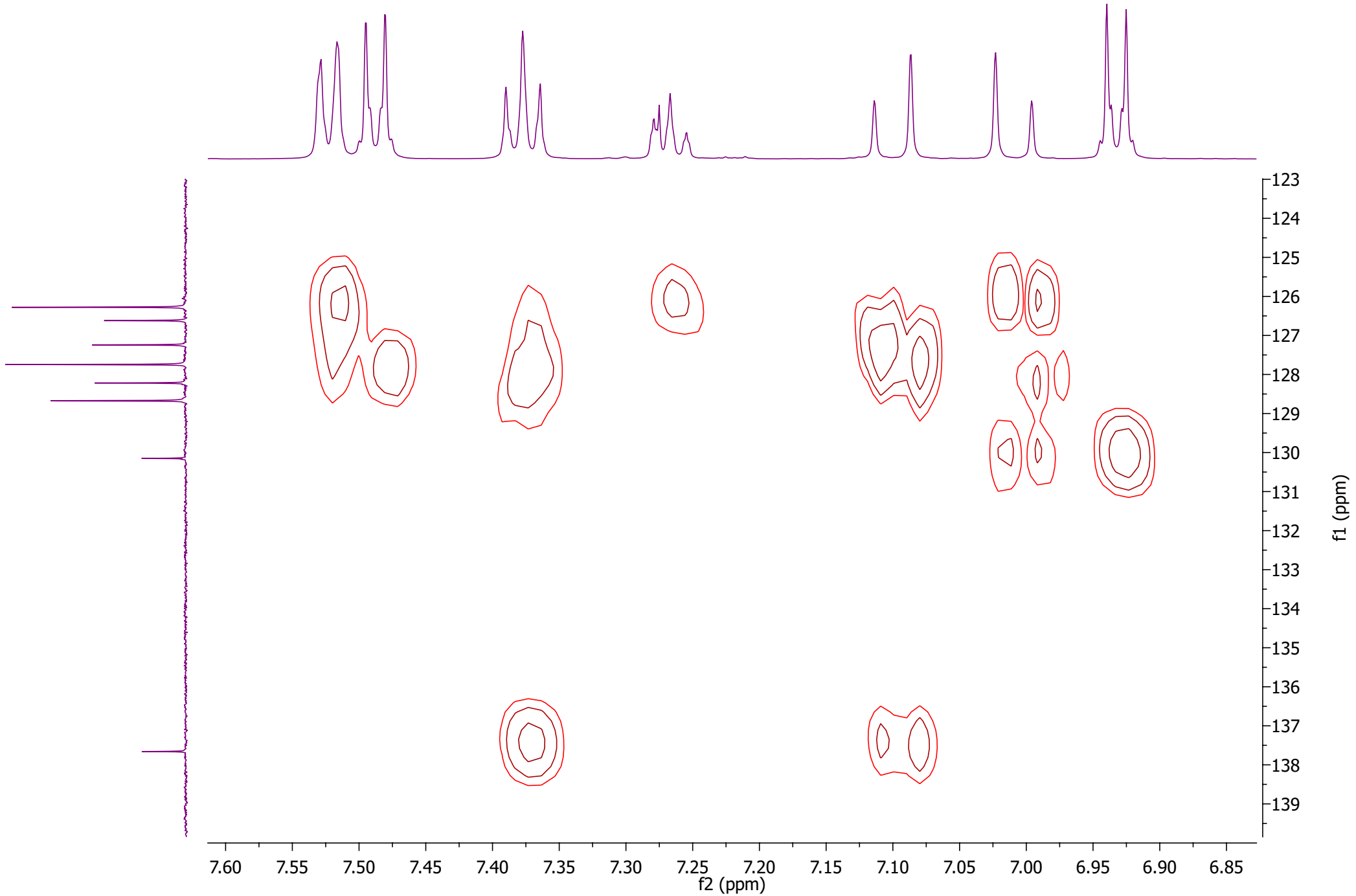
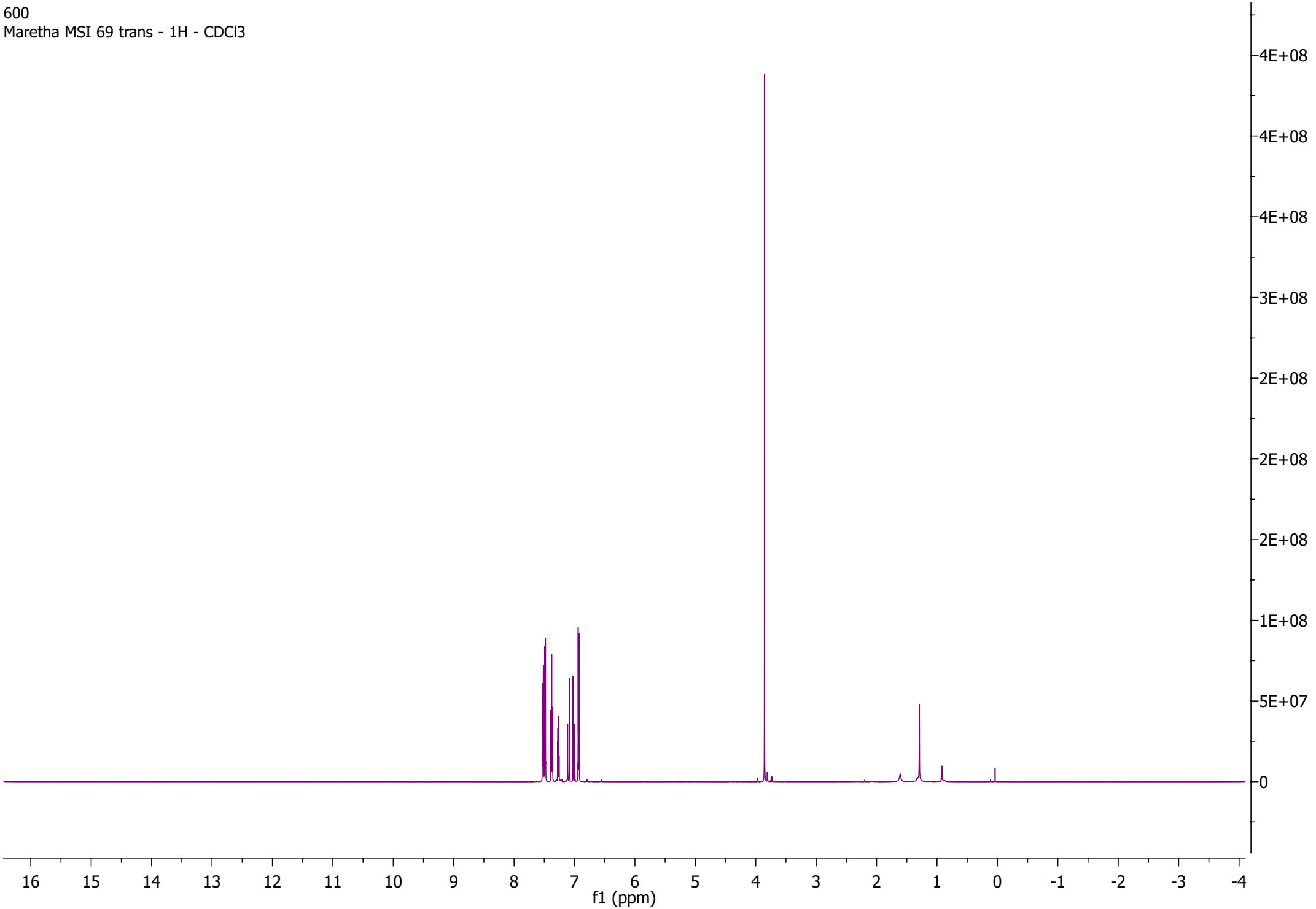


Plate 16g - HMBC (expansion) NMR [$CDCl_3$]: *trans*-4-methoxystilbene (**387**)




600
Maretha MSI 69 trans - 1H - CDCl3
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

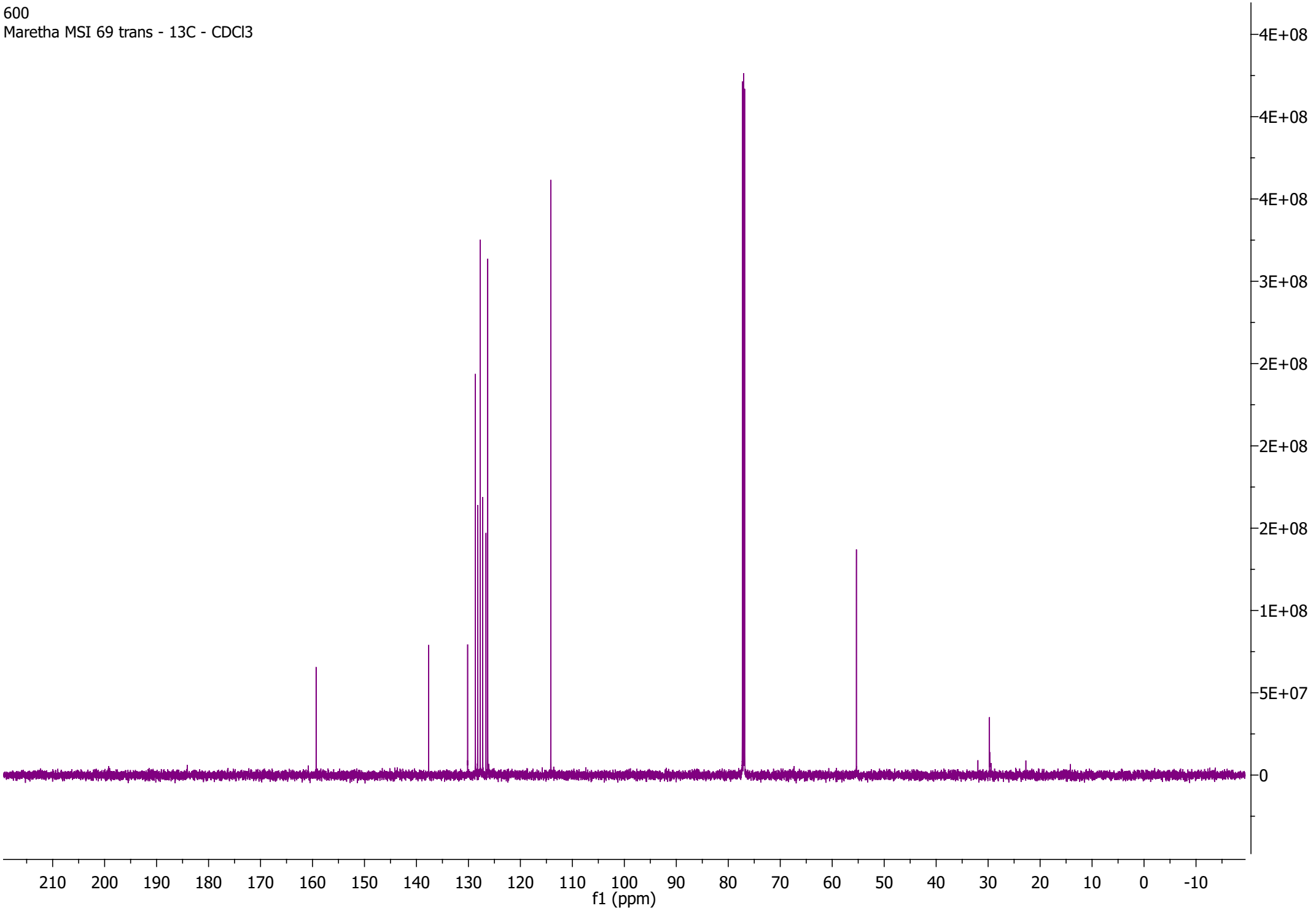
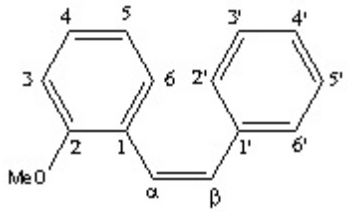

600
Maretha MSI 69 trans - 13C - CDCl3
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Plate 17a - ^{1}H NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.13 (7H, m, H-4, H-6, H-2', H-3', H-4', H-5' and H-6'), 6.90-6.88 (1H, m, H-3), 6.76-6.74 (1H, m, H-5), 6.69 (1H, d, J = 12.26 Hz, H-*α*), 6.63 (1H, d, J = 12.26 Hz, H-*β*), 3.82 (3H, s, -OMe)

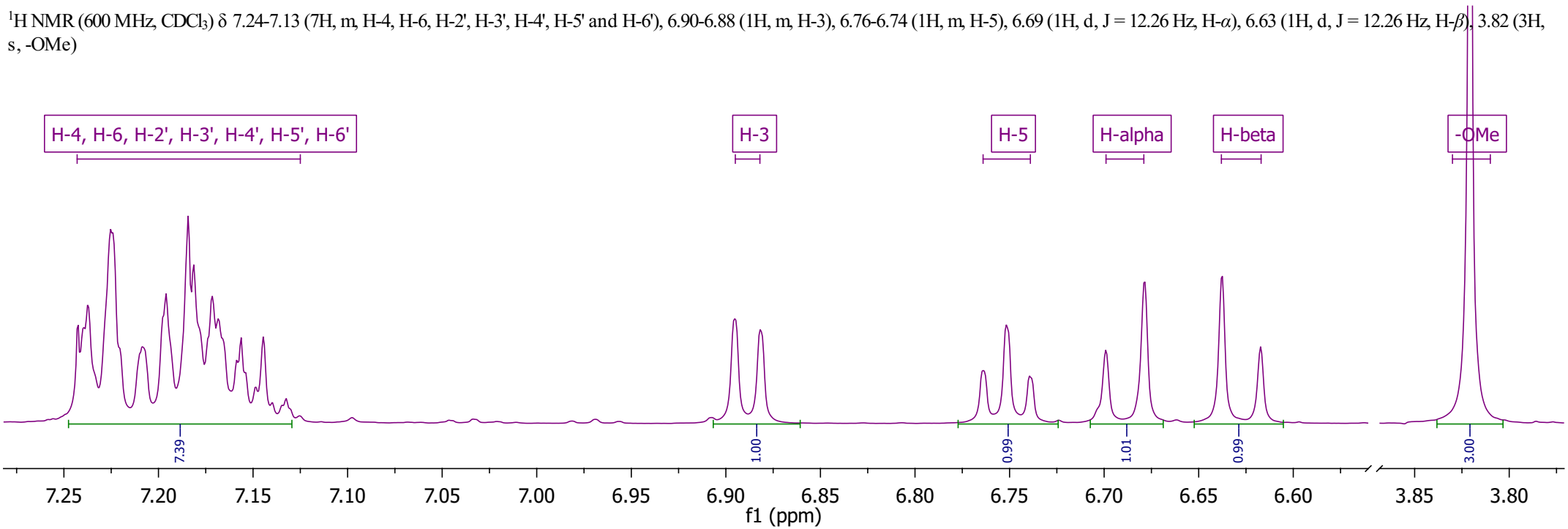
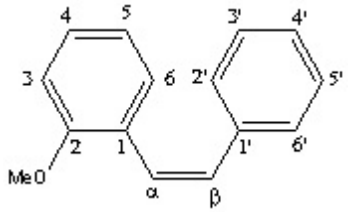


Plate 17b - ^{13}C NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)



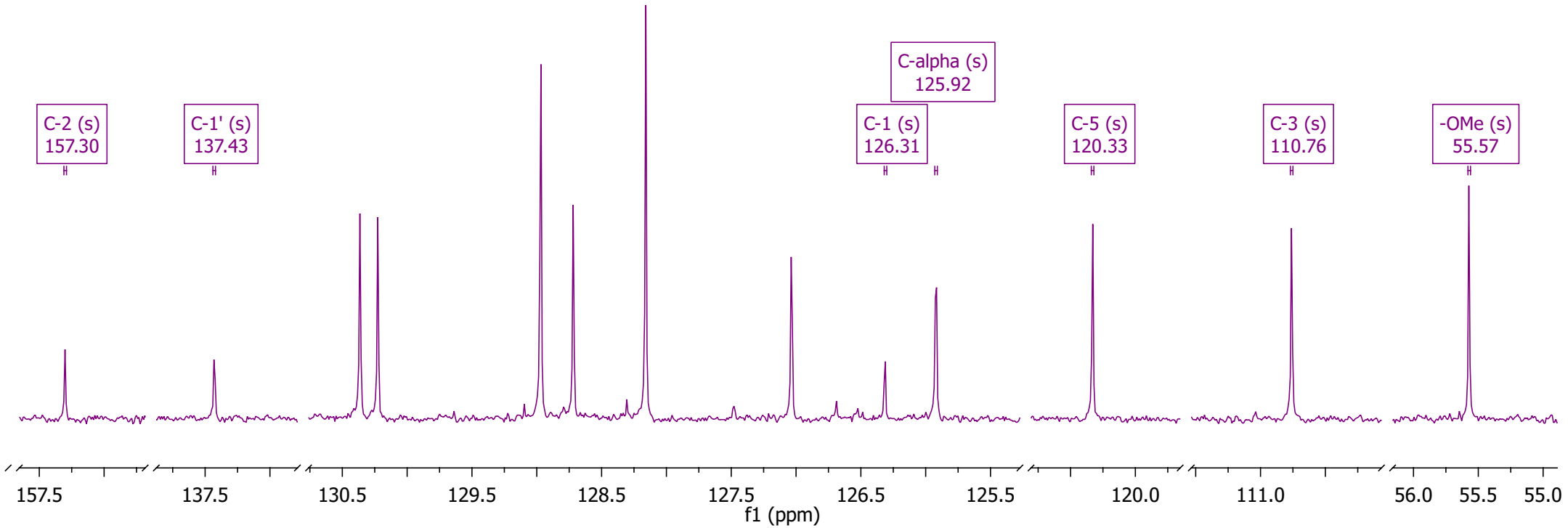


Plate 17c - DEPT NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)

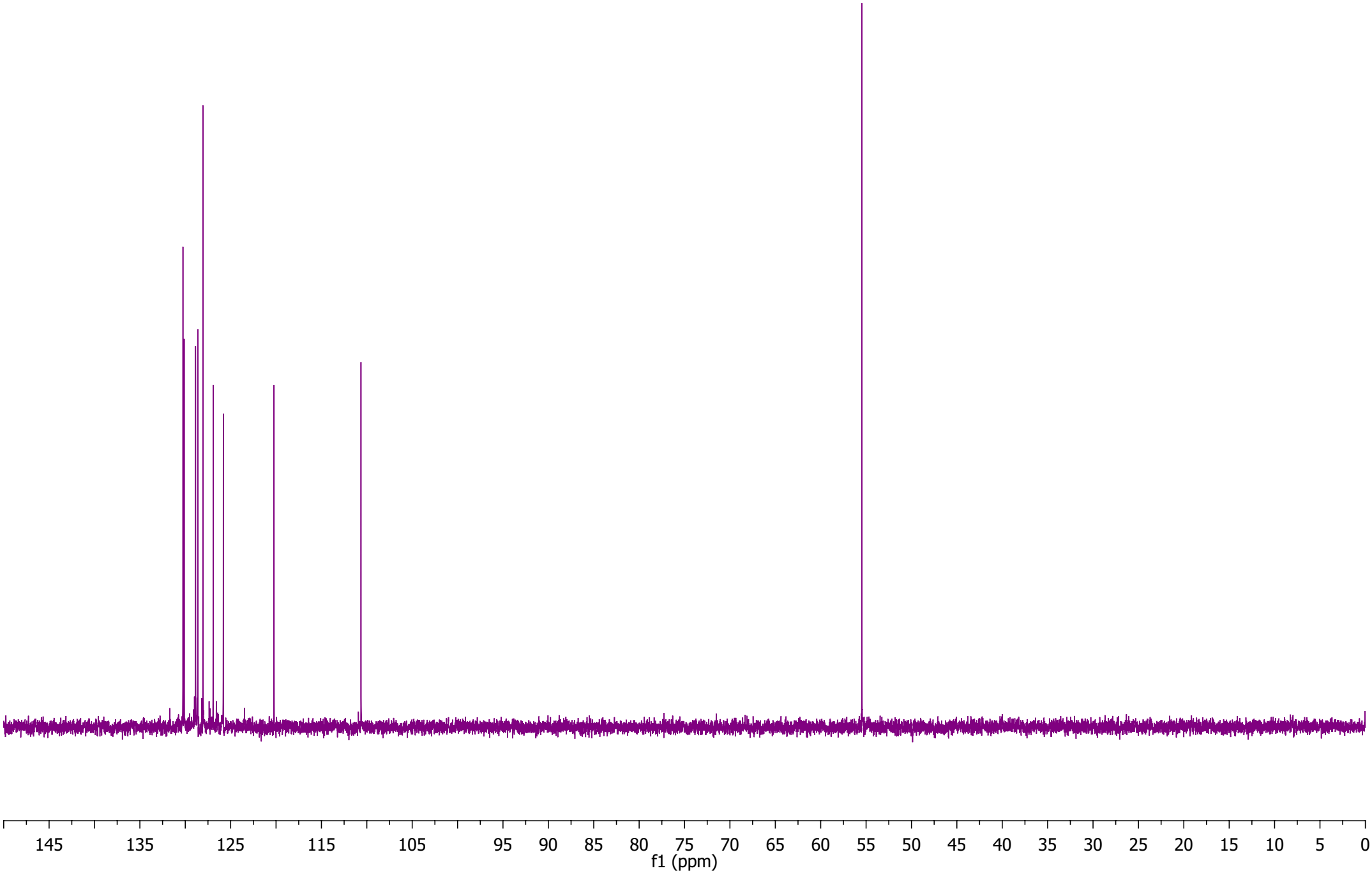


Plate 17d - HSQC NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)

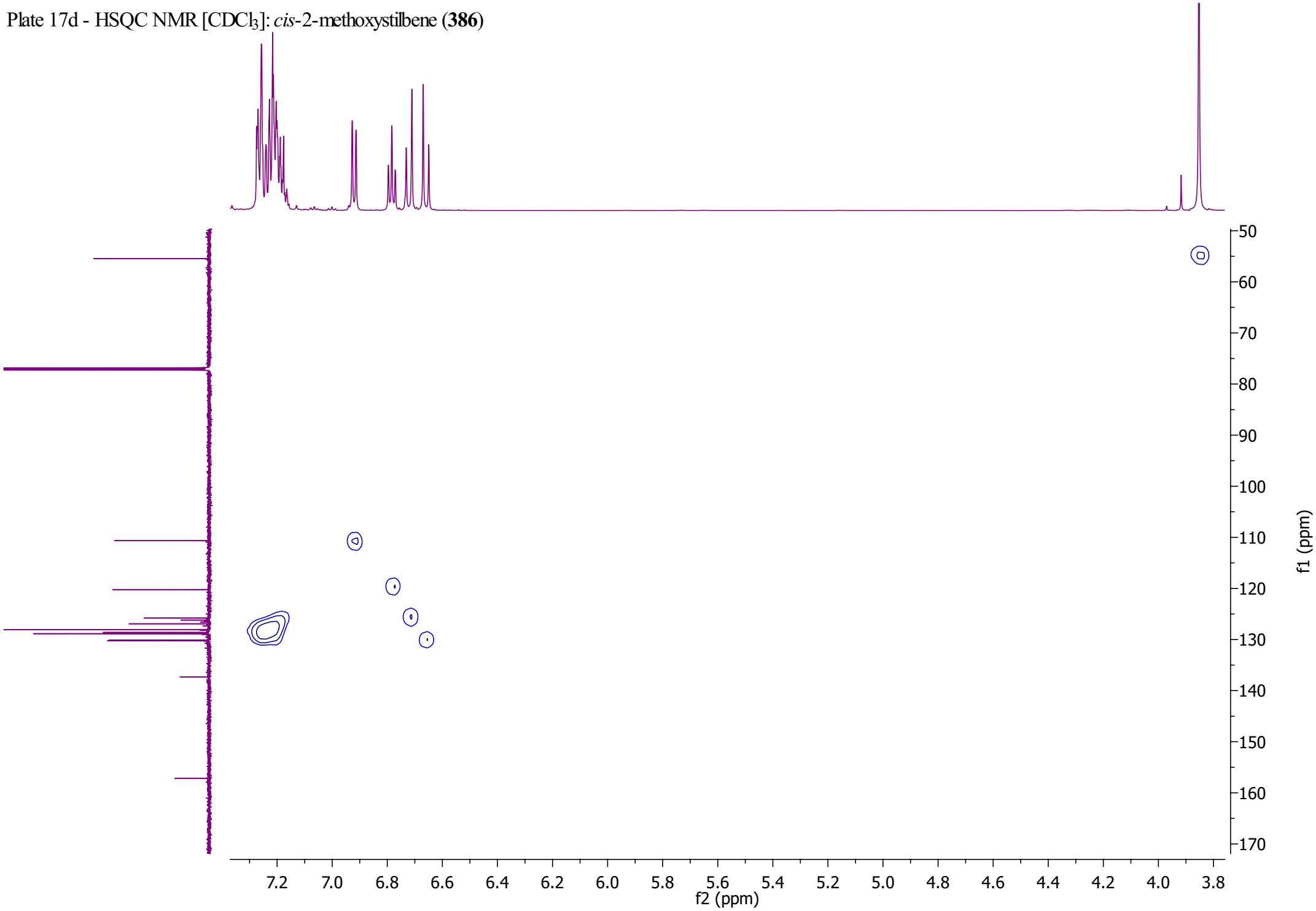


Plate 17e - HSQC(expansion) NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)

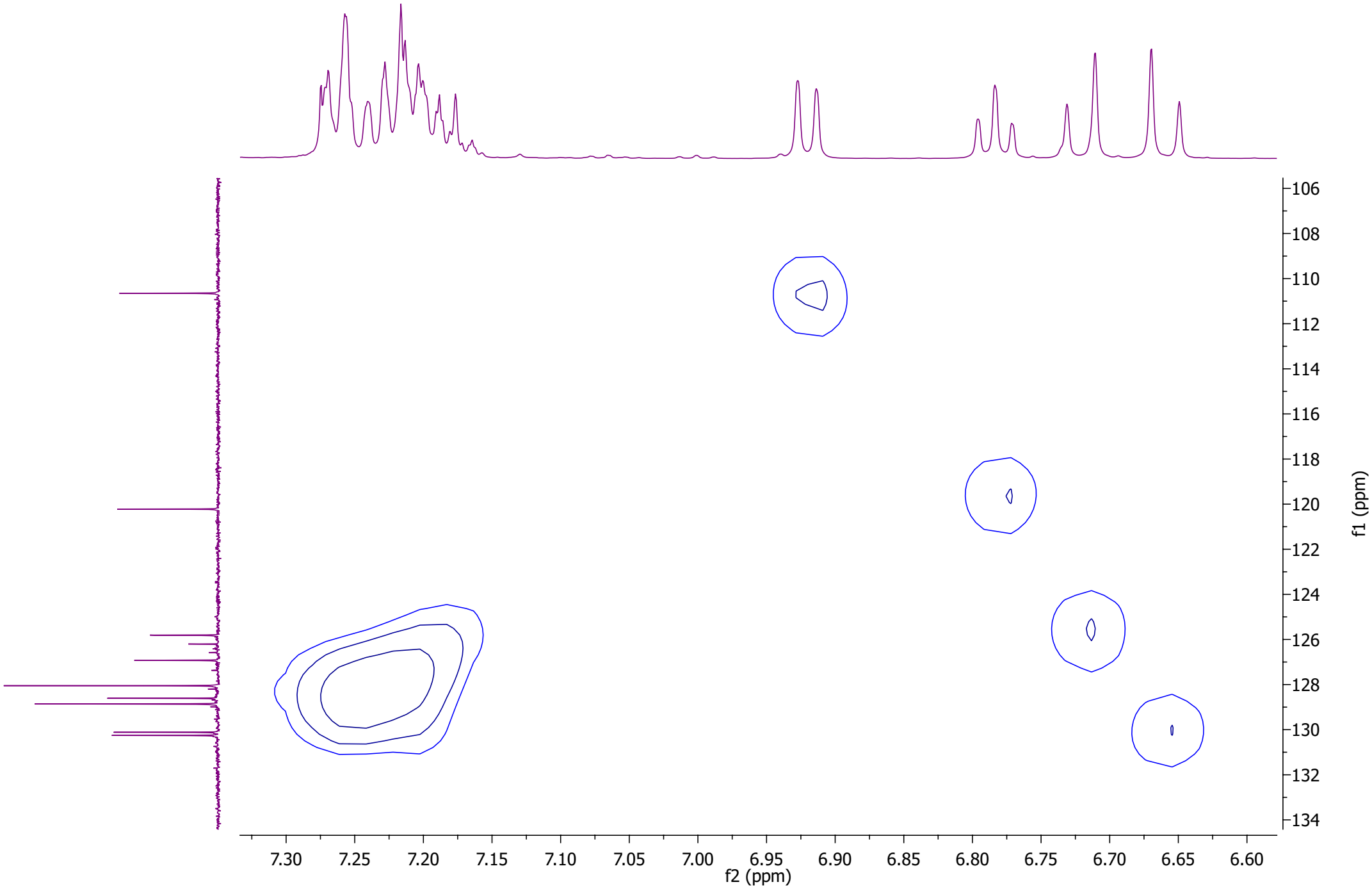


Plate 17f - HMBC NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)

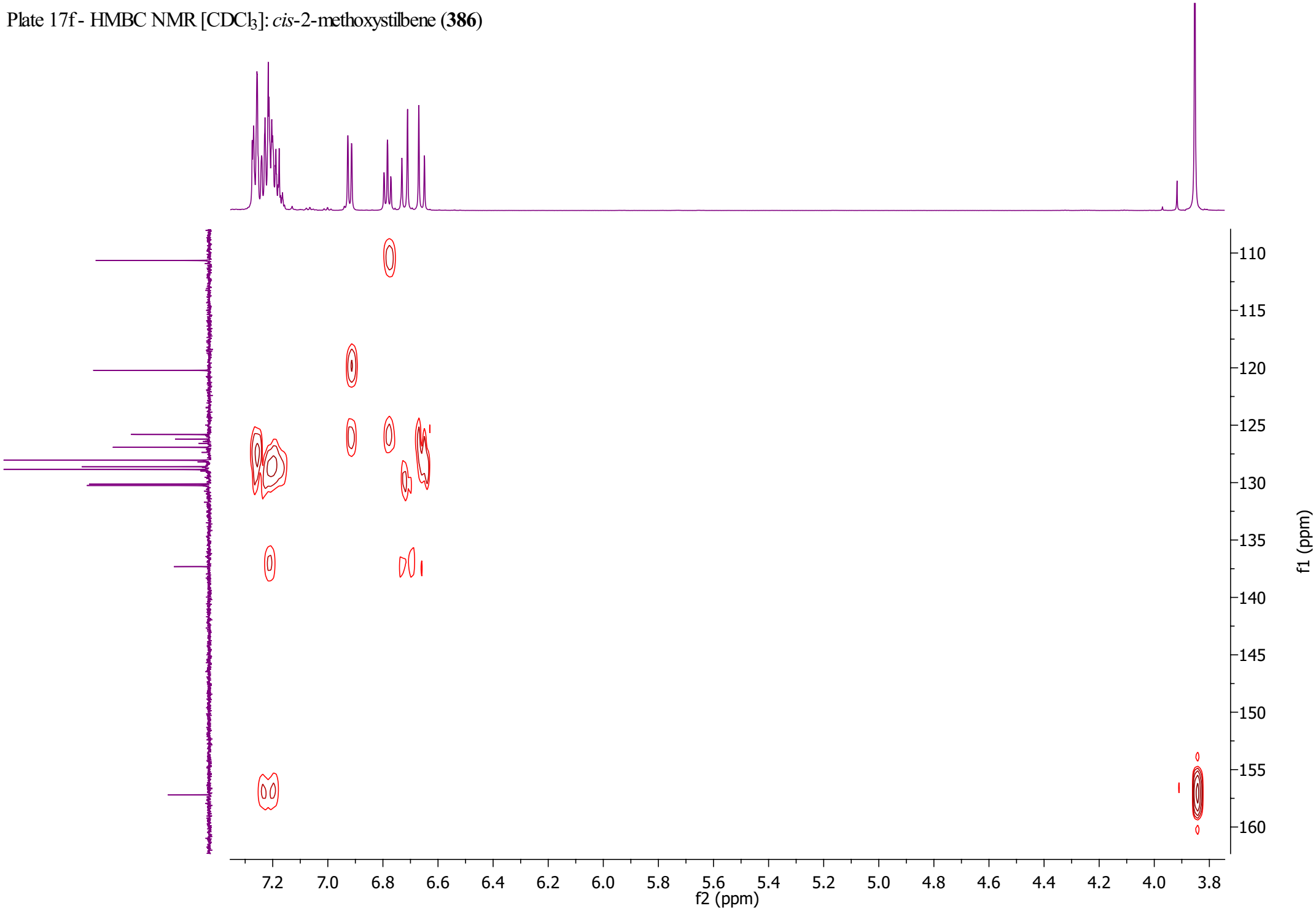


Plate 17g - HMBC (expansion) NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**)

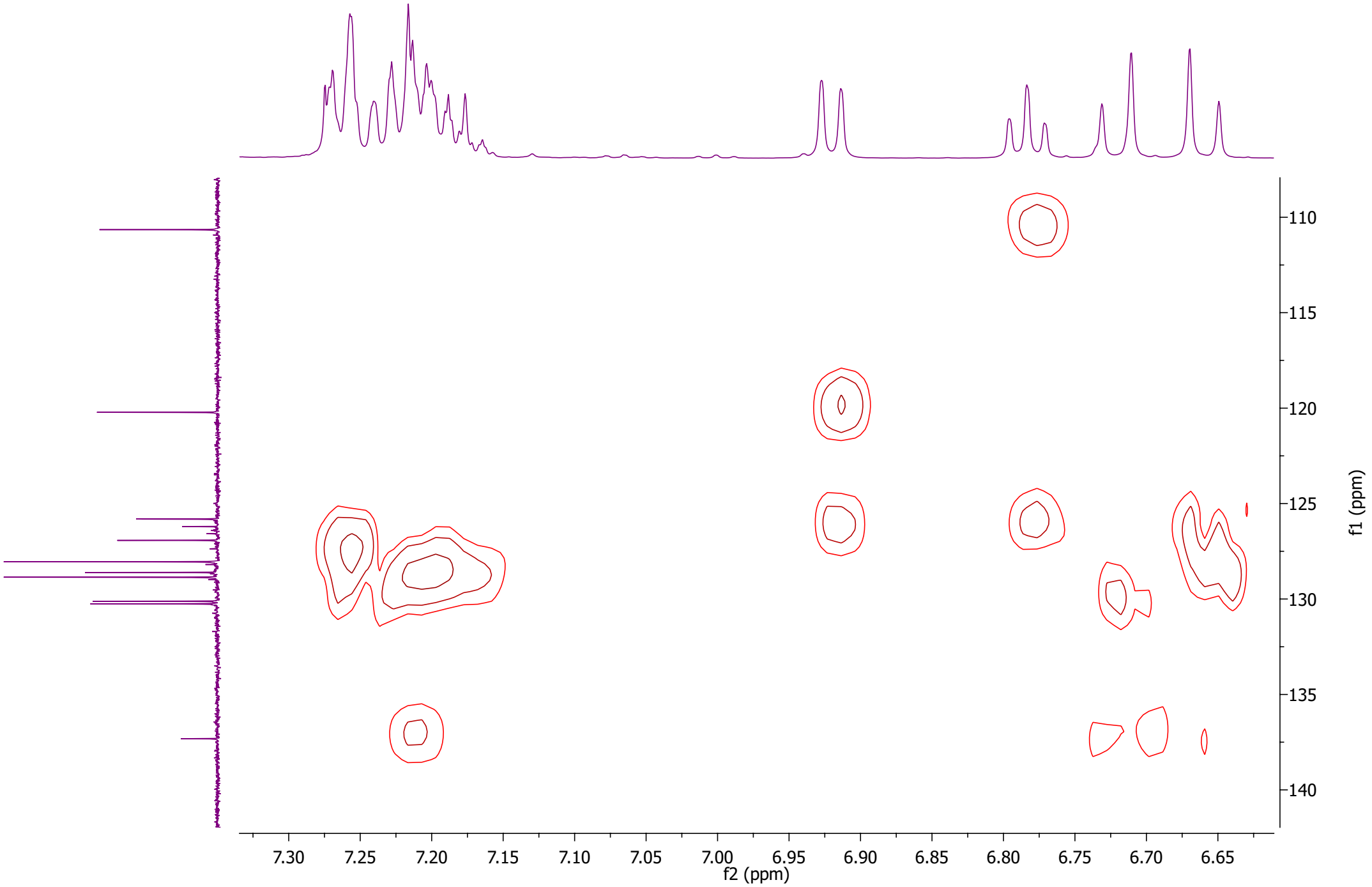
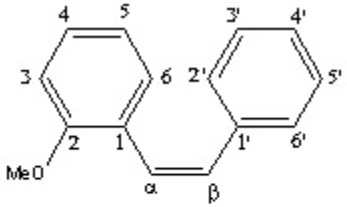
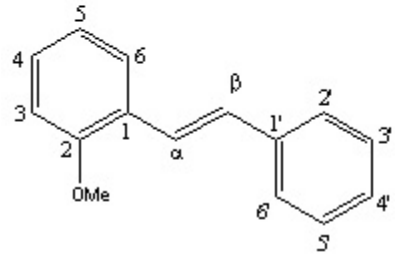


Plate 18 - ^{1}H NMR [$CDCl_3$]: *cis*-2-methoxystilbene (**386**) and *trans*-2-methoxystilbene (**388**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60-7.59 [0.4H, m, H-Ar, (**388**)], 7.54-7.53 [0.8H, m, H-Ar, (**388**)], 7.48 [0.4H, d, *J* = 16.48 Hz, H-*α*, (**388**)], 7.36-7.33 [0.8H, m, H-Ar, (**388**)], 7.26-7.13 [7.8H, m, H-Ar, (**386**) and (**388**)], 7.11 [0.4H, d, *J* = 16.48 Hz, H-*β*, (**388**)], 6.98-6.95 [0.4H, m, H-Ar, (**388**)], 6.91-6.90 [0.2H, m, H-Ar (**388**)], 6.90-6.88 [1H, m, H-3, (**386**)], 6.76-6.74 [1H, m, H-5, (**386**)], 6.69 [1H, d, *J* = 12.26 Hz, H-*α*, (**386**)], 6.63 [1H, d, *J* = 12.26 Hz, H-*β*, (**386**)], 3.88, [1.2H, s, -OMe, (**388**)], 3.82 [3H, s, -OMe, (**386**)]

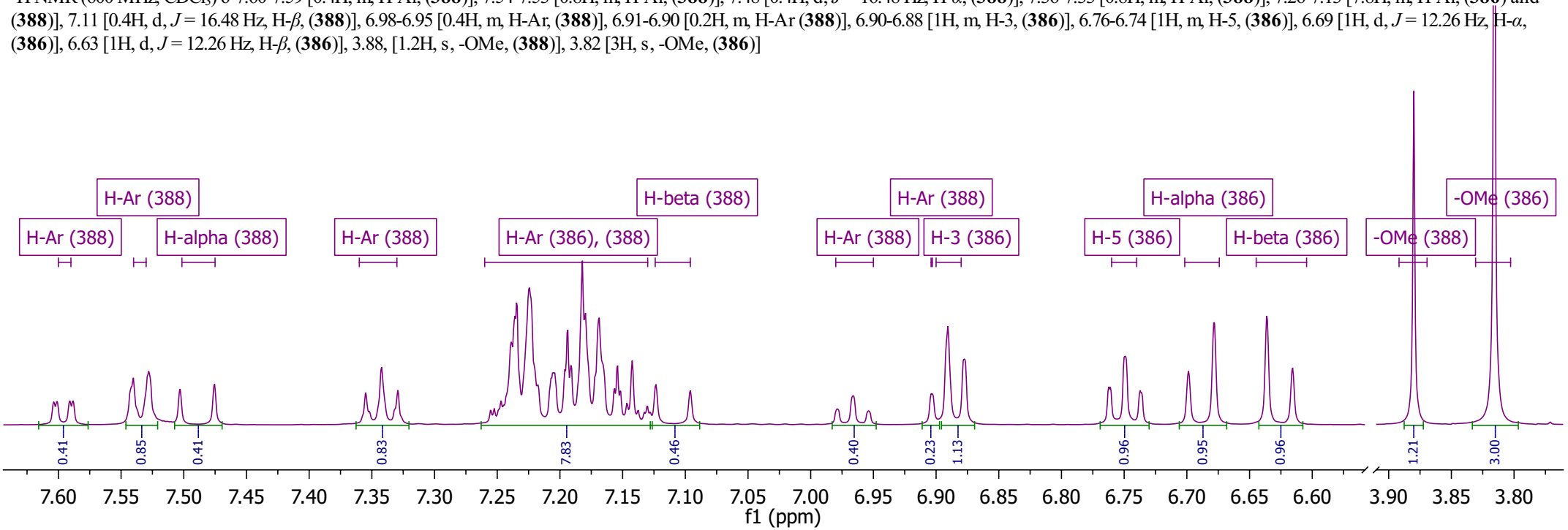
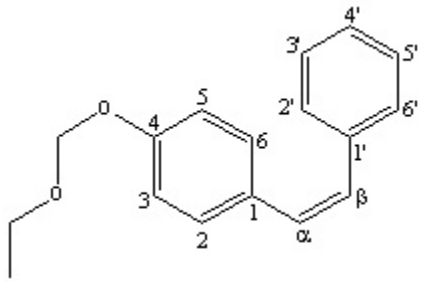
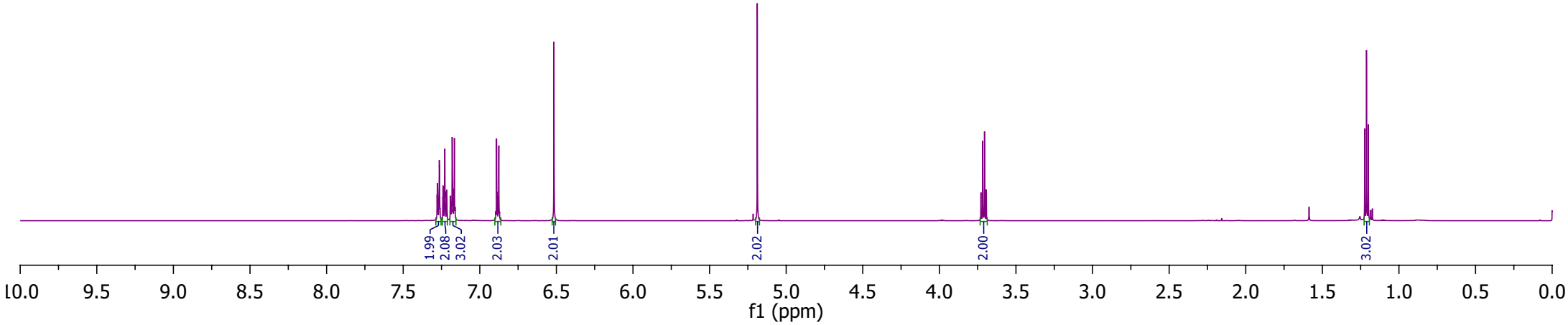


Plate 19a - ^{1}H NMR [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.26 (2H, m, H-2' and H-6'), 7.24-7.22 (2H, m, H-3' and H-5'), 7.19-7.16 (3H, m, H-2, H-6 and H-4'), 6.88 (2H, d, *J* = 8.77 Hz, H-3 and H-5), 6.52 (2H, s, H-*α* and H-*β*), 5.19 (2H, s, -OCH_2O-), 3.71 (2H, q, *J* = 7.05 Hz, -OCH_2-), 1.21 (3H, t, *J* = 7.05 Hz, -CH_3).

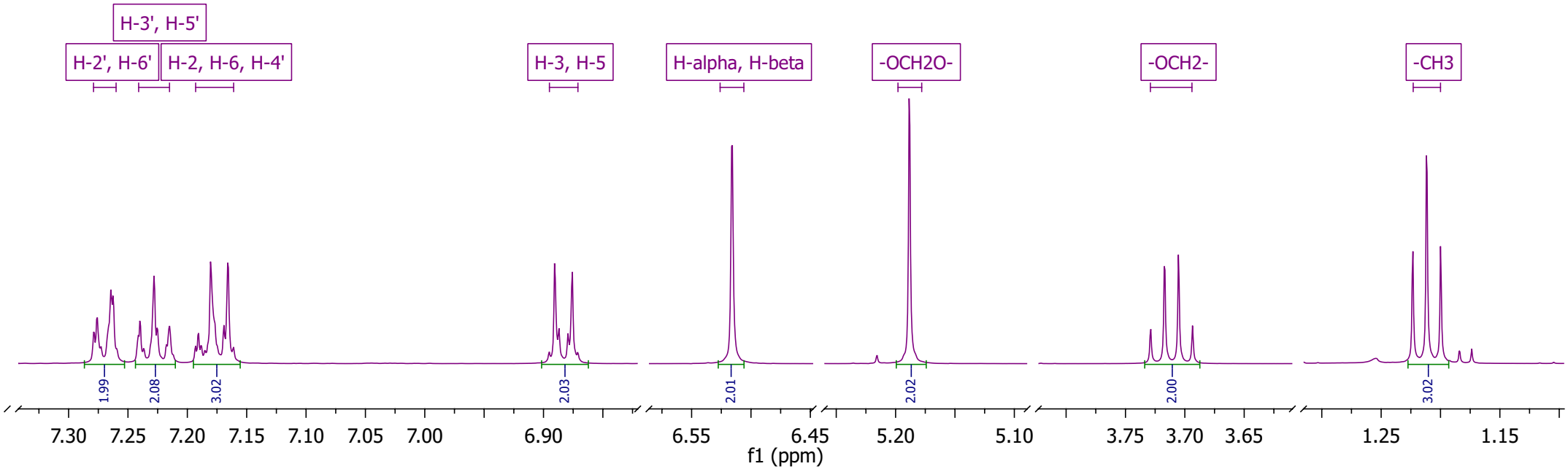
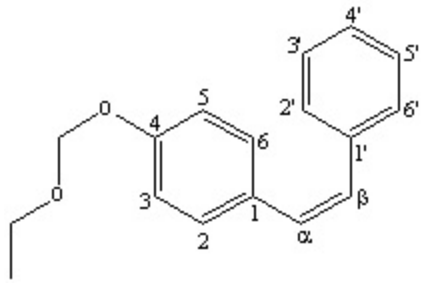
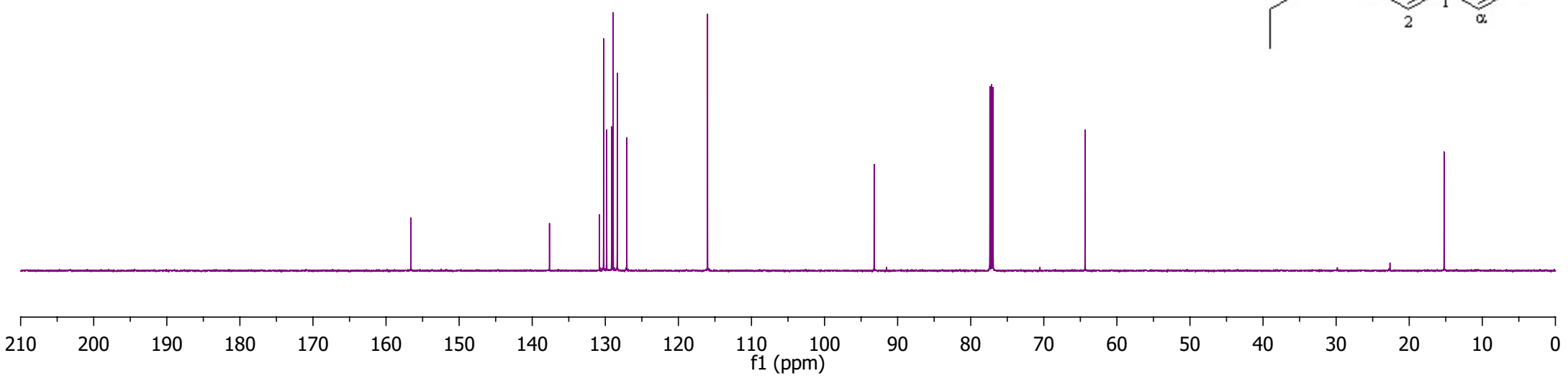


Plate 19b - ^{13}C NMR [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)





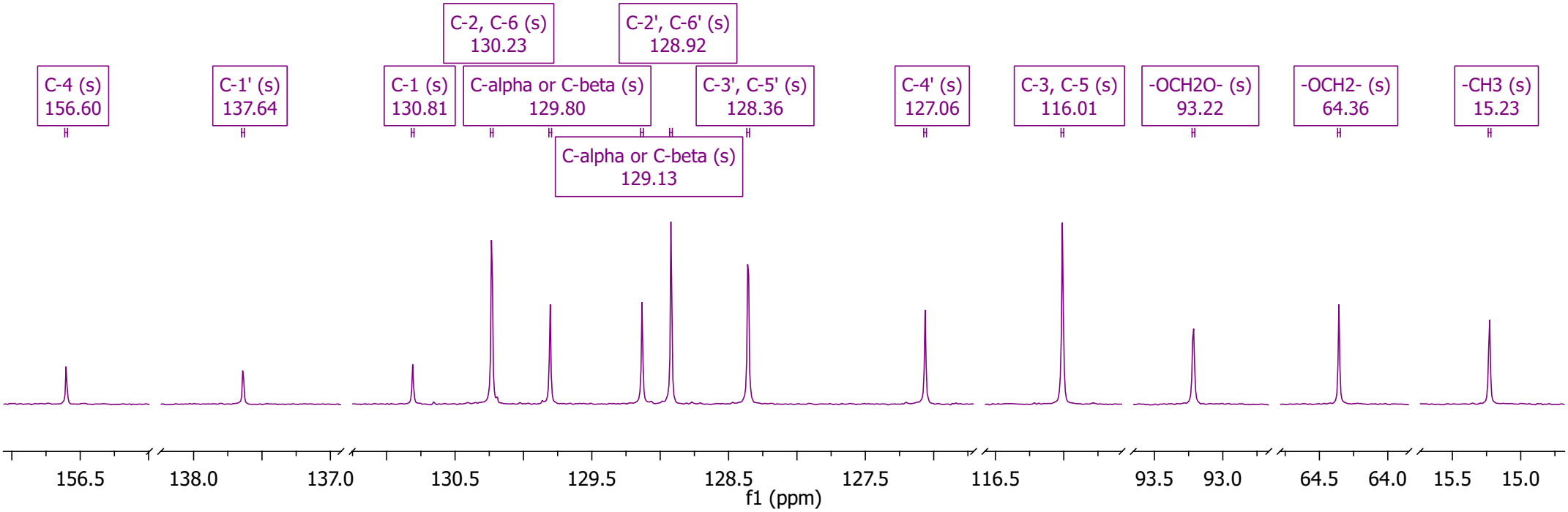


Plate 19c - DEPT [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)

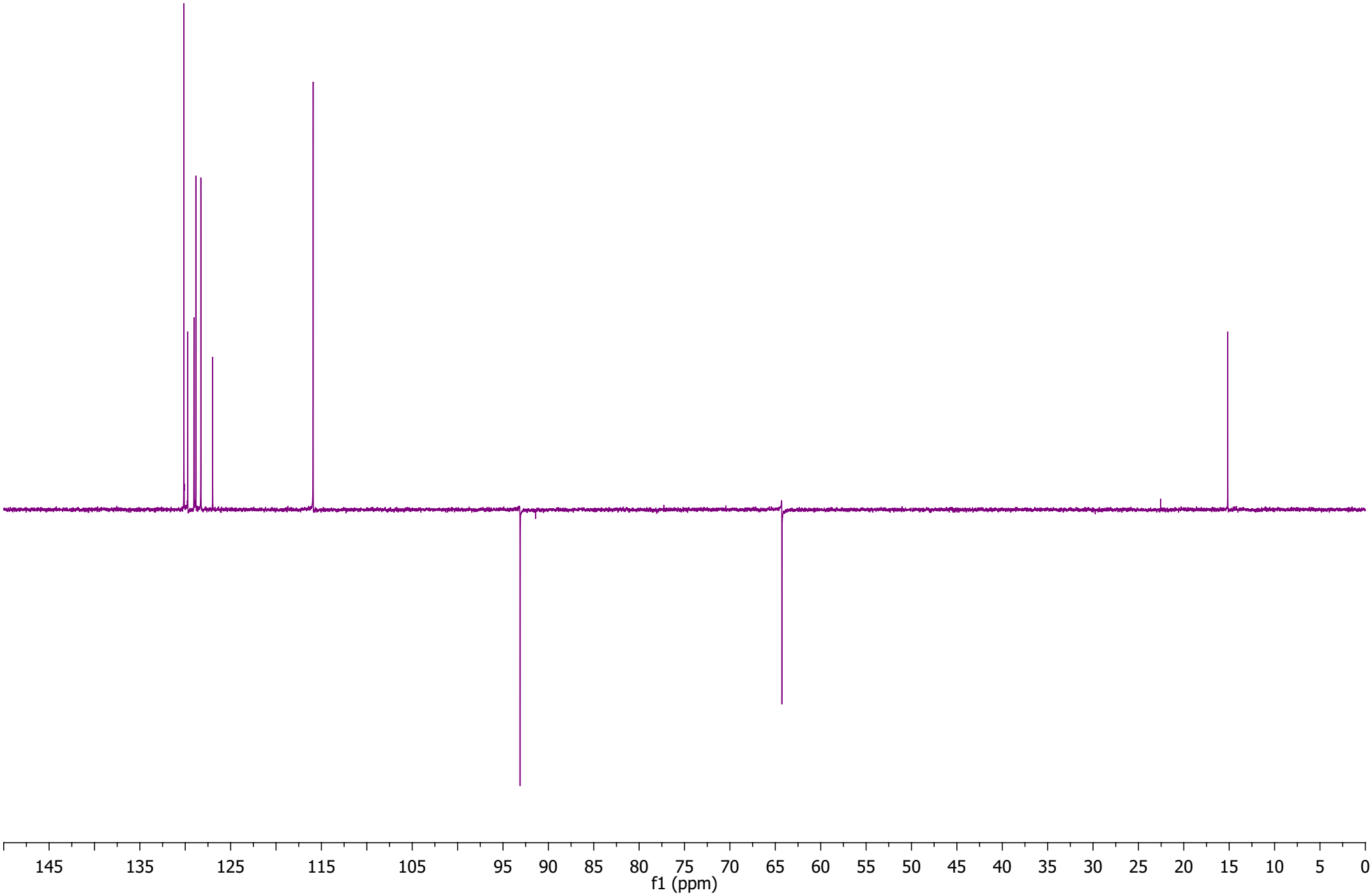


Plate 19d - HSQC [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)

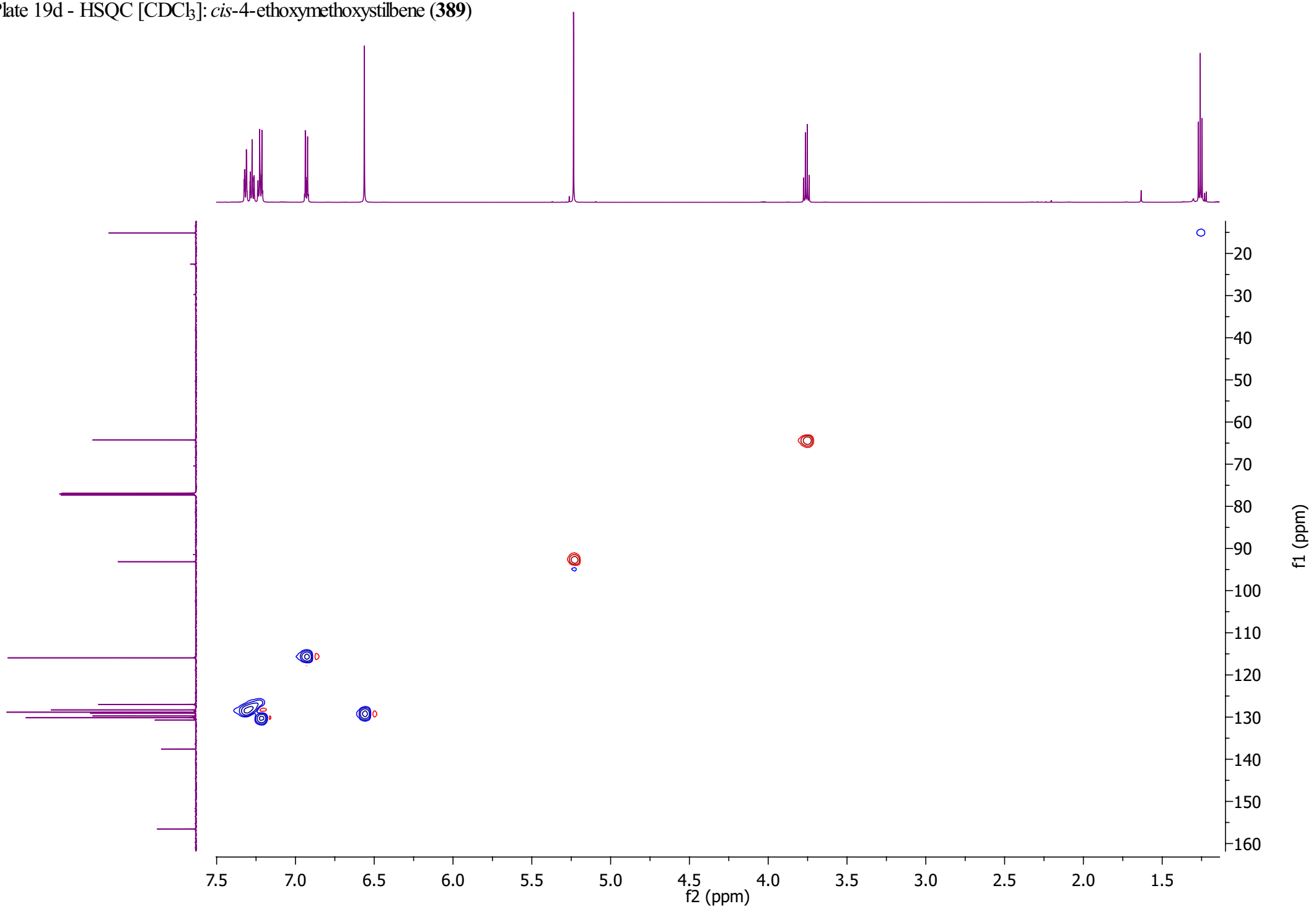


Plate 19e - HSQC (expansion) [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)

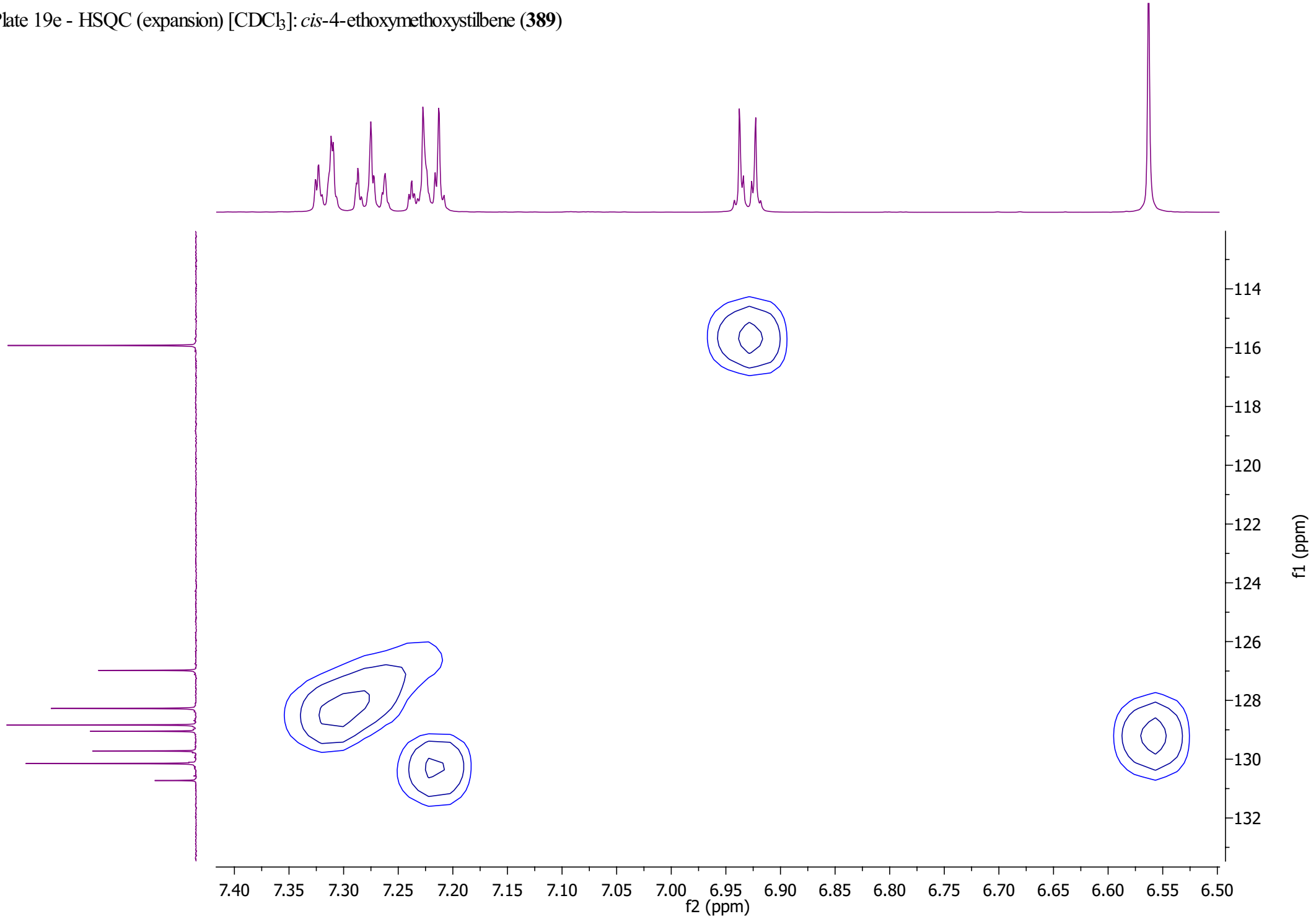


Plate 19f - HMBC [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)

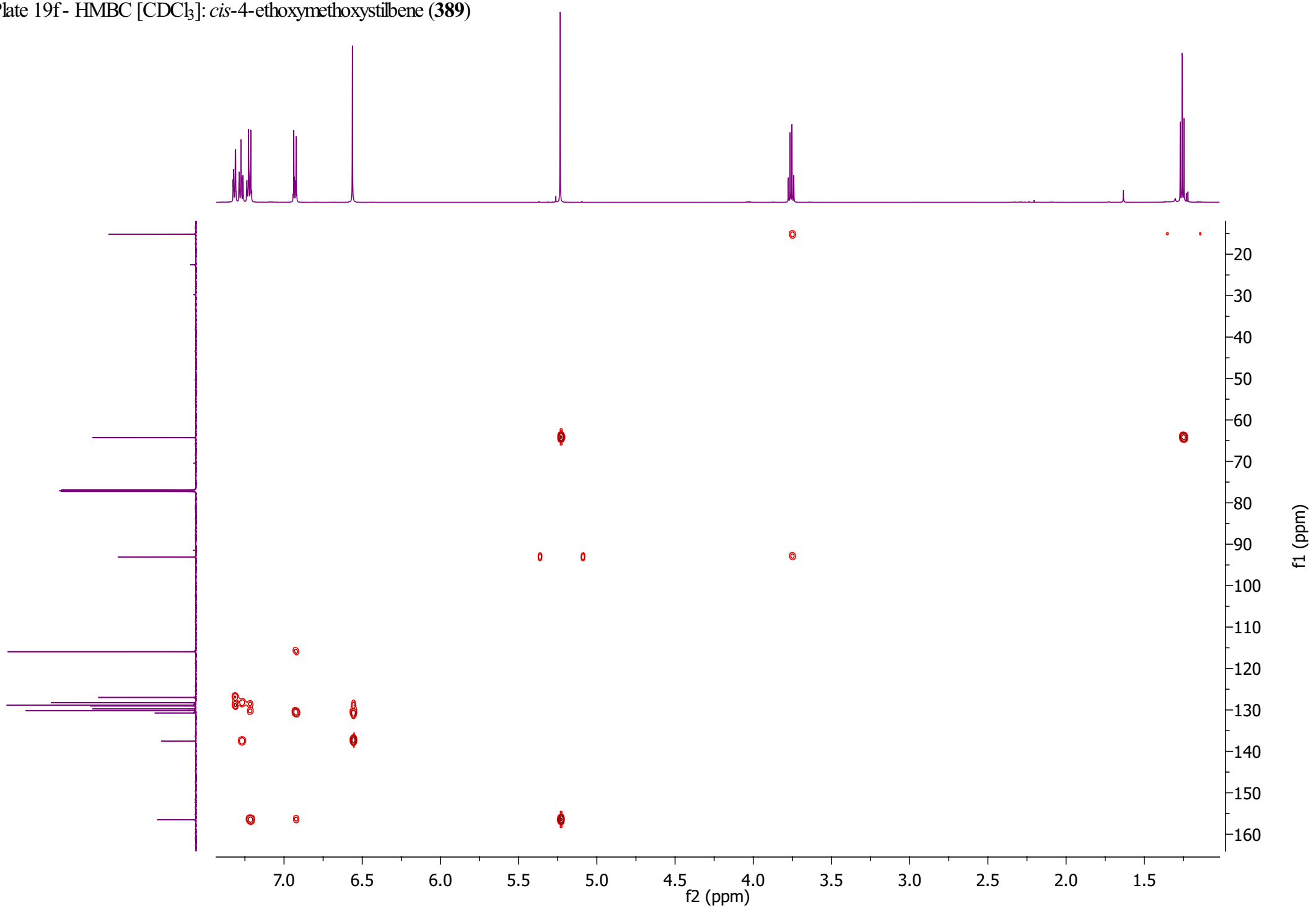


Plate 19g - HMBC (expansion) [$CDCl_3$]: *cis*-4-ethoxymethoxystilbene (**389**)

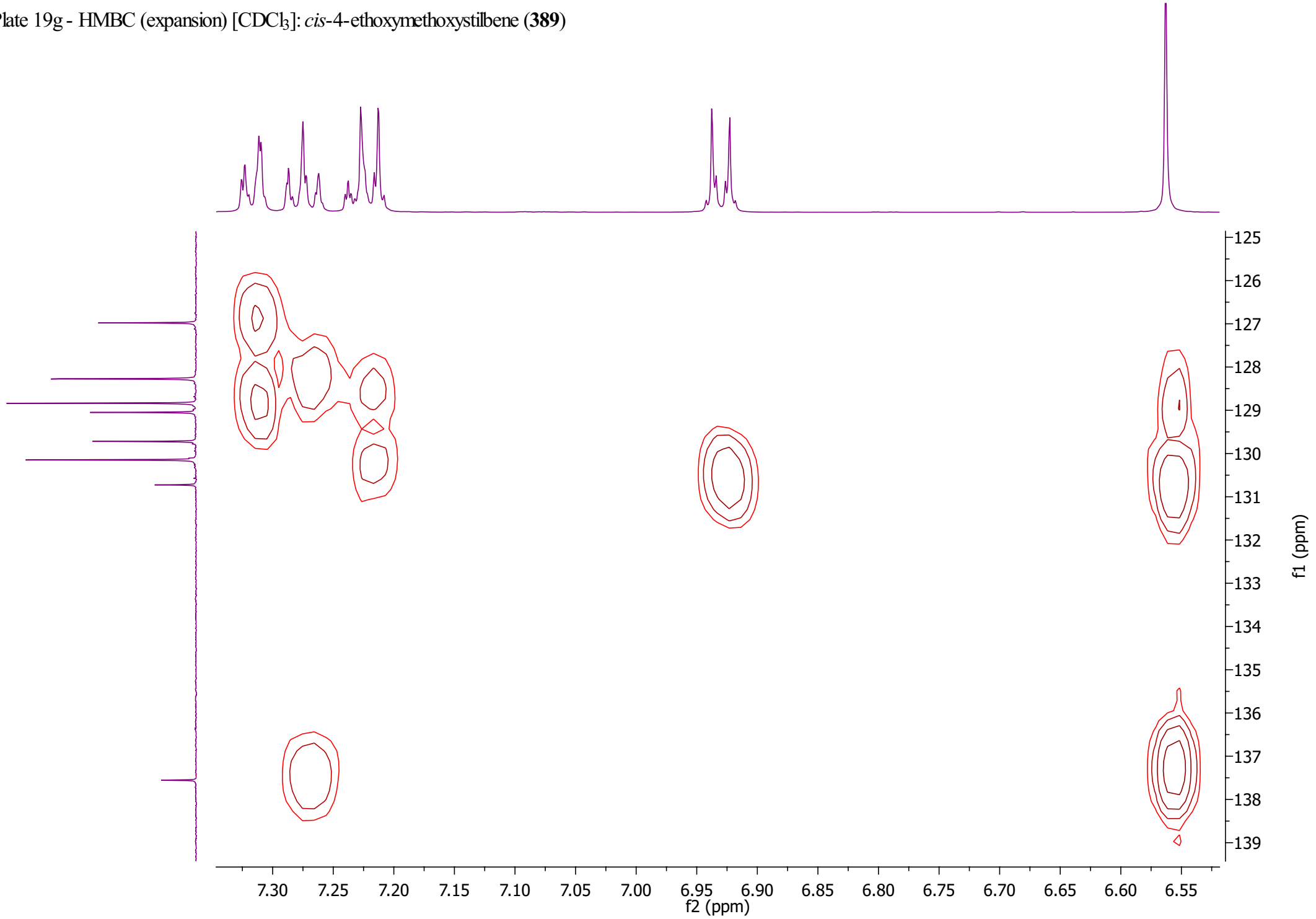
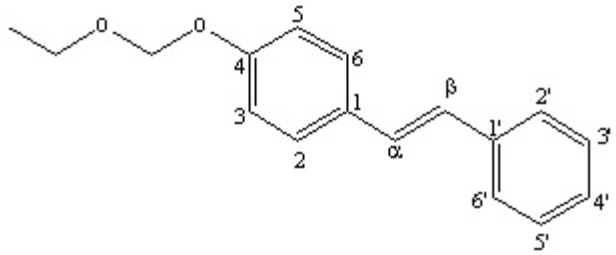
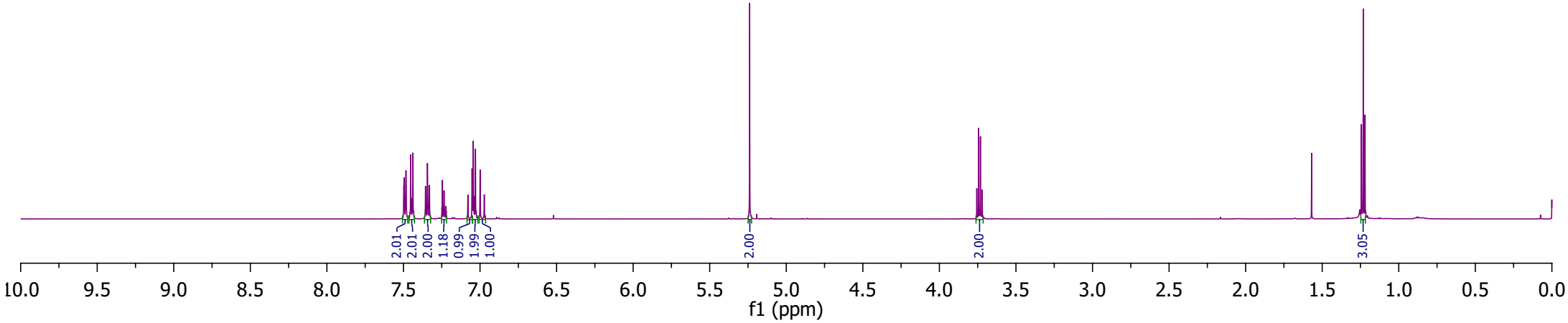


