WITTIG REAGENTS AND NATURAL PRODUCT SYNTHESIS

TRIALKYL PHOSPHINE - DERIVED REAGENTS FOR ALDEHYDE HOMOLOGATION AND THEIR APPLICATION TO MEROTERPENE SYNTHESIS

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements

for the Degree of Doctor of Philosophy

McMaster University

McMaster University DOCTOR OF PHILOSOPHY (2023) Hamilton, Ontario (Chemistry)

TITLE: Trialkyl Phosphine Derived Reagents for The Carbon Homologation of Aldehydes and Their Application to Meroterpene Synthesis AUTHOR: David Hurem, B.Sc., M.Sc. (McMaster University) SUPERVISOR: Professor J. McNulty NUMBER OF PAGES: xx, 247

Methodologies for the extension of aldehydes to functionalized olefins and their application to the synthesis of cannabinolic acid methyl ester are presented.

ABSTRACT

Chapter One presents an overview of phosphorus reagents for the carbon homologations of aldehydes and ketones leading to functionalized carbonyl derivatives. Select examples are provided to exemplify the utility of carbon homologation methodology in synthesis and asymmetric organocatalysis and in the total synthesis of natural products.

The directing effect of acetals on regioselective ylide formation is explored in Chapter Two. Evidence is presented for ylide formation through a complex induced proximity effect with lithium bases under coordinating conditions. Moreover, four-carbon donors represent a limit for useful directed ylide formation with trialkylphosphine-derived Wittig salts in carbonyl homologation reactions.

A facile approach to the synthesis of methyl vinyl ketones (MVKs), using acetonyl tripropylphosphoranes under mild conditions, is reported in Chapter Three. A library of diversely functionalized MVKs was synthesized as a demonstration of the scope and generality of the methodology. The application of MVKs as substrates for organocatalysis and as building blocks for useful polyketide intermediates is briefly highlighted.

In Chapter Four, the two-carbon homologation methodology that was presented in the previous chapter is applied to the synthesis of the polyketide olivetol and a series of *O*-methyl derivatives. Cyclic diketone intermediates were aromatized with catalytic iodine and DMSO as a terminal

oxidant. Modification of the solvent system allowed for the selective synthesis of mono- or dimethyl ethers of methyl olivetolate. The selectivity of this aromatization is further explored in the final chapter with more complex substrates.

Chapter Five focuses on the synthesis of the meroterpene phytocannabinoids found in *Cannabis sativa*. A synthetic strategy involving the sequential condensation/[3+3]-annulation of citral with cyclic 1,3-diketones synthesized in the previous chapter. This afforded non-aromatic meroterpenes that were subjected to acid-mediated thermal rearrangement and catalytic oxidative aromatization. Evidence for chemoselectivity of the aromatization methodology was demonstrated and a synthesis of methyl cannabinolate is presented.

ACKNOWLEDGMENTS

I would like to start by acknowledging those who mentored me in chemistry throughout my career. Professor Dr. James McNulty supervised this work and provided careful guidance throughout this endeavor. Professor Dr. Travis Dudding, served as my M.Sc. and B.Sc. supervisor at Brock University and who instilled a strong foundation in asymmetric organic synthesis from a physical perspective. The late professor Dr. Tomas Hudlicky of Brock University taught me the importance of rigour in organic synthesis and whose courses during my late undergraduate and early graduate career built a great appreciation for the art of natural product total synthesis. My late father and very first mentor, Dr. Zihnija Hurem, provided my earliest experiences in the chemistry laboratory and fostered in me a curiosity for the natural world.

Furthermore, the completion of this work would never have been possible without my peers in the McNulty Laboratory here at McMaster, who were a consistent source of inspiration and provided hours of lively discussion with regard to our research projects. To this end I would like to specifically thank Dr. Chanti Dokuburra, Dr. David McLeod, Dr. Alex Nielsen, Dr. Carla Brown, Dr. Manjeet Sharma, Dr. Omkar Revu, Arkesh Narayanappa and Vassilios Kannelis.

LIST OF ABREVIATIONS

APCI	atmospheric pressure chemical ionization
CBD	cannabichromene
CBG	cannabigerol
CBN	cannabinol
COSY	correlation spectroscopy
mCPBA	*meta*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDDA	ethylenediamine diacetic acid
ESI	electrospray ionization
GC	gas chromatography
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
MOM	methoxymethyl
MS	mass spectrometry

MVK	methyl vinyl ketone
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
PTSA	para-toluenesulfonic acid
SAE	Sharpless Asymmetric Epoxidation
SG	Still-Gennari
TBAF	*tert*-butylammonium fluoride
TFA	trifluoroacetic acid
THC	tetrahydrocannabinol
THF	tetrahydrofuran
THP	tetrahydropyran
THT	tetrahydrothiophene
TLC	thin layer chromatography
TMOF	trimethylorthoformate
TMS	tetramethylsilane
TPP	triphenylphosphine

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

ACADEMIC STATEMENT

All sections of Chapter One, excluding Section 1.1 appear as a chapter in:

D. Hurem, J, McNulty, Phosphorus Reagents for Two-, Three-, and Four-Carbon Homologation of Carbonyl Compounds to Functionalized Olefins, Homologation Reactions, V. Pace (Ed), Wiley-VCH (**2022**).

The review of literature was conducted by myself. Writing was done by myself and Prof. McNulty.

All sections of Chapter Two, excluding Section 2.4 appear in Reference 81 of Chapter One:

Narayanappa, A., Hurem, D. and McNulty, J. (2017). *Synlett* 28, 2961-2965.

The work presented in Table 3 and Figure 1 of this chapter was conducted by Arkesh Narayanappa. All other work presented in Chapter 2 was done by myself. The published manuscript was written by myself and Professor James McNulty.

The results reported in Table 8 of Section 3.4 of this chapter were obtained collaboratively with then undergraduate student Lila Begovic, while working under my direction. All other results reported in Chapter Three were obtained by myself.

All parts of Chapter Four, excluding Section 4.4 also appear in Reference 35 of Chapter 3:

Hurem, D.; Macphail, B. J.; Carlini, R.; Lewis, J.; McNulty, J. *SynOpen* **2021**; *01*, 86.

All laboratory work was conducted by myself. The article was written by myself and Dr. James McNulty. The remaining authors contributed to editing and discussions which guided this work.

The results presented in Chapter 5 were obtained by myself.

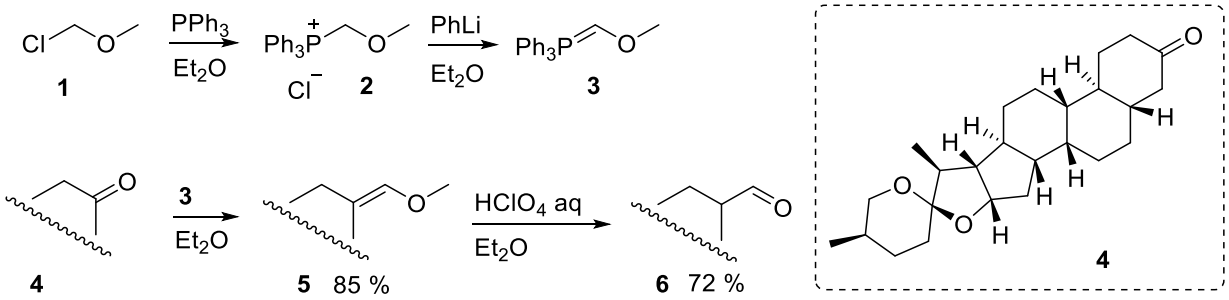
1.0. INTRODUCTION: PHOSPHORUS REAGENTS FOR CARBON HOMOLOGATION OF CARBONYL COMPOUNDS TO FUNCTIONALIZED OLEFINS

The entirety of Sections 1.2 to 1.10 of this chapter appears as a chapter in:

D. Hurem, J, McNulty, Phosphorus Reagents for Two-, Three-, and Four-Carbon Homologation of Carbonyl Compounds to Functionalized Olefins, Homologation Reactions, V. Pace (Ed), Wiley-VCH (**2022**).

1.1 Wittig reagents for the synthesis of C1-homologated vinyl ethers as aldehyde and ketone equivalents.

The use of Wittig salts for the synthesis of enol ethers was reported as a method for the synthesis of one-carbon homologated aldehydes from ketones as early as 1958.[1] The phosphonium salt **2** was generated from the reaction of chloromethyl methyl ether **1** and triphenylphosphine (TPP) in anhydrous ether (Scheme 1). Deprotonation *in situ* with phenyllithium formed the phosphonium ylide that was reacted with tigogenone **4** in an excess of the ylide to give the corresponding homologated methyl enol ether **5** in 85 % yield. Stirring in diethyl ether saturated with 72 % perchloric acid afforded the homologated aldehyde **6**.

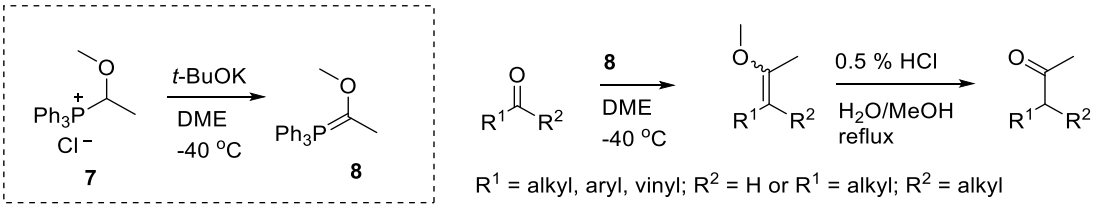


Scheme 1. Synthesis of homologated aldehyde of tigogenone.

Later Wittig and coworkers explored the scope and reaction conditions of this transformation. Ketones and aldehydes were investigated. Competing aldol condensation was observed with cyclopentanone.[2]

Coulsen and coworkers later reported the one-carbon homologation of aldehydes to give methyl ketones through the intermediate vinyl ether.[3] The method used a modified version of the Levine reagent **2**, that was prepared from triphenyl phosphine and α-chloroethyl methyl ether. The ylide generated from the methyl alkoxyphosphonium salt **7** was found to be unstable at room temperature, but reacted successfully at – 40 ˚C with aldehydes (Table 1, Entries 1 – 4) to give the isolatable vinyl ether as a mixture of isomers. Hydrolysis allowed access to the methyl ketone, although poor yields were obtained with ketones (Table 1, Entries 5 – 7).

Table 1. Synthesis of C1-homologated methyl ketones from carbonyl compounds.

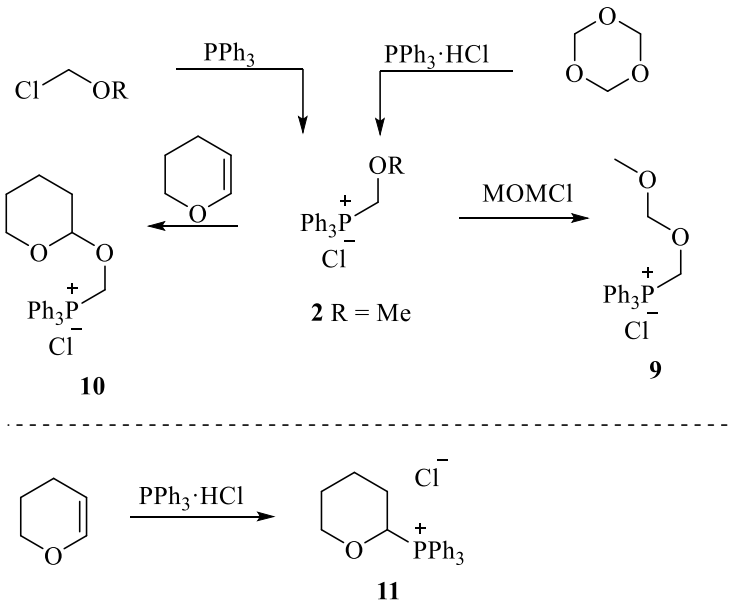


Entry	Carbonyl	Methyl Ketone Product	Yield (%)
1	**benzaldehyde**	**3-phenyl-2-propanone**	**88**
2	**cinnamaldehyde**	**3-styryl-2-propanone**	**82**
3	***n*-heptanaldehyde**	**2-nonanone**	**57**
4	**pelargonaldehyde**	**2-undecanone**	**51**
5	**cyclohexanone**	**methyl cyclohexyl ketone**	**45**
6	**cyclopentanone**	**methyl cyclopentanone**	**0**
7	**2-octanone**	**3-methyl-2-nonanone**	**15**

The generated ylide **8** was reacted in a slight excess with aldehyde to afford the homologated enol ethers which were isolated by distillation and subsequently hydrolyzed by reflux in dilute HCl in near quantitative yields. Non-enolizable aldehydes were homologated to their

corresponding methyl ketones with high yields, while enolizable aldehydes and ketones gave lower overall yields of methyl ketones. The olefination step with ketones did not proceed to completion, with mixtures of methyl enol ether and unreacted ketone isolated from reaction mixtures. Reactions with cyclopentanone, as previously reported by Wittig and coworkers with reagent **2**, yielded only the aldol condensation product and no detectable enol ether.

The C1-homologation methodology was applied to a synthesis of nitroxyl aldehydes and called for the hydrolysis of an enol ether intermediate under mild conditions to maintain orthogonality with the acid sensitive nitroxyl group.[4] A model study was conducted with a series of enol ether homologues.[5] The first series of phosphonium salts were synthesized in the same manner as the Levine reagent **2**, through TPP substitution on the corresponding chloromethyl ether. (Scheme 2).

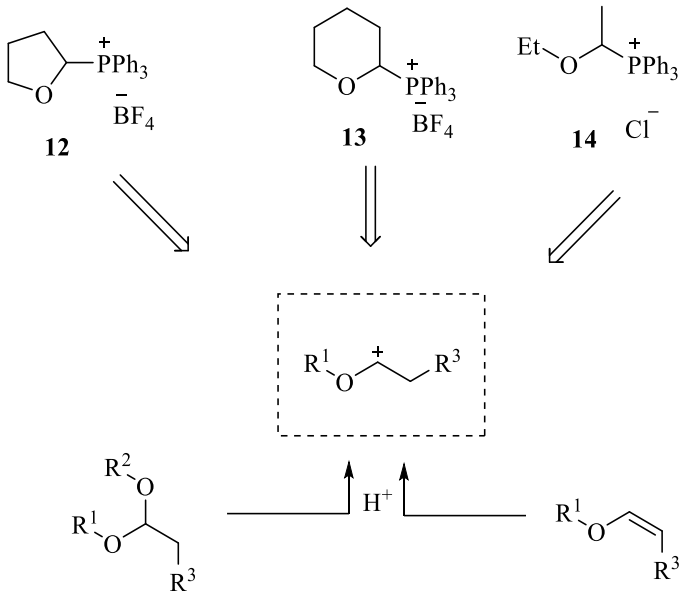


Scheme 2. Synthesis of triphenylphosphonium ethers.

Methoxymethyloxy and tetrahydropyranyloxy salts, **9** and **10** respectively, were synthesized in about 42 % yield by reaction of chloromethyl methyl ether (MOMCl) or dihydropyran with Levine reagent **2**, which in turn was generated under acidic conditions from paraformaldehyde. The α-phosphonium tetrahydropyran (THP) salt **11** was found as a byproduct if excess triphenylphosphonium chloride was present in the reaction with dihydropyran and could be synthesized in 72 % yield from dihydropyran and triphenylphosphonium chloride. The synthesized homologation reagents were used to generate a series of amino and nitroxy enol ethers under standard condition with generally high yields.

Hydrolysis of the resulting model enol ethers to homologated carbonyls was studied. Ease of hydrolysis was found to follow closely with the basicity of the enolic oxygen such that the THP ethers were most easily hydrolyzed. Further, it was proposed that internal hydrogen bonding of the protonated MOM-enol ethers led to their apparent stability to hydrolysis.

A series of α-phosphorous tetrahydrofurans (THF) and tetrahydrothiophenes (THT) were synthesized by addition of phosphorous nucleophiles to respective heterocycles containing α-leaving groups. Reaction of triphenylphosphonium tetrafluoroborate to alkoxy-THF formed the Wittig salt **12** in 92 % yield (Scheme 3).[6]

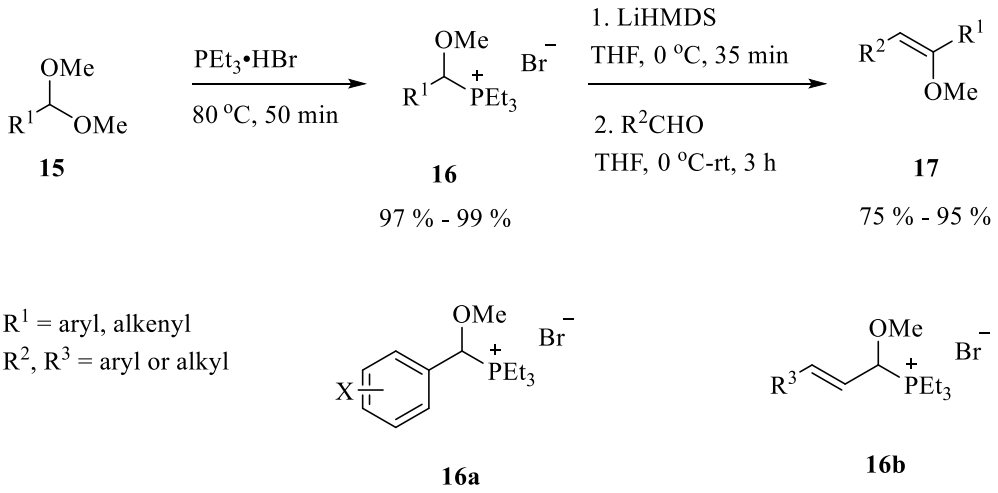


Scheme 3. General synthesis of alkoxy phosphonium salts using phosphine-acid adducts.

Similarly, α-phosphonium THP **13** was synthesized in near quantitative yields by reaction of α-methoxy-THP with triphenylphosphonium tetrafluoroborate.[7] Meanwhile, the addition of TPP-HCl to dihydropyran was studied and the methodology was expanded to include cyclic and acyclic vinyl ethers as nucleophiles. The methyl ketone homologating reagent **14**, which is an analogue of Coulsen's reagent **7**, was prepared from ethyl vinyl ether in this manner.[8]

The utility of this method was significantly improved through the development of a general route to α-methoxy substituted phosphonium salts **16** (Scheme 4).[9] It was found that triethylphosphine hydrobromide reacted with dimethyl acetals **15** derived from aromatic and unsaturated alkenals to yield the corresponding α-methoxy substituted phosphonium salts **16** as a general reaction.

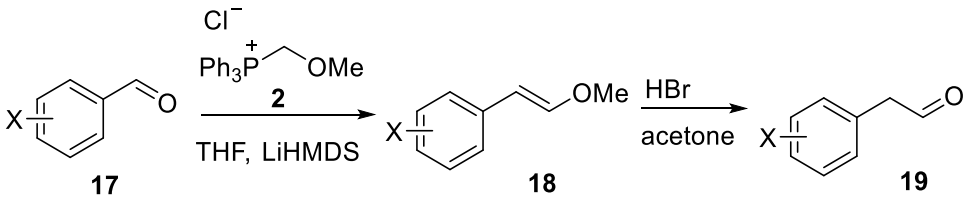
The corresponding triphenylphosphine salts could not be obtained using this method, with P-methylation identified as the outcome of corresponding reaction, illustrating the often unique reactivity of short chain organophosphines.

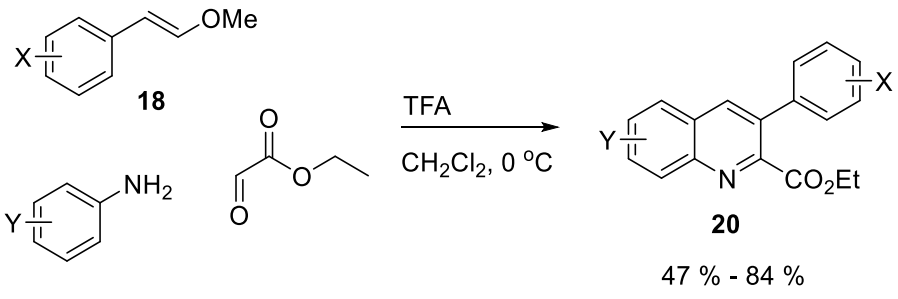


Scheme 4. Synthesis of trialkylphosphonium salts and Wittig reactions to generate methyl enol ethers.

Reactions of the ylide derived from **16a** with aldehydes gave the corresponding vinyl ethers. In contrast, ylides derived from the salt **16b** gave 2-methoxy-1,3-dienes. The corresponding ylides **16** could be generated using lithium hexamethyldisilazide (LiHMDS) and, unlike with reagent **7**, were stable at 0 °C. A series of methyl enol ethers **17** were synthesized by Wittig olefination with a wide scope of aldehydes. In contrast with Wittig reactions preformed with the corresponding Levine reagent or Coulsen reagent, the yields of enol ethers derived from enolizable aldehydes were improved and some degree of *E*-selectivity was observed, in some cases as high as 7:1 *E*/*Z* was obtained.

It should be noted that hydrolysis of vinyl ethers that are obtained through the use of alkoxy-substituted ylides reveals the free homologated carbonyl compound. These are often highly reactive aldehydes and ketones containing active methylenes such as phenylacetone or phenylacetaldehyde derivatives. An added advantage in obtaining the vinyl ether intermediate is its direct application in subsequent cycloaddition chemistry as a carbonyl (or enol) surrogate. As an example, in a recent synthesis of anti-parasitic quinolines, the vinyl ether **18** was prepared using the Levine reagent **2** (Scheme 5). The vinyl ether readily underwent Povarov cycloaddition with *in-situ* generated imine to yield the poly-substituted quinoline **20**. In contrast, hydrolysis of intermediate **18** furnished the reactive phenylacetaldehyde **19** that rapidly decomposed on all attempts to engage in the Povarov cycloaddition.[10]

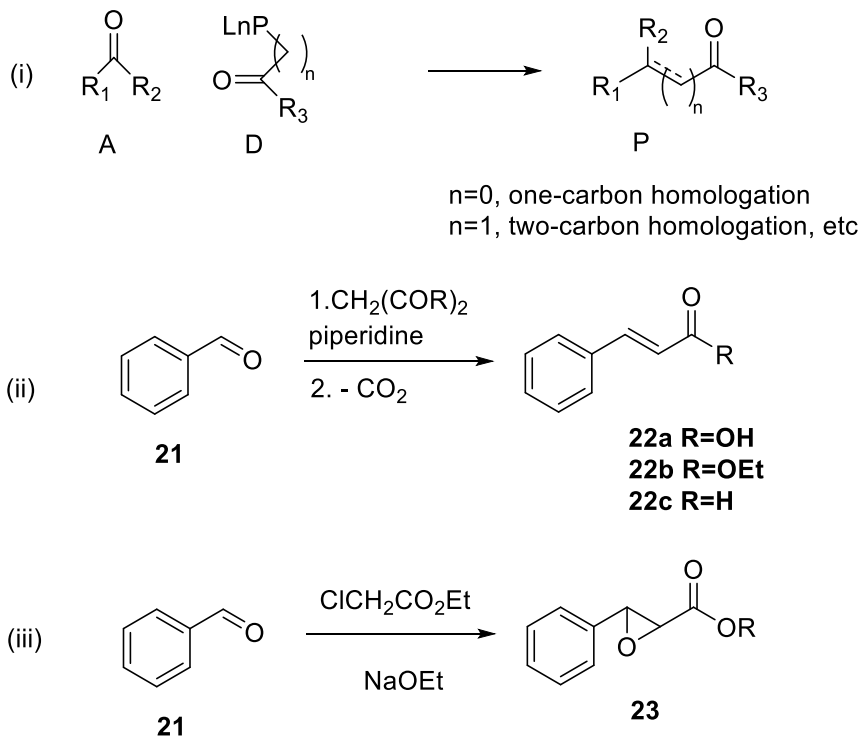




Scheme 5. Quinoline synthesis using C1-homologated vinyl ethers as aldehyde equivalents in Povarov cycloaddition reactions.

1.2 Classical methods for two-carbon homologation.

An attempt to delineate the most general view of the n-carbon homologation reaction processes, employing phosphorous-based reagents, is shown in Scheme 6 (i). The acceptor component A is generally and aldehyde, with ketones reacting in certain cases. The donor component D contains a carbonyl or equivalent directing unit attached to an ylide or phosphonate anion, as the most common examples. The product P does not contain phosphorus, retains the extended carbonyl or latent carbonyl-equivalent, such as a vinyl ether or acetal, and may or may not retain a double bond. One of the earliest methods to achieve the two-carbon homologation of aromatic aldehydes **21** to cinnamic acid **22a** and ester **22b** derivatives was described by Knoevenagel in a series of three publications in 1898.[11]



Scheme 6. The general scope of n-carbon homologation (i), classic Knoevenagel condensation reaction and crossed aldol (Claisen-Schmidt) reactions (ii) and Darzens reaction (iii) of aromatic aldehydes to yield unsaturated acid or ester derivatives **22a**,**b**, alkenals **22c** or epoxy-esters **23**.

In this work malonic acid was condensed with aromatic aldehydes **21** in the presence of an amine catalyst such as piperidine or ammonia, Scheme 1. The application of the Knoevenagel reaction to a wide range of substituted malonates, β-keto esters and other activated methylenes and to other aldehyde substrates has been extensively developed over the years.[11]

The Knoevenagel condensation produces the condensed 1,3-diacid or diester intermediate that can be isolated or decarboxylated thermally to yield the (*E*)-α,β-unsaturated acid or ester

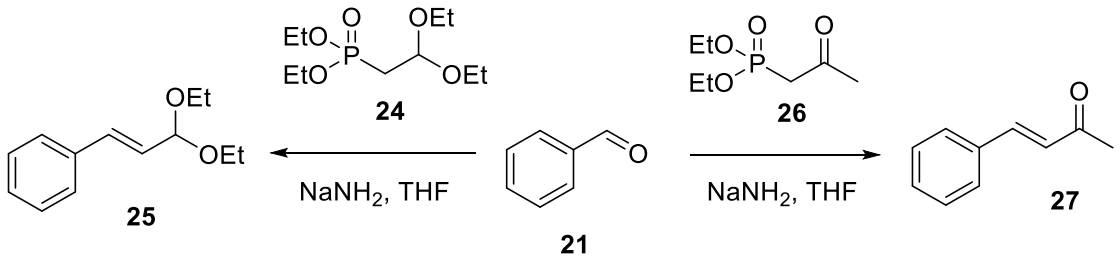
derivative **22a**/**b**. High yields of cinnamic acid derivatives can be obtained from reactive and sterically congested aldehydes with decarboxylation occurring at room temperature upon the application of ultrasound.[12] The reaction is also notable as being the first generally accepted development in the field of aminocatalysis involving the intermediacy of iminium ion intermediates.[13] Crossed aldol reactions using acetaldehyde as the donor substituent (Claisen-Schmidt reaction) leading to alkenals **22c** have proved challenging until recently due to self condensation reactions.[14] Phosphorous-based reagents that permit this extremely valuable two-carbon homologation and applications of the reactive alkenals are described in detail here. Although the Knoevenagel reaction and aldol condensation reaction do not utilize phosphorus-based reagents, they are notable for their simplicity and atom-economy and, despite obvious limitations in terms of chemoselectivity, serve as a useful starting point for consideration of any two-carbon homologation. Although generally of lesser synthetic utility, the Darzens[15] condensation reaction of α-halocarbonyl compounds with aldehydes is also a classical method for two-carbon homologation of aldehydes leading to stereoisomeric mixtures of the corresponding functionalized epoxy-esters **23**.[16]

1.3 Horner-Wadsworth-Emmons and related reagents for two-carbon homologation.

The use of phosphonate carbanions for the homologation of ketones and aldehydes to carboxylic acid derivatives was initially described by Horner[17] and subsequently developed by Wadsworth and Emmons.[18] The use of triethylphosphonocaetate or the trimethyl equivalent, the so-called

HWE reagents, are extensively utilized in organic synthesis and have been reviewed,[19,20] and only two-carbon homologations will be covered here. In order to obtain α,β-unsaturated aldehydes utilizing this chemistry, the unsaturated esters must be reduced to the corresponding allylic alcohol (usually using DIBAL-H at cryogenic temperatures), followed by selective oxidation (Swern oxidation or use of the Dess-Martin periodinane) to obtain the desired alkenal. The overall efficiency of the three-step process, often requiring purification of each intermediate, in terms of cost and atom-economy can be prohibitive on scale.

The preparation and use of the α-phosphonoacetal **24** for the synthesis of the homologated alkenals or protected acetals such as **25** and the α-phosphonoketone **26** for the synthesis of enone **27** directly from carbonyl compound **21** has also been reported (Scheme 7), but less frequently investigated.[21-23] Cinnamaldehyde acetals, and benzylidene acetones were both synthesized from reaction of benzaldehydes with phosphonates **24** and **26** respectively (Scheme 7),[21] yielding predominantly the (*E*)-alkenes.



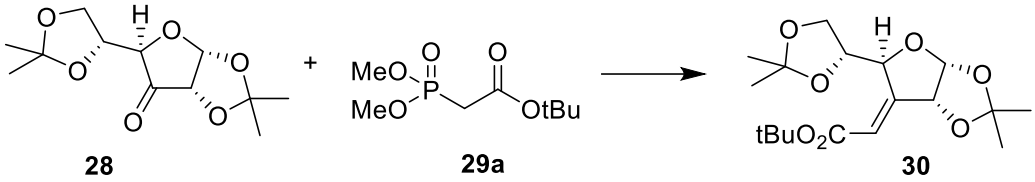
Scheme 7. Use of functionalized acetal and ketone containing phosphonate carbanions for the synthesis of protected alkenals and enones.

In related work, the synthesis of formylmethylenephosphonates has been reported, Horner-Wadsworth-Emmons (HWE) reactions could not be accomplished due to self-condensation of the phosphonate anions.[24] The synthesis of homologated alkenals can be accomplished using imine-protected reagents, although the lability of imines to hydrolysis can prove operationally difficult in some cases.[25] Homologated alkenals were synthesized using dimethylhydrazones of formylmethylenediethylphosphonates.[26] The phosphonate anion was generated using LDA at room temperature and reacted with a variety of ketones and aldehydes to give the homologated dimethylhydrazones in high yields. Reactions with aldehydes gave high (*E*)-selectivity, while reactions with ketones afforded mixtures of stereoisomers. Subsequent hydrolysis using aqueous 1 M HCl afforded the α,β-unsaturated carbonyls in near quantitative yield with concomitant olefin isomerization to give almost exclusively (*E*)-olefin.

One of the advantages of the use of phosphonate carbanions is their high reactivity and the ability to generate the anion under relatively mild conditions. This allows for the successful homologation of enolizable and sensitive α-chiral aldehydes.[19,20] The use of lithium chloride has been shown to increase the acidity of the phosphonate allowing for the successful use of weak bases including Hunig's base or DBU in the reaction.[27]

The high reactivity of phosphonate carbanions also allows two-carbon homologation of ketones in many cases. For example, Mulzer and co-workers (Scheme 8) reported the addition of various phosphonates to the hindered ketone **28**, yielding the unsaturated ester **30**.[28] In addition to the

successful olefination, the stereochemistry was shown to depend on the nature of the carboxylic ester substituent, with hindered esters, such as the *t*-butyl derivative **29a** providing unusually high (90 %) olefin stereoselectivity.



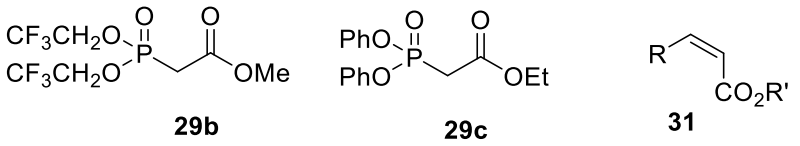
28 **29a** **30**

Scheme 8. HWE olefination of the sterically hindered ketone **28** with the *t*-butylphosphonoacetate ester **29a.**

1.4 Still-Gennari and Ando reagents for two carbon homologation.

A significant synthetic advantage in two-carbon homologation using phosphonate carbanions is the high stereocontrol achievable in the olefin formation. Phosphonoacetates yield the unsaturated ester with high (*E*)-stereoselectivity, generally >90%.[31] The preparation of (*Z*)-alkenes can be achieved using either the Still-Gennari reagent **29b** or Ando reagent **29c** as a result of kinetic control. The Still-Gennari reagent[32] generally yields the (*Z*)-α,β-unsaturated ester **31** with 90-95% stereoselectivity while the Ando reagent[33] typically provides 95% (*Z*)-stereoselectivity (Scheme 9). Two-carbon homologation reactions on ketones using the Still-Gennari reagents are covered in detail in a recent review.[30] Although high degrees of (*Z*)-selectivity can be attained in many cases, unhindered aromatic aldehydes and sterically hindered aldehydes provide modest selectivity towards the (*Z*)-olefin.[33] In addition, two-carbon

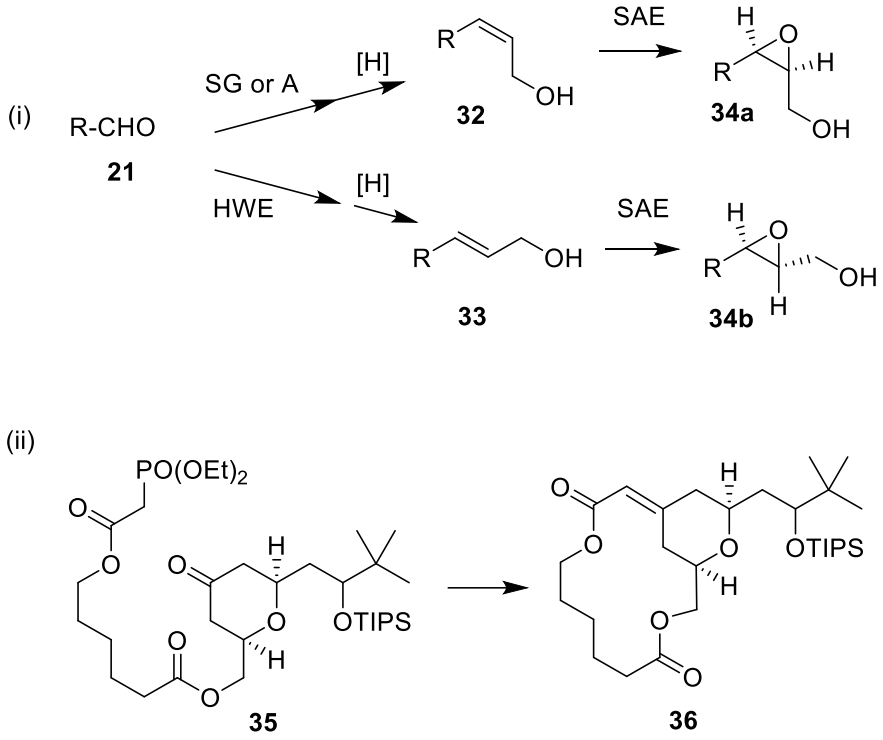
homologation reactions on pyruvates demonstrated only modest (*Z*)-selectivity using the Still-Gennari reagent.[29,30] In certain cases, Wittig homologation (see section 1.5) followed by photoisomerization proved to be a more advantageous route to the (*Z*)-olefin.[30]



Scheme 9. Still-Gennari reagent **29b** and the Ando reagent **29c** for (*Z*)-selective two-carbon homologation of aldehydes and ketones to unsaturated esters **31**.

The last result highlights the importance on the advantages of having multiple synthetic methodologies available. Overall, considering the available methods for two-carbon homologation of carbonyl compounds to unsaturated esters or analogs, the HWE, Still-Gennari and Ando reagents offer the advantages of high reactivity, including to ketones, and reliable stereocontrol available in comparison to the classic Knoevenagel condensation. The use of mild base allows limited side reactions, such as homo-aldol reactions, and polymerization, that can occur under Knoevenagel conditions. The Knoevenagel condensation also requires heat and the use of mineral acid to effect decarboxylation and is thus applicable to limited substrates. The availability of either the (*E*)- or (*Z*)-α,β-unsaturated ester also allows access to the corresponding allylic alcohols through DIBAL-H-mediated reduction, which expands the synthetic potential of the methodology considerably. For example, stereochemically defined allylic alcohols serve as

important substrates in asymmetric catalysis, including the Sharpless asymmetric epoxidation reaction,[34] and dihydroxylation reactions. As shown in Scheme 10(i),



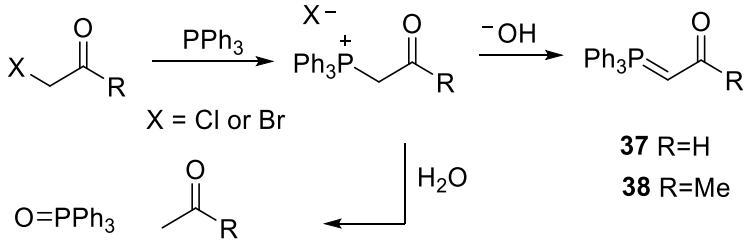
Scheme 10. Synthetic utility of two-carbon homologation using phosphonate carbanions. (i) Preparation of (*Z*)-or (*E*)-allylic alcohols **32** or **33** *via* use of Still-Gennari (SG), Ando (A) or HWE phosphonates, reduction and asymmetric conversion to the corresponding epoxyalcohols (**34a**, **34b**) *via* Sharpless Asymmetric Epoxidation (SAE). (ii) Intramolecular olefination using the two-carbon phosphonate synthon with ketone **35** to afford macrolactone **36**.

the selective combination of only three reactions, stereocontrolled two-carbon homologation, reduction, leading to **32** or **33**, and asymmetric epoxidation can yield any of the four possible stereoisomers, such as **34a** (or enantiomer) or **34b** (or enantiomer). This contrasts with the classic Darzens reaction (Scheme 6), that yields racemic epoxy-esters. The broad scope of

Sharpless epoxidation and wide utility of the chiral epoxy-alcohols in asymmetric synthesis exemplifies the synthetic power of this three-step sequence alone.[35] Phosphonate carbanions have also been creatively employed in intramolecular two-carbon homologation. In one example, intramolecular olefination of ketone **35**, Scheme 5 (ii), using the mild lithium chloride method, yielded the macrolactone **36** as a single geometric isomer in 86% yield.[36] Finally, in addition to two-carbon homologation, the ready availability of β-ketophosphonates via the Michaelis-Arbuzov reaction of α-halocarbonyl compounds expands the generality of this methodology considerably.

1.5 Stabilized Wittig reagents for two carbon homologation.

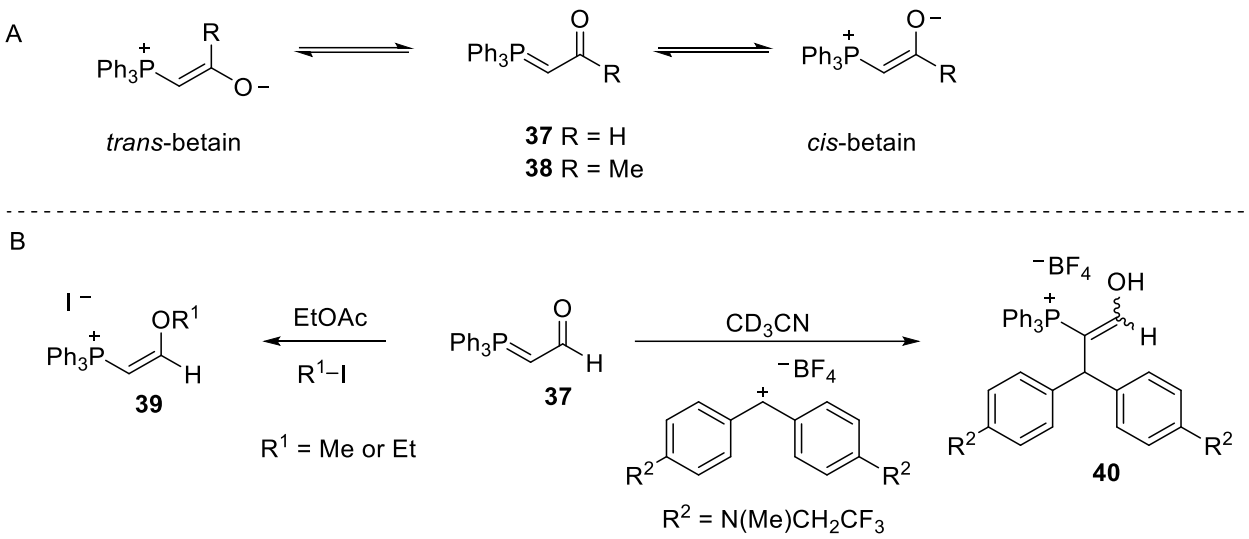
Applications of the Wittig reaction, employing stabilized ylides derived from α-carbonyl-containing phosphonium salts have been extensively investigated.[37,38] In early studies, the two-carbon homologation of aldehydes was reported using β-phosphonium carbonyls (Scheme 11).[39,40]



Scheme 11. Stabilized α-keto ylides (phosphoranes) and their hydrolytic disproportionation.

The triphenylphosphonium salts of these were said to decompose in the presence of water yielding triphenylphosphine oxide and so the success of quaternization depended on the dryness of the halo-carbonyl compound. Extensions of similar procedures including aqueous and organocatalytic two-carbon homologations are discussed in Section 1.6. The relatively stable ylides or phosphoranes were readily obtained by treatment of the salts with aqueous hydroxide. The stabilized ylides **37** or **38** reacted with aldehydes in refluxing benzene to give the homologated alkenals or enones. In contrast to phosphonate carbanions, stabilized dipolar ylides generally do not react with ketones and gave poor results with electron rich or sterically hindered aldehydes. Recently, the acetonyltriphenylphosphorane **38** was used to convert highly electrophilic ethyl pyruvate to the corresponding vinyl ketone in excellent yield and with almost complete (*E)*-selectivity.[39,40]

Structural studies on these ylides indicated that they exist as the *cis* and *trans* isomeric forms of the dipolar ylide (Scheme 12A),[41,42] reminiscent of amide rotamers.



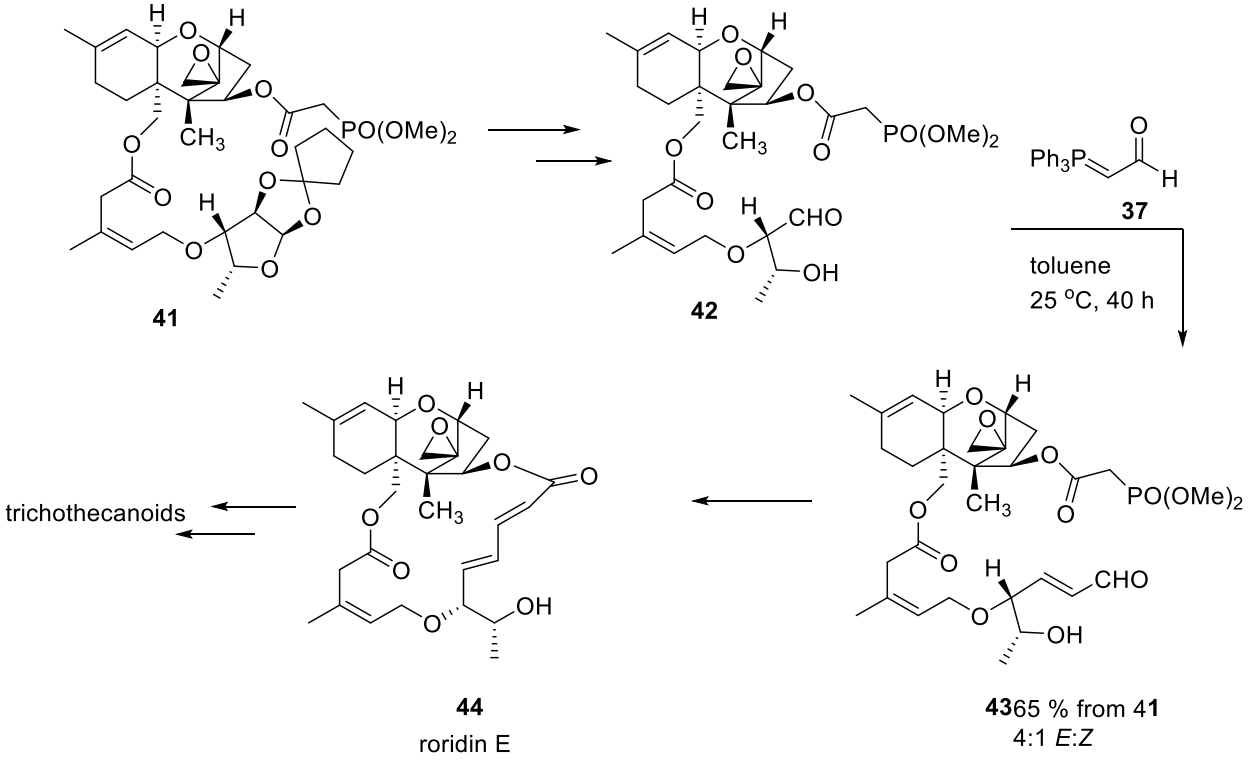
Scheme 12. Tautomerization and nucleophilicity of stabilized ylides.

Although the formylmethylenetriphenylphosphorane betaine exists as a mixture of *cis*- and *trans*-isomers, the acetonyltriphenylphosphorane betaine only shows a single rotamer with the oxyanion *cis* to phosphorous. However, later ^{31}P NMR studies seem to suggest that only the *cis*-isomer exists in both cases.[42] Reaction with electrophiles can yield *O*-alkylated or *C*-alkylated products. The site of alkylation followed trends based on the hard/soft - acid/base principle, such that the hard alkyl iodide reacts with the soft *O*-nucleophile to form **39**, meanwhile the soft benzhydrilium ion reacts with the hard *C*-nucleophile to give **20** (Scheme 12B).[43]

An interesting telescoped procedure has been demonstrated using α-halo-acetone, an aldehyde and a bifunctional polymer containing tertiary amine and tertiary phosphine moieties. The immobilization of base and phosphine eliminated the process chemistry difficulties associated

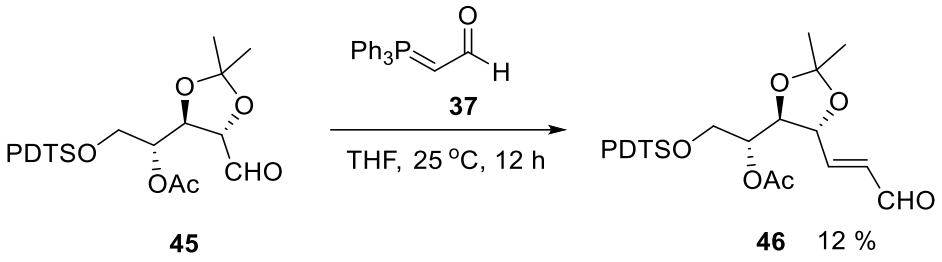
with removal of triphenylphosphine oxide and allowed for the isolation of homologated methyl vinyl ketones by filtration and evaporation of solvent.[44]

The formylmethylenetriphenylphosphorane **37** was used in a total synthesis of macrocyclic trichothecanoids (Scheme 13).[45] The phosphonate derivative **41** was elaborated to aldehyde **42** and **37** was used to accomplish the two-carbon homologation leading to the corresponding alkenal **43** with 4:1 (*E*)/(*Z*)-selectivity, now set up for an intramolecular Horner reaction.



Scheme 13. Two-carbon homologation of a complex aldehyde **42** to an enal **46** using formylmethylenetriphenylphosphorane **37** in the synthesis of trichothecanoids.

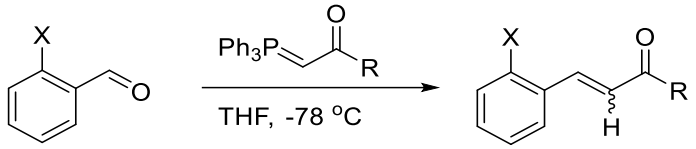
In another example in the early stages of a synthesis of the depsipeptide FR-901375, a linear aliphatic aldehyde was converted to the homologated product using **37**, giving the product exclusively as the (*E)*-alkenal.[46] In the synthesis of α-methyl 1',2'-dideoxycellobioside, an early intermediate aldehyde **45** (Scheme 14), derived from arabinose gave the homologated alkenal **46** in only 12 % yield. The majority of mass balance was attributed to polymeric material.[47]



Scheme 14. Homologation of hindered aldehyde with formylmethylenetriphenylphosphorane.

Although generally high (*E*)-selectivity was generally observed with these reagents, it was reported that reactions with hindered *ortho*-substituted benzaldehydes gave unusually high (*Z)*-olefin (see summary in Table 2).[48] It was proposed that an interaction between phosphorous and the *ortho*-substituent stabilizes the formation of *syn*-oxaphosphetane, which is further augmented by the presence of bulky substituents on the ketone α-carbon.

Table 2. Effects of *ortho*-substituents and steric bulk on stereo-outcome of two-carbon homologation of substituted benzaldehydes with α-keto triphenylphosphoranes.

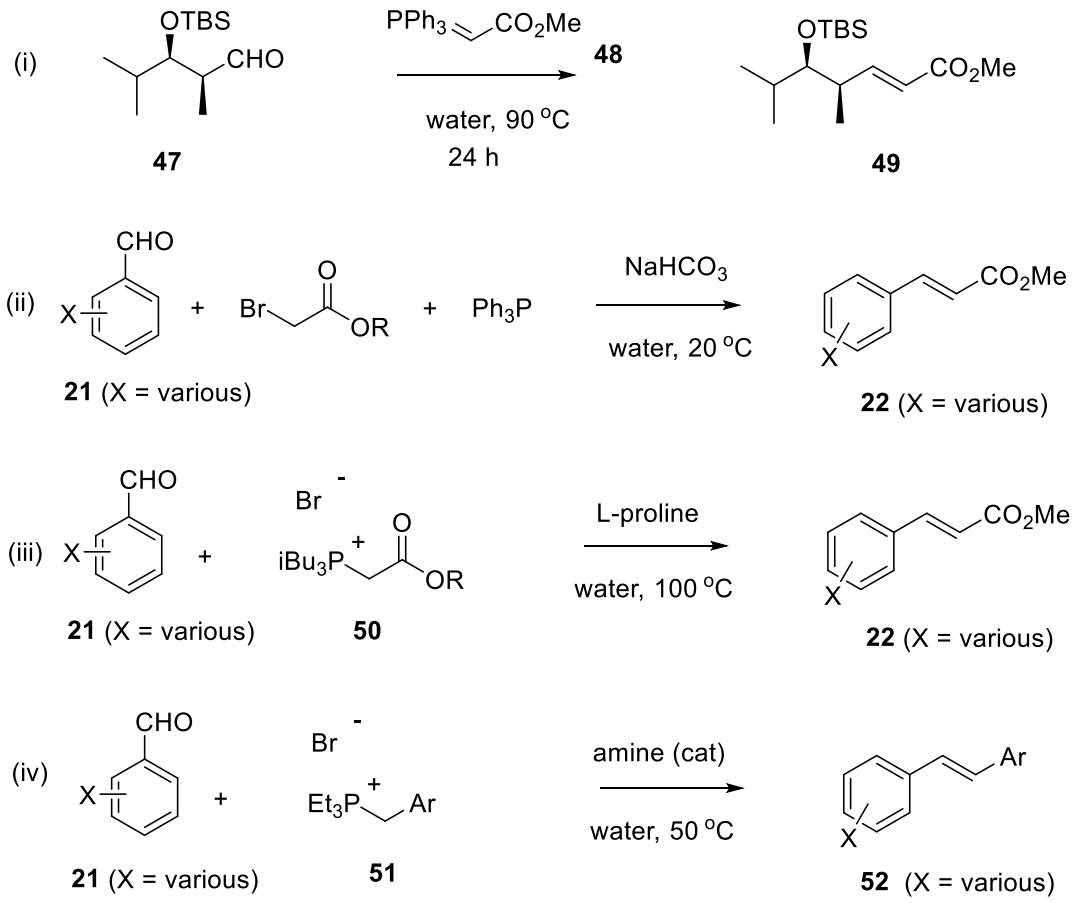


Entry	X	R	*E*:*Z*
1	**H**	**Me**	**97:3**
2	**OMe**	**Me**	**90:10**
3	**Br**	**Me**	**89:11**
4	**Br**	***t*-Bu**	**52:48**

1.6 Aqueous mild base and organocatalytic two-carbon homologation.

The use of water as solvent for two-carbon homologation using stabilized ylides has been extensively investigated. Bergdahl and co-workers reported the use of stabilized ylides derived from α-haloacetate esters (the phosphonium salt equivalents of the HWE reagent) in water at elevated temperatures.[49] Olefination reactions on the sensitive α-chiral aldehyde **47** gave epimeric product with phosphonate carbanions, due to base-mediated epimerization (Scheme 15 (i)). In contrast, use of the ylide **48** in water yielded the unsaturated ester **49** in 67% yield and 87:13 (*E*):(Z) stereoselectivity. These authors also showed that a wide range of aromatic aldehydes **21** could be reacted in the presence of an α-haloester and triphenylphosphine in aqueous bicarbonate at room temperature to yield the two-carbon homologated cinnamate esters **22** with typical yields of 90% and 95:5 (*E*):(Z) stereoselectivity (Scheme 15, (ii)).[49] It was

subsequently demonstrated that the homologation could also be conducted organocatalytically using an amine catalyst such as L-proline (Scheme 15, (iii)) employing the triisobutylphosphonium salt **50**. This chemistry involved the formation of the intermediate iminium hydroxide salt of the aldehyde, with *in situ* ylide formation and homologation. The same mild aqueous chemistry was also extended to less reactive semi-stabilized benzylphosphonium salts. In these reactions, ylides could be generated from the salt **51** (Scheme 15, (iv)) in water using a catalytic amount of an amine (such as morpholine or proline) or a sulfonamide, and trapped with aldehydes to yield a wide range of stilbenes **52** in high yield and very high (>99%) (*E*)-stereoselectivity.[50] The reaction conditions are so mild that the first examples of a biorthogonal Wittig homologation were demonstrated in a living plant. In this work, separate lines of aldehyde and phosphonium salt were injected into growing seedlings of the plant *Calystegia sepium*, known to produce an array of amine secondary metabolites. The *in vivo* formation of fluorescent donor-acceptor flanked stilbenes was demonstrated in this plant.[51]

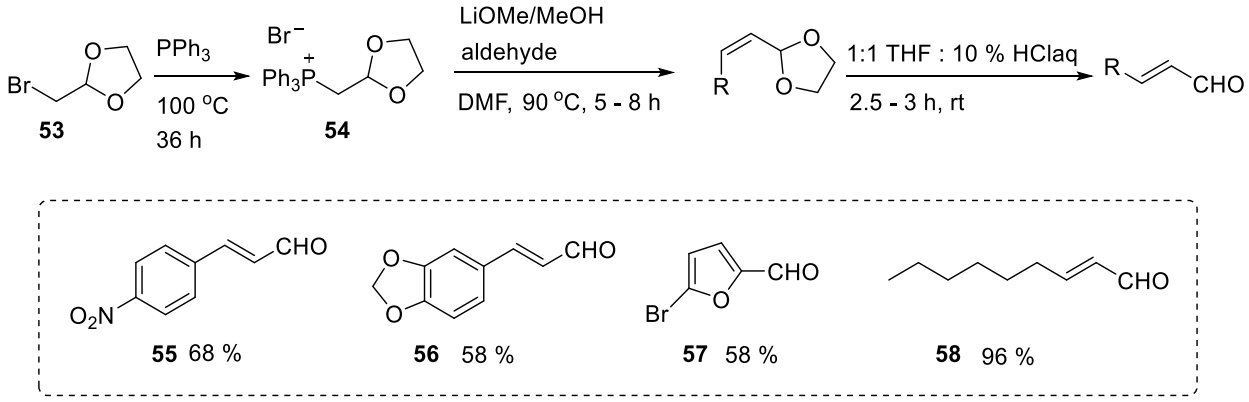


Scheme 15. Two-carbon aldehyde to unsaturated ester homologation under increasingly milder aqueous, mild base, organocatalytic and even biorthogonal (see text) conditions.

1.7 Acetal-protected Wittig reagents for the synthesis of C2-homologated alkenals.

Acetal-protected phosphonium salts have been used in the synthesis of α,β-unsaturated aldehyde equivalents from aldehydes. The phosphonium reagent **54** was synthesized from triphenylphosphine and bromoacetaldehyde ethylene acetal **53** (Scheme 16).[52] Reaction of salt **54** with lithium methoxide in dimethyl formamide (DMF) followed by addition of an aldehyde gave

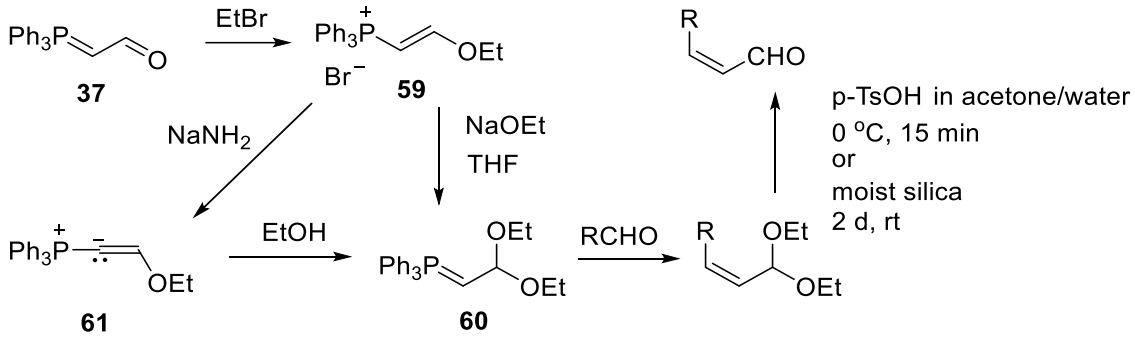
predominantly (*Z)*-alkylidene acetals, which were subsequently hydrolyzed and isomerized to the corresponding (*E)*-alkenals using 10 % HCl at room temperature. A series of aldehydes was screened in this process. The non-stabilized ylides proved to be more reactive than their stabilized counterparts, giving moderate yields with both electron-poor **55** and electron-rich **56** benzaldehyde derivatives as well as furan **57** and thiophene carbaldehydes. Highly electron deficient fluorenone was also successfully homologated. Homologation of enolizable heptanal afforded nonen-2-al **58** in 96 % yield.



Scheme 16. Homologation of aldehydes and hydrolysis of alkenal acetals to give two-carbon homologated alkenals**.**

A diethylacetal-protected ylide **60** was synthesized from formylmethylenetriphenylphosphorane **37**.[53] Reaction of **37** with bromoethane gave an intermediary *O*-alkylated vinylphosphonium salt **59** which was then reacted with sodium ethoxide in dry THF to form the desired ylide **60** to which was added the aldehyde (Scheme 17). Conversely, the vinyl phosphonium salt **59** was deprotonated using sodamide in liquid ammonia to give the phosphaallenylide **61** which formed

the desired ylide **60** upon treatment with dry ethanol in dry ether. Although the stereoselectivity of the direct Wittig product could not be determined, milder acetal hydrolysis conditions were used to give almost exclusively (*Z*)-*α*,*β*-unsaturated alkenals.



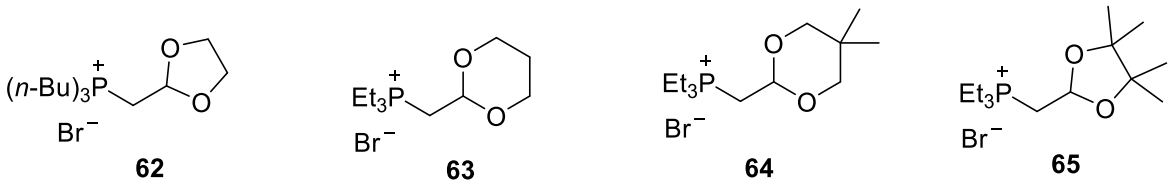
Scheme 17. Synthesis of acetal-protected homologation reagents from stabilized formylmethylenetriphenylphosphorane.

Phase transfer reaction conditions allowed for mild deprotonation of the triphenylphosphonium salt.[54] A competing background hydrolysis of the salt occurred in the presence of aqueous carbonate under the biphasic conditions, sometimes requiring up to 8 equivalents of salt for full consumption of particularly unreactive aldehydes. Nevertheless, electron rich benzaldehydes and alkyl aldehydes were successfully homologated to corresponding alkenal acetals. It should be noted that 4-dimethylaminobenzaldehyde was completely unreactive under these conditions.

The triphenylphosphonium salt **54** was employed in a one-pot oxidation-Wittig sequence to give homologated aldehydes upon hydrolysis.[55] A series of allylic alcohols were oxidized with MnO_2 and the resulting aldehydes were trapped *via* Wittig reaction with salt **54** in the presence of a guanidine base. The methodology suffered from problems with enolizable aldehydes and electron rich aryl aldehydes.

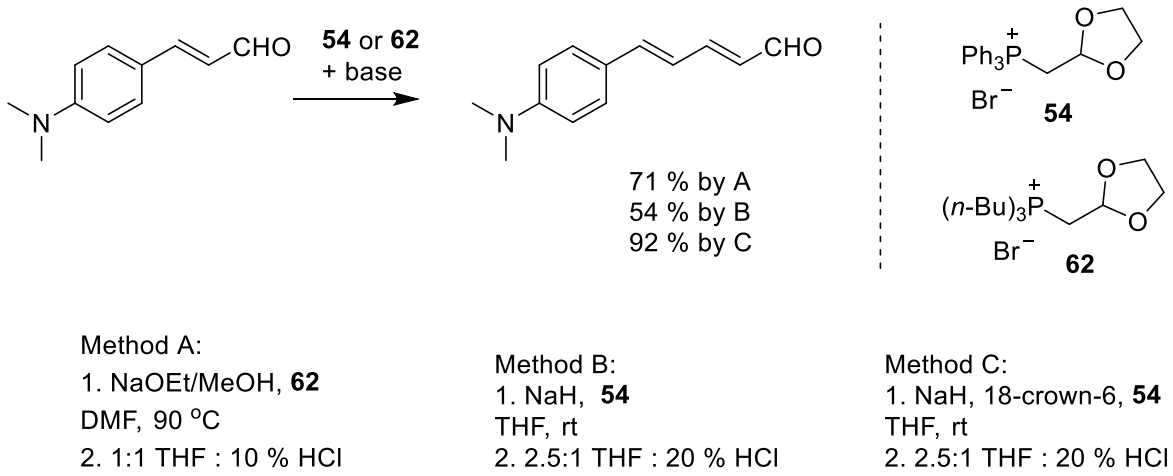
The phosphonium salt **54** was used to introduce the carbon framework of a piperidine ring during the synthesis of a dopamine antagonist,[56] as well as to construct a linker in a porphyrin-quinone cyclophane.[57]

Despite its clear utility in synthesis, the triphenylphosphonium salt **54** suffers from problems with reactivity, leading to low isolated yields with unreactive substrates. A series of more reactive trialkylphosphonium salts have also been reported (Scheme 18).



Scheme 18. Trialkylphosphine derived reagents for two-carbon aldehyde to alkenal homologation.

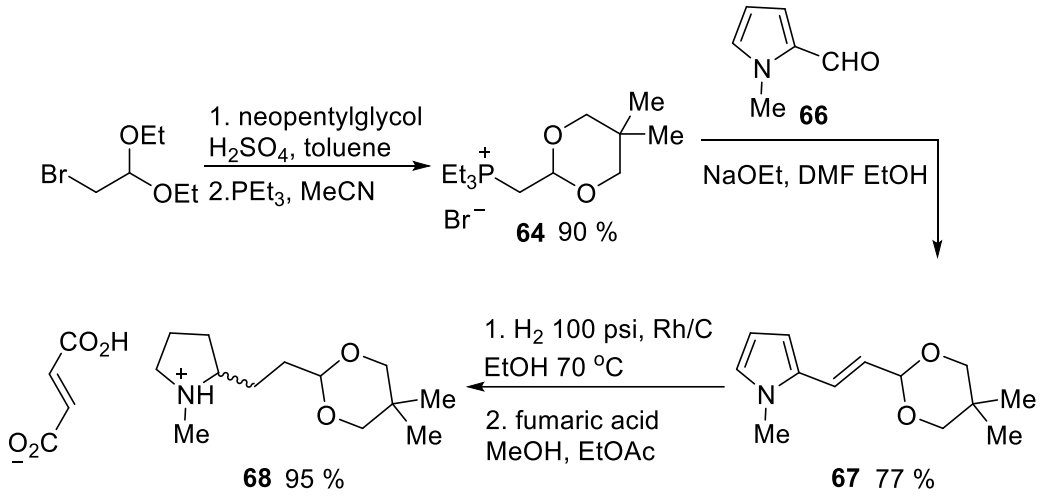
The ethylene glycol-derived acetal salt **62** was synthesized by alkylation of tri-*n*-butylphosphine with 2-bromomethyl-1,3-dioxolane under solvent-free conditions.[58] High yields of electron rich conjugated dienes could be obtained using a two-step iterative sequence (Scheme 19) with the ylide derived from **62**.



Scheme 19. Increased reactivity using trialkylphosphonium salts and effects of solvation on ylide formation.

Moreover, the side product tri-*n*-butylphosphine oxide was reported to be removeable by an extractive aqueous workup,[58] although it is only sparingly water soluble.[59] Later investigations have shown that improved yields of electron rich polyenes, using lower excesses of the triphenylphosphonium salt could be obtained with the addition of crown ether and use of sodium hydride as base.[60] The authors suggested that incomplete deprotonation of the triphenylphosphonium salt **54** may have led to previously reported low yields.

A total synthesis effort towards eletriptan required pyrrolidine acetal **68** for subsequent use in a Fischer indole synthesis to the desired natural product (Scheme 20).[59]

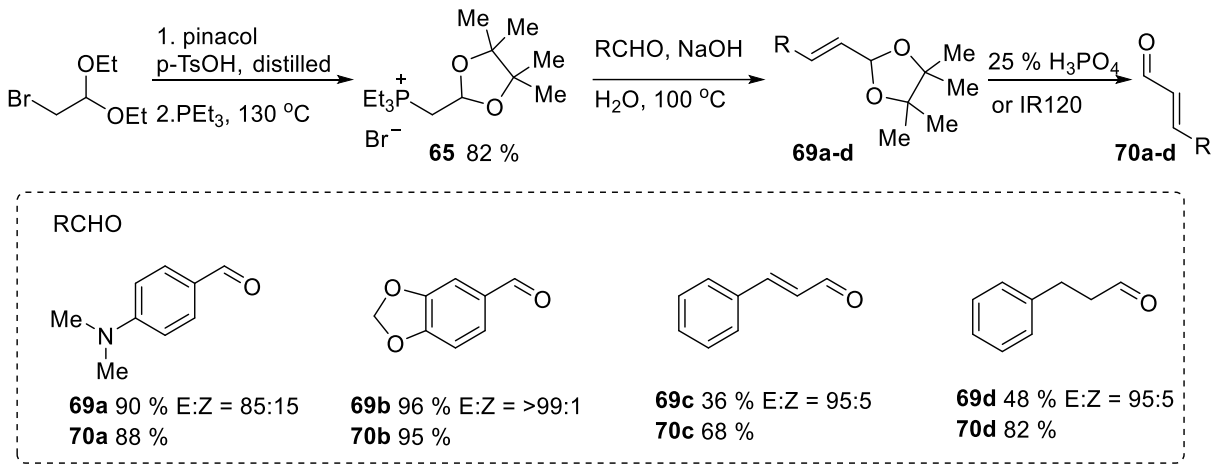


Scheme 20. Synthesis of phosphonium salt **38** and conversion to the protected alkenal **67** *via* Wittig reaction with **66.**

The desired pyrrolidine was obtained from a two-carbon homologation of *N*-methylpyrole carbaldehyde **66** using triethylphosphonium salt **64**. The authors reported difficulty with acetal hydrolysis during exhaustive aqueous extraction of tri-*n*-butylphosphonium oxide from reactions with the previously reported salt **62**. It was found that the triethylphosphonium oxide was much more water soluble, allowing for a shorter aqueous extraction which, when paired with the use of the more stable acetals, **63** and **64**, led to improved yields of alkenal acetal **67**. The utility of the acetal protected alkenal was demonstrated, whereby both alkene and aldehyde can be

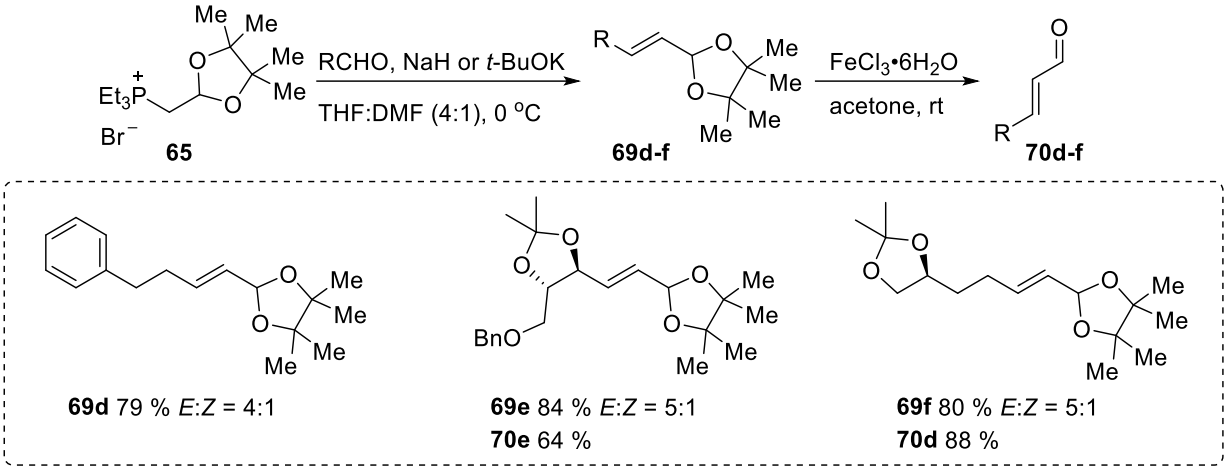
orthogonally modified. In this case, selective hydrogenation of the alkene gives the saturated two-carbon homologated acetal.

As Wittig reactions generally employ a mildly acidic hydrolysis/work-up procedure, the use of salts such as **62** and **63** results in immediate formation of the often highly reactive alkenal. In the case of the hindered reagent **64**, the protected alkenal, such as **67** can be isolated. As shown above (Scheme 16), triphenylphosphine-derived ylides typically provide alkenes with high (*Z*)-stereoselectivity. In contrast, the use of ylides derived from short-chain trialkylphosphines strongly favours increased (*E*)-stereoselectivity. From a process chemistry view, the use of Wittig reagents derived from triphenylphosphine results in the formation of triphenylphosphine oxide by-product that can be difficult to remove. The use of short chain trialkylphosphine (triethyl or tripropylphoshpine) derived ylides allows an operationally simplified work-up due to the high water-solubility of the shorter chain trialkylphosphine oxides. These side products can be completely removed through simple aqueous/organic solvent partitioning. These factors, combined, prompted the development of the acetone-pinacol protected, triethylphosphine derivative **65** (DualPhos). This reagent has been successfully exploited under aqueous and non-aqueous Wittig conditions to afford either the protected homologated (*E*)-alkenal acetal derivatives **69** or the corresponding alkenals **70** through hydrolysis (Scheme 21).[61]



Scheme 21. Synthesis of DualPhos **65** and aqueous Wittig reaction to yield the two-carbon homologated protected alkenals **69** or hydrolyzed to give the free alkenals **70**.

