REACTIONS OF ACYL PHOSPHONATES WITH ORGANOALUMINUM REAGENTS AND HETERO DIELS-ALDER REACTIONS WITH UNACTIVATED DIENES

MD SHAKHAWOAT HOSSAIN

FEBRUARY 2014

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Approval of the thesis:

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all materials and results that are not original to this work.

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ABSTRACT

REACTIONS OF ACYL PHOSPHONATES WITH ORGANOALUMINUM REAGENTS AND HETERO DIELS-ALDER REACTIONS WITH UNACTIVATED DIENES

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α-Hydroxy phosphonates medicinally important compounds due to broad spectrum of biological activities. Addition reaction of commercially available trialkylaluminum reagents (trimethylaluminum and triethylaluminum) to benzoyl and alkanoyl phosphonates were investigated. Nucleophilic Me_3Al solely gave tertiary α-hydroxy phosphonates in good yields. On the other hand, when Et_3Al addition was carried out at 0 °C hydride addition product rather than ethyl addition was isolated in good yields. When the temperature was lowered to -100 °C , Et_3Al addition was achieved but in low yields.

We have also investigated the addition reactions of trialkynylaluminum reagents, mainly triethynyl, tris-propynyl and tris-phenylethynyl, to benzoyl and akanoyl phosphonates to synthesize tertiary α-hydroxy propargylic phosphonates. Addition of triethynylaluminium gave the propargylic compounds in low to moderate yields (15-67%). Addition of tris-propynyl and tris-phenylethynyl reagents formed the expected products in moderate to good yields (30-75%). In all cases, electronic features of the aromatic unit affected the chemical yield. Presence of an electron-withdrawing group on the phenyl ring provided the product in better chemical yield. When benzoyl and alkanoyl phosphonates were compared in terms of yields, first one formed the product in better yields at a shorter reaction times.

Hetero Diels-Alder (HDA) reaction is an important reaction for the construction of the pyranosyl unit of many biologically active compounds. HDA reactions of acyl phosphonates with 2,3-dimethyl-1,3-butadine were investigated to prepare glycosyl type phosphonates. To activate the HDA reaction, several Lewis acids were tested. $AlCl_3$ was found to be the most effective catalyst by forming glycosyl phosphonates in acceptable to good yields (40-79%) depending on the acyl phosphonates.

Keywords: Acyl phosphonate, Organoaluminum, α-Hydroxy phosphonate, Glycosyl phosphonate.

ÖZ

AÇİL FOSFONATLARIN ORGANOALÜMİNYUM REAKTİFLERİYLE TEPKİMELERİ VE AKTİVE EDİLMEMİŞ DİENLERLERLE HETERO DİELS-ALDER TEPKİMELERİ

Hossain, Md. Shakhawoat

Doktora Öğrencisi, Kimya Bölümü

Tez Danışmanı: Prof. Dr. Ayhan Sıtkı Demir

Şubat 2014, 231 sayfa,

α-Hidroksi fosfonatlar geniş spektrumda biyolojik aktiviteye sahip olmalarından dolayı tibbi açıdan oldukça önemli bileşiklerdir. Bu tezde ticari olarak erişilebilir trialkilalüminyum reaktiflerinin (trimetilalüminyum ve trietilalüminyum) benzoil ve alkanoil fosfonatlara olan katılma reaksiyonları araştırılmıştır. Nükleofilik Me_3Al katılmasıyla tersiyer α-hidroksi fosfonatlar tek ürün olarak iyi verimlerle elde edilmiştir. Diğer taraftan, 0 ^oC'de Et_3Al katılması ile beklenen etil katılma ürünü yerine hidrür katılma ürünü iyi verimle elde edilmiştir. Sıcaklık -100 °C 'ye düşürüldüğünde Et_3Al katılması gerçekleşmiş ancak verim düşük olmuştur.

Bunlara ek olarak trialkilalüminyum reaktiflerinden trietinil, tris propinil ve tris feniletinil bileşenlerinin benzoil ve alkanoil fosfonatlara katılmasıyla α-hidroksi propargil fosfonatların sentezide araştırılmıştır. Trietinilalüminyum katılmasıyla beklenen proparjilik bileşikler düşük ve orta verimlerle (%15-67) elde edilmiştir. Tris-isopropinilalüminyum ve tris-feniletinilalüminyu orta ile iyi arasında verimlerle (%30-75) beklenen ürünleri oluşturmuştur. Her durumda aromatik yapının elektronik özelliği verim üzerine etkili olmuştur. Fenil halkasında elektron çeken gruplar varken verimler daha iyi olmuştur. Benzoil ve alkanoil fosfonatlar kıyaslandığında katılma tepkimeleri birinci grup bileşiklerle daha yüksek verimlerle daha kısa sürede gerçekleşmiştir.

Hetero Diels-Alder tepkimesi (HDA) piranosil yapısı içeren bir çok biyolojik aktif bileşiğin sentezi için önemlidir. Açil fosfonatların 2,3-dimetil-1,3-bütadin ile olan HDA tepkimesi sonucu glikosil tipi fosfonatların eldesi araştırılmıştır. HDA tepkimesini aktive etmek için farklıLewis asitler denenmiştir.. Glikosil fosfonatları kabul edilir ile iyi seviyelerdeki verimlerle (%40-79) oluşturmak için en etkili katalizör $AlCl_3$ olmuştur.

Anahtar kelimeler: Açil fosfonat, Organoaluminyum, α-Hidroksi fosfonat, Glikosil fosfonat.

Dedicated to Prof. Dr. Ayhan Sıtkı Demır and my family

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ABBREVIATIONS

C-C	Carbon-Carbon
C-P	Carbon-Phosphorus
Nu	Nucleophile
M	Metal
L	Ligand
Cat	Catalyst
DMF	N,N-dimethylformamide
TMS	Trimethylsilyl
ee	Enantiomeric excess
dr	Diastereomeric Ratio
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
LA	Lewis Acid
DMSO	Dimethyl Sulfoxide
TS	Transition State
THF	Tetrahydrofuran
r.t	Room Temperature
DET	Diethyl Tartarate
TLC	Thin Layer Chromatography
IR	Infra-Red
MeCN	Acetonitrile
DCM	Dichloromethane
°C	degree Celsius
cm^{-1}	wavenumber
δ	parts per million
Equiv.	Equivalents
J	coupling constant in Hertz
mg	miligram

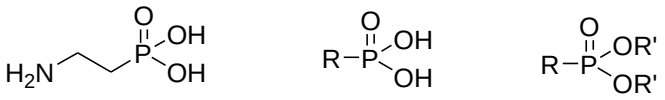
min	minutes
mL	millilitre
NMR	nuclear magnetic resonance
Calcd	calculated
Me_3Al	Trimethylaluminum
Et_3Al	Triethylaluminum
FPT	Farnesyl protein tranferase
PTP	Human protein tyrosine phosphatise
PNP	Purine nucleoside phosphorylase
HIV	Human immunodeficiency virus
AEP	Aminoethylphosphonic acid

CHAPTER 1

INTRODUCTION

1.1 Organophosphorus compounds

Organophosphorus compounds having a C–P bond are one of the functional groups in organic chemistry. These structures were unknown until 1959.[1-3] Aquatic and terrestrial animals and microorganisms are the best source of new types of organophosphorus compounds. In 1959, aminoethylphosphonic acid (AEP, **1**) (Figure 1.1) was the first organophosphorus compound isolated from sheep rumen by Horiguchi and Kandatzu.[3] These compounds are important because of their wide variety of biological activities, i.e. anticancer, antibacterial, antiviral, antibiotic, pesticidal, and enzyme inhibitory properties.[4-8] Organophosphorus compounds are bioactive due to the relatively inert nature of the C-P bond. They are structurally similar to the biologically important phosphate ester and carboxylic acid functional groups. These compounds can often act as substrate mimics and interfere with enzymatic processes. For example, the phosphonic acid analog of glycine is a plant-growth regulator and the phosphonic acid analog of phenylalanine is a competitive inhibitor of phenylalanyl-5-RNA-synthase.[9-11]



1 **2** **3**

Figure 1.1 Structure of AEP and general structure for phosphonic acids and phosphonates

Phosphonic acids **2** and their phosphonate derivatives **3** (Figure 1.1) are very common units in organic chemistry. They are usually employed in synthetic chemistry for the carbon-carbon bond formation reactions.[12] In Figure 1.2, few

examples of natural hydroxyphosphonic acids such as phosphonothrixin **4** and dihydroxyphosphonic acid **5** are shown. Phosphonic acids **6** and **7** inhibit human protein tyrosine phosphatase (PTP).[13-19] 1,1-Difluoroalkylphosphonic acids **8** and **9** inhibit purine nucleoside phosphorylase (PNP).[20] Inhibitors of PTP have been shown to have high pharmacological activity in the treatment of different diseases.[21] Their structures are also shown in Figure 1.2.

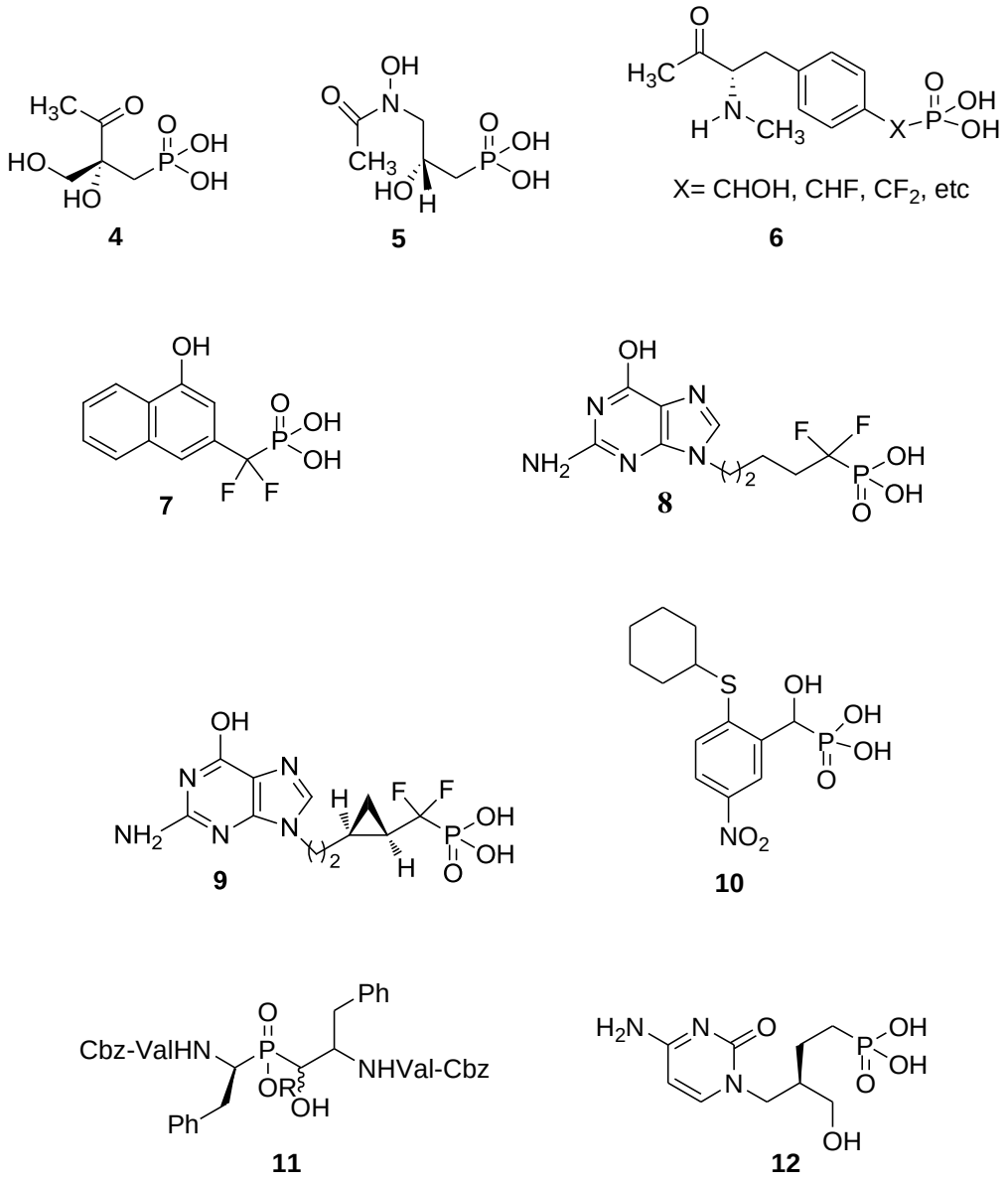


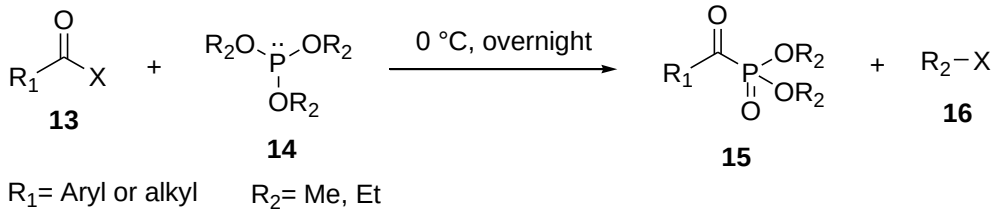
Figure 1.2 Selected biologically important organophosphorus compounds

Derivatives of phosphonic acids, i.e. α-hydroxy-β-amino phosphonates, polyhydroxy phosphonates, difluoromethylene phosphonates and β-hydroxy phosphonates are inhibitors of enzymes.[22-26] Compound **10** is one of the derivatives of phosphonic acids and is a regulator of cell activation and proliferation in haematopoetic cells (Figure 1.2).[27] Hydroxyphosphonate **11** inhibits HIV protease, and is a prospective drug for the treatment of AIDS.[28] Compound **12** is used as an antiviral medicine for the treatment of cytomegalovirus infections as well as smallpox.[23]

1.2 Acyl Phosphonates

Acyl phosphonates are particular class of functional organophosphorous compounds. Their general structure is $R_1COPO(OR_2)_2$. The carbonyl group of acyl phosphonates are activated by the presence of phosphonate group. Acyl phosphonates can be considered as close analogs of aldehydes and can be prepared via Michaelis–Arbuzov reaction (Scheme 1.1).[29] This reaction goes by addition-elemination reaction mechanism. The nucleophilic phosphite **14** attacks the electrophilic part of the acyl halide **13** to give a phosphonium intermediate. Later S_N2 reaction takes place and the halide anion reacts with the phosphonium intermediate to afford the desired phosphonate **15** and alkyl halide **16**.

Employment of the acyl phosphonates in organic reactions is difficult. Under the influence of various nucleophiles, the C-P bond can be easily broken. Decomposition of acyl phosphonates under the influence of a weak nucleophile such as water is a common reaction of acyl phosphonates. Effect of nucleophiles on acyl phosphonates were classified by Pudovik and Gareev.[30] Proton containing compounds cleaved at the C-P bond forming an acetic acid and dialkyl phosphate, and aprotic nucleophiles dissociates the C-P bond through the migration of the phosphorous containing fragment. Thus all the reactions carried out in our research were done under argon atmosphere to avoid the nucleophilic attack of moisture and air.



Scheme 1.1 Synthesis of acyl phosphonates by Michaelis–Arbuzov reaction

1.3 *α*- Hydroxy Phosphonates and their synthesis

α-Hydroxy phosphonates, $R_1CH(OH)PO(OR_2)_2$[31] are close analogs of α-hydroxy phosphonic acids, $R_1CH(OH)PO(OH)_2$. They are biologically important compounds as enzyme inhibitors including farnesyl protein tranferase (FPT),[32] human rennin,[33] human protein tyrosine phosphatase (PTP),[14-20] purine nucleoside phosphorylase (PNP),[20] and 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase.[34] They also show antiproliferative activity against several human cancer cell[25-28] and prospective drugs for the treatment of AIDS.[28]

The development of chemistry of α-hydroxy phosphonates in recent years is due to its diverse biological application. There are several methods available for the preparation of α-hydroxy phosphonates in the literature (Figure 1.3). Optically active hydroxyphosphonates can be synthesized through chemoenzymatic method.[35] *α*-Hydroxy phosphonates can also be synthesized by the reduction of acyl phosphonates,[36] hydroxylation of phosphonate stabilized carbanions,[37] and [2,3]-sigmatropic Wittig rearrangements.[38]

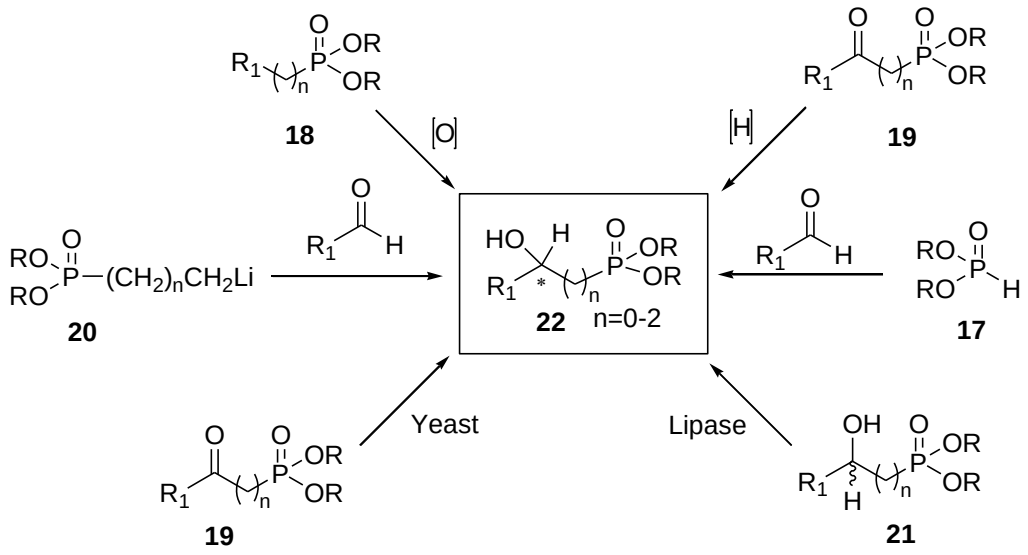
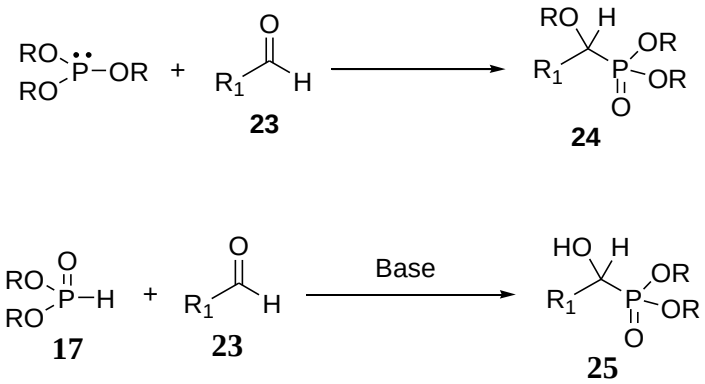


Figure 1.3 General synthetic methods for hydroxyphosphonates

Different synthetic methods for the preparation α-hydroxy phosphonates are discussed in the following sections.

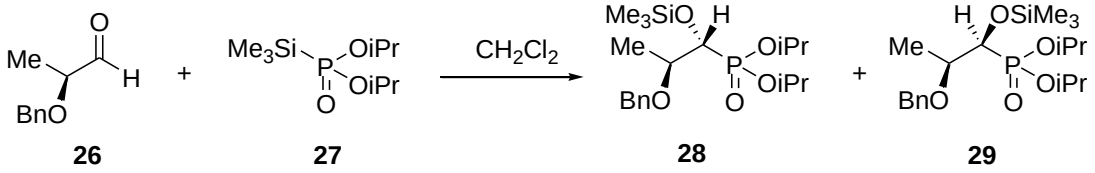
1.3.1 Phosphonylation of carbonyl compounds

The most well known method for synthesizing α-hydroxy phosphonates is phosphonylation of carbonyl compounds. One of the method is known as Abramov reaction where trialkyl phosphites are directly added to an aldehyde (Scheme 1.2).[39-40] The second one is Pudovik reaction where dialkyl phosphites are added to either an aldehyde or ketone (Scheme 1.2).[39-40]



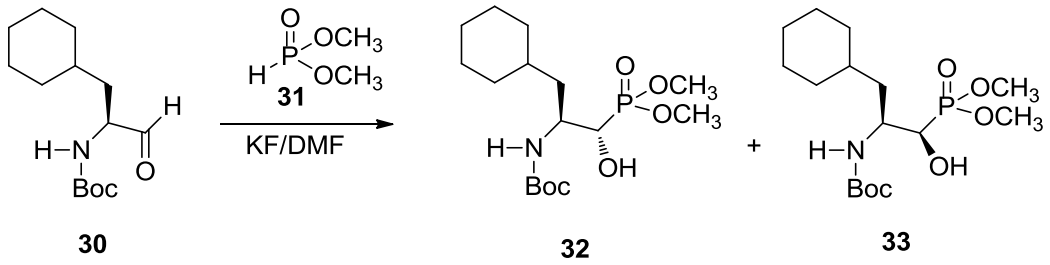
Scheme 1.2 General scheme for Abramov and Pudovik reaction

Hammerschmidt has reported a study of diastereoselectivity of aldehyde **26** under both Pudovic and Abramov conditions to give the greatest erythro/threo ratio shown in Scheme 1.6.[41] He has found that an Abramov reaction with diisopropyl trimethylsilyl phosphate **27** (Scheme 1.3) gave the best erythro/threo ratio as 3:1 for compounds **28**:**29**.



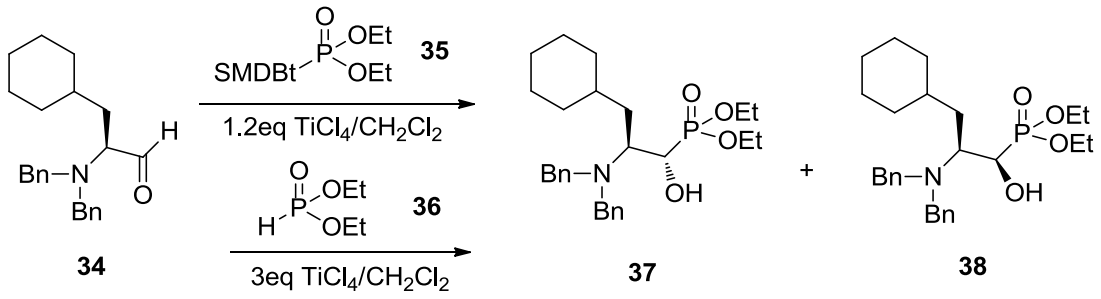
Scheme 1.3 Synthesis of *α*-hydroxy phosphonates from aldehyde **26**

Patel *et al*. has reported[42] that carbonyl compounds derived from amino acids, for an example, the Boc amino aldehyde **30** derived from L-phenylalanine, undergoes diastereoselective addition of dimethyl phosphite to give α-hydroxy phosphonates **32** and **33** with diastereomeric excess (*de*) of up to 12:1 (Scheme 1.4).



Scheme 1.4 Phosphite additions to phenylalanine derivatives **30**

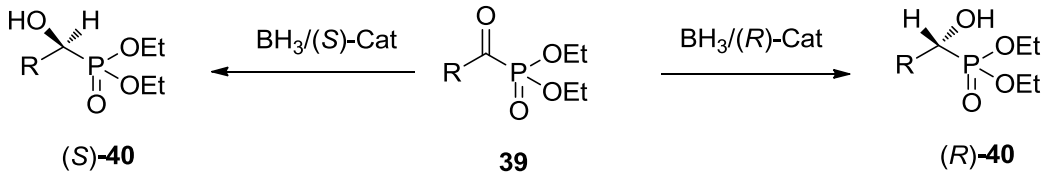
In another study related with the synthesis of α-hydroxy phosphonates **37** and **38,** *t*-butyldimethylsilyl diethyl phosphate **35** was reacted with α-dibenzylamino aldehyde **34** in the presence of $TiCl_4$.[43] High *de*'s (up to >98:2) in formation of α-hydroxy phosphonates **38** (98%) were observed. A reversal of the addition stereochemistry **37** (93%) was achieved when diethyl phosphate **36** was employed in place of the *t*-BDMS phosphate. Streochemical outcome was explained by the weakened nucleophilicity of diethyl phosphate. In both cases, removal of the amine protecting groups gave the related β-amino α-hydroxy phosphonates (Scheme 1.5).



Scheme 1.5 Phosphite additions to phenylalanine derivatives **34**

1.3.2 Reduction of acyl phosphonates

α-Hydroxy phosphonates can also be synthesized by reduction of acyl phosphonates. In one research, Gajda *et al*. has synthesized diethyl 1-hydroxy phosohonate (*S*)-**40** or (*R*)-**40** in good yields and moderate enantiomeric excesses (53–83% ee) by the reduction of diethyl acyl phosphonates **39** with borane in the presence of chiral β-butyloxazoborolidines as a catalyst (Cat) (Scheme 1.6).[44]



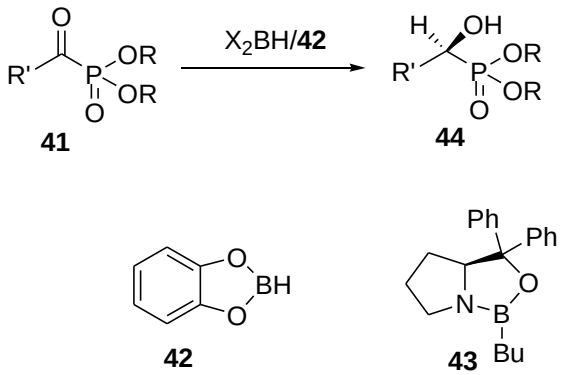
(*S*)-**40** **39** (*R*)-**40**

Cat=β-butyloxazoborolidine,

R=Et (80% *ee*), Bu (53% *ee*), *i*-Bu (76% *ee*), Ph (82% *ee*)

Scheme 1.6 Borane reduction of α-ketophosphonates **39**

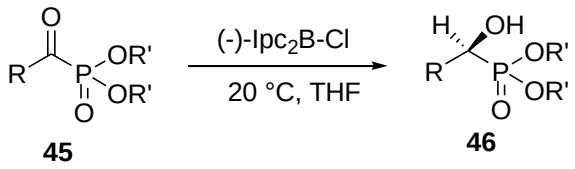
Meier *et al.*[45-46] reduced acyl phosphonates **41** with both catecholborane **42** and borane/dimethylsulfide complex in the presence of a 1,3,2-oxazaborolidine catalyst **43** to produce α-hydroxy phosphonates **44**. Reduction of acylphosphonates **41** with (*S*)-oxazaborolidine-catecholborane formed (*S*)-1-hydroxylkylphosphonates **44**, and accordingly reduction with corresponding (*R*)-oxazaborolidine-catecholborane afforded (*R*)-1-hydroxylkylphosphonates with the same stereoselectivity (53–83% ee) (Scheme 1.7).



R=Et, *i*-Pr; R'=Alk, Ar

Scheme 1.7 Oxazaborolidine-catecholborane reduction of acyl phosphonates **41**

Meier and co-workers also showed[36,46] that when acyl phosphonates **45** were reduced in the presence of (-)-chlorodiisopinocampheylboranes (Ipc_2B–Cl), it produced (*S*)-configurated α-hydroxy phosphonates **46** in 65% enantiomeric excess (Scheme 1.8).

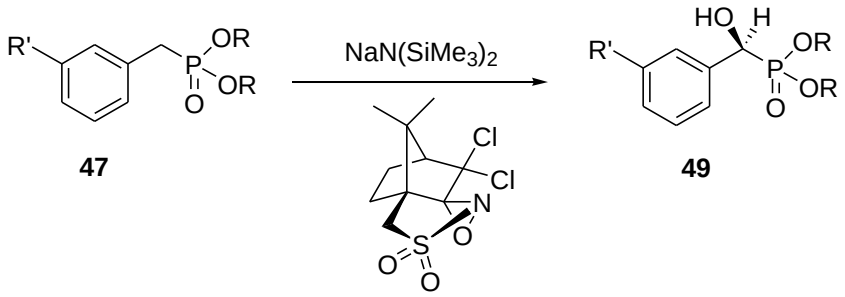


R=Me, Pr-*i*, Bn, Ph; R'=Me, Et, Pr-*i*

Scheme 1.8 Reduction of acylphosphonates **45** with (-)-Ipc_2BCl

1.3.3 Oxidation reactions of Phosphonates

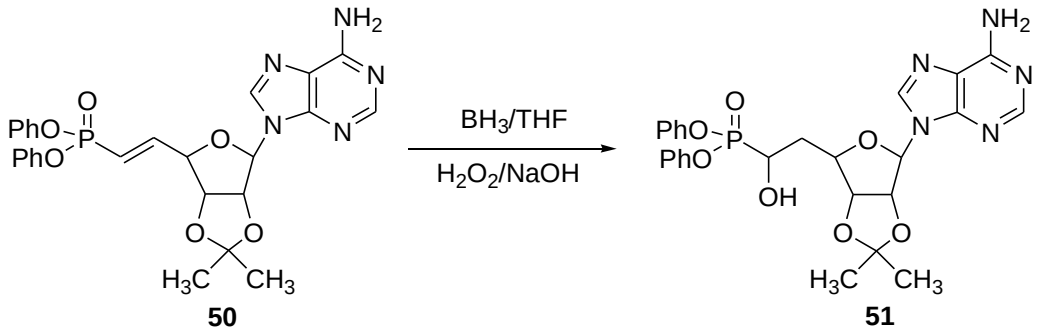
Another route in the literature for the synthesis of α-hydroxy phosphonates is oxidation of the related phosphonates. As an example, Skropeta and co-workers synthesized compound **49** in high yields by the stereoselective oxaziridine **48** mediated hydroxylation of dialkyl benzylphosphonates **47** (Scheme 1.9).[47]



R = H, Me, Et, CH_2=$CHCH_2$ R' = H, NO_2, Cl, MeO, CF_3

Scheme 1.9 Oxidation of benzylphosphonates **47** with chiral oxaziridines

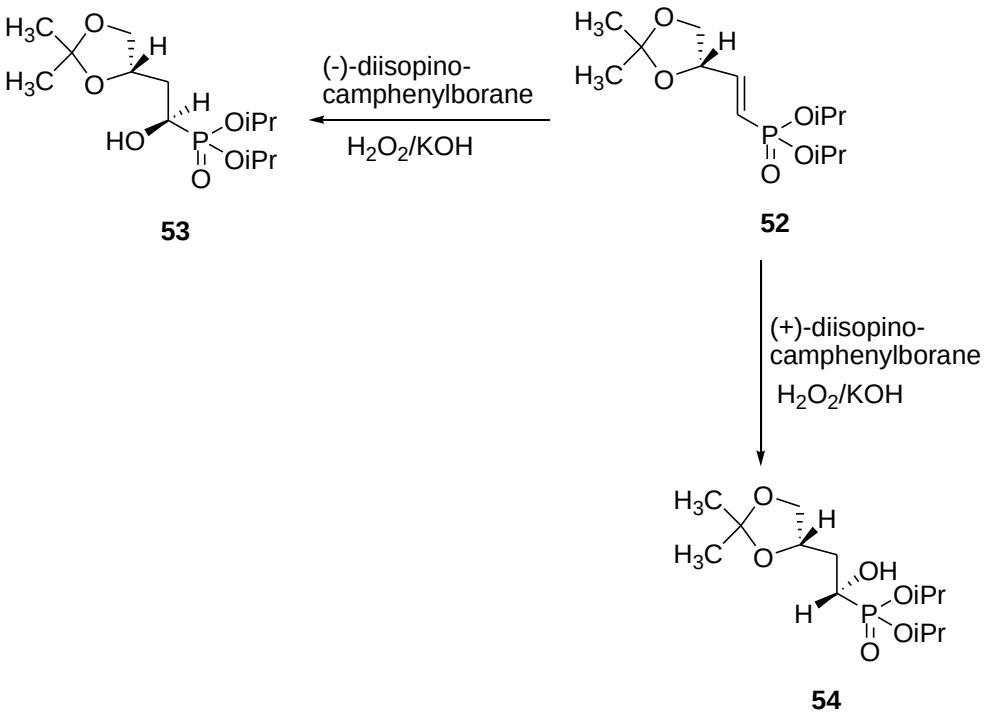
α-Hydroxy phosphonates can also be synthesized by hydroboration/oxidation of vinyl phosphonates. The reaction of vinyl phosphonate **50** with borane in THF was done by Hampton *et al.*[48] When compound **50** was treated with H_2O_2 and sodium hydroxide, oxidation and partial hydrolysis resulted in formation of the α-hydroxy phosphonate **51** as a 1:1 mixture of diastereomers (Scheme 1.10).



50 **51**

Scheme 1.10 Hydroboration/oxidation of vinyl phosphonate **50**

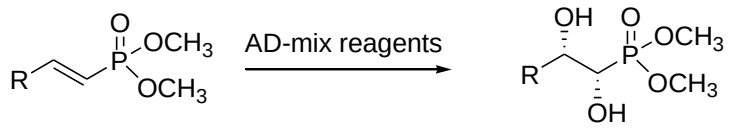
To prepare α-hydroxy phosphonates Lalinde and co-workers[49] examined hydroboration/oxidation of vinyl phosphonate **52** with (-)- and (+)-diisopinocamphenylborane. Diastereomer **53** (with 1*R*, 3*S* stereochemistry) was isolated from reaction of the nonracemic olefin **52** with the (-)-borane reagent. On the other hand diastereomer **54** was obtained from the parallel reaction with the (+)-borane. This selectivity arose from the steric bulk of the phosphoryl group controlled approach of the chiral borane reagent (Scheme 1.11).



53 **52** **54**

Scheme 1.11 Oxidation of vinyl phosphonate **52**

Dihydroxy phosphonates are easily obtained by the method of Yokomatsu *et al.*[50] Alkyl substituted vinyl phosphonates **55** (Scheme 1.12) proceeded with moderate yield and enantioselectivity when subjected to AD-mix oxidations. But phenyl and *p*-methoxyphenyl substituents resulted in better ee's.[51] The high ee and the synthetic transformations demonstrated with the *p*-methoxyphenyl product attracted more interest to this method.



55 **56**

55a R = CH_3 **56**a R = CH_3 (33% ee)

b R = $C_6H_5CH_2OCH_2CH_2$ b R = $C_6H_5CH_2OCH_2CH_2$ (44% ee)

c R = C_6H_5 c R = C_6H_5 (91% ee)

d R = p-$MeOC_6H_4$ d R = p-$MeOC_6H_4$ (>95% ee)

Scheme 1.12 Oxidation of vinyl phosphonates **55**

1.3.4 Chemoenzymetic synthesis of α-hydroxyphosphonates

Chemoenzymatic synthesis is an effective pathway for synthesis of fine chemicals in their optically active forms. The use of enzymatic synthesis in organophosphorus compound is limited to the synthesis of optically active hydroxyphosphonic acids and their esters. Bacteria, fungi, and various lipases are used as biocatalysts for the preparation of optically active hydroxyphosphonates.[52] Four general processes applied to the enzymatic synthesis of hydroxyalkylphosphonates are:

(a) Baker's yeast or other fungi for the bio-reduction of ketophosphonates.

(b) Microorganisms and lipases for the separation of chiral hydroxyphosphonates via acylation.

(c) Use of lipolytic organisms for hydrolysis of acyloxyalkanephosphonates.

(d) Use of Bacteria and fungi for hydrolytic oxirane ring opening in substituted 1,2-epoxyethanephosphonates (Figure 1.4).

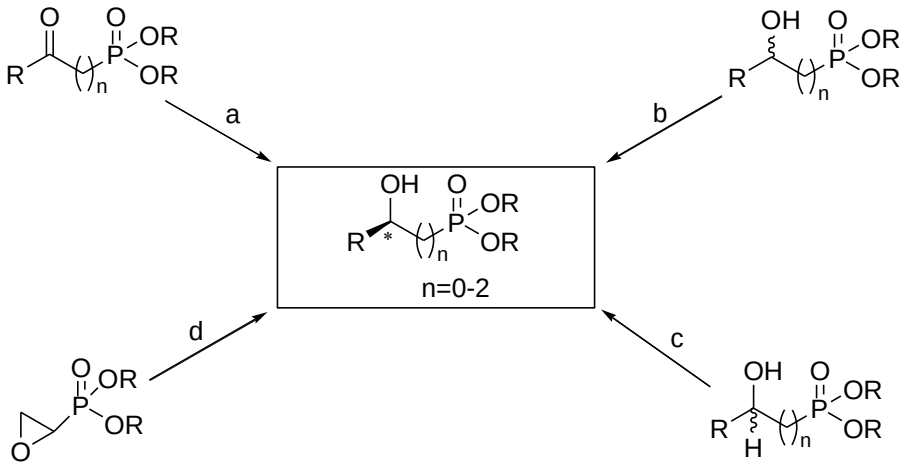
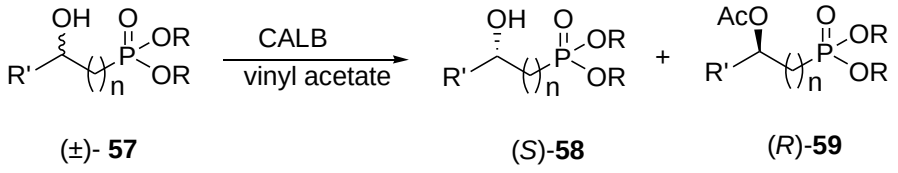


Figure 1.4 Enzymatic synthesis of hydroxyphosphonates

Racemic α-hydroxyalkylphosphonates were resolved by catalytic acetylation with Candida antarctica B lipases (CALB) and Candida rugosa lipases (CRL) to (*R*)- and (*S*)-isomers in high enantiomeric excess.[53-54] Yuan *et al*.[55] used the lipase CALB in organic solvents for enantioselective acetylation and resolution of racemic α-hydroxy alkylphosphonates **57**. The subsequent separation of unreacted alcohol (*S*)-**58** and ester (*R*)-**59** afforded the pure stereoisomers. This method is simple and furnishes chiral hydroxyalkylphosphonates in high enantiomeric excess (85–95%) (Scheme 1.13).

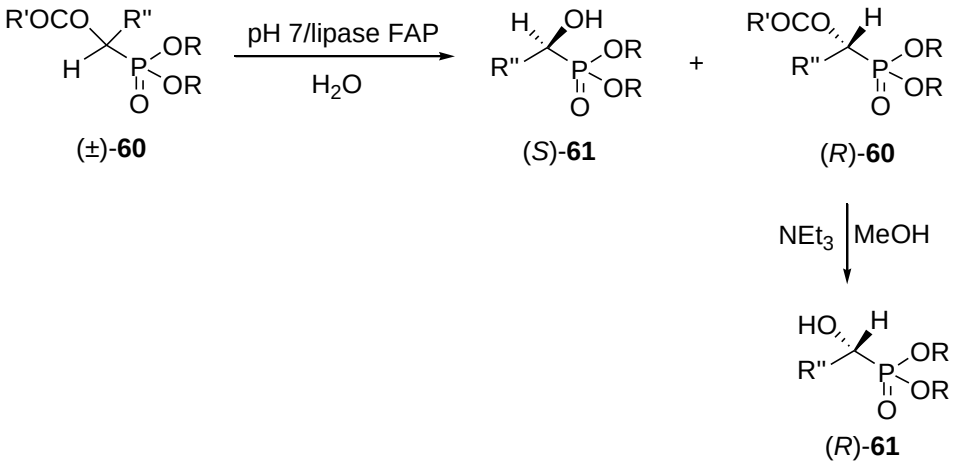


(±)- **57** (*S*)-**58** (*R*)-**59**

R'=Me, Et, vinyl; R=Me, Et; n=0

Scheme 1.13 CALB catalyzed enzymatic kinetic resolution of racemic hydroxyphosphonates

Hammerschmidt and co-workers[56-64] reported a widely used method for the resolution of racemic α-hydroxy phosphonates **60** by lipases and proteases in a two-phase system (organic solvent-water) where a phosphate buffer of pH 7 was used. This method afforded the chiral α-hydroxy phosphonates in an enantiomeric excess of 98%. Acetates of racemic α-hydroxy phosphonates **61** undergo enzymatic hydrolysis controlled with various lipases, including esterase of pig liver in the two-phase system. The highest enantioselectivity was achieved with lipase FAP 15 and (acetoxy)phenylmethylphosphonates as substrate. Only the (*S*)-enantiomers of phosphonates were hydrolyzed to afford enantiomerically pure (*S*) alcohols. Lipases AP 6 and FAP 15 were used for the preparation of (*S*)-phosphonates on a preparative scale with 81–89% ee (Scheme 1.14).[58-59]

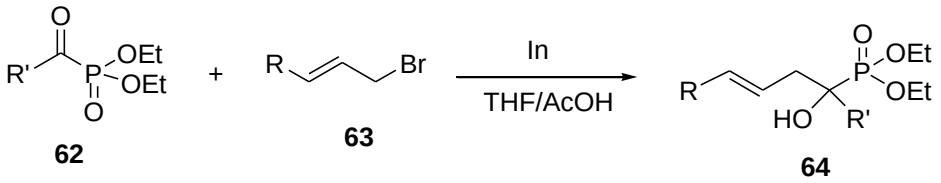


R=Et, i-Pr, t-Bu, $MeS(CH_2)_2$; R'= CH_2Cl, Pr; R"=i-Pr

Scheme 1.14 Two phase enzymatic kinetic resolution of racemic hydrophosphonates

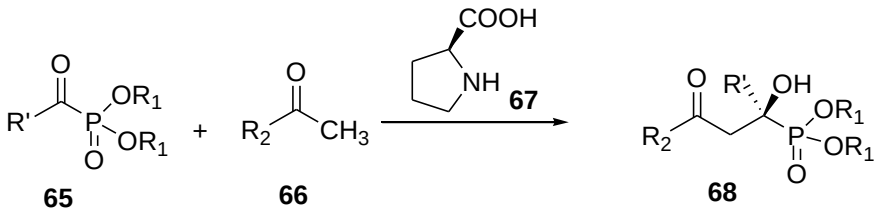
1.3.5 Miscellaneous addition reactions of acyl phosphonates

In the current literature, there are some examples for the synthesis of α-hydroxy phosphonates by direct addition to acyl phosphonates. Kim *et al*. have reported[65] *in situ* addition of allyl indium reagents to acyl phosphonates (Scheme 1.15). According to their method, compound **62** was simply treated with allyl bromide derivative **63** and indium metal in water, or in a mixture of water and an organic co-solvent. The desired α-hydroxy phosphonates **64** were isolated in moderate to low yields.



Scheme 1.15 Addition of allylindium reagents to acyl phosphonates **62**

Tertiary α-hydroxy phosphonates **68** were synthesized by a novel cross aldol reaction of α-keto phosphonates **65** with ketones **66** (Scheme 1.16).[66] Diethyl benzoylphosphonate and acetone was used as the model compounds and L-proline **67** as the catalyst. The crossed aldol reaction went smoothly at room temperature in acetone to form the expected products in good yields.



R'= Ph, Me, Ph-CH_2, etc...
R_1= Et, Me, i-Pr
R_2= Me, -OCH_3

Scheme 1.16 Synthesis of tertiary α-hydroxy phosphonates by crossed aldol reaction

1.4 Synthesis of Propargylic Alcohols

In this dissertation one of our interests was to develop a new method for the synthesis of α-hydroxy phosphonates and then extend this method to the synthesis of propargylic phosphonates.

Propargylic phosphonates can be considered as close analogue of propargylic alcohols. Propargylic alcohols are useful building blocks for a large number of pharmaceutically significant molecules (Figure 1.5).[67] For that reason there are several methods available in the literature for their synthesis. The addition of acetylides to carbonyl substrates gives access to propargylic alcohols, which are valuable intermediates for the synthesis of complex natural products.[68] Moreover, the addition of alkynes to ketones is a practical strategy to create tertiary alcohols with a new stereogenic center under mild conditions.[69] Traditionally, propargylic alcohols are synthesized by addition of a metal acetylide to aldehydes or ketones with a stoichiometric or catalytic amount of a base.[70]

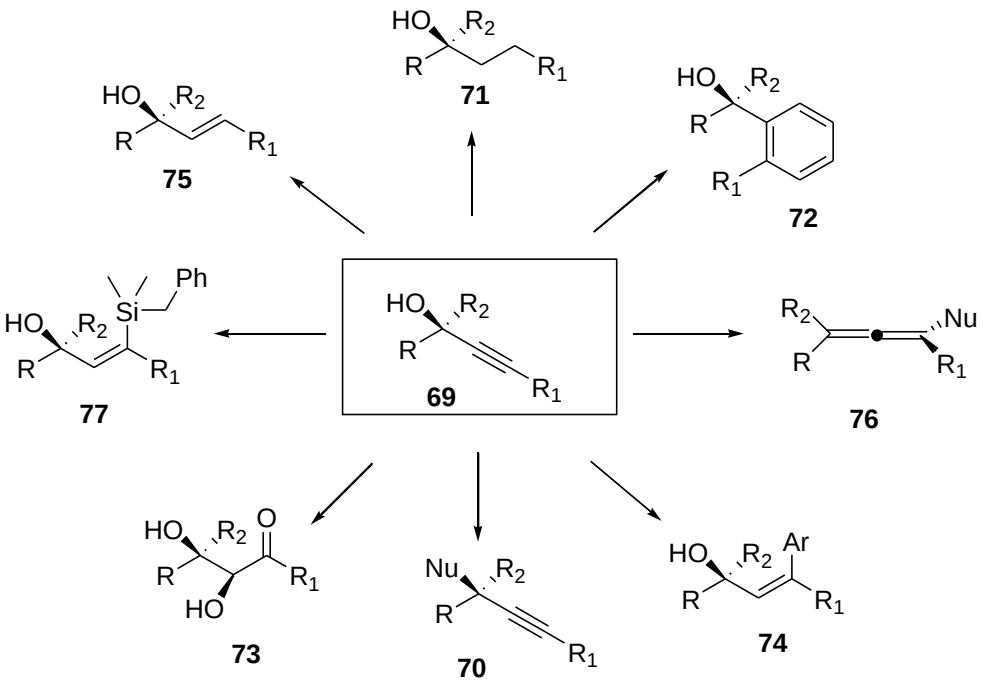
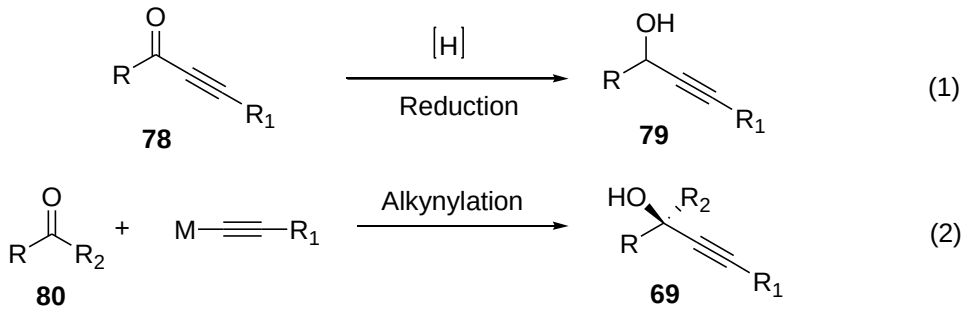


Figure 1.5 Propargylic alcohols as synthetic intermediates

The most common methods to prepare propargylic alcohols are through

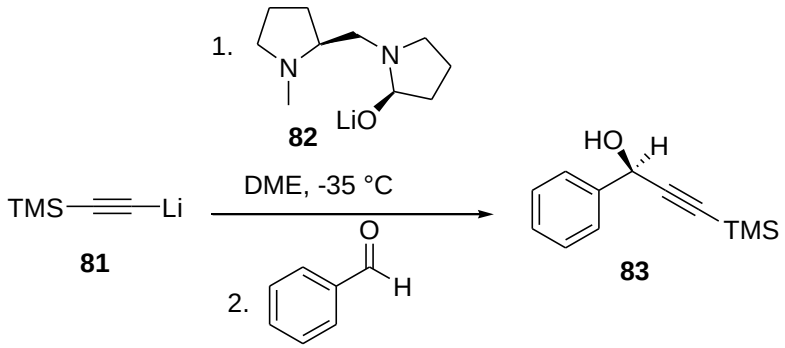
i) Reduction of an ynone [Scheme 1.17, Eq. (1)] and

ii) Metal-catalyzed alkynylation of a carbonyl group [Scheme 1.17, Eq. (2)]



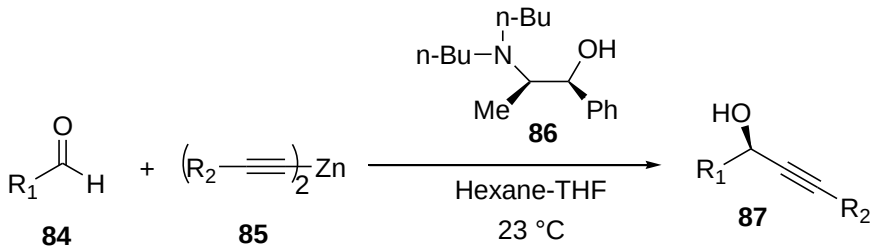
Scheme 1.17 Common methods for the synthesis of propargylic alcohols **69** and **79**

Here are some examples from the literature for the synthesis of propargylic alcohols. The first alkyne addition to an aldehyde was published by Mukaiyama and co-workers (Scheme 1.18).[71] According to their work, lithium acetylides was reacted with various aldehydes to get corresponding propargylic alcohols with moderate *ee* values. They reported that slow addition of the aldehyde led to increase in chemical yields. The substrate scope for this reaction was also investigated by changing silylacetylenes (TES, TBS, Ph_3Si and Ph_2MeSi).



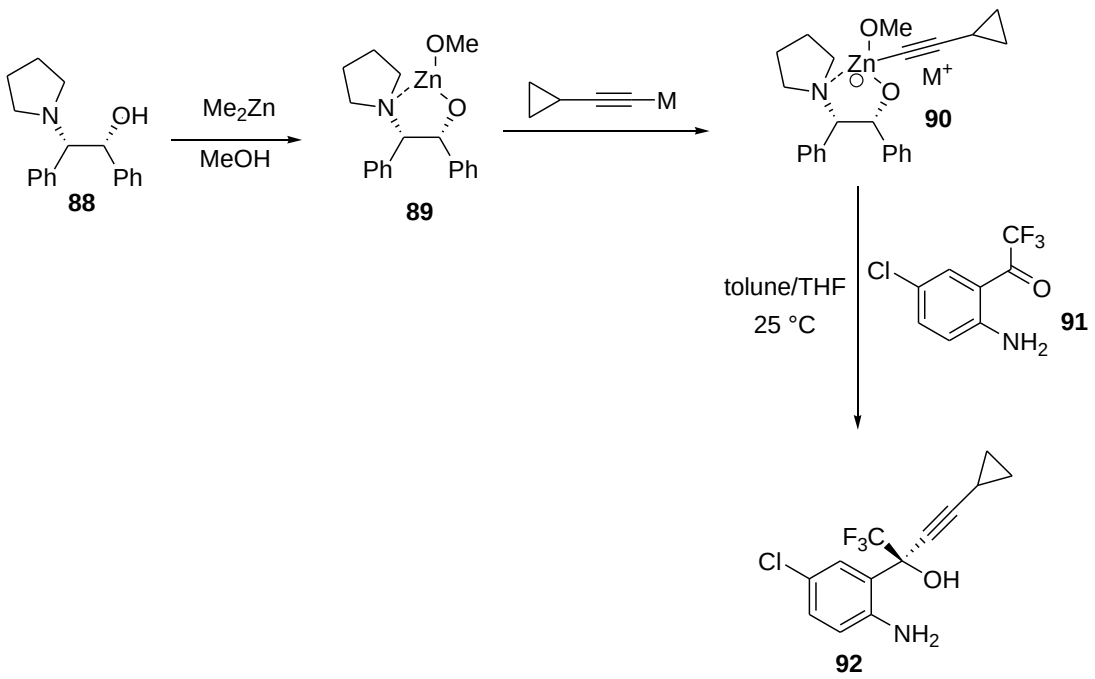
Scheme 1.18 First example of alkynylation of benzaldehyde

The addition of alkylzinc reagents to aldehydes has been well documented area of research since 1978.[72] Alkynylzinc reagents were also found to be very useful due to high functional group tolerance.[73] Soai and co-workers were reported the first addition of alkynylzinc reagents to aldehydes (Scheme 1.19)[74] *In situ* formation of bisalkynylzinc **85** was added to corresponding aldehydes in the presence of amino alcohol **86**. Propargylic alcohols **87** were obtained in excellent yields.



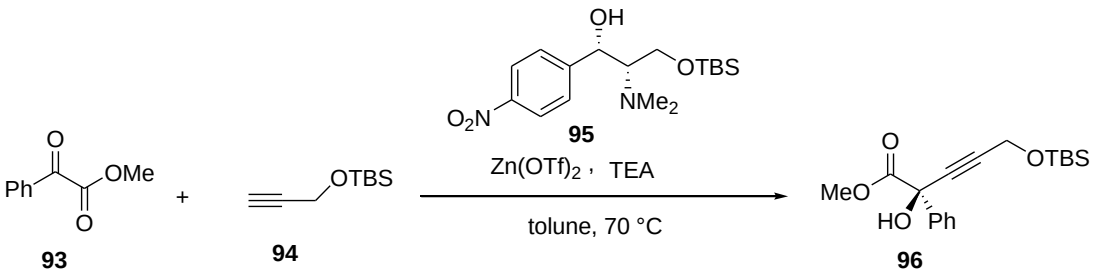
Scheme 1.19 Addition of alkynylzinc to aldehydes **84**

The example given below represents the first alkynylation reaction of a ketone was reported by Merck and Dupont. They used their method for the synthesis of anti-AIDS drug efavirenz (Scheme 1.20).[75-76] In this method pyrrolidine-ephedrine derivative **88** was treated with dimethylzinc to form **89**. Later compound **89** was added to a metal acetylide to obtain intermediate zincate **90**. The reaction between trifluoromethyl ketone **91** and zincate **90** furnished the resultant propargylic alcohol **92**.



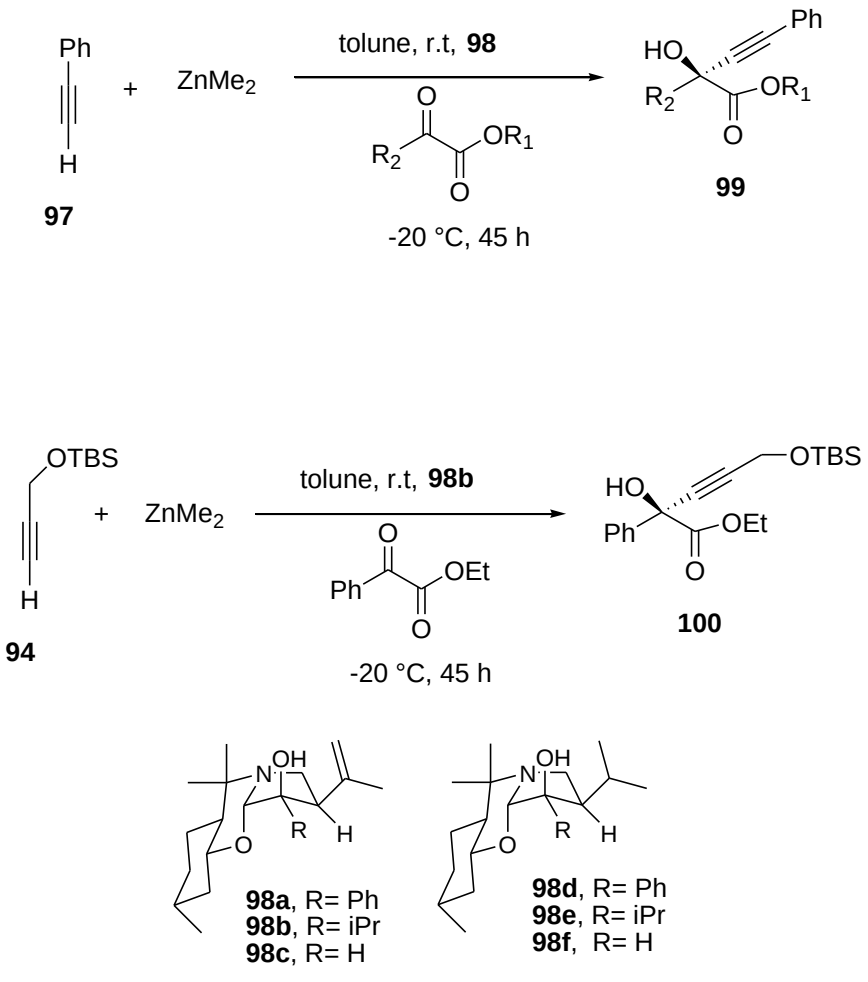
Scheme 1.20 First example of alkynylide addition to ketone **91**

Alkynylation of α-keto ester is very useful method to access highly functionalized propargylic alcohols. Propargylic alcohols having C-P bond can be considered as close analogues of propargylic carboxylates. Herein, only two examples from the literature related to alkynylation of α-keto ester were given. Jiang and co-workers showed that[77] aliphatic alkynes and phenylacetylene are valuable nucleophiles for the alkynylation of α-keto esters in presence of catalytic zinc(II) triflate and amino alcohol **95** (Scheme 1.21). Both linear and cyclic keto esters gave excellent yields and enantioselectivities. However, enolizeable ketones did not show good results.



Scheme 1.21 Alkynylation of activated ketone **93** with catalytic amount of zinc salt

Rebeca and co-workers synthesized propargylic alcohols through the zinc mediated alkynylation of α-keto esters (Scheme 1.22).[78] The reaction was efficiently promoted by perhydro-1,3-benzoxazines **98** derived from 8-aminomenthol. Under optimum reaction conditions, they were able to obtain high enantioselectivity. Various aromatic and heteroaromatic α-keto esters were used in this method. Both electronic effects or steric hindrance on the aromatic ring were not observed. Aliphatic alkynes were also used as a substrate and good enantioselectivity was observed.



Scheme 1.22 Addition of alkynylzinc derivatives to α-keto esters in presence of **98**

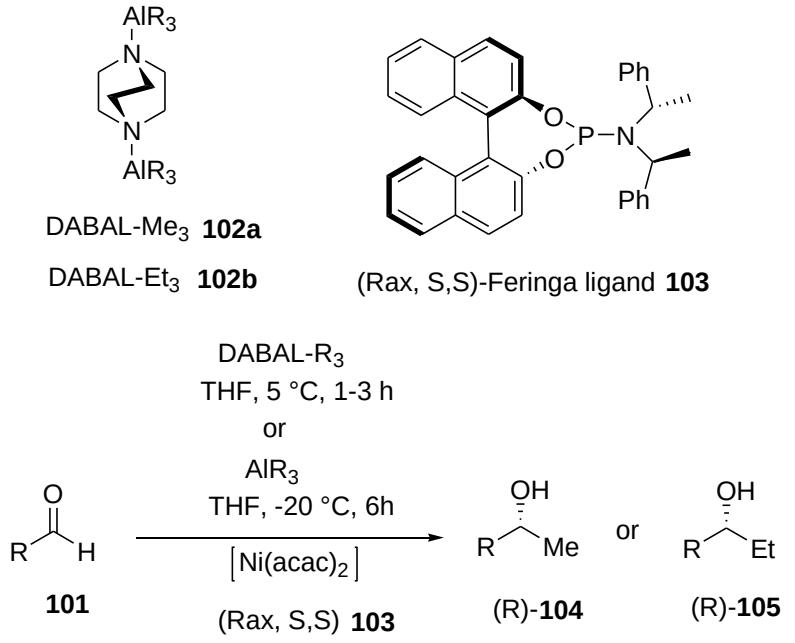
1.5 Reactions of Organoaluminum Reagents

The role of organoaluminum reagents are well-established in olefin oriented petrochemicals and are useful tools in selective organic syntheses. Properties of these reagents depend on the high Lewis acidity of the organoaluminum monomers which depend on the tendency of the aluminium atom to complete electron octets. Almost all alkylaluminum compounds react vigorously with oxygen or air and trialkylaluminum and dialkylaluminum halides are particularly reactive and often ignite spontaneously.[79] For that reason, they are difficult to handle and need special precautions. Organoaluminum compounds show great tendency to form 1:1 complexes, even with neutral bases such as ethers. "Oxygenophilicity" of organoaluminum reagents are of great value in the design of selective synthetic reactions. The coordination of a molecule with organoaluminum reagent causes a change of reactivity, and the coordinated group may be activated or deactivated depending upon the type of reaction.

Since this dissertation focuses on addition of organoaluminum reagents to acyl phosphonates, we would like to present few examples from literature that involves organoaluminum reagents.

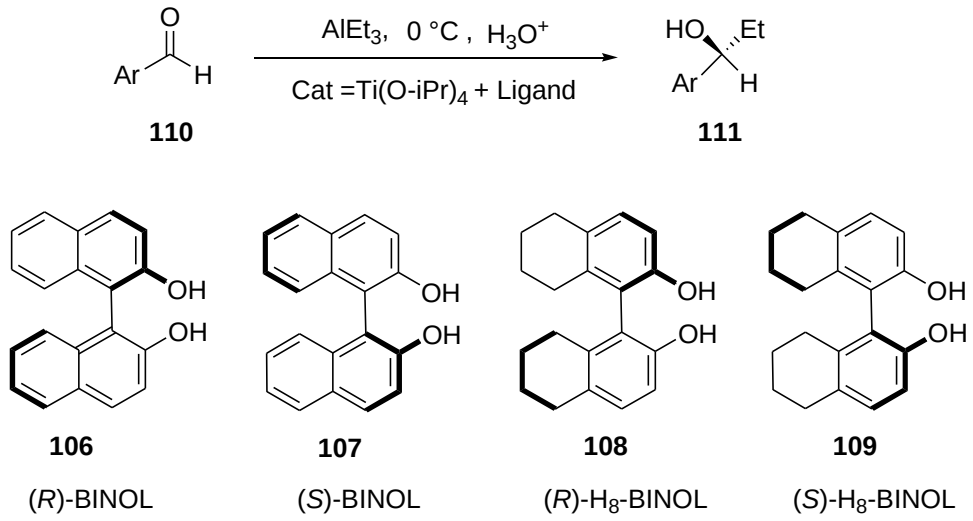
Trialkylaluminum reagents are one of the useful organoaluminum reagents for alkylation reactions because they are economically obtained on an industrial scale from aluminum hydride and olefins.[80] Unfortunately, their use in chemistry is still rare. One successful catalyst for the enantioselective addition of trialkylaluminum to aldehydes is titanium complexes bearing chiral diols or N-sulfonylated amino alcohols as ligands.[81] However, high catalyst loadings and the slow reaction rate hamper the potential utility of these catalytic systems. Woodward and co-workers reported[82] the addition of trialkylaluminum to aldehydes in the presence of nickel catalyst. Excellent enantioselectivities with low catalyst loadings were attained. When prepared DABAL-Me_3 (1.0–1.5 equiv) **102a** was added to benzaldehyde in THF in the presence of [$Ni(acac)_2$] (acac=acetylacetone; 1 mol%) and Feringa ligand

103 (Rax, S,S, 2 mol%) at 5 °C , the resulting alcohol **104** (R=Ph) was isolated in high yield and enantioselectivity (Scheme 1.23).



Scheme 1.23 The asymmetric synthesis of chiral secondary alcohols from aldehydes using organoaluminum reagents

In another work Albert and co-workers have examined the addition reactions of triethylaluminum reagent to aldehydes by using (*S*)- or (*R*)-BINOL (Scheme 1.24).[83] Triethylaluminum was added to benzaldehyde in the presence of chiral ligands i.e. BINOL and H_8-BINOL. Benzaldehyde was easily alkylated to give 1-phenyl-1-propanol quantitatively with 81% ee when (*R*)-BINOL **106** was used as the chiral ligand. In the case of (*S*)-H_8-BINOL, the expected alcohol was obtained with improved enantioselectivity. This method was found to be very practical and general in terms of providing high yields for a variety of aromatic aldehydes **110**.



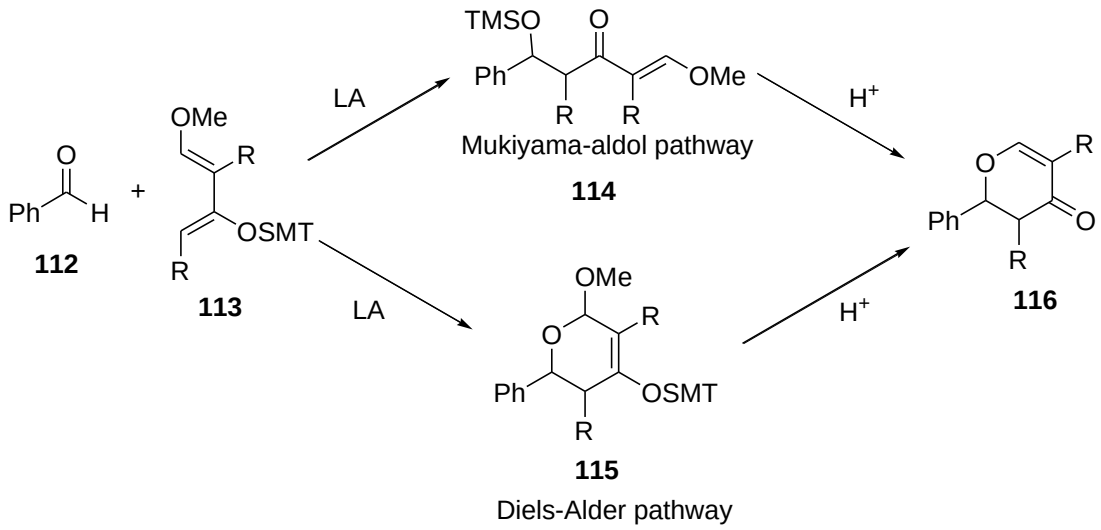
Scheme 1.24 Asymmetric synthesis of chiral secondary alcohols from benzaldehydes using organoaluminum reagents

1.6 Hetero Diels-Alder Reactions

Diels-Alder reaction is a very well known reaction for the construction of six membered rings.[84] Hetero Diels-Alder (HDA) reaction is a type of Diels-Alder reaction which is very useful for the construction of heterocycles in one step.[85] First report of a hetero Diels-Alder (HDA) reaction was appered in 1951 by Gresham and Steadman. In 1982 the HDA was extended to non-activated aldehyde as dienophile by Danishefsky and co-workers using Lewis acid catalyst.[86] Since that time, several manuscripts were published related to HDA reactions for the synthesis of dihydropyranone units (Scheme 1.25). HDA reaction is very practical in terms of having pyran containing heterocycles which are very common unit in many natural products.

Roberson *et al.* have examined the mechanism of the Lewis acid catalyzed HDA of aldehydes with activated dienes both experimentally and theoretically for several systems.[87] Two reaction pathways were observed from these studies. In the first case,

the HDA product formed through a Mukiyama-type aldol addition step and subsequent cyclization took place under acidic conditions. In the second case, concerted [4+2] cycloaddition reactions take place to form the HDA product (Scheme 1.30).



Scheme 1.25 Mukiyama aldol vs Diels-Alder pathway for the pyran ring formation

There are mainly two types of HDA reactions. In the first one, a diene reacts with aldehyde which participates as a heterodienophile. This reaction goes with normal electron demand HDA. In the second one, an enal reacts as the diene with electron rich dienophiles. This reaction is called inverse electron demand HDA reaction. According to Frontier Molecular Orbital (FMO) analysis the controlling orbitals for normal electron demand HDA reactions are HOMO of diene and LUMO of dienophile. Theoretical studies[87] revealed that Lewis acids lower the LUMO of the dienophile and enhance the reaction rate. Similarly, in the inverse electron demand HDA reactions the HOMO of the dienophile and the LUMO of the diene are the controlling orbitals. Lewis acids coordinate to the diene and enhance the rate by decreasing the HOMO-LUMO gap of the reaction. A summary of these FMO considerations is presented in Figure 1.6.

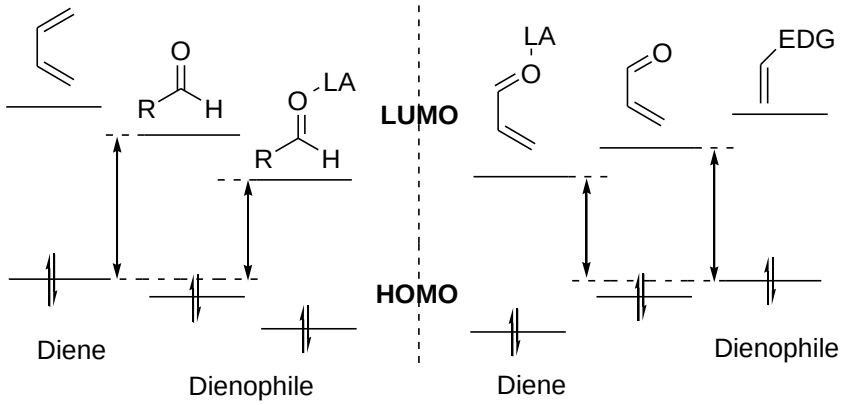
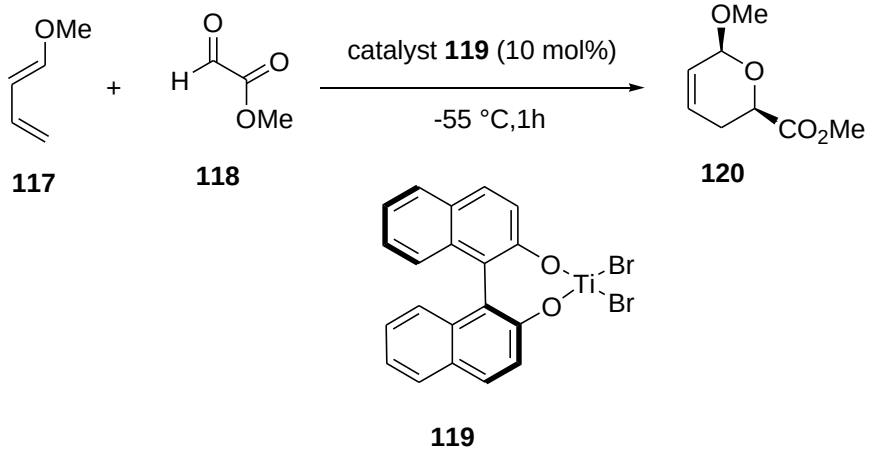


Figure 1.6 A FMO diagram of the uncatalyzed and Lewis acid catalyzed normal electron HDA (left) and inverse electron demand HDA (right).[85]

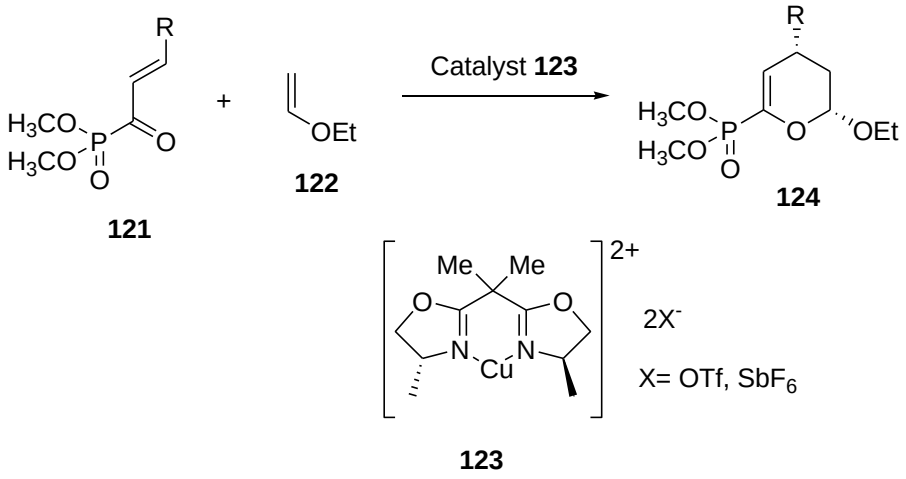
In this dissertation, we also focused on the Hetero Diels-Alder reactions of acyl phosphonates with unactivated dienes. Based on literature survey, we have tried to select HDA reactions that involves close analogue of acyl phosphonates. HDA reaction of unactivated diene **117** with methyl glyoxylate by using a Ti-BINOL complex **119** formed the HDA product in reasonable yield and moderate to good enantioselectivity (Scheme 1.26).[88] This work was reported by Nakai *et al*.



117 **118** **120** **119**

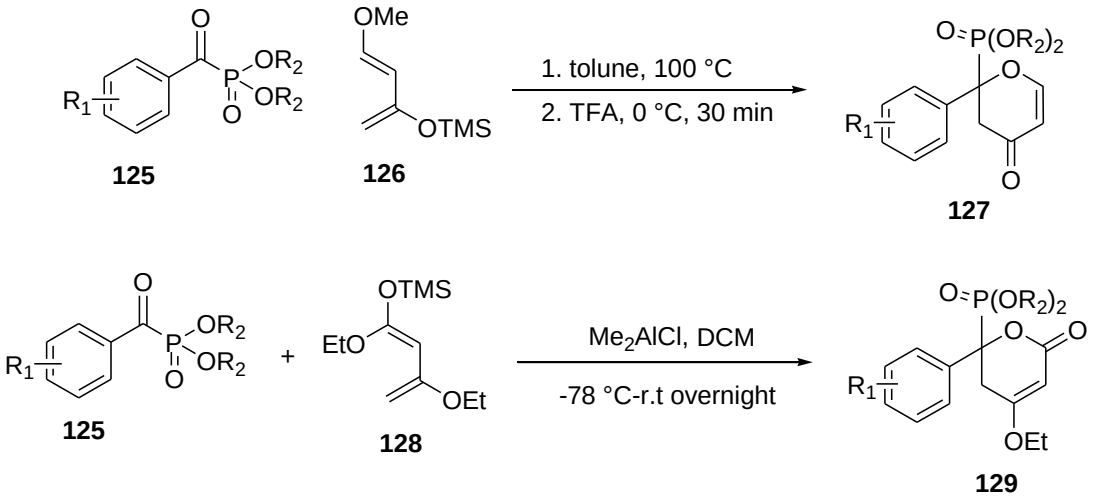
Scheme 1.26 Ti-BINOL catalysed HDA reactions of unactivated diene

Evans *et al*. have used α,β-unsaturated acyl phosphonates **121** as diene for HDA reactions with enol ether **122** as dienophile. Chiral Cu(II) complexes **123** was used to catalyze the HDA reaction which afforded cyclic enol phosphonates **124** (Scheme 1.27).[89]



Scheme 1.27 HDA reactions of α,β-unsaturated acyl phosphonates with enol ether

Demir *et al*.[90] have published the first hetero Diels-Alder reactions of acyl phosphonates with electron rich dienes where the acyl phosphonate serves as dienophile (Scheme 1.28). Glycosyl type phosphonates were obtained as the HDA product in good yields. Two types of electron rich dienes were used i.e. Danishefsky and Brassard's dienes. The former was activated easily by temperature, the later was promoted by aLewis acid to afford glycosyl type phosphonates. Glycosyl phosphates are biological glycosyl donors and participate in the glycosylation process.[91]



Scheme 1.28 First HDA reactions of acyl phosphonates **125** as dienophile

1.7 The aim of the work

α-Hydroxy phosphonate derivatives have shown to be very important enzyme inhibitors such as they are inhibitors of renin or human immunodeficiency virus (HIV) protease and polymerase. Besides, they also show antivirus and anticancer activities. Because of their diverse biological activities, *α*-hydroxy phosphonates have attracted significant attention. In the first part of this dissertation, our goal was to develop a new method for the synthesis of α-hydroxy phosphonates by using either commercial or non-commercial organoaluminum reagents.

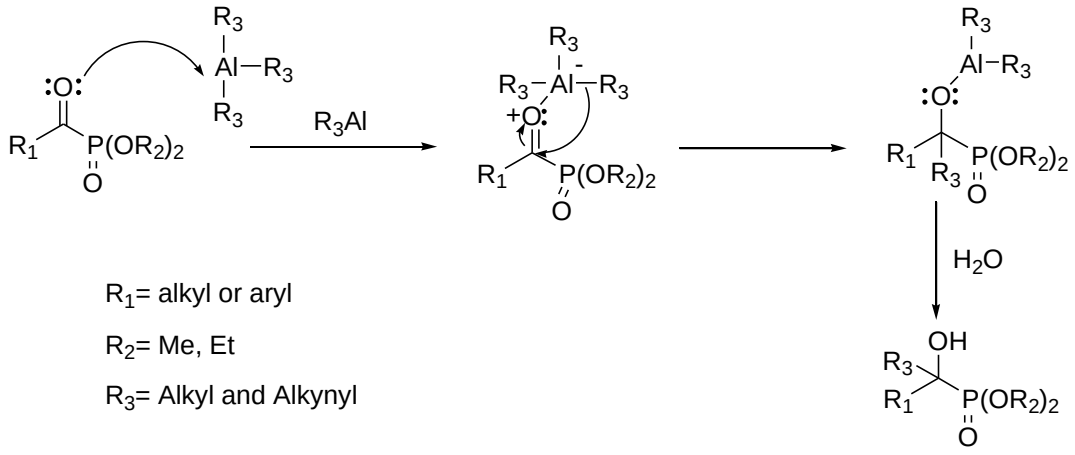
Recently, our group reported the first hetero Diels-Alder reactions of acyl phosphonates used as dienophiles with electron rich dienes to form glycosyl type phosphonates. In the second part of this dissertation, we aimed to extend the scope of hetero Diels-Alder reactions of acyl phosphonates and investigate the HDA reactions of acyl phosphonates with unactivated dienes.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Addition of trialkylaluminium reagent to acyl phosphonate

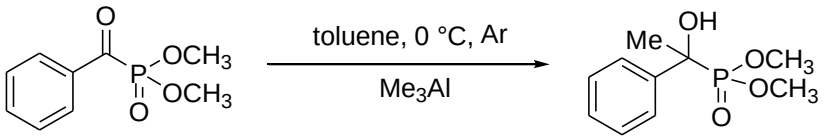
α-Hydroxy phosphonates was obtained by simple addition of organoaluminum reagents to acyl phosphonates. Acyl phosphonates were synthesized according to the literature procedure.[29] The addition of trialkyl phosphite to acyl chlorides at 0 °C led to formation of desired acyl phosphonates. A proposed reaction mechanism for the addition of organoaluminum reagents to acyl phosphonates is shown in (Scheme 2.1).



Scheme 2.1 Proposed mechanism for the addition of organoaluminum reagents to acyl phosphonates

Our first attempt was the addition of commercially available trimethylaluminum to benzoyl phosphonate **130** in order to obtain compound **131** as a reference reaction shown in (Scheme 2.2). Compound **130** was treated with 1.5 equivalent of Me_3Al at -78 °C in toluene, but no product formation was observed. Then we gradually increased the reaction temperature. Finally at 0 °C product formation was observed.

To have optimum reaction condition, we have screened the following organic solvents; THF, toluene, CH_2Cl_2, and hexane at 0 °C . Among these solvents, toluene gave the best results in terms of chemical yield. Secondly, we have screened the number of equivalents of the Me_3Al reagent. We found that three equivalents of Me_3Al reagent were necessary to give the desired compound **131** in good yield. After work-up the crude product was purified by flash column chromatography and identified by NMR spectroscopy (Figures 2.1 and 2.2).



130 **131**

Scheme 2.2 Addition of Me_3Al to benzoyl phosphonate **130**

Both ^1H and ^{13}C NMR strongly confirmed the formation of the product **131**. From ^{13}C NMR the first identifier is the peak of quartenary carbon atom which is directly attached to the phosphorus atom. This carbon showed a peak at 73.6 ppm as a doublet. The coupling constant $J_{C\text{-}P}$ was found as 159.1 Hz which is typical for this type of a C-P bond. In ^1H NMR, the doublet at 4.4 ppm (J = 4.7 Hz) for one proton clearly indicated the presence of the "OH" group. The doublet at 1.75 ppm ($J_{H\text{-}P}$) represents the methyl group. In the ^{31}P NMR the compound also gave a characteristic singlet peak at 26.18 ppm.

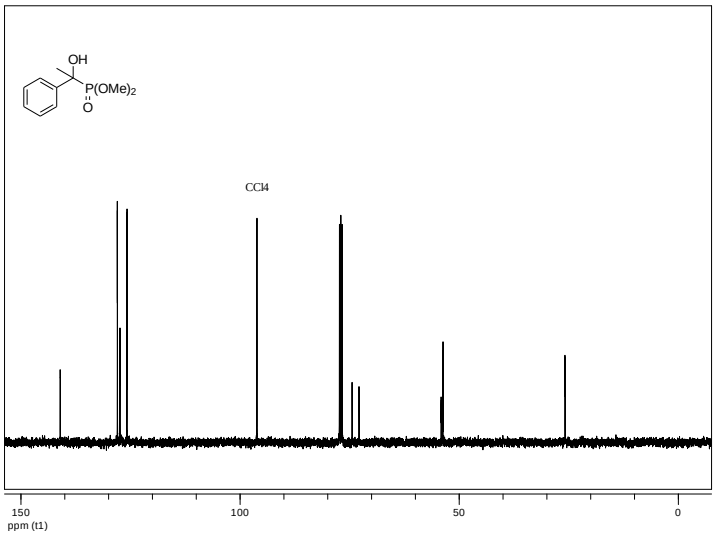


Figure 2.1 ^{13}C NMR spectrum of **131**

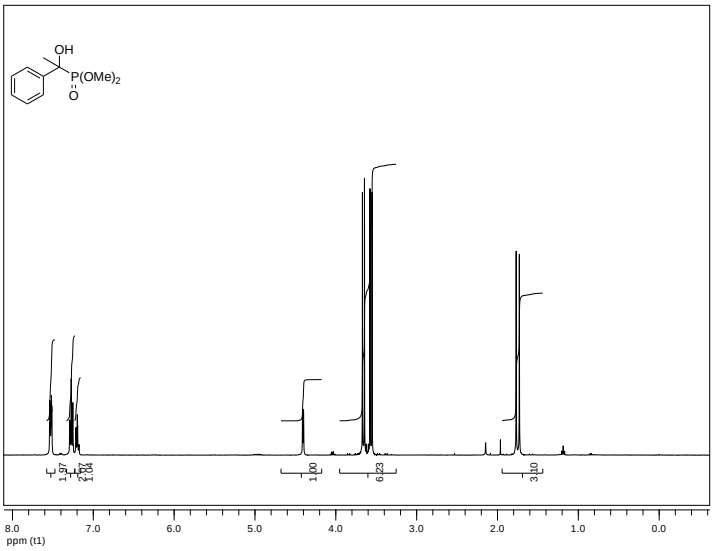
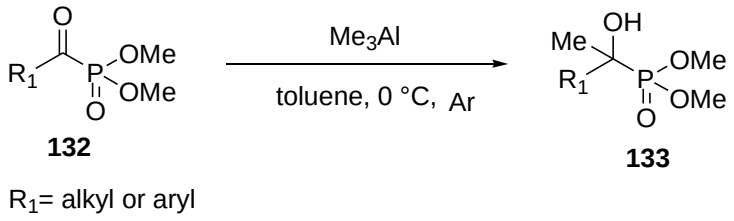


Figure 2.2 ^{1}H NMR spectrum of **131**

Maeda *et al.*[92] have utilized the addition of Grignard and organolithium reagents to acyl phosphonate **130** for the synthesis of α-hydroxy phosphonate **131**. Compound **131** was obtained by the addition of MeMgBr in around 44% yield while the addition of MeLi resulted in 20% yield. The reactions of both Grignard and organolithium reagents with benzoyl phosphonate **130** gave the desired products, but in low yield. Grignard and organolithium reagents are good source of carbon-based nucleophiles but in this case they found to be very reactive that lowers the yield. Comparing our

results with their findings, organoaluminum reagents are mild nucleophilic sources for the synthesis of α-hydroxy phosphonates in better chemical yields.