Plate 20a - ^{1}H NMR [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.48 (2H, m, H-2' and H-6'), 7.45 (2H, d, *J* = 8.68 Hz, H-2 and H-6), 7.36-7.33 (2H, m, H-3' and H-5'), 7.25-7.22 (1H, m, H-4'), 7.07 (1H, d, *J* = 16.32 Hz, H-*α*), 7.04 (2H, d, *J* = 8.68 Hz, H-3 and H-5), 6.99 (1H, d, *J* = 16.32 Hz, H-*β*), 5.24 (2H, s, -OCH_2O-), 3.74 (2H, q, *J* = 7.08 Hz, -OCH_2-), 1.23 (3H, t, *J* = 7.08 Hz, -CH_3)

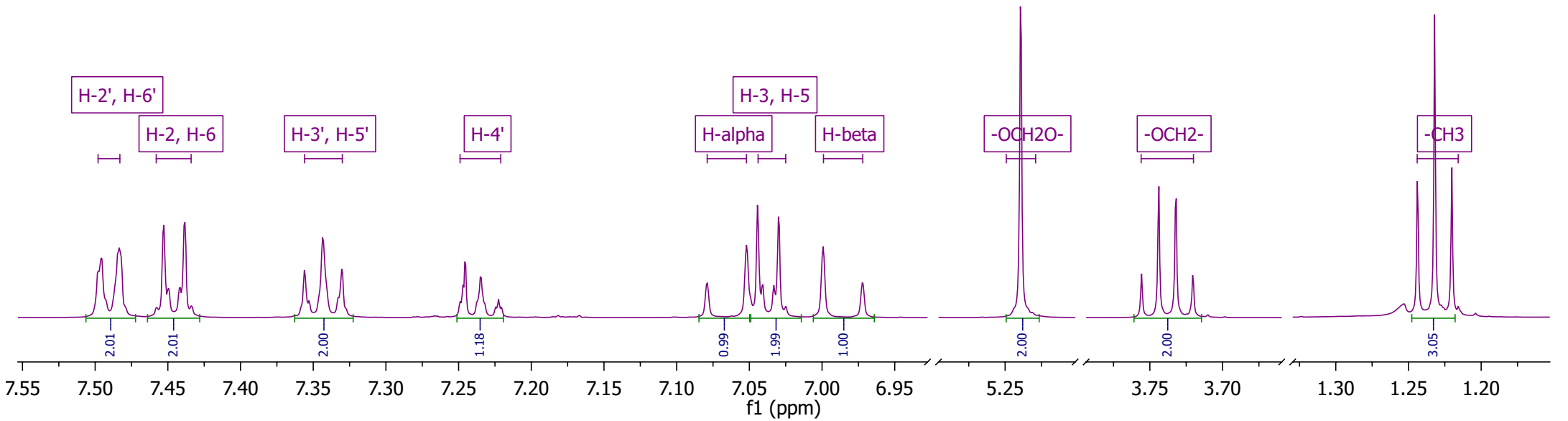
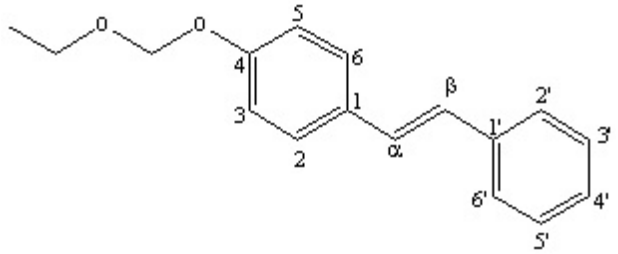
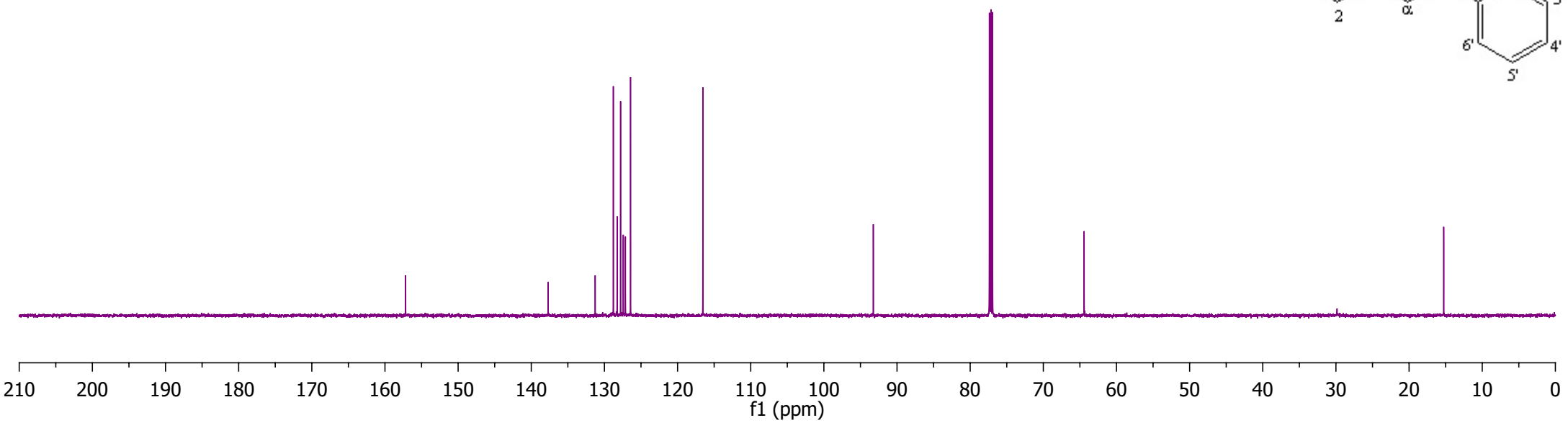


Plate 20b - ^{13}C NMR [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)





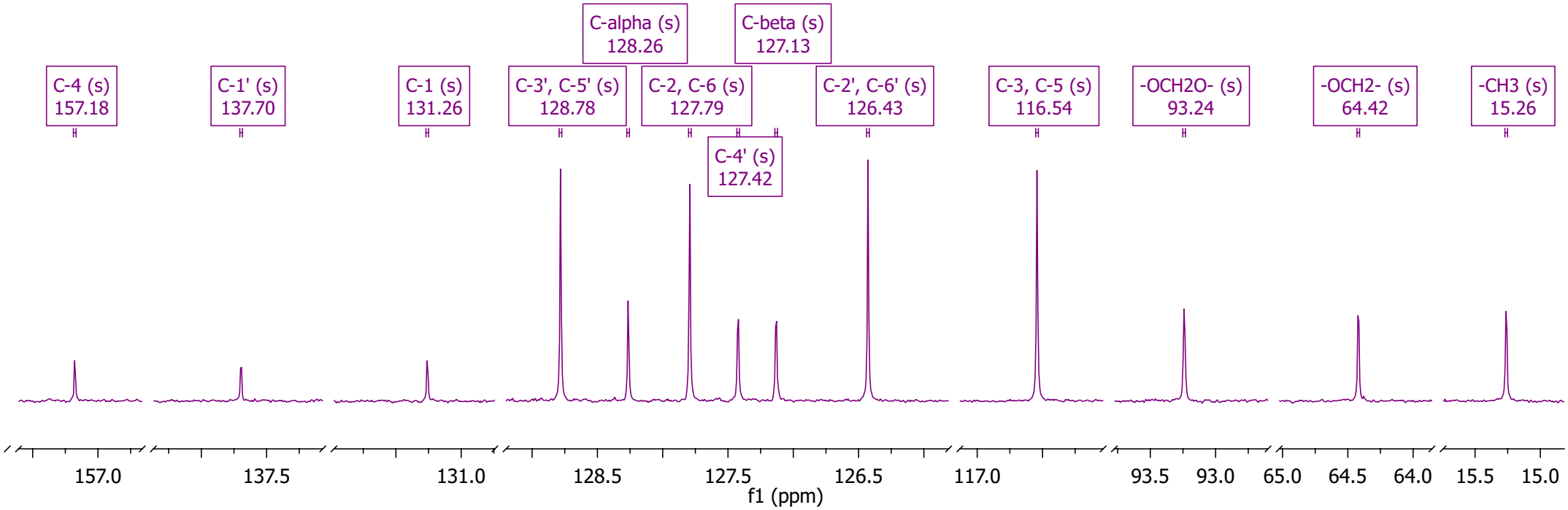


Plate 20c - DEPT [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)

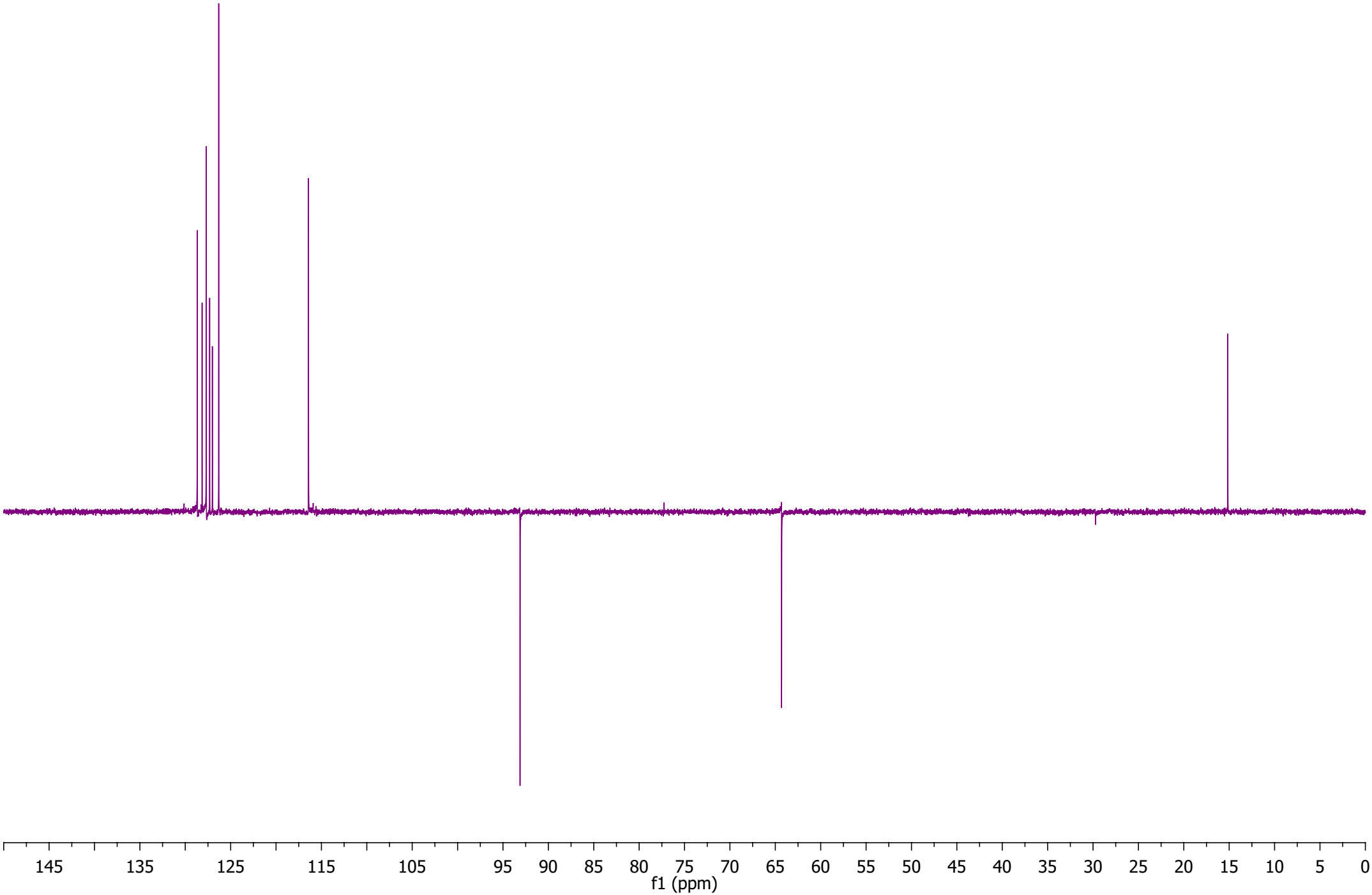


Plate 20d - HSQC [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)

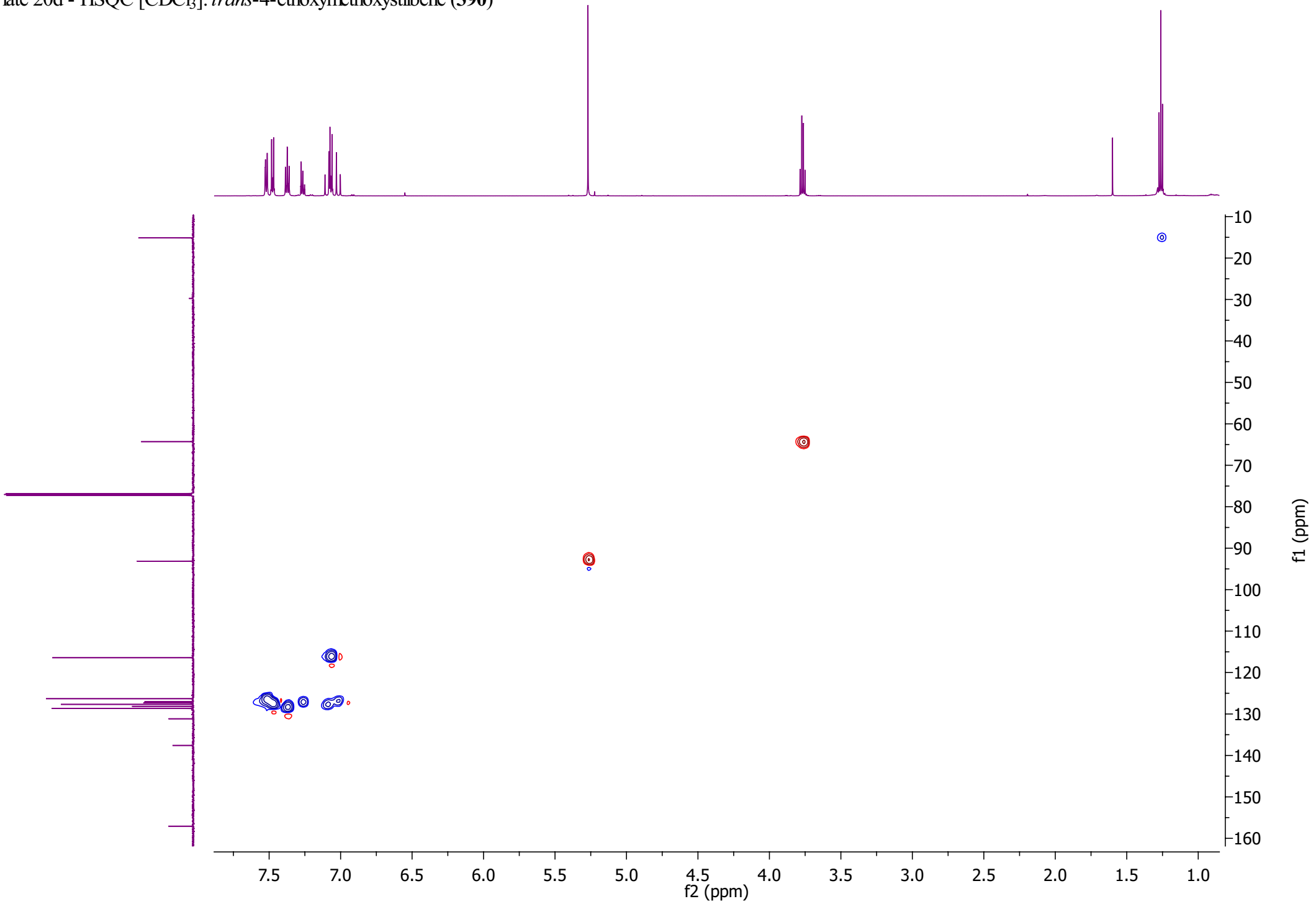


Plate 20e - HSQC (expansion) [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)

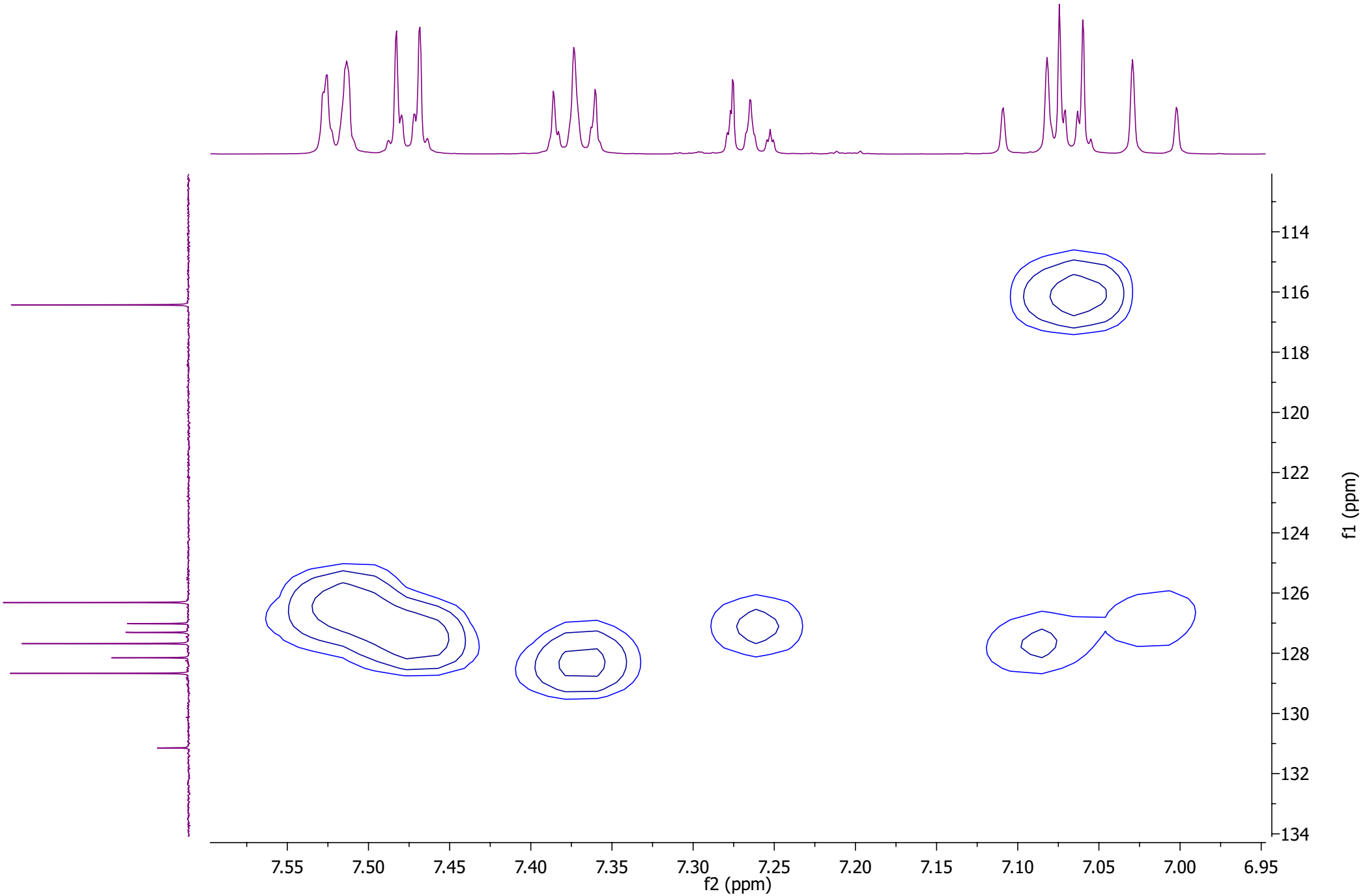


Plate 20f - HMBC [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)

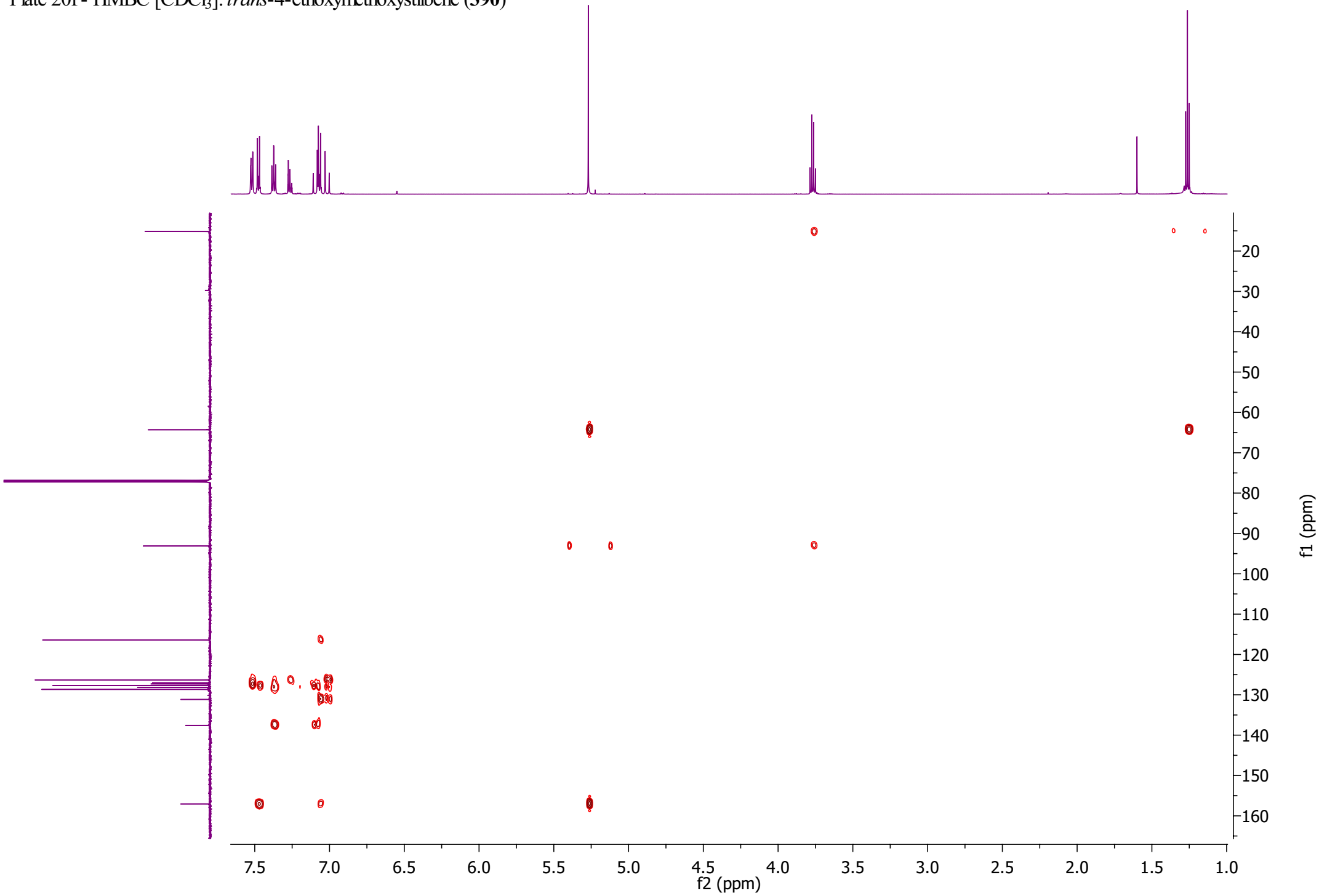


Plate 20g - HMBC (expansion) [$CDCl_3$]: *trans*-4-ethoxymethoxystilbene (**390**)

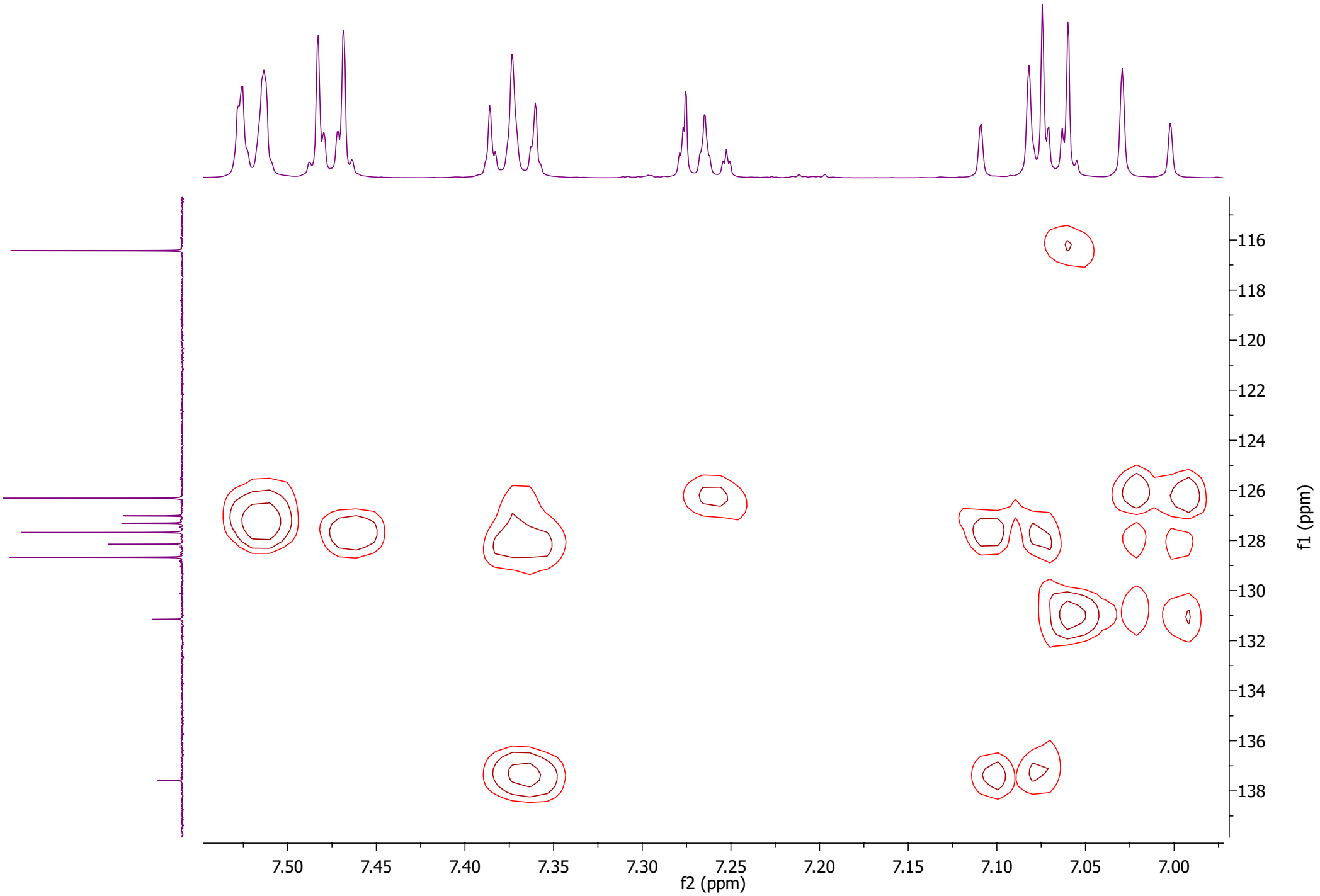
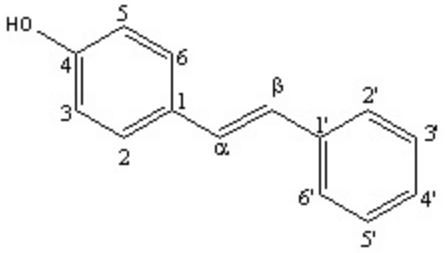


Plate 21a - ^{1}H NMR [$(CD_3)_2CO$]: *trans*-4-hydroxystilbene (**394**)



^{1}H NMR (600 MHz, Acetone) δ 6.53-6.52 (2H, m, H-2' and H-6'), 6.44 (2H, d, *J* = 8.54 Hz, H-2 and H-6), 6.33-6.31 (2H, m, H-3' and H-5'), 6.21-6.19 (1H, m, H-4'), 6.15 (1H, d, *J* = 16.4 Hz, H-*α*), 6.03 (1H, d, *J* = 16.4 Hz, H-*β*), 5.83 (2H, d, *J* = 8.54 Hz, H-3 and H-5)

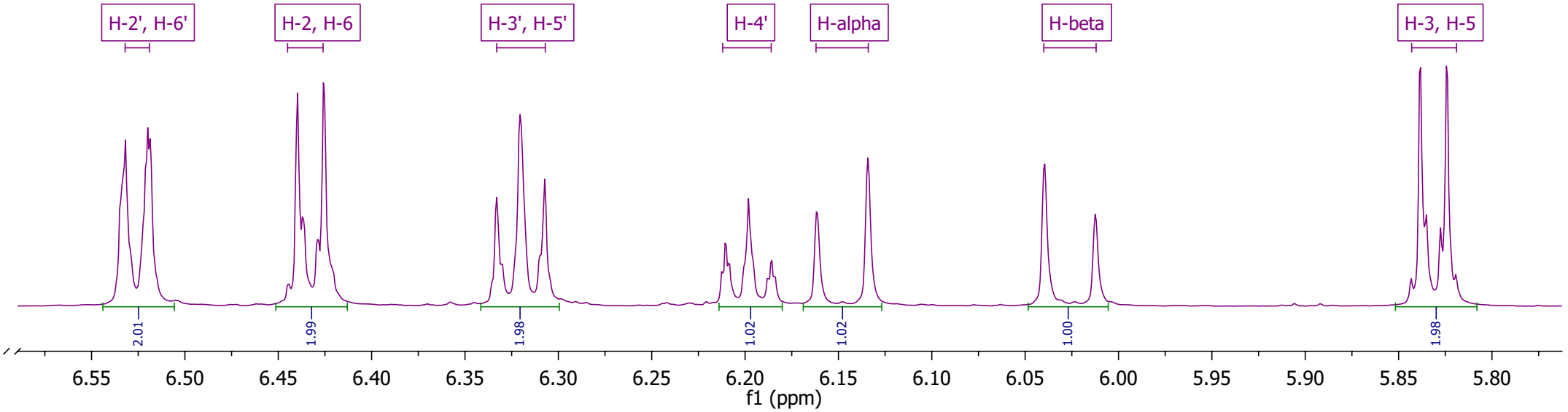
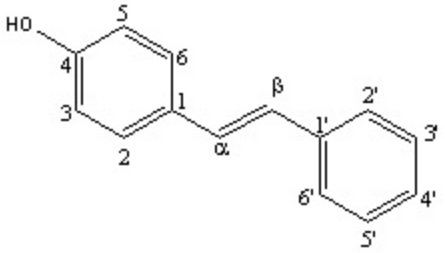


Plate 21b - ^{13}C NMR [$(CD_3)_2CO$]: *trans*-4-hydroxystilbene (**394**)



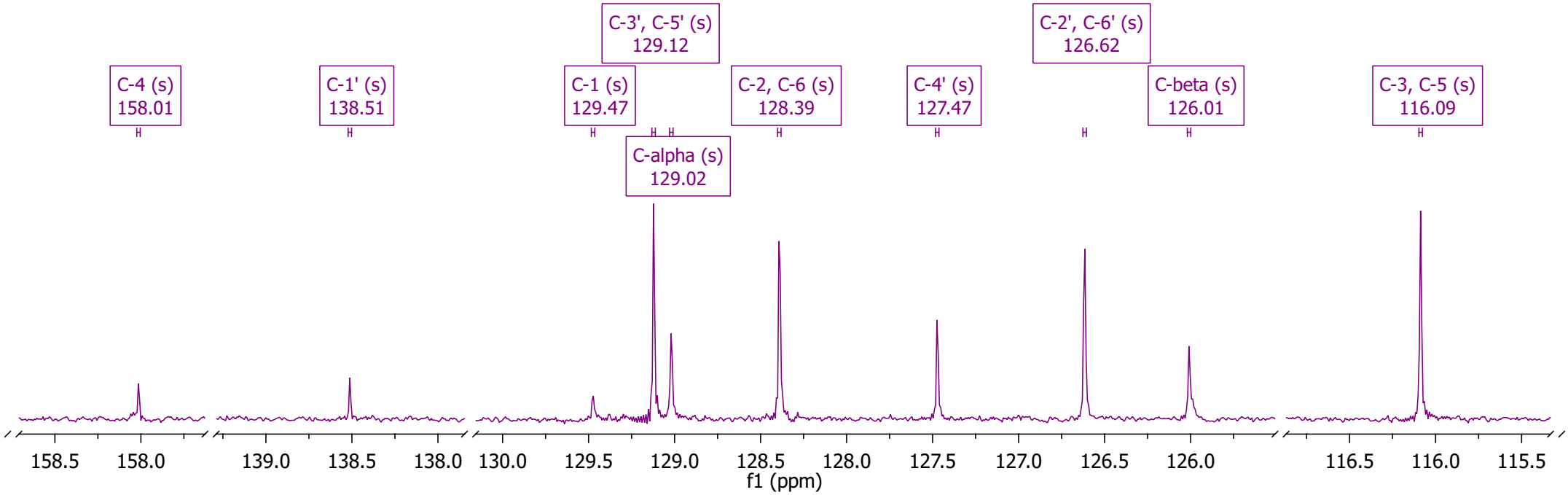


Plate 21c - DEPT [$(CD_3)_2CO$]: *trans*-4-hydroxystilbene (**394**)

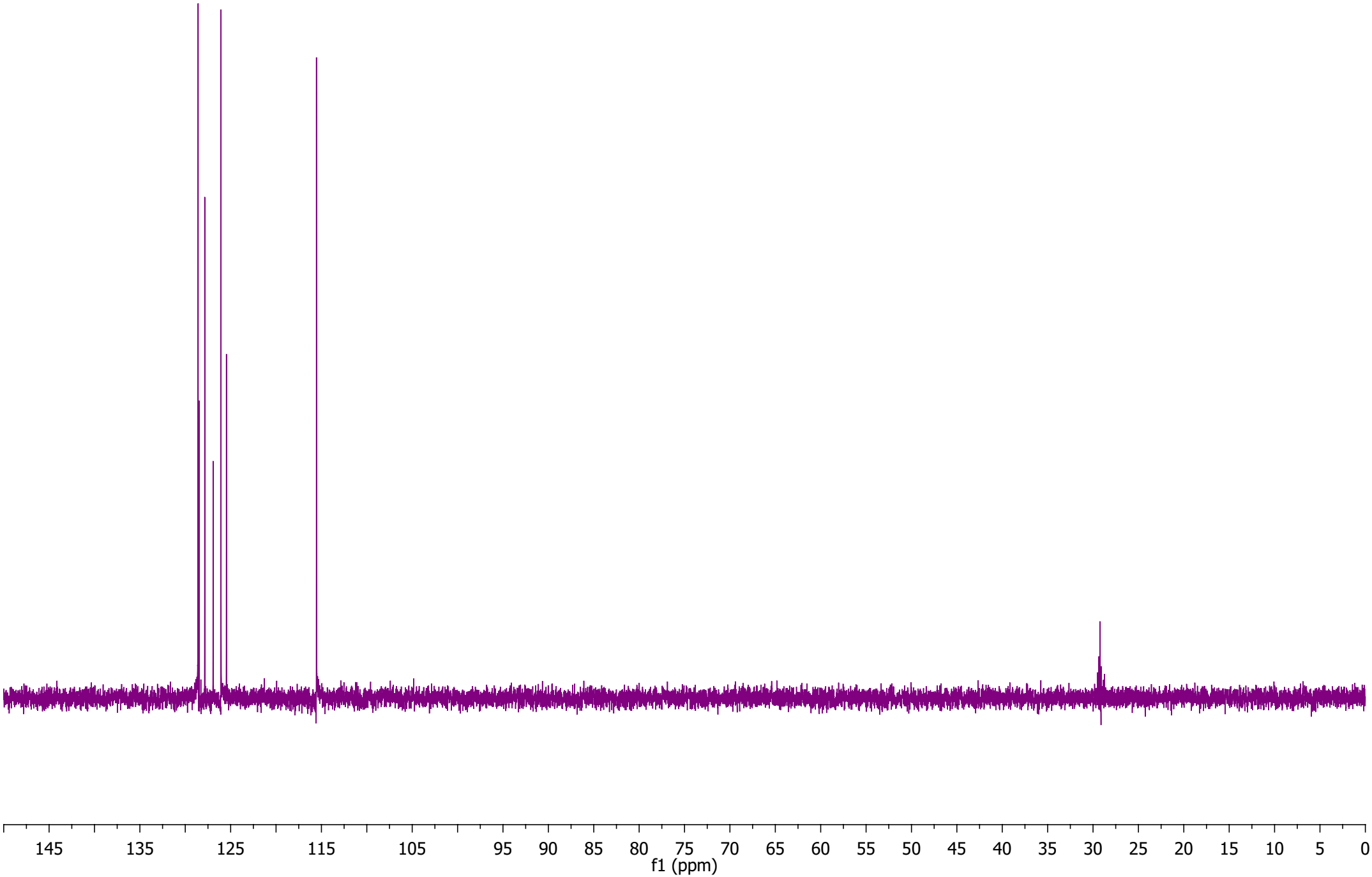


Plate 21d - HSQC [$(CD_3)_2CO$]: *trans*-4-hydroxystilbene (**394**)

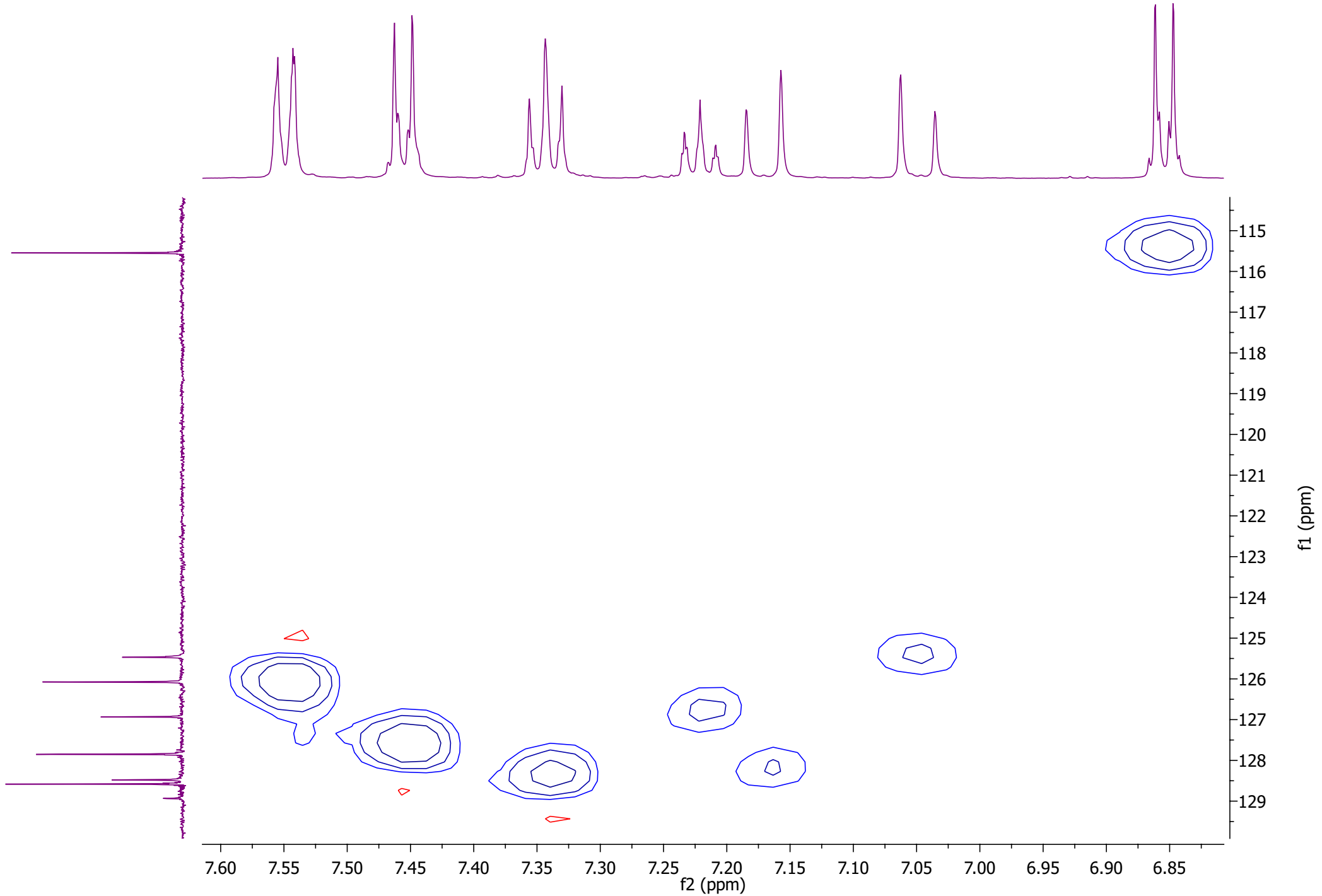


Plate 21e - HMBC [$(CD_3)_2CO$]: *trans*-4-hydroxystilbene (**394**)

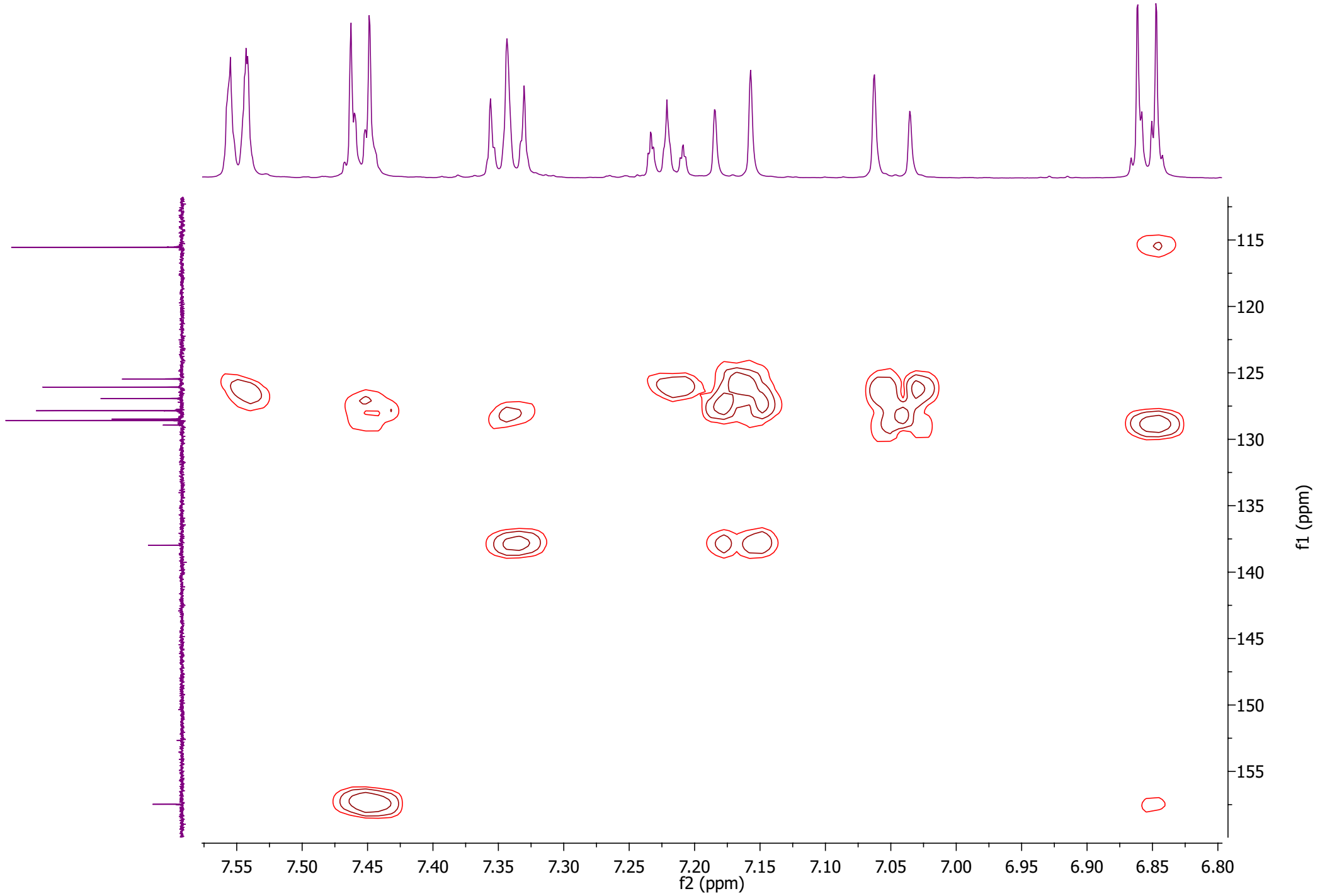
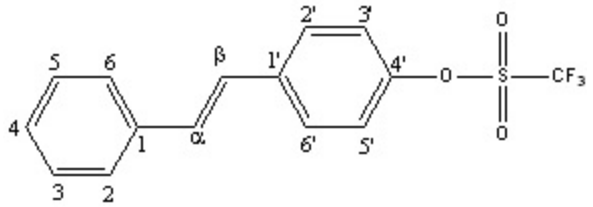
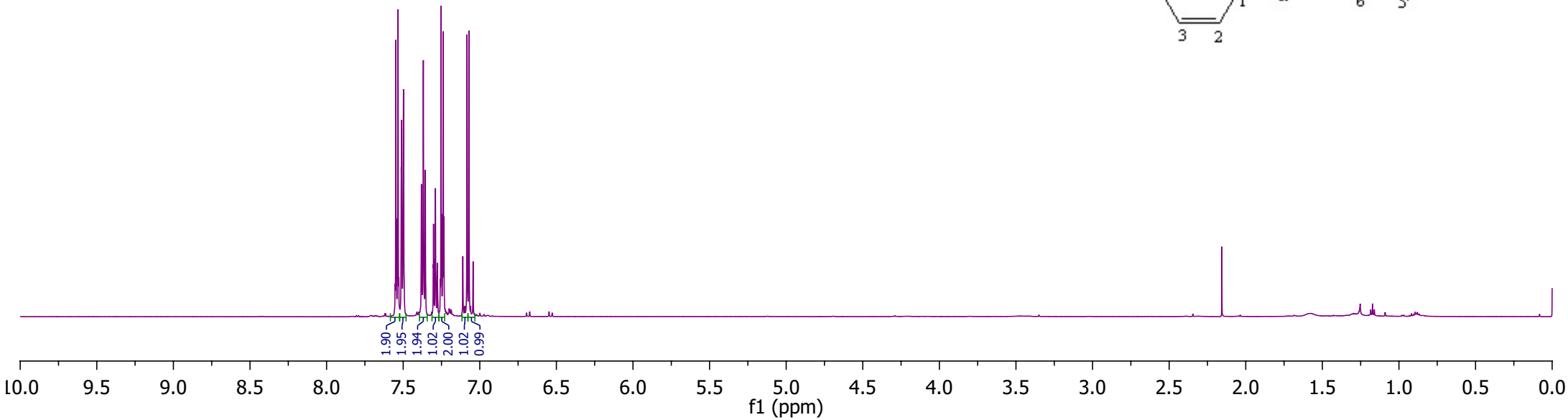


Plate 22a - ^{1}H NMR [$CDCl_3$]: *trans*-4'-trifluoromethanesulfonyloxystilbene (**395**)





^{1}H NMR (600 MHz, $CDCl_3$) δ7.53 (2H, d, *J* = 8.76 Hz, H-2' and H-6'), 7.51-7.50 (2H, m, H-2 and H-6), 7.38-7.36 (2H, m, H-3 and H-5), 7.30-7.28 (1H, m, H-4), 7.25 (2H, d, *J* = 8.76 Hz, H-3' and H-5'), 7.10 (1H, d, *J* = 16.38 Hz, H-*α*), 7.08 (1H, d, *J* = 16.38 Hz, H-*β*)

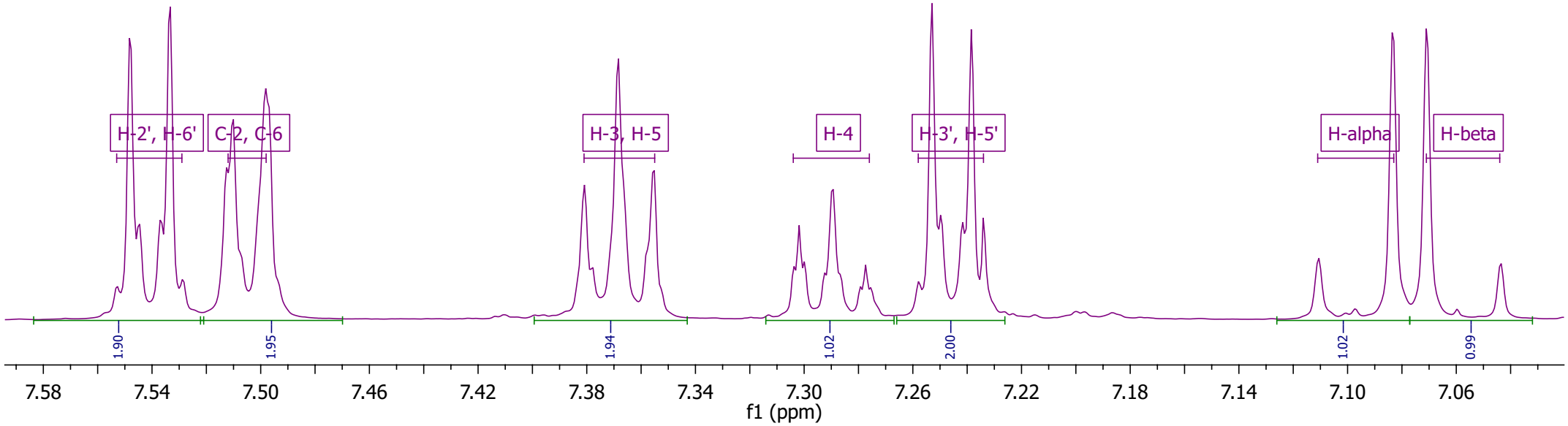
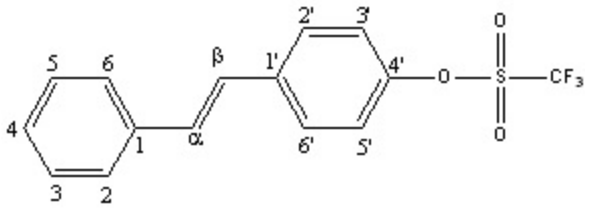
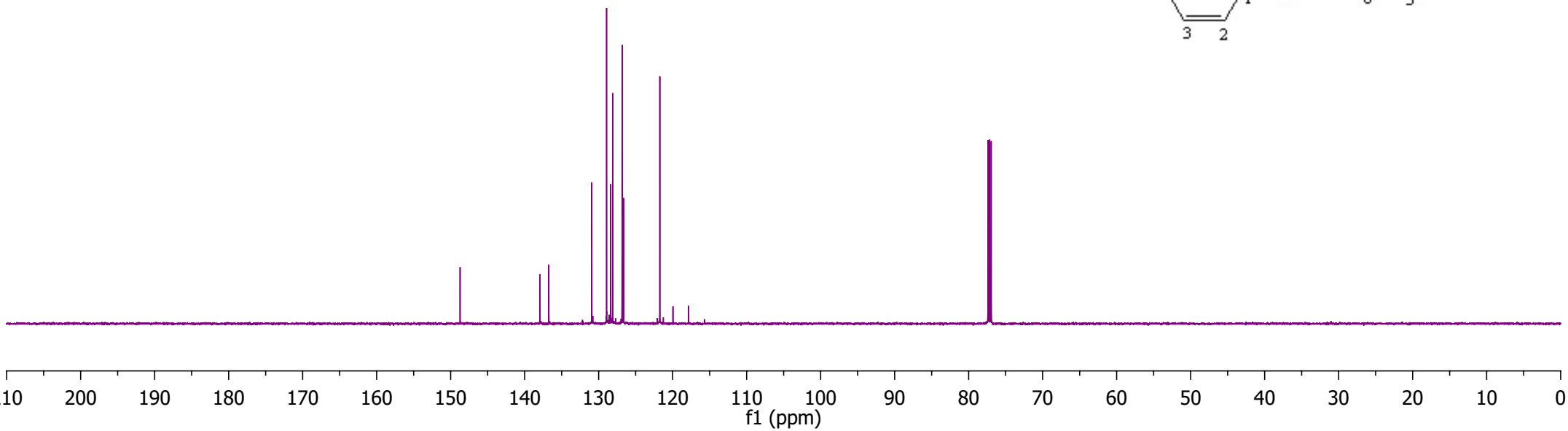


Plate 22b - ^{13}C NMR [$CDCl_3$]: *trans*-4'-trifluoromethanesulfonyloxystilbene (**395**)





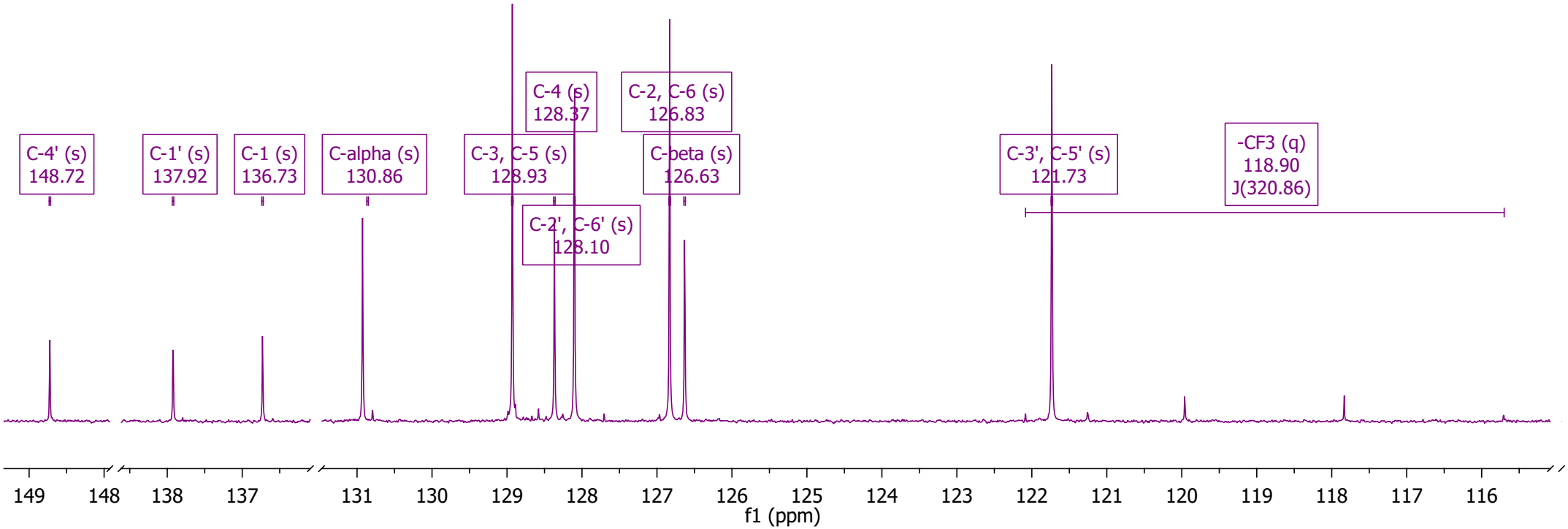


Plate 22c - DEPT [$CDCl_3$]: *trans*-4'-trifluoromethanesulfonyloxystilbene (**395**)

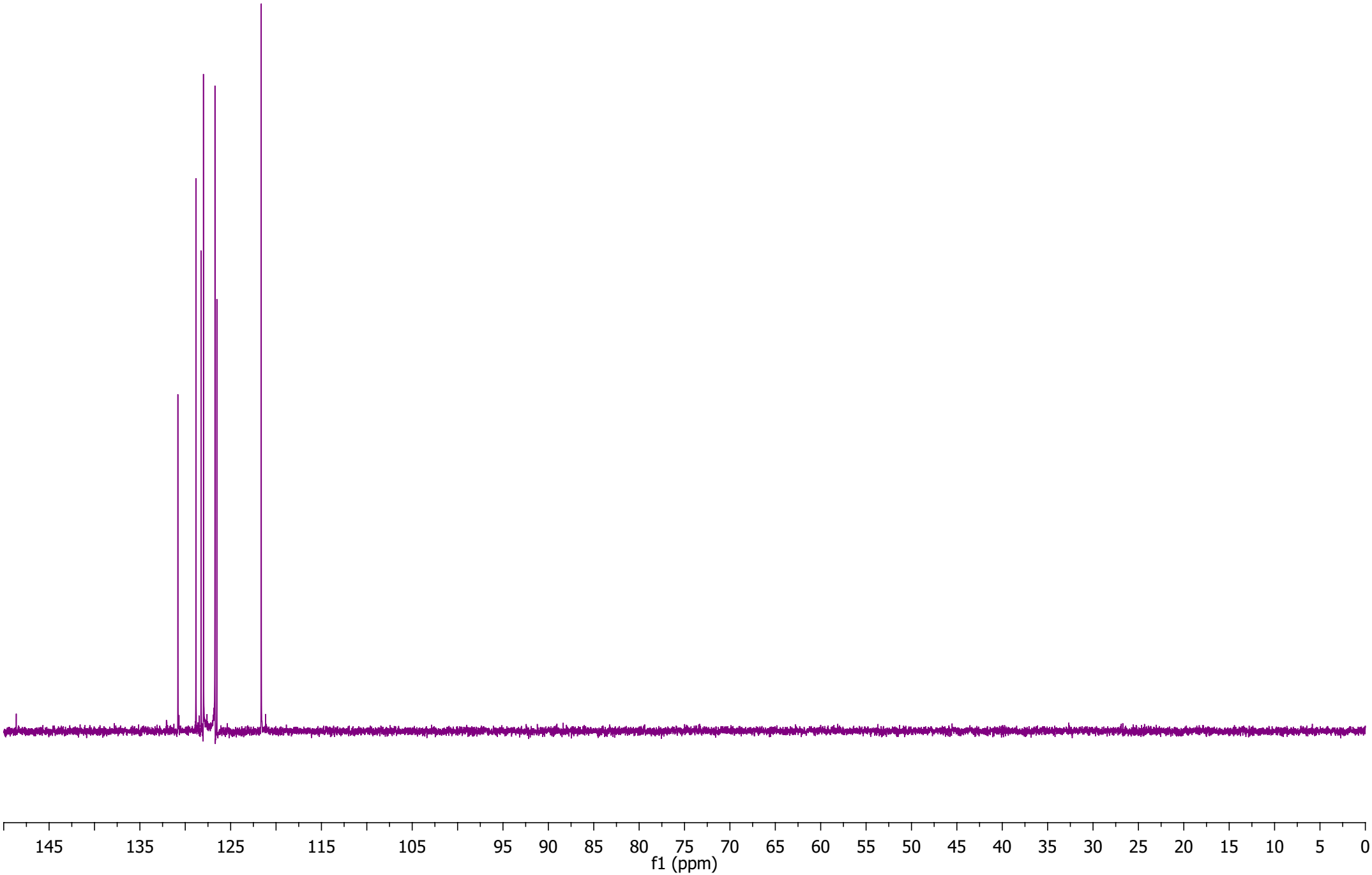


Plate 22d - HSQC [$CDCl_3$]: *trans*-4'-trifluoromethanesulfonyloxystilbene (**395**)

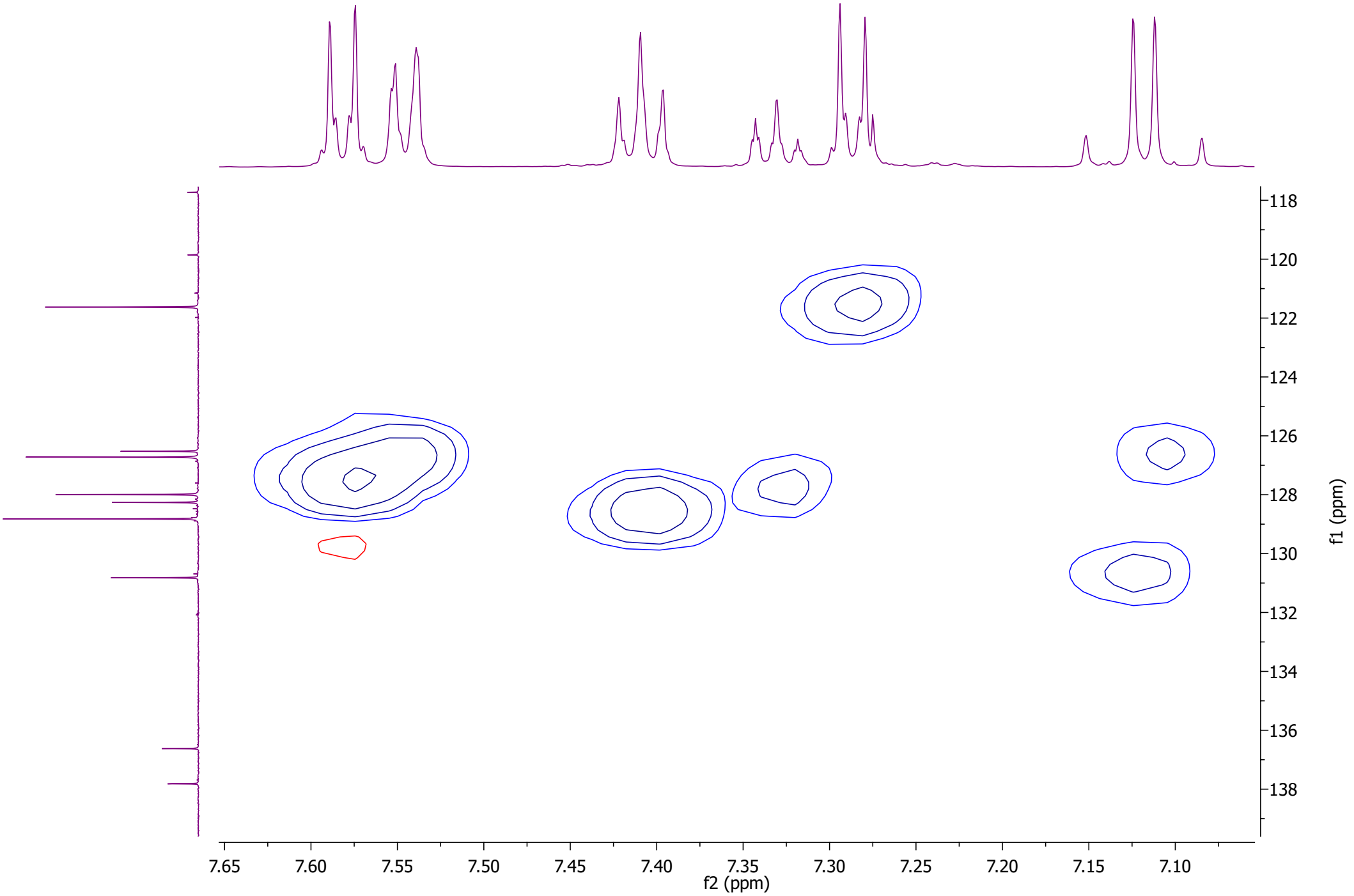


Plate 22e - HMBC [$CDCl_3$]: *trans*-4'-trifluoromethanesulfonyloxystilbene (**395**)

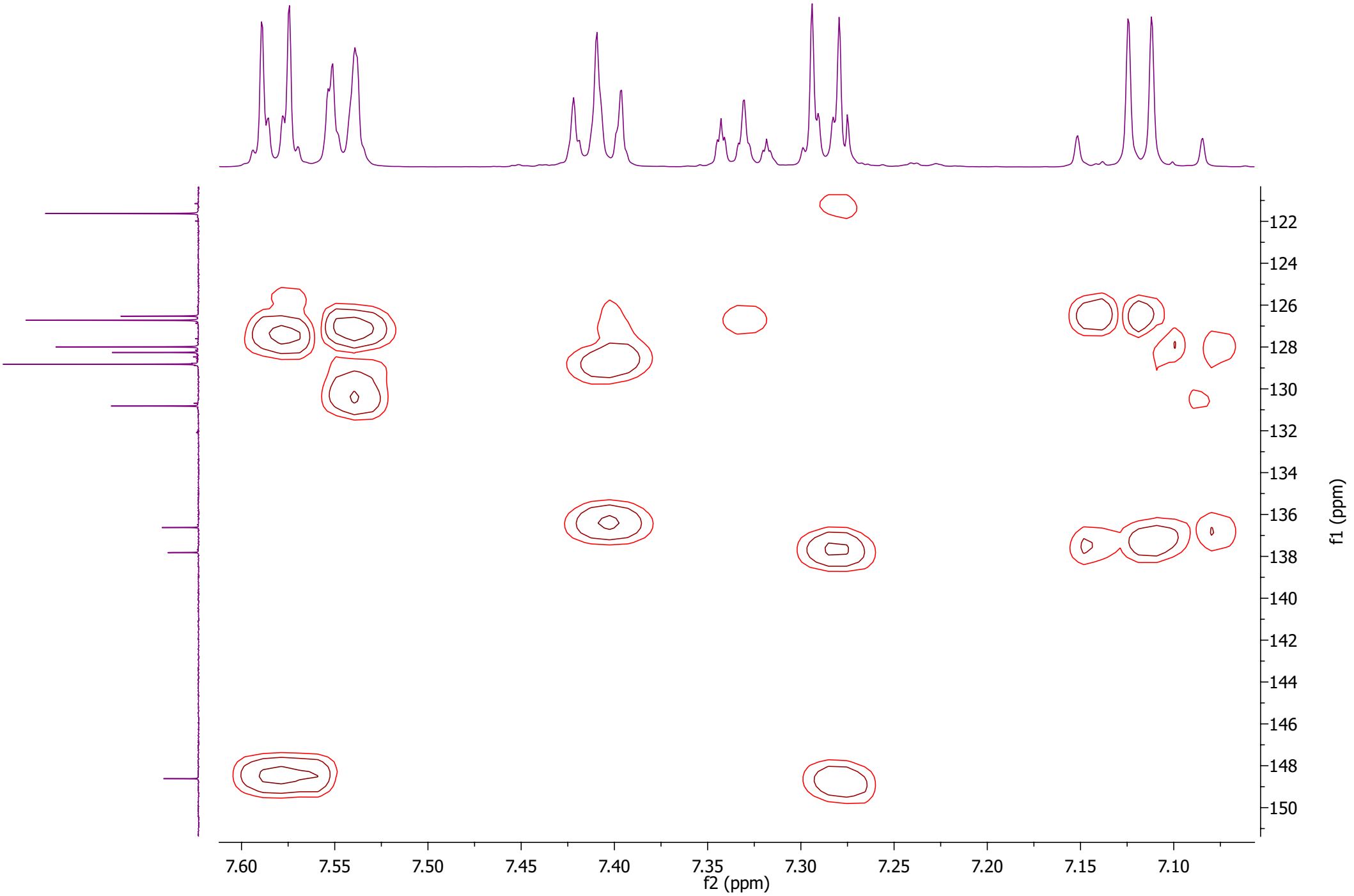


Plate 22f - HMBC (expansion) [$CDCl_3$]: *trans*-4'-trifluoromethanesulfonyloxystilbene (**395**)

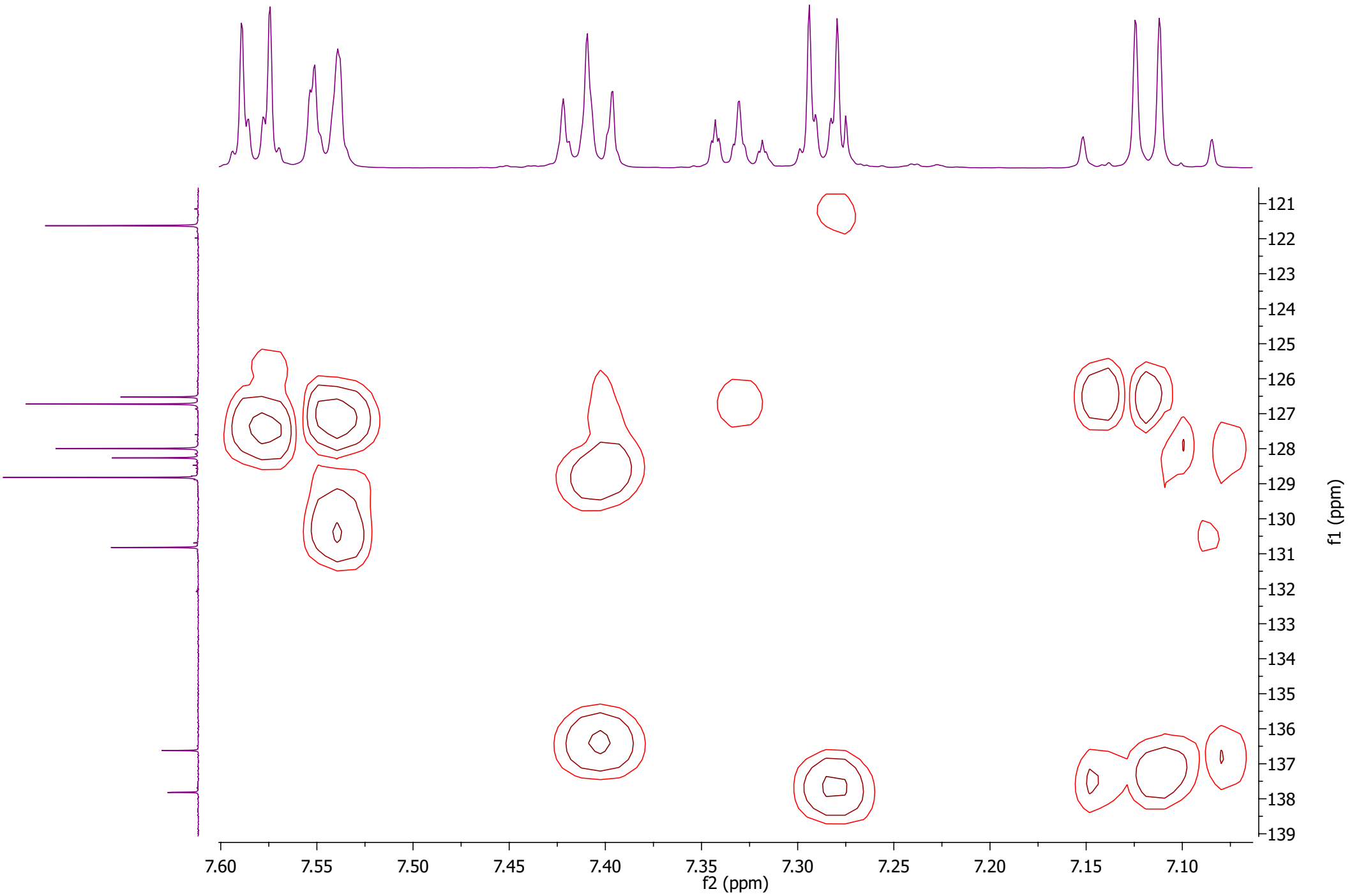
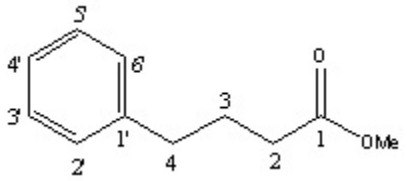


Plate 23a - ^{1}H NMR [$CDCl_3$]: methyl 4-phenylbutanoate (**401**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.28 (2H, m, H-3' and H-5'), 7.21-7.18 (3H, m, H-2', H-4' and H-6'), 3.67 (3H, s, -OMe), 2.66 (2H, t, J = 7.56 Hz, H-4), 2.34 (2H, t, J = 7.56 Hz, H-2), 1.97 (2H, p, J = 7.56 Hz, H-3).