DualPhos was prepared in two steps from bromoacetaldehyde diethylacetal as shown in Scheme 13 and has been prepared in batches of up to 60 grams. The use of DualPhos under aqueous Wittig reaction conditions is successful due to the highly stable pinacol acetal that completely avoids in-situ acetal hydrolysis. The intermediate protected alkenals **69a-d** can be isolated as-is, or deprotected subsequently or during work-up in a controlled fashion. Thus, the use of DualPhos permits two-carbon aldehyde-alkenal homologation with the advantage of isolating the protected analog of the highly reactive unsaturated aldehyde, or immediate hydrolysis to the free alkenal during work-up. Three separate methods have been developed for cleavage of this acetal including dilute phosphoric acid, solid-supported resin IR120 (Scheme 22)[61] and the use of iron (III) chloride in organic media.[62]



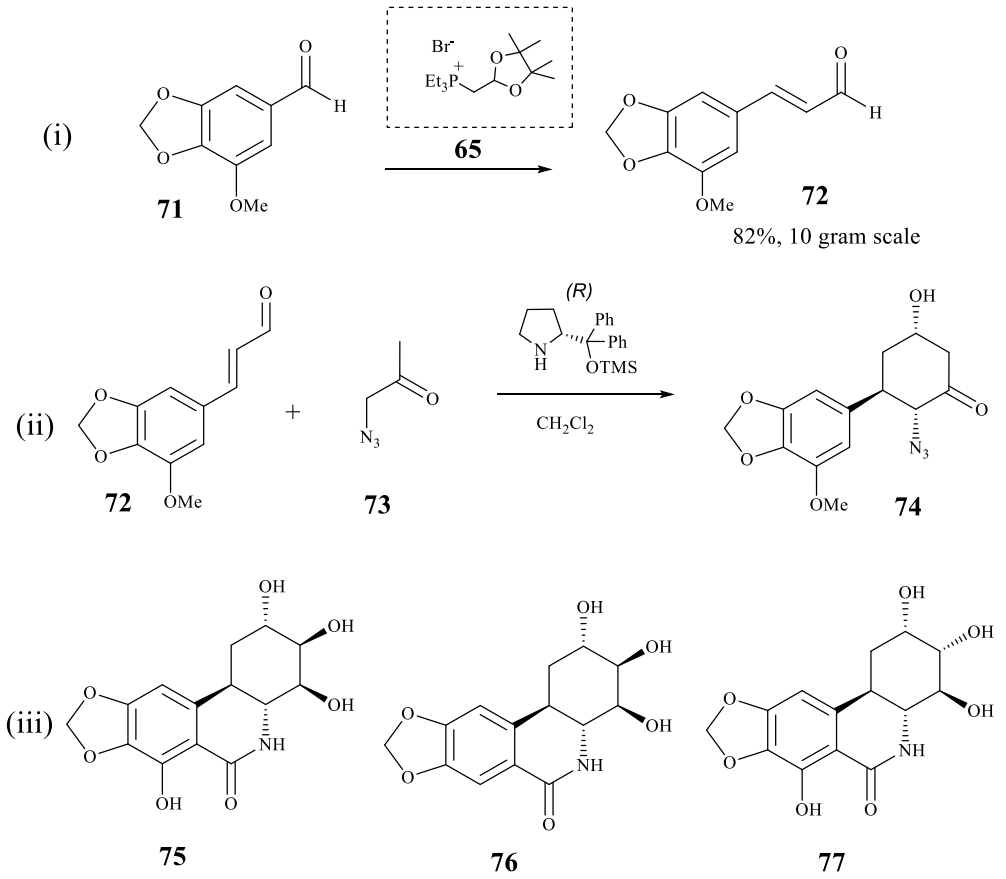
Scheme 22. Use of DualPhos (**65**) in the two-carbon homologation of enolizable and sensitive chiral aldehydes to the protected alkenals **69** and hydrolysis using iron (III) chloride to yield the free reactive alkenals **70**.

The aqueous methodology allowed for two-carbon homologation of non-enolizable aldehydes, including those with strong electron donating groups, in high isolated yields and predominantly (*E*)-stereoselectivity.[61] In the case of enolizable aldehydes and sensitive, α-chiral aldehydes, DualPhos **65** was found to react readily under classic Wittig reaction conditions in organic solvents and strong bases, Scheme 22.[62] For example, reaction with dihydrocinnamic acid yielded the protected two-carbon homologated adduct **69d**. A deprotection protocol was developed to allow acetal hydrolysis under mild conditions where aqueous acid or acidic resin is not desirable. The use of the Lewis acid iron (III) chloride hexahydrate in acetone was found to hydrolyze the highly stable pinacol acetals to the corresponding alkenals with a high degree of chemoselectivity. For example, the highly sensitive substrates, the tartaric acid derived aldehyde

gave the protected alkenal **69e**, which could be hydrolyzed to the free alkenal **70e**, while a sensitive chiral pentanal derivative gave **69f**, was cleaved to the free alkenal **70d** (Scheme 22).

Homologation methods permit the rapid elaboration of inexpensive and often readily available carbonyl compounds such as aldehydes, aromatic aldehydes, ketones to synthetically useful functionalized alkene and/or carbonyl derivatives in one step. Functionalized derivatives including alkenals, methyl ketones, vinyl ethers, are reactive intermediates and represent a privileged class of substrates utilized in cycloaddition chemistry, aldol reactions, and in asymmetric organocatalysis. For example, the use of chiral amine catalysts in the enamine-mediated activation of carbonyl compounds[63] and iminium ion-mediated activation of alkenals and unsaturated ketones[64] are two of the most prominent entry points in the field of asymmetric organocatalysis and activation of cascade sequences.

The assembly of highly reactive, often planar intermediates followed by a designed iminium-ion or enamine mediated cascade represents a very powerful strategy for the assembly of complex, chiral adducts in one step. For example (Scheme 23 (i)), the methoxy-substituted piperonal derivative **71** was converted to the two-carbon homologated alkenal **72** using DualPhos **65**,[61,62] with hydrolytic work-up delivering the free (*E*)-alkenal in 82% yield (10 gram scale).

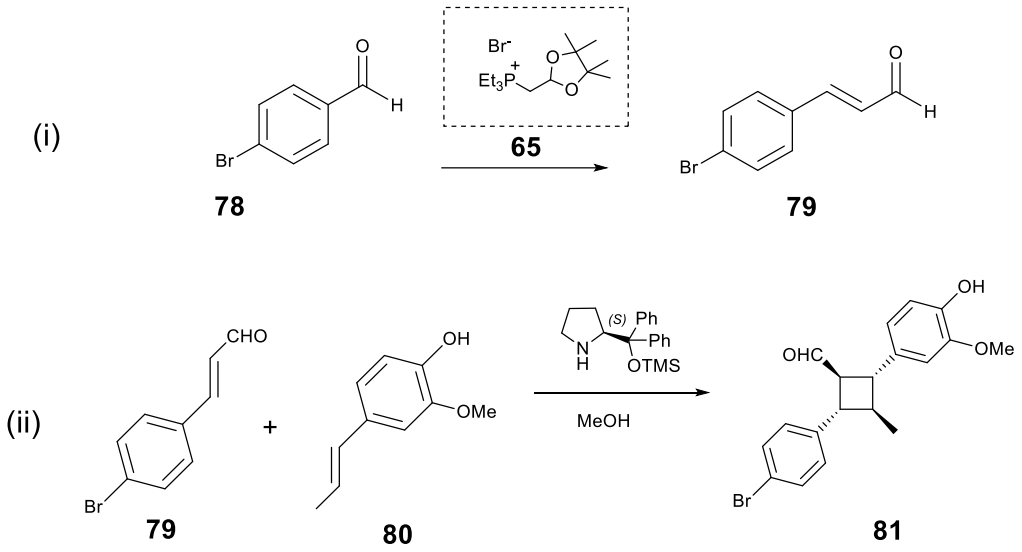


Scheme 23. Aldehyde homologation using DualPhos to give a substituted cinammaldehydes and the subsequent organocatalyzed [3+3] cycloaddition for asymmetric cyclohexanone synthesis.

The alkenal was subject to an iminium-ion initiated cascade with the chiral secondary amine (diphenylsilaprolinol) catalyst, utilizing azido-acetone **73** as the nucleophilic component (Scheme 23 (ii)). In this reaction the regioselectivity of the Michael addition is completely controlled through enol-formation at the azido-methylene. Hydrolysis of the resulting enamine, followed by intramolecular aldol reaction occur spontaneously under the reaction conditions delivering the functionalized cyclohexanone **74** in 58% yield and >99% e.e.[65] This strategy was

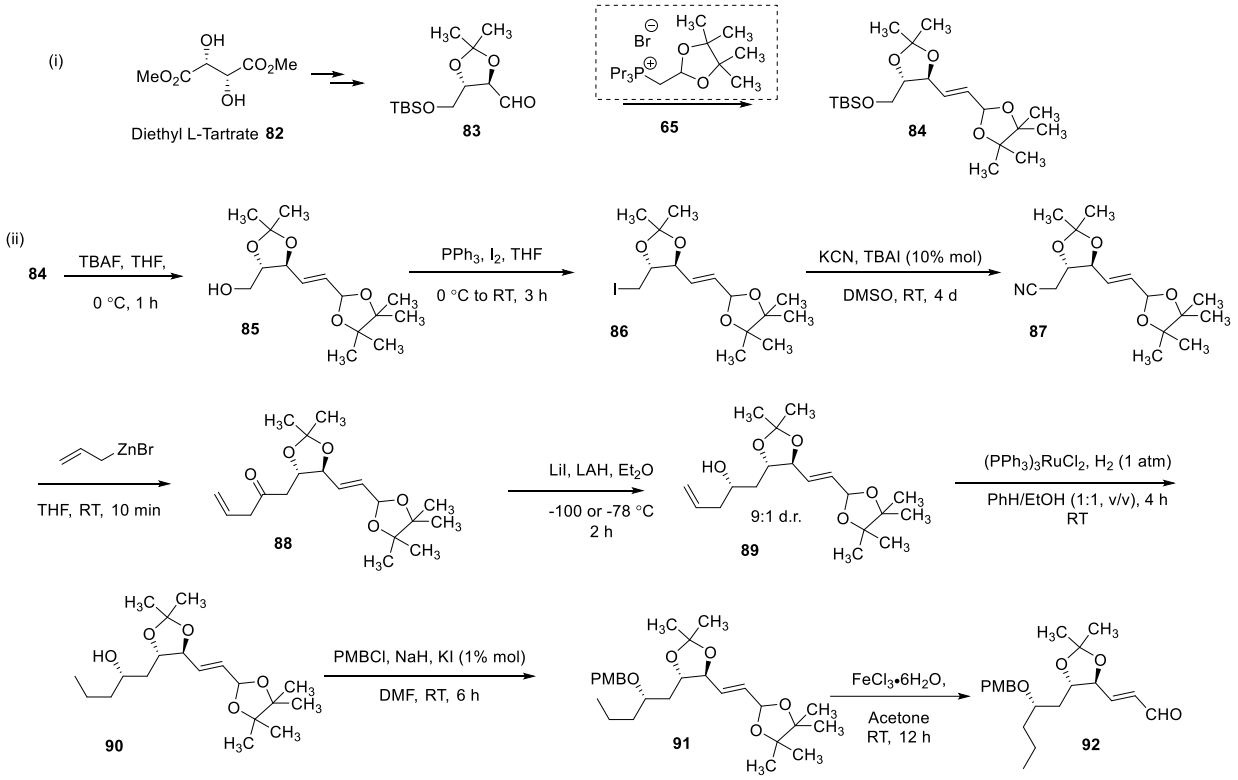
employed for the elaboration of intermediate **74** to the potent antiviral natural product (+)-*trans*-dihydronarciclasine **75** in 8 steps from **74**. Modifications to the aromatic alkenal acceptor portion[66] and, separately, the azido-acetone donor[67,68] were readily tolerated allowing the asymmetric synthesis of the related alkaloids **76** and **77** and permitting a detailed investigation into their potent anti-Zika and Herpes virus biological activities (Scheme 23 (iii)).[69]

The synthetic utility of the two-carbon homologation, asymmetric organocatalytic strategy is further illustrated in Scheme 24, concerning the synthesis of non-symmetrical lignan dimers. The bromoaldehyde **78** was converted to two-carbon homologated (*E*)-alkenal **79** in one pot employing DualPhos (Scheme 24 (i)). The alkenal was reacted with the electron rich deoxyconiferyl alkene **80** under iminium-ion catalysis giving the highly substituted cyclobutane **81** *via* a stepwise Michael-Michael cascade sequence, in one step essentially as a single enantiomer (> 80 % yield).[70] The strategy illustrates the transfer of chirality, employing only the chiral amine catalyst, from four planar sp^2-hybrid carbon atoms in **79** and **80** to the three-dimensional chiral cyclobutane **81**, containing four stereogenic centres, in 99 % e.e.



Scheme 24. Cinnamaldehyde synthesis with DualPhos (**65**) and organocatalytic [2+2] cycloaddition in the synthesis of chiral cyclobutanes.

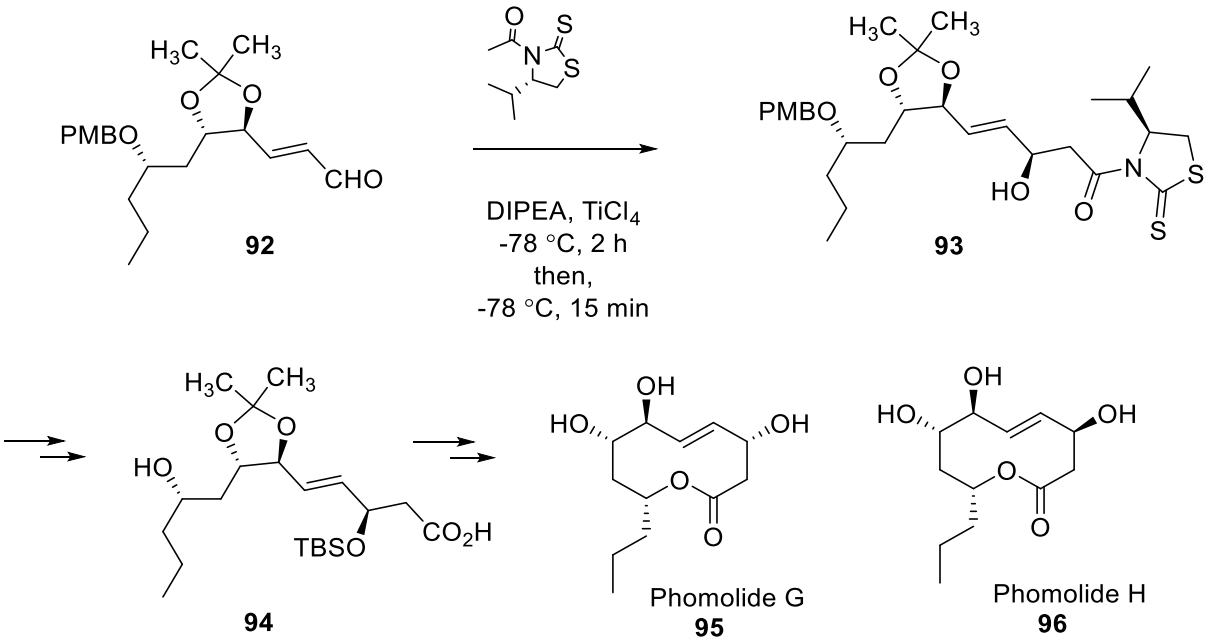
The above examples illustrate the utility of DualPhos for the two-carbon aldehyde to (*E*)-*α,β*-unsaturated aldehyde homologation reaction with direct applications of the reactive alkenal. A significant advantage in the use DualPhos reagent, as described earlier, is the intrinsic hydrolytic stability of the hindered pinacol-acetal functionality. The allows for the two-carbon installation but retaining the pinacol-acetal as the latent alkenal. The reactive unsaturated alkenal can then be revealed as desired during a synthetic sequence as desired.[61,62] This synthetic versatility is illustrated in Schemes 25 and 26 in studies directed towards the total synthesis of the phomolide class of polyketide natural products.[71]



Scheme 25. Two-carbon homologation on the sensitive *α*-chiral aldehyde **83** using DualPhos and elaboration of the latent alkenal in **84** to **91** illustrating the chemoselectivity achievable with the intact pinacol acetal.

The synthesis began with diethyl L-tartrate **82**, which was converted to the known aldehyde **83** in four steps, and then to the two-carbon homologated latent alkenal **84** using DualPhos **65**, as before (Scheme 25 (i)). Compound **84** was now converted to the late intermediate **91** in seven steps demonstrating the robust nature of the pinacol-acetal protected alkenal. As shown (Scheme 25 (ii)), the protected allylic acetal survives TBAF-mediated desilylation to **85**, an Appel reaction with the electrophilic oxidant iodine and triphenylphosphine giving **86**, nucleophilic substitution in DMSO to **87**, reaction with an allylzinc reagent in THF yielding **88**, chelation-

assisted LAH mediated reduction giving **89**, catalytic hydrogenation and finally benzylation on **90** leading to **91** with the intact latent alkenal. Numerous work-up and chromatographic purification steps are also involved throughout the sequence. Intermediate **91** is then deprotected chemoselectively using iron(III)chloride in acetone to reveal the reactive alkenal **92**.



Scheme 26. Nagao aldol reaction on the "free" two-carbon homologated alkenal **92** and elaboration to natural product polyketides phomolides G **95** and H **96**.

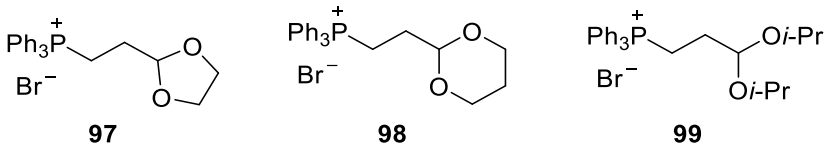
The free alkenal **92** was next subjected to a Nagao, auxiliary directed acetate aldol to give **93** which was elaborated to the *seco*-acid **94**. Various macrolactonization reactions under Mitsunobu and Yamaguchi conditions were employed to complete the total synthesis of Phomolide G **95** and Phomolide H **96**, both involving structural revisions of the original natural product structure determination.[71,72]

These examples illustrate the dual nature of DualPhos as a two-carbon homologation reagent, its utility in the conversion of aldehydes to alkenals for direct use, or to *latent* alkenals, permitting elaboration of intermediates containing the robust pinacolacetal, and allowing revelation and reactivity on the free alkenal as desired.

1.8 Three-carbon and four-carbon homologation reagents.

Higher order *C*3 and *C*4- carbonyl homologation reactions of ketones and aldehydes have focused primarily on the use of functionalized phosphonium salts containing acetal protected carbonyl moieties. An interesting issue that we will attempt to resolve here is the distinction between a true carbonyl homologation reaction in contrast to an olefination or aldol-type addition to a carbonyl, with a functionalized reagent containing a carbonyl or equivalent.

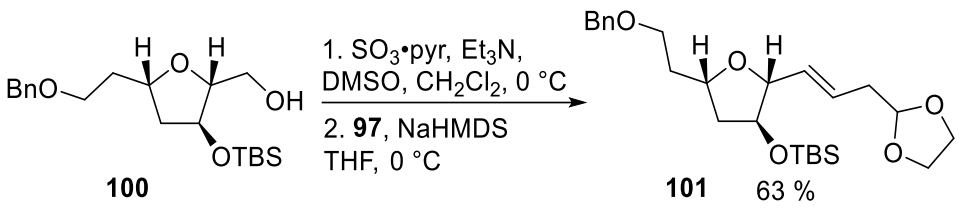
Reagents for the *C*3-homologation of aldehydes to corresponding alkenal acetals have been reported (Scheme 27). Acyclic diisopropylacetal in the form of salt **99**, as well as cyclic acetals in the form of 1,3-dioxanes **98** and 1,3-dioxolanes **97** have been synthesized from acrolein using an acetalization-alkylation sequence, either directly or *via* the alkyl halide. The *C*3-homologated alkenals are useful substrates for catalytic cascade reactions due to their amphoteric reactivity.[73]



Scheme 27. Triphenylphosphonium salts for the three-carbon homologation of aldehydes and ketones.

A series of linear alkyl aldehydes were converted to *C*3-homologated, giving predominantly the normal (*Z*)-alkenal acetals, using potassium *tert*-butoxide and salt **98**.[74] The acetals were converted to the dimethyl acetal then hydrolyzed with aqueous acetic acid with retention of the olefin stereochemistry. Conversely, treatment with aqueous hydrochloric acid and chromium(III)chloride afforded the (*E*)-alkene. Orthogonal hydrogenation of the direct Wittig product, followed by hydrolysis, was demonstrated as a route to saturated homologues.

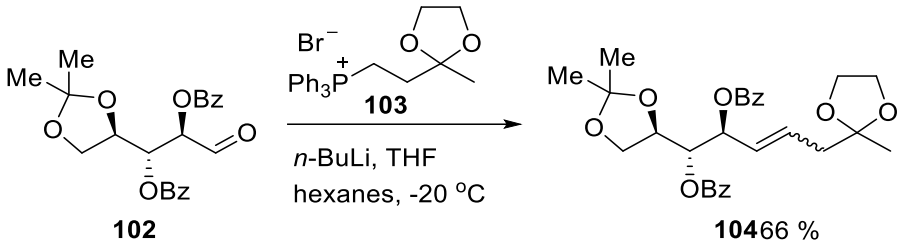
Similarly, the dioxolane-containing salt **97** has been developed, providing slightly higher yields of the three-carbon homologated alkenal acetals in reactions with acetaldehyde and pentanal, using *n*-butyllithium as base, than the methodology reported with dioxane salt **98**.[75] Moreover, the (*Z*) alkene was obtained by direct hydrolysis of the ethylene acetal with aqueous acetic acid. The salt **97** was used in a sequence to generate a key enol phosphate in the total synthesis of marine ether gymnocin-A.[76] The Wittig reaction was accomplished using NaHMDS as base, giving the homologated acetal in 63 % yield over two steps from a primary alcohol **100** and *via* a transient α-chiral aldehyde (Scheme 28). Subsequent hydrolysis was accomplished carefully using HCl in THF.



Scheme 28. Telescoping oxidation – homologation sequence.

The acyclic diisopropyl acetal functionalized phosphonium salt **99** has also been reported. Interestingly, the synthesis of this salt **99** proceeded from acrolein by Michael addition of triphenylphosphonium hydrobromide across the double bond, followed by acetalization using triisopropylorthoformate.[77] The reagent was shown to allow for homologation of both methyl ketones and aldehydes with moderately high yields and good selectivity. Hydrolysis of the acetal was accomplished in refluxing THF with pTSA without any reported olefin isomerization. The diisopropyl reagent **99** was used to synthesize a ^{13}C-labled arachidonic acid substrate by reaction with ^{13}C-hexanal.[78] The salt **99** has also been used to homologate linear aldehydes to the (*E*)-alkenes under Schlosser-modified Wittig conditions, however only moderate stereoselectivity (80:20) was observed.[79]

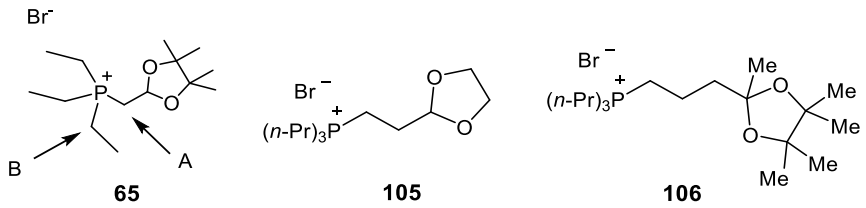
A similar reagent for the three-carbon carbonyl homologation of aldehydes to methyl enones *via* ethylene acetals has been reported.[81] The reagent **103** was used in the synthesis and structural assignment of the natural product brevicomin (Scheme 29).



Scheme 29. Acetal-protected methyl ketone from three-carbon homologation of aldehyde in the synthesis of brevicomin.

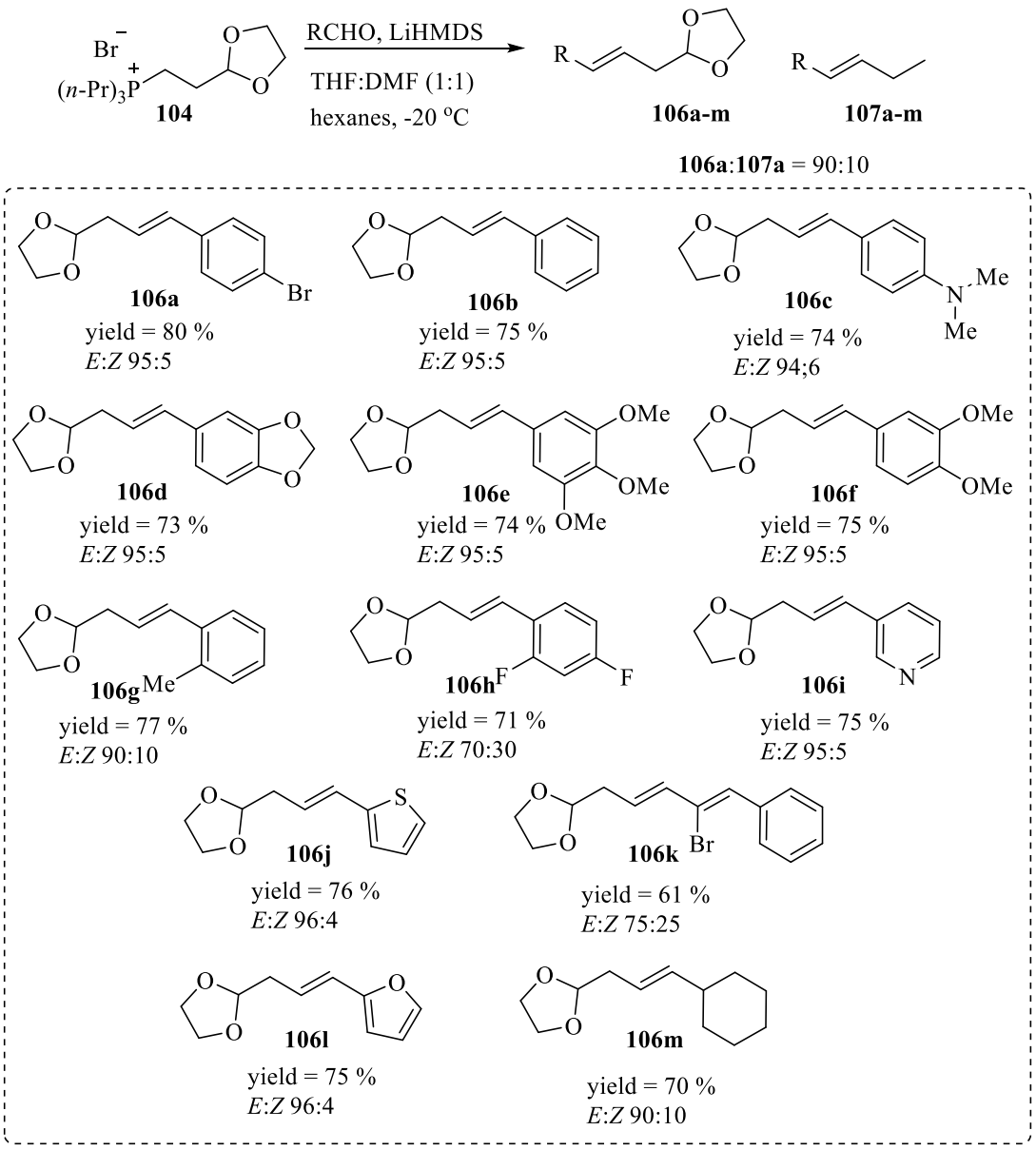
The Wittig reaction was accomplished using *n*-butyllithium in THF to give the desired intermediate in 66 % yield. The latent protected ketal was carried through a sequence of functional group conversions followed by hydrogenation and acetal hydrolysis to the final product.

The conversion of aldehydes to the corresponding three-carbon homologated alkenal acetals has been reported using tripropylphosphonium salt **105** (Scheme 30).[81] The use of the *triphenyl* phosphonium salts, allow for complete regioselective ylide formation at the active CH adjacent to phosphorus and thus the contribution of the neighboring acetal cannot be determined. One of the most intriguing aspects of the use of DualPhos **65** is the chemoselectivity observed in deprotonation selectively at the methylene position A (Scheme 30) in preference to the three adjacent methylenes B. DualPhos has been utilized in many applications in aqueous and non-aqueous conditions yielding only products of the desired two-carbon homologation. This selectivity was attributed to the engagement of a neighboring group affect of the acetal oxygen atoms, or a complex-induced proximity effect.[81]



Scheme 30. Functionalized trialkyl-phosphonium salts: Probing the extent of neighbouring group directed deproptonation in two, three and four-carbon homologation.

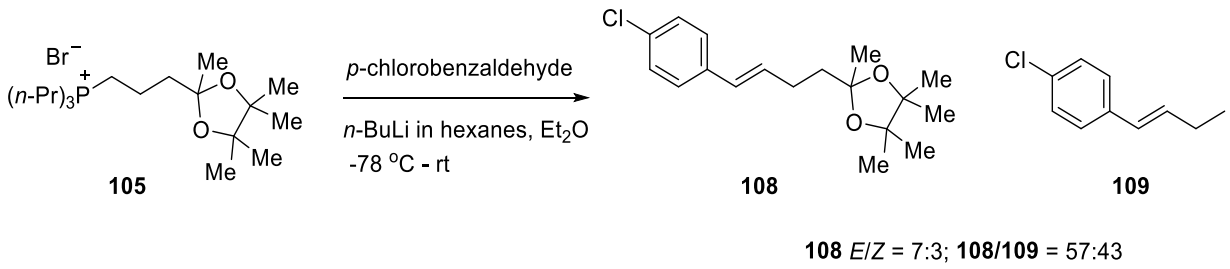
In order to probe the extent of this directing effect on deprotonation, two trialkylphosphonium salts **105** and **106** were prepared, pushing the position of the protected carbonyl one carbon further from the desired site of deprotonation.



Scheme 31. Three-carbon homologation of aldehydes to ethylene acetals using tri-*n*-propyl phosphonium salts with selective ylide formation.

The reagent **104** was synthesized *via* the quaternization of tripropylphosphine with commercially available 2-(2'bromoethyl)-1,3-dioxolane in 95% yield.[81] Remarkably, chemoselective ylide

formation was readily accomplished through careful control of reaction conditions. It was postulated that the distal acetal moieties played a role in directing ylide formation. For the three-carbon homologation reagent **104**, up to 80 % selectivity for the desired deprotonation site was observed and a series of aldehydes were homologated to the corresponding ethylene acetals in high to moderate yields, the full scope is detailed in Scheme 31. Notably, enolizable aldehydes, as well as electron rich aldehydes were homologated using this methodology. Hydrolysis under acidic conditions was demonstrated, as well as asymmetric dihydroxylation of the protected olefin.



Scheme 32. Acetal as distal directing group for regioselective ylide formation.

The use of ylides developed for four-carbon carbonyl homologation reactions have been reported derived from triphenylphosphonium salts carrying δ-aldehyde equivalents in the form of remote cyclic acetals.[82,83,84] These reagents have proved themselves as useful building blocks for terpene synthesis, however the contribution of the distal acetal in directing α-deprotonation cannot be determined. In order to determine the limit of carbon separation of the directing group, the tripropylphosphonium salt **105** was synthesized in order to probe the chemoselectivity favoring

this four-carbon homologation (see Chapter 2). It was found that ylide formation using *n*-butyllithium under non-coordinating conditions (ether/hexanes) gave the desired Wittig product (Scheme 32, **108/109** = 57:43). Remarkably selective ylide formation occurred even with the directing acetal positioned three carbons away.[81] Nonetheless, the significant amount of ylide formation from the propyl side chain indicates the limit of the neighboring directing effect of the acetal on selective ylide formation. This indicates that a four carbon unit is the limit for n-carbon homologations and that other four-carbon[82,83,84] and more remote extensions are simply olefination reactions utilizing functionalized phosphonium salts, having no direct participation in the chemistry.

1.9 Summary and outlook.

In summary, it is fair to state that homologation methods represent synthetic methodology of fundamental importance and utility in synthetic organic chemistry. The continued development of functionalized phosphorus-based reagents over the last 70 years has expanded the classic aldol, Knoevenagel and Darzens homologation methodologies to an extensive range of substrates. Chemoselective homologation reactions of enolizable and sensitive α-chiral carbonyl compounds can be achieved in a controlled fashion and with a high degree of olefin stereoselectivity when applicable.

The conversion of readily available aldehydes and ketones to functionalized higher order analogs expands the utility of this methodology considerably. For example, these extensions provide the foundational structures that are the basis for important asymmetric transformations including the asymmetric epoxidation or dihydroxylation of allylic alcohols, enamine activation of ketones and iminium ion mediated activation of unsaturated carbonyl compounds. We present selected examples illustrating the rapid increase in structural complexity that is attainable building upon this foundational homologation methodology. The ability to transform a single substrate alone, or to engage two planar carbonyl extended products in a designed catalytic asymmetric process allows expansion of the chemistry into the third dimension. The design of cascade processes utilizing this chemistry permits access to complex core structures in few steps that have allowed the asymmetric synthesis of complex natural products and analogs. Given these achievements, it is also fair to state that the development of other useful homologation methodologies will continue as methodological gaps, such as the direct conversion of an aldehyde to an allylic alcohol or ester,[85] are addressed. Taken together, fundamental developments in carbonyl homologation methodologies and their applications in synthetic organic chemistry is a powerful strategy for the total synthesis of complex natural products and analogs and permits the detailed exploration of the structural basis for their chemical-biological interactions. This ensures that significant interest will remain in expanding homologation methodology and further applications development in total synthesis and chemical biology for many years to come.

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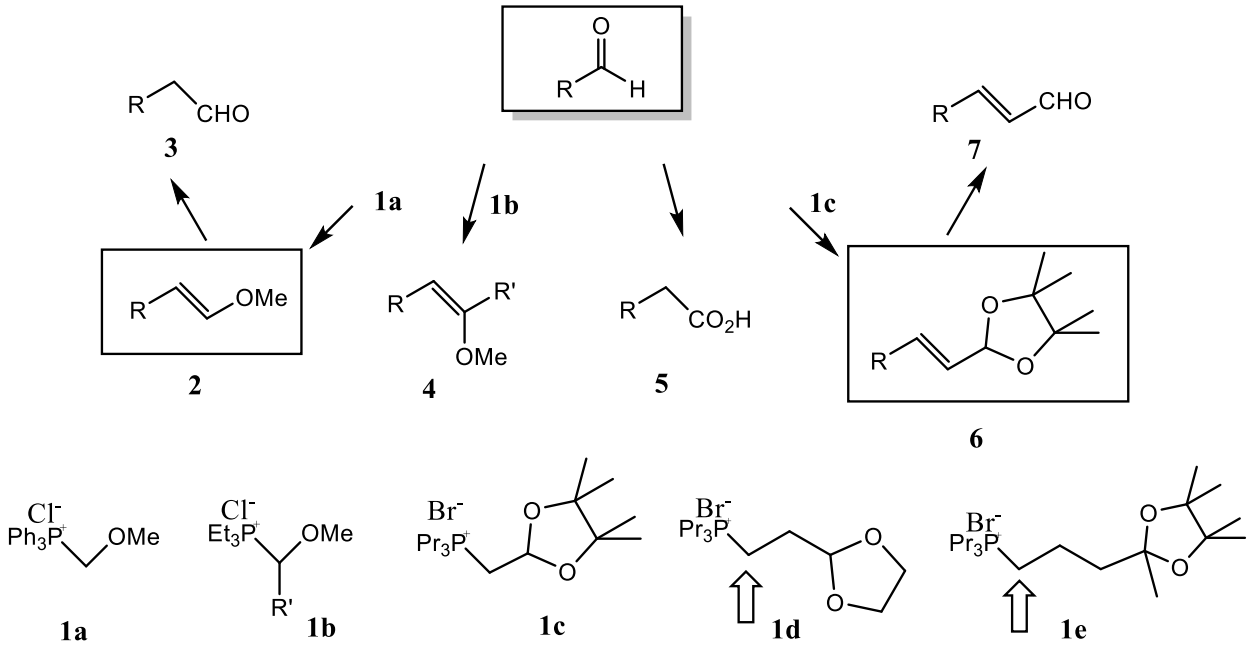
2.0 DIRECTING EFFECT OF ACETALS ON YLIDE FORMATION WITH QUATERNERIZED ALKYL PHOSPHONIUM SALTS

Parts of sections 2.1, 2.5 and 2.6 as well as all of sections 2.2 and 2.3 appear in:

Arkesh Narayanappa, David Hurem, James McNulty, *Synlett* **2017**; *28*, 2961-2965.

2.1 Introduction.



Scheme 33. Carbonyl homologation strategies (top) using functionalized phosphonium salts **1a-c** and new derivatives **1d** and **1e** (bottom).

Carbonyl homologation methodologies are actively sought in view of their great strategic value in assembling elongated sub-structures and in the total synthesis of natural products and complex targets. The methoxymethyl-triphenylphosphonium salt **1a** (Scheme 33) is most often employed for one-carbon homologation[1] through Wittig olefination,[2] leading to intermediate vinyl ethers **2**, which can be isolated and used in cycloaddition reactions,[1f] or directly hydrolyzed to yield the homologated aldehyde **3**. The scope of this reaction can be extended using functionalized phosphonium salts **1b**,[3] readily available from the corresponding dimethylacetals,[3a] leading to a

wide range of substituted vinyl ethers **4** and synthetically valuable 1- or 2-alkoxy 1,3-dienes. Direct homologation of aldehydes to the one-carbon extended carboxylic acids **5** can also be achieved.[4] The Wittig reaction[2] involving ylides derived from triphenylphosphine is most often employed in these reactions despite the noted problems of stereocontrol and purification (phosphine oxide removal) often encountered. The utility of stabilized and semi-stabilized ylides derived from short-chain trialkyl phosphonium salts as Wittig reagents for the synthesis of olefins with high degrees of (*E*)-selectivity has been demonstrated in recent years.[5] From a technical point of view, the short chain (i.e.: ethyl, *n*-propyl and *n*-butyl) trialkylphosphine oxides that form as by-products of Wittig olefinations are readily soluble in water, often allowing facile work-up as the olefin reaction product can be removed by direct crystallization or extraction from water.

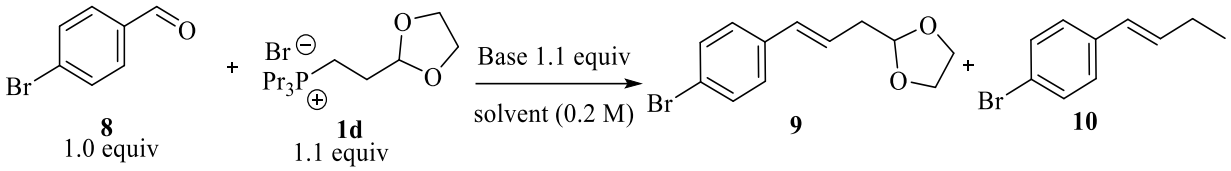
We recently introduced the phosphonium salt DualPhos **1c** as a novel functionalized two-carbon homologation reagent and have demonstrated its utility in both aqueous,[6a] and non-aqueous olefination reactions employing sensitive chiral aldehydes.[6b] Olefination reactions with DualPhos yield the readily isolatable "latent alkenals" **6**, which are robust enough to be carried through many subsequent steps intact,[6b, 6f] but which can be selectively hydrolysed to yield synthetically valuable (*E*)-alkenals **7**.[6] A most remarkable feature on the reactivity of DualPhos **1c** is the very high degree of regiocontrol observed on ylide formation under basic conditions. No butene-containing adducts are observed whatsoever, indicating the possible involvement of a kinetic or thermodynamic complex-induced effect favouring ylide formation on the acetal-

containing side chain. It is not clear if the β-acetal in **1c** activates the desired α-methylene *via* electronic induction through the sigma framework or through space *via* coordination with sodium or lithium cations.

In order to gain further insight into the nature of this observed directing effect, and exploit the synthetic possibilities of such directed-ylide formation, we designed the two novel trialkylphosphonium salts **1d** and **1e** (Scheme 33) containing side chains functionalized with γ- and δ-cyclic acetals respectively. Herein we describe the preparation and regioselective trapping of the ylides derived from these functionalized phosphonium salts.

The phosphonium salt **1d** was readily prepared by quaternization of tripropylphosphine with commercially available 2-(2'-bromoethyl)-1,3-dioxolane (95% yield). We investigated the reaction of 4-bromobenzaldehyde with salt **1d** extensively under aqueous conditions with various cations present.[7] The desired functionalized olefin **9** (Table 3) was always obtained in a regioselective fashion, however the butene-containing side product **10** was also observed.

Table 3. Three-carbon aldehyde homologation under aqueous and non-aqueous conditions.



Entry	Salt (eq.)	Base (eq.)	Yield 9 (%)	Ratio (9:10)
1[a]	1.1	NaOH (3.0)	29	95:5
2[a]	1.1	KOH (3.0)	48	95:5
3[a]	1.1	KOH (5.0)	38	95:5
4[a]	1.5	KOH (3.0)	48	95:5
5[b]	1.1	LiHMDS	70	60:40
6[c]	1.1	LiHMDS	55	90:10
7[d]	1.1	KHMDS	60	90:10
8[d]	1.1	LiHMDS	80	90:10

Solvent: [a]Water, [b]THF, [c]DMF, [d]THF:DMF 1:1

Isolated yields of the functionalized olefin **9** proved to be low using aqueous conditions (entries 1-4), however we were delighted to find that use of THF, DMF and THF/DMF combinations (entries 5-7) increased both the yield and regioselectivity in favour of **9**. We identified an optimal condition using lithium hexamethyldisilazide (LiHMDS) as base in a 50:50, THF:DMF solution at 0 °C, adding the aldehyde and slowly warming to room temperature over 10h (entry 8). This set of conditions proved to be of general use and were applied to the three-carbon homologation of a wide range of aldehydes, unsaturated aldehydes and hetero-substituted aldehydes yielding the functionalized olefins collected in Figure 1.

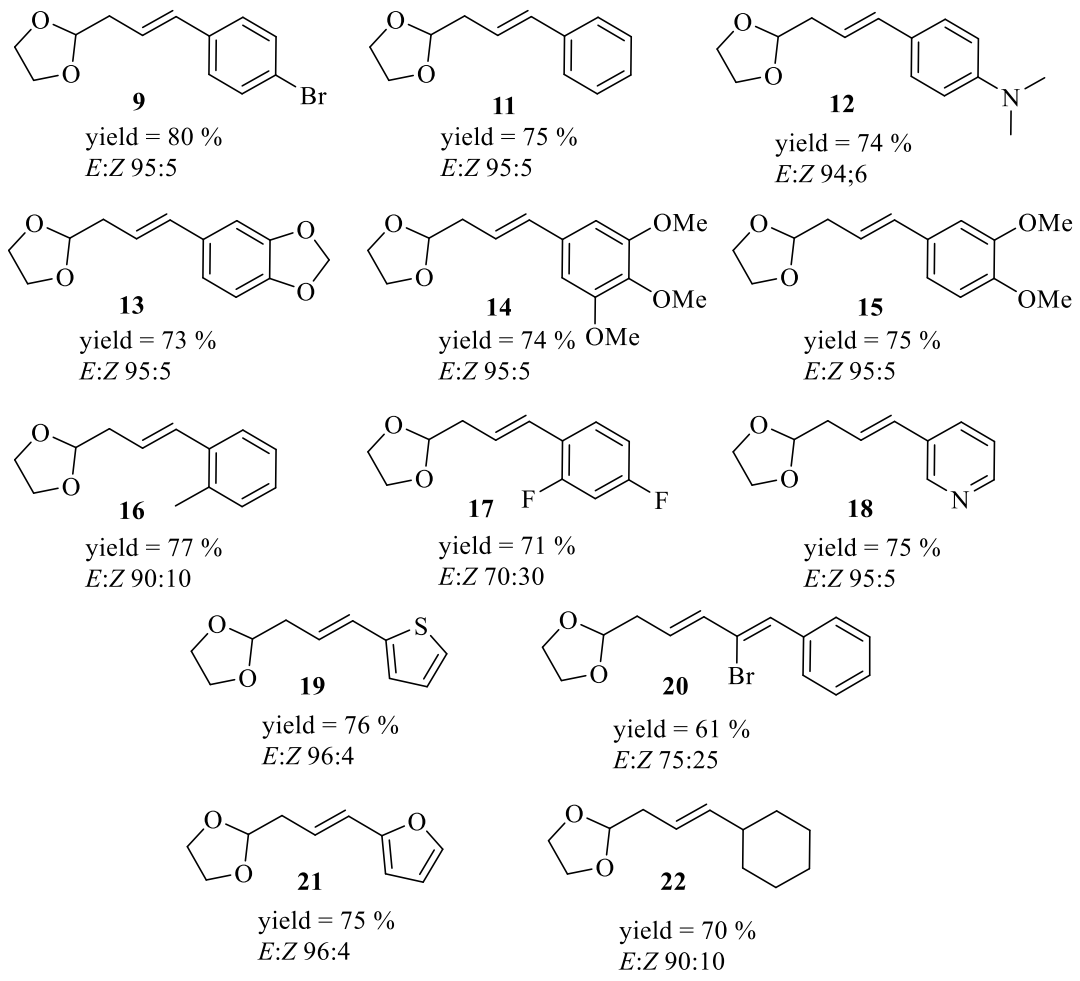
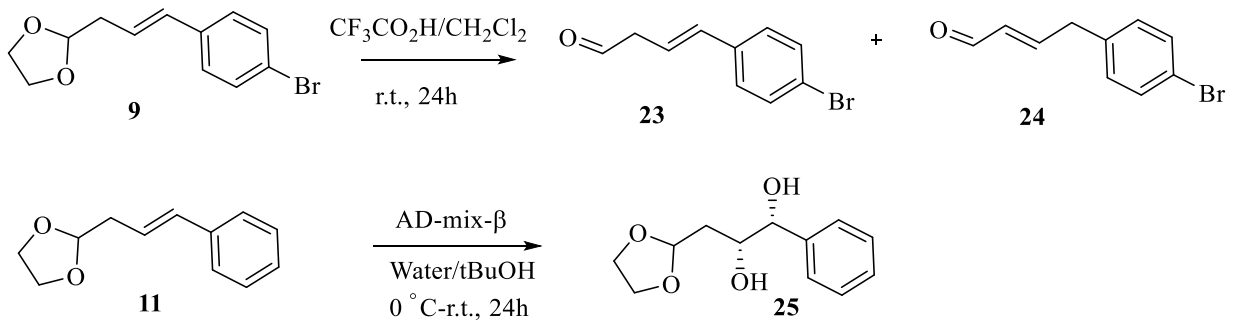


Figure 1. Substrate scope and yields of three-carbon homologated products obtained from the acetal-directed ylide formation on salt **1d**.

Overall, the regioselectivity of the directed-ylide formation on salt **1d**, as evidenced by the ratio of olefins **9**:**10**, varied from a worst-case scenario of 60:40 to a maximum of 96:4 under the conditions investigated. Given that the "statistical" distribution of olefins expected is 25:75 in favour of the non-desired butene (such as **10**), this is a remarkable degree of regiocontrol. Steric considerations are also expected to erode selectivity through favouring deprotonation at the least

hindered propyl substituents, leading to further selection favouring **10**. In the case of salt **1d**, the acetal is positioned too far (one methylene further in comparison to DualPhos **1c**) from the α – site of deprotonation to consider electronic inductive effects as being significant. The high degree of regioselectivity is most likely due to the involvement of a complex-induced proximity effect with chelation to the acetal directing ylide formation.[8]

The synthetic potential of the three-carbon homologated adducts summarized in Figure 1 has not been fully explored. Nonetheless, deprotection of the 4-bromophenyl acetal derivative **9** was investigated under a range of conditions, for example, use of PTSA in DCM gave a 40:60 mixture of **23**:**24**, whereas use of TFA (Scheme 34) gave the deprotected/isomerized alkenal **24** cleanly in 90% yield.[7] Intermediates such as **24** appear ideal as substrates for dienamine directed organocatalysis.[9] Sharpless asymmetric dihydroxylation[10] on the protected olefin **11** give the protected diol **25**,[7] an intermediate that appears suited towards the synthesis of naturally occurring arenediols.[11]



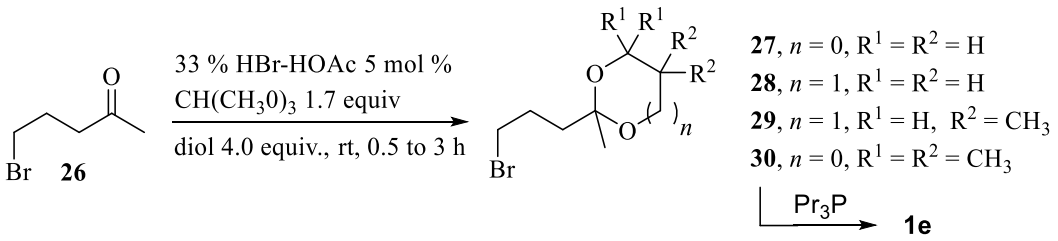
Scheme 34. Deprotection/isomerization of the three-carbon homologated intermediate **9** yielding the carbonyl-conjugated enal **24** (90%) and dihydroxylation of **11** yielding the protected diol **25**.

Given the success of the acetal-directed ylide formation demonstrated using reagent **92**, and in order to probe the scope of regioselective ylide generation reagents with the acetal protecting/directing group still one methylene further were envisioned. In terms of reagent design, we considered that ketals derived from 5-bromo-2-pentanone **26** would be ideal to explore both the directing group effect. while at the same time useful methodology for terpene synthesis.

2.2 Synthesis of Wittig salts bearing a distal ketal.

The protected ketals **27-30** (Table 4) were readily obtained following standard chemistry, however compounds **27** and **28** proved hydrolytically unstable. In contrast, both the neopentyl ketal **29** and acetone-pinacol derivative **30** proved to be chemically robust. The desired ketal-functionalized phosphonium salt **1e** was now readily accessed from **30** through quaternization with tripropylphosphine (Table 4).

Table 4. Synthesis and stability of 4-bromo δ-cyclic acetals **27**-**30** and conversion of **30** to the phosphonium salt **1e**



Entry	Ketal	Time (h)	Yield (%)[a]	26 after 24 h (%)[b]
1	**27**	0.5	74	5
2	**28**	3	33[c]	20
3	**29**	1.5	89	2
4	**30**	3	82	<1

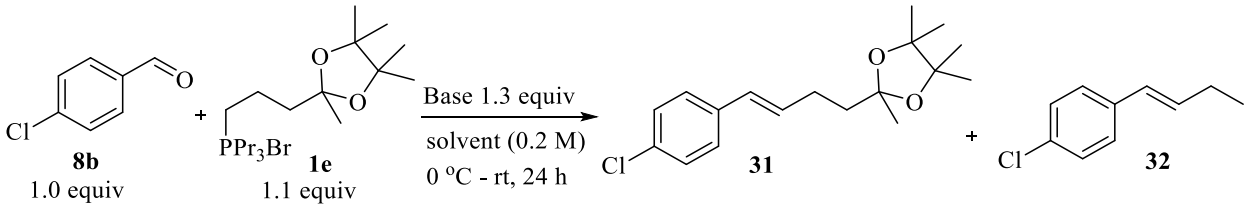
[a] 1.0 mmol scale, [b] hydrolysis products determined after 24 h in $CDCl_3$ by relative integration of ^1H NMR signals arising from methyl protons, [c] isolated as mixture of **26** and **28**.

2.3 Probing reaction conditions with respect to regioselectivity of ylide formation.

Regioselective ylide formation using the salt **1e** was now investigated with 4-chlorobenzaldehyde **8b** under a range of conditions (Table 5) in order to probe selectivity in favour of the functionalized olefin **31** over the butene **32**. Considering that the "statistical" distribution of olefins should at most comprise 25% of **31** (lower than this figure taking steric parameters into account) and >75% of the butene **32**, the initial results proved disappointing (Table 5). Olefin **31** was obtained in statistical mixtures (entries 1-10) with **32** or with slight selectivity (e.g. 40:60), indicating only a 1.6 selectivity in favour of **31**. This reaction was

investigated with various solvents and coordinating cations with little improvement, leading us to consider that salt **1e** may now exceed the limit of the acetal/ketal directed pathway. Finally, we investigated the reaction in the non-coordinating solvent diethyl ether and in the presence of lithium salts (entry 11) resulting in a substantial change in the olefin ratio. The desired functionalized olefin **31** was now obtained over **32** (57:43), demonstrating a synthetically useful selectivity of 2.28 in the desired direction. While solubility of the phosphonium salt **1e** is an issue, this positive result is a strong impetus to improve the regioselective ylide formation further employing various coordinating cations in diethyl ether and other non-coordinating media.

Table 5. Regiocontrolled olefination using the δ-ketal-containing phosphonium salt **1e**.



Entry	Base	Deprotonation Time (h)	Aldehyde Addition T (°C)	Solvent	Conv. (%)[a]	31:32[b]	*E*:*Z*[b]
1	*t*BuOK	0.5	0	Toluene	99	19:81	9:1
2	*t*BuONa	0.5	0	Toluene	>99	35:67	9:1
3	*t*BuONa	0.5	rt	Toluene	97	38:62	9:1
4	*t*BuONa	0.5	rt	THF	>99	35:65	9:1
5	*t*BuONa	0.5	0	THF	>99	32:68	9:1
6	*t*BuONa	0	0	THF	>99	42:58	9:1

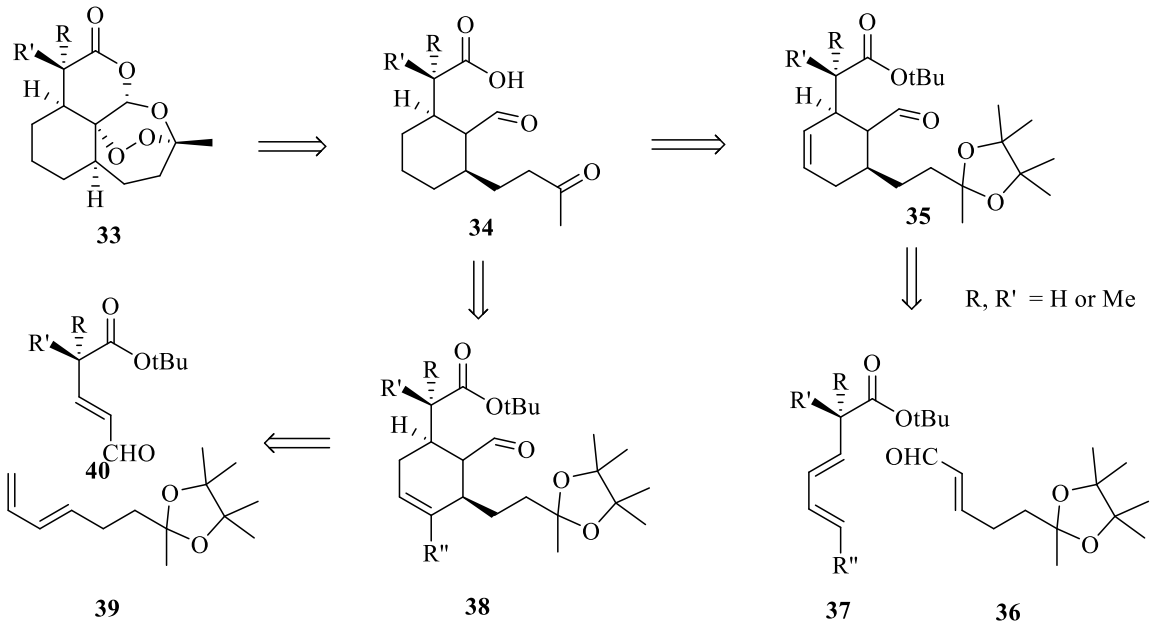
7	KHMDS	0.5	0	THF	98	35:75	9:1
8	LiHMDS	0.5	0	THF	91	38:62	7:3
9	LiHMDS	1	0	THF	85	43:57	9:1
10	LiHMDS	0.5	0	THF/DMF (1:1)	>99	26:74[(c)]	8:2
11	*n*BuLi	0.5	0	Et_2O	>99	57:43	7:3

[a)] Calculated from consumption of aldehyde using ^{1}H NMR. [(b)] Determined with ^{1}H NMR using relative integrals of olefinic protons. [(c)] Calculated based on isolated mass.

As in the case of salt **1d**, the ketal present in **1e** is positioned too far from the α–site of deprotonation and now rules out inductive effects being involved in the selectivity that favours functionalized olefin **31**. The high degree of regioselectivity can only now be explained in terms of a complex-induced proximity effect[8] of the acetal, directing ylide formation. Such effect may be manifest thermodynamically, though reversible deprotonation[8b] at the desired α-position. Nonetheless, in consideration of the reaction conditions described here (Scheme 2, entry 8; Scheme 5, entry 11) the results are more consistent with kinetic deprotonation *via* pre-complexation to the acetal/ketal and deprotonation at the now closer α-methylene.[8d] No significant difference is observed in regioselectivity as a function of time elapsed before addition of the aldehyde after ylide formation (entries 8 and 9), under otherwise identical conditions (THF, lithium salts). Conversely, switching solvent to diethyl ether and use of the strong base butyl lithium (entry 11) results in a significant shift in favour of the chelation-assisted pathway.

2.4 Efforts towards the preparation of building blocks for the total synthesis of artemisinin derivatives.

With this methodology in hand we attempted to apply it to the synthesis of diene **39** which would be expected to give the advanced intermediate **38** towards the total synthesis of dimethyl artemisin analogues (Scheme 35).

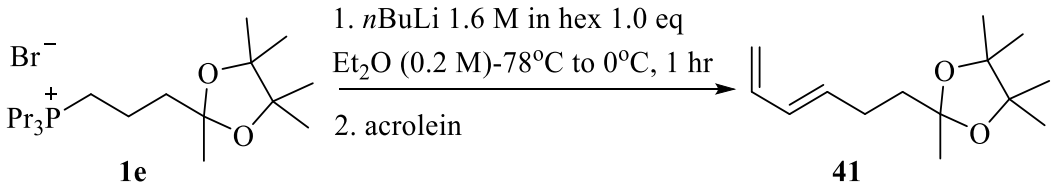


Scheme 35. Retrosynthetic analysis of structural analogues of artemisinin.

A sequence of hydrogenation, acid catalysed deprotection of intermediate **38** followed by photooxidation of the product by known methods to artemisinin through an analogous intermediate of **34** was expected to yield previously unaccessed artemisin derivatives.

Efforts were made to synthesize diene **39** by reaction of Wittig salt **1c** with acrolein using the previously developed conditions. Unfortunately, only low yields of product could be isolated and the majority of the reaction mass was converted to a poorly soluble white solid that was thought to form due to the polymerization of acrolein (Table 6, Entry 1). In order to limit the formation of this by-product methods to introduce acrolein to the basic reaction environment were explored (Entries 2 – 4).

Table 6. Synthesis of terminal conjugated diene using acrolein.



1e **41**

Entry	**Addition of acrolein**	**Equiv. of acrolein**	**Temp. (°C)**	**Yield (%)**	***E*:*Z***
1	Neat	2.0	0	0.7	87:13
2	1M Et_2O (5 min)	2.0	0	19	88:12
3	0.2M Et_2O (30 min)	2.0	-78	7	85:15
4	Vapour in N_2 (15 min)	5.0	-78	6	83:17

Although a yield of 19 % was obtained by introducing acrolein as a 1M solution in ether, further dilution of the aldehyde or introduction of acrolein as a vapour carried by nitrogen failed to increase yields (Entries 3 and 4).

Although subsequent efforts at organocatalytic cycloaddition failed, with consumption of the electron poor dienophile while the diene remained inert to the reaction conditions, the synthesis of the diene demonstrates the utility of the homologation methodology.

2.5 Experimental.

5-Bromo-2-pentanone (26)

In a 200 ml round bottom flask equipped with a magnetic stir bar was combined α-acetyl-γ-butyrolactone (5.1 ml, 47.1 mmol) and CH_2Cl_2 (50 ml). To the clear solution was added HBr (48 % aqueous, 50 ml, 440 mmol) dropwise and with vigorous stirring. To the biphasic mixture H_2SO_4 (0.27 ml, 5.1 mmol) was quickly added, the flask was fitted with a condenser and the mixture was heated under reflux for 3 h under a flow of N_2. Heating was discontinued and H_20 (60 ml) was added to the reaction mixture. Upon cooling, the organic phase was collected and the aqueous was extracted with CH_2Cl_2 (4 x 25 ml). The combined organic phase was washed with H_2O (3 x 25 ml), dried ($MgSO_4$) and solvent was removed under reduced pressure to afford a clear light brown liquid (12.1 g). The crude product was purified by vacuum distillation to afford **26** as a clear colourless liquid (7.01 g, 42.5 mmol, 90 % yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.44 (t, 2H, J = 6.4 Hz), 2.64 (t, 2H, J = 7.0 Hz) 2.16 (s, 3H), 2.10 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.31, 41.41, 33.31, 30.06, 26.36.

General procedure for ketal synthesis:

To a 10 ml round bottom flask equipped with a magnetic stir bar was added 5-bromo-2-pentanone (165 mg, 1.00 mmol), trimethyl orthoformate (180 mg, 1.70 mmol) and a glycol (4.00 mmol). Mixture was stirred open to the atmosphere until a clear solution was obtained. To the resulting solution was added 1 drop of 33 % HBr in acetic acid and stirred for the required amount of time under N_2 atmosphere. The reaction was quenched with trimethylamine (0.5 ml). The solution as poured into sat. $NaHCO_3$ (25 ml) and extracted with hexanes (3 x 20 ml). Combined organic extract was filtered through a plug of silica (0.5 cm x 3 cm). Upon removal of solvent under reduced pressure, the crude extract was purged under high vacuum for 3 h to afford the desired ketal as a clear colourless liquid

Ethylene glycol ketal (27):

(154 mg, 74 % yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.90-3.87 (m, 4H), 3.39 (t, 2H), 1.93-1.91 (m, 2H), 1.74 (t, 2H), 1.27 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 109.34, 64.54, 37.44, 33.84, 27.38, 23.80.

1,3-propylene glycol ketal (28):

(75 mg, 33 % yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91-3.83 (m, 4H), 1.99-1.95 (m, 2H), 1.81-1.77 (m, 2H), 1.77-1.75 (m, 1H), 1.57-1.55 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 98.65, 37.15, 34.39, 33.30, 26.99, 25.46, 20.84.

neopentyl glycol ketal: (29)

(225 mg, 89 % yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.57-3.45 (m, 4H), 3.43 (t, 2H), 2.04-2.02 (m, 2H), 1.83-1.81 (m, 2H), 1.37 (s, 3H), 1.02 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 98.48, 70.41, 37.19, 34.39, 29.90, 22.83, 22.45, 20.21.

pinacol ketal: (30)

(348 mg, 82 % yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43-3.41 (m, 2H), 1.97-1.95 (m, 2H), 1.76 (t, 2H), 1.36 (s, 3H), 1.22 (s, 6H), 1.21 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ. 106.94, 82.59, 41.39, 34.10, 28.64, 26.94, 24.72, 24.65.

Large scale synthesis of 2-(3-bromopropyl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (30):

To a 50 ml two-neck round bottom flask equipped with magnetic stir bar and fitted with a glass stopper and adapter to a Schlenk line was added **26** (6.61 g, 40.0 mmol), trimethyl orthoformate (7.5 ml, 73 mmol) and pinacol (12.17 g, 103.0 mmol) under N_2 flow. The vessel was stoppered

and mixture was stirred until a clear colourless solution was obtained. To the resulting solution was added HBr (33 % in acetic acid, 0.16 g, 2.0 mmol). The yellow solution was stirred at room temperature for 3 h, then the flask was equipped with a short-path vacuum distillation apparatus and was stirred at 60 °C overnight. The flask was fitted with a 10 cm Vigreux column topped with a short-path distillation head and the product was isolated under reduced pressure as the highest boiling fraction with the bath temperature set to 80 °C. the title compound was isolated as a clear colourless liquid (8.68 g, 32.7 mmol, 87 % yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43-3.41 (m, 2H), 1.97-1.95 (m, 2H), 1.76 (t, 2H), 1.36 (s, 3H), 1.22 (s, 6H), 1.21 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ. 106.94, 82.59, 41.39, 34.10, 28.64, 26.94, 24.72, 24.65.

(3-(2,4,4,5,5-pentamethyl-1,3-dioxolan-2-yl)propyl)tripropylphosphonium bromide (1e)

To a 50 ml two-neck round bottom flask epuipped with a magnetic stir bar, condenser connected to N_2 Schlenk line and a septum on the second port, charged with **30** (5.308 g, 20.01 mmol) and NaI (0.134 g, 0.895 mmol), was added THF (20 ml). The septum was replaced with a glass stopper and the suspension was heated at reflux for 5 min under N_2, allowed to cool to rt. The glass stopper was replaced with septum and tripropylphosphine (4.65 ml, 23.2 mmol) was added to the reaction mixture. The septum was again replaced with a glass stopper and the mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure and CH_2Cl_2 (25 ml) was added to the viscous residue and the resulting solution was filtered through celite. The solution was concentrated under reduced pressure then the viscous residue was purged of

volatiles under vacuum at 65 ^{o}C for 2 hours, back filling with N_2 every 0.5 h to afford the title compound as a white solid (8.41 g, 19.8 mmol, 99 % yield)^{1}H NMR (600 MHz, $CDCl_3$) δ 2.46-2.42 (m, 8H), 1.79-1.78 (m, 2H), 1.65-1.60 (m, 8H), 1.36 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.13 (t, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 106.37, 82.81, 43.62, 43.53, 26.88, 24.70, 24.64, 21.46, 21.14, 19.63, 19.32, 17.69, 15.79, 15.76, 15.60, 15.49; ^{31}P NMR (243 MHz, $CDCl_3$) δ 32.15.

General Procedure A: (Entry 1, 2, 5, 7, 8, 10)

A two-neck flask equipped with a magnetic stirring bar, glass stopper, adapter to a two-line Schlenk manifold, charged with salt **1e** (85 mg, 0.20 mmol) was purged under vacuum for 0.5 h then filled with N_2. The glass stopper was quickly exchanged with a rubber septum under rapid N_2 flow and solvent (1.0 ml) was added *via* syringe then the septum was quickly replaced with a glass stopper. The mixture was stirred until a solution was formed then cooled to 0 ^{o}C. To the cooled solution base (0.26 mmol) was quickly added under rapid N_2 flow. Upon stirring for 0.5 h, 4-chlorobenzaldehyde (25 mg, 0.18 mmol) was quickly added and the reaction was allowed to warm to rt overnight. The reaction was quenched with the addition of NH_4Cl (10 mg), solvent was removed under reduced pressure and the pot residue was extracted with Et_2O (3 x 1 ml). The combined extract was washed with sat. NH_4Cl (2 ml), water (2 ml), brine (2 ml), dried with $MgSO_4$ and solvent was removed under reduced pressure to give a crude extract as a yellow oil that was subject to ^{1}H NMR analysis.

General Procedure B: (Entry 3, 4)

A two-neck flask equipped with a magnetic stirring bar, glass stopper, adapter to a two-line Schlenk manifold, charged with salt **1e** (85 mg, 0.20 mmol) was purged under vacuum for 0.5 h then filled with N_2. The glass stopper was quickly exchanged with a rubber septum under rapid N_2 flow and solvent (1.0 ml) as added *via* syringe then the septum was quickly replaced with a glass stopper. The mixture was stirred until a solution was formed then cooled to 0 ^oC. To the cooled solution base (0.26 mmol) was quickly added under rapid N_2 flow. The reaction was allowed to warm to rt over 0.5 h, then 4-chlorobenzaldehyde (25 mg, 0.18 mmol) was quickly added, the septum was replaced, and the reaction was stirred overnight. The reaction was quenched with the addition of NH_4Cl (10 mg), solvent was removed under reduced pressure and the pot residue was extracted with Et_2O (3 x 1 ml). The combined extract was washed with sat. NH_4Cl (2 ml), water (2 ml), brine (2 ml), dried with $MgSO_4$ and solvent was removed under reduced pressure to give a crude extract as a yellow oil that was subject to ^1H NMR analysis.

General Procedure C: (Entry 11)

A two-neck flask equipped with a magnetic stirring bar, glass stopper, adapter to a two-line Schlenk manifold, charged with salt **1e** (85 mg, 0.20 mmol) was purged under vacuum for 0.5 h then filled with N_2. The glass stopper was quickly exchanged with a rubber septum under rapid N_2 flow and Et_2O (0.8 ml) as added *via* syringe. The mixture was cooled to -78 ^{o} C. To the

cooled solution *n*-BuLi (1.6 M in hexanes, 1.3 equiv) was quickly added under rapid N_2 flow. The reaction was allowed to warm to 0 ^{o} C over 0.5 h, then 4-chlorobenzaldehyde (25 mg, 0.18 mmol) in Et_2O (0.2 ml) was transferred to the reaction pot *via* syringe, the reaction was then allowed to warm to rt, the septum as quickly replaced with a glass stopper and the reaction was stirred overnight. An additional volume of Et_2O (2 ml) was added and the reaction was quenched with the addition of sat. NH_4Cl (2 ml). The aqueous was removed and the organic phase was washed with water (2 ml), brine (2 ml), dried with $MgSO_4$ and solvent was removed under reduced pressure to give a crude extract as a yellow oil that was subject to ^{1}H NMR analysis.

(*E*)-2-(4-(4-chlorophenyl)but-3-en-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (31):

Scheme 5, Entry 10: General procedure A was followed using salt **1e** (427 mg, 1.0 mmol), 4-chlorobenzaldehyde (127 mg, 0.90 mmol) and 1.3 eq of LiHMDS in THF/DMF (1:1). The crude material was purified by flash chromatography (20:1 hexanes/EtOAc) to give separated **31** and **32** as a pale yellow oils containing a mixture of isomers and ~10 % impurities by integral count. A second purification (40:1 hexanes/EtOAc) gave **31** as a pale yellow oil, with depleted (*Z*)-isomer (6.9 mg, 0.022 mmol) ^{1}H NMR (600 MHz, CDCl3) δ 7.15-7.16 (m, 4H), 6.24 (dt, 1H, J = 15.8 Hz), 6.11 (dt, 1H, J = 15.8 Hz), 2.24-2.20 (m, 2H), 1.72 (m, 2H), 1.32 (s, 3H), 1.15 (s, 6H), 1.12 (s, 6H); ^{13}C NMR (151 MHz, CDCl3) δ 139.31, 132.33, 131.47, 128.57, 128.38, 127.10, 107.22, 82.59, 42.46, 29.70, 28.65, 26.95, 24.80, 24.73. Compound **32** was isolated as a pale yellow oil (10.7 mg, 0.064 mmol) ^{1}H NMR (600 MHz, CDCl3) δ 7.15 (m, 4H), 6.22 (dt, 1H, J =

15.8 Hz), 6.14 (dt, 1H, J = 15.8 Hz), 2.13-2.10 (m, 2H), 0.99 (s, 3H); 13C NMR (151 MHz, CDCl3) δ 136.46, 133.37, 128.59, 127.66, 127.12, 29.74, 26.04, 13.54.

