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Synthetic Methods for the Preparation of 1,3-S,O-Esters, α-Phosphonovinyl Triflates, and α-Alkynylphosphonates

David P. Kercher
Kennesaw State University

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Synthetic Methods for the Preparation of 1,3-*S*,*O*-Esters, α-Phosphonovinyl Triflates, and α-Alkynylphosphonates

by

David P. Kercher

Bachelor of Science in Biochemistry

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Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in the

Department of Chemistry and Biochemistry

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Committee Chair   Graduate Program
Coordinator

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Committee Member   Department Chair

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Committee Member   College Dean

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First Name, Middle Initial, Last Name: David P. Kercher

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GENERAL ABSTRACT

SYNTHETIC METHODS FOR THE PREPARATION OF 1,3-*S*,*O*-ESTERS, α-PHOSPHONOVINYL TRIFLATES, AND α-ALKYNYLPHOSPHONATES

Master of Science in Chemical Sciences, Department of Chemistry and Biochemistry

Principal Investigator: Dr. Christopher W. Alexander

May 2016

A broad and systematic study was conducted on synthetic methods to efficiently synthesize 1,3-*S*,*O*-esters, α-phosphonovinyl triflates, and α-alkynylphosphonates under mild reaction conditions. The master's thesis is composed of two projects; the first project is titled "Synthesis of 1,3-*S*,*O*-Esters" and the second project is titled "Synthesis of α-Phosphonovinyl Triflates and α-Alkynylphosphonates." The first project outlines a synthetic route to conveniently prepare novel α-functionalized 1,3-*S*,*O*-esters via an acid-promoted hydrolysis of α-functionalized α-oxoketene dimethylthioacetals. The second project, unrelated to the first project, primarily focuses on extensive synthetic methodology developed to prepare novel β-functionalized α-phosphonovinyl triflates and display their synthetic application by performing a base-promoted β-elimination to produce β-functionalized α-alkynylphosphonates.

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I would like to dedicate my Master's Thesis to my dear, caring and loving parents, Dan and Dolly Kercher, who have always been supportive in all my endeavors and their unconditional love and encouragement. I cannot fully express in words how grateful, lucky, and fortunate I am to be your son. I love you and thank you.

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LIST OF ABBREVIATIONS

°C	Degrees Celsius
g	Gram
mg	Milligram
Hz	Hertz
J	Coupling constant
mL	Milliliter(s)
min	Minute(s)
h	Hour(s)
d	Day(s)
mmol	Millimole
Ph	Phenyl
rt	Room temperature
TLC	Thin layer chromatography
DI-H_2O	Deionized water
TBAB	Tetrabutylammonium bromide
TsCl	*p*-Toluenesulfonyl chloride
NfCl	Nonafluorobutanesulfonyl chloride
OTf	trifluoromethanesulfonyloxy (-OSO_2CF_3)
Tf_2O	Trifluoromethanesulfonic anhydride

DIA	Diisopropylamine
LDA	Lithium Diisopropylamide
LHMDS	Lithium Hexamethyldisilazide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DIPEA	Diisopropylethylamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DCE	1,2-Dichloroethene
EtOAc	Ethyl Acetate
THF	Tetrahydrofuran
DMF	N, N-Dimethylformamide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
AlBN	Azobisisobutyronitrile
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
DMAP	4-(dimethylamino) pyridine
ee	enantiomeric excess
ppm	Part per million
NMR	Nuclear Magnetic Resonance Spectroscopy
LRMS	Low-Resolution Mass Spectrometry
HRMS	High-Resolution Mass Spectrometry
FT-IR	Fourier Transform Infrared Spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry

A15   Amberlyst-15: sulfonic acid resin

A26   Amberlyst-26: amine base resin

EWG   Electron-Withdrawing Group

TMS   Tetramethylsilane

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CHAPTER 1

SYNTHESIS OF 1,3-*S,O*-ESTERS

ABSTRACT

1,3-*S,O*-Esters are molecular building blocks used in the synthesis of heterocycles, natural products, and other ester-functionalized derivatives. They are a versatile class of compounds that are more reactive than *O*-esters, more stable and easily handled than acid chlorides and acid anhydrides, and are potent acylating agents. The project outlines an efficient preparation of functionalized 1,3-*S,O*-esters from α-oxoketene dimethylthioacetals in high yields via an acid-promoted hydrolysis catalyzed by Amberlyst-15. Amberlyst-15 is an insoluble, recyclable sulfonic acid resin commonly used as an acid alternative to sulfuric acid. It is an ideal reagent because it is milder relative to sulfuric acid, inexpensive, readily available, recyclable, and can be easily filtered out of reactions thus avoiding the need for tedious reaction work-up. The synthetic method developed provides a simple route, conducted under mild reaction conditions to prepare novel α-functionalized 1,3-*S,O*-esters.

Keyword: 1,3-*S,O*-esters, α-oxoketene dimethylthioacetal, Amberlyst-15

1.1 Project Introduction, Significance, and Aim

The project provides an efficient, convenient route to prepare 1,3-*S*,*O*-esters by acid-promoted hydrolysis of α-oxoketene dimethylthioacetals under mild reaction conditions. The method described is more resourceful, milder, and more efficient pathway prepare 1,3-*S*,*O*-esters relative to literature publications. There are only a handful of published methods, which are challenging, often accompanied by poor reaction yields, and typically employ toxic, and/or moisture/air sensitive reagents. The method developed for the synthesis of 1,3-*S*,*O*-esters can be treated with less caution and conducted under milder reaction conditions. The reagents and chemicals used are relatively inexpensive, less toxic, chemically stable, and not air/moisture sensitive. The scope and limitations of the newly designed synthetic method is the primary study based on the analysis of reaction reliability based on functional group tolerance and mild reaction conditions.

The research study aimed to provide a simple and convenient approach to prepare α-functionalized 1,3-*S*,*O*-esters and expand on the chemical versatility of α-oxoketene dimethylthioacetals. α-Oxoketene dithioacetals are a unique class of compounds and have interesting chemistries associated with them due to the chemical reactivity and properties imparted by the thioacetal functionality. They are considered masked synthons in the sense that they have the chemical properties and electronics to behave very similar to a ketene functionality or ester functionality. The chemical stability, ease of functionalizing the β-carbon, and straightforward preparation make the use of α-oxoketene dimethylthioacetal precursors ideal and more advantageous to prepare functionalized 1,3-*S*,*O*-esters relative to the reagents commonly employed in published procedures [1].

The method relies on Amberlyst-15 sulfonic acid resin and water, which facilitates the hydrolysis of α-oxoketene dimethylthioacetals to afford β-methylthioesters. Amberlyst-15 is an air/moisture-stable, insoluble, recyclable, acidic resin that is easy to handle and provides a simple reaction procedure. The Amberlyst-15 catalyst is relatively inexpensive (e.g., Sigma Aldrich - 250 g for $89.10 or $0.36/g) and a safer/milder alternative to sulfuric acid. Conveniently, the Amberlyst-15 resin can be filtered out of reactions and the crude product is easily isolated by washing/rinsing with appropriate solvent. The Amberlyst-15 resin can also be recycled and used again.

A convenient and facile synthetic route is described for the smooth preparation of α-functionalized 1,3-*S,O*-esters **2** afforded by the hydrolysis of β-functionalized α-oxoketene dimethylthioacetals **1** promoted by Amberlyst-15 sulfonic acid resin (**Scheme 1**). Overall, the newly designed method for preparing α-functionalized 1,3-*S,O*-esters is mild and tolerates a range of functional groups. In addition, high product yields are obtained, rapid reaction work-up/crude product isolation is simple, and little waste is generated.
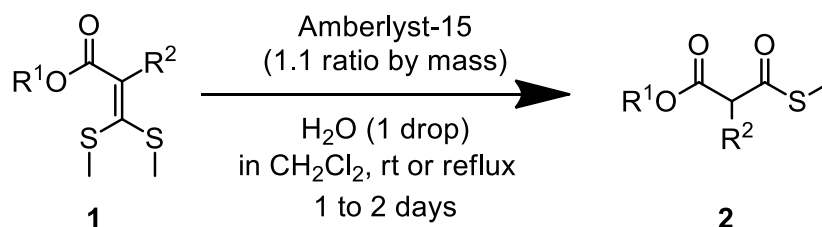
R^1 = CH$_3$ or CH$_2$CH$_3$
R^2 = H, alkyl, aryl, SO$_2$Ph, COOR, P(O)(OEt)$_2$

Scheme 1. Synthetic methodology for 1,3-*S,O*-esters

1.2 Properties and Chemistry of α-Oxoketene Dithioacetals

From the 1970s to the early 1990s, a lot of groundwork was accomplished to elucidate the chemical reactivity and utility of α-oxoketene dithioacetals. As a result, α-oxoketene dithioacetals (**3-5**, **Figure 1**) have proven to be quite versatile and possesses considerable synthetic value in organic synthesis [2]. The literature contains a plethora of publications that highlight the numerous chemical tranformations and complex synthetic targets that are accessible through the functionalized ketene dithioacetals. The α-oxoketene dithioacetal class of compounds highly resembles O, O-acetals, but the unique structural features imparted by the alkylthio moieties in ketene dithioacetals cause the vinyl group to be activated and interesting chemistries can take place. The increased reactivity that is observed is owed to the replacement of the oxygen atoms with sulfur atoms. Sulfur is less electronegative relative to oxygen and consequently, the alkylthio groups tend to donate electron-density.

R^1 = H, alkyl, aryl, OEt,
R^2 = NO$_2$, CN, SO$_2$R, P(O)(OEt)$_2$, Br, I, Cl, SiMe$_3$
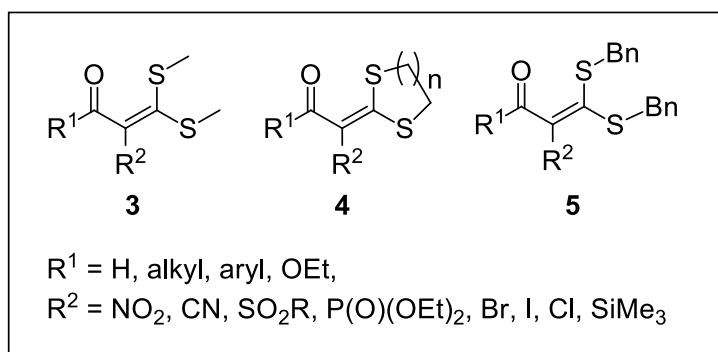
Figure 1. Various functionalized α-oxoketene dithioacetals

In the ketene dithioacetal functional group, electrons are delocalized due to π orbital overlap of the vinyl carbon and sulfur atoms. The π orbital overlap allows the alkylthio groups to donate electron-density to the vinyl functionality which enhances the α-carbon's nucleophilicity towards electrophiles relative to simple alkenes. Ketene dithioacetals are classified by the functional groups substituted at the α-carbon of the vinyl group in ketene dithioacetals. A notable and unique class of ketene dithioacetals is α-oxoketene dithioacetals (**3-5**, **Figure 1**), which are ketene dithioacetals conjugated to carbonyl groups substituted at the α-carbon of the vinyl group. α-Oxoketene dithioacetals are versatile and robust chemical intermediates that commonly serve as 1,3-electrophilic three-carbon synthons in organic chemistry[3, 4]. The reactivity of α-oxoketene dithioacetals (**3-5**, **Figure 1**) can be further modulated by functionalizing the β-carbon of the olefin (for example, nitro, cyano, morpholino, phosphoryl, halides, sulfonyl, silyl, etc.). α-Oxoketene dithioacetals have received significant attention due to their ability to undergo many different reaction types to provide a pathway to prepare a wide variety of functionalized heterocyclic compounds (e.g., pyrimidines, thiophenes, pyrones, pyridinones, etc.) and are of great interest in the pharmaceutical industry due to their biological activity [5-8]. Their preparations and diverse applications have been reviewed extensively in the literature and numerous synthetic targets are accessible through α-oxoketene dithioacetals. Only a handful of reaction procedures will be described.

Kirsch et al., reported the smooth preparation of 3,4-disubstituted thiophenes **7** and **8** by base-catalyzed intramolecular condensation of α-oxoketene dibenzyllthioacetals **6** in moderate to good yields (**Scheme 2**) [9]. The reaction can form two 3,4-disubstituted thiophene products depending on the R^2 substituent. In the case of an ester functionality,

the ethoxy group is subsequently eliminated when attacked by the benzyl nucleophile to yield compound **8**. On the other hand, water is eliminated when attacked by the benzyl nucleophile to afford compound **7** when a ketone is present [10].

R^1 = H, CH$_3$C(O), PhC(O), MeOC(O), EtOC(O)
R^2 = CH$_3$, Ph, p-CH$_3$C$_6$H$_4$, EtO
X = OH, CH$_3$, Ph, p-CH$_3$C$_6$H$_4$
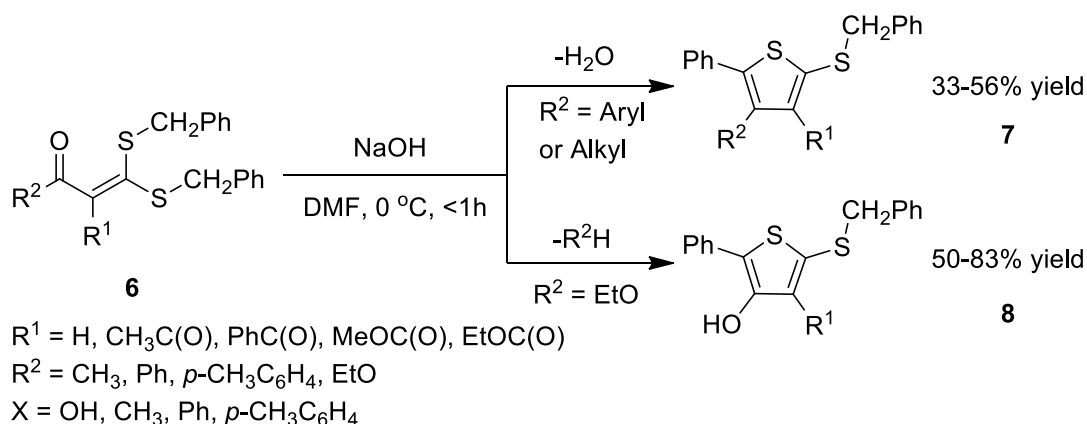
Scheme 2. Synthesis of 3,4-disubstituted thiophenes via intramolecular condensation of α-oxoketene dibenzyllthioacetals

The reaction of bisnucleophiles such as *N, N*-diethylguanidine sulfate with α-oxoketenedithioacetals **9** permits the efficient synthesis of functionalized pyrimidines **10** carrying a remote thiol group in 58% yield (**Scheme 3**) [11]. The reaction proceeds by nucleophilic ring-opening of the cyclic dithioacetal via 1,4-addition, followed by a subsequent condensation reaction to afford compound **10** [11].

a: R^1 = CH$_3$ R^2 = CH$_3$C(O)
b: R^1 = CF$_3$ R^2 = H
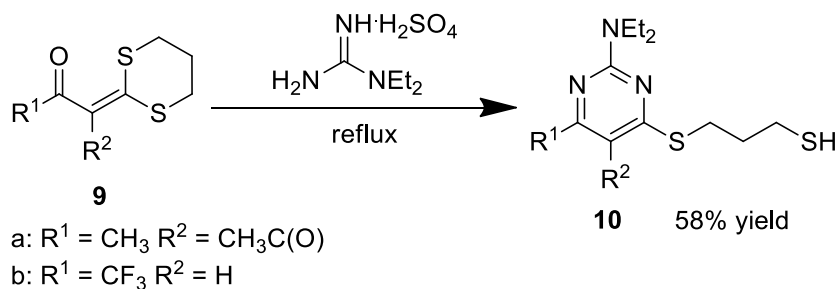
Scheme 3. Synthesis of pyrimidines treated with *N,N*-diethylguanidine sulfate

There has been reported the reaction of ethyl 2-cyano-3,3'-dimethylthioacrylate **11** with arylureas in basic-medium, followed by reflux in anhydrous alcohol to afford 3-aryl-5-cyano-6-methylthiopyrimidine-2,4-dione **12** in 84-91% yield (**Scheme 4**) [12]. The reaction proceeds through a Michael-addition to the dithioacetal, followed by a subsequent elimination of methylthiol, then cyclization under reflux to form the amide while eliminating ethanol.