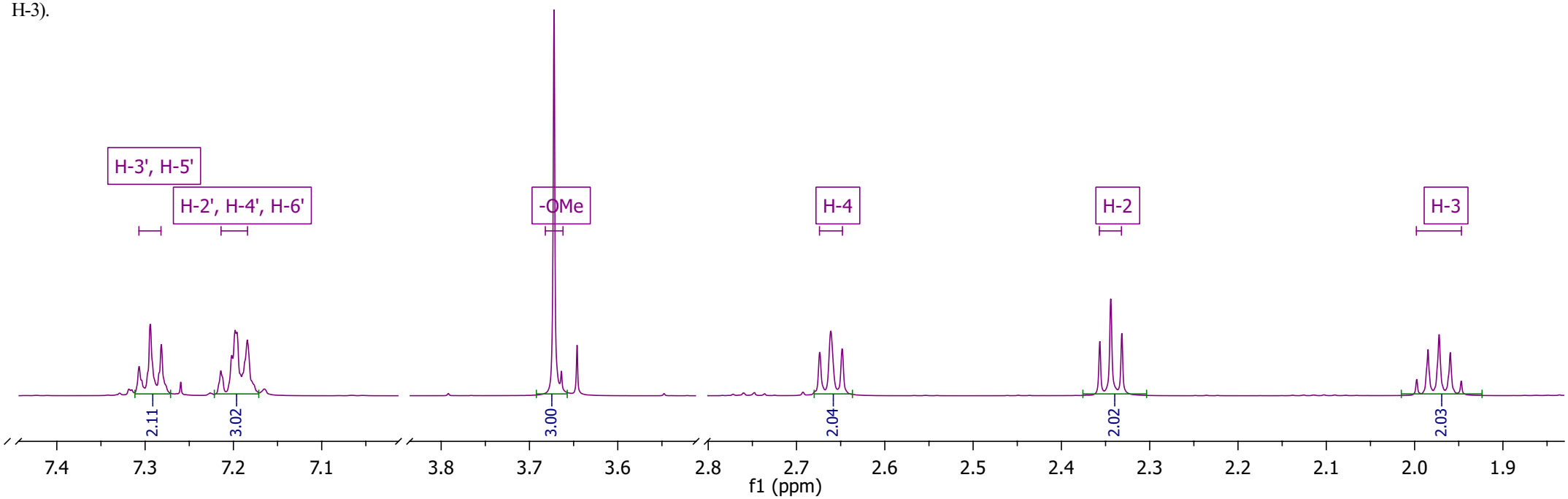
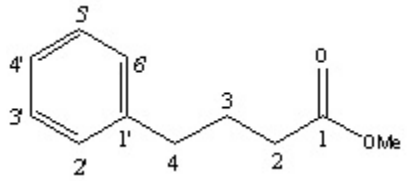


Plate 23b - ^{13}C NMR [$CDCl_3$]: methyl 4-phenylbutanoate (**401**)



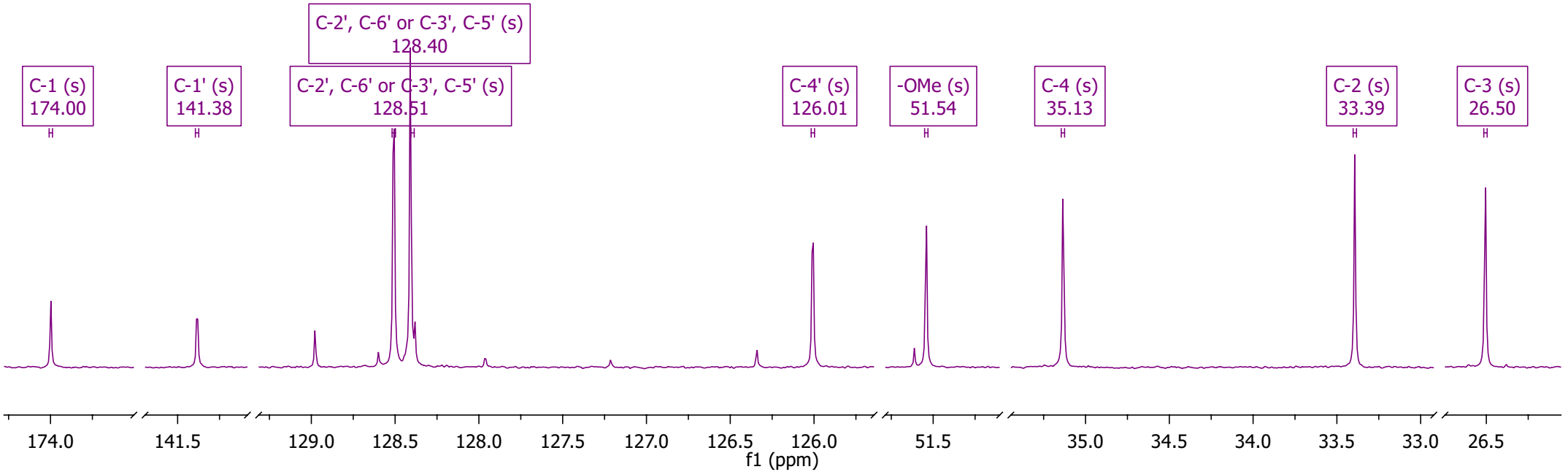


Plate 23c - DEPT [$CDCl_3$]: methyl 4-phenylbutanoate (**401**)

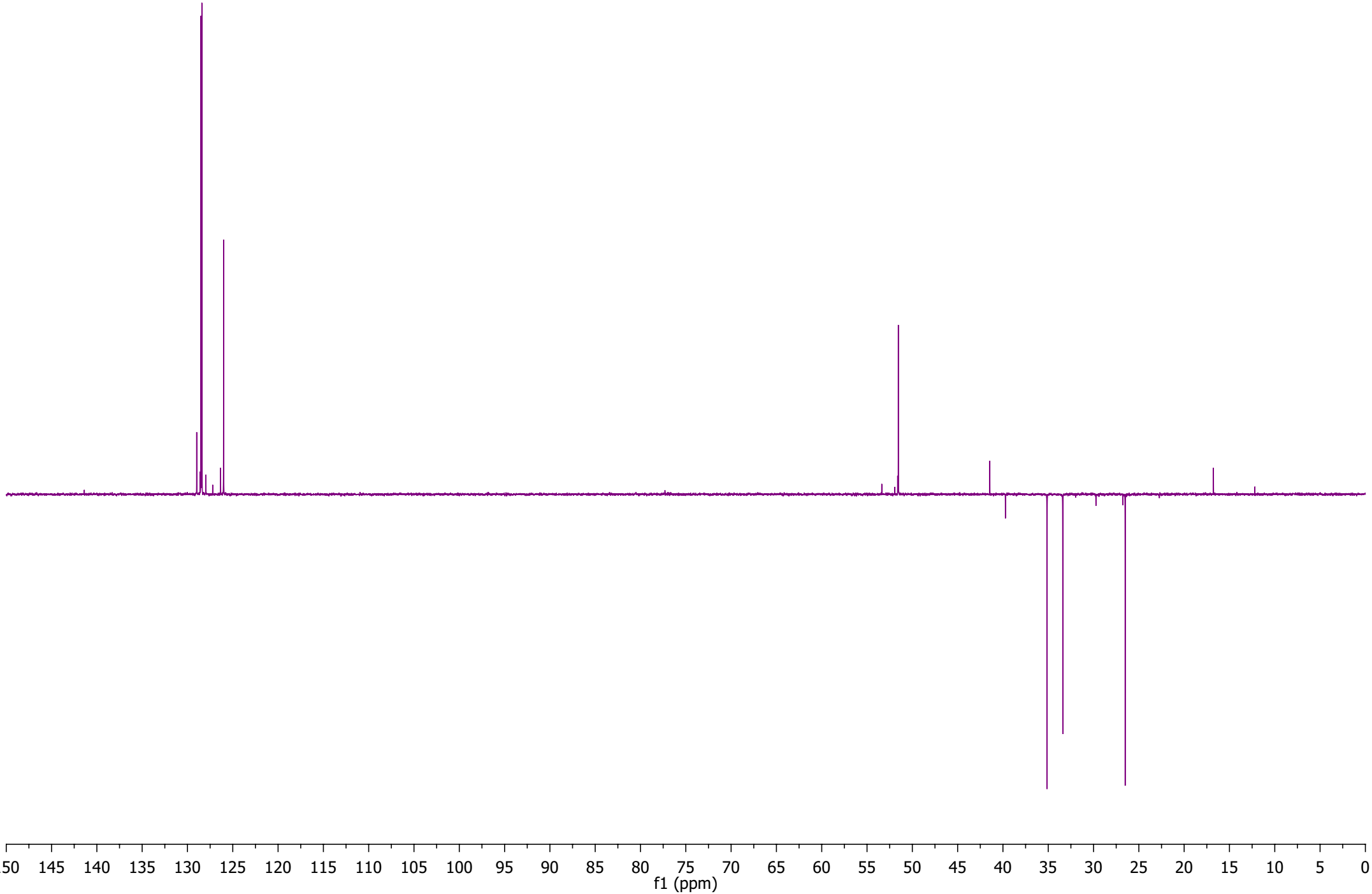


Plate 23d - HSQC NMR [$CDCl_3$]: methyl 4-phenylbutanoate (**401**)

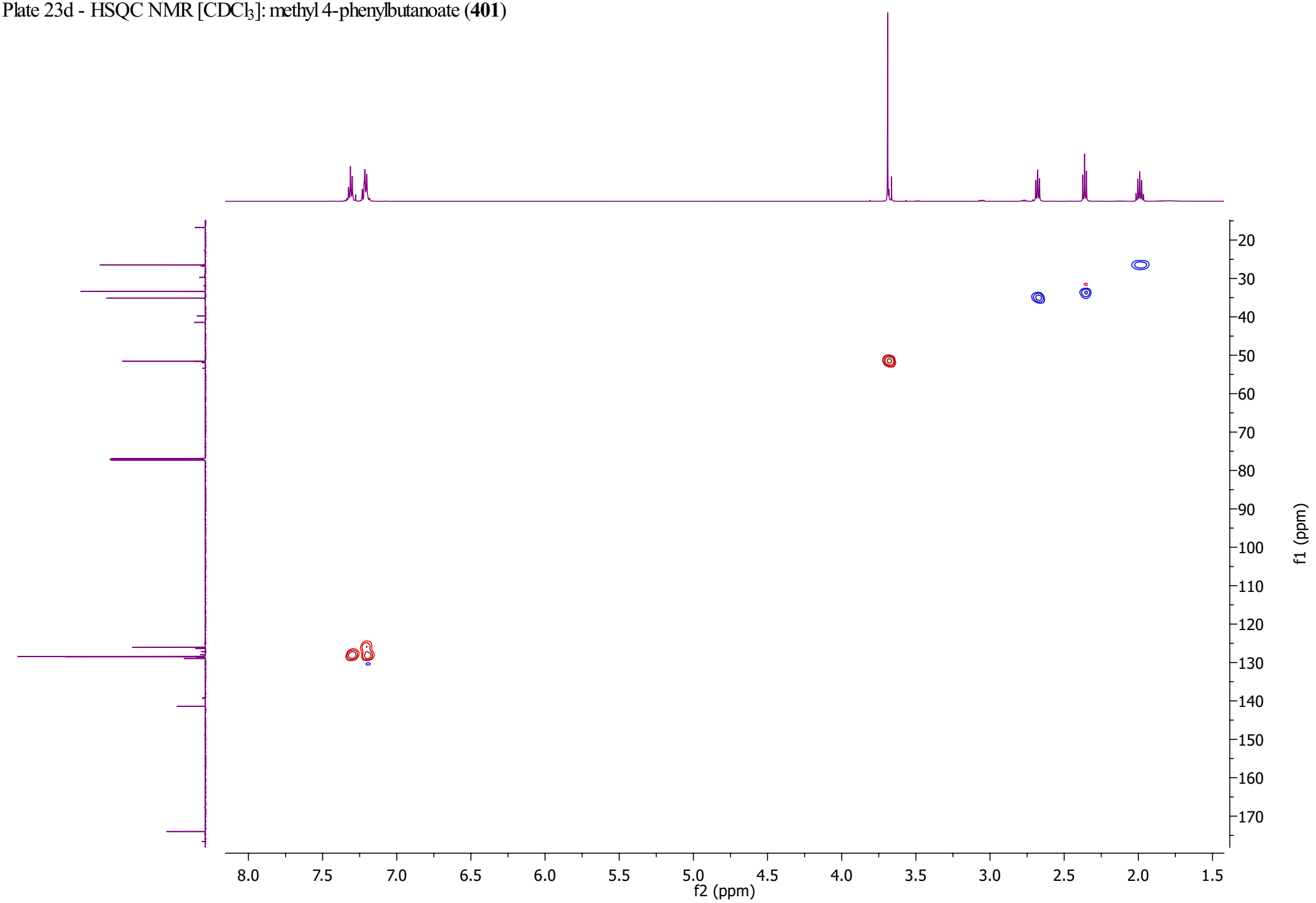


Plate 23e - HMBC NMR [$CDCl_3$]: methyl 4-phenylbutanoate (**401**)

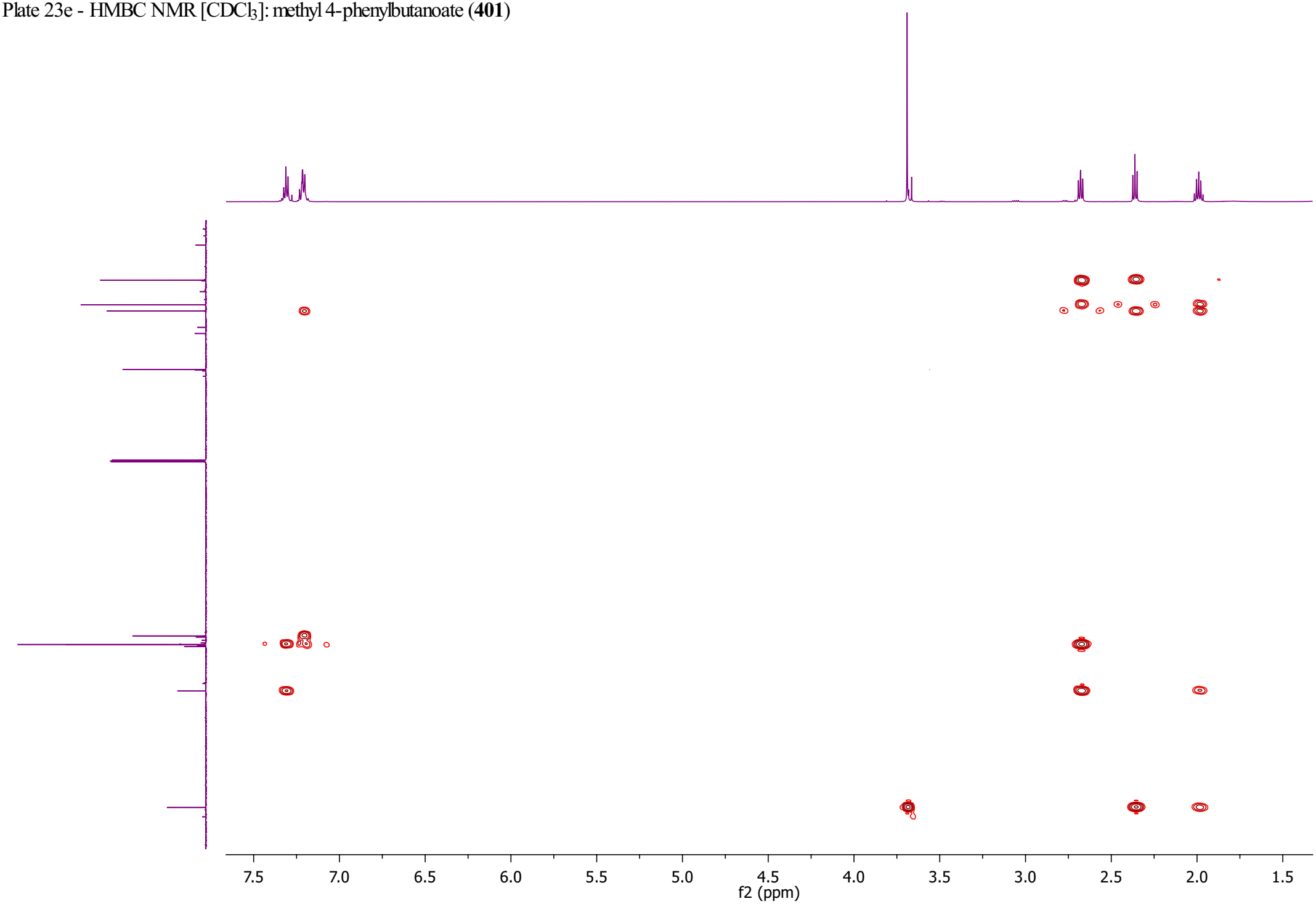


Plate 23f - HMBC (expansion) NMR [$CDCl_3$]: methyl 4-phenylbutanoate (**401**)

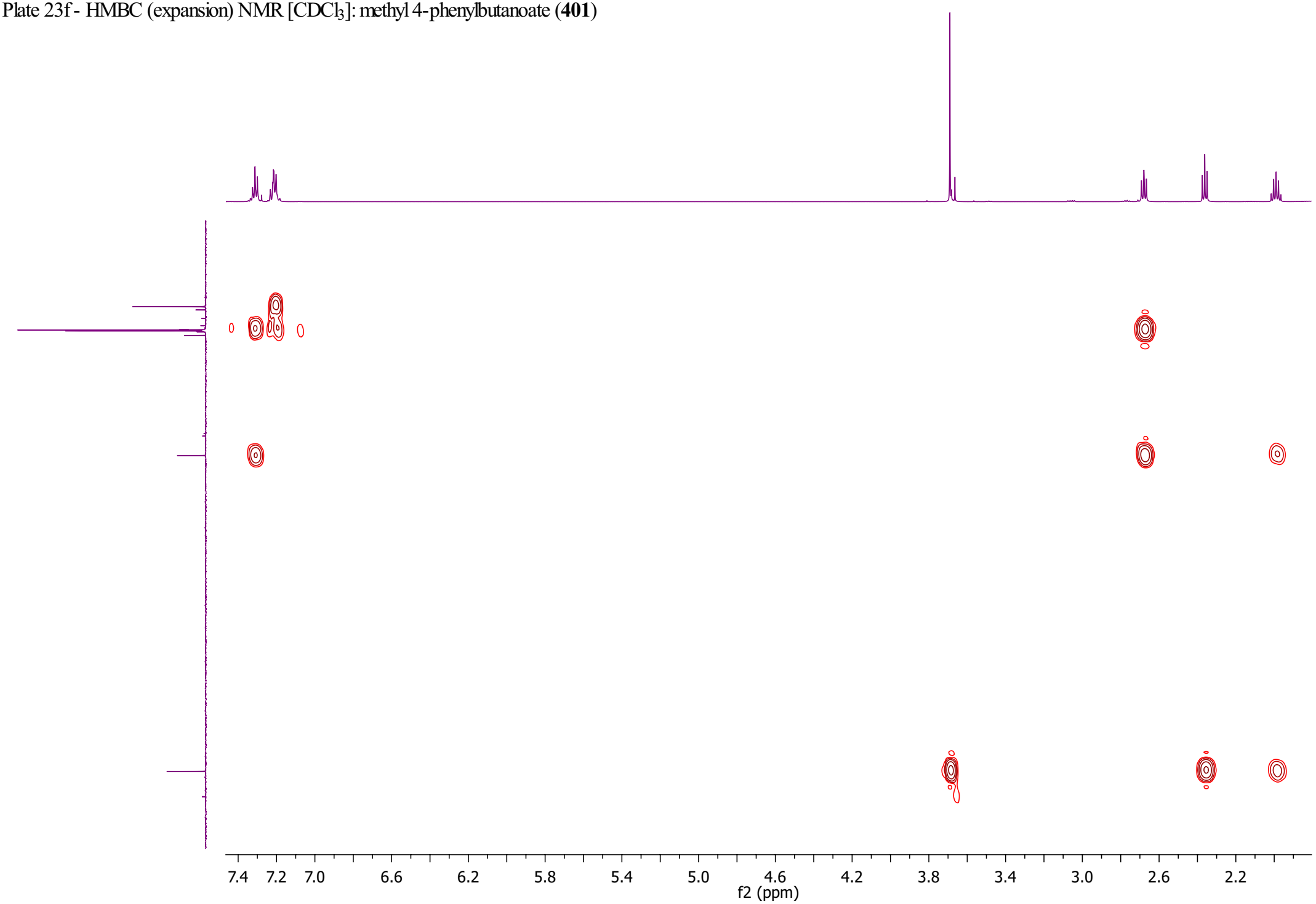
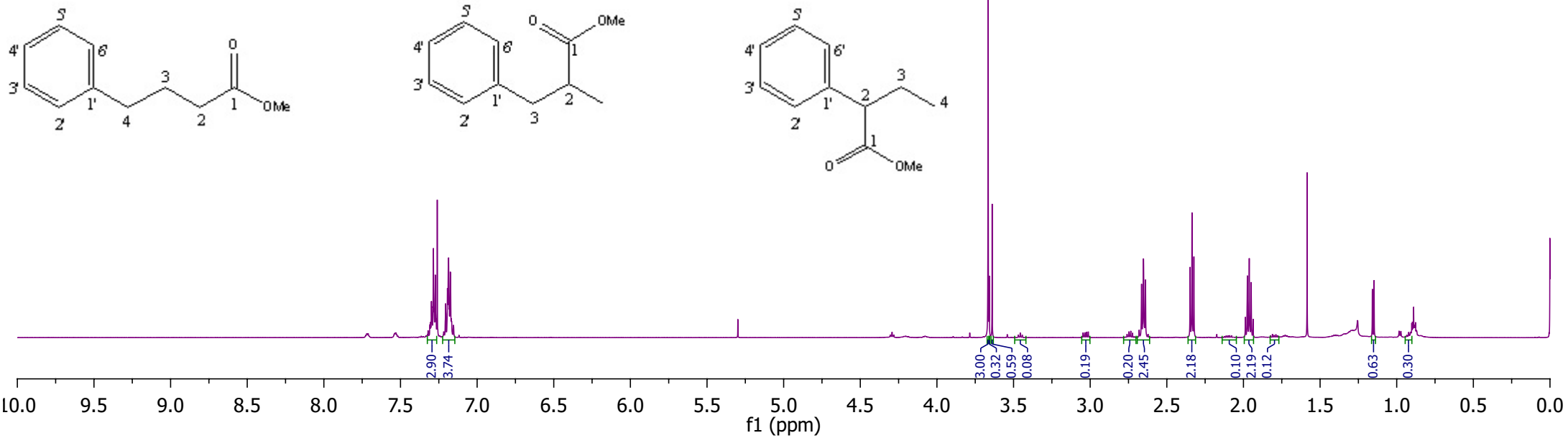


Plate 24a - ^{1}H NMR [$CDCl_3$]: methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.26 [2.9H, m, H-Ar, (**401**) (**403**) (**404**)], 7.21-7.16 [3.7H, m, H-Ar, (**401**) (**403**) (**404**)], 3.67 [3H, s, -OMe, (**401**)], 3.66 [0.3H, s, -OMe, (**404**)], 3.64 [0.6H, s, -OMe, (**403**)], 3.46 [0.1H, t, *J* = 7.71 Hz, H-2, (**404**)], 3.03 [0.2H, dd, *J* = 6.83 and 13.56 Hz, H-3a/b, (**403**)], 2.76-2.71 [0.2H, m, H-2, (**403**)], 2.65 [0.4H, dd, *J* = 6.83 and 13.56 Hz, H-3a/b, (**403**)], 2.65 [2H, t, *J* = 7.56 Hz, H-4, (**401**)] 2.34 [2H, t, *J* = 7.56 Hz, H-2, (**401**)], 2.13-2.08 [0.1H, m, H-3a/b, (**404**)], 1.96 [2H, p, *J* = 7.56 Hz, H-3, (**401**)], 1.82-1.78 [0.1H, m, H-3a/b, (**404**)], 1.15 [3H, d, *J* = 6.9 Hz, 2-CH_3, (**403**)], 0.92 [0.3H, t, *J* = 7.43 Hz, H-4, (**404**)].

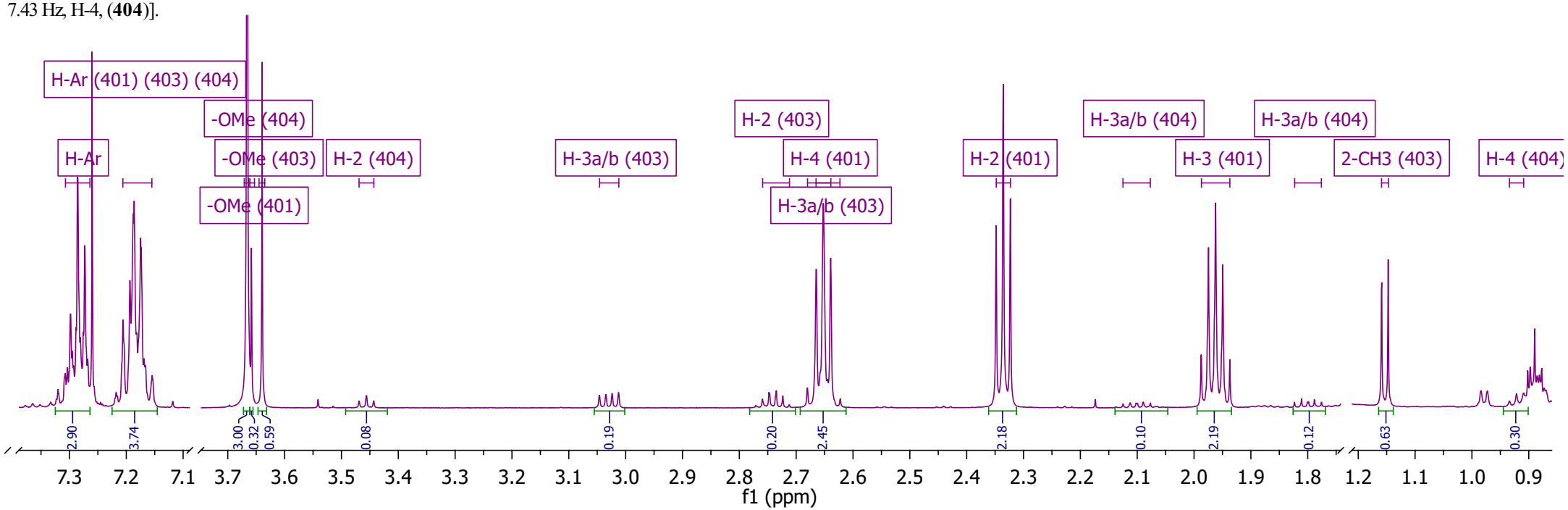
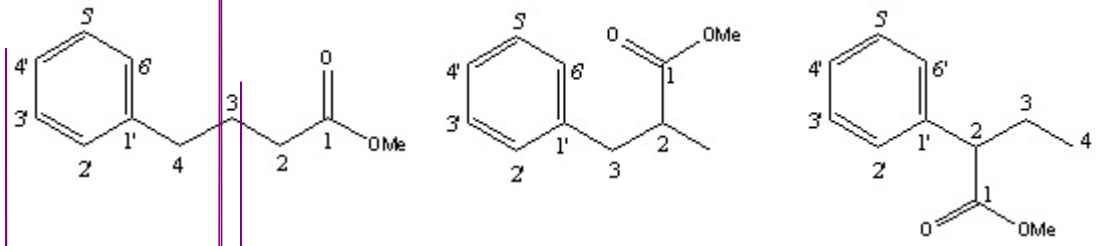
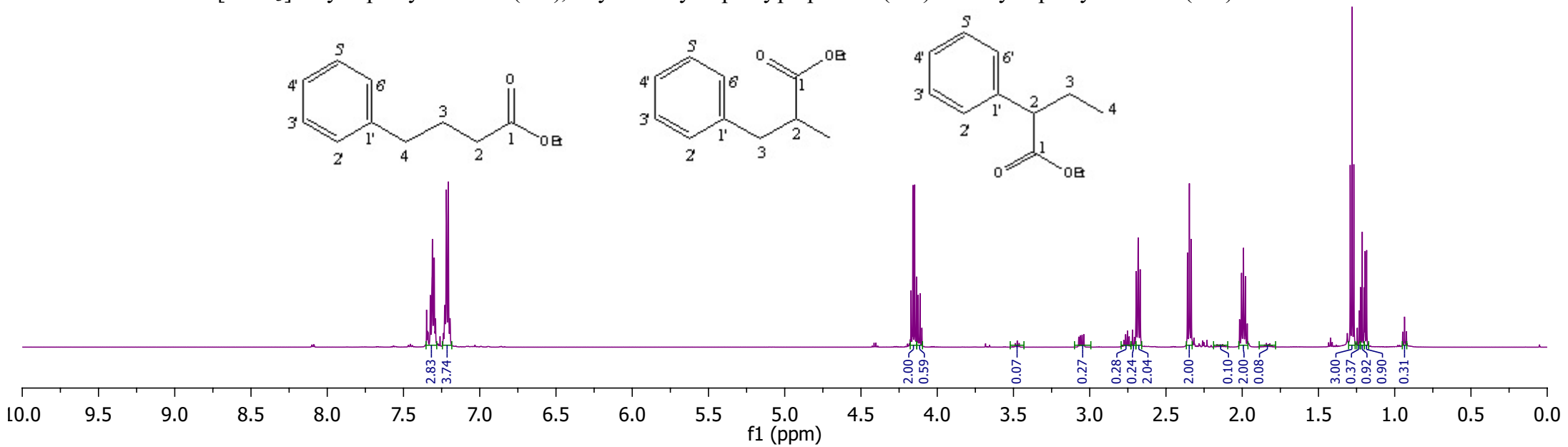


Plate 24b - ^{1}H NMR (expansion) [$CDCl_3$]: methyl 4-phenylbutanoate (**401**), methyl 2-methyl-3-phenylpropanoate (**403**) and methyl 2-phenylbutanoate (**404**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.26 [2.9H, m, H-Ar, (**401**) (**403**) (**404**)], 7.21-7.16 [3.7H, m, H-Ar, (**401**) (**403**) (**404**)], 3.67 [3H, s, -OMe, (**401**)], 3.66 [0.3H, s, -OMe, (**404**)], 3.64 [0.6H, s, -OMe, (**403**)], 3.46 [0.1H, t, *J* = 7.71 Hz, H-2, (**404**)], 3.03 [0.2H, dd, *J* = 6.83 and 13.56 Hz, H-3a/b, (**403**)], 2.76-2.71 [0.2H, m, H-2, (**403**)], 2.65 [0.4H, dd, *J* = 6.83 and 13.56 Hz, H-3a/b, (**403**)], 2.65 [2H, t, *J* = 7.56 Hz, H-4, (**401**)] 2.34 [2H, t, *J* = 7.56 Hz, H-2, (**401**)], 2.13-2.08 [0.1H, m, H-3a/b, (**404**)], 1.96 [2H, p, *J* = 7.56 Hz, H-3, (**401**)], 1.82-1.78 [0.1H, m, H-3a/b, (**404**)], 1.15 [3H, d, *J* = 6.9 Hz, 2-CH_3, (**403**)], 0.92 [0.3H, t, *J* = 7.43 Hz, H-4, (**404**)].

Plate 25a - ^{1}H NMR [$CDCl_3$]: ethyl 4-phenylbutanoate (**406**), ethyl 2-methyl-3-phenylpropanoate (**407**) and ethyl 2-phenylbutanoate (**408**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.29 [2.8H, m, H-Ar, (**406**) (**407**) (**408**)], 7.24-7.20 [3.7H, m, H-Ar, (**406**) (**407**) (**408**)], 4.16 [2H, q, *J* = 7.14 Hz, -OCH_2-, (**406**)], 4.12 [0.3H, q, *J* = 7.13 Hz, -OCH_2- (**408**)], 4.12 [0.6H, q, *J* = 7.15 Hz, -OCH_2- (**407**)], 3.48 [0.1H, t, *J* = 7.71 Hz, H-2, (**408**)], 3.06 [0.3H, dd, *J* = 6.83 and 13.20 Hz, H-3a/b, (**407**)], 2.79-2.73 [0.3H, m, H-2, (**407**)], 2.72 [0.3H, dd, *J* = 7.07 and 13.20 Hz, H-3a/b, (**407**)], 2.68 [2H, t, *J* = 7.57 Hz, H-4, (**406**)], 2.35 [2H, t, *J* = 7.57 Hz, H-2, (**406**)], 2.18-2.10 [0.1H, m, H-3a/b, (**408**)], 2.00 [2H, p, *J* = 7.57 Hz, H-3, (**406**)], 1.88-1.79 [0.1H, m, H-3a/b, (**408**)], 1.28 [3H, t, *J* = 7.14 Hz, -$OCH_2\underline{CH_3}$, (**406**)], 1.24 [0.3H, t, *J* = 7.13 Hz, -$OCH_2\underline{CH_3}$, (**408**)], 1.22 [0.9H, t, *J* = 7.15 Hz, -$OCH_2\underline{CH_3}$ (**407**)], 1.19 [0.9H, d, *J* = 6.86 Hz, 2-CH_3 (**407**)], 0.94 (0.3H, t, *J* = 7.37 Hz, H-4, (**408**)].

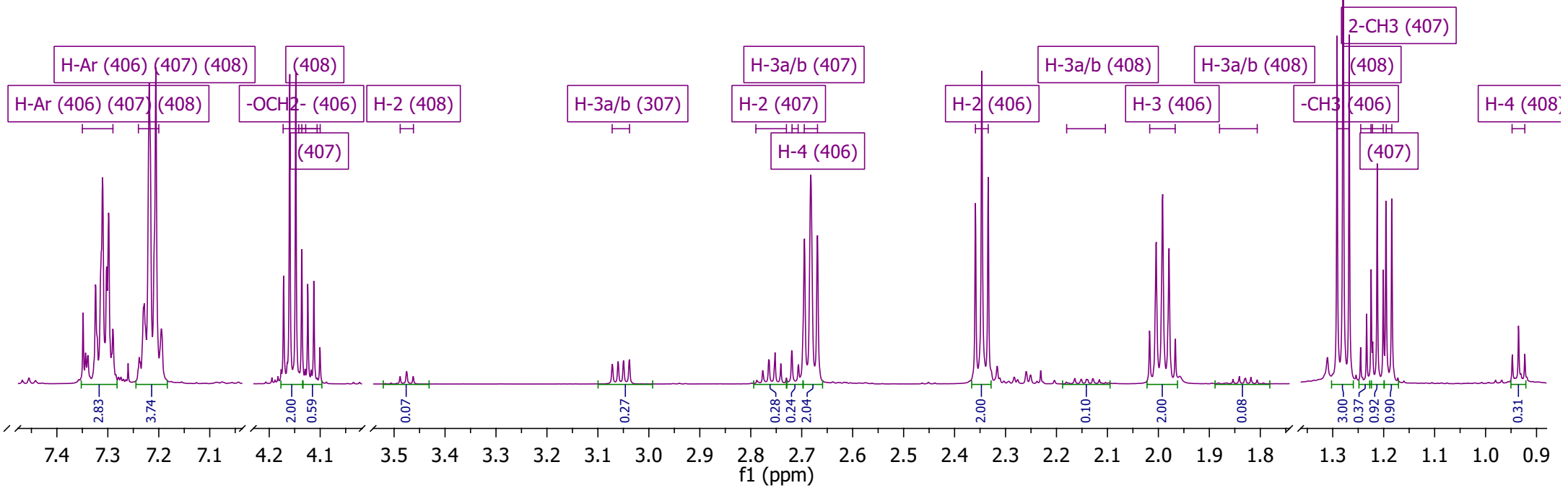
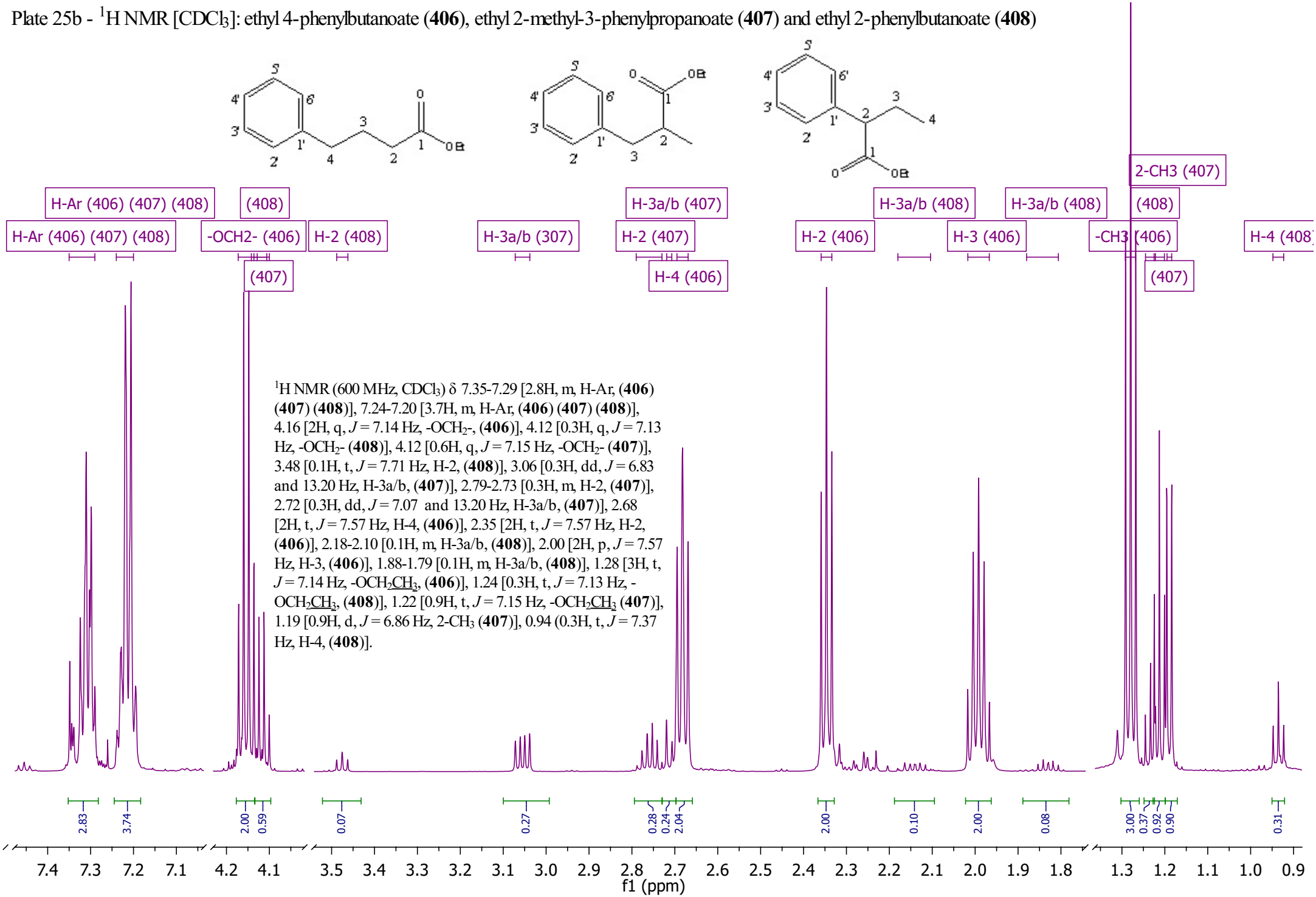
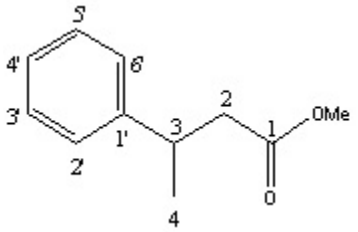


Plate 25b - ^{1}H NMR [$CDCl_3$]: ethyl 4-phenylbutanoate (**406**), ethyl 2-methyl-3-phenylpropanoate (**407**) and ethyl 2-phenylbutanoate (**408**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.29 [2.8H, m, H-Ar, (**406**) (**407**) (**408**)], 7.24-7.20 [3.7H, m, H-Ar, (**406**) (**407**) (**408**)], 4.16 [2H, q, J = 7.14 Hz, -OCH_2-, (**406**)], 4.12 [0.3H, q, J = 7.13 Hz, -OCH_2- (**408**)], 4.12 [0.6H, q, J = 7.15 Hz, -OCH_2- (**407**)], 3.48 [0.1H, t, J = 7.71 Hz, H-2, (**408**)], 3.06 [0.3H, dd, J = 6.83 and 13.20 Hz, H-3a/b, (**407**)], 2.79-2.73 [0.3H, m, H-2, (**407**)], 2.72 [0.3H, dd, J = 7.07 and 13.20 Hz, H-3a/b, (**407**)], 2.68 [2H, t, J = 7.57 Hz, H-4, (**406**)], 2.35 [2H, t, J = 7.57 Hz, H-2, (**406**)], 2.18-2.10 [0.1H, m, H-3a/b, (**408**)], 2.00 [2H, p, J = 7.57 Hz, H-3, (**406**)], 1.88-1.79 [0.1H, m, H-3a/b, (**408**)], 1.28 [3H, t, J = 7.14 Hz, -$OCH_2\underline{CH_3}$, (**406**)], 1.24 [0.3H, t, J = 7.13 Hz, -$OCH_2\underline{CH_3}$, (**408**)], 1.22 [0.9H, t, J = 7.15 Hz, -$OCH_2\underline{CH_3}$ (**407**)], 1.19 [0.9H, d, J = 6.86 Hz, 2-CH_3 (**407**)], 0.94 (0.3H, t, J = 7.37 Hz, H-4, (**408**)].

Plate 26a - ^{1}H NMR [$CDCl_3$]: methyl 3-phenylbutanoate (**410**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m, H-3' and H-5'), 7.21-7.17 (3H, m, H-2', H-4' and H-6'), 3.59 (3H, s, -OMe), 3.30-3.24 (1H, m, H-3), 2.61 (1H, dd, *J* = 15.20, 6.91 Hz, H-2a or H-2b), 2.54 (1H, dd, *J* = 15.20, 8.23 Hz, H-2a or H-2b), 1.29 (3H, d, *J* = 7.0 Hz, H-4).

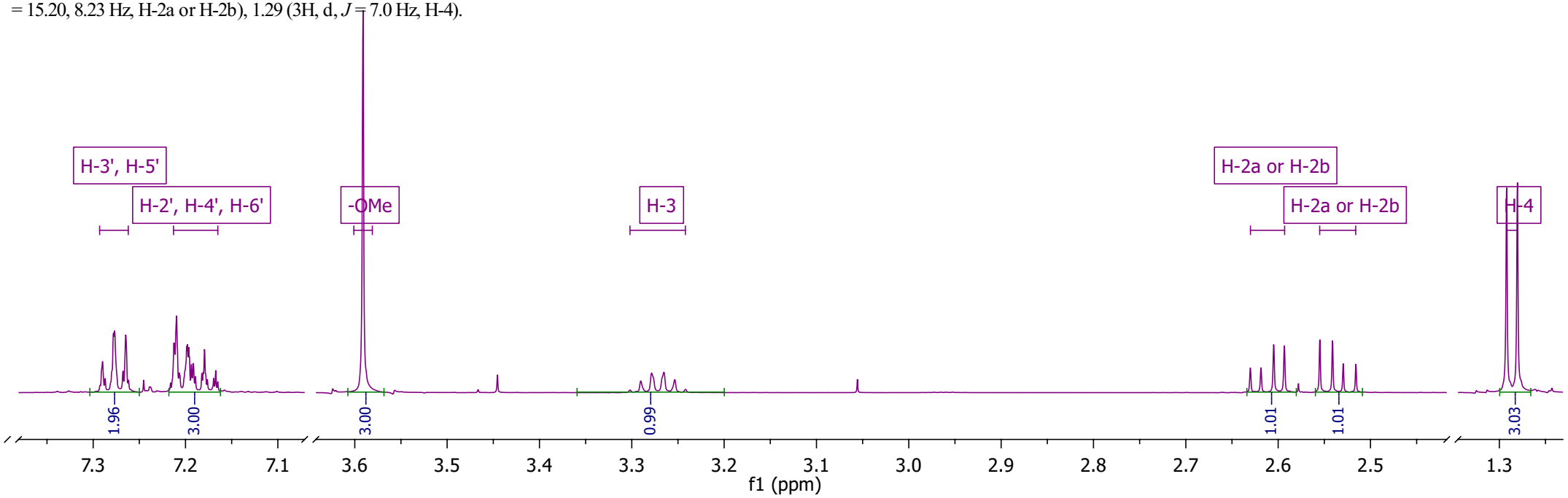
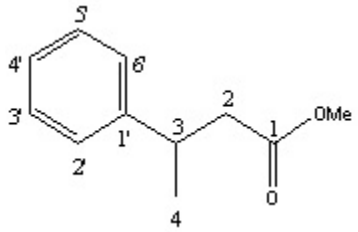


Plate 26b - ^{13}C NMR [$CDCl_3$]: methyl 3-phenylbutanoate (**410**)



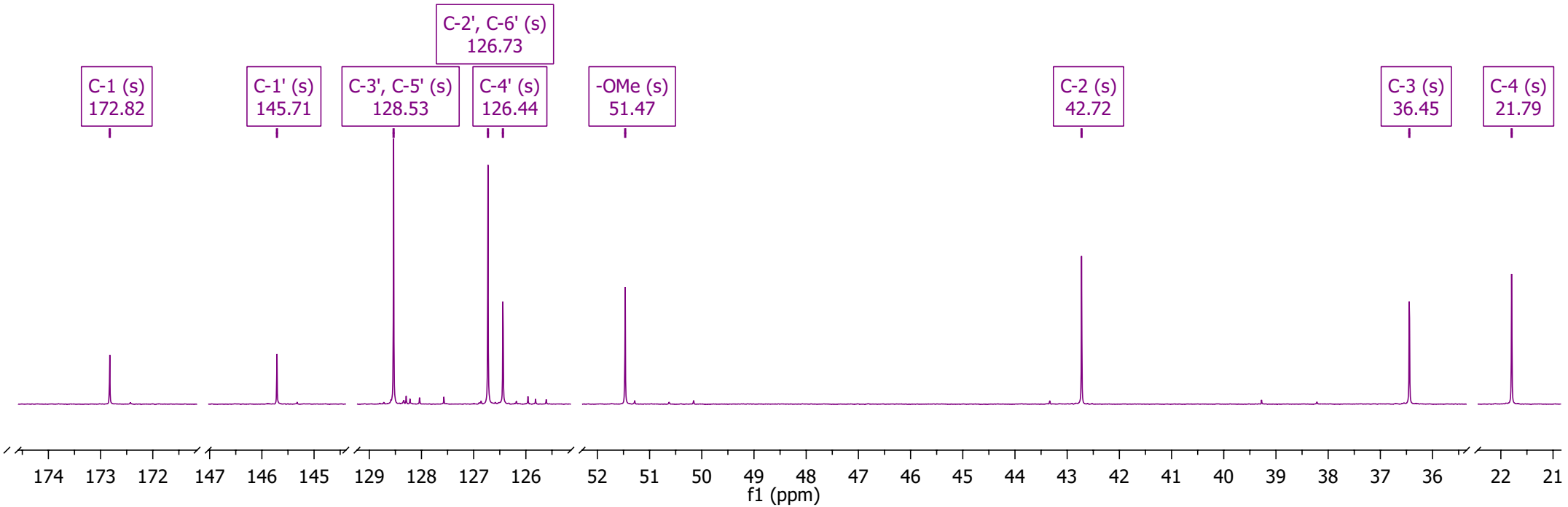


Plate 26c - DEPT [$CDCl_3$]: methyl 3-phenylbutanoate (**410**)

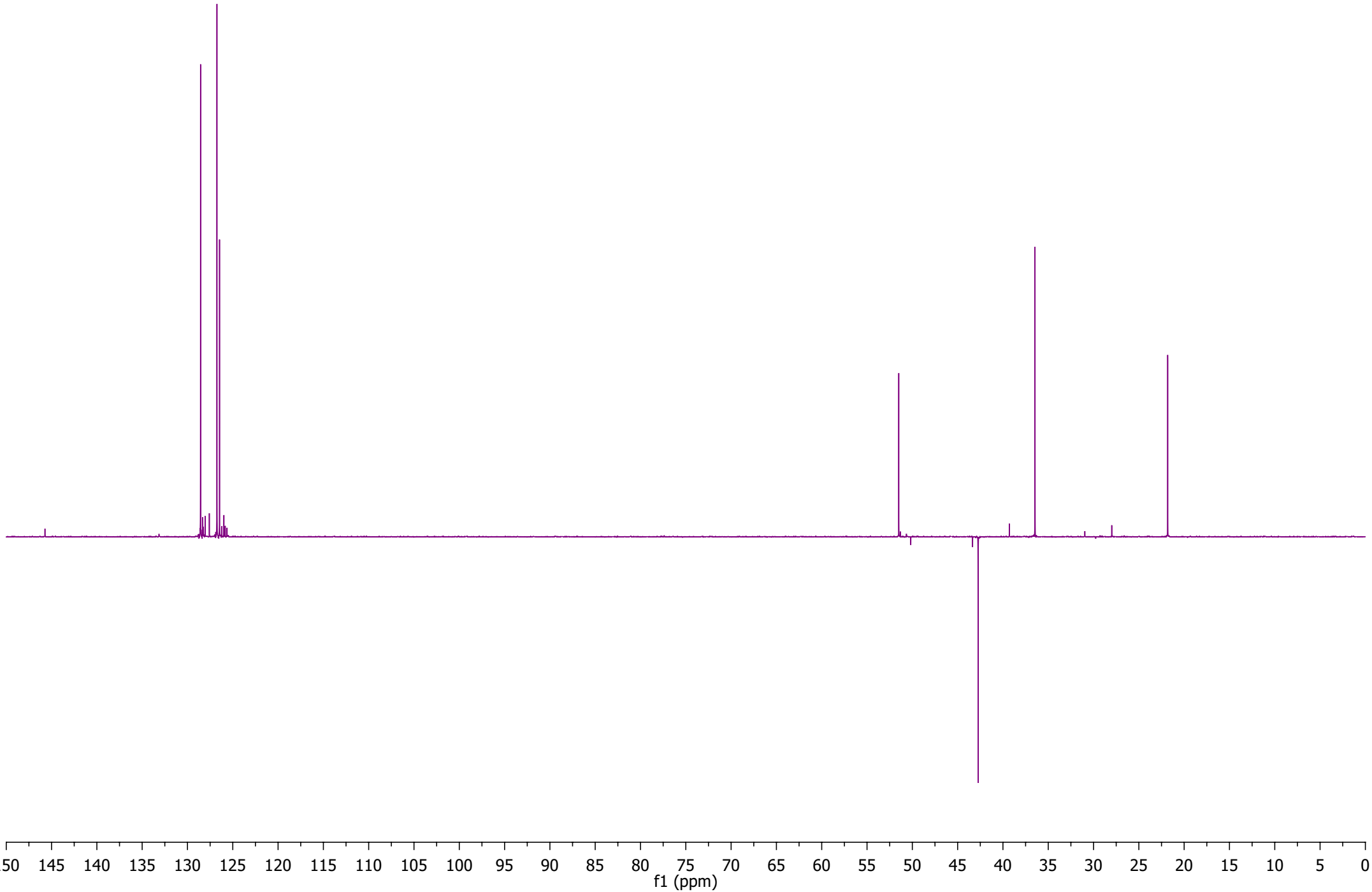


Plate 26d - HSQC [$CDCl_3$]: methyl 3-phenylbutanoate (**410**)

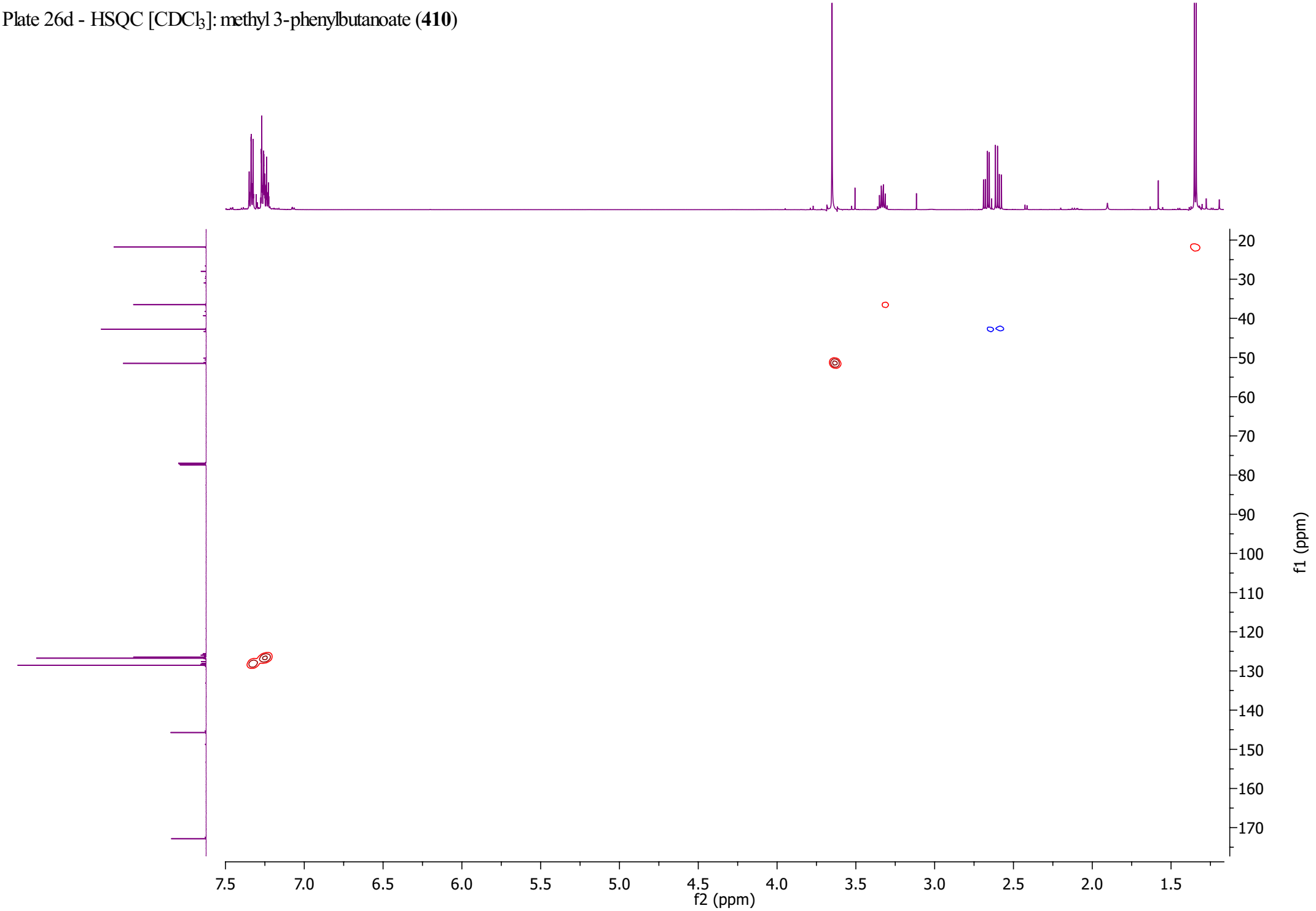


Plate 26e - HMBC [$CDCl_3$]: methyl 3-phenylbutanoate (**410**)

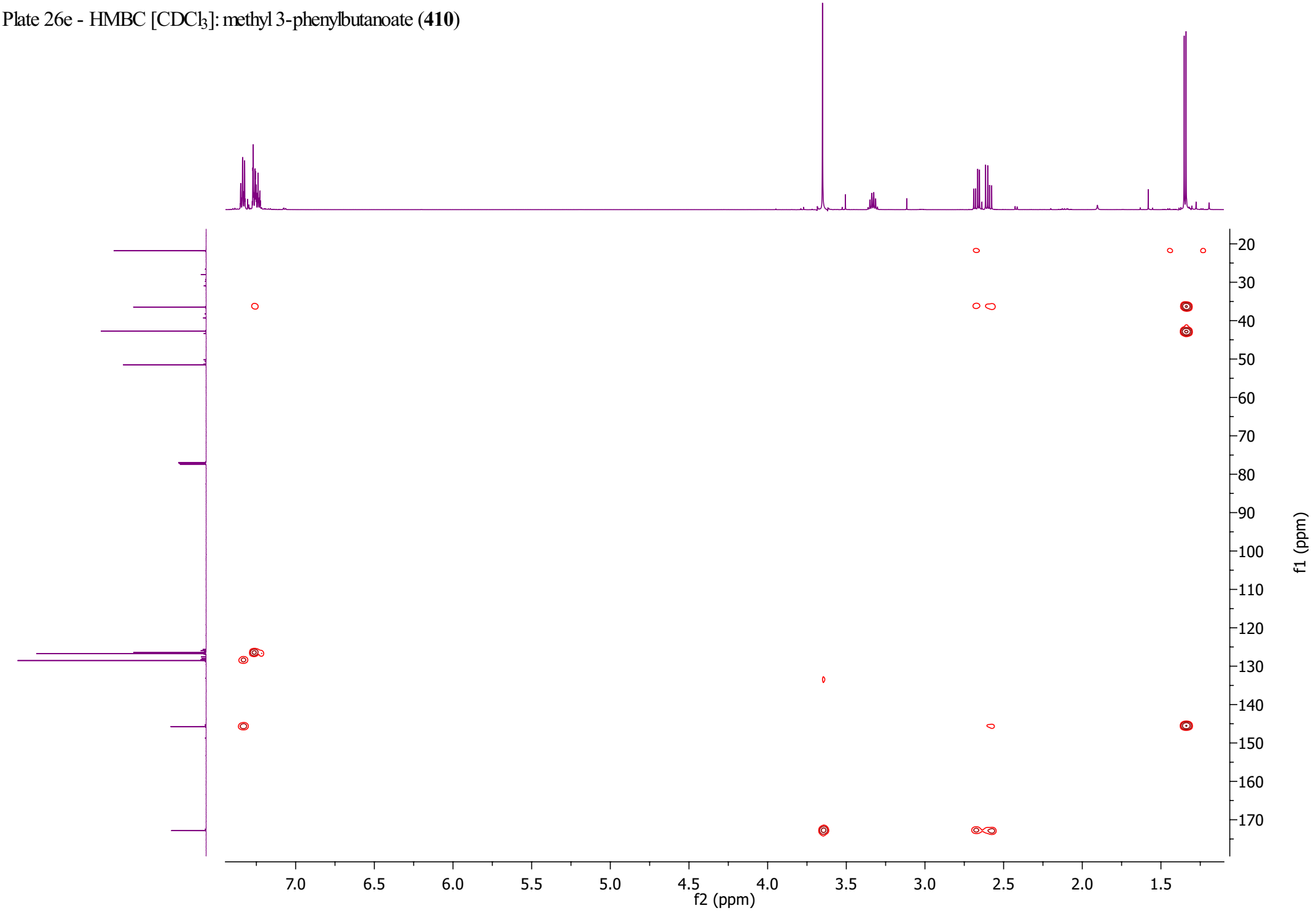
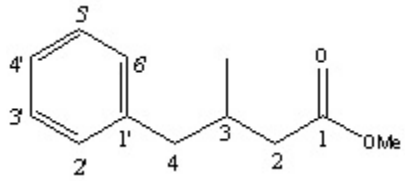


Plate 27a - ^{1}H NMR [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.27 (2H, m, H-3' and H-5'), 7.21-7.18 (1H, m, H-4'), 7.17-7.15 (2H, m, H-2' and H-6'), 3.65 (3H, s, -OMe), 2.62 (1H, dd, *J* = 13.45, 6.76 Hz, H-4a or H-4b), 2.51 (1H, dd, *J* = 13.45, 7.44 Hz, H-4a or H-4b), 2.34 (1H, dd, *J* = 14.66, 5.76 Hz, H-2a or H-2b), 2.31-2.25 (1H, m, H-3), 2.14 (1H, dd, *J* = 14.66, 7.87 Hz, H-2a or H-2b), 0.94 (3H, d, *J* = 6.58 Hz, 3-CH_3)

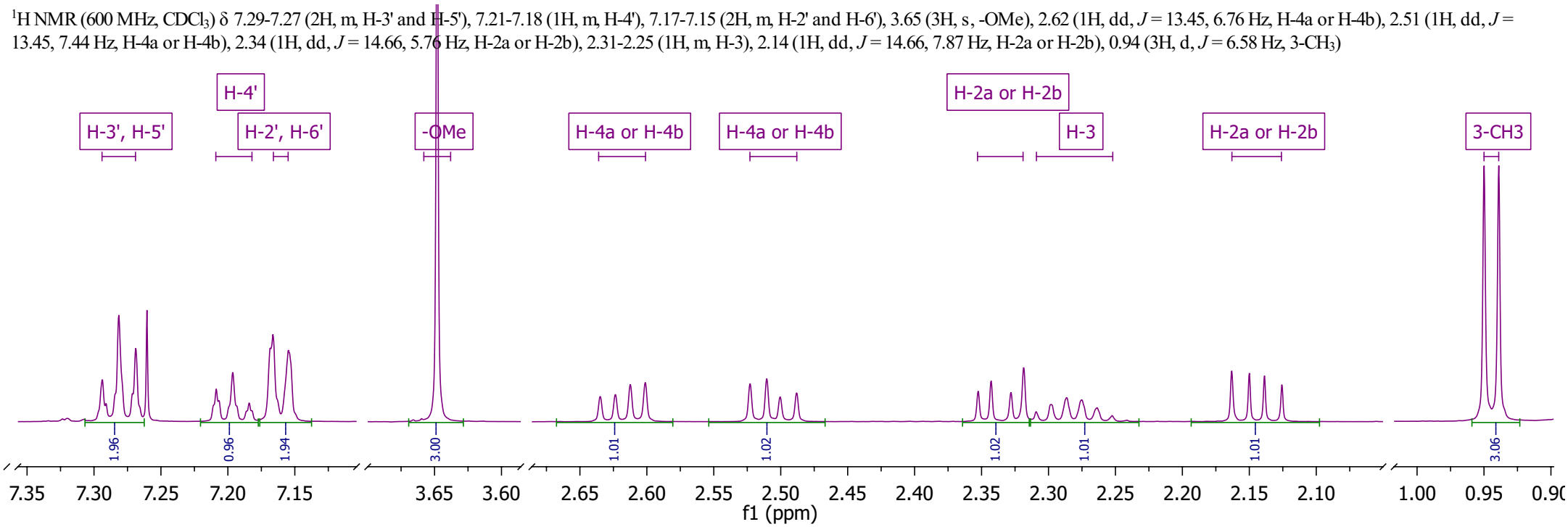
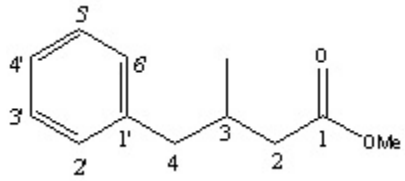


Plate 27b - ^{13}C NMR [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)



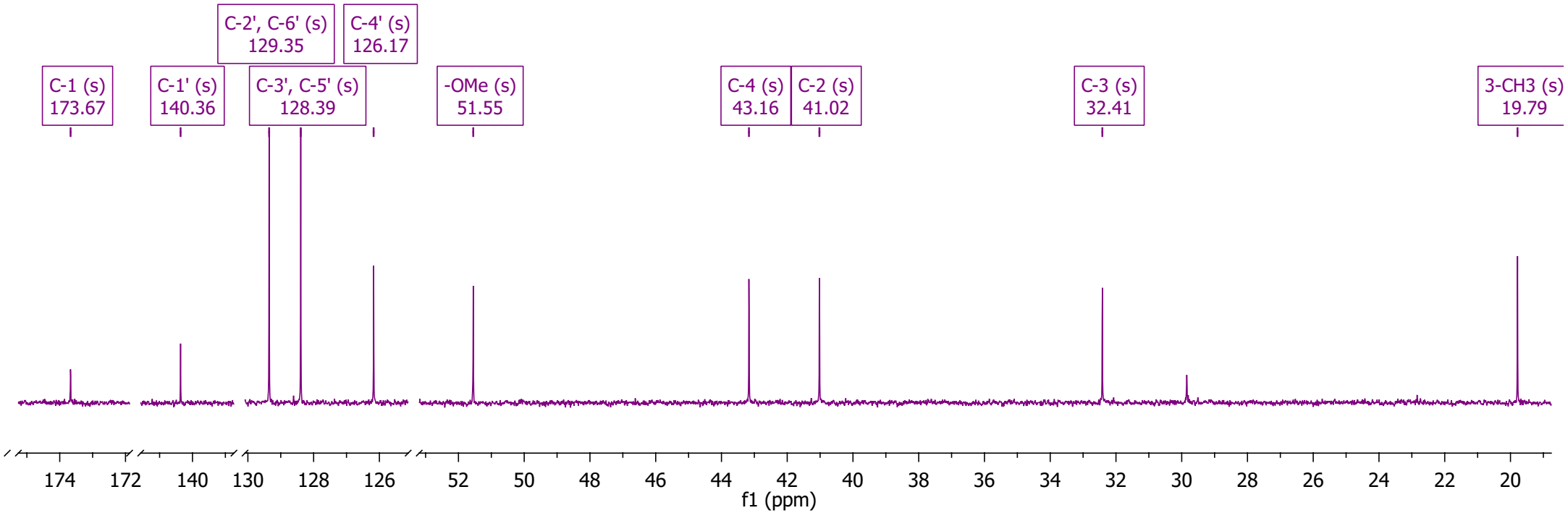


Plate 27c - DEPT [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)

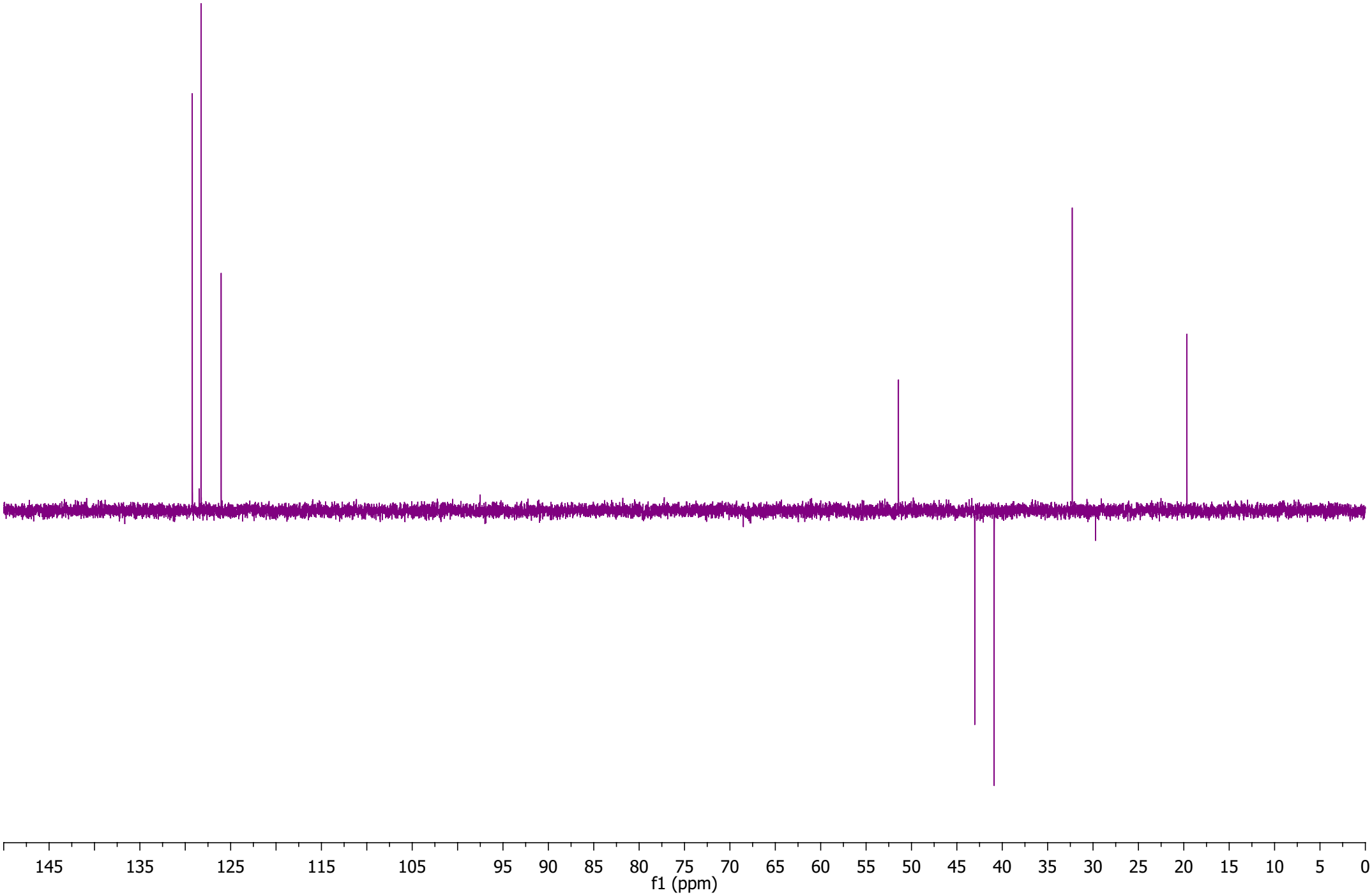


Plate 27d - HSQC [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)

