TOWARDS THE TOTAL SYNTHESIS OF A NOVEL DIARYLHEPTANOID

By

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"In the name of God, most Gracious, most Compassionate"

This thesis is dedicated to my loving parents

"Study nature, Love nature, stay close to nature. It will never fail you"

- Frank Lloyd Wright-

ABSTRACT

Diarylheptanoids are a family of plant metabolites with a characteristic structure of two hydroxylated aromatic rings attached by a linear seven-carbon chain. Diarylheptanoids have mostly been isolated from plants belonging to the Zingiberaceae family. The South African medicinal plant *Siphonochilus aethiopicus*, more commonly known as 'wild ginger', also belongs to the Zingiberaceae family. One of the compounds isolated from this plant it a novel diarylheptanoid. In this study, the synthesis of this novel diarylheptanoid will be investigated.

The targeted diarylheptanoid has two substituted phenyl rings attached by a seven-carbon aliphatic chain with two sterogenic centers and a carbon-carbon double bond. Osmium-catalysed asymmetric dihydroxylation was used to generate the two stereogenic centres. The Horner Wadsworth-Emmons (HWE) reaction was investigated, in order to generate the *trans*-double bond on the seven carbon aliphatic chain. HWE reaction is a *trans*-selective reaction leading to the formation of only the desired isomer.

The synthetic strategy used for the synthesis of the targeted diarylheptanoid is the C_2-moiety + C_5-moiety strategy. The C_2-moiety is the phosphonate ester and the C_5-moiety is the aldehyde for the HWE reaction. In this investigation we were able to successfully synthesis the required C_2-moiety and the C_5-moiety. Both the precursors were synthesised from commercially available starting materials, utilising functional group transformation reactions. However, modifications to the C_5-moiety were made due to its instability under the HWE reaction conditions. When the C_5-moiety was an aldehyde, decomposition was seen under HWE reaction conditions. Thus the C_5-moiety was converted to the corresponding lactol and then subjected to the HWE reaction. Nevertheless, this reaction was not successful, thus we were not able to couple the two precursors to form the desired seven-carbon aliphatic chain.

Even though the targeted diarylheptanoid was not successfully synthesised, the synthetic route developed in this investigation is not only viable to the target compound but is also versatile enough to allow the synthesis of its analogues.

Declaration

I hereby certify that this work is a result of my own investigation, which has not already been accepted in substance for any other degree and is not being in candidature for any other degree.

Signed:_____(Shifaza Mohamed) Date:_____

I hereby certify that this statement is correct

Signed:_____ Professor F.R. van Heerden Date:_____
(Supervisor)

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Plagiarism

I *Shifaza Mohamed* declare that:

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List of Abbreviations

Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
H^+	acid
aq.	aqueous
MeCN	acetonitrile
BCl_3	Boron trichloride
Bn	benzyl
BnCl	benzyl chloride
BuLi	butyllithium
br	broadened
BMS	boron methylsulfide
cat.	catalytic
conc.	concentrated
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DDQ	dichloro dicyano benzoquinone
DMP	2,2-dimethoxypropane
DMF	*N*,*N*-dimethylformaide
DMSO	dimethyl sulfoxide
d	doublet (spectral)
dd	doublet of doublet (spectral)
dt	doublet of triplet (spectral)
Et_2O	diethyl ether
DMSO	dimethyl sulfoxide
EtOH	ethanol
OEt	ethoxy
EtOAc	ethyl acetate
h	hour (s)
hz	hertz
IR	Infrared

MeI	Iodomethane
^{i}Pr	Isopropyl
J	coupling constant
LDA	lithium diisopropylamine
MS	mass spectroscopy
m/z	mass to charge ratio
Mp	melting point
MeOH	methanol
OMe	methoxy
min	minute (s)
mmol	millimole
m	multiplet (spectral)
NMR	nuclear magnetic resonance spectroscopy
PCC	pyridinium chlorochromate
Ph	Phenyl
p	*para*
P-TsOH	*para*-toluenesulfonic acid
ppm	parts per million
py	pyridine
KO^{t}Bu	potassium *tert*-butoxide
q	quartet (spectral)
qr	quintet
s	singlet (spectral)
t-BuOH	*tert*-Butanol
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TFA	Triflouroacetic acid
Et_3N	triethylamine
t	triplet (spectral)
vacuo	reduced pressure

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1 INTRODUCTION

1.1 Role of Natural Products in Drug Discovery

1.1.1 History

The term 'natural product' refers to secondary metabolites that are derived from natural sources such as plants, animals and microorganisms[1]. Secondary metabolites are compounds unique to a specific organism and are often produced by living organisms for the purpose of defence, communication and predation[2]. The role of natural products as medicines has been enormous throughout human evolution. It has been documented that our earliest ancestors chewed on certain herbs to relieve pain and wrapped leaves around wounds to facilitate healing[3].

Even though medicinal plants were used widely in Orient and Occident medicinal systems, their active components remained unknown until the eighteenth and nineteenth centuries[3]. The advent of modern chemistry opened a new era for natural products and their use in the pharmaceutical industry. Morphine from opium was the first naturally derived medicine and the first to be commercialised in 1826[3]. Natural product discovery efforts kick started after the large scale production of penicillin, isolated from the mould *Penicillium notatum* during World War II[1]. Some well-known compounds that were isolated from natural products include salicin from *Salix alba*, quinine from *Cinchona ledgeriana*, caffeine from *Coffea arabica*, nicotine from *Nicotiana tabacum* and cocaine from *Erythroxylum coca*[1, 3, 4].

1.1.2 Decline of natural product research in the pharmaceutical industry

Natural product research in industry decreased drastically in the early 1990s and the early 2000s[1]. The main reasons for this steep decline were difficulties involved in extraction and

synthesis of natural products on industrial scale at an acceptable cost[4]. Also, the advent of combinatorial chemistry and high-throughput screening to generate and identify new drug candidates made natural products less attractive[3, 4]. However, combinatorial chemistry did not give the anticipated outcome in terms of new drug candidates. In 2007, only 17 new drug candidates were approved compared to 1998, when a total of 53 drugs were approved[3]. Despite the decrease in natural product research, drugs derived from natural products still bring in a significant revenue for many of the major pharmaceutical companies[1]. For example, drugs such as Lipitor® and Pravachol®, which are natural product-inspired drugs, continue to produce multi-billion dollar revenue[1].

1.1.3 Natural products as sources of new drugs

Natural product compounds hold great promises for finding better and new drugs since they are a source of novel leads and an inspiration for the synthesis of non-natural molecules with improved pharmacological and pharmaceutical properties. Natural products from plants are highly potent and selective as a result of evolutionary selection[1]. Thus they are ideal lead compounds for the development of therapeutic agents for oncology and infectious diseases. Approximately 25% of all prescription medicines and 60% of anti-cancer drugs on clinical trials at the end of 2005 were of plant oringin[2, 5, 6].

Drugs based on natural products include compounds isolated from plants, microbial fermentation, marine, synthetic and semi-synthetic compounds based on natural products. Amongst the natural product sources, plants and microbials have been the major sources of lead compounds[4]. Even so, it has been reported that the percentage of plants and microorganisms that have been screened for bioactivity, is relatively small[4]. Thus, more extensive screening of these rich natural product resources could provide far more novel chemicals for drug discovery.

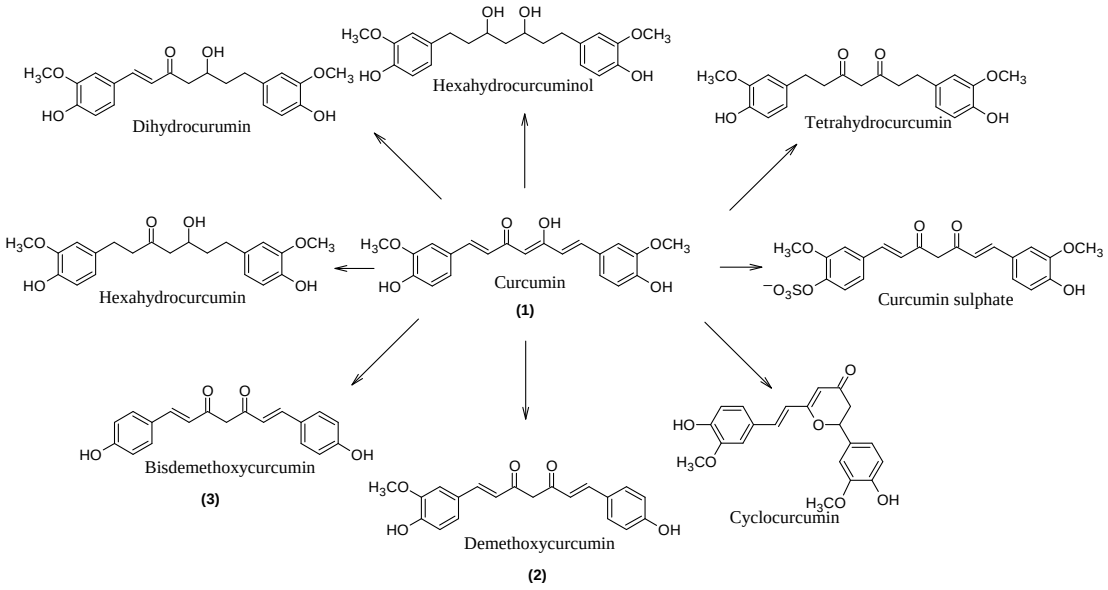
1.2 Zingiberaceae

Plant from the Zingiberaceae (ginger family) have been used for centuries as foods, spices, dyes and in traditional oriental medicine[7, 8]. Plants belonging to this family include

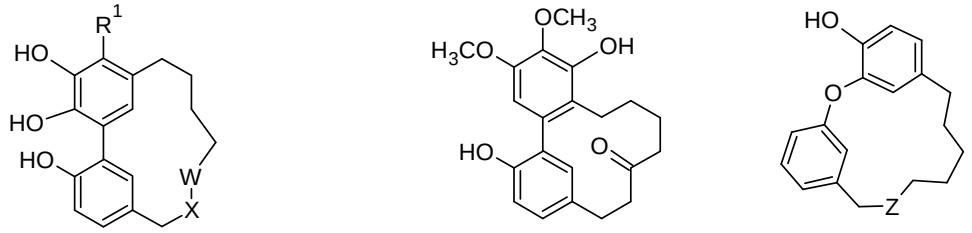
Zingiber officinale (ginger), *Curcuma longa* (curcuma) and *Alpinia blepharocalyx*[7]. Chemical investigations of plants belonging to this family have led to the isolation of a large number of biologically active compounds. Two major groups of biologically active compounds that have been isolated from the Zingiberaceae include gingerol-related compounds and diarylheptanoids[7, 9]. Diarylheptanoids have mainly been isolated from *Curcuma* and *Zingiber* species. Amongst the diarylheptanoids that have been isolated from these plants, curcumin **(1)** is one of the most well-known compounds.

1.2.1 *Curcuma* species

Curcumin **(1)**, the major orange pigment found in turmeric (*Curcuma longa*) rhizomes was the first diarylheptanoid isolated in 1815 and its structure determined in 1910[10]. Ever since, varieties of diarylheptanoids have been isolated from different species of *Curcuma*. Since the discovery of curcumin **(1)**, various natural analogues and metabolites of curcumin have been isolated from turmeric[11]. Curcumin **(1)**, demethoxycurcumin **(2)** and bisdemethoxycurcumin **(3)** are the three most important analogues from turmeric and are collectively known as curcuminoids[11]. Scheme 1.1 shows some of the diarylheptanoids that were isolated from *Curcuma longa.* Furthermore, Ishidha and co-workers[12] isolated and characterised cyclic diarylheptanoids **(4-8)** from the *Curcuma longa* and Suksamrarn *et al.*[13] isolated three new diarylheptanoids and nine known diarylheptanoids from the rhizomes of *Curcuma comosa*.



Scheme 1.1**:** Natural analogues of curcumin **(1)**[*]



(4) R^1= OH, W= C=O, X=H

(5) R^1= OCH_3, W= H, X= C=O

(6)

(7) Z= C-OH

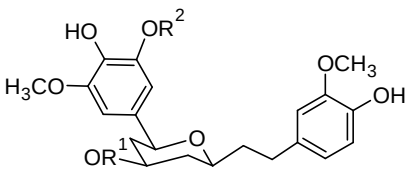
(8) Z= C=O

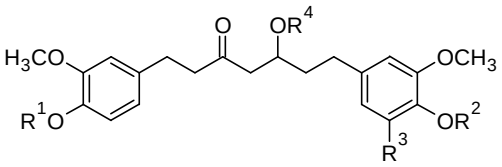
Figure 1.1: Cyclic diarylheptanoids isolated from *Curcuma longa*

1.2.2 *Zingiber officinale*

Numerous chemical investigations of *Zingiber officinale*, have led to the isolation of a wide variety of diarylheptanoids. From the rhizomes of *Zingiber officinale*, Kikuzaki *et al.* isolated five new diarylheptanoids[14] **(9-11)**. In addition to this, Liu and co-workers isolated several different diarylheptanoids, both linear and cyclic, from the rhizomes of this plant[8, 15] **(12-14)**.

[*] The keto moiety of curcumin and its analogues will exist in equilibrium with the enol form.





(9) R_1= Ac, R_2 = H

(10) R_1= R_2 = H

(11) R_1= H, R_2 = CH_3

(12) R^1= R^2= R^3= R^4= H

(13) R^1= R^2= R^4= H, R^3= OCH_3

(14) R^1= R^2= R^4= Ac, R^3= H,

Figure 1.2: Diarylheptanoids from *Zingiber officanale*

1.2.3 *Siphonochilus aethiopicus*

The South-African medicinal plant *Siphonochilus aethiopicus* B.L., more commonly known as wild ginger, is a forest floor plant with aromatic rhizomes. The generic name *Siphonochilus* is derived from the Greek *siphon*, meaning tube, and *chilus*, meaning lip in reference to the shape of the flower. The specific name *aethiopicus* means from southern Africa. African wild ginger is deciduous with hairless leaves, a cone-shaped rhizome, pink flowers and annually sprouts from underground stems in spring.

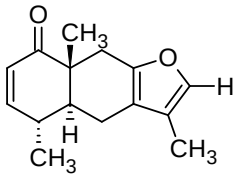
Figure 1.3: African wild ginger[†]

African Wild ginger has a long history of use in African traditional medicine and thus has been over harvested from the forests leading to its extinction[16]. The aromatic rhizomes of

[†] Permission for publishing this picture was obtained from the website www.pacificbulbsociety.org

this plant are used to relieve colds, coughs, influenza, menstrual pain and several other illnesses[16-18]. Furthermore, the rhizomes of the South African wild ginger are known to exhibit natural anti-inflammatory activities[16].

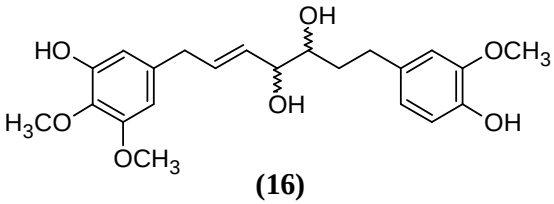
Even though the African wild ginger is famous for its medicinal properties, only a limited number of studies have been done on this plant. So far no comprehensive taxonomical studies have been done on the genus *Siphonochilus* and thus exact distribution of this plant in Africa is poorly known. From the studies conducted by Van Wyk[16]and Holzapfel *et al.*[18], it has been found that the major chemical constituents of this plant are sesquiterpenoids of the furanoid type. The essential oil of this plant contains a high concentration of a single compound referred to as *Siphonochilus sesquiterpenoid* or siphonochilone[16] **(15)**. In addition to this diarylheptanoids **(16)** has also been isolated from the African wild ginger[19].



(15)

1.3 Aim of this Investigation

The aim of this study is the total synthesis of a novel diarylheptanoid isolated from the South African medicinal plant *Siphinochilus aethiopicus* (Wild ginger)[19]. The absolute stereochemistry of the isolated diarylheptanoid **16** has not been established, thus we aim at synthesising the isomer **17** with known relative and absolute stereochemistry. Furthermore, the developed synthetic method should be versatile, so that it could allow for the synthesis of the other stereoisomers of this compound.



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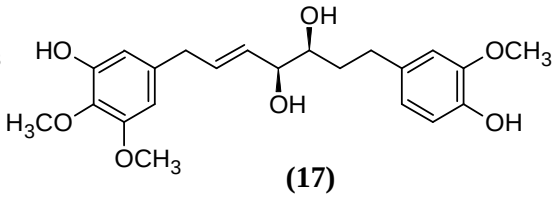

(17)

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2 Diarylheptanoids: An Overview

2.1 Introduction

Diarylheptanoids are a family of plant secondary metabolites which have shown to exhibit a variety of biological activities. Diarylheptanoids have mainly been isolated from plants belonging to the Zingiberaceae family, as outlined in Chapter 1. The aim of this chapter is to give a brief introduction to the diarylheptanoids.

2.2 Classification

Diarylheptanoids are a family of plant metabolites based on 1,7-diphenylheptane with a characteristic structure of two hydroxylated aromatic rings attached by a linear seven carbon chain[1,2]. Their structures are classified into linear **(I)** and cyclic types. The latter is further subdivided into three main groups, *meta,meta*-biarylmacrocycles **(II)** and *meta, para*-cylclophane **(III)**[2] and tetrahydropyrans **(IV)**. Linear diarylheptanoids are the biogenetic precursors of the macrocyclic diarylheptanoids and can be formed by phenolic oxidative coupling of the corresponding linear one[1]. Such coupling may lead *via* C-C coupling or C-O coupling to form type **(II)** or type **(III)** diarylheptanoids, respectively[3]. Linear diarylheptanoids are found in various monocotyledon and dicotyledon plant species and more than 70 different linear diarylheptanoids have been isolated from various plants[4]. The most well-known linear diarylheptanoid is curcumin **(1)**, which was isolated from turmeric (*Curcuma longa*). Turmeric belongs to Zingiberaceae family of plants which are a very rich source of diarylheptanoids. Cyclic diarylheptanoids have been isolated from various plant species. In 1995, Kikuzaki and Nakatani isolated five cyclic diarylheptanoids from the rhizomes of *Zingiber officinale*[5]. In 1976, Nagumo *et al.*[6] isolated acerogenin **(23)**, which is a *m,p*-cylcophane and since then several dozens of structurally-related

compounds with an endocyclic biaryl ether bond have been isolated and identified from various plants of the Zingiberaceae family.

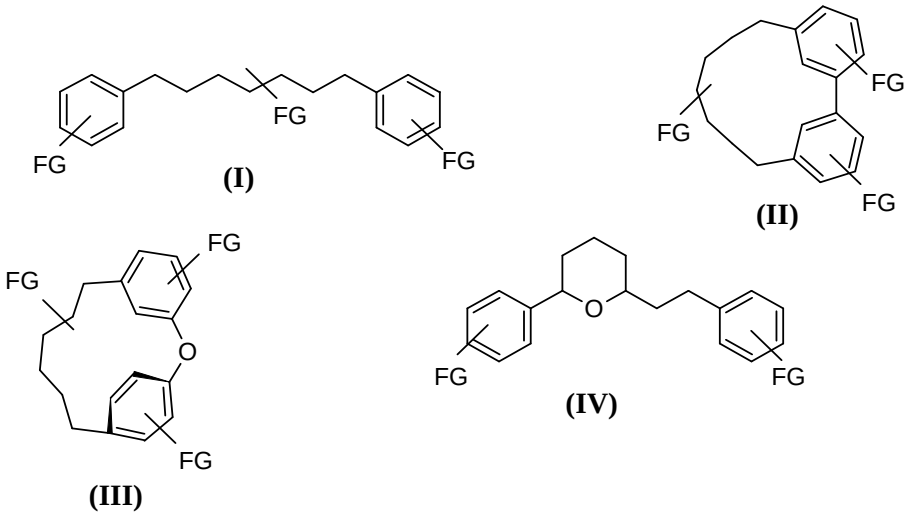


Figure 2.1. Types of diarylheptanoids[7*]

2.3 Phytochemistry of Diarylheptanoids

Diarylheptanoids have mainly been isolated from *Curcuma*, *Zingiber*, *Alnus*, *Alpinia* and *Acer* species belonging to the family of gingers (Zingiberaceae), and from *Centrolobium*[4]. Diarylheptanoids isolated from *Curcumin* species and *Zingiber officinale* have been discussed in Chapter 1. In this section the focus will be given to diarylheptanoids that have been isolated from *Alpinia*, *Acer* and *Alnus* species.

2.3.1 *Alpinia* species

A variety of diarylheptanoids have also been isolated from the seeds of *Alpinia blepharocalyx* (Zingiberaceae). Both linear and cyclic diarylheptanoids have been isolated from the *A. blepharocalyx*[4]. Figure 2.2 shows some of the diarylheptanoids that were isolated from *A. blepharocalyx.* Dong *et al.*[8] isolated a variety of diarylheptanoids from the seeds of *A. blepharocalyx* which showed antiplatelet activity **(18 - 23)**. In addition to this,

* FG indicates functional groups

a new family of diarylheptanoids, calyxins **(24 - 25)**, was also isolated from the seeds of *A. blepharocalyx*[9]. Calyxins **(24 - 25)** are cyclic diarylheptanoids with a 2,4,6-*cis*-trisubstituted tetrahydropyran ring in their structure. Blephacocalyxins **(24)** was the first examples of a dimeric diarylheptanoid wherein the two diarylheptanoids are directly connected by a C-C bond[9].

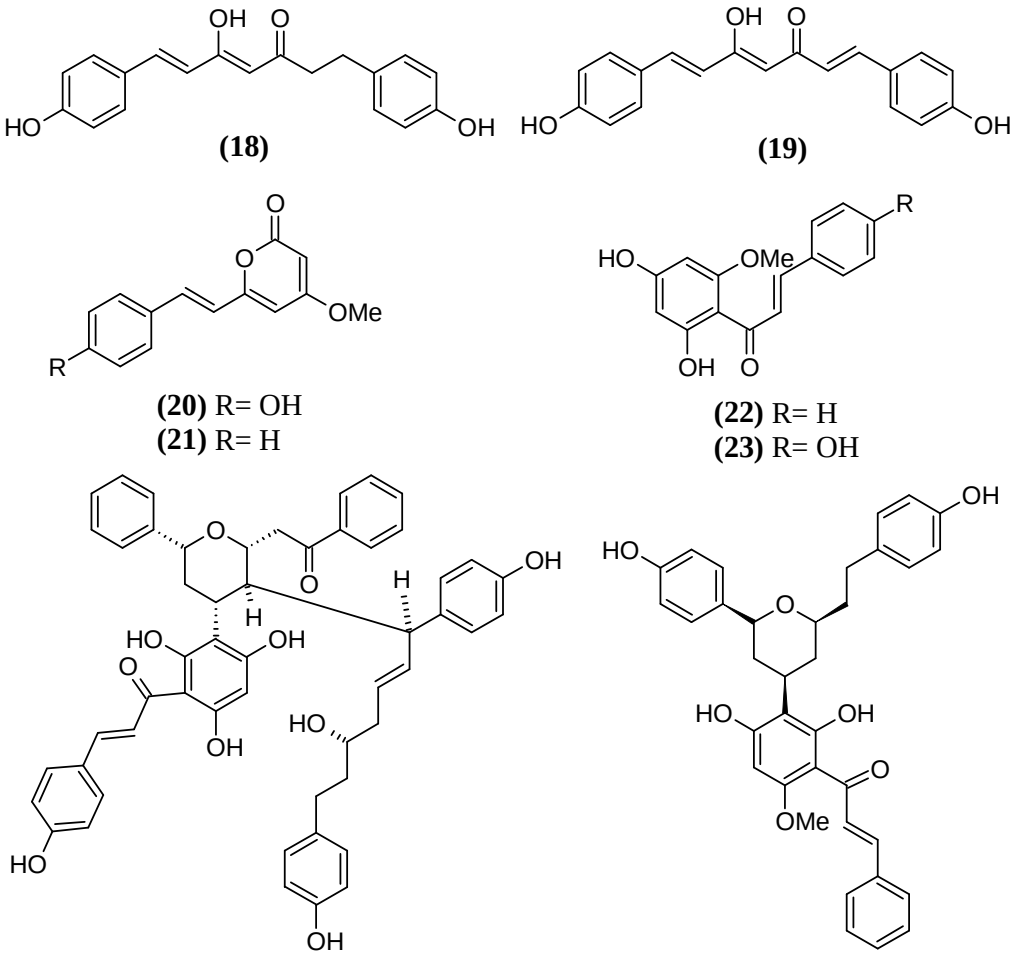
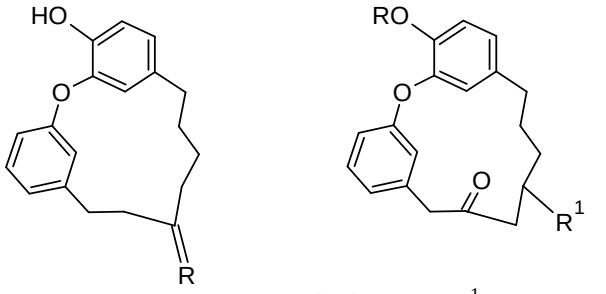


Figure 2.2. Diarylheptanoids isolated from *Alpinia blepharocalyx*

2.3.2 *Acer nikoense*

Acer nikoense (Zingiberaceae) has proven to be a rich source of diarylheptanoids, over the years a variety of diarylheptanoids have been isolated from this plant. In 1996, Nagumo *et*

al.[6] isolated acerogenin variants **(26 - 27)** from the bark of *A. nikoense*. Furthermore, Akazawa *et al.*[10] isolated new cyclic diarylheptanoids named acerosides **(28)** and aceroketoside **(29)** from the bark of *A. nikoense*.



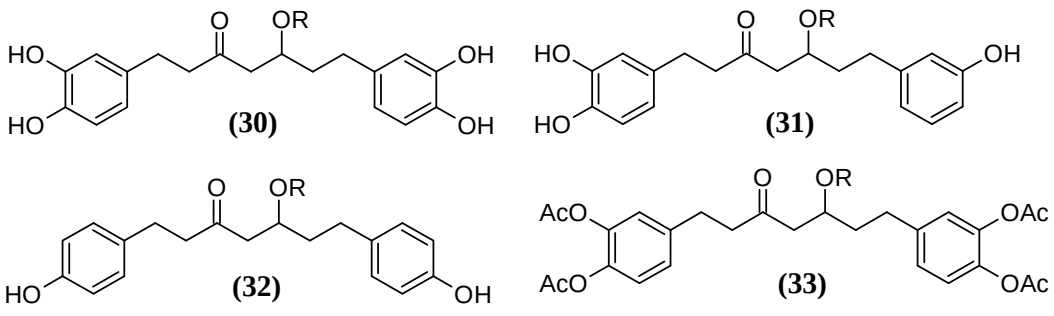
(26) R= OH
(27) R= O

(28) R= H, R^1= OH
(29) R= Glucose, R^1= H

Figure 2.3. Diarylheptanoids from *Acer nikoense*

2.3.3 *Alnus* species

Alnus species have been found to be a rich source of diarylheptanoids. Amongst this species, *A. japonica* is one of the richest sources of diarylheptanoids. Kuroyanagi *et al.*[11] and Choi *et al.*[12] isolated a variety of diarylheptanoids from the bark of *A. japonica* **(27-30)**. *A. formosana* has also been found to contain diarylheptanoids including curcumin[13].



R= β-D-Glucosyl or β-D-Xyloside or H

Figure 2.4. Diarylheptanoids isolated form *Alnus japonica*

2.4 Biological Activities of Diarylheptanoids Isolated from Various Plants

Plants species known to contain diarylheptanoids are widely used in traditional medicine. Some examples of such plants include; *Curcuma longa* rhizomes which are widely used in traditional Asian medicine for the treatment of various diseases including hepatic disorder and rheumatism[14]; *Alpinia blepharocalyx*, seeds of which are used for the treatment of stomach disorders in Chinese medicine[9]; bark of *Alnus japonica* has been used for fever, hemorrhage, diarrhoea, gastroenteric disorder and cancer in oriental traditional medicine[12].

Diarylheptanoids have been found to possess a broad range of potent biological activities. Curcumin **(1)**, amongst the diarylheptanoids, is the most well known, for its biological activities. Curcumin **(1)** has been found to exhibit biological activities such as anti-inflammatory, anti-oxidative and anti-carcinogenic activities[1, 15-17]. In spite of its efficacy, curcumin **(1)** has not yet been approved as a therapeutic agent because of its poor aqueous solubility, low bioavailability and its intense staining colour. Several biological activities of diarylheptanoids characteristic of *Alnus* species have been reported. These include anti-oxidative activity, nitric oxide synthase inhibitory activity[18], melanogenesis inhibitory activity[10], free radical scavenging activities[10], anti-inflammatory effects and cytotoxic activities[12]. Diarylheptanoids isolated from the Chinese ginger (*Zingiber officinale*) have also been found to have cytotoxic and apoptotic activities[19]. Furthermore, diarylheptanoids from *Acer nikoense* have been shown to be inhibitors of nitric oxide production[18] and melanogenesis[10]. The diarylheptanoids isolated from *Alpinia officinarum* have shown promising inhibitory and bacterial activity against enteropathogenic *Escherichia coli*[20] and diarylheptanoids from *Alpinia blepharocalyx* have shown anti-platelet activity[8].

2.4.1 Structure–activity correlation of biologically active diarylheptanoids

Structural variations in any biologically active compound is important because altering its structure could lead to changes in physiological activity and its pharmacokinetics, i.e. how easily the drug is absorbed, distributed, metabolised and excreted[17]. Once a biologically

active compound is isolated from natural sources, extensive structure-activity relationship studies are carried out in order to optimize its potency and to define a drug profile for the compound.

2.4.1.1 Antioxidative activity

It has been found that the *o*-methoxy substituents on curcumin **(1)** and its analogues play a role in their potency as antioxidants. Anand *et al*[17] reported that curcumin has better radical scavenging and antioxidant ability than the other two analogues of which demethoxycurcumin (DMC) **(2)** shows better activity than bisdemethoxycurcumin (BDMC) **(3)**. Curcumin **(1)**, DMC **(2)** and BDMC **(3)** differ in their chemical structure only by methoxy substitution (Scheme 1.1); curcumin has two methoxy groups, one on each phenyl group but DMC **(2)** has only one methoxy group on one of the phenyl groups where as BDMC **(3)** does not contain a methoxy group. In spite of the similar structures, the three analogues exhibit significantly different antioxidant activity. Anand and coworkers propose that the hydrogen bonding interaction between the phenolic OH and the *o*-methoxy group of curcumin influences the O-H energy and H-atom abstraction by free-radicals thus making it a superior free radical scavenger compared to BDMC[17].

Kuroyanagi and co-workers studied the antioxidative activity of the diarylhepatanoids isolated from *Alnus japonica*[11]. From their study it was found that linear diarylheptanoids containing two 3,4-dihydroxyphenyl moieties showed potent activity whereas compounds having a 3,4-dihydroxyphenyl and a 4-hydroxyphenyl moiety showed moderate activity and compounds having two 4-hydroxyphenyl moieties showed no activity[11]. Based on these results, it can be concluded that the catachol structure of the diarylheptanoids is important for it to be a potent antioxident[11].

2.4.1.2 Cytotoxicity

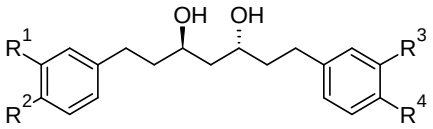
Chio *et al.*[12] studied the variation in cytotoxic activity amongst the diarylheptanoids which were isolated from the bark of *Alnus japonica*. From their studies, it was found that diarylheptanoids with a keto-enol moiety in the molecule were more potent than

compounds with only an enol moiety[12]. Furthermore, it was found that the presence of one OH group on the aromatic ring improved the cytotoxic activity against murin B16 melanoma cells and SNU-1 gastric cancer cells, of the diarylheptanoid[12].

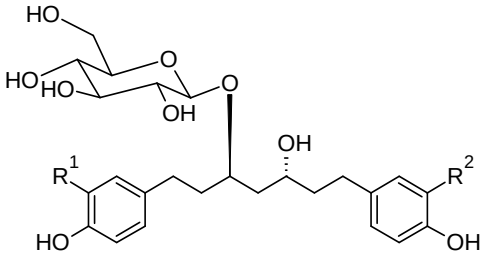
Yokosuka and his group also studied the cytotoxic activity of the diarylheptanoids which were isolated form *Tacca chantriei*[21]. These studies showed that the diarylheptanoids with three or four phenolic groups, for example compound **20**, exhibit moderate cytotoxic activity against HL-60 human promyelocytic leukaemia and HSC-2 human oral squamous carcinoma cells, while diarylheptanoids with two phenolic OH groups **(19)** did not show significant activity. Furthermore, diarylheptanoids **(21)** with hydroxyl groups fully masked with methoxy groups also showed significant cytotoxic activity. Based on these results, Yokosuka *et al.* drew the conclusion that the number of hydroxyl groups on the biphenyl rings of the diarylheptanoids contribute to the cytotoxicity of the compounds[21].

2.4.1.3 Platelet inhibition activity

Dong *et al.*[8] studied the variation of antiplatelet activity of diarylheptanoids, isolated from *Alpinia blepharocalyx* (Figure 2.5). Platelet aggregation is induced by collagen, arachidonic acid (AA), adenosin diphosphate (ADP) and ristocetin. From this study it was found that compound **35** showed strong platelet inhibition activity caused by all four inducers as compared to compound **36**, which showed activity against AA induced platelet aggregation[8]. The only difference in the structure of compound **35** and **36** is the presence of a hydroxy group at C-4' position of the benzene ring in **35**. Compound **37** and **38** both were found to be active against AA induced platelet aggregation[8]. Thus the structural variation of the diarylheptanoids plays an important role in determining the potency of the compound.



(34) R^1= H, R^2= OH, R^3= H, R^4= OH
(35) R^1= R^2= R^3= R^4= OH
(36) R^1= R^2= R^3= R^4= OCH_3



(37) R^1= OH, R^2= H
(38) R^1= R^2= OH
(39) R^1= R^2= OCH_3

Figure 2.5. Diarylheptanoids isolated from *Alpinia blepharocalyx*

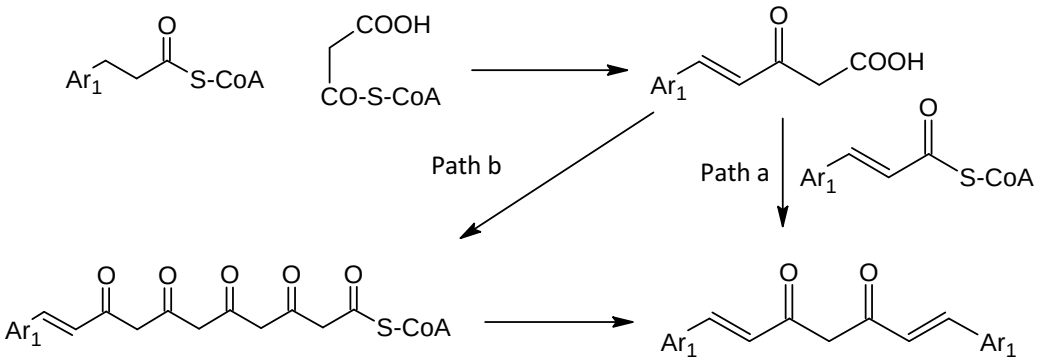
2.5 Synthesis of Diarylheptanoids

Even though the structural complexity of most natural products makes their synthesis challenging, numerous natural products have been successfully synthesised. Since the discovery of diarylheptanoids, various diarylheptanoids and their analogues have been synthesised successfully. This section of the chapter will concentrate on giving an overview of the various approaches that have been used in the synthesis of both linear and cyclic diarylheptanoids.

2.5.1 Synthesis of linear diarylheptanoids

2.5.1.1 Biosynthesis of linear diarylheptanoids

The biosynthesis of curcumoids has been investigated owing to their importance to human health and nutrition. The initial investigation of the biosynthesis of curcumoids was carried out by Whiting *et al.*[22] They proposed two mechanistic pathways by which curcumoids are synthesised biologically and Scheme 2.1 outlines the proposed biosynthetic pathways[23].



Scheme 2.1. Biosynthesis of linear diarylheptanoids

Enough experimental evidence has not been obtained to confirm either of the pathways. However, studies with different plant species have indicated that both pathway a and b may operate in the biosynthesis of diarylheptanoids[7].

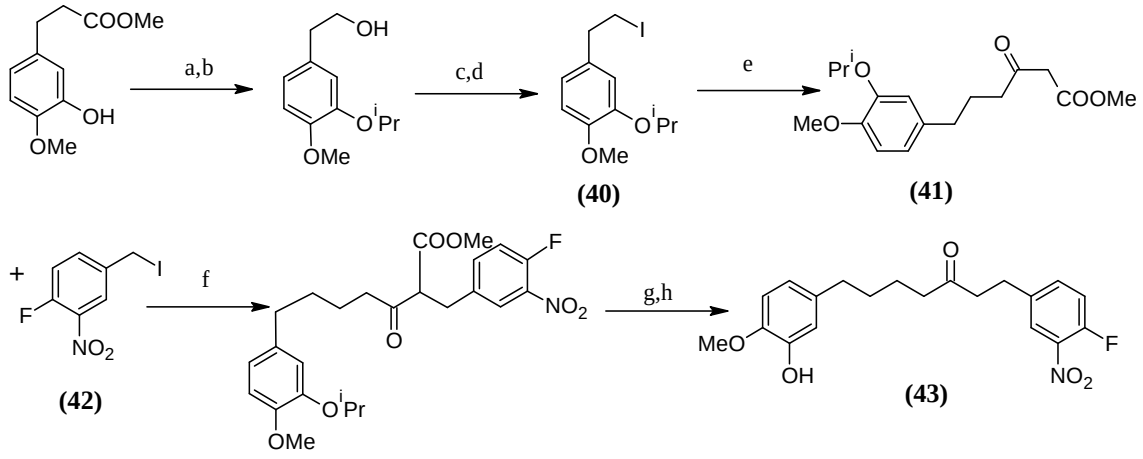
2.5.1.2 Synthesis of linear diarylheptanoids

Linear diarylheptanoids have relatively simple structures and thus easily accessible using today's synthetic methodologies. Linear diarylheptanoids differ by the substituents on the phenyl rings and by the oxygen functional groups such as OH and C=O on the seven-carbon aliphatic chain. In addition to this, diarylheptanoids with both unsaturated and saturated aliphatic chains have been isolated. Thus a general strategy for the synthesis of linear diarylheptanoids should allow ready variation of the substituents on the phenyl rings and incorporation of various oxygen functional groups on the aliphatic chain. The synthesis of linear diarylheptanoids can be classified according to the ways in which the seven carbon aliphatic chain could be assembled; C_1-moiety + C_6-moiety strategy, C_2-moiety + C_5-moiety strategy, C_3-moiety + C_4-moiety strategy, C_1-moiety + C_5-moiety + C_1-moiety strategy.

2.5.1.2.1 C_1-Moiety + C_6-moiety

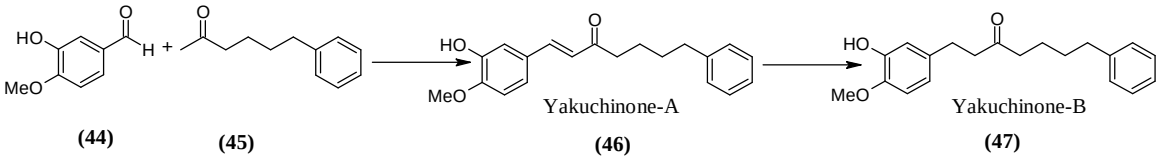
Gonzalez and Zhu used the C_6-moiety + C_1-moiety strategy to synthesis the diarylheptanoid **43**[7]. The synthetic strategy used by Gonzalez and Zhu used standard

transformations to afford the desired diarylheptanoid (Scheme 2.4). The key steps of the reaction is the chain elongation to form the C_6-moiety which was obtained by the double deprotonation of methyl acetoacetate using LDA followed by addition of the iodide **40**, The C_1-moiety was synthesised using the Finkelstein reaction, in which the bromide group of 4-fluoro-3-nitrobenzyl bromide was replaced by an iodide group to form **42**. The two precursors were then combined by nucleophilic substitution of the C_1-moity **(42)** to the C_6-moiety **(41)** to form the seven carbon aliphatic chain. This was followed by the chemoselective removal of the isopropyl protecting group followed by decarboxylation to afford the desired diarylheptanoid.



Scheme 2.2. Reagents and yields: (a) ^{i}PrBr, K_2CO_3, 96%, (b) $LiAlH_4$, 97%, (c) TsCl, Py, 87% (d) NaI, 80%, (e) methyl acetoacetate, LDA, 80% (f) NaH, 76% (g) BCl_3 (h) 6N HCl, 93%

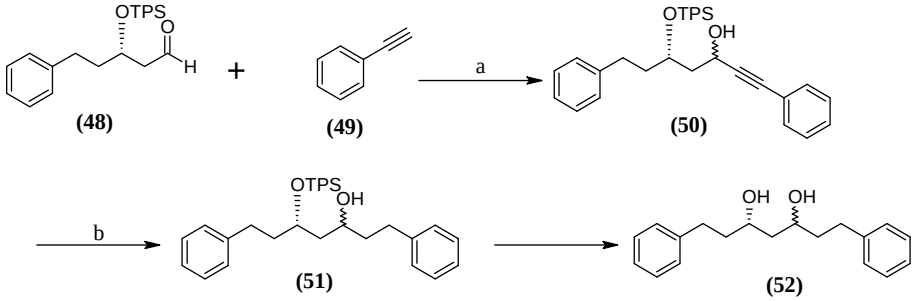
Itokawa *et al.*[24] also used the C_1-moiety + C_6 moiety for the synthesis of yakuchinone-A **(46)** and B **(47)**, linear diarylheptanoids isolated from *Alpinia oxyphylla*. Scheme 2.5 outlines the major step in the synthesis of **46** and **47**. They utilized the Claisen-Schmidt reaction for the condensation of vanillin **(44)** (C_1-moiety) with 6-phenyl-2-hexanone **(45)** (C_6-moiety) to form **46**, which was then hydrogenated to form **47**[24].



Scheme 2.3. Synthesis of yakuchinone-A and -B

2.5.1.2.2 C_2-Moiety + C_5-moiety strategy

Narasimhulu *et al.*[25] synthesized the diarylheptanoid yashabushidiol **(52)**, isolated from the male flowers of *Alnus sieboldiana*. The readily available starting material D-mannitol diacetonide was used as the starting material for the synthesis of the C_5-moiety **(48)**, whereas vanillin was used as the starting material for the C_2-moiety **(49)**. The key step of the synthesis was the alkenylation reaction in which the C_2-moiety adds to the C_5-moiety via nucleophilic addition. Scheme 2.6 outlines the synthetic procedure used for the coupling of the C_2 and C_5-moiety to obtain the seven-carbon aliphatic chain. The reaction proceeded in 90% yield to afford a mixture of two diastereomers **(51)** in a ratio 40:60 (*syn:anti*) which were then separated by chromatographic methods to yield **52**.

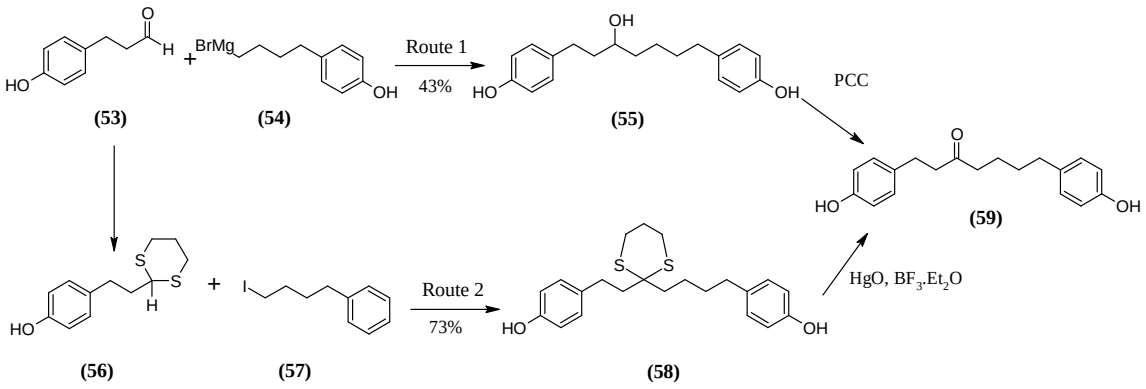


Scheme 2.4. Reagents and yields: (a) n-BuLi, 90%; (b) 10% Pd/C, 95% (c) PTSA, MeOH, rt, 1 h, 95%

2.5.1.2.3 C_3-Moiety + C_4-moiety strategy

Henly-Smith *et al.*[3] reported the synthesis of a linear diarylheptanoid using a C_3-moiety + C_4-moiety strategy. The synthesis used by Whiting and co-workers used both the Grignard

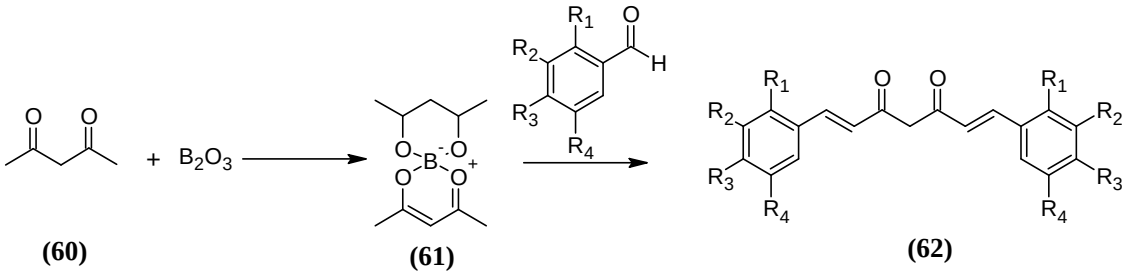
reaction (Route 1) and a reaction based on dithiane chemistry (Route 2) to couple the two moieties. Scheme 2.5 outlines the synthetic route used by Henly-Smith *et al.*[3] to assemble the seven-carbon aliphatic chain. The assembly of the two moieties using Grignard reaction between **53** and **54** gave only a 48% yield of **55**, whereas the dithiane route in which **56** and **57** were reacted, gave a 73% yield of **59**[3].



Scheme 2.5. Synthesis of a diarylheptanoid using the Grignard reaction route and dithiane route.

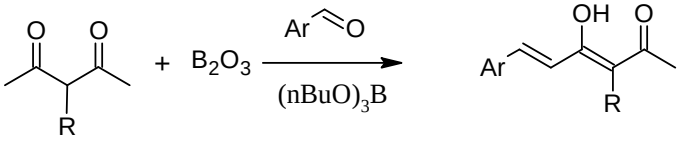
2.5.1.2.4 C_1-Moiety + C_5-moiety + C_1-moiety strategy

Venkateswarlu *et al.*[26] devised an efficient and short synthetic strategy for the synthesis of curcumin analogues using the aldol condensation. The main steps in the synthetic route, as shown in Scheme 2.8, was the protection of carbonyl group of acetylacetone (C_5-moiety) **(60)** with boric oxide to form an acetylacetone-boric oxide complex **(61)**, which was then reacted with substituted benzaldehydes (C_1-moiety) and finally the boron complex of the product was decomposed using aqueous acetic acid to get the desired curcumin analogs **(62)**[26]. The C-3 of 2,4-pentadione bears more acidic protons than C-1/C-5 and thus Knoevenagel condensation at C-3 competes with the aldol condensation on the terminal methyl groups. However, boron-based protecting groups reduce the nucleophilicity of the C-3 position and so the reaction occurs at the terminal active methylenes resulting in diarylheptanoids.

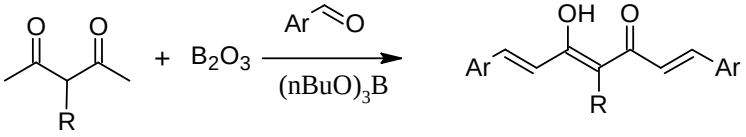


Scheme 2.6. Synthesis of diarylheptanoids using boron based protecting groups

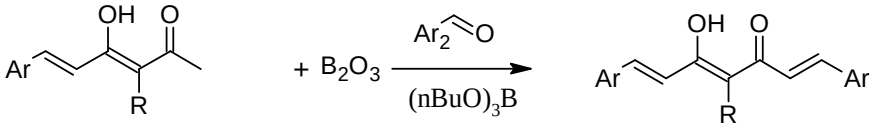
Later on, Lee *et al.*[13] used the same strategy to synthesise heterocycles containing curcumin analogues and symmetric and asymmetric curcumin analogues with different substituents on the phenyl rings. Scheme 2.7 outlines the general synthetic routes followed by them.



Synthetic method for monophneyl curcumin analogues



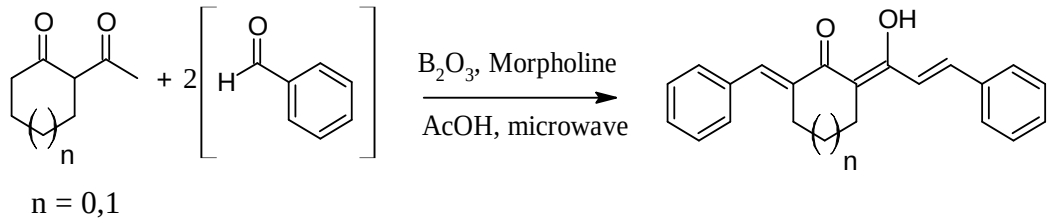
Synthetic method of symmetric curumin analogues



Synthetic method for assymetric curcumin analogues

Scheme 2.7.General synthetic routes for the synthesis of curcumin analogues

Nichols *et al.*[27] performed the same reaction described above for the synthesis of curcumin analogues using microwave energy (Scheme 2.8). The procedure adopted by them allowed the synthesis of the desired analogues in a short time period compared to the heating under reflux, followed by Venkateswarlu *et al.*[26] *and* Lee *et al.*[13] and gave moderate to excellent yields[27].



n = 0,1

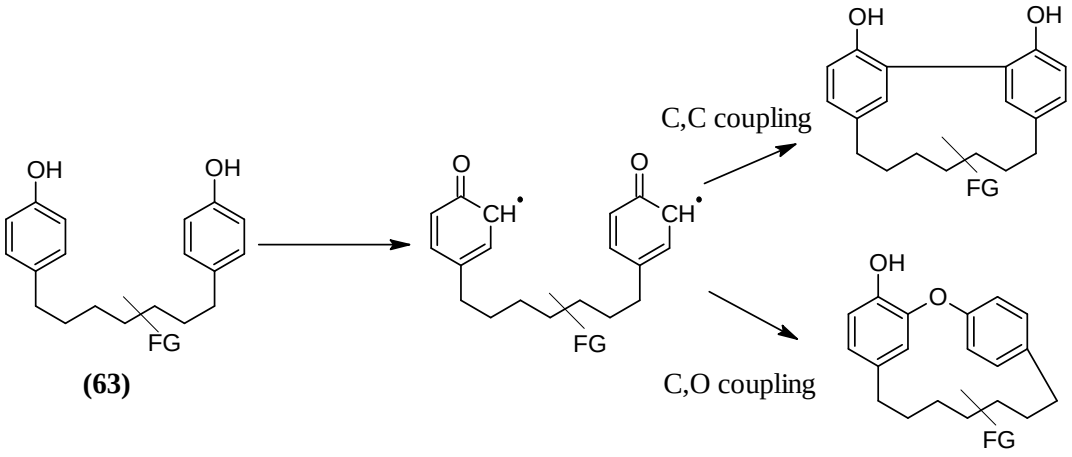
Scheme 2.8. Synthesis of diarylheptanoids using boron-based protecting groups under microwave irradiation

2.5.2 Synthesis of cyclic diarylheptanoids

The total synthesis of cyclic diarylheptanoids has interested chemists for decades owing to their biological activities. Thus various synthetic methods have been developed for the synthesis of cyclic diarylheptanoids such as intramolecular ring-closure metathesis, intramolecular Wittig reactions, intramolecular oxidative coupling, intramolecular nucleophilic aromatic substitution reaction (S_NAr) and transition metal-catalyzed reactions[7]. Synthesis of cyclic diarylheptanoids involves the formation of carbon-carbon bonds at the aliphatic chains or macrocyclisation *via* formation of an aryl-aryl or an aryl-aryl ether bond. This section will review the various synthetic strategies that have been used for the synthesis of the cyclic diarylheptanoids.

2.5.2.1 Biosynthesis of cyclic diarylheptanoids

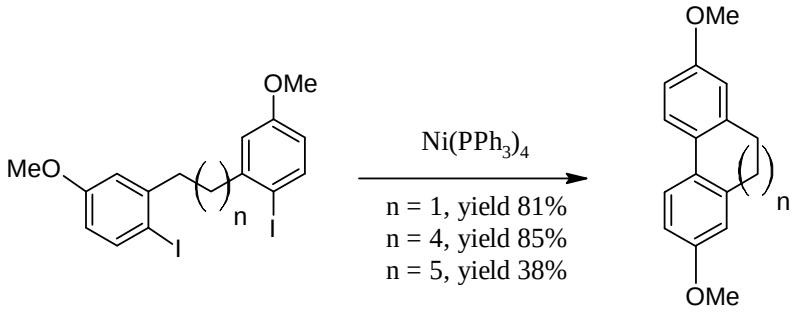
Cyclic diarylheptanoids have been found in co-occurrence with their corresponding linear diarylheptanoids in plants such as *A. japonica* and *A. nikoense.* Thus intramolecular phenolic oxidative coupling have been the biosynthetic route proposed for cyclic diarylheptanoids. Scheme 2.11 outlines the proposed biosynthetic route. The linear precursor **(63)** would be obtained by combining two units of cinnamate with one malonate[7].



Scheme 2.9. Biosynthesis of cyclic diarylheptanoids

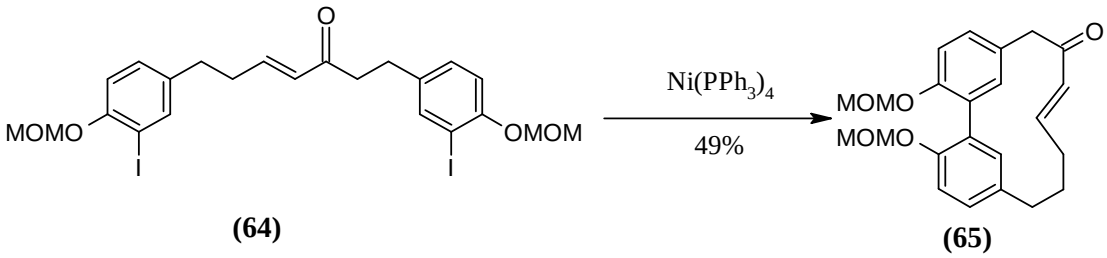
2.5.2.2 *meta,meta*-Bridged biphenyls

Semmelhack *et al.*[28] investigated the zerovalent nickel promoted aryl-aryl bond formation. From their study it was found that tetrakis(triphenylphosphine)nickel gave the desired aryl-aryl coupling in good yield. According to Semmelhack *et al.*[28], the reaction proceeds via oxidative addition of the organic halide to Ni(0). However, this cyclisation technique does not yield good results with sterically hindered *ortho*-disubstituted substrates (Scheme 2.10). Even so, this methodology is a good alternative to the traditional Ullmann reaction, which requires drastic conditions thus making it less efficient for the construction of structurally complex molecules[28].



Scheme 2.10. Nickel promoted aryl-aryl bond formation

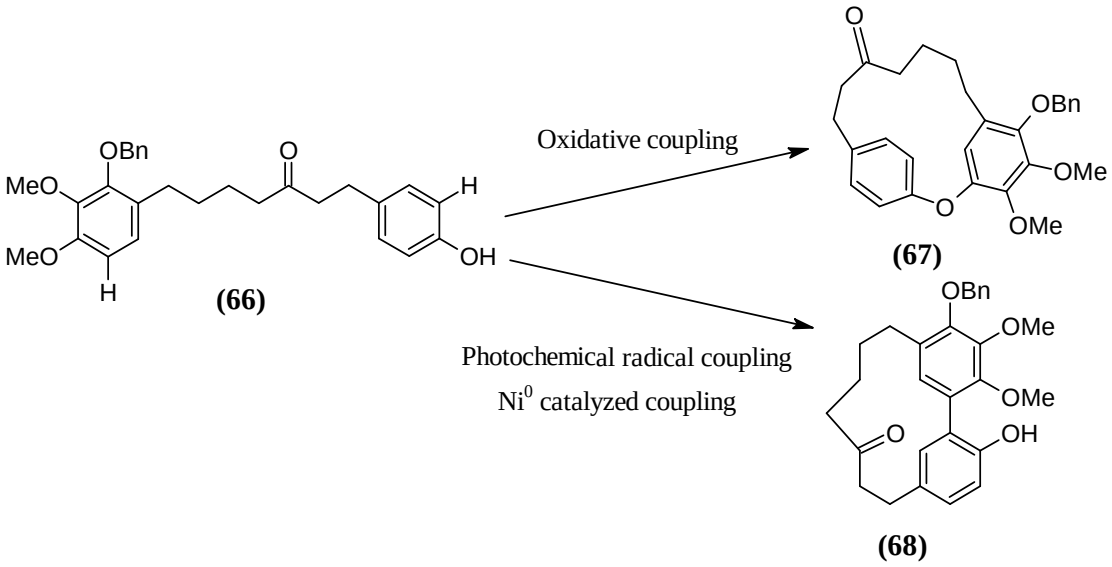
Semmelhack and co-workers, utilised the method which they developed, for the synthesis of alnusone **(65)**, a *m,m*-bridged biphenyl (Scheme 2.11). The cyclisation of **64** using tertrakis(triphenylphosphine)nickel afforded the desired product **65** in 46% yield[28].