After optimizing the reaction conditions and characterizing our reference compound **131** we extended our investigation of the 1,2-addition reactions of trimethylaluminum reagents with a variety of acyl phosphonates having aryl and alkyl groups at acyl unit (R_1) (Scheme 2.3). The results were summarized in Table 1.



132 **133**

R_1= alkyl or aryl

Scheme 2.3 General reaction scheme for addition of Me_3Al to acyl phosphonates

As seen in Table 1, when the electron donating groups (-CH_3 and -OCH_3) were introduced to the aromatic unit of benzoyl phosphonate at para position, the reactivity was reduced and the yields were lower (entries 2 and 3) as compared to the unsubstituted substrate **130**. Benzoyl phosphonates **138** and **140** containing floride and chloride atoms at the para position gave the desired product **139** and **141** in 72 and 64% yields, respectively. It was expected that electronegative halides increase the reactivity of acyl carbonyl; therefore better yields could have been obtained. However, the yields were even lower that the substrates having electron donating groups. When the position of chloride changed from para (**140**) to meta (**142**) and ortho (**144**) yields increased (64, 73, and 77% respectively). Highest yield was obtained in the case of ortho-chlorobenzoyl phosphonates. This may result by the coordination of aluminum both to carbonyl oxygen and chloride at ortho position. Clearly no steric effect was observed for the ortho substituted benzoyl phosphonate

142. The reactions of Me_3Al with alkyl phosphonates **146** and **148** (entries 8 and 9) proceeded efficiently to afford the compounds **147** and **149** in 78 and 63% yields.

Table 1. Addition of trimethylaluminium to acyl phosphonates

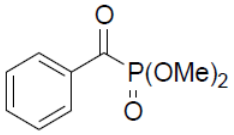
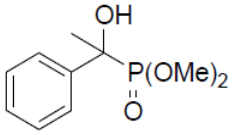
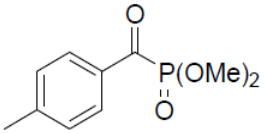
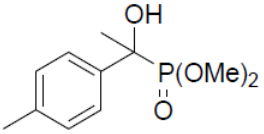
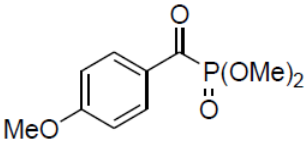
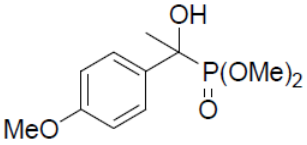
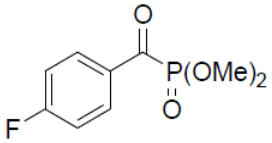
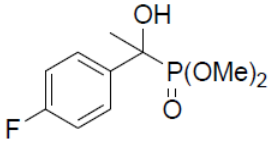
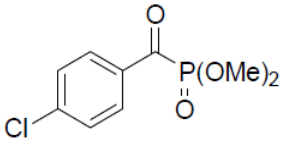
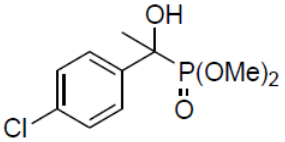
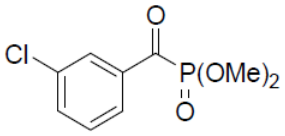
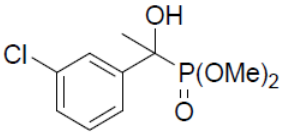
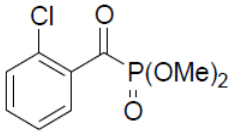
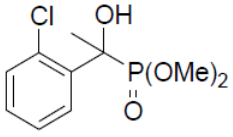
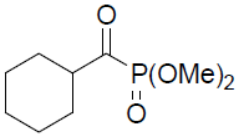
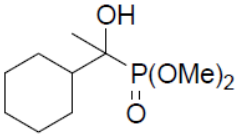
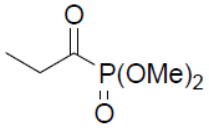
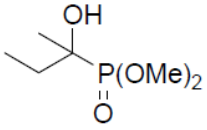
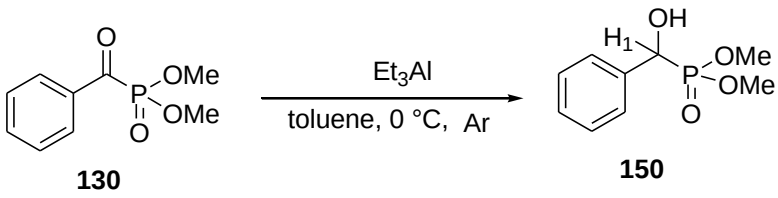
Entry	Acyl phosphonate	Product	Yield[a] (%)
1	 **130**	 **131**	85
2	 **134**	 **135**	83
3	 **136**	 **137**	77
4	 **138**	 **139**	72
5	 **140**	 **141**	64
6	 **142**	 **143**	73
7	 **144**	 **145**	77

Table 1 (continued)

Entry	Acyl phosphonate	Product	Yield[a] (%)
8	 **146**	 **147**	78
9	 **148**	 **149**	63

[a]Yields refer to purified compounds

Encouraged by the results obtained from the addition reactions of Me_3Al to acyl phosphonates, we continued our research and investigated addition of Et_3Al reagent as an ethyl donor to acyl phosphonates. However under the same reaction condition mentioned above, the addition of Et_3Al to benzoyl phosphonate **130** at 0 °C only afforded the hydride addition product **150** in 75% yield (Scheme 2.4). Structure of compound **150** was confirmed by ^1H and ^{13}C NMR spectra (Figures 2.3 and 2.4).



130 **150**

Scheme 2.4 Addition of Et_3Al to benzoyl phosphonate **130** at 0 °C

The first characteristic peak for identification of compound **150** is the H_1 proton which appeared as a doublet at 5.03 ppm due to coupling with phosphorus atom ($J_{C\text{-}H}$ 10.9 Hz). Besides, the proton of OH-group appeared as a broad singlet at around 4.40 ppm. In ^{13}C NMR, the tertiary carbon atom which is directly attached to both

phosphorus and OH-group appeared as a doublet at 70.7 ppm. (J_{C-P} =159.1 Hz). In addition to ^{1}H and ^{13}C NMR, ^{31}P NMR also showed expected signal at 22.92 ppm.

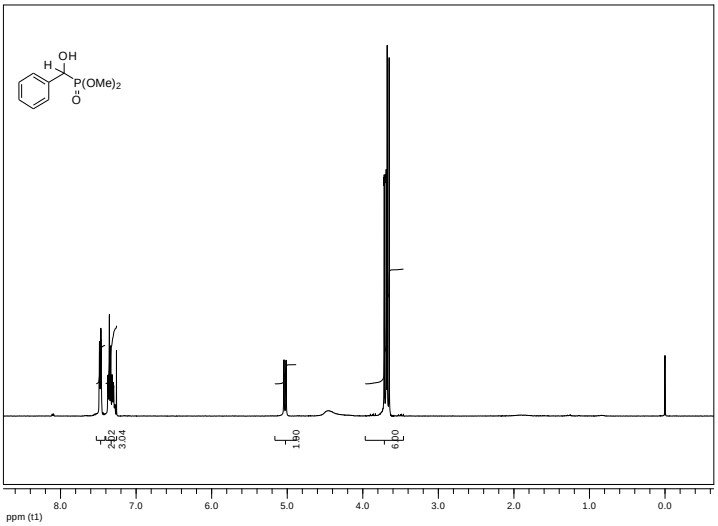


Figure 2.3 ^{1}H NMR spectrum of **150**

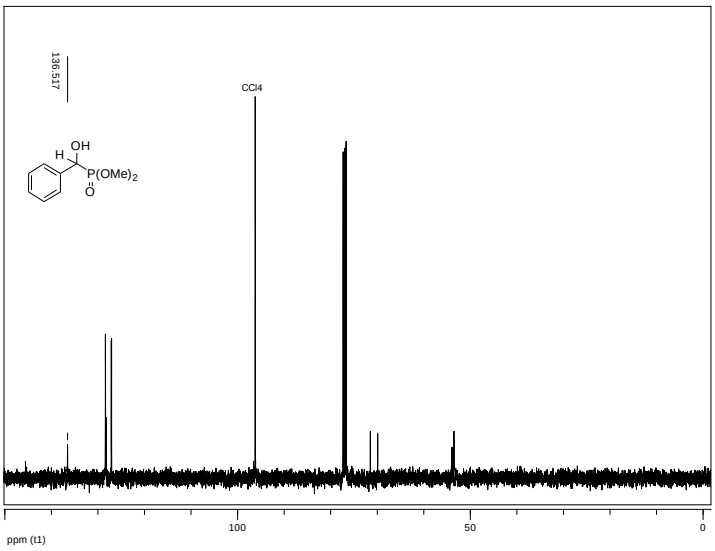
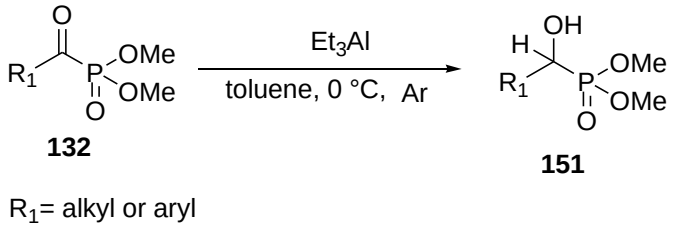


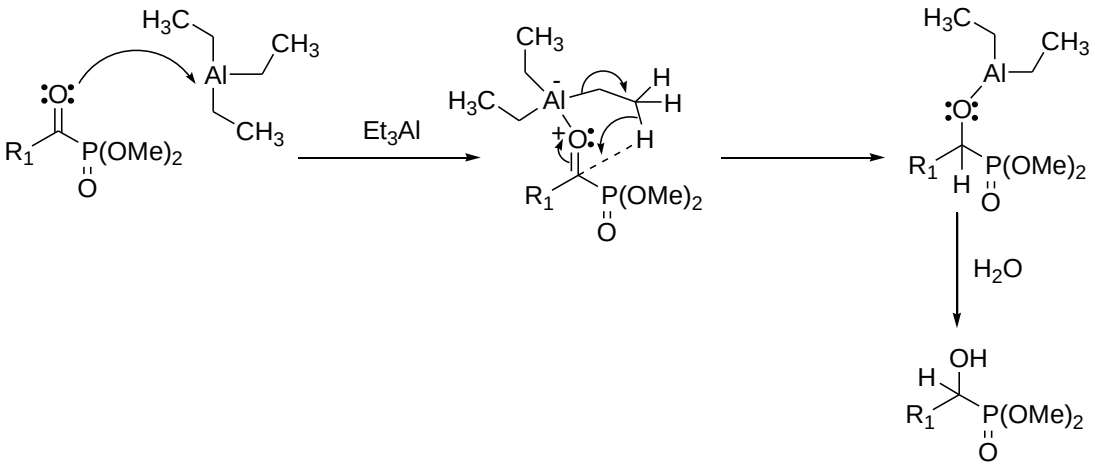
Figure 2.4 ^{13}C NMR spectrum of **150**

In order to obtain secondary α-hydroxy phosphonates we decided to continue the addition reactions of Et_3Al to different acyl phosphonates at 0 °C (Scheme 2.5). The experimental results are presented in Table 2.



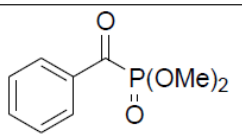
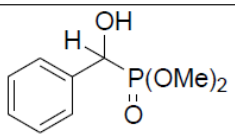
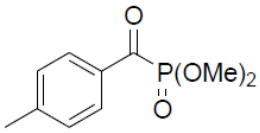
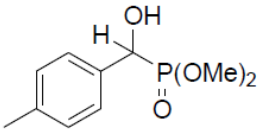
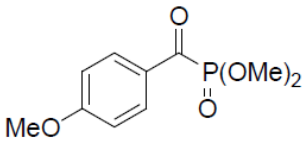
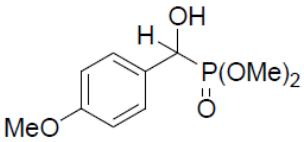
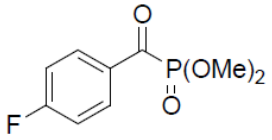
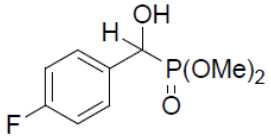
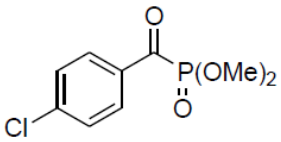
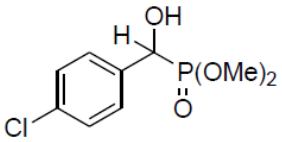
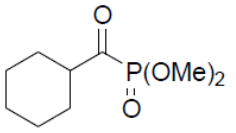
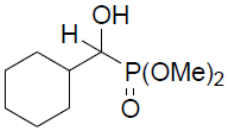
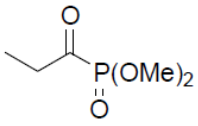
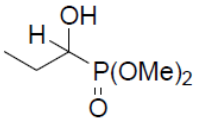
Scheme 2.5 General reaction scheme for hydride addition

A proposed mechanism for the formation of hydride addition product is shown in (Scheme 2.6).



Scheme 2.6 Proposed mechanism for hydride addition to acyl phosphonates

Table 2. Addition of triethylaluminum to acyl phosphonates at 0 °C

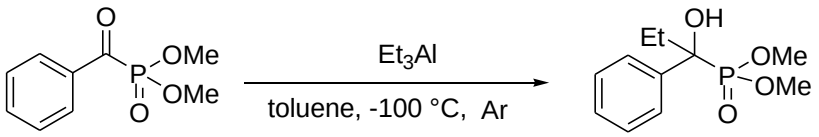
Entry	Acyl phosphonate	Product	Yield[a](%)
1	 **130**	 **150**	75
2	 **134**	 **152**	81
3	 **136**	 **153**	80
4	 **138**	 **154**	56
5	 **140**	 **155**	58
6	 **146**	 **156**	85
7	 **148**	 **157**	48

[a]Yields refer to purified compounds

In all cases (Table 2), we have obtained secondary α-hydroxy phosphonate derivatives in moderate to good yields. When electron donating -CH_3 and -OMe, groups were present as a substituent on benzene ring (entries 2 and 3, Table 2) better yields were obtained than the unsubstituted benzoyl phosphonate. When halide

substituted benzoyl phosphonates (entries 4 and 5) were tried yields were lower than that of unsubstituted one. Moderate chemical yields were observed in both cases with 56 and 58% yields respectively. Highest yield (85%) was obtained with the cyclohexyl substituted (**146**) case (entry 6). Another alkyl substituent (**148**) formed the product in lowest yield (48%) (entry 7).

Our efforts to add Et_3Al to acyl phosphonates continued by changing the reaction temperature. By decreasing the temperature from 0 °C to -100 °C, the expected ethyl addition product **158** was obtained in 44% yield (Scheme 2.7). The structure of compound **158** was confirmed by using NMR spectroscopy (Figures 2.5 and 2.6).



130 **158**

Scheme 2.7 Addition of Et_3Al to benzoyl phosphonate **130** at -100 °C

In ^{13}C NMR, the quaternary carbon atom gave a signal at 76.9 ppm ($J_{C\text{-}P}$ = 157.0 Hz). This result was consistent with our earlier addition reactions. In ^{1}H NMR, we identified the ethyl peak (triplet at around 0.71 ppm for CH_3 protons and multiplet at around 2.05-2.3 ppm for CH_2 protons). In addition, ^{31}P NMR spectrum also showed expected peak at 26.23 ppm.

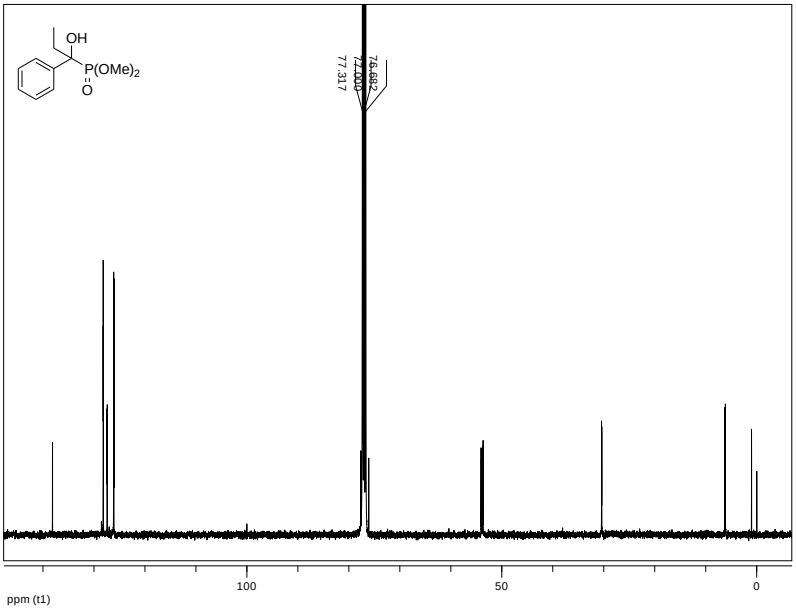


Figure 2.5 ^{13}C NMR spectrum of **158**

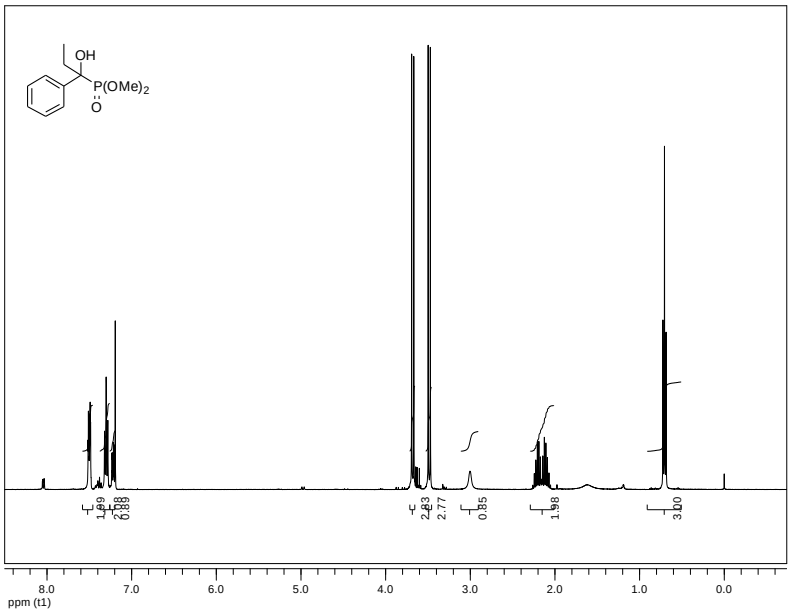
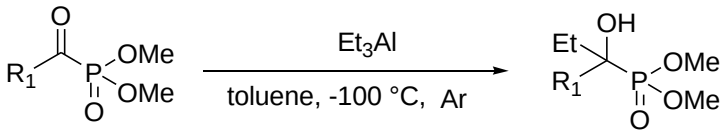


Figure 2.6 ^{1}H NMR spectrum of **158**

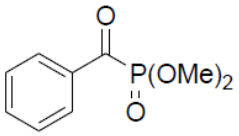
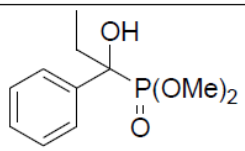
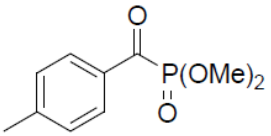
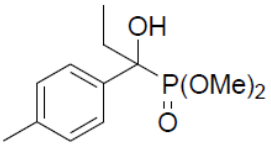
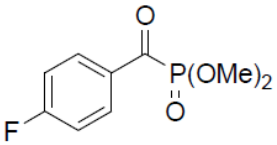
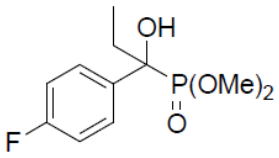
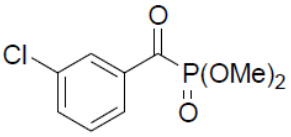
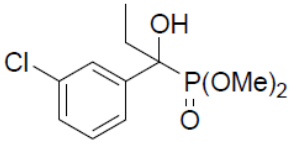
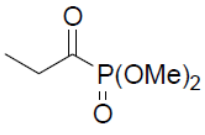
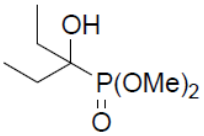
After characterizing the compound **158** by NMR, we extended the reactions of Et_3Al addition at -100 °C to other substrates to see the applicability (Scheme 2.8). Results of these studies were presented in Table 3.



132 159

Scheme 2.8 General reaction scheme for addition of Et_3Al to acyl phosphonates

Table 3. Addition of triethylaluminum to acyl phosphonates at -100 °C

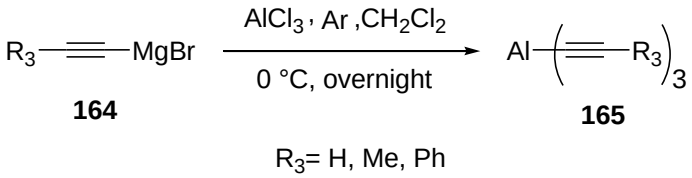
Entry	Acyl phosphonate	Product	Yield[a] (%)
1	 **130**	 **158**	**44**
2	 **134**	 **160**	**35**
3	 **138**	 **161**	**10**
4	 **142**	 **162**	**32**
5	 **148**	 **163**	**9**

[a]Yields refer to purified compounds

As shown in Table 3, yields were not high. Substrate **134** including electron donating CH_3 group, formed the product in 35% which was reasonably lower than the unsubstituted substrate **130**. With the substrate having floride at para position yield was 10% (entry 3). We believe that the carbonyl group of acyl phosphonate was highly deactivated through the resonance effect of –F atom. Similar result was also observed with alkyl substituent (entry 4). Due to low yield, no further study was done related to this reaction.

2.2 Addition of trialkynylaluminum reagents to acyl phosphonates

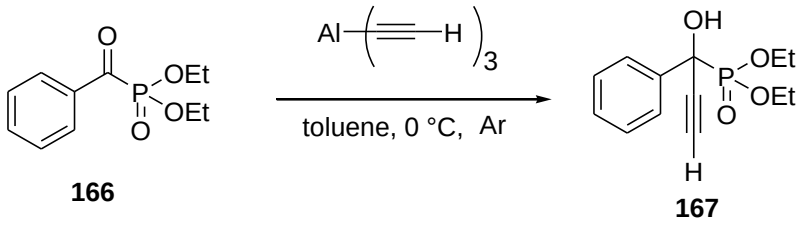
Investigation of the addition of trialkynylaluminum reagents to acyl phosphonates was started by the preparation of trialkynylaluminium reagents **165**. They were prepared by following a literature procedure (Scheme 2.9).[93] Three equivalents of commercialy available Grignard reagents **164** were reacted with one equivalent of $AlCl_3$ in DCM at 0 °C to afford the trialkynylaluminum reagents **165**. In each trial, organoaluminum reagents were prepared freshly.



Scheme 2.9 Synthesis of trialkynylaluminum reagents from Grignard reagents

Our first attempt was to investigate the addition reactions of acyl phosphonates with triethynylaluminum reagent. We have chosen benzoyl phosphonate **166** as first substrate for this reaction. Following the similar procedure used for alkyl addition reaction, acyl phosphonate **166** was reacted with 3 equivalents of triethynylaluminum in tolune at 0 °C to afford tertiary α-hydroxy propargylic

phosphonate **167** in a short reaction time (10-15 minutes) (Scheme 2.10). Formation of compound **167** was confirmed with the help of NMR spectroscopy (Figures 2.7 and 2.8)



166 **167**

Scheme 2.10 Addition of triethynylaluminum to benzoyl phosphonate **166**

The first identifier is the quaternary carbon peak at ^{13}C NMR. The quaternary carbon which has a direct attachment with phosphate and hydroxyl groups showed a doublet peak at 71 ppm with a large coupling constant of $J_{C\text{-}P}$ = 166.4 Hz. The proton connected to the triple bond appeared as a doublet at 2.82 ppm in ^{1}H NMR with a coupling contant of 5.3 Hz. Proton of the hydroxyl group appeared as a doublet at 3.89 ppm. Compound **167** also showed a characteristic ^{31}P NMR peak at 16.49 ppm.

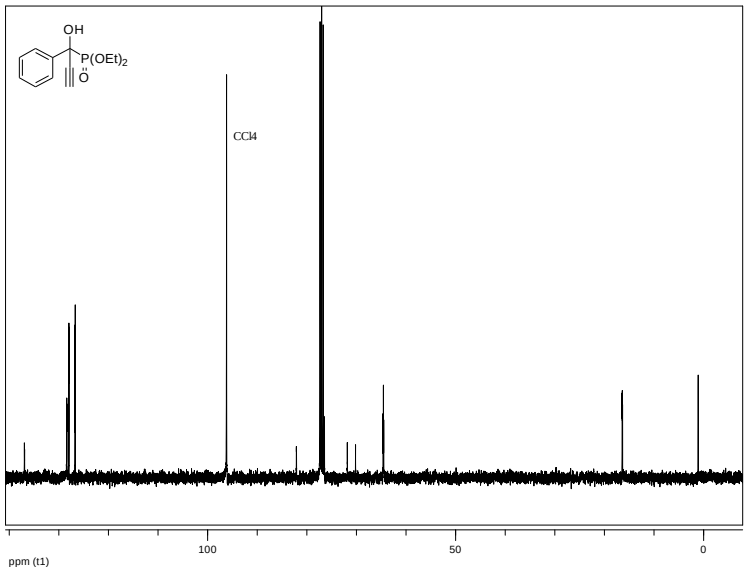


Figure 2.7 ^{13}C NMR spectrum of **167**

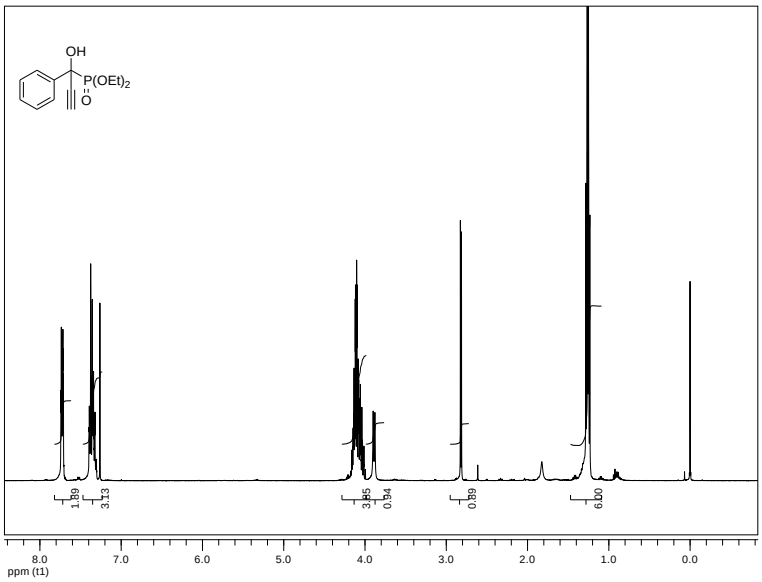
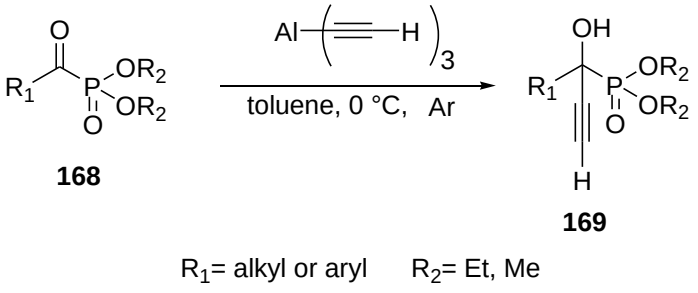


Figure 2.8 ^{1}H NMR spectrum of **167**

After optimizing the reaction conditions and identifying the compound **167** properly, we extended the addition of triethynylaluminum reagent to a variety of acyl phosphonates (Scheme 2.11). The results of these studies were summarized in Table 4.



Scheme 2.11 General reaction scheme for the addition of triethynylaluminum to acyl phosphonates.

Table 4. Alkynylation of acyl phosphonates with triethynylaluminum reagent

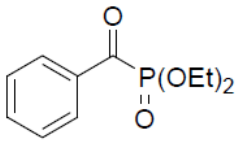
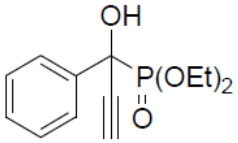
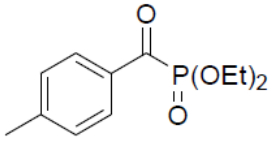
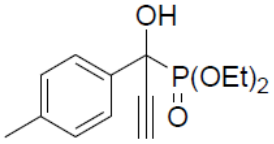
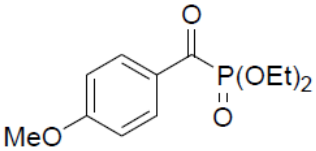
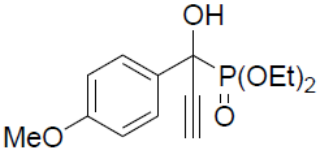
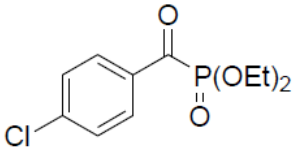
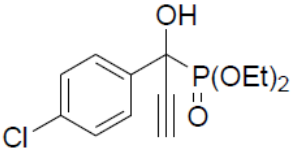
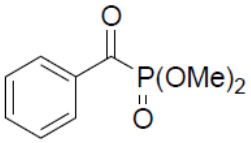
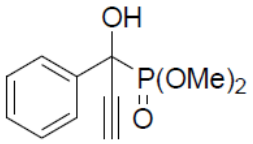
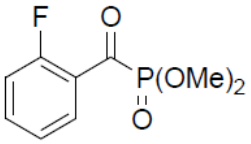
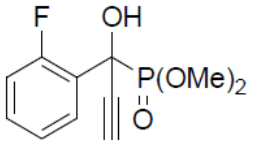
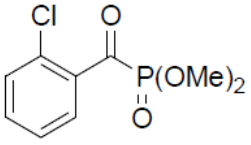
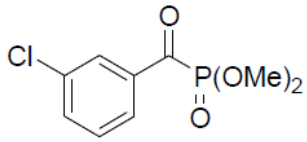
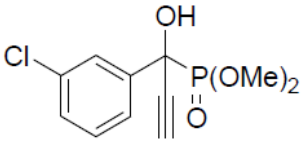
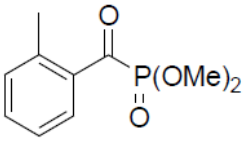
Entry	Acyl phosphonates	Products	Yields(%)[a]
1	 **166**	 **167**	67
2	 **170**	 **171**	57
3	 **172**	 **173**	22
4	 **174**	 **175**	44
5	 **130**	 **176**	58
6	 **177**	 **178**	14
7	 **179**	Decomposition	...

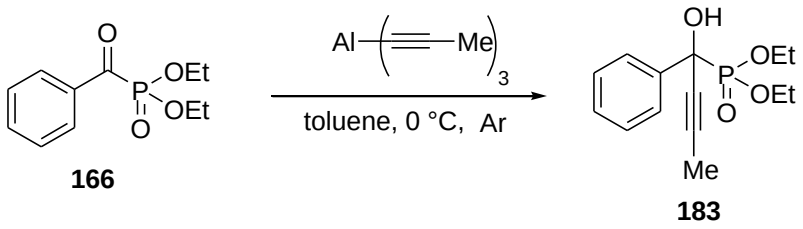
Table 4 (Continued)

Entry	Acyl phosphonates	Products	Yields(%)[a]
8	 **180**	 **181**	15
9	 **182**	Decomposition	...

[a]Yields refer to purified compounds

As seen in Table 4, electron donating groups attached to the benzene ring formed the product in lower yields (entry 2 and 3) than the unsubstituted substrate (entry 1). In the case of strong electron withdrawing floride at ortho position of benzoyl group, product was isolated in lowest yield (entry 6). When bulky groups were present at ortho position of the benzene ring (entries 7 and 9) we did not observe expected tertiary α-hydroxy phosphonates. The reason might be the bulky groups which introduced steric effect at ortho position and destabilized the intermediate. As a result, rearrangements took place to give complex mixture of unidentified compounds after quenching with water.

After observing relatively positive results with triethynylaluminum reagent, we planned to extend our scope of addition reactions to some other trialkynylaluminum reagents. We initially investigated the addition of tris-(propynyl)aluminum reagent to acyl phosphonate **166**. Tris-(propynyl)aluminum reagent was prepared first by following the procedure mentioned in Scheme 2.9. For the addition reaction we applied the same conditions and obtained compound **183** in 56% yield (Scheme 2.12).



Scheme 2.12 Addition of tris-(propynyl)aluminum to benzoyl phosphonate **166**

We characterized compound **183** as of our desired product by analyzing its proton and carbon NMR spectra (Figures 2.9 and 2.10).

The most important signal that indicates the formation of compound **183** is the quaternary carbon atom which appeared as a doublet at 71.2 ppm with a coupling constant of $J_{C\text{-}P}$ = 167.4 Hz. Protons of the methyl group attached to the triple bond appeared at 1.97 ppm as a doublet ($J_{H\text{-}P}$ = 5.1). Proton of the hydroxy group showed a doublet at 3.66 ppm with a coupling constant $J_{H\text{-}P}$ = 8.5 Hz. The compound also gave a characteristic ^{31}P NMR peak at 17.36 ppm.

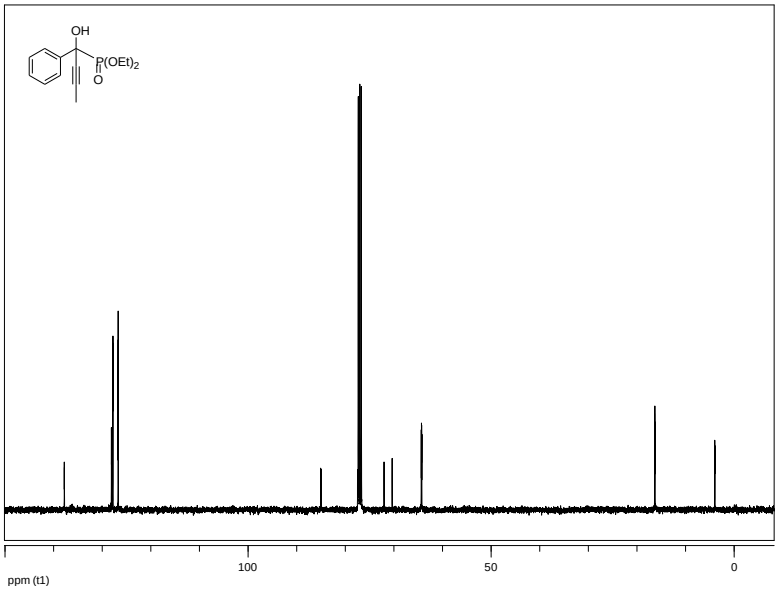


Figure 2.9 ^{13}C NMR spectrum of **183**

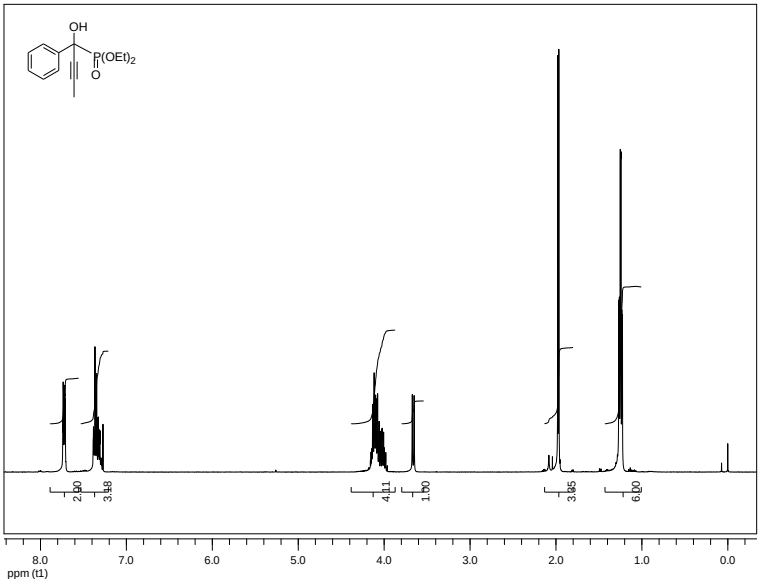
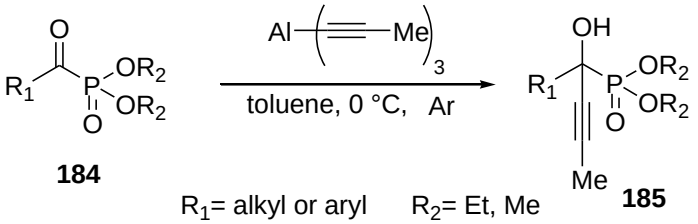


Figure 2.10 ^{1}H NMR spectrum of **183**

The addition reactions were then repeated with different acyl phosphonates to show the applicability. In all cases, tertiary propargylic alcohols were obtained without the cleavage of C-P bond in moderate to good yields (Scheme 2.13). Results were presented in Table 5.



Scheme 2.13 General reaction scheme for the addition of tris-(propynyl)aluminum to acyl phosphonates

Table 5. Alkynylation of acyl phosphonates with tris-(propynyl) aluminum reagent

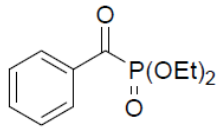
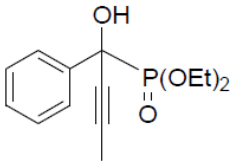
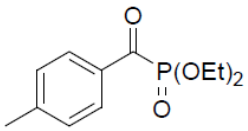
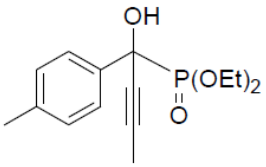
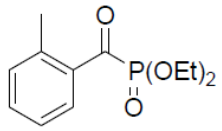
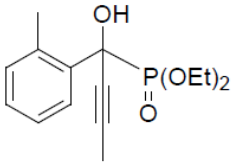
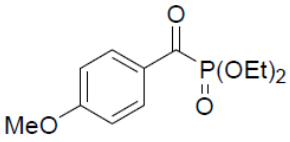
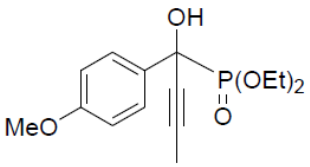
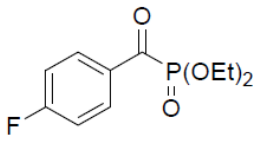
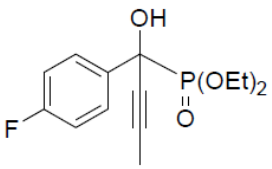
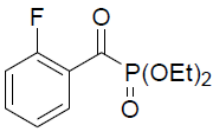
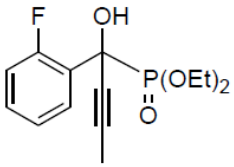
Entry	Acyl phosphonate	Product	Yield (%)[a]
1	 **166**	 **183**	56
2	 **170**	 **186**	53
3	 **187**	 **188**	32
4	 **172**	 **189**	**41**
5	 **190**	 **191**	**70**
6	 **192**	 **193**	**61**

Table 5 (Continued)

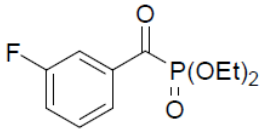
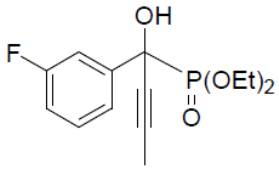
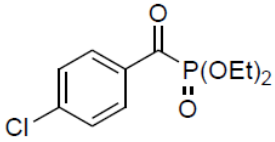
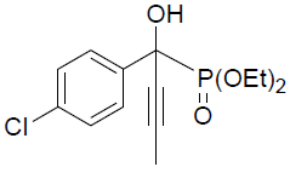
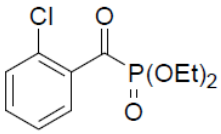
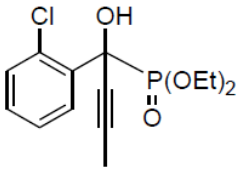
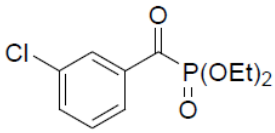
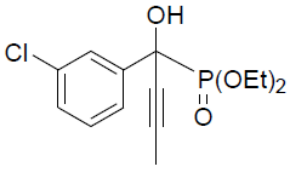
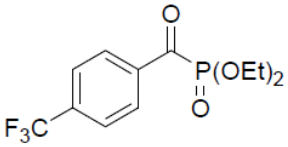
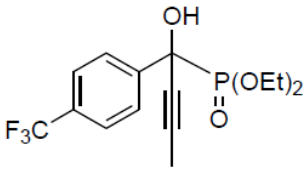
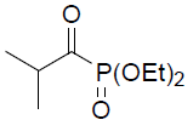
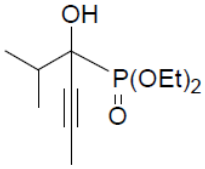
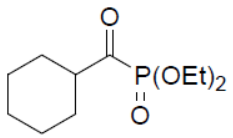
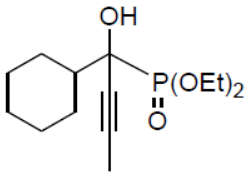
Entry	Acyl phosphonate	Product	Yield (%)[a]
7	 **194**	 **195**	**65**
8	 **174**	 **196**	**61**
9	 **197**	 **198**	49
10	 **199**	 **200**	62
11	 **201**	 **202**	75
12	 **203**	 **204**	32

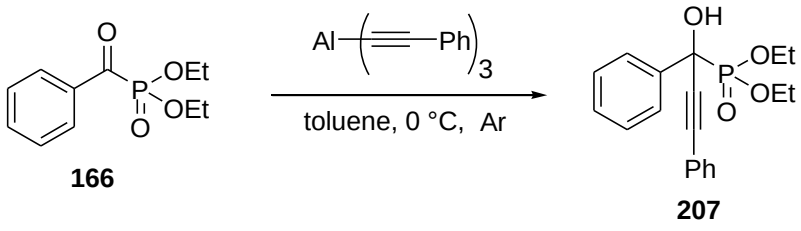
Table 5 (Continued)

Entry	Acyl phosphonate	Product	Yield (%)[a]
13	 **205**	 **206**	38

[a]Yields refer to purified compounds

We checked the effect of electron donating and electron withdrawing groups on the acyl phosphonates in terms of yields. When $–CH_3$ and –OMe are placed at the para position (entries 2 and 4) yield were lower compared to unsubstituted case (entry 1). Strong electron withdrawing $–CF_3$ group gave compound **202** in highest yield (75%). Electron withdrawing F and Cl at para position also activated the acyl phosphonates and good chemical yields were obtained (entries 5 and 8). Alkyl substituents were also tested, unfortunately products were isolated in low yields.

Next attempt was to apply tris-(phenylethynyl)aluminum reagent in alkynylation of acyl phosphonates. The reaction of benzoyl phosphonate **166** with freshly prepared tris-(phenylethynyl) aluminum gave compound **207** in 61% yield (Scheme 2.14). The structure of compound **207** was easily confirmed by using spectroscopic technique (Figures 2.11 and 2.12).



166 **207**

Scheme 2.14 Addition of tris-(phenylethynyl) aluminum to benzoyl phosphonate **166**

One of the important identifier of compound **207** is the quaternary carbon that appeared as a doublet at 70.5 ppm with a coupling constant of $J_{C\text{-}P}$ = 166.9 Hz (Figure 2.11). Besides, in ^{1}H NMR, the –OH proton showed a broad singlet in the range of 4.4-4.6 ppm. The characteristic ^{31}P NMR peak was observed at 16.13 ppm.

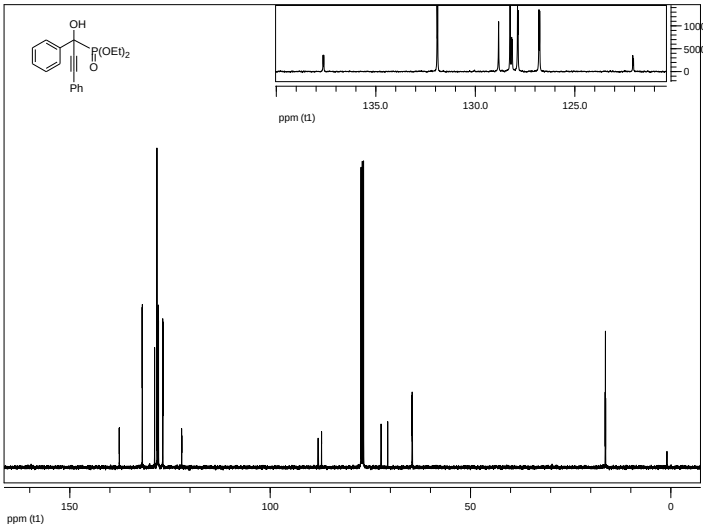


Figure 2.11 ^{13}C NMR spectrum of **207**

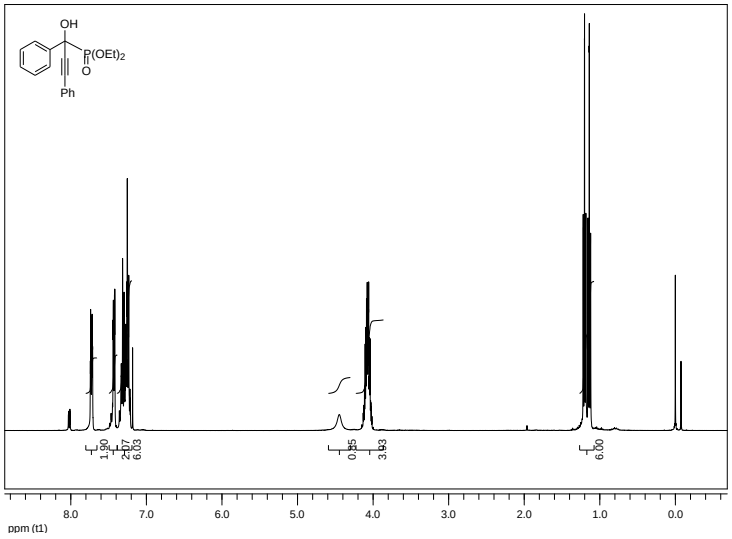
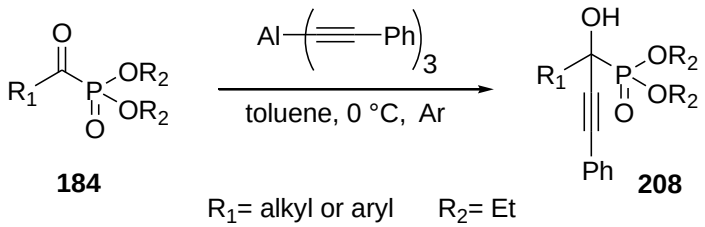


Figure 2.12 ^{1}H NMR spectrum of **207**

Compound **207** was also synthesized by direct addition of organolithium reagent PhC≡CLi to benzoyl phosphonate **166**. This was reported by Zbiral et al.[94] But their chemical yield was lower than ours.

In order to the applicability of this reaction tris-(phenylethynyl) aluminum reagent was also added to different acyl phosphonates (Scheme 2.15). The results of these studies were summarized in Table 6. The related propargylic alcohols were obtained in moderate to good yields.



Scheme 2.15 General reaction scheme for the addition of tris-(phenylethynyl) aluminum to acyl phosphonates

As seen in Table 6, similar trends observed for the previous reaction were operating here. Electron donating groups $–CH_3$ and $–OCH_3$ formed products in lower yields than the unsubstituted benzoyl phosphonate (entries 2-4). Phosphonates with the activating electron withdrawing groups F, Cl, CF_3 (entries 5-9) afforded the desired propargylic alcohols in good yields.

Table 6. Alkynylation of acyl phosphonates with tris-(phenylethynyl)aluminum reagent

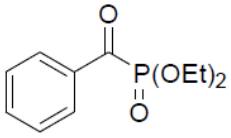
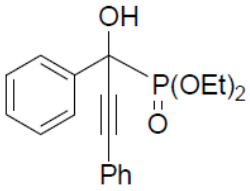
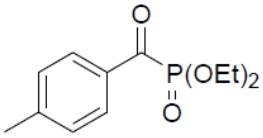
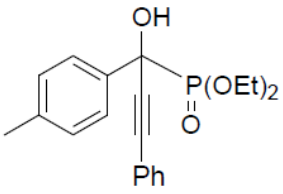
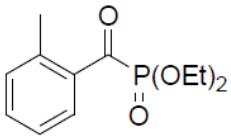
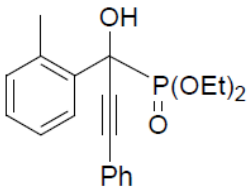
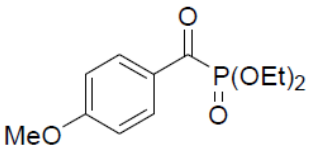
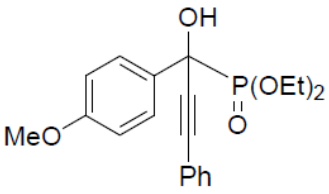
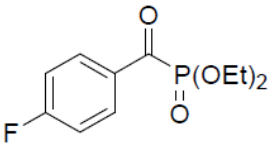
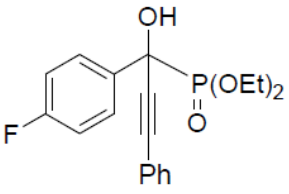
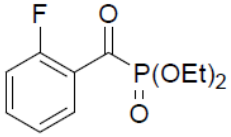
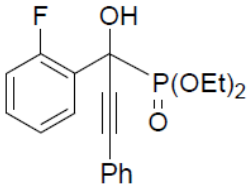
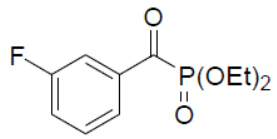
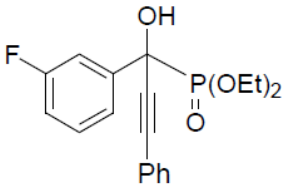
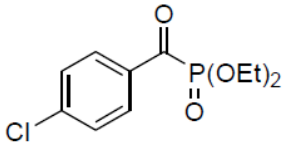
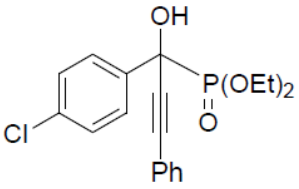
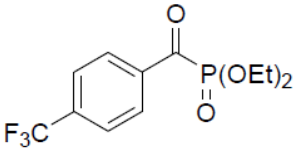
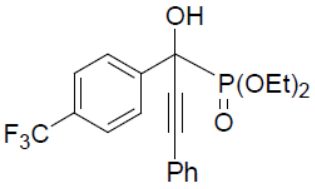
Entry	Acyl phosphonate	Product	Yield (%)[a]
1	 **166**	 **207**	61
2	 **170**	 **209**	59
3	 **187**	 **210**	30
4	 **172**	 **211**	39
5	 **190**	 **212**	68
6	 **192**	 **213**	72

Table 6 (Continued)

Entry	Acyl phosphonate	Product	Yield (%)[a]
7	 **194**	 **214**	72
8	 **174**	 **215**	52
9	 **201**	 **216**	60

[a]Yields refer to purified compounds

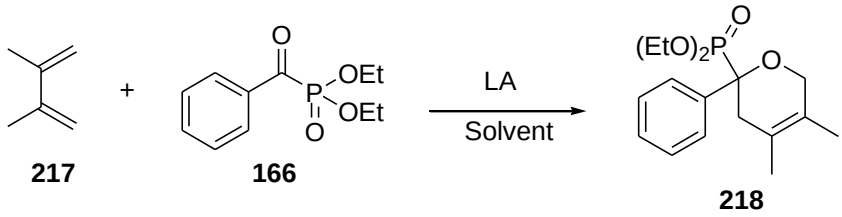
Over all better chemical yields were obtained with tris-(phenylethynyl)aluminum when compared to tris-(propynyl)aluminum probably due to the stability of the resulting propargylic phosphonates.

2.3 Hetero-Diels-Alder reactions of acyl phosphonates with 2,3-Dimethy-1,3-butadiene

The first hetero Diels-Alder reactions of acyl phosphonates with electron rich dienes where the acyl phosphonates serves as dienophile have already been published by our group (Scheme 1.28).[90] As a continuation of our research on extension of acyl phosphonate chemistry, we have planned to used unactivated dienes for HDA reactions of acyl phosphonates.

In our first trial, we used an unactivated diene in HDA reaction. 2,3-Dimethyl-1,3-butadiene was chosen as of our unactive diene because it is easily available and very easy to handle. HDA reaction between benzoyl phosphonate **166** and 2,3-dimethyl-1,3-butadiene was carried out by using different Lewis acids to activate the reaction (Scheme 2.16). The results were shown in Table 7.

As seen in Table 7, only $AlCl_3$ was very active Lewis acid to promote the reaction by forming compound **218**. Other aluminum based Lewis acids Et_2AlCl, Et_3Al, Me_3Al (entries 6, 7 and 8) gave addition product rather than HDA product. In the presence of different Lewis acids (entries 1-5) mostly decomposition of the starting material was observed. In all cases, we used DCM as the reaction solvent based on our previous experience and maintained the same reaction condition in each trial.



217 **166** **218**

Scheme 2.16 HDA reaction of 2,3-dimethyl-1,3-butadiene with acyl phosphonate **166**

Table 7. Lewis Acid screening for HDA reaction of 2,3-Dimethyl-1,3-butadine.

Entry	LA (-78 °C, 0 °C to rt in DCM)	Result
1	$SnCl_4$ (0.25 eq.)	Decomposition
2	$Bi(OTf)_2$ (0.1 eq.)	Decomposition
3	$In(OTf)_2$ (0.1 eq.)	Decomposition
4	$Zn(OTf)_2$	Decomposition
5	$ZnCl_2$ (1.1 eq)	No Reaction, (SM)
6	Et_2AlCl (1.1 eq)	Hydride addition product
7	Et_3Al (1.1 eq)	Hydride addition product
8	Me_3Al (1.1 eq)	Methyl addition product
9	$AlCl_3$ (1.1 eq)	HDA product (40%)

HDA product **218** was purified by flash column chromatography and was characterized by ^{1}H and ^{13}C NMR (Figures 2.13 and 2.14).

The important characteristics peaks that we observed for this compound were two methyl peaks appearing at 1.28 and 1.63 ppm. Another characteristic signal was observed for the quaternary carbon at 77.1 ppm with a coupling constant of $J_{C\text{-}P}$ = 170.1 Hz. ^{31}P NMR spectrum also showed expected peak at 21.31 ppm.

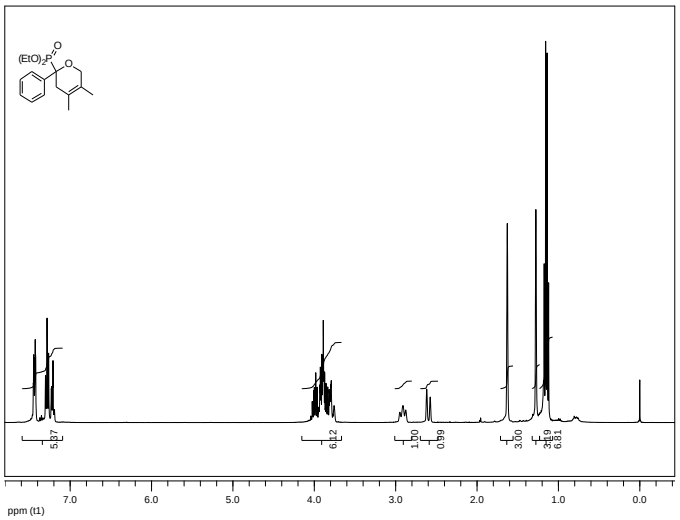


Figure 2.13 ^{1}H NMR spectrum of **218**

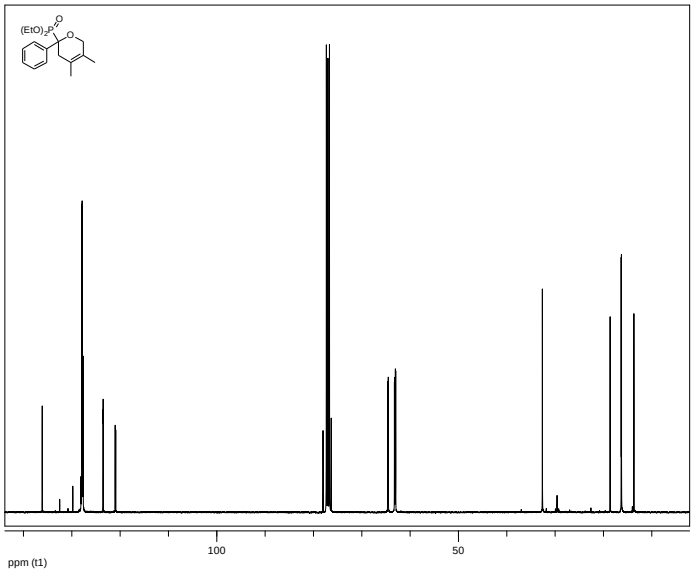


Figure 2.14 ^{13}C NMR spectrum of **218**

In order to prove the structure of HDA cycloadduct, structurally simple compound **220** was synthesized (Table 9, entry 2) and its full analysis (COSY, DEPT, HSQC, see: Appendix, pages 208 and 209) was performed. From this analysis, the HSQC spectrum (Figure 2.15) showed the cross peaks of two CH_2 carbons with their diastereotopic hydrogens. Protons of C-5 (32.5 ppm) showed two signals as doublet and triplet at 2.60 and 2.89 ppm. The protons of other CH_2 carbon (C-2, 64.4 ppm) appeared as doublet at 3.84 ppm.

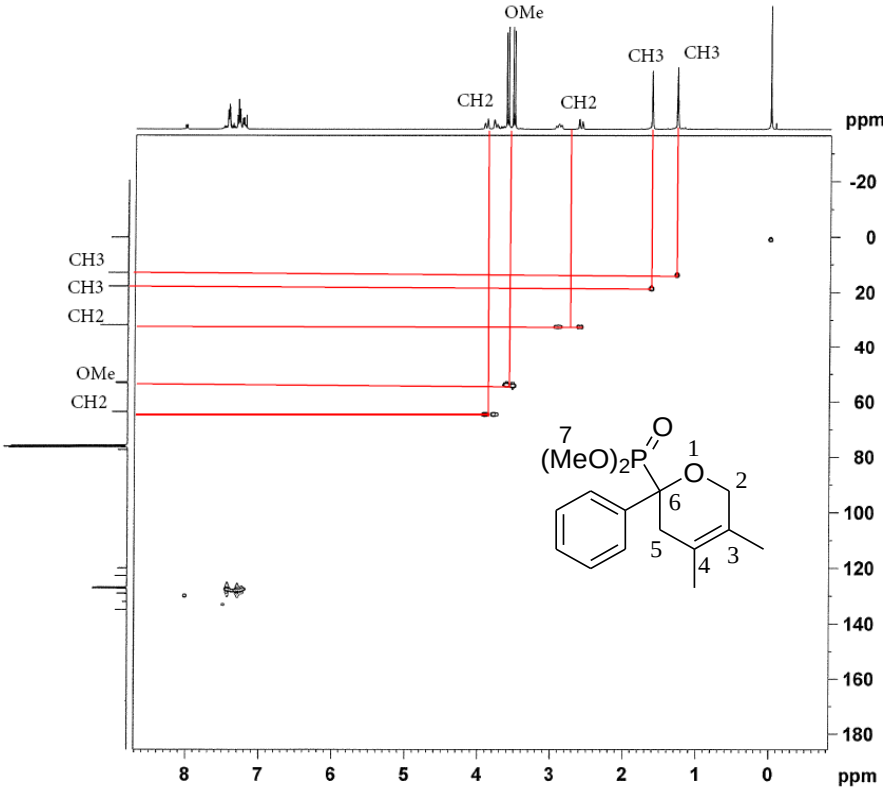


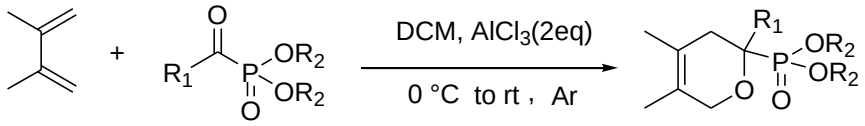
Figure 2.15 HSQC NMR spectrum of **220**

In order to find the best reaction conditions, we have done solvent screening studies. For this purpose tolune, hexane, DCM and THF were used. The best results was obtained in DCM (Table 8).

Table 8. Solvent screening for had reaction of 2,3-dimethyl-1,3-butadine

Entry	Solvent	Result	Reaction Conditions
1	Toluene	22%	$AlCl_3$ (1.1 eq.) and diene (2 eq.)
2	Hexane	9%	$AlCl_3$ (1.1 eq.) and diene (2 eq.)
3	DCM	40%	$AlCl_3$ (1.1 eq.) and diene (2 eq.)
4	THF	No reaction and SM was recoverd	$AlCl_3$ (1.1 eq.) and diene (2 eq.)

In order to show the applicability of this reaction HDA reactions were repeated under optimized conditions with different acyl phosphonates. Over all HDA products i.e. glycosyl type phosphonates were obtained in moderate to good yields (Scheme 2.17). The results of HDA reactions were presented in Table 9.



217 **168** **219**

R_1= alkyl or aryl R_2= Et, Me

Scheme 2.17 General reaction scheme for HDA reactions of acyl phosphonates

Once again introducing electron donating groups, i.e. $–CH_3$ and $–OCH_3$ at para position of benzoyl phosphonates (entries 3 and 4), compounds **221** and **222** were isolated in lower yields compared to unsubstituted benzoyl phosphonate (entry 1).

Table 9. HDA reactions of 2,3-Dimethyl-1,3 butadiene with acyl phosphonates

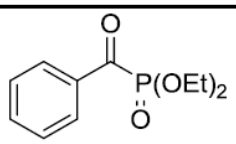
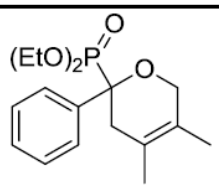
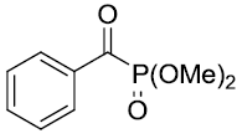
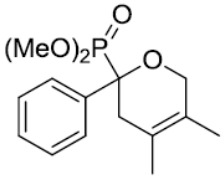
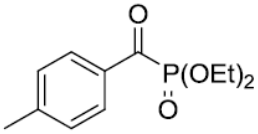
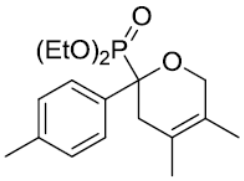
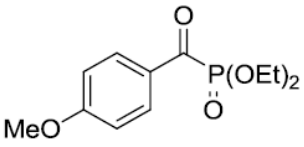
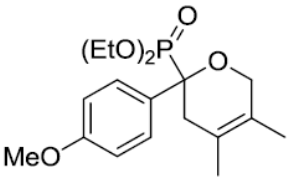
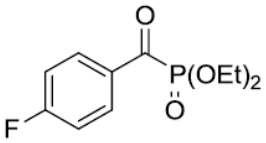
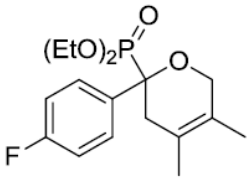
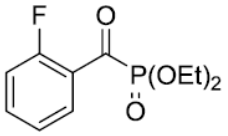
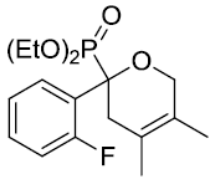
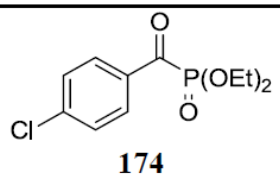
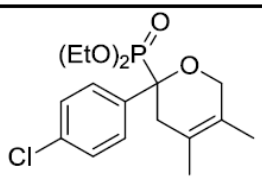
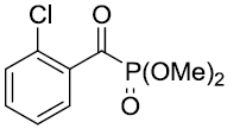
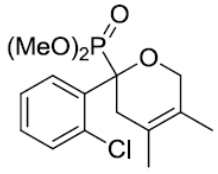
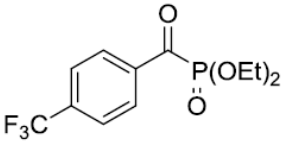
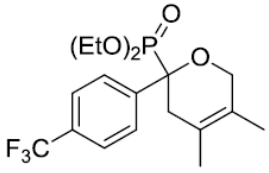
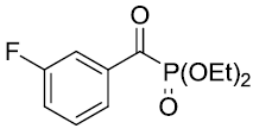
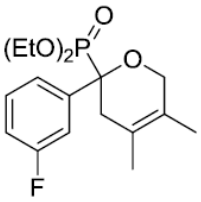
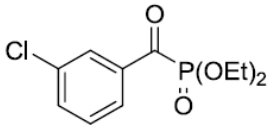
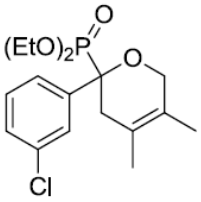
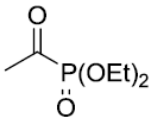
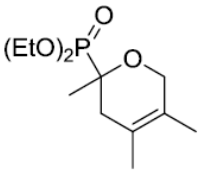
Entry	Acyl phosphonate	Product	Yield(%)[a]
1	 **166**	 **218**	68
2	 **130**	 **220**	49
3	 **170**	 **221**	43
4	 **172**	 **222**	39
5	 **190**	 **223**	44
6	 **192**	 **224**	24

Table 9 (Continued)

Entry	Acyl phosphonate	Product	Yield(%)[a]
7	 **174**	 **225**	49
8	 **179**	 **226**	25
9	 **201**	 **227**	79
10	 **194**	 **228**	56
11	 **199**	 **229**	42
12	 **230**	 **231**	44

[a]Yields refer to purified compounds

All halogenated aryl phosphonates formed the products in moderate yields such as 44, 49, 56, and 42% (entries 5, 7, 10, and 11). However, ortho halogenated aryl phophonates formed the product in lowest yields due to steric effect on the reaction

site. Highest yield (79%) was observed with very strong electron withdrawing group present at para position on the benzoyl phosphonate (entry 9). As the alkyl substituted phosphonate only acetyl phosphonate **230** was tried which formed HDA product **231** in 44% yield.

CHAPTER 3

EXPERIMENTAL

Both ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400. ^{1}H NMR chemical shifts were reported in ppm using $CDCl_3$ as solvent and tetramethylsilane was used as an internal reference. ^{13}C NMR chemical shifts were reported in ppm and the chloroform solvent signals ($CDCl_3$ at 77.0 ppm) were used as an internal reference. Data are presented as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Coupling constant(s) were expressed in Hz. HPLC grade DCM was freshly distilled from calcium hydride. THF, toluene and other solvents were distilled following standard procedures. Flash column chromatography was performed using 230-400 mesh silica gel using ethyl acetate/hexane mixture as eluting solvent. Melting points are uncorrected and were determined on a hot stage microscope.

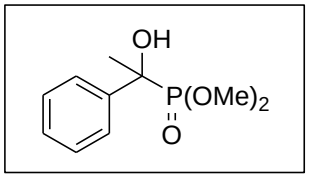
3.1 Synthesis of Secondary and Tertiary α-hydroxy Phosphonates

All commercially available reagents were used as received without further purification. Benzoyl and alkanoyl phosphonates were synthesized according to literature procedure.[29] The progress of all reactions was monitored by TLC, which was carried out on silica gel plates with fluorescent indicator. TLC plates were initially visualized by UV light source, and then dipped into an ethanolic solution of phosphomolybdic acid.

3.1.1 General Procedure for the Addition of Trimethylaluminum to Acyl Phosphonates

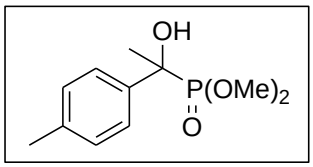
To a solution of acyl phosphonate (100 mg, 1 equiv) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added trimethylaluminum (3 equiv, 2 M solution in heptane) dropwise. After stirring for 10 min at the same temperature, the reaction mixture was cautiously hydrolyzed with water (warning: these hydrolysis are exothermic and are accompanied by gas evolution). The reaction mixture was filtrated over Celite and washed with ethyl acetate. After evaporation of solvent in vacuo, the crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluting solvent.

3.1.1.1 Characterization of 131



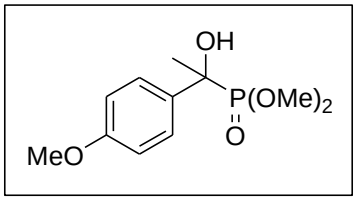
Dimethyl 1-hydroxy-1-phenylethylphosphonate: Yield 92 mg (85%), crystalline white solid (mp: 142-143 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.75 (3H, d, *J*=15.7 Hz, -CH_3), 3.56 (3H, d, *J*=10.3 Hz, $(CH_3O)_2P$), 3.66 (3H, d, *J*=10.2 Hz, $(CH_3O)_2P$), 4.40 (1H, d, *J*=4.7 Hz,-OH), 7.17-7.21 (1H, m), 7.27 (2H, t, *J*=7.5 Hz), 7.51-7.54 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8 (d, $J_{C\text{-}P}$=3.8 Hz, -CH_3), 53.7 (d, $J_{C\text{-}P}$=7.8 Hz, $(CH_3O)_2P$), 54.1 (d, $J_{C\text{-}P}$=7.3 Hz, $(CH_3O)_2P$), 73.6 (d, $J_{C\text{-}P}$=159.1 Hz, quaternary C-atom in -C(OH)), 125.8 (d, $J_{C\text{-}P}$=4.4 Hz), 127.4 (d, $J_{C\text{-}P}$=2.9 Hz), 128.0 (d, $J_{C\text{-}P}$=2.3 Hz), 141.0 (d, $J_{C\text{-}P}$=0.9 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.18; IR (ATR technique, cm^{-1}): 3278, 2980, 1447, 1225, 1202, 1186, 1055, 1023; HRMS: calculated for $C_{10}H_{15}O_4P$ $[M+Na]^+$ 253.0606 and found 253.0613.

3.1.1.2 Characterization of 135



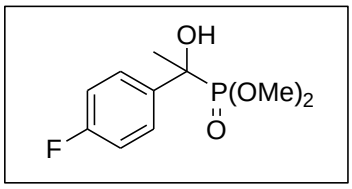
Dimethyl 1-hydroxy-1-p-tolylethylphosphonate: Yield 89 mg (83%), crystalline white solid (mp: 156-157 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (3H, d, *J*=15.5 Hz), 2.28 (3H, s), 3.54 (3H, d, *J*=10.2 Hz), 3.67 (3H, d, *J*=10.2 Hz), 7.10 (2H, d, *J*=8.2 Hz), 7.40 (2H, dd, *J*=2.2, 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 25.9 (d, *J*=3.8 Hz), 53.7 (d, *J*=7.6 Hz), 54.0 (d, *J*=8.0 Hz), 73.6 (d, *J*=159.6 Hz), 125.7 (d, *J*=4.4 Hz), 128.8, 137.0, 138.0 (d, *J*=8.4 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.38; IR (ATR technique, cm^{-1}): 3265, 2980, 1451,1410, 1224, 1203, 1185, 1124, 1099, 1017; HRMS: calculated for $C_{11}H_{17}O_4P$ $[M+Na]^+$ 267.0762 and found 267.0763.

3.1.1.3 Characterization of 137



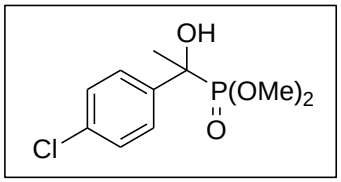
Dimethyl 1-hydroxy-1-(4-methoxyphenyl) ethylphosphonate: Yield 82 mg (77%), crystalline white solid (mp: 172-173 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72 (3H, d, *J*=15.5 Hz), 3.25 (1H, d (broad), *J*=5.4 Hz), 3.54 (3H, d, *J*=10.2 Hz), 3.66 (3H, d, *J*=10.2 Hz), 3.74 (3H, s), 6.81 (2H, d, *J*=9.0 Hz), 7.43 (2H, dd, *J*=2.3 and 9.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8 (d, *J*=4.5 Hz), 53.9 (t, *J*=7.4 Hz), 55.2, 73.4 (d, *J*=160.0 Hz), 113.5 (d, *J*=2.1 Hz), 127.0 (d, *J*=4.5 Hz), 132.7, 159.0 (d, *J*=2.7 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.46; IR (ATR technique,cm^{-1}): 3283, 2993, 1580, 1455, 1438, 1250, 1205, 1172, 1068, 1045, 1019; HRMS: calculated for $C_{11}H_{17}O_5P$ $[M+Na]^+$ 283.0711 and found 283.0706.

3.1.1.4 Characterization of 139



Dimethyl1-(4-fluorophenyl)-1-hydroxyethylphosphonate: Yield 77 mg (72%), crystalline white solid (mp: 157-158 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.82 (3H, d, *J*=5.6 Hz), 3.66 (3H, d, *J*=10.3 Hz),3.75 (3H, d, *J*=10.3 Hz), 4.44 (1H, d, *J*=4.8 Hz), 7.03 (2H, t, *J*=9.0 Hz), 7.59 (1H, ddd, *J*=9.0, 5.2, and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.9 (d, *J*=4.2 Hz), 53.8 (d, *J*=7.6 Hz), 54.2 (d, *J*=7.3 Hz), 73.3 (d, *J*=160.4 Hz), 114.8 (dd, *J*=21.4 and 2.3 Hz), 127.6 (dd, *J*=8.1 and 4.4 Hz),136.7 (d, *J*=2.7 Hz),160.9 (dd, *J*=246.3 and 3.2 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.96; IR (ATR technique, cm^{-1}): 3283, 2984, 1507, 1452, 1411, 1223, 1201, 1161, 1128, 1080, 1064, 1030; HRMS: calculated for $C_{10}H_{14}FO_4P$ $[M+Na]^+$ 271.0511 and found 271.0513.

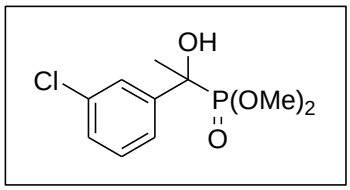
3.1.1.5 Characterization of 141



Dimethyl 1-(4-chlorophenyl)-1-hydroxyethylphosphonate: Yield 68 mg (64%), crystalline white solid (mp: 161-162 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (3H, d, *J*=15.6 Hz), 3.60 (3H, d, *J*=10.2 Hz), 3.68 (3H, d, *J*=10.2 Hz), 4.44 (1H, s (broad)), 7.25 (2H, d, *J*=8.5 Hz), 7.46 (2H, dd, *J*=2.3 and 8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.9 (d, *J*=3.8 Hz), 53.7 (d, *J*=7.9 Hz), 54.3 (d, *J*=7.0 Hz), 73.4 (d, *J*=159.8 Hz), 127.3 (d, *J*=4.3 Hz), 128.2 (d, *J*=2.4 Hz), 133.5 (d, *J*=3.3 Hz), 139.6;

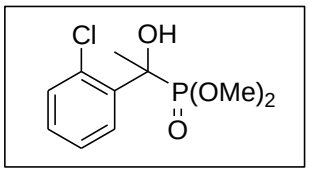
^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.64; IR (ATR technique, cm^{-1}): 3266, 2950,1489, 1225, 1203, 1182, 1090, 1071, 1030; HRMS: calculated for $C_{10}H_{14}ClO_4P$ (35 Cl-isotope) $[M+Na]^+$ 287.0216 and found 287.0211.

3.1.1.6 Characterization of 143



Dimethyl 1-(3-chlorophenyl)-1-hydroxyethylphosphonate: Yield 78 mg (73%), crystalline white solid (mp: 136-137 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.73 (3H, d, *J*=15.7 Hz), 3.63 (3H, d, *J*=10.3 Hz), 3.69 (3H, d, *J*=10.0 Hz), 7.17-7.23 (2H, m), 7.38-7.41 (1H, m), 7.54-7.56 (1H, m); ^{13}C NMR ($CDCl_3$, 100MHz): δ 25.84, 53.8 (d, *J*=7.9 Hz), 53.4 (d, *J*=7.8 Hz), 73.4 (d, *J*=159.9 Hz), 124.1 (d, *J*=4.1 Hz), 126.1 (d, *J*=4.4 Hz), 127.6 (d, *J*=1.9 Hz), 129.2 (d, *J*=2.1 Hz), 134.2, 143.3; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.51; IR (ATR technique, cm^{-1}): 3260, 2954, 1456, 1423, 1228, 1194, 1122, 1084, 1049; HRMS: calculated for $C_{10}H_{14}ClO_4P$ (35 Cl-isotope) $[M+Na]^+$ 287.0216 and found 287.0219.

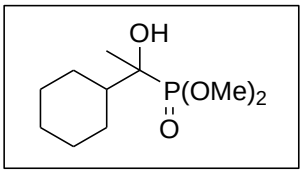
3.1.1.7 Characterization of 145



Dimethyl 1-(2-chlorophenyl)-1-hydroxyethylphosphonate: Yield 82 mg (77%), crystalline white solid (mp: 143-144 °C); ^{1}H NMR ($CDCl_3$,400 MHz): δ 1.93 (3H,

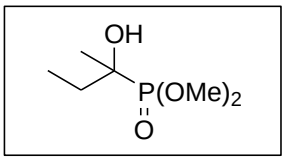
d, *J*=15.5 Hz), 3.64 (3H, d, *J*=10.3 Hz), 3.70 (3H,d, *J*=10.3 Hz), 7.12-7.22 (2H, m), 7.29 (1H, dd, *J*=1.1 and 7.6 Hz), 7.70 (1H, td, *J*=7.9, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 25.0, 54.0 (t, *J*=5.9 Hz, -C=OPO(OCH3)2, both -OMe groups are overlapping), 75.1 (d, *J*=160.9 Hz), 126.7 (d, *J*=1.8 Hz), 129.0 (d, *J*=2.3 Hz), 129.7 (d, *J*=4.5 Hz), 131.8 (d, *J*=1.7 Hz), 132.0 (d, *J*=5.8 Hz), 137.7 (d, *J*=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.44; IR (ATR technique, cm^{-1}): 3260, 2954, 1456, 1423, 1228, 1194, 1122, 1084, 1049, 1021; HRMS: calculated for $C_{10}H_{14}ClO_4P$ (35 Cl-isotope) $[M+Na]^+$ 287.0216 and found 287.0220.

3.1.1.8 Characterization of 147



Dimethyl 1-cyclohexyl-1-hydroxyethylphoshonate: Yield 84 mg (78%), crystalline white solid (mp: 82-83 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.97-1.17 (5H, m), 1.26 (3H, d, *J*=16.0 Hz), 1.60-1.90 (6H, m), 3.74 (6H, dt, *J*=1.6 and 10.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (d, *J*=4.2 Hz), 26.0 (d, *J*=8.2 Hz), 26.4 (d, *J*=4.0 Hz), 26.5, 27.8 (d, *J*=2.6 Hz), 44.5 (d, *J*=5.4 Hz), 53.0 (d, *J*=7.9 Hz), 53.6 (d, *J*=7.4 Hz), 75.3 (d, *J*=157.1 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.46; IR (ATR technique, cm^{-1}): 3319, 2994, 2849, 1146, 1224, 1190, 1077, 1054, 1028; HRMS: calculated for $C_{10}H_{21}O_4P$ $[M+Na]^+$ 259.1075 and found 259.1070.

3.1.1.9 Characterization of 149

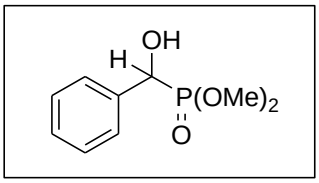


Dimethyl 2-hydroxybutan-2-yl phosphonate: Yield 69 mg (63%), colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (3H, t, *J*=7.5 Hz), 1.30 (3H, d, *J*=16.0 Hz), 1.57-1.68 (1H, m), 1.71-1.84 (1H, m), 3.73 (3H, d, *J*=10.1 Hz), 3.72 (3H, d, *J*=10.1 Hz), 4.45 (1H, s (broad)); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.8 (d, *J*=8.6 Hz), 21.1 (d, *J*=4.7 Hz), 29.8 (d, *J*=5.3 Hz), 53.3 (t, *J*=6.2 Hz), 72.0 (d, *J*=161.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 30.03; IR (ATR technique, cm^{-1}): 3311, 2956, 1460, 1226,1167,1131,1023; HRMS: calculated for $C_6H_{15}O_4P$ $[M+Na]^+$ 205.0606 and found 205.0599.

3.1.2 General Procedure for hydride addition to Acyl Phosphonates

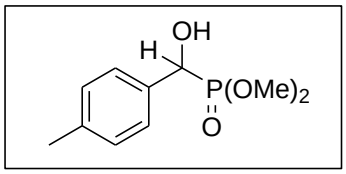
To a solution of acyl phosphonate (100 mg, 1 equiv) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added triethylaluminum (3 equiv, 1 M solution in heptane) dropwise. After the completion of reaction in 10 min, which was monitored by a TLC plate, the reaction mixture was cautiously hydrolyzed with water. The reaction mixture was filtrated over Celite and washed with ethyl acetate. After evaporation of solvent in vacuo, the crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluting solvent.