(*E*)-2-(hexa-3,5-dien-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane: (41)

General procedure C was followed using salt **1e** (434 mg, 1.02 mmol), acrolein (0.20 ml, 0.90 mmol) and *n*-BuLi (1.6M in hexanes, 0.62 ml, 1.00 mmol). The crude material was purified by flash chromatography (20:1 hexanes/EtOAc) to give **41** as a pale yellow oil (42.8 mg, 19 %) ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 17.1, 10.3 Hz, 1H), 5.99 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.69 – 5.62 (m, 1H), 5.02 (d, *J* = 16.8 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 2.13 (m, 2H), 1.69 – 1.65 (m, 2H), 1.32 (s, 3H), 1.17 (s, 6H), 1.15 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.2, 134.0, 129.7, 113.8, 81.5, 41.3, 28.7, 27.2, 25.9, 23.8, 23.6.

2.6 Conclusions and outlook.

Pre-complexation/deprotonation sequences have been shown to play a pivotal role in the regioselective functionalization of aromatic systems by Snieckus and co-workers, in the vast array of directed metalation/trapping reactions pioneered by this group.[8c,8d] The results presented here demonstrate that the “complex-induced-proximity effect” concept may be extended to regioselective ylide formation on differentially functionalized phosphonium salts leading to useful, homologated functionalized carbonyl compounds. Further studies to explore the reactivity

of the three—carbon extended functionalized olefins and extend the concept of directed ylide formation to other homologation processes is under active investigation in our laboratories.

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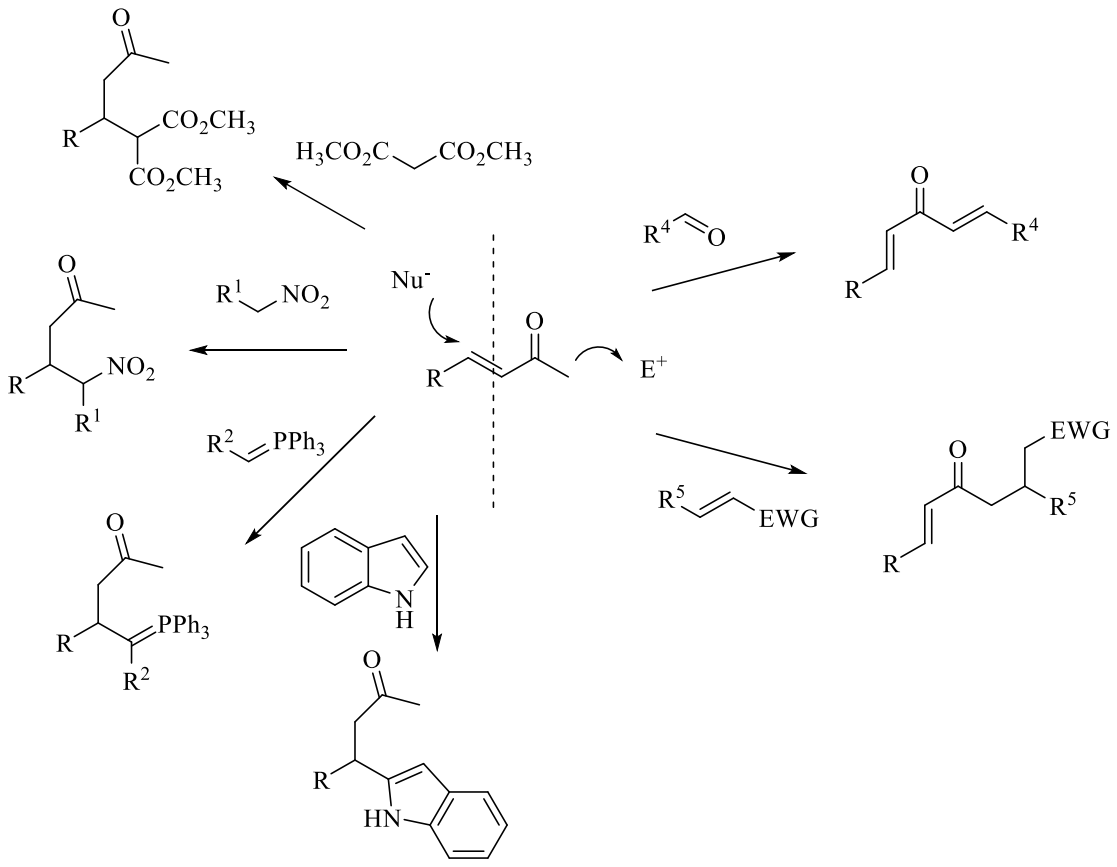
3.0 ACETONYL TRIPROPYLPHOSPHORANE AS A REAGENT FOR FACILE AND GENERAL SYNTHESIS OF METHYL VINYL KETONES *VIA* TWO-CARBON HOMOLOGATION OF ALDEHYDES

3.1 Introduction.

The chemistry of methyl vinyl ketones (MVKs) is dominated by their dual reactivity with both electrophilic and nucleophilic properties (Scheme 36).



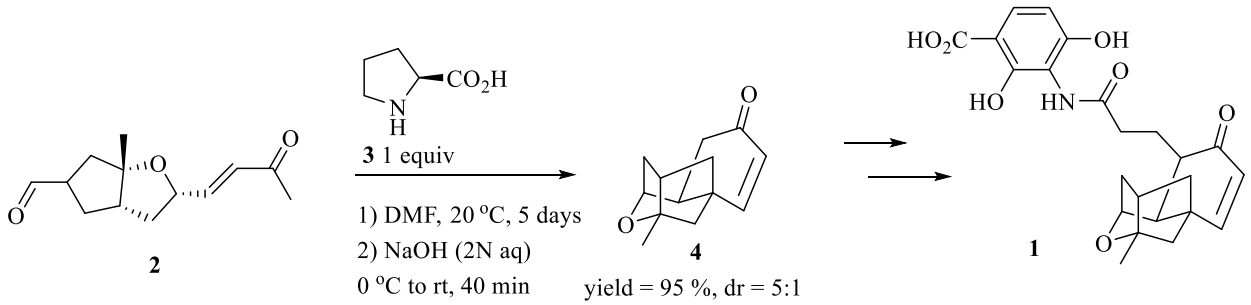
Scheme 36. Selected examples of carbon-carbon bond forming reactions employing methyl vinyl ketones.

Conjugate addition of a wide range of nucleophiles to MVKs including nitroalkanes,[1-6] malonates,[7,8] electron rich arenes,[9] and phosphoranes,[10] have been reported. Moreover, various *N*-,[11] *O*-,[12] and *S*-centered[13] nucleophiles have been employed as Michael donors

to vinyl ketones. Conversely, enolization at the α-methyl group allows for addition to activated olefins,[14-16] and non-enolizable carbonyl compounds.[17]

This dual reactivity of MVKs has been exploited for tandem reaction sequences to generate cyclic compounds. The classic example of this was first demonstrated by the Robinson reaction in 1935,[18] and its various enantioselective variants.[19] The Robinson annulation continues to be of relevance in the total synthesis of natural products.

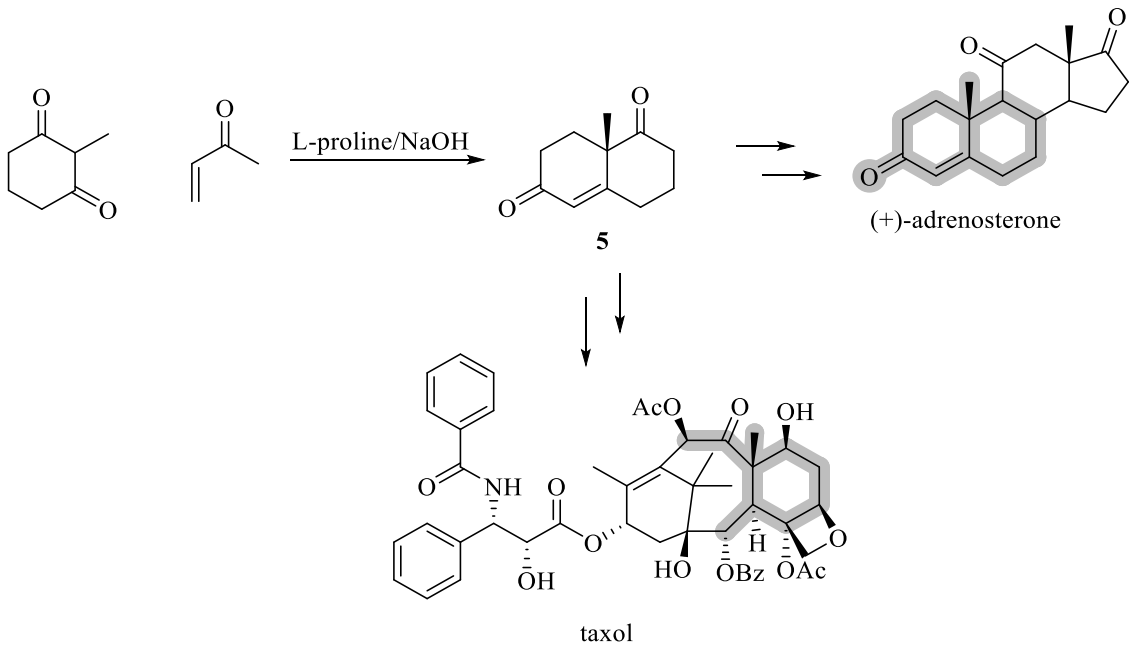
An example is the use of the proline mediated Robinson annulation as a key step in a formal synthesis of platensimycin (Scheme 37, **1**).[20]



Scheme 37. Robinson annulation as a key step in the synthesis of platensimycin.

The L-proline (**3**) mediated *si*-face intramolecular Michael addition in **2** gave the desired epimer **4** with 5:1 diastereoselectivity after treatment with sodium hydroxide to complete the aldol condensation. The tetracyclic product **4** was previously established as a key intermediate in the total synthesis of platensimycin (**1**).[21]

Wieland-Miescher ketones (i.e. **5**) have seen extensive applications as building blocks in organic synthesis (Scheme 38),[22,23] as they can easily be synthesized *via* chiral amine mediated Robinson annulation with high enantioselectivity.[24-27]



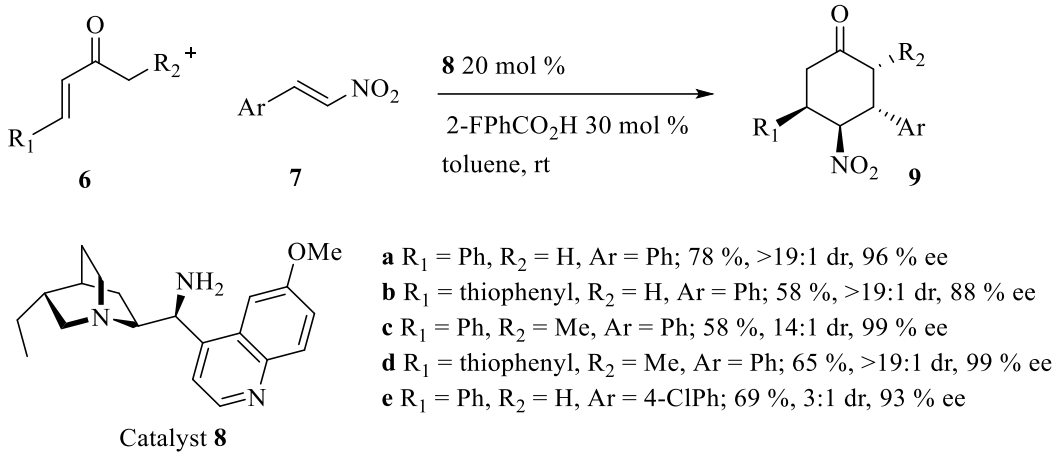
Scheme 38. Wieland-Miescher ketones in total synthesis.

The chiral bicyclic diketones have been prominent as key intermediates in the synthesis of terpenoid natural products as exemplified by the synthesis of (+)-adrenosterone,[28] and the Danishefsky synthesis of taxol.[29]

A range of substituted cyclohexanes and cyclohexenes can be formed from the tandem reactions of MVKs with various substrates. Reactions with ketones give cyclohexenones *via* the Robinson annulation. Reaction with malonate ester anions proceed to a

concomitant Claisen reaction of the adduct to yield 1,3-cyclohexanediones,[7] and reactions with activated olefins give substituted cyclohexanones.[14-17]

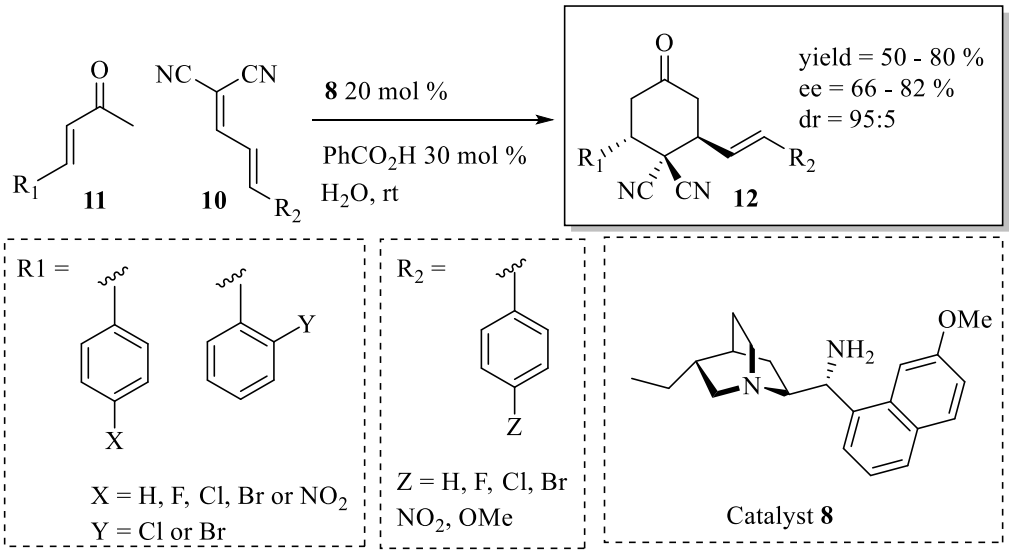
The classic work laid the groundwork for tandem reactions with a wide range of substrates mediated by chiral amine catalysts to generate an extensive library of cyclic compounds which have been extensively reviewed.[30-32] Control of reactivity can be achieved by employing either primary or secondary amine catalysts, which favour the formation of either iminium or enamine reactive intermediates.[30,31] Reactions with electron poor olefins have yielded highly substituted cyclohexanones *via* formal normal electron demand cycloaddition reactions (Scheme 39).[16]



Scheme 39. Formal cycloaddition of vinyl ketones with nitro olefins catalyzed by chinchonamine.

Normal electron demand Diels-Alder reactions activated by enamine catalysis can be viewed either as a completely concerted non-ionic process or as a stepwise Michael-Aldol sequence.[31] A

recent example involves the enamine activation of MVKs to generate an electron rich crossed dienamines that were added to electron poor allylidene malononitriles.[33] The cycloadditions were mediated by various primary amines in the presence of an organic acid additive, however optimal yield and selectivity was observed using cinchonamine derivative **8** with benzoic acid. The addition of various aryl substituted allylidene malononitriles **10** to various *β*-aryl substituted MVKs **11** yielded product **12** with high to complete diastereoselectivity but proceeded with only moderate to poor yields and enantioselectivities (Scheme 40).



Scheme 40. Formal cycloaddition of vinyl ketones with allylidene malononitriles catalyzed by chinchonamine.

Inverse electron demand Diels-Alder reactions activated through enamine catalysis using the Jorgensen catalysts have been explored in detail.[34] In this case, electron rich dienophiles in the

form of catalyst activated enamines are added to extended conjugated dienaldehydes that function as electron poor dienes. cycloaddition products yield cyclic enols or dienes.

β-Substituted MVKs have been synthesized from aldehydes by classic methods using aldol and Knoevenegel chemistry (see section 1.2). The classical methods suffered from selectivity issues, especially when homologation of enolizeable aldehydes was required, as is the case with general crossed aldol approaches. The Knoevenagel chemistry avoids the issues with selectivity by use of acetyl acetates, however an extra hydrolysis-decarboxylation sequence is required to afford the homologated MVK.

Phosphorous reagents have become useful reagents for the direct synthesis of homologated MVKs from aldehydes, when the requisite functionality of the substrates is not tolerated under classical conditions (see sections 1.3-1.5).

The use of triphenylphosphine derived ylides has allowed the homologation of a wide range of aldehydes to give (*E*)-MVKs. These reactions suffer from long reaction times and often elevated temperatures required for the homologation of most aldehydes (see section 1.5).

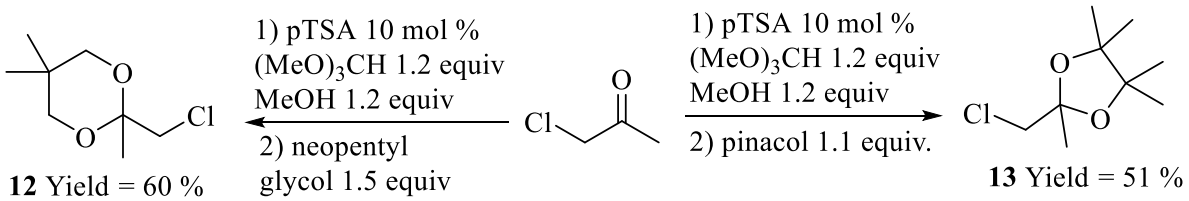
The utility of trialkylphosphine-derived non-stabilized and semi-stabilized phosphonium salts as Wittig reagents for the synthesis of olefins with high degrees of (*E*)-selectivity has

been demonstrated in recent years (see Section 1.6 and 1.7). The utility of the two-carbon aldehyde homologation reagent (DualPhos) was demonstrated under aqueous, and anhydrous conditions (see Section 1.7).

The often-increased reactivity observed for trialkyl phosphine derived Wittig reagents prompted an investigation into their application to the general synthesis of homologated MVKs from aldehydes.

3.2 Attempts at preparation of DualPhos ketone analogues.

There was an interest to develop an analogous ketal-protected acetone α-phosphonium salts for the two-carbon homologation of aldehydes to MVK equivalents. Although protected chloroacetones could be readily obtained (Scheme 41), both alkyl halides **12** and **13** remained completely inert to substitution with tripropylphosphine. It was postulated that the neopentyl positioning of the leaving group was too sterically encumbered.

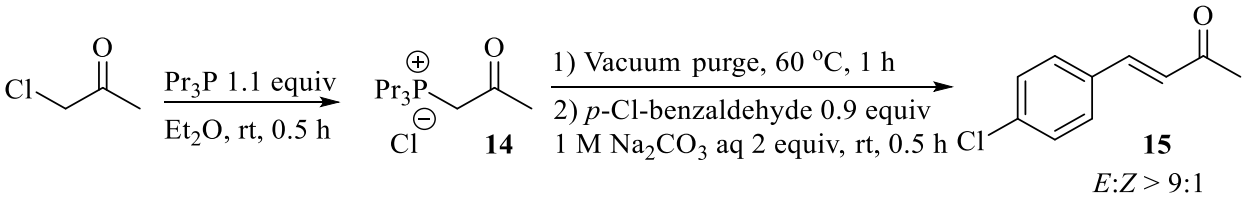


12 Yield = 60 % **13** Yield = 51 %

Scheme 41. Cyclic acetals of chloroacetone.

3.3 Synthesis of methyl vinyl ketones using a telescoping homologation procedure under aqueous conditions.

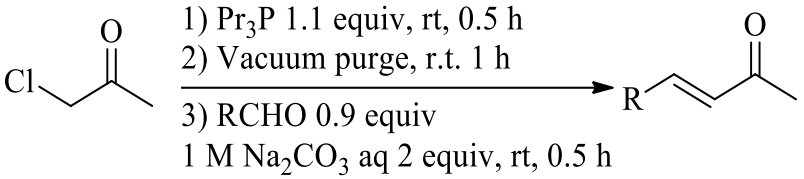
The reaction of chloroacetone with tripropyl phosphine in diethyl ether formed salt **14** as a white precipitate, however the solid quickly decomposed on vacuum filtration (Scheme 42). Although ^{1}H NMR analysis of the resulting yellow oil indicated a mixture of products, dissolving the oil in CH_2Cl_2, followed by removal of the solvent yielded a white solid that corresponded to salt **14** by ^{1}H NMR. A Wittig reaction was attempted by a one-pot, two-step process. Although only minimal product formation could be detected by TLC the reaction proceeded to completion with the addition of sodium carbonate to give MVK **15** (Scheme 42).

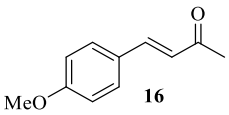
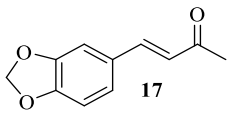
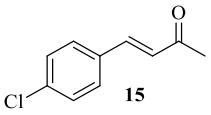
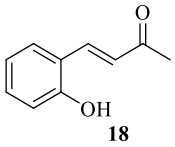


Scheme 42. Telescoping aqueous Wittig for the synthesis of MVK.

A series of substituted benzaldehydes were successfully homologated to their corresponding MVKs using this telescoping procedure. (Table 7).

Table 7. Telescoping method for MVK synthesis in aqueous media.



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **16**	66	3	 **17**	38[(a)]
2	 **15**	75	4	 **18**	46[(b)]

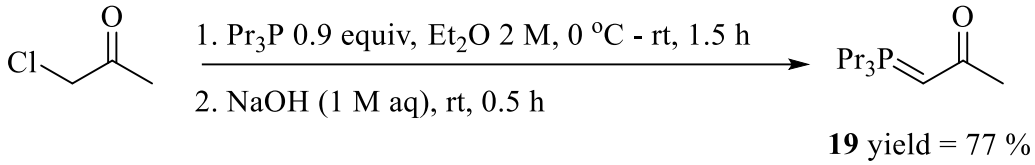
Reactions were conducted using General Procedure A. Products generally precipitated from the reaction mixture, if necessary, they were (a) recrystallized, (b) extracted then recrystallized.

Products generally formed crystalline precipitates under the reaction conditions and could be obtained with high purity simply by vacuum filtrations of the reaction mixture followed by aqueous washing of the solid product. In the case of Entry 3 in Table 7, a crude amorphous solid was obtained by filtration, and recrystallization from hexanes was required to obtain the pure MVK (**17**). In cases where solid precipitate was not formed (Entry 4), extraction with organic solvent had to be employed to isolate **18**. Yields of recrystalized products were low, while reactions with enolizeable alkyl aldehydes yielded complex mixtures of products in the basic aqueous conditions. It was thought that

reactions with an isolated ylide in organic solvent would improve yields of homologation reactions with base-sensitive aldehydes.

3.4 Synthesis of methyl vinyl ketones using an isolated ylide.

It was reasoned that isolating the phosphonium ylide might allow for homologation of more sensitive aldehydes and allow for greater functional group compatibility by omitting excess base from the reaction environment (Scheme 43).

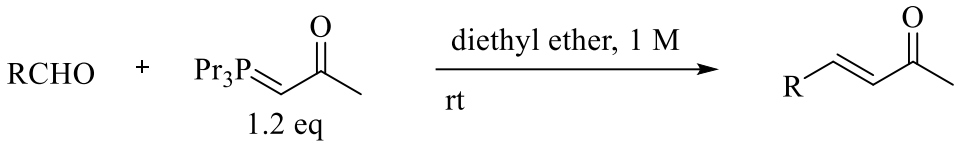


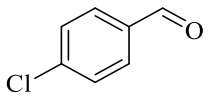
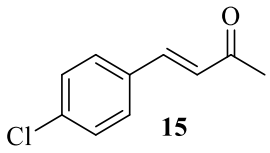
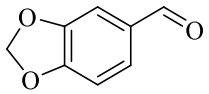
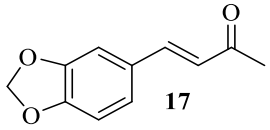
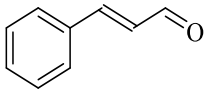
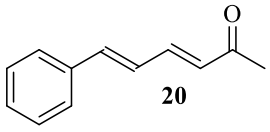
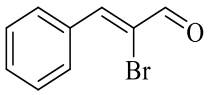
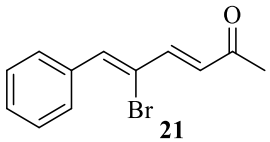
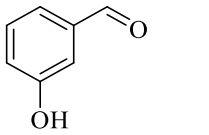
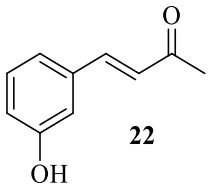
Scheme 43. Synthesis and isolation of stabilized ylide.

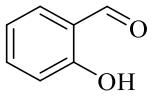
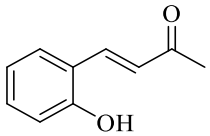
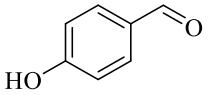
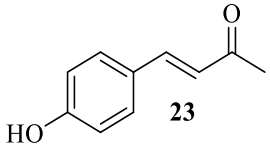
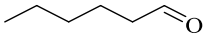
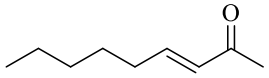
Synthesis of the stabilized ylide **19** was accomplished by substitution of chloroacetone with tripropyl phosphine in anhydrous diethyl ether. Careful control of stoichiometry and addition time afforded a white crystalline product that could be washed by successive decantation of ether from the dense phosphonium salt. Addition of aqueous sodium hydroxide (1 M) to a solution of the salt **14** in dichloromethane allowed for the successful deprotonation of the Wittig salt and subsequent extraction of the ylide into dichloromethane, followed by removal of the solvent afforded the ylide as a crystalline white solid that could be handled on the bench and stored under argon at -7 °C for over one month.

With the ylide in hand, a series of aldehydes were homologated at room temperature in diethyl ether (Table 1). Analytically pure MVKs were obtained after the removal of tripropylphosphine oxide and excess ylide by aqueous workup.

Table 8. Homologation of aldehydes to MVKs using an isolated ylide.



Entry	Aldehyde	Time (h)	Yield (%)	Product	*E*:*Z*
1		2	87	 **15**	>20:1
2		2	85	 **17**	>20:1
3		2	89	 **20**	>20:1
4		2	86	 **21**	>20:1 (50:1*)
5		3	82	 **22**	>20:1

6		16	81	 **18**	>20:1
7		16	82	 **23**	>20:1
8		2	91	 **24**	>20:1

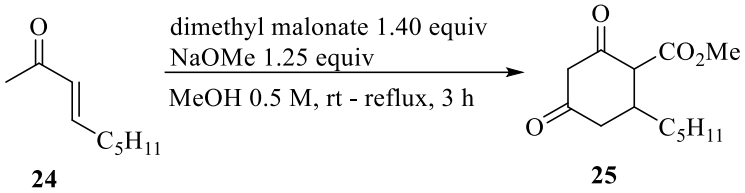
Reactions were conducted according to the general procedure B (see experimental Section 3.6). *E*:*Z* ratios were determined by relative integrals of olefinic signals from ^{1}H NMR spectra. *Ratio was determined using relative integrals of peaks from GC-MS.

Homologated MVKs were obtained in high yields and nearly complete selectivity for the *E*-olefin. Substituted benzaldehydes, cinnamaldehydes and aliphatic aldehydes were successfully homologated to their corresponding MVKs. Although aldehydes containing acidic phenolic groups (Entry 6 and 7) required longer reaction times, they were successfully homologated to their corresponding MVKs (**18** and **23**) nonetheless.

3.5 Methyl vinyl ketones as Michael acceptors.

Treatment of 3-nonene-2-one (**24**) with dimethyl malonate and sodium methoxide afforded the cyclohexadione **25** (Scheme 44). This product was a known precursor in the synthesis of the

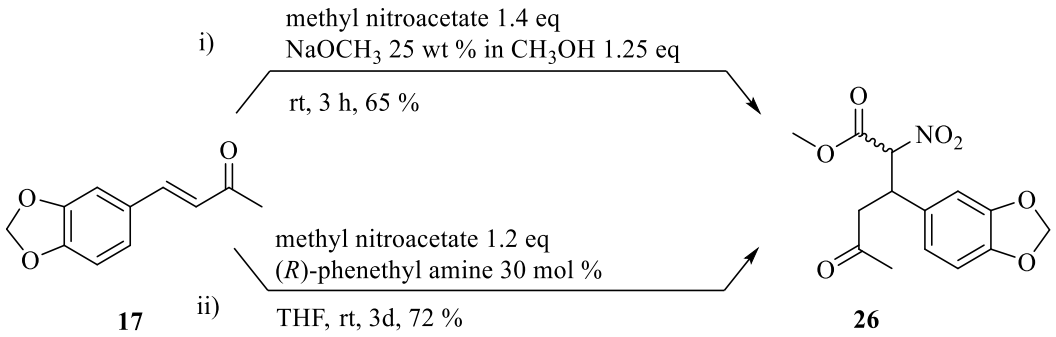
natural product olivetol and as a key intermediate in the synthesis of cannabinolic acid methyl ester (see Chapter 4 and 5).[7,35]



24 **25**

Scheme 44. Tandem Michael-Claisen reaction for synthesis of phytocannabinoid precursor.

In an attempt to extend the scope of the Michael-Claisen sequence described above, MVK **17** was reacted with methyl nitroacetate using (*R*)-(+)-*α*-phenethyl amine as a model primary amine catalyst (Scheme 45). Synthesis of the corresponding cyclohexadione was envisioned as a platform towards the synthesis of Amaryllidaceae alkaloids, however treatment of the Michael adduct with sodium methoxide failed to provide the Claisen product. The Michael adduct was isolated as a mixture of two diastereomers with the relative abundance of each being same in the products obtained under organocatalytic conditions and under base mediated conditions, suggesting that the product is epimerizable in solution.



Scheme 45. Michael addition of methyl nitroacetate to MVK.

Although the desired Claisen product could not be obtained and the product **26** was isolated as a mixture of diastereomers with a near 0 ^{o} rotation, similar Michael adducts have been synthesized using more sophisticated chiral primary amine catalysts and reduced to esters of non-natural amino acids with high degrees of enantioinduction.[36,37]

3.6 Experimental.

2-(chloromethyl)-2,5,5-trimethyl-1,3-dioxane (12): A 10 mL round bottom flask, fitted with a stir bar and a short path distillation apparatus, was charged with chloroacetone (1.1 mL, 10 mmol), trimethyl orthoformate (1.4 mL, 12 mmol), methanol (0.5 mL, 12 mmol), and *p*-toluene sulfonic acid (19 mg, 0.10 mmol) under N_2 atmosphere. The mixture was stirred at room temperature over 16 h until the consumption of chloroacetone was noted by TLC. To the reaction flask was added neopentyl glycol (1.562 g, 15.0 mmol) and the mixture was distilled by heating at 100 ˚C until no further distillate was observed. Upon cooling to room temperature, the pot

residue was vacuum distilled (45 ˚C – 48 ˚C, 0.1 mmHg) to obtain the target compound as a colourless liquid (1.046 g, 60 %): ^{1}H NMR (600 MHz, CDCl3) δ 3.56 (s, 2H), 3.53 (d, *J* = 11.5 Hz, 2H), 3.45 (d, *J* = 11.5 Hz, 2H), 1.44 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 97.3, 70.6, 46.9, 29.9, 22.4, 22.3, 19.2.

2-(chloromethyl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (13): A 10 mL round bottom flask, fitted with a stir bar and a short path distillation apparatus, was charged with chloroacetone (1.1 mL, 10.0 mmol), trimethyl orthoformate (1.4 mL, 12.5 mmol), methanol (0.5 mL, 12.5 mmol), and *p*-toluene sulfonic acid (19 mg, 0.10 mmol) under N_2 atmosphere. The mixture was stirred at room temperature over 16 h until the consumption of chloroacetone was noted by TLC. To the reaction flask was added pinacol (1.242 g, 10.5 mmol) and the mixture was distilled by heating in 100 ˚C until no further distillate was observed. Upon cooling to room temperature, the pot residue was vacuum distilled (44 ˚C, 0.1 mmHg) to obtain the target compound as a colourless liquid (0.992 g, 51 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 (s, 1H), 1.50 (s, 2H), 1.24 (s, 3H), 1.21 (s, 3H).

2-oxopropyl)tripropylphosphonium chloride (14): To an oven-dried two-neck flask charged with tripropylphosphine (4.0 mL, 20 mmol) in dry diethyl ether (10 mL) was added chloroacetone (1.7 ml, 21 mmol) dropwise over 15 minutes under nitrogen at 0 ^{o}C. Upon addition of chloroacetone, the mixture was stirred at 0 ^{o}C for an additional 15 min. The flask was then removed from the ice-bath and allowed to slowly warm to room temperature while stirring

over 1 h. The white precipitate was carefully washed with dry diethyl ether by decantation (5 x 10 mL). Volatiles were removed under a stream of nitrogen, then under reduced pressure (~ 0.1 mmHg) to give the tittle compound as a crystalline white solid (3.55 g, 86 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.79 (d, *J* = 12.3 Hz, 2H), 2.44 (s, 3H), 2.43 – 2.38 (m, 6H), 1.62 (dd, *J* = 15.6, 7.6 Hz, 6H), 1.10 (t, *J* = 6.7 Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.5, 35.7, 35.3, 32.2, 32.2, 21.8, 21.5, 15.9, 15.9, 15.6, 15.5.^{31}P NMR (243 MHz, $CDCl_3$) δ 29.8.

1-(tripropyl-λ5-phosphaneylidene)propan-2-one (19): To a flask charged with **14** (3.55 g, 16.4 mmol) was added water (3 mL) and CH_2Cl_2 (2 mL) and the mixture was stirred until all solid had dissolved. To the colourless mixture was added 1 M NaOH solution (20 mL) and stirred at room temperature over 0.5 h. The mixture was extracted with CH_2Cl_2 (4 x 10 mL) The combined organic extract was washed with brine (10 mL), dried with sodium sulfate and the solvent was removed under reduced pressure to give the title compound as a white solid (3.32 g, 77 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.91 (br d, *J* = 18.2 Hz, 1H), 1.85 (s, 3H), 1.87 – 1.80 (m, 6H), 1.49 – 1.40 (m, 6H), 0.97 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.4, 49.0, 48.4, 28.2, 28.1, 24.2, 23.8, 15.9, 15.8, 15.7, 15.6. ^{31}P NMR (243 MHz, $CDCl_3$) δ 16.7.

General Homologation Procedure A: To a two-neck round bottom flask (10 mL) was added chloroacetone (0.08 mL, 1 mmol) and was stirred at 0 ˚C over 15 min under a N_2 atmosphere. Through a rubber septum was added tripropylphosphine (0.22 mL, 1.1 mmol) over 5 min. The contents of the flask quickly formed a white crystalline precipitate. The volatiles were purged

with heating under reduced pressure (65 ˚C, 0.1 mmHg) over 30 min. The contents were again cooled to 0 ˚C and a solution of sodium carbonate (1 M, 2.0 mL) was added to form a slightly yellow solution. To this solution was added aldehyde (0.90 mmol) and the mixture was allowed to warm to room temperature with stirring over 3 h. The reaction was quenched with the addition of sat. ammonium chloride (2 mL) and the product was obtained by filtration of the resulting precipitate. In the case where an oil was formed, the biphasic mixture was extracted with ethyl acetate (3 x 5 mL). the combined organic extracts were dried ($MgSO_4$) and solvent was removed under reduced pressure to give the target compound as described.

General Homologation Procedure B: To a vial charged with phosphorane **19** (1.2 equiv) in diethyl ether (1 M in aldehyde) was added aldehyde (1.0 equiv). The solution was stirred at room temperature until the disappearance of aldehyde was observed by TLC. The mixture was then diluted with diethyl ether (2 mL) and the solution was extracted with 1 % HCl aq (4 x 1 mL), water (1 mL), then brine (1 mL). The organic solution dried ($MgSO_4$), then was concentrated and trace solvent was removed under reduced pressure (~ 1 mmHg) to afford the target compound as described.

(*E*)-4-(4-chlorophenyl)-3-buten-2-one (15): Following the general procedure A, 4-chlorobenzaldehyde (126 mg, 0.90 mmol) was reacted as described. The product **15** was isolated as a white solid by vacuum filtration (122 mg, 75 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, CDCl3) δ 7.43 (m, 3H), 7.34 – 7.30 (m, 2H), 6.64 (d, *J* = 16.25 Hz, 1H), 2.35 – 2.33 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.1, 141.9, 136.4, 132.9, 129.4, 127.5, 27.7. Spectral data were in agreement with those previously reported in literature.

Following the general procedure B, phosphorane **19** (83.8 mg, mmol) was reacted with 4-chlorobenzaldehyde (52.1 mg, mmol) over 2 h, as described. The product **15** was isolated as a white solid (52.3 mg, 87 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (m, 3H), 7.34 – 7.30 (m, 2H), 6.64 (d, *J* = 16.25 Hz, 1H), 2.35 – 2.33 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.1, 141.9, 136.4, 132.9, 129.4, 127.5, 27.7. Spectral data were in agreement with those previously reported in literature.

(*E*)-4-(4-methoxyphenyl)but-3-en-2-one (16): Following the general procedure A, *p*-anisaldehyde (0.11 mL, 0.90 mmol) was homologated as described. The product **16** was isolated as a white solid (105 mg, 66 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (m, 3H), 6.92 (d, *J* = 8.76 Hz, 2H), 6.61 (d, *J* = 16.16 Hz, 1H), 3.85 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.4, 161.6, 143.2, 129.9, 127.1, 125.0, 114.4, 55.4, 27.4. Spectral data were in agreement with those previously reported in literature.

(*E*)-4-(1,3-benzodioxol-5-yl)-3-buten-2-one (17): Following the general procedure A, piperonal (146 mg, 0.97 mmol) was reacted as described. The product **17** was isolated as a white solid upon crystallization from diethyl ether (70.1 mg, 38 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, CDCl3) δ 7.43 (d, *J* = 16.15 Hz, 1H), 7.05 (d, *J* = 1.66 Hz, 1H), 7.03 (dd, *J* = 8.01, 1.66 Hz, 1H),

6.83 (d, *J* = 8.01 Hz, 1H), 6.56 (d, *J* = 16.15 Hz, 1H), 6.02 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.2, 149.9, 148.5, 143.2, 128.8, 125.3, 124.8, 108.6, 106.5, 101.6, 27.5.

Following the general procedure B, piperonal (54.5 mg, 0.40 mmol) was reacted over 2 h, as described. The product **17** was isolated as a white solid (66.3 mg, 87 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, CDCl3) δ 7.43 (d, *J* = 16.15 Hz, 1H), 7.05 (d, *J* = 1.66 Hz, 1H), 7.03 (dd, *J* = 8.01, 1.66 Hz, 1H), 6.83 (d, *J* = 8.01 Hz, 1H), 6.56 (d, *J* = 16.15 Hz, 1H), 6.02 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.2, 149.9, 148.5, 143.2, 128.8, 125.3, 124.8, 108.6, 106.5, 101.6, 27.5; HRMS (APCI): m/z calcd for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0703, found 191.0712.

(*E*)-4-(2-hydroxyphenyl)but-3-en-2-one (18): Following the general procedure A, salicylaldehyde (94 μL, 0.90 mmol) was reacted as described. The crude product **18** was isolated by extraction (217.1 mg), followed by recrystallization from diethyl ether to afford the target **18** as a white solid (66.8 mg, 46 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 16.44 Hz, 1H), 7.48 (dd, *J* = 7.99, 1.52 Hz, 1H), 7.46 (bs, 1H) 7.25-7.23 (m, 1H), 6.96 (d, *J* = 16.44 Hz, 1H), 6.94 – 6.89 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 201.1, 156.0, 140.7,131.9, 129.7, 127.7, 121.5, 120.7, 116.6, 26.9.

Following the general procedure B, salicylaldehyde (42.0 μL, 0.40 mmol) was reacted over 16 h, as described. The product **18** was isolated as a white solid (52.3 mg, 81 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.44 Hz, 1H), 7.48 (dd, *J* = 7.99, 1.52 Hz, 1H), 7.46 (bs, 1H)

7.25-7.23 (m, 1H), 6.96 (d, *J* = 16.44 Hz, 1H), 6.94 – 6.89 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 201.1, 156.0, 140.7,131.9, 129.7, 127.7, 121.5, 120.7, 116.6, 26.9; HRMS (ESI): m/z calcd for $C_{10}H_9O_2$ $[M-H]^-$ 161.0608, found 161.0595 and $C_{20}H_{19}O_4$ $[2M-H]^-$ 323.1289, found 1323.1286.

(3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one (20): Following the general procedure B, cinnamaldehyde (23μL, 0.165 mmol) was homologated over 2 h, as described. The product **20** was isolated as a white solid after recrystallization from hexanes (25.3 mg, 89 %, *E*/*Z* >20:1): ^{1}H NMR (600 MHz, CDCl3) δ 7.52 – 7.44 (m, 2H), 7.40 – 7.34 (m, 2H), 7.34 – 7.27 (m, 2H), 6.98 – 6.86(m, 2H), 6.27 (d, *J* = 15.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.43, 143.44, 141.28, 135.98, 130.52, 129.24, 128.87, 127.26, 126.68, 27.39; HRMS (APCI): m/z calcd for $C_{12}H_{13}O$ $[M+H]^+$ 173.0961, found 173.0965.

(3*E*,5*Z*)-5-bromo-6-phenyl-3,5-hexadien-2-one (21): Following the general procedure B, α-bromocinnamaldehyde (68.2 mg, 0.323 mmol) was reacted over 2 h, as described. The product **21** was isolated as a white solid (69.7 mg, 86 %, *E*/*Z* = 50:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.43 – 7.36 (m, 3H), 7.34 – 7.30 (m, 2H), 6.66 (d, *J* = 14.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.50, 143.26, 139.88, 134.73, 130.74, 130.08, 129.61, 128.41, 120.59, 28.91. Spectral data were in agreement with those previously reported in literature.

(*E*)-4-(3-hydroxyphenyl)but-3-en-2-one (22): Following the general procedure B, 3-hydroxybenzaldehyde (43.8 mg, 0.359 mmol) was reacted over 3 h, as described. The product **22** was isolated as a white solid (47.7 mg, 82 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 16.3 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.07 (m, 2H), 6.95 – 6.91 (m, 1H), 6.69 (d, *J* = 16.3 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.41, 156.62, 144.04, 135.78, 130.17, 127.18, 120.95, 118.10, 114.66, 27.46. Spectral data were in agreement with those previously reported in literature.

(*E*)-4-(4-hydroxyphenyl)but-3-en-2-one (23): Following the general procedure B, 4-hydroxybenzaldehyde (51.7 mg, 0.424 mmol) was reacted over 16 h, as described. The product **23** was isolated as a white solid upon recrystallization from benzene (56.3 mg, 82 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 16.2 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 16.2 Hz, 1H), 6.51 (s, 1H), 2.38 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.38, 158.56, 144.11, 130.35, 126.79, 124.67, 116.13, 27.32; HRMS (ESI): m/z calcd for $C_{10}H_9O_2$ $[M-H]^-$ 161.0608, found 161.0604 and $C_{20}H_{19}O_4$ $[2M-H]^-$ 323.1289, found 1323.1287.

(*E*)-3-nonen-2-one (24): Following the general procedure B, hexanal (40 µL, 0.324 mmol) was reacted over 2 h, as described. The product **24** was isolated as a colourless oil (41.4 mg, 91 %, *E*/*Z* > 20:1): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.04 (dt, *J* = 15.9, 1.4 Hz, 1H), 2.21 (s, 3H), 2.21 – 2.17 (m, 2H), 1.47 – 1.41 (m, 2H), 1.32 – 1.26 (m, 4H), 0.87 (t, *J* =

7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.69, 148.60, 131.26, 32.40, 31.32, 27.74, 26.78, 22.39, 13.91.

methyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-nitro-5-oxohexanoate (26): To a two-neck round bottom flask equipped with a stir-bar and a condenser attached to a two-line Schlenk manifold was added methyl nitroacetate (68 μL, 0.736 mmol), methanol (2 mL), and 25% sodiummethoxide solution in methanol (0.15 mL, 0.66 mmol), under N_2 atmosphere. The mixture was stirred at room temperature over 1 h. to the resulting solution was added MVK **17** (105.2 mg, 0.553 mmol) and the mixture was heated at reflux over 3 h. Water (5 mL) was added to the mixture upon cooling and the aqueous was washed with chloroform (2 mL). The aqueous solution was slowly acidified to pH 4 (1M HCl) and the acidic mixture was extracted with diethyl ether (3 x 5 mL). The combined ethereal extract was concentrated and purified by flash chromatography (hexanes-ethyl acetate) to afford the title compound as a yellow oil (111 mg, 65 %): ^{1}H NMR (600 MHz, CDCl3) δ 6.75 – 6.68 (m, 3H), 5.93 (d, *J* = 2.7 Hz, 1H), 5.93 (s, 1H), 5.41 (d, *J* = 9.7 Hz, 1H), 5.37 (d, *J* = 8.3 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.12 – 2.97 (m, 1H), 2.96 – 2.87 (m, 1H), 2.09 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.85, 204.72, 164.01, 163.55, 148.02, 147.38, 131.27, 130.40, 121.65, 121.49, 108.60, 108.53, 108.35, 101.28, 91.30, 91.21, 53.68, 53.53, 45.58, 45.07, 41.21, 41.08, 30.39, 30.28, 29.70.

To a 8 mL vial equipped with a stir bar and a ground glass stopper charged with MVK **17** (57.5 mg, 0.302 mmol) was added THF (1 mL) followed by methyl nitroacetate (34 μL, 0.369 mmol)

then (*R*)-(+)-α-phenethyl amine (10 μL, 0.078 mmol). The mixture was stirred at room temperature over 3 days. The solvent was removed by rotary evaporator, and the concentrate was purified by flash chromatography (hexanes-ethyl acetate) to afford the title compound as a yellow oil (67.2 mg, 72 %): ^{1}H NMR (600 MHz, CDCl3) δ 6.75 – 6.68 (m, 3H), 5.93 (d, *J* = 2.7 Hz, 1H), 5.93 (s, 1H), 5.41 (d, *J* = 9.7 Hz, 1H), 5.37 (d, *J* = 8.3 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.12 – 2.97 (m, 1H), 2.96 – 2.87 (m, 1H), 2.09 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.85, 204.72, 164.01, 163.55, 148.02, 147.38, 131.27, 130.40, 121.65, 121.49, 108.60, 108.53, 108.35, 101.28, 91.30, 91.21, 53.68, 53.53, 45.58, 45.07, 41.21, 41.08, 30.39, 30.28, 29.70.

3.7 Conclusions and outlook.

It was demonstrated that the reagent **19** serves as a general aldehyde homologating reagent for the facile synthesis of MVKs under very mild conditions. The short reaction times and operational simplicity of the methodology allow for the synthesis of libraries of MVKs which are themselves useful substrates for the synthesis of natural products.

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4.0 TOTAL SYNTHESIS OF OLIVETOL AND DERIVATIVES STARTING FROM A COMMON METHYL VINYL KETONE PRECURSOR

The contents of this chapter also appear in:

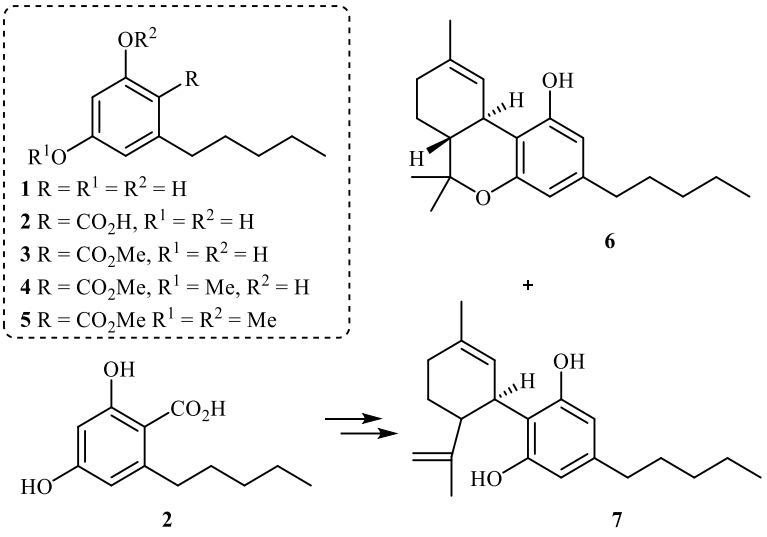
David Hurem, Benjamin J. Macphail, Rina Carlini, Jason Lewis, James McNulty, SynOpen 2021; 05(01): 86-90

4.1 Introduction.

Resorcylates such as orcinol (3,5-dihydroxytoluene) and olivetol **1** (Scheme 46) form the central core of many condensed polyketide aromatic natural products and higher analogs. These include methylated derivatives and dimers such as griseofulvin, usnic acid and alternariol, as well as the large class of prenylated meroterpenoid natural products. Of notable significance among the latter class are the phytocannabinoids isolated from *Cannabis sativa.* Over 100 such phytocannabinoids, including (-)-*trans*-Δ^9-tetrahydrocannbinol **6** (THC) and (-)-cannabidiol **7** (CBD) have been identified[1d] among almost 600 natural products that have been profiled in cannabis extracts.[1e] While much attention has focused on the pharmacological properties of THC **6**,[1f] CBD **7**[1g] and cannabinol,[1h] a wide range of biological activities continues to be reported for these and the lesser known cannabinoids.[1,2] The natural products are biosynthesized through geranylation of 5-alkyl resorcinol carboxylic acid derivatives such as orsellinic acid and olivetolic acid **2**. Olivetolic acid is thus a central intermediate in the biosynthesis of the phytocannabinoids, while olivetolic acid and more commonly olivetol are crucial building blocks in the chemical synthesis of phytocannabinoids and analogs. Efforts in the chemical synthesis of these phytocannabinoids and similar meroterpenes have therefore historically and continue to involve the regioselective terpenylation of olivetol **1**.[3]

We became interested in the synthesis of 5-alkylresorcinols such as olivetol and olivetolic ester derivatives for several reasons. Recently, olivetol and olivetolic acid derivatives have been

shown to modulate (selective agonists or antagonists) the pharmacology of human cannabinoid CB_1 and CB_2 receptors,[4a,b]

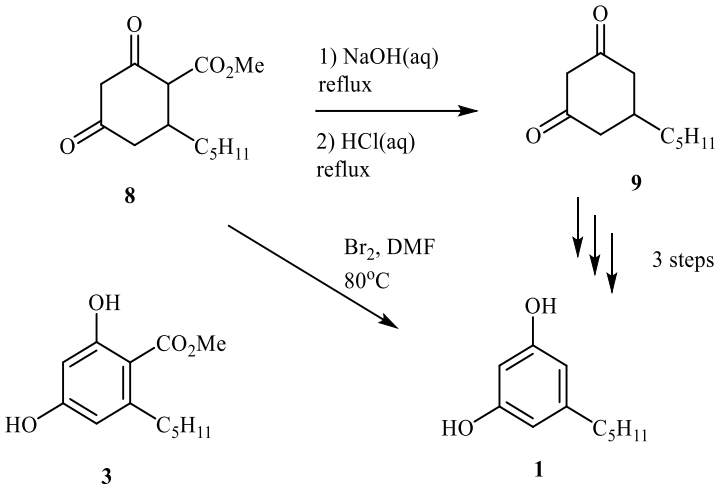


Scheme 46. Polyketide precursors in the chemical and biological synthesis of phytocannabinoids.

and cannabidiolic acid analogs have been shown to exhibit anticonvulsant activity in a mouse model of Dravet syndrome.[4c] It has also been shown that variations in the length and branching of the C5-substituent on the olivetol fragment can have significant effects on the potency of the derived cannabinoids.[1d,4d,e,f] The regioselective terpenylation of olivetolic ester derivatives has been shown to proceed with very high regioselectivity in favour of the natural meroterpenoid cores. [5e,f] The various synthetic efforts towards olivetol **1**[5] require the use of stoichiometric oxidants, such as elemental bromine, under harsh conditions that do not permit access to olivetolate esters, which are otherwise not commercially available. In this communication, we

report a short synthesis of olivetol **1** through a mild, atom-economical oxidative process catalytic in iodine as well as methyl olivetolate **3** and the orthogonally methylated ether analogs **4**-**5**.

The most efficient synthesis of olivetol **1** to date involves preparation of the cyclic diketo ester **8** and subsequent saponification/decarboxylation to diketone **9**. Intermediate **8** (or less efficiently **9**) is then converted to olivetol through thermolysis is DMF using a stoichiometric amount of bromine (Scheme 47).[5a]

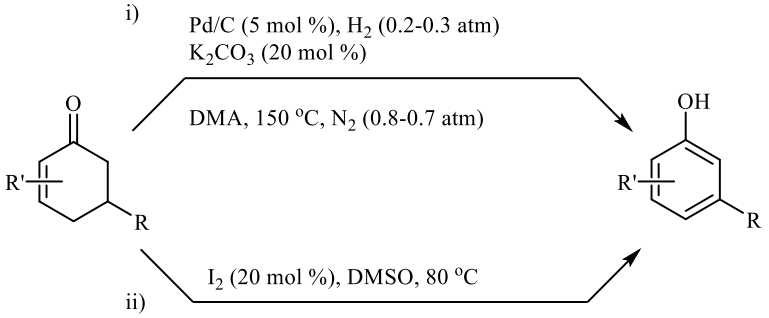


Scheme 47. Previous routes to olivetol and olivetolic acid methyl ester.

The oxidation process required forcing conditions which must be controlled carefully to limit the formation of over brominated aromatic by-products.[5b] Although other routes have been reported, they generally suffer from either high cost of starting materials, such as 3,5-dimethoxybenzene or 3,5-dimethoxybenzoic acid, or employ techniques that are operationally prohibitive at

scale.[5b-f] Olivetolic acid or ester derivatives such as **3** are not directly obtained in this method but may be subsequently accessed from olivetol **1** *via* ortho-lithiation and carbonylation of the its dimethyl ether derivative,[5h] or via other more complex routes.[5e]

Oxidative aromatization (dehydrogenation) of cyclohexanones as a method for synthesis of arenes, including phenols, has been investigated for decades, and has received recent renewed interest (Scheme 48).[6]



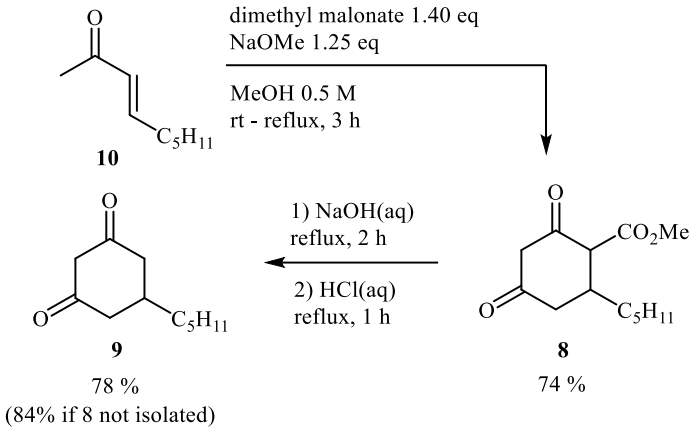
Scheme 48. Methods for catalytic oxidative aromatization.

Catalytic dehydrogenation of cyclic enones using palladium on carbon was reported to afford phenols with varying degrees of success (Scheme 48, i).[7] However, the use of transition metal catalysts in the late stage of olivetol synthesis was considered not ideal for the purpose of this synthetic effort due to issues of cost (Pd) and possible transition-metal contamination in the products. In a different report, the oxidative aromatization of enones to the corresponding phenols using a catalytic quantity of iodine and DMSO as the terminal oxidant was reported (Scheme 48, ii).[8] An earlier report described the use of excess iodine (2.00 equivalents) to give a

5-methyl resorcinol monomethyl ether from a cyclic diketone similar to **9**.[9] We therefore hypothesized that the redox equivalent 1,3-diketones, **8** and **9**, could be oxidized using catalytic quantities of iodine in DMSO to afford alkyl resorcinols and resorcylate esters, while resorcinol monomethyl ethers could be expected in alcoholic solvents. Olivetol and a set of analogues that represent useful synthetic intermediates towards the synthesis of various cannabinoids were synthesized using I_2/DMSO as a method for catalytic oxidative aromatization.

4.2 Synthesis of olivetol and olivetolic acid methyl ester.

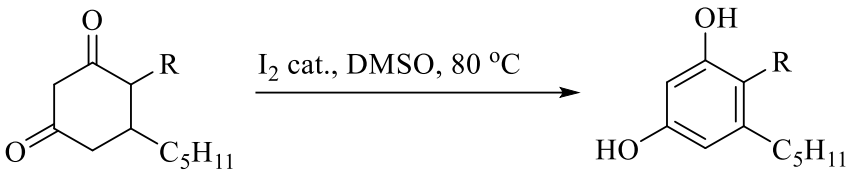
The syntheses of the cyclic diketo-ester **8** and diketone **9** were accomplished as previously outlined by Focella *et al*.[5a] The isolation of both intermediates was explored and it was found that both **8** and **9** could be isolated by precipitation from the corresponding reaction mixtures, and that the entire sequence can be carried through sequentially to obtain **9** in 84 % isolated yield over three steps (Scheme 49).



Scheme 49. Synthesis of diketone intermediates.

Turning to the oxidation/aromatization process, we initially focussed on the ester derivative **8**. To our delight, oxidative aromatization was observed to proceed smoothly using a catalytic quantity (20 mol%) of molecular iodine in dimethyl sulfoxide (DMSO) giving methyl olivetolate **3** in 88% isolated yield (Table 9, entry 1).

Table 9. Catalytic oxidation of ketones.



8 R = CO_2CH_3
9 R = H

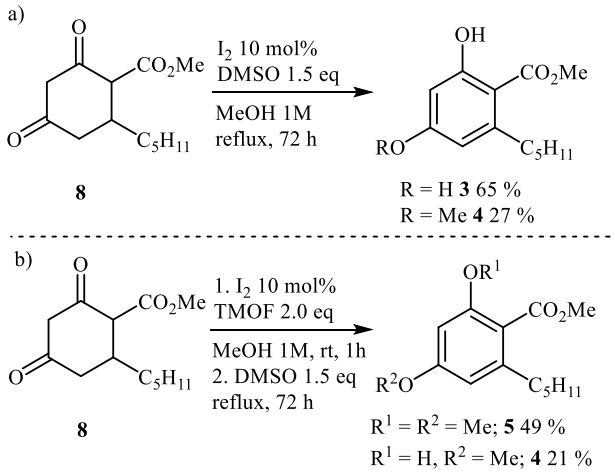
3 R = CO_2CH_3
1 R = H

Entry	Substrate	Concentration (M)	Loading (mol %)	Time (h)	Yield (%)
1	**8**	0.5	20	24	88
2	**8**	6.0	14	24	88
3	**8**	1.0	10	20	87
4	**9**	6.0	10	27	48

The reaction was equally successful at higher concentrations (Table 9, entry 2) requiring less solvent use, and the loading of the catalytic amount of iodine could be lowered to 10% (Table 9, entry 3) with no detriment to yield. The reaction appeared to be incredibly robust with respect to concentration and catalyst loading. The aromatic methyl ester (**3**) was readily isolated by solvent partition (EtOAc) from aqueous sodium thiosulfate, filtration through a short silica-gel plug and removal of solvent, yielding the desired product as a slightly yellow crystalline solid. Conditions to effect oxidation of **9** were similarly developed (Table 9, entry 4) leading to olivetol **1**. The conversion could be effected in high yield. Work-up as before and removal of solvent yielded olivetol **1** in high yield. Purification *via* high vacuum distillation resulted produced highly pure olivetol **1**, isolated in 48 % yield as a colorless crystalline solid.

4.3 Synthesis of *O*-methylated derivatives of olivetolic acid methyl ester.

Aromatization in the presence of methanol was next explored as method of obtaining methylated derivatives of **3** (Scheme 50).



Scheme 50. Synthesis of methylated derivatives.

To this end, it was found that selective methyl ether formation could be accomplished by using methanol as a solvent with a stoichiometric amount of DMSO and catalytic iodine (Scheme 50, a). This procedure results in formation of methyl olivetolate **3** and the mono methyl ether **4**, in a 70:30 ratio, readily separable using flash column chromatography resulting in the efficient isolation of **3** (65%) and **4** (27%). Various modification of these reaction conditions did not appear to have a noticeable effect on the overall ratio of products observed. We postulated that enol ether hydrolysis (vinylogous ester) may be taking place during the aromatization process. In order to limit this potential, trimethyl orthoformate (TMOF) was used (Scheme 50, b) to

dramatic effect. In this case the mono methyl ether **4** and methyl olivetolate-dimethyl ether **5** were obtained in high yield and no trace of methyl olivetolate **3** observed. The orthogonally protected methyl olivetolates were readily separable using silica-gel flash chromatography resulting in the efficient preparation of **5** (49%) and **4** (21%) in high isolated yields. This method represents a simple alternative to *O*-methylation of the resorcylates using dangerous methylating agents and permits selective access to the orthogonally protected methyl olivetolate mono- and dimethyl ethers in 100-200 mg quantities at the scale reported herein.

4.5 Experimental.

Methyl 2,4-dioxo-6-pentylcyclohexanecarboxylate (8): To a solution of dimethylmalonate (12 mL, 100 mmol) in methanol (20 mL) was added a 25 wt% solution of sodium methoxide in methanol (20 mL, 89 mmol). To the resulting solution was added (*E*)-3-nonen-2-one (**8**) (12 mL, 70 mmol) over 0.5 h with vigorous stirring. The pale-yellow slurry was heated at reflux over 3 h under a nitrogen atmosphere. Upon cooling, the resulting yellow solution was cooled to room temperature then methanol was removed using a rotary evaporator with heating not exceeding 40 ℃. The pale-yellow solid was added water (70 mL) and diethyl ether (10 mL) and the mixture was stirred until no visible solid remained. The biphasic mixture was extracted with diethyl ether (2 x 50 mL). The clear orange aqueous solution was carefully adjusted to pH 4 with HCl conc. and allowed to stand at room temperature for 12 h. The desired product (**8**) was obtained as a mixture of isomers by vacuum filtration as a white crystalline solid (12.54 g, 74 %). ^{1}H NMR

(600 MHz, $CDCl_3$) δ 5.48 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.68 (dd, J = 17.2, 0.8 Hz, 1H), 3.45 (d, *J* = 6.7 Hz, 1H), 3.39 (d, *J* = 17.2 Hz, 1H), 3.17 (d, *J* = 10.0 Hz, 1H), 2.84 (dd, *J* = 15.4, 4.5 Hz, 1H), 2.61 (dd, *J* = 17.5, 4.8 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.43 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.19 (dd, *J* = 17.5, 9.9 Hz, 1H), 1.46 – 1.17 (m, 8H), 0.87 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.69, 202.36, 198.93, 191.19, 185.55, 171.94, 171.32, 169.34, 167.94, 103.98, 102.84, 60.78, 57.53, 56.86, 52.78, 52.38, 51.80, 44.03, 43.12, 42.62, 36.24, 35.71, 34.73, 33.77, 33.48, 33.41, 31.75, 31.62, 31.57, 31.34, 26.57, 25.95, 25.85, 22.47,22.38, 13.96, 13.91.

5-Pentylcyclohexane-1,3-dione (9): To a solution of dimethylmalonate (11.5 mL, 100.4 mmol) in methanol (20 mL) was added a 25 wt% solution of sodium methoxide in methanol (20 mL, 89 mmol). To the resulting slurry was added (*E*)-3-nonen-2-one (11.6 mL, 70.2 mmol) over 0.5 h with vigorous stirring. The pale-yellow slurry was heated at reflux over 3 h under a nitrogen atmosphere. The resulting yellow solution was cooled to room temperature whereupon the methanol was removed using a rotary evaporator with heating not exceeding 40 ^oC. The resulting yellow solid was dissolved in 20 wt% sodium hydroxide solution (70 mL) then heated at reflux over 2.5 h. The solution was cooled to room temperature, then extracted with diethyl ether (2 x 50 mL). To the aqueous solution was added HCl until rapid gas evolution was observed (30 mL), the effervescent, clear yellow solution was heated at reflux over 1 h. the aqueous solution was slowly acidified with HCl conc. to the first appearance precipitate (pH 5) and left to stand over 12 h. The desired product (**9**) was obtained by vacuum filtration, then drying under high vacuum (~0.1 mmHg) to afford a light pink solid as a mixture of tautomers (10.88 g, 84 %). ^1H NMR

(600 MHz, $CDCl_3$) δ 5.49 (s, 1H), 3.66 (s, 1H), 3.37 (s, 2H), 2.73 (dd, *J* = 15.5, 3.8 Hz, 1H), 2.45 (d, *J* = 12.5 Hz, 1H), 2.36 (dd, *J* = 15.4, 10.3 Hz, 1H), 2.20 – 1.98 (m, 2H), 1.45 – 1.19 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.84, 191.74, 104.24, 57.99, 46.39, 38.82, 35.44, 35.21, 33.75, 31.76, 31.57, 30.66, 26.26, 26.21, 22.56, 22.48, 14.01, 13.96.

Olivetol (1): To solution of **9** (10.88 g, 59.7 mmol) in DMSO (10 mL) was added iodine (0.4837 g, 1.9 mmol) and the brown solution was stirred in an 80 °C bath over 27 h. The reaction mixture was diluted with ethyl acetate (100 ml) then extracted with 0.1 M sodium thiosulfate (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), Organic fractions were pooled, concentrated in vacuo to afford a viscous dark red liquid. The crude material was distilled under reduced pressure (~0.1 mmHg, 80 °C) to afford olivetol **1** as a white crystalline solid (5.051 g, 48 %). ^1H NMR (600 MHz, $CDCl_3$) δ 6.26 (d, *J* = 2.1 Hz, 2H), 6.18 (t, *J* = 2.2 Hz, 1H), 5.01 (s, 2H), 2.51 – 2.44 (m, 2H), 1.61 – 1.53 (m, 2H), 1.40 – 1.21 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.46, 146.26, 108.16, 100.20, 35.79, 31.46, 30.72, 22.53, 14.02.

Methyl olivetolate (Methyl 2,4-dihydroxy-6-pentylbenzoate) (3): To a solution of **8** (6.9391 g, 28.87 mmol) in DMSO (7 mL) was added iodine (1.0236 g, 4.03 mmol) and the brown solution was stirred in an 80 °C bath over 24 h. The reaction mixture was diluted with ethyl acetate (70 mL), then extracted with 0.1 M sodium thiosulfate (3 x 10 mL), then water (10 mL). Organic solution was concentrated in vacuo to afford a viscous dark red liquid. The crude material was passed through a plug of silica, using hexanes – ethyl acetate (4:1) to elute. The eluent was

concentrated and dried under reduced pressure (~0.1 mmHg) to afford the desired product (**3**) as a pale-yellow crystalline solid (6.050 g, 88 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.78 (s, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 3.92 (s, 3H), 2.81 (dd, *J* = 8.9, 6.8 Hz, 2H), 1.58 – 1.47 (m, 2H), 1.39 – 1.28 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.03, 165.08, 160.59, 149.00, 110.96, 104.91, 101.39, 51.95, 36.81, 32.07, 31.47, 22.51, 14.07.

Methyl 2-hydroxy-4-methoxy-6-pentylbenzoate (4): To a round bottom flask charged with methanol (4 mL) was added **8** (480.6 mg, 2.00 mmol), iodine (100.0 mg, 0.394 mmol) and DMSO (234.0 mg, 3.00 mmol) and the mixture was heated at reflux over 72 h until disappearance of **8** was observed. The reaction mixture was quenched with dropwise addition of $Na_2S_2O_3$ (0.1 M, 10 ml), then extracted with hexanes (3 x 5 mL). The combined organic fractions were washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated to give a light-yellow oil. The crude mixture was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give **4** as a colourless oil (138.2 mg, 27 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.73 (s, 1H), 6.32 (d, *J* = 2.6 Hz, 1H), 6.28 (d, *J* = 2.6 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 2.85 – 2.81 (m, 2H), 1.56 – 1.48 (m, 2H), 1.35 – 1.31 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.98, 165.59, 163.97, 148.04, 110.60, 104.59, 98.75, 55.20, 51.78, 36.89, 32.08, 31.55, 22.52, 14.06.

Methyl 2,4-dimethoxy-6-pentylbenzoate (5): To a round bottom flask charged with methanol (4 mL) was added **8** (481.0 mg, 2.00 mmol), iodine (101.2 mg, 0.399 mmol) and trimethyl

orthoformate (0.8 mL, 8.0 mmol). The solution was stirred under nitrogen, at room temperature, over 1 h, until consumption of **8** was observed. DMSO (234.1 mg, 3.00 mmol) was added and the mixture was heated at reflux over 72 h. The reaction mixture was quenched with dropwise addition of $Na_2S_2O_3$ (0.1 M, 10 mL), then extracted with hexanes (3 x 5 mL). The combined organic fraction was washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated to give a light-yellow oil. The crude mixture was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give **4** as a colourless oil (108.3 mg, 21 %) and **5** as a colourless oil (210.9 mg, 49 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.33 (d, *J* = 2.1 Hz, 1H), 6.31 (d, *J* = 2.2 Hz, 1H), 3.88 (s, 1H), 3.81 (s, 1H), 3.79 (s, 1H), 2.56 – 2.51 (m, 1H), 1.61 – 1.54 (m, 1H), 1.33 – 1.29 (m, 1H), 0.88 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.98, 161.40, 157.99, 143.10, 116.20, 105.83, 96.09, 55.84, 55.31, 52.03, 33.90, 31.68, 30.86, 22.43, 13.96.

4.6 Conclusions and outlook.

In conclusion, the synthesis of olivetolic acid methyl ester (**3**) was achieved in 65 % isolated yield in two steps from the cyclic diketone **8** employing an oxidative aromatization strategy catalytic in iodine in DMSO. Similarly, a synthesis of olivetol (**1**) was achieved in 40 % yield over two steps from diketone **9** using this method. Process methods were developed that allow isolation of both products without the use of preparative chromatography. The oxidative aromatization reaction performed in the presence of methanol and, more strikingly trimethylorthoformate, resulted in the development of efficient routes to the mono- (**4**) and

dimethyl (**5**) ethers of methyl olivetolate. These results demonstrate the success of the catalytic oxidative aromatization synthetic route to olivetol and orthogonally protected methyl olivetolate ethers. The selective oxidative aromatization proceeds with no detectable over halogenation[5a,b] and process routes developed provide the products with high mass balance. The compounds prepared here provide a valuable platform for the synthesis of other resorcylates and to access resorcinol and olivetol derivatives with variable length alkyl chains.