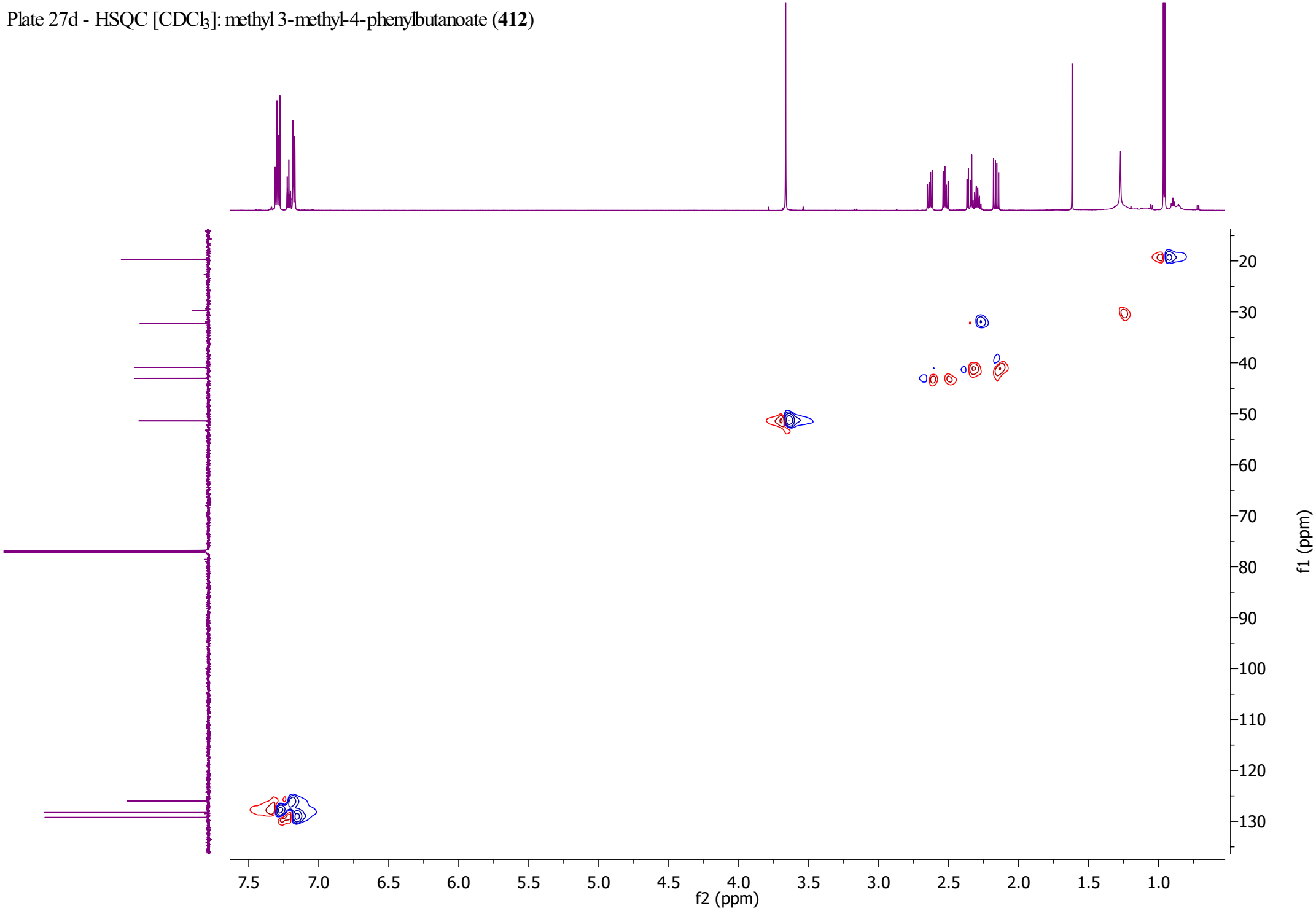


Plate 27e - HSQC (expansion) [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)

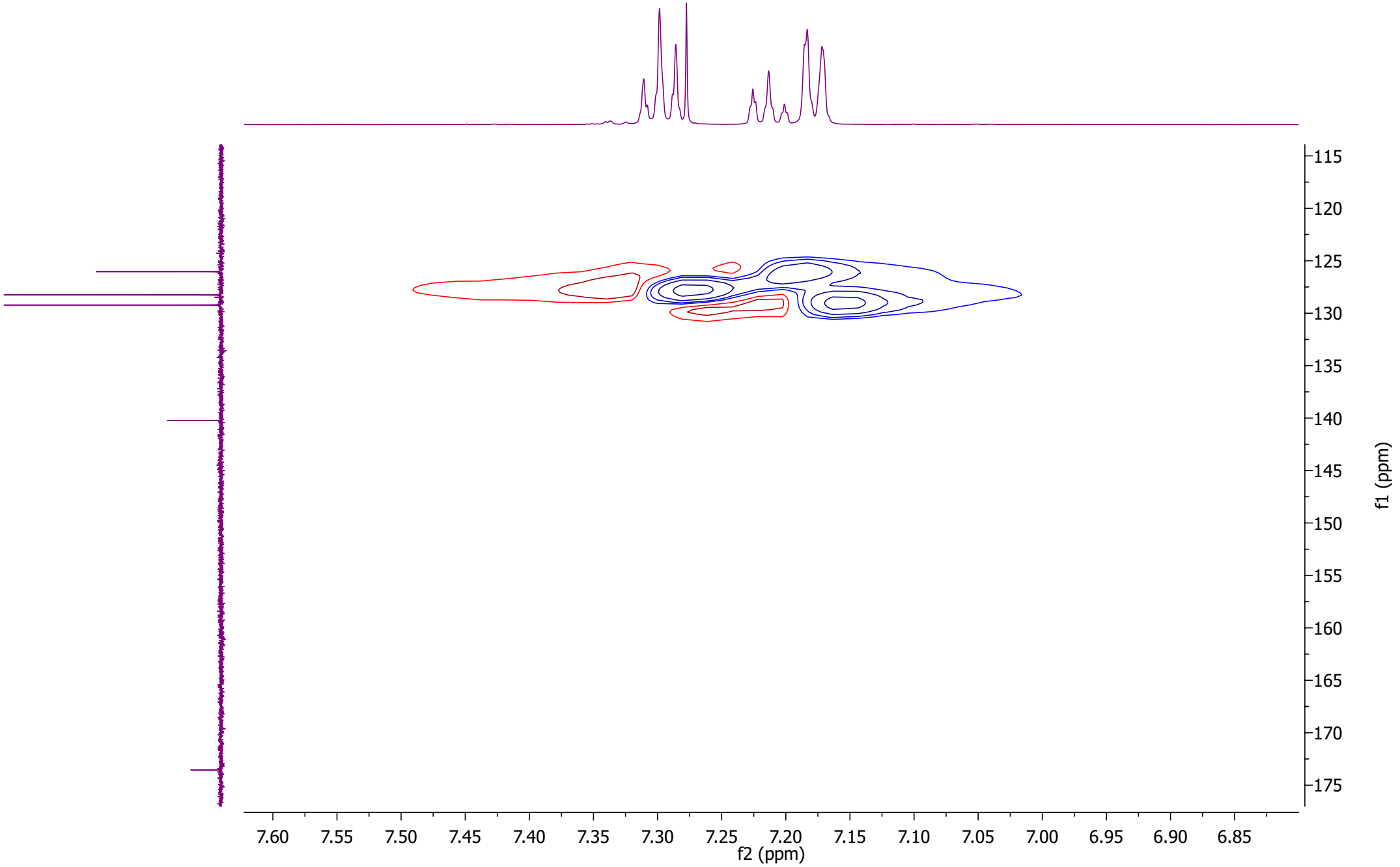


Plate 27f - HMBC [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)

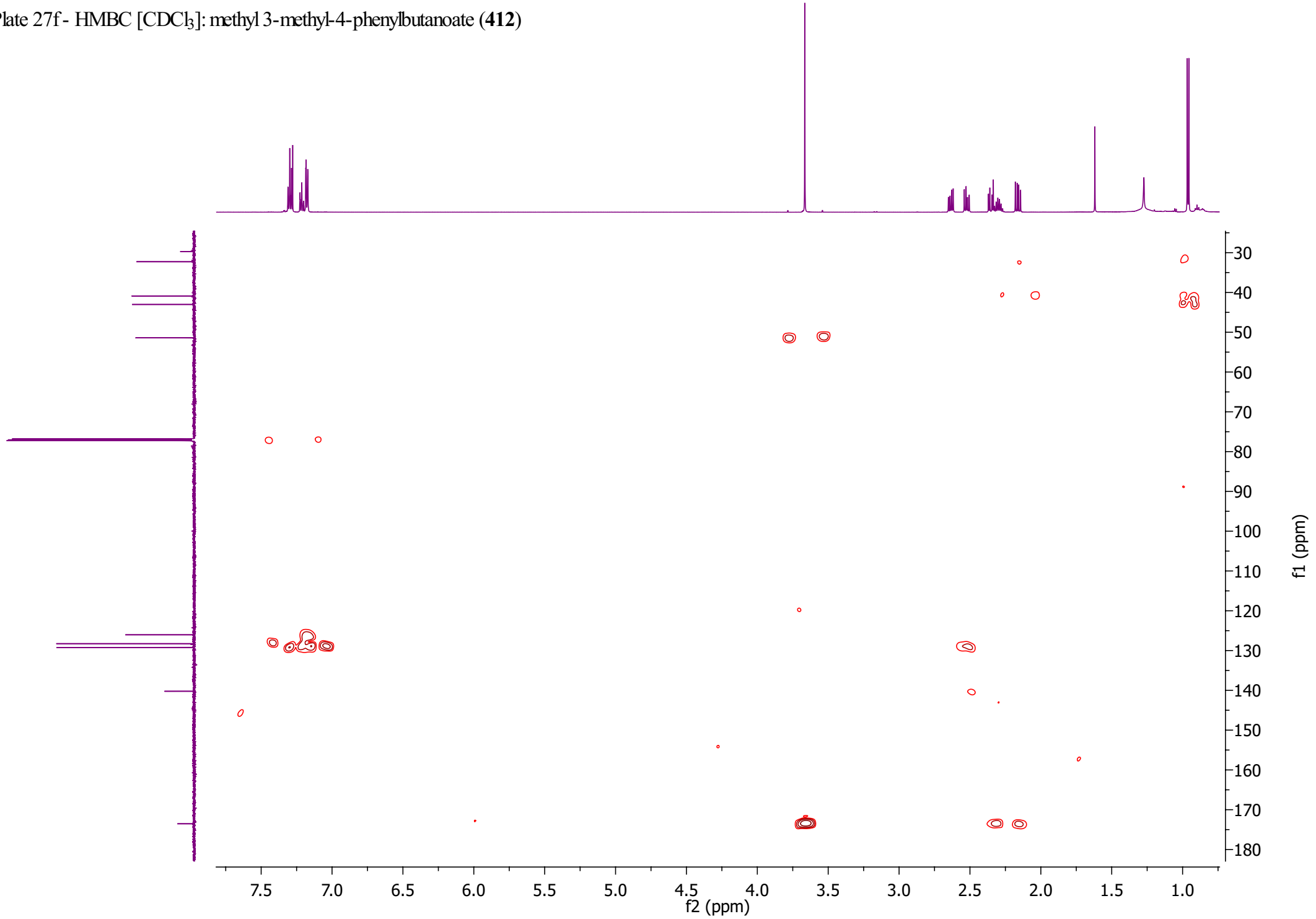


Plate 27g - HMBC (expansion) [$CDCl_3$]: methyl 3-methyl-4-phenylbutanoate (**412**)

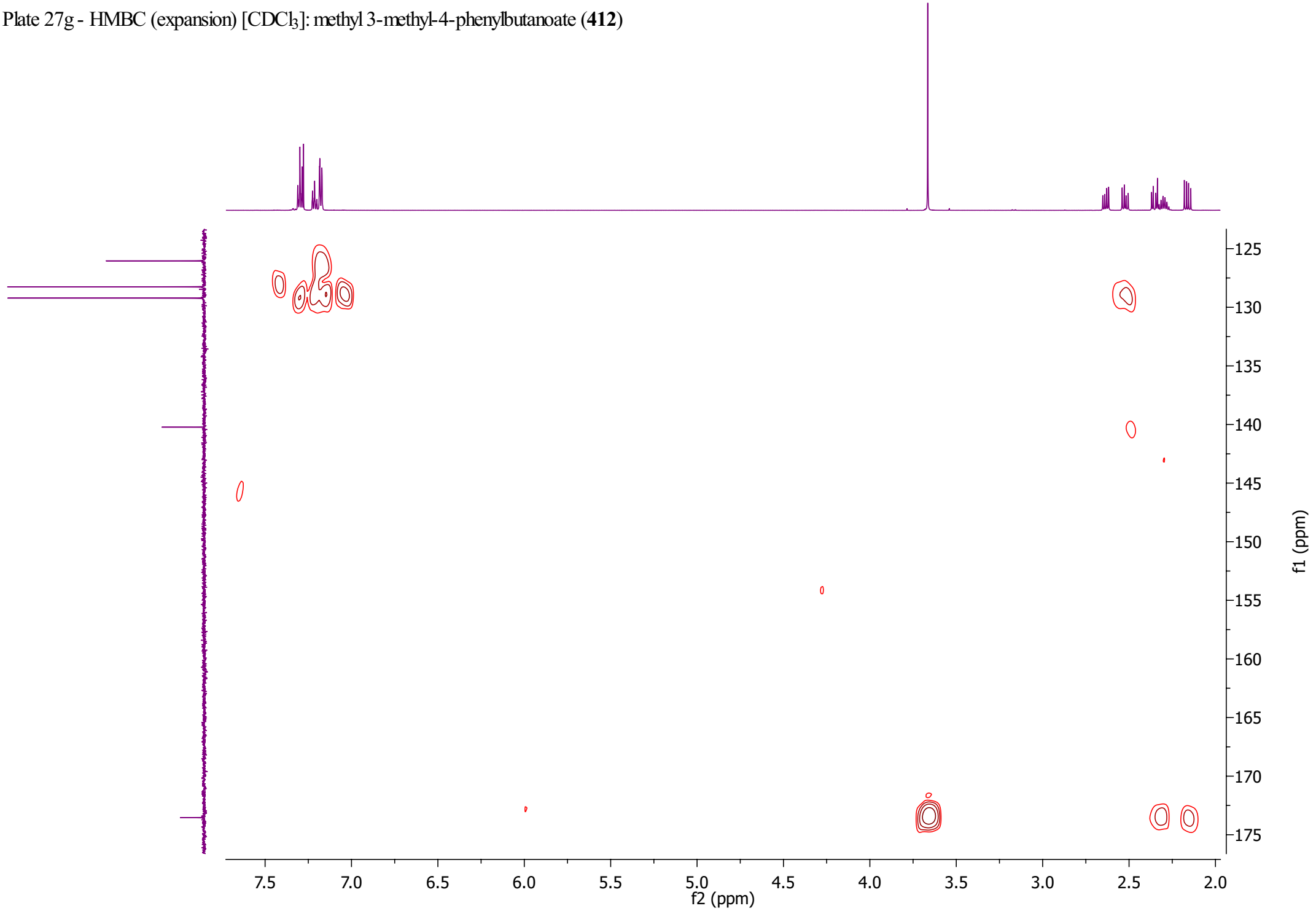
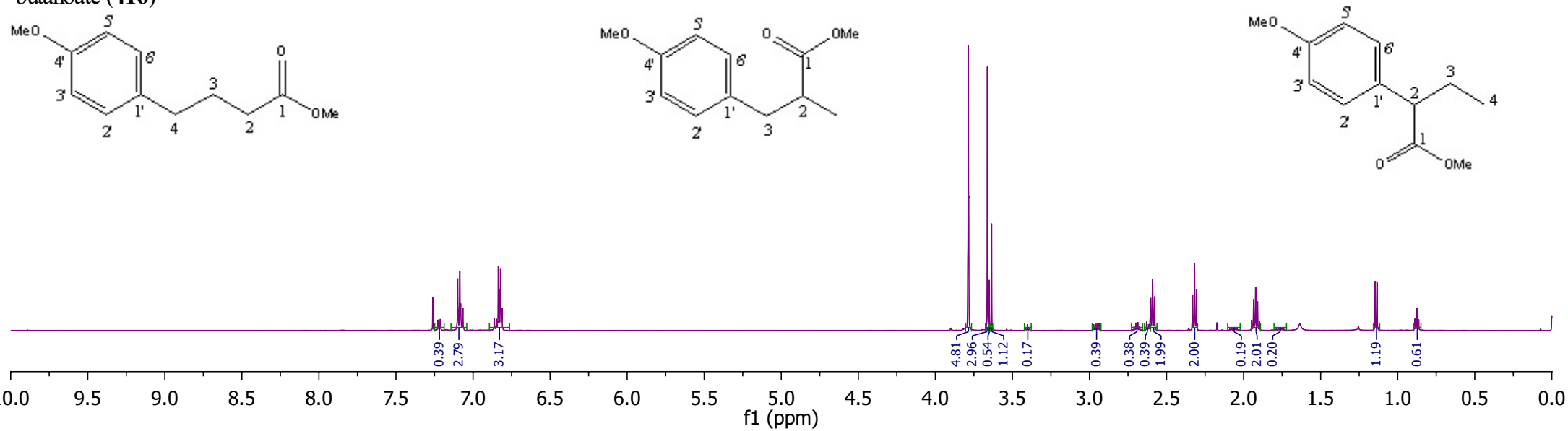


Plate 28a - ^{1}H NMR [$CDCl_3$]: methyl 4-(4'-methoxyphenyl)butanoate (**414**), methyl 2-methyl-3-(4'-methoxyphenyl)propanoate (**415**) and methyl 2-(4'-methoxyphenyl)-butanoate (**416**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 [0.4H, d, J = 8.67 Hz, H-2' and H-6', (**416**)], 7.10 [2H, d, J = 8.51 Hz, H-2' and H-6', (**414**)], 7.08 [0.8H, d, J = 8.46 Hz, H-2' and H-6', (**415**)], 6.86 [0.4H, d, J = 8.67 Hz, H-3' and H-5', (**416**)], 6.83 [2H, d, J = 8.51 Hz, H-3' and H-5', (**414**)], 6.82 [0.8H, d, J = 8.46 Hz, H-3' and H-5', (**415**)], 3.79 [4.8H, s, -PhOMe, (**414**), (**415**), (**416**)], 3.66 [3H, s, -COOMe, (**414**)], 3.65 [0.6H, s, -COOMe, (**416**)], 3.64 [1.2H, s, -COOMe, (**415**)], 3.40 [0.2H, t, J = 7.71 Hz, H-2, (**416**)], 2.96 [0.4H, dd, J = 6.93 and 13.53 Hz, H-3a/b (**415**)], 2.72-2.66 [0.4H, m, H-2 (**415**)], 2.62 [0.4H, dd, J = 7.68 and 13.53 Hz, H-3a/b, (B)], 2.59 [2H, t, J = 7.54 Hz, H-4, (**414**)], 2.32 [2H, t, J = 7.54 Hz, H-2, (**414**)], 2.09-2.03 [0.2H, m, H-3a/b (**416**)], 1.92 [2H, p, J = 7.54 Hz, H-3, (**414**)], 1.80-1.73 (0.2H, m, H-3a/b (**416**)], 1.14 [1.2H, d, J = 6.92 Hz, 2-CH_3, (**415**)], 0.87 [0.6H, t, J = 7.36 Hz, H-4 (**416**)].

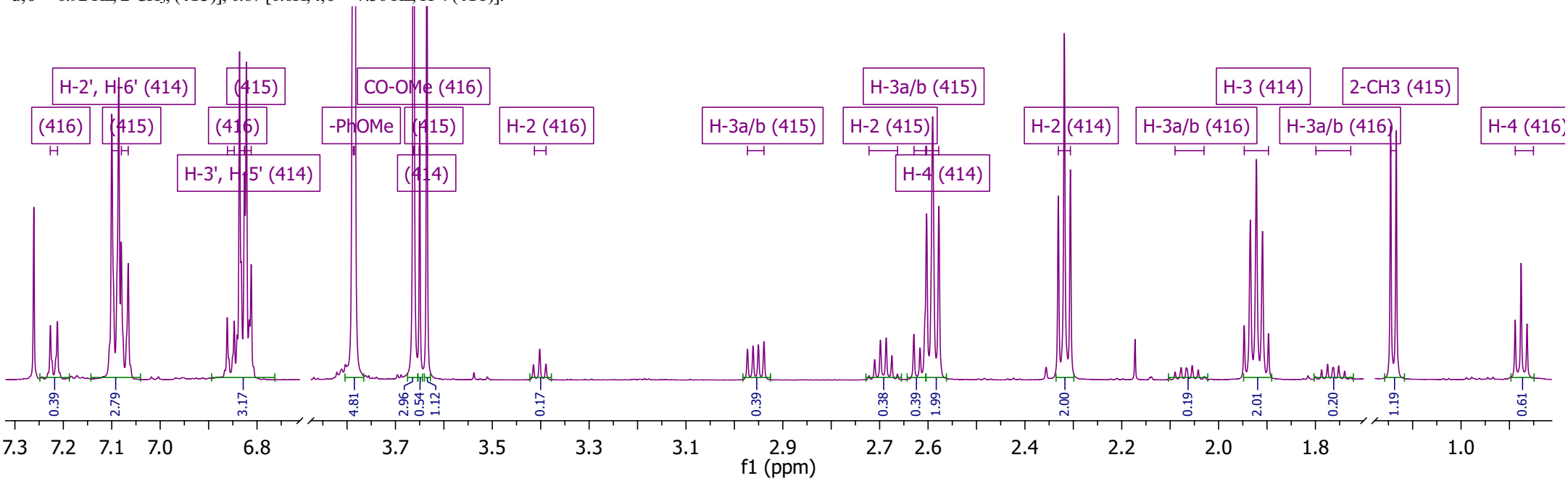
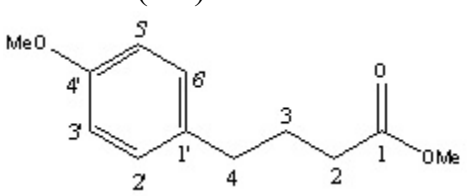
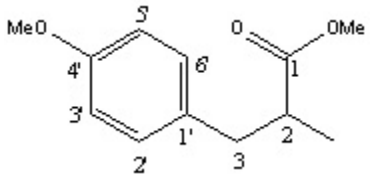
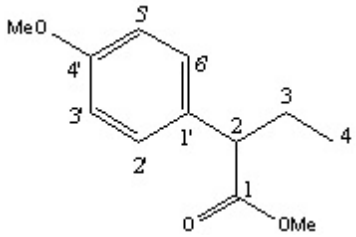
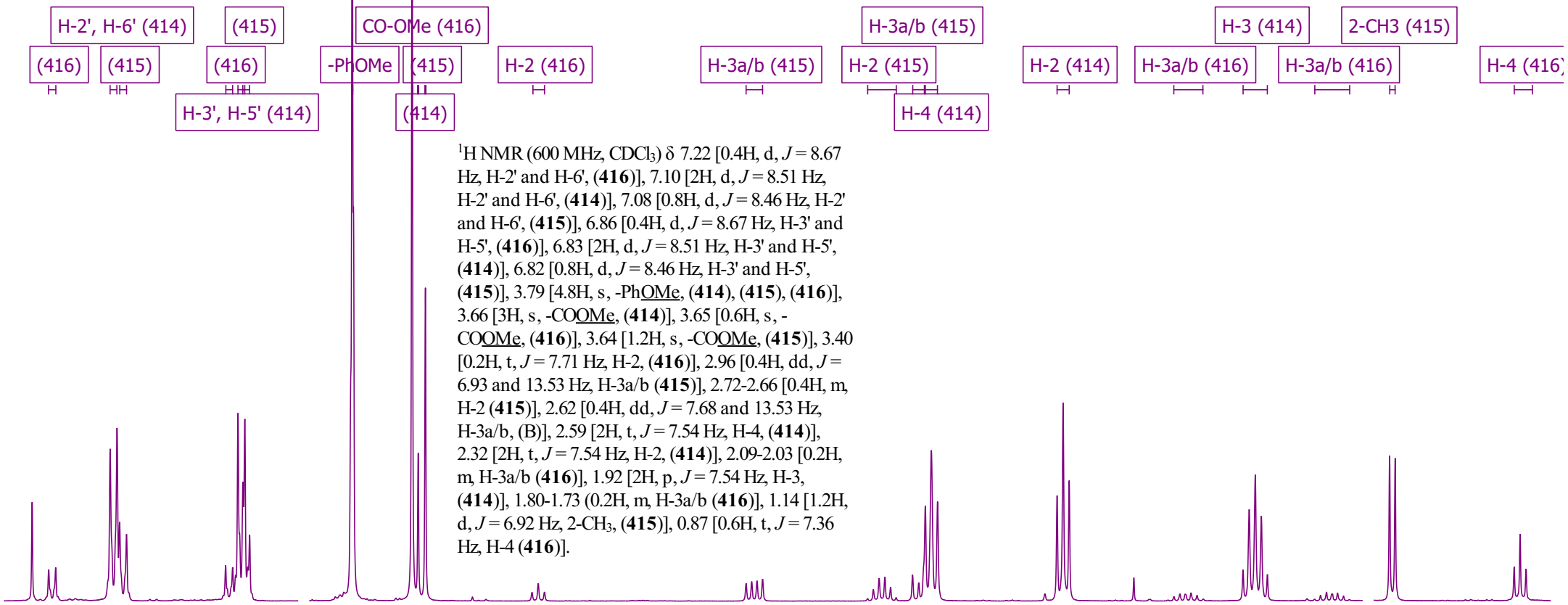


Plate 28b - ^{1}H NMR [$CDCl_3$]: methyl 4-(4'-methoxyphenyl)butanoate (**414**), methyl 2-methyl-3-(4'-methoxyphenyl)propanoate (**415**) and methyl 2-(4'-methoxyphenyl)-butanoate (**416**)



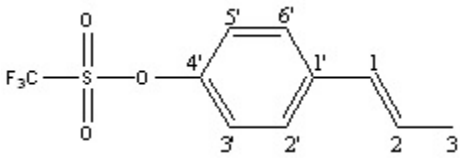


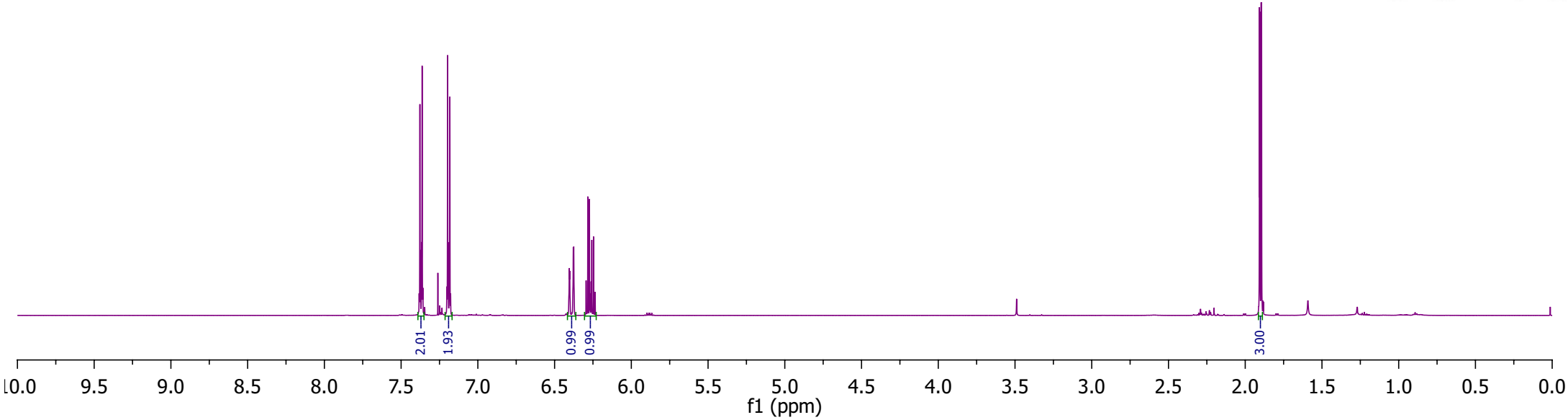




^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 [0.4H, d, J = 8.67 Hz, H-2' and H-6', (**416**)], 7.10 [2H, d, J = 8.51 Hz, H-2' and H-6', (**414**)], 7.08 [0.8H, d, J = 8.46 Hz, H-2' and H-6', (**415**)], 6.86 [0.4H, d, J = 8.67 Hz, H-3' and H-5', (**416**)], 6.83 [2H, d, J = 8.51 Hz, H-3' and H-5', (**414**)], 6.82 [0.8H, d, J = 8.46 Hz, H-3' and H-5', (**415**)], 3.79 [4.8H, s, -PhOMe, (**414**), (**415**), (**416**)], 3.66 [3H, s, -COOMe, (**414**)], 3.65 [0.6H, s, -COOMe, (**416**)], 3.64 [1.2H, s, -COOMe, (**415**)], 3.40 [0.2H, t, J = 7.71 Hz, H-2, (**416**)], 2.96 [0.4H, dd, J = 6.93 and 13.53 Hz, H-3a/b (**415**)], 2.72-2.66 [0.4H, m, H-2 (**415**)], 2.62 [0.4H, dd, J = 7.68 and 13.53 Hz, H-3a/b, (B)], 2.59 [2H, t, J = 7.54 Hz, H-4, (**414**)], 2.32 [2H, t, J = 7.54 Hz, H-2, (**414**)], 2.09-2.03 [0.2H, m, H-3a/b (**416**)], 1.92 [2H, p, J = 7.54 Hz, H-3, (**414**)], 1.80-1.73 (0.2H, m, H-3a/b (**416**)], 1.14 [1.2H, d, J = 6.92 Hz, 2-CH_3, (**415**)], 0.87 [0.6H, t, J = 7.36 Hz, H-4 (**416**)].

Plate 29a - ^{1}H NMR [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.80 Hz, H-2' and H-6'), 7.19 (2H, d, *J* = 8.80 Hz, H-3' and H-5'), 6.39 (1H, br dd, *J* = 15.76, 1.65 Hz, H-1), 6.27 (1H, dq, *J* = 15.76, 6.59 Hz, H-2), 1.90 (3H, dd, *J* = 6.59, 1.65 Hz, H-3)

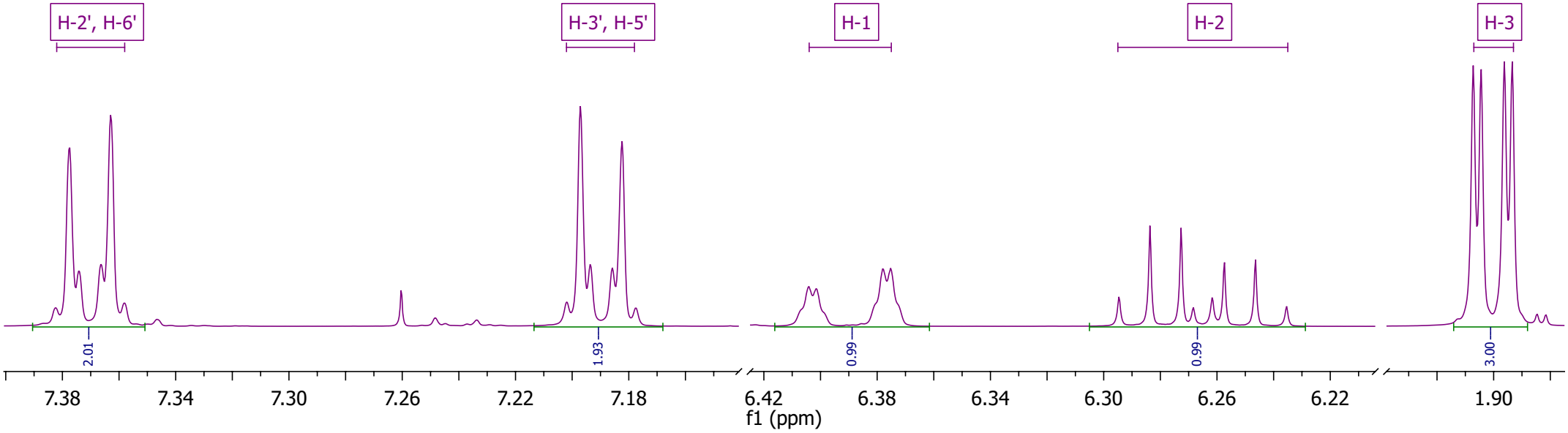
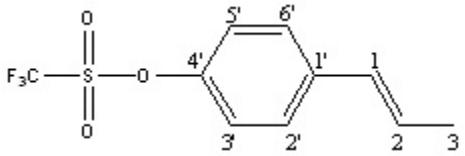


Plate 29b - ^{13}C NMR [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)



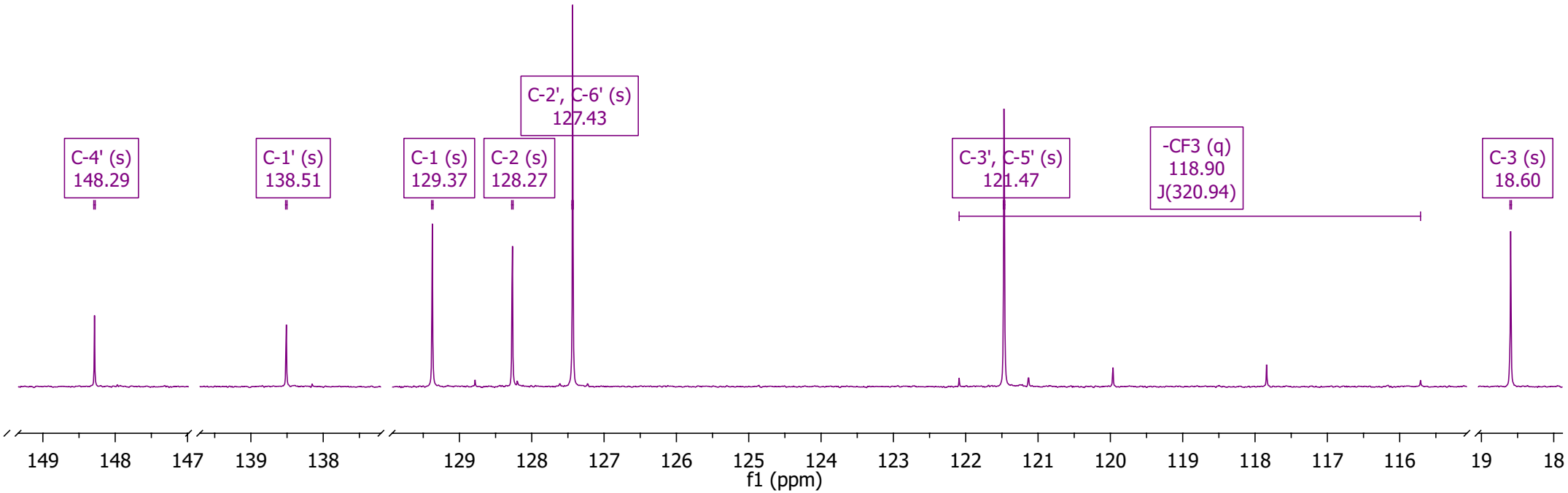


Plate 29c - DEPT [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)

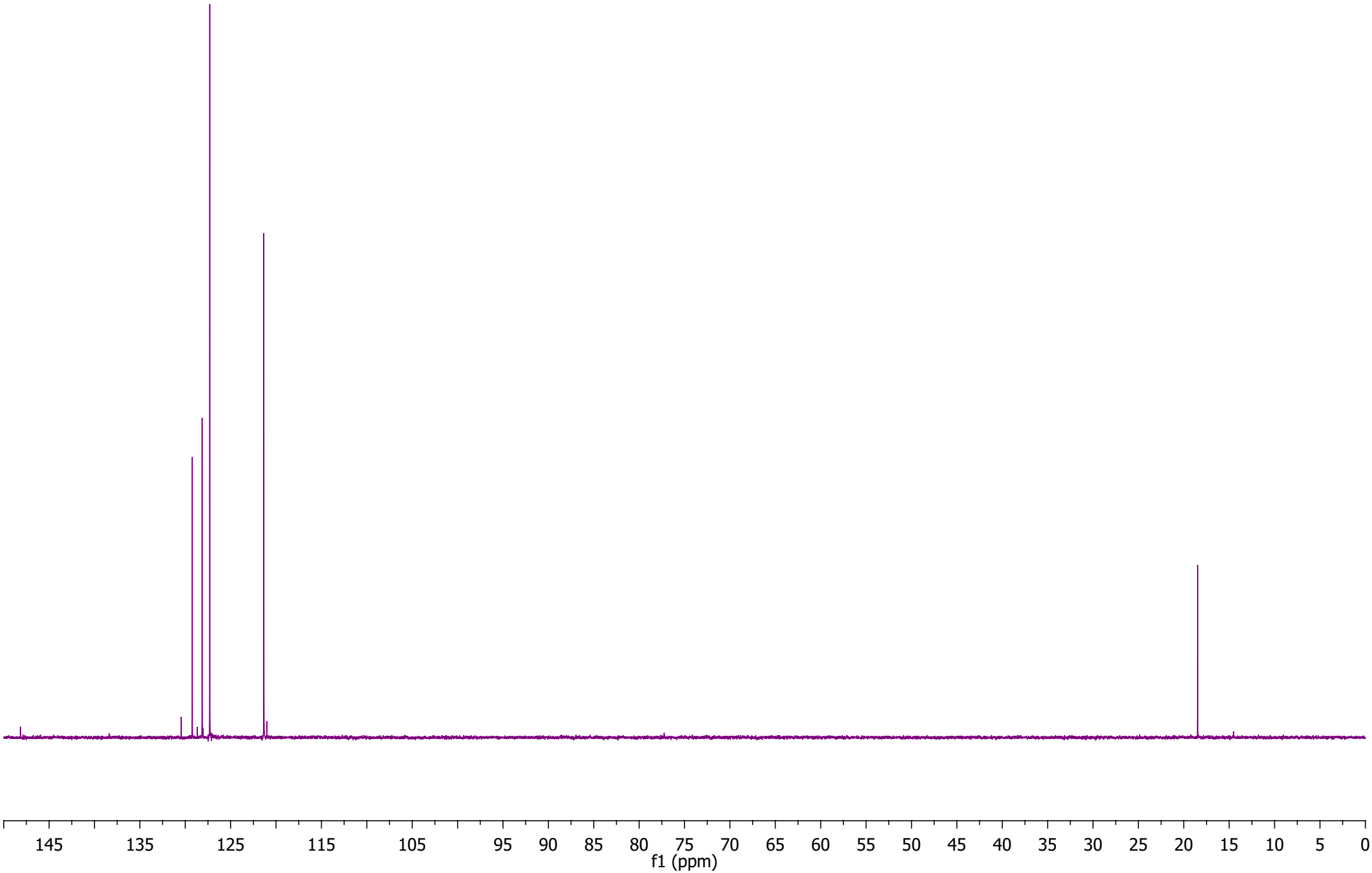


Plate 29d - HSQC [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)

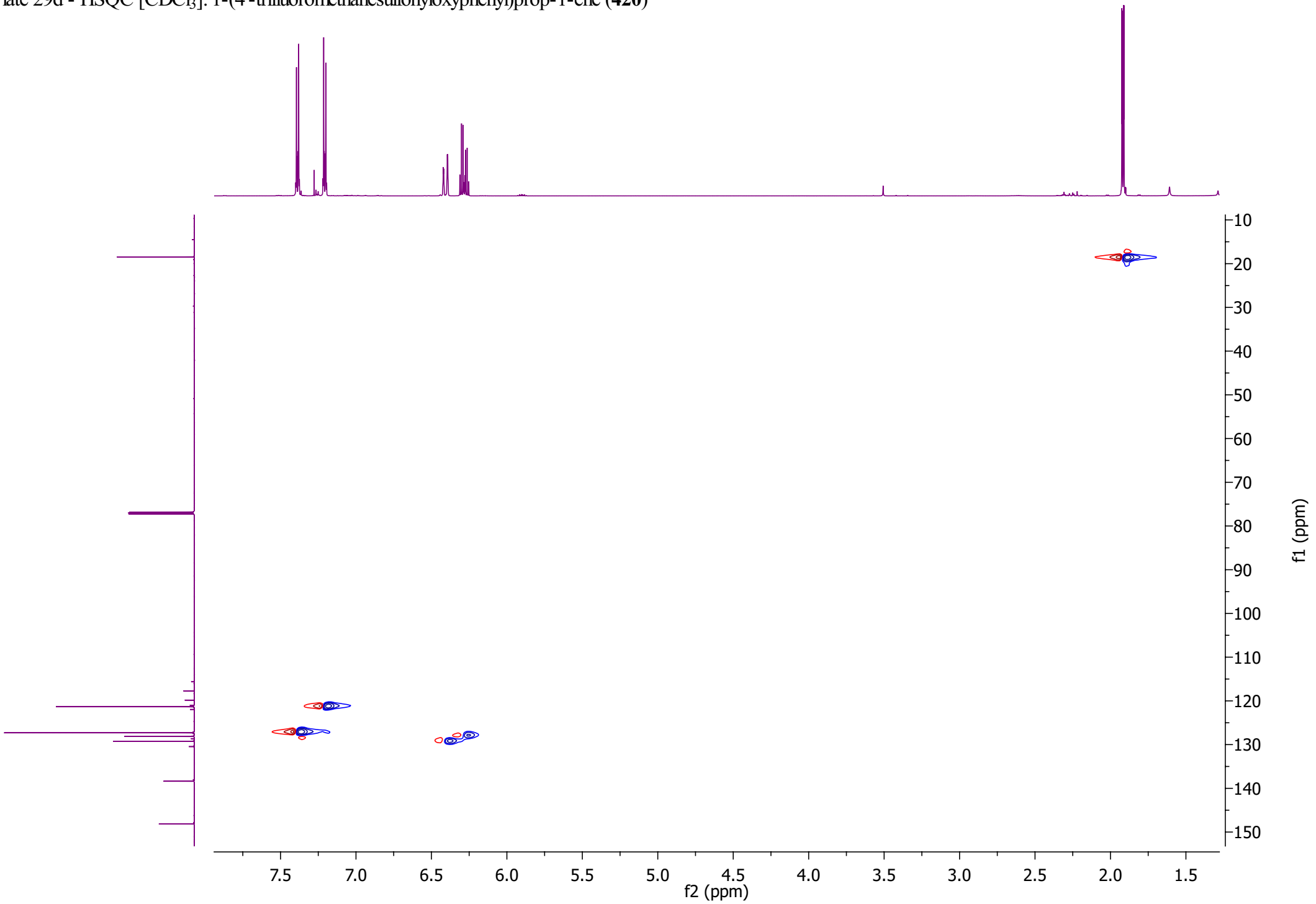


Plate 29e - HSQC (expansion) [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)

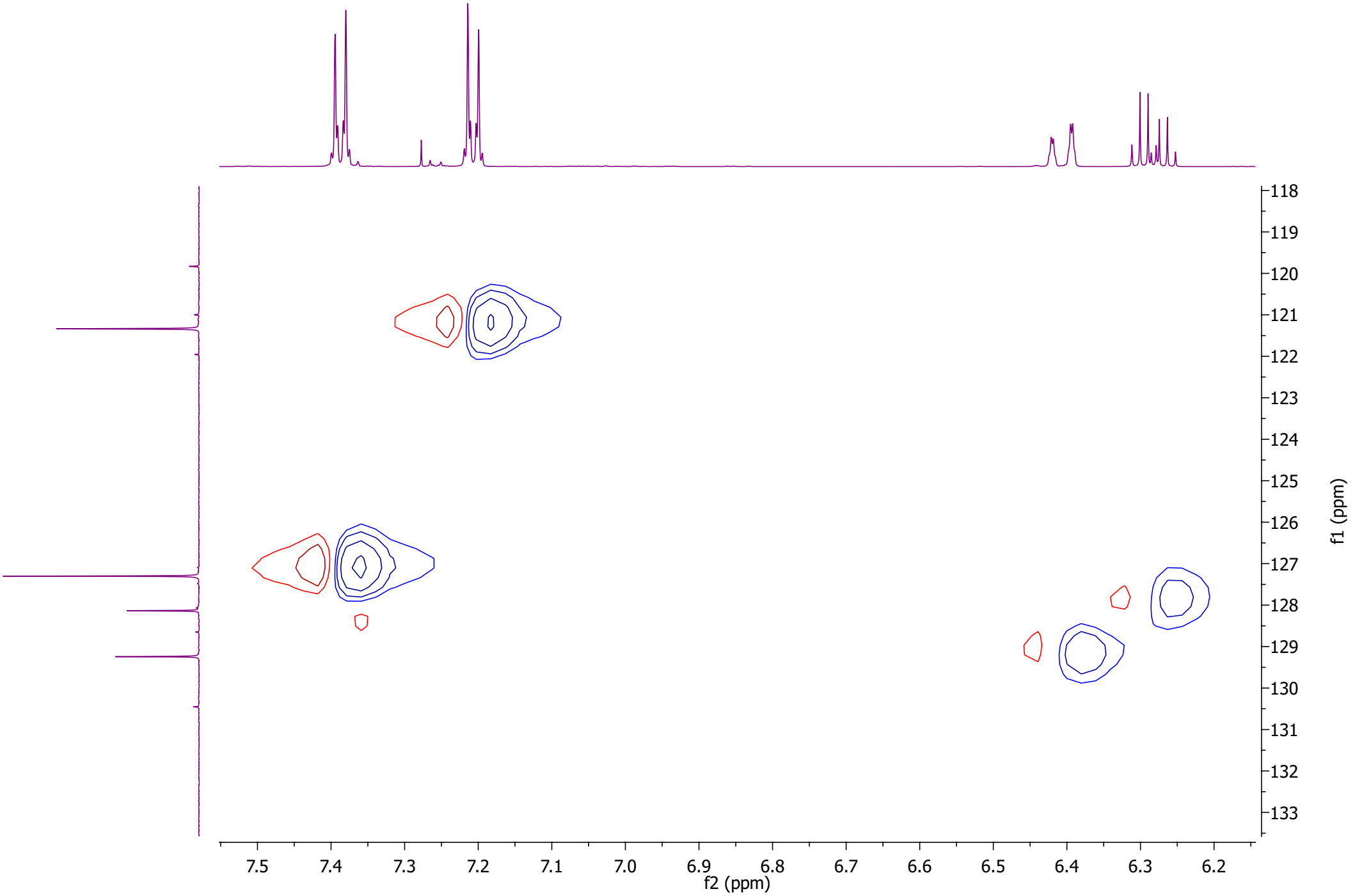


Plate 29f - HMBC [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)

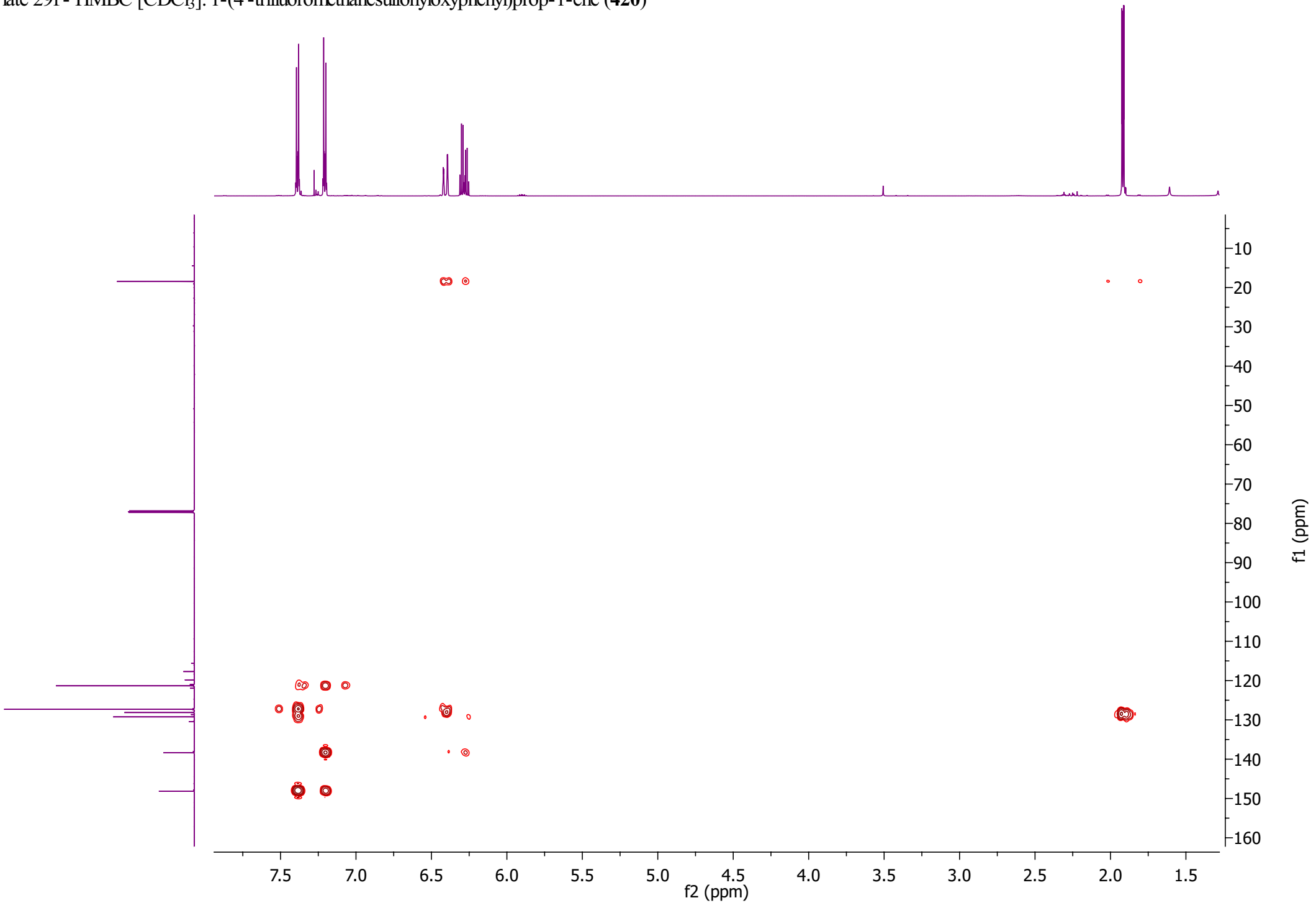


Plate 29g - HMBC (expansion) [$CDCl_3$]: 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene (**420**)

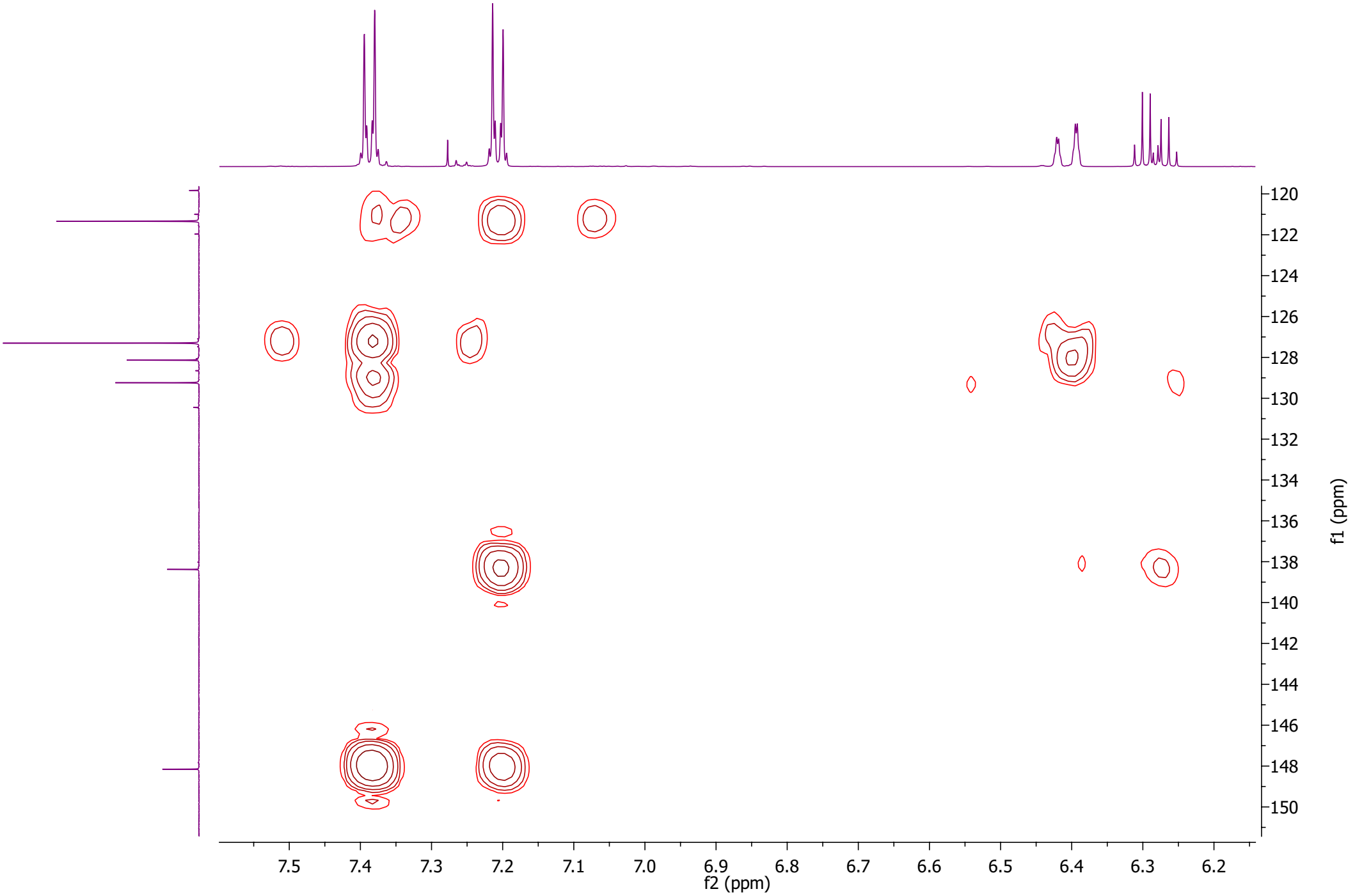
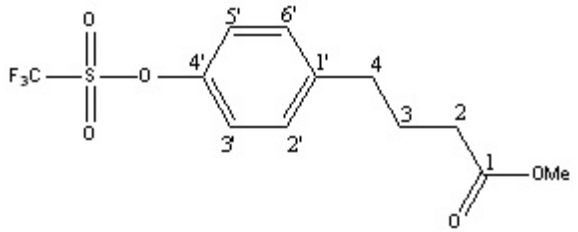


Plate 30a - ^{1}H NMR [$CDCl_3$]: methyl 4-(4'-trifluoromethanesulfonyloxy-phenyl)butanoate (**421**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.64 Hz, H-3' and H-5'), 7.19 (2H, d, *J* = 8.64 Hz, H-2' and H-6'), 3.67 (3H, s, -OMe), 2.68 (2H, t, *J* = 7.55 Hz, H-4), 2.34 (2H, t, *J* = 7.55 Hz, H-2), 1.96 (2H, p, *J* = 7.55 Hz, H-3).

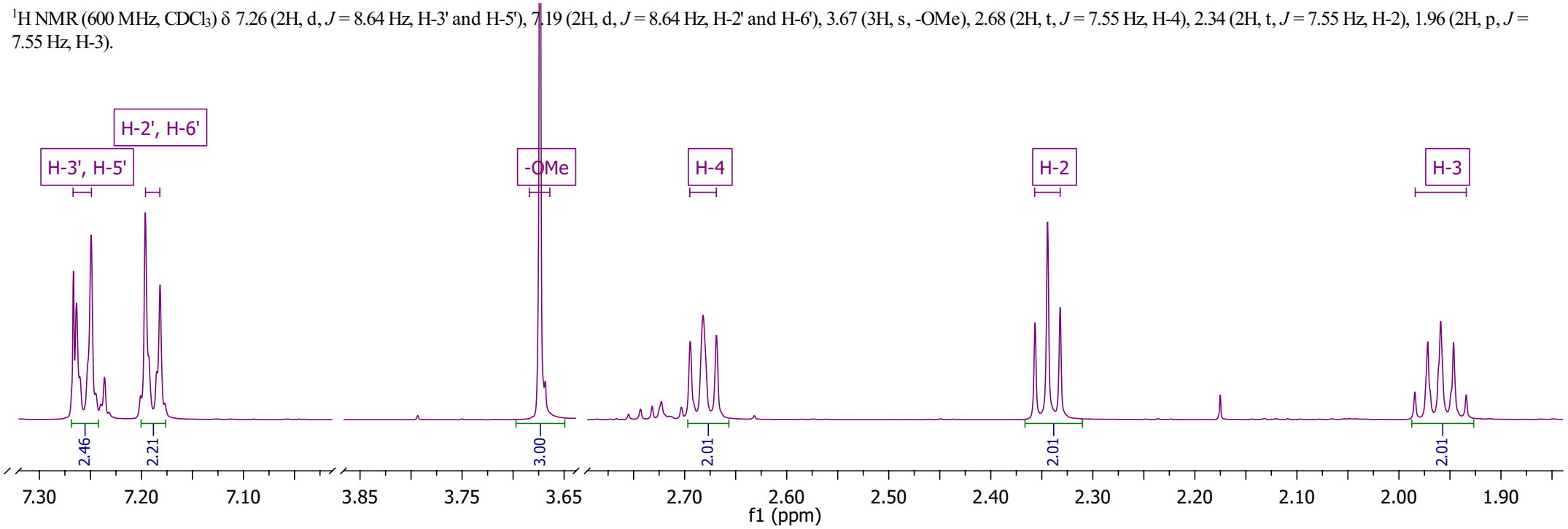
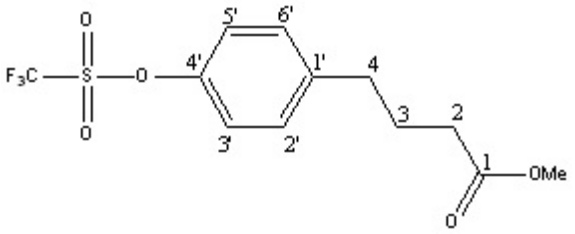


Plate 30b - ^{13}C NMR [$CDCl_3$]: methyl 4-(4'-trifluoromethanesulfonyloxy-phenyl)butanoate (**421**)



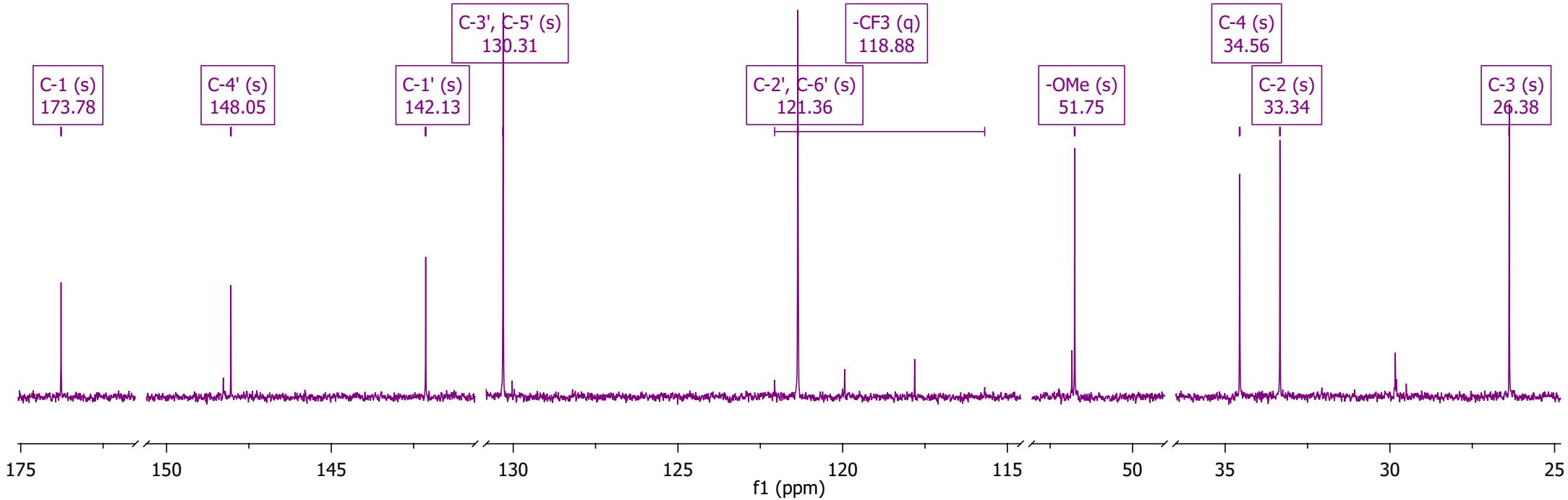


Plate 30c - DEPT [$CDCl_3$]: methyl 4-(4'-trifluoromethanesulfonyloxy-phenyl)butanoate (**421**)

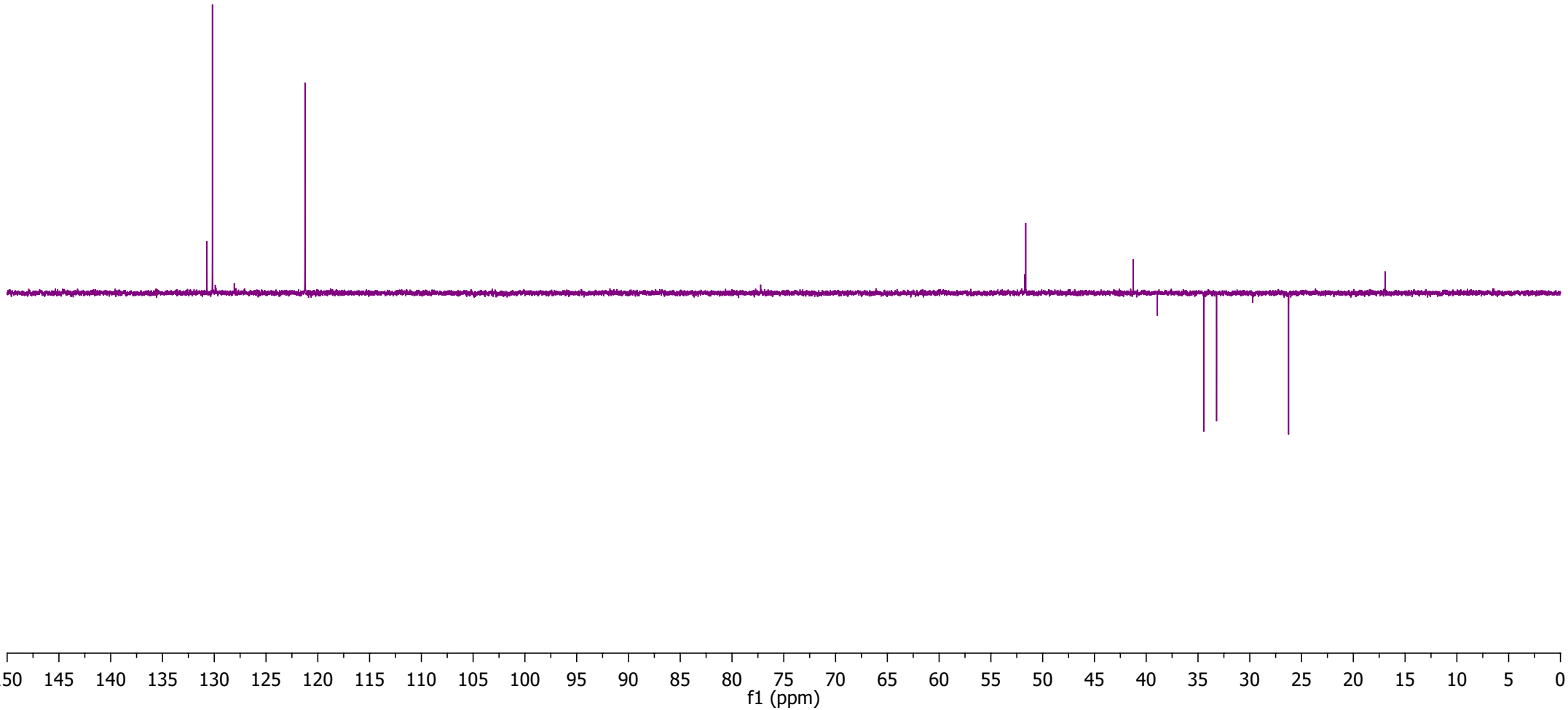


Plate 30d - HSQC [$CDCl_3$]: methyl 4-(4'-trifluoromethanesulfonyloxy-phenyl)butanoate (**421**)

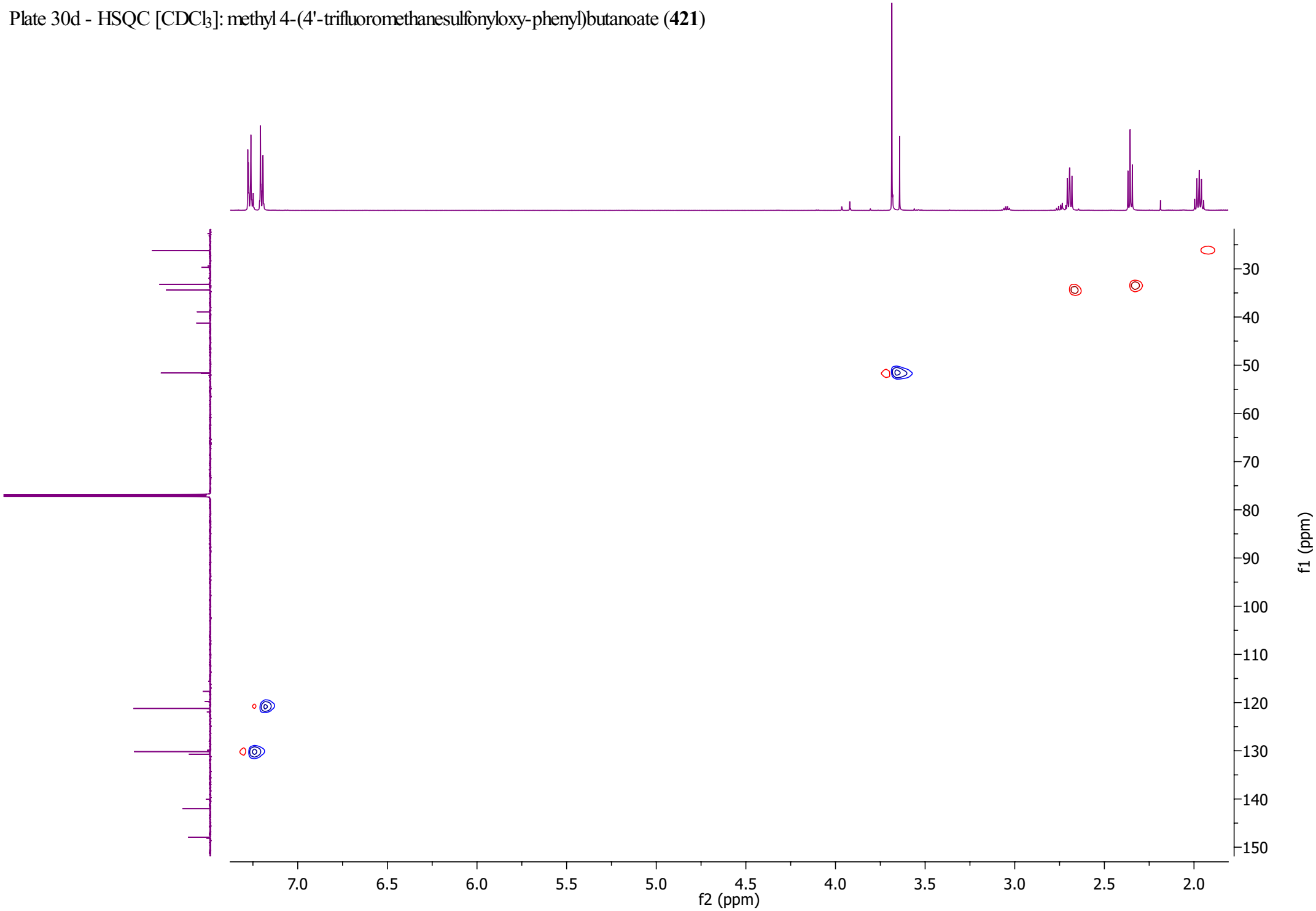


Plate 30e - HMBC [$CDCl_3$]: methyl 4-(4'-trifluoromethanesulfonyloxy-phenyl)butanoate (**421**)