(64) **(65)**

Scheme 2.11. Zerovalent nickel promoted synthesis of *m,m*-bridged biphenyl diarylheptanoid

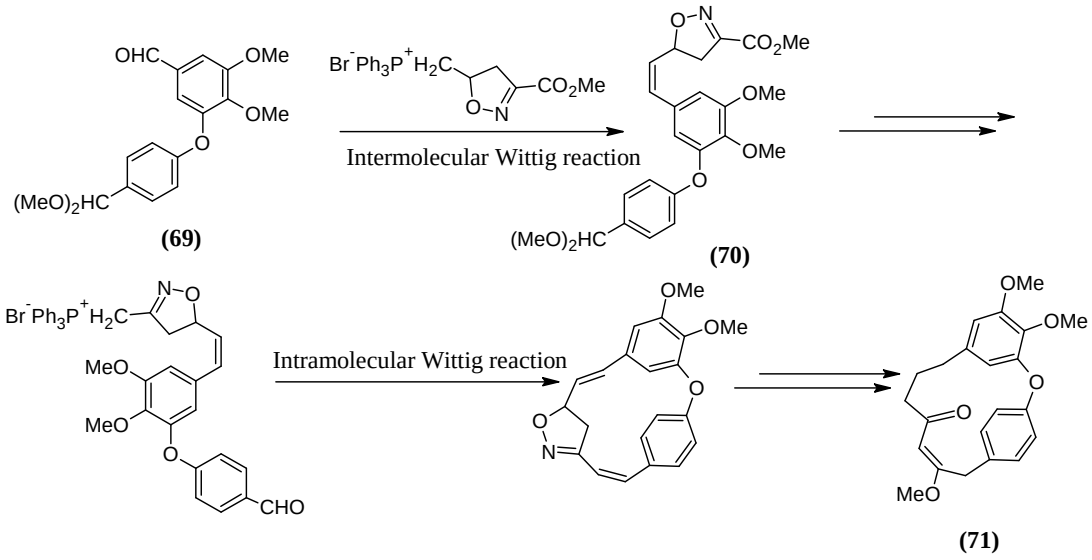
Whiting *et al.*[22] investigated the aryl-aryl cyclisation of appropriate 1,7-diarylheptanoids to form *m,m*-bridged biphenyl diarylheptanoids. In their study, different coupling strategies were used namely, oxidative coupling, photochemical radical coupling and Ni^0 catalysed coupling[22]. Scheme 2.12 summarises the results obtained in this study. The oxidative coupling of **66** using thallium(III) tristrifluoroacetate yielded the C-O coupling to form *m,p*-bridged biphenyl **(67)**, but both photochemical radical coupling and Ni^0 catalysed coupling gave the desired C-C coupling product **(68)** with the latter procedure giving higher yield[22].



Scheme 2.12. Cyclisation to form *m,m*-bridged biphenyls using different strategies

2.5.2.3 *meta,para*-Bridged biphenyls

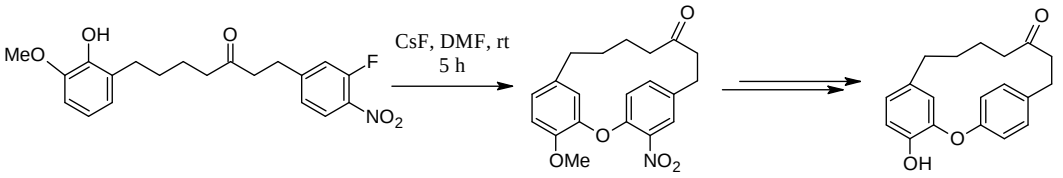
Keseru and co-workers developed a synthetic scheme for the synthesis of garuganin III **(71)**, a macrocylic diarylheptanoid isolated from the Indian medicinal plant *Garuga pinnata*[4]. The key steps for the synthesis followed by them are; (i) preparation of an unsymetrically substituted diphenyl ether **(69)** (ii) addition of a C_5 unit to the diphenyl ether as an isoxazol, which also served as a masked 1,3-dicarbonyl synthon to form **70** (iii) ring closure using an intramolecular Wittig reaction and lastly transformation of the isoxazole into the desired β-methoxy enone **71**[4]. The synthetic route followed by Keseru and co-workers is outlined in Scheme 2.13.



Scheme 2.13. Synthesis of garuganin III **(71)**

In another report, Vermes *et al.* used a similar strategy to synthesise garugamblin-1, a variant of garuganin III **(73)** but the ring closure was accomplished by the Wurtz-Boekelheide method[29]. In this method, the intermediate **(70)** is treated with a radical anion generated from sodium and tetraphenylethene[29].

Gonzalez and Zhu utilised the intramolecular S_NAr reaction for the synthesis of the aryl ether bond of the *m,p*-bridged diarylheptanoid, acerogenin A **(74)**[2]. The synthesis was carried out by firstly preparing the corresponding linear diarylheptanoid **72** which was then subjected cylcoetherification. Scheme 2.14 outlines the synthetic route starting from the linear diarylheptanoid. The cyclisation occurred smoothly to give the macrocylce **73** in quantitative yield[2]. Gonzalez and Zhu reported that even at high concentrations of the linear diarylheptanoid, the cyclic product was obtained in quantitative yield. This provides evidence that the intramolecular reaction of the linear diarylheptanoid is highly competitive with the alternative intermolecular process[2].



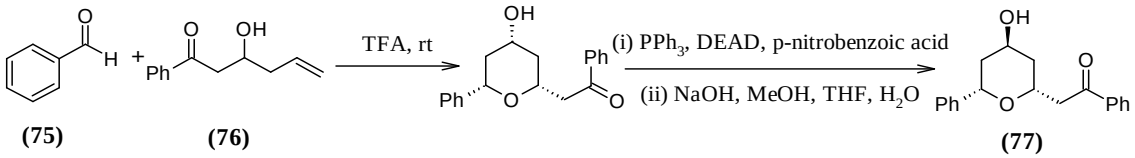
(75) **(76)** Acerogenin A **(74)**

Concentration	Isolated yield
0.01 M	90-95%
0.05 M	90-95%
0.1 M	75-80%
1 M	45-50%

Scheme 2.14. Synthesis of acerogenin A **(77)**

2.5.2.4 Tetrahydropyran-type cyclic diarylheptanoids

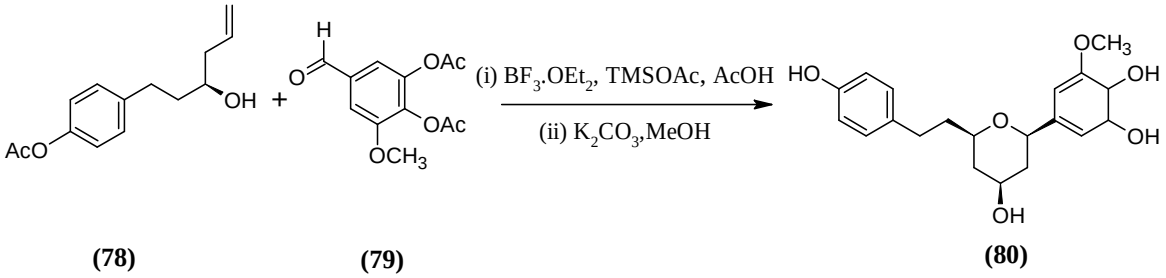
One of the most commonly used reaction for the formation of tetrahydropyran-type diarylheptanoids is the Prins reaction. Hiebel *et al.*[15] used Prins cyclisation for the synthesis of diospongin A **(77)**, which has a 2,4,6-trisubstituted tetrahydropyran ring as the core. The key step of the synthesis was the acid-mediated Prins reaction between the homoallylic alcohol **(76)** and benzaldehyde **(75)** to form the tetrahydropyran ring, which was then subjected to the Mitsunobu reaction in order to get the desired stereochemistry (Scheme 2.15). Using this method, total synthesis of **77** was achieved with 23% overall yield[15].



(75) **(76)** **(77)**

Scheme 2.15. Synthesis of (±)-diospongin A **(77)**

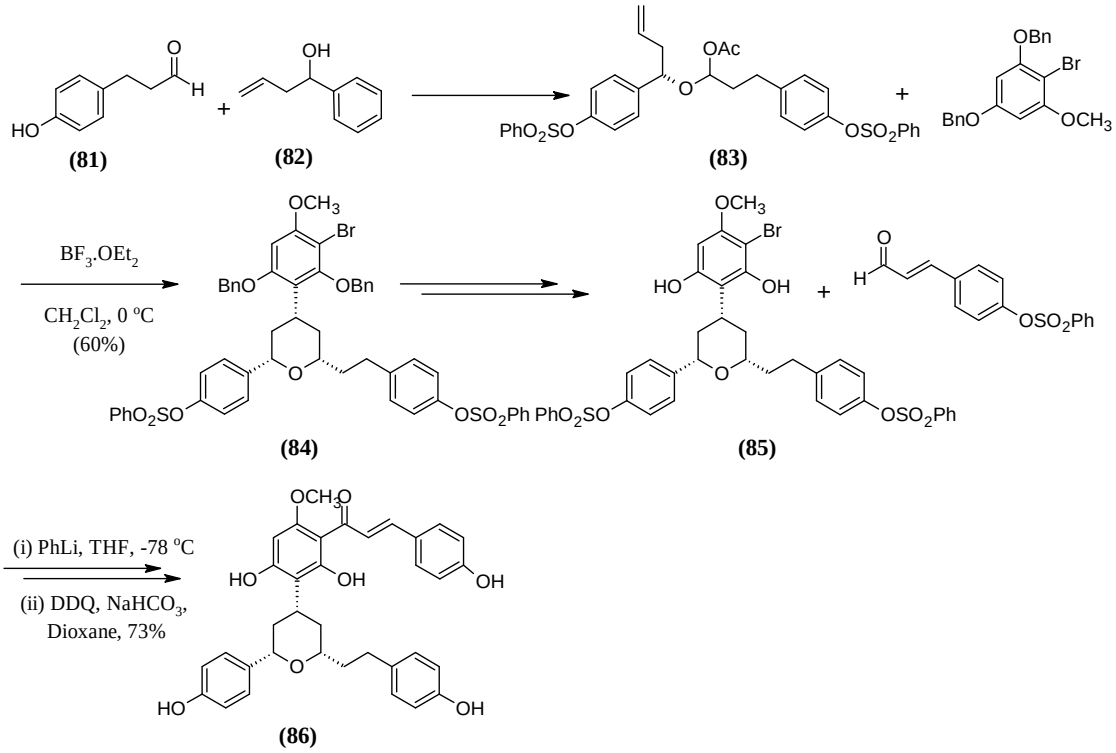
Parker *et al.*[30] also used Prins cyclisation as the key step for the synthesis of the calyxin-type natural product, 4-acetoxy-2,6-disubstituted tetrahydropyrans **(80)**, isolated from *Zingiber officinale*. The Prins cyclisation between the homoallylic alcohol **(78)** and the trisubstituted benzaldehyde **(79)** afforded the diarylheptanoid **80** in 77% yield.



(78) **(79)** **(80)**

Scheme 2.16. Synthesis of 4-acetoxy-2,6-disubstituted tetrahydropyrans

Tian *et al.*[9] used a tandem Prins cyclisation and a Friedel-Crafts reactions with an electron-rich aromatic ring to synthesise the core structures of a calyxin natural product (Scheme 2.17). Even though the Prins cyclisation normally leads to a tetrahydropyran rings with a heteroatom at the C-4 position, Tian *et al.* reported that under certain circumstances the electrophilic C-4 position reacts with an aromatic ring in a Friedel-Crafts alkylation reaction, introducing an aryl group in the equatorial position[9]. As a result, this reaction enables the introduction of structural complexity thus making it a useful synthetic method. The carbon skeleton of epicalyxin F **(86)** was assembled in a single step by the Prins cyclisation and Friedel-Crafts trapping of the ester of alcohol **82** with acid **81** to form the acetoxy ether **83**. Precursor **83** was then subjected to another Prins cyclisation to form the core unit of epicalyxin F **(84)**. This was followed by the lithiation of the aryl bromide **(85)** and addition of the unsaturated aldehyde leading to the formation of epicalyxin F **(86)**.



Scheme 2.17.Synthesis of epicalyxin F **(86)**

2.6 Conclusion

In summary, diarylheptanoids are an important class of plant secondary metabolites exhibiting a broad range of biological activities. Diarylheptanoids have mostly been isolated from plants of Zingiberacea family. Diarylheptanoids that have been isolated from various plant species vary significantly in their structure. Owing to their significant biological activities, the total synthesis of natural diarylheptanoids and their analogues have been investigated. Thus total synthesis of many of the diarylheptanoids has been accomplished by various researchers.

2.7 References

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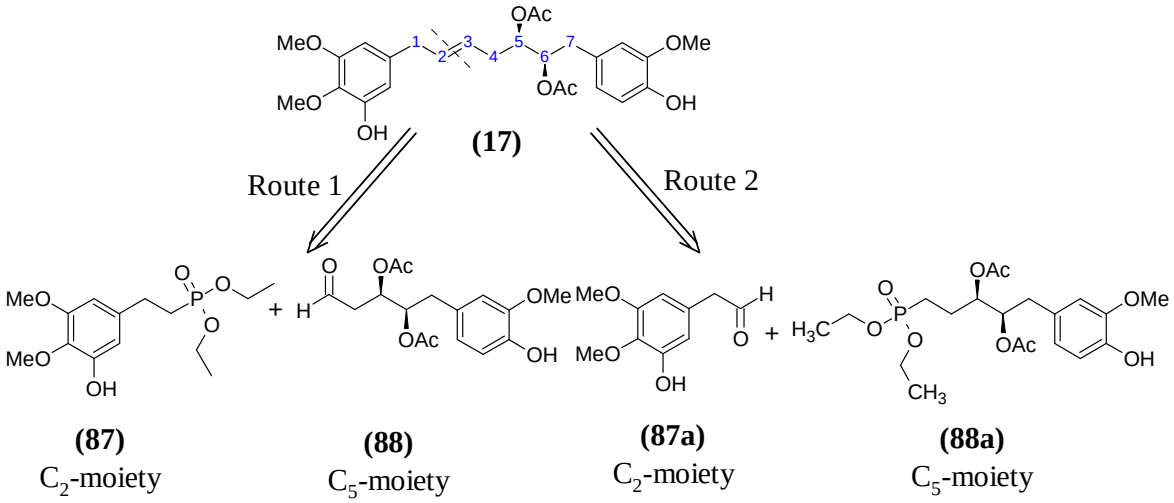
3 Towards the Synthesis of a Novel Diarylheptanoid

3.1 Introduction

The aim of this investigation was to synthesise a novel diarylheptanoid **(17)** isolated from the South African medicinal plant *Siphonochilus aethiopicus*. As outlined in Chapter 2, diarylheptanoids are a class of plant metabolites exhibiting a variety of biological activities. The total synthesis of compound **17** would enable the evaluation of its biological activities and also would provide a means for synthesising analogues of this compound. In the literature, various synthetic methodologies have been published for the synthesis of diarylheptanoids, which have been briefly explained in Chapter 2. This Chapter will describe the work that has been done towards the total synthesis of compound **17** during this research.

3.2 Retrosynthetic Analysis

The targeted diarylheptanoid **(17)** contains two electron-rich aromatic rings connected by a seven-carbon aliphatic chain containing a *trans*-alkene functional group and two stereogenic centres at positions 5 and 6, respectively. The intended synthetic strategy is the C_2-moiety + C_5-moiety strategy. Thus the molecule was disconnected at the double bond at the C-2 positions of the aliphatic chain, leading to two major precursors. Scheme 3.1 shows the retrosynthetic analysis of the diarylheptanoid **(17)**.



Scheme 3.1. Retrosynthetic analysis of the novel diarylheptanoid

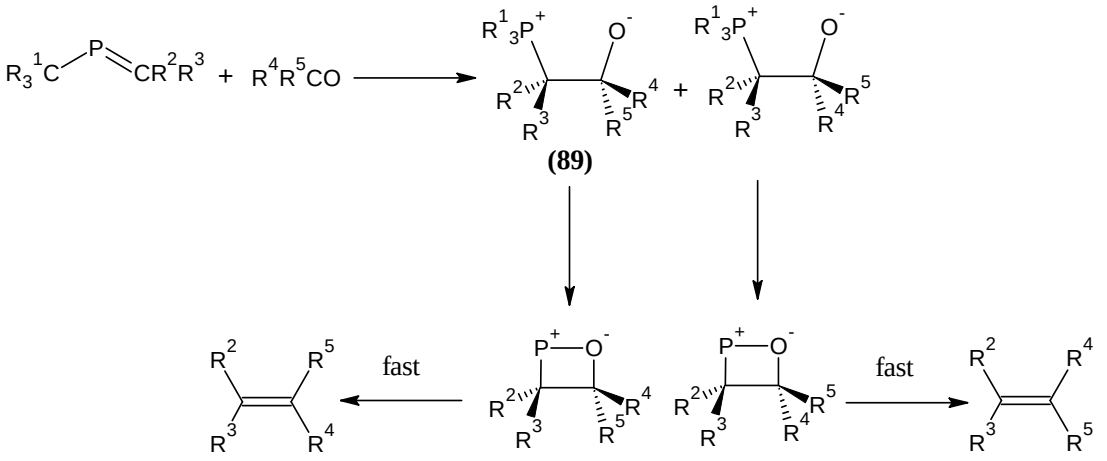
Rout 1 (Scheme 3.1), was the chosen synthetic pathway for the synthesis of compound **17**. The alternative route (Route 2) for the synthesis of the compound **17** with starting material **87a** and **88a**, outlined in Scheme 3.1, was also considered. However, owing to the instability of the aldehyde under basic conditions, this route is not feasible for the total synthesis of compound **17**. The instability of aldehyds of the type **87a** could be attributed to the acidic protons which would be deprotonated under mild basic conditions thus leading to self condensation.

The synthesis of the target compound was based on three major sections; synthesis of C_2-moiety **(87)**, synthesis of C_5-moiety (**88)** and the coupling of the two moieties to form the required diarylheptanoid. Simple functional group conversions will be utilised for the synthesis of both the precursors and Wittig-type olefination reactions will be used for the formation of the *trans*-double bond eventually leading to the required diarylheptanoid.

3.3 Preliminary Investigation

A preliminary investigation was carried out in order to evaluate different Wittig reactions for the selective formation of the *E*-alkene present in the targeted diarylheptanoid **(17)**.

Wittig reactions are very useful for generating double bonds, usually with high geometrical control. Owing to its wide use in synthetic chemistry, we decided to utilise a Wittig-type reaction for the construction of the *E*-alkene. Consideration of the mechanistic details of the reaction has revealed ways of controlling the stereoselectivity of the Wittig reaction[1]. Scheme 3.2 outlines the general mechanistic pathway for the Wittig reaction. This reaction proceeds in three steps: addition of the phosphorane to an aldehyde forming an intermediate betaine **(89)**, followed by the formation of the phosphorous-oxygen bond and finally collapse of the oxophosphetane intermediate by *syn*-elimination to form the *cis* or *trans* olefin. The stereoselectivity of the Wittig reaction is dependent on the type of ylide and on the substituents bonded to the phosphorus atom. Non-stabilised ylides favour *Z*-alkenes, semi-stabilised ylids lead to both *Z* and *E* alkenes and stabilised ylides favour *E*-alkenes[2].

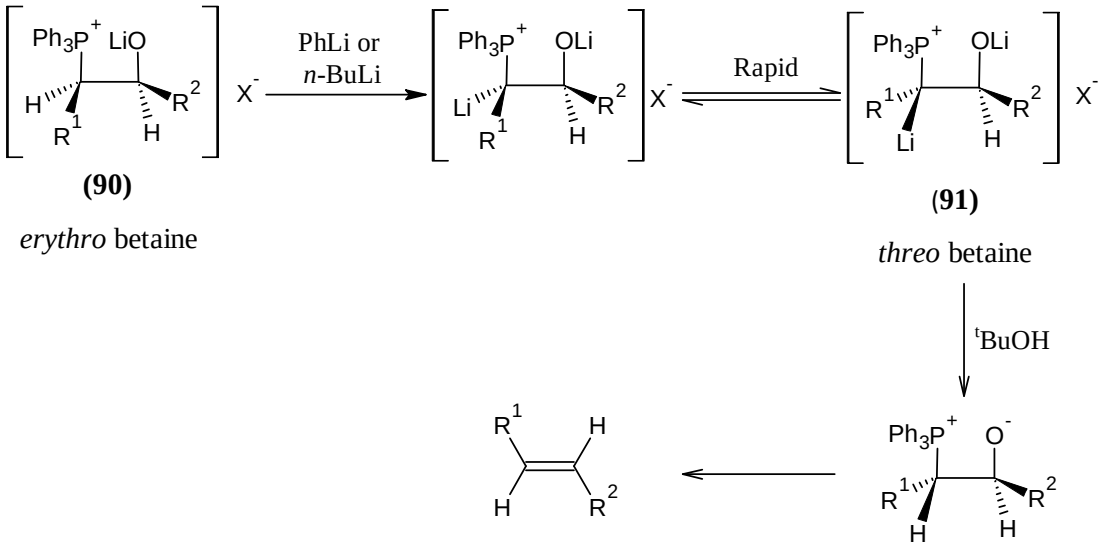


Scheme 3.2. General mechanistic pathway for Wittig reaction

Over the past decade various modifications of the Wittig reaction has been introduced. These include the Wittig-Schlosser[3] reaction and the Horner-Wadsworth-Emmons reaction for *E*-selective olefination. We decided to investigate these two modifications of the Wittig reaction in order to utilise it in the total synthesis of the targeted diarylheptanoid.

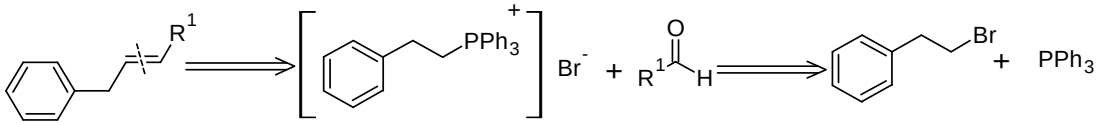
3.3.1 Wittig-Schlosser reaction

The Schlosser modification of the Wittig reaction allows the selective formation of the *E*-alkenes[1]. In this variant of the Wittig reaction, excess lithium adduct is used in the addition of the ylide and in the subsequent deprotonation step[3].When excess lithium adduct is added, the *erythro*-betaine intermediate **(90)** which leads to the formation of the *Z*-alkene, is converted to *threo*-betaine intermediate **(91)** which results in the *E*-alkene (Scheme 3.3)[3].



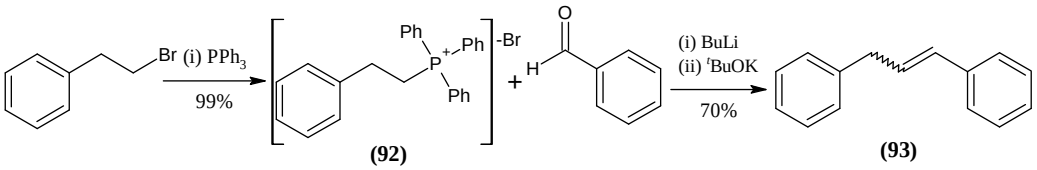
Scheme 3.3. The Schlosser modification of the Wittig reaction

To investigate the stereoselectivity of the Wittig-Schlosser reaction, we designed a model reaction. Scheme 3.4 outlines the retrosynthetic analysis based on a model compound.



Scheme 3.4. Retrosynthetic analysis for a model compound

The synthesis of compound **93** began with the formation of the phosphorous ylide **92** as shown in Scheme 3.5. Compound **92** was synthesized in 99% yield by refluxing a mixture of 2-phenylethyl bromide and triphenylphosphine in toluene. Formation of compound **92** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of this compound showed significant ^{13}C-^{31}P coupling (Plate 1b).



Scheme 3.5. Synthesis of compound **93**

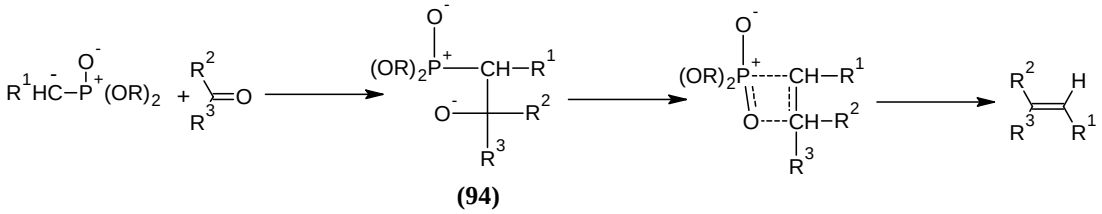
Having synthesised the Wittig ylide **(92)**, we attempted the Wittig-Schlosser reaction. The reaction was carried out by firstly stirring the base with the Wittig ylide at room temperature for one hour. This was then followed by another addition of the base to facilitate the inter-conversion of the *erythro* betaine to the *threo* betaine. The aldehyde was then added to the reaction mixture. The required product, **93**, was obtained in 70% yield as mixture of both the *cis*- and *trans*- isomers. ^{1}H NMR spectroscopy of compound **93** was used to determine the stereoselectivity of the reaction. The ^{1}H NMR spectrum (Plate 3a), showed peaks corresponding to both the *E*- and the *Z*-isomers, with the *Z*-isomer as the major product of the reaction (*Z*:*E*, 8:2). The peaks which correspond to the *Z*-isomer are a doublet at δ_H 3.72 (Ar-**C**H$_2$-CH=CH), doublet of triplet at δ_H 5.91 (Ar-CH$_2$-C**H**=CH) and the doublet at δ_H 6.63 (Ar-CH$_2$-CH=C**H**) with an olefinic coupling constant of 11.6 Hz, characteristic of that of a *Z*-alkene. The ^{1}H NMR peaks which corresponds to the *E*-alkene are further upfield compared to that of the *Z*-alkene; a doublet at δ_H 3.59 (Ar-**C**H$_2$-CH=CH), a doublet of triplets at 6.40 (Ar-CH$_2$-C**H**=CH) and a doublet at δ_H 6.50 (Ar-CH$_2$-CH=C**H**) with a olefinic coupling constant of 15.8 Hz, characteristic of a *E*-alkene.

Having failed to obtain the *E*-isomer exclusively, we attempted to increase the *E*:*Z* ratio by changing the reaction conditions. The reaction was initially started at -70 °C and allowed to warm to 0 °C. We increased the temperature to 0 °C-25 °C, but isolated only the *Z*-isomer. Then we decided to decrease the reaction temperature from -70 °C- -30 °C,

this also failed to bring about any significant change in the *E*:*Z* ratio. Changes in reaction temperature had little effect upon the product ratio. Since the Wittig-Schlosser reaction did not yield the *E*-isomer exclusively, it cannot be used in the total synthesis of the targeted diarylheptanoid.

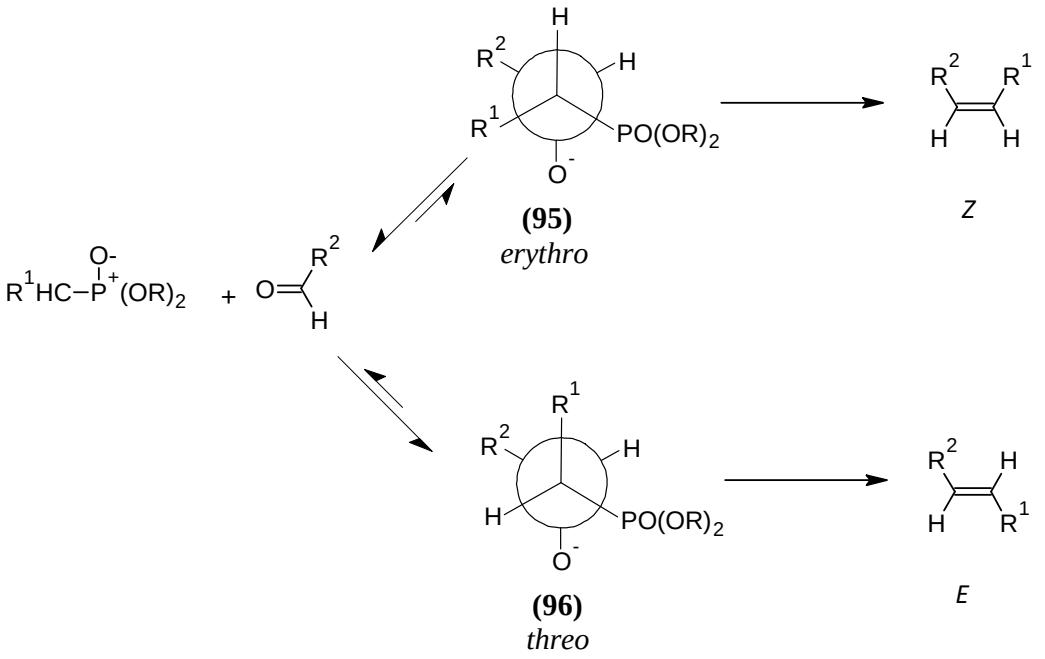
3.3.2 Horner-Wadsworth-Emmons Reaction

The phosphonate modification of the Wittig reaction is known as the Horner-Wadsworth-Emmons (HWE) reaction. The HWE reaction uses a resonance-stabilised phosphonate carbanion which undergoes reaction with carbonyl compounds[2]. The HWE reaction is advantageous over the conventional Wittig reaction since the phosphonate carbanions are more nucleophilic than the phosphonium ylides and thus react with a wider variety of aldehydes and ketones under milder conditions[2]. In contrast to the conventional Wittig reaction, HWE reaction has a two-step mechanism (Scheme 3.6). In the first step, the carbanion reacts with the carbonyl compound to form an intermediate oxyanion **(94)**[3]. In the second step, the intermediate decomposes by oxygen transfer to the phosphorous atom to form the olefin as shown in Scheme 3.6.



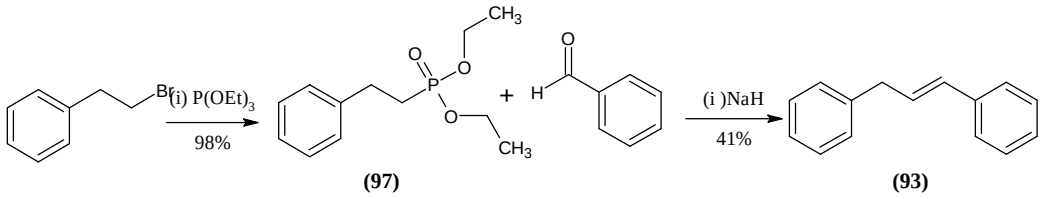
Scheme 3.6. Mechanism for the HWE reaction

The stereochemistry of the HWE reaction generally favors the formation of the *E*-alkene, thus the formation and the decomposition of the *threo* betaine **(96)** would be much faster than that of the *erythro* betaine **(95)**[2, 4] (Scheme 3.7). This outcome could be explained by considering the steric effects of the two betaine intermediates. The *erythro* betain **(95)** is much more sterically hindered than the *threo* betaine **(96)** in the eclipse conformation required for the *syn* elimination. Thus the *erythro* betaine **(95)**, which will lead to the *Z*-alkene, will be formed at a slower rate than the *threo* betaine **(96)**[2, 4]. However, methods have been developed for the stereoselective formation of the *Z*-alkene using the HWE reaction[5, 6].



Scheme 3.7. Mechanism for the HWE reaction

To investigate the stereoselectivity of the HWE reaction, we designed a model reaction similar to that shown in Scheme 3.5. Scheme 3.8 outlines the synthesis of a model compound **(93)** using the HWE reaction.



Scheme 3.8. Synthesis of **93** using the HWE reaction

The first step was the synthesis of the phosphonate **(97)** by refluxing a mixture of 2-phenylethyl bromide and triethyl phosphite. Compound **97** was obtained as a yellow oil in an excellent yield of 98%. The formation of phosphonate **97** was confirmed by ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of compound **97** showed a triplet at δ_H 1.30 and a quartet at δ_H 4.15 corresponding to the ethyl group of the phosphonate ester (Plate 2a). Furthermore, the ^{13}C NMR spectrum of **97** showed significant ^{31}P-^{13}C coupling. The

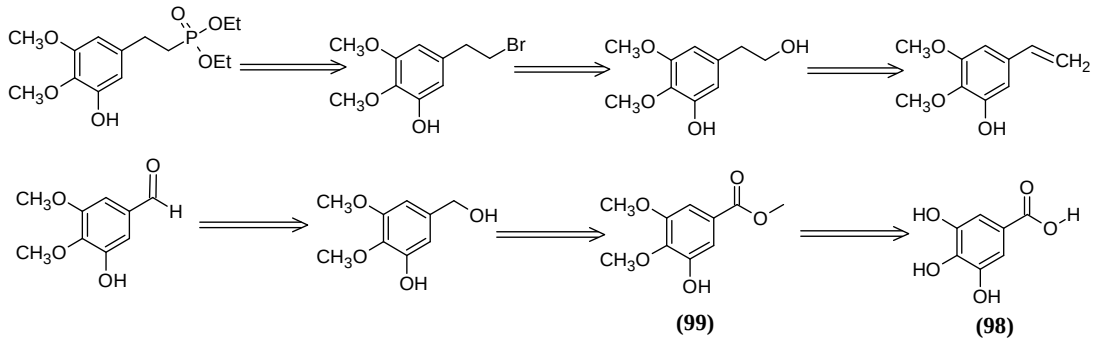
Ph-CH_2**C**H_2P had the largest coupling constant of 139.7 Hz. Both ^1J and ^2J coupling were seen on the ^{13}C NMR spectrum of the phosphonate ester (Plate 2b).

Having compound **97** in hand, we attempted the HWE reaction using benzaldehyde as shown in Scheme 3.8. The required *E*-isomer was obtained in this reaction in 41% yield. The ^{1}H NMR spectrum of the product showed that the major product of the reaction was the *E*-isomer (Plate 4a) with a minute quantity of the *Z*-isomer present. Thus we decided to use the HWE reaction to couple the two moieties, **87** and **88**, in order to form the targeted olefin.

3.4 Synthesis of Precursors

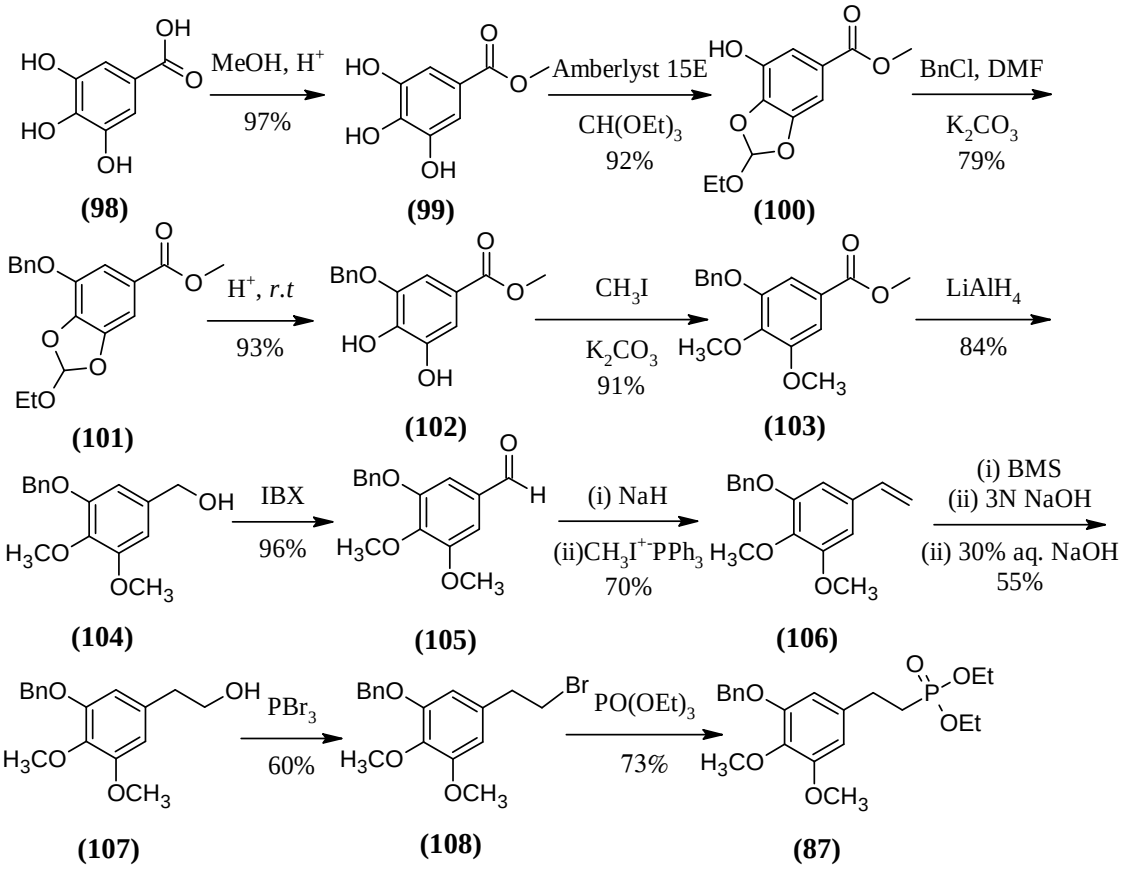
3.4.1 Synthesis of C_2-moiety

The C_2-moiety is the diethyl phosphonate for the HWE reaction. Scheme 3.9 outlines the retrosynthetic analysis of compound **87**. As outlined in this Scheme 3.9, the synthesis of compound **87** is based on simple functional group conversion thus making it a convenient synthesis. The starting material for the synthesis of compound **87** was gallic acid **(98)**, which has a *m*-hydroxylated aromatic ring, consistent with the substitution pattern of the aromatic ring of compound **87**. Selective protection of the two adjacent hydroxy groups of gallic acid **(98)** would enable us to obtain the required aromatic substitution for compound **87**.



Scheme 3.9. Retrosynthesis for compound **87**

Scheme 3.10 outlines the strategy for the synthesis of compound **87**. The first step of the synthesis was the esterification of the carboxylic acid group of gallic acid **(98)** to form methyl gallate **(99)**. This reaction was carried out under acidic conditions to form the required compound in an excellent yield of 97%. Formation of compound **99** was confirmed by ^{1}H NMR which showed a distinguishing singlet for the methoxy group at δ_H 3.74 (Plate 5a).



Scheme 3.10. Synthetic route for **87**

The second step of the synthesis was the regioselective protection of two adjacent hydroxy groups of **99** as an acetal using ethyl orthoformate. The orthoformate protecting was performed under acid-catalysed conditions. Since **99** is a symmetrical molecule, this reaction is chemoselective thus leading to the formation of one compound even though there are three hydroxy groups on the substrate. This reaction proceeded in 92% yield to

form compound **100**. Both benzene and toluene were used as solvents for this reaction. It was found that when using toluene as the solvent, the reaction time decreased significantly. This decrease in reaction time could be attributed to higher reaction temperature when refluxed in toluene. The boiling point to toluene is 110 °C whereas the boiling point of benzene is 80 °C. Formation of compound **100** was confirmed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum showed a triplet at δ_H 1.17 and a quartet at δ_H 3.70, corresponding to the ethyl orthoformate group of compound **100** (Plate 6a).

The next step of the synthesis was the protection of the remaining hydroxy group. Since the protecting group needs to be kept intact throughout the synthesis, a less sensitive protecting group had to be chosen. Thus the free hydroxy group was protected as a benzyl ether. This reaction proceeds in 79% yield to form the required compound **101**. The ^{1}H NMR spectrum of compound **101** had a singlet at δ_H 5.24 and a multiplet at δ_H 7.36-7.50, which corresponded to the benzyl group.

Having compound **101** in hand, the deprotection of the acetal protecting group to form **102** was achieved by stirring acetal **101** in MeOH under acidic conditions. The ^{1}H NMR spectrum of **102** did not have the peaks corresponding to the ethyl orthoformate protecting group, which were at δ_H 1.17 and δ_H 3.10 in the ^{1}H NMR spectrum of **101** (Plate 7a).

The subsequent methylation of the two phenolic groups at C-4 and C-5 of the phenyl ring furnished compound **103** in an excellent yield of 95%. The three singlets at δ_H 3.91, 3.92 and 3.94, each integrating for three protons in the ^{1}H NMR spectrum (Plate 8a) of compound **103**, correspond to the three methoxy groups in **103.** With the successful synthesis of ester **103**, we have managed to obtain the required substitution of the phenyl ring, which is consistent with the substitution on the phenyl ring of compound **87**.

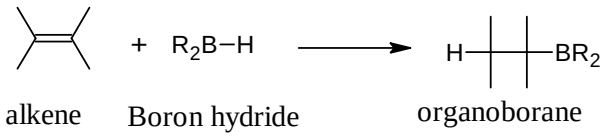
The next step was to synthesise the required two-carbon aliphatic chain. In order to accomplish this, the ester group of **103** was first reduced to the alcohol using $LiAlH_4$ to form alcohol **104**. This reaction gave a good yield of 84%. The ^{1}H NMR spectrum of **104** had three singlets at δ_H 3.84, 3.87 (corresponding to two methoxy groups) and δ_H 4.56 (corresponding to CH_2OH) (Plate 9a). Furthermore, due to the increase in electron density on the phenyl ring because of the removal of the electron-withdrawing ester group, the signals corresponding to the phenyl protons in the ^{1}H NMR spectrum moved upfield. For compound **103**, the signals for the two phenyl protons are very close to the benzyl proton signals and together appeared as a multiplet, whereas in the ^{1}H NMR spectrum of

compound **104** (Plate 9a), the signals for the two phenyl protons appeared separately from the benzyl protons at δ_H 6.59 and δ_H 6.63.

Following the successful synthesis of the alcohol, it was oxidised to the aldehyde using 2-iodoxybenzoic acid. 2-Iodoxybenzoic acid is an organic compound used in organic synthesis as an oxidizing agent. It is especially suited to oxidize alcohols to aldehydes. IBX is prepared from 2-iodobenzoic acid, potassium bromate and sulfuric acid[7]. This reaction proceeded in 96% yield to afford the required compound **105**. The formation of aldehyde **105** was confirmed by the ^{1}H NMR spectrum, which had the diagnostic aldehyde proton peak at δ_H 9.84 and the ^{13}C NMR spectrum also showed the carbonyl carbon peak at δ_C 190.9 (Plate 11a and 11b). Furthermore, the ^{1}H NMR and ^{13}C NMR peaks for **105** moved downfield as compared to the peaks of **104**. This is due to the replacement of the hydroxy group of **105** with an electron-withdrawing carbonyl group thus decreasing the electron density of the phenyl ring.

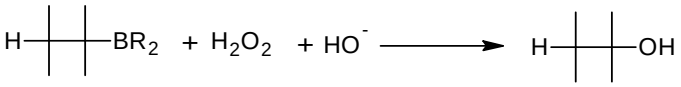
The subsequent Wittig olefination of aldehyde **105** with methyltriphenylphosphonium iodide furnished styrene **106** in 70% yield. The ^{1}H NMR spectrum of **106** showed the peaks corresponding to the $CH=CH_2$ group protons; a doublet at δ_H 5.63 with a coupling constant of 17.5 Hz corresponding to the *trans* terminal proton on the $CH=CH_2$ group and the doublet of doublets at δ_H 6.62 with a coupling constant of 17.5 Hz for C**H**$=CH_2$ proton (Plate 12a). The doublet of doublets seen for C**H**$=CH_2$, indicates that the terminal two protons are non-identical, even though they are bonded to the same sp^2 carbon. The peak intensities of the signal for C**H**$=CH_2$ proton was 1:1:1:1, thus confirming that it is a doublet of doublets.

The next step of the synthesis was the hydroboration-oxidation of the alkene **106** to form the alcohol **107**. This is a two-step reaction in which hydroboration is accomplished by the addition of a boron hydride to the C=C bond as shown in Scheme 3.11.



Scheme 3.11. Hydroboration

Following hydroboration, the organoborane is oxidised using hydrogen peroxide in aqueous base thus converting the organoborane to an alcohol (Scheme 3.12).



Scheme 3.12. Hydroboration-oxidation

Hydroboration-oxidation was chosen for this step because it leads to the anti-Markovnikov product, whereas acid-catalysed conversion of alkenes to alcohols will lead to the Markovnikov product. This difference in regioselectivity could be attributed to steric effects; boron has a tendency to become bonded to the less substituted carbon of the double bond thus leading to the anti-Markovnikov product. The hydroboration-oxidation of **106** yielded **107** as the major product (55% yield) and Markovnikov product (15% yield) as the minor product. The formation of **107** was confirmed by ^{1}H NMR which showed two triplets at δ_H 2.78 and 3.81, corresponding to C**H$_2$**C**H$_2$**OH signals (Plate 13a).

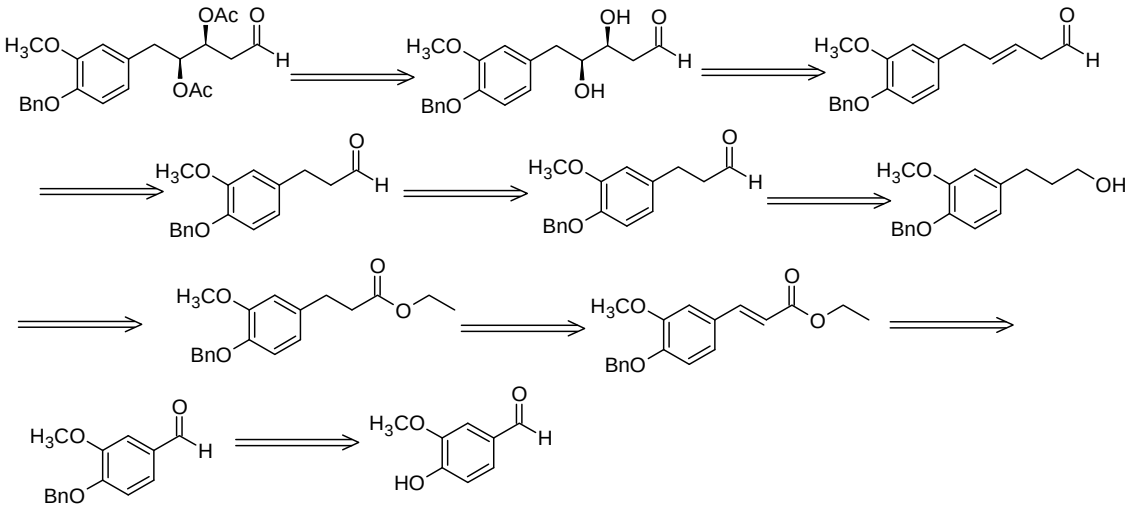
Having the required alcohol **107** in hand, the next step was the conversion of the alcohol **107** to the alkyl halide **108**, which could then be converted into the phosphonate ester **(87)**. This was done by bromination of the alcohol group using PBr_3 to form bromide **108** in 60% yield. The triplets corresponding to the CH_2C**H$_2$**Br, in the ^{1}H NMR spectrum of compound **108** shifted downfield compared to that of alcohol **107** because of the introduction of a more electronegative bromide group (Plate 14a).

The last step is the synthesis of the C_2-moiety was the preparation of the phosphonate ester **87**. Compound **87** was synthesised by refluxing **107** with triethyl phosphite. The reaction proceeded in 73% yield to give the required compound **87**. ^{1}H NMR and ^{13}C NMR spectroscopy were used to confirm the formation of **87**. The ^{1}H NMR spectrum of compound **87** had a triplet at δ_H 1.34 and a quartet at δ_H 4.11, corresponding to the diethyl phosphonate group of **87** (Plate 15a). The ^{13}C NMR spectrum of **87** showed significant ^{13}C-^{31}P coupling. A coupling constant of 139.2 Hz was seen for the ^{1}J coupling, 4.4 Hz for ^{2}J coupling and 17.4 Hz for ^{3}J coupling of carbon-13 to phosphorous-31 (Plate 15b). The coupling constants that were obtained are in agreement with those from the literature. The coupling constants reported for ^{13}C-^{31}P coupling in compounds similar to **87** by Takahashi

and co-workers were in close agreement with the *J* values we obtained[8]. Takahashi *et al*. reported 140.3 Hz for ^{1}J coupling, 4.4 Hz for ^{2}J coupling and 17.4 Hz for ^{3}J coupling[8]. Furthermore, the ^{31}P NMR spectrum of compound **87** showed a sharp peak at δ_P 30.56, indicating the presence of a phosphorous atom in the compound.

3.4.2 Synthesis of C_5-moiety

Structural analysis of the C_5-moiety shows an electron-rich aromatic ring and a five-carbon aliphatic chain with two stereogenic centres. Scheme 3.13 outlines the retrosynthetic analysis for the synthesis of **88**. Based on the retrosynthetic analysis outlined in Scheme 3.13, a synthetic strategy was developed and is shown in Scheme 3.14. The starting material chosen for the synthesis of **88** was vanillin **(109)** which has substituents on the *meta* and *para* positions of the aromatic ring, consistent with the substituents on the aromatic ring of the C_5-moiety. The first step of the synthesis would be the protection of the *para*-hydroxy group of vanillin as a benzyl ether. This would be the right choice of protecting group since **87** also contains a benzyl ether protecting group. Furthermore, the protecting group of the *p*-OH group is kept all throughout the synthesis, thus a fairly stable protecting group such as a benzyl ether group is appropriate. The second step of the synthesis would be the HWE reaction which would then be followed by the sequential reductions of the C=C bond and the ester group. The resulting hydroxy would then be oxidised to an aldehyde and reacted with malonic acid to form the required five carbon aliphatic chain with a C=C double bond between C-3 and C-4 position. The next step would be the Sharpless asymmetric dihydroxyation of the C=C bond. In order to achieve the required stereochemistry, AD-mix, which is a mixture of reagents containing a chiral ligand, will be used.



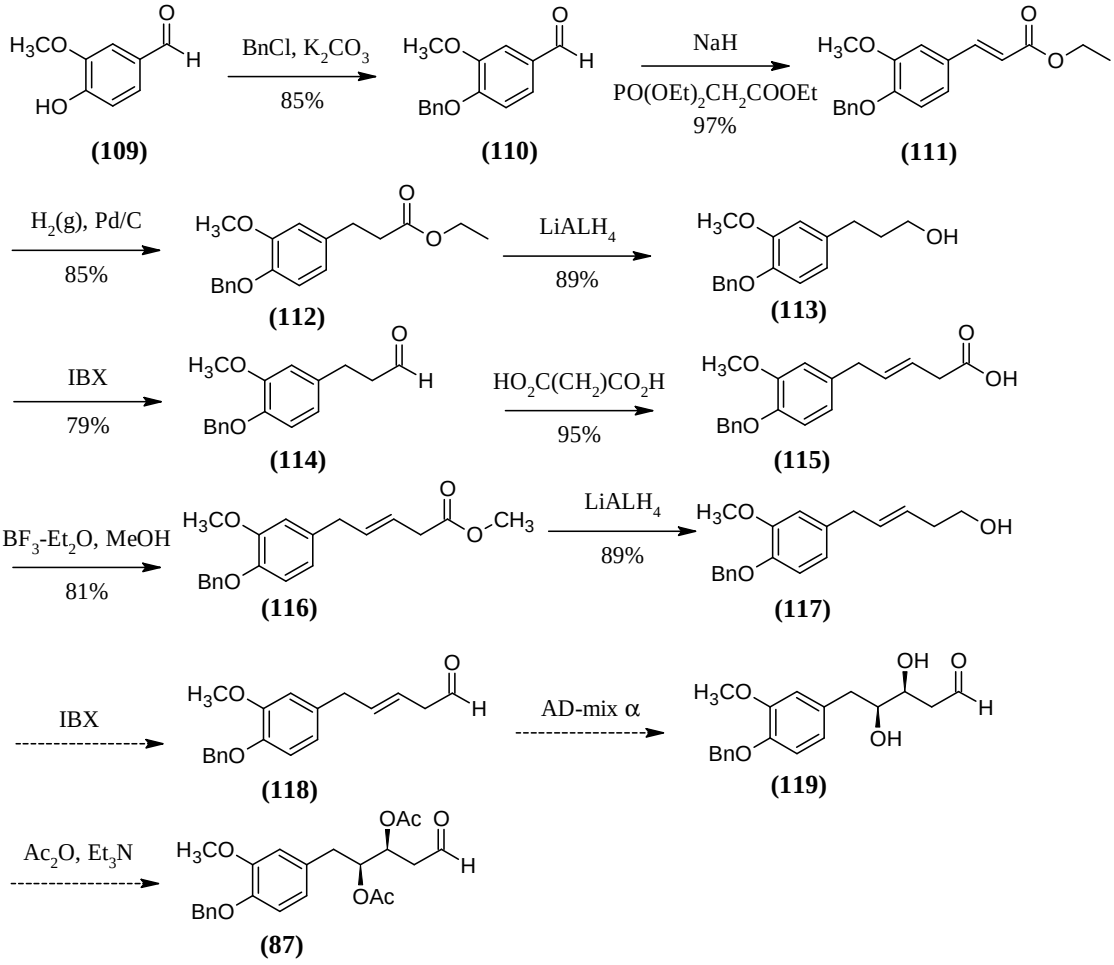
Scheme 3.13. Retrosynthesis for C_5-moiety

The benzylation of the commercially available vanillin **(109)** was performed using benzyl chloride in the presence of K_2CO_3 (Scheme 3.14). This reaction proceeded in 85% yield to give **110**. The diagnostic peaks of the benzyl ether were seen on the ^{1}H NMR spectrum of **110**, a singlet corresponding to the O-CH_2 protons at δ_H 5.26 and a multiplet corresponding to the benzyl protons at δ_H 7.31-7.47 (Plate 16a).

This was followed by the HWE reaction of compound **110** with triethyl phosphonoacetate using NaH as a base, to form the α,β-unsaturated ester **111**. This reaction proceeded in an excellent yield of 97%. The successful synthesis of **111** was confirmed by ^{1}H NMR spectroscopy. The spectrum (Plate 17a) showed two doublets at δ_H 6.32 and δ_H 7.63 with a coupling constant of 15.9 Hz, corresponding to the two *trans*-olefinic protons on the aliphatic chain of **111**.

The subsequent reduction of the C=C bond using H_2 in the presence of 10% Pd/C catalyst, led to the formation of compound **112**. This reaction had to be done under careful time control because elongated reaction times cause reduction of not only the double bonds, but also lead to debenzylation. The optimum time was found to be 15 min for 2 g of compound **111**. The successful reduction of the C=C bond was corroborated by the ^{1}H NMR spectrum which showed two triplets at δ_H 2.61 and 2.91, corresponding to the C**H$_2$**C**H$_2$** protons of **112** (Plate 18a).

Compound **112** was then successfully reduced to the corresponding alcohol **(113)**. The reducing agent used was $LiAlH_4$ and the reaction proceeded in an excellent yield of 89% to form alcohol **113**. The ^1H NMR spectrum (Plate 19a) for **113** confirmed the success of the reaction; the quintet at δ_H 1.89 corresponding to the $CH_2C\underline{\mathbf{H}}_2CH_2OH$ protons is diagnostic for compound **113**. Furthermore, the peaks corresponding to the aliphatic protons moved downfield compared to that of the aliphatic proton peaks of **112** due to the absence of the electron-withdrawing ester group.



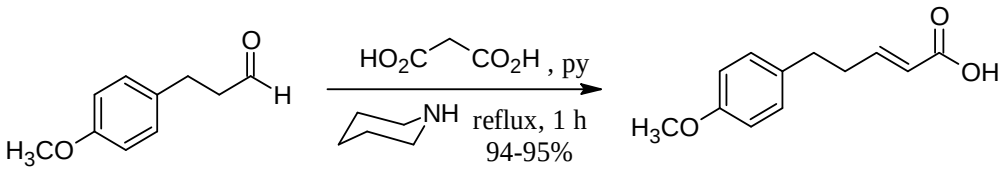
Scheme 3.14. Synthetic route for the C_5-moiety

The alcohol **113** was then oxidised to form the subsequent aldehyde **(114)**. The oxidising agent used for this step was 2-iodoxybenzoic acid and the reaction proceeded in a good yield of 79%. The ^1H NMR spectrum of compound **114** had the characteristic aldehyde proton peak at δ_H 9.83 (Plate 20a). In addition to this, the quintet at δ_H 1.89 in the ^1H NMR

of **113** was not present in the ^{1}H NMR of compound **114**; instead two triplets at δ_H 2.77 and δ_H 2.92, corresponding to the aliphatic protons were seen.

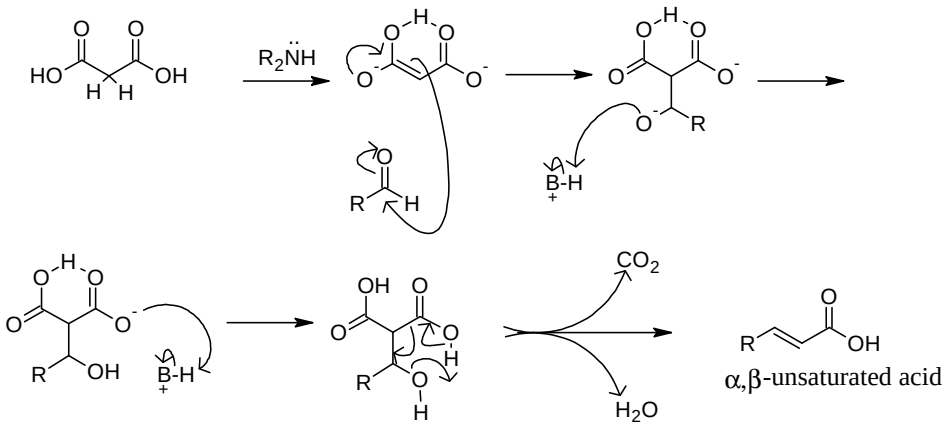
Having successfully synthesised the aldehyde, the next step of the synthesis was the Knoevenagel condensation of aldehyde **114** with malonic acid to form the β,γ-unsaturated acid **115.** The formation of the β,γ-unsaturated acid **115** was confirmed by using ^{1}H NMR and ^{13}C NMR. The ^{1}H NMR spectrum of compound **115** showed two doublets at δ_H 3.14 and δ_H 3.34, which correspond to the two pairs of CH_2-protons on the aliphatic chain. Furthermore, a multiplet was present in the ^{1}H NMR spectrum between δ_H 5.68-5.59, corresponding to the two CH=CH-protons (Plate 21a). Although it has been reported by Kumar *et al.* that the major product of this type for condensation is the α,β-unsaturated acid[9], we obtained the β,γ-unsaturated acid as our sole product in excellent yield of 99%.

The Knoevenagel condensation using malonic acid has been reported to yield both the α,β- and β,γ-unsaturated acids but affords the highest yield of the β,γ-unsaturated acid[10]. Duarte *et al.* reported the formation of the α,β-unsaturated acid in 94-95% yield using the reagents malonic acid, pipyridine and pyridine under reflux[11] (Scheme 3.16).



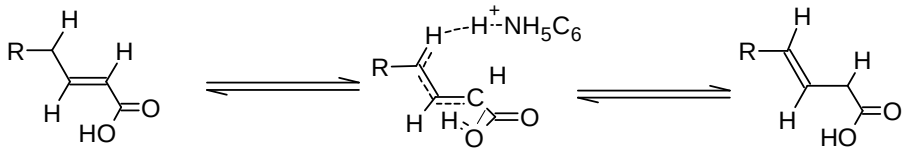
Scheme 3.15. Knoevenagel condensation

We also utilised the same reagents, but under microwave irradiation, to obtain solely the β,γ-unsaturated acid. It is also worth noting that we obtained the β,γ-unsaturated acid, even under reflux using the same reagents, but in a much lower yield of 45%. The results obtained for the Knoevenagel condensation are in agreement with the results obtained by Sabitha *et al.*[12]. Sabitha *et al.*[12] used a modified Knoevenagel condensation method which utilises SiO_2 as a catalyst under microwave irradiation, described by Kumar *et al.*[9], to form the β,γ-unsaturated acid in 60% yield. Scheme 3.17 shows the proposed mechanism for the formation of the α,β-unsaturated acid.



Scheme 3.16. Mechanism for Knoevenagel condensation

There are three steps in the proposed mechanism: addition of the enolate to the aldehyde, decarboxylation and double bond rearrangement. In the addition step, an enolate ion is formed which then attacks the aldehyde. This step is followed by decarboxylation leading to the *E*-alkene. In the next step the double bond moves from the conjugated α,β-position to the non-conjugated β,γ-position. According to E.J. Corey, the formation of the β,γ-unsaturated acid follows the mechanism shown in Scheme 3.17[10].