4.7 References.

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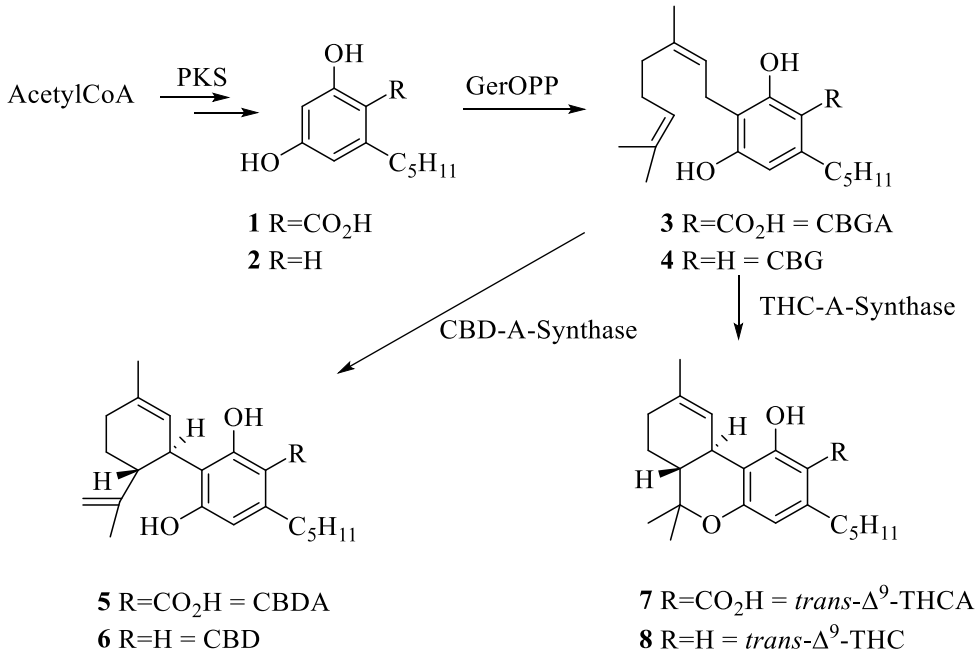
5.0 SYNTHESIS OF CANNABINOLIC ACID METHYL ESTER USING HETEROGENOUS ORGANOCATALYSIS.

5.1 Introduction.

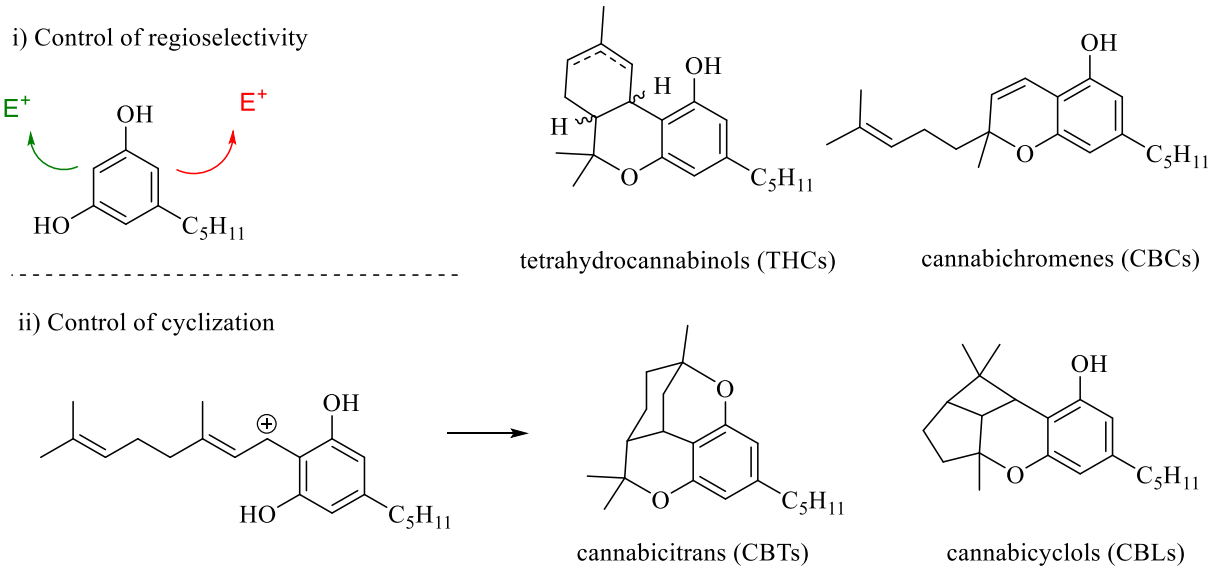
Since the initial discovery of meroterpene phytocannabinoids of *Cannabis sativa*,[1-4] a substantial body of research has emerged over the years.[5] In recent times interest in this class of compounds, driven by economic incentives and potential for therapeutic applications, has helped to provide a sophisticated understanding of their biosynthesis,[5-9] and biological activities.[10-18] This research has, both directly and indirectly, produced a range of chemical synthesis efforts of both natural and non-natural cannabinoids.[19-39]

The cannabinoid natural products are produced *via* the general biosynthetic mechanism shown (Scheme 51). The pathway involves the assembly and cyclization of a linear hexaketide to olivetolic acid (**1**).[5] Alkylation of **1** with geranyl pyrophosphate (GerOPP) forms the linear meroterpene cannabigerolic acid (**3**), which is a common precursor to the over 60 cannabinoids produced by the plant. Cyclization *via* benzylic oxidation followed by spontaneous decarboxylation afford the major cannabinoids cannabidiol (CBD, **6**) and Δ^9-tetrahydrocannabinol (THC, **8**). The cyclization of CBD is mediated by separate enzymes and CBD and THC are not biochemically interconvertible,[6] although the chemical conversion is known to occur under acidic conditions.[5, 21]



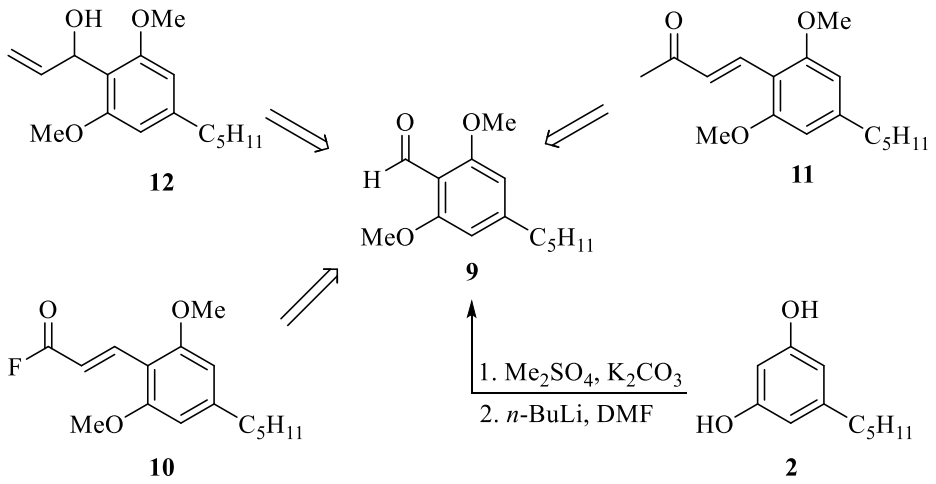
Scheme 51. Biosynthesis of *trans*-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

A biomimetic approach to the synthesis of these phytocannabinoids would potentially provide access to not only the major natural products with well established biological activities **8** and **9**,[10-18] but also of the biosynthetic precursors and less common cannabinoids that exist in low concentrations in the plant. Several obstacles were identified regarding a biomimetic approach from the total synthesis efforts of the past: (i) regioselective alkylation of olivetol,[28,30,31] (ii) selectivity of the oxidative cyclization of the linear meroterpene cannabigerol (CBG, **4**) (Scheme 52).[28-31]



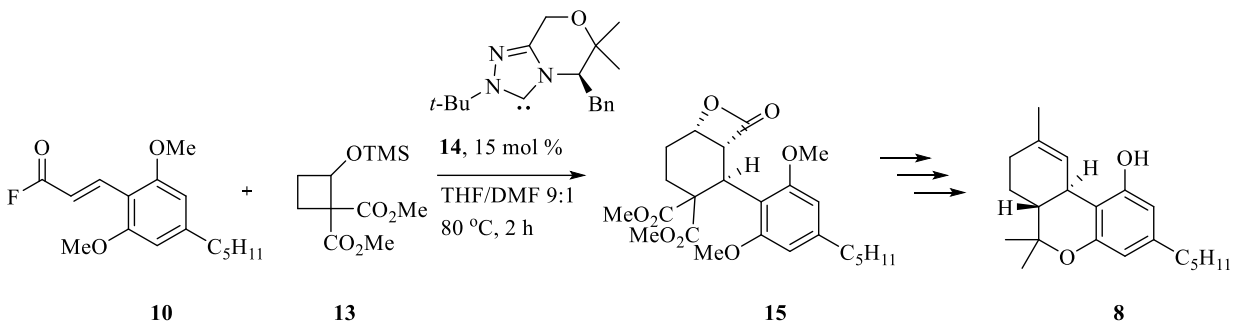
Scheme 52. Problems associated with biomimetic cannabinoid synthesis.

Dimethylation of olivetol (**2**), followed by formylation *via* directed lithiation has been used in non-biomimetic syntheses to circumvent the problem of regioselective terpenylation of olivetol (Scheme 53).[24-27] Functionalization to the benzaldehyde **9** allowed for sequential construction of the terpene carbon framework through intermediates **10**,[27] **11**[26] and **12**.[25]



Scheme 53. Synthesis of precursor **9** as a common starting material for sequential synthesis of terpene portion of THC.

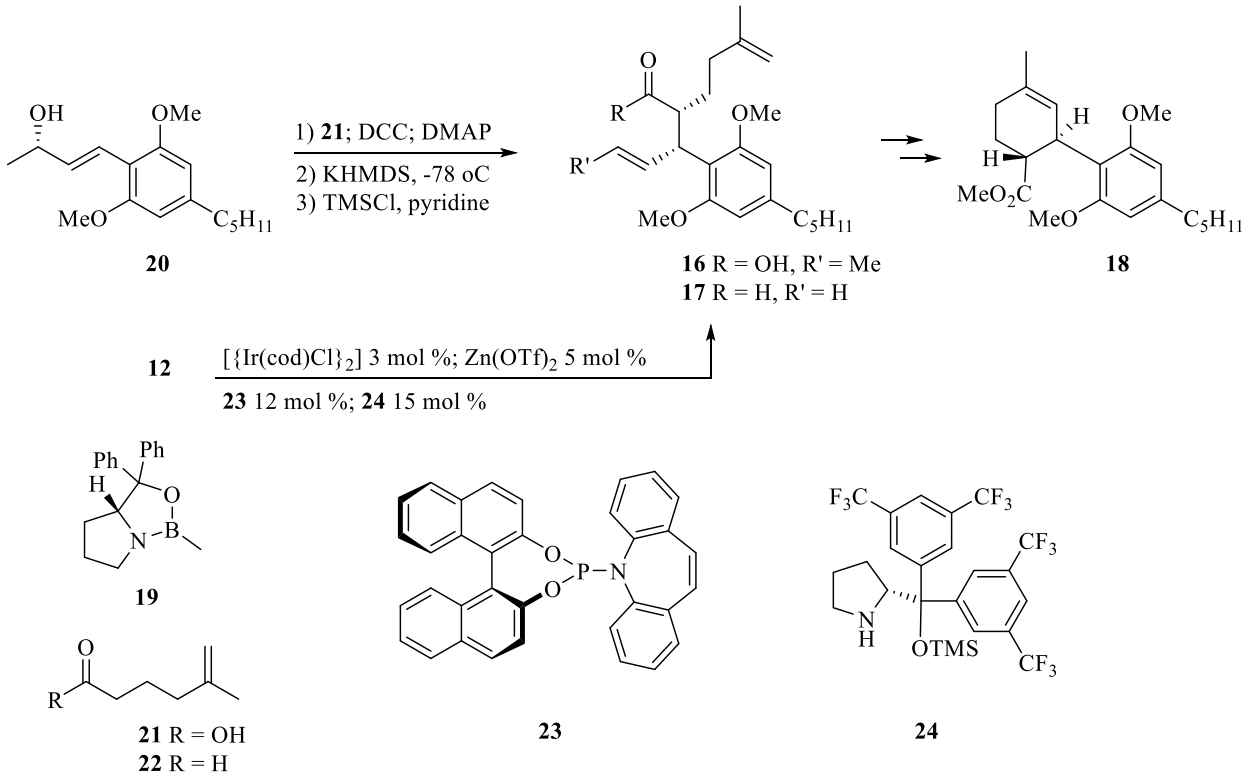
The problem of selective cyclization of the linear meroterpene has generally been avoided in total synthesis efforts by sequential construction of the menthyl framework from modified olivetol derivatives derived from **9** (Scheme 53).[24-27] One method involved asymmetric annulation of **10** with the opening of cyclobutane **13** using a chiral *N*-heterocyclic carbene (NHC) **14** catalyst to afford the advanced intermediate **15** (Scheme 54).[27] Intermediate **15** was then carried forward over six steps to THC (**8**).



10 **13** **15** **8**

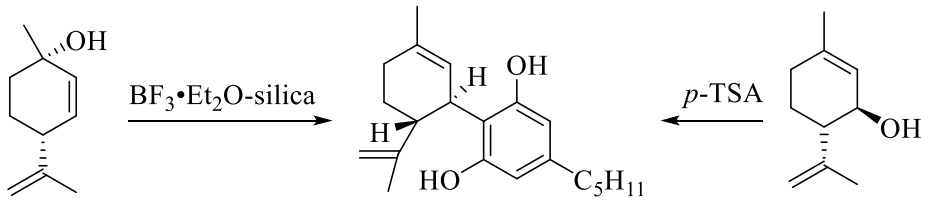
Scheme 54. Synthesis of THC by chiral NHC-catalysis.

A second strategy relied on the cyclization of **16** or **17** by way of ring closing metathesis to give the common cyclic intermediate **18** that was carried forward to THC through a series of demethylations and Grignard additions (Scheme 55).[25,26] In the first case, asymmetric reduction of a vinyl ketone **11** using a chiral oxazaborolidine **19**, afforded the chiral allylic alcohol **20**.[26] Esterification of acid **21** followed by Ireland-Claisen rearrangement gave intermediate **16**. A second strategy gave **17** directly by way of asymmetric α-allylation of aldehyde **22** with racemic allyl alcohol **12** using a chiral iridium complex formed with ligand **23** in conjunction with a chiral secondary amine **24**.[25] The latter strategy was applied to the stereodivergent synthesis of all four stereoisomers of THC by varying the stereochemistry of **23** and **24**.[25]



Scheme 55. Synthesis of common intermediate **18**.

A different strategy involved the synthesis of a chiral cyclic building block, obtained either from the chiral pool (**25**)[22] or from the asymmetric cyclization of neral (**26**),[23] which was then used to alkylate olivetol directly by activation with acid (Scheme 56). In both cases, yields are low and undesired alkylation products are formed due to poor regiocontrol of alkylation.[22]



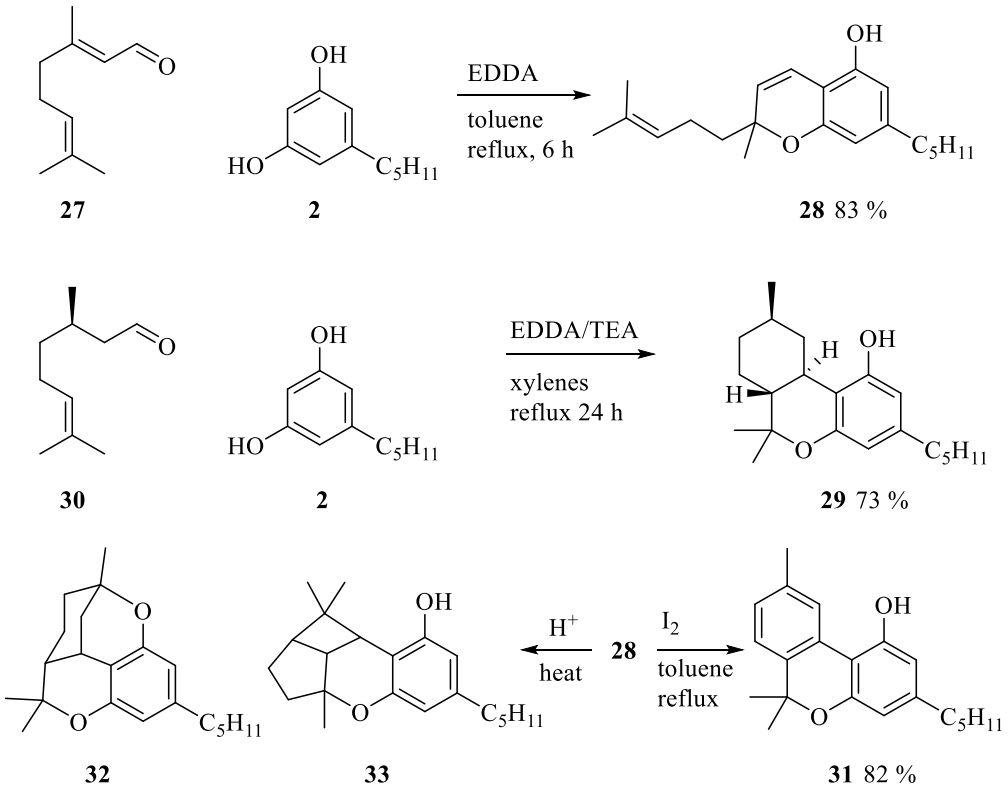
25 **6** **26**

41 % from **25**
35 % from **26**

Scheme 56. Synthesis of CBD by alkylation of olivetol with cyclic terpene alcohols.

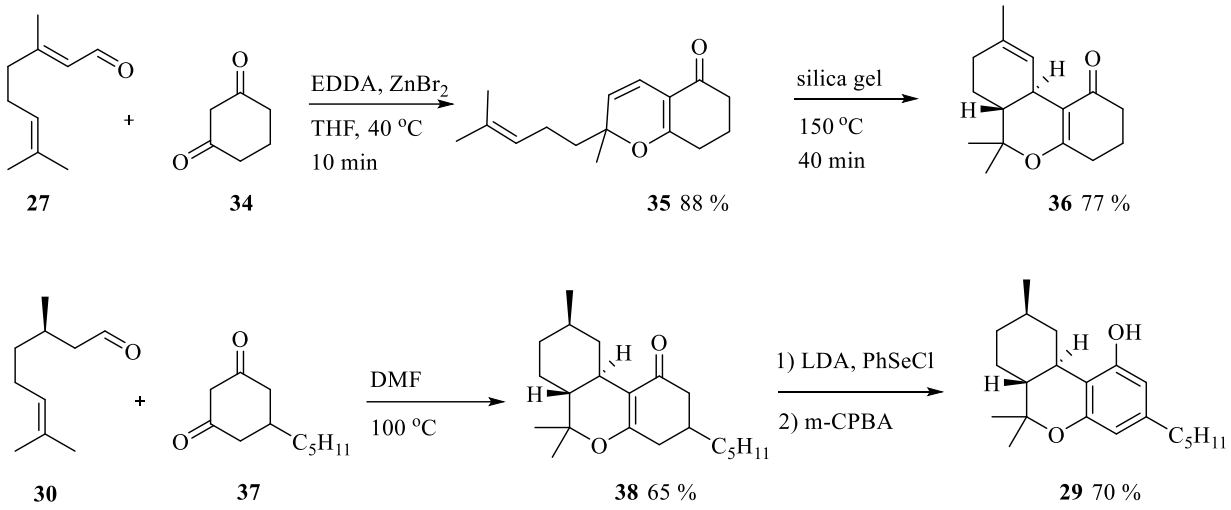
Control of double-bond positional isomers of THC was not of significant interest from a synthetic point of view as the selective isomerization between them by means of addition/elimination sequences has been documented.[36,37]

The existing approaches successfully circumvent the common problems associated with the synthesis of THC and CBD however, they introduce added complexity to the synthetic intermediates and decrease the overall brevity of the synthesis. The condensation and annulation of citral (**27**) with olivetol (**2**), on the other hand, is known to proceed selectively to give the racemic CBC (**28**) with apparent regiospecificity (Scheme 57).[29] This high degree of regiospecificity was exploited in the synthesis of hexahydrocannabinol (**29**) from citronellal (**30**) and olivetol.[32] Acid-mediated thermal isomerization of CBC (**28**) has generally resulted in the formation of undesired by-products.[29,31]The iodine-mediated condensation/annulation afforded the desired cyclization product, but it led to the aromatization of the cyclohexene to yield cannabinol (**31**).[29]



Scheme 57. Reactions of aldehydes with olivetol.

It was demonstrated that the condensation and annulation of citral (**27**) to 1,3-cyclohexadione (**34**), catalyzed by EDDA rapidly afford a non-aromatic CBC-derivative **35** in excellent yield (Scheme 58).[35] Further, it was shown that heating the electrocyclization product with silica gel resulted in a thermal rearrangement favouring the intramolecular oxa-[4+2] pathway to give the product **36** exclusively. Previously, the condensation citronellal (**30**) with diketone **37** directly afforded the non-aromatic derivative **38** which was aromatized by conversion to the selenide, followed by oxidative elimination with *meta*-chloroperoxybenzoic acid (*m*CPBA) to give the hexahydrocannabinol (**29**, Scheme 58).[33,34]



Scheme 58. Reactions of aldehydes with diketone intermediates.

It was postulated that stereoinduction may be accomplished in the thermal rearrangement by use of chiral acidic catalysts in the place of silica, while solid supported amines could allow for catalyst recycling in the condensation reaction. Selective oxidation of the polyketide-derived ring would need to be accomplished in order to access the THC target. Moreover, synthesis of cannabinoid methyl esters, derived from cyclic diketone **40** (Scheme 60),[40] would provide a formal synthesis to both acid and neutral cannabinoids, as both hydrolysis and decarboxylation conditions have been previously reported.[38,39]

5.2 Preparation of modified clays for use as solid-bound organocatalysts.

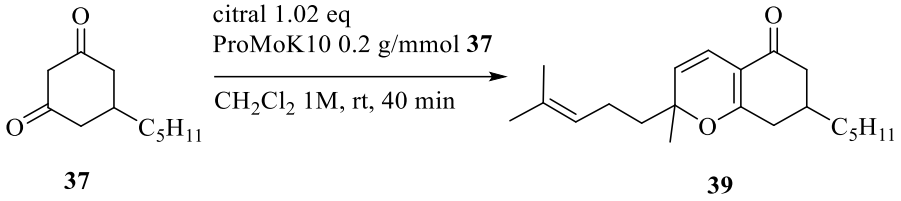
Clay-bound organocatalysts were prepared by adsorption to appropriate clay substrates. A methanolic solution of L-proline (1% w/v) was stirred with montmorillonite K10 (10 % w/v). It

was postulated that montmorillonite K10 (a sulphuric acid-washed aluminosilicate clay) would form an ammonium salt with L-proline. Upon filtration, the solvent was evaporated, and the pot residue was analyzed gravimetrically and by ^{1}H NMR to determine the extent of retention of L-proline on the clay. Gravimetric analysis indicated no dissolved solids were present in the methanolic solution upon filtration. Washing of the pot with deuterated chloroform and analysis of the resulting solution by ^{1}H NMR showed only water and chloroform signals. The solid was purged of volatiles under vacuum and was used in subsequent reactions titled as ProMoK10.

It was postulated that adsorption of a chiral organic acid could be accomplished with a base-washed clay via an acid/base reaction and adsorption of the resulting salt to the polar aluminosilicate surface. To this end, a methanolic solution of (*R*)-camphorsulfonic acid ((*R*)-CSA, 0.5% w/v) was stirred with base-washed bentonite (nanomer® nano clay, 10 % w/v). Upon separation of the solid by vacuum filtration, the solution was evaporated and analyzed gravimetrically to determine the extent of adsorption. Gravimetric analysis indicated no presence of dissolved solids in the filtered methanolic solution. The solid fraction was purged of volatiles under vacuum and the resulting material was used in subsequent reactions titled as CSA-bentonite.

5.3 Terpenylation of diketone precursors using a montmorillonite-bound L-proline catalyst.

Reaction of citral with diketone **37**,[40] in the presence of L-proline, proceeded through Knoevenagel condensation with concomitant annulation to give cyclized intermediate **39**. The product was isolated from the reaction mixture by filtration from the ProMoK10 catalyst. The viscous oil obtained upon removal of volatiles from the extract gave pure **39** as a mixture of diastereomers. Previous reports of reactions with citral and longer chain terpenoid aldehydes have shown that condensation could be achieved using proline, pyrrolidine or EDDA in the presence of an acid catalyst.[31] It has been demonstrated that ProMoK10 functions as a dual catalyst (imminium ion/ H^+) and eliminated the need for a secondary acid catalyst (Scheme 59).

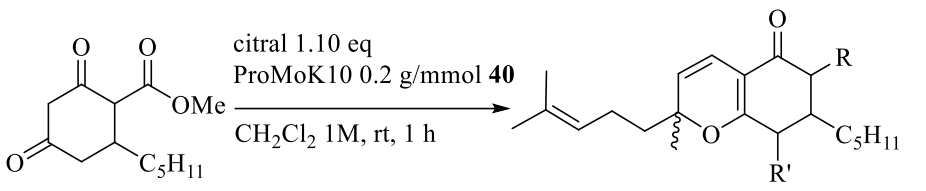


37 **39**

84 % as a mixture of diastereomers

Scheme 59. Reaction of citral with diketoester using ProMoK10.

Similarly, diketoester **40**,[40] was converted to the corresponding dihydrochromenones **41** and **42** under identical reaction conditions. In this case a more complex mixture of positional isomers and diastereomers was obtained (Scheme 60).



40

41 R = CO_2Me, R' = H
42 R = H, R' = CO_2Me
86 % as a mixture of isomers

Scheme 60. Reaction of citral with diketoester using ProMoK10.

The condensation reactions were repeated using previously used catalysts beds in order to investigate the potential for catalyst recycling. In case subsequent reloading of fresh starting material to the previously used catalyst bed had no detrimental effect on reaction yields or product purity (Table 10).

Table 10. Recycling of ProMoK10 in condensation reactions with citral and diketones.

Entry	Diketone	Yield (%)
1	**37**	84
2	**37**	82
3	**37**	85
4	**40**	86
5	**40**	88
6	**40**	86

Reactions were carried out as described in the experimental procedure. The catalyst bed was purged of volatiles under reduced pressure until a free-flowing solid was obtained and used again in subsequent reactions with the same diketone.

5.4 Solvent - free thermal rearrangement and late-stage oxidative aromatization.

Adsorption of chromenone **39** to ProMoK10 followed by heating the mixture to 150 ^{o}C under reduced pressure indicated partial consumption of **39** to a formal retrocyclization – intramolecular hetero-[4+2] cycloaddition product **43** (Figure 2-2). The olefinic signal attributed to 43 matched exactly with that previously reported in literature.[35] In the same report it was observed that the addition of amines to rearrangements mediated by silica gel had inhibited the conversion of starting material.[35] It was postulated that CSA-bentonite could function as a proof of principle as a chiral acid catalyst for this reaction. To this end, **39** was adsorbed to CSA-bentonite (0.1 g/mmol) catalyst and heated at 150 ^{o}C under reduced pressure. Under these conditions a greater conversion of starting material to products **43** and presumably **44** was observed (Figure 2-3). The second signal was assigned as the olefinic proton of **44** by analogy to that of Δ^{8}-THC,[40] this was deemed appropriate as the chemical shift of olefinic signals from 43 matched closely with its aromatic counterpart *cis*/*trans*-Δ^{9}-THC.[35,40] Further increase of catalyst loading to 1 g/mmol indicated complete consumption of starting material with a nearly equal mixture of signals associated with **43** and **44** (Figure 2-4). Only upon increasing of catalyst loading to 2 g/mmol was the conversion of starting material to only **44** observed (Figure 2-5).

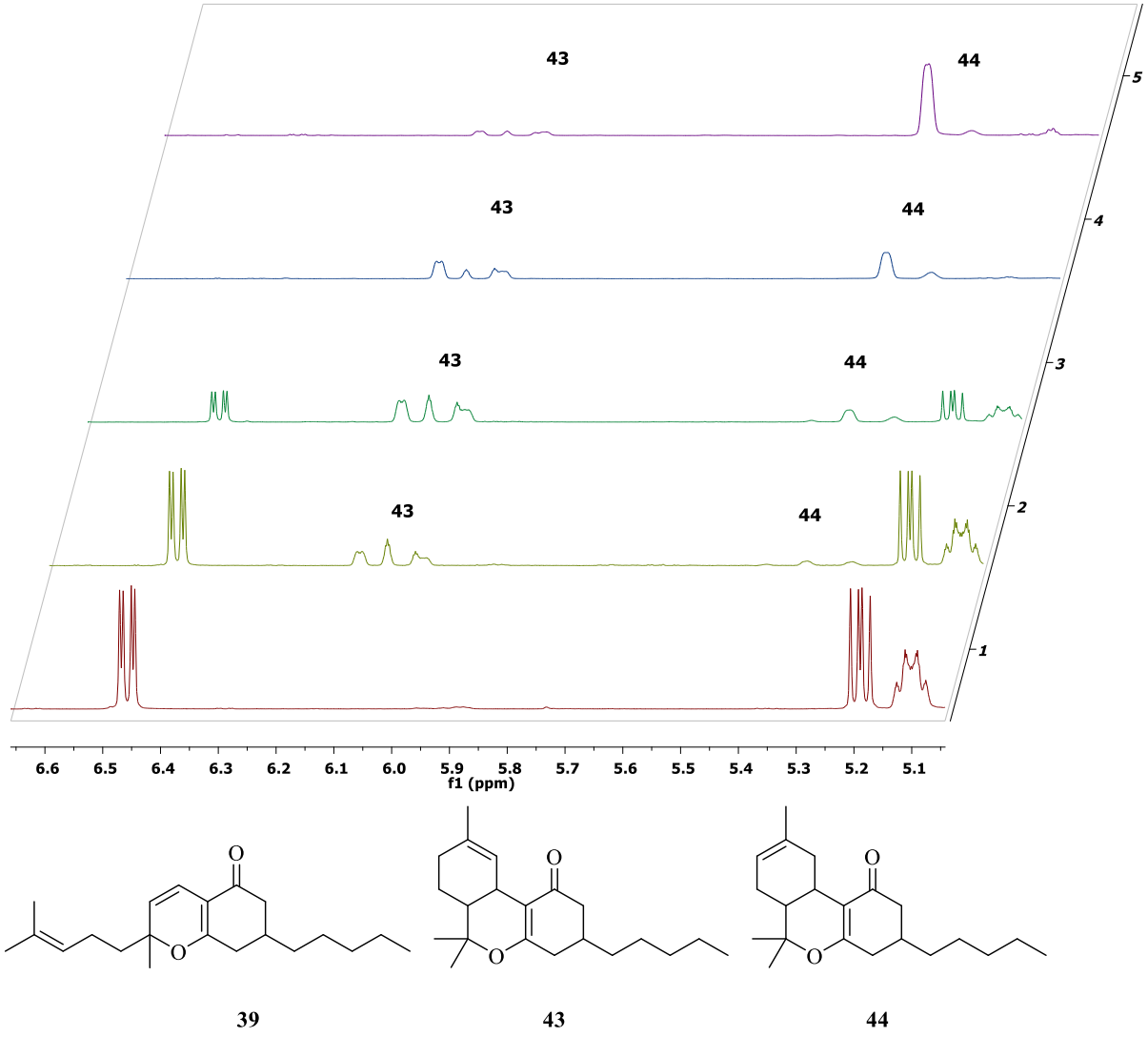
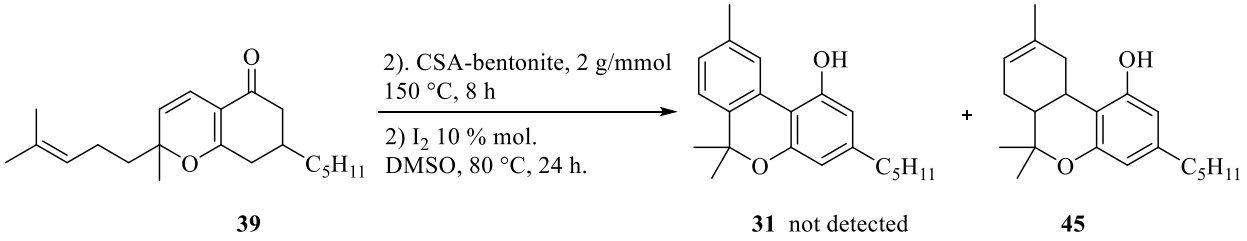


Figure 2. Thermal isomerization of condensation product **39** with chiral acidic catalysts.

Olefinic region of ^{1}H NMR spectra for (1) starting material **39**, (2) for product obtained upon heating with 0.1 g/mmol ProMoK10, (3) product obtained from heating with 0.1 g/mmol CSA-bentonite, (4) product obtained from heating with 1g/mmol CSA-bentonite, (5) product obtained from heating with 2 g/mmol CSA-bentonite.

With established conditions for thermal isomerization of **39**, attention was shifted to the selective aromatization of the polyketide ring. It was found that using catalytic iodine in DMSO led to complete aromatization of the polyketide fragment, while no signals corresponding to cannabinol (**31**) were detected (Scheme 61).



Scheme 61. Thermal rearrangement and aromatization of **39**.

Moreover, signals characteristic to Δ^8-THC (**45**) were present in the ^{1}H NMR spectrum of the crude reaction mass, however the presence of contaminating species did not allow for its effective purification even after exhaustive chromatographic purification (Figure 3). This was consistent with findings that Δ^8-THC did not undergo aromatization to cannabinol (**31**) in the presence of iodine in the same manner as Δ^9-THC.[31]

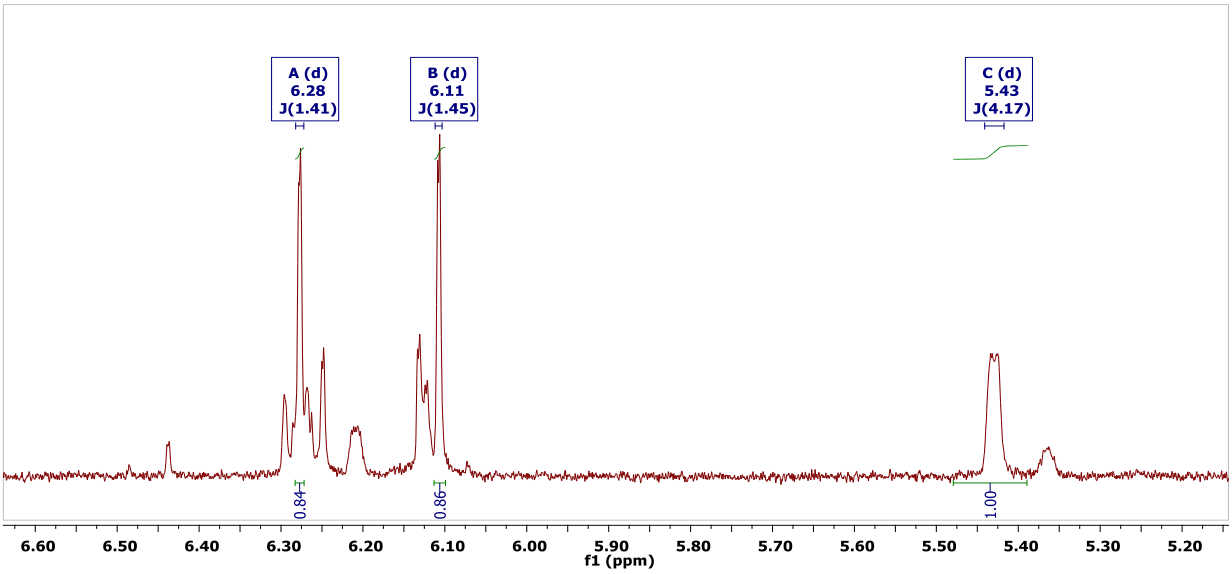
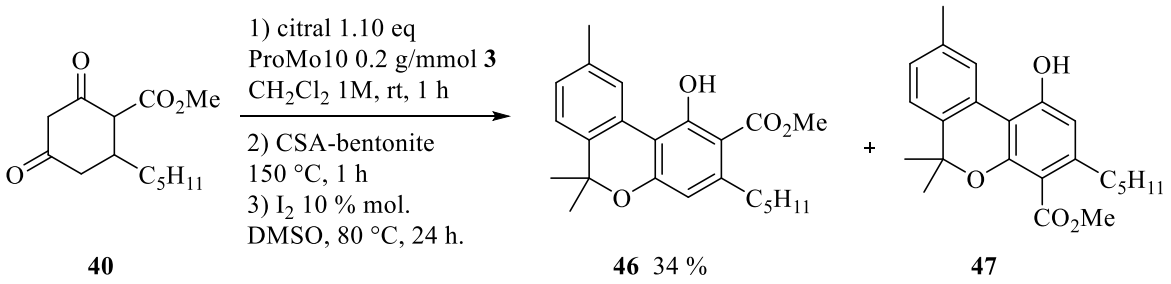


Figure 3. Expanded olefinic region of ^{1}H NMR spectrum obtained from a product isolated from aromatization with I_2/DMSO.

Nevertheless, this result showed that thermal rearrangement followed by selective oxidation of intermediate **39** could be accomplished and sets the groundwork for further investigation.

In an attempt to access methyl ester derivatives of cannabinoids, diketoesters **41** and **42** were transformed to a complex series of isomers by the thermal isomerization procedure described for **39**. However, upon treatment of the resulting complex mixture with iodine/DMSO, two positional isomers of cannabinolic acid methyl esters (**46** and **47**) were formed with the natural isomer **46** isolated in 34 % yield from **40** (Scheme 62).



40 **46** 34 % **47**

Scheme 62. Telescoping sequence for the synthesis of cannabinolate methyl esters.

The difference in the outcome for the oxidation of **39** and the mixture of esters (**41** and **42**) may be attributed to a different rearrangement product. Looking to the crude NMR of the pyrolysis product of **41** and **42** it was noted that the characteristic olefinic protons observed for compounds **43** and **44** (~6.5 ppm and ~5.5 ppm) were not present (Figure 4).

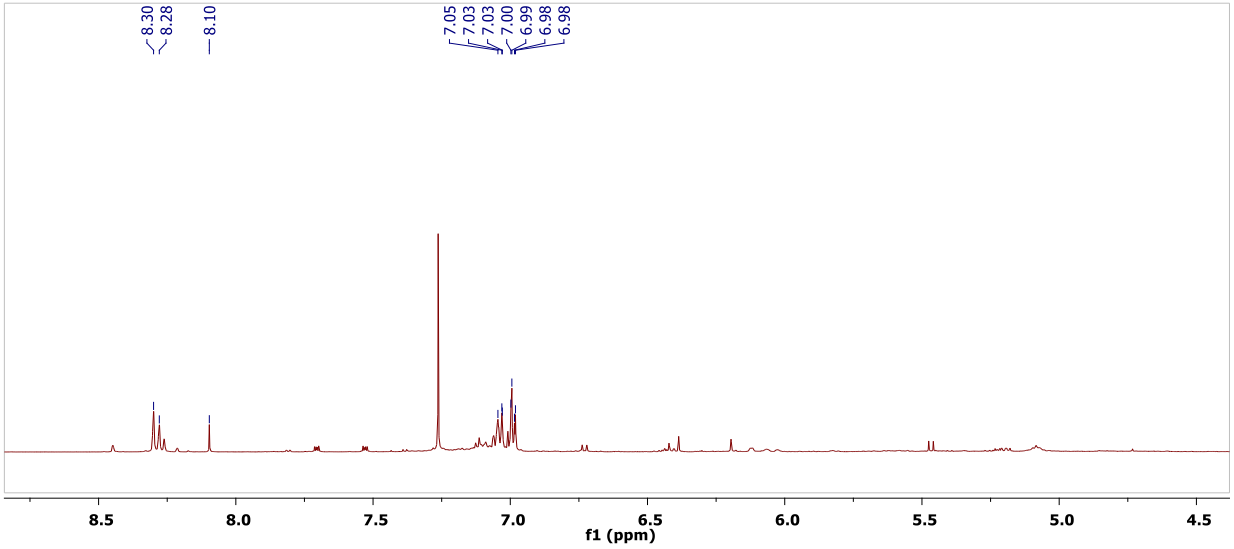
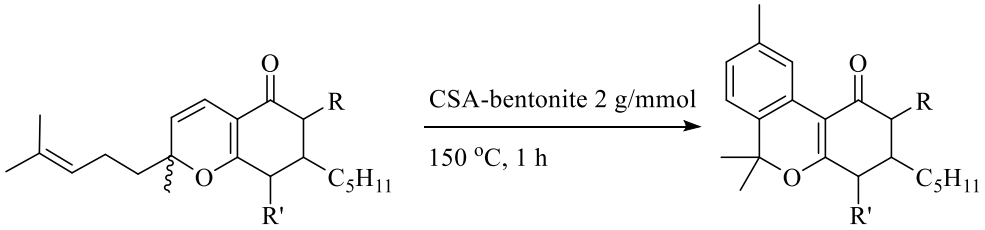


Figure 4. Aromatic and olefinic region of ^{1}H NMR spectrum obtained from thermal isomerization of **41** and **42**.

Instead, signals associated with the aromatic terpene of cannabinolate esters **46** and **47** were observed (8.0-8.3 ppm and ~7.0 ppm), however the signals associated with aromatic proton of the phenolic ring (6.4 ppm) was missing. Based on this information it can be inferred that spontaneous oxidation of the terpene ring had occurred (**48** and **49**, Scheme 63).



41 R = CO_2Me, R' = H
42 R = H, R' = CO_2Me

48 R = CO_2Me, R' = H
49 R = H, R' = CO_2Me

Scheme 63. Proposed spontaneous oxidation of the terpene-derived ring.

This sequence represents a total synthesis of cannabinolic acid methyl ester from readily available starting materials in one pot. Furthermore, methodologies for the hydrolysis and decarboxylation of **46** and **47** have been reported, therefore the reported synthesis is also a formal synthesis of CBN (**31**).[38,39]

5.5 Experimental.

Adsorption of L-proline to montmorillonite K10 (ProMoK10): To a round bottom flask charged with a solution of L-proline (1.0026 g) in methanol (100 mL) was added montmorillonite K10 (10.0167 g). The mixture was stirred at room temperature over 15 minutes.

The contents were filtered through a glass frit and washed with methanol (3 x 10 mL). The liquid was concentrated by rotary evaporator followed by purging of the residue under reduced pressure. The pot residue had no measurable mass and showed no presence of L-proline by ^{1}H NMR in d4-methanol. The solid was dried under vacuum to a constant weight to obtain the ProMo10 catalyst as a free-flowing brown solid (10.7988 g, 98 % mass recovery). The solid catalyst was used in subsequent reactions assuming a 10 % w/w loading of L-proline.

Adsorption of (*R*)-CSA to bentonite clay (CSA-bentonite): To a round bottom flask charged with a solution of (*R*)-CSA (0.0529 g) in methanol (10 mL) was added bentonite clay (1.1103g). The mixture was stirred at room temperature over 15 minutes. The contents were filtered through a glass frit and washed with methanol (3 x 1 mL). The liquid was concentrated by rotory evapourator followed by purging of the residue under reduced vacuum. The pot residue had no measurable mass. The solid was dried under vacuum to obtain the CSA-bentonite catalyst as a free-flowing pink solid (1.1284 g, 97 % mass recovery). The solid catalyst was used in subsequent reactions assuming a 5 % w/w loading of (*R*)-CSA.

2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2,6,7,8-tetrahydro-5*H*-chromen-5-one (39): To a solution of 5-pentylcyclohexane-1,3-dione (182.2 mg, 1.00 mmol) and citral (155.6 mg, 1.02 mmol) in dichloromethane (1 mL) was added ProMo10 (202 mg). The mixture was stirred under argon over 40 minutes at room temperature. The solid was allowed to settle and the liquid phase was decanted over a plug of celite. The solid phase was further extracted with

dichloromethane (5 x 4 mL). the combined solutions were dried (Na_2SO_4), concentrated and volatiles were removed under vacuum to afford a viscous pale-yellow oil (266.5 mg, 84 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.44 (d, *J* = 10.1 Hz, 1H), 6.43 (d, *J* = 10.1 Hz, 1H), 5.18 (d, *J* = 10.1 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 2.47, 2.42 (d, *J* = 12.1, 17.4 Hz, 2H), 2.18 – 1.95 (m, 5H), 1.77 – 1.65 (m, 1H), 1.67, 167 (s, 3H), 1.59, 1.58 (s, 3H), 1.62 – 1.53 (m, 1H), 1.40 – 1.23 (m, 8H), 1.39, 1.33 (s, 3H) 0.88 (t, *J* = 6.8 Hz, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.84, 194.76, 171.61, 171.50, 131.97, 123.68, 121.58, 121.55, 116.53, 116.41, 110.07, 109.95, 82.47, 43.15, 41.75, 41.72, 35.69, 35.62, 35.14, 34.99, 33.26, 33.05, 31.75, 27.61, 27.31, 26.18, 26.15, 25.68, 22.76, 22.57, 22.34, 17.64, 14.01; HRMS (ESI): m/z calcd for $C_{21}H_{32}O_2$ $[M+H]^+$ 317.2475, found 317.2474.

methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylate (41) and methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-8-carboxylate (42): To a solution of Methyl 2,4-dioxo-6-pentylcyclohexanecarboxylate **3** (244.3 mg, 1.00 mmol) and citral (171.0 mg, 1.12 mmol) in dichloromethane (1 mL) was added ProMoK10 (225 mg). The mixture was stirred under argon over 1 hour at room temperature. The solid was allowed to settle and the liquid phase was decanted over a plug of celite. The solid phase was further extracted with dichloromethane (5 x 4 mL). the combined solutions were dried (Na_2SO_4), concentrated and volatiles were removed under vacuum to afford a viscous pale-yellow oil (321.6 mg, 86 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.48-6.36 (m, 1H), 5.32 – 5.14 (m, 1H), 5.14 – 4.98 (m, 1H), 3.76-

3.66 (s, 3H), 3.44-3.16 (m, 1H), 2.70 – 2.51 (m, 1H), 2.50 – 2.24 (m, 1H), 2.21 – 2.10 (m, 1H), 2.07 – 1.93 (m, 2H), 1.76 – 1.63 (m, 4H), 1.63 – 1.52 (m, 4H), 1.48 – 1.17 (m, 12H), 0.91 – 0.83 (m, 3H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.33, 189.60, 189.48, 171.20, 171.05, 170.99, 170.92, 165.96, 165.81, 132.08, 132.06, 132.02, 123.64, 123.58, 123.55, 123.53, 122.78, 122.66, 121.96, 121.91, 116.63, 116.22, 116.12, 115.98, 115.92, 110.76, 110.51, 109.36, 109.25, 83.21, 83.06, 83.00, 82.89, 58.98, 58.90, 55.99, 52.32, 52.28, 52.13, 52.11, 51.58, 51.10, 41.76, 41.74, 41.54, 40.05, 39.88, 36.26, 36.03, 35.43, 35.28, 33.96, 33.73, 33.69, 32.79, 32.62, 31.63, 31.61, 31.56, 27.64, 27.44, 27.41, 26.91, 26.24, 26.18, 26.04, 25.83, 25.75, 25.67, 22.71, 22.68, 22.47, 22.38, 22.24, 17.65, 17.63, 13.96; HRMS (ESI): m/z calcd for $C_{23}H_{34}O_4$ $[M+Na]^+$ 397.2349, found 397.2341.

Thermal isomerization general procedure: The appropriate chromenone (**39** or **41**/**42**) was adsorbed to a solid acid catalyst in a microwave vial. The vial was evacuated (0.1 mmHg) and then heated at 150 ^oC over 1 h. The contents of the vial was allowed to cool to room temperature and was then extracted with 5 % EtOAc in hexanes (4 x 10 mL). The extraction solution was filtered through silica and concentrated to give a yellow oil that was taken forward to oxidation without further purification.

Aromatization general procedure: To a screw-cap vial (5 mL) was added a solution of the product obtained from the thermal isomerization procedure in DMSO (1 mL/g) followed by I_2 (10 mol %). The vial was heated at 80 ^oC over 24 h. The contents were allowed to cool and were

then diluted with ethyl acetate (10 ml), then extracted with 0.1 M sodium thiosulfate (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), Organic fractions were pooled, concentrated *in vacuo* to afford a viscous brown oil. The crude oil was purified by column chromatography using silica gel.

methyl 1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene-2-carboxylate (46): A mixture of **41** and **42** (7.8 mg, 0.021 mmol) was adsorbed to CSA-bentonite (44.1 mg) in a 10 mL vial and was allowed to react following the thermal isomerization general procedure (*vide supra*). The yellow concentrate (31.6 mg) was then reacted using the aromatization general procedure (*vide supra*) to give a colourless oil upon column chromatography using a gradient of hexanes to 5% Et_2O in hexanes. (3.1 mg, 40 %): ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.81 (s, 1H), 8.45 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.09 (dd, J = 7.8, 1.0 Hz, 1H), 6.39 (s, 1H), 3.96 (s, 3H), 2.88 – 2.84 (m, 2H), 2.40 (s, 3H), 1.61 (s, 6H), 1.38 – 1.32 (m, 6H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.82, 162.42, 158.33, 147.45, 137.02, 135.89, 127.91, 127.13, 126.89, 122.28, 112.64, 108.97, 105.47, 78.31, 51.99, 37.04, 32.11, 31.31, 29.71, 27.38, 22.55, 21.60, 14.10. Spectral data were in agreement with those previously reported in literature.[38,41] A second fraction (3.6 mg) contained a mixture of isomer **47** and an unidentified impurity (See appendix).

5.6 Conclusions and outlook.

The methyl ester derivative of cannabinolic acid (**46**) was synthesized in a telescoping sequence from citral and diketoester **40** in 34 % overall yield. It was further demonstrated that CSA-bentonite catalyzed the thermal rearrangement of non-aromatic CBC analogue **39** to a non-aromatic Δ^8-THC analogue **44** which was subsequently oxidized to Δ^8-THC (**45**) using catalytic iodine with DMSO. Meanwhile the thermal rearrangement of the ester-containing derivatives **41** and **42** underwent spontaneous oxidation during thermolysis with CSA-bentonite.

Future work would focus on optimizing oxidation conditions such that **44** can be isolated and fully characterized. In the same facet, the oxidation of the Δ^9-THC analogue **36** should be investigated. Furthermore, chiral acid catalysts (i.e., chiral phosphoric acids) for the thermolytic rearrangement of these species should be screened for stereoselectivity.

5.7 References.

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6.0 CONCLUSIONS AND OUTLOOK

In summary, the development of trialkyl phosphine-based homologation methods for the synthesis of unsaturated aldehydes and ketones has been presented and the fundamental importance and utility to organic synthesis has been demonstrated.

It was shown that trialkyl phosphine-derived Wittig reagents can be selectively deprotonated using lithium bases through a pre-complexation interaction with a directing group located up to four carbons from the acidic proton. The results presented here demonstrate that the "complex-induced-proximity effect" concept may be extended to regioselective ylide formation on differentially functionalized phosphonium salts leading to useful, homologated functionalized carbonyl compounds.

Furthermore, a general aldehyde homologating reagent for the facile synthesis of MVKs under very mild conditions was presented. The short reaction times and operational simplicity of the methodology allowed to for the synthesis of a libraries of MVKs and their utility for the synthesis of natural products was demonstrated.

The homologation methodology was applied to the synthesis of olivetol, olivitolic acid methyl ester and methyl ether-containing derivatives using a selective catalytic oxidative aromatization. These results demonstrate the success of the catalytic oxidative aromatization synthetic route to

olivetol and orthogonally protected methyl olivetolate ethers. The compounds prepared here provided a platform for the subsequent synthesis of cannabinoids.

The methyl ester derivative of cannabinolic acid was synthesized in a telescoping sequence from citral. It was further demonstrated that CSA-bentonite catalyzed the thermal rearrangement of a non-aromatic CBC analogue to a non-aromatic Δ^8-THC analogue, which was subsequently oxidized to Δ^8-THC using the aforementioned catalytic oxidative aromatization. Meanwhile the thermal rearrangement of the ester-containing derivatives underwent spontaneous oxidation during thermolysis with CSA-bentonite.

Taken together, fundamental developments in carbonyl homologation methodologies and their applications in synthetic organic chemistry is a powerful strategy for the total synthesis of complex natural products and analogs and permits the detailed exploration of the structural basis for their chemical-biological interactions. This ensures that significant interest will remain in expanding homologation methodology and further applications development in total synthesis and chemical biology for many years to come.

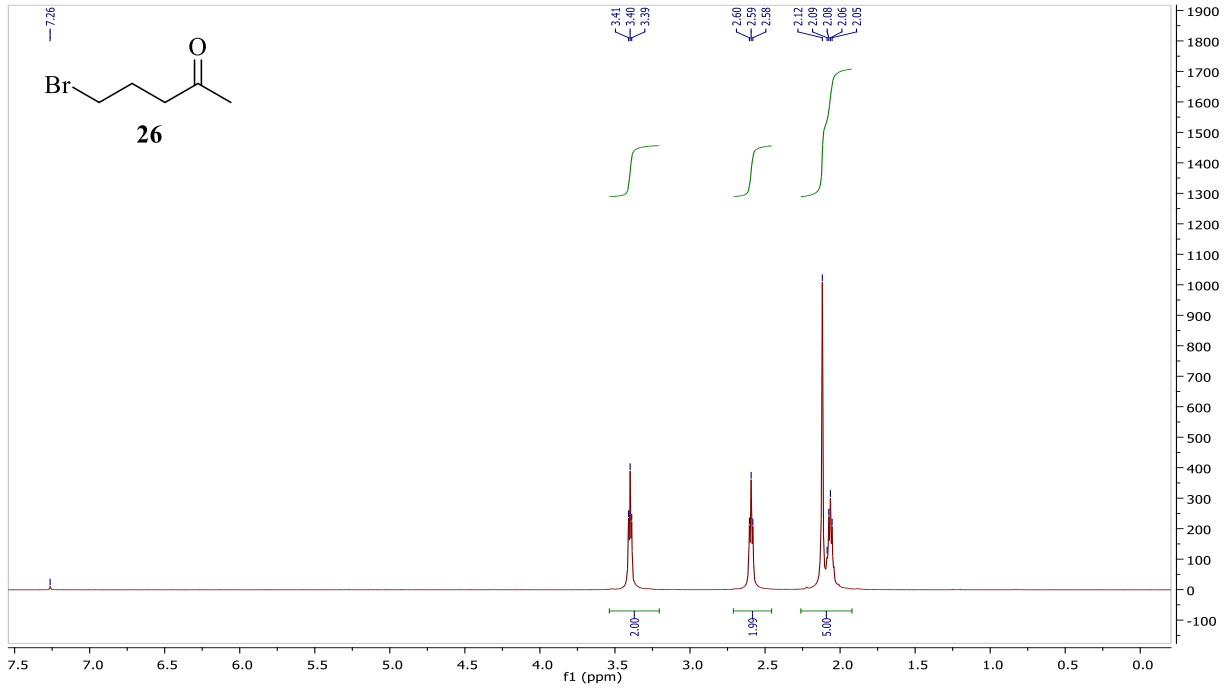
APPENDIX 1. GENERAL EXPERIMENTAL PROCEDURES

All reactions were performed in oven-dried glassware under ambient atmosphere, unless otherwise indicated. ^{1}H and ^{13}C spectra were recorded on Bruker AV 500 or 600 MHz spectrometers in $CDCl_3$. Sodium methoxide in methanol (25%) and all fine chemicals were obtained from Sigma-Aldrich and used without purification. Methanol was distilled from magnesium turnings; dichloromethane distilled over calcium hydride; diethyl ether, toluene and THF were distilled over sodium; and DMSO used as obtained (99%, septa-sealed). Reactions were monitored using thin layer chromatography (TLC) using Macherey-Nagel silica gel 60 F_{254} TLC aluminum plates and visualized with UV fluorescence and staining with 2,4-dinitrophenylhydrazine or vanillin stains. Bulk solvent removal was performed by rotary evaporation under reduced pressure. For reactions with solvent volumes under 3 mL, the solvent was evaporated under a stream of nitrogen. Column chromatographic purification was performed using Silicycle silica gel (40–63 μM, 230-400 mesh) with technical grade solvents. Yields are reported for spectroscopically pure compounds, unless stated otherwise. Coupling constants are recorded in Hz and chemical shifts are reported in ppm downfield of TMS. HRMS (ESI^+) was performed on a Waters Micromass Q-ToF Ultima Global. EI HRMS was performed on a Micromass GCT.

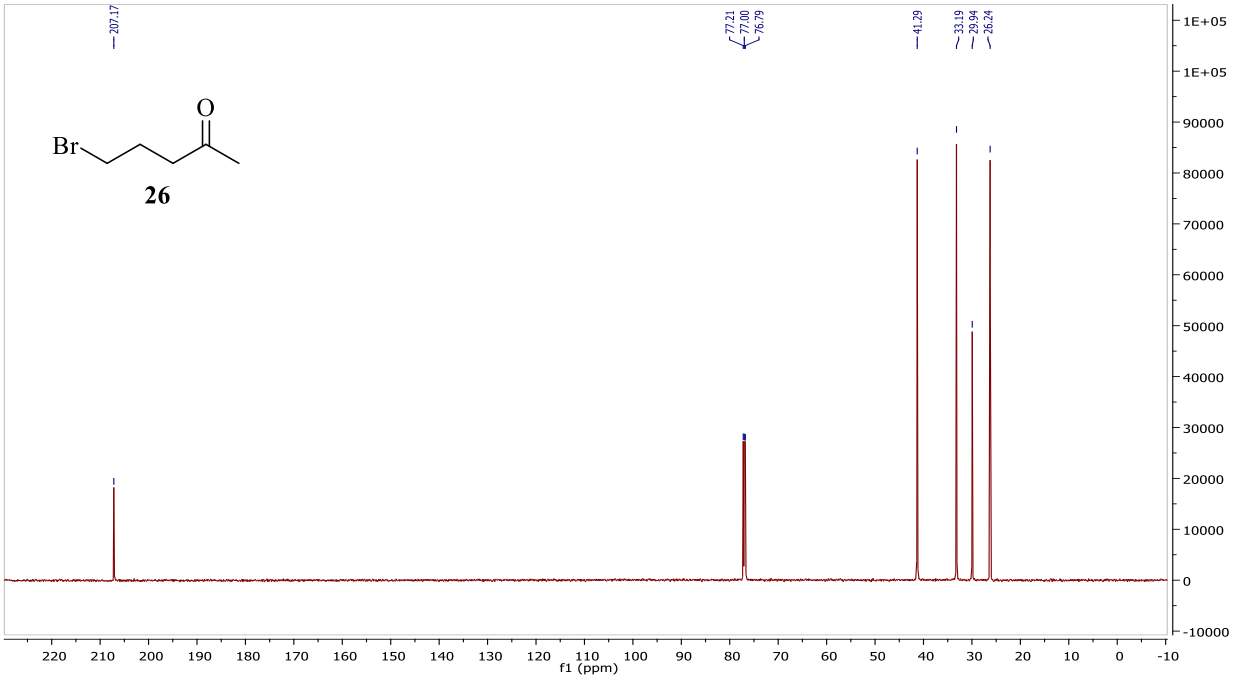
APPENDIX 2. SPECTRAL DATA

Chapter 2

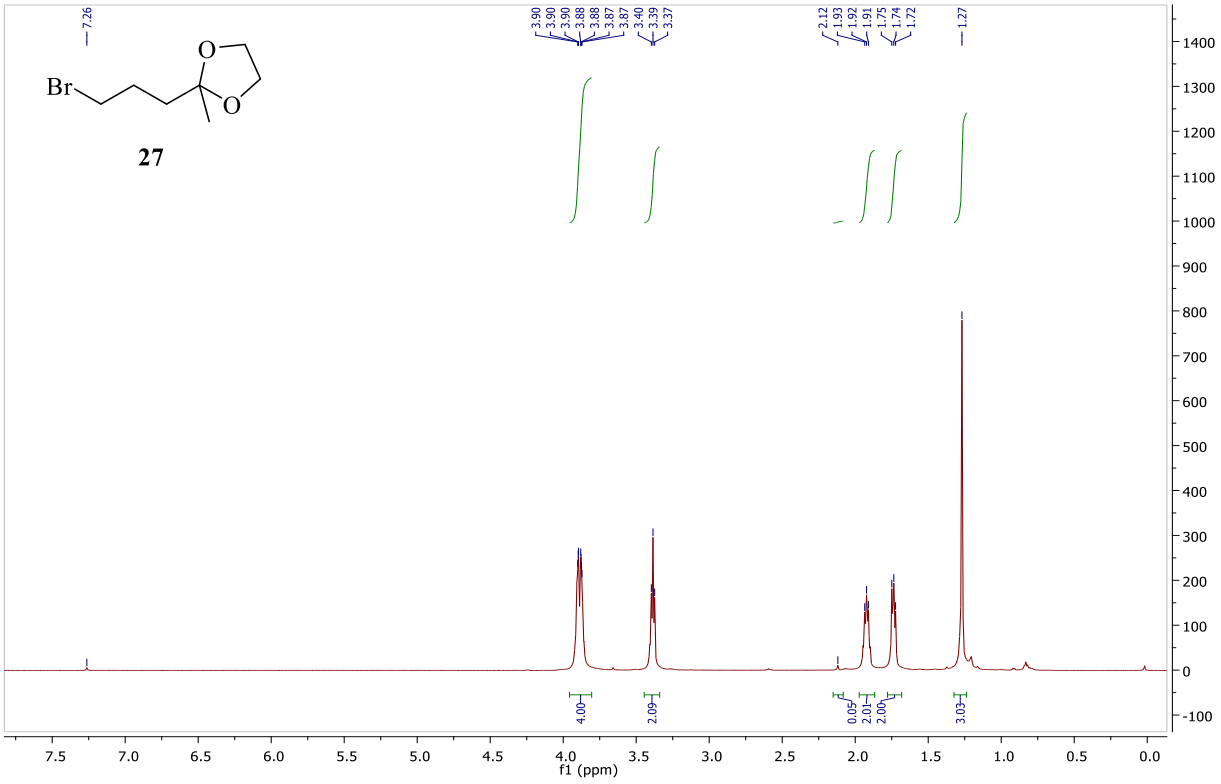
^{1}H NMR spectrum of 5-bromo-2-pentanone (**26**)



^{13}C NMR spectrum of 5-bromo-2-pentanone (**26**)



^{1}H NMR spectrum of 2-(3-bromopropyl)-2-methyl-1,3-dioxolane (**27**)



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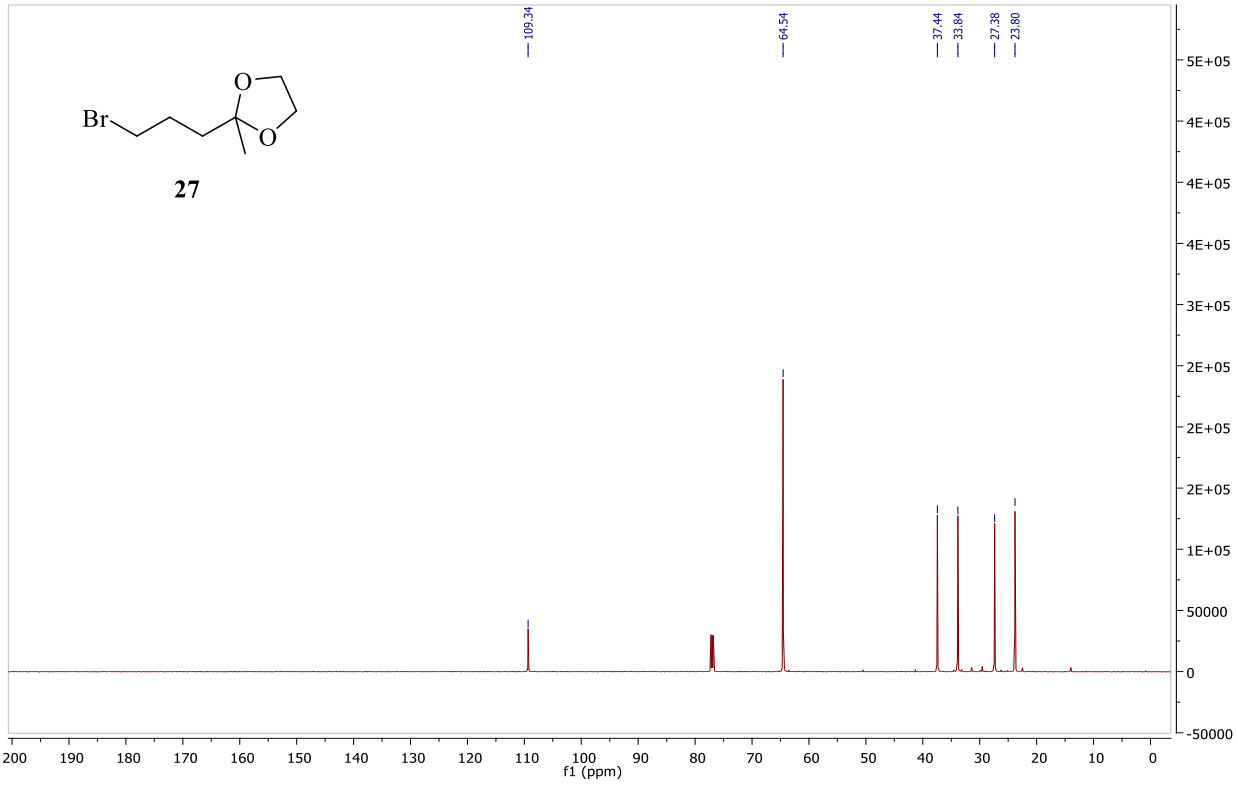

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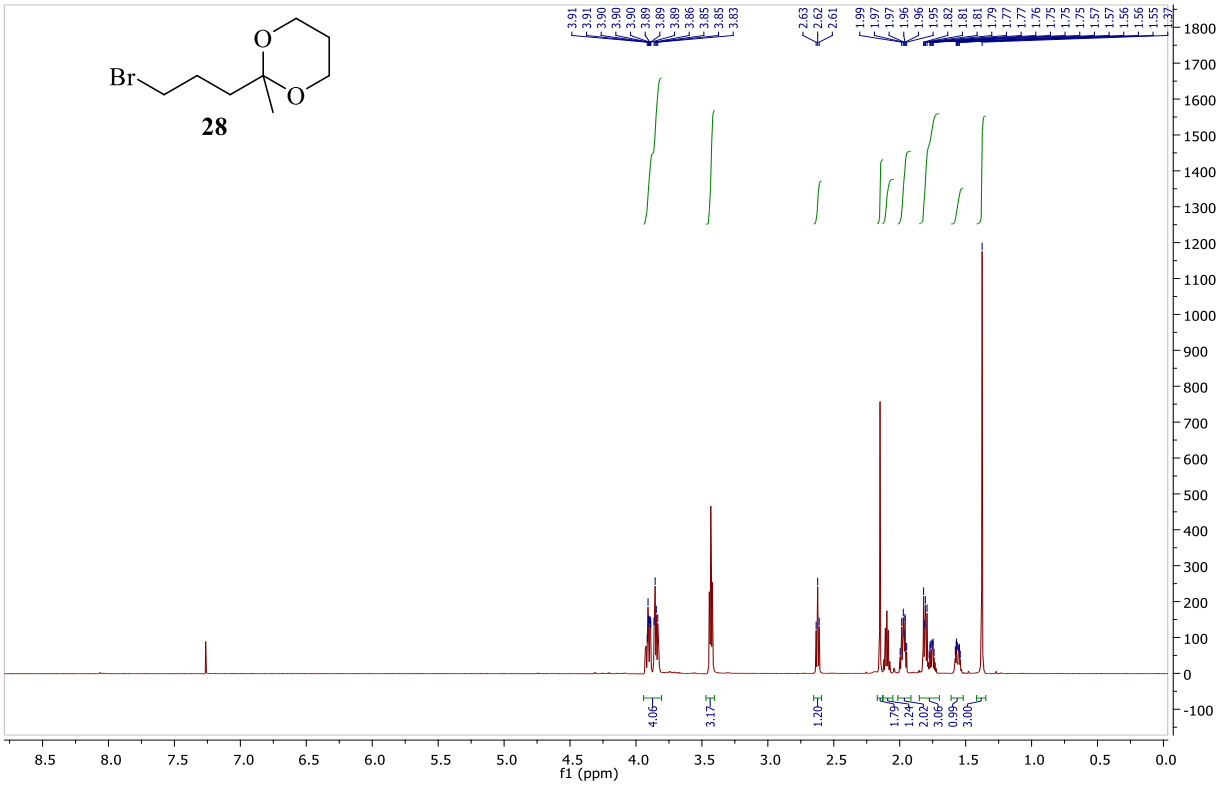

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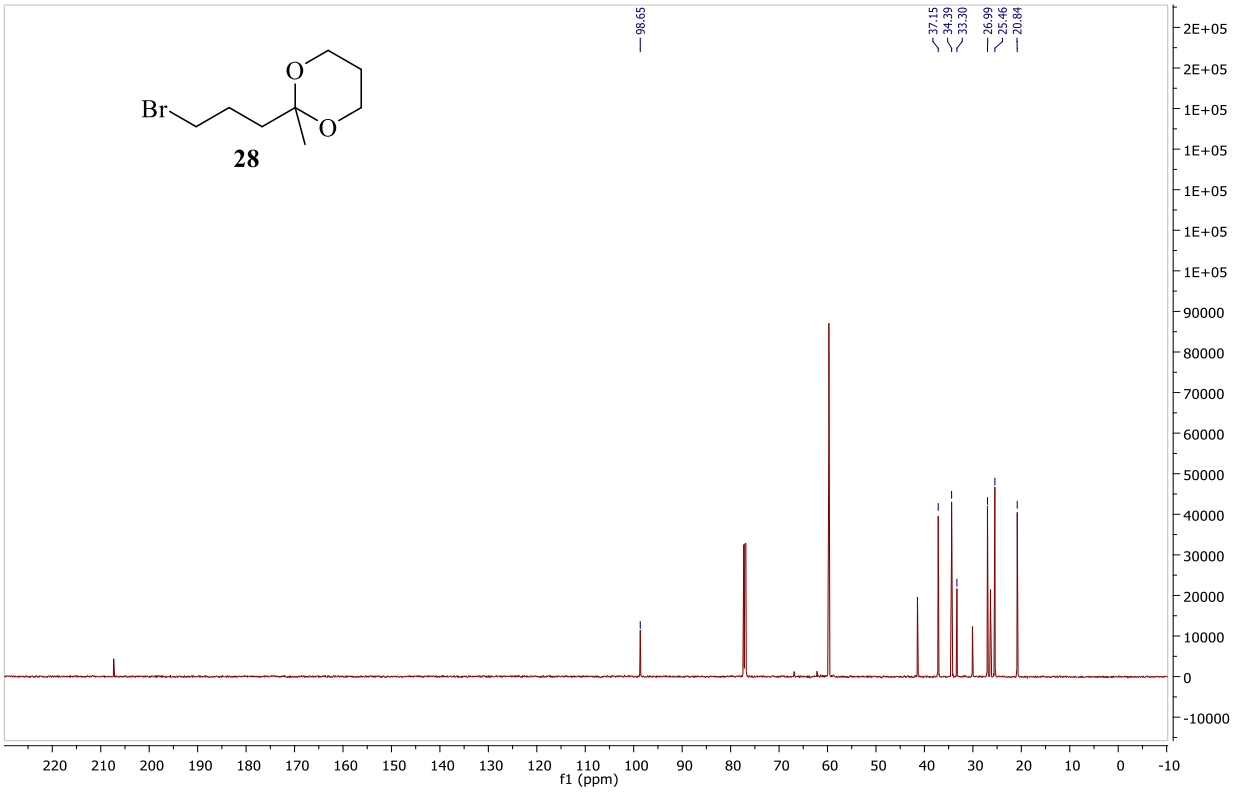