Ar = Ph, *p*-CH$_3$OC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-CH$_3$C$_6$H$_4$, *m*-CH$_3$C$_6$H$_4$, *o*-ClC$_6$H$_4$
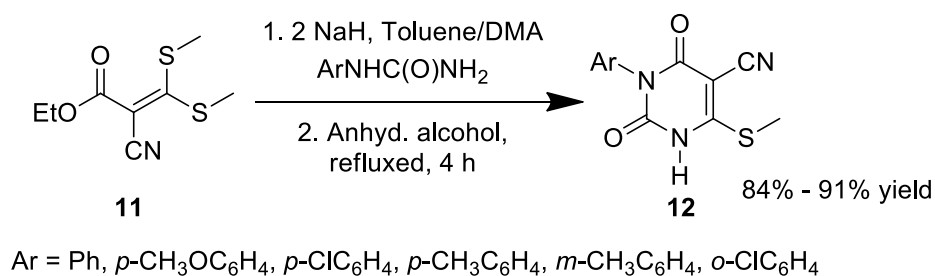
Scheme 4. Synthesis of pyrimidine-2,4-diones

Isoxazoles **15** can be easily accessed by the reaction of α-oxoketene dimethylthioacetal **13** in the presence of hydroxylamine in refluxing ethanol to afford the corresponding oximes **14**, followed by treatment of Amberlyst-15 heated to reflux in acetonitrile (**Scheme 5**) [13].
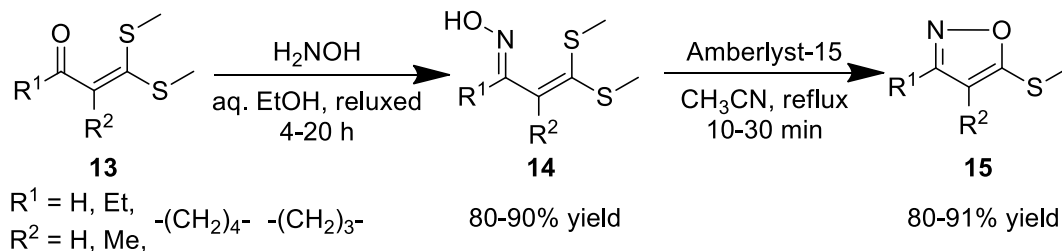
Scheme 5. Synthesis of oximes and isoxazoles

Junjappa et al. reported the preparation of functionalized aromatic compounds by treatment of α-oxoketene dimethylthioacetals in the presence of Grignard reagents followed by $BF_3 \cdot Et_2O$-assisted cycloaromatization (**Scheme 6**) [14]. It was noted that when α-oxoketene dimethylthioacetals **16** were treated with allylmagnesium bromide, 1,2-addition occurred to give rise to allyl-substituted carbinol acetals **17**, which undergo cycloaromatization when treated with $BF_3 \cdot Et_2O$ in refluxing toluene to afford methylthio substituted aromatics **18** in 54-74% yields. In the case of α-oxoketene dimethylthioacetals **16** in the presence of benzylmagnesium chloride, nucleophilic addition occurred via a sequential 1,2- and 1,4-addition to produce benzyl substituted carbinol acetals **19**, followed by $BF_3 \cdot Et_2O$-assisted cycloaromatization to furnish corresponding benzyl substituted benzoannelated products **20** in 58-81% yield.
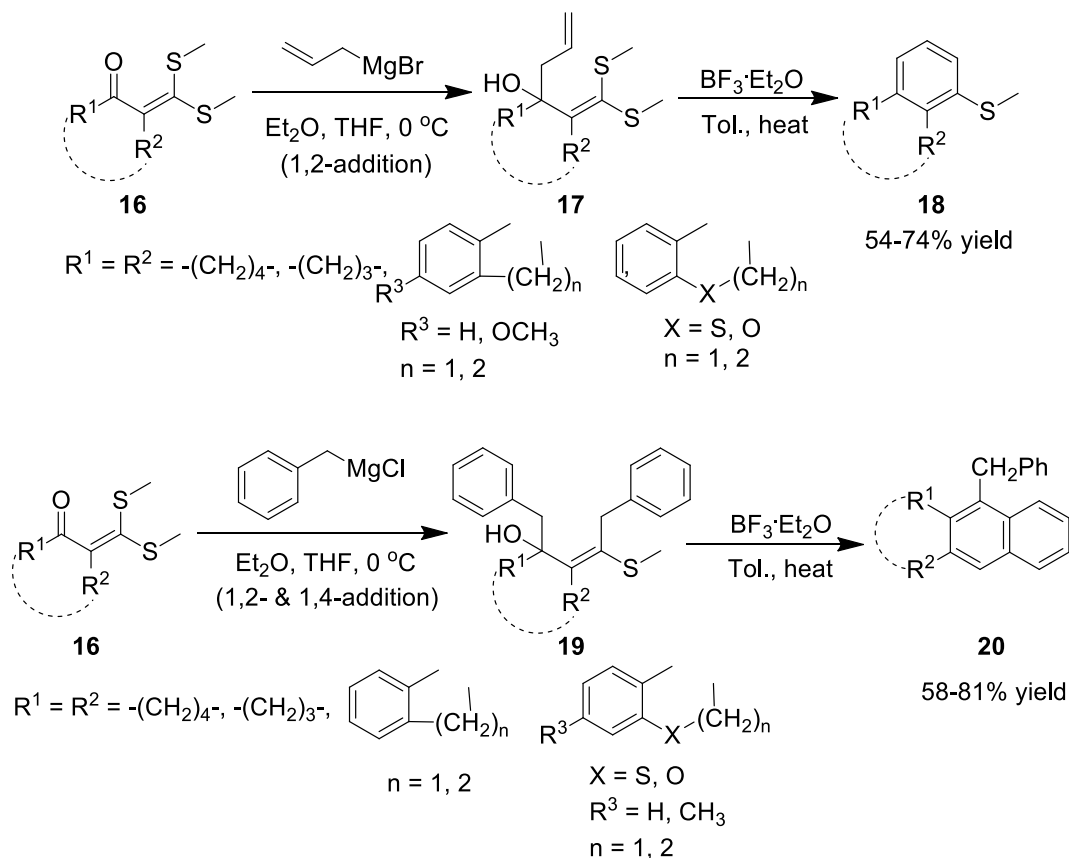
Scheme 6. Synthesis of substituted aromatics via [3+3] aromatic annulation

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The α-oxoketene dimethylthioacetals in conjunction with various functional groups have been exploited in a variety of synthetic applications as substrates due to their masked synthon properties, and sequential carbon-carbon/heteroatom bond formation is easily attained [15]. The α-oxoketene dimethylthioacetal class of compounds has been recently employed to produce novel triazolo[1,5-α]pyrimidine derivatives that hold considerable antimicrobial activity against bacterial and fungal strains[16] and have been found to be potent B-Raf kinase inhibitors in treating cancerous tumors [17].

1.3   Synthesis of 1,3-*S*,*O*-Esters

Upon a thorough literature search, only a handful of methods to prepare 1,3-*S*,*O*-esters were noted. The majority of the methods in the literature includes the use of sensitive and toxic reagents and gives moderate to good product yields. The following reaction procedures summarize literature methods to prepare 1,3-*S*,*O*-esters.

Matsuo and Shindo reported the synthesis of malonic acid *S*,*O*-esters via monoalcoholysis of symmetric dithiomalonates under neutral conditions using a copper catalyst (**Scheme 7**) [18].
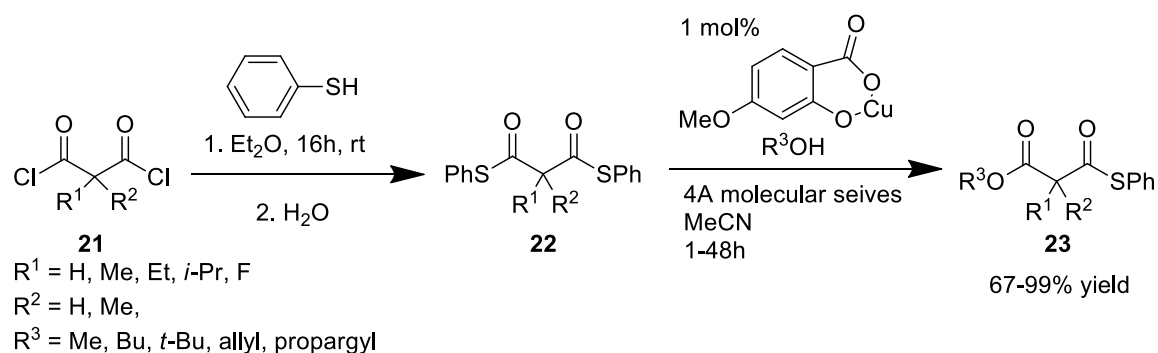
Scheme 7. Synthesis of 1,3-*S*,*O*-esters by monoalcoholysis

The preparation of 1,3-*S,O*-esters has also been afforded through the employment of Horner-Wadsworth-Emmons reagents treated with *n*-butyllithium in the presence of ethylthiochloroformate (**Scheme 8**) [19].
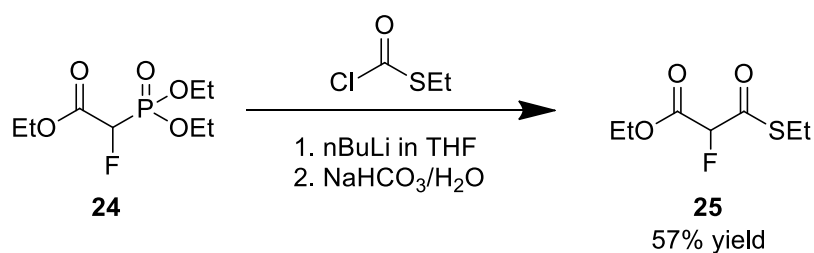
Scheme 8. Synthesis of 1,3-*S,O*-esters via Horner-Wadsworth-Emmons reagents

In addition to Horner-Wadsworth-Emmons reagents, reaction of malonate acid chlorides via 1,2-nucleophilic acyl addition and then subsequent elimination reaction to provide 1,3-*S,O*-esters (**Scheme 9**) [20].
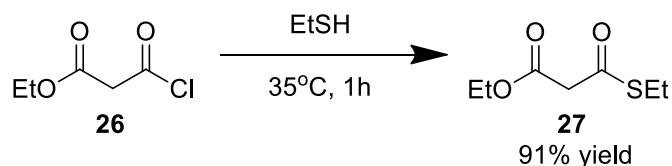
Scheme 9. Synthesis of 1,3-*S,O*-esters via thiols and acid chlorides

Using EDCI to couple thiols to carboxylic acids has provided a means to prepare 1,3-*S,O*-esters. This method has been used to afford malonyl analogs to go on to prepare complex organic compounds (**Scheme 10**) [21].
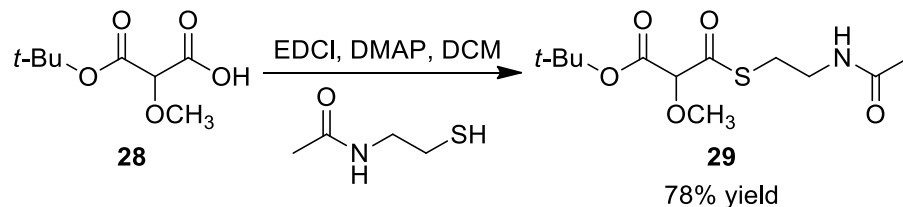
Scheme 10. Synthesis of 1,3-*S*,*O*-esters via thiols and carboxylic acids

Upon conducting a more extensive literature search, only one publication was found that makes use of α-oxoketene dimethylthioacetal precursors to afford β-oxothiolesters. In 2001, Nair and Asokan reported the refluxing of a ketone-functionalized α-oxoketene dimethylthioacetal in dioxane in the presence of an equivalent amount of BF$_3$·Et$_2$O, followed by treatment with water to afford β-oxothiolesters in moderate to excellent yields (**Scheme 11**) [22]. Note that this synthetic method is reported to be limited to ketone-functionalized α-oxoketene dimethylthioacetals and no studies were found on the ester-functionalized α-oxoketene dimethylthioacetals.