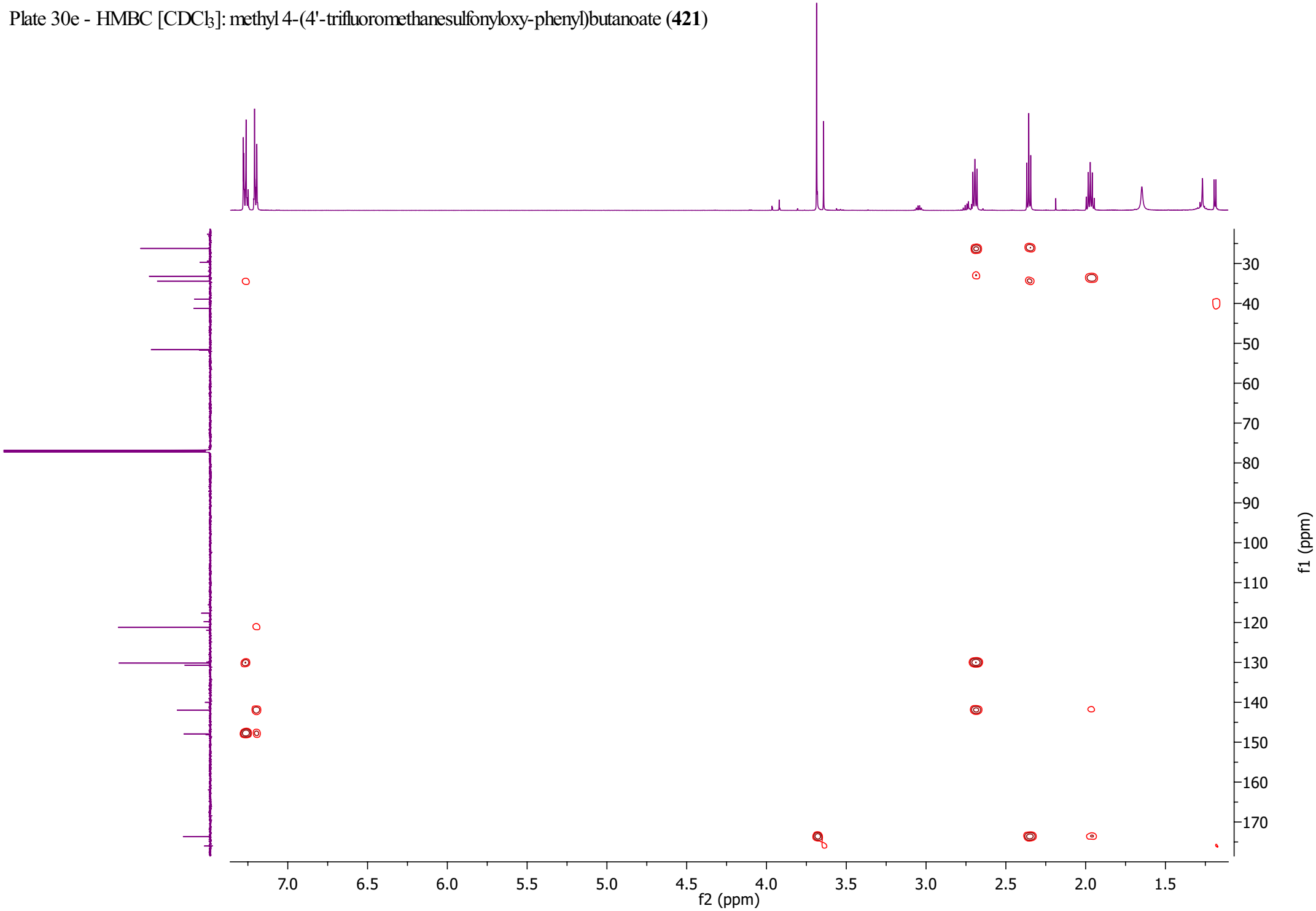
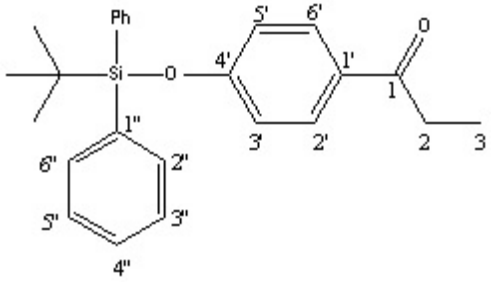


Plate 31a - ^{1}H NMR [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.77 Hz, H-2' and H-6'), 7.70 (4H, dd, *J* = 7.04, 1.31 Hz, H-2" and H-6"), 7.46-7.43 (2H, m, H-4"), 7.38 (4H, dd, *J* = 7.58, 7.04 Hz, H-3" and H-5"), 6.79 (2H, d, *J* = 8.77 Hz, H-3' and H-5'), 2.88 (q, *J* = 7.27 Hz, H-2), 1.16 (t, *J* = 7.3 Hz, H-3), 1.10 (9H, s, -Me)

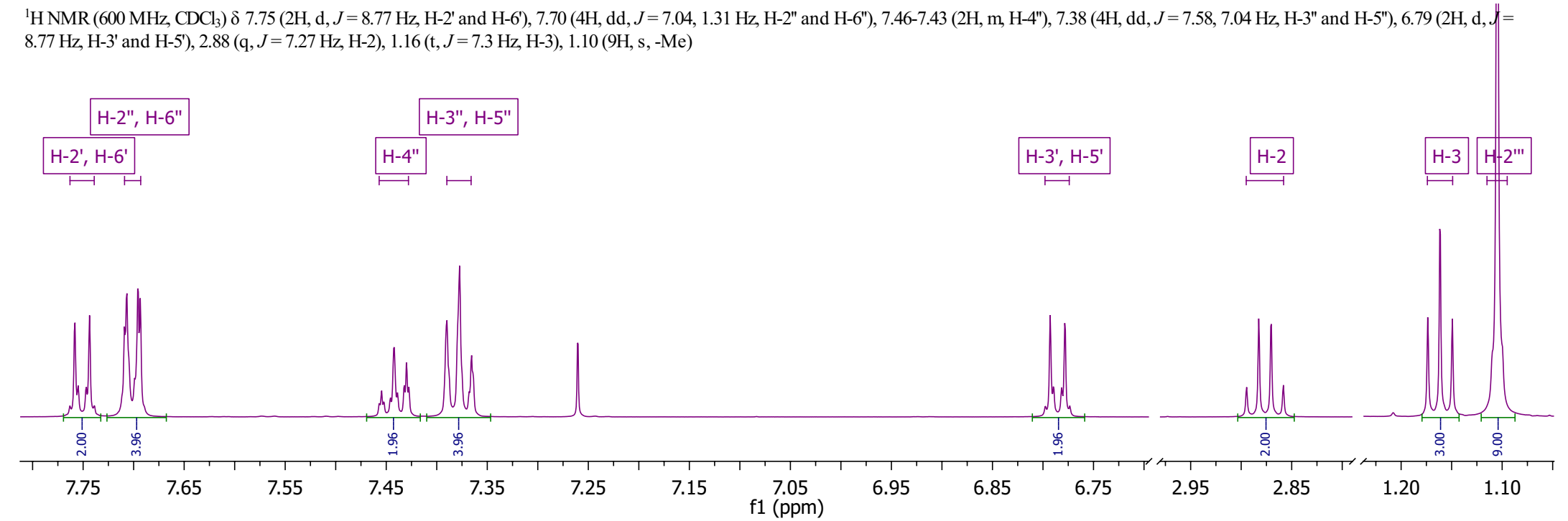
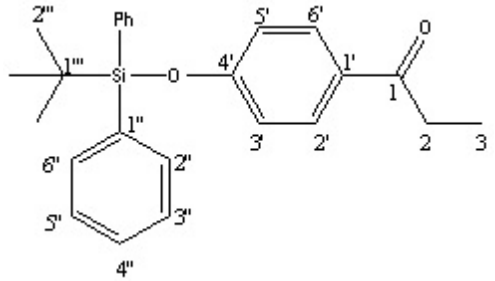
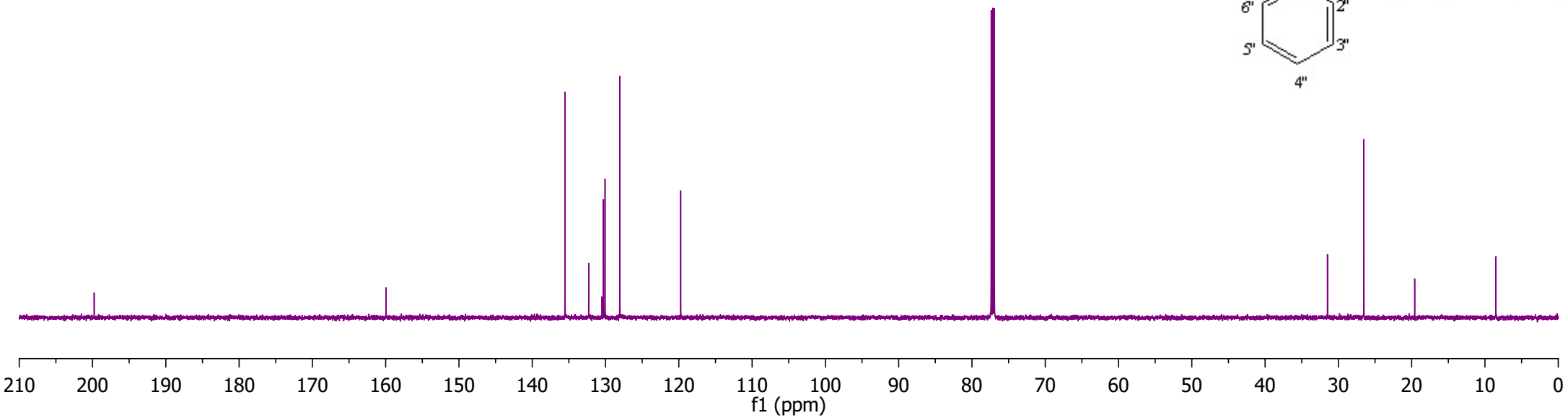


Plate 31b - ^{13}C NMR [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**





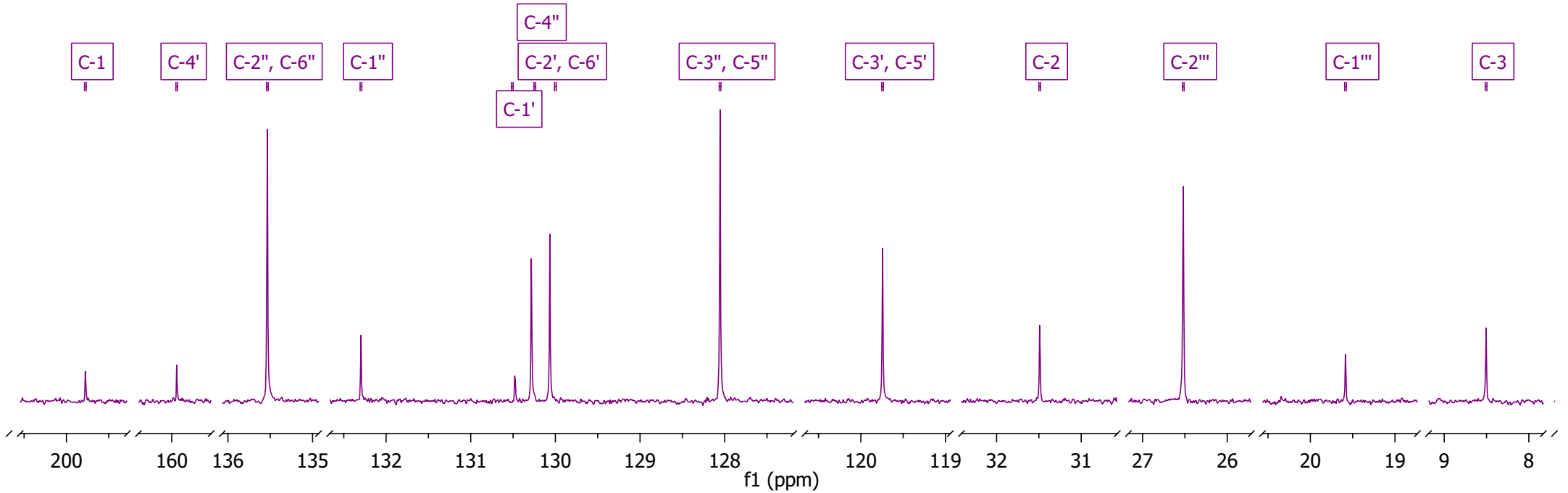


Plate 31c - DEPT [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**

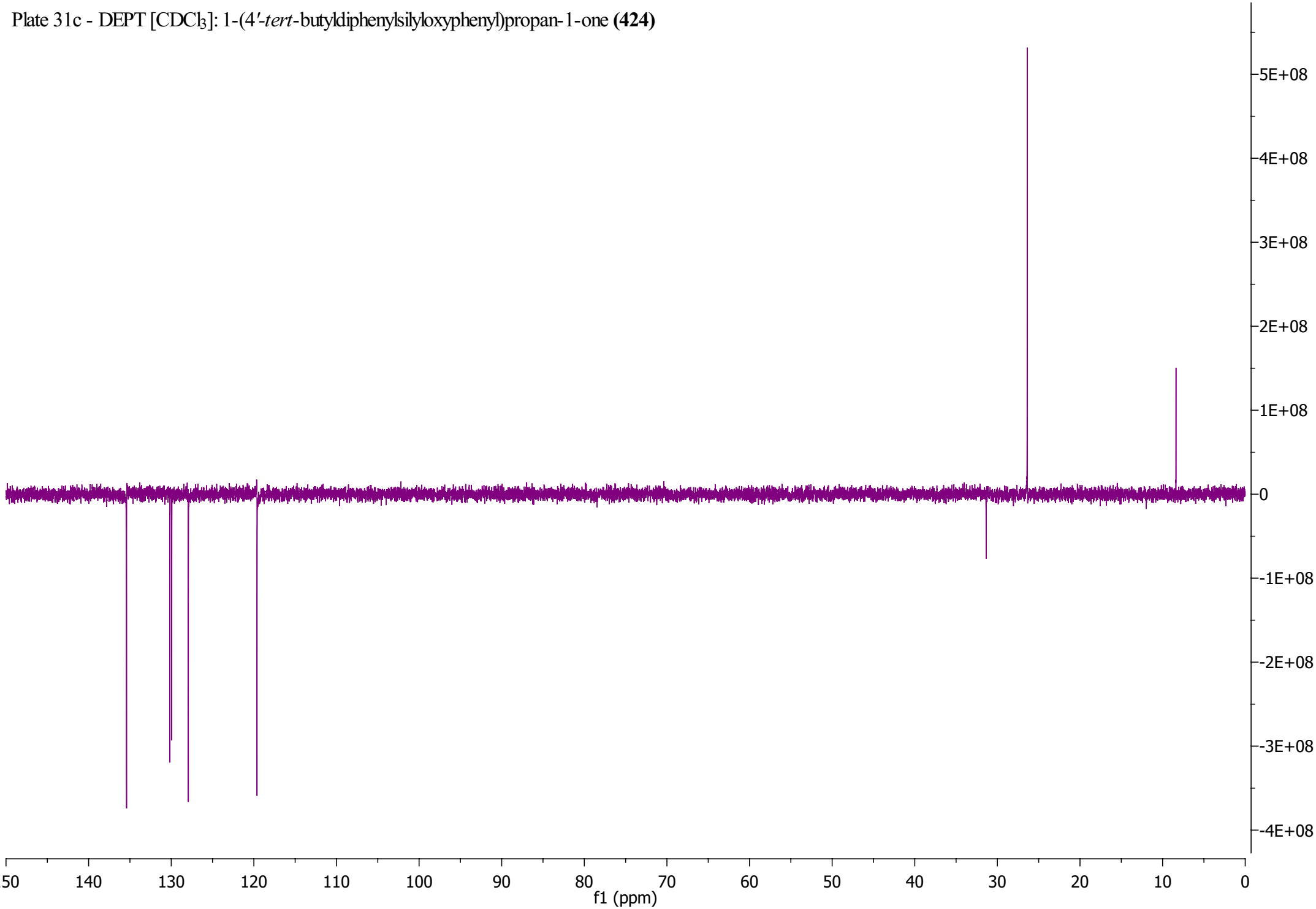


Plate 31d - HSQC [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**

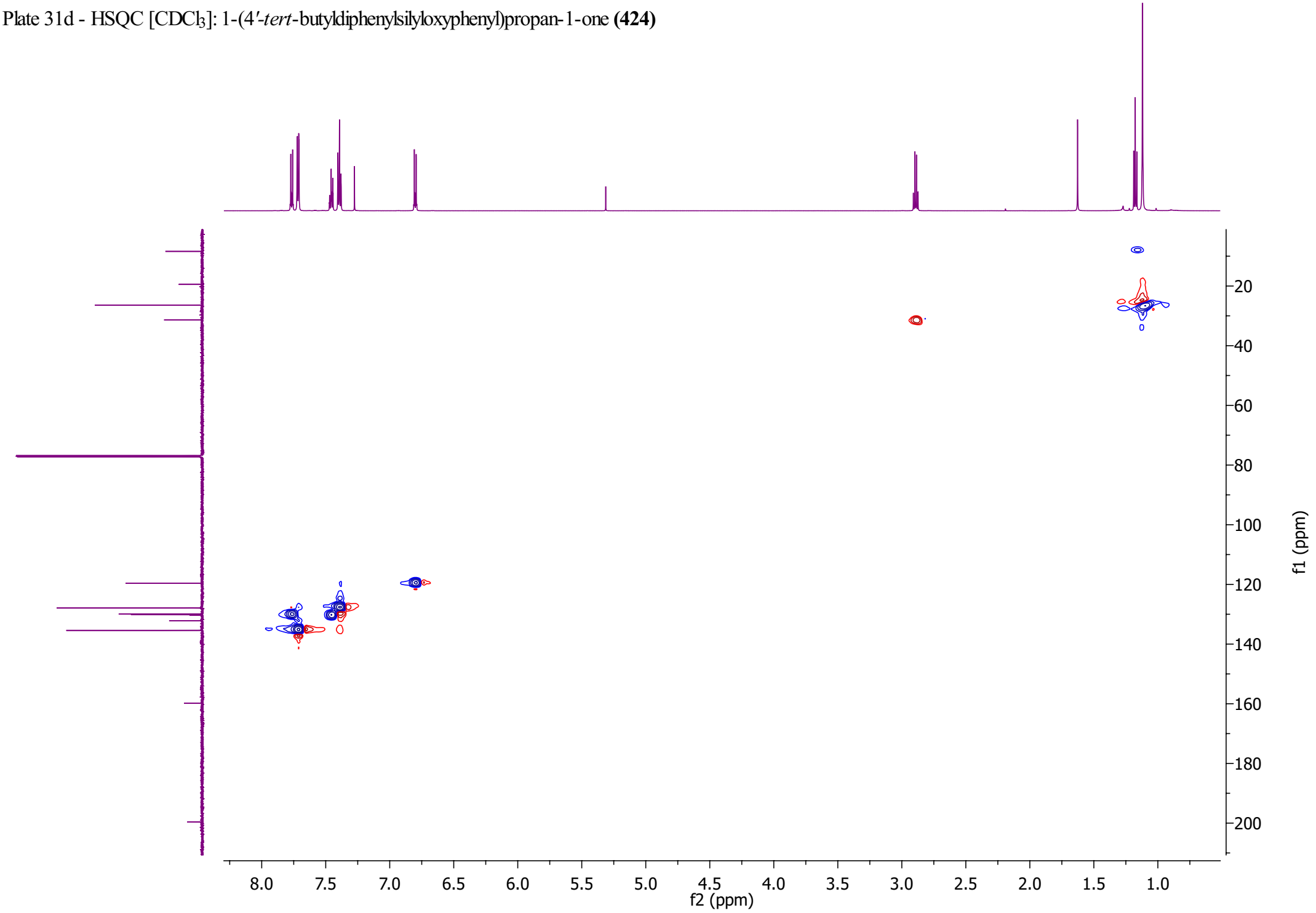


Plate 31e - HSQC expansion [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**

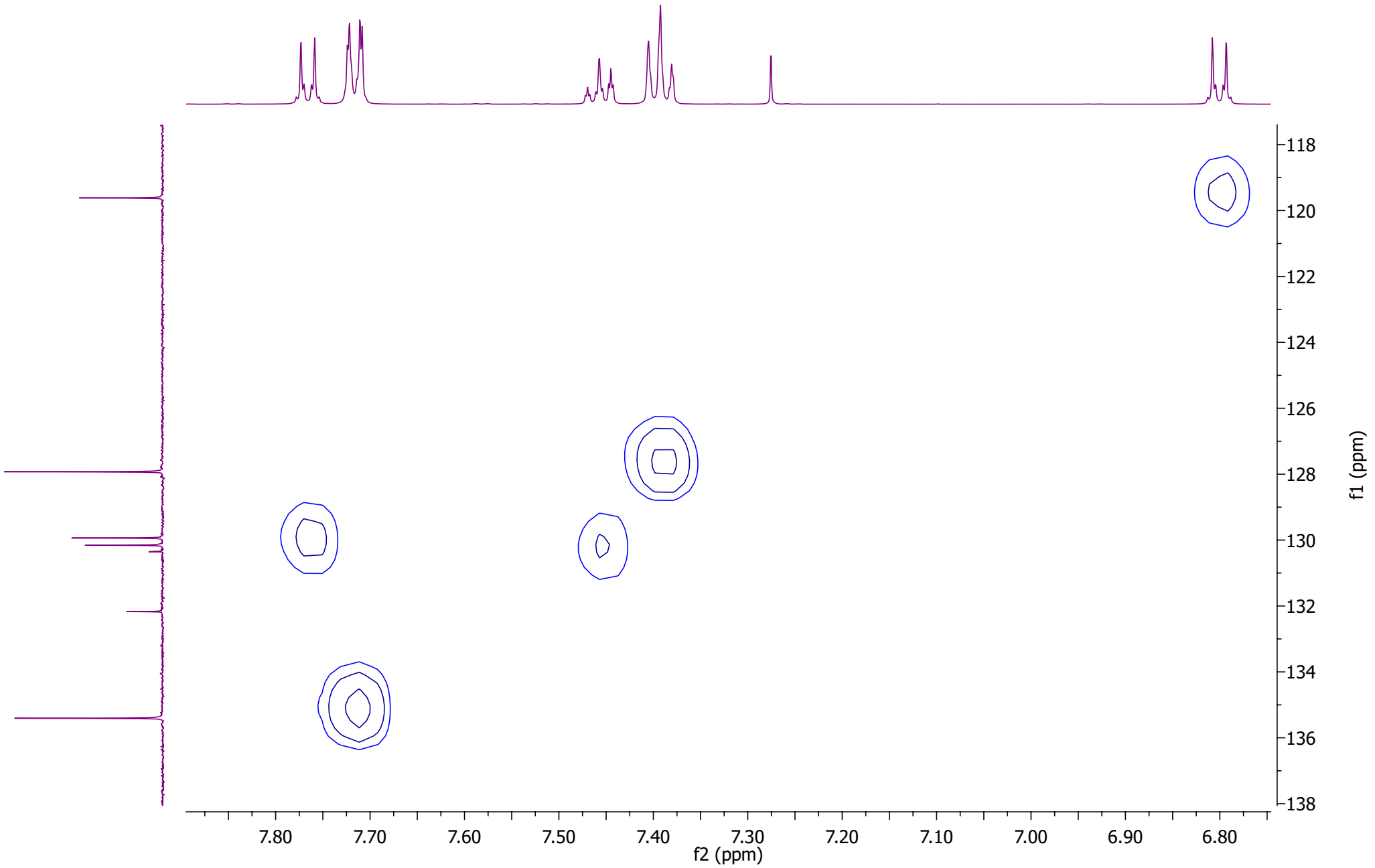


Plate 31f - HMBC [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**

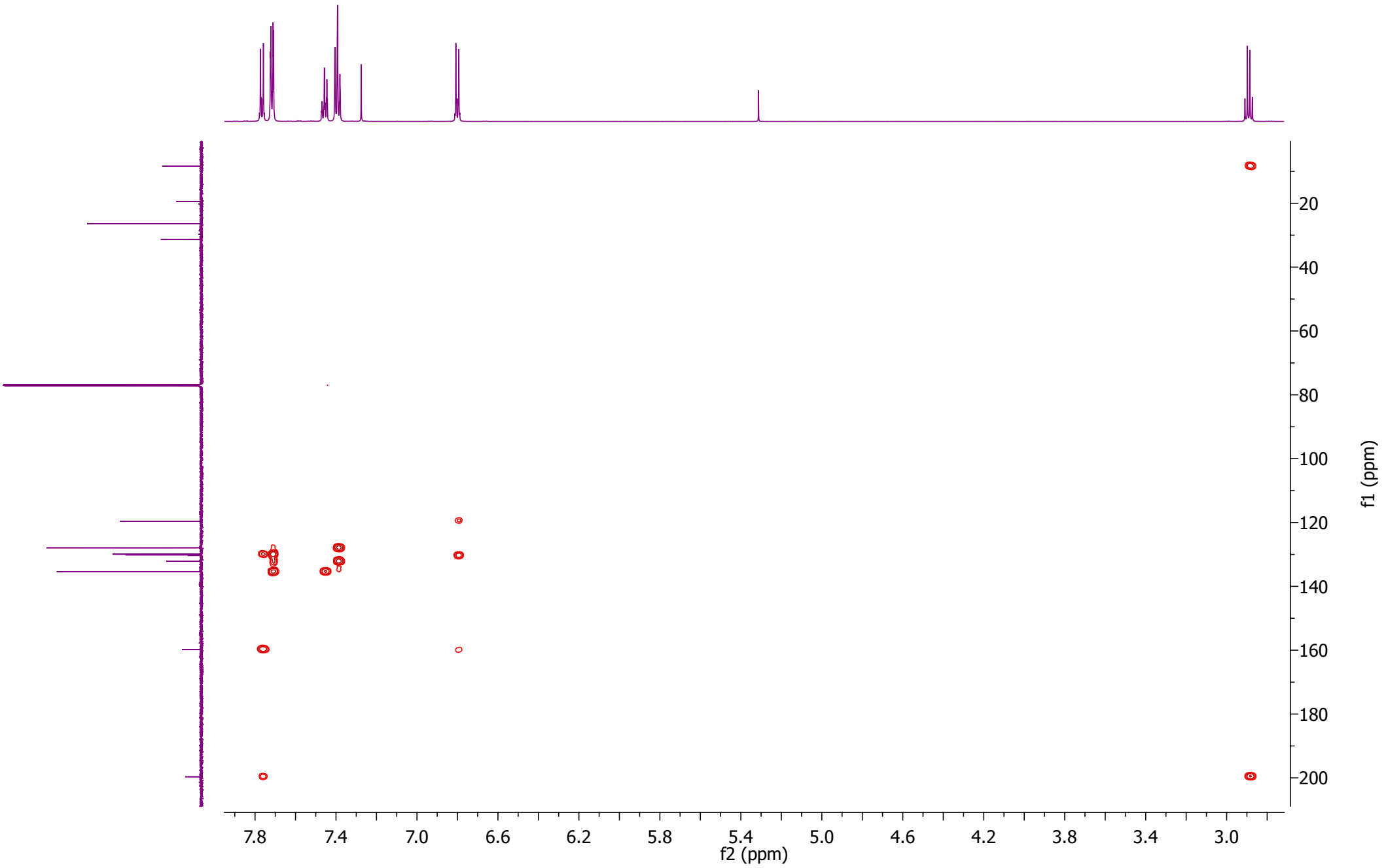


Plate 31g - HMBC expansion [$CDCl_3$]: 1-(4′-*tert*-butyldiphenylsilyloxyphenyl)propan-1-one **(424)**

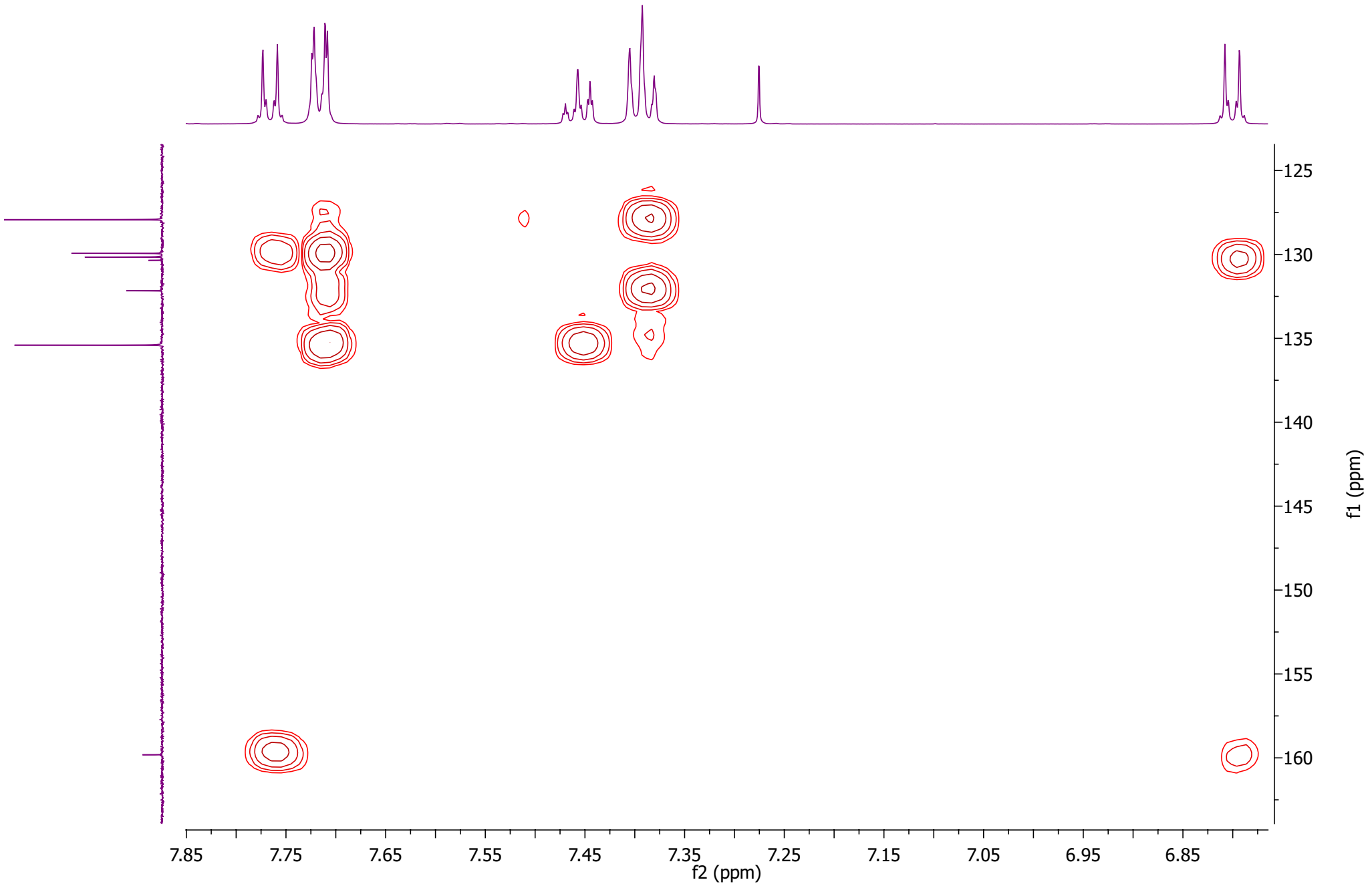
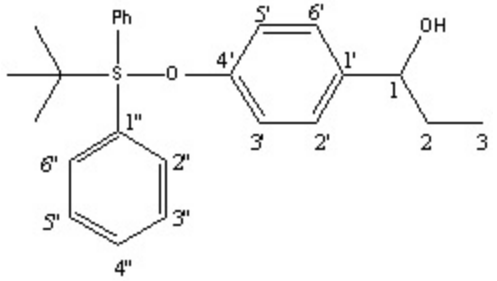


Plate 32a - ^{1}H NMR [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.74 (4H, m, H-2" and H-6"), 7.46-7.43 (2H, m, H-4"), 7.40-7.37 (4H, m, H-3" and H-5"), 7.08 (2H, d, *J* = 8.39 Hz, H-2' and H-6'), 6.77 (2H, d, *J* = 8.39 Hz, H-3' and H-5'), 4.46 (1H, t, *J* = 6.67 Hz, H-1), 1.81-1.74 (1H, m, H-2a or H-2b), 1.71-1.64 (1H, m, H-2a or H-2b), 1.14 [9H, s, $-CH_3)_3$], 0.86 (3H, t, *J* = 7.42 Hz, H-3).

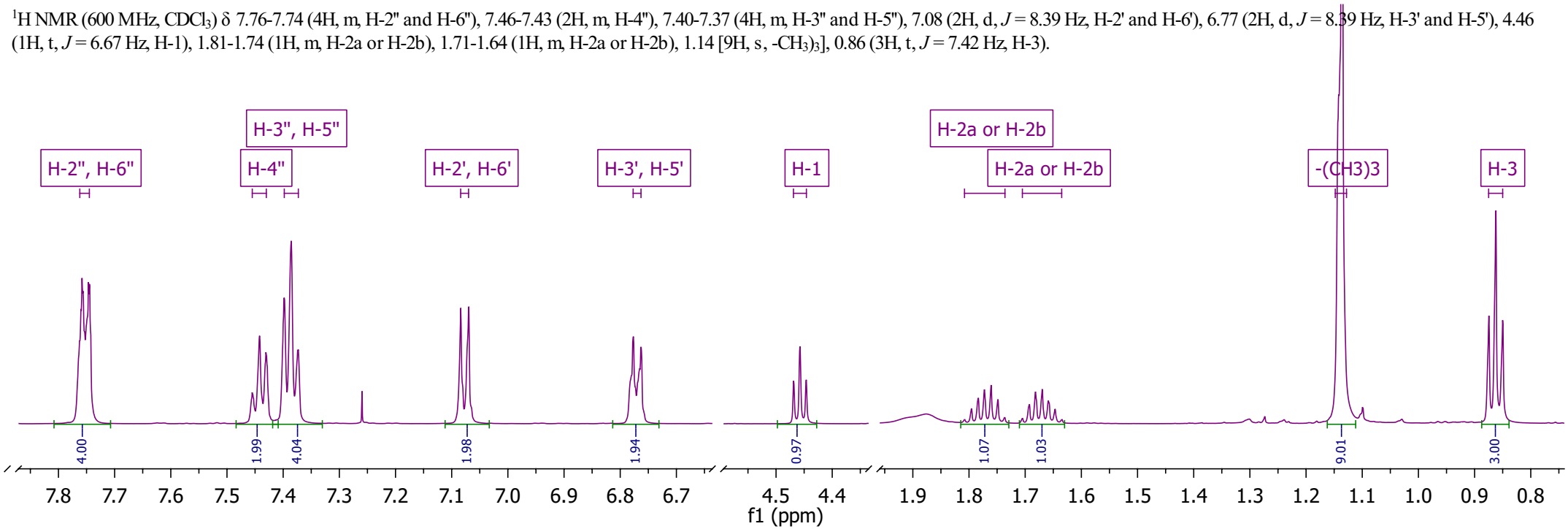
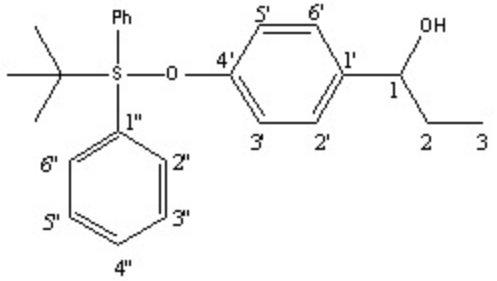


Plate 32b - ^{13}C NMR [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)



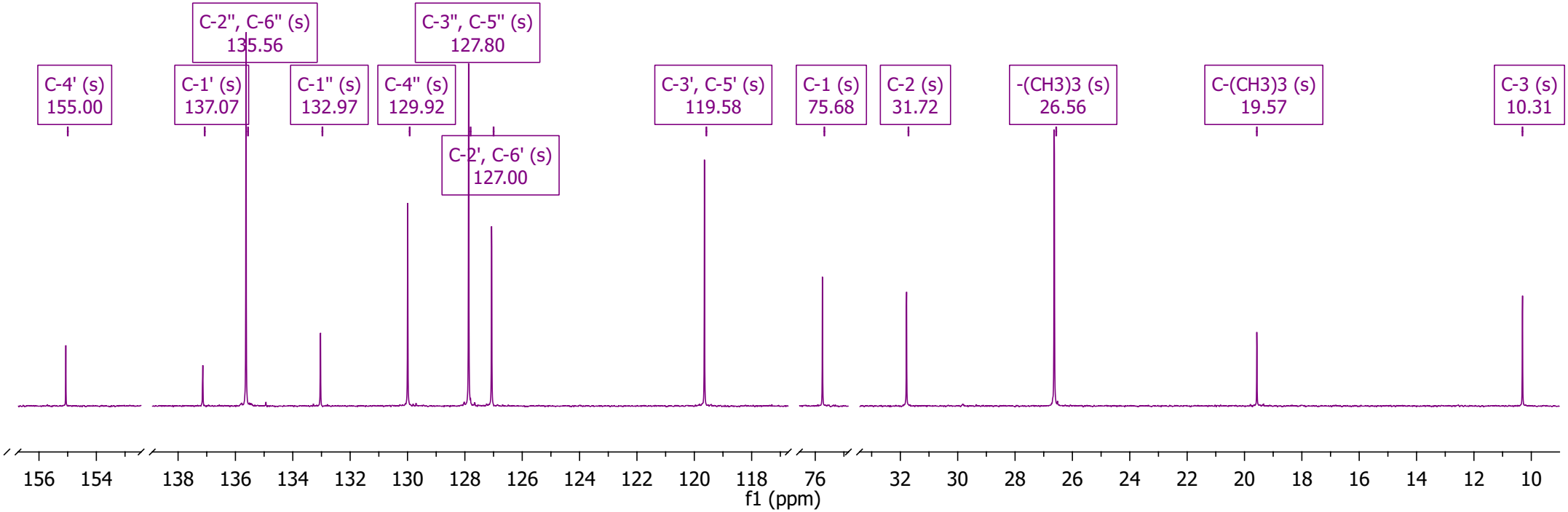


Plate 32c - DEPT [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)

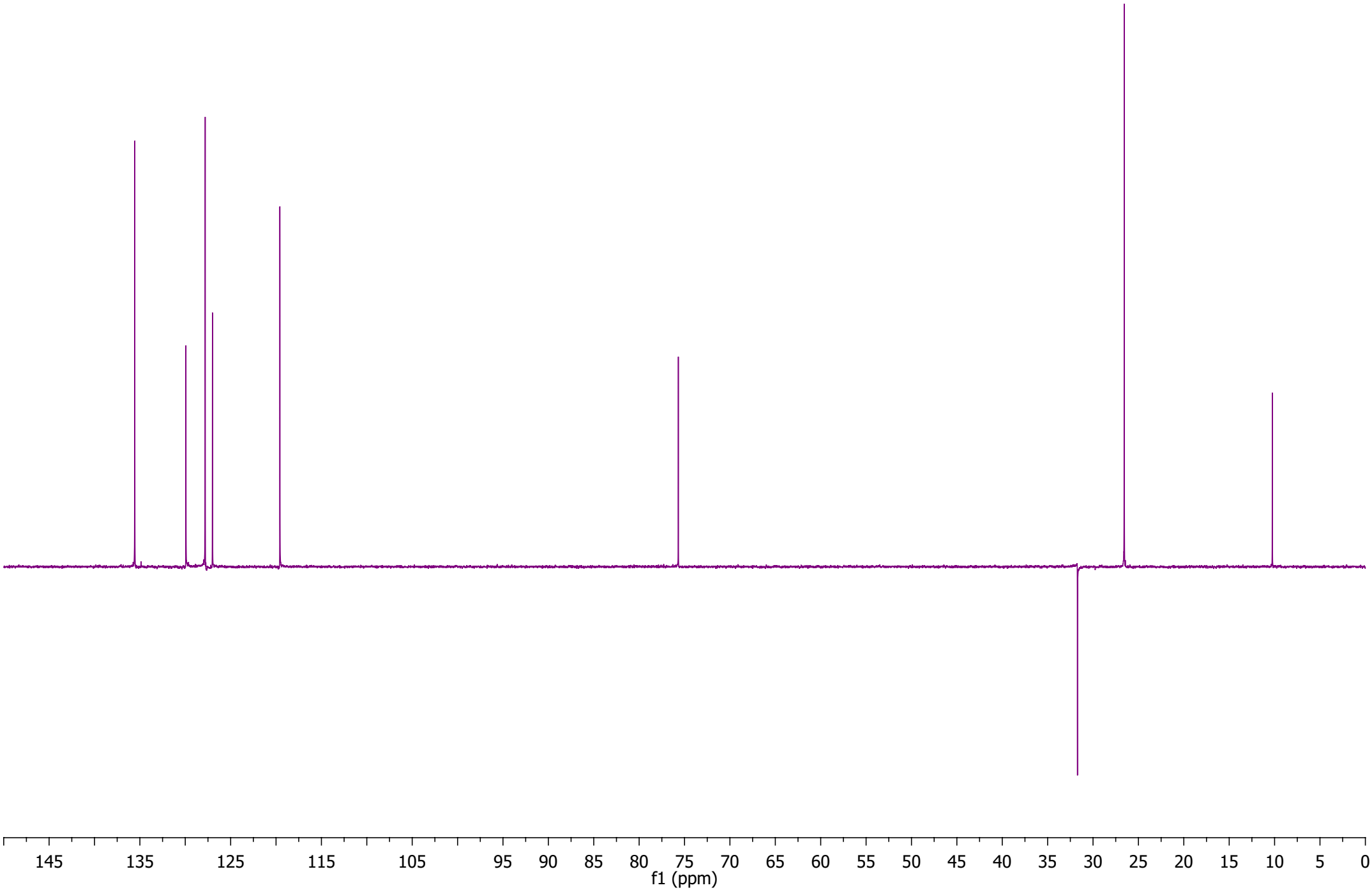


Plate 32d - HSQC [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)

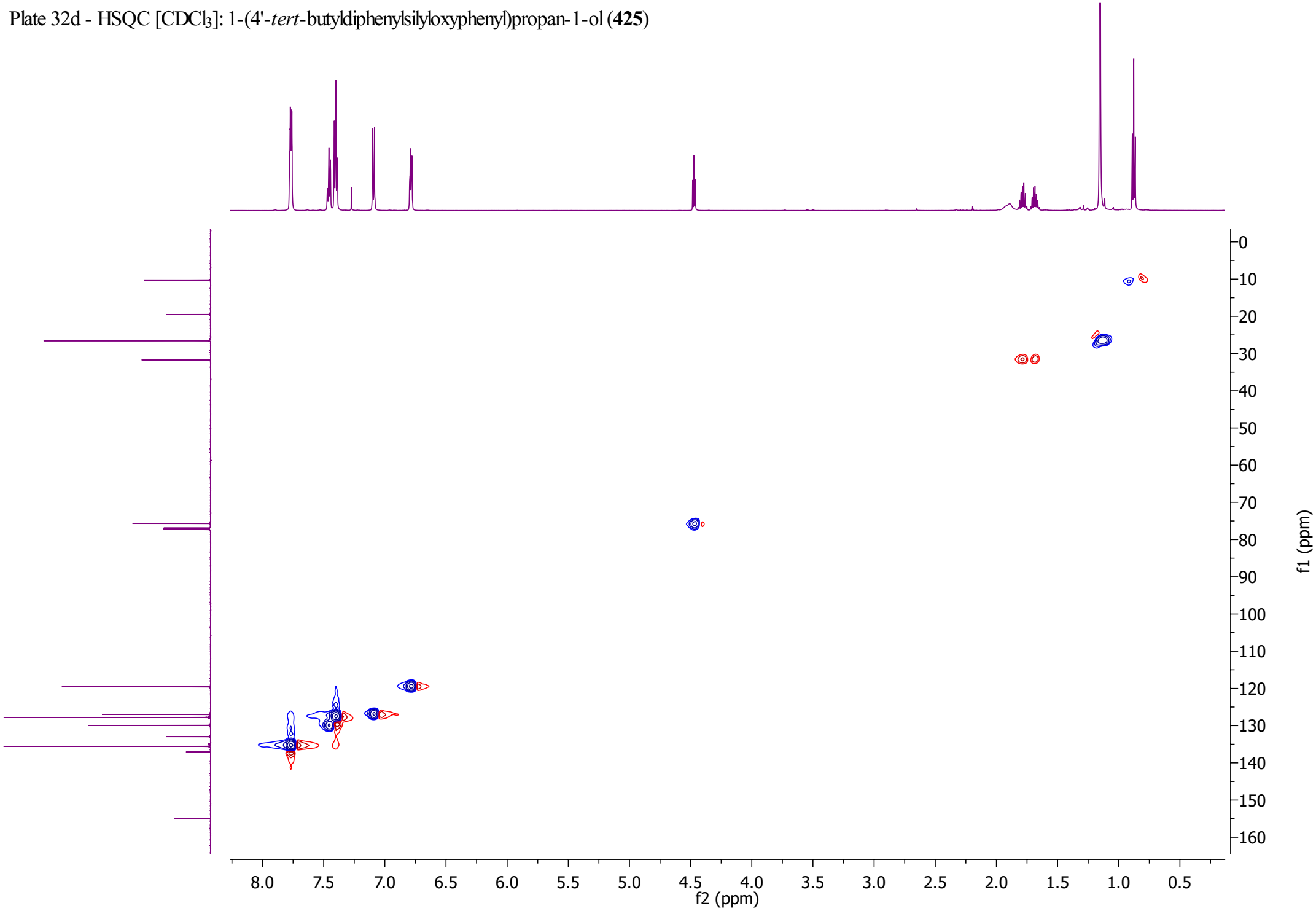


Plate 32e - HSQC (expansion) [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)

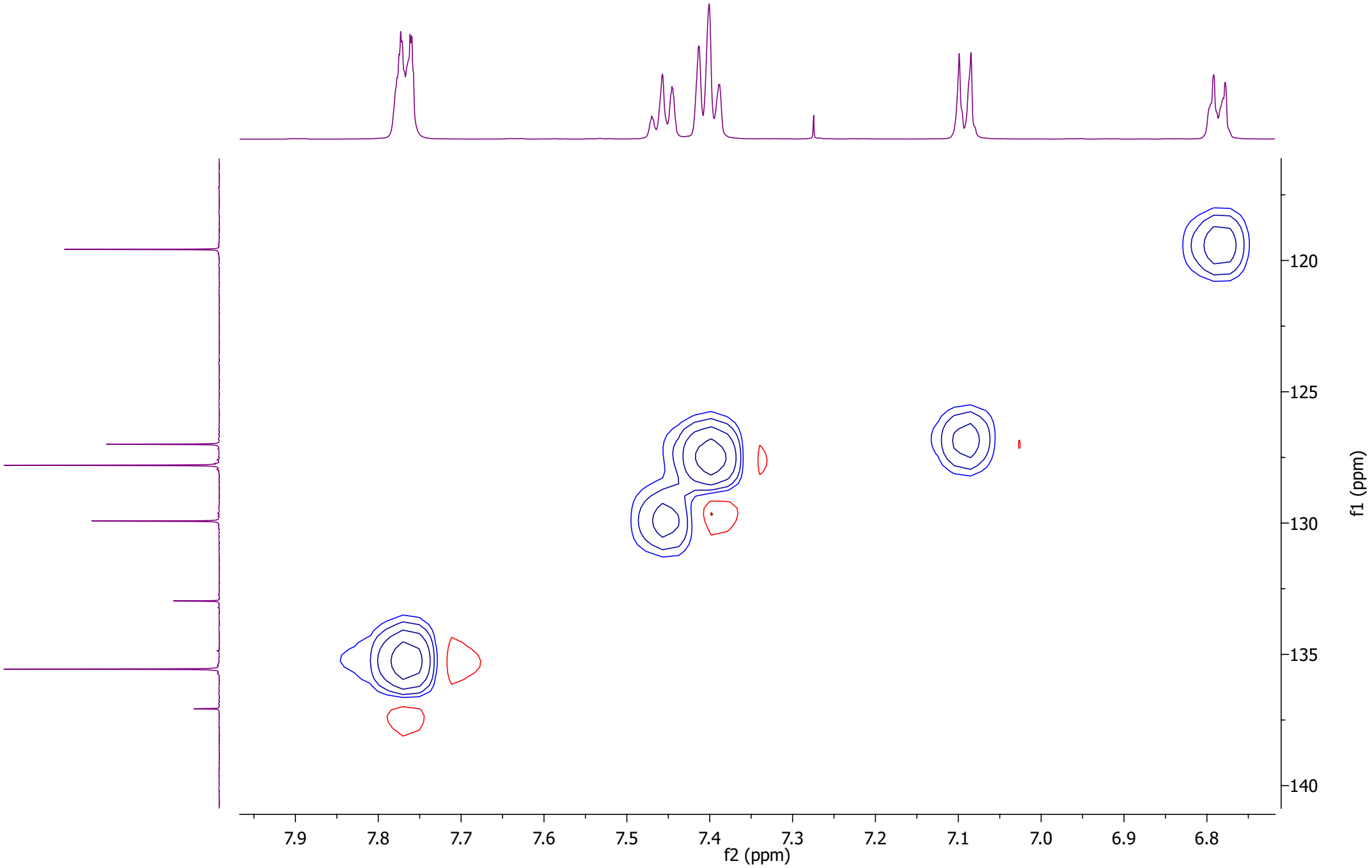


Plate 32f - HMBC [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)

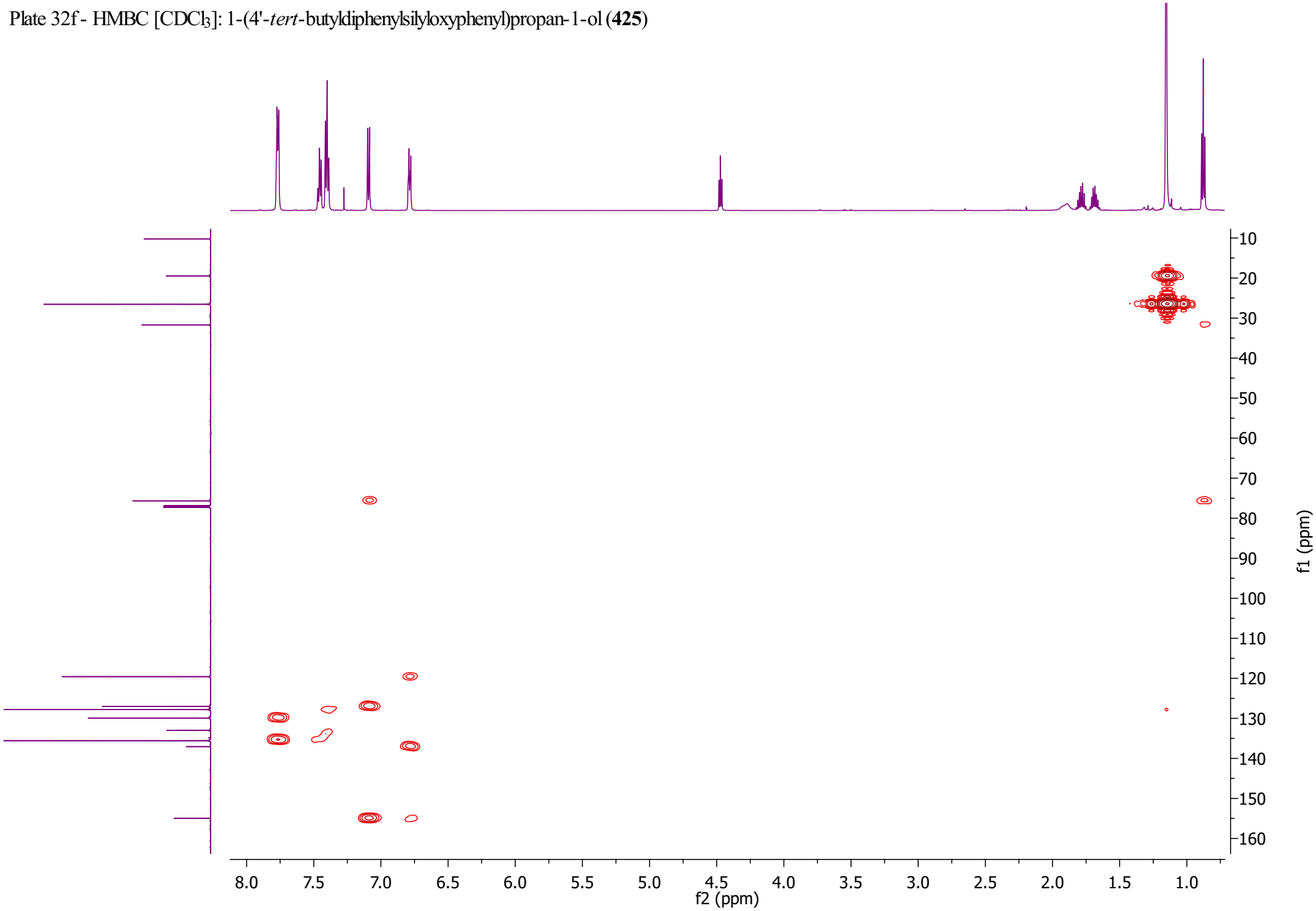


Plate 32g - HMBC (expansion) [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)propan-1-ol (**425**)

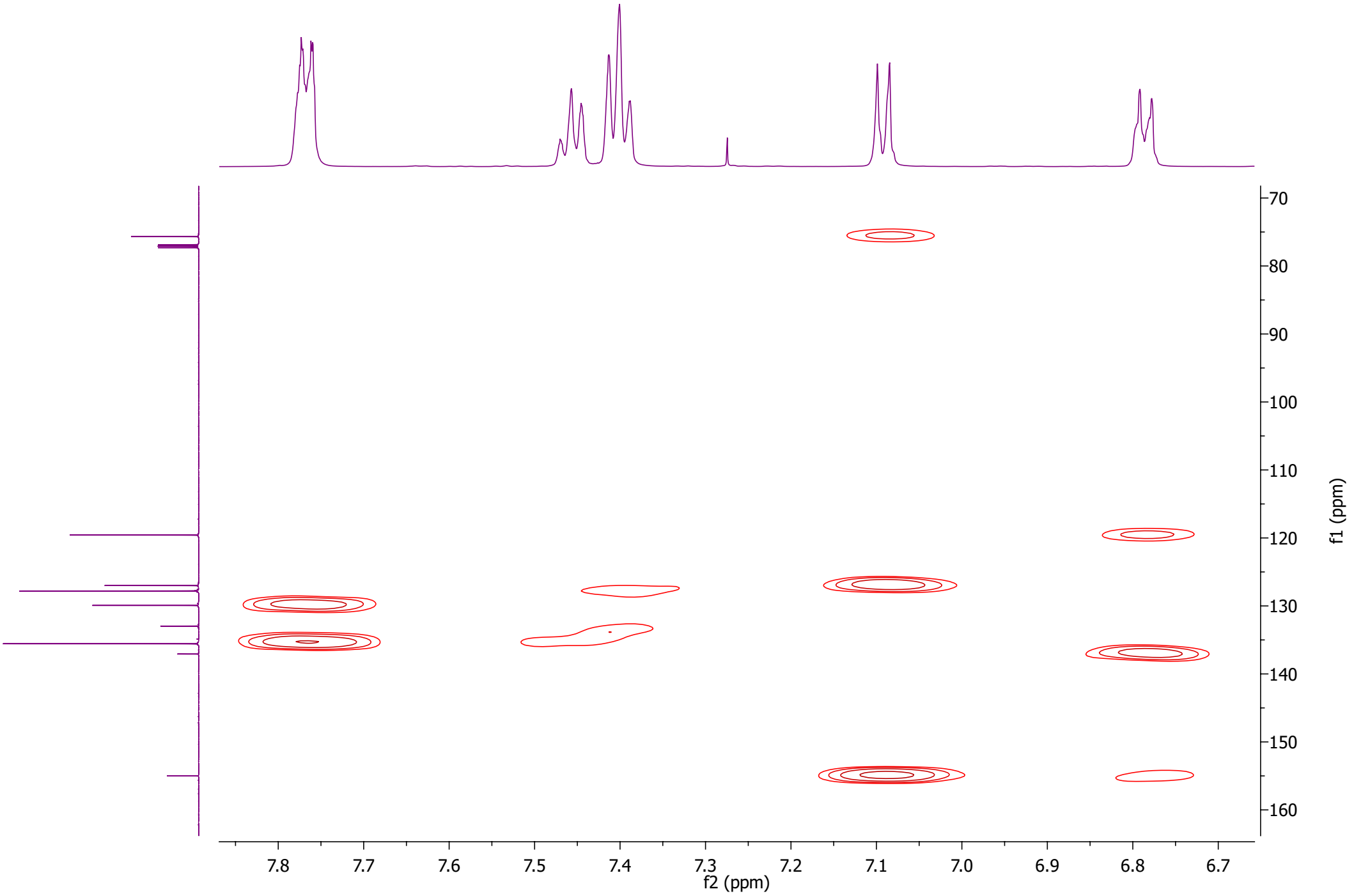
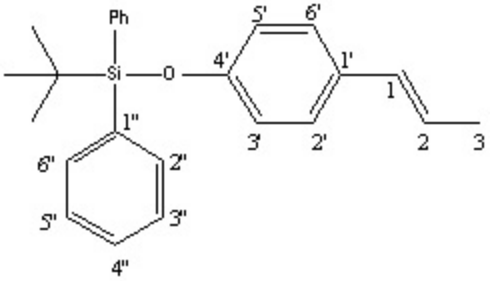
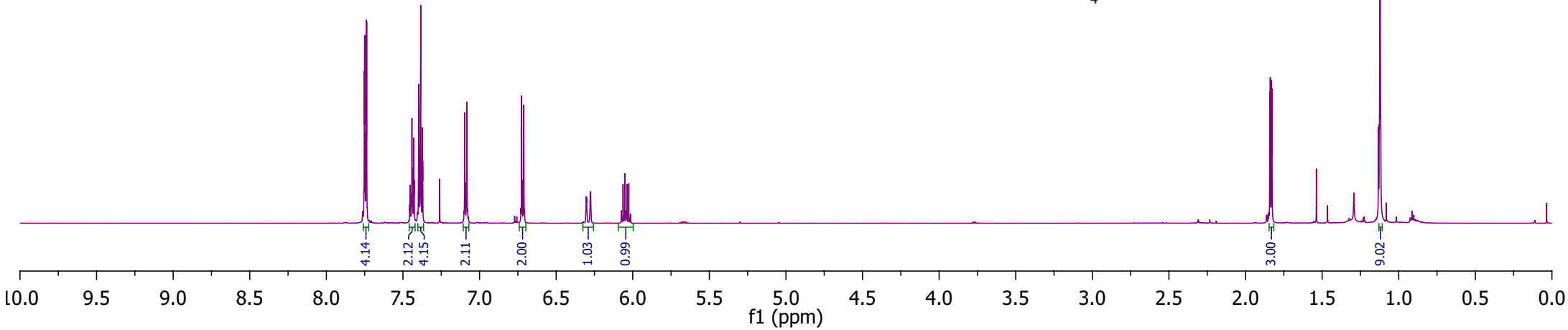


Plate 33a - ^{1}H NMR [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.73 (4H, m, H-2" and H-6"), 7.46-7.43 (2H, m, H-4"), 7.40-7.37 (4H, m, H-3" and H-5"), 7.09 (2H, d, *J* = 8.64 Hz, H-2' and H-6'), 6.72 (2H, d, *J* = 8.64 Hz, H-3' and H-5'), 6.29 (1H, dd, *J* = 15.70, 1.64 Hz, H-1), 6.05 (1H, dd, *J* = 15.70, 6.64 Hz, H-2), 1.83 (1H, dd, *J* = 6.64, 1.64 Hz, H-3), 1.12 [9H, s, -$(CH_3)_3$].

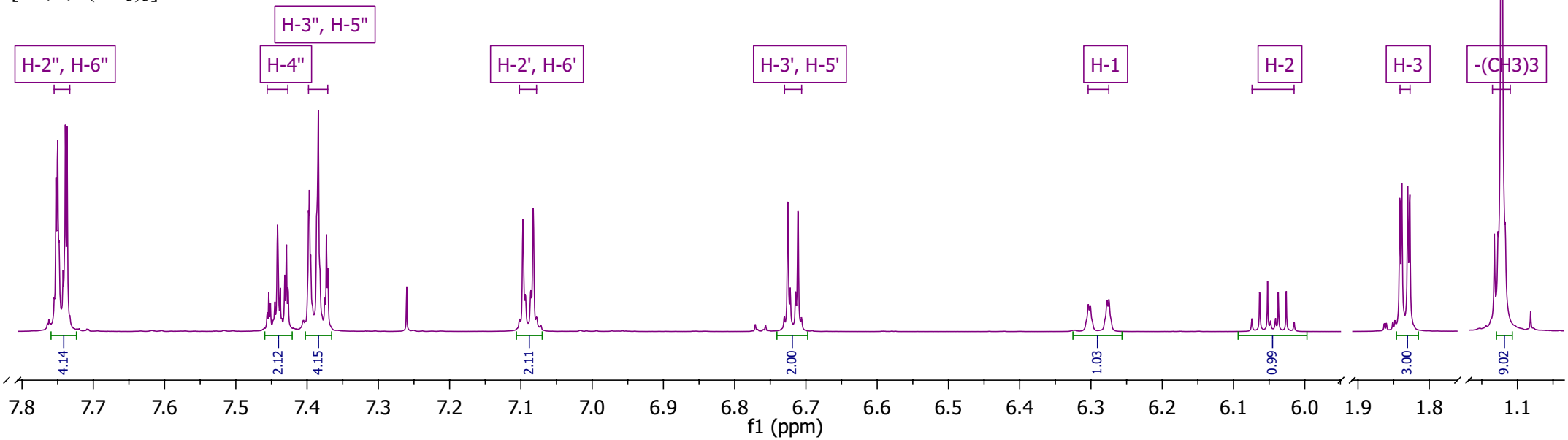
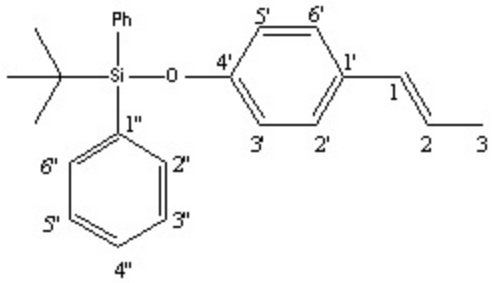
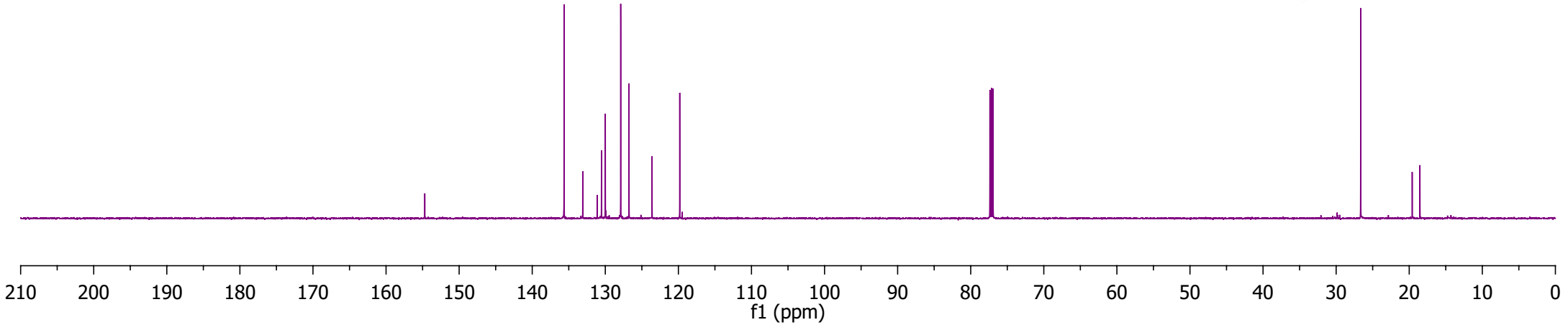


Plate 33b - ^{13}C NMR [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**)





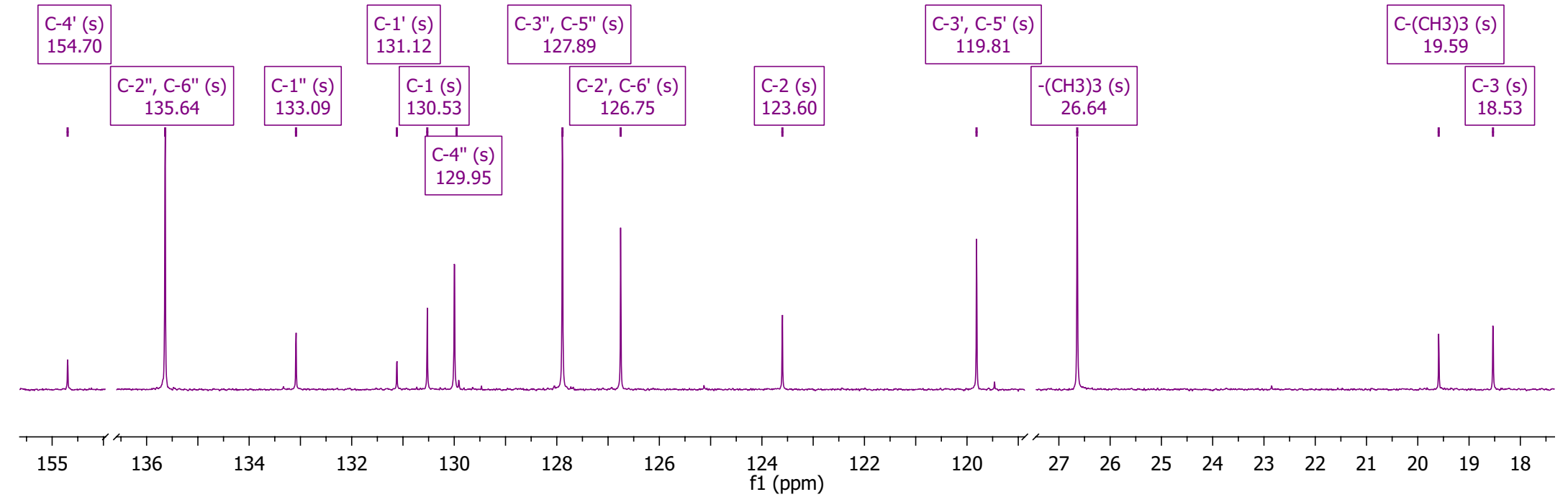


Plate 33c - DEPT [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**)

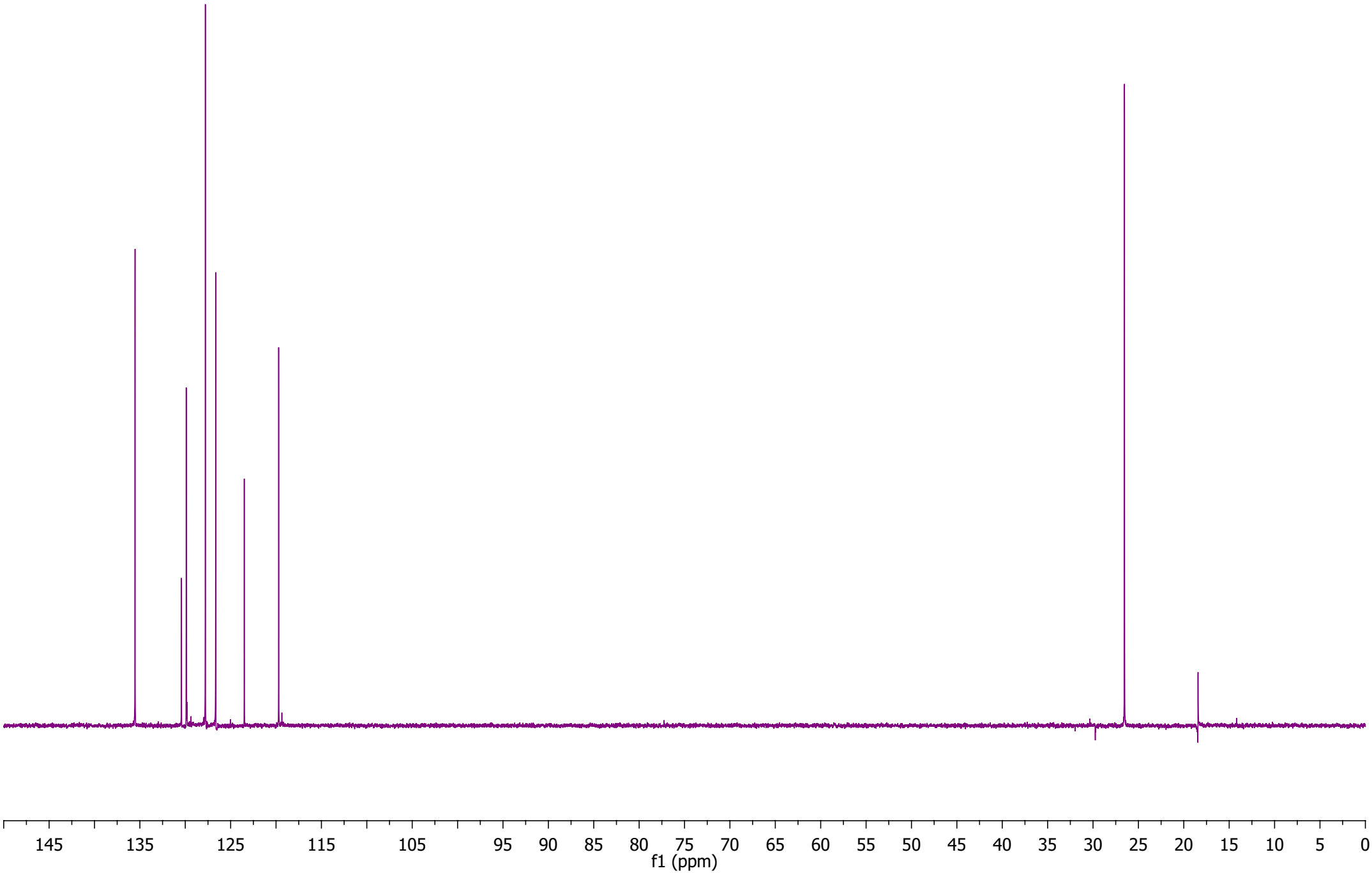


Plate 33d - HSQC [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**)