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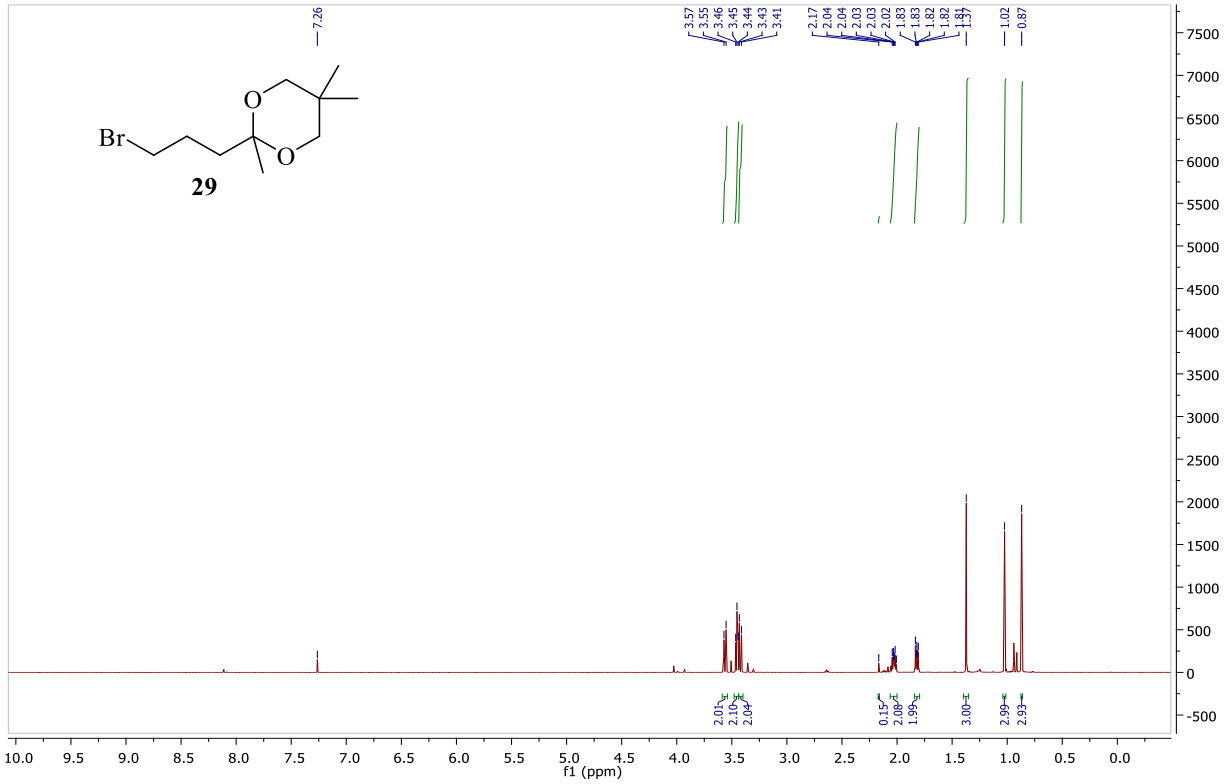

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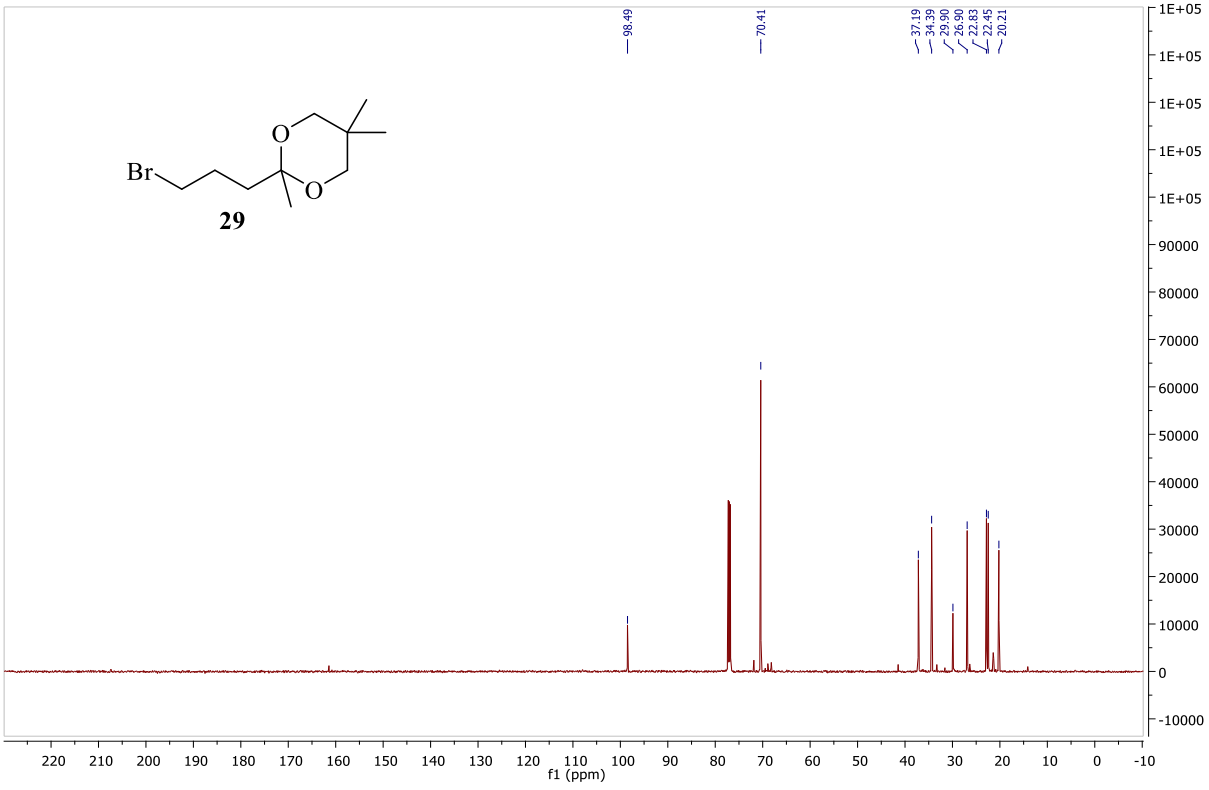

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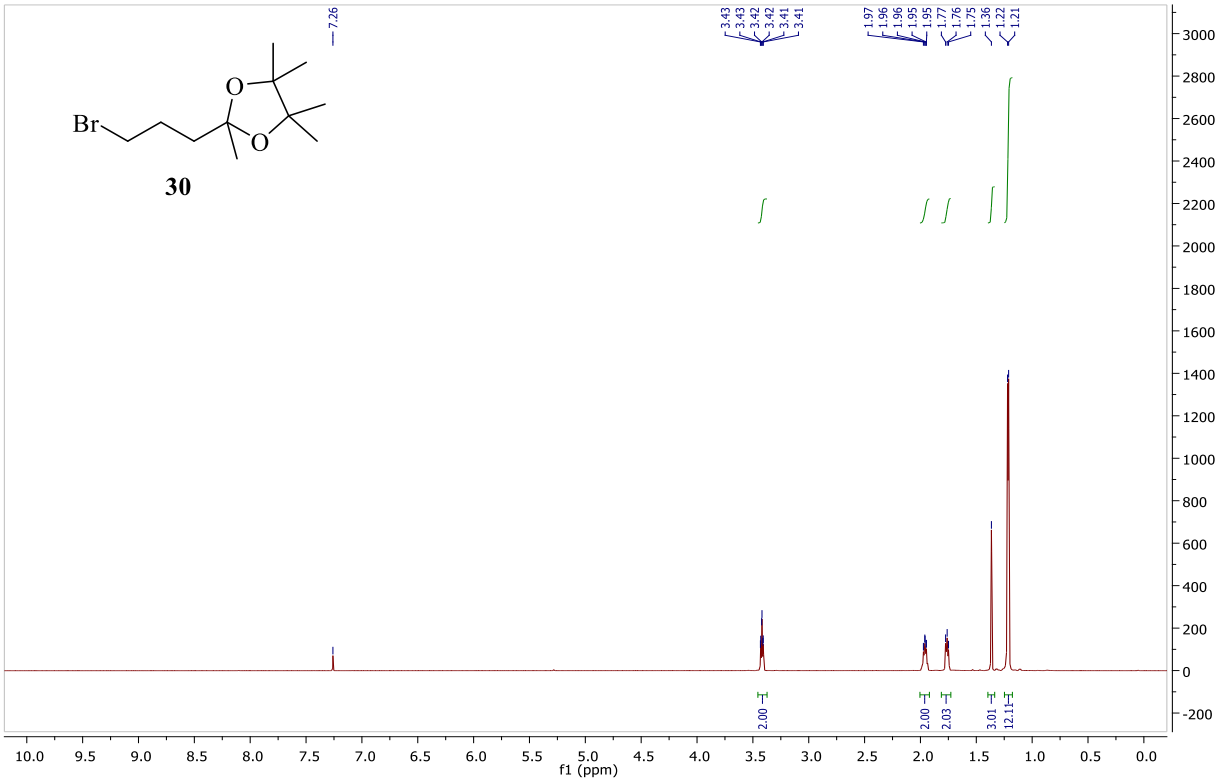

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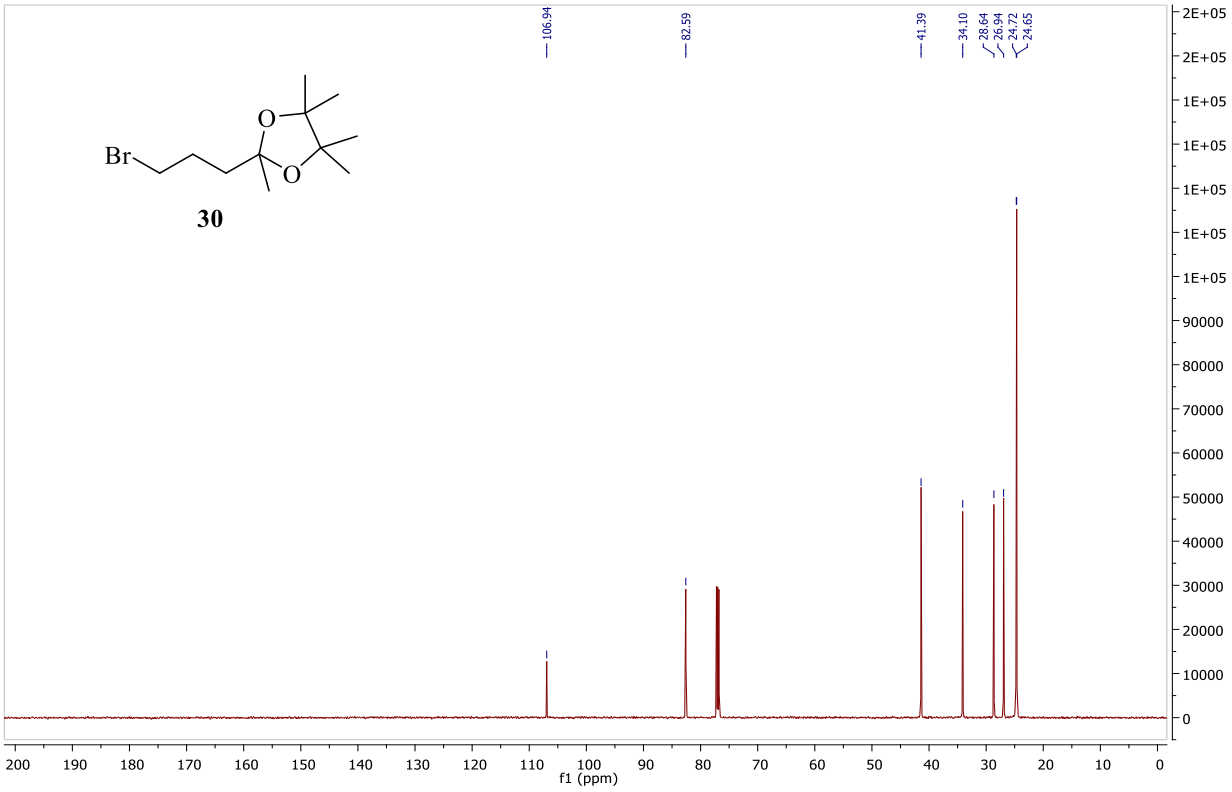
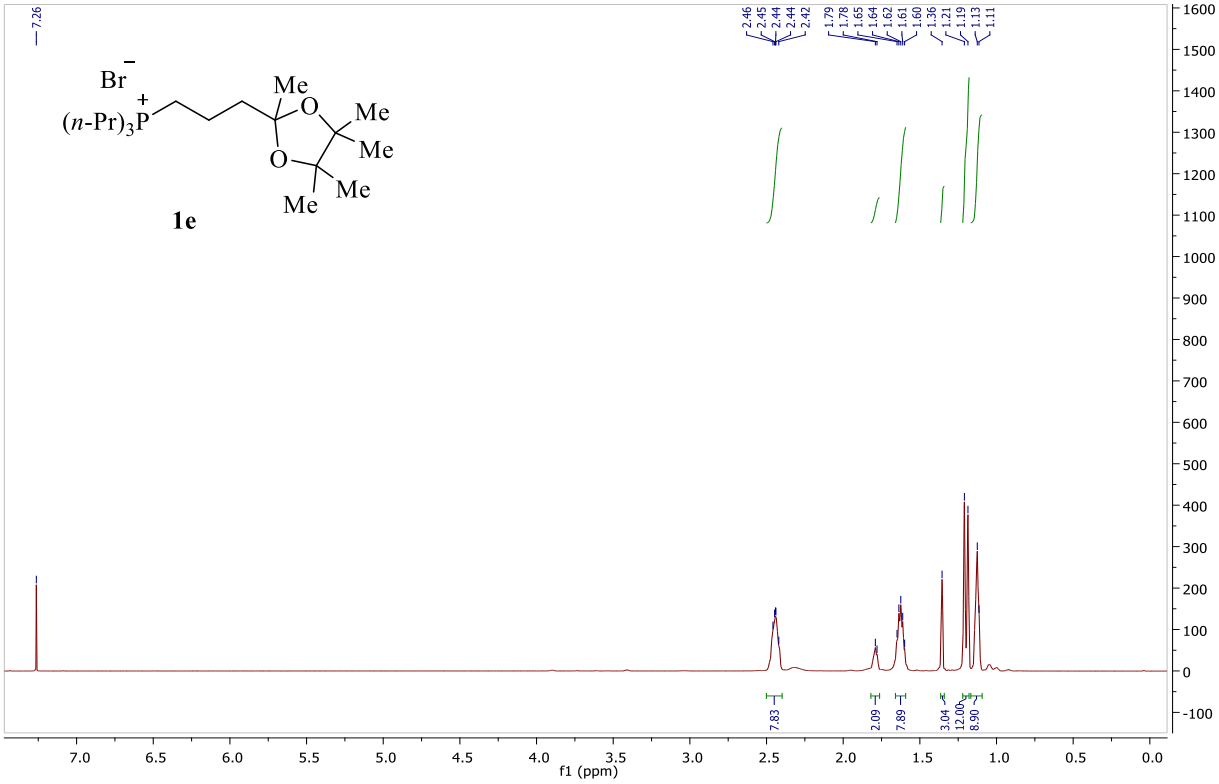


^{1}H NMR spectrum of (3-(2,4,4,5,5-pentamethyl-1,3-dioxolan-2-yl)propyl)tripropylphosphonium bromide (**1e**)



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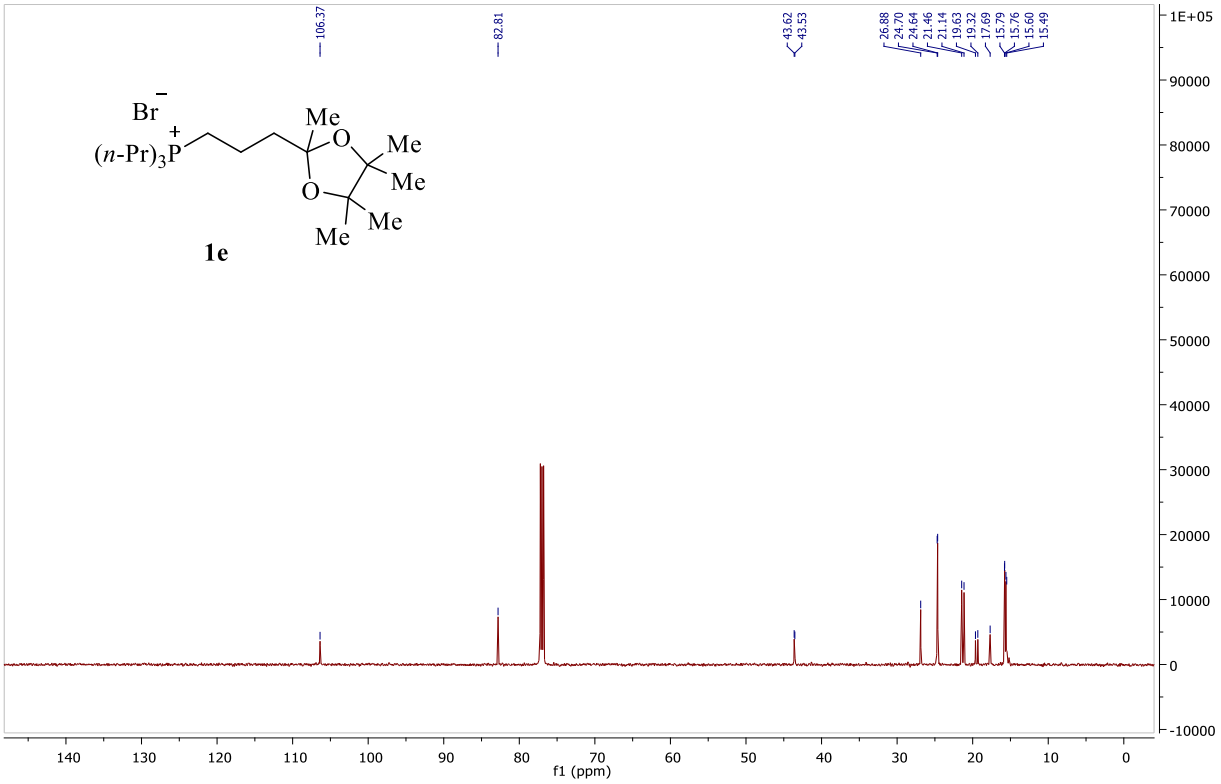

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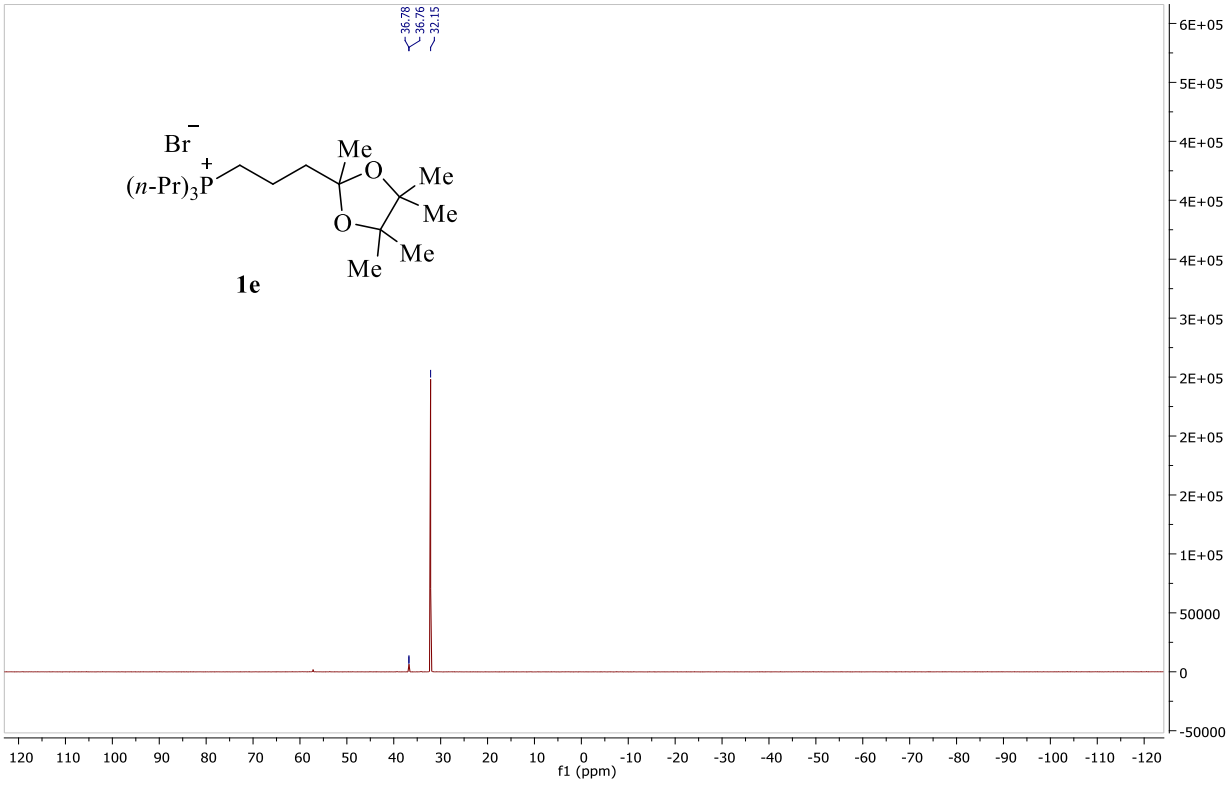
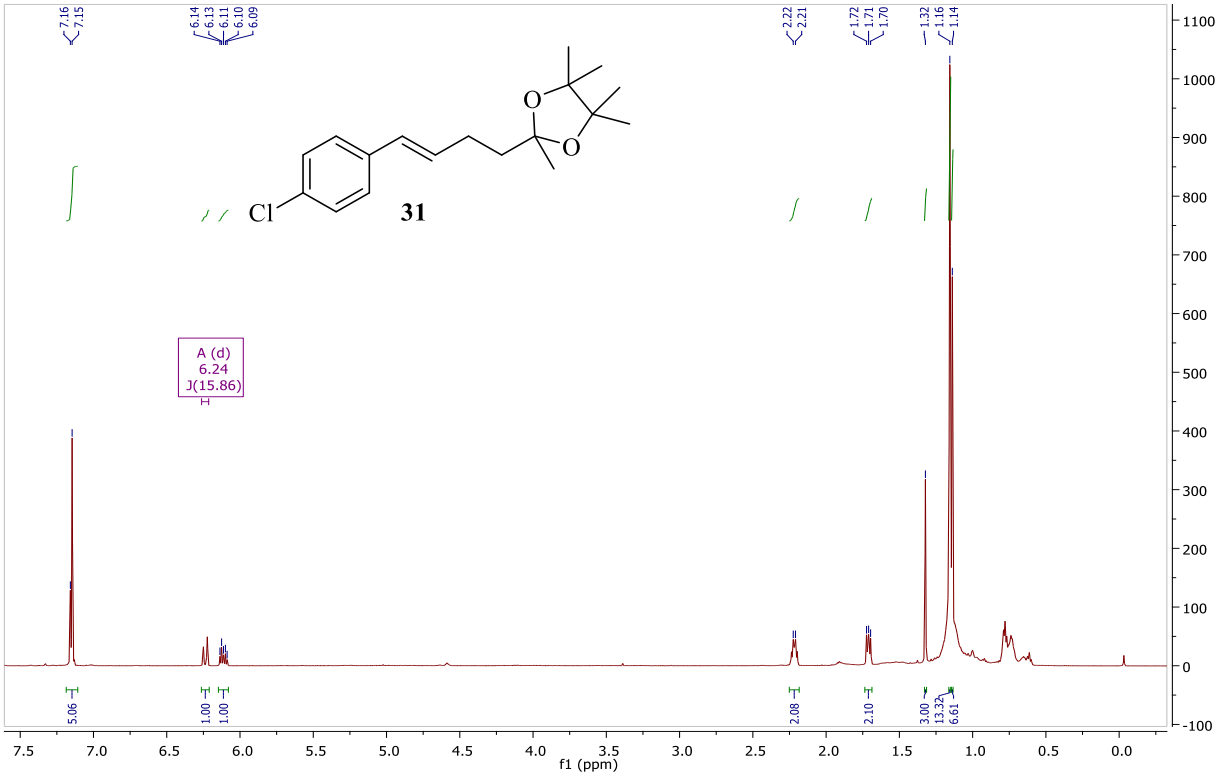
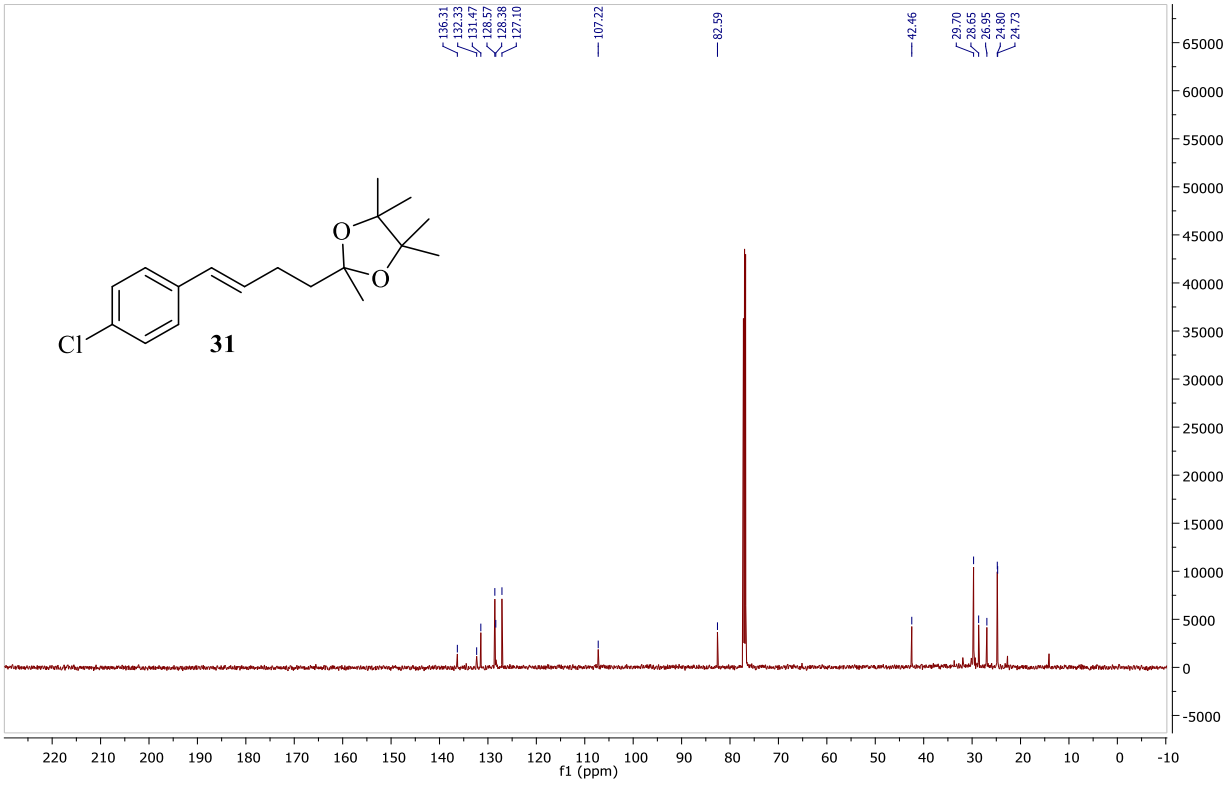


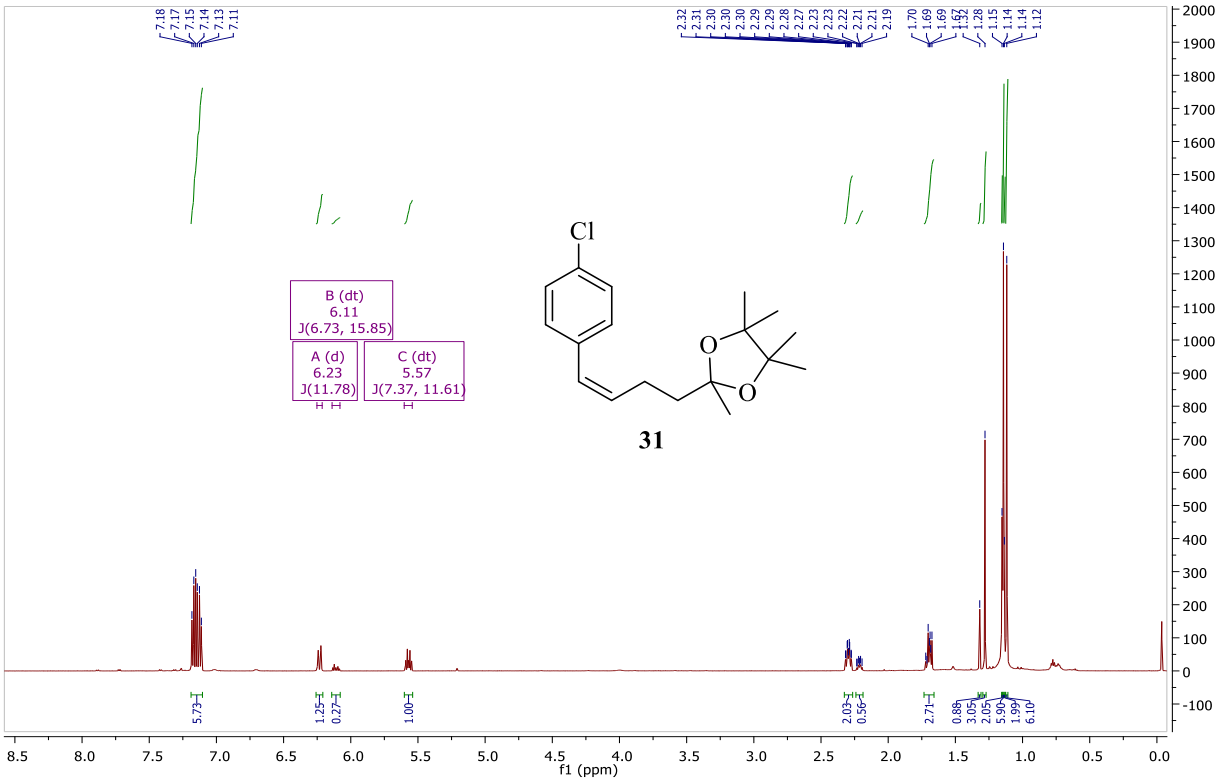
^{1}H NMR spectrum of (*E*)-2-(4-(4-chlorophenyl)but-3-en-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (**31**)



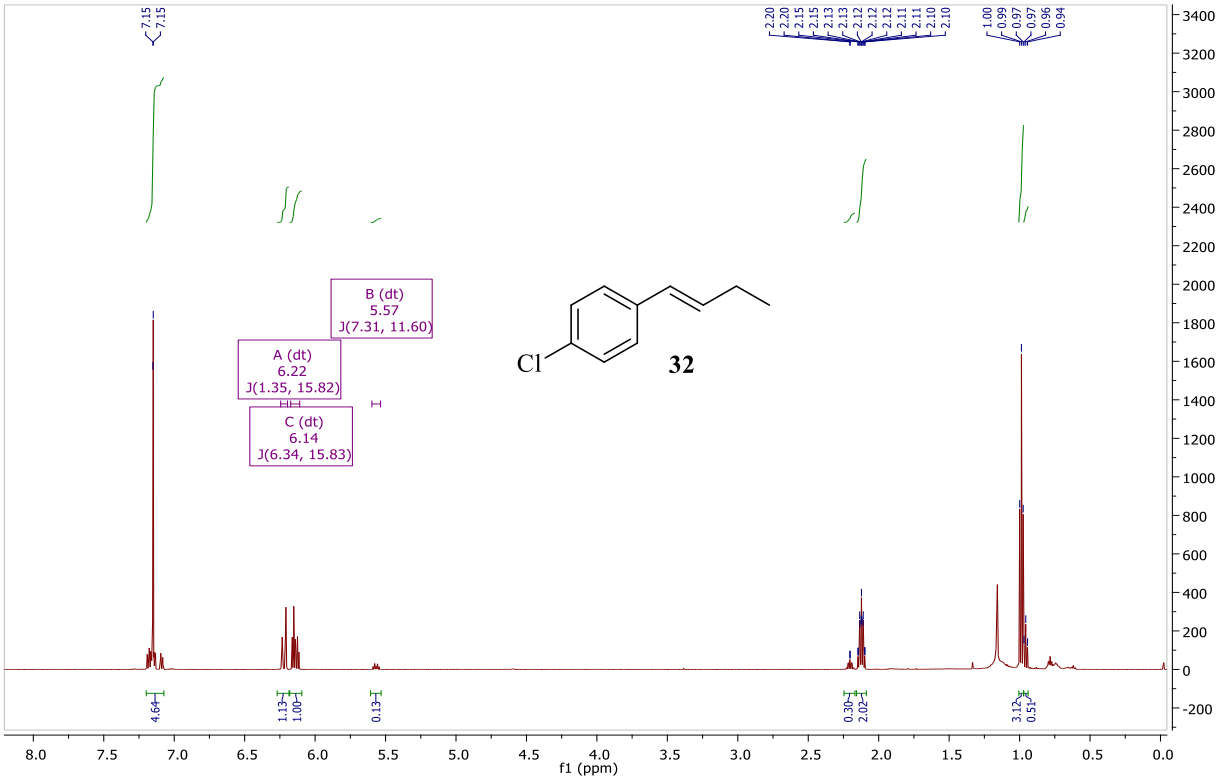
^{13}C NMR spectrum of (*E*)-2-(4-(4-chlorophenyl)but-3-en-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (**31**)



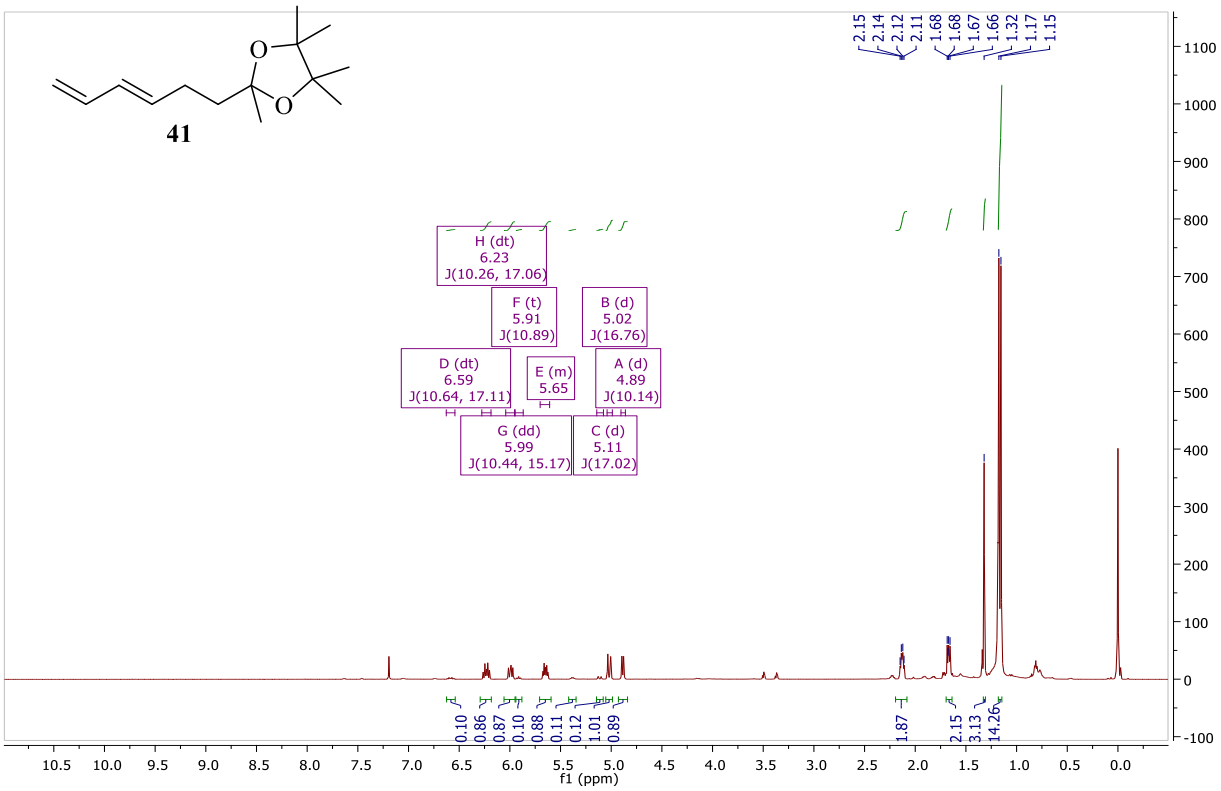
^{1}H NMR spectrum of (*Z*)-2-(4-(4-chlorophenyl)but-3-en-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (**31**)



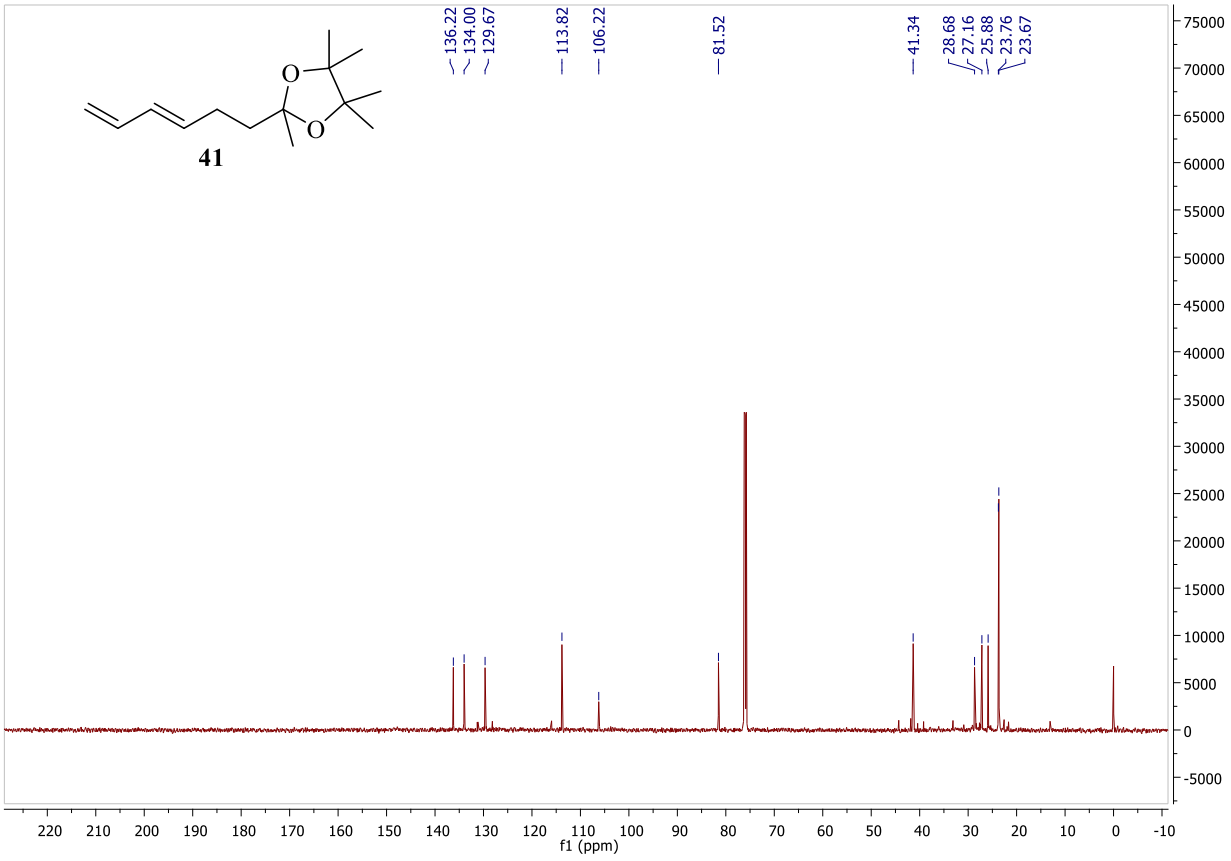
^{1}H NMR spectrum of (*E*/*Z*)-1-(but-1-en-1-yl)-4-chlorobenzene (**32**)



^{1}H NMR spectrum of (*E*)-2-(hexa-3,5-dien-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (**41**)

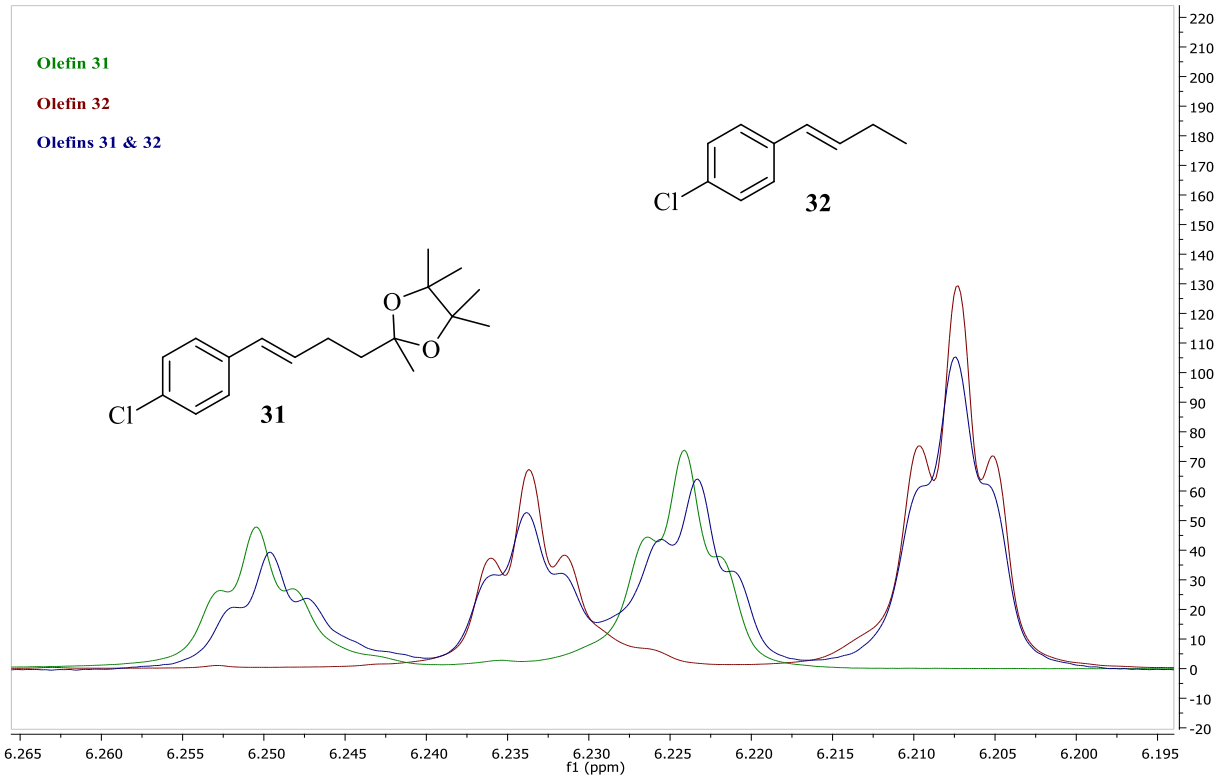


^{13}C NMR spectrum of (*E*)-2-(hexa-3,5-dien-1-yl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (**41**)



^{1}H NMR Data for Scheme 5

Stacked Spectrum of Characteristic Olefin Proton



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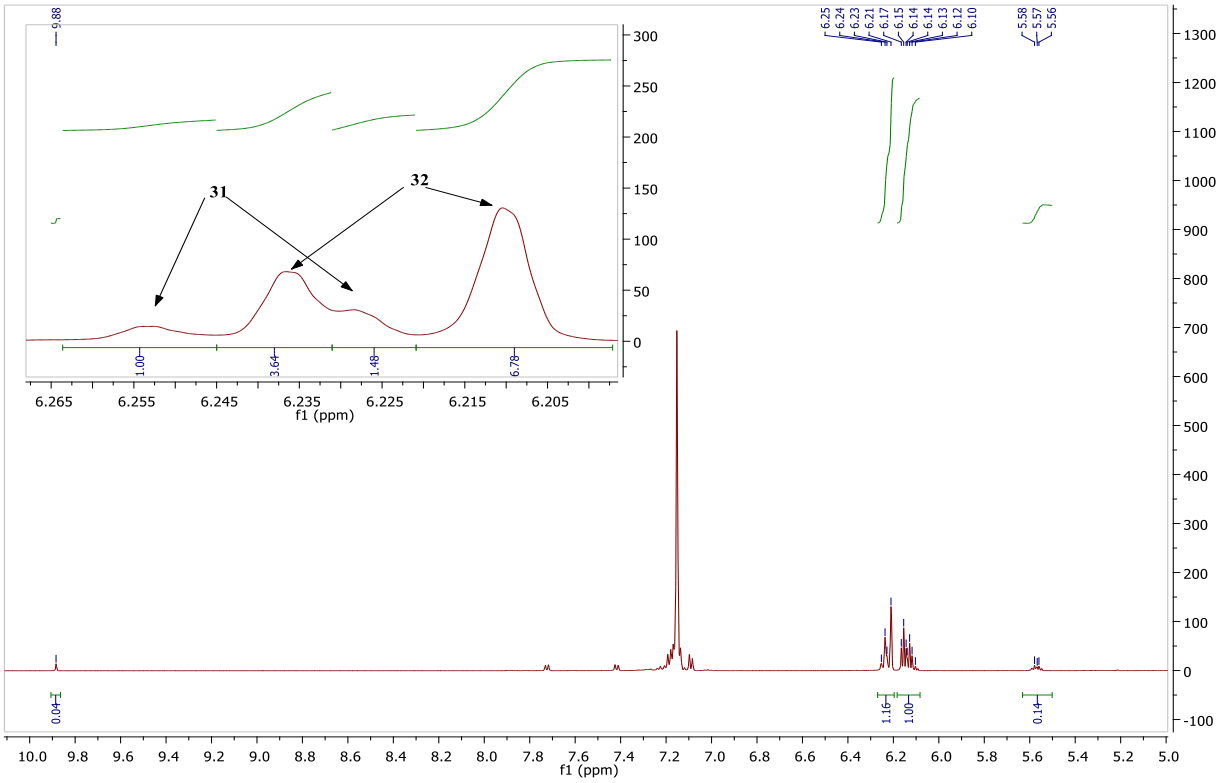

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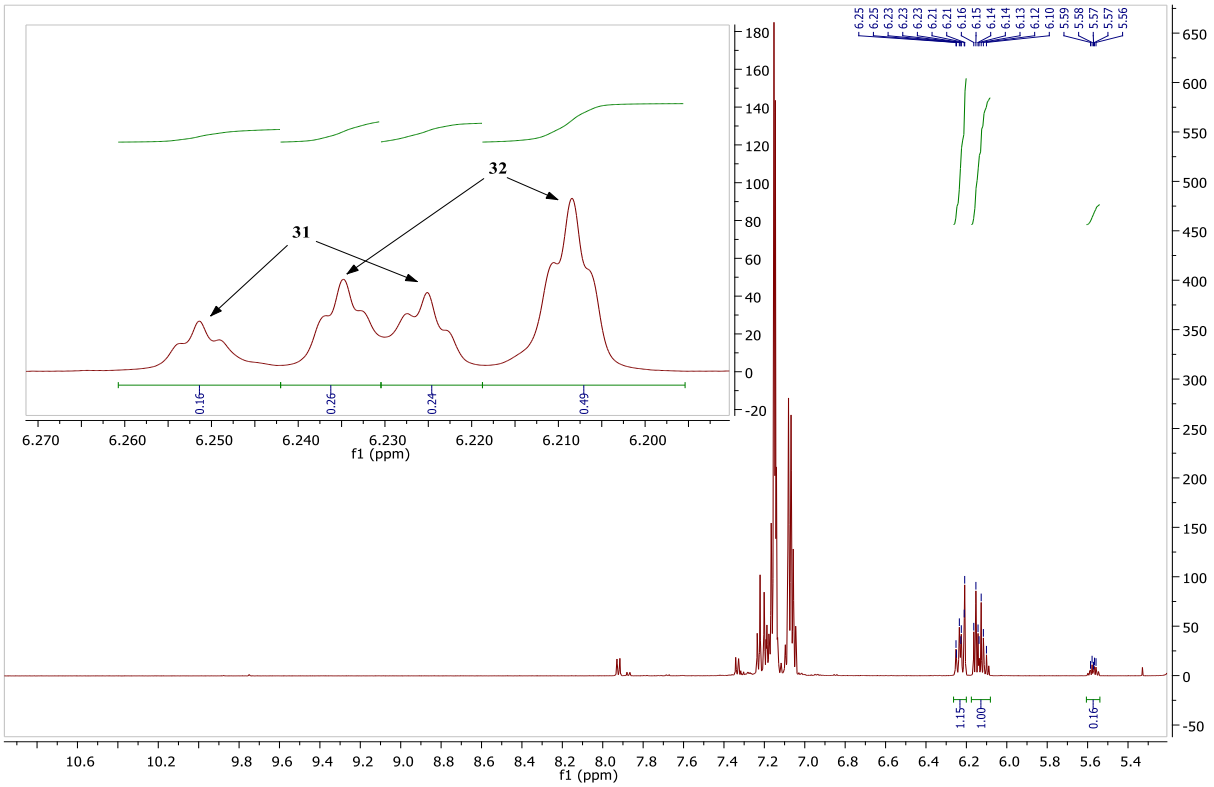
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31
0.16
0.26
0.24
0.49
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6.260
6.250
6.240
6.230
6.220
6.210
6.200
f1 (ppm)
1.15
1.00
0.16
10.6
10.2
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
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f1 (ppm)

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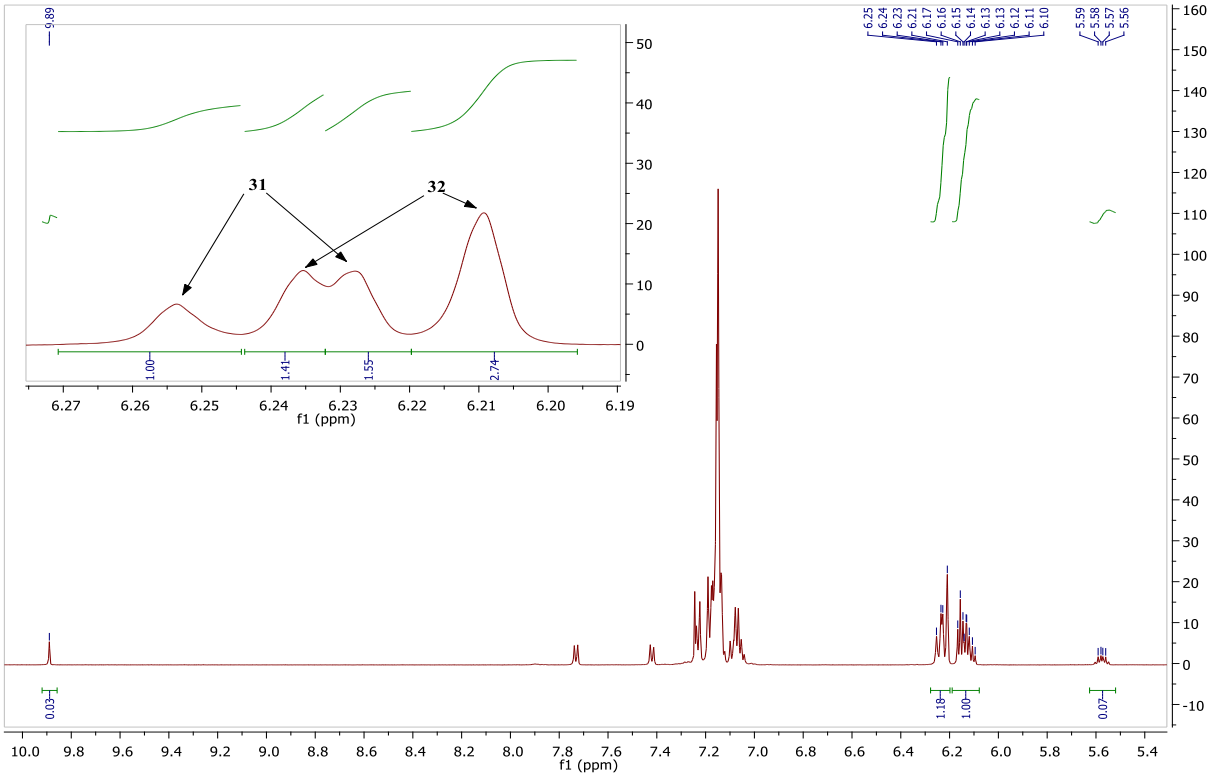

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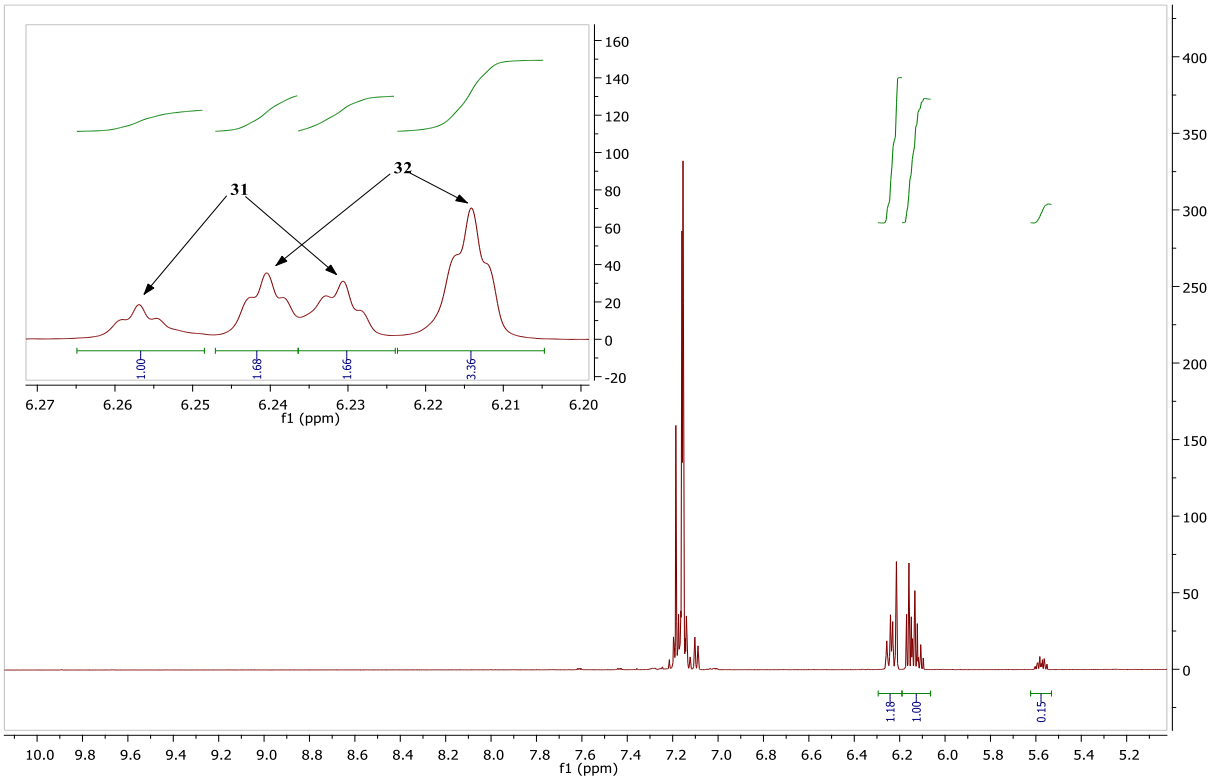

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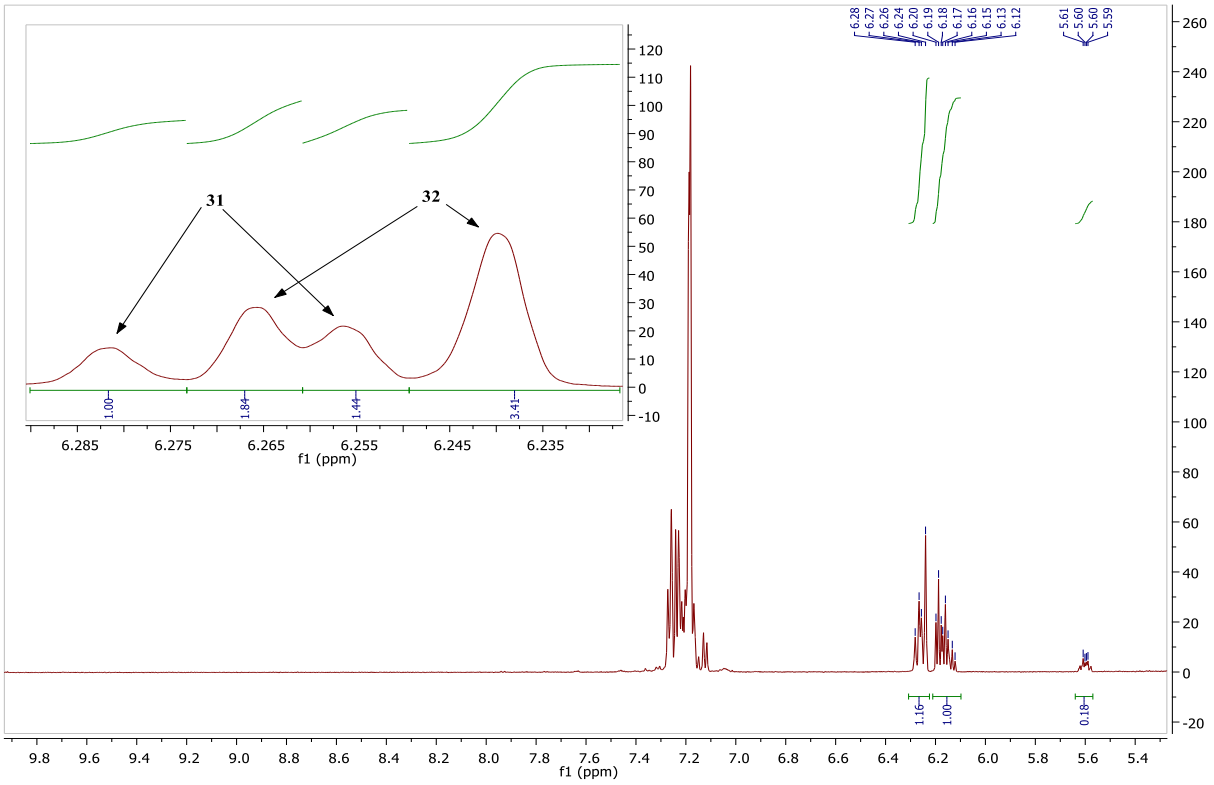
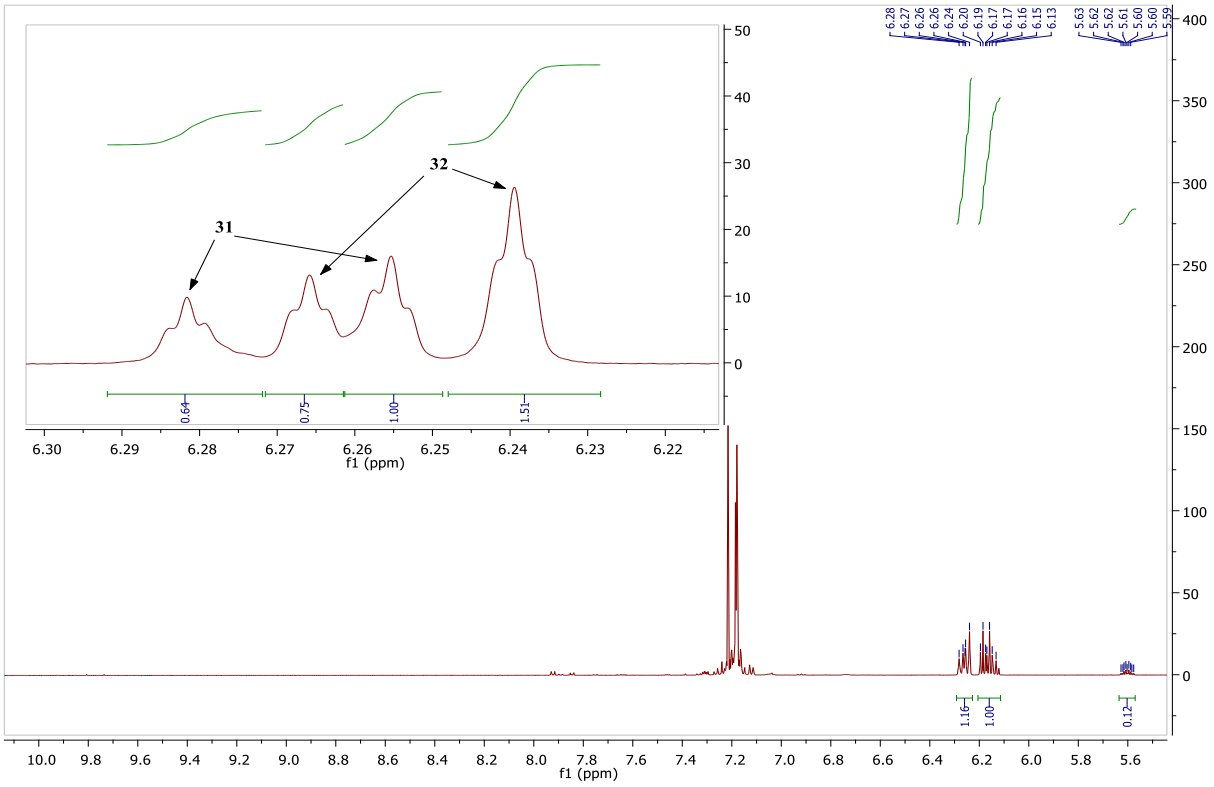


Entry 6



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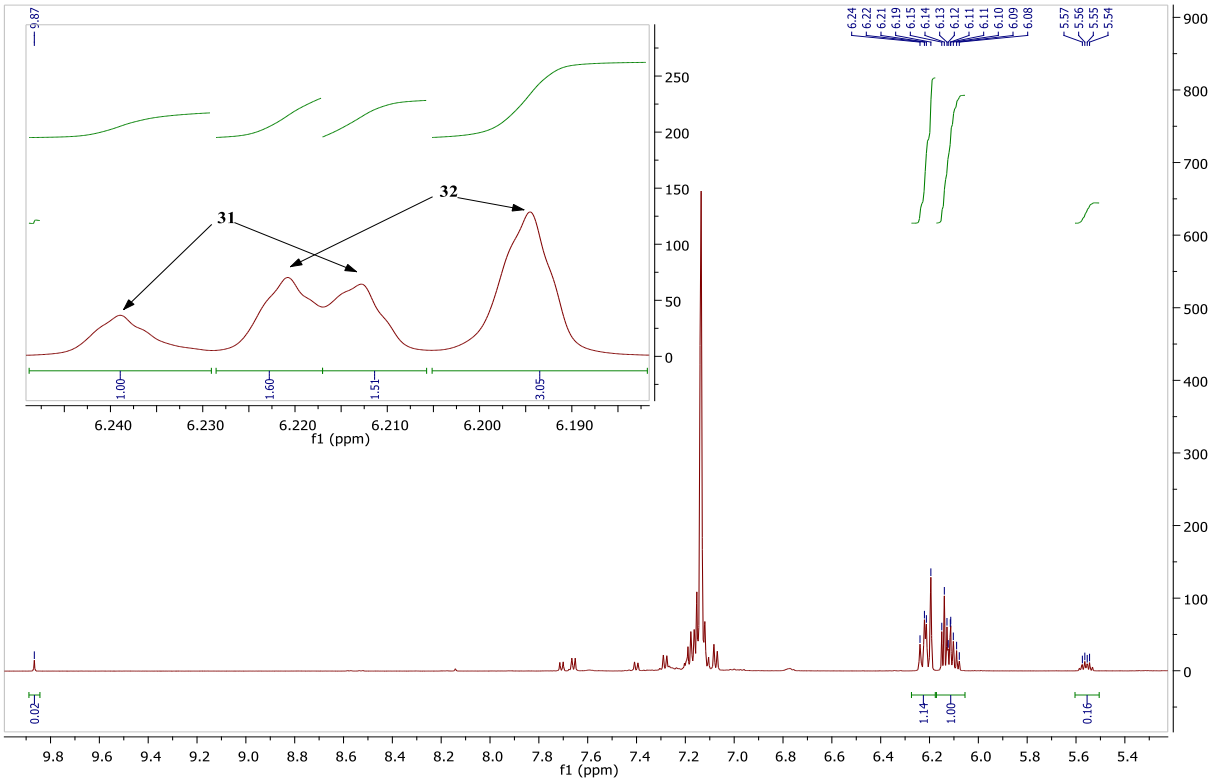

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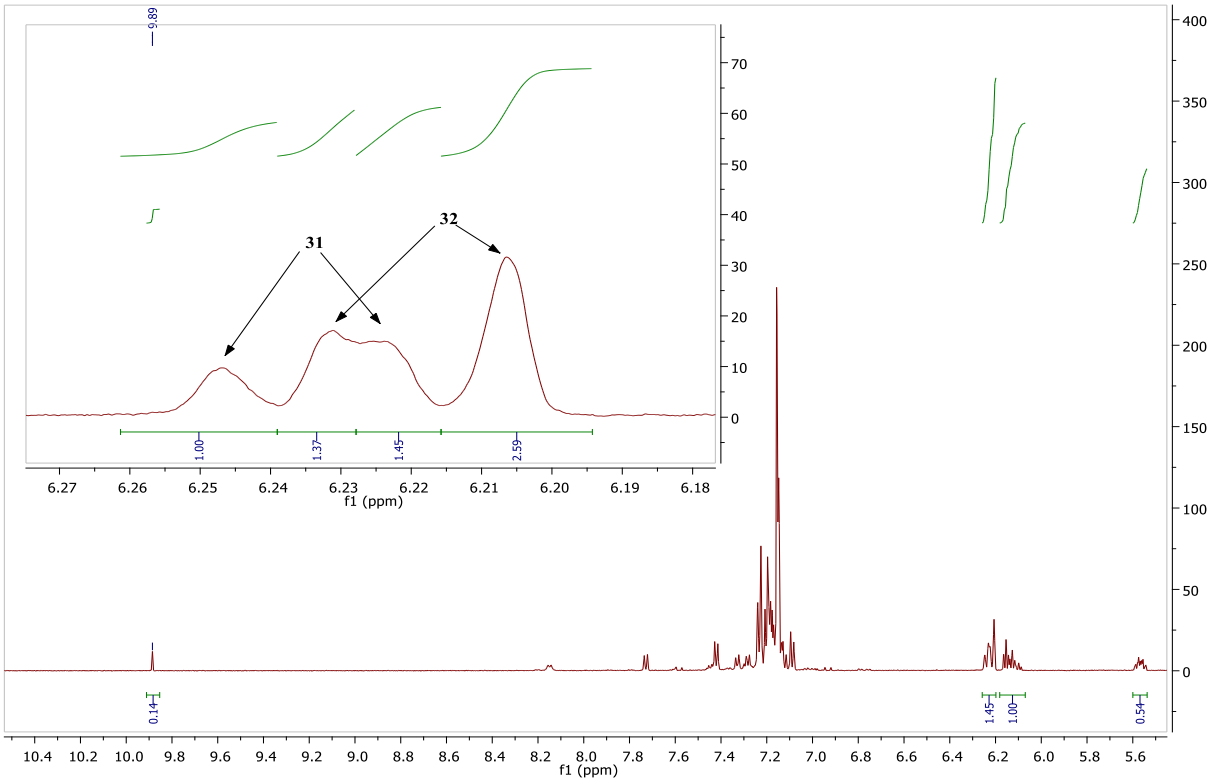
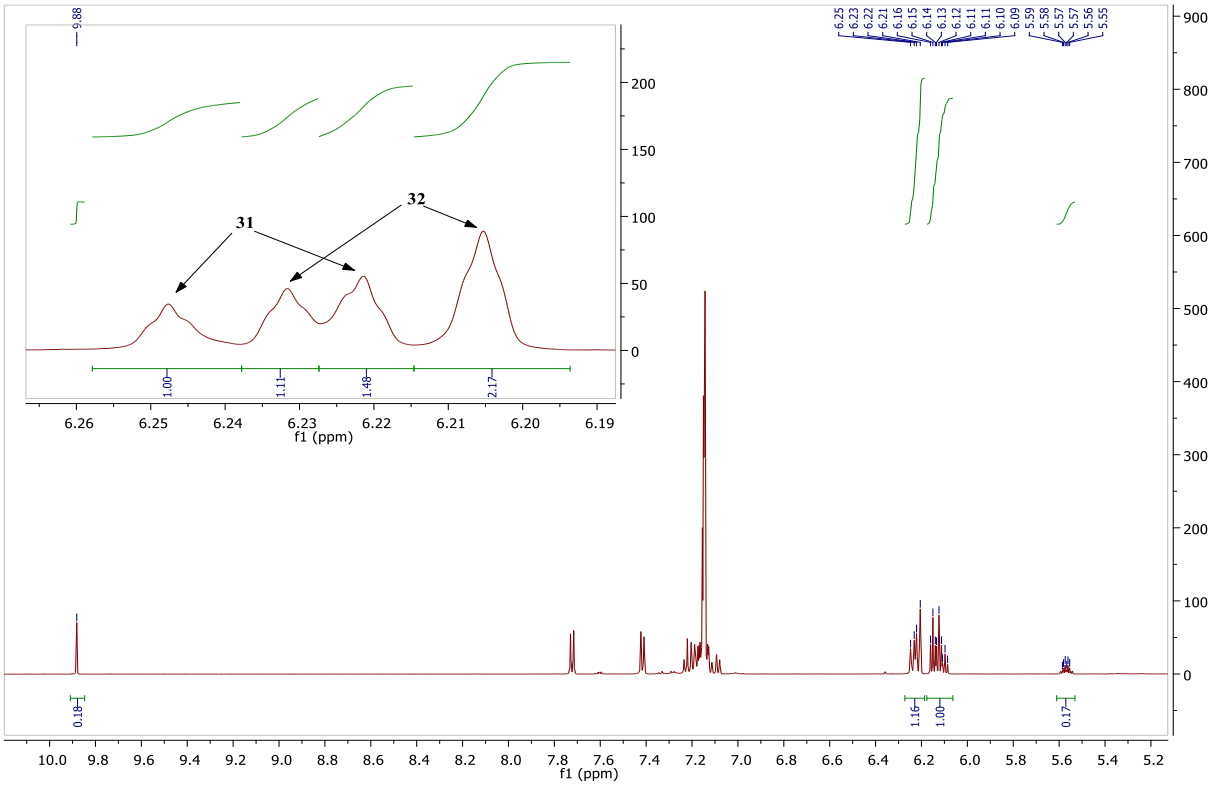
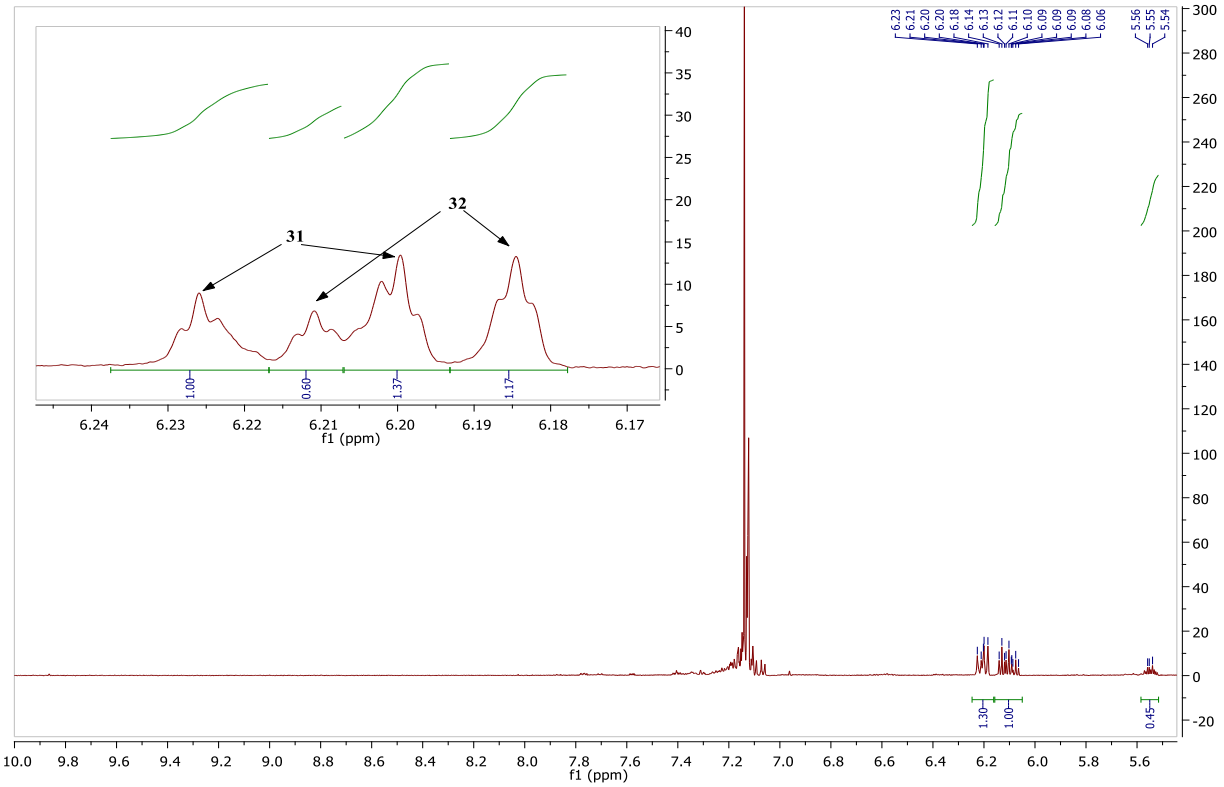