R^1 = CH$_3$, Ar, (Ar = C$_6$H$_5$, 4-CH$_3$C$_6$H$_4$, 4-ClC$_6$H$_4$, 4-CH$_3$OC$_6$H$_4$)
R^2 = H
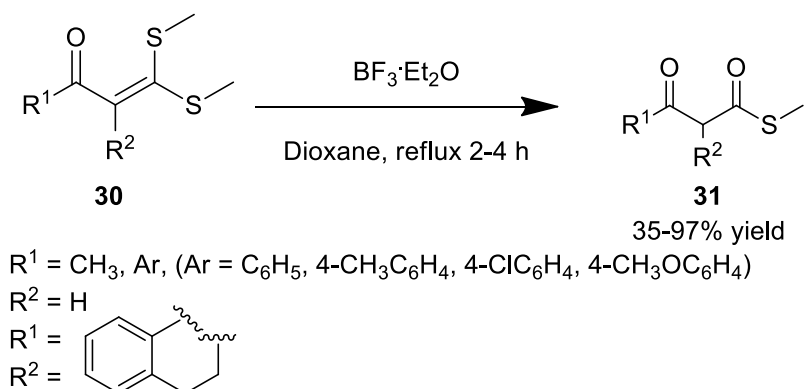
Scheme 11. Synthesis of β-keto-mixed thioesters by Lewis-acid promoted hydrolysis

1.4 Chemistry of 1,3-*S,O*-Esters

The 1,3-*S,O*-ester embraces a malonate backbone that has an ester functionality and mixed thio ester functionality and can be considered 1,3-electrophilic three-carbon synthons. Relative to simple esters, the reactivity is enhanced by the thiol ester moiety and can act as an acylating agent by elimination of a stable alkylthio group. It can serve as an alternative to potent acylating agents such as acid chlorides or acid anhydrides because it is a lot more stable and easily handled [23]. In synthetic application, 1,3-*O,S*-mixed esters are versatile and can be exploited in organic synthesis [23]. Many organic transformations, and, in particular, cyclizations can be accomplished through β-thiol ester precursors.

Shindo and Matsuo displayed the synthetic utility of *S,O*-dissymmetric malonates by alcoholysis, aminolysis, and reduction to yield dissymmetric products **33**, **34**, and **35** in good yields (**Scheme 12**) [18].
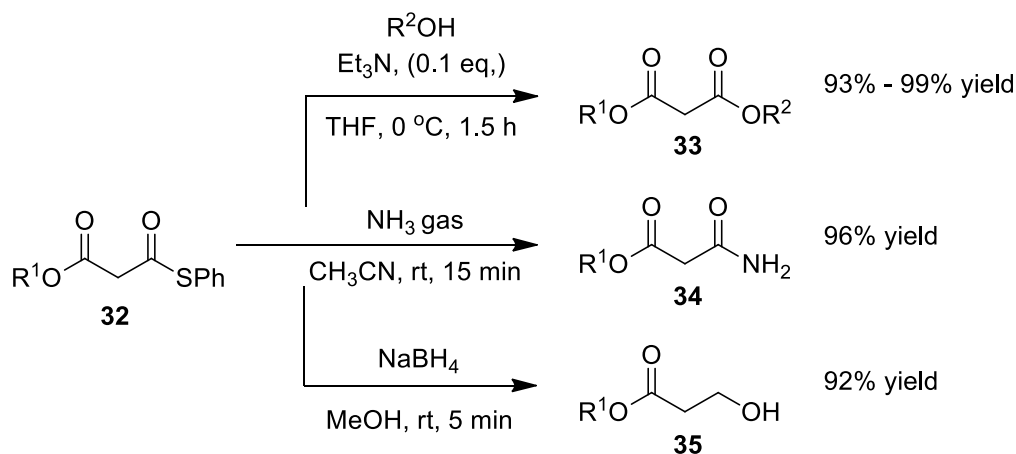
Scheme 12. Hydrolysis, alcoholysis, and aminolysis of 1,3-*S,O*-esters

Methylene insertions have been reported to provide access to γ-thioesters **37** from dissymmetric half-thioesters **36** in the presence of sodium hydride and diiodomethane, followed by treatment with tributyltin hydride to initiate a methylene rearrangement via a radical pathway (**Scheme 13**) [24].
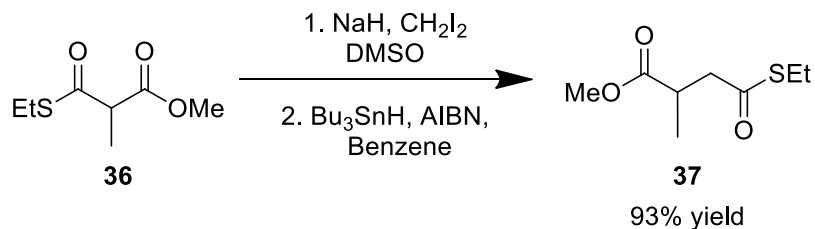
Scheme 13. Preparation of γ-thioesters

α-Substituted monothiomalonates were demonstrated as thioester enolate equivalents and were reported to react cleanly with nitroolefins in the presence of 1–6 mol % of cinchona alkaloid urea derivatives to provide access to γ-nitrothioesters **39** with quaternary stereocenters in high yields and high diastereo- and enantioselectivities [25]. The reactivity of the thioester within the conjugate addition partner, γ-nitrothioesters, allows for straightforward access to other compounds with quaternary stereogenic centers, such as γ-nitroaldehydes **40** and γ-butyrolactams **41** (**Scheme 14**) [25].
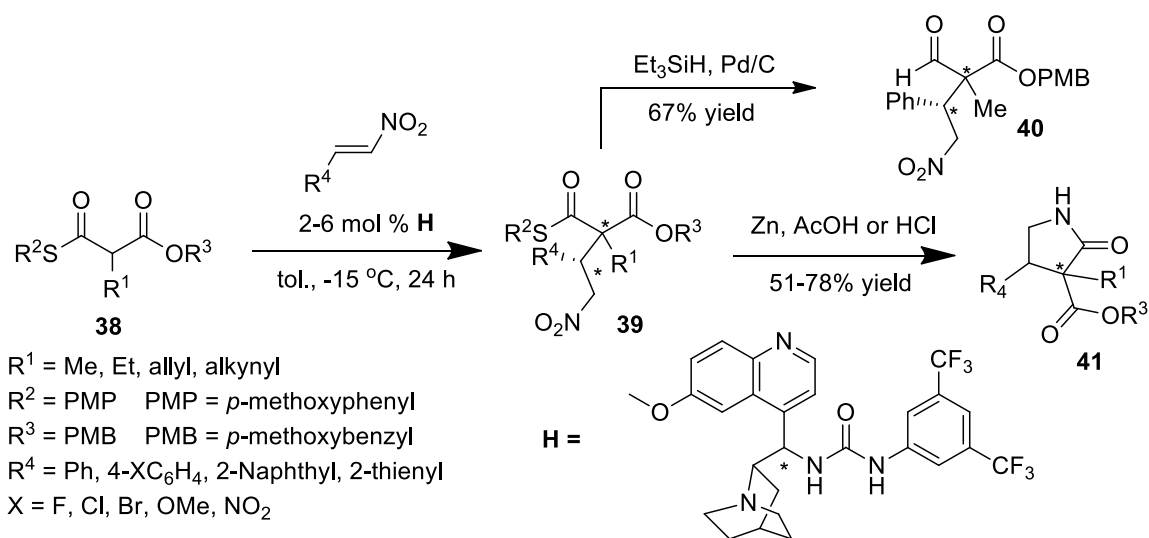
Scheme 14. Synthesis of γ-nitrothioesters, γ-nitroaldehydes, γ-butyrolactams

Thioesters can also be substrates in the Liebeskind–Srogl cross-coupling reaction where carbon–carbon bond formation occurs between thioesters and boronic acids in the presence of a palladium catalyst to prepare β-ketoesters **43** (**Scheme 15**) [26]. The metal catalyst depicted uses TFP = tris(2-furyl)phosphine as an additional ligand and CuTC = copper(I) thiophene-2-carboxylate as a co-metal catalyst [26].
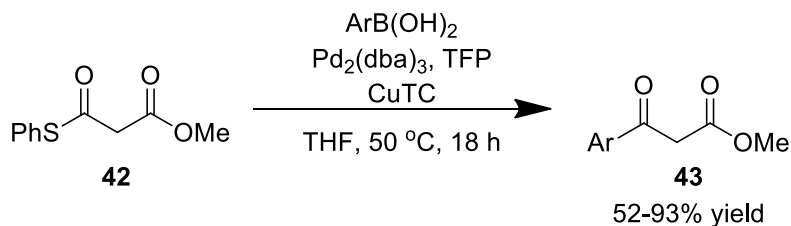
Scheme 15. Synthesis of β-ketoesters via Liebeskind–Srogl cross-coupling

The 1,3-*O,S*-mixed ester class of compounds can also serve as synthetic precursors to novel β-lactam compounds and, most recently, indoline compounds. In

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addition to γ-lactams, α-thietanones can be afforded by the formation of organocobaloximes having alkyl and (alkylthio)carbonyl groups on the β-position from the 1,3-*S,O*-ester precursor [27]. A straightforward stereoselective synthetic route to indolin-3-yl acetates **45** has been recently reported using organocatalytic addition reactions of monothiomalonates **44** to ortho-bromo nitrostyrenes as the key step (**Scheme 16**) [28]. The addition products of the highly stereoselective one-pot addition–deprotection–decarboxylation sequence were easily further converted to indolin-3-yl acetate via an intramolecular Buchwald–Hartwig coupling reaction (**Scheme 16**) [28]. The route provided indolin-3-yl acetates bearing tertiary and exocyclic quarternary stereogenic centers in excellent stereoselectivities and overall yields of 34–83% [28].

$R^1 = R^2 = H$ or Me
PMB = *p*-methoxybenzyl
PMP = *p*-methoxyphenyl

34-83% yield
ee = 91-97%
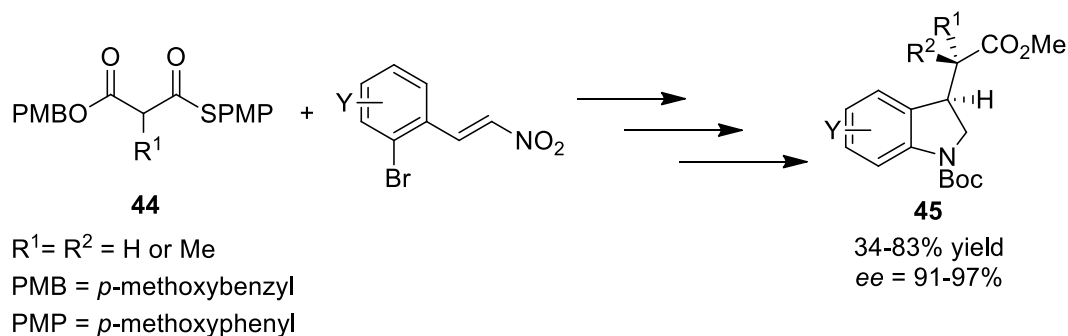
Scheme 16. Synthesis of indolin-3-yl acetates via Buchwald–Hartwig cross-coupling

In addition to indolin-3-yl acetates, monothiomalonates **46** have been shown to be great substrates for a catalytic asymmetric Mannich reaction to prepare 3-aminooxindoles **47** with high diastereo- and enantioselectivity and having high yields of 80%-98% (**Scheme 17**) [29].

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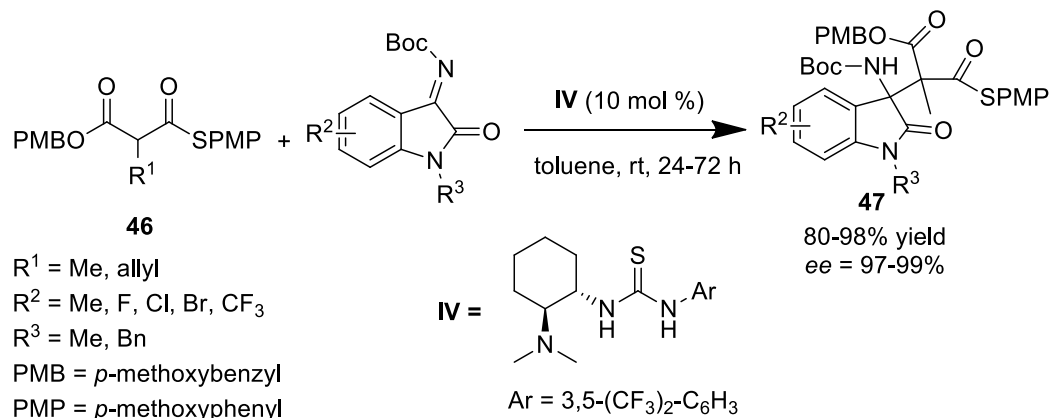
Scheme 17. Preparation of 3-aminooxindoles via asymmetric Mannich reaction

From an organic chemist's perspective and a pharmaceutical standpoint, 1,3-*S*,*O*-esters are versatile chemical building blocks and can be cleverly exploited in strategic syntheses to prepare complex molecular targets and pharmaceuticals. In addition, they can serve as alternatives to acid chlorides and acid anhydrides as acylating agents to provide milder reaction conditions. For the most part, 1,3-*S*,*O*-esters have been unexplored due to the lack of functional group tolerance and the limited number of methods to prepare this unique class of compounds. In summary, there are not many synthetic protocols in the literature to effortlessly prepare functionalized 1,3-*S*,*O*-esters. Through the development of a new, facile, eco-friendly and convenient method to prepare 1,3-*S*,*O*-esters, their chemical versatility and reactivity can be explored readily.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthetic Methodology of 1,3-*S*,*O*-Esters

In this study, novel α-functionalized 1,3-*S*,*O*-esters were cleanly prepared in high yields by the hydrolysis of β-functionalized α-oxoketene dimethylthioacetals promoted by Amberlyst-15 supported sulfonic acid resin. The α-oxoketene dimethylthioacetal precursors were prepared by exploiting enolate chemistry of α-functionalized ester derivatives, which are readily available and affordable from chemical suppliers.

2.2 Synthesis of α-Oxoketene Dimethylthioacetal Derivatives

In order to examine the scope and limitations of the newly developed method and analyze reaction reliability, it was crucial to have substituents possessing various stereoelectronics, steric bulk, electron-donating properties, and electron-withdrawing properties on the β-carbon of α-oxoketene dimethylthioacetal starting materials. When preparing α-oxoketene dimethylthioacetal derivatives, literature procedures were followed and, when necessary, slight modifications were made to meet the demands of

various ester derivatives possessing variations in stereoelectronics, steric bulk, and EDGs/EWGs at the α-carbon position.

The ester functionalized α-oxoketene dimethylthioacetals were prepared by removal of acidic α-hydrogens with appropriate base to generate the carbanion, followed by nucleophilic attack on carbon disulfide, and quenching with an alkylating agent [1].