3.1.2.1 Characterization of 150



Dimethyl hydroxy(phenyl)methylphosphonate: Yield 76 mg (75%), crystalline white solid (mp: 106-107 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66 (3H, d, *J*=10.3 Hz), 3.70 (3H, d, *J*=10.3 Hz), 5.03 (1H, d, *J*=10.9 Hz), 7.28-7.37 (3H, m), 7.47-7.48 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 53.5 (d, *J*=7.5 Hz), 53.9 (d, *J*=6.4 Hz), 70.7 (d, *J*=159.1 Hz), 127.1 (d, *J*=5.9 Hz), 128.2 (d, *J*=2.8 Hz), 128.4 (d, *J*=2.1 Hz), 136.5; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 22.92; IR (ATR technique, cm^{-1}): 3258, 2956, 1192, 1049, 1023, 774; HRMS: calculated for $C_9H_{13}O_4P$ $[M+Na]^+$ 239.0449 and found 239.0445.

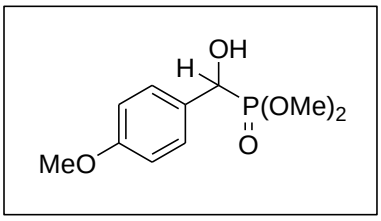
3.1.2.2 Characterization of 152



Dimethyl hydroxy(p-tolyl)methylphosphonate: Yield 82 mg (81%), crystalline white solid (mp: 102-103 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (3H, d, *J*=1.7 Hz), 3.66 (3H, d, *J*=10.3 Hz), 3.71 (3H, dd, *J*=10.3 Hz), 4.16 (1H, dd, *J*=8.7 and 5.7 Hz), 4.98 (1H, dd, *J*=10.5 and 5.1 Hz), 7.16 (2H, *J*=8.0 Hz), 7.35 (2H, dd, *J*=8.0 and 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 53.4 (d, *J*=7.3 Hz), 53.7 (d, *J*=6.7 Hz), 70.1 (d, *J*=161.1 Hz), 126.9 (d, *J*=6.0 Hz), 128.8 (d, *J*=2.2 Hz), 133.5, 137.6 (d, *J*=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.91; IR (ATR technique, cm^{-1}): 3258,

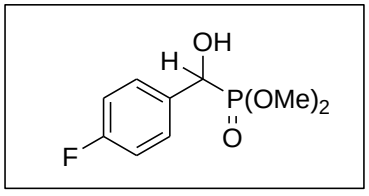
2957, 1204, 1046, 1022, 818; HRMS: calculated for $C_{10}H_{15}O_4P$ $[M+Na]^+$ 253.0606 and found 253.0606.

3.1.2.3 Characterization of 153



Dimethyl hydroxy(4-methoxyphenyl)methylphosphonate: Yield 81 mg (80%), crystalline white solid (mp: 94-95 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 3.58 (3H, d, *J*=10.3 Hz), 3.63 (3H, d, *J*=10.3 Hz), 3.73 (3H, s), 4.90 (1H, d, *J*=10.2 Hz), 6.81 (2H, d, *J*=8.5 Hz), 7.33 (2H, dd, *J*=8.5 and 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 53.5 (d, *J*=7.3 Hz), 53.8 (d, *J*=7.1 Hz), 55.1, 70.1 (d, *J*=162.0 Hz), 113.8 (d, *J*=1.5 Hz), 128.4 (d, *J*=6.2 Hz), 128.5 (d, *J*=1.0 Hz), 159.5 (d, *J*=1.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 24.06; IR (ATR technique, cm^{-1}): 3258, 2956, 1205, 1190, 1047, 1022, 833, 774; HRMS: calculated for $C_{10}H_{15}O_5P$ $[M+Na]^+$ 269.0555 and found 269.0556.

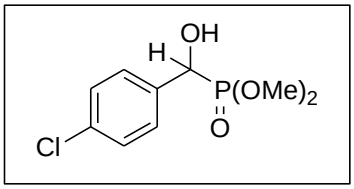
3.1.2.4 Characterization of 154



Dimethyl (4-fluorophenyl)(hydroxy)methylphosphonate: Yield 56 mg (56%), crystalline white solid (mp: 97-98 °C); ^{1}H NMR ($CDCl_3$,400MHz): δ 3.17 (1H, dd, *J*=9.2 and 4.6 Hz), 3.69 (3H, d, *J*=10.4 Hz), 3.72 (3H, d, *J*=10.4 Hz), 5.03 (1H, dd,

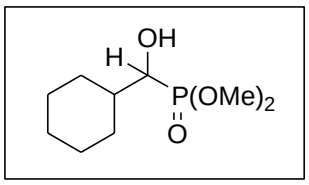
J=10.2 and 3.8 Hz), 7.06 (2H, t, *J*=8.4 Hz), 7.45-7.49 (2H, m); ^{13}C NMR ($CDCl_3$, 100MHz): δ 53.5 (d, *J*=7.4 Hz), 54.0 (d, *J*=6.9 Hz), 69.9 (d, *J*=161.0 Hz), 115.3 (d, *J*=2.3 Hz), 128.8 (d, *J*=6.0 Hz), 128.9 (d, *J*=6.0 Hz), 132.4, 160.6 (dd, *J*=246.6 and 3.5 Hz); ^{31}P NMR ($CDCl_3$,161MHz): δ 23.25; IR (ATR technique, cm^{-1}): 3258, 2956, 1205, 1047, 1022, 833, 790; HRMS: calculated for $C_9H_{12}FO_4P$ $[M+Na]^+$ 257.0355 and found 257.0352.

3.1.2.5 Characterization of 155



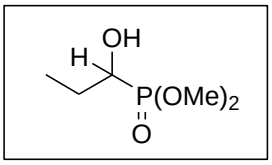
Dimethyl (4-chlorophenyl)(hydroxy)methylphosphonate: Yield 58 mg (58%), crystalline white solid (mp: 104-105 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 3.63 (3H, d, *J*=10.3 Hz), 3.64 (3H, d, *J*=10.3 Hz), 4.95 (1H, d, *J*=11.0 Hz), 7.25 (2H, d, *J*=8.3 Hz), 7.34 (2H, dd, *J*=8.3 and 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 53.6 (d, *J*=7.4 Hz), 54.1 (d, *J*=7.1 Hz), 69.9 (d, *J*=160.0 Hz), 128.4 (d, *J*=5.8 Hz), 128.5 (d, *J*=2.5 Hz), 134.0 (d, *J*=3.7 Hz), 135.1 (d, *J*=1.2 Hz); ^{31}P NMR ($CDCl_3$, 161MHz): δ 22.58; IR (ATR technique, cm^{-1}): 3258, 2956, 1204, 1191, 1047, 1022, 833, 773; HRMS: calculated for $C_9H_{12}ClO_4P$ $[M+Na]^+$ 273.0059 and found 273.0056.

3.1.2.6 Characterization of 156



Dimethyl cyclohexanecarbonylphosphonate: Yield 86 mg (85%), colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04-1.27 (5H, m), 1.58-1.69 (5H, m), 1.93 (1H, d (broad), *J*=11.8 Hz), 3.11 (1H, s (broad)), 3.63 (1H, d (broad), *J*=5.2 Hz), 3.72 (3H, d, *J*=3.0 Hz), 3.75 (3H, d, *J*=3.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.0, 26.2 (d, *J*=2.7 Hz), 27.8 (d, *J*=7.4 Hz), 29.8 (d, *J*=8.8 Hz), 39.7 (d, *J*=1.9 Hz), 52.9 (d, *J*=6.9 Hz), 53.1 (d, *J*=7.3 Hz), 72.4 (d, *J*=156.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 25.58; IR (ATR technique, cm^{-1}): 3262, 2923, 2851,1210, 832; HRMS: calculated for $C_9H_{19}O_4P$ $[M+Na]^+$ 245.0919 and found 245.0921.

3.1.2.7 Characterization of 157



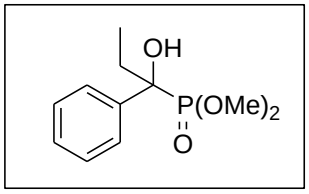
Dimethyl 1-hydroxypropylphosphonate: Yield 49 mg (48%), colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02 (3H, t, *J*=7.4 Hz), 1.60-1.80 (2H, m), 3.73 (3H, d, *J*=10.3 Hz), 3.74 (3H, d, *J*=10.3 Hz), 4.46 (1H, dd, *J*=6.7 and 2.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.3(d, *J*=13.6 Hz), 24.7 (d, *J*=1.2 Hz), 53.0 (d, *J*=7.3 Hz), 53.2 (d, *J*=7.2 Hz), 69.0 (1H, d, *J*=160.0 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 27.71; IR (ATR technique, cm^{-1}): 3259, 2956, 1205, 1046, 1022, 833, 774; HRMS: calculated for $C_5H_{13}O_4P$ $[M+Na]^+$ 191.0449 and found 191.0446.

3.1.3 General Procedure for the Addition of Triethylaluminum to Acyl Phosphonates

To a solution of acyl phosphonate (100 mg, 1 equiv) in dry toluene (0.5 M) at -100 °C under argon atmosphere was added triethylaluminum (3 equiv, 1 M solution in

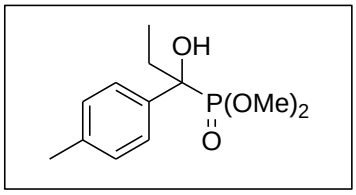
heptane) dropwise. After stirring for 10 min at the same temperature, the reaction mixture was cautiously hydrolyzed with water. The reaction mixture was filtrated over Celite and washed with ethyl acetate. After evaporation of solvent in vacuo, the crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluting solvent.

3.1.3.1 Characterization of 158



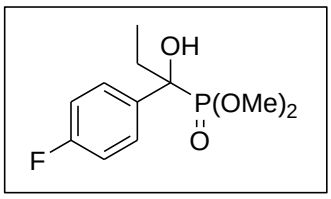
Dimethyl 1-hydroxy-1-phenylpropylphosphonate: Yield 50 mg (44%), crystalline white solid (mp: 120-121 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.71 (3H, t, *J*=7.4 Hz), 2.05-2.62 (2H, m), 3.48 (3H, d, *J*=10.2 Hz), 3.68 (3H, d, *J*=10.2 Hz), 7.20-7.24 (1H, m), 7.29 (2H, t (broad), *J*=8.1 Hz), 7.48-7.51 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.2 (d, *J*=11.0 Hz), 30.4 (d, *J*=4.5 Hz), 53.7 (d, *J*=7.4 Hz), 54.0 (d, *J*=7.6 Hz), 76.9 (d, *J*=157.0 Hz), 126.1 (d, *J*=4.5 Hz), 127.4 (d, *J*=3.0 Hz), 128.1 (d, *J*=2.6 Hz), 138.1; ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.23; IR (ATR technique, cm^{-1}): 3283, 2968, 2938, 1220, 1058, 1020, 833; HRMS: calculated for $C_{11}H_{17}O_4P$ $[M+Na]^+$ 267.0762 and found 267.0756.

3.1.3.2 Characterization of 160



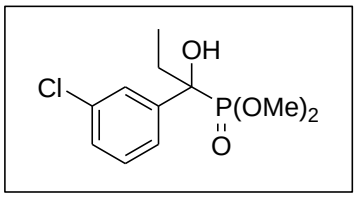
Dimethyl 1-hydroxy-1-p-tolylpropylphosphonate: Yield 40 mg (35%), crystalline white solid (mp: 114-115 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 0.77 (3H, t, *J*=7.4 Hz), 2.11-2.31 (2H, m), 2.34 (d, *J*=1.7 Hz, 3H), 3.05 (1H, d, *J*=5.8 Hz), 3.55 (3H, d, *J*=10.2 Hz), 3.74 (3H, d, *J*=10.2 Hz), 7.18 (2H, d, *J*=8.3 Hz), 7.45 (2H, dd, *J*=8.3, 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.1 (d, *J*=11.0 Hz), 21.0, 30.1 (d, *J*=4.3 Hz), 53.7 (d, *J*=7.6 Hz), 53.9 (d, *J*=7.6 Hz), 76.7 (d, *J*=157.7 Hz), 126.0 (d, *J*=4.6 Hz), 128.8 (d, *J*=2.4Hz), 135.1, 136.9 (d, *J*=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 26.32; IR (ATR technique, cm^{-1}): 3253, 2977, 2951, 1220, 1054, 1022; HRMS: calculated for $C_{12}H_{19}O_4P$ $[M+Na]^+$ 281.0919 and found 281.0912.

3.1.3.3 Characterization of 161



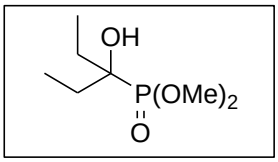
Dimethyl 1-(4-fluorophenyl)-1-hydroxypropylphosphonate: Yield 11 mg (10%), crystalline white solid (mp: 153-155 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 0.77 (3H, d, *J*=7.3 Hz), 2.28-2.09 (2H, m), 3.0 (1H, d, *J*=5.3 Hz), 3.56 (3H, d, *J*=10.2 Hz), 3.75 (3H, d, *J*=10.2Hz), 7.04 (2H, t, *J*=8.4 Hz), 7.54 (2H, dtd, *J*=7.8, 5.3, 2.7 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 6.2 (d, *J*=10.8 Hz), 30.5 (d, *J*=4.9 Hz), 53.8 (d, *J*=7.4 Hz), 53.9 (d, *J*=7.6 Hz), 76.5 (d, *J*=146.9 Hz),114.9 (dd, *J*=21.3, 2.7 Hz),128.0 (dd, *J*=7.8, 4.6 Hz), 134.0 (d, *J*=3.2 Hz), 162.2 (d, *J*=250.0 Hz); ^{31}P NMR ($CDCl_3$, 161MHz): δ 25.96; IR (ATR technique, cm^{-1}): 3246, 2956, 2923, 1507, 1221, 1047, 1012, 812; HRMS: calculated for $C_{11}H_{16}FO_4P$ $[M+Na]^+$ 285.0668 and found 285.0662.

3.1.3.4 Characterization of 162



Dimethyl 1-(3-chlorophenyl)-1-hydroxypropylphosphonate: Yield 36 mg (32%), crystalline white solid (mp: 129-130 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.74 (3H, t, *J*=7.4 Hz), 2.13-2.24 (2H, m), 3.67 (3H, d, *J*=10.3 Hz), 3.76 (3H, d, *J*=10.2 Hz), 4.16 (1H, d, *J*=2.2 Hz), 7.27-7.23 (2H, m), 7.43 (1H, ddd, *J*=7.5, 4.0, 2.0 Hz), 7.58 (1H, dd, *J*=4.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 6.2 (d, *J*=11.5 Hz), 30.2 (d, *J*=4.1 Hz), 53.8 (d, *J*=7.7 Hz), 54.1 (d, *J*=7.7 Hz), 75.7, 124.4 (d, *J*=4.2 Hz), 126.6 (d, *J*=4.6 Hz), 127.4 (d, *J*=2.9 Hz), 129.2 (d, *J*=2.7 Hz), 134.3 (d, *J*=2.7 Hz), 141.0; ^{31}P NMR ($CDCl_3$, 161MHz): δ 25.42; IR (ATR technique, cm^{-1}): 3241, 2956, 1413, 1223, 1189, 1058, 1026, 777; HRMS: calculated for $C_{11}H_{16}ClO_4P$ $[M+Na]^+$ 301.0372 and found 301.0369.

3.1.3.5 Characterization of 163



Dimethyl 3-hydroxypentan-3-ylphosphonate: Yield 11 mg (9%), colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (6H, t, *J*=7.5 Hz), 1.62-1.78 (4H, m), 2.30 (1H, d, *J*=3.7 Hz), 3.74 (6H, d, *J*=10.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.3 (d, *J*=5.6 Hz), 27.2 (d, *J*=4.8 Hz), 53.2 (d, *J*=5.7 Hz), 75.4 (d, *J*=157.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 30.03; IR (ATR technique, cm^{-1}): 3309, 2981, 2955, 1460, 1219, 1027, 823; HRMS: calculated for $C_7H_{17}O_4P$ $[M+Na]^+$ 219.0762 and found 219.0765.

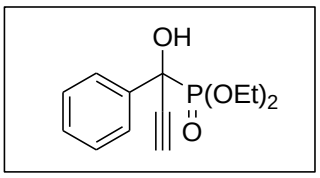
3.2 Synthesis of Propargylic Phosphonates

Triethynylaluminum tris-(phenylethynyl) aluminum and tris-(propynyl) aluminum reagents were prepared by following the literature procedure.[93] Benzoyl and alkanoyl phosphonates were also synthesized according to standard literature procedure.[29]

3.2.1 General Procedure for the Addition of Triethynylaluminum to Acyl Phosphonates

Freshly prepared triethynylaluminum reagent (3 equiv) was added to a solution of acyl phosphonate (100 mg, 1 equiv) in dry toluene (0.25 M) at 0 °C. After stirring for 15-30 min, the reaction mixture was carefully quenched with water and then filtrated over Celite. The solvent was evaporated and crude product was purified by flash column chromatography to afford corresponding a-hydroxy phosphonates.

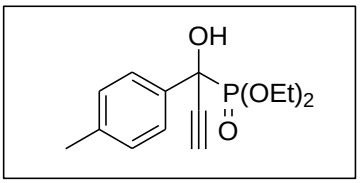
3.2.1.1 Characterization of 167



Diethyl 1-hydroxy-1-phenylprop-2-ynylphosphonate: Yield 74 mg (67%), crystalline white solid (mp: 112-113 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (3H, dt, *J*=5.6 and 0.6 Hz), 1.28 (3H, dt, *J*=5.6 and 0.6 Hz), 2.82 (1H, d, *J*=5.3 Hz), 3.89 (1H, d, *J*=8.5 Hz), 4.16-4.01 (4H, m), 7.40-7.30 (3H, m), 7.74-7.71 (2H, m); ^{13}CNMR ($CDCl_3$,100 MHz): δ 16.3 (d, *J*=2.5 Hz), 16.4 (d, *J*=2.7 Hz), 64.6 (t, *J*=6.3 Hz), 71.0 (d, *J*=166.4 Hz), 76.5 (d, *J*=9.2 Hz), 82.1 (d, *J*=1.7 Hz), 126.7 (d, *J*=4.0 Hz), 127.9 (d, *J*=2.5 Hz), 128.4 (d, *J*=2.9 Hz), 136.9 (d, *J*=3.8 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.49; IR (ATR technique, cm^{-1}): 3246, 3188, 2993, 1234,

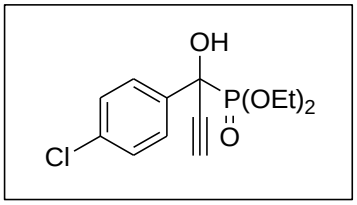
1004, 972, 950, 699; HRMS: calculated for $C_{13}H_{17}O_4P$ $[M+Na]^+$ 291.0762 and found 291.0757.

3.2.1.2 Characterization of 171



Diethyl 1-hydroxy-1-p-tolylprop-2-ynylphosphonate: Yield 63 mg (57%), crystalline white solid (mp: 96-98 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.17 (3H, t, *J*=7.0 Hz), 1.22 (3H, t, *J*=7.0Hz), 2.29 (3H, d, *J*=1.6Hz), 2.72 (1H, d, *J*=5.3 Hz), 4.09-3.96 (4H, m), 4.13 (1H, d, *J*=8.1 Hz), 7.09 (2H, d, *J*=8.3 Hz), 7.51 (2H, dd, *J*=2.2 and 8.3 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 16.36 (d, *J*=2.8 Hz), 16.4 (d, *J*=2.6 Hz), 21.0, 64.4 (d, *J*=7.3 Hz), 70.8 (d, *J*=167.2 Hz), 76.3 (d, *J*=9.2 Hz), 82.2, 126.6 (d, *J*=4.0 Hz), 128.6 (d, *J*=2.4 Hz), 134.0 (d, *J*=3.8 Hz), 138.0 (d, *J*=3.8 Hz); ^{31}P NMR ($CDCl_3$, 161MHz): δ 16.72; IR (ATR technique, cm^{-1}): 3275, 3255, 3214, 2961, 2925, 1073, 1011, 961, 799; HRMS: calculated for $C_{14}H_{19}O_4P$ $[M+Na]^+$ 305.0919 and found 305.0919.

3.2.1.3 Characterization of 175

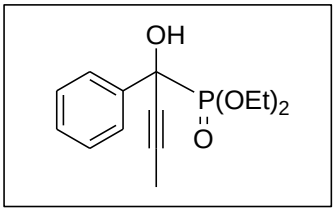


Diethyl 1-(4-chlorophenyl)-1-hydroxyprop-2-ynylphosphonate: Yield 48 mg (44%), crystalline white solid (mp: 105-107 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (6H, q (broad), *J*=7.4 Hz), 2.74 (1H, d, *J*=5.3 Hz), 4.12-4.00 (4H, m), 4.29 (1H, d (broad), *J*=7.0 Hz), 7.27 (2H, d, *J*=8.4 Hz), 7.58 (2H, dd, *J*=8.4 and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.29 (d, *J*=3.7 Hz), 16.3 (d, *J*=3.6 Hz), 64.7 (d, *J*=7.4 Hz), 70.6 (d, *J*=166.7 Hz), 76.8 (d, *J*=9.1 Hz), 81.6 (d, *J*=1.2 Hz), 128.1 (d, *J*=2.6 Hz), 128.2, 134.4 (d, *J*=4.0 Hz), 135.6 (d, *J*=3.4 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.09; IR (ATR technique, cm^{-1}): 3289, 3212, 2924, 1236, 1006, 946; HRMS: calculated for $C_{13}H_{16}ClO_4P$ $[M+Na]^+$ 325.0372 and found 325.0369.

3.2.2 General Procedure for the Addition of tris-(propynyl) aluminum reagent to Acyl Phosphonates

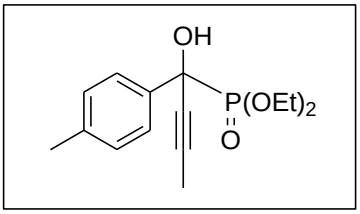
To a solution of acyl phosphonate (100 mg, 1 equiv.) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added tris-(propynyl) aluminum reagent (3 equiv., 0.23 M solution) dropwise. The resultant mixture was stirred at 0 °C , and warmed to room temperature. After the completion of reaction in 2-3 hours, which was monitored by a TLC plate, the reaction mixture was cautiously hydrolyzed with water. The reaction mixture was filtrated over celite and washed with ethyl acetate. The organic layer was then dried over anhydrous $MgSO_4$, filtered again and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexane-EtOAc mixtures.

3.2.2.1 Characterization of 183



Diethyl 1-hydroxy-1-phenylbut-2-ynylphosphonate: Yield 65 mg (56%), crystalline white solid (mp: 157-158 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (6H, dt, *J*=7.0 and 2.9 Hz, OCH_2CH_3), 1.97 (3H, d, *J*=5.1 Hz, C≡C-CH_3), 3.66 (1H, d, *J*=8.5 Hz, -OH), 3.90-4.22 (4H, m, OCH_2CH_3), 7.27-7.42 (m, 3H), 7.69-7.77 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.7 Hz, C≡C-CH_3), 16.4 (t, J_{C-P}= 4.0 Hz, OCH_2CH_3), 64.4 (dd, J_{C-P}=73.5 and 4.0 Hz, OCH_2CH_3), 71.2 (d, J_{C-P}=167.4 Hz, quaternary C atom), 77.5 (d, J_{C-P}=2.3 Hz, C≡C-CH_3) 85.0 (d, J_{C-P}=8.8 Hz, C≡C-CH_3), 126.7 (d, J_{C-P}=4.2 Hz), 127.8, (d, J_{C-P}=2.6 Hz), 128.1 (d, J_{C-P}=3.0 Hz) 137.8 (d, J_{C-P}=3.0 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 17.36; IR (ATR technique, cm^{-1}): 3241, 2988, 1228, 1015, 972, 757, 703, 577; HRMS: calculated for $C_{14}H_{19}O_4P$ $[M+H]^+$ 283.1099 and found 283.1129.

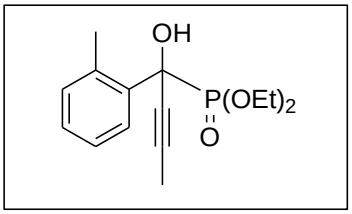
3.2.2.2 Characterization of 186



Diethyl 1-hydroxy-1-p-tolylbut-2-ynylphosphonate: Yield 61 mg (53%), crystalline white solid (mp: 127-128 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (6H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 1.96 (3H, d, J_{C-P}=5.1 Hz, C≡C-CH_3), 2.34 (3H, d, J_{C-P}=1.3 Hz, CH_3), 3.66 (1H, t,-OH, J_{C-P}=12.2 Hz), 3.90-4.30 (4H, m, OCH_2CH_3), 7.16 (2H, d, J_{C-P}=8.0 Hz), 7.60 (2H, dd, J_{C-P}=8.3 and 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.4 Hz, C≡C-CH_3), 16.4 (t, J_{C-P}=4.0 Hz, OCH_2CH_3), 21.0 (s, -CH_3), 64.3 (d, J_{C-P}=7.4 Hz, OCH_2CH_3), 71.1 (d, J_{C-P}=168.3 Hz, quaternary C atom), 77.6, 84.9 (d, J_{C-P}=8.4 Hz), 126.6 (d, J_{C-P}=4.2 Hz), 128.6 (d, J_{C-P}=4.2 Hz) 128.6 (d, J_{C-P}=2.4 Hz), 134.9, 137.9 (d, J_{C-P}= 2.8 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 17.52; IR

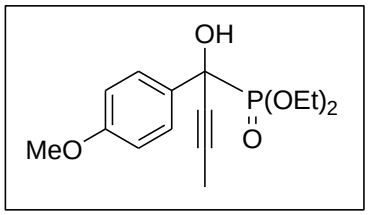
(ATR technique, cm^{-1}): 3238, 2986, 1231, 1017, 970, 573; HRMS: calculated for $C_{15}H_{21}O_4P$ $[M+H]^+$ 297.1255 and found 297.1289.

3.2.2.3 Characterization of 188



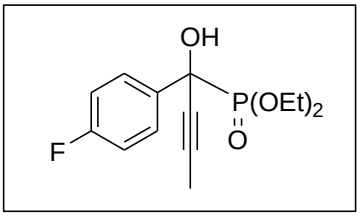
Diethyl 1-hydroxy-1-o-tolylbut-2-ynylphosphonate: Yield 37 mg (32%), crystalline white solid (mp: 104-105 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (3H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 1.29 (3H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 1.95 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 2.69 (3H, d, J_{C-P}=1.5 Hz, CH_3), 3.25 (1H, d, OH, J_{C-P}=8.0 Hz), 3.80-4.30 (4H, m, OCH_2CH_3), 7.12-7.23 (3H, m), 7.72-7.82 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.5 Hz, C≡C-CH_3), 16.4 (dd, J_{C-P}=9.3 and 5.5 Hz, OCH_2CH_3), 21.9 (-CH_3), 64.2 (t, J_{C-P}=8.3 Hz, OCH_2CH_3), 71.6 (d, J_{C-P}=167.5 Hz, quaternary C atom), 77.6 , (d, J_{C-P}=2.2 Hz), 85.7 (d, J_{C-P}=9.0 Hz) 125.4 (d, J_{C-P}=2.3 Hz), 127.7 (d, J_{C-P}=4.2 Hz) , 128.2 (d, J_{C-P}=2.7 Hz), 132.3 (d, J_{C-P}=2.3 Hz), 134.8 (d, J_{C-P}=1.5 Hz), 137.4 (d, J_{C-P}=4.8 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 18.00; IR (ATR technique, cm^{-1}): 3246, 2982, 1229, 1015, 970; HRMS: calculated for $C_{15}H_{21}O_4P$ $[M-H]^+$ 295.1099 and found 295.1152.

3.2.2.4 Characterization of 189



Diethyl 1-hydroxy-1-(4-methoxyphenyl)but-2-ynylphosphonate: Yield 47 mg (41%), crystalline white solid (mp: 111-112 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (6H, dt, J_{C-P}=7.0 and 3.7 Hz, OCH_2CH_3), 1.97 (3H, d, J_{C-P}=5.1 Hz, C≡C-CH_3), 3.38 (1H, d,-OH, J_{C-P}= 9.0 Hz), 3.81 (3H, s, OCH_3), 3.92-4.20 (4H, m, OCH_2CH_3), 6.90 (2H, d, J_{C-P}=8.7 Hz), 7.64 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.6 Hz, C≡C-CH_3), 16.4 (dd, J_{C-P}= 5.2 and 3.6 Hz, OCH_2CH_3), 55.3 (OCH_3), 64.3 (dd, J_{C-P}=7.3 and 3.5 Hz, OCH_2CH_3), 70.9 (d, J_{C-P}=169.4 Hz, quaternary C atom), 77.5, 85.1 (d, J_{C-P}=8.8 Hz), 113.3 (d, J_{C-P}=2.3 Hz) 128.1 (d, J_{C-P}=4.0 Hz), 129.7 (d, J_{C-P}=3.4 Hz), 159.6 (d, J_{C-P}=2.5 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 17.58; IR (ATR technique, cm^{-1}): 3240, 2980, 1225, 1019, 970; HRMS: calculated for $C_{15}H_{21}O_5P$ $[M+H]^+$ 313.1205 and found 313.1247.

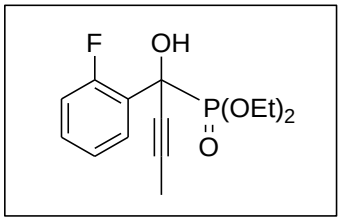
3.2.2.5 Characterization of 191



Diethyl 1-(4-fluorophenyl)-1-hydroxybut-2-ynylphosphonate: Yield 81 mg (70%), crystalline white solid (mp: 160-161 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (6H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 1.97 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 3.96-4.22 (5H, m, OCH_2CH_3 and OH), 7.04 (2H, t, J=8.6 Hz), 7.65-7.75 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.3 Hz, C≡C-CH_3), 16.4 (dd, J_{C-P}=5.2 and J_{C-P}=4.1 Hz, OCH_2CH_3), 64.4 (d, J_{C-P}=7.4 Hz, OCH_2CH_3), 70.7 (d, J=168.9 Hz, quaternary C atom), 77.2, 85.2 (d, J_{C-P}=8.9 Hz), 114.7 (dd, J_{C-F}=21.7 Hz and J_{C-P}=2.6 Hz) 128.7(dd, J_{C-F}=8.2 Hz and J_{C-P}= 4.2 Hz), 133.8 (t, J_{C-F}=3.0 Hz) 162.6 (dd, J_{C-F}=250.0 and J_{C-P}=3.3 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.42; IR (ATR technique, cm^{-1}):

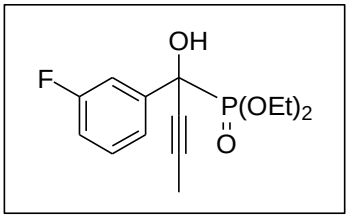
3233, 1231, 1021, 971,804, 572; HRMS: calculated for $C_{14}H_{18}FO_4P$ $[M+H]^+$ 301.1005 and found 301.1045.

3.2.2.6 Characterization of 193



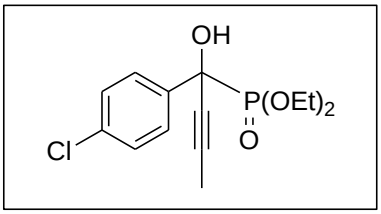
Diethyl 1-(2-fluorophenyl)-1-hydroxybut-2-ynylphosphonate: Yield 70 mg (61%), crystalline white solid (mp: 145-146 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 1.31 (3H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 1.97 (3H, d, J_{C-P}=5.1 Hz, C≡C-CH_3), 4.04 (1H, s (broad), OH), 4.08-4.32 (4H, m, OCH_2CH_3), 7.05 (1H, dd, J_{C-F}=11.9 and J_{C-P}=8.2 Hz), 7.15 (1H, t, J_{C-F}=7.6 Hz), 7.25-7.35 (1H, m), 7.74 (1H, tt, J_{C-F}=8.0 and J_{C-P} = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.5 Hz, C≡C-CH_3), 16.3 (d, J_{C-P}=5.5 Hz, OCH_2CH_3), 64.6 (dd, J_{C-F}=7.2 and J_{C-P}=5.1 Hz, OCH_2CH_3), 79.6 (d, J_{C-P}=168.6 Hz, quaternary C atom), 69.6 (dd, J_{C-P}=168.6 and J_{C-F}=2.0 Hz), 76.0 (d, J_{C-P}=3.8 Hz), 85.3 (dd, J_{C-P}=8.8 and J_{C-F}=1.9 Hz), 116.3 (dd, J_{C-F}=23.0 and J_{C-P}=2.3 Hz), 123.7 (t, J=2.3 Hz), 125.1(dd, J_{C-F}=9.2 and J_{C-P}=2.0 Hz), 129.3 (dd, J_{C-F}=8.7 and J_{C-P}=2.7 Hz), 160.2 (dd, J_{C-F}=250.3 and J_{C-P}=4.3 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.42; IR (ATR technique, cm^{-1}):3229, 2983, 1235, 1028, 974, 774, 580; HRMS: calculated for $C_{14}H_{18}FO_4P$ $[M+H]^+$ 301.1005 and found 301.1040.

3.2.2.7 Characterization of 195



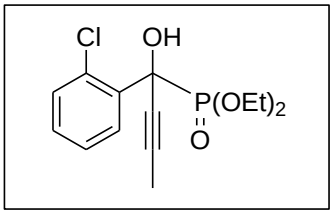
Diethyl 1-(3-fluorophenyl)-1-hydroxybut-2-ynylphosphonate: Yield 74 mg (65%), crystalline white solid (mp: 152-153 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (6H, dt, J_{C-P}=7.0 Hz and J_{C-F}=5.8 Hz, OCH_2CH_3), 1.97 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 4.03-4.23 (4H, m, OCH_2CH_3), 4.37 (1H, d, J_{C-P}=7.5 Hz, OH), 6.96-7.05 (1H, m), 7.32 (1H, dt, J_{C-F}=8.0 and 6.10 Hz), 7.45 (1H, ddd, J=10.4, 4.2 and 2.3 Hz), 7.51 (1H, td, J=7.9 and 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (J_{C-P}=4.2 Hz, C≡C-CH_3), 16.4 (t, J_{C-P}=4.2 Hz, OCH_2CH_3), 64.5 (dd, J_{C-P}=7.4 and J_{C-F}=2.0 Hz, OCH_2CH_3), 70.8 (dd, J_{C-P}=167.9 and J_{C-F}=1.8 Hz, quaternary C atom), 85.2 (d, J_{C-P}=8.8 Hz), 114.1 (dd, J_{C-P}=4.0 and J_{C-F}=23.9 Hz), 114.9 (dd, J_{C-F}=21.2 and J_{C-P}=2.8 Hz), 122.6 (t, J= 3.5 Hz) ,129.2 (dd, J_{C-F}=8.1 and J_{C-P}=2.7 Hz), 140.8 (dd, J_{C-F}=7.4 and J_{C-P}=3.1 Hz), 162.4 (dd, J_{C-F}=247.8 and J_{C-P}=2.9 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.75; IR (ATR technique, cm^{-1}): 3229, 1228, 1018, 977, 798; HRMS: calculated for $C_{14}H_{18}FO_4P$ $[M+H]^+$ 301.1005 and found 301.1055.

3.2.2.8 Characterization of 196



Diethyl 1-(4-chlorophenyl)-1-hydroxybut-2-ynylphosphonate: Yield 70 mg (61%), crystalline white solid (mp: 124-125 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (6H, dt, J_{C-P}=7.0 and J_{C-P}=1.2 Hz, OCH_2CH_3), 1.96 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 3.95-4.22 (4H, m, OCH_2CH_3), 4.26 (1H, d, OH, J_{C-P}=7.6 Hz), 7.33 (2H, d, J_{C-C}=8.6 Hz), 7.66 (2H, dd, J_{C-C}=8.7 and J_{C-P}= 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.2 Hz, C≡C-CH_3), 16.4 (t, J_{C-P}= 4.5 Hz, OCH_2CH_3), 64.4 (dd, J_{C-P}=7.3 and 4.2 Hz, OCH_2CH_3), 70.7 (d, J_{C-P}=168.5 Hz, quaternary C atom), 85.3 (d, J_{C-P}=8.8 Hz), 127.9 (d, J_{C-P}=2.7 Hz), 128.3 (d, J_{C-P}= 4.2 Hz) 134.0 (d, J_{C-P}=3.7 Hz), 136.7 (d, J_{C-P}=3.0 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.16; IR (ATR technique, cm^{-1}): 3229, 2986, 1230, 1013, 974; HRMS: calculated for $C_{14}H_{18}ClO_4P$ $[M+H]^+$ 317.0709 and found 317.0751.

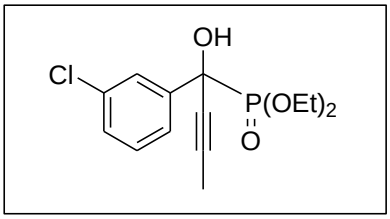
3.2.2.9 Characterization of 198



Diethyl 1-(2-chlorophenyl)-1-hydroxybut-2-ynylphosphonate: Yield 56 mg (49%), crystalline white solid (mp: 137-138 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (3H, t, J_{C-P}=7.04 Hz, OCH_2CH_3), 1.31 (3H, t, J_{C-P}=7.1 Hz, C≡C-CH_3), 1.96 (3H, d, J_{C-P}= 5.2 Hz), 4.07 (1H, d, -OH, J_{C-P}=7.7 Hz), 4.08-4.32 (4H, m, OCH_2CH_3), 7.20-7.33 (2H, m), 7.38 (1H, dd, J=7.5 and 1.5 Hz), 7.91 (1H, td, J= 7.8 and 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100MHz): δ 4.0 (d, J=2.4 Hz, C≡C-CH_3), 6.4 (t, J_{C-P}= 5.8 Hz, OCH_2CH_3), 64.5 (dd, J_{C-P}=7.6 and 1.5 H, OCH_2CH_3), 71.3 (d, J_{C-P}=167.9 Hz, quaternary C atom), 76.3 (d, J_{C-P}=4.6 Hz), 86.2 (d, J_{C-P}=9.0 Hz), 126.5 (d, J_{C-P}=2.1 Hz), 129.4 (d, J_{C-P}=2.3 Hz), 129.9 (d, J_{C-P}=4.1 Hz), 131.5 (d, J_{C-P}=2.0 Hz), 132.4 (d, J_{C-P}=5.3 Hz), 134.7; ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.79; IR (ATR technique, cm^{-}

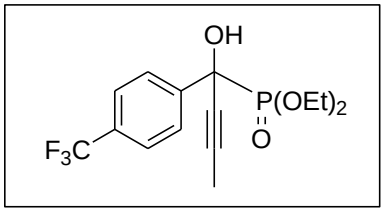
[1]): 3221, 2983, 1231, 1022, 972; HRMS: calculated for $C_{14}H_{18}ClO_4P$ $[M+H]^+$ 317.0709 and found 317.0774.

3.2.2.10 Characterization of 200



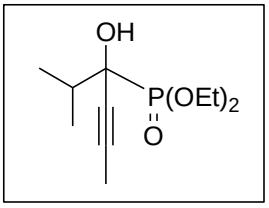
Diethyl 1-(3-chlorophenyl)-1-hydroxybut-2-ynylphosphonate: Yield 71 mg (62%), crystalline white solid (mp: 168-169 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (6H, t, Jc-$_P$=7.1 Hz, OCH_2CH_3), 1.98 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 3.80 (1H, d, J_{C-P}=7.8 Hz, -OH), 4.0-4.23 (4H, m, OCH_2CH_3), 7.3 (2H, d, J_{C-P}=4.8 Hz), 7.55-7.65 (1H, m), 7.71 (1H, d, J=1.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 4.0 (d, J_{C-P}=2.4 Hz, C≡C-CH_3), 16.4 (t, J= 4.9 Hz, CH_2CH_3), 64.5 (dd, J_{C-P}=7.4 and 2.6 Hz, OCH_2CH_3), 70.8 (d, J_{C-P}=167.8 Hz, quaternary C atom), 77.0, 85.5 (d, J_{C-P}=8.8 Hz), 125.1 (d, J_{C-P}=3.9 Hz), 127.0 (d, J_{C-P}=4.0 Hz), 128.3 (d, J_{C-P}=2.9 Hz), 129.1 (d, J_{C-P}=2.8 Hz), 133.8 (d, J_{C-P}=3.0 Hz), 140.1(d, J_{C-P}=3.2 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.64; IR (ATR technique, cm^{-1}): 3233, 2981, 1231, 1016, 975, 797, 695; HRMS: calculated for $C_{14}H_{18}ClO_4P$ $[M+H]^+$ 317.0709 and found 317.0765.

3.2.2.11 Characterization of 202



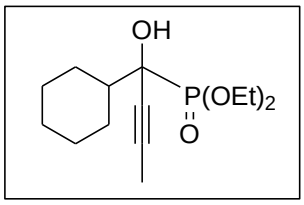
Diethyl 1-(4-(trifluoromethyl)phenyl)-1-hydroxybut-2-ynylphosphonate: Yield 85 mg (75%), crystalline white solid (mp: 119-120 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (6H, dt, J_{C-P}=7.0 and J_{C-P}=5.5 Hz, OCH_2CH_3), 1.97 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 4.0-4.26 (4H, m, OCH_2CH_3), 4.62 (1H, d, OH, J_{C-P}=6.8 Hz), 7.61 (2H, d, J_{C-P}=8.6 Hz), 7.85 (2H, dd, J=1.5 and J= 8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 3.9 (d, J_{C-P}=2.2 Hz, C≡C-CH_3), 16.3 (t, J_{C-P}=4.9 Hz, OCH_2CH_3), 64.5 (t, J_{C-P}=7.6 Hz, OCH_2CH_3), 70.9 (d, J_{C-P}=167.3 Hz, quaternary C atom), 77.2, 85.4 (d, J_{C-P}=8.9 Hz), 124.7 (t, J_{C-F}=6.7), 124.1 (d, J_{C-F}=271.2 Hz), 127.2 (d, J_{C-P}=3.8 Hz), 129.8 (q, J_{C-F}=32.2 Hz, CF_3), 142.3 (d, J_{C-F}=1.7 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 15.84; IR (ATR technique, cm^{-1}): 3220, 1238, 1016, 972,883; HRMS: calculated for $C_{15}H_{18}F_3O_4P$ $[M+H]^+$ 351.0973 and found 351.1018.

3.2.2.12 Characterization of 204



Diethyl 3-hydroxy-2-methylhex-4-yn-3-ylphosphonate: Yield 38 mg (32%), crystalline white solid (mp: 68-69 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.09 (6H, d, J=6.7 Hz, CH_3), 1.36 (6H, t, J=7.1 Hz, OCH_2CH_3), 1.91 (3H, d, J_{C-P}=5.2 Hz, C≡C-CH_3), 2.08-2.12 (1H, m, CH), 2.85 (1H, d, OH, J_{C-P}=4.7 Hz), 4.10- 4.33 (4H, m, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): δ 3.8 (d, J_{C-P} =2.6 Hz, C≡C-CH_3), 16.5 (d, J_{C-P} =5.2 Hz, OCH_2CH_3), 17.0 (d, J_{C-P} =9.5 Hz), 18.4 (d, J_{C-P}=1.9 Hz), 34.5 (d, J_{C-P}=1.0 Hz), 63.8 (dd, J_{C-P}=20.4 and 7.4 Hz) 73.4 (d, J_{C-P} =168.7 Hz, quaternary C atom), 75.2, 85.0 (d, J_{C-P}=9.6 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 20.92; IR (ATR technique, cm^{-1}): 3270, 2986, 1228, 1021, 962; HRMS: calculated for $C_{11}H_{21}O_4P$ $[M+H]^+$ 249.1256 and found 249.1300.

3.2.2.13 Characterization of 206



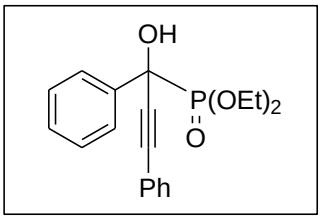
Diethyl 1-cyclohexyl-1-hydroxybut-2-ynylphosphonate: Yield 44 mg (38%), crystalline white solid (mp: 62-63 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08-1.30 (5H, m), 1.36 (6H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 1.66 (1H, d, *J*=10.3 Hz), 1.72-1.88 (3H, m), 1.91 (3H, d, J_{C-P}=5.3 Hz, C≡C-CH_3), 2.04 (2H, t, *J*=9.3 Hz), 2.72 (1H, s (broad), -OH), 4.18-4.32 (4H, m, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 3.9 (d, J_{C-P}=2.8 Hz, C≡C-CH_3), 16.5 (d, J_{C-P}=5.5 Hz, OCH_2CH_3), 26.2 (d, J_{C-P}=9.5 Hz, CH_2), 26.5 (d, J_{C-P}=8.6 Hz, CH_2), 28.1 (d, J_{C-P}=2.1 Hz, CH_2), 44.2, 63.8 (dd, J_{C-P}=17.1 and 7.5 Hz, OCH_2CH_3), 72.9 (d, J_{C-P}=167.8 Hz, quaternary C atom), 75.8, 84.9 (d, J_{C-P}=9.5 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 20.71; IR (ATR technique, cm^{-1}): 3263, 2921, 1224, 1017, 983,939; HRMS: calculated for $C_{14}H_{25}O_4P$ $[M+H]^+$ 289.1569 and found 289.1630.

3.2.3 General Procedure for the Addition of tris-(phenylethynyl) aluminum reagent to Acyl Phosphonates

To a solution of acyl phosphonate (100 mg, 1 equiv.) in dry toluene (0.5 M) at 0 °C under argon atmosphere was added tris-(phenylethynyl) aluminum reagent (3 equiv., 0.23 M solution) dropwise. The resultant mixture was stirred at 0 °C , and warmed to room temperature. After the completion of reaction in 2-3 hours, which was monitored by a TLC plate, the reaction mixture was cautiously hydrolyzed with water. The reaction mixture was filtrated over Celite and washed with ethyl acetate. The organic layer was then dried over anhydrous MgSO4, filtered again and

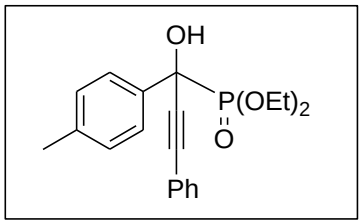
concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexane-EtOAc mixtures.

3.2.3.1 Characterization of 207



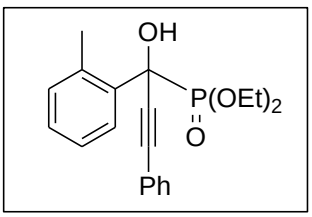
Diethyl 1-hydroxy-1,3-diphenylprop-2-ynylphosphonate: Yield 86 mg (61%), crystalline white solid (mp: 120-121 °C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.14 (3H, t, J_{C-P}=7.1Hz, OCH_2CH_3), 1.20 (3H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 4.0-4.14 (4H, m, OCH_2CH_3), 4.4-4.6 (1H, s (broad), OH), 7.20-7.36 (6H, m), 7.40-7.46 (2H, dd, *J*=7.5 and 1.7 Hz), 7.70-7.75 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.3 (t, J_{C-P}=5.6 Hz, OCH_2CH_3), 63.6 (dd, J_{C-P}=7.2 and 4.1Hz, OCH_2CH_3), 70.5 (d, J_{C-P}=166.9 Hz, quaternary C atom), 86.2 (d, J_{C-P}=2.1 Hz, C≡C-Ph), 87.0 (d, J_{C-P}=9.0 Hz, C≡C-Ph), 121.1 (d, J_{C-P}=3.2 Hz) 125.8 (d, J_{C-P}=3.9 Hz), 126.9 (d, J_{C-P}=2.7 Hz), 127.2 (d, J_{C-P}=2.9 Hz), 127.3, 127.9, 130.9 (d, J_{C-P}=2.8 Hz), 136.7 (d, J_{C-P}=3.6 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.13; IR (ATR technique, cm^{-1}): 3187, 2978, 1227, 1049, 1010, 952, 758, 693, 579; HRMS: calculated for $C_{19}H_{21}O_4P$ $[M+H]^+$ 345.1255 and found 345.1313.

3.2.3.2 Characterization of 209



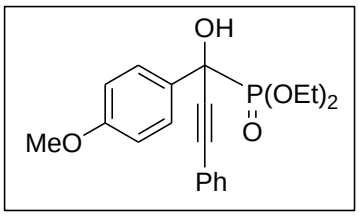
Diethyl 1-hydroxy-3-phenyl-1-p-tolylprop-2-ynylphosphonate: Yield 82 mg (59%), crystalline white solid (mp: 118-119 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 1.28 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 2.35 (3H, d, J_{C-P}=1.6 Hz, CH_3), 4.05-4.22 (4H, m, OCH_2CH_3), 4.66 (1H, d, J=7.4 Hz, OH), 7.18 (2H, d, J=8.4 Hz), 7.28-7.38 (3H, m), 7.51 (2H, dd, J=7.5 Hz and 1.9 Hz), 7.68 (2H, dd, J_{C-P}=8.3 and 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P}=5.6 Hz, OCH_2CH_3), 21.2 (CH_3), 64.6 (t, J_{C-P}=7.5 Hz, OCH_2CH_3), 71.4 (d, J=167.4 Hz, quaternary C atom), 87.4, 88.0 (d, J_{C-P}=9.5 Hz), 122.2 (d, J_{C-P}=3.3 Hz) 126.7 (d, J_{C-P}=4.2 Hz), 128.3, 128.7 (d, J_{C-P}=2.5 Hz), 128.8, 132.0 (d, J_{C-P}=2.6 Hz), 134.7 (d, J_{C-P}=3.7 Hz), 138.0 (d, J_{C-P}=3.1 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.96; IR (ATR technique, cm^{-1}): 3199, 2979, 1225, 1050, 1018, 952, 757, 691, 573; HRMS: calculated for $C_{20}H_{23}O_4P$ $[M+H]^+$ 359.1412 and found 359.1481.

3.2.3.3 Characterization of 210



Diethyl 1-hydroxy-3-phenyl-1-o-tolylprop-2-ynylphosphonate: Yield 42 mg (30%), crystalline white solid (mp: 111-112 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (6H, dt, J_{C-P} =7.1 Hz and 16.0 Hz, OCH_2CH_3), 2.76 (3H, d, J_{C-P}=1.5 Hz, CH_3), 3.65 (1H, unresolved q, OH), 3.92-4.25 (4H, m, OCH_2CH_3), 7.12- 7.24 (3H, m), 7.27-7.38 (3H, m), 7.47 (2H, dd, *J*=7.5 and 1.9 Hz), 7.79 -7.88 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P}=5.5 Hz, OCH_2CH_3), 22.0 (-CH_3), 64.5 (dd, J_{C-P}=7.5 Hz and 3.9 Hz, OCH_2CH_3), 71.8 (d, J_{C-P} =166.7 Hz), 87.2 (d, J_{C-P}=2.1 Hz), 88.7 (d, J_{C-P}=9.5 Hz), 122.2 (d, J_{C-P}=3.4 Hz), 125.5 (d, J_{C-P}=2.3 Hz), 127.6 (d, J_{C-P}=3.9 Hz), 128.3 (d, J_{C-P}=2.8 Hz), 128.4, 128.9, 131.7 (d, J_{C-P}=2.8 Hz), 132.4 (d, J_{C-P}=2.2 Hz), 134.6 (d, J_{C-P}=2.2 Hz), 137.4 (d, J_{C-P}=5.0 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 17.43; IR (ATR technique, cm^{-1}): 3187, 2979, 1212, 1053, 1012, 947, 758, 694; HRMS: calculated for $C_{20}H_{23}O_4P$ $[M+H]^+$ 359.1412 and found 359.1477.

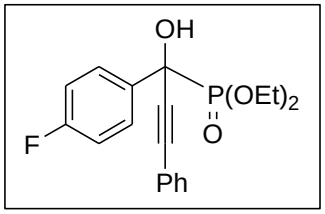
3.2.3.4 Characterization of 221



Diethyl 1-hydroxy-1-(4-methoxyphenyl)-3-phenylprop-2-ynylphosphonate: Yield 54 mg (39%), crystalline white solid (mp:115-116 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 1.28 (3H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 4.0-4.22 (4H, m, OCH_2CH_3), 4.24-4.40 (1H, s (broad), OH), 6.91 (2H, d, *J*=8.7 Hz), 7.28-7.38 (3H, m), 7.51 (2H, dd, *J*=7.5 and 1.9 Hz), 7.72 (2H, dd, *J*= 9.0 and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P}=4.2 Hz, OCH_2CH_3), 55.3 (OCH_3), 64.5 (dd, J_{C-P}=7.3 and 2.6 Hz, OCH_2CH_3), 71.2 (d, J_{C-P}=168.6 Hz, quaternary C atom), 87.2, 88.1 (d, J_{C-P}=9.1 Hz), 113.4 (d, J_{C-P}=2.2 Hz), 122.1 (d, J_{C-P}=2.9 Hz), 128.2 (d, J_{C-P}=4.0 Hz), 128.3, 128.9, 129.6, 131.9 (d, J_{C-P}=2.7

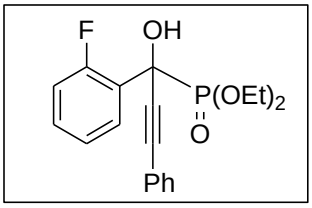
Hz), 159.6 (d, J_{C-P}=2.6 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 17.05; IR (ATR technique, cm^{-1}): 3199, 2980, 1225, 1051, 1015, 953, 758, 573; HRMS: calculated for $C_{20}H_{23}O_5P$ $[M+H]^+$ 375.1361 and found 375.1426.

3.2.3.5 Characterization of 212



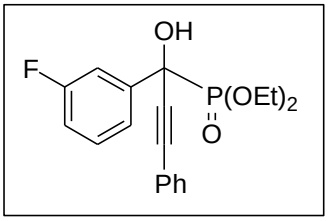
Diethyl 1-(4-fluorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate: Yield 94 mg (68%), crystalline white solid (mp: 115-116 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 1.27 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 4.04-4.22 (4H, m, OCH_2CH_3), 5.11 (1H, d, J_{C-P}=6.3 Hz, OH), 7.05 (2H, t, J=8.6 Hz), 7.28-7.40 (3H, m), 7.51 (2H, dd, J=7.7 and 1.7 Hz), 7.73-7.81 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (t, J_{C-P}=6.3 Hz, OCH_2CH_3), 64.6 (dd, J_{C-P}=9.4 and 7.5 Hz, OCH_2CH_3), 71.0 (d, J=168.2 Hz, quaternary C atom), 87.0 (d, J_{C-P}=1.1 Hz), 88.2 (d, J_{C-P}=9.0 Hz), 114.6 (d, J=2.3 Hz), 114.9.7 (d, J=2.5 Hz), 122.0 (d, J=3.0 Hz), 128.3, 128.8 (dd, J_{C-F}=8.3 and J_{C-P}=4.1 Hz), 129.0, 132.0 (d, J=2.6 Hz), 133.7 (t, J=3.3 Hz), 162.0 (dd, J_{C-F}=249.7 Hz and J_{C-P}=3.4 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 15.84; IR (ATR technique, cm^{-1}): 3203, 2981, 1233, 1050, 1017, 951, 762, 695, 572; HRMS: calculated for $C_{19}H_{20}FO_4P$ $[M+H]^+$ 363.1161 and found 363.1223.

3.2.3.6 Characterization of 213



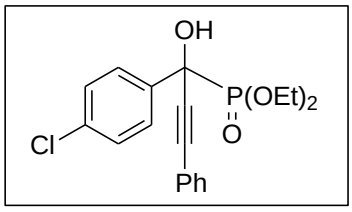
Diethyl 1-(2-fluorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate: Yield 99 mg (72%), crystalline white solid (mp: 122-123 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 (3H, t, J_{C-P}=7.0 Hz, OCH_2CH_3), 1.32 (3H, t, J_{C-P}=7.1 Hz, OCH_2CH_3), 4.05-4.22 (2H, m, OCH_2CH_3), 4.31 (2H, m, J=7.1 Hz, OCH_2CH_3), 5.2 (1H, s (broad), OH), 7.06 (1H, dd, J=11.7 and 8.2 Hz), 7.16 (1H, t, J=7.6 Hz), 7.22 -7.37 (4H, m), 7.51 (2H, dd, J=7.5 and 1.9 Hz), 7.78-7.87 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3 (dd, J_{C-P}=13.8 and 5.8 Hz, OCH_2CH_3), 64.9 (dd, J_{C-P}=12.3 and 7.3 Hz, -OCH_2CH_3), 69.3 (dd, J_{C-P}=168.2 Hz and J_{C-F}=2.0 Hz, quaternary C atom), 85.8 (d, J_{C-P}=2.7 Hz), 87.9 (dd, J_{C-P}=9.3 and J_{C-F}=2.5 Hz), 116.3 (dd, J_{C-F}=22.9 and J_{C-P}=2.2 Hz), 122.2 (d, J=3.1 Hz), 123.8 (t, J=2.8 Hz), 125.0 (dd, J_{C-F}=9.3 Hz and J_{C-P}=2.7 Hz) , 128.3, 128.8, 129.1 (dd, J_{C-F}=4.0 Hz and J_{C-F}=2.0 Hz), 130.1 (dd, J_{C-F}=8.6 and J_{C-P}=2.8 Hz), 131.8 (d, J=2.7 Hz), 160.0 (dd, J_{C-F}=251.0 and J_{C-P}=4.2 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.01; IR (ATR technique, cm^{-1}): 3189, 2979, 1224, 1051, 1015, 952, 760, 692; HRMS: calculated for $C_{19}H_{20}FO_4P$ $[M+H]^+$ 363.1161 and found 363.1227.

3.2.3.7 Characterization of 214



Diethyl 1-(3-fluorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate: Yield 99 mg (72%), crystalline white solid (mp: 113-114 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.28 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 4.05-4.27 (4H, m, OCH_2CH_3), 5.45-5.60 (1H, s (broad), OH), 7.01 (1H, t, *J*=8.3 Hz), 7.27-7.40 (4H, m), 7.47-7.63 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (dd, *J*=10.5 and 5.6 Hz, OCH_2CH_3), 64.8 (dd, *J*=7.4 and 14.4 Hz, OCH_2CH_3), 71.0 (d, J_{C-P}=167.0 Hz, quaternary C atom), 86.8 (d, J_{C-P}=1.3 Hz) , 88.2 (d, *J*=9.4 Hz), 114.6 (d, *J*=3.8 Hz), 114.3(d, *J*=4.1 Hz), 114.9 (d, *J*= 2.7 Hz) 115.1 (d, *J*=2.9 Hz), 121.9 (d, *J*=3.1 Hz), 122.7 (d, *J*= 3.4 Hz), 128.4, 129.0, 129.3 (dd, J_{C-F}= 8.0 and J_{C-P}=2.6 Hz), 132.0 (d, *J*=2.6 Hz), 140.7 (dd, J_{C-F}=7.5 and J_{C-P}=3.6 Hz), 161.3(dd, J_{C-F}=242.0 J_{C-P}=3.1 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 16.20; IR (ATR technique, cm^{-1}): 3186, 2977, 1226, 1015, 964,759; HRMS: calculated for $C_{19}H_{20}FO_4P$ $[M+H]^+$ 363.1161 and found 363.1226.

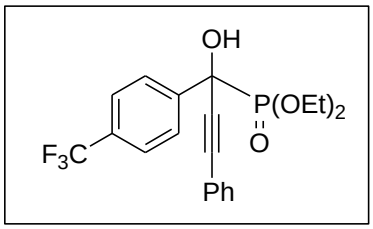
3.2.3.8 Characterization of 215



Diethyl 1-(4-chlorophenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate: Yield 71 mg (52%), crystalline white solid (mp: 102-103 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.26 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 4.02-4.24 (4H, m, OCH_2CH_3), 5.34 (1H, d, *J*=5.9 Hz, OH), 7.28-7.40 (5H, m), 7.50 (2H, dd, *J*=7.8 and 1.6 Hz), 7.73 (2H, dd, *J*=8.8 and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (dd, J_{C-P}=8.5 and 5.7 Hz, OCH_2CH_3), 64.7 (dd, J_{C-P}=14.2 and 7.5 Hz, OCH_2CH_3), 71.0 (d, J_{C-P}=167.8 Hz, quaternary C atom), 86.8 (d, J_{C-P}=1.52 Hz), 88.2

(d, J_{C-P}=8.9 Hz) 121.9 (d, J_{C-P}=3.0 Hz), 128.0 (d, J_{C-P}=2.7 Hz), 128.4, 129.0, 132.0 (d, J_{C-P}=2.8 Hz), 134.1 (d, J_{C-P}=3.5 Hz), 136.6 (d, J_{C-P}=3.6 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 15.60; IR (ATR technique, cm^{-1}): 3201, 2985, 1230, 1053, 1012, 949, 754, 688; HRMS: calculated for $C_{19}H_{20}ClO_4P$ $[M+H]^+$ 379.0866 and found 379.0935.

3.2.3.9 Characterization of 216



Diethyl 1-(4-(trifluoromethyl)phenyl)-1-hydroxy-3-phenylprop-2-ynylphosphonate: Yield 79 mg (60%), crystalline white solid (mp: 88-89 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.28 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 4.08-4.25 (4H, m, OCH_2CH_3), 5.59 (1H, d, *J*=5.5 Hz, OH), 7.3-7.4 (3H, m), 7.52 (2H, dd, *J*=7.8 and 1.5 Hz), 7.62 (2H, d, *J*=8.3 Hz), 7.92 (2H, d, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3 (dd, *J*=10.5 and 5.5 Hz, OCH_2CH_3), 64.8 (dd, *J*=16.4 and 7.5 Hz, OCH_2CH_3), 71.2 (d, *J*=166.7 Hz, quaternary C atom), 86.6 (d, J_{C-P}=2.1 Hz), 88.3 (d, J_{C-P}=9.2 Hz), 121.8 (d, J_{C-P}=3.2 Hz), 121.4 (q, J_{C-F}=272.0 Hz, -CF_3), 124.8 (t, *J*=3.2 Hz), 127.3, (d, *J*=3.8 Hz), 128.3, 129.1, 129.9 (qd, J_{C-F}=32.2 Hz and J_{C-P}= 2.9 Hz), 132.0 (d, *J*=2.8 Hz), 142.2; ^{31}P NMR ($CDCl_3$,161 MHz): δ 15.30; IR (ATR technique, cm^{-1}): 3180, 2988, 1227, 1067, 1018, 952, 755, 687; HRMS: calculated for $C_{20}H_{20}F_3O_4P$ $[M+H]^+$ 413.1129 and found 413.1226.

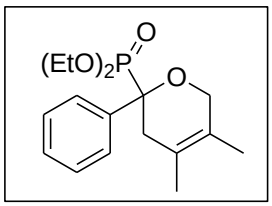
3.3 Synthesis of Glycosyl Phosphonates

All commercially available reagents were used as received. Acyl phosphonates were easily prepared according to the published procedure and used freshly in the cycloaddition reactions.

3.3.1 General procedure for the HDA reactions of Acyl phosphonates with 2,3-Dimethyl-1,3 butadiene

To a solution of acyl phosphonates (100 mg, 1 equiv) in DCM (2 mL) was added Lewis acid $AlCl_3$ (2 equiv) at 0 °C under argon atmosphere. After stirring for 10 min, 2,3-Dimethyl-1,3 butadiene (2 equiv) was added to the reaction mixture at the same temperature. After the completion of reaction in 1-3 hours, which was monitored by TLC, the reaction mixture was carefully quenched by adding few drops of water at 0 °C and then filtered and concentrated. The crude product was purified by flash column chromatography using hexane-EtOAc mixtures.

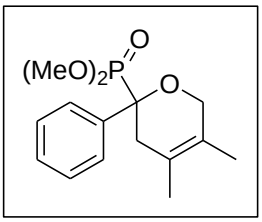
3.3.1.1 Characterization of 218



Diethyl (4,5-dimethyl-2-phenyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 90 mg (68%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.13 (6H, q, $J_{C\text{-}P}$=7.3 Hz, -OCH_2CH_3), 1.28 (3H, s), 1.63 (3H, s), 2.60 (1H, d, *J*=17.0 Hz), 2.89 (1H, t, *J*=13.2 Hz), 3.75-4.04 (6H, m), 7.19-7.23 (1H, m), 7.29 (2H, t, *J*=7.5 Hz), 7.45-7.42 (2H,

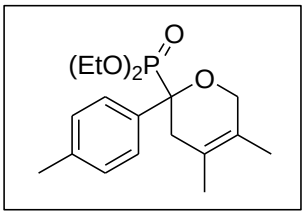
m); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.7, 16.3 (d, J_{C-P} =5.5 Hz, -OCH_2CH_3), 18.6, 32.6, 63.0 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 62.2 (J_{C-P} =7.0 Hz, -OCH_2CH_3), 64.5 (d, J_{C-P}=11.2 Hz, -OCH_2-), 77.1 (d, J_{C-P}=170.1 Hz, quaternary C atom), 120.9 (d, J_{C-P}=11.1 Hz), 123.5 (d, J_{C-P}=1.7 Hz), 127.6 (d, J_{C-P}=3.1 Hz), 127.8 (d, J_{C-P}=4.9 Hz), 127.9 (d, J_{C-P}=2.5 Hz), 136.1; ^{31}P NMR ($CDCl_3$,161 MHz): δ 21.11; IR (ATR technique, cm^{-1}): 2986, 1449, 1215, 1021, 747; HRMS: calculated for $C_{17}H_{25}O_4P$ $[M+Na]^+$ 347.1388 and found 347.1386.

3.3.1.2 Characterization of 220



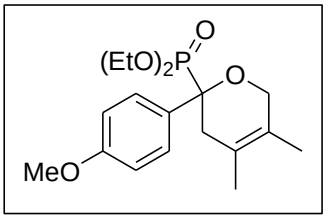
Dimethyl (4,5-dimethyl-2-phenyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 68 mg (49%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.27 (3H, s), 1.62 (3H, s), 2.60 (1H, d, *J*=17.0 Hz), 2.89 (1H, t, *J*=13.8 Hz), 3.53 (3H, d, *J*=10.3 Hz, -OCH_3), 3.61 (3H, d, *J*=10.4 Hz, -OCH_3), 3.77 (1H, d, *J*=15.7 Hz), 3.84 (1H, d, *J*=15.7), 7.19-7.47 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.6, 18.5, 32.5, 53.8 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 54.0 (J_{C-P} =7.0 Hz, -OCH_2CH_3), 64.4 (d, J_{C-P}=11.2 Hz, -OCH_2-), 77.3 (d, J_{C-P}=171.0 Hz, quaternary C atom), 120.8 (d, J_{C-P}=11.2 Hz), 123.5 (d, J_{C-P}=1.1 Hz), 127.7 (d, J_{C-P}=4.7 Hz), 127.8 (d, J_{C-P}=2.8 Hz), 128.1 (d, J_{C-P}=3.1 Hz), 129.8, 135.7; ^{31}P NMR ($CDCl_3$,161 MHz): δ 23.26; IR (ATR technique, cm^{-1}): 2986, 1449, 1215, 1021, 747; HRMS: calculated for $C_{15}H_{21}O_4P$ $[M+Na]^+$ 319.1075 and found 319.1078.

3.3.1.3 Characterization of 221



Diethyl (4,5-dimethyl-2-(p-tolyl)-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 57 mg (43%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.15 (6H, t, $J_{C\text{-}P}$=7.0 Hz, -OCH_2CH_3), 1.29 (3H, s), 1.63 (3H, s), 2.54 (1H, d, *J*=16.9 Hz), 2.89 (1H, t, *J*=12.4 Hz), 3.71 (1H, d, *J*=15.9 Hz), 3.86-4.03 (5H, m), 6.96 (2H, t, *J*=8.6 Hz), 7.40 (2H, t, *J*=5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.7, 16.3 (d, $J_{C\text{-}P}$ =5.5 Hz, -OCH_2CH_3), 18.6, 21.0, 32.6, 63.0 ($J_{C\text{-}P}$=7.1 Hz, -OCH_2CH_3), 63.2 ($J_{C\text{-}P}$=7.0 Hz, -OCH_2CH_3), 64.5 (d, $J_{C\text{-}P}$=11.3 Hz, -OCH_2-), 77.1 (d, $J_{C\text{-}P}$=171.0 Hz, quaternary C atom), 121.0 (d, $J_{C\text{-}P}$=11.1 Hz), 123.5 (d, $J_{C\text{-}P}$=1.0 Hz), 127.8 (d, $J_{C\text{-}P}$=4.6 Hz), 127.8 (d, $J_{C\text{-}P}$=4.6 Hz), 128.8 (d, $J_{C\text{-}P}$=2.2 Hz), 132.9; ^{31}P NMR ($CDCl_3$,161 MHz): δ 21.34; IR (ATR technique, cm^{-1}): 2989, 1444, 1215, 1022, 746; HRMS: calculated for $C_{18}H_{27}O_4P$ $[M+Na]^+$ 361.1545 and found 361.1547.

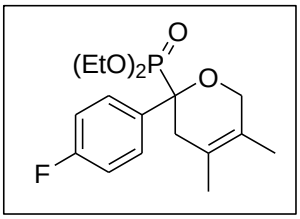
3.3.1.4 Characterization of 222



Diethyl (2-(4-methoxyphenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 51 mg (39%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.16 (6H, dt, $J_{C\text{-}P}$ =2.3 and 7.1Hz OCH_2CH_3), 1.28 (3H, s), 1.63 (3H, s), 2.54 (1H, d,

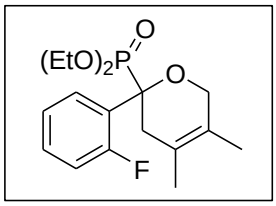
J=17.0 Hz), 2.86 (1H, t, *J*=13.0 Hz), 3.73 (3H, s), 3.73-4.00 (4H, m), 6.81 (2H, d, *J*=8.7Hz), 7.40 (2H, dd, *J*=2.3 and 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.7, 16.3 (d, J_{C-P} =5.6 Hz, -OCH_2CH_3), 18.6, 32.6, 55.1 (-OCH_3), 62.9 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 63.1 (J_{C-P} =7.0 Hz, -OCH_2CH_3), 64.4 (d, J_{C-P}=11.4 Hz, -OCH_2-), 76.8 (d, J_{C-P}=172.4 Hz, quaternary C atom), 113.4 (d, J_{C-P}=2.5 Hz), 120.9 (d, J_{C-P}=11.0 Hz), 123.6 (d, J_{C-P}=1.7 Hz), 127.8, 129.2 (d, J_{C-P}=4.8 Hz), 159. 1 (d, J_{C-P}=2.9 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 22.06; IR (ATR technique, cm^{-1}): 2987, 1510, 1243, 1023, 906, 727, 647; HRMS: calculated for $C_{18}H_{27}O_5P$ $[M+Na]^+$ 377.1494 and found 377.1503.

3.3.1.5 Characterization of 223



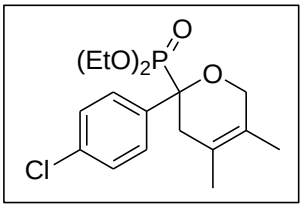
Diethyl (2-(4-fluorophenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 57 mg (44%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.15 (6H, dt, J_{C-P} =1.9 and 7.1 Hz), 1.28 (3H, s), 1.62 (3H, s), 2.53 (1H, d, *J*=17.0 Hz), 2.88 (1H, t, *J*=13.7 Hz), 3.70 (1H, d, *J*=15.8 Hz), 3.85-4.02 (5H, m), 6.94 (2H, t, *J*=8.7 Hz), 7.38-7.42 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.5, 16.1 (d, J_{C-P} =5.5 Hz, -OCH_2CH_3), 18.4, 32.6 (-CH_2-), 62.8 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 63.0 (J_{C-P} =7.1 Hz, -OCH_2CH_3), 64.4 (d, J_{C-P}=11.0 Hz and, -OCH_2-), 76.6 (d, J_{C-P}=171.7 Hz, quaternary C atom), 114.6 (dd, J_{C-F}=21.3 and J_{C-P}=2.6 Hz), 120.7 (d, J_{C-P}=10.7 Hz), 123.5 (d, J_{C-P}=1.4 Hz), 129.5 (dd, J_{C-P}=8.1 and J_{C-F}=4.9 Hz), 131.9 (d, J_{C-F}=6.7 Hz), 162.1 (dd, J_{C-F}=246.7 and J_{C-P}=3.2 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz): δ 21.41; IR (ATR technique, cm^{-1}): 2985, 2920, 1506, 1241, 1019, 964, 679; HRMS: calculated for $C_{17}H_{24}FO_4P$ $[M+Na]^+$ 365.1294 and found 365.1301.

3.3.1.6 Characterization of 224



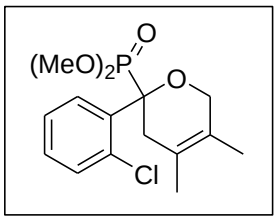
Diethyl (2-(2-fluorophenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 31 mg (24%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz):δ 1.15-1.93 (6H, m), 1.29 (3H, s), 1.63 (3H, s), 2.1 (1H, d, *J*=5.3 Hz), 3.78 (1H, d, *J*=15.8 Hz), 3.92-4.07 (5H, m), 6.91 (1H, dd, *J*=12.5 Hz and 8.1 Hz), 7.06 (1H, t, *J*=7.7 Hz), 7.17- 7.21 (1H, m), 7.55 (1H, t, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.6, 16.2 (d, J_{C-P} =2.8 Hz, -OCH_2CH_3), 16.3 (d, J_{C-P} =2.8 Hz, -OCH_2CH_3), 18.3, 33.4 (d, J_{C-P} =10.1 Hz, -CH_2-), 63.1 (d, J_{C-P} =2.9 Hz, -OCH_2CH_3), 63.1 (d, J_{C-P} =3.0 Hz, -OCH_2CH_3), 65.1 (d, J_{C-P}=11.1 Hz and, -OCH_2-), 75.6 (d, J_{C-F}=1.2, quaternary C atom), 116.5 (d, J_{C-P}=22.9 Hz), 122.0 (d, J_{C-P}=11.4 Hz), 122.5 (d, J_{C-P}=11.4 Hz), 123.1 (d, J_{C-P}=11.4 Hz), 123.6 (t, J_{C-P}=2.9 Hz), 129.6 (dd, J_{C-P}=3.0 and J_{C-F}=8.9 Hz), 131.3 (t, *J*=3.8 Hz), 160.7 (dd, J_{C-F}=250.0 and J_{C-P}=5.2 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 20.77; IR (ATR technique, cm^{-1}): 2926, 1485, 1249, 1021, 966, 759; HRMS: calculated for $C_{17}H_{24}FO_4P$ $[M+Na]^+$ 365.1294 and found 365.1295.

3.3.1.7 Characterization of 225



Diethyl (2-(4-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 63 mg (49%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.17 (6H, dt, J_{C-P} =2.1 and 7.0 Hz), 1.29 (3H, s), 1.62 (3H, s), 2.52 (1H, d, *J*=17.0 Hz), 2.88 (1H, t, *J*=13.8 Hz), 3.71 (1H, d, *J*=15.9 Hz), 3.84-4.06 (5H, m), 7.25 (2H, d, J_{C-C} =8.5 Hz), 7.36 (2H, dd, J_{C-C}=8.5 and J_{C-P}=2.3 Hz); ^{13}C NMR ($CDCl_3$, 100 M Hz): 13.7, 16.4 (d, J_{C-P} =5.6 Hz, -OCH_2CH_3), 18.7, 32.8 (-CH_2-), 63.2 (d, J_{C-P} =7.3 Hz, -OCH_2CH_3), 63.3 (d, J_{C-P} =7.0 Hz, -OCH_2CH_3), 64.7 (d, J_{C-P}=11.1 Hz, -OCH_2-), 76.9 (d, J_{C-P}=171.1 Hz, quaternary C atom), 120.9 (d, J_{C-P}=10.9 Hz), 123.7 (d, J_{C-P}=1.4 Hz), 128.2 (d, J_{C-P}=2.5 Hz), 129.3 (d, J_{C-P}=4.6 Hz), 133.7 (d, J_{C-P}=3.8 Hz), 135.1; ^{31}P NMR ($CDCl_3$,161 MHz): δ 21.14; IR (ATR technique, cm^{-1}): 2991, 1489, 1443, 1216, 747; HRMS: calculated for $C_{17}H_{24}ClO_4P$ $[M+Na]^+$ 381.0998 and found 381.1007.

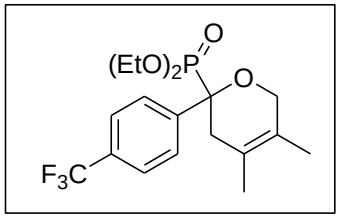
3.3.1.8 Characterization of 226



Dimethyl (2-(2-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 33 mg (25%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): 1.30 (3H, s), 1.65 (3H, s), 2.94 (1H, t, *J*=14.8 Hz), 3.25 (1H, d, J_{C-P}=17.0 Hz), 3.60 (3H, d, J_{C-P}=10.4 Hz), 3.67 (3H, d, *J*=10.4 Hz), 3.81 (1H, d, *J*=15.0 Hz), 3.97 (1H, d, *J*=15.8 Hz), 7.11-7.22 (1H, m), 7.18-7.22 (1H, m), 7.29 (1H, d (broad), *J*=7.79 Hz), 7.56 (1H, td, *J*=2.0 and 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.6, 18.3, 33.8 (-CH_2-), 53.7 (d, J_{C-P} =7.1 Hz, -OCH_3), 53.8 (d, J_{C-P} =7.1 Hz, -OCH_3), 65.3 (d, J_{C-P}=11.5 Hz, -OCH_2-), 78.7 (d, J_{C-P}=170.8 Hz, quaternary C atom), 121.5 ((d, J_{C-P}=11.2 Hz), 123.2 (d, J_{C-P}=1.4 Hz), 126.5 (d, J_{C-P}=2.5 Hz), 129.1 (d, J_{C-P}=2.9 Hz),

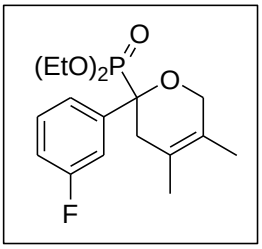
131.5 (d, J_{C-P}=4.4 Hz), 132.2 (d, J_{C-P}=2.6 Hz), 133.2, 133.4 (d, J_{C-P}=5.3 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 23.12; IR (ATR technique,cm^{-1}): 2919, 14265, 1250, 1024, 747; HRMS: calculated for $C_{15}H_{20}ClO_4P$ $[M+Na]^+$ 353.0685 and found 353.0690.

3.3.1.9 Characterization of 227



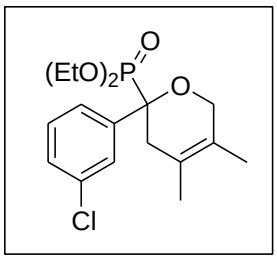
Diethyl (4,5-dimethyl-2-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran-2-yl)- phosphonate: Yield 99 mg (79%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.12 (6H, dt, J_{C-P} =5.1 and 7.1 Hz), 1.25 (3H, s), 1.60 (3H, s), 2.54 (1H, d, *J*=17.0 Hz), 2.92 (1H, t, *J*=14.6 Hz), 3.70 (1H, d, *J*=15.7 Hz), 3.84-4.03 (5H, m), 7. 50 (4H, t, *J*=10.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.6, 16.2 (d, J_{C-P} =6.0 Hz, -OCH_2CH_3), 18.5, 32.8 (-CH_2-), 63.1 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 63.2 (J_{C-P} =7.1 Hz, -OCH_2CH_3), 64.7 (d, J_{C-P}=11.0 Hz, -OCH_2-), 77.0 (d, J_{C-P}=170.0 Hz, quaternary C atom), 120.8 (d, J_{C-P}=10.8 Hz), 123.6 (d, J_{C-P}=1.3 Hz), 124.8 (t, J_{C-P}=3.3 Hz), 127.3 (dd, J_{C-P}=3.8 and J_{C-F}=69.7 Hz), 128.1 (d, J_{C-P}=4.5 Hz), 129.7 (dq, J_{C-P}=3.2 and J_{C-F}=32.4 Hz), 140.9; ^{31}P NMR ($CDCl_3$,161 MHz): δ 22.34; IR (ATR technique, cm^{-1}): 2956, 2917, 1448, 1325, 1122, 1110, 755; HRMS: calculated for $C_{18}H_{24}F_3O_4P$ $[M+Na]^+$ 415.1262 and found 415.1289.

3.3.1.10 Characterization of 228



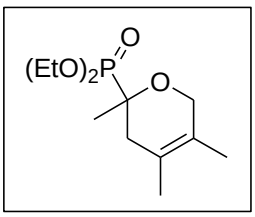
Diethyl (2-(3-fluorophenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 73 mg (56%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.22 (6H, q, J_{C-P} =7.1 Hz), 1.37 (3H, s), 1.70 (3H, s), 2.60 (1H, d, *J*=17.0 Hz), 2.97 (1H, t, *J*=13.5 Hz), 3.85 (1H, d, *J*=15.8 Hz), 3.91-4.15 (5H, m), 6.97 (1H, t, *J*=9.2 Hz), 7.21-7.35 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.6, 16.1 (d, J_{C-P} =2.6 Hz, -OCH_2CH_3), 16.2 (d, J_{C-P} =2.5 Hz, -OCH_2CH_3), 18.5, 32.8 (-CH_2-), 63.0 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 63.1 (J_{C-P} =7.1 Hz, -OCH_2CH_3), 64.6 (d, J_{C-P}=11.0 Hz and , -OCH_2-), 76.8 (d, J_{C-P}=170.0 Hz and J_{C-F}=1.2, quaternary C atom), 114.4 (dd, J_{C-F}=21.1 and J_{C-P}=3.0 Hz), 114.8 (dd, J_{C-F}=23.2 and J_{C-P}=4.7 Hz), 120.8 (t, J_{C-P}=10.8 Hz), 123.3 (dd, J_{C-P}=4.4 and J_{C-F}=2.9 Hz), 123.5 (d, J_{C-P}=1.2 Hz), 129.2 (dd, J_{C-P}=8.0 and J_{C-F}=2.6 Hz), 139.4 (d, J_{C-F}=6.7 Hz), 162.5 (dd, J_{C-F}=244.8 and J_{C-P}=3.0 Hz); ^{31}P NMR ($CDCl_3$,161 MHz): δ 20.96; IR (ATR technique, cm^{-1}): 2989, 2926, 1442, 1244, 1021, 967, 748; HRMS: calculated for $C_{17}H_{24}FO_4P$ $[M+Na]^+$ 365.1294 and found 365.1302.