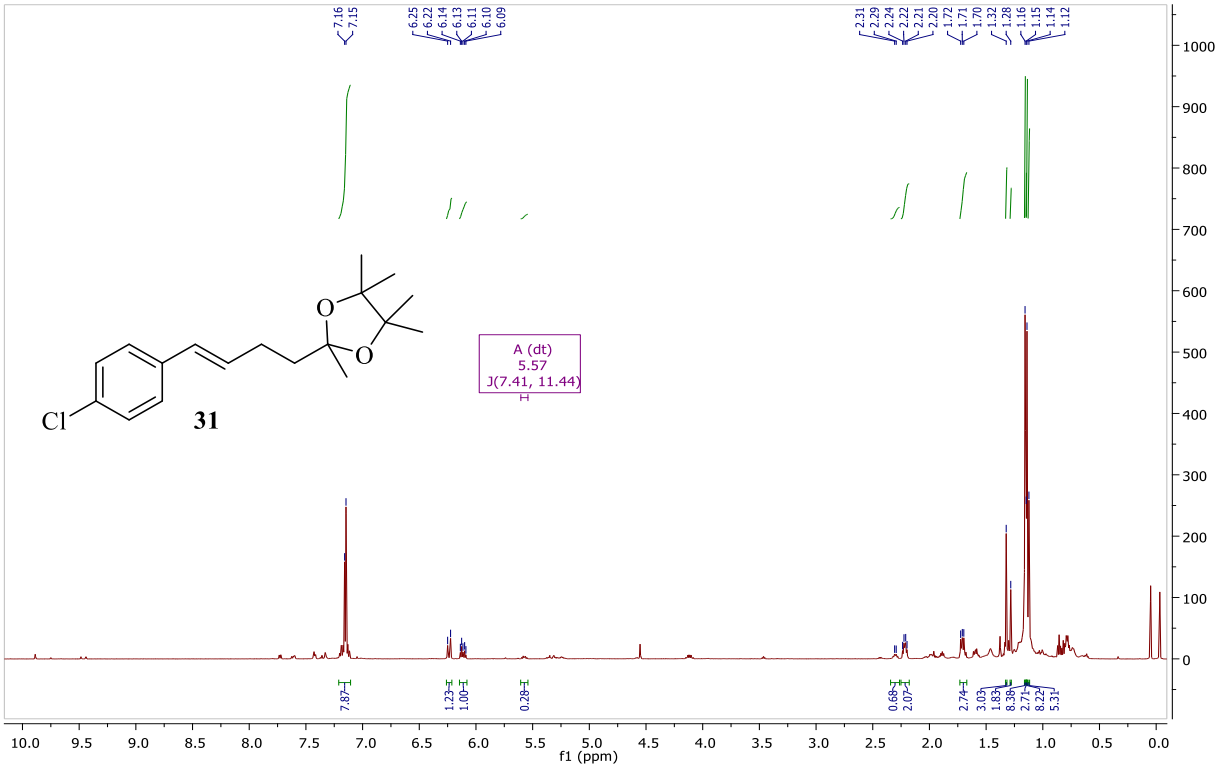
Entry 9



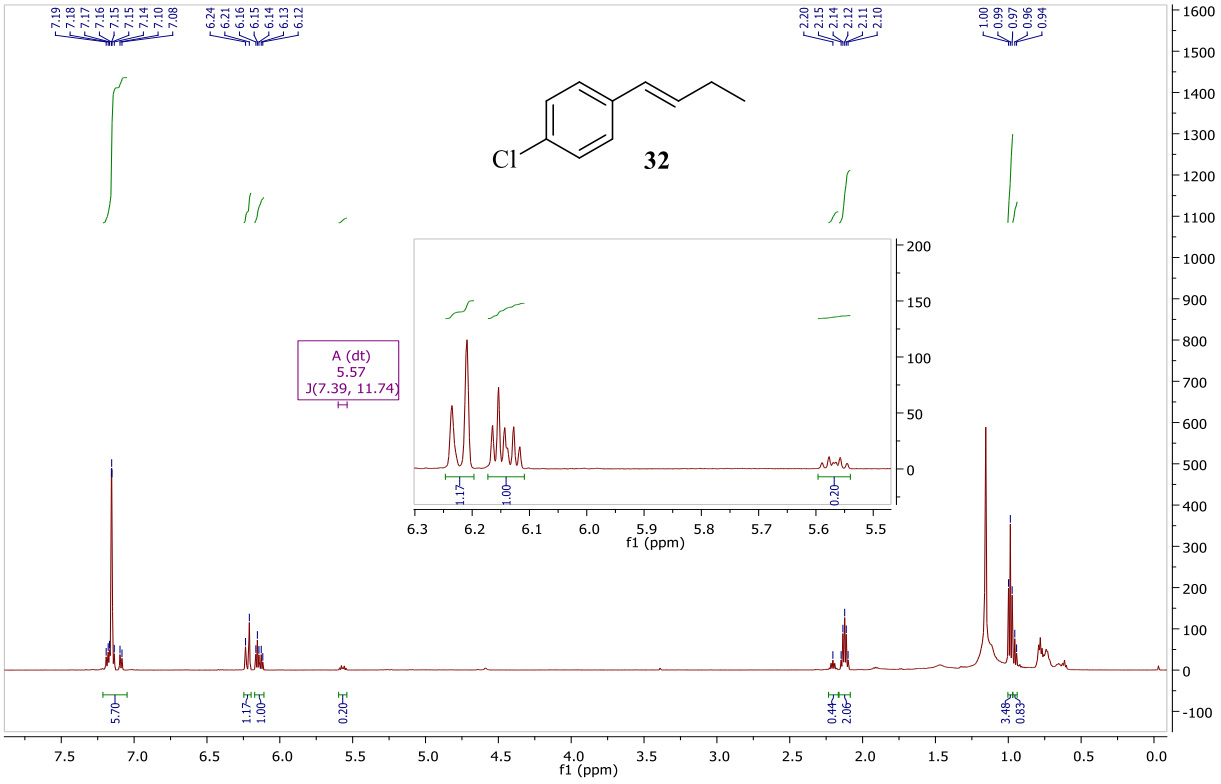
Entry 11



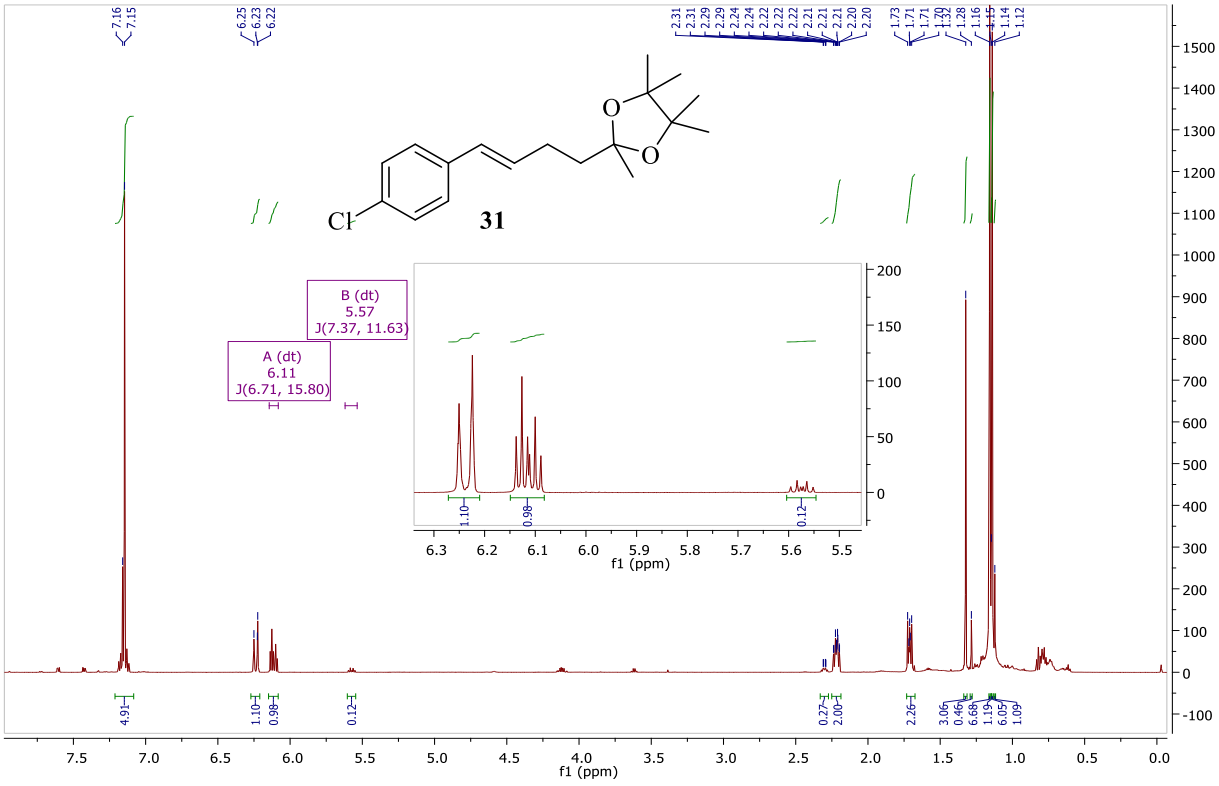
(**31**) crude for E/Z-determination



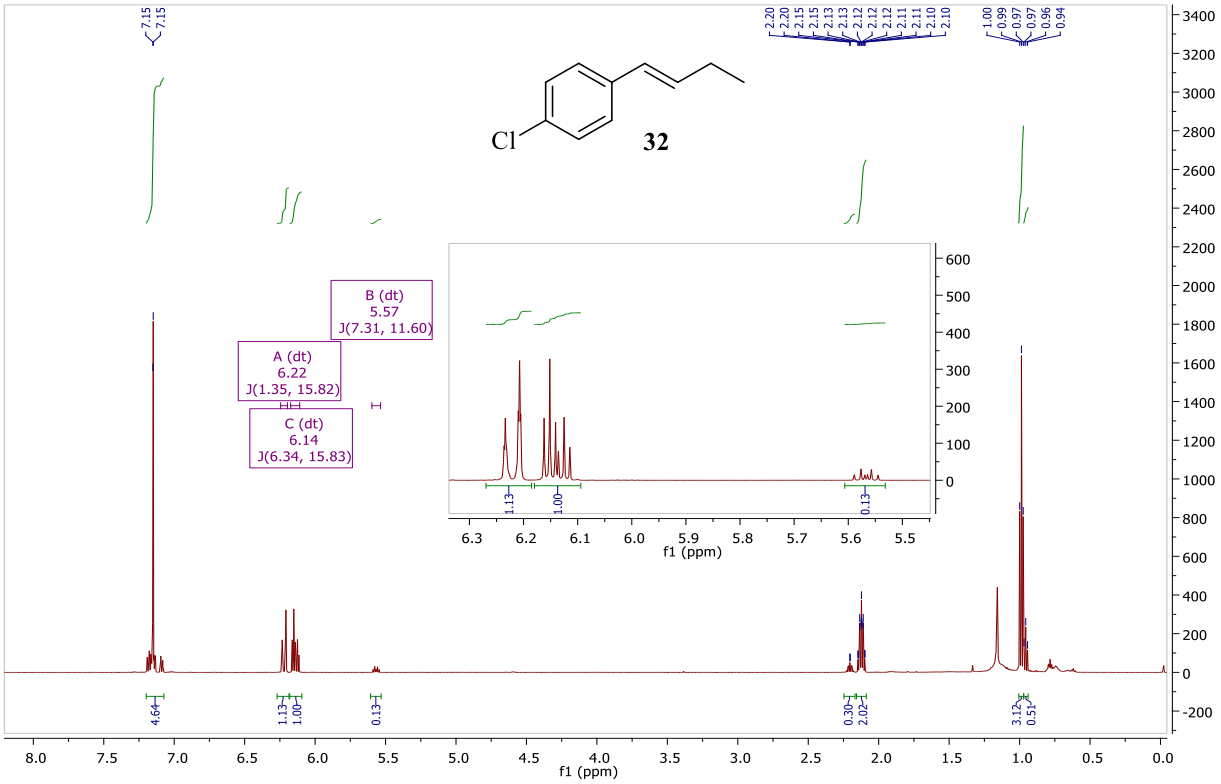
(**32**) crude for E/Z-determination



(**31**) Purified with depleted (Z)-isomer

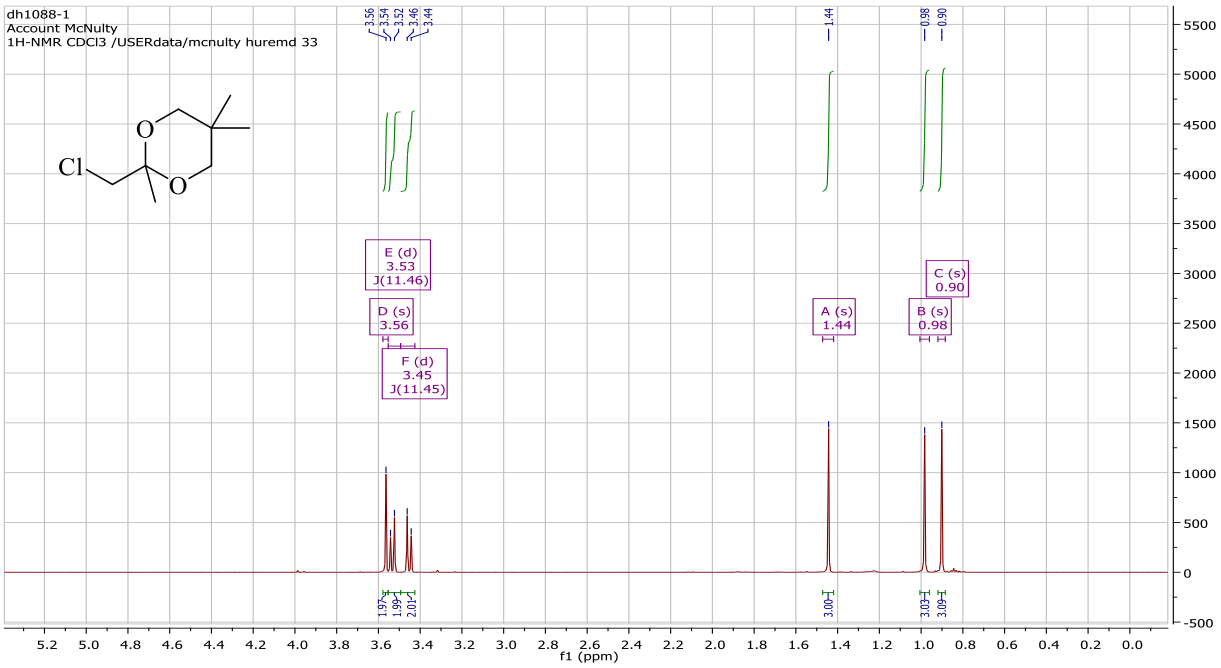


(**32**) Purified with depleted (Z)-isomer

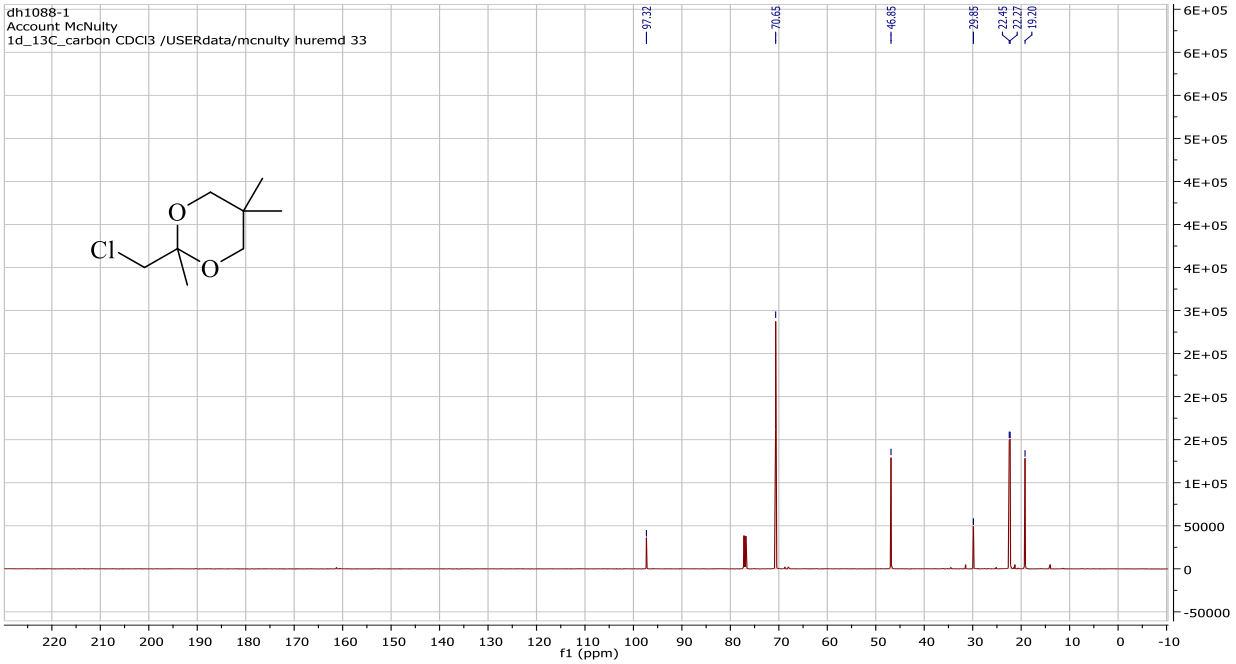


Chapter 3

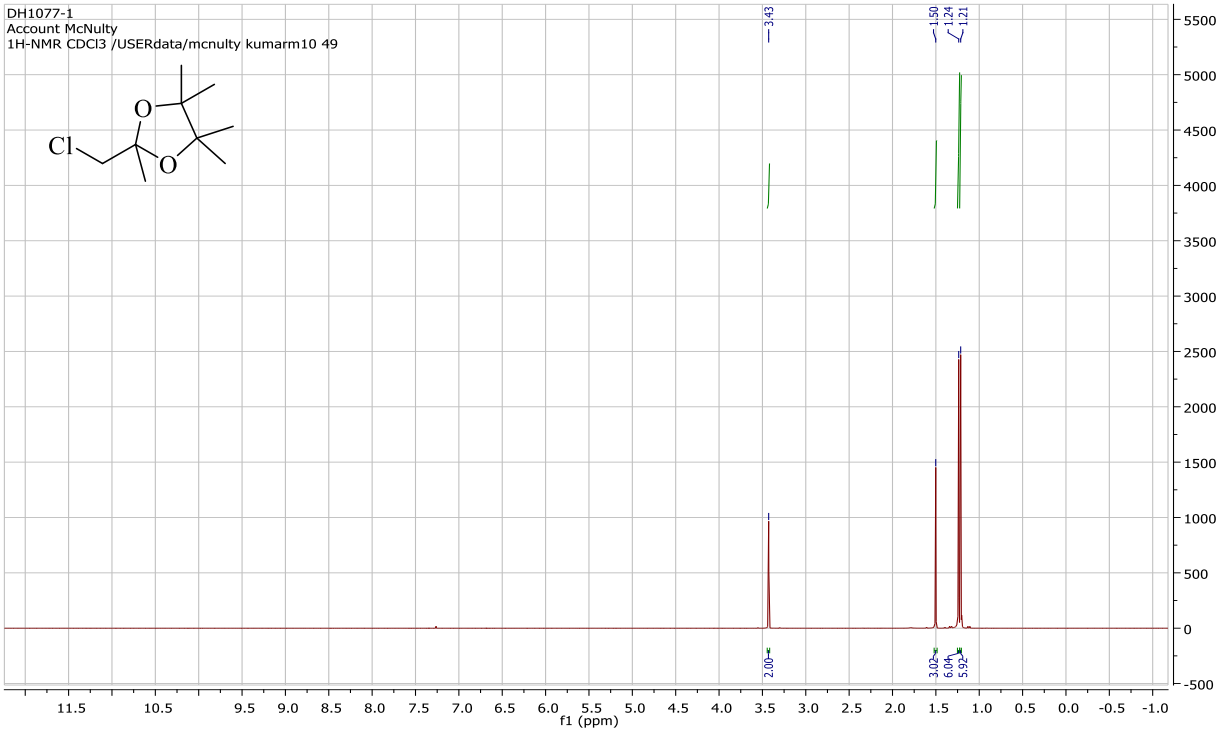
^{1}H NMR spectrum of 2-(chloromethyl)-2,5,5-trimethyl-1,3-dioxane (**12**)



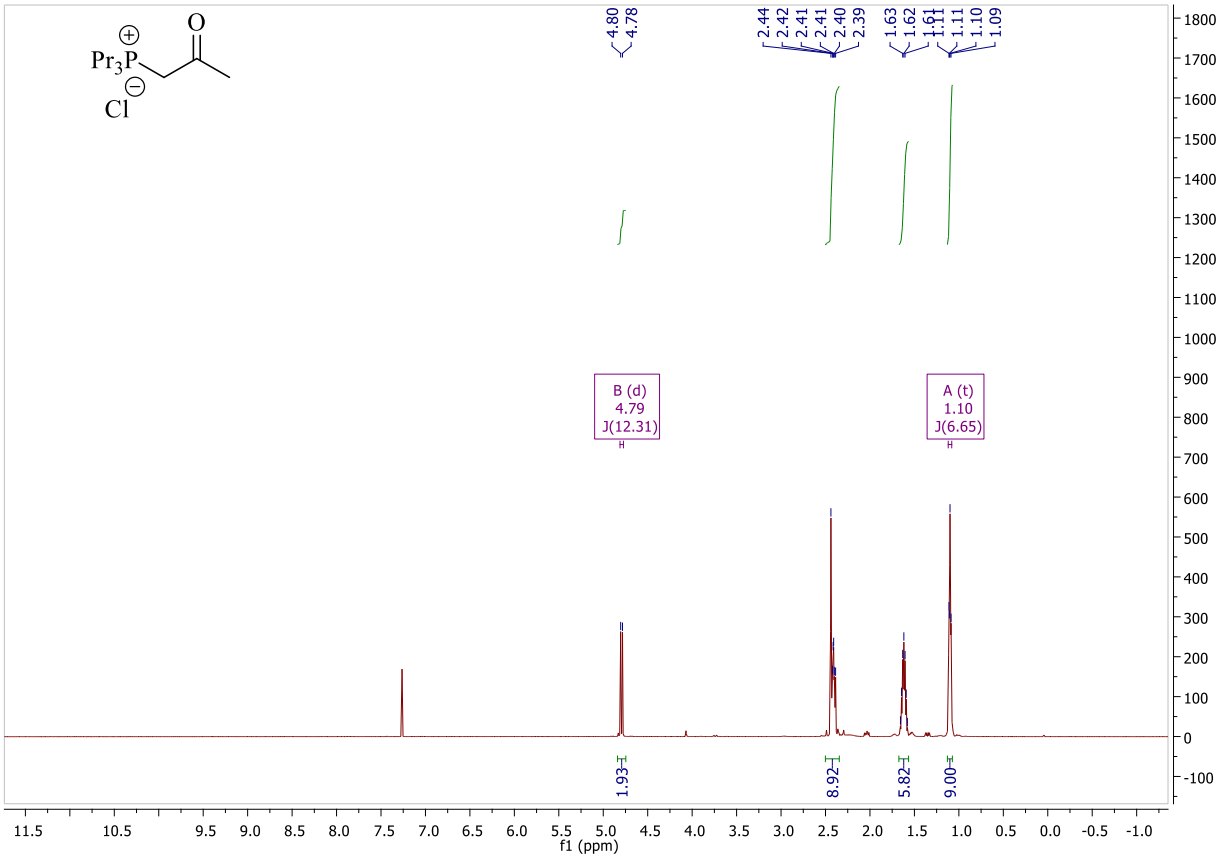
^{13}C NMR spectrum of 2-(chloromethyl)-2,5,5-trimethyl-1,3-dioxane (**12**)



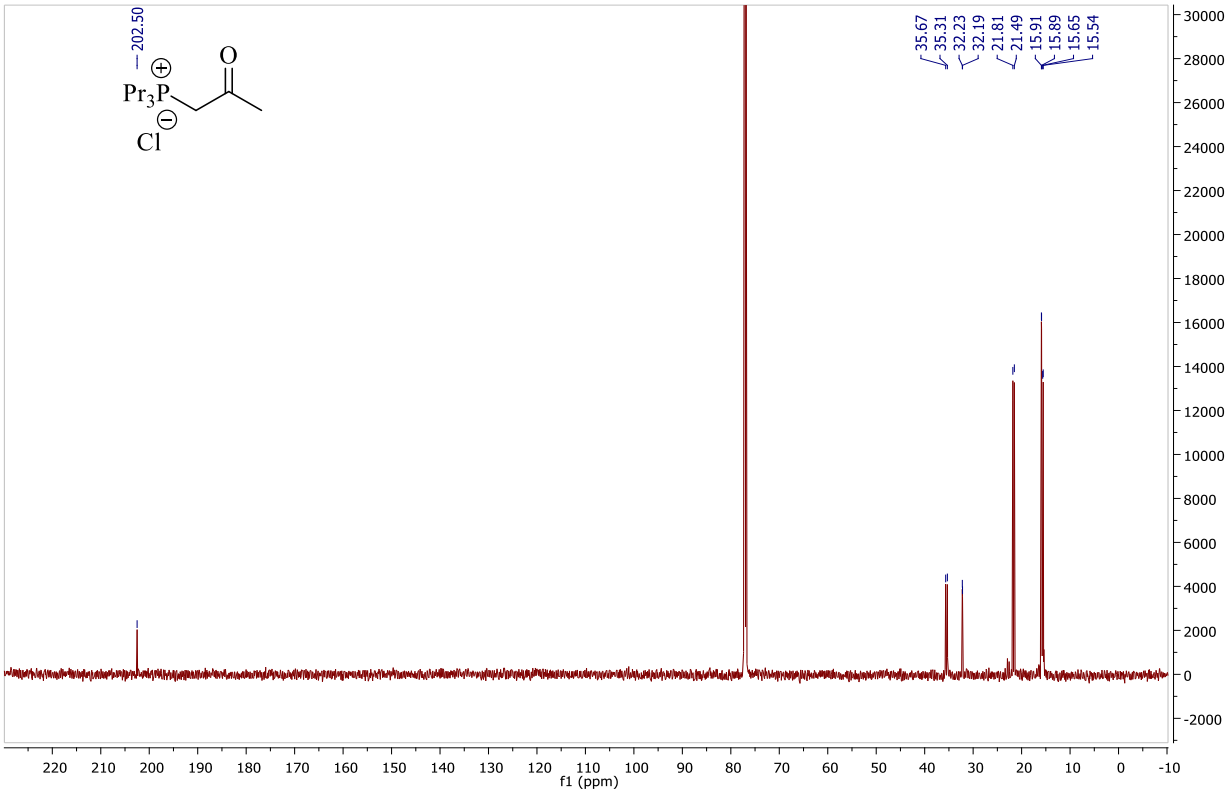
^{1}H NMR spectrum of 2-(chloromethyl)-2,4,4,5,5-pentamethyl-1,3-dioxolane (**13**)



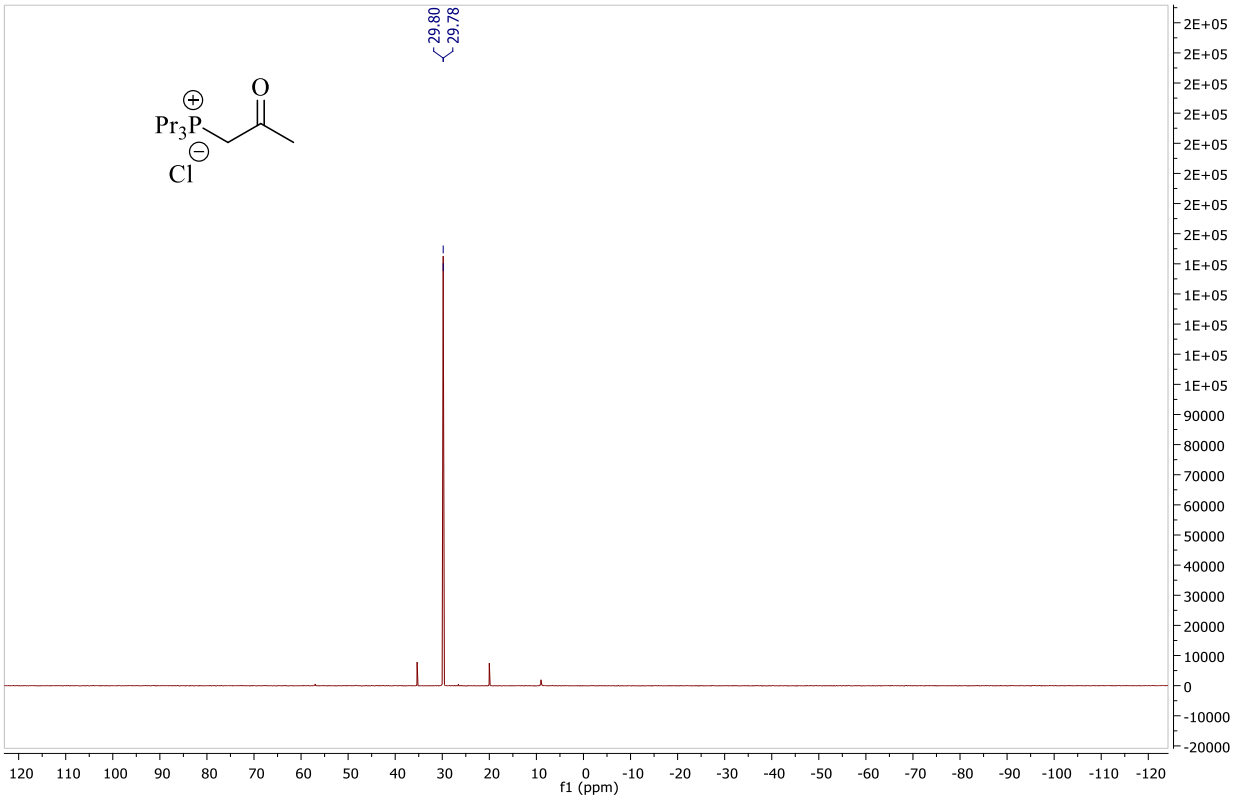
^{1}H NMR spectrum of (2-oxopropyl)tripropylphosphonium chloride (**14**)



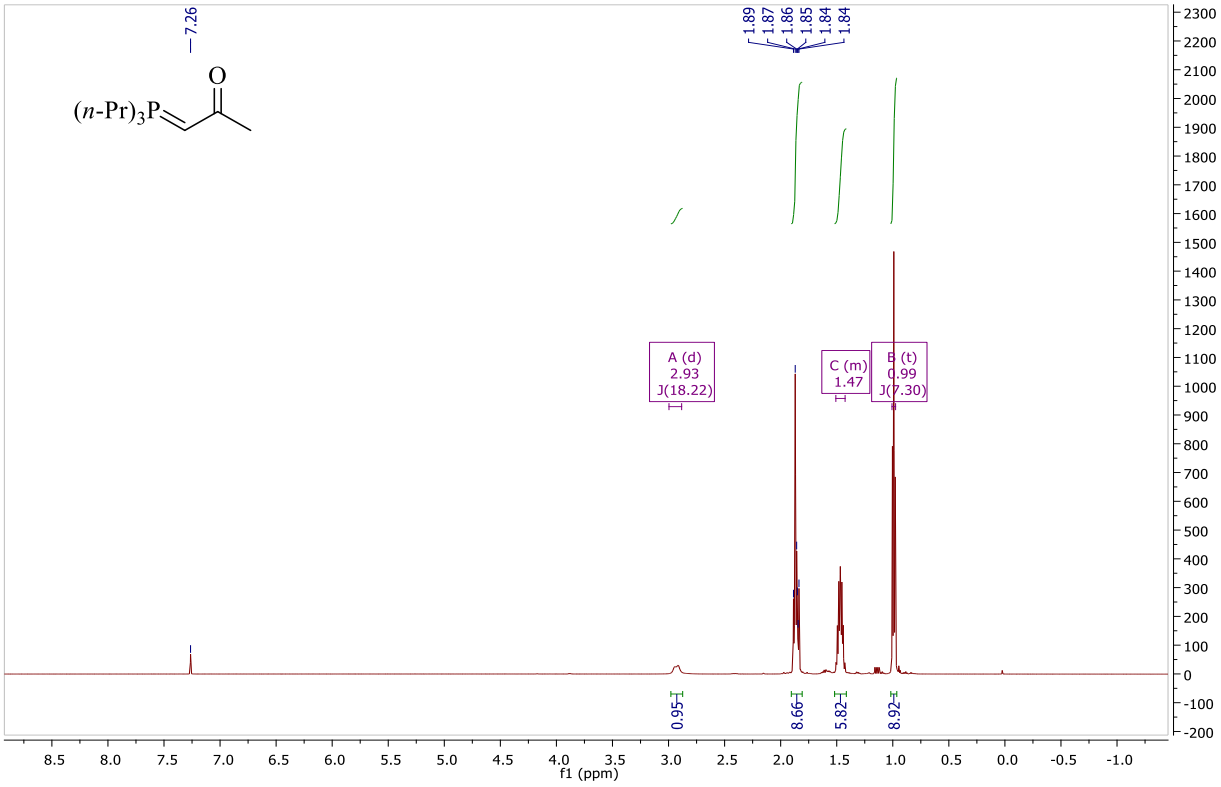
^{13}C NMR spectrum of (2-oxopropyl)tripropylphosphonium chloride (**14**)



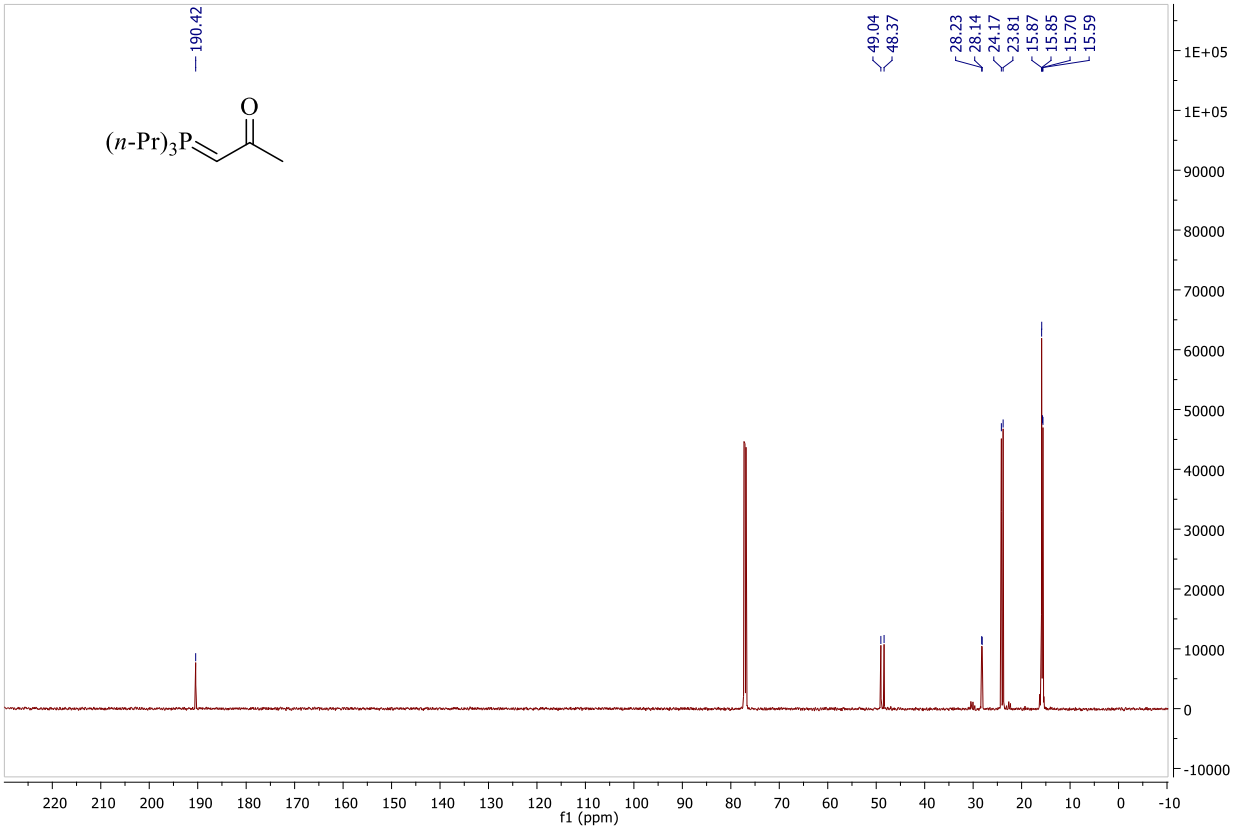
^{31}P NMR spectrum of (2-oxopropyl)tripropylphosphonium chloride (**14**)



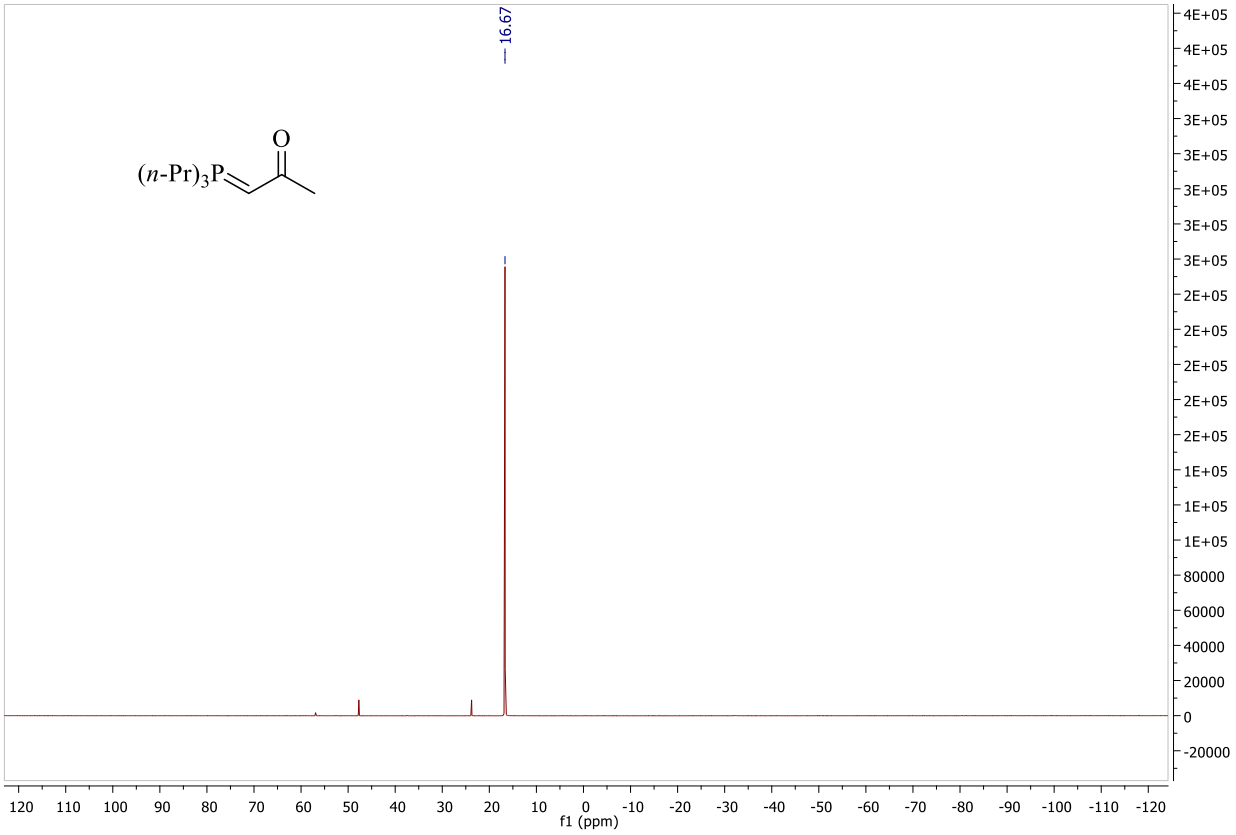
^{1}H NMR spectrum of 1-(tripropyl-λ5-phosphaneylidene)propan-2-one (**19**)



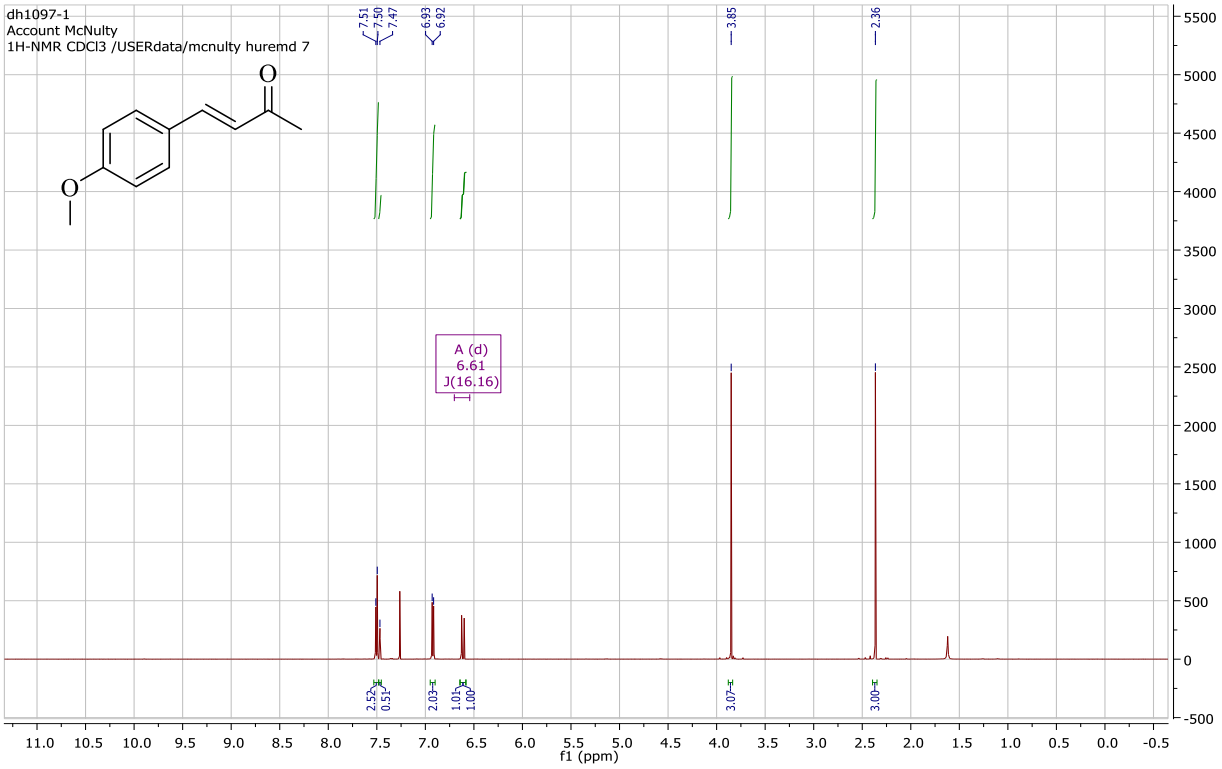
^{13}C NMR spectrum of 1-(tripropyl-λ5-phosphaneylidene)propan-2-one (**19**)



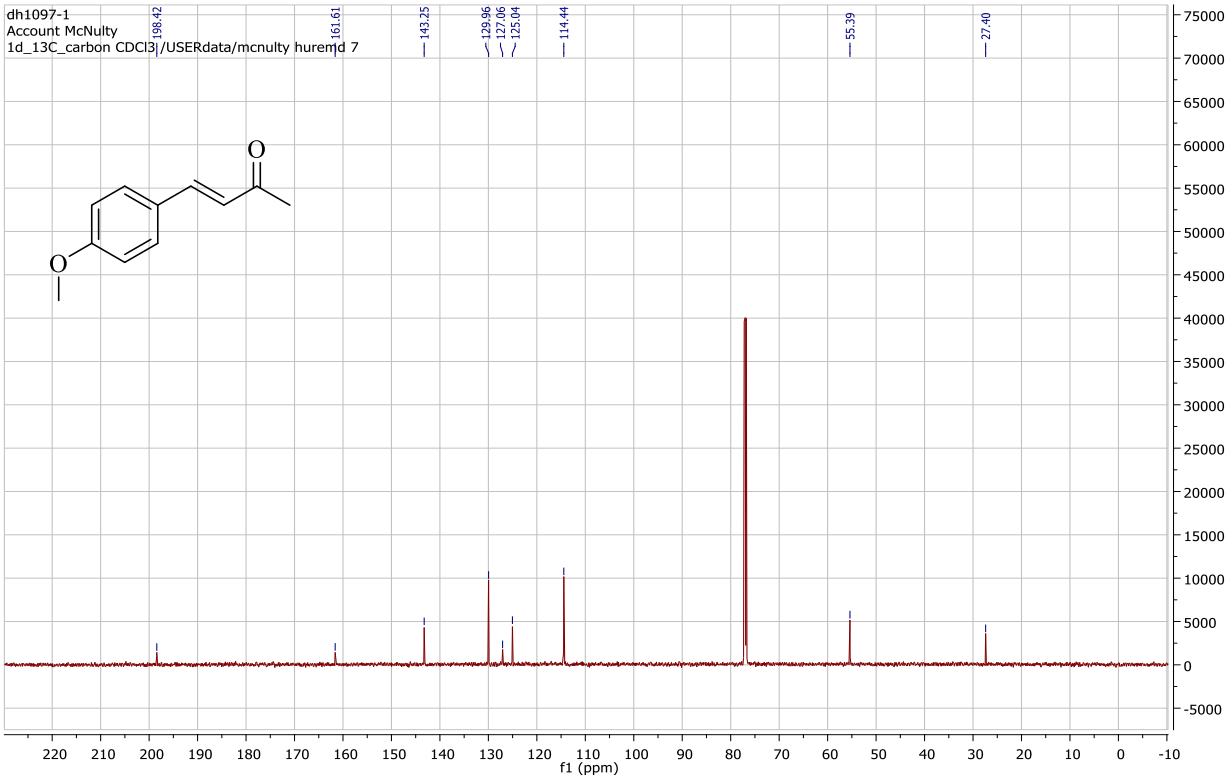
^{31}P NMR spectrum of 1-(tripropyl-λ5-phosphaneylidene)propan-2-one (**19**)



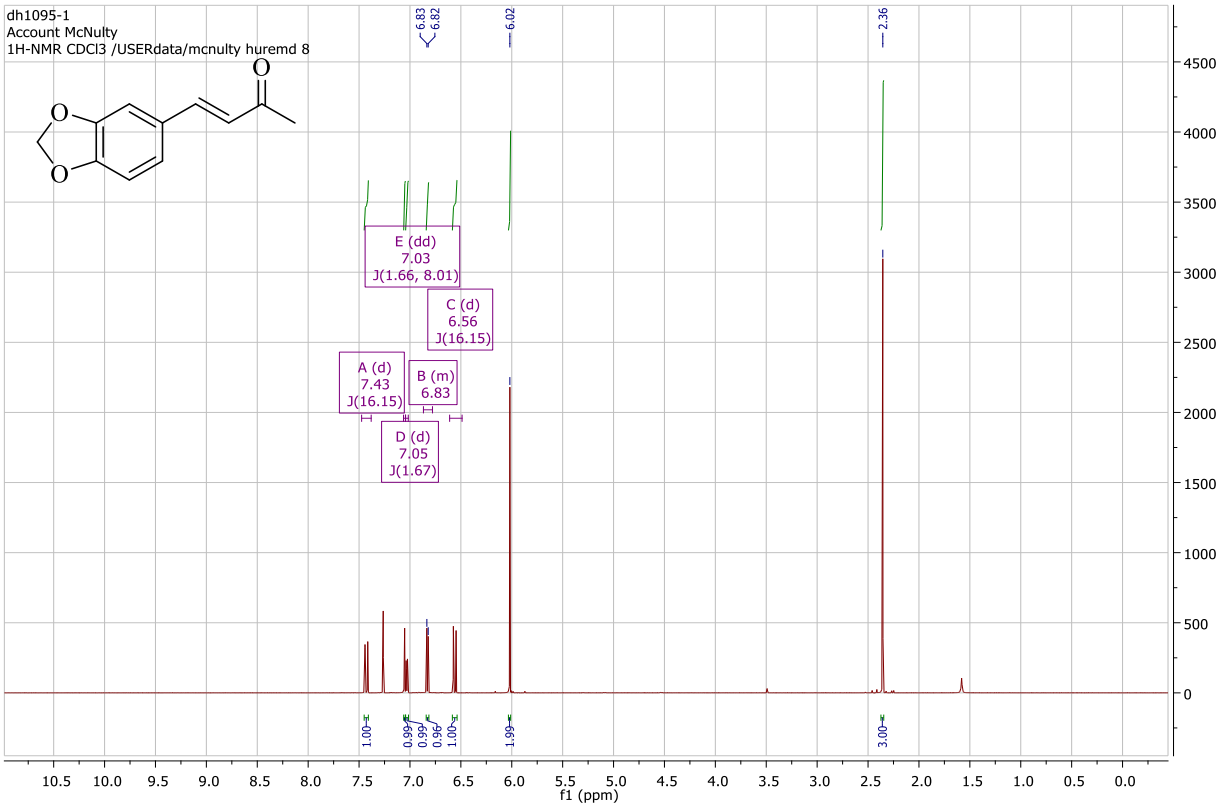
^{1}H NMR spectrum of (*E*)-4-(4-methoxyphenyl)but-3-en-2-one (**16**)



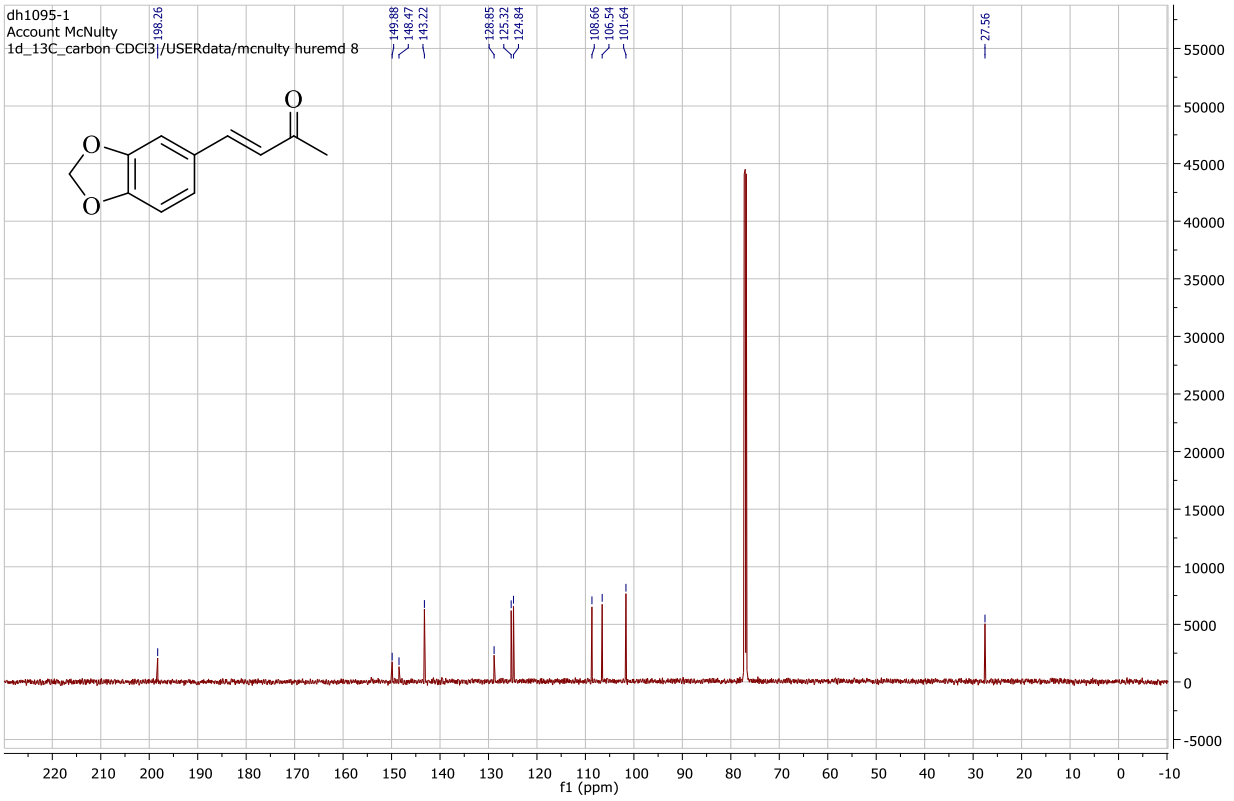
^{13}C NMR spectrum of (*E*)-4-(4-methoxyphenyl)but-3-en-2-one (**16**)



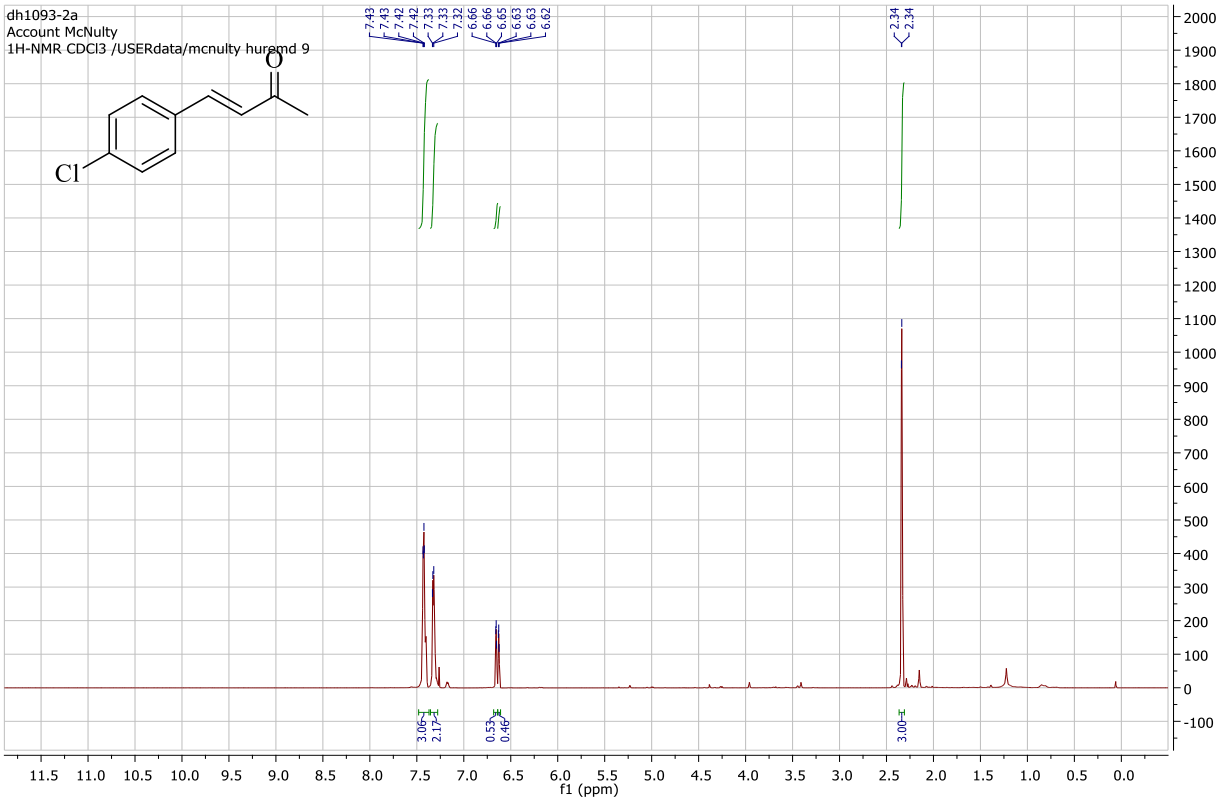
^{1}H NMR spectrum of (*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)but-3-en-2-one (**17**)



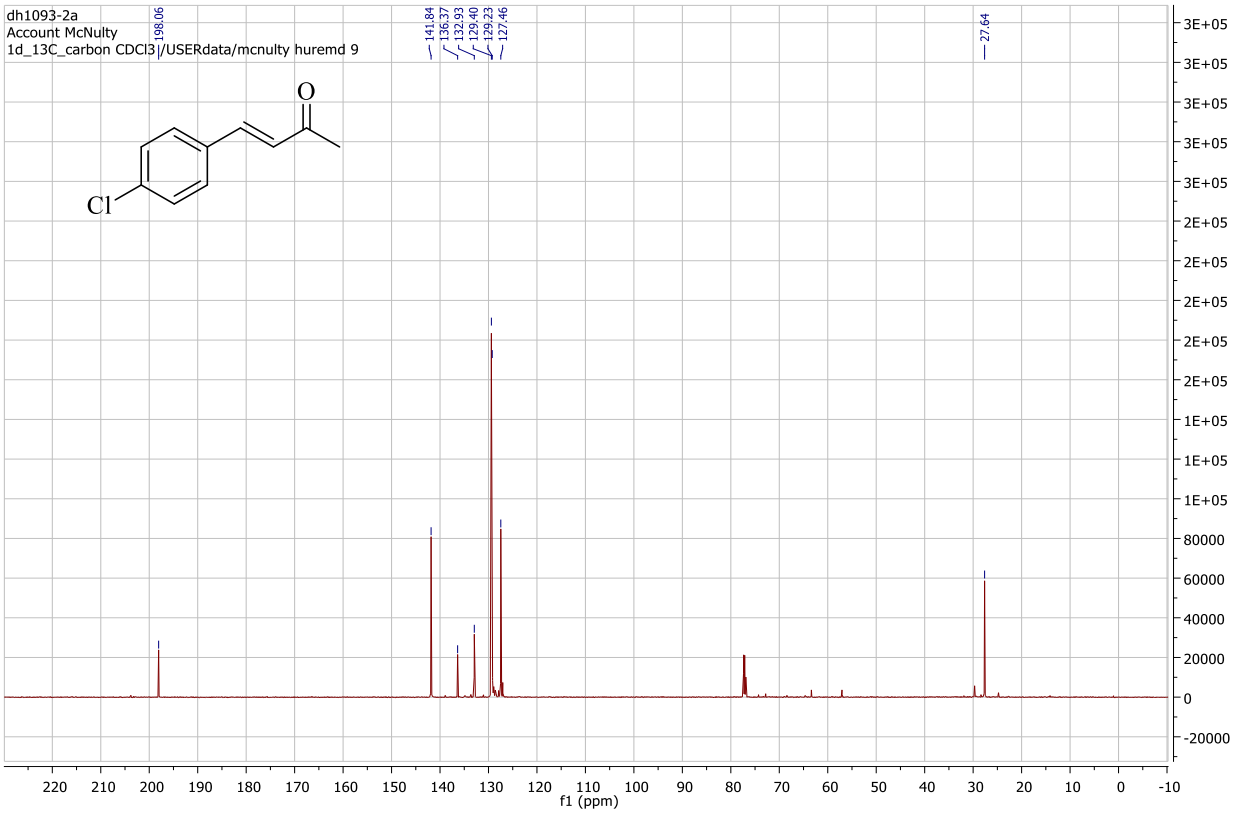
^{13}C NMR spectrum of (*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)but-3-en-2-one (**17**)



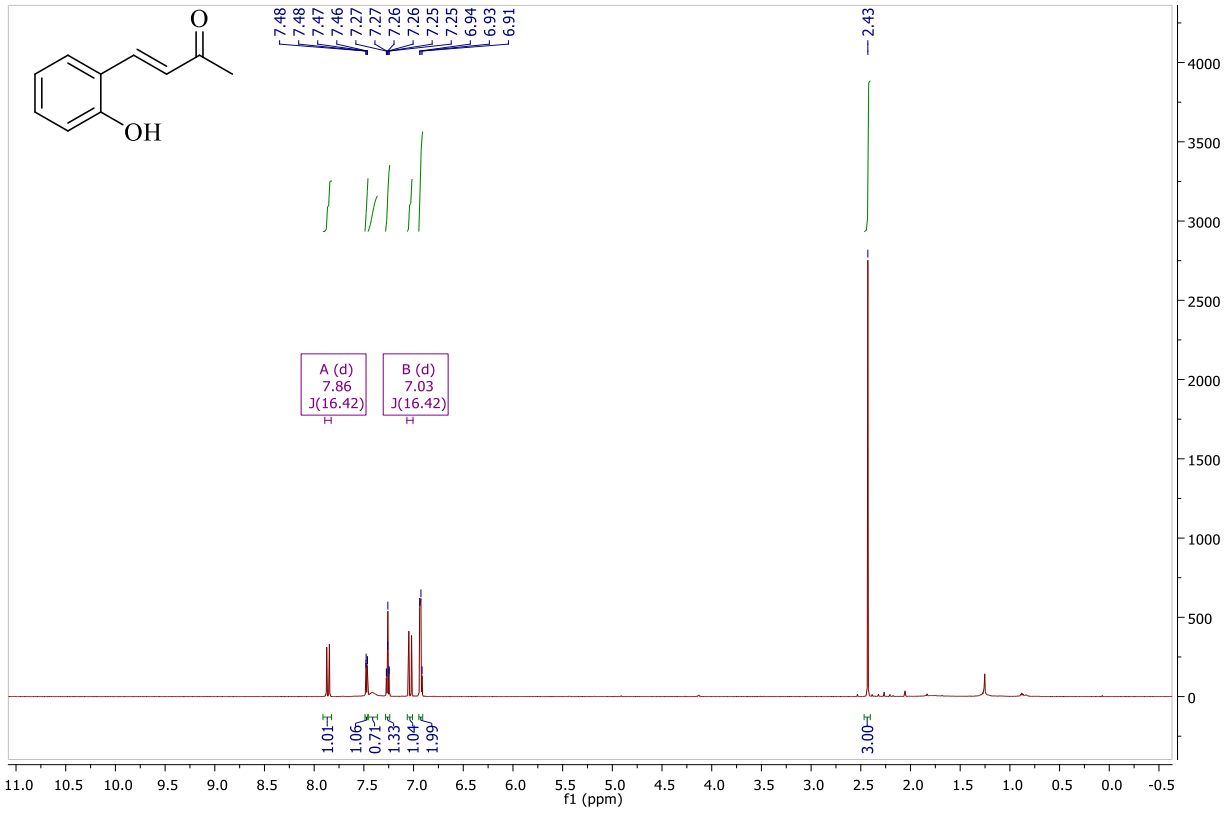
^{1}H NMR spectrum of (*E*)-4-(4-chlorophenyl)but-3-en-2-one (**15**)



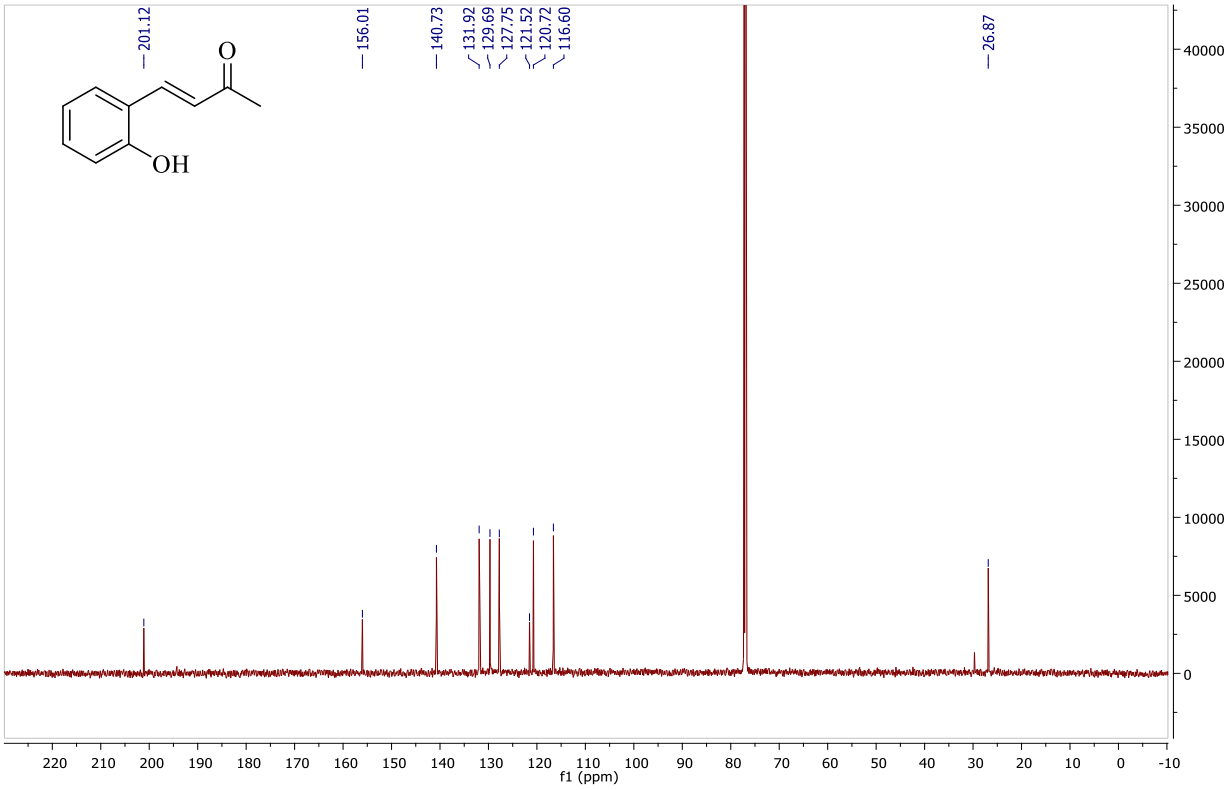
^{13}C NMR spectrum of (*E*)-4-(4-chlorophenyl)but-3-en-2-one (**15**)