The preparation of **1a** was accomplished by dissolving TBAB (0.2 eq.) and K₂CO₃ (2.2 eq.) in DI-H₂O. In a separate flask, ethyl acetoacetate **I** was dissolved in carbon disulfide (1.1 eq.), then transferred to reaction flask, allowed to stir at r.t. for 1 hour, and treated with methyliodide (2.1 eq). The reaction mixture was allowed to stir for 2 days, and the reaction was worked up (**Scheme 18**) [30]. Crude isolate was purified via column chromatography and **1a** was obtained in 43% yield (**Entry 1**, **Table 1**). This method will be referred to as "Method A."

Scheme 18. Synthesis of ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate

In the case of esters derivatives having aliphatic/aryl α-substituents, bulky amine bases were used to furnish the corresponding α-oxoketene dimethylthioacetals. For α-oxoketene dimethylthioacetals **1b**, **1c**, and **1d**, 1.0-1.3 eq. of LDA or LHMDS was used in the presence of starting ester in dry THF under nitrogen atmosphere. The reaction was stirred at -78 °C for 30 minutes, followed by the addition of 3.0 eq. of carbon disulfide.

The reaction was allowed to stir at -78 °C for an hour, followed by addition of 2.0-3.0 eq. of methyl iodide dropwise. The reaction was allowed to warm to room temperature over a period of one to three days, followed by neutralization and work-up (**Scheme 19**) [31]. α-Oxoketene dimethylthioacetals **1b**, **1c**, and **1d**, were obtained in 36% yield, 20% yield, and 80% yield, respectively, after purification via column chromatography (**Entries 2-4**, **Table 1**). This method will be referred to as "Method B."
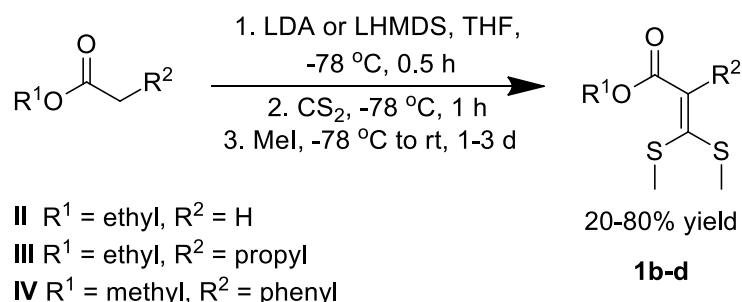
Scheme 19. Synthesis of aliphatic/aryl β-substituted α-oxoketene dimethylthioacetals

In the case of 1,3-dicarbonyl esters and ester derivatives having heteroatoms α-substituted, NaH served as a suitable base to afford the corresponding α-oxoketene dimethylthioacetals. For α-oxoketene dimethylthioacetals **1e**, **1f**, **1g**, **1h** and **1i**, the ester starting material and 1.0-1.2 eq. of carbon disulfide was dissolved in dry DMF at 0 °C under nitrogen atmosphere. The reaction mixture was treated with 2.0-2.5 eq. of NaH and allowed to stir at 0 °C for 1 hour. The reaction was allowed to warm to room temperature and then treated with 2.0-2.5 eq. of methyl iodide. The reaction was allowed to stir for one to three days, and then neutralized and worked-up (**Scheme 20**) [32]. Crude isolate was purified via column chromatography and compounds **1e**, **1f**, **1g**, **1h** and **1i** were

obtained 58-83% yield (**Entries 5-9**, **Table 1**).   This method will be referred to as "Method C."

Reagents:
1. CS_2, DMF, 0 °C, 5 min
2. NaH, 0 °C, 1 h
3. MeI, rt, 1-3 d

V R^1 = ethyl, R^2 = C(O)OEt
VI R^1 = methyl, R^2 = SO_2Ph
VII R^1 = ethyl, R^2 = P(O)(OEt)$_2$
VIII R^1 = ethyl, R^2 = CN
IX R^1 = ethyl, R^2 = C(O)N(CH$_2$)$_4$O
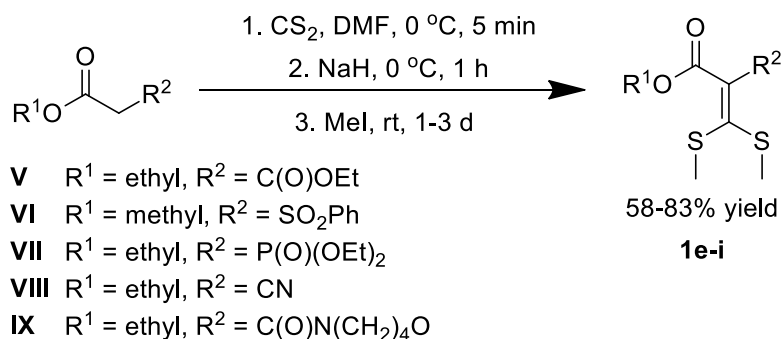
58-83% yield
1e-i

Scheme 20. Synthesis of functionalized β-substituted α-oxoketene dimethylthioacetals

Using these three literature procedures, we obtained α-oxoketene dimethylthioacetals in poor to moderate yields (20-83% yields) after column chromatography and we thus had sufficient starting materials to prepare 1,3-*S,O*-esters. The structures of β-functionalized α-oxoketene dimethylthioacetals are easily determined by ^{1}H-NMR due to the presence of two *S*-methyl peaks around 2.4–2.6 ppm and the reaction can be monitored by the disappearance of the hydrogen peak on the α-carbon of the corresponding ester starting materials. The structures of α-oxoketene dimethylthioacetals are also easily verified by ^{13}C-NMR by the presence of the olefin functionality, the signals which appear between the range of 170-120 ppm.

Table 1. Summary of results for the synthesis of α-oxoketene dimethylthioacetals

Entry	Method (A, B, C)	Time (h)	Yield[a] (%)	α-Oxoketene dimethylthioacetal	
1	A	48	43	1a	
2	B	17	36	1b	
3	B	86	20	1c	
4	B	34	80	1d	
5	C	24	78	1e	
6	C	24	58	1f	
7	C	73	83	1g	
8	C	22	82	1h	
9	C	24	83	1i	

[a] Isolated yield after column chromatography.
Method A: 1) TBAB, K_2CO_3, CS_2, r.t., 1 h. 2) MeI, r.t., 2 d.
Method B: 1) LDA or LHMDS, THF, -78 °C, 0.5 h. 2) CS_2, -78 oC, 1 h. 3) MeI, -78 °C to r.t., 1-3 d.
Method C: 1) CS_2, DMF, 0 °C, 5 min. 2) NaH, 0 °C, 1 h. 3) MeI, r.t., 1-3 d.

2.3 Synthesis of 1,3-S,O-Esters

In an initial reaction, ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate, **1a**, was treated with H_2SO_4/H_2O and heated to reflux to deacylate substrate to provide starting material for another project. This reaction proved to be difficult and many side-reactions occurred. Very little of the desired compound was isolated, therefore an alternative to sulfuric acid was sought to perform the deacylation of ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate, **1a**. In the next reaction, ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate, **1a**, was treated with Amberlyst-15, sulfonic acid supported on a resin-based polymer, was refluxed in DCM. The reaction was very clean, but surprisingly the desired product did not form at all. Instead the reaction afforded the simplest 1,3-*S,O*-ester, **2a**, as colorless oil in 60% yield, which was verified by GC-MS (**Entry 1**, **Table 2**). Delighted with this result, the goal was to apply similar reaction conditions to other substrates bearing functionality at the β-carbon position to examine the scope and limitation of the newly developed procedure. It was also noted that water is necessary for the desired product because the reaction is an acid-catalyzed hydrolysis and the oxygen in the mixed thioester moiety is gained from a water molecule.

Table 2. Synthesis of 1,3-*S,O*-esters via Amberlyst-15 promoted hydrolysis of α-oxoketene dimethylthioacetal derivatives

60-99% yield
2a-g

Entry	Temp.	Time (h)	Yield (%)	1,3-*S,O*-Ester	
1	reflux	12	**94**[a]	**2a**	
2	reflux	24	**94**[a]	**2b**	
3	reflux	18	**89**[b]	**2c**	
4	reflux	18	**96**[a]	**2d**	
5	reflux	24	**89**[b]	**2e**	
6	reflux	48	**99**[b]	**2f**	
7	r.t. reflux	24	**94**[b] **(84%)**[c]	**2g**	
8	reflux	96	**0**[d]	**2h**	
9	reflux	96	**0**[d]	**2i**	

[a] Represents isolated yield after column chromatography.
[b] Represent isolated yield, no purification necessary.
[c] Represents isolated yield when reaction was heated to reflux. Decomposition noted in ^{1}H NMR
[d] No reaction. Starting material recovered.

In order to establish the synthetic methodology and gain mechanistic insight in reaction mechanism, it seemed most appropriate to apply the conditions to the simplest α-oxoketene dimethylthioacetal, **2b**. When treated with Amberlyst-15, along with an excess amount of water, refluxed in DCM for 24 hours, compound **2b** was afforded as a colorless oil in 94% yield after purification (**Entry 2**, **Table 2**). By performing this reaction, it was noted that a deacetylation process was not necessary to carry out the hydrolysis of α-oxoketene dimethylthioacetals to afford 1,3-*S*,*O*-esters. The methodology was extended to more diverse α-oxoketene dimethylthioacetal systems. **Table 2** summarizes the results obtained by the Amberlyst-15-promoted acid-catalyzed hydrolysis of α-oxoketene dimethylthioacetals to furnish 1,3-*S*,*O*-esters.

The same reaction conditions were applied to an α-oxoketene dimethylthioacetal that had an alkyl chain increased by three carbons and a clean hydrolysis took place to afford **2c** as colorless oil in 89% yield after column chromatography (**Entry 3**, **Table 2**). The method was further tested on an aryl β-functionalized α-oxoketene dimethylthioacetal to furnish compound **2d** as colorless oil in 96% yield after column chromatography (**Entry 4**, **Table 2**).

The method's scope was further analyzed by observing the effects of steric bulk and electron-withdrawing groups present on the β-carbon position. In the case of dicarbonyl system bearing ester functionality on the β-carbon, the reaction proved to be tolerant, affording compound **2e** as a colorless oil in 89% yield with no purification necessary indicacted spectroscopically (**Entry 5**, **Table 2**). When further testing the effects of electron-withdrawing groups, a phenylsulfonyl substituent present on the β-carbon gave compound **2f** as a white solid in a yield of 99%, with no purification

necessary indicated by ^{1}H NMR (**Entry 6**, **Table 2**). In the case of a phosophono-functionlized α-oxoketene dimethylthioacetal, the reaction conditions gave great results producing compound **2g** as colorless oil in 84%, but a little decomposition was noted by NMR. When the same reaction was carried out at room temperature, an increase in yield was noted and gave compound **2g** in 94%, no purification was necessary as indicated by ^{1}H NMR (**Entry 7**, **Table 2**).

Reaction scope was further tested on α-oxoketene dimethylthioacetals bearing nitrogen-based substituents on the β-carbon. Surprisingly, in the case of α-oxoketene dimethylthioacetal bearing a cyano or morpholino substituent, compounds **2h** and **2i** gave no indication of product formation and quantitative amounts of starting material were recovered (**Entries 8** and **9**, **Table 2**). Attempts were made to optimize the reaction conditions to accommodate these substrates. The first variable explored was alternative solvents to DCM, which included more polar solvents to better stabilize charged intermediates and having higher boiling points to provide the reaction with more energy when refluxed. Several solvents such as 1,4-dioxane, diethyl ether, acetonitrile, tetrahydrofuran, and petroleum ether were tested. The desired products were not formed and unreacted starting material was recovered each time. In addition to solvent changes, the acid-promoted hydrolysis was attempted with H_2SO_4, in which decomposition of the starting material was observed and the desired 1,3-*S*,*O*-ester products were never formed. Upon further attempts to optimize reaction conditions, several trials were carried out involving the Lewis acid $BF_3 \cdot Et_2O$, which was used in a literature procedure to prepare ketone-functionalized mixed thioesters [22]. Several sets of reaction conditions were tried and no indication of desired product **2h** or **2g** was noted.

In the proposed mechanism, the first step is the abstraction of a proton from hydronium and the subsequent nucleophilic attack of water of the γ-carbon of the ketene dimethylthioacetal to yield the tetrahedral oxonium cation intermediate (**Figure 2**). The second step consists of proton abstraction of the oxonium cation by water to produce hydronium and leave an uncharged tetrahedral intermediate. The next step is abstraction of a hydronium proton by one of the sulfur atoms of the thioacetal to produce a tetrahedral intermediate with a positive charge on one of the methylthio groups. Water then abstracts a proton from the enol, the electrons flow toward the charged thioacetal and eliminates the positively charged *S*-methyl is eliminated as methylthiol and the neutral 1,3-*S,O*-ester is formed as the enol tautomer. The last "step" is an enol-keto tautomerization to give the 1,3-*S,O*-ester in the keto form.
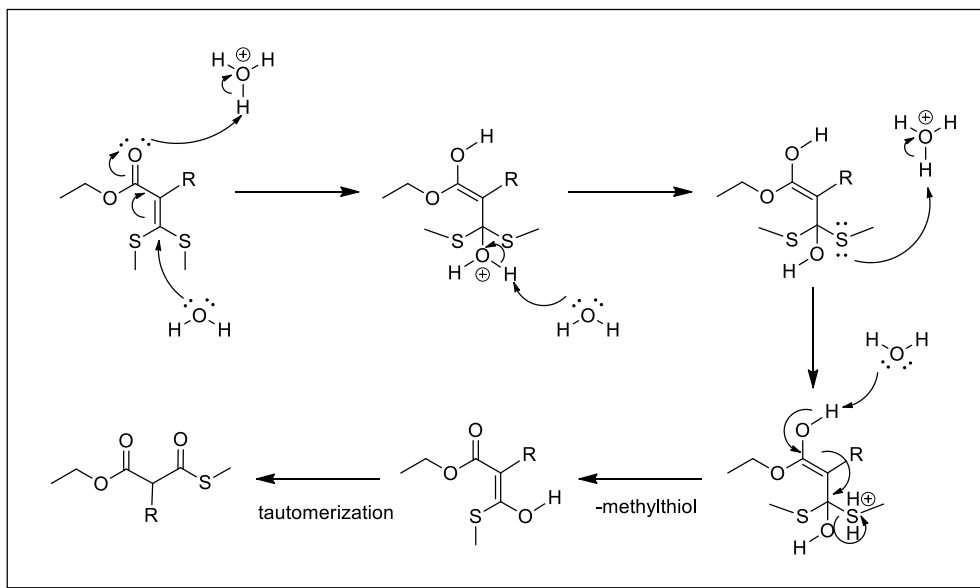
Figure 2. Proposed mechanism for Amberlyst-15 promoted hydrolysis of α-oxoketene dimethylthioacetals to afford 1,3-*S,O*-esters

2.4 Characterization of 1,3-*S*,*O*-Esters

All of the 1,3-*S*,*O*-esters prepared are novel and their properties are unknown in the literature. All 1,3-*S*,*O*-esters were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, LRMS, and HRMS. The following section describes critical ^{1}H NMR spectral data that characterizes the 1,3-*S*,*O*-esters. All spectral data can be found in Appendix A for the α-oxoketene dimethylthioacetals and Appendix B for 1,3-*S*,*O*-esters.
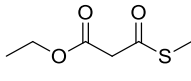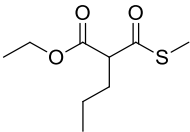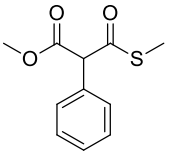
2.4.1 ^{1}H NMR Characterization of 1,3-*S*,*O*-Esters

The reaction of the acid-catalyzed hydrolysis of α-oxoketene dimethylthioacetal derivatives can be easily monitored by ^{1}H NMR by the disappearance of the two *S*-methyl peaks of the ketene dimethylthioacetal functionality. The formation of 1,3-*S*,*O*-ester products can be verified by the emergence of the mixed methylthio ester proton signal that appears as a singlet and the presence of the α-hydrogen that can give rise to a range of splitting patterns based on the β-substituent present. In general, the *S*-methyl signal of the mixed methylthio ester group resonates between a narrow range of 2.31 – 2.40 ppm. Generally, the methine protons (CH) of the α-carbon resonate in the chemical shift range of 3.54 – 5.13 ppm integrating to one proton and can have a variety of splitting patterns based on the γ-substituent.