3.3.1.11 Characterization of 229



Diethyl (2-(3-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 54 mg (42%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.17 (6H, dt, J_{C-P} =7.1 Hz and 11.9 Hz), 1.30 (3H, s), 1.63 (3H, s), 2.52 (1H, d, *J*=17.0 Hz), 2.88 (1H, t, *J*=12.7 Hz), 3.76 (1H, d, *J*=15.8 Hz), 3.84-4.06 (5H, m), 7.20-7.22 (2H, m), 7.29-7.32 (1H, m), 7.42 (1H, d, *J*=1.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.8, 16.2 (d, J_{C-P} =3.6 Hz, -OCH_2CH_3), 16.3 (d, J_{C-P} =3.6 Hz, -OCH_2CH_3), 18.7, 32.8 (-CH_2-), 63.2 (J_{C-P} =7.3 Hz, -OCH_2CH_3), 63.3 (J_{C-P} =7.1 Hz, -OCH_2CH_3), 64.7 (d, J_{C-P}=11.0 Hz and , -OCH_2-), 77.0 (d, J_{C-P}=170.7 Hz, quaternary C atom), 120.9 (d, J_{C-P}=10.8 Hz), 123.6 (d, J_{C-P}=1.7 Hz), 126.0 (d, J_{C-P}=4.8 Hz), 127.9 (d, J_{C-P}=3.0 Hz), 128.0 (d, J_{C-P}=4.8 Hz), 129.3 (d, J_{C-P}=2.7 Hz), 134.0 (d, J_{C-P}=3.1 Hz), 138.9; ^{31}P NMR ($CDCl_3$,161 MHz): δ 20.91; IR (ATR technique, cm^{-1}): 2925, 1445, 1241, 1022, 750; HRMS: calculated for $C_{17}H_{24}ClO_4P$ $[M+Na]^+$ 381.0998 and found 381.1006.

3.3.1.12 Characterization of 231



Diethyl (2,4,5-trimethyl-3,6-dihydro-2H-pyran-2-yl)phosphonate: Yield 64 mg (44%), yellow oil; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.34 (6H, dt, J_{C-P}=1.7 and 7.0 Hz), 1.45 (3H, d, J_{C-P}=15.7 Hz, -CH_3), 1.54 (3H, s), 1.67 (3H, s) 1.79 (1H, d, *J*=16.6 Hz), 2.59 (1H, t, *J*=13.9 Hz), 3.99 (2H, s), 4.16-4.23 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.7, 16.4 (d, J_{C-P} =5.3 Hz, -OCH_2CH_3), 18.4, 18.8, 35.1 (-CH_2-), 62.49 (J_{C-P} =2.0 Hz, -OCH_2CH_3), 62.54 (J_{C-P}=2.0 Hz, -OCH_2CH_3), 64.2 (d, J_{C-P}=10.3 Hz and , -OCH_2-), 72.2 (d, J_{C-P}=173.7 Hz, quaternary C atom), 120.6 (d, J_{C-P}=9.3 Hz), 123.0; ^{31}P NMR ($CDCl_3$,161 MHz): δ 24.94; IR (ATR technique, cm^{-1}): 2979, 1243, 1020, 957, 790, 631; HRMS: calculated for $C_{12}H_{23}O_4P$ $[M+Na]^+$ 285.1232 and found 285.1237

CHAPTER 4

CONCLUSIONS

In this dissertation, a new method has been developed for the synthesis of secondary and tertiary α-hydroxy phosphonates by 1,2-addition reactions of commercially available trialkylaluminum reagent to a series of substituted benzoyl phosphonates and alkanoyl phosphonates. All trialkylaluminum reagents used in this part of the dissertation are commercially available. Desired α-hydroxy phosphonates were synthesized in moderate to good yields depending on the reaction conditions. In the trials of trimethylaluminum reagent to acyl phosphonates, tertiary α-hydroxy phosphonates were attained at 0 °C. The addition of triethylaluminum to acyl phosphonates at 0 °C led to the formation of hydride addition products. By changing the temperature from 0 °C to -100 °C , the ethylation of acyl phosphonates gave the tertiary α-hydroxy phosphonates without the cleavage of C-P bond albeit in low yields. By this method, we provide a convenient access to secondary and tertiary α-hydroxy phosphonates in resonable yields and short reaction times. We have also reported first organoalumnium addition to acyl phosphonate derivatives that yielded α-hydroxy phosphonates without the C-P bond breakage.

In the second part of this thesis (section 2.2), we extended our research to addition of trialkynylaluminum reagents to acyl phosphonates. Ttrialkynylaluminum reagents are not available commercially; for that reason they were prepared and used freshly prior to each reaction. For the alkynylation of acyl phosphonates, three different organoaluminum reagents, triethynylaluminum, tris-(propynyl)aluminum, and tris-(phenylethynyl) aluminum were used. α-Hydroxy propargylic phosphonates having C-P bond were attained in moderate to good yields. Generally alkynylation reactions of acyl phosphonates works better with aryl substituted acyl phosphonates than the alkyl substituted ones. Moreover, the electronic features of the aromatic moiety affected the chemical yield. Electron-withdrawing group on the phenyl ring gave a

better chemical yield than electron donating groups.. This route offers a simple and efficient method for the synthesis of tertiary propargylic phosphonates.

In the last part of this theses (section 2.3), we have studied hetero Diels-Alder reactions of acyl phosphonates with 2,3-dimethy-1,3-butadine in the presence of a Lewis acid. Lewis acid screening studies showed that $AlCl_3$ was the most effective Lewis acid catalyst for this reaction. From these reactions, glycosyl type phosphonates were obtained in moderate yields.

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APPENDIX A

NMR AND HRMS SPECTRA OF COMPOUNDS SYNTHESIZED IN THE FIRST PART

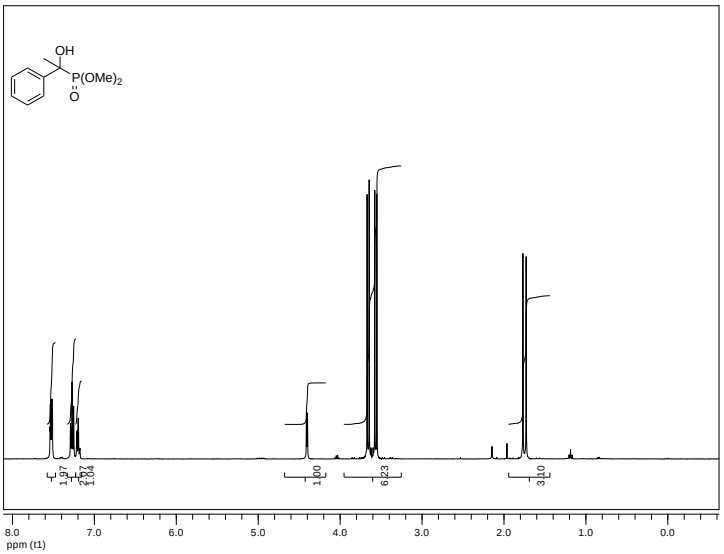


Figure A1. ^{1}H NMR spectrum of **131**

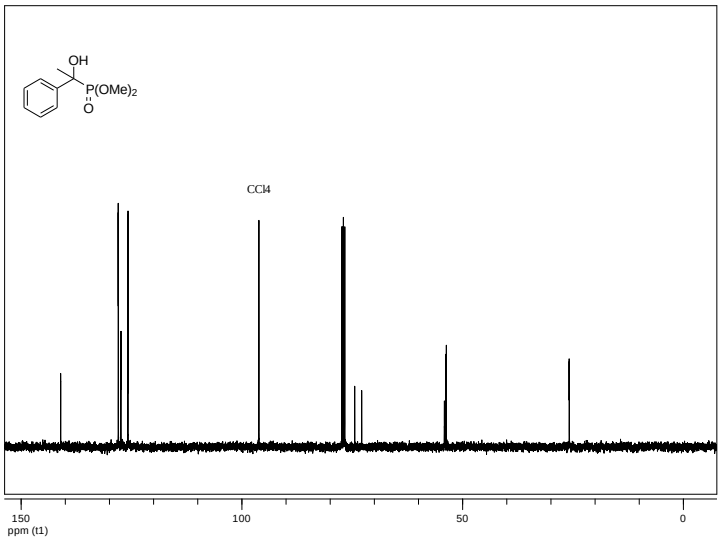


Figure A2. ^{13}C NMR spectrum of **131**

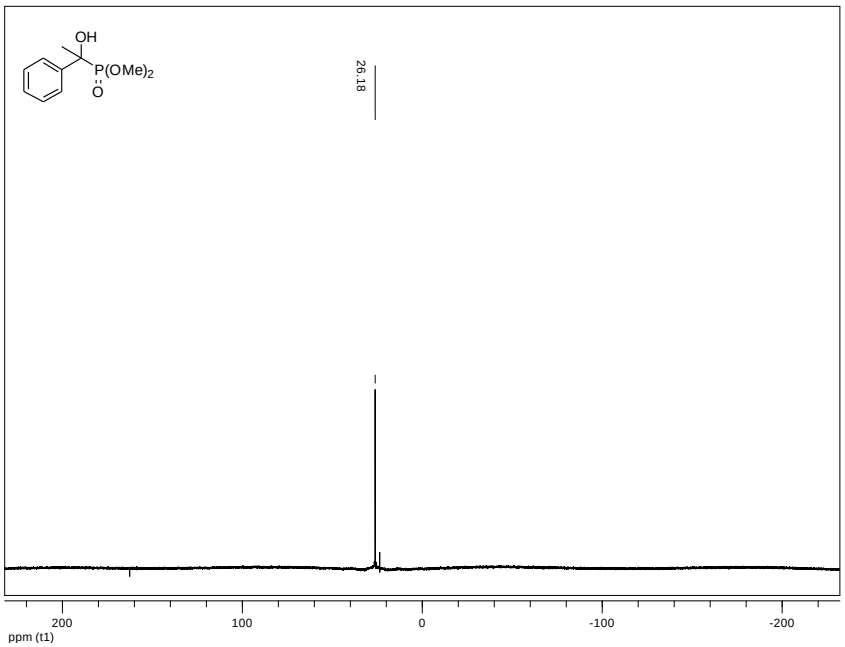
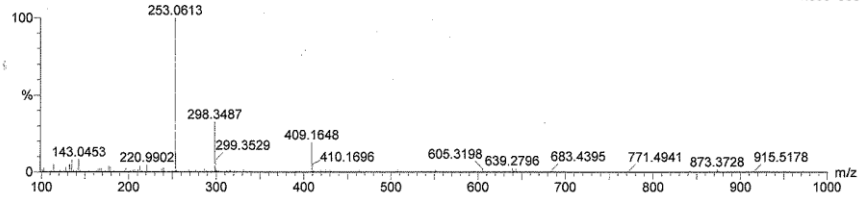


Figure A3. ^{31}P NMR spectrum of **131**

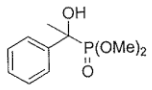
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
26 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 1-1
5275 ASD
20100902_SPC01_01 225 (0.788) Cm (208:282) 1: TOF MS ES+ 1.09e+006



Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
253.0613	253.0606	0.7	2.8	3.5	871.1	0.0	C10 H15 O4 Na P



2a

Figure A4. HRMS of compound **131**

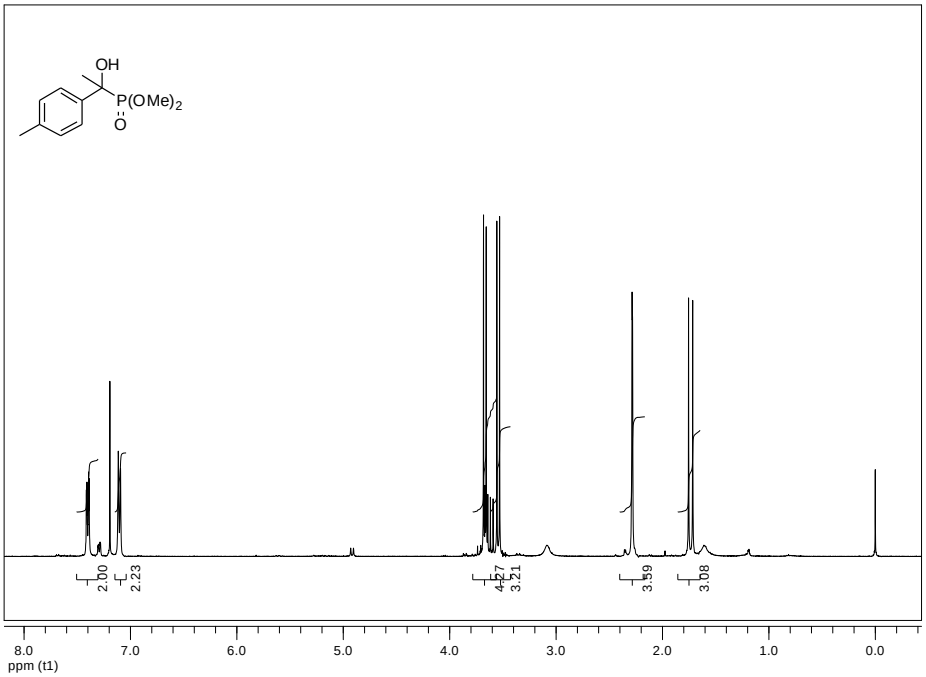


Figure A5. ^{1}H NMR spectrum of **135**

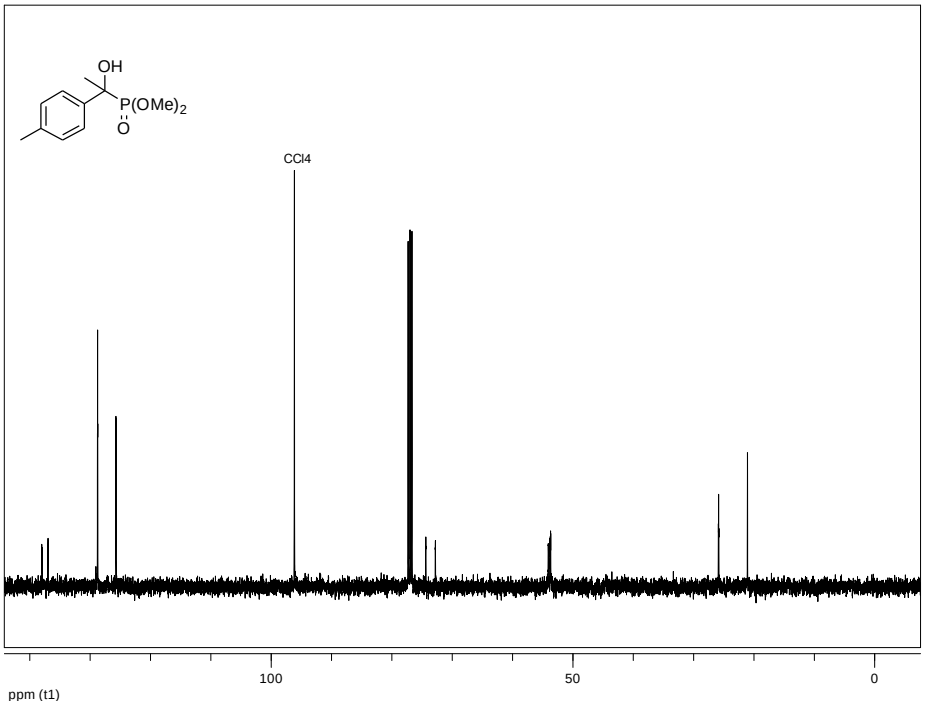


Figure A6. ^{13}C NMR spectrum of **135**

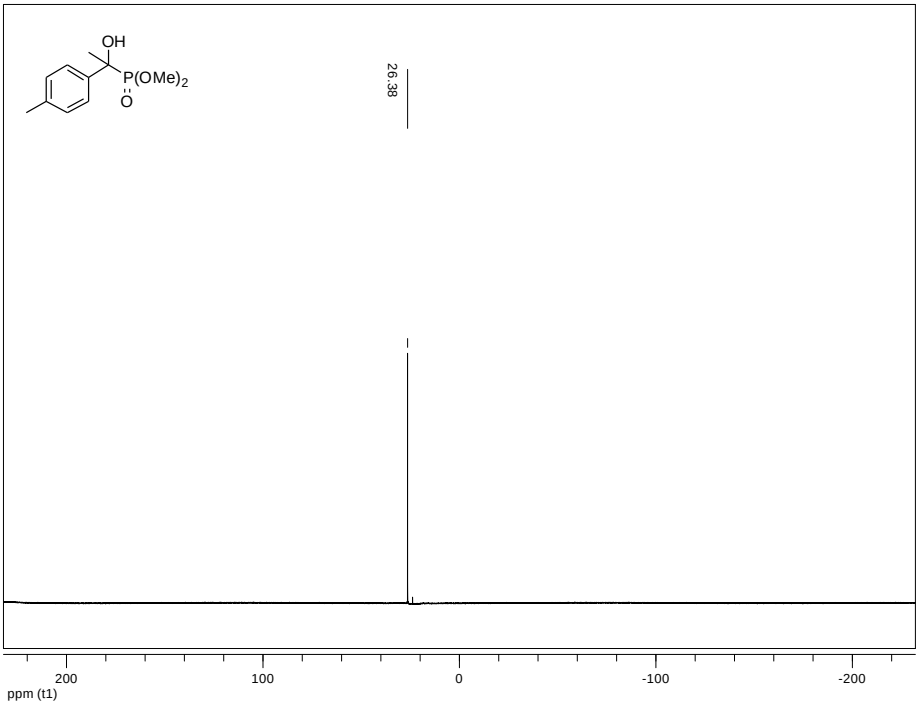
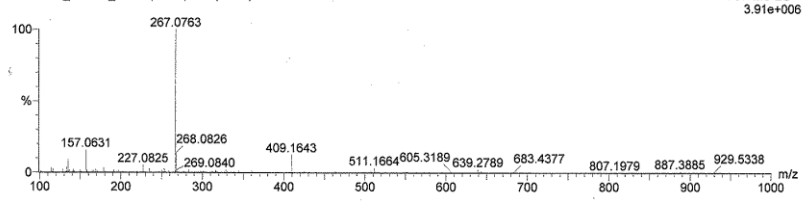


Figure A7. ^{31}P NMR spectrum of **135**

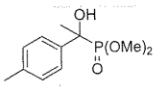
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 1-1
5275 ASD
20100902_SPC02_02 31 (0.124) Cm (2:198) 1: TOF MS ES+ 3.91e+006



Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
267.0763	267.0762	0.1	0.4	3.5	1027.1	0.0	C11 H17 O4 Na P



2b

Figure A8. HRMS of compound **135**

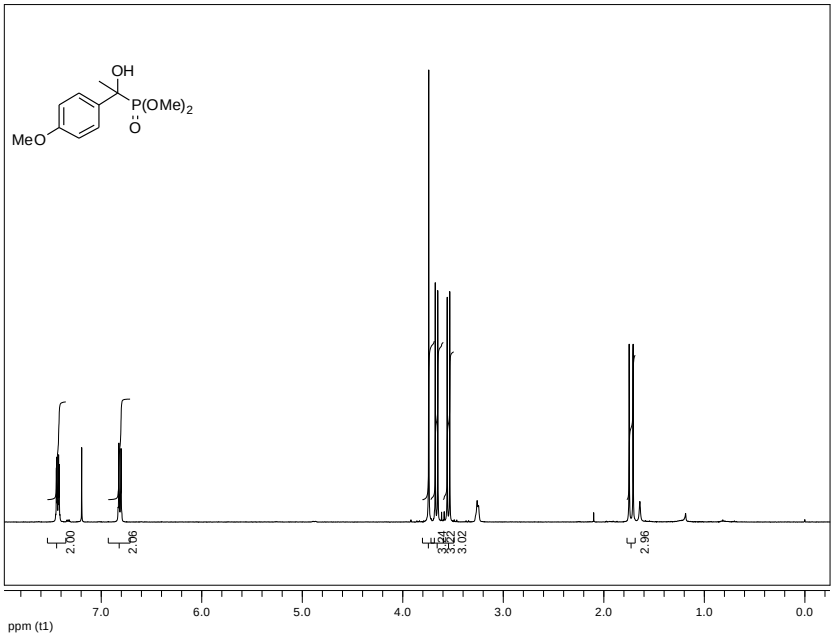


Figure A9. ^{1}H NMR spectrum of **137**

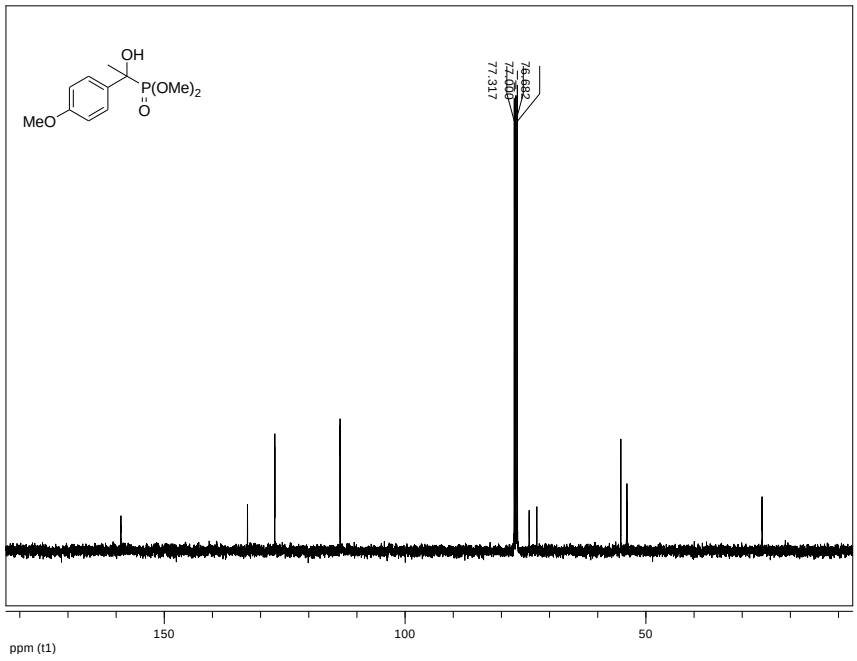


Figure A10. ^{13}C NMR spectrum of **137**

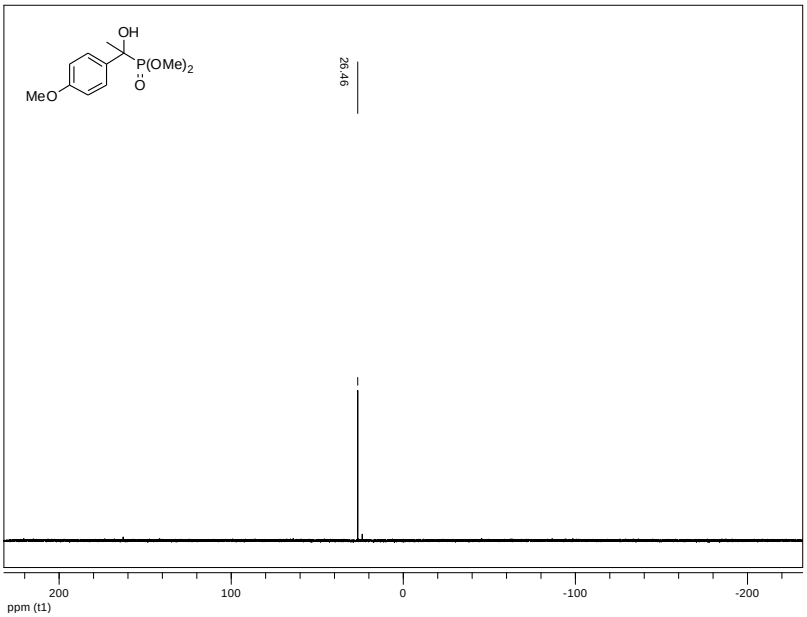
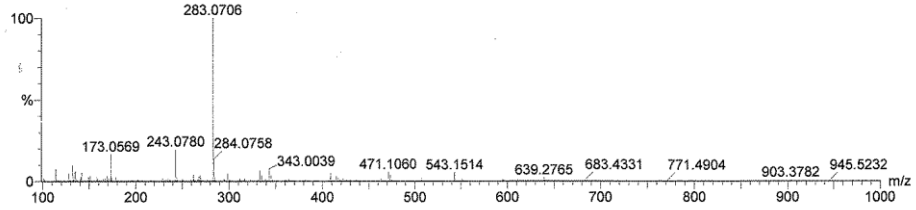


Figure A11. ^{31}P NMR spectrum of **137**

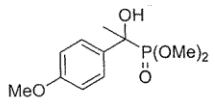
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
27 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 1-1
5275 ASD
20100902_SPC03_01 16 (0.074) Cm (1:282) 1: TOF MS ES+ 2.51e+006



Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
283.0706	283.0711	-0.5	-1.8	3.5	1002.7	0.0	C11 H17 O5 Na P



2c

Figure A12. HRMS of compound **137**

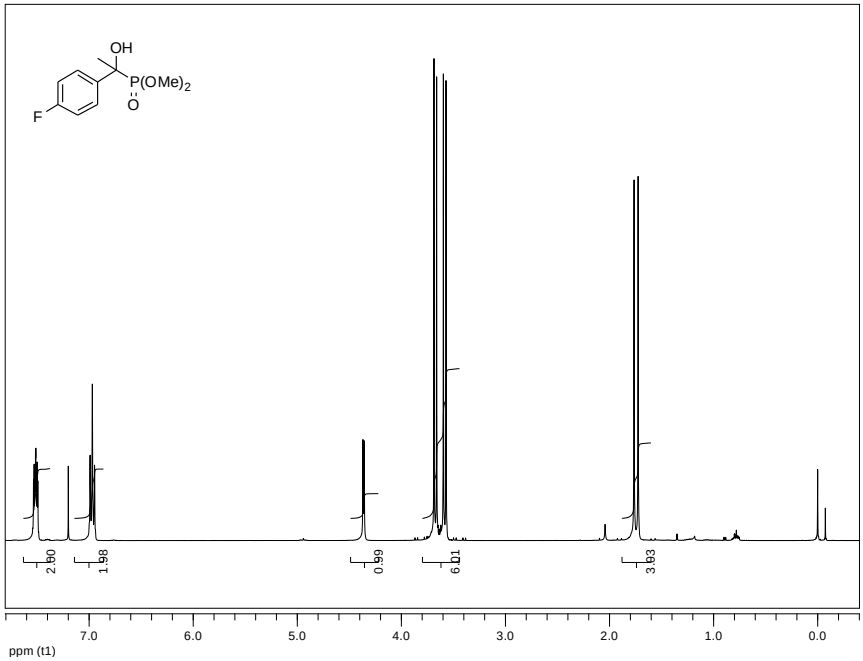


Figure A13. ^{1}H NMR spectrum of **139**

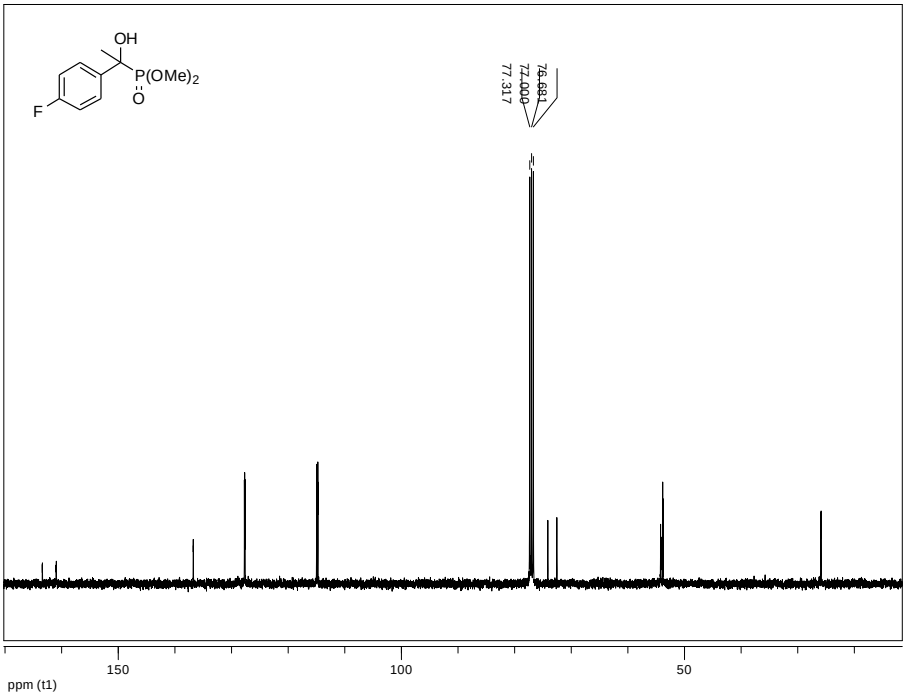


Figure A14. ^{13}C NMR spectrum of **139**

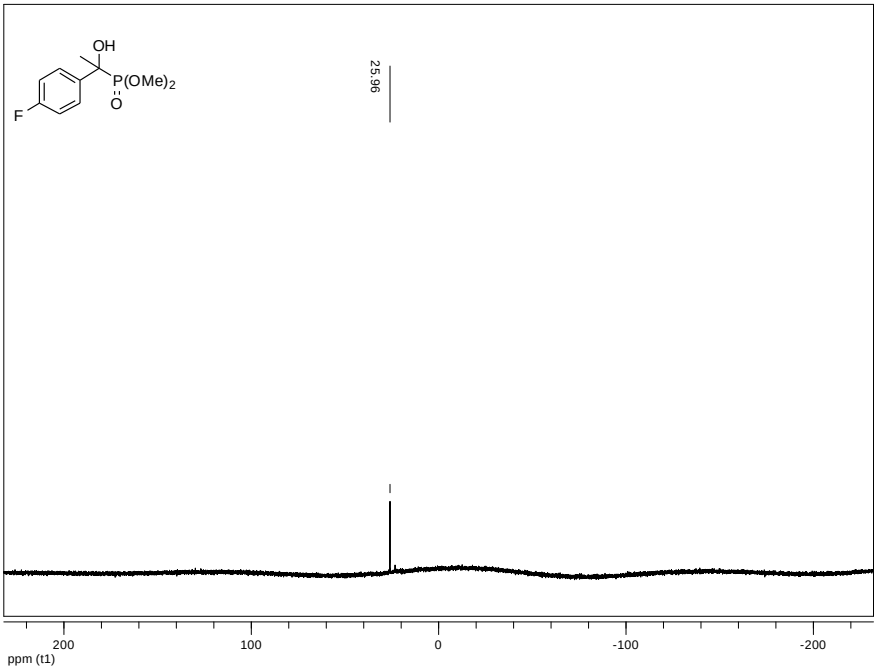
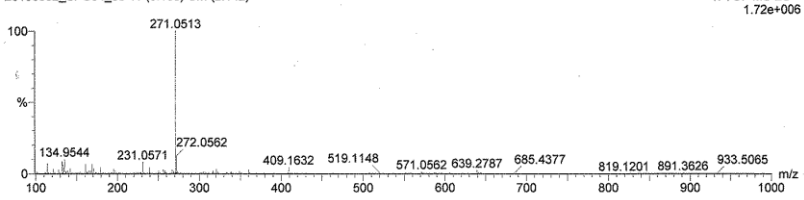


Figure A15. ^{31}P NMR spectrum of **139**

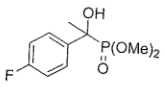
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
54 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 F: 0-1 Na: 0-1 P: 1-1
5275 ASD
20100902_SPC04_03 41 (0.158) Cm (2:142) 1: TOF MS ES+ 1.72e+006



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
271.0513	271.0511	0.2	0.7	3.5	902.8	0.1	C10 H14 O4 F Na P
	271.0524	-1.1	-4.1	10.5	907.1	4.3	C15 H12 O3 P
	271.0500	1.3	4.8	7.5	906.0	3.3	C13 H13 O3 Na P



2d

Figure A16. HRMS of compound **139**

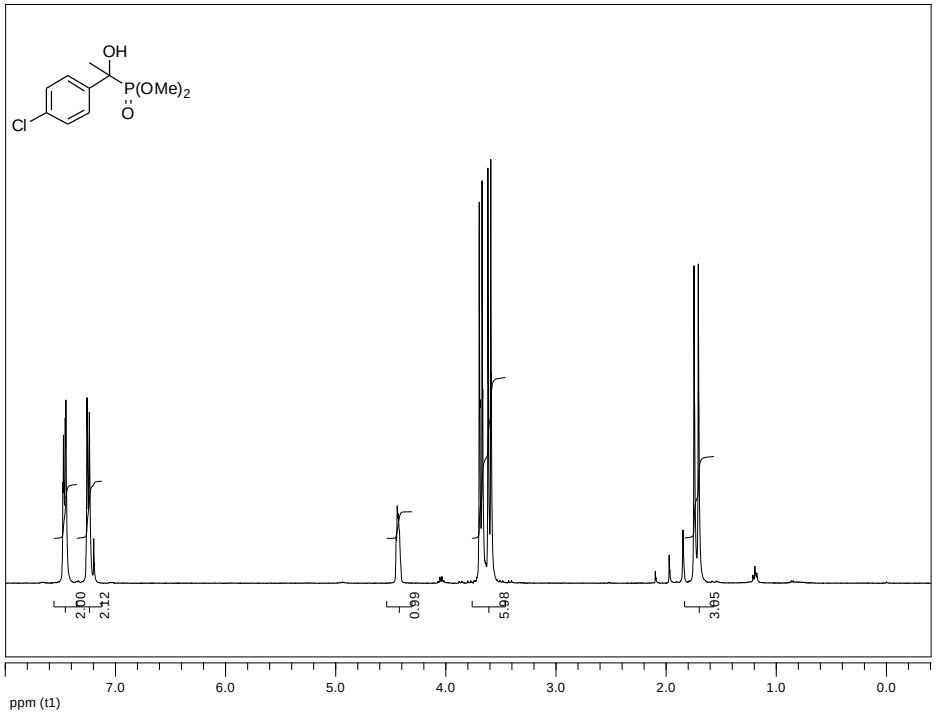


Figure A17. ^{1}H NMR spectrum of **141**

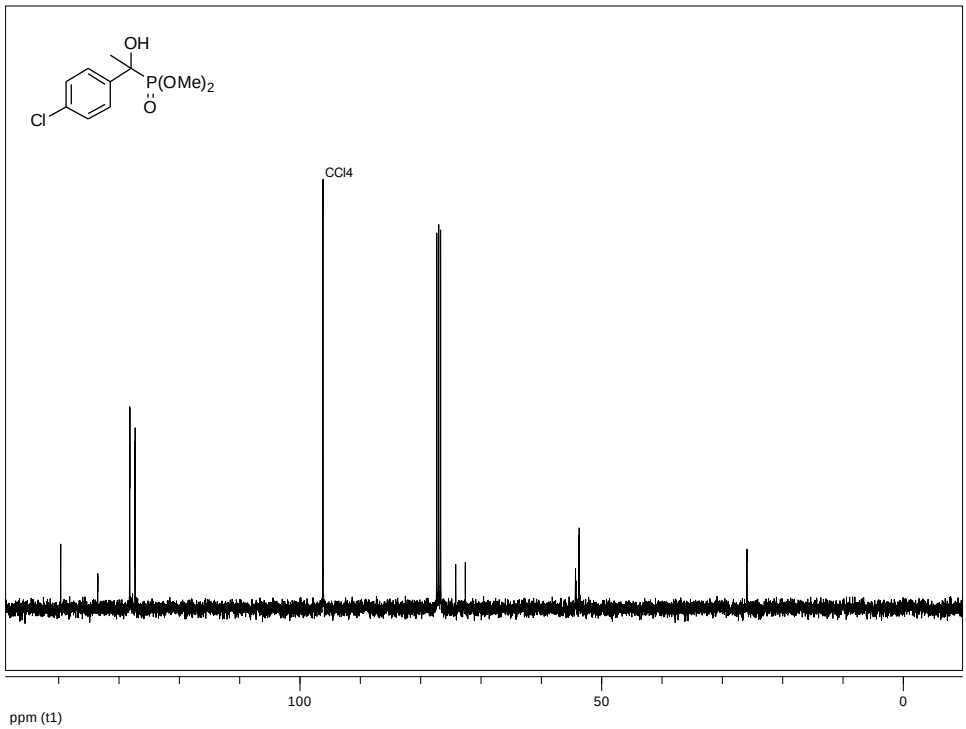


Figure A18. ^{13}C NMR spectrum of **141**

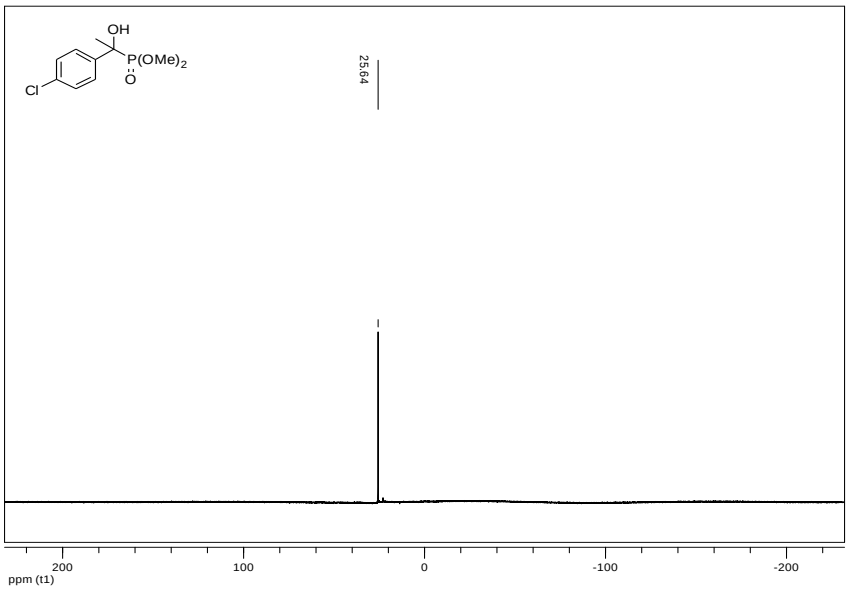


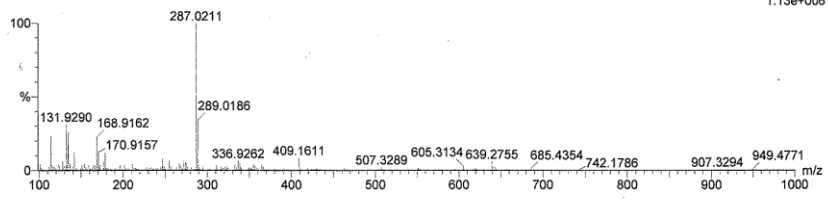
Figure A19. ^{31}P NMR spectrum of **141**

Elemental Composition Report **Page 1**

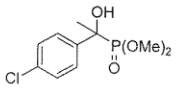
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
53 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 1-1 Cl: 0-1
5275 ASD
20100902_SPC05_02 258 (0.903) Cm (1:286)

1: TOF MS ES+
1.13e+006



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
287.0211	287.0216	-0.5	-1.7	3.5	910.4	0.0	C10 H14 O4 Na P Cl
	287.0238	-2.7	-9.4	12.5	936.7	26.3	C16 H9 O2 Na P



2e

Figure A20. HRMS of compound **141**

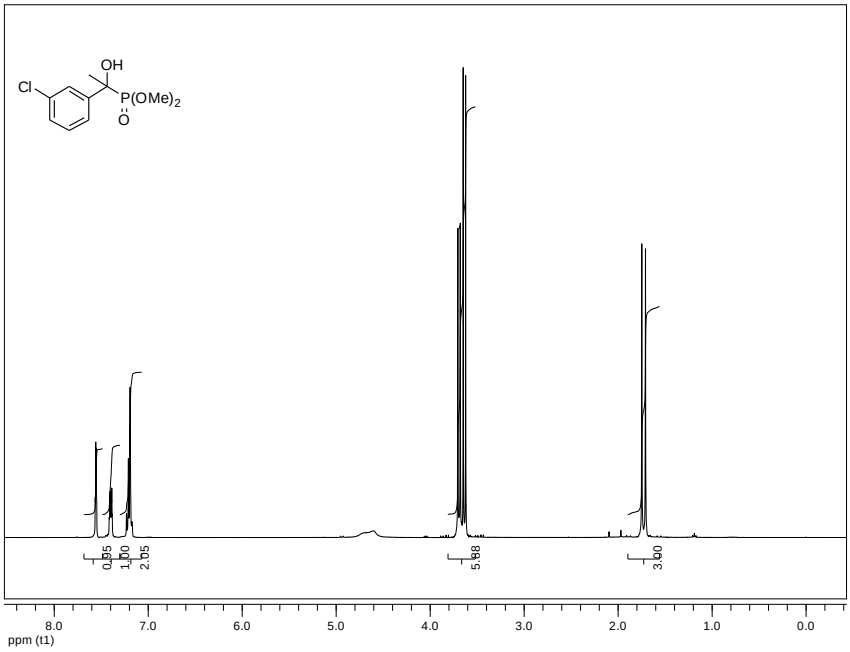


Figure A21. ^{1}H NMR spectrum of **143**

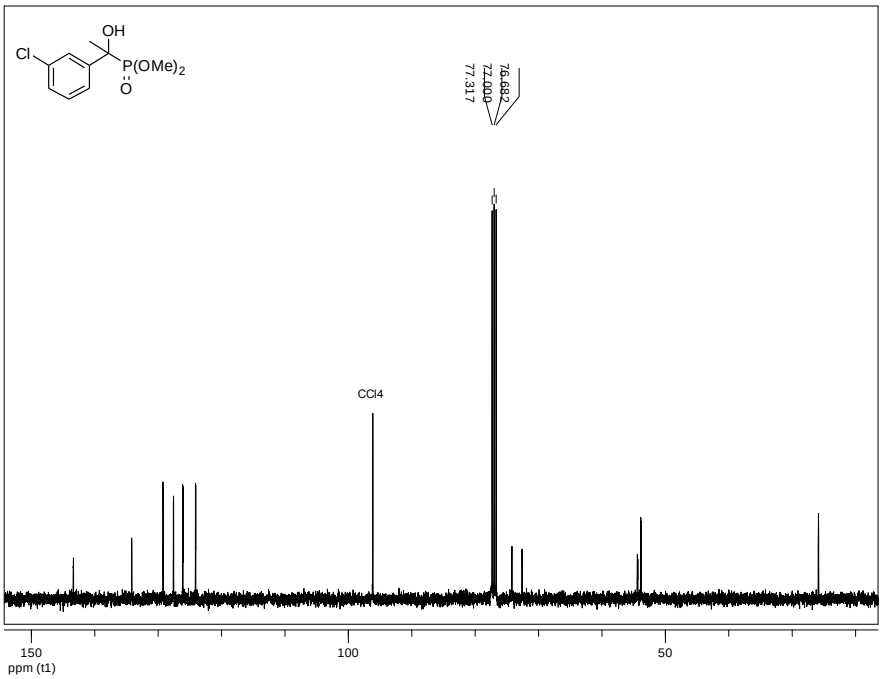


Figure A22. ^{13}C NMR spectrum of **143**

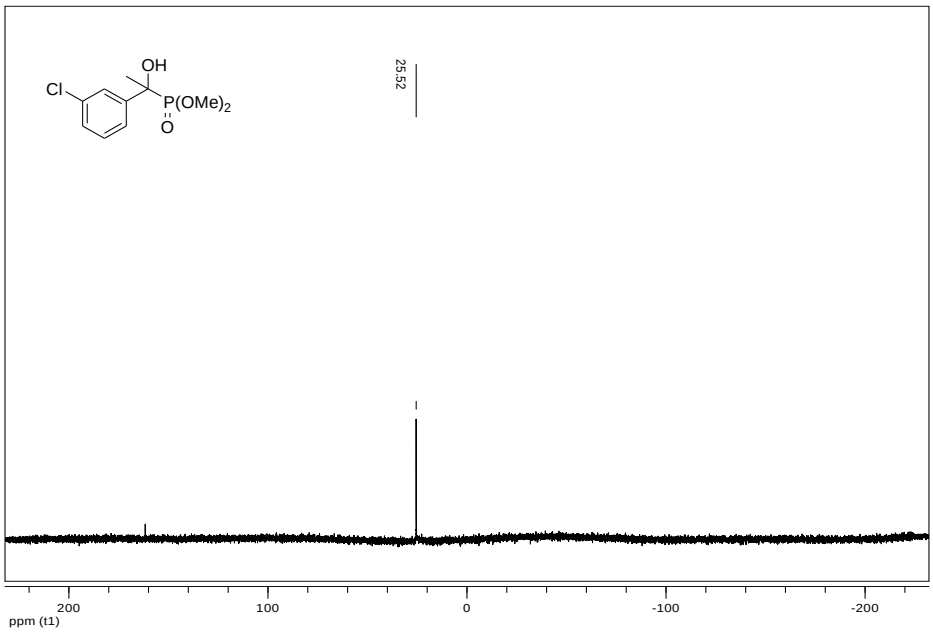


Figure A23. ^{31}P NMR spectrum of **143**

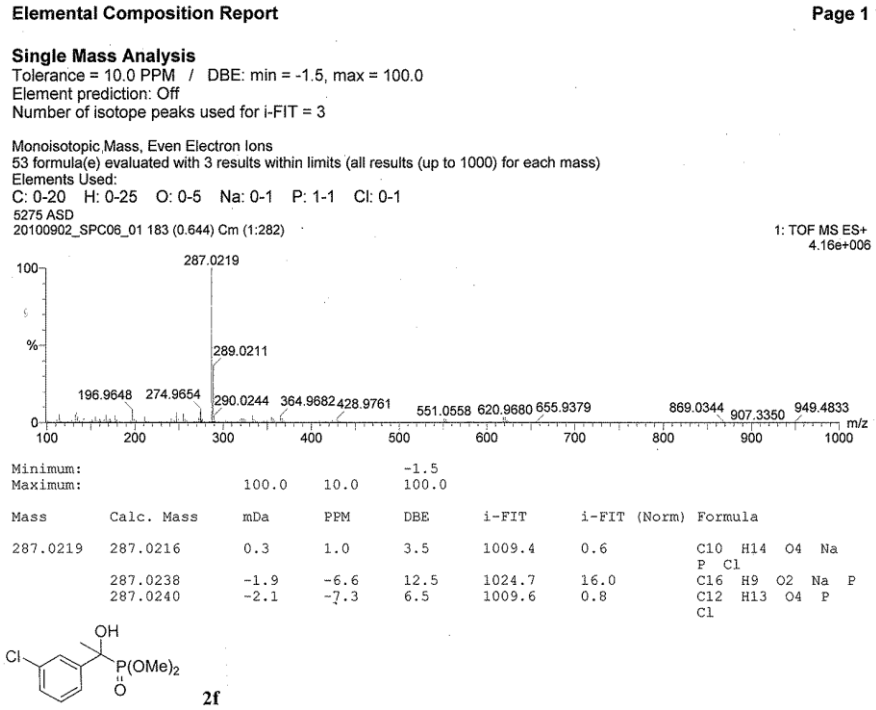


Figure A24. HRMS of compound **143**

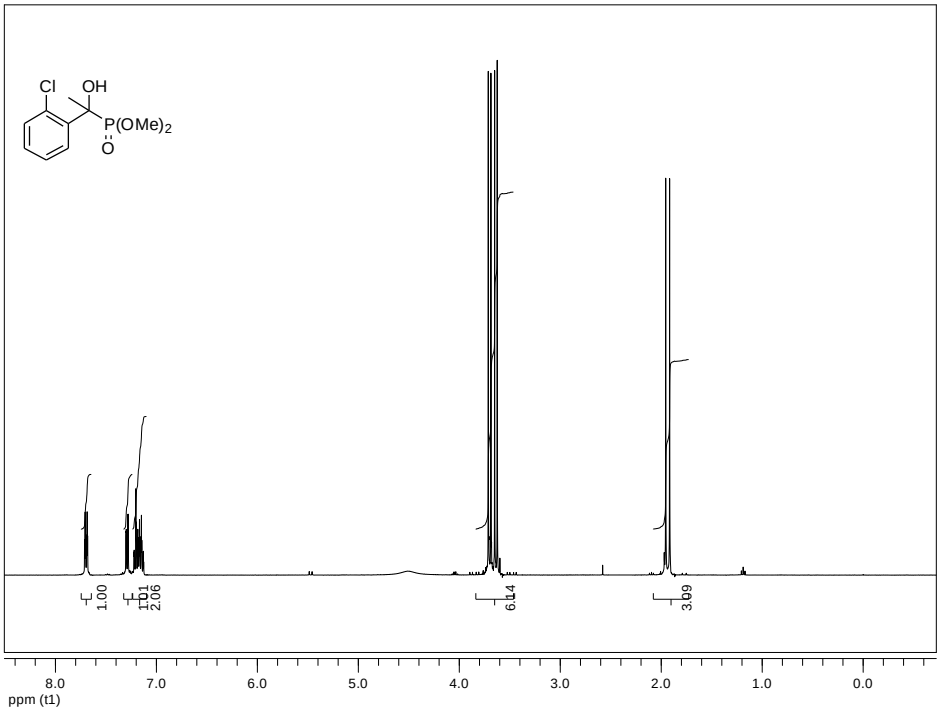


Figure A25. ^{1}H NMR spectrum of **145**

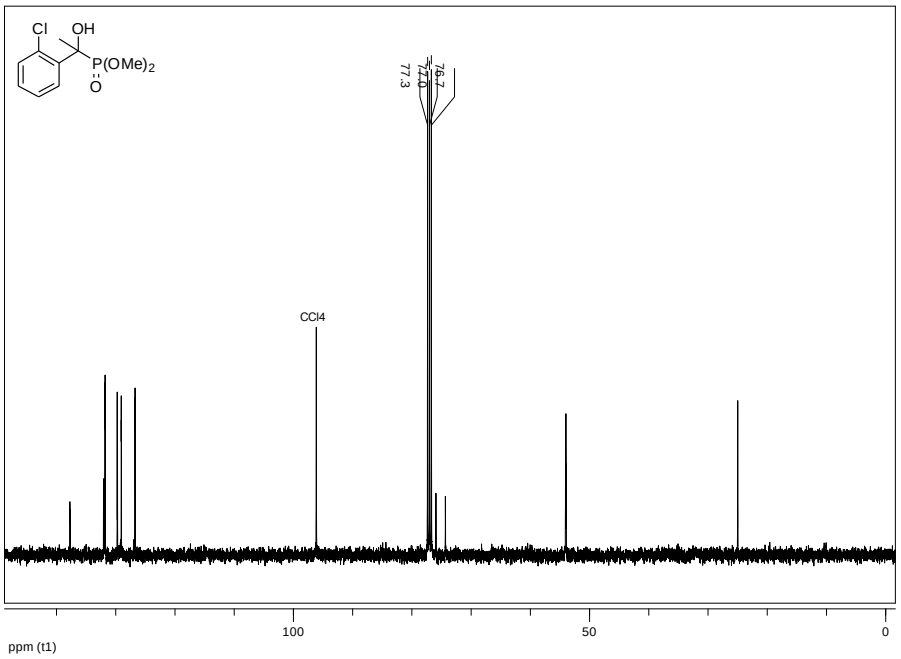


Figure A26. ^{13}C NMR spectrum of **145**

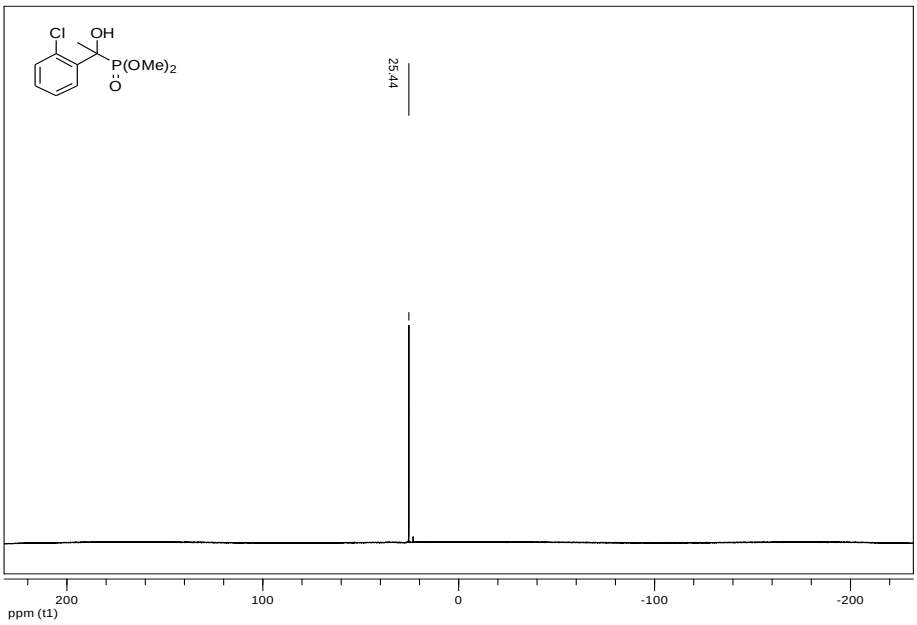
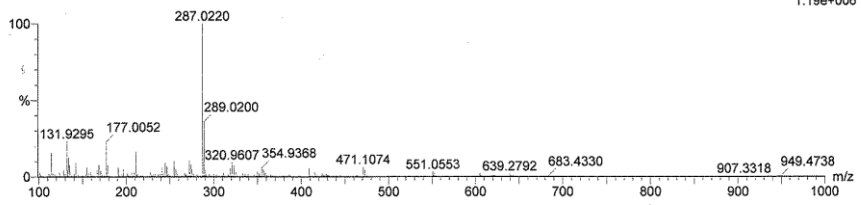


Figure A27. ^{31}P NMR spectrum of **145**

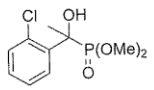
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
53 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 1-1 Cl: 0-1
5275 ASD
20100902_SPC07_01 207 (0.728) Cm (74:284) 1: TOF MS ES+ 1.19e+006



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
287.0220	287.0216	0.4	1.4	3.5	902.6	0.1	C10 H14 O4 Na P Cl
	287.0238	-1.8	-6.3	12.5	924.0	21.5	C16 H9 O2 Na P
	287.0240	-2.0	-7.0	6.5	905.1	2.6	C12 H13 O4 P Cl



2g

Figure A28. HRMS of compound **145**

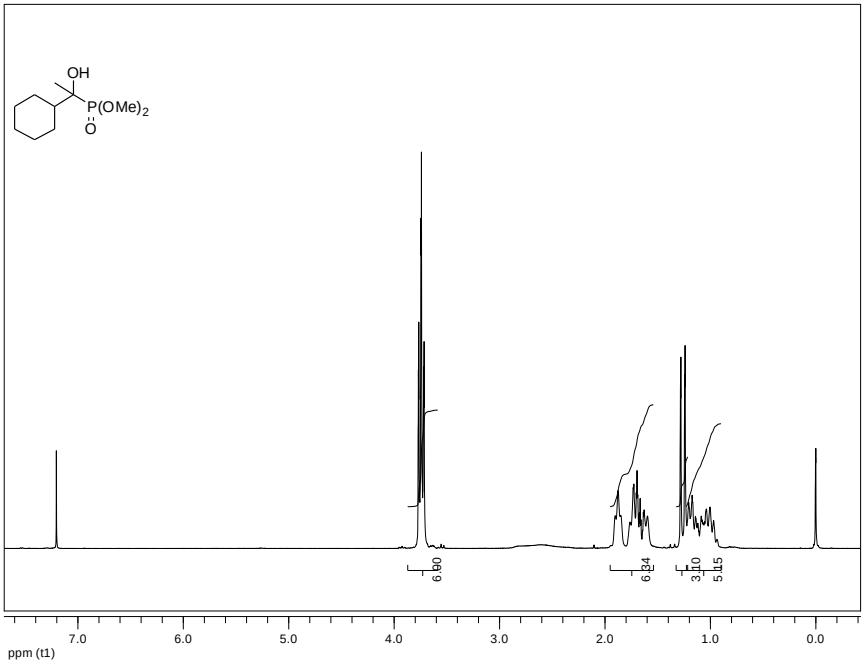


Figure A29. ^{1}H NMR spectrum of **147**

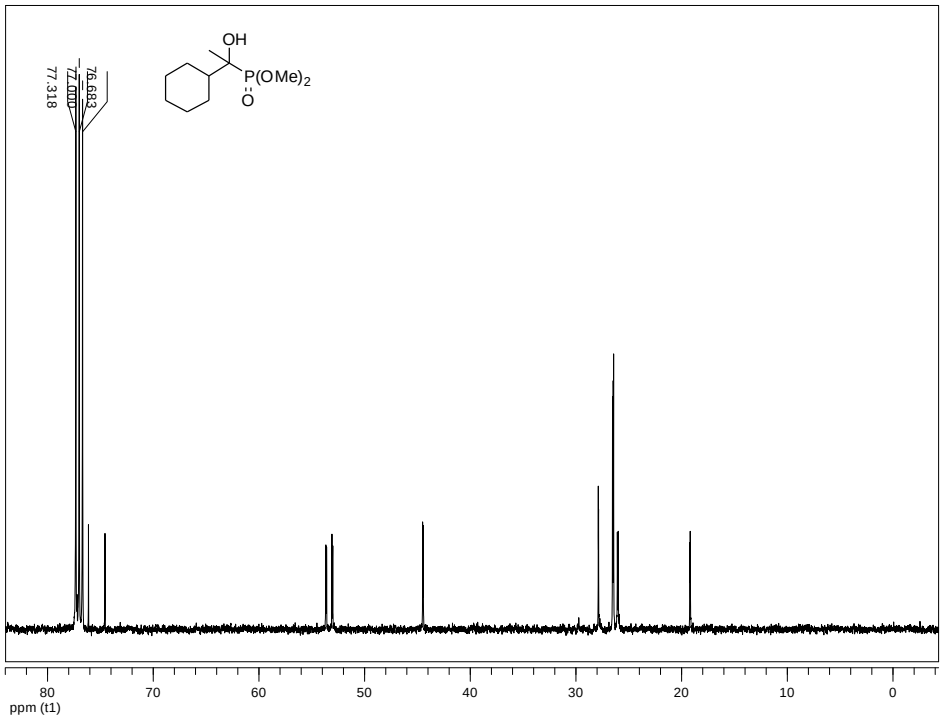


Figure A30. ^{13}C NMR spectrum of **147**

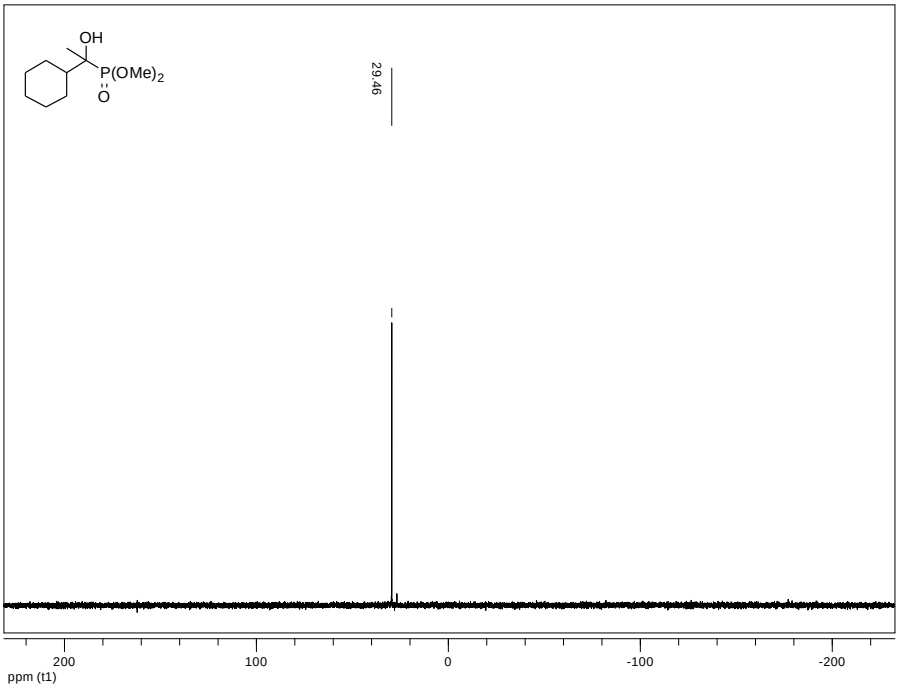
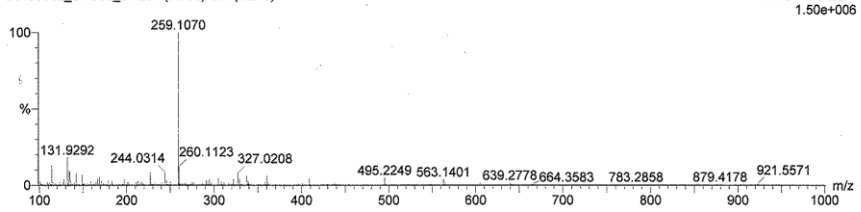


Figure A31. ^{31}P NMR spectrum of **147**

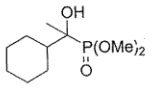
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
55 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 0-1
5275 ASD
20100902_SPC08_01 201 (0.708) Cm (1:213) 1: TOF MS ES+ 1.50e+006



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
259.1070	259.1075	-0.5	-1.9	0.5	949.3	0.0	C10 H21 O4 Na P



2h

Figure A32. HRMS of compound **147**

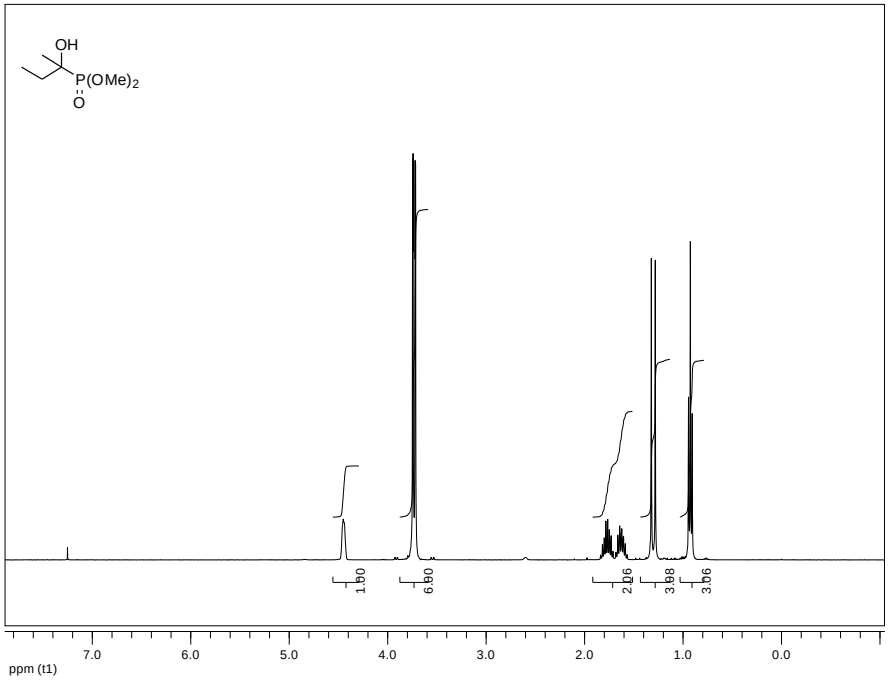


Figure A33. ^{1}H NMR spectrum of **149**

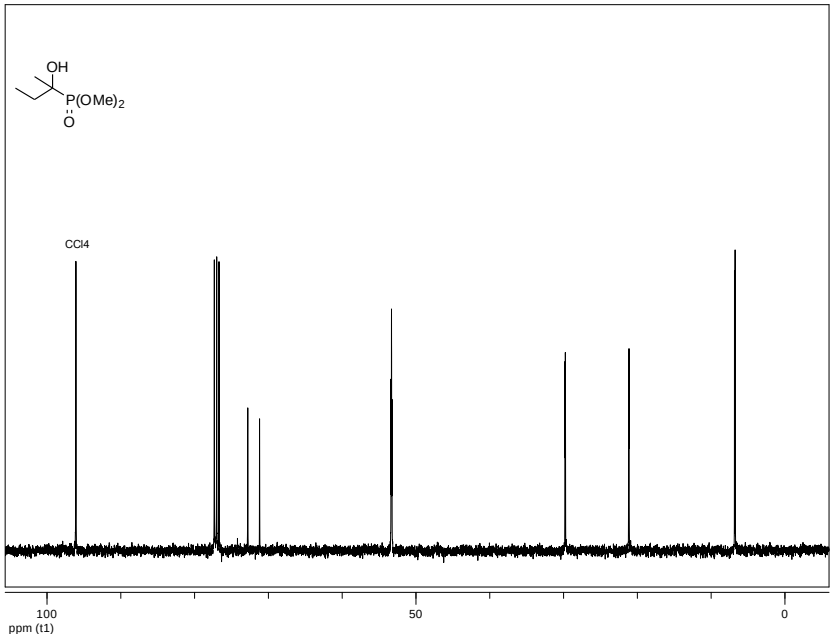


Figure A34. ^{13}C NMR spectrum of **149**

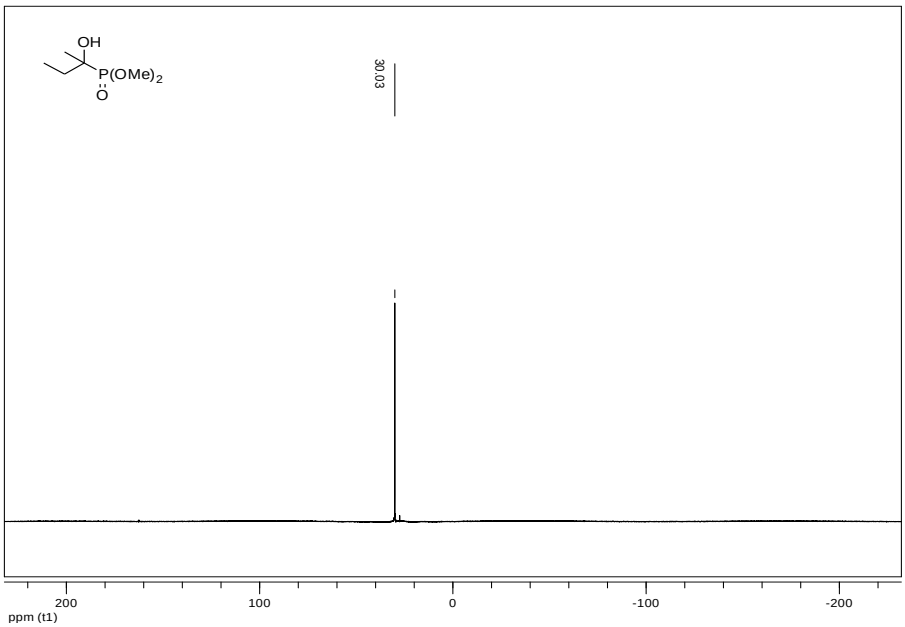


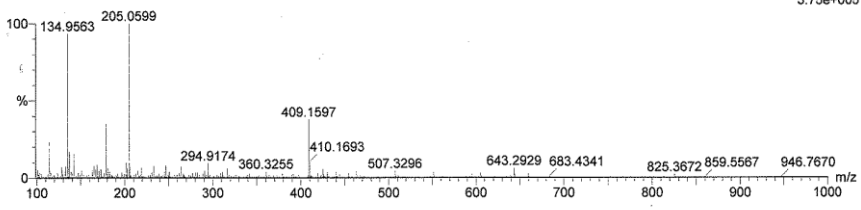
Figure A35. ^{31}P NMR spectrum of **149**

Elemental Composition Report **Page 1**

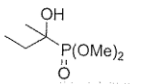
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
51 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 0-1
5275 ASD
20100902_SPC09_01 96 (0.345) Cm (1:141)

1: TOF MS ES+
3.75e+005



Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
205.0599	205.0606	-0.7	-3.4	-0.5	818.9	0.0	C6 H15 O4 Na P



2i

Figure A36. HRMS of compound **149**

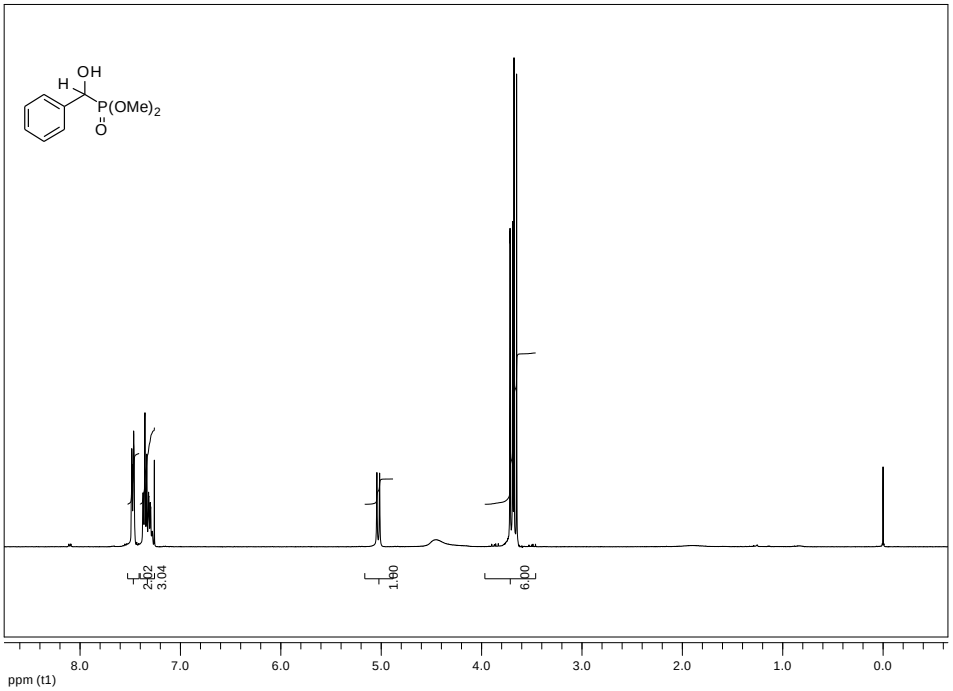


Figure A37. ^{1}H NMR spectrum of **150**

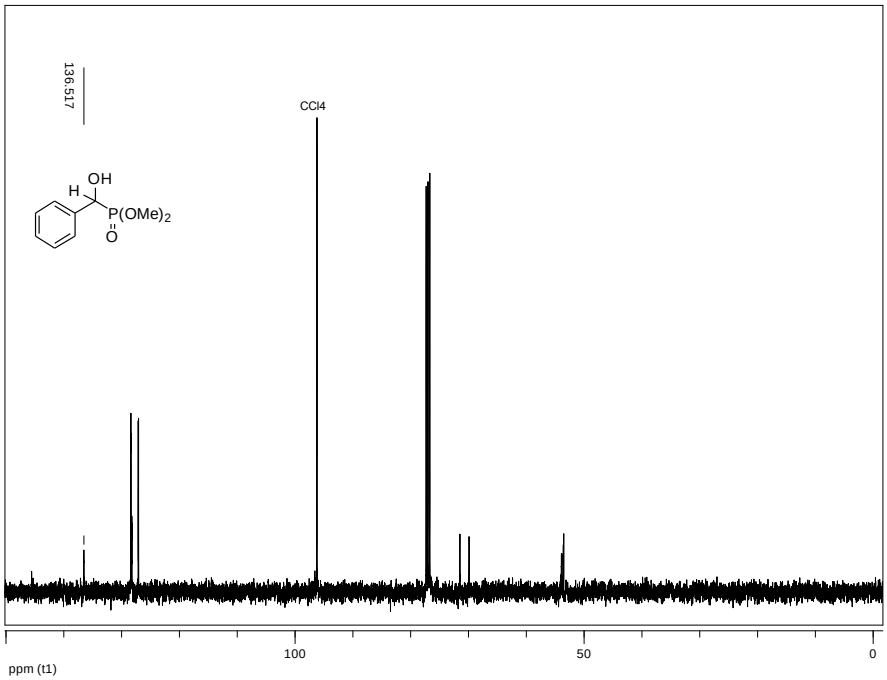


Figure A38. ^{13}C NMR spectrum of **150**

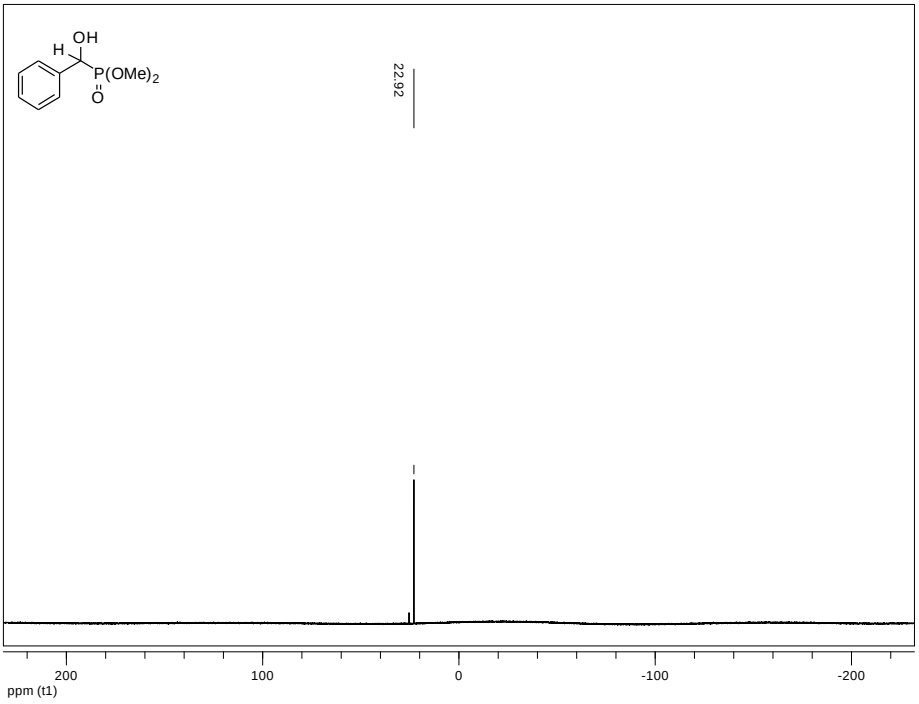


Figure A39. ^{31}P NMR spectrum of **150**

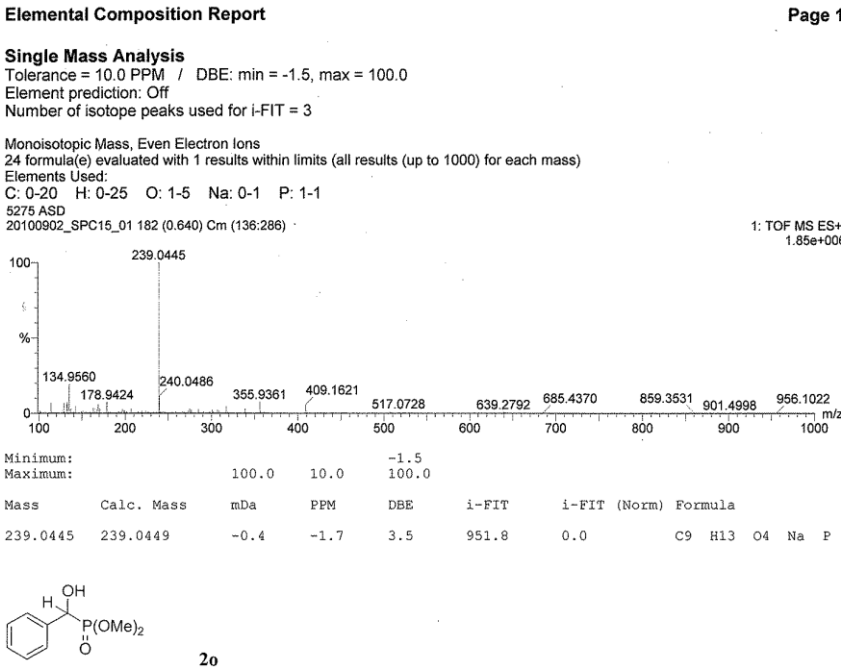


Figure A40. HRMS of compound **150**

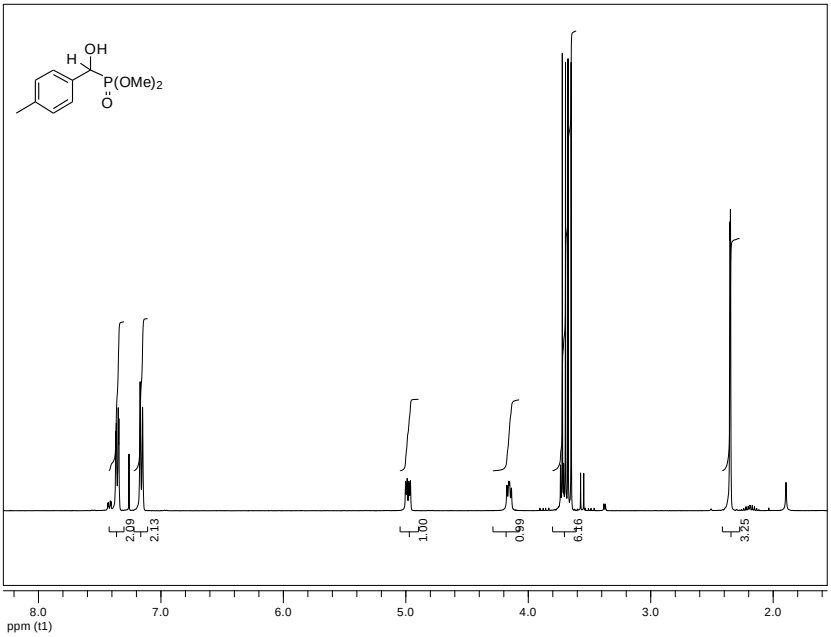


Figure A41. ^{1}H NMR spectrum of **152**

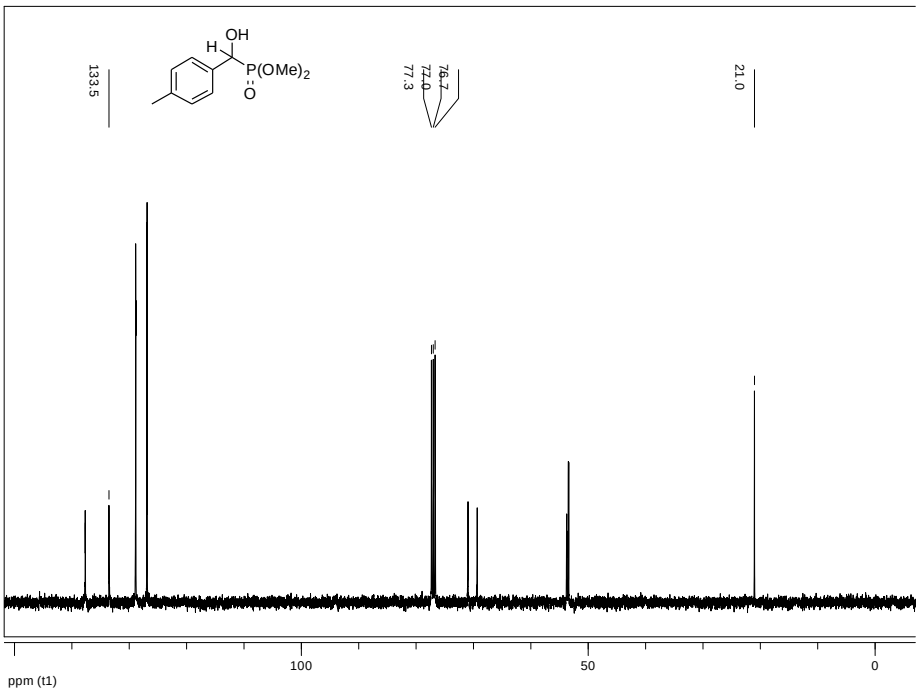


Figure A42. ^{13}C NMR spectrum of **152**

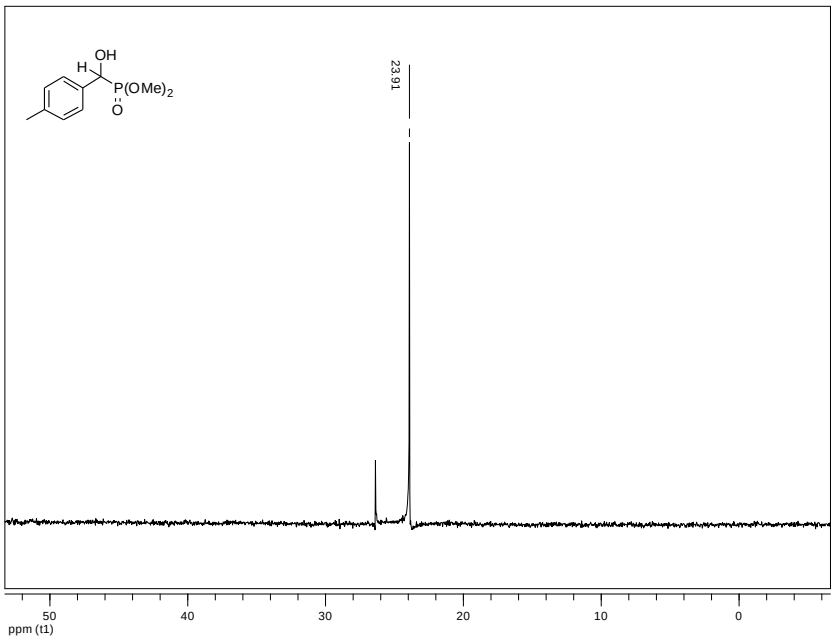
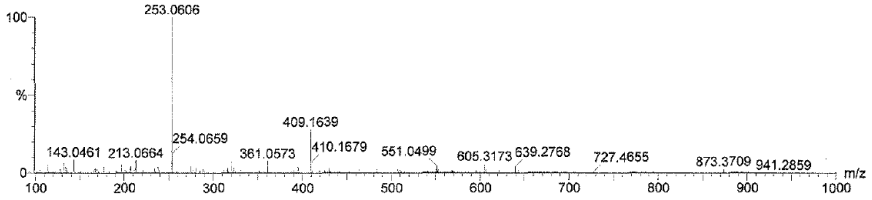


Figure A43. ^{31}P NMR spectrum of **152**

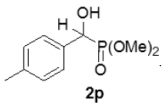
ental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
51 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-40 H: 0-30 O: 0-4 Na: 0-1 P: 1-1 Fe: 0-1
5394 ASD
20100929_SPC1601_01 241 (0.842) Cm (72:284) 1: TOF MS ES+ 2.99e+006