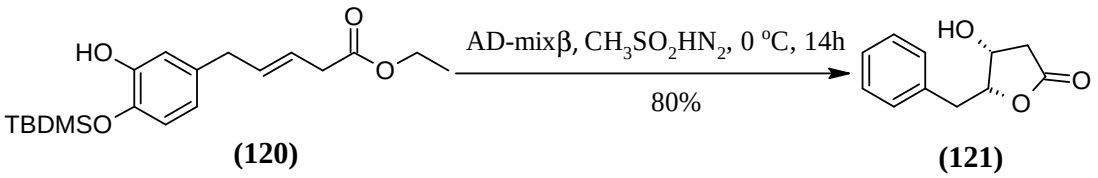


Scheme 3.17. Mechanism for the formation of β,γ-unsaturated acid isomer in Knoevenagel condensation

Having made the β,γ-unsaturated acid **(115)**, it was converted into the corresponding ester, **116**. The treatment of acid, **115** with $BF_3.OEt_2$ in methanol under standard conditions lead to the compound **116**. The ^1H NMR was used to confirm the formation of the product which had two singlets each integrating to three at δ_H 3.71 and 3.90 corresponding to the two methoxy groups (Plate 22a).

This was then followed by the reduction of the ester group to the corresponding alcohol **117**. The reduction of the ester **(116)** to the alcohol **(117)** was necessary since this would

be followed by the asymmetric dihydroxyation of the double bonds. If the dihydroxyation was carried out on **116**, the corresponding lactone would result. Sabitha *et al.*[12] formed the lactone **(121)** by the dihydroxyation of **120**, which is similar in structure to compound **116** (Scheme 3.18).



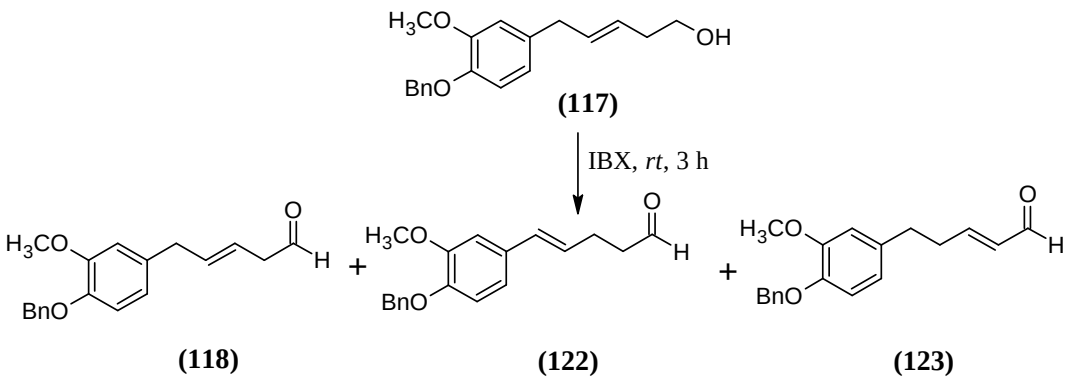
(120) **(121)**

Scheme 3.18. Asymmetric dihydroxylation

The ^{1}H NMR spectrum (Plate 23a) of compound **117** had a quartet at δ_H 2.32 and a triplet at δ_H 3.67 which distinguishes it from the ^{1}H NMR spectrum (Plate 22a) of compound **116**. As expected, the singlet corresponding to the COOC**H$_3$** group, on the ^{1}H NMR spectrum of **116** was not seen on the ^{1}H NMR spectrum of compound **117**.

Having the required alcohol in hand, we attempted to oxidize the alcohol **(117)** to the subsequent aldehyde **(118)** using 2-iodoxybenzoic acid. However, we were not able to obtain the required aldehyde **118** as the sole product of the reaction, instead a mixture of products was isolated. Scheme 3.19 outlines the products obtained in this reaction. The plausible explanation for this outcome is the movement of the double bond to form the more stable conjugated systems. The carbon-carbon double bond of compound **118** is not conjugated to either the phenyl group or the carbonyl group but in compound **122** and **123** the double bond is conjugated to the phenyl group and the carbonyl group respectively, thus making them more stable. Under acidic conditions, carbon carbon double bonds have a tendency to migrate to a more conjugated position. The acidity of this reaction can be attributed to the oxidizing agent, 2-iodoxybenzoic acid. Gallen *et al.*[13] investigated the acidity of 2-iodoxybenzoic acid in different solvents and it was found that 2-iodoxybenzoic acid has a pKa value of 2.4 in water and 6.65 in DMSO. Since DMSO was the solvent used for dissolving the 2-iodoxybenzoic aicd for the reaction, the reaction conditions would be slightly acidic. This would favour the movement of the carbon-carbon double bond to the conjugated positions. The three products obtained had the same R_f value as one would expect but the ^{1}H NMR spectrum of the mixture confirmed the presence of the three compounds since it had three distinguishing peaks corresponding to

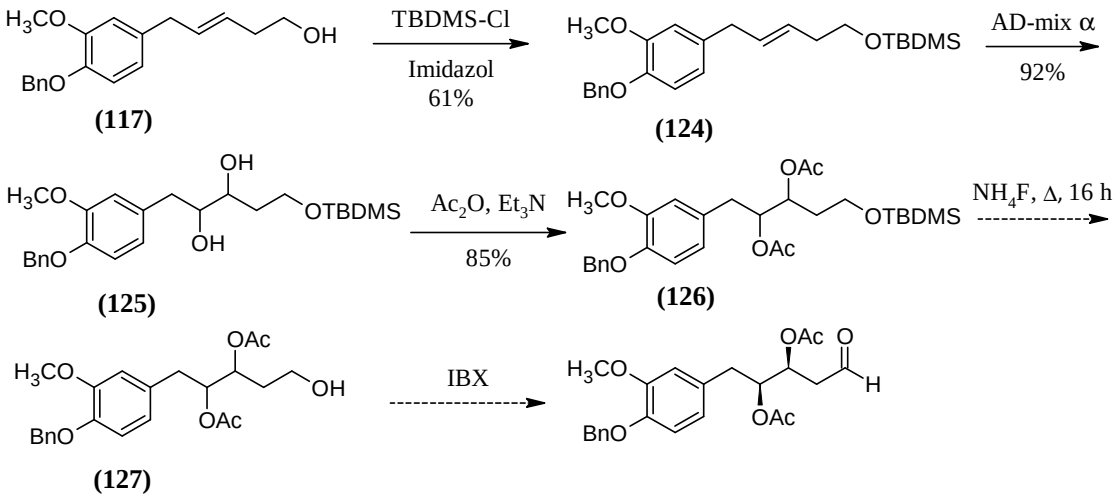
the three different aldehyde proton at δ_H 9.70, 9.83 and 9.78. In addition to this, mass spectral analysis of the mixture gave a single mass of $[M + Na]^+$ equal to 319.1311 m/z, since all three compounds formed would have the same molecular mass. This confirms that the products that were formed in this reaction were in accordance to Scheme 3.19.



Scheme 3.19. Carbon-carbon double bond movement

3.4.2.1 Modification of C_5-moiety

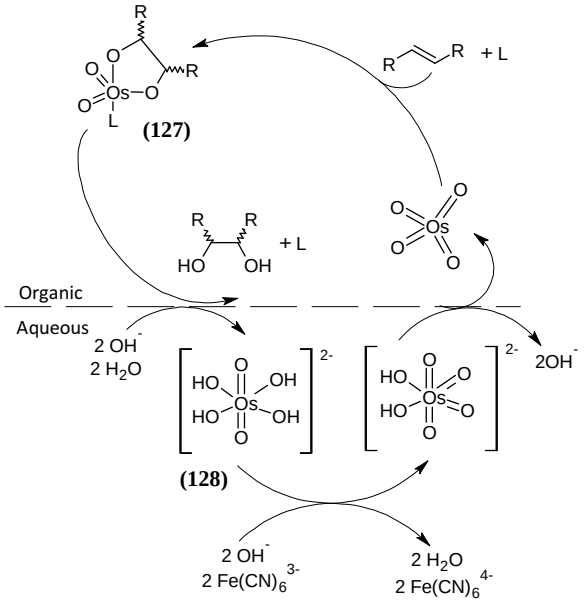
Having failed the successful oxidation of compound **117** to form **118** as the sole product, we had to modify our synthetic route, for the synthesis of C_5-moiety **(88)**. The new synthetic route that was put forth is shown in Scheme 3.20. In this synthetic route the terminal hydroxy group of compound **117** would be protected as the silyl ether prior to the osmium catalysed dihydroxyation of the double bond. This is necessary for the chemoselective acetylation of the resulting two hydroxy groups, which follows the dihydroxyation.



Scheme 3.20. Synthetic route 2

Compound **124** was synthesised in 65% yield using TBDMS-Cl and imidazol as the base. TBDMS was chosen for the protection of the free hydroxy group because it removal should not affect the acetyl protecting groups which would be introduced in the following synthetic steps. The ^{1}H NMR spectrum (Plate 24a) of compound **125** had two singlets at δ_H 0.06 and at 0.92, integrating to six protons and nine protons, respectively. These two peaks are characteristic of the silyl ether protecting group.

Having successfully protected the terminal hydroxy group of compound **124**, the next step was the osmium catalysed asymmetric dihydroxyation. Osmium catalysed asymmetric dihydroxyation (AD) provides a path to induce chirality in olefins[14]. The reagent used for this reaction was AD-mix α, which is a premix consisting of OsO_4, a chiral ligand dihydroquinine (DHQ), phthalazine (PHAL) and $K_3Fe(CN)_6$ complex which acts as a co-oxident in the reaction[14]. The stereochemistry of the product obtained in this reaction depends on the type of chiral ligand that is used. Scheme 3.21 outlines the catalytic cycle proposed for the AD reaction. As can be seen from Scheme 3.21, OsO_4 acts as the oxidant in the reaction and forms complex **127** which then undergoes hydrolysis, releasing the *syn*-diol and ligand to the organic layer. The hydrolysed osmium complex **128** is oxidised back to OsO_4 in the aqueous layer.



Scheme 3.21. Catalytic cycle for asymmetric dihydroxylation

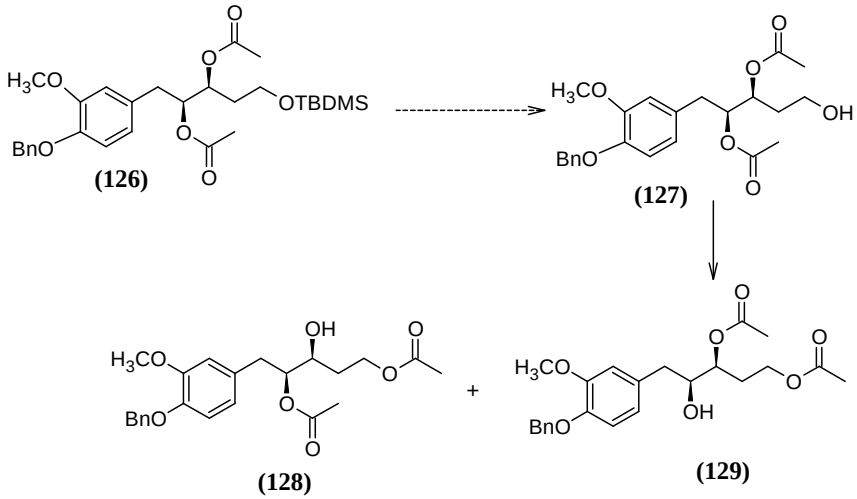
Compound **125** was obtained in an excellent yield of 92% by utilizing the AD reaction. The presence of compound **125** was confirmed by ^{1}H NMR spectroscopy (Plate 25a) which showed a multiplet at δ_H 2.72-2.89 corresponding to the C**H**(OH)C**H**(OH) signals. Furthermore the aliphatic proton signals of compound **125** are further upfield as compared with that of compound **124**, due to the introduction of electron-donating hydroxy groups.

As mentioned previously, the stereochemistry resulting from the AD reaction is dependent on the ligand that is used. According to Kolb *et al.*, AD-mix α, leads to the *R,R*-stereoisomer, whereas AD-mix β leads to the *S,S*-stereoisomer, when a *trans*-alkene is dihydroxylated[14]. In AD-mix β the chiral ligand used is dihydroquinidine (DHQD) whereas in AD-mix α DHQ. Kamal *et al.* utilised AD-mix α to obtain the *S,S*-stereoisomer in 92% enantiomeric excess[15]. We utilised a chiral shift reagent to determine the *ee* value of the dihydroxylation reaction. A chiral shift reagent (EuFOD) was added to **125** in $CDCl_3$ and an ^{1}H NMR spectrum was obtained. From the ^{1}H NMR spectra (Plate 25c), two peaks of approximately equal intensity was observed for the C**H$_3$**-Si protons, indicating the presence of a racemic mixture. Kamal and co-workers carried out the AD reaction at 0 °C but our reaction was done at room temperature. Thus the difference in reaction conditions may have lead to the difference in the enantioselectivity. Since the main target of the

investigation, at this point was to establish a synthetic route to the diarylheptanoid **17**, we did not do any further investigations on the enantioselectivity of the reaction.

The next step of the synthesis was the protection of the two hydroxy groups of compound **125** as acetate esters to form compound **126**. The ^{1}H NMR spectrum (Plate 26a) of **126** showed two singlets at δ_H 2.01 and 2.12 which corresponds to the acetate protecting groups. In addition to this, the mutiplet for C**H**(Ac)C**H**(Ac) signals moved downfield by 0.19, due to the introduction of the electron-withdrawing etser groups.

Having compound **126** in hand, we attempted to remove the silyl ether protecting group of compound **126** to form compound **127**. Ammonium fluoride, which is an effective silyl cleavage agent, was used for this reaction. Firstly the reaction was carried out at room temperature by stirring **126** in MeOH in the presence of NH_4F. This reaction did not lead to the deprotection of the silly group upon stirring for 24 h. However, when **126** was refluxed in MeOH in the presence of NH_4F, the silyl group was cleaved. However, a mixture of products was formed in this reaction due to the migration of the acetyl group to the terminal hydroxy group (Scheme 3.22). Since compound **128** and **129** formed in the reaction had the same R_f values on a TLC plate, we were not able to isolate and purify the products formed. However, the ^{1}H NMR and COSY spectra of the mixture of products confirmed the formation compounds **128** and **129**. Due to the time limitation, we did not investigate other deprotecting reagents and their effects on the acetyl protecting groups.

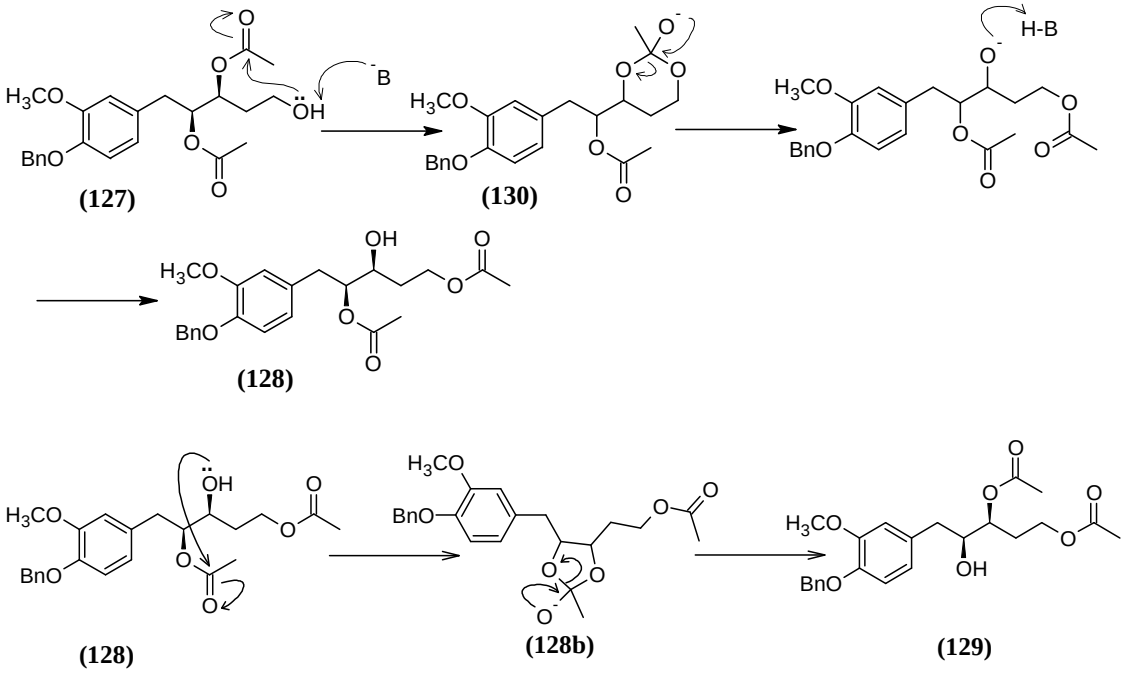


Scheme 3.22. Removal of the silyl protecting groups*

* Stereochemistry indicators only indicate relative configuration

Intramolecular acetyl migration can be either base or acid catalysed. In this case the fluoride ions are basic and thus catalyses the reaction. The mechanistic detail of acetate ester migration provides a reasonable explanation for the results obtained. Scheme 3.23 shows the possible mechanism by which the acetate migration might have occurred. The intramolecular attack of the terminal alcohol on the carbonyl carbon of the acetyl group on the C-3 position leads to a six-membered ring intermediate **(130)** which is thermodynamically stable. The formation of a stable intermediate would in turn favour the formation of compound **128**.

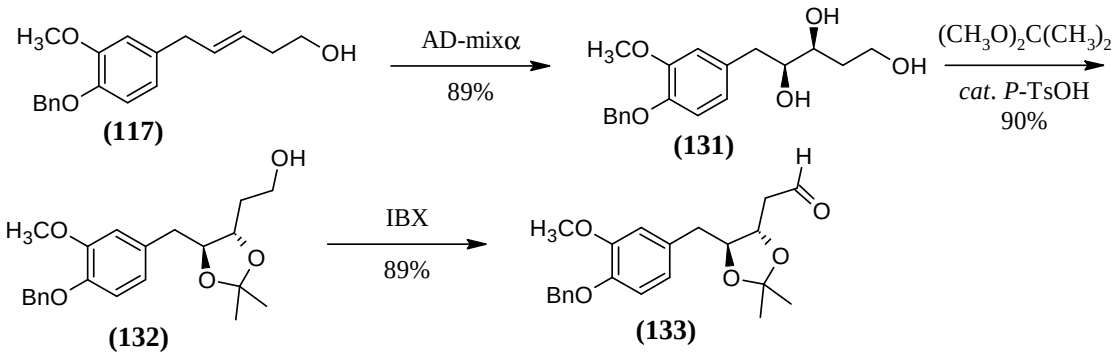
Once compound **128** is formed, the Ac group on the C-2 carbon of compound **128** migrates to form compound **129** as shown in Scheme 3.33.The stable five membered ring intermediate **(128b)**, formed in this reaction would favour the formation of compound **129**.



Scheme 3.23. Acetyl migration to form compound **128** and **129**

Having failed to deprotect the silyl group successfully to form the required alcohol, **127**, protective group tuning had to be done. We decided to change the acetyl protecting groups to the acetonide. Acetonide formation is a commonly used protection for 1,2-diols. The

new synthetic route for the synthesis of the modified C_5-moiety **(133)** is shown in Scheme 3.24. Compound **117** was subjected to the AD-reaction to form the triol **131**. The reaction gave a good yield of 89%. The peak on the ^{1}H NMR spectrum of compound **131**, which had a significantly different chemical shift from that of compound **117**, was the multiplet at δ_H 5.46-5.55 (Plate 28a). This multiplet corresponds to the protons on the same carbon as the two tertiary alcohol groups. The peaks which resulted from the CH=CH group, for compound **117** were not seen on the ^{1}H NMR spectrum of compound **131**, thus confirming the formation of compound **131**.



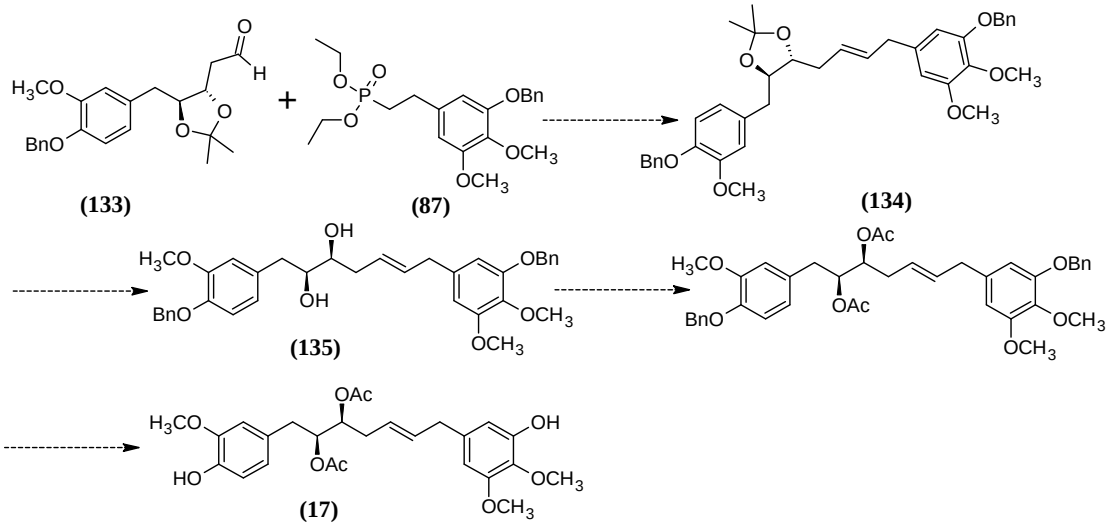
Scheme 3.24. Synthetic route 3

Compound **131** was then exposed to 2,2-dimethoxy propane in the presence of catalytic PTSA to form compound **132** in 90% yield. Only one regioisomer forms in this reaction. Three different rings can form: a seven-membered ring, a six membered ring or a five membered ring. As was reported by other workers in carbohydrate chemistry, the five-membered dioxolane is formed exclusively. Formation of compound **132** was confirmed using ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of compound **132** had two singlets at δ_H 1.34 and 1.37, integrating for three protons each, which correspond to the two methyl groups of the acetonide (Plate 29a).

Having successfully synthesised alcohol **132**, the next step was to oxidise compound **132** to the subsequent aldehyde, **133**. IBX was utilised for the oxidation reaction. This reaction proceeded in an excellent yield of 89% to form the required compound **133**. The ^{1}H NMR spectrum of compound **133** had the characteristic aldehyde proton peak at δ_H 9.71 (Plate 30a).

3.5 Attempted Coupling of C_2-moiety and C_5-moiety

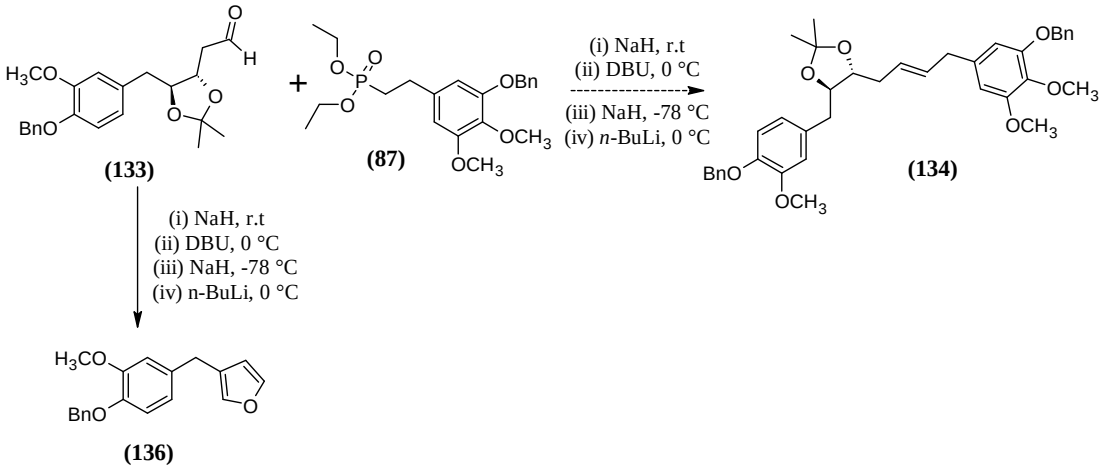
Upon the successful synthesis of the required C_2-moiety **(87)** and the C_5-moiety **(133)**, we attempted to couple compound **87** and **133** using the HWE reaction to form the required diarylheptanoid **(17)**. Scheme 3.25, outlines the proposed synthetic strategy for the synthesis of **17**. The first reaction would be the HWE reaction in which an *E*-alkene bond is formed between the C_2-moiety **(87)** and the C_5-moiety **(133)**, to form the seven carbon aliphatic chain. Then we planned on deprotecting the acetoxy ether group to form compound **135.** The secondary hydroxy groups would then be protected as the acetate ester using Ac_2O to form compound **136**. The last step would be the deprotection of the benzyl ether groups on the two phenyl rings to form the targeted diarylheptanoid **(17)**.



Scheme 3.25. Proposed synthetic route for diarylheptanoid, **17**

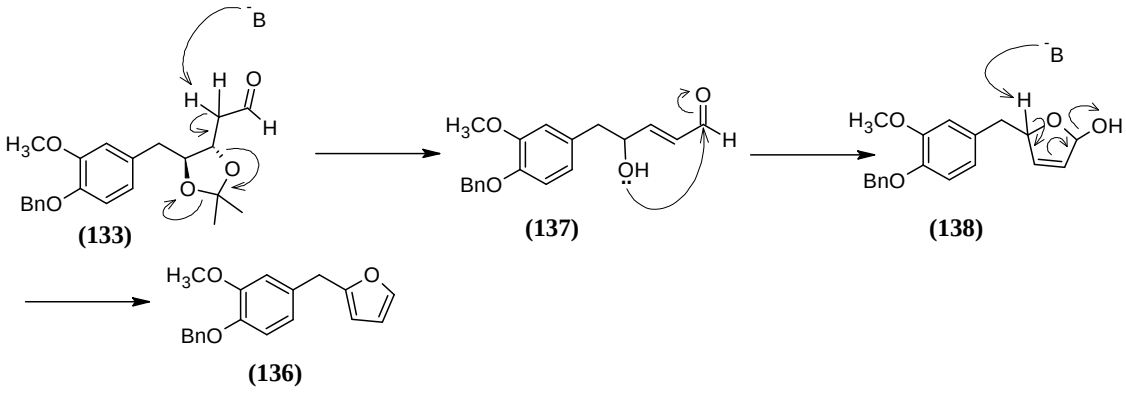
We commenced the above synthetic strategy with the HWE reaction. Unfortunately the required compound **134** was not obtained but it was seen that compound **133** underwent β-elimination to form compound **136** under the HWE reaction conditions (Scheme 3.26). Thus we altered the reaction conditions and utilised different bases for the reaction in order to prevent the rearrangement of **133**. Scheme 3.25 outlines the different reaction conditions that were tested. The rearrangement of compound **133** to form **136** was seen under all the reaction conditions and occurred within 15 to 20 min under the reaction conditions used,

implying that the decomposition reaction was more kinetically favoured than the HW reaction.



Scheme 3.26: Attempted coupling of the C_2-moiety and C_5-moiety using HWE reaction

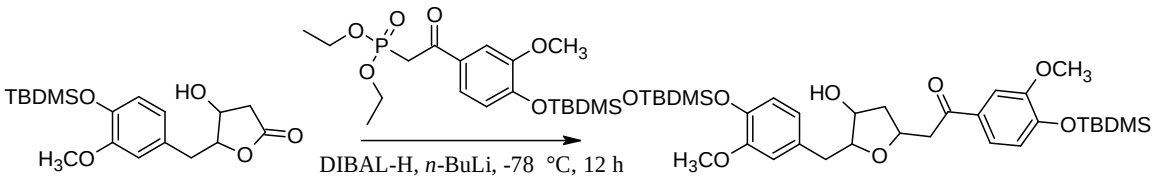
The structure of compound **136** was confirmed using ^{1}H NMR and COSY spectra. The depicted mechanism for β-elimination of compound **133** is shown in Scheme 3.27. Firstly, the acidic proton of compound **133** is abstracted by the base leading to the cleavage of the acetonide protecting group. This leads to the formation of intermediate **137**. Then intermediate **137** undergoes an intramolecular nucleophilic reaction, in which the nucelophilic hydroxy group attacks the electrophilic carbonyl carbon leading to the formation of intermediate **138**. Finally, removal of the acidic proton in intermediate **137**, leads to the formation compound **136**.



Scheme 3.27. Proposed mechanism for the formation of compound **136**

3.5.1 HWE reaction utilising a lactol as the C_5-moiety

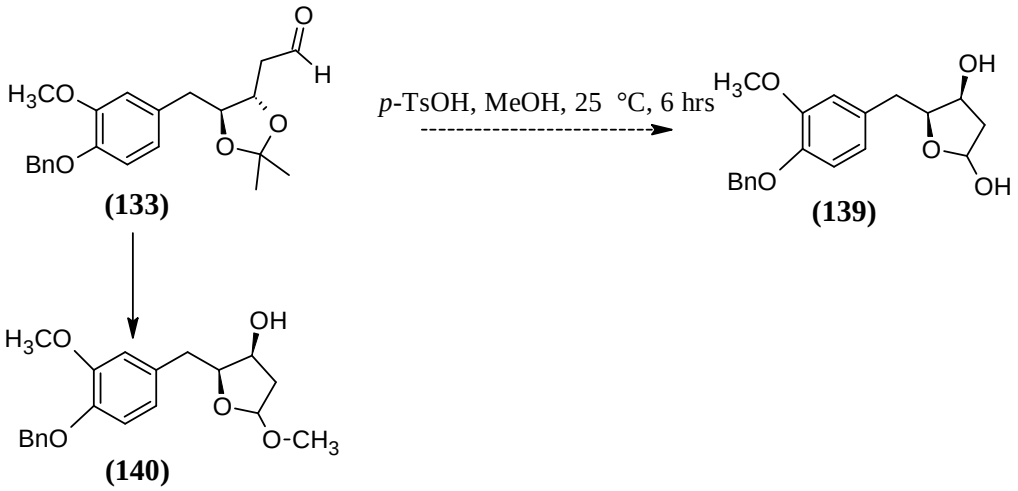
Having failed to successfully couple the C_2-moiety **(87)** and C_5-moiety **(133)** *via* HWE reaction, we decided to convert the C_5-moiety **(133)** into the corresponding lactol **(139)**. In the total synthesis of renealtins A and B, Sabitha *et al.*[12] used HWE reaction to couple the precursors to obtain the required product. In their synthesis, firstly the lactone was synthesised which was then converted to the subsequent lactol in-situ. Scheme 3.28 outlines the synthesis followed by them. Sabitha *et al.*[12] reported that the reaction proceeded in a 60% yield over two steps.



Scheme 3.28. HWE reaction of a lactol

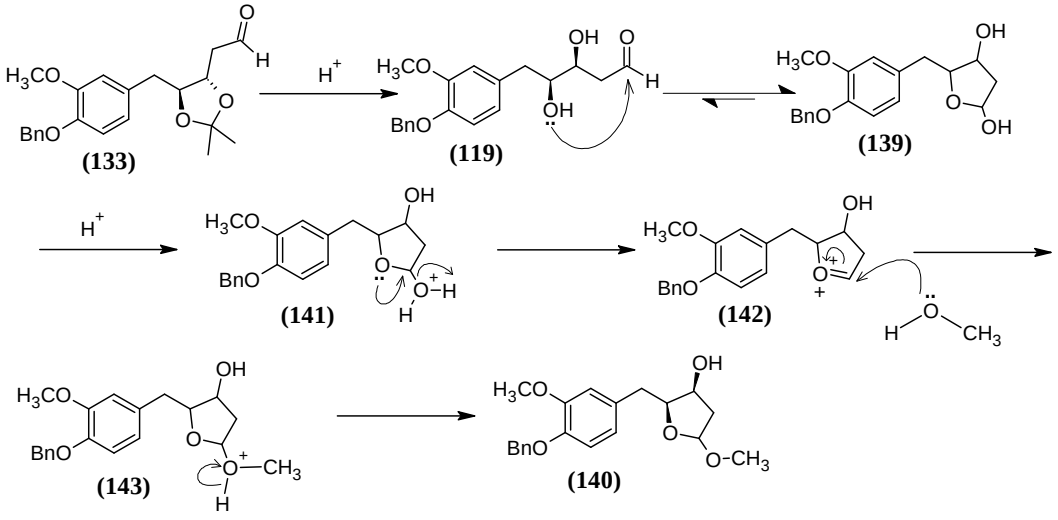
Scheme 3.29 outlines the reaction conditions under which the conversion of compound **133** to the lactol **139** was firstly attempted. The formation of lactol **139** from compound **133** is a one-pot reaction. Under the acidic conditions the acetonide protecting group cleaves leading to the formation of compound **119**. The nucleophilic hydroxy group on the C-2 carbon of compound **119** attacks the electophilic carbonyl carbon to form the lactol **139** as shown in Scheme 3.30.

The acetonide protecting group of compound **133** was removed under acidic conditions using MeOH as the solvent. The reaction took approximately 6 hrs to go to completion. On analysis of the product obtained from this reaction using ^{1}H NMR it was found that the required lactol **139** did not form, instead compound **140** was isolated. Formation of compound **140** was confirmed by ^{1}H NMR, COSY and ^{13}C NMR spectra.



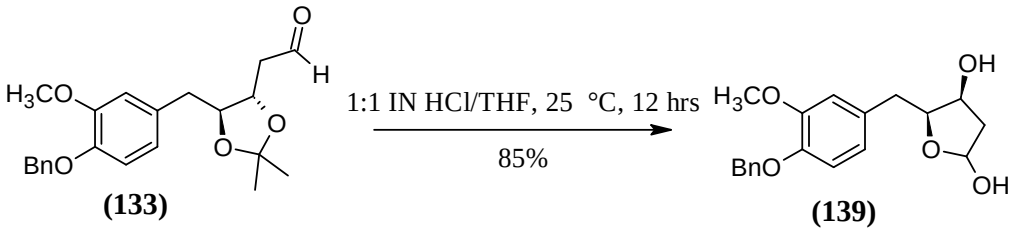
Scheme 3.29. Formation of acetal **140**

Scheme 3.30 outlines the mechanism by which compound **140** was formed. Firstly, Compound **119** undergoes intramolecular nucleophilic reaction to form the hemiacetal **139**. This reaction is in equilibrium but the position of the equilibrium lies almost completely on the side of the hemiacetal. Thus the amount of open chain hydroxy-aldehyde **(119)** is negligible. Under acidic conditions hemiacetals undergo reactions with alcohols such as MeOH to form acetals. The OH group of compound **139** is protonated by the acid in the reaction medium forming intermediate **141**, which looses a water molecule to form **142**. Intermediate **142** is attacked by the nucleophilic OH group of MeOH to form compound **143** and is then deprotonated to form the acetal **140**.



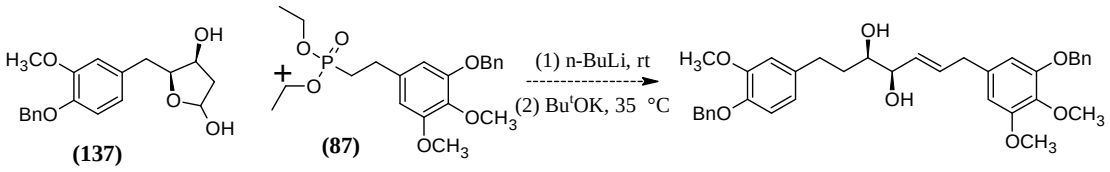
Scheme 3.30. Mechanism for the formation of compound **140**[16]

Having failed to synthesise the lactol **139** using MeOH as the solvent, we decided to change the solvent for the reaction. We have to use a non-nucleophilic solvent, in order to prevent the formation of the acetal. A method used by Angyal *et al.*[17] for the deprotection of an acetonide utilises a 1:1 aq. HCl/THF. We then decided to use this solvent system for the deprotection. Using this reaction condition the required compound **139** was obtained in 85% yield (Scheme 3.31). The formation of lactol **139** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy (Plate 31a and 31b).



Scheme 3.31. Synthesis of compound **139**

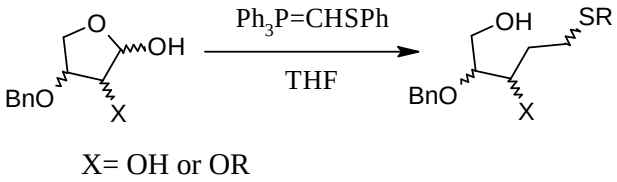
Having successfully synthesised compound **139**, we attempted the HWE reaction with the lactol as shown in Scheme 3.32. Several attempts to couple compound **139** and **87** using HWE reaction failed to yield the required product. Instead a complex mixture of products was isolated each time. As mentioned previously, similar Wittig-type reactions have been carried out successfully on sugar lactols[18-20].



Scheme 3.32. HWE reaction utilising the lactol as the C_5-moiety

Aucagne *et al.*[21] used the Wittig reaction to couple phenylthiomethylidine phosphorane with a variety of sugars, as shown in Scheme 3.33. They reported that pyrano- or furano-lactols containing one or more hydroxy groups did not react with the Wittig ylide. Instead mixtures of products were obtained. Upon protection of the free hydroxy groups as benzyl ethers, the reaction proceeded in good yield. Thus, Aucagne and co-workers came to the

conclusion that the protecting groups were crtitical for the Wittig reaction[21]. In contrast, other authors were able to obtain the Wittig product in the presence of one free hydroxy group on the lactol[20].



X= OH or OR

Scheme 3.33. HWE reaction of a lactol

Based on the observations made by Aucagne *et al.*[21], the protection of the free hydroxy groups on compound **139** may lead to the successful coupling of the lactol **(139)** and phosphonate ester **(87)** to form the required seven-carbon aliphatic chain.

Although a similar phosphonate was used successfully in a model HWE reaction (Section 3.2.2, Scheme 3.8) it seems that the reaction conditions required for the HWE reaction using a phosphonate ylide which is not stabilised by a second electron-withdrawing group, are too harsh for the lactol **139**. Harcken and Martin report that the basic HWE reactions conditions often lead to racemisation or cyclisation of the initially formed hydroxyenoates in sugar lactols[19].

At this point, it was clear that a Wittig-type reaction is not suitable for the formation of the *trans*-double bond. Thus a different approach will need to be considered. However, due to the time constraints, these methods were not investigated in this study.

3.6 Conclusion

In conclusion, diarylheptanoids are biologically active molecules which exist in minute quantities in some plant species. Owing to their interesting biological activities, the total synthesis of these compounds which could provide an alternative source to these biologically active compounds, have been investigated extensively. In this work, we investigated the total synthesis of a novel diarylheptanoid **17**, which was isolated from the

African medicinal plant *Siphonochilus aethiopicus.* The synthetic strategy used in this research was the C_2-moiety + C_5-moiety strategy.

Since the targeted diarylheptanoid **17**, contains a *trans*-carbon-carbon double bond, a stereoselective olefination reaction was chosen for the coupling of the two moieties. Thus *trans*-selective HWE reaction, which is a variant of the Wittig olefination was studied. The C_2-moiety which is the Horner phosphate and the C_5-moiety, were both synthesised from commercially available starting materials by using simple functional group transformation reactions. However, we were unable to couple the two moieties to form the required seven-carbon aliphatic chain using the HWE reactions. When the C_5-moiety was an aldehyde, it was seen that it readily decomposed under the HWE reaction condition. Thus the C_5-moiety was converted into the corresponding lactol which was then subjected to the HWE reaction. Even with this modification we were not able to successfully couple the two moieties. The reason for the failure encountered with the HWE reaction with the lactol may be due to the free hydroxy groups on the lactol. Thus protection of these free hydroxy groups may lead to the successful synthesis of the *trans*-seven-carbon aliphatic chain.

Even though the synthesis of the targeted diarylheptanoid **17** was not achieved in this investigation, we have made valuable progress towards the total synthesis of this compound:

- A suitably substituted phenylethyl precursor was prepared for the C_2-moiety + C_5-moiety coupling strategy. Although the phosphonate derivative was not useful for the synthesis of the diarylheptanoid **17**, it may be useful for the preparation of other natural products.
- Phenylethyl derivatives with the correct substitution pattern and relative stereochemistry were prepared as the C_5-component of the synthetic strategy.

3.7 Future Work

Since the target compound was not successfully synthesised, there is scope for future work in this area. Most importantly, a method needs to be developed which could successfully couple the precursors to form the *trans*-carbon-carbon double bond on the aliphatic chain

of the target compound **(17)**. Thus further investigation needs to be done on the HWE reaction in order to find suitable reaction conditions which would favour the formation of the *E*-alkene. For example, the effect of protecting the free hydroxy groups of compound **137**, on the HWE reaction needs to be investigated. In addition to this, the synthetic methodology developed during this investigation needs to be optimized. This includes optimizing the enantioselectivity of the dihydroxyation reaction.

Other options which must be considered for the formation of the double bond are the Julia olefination and its variants and also metathesis with a Grubb's catalyst.

Upon the successful synthesis of the novel diarylheptanoid **17**, its analogues need to be synthesised. This is important in order to study the possible anti-inflammatory activity of this class of compounds.

3.8 References

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4 Experimental procedures

4.1 General experimental procedure

4.1.1 Chromatography

Thin-layer chromatography was performed on aluminium-backed 0.2 mm silica gel plates (Merck Silica gel 60 F_{254}). Normal and flash chromatography were done using Merck Kieselgel 60 silica with particle size 200-400 mm and on columns varying from 1 cm to 6 cm in diameter. Centrifugal chromatography was performed on a Harrison Research Chromatotram, on glass plates coated with 2 or 4 mm Merck silica gel 60 with particle size 0.040-0.063 mm.

4.1.2 Spectroscopic and Physical Data

All melting points were obtained on a Reichert hot-stage microscope.

Nuclear magnetic resonance spectroscopy (NMR) of the isolated compounds was done on a Bruker Avance lll 400 MHz spectrometer. All NMR spectra were recorded at 30 $^{\circ}$C in deuterated solvents and chemical shifts were recorded in ppm referenced to the solvent shift.

Mass spectra were obtained using a Waters LCT Premier mass spectrometer using positive or negative electroscopy ionization (high resolution) and or a ThermoFinnigan Trace GC coupled to PolarisQ mass spectrometer (low resolution).

Infrared (IR) spectra were obtained using a Smiths FT-IR spectrometer.

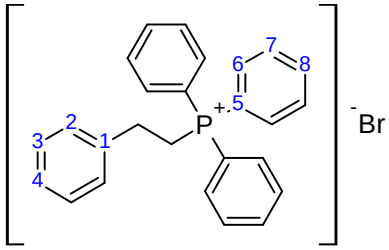
4.1.3 Solvents and chemicals

All the required chemicals were obtained from Fluka, Sigma-Aldrich or Merck and used without further purification unless otherwise specified.

Anhydrous solvents were obtained from a Pure-Solv Solvent Purification System supplied by Innovative Technology, Inc. Water and oxygen present in the solvent are removed effectively using this system to produce dry deoxygenated high-purity solvents by passing through activated columns under low pressure to remove trace impurities. Hexane used for column chromatography was distilled under reduced pressure prior to use. 'Hexane' refers to a commercial mixture of hexane isomers that was used for chromatography.

4.2 Synthetic Procedures

4.2.1 Phenylethyltriphenylphosphonium bromide (92)[1]



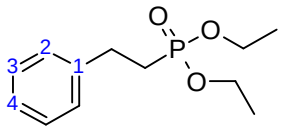
A solution of (2-bromoethyl)benzene (2.07 g, 11 mmol) and triphenylphosphine (3.08 g, 12 mmol) in anhydrous toluene (25 mL) was refluxed for 48 h. After cooling, the upper solvent layer was removed and the residue obtained was washed with toluene (2 x 10 mL) followed by ether (10 mL). The glassy solid obtained was dried under vacuum. The resulting phosphonium salt **(92)** was obtained as a hygroscopic, glassy compound (yield 4.95 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (2H, m, Ar-CH_2-C**H$_2$**-P), 4.22 (2H, m, Ar-C**H$_2$**-CH_2-P), 7.24 (5H, m, **H**-Ar-CH_2), 7.78 (15H, m, P-Ar-**H**). (*Plate 1a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 24.8 (Ar-**C**H_2-CH_2), 28.5 (d, J_{PC} = 3.6 Hz, Ar-CH_2-**C**H_2), 128.3 (C-5), 128.4 (C-4), 128.8 (d, J_{PC} = 16.7 Hz, C-3), 130.6 (d, J_{PC} = 12.6 Hz, C-7), 133.9 (d, J_{PC} = 9.9 Hz C-6), 135.1 (d, J_{PC} = 2.9 Hz, C-1). (*Plate 1b*)

^{31}P NMR δ_P (162 MHz, $CDCl_3$): 21.80

4.2.2 Diethyl 2-phenylethyphosphonate (97)[2]



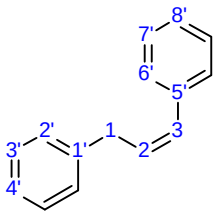
(2-Bromoethyl)benzene (5.0 mL, 37.0 mmol) and triethyl phosphite (8.3 mL, 48.0 mmol) in a 50 mL round-bottomed flask was refluxed vigorously for 16 h. The flask was then allowed to cool and the excess triethyl phosphite was removed by distillation under vacuum. The crude product obtained was purified using column chromatography to yield the diethyl 2-phenylethyphosphonate **(97)** as a yellow oil (yield 8.50 g, 98 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.30 (t, 6H, C**H**$_3$-CH_2-O), 1.94-2.14 (m, 2H, Ar-C**H**$_2$-CH_2), 2.80-3.02 (m, 2H, Ar-CH_2-C**H**$_2$), 4.15 (q, 4H, O-C**H**$_2$-CH_3), 7.10-7.40 (m, 5H, Ar-**H**). (*Plate 2a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 16.4 (d, J_{PC} = 5.9, Hz, $POCH_2$**C**H_3), 27.6 (d, J_{PC} = 139.7 Hz, Ph-CH_2**C**H_2P), 28.6 (d, J_{PC} = 4.3 Hz, Ph-**C**H_2CH_2P), 61.7 (d, J_{PC} = 6.6 Hz, PO**C**H_2CH_3), 126.2 (C-4), 128.1 (C-2) 128.6 (C-3), 141.0 (d, J_{PC} = 17.5 Hz, C-1). (*Plate 2b*)

^{31}P NMR δ_P (162 MHz, $CDCl_3$): 30.74

4.2.3 (Z)-1,1-prop-1-ene-1,3-diyldibenzene (93)[3]

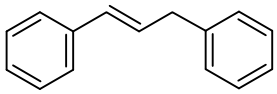


2-Phenylethyltriphenylphosphonium bromide **(92)** (1.00 g, 2.0 mmol) was suspended in tetrahydrofuran (10 mL) and ether (6 mL) and stirred with butyllithium (BuLi) (0.23 mL, 2.0 mmol) for 1 h at room temperature. The solution was cooled to -70 °C and benzaldehyde (0.26 mL, 2.3 mmol) was added, the mixture was stirred vigorously for 15 min. Then BuLi (0.23 mL, 2.0 mmol) was added again and the reaction mixture was kept at -30 °C for 15 min. The solution was then treated with ethereal hydrogen chloride (2.2 mmol) and potassium *t*-BuOH (0.3 g, 3.0 mmol). The mixture was stirred at room temperature for 16 h, centrifuged, and the clear supernatant liquor was poured off and solvent evaporated. The crude product so obtained was purified using column chromatography (9:1 hexane/EtOAc) to afford a yellowish oil containing both 1,3-diphenyl-1-propene (*E*) and (*Z*) isomers **(93)** (yield 0.302 g, 70%, *Z*:*E* = 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.72 (2H, d, 7.47 Hz, Ar-C**H$_2$**-CH=CH), 5.91 (1H, dt, 7.35Hz and 3.54Hz, Ar-CH_2-C**H**=CH), 6.63 (1H, d, *J*= 11.6Hz, Ar-CH_2-CH=C**H**), 7.27 (5H, m, CH=CH-Ar-**H**), 7.37 (5H, m, **H-**Ar-CH_2-CH). (*Plate 3a*)

^{13}C NMR (400 MHz, $CDCl_3$) δ_C: 34.7 (C-3), 126.1 (C-8'), 126.8 (C-2'), 128.3 (C-3'), 128.4 (C-7'), (C2'), 128.5 (C-5'),128.7 (C-4'), 130.0 (C-1), 130.7 (C-2), 137.3 (C-1'), 140.8 (C-5'). (*Plate 3b*)

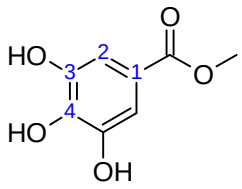
4.2.4 (*E*)-1,1-prop-1-ene-1,3-diyldibenzene (93)



To a stirred solution of diethyl 2-phenylethylphosphonate **(97)** (0.7 g, 2.7 mmol) in dry THF (10 mL) at 0 °C was added NaH (0.2 g, 7.7 mmol) in small portions. After the suspension has warmed to room temperature, benzyldehyde (2.57 mmol, 0.26 mL) was added all at once. The reaction was then refluxed until all the starting material was consumed (TLC monitoring). The reaction mixture was diluted with water and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The crude product was then purified using column chromatography (9:1 hexane/EtOAc) to afford (*E*)-1,1-prop-1-ene-1,3-diyldibenzene **(93)** as a yellow oil (yield 0.20 g, 41%,).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.70 (2H, d, 6.71 Hz, Ar-C**H$_2$**-CH), 6.48 (1H, dt, 6.58Hz and 2.53Hz, Ar-CH_2-C**H**=CH), 6.58 (1H, d, 15.8Hz, Ar-CH_2-CH=C**H)**, 7.27-7.51 (m, 10H, Ar-**H**). (*Plate 4a*)

4.2.5 Methyl 3,4,5-trihydroxybenzoate (99)[4]



3,4,5-Trihyhydroxybenzoic acid (20.0 g, 117.6 mmol) was dissolved in dry methanol and conc. H_2SO_4 (1.0 mL) was added. This mixture was refluxed for 24 h and the solvent evaporated to yield a white solid. This residue was dissolved in Et_2O (20 mL) and washed with saturated $NaHCO_3$ solution and brine. The resulting organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the desired product which was then recrystallized in water to yield the pure white crystalline solid of methyl 3,4,5-trihydroxybenzoate **(99)** (yield 19.5 g, 97%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.74 (s, 3H, CO_2,C**H**$_3$), 6.93 (s, 2H, Ar-**H**). (*Plate 5a*)

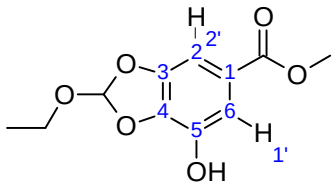
^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 52.0 (O**C**H$_3$), 109.0 (C-2), 119.8 (C-1), 138.9 (C-4), 146.0 (C-3), 166.8 (**C**OOCH$_3$). (*Plate 5b*)

MS (*m/z*): 183.90

IR ν_{max} (cm^{-1}): 3330 (OH), 1683 (C=O),

Melting point (H_2O): 183-184 $^{\circ}$C (lit.[5] 188-191 °C (MeOH))

4.2.6 Methyl 3-hydroxy-4,5-(ethoxymethylenedioxy)benzoate(100)[6]



A mixture of methyl 3,4,5-trihydroxybenzoate **(99)** (5.0 g, 20.8 mmol), triethyl orthoformate (6.0 g, 40.5 mmol) and Amberlyst 15E (0.6 g) in toluene was refluxed for 4 h with azeotropic removal of the EtOH/toluene mixture using a Dean-Stark trap. The reaction mixture was then filtered and concentrated *in vacuo*. Subsequent column chromatography (5:5 hexane/EtOAc) of the crude mixture yielded methyl 3-hydroxy-4,5-(ethoxymethylenedioxy)benzoate **(100)** as a white solid which was recrystalised from MeOH (yield 6.04 g, 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.17 (t, 3H, J = 7.3Hz, $OCH_2C\underline{\mathbf{H}}_3$), 3.70 (q, 2H, J = 7.1 Hz, $OC\underline{\mathbf{H}}_2CH_3$), 3.79 (s, 3H, $OC\underline{\mathbf{H}}_3$), 7.00 (d, 1H, J = 1.6 Hz, $H_{2'}$), 7.16 (s, 1H, $C\underline{\mathbf{H}}O_3CH_2CH_3$), 7.19 (d, 1H, J = 1.6 Hz, $H_{1'}$).

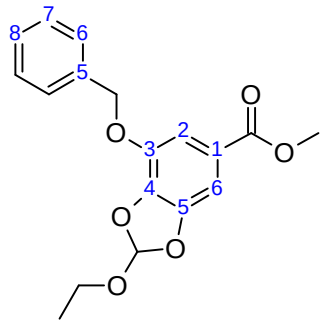
^{13}C NMR (100 MHz, DMSO-d_6) δ_C**:** 14.8($\underline{\mathbf{C}}H_3CH_2O$), 52.3 ($O\underline{\mathbf{C}}H_3$), 59.7 ($O\underline{\mathbf{C}}H_2CH_3$), 102.7(C-6), 113.9 ($\underline{\mathbf{C}}O_3CH_2$), 120.0 (C-1), 124.3(C-2), 137.1 (C-4), 138.8 (C-5), 147.2 (C-3), 166.7 ($\underline{\mathbf{C}}OOCH_3$).

MS (*m/z*): 240

IR ν_{max} (cm^{-1}): 3298 (OH), 1696 (C=O)

Melting point (MeOH): 73-74 °C (lit.[6] 91-92 °C)

4.2.7 Methyl 3-benzyloxy-4,5-(ethoxymethylenedioxy)benzoate (101)

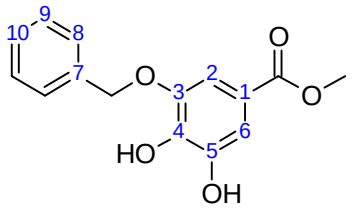


To a solution of methyl 3-hydroxy-4,5-(ethoxymethylenedioxy)benzoate **(100)** (6.3 g, 26.2 mmol) in MeCN (30 mL) was added potassium carbonate (6.8 g, 52.5 mmol) and benzyl bromide (6.8 g, 39.3 mmol). This mixture was stirred at 70-80 °C for 12 h. After completion of the reaction as determined by TLC monitoring, the reaction mixture was diluted with water and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The crude product was then purified using column chromatography (8:2 hexane/EtOAc) to yield methyl 3-benzyloxy-4,5-(ethoxymethylenedioxy)benzoate **(101)** as a orange oil (yield 6.8 g, 79%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.28 (t, 3H, *J*= 7.1 Hz, $OCH_2C\underline{\mathbf{H}}_3$), 3.73 (q, 2H, *J*= 7.3 Hz, $OC\underline{\mathbf{H}}_2CH_3$), 3.89 (s, 3H, $OC\underline{\mathbf{H}}_3$), 5.24 (s, 2H, $OC\underline{\mathbf{H}}_2$), 6.97 (s, 1H, $CO_3\underline{\mathbf{H}}CH_2$), 7.28 (s, 1H, H-6), 7.36-7.50 (m, 6H, Ar-**H** and H-2). (*Plate 6a*)

^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 14.8 ($\underline{\mathbf{C}}H_3CH_2O$), 52.3 ($O\underline{\mathbf{C}}H_3$), 59.7 ($O\underline{\mathbf{C}}H_2CH_3$), 71.1 ($O\underline{\mathbf{C}}H_2A_r$), 103.8 (C-6), 112.3 ($\underline{\mathbf{C}}O_3CH_2$), 120.1 (C-1), 124.4 (C-2), 127.7 (C-9), 128.2 (C-8), 128.6 (C-7), 136.6 (C-4), 138.6 (C-5), 147.4 (C-3), 166.4 ($\underline{\mathbf{C}}OOCH_3$).