For aliphatic β-functionalized 1,3-*S*,*O*-esters, the simplest 1,3-*S*,*O*-esters **2a** and **2b**, the *S*-methyl peak resonates at 2.36 ppm and the β-hydrogen resonates 3.58 ppm as a singlet. The 1,3-*S*,*O*-ester having an alkyl chain increased by three carbons, **2c**, the *S*-methyl peak resonates at 2.34 ppm and the β-hydrogen resonates at 3.57 ppm as a triplet having a coupling constant of $J = 7$ Hz. In the case of aryl α-substituted 1,3-*S*,*O*-ester **2d**,

the *S*-methyl peak resonates at 2.32 ppm and the α-hydrogen resonates at 4.81 ppm. [1]H

NMR spectral data for compounds **2a–2d** are summarized in **Table 3**.

Table 3. ^{1}H NMR spectral data for 1,3-*S,O*-esters 2a–2d

	2a, 2b	2c	2d
1,3-*S,O*-Esters			
***S*-methyl (ppm)**	2.36	2.34	2.32
Splitting Pattern	*s*	*s*	*s*
α-Hydrogen (ppm)	3.58	3.57	4.81
Splitting Pattern	*s*	*t*	*s*
Coupling Constant (Hz)	-------	7	-------

In the case of 1,3-*S,O*-esters having electron-withdrawing substituents on the α-carbon, the 1,3-tricarbonyl 1,3-*S,O*-ester **2e**, the *S*-methyl peak resonates at 2.42 ppm and the α-hydrogen resonates at 4.61 ppm. For the 1,3-*S,O*-ester bearing a phenylsulfonyl functionality, **2f**, the *S*-methyl peak resonates at 2.34 ppm and the α-hydrogen resonates at 5.14 ppm. Lastly, for the phosphono-β-functionalized 1,3-*S,O*-ester **2g**, the *S*-methyl peak resonates at 2.39 ppm and the β-hydrogen resonates at 4.41 ppm as a doublet due to phosphorus-hydrogen coupling. ^{1}H NMR spectral data for compounds **2e–2g** are summarized in **Table 4**.

Table 4. ^{1}H NMR Spectral Data for 1,3-S,O-Esters 2e–2g

	2e	2f	2g
1,3-S,O-Esters			
***S*-methyl (ppm)**	2.42	2.34	2.39
Splitting Pattern	*s*	*s*	*s*
α-Hydrogen (ppm)	4.61	5.14	4.41
Splitting Pattern	*s*	*s*	*d*
Coupling Constant $J_{P\text{-}H}$ (Hz)	-------	-------	21.6

CHAPTER 3

CONCLUSION

As a result of this study, a new, facile, and convenient route for the synthesis of novel, α-functionalized 1,3-*S,O*-esters was developed. The synthetic methodology proceeds by the acid-catalyzed hydrolysis of α-oxoketene dimethylthioacetals by treatment with Amberlyst-15 to furnish functionalized 1,3-*S,O*-esters in high purity and yield. In total, six α-functionalized 1,3-*S,O*-esters were prepared and five of the 1,3-*S,O*-esters are novel, unreported in the literature and they were fully characterized. Out of the six 1,3-*S,O*-esters, five of them have a chirality center at the α-carbon and the stereochemistry for the 1,3-*S,O*-ester derivatives of these five compounds was not investigated in this research study. In a follow-up research project the goal is to broaden substrate scope and address the problematic α-oxoketene dimethylthioacetal substrates, **2h** and **2i**.

In summary, the methodology describes a clean acid-promoted hydrolysis on six α-oxoketene dimethylthioacetals having broad substrate scope and compounds **2a-g** were obtained in excellent yields (89-99%). The methodology developed is a great improvement in direct comparison to the literature procedures ,which employ harmful and/or moisture/air-sensitive reagents that require special handling, utilize transition

metals to mediate chemistry, suffer from poor substrate scope, have poor yields, and require multiple reaction steps to prepare 1,3-*S,O*-esters.

The methodology developed is a two reaction pathway that utilizes starting materials that can be prepared from affordable α-functionalized ester systems that can be purchased from chemical vendors or simply prepared in the lab. In addition, the method is environmentally friendly due to the incorporation of the Amberlyst-15 sulfonic acid resin. Less waste is generated, costs are kept at a minimum, and it provides a quick and easy reaction work-up affording products in high yield and purity.

CHAPTER 4

MATERIALS AND METHODS

GENERAL

All reactions utilizing sensitive reagents were carried out using anhydrous solvents under nitrogen atmosphere. All glassware necessary for sensitive reactions was kept in a 110 °C – 140 °C oven and cooled to room temperature under nitrogen gas dried by passing through a Drierite column prior to use. Reagent grade THF, DMF, and DCM was dried over 3Å molecular sieves and DIA was dried by distillation over CaH_2. Deionized H_2O was used in reactions and reaction work-ups. Reactions were monitored by silica gel thin layer chromatography (Sorbent Technologies). Visualization of compounds was accomplished with UV light, vanillin stain and/or potassium permanganate stain followed by heating. α-Oxoketene dimethylthioacetals were prepared according to literature procedures with modifications applied when necessary and purified by vacuum distillation or column chromatography. A 0 °C temperature was obtained using and ice/water bath and -78 °C temperature was obtained using dry ice/acetone bath. Purification of 1,3-*S,O*-ester products was carried out by flash column chromatography using grade silica gel 60 (Sorbent Technology). All NMR spectra were taken using a Bruker DPX 300 MHz. ^{1}H-NMR spectra was recorded for $CDCl_3$ solutions are reported

in ppm with tetramethylsilane as an internal standard (TMS δ = 0.00 ppm). Data are reported as splitting pattern, coupling constant, and integration (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintet, sex = sextet, b = broad; coupling constant(s) in Hz). Proton-decoupled ^{13}C-NMR spectra were recorded for CDCl$_3$ solutions and are reported in ppm using residual chloroform as internal standard (CHCl$_3$ δ = 77.0 ppm). All FT-IR were taken using a Perkin Elmer ATR.

4.1 Experimental for α-Oxoketene Dimethythioacetals

Synthetic Procedure for:

Ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate (1a)
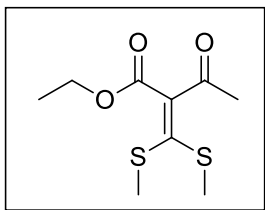
In a 150-mL round-bottom flask, TBAB (2.2683 g, 7.0 mmol) and K$_2$CO$_3$ (12.8315 g, 77.0 mmol) were dissolved in DI-H$_2$O (30 mL). In a vial, ethyl acetoacetate (4.46 mL, 35.0 mmol) was dissolved in carbon disulfide (2.31 mL, 38.5 mmol) and then transferred to the reaction flask. The reaction mixture was allowed to stir at r.t. for 1 h, followed by the addition of iodomethane (4.58 mL, 73.5 mmol). The reaction was monitored by TLC and was determined complete after 48 h of stirring at r.t. The crude product was obtained by extraction 3x with EtOAc and the combined organic extracts were washed sequentially with H$_2$O and brine. The organic extract was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. After triturating with Et$_2$O and concentrating in vacuuo the crude material was purified by short-path distillation (0.38 mm Hg, 110–117 °C to provide 3.4727 g of yellow/orange liquid (43% yield). ^{1}H-NMR

(300 MHz, CDCl$_3$/TMS) δ 1.34 (t, 3H, J = 7.1 Hz), 2.35 (s, 3H), 2.44 (s, 6H) 4.29 (q, 2H, J = 7.1 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.99, 18.51, 29.94, 61.45, 135.14, 157.20, 165.06, 195.38. [30]

Synthetic Procedure for:

Ethyl 3,3-bis(methylsulfanyl)prop-2-enoate (1b)
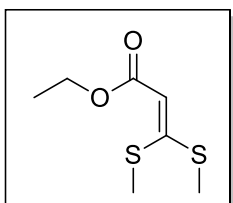
An oven-dried 25-mL round-bottom flask was cooled under nitrogen gas and charged with anhydrous ethyl acetate (0.10 mL, 1.0 mmol), DMPU (0.36 mL, 3.0 mmol), and 2.5 mL dry THF. The mixture was cooled to -78 °C with a dry-ice/acetone bath and LHMDS (1.0 mL, 1.0 M in THF/ethylbenzene, 1.0 mmol) was added to the mixture dropwise over about 5 min. After stirring for 1 h at the same temperature, carbon disulfide (0.07 mL, 1.2 mmol) was added in one portion. The mixture was removed from the cooling bath and stirred at r.t. for 1 h. The mixture was cooled to -78 °C and LHMDS (1.0 mL, 1.0 M in THF/ethylbenzene, 1.0 mmol) was added dropwise. The mixture was stirred for 1 h at -78 °C and then iodomethane (0.12 mL, 2.0 mmol) was added dropwise. The reaction mixture was stirred for 17 h at r.t. After quenching with 2.5 mL saturated ammonium chloride and diluting with DI-H$_2$O (5 mL), the mixture was extracted 3x with ethyl acetate. The combined organic extracts were washed with 5% citric acid, 3x DI-H$_2$O, and brine. After drying over anhydrous Na$_2$SO$_4$, the crude solvent was removed in vacuo and the resulting oil was purified by column chromatography (silica, ethyl acetate) which provided 70.4 mg of colorless crystals (36% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.28 (t, 3H, J = 7.1 Hz), 2.42 (s, 3H), 2.50 (s, 3H), 4.18 (q, 2H, J = 7.1

Hz), 5.57 (s, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 14.34, 14.61, 16.85, 59.61, 104.78, 161.41, 165.05. [31]

Synthetic Procedure for:

Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate (1c)
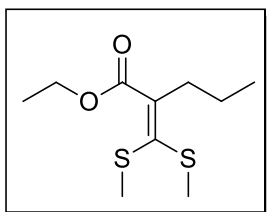
To an oven-dried 250-mL round-bottom flask, cooled under nitrogen gas, was added diisopropylamine (5.46 mL, 39 mmol) and dry THF (40 mL). After cooling to -78 °C with a dry-ice/acetone bath, *n*-BuLi (13.27 mL, 2.26 M in hexanes) was added dropwise over 5 min and the resulting mixture was stirred further for about 30 min. After the addition, the reaction was warmed to 0 °C with an ice-water bath. A solution of ethyl pentanoate (4.45 mL, 30 mmol) in dry THF (7 mL) was added to the mixture by cannula. The mixture was stirred at 0 °C for 1 h then cooled to -78 °C at which point carbon disulfide (2.71 mL, 45 mmol) was added dropwise. The mixture was stirred at -78 °C for 30 min; then iodomethane (5.60 mL, 90 mmol) was added dropwise and the reaction mixture was allowed to warm to r.t. and was stirred for 86 h. The mixture was diluted with DI-H$_2$O (50 mL) and extracted 3x with EtOAc. The combined organic extracts were washed with saturated NH$_4$Cl, 2x DI-H$_2$O and brine. After drying over anhydrous Na$_2$SO$_4$ and filtering, the solvent was removed in vacuo. The crude material was purified via short-path distillation (distillate came over at 79-80 °C at 0.486 mmHg) and a yellow oil was obtained (1.4473 g, 20% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.31 (t, 3H, *J* = 7.1 Hz), 1.45 (sex, 2H, *J* = 7.0 Hz), 2.29 (s, 3H), 2.32 (s, 3H), 2.54-2.60 (m, 2H), 4.25 (q, 2H, *J* = 7.1 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.72, 14.14,

16.61, 17.63, 21.80, 35.17, 60.86, 137.52, 141.20, 168.64; FT-IR (ATR, neat) v_{max}/cm^{-1}:

2961, 2923, 2871, 1717, 1575, 1462, 1433, 1365, 1270, 1217, 1172, 1132, 1017, 970,

899, 856, 743. [31]

Synthetic Procedure for:

Methyl 3,3-bis(methylsulfanyl)-2-phenylprop-2-enoate (1d)
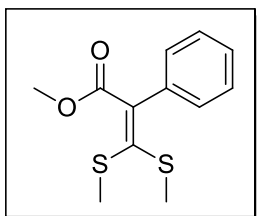
An oven-dried 50-mL round-bottom flask was cooled to rt under nitrogen gas. The flask was charged with diisopropylamine (0.70 mL, 5.0 mmol) and dry THF (10 mL). After cooling to 0 °C using an ice-water bath, *n*-BuLi (2.60 mL, 5.0 mmol, 1.94 M in hexanes) was added dropwise and the resulting mixture was allowed to stir for 30 min at 0 °C. Methyl phenylacetate (0.71 mL, 5.0 mmol) was added dropwise and the cold mixture was stirred for 1 h. The reaction vessel was cooled to -78 °C using a dry ice/acetone bath, carbon disulfide (0.90 mL, 15 mmol) was added dropwise and after 30 min of stirring, iodomethane (0.93 mL, 15 mmol) was added dropwise. The reaction was allowed to warm to r.t. overnight and was stirred for 34 h at which point the mixture was diluted with DI-H$_2$O (10 mL). The mixture was extracted 3x with ethyl acetate and the combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified via column chromatography (silica, 15% diethyl ether, 85% petroleum ether) to provide 1.019 g light yellow oil (80% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 2.20 (s, 3H), 2.42 (s, 3H), 3.76 (s, 3H), 7.31-7.36 (m, 5H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 17.39, 18.01, 52.28, 128.05, 128.16, 128.97, 136.23, 137.34, 142.89, 167.75. [31]