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
253.0606	253.0606	0.0	0.0	3.5	989.4	1.2	C10 H15 O4 Na P
	253.0630	-2.4	-9.5	6.5	988.5	0.3	C12 H14 O4 P



2p

Figure A44. HRMS of compound **152**

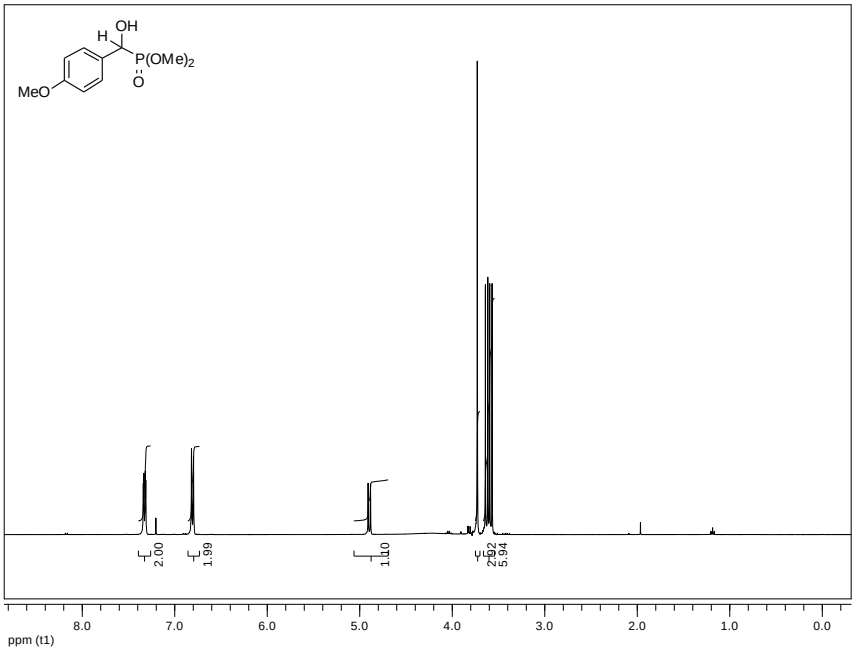


Figure A45. ^{1}H NMR spectrum of **153**

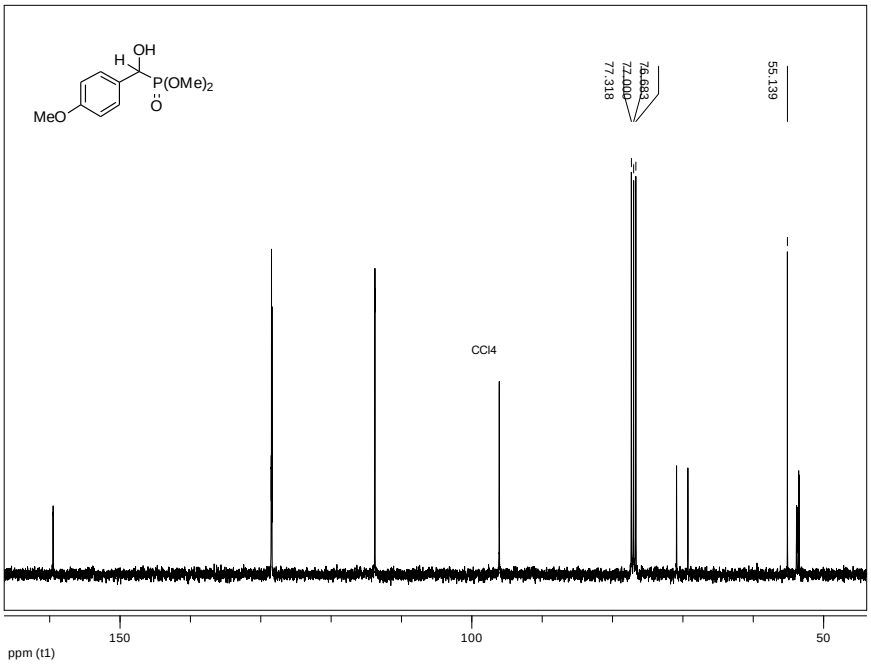


Figure A46. ^{13}C NMR spectrum of **153**

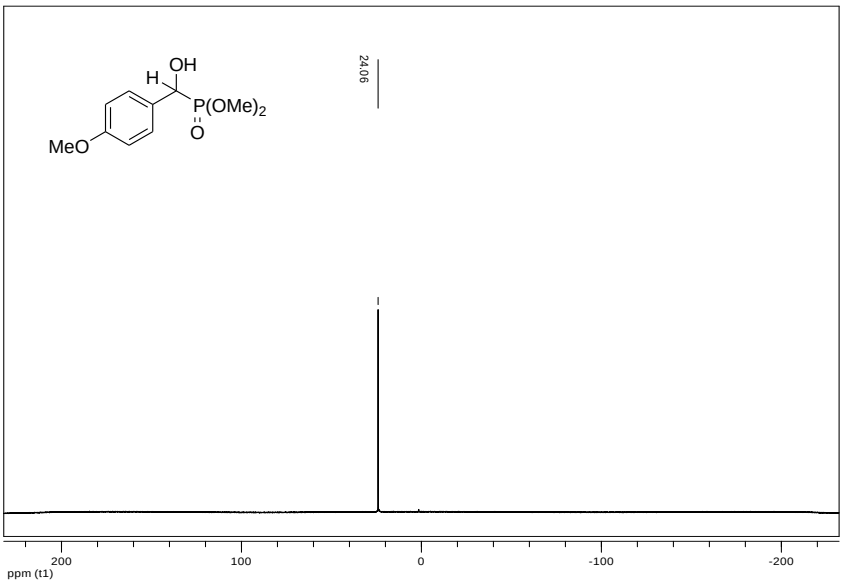
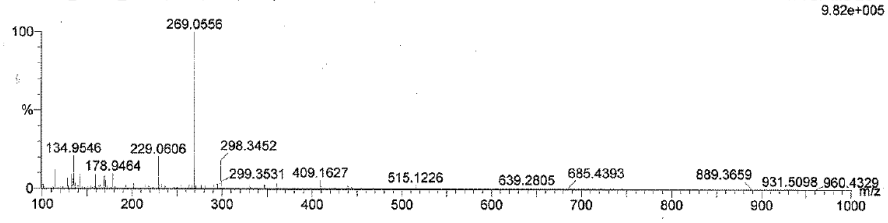


Figure A47. ^{31}P NMR spectrum of **153**

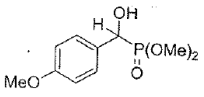
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
21 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1
5275 ASD
20100902_SPC17_02 55 (0.209) Cm (1:145) 1: TOF MS ES+ 9.82e+005



Minimum:				-1.5						
Maximum:		100.0	10.0	100.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
269.0556	269.0555	0.1	0.4	3.5	877.0	0.3	C10 H15 O5 Na P			
	269.0579	-2.3	-8.5	6.5	877.9	1.2	C12 H14 O5 P			



2q

Figure A48. HRMS of compound **153**

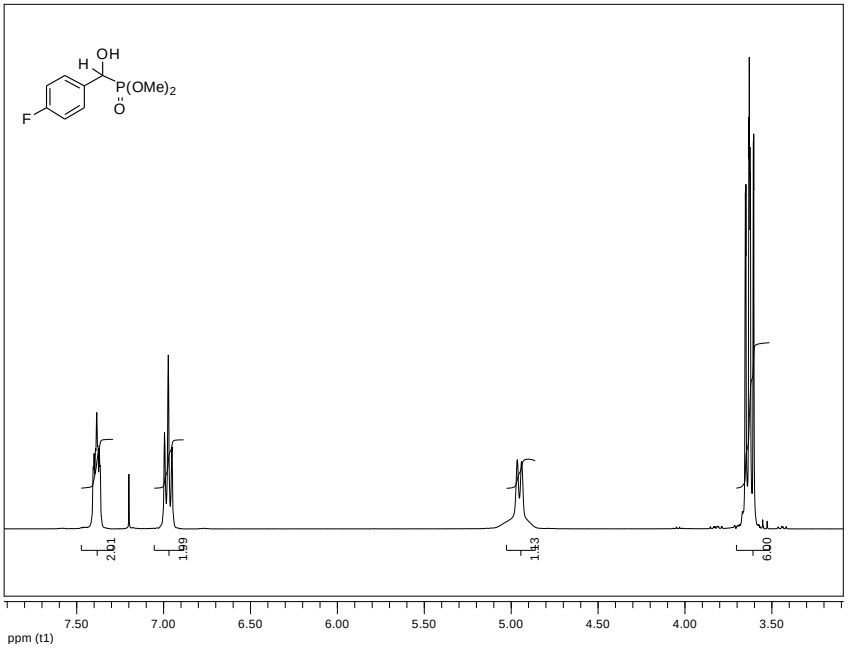


Figure A49. ^{1}H NMR spectrum of **154**

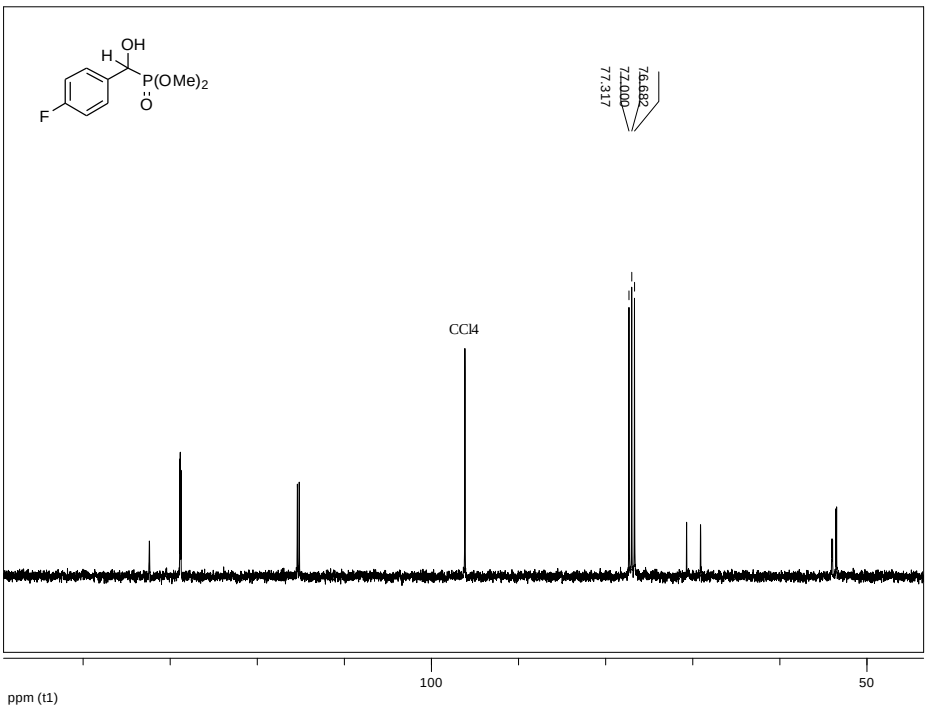


Figure A50. ^{13}C NMR spectrum of **154**

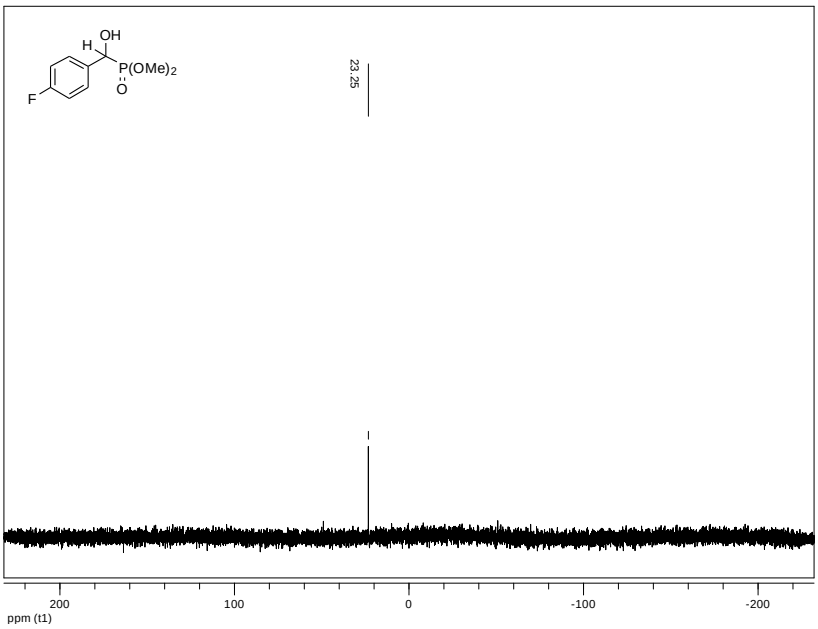


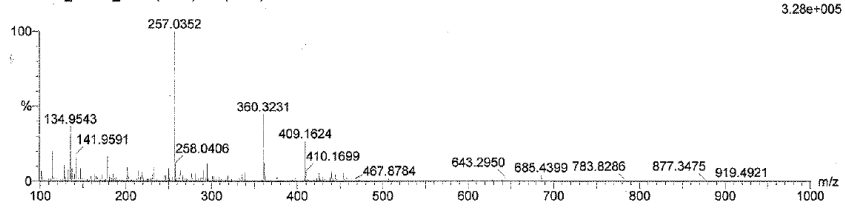
Figure A51. ^{31}P NMR spectrum of **154**

Elemental Composition Report **Page 1**

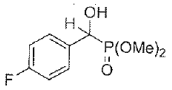
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1 F: 1-1

5275 ASD
20100902_SPC18_01 48 (0.181) Cm (1:141) 1: TOF MS ES+
3.28e+005



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
257.0352	257.0355	-0.3	-1.2	3.5	780.0	0.0	C9 H12 O4 Na P F



2r

Figure A52. HRMS of compound **154**

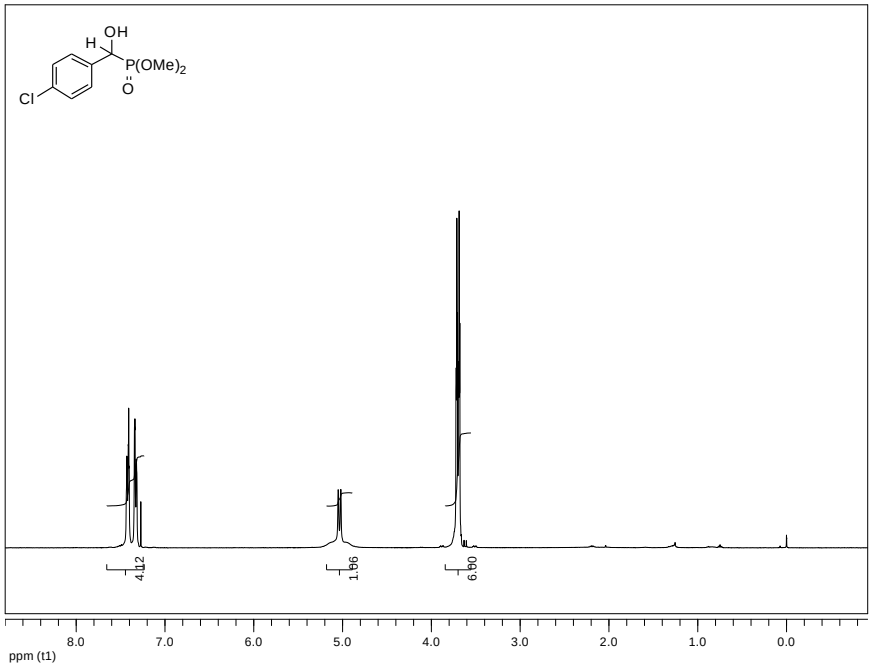


Figure A53. ^{1}H NMR spectrum of **155**

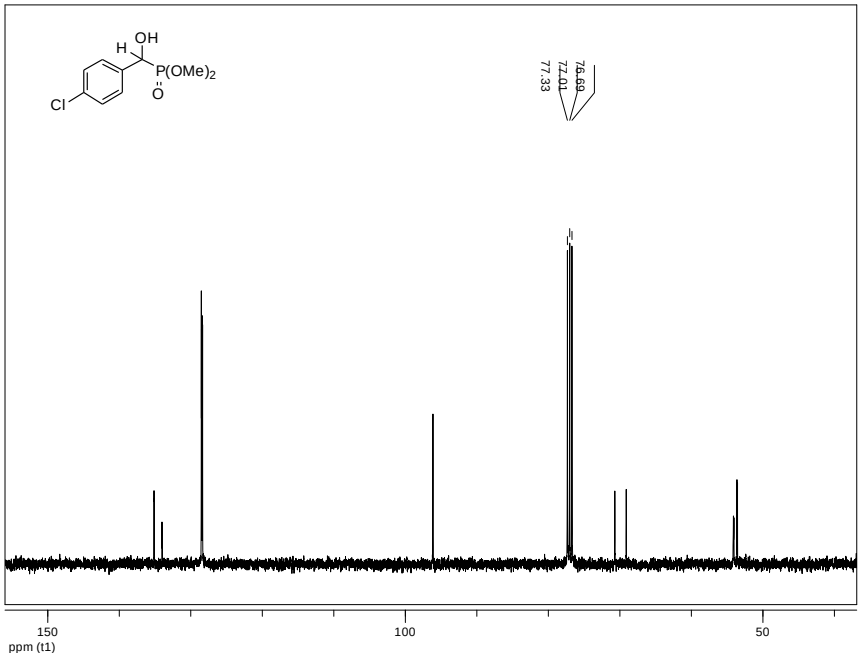


Figure A54. ^{13}C NMR spectrum of **155**

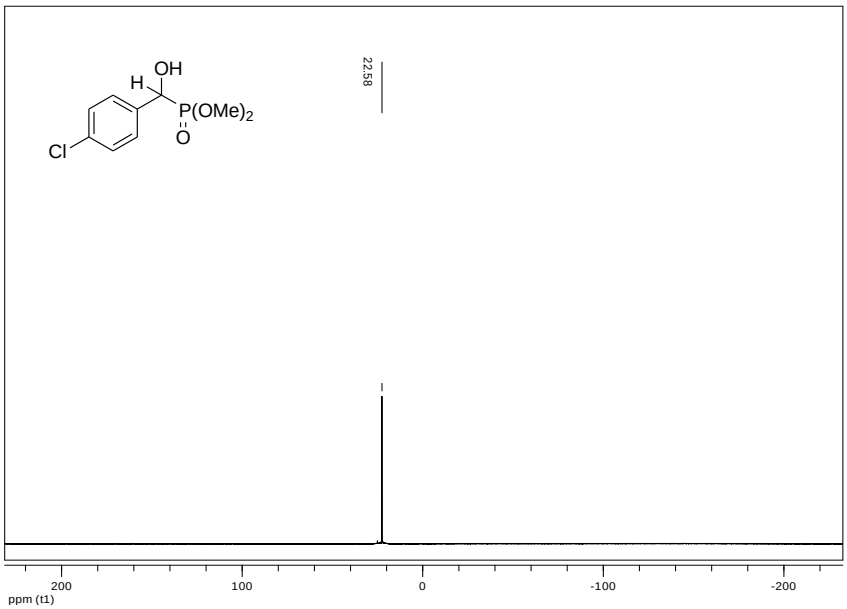
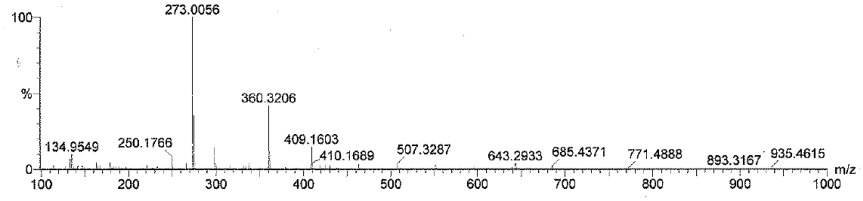


Figure A55. ^{31}P NMR spectrum of **155**

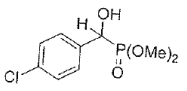
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1 Cl: 1-1
5275 ASD
20100903_SPC19_01 218 (0.765) Cm (1:271) 1: TOF MS ES+ 1.10e+006



Minimum:				-1.5			
Maximum:		100.0	50.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
273.0056	273.0059	-0.3	-1.1	3.5	899.1	0.1	C9 H12 O4 Na P Cl
	273.0084	-2.8	-10.3	6.5	901.5	2.6	C11 H11 O4 P Cl



2s

Figure A56. HRMS of compound **155**

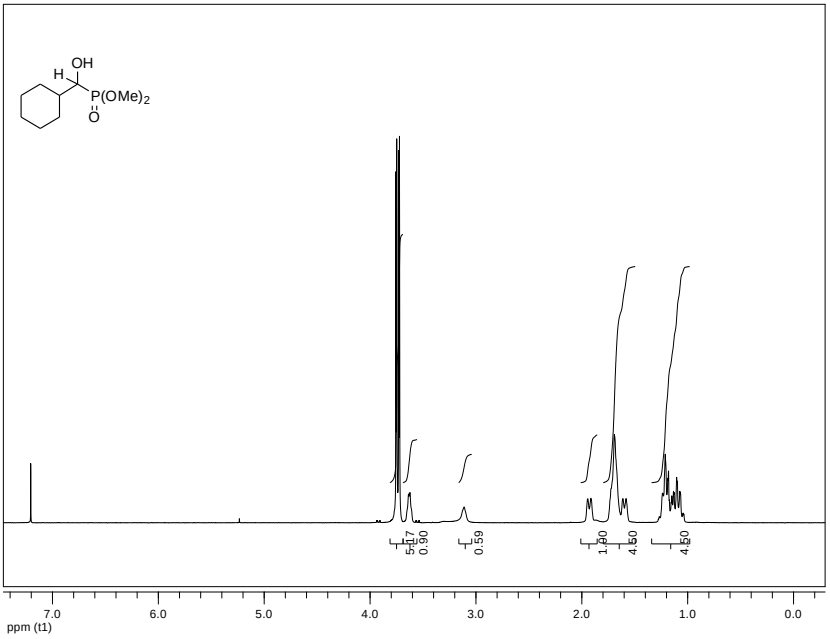


Figure A57. ^{1}H NMR spectrum of **156**

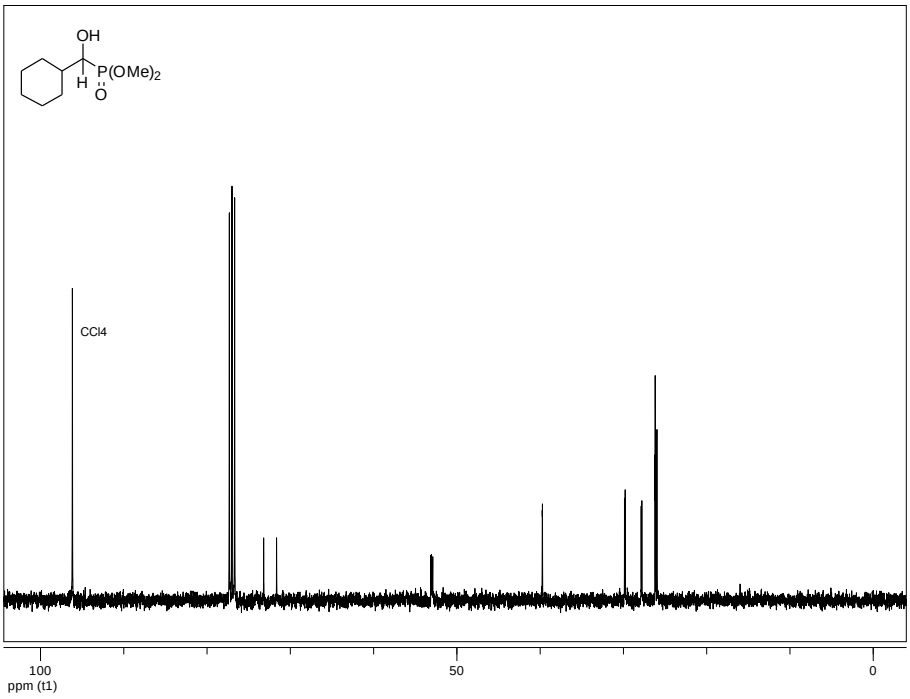


Figure A58. ^{13}C NMR spectrum of **156**

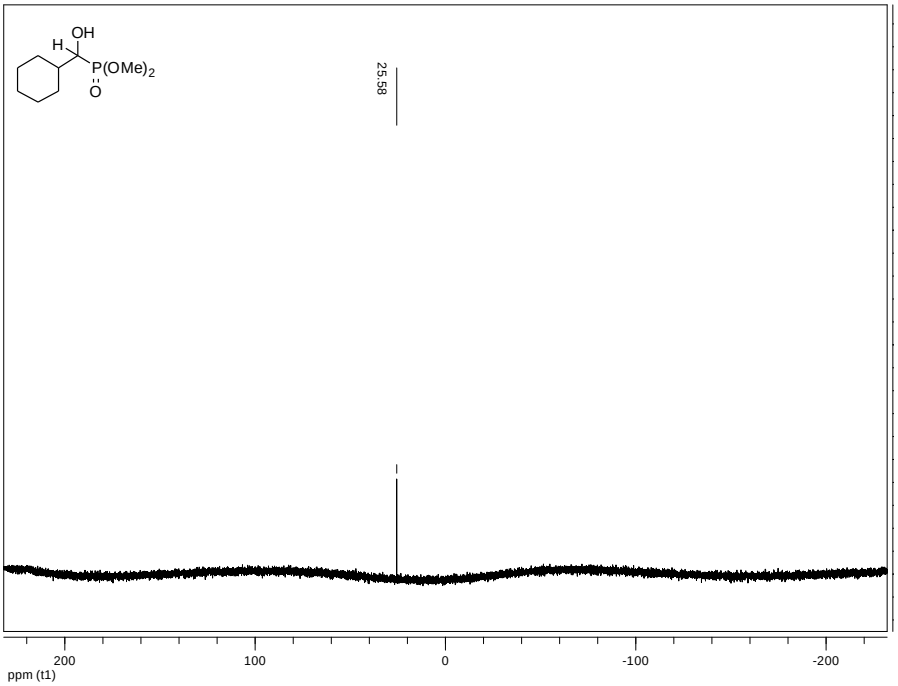


Figure A59. ^{31}P NMR spectrum of **156**

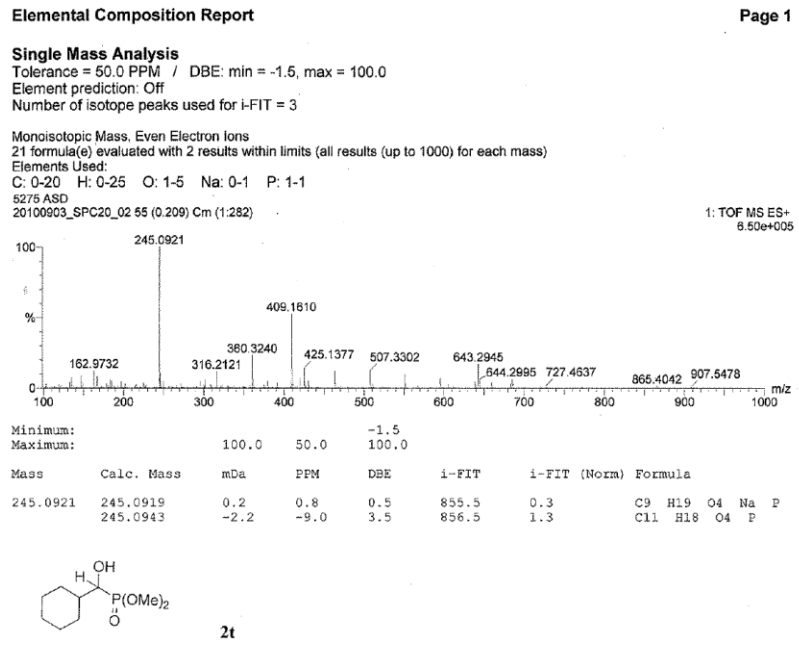


Figure A60. HRMS of compound **156**

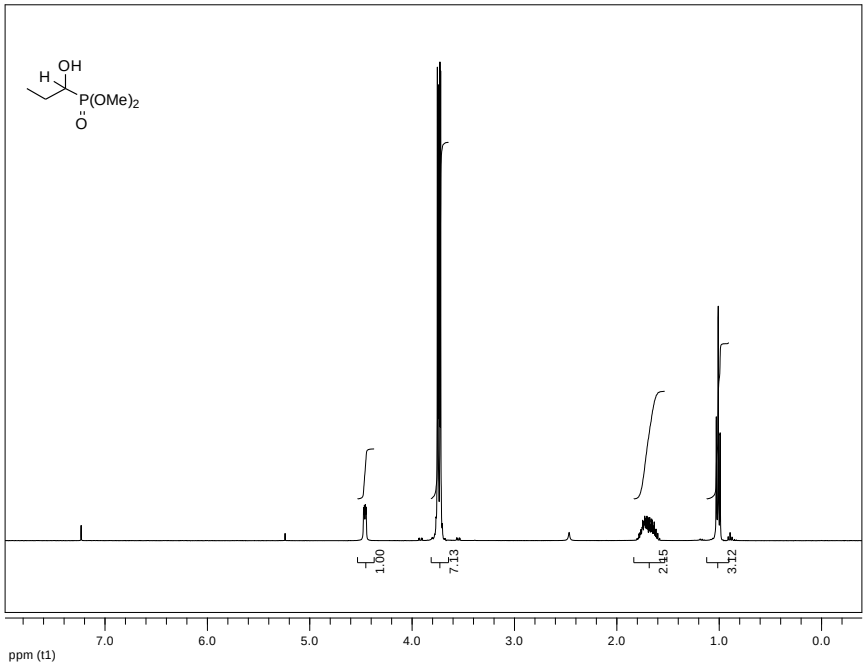


Figure A61. ^{1}H NMR spectrum of **157**

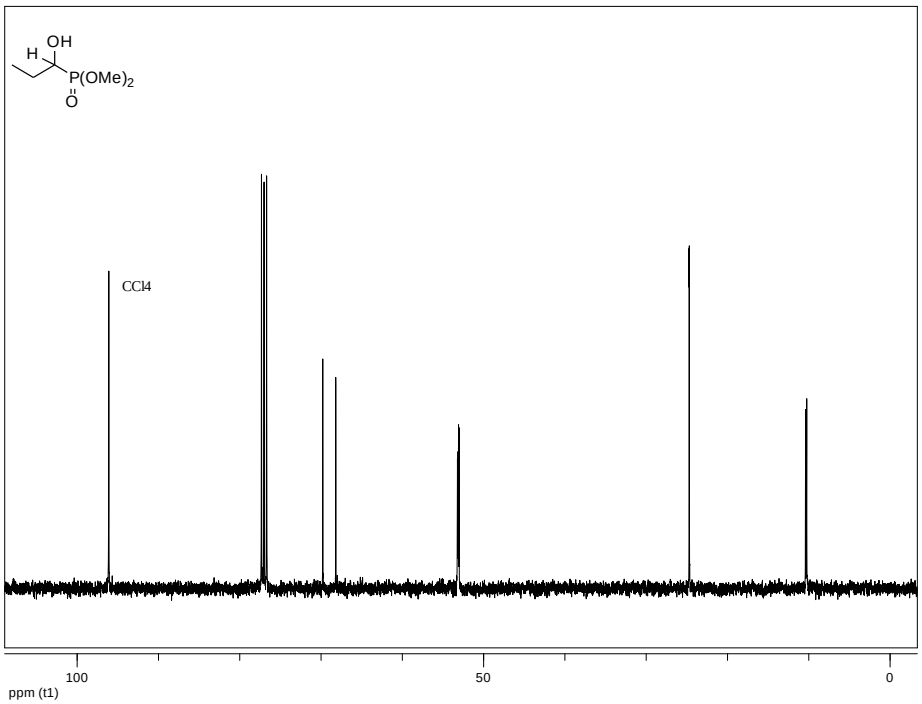


Figure A62. ^{13}C NMR spectrum of **157**

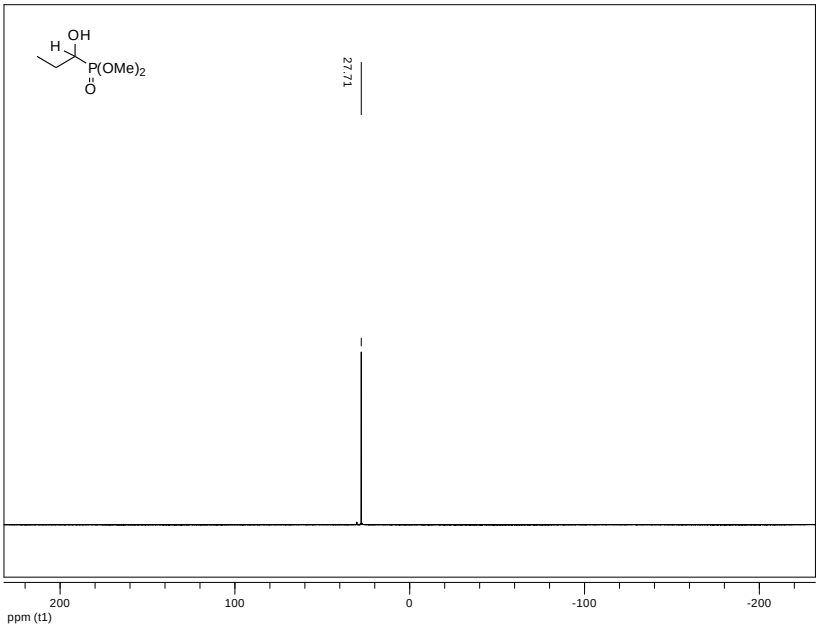


Figure A63. ^{31}P NMR spectrum of **157**

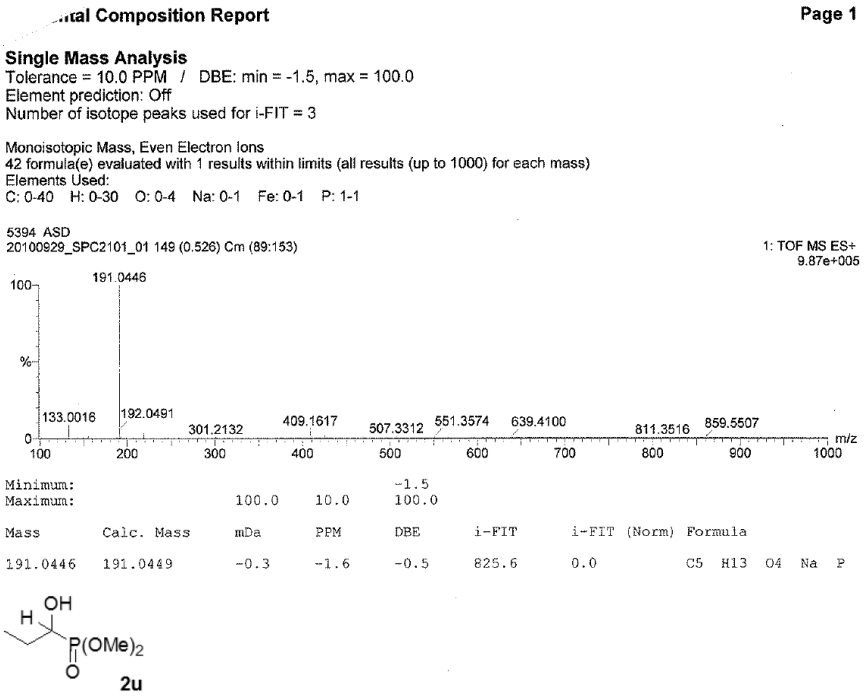


Figure A64. HRMS of compound **157**

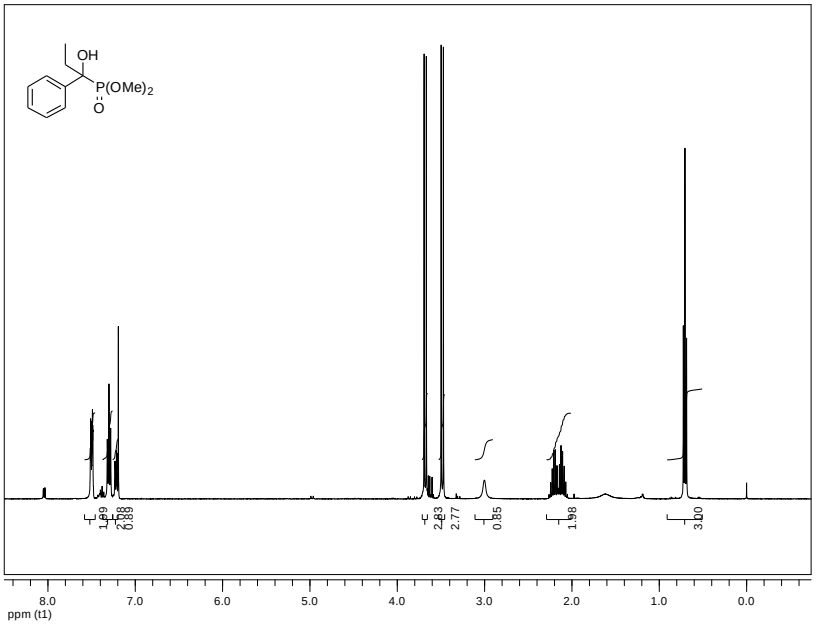


Figure A65. ^{1}H NMR spectrum of **158**

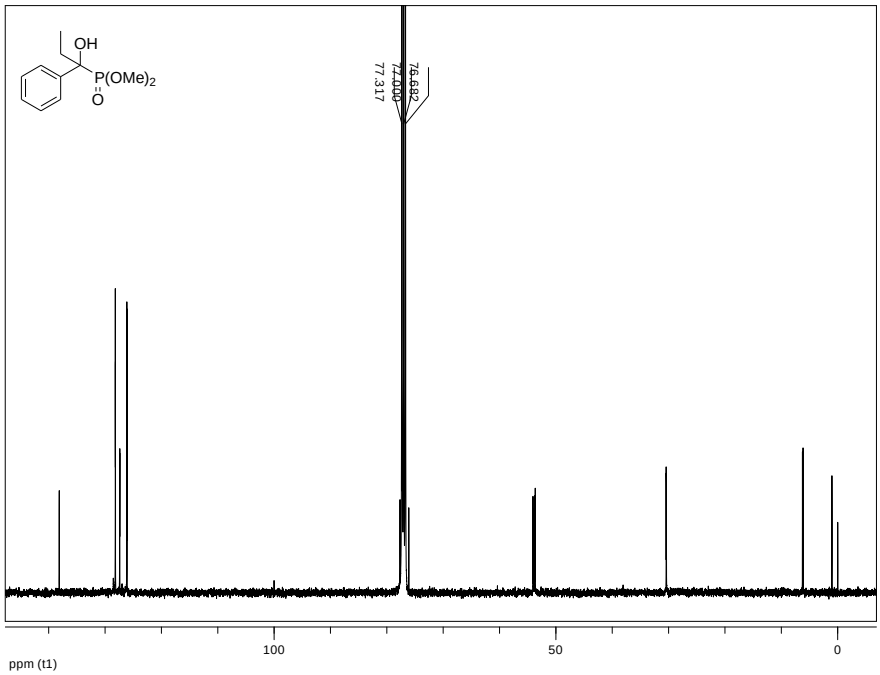


Figure A66. ^{13}C NMR spectrum of **158**

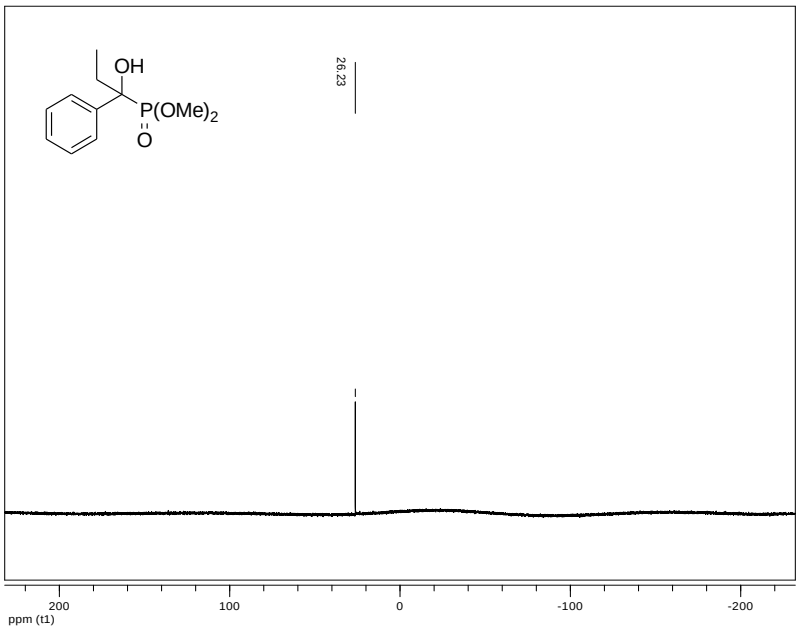
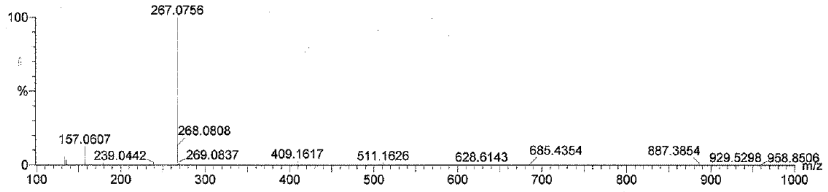


Figure A67. ^{31}P NMR spectrum of **158**

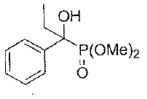
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
53 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 0-1
5275 ASD
20100902_SPC10_01 7 (0.044) Cm (1:137) 1: TOF MS ES+ 1.64e+006



Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
267.0756	267.0762	-0.6	-2.2	3.5	914.0	0.0	C11 H17 O4 Na P



2j

Figure A68. HRMS of compound **158**

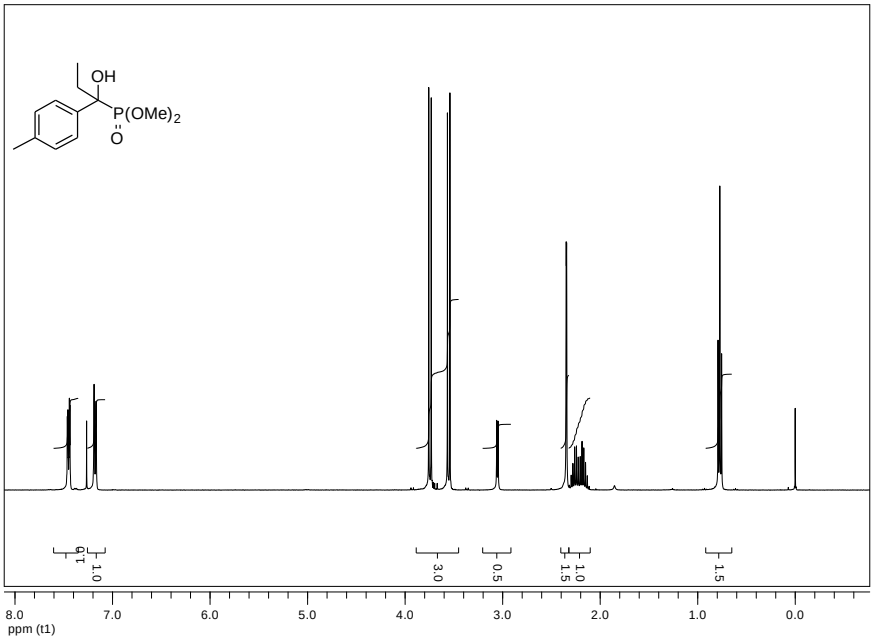


Figure A69. ^{1}H NMR spectrum of **160**

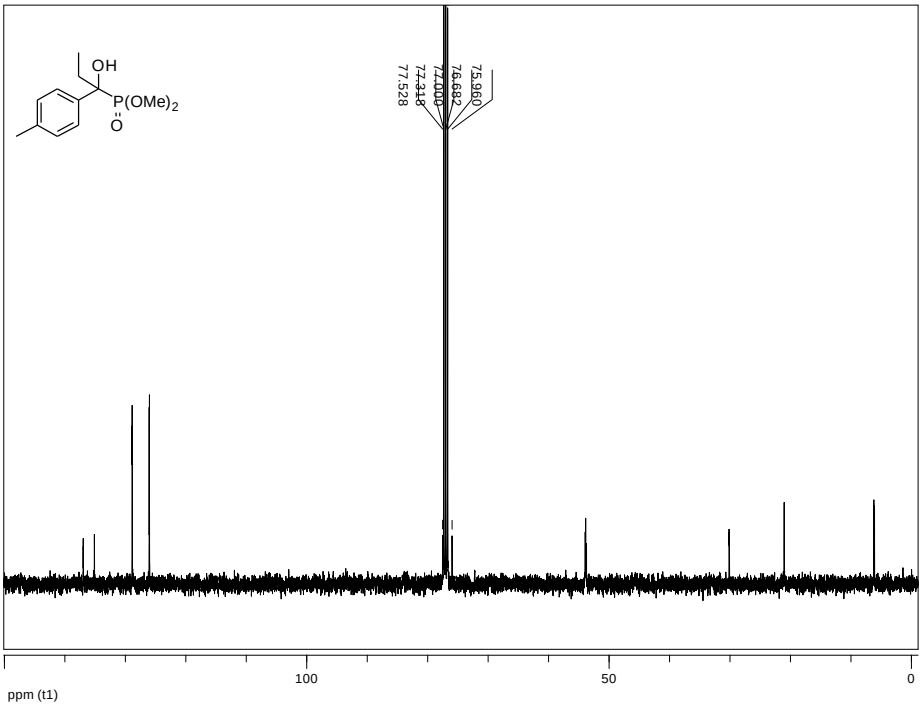


Figure A70. ^{13}C NMR spectrum of **160**

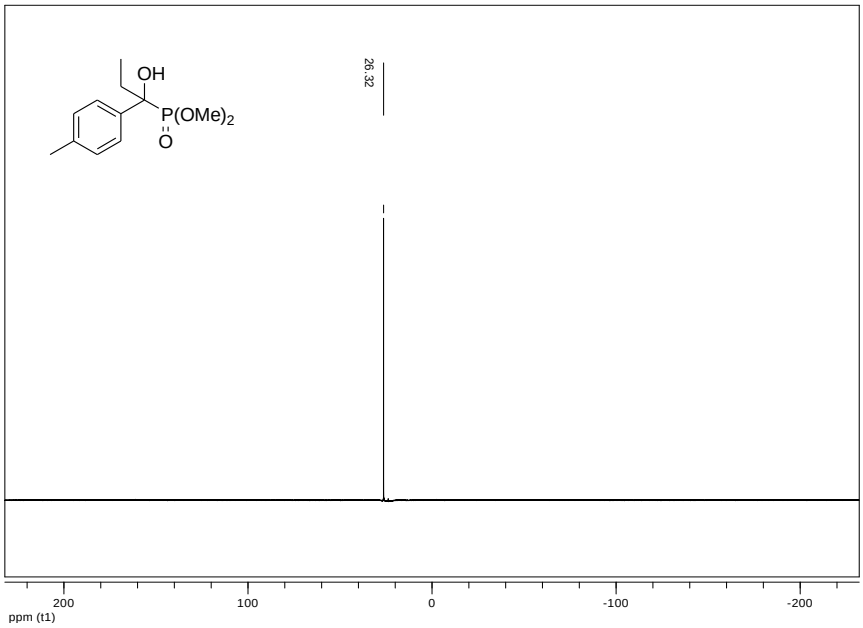


Figure A71. ^{31}P NMR spectrum of **160**

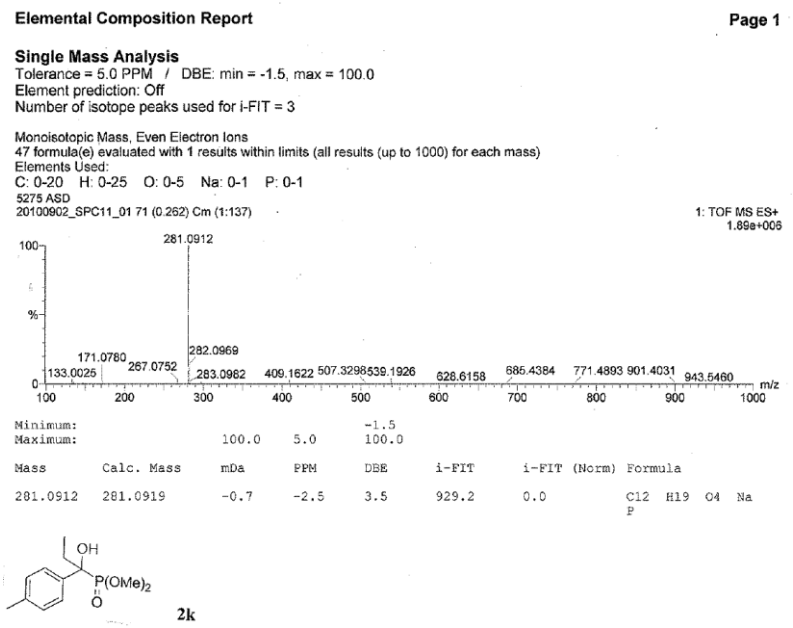


Figure A72. HRMS of compound **160**

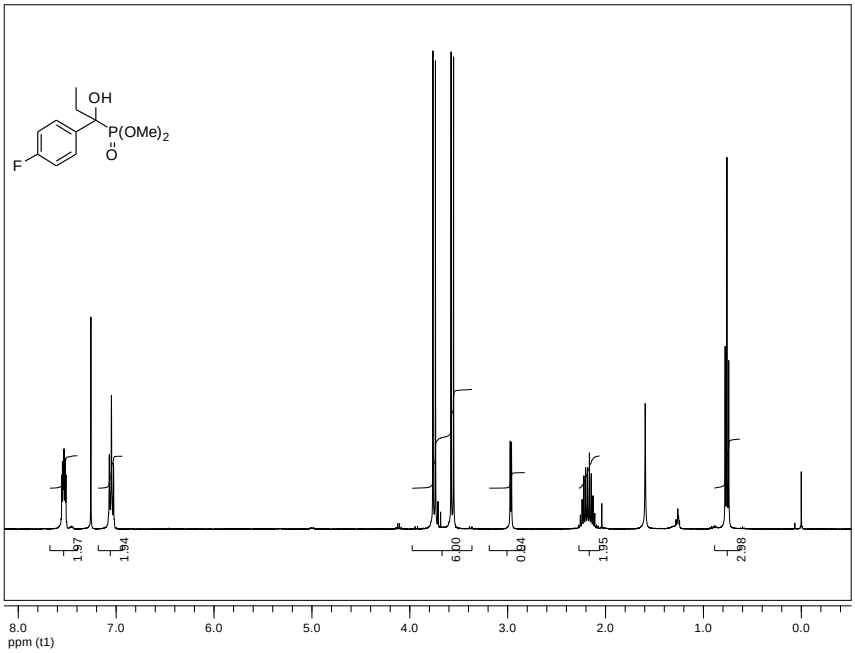


Figure A73. ^{1}H NMR spectrum of **161**

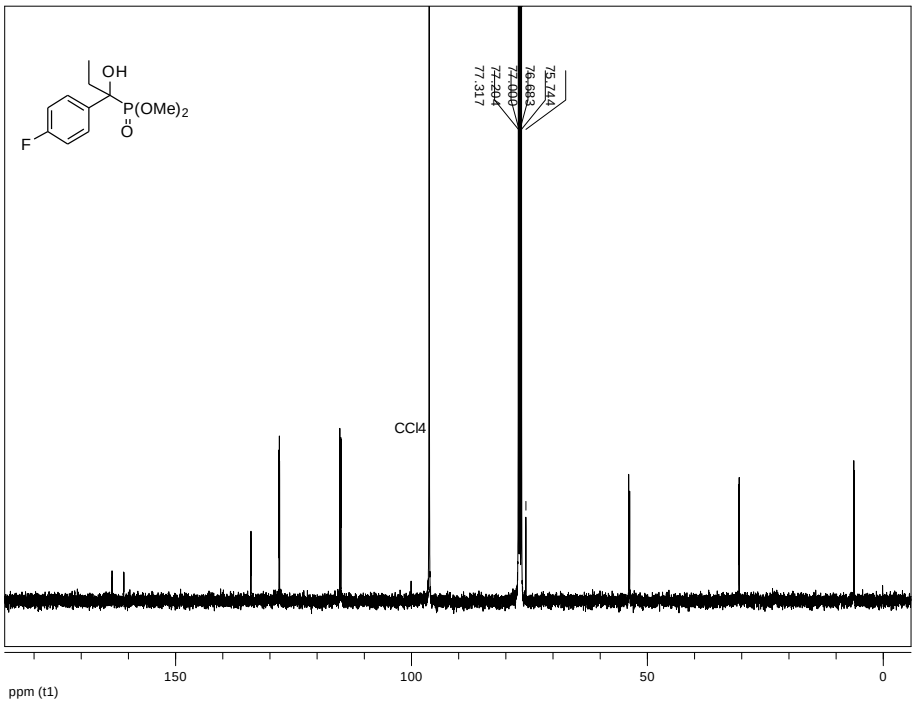


Figure A74. ^{13}C NMR spectrum of **161**

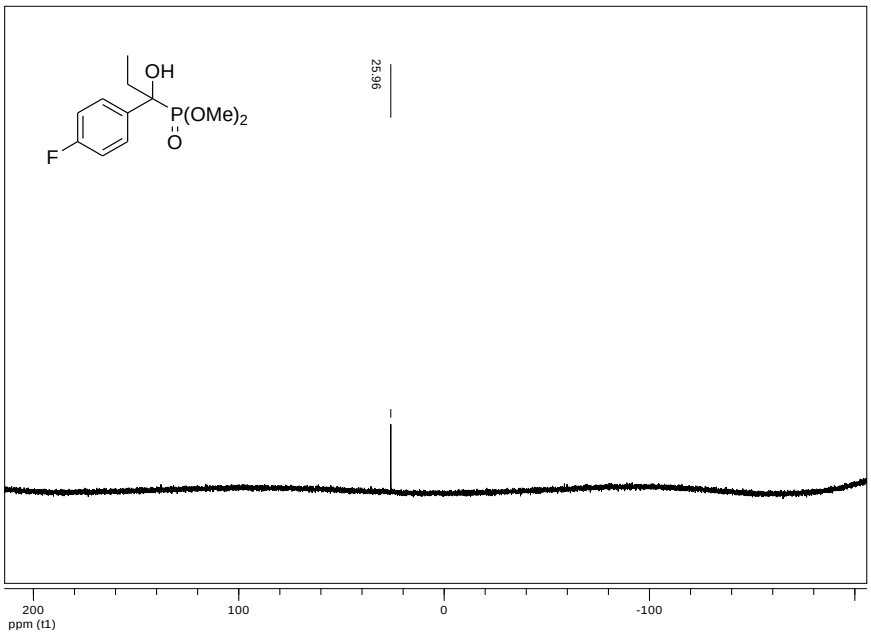


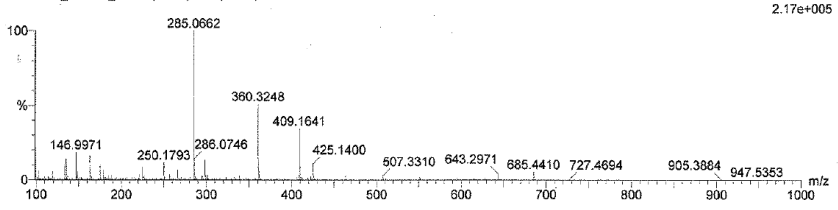
Figure A75. ^{31}P NMR spectrum of **161**

Elemental Composition Report **Page 1**

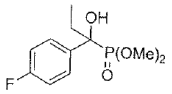
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
52 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 0-5 Na: 0-1 P: 0-1 F: 1-1

5275 ASD
20100902_SPC12_02 32 (0.128) Cm (1:142)
1: TOF MS ES+
2.17e+005



Minimum:				-1.5			
Maximum:		100.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
285.0662	285.0668	-0.6	-2.1	3.5	686.7	0.0	C11 H16 O4 Na P F



2l

Figure A76. HRMS of compound **161**

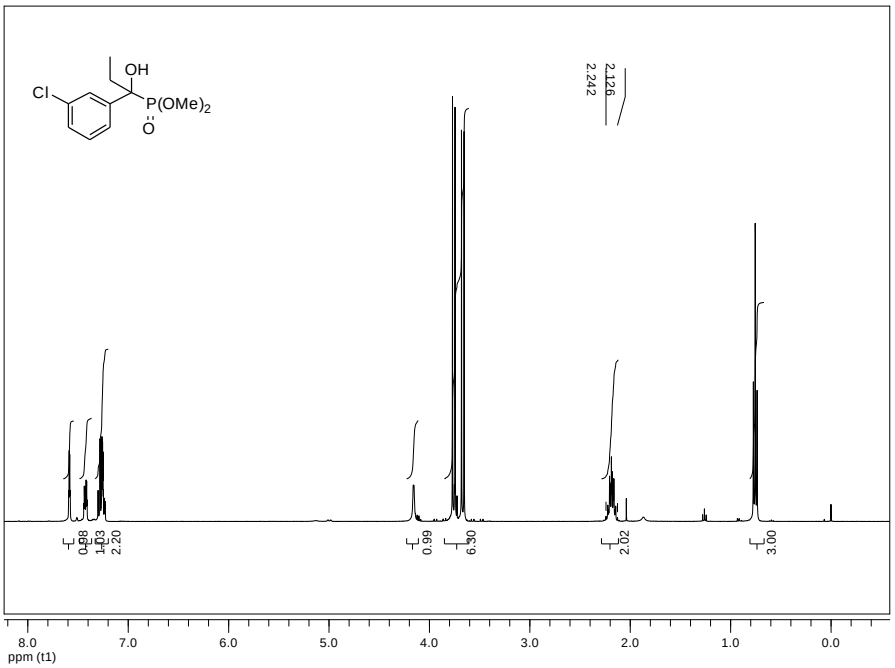


Figure A77. ^{1}H NMR spectrum of **162**

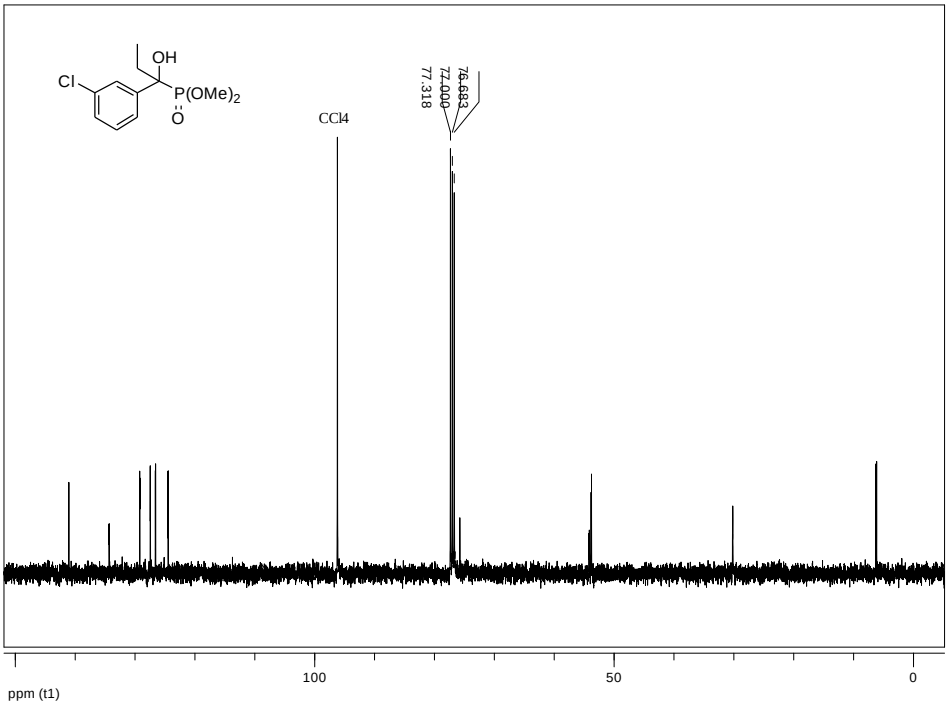


Figure A78. ^{13}C NMR spectrum of **162**

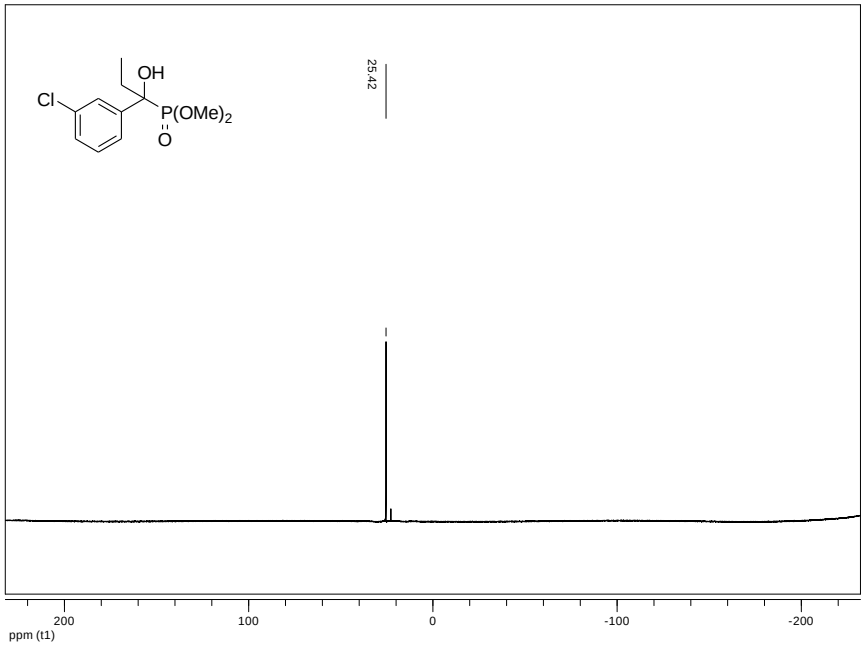
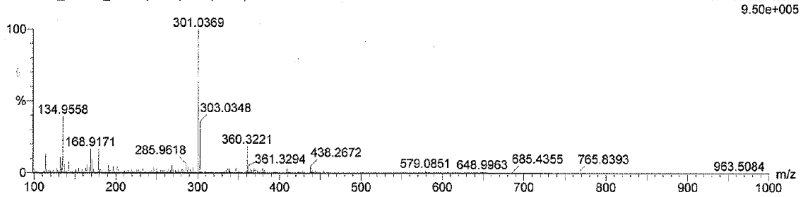


Figure A79. ^{31}P NMR spectrum of **162**

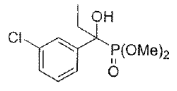
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1 Cl: 1-1
5275 ASD
20100902_SPC13_03 42 (0.161) Cm (1:144) 1: TOF MS ES+ 9.50e+005



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
301.0369	301.0372	-0.3	-1.0	3.5	803.5	0.0	C11 H16 O4 Na P Cl
	301.0397	-2.8	-9.3	6.5	807.7	4.2	C13 H15 O4 P Cl



2m

Figure A80. HRMS of compound **162**

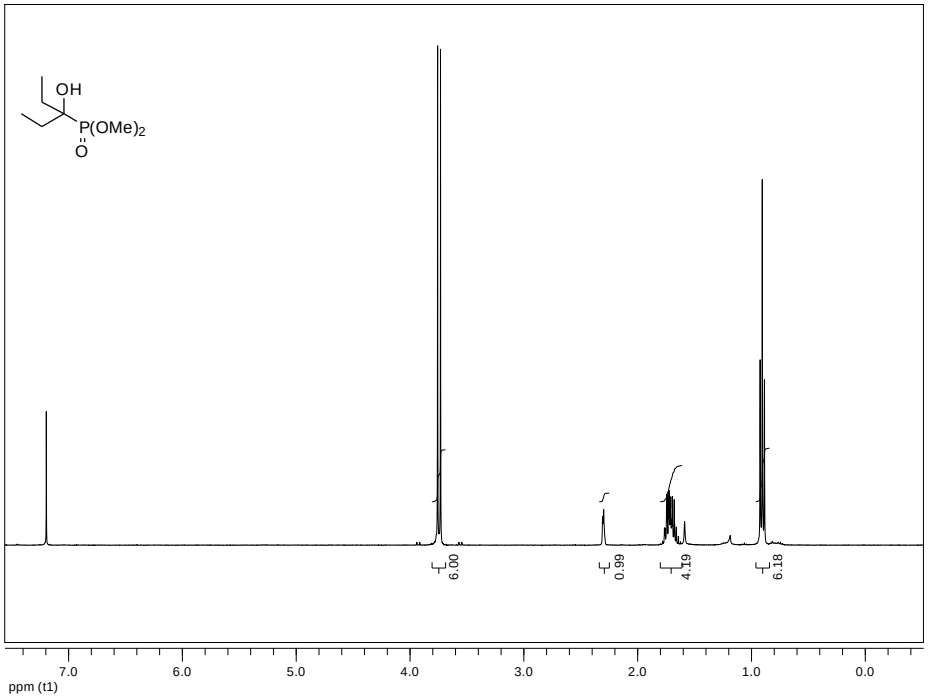


Figure A81. ^{1}H NMR spectrum of **163**

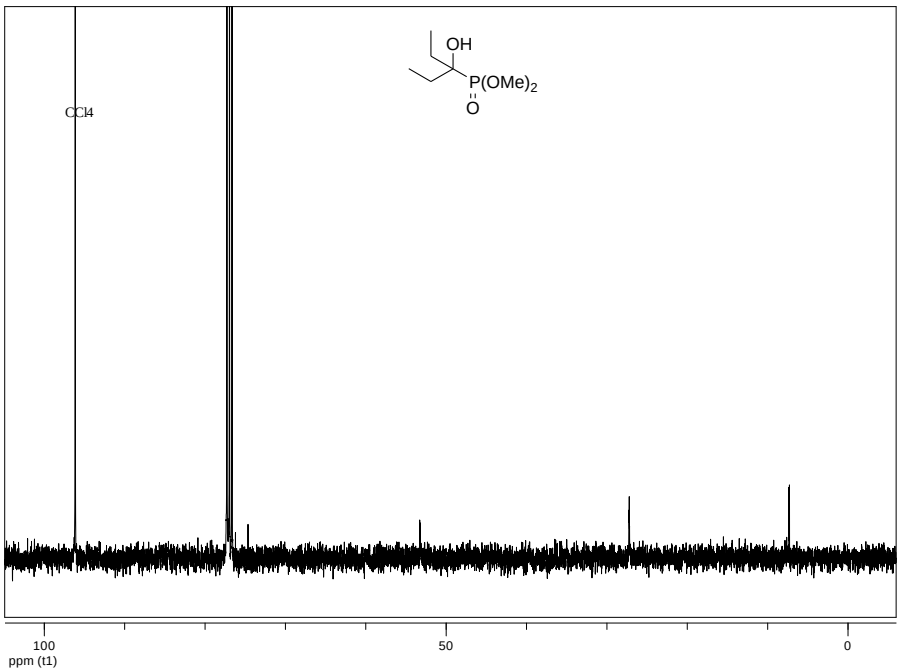


Figure A82. ^{13}C NMR spectrum of **163**

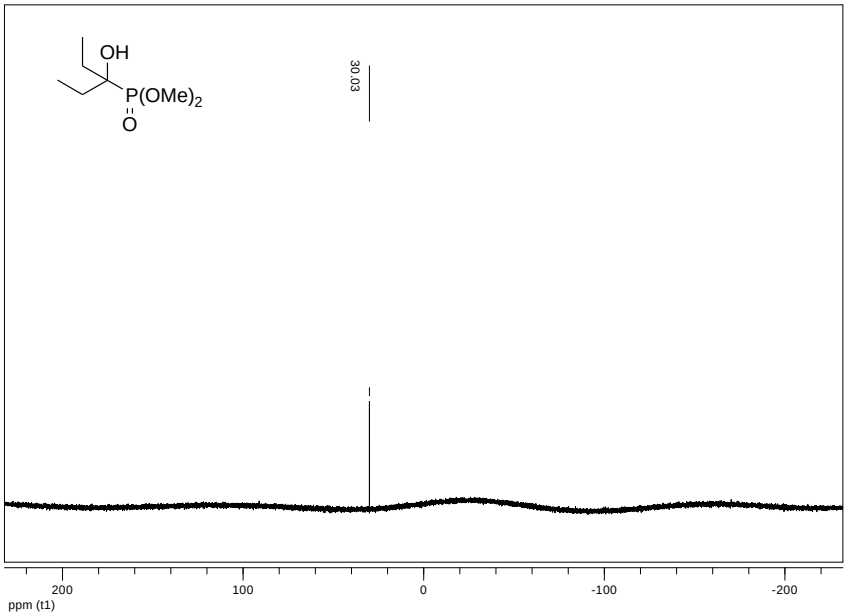
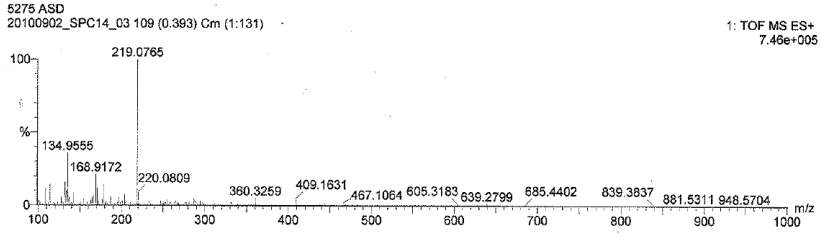


Figure A83. ^{31}P NMR spectrum of **163**

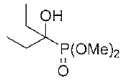
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
23 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1
5275 ASD
20100902_SPC14_03 109 (0.393) Cm (1:131)



Minimum:				-1.5			
Maximum:		100.0	10.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
219.0765	219.0762	0.3	1.4	-0.5	853.5	0.2	C7 H17 O4 Na P
	219.0796	-2.1	-9.6	2.5	855.3	1.9	C9 H16 O4 P



2n

Figure A84. HRMS of compound **163**

APPENDIX B

NMR AND HRMS SPECTRA OF COMPOUNDS SYNTHESIZED IN THE SECOND PART

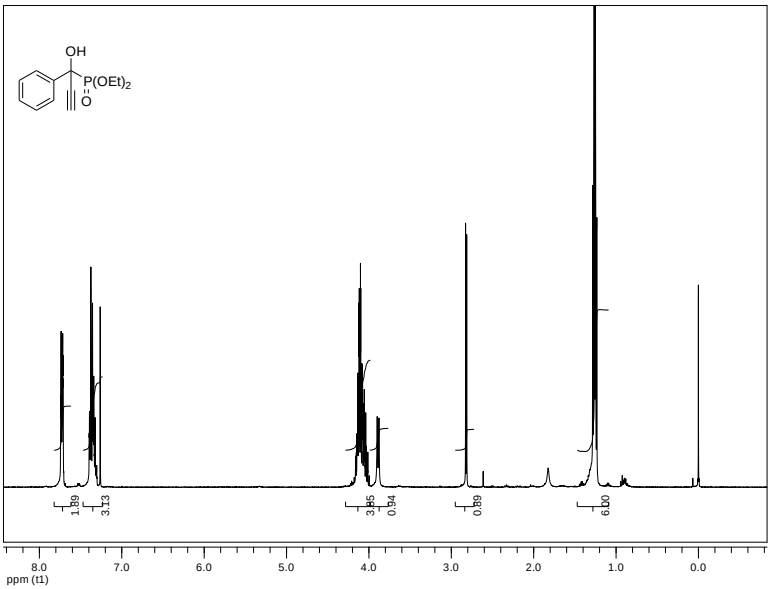


Figure B1. ^{1}H NMR spectrum of **167**

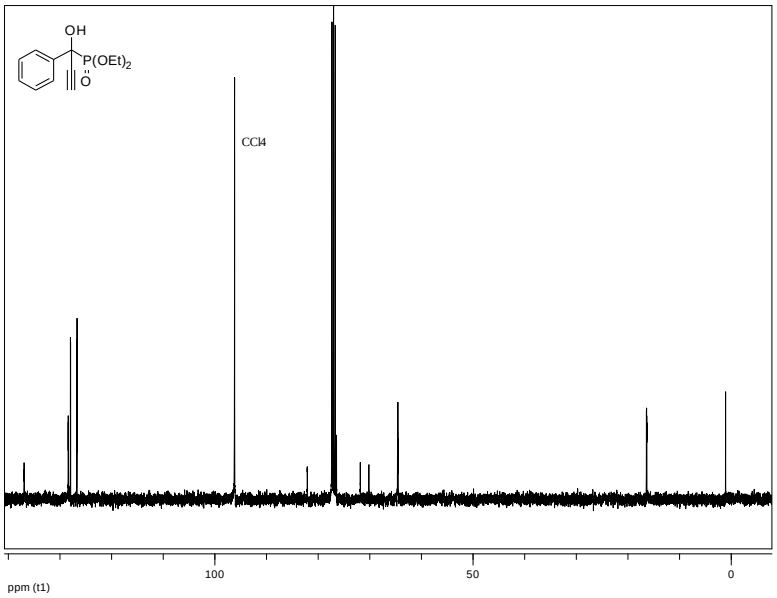


Figure B2. ^{13}C NMR spectrum of **167**

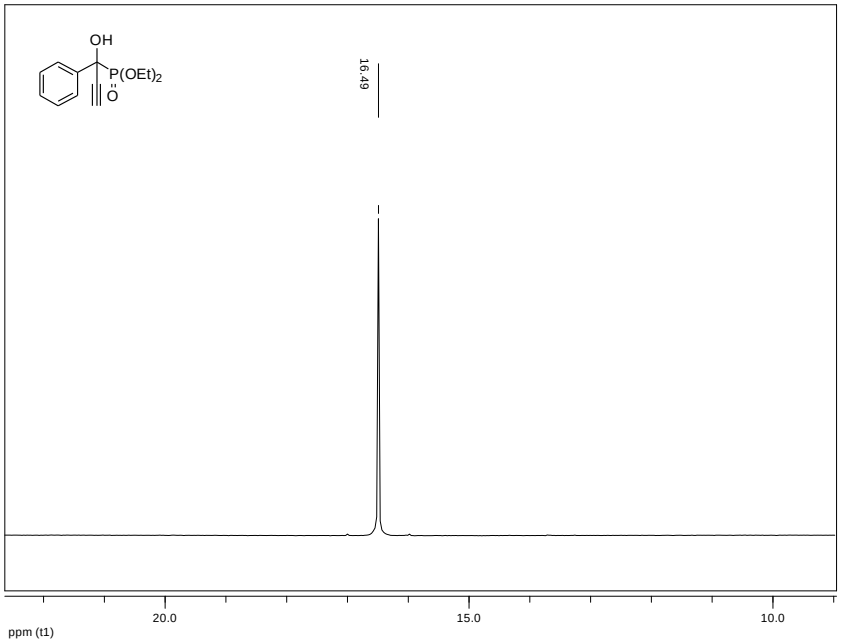
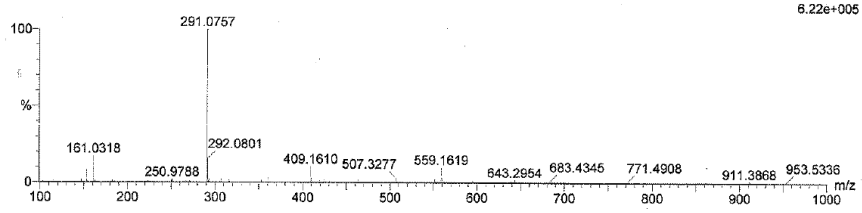


Figure B3. ^{31}P NMR spectrum of **167**

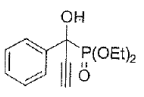
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1
5275 ASD
20100903_SPC22_02 61 (0.229) Cm (1:103) 1: TOF MS ES+ 6.22e+005



Minimum:				-1.5						
Maximum:		100.0	50.0	100.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
291.0757	291.0762	-0.5	-1.7	5.5	790.2	0.2	C13 P	H17	O4	Na
	291.0786	-2.9	-10.0	8.5	791.7	1.7	C15	H16	O4	P



2v

Figure B4. HRMS of compound **167**

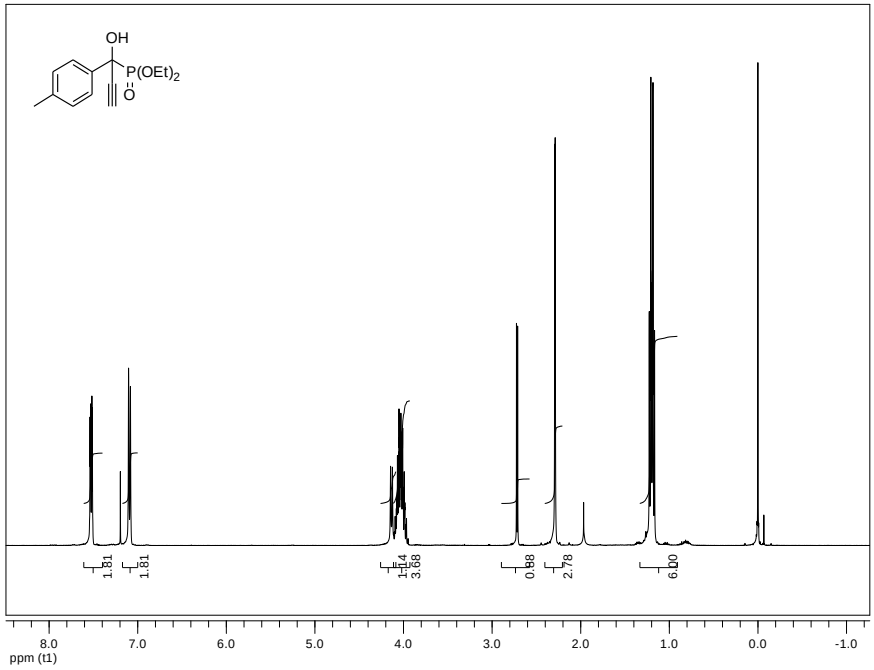


Figure B5. ^{1}H NMR spectrum of **171**

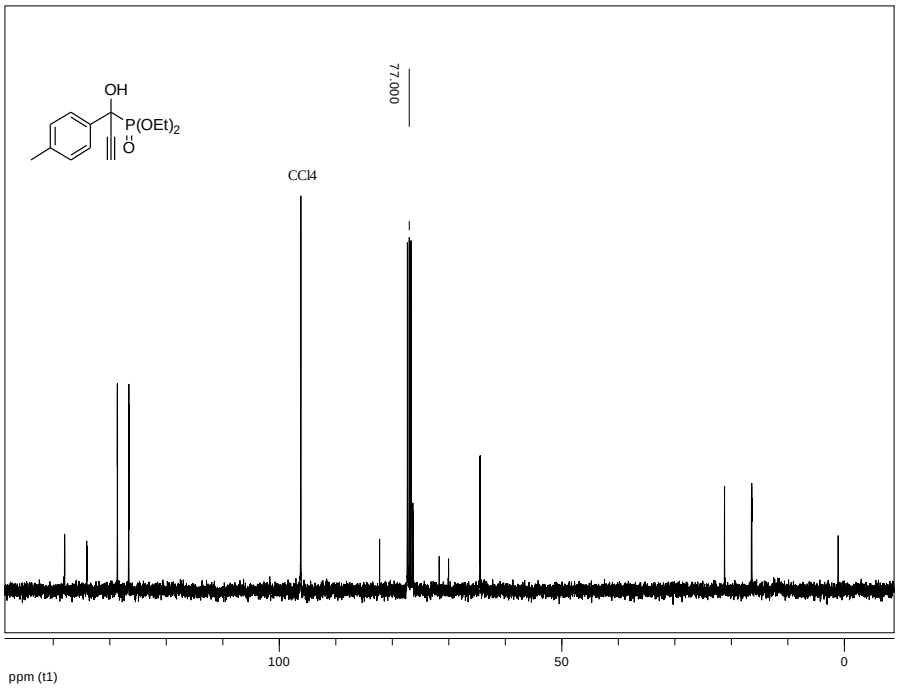


Figure B6. ^{13}C NMR spectrum of **171**

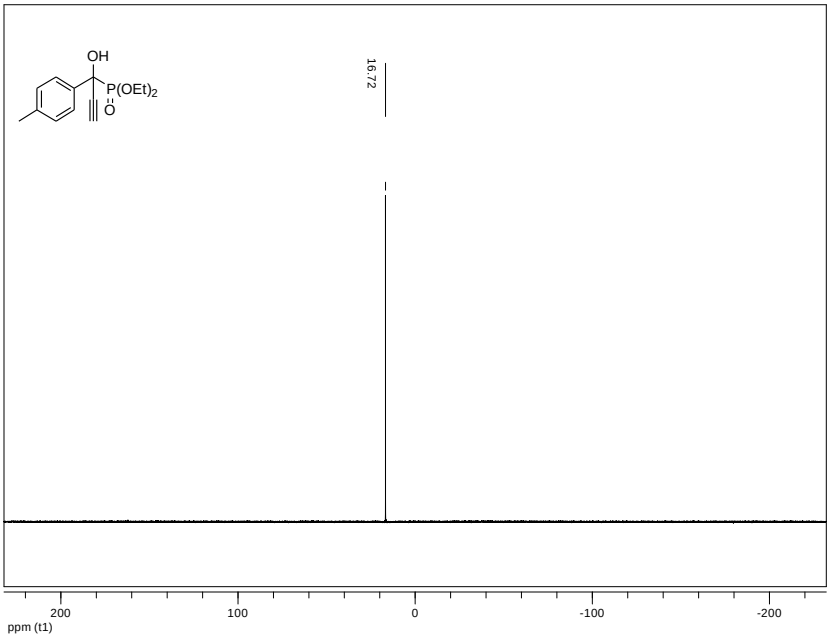
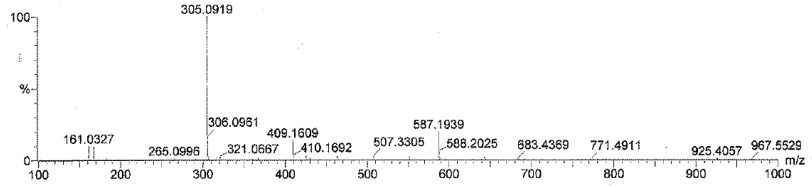


Figure B7. ^{31}P NMR spectrum of **171**

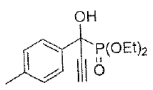
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
20 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1
5275 ASD
20100903_SPC23_01 102 (0.370) Cm (1:283) 1: TOF MS ES+ 2.02e+006