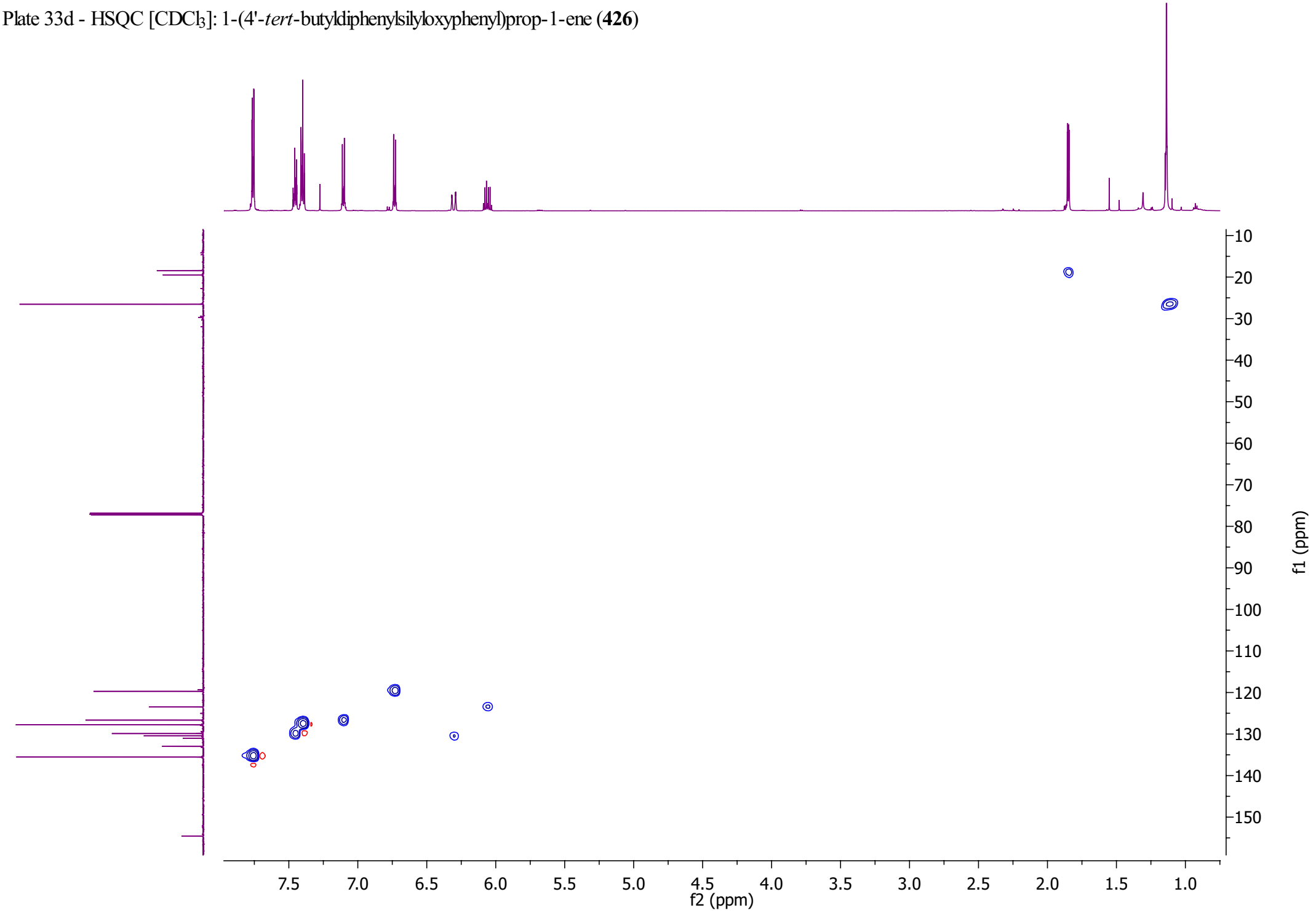


Plate 33e - HSQC (expansion) [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**)

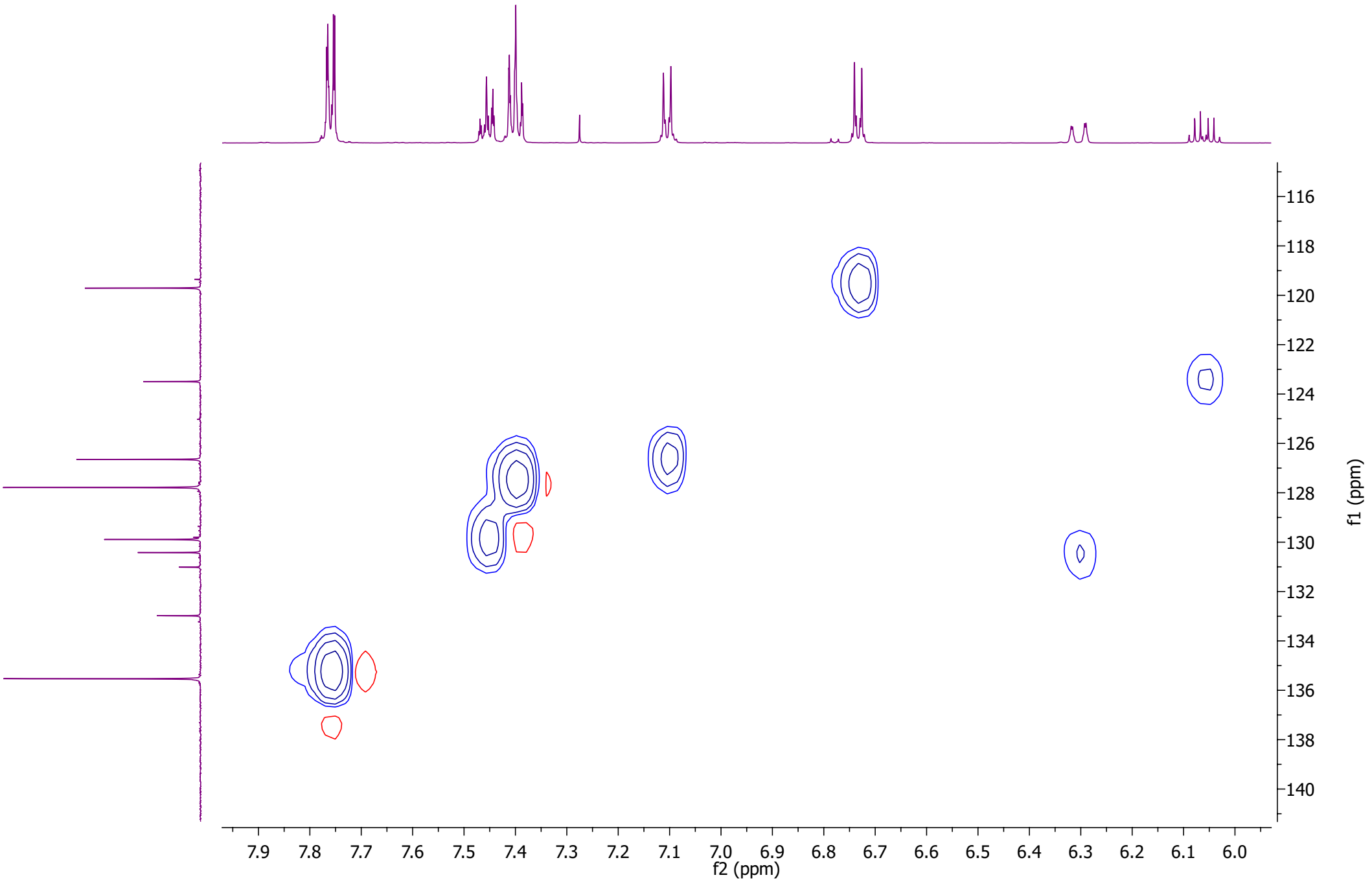


Plate 33f - HMBC [$CDCl_3$]: 1-(4'-*tert*-butyldiphenylsilyloxyphenyl)prop-1-ene (**426**)

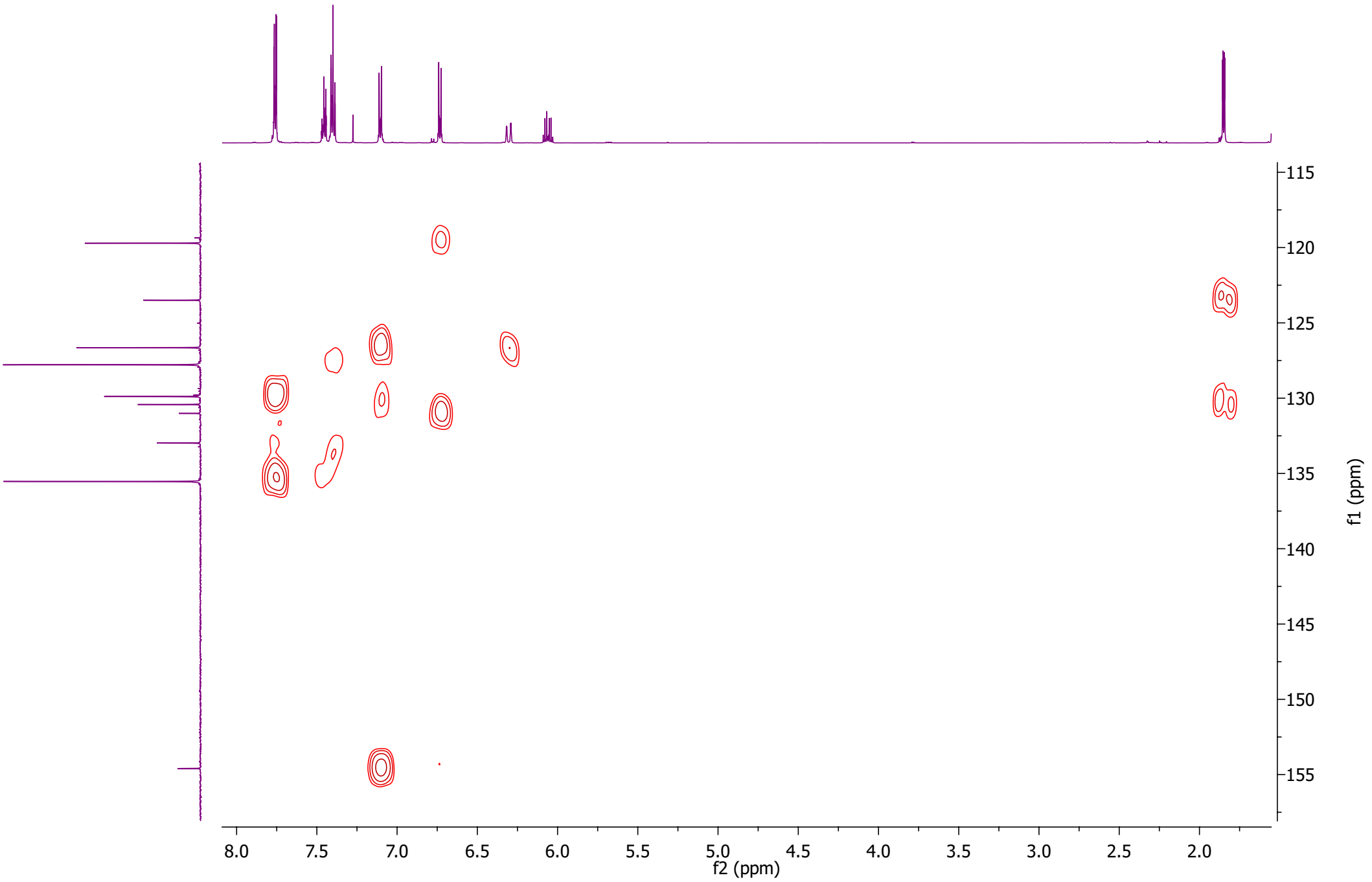
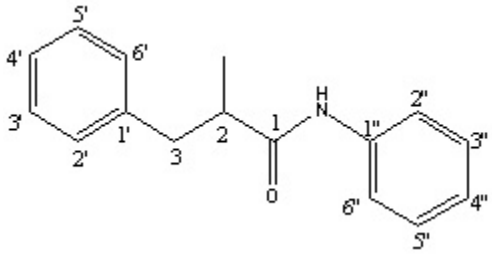
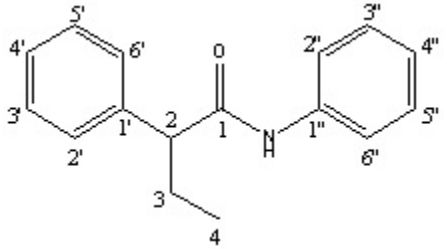


Plate 34a - ^{1}H NMR [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)





^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.44-7.43 [2H, m, H-Ar, (**444A**) (**444B**)], 7.35-7.36 [4H, m, H-Ar, (**444A**) (**444B**)], 7.32-7.14 [6H, m, H-Ar, (**444A**) (**444B**)], 7.07-7.05 [1H, m, H-Ar, (**444A**) (**444B**)], 3.40 [1H, t, *J* = 7.55 Hz, H-2, (**444A**)], 3.03 [0.15H, dd, *J* = 8.52, 13.55 Hz, H-3a/b, (**444B**)], 2.76 [0.15H, dd, *J* = 6.33, 13.55 Hz, H-3a/b, (**444B**)], 2.63-2.57 [0.15H, m, H-2, (**444B**)] 2.31-2.23 [1H, m, H-3a/b, (**444A**)], 1.90-1.83 [1H, m, H-3a/b, (**444A**)], 1.28 [0.5H, d, *J* = 6.79 Hz, 2-CH_3, (**444B**)] 0.92 [3H, t, *J* = 7.38 Hz, H-4, (**444A**)]

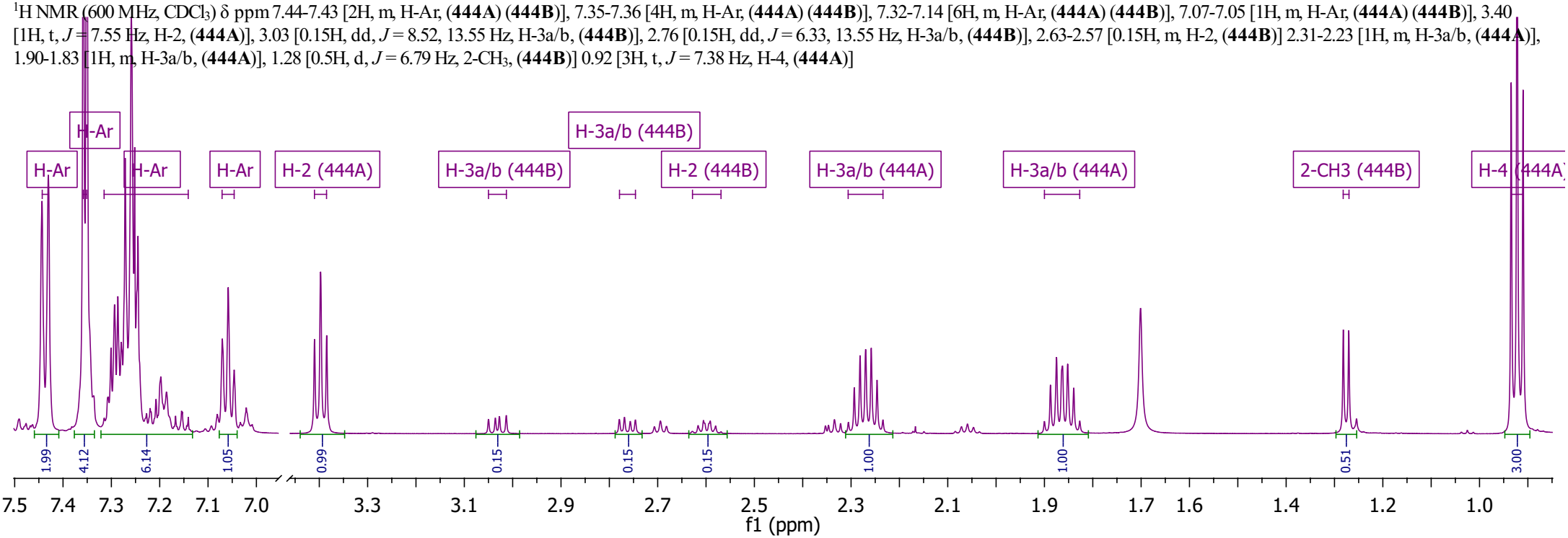
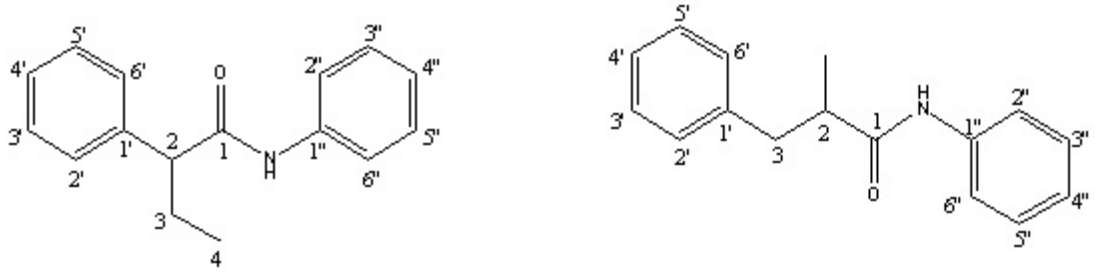
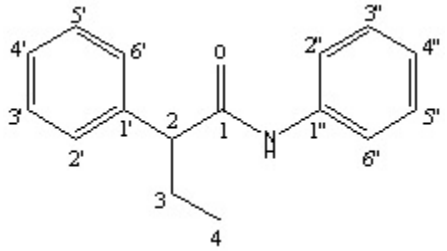


Plate 34b - ^{1}H NMR [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)



^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.44-7.43 [2H, m, H-Ar, (**444A**) (**444B**)], 7.35-7.36 [4H, m, H-Ar, (**444A**) (**444B**)], 7.32-7.14 [6H, m, H-Ar, (**444A**) (**444B**)], 7.07-7.05 [1H, m, H-Ar, (**444A**) (**444B**)], 3.40 [1H, t, *J* = 7.55 Hz, H-2, (**444A**)], 3.03 [0.15H, dd, *J* = 8.52, 13.55 Hz, H-3a/b, (**444B**)], 2.76 [0.15H, dd, *J* = 6.33, 13.55 Hz, H-3a/b, (**444B**)], 2.63-2.57 [0.15H, m, H-2, (**444B**)] 2.31-2.23 [1H, m, H-3a/b, (**444A**)], 1.90-1.83 [1H, m, H-3a/b, (**444A**)], 1.28 [0.5H, d, *J* = 6.79 Hz, 2-CH_3, (**444B**)] 0.92 [3H, t, *J* = 7.38 Hz, H-4, (**444A**)]

Plate 34c - ^{13}C NMR [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)



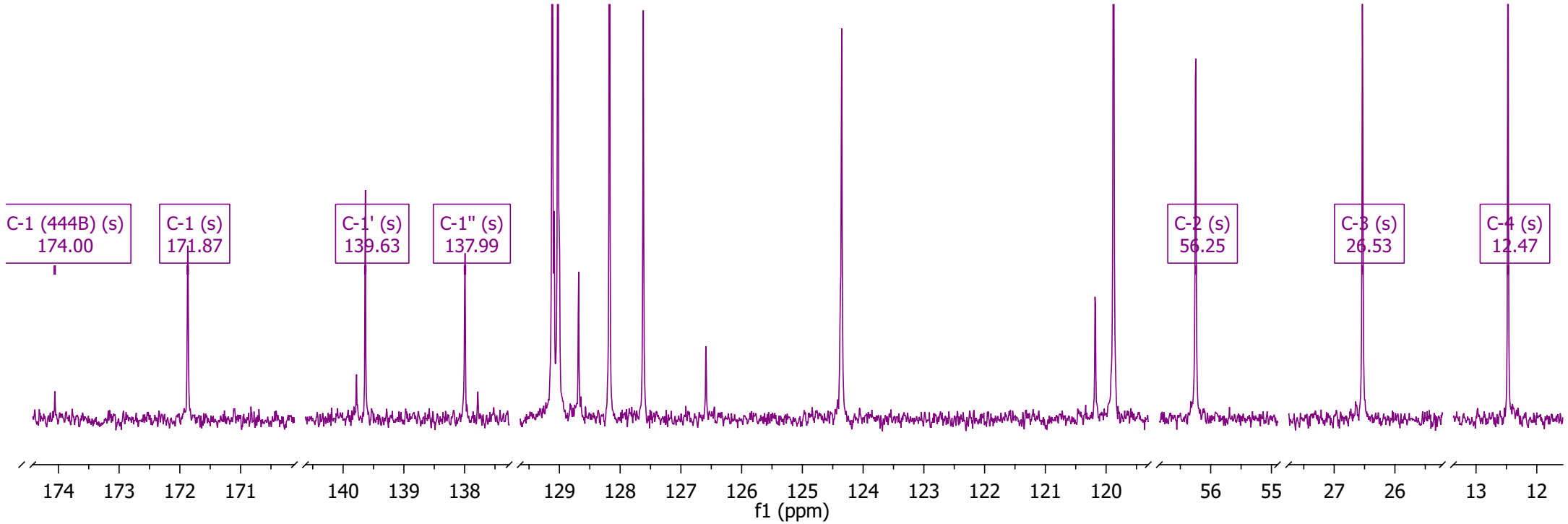


Plate 34d - DEPT [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)

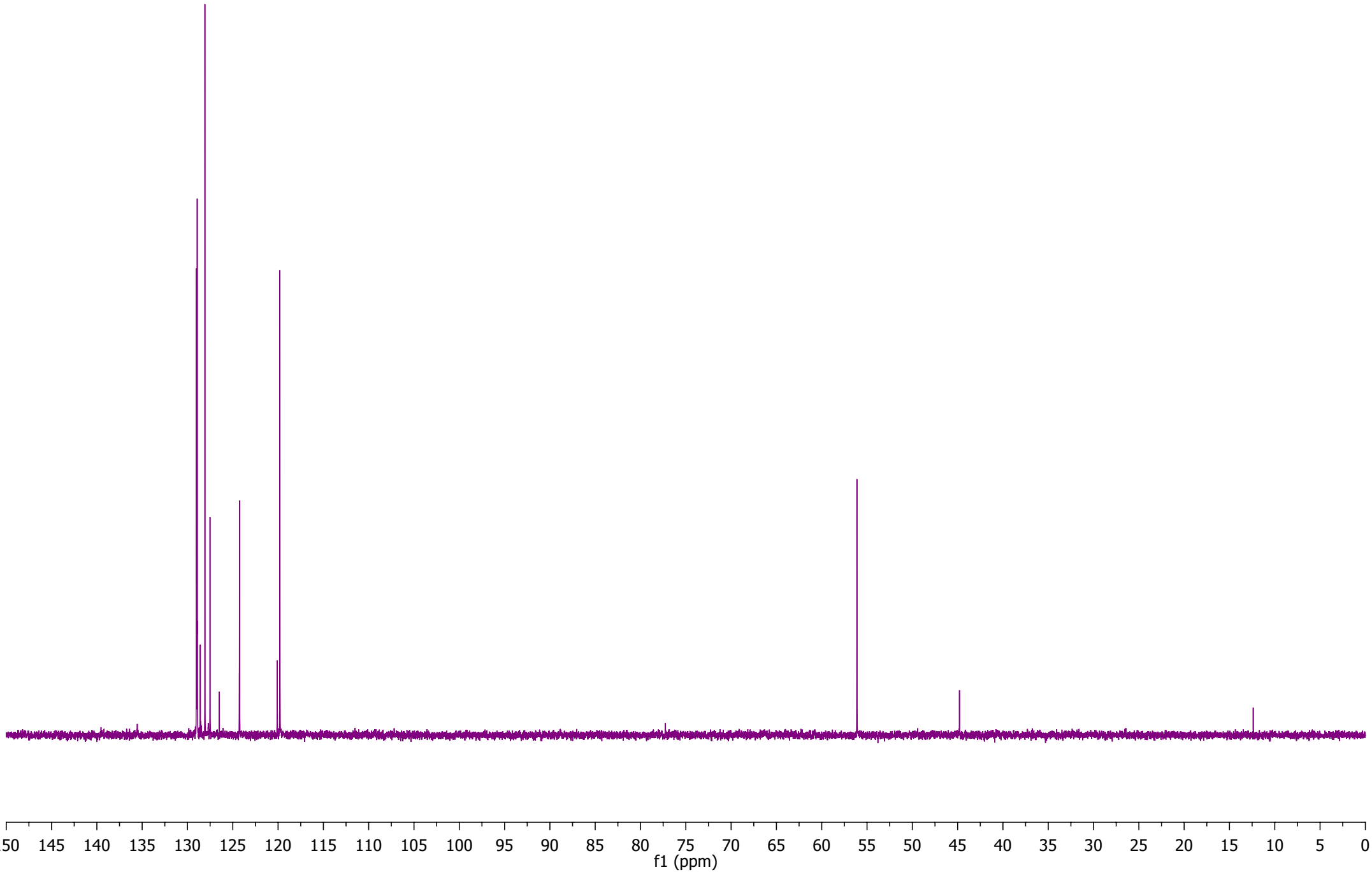


Plate 34e - HSQC [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)

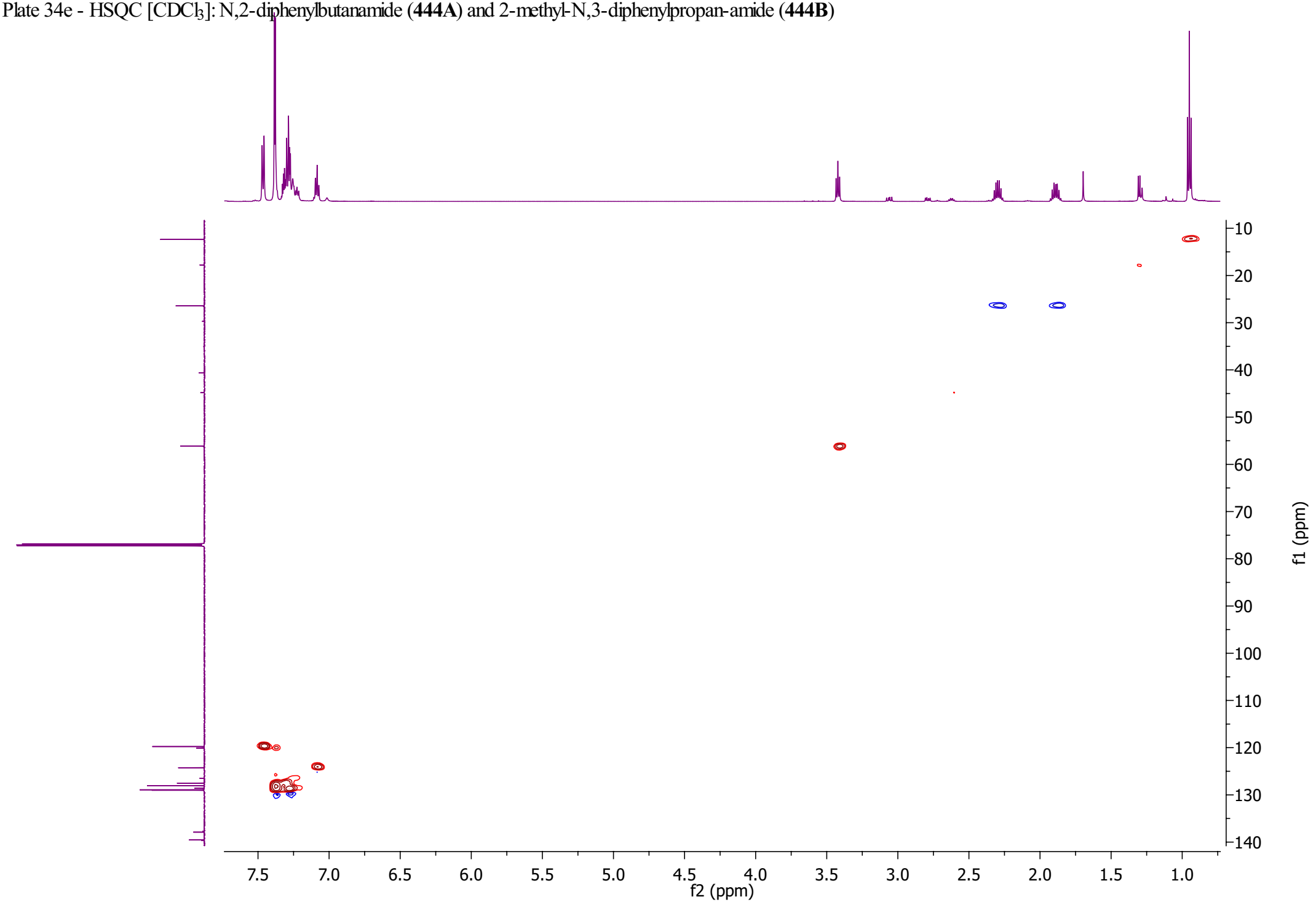


Plate 34f - HSQC (expansion) [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)

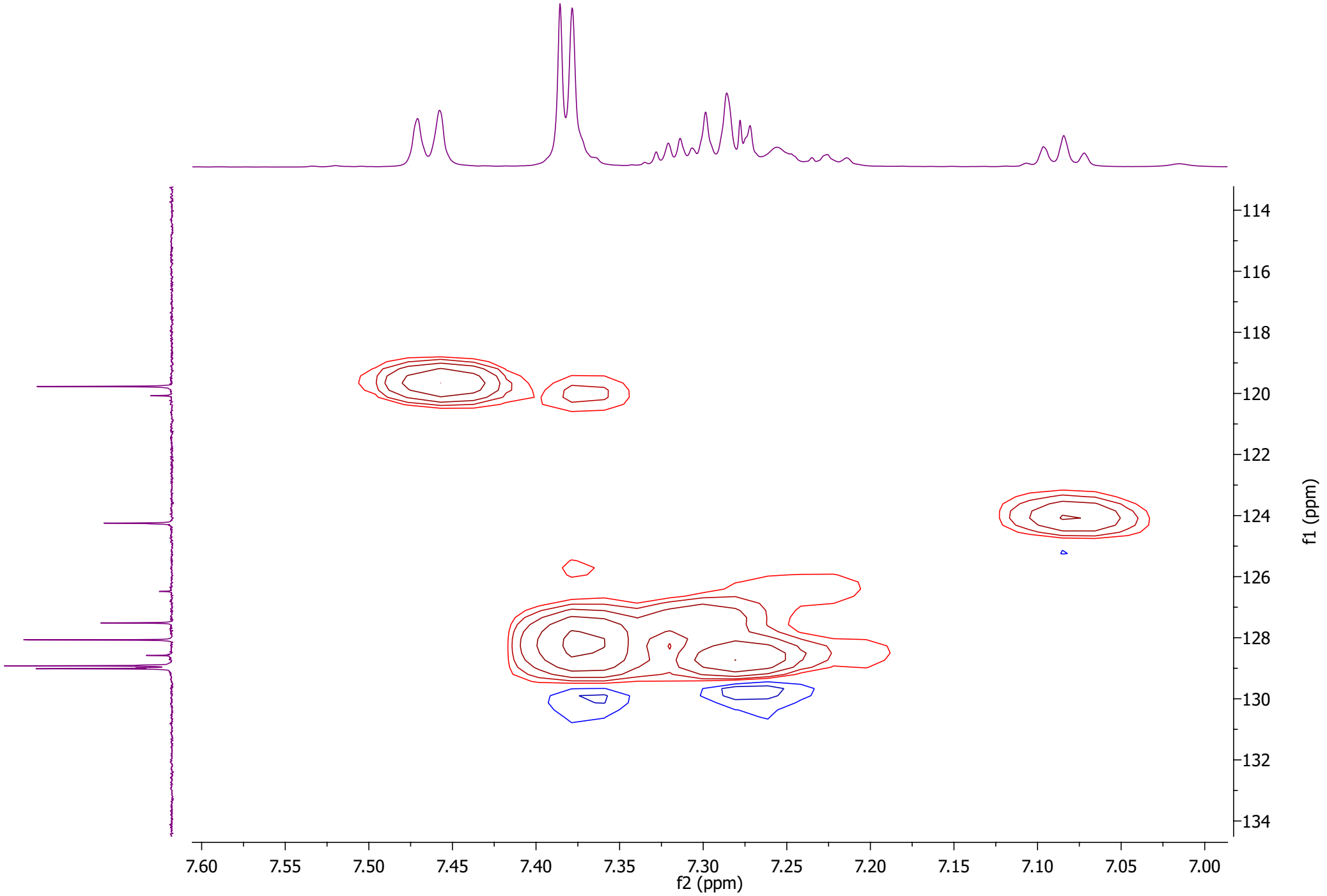


Plate 34g - HMBC [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)

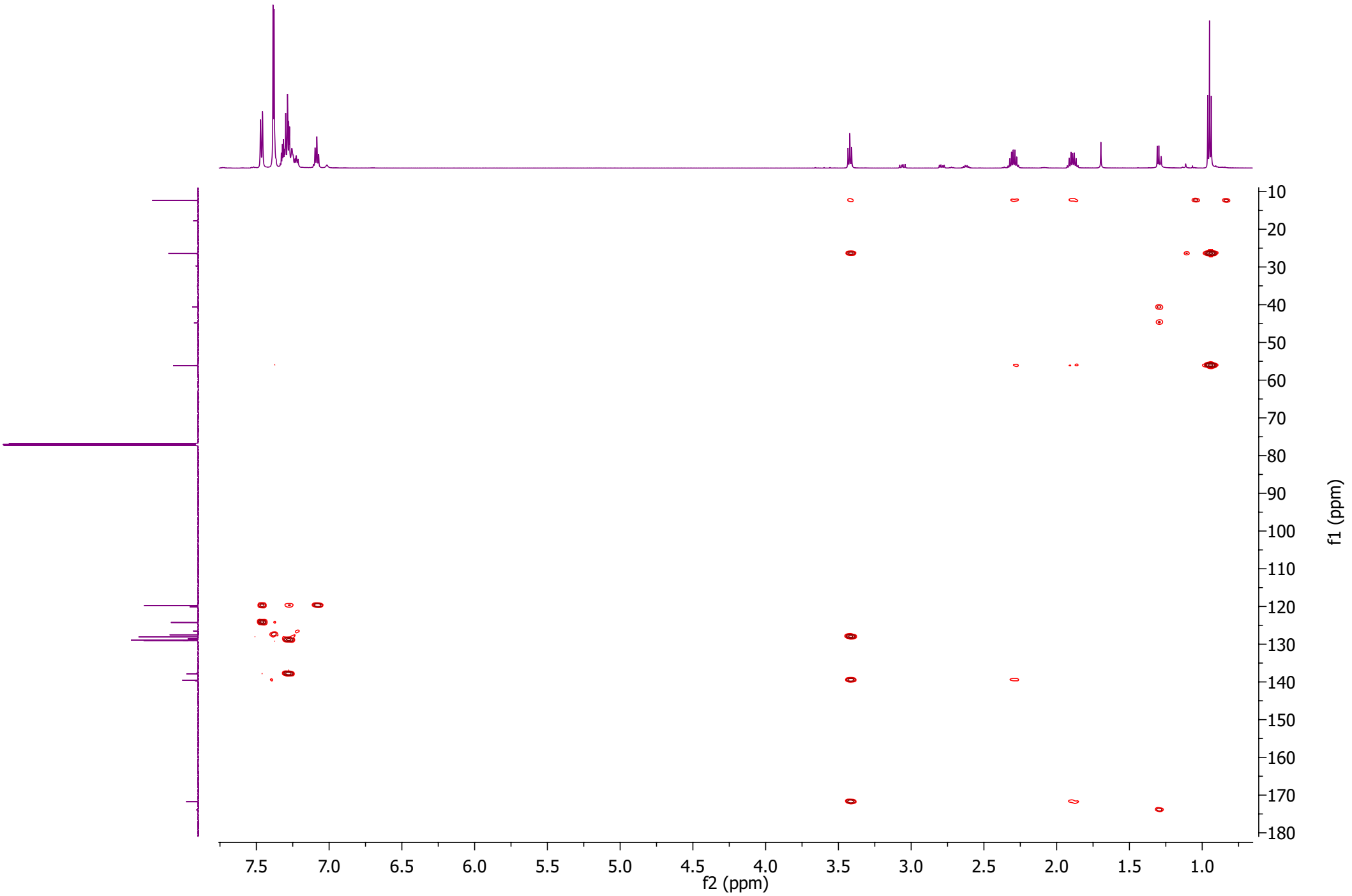


Plate 34h - HMBC (expansion) [$CDCl_3$]: N,2-diphenylbutanamide (**444A**) and 2-methyl-N,3-diphenylpropan-amide (**444B**)

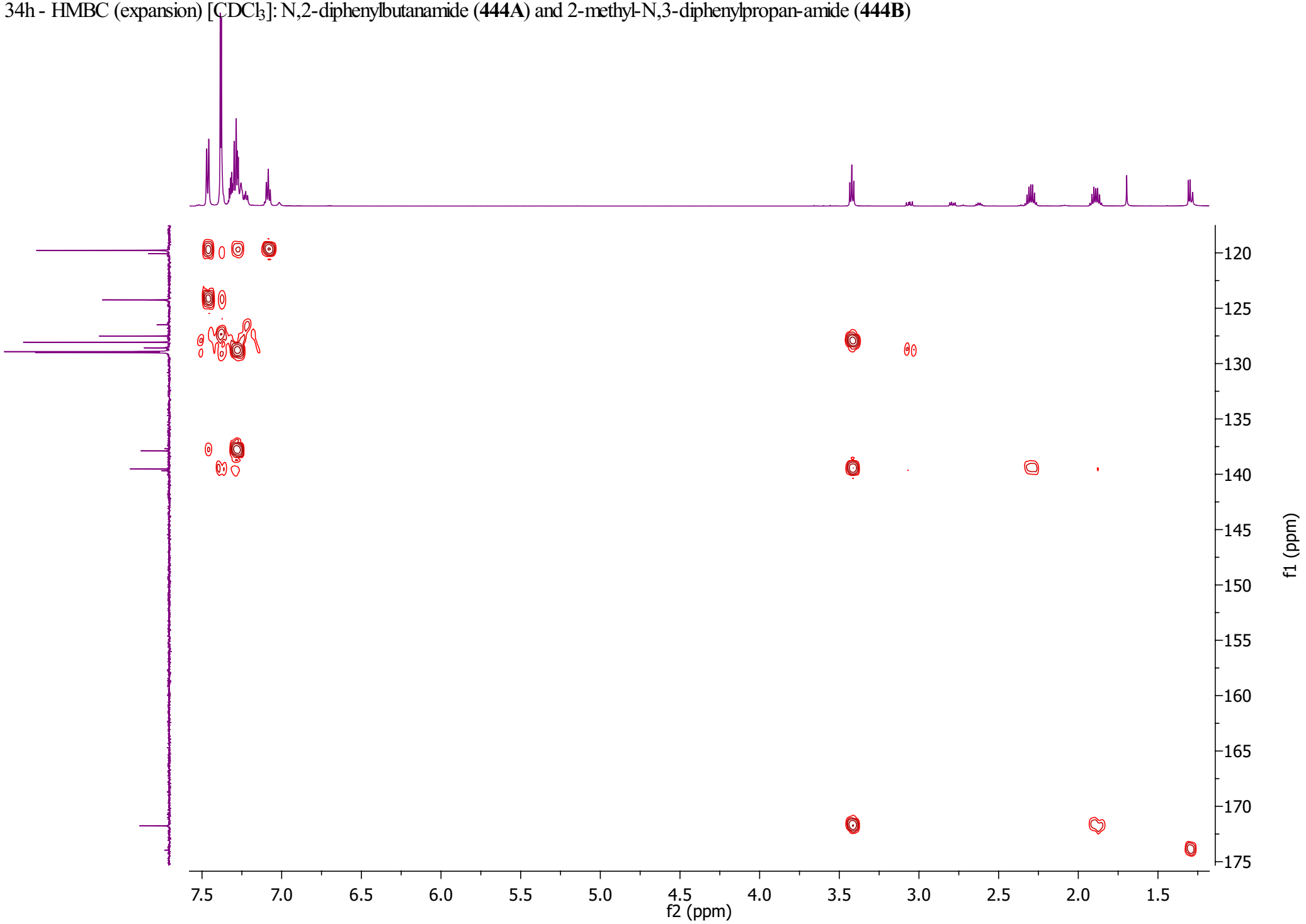
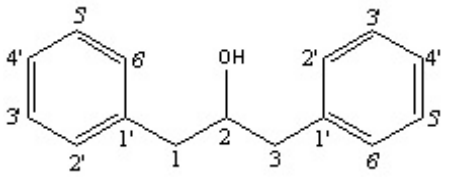
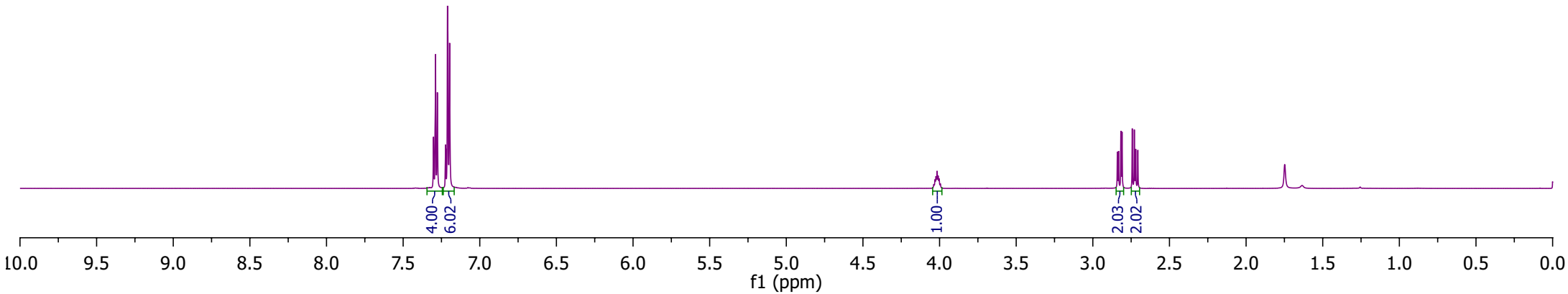


Plate 35a - ^{1}H NMR [$CDCl_3$]: 1,3-diphenylpropan-2-ol (**450**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.28 (4H, m, H-3' and H-5'), 7.22-7.20 (6H, m, H-2', H-4' and H-6'), 4.04-4.00 (1H, m, H-2), 2.82 (2H, dd, *J* = 13.67, 4.66 Hz, H-1 or H-3), 2.72 (2H, dd, *J* = 13.67, 8.19 Hz, H-1 or H-3)

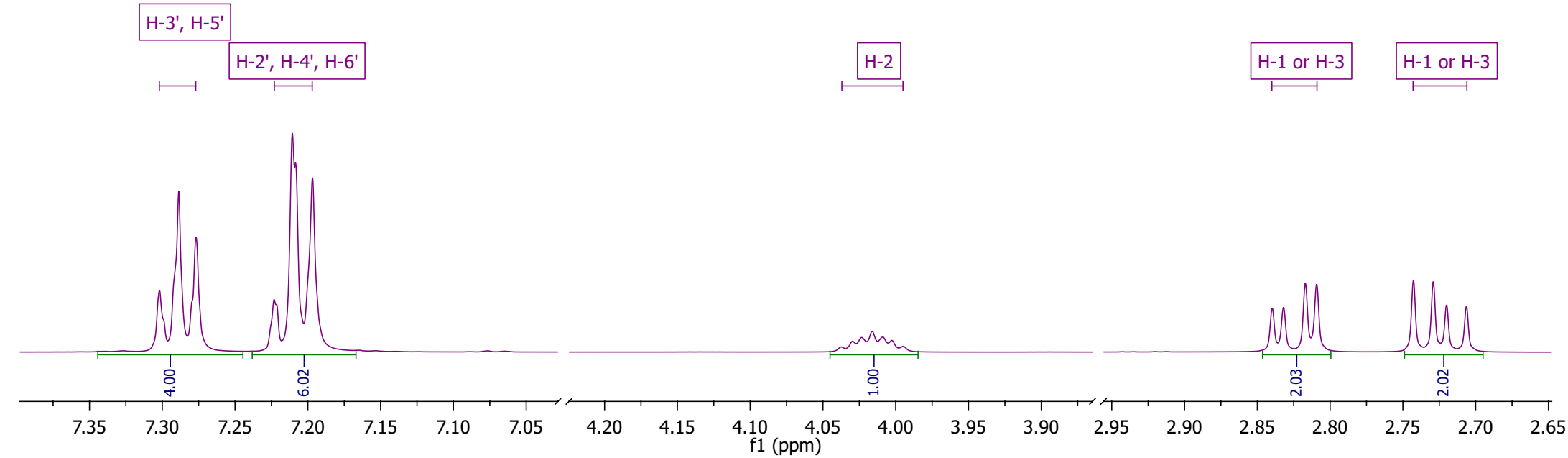
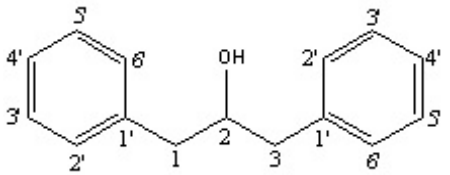


Plate 35b - ^{13}C NMR [$CDCl_3$]: 1,3-diphenylpropan-2-ol (**450**)



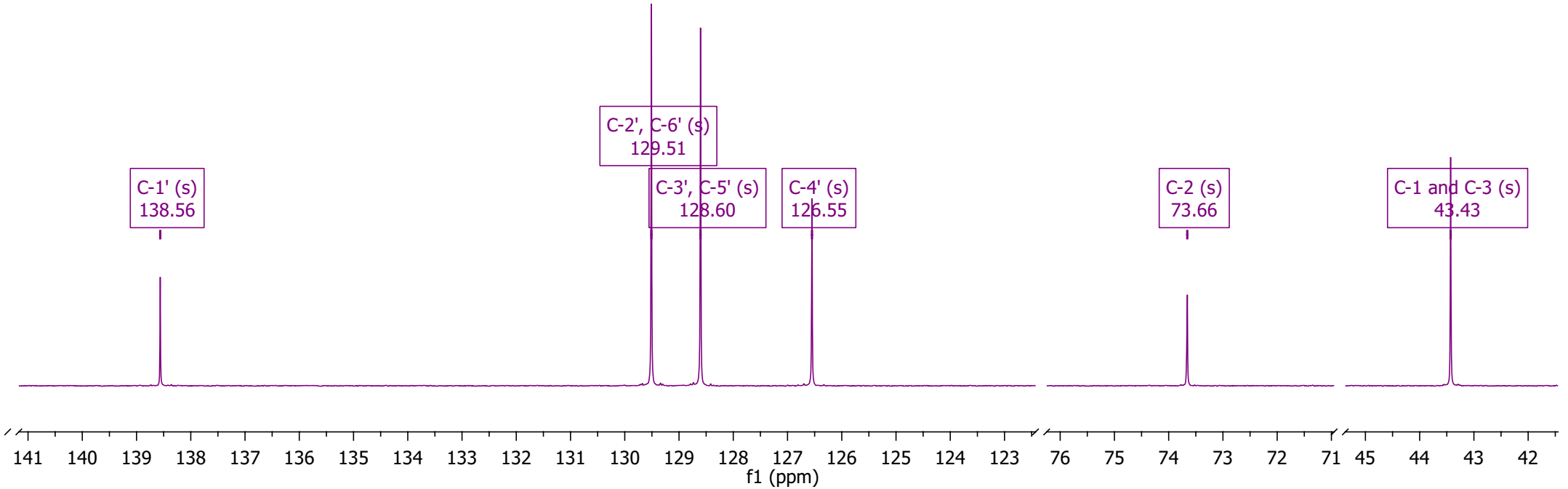


Plate 35c - DEPT [$CDCl_3$]: 1,3-diphenylpropan-2-ol (**450**)

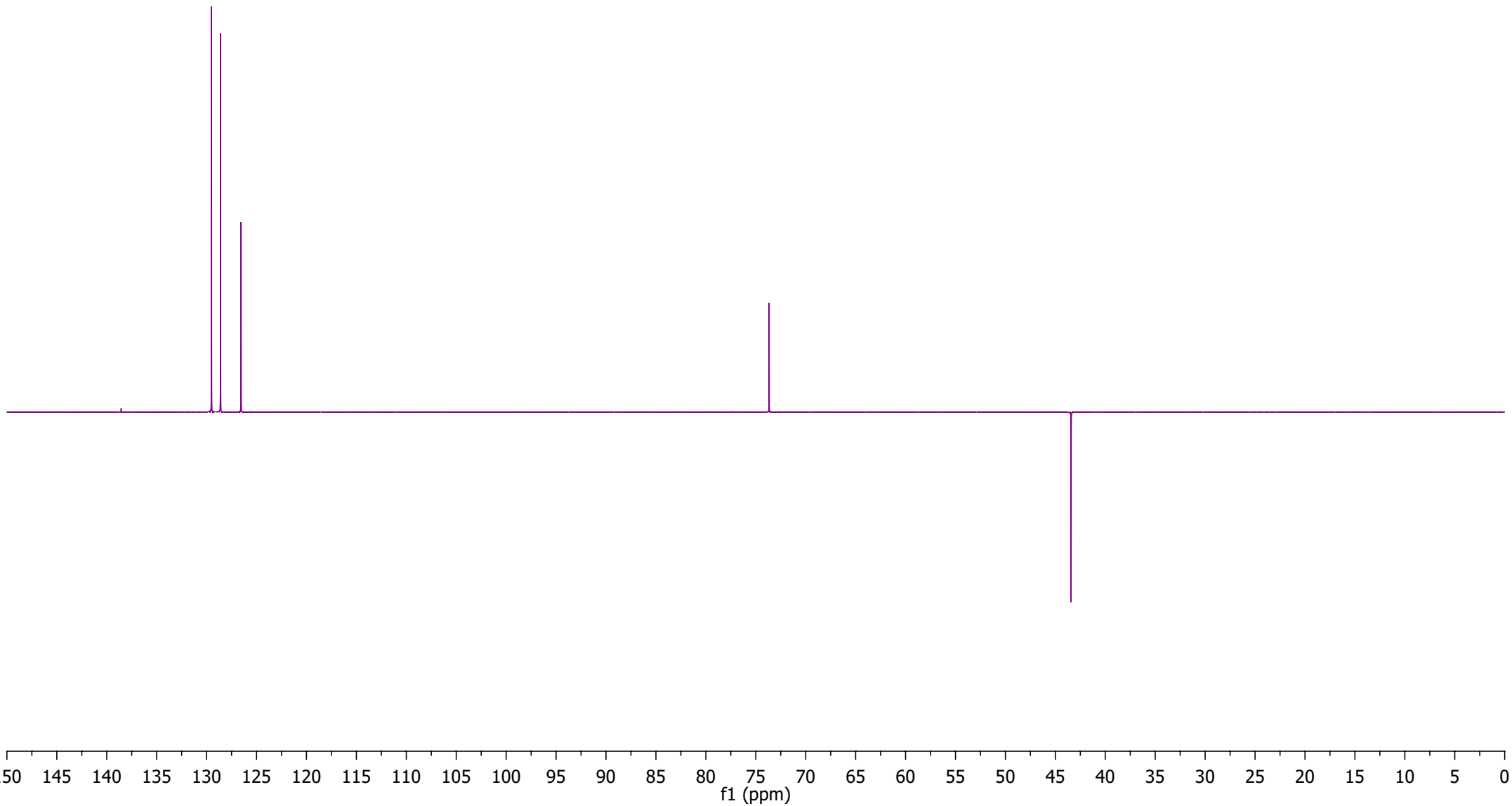


Plate 35d - HSQC [$CDCl_3$]: 1,3-diphenylpropan-2-ol (**450**)

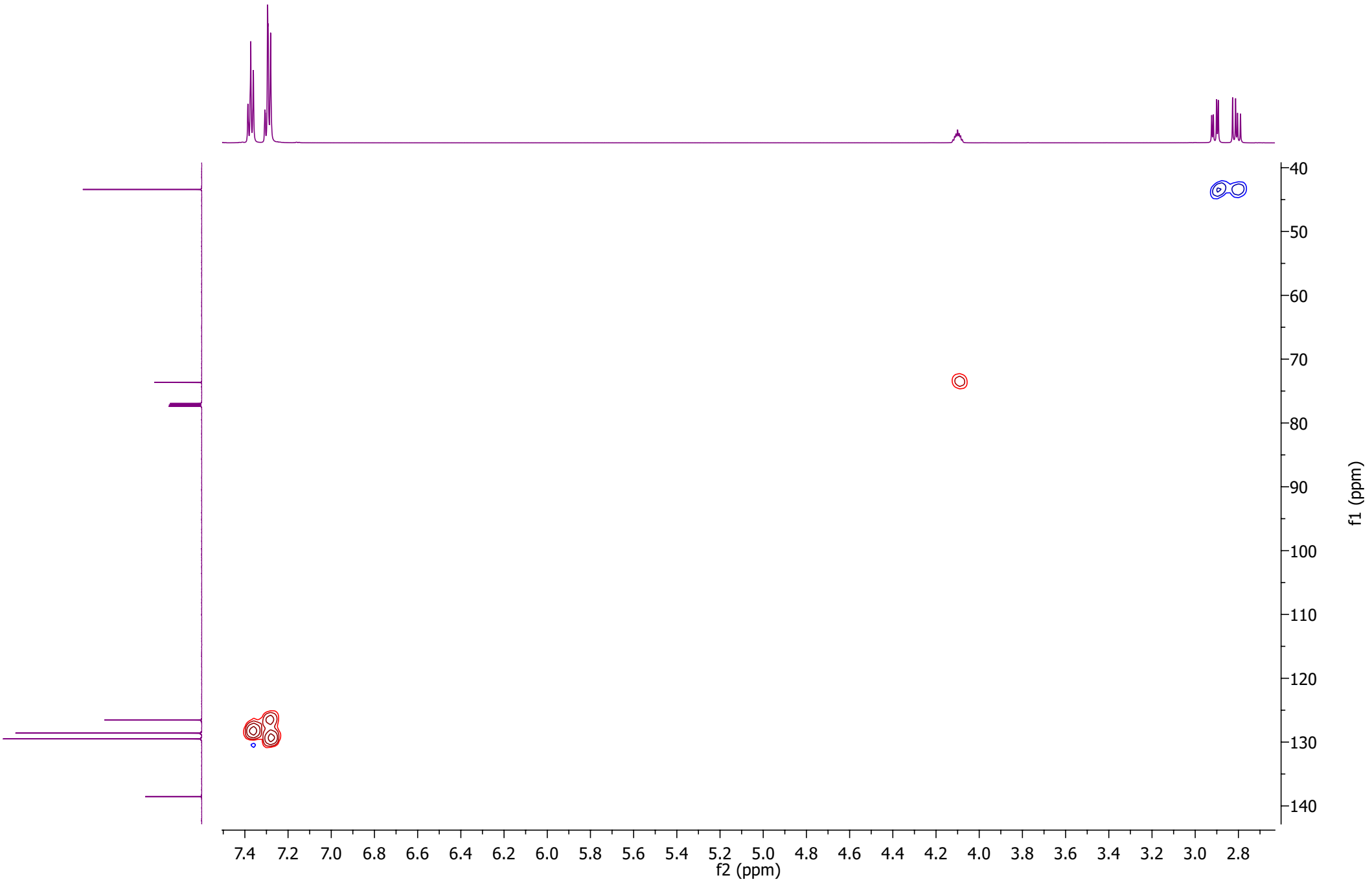


Plate 35e - HMBC [$CDCl_3$]: 1,3-diphenylpropan-2-ol (**450**)

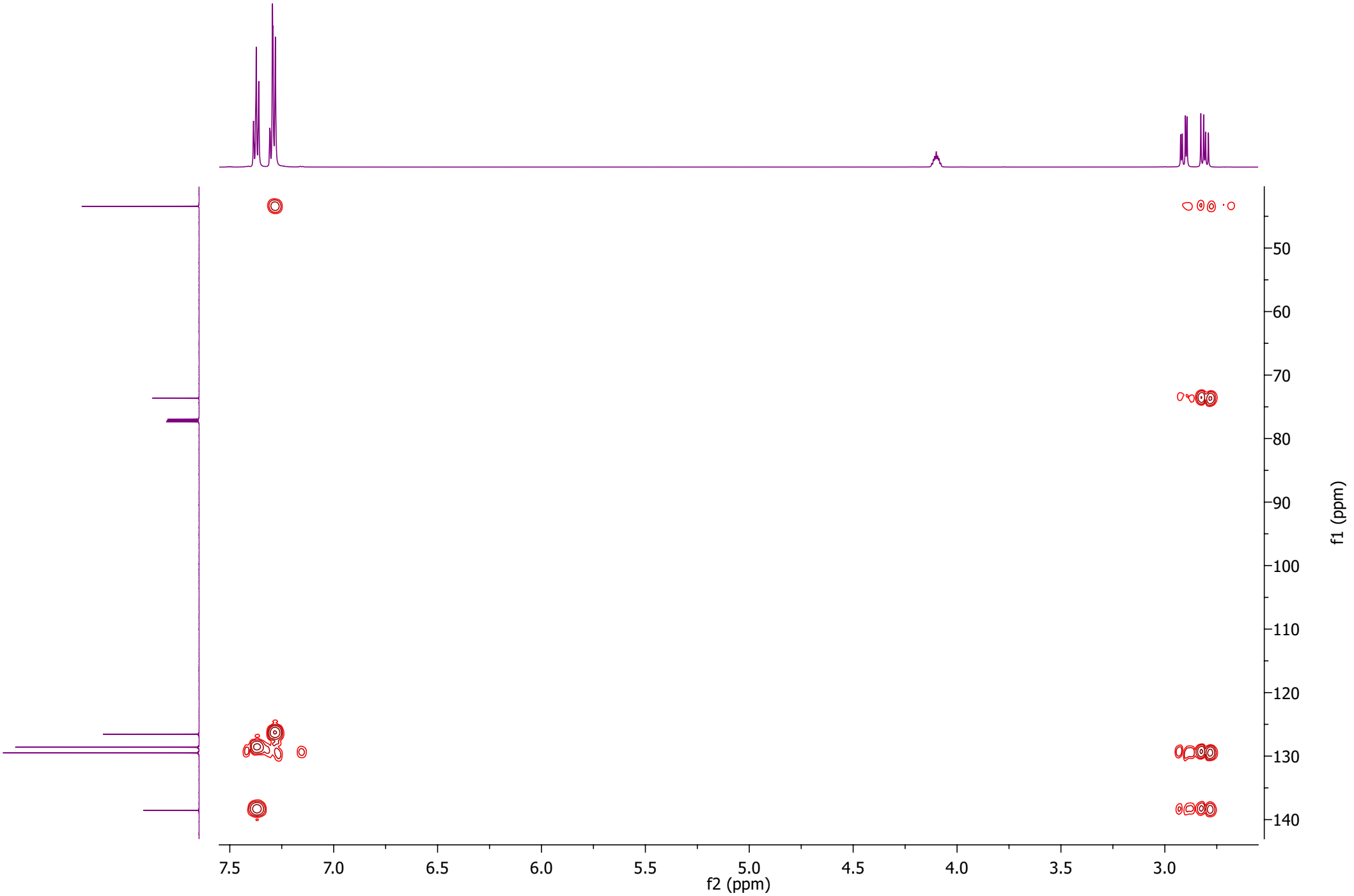
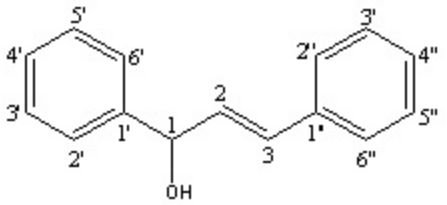
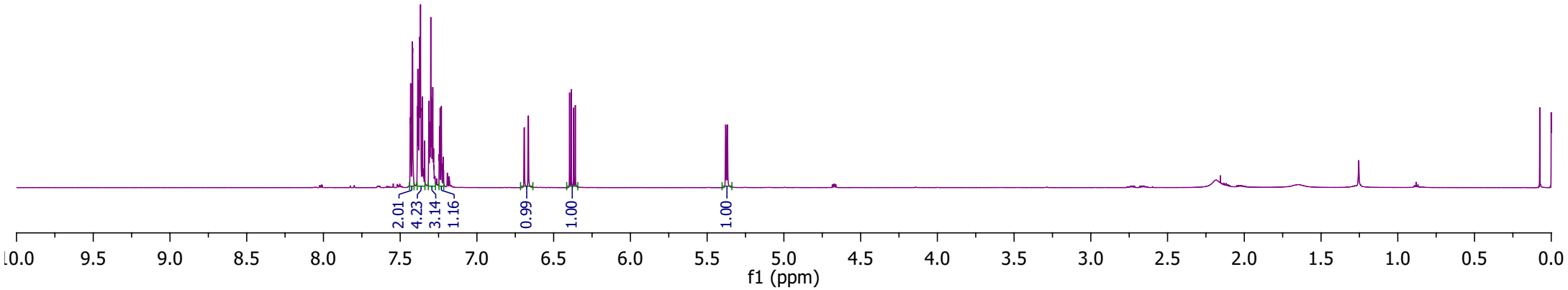


Plate 36a - ^{1}H NMR [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.42 (2H, m, H"-2 and H-6"), 7.39-7.35 (4H, m, H'-2, H-3', H-5' and H-6'), 7.31-7.28 (3H, m, Ar-H) 7.25-7.22 (1H, m, Ar-H) 6.68 (1H, d, *J* = 15.86 Hz, H-3), 6.38 (1H, dd, *J* = 15.86, 6.55 Hz, H-2), 5.37 (1H, d, *J* = 6.55 Hz, H-1).