Synthetic Procedure for:

Diethyl [bis(methylsulfanyl)methylidene]propanedioate (1e)
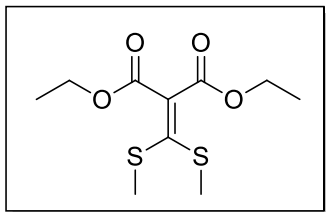
An oven-dried 50-mL round-bottom flask was cooled under nitrogen gas and loaded with diethyl malonate (0.76 mL, 5.0 mmol), carbon disulfide (0.36 mL, 6.0 mmol), and anhydrous DMF (20 mL). The reaction flask was then cooled to 0 °C and NaH (0.4921 g, 12 mmol, 60% NaH dispersion in mineral oil) was added in portions. The reaction mixture was allowed to warm to r.t. and allowed to stir for 1 h, then iodomethane (0.75 mL, 12 mmol) was added dropwise. Reaction progress was monitored by TLC and determined complete after 24 h stirring at r.t. The reaction mixture was quenched with 10% NH_4Cl and extracted 4x with ethyl acetate. The combined organic extracts were washed with 2x H_2O and brine. After drying over anhydrous Na_2SO_4 and filtering, the solvent was removed in vacuo. The crude material was purified via column chromatography (silica, 20% hexane: 80% ethyl acetate) to afford 1.0296 g of light yellow liquid (78% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.31 (t, 6H, J = 7.1 Hz), 2.45 (s, 6H), 4.27 (q, 2H, J = 7.1 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.86, 18.28, 61.21, 127.19, 158.49, 163.78; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2981, 2928, 2905, 1725, 1702, 1525, 1464, 1445, 1365, 1265, 1211, 1173, 1081, 1021, 972, 903, 861, 740. [32]

Synthetic Procedure for:

Methyl 3,3-bis(methylsulfanyl)-2-(phenylsulfonyl)prop-2-enoate (1f)
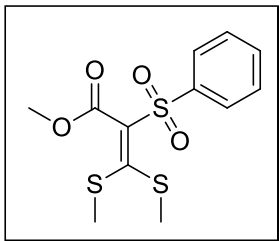
An oven-dried 25-mL round-bottom flask was cooled to rt under nitrogen gas. The flask was charged with methyl α-(phenylsulfonyl) acetate (0.6474 g, 3.0 mmol), carbon disulfide (0.18 mL, 3.0 mmol), and anhydrous DMF (12 mL). The reaction flask was then cooled to 0 °C, followed by the portion-wise addition of 60% NaH in mineral oil (0.2562 g, 6.3 mmol). The reaction mixture was allowed to warm to r.t. and allowed to stir for 1 h, followed by the dropwise addition of iodomethane (0.40 mL, 6.3 mmol). The reaction was monitored by TLC and determined complete after 24 h stirring at r.t. The reaction mixture was subsequently neutralized with 10% $NaHCO_3$ and extracted 3x with EtOAc. The combined organic extracts were washed 4x with DI-H_2O and then brine. After drying over anhydrous Na_2SO_4 and filtering, the crude material was concentrated in vacuo. The product was purified via column chromatography (60% hexane: 40% ethyl acetate) to afford 0.5548 g of white solid (58% yield). ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ 2.20 (s, 3H), 2.38 (s, 3H), 3.91 (s, 3H), 7.51-7.56 (m, 2H), 7.61-7.66 (m, 1H), 8.08-8.10 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ 17.18, 18.11, 53.30, 128.44, 128.59, 133.57, 136.98, 140.62, 157.12, 163.25; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3064, 3019, 2954, 2933, 1718, 1519, 1447, 1426, 1318, 1302, 1290, 1244, 1143, 1088, 1053, 941, 877, 822, 755, 722. [32]

Synthetic Procedure for:

Ethyl 3,3-bis(methylsulfanyl)prop-2-(diethylphosphono)acetate (1g)
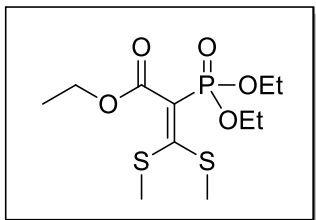
An oven-dried 50-mL round-bottom flask was cooled under nitrogen gas. The flask was charged with triethyl phosphonoacetate (1.98 mL, 10 mmol), carbon disulfide (0.60 mL, 10 mmol), and dry DMF (20 mL). The flask was cooled to 0 °C with an ice-water bath and then was briefly opened to air to add NaH (0.8473 g, 21 mmol, 60% dispersion in mineral oil) in portions. About 3 mL of dry DMF was used to rinse the sides of the flask and the reaction mixture turned red. After stirring for about 5 min at 0 °C, the reaction was moved to r.t. to stir for 1 h. The flask was cooled to 0 °C and iodomethane (1.30 mL, 21 mmol) was added. After stirring at r.t. for 73 h, the reaction was quenched with saturated ammonium chloride and extracted 3x with ethyl acetate. The combined organic extracts were washed with 1x DI-H_2O, 2x brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified via column chromatography (silica, ethyl acetate) to provide 2.7511 g of light yellow liquid (83 % yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.33 (t, 9H, $J = 7.1$ Hz), 2.39 (s, 3H), 2.43 (s, 3H), 4.09-4.23 (m, 4H), 4.28 (q, 2H, $J = 7.1$ Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.91, 18.01, 16.13 (d, $J_{P\text{-}C} = 6$ Hz), 61.73, 62.70 (d, $J_{P\text{-}C} = 6$ Hz), 127.63, 130.06, 157.78 (d, $J_{P\text{-}C} = 6.8$ Hz), 165.18 (d, $J_{P\text{-}C} = 12.8$ Hz). [32]

Synthetic Procedure for:

Ethyl 3,3-bis(methylsulfanyl)prop-2-cyanoacetate (1h)
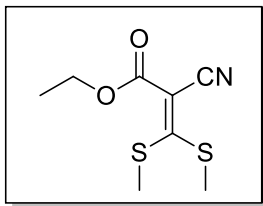
An oven-dried 50-mL round-bottom flask was cooled under nitrogen gas and loaded with ethyl cyanoacetate (0.532 mL, 5.0 mmol), anhydrous DMF (10 mL), and carbon disulfide (0.36 mL, 6.0 mmol). To this solution was added NaH (0.5065, 12.7 mmol, 60% dispersion in mineral oil) by portions. After stirring for 1 h at r.t., iodomethane (0.75 mL, 12 mmol) was added dropwise. The resulting solution was stirred for 22 h, quenched with saturated ammonium chloride, and diluted with DI-H$_2$O. The precipitate was filtered and the filter cake was recrystallized from hot ethanol to provide white crystals; (0.9009 g, 82% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.35 (t, 3H, $J = 7.1$ Hz), 2.60 (s, 3H), 2.76 (s, 3H), 4.29 (q, 2H, $J = 7.1$ Hz); FT-IR (ATR, neat) v_{max}/cm^{-1}: 2985, 2940, 2904, 2207, 1693, 1449, 1416, 1365, 1322, 1255, 1166, 1144, 1109, 1030, 969, 911, 857, 766. [32]

**Synthetic Procedure for:**

Ethyl 3,3-bis(methylsulfanyl)-2-(morpholin-4-yl)propanoate (1i)
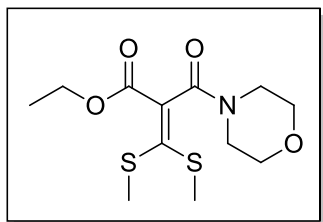
An oven-dried 50-mL round-bottom flask was cooled under nitrogen gas. The flask was loaded with ethyl 3-morpholinepropanoate (1.0035 g, 5.0 mmol) and anhydrous DMF (8 mL), followed by the addition of carbon disulfide (1.30 mL, 5.0 mmol). To this mixture was added NaH (0.4220 g, 11 mmol, 60% dispersion in mineral oil) by portions. After stirring for 1 h at r.t., iodomethane (0.65 mL,

11 mmol) was added dropwise. After stirring for 24 h at r.t., the mixture was diluted with water and extracted 3x with ethyl acetate. The combined organic extract was washed 2x with DI-H_2O, brine, and dried over Na_2SO_4. After filtering and concentrating in vacuo, the crude material was purified via column chromatography (silica, ethyl acetate) which provided a colorless liquid; (1.2698 g, 83% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.30 (t, 3H, J = 7.2 Hz), 2.42 (s, 3H), 2.50 (s, 3H), 3.36-3.39 (m, 2H), 3.64-3.68 (m, 2H), 3.73 (s, 4H), 4.24 (q, 2H, J = 7.2 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 14.25, 17.40, 18.97, 42.03, 46.82, 61.27, 66.50, 66.53, 128.47, 155.60, 162.60, 164.76; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2982, 2963, 2925, 2899, 2860, 1701, 1632, 1533, 1440, 1362, 1300, 1278, 1236, 1111, 1072, 1018, 951, 908, 813, 754; HRMS (Direct Probe) calculated for [$C_{12}H_{19}NO_4S_2$] ([M +]) 305.0756, observed 305.0755.

4.2 Experimental for 1,3-*S*,*O*-Esters

GENERAL

All reactions were carried out using Amberlyst-15 sulfonic acid resin (1.1 ratio by mass of starting material), deionized water (1 drop or 0.1 mL), and reagent grade dichloromethane (15 mL per mmol of starting material). All substrates and products were air and moisture stable and reaction mixture were prepared and heated open to the air.

GENERAL PROCEDURE FOR THE SYNTHESIS 1,3-*S*,*O*-ESTERS

In a round-bottom flask, the α-oxoketene dimethylthioacetal starting material (0.3 mmol) was dissolved in reagent grade methylene chloride (15 mL/mmol), followed by

the addition of deionized water (~1 drop or 0.1 mL). The reaction was initiated by the addition of Acros brand Amberlyst-15 resin (1.1 ratio by mass of starting material) and subjected to reflux open to the air. Reaction progress was monitored by TLC, and completion was observed in a 12-24 hour period. The Amberlyst-15 resin was removed by gravity filtration and the filtrate was concentrated under reduced pressure using a rotary evaporator and vacuum pump. Crude isolates were taken on to column chromatography to afford spectroscopically pure 1,3-*S,O*-esters, confirmed by NMR, in high yield.

Synthetic Procedure for:

Ethyl 3-(methylsulfanyl)-3-oxopropanoate (2a)
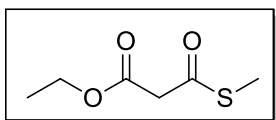
In a 25-mL round-bottom flask, methyl 3,3-bis(methylsulfanyl)-prop-2-enoate (0.1123 g, 0.58 mmol) was dissolved in methylene chloride (5 mL), followed by the addition of 0.01 mL of deionized water. Amberlyst-15 (0.1174 g) was added and the reaction was heated to reflux for 25 h. Reaction progress was monitored by TLC (1:1 hexanes: ethyl acetate). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was rinsed with methylene chloride and the solvent was removed in vacuo. Crude isolation was purified via column chromatography and the target was isolated as a colorless liquid; (0.0895 g, 96% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.28 (t, 3H, *J* = 7.2 Hz), 2.36 (s, 3H), 3.58 (s, 2H), 4.20 (q, 2H, *J* = 7.2 Hz). [33]

Synthetic Procedure for:

Ethyl 3-(methylsulfanyl)-3-oxopropanoate (2b)
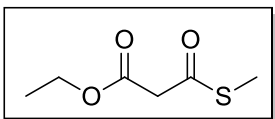
 In a 100-mL round-bottom flask, methyl ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate (1.2615 g, 5.38 mmol) was dissolved in methylene chloride (25 mL), followed by the addition of 0.05 mL of deionized water. Amberlyst-15 (1.3846 g) was added and the reaction was heated to reflux for 46 h. Reaction progress was monitored by TLC (30:70 diethyl ether:hexanes). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was rinsed with methylene chloride and the solvent was removed in vacuo. The target was isolated as a colorless liquid after purification via column chromatography (silica, 40% hexanes: 60% ethyl acetate); (0.5531 g, 63% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.29 (t, 3H, J = 7.2 Hz), 2.37 (s, 3H), 3.59 (s, 2H), 4.21 (q, 2H, J = 7.2 Hz). [33]

Synthetic Procedure for:

Ethyl 3-(methylsulfanyl)pentanoate (2c)
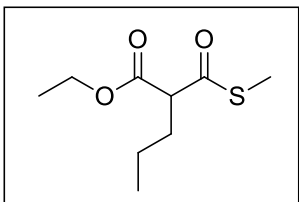
 In a 25-mL round bottom flask, ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate (0.1156 g, 0.49 mmol) was dissolved in methylene chloride (5.0 mL), followed by the addition of 0.01 mL of deionized water. Amberlyst-15 (0.1183 g) was added and the reaction was heated to reflux for 17 h. Reaction progress was monitored by TLC (50% ethyl acetate, 50% hexanes). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was

rinsed with methylene chloride and the solvent was removed in vacuo. The target was isolated as colorless liquid that that was spectroscopically pure based on ^{1}H NMR; (0.0893 g, 89 % yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 0.93 (t, 3H, J = 7.3 Hz), 1.30 (t, 6H, J = 7.1 Hz), 1.34-1.39 (sex, 2H, J = 7.3 Hz), 1.87-1.96 (m, 2H), 2.34 (s, 3H), 3.57 (t, 1H, J = 7.5 Hz), 4.19 (q, 2H, J = 7.1 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 11.80, 13.61, 13.95, 20.38, 31.50, 59.64, 61.43, 168.69, 195.47; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2964, 2934, 2874, 1738 (C=O stretch, ester), 1683 (C=O stretch, thioester), 1465,1370,1299, 1280, 1233, 1180, 1115, 1021, 991, 902; HRMS (Direct Probe) calculated for [C$_9$H$_{16}$O$_3$S+] ([M +]) 204.0820, observed 204.0825.