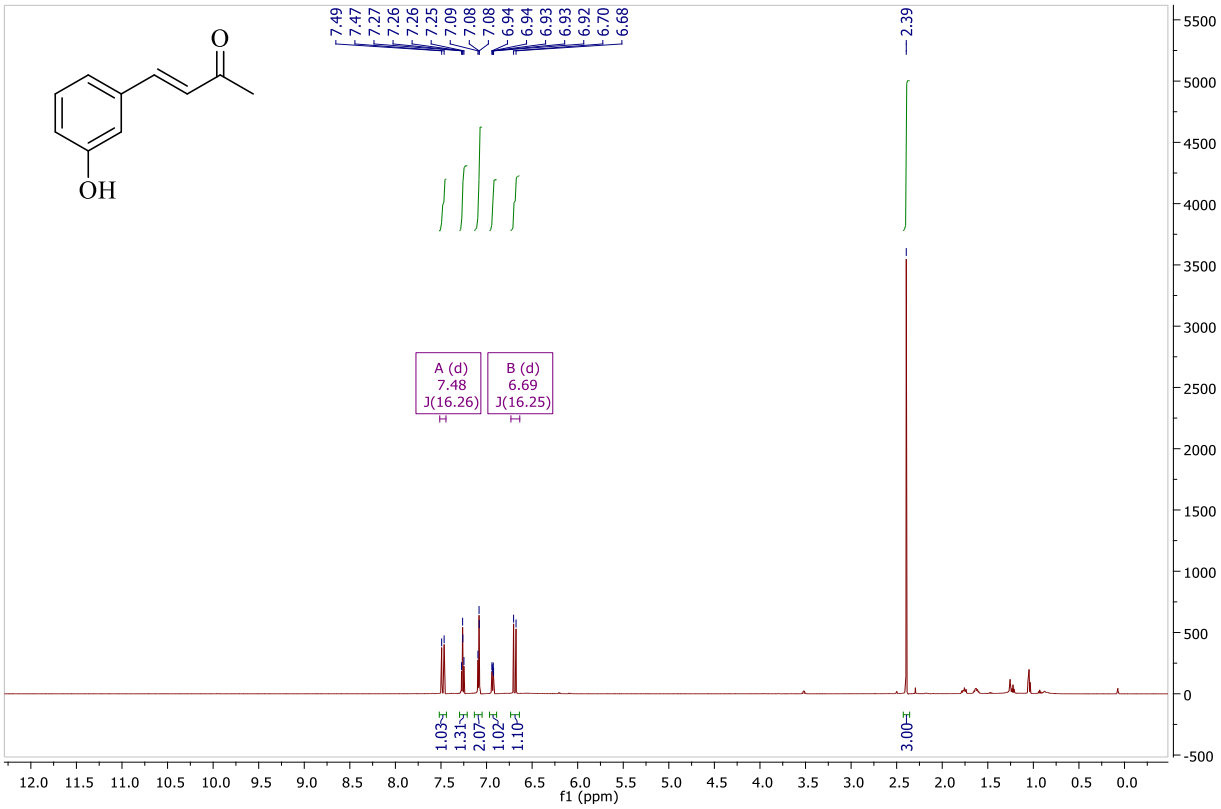
^{1}H NMR spectrum of (*E*)-4-(2-hydroxyphenyl)but-3-en-2-one (**18**)



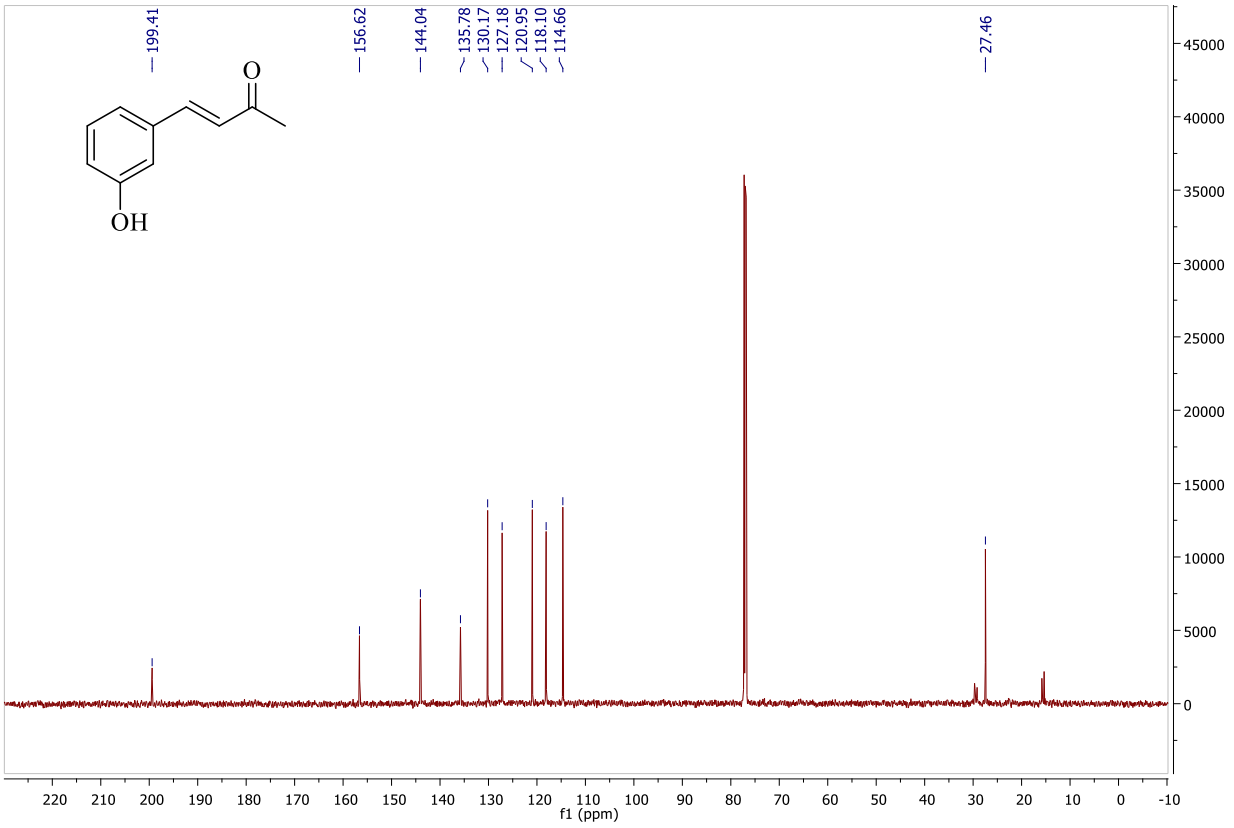
^{13}C NMR spectrum of (*E*)-4-(2-hydroxyphenyl)but-3-en-2-one (**18**)



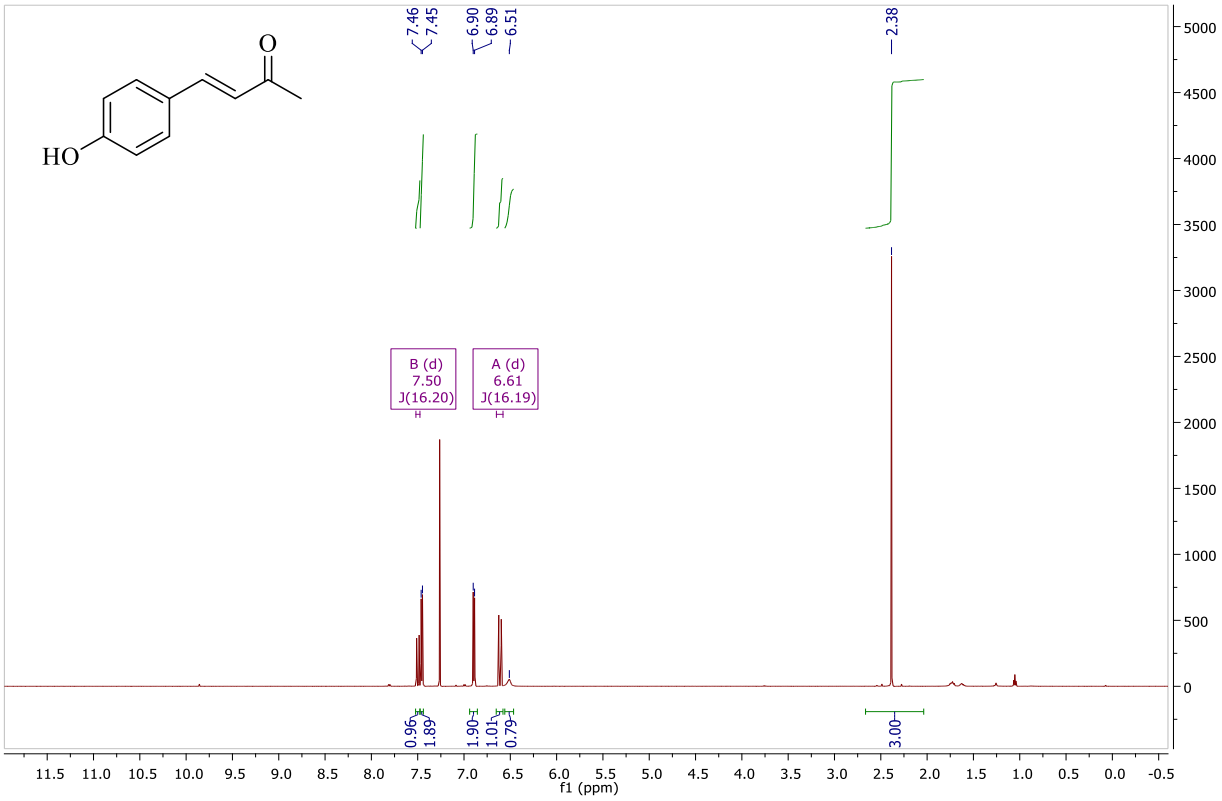
^{1}H NMR spectrum of (*E*)-4-(3-hydroxyphenyl)but-3-en-2-one (**22**)



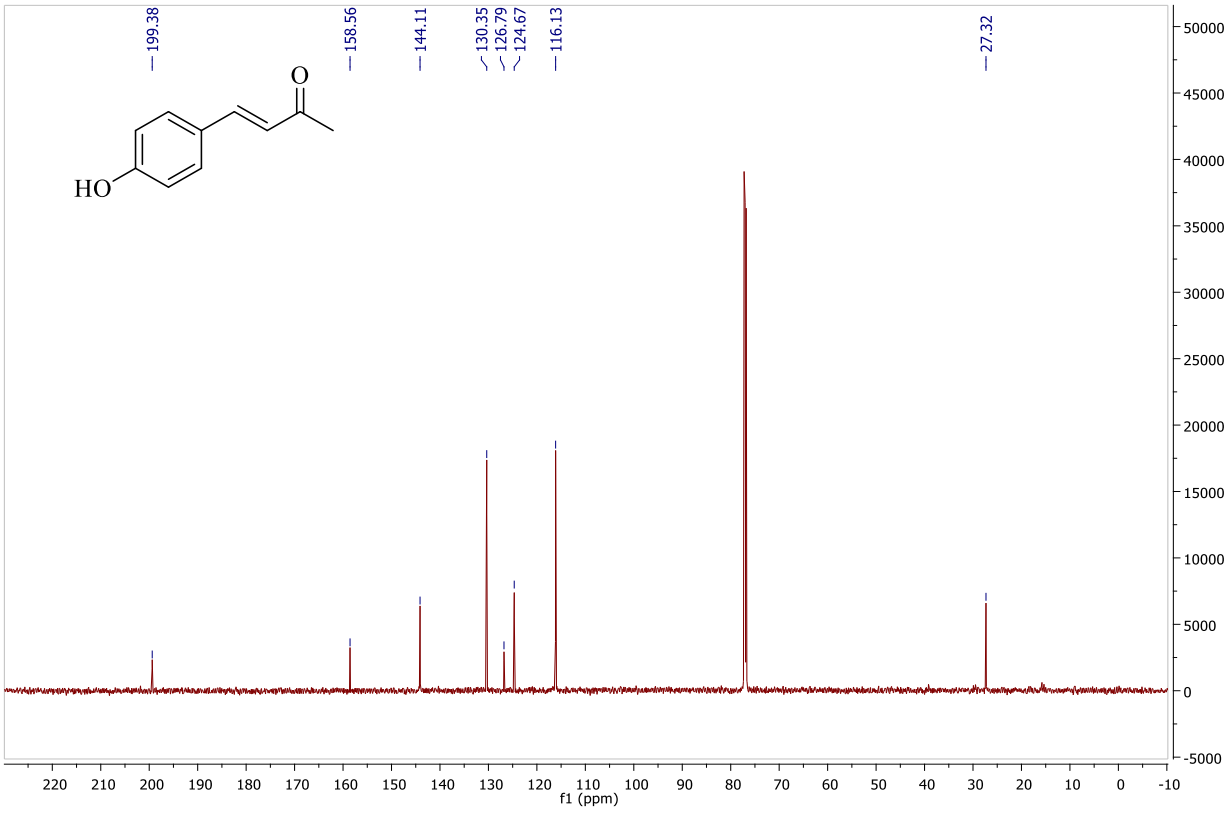
^{13}C NMR spectrum of (*E*)-4-(3-hydroxyphenyl)but-3-en-2-one (**22**)



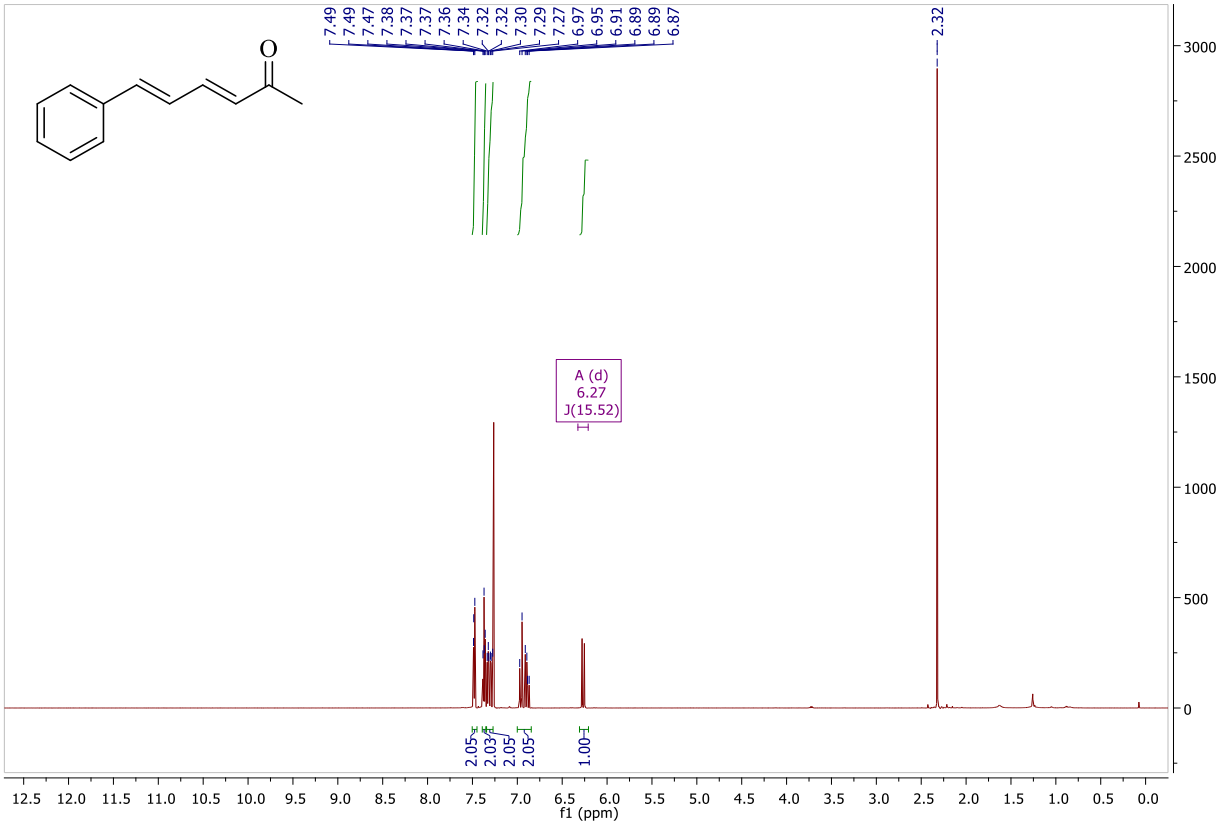
^{1}H NMR spectrum of (*E*)-4-(4-hydroxyphenyl)but-3-en-2-one (**23**)



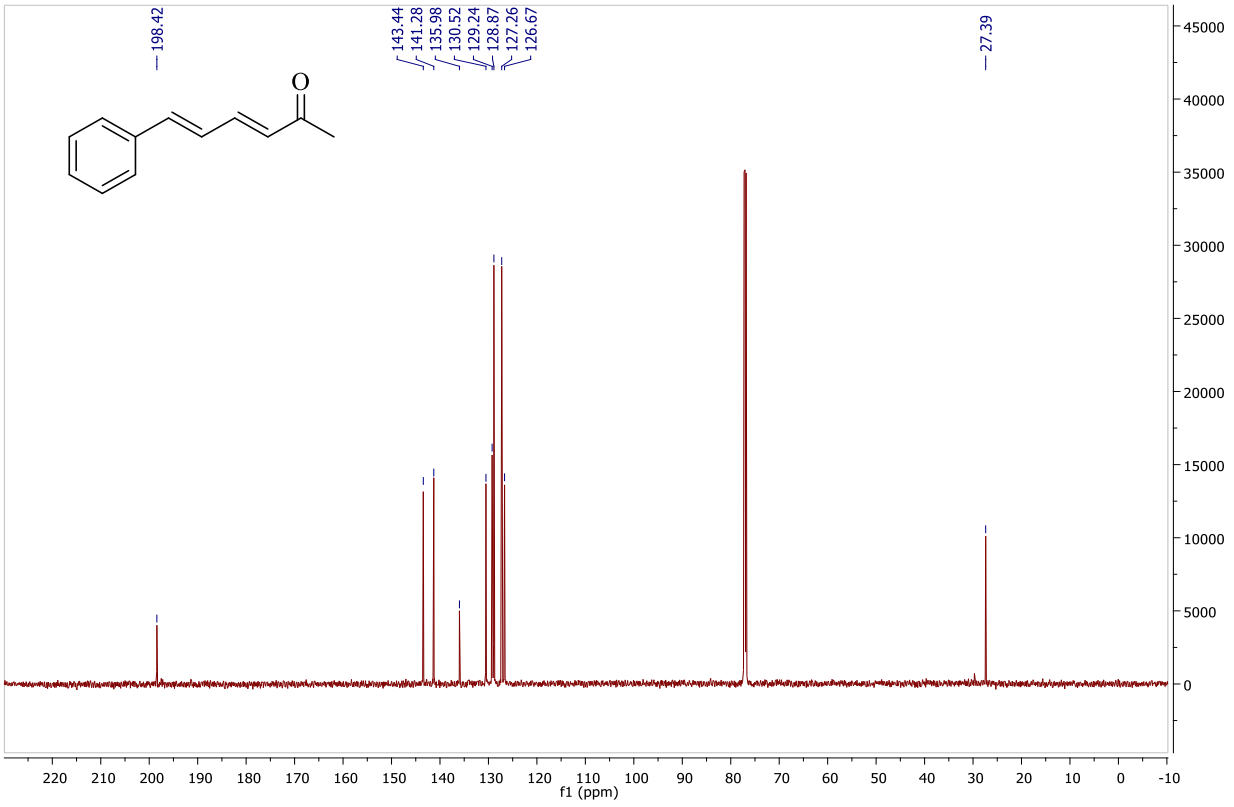
^{13}C NMR spectrum of (*E*)-4-(4-hydroxyphenyl)but-3-en-2-one (**23**)



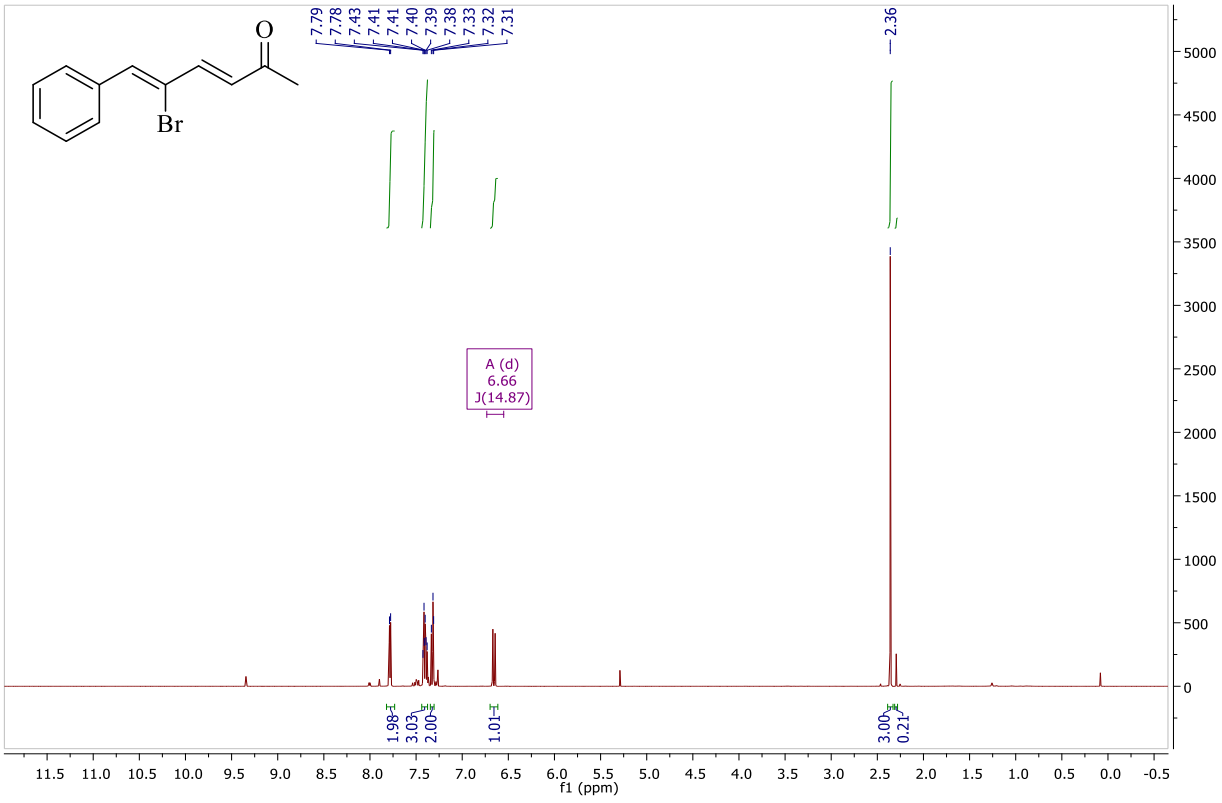
^{1}H NMR spectrum of (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one (**20**)



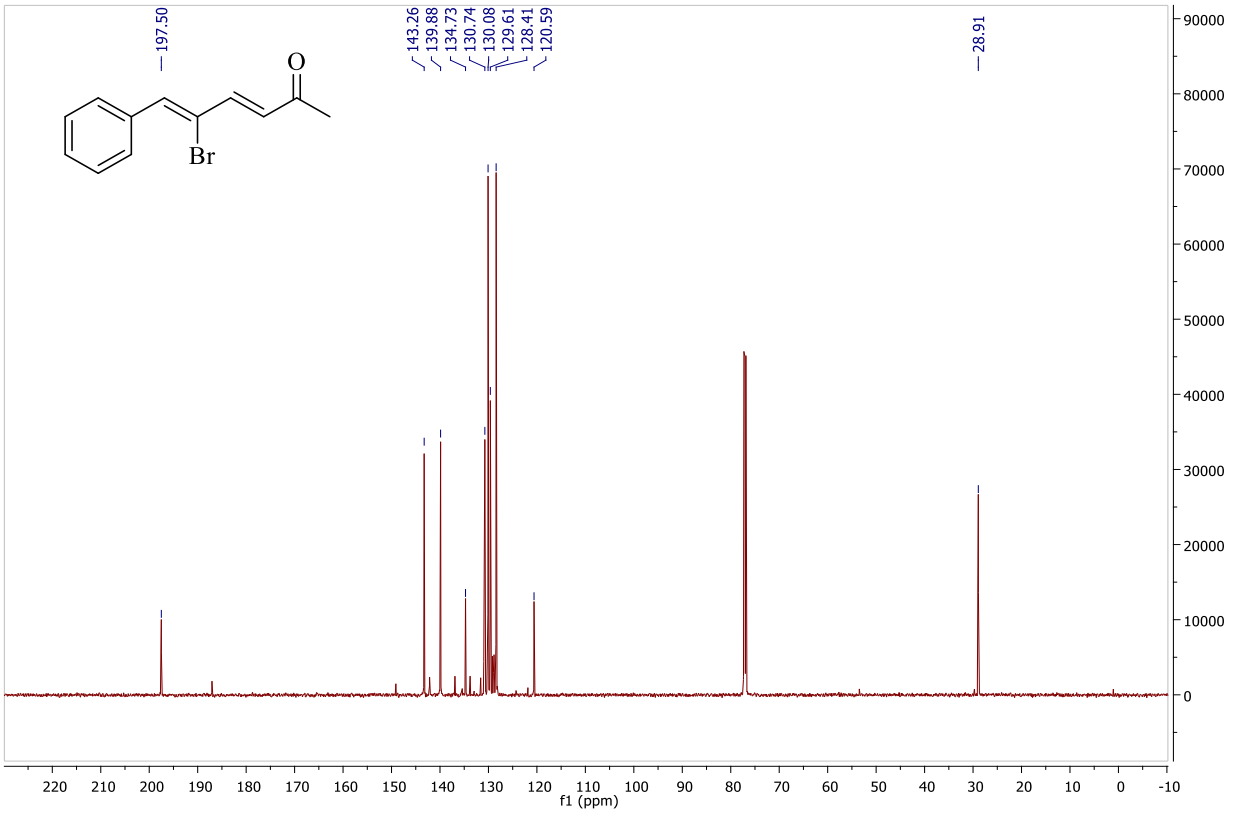
^{13}C NMR spectrum of (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one (**20**)



^{1}H NMR spectrum of (3*E*,5*Z*)-5-bromo-6-phenylhexa-3,5-dien-2-one (**21**)



^{13}C NMR spectrum of (3*E*,5*Z*)-5-bromo-6-phenylhexa-3,5-dien-2-one (**21**)



GC/MS data for (3*E*,5*Z*)-5-bromo-6-phenylhexa-3,5-dien-2-one (**21**)

F1. Total ion chromatogram of sample in DCM

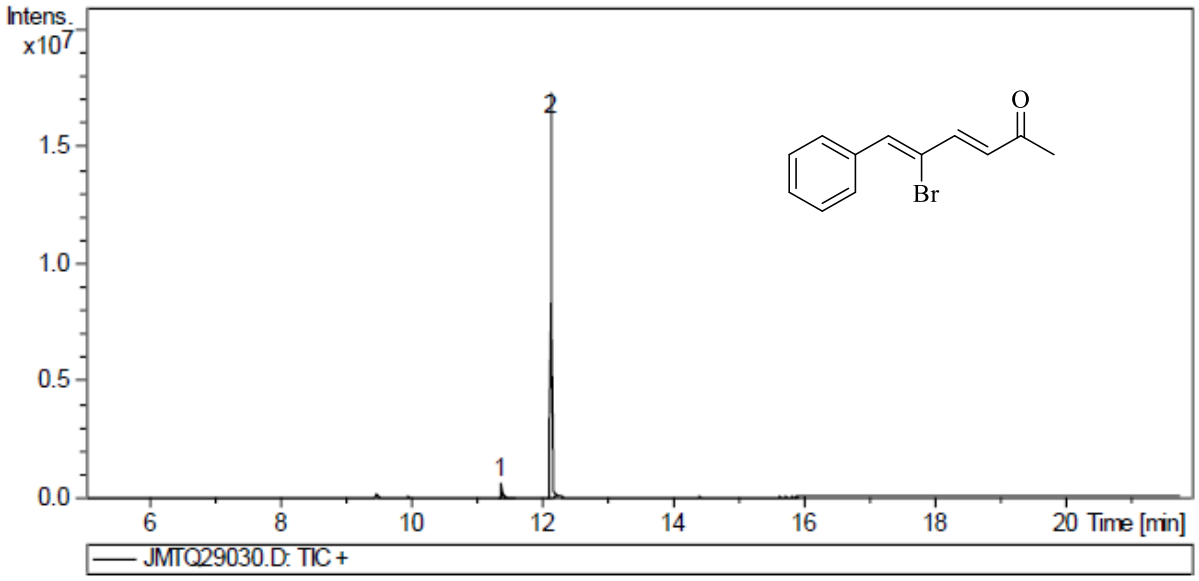
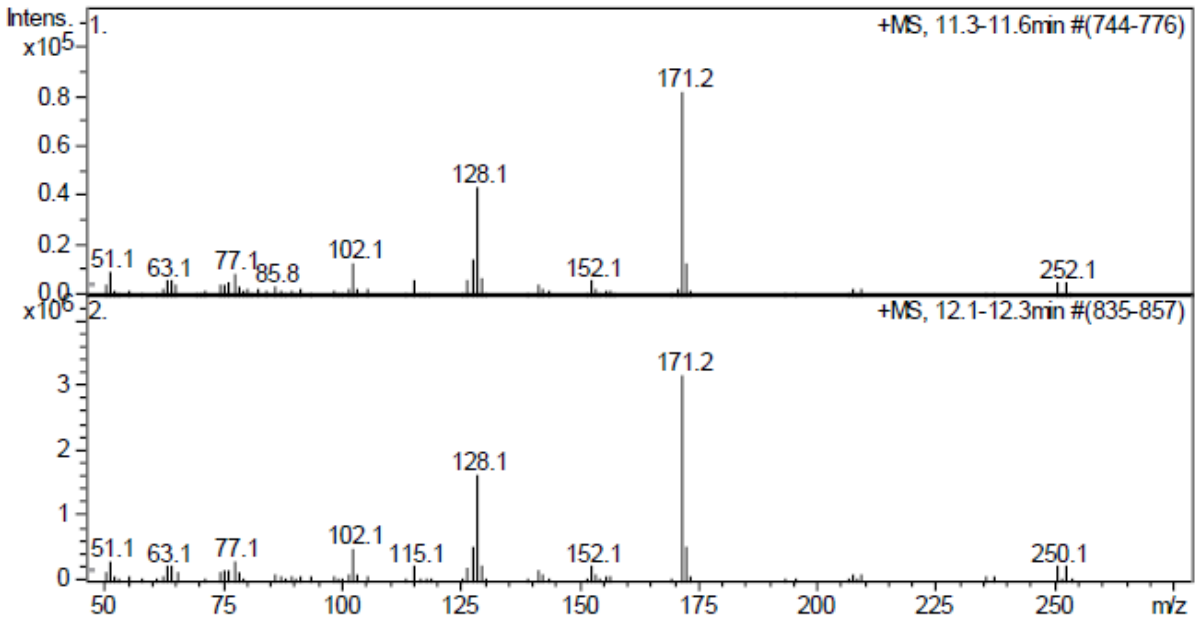
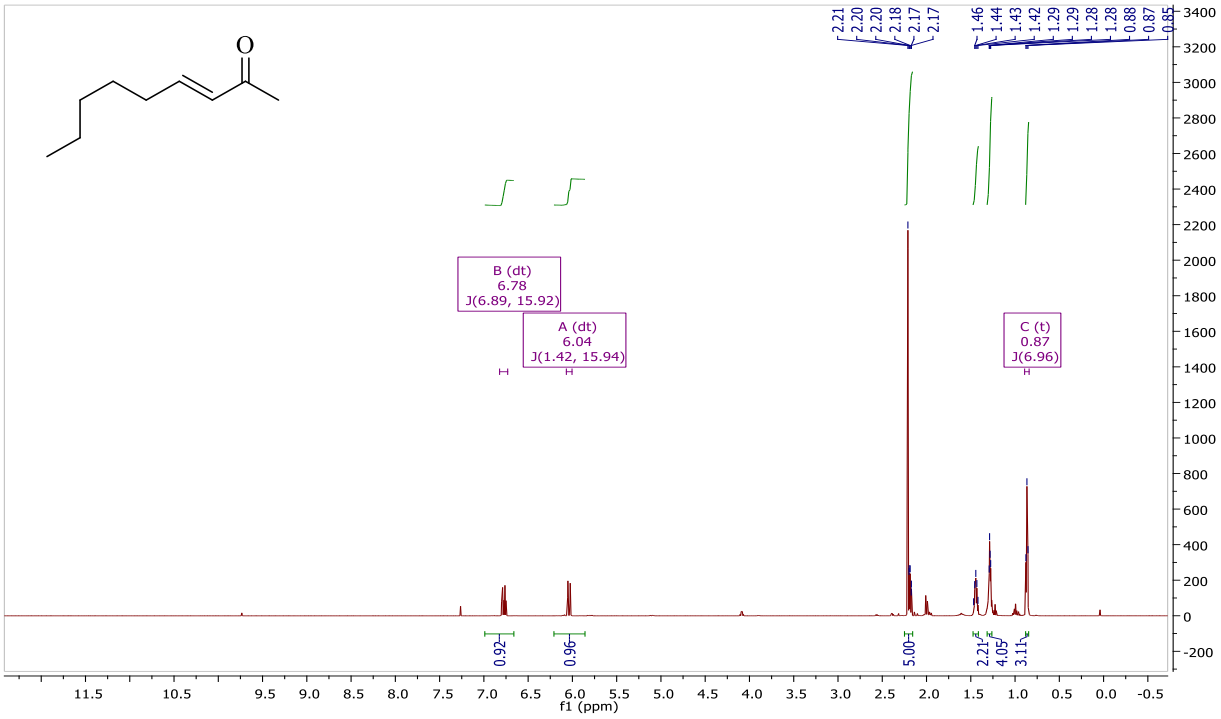


Figure 2. EI spectra of the impurity (top) and the target (bottom)

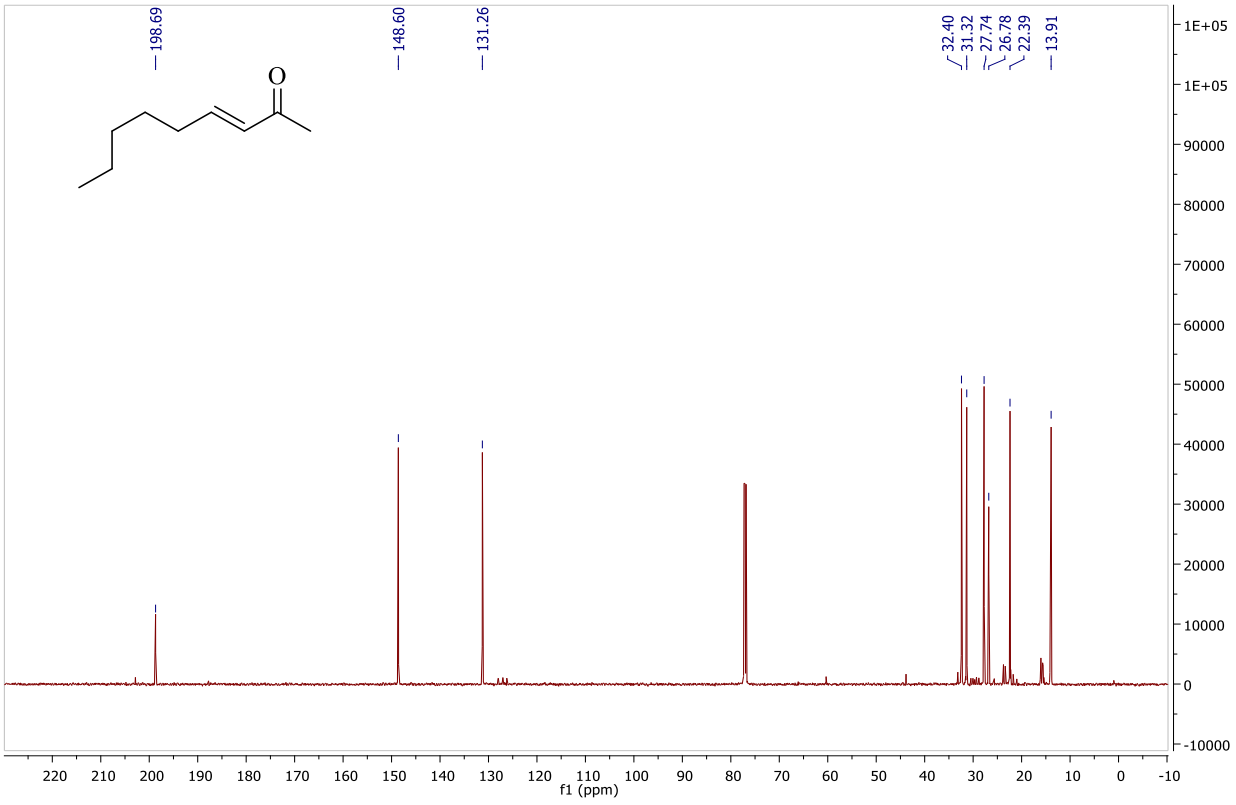


#	RT [min]	Area	
1	11.4	983609	
2	12.1	26786945	Target

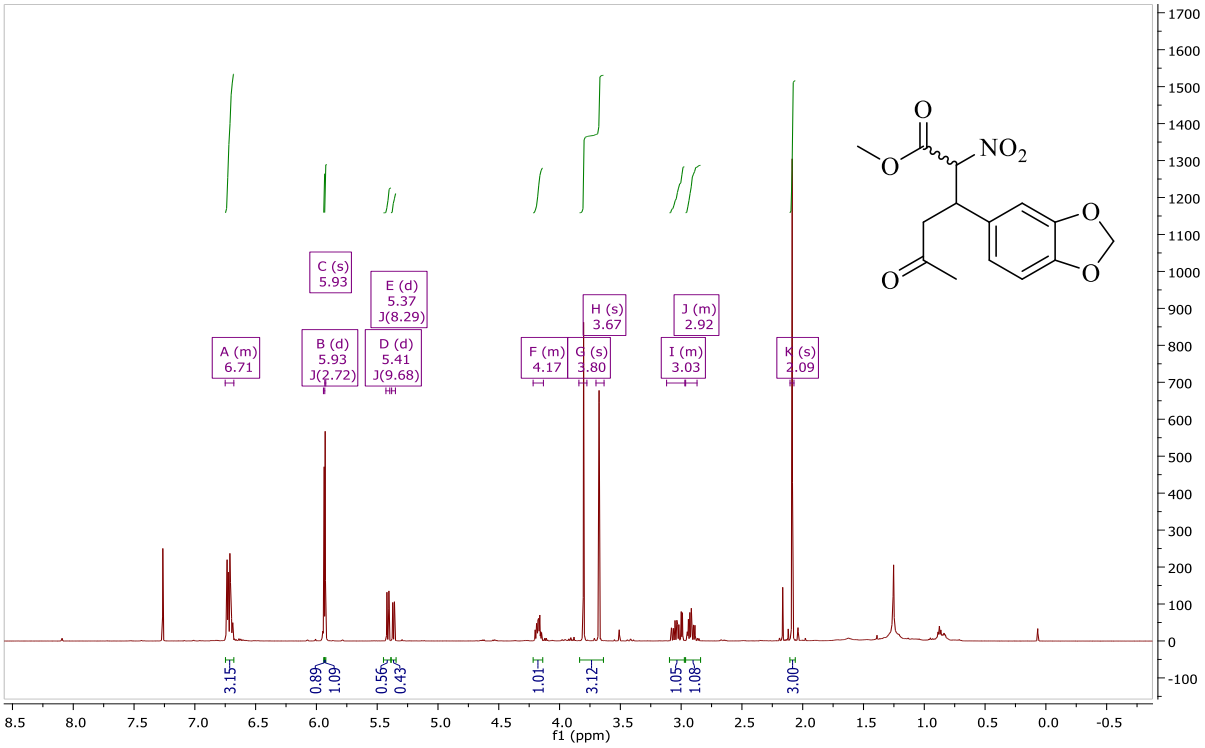
^{1}H NMR spectrum of (*E*)-non-3-en-2-one (**24**)



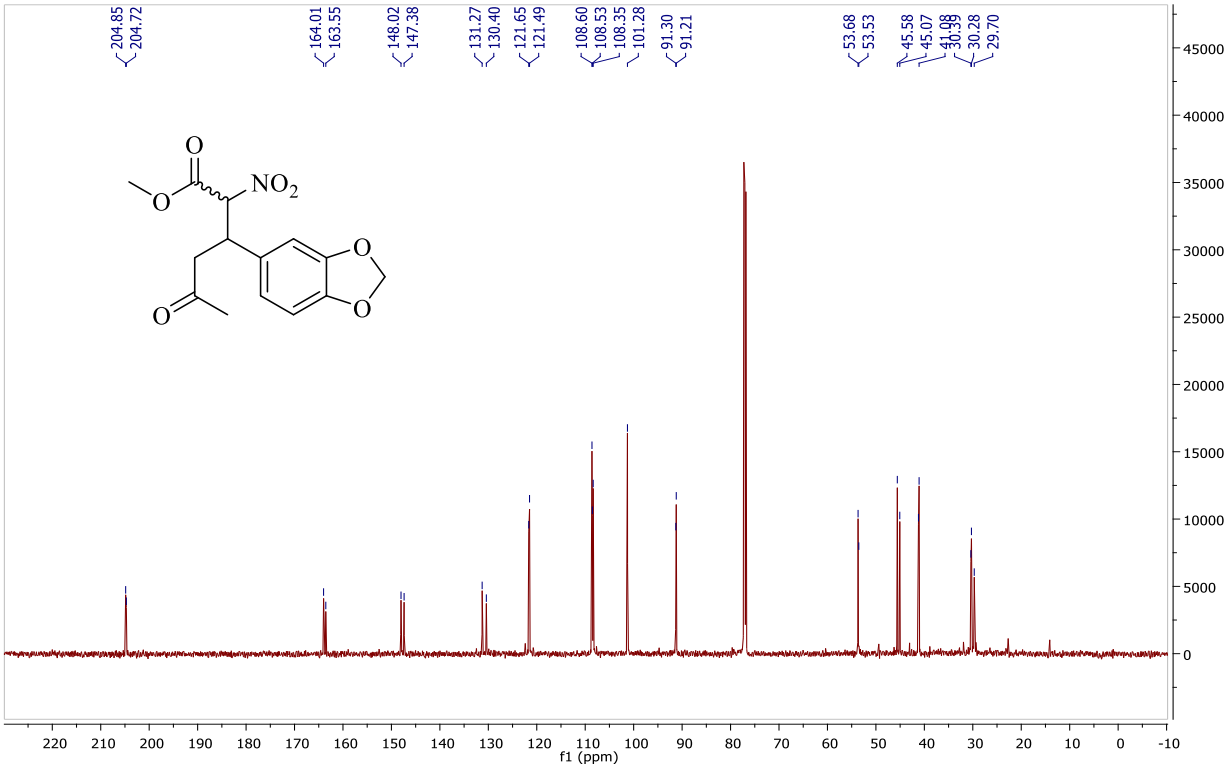
^{13}C NMR spectrum of (*E*)-non-3-en-2-one (**24**)



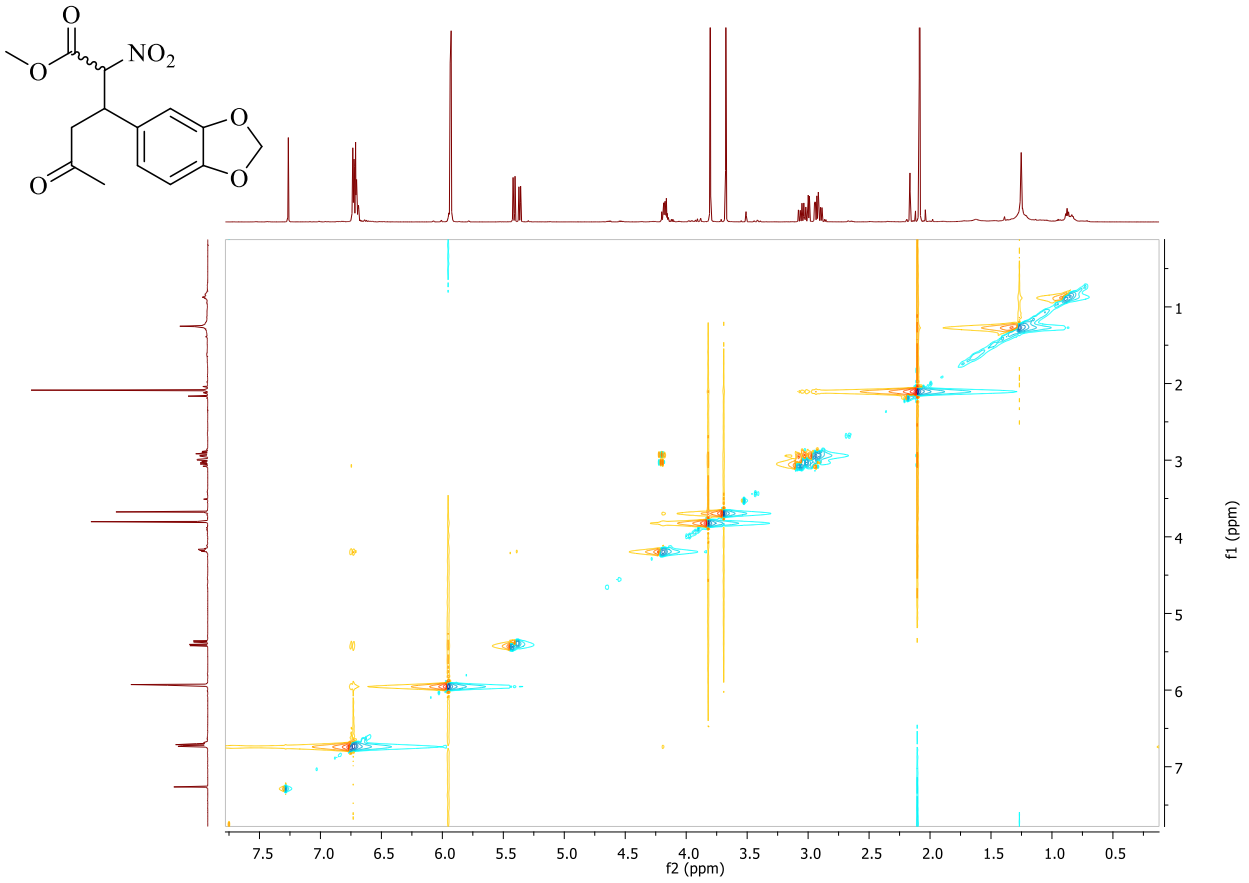
^{1}H NMR spectrum of methyl 3-(benzo[d][1,3]dioxol-5-yl)-2-nitro-5-oxohexanoate (**26**)



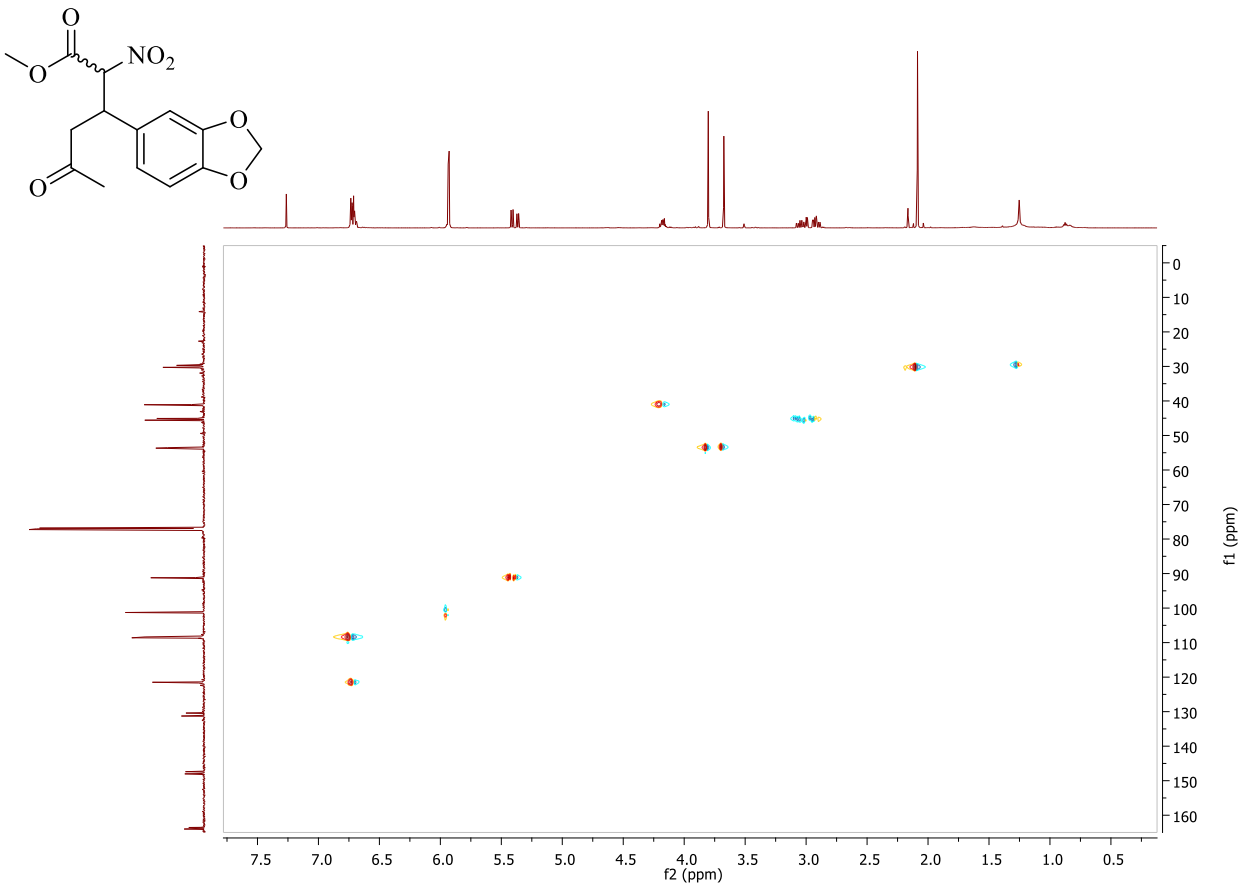
^{13}C NMR spectrum of methyl 3-(benzo[d][1,3]dioxol-5-yl)-2-nitro-5-oxohexanoate (**26**)



^{1}H – ^{1}H COSY spectrum of methyl 3-(benzo[d][1,3]dioxol-5-yl)-2-nitro-5-oxohexanoate (**26**)

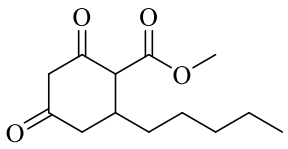


^{1}H – ^{13}C HSQC spectrum of methyl 3-(benzo[d][1,3]dioxol-5-yl)-2-nitro-5-oxohexanoate (**26**)

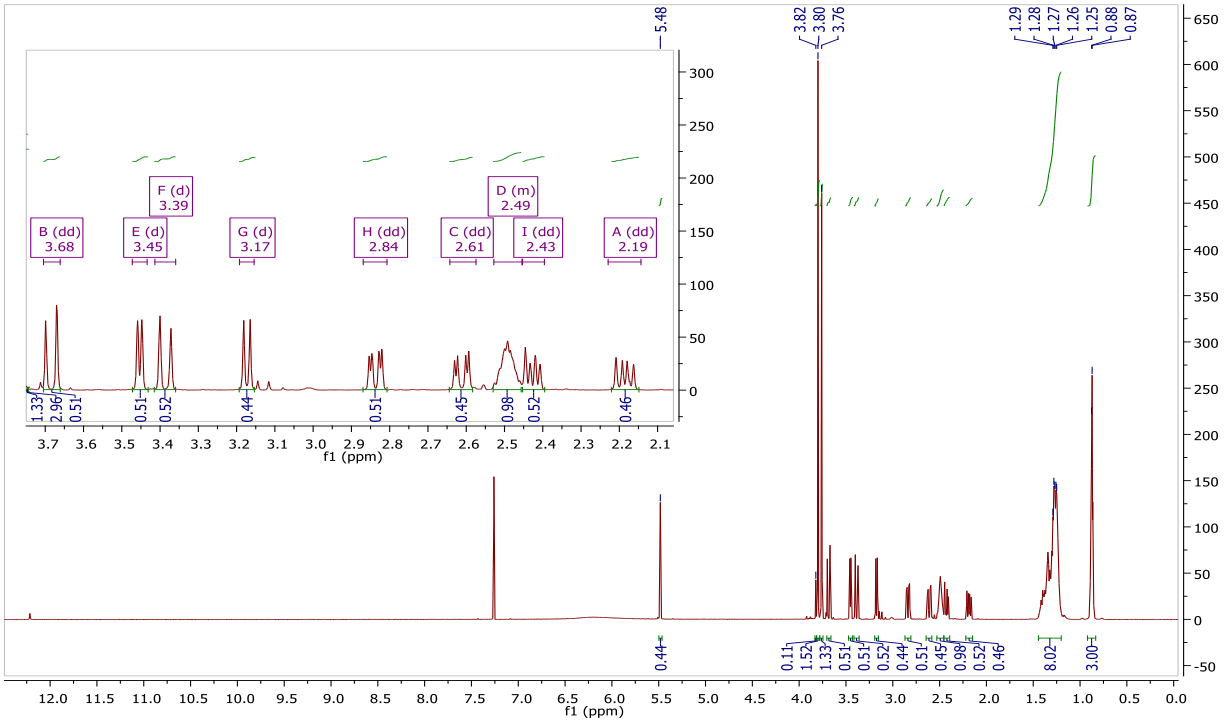


Chapter 4

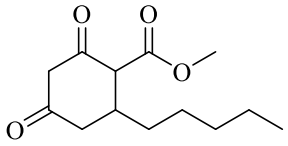
^{1}H NMR spectrum of methyl 2,4-dioxo-6-pentylcyclohexanecarboxylate (**13**)



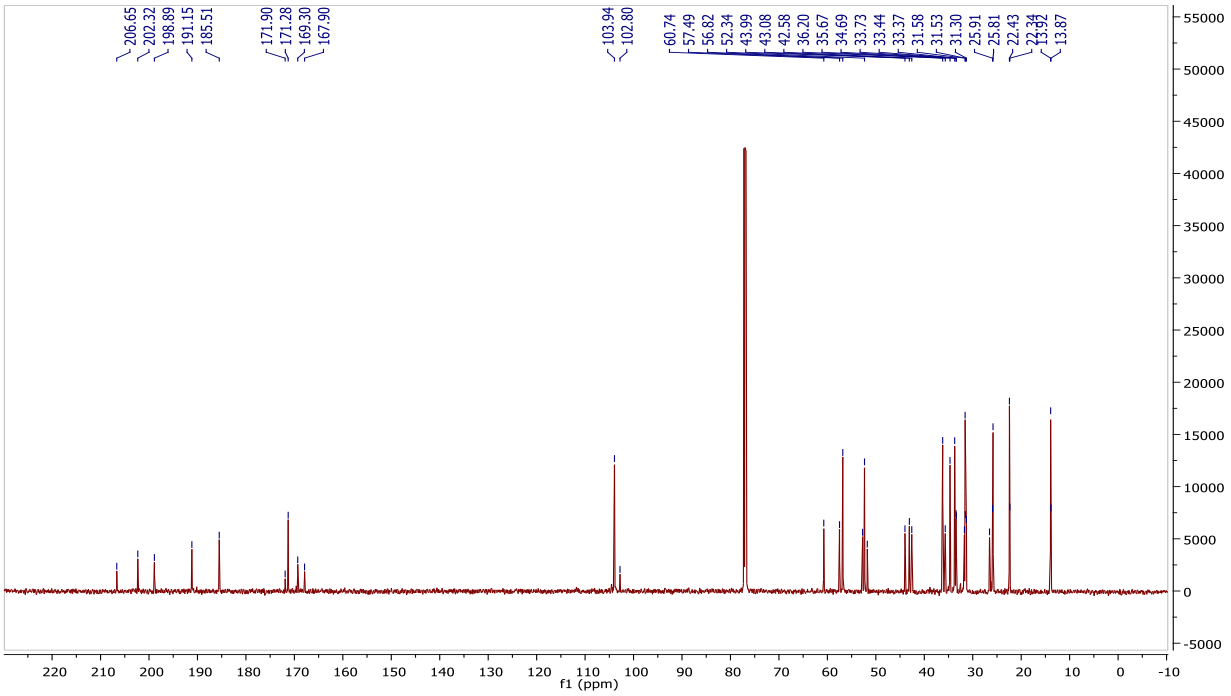
13



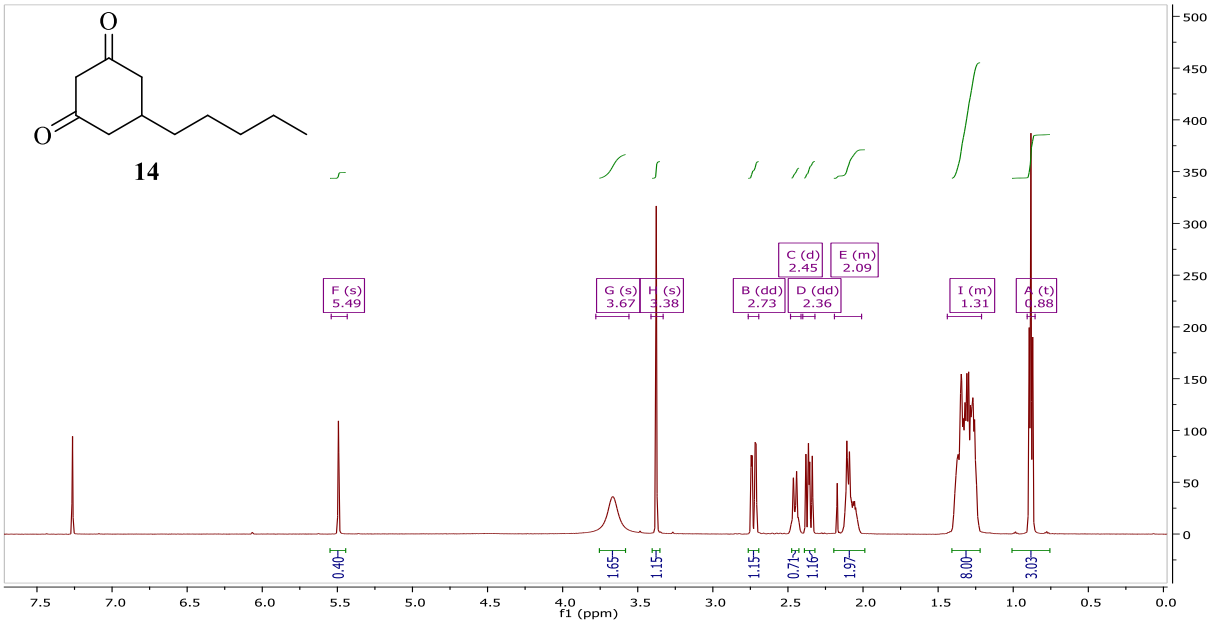
^{13}C NMR spectrum of methyl 2,4-dioxo-6-pentylcyclohexanecarboxylate (**13**)



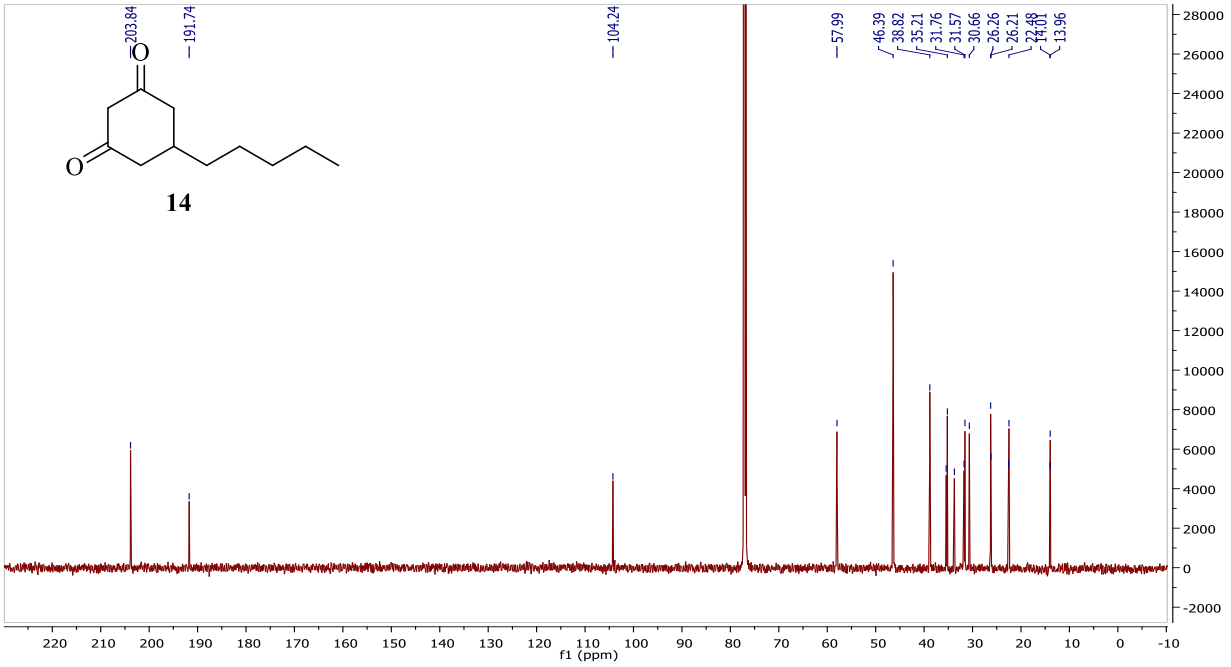
13



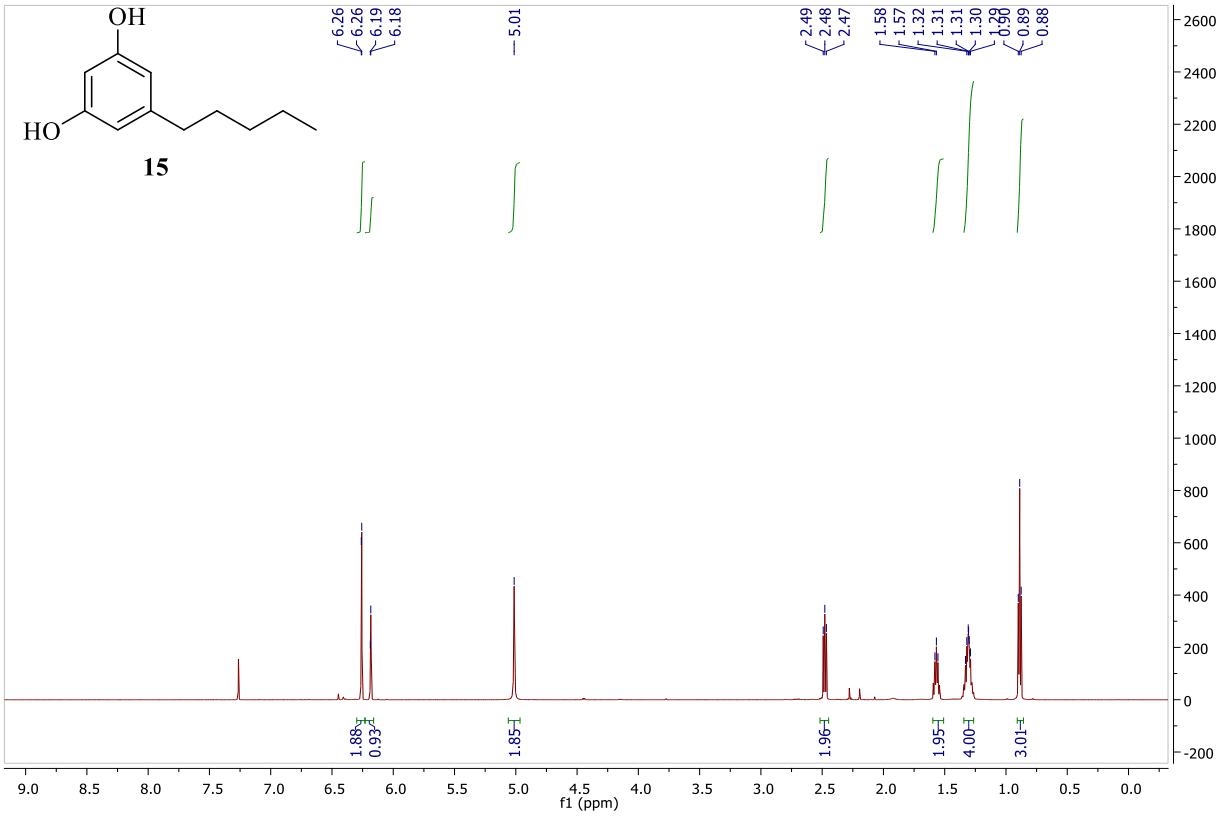
^{1}H NMR spectrum of 5-pentylcyclohexane-1,3-dione (**14**)



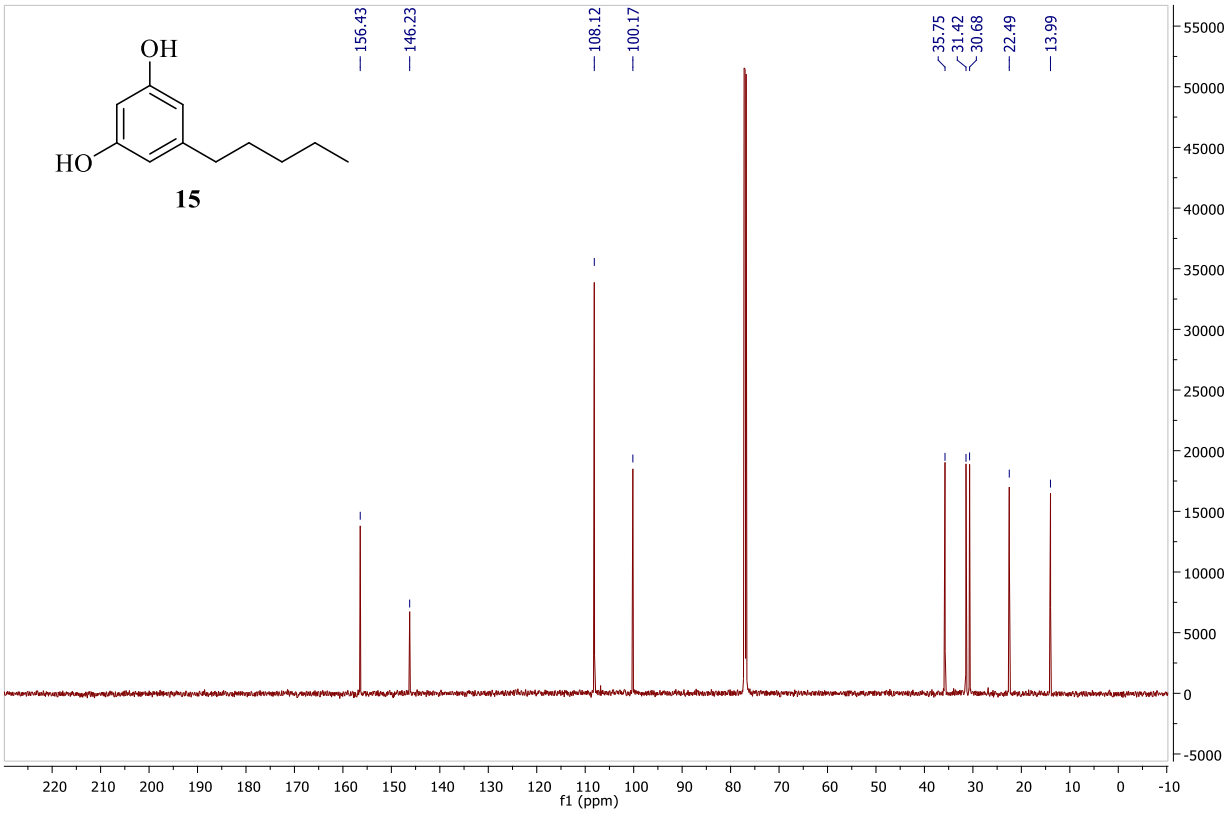
^{13}C NMR spectrum of 5-pentylcyclohexane-1,3-dione (**14**)



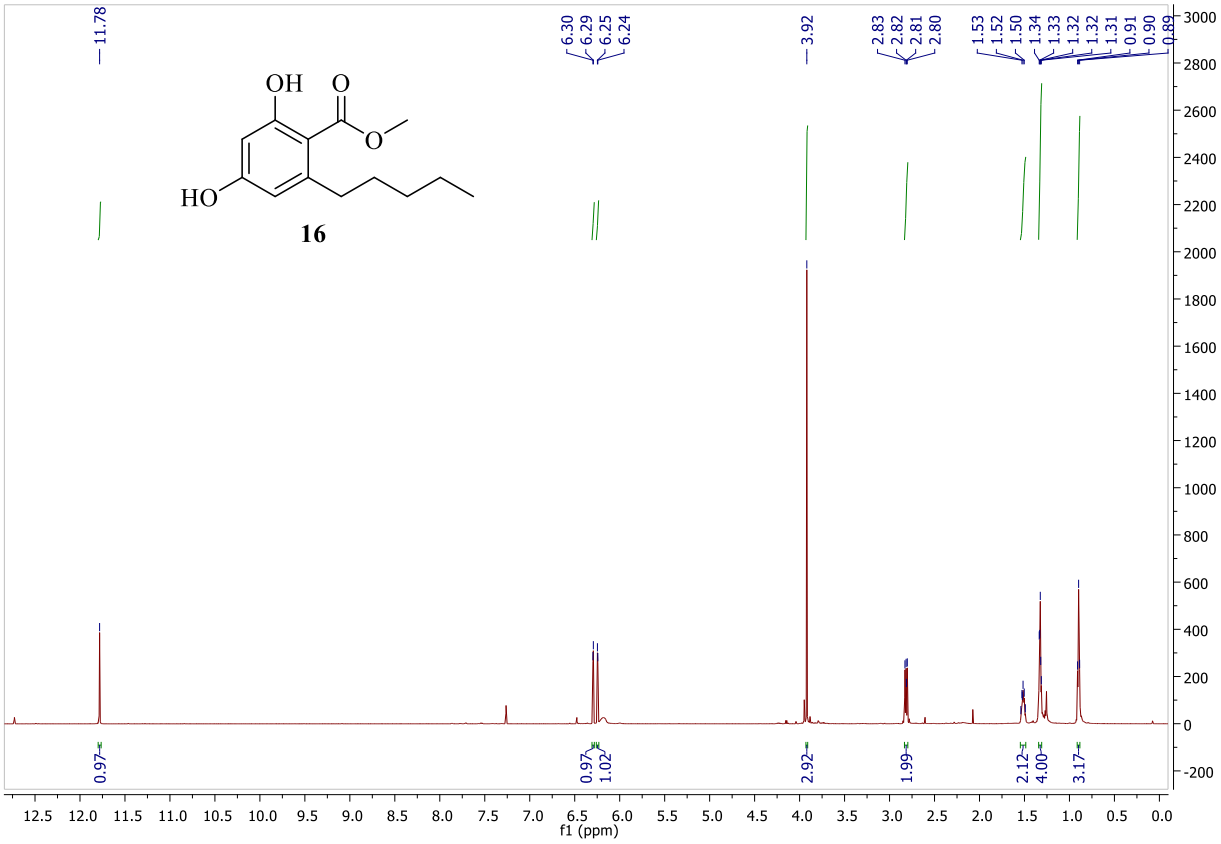
^{1}H NMR spectrum of olivetol, (5-pentylbenzene-1,3-diol) (**15**)