Minimum:				-1.5			
Maximum:		100.0	50.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
305.0919	305.0919	0.0	0.0	5.5	939.8	0.1	C14 H19 O4 Na P
	305.0943	-2.4	-7.9	8.5	941.8	2.2	C16 H18 O4 P
	305.1071	-15.2	-49.8	9.5	946.3	6.6	C18 H19 O Na P



2w

Figure B8. HRMS of compound **171**

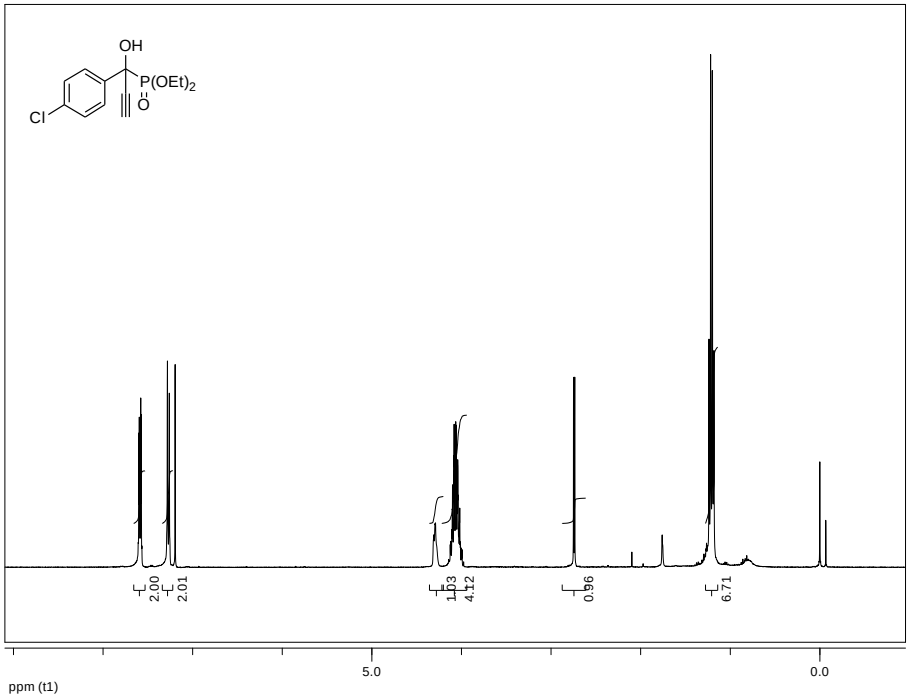


Figure B9. ^{1}H NMR spectrum of **175**

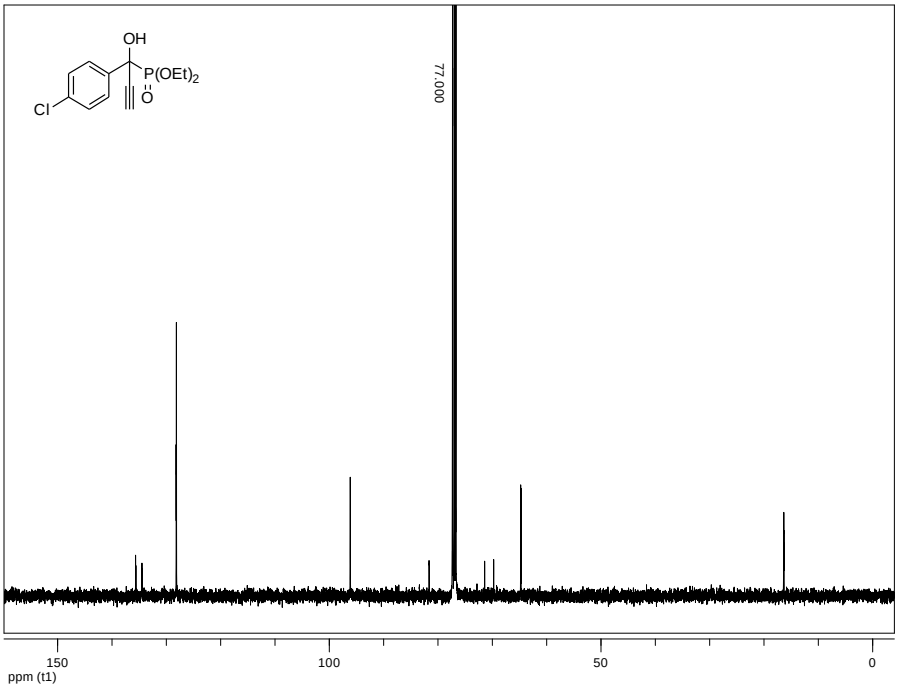


Figure B10. ^{13}C NMR spectrum of **175**

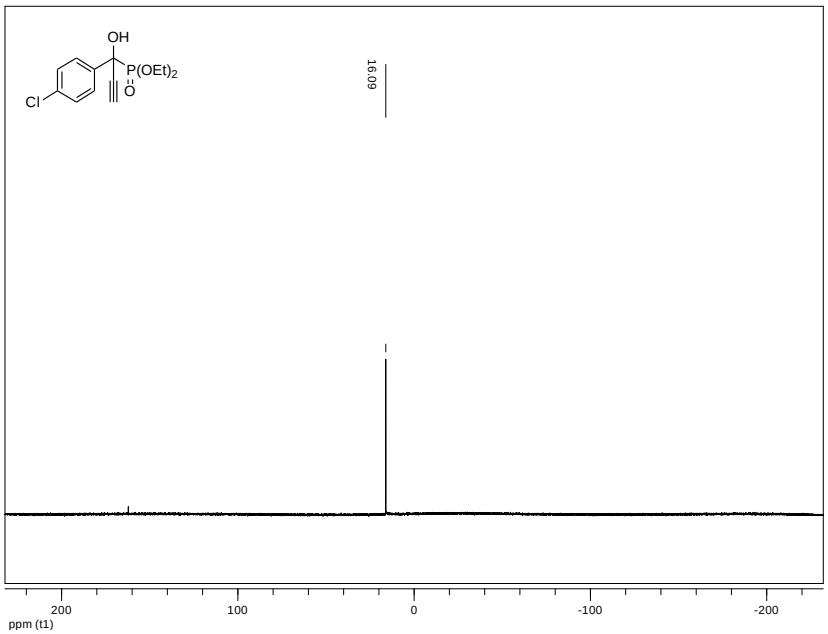


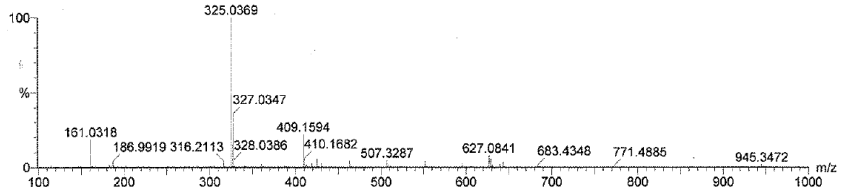
Figure B11. ^{31}P NMR spectrum of **175**

Elemental Composition Report **Page 1**

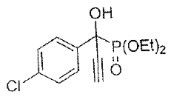
Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-20 H: 0-25 O: 1-5 Na: 0-1 P: 1-1 Cl: 1-1
5275 ASD
20100903_SPC24_01 275 (0.960) Cm (114:286)

1: TOF MS ES+
8.45e+005



Minimum:				-1.5			
Maximum:		100.0	50.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
325.0369	325.0372	-0.3	-0.9	5.5	787.3	0.0	C13 H16 O4 Na P Cl
	325.0397	-2.8	-8.6	8.5	791.0	3.7	C15 H15 O4 P Cl
	325.0525	-15.6	-48.0	9.5	796.0	8.8	C17 H16 O Na P Cl