Synthetic Procedure for:

Methyl 3-(methylsulfanyl)-3-oxo-2-phenylpropanoate (2d)
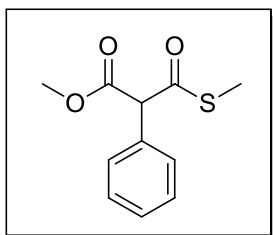
In a 25-mL round-bottom flask, methyl 3,3-bis(methylsulfanyl)-2-phenylprop-2-enoate (0.0997 g, 0.39 mmol) was dissolved in methylene chloride (4 mL), followed by the addition of 1 drop (0.1 mL) of deionized water. Amberlyst-15 (0.1046 g) was added and the reaction was heated to reflux for 21 h. Reaction progress was monitored by TLC (20% ethyl acetate, 80% hexanes). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was rinsed with methylene chloride and the solvent was removed in vacuo. The target was isolated as colorless liquid after purification via column chromatography (silica, 20% ethyl acetate, 80% hexanes); (0.0767 g, 87 % yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 2.32 (s, 3H), 3.77 (s, 3H), 4.81 (s, 3H), 7.36-7.46 (m, 5H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 12.29, 52.86,

128.57, 128.68, 129.42, 132.22, 168.01, 194.24; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3063, 3033, 3003, 2955, 2931, 1740 (C=O stretch, ester), 1676 (C=O stretch, thioester), 1496, 1454, 1436, 1305, 1253, 1200, 1154, 1006, 986; HRMS (Direct Probe) calculated for [C$_{11}$H$_{12}$O$_3$S+] ([M +]) 224.0507, observed 224.0507.

Synthetic Procedure for:

Diethyl [(methylsulfanyl)carbonyl] propanedioate (2e)
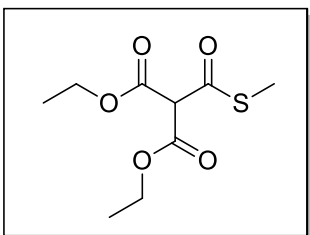
In a 25-mL round-bottom flask, diethyl [bis(methylsulfanyl)methylidene]-propanedioate (0.1150 g, 0.35 mmol) was dissolved in methylene chloride (2 mL), followed by the addition of deionized water (0.1 mL). Amberlyst-15 (0.1178 g) was added and the reaction was heated to reflux for 22 h. Reaction progress was monitored by TLC (ethyl acetate). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was rinsed with methylene chloride and the solvent was removed in vacuo. The target was isolated as colorless liquid that was spectroscopically pure based on ^{1}H NMR; (0.0937 g recovered, 89 % yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.29 (t, 3H, J = 7.3 Hz), 1.30 (t, 6H, *J* = 7.1 Hz), 2.42 (s, 3H), 4.28 (q, 2H, *J* = 7.1 Hz), 4.61 (s, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 12.30, 62.53, 65.14, 163.43, 188.60; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2985, 2937, 1733 (C=O stretch, ester), 1687 (C=O stretch, thioester), 1367, 1298, 1235, 1175, 1145, 1029, 1007, 901; HRMS (Direct Probe) calculated for [C$_9$H$_{14}$O$_5$S+] ([M +]) 234.0562, observed 234.05649.

Synthetic Procedure for:

Methyl 3-(methylsulfanyl)-3-oxo-2-(phenylsulfonyl)propanoate (2f)
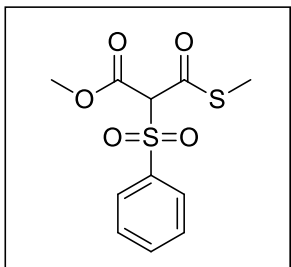
In a 25-mL round bottom flask, methyl 3,3-bis(methylsulfanyl)-2-(phenylsulfonyl)prop-2-enoate (0.2492 g, 0.75 mmol) was dissolved in methylene chloride (5 mL), followed by the addition of deionized water (0.1 mL). Amberlyst-15 (0.2627 g) was added and the reaction was heated to reflux for 48 h. Reaction progress was monitored by TLC (1:1 hexanes: ethyl acetate). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was rinsed with methylene chloride and the solvent was removed in vacuo. The target crystallized as a white solid that was spectroscopically pure based on ^{1}H NMR; (0.2126 g, 94% yield, M. P. = 34–37 °C). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 2.34 (s, 3H), 3.79 (s, 3H), 5.14 (s, 3H), 7.56 (t, 2H, J = 7.2 Hz), 7.60-7.75 (m, 1H), 7.94-7.97 (m, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 12.86, 53.73, 128.85, 130.12, 134.83, 136.76, 160.91, 185.35; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3066, 3033, 3003, 2955, 2904, 1738 (C=O stretch, ester), 1672 (C=O stretch, thioester), 1496, 1436, 1264, 1210, 1170, 1014, 1007, 992, 728, 707; HRMS (Direct Probe) calculated for [C$_{11}$H$_{12}$O$_5$S$_2$+] ([M +]) 288.0126, observed 288.0128.

Synthetic Procedure for:

Ethyl 2-(diethoxyphosphoryl)-3-(methylsulfanyl)-3-oxopropanoate (2g)
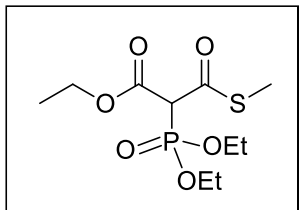
In a 25-mL round-bottom flask, ethyl 3,3-bis(methylsulfanyl)prop-2-(diethylphosphono)acetate (0.0593 g, 0.18 mmol) was dissolved in methylene chloride (5 mL), followed by the addition of deionized water (0.1 mL). Amberlyst-15 (0.0682 g) was added and the reaction was heated to reflux for 26 h. Reaction progress was monitored by TLC (ethyl acetate). Upon completion, the mixture was cooled and filtered by gravity. The Amberlyst-15 resin was rinsed with methylene chloride and the solvent was removed in vacuo. The target was isolated as colorless liquid that was spectroscopically pure based on ^{1}H NMR; 0.0501 g was recovered (93% yield). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.28-1.38 (m, 9H), 2.39 (s, 3H), 4.21-4.31 (m, 2H), 4.41 (d, 1H, J_{P-H} = 21.8 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 12.58, 13.87, 16.19 (d, J_{P-C} = 6.8 Hz), 60.88 (d, J_{P-C} = 128.2 Hz), 62.51, 63.81 (d, J_{P-C} = 6.8 Hz), 63.95 (d, J_{P-C} = 6.8 Hz), 162.95 (d, J_{P-C} = 5.3 Hz), 187.91; ^{31}P-NMR (121 MHz, CDCl$_3$) 19.89; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2985, 2931, 1736 (C=O stretch, ester), 1683 (C=O stretch, thioester), 1257, 1162, 1013, 964, 885, 824, 741; HRMS (Direct Probe) calculated for [C$_{10}$H$_{19}$O$_6$PS+] ([M +]) 298.0604, observed 298.0627.

CHAPTER 5

SYNTHESIS OF α-PHOSPHONOVINYL TRIFLATES

AND α-ALKYNYLPHOSPHONATES

ABSTRACT

The project outlines a synthetic procedure for the two-step synthesis of β-substituted α-alkynylphosphonates (or 1-alkynylphosphonates) **50** starting from β-substituted α-ketophosphonates **48** proceeding through α-triflated vinylphosphonate intermediates **49** (**Figure 3**).
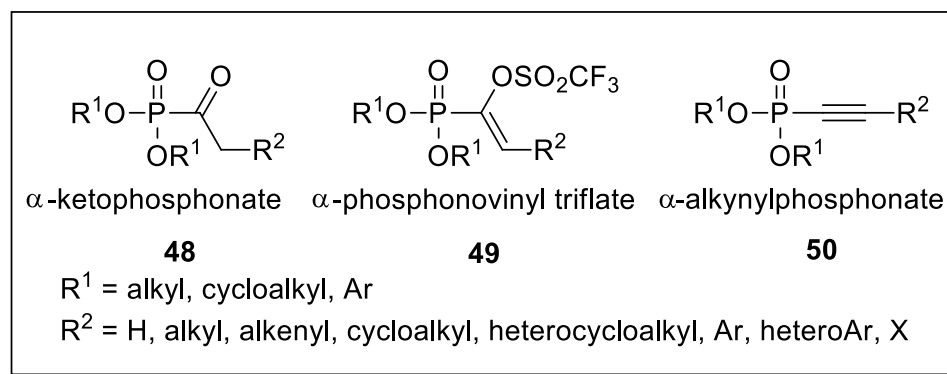
Figure 3. Various β-substituted phosphonate derivatives

The advantages of starting from α-ketophosphonate precursors is that they are easily prepared and are obtained in high yields and purity via the Michaelis-Arbuzov reaction and the Abramov reaction. In addition, the starting materials to prepare α-ketophosphonates are affordable and readily available from chemical suppliers. The study describes a simple, facile method for the preparation of novel α-phosphonovinyl triflates from β-substituted α-ketophosphonate precursors. Currently, the literature procedures developed to prepare α-phosphonovinyl sulfonates lack substrate scope and there are very few examples of β- substitution on α-phosphonovinyl sulfonates. Therefore, the scope and limitations of the methodology developed to prepare α-phosphonovinyl triflate derivatives is thoroughly explored and substrate scope and functional group compatibility are a strong focus. Furthermore, the study addresses the synthetic utility of α-phosphonovinyl triflates by performing base-catalyzed β-eliminations under mild reaction conditions to prepare β-substituted α-alkynylphosphonates.

5.1 Project Introduction, Significance, and Aim

Alkynes are found in nature and range in complexity from simple alkynes found in petroleum sources to complex natural products and biomolecules found in nature. In general, alkynes are valuable building blocks used in numerous chemical applications because they can be directly functionalized or readily transformed into other functional groups. Simple alkynes like acetylene can be isolated and prepared from petroleum sources (oil, gas, coal) and can be converted into more useful commercial products, e.g., polymers, and synthetic intermediates (alcohols, aldehydes, alkyl halides, alkenyl halides, and vinyl arenes) via oxidation, polymerization, hydration, halogenation, and alkylation

reactions [1]. There are numerous chemical methods for synthesizing functionalized alkynes in the laboratory such as elimination reactions, nucleophilic substitution reactions, and cross-coupling reactions (e.g., Sonogashira coupling). In turn, functionalized alkynes are versatile chemical intermediates that can be exploited to prepare other desired functionalities or prepare complex organic molecules [1].

The phosphorus atom is essential to all living organisms. It is necessary to form the sugar-phosphate backbone of DNA and RNA, responsible for energy transfer in cells as part of ATP (adenosine triphosphate), and charged phosphates play an integral role in covalent protein modification, giving rise to various protein conformations. Phosphorus is found in many biologically important molecules and phosphorus-functionalized alkynes are becoming increasingly important targets for research and developmental chemistry due to the unique reactivity imparted by the phosphorus atom [2]. The phosphorus atom possesses unique chemical properties and contributes to the biological and pharmacological properties. Phosphorus-functionalized alkynes can be used as biochemical tools, gateways to prepare simple or complex pharmaceutical/therapeutic drugs, and other phosphorus-functionalized organic molecules.

In a recent publication, Wanat et al. describe the synthesis of nucleotide analogues containing modifications at the terminal phosphate via CLICK chemistry, in particular, the copper catalyzed azide-alkyne cycloaddition (CuAAC) of nucleotide analogues containing a terminal alkynylphosphonate functionality, **51**, to produce fluorescently labeled nucleotides **52** (**Scheme 21**) [3].
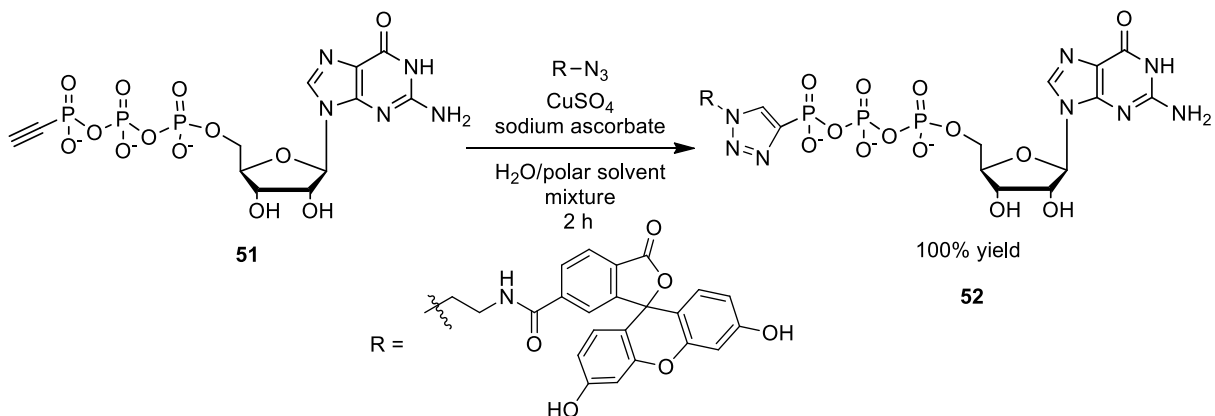
Scheme 21. Synthesis of nucleotide conjugates from C-phosphonate analogues using CLICK chemistry - CuACC

Mononucleotide analogues modified at the terminal phosphate are particularly useful as binding probes [4], reporter substrates [5], enzyme inhibitors [5], donors of labeled phosphate moieties [6], and reagents for single-nucleotide sequencing [7]. The incorporation of a phosphonate moiety has potential to modulate the properties of a bioactive molecule by changes in solubility, lipophilicity, metabolic stability, conformation, hydrogen-bonding ability, and/or chemical reactivity. In 2011, Salomon et al. reported the potent anti-cancer effects of a novel alkynylphosphono-functionalized analogue of calcitriol (vitamin D), **54**, by integrating an alkynylphosphonate moiety into the calcitriol (**53**) molecular structure (**Figure 4**) [8].
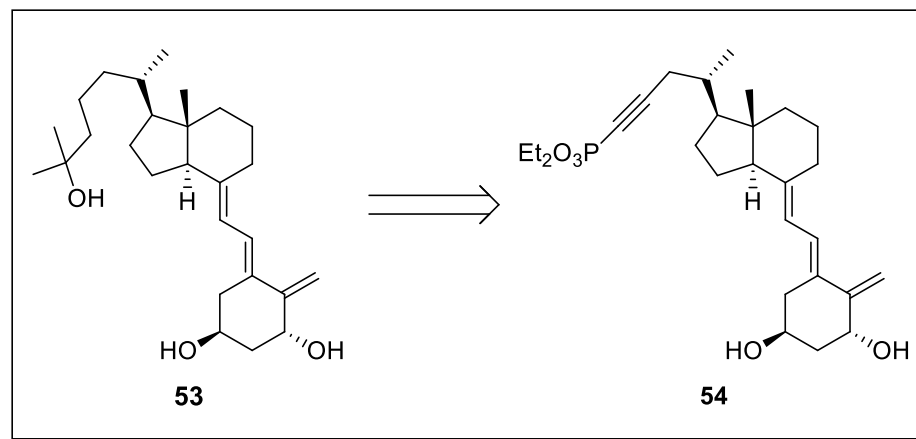
Figure 4. Alkynylphosphonate analogue of calcitriol (vitamin D)

Carbon-phosphorus bond construction for the synthesis of organophosphorus compounds is a fundamental and significant research topic in both organic synthesis and industrial processes. α-Alkynylphosphonates are extremely valuable synthetic precursors that can be easily functionalized further on the alkyne functionality through conjugate-addition, cycloaddition, and many other reactions, making them potentially useful in organic synthesis, and pharmaceutical and biological applications [9]. Currently, the literature lacks methods to prepare α-alkynylphosphonate compounds from α-ketophosphonates; therefore, this is an area for discovering new methodologies for synthesizing α-alkynylphosphonates and expanding on α-ketophosphonate chemistry.