4.2.8 Methyl 3-benzyloxy-4,5-dihydroxybenzoate (102)[6]



A 2N HCl (10 mL) solution was added dropwise to a solution of methyl 3-benzyloxy-4,5-(ethoxymethylenedioxy)benzoate **(101)** (5.5 g, 16.7 mmol) in MeOH (20 mL) over 10 min at room temperature. This mixture was then stirred for 2-3 h. The resulting white precipitate, methyl 3-benzyloxy-4,5-dihydroxybenzoate **(102)** was filtered and recrystalised from MeOH (yield 4.2 g, 93%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.74 (s, 3H, $CO_2C\underline{\mathbf{H}}_3$), 5.16 (s, 2H, $OC\underline{\mathbf{H}}_2$), 7.34 (s, 1H, H-6), 7.37 (s, 1H, H-2), 7.38-7.47 (m, 5H Ar-**H**). (*Plate 7a*)

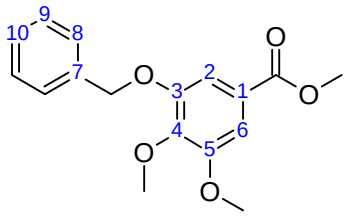
^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 52.0 ($O\underline{\mathbf{C}}H_3$), 71.6 ($O\underline{\mathbf{C}}H_2$), 106.2 (C-2), 111.2 (C-6), 121.9 (C-1), 128.1 (C-9), 128.7 (C-10), 128.8 (C-8) 135.8 (C-7), 137.1 (C-4) 143.6 (C-5), 145.6 (C-3), 166.8 ($\underline{\mathbf{C}}OOCH_3$). (*Plate 7b*)

MS (*m/z*): 274.10

IR ν_{max} (cm^{-1}): 3458 (OH)

Melting point (MeOH): 88-89 $^{\circ}$C

4.2.9 Methyl 3-benzyloxy-4,5-dimethoxybenzoate (103)



To a solution of methyl 3-benzyloxy-4,5-dihydroxybenzoate **(102)** (4.0 g, 14.5 mmol) in MeCN (20 mL) was added potassium carbonate (3.8 g, 29.2 mmol) and methyl iodide (5.1 g, 36.3 mmol). This mixture was stirred at 70-80 °C for 12 h. After completion of the reaction as observed by TLC monitoring, the reaction mixture was diluted with water and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The crude product was then purified using column chromatography (8:2 hexane/EtOAc) to yield methyl 3-benzyloxy-4,5-dimethoxybenzoate **(103)** as a white solid (yield 4.0 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.91 (s, 3H, OC**H**$_3$), 3.92(s, 3H, OC**H**$_3$), 3.94(s, 3H, CO_2C**H**$_3$), 5.17 (s, 2H, OC**H**$_2$), 7.32-7.48 (m, 6H, Ar-**H**). (*Plate 8a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C**:** 52.2(O**C**H$_3$), 56.3(O**C**H$_3$), 60.9(O**C**H$_3$), 71.3(O**C**H$_2$), 107.2 (C-6), 109.0 (C-2), 125.0(C-1), 127.4 (C-9), 128.0 (C-10), 128.6 (C-8), 136.7(C-7), 143.0 (C-4), 152.1 (C-3), 153.2 (C-5), 166.7(**C**OOCH$_3$). (*Plate 8b*)

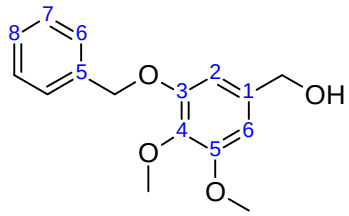
ER$^+$-HRMS *m/z* $[M + Na]^+$: 325.1049

(Calculated for $C_{17}H_{18}O_5$+Na, 325.1052)

IR ν_{max} (cm^{-1}): 1711 (C=O)

Melting point (H_2O): 59-58°C

4.2.10 3-Benzyloxy-4,5-dimethoxyphenylmethanol (104)



A solution of 3-benzyloxy-4,5-dimethoxybenzoate **(103)** (3.8 g, 12.5 mmol) in dry THF (10 mL) was added dropwise to a stirred solution of $LiAlH_4$ (0.5 g, 12.5 mmol) in dry THF (10 mL) at 0 °C under N_2 atmosphere. This mixture was then stirred at room temperature until the reaction was complete (2-3 h, TLC monitoring). The excess hydride was quenched with H_2O followed by aqueous (10%) H_2SO_4 (10 mL). This mixture was then extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using column chromatography (5:5 hexane/EtOAc) to afford 3-benzyloxy-4,5-dimethoxyphenylmethanol **(104)** as a colourless oil (yield 2.9 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.84 (s, 3H, OC**H**$_3$), 3.87 (s, 3H, OC**H**$_3$), 4.56 (s, 2H, C**H**$_2$OH), 5.11 (s, 2H, OC**H**$_2$), 6.59 (s, 1H, H-6), 6.63 (s, 1H, H-2), 7.29-7.46 (m, 5H, Ar-**H**). (*Plate 9a*)

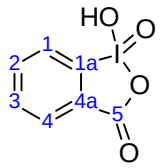
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 56.1 (O**C**H$_3$), 60.9 (O**C**H$_3$), 65.2 (**C**H$_2$OH), 71.2 (O**C**H$_2$), 104.3 (C-6), 106.1 (C-2), 127.3 (C-9), 127.9 (C-10), 128.9 (C-8), 136.7 (C-1), 137.1 (C-7), 138.0(C-4), 152.5 (C-3), 153.0 (C-5). (*Plate 9b*)

ER$^+$-HRMS *m/z:* 297.1077 $[M + Na]^+$

(calculated for $C_{16}H_{18}O_4$+Na, 297.1078)

IR ν_{max} (cm^{-1})**:** 3404 (OH), 1593 (C=O)

4.2.11 2-Iodoxybenzoic acid (IBX)[7]

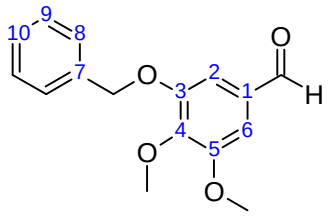


$KBrO_3$ (8.0 g, 48 mmol) was dissolved in H_2SO_4 (2 M, 76 mL) in a two-necked round bottom flask equipped with a magnetic stirrer bar, reflux condenser and thermometer. The clear solution was heated to 60 °C and *o*-iodobenzoic acid (8.00 g, 32 mmol) was added over 40 min in small (0.5 g) portions. The mixture became a bright orange colour as Br_2 gas was evolved and a white precipitate formed. After the addition was complete, the temperature was maintained at 65 °C for 3 h. The solution was then cooled in an ice bath and the solid material was collected by vacuum filtration with a Buchner funnel and flask. The white precipitate was washed with cold H_2O (1000 mL), cold EtOH (1000 mL) followed by cold water (1000 mL). The IBX was air dried and weighed (yield 8.2 g, 29 mmol, 91%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 7.83 (1H, *t*, *J* = 8.3 Hz, H-3), 7.98 (1H, *t*, *J* = 8.3 Hz, H-2), 8.02 (1H, *d*, *J* = 12.8 Hz, H-4), 8.14 (1H, *d*, *J* = 12.8 Hz, H-1).

^{13}C NMR (400 MHz, DMSO-d_6) δ_C: 125.5 (C-1), 130.6 (C-4), 131.6 (C-4a), 133.5 (C-3), 134.9 (C-2), 147.0 (C-1a), 168.0 (C-5).

4.2.12 3-Benzyloxy-4,5-dimethoxybenzaldehyde (105)[8]



To a stirred solution of 2-iodoxybenzoic acid (IBX) (3.0 g, 11.0 mmol) in DMSO (10 mL), was added a solution of the alcohol, 3-benzyloxy-4,5-dimethoxyphenylmethanol **(104)** (2.0 g, 7.4 mmol) in THF (20 mL) at room temperature and was stirred for 3 hours. After completion of the reaction as observed by TLC monitoring, water (10 mL) was added to the reaction mixture and the precipitated solid was filtered off. The filtrate was diluted with water (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed successively with $NaHCO_3$, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified using column chromatography (7:3 hexane/EtOAc) to afford the desired product, 3-benzyloxy-4,5-dimethoxybenzaldehyde **(105)** as a white solid (yield 1.99 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.94 (s, 3H, OC**H**$_3$), 3.98 (s, 3H, OC**H**$_3$), 5.20 (s, 2H, OC**H**$_2$), 7.16 (s, 1H, H-6), 7.19 (s, 1H, H-2), 7.33-7.48 (m, 5H, Ar-**H**), 9.84 (s, 1H, CO**H**). (*Plate 10a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 56.3 (O**C**H$_3$), 61.0 (O**C**H$_3$), 71.3 (O**C**H$_2$), 106.7 (C-6), 109.3 (C-2), 127.4 (C-9), 128.2 (C-10), 128.6 (C-8), 131.7 (C-1), 136.5 (C-7), 144.4 (C-4), 152.7 (C-3), 153.9 (C-5), 190.9 (**C**OH). (*Plate 10b*)

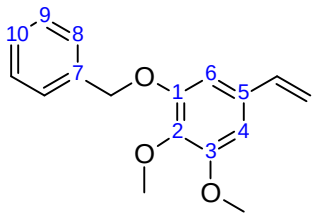
ER$^+$-HRMS *m/z*: 295. 0945 $[M + Na]^+$

(calculated for $C_{16}H_{16}O_4$+Na, 295.0946)

IR $\nu_{max}(cm^{-1})$: 1684 (C=O), 1110 (C-O)

Melting point (Et_2O): 56-57 °C

4.2.13 1-Benzyloxy-2,3-dimethoxy-5-vinylbenzene (106)[9]



NaH was added to a stirred suspension of the methyltriphenylphosphonium iodide (3.5 g, 8.8 mmol) in dry THF (20 mL) containing 3-(benzyloxy)-4,5-dimethoxybenzaldehyde **(105)** (1.9 g, 6.9 mmol). The suspension was stirred for 5 h at room temperature and was poured into ice water and extracted with Et_2O (3 x 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography (7:3 hexane/EtOAc) to afford the desired product**,** 1-benzyloxy-2,3-dimethoxy-5-vinylbenzene **(106)** as a yellow oil (yield 1.31 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.90 (s, 3H, OC**H**$_3$), 3.91 (s, 3H, OC**H**$_3$), 5.17 (s, 2H, OC**H**$_2$), 5.21 (d, 1H, *J*=10.8 Hz, CHC**H**$_2$), 5.63 (d, 1H, *J*=17.5 Hz, CHC**H**$_2$), 6.62 (dd, 2H, *J*=17.5 Hz, C**H**CH_2), 6.67 (s, 1H, H-6), 6.71 (s, 1H, H-4), 7.33-7.50 (m, 5H, Ar-**H**). (*Plate 11a*)

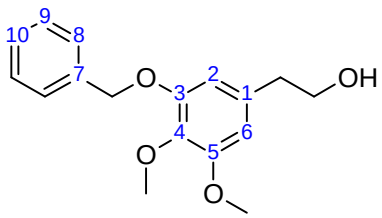
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 56.1 (O**C**H_3), 60.4 (O**C**H_3), 61.0, 71.3 (O**C**H_2-Ar), 103.8 (C-4), 105.9 (C-6), 113.2 (CH**C**H_2), 127.3 (C-9), 127.9 (C-10), 128.5 (C-8), 133.2 (C-5), 136.7 (C-7), 137.2 (**C**HCH_2), 138.9 (C-2), 1582.5 (C-1), 153.5 (C-3). (*Plate 11b*)

ER$^+$-HRMS *m/z*: 293.1158 $[M + Na]^+$

(Calculated for $C_{17}H_{18}O_3$+Na, 293.1154)

IR ν_{max} (cm^{-1}): 1579 (C=C), 1112 (C-O).

4.2.14 2-(3-Benzyloxy-4,5-dimethoxyphenyl)ethanol (107)[10]



A dry flask equipped with a magnetic stirrer bar and a reflux condenser was flushed with nitrogen and maintained under a positive nitrogen pressure. The flask was then charged with 1-benzyloxy-2,3-dimethoxy-5-vinylbenzene **(106)** (1.1 g, 3.4 mmol) in dry THF (20 mL) and cooled to 0 °C with an ice-water bath. This was followed by dropwise addition of a borane-methyl sulfide (BMS) (0.1 g, 1.3 mmol). The cooling bath was removed and the solution was stirred for 3 hours at room temperature. 3N NaOH (0.5 mL) was then added and the reaction cooled to 0°C. This was followed by dropwise addition of hydrogen peroxide (0.5 mL of 30% aqueous solution). The reaction mixture was refluxed for 1 h and was poured into ice water (20 mL). The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified using column chromatography (5:5 hexane/EtOAc) to afford the desired product, (3-benzyloxy-4,5-dimethoxyphenyl)ethanol **(107)** as a yellow oil (yield 0.63 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.78 (t, 2H, 6.50Hz, C**H$_2$**CH_2OH), 3.81 (t, 2H, 6.42 Hz, CH_2C**H$_2$**OH), 3.87 (s, 3H, OC**H$_3$**), 3.88(s, 3H, OC**H$_3$**), 5.14 (s, 2H, OC**H$_2$**), 6.47 (s, 1H, H-6), 6.50 (s, 1H, H-2), 7.30-7.46 (m, 5H, Ar-**H**). (*Plate 12a*)

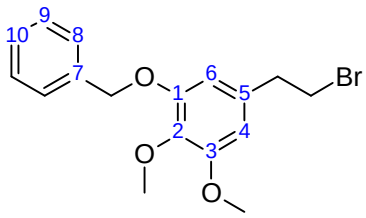
^{13}C NMR (100 MHz, $CDCl_3$) δ_C**:** 39.5 (**C**H_2CH_2OH), 56.2 (O**C**H_3), 60.9 (O**C**H_3), 63.5 (**C**H_2OH), 71.2 (O**C**H_2), 106.5 (C-6), 108.4 (C-2), 127.4 (C-9), 127.9 (C-10), 128.5 (C-8), 134.1 (C-1), 137.2 (C-7), 137.6 (C-4), 152.4 (C-3), 153.6 (C-5). (*Plate 12b*)

ER$^+$-HRMS *m/z*: 311.1257 $[M + Na]^+$

(Calculated for $C_{17}H_{20}O_4$+Na, 311.1259)

IR ν_{max} (cm^{-1})**:** 3450 (OH), 1112 (C-O)

4.2.15 1-Benzyloxy-5-(2-bromoethyl)-2,3-dimethoxybenzene (108)[11]



A solution of phosphorous tribromide (0.2 g, 0.9 mmol) in dry Et_2O (5 mL) was added dropwise to a stirred solution of 2-(3-benzyloxy-4,5-dimethoxyphenyl)ethanol **(107)** (0.6 g, 2.2 mmol) in dry Et_2O (15 mL) at 0 °C over 15 min. The mixture was stirred at room temperature for 1 h and was then quenched with water. The aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were washed with $NaHCO_3$ followed by brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography (8:2 hexane/EtOAc) to afford the desired product, 1-benzyloxy-5-(2-bromoethyl)-2,3-dimethoxybenzene **(108)** as a yellow oil (yield 0.46 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (t, 2H, *J*=6.50Hz, C**H$_2$**CH_2Br), 3.53 (t, 2H, *J* = 6.42 Hz, CH_2C**H$_2$**Br), 3.87 (s, 3H, OC**H$_3$**), 3.88(s, 3H, OC**H$_3$**), 5.14 (s, 2H, OC**H$_2$**), 6.45 (s, 1H, H-4), 6.48 (s, 1H, H-6), 7.38-7.47 (m, 5H, Ar-**H**). (*Plate 13a*)

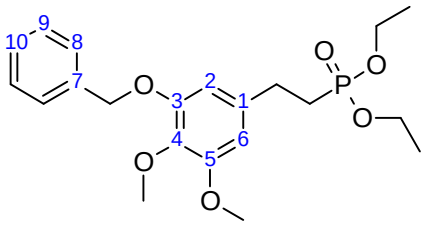
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 32.6 (**C**H_2CH_2Br), 39.7 (CH_2**C**H_2Br) 56.2 (O**C**H_3), 60.9 (O**C**H_3), 71.3 (O**C**H_2), 106.3 (C-4), 108.2 (C-6), 127.3 (C-9), 127.9 (C-10), 128.6 (C-8), 134.5 (C-5), 137.2 (C-7), 137.9 (C-2), 152.5 (C-1), 153.5 (C-3). (*Plate 13b*)

ER$^+$-HRMS *m/z*: 373.0411 $[M + Na]^+$

(Calculated for $C_{17}H_{19}O_3Br$+Na, 373.0415)

IR ν_{max} (cm^{-1}): 1108 (C-O)

4.2.16 Diethyl 2-(3-benxyloxy-4,5-dimethoxyphenyl)ethylphosphonate (87)[2]



1-(benzyloxy)-5-(2-bromoethyl)-2,3-dimethoxybenzene **(108)** (0.5 g, 1.3 mmol) was refluxed in triethyl phosphonate (5 mL) for 16 h. After the completion of the reaction as determined by TLC monitoring, excess triethyl phosphonate was distilled off under vacuum and the crude product obtained was purified using column chromatography (7:3 hexane/EtOAc) to yield the Horner-Wittig phosphate, **(87)** as a yellow oil (yield 0.37 g, 73%)

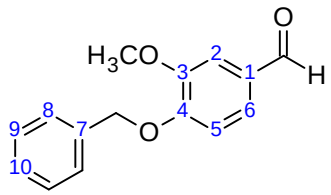
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.34 (t, 6H, *J* = 7.20 Hz, $POCH_2$C**H$_3$**), 1.97-2.08 (m, 2H, 6.42 Hz, CH_2C**H$_2$**P), 2.80-2.87 (m, 2H, C**H$_2$**CH_2P), 3.86(s, 6H, OC**H$_3$**), 4.11 (q,

4H, *J* = 7.51 Hz, POC**H**$_2$CH$_3$) 5.13 (s, 2H, OC**H**$_2$), 6.45 (s, 1H, Ph-**H**), 6.47 (s, 1H, Ph-**H**), 7.30-7.46 (m, 5H, Ar-**H**). (*Plate 14a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 16.5 (d, J_{PC} = 6.4 Hz, OCH$_2$**C**H$_3$,), 27.7 (d, J_{PC} = 139.2 Hz, Ph-CH$_2$**C**H$_2$P), 28.9 (d, J_{PC} = 4.4 Hz, Ph-**C**H$_2$CH$_2$P), 56.2 (O**C**H$_3$), 60.9 (OCH$_3$), 61.6 (d, J_{PC} = 6.3 Hz O**C**H$_2$CH$_3$), 71.2 (O**C**H$_2$), 105.6 (C-2), 107.5 (C-6), 127.3 (C-9), 127.8 (C-10), 128.5 (C-8), 136.5 - 136.7 (d, J_{PC} = 17.4 Hz, C-1), 137.2 (C-7), 137.4 (C-4)), 152.4(C-3), 153.5 (C-5). (*Plate 14b*)

^{31}P NMR δ_P (162 MHz, $CDCl_3$): 30.56 (s, 1P) (*Plate 14c*)

4.2.17 4-Benzyloxy-3-methoxybenzaldehyde (110)



To a solution of 4-hydroxy-3-methoxybenzaldehyde (6.0 g, 39.4 mmol) in MeCN (100 mL) was added potassium carbonate (10.9 g, 79.3 mmol) and benzyl chloride (5.5 g, 43.7 mmol). This mixture was stirred at 70-80 °C for 12 h. After completion of the reaction, as observed by TLC monitoring, the reaction mixture was poured into distilled water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed successively with water, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography (7:3 hexane/EtOAc) to yield 4-benzyloxy-3-methoxybenzaldehyde **(110)** as white crystals (yield 8.1 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.96 (s, 3H, OC**H**$_3$), 5.26(s, 2H, OC**H**$_2$), 7.00 (d, 1H, *J*=8.1 Hz, H-5), 7.31-7.47 (m, 7H, Ar-**H**, H-2, 6), 9.85 (s, 1H, CO**H**). (*Plate 15a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 56.1 (O**C**H_3), 70.9 (O**C**H_2), 109.6 (C-2), 112.5 (C-5), 126.5 (C-6), 127.2 (C-9), 128.2 (C-10), 128.7, (C-8), 130.4 (C-1), 136.1 (C-7), 150.2 (C-3), 153.7 (C-4), 190.9 (**C**OH). (*Plate 15b*)

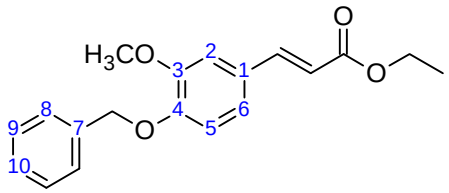
ER$^+$-HRMS *m/z*: 265.0837 $[M + Na]^+$

(Calculated for $C_{15}H_{14}O_3$+Na, 265.0841)

IR ν_{max} (cm^{-1}): 1671 (C=O), 1131 (C-O)

Melting point (Et_2O): 54-55 °C (lit.[12] 60-61 °C (EtOAc))

4.2.18 Ethyl 4-benzyloxy-3-methoxycinnamate (111)[13]



To a stirred solution of triethyphosphoacetate (9.3 g, 41.3 mmol) in dry THF (50 mL) at 0 °C was added NaH (1.0 g, 41.3 mmol). This mixture was stirred at 0 °C for 30 min followed by the dropwise addition of 4-benzyloxy-3-methoxybenzaldehyde **(110)** (5.0 g, 20.6 mmol) in dry THF (10 mL) and the reaction mixture was stirred at room temperature for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were then washed with brine and concentrated *in vacuo*. The crude product was purified using column chromatography (8:2 hexane/EtOAc) to yield ethyl 4-benzyloxy-3-methoxycinnamate **(111)** as white crystals (yield 6.21 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.35 (t, 3H, *J*=7.2 Hz, $OCH_2C\mathbf{H_3}$), 3.92 (s, 3H, $OC\mathbf{H_3}$), 4.27 (q, 2H, *J*=7.0 Hz, $OC\mathbf{H_2}CH_3$), 5.19 (s, 2H, $OC\mathbf{H_2}$), 6.32 (d, 1H, *J*=15.9,

CHC**H**COO), 6.88 (d, 1H, *J*=8.4 Hz, H-6), 7.04 (d, 1H, *J*= 8.87, H-5), 7.08 (s, 1H, H-2), 7.23-7.46 (m, 5H), 7.63 (d, 1H, *J*=15.9 Hz, C**H**CHCOO). (*Plate 16a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 14.0 ($COOCH_2\underline{\mathbf{C}}H_3$), 56.1 ($O\underline{\mathbf{C}}H_3$), 60.5 ($COO\underline{\mathbf{C}}H_2CH_3$), 71.0 ($O\underline{\mathbf{C}}H_2$), 110.3 (C-2), 113.6 (C-5), 116.2 (CH**C**HCOO), 122.4 (C-6), 127.3 (C-9), 127.9 (C-10), 128.1 (C-1), 128.7 (C-8), 136.7 (C-7), 144.6 (**C**HCHCOO), 149.9 (C-4), 150.4 (C-3), 167.2 (**C**OOCH$_2$CH$_3$). (*Plate 16b*)

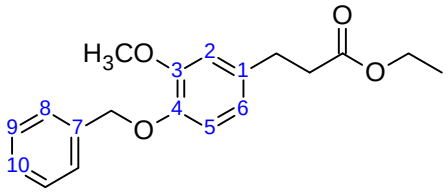
ER$^+$-HRMS *m/z*: 335.1478 $[M + Na]^+$

(Calculated for $C_{19}H_{18}O_4$+Na, 335.1479)

IR ν_{max} (cm^{-1}): 1698 (C=O), 1159 (C-O), 1600 (C=C)

Melting point (pet. Ether): 62 °C (lit.[14] 64 °C)

4.2.19 Ethyl 3-(4-benzyloxy-3-methoxyphenyl)propanoate (112)[15]



Ethyl 4-benzyloxy-3-methoxycinnamate **(111)** (2.0 g, 6.4 mmol) was dissolved in absolute EtOH (20 mL) and catalytic amount of 10% Pd/C (2.5 mg) was added to this mixture. This mixture was then placed in a reactor with H_2 gas at a pressure of 2 atm for 30 minutes. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography (8:2 hexane/EtOAc) to yield Ethyl 3-(4-benzyloxy-3-methoxyphenyl)propanoate **(112)** as a colorless oil (yield 1.70 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.25 (t, 3H, *J*=7.0 Hz, $OCH_2C\underline{\mathbf{H_3}}$),2.61 (t, 2H, *J*=7.97 Hz, $C\underline{\mathbf{H_2}}CH_2COO$), 2.91 (t, 2H, *J*=7.7 Hz $CH_2C\underline{\mathbf{H_2}}COO$), 3.89 (s, 3H, $OC\underline{\mathbf{H_3}}$), 4.14 (q, 2H, *J*=7.1 Hz, $OCH_2C\underline{\mathbf{H_3}}$), 5.14 (s, 2H, $OC\underline{\mathbf{H_2}}$), 6.69 (d, 1H, *J*=8.0 Hz, H-5), 6.76 (s, 1H, H-2), 6.82 (d, 1H, *J*=8.1, H-6), 7.29-7.40 (m, 5H, Ar-**H**). (*Plate 17a*)

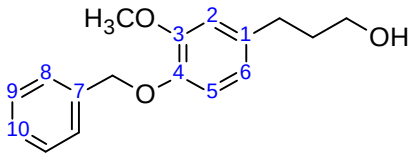
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 14.2 ($COOCH_2\underline{\mathbf{C}}H_3$), 30.7 ($\underline{\mathbf{C}}H_2CH_2COO$), 36.2 ($CH_2\underline{\mathbf{C}}H_2COO$), 56.0 ($O\underline{\mathbf{C}}H_3$), 60.4 ($COO\underline{\mathbf{C}}H_2CH_3$), 71.3($O\underline{\mathbf{C}}H_2$), 112.4(C-2), 114.5 (C-5), 120.2 (C-6), 127.4 (C-9), 127.8(C-10), 128.5 (C-8), 133.9 (C-1), 137.4 (C-7), 146.7 (C-4), 149.7 (C-3), 172.9 (**C**OO). (*Plate 17b*)

ER^{+}-HRMS *m/z*: 337.1714 $[M + Na]^{+}$

(Calculated for $C_{19}H_{18}O_4$+Na, 337.1710)

IR ν_{max} (cm^{-1}): 1724 (C=O), 1149 (C-O)

4.2.20 3-(4-Benzyloxy-3-methoxyphenyl)propan-1-ol (113)



A solution of ethyl 3-(4-benzyloxy-3-methoxyphenyl)propanoate **(112)** (15.0 g, 47.7 mmol) in dry THF (15 mL) was added dropwise to a stirred solution of $LiAlH_4$ (1.8 g, 47.7 mmol) in dry THF (20 mL) at 0 °C under N_2 atmosphere. This mixture was then stirred at room temperature until the reaction was complete (1-2 h, TLC control). The excess hydride was quenched with H_2O followed by aqueous 10% H_2SO_4 (10 mL). This mixture was then extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was then

evaporated *in vacuo* and the product purified using column chromatography (6:4 hexane/EtOAc) to yield 3-(4-benzyloxy-3-methoxyphenyl)propan-1-ol **(113)** as white solid (yield 11.53 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.89 (qr, 2H, *J*=6.7 Hz, $CH_2C\underline{\mathbf{H}_2}CH_2OH$),2.67 (t, 2H, *J*=7.4 Hz $C\underline{\mathbf{H}_2}CH_2CH_2OH$), 3.69 (t, 2H, *J*=6.3 Hz, $CH_2CH_2C\underline{\mathbf{H}_2}OH$), 3.90 (s, 3H, $OC\underline{\mathbf{H}_3}$), 5.14 (s, 2H, $OC\underline{\mathbf{H}_2}$), 6.69 (d, 1H, *J*=8.0 Hz, H-5), 6.77 (s, 1H, H-2), 6.83 (d, 1H, *J*=8.1, H-6), 7.30-7.47 (m, 5H, Ar-**H**). (*Plate 18a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 31.7 ($CH_2\underline{\mathbf{C}}H_2CH_2OH$), 34.3 ($\underline{\mathbf{C}}H_2CH_2CH_2OH$), 56.0 ($O\underline{\mathbf{C}}H_3$), 62.3 ($CH_2CH_2\underline{\mathbf{C}}H_2OH$), 71.3 ($O\underline{\mathbf{C}}H_2$), 112.5 (C-2), 114.5 (C-5), 120.3 (C-6), 127.3 (C-9), 127.7 (C-10), 128.5 (C-8), 135.2 (C-1), 137.5 (C-7), 146.5 (C-4), 149.7 (C-3). (*Plate 18b*)

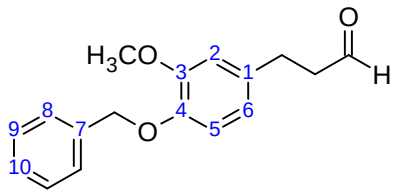
ER$^+$-HRMS *m/z*: 295.1314 $[M + Na]^+$

(Calculated for $C_{17}H_{20}O_3$+Na, 295.1310)

IR ν_{max} (cm^{-1}): 3561 (OH), 1220 (C-O)

Melting point (pet. Ether): 55 °C

4.2.21 3-(4-Benzyloxy-3-methoxyphenyl)propanal (114)[8]



To a stirred solution of 2-iodoxybenzoic acid (IBX) (16.3 g, 58.2 mmol) in DMSO (20 mL), was added a solution of alcohol 3-(4-benzyloxy-3-methoxyphenyl)propanol **(113)** (10.5 g,

38.8 mmol) in THF (30 mL) at room temperature and the resulting solution was stirred for 3 h. After completion of the reaction as observed by TLC monitoring, water (20 mL) was added to the reaction mixture and the precipitated solid was filtered off. The filtrate was diluted with water (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed successively with $NaHCO_3$ solution, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified using column chromatography (8:2 hexane/EtOAc) to afford the desired product, 3-(4-benzyloxy-3-methoxyphenyl)propanal **(114)** as a white solid (yield 8.22 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.77 (t, 2H, *J*=7.1 Hz, $CH_2C\underline{\mathbf{H_2}}COH$),2.92 (t, 2H, *J*=7.5 Hz $C\underline{\mathbf{H_2}}CH_2COH$), 3.90 (s, 3H, $OC\underline{\mathbf{H_3}}$), 5.14 (s, 2H, $OC\underline{\mathbf{H_2}}$), 6.68 (d, 1H, *J*=8.2 Hz, H-5), 6.76 (s, 1H, H-2), 6.83 (d, 1H, *J*=8.2, H-6), 7.32-7.47 (m, 5H, Ar-**H**), 9.83 (s, 1H, $CH_2CH_2CO\underline{\mathbf{H}}$). (*Plate 19a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.8 ($\underline{\mathbf{C}}H_2CH_2COH$), 45.4 ($CH_2\underline{\mathbf{C}}H_2COH$), 56.0 ($O\underline{\mathbf{C}}H_3$), 71.3 ($O\underline{\mathbf{C}}H_2$), 112.4 (C-2), 114.50 (C-5), 120.1 (C-6), 127.3 (C-9), 127.8 (C-10), 128.50 (C-8), 133.6 (C-1), 137.3 (C-7), 146.8 (C-4), 149.8 (C-3), 201.6 ($CH_2CH_2\underline{\mathbf{C}}OH$). (*Plate 19b*)

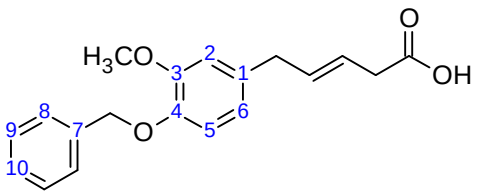
ER^+-HRMS *m/z* $[M + Na]^+$: 325.1414 $[M + Na]^+$

(Calculated for $C_{18}H_{22}O_4$+Na, 325.1416)

IR ν_{max} (cm^{-1}): 1709 (C=O), 1220 (C-O)

Melting point (Hexane/EtOAc): 35 °C

4.2.22 (*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoic acid (115)[16]



To a pyrex test tube attached to a reflux condenser was added 3-(4-benzyloxy-3-methoxyphenyl)propanal **(114)** (6.0 g, 22.4 mmol), pyridine (10 mL), piperidine (20 mL) and malonic acid (3.48 g, 34.0 mmol). The resulting mixture was irradiated with an output of 100 W using a microwave for 30 min. After completion of the reaction as observed by TLC monitoring, the reaction mixture was cooled to room temperature and neutralised with 1N HCl. The reaction mixture was then cooled to 0 °C and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using flash chromatography (2:8 hexane/EtOAc) to yield (*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoic acid **(115)** as a yellow oil (yield 6.64 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.14, (d, 2H, *J*=7.2 Hz, $CH_2CHCHC\underline{\mathbf{H}}_2COOH$), 3.34 (d, 2H, *J*=6.8 Hz, $C\underline{\mathbf{H}}_2CHCHCH_2COOH$), 3.90 (s, 3H, $OC\underline{\mathbf{H}}_3$), 5.14 (s, 2H, $OC\underline{\mathbf{H}}_2$), 5.68-5.59 (m, 1H, $CH_2CHC\underline{\mathbf{H}}CH_2COOH$), 5.71- 5.89 (m, 1H, $CH_2C\underline{\mathbf{H}}CHCH_2COOH$), 6.67 (d, 1H, *J*= 8.6 Hz, H-5), 6.79 (s, 1H, H-2), 6.83 (d, 1H, *J*= 8.2 Hz, H-6), 7.32-7.47 (m, 5H, Ar-**H**). (*Plate 20a*)

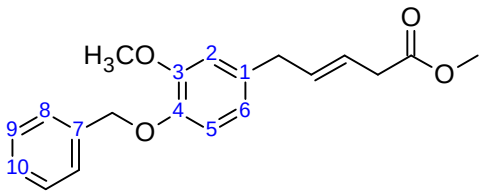
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 37.5 ($CH_2CHCH\underline{\mathbf{C}}H_2COOH$), 38.4 ($C\underline{\mathbf{H}}_2CHCHCH_2COOH$), 56.0 ($O\underline{\mathbf{C}}H_3$), 71.3 ($O\underline{\mathbf{C}}H_2$), 112.5 (C-2), 114.4 (C-5), 120.4 (C-6), 122.3 ($CH_2CH\underline{\mathbf{C}}HCH_2COOH$), 127.3 (C-9), 127.7 (C-10), $CH_2\underline{\mathbf{C}}HCHCH_2COOH$), 128.5(C-8), 133.3 (C-1), 134.0 ($CH_2\underline{\mathbf{C}}HCHCH_2COOH$), 137.4 (C-7), 146.7 (C-4), 149.7 (C-3), 177.1 ($CH_2CH_2\underline{\mathbf{C}}OOH$). (*Plate 20b*)

ER$^+$-HRMS *m/z*: 335.1259 $[M + Na]^+$

(Calculated for $C_{19}H_{20}O_4$+Na, 335.1259)

IR ν_{max} (cm^{-1}): 2959(O-H), 1692 (C=O), 1222 (C-O)

4.2.23 (*E*)-Methyl 5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoate (116)[2]



To a stirred solution of (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoic acid **(115)** (6.6 g, 21.1 mmol) in MeOH (20 mL) at 0 °C was added BF_3-Et_2O (3.2 mL, 25.3 mmol). This mixture was stirred at room temperature for 2 h. After completion of the reaction as determined by TLC monitoring, the reaction mixture was diluted with water and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using flash chromatography (7:3 hexane/EtOAc) to yield (*E*)-methyl 5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoate **(116)** as a yellow oil (yield 5.58 g, 81%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.10, (d, 2H, *J*=6.7 Hz, C**H**$_2$COOCH$_3$), 3.34 (d, 2H, *J*=6.4 Hz, C**H**$_2$CHCHCH$_2$COOCH$_3$), 3.71 (s, 3H, OC**H**$_3$),3.90 (s, 3H, COOC**H**$_3$), 5.15 (s, 2H, OC**H**$_2$-Ar), 5.60-5.78 (m, 2H, CH$_2$C**H**C**H**CH$_2$), 6.68 (d, 1H, *J*= 8.1 Hz, H-5), 6.76 (s, 1H, H-2), 6.84 (d, 1H, *J*= 8.2 Hz, H-6), 7.32-7.48 (m, 5H, Ar-**H**). (*Plate 21a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 37.7 (CH$_2$CHCH**C**H$_2$COOH), 38.5 (C**H**$_2$CHCHCH$_2$COOH), 51.8 (COO**C**H$_3$), 56.0 (O**C**H$_3$), 71.3 (O**C**H$_2$), 112.6 (C-2), 114.5 (C-5), 120.4 (C-6), 123.0 (CH$_2$CH**C**HCH$_2$COOH), 127.3 (C-9), 127.7 (C-10),

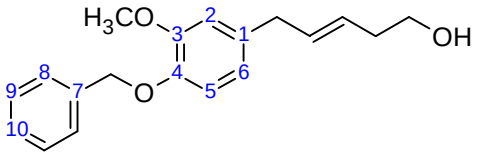
128.4 (C-8), 133.4 (C-1), 133.5 (CH_2**C**HCHCH_2COOH) , 137.4 (C-7), 146.6 (C-4), 149.8 (C-3), 172.3 (**C**OOCH_3). (*Plate 21b*)

ER$^+$-HRMS *m/z*: 349.1418 $[M + Na]^+$

(Calculated for $C_{20}H_{22}O_4$+Na, 349.1416)

IR ν_{max} (cm^{-1}): 1733 (C=O)

4.2.24 (*E*)-5-(4-Benzyloxy-3-methoxyphenyl)pent-3-en-1-ol (117)



A solution of methyl (*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoate **(116)** (3.7 g, 11.0 mmol) in dry THF (20 mL) was added dropwise to a stirred solution of $LiAlH_4$ (0.5 g, 13.7 mmol) in dry THF (10 mL) at 0 °C under N_2 atmosphere. This mixture was then stirred at room temperature until the reaction was complete (2-3 h, TLC control). The excess hydride was quenched with H_2O followed by 10% aqueous H_2SO_4 (10 mL). This mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. The solvent was then evaporated in *vacuo* and the product purified using column chromatography (5:5 hexane/EtOAc). (*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-en-1-ol **(117)** was isolated as a colourless oil (yield 2.93 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.32 (q, 2H, *J*=6.3 Hz, CH_2CHCHC**H**$_2CH_2OH$), 3.32 (d, 2H, *J*=6.9 Hz, C**H**$_2CHCHCH_2CH_2OH$), 3.67 (t, 2H, *J*=6.3 Hz,

$CH_2CHCHCH_2C\underline{\mathbf{H}}_2OH$), 3.89 (s, 3H, $OC\underline{\mathbf{H}}_3$), 5.14 (s, 2H, $OC\underline{\mathbf{H}}_2$), 5.46-5.55 (m, 1H, $CH_2C\underline{\mathbf{H}}CHCH_2CH(OH)$), 5.67-5.76 (m, 1H, $CH_2CHC\underline{\mathbf{H}}CH_2CH(OH)$), 6.67 (d, 1H, *J*=8.1 Hz, H-5), 6.75 (s, 1H, H-2), 6.83 (d, 1H, *J*=8.1 Hz, H-6), 7.28-7.48 (m, 5H, Ar-**H**). (*Plate 22a*)

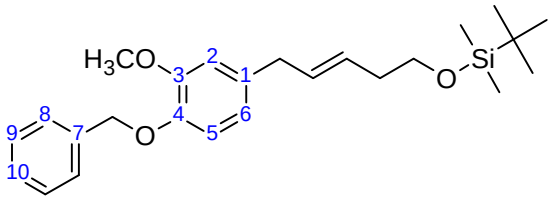
^{13}C NMR (100 MHz, $CDCl_3$)δ_C: 35.9 ($CH_2CHCH\underline{\mathbf{C}}H_2CH_2OH$), 38.7 ($\underline{\mathbf{C}}H_2CHCHCH_2CH_2OH$), 56.0 ($O\underline{\mathbf{C}}H_3$), 62.1 ($CH_2CHCHCH_2\underline{\mathbf{C}}H_2OH$), 71.3 ($O\underline{\mathbf{C}}H_2$), 112.5 (C-2), 114.5 (C-5), 120.3 (C-6), 127.3 (C-9), 127.4 ($CH_2\underline{\mathbf{C}}HCHCH_2CH_2OH$), 127.7 (C-10), 128.5 (C-8), 132.6 ($CH_2CH\underline{\mathbf{C}}HCH_2CH_2OH$), 133.9 (C-1), 137.4 (C-7), 146.6 (C-4), 149.7 (C-3). (*Plate 22b*)

ER^+-HRMS *m/z*: 321.1469 $[M + Na]^+$

(Calculated for $C_{19}H_{22}O_3$+Na, 321.1467)

IR ν_{max} (cm^{-1}): 3396 (OH), 1509 (C=C), 1220 (C-O)

4.2.25 [(*E*)-5-(4-Benzyloxy-3-methoxyphenyl)pent-3-enoxy]-*tert*-butyl-dimethylsilane (124)[17]



To a stirred solution of (*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-en-1-ol **(117)** (2.9 g, 9.6 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added imidazol (1.3 g, 19.1 mmol) followed by TBDMS-Cl (3.24 g, 21.50 mmol). The reaction mixture was then stirred at room temperature for 6 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water

(50 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the purification of the crude product by flash chromatography (8:2 hexane/EtOAc) afforded [(*E)*-5-(4-Benzyloxy-3-methoxyphenyl)pent-3-enoxy]-*tert*-butyl-dimethylsilane **(124)** as a yellow oil (yield 2.42 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.06 (s, 6H, OSi(C**H$_3$**)$_2$C(CH$_3$)$_3$), 0.92 (s, 9H, OSi(CH$_3$)$_2$C(C**H$_3$**)$_3$), 2.28 (q, 2H, *J*=6.8 Hz, CH$_2$CHCHC**H$_2$**CH$_2$OSi), 3.30 (d, 2H, *J*=6.7 Hz, C**H$_2$**CHCHCH$_2$CH$_2$OSi), 3.67 (t, 2H, *J*=6.8 Hz, CH$_2$CHCHCH$_2$C**H$_2$**OSi), 3.90 (s, 3H, OC**H$_3$**), 5.15 (s, 2H, OC**H$_2$**-Ar), 5.48-5.56 (m, 1H CH$_2$C**H**CHCH$_2$CH$_2$OSi), 5.60-5.69 (m, 1H, CH$_2$CHC**H**CH$_2$CH$_2$OSi), 6.68 (d, 1H, *J*=8.4 Hz, H-5), 6.75 (s, 1H, H-2), 6.83 (d, 1H, *J*= 8.2 Hz, H-6), 7.30-7.50 (m, 5H, Ar-**H**). (*Plate 23a*)

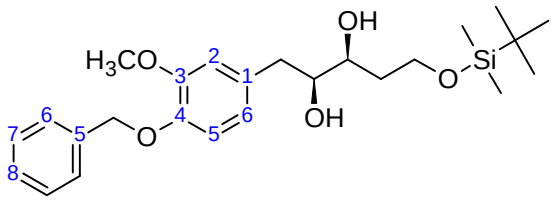
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: -5.2 (OSi(**C**H$_3$)$_2$), 18.4 (OSi(CH$_3$)$_2$**C**(CH$_3$)$_3$), 26.0 (OSi(CH$_3$)$_2$C(**C**H$_3$)$_3$), 36.2 (CH$_2$CHCH**C**H$_2$CH$_2$OSi), 38.7 (**C**H$_2$CHCHCH$_2$CH$_2$OSi), 56.0 (O**C**H$_3$), 63.2 (CH$_2$CHCHCH$_2$**C**H$_2$OSi), 71.3 (O**C**H$_2$), 112.6 (C-2), 114.5 (C-5), 120.4 (C-6), 127.3 (C-9), 127.7 (C-10), 128.1 (CH$_2$**C**HCHCH$_2$**C**H$_2$OSi), 128.5 (C-8), 131.1 (CH$_2$CH**C**HCH$_2$CH$_2$OSi), 134.2 (C-1), 137.5 (C-7), 146.5 (C-4), 149.7 (C-3). (*Plate 23b*)

ER$^+$-HRMS *m/z*: 435.2333 $[M + Na]^+$

(Calculated for $C_{25}H_{36}O_3Si$+Na, 435.2331)

IR ν_{max} (cm^{-1}): 1511 (C=C), 1255 (C-O)

4.2.26 1-(4-Benzyloxy-3-methoxy phenyl)-5-(*tert*-butyl(methyl)silyl)oxypentane-2,3-diol (125)[18]



To a solution of [(*E*)-5-(4-Benzyloxy-3-methoxyphenyl)pent-3-enoxy]-*tert*-butyl-dimethylsilane **(124)** (0.5 g, 1.21 mmol) in *t*-BuOH: H_2O (1:1, 10 mL) was added AD-mix-α (1.8 g). This mixture was stirred at room temperature for 24 h. The reaction was quenched by adding sodium sulfite (2.0 g) and it was stirred for further 10 min. The reaction mixture was then extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with aqueous 2N KOH solution, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the purification of the crude product by flash chromatography afforded 1-(4-Benzyloxy-3-methoxy phenyl)-5-(*tert*-butyl(methyl)silyl)oxypentane-2,3-diol **(125)** as a yellow oil (yield 0.498 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.10 (s, 6H, OSi(C**H**$_3$)$_2$C(CH$_3$)$_3$), 0.93 (s, 9H, OSi(CH$_3$)$_2$C(C**H**$_3$)$_3$), 1.65-1.92 (m, 2H, CH$_2$CH(OH)CH(OH)C**H**$_2$CH$_2$O), 2.72-2.89 (m, 2H, CH$_2$C**H**(OH)C**H**(OH)CH$_2$CH$_2$O), 3.73 (d, 2H, *J*=34.4, C**H**$_2$CH(OH)CH(OH)CH$_2$CH$_2$O), 5.14 (s, 2H, OC**H**$_2$), 3.83-3.94 (m, 5H, OCH$_3$, CH$_2$CH(OH)CH(OH)CH$_2$C**H**$_2$O), 6.73 (d, 1H, *J*=8.2 Hz, H-5), 6.83-6.86 (m, 2H, H-2, H-6), 7.30-7.49 (m, 5H, Ar-**H**). (*Plate 24a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: -5.5 (OSi(**C**H$_3$)$_2$), 18.1 (OSi(CH$_3$)$_2$**C**(CH$_3$)$_3$), 25.8 (OSi(CH$_3$)$_2$C(**C**H$_3$)$_3$), 35.4 (CH$_2$CH(OH)CH(OH)**C**H$_2$CH$_2$OSi), 39.6 (**C**H$_2$CH(OH)CH(OH)CH$_2$CH$_2$OSi), 56.0 (O**C**H$_3$), 62.0

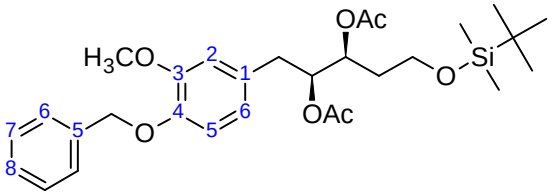
($CH_2CH(OH)CH(OH)CH_2\underline{\mathbf{C}}H_2OSi$), 71.2 ($CH_2\underline{\mathbf{C}}H(OH)CH(OH)CH_2CH_2OSi$), 72.8 ($CH_2CH(OH)\underline{\mathbf{C}}H(OH)CH_2CH_2OSi$), 75.2 ($O\underline{\mathbf{C}}H_2$) 113.3 (C-2), 114.4 (C-5), 121.3 (C-6), 127.3 (C-9), 127.7 (C-10), 128.5 (C-8), 131.8 (C-1), 137.4 (C-7), 146.8 (C-4), 149.7 (C-3). (*Plate 24b*)

ER^+-HRMS *m/z*: 469.2384 $[M + Na]^+$

(Calculated for $C_{25}H_{38}O_5Si$+Na, 469.2386)

IR ν_{max} (cm^{-1}): 3371 (OH), 1257 (C-O)

4.2.27 5-(4-Benzyloxy-3-methoxy phenyl)-1-[2-*tert*-butyl(dimethyl)silyl]oxypentane-2,3-diacetate (126)



To a solution of 1-(4-Benzyloxy-3-methoxy phenyl)-5-(*tert*-butyl(methyl)silyl)oxypentane-2,3-diol **(125)** (0.3 g, 0.6 mmol) in DCM (10 mL) at room temperature was added a Et_3N (0.3 mL, 2.2 mmol) and acetic anhydride (0.2 mL, 2.2 mmol). This mixture was refluxed for 6 h. After completion of the reaction as determined by TLC monitoring, the reaction mixture was diluted with water and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using flash chromatography (8:2 hexane/EtOAc) to yield 5-(4-Benzyloxy-3-methoxy phenyl)-1-[2-*tert*-butyl(dimethyl)silyl]oxypentane-2,3-diacetate **(126)** as a colourless oil (yield 0.25 g, 85%).

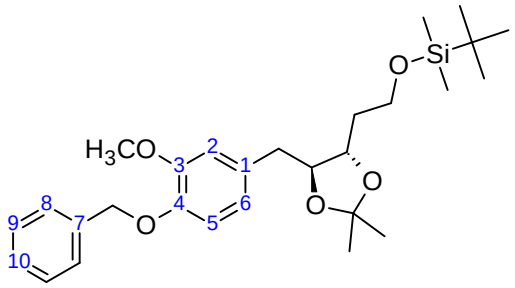
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.02 (s, 6H, O-Si(C**H**$_3$)$_2$C(CH$_3$)$_3$), 0.87 (s, 9H, O-Si(C**H**$_3$)$_2$C(C**H**$_3$)$_3$), 1.74-1.86 (m, 2H, CH$_2$CH(COOCH$_3$)CH(COOCH$_3$)C**H**$_2$CH$_2$O), 2.01 (s, 3H, CH$_2$CH(OOCH$_3$)CH(OOC**H**$_3$)), 2.12 (s, 3H, CH$_2$CH(OOC**H**$_3$)CH(OOCH$_3$)), 2.71-2.86 (m, 2H, C**H**$_2$CH(COOCH$_3$)CH(COOCH$_3$)CH$_2$CH$_2$O), 3.56-3.67 (m, 2H, CH$_2$CH(COOCH$_3$)CH(COOCH$_3$)CH$_2$C**H**$_2$O), 3.88 (s, 3H, OC**H**$_3$), 5.12 (s, 2H, OC**H**$_2$), 5.17-5.34 (m, 2H, CH$_2$C**H**(COOCH$_3$)C**H**(COOCH$_3$)CH$_2$CH$_2$O), 6.67 (d, 1H, *J* = 8.4 Hz, H-5), 6.75 (s, 1H, H-2), 6.80 (d,1H, J= 8.2 Hz, H-6)7.30-7.46 (m, 5H, Ar-**H**). (*Plate 25a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: -5.5 (OSi(**C**H$_3$)$_2$), 18.2 (OSi(CH$_3$)$_2$**C**(CH$_3$)$_3$), 20.9 (OCO**C**H$_3$), 25.8 (OSi(CH$_3$)$_2$C(**C**H$_3$)$_3$), 34.0 (CH$_2$CH(Ac)CH(Ac)**C**H$_2$CH$_2$O), (**C**H$_2$CH(Ac)CH(Ac)CH$_2$CH$_2$O), 56.1 (O**C**H$_3$), 59.1 (CH$_2$CH(Ac)CH(Ac)CH$_2$**C**H$_2$O), 70.7 (CH$_2$**C**H(Ac)CH(Ac)CH$_2$CH$_2$O), 70.9 (CH$_2$CH(Ac)**C**H(Ac)CH$_2$CH$_2$O), 71.2 (O**C**H$_2$), 113.2 (C-2), 114.3 (C-5), 121.4 (C-6), 127.3 (C-9), 127.7 (C-10), 128.5 (C-8), 129.9 (C-1), 136.1 (C-5), 149.6 (C-4),170.1 (OCO**C**H$_3$), 170.2(OCO**C**H$_3$)

ER^{+}-HRMS *m/z*: 553.2596 [M + Na]$^{+}$

(Calculated for $C_{29}H_{42}O_7Si$+Na, 553.2598)

4.2.28 2-[5-[(4-Benzyloxy-3-methoxyphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]*tert*-butyldimethylsilane (138)[19]



A solution of 2,3-[5-[(1,1-dimethylethyl)dimethylsilyloxy]-5-(4-benzyloxy-3-methoxy) phenyl]dihydroxypentane **(125)** (0.4 g, 0.9 mmol), DMP (0.2 mL, 1.7 mmol) and cat. *P*-TsOH in DCM (10 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ solution, water, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using flash chromatography (8:2 hexane/EtOAc) to yield 2-[5-[(4-Benzyloxy-3-methoxyphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]*tert*-butyldimethylsilane **(138)** as a colourless oil (yield 0.35 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.01 (s, 6H, O-Si(C**H**$_3$)$_2$C(CH$_3$)$_3$), 0.86 (s, 9H, O-Si(C**H**$_3$)$_2$C(C**H**$_3$)$_3$), 1.31 (s, 3H, CHO(C(C**H**$_3$)$_2$)OCH), 1.35 (s, 3H, CHO(C(C**H**$_3$)$_2$)OCH), 1.58 (q, 2H, *J*=6.1 Hz, CH$_2$CHO(C(CH$_3$)$_2$)OCHC**H**$_2$CH$_2$O), 2.74-2.87 (m, 2H, C**H**$_2$CHO(C(CH$_3$)$_2$)OCHCH$_2$CH$_2$O), 3.62-3.73 (m, 2H, CH$_2$CHO(C(CH$_3$)$_2$)OCHCH$_2$C**H**$_2$O), 3.75-3.88 (m, 2H, CH$_2$C**H**O(C(CH$_3$)$_2$)OC**H**CH$_2$CH$_2$O), 3.85 (s, 2H, OCH$_3$), 5.09 (s, 2H, OCH$_2$), 6.67 (d, 1H, J= 8.2 Hz, H-5), 6.76-6.79 (m, 2H, H-2 & H-6), 7.23-7.46 (m, 5H, Ar-**H**). (*Plate 26a*)

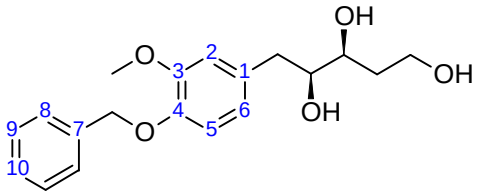
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: -5.36 (O-Si(**C**H$_3$)$_2$C(CH$_3$)$_3$), 18.3 18.1 (OSi(CH$_3$)$_2$**C**(CH$_3$)$_3$), 25.9 (OSi(CH$_3$)$_2$C(**C**H$_3$)$_3$), 27.2 (CHO(C(**C**H$_3$)$_2$)OCH), 27.4 CHO(**C**(CH$_3$)$_2$)OCH), 36.0(CH$_2$CHO(C(CH$_3$)$_2$)OCH**C**H$_2$CH$_2$O) ,38.4 (**C**H$_2$CHO(C(CH$_3$)$_2$)OCHCH$_2$CH$_2$O), 56.0(O**C**H$_3$), 59.9 (CH$_2$CHO(C(CH$_3$)$_2$)OCHCH$_2$**C**H$_2$O), 71.2(O**C**H$_2$), 81.2 (CH$_2$**C**HO(C(CH$_3$)$_2$)O**C**HCH$_2$CH$_2$O), 108.1 (CHO(**C**(CH$_3$)$_2$)OCH), 113.5 (C-2), 114.2 (C-5), 121.5 (C-6), 127.3 (C-9), 127.7 (C-10), 128.5 (C-8), 130.9 (C-1), 137.4 (C-7), 146.9 (C-4), 149.5 (C-3). (*Plate 26b*)

ER$^+$-HRMS *m/z*: 509.2697 $[M + Na]^+$

(Calculated for $C_{28}H_{42}O_5Si$+Na, 509.2699)

IR ν_{max} (cm^{-1}): 1082 (C-O)

4.2.29 5-(4-Benzyloxy-3-methoxy)phenyl]pentane-1,3,4-triol (131)[18]



To a solution of (*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-en-1-ol **(117)** (0.8 g, 2.7 mmol) in *t*-BuOH: H_2O (1:1, 20 mL) was added AD-mix-α (1.0 g). This mixture was stirred at room temperature for 24 h. The reaction was quenched by adding sodium sulfite (1.00 g) and was stirred for further 10 min. The reaction mixture was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with aqueous 2N KOH solution, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the purification of the crude product by flash chromatography (EtOAc) afforded 5-(4-Benzyloxy-3-methoxy)phenyl]pentane-1,3,4-triol (**131)** as a white solid. (yield 0.79 g, 89%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.71-1.90 (m, 2H, $CH_2CH(OH)CH(OH)C\underline{\mathbf{H_2}}CH_2OH$), 2.52 (br, OH), 2.63-3.11 (m, 2H, $C\underline{\mathbf{H_2}}CH(OH)CH(OH)CH_2CH_2OH$), 3.64-3.80 (m, 2H, $CH_2CH(OH)CH(OH)CH_2C\underline{\mathbf{H_2}}OH$), 3.81-3.93 (m,s, 5H $CH_2C\underline{\mathbf{H}}(OH)C\underline{\mathbf{H}}(OH)CH_2CH_2OH$, $OC\underline{\mathbf{H_3}}$), 5.13 (s, 2H, $OC\underline{\mathbf{H_2}}$), 6.72 (d, 1H, *J* = 8.30 Hz, H-5), 6.81 (s, 1H, H-2), 6.85 (d, *J* = 8.12 Hz, H-6), 7.30-7.47 (m, 5H, Ar-**H**). (*Plate 27a*)

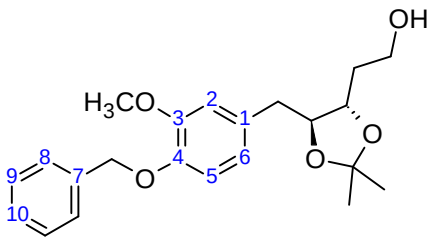
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 35.3 ($CH_2CH(OH)CH(OH)\underline{\mathbf{C}}H_2CH_2OH$), 39.6 ($\underline{\mathbf{C}}H_2CH(OH)CH(OH)CH_2CH_2OH$), 56.1 ($O\underline{\mathbf{C}}H_3$), 60.8 ($CH_2CH(OH)CH(OH)CH_2\underline{\mathbf{C}}H_2OH$), 71.2 ($O\underline{\mathbf{C}}H_2$), 72.9 ($CH_2CH(OH)\underline{\mathbf{C}}H(OH)CH_2CH_2OH$), 75.2 ($CH_2\underline{\mathbf{C}}H(OH)CH(OH)CH_2CH_2OH$), 113.3 (C-2), 114.5 (C-5), 121.4 (C-6), 127.3 (C-9), 127.8 (C-10), 128.5 (C-8), 131.2 (C-1), 137.3 (C-7), 147.0 (C-4), 149.8 (C-3). (*Plate 27b*)

ER$^+$-HRMS *m/z* [M + Na]$^+$:

IR ν_{max} (cm^{-1}): 3353-3539 (OH)

Melting point (Hexane/EtOAc): 51-52 °C

4.2.30 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol (132)[20]



Method 1

A solution of 2-[5-[(4-Benzyloxy-3-methoxyphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]*tert*-butyldimethylsilane **(138)** (0.3 g, 0.6 mmol) and NH_4F (0.1 g, 1.3 mmol) in dry MeOH was refluxed for 16 h. After completion of the reaction as determined by TLC monitoring, the reaction mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The crude product was then purified using flash chromatography (5:5 hexane/EtOAc) to yield 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol **(132)** as a yellow oil (yield 0.21 g, 90%).