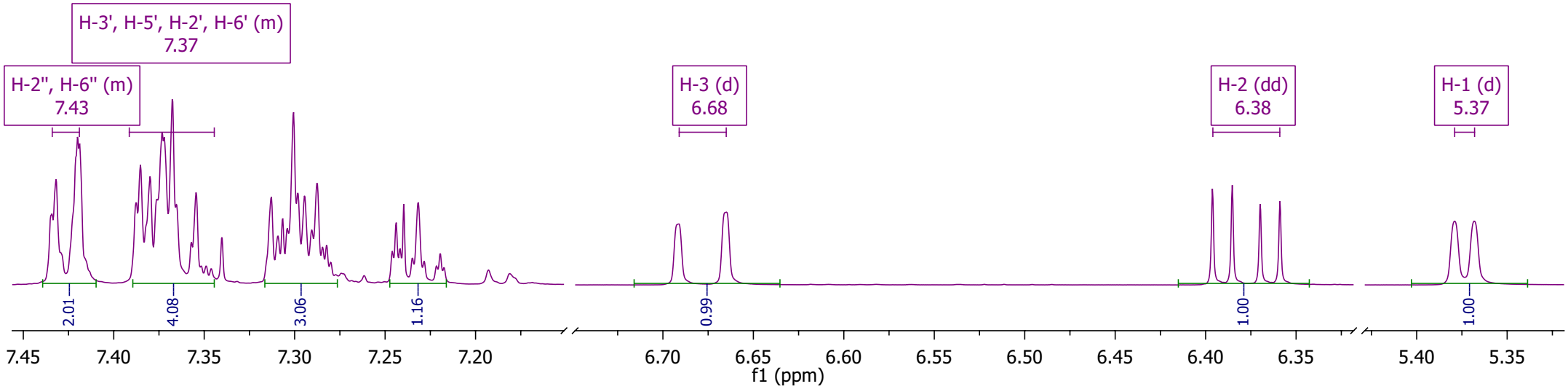
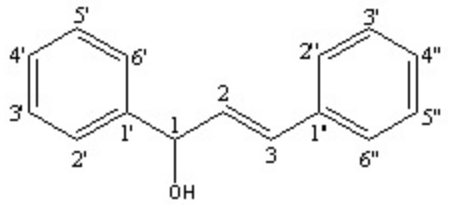


Plate 36b - ^{13}C NMR [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)



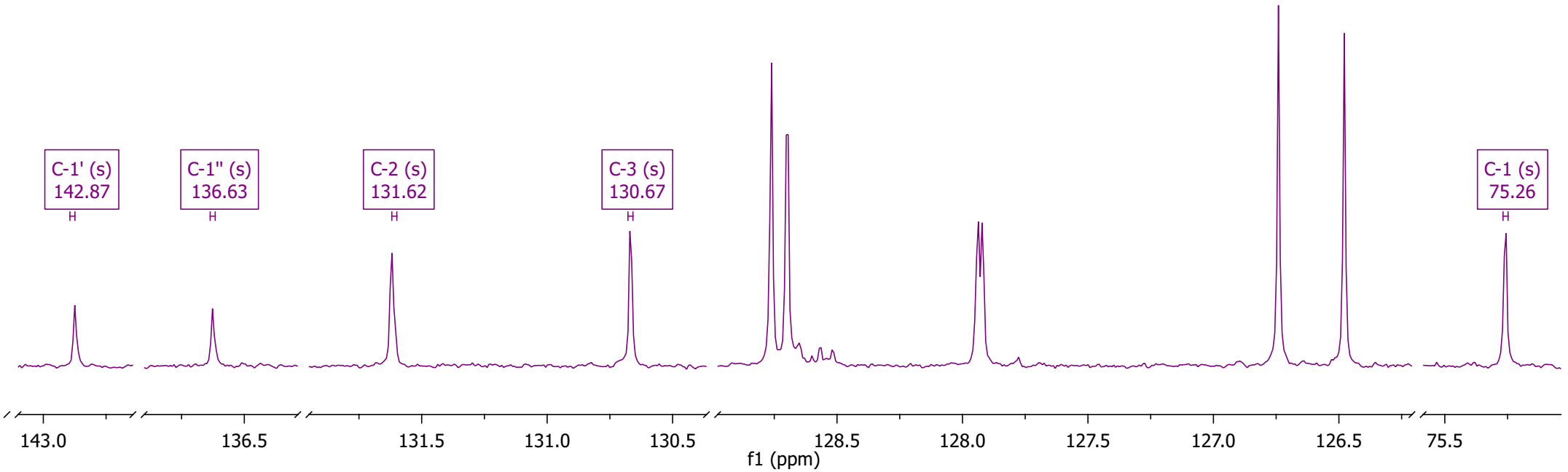


Plate 36c - DEPT [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)

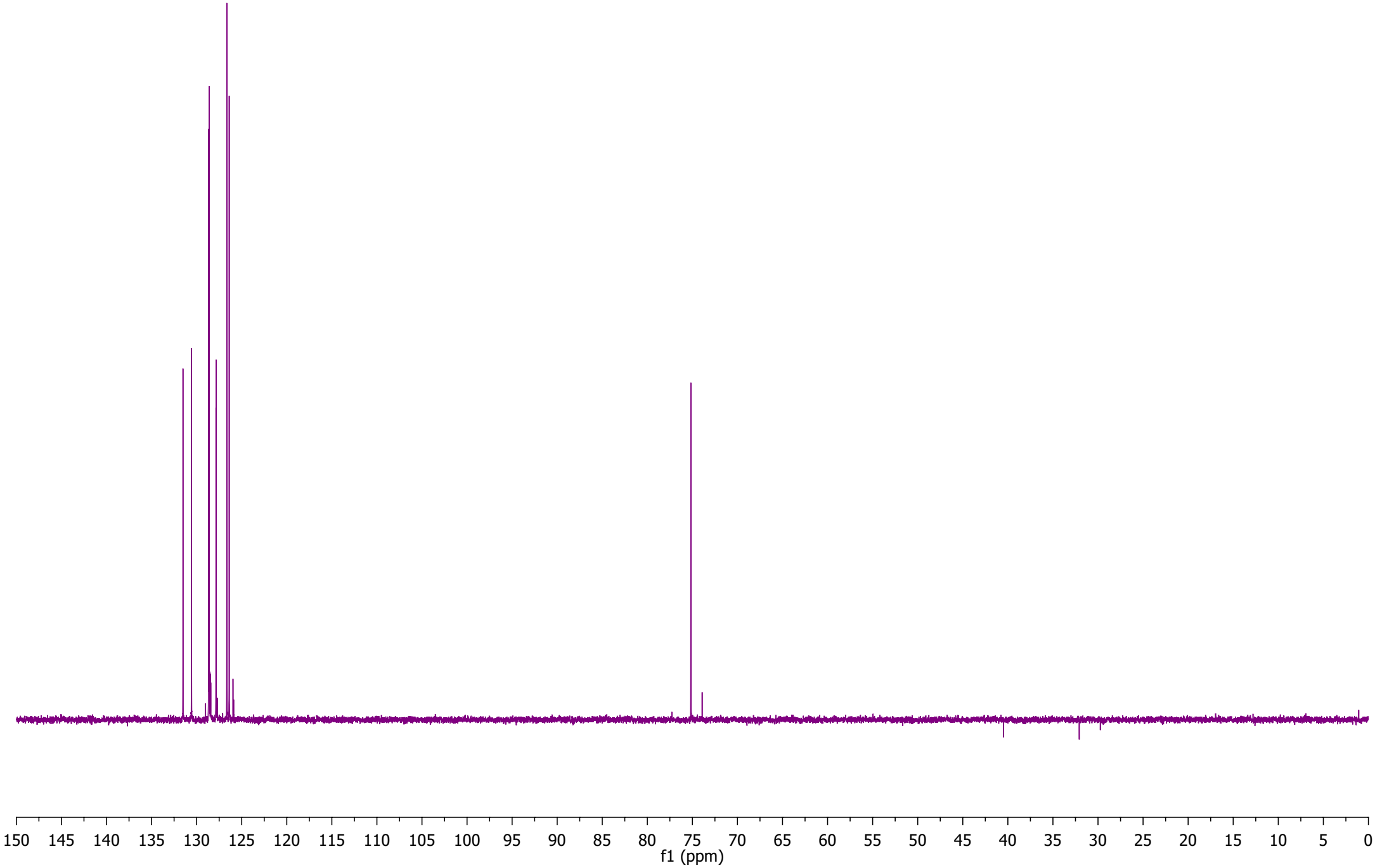


Plate 36d - HSQC [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)

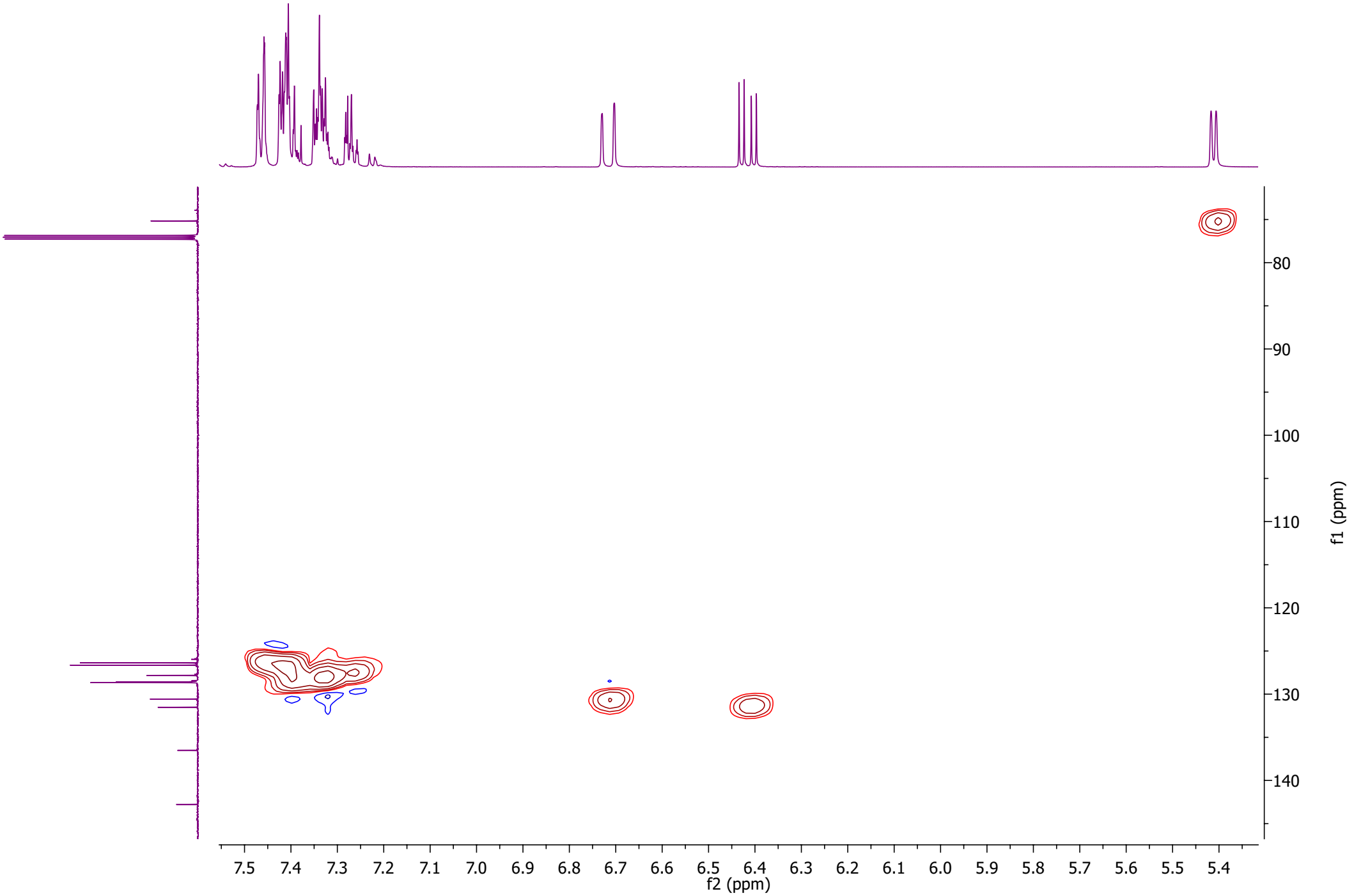


Plate 36e - HSQC (expansion) [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)

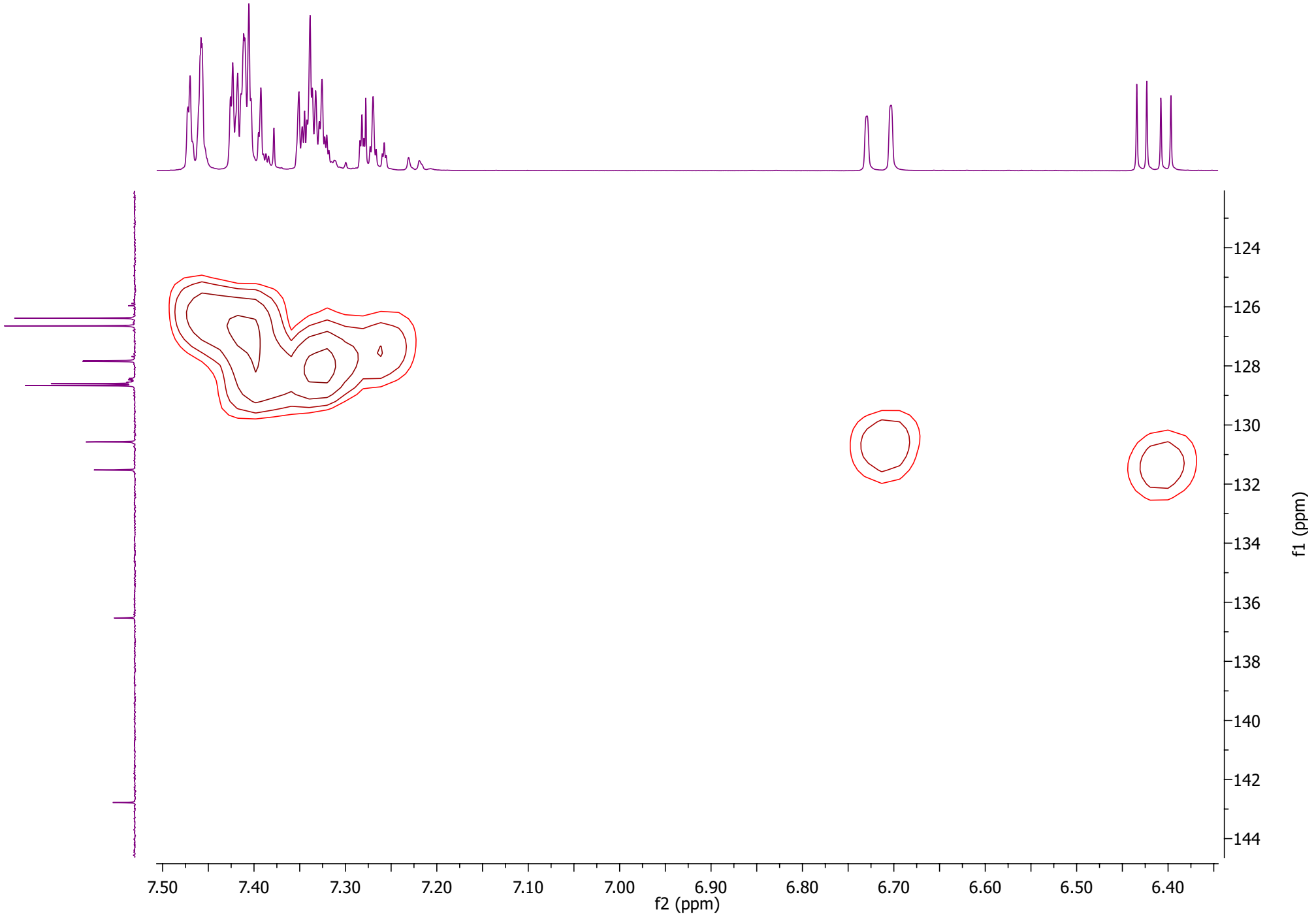


Plate 36f - HMBC [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)

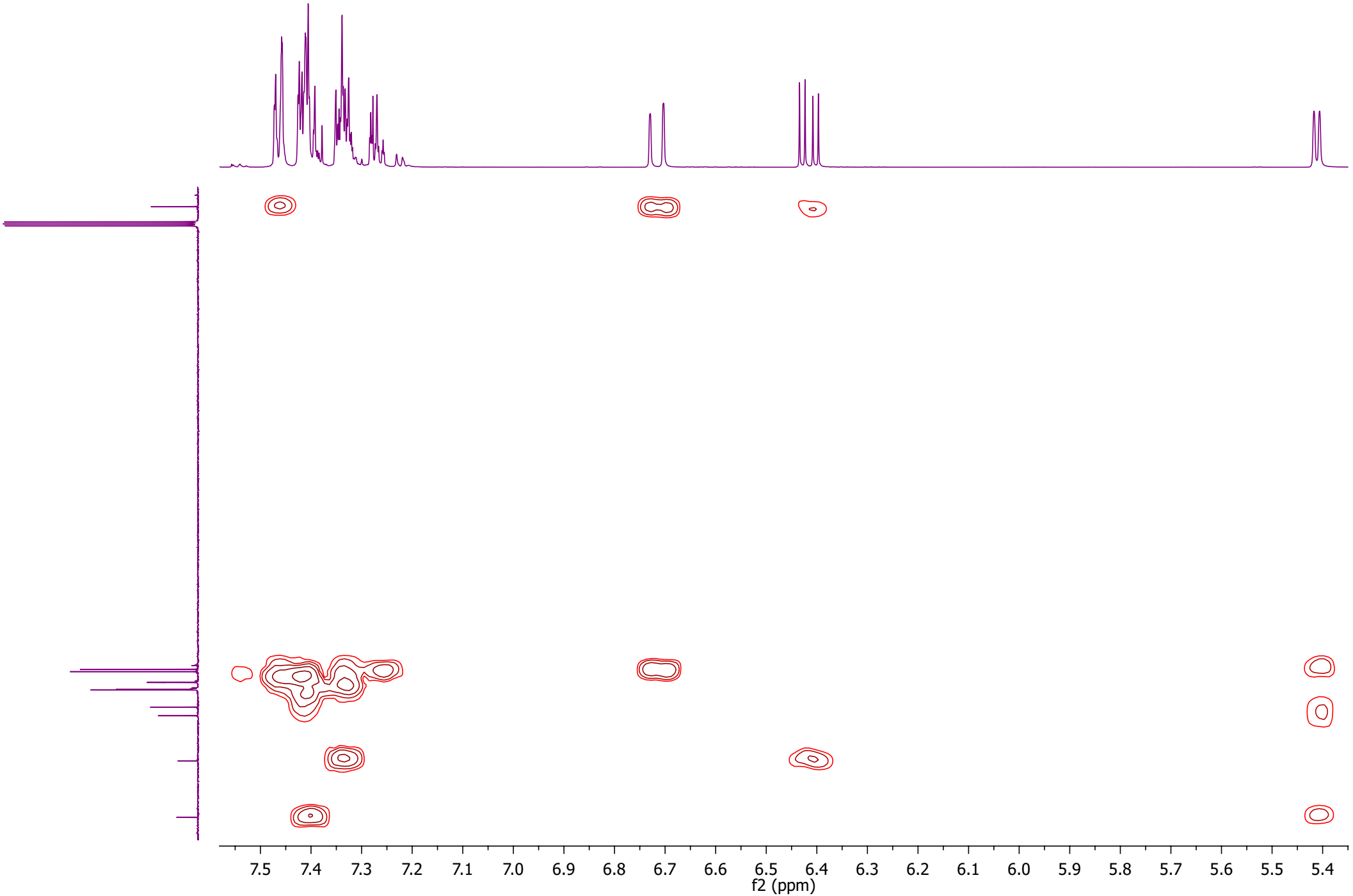


Plate 36g - HMBC (expansion) [$CDCl_3$]: 1,3-diphenylprop-2-en-1-ol (**453**)

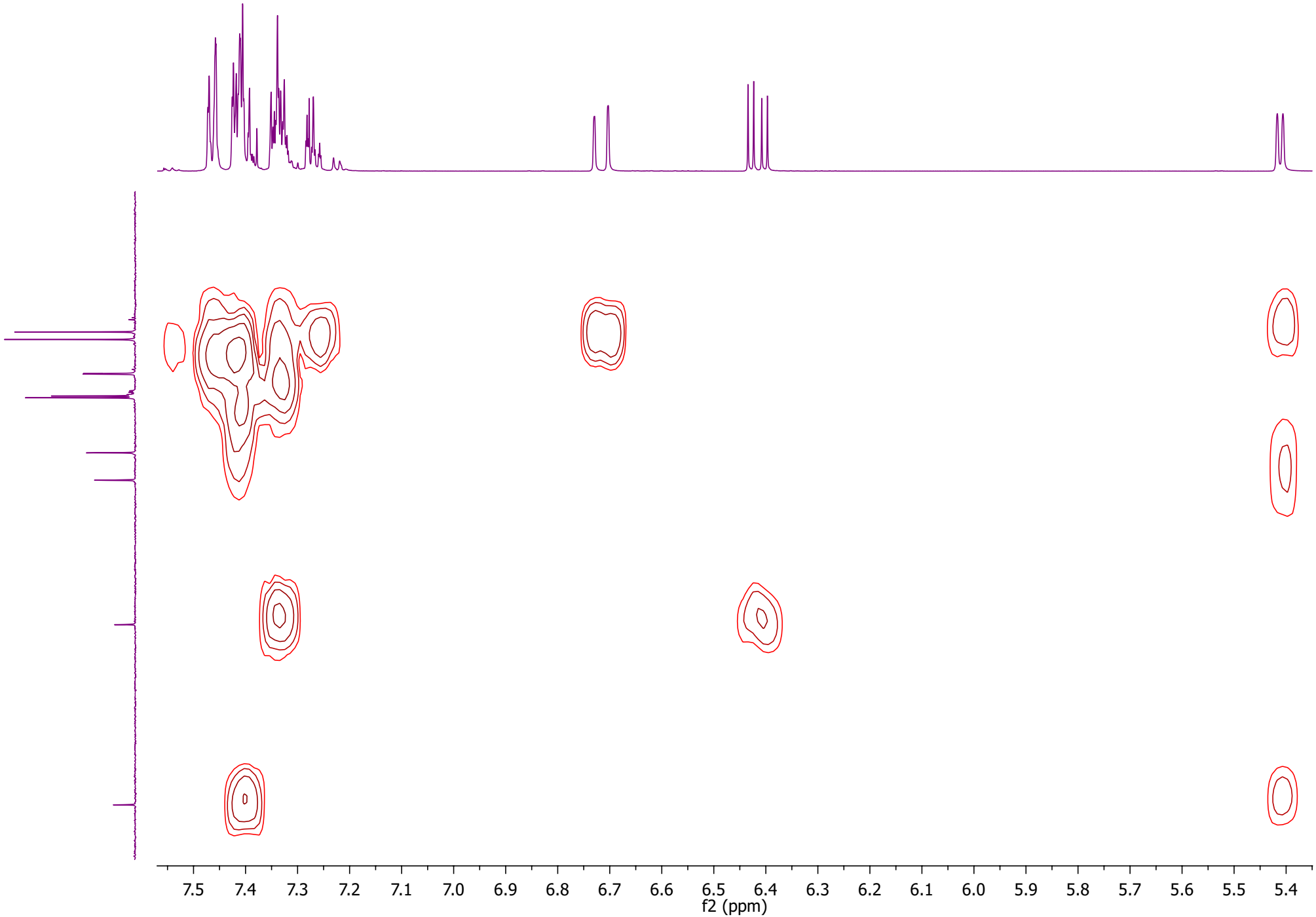
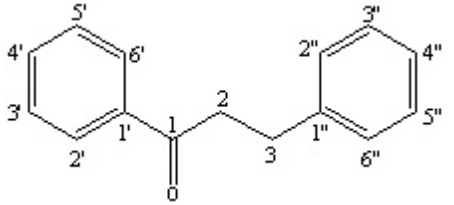


Plate 37a - ^{1}H NMR [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97-7.95 (2H, m, H-2' and H-6'), 7.56-7.53 (1H, m, H-4'), 7.46-7.43 (2H, m, H-3' and H-5'), 7.31-7.29 (2H, m, H-3" and H-5"), 7.26-7.25 (2H, m, H-2" and H-6"), 7.22-7.19 (1H, m, H-4"), 3.30 (2H, t, *J* = 7.75 Hz, H-2), 3.07 (2H, t, *J* = 7.75 Hz, H-3)

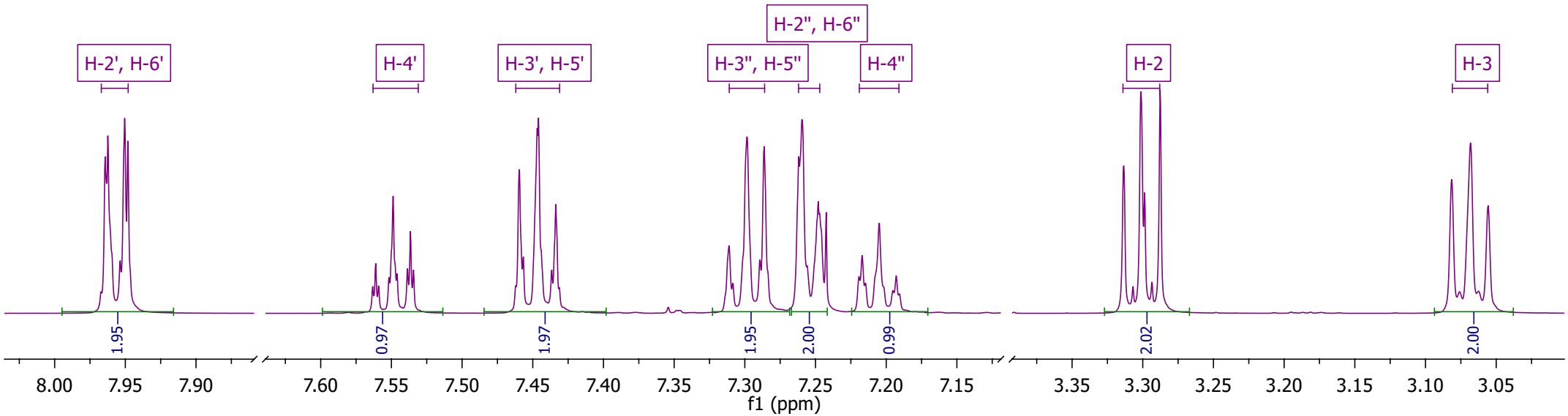
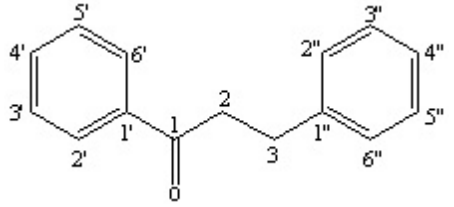


Plate 37b - ^{13}C NMR [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)



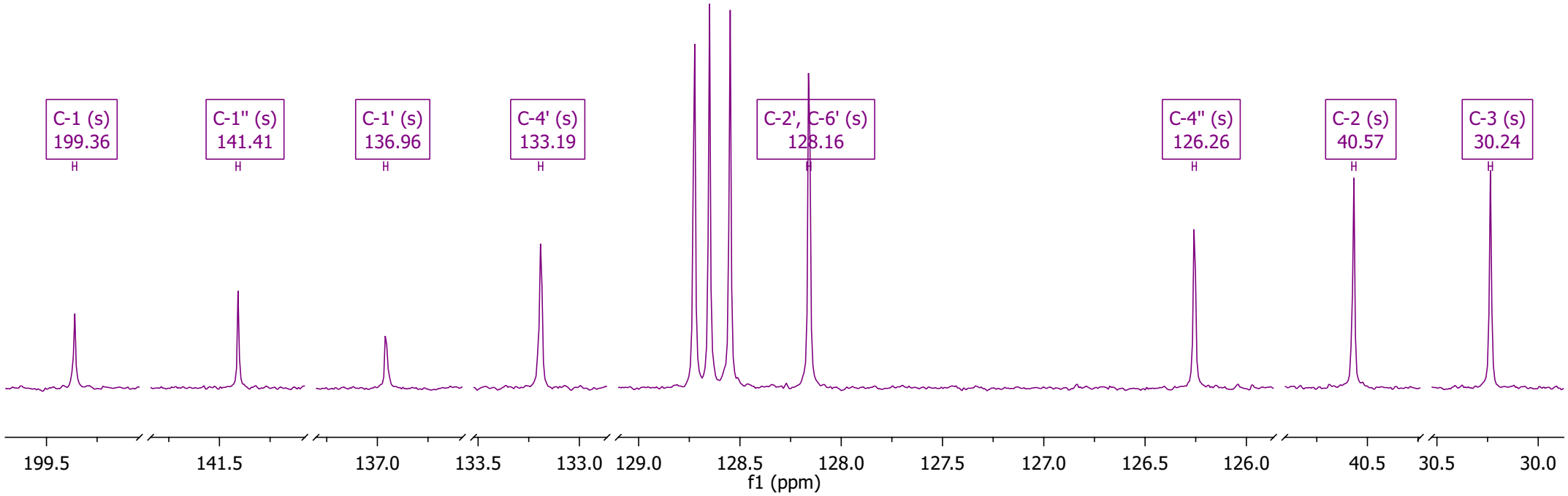


Plate 37c - DEPT [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)

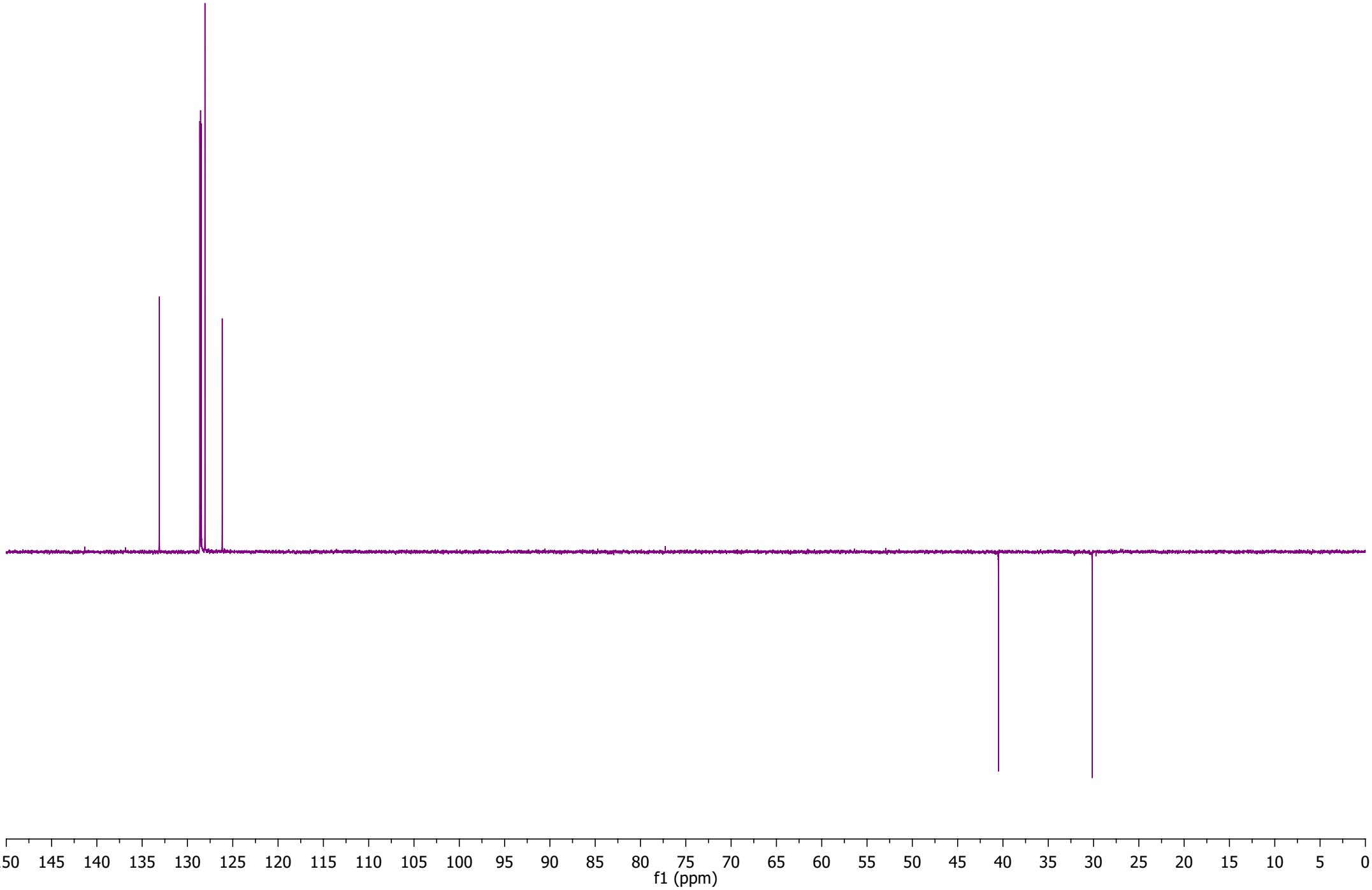


Plate 37d - HSQC [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)

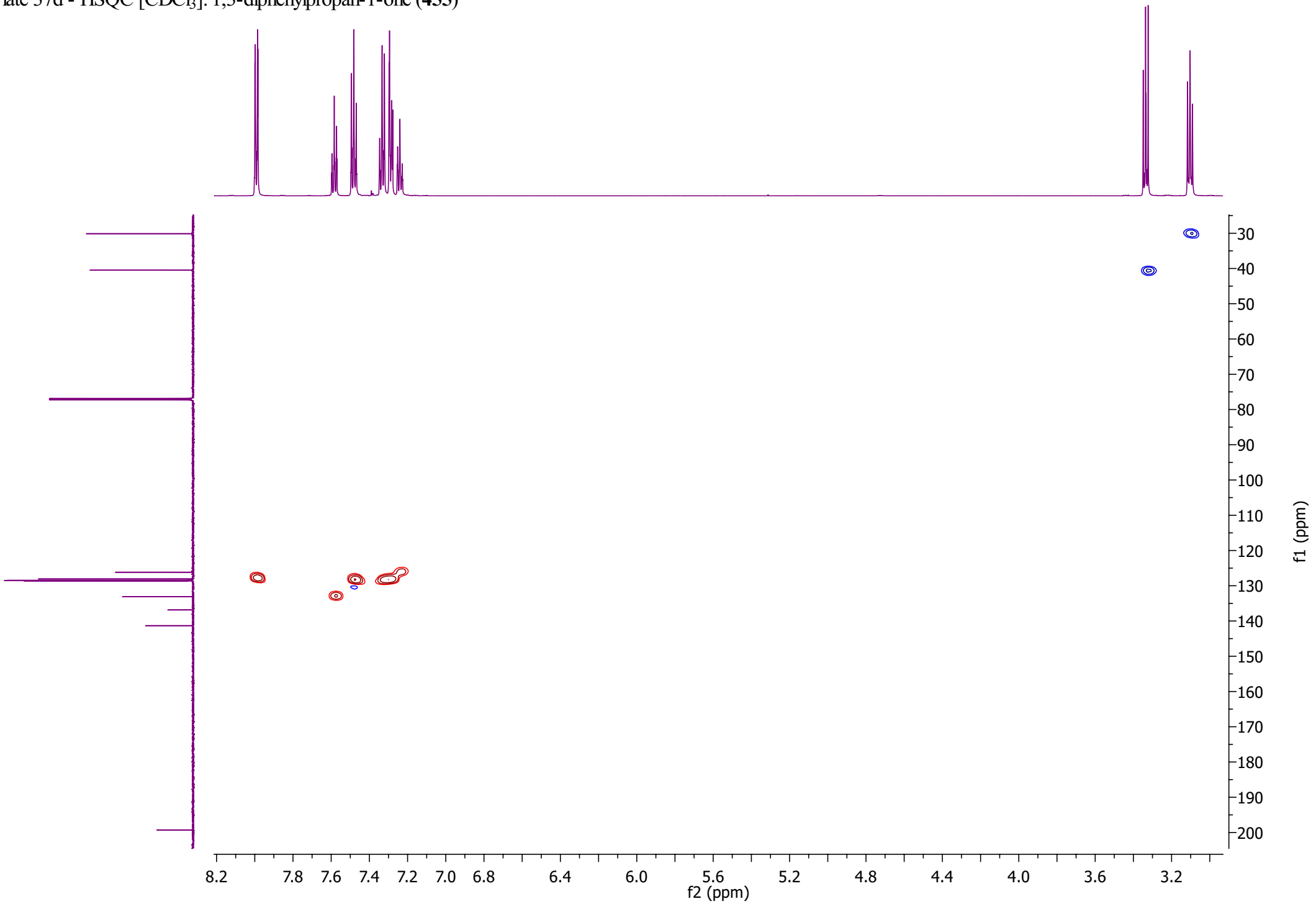


Plate 37e - HSQC (expansion) [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)

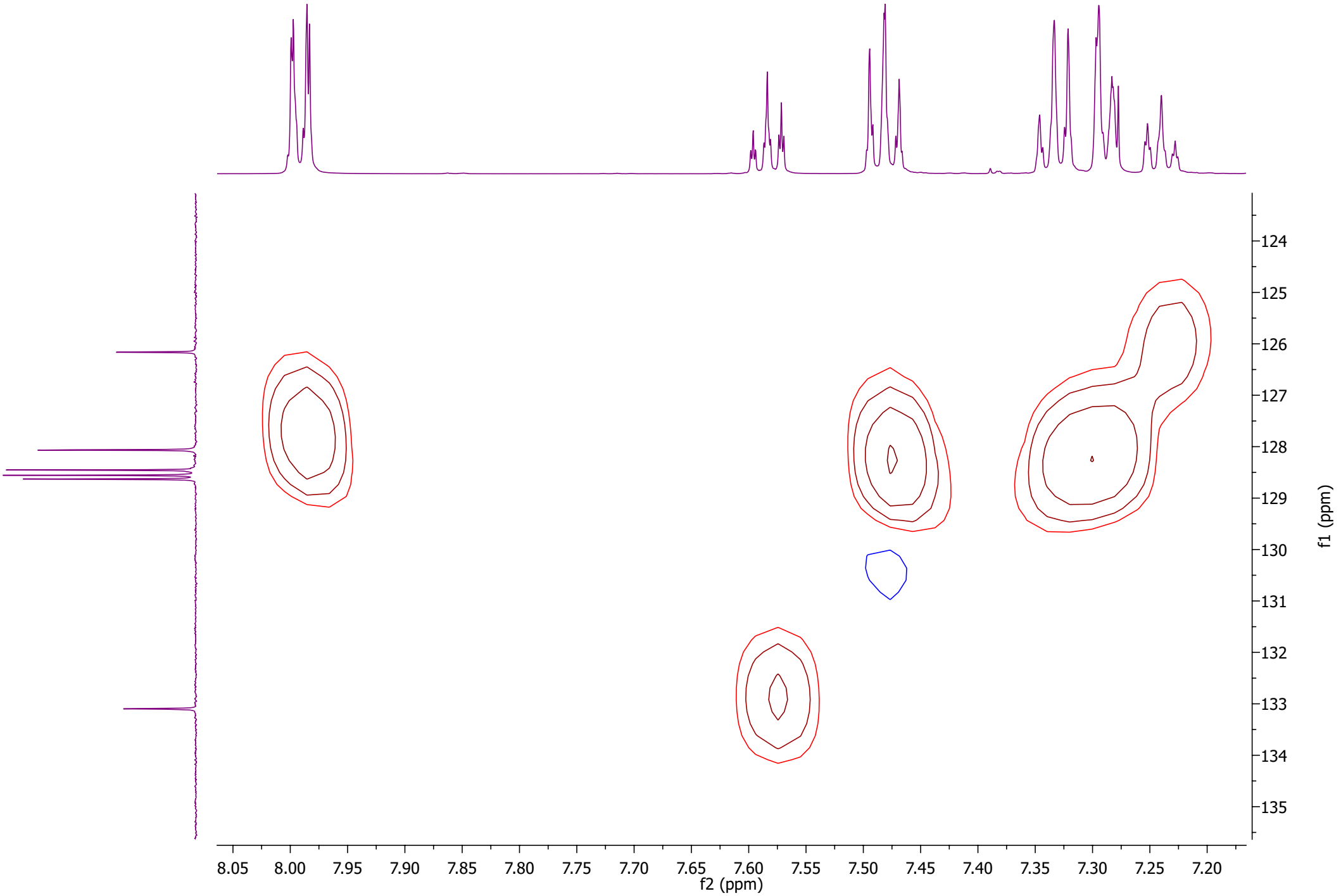


Plate 37f - HMBC [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)

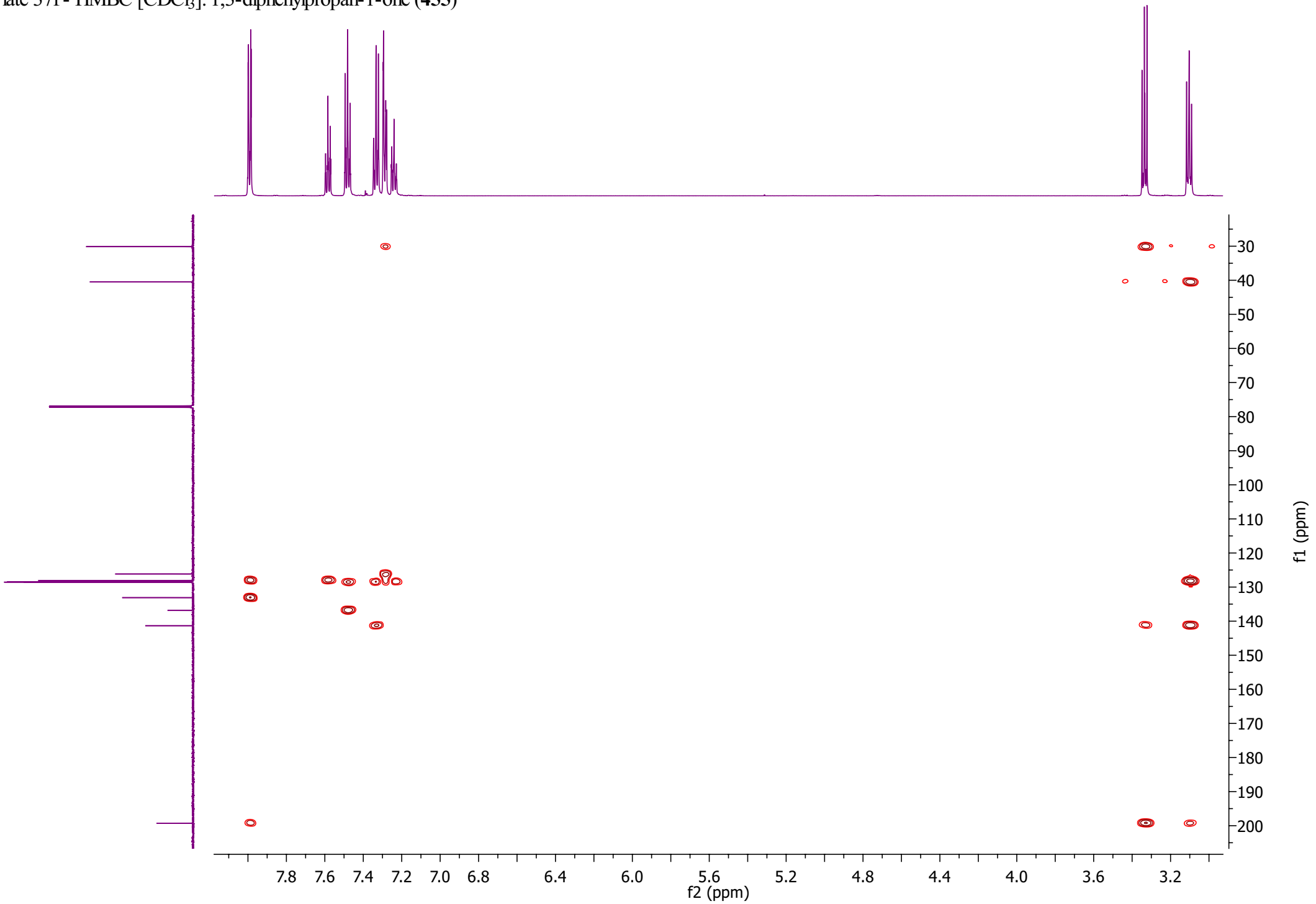


Plate 37g - HMBC (expansion) [$CDCl_3$]: 1,3-diphenylpropan-1-one (**455**)

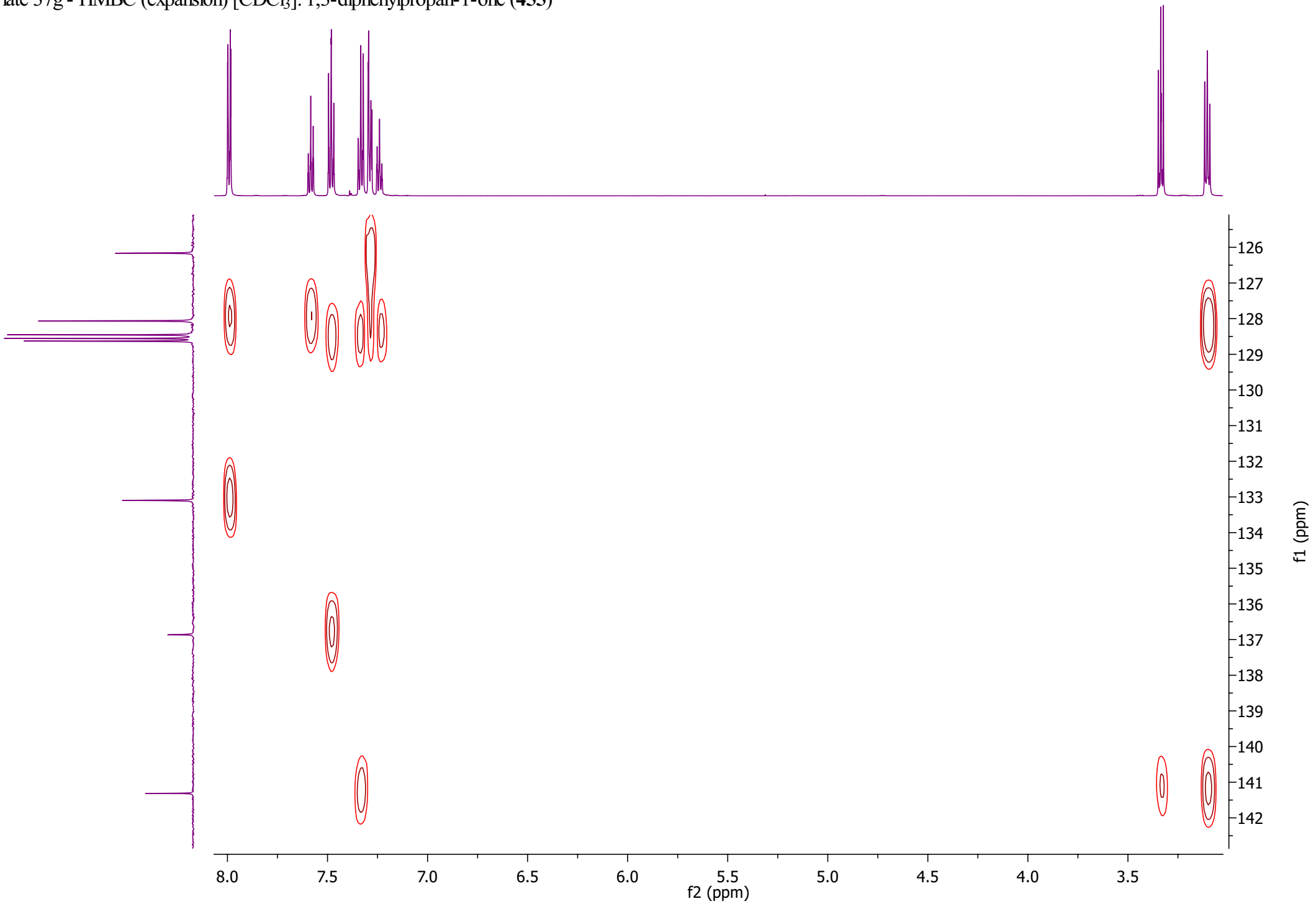
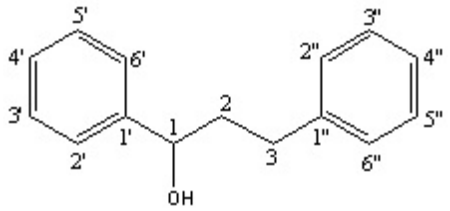


Plate 38a - ^{1}H NMR [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.30 (4H, m, Ar-H), 7.27-7.25 (3H, m, Ar-H), 7.18-7.16 (3H, m, Ar-H), 4.64 (1H, br t, *J* = 6.57 Hz, H-1), 2.74-2.69 (1H, m, H-3a or H-3b), 2.66-2.61 (1H, m, H-3a or H-3b), 2.13-2.07 (2H, m, -OH and H-2a or H-2b), 2.03-1.97 (1H, m, H-2a or H-2b)

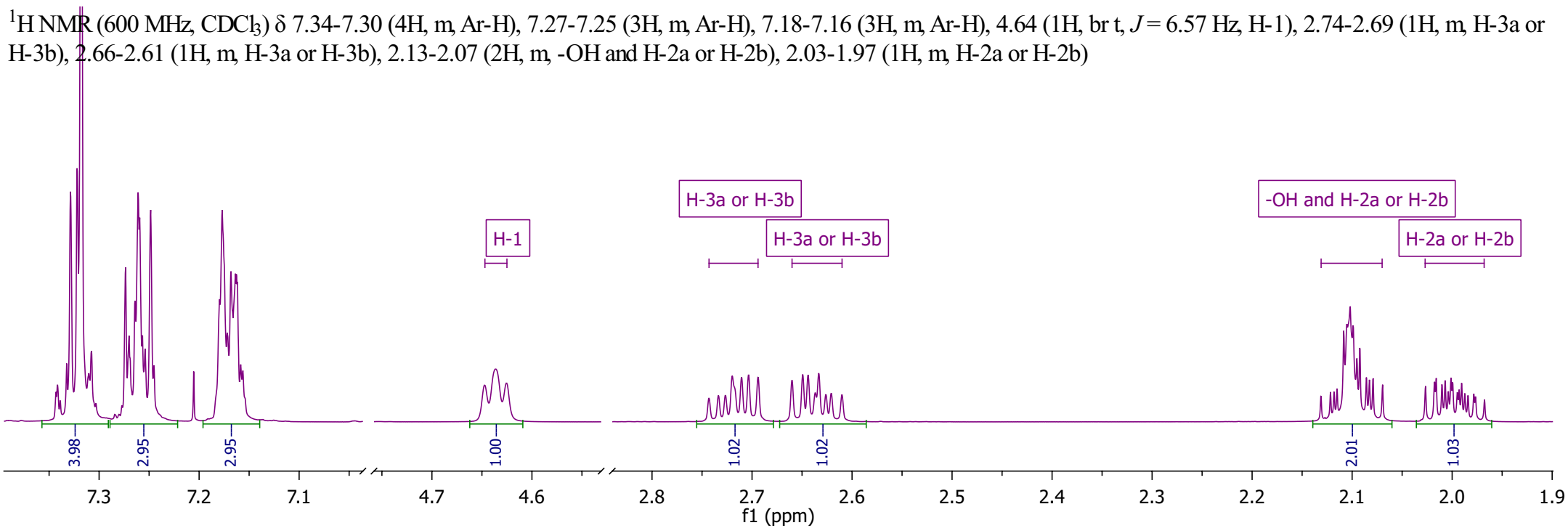
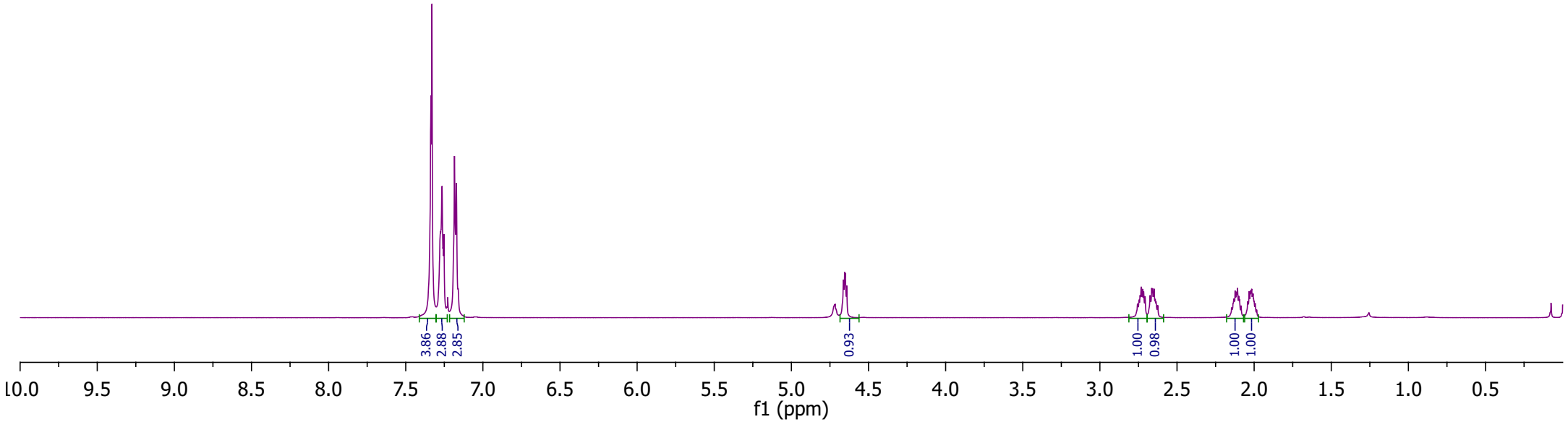


Plate 38b - ^{1}H NMR [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**) with D_2O



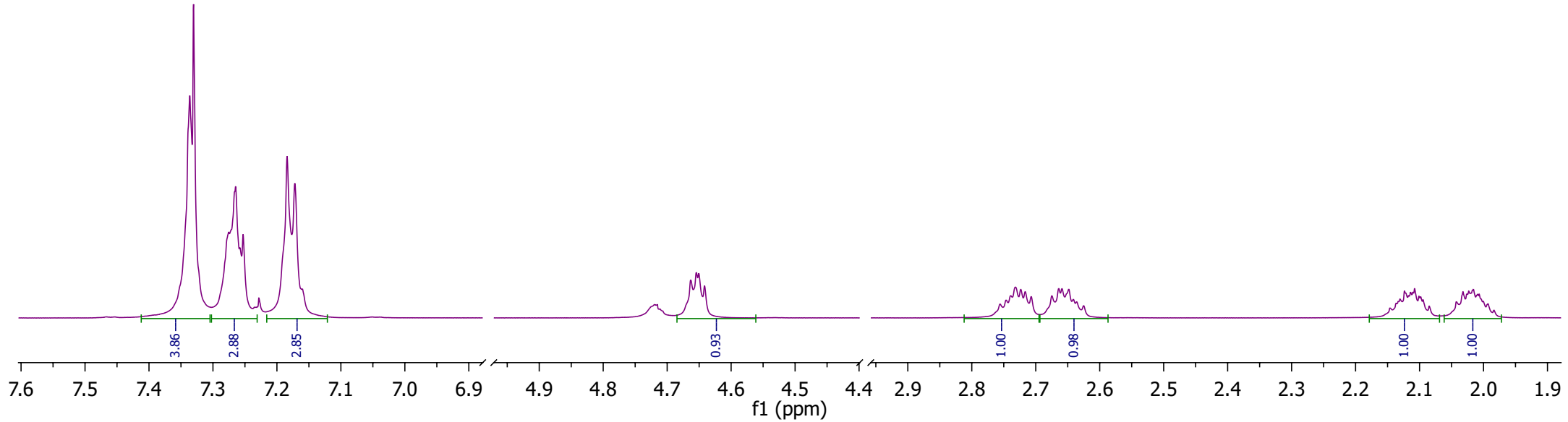
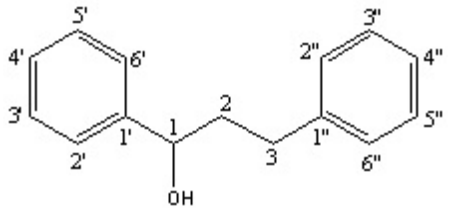


Plate 38c - ^{13}C NMR [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)



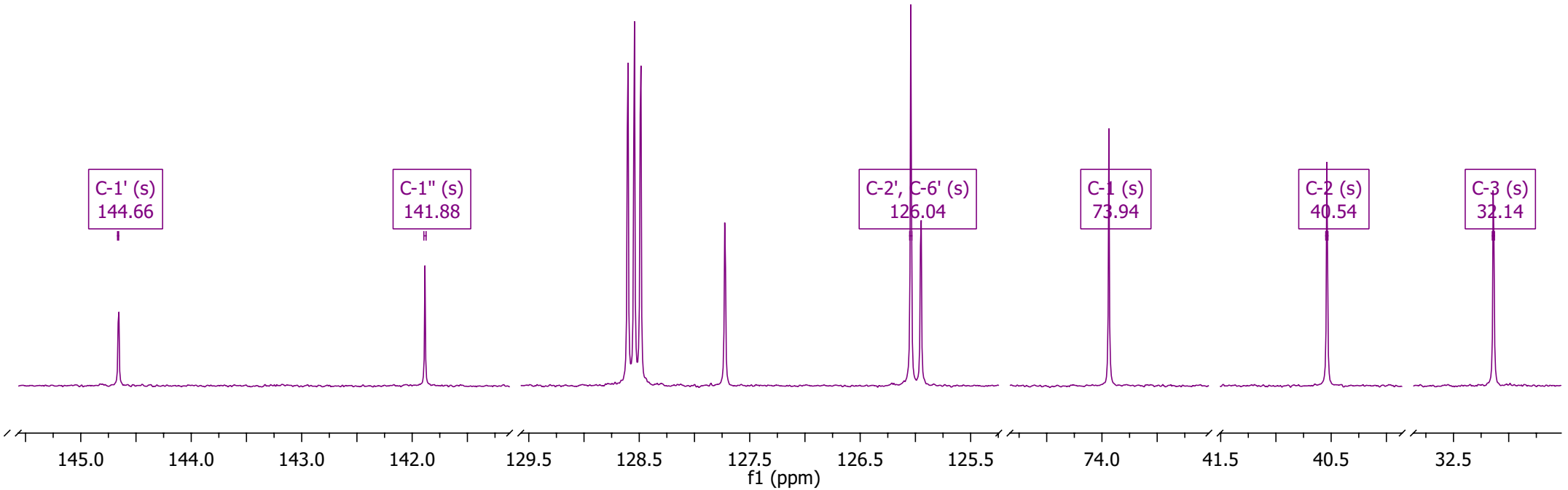


Plate 38d - DEPT [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)

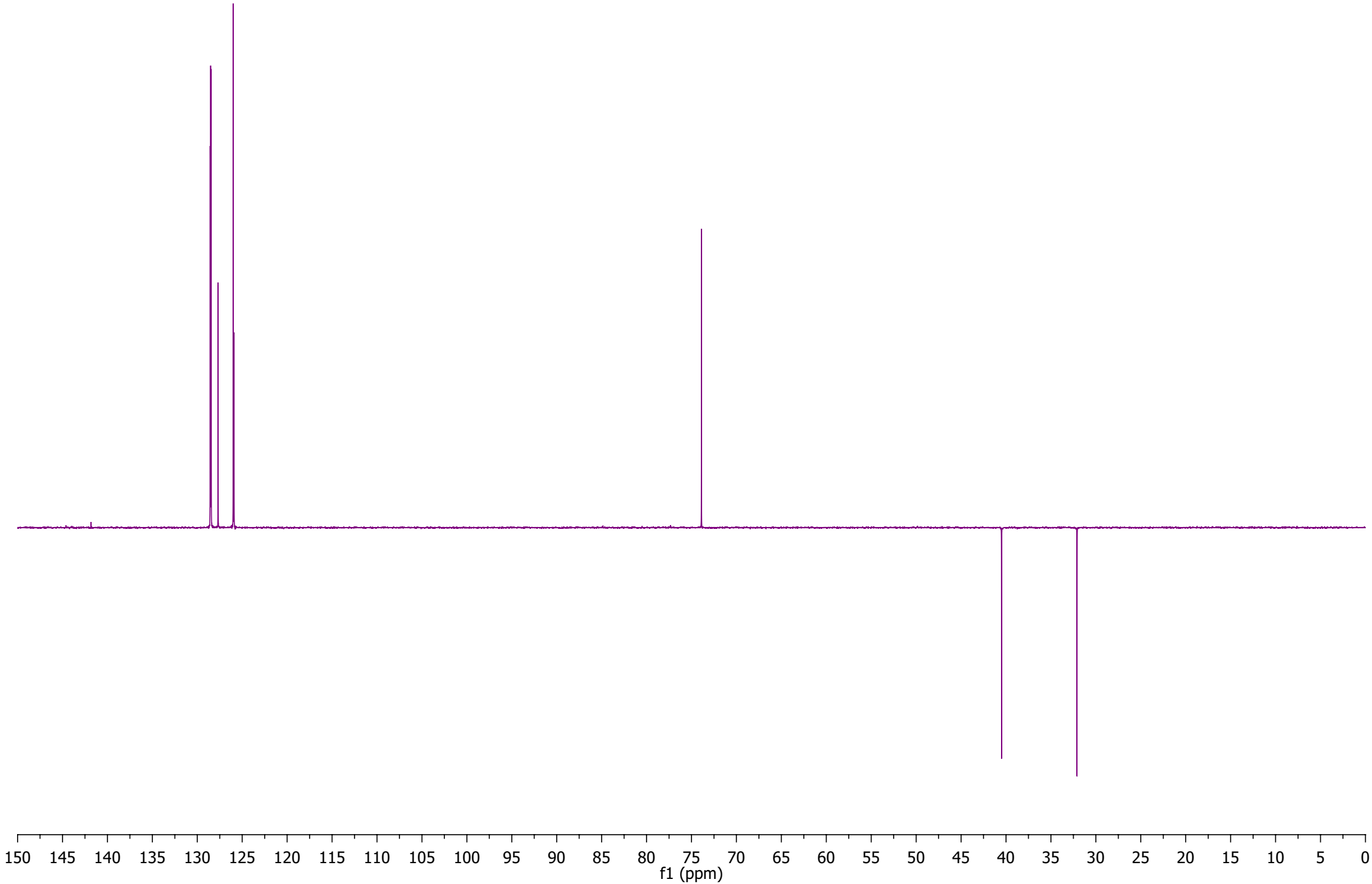


Plate 38e - HSQC [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)

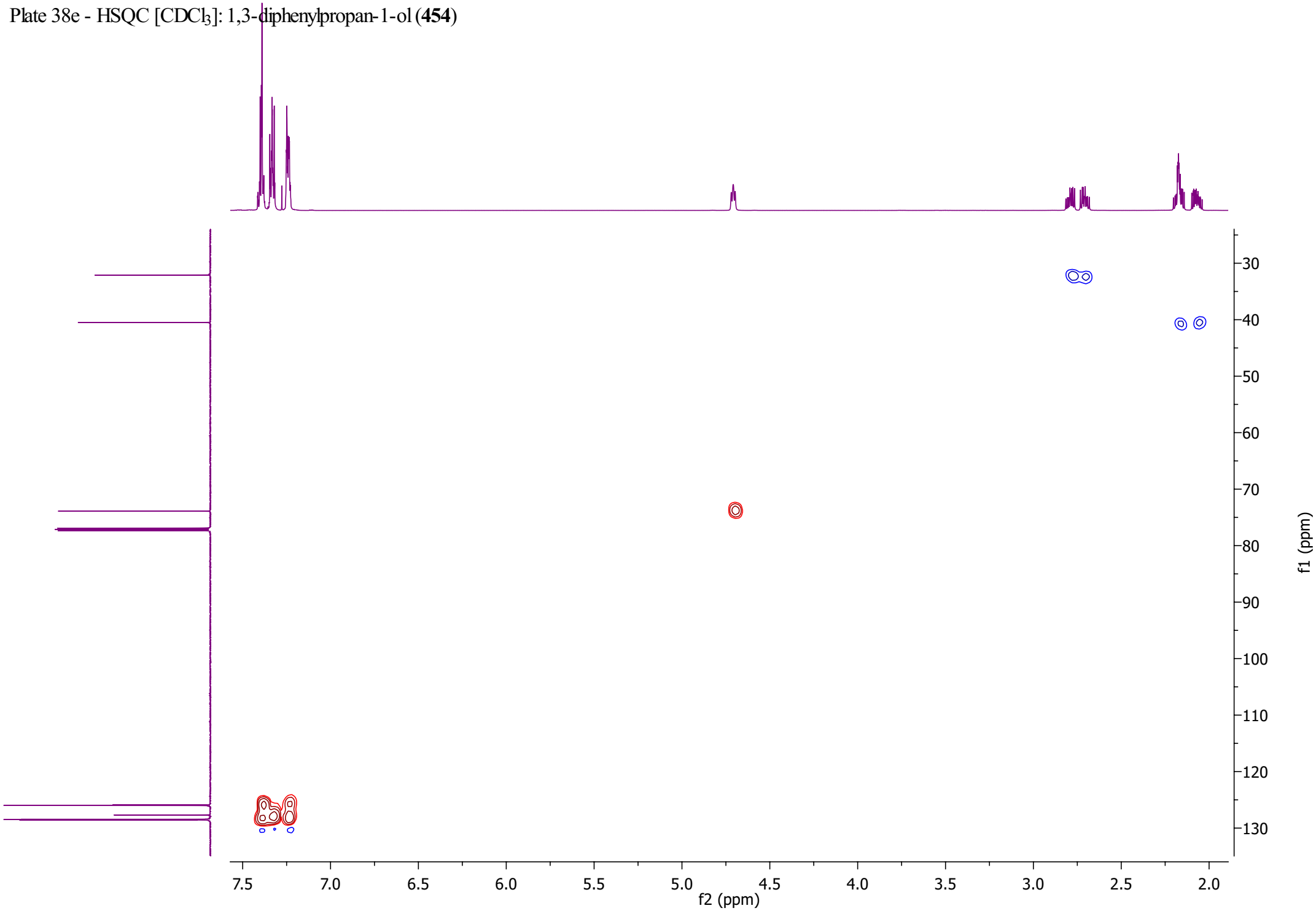


Plate 38f - HSQC (expansion) [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)

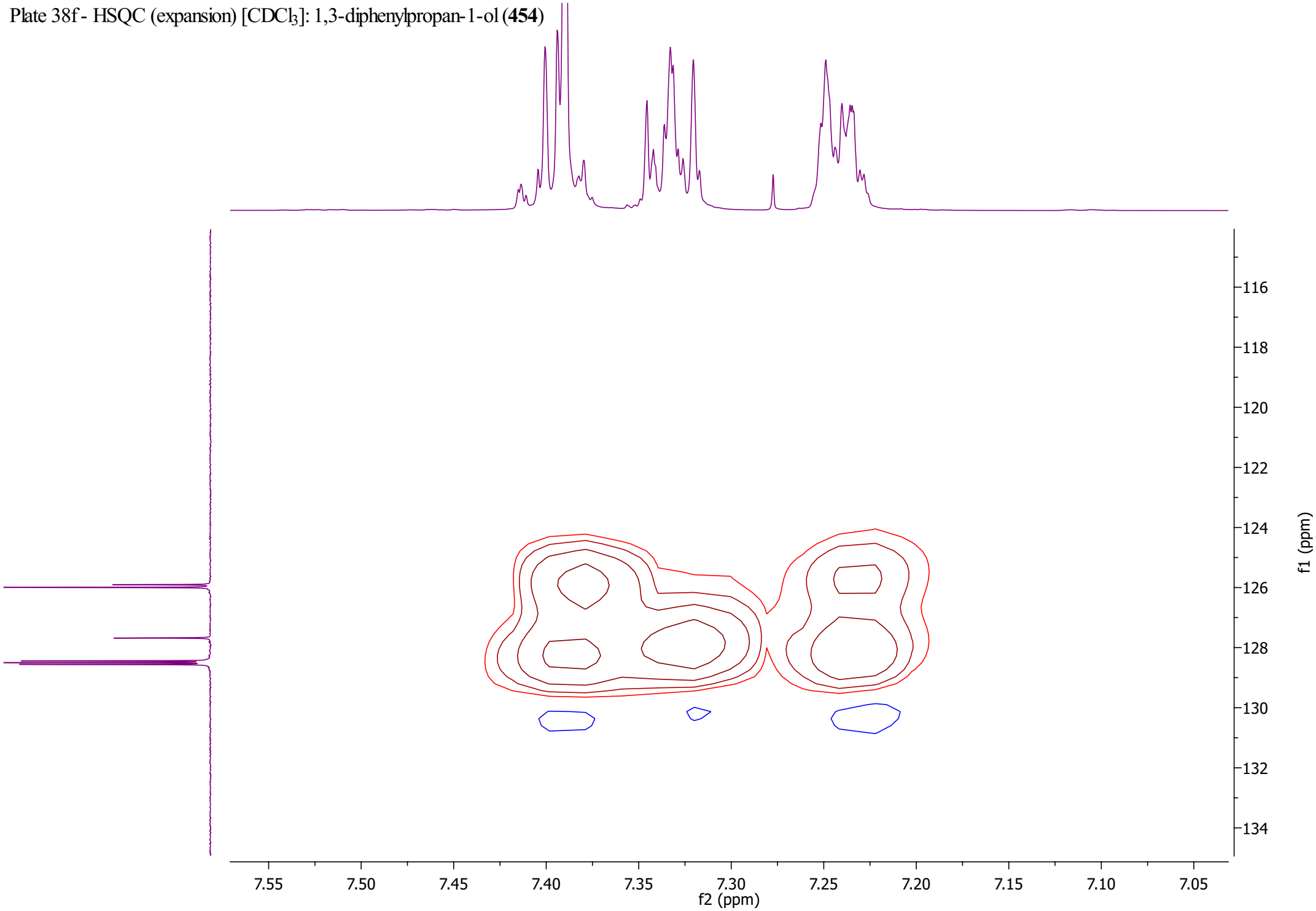


Plate 38g - HMBC [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)

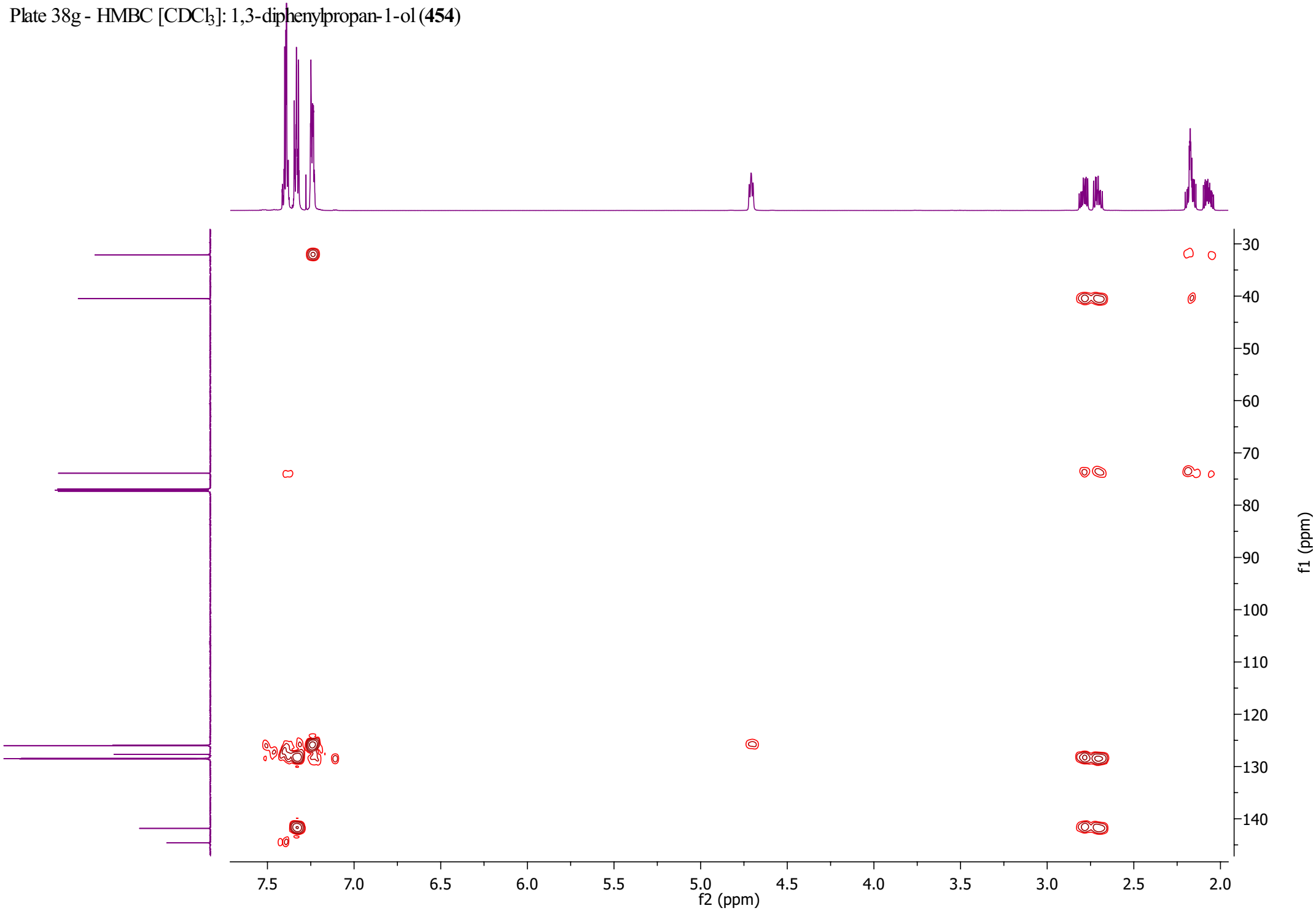


Plate 38h - HMBC (expansion) [$CDCl_3$]: 1,3-diphenylpropan-1-ol (**454**)

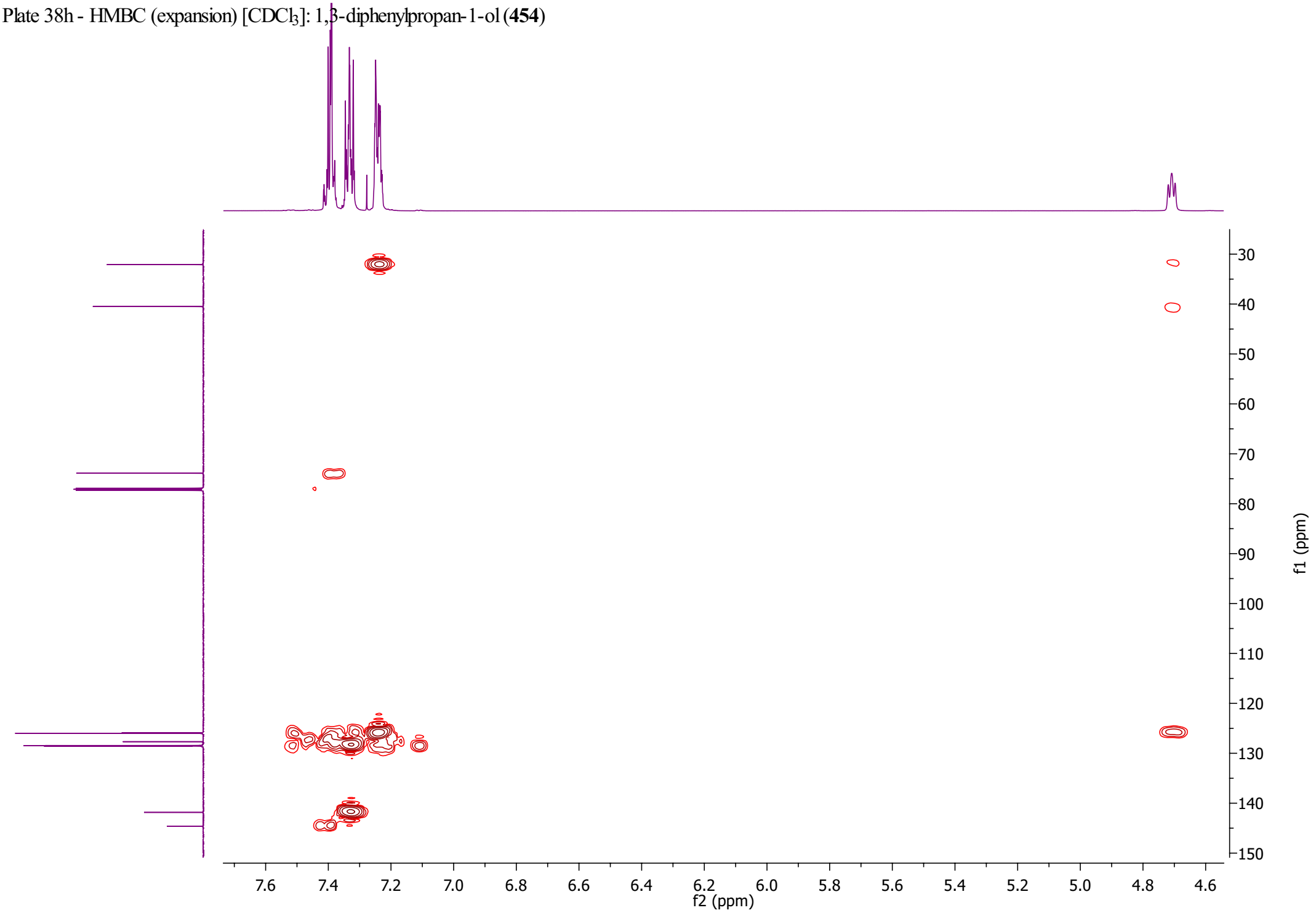
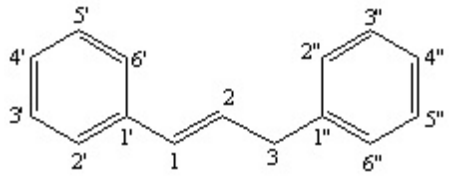
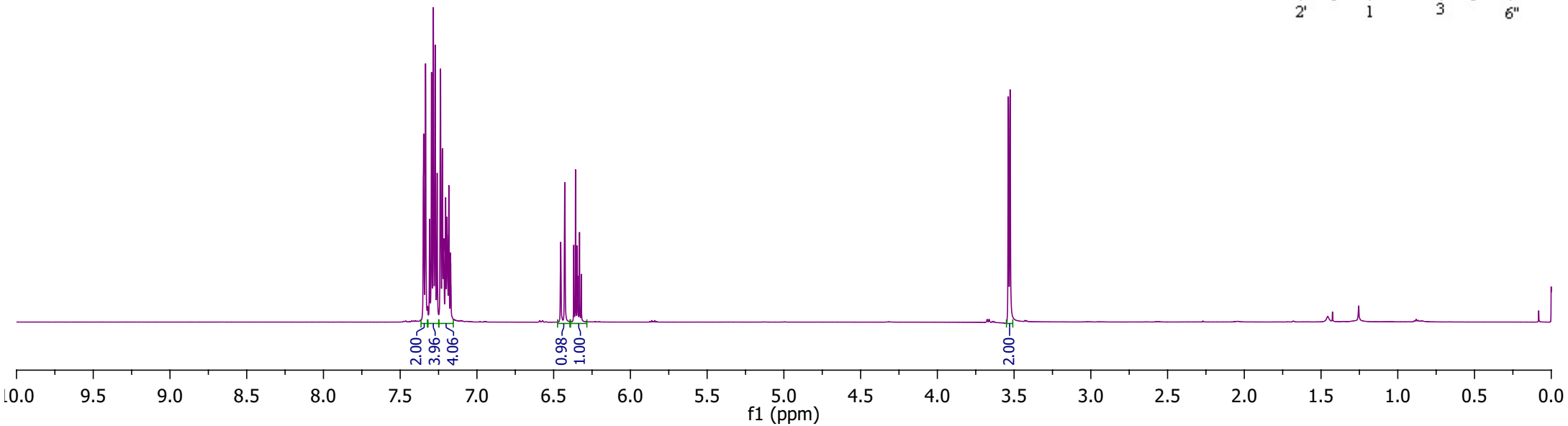