2x

Figure B12. HRMS of compound **175**

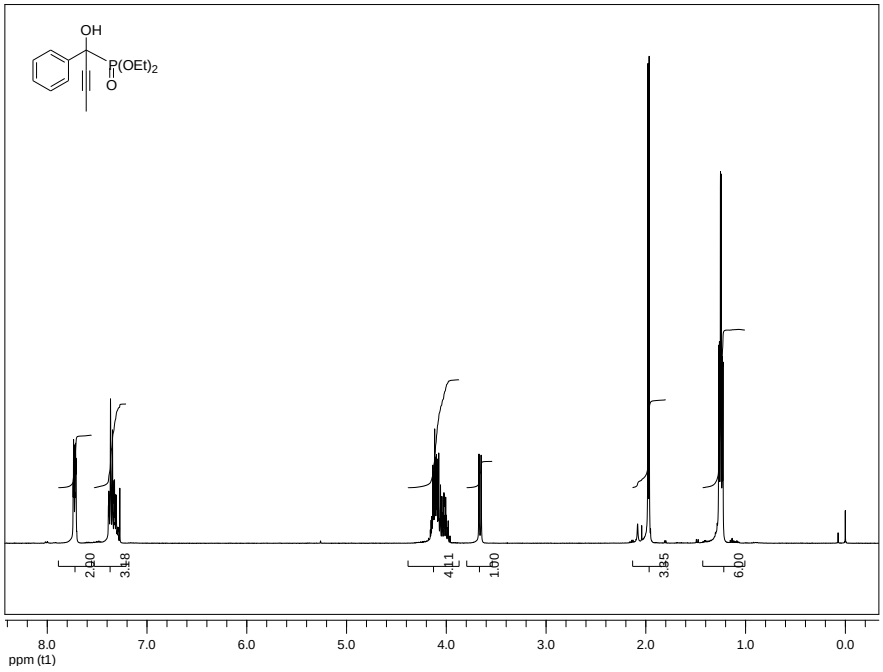


Figure B13. ^{1}H NMR spectrum of **183**

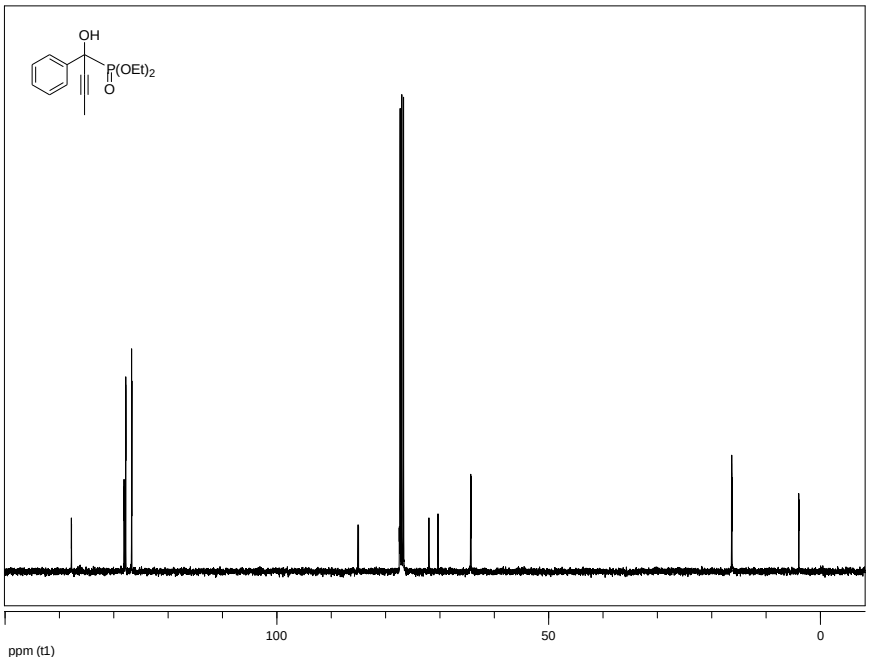


Figure B14. ^{13}C NMR spectrum of **183**

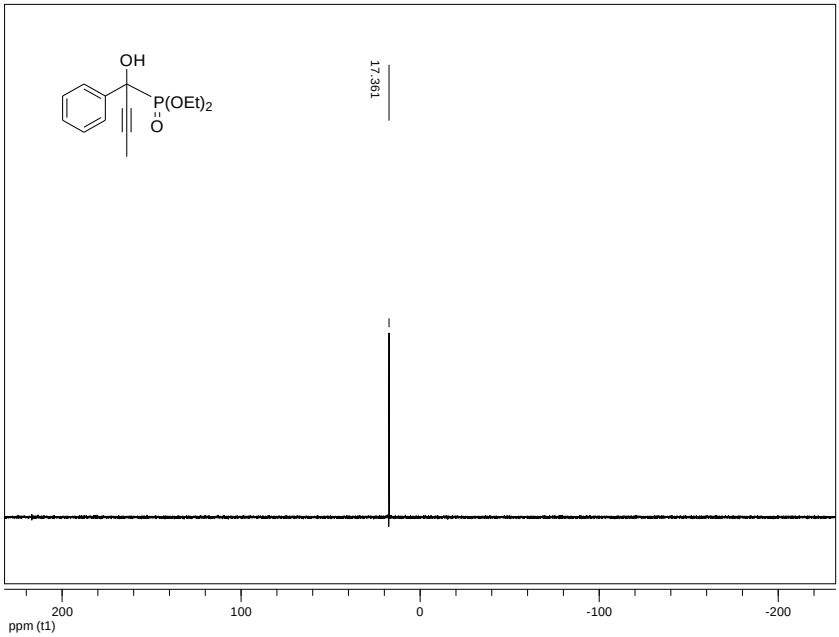


Figure B15. ^{31}P NMR spectrum of **183**

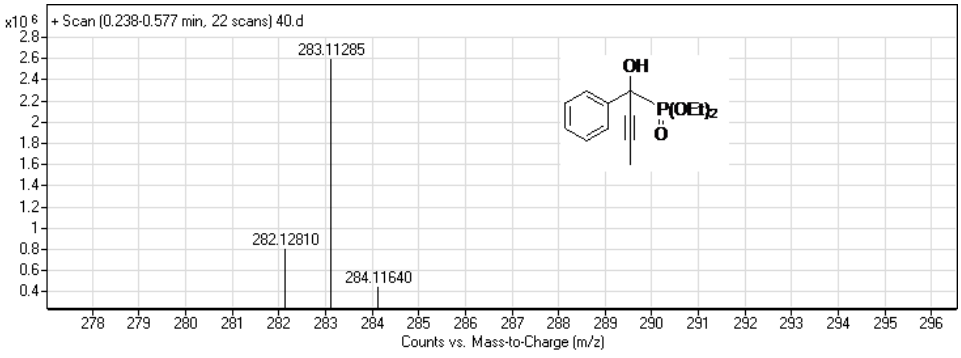


Figure B16. HRMS of compound **183**

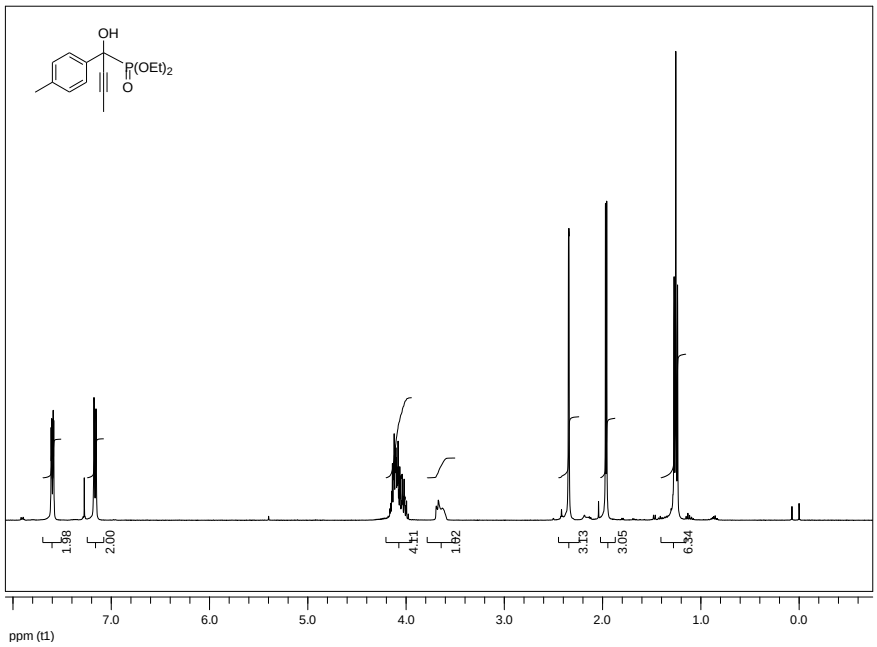


Figure B17. ^{1}H NMR spectrum of **186**

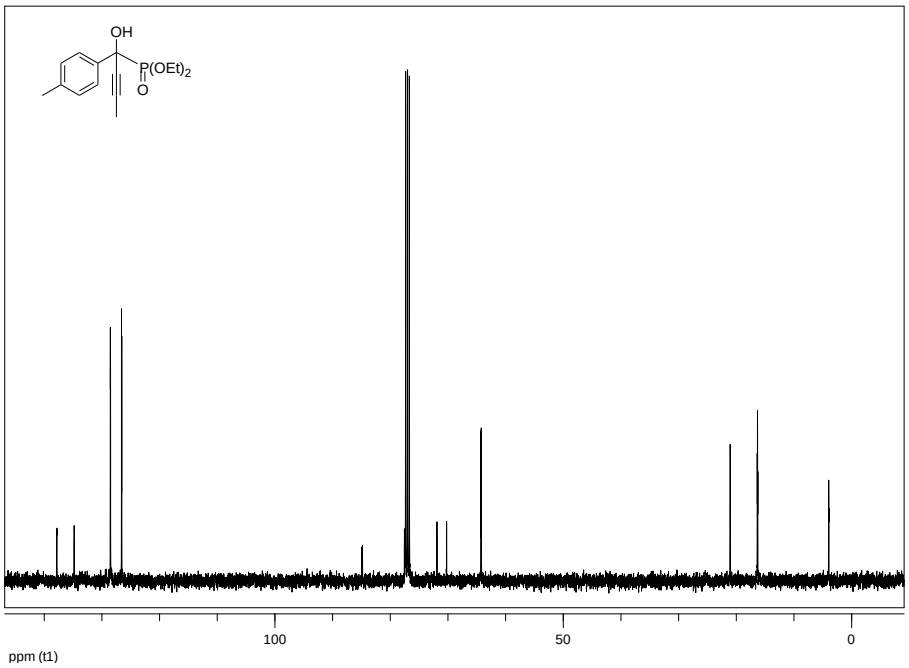


Figure B18. ^{13}C NMR spectrum of **186**

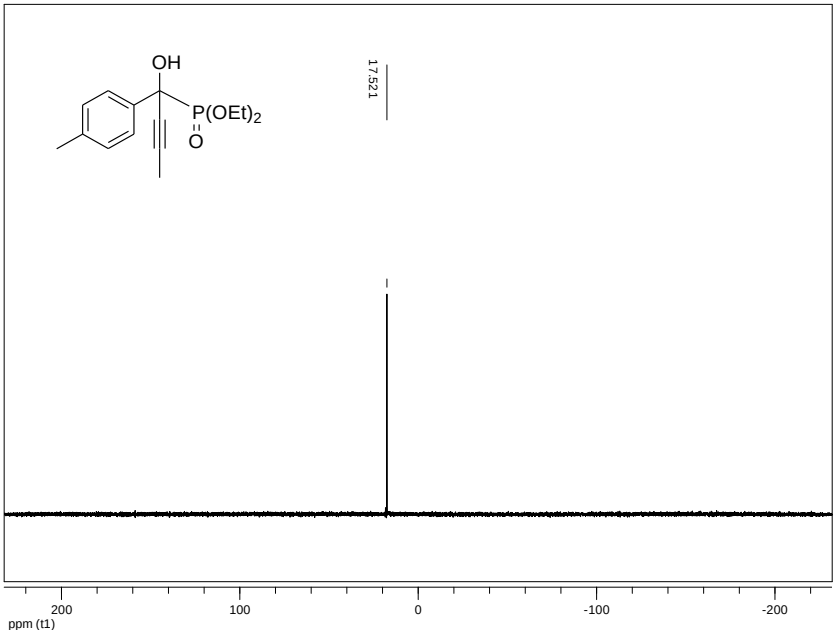


Figure B19. ^{31}P NMR spectrum of **186**

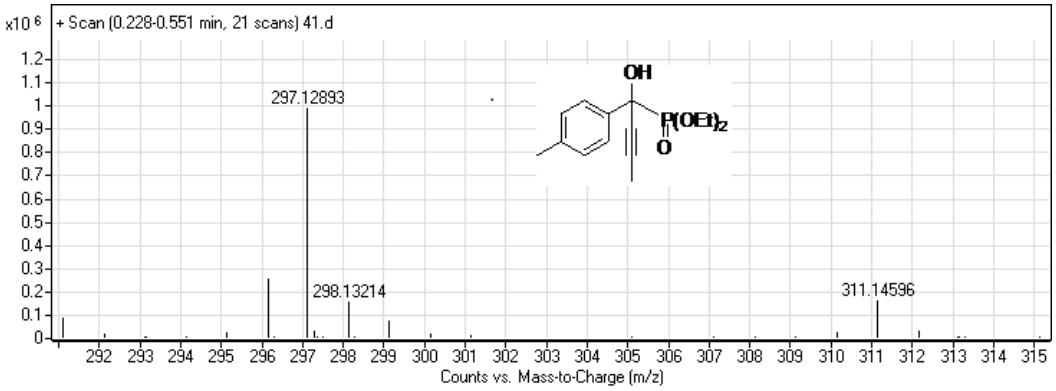


Figure B20. HRMS of compound **186**

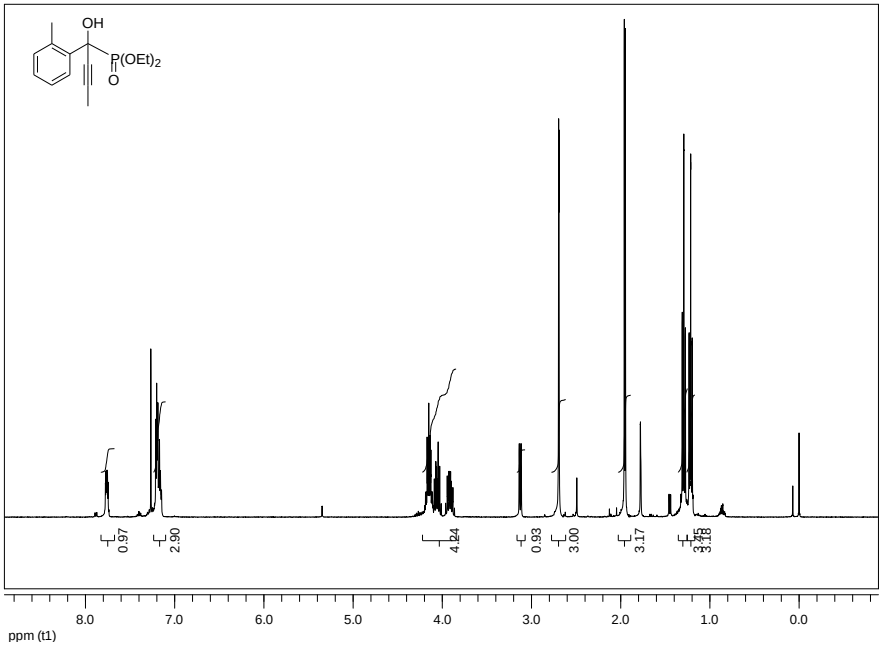


Figure B21. ^{1}H NMR spectrum of **188**

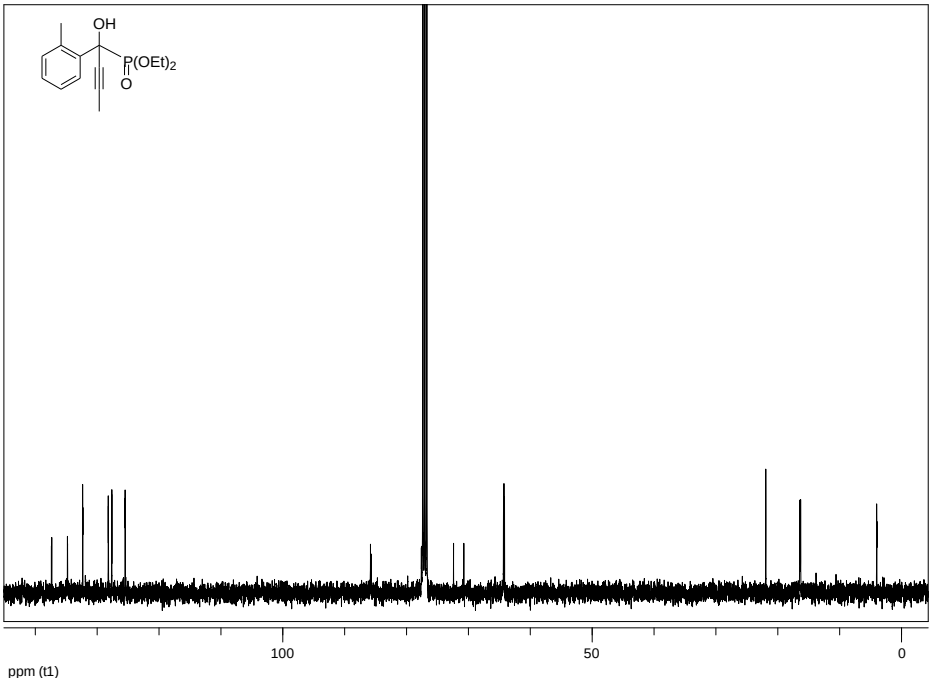


Figure B22. ^{13}C NMR spectrum of **188**

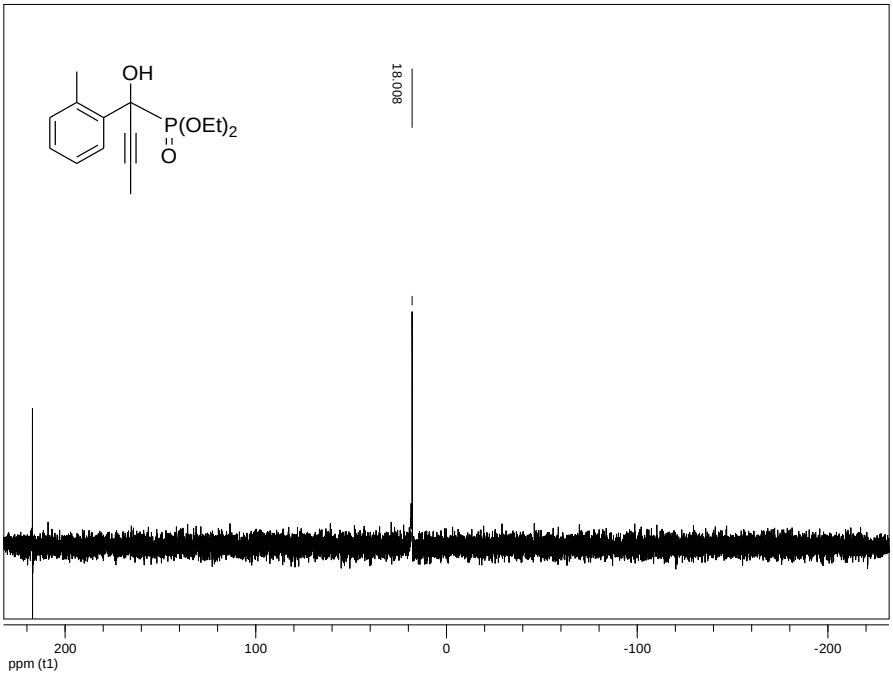


Figure B23. ^{31}P NMR spectrum of **188**

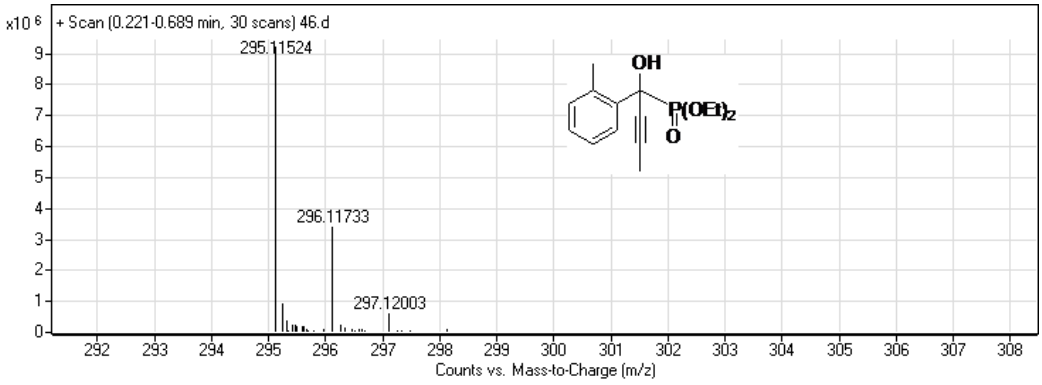


Figure B24. HRMS of compound **188**

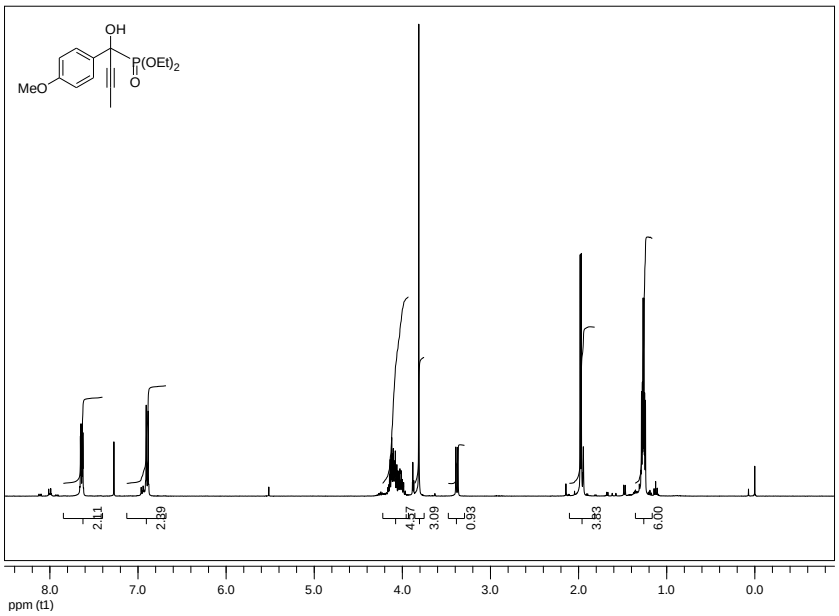


Figure B25. ^{1}H NMR spectrum of **189**

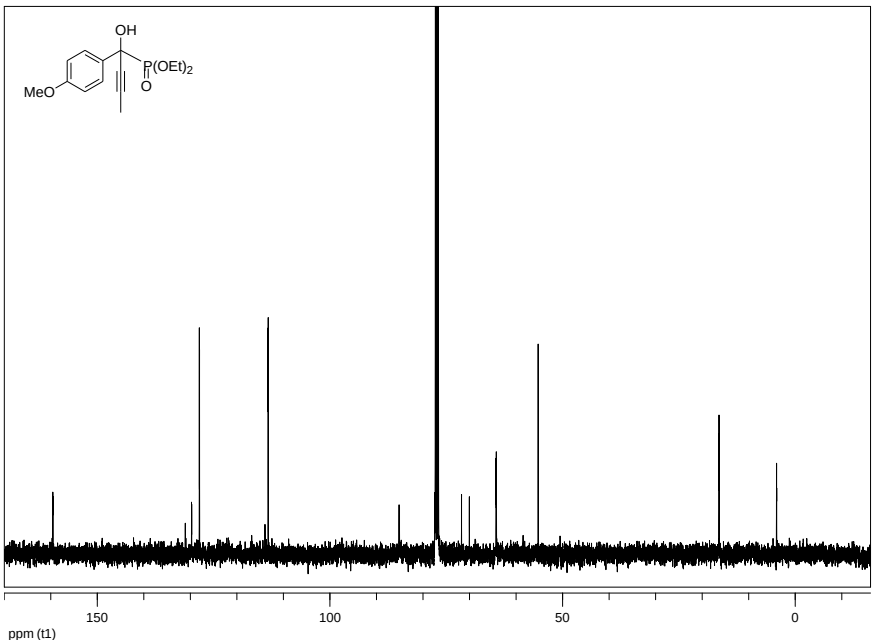


Figure B26. ^{13}C NMR spectrum of **189**

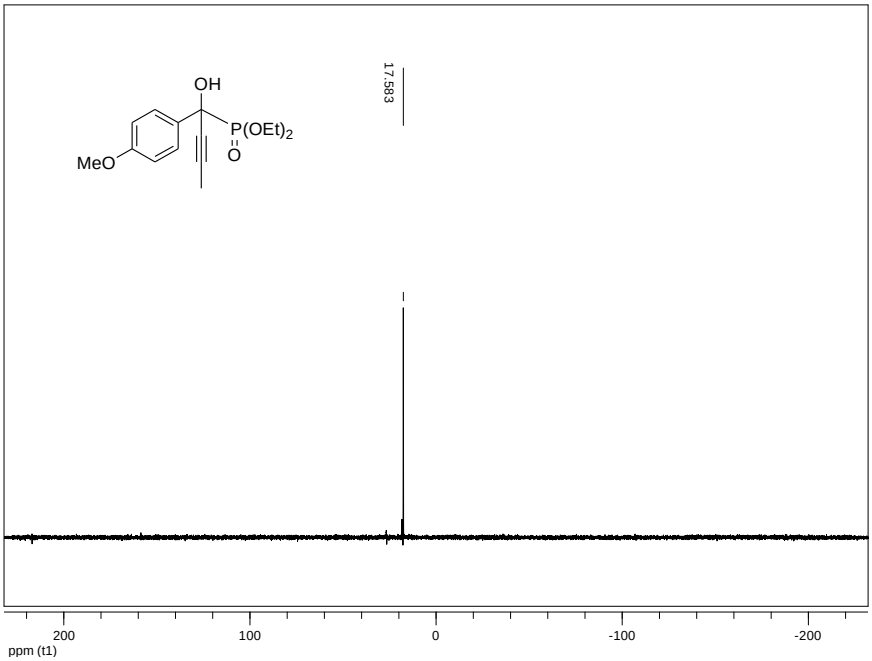


Figure B27. ^{31}P NMR spectrum of **189**

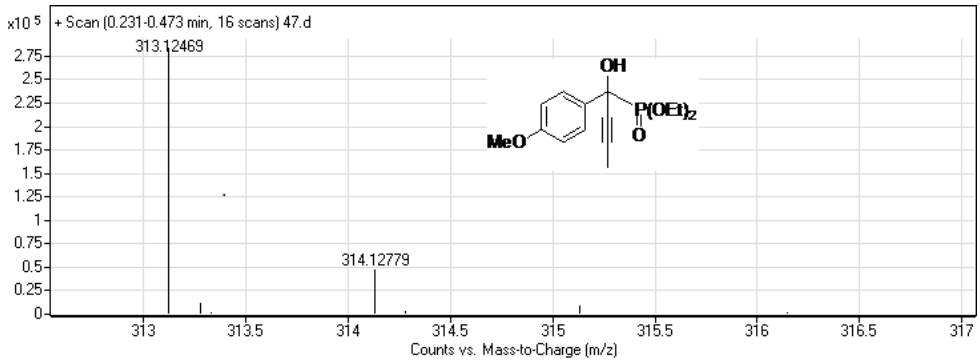


Figure B28. HRMS of compound **189**

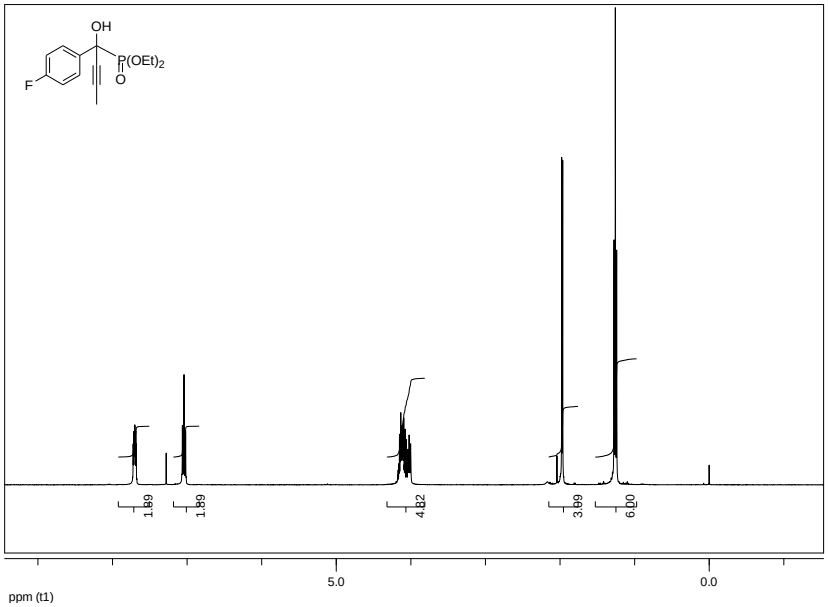


Figure B29. ^{1}H NMR spectrum of **191**

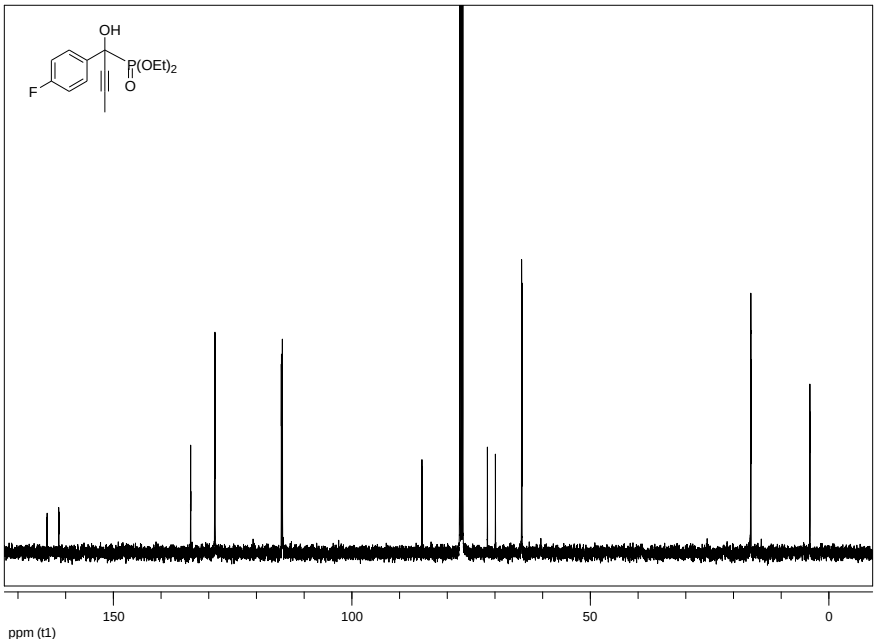


Figure B30. ^{13}C NMR spectrum of **191**

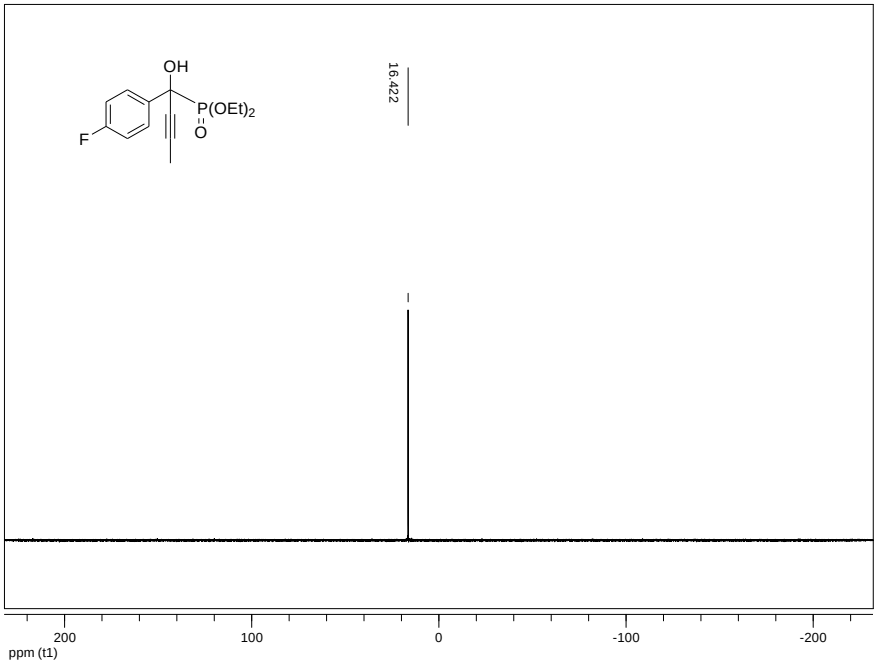


Figure B31. ^{31}P NMR spectrum of **191**

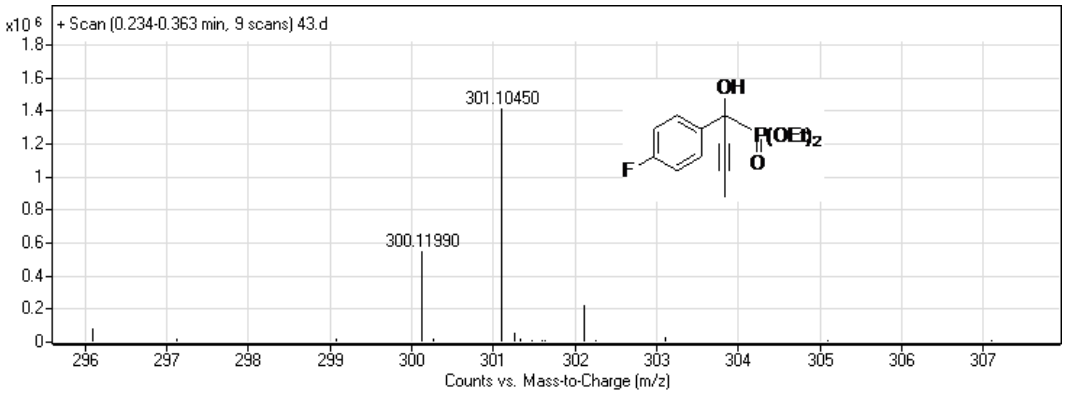


Figure B32. HRMS of compound **191**

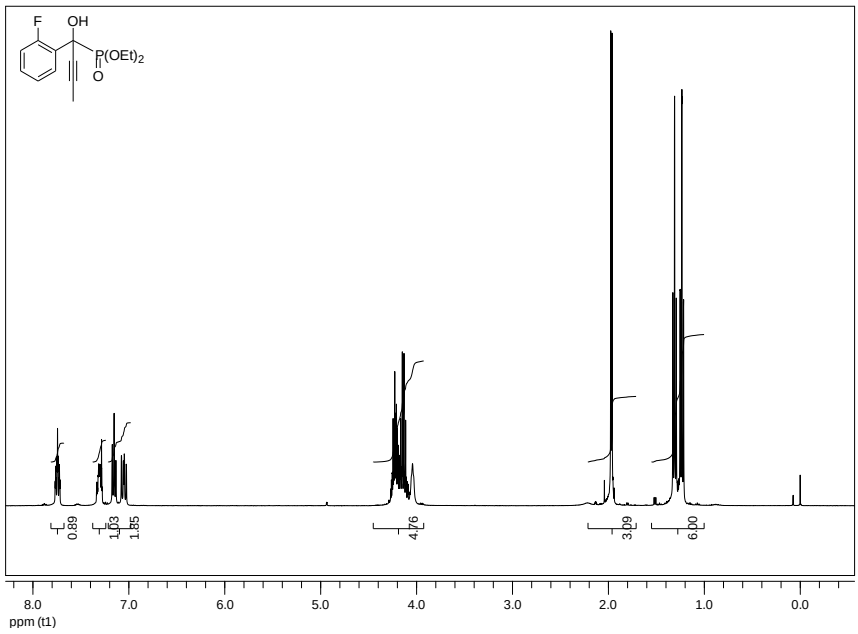


Figure B33. ^{1}H NMR spectrum of **193**

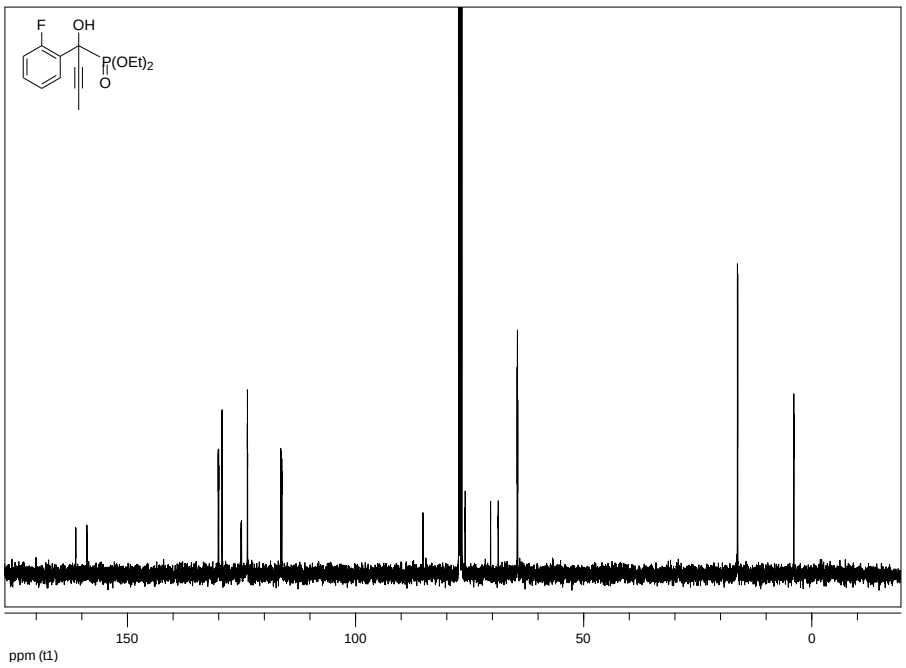


Figure B34. ^{13}C NMR spectrum of **193**

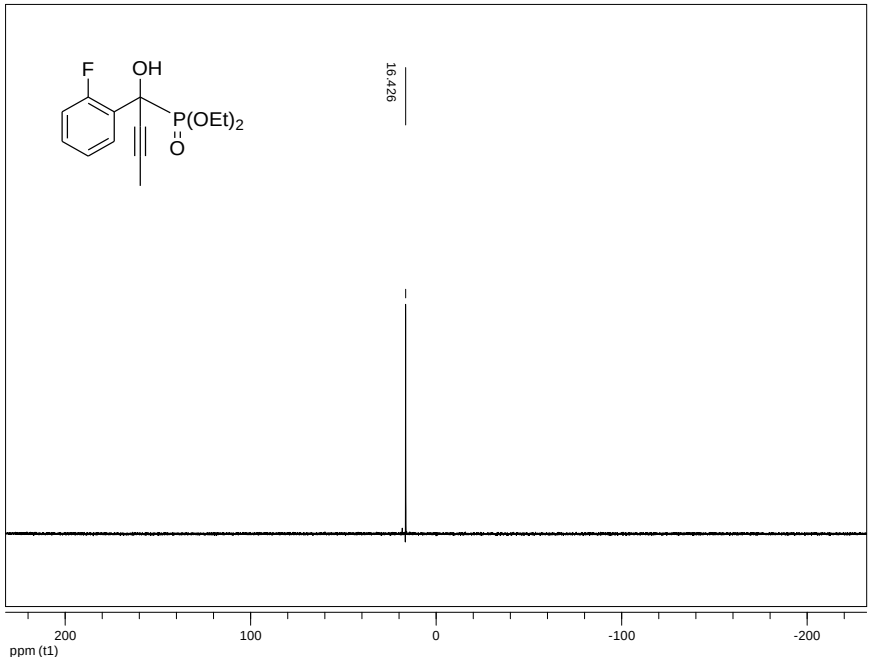


Figure B35. ^{31}P NMR spectrum of **193**

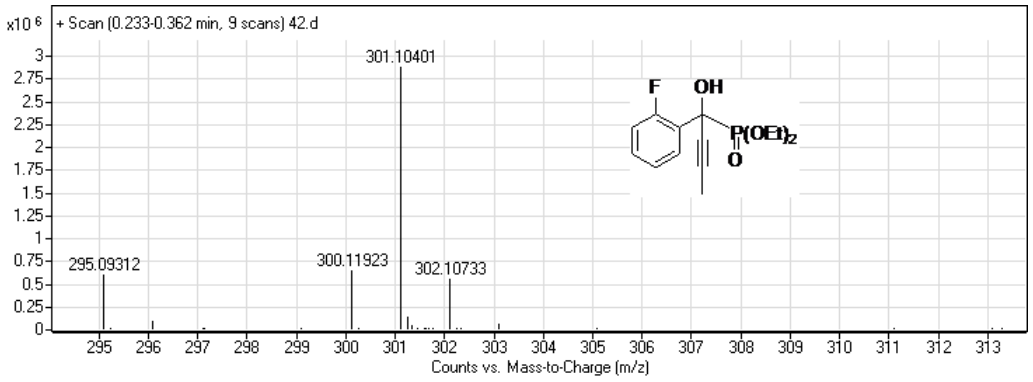


Figure B36. HRMS of compound **193**

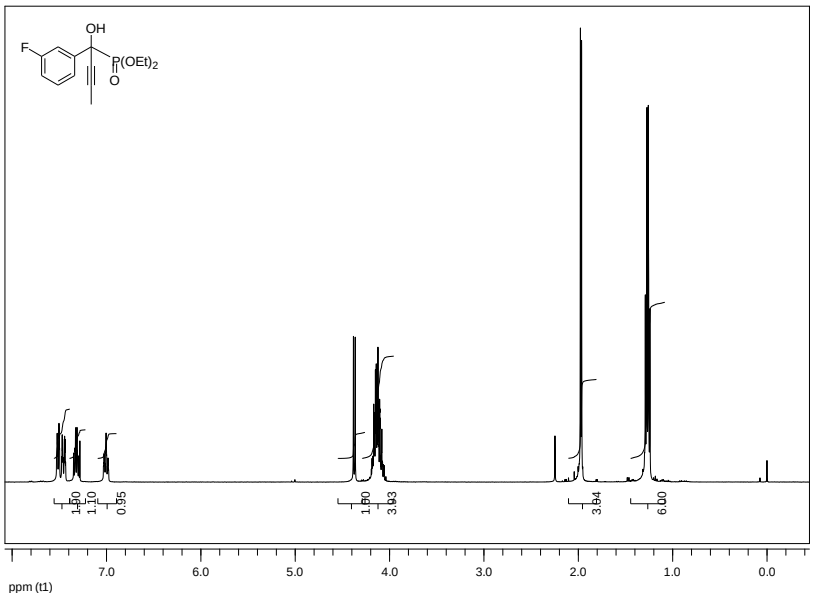


Figure B37. ^{1}H NMR spectrum of **195**

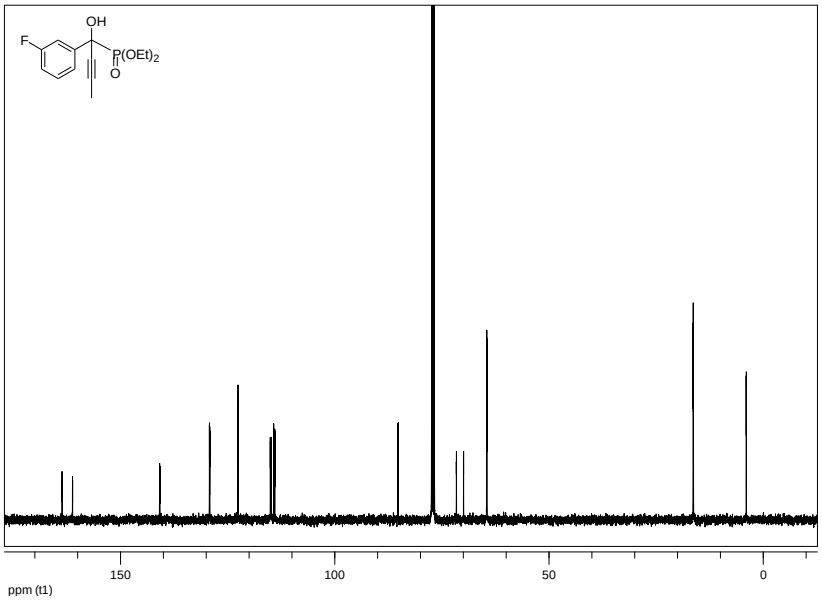


Figure B38. ^{13}C NMR spectrum of **195**

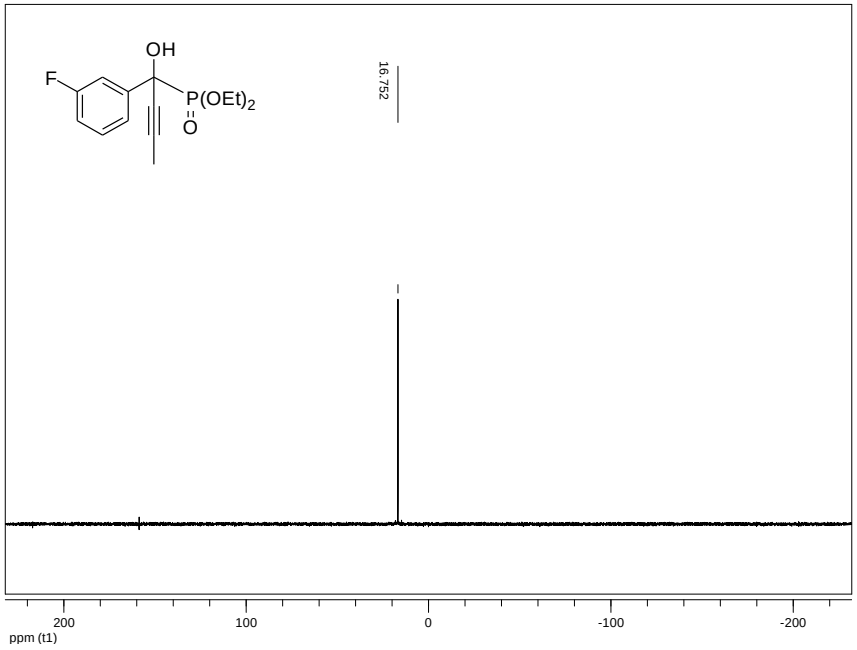


Figure B39. ^{31}P NMR spectrum of **195**

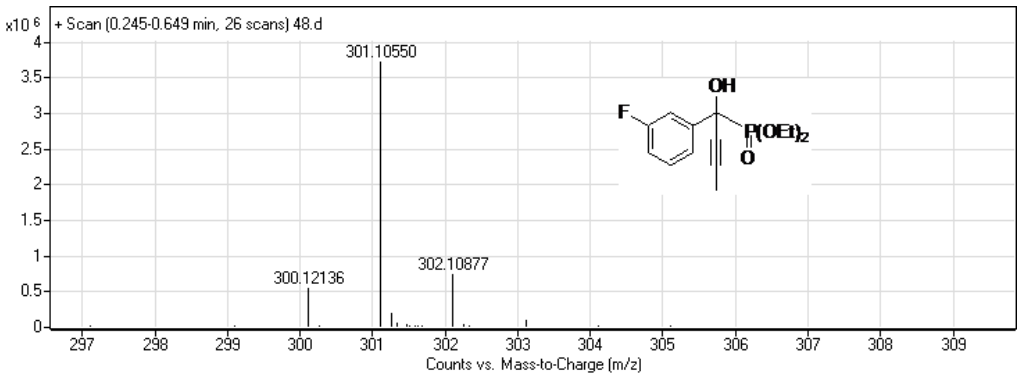


Figure B40. HRMS of compound **195**

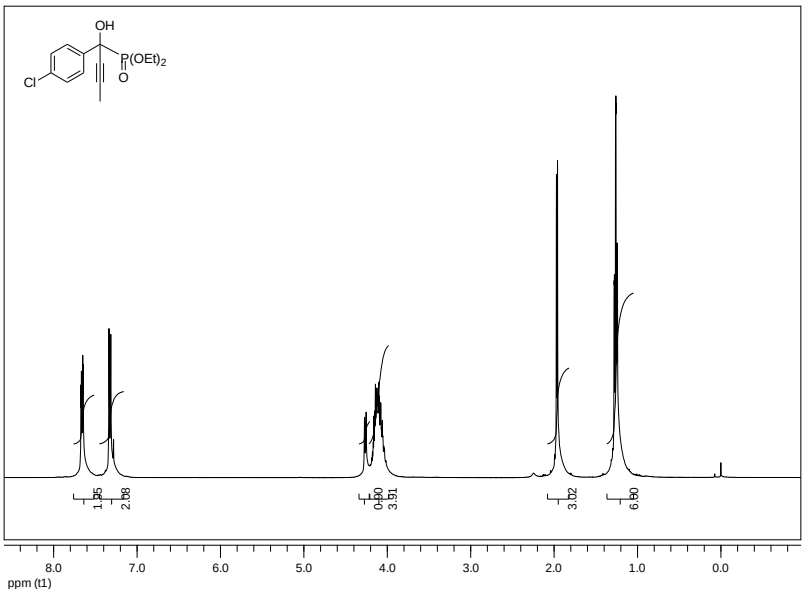


Figure B41. ^{1}H NMR spectrum of **196**

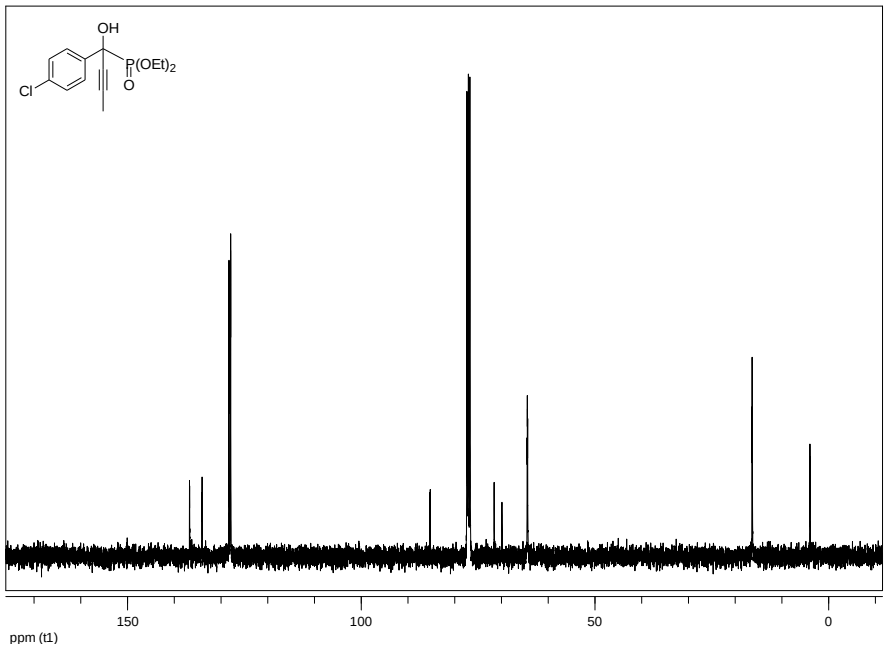


Figure B42. ^{13}C NMR spectrum of **196**

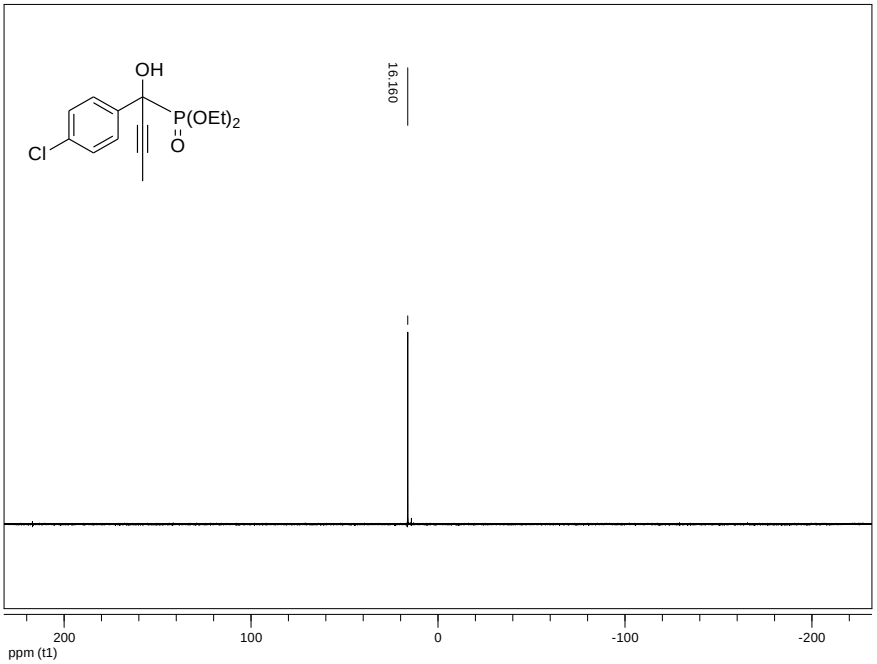


Figure B43. ^{31}P NMR spectrum of **196**

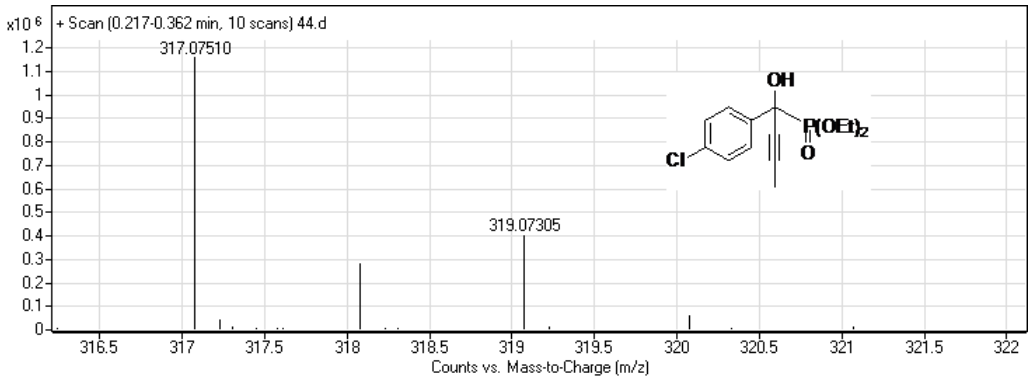


Figure B44. HRMS of compound **196**

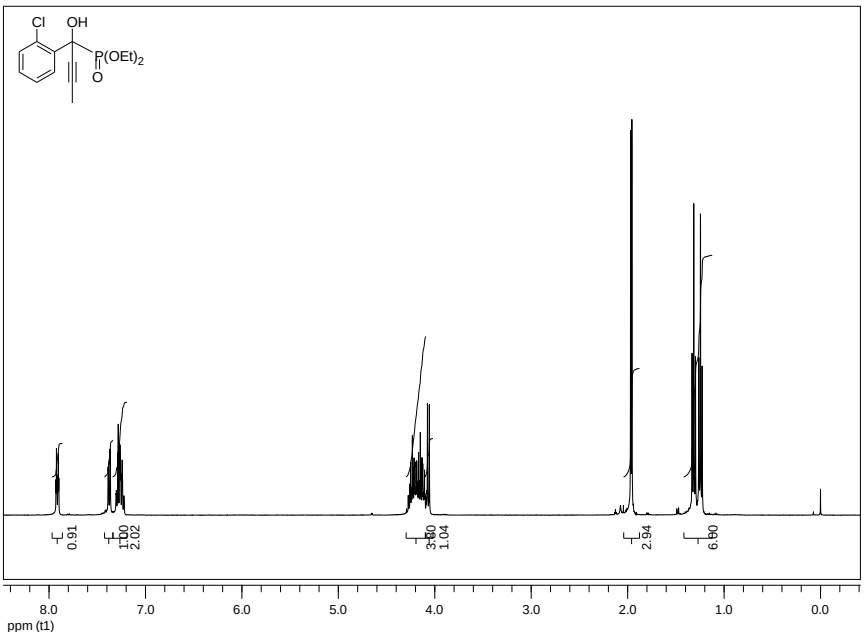


Figure B45. ^{1}H NMR spectrum of **198**

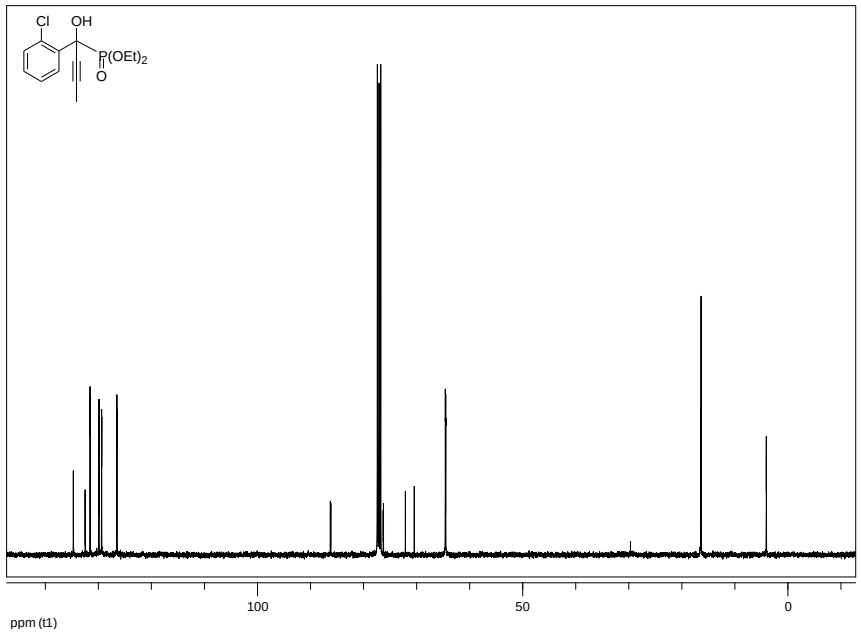


Figure B46. ^{13}C NMR spectrum of **198**

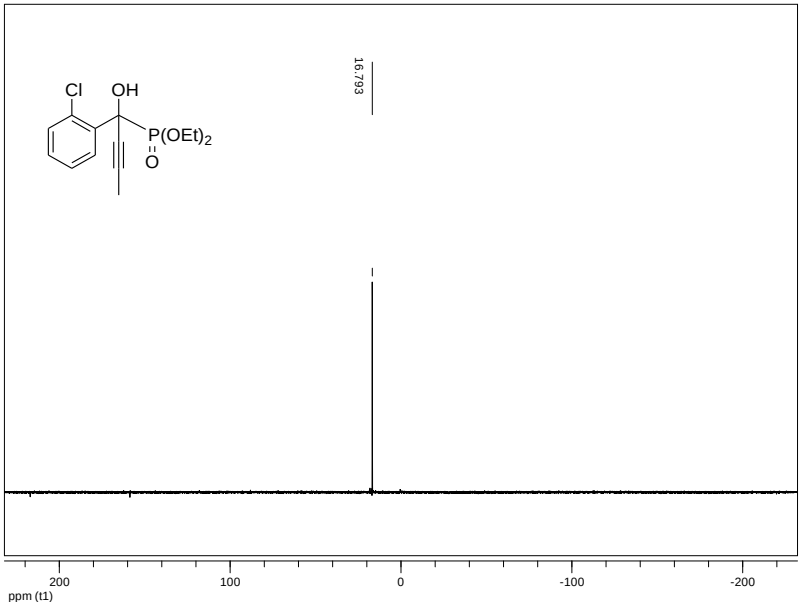


Figure B47. ^{31}P NMR spectrum of **198**

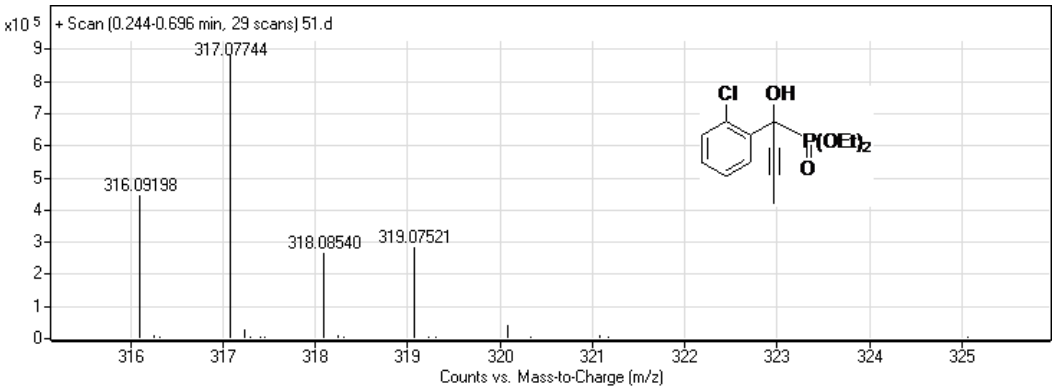


Figure B48. HRMS of compound **198**

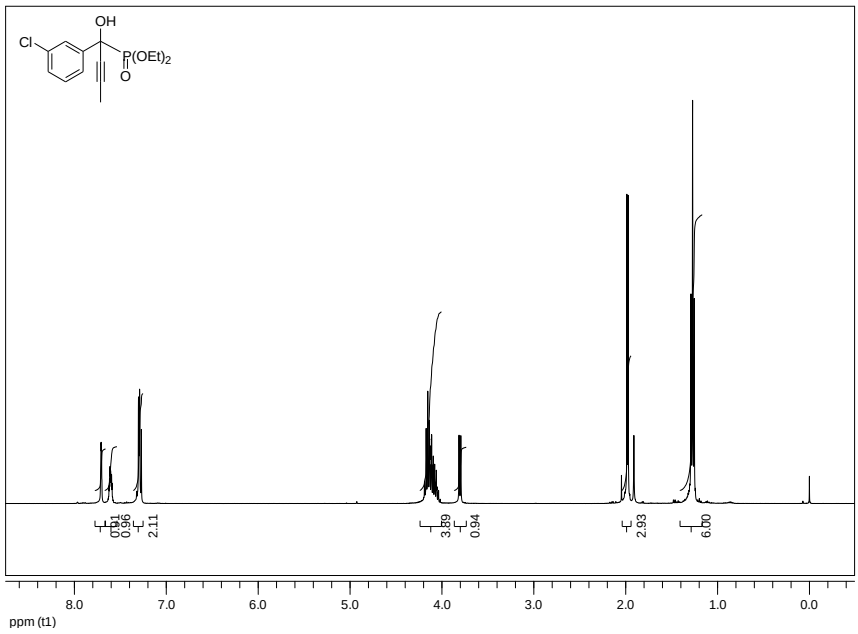


Figure B49. ^{1}H NMR spectrum of **200**

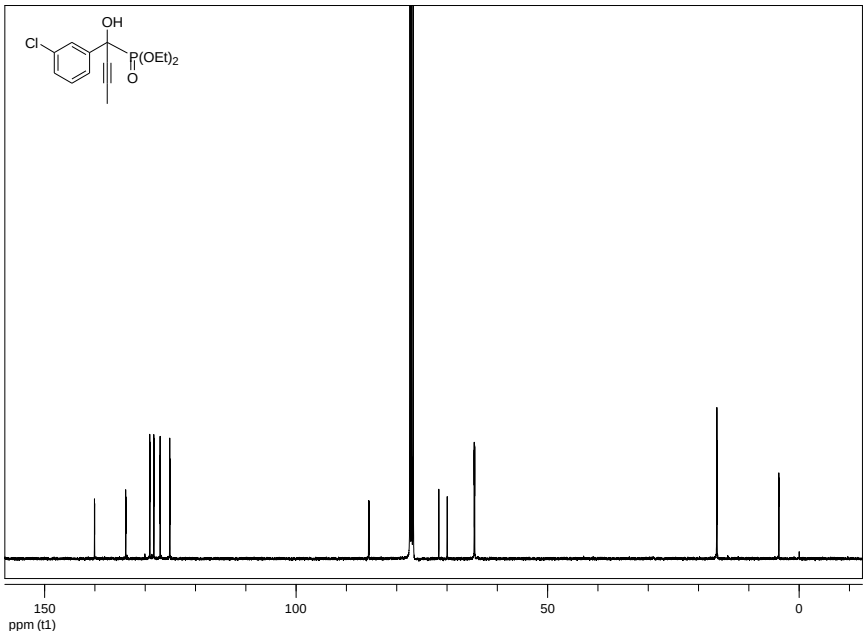


Figure B50. ^{13}C NMR spectrum of **200**

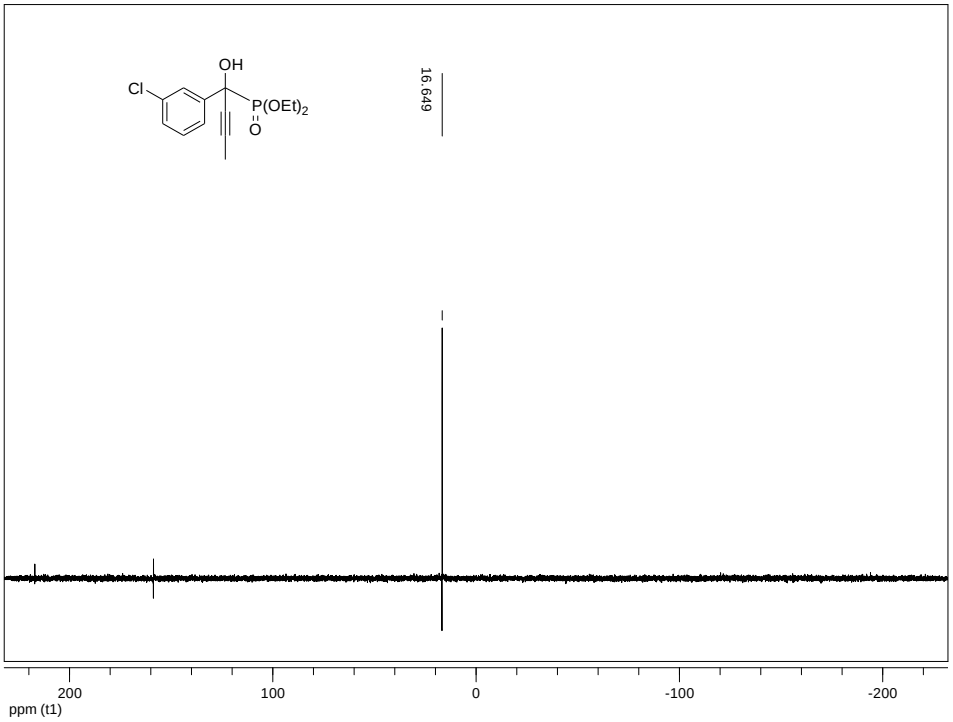


Figure B51. ^{31}P NMR spectrum of **200**

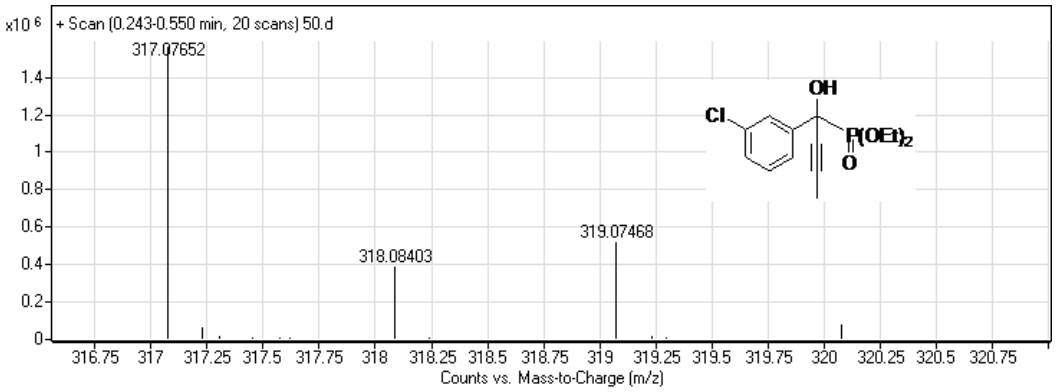


Figure B52. HRMS of compound **200**

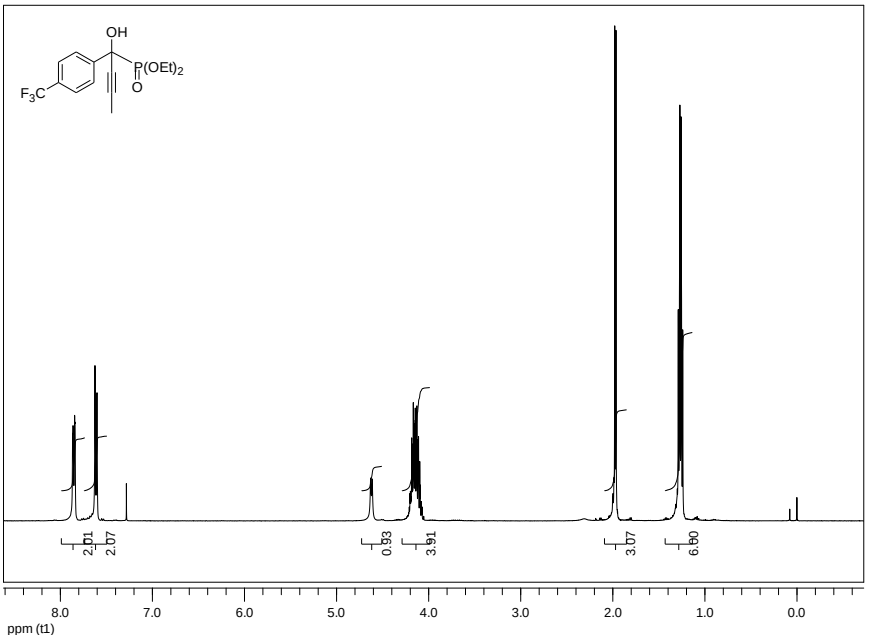


Figure B53. ^{1}H NMR spectrum of **202**

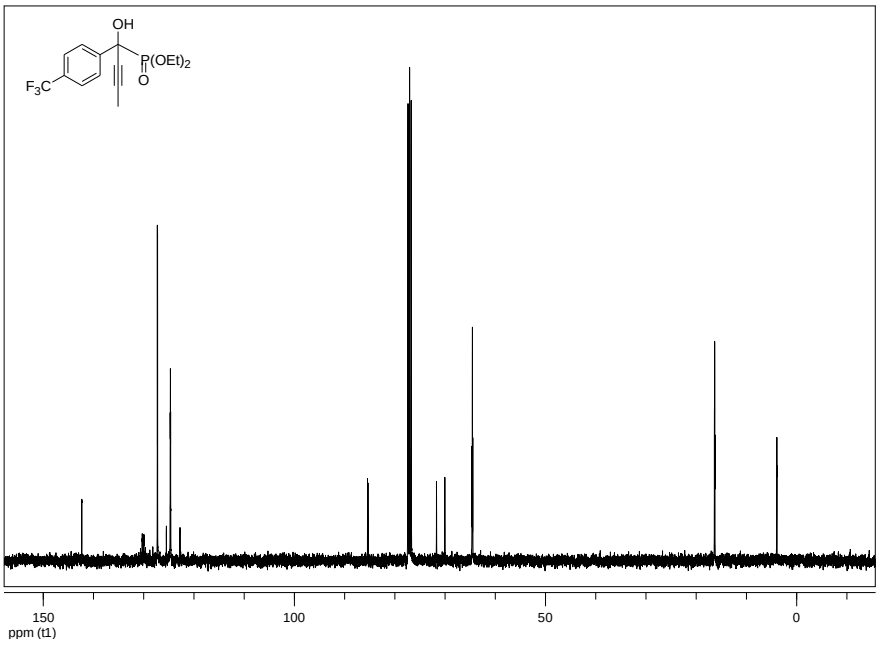


Figure B54. ^{13}C NMR spectrum of **202**

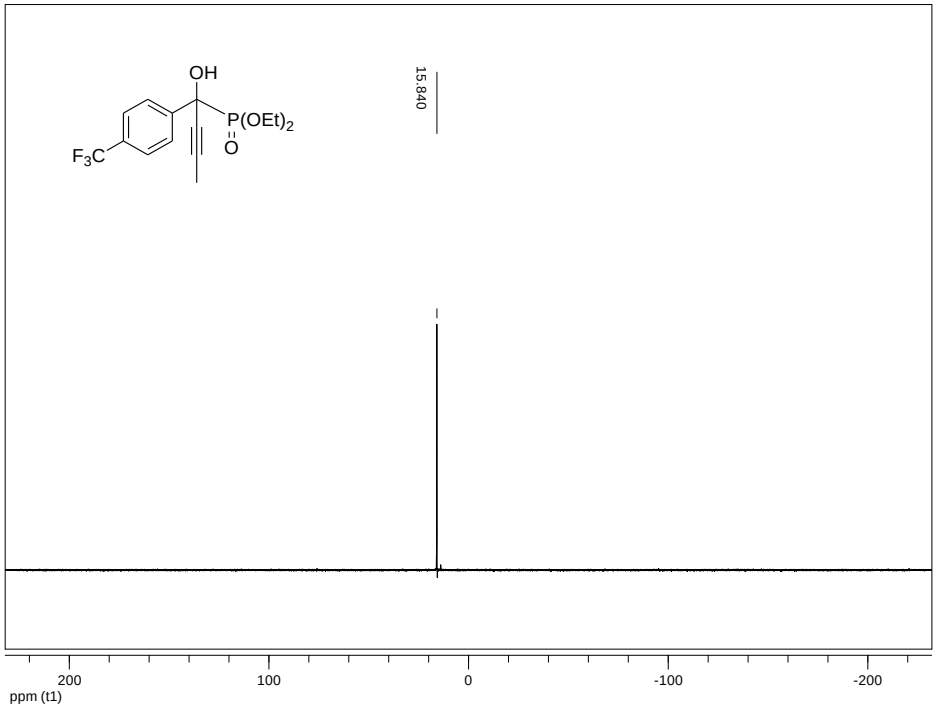


Figure B55. ^{31}P NMR spectrum of **202**

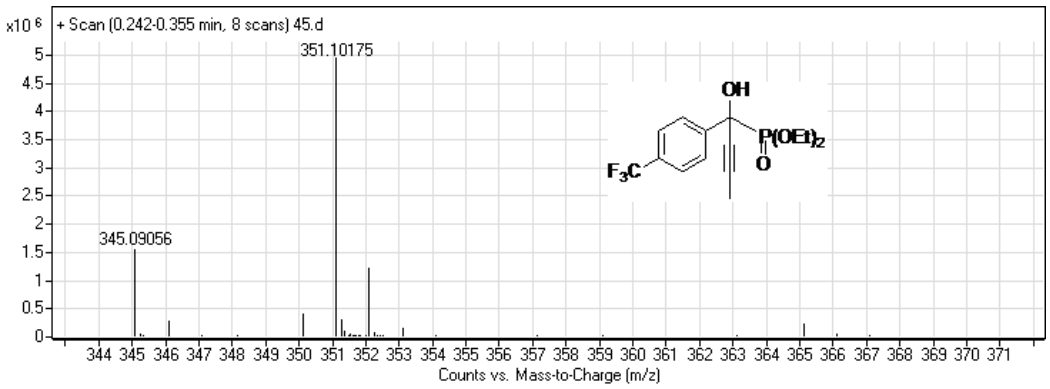


Figure B56. HRMS of compound **202**

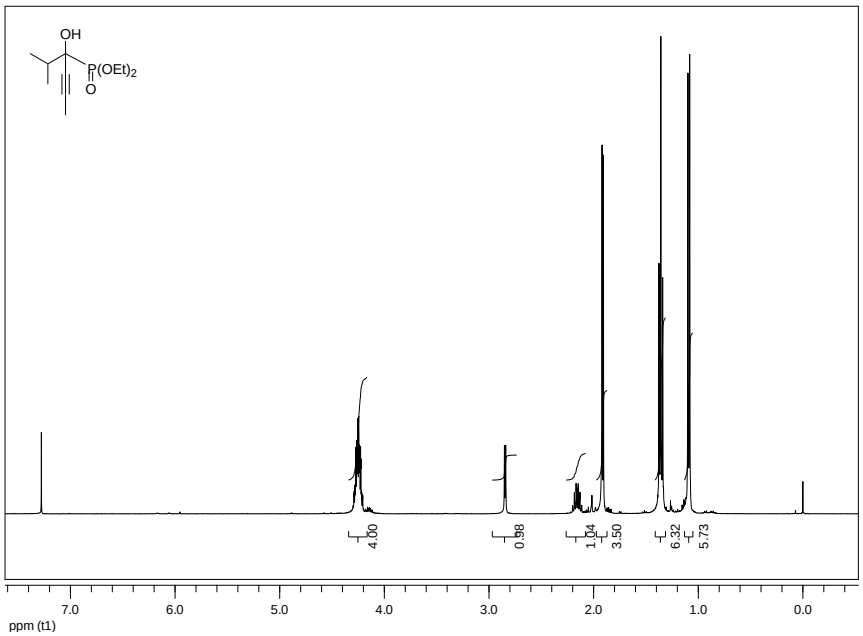


Figure B57. ^{1}H NMR spectrum of **204**

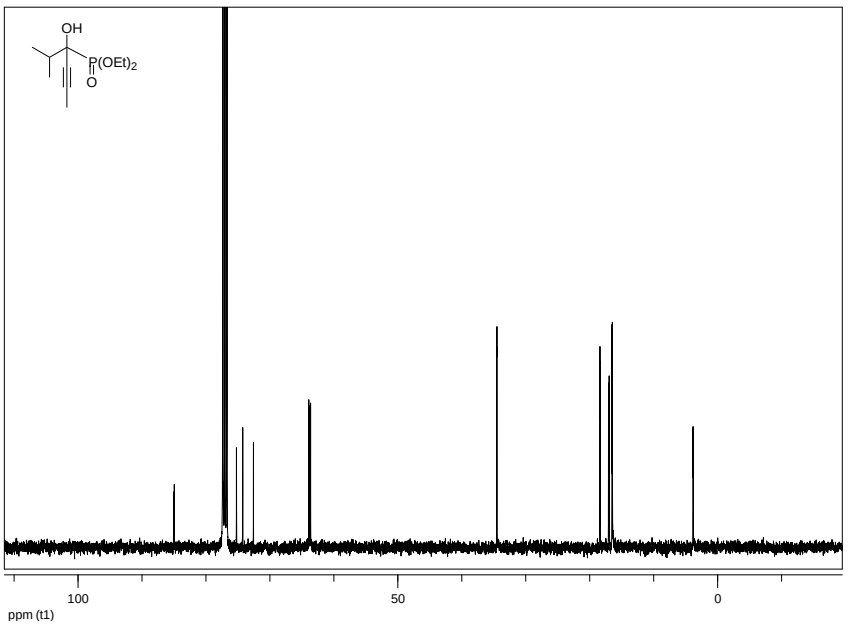


Figure B58. ^{13}C NMR spectrum of **204**

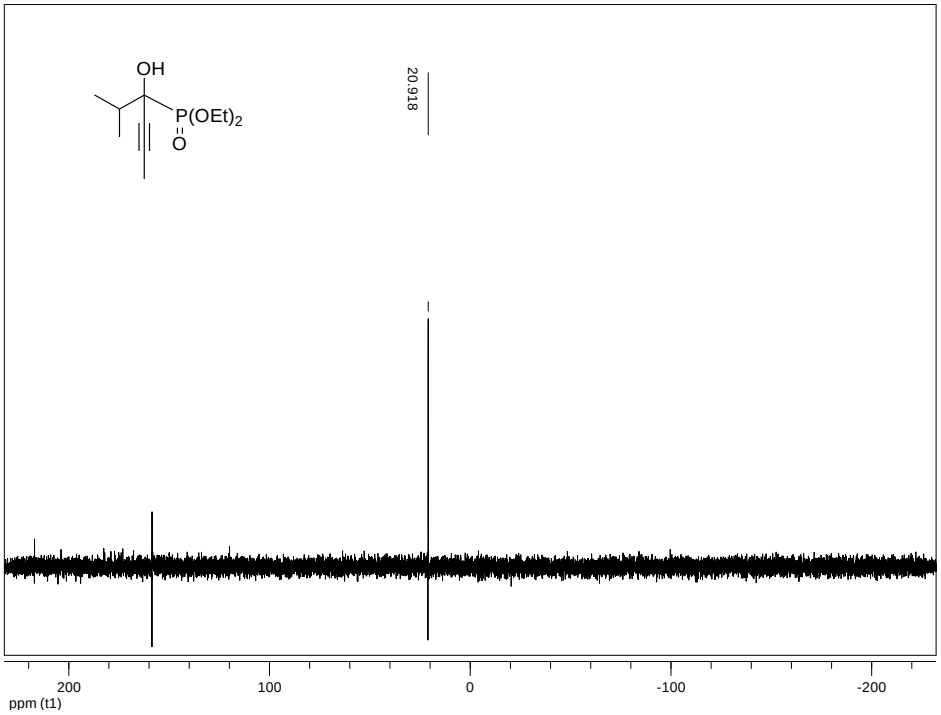


Figure B59. ^{31}P NMR spectrum of **204**

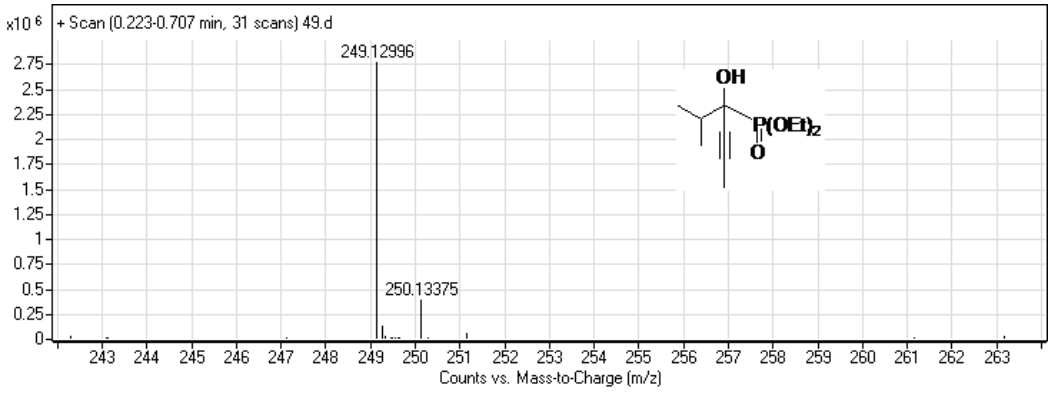


Figure B60. HRMS of compound **204**

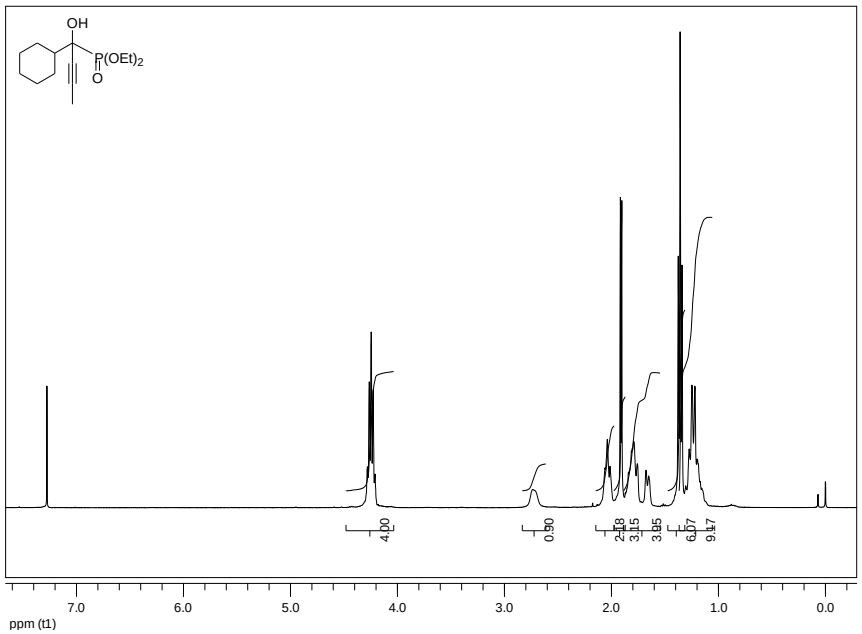


Figure B61. ^{1}H NMR spectrum of **206**

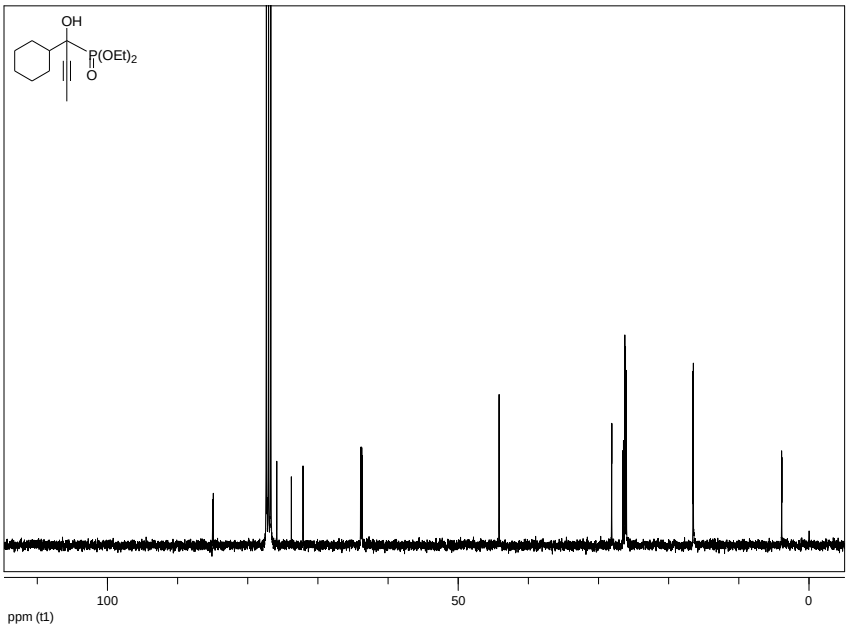


Figure B62. ^{13}C NMR spectrum of **206**

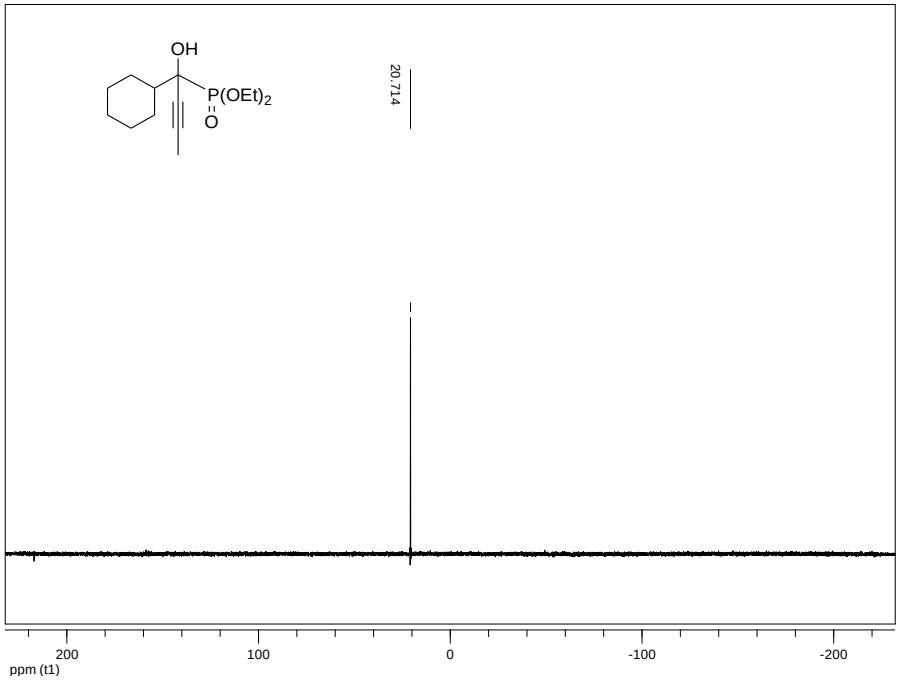


Figure B63. ^{31}P NMR spectrum of **206**

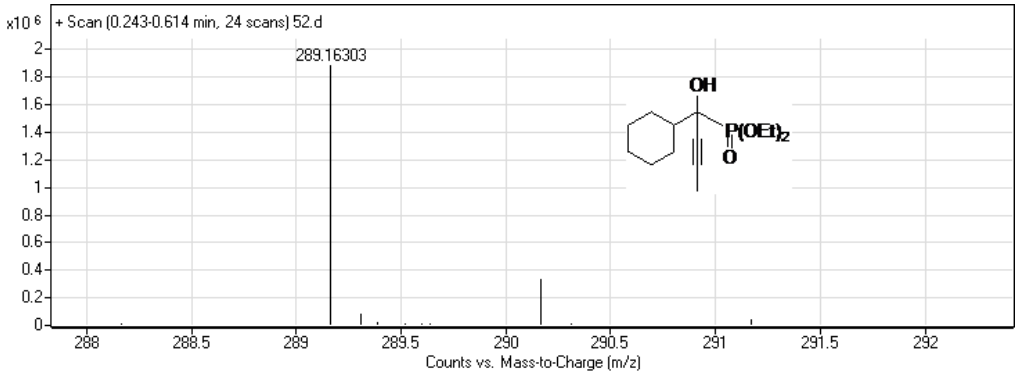


Figure B64. HRMS of compound **206**

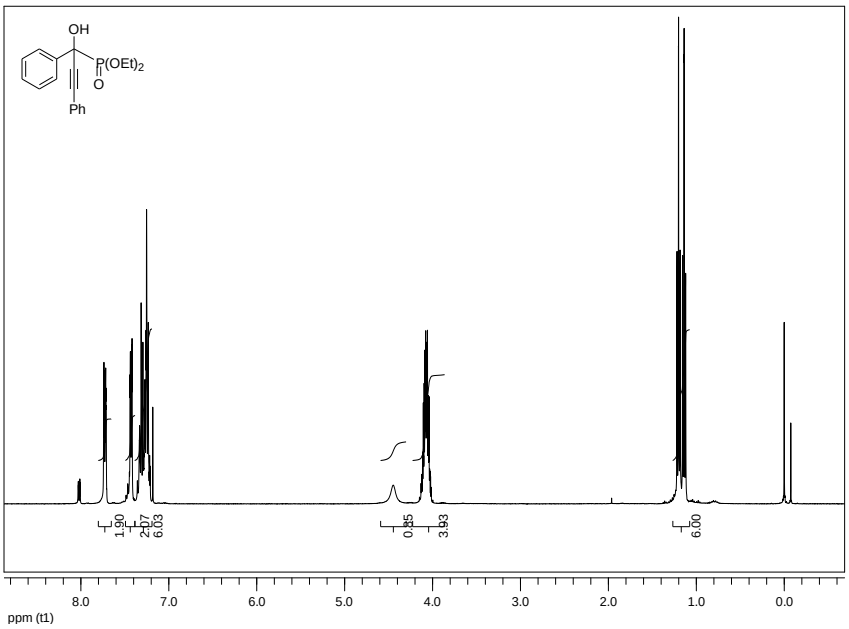


Figure B65. ^{1}H NMR spectrum of **207**

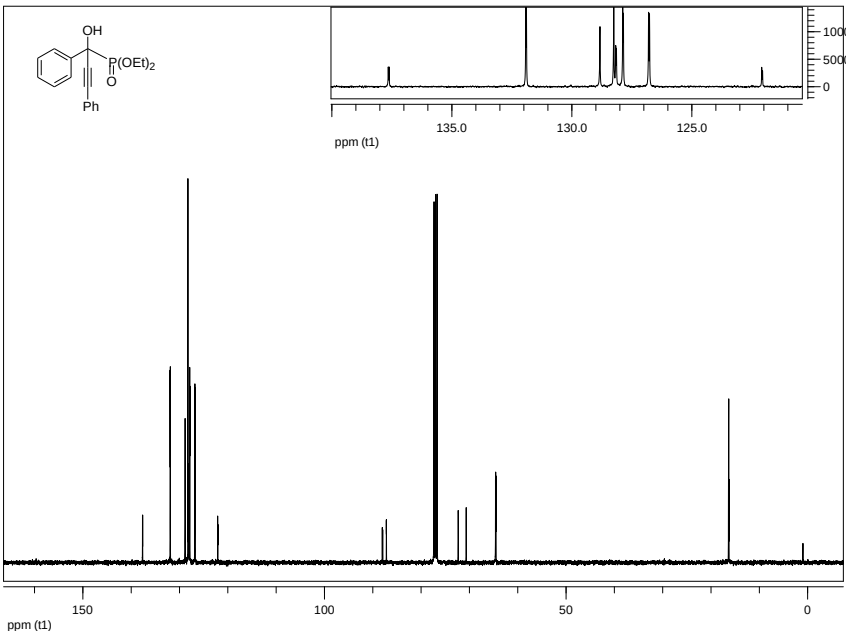


Figure B66. ^{13}C NMR spectrum of **207**

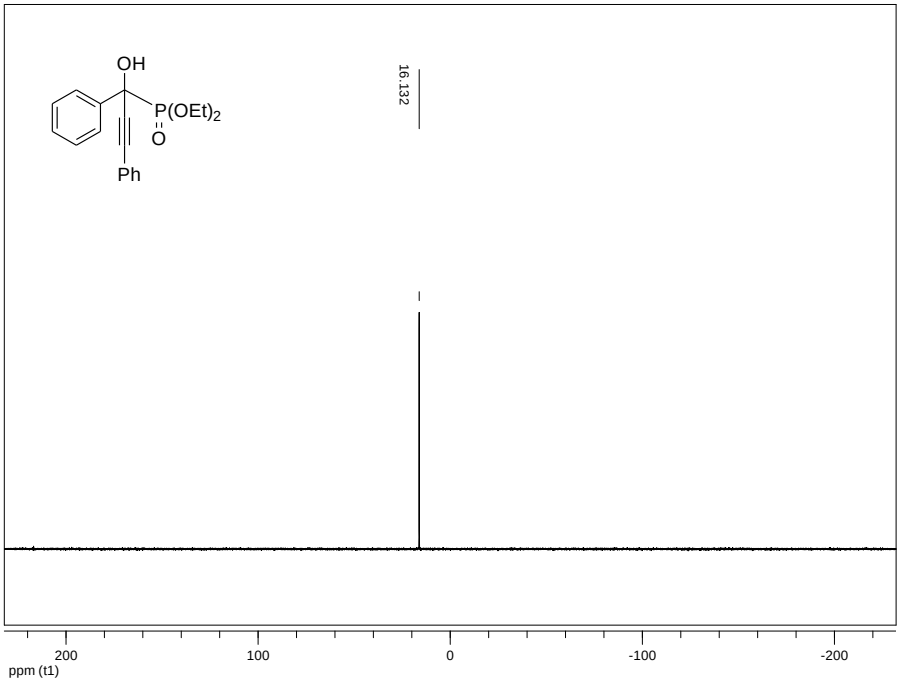


Figure B67. ^{31}P NMR spectrum of **207**

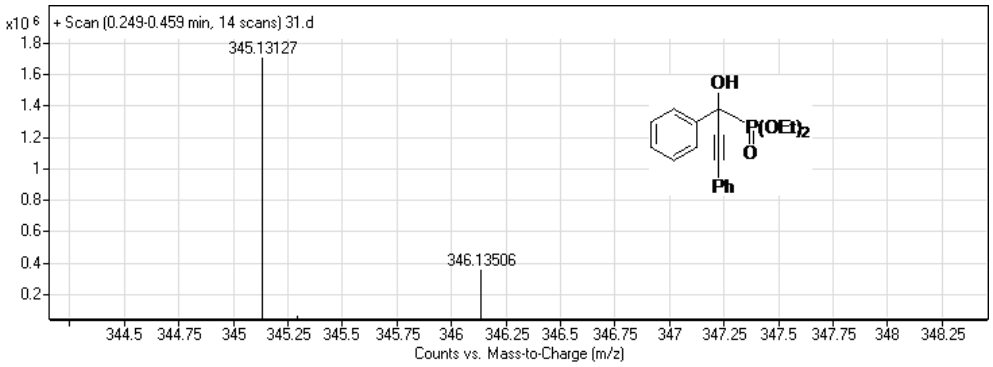


Figure B68. HRMS of compound **207**

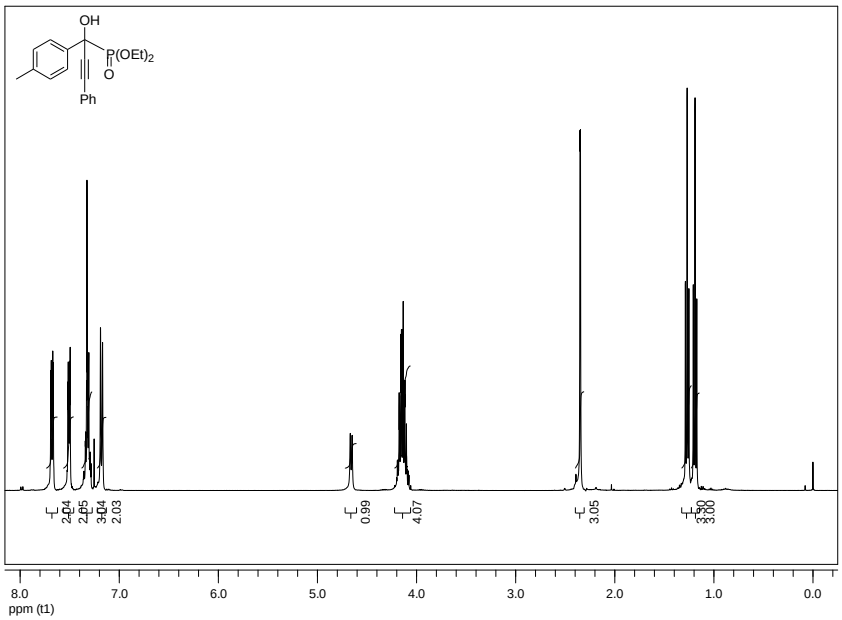


Figure B69. ^{1}H NMR spectrum of **209**

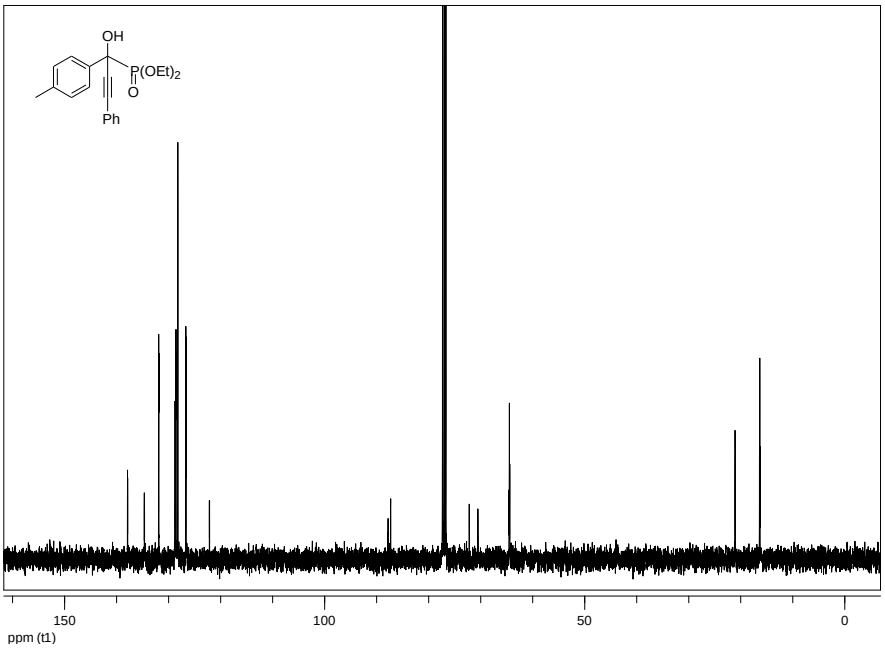


Figure B70. ^{13}C NMR spectrum of **209**

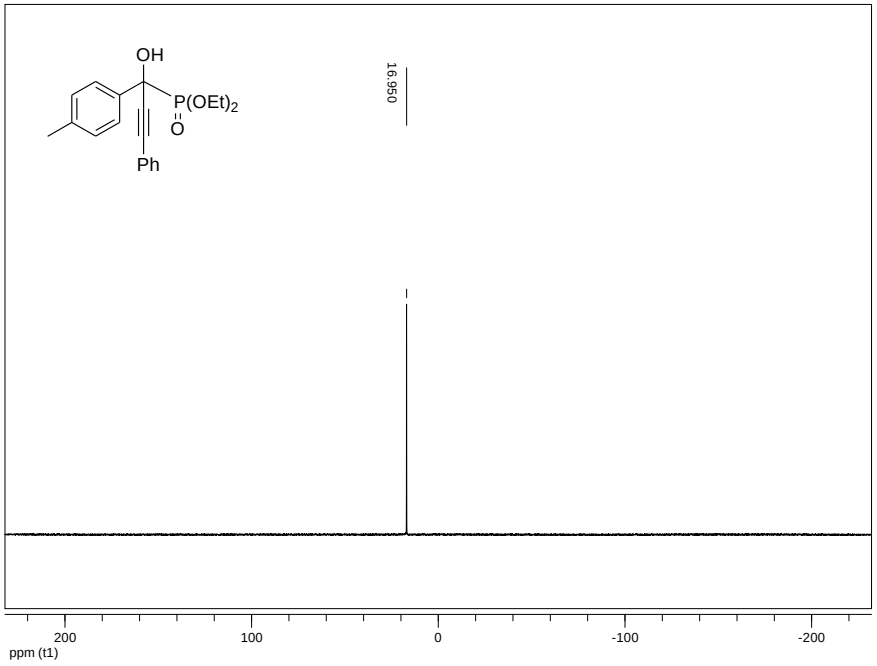


Figure B71. ^{31}P NMR spectrum of **209**

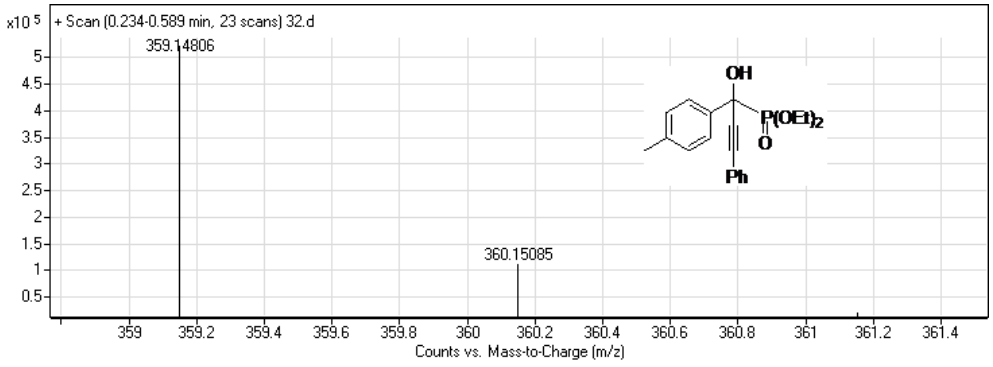


Figure B72. HRMS of compound **209**

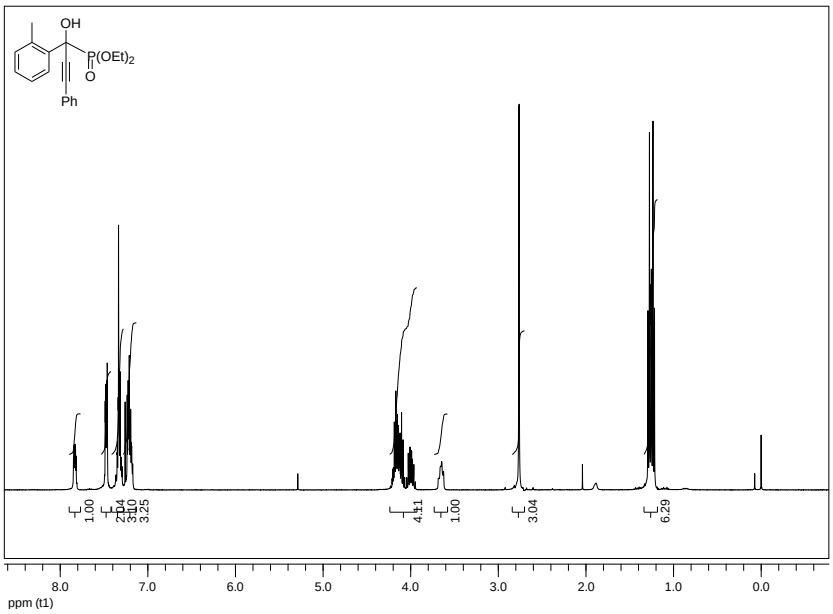


Figure B73. ^{1}H NMR spectrum of **210**

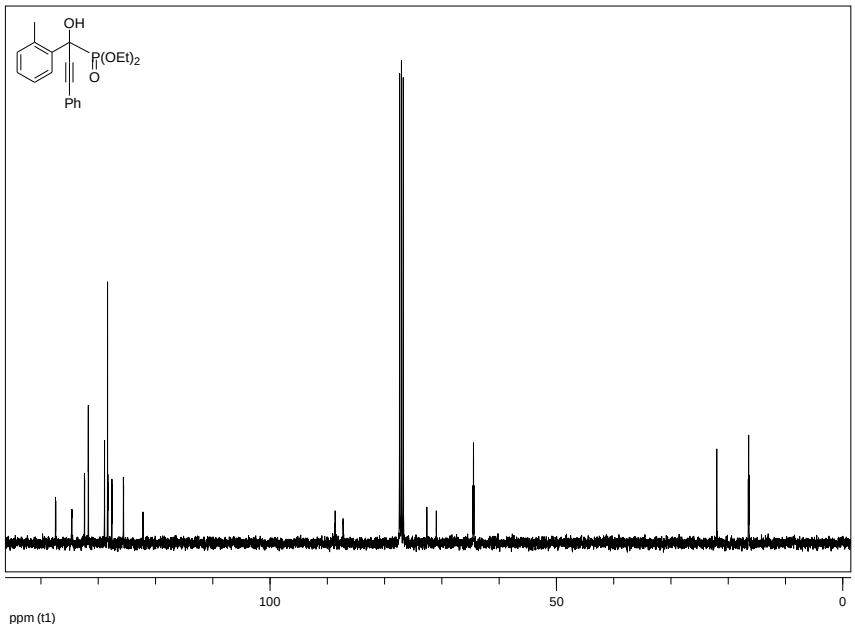


Figure B74. ^{13}C NMR spectrum of **210**

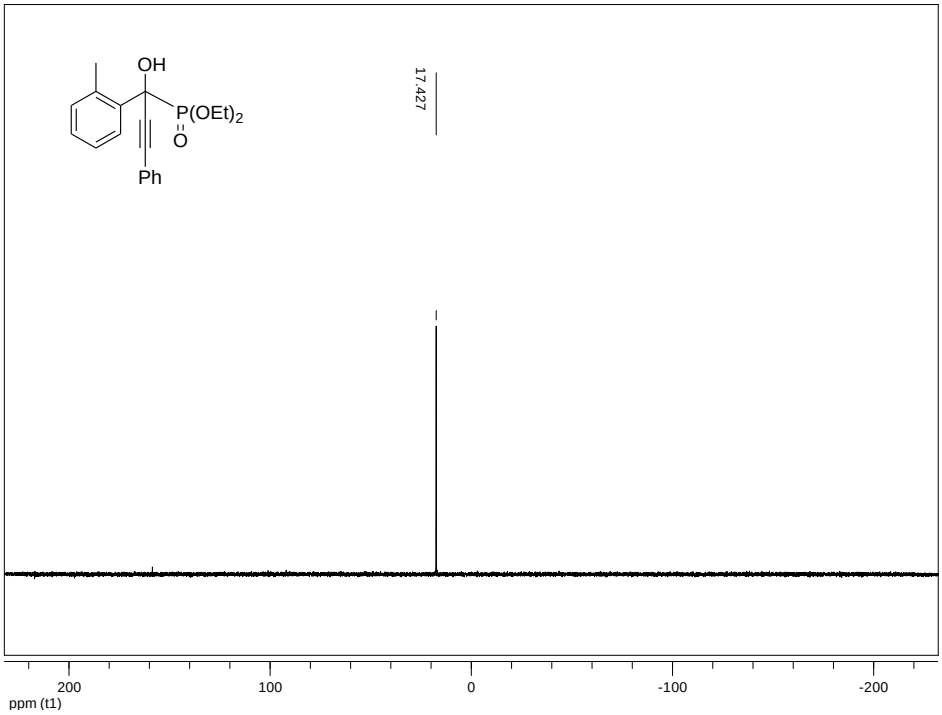


Figure B75. ^{31}P NMR spectrum of **210**

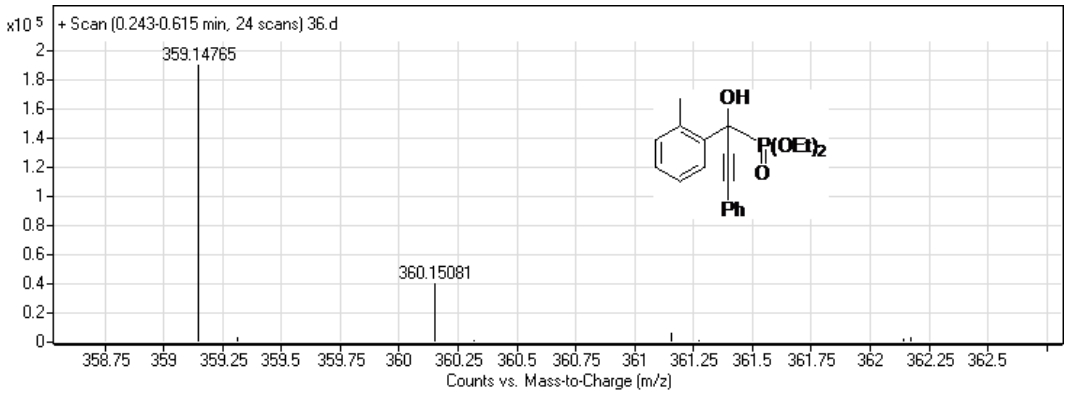


Figure B76. HRMS of compound **210**

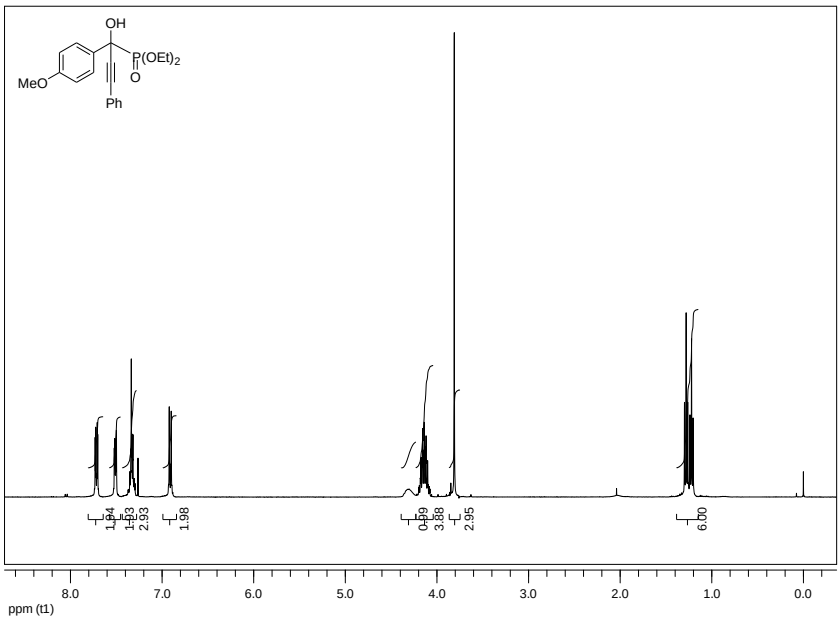


Figure B77. ^{1}H NMR spectrum of **211**

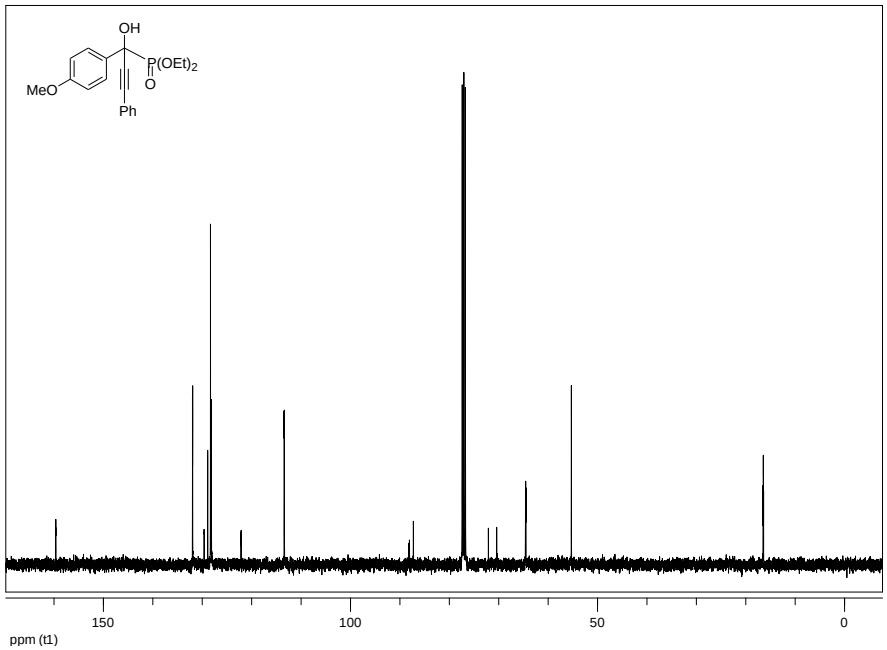


Figure B78. ^{13}C NMR spectrum of **211**

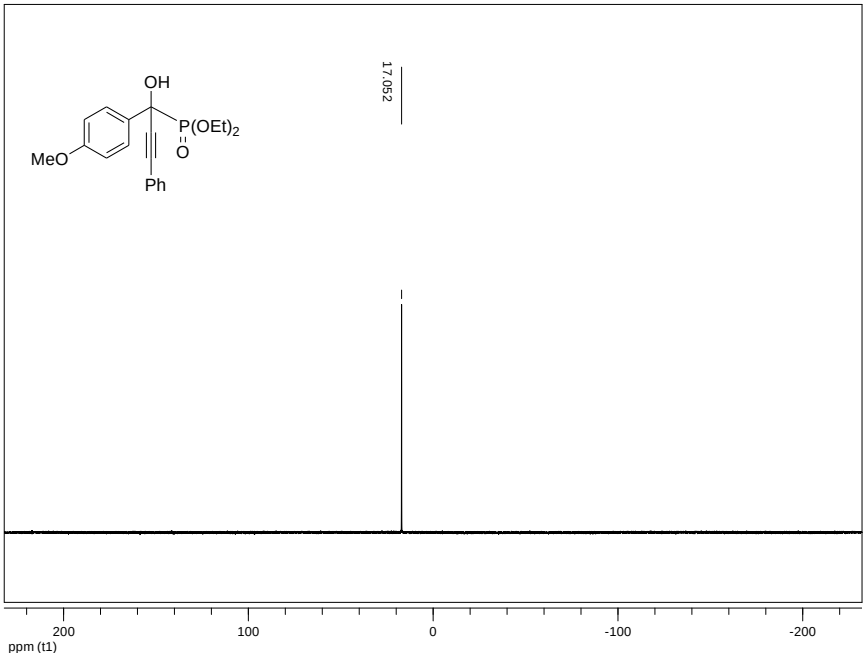


Figure B79. ^{31}P NMR spectrum of **211**

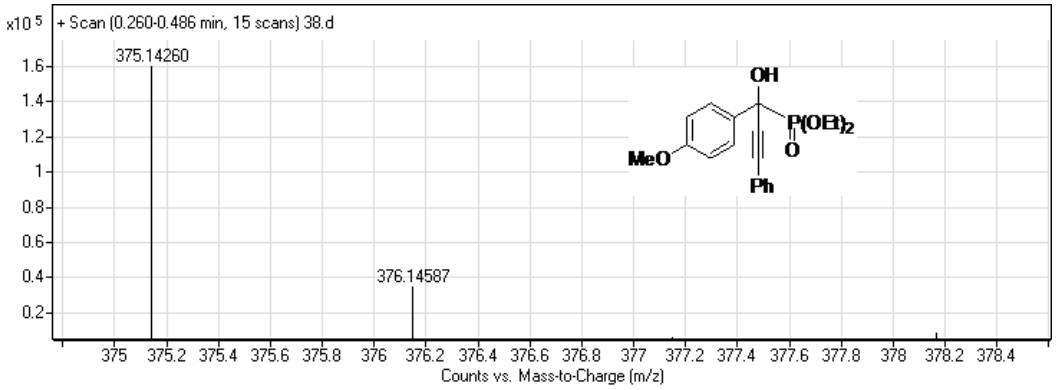


Figure B80. HRMS of compound **211**

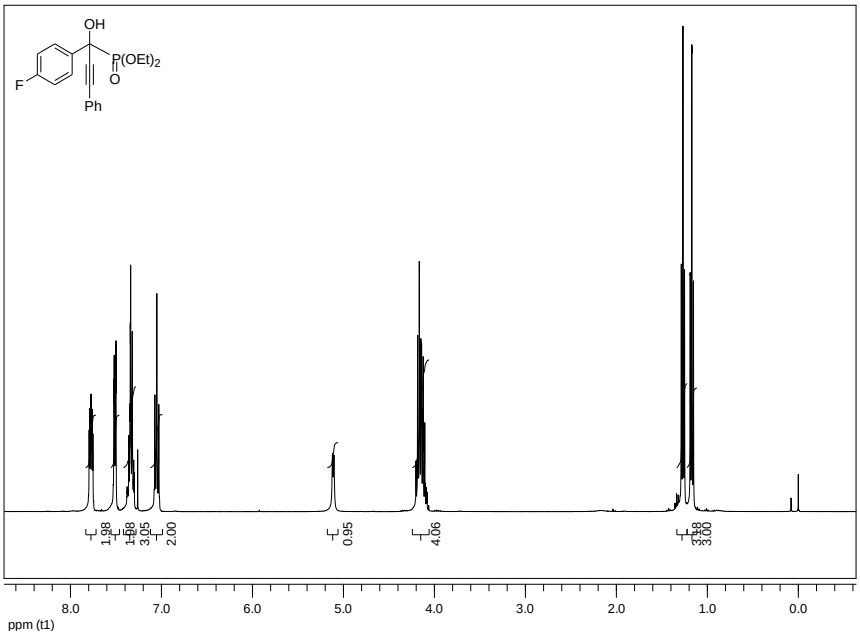


Figure B81. ^{1}H NMR spectrum of **212**

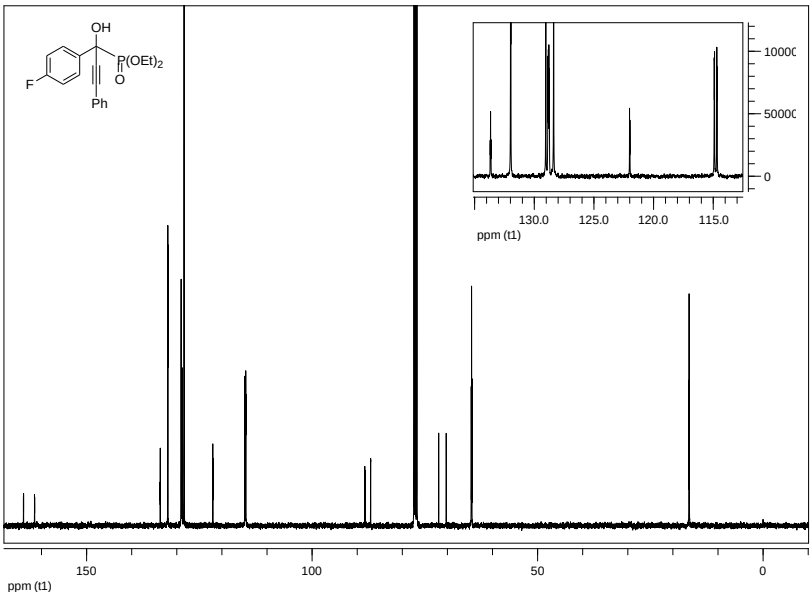


Figure B82. ^{13}C NMR spectrum of **212**

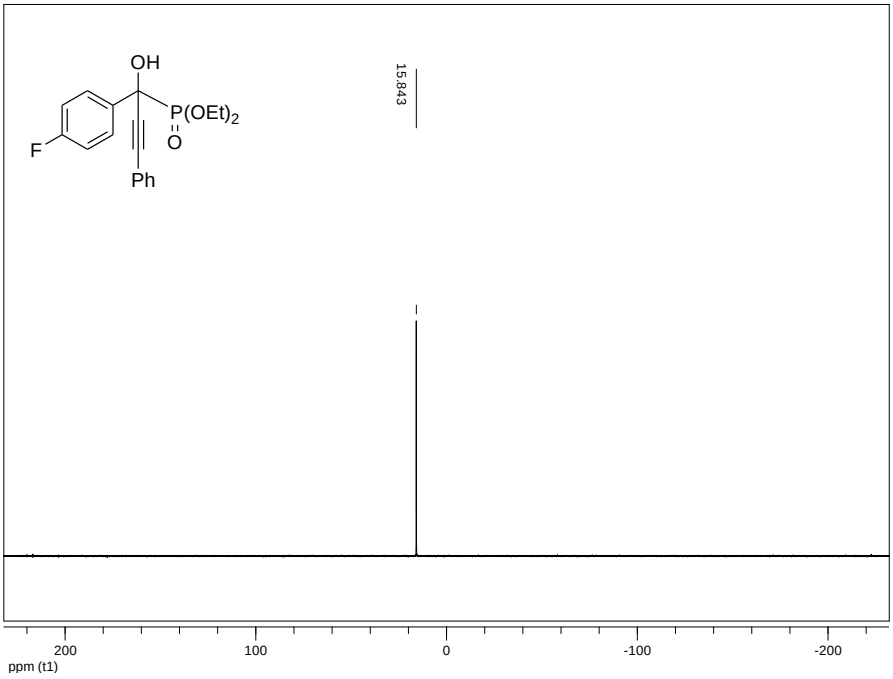


Figure B83. ^{31}P NMR spectrum of **212**

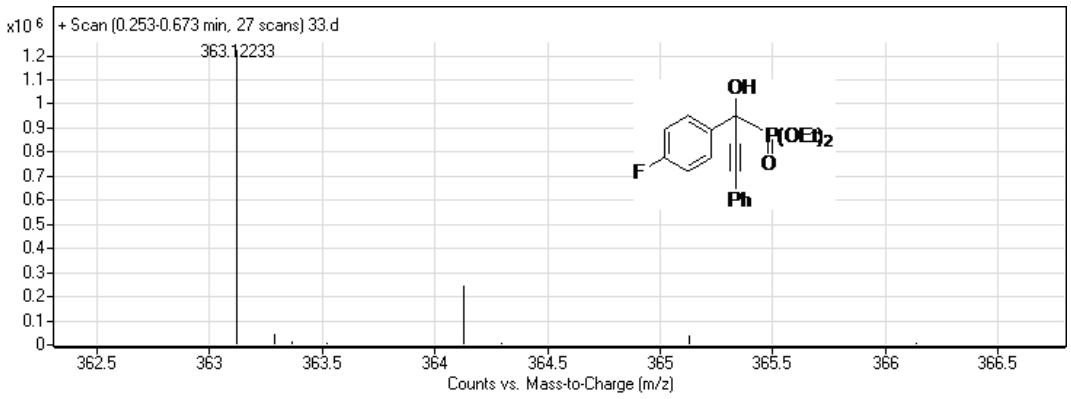


Figure B84. HRMS of compound **212**

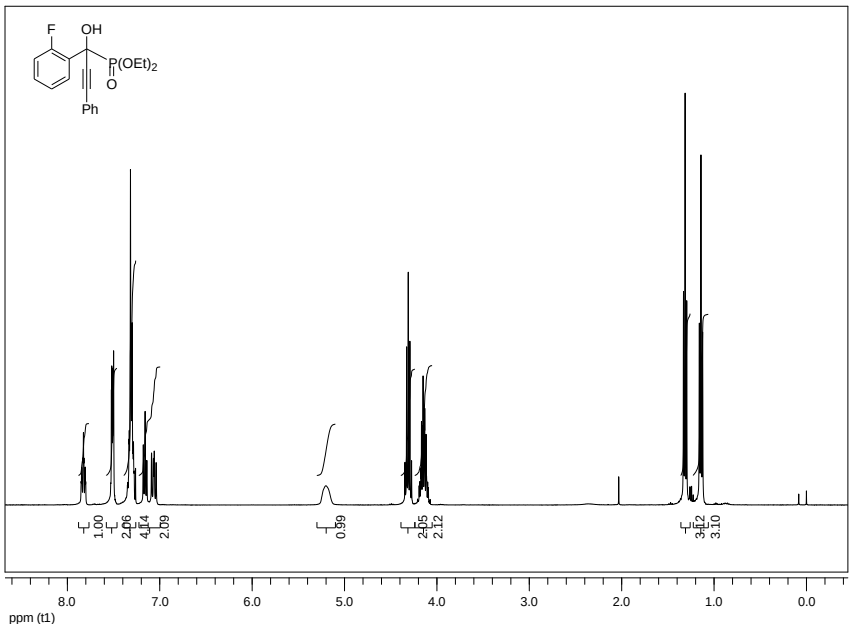