Method 2

A solution of 5-(4-benzyloxy-3-methoxyphenyl)pentane-1,3,4-triol **(131)** (0.7 g, 2.1 mmol), DMP (0.4 mL, 3.2 mmol) and cat. *P*-TsOH in DCM (20 mL) was stirred at room temperature for 3 h. The reaction mixture was then diluted with Et_2O and washed with saturated $NaHCO_3$ solution, water, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The crude product was then purified using flash chromatography (5:5 hexane/EtOAc) to yield 2-[5-(4-

Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol **(132)** as a yellow oil (yield 0.71 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.34 (s, 3H, CHO(C(C**H**$_3$)$_2$)OCH), 1.37 (s, 3H, CHO(C(C**H**$_3$)$_2$)OCH), 1.46-1.61 (m, 2H, $CH_2CHO(C(CH_3)_2)OCHC$**H**$_2CH_2O$), 2.74 (dd, 1H, C**H**$_2CHO(C(CH_3)_2)OCHCH_2CH_2O$), 2.87-2.93 (m, 1H, C**H**$_2CHO(C(CH_3)_2)OCHCH_2CH_2O$), 3.68 (t, 2H, *J*=5.6 Hz, $CH_2CHO(C(CH_3)_2)OCHCH_2C$**H**$_2$O), 3.84 (s, 3H, OC**H**$_3$), 3.86-3.91 (m, 2H, CH_2C**H**$O(C(CH_3)_2)OC$**H**CH_2CH_2O), 5.10 (s, 2H, OC**H**$_2$), 6.65 (d, 1H, J= 8.3 Hz, H-5), 6.74-6.80 (m, 2H, H-2 & H-6), 7.23-7.47 (m, 5H, Ar-**H**). (*Plate 28a*)

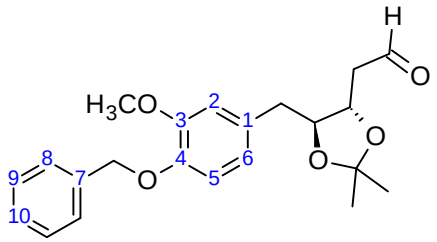
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.3 (CHO(C(**C**H_3)$_2$)OCH), 34.8 ($CH_2CHO(C(CH_3)_2)OCH$**C**H_2CH_2OH), 38.6 (**C**$H_2CHO(C(CH_3)_2)OCHCH_2CH_2OH$), 56.0 (O**C**$H_3$), 60.8 ($CH_2CHO(C(CH_3)_2)OCHCH_2$**C**$H_2OH$), 71.2 (O**C**$H_2$), 79.8 ($CH_2CHO(C(CH_3)_2)O$**C**$HCH_2CH_2OH$), 81.6 ($CH_2$**C**$HO(C(CH_3)_2)OCHCH_2CH_2OH$), 108.6 (CHO(**C**$(CH_3)_2$)OCH), 113.3 (C-2), 114.3 (C-5), 121.3 (C-6), 127.3 (C-9), 127.8 (C-10), 128.5 (C-8), 130.4 (C-1), 137.3 (C-7), 146.8 (C-4), 149.7 (C-3). (*Plate 28b*)

ER$^+$-HRMS *m/z*: 395.1837 $[M + Na]^+$

(Calculated for $C_{22}H_{28}O_5$+Na, 395.1834)

IR ν_{max} (cm^{-1}): 3409 (OH), 1259 (C-O)

4.2.31 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde (133)[20]



To a stirred solution of 2-iodoxybenzoic acid (IBX) (0.8 g, 2.7 mmol) in DMSO (5 mL), was added a solution of alcohol **132** (0.5 g, 1.4 mmol) in THF (10 mL) at room temperature and was stirred for 3 hours. After completion of the reaction as observed by TLC monitoring, water (10 mL) was added to the reaction mixture and the precipitated solid was filtered off. The filtrate was diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed successively with $NaHCO_3$, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified using column chromatography (7:3 hexane/EtOAc) to afford the desired product, 2-[5-(4-benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde **(133)** as a yellow oil (yield 0.45 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.41 (s, 6H, CHO(C(C**H**$_3$)$_2$)OCH), 2.21-2.28 (m, 1H, CH_2CHO(C(CH_3)$_2$)OCHC**H**$_2$COH),2.41-2.50(m,1H, CH_2CHO(C(CH_3)$_2$)OCHC**H**$_2$COH), 2.74-2.82 (m, 1H, C**H**$_2$CHO(C(CH_3)$_2$)OCHCH_2COH), 2.97-3.06 (m, 1H, *J*=5.6 Hz, C**H**$_2$CHO(C(CH_3)$_2$)OCHCH_2COH), 3.89 (s, 3H, OC**H**$_3$), 3.89-3.96 (m, 2H, CH_2C**H**O(C(CH_3)$_2$)OC**H**CH_2COH), 4.13-4.20 (m, 1H), 5.14 (s, 2H, OC**H**$_2$), 6.70 (d, 1H, J= 8.3 Hz, H-5), 6.77-6.85 (m, 2H, H-2 & H-6), 7.28-7.48 (m, 5H, Ar-**H**), 9.71 (t, 1H, *J*= 2.0 Hz, CH_2CHO(C(CH_3)$_2$)OCHCH_2CO**H**). (*Plate 29a*)

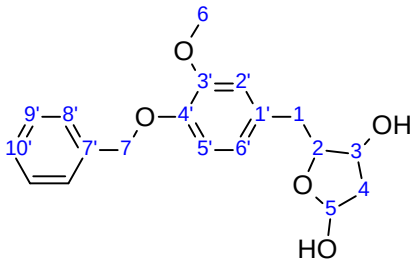
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.1 ($CHO(C(\underline{\mathbf{C}}H_3)_2)OCH$), 27.2 ($CHO(C(\underline{\mathbf{C}}H_3)_2)OCH$) 38.4 ($CH_2CHO(C(CH_3)_2)OCH\underline{\mathbf{C}}H_2COH$), 46.6 ($\underline{\mathbf{C}}H_2CHO(C(CH_3)_2)OCHCH_2COH$), 56.0($O\underline{\mathbf{C}}H_3$), 71.2 ($O\underline{\mathbf{C}}H_2$), 75.7 ($CH_2CHO(C(CH_3)_2)O\underline{\mathbf{C}}HCH_2CH_2O$), 80.8 ($CH_2\underline{\mathbf{C}}HO(C(CH_3)_2)OCHCH_2COH$), 108.9 ($CHO(\underline{\mathbf{C}}(CH_3)_2)OCH$), 113.2 (C-2), 114.4 (C-5), 121.3 (C-6), 127.3 (C-9), 127.8 (C-10), 128.5 (C-8), 129.9 (C-1), 137.2 (C-7), 147.0 (C-4), 149.8 (C-3), 199.7 ($CH_2CHO(C(CH_3)_2)OCHCH_2\underline{\mathbf{C}}OH$). (*Plate 29b*)

ER^+-HRMS *m/z*: 393.1680 $[M + Na]^+$

(Calculated mass for $C_{22}H_{26}O_5$+Na, 393.1678)

IR ν_{max} (cm^{-1}): 1724 (C=O), 1259 (C-O)

4.2.32 5-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-2,4-diol (139)[21]



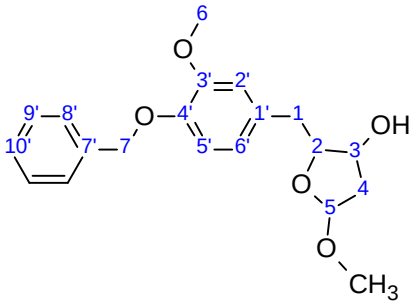
2-[5-(4-Benzyloxy-3-methoxy)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde (0.5 g, 1.3 mmol) **(133)** was dissolved in a mixture of (1:1) THF: 1N HCl (10 mL), this mixture was then stirred at room temperature for 12 h. After completion of the reaction as determined by TLC monitoring, the reaction mixture was diluted with water and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using flash chromatography

(3:7 hexane/EtOAc) to yield 5-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-2,4-diol **(137)** as a yellow oil (yield 0.35 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.07-2.22 (m, 2H, H-1), 2.90-3.12 (m, 2H, H-4), 3.90 (s, 3H, OC**H$_3$**), 4.07-4.19 (m, 2H, H-2, H-3), 5.14 (s, 2H, OC**H$_2$**), 5.52 (d, 1H, *J*= 4.7 Hz, H-5), 6.75- 6.91 (m, 3H, Ph-**H**), 7.30- 7.47 (m, 5H, Ar-**H**). (*Plate 30a*)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 36.4 (C-1), 42.0 (C-4), 56.0 (O**C**H$_3$), 71.2 (C-3), 71.6 (O**C**H$_2$), 85.8 (C-2), 98.7 (C-5), 113.2 (C-2'), 114.4 (C-5'), 121.1 (C-6'), 127.3 (C-9'), 127.8 (C-10'), 128.5 (C-8'), 131.6 (C-1'), 137.4 (C-7'), 146.9 (C-4'), 149.7 (C-3'). (*Plate 30b*)

4.2.33 2-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-3-ol (140)



2-[5-(4-Benzyloxy-3-methoxy)phenyl]-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde (0.5 g, 1.3 mmol) **(133)** was dissolved in MeOH with cat. amount of P-TsOH. This mixture was then stirred at room temperature for 6 h. After completion of the reaction as determined by TLC monitoring, the reaction mixture was diluted with water and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified using flash chromatography (3:7 hexane/EtOAc) to yield 5-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-2,4-diol **(137)** as a yellow oil (yield 0.35 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.14-2.22 (m, 2H, H-1), 3.20-3.23 (m, 2H, H-4), 3.22 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 4.10-4.19 (m, 2H, H-2, H-3), 5.14 (s, 2H, OC**H$_2$**), 5.52 (d, 1H, *J*= 4.7 Hz, H-5), 6.77- 6.95 (m, 3H, Ph-**H**), 7.32- 7.46 (m, 5H, Ar-**H**).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 36.2 (C-1), 42.6 (C-4), 54.7 (OC**H$_3$**), 56.0 (O**C**H$_3$), 71.7 (C-3), 71.9 (O**C**H$_2$), 85.2 (C-2), 98.5 (C-5), 113.4 (C-2'), 114.7 (C-5'), 121.8 (C-6'), 127.7 (C-9'), 127.4 (C-10'), 128.2 (C-8'), 131.7 (C-1'), 137.4 (C-7'), 146.9 (C-4'), 149.4 (C-3').

4.3 References

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APPENDIX

Plate 1a: ^{1}H NMR spectrum for phenylethyltriphenylphosphonium bromide (92)

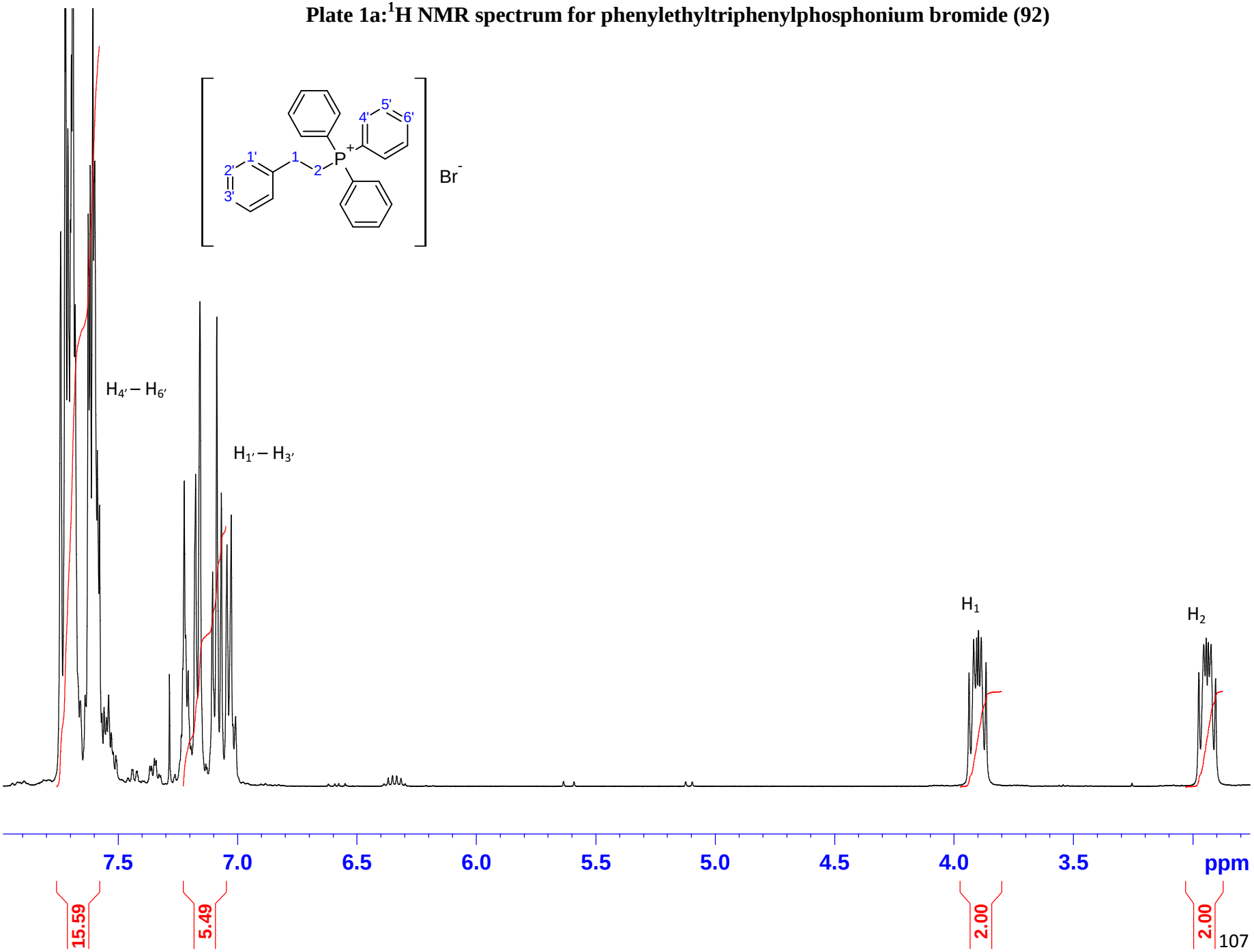

Plate 1a:^{1}H NMR spectrum for phenylethyltriphenylphosphonium bromide (92)

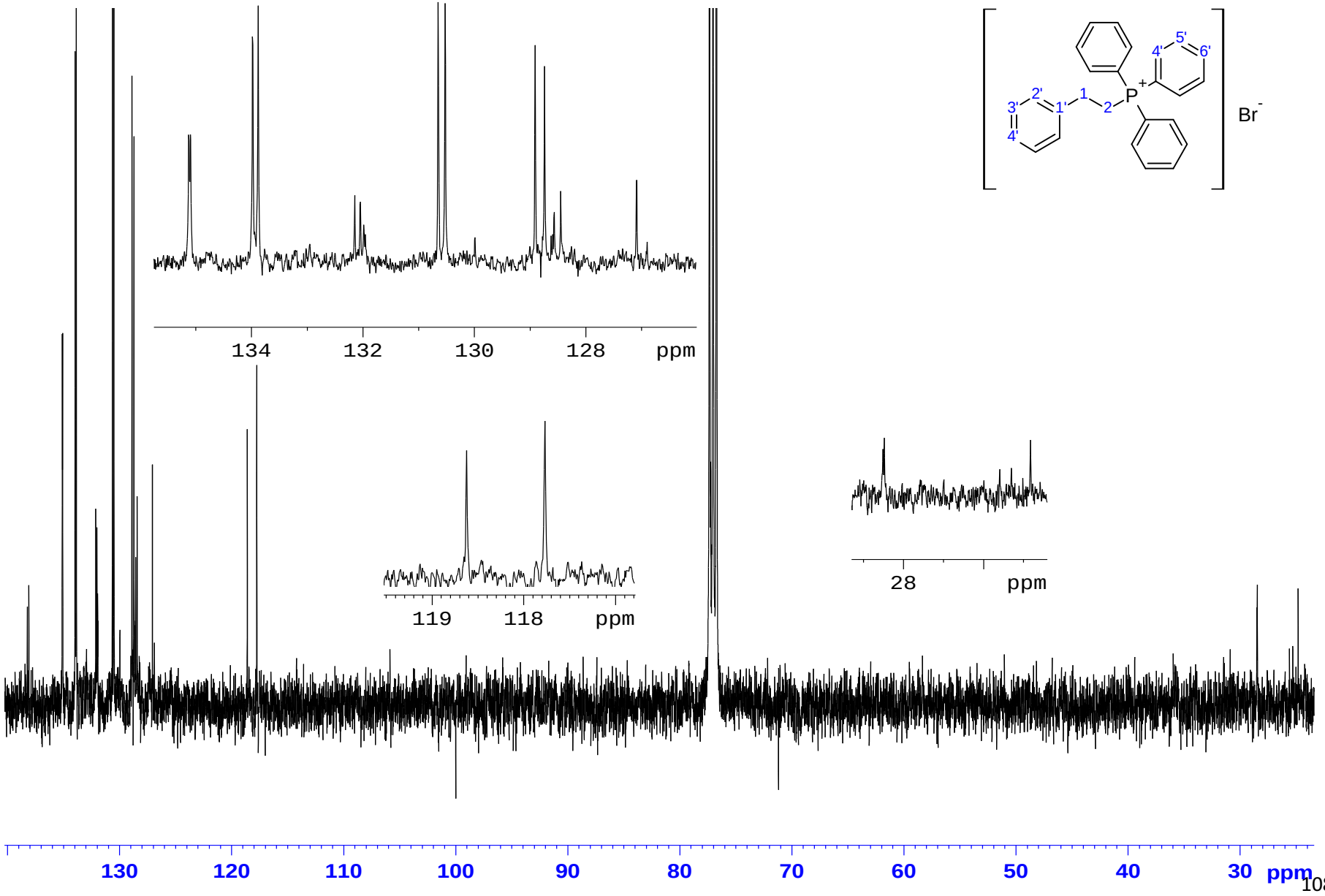

Plate 2a: ^{1}H NMR spectrum for diethyl-2-phenylethyphosphonate (97)

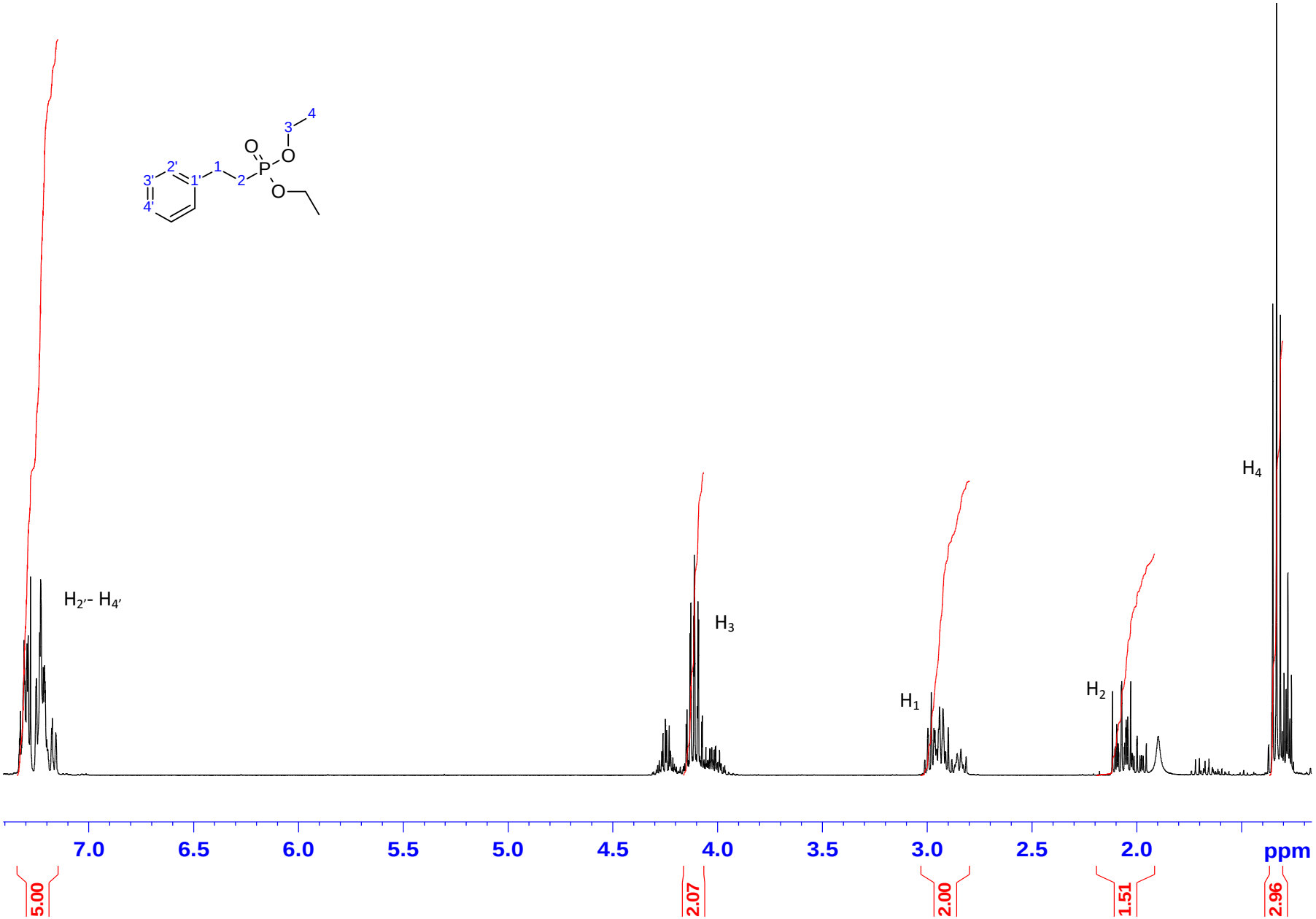

Plate 2b: ^{13}C NMR spectrum for diethyl-2-phenylethyphosphonate (97)

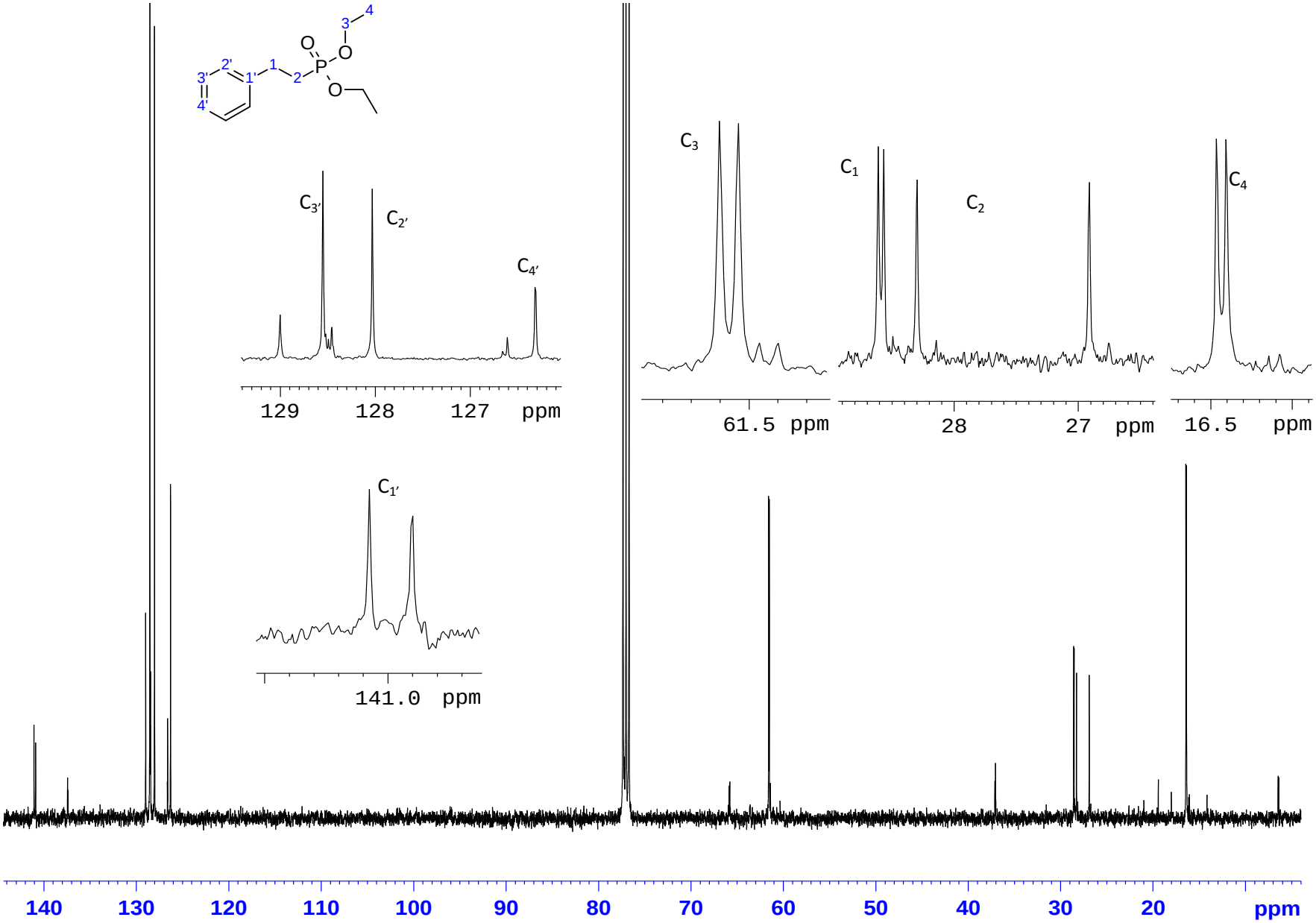

Plate 2c: ^{31}P NMR spectrum for diethyl-2-phenylethyphosphonate (97)

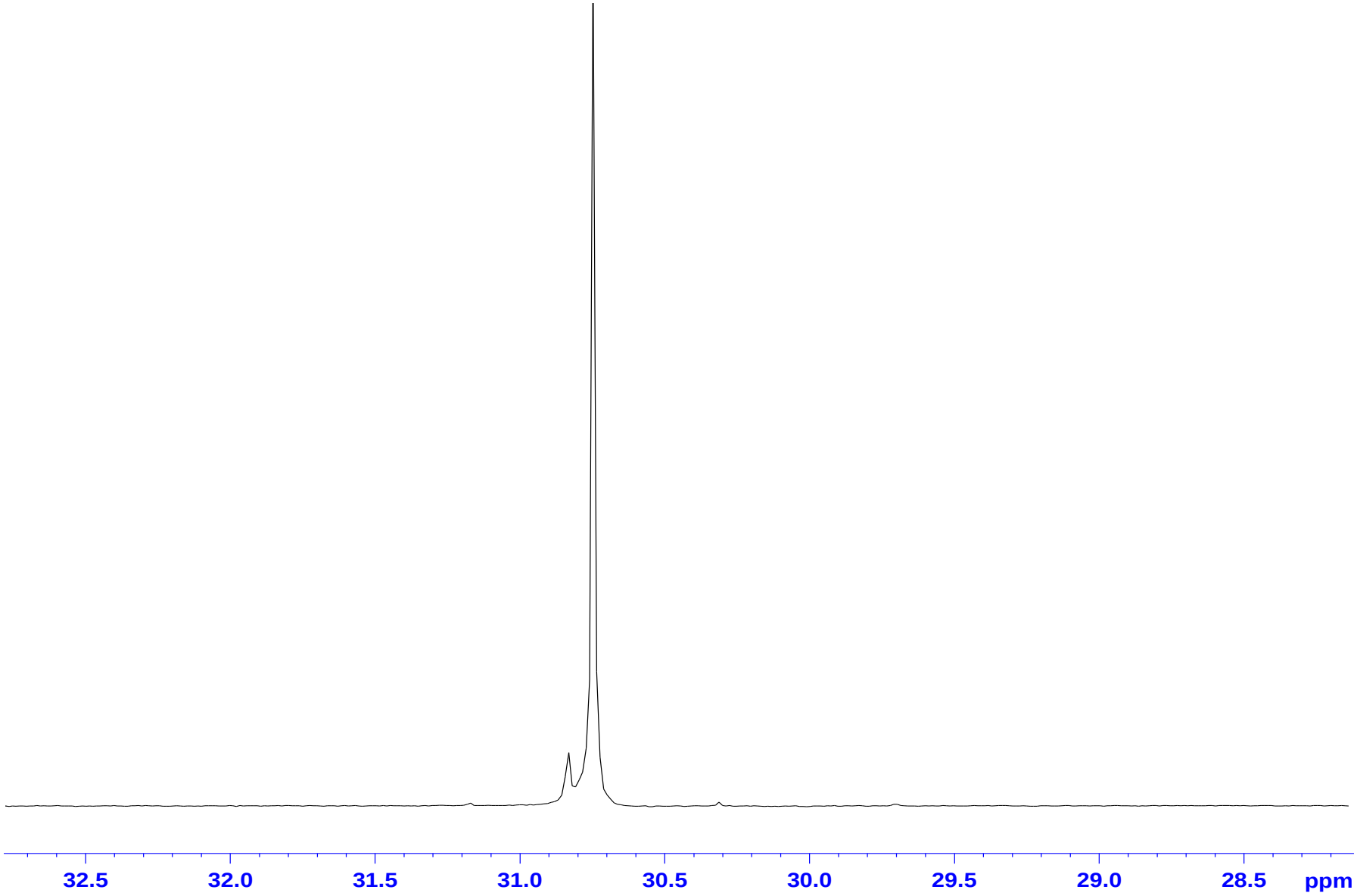

Plate 3a: (*Z*)-1,1'-prop-1-ene-1,3-diyldibenzene (93)

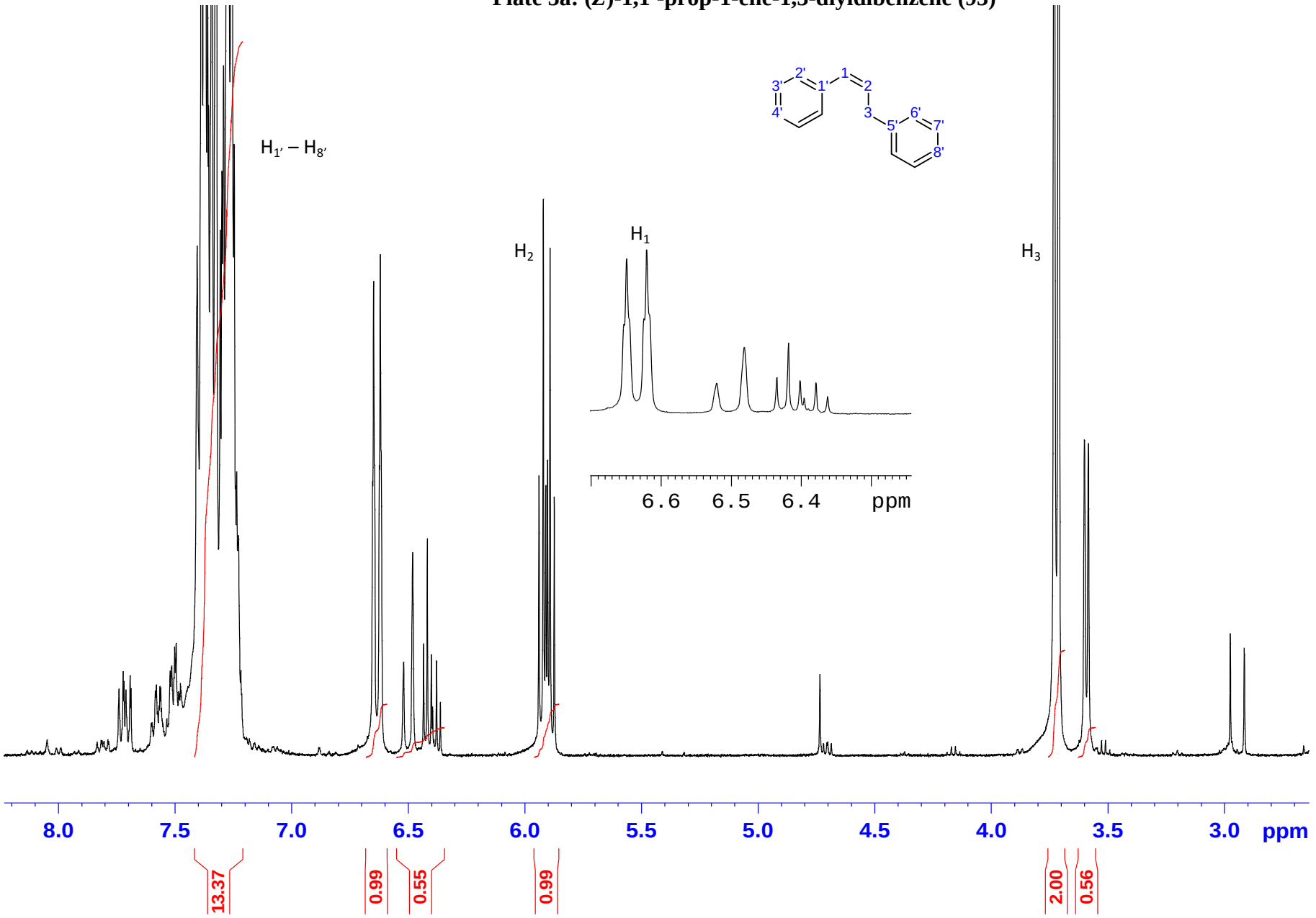

Plate 3b: ^{13}C NMR spectrum for (*Z*)-1,1'-prop-1-ene-1,3-diyldibenzene (93)

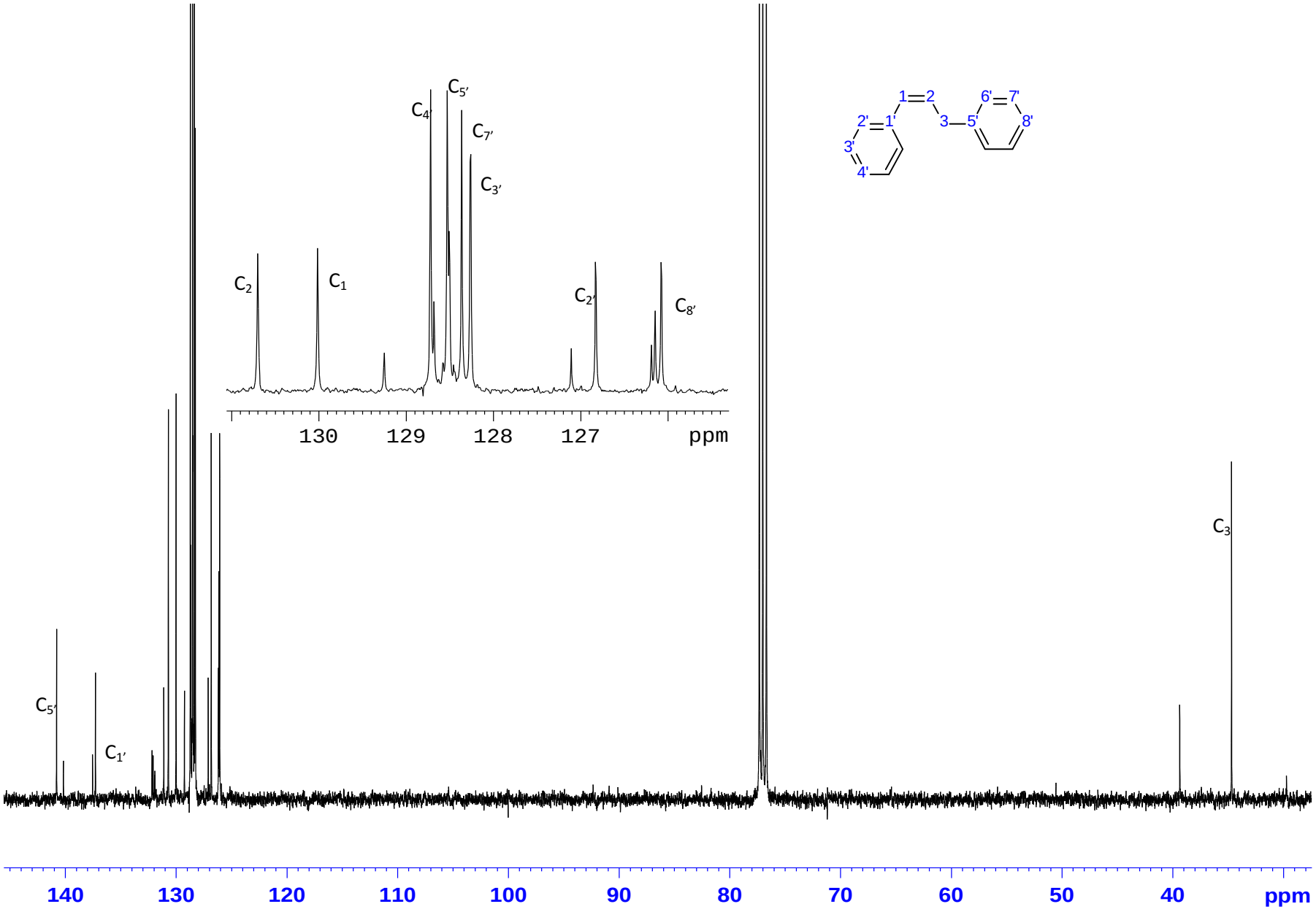

Plate 4a: ^{1}H NMR spectrum for (*E*)-1,1-prop-1-ene-1,3-diyldibenzene (93)

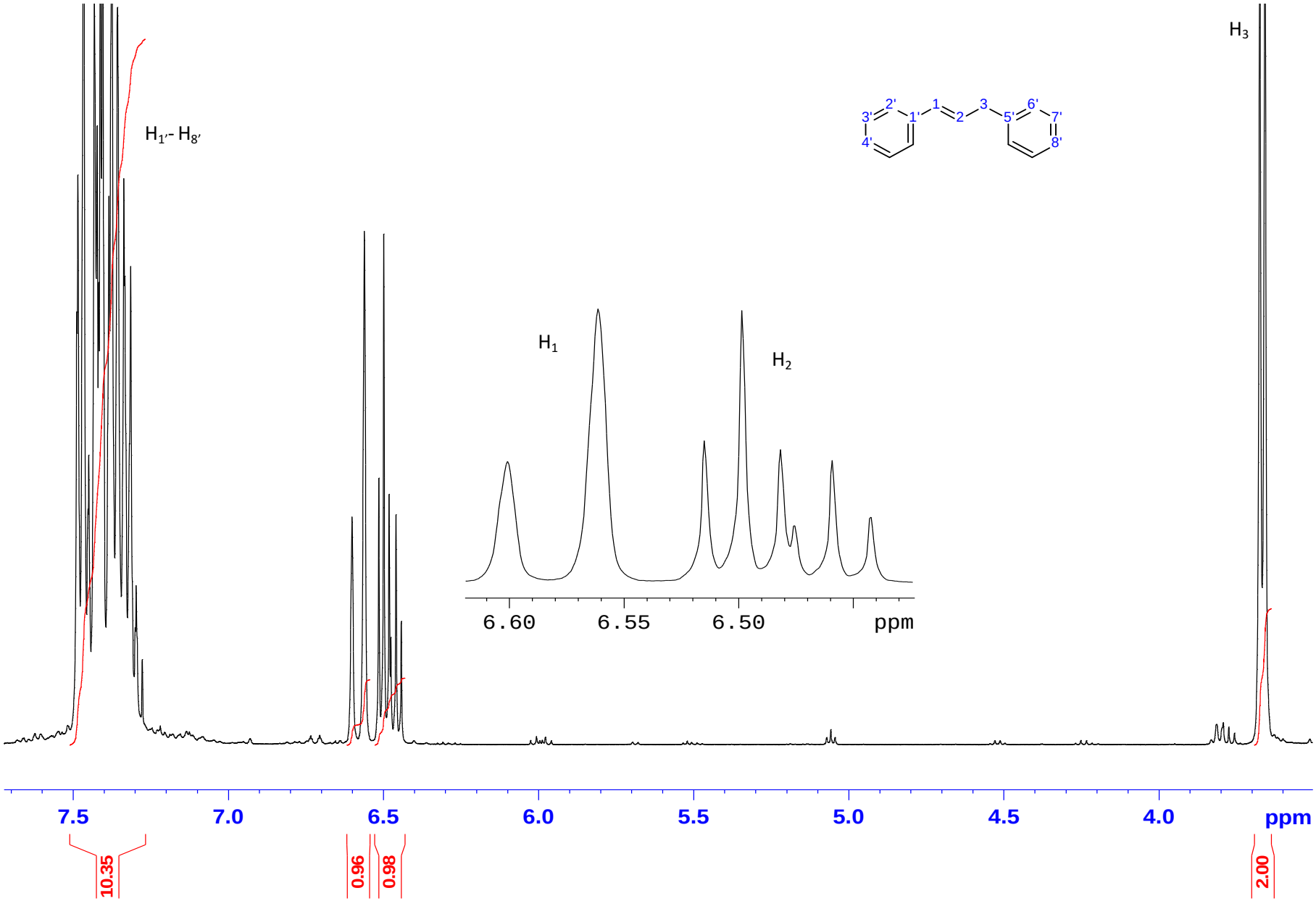

Plate 5a: ^{1}H NMR spectrum for methyl 3,4,5-trihydroxybenzoate (99)

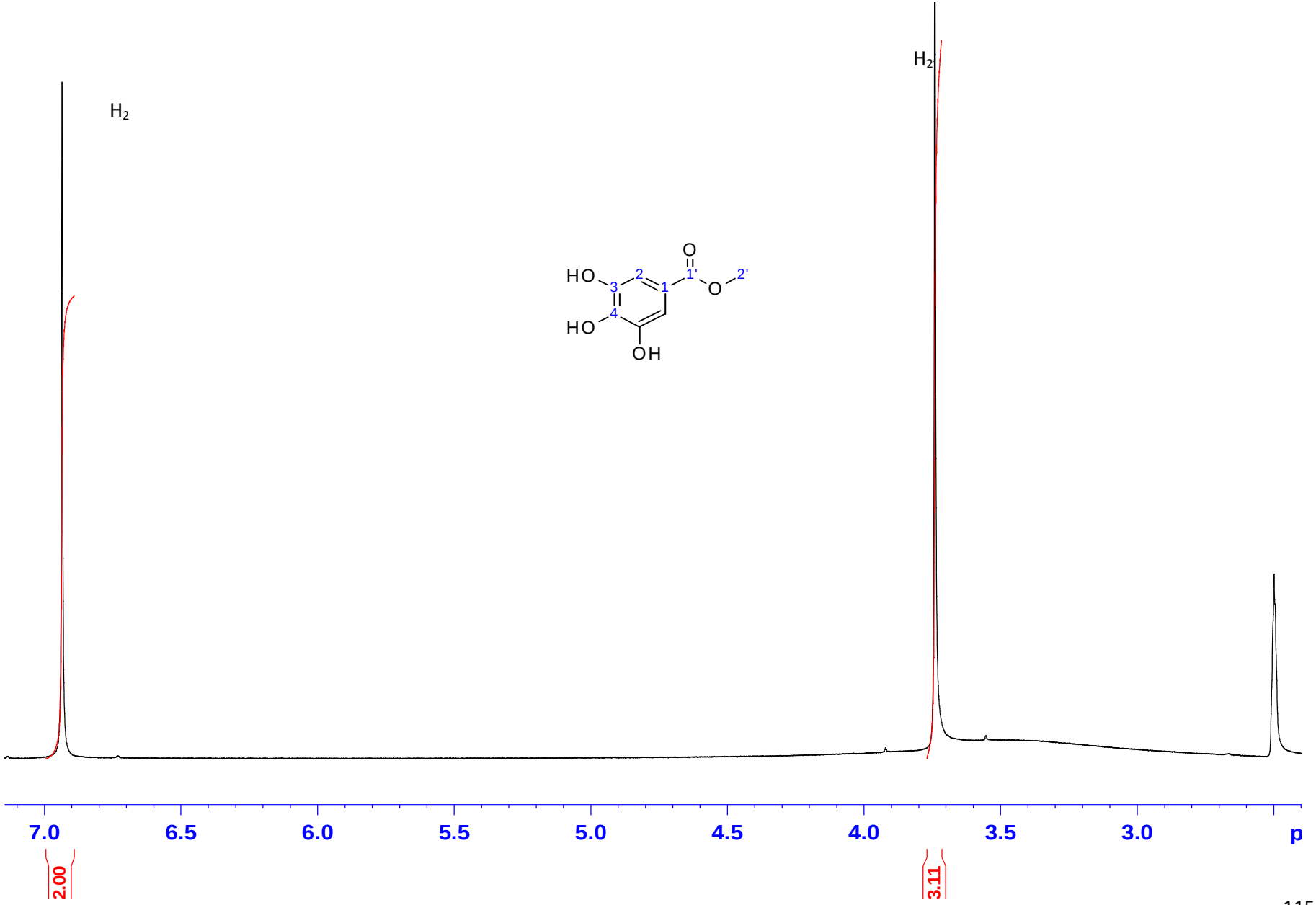

Plate 5b: ^{13}C NMR spectrum for methyl 3,4,5-trihydroxybenzoate (99)

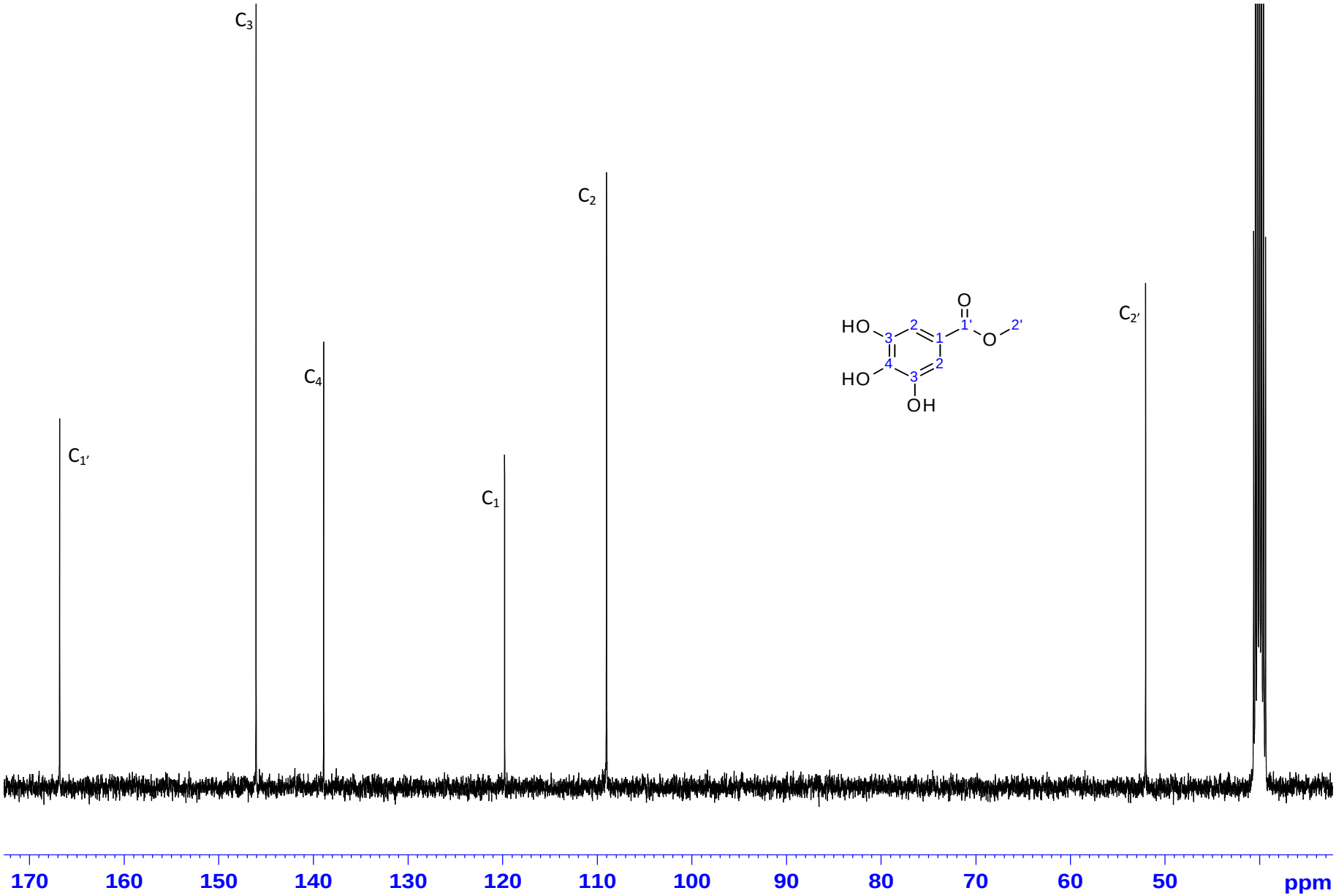

Plate 6a: ^{1}H NMR spectrum for Methyl 3-benzyloxy-4,5-(ethoxymethylenedioxy)benzoate (101)

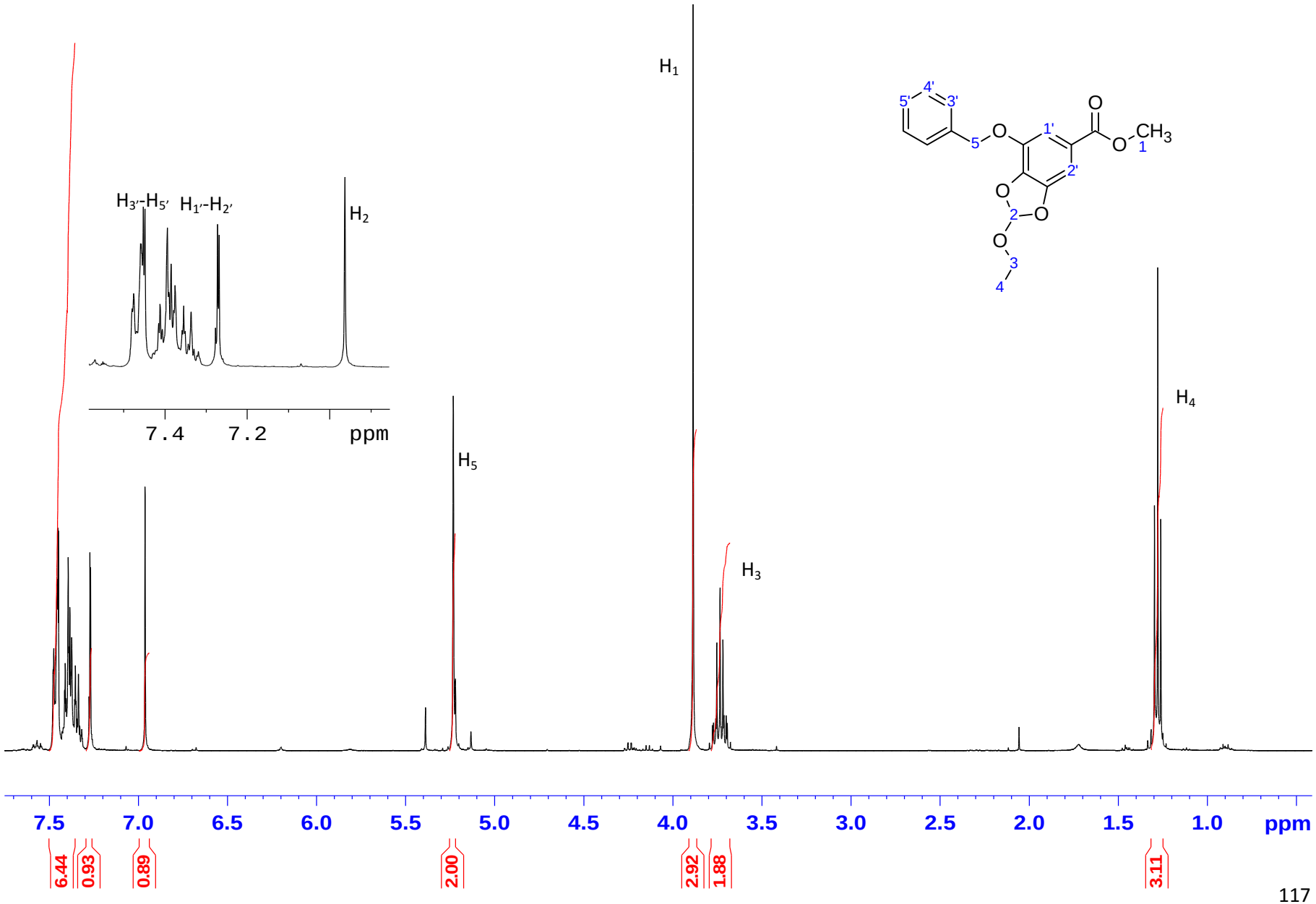

Plate 7a: ^{1}H NMR spectrum for methyl 3-benzyloxy-4,5-dihydroxybenzoate (102)

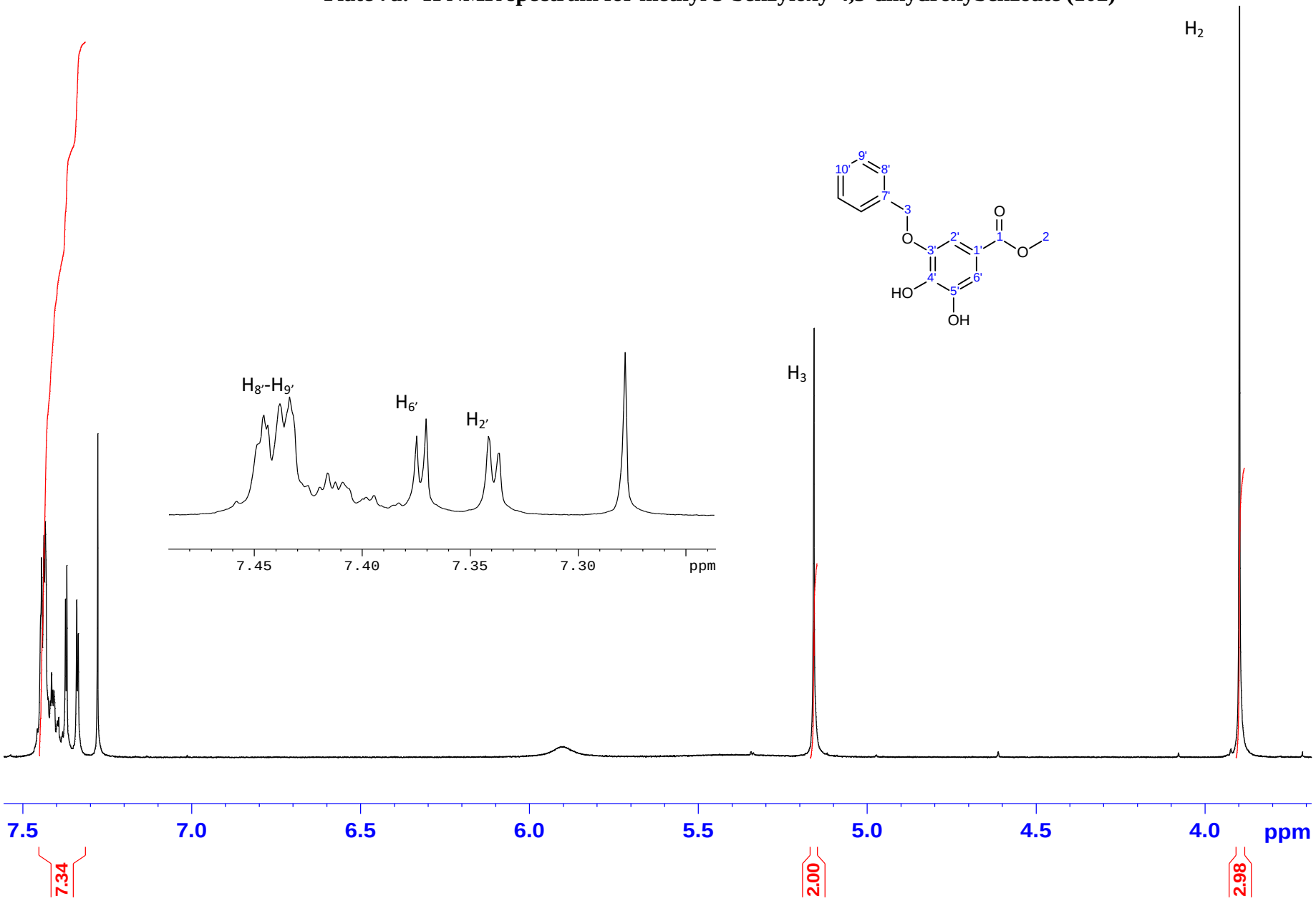

Plate 7b: ^{13}C NMR spectrum for methyl 3-benzyloxy-4,5-dihydroxybenzoate (102)

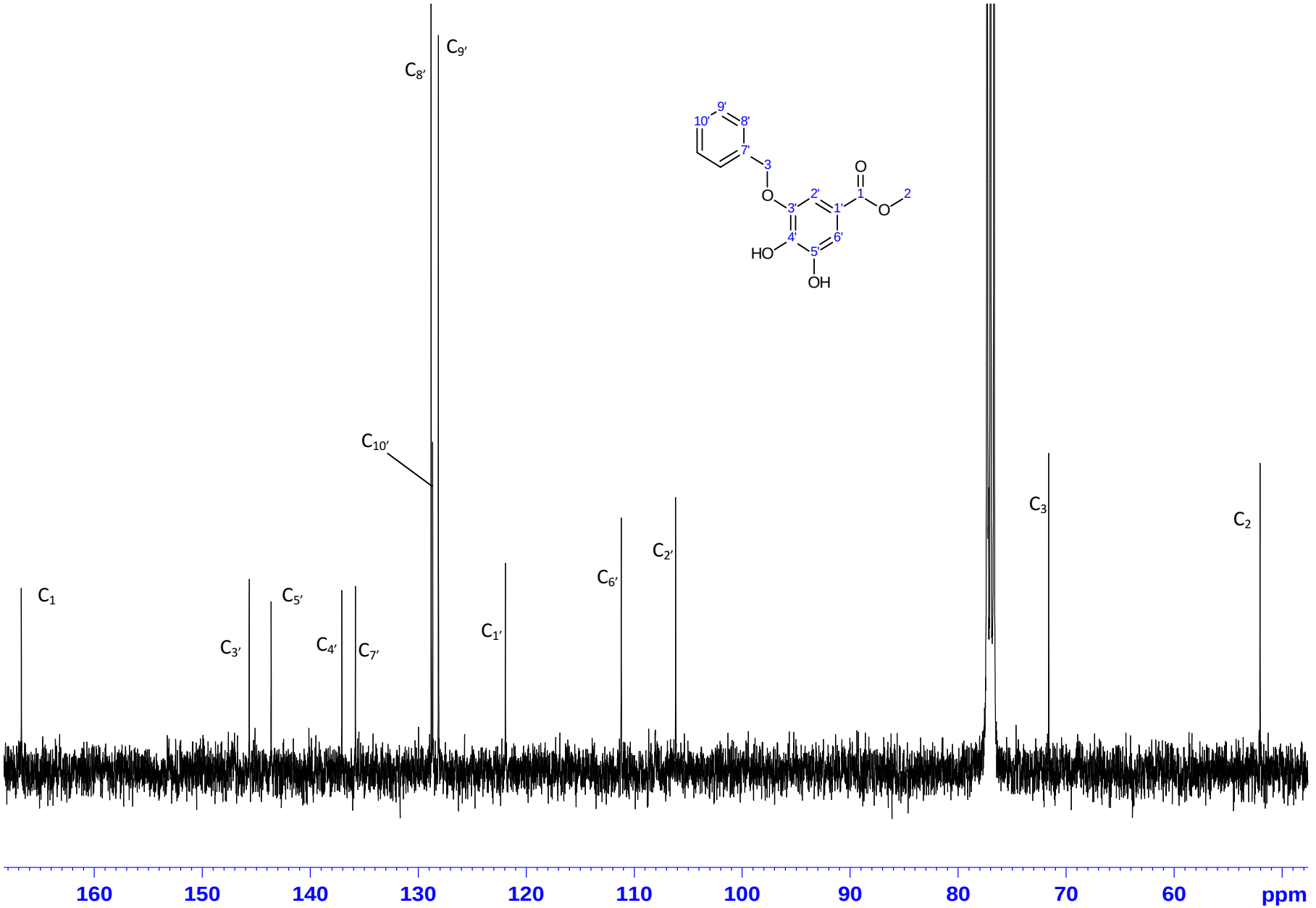

Plate 8a: ^{1}H NMR spectrum for methyl 3-benzyloxy-4,5-dimethoxybenzoate (103)