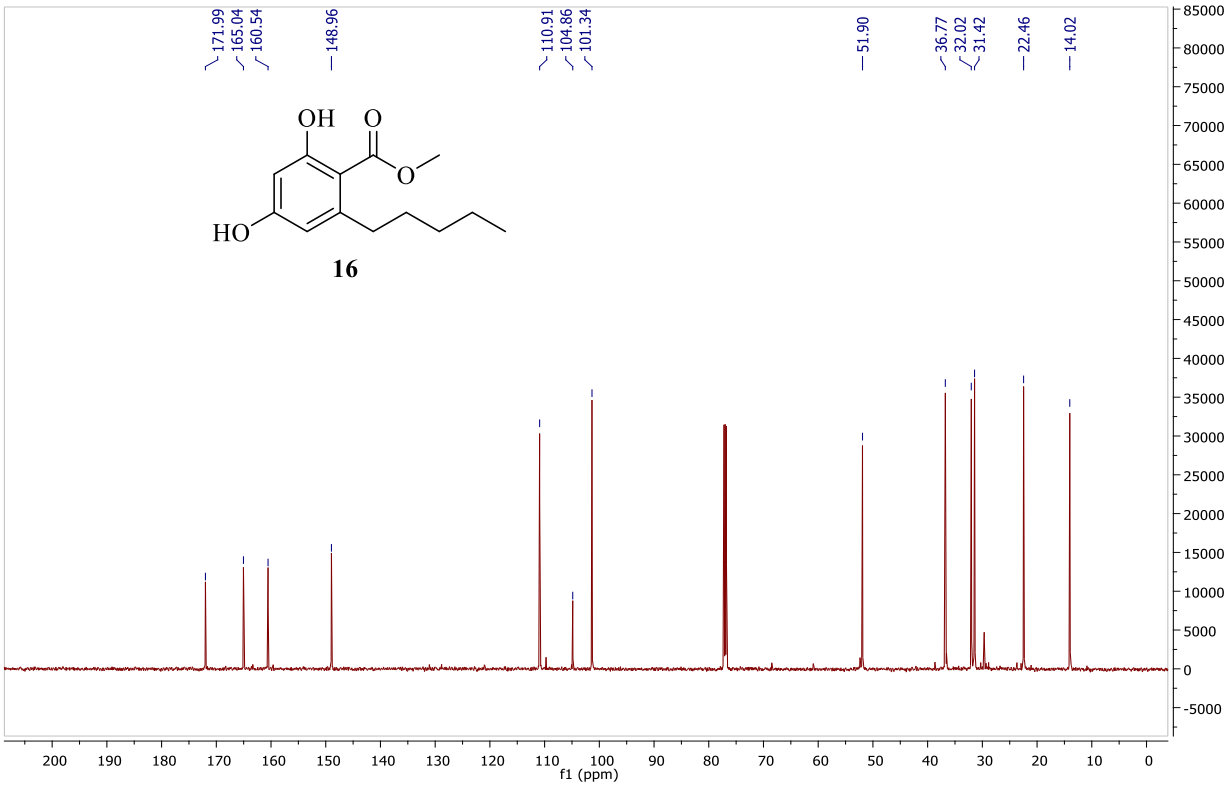
^{13}C NMR spectrum of olivetol, (5-pentylbenzene-1,3-diol) (**15**)



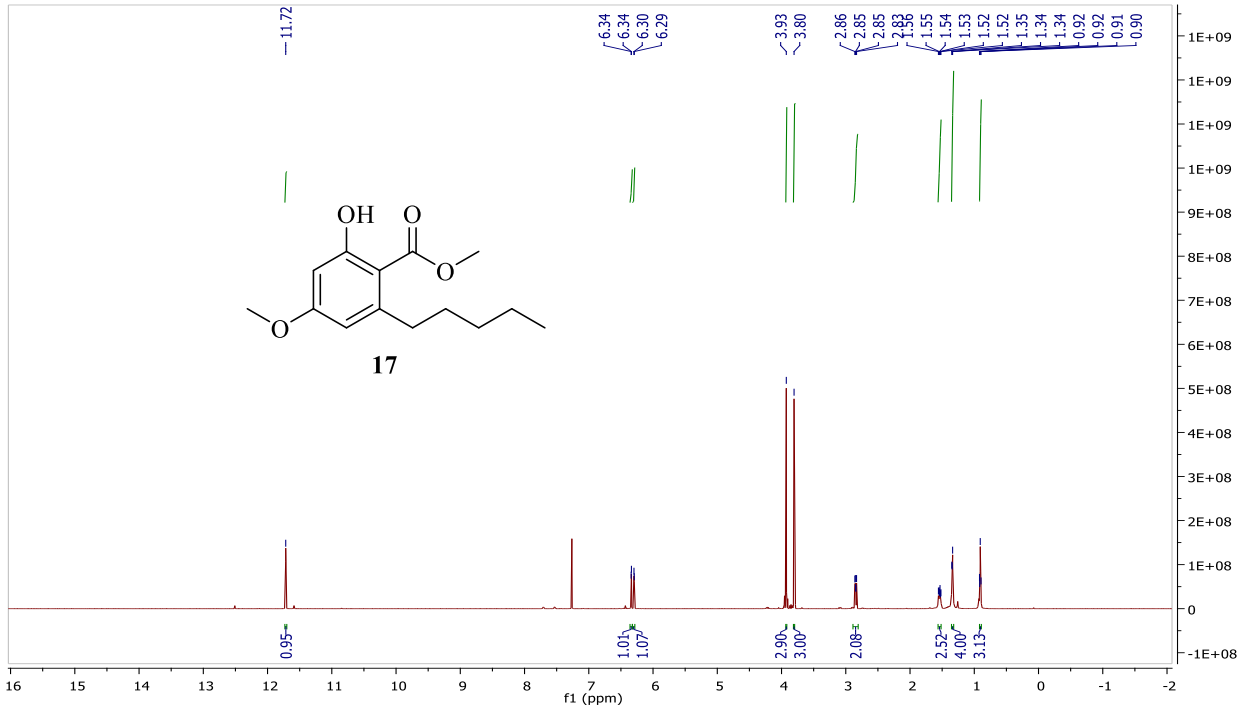
^{1}H NMR spectrum of methyl 2,4-dihydroxy-6-pentylbenzoate (**16**)



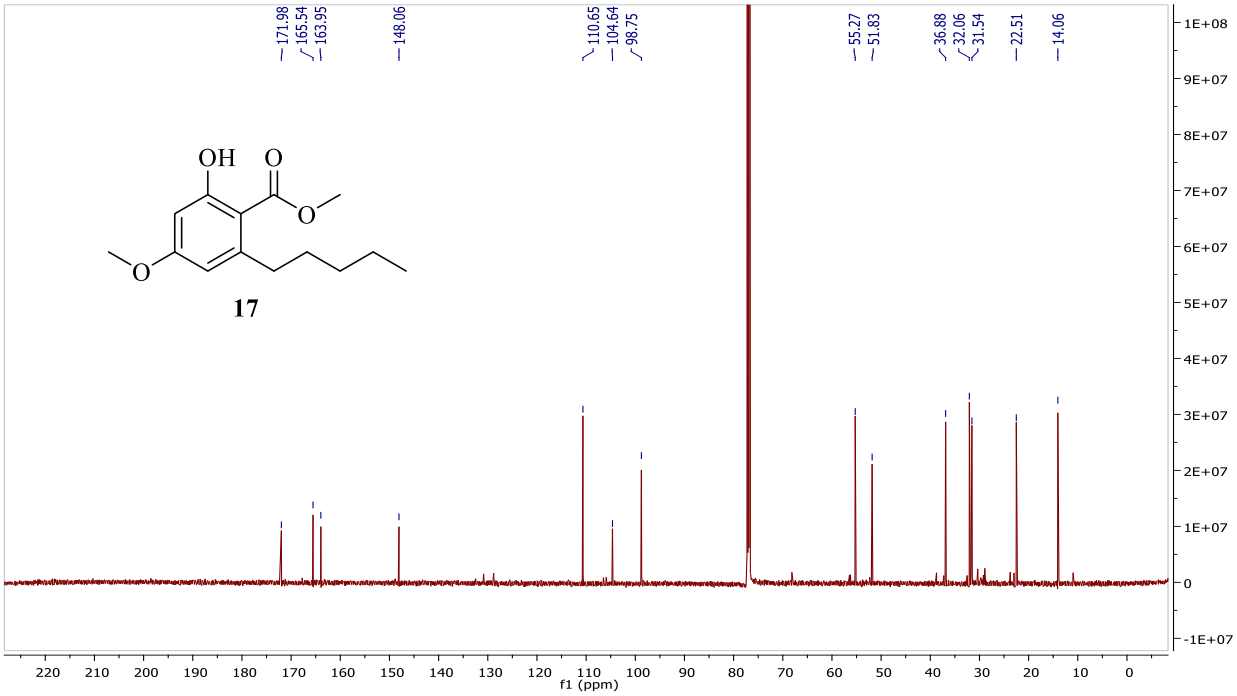
^{13}C NMR spectrum of methyl 2,4-dihydroxy-6-pentylbenzoate (**16**)



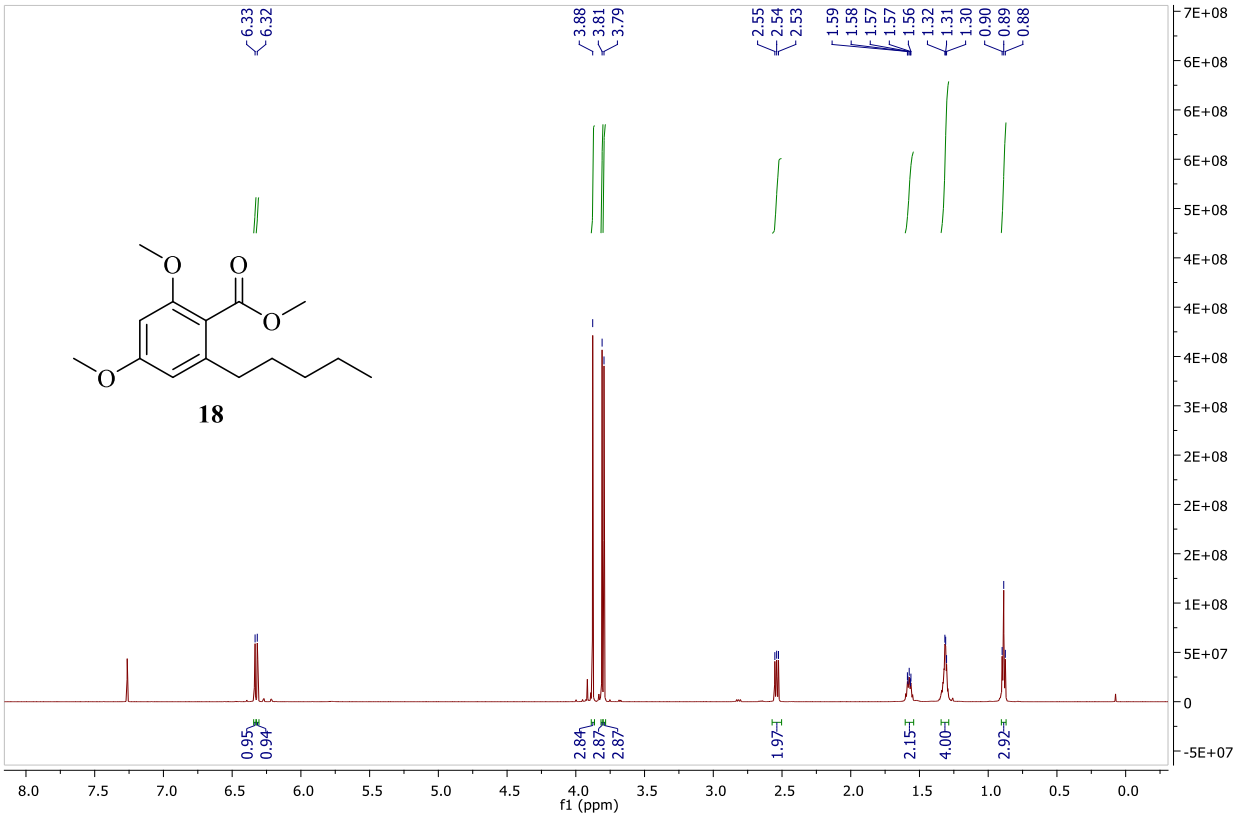
^{1}H NMR spectrum of methyl 2-hydroxy-4-methoxy-6-pentylbenzoate (**17**)



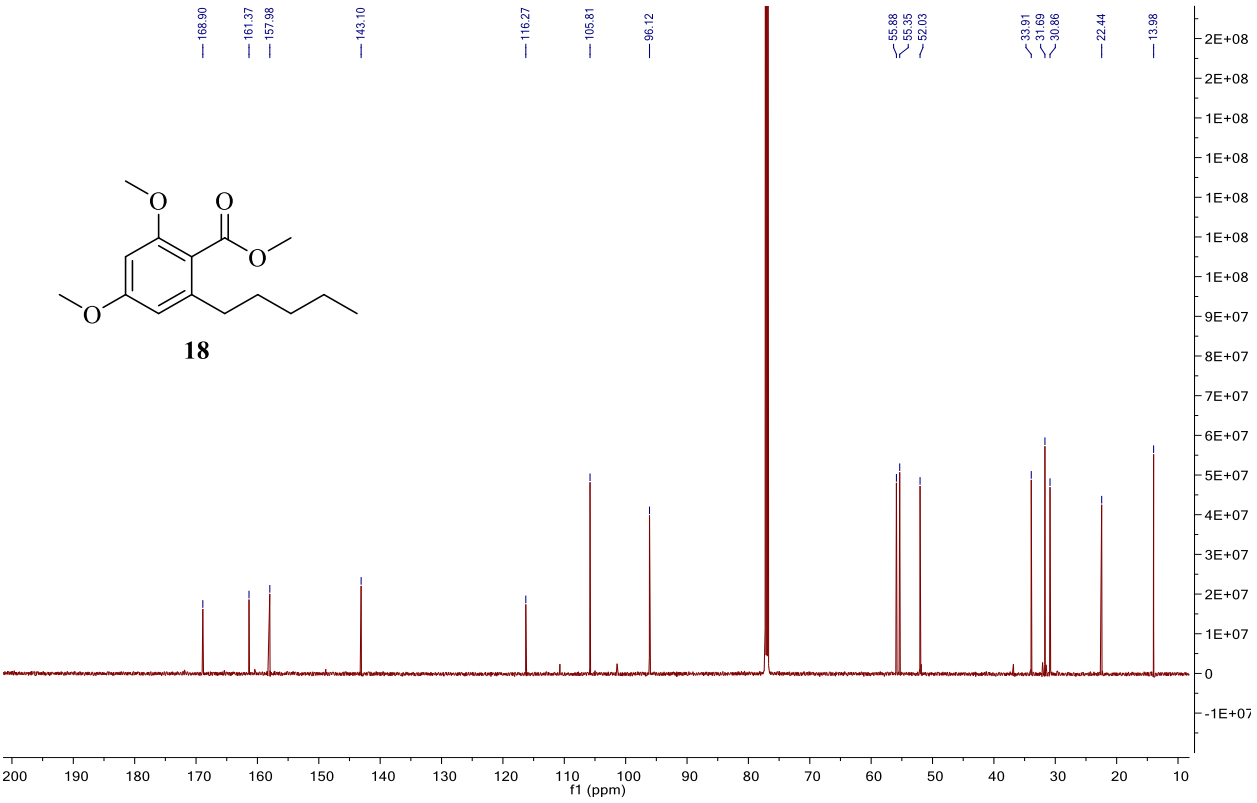
^{13}C NMR spectrum of methyl 2-hydroxy-4-methoxy-6-pentylbenzoate (**17**)



^{1}H NMR spectrum of methyl 2,4-dimethoxy-6-pentylbenzoate (**18**)

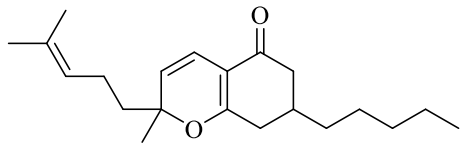


^{13}C NMR spectrum of methyl 2,4-dimethoxy-6-pentylbenzoate (**18**)

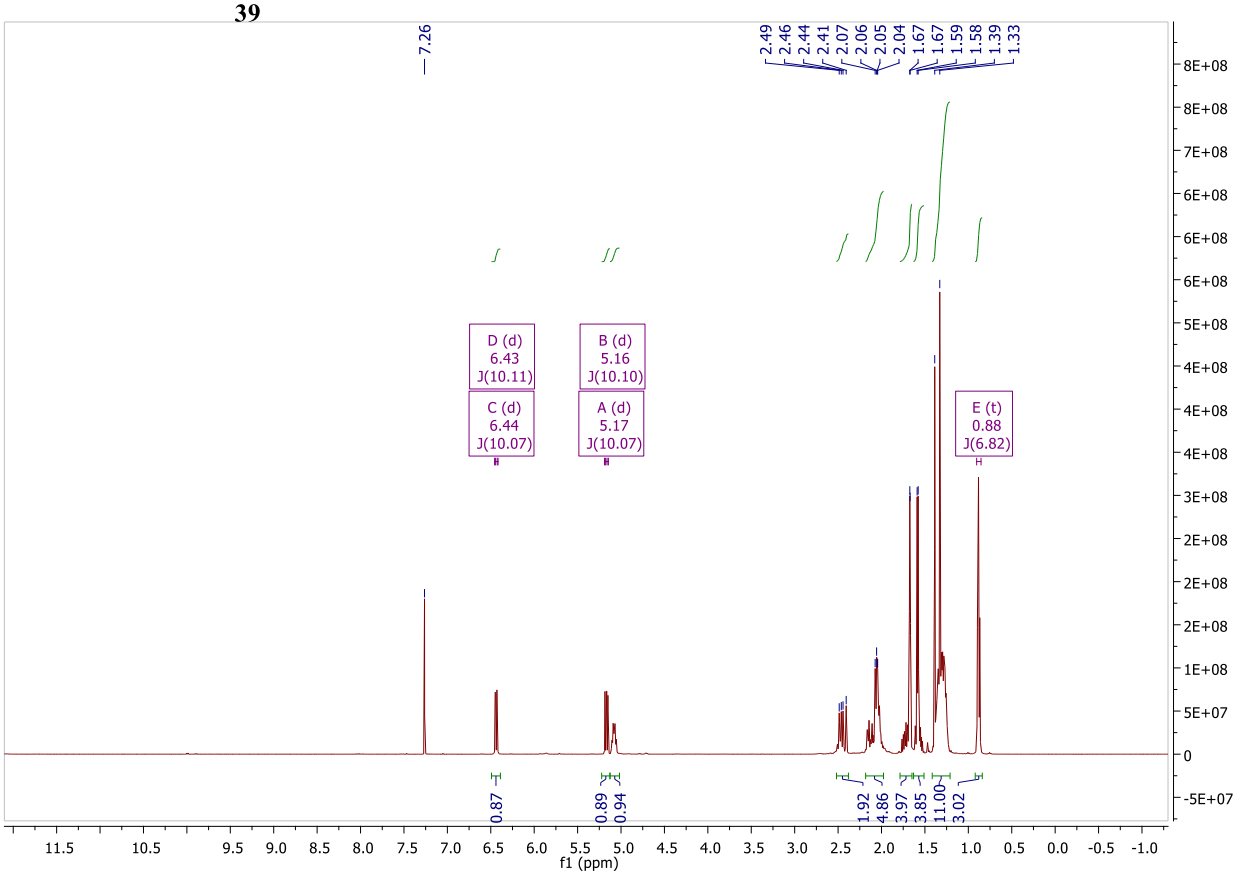


Chapter 5

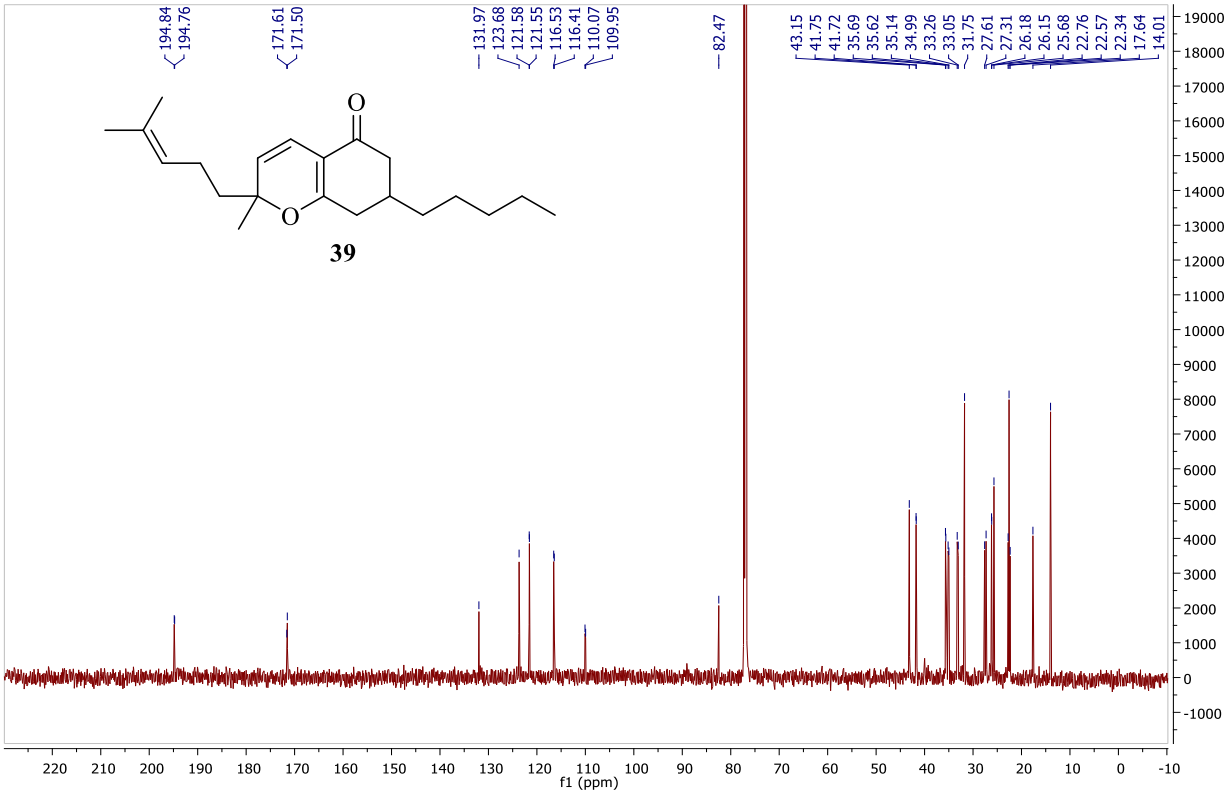
^{1}H NMR spectrum of 2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2,6,7,8-tetrahydro-5*H*-chromen-5-one (**39**)



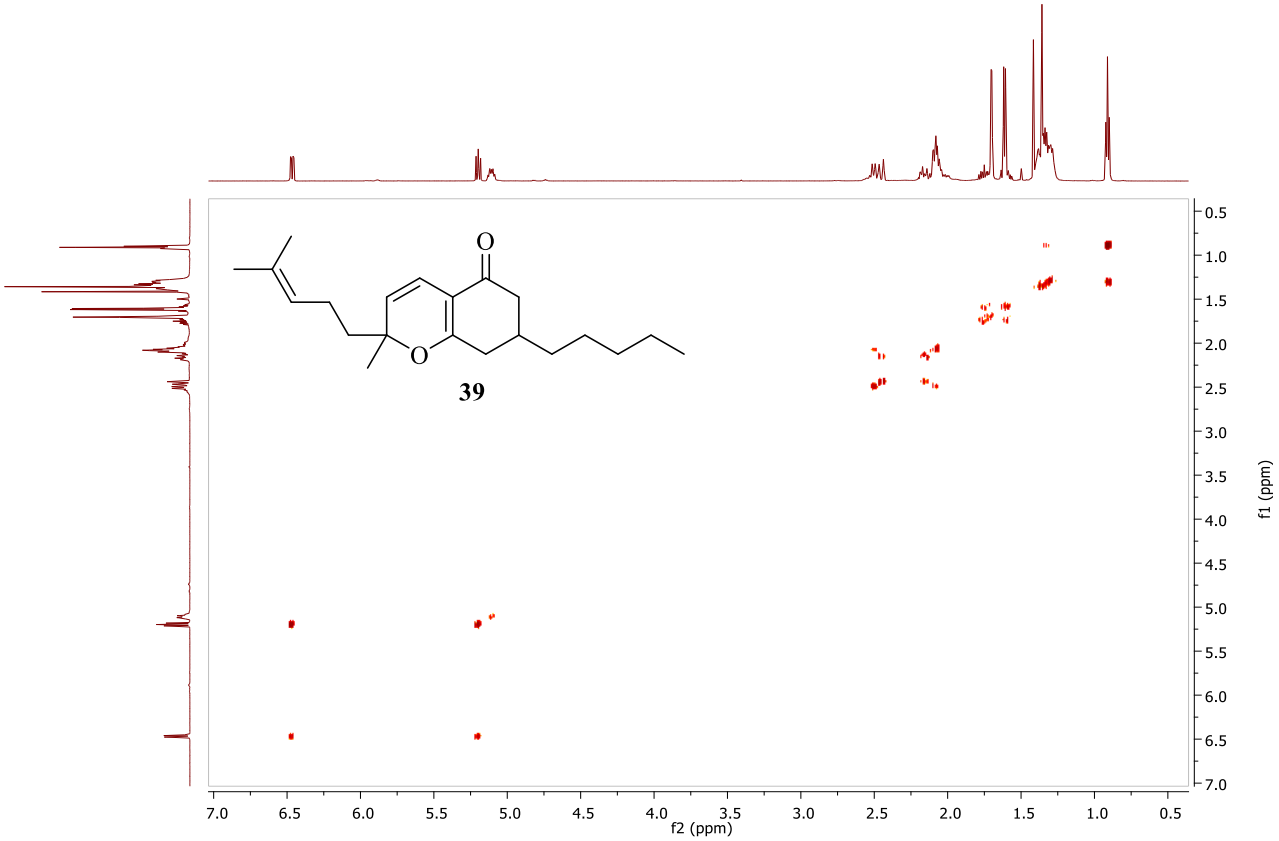
39



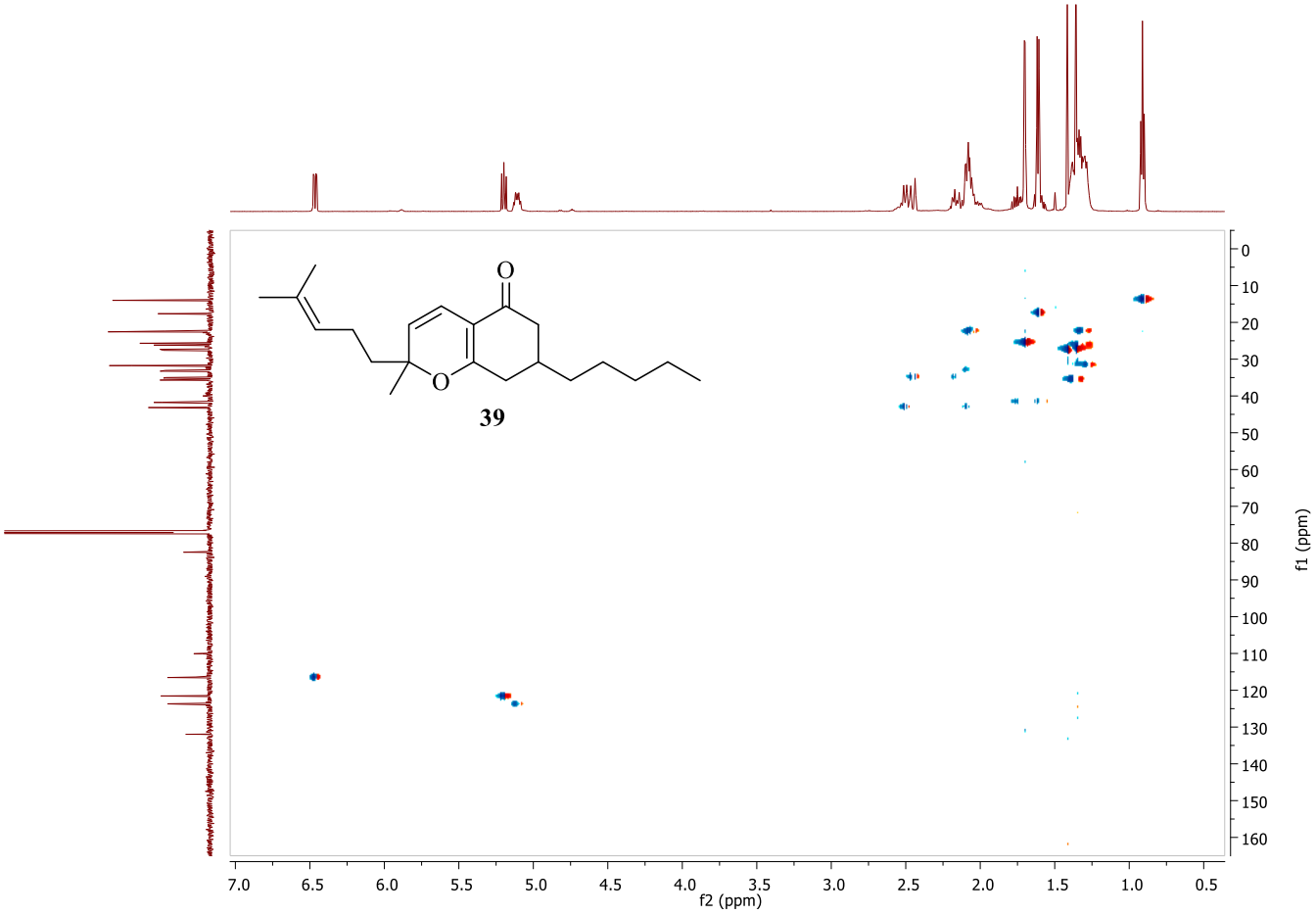
^{13}C NMR spectrum of 2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2,6,7,8-tetrahydro-5*H*-chromen-5-one (**39**)



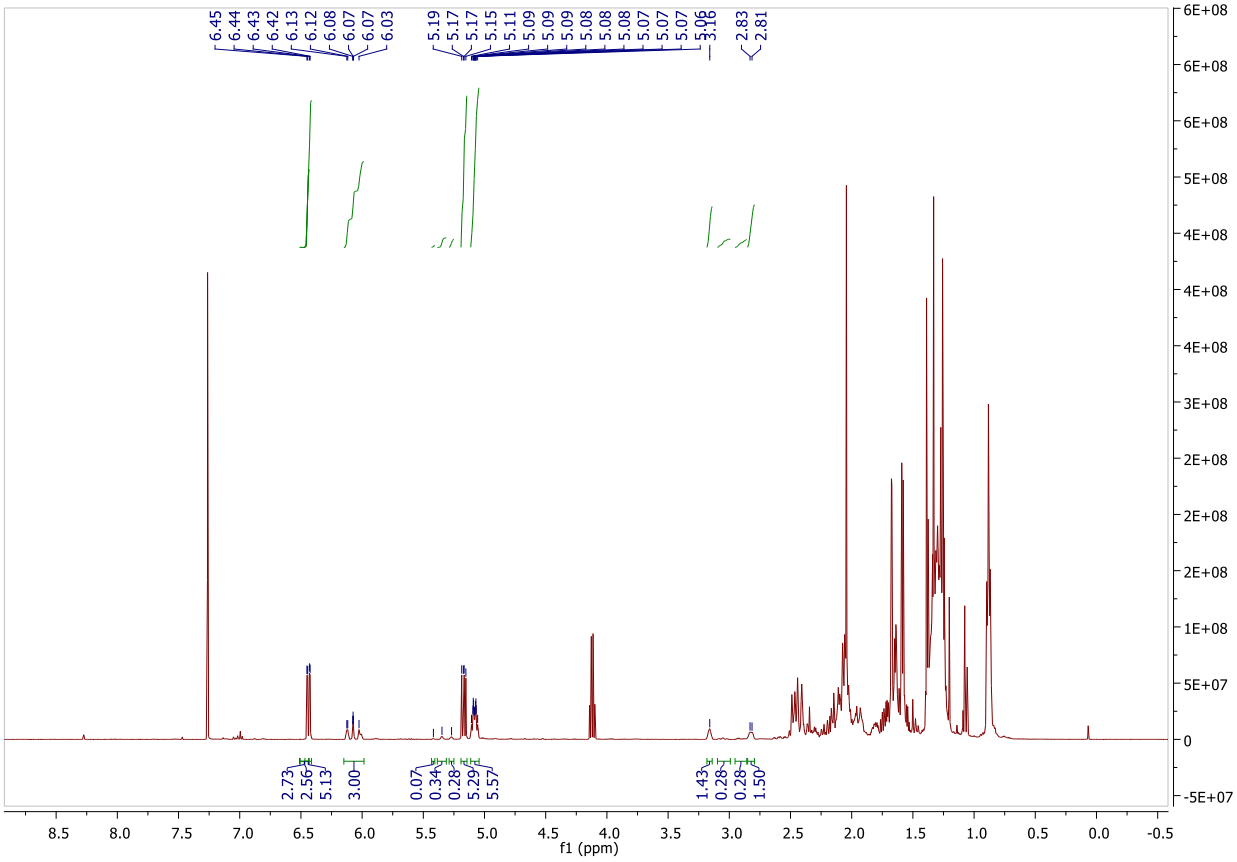
^{1}H – ^{1}H COSY spectrum of 2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2,6,7,8-tetrahydro-5*H*-chromen-5-one (**39**)



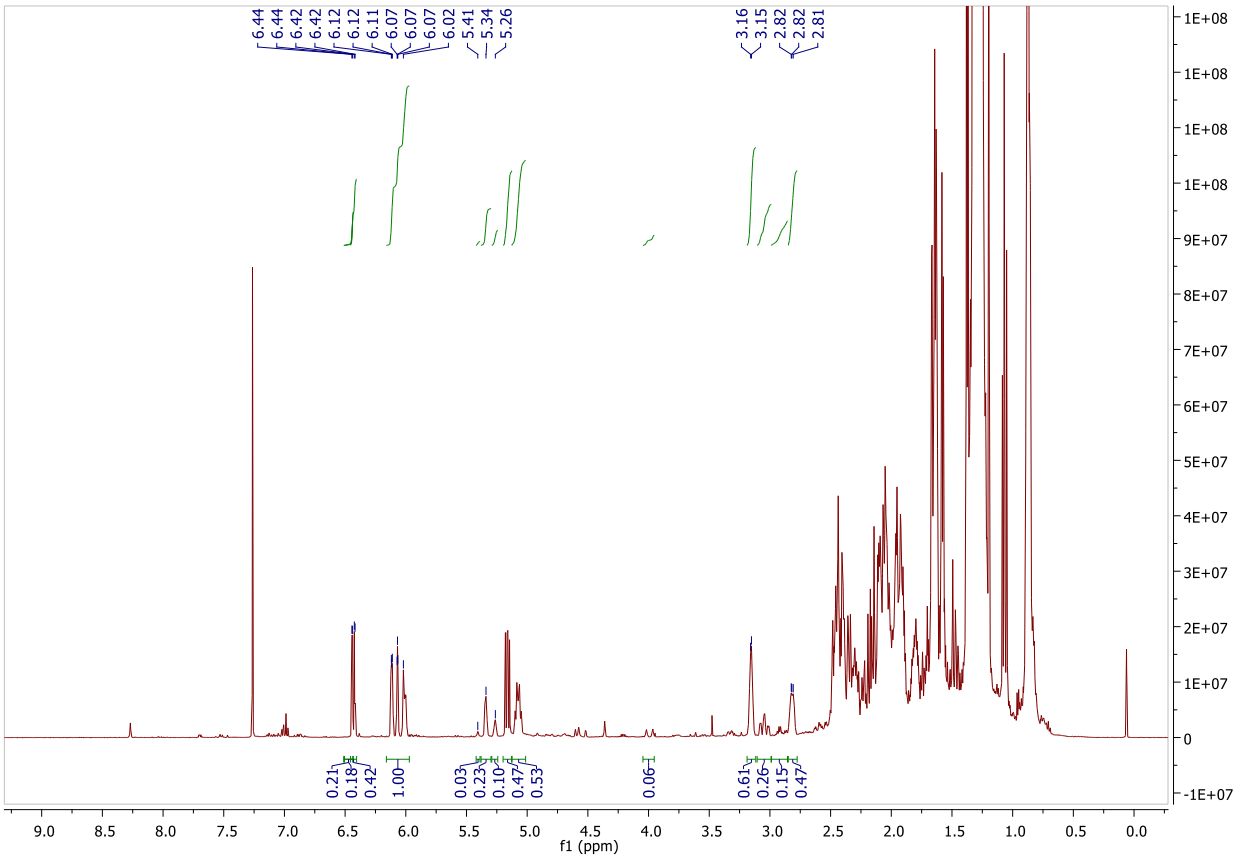
^{1}H – ^{13}C HSQC spectrum of 2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2,6,7,8-tetrahydro-5*H*-chromen-5-one (**39**)



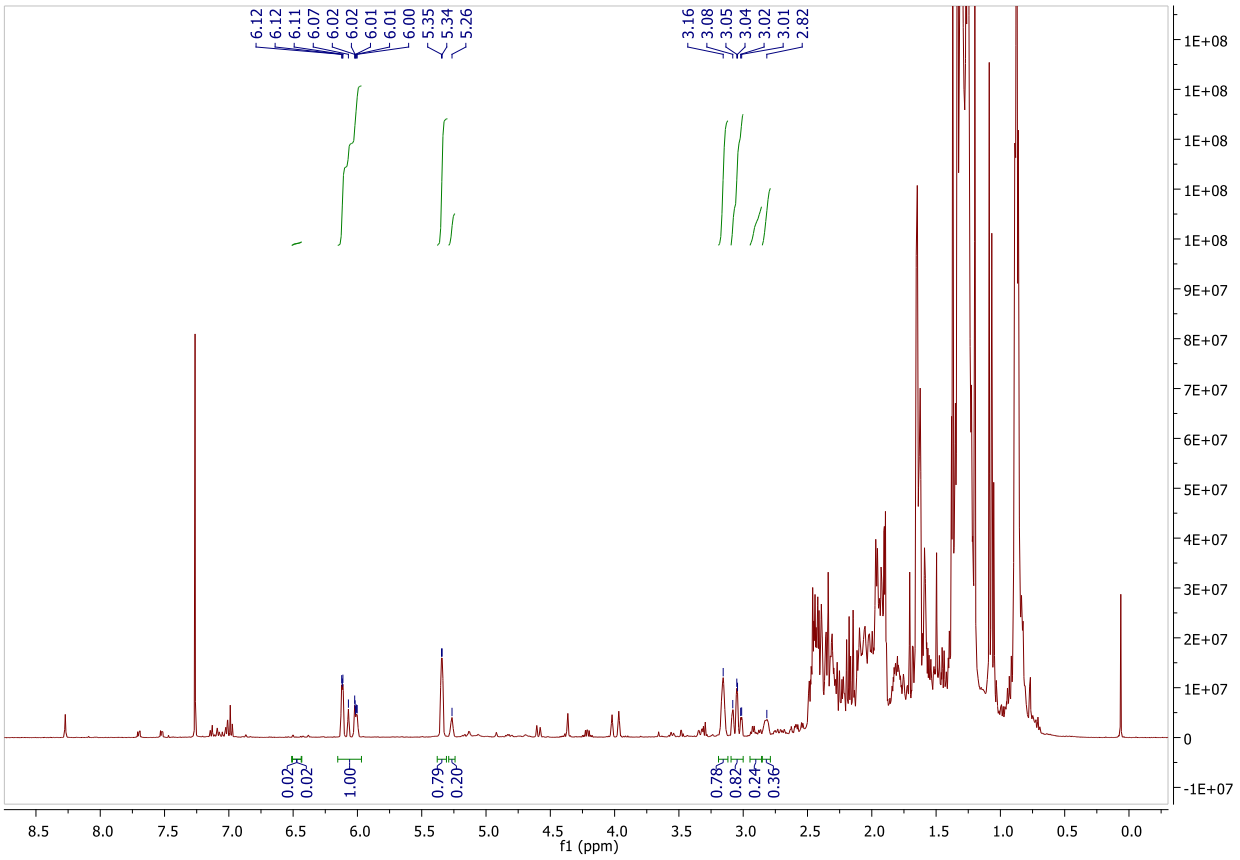
Full ^{1}H NMR spectrum from Figure 2-2.



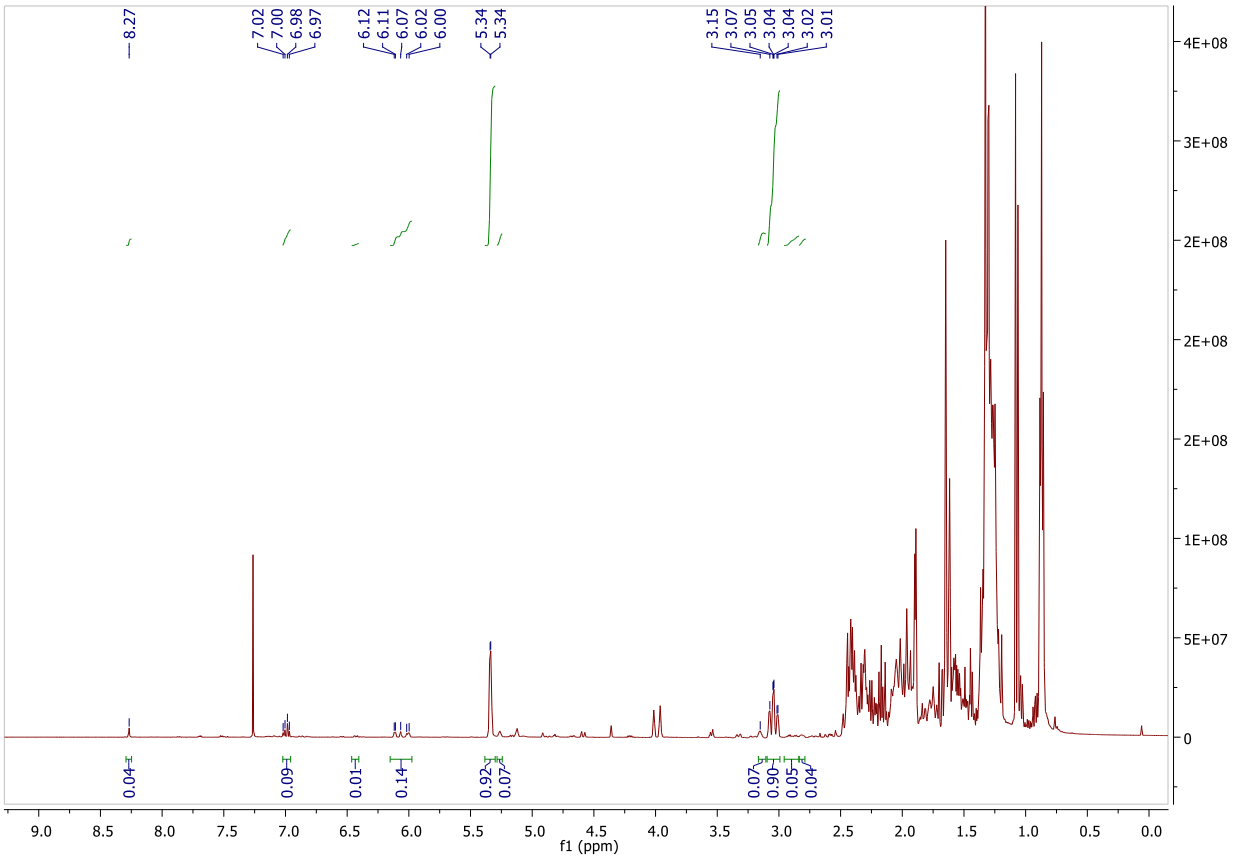
Full ^{1}H NMR spectrum from Figure 2-3.



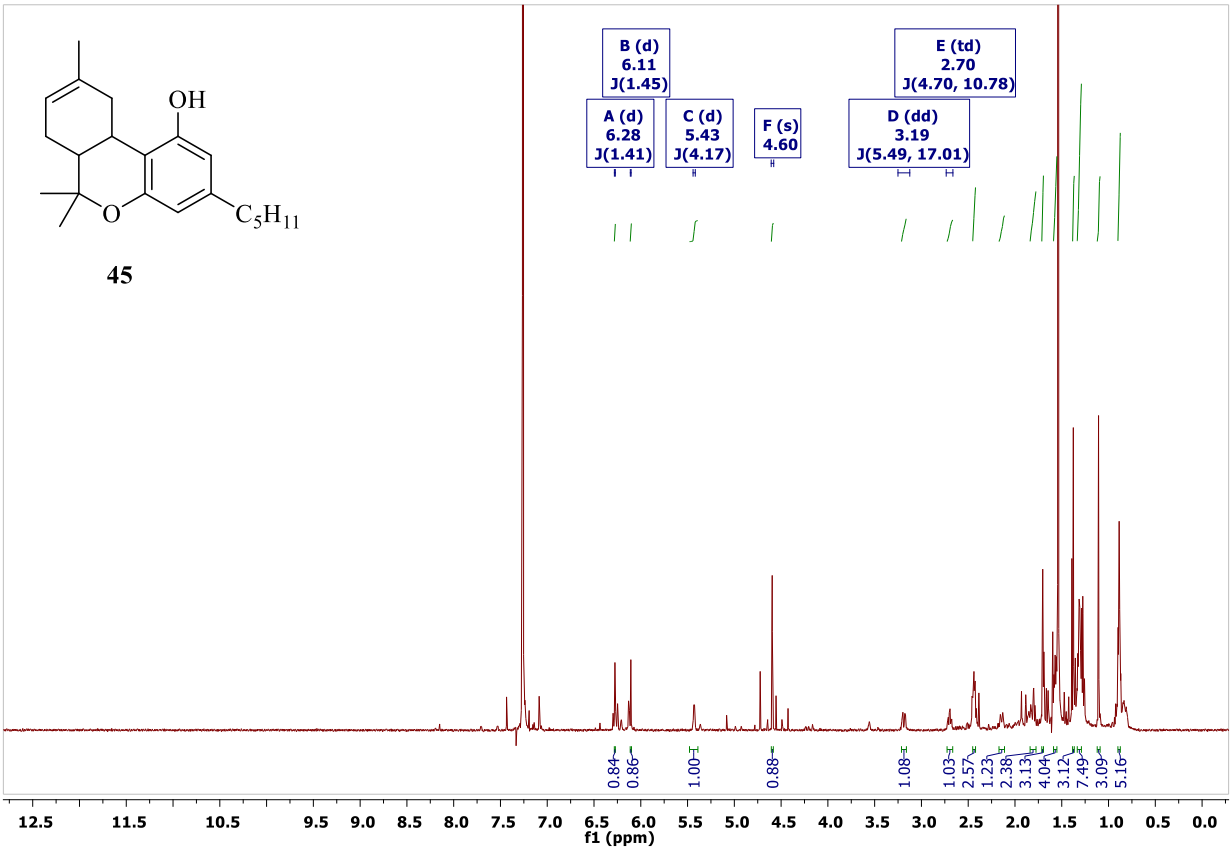
Full ^{1}H NMR spectrum from Figure 2-4.



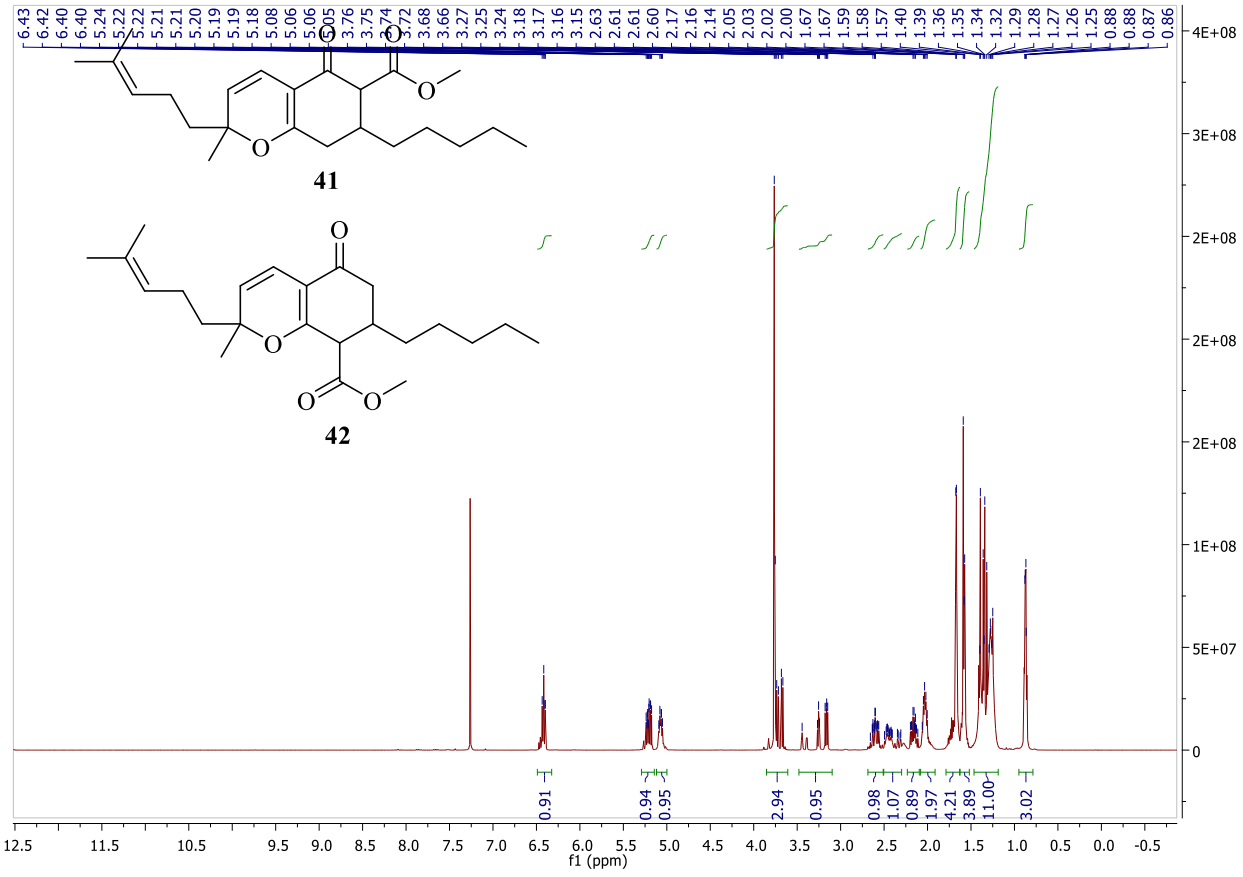
Full ^{1}H NMR spectrum from Figure 2-5.



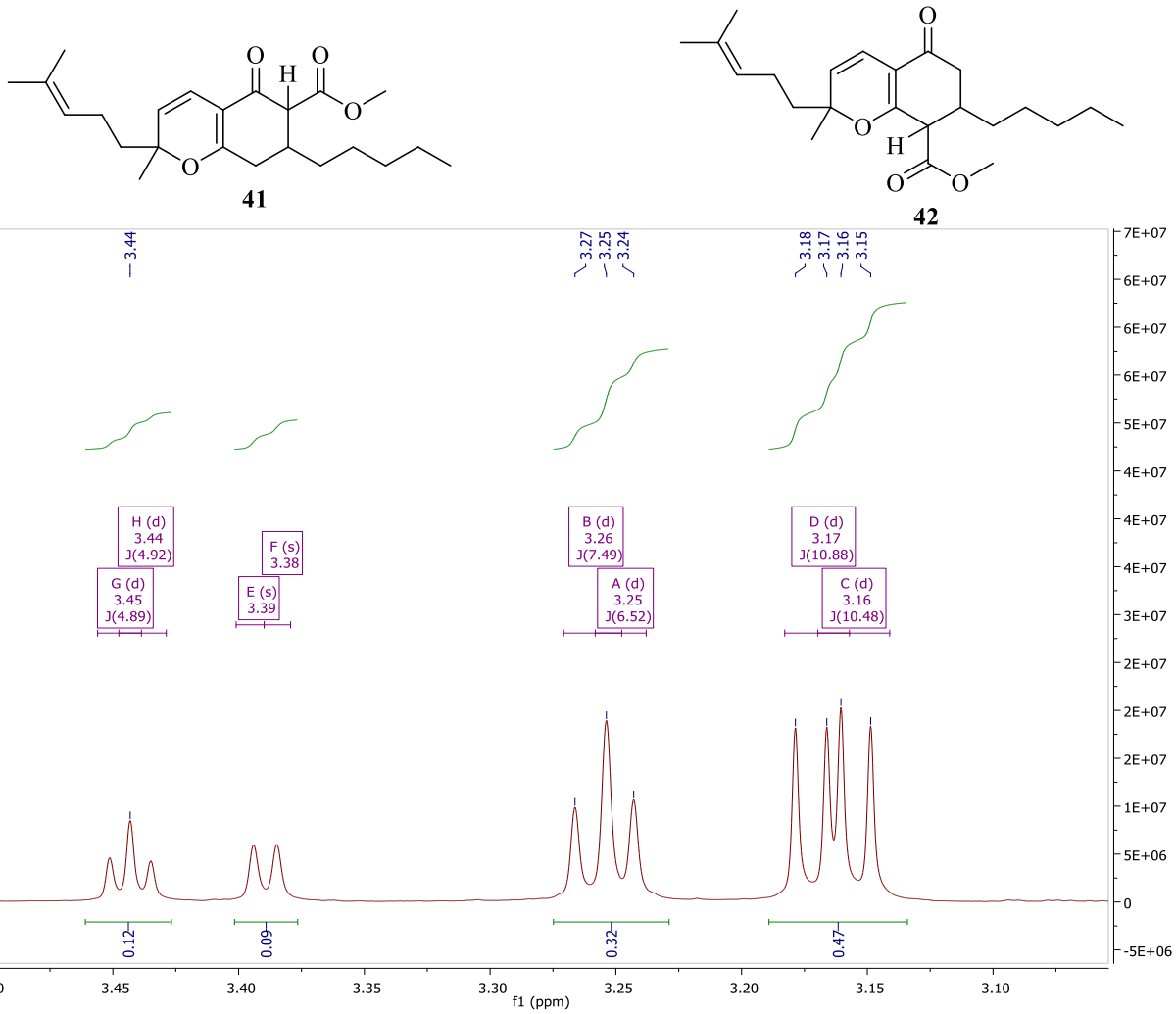
Full ^{1}H NMR spectrum from Figure 3, showing characteristic signals for Δ^{8}-THC (**45**)



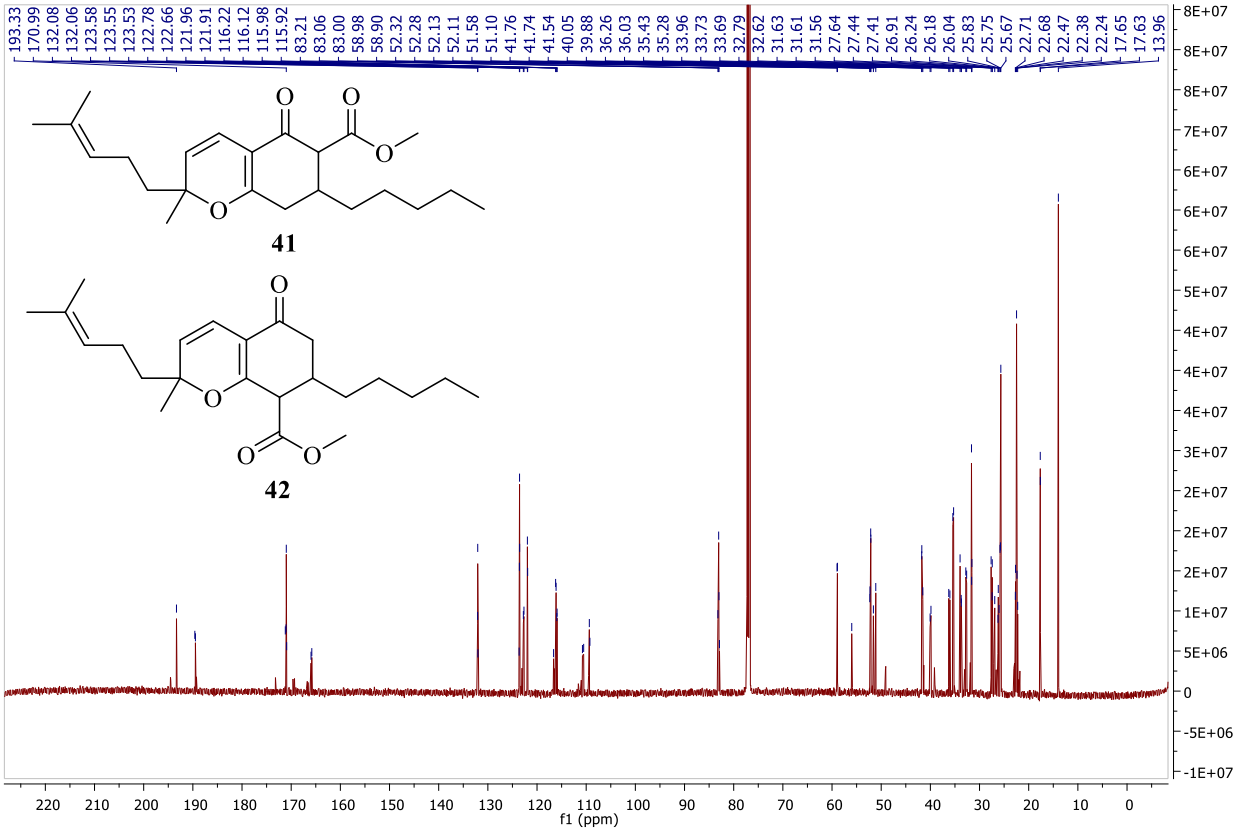
^{1}H NMR spectrum of methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylate (**41**) and methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-8-carboxylate (**42**).



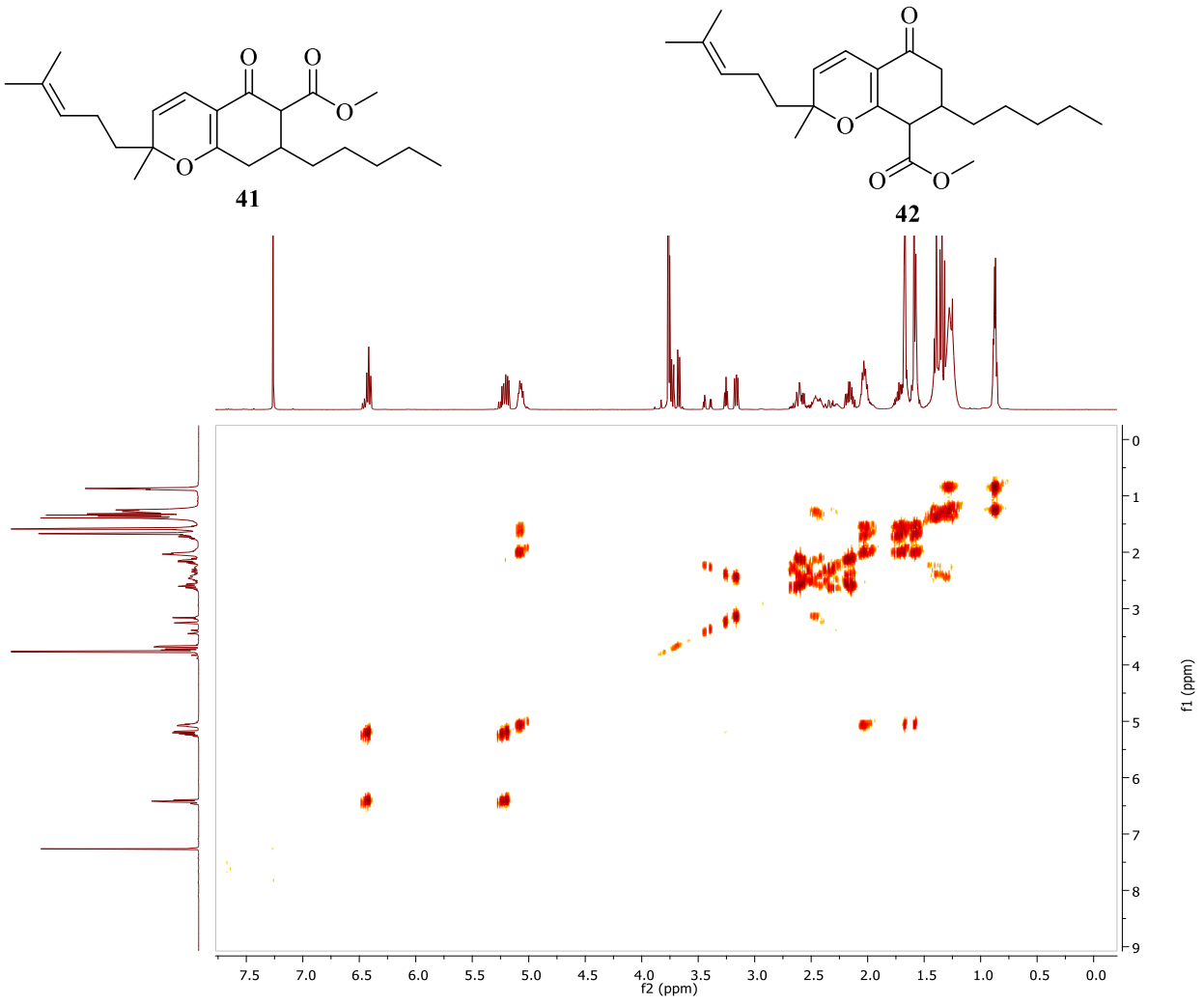
Expanded ^{1}H NMR spectrum of **41** and **42**.



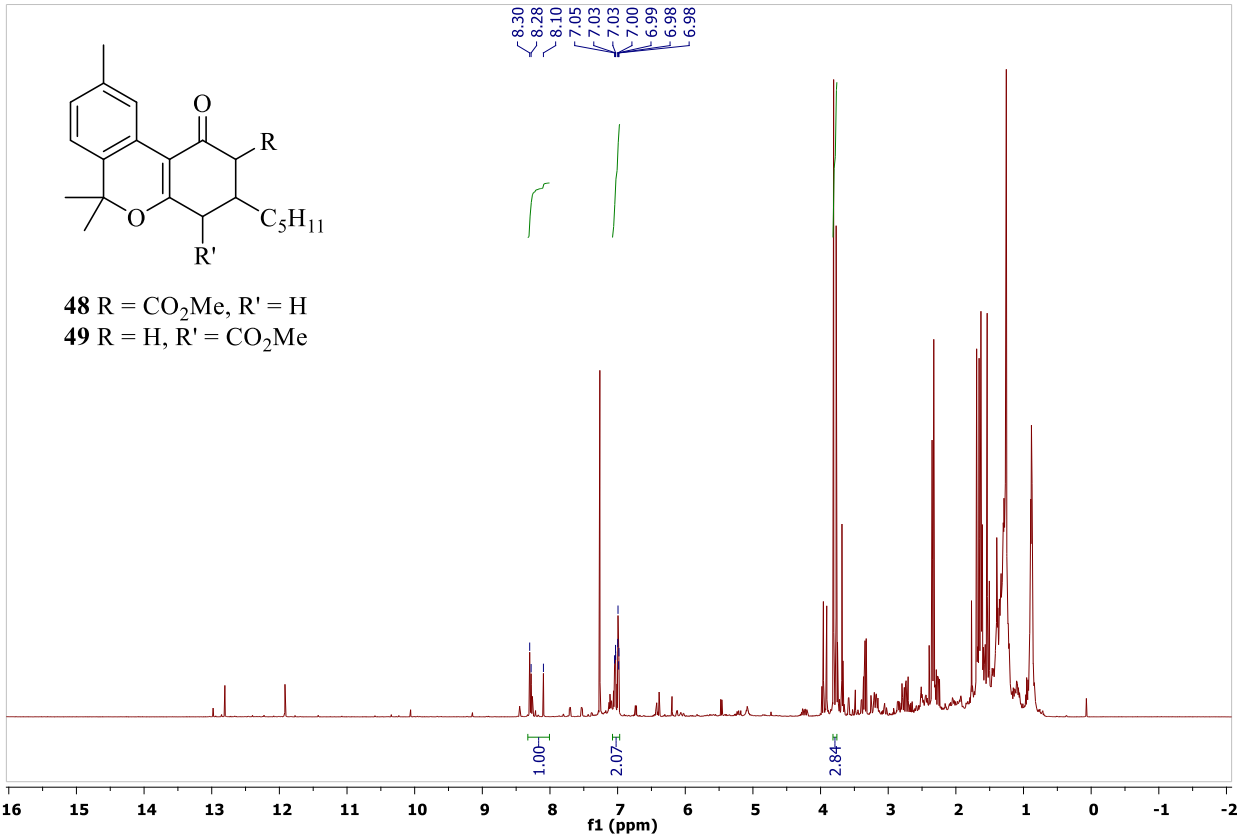
^{13}C NMR spectrum of methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylate (**41**) and methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-8-carboxylate (**42**).



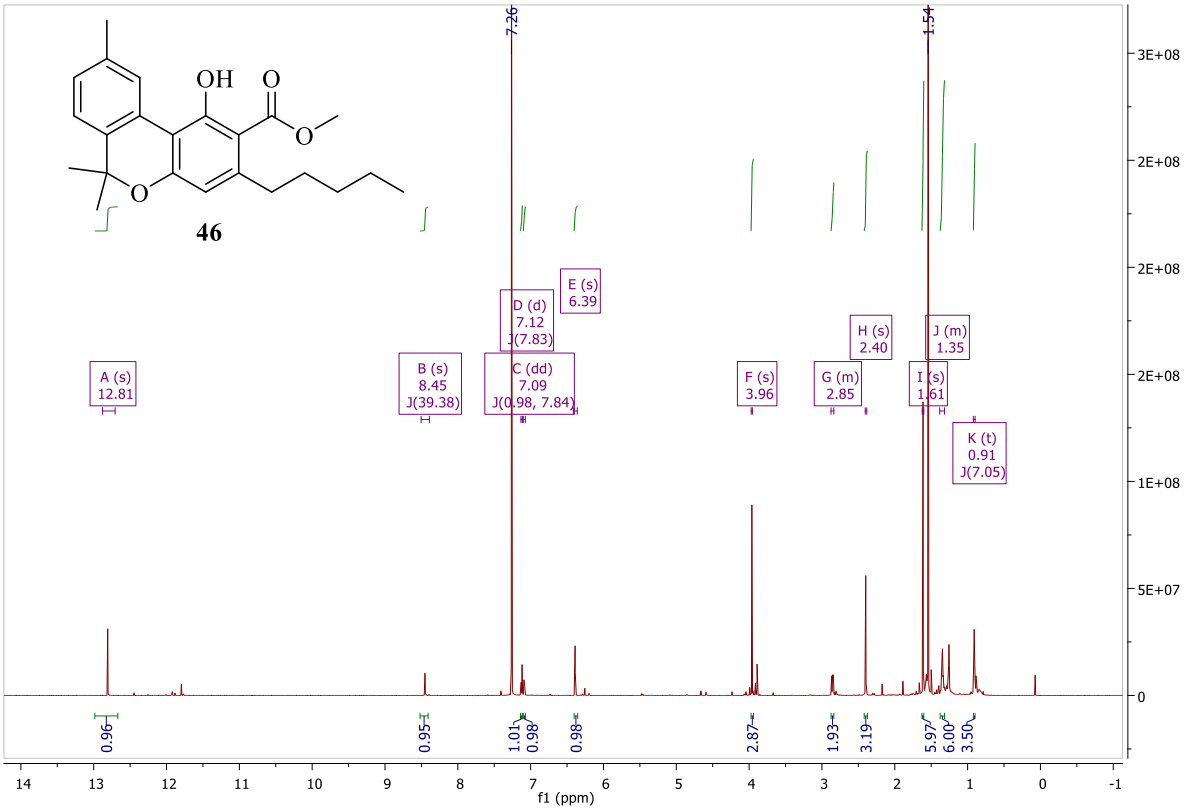
^{1}H – ^{1}H COSY spectrum of methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylate (**41**) and methyl 2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-7-pentyl-5,6,7,8-tetrahydro-2*H*-chromene-8-carboxylate (**42**).



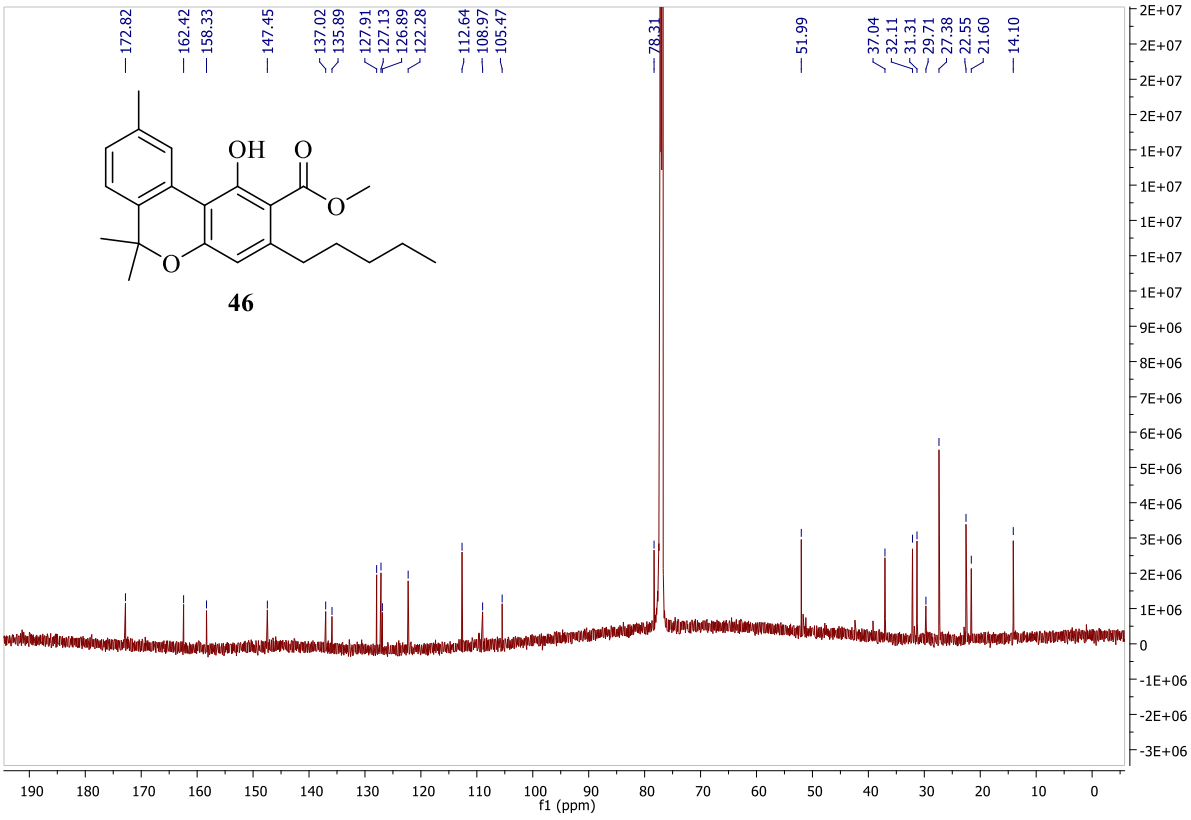
Full ^{1}H NMR spectrum from Figure 4, showing aromatization of terpene-derived ring upon thermal isomerization of **41**/**42**.



^{1}H NMR spectrum of methyl 1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene-2-carboxylate (**46**)



^{13}C NMR spectrum of methyl 1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene-2-carboxylate (**46**)



^{1}H NMR spectrum of methyl 1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene-4-carboxylate (**47**)