Figure B85. ^{1}H NMR spectrum of **213**

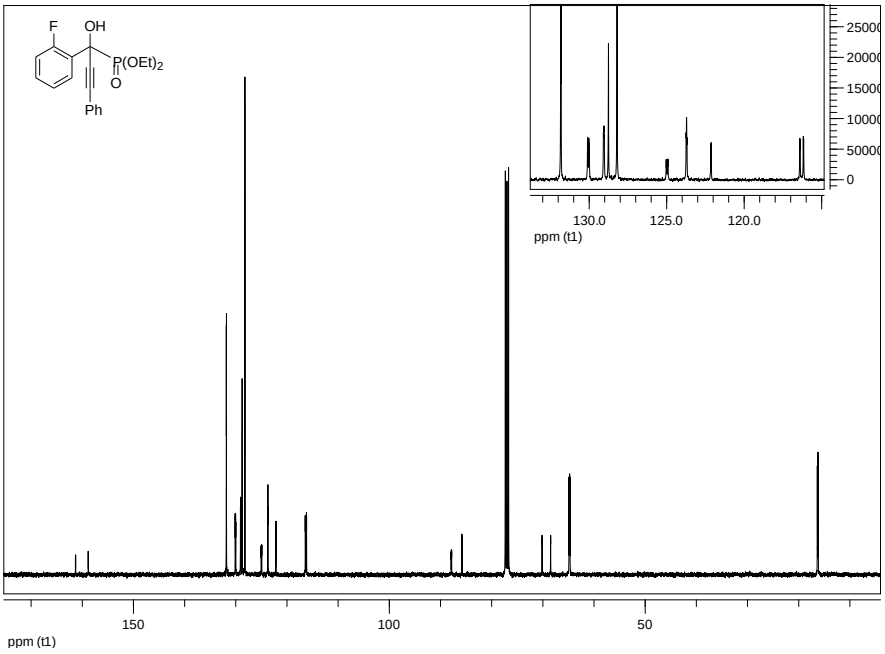


Figure B86. ^{13}C NMR spectrum of **213**

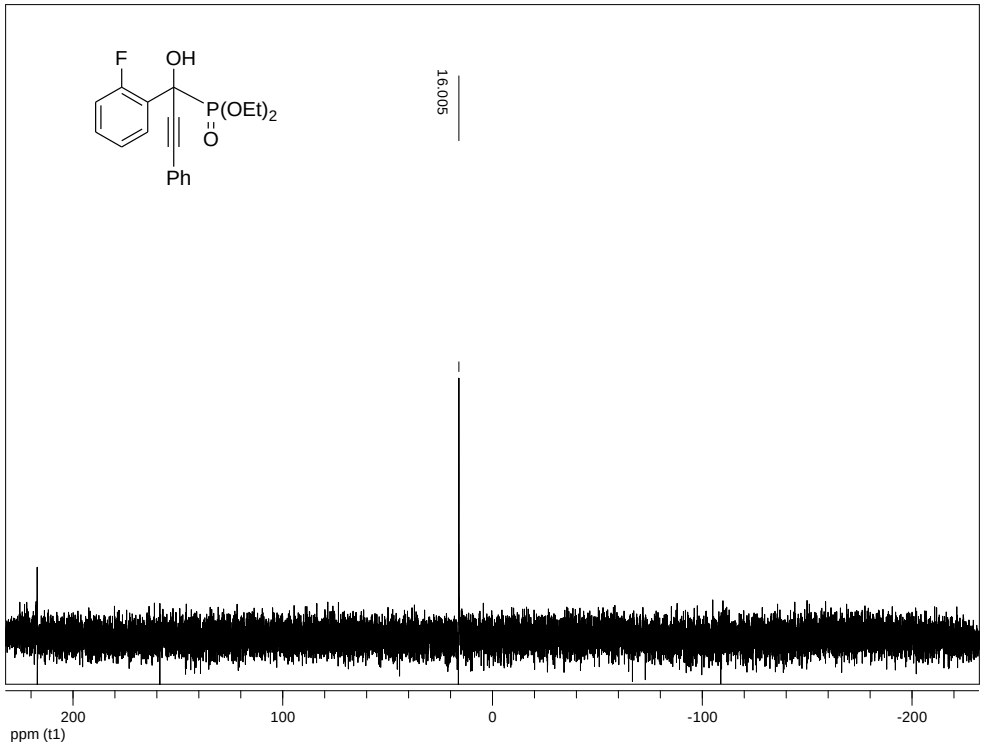


Figure B87. ^{31}P NMR spectrum of **213**

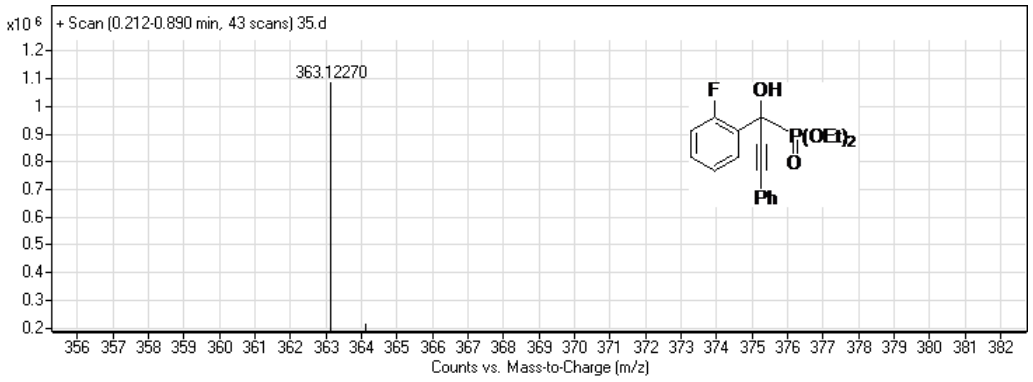


Figure B88. HRMS of compound **213**

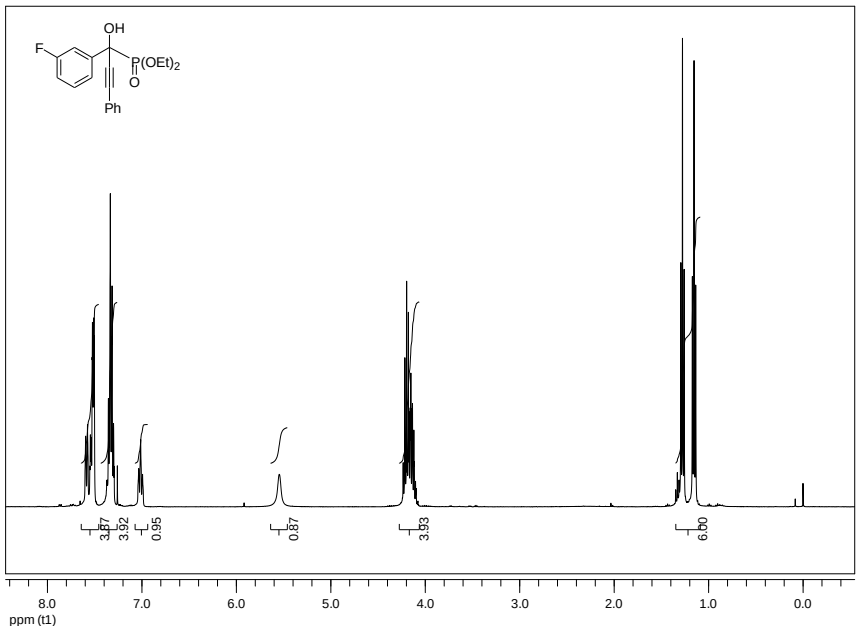


Figure B89. ^{1}H NMR spectrum of **214**

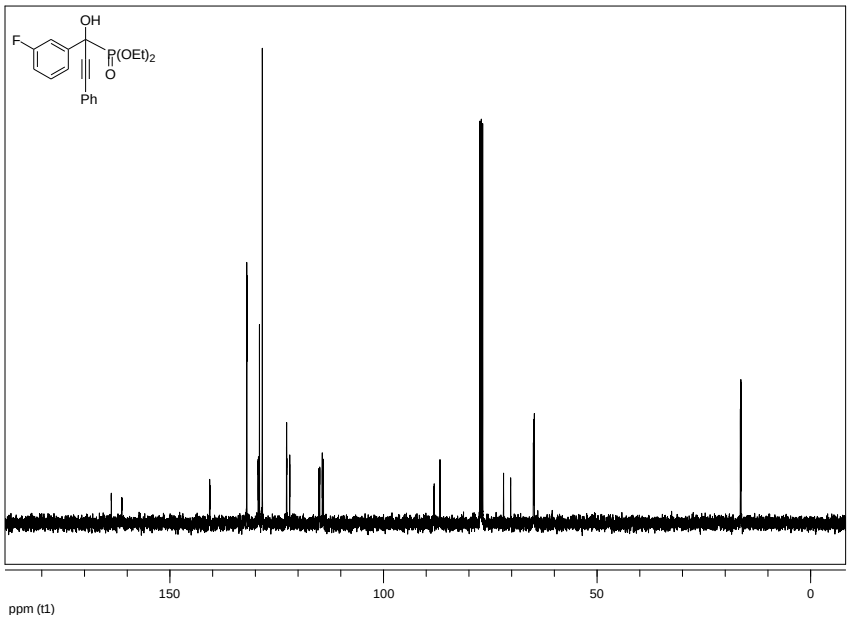


Figure B90. ^{13}C NMR spectrum of **214**

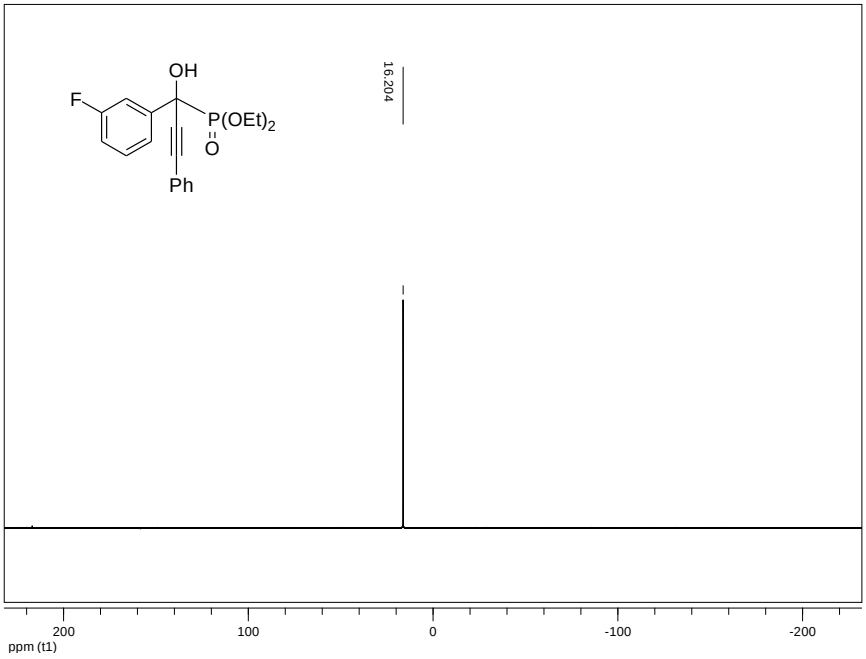


Figure B91. ^{31}P NMR spectrum of **214**

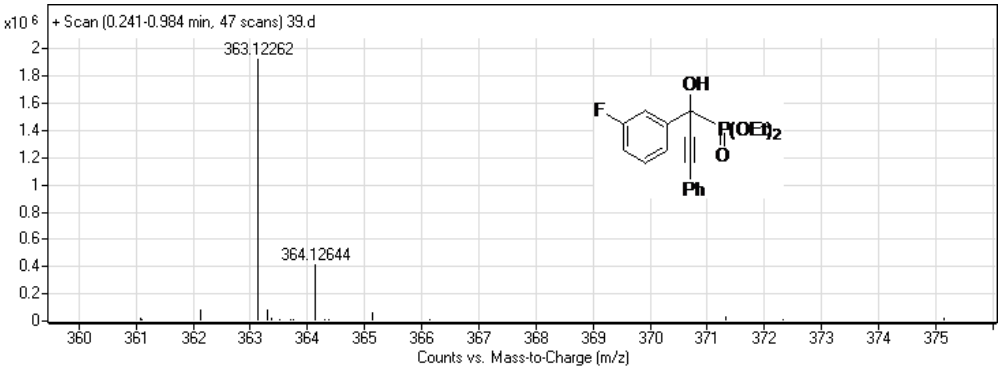


Figure B92. HRMS of compound **214**

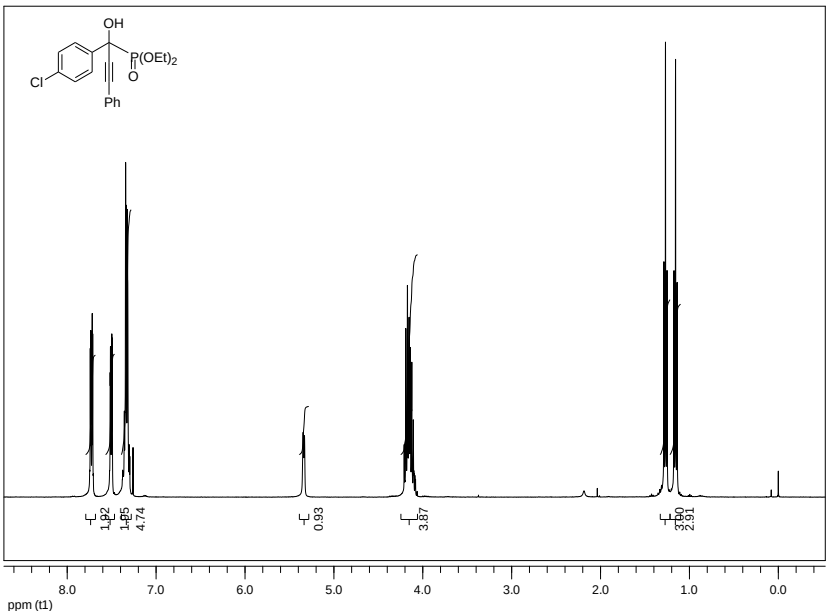


Figure B93. ^{1}H NMR spectrum of **215**

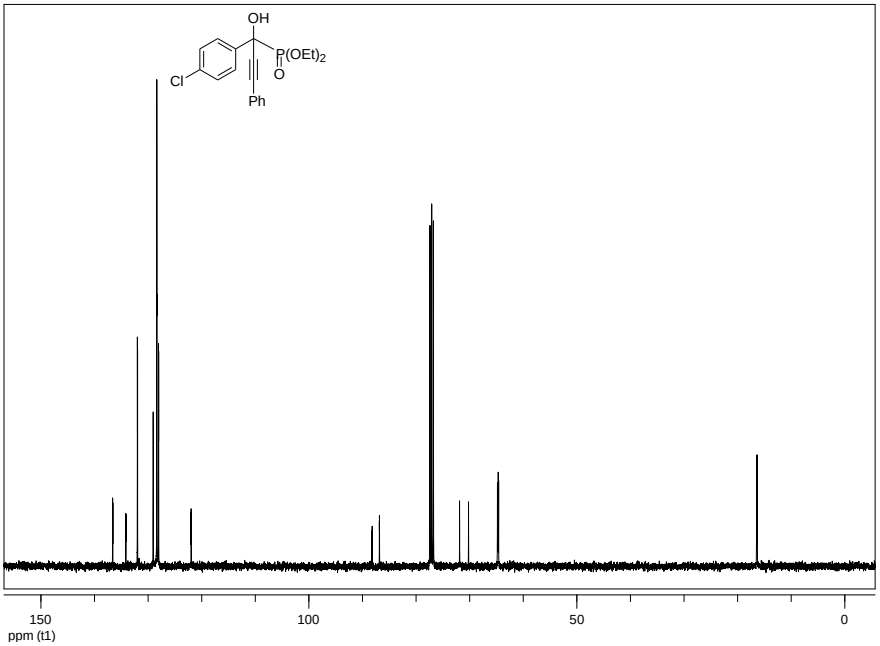


Figure B94. ^{13}C NMR spectrum of **215**

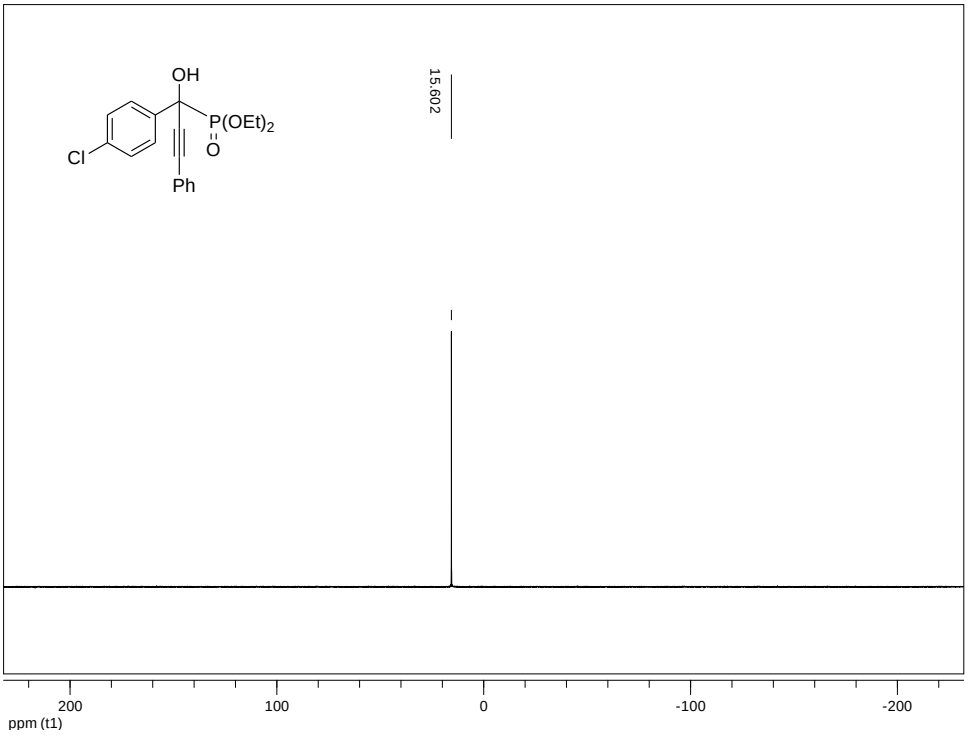


Figure B95. ^{31}P NMR spectrum of **215**

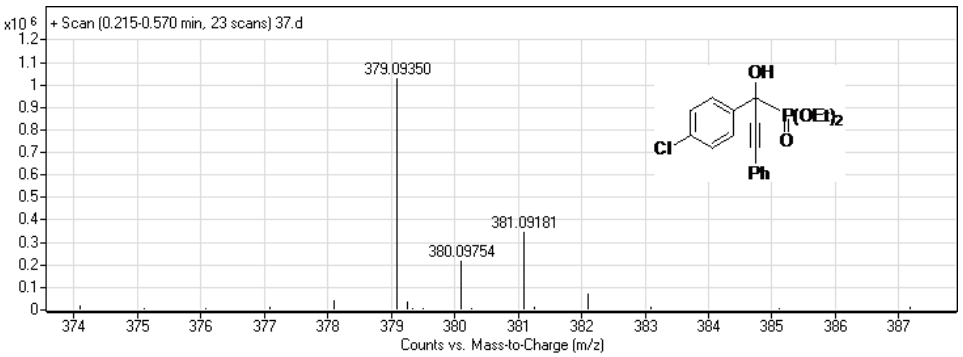


Figure B96. HRMS of compound **215**

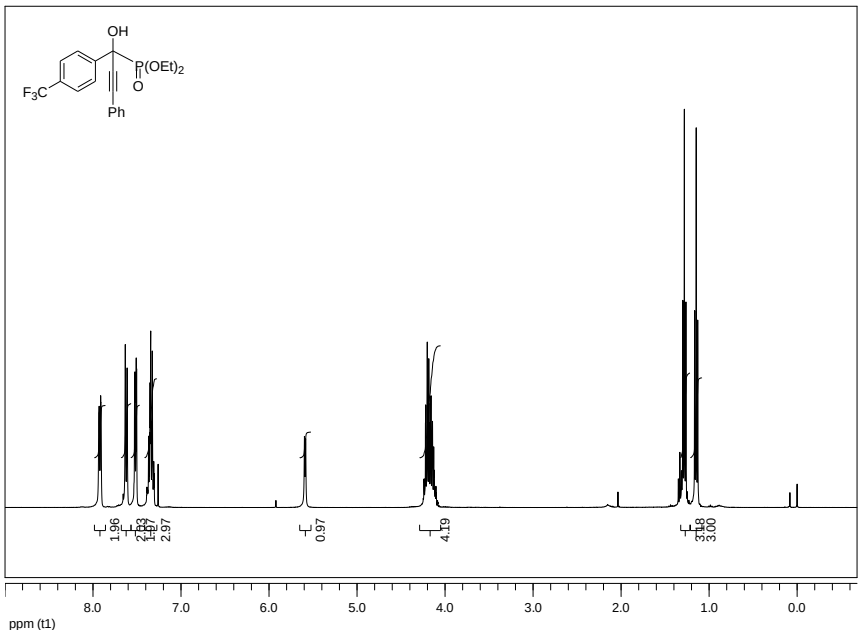


Figure B97. ^{1}H NMR spectrum of **216**

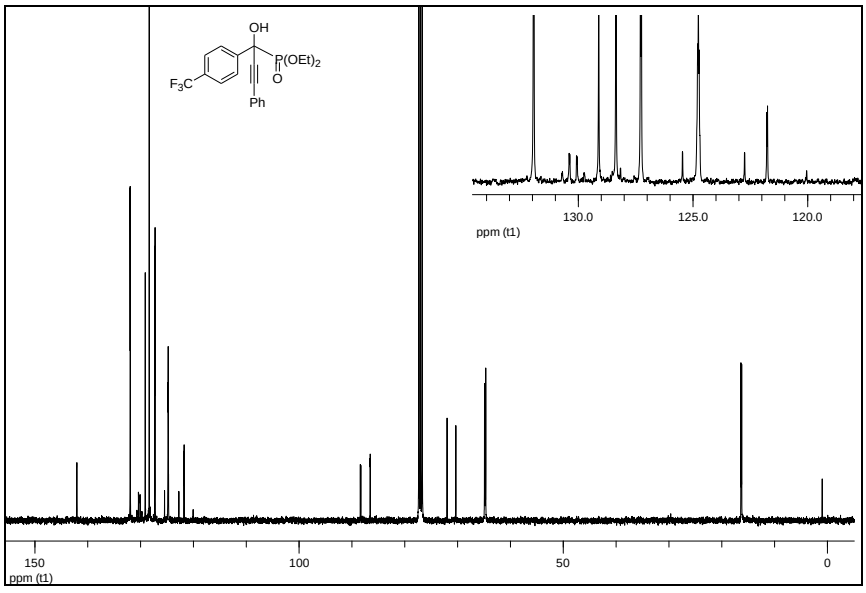


Figure B98. ^{13}C NMR spectrum of **216**

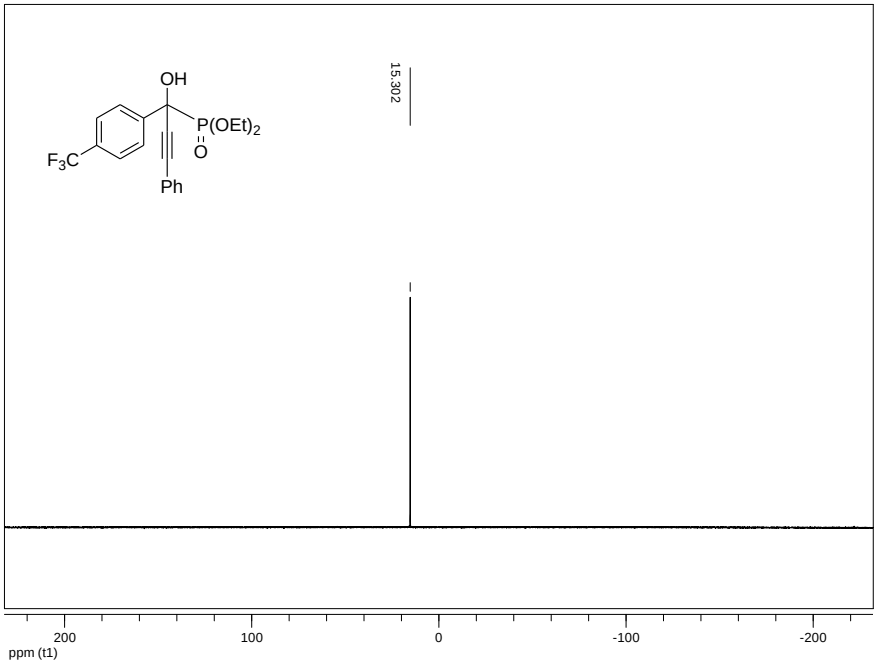


Figure B99. ^{31}P NMR spectrum of **216**

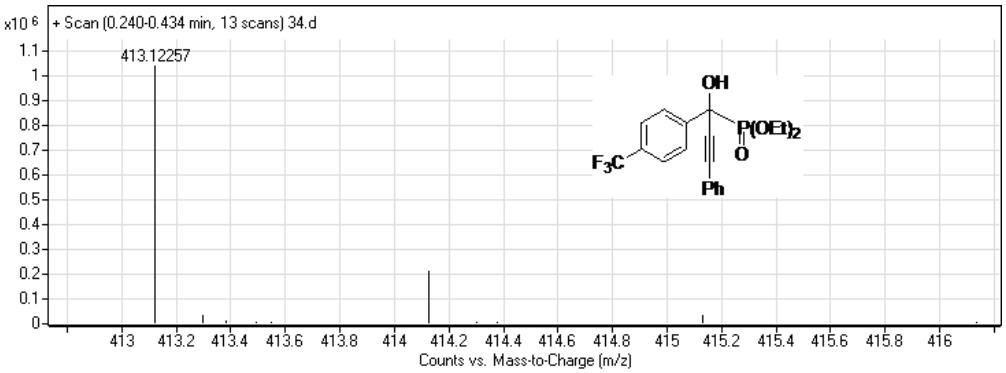


Figure B100. HRMS of compound **216**

APPENDIX C

NMR AND HRMS SPECTRA OF COMPOUNDS SYNTHESIZED IN THE THIRD PART

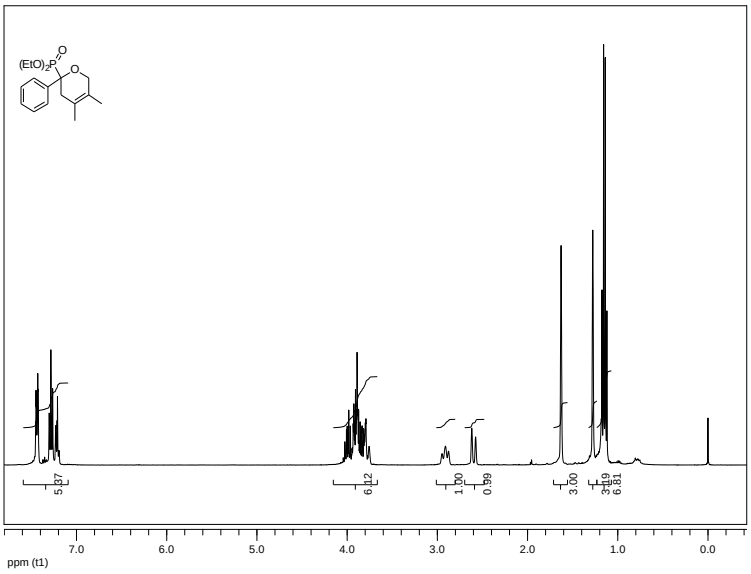


Figure C1. ^{1}H NMR spectrum of **218**

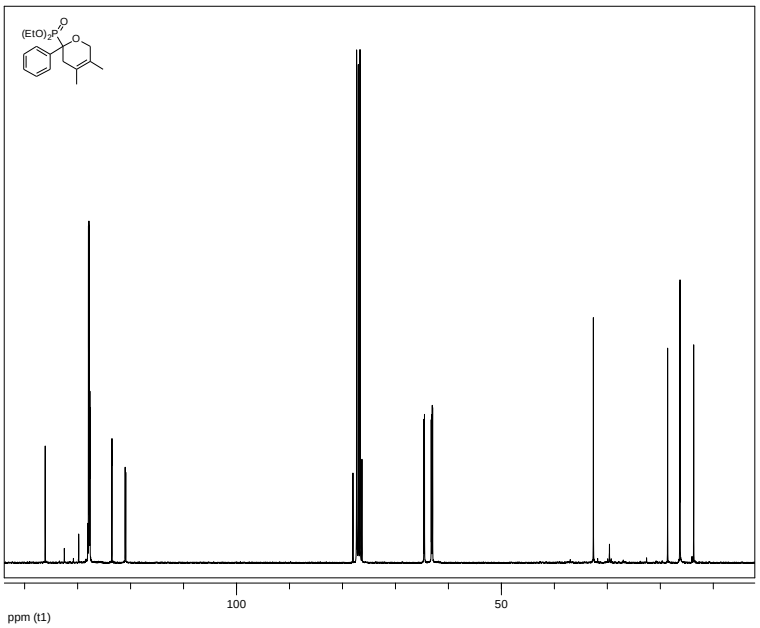


Figure C2. ^{13}C NMR spectrum of **218**

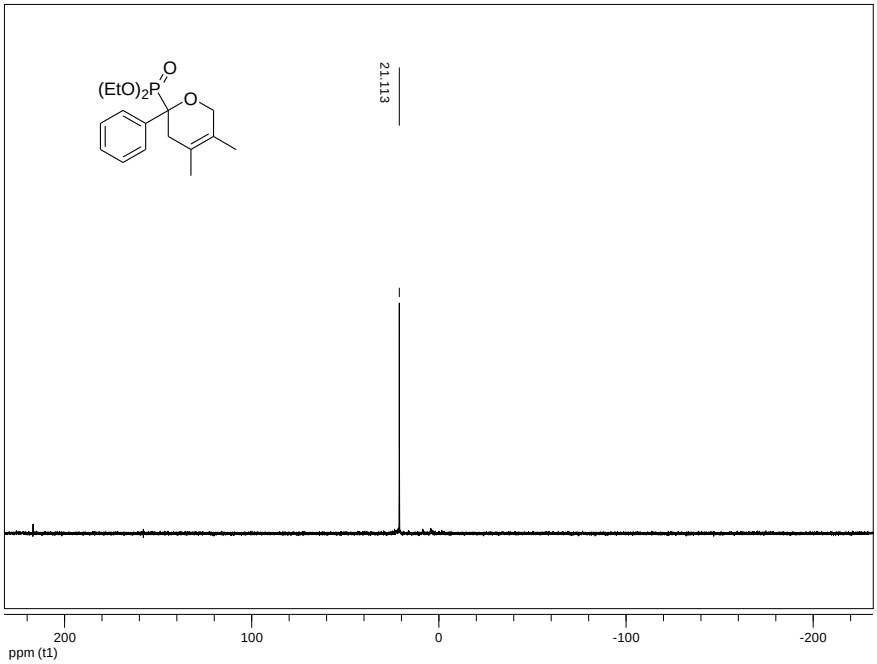


Figure C3. ^{31}P NMR spectrum of **218**

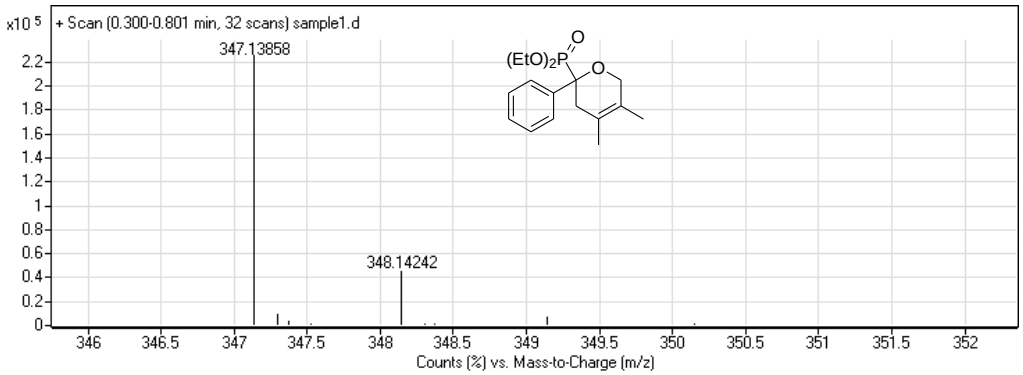


Figure C4. HRMS of compound **218**

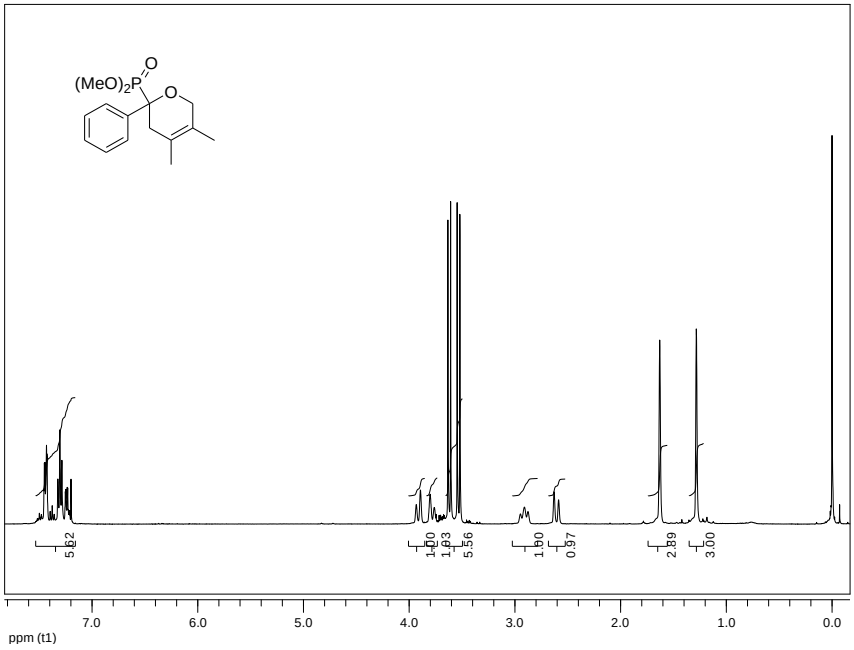


Figure C5. ^{1}H NMR spectrum of **220**

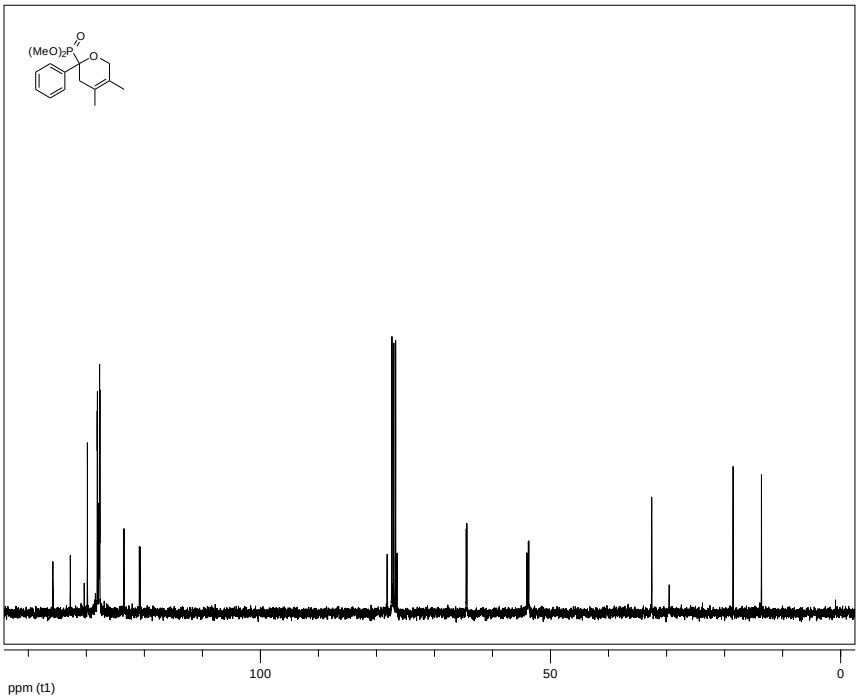


Figure C6. ^{13}C NMR spectrum of **220**

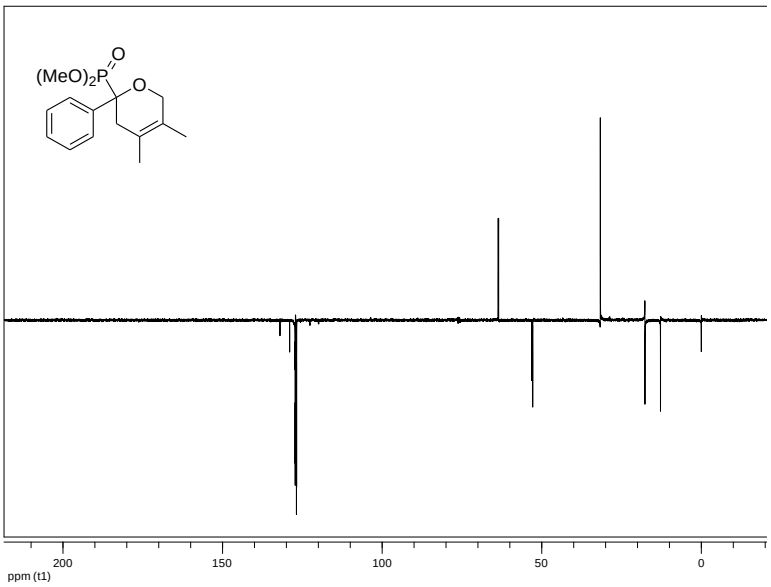


Figure C7. DEPT-135 of compound **220**

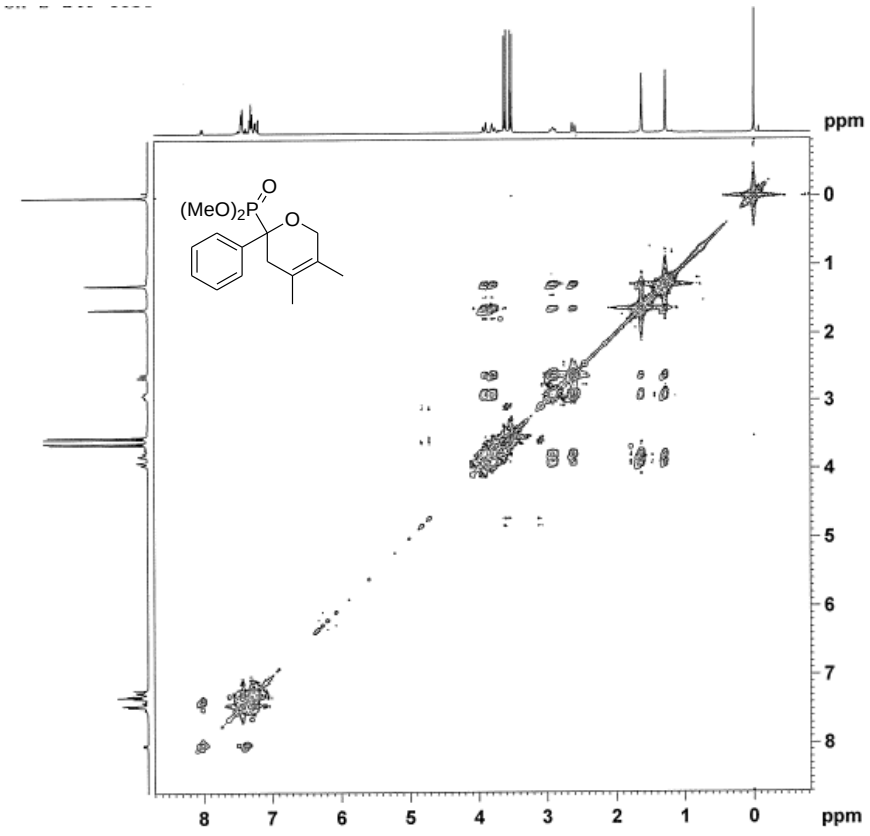


Figure C8. COSY of compound **220**

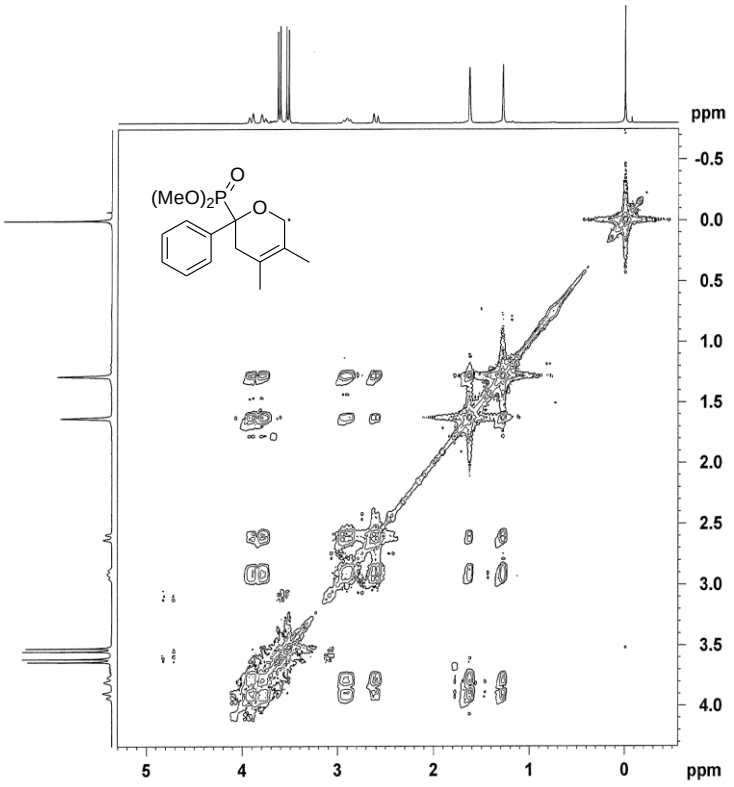


Figure C9. Extended COSY of compound **220**

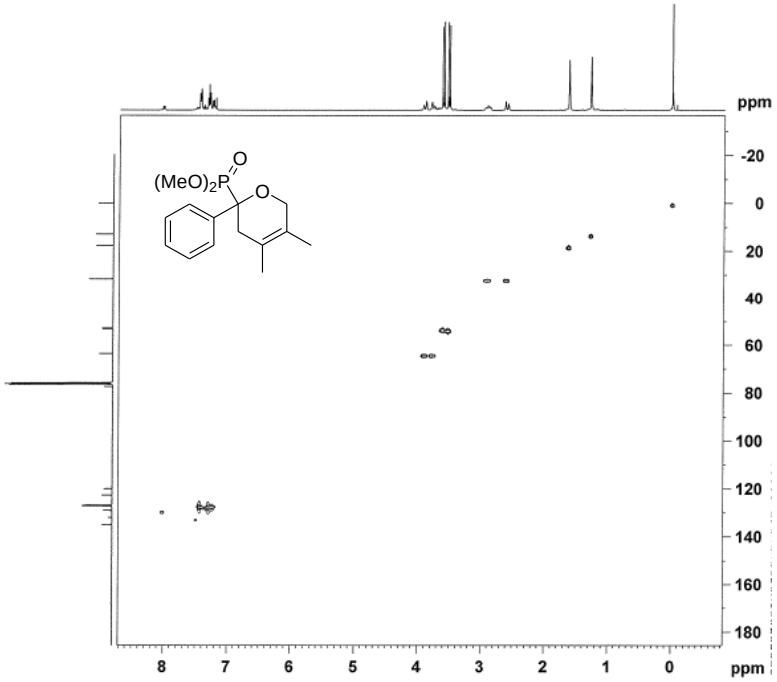


Figure C10. HSQC of compound **220**

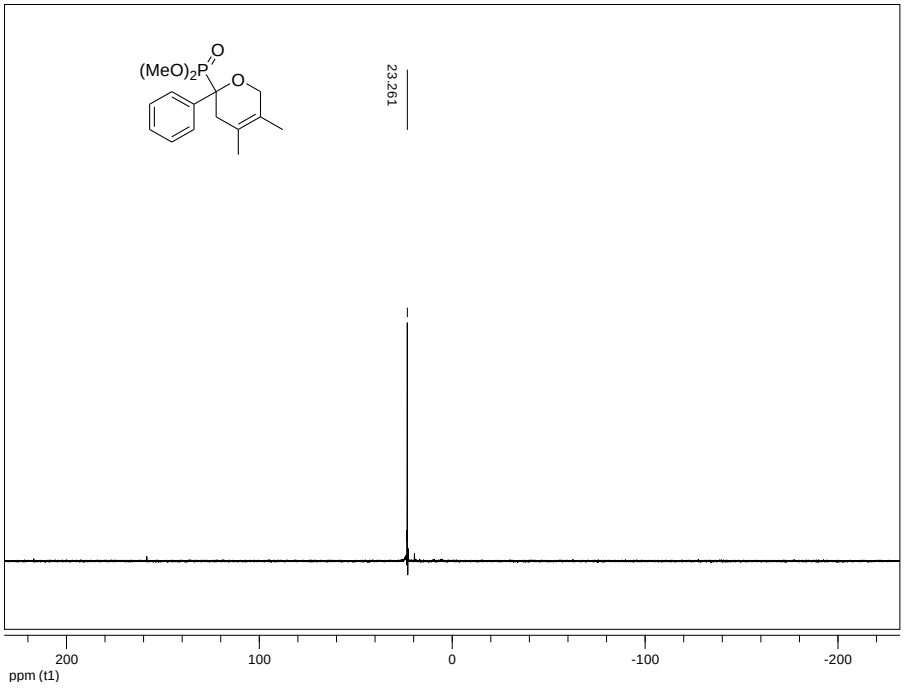


Figure C11. ^{31}P NMR spectrum of **220**

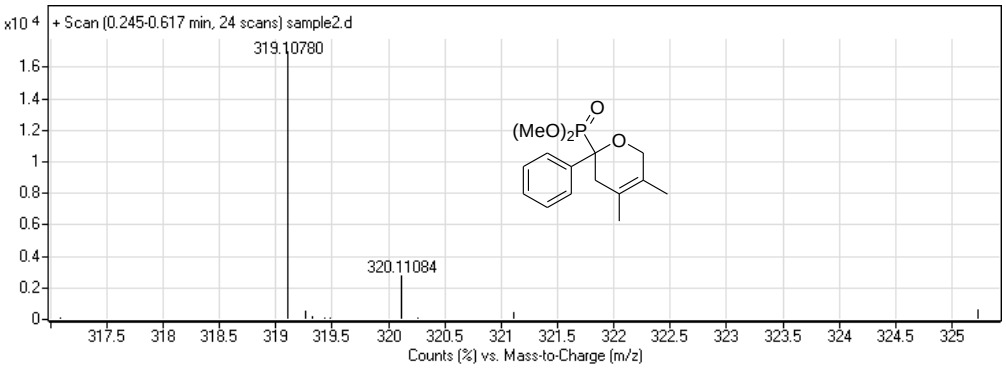


Figure C12. HRMS of compound **220**

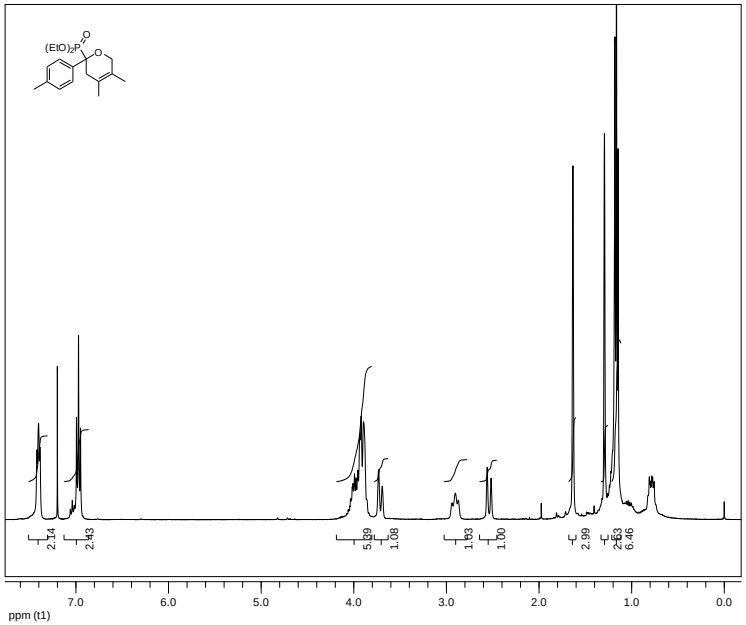


Figure C13. ^{1}H NMR spectrum of **221**

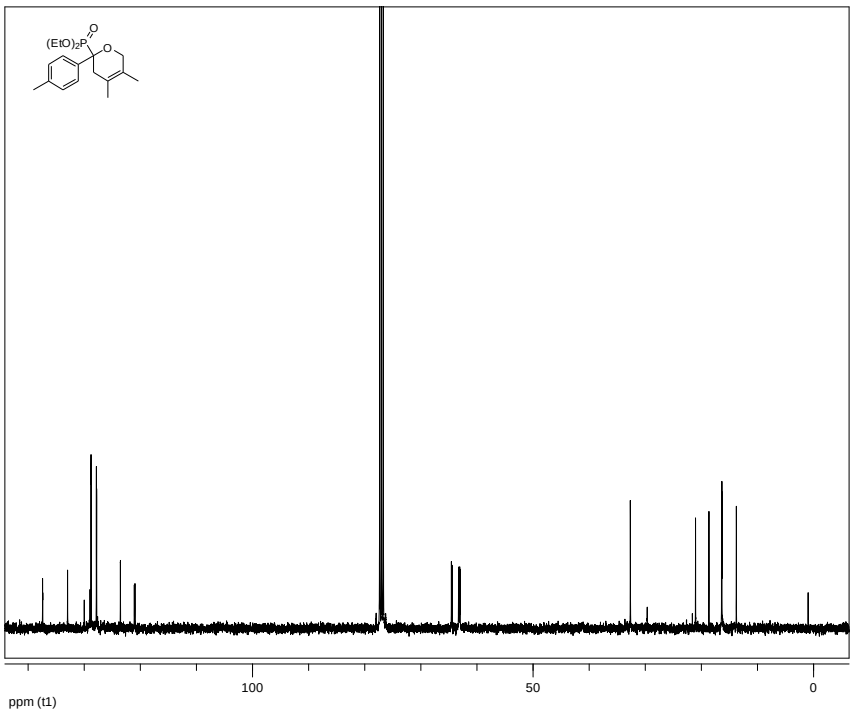


Figure C14. ^{13}C NMR spectrum of **221**

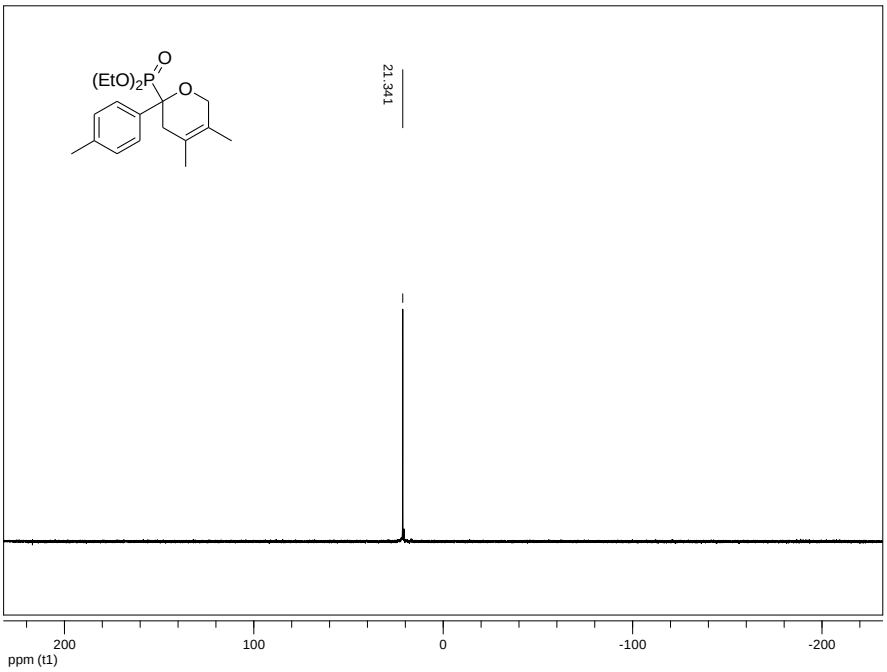


Figure C15. ^{31}P NMR spectrum of **221**

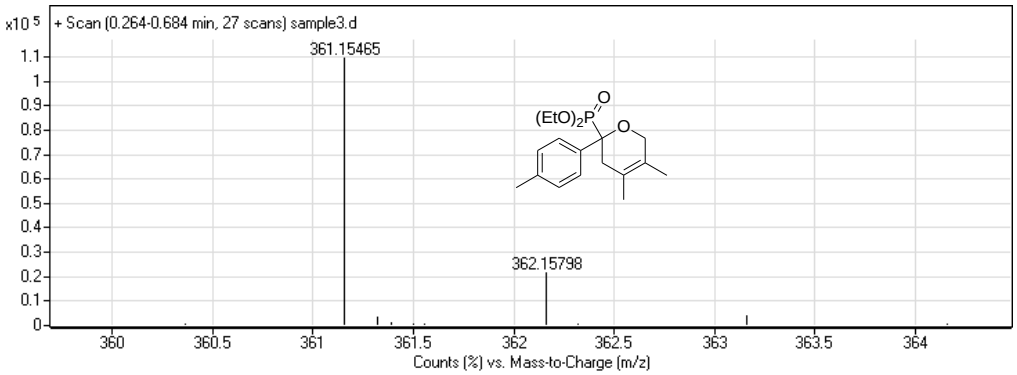


Figure C16. HRMS of compound **221**

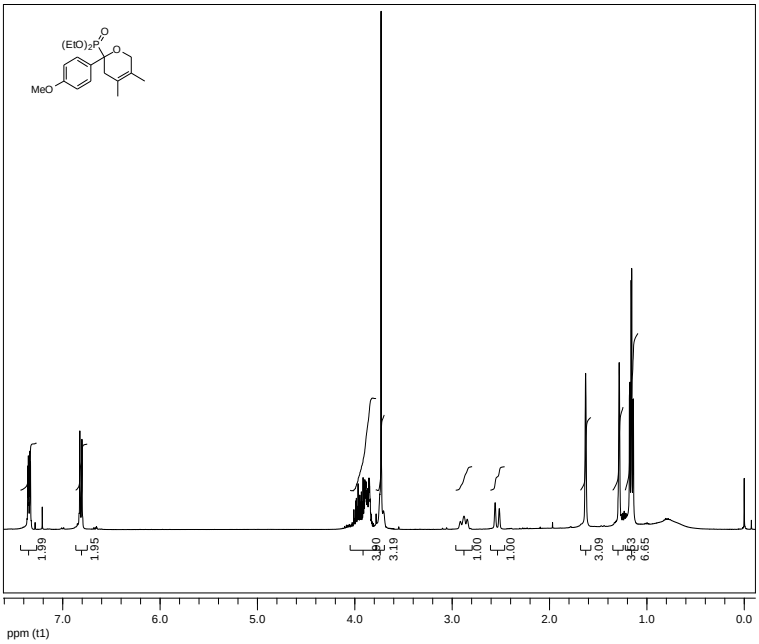


Figure C17. ^{1}H NMR spectrum of **222**

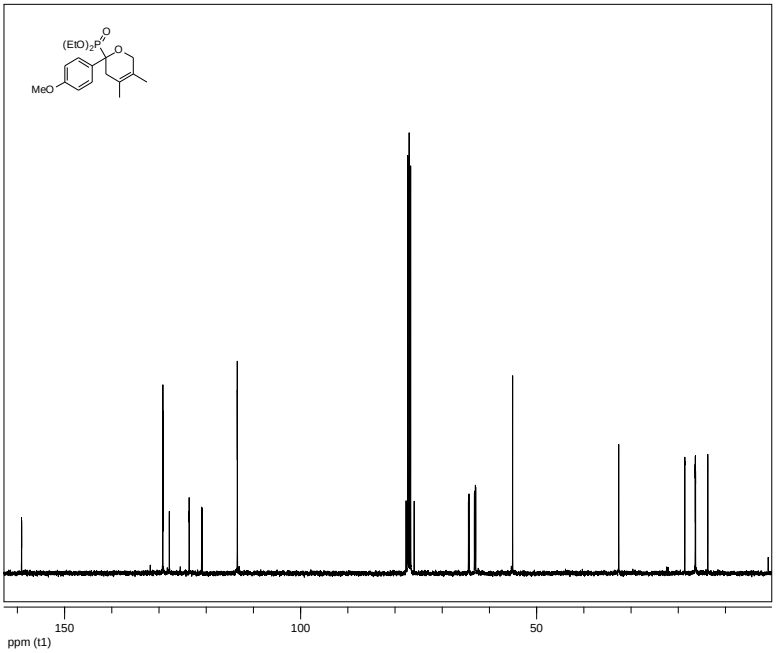


Figure C18. ^{13}C NMR spectrum of **222**

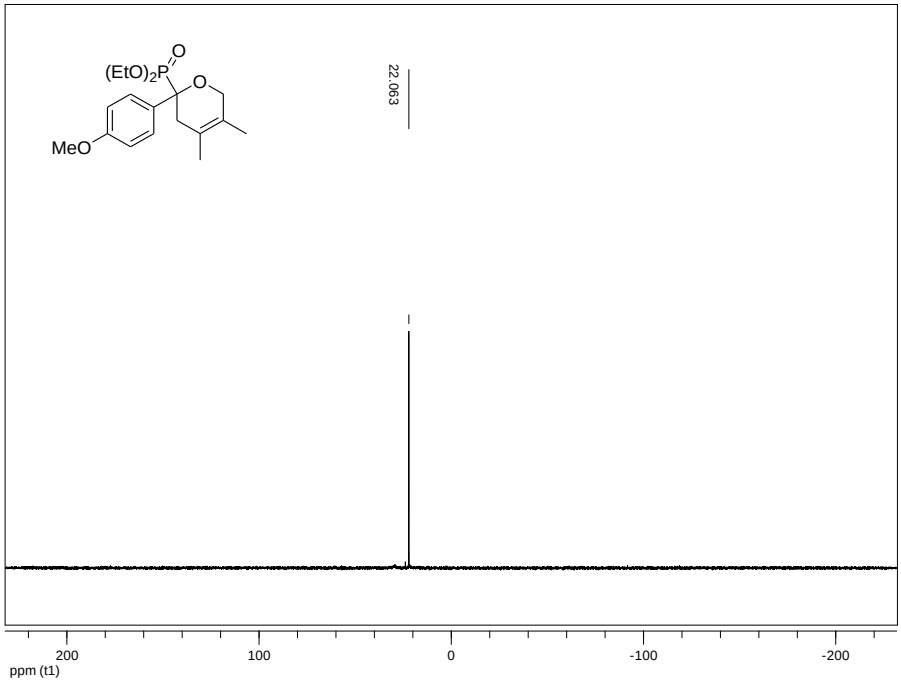


Figure C19. ^{31}P NMR spectrum of **222**

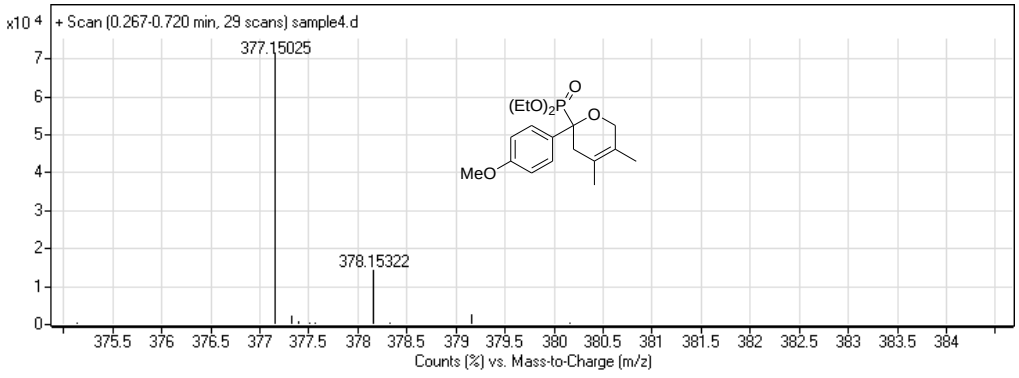


Figure C20. HRMS of compound **222**

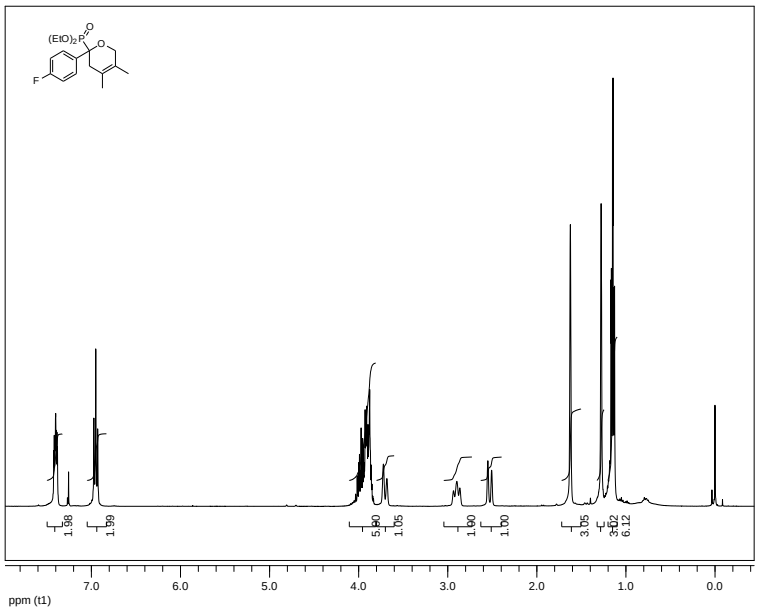


Figure C21. ^{1}H NMR spectrum of **223**

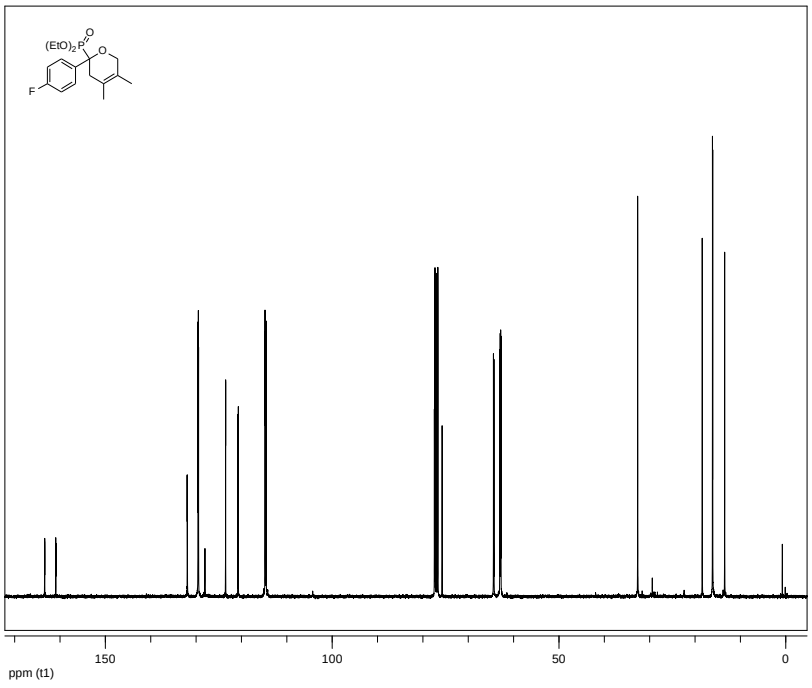


Figure C22. ^{13}C NMR spectrum of **223**

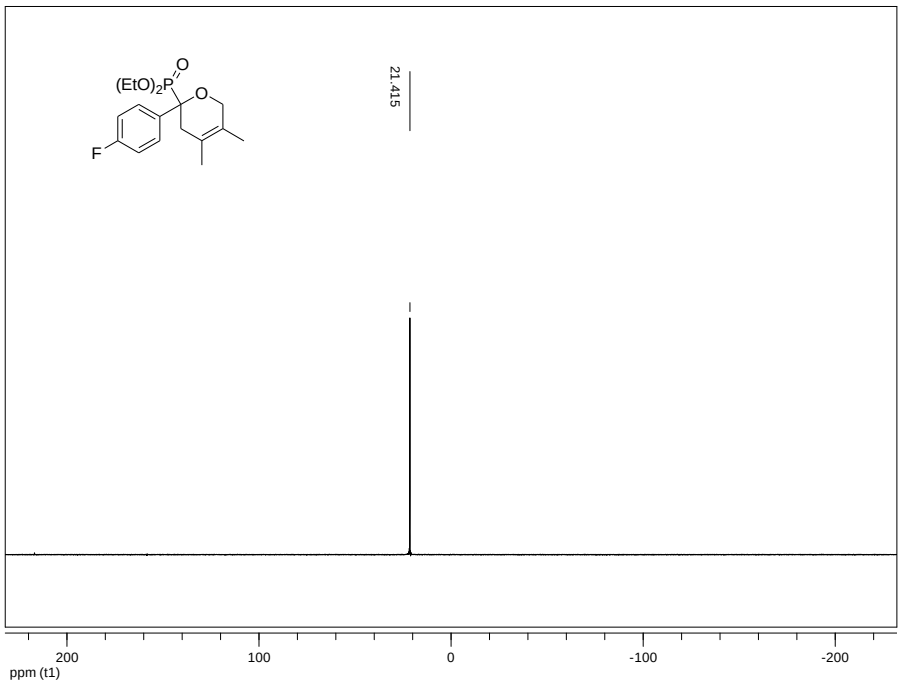


Figure C23. ^{31}P NMR spectrum of **223**

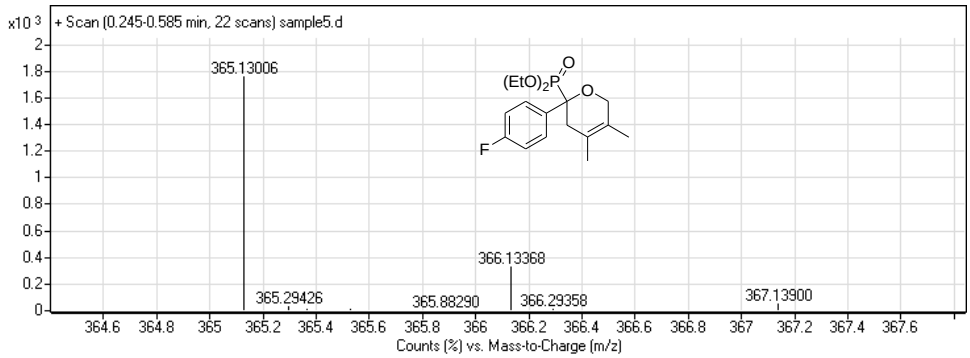


Figure C24. HRMS of compound **223**

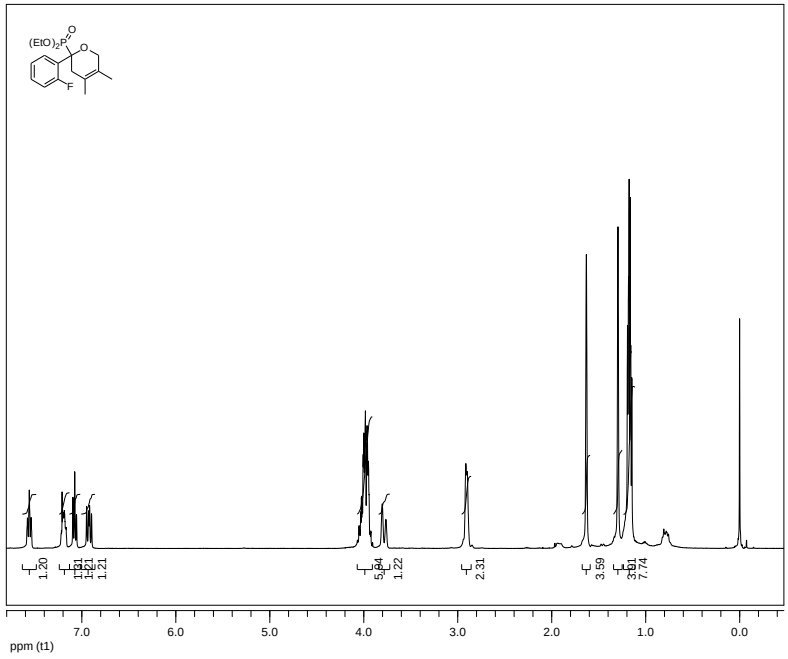


Figure C25. ^{1}H NMR spectrum of **224**

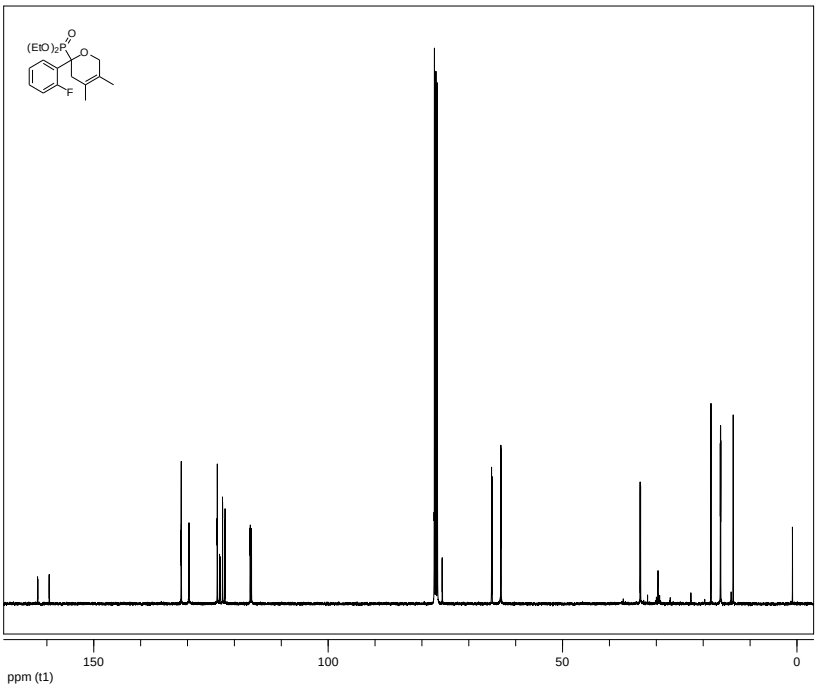


Figure C26. ^{13}C NMR spectrum of **224**

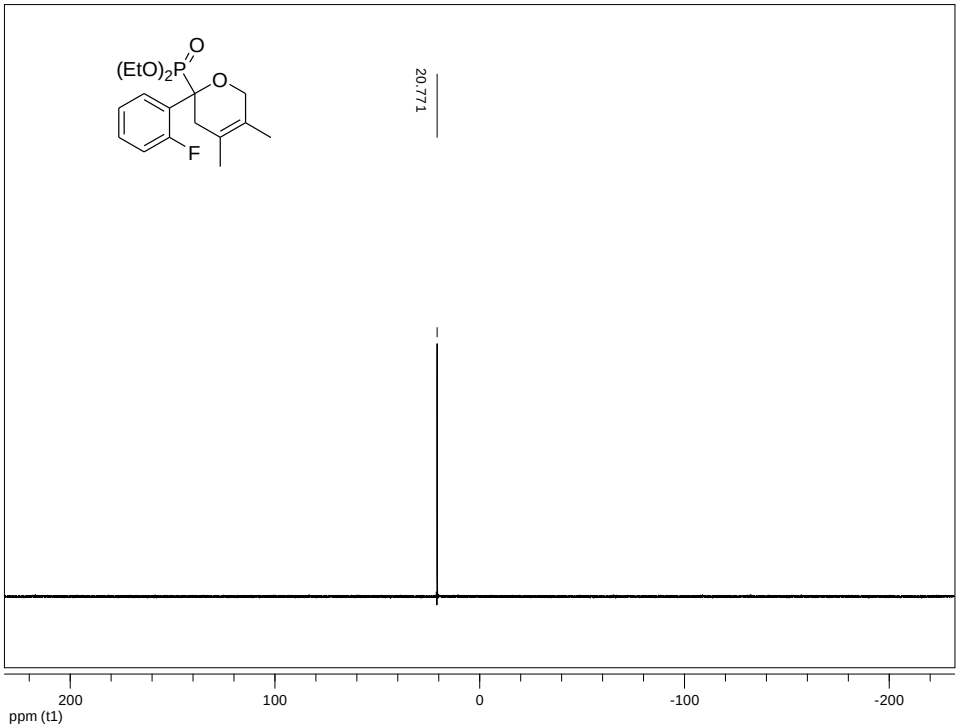


Figure C27. ^{31}P NMR spectrum of **224**

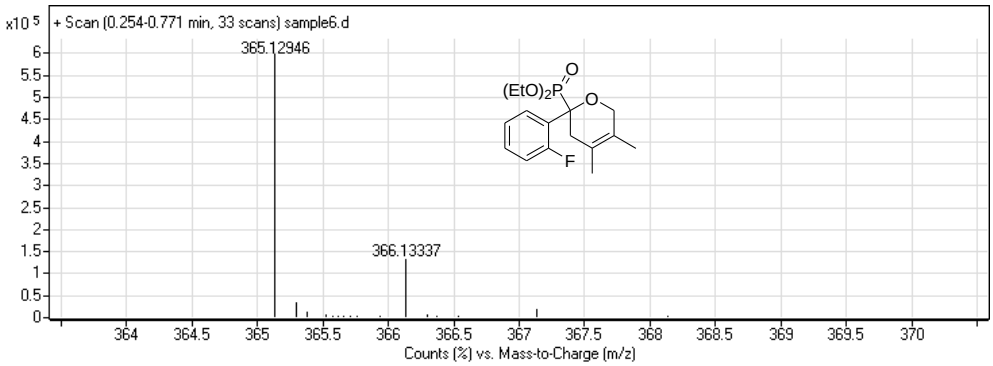


Figure C28. HRMS of compound **224**

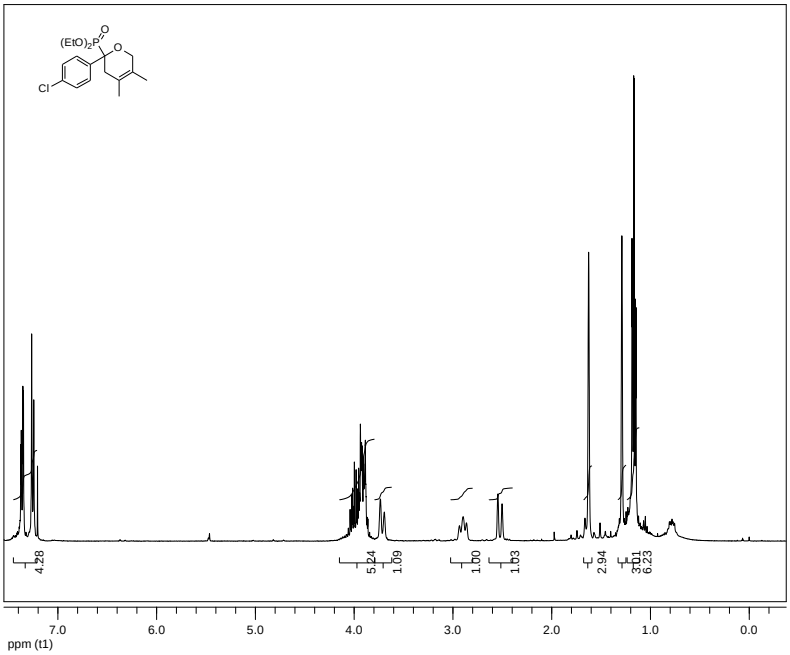


Figure C29. ^{1}H NMR spectrum of **225**

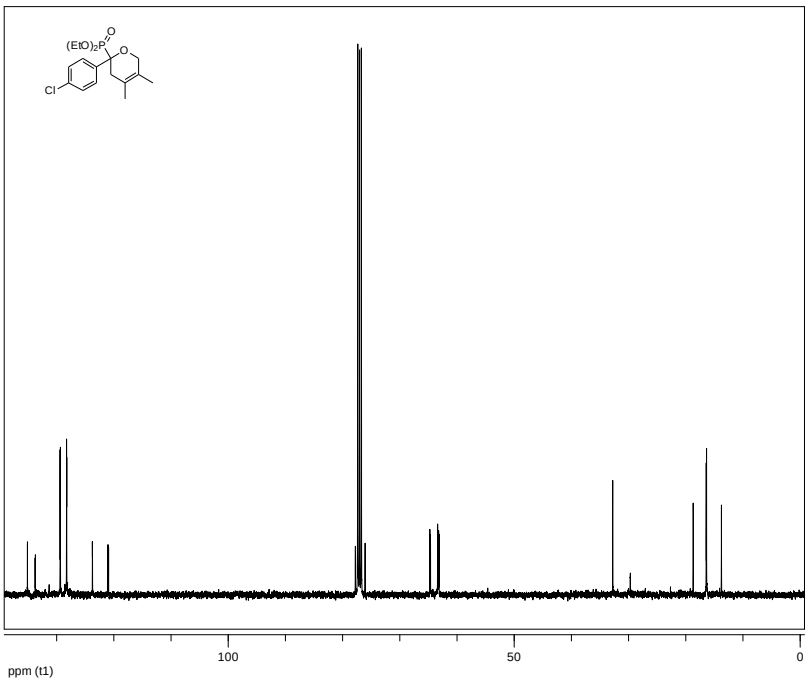


Figure C30. ^{13}C NMR spectrum of **225**

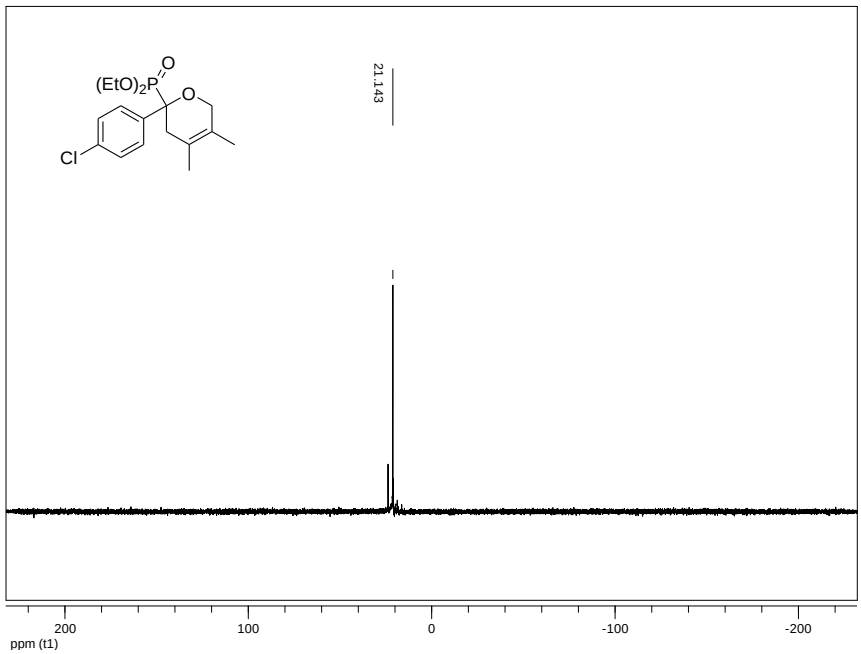


Figure C31. ^{31}P NMR spectrum of **225**

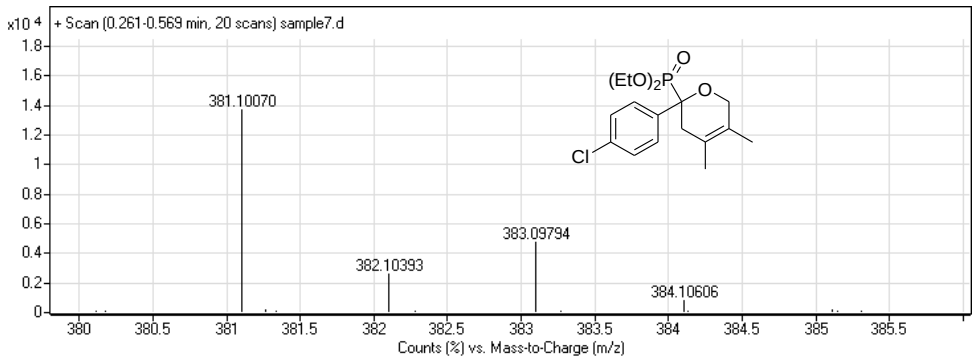


Figure C32. HRMS of compound **225**

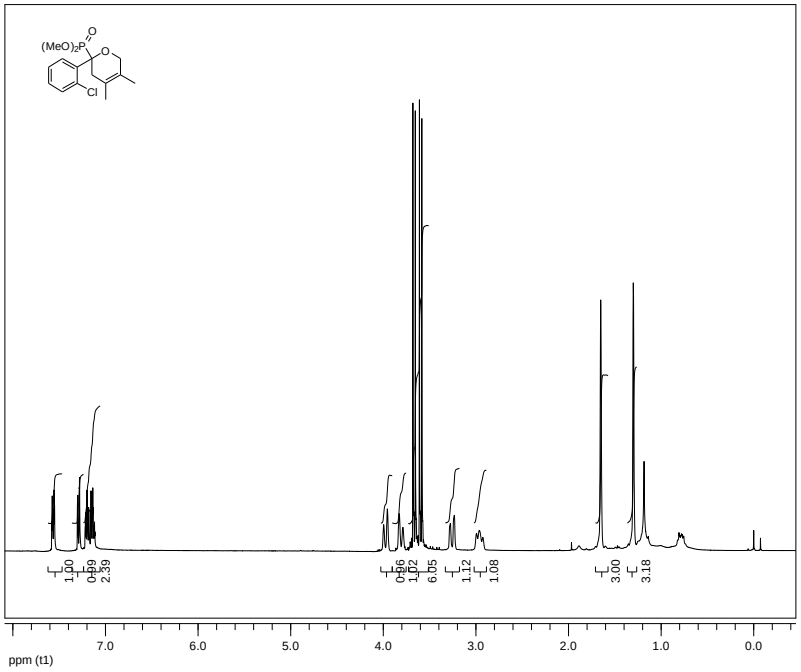


Figure C33. ^{1}H NMR spectrum of **226**

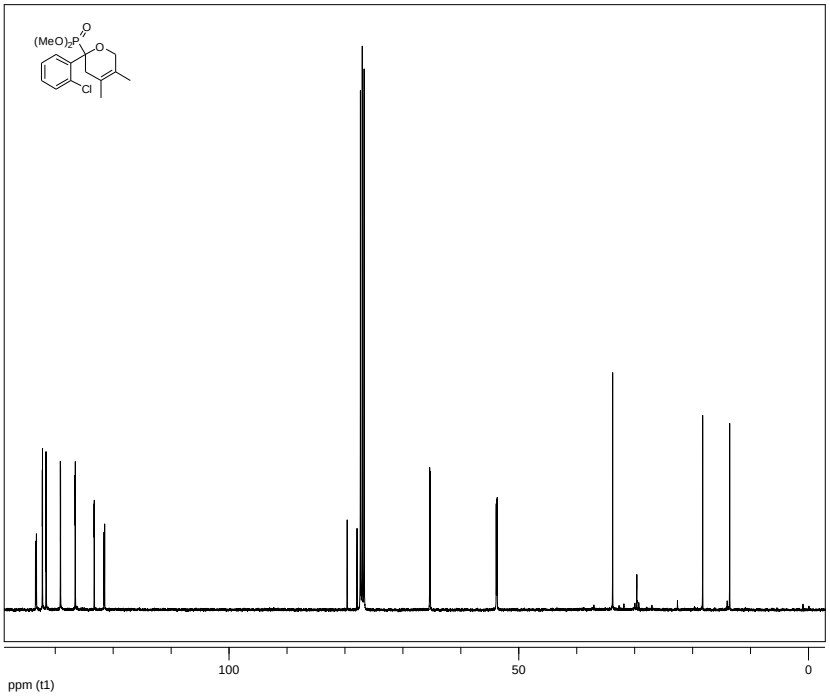


Figure C34. ^{13}C NMR spectrum of **226**

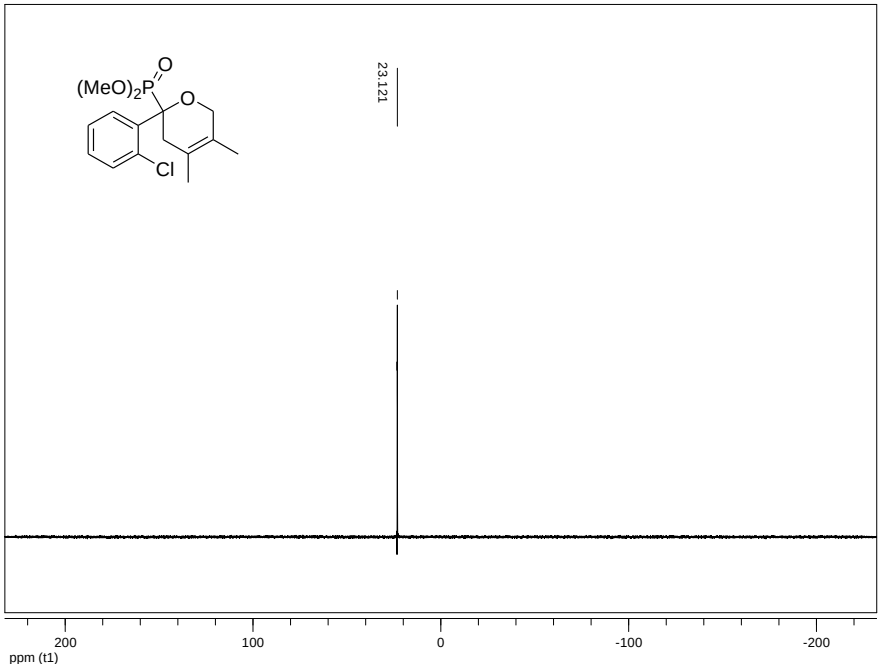


Figure C35. ^{31}P NMR spectrum of **226**

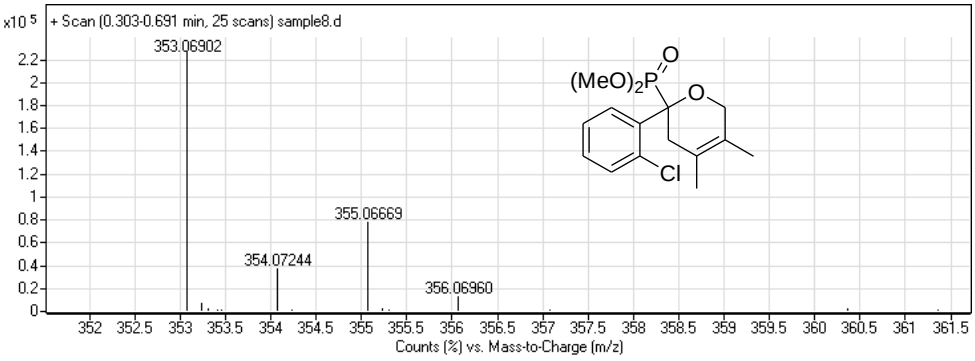


Figure C36. HRMS of compound **226**

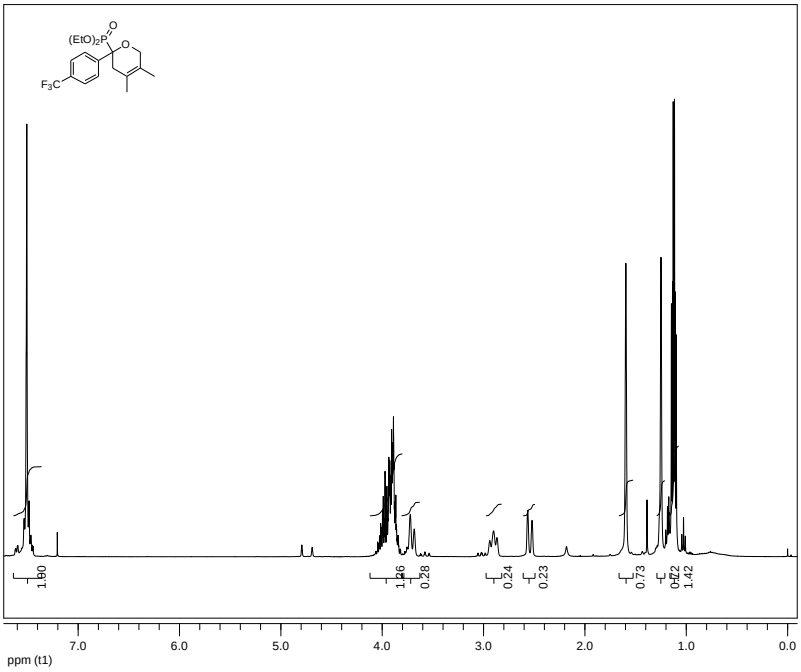


Figure C37. ^{1}H NMR spectrum of **227**

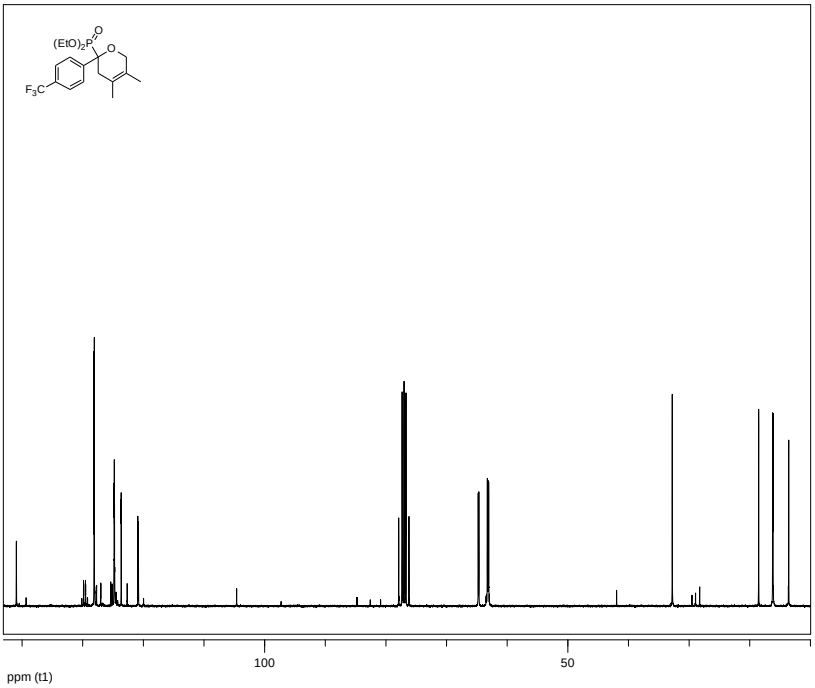


Figure C38. ^{13}C NMR spectrum of **227**

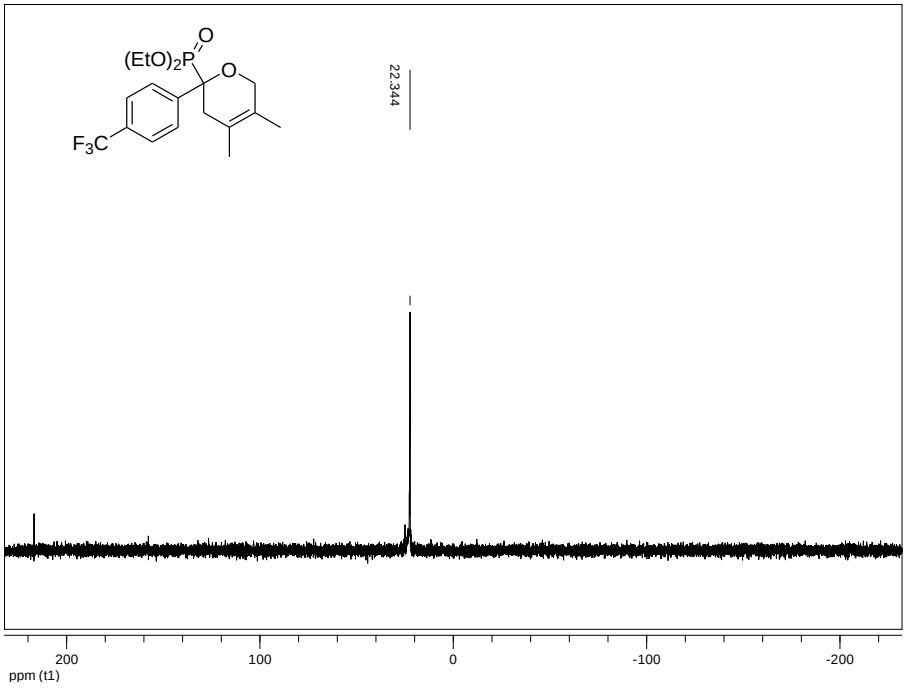


Figure C39. ^{31}P NMR spectrum of **227**

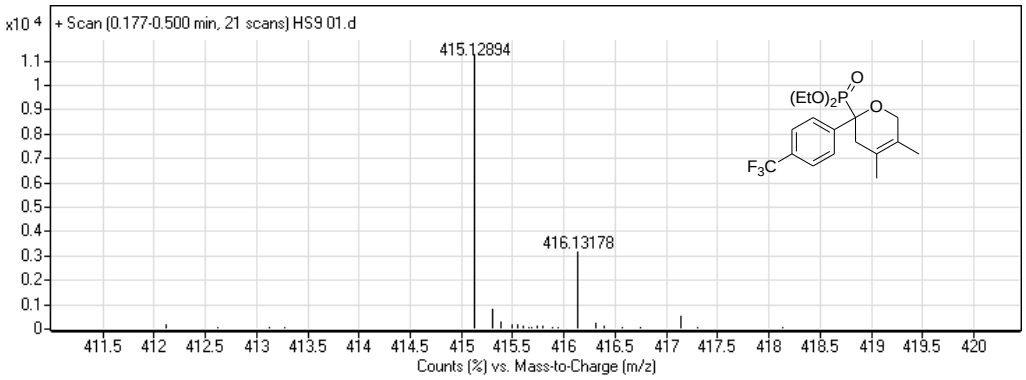


Figure C40. HRMS of compound **227**

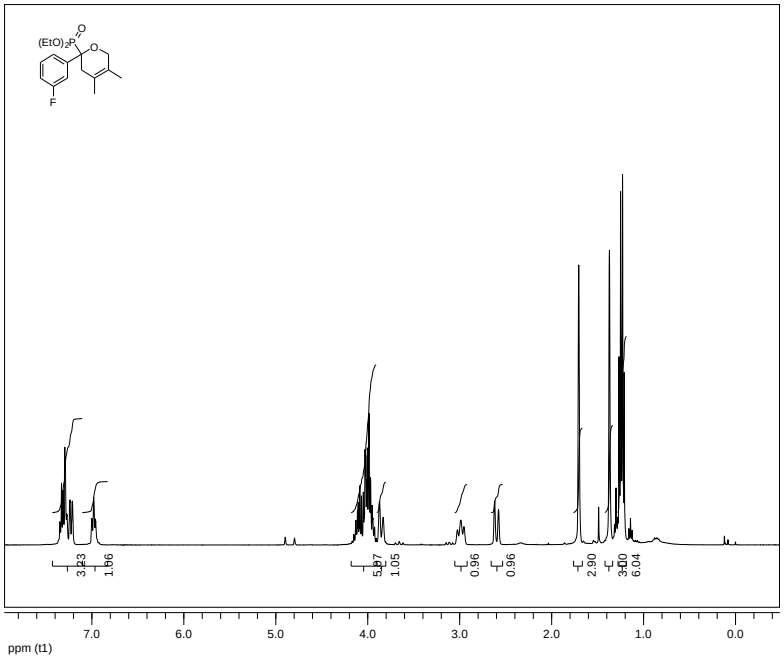


Figure C41. ^{1}H NMR spectrum of **228**

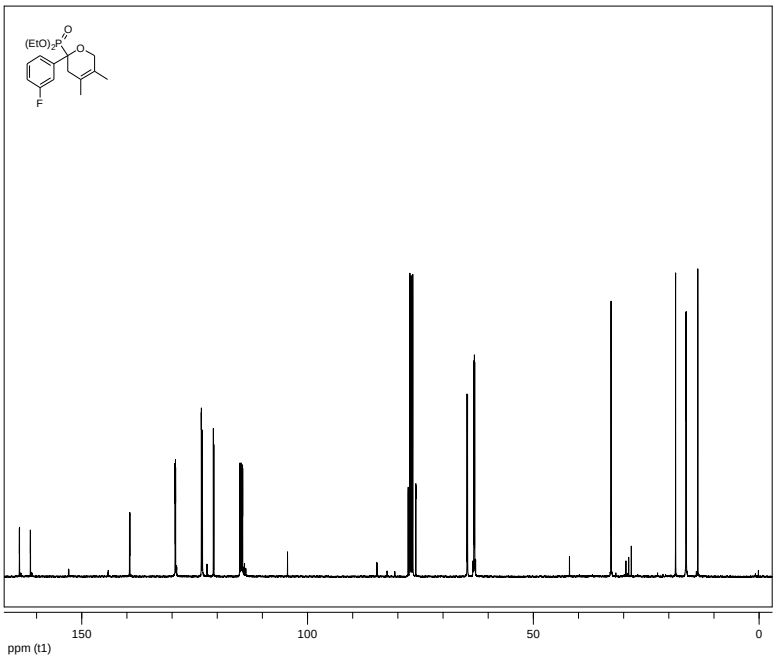


Figure C42. ^{13}C NMR spectrum of **228**

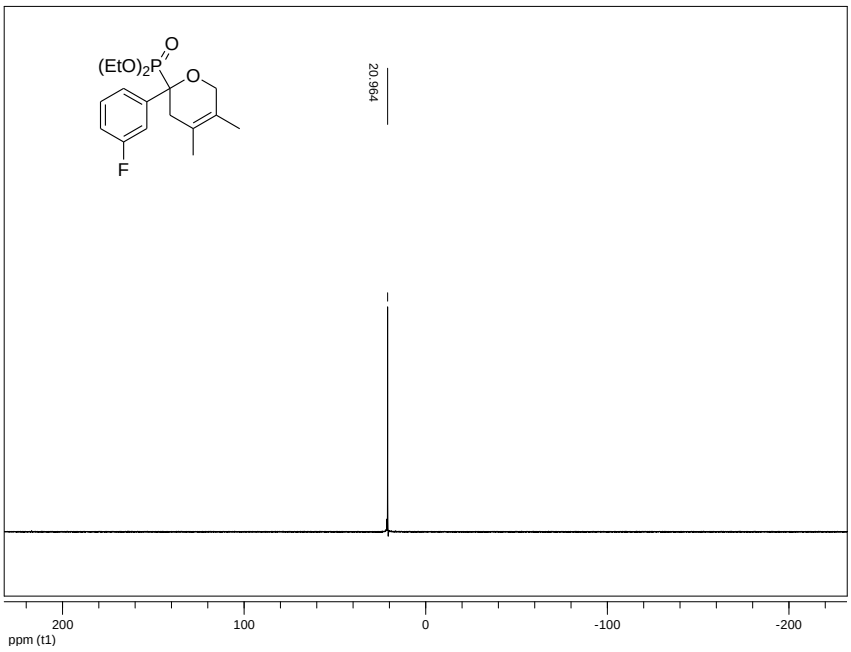


Figure C43. ^{31}P NMR spectrum of **228**

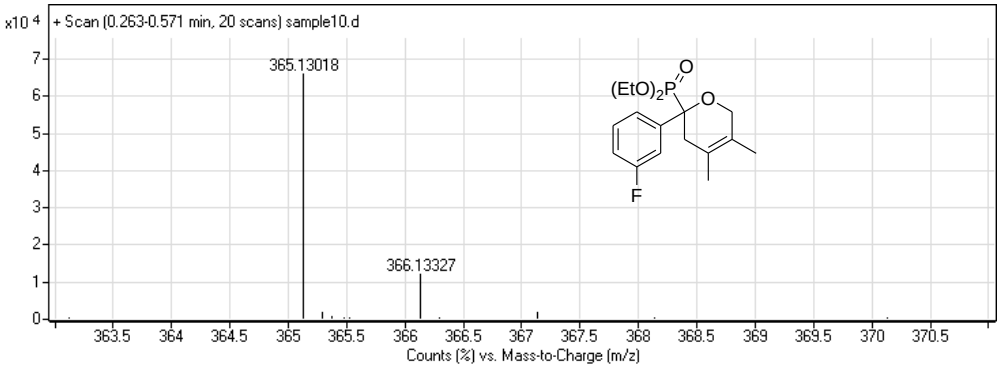


Figure C44. HRMS of compound **228**

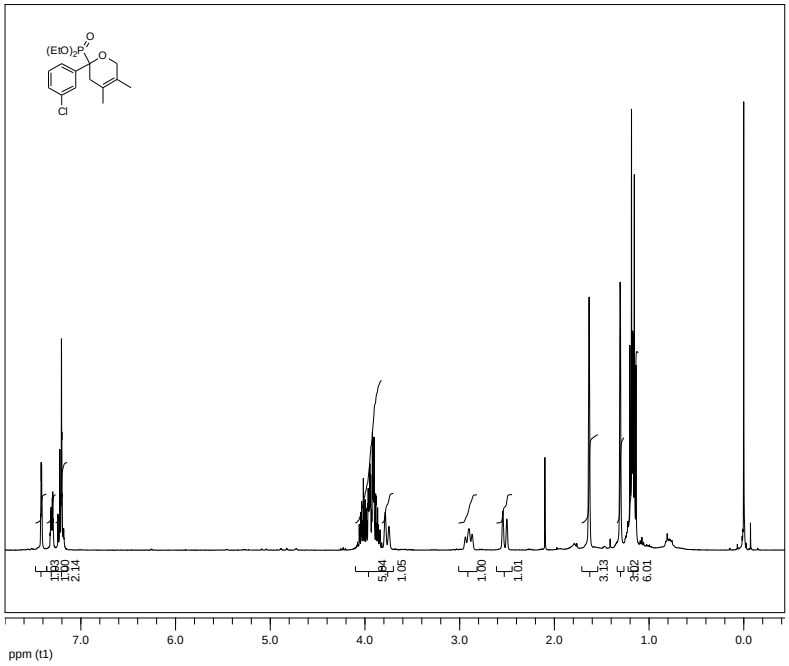


Figure C45. ^{1}H NMR spectrum of **229**

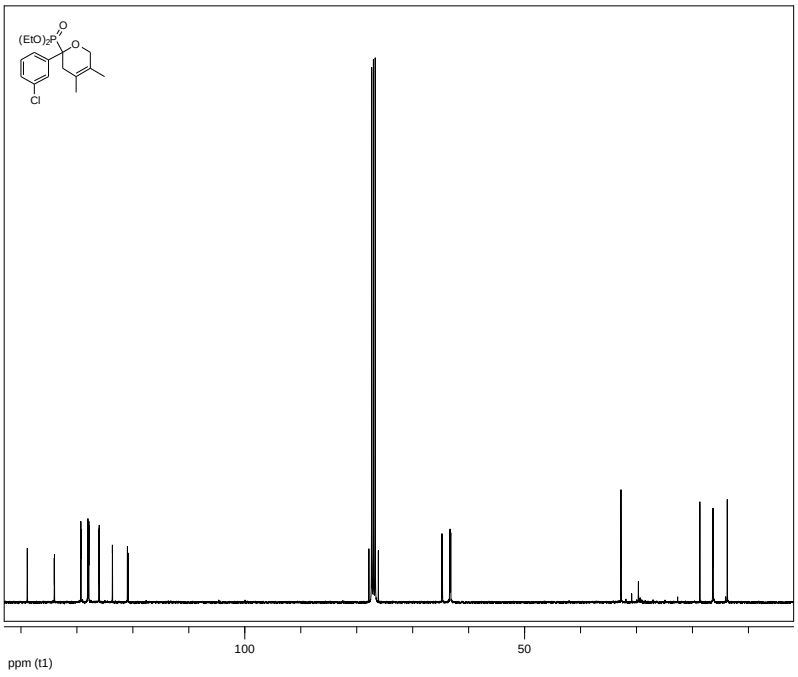


Figure C46. ^{13}C NMR spectrum of **229**

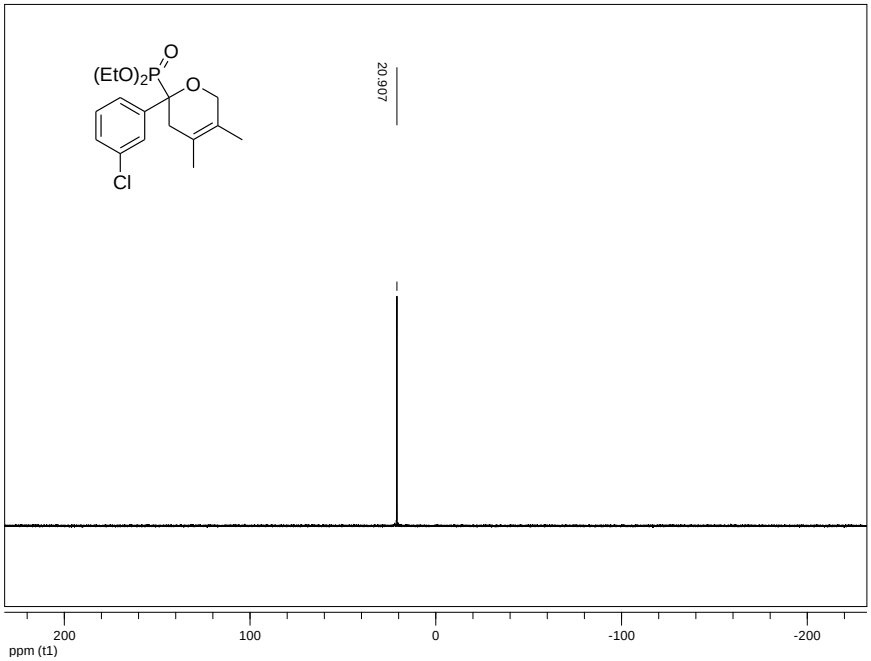


Figure C47. ^{31}P NMR spectrum of **229**

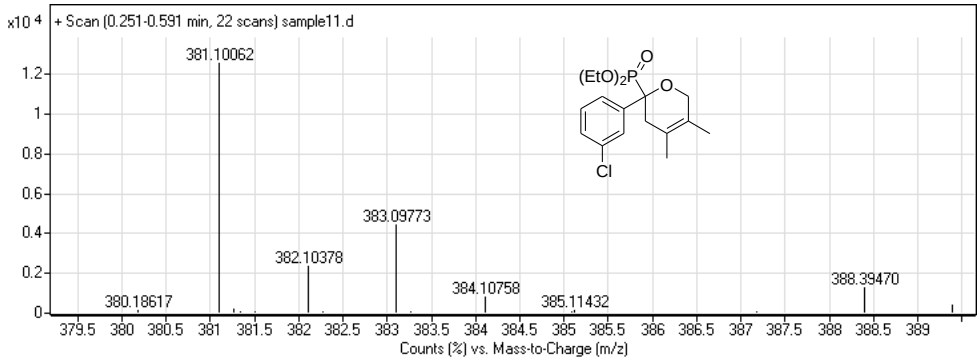


Figure C48. HRMS of compound **229**

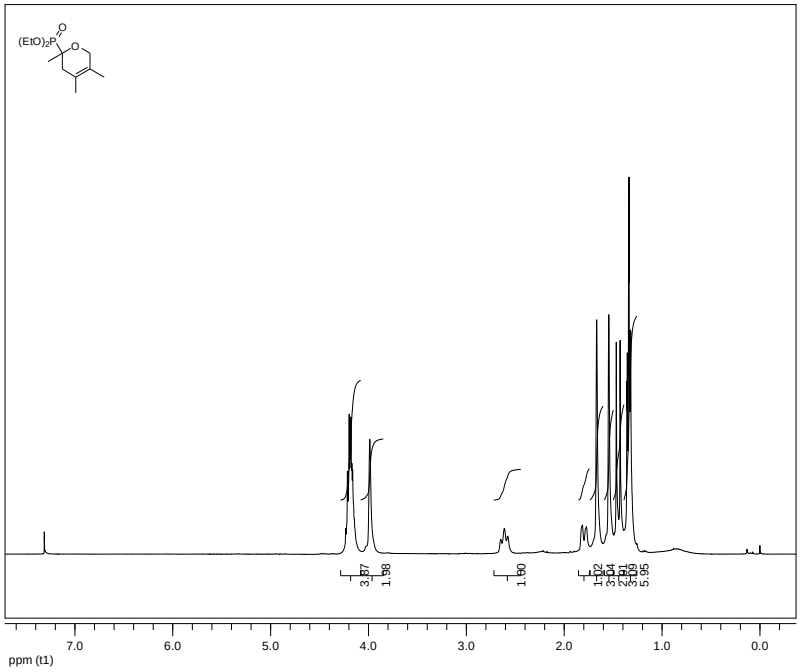


Figure C49. ^{1}H NMR spectrum of **231**

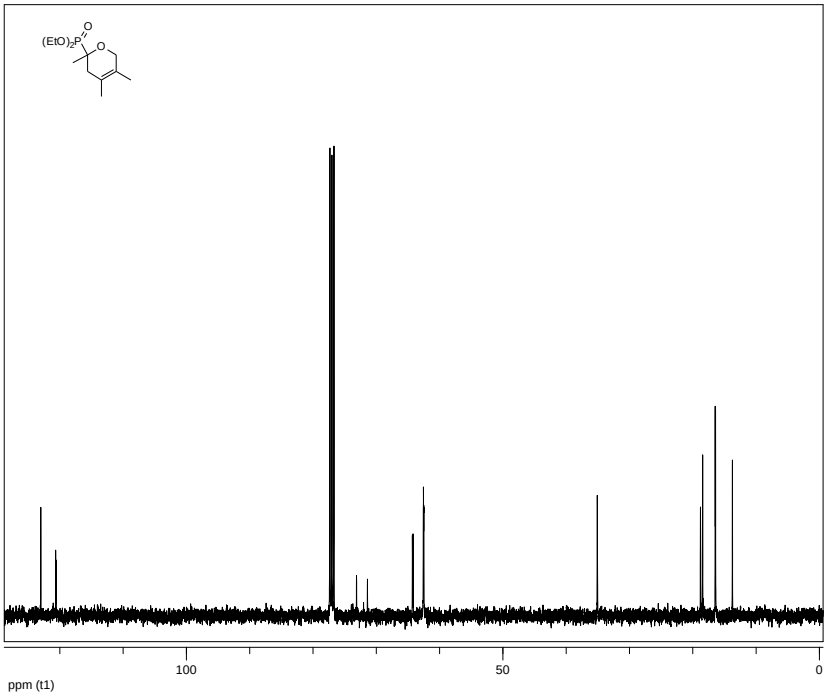


Figure C50. ^{13}C NMR spectrum of **231**

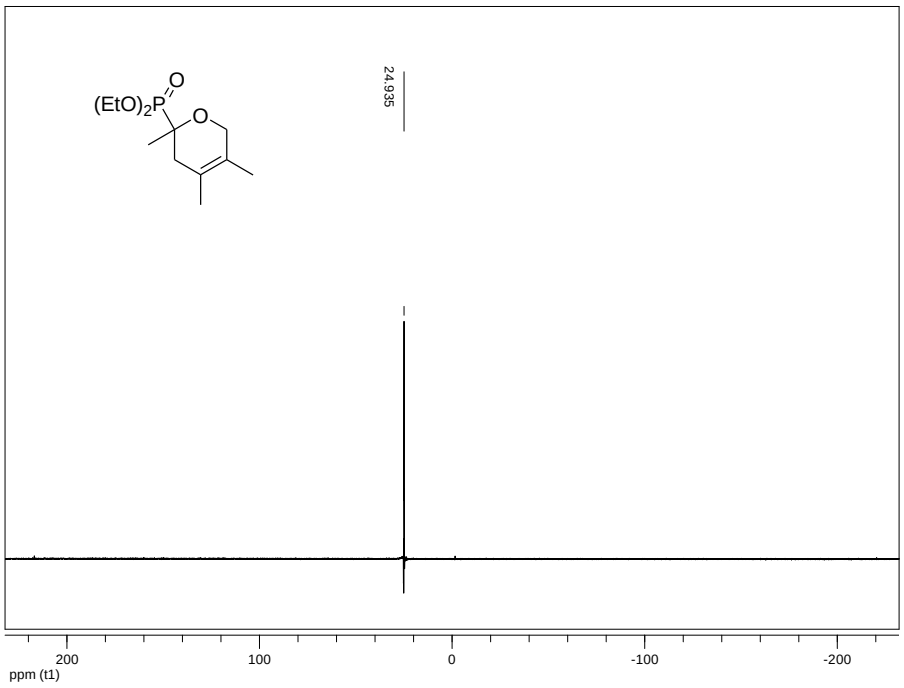


Figure C51. ^{31}P NMR spectrum of **231**

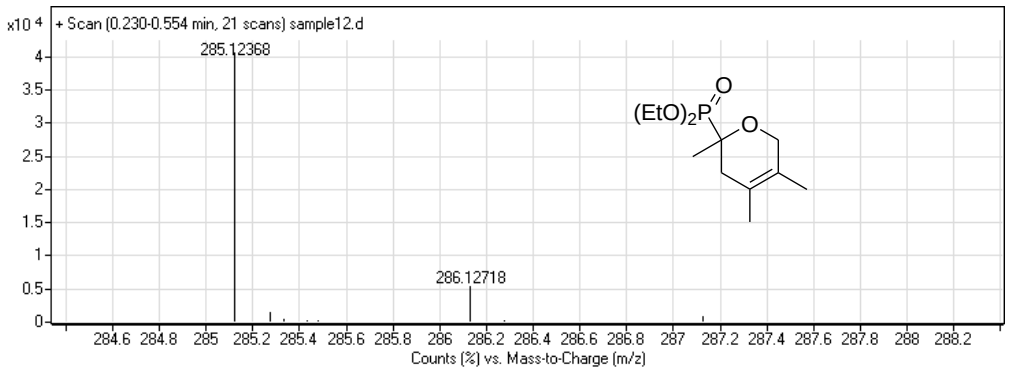


Figure C52. HRMS of compound **231**

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FOREIGN LANGUAGES

English

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Özlem Seven, Sıdıka Polat Çakır, **Md. Shakhawoat Hossain**, Mustafa Emrullahoğlu, Ayhan S. Demir. Reactions of Acyl Phosphonates with Organoaluminum Reagents: A New Method for the Synthesis of Secondary and Tertiary α-Hydroxy Phosphonates. Tetrahedron, 67(19), 3464-3469 (2011).