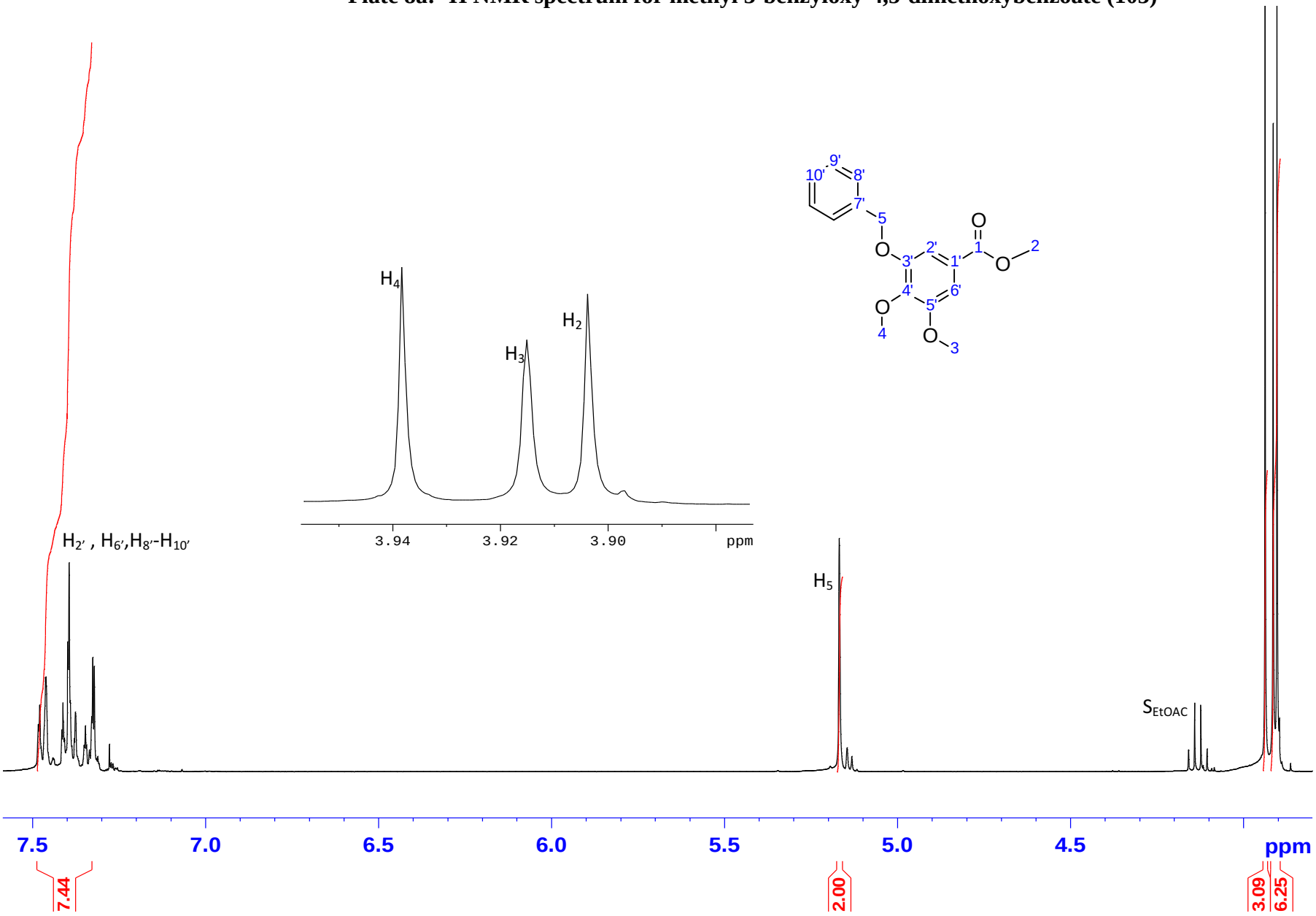

Plate 8b: ^{13}C NMR spectrum for methyl 3-benzyloxy-4,5-dimethoxybenzoate (103)

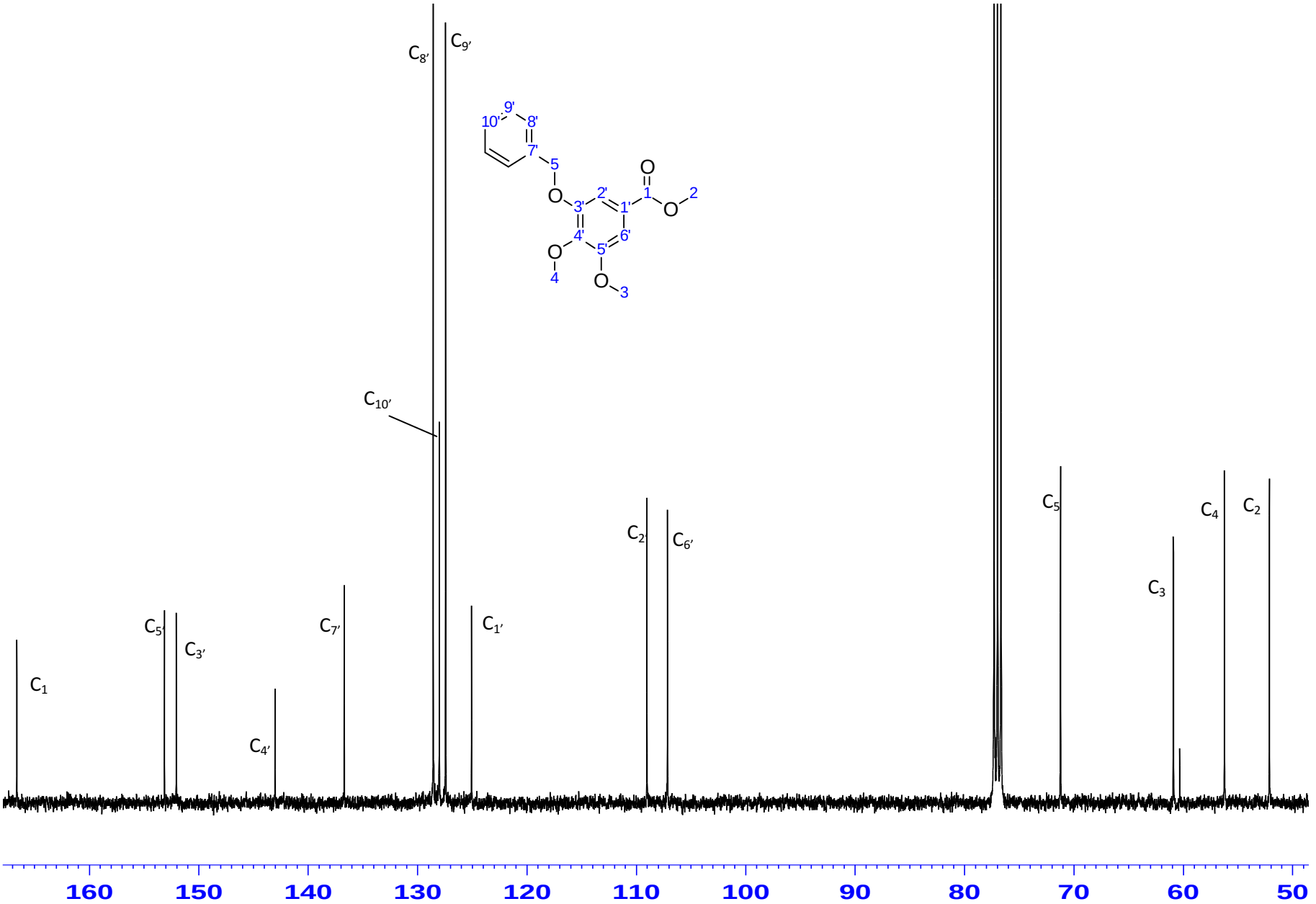

Plate 9a: ^{1}H NMR spectrum for 3-benzyloxy-4,5-dimethoxyphenylmethanol (104)

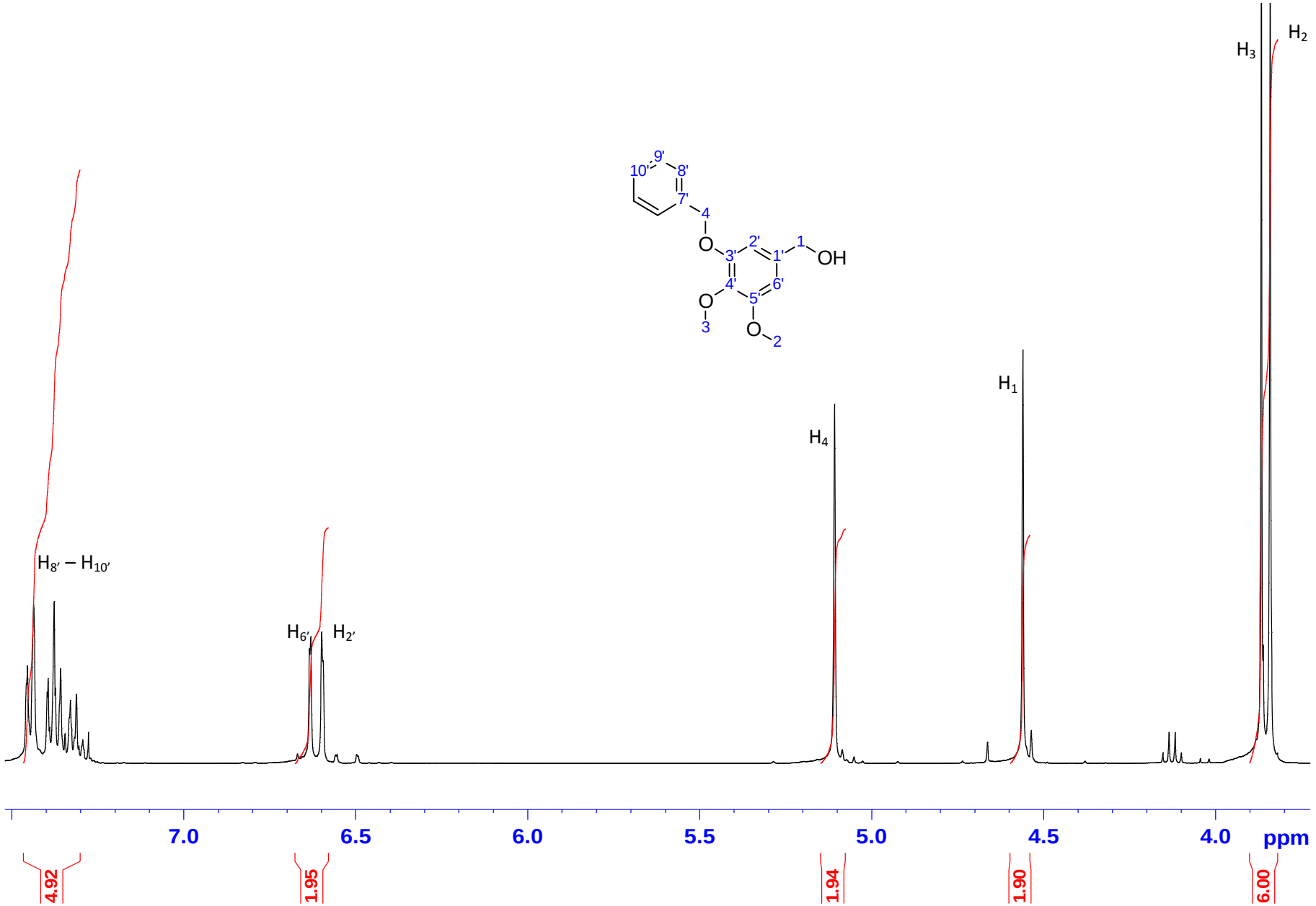

Plate 9b: ^{13}C NMR spectrum for 3-benzyloxy-4,5-dimethoxyphenylmethanol (104)

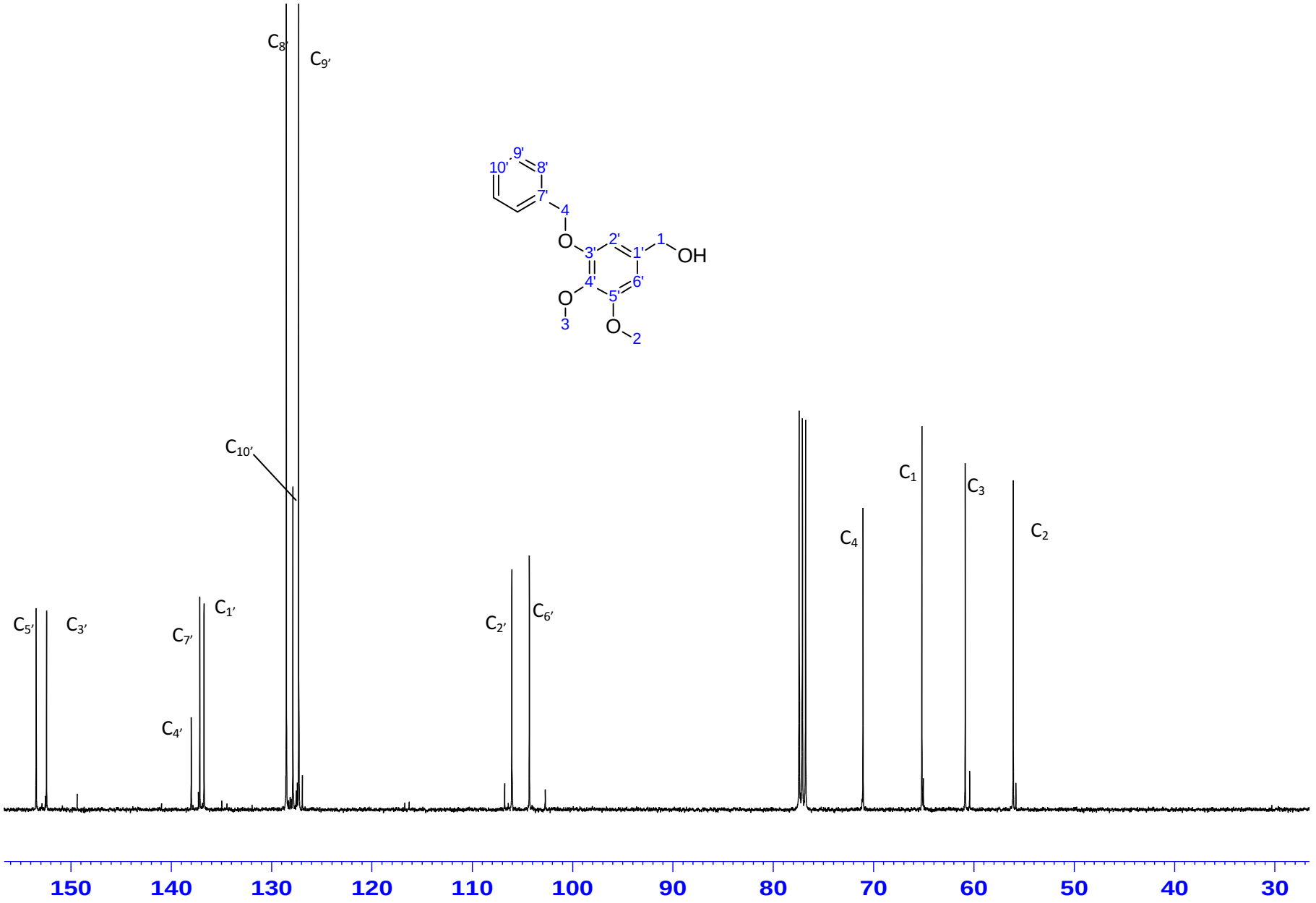

Plate 10a: ^{1}H NMR spectrum for 3-benzyloxy-4,5-dimethoxybenzaldehyde (105)

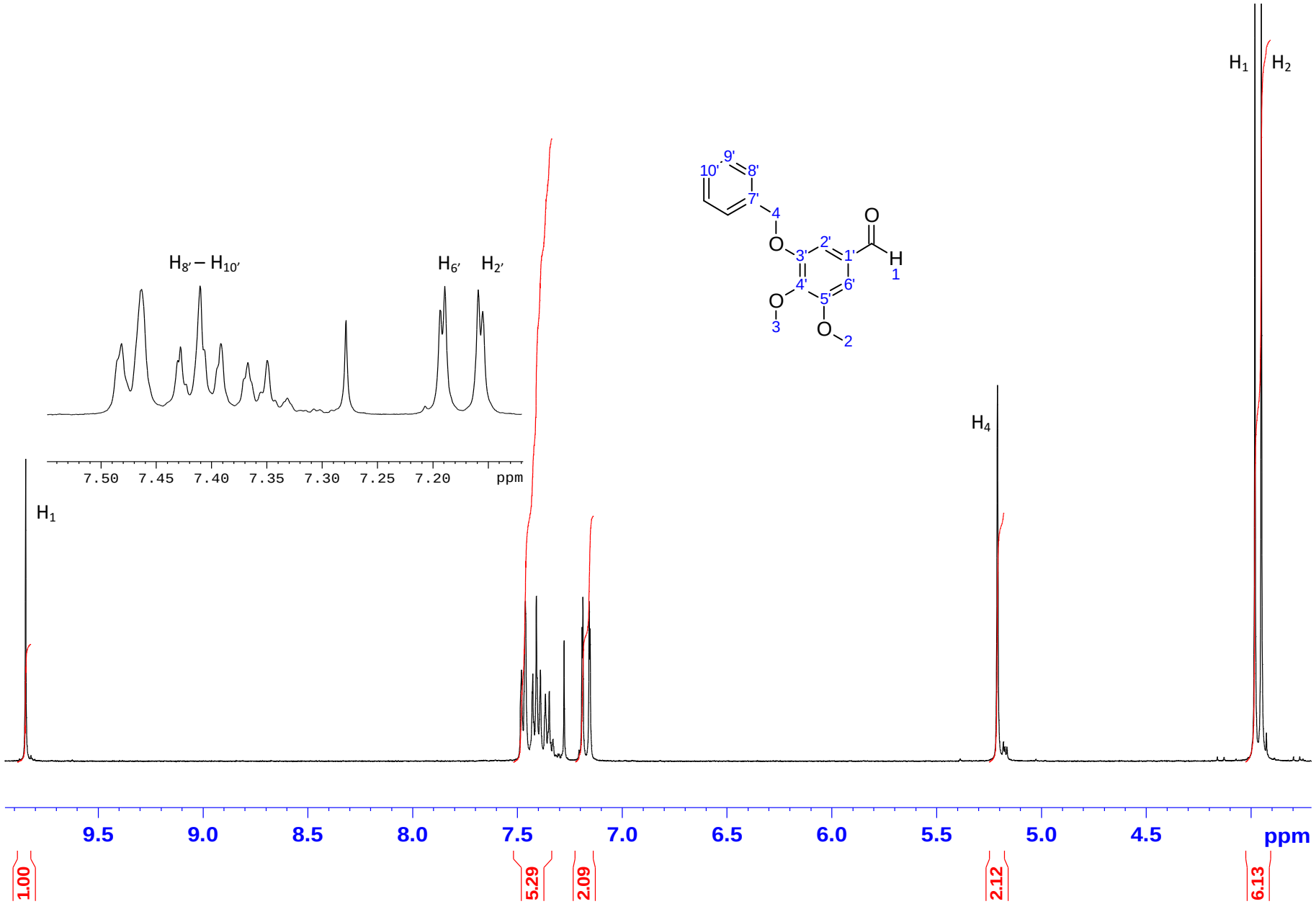

Plate 10b: ^{13}C NMR spectrum for 3-(benzyloxy)-4,5-dimethoxybenzaldehyde (105)

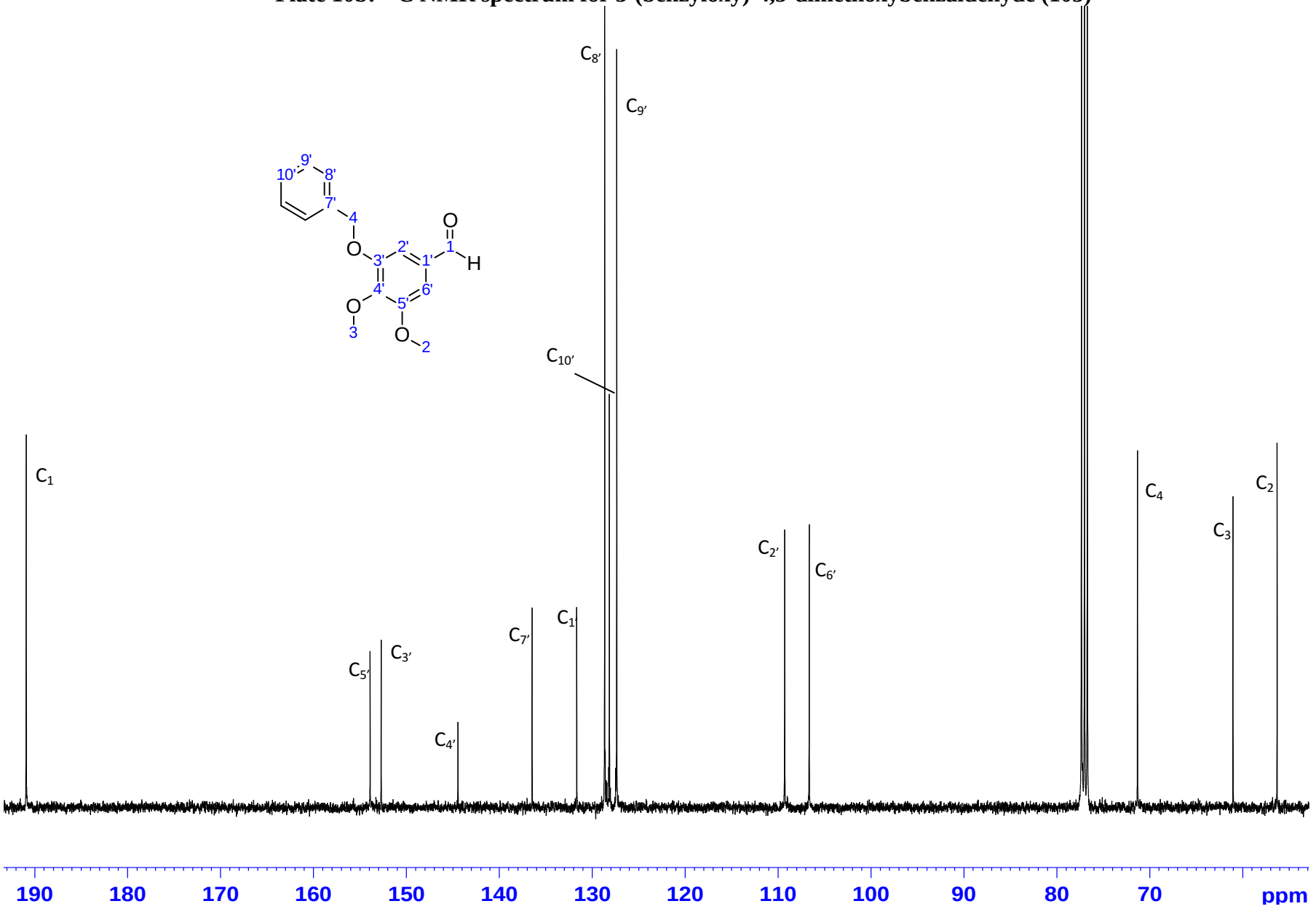

Plate 11a: ^{1}H NMR spectrum for 1-benzyloxy-2,3-dimethoxy-5-vinylbenzene (106)

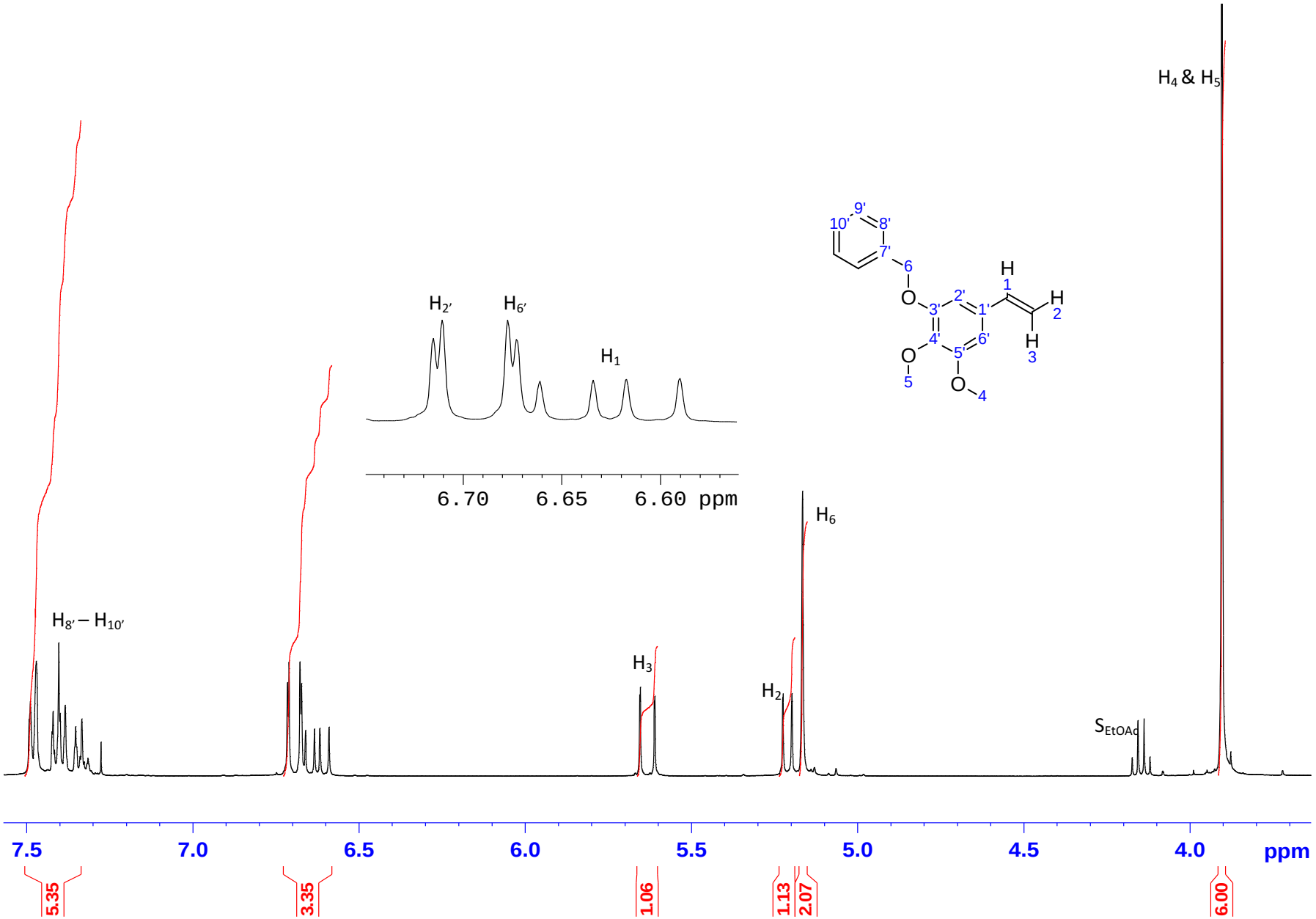

Plate 11b: ^{13}CNMR spectrum for 1-benzyloxy-2,3-dimethoxy-5-vinylbenzene (106)

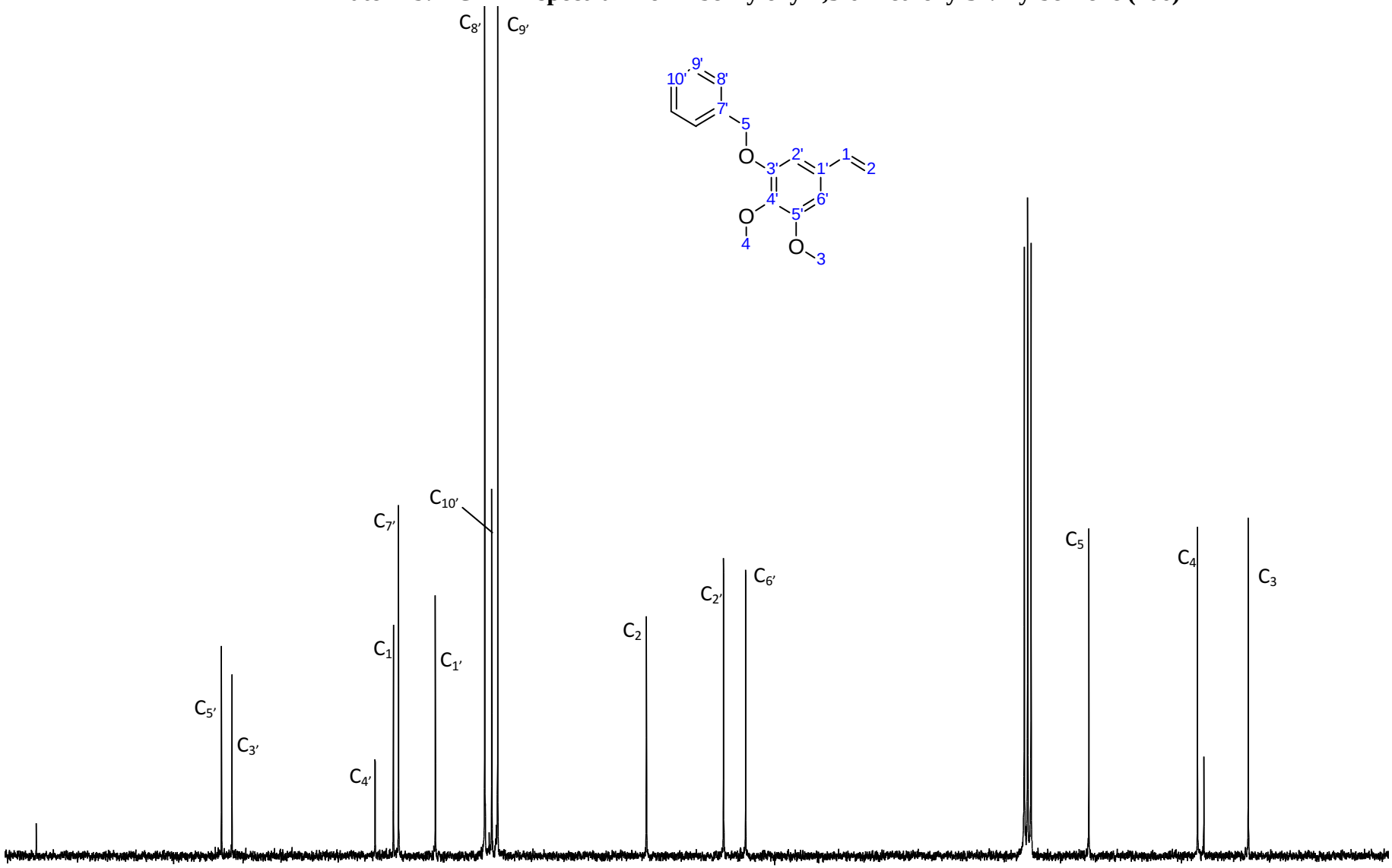

Plate 12a: ^{1}H NMR spectrum for 2-(3-benzyloxy-4,5-dimethoxyphenyl)ethanol (107)

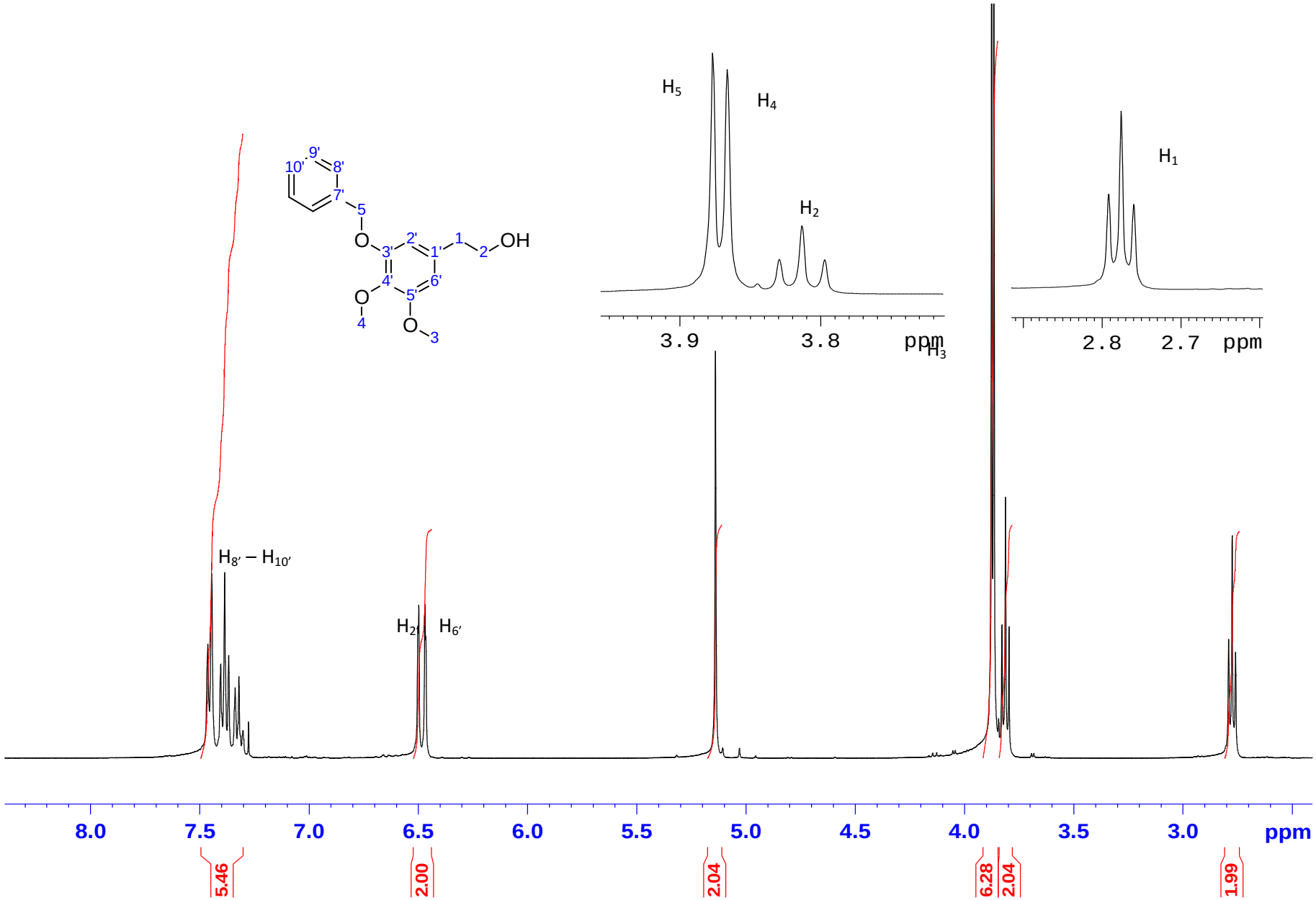

Plate 12b: ^{13}C NMR spectrum for 2-(3-benzyloxy-4,5-dimethoxyphenyl)ethanol (107)

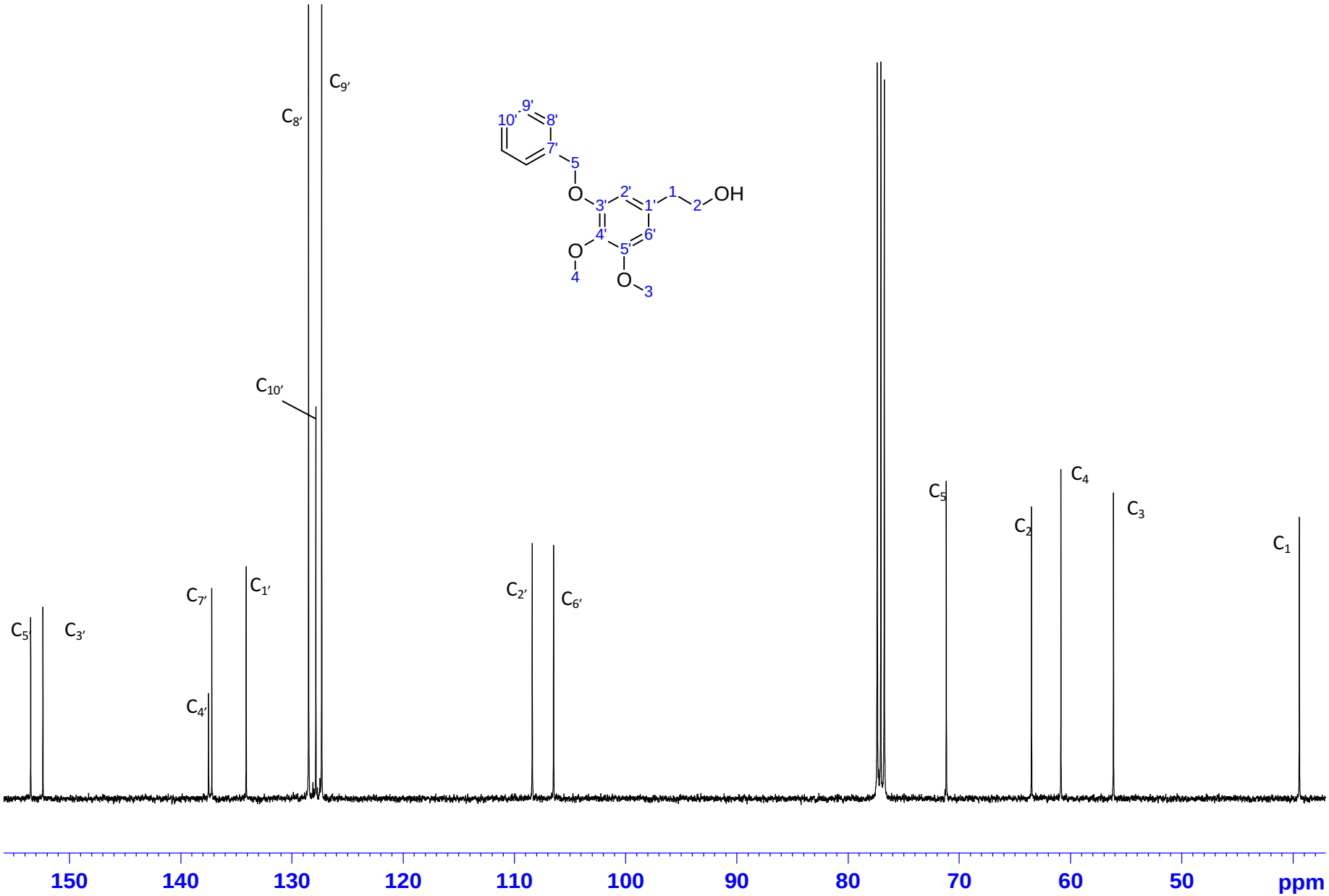

Plate 13a: ^{1}H NMR spectrum for 1-benzyloxy-5-(2-bromoethyl)-2,3-dimethoxybenzene (108)

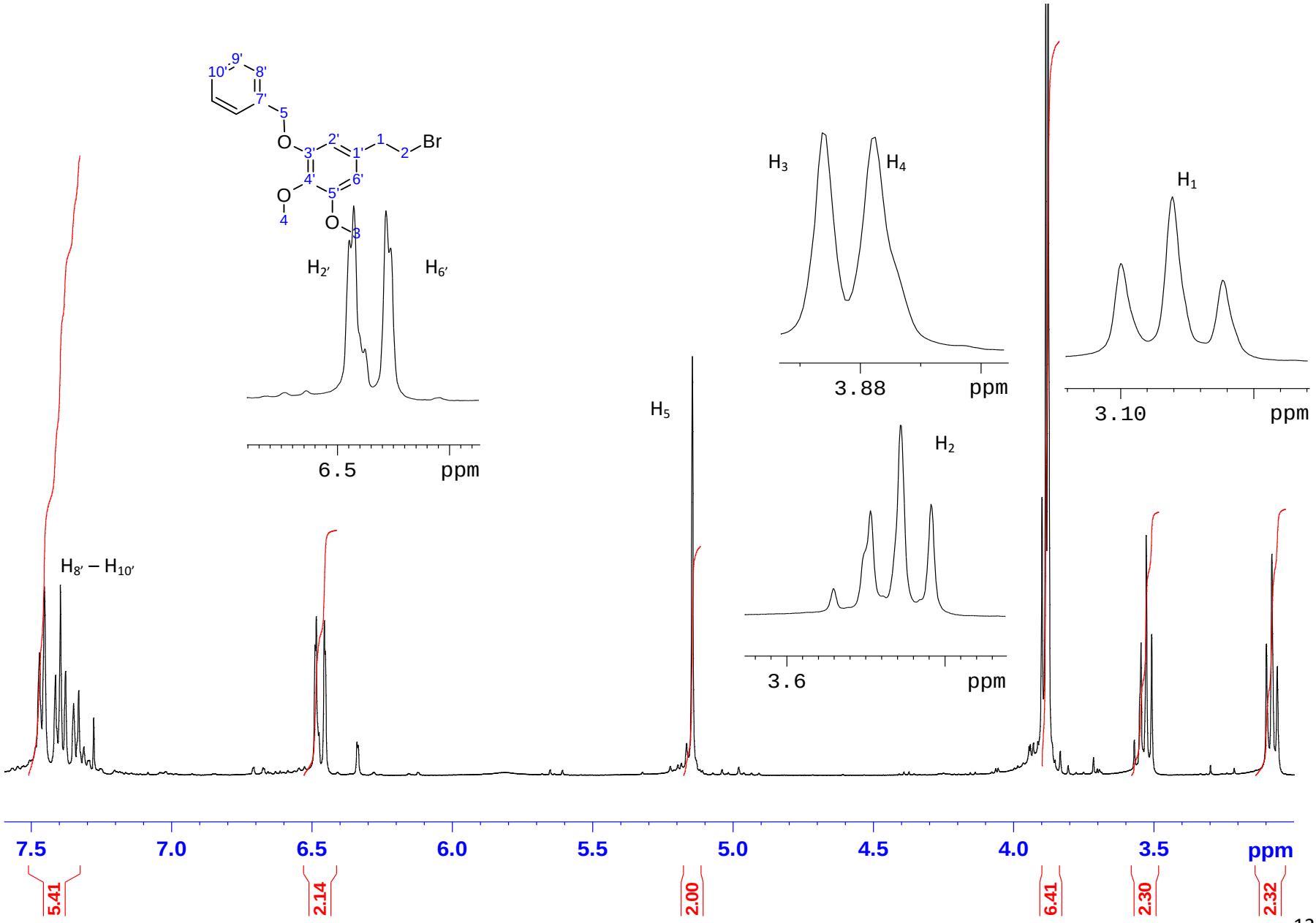

Plate 13b: ^{13}C NMR spectrum for 1-benzyloxy-5-(2-bromoethyl)-2,3-dimethoxybenzene (108)

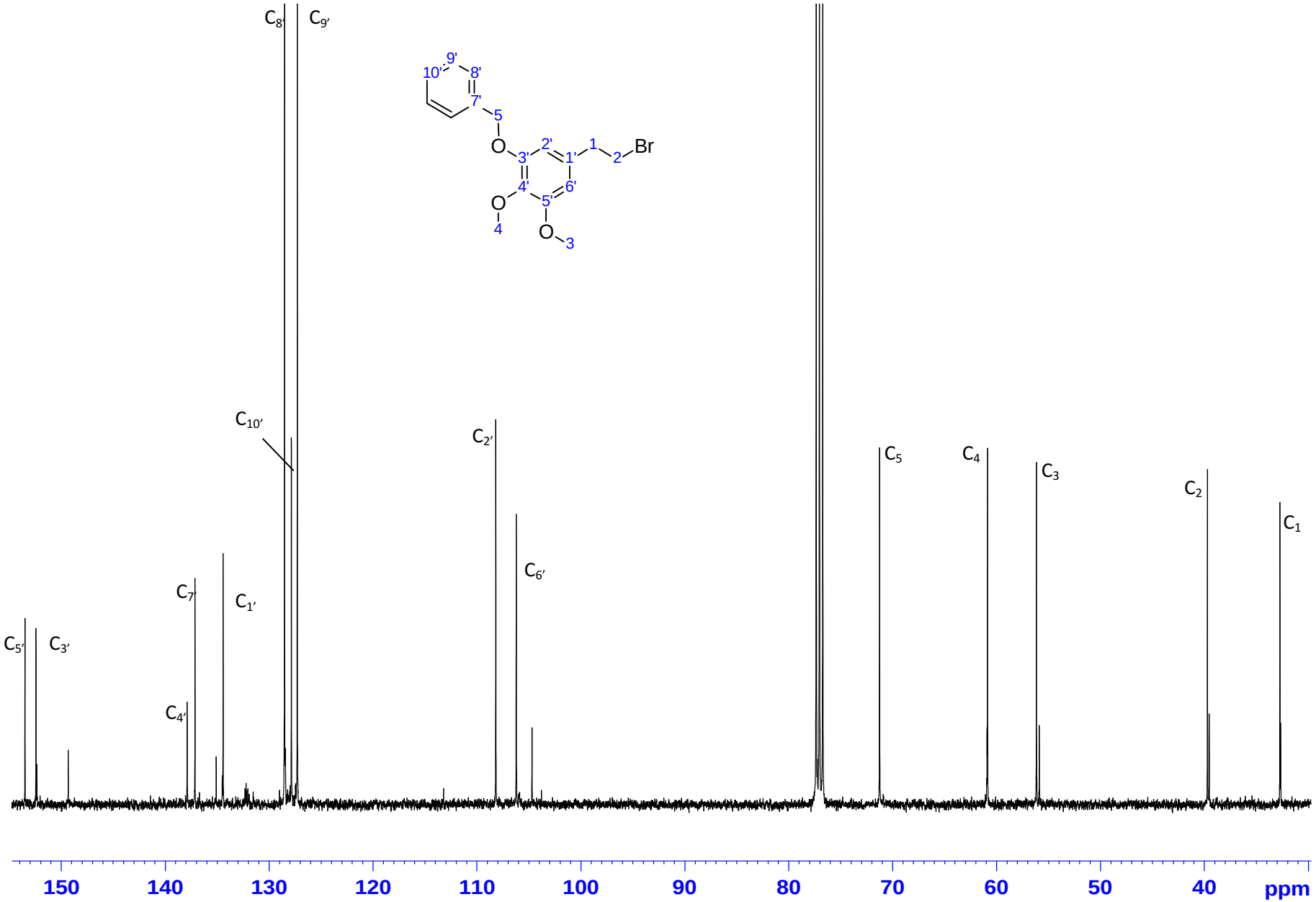

Plate 14a: ^{1}H NMR spectrum for Diethyl 2-(3-benxyloxy-4,5-dimethoxyphenyl)ethylphosphonate (87)

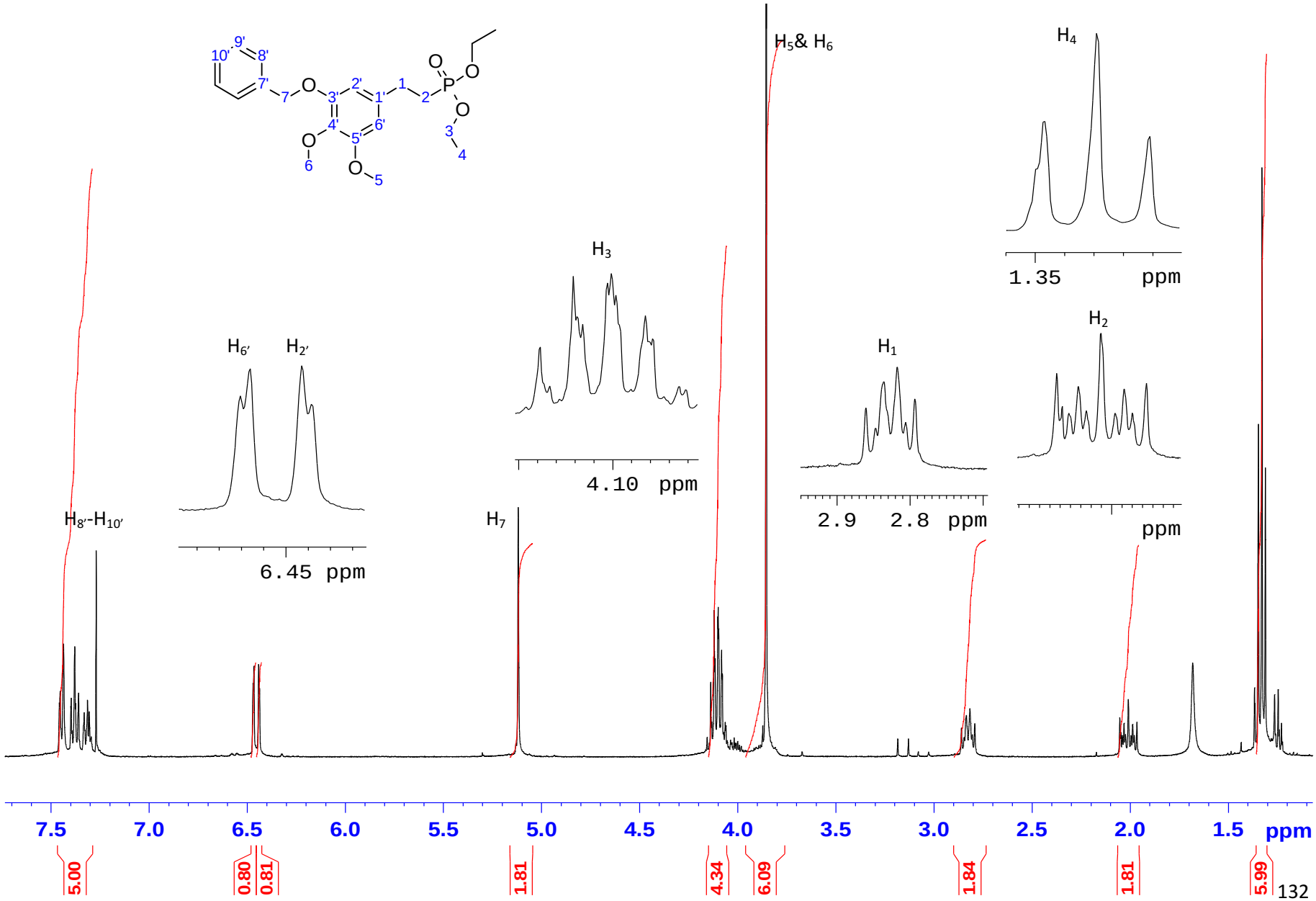

Plate 14b: ^{13}C NMR spectrum for Diethyl 2-(3-benxyloxy-4,5-dimethoxyphenyl)ethylphosphonate (87)

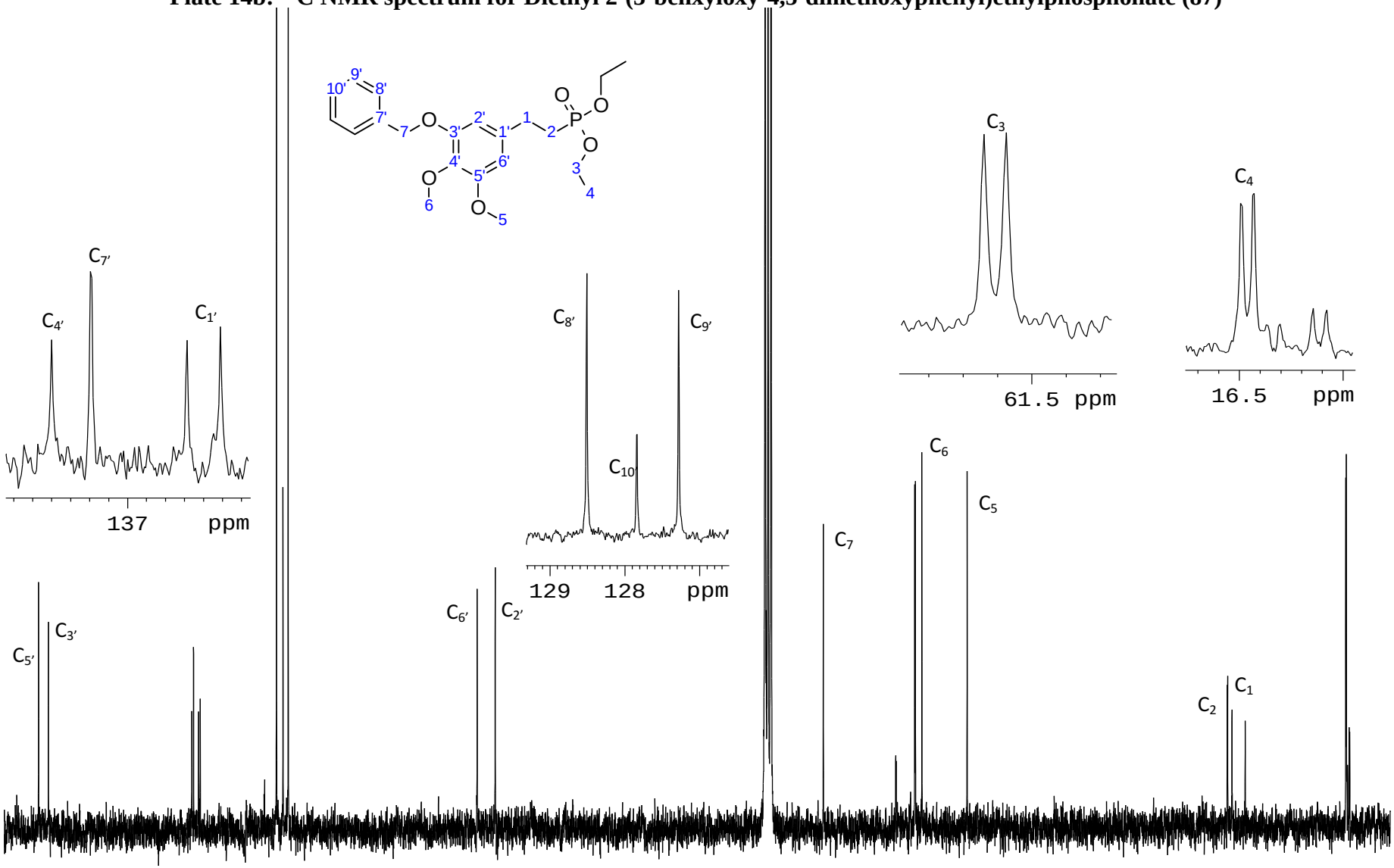

Plate 14c: ^{31}P NMR spectrum for Diethyl 2-(3-benxyloxy-4,5-dimethoxyphenyl)ethylphosphonate (87)

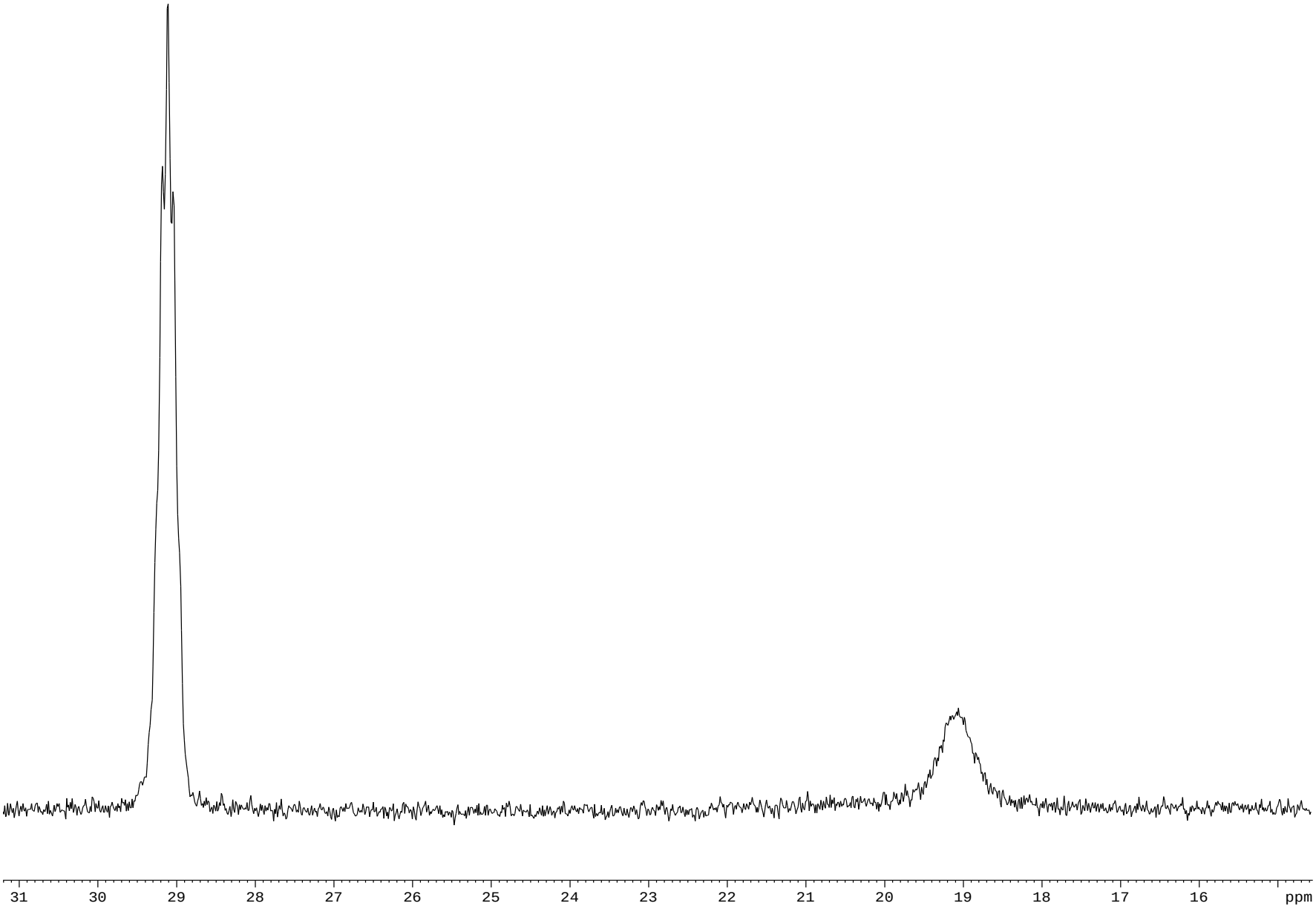

Plate 15a: ^{1}H NMR spectrum for 4-benzyloxy-3-methoxybenzaldehyde (110)