The first specific aim of this project is the facile, convenient preparation of α-phosphonovinyl triflates, which in itself is a versatile synthetic precursor with the potential to undergo a plethora of organic reactions. In addition, the project is focused on the development of a new chemical route to synthesize α-alkynylphosphonates from α-ketophosphonate building blocks by the utility of α-phosphonovinyl triflates. The methodology provides a convenient route to a range of α-alkynylphosphonates bearing

various groups at the β-carbon position and overcomes some of the limitations present in the currently reported methods. Outlined in **Scheme 22** is a chemical route to prepare β-substituted α-alkynylphosphonates **50** via base-catalyzed β-elimination within α-phosphonovinyl triflate **49** and starting from α-ketophosphonates **48**.

R^1 = alkyl, cycloalkyl, Ar
R^2 = H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, Ar, heteroAr, X
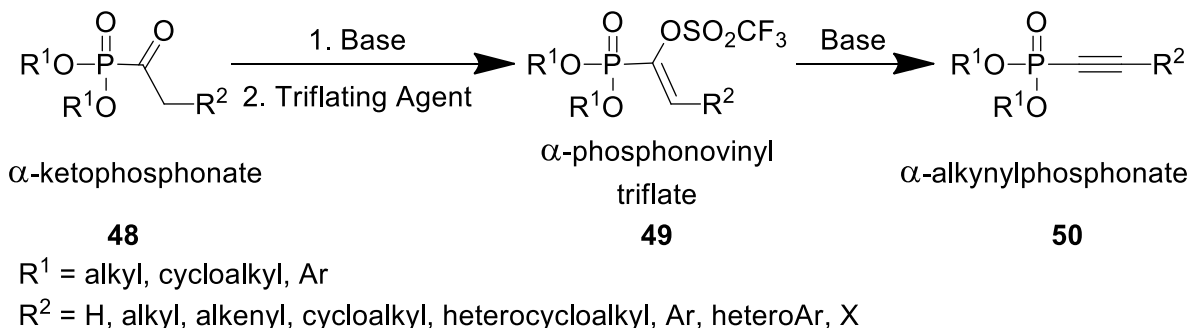
Scheme 22. Synthetic pathway to α-alkynylphosphonates via α-phosphonovinyl triflates

The interest of this transformation arose from a chance discovery made during work on synthesizing α-functionalized vinylphosphonates from α-phosphonovinyl triflates in organocopper cross-coupling reactions. While attempting to prepare α-functionalized vinylphosphonates, we were curious to know if organolithium reagents would couple with higher efficiency than the organocuprate reagents or would a conjugate addition occur instead; therefore, methyllithium was employed as the nucleophile rather than lithium dimethylcuprate in a pilot reaction (**Scheme 23**). The methyllithium acted as a base rather than as a nucleophile and a clean β-elimination took place on substrates bearing β-hydrogens on the α-phosphonovinyl triflates intermediates **55** (derived from α-ketophosphonate starting materials) to yield β-functionalized α-alkynylphosphonates **56**.

53
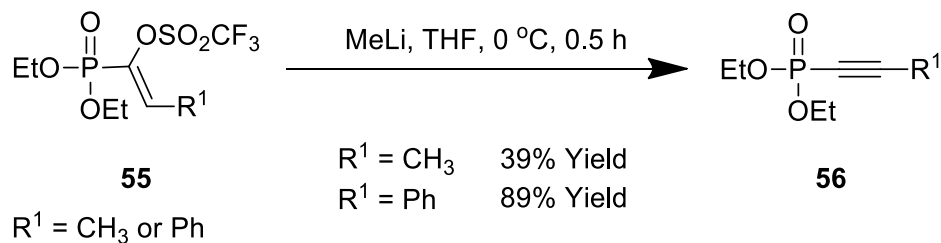
Scheme 23. Pilot reaction leading to β-functionalized α-alkynylphosphonates

In an initial literature search, an example was noted that employs β-ketoesters **57** treated with lithium hexamethyldisilazide followed by triflic anhydride to prepare vinyl triflate monoanion intermediates **58** that lead to the selective formation of alkynes **59** and **60** (**Scheme 24**) [10]. This method is analogous to the methodology developed for the preparation of α-alkynylphosphonates.
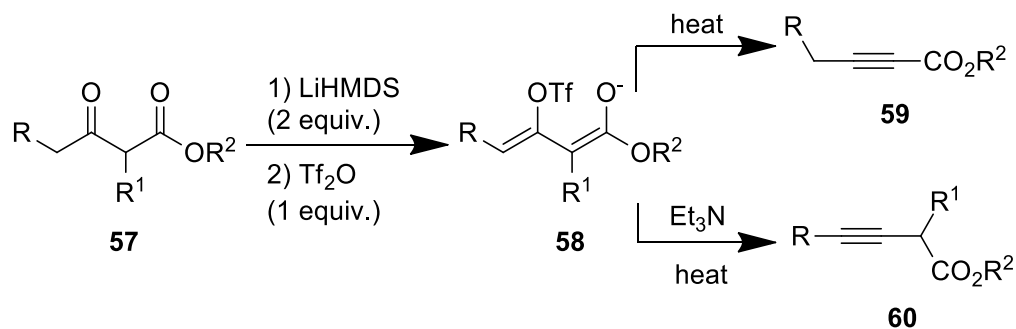
Scheme 24. Method to prepare alkynes

5.2 Synthesis of α-Alkynylphosphonates

Alkynylphosphonates have been prepared by many reported methods, with about 13 reports in the literature for 2015–2016 alone. They are used as substrates in chemical reactions or sought after as desired targets. Traditionally, alkynylphosphonates **62** and **64** are prepared by a nucleophilic substitution reaction of alkynylmagnesium bromides **60** or alkynyllithiums **63** with $R_2P(O)Cl$ compounds **61** (**Scheme 25** and **Scheme 26**) [11]. These reported procedures typically give moderate to good yields of alkynylphosphonates, but despite the efficiency of these methods, limitations such as lack of functional group tolerability and the employment of sensitive/toxic reagents (i.e., dialkyl phosphorochloridates) call for improvements and milder reaction conditions.
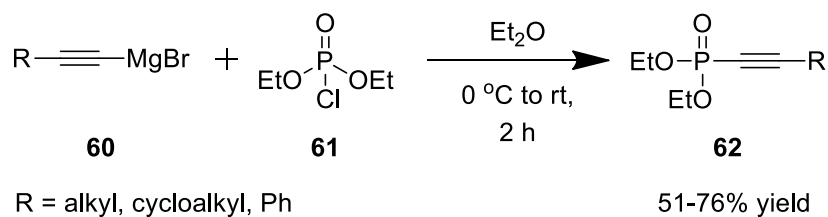
Scheme 25. Preparation of α-alkynylphosphonates via Grignard reagents
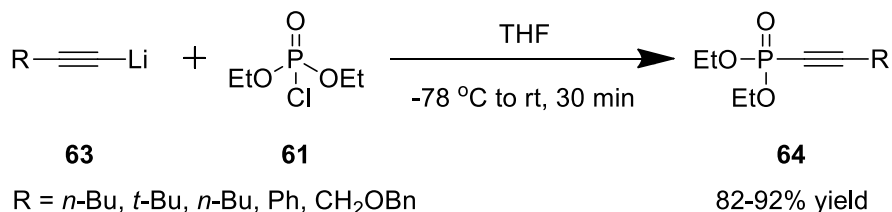
Scheme 26. Preparation of α-alkynylphosphonates via alkyllithium reagents

To overcome these problems, several methods for the synthesis of α-alkynylphosphonates have been developed, which incorporate the utility of transition metal catalysts. The following reactions describe a small review for the preparation of α-alkynylphosphonates in the presence of palladium catalyst: Pd-catalyzed cross-coupling of 1,1-dibromo-1-alkenes **65** with methyl phosphite **66** to prepare functionalized dimethyl alkynylphosphonates **67** (**Scheme 27**) [12], Pd-catalyzed oxidative deacetonative coupling of 4-aryl-2-methyl-3-butyn-2-ols **68** with H-phosphonates **69** to prepare aryl functionalized α-alkynylphosphonates **70** (**Scheme 28**) [13], Pd-catalyzed dehydrogenative coupling of terminal alkynes with secondary phosphine oxides [14], and Pd-catalyzed dehydrogenative cross-coupling of terminal alkynes and P(O)—H compounds [15].

R^1 = Ph, *p*-AcO-Ph, *p*-NO$_2$-Ph, *p*-MeO-Ph, *n*-heptyl, cyclohexyl, furanyl
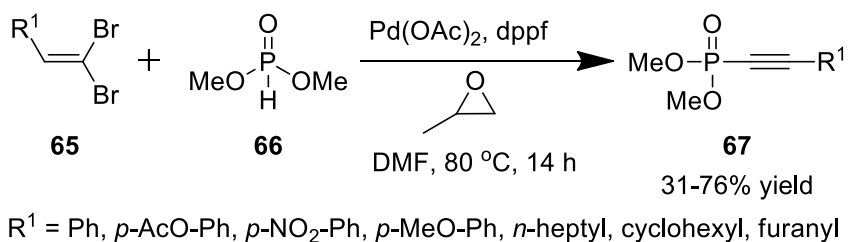
Scheme 27. Pd-catalyzed cross-coupling to prepare α-alkynylphosphonates

R = Et, *i*Pr, *n*Bu
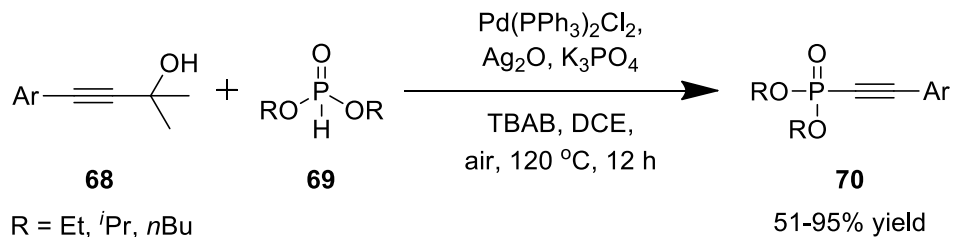
Scheme 28. Preparation of α-alkynylphosphonates via Pd-catalyzed oxidative deacetonative coupling

In addition to palladium catalysts, copper catalysts have been employed as well to furnish α-alkynylphosphonates and two literature methods are described. Cu-catalyzed aerobic oxidative coupling of terminal alkynes **71** with H-phosphonates **72** have led to α-alkynylphosphonates **73** in good to excellent yields (**Scheme 29**) [16], along with Cu-catalyzed decarboxylative coupling of arylpropiolic acids **74** with H-phosphonates **75** that have furnished aryl functionalized α-alkynylphosphonates **76** in moderate to good yields (**Scheme 30**) [17]. In addition, base-free direct synthesis of alkynylphosphonates **79** from terminal alkynes **77** with diethyl phosphite **78** in the presence of a Cu_2O has been recently published with claims of moderate to excellent yields (**Scheme 31**) [18].

R^1 = H, alkyl, cycloalkyl, OH, OPh, $C(O)CH_3$, $C(O)NHBn$, $NEt(PhCH_2)$, $NHSO_2p$-tol
R^2 = Et, ^iPr, ^nBu
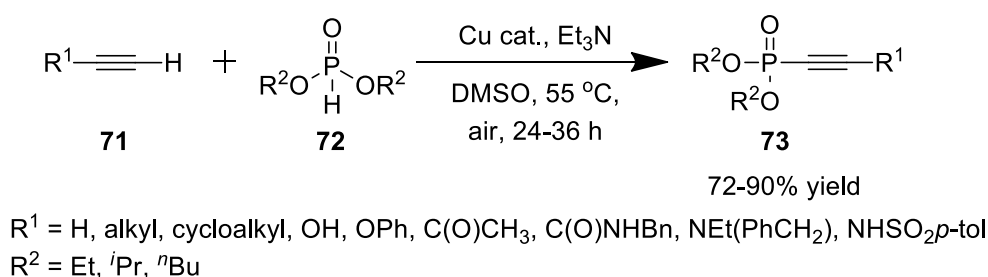
Scheme 29. Aerobic oxidative coupling of terminal alkynes with H–P(O) compounds

R^1 = H, Me, Et, OMe, t-butyl, F, Br, $C(O)CH_3$, NO_2, CF_3
R^2 = Me, Et, ^nPr, ^iPr, ^nBu, Bn
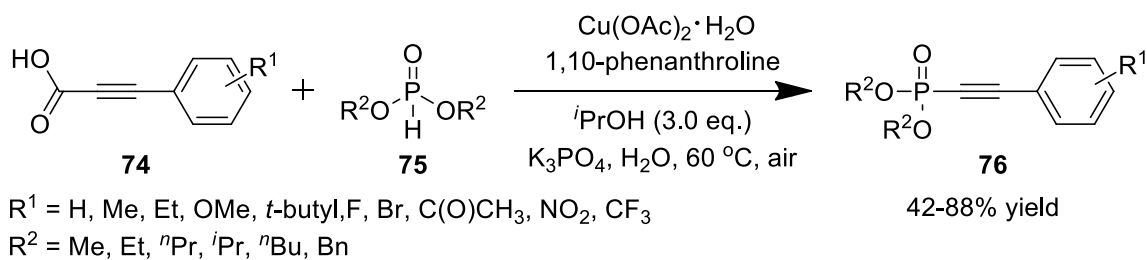
Scheme 30. Decarboxylative coupling of propiolic acids with H-phosphonates