Plate 39a - ^{1}H NMR [$CDCl_3$]: 1,3-diphenylpropene (**451**)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.34 (2H, m, H-2' and H-6'), 7.31-7.26 (4H, m, H-3', H-5', H-3" and H-5"), 7.24-7.23 (2H, m, H-2" and H-6"), 7.22-7.17 (2H, m, H-'4 and H-4"), 6.44 (1H, br d, *J* = 15.75 Hz, H-1), 6.34 (1H, dt, *J* = 15.75, 6.82 Hz, H-2), 3.53 (2H, br d, *J* = 6.82 Hz, H-3)

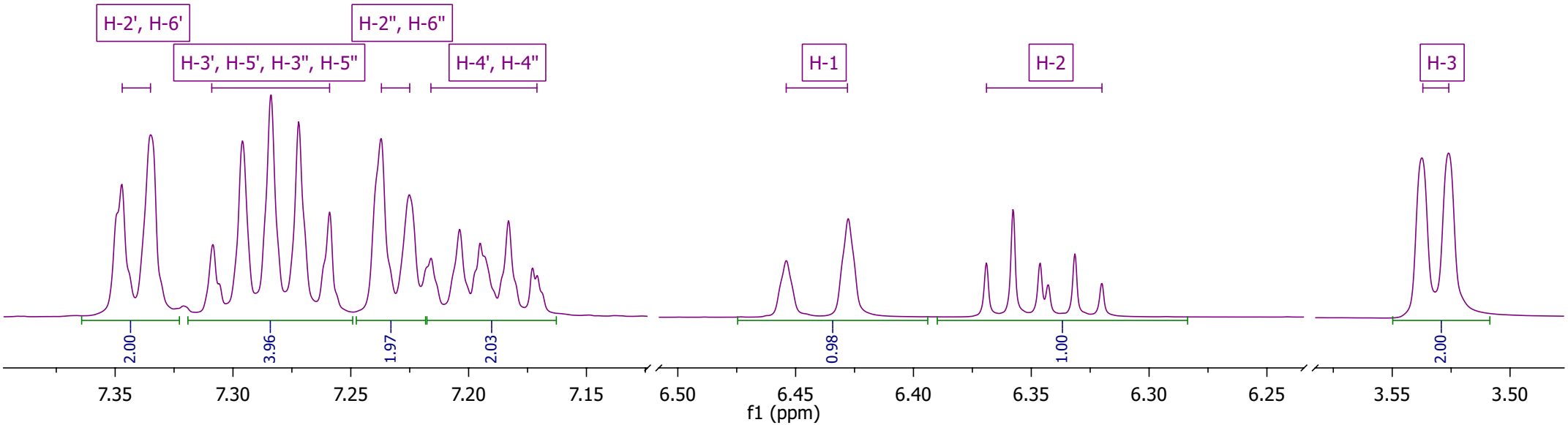
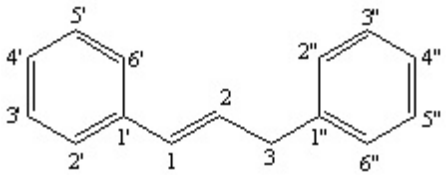


Plate 39b - ^{13}C NMR [$CDCl_3$]: 1,3-diphenylpropene (**451**)



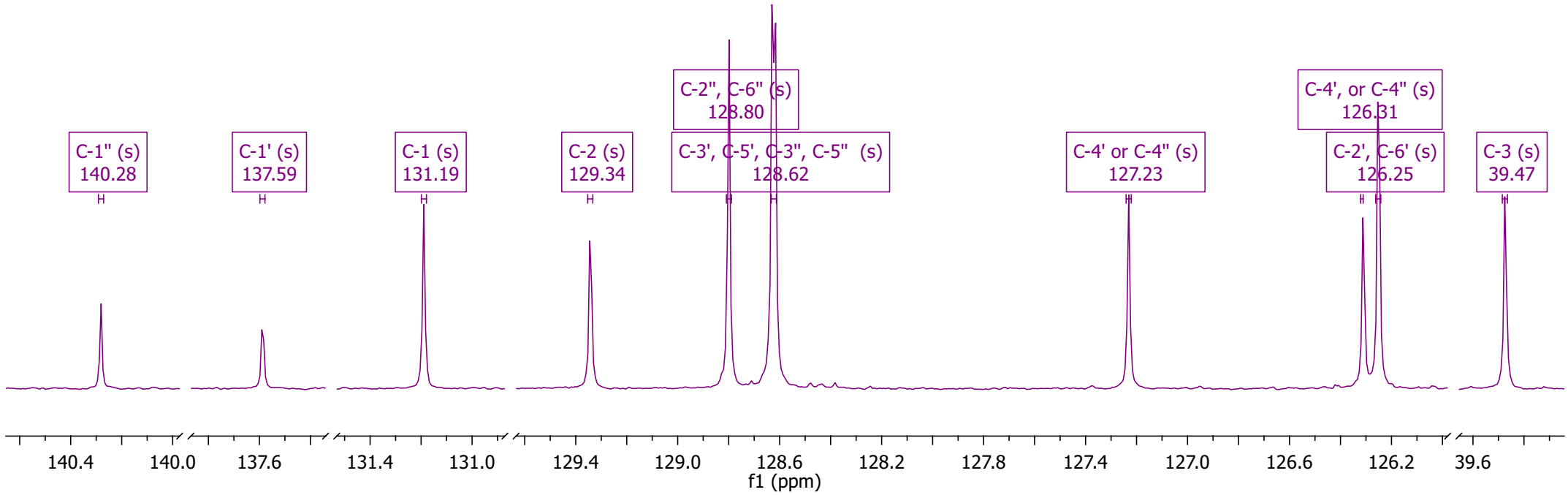


Plate 39c - DEPT [$CDCl_3$]: 1,3-diphenylpropene (**451**)

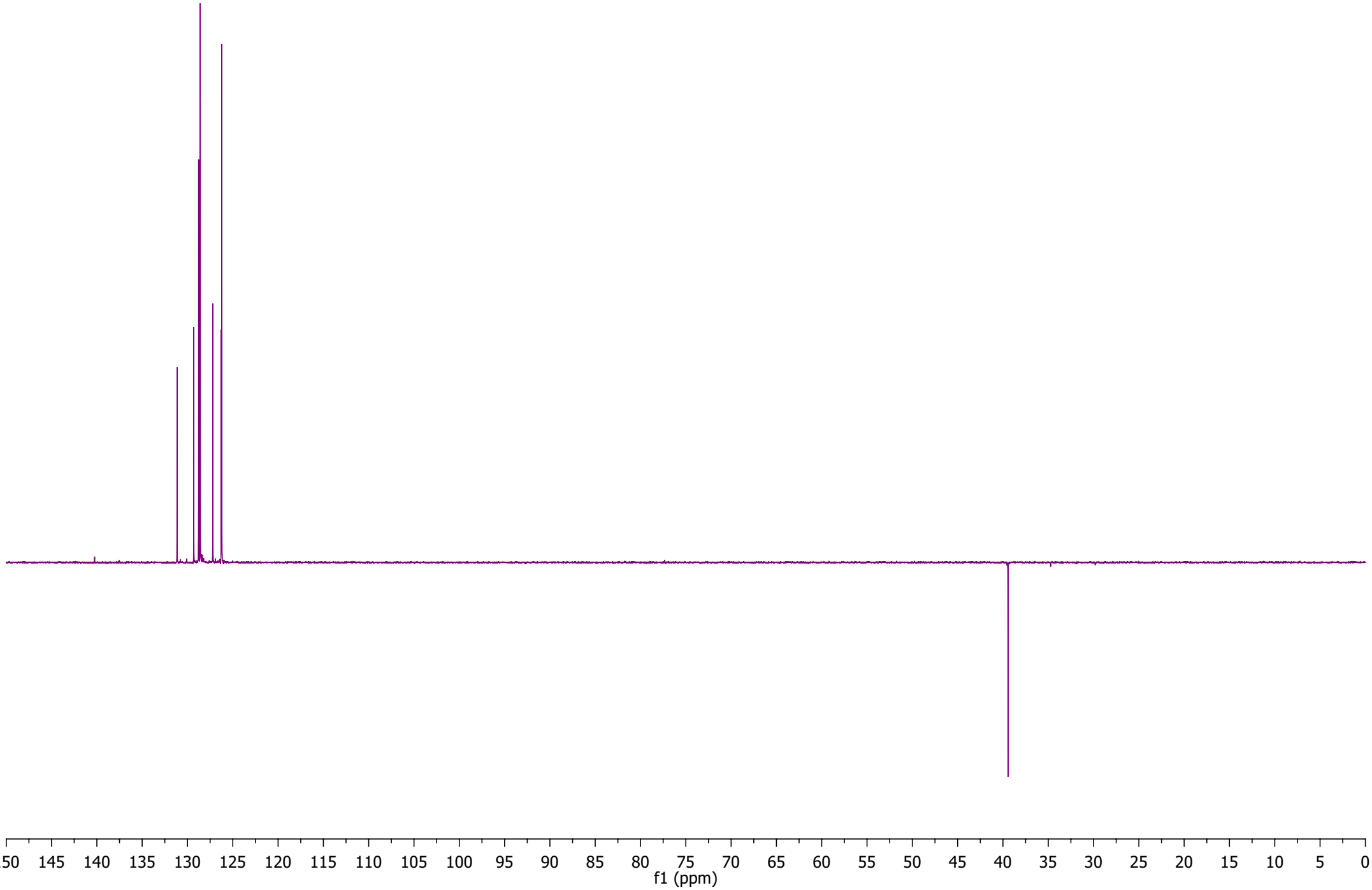


Plate 39d - HSQC [$CDCl_3$]: 1,3-diphenylpropene (**451**)

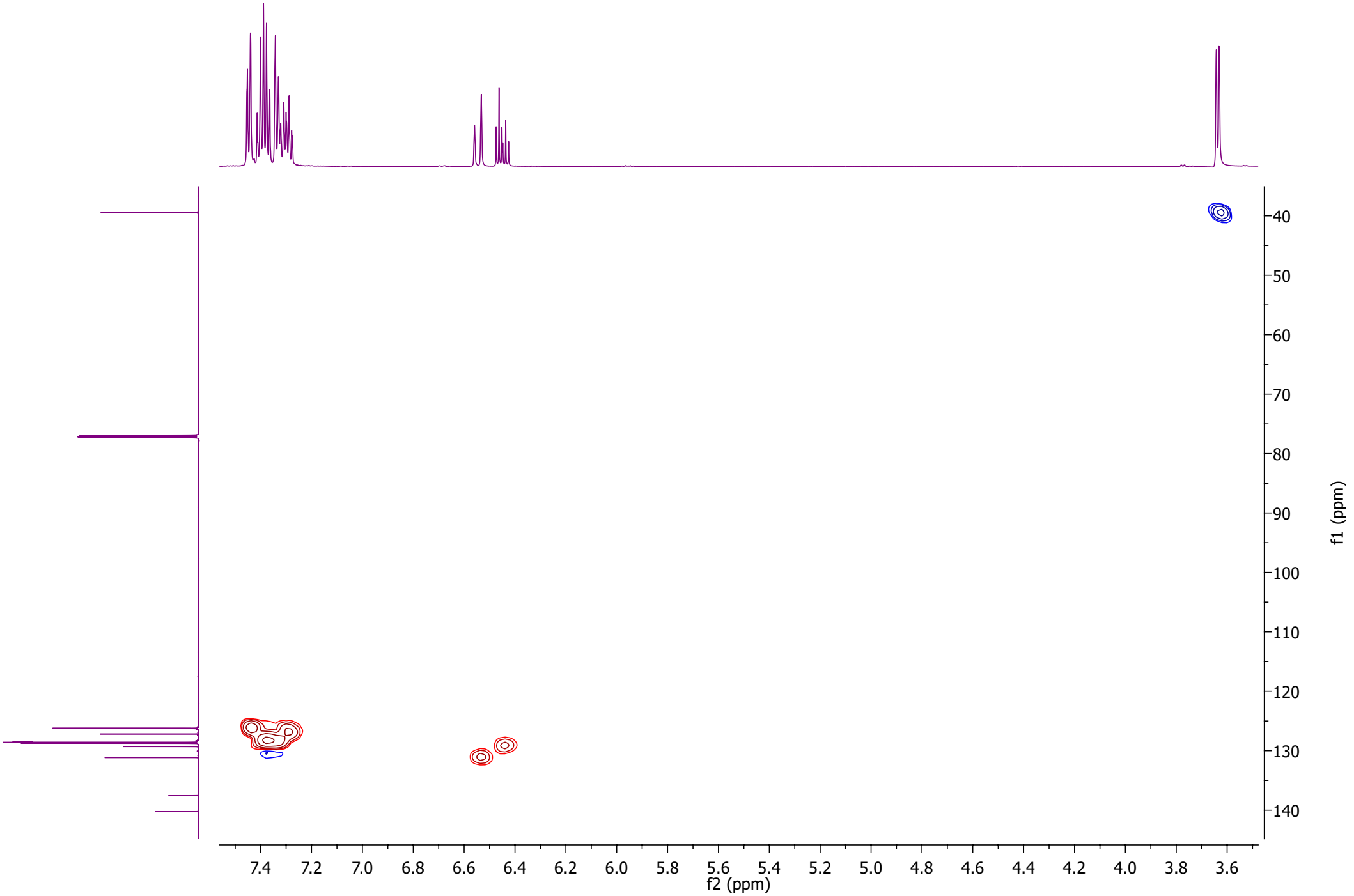


Plate 39e - HSQC (expansion) [$CDCl_3$]: 1,3-diphenylpropene (**451**)

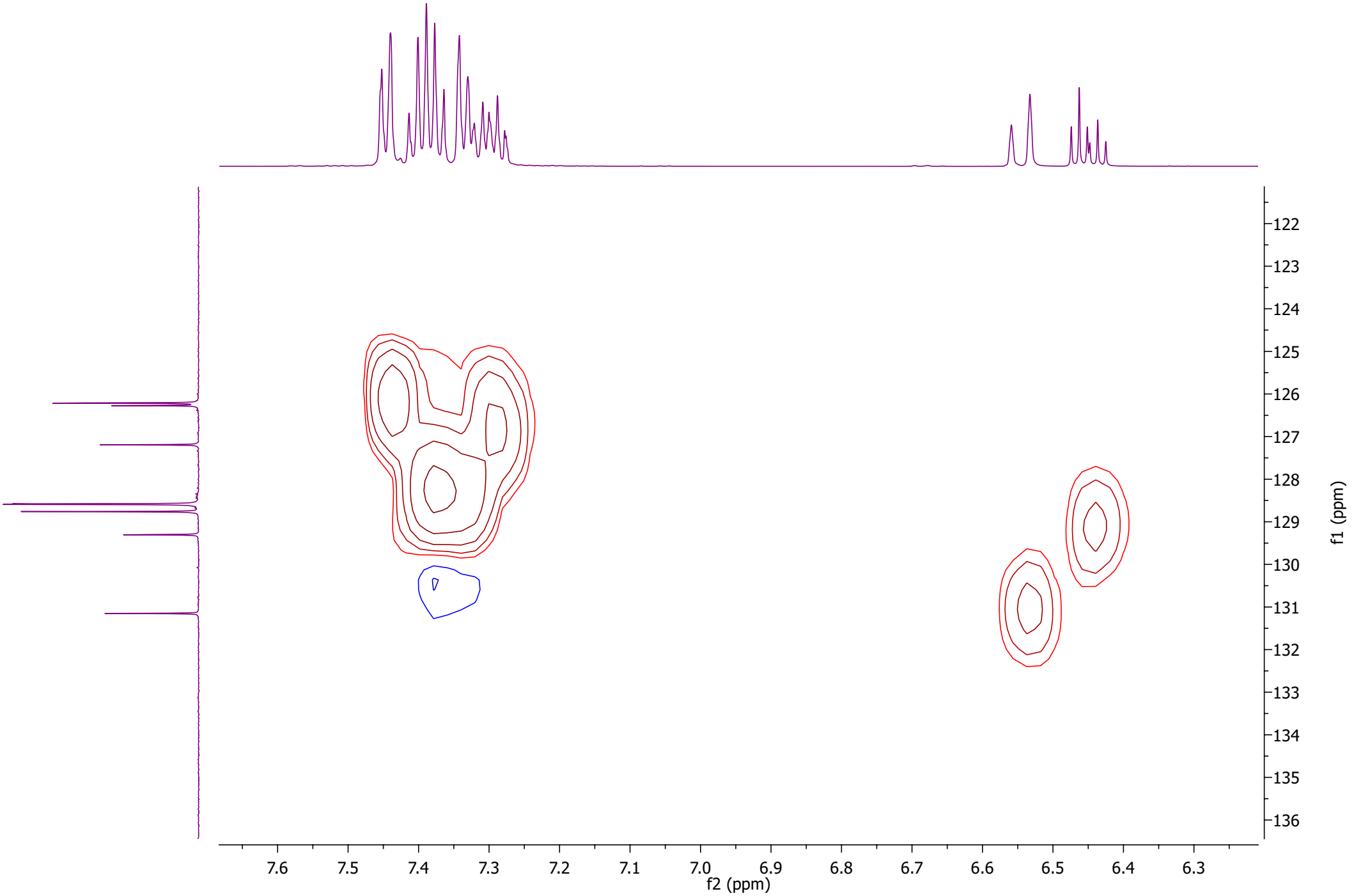


Plate 39f - HMBC [$CDCl_3$]: 1,3-diphenylpropene (**451**)

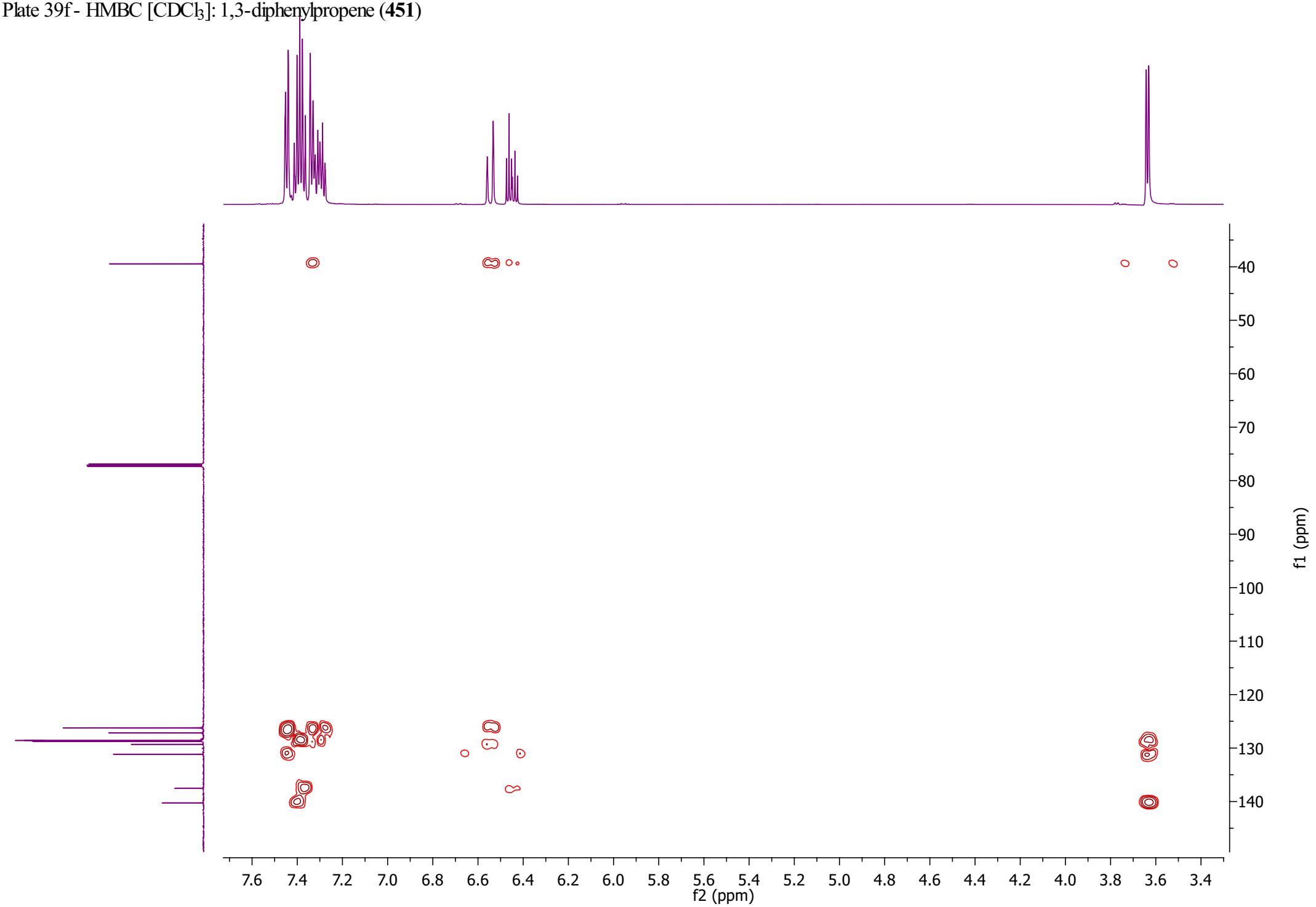


Plate 39g - HMBC (expansion) [$CDCl_3$]: 1,3-diphenylpropene (**451**)

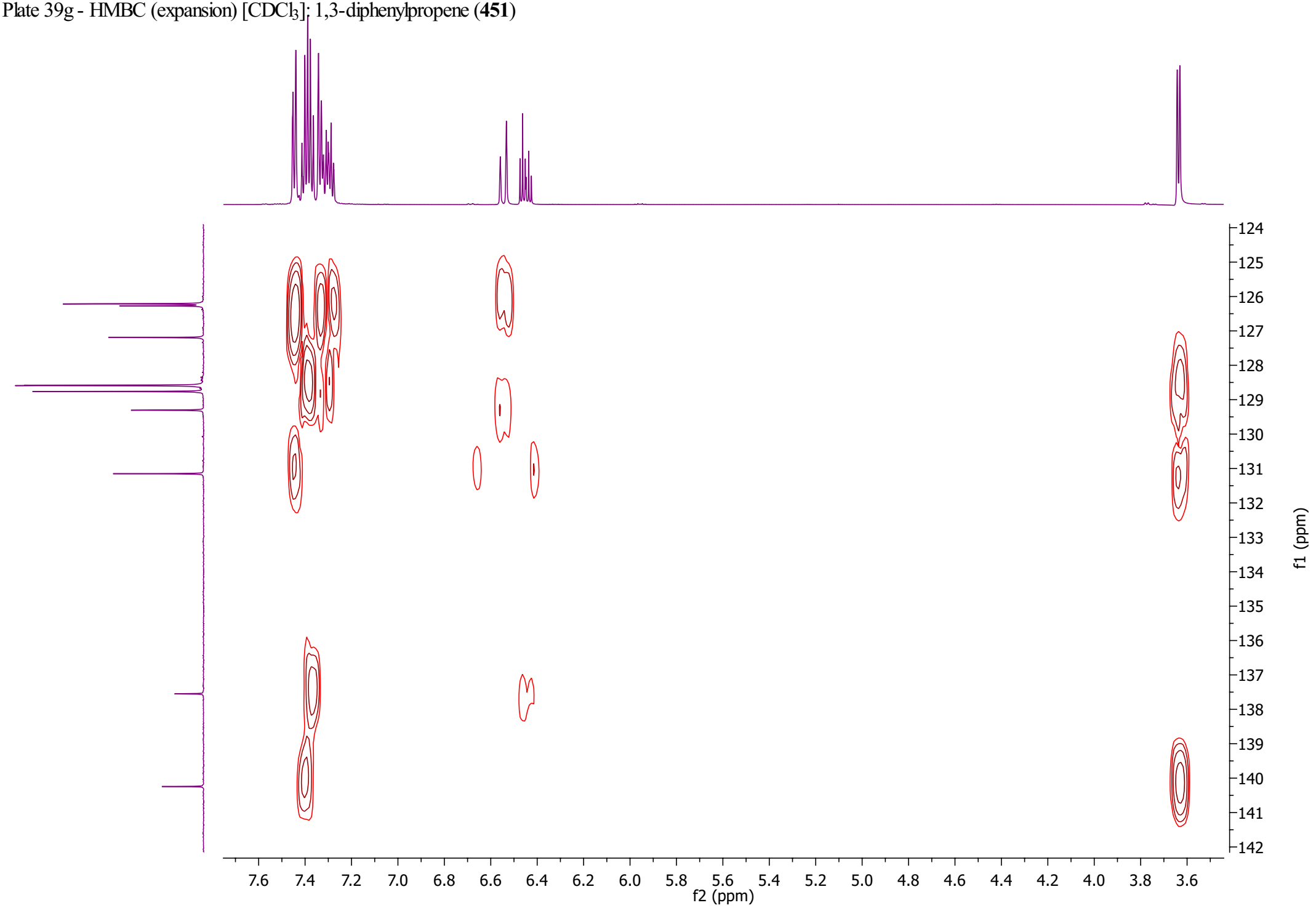
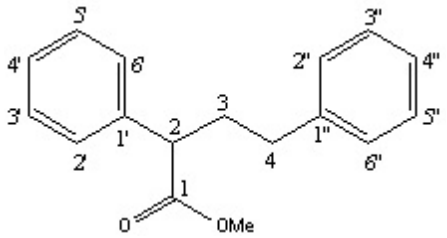


Plate 40a - ^{1}H NMR [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.24 (7H, m, H-Ar), 7.19-7.16 (1H, m, H-Ar), 7.15-7.13 (2H, m, H-2" and H-6"), 3.63 (3H, s, -OMe), 3.56 (1H, t, *J* = 7.65 Hz, H-2), 2.56 (2H, t, *J* = 7.76 Hz, H-4), 2.44-2.38 (1H, m, H-3a or H-3b), 2.13-2.07 (1H, m, H-3a or H-3b).

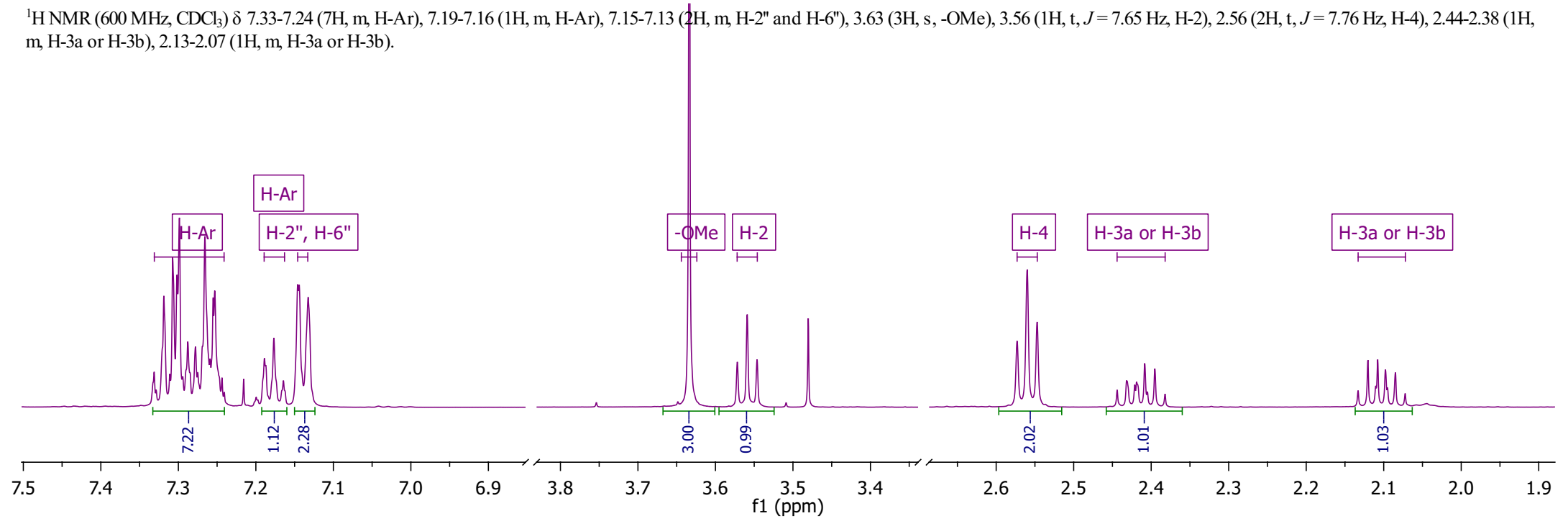
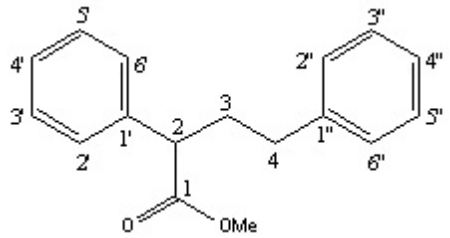


Plate 40b - ^{13}C NMR [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)



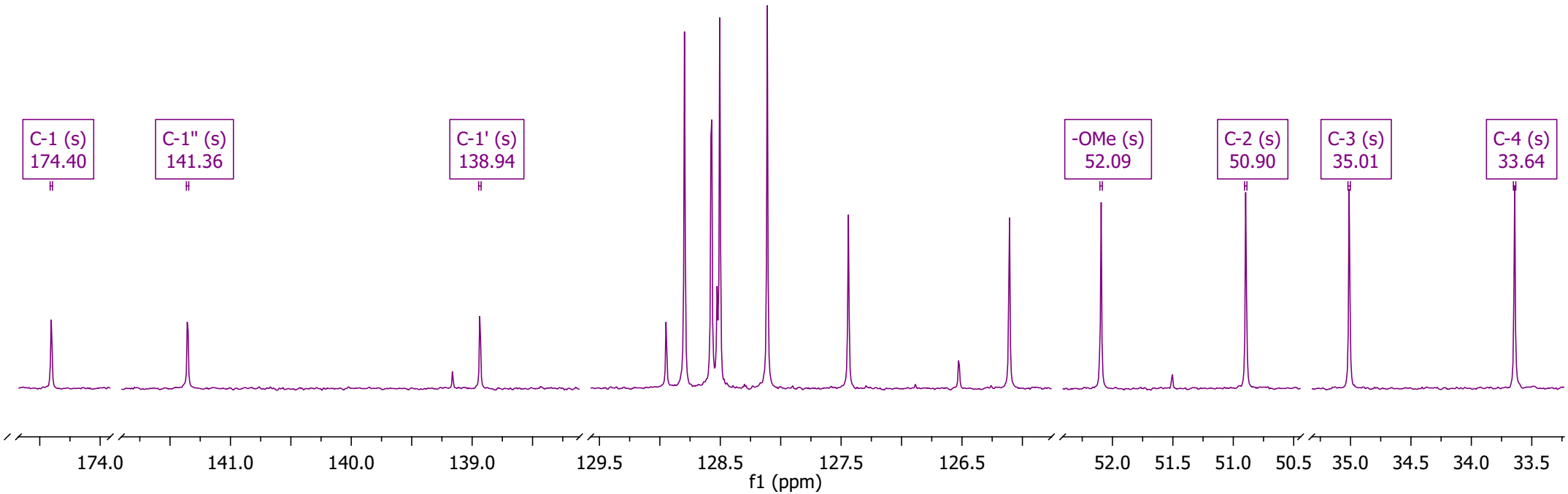


Plate 40c - DEPT [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)

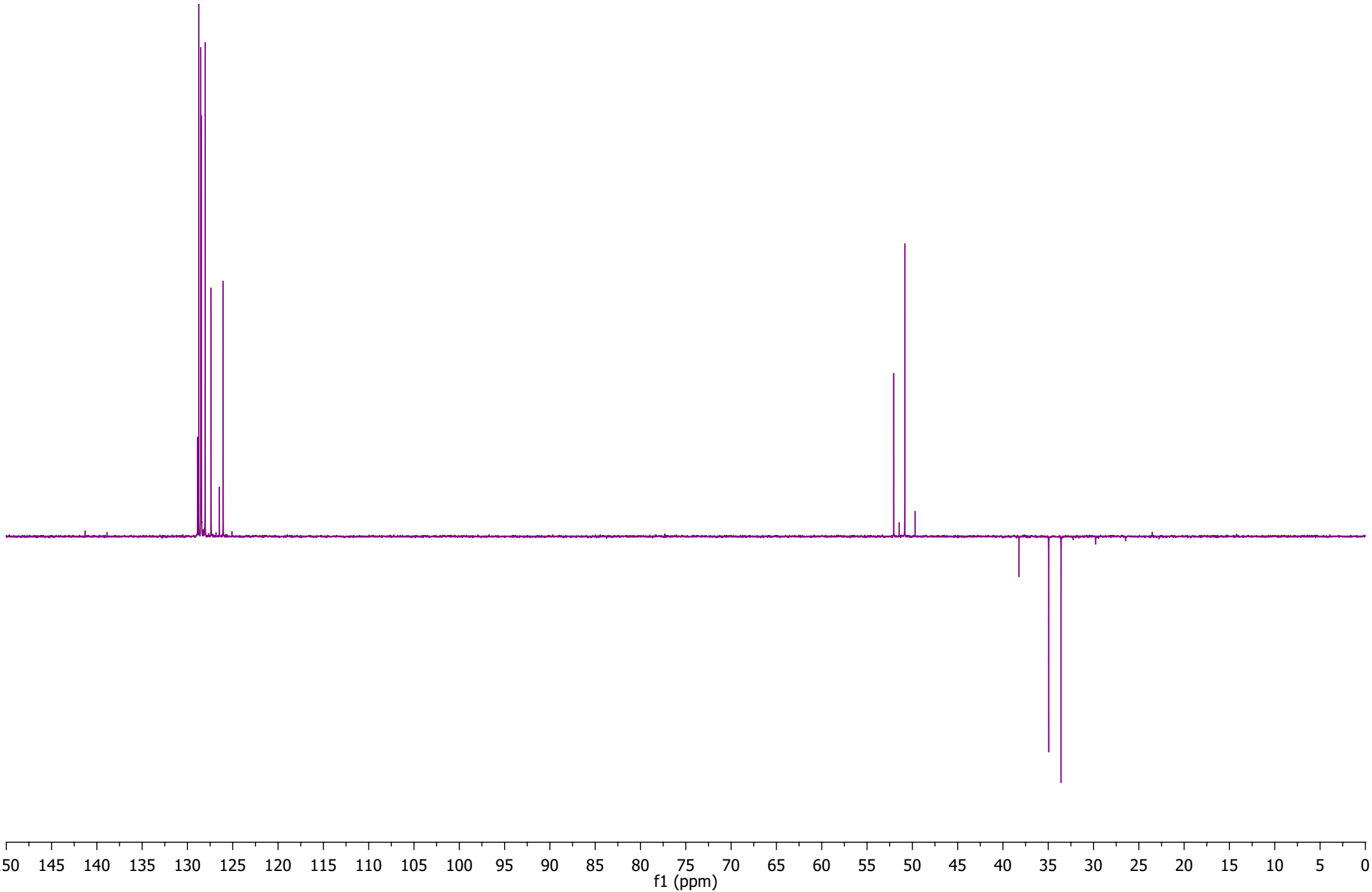


Plate 40d - HSQC [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)

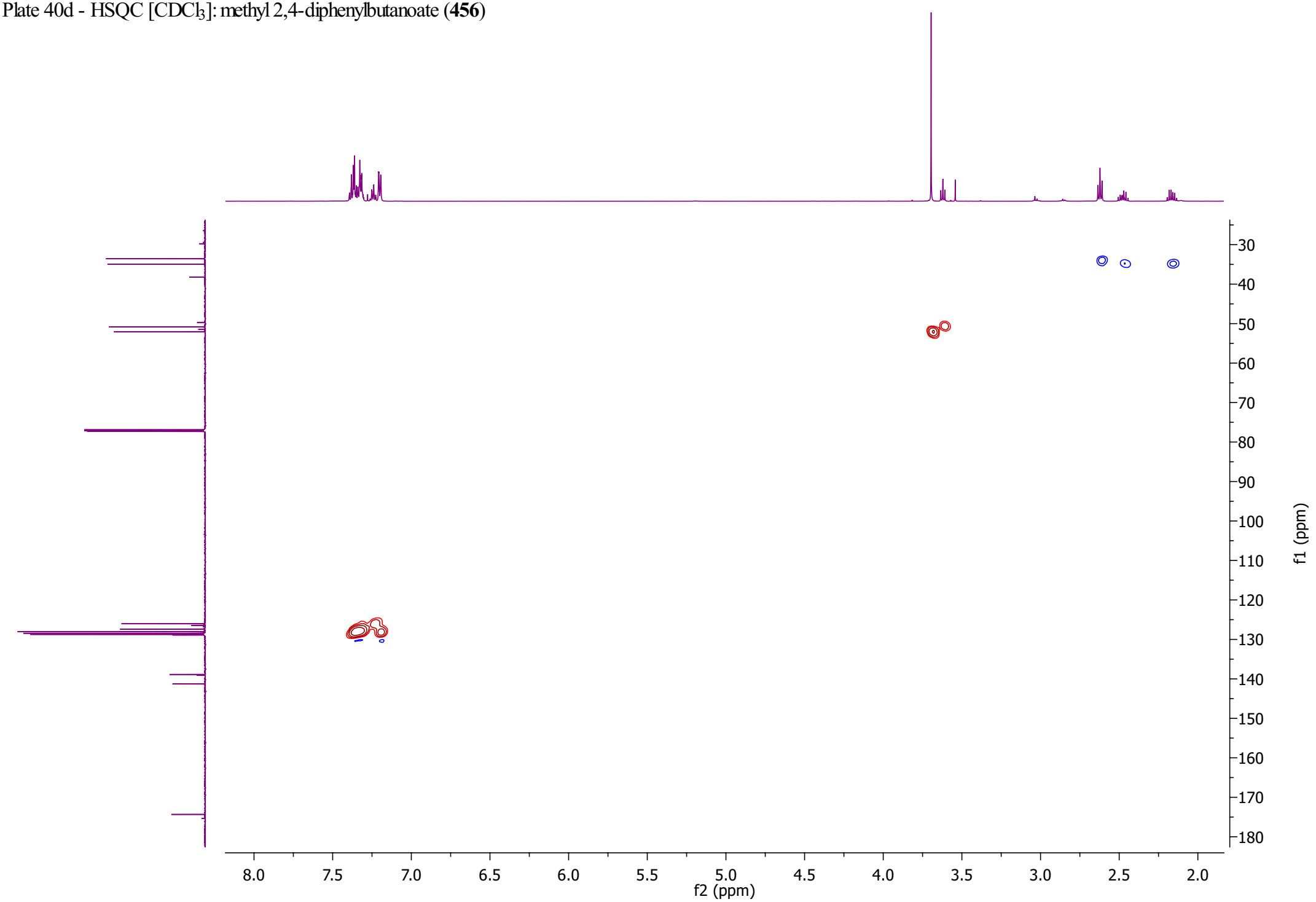


Plate 40e - HSQC (expansion) [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)

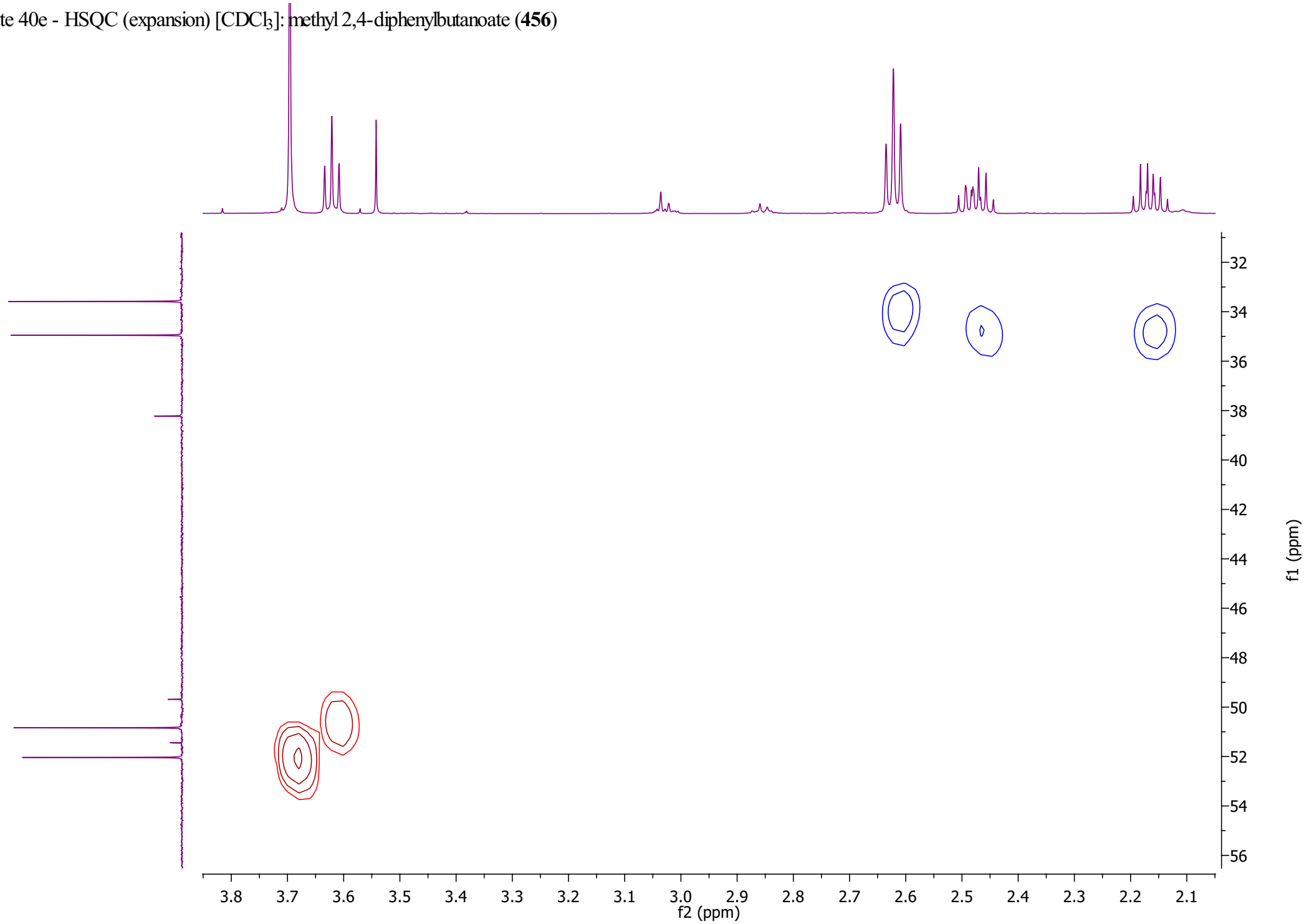


Plate 40f - HMBC [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)

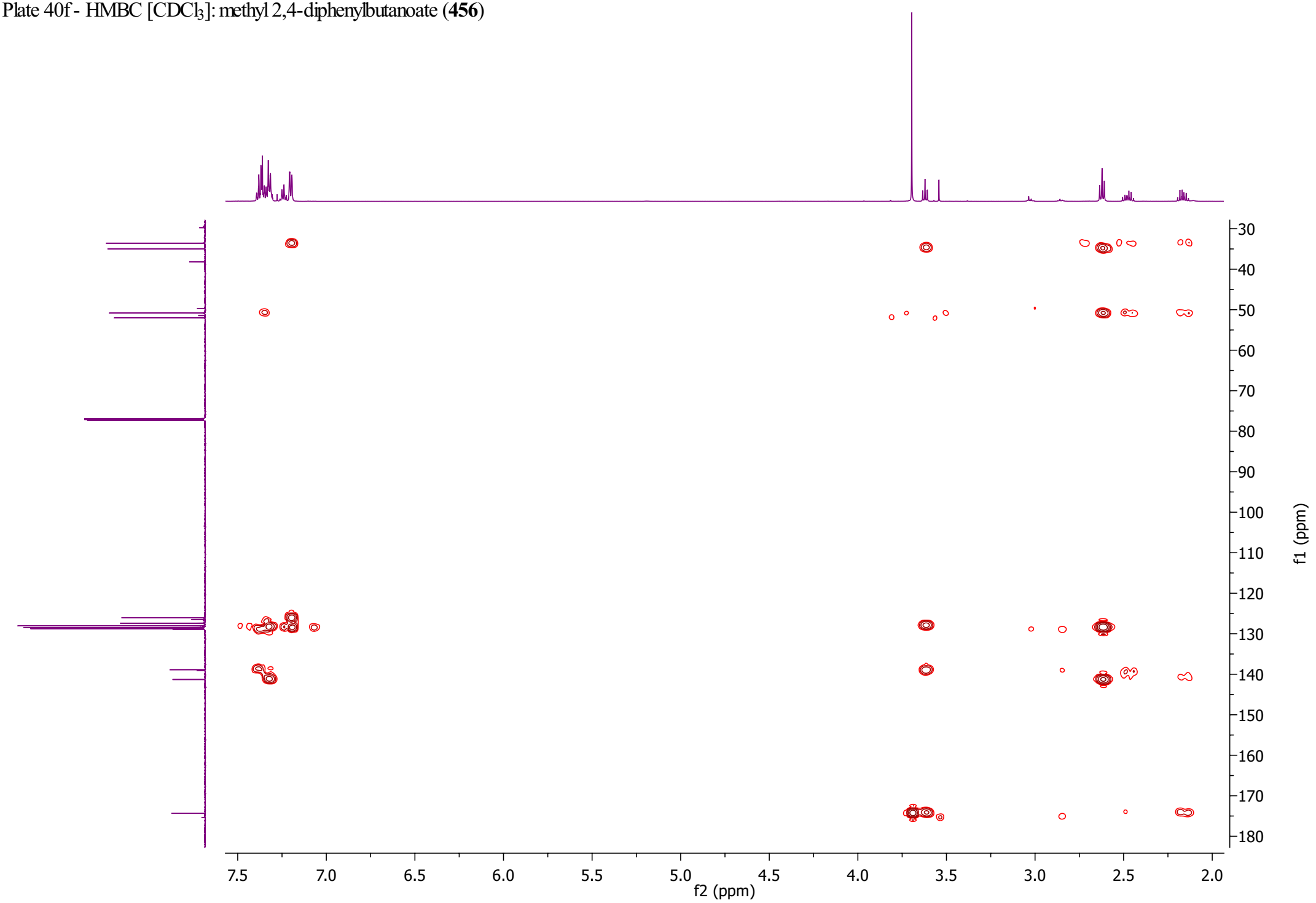
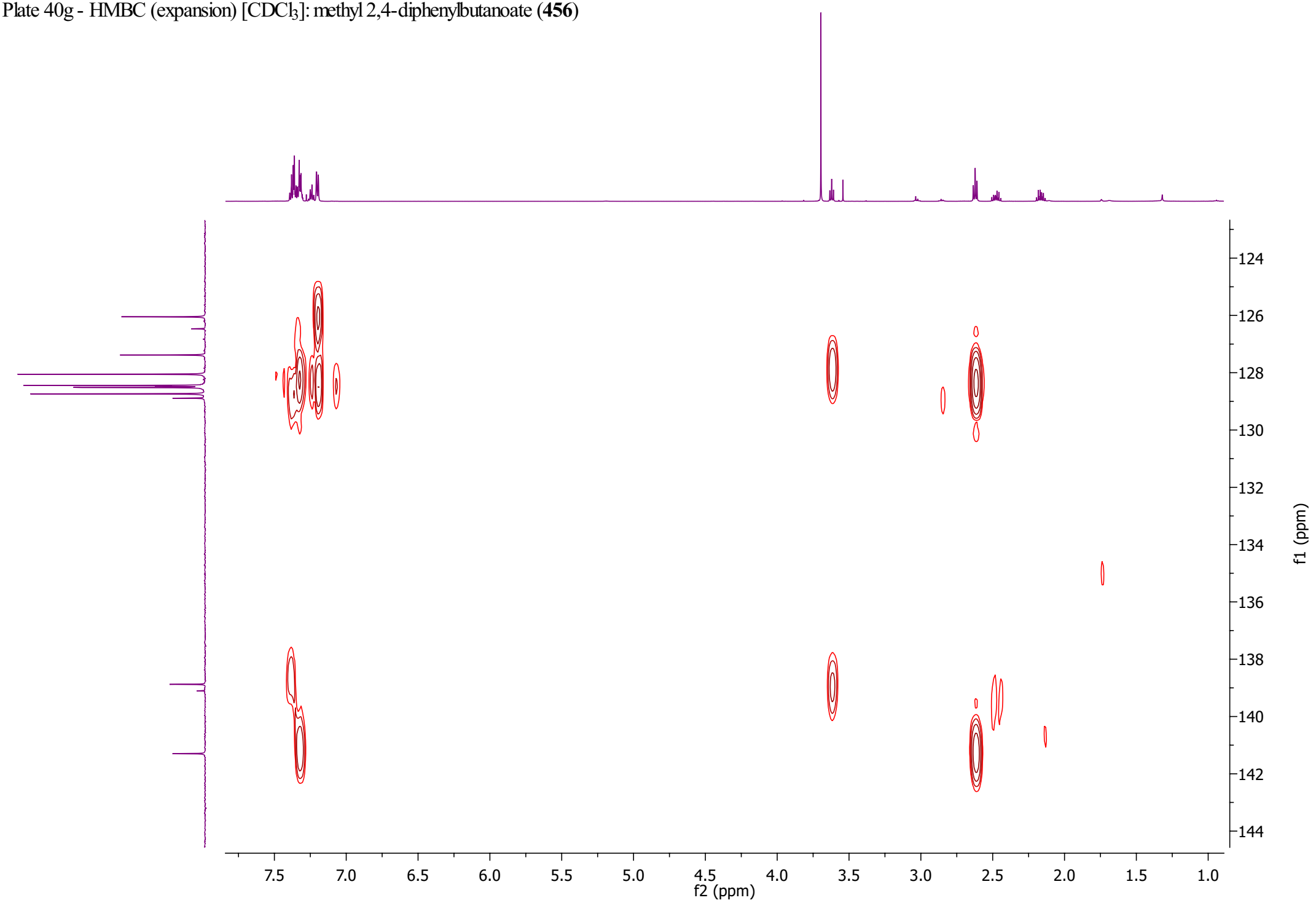


Plate 40g - HMBC (expansion) [$CDCl_3$]: methyl 2,4-diphenylbutanoate (**456**)



SUMMARY

Flavonoids are polyphenolic naturally occurring compounds with a wide variety of biological and physiological activities, like anti-platelet, anti-inflammatory, antioxidant, antiviral, antiallergenic, and antitumor properties. The potential therapeutic value of these compounds gave impetus to the development of numerous synthetic routes to not only get access to more material than possible through the isolation thereof from natural sources, but also to have access to flavonoids with substitution patterns different to those of naturally occurring analogues. Existing synthetic methodologies, however, involve tedious multistep processes, stoichiometric amounts of sometimes toxic reagents that produce large amounts of waste, harsh reaction conditions and are not always high yielding.

With this in mind, it was envisaged that isoflavonoids might be accessible *via* a catalytic process entailing hydroesterification of 2-hydroxystilbenes. If the desired regio-isomer could be obtained during this reaction, cyclization between the 2-hydroxy group and the introduced ester moiety would give rise to the heterocyclic C-ring of the corresponding isoflavonoid. Although it is known that steric factors play a prominent role in regioselective control during hydroesterification processes, little is known about the role of the electronic environment around the double bond during these reactions. To address this issue and determine the feasibility of hydroesterification methodology for the synthesis of isoflavonoids, various stilbenes with electron-withdrawing and electron-donating groups, respectively on the two aromatic rings were envisaged as substrates to be subjected to palladium catalysed hydroesterification reactions.

Since the Wittig reaction is well-known for the formation of alkenes such as the envisaged stilbenes, this approach was followed in order to prepare the required starting materials. Although the phosphonium salts, benzyltriphenylphosphonium bromide and *p*-methoxybenzyltriphenylphosphonium chloride, required as reactant in the Wittig reaction, could easily be prepared from the benzyl halide and triphenylphosphine (PPh_3) in good yields (98 % and 76 %, respectively), preparation of the *p*-methoxybenzyl bromide/chloride were more challenging and led to an overall yield for the phosphonium salt of only 45 %. Other methodologies towards the synthesis of substituted phosphonium salts, *i.e.* treatment of *p*-methoxybenzyl alcohol with PPh_3 in trifluoroacetic acid and cleavage of the benzyl methyl ether, *p*-methoxybenzyl methyl ether, with PPh_3·HBr, were therefore investigated but yields of only 10 and 38 %, respectively, were obtained.

With the best methodology for the synthesis of phosphonium salts determined, attention was subsequently turned towards the final step in the preparation of the envisaged starting materials, *i.e.* synthesis of the oxygenated stilbenes. Methoxystilbene was therefore prepared according to the traditional Wittig reaction between benzyltriphenylphosphonium bromide and *p*-anisaldehyde, with BuLi as base and the product obtained in only 33 %. In an effort to improve on the yield, the same Wittig reaction was performed utilizing an organic/aqueous (aldehyde and *aq.* NaOH) biphasic solvent system with NaOH as base, which

led to an increase in yield (54 %). Application of the same methodology to the synthesis of 2-methoxystilbene and 4-ethoxymethoxystilbene resulted in the formation of the desired products in 53 and 55 % yields, respectively. The latter compound, 4-ethoxymethoxystilbene, was subsequently subjected to acid catalysed deprotection (quantitative yield) followed by reaction with trifluoromethanesulfonyl chloride and triethylamine to obtain a stilbene, 4-trifluorosulfonyloxystilbene, protected with an electron-withdrawing substituent in 54 % yield. In an effort to improve the yields obtained for the stilbene preparation process to beyond *ca.* 50 %, a microwave assisted Perkin-type reaction between *p*-hydroxybenzaldehyde and phenylacetic acid with a piperidine-imidazole catalyst system and PEG-400 as solvent, was embarked upon and hydroxystilbene obtained in 42 % yield. Although the yield was almost the same as what was found with the Wittig method, this reaction did not require protection of the free phenolic hydroxy group or the time consuming preparation of starting materials and needed reaction times of only 10 minutes, as well as the added advantage of it being an environmentally more favourable procedure compared to the Wittig reaction.

Since $Pd(OAc)_2$ together with PPh_3 and the Lewis acid activator/co-catalyst $Al(OTf)_3$ have been reported as one of the best catalyst systems for the methoxycarbonylation of many different aliphatic alkenes, this catalyst system was utilized in the methoxycarbonylation (35 bar CO pressure, 95 °C) of model substrates like hex-1-ene, styrene and allylbenzene and obtained conversions to the corresponding methyl ester products of 70, 99 and 57 %, respectively. When *trans*-stilbene was, however subjected to the same reaction conditions and catalyst system, virtually no product was formed, so it was decided to use the model substrate, *trans*-*β*-methylstyrene, for determining the best catalyst system and reaction conditions for the methoxycarbonylation of substrates that has the double bond in conjugation with an aromatic ring. While it was found during this investigation that the reaction conditions of 35 bar and 95 °C was indeed the optimum for *trans*-*β*-methylstyrene, $PdCl_2$ proved to be more reactive than $Pd(OAc)_2$ when applied to the methoxycarbonylation of substrates with conjugated double bonds, with a 90 % conversion to the products, methyl 4-phenylbutanoate, methyl 2-methyl-3-phenylpropanoate and methyl 2-phenylbutanoate, in a 6:2:1 ratio. Due to the insolubility of *trans*-stilbene in pure methanol, a solvent study was embarked upon and MeOH:THF (1:1) was found to be the best alternative to pure methanol (conversion of 61 *vs.* 90 % in pure MeOH).

With the optimum reaction conditions determined, the influence of a higher degree of substitution around the double bond as well as position of substituents attached to the double bond were investigated, it was also decided to evaluate the effect of the electron-donating and electron-withdrawing substituents attached to the aromatic ring, on the outcome of the reaction. Subjecting *α*-methylstyrene and 2-methyl-1-phenylprop-1-ene to the reaction conditions, led to the conversion (38 and 22 %, respectively) and isolation of the expected products, methyl 3-phenylbutanoate and methyl 3-methyl-4-phenylbutanoate, indicating that the steric environment around the double bond indeed has a significant influence on the reaction. The electronic effects were studied through the methoxycarbonylation of *trans*-anethole (the p-methoxy equivalent of *trans*-*β*-methylstyrene) and 1-(4'-trifluoromethanesulfonyloxyphenyl)prop-1-ene and, while

the three expected products were obtained, it was found that an aromatic methoxy substitutent has an inhibiting effect on the reaction (21 % *vs.* 90 % conversion of *trans*-*β*-methylstyrene), while the substrate with the deactivating group showed a much improved conversion (31 %) compared to the *p*-methoxy analogue. Performing the methoxycarbonylation of *trans*-*β*-methylstyrene (in MeOH) in the presence of anisole (1:1) proved that aromatic methyl ethers indeed have a detrimental effect on the reaction, since only trace amounts of the products could be detected in this instance.

Since chiral induction during the enantioselective synthesis of isoflavonoids has been achieved through utilization of amide chiral auxiliaries, like 2-imidazolidinones, it was decided to investigate the possibility of transforming an alkene into an amide in a one-step reaction and therefore circumvent the need for a second reaction to obtain the desired amide. *Trans*-*β*-methylstyrene was therefore subjected to the methoxycarbonylation conditions developed before [$PdCl_2$/$Al(OTf)_3$/PPh_3, 35 bar CO, 95 °C], but in an inert solvent (THF) containing aniline as nucleophile and 53 % conversion to *N*,2-diphenylbutanamide and 2-methyl-*N*,3-diphenylpropanamide in a 6:1 ratio was obtained. Encouraged by the success of the first ever palladium catalysed aminocarbonylation reaction, the scope of the reaction was extended to include substrates like benzamide, *n*-butylamine and piperidine, but these nucleophiles were found to be unreactive, so more work is clearly needed to determine the conditions necessary for the successful utilization of these compounds in aminocarbonylation reactions.

Finally, attention was turned to the methoxycarbonylation of the stilbenes, therefore *trans*- and *cis*-stilbene as well as *trans*-2-methoxystilbene were subjected to the palladium catalysed reaction, but only very low conversions (trace amounts up to 4 %) were found. Since everything pointed towards the electronic effect of conjugation, which deactivates the double bond to such an extent that the reaction with the palladium catalyst is supressed, being the cause of the failure of stilbenes to undergo methoxycarbonylation, 1,3-diphenylprop-1-ene, a substrate with the double bond not in conjugation with the two aromatic rings, were therefore subjected to the reaction and a conversion of 27 % to the product, methyl 2,4-diphenylbutanoate, was obtained. This result clearly demonstrates that the failure of stilbenes to undergo hydroesterification reactions originates in the fact that the double bond is in conjugation with two aromatic rings.

SAMEVATTING

Flavonoïede verteenwoordig polifenoliese verbindings met ‘n verskeidenheid biologiese en fisiologiese aktiwiteite, onder andere anti-inflammatoriese, antivirale, antiallergeniese en antigewas-vormende eienskappe, wat algemeen in die natuur voorkom. Die potensiële terapeutiese waarde van hierdie verbindings was dan ook die dryfkrag agter die ontwikkeling van metodologie om nie net toegang te verkry tot meer material as wat vanuit die natuur geïsoleer kan word nie, maar ook om flavonoïede te kan sintetiseer met spesifieke, nie beskikbare, substitusie patrone. Bestaande metodes vir die sintese van hierdie groep verbindings maak egter gebruik van tydrowende multistap prosesse, stoichiometriese hoeveelhede soms giftige reagense wat groot hoeveelhede giftige afval genereer en ekstreme reaksie kondisies, terwyl hoë opbrengste nie altyd haalbaar is nie.

Ten einde hierdie leemtes aan te spreek, is die moontlikheid geïdentifiseer dat isoflavonoïede berei kan word deur middel van ‘n katalitiese proses gebaseer op die hidro-esterifisering van 2-hidroksistilbene. Die sukses van genoemde benadering is egter daarvan afhanklik dat die verlangde regio-isomeer, wat siklisering tussen die hidroksigroep van die stilbeen en die nuut gevormde ester funksie na ‘n seslid ring moontlik sal maak, tydens die hidro-esterifiseringsreaksie verkry moet word. Alhoewel die invloed van steriese faktore op die regioselektiewe uitkoms van hidro-esterifiseringsreaksies bekend is, is die effek van die elektroniese omgewing rondom die dubbelbinding van die alkeen steeds nie behoorlik ondersoek nie. Een van die doelstellings van hierdie ondersoek was dus die vasstelling van die invloed wat elektron-onttrekkende substituente op een van die aromatiese ringe van die stilbeen en elektron-donerende substituente geheg aan die ander ring, op die palladium gekataliseerde hidro-esterifiseringsreaksie sou hê.

Aangesien die Wittig reaksie een van die beste metodes vir die vorming van alkene verteenwoordig, is besluit om hierdie roete vir die sintese van die verlangde stilbene te volg en is die bereiding van die benodigde fosfoniumsoute as eerste stap in die ondersoek aangepak. Hoewel die eenvoudige fosfoniumsoute, bensieltrifenielfosfoniumbromied en *p*-metoksibensieltrifenielfosfoniumbromied of chloried, wat vir die ondersoek benodig is, maklik deur behandeling van die ooreenstemmende bensielbromied met trifenielfosfien (PPh_3) in 98 % en 76 % opbrengste onderskeidelik verkry kon word, was bereiding van die geöksigeneerde bensielhalied nie so eenvoudig nie en het dit die algehele opbrengs oor die twee stappe tot slegs 45 % verlaag. Verskeie ander metodes, soos behandeling van *p*-metoksi-bensielalkohol met PPh_3 in trifluoroasynsuur en splyting van die bensielmetieleter, *p*-metoksibensielmetiel-eter, met PPh_3·HBr, is vir die bereiding van die suurstofdraende fosfoniumsoute ondersoek, maar slegs 10 en 38 % opbrengste kon onderskeidelik vir hierdie twee metodes verkry word.

Met die evaluering van metodes vir die bereiding van fosfoniumsoute afgehandel is aandag vervolgens aan die bereiding van die verlangde stilbene geskenk. Metoksistilbeen is gevolglik met behulp van ‘n tradisionele Wittig-reaksie (BuLi) tussen bensieltrifenielfosfoniumbromied en *p*-anisaldehied berei, en ‘n

lae opbrengs van slegs 33 % is verkry. Ten einde die opbrengs uit die reaksie te verbeter, is dieselfde reaksie in ‘n organies-waterige (aldehied en *aq.* NaOH) bifasiese sisteem met natriumhidroksied as basis herhaal wat daartoe gelei het dat die produk in 54 % opbrengs verkry kon word. Toepassing van dieselfde metode op die bereiding van 2-metoksi- en 4-etoksimetoksistilbeen het daartoe gelei dat die onderskeie produkte in 53 en 55 % opbrengs verkry kon word. Laasgenoemde verbinding (4-etoksimetoksistilbeen) is dan ook in 54 % opbrengs na die ooreenstemmende 4-trifluorometaansulfonieloksistilbeen omgeskakel deur middel van suur gekataliseerde hidroliese (kwantitatiewe opbrengs) gevolg deur reaksie met trifluorometaansulfonielchloried en triëtielamien. Aangesien opbrengste van hoër as *ca.* 50 % vir die vorming van stilbene nie verkry kon word nie, is die toepassing van ‘n mikrogolf gebaseerde Perkin-tipe-reaksie vir die bereiding van hidroksistilbene vervolgens ondersoek. ‘n Mengsel van *p*-hidroksi-bensaldehied en fenielasynsuur in PEG-400 is dus in die teenwoordigheid van ‘n piperidien-imidasool katalisator vir 10 minute aan mikrogolf bestraling blootgestel wat toe daartoe gelei het dat 4-hidroksistilbeen in 42 % opbrengs verkry kon word. Hoewel die opbrengs nie dramaties beter was as wat met die Wittig-reaksie gevind is nie, moet dit in aanmerking geneem word dat beskerming van hidroksigroepe tydens toepassing van hierdie proses nie nodig is nie, dat die tydrowende bereiding van reagense omseil word en dat die reaksietyd slegs 10 minute beloop sowel as die gebruik van omgewingsvriendeliker reaksie kondisies.

Aangesien $Pd(OAc)_2$, tesame met trifenielfosfien (PPh_3) en die Lewissuur, $Al(OTf)_3$, aktiveerder/ko-katalisator, algemeen in die literatuur vir die metoksikarbonilering van verskillende alifatiese alkene bedryf is, is hierdie sisteem vir die metoksikarbonilering (35 bar CO druk en 95 °C) van ‘n aantal modelsubstrate soos heks-1-een, stireen en allielbenseen benut en omskakelings van 70, 99 en 57 %, na die ooreenstemmende metielester produkte, is verkry. Benutting van hierdie katalisatorsisteem en reaksiekondisies tydens die metoksikarbonilering van *trans*-stilbeen het egter tot geen noemenswaardige produkvorming gelei nie, daarom is besluit om optimisering van die katalisatorsisteem en reaksiekondisies vir substrate met dubbelbindings in konjugasie met ‘n aromatiese ring met behulp van *trans*-*β*-metielstireen, as modelverbinding, uit te voer. Hoewel tydens die ondersoek gevind is dat 95 °C en 35 bar inderdaad die optimale reaksiekondisies vir die metoksikarbonilering van *trans*-*β*-metielstireen verteenwoordig, is egter gevind dat $PdCl_2$ ‘n meer reaktiewe katalisatorsisteem as $Pd(OAc)_2$ tot gevolg het en het die toepassing daarvan op *trans*-*β*-metielstireen tot ‘n 90 % omskakeling na die produkte, metiel-4-fenielbutanoaat, metiel-3-feniel-2-metielpropanoaat en metiel-2-fenielbutanoaat, in ‘n 6:2:1 verhouding gelei. Weens die on-oplosbaarheid van *trans*-stilbeen in suiwer metanol, is ‘n ondersoek na die beste oplosmiddelsisteem vir nie-polêre verbindings ook onderneem en is vasgestel dat ‘n MeOH:THF (1:1) mengsel die beste alternatiewe oplosmiddel vir hierdie tipe substraat verteenwoordig (omskakeling 61 *vs.* 90 % vir suiwer MeOH).

Met die beste katalissisteem en reaksiekondisies vir die metoksikarbonilering van gekonjugeerde alkeen substrate bepaal, is aandag vervolgens aan die effek van meer substituente geheg aan die dubbelbindingkoolstowwe en verskillende posisies vir die substituente gegee, terwyl die invloed van

elektron-onttrekkende en elektron-skenkende groepe gebind aan die aromatiese ringe ook bestudeer is. Ten einde die invloed van groepe gebind aan die dubbelbinding te bepaal, is *α*-metielstireen en 1-feniel-2-metielprop-1-een aan die beste metoksikarbonileringskondisies blootgestel en ‘n omskakeling van 38 en 22 % na die verwagte produkte, metiel-3-fenielbutanoaat en metiel-4-feniel-3-metielbutanoaat, verkry. Bogenoemde toon aan dat die steriese omgewing rondom die dubbelbinding inderdaad ‘n groot effek op die reaktiwiteit van die dubbelbinding uitoefen. Die elektroniese effek van groepe gebind aan die aromatiese ringe is met behulp van ‘n vergelyking van die reaktiwiteit van *trans*-anetool (die 4-metoksi-ekwivalent van *β*-metielstireen) met die van 1-(4'-trifluorometaansulfonieloksifeniel)prop-1-een, ondersoek en is ‘n omsetting van slegs 21 % na die verwagte produkte uit die anetoolreaksie gevind (vergelyking met 90 % vir *trans*-*β*-metielstireen), terwyl die substraat met die elektron-onttrekkende groep ‘n omsetting van 32 % gelewer het. Dit was dus duidelik dat ‘n aromatiese metoksigroep die metoksikarbonileringsreaksie nadelig beïnvloed. Ten einde hierdie waarneming te bevestig, is die metoksikarbonilering van *trans*-*β*-metielstireen (in metanol) in die teenwoordigheid van anisool (1:1) herhaal en is slegs spoorhoeveelhede van die produkte gevind.

Aangesien chirale induksie tydens die enantioselektiewe sintese van isoflavonoïede deur middel van die benutting van amied chiralehulpmiddels soos 2-imidasolidinone, bereik is, is besluit om die moontlikheid dat alkene deur middel van ‘n hidro-esterifiseringstipe reaksie direk in n amied omgeskep kan word, te ondersoek. *Trans*-*β*-metielstireen is gevolglik aan metoksikarbonilering onderwerp [$PdCl_2$/$Al(OTf)_3$/PPh_3, 35 bar CO, 95 °C], maar in ‘n inerte oplosmiddel (THF) en die teenwoordigheid van anilien as model nukleofiel (alkeen:anilien, 1:1) en die verwagte produkte, *N*,2-difenielbutaanamied en *N*,2-difeniel-2-metielpropaanamied, in 51 % omsetting en ‘n 6:1 verhouding gevind. Uitbreiding van die eerste palladium gekataliseerde aminokarbonilering deur ander nukleofiele soos bensamied, *n*-butielamien en piperidien in te sluit, was egter onsuksesvol, daardeur blyk dit dat heelwat navorsing nog gedoen moet word ten einde die algemene toepaslikheid van hierdie nuwe reaksie moontlik te maak.

Met die bostaande kennis beskikbaar, is aandag weereens na die metoksikarbonilering van stilbene gedraai en is *trans*- en *cis*-stilbeen sowel as *trans*-2-metoksistilbeen aan die palladium gekataliseerde reaksie onderwerp. Aangesien slegs spoorhoeveelhede van die verlangde produkte verkry kon word, het alle data dus daarop gedui dat konjugasie tussen die dubbelbinding en die twee aromatiese ringe die dubbelbinding sodanig deaktiveer dat die reaksie met die palladium katalisator bykans ten volle onderdruk word. Ten einde vas te stel of hierdie toestand wel die oorsaak van die mislukte metoksikarbonilering van stilbene was, is ‘n substraat, 1,3-difenielprop-1-een, waarin ‘n addisionele koolstofatoom tussen een fenielring en die dubbelbinding ingevoeg is, berei en aan metoksikarbonilering onderwerp. Die feit dat die produk, metiel-2,4-difenielbutanoaat, in 27 % omsetting verkry kon word, het dan ook eenduidig bewys dat die oorsaak van die onreaktiwiteit van stilbene in die konjugasie van die dubbelbinding met die twee aromatiese ringe geleë is.