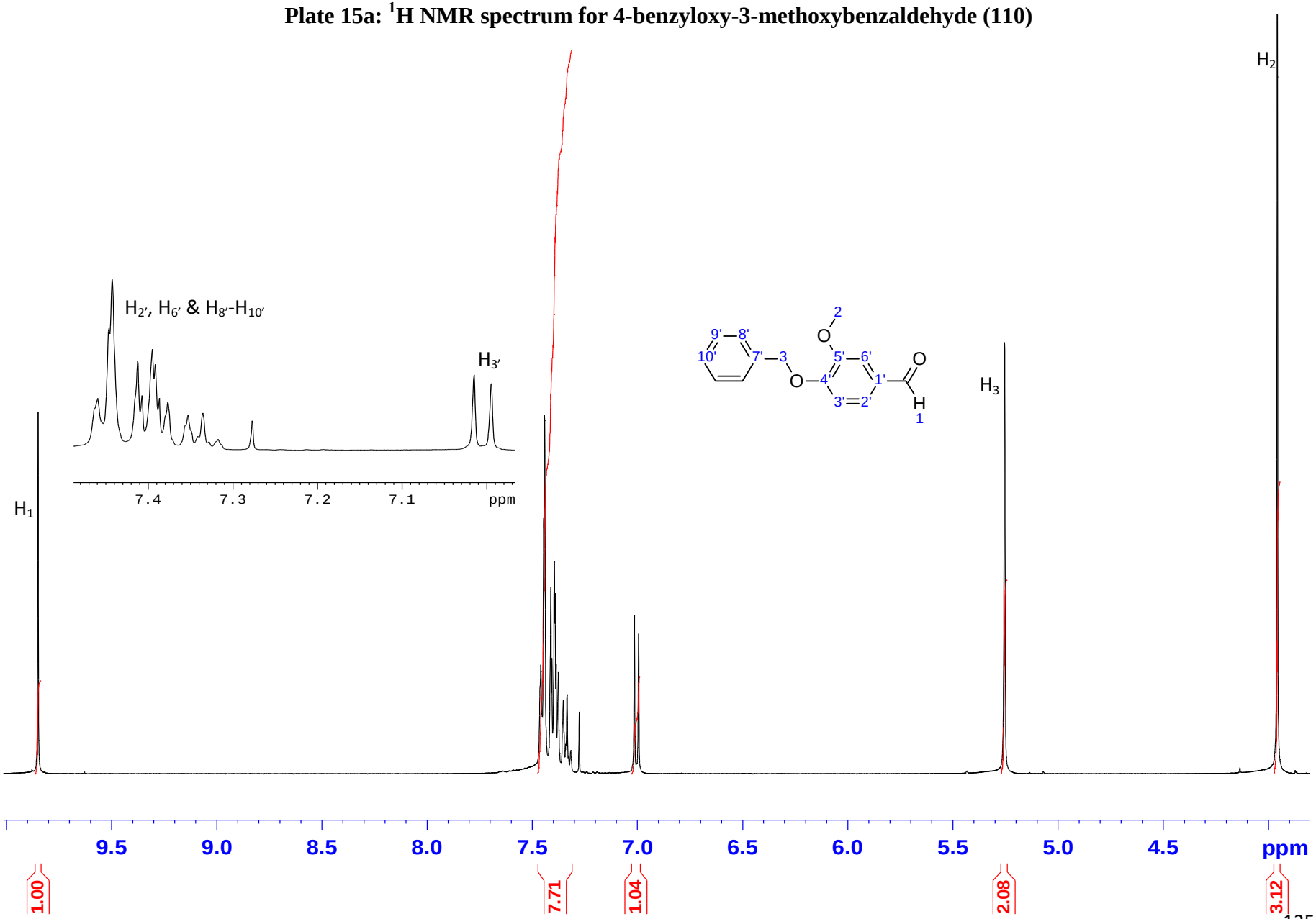

Plate 15b: ^{13}C NMR spectrum for 4-benzyloxy-3-methoxybenzaldehyde (110)

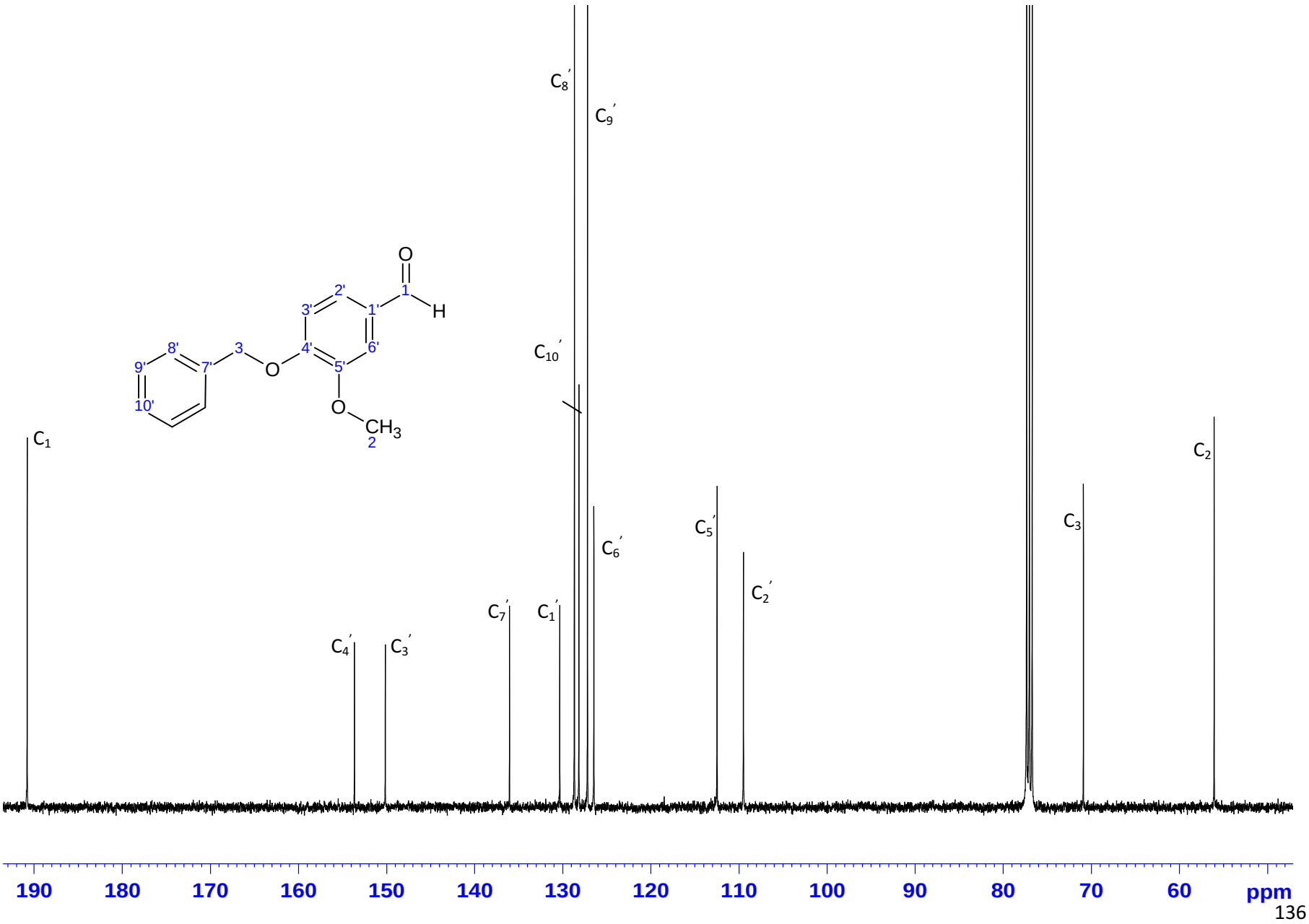

Plate 16a: ^{1}H NMR spectrum for ethyl 4-benzyloxy-3-methoxycinnamate (111)

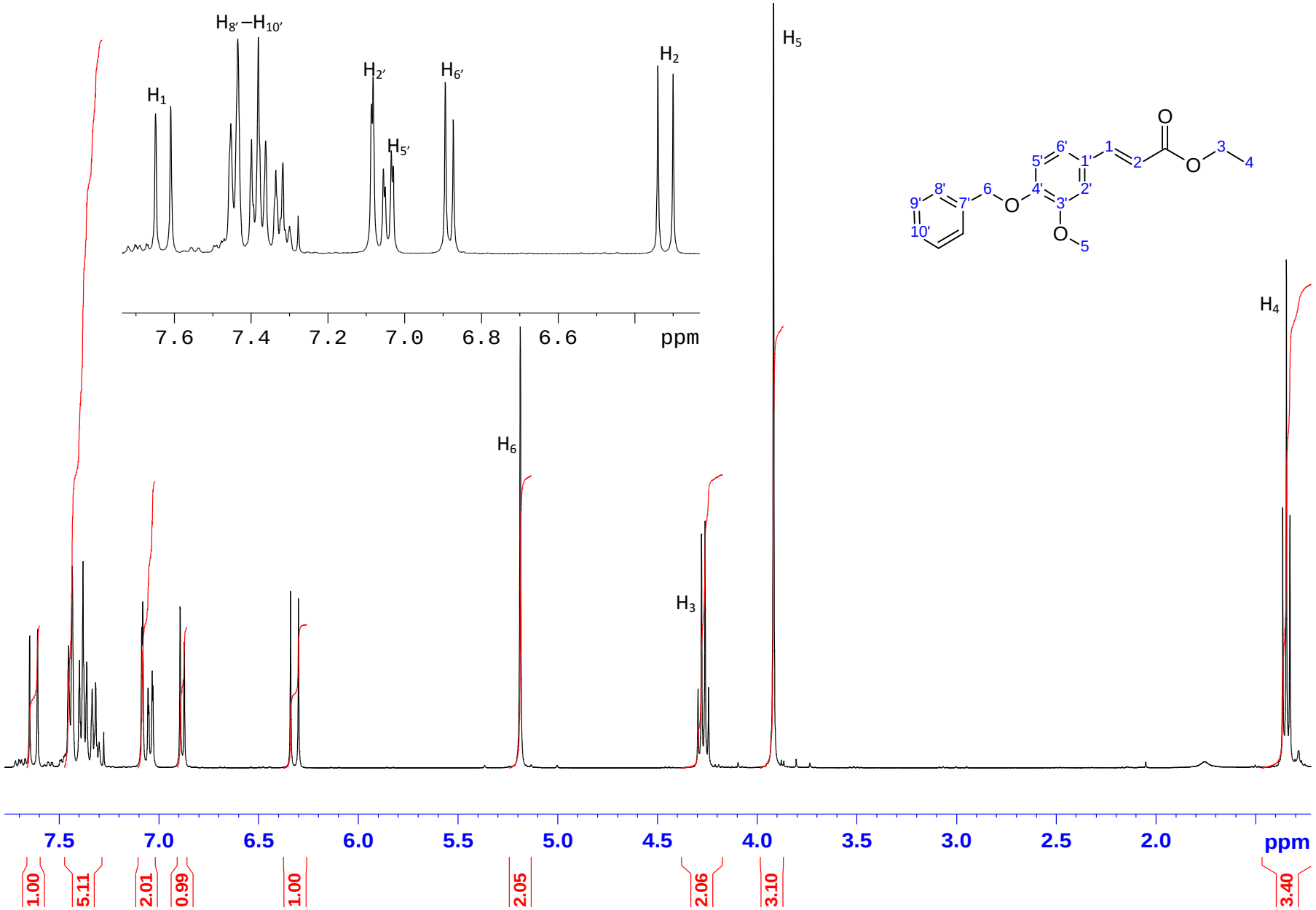

Plate 16b: ^{13}C NMR spectrum for ethyl 4-benzyloxy-3-methoxycinnamate (111)

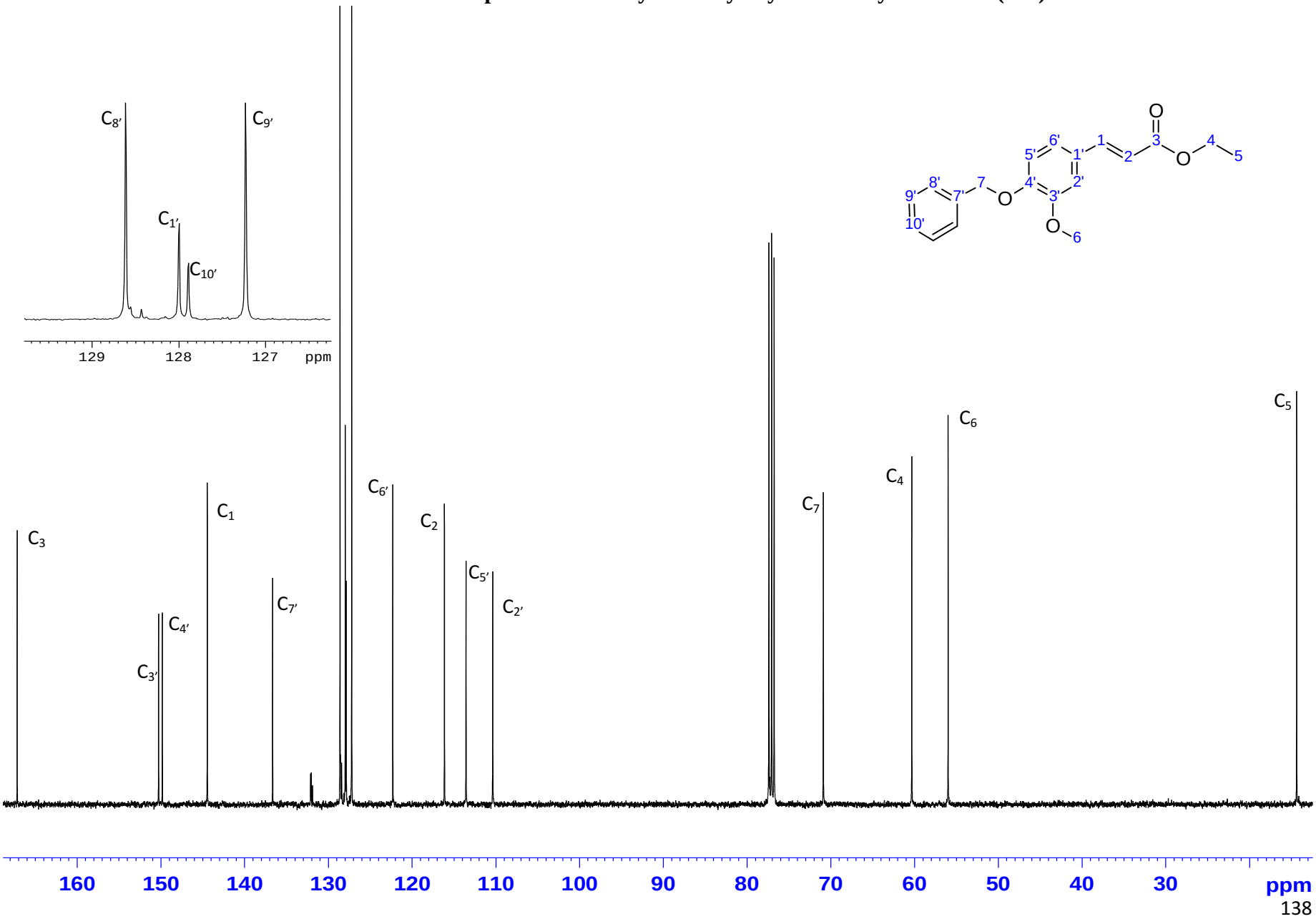

Plate 17a: ^{1}H NMR spectrum for ethyl ethyl 3-(4-benzyloxy-3-methoxyphenyl)propanoate (112)

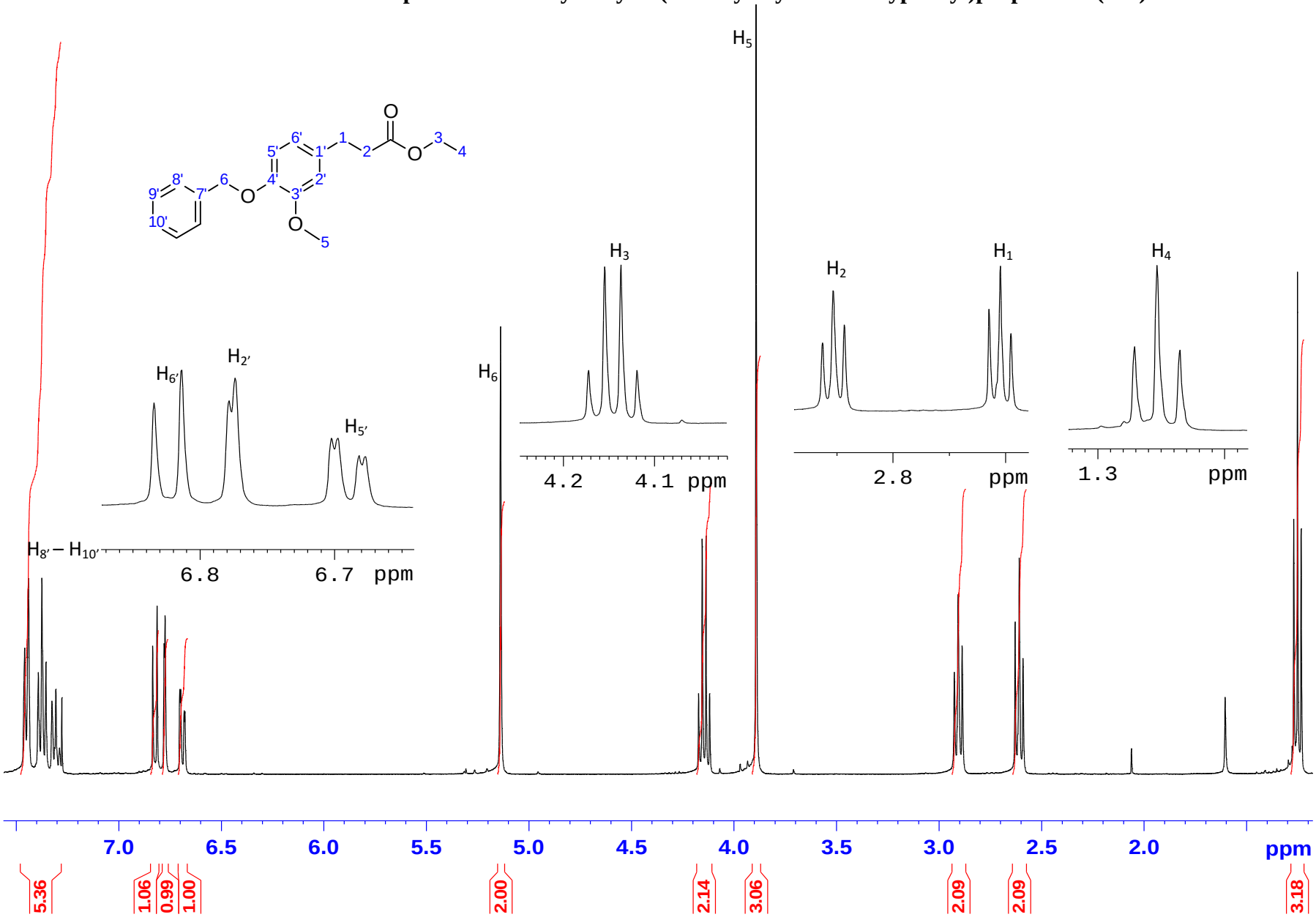

Plate 17b: ^{13}C NMR spectrum for ethyl ethyl 3-(4-benzyloxy-3-methoxyphenyl)propanoate (112)

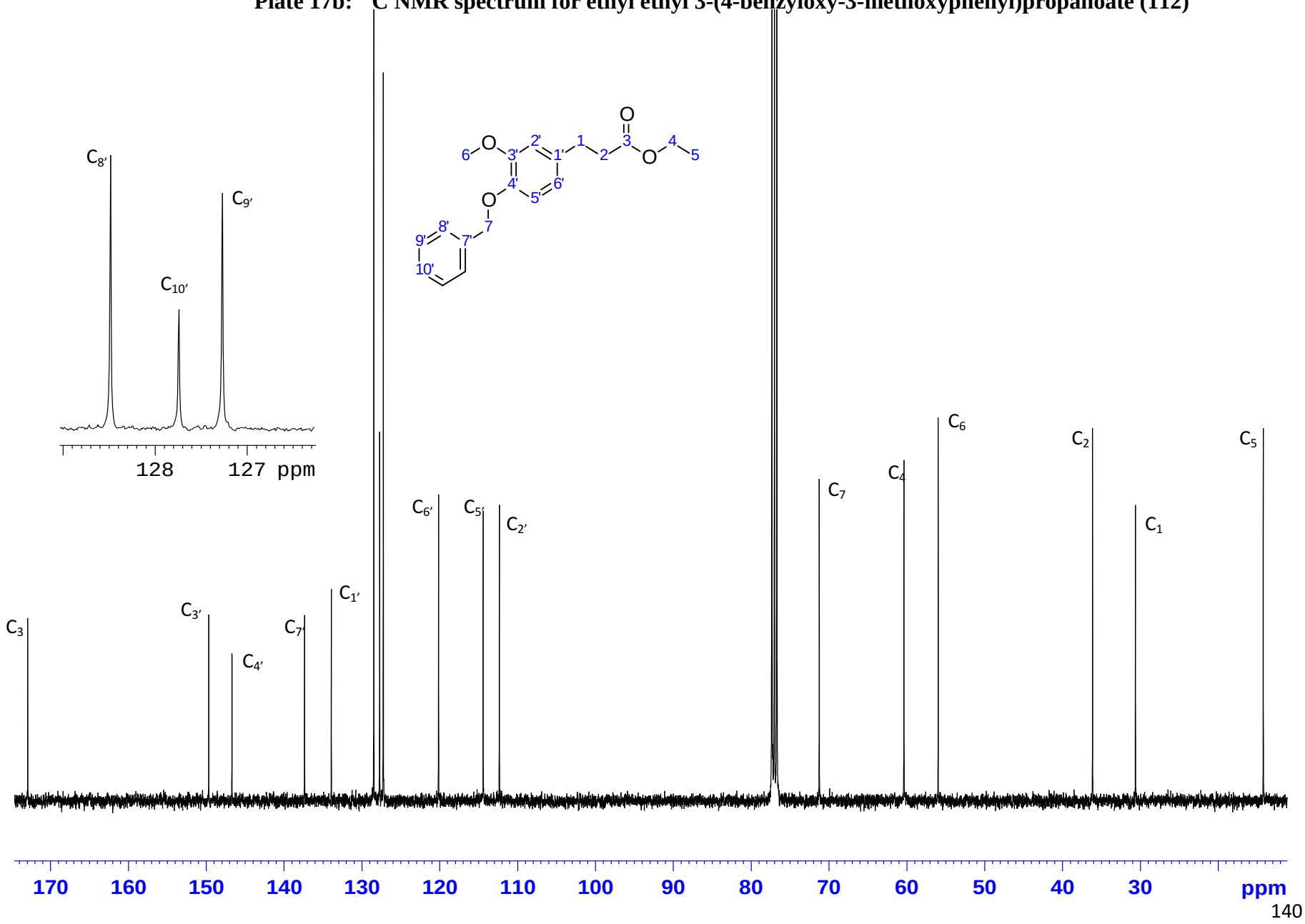

Plate 18a: ^{1}H NMR spectrum for 3-(4-benzyloxy-3-methoxyphenyl)propan-1-ol (113)

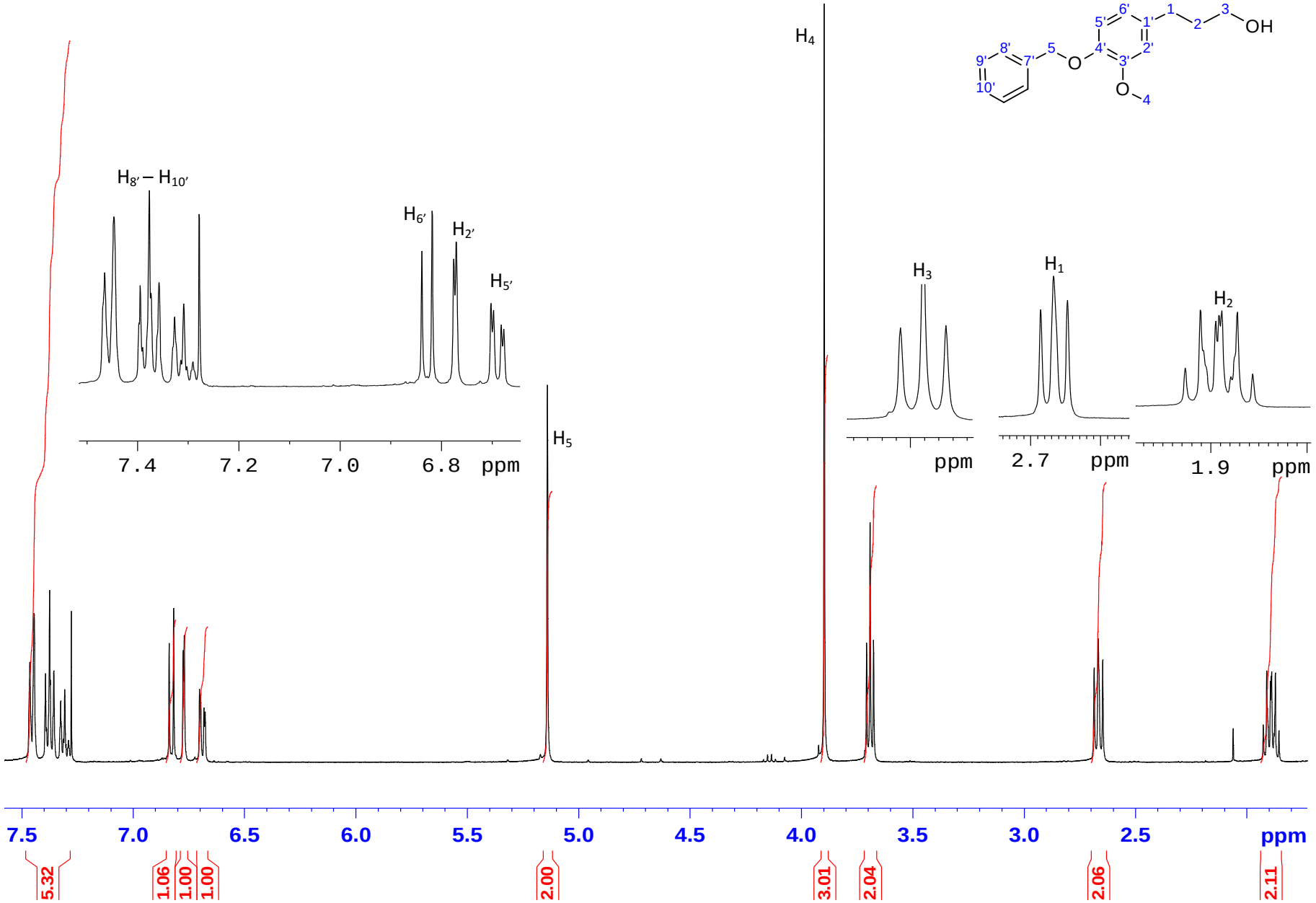

Plate 18b: ^{13}C NMR spectrum for 3-(4-benzyloxy-3-methoxyphenyl)propan-1-ol (113)

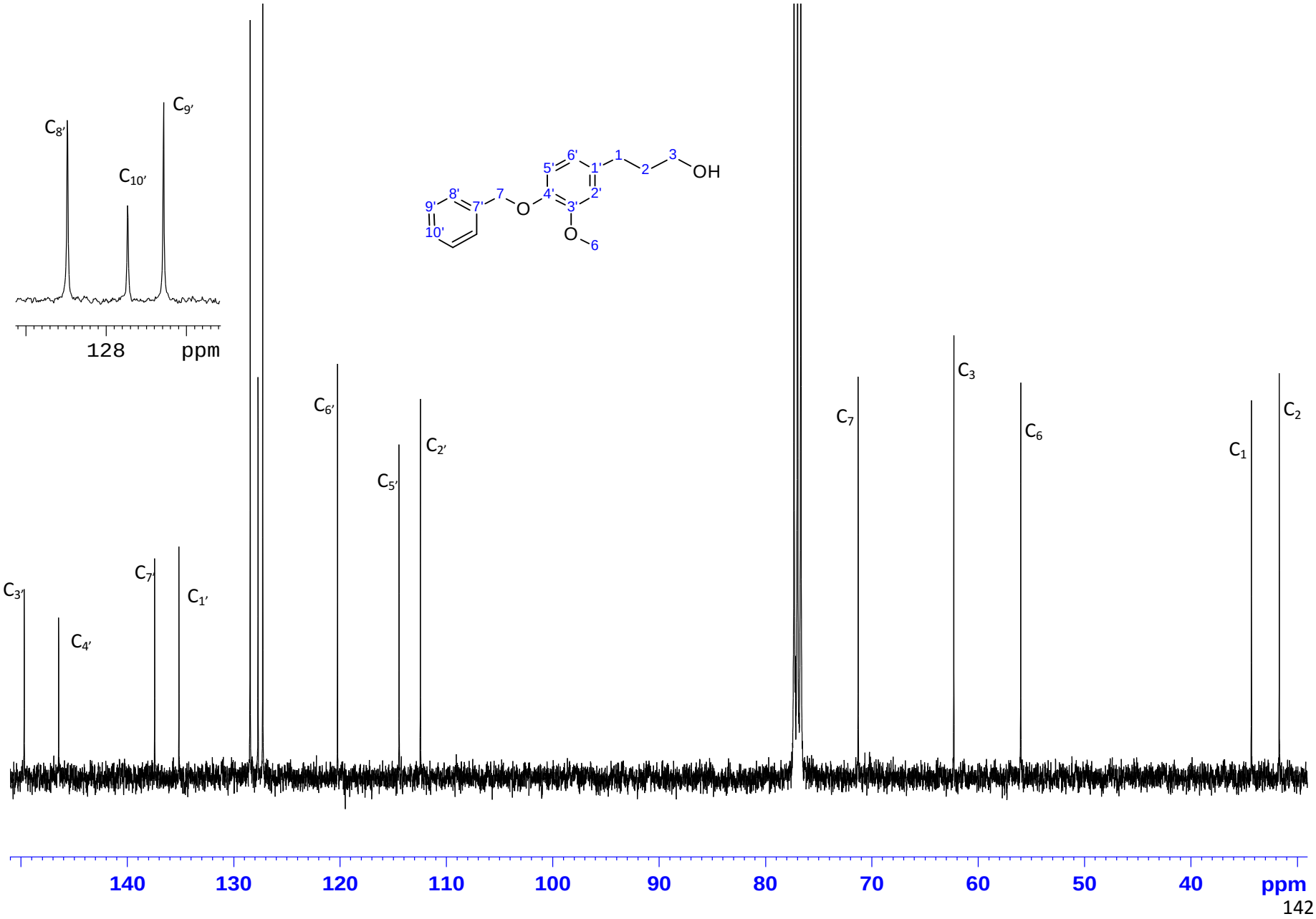

Plate 19a: ^{1}H NMR spectrum for 3-(4-benzyloxy-3-methoxyphenyl)propanal (114)

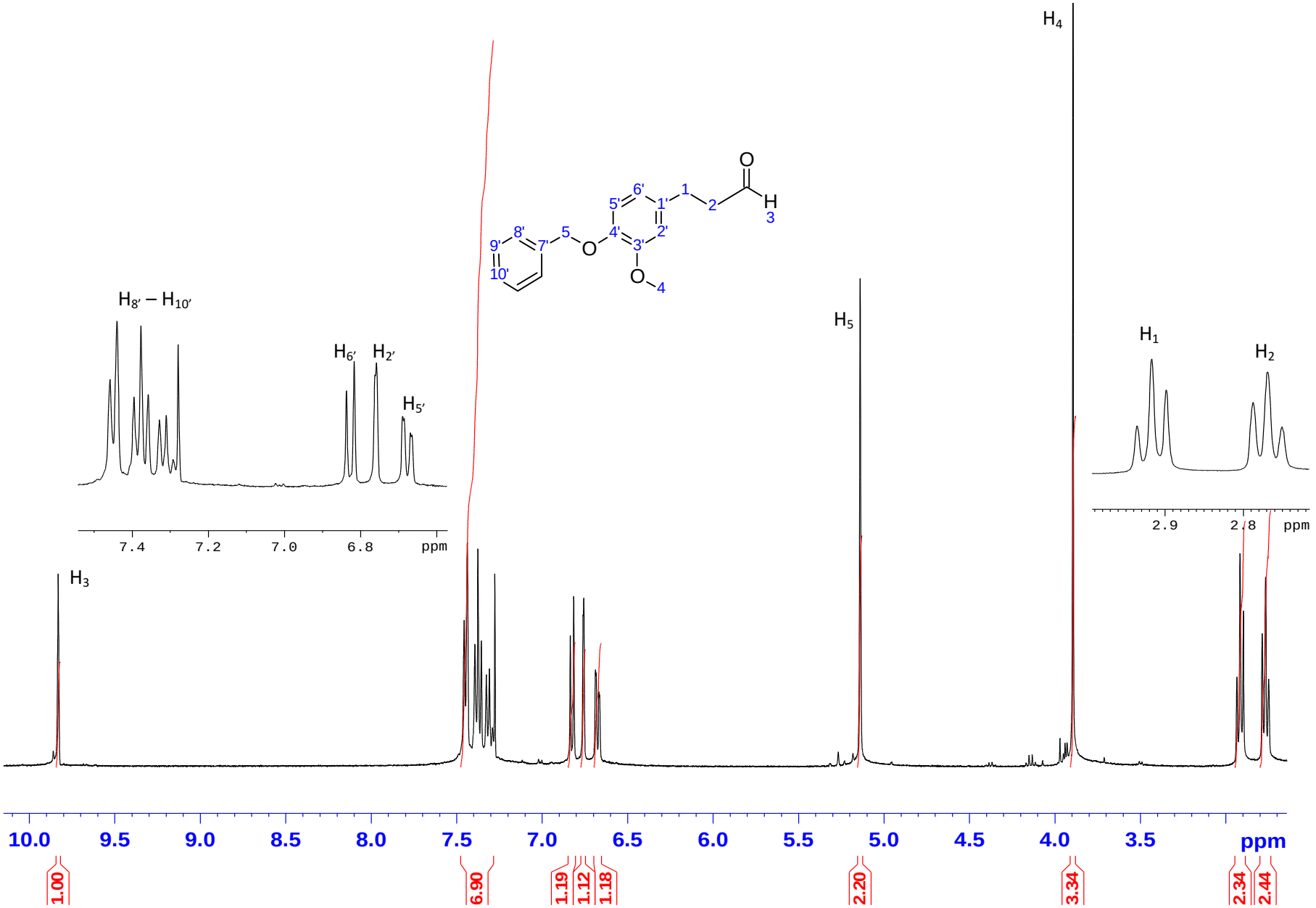

Plate 19b: ^{13}C NMR spectrum for 3-(4-benzyloxy-3-methoxyphenyl)propanal (114)

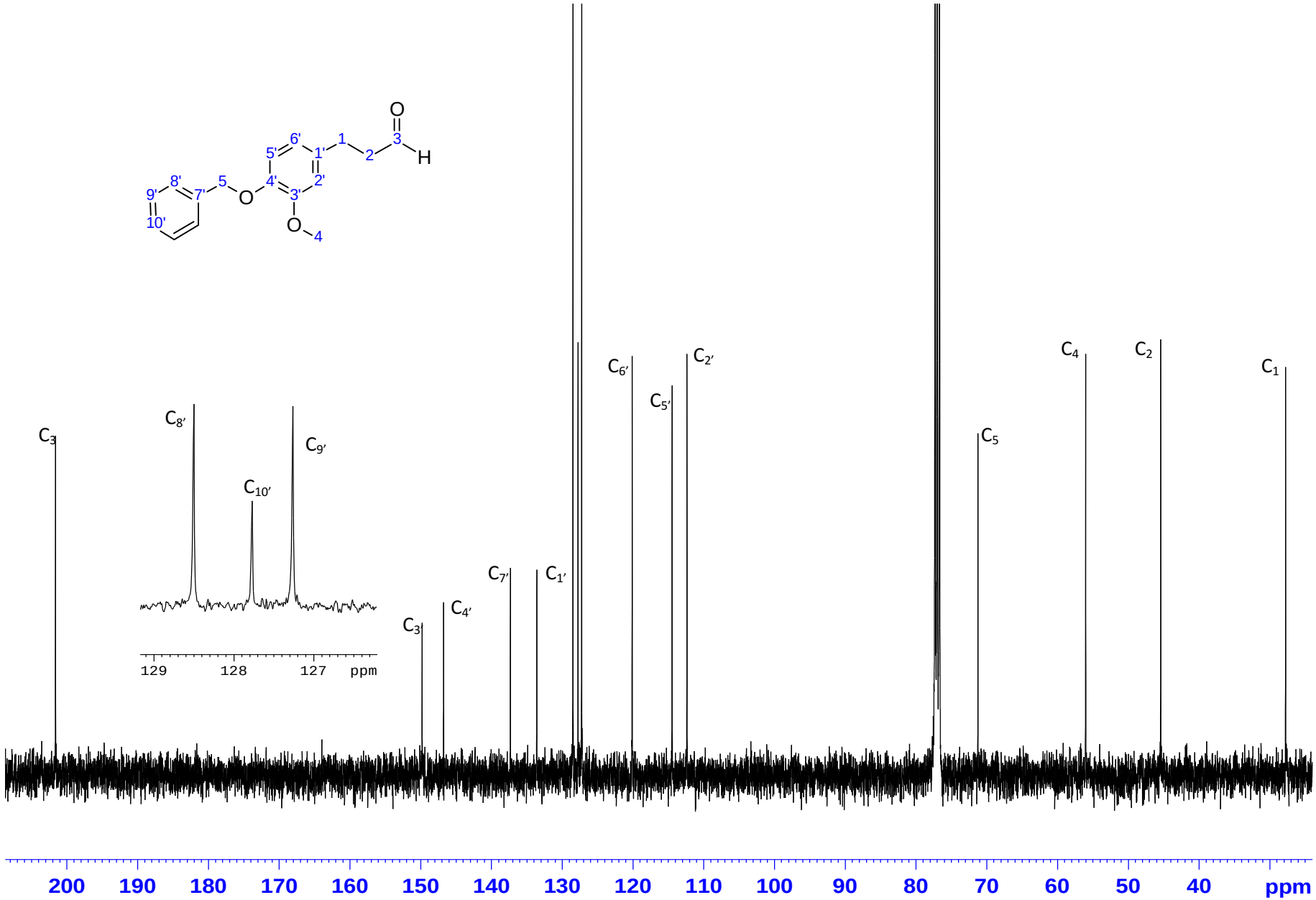

Plate 20a: ^{1}H NMR spectrum for (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoic acid (115)

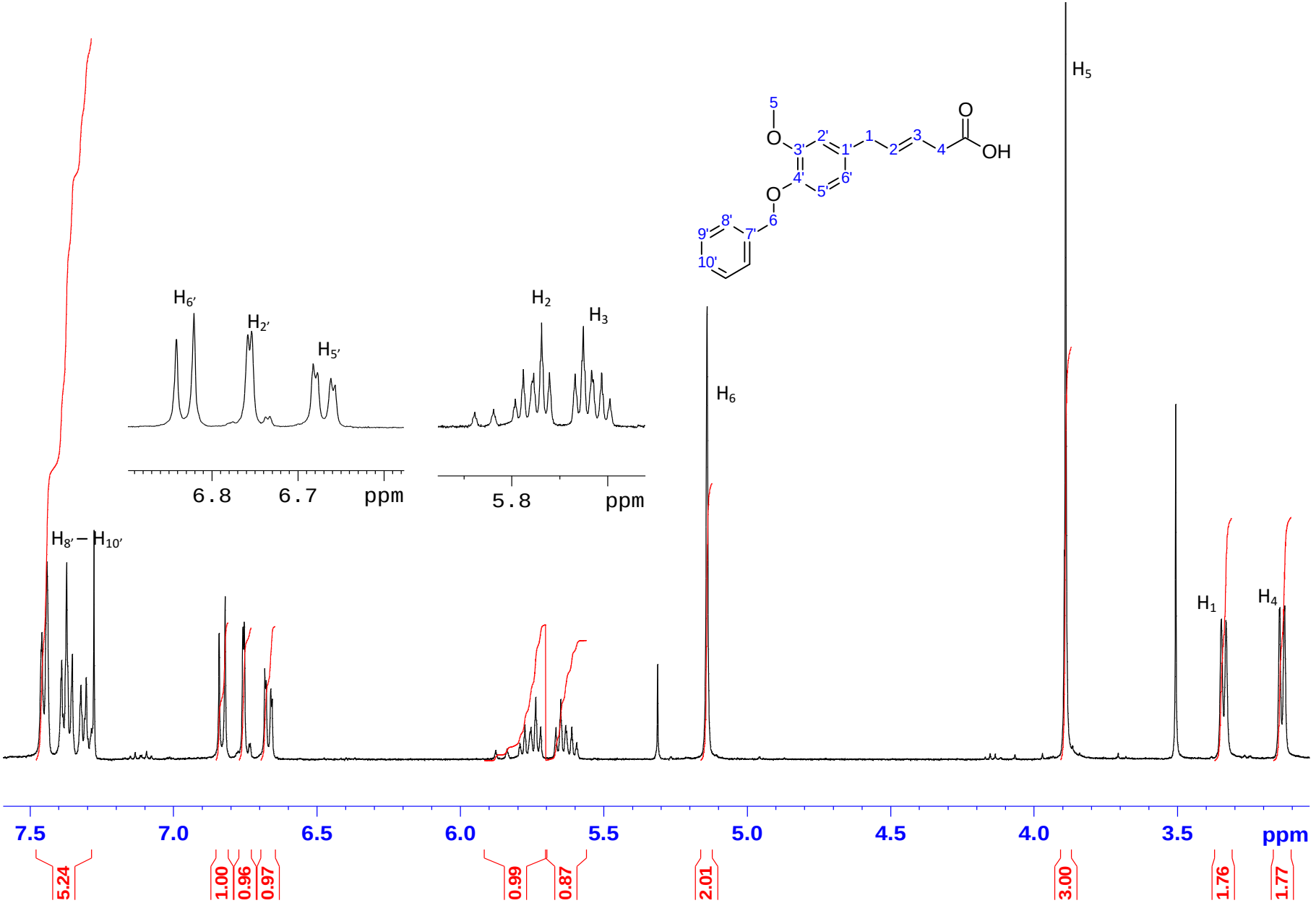

Plate 20b: ^{13}C NMR spectrum for (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoic acid (115)

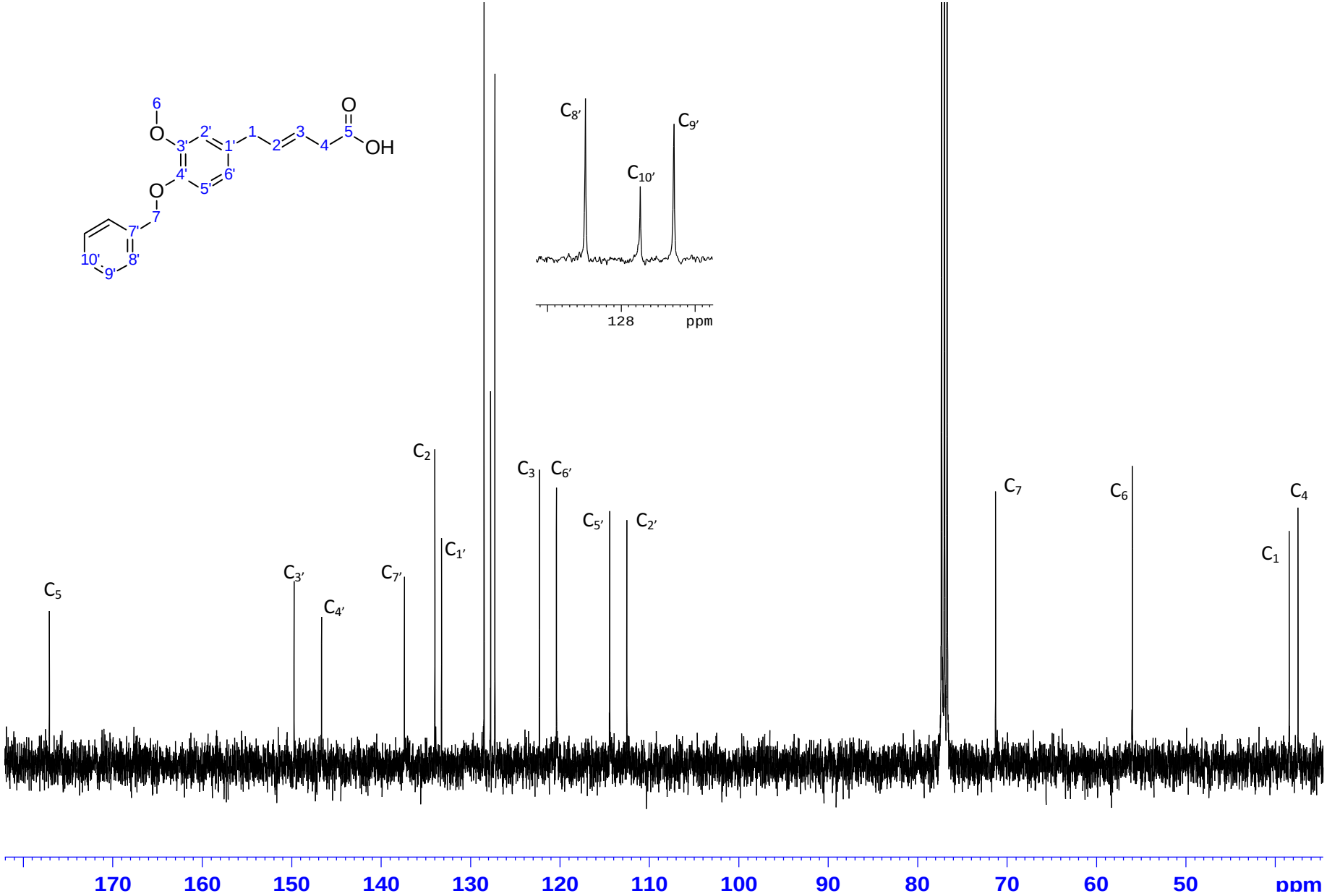

Plate 21a: ^{1}H NMR spectrum for methyl (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoate (116)

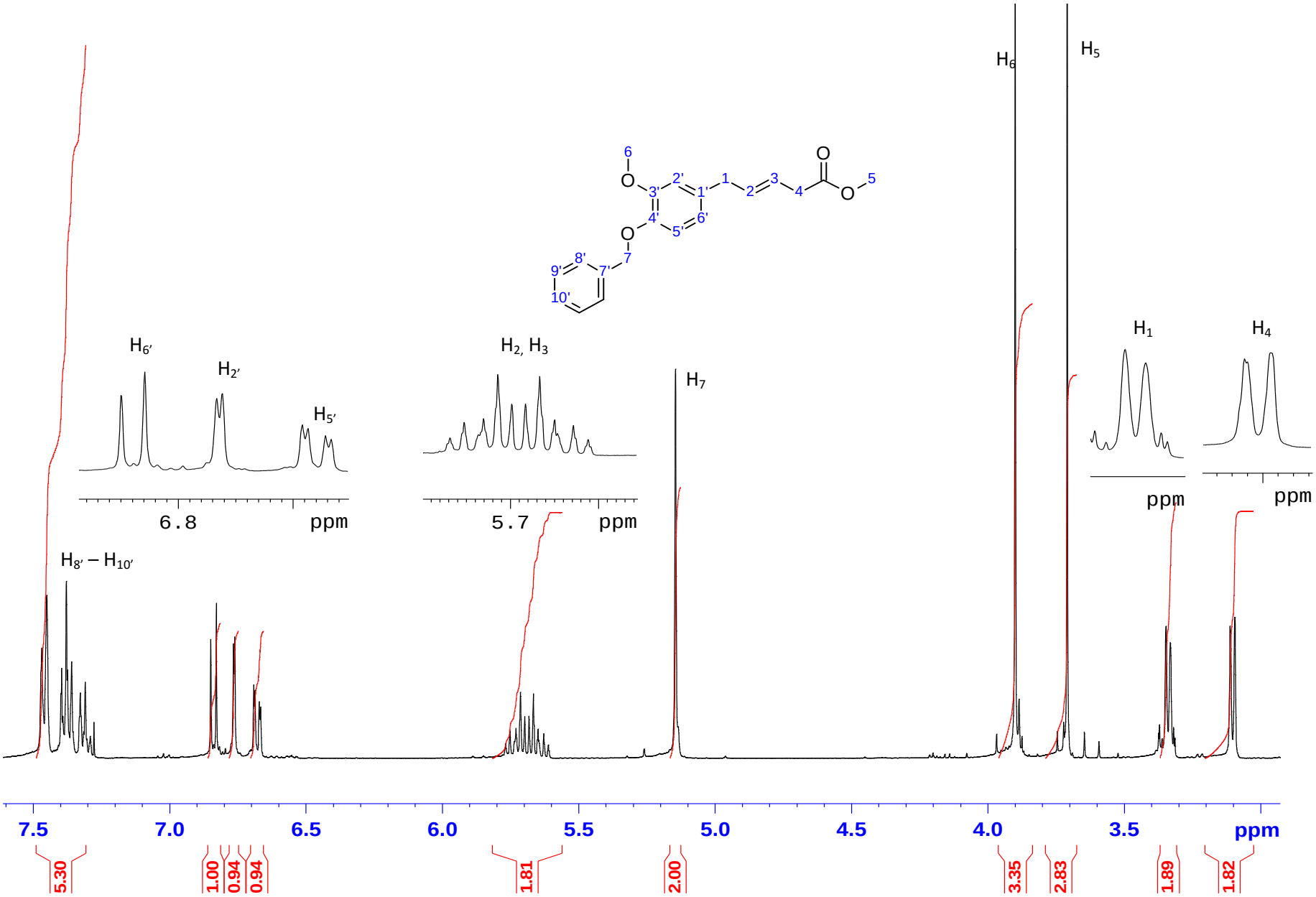

Plate 21b: ^{13}C NMR spectrum for methyl (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-enoate (116)

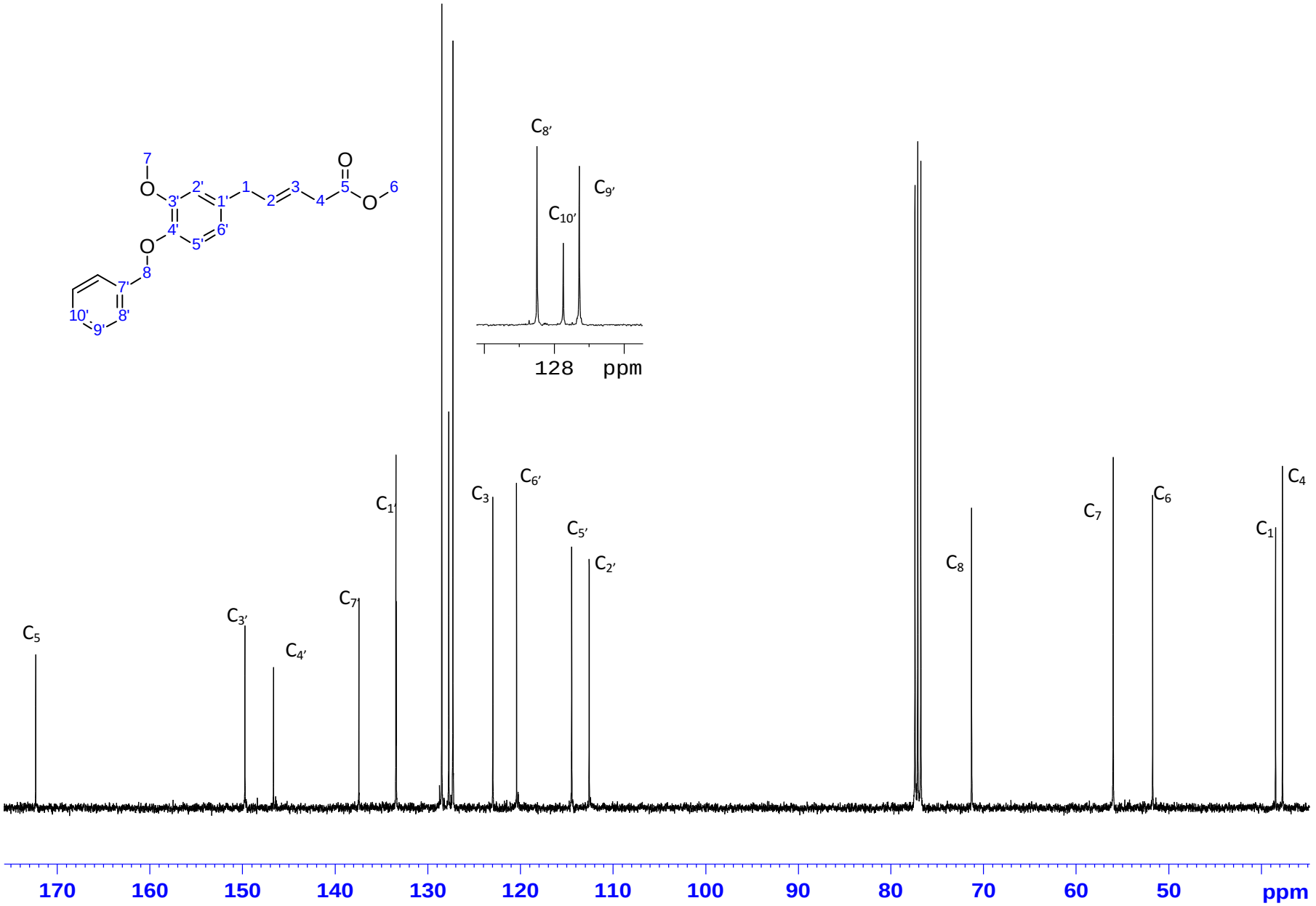

Plate 22a: ^{1}H NMR spectrum for (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-en-1-ol (117)

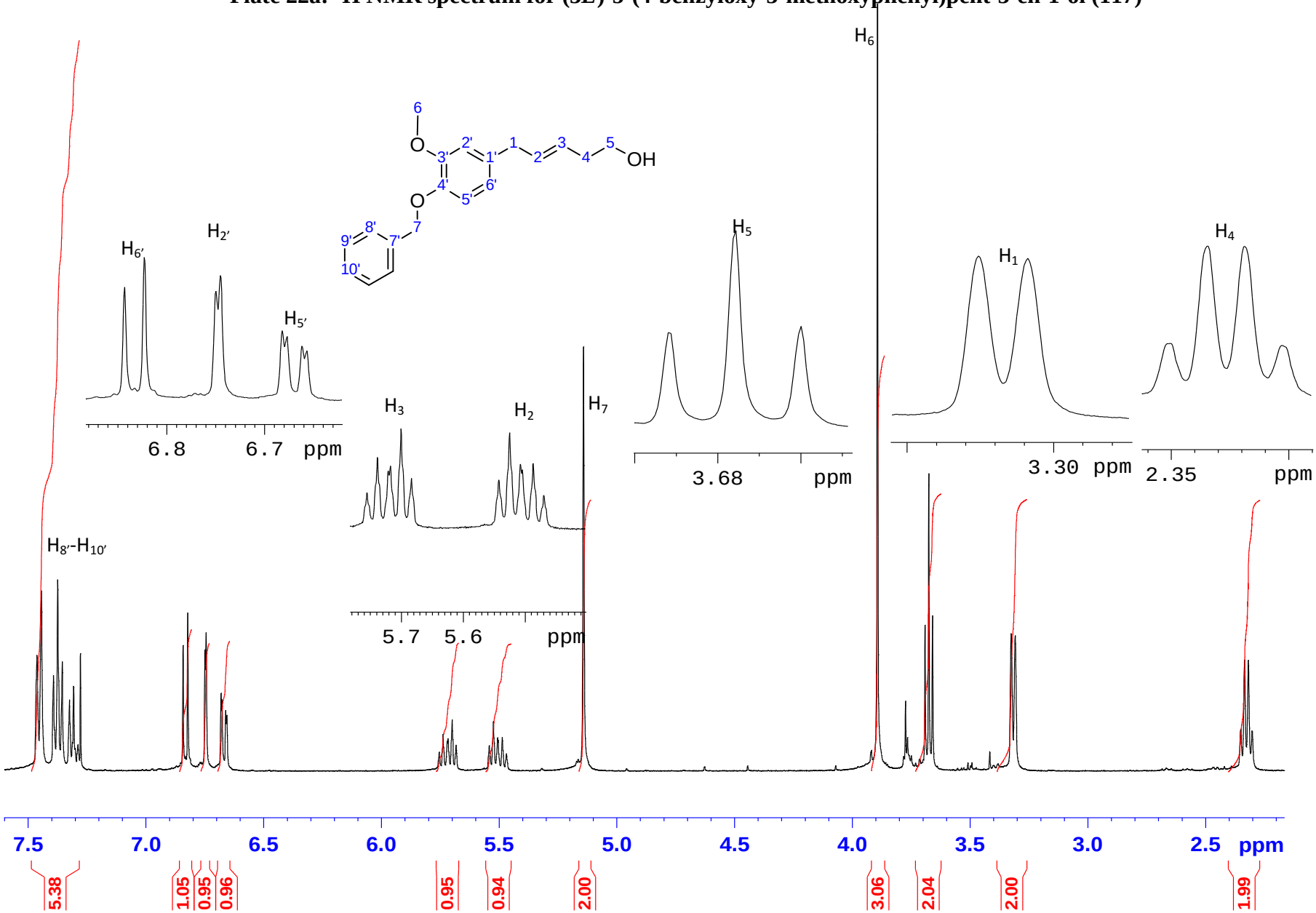

Plate 22b: ^{13}C NMR spectrum for (3*E*)-5-(4-benzyloxy-3-methoxyphenyl)pent-3-en-1-ol (117)

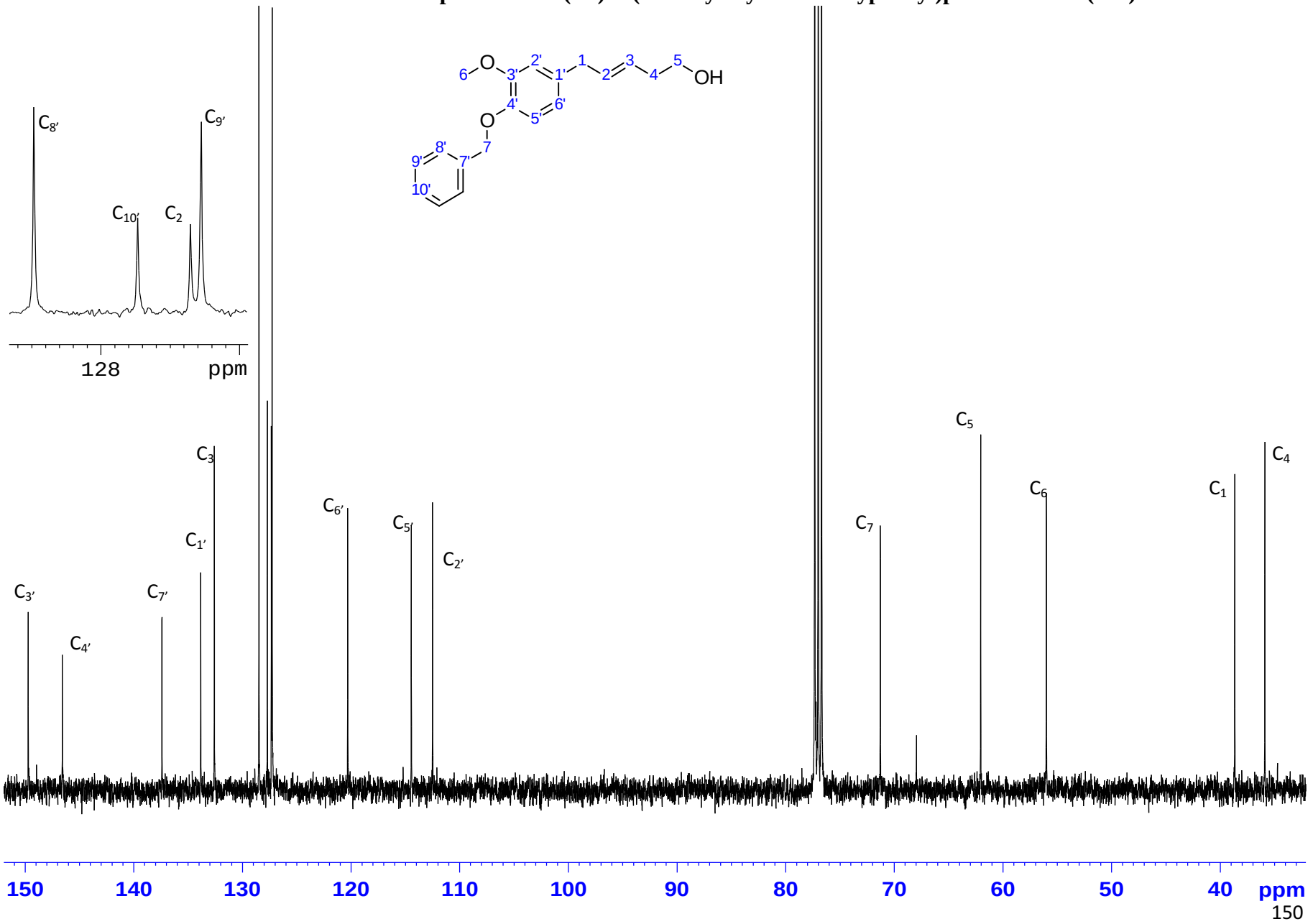

Plate 23a: ^{13}H NMR spectrum for [(*E*)-5-(4-Benzyloxy-3-methoxyphenyl)pent-3-enoxy]-*tert*-butyl-imethylsilane (124)

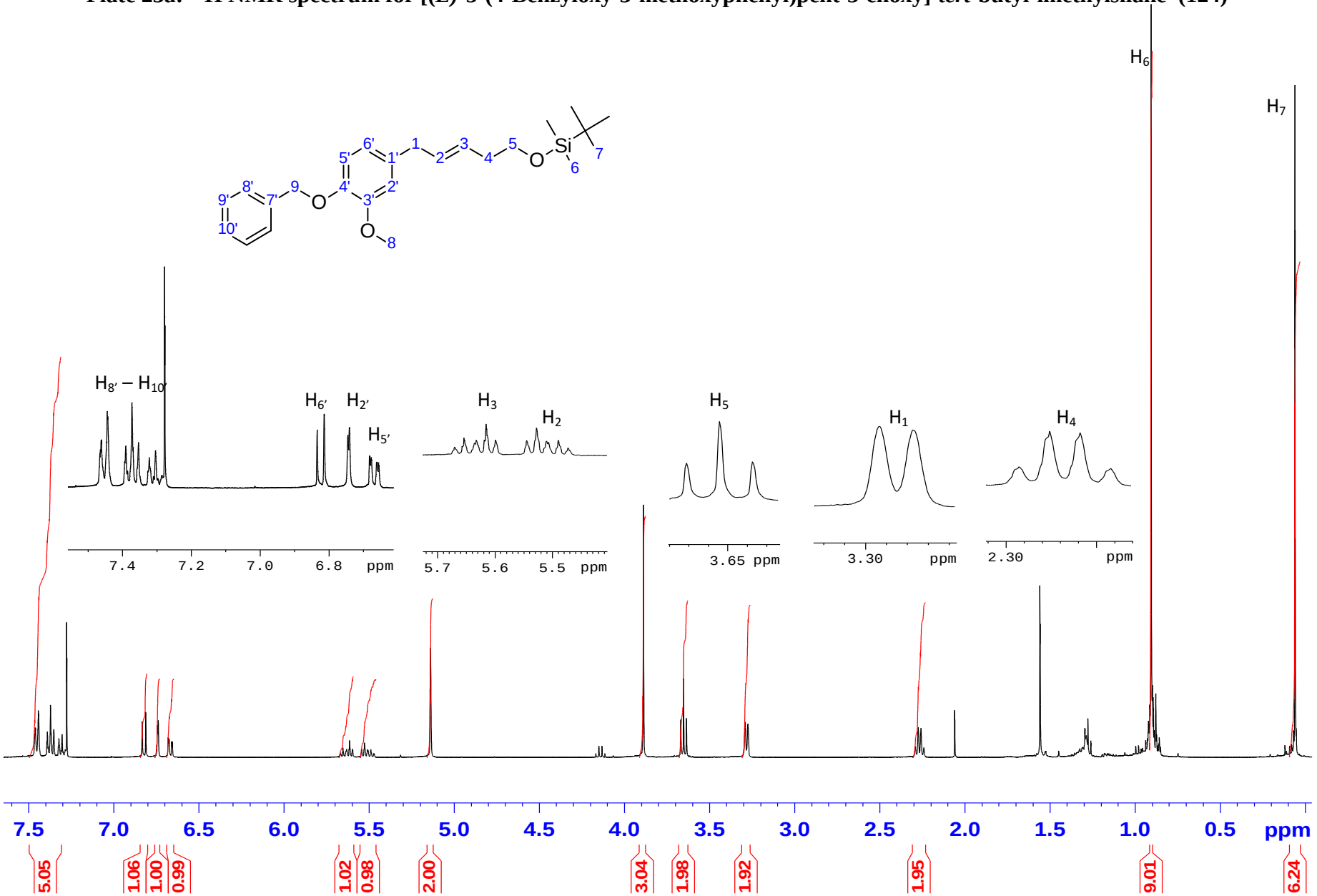

Plate 23b: ^{13}C NMR spectrum for [(*E*)-5-(4-Benzyloxy-3-methoxyphenyl)pent-3-enoxy]-*tert*-butyldimethylsilane (124)

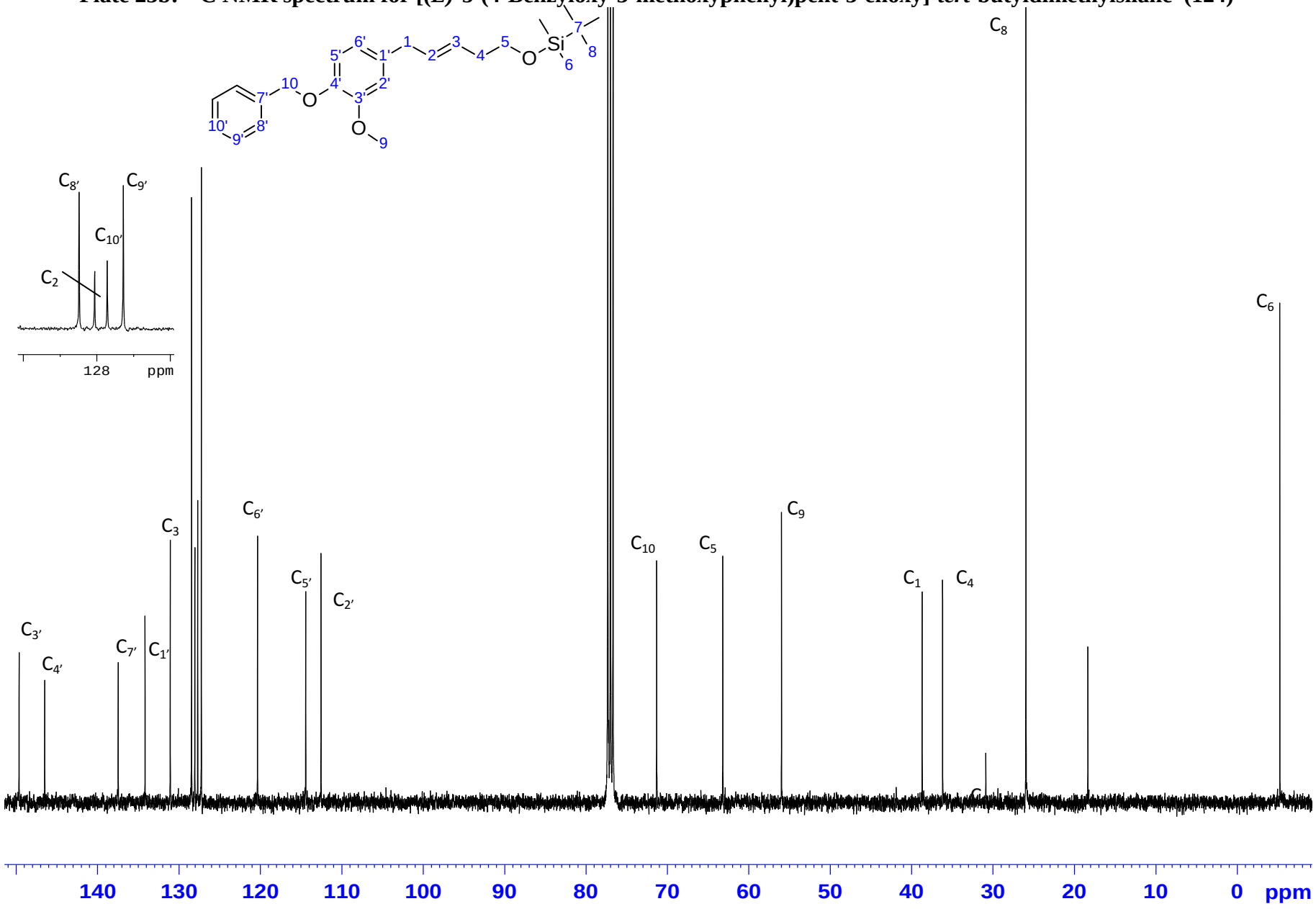

Plate 24a: ^{1}H NMR spectrum for 1-(4-Benzyloxy-3-methoxyphenyl)-5-(*tert*-butyl(methyl)silyl)oxypentane-2,3-diol (125)

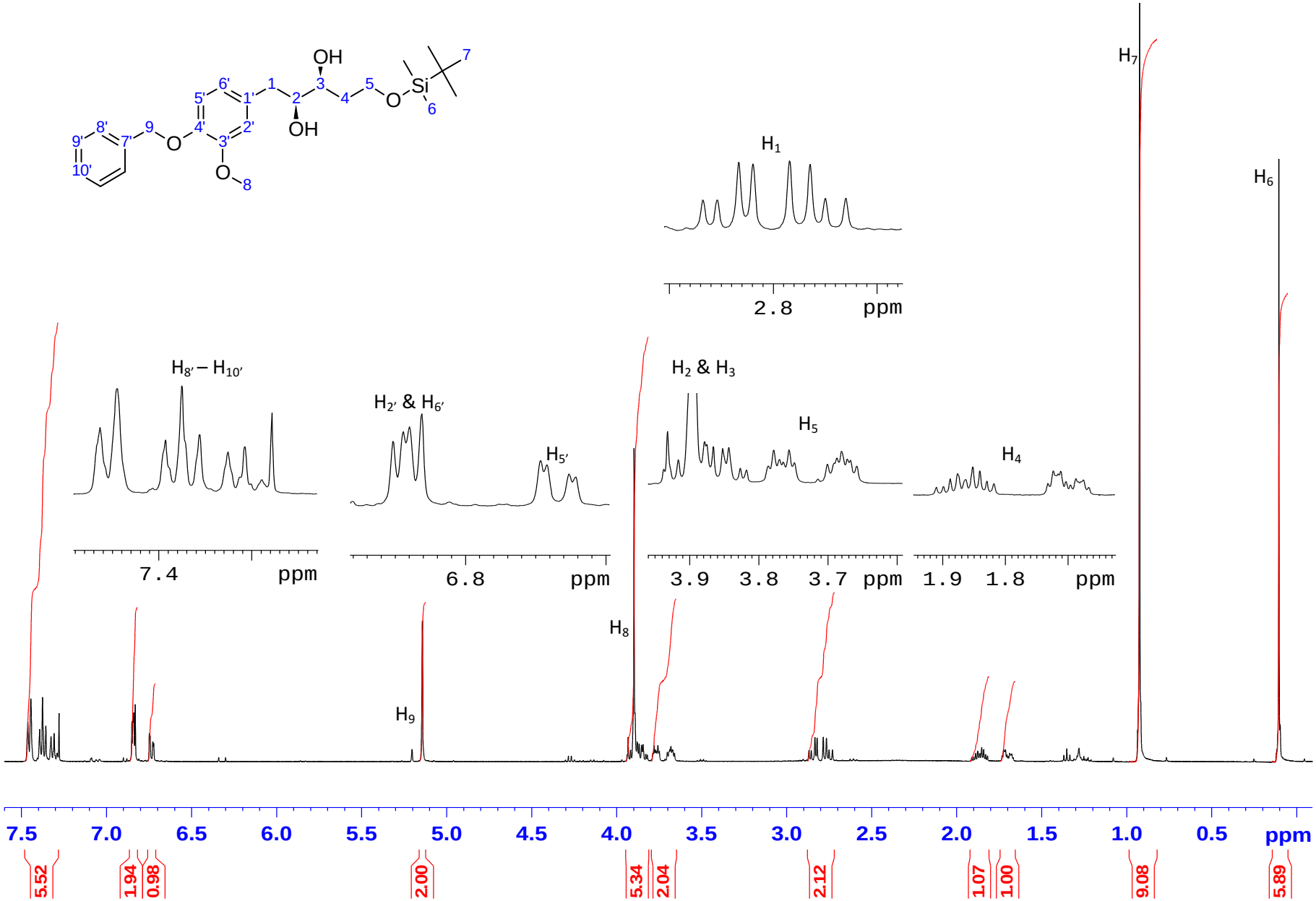

Plate 24b: ^{13}C NMR spectrum for 1-(4-Benzyloxy-3-methoxyphenyl)-5-(*tert*-butyl(methyl)silyl)oxypentane-2,3-diol (125)

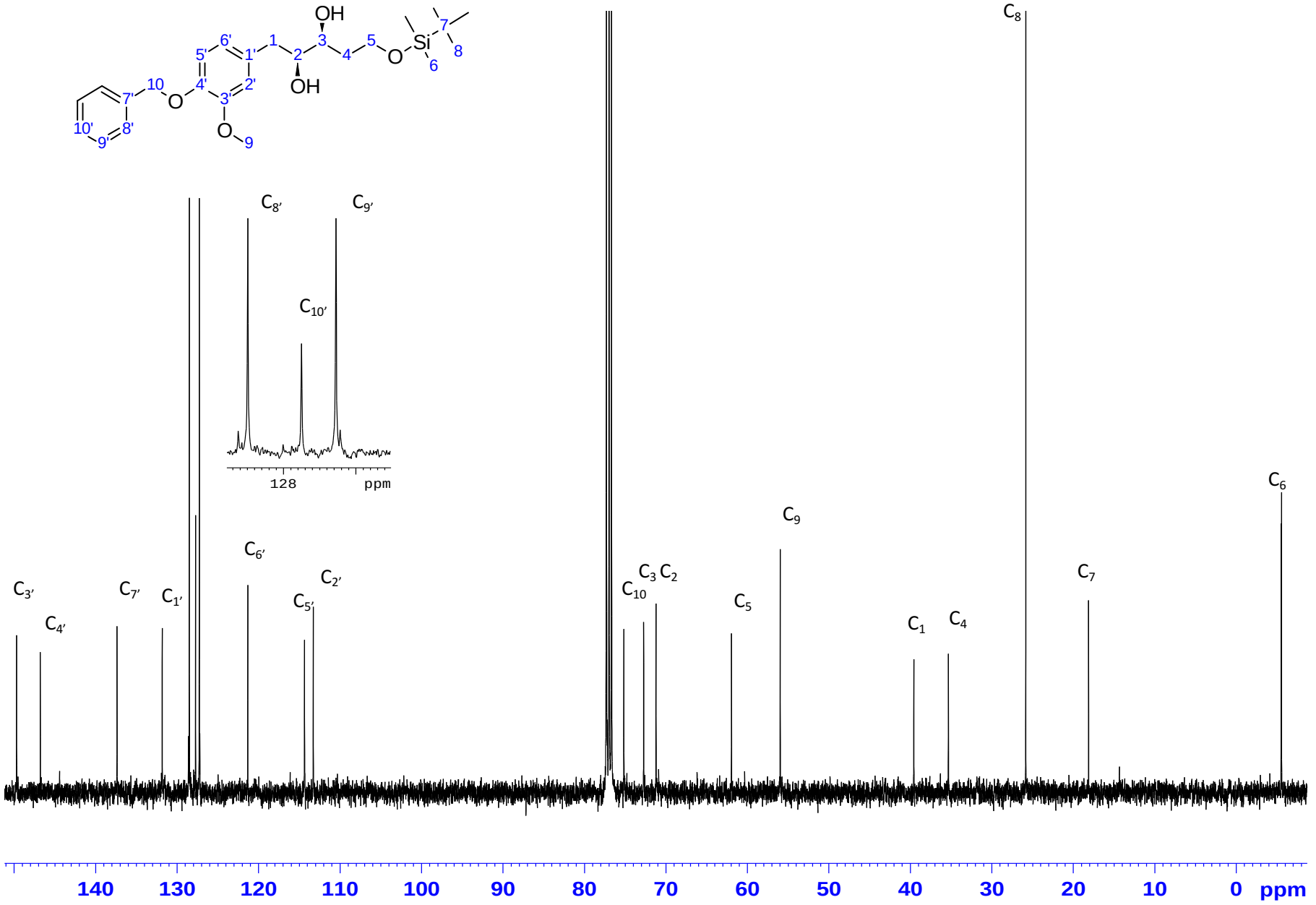

Plate 24c: ^{1}H NMR spectrum for 1-(4-Benzyloxy-3-methoxyphenyl)-5-(*tert*-butyl(methyl)silyl)oxypentane-2,3-diol (125) coordinated to the chiral shift reagent EuFOD

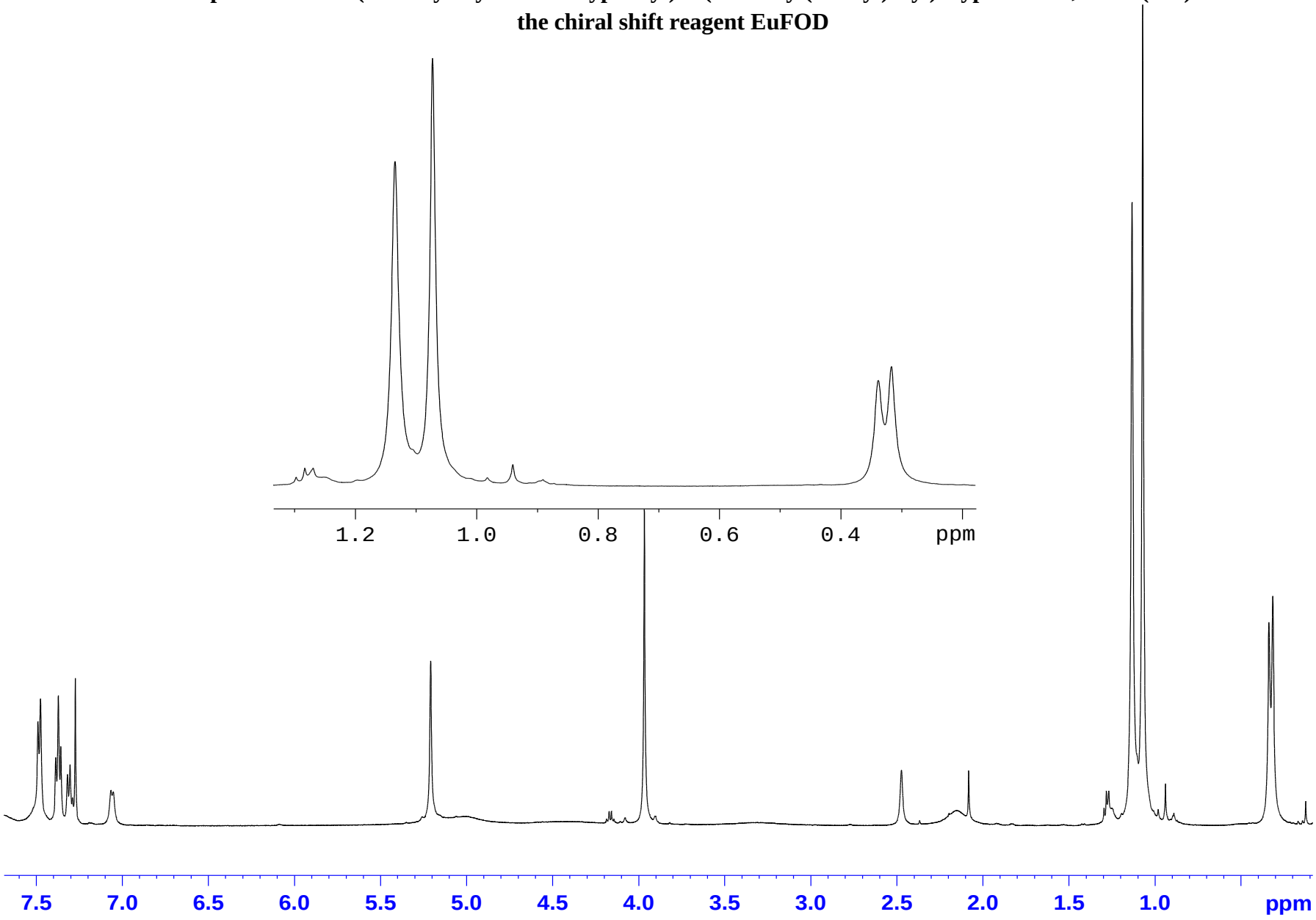

Plate 25a: 1H NMR spectrum of 5-(4-Benzyloxy-3-methoxyphenyl)-1-[2-*tert*-butyl(dimethyl)silyl]oxypentane-2,3-diacetate (126)

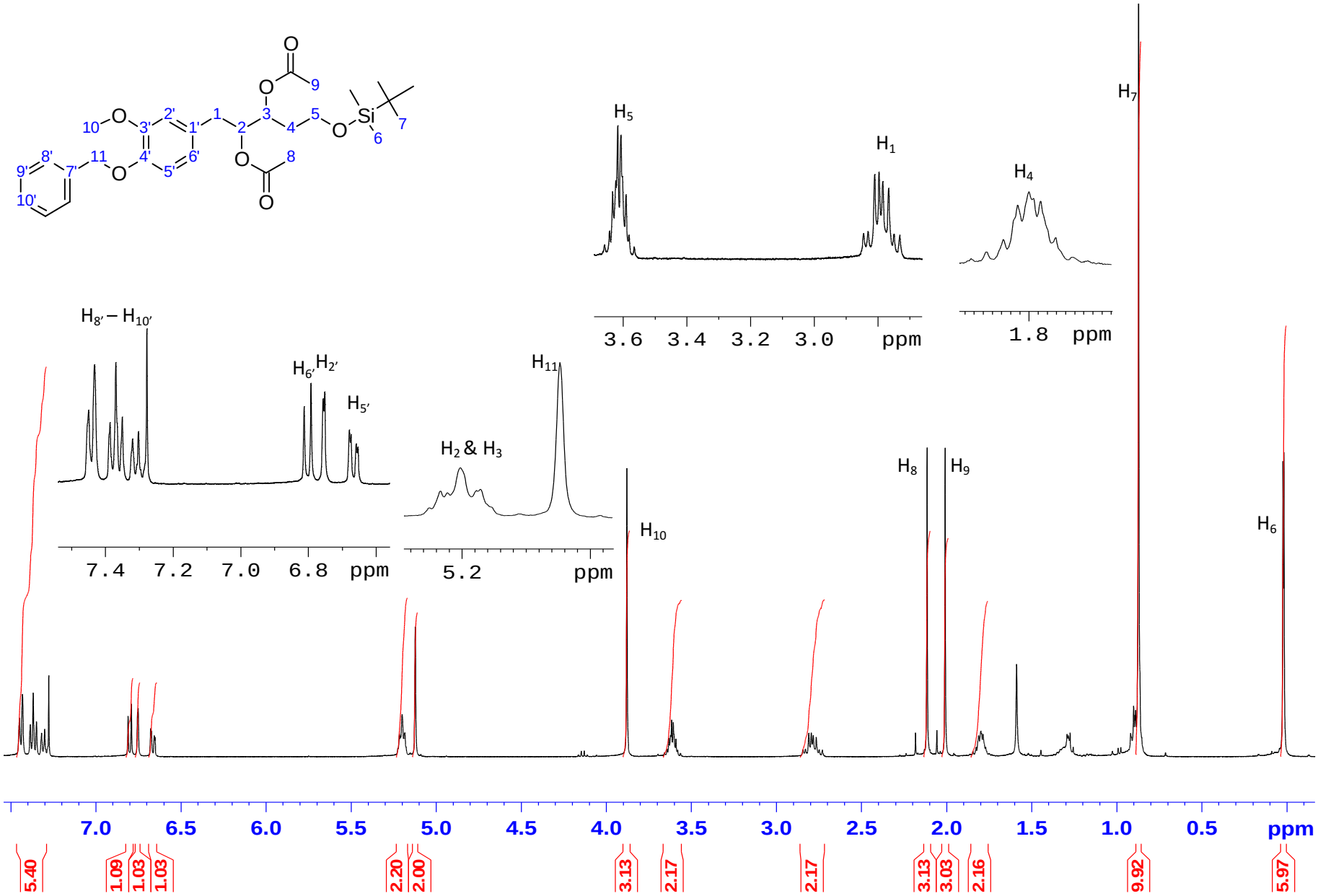

Plate 26a: ^{1}H NMR spectrum for 2-[5-[(4-Benzyloxy-3-methox phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]*tert*-butyldimethylsilane (138)

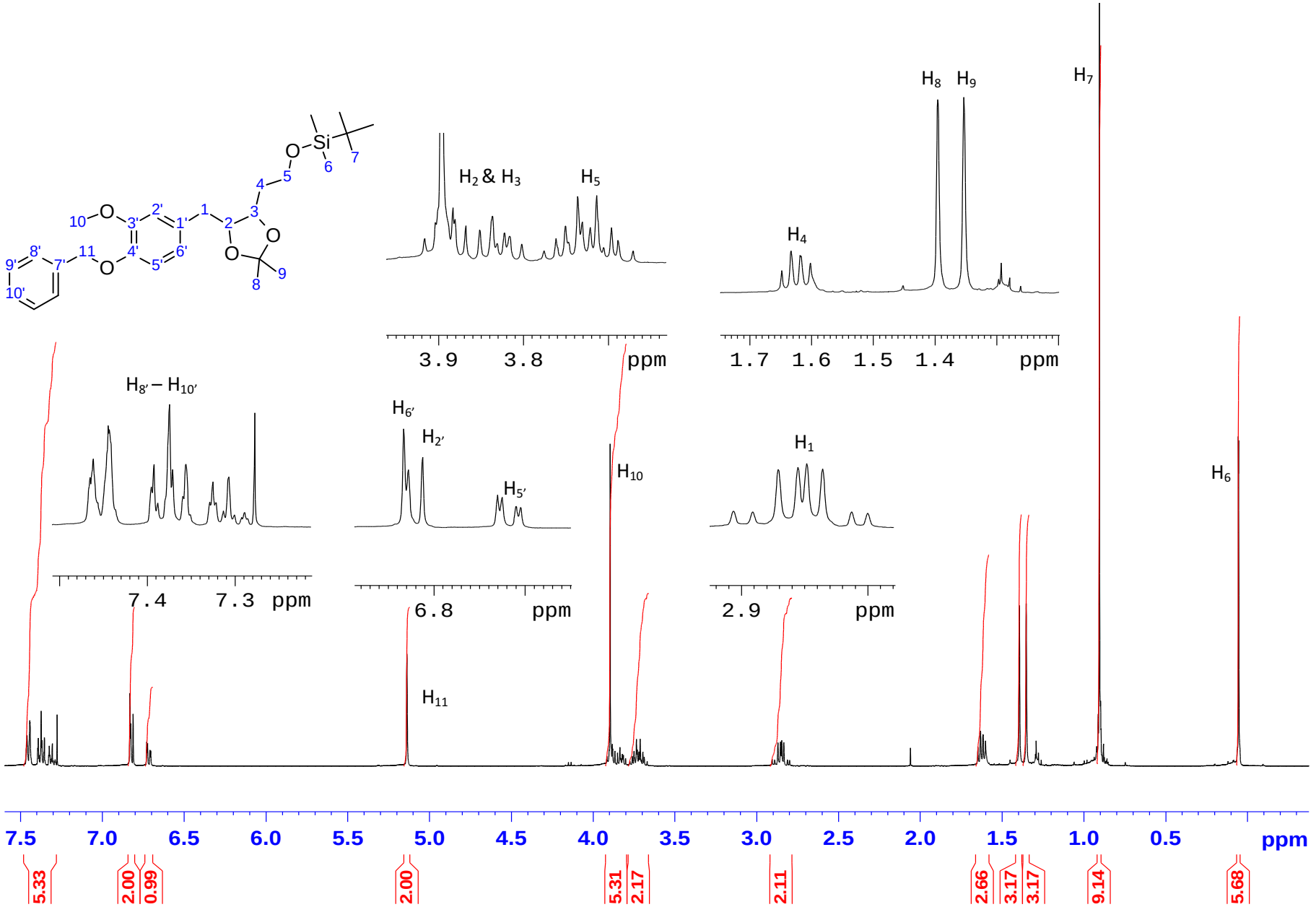

Plate 26b: ^{13}C NMR spectrum for 2-[5-[(4-Benzyloxy-3-methoxy phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]tert-butyl-dimethyl-silane (138)

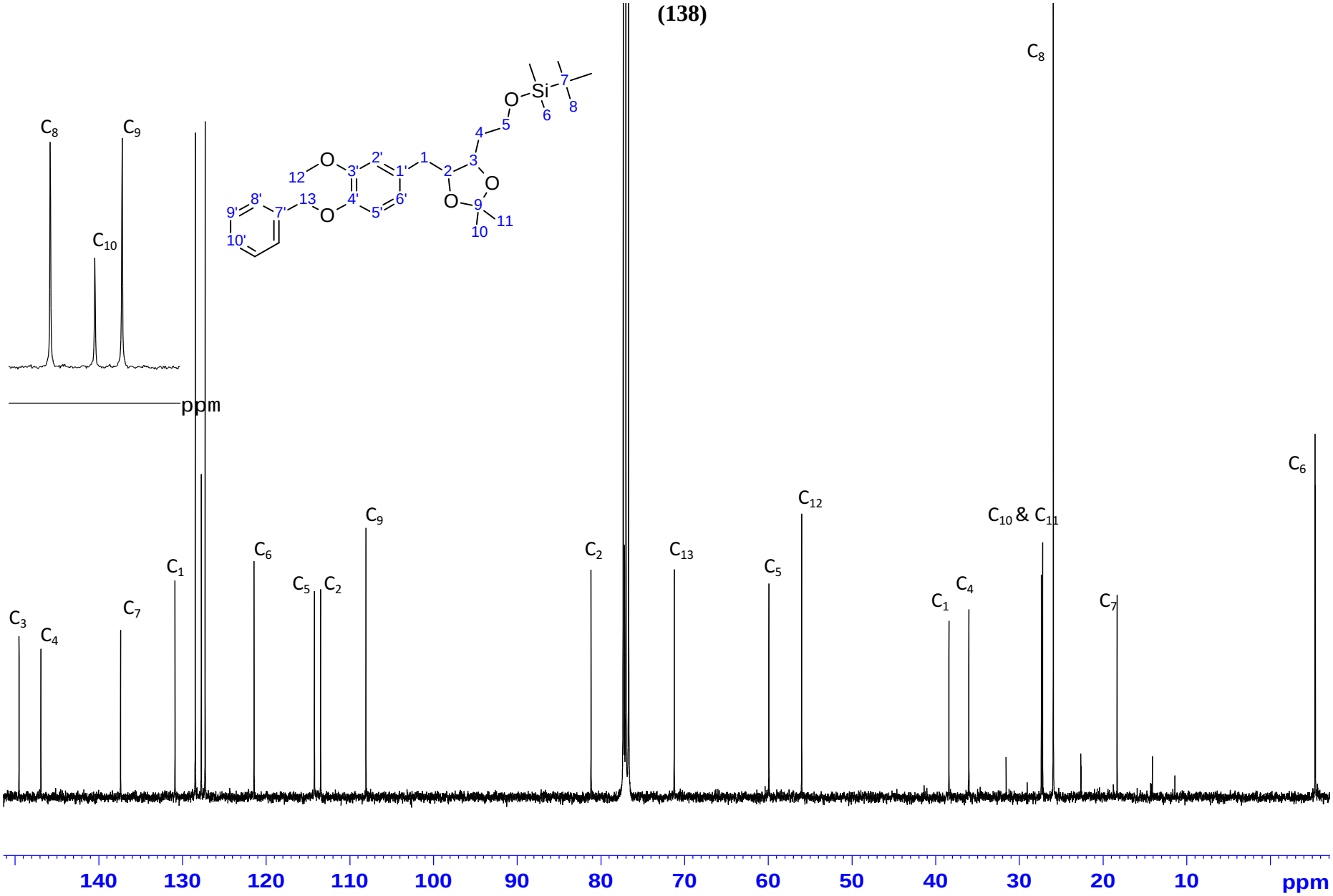

Plate 27a: ^{1}H NMR spectrum for 5-(4-benzyloxy-3-methoxy)phenyl]pentane-1,3,4-triol (131)

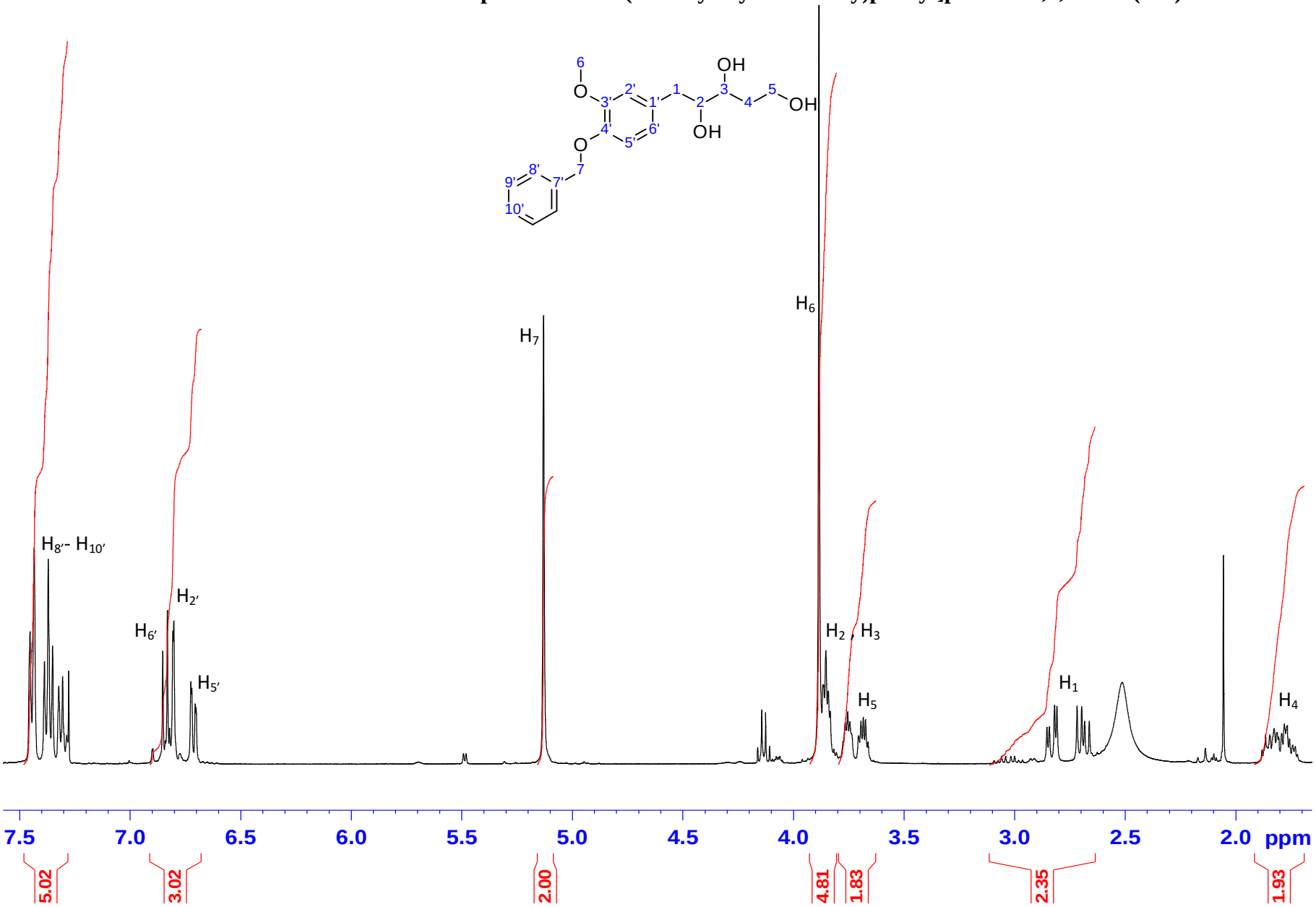

Plate 27b: ^{13}C NMR spectrum for 5-(4-benzyloxy-3-methoxy)phenyl]pentane-1,3,4-triol (131)

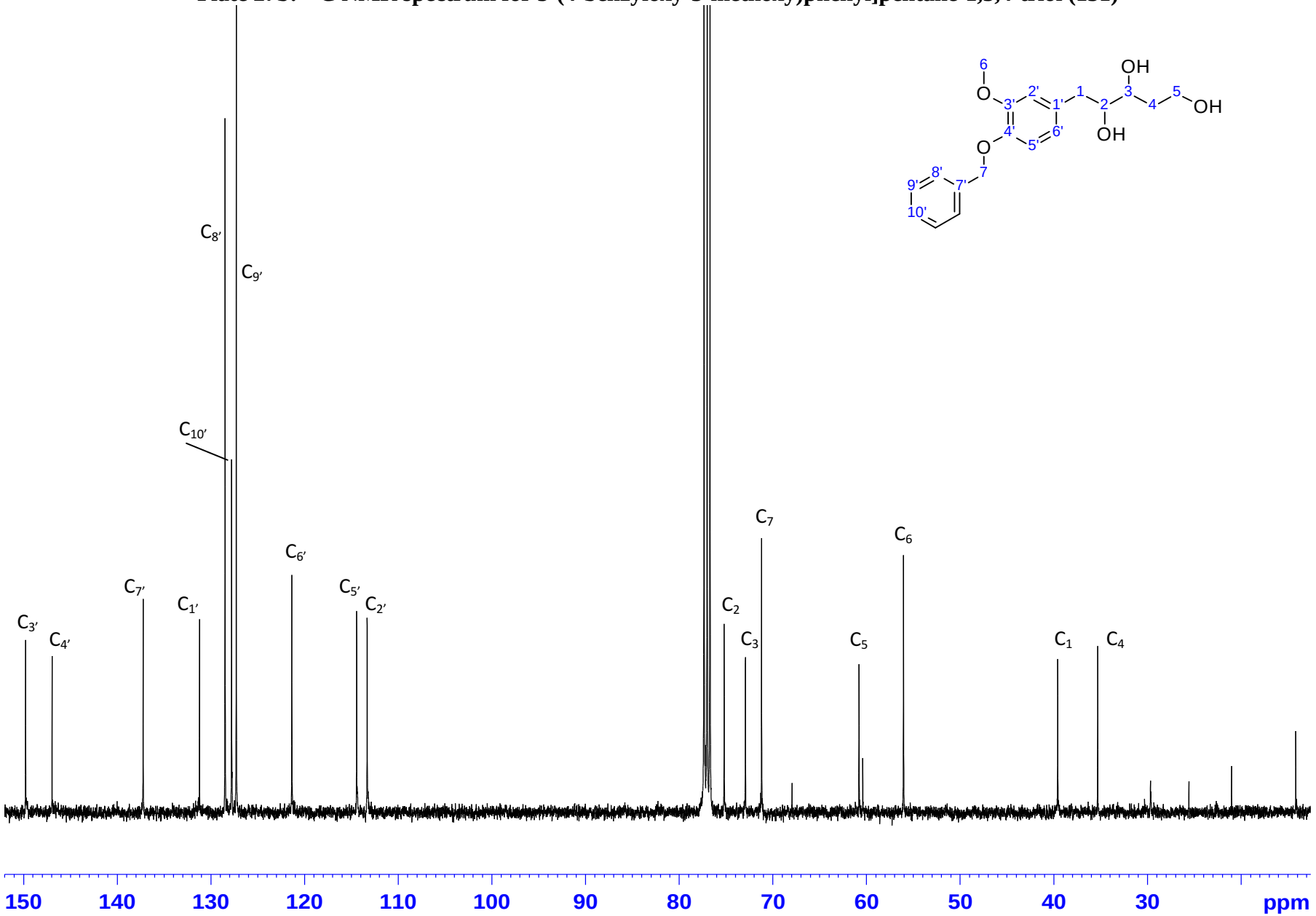

Plate 28a: ^{1}H NMR spectrum for 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol

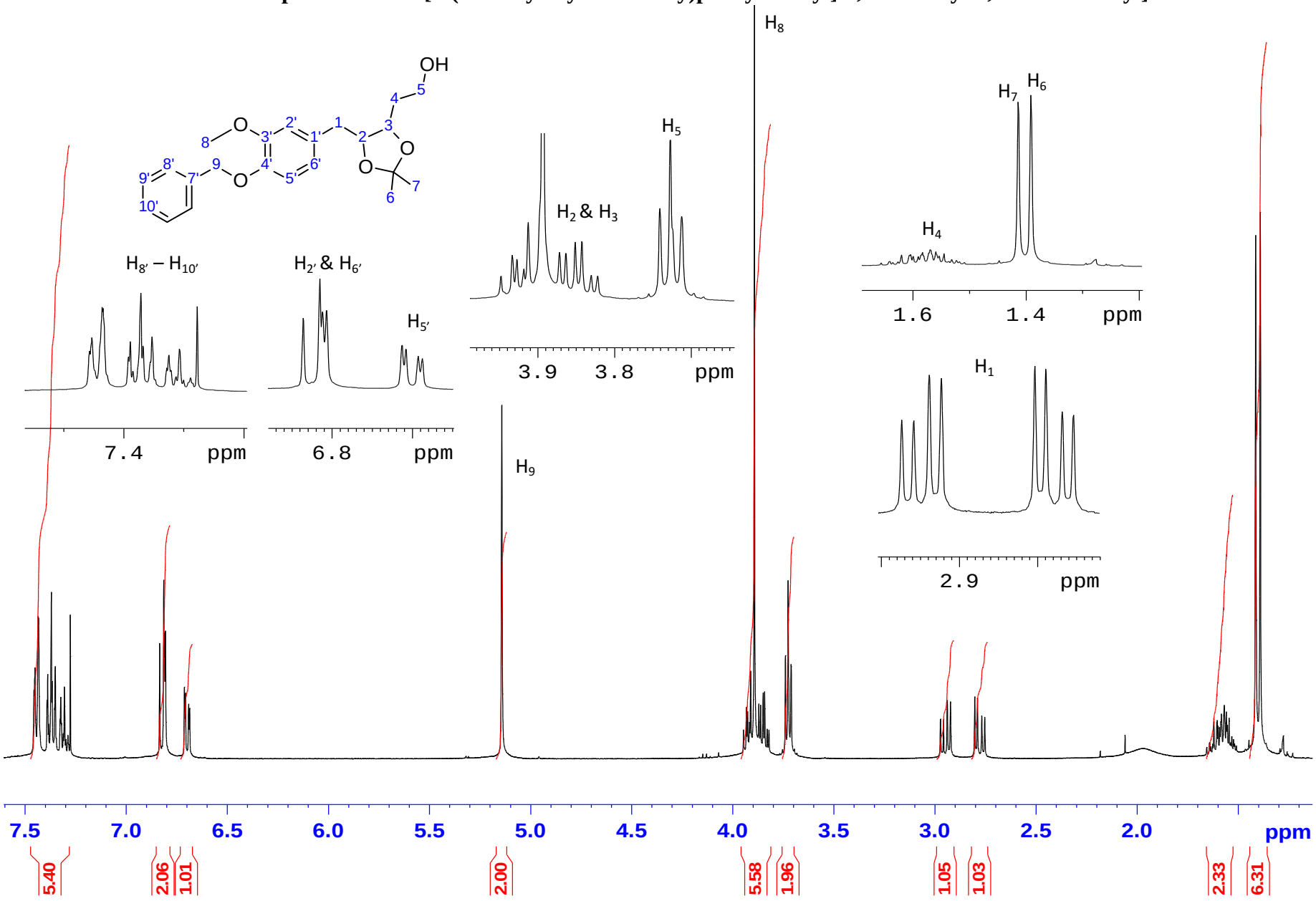

Plate 28b: ^{13}C NMR spectrum for 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol

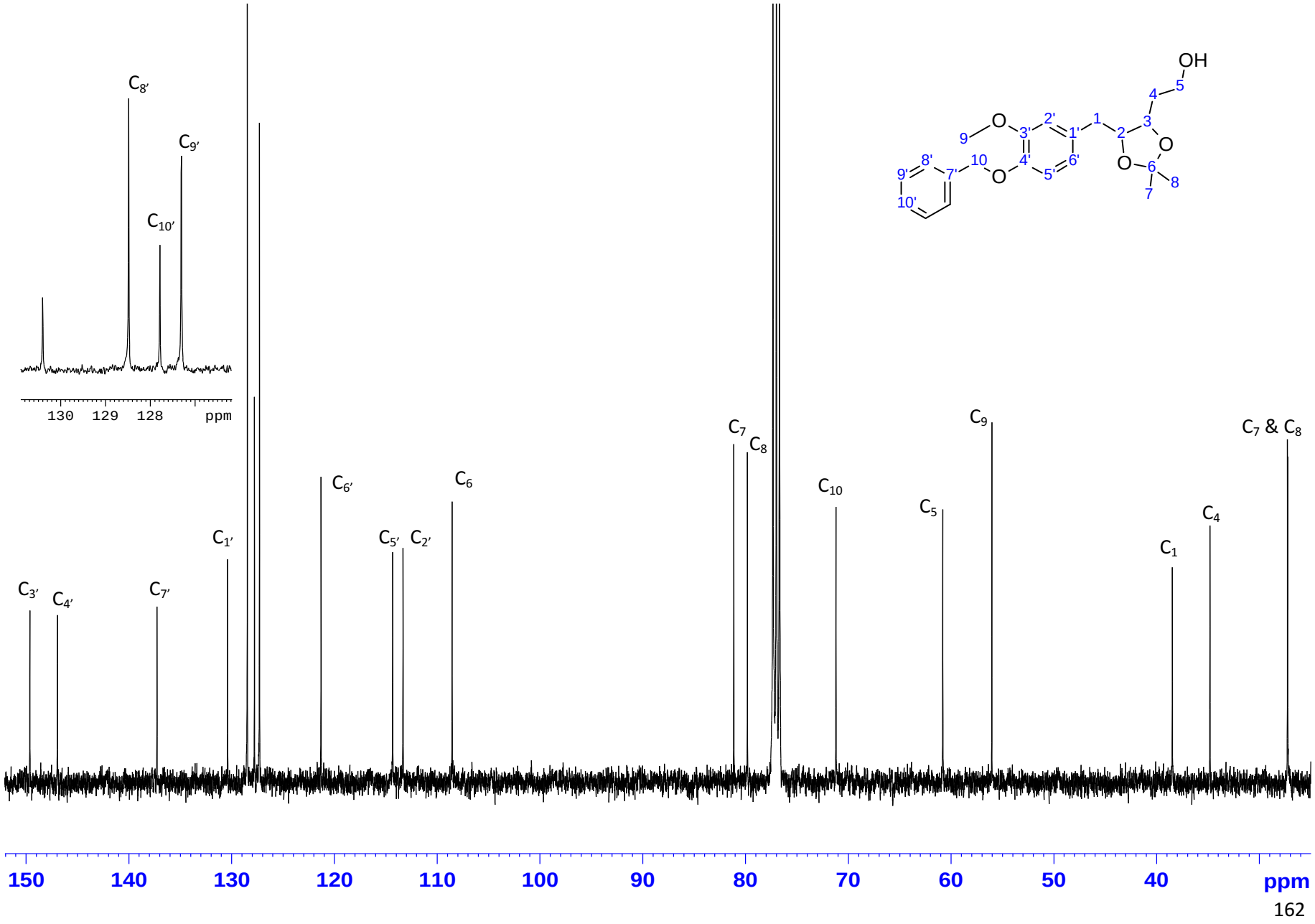

Plate 29a: ^{1}H NMR spectrum for 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde (133)

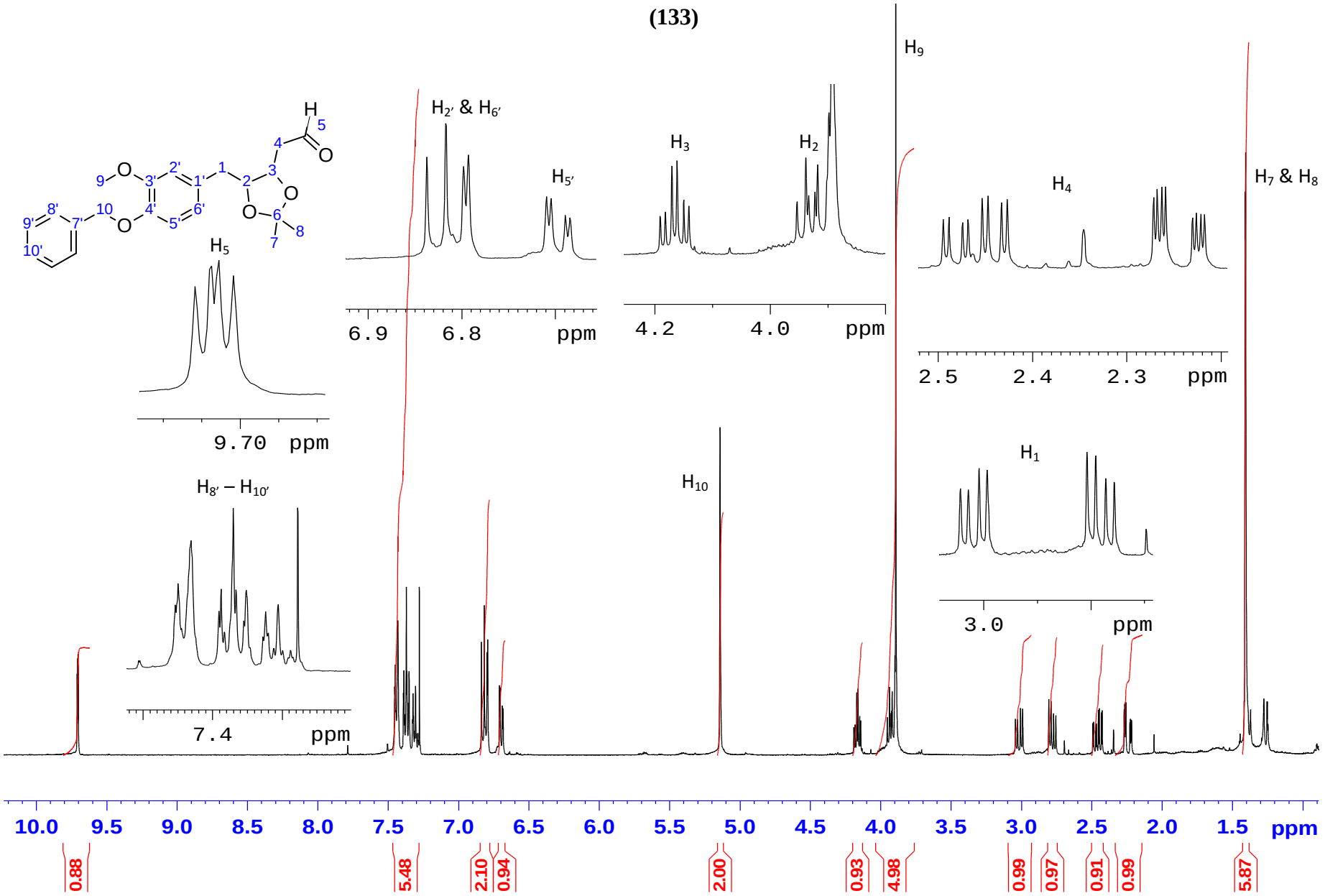

Plate 29b: ^{13}C NMR spectrum for 2-[5-(4-Benzyloxy-3-methoxy)phenylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde (133)

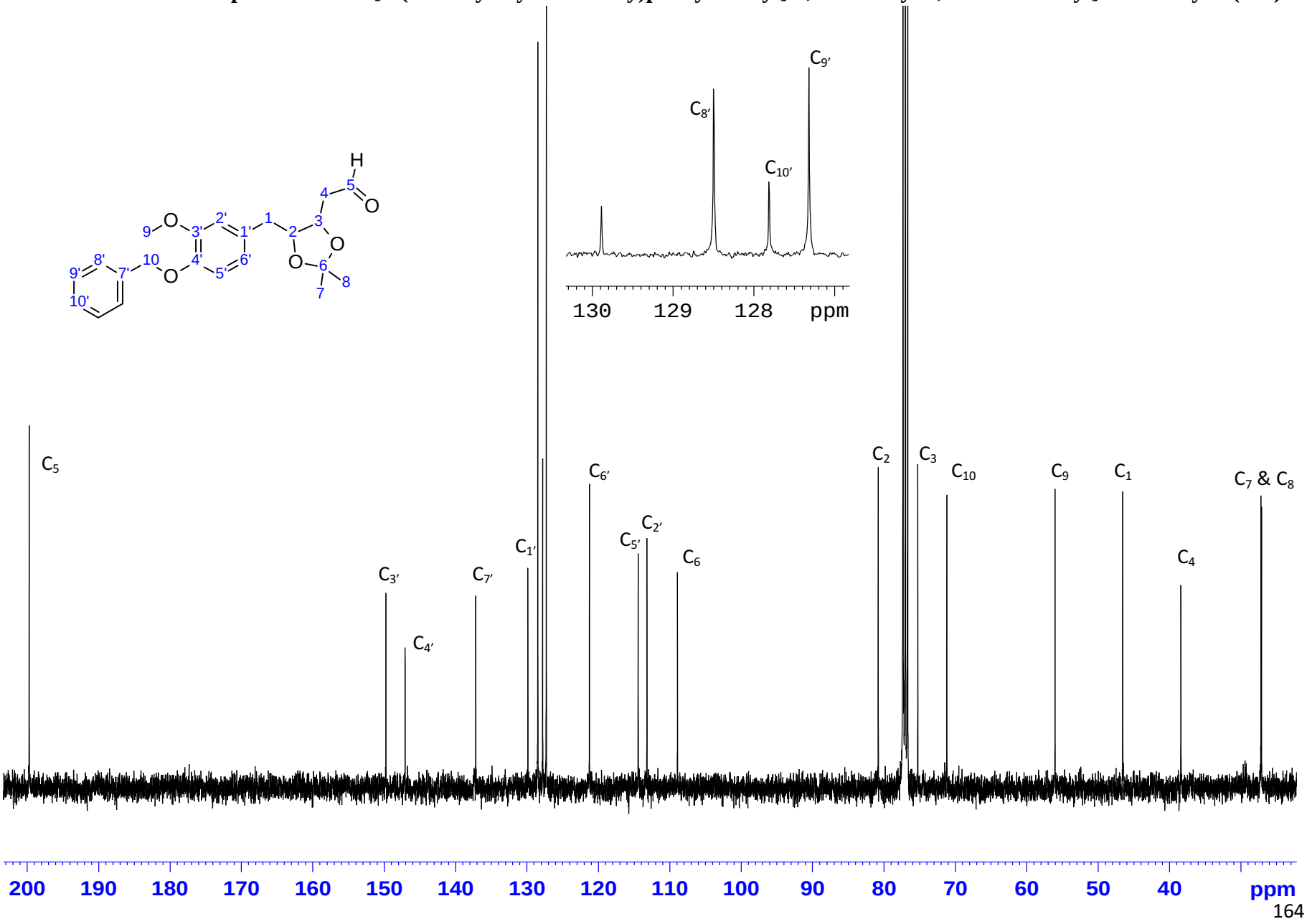

Plate 30a: ^{1}H NMR spectrum for 5-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-2,4-diol (137)

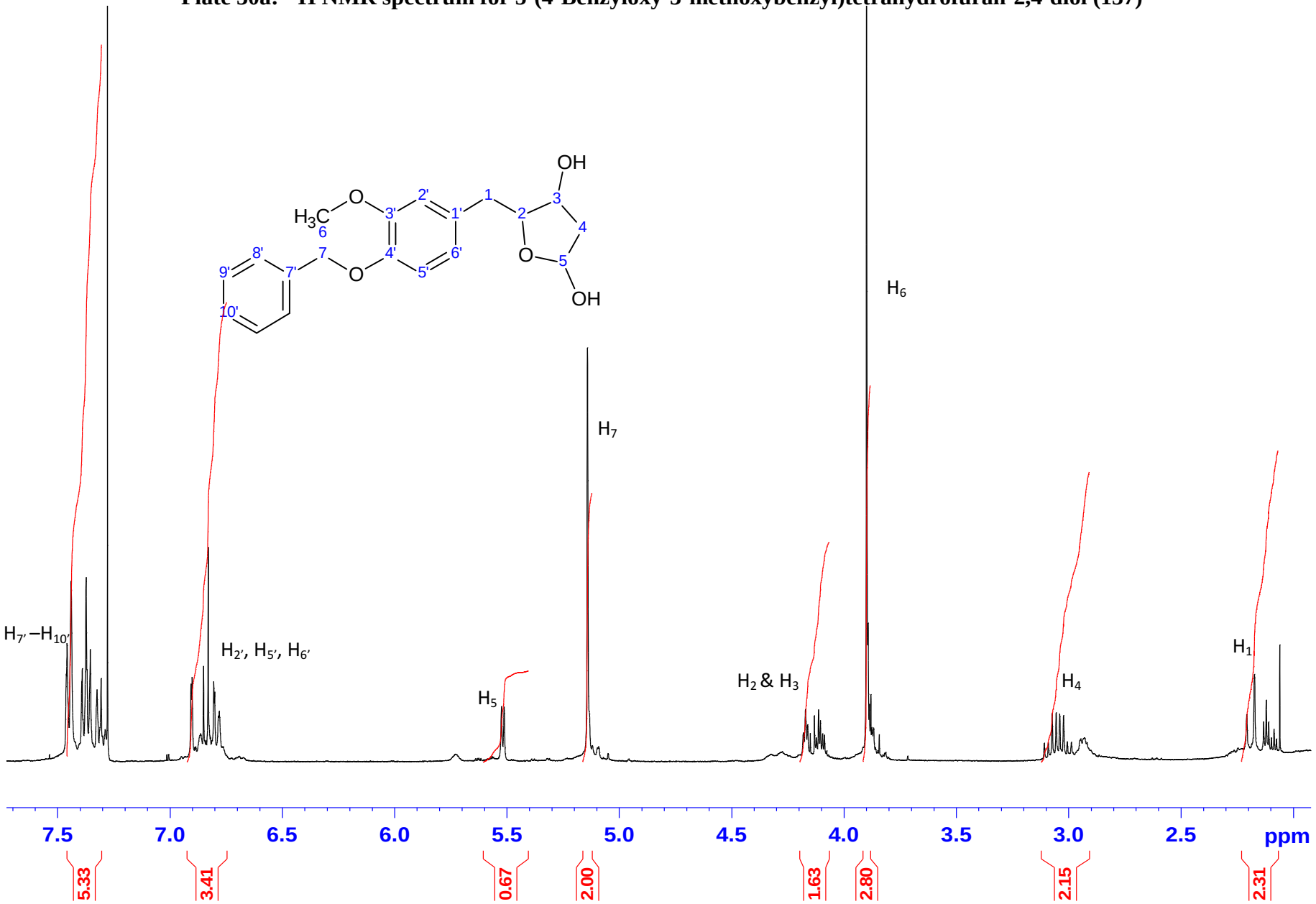

Plate 30b: ^{13}C NMR spectrum for 5-(4-Benzyloxy-3-methoxybenzyl)tetrahydrofuran-2,4-diol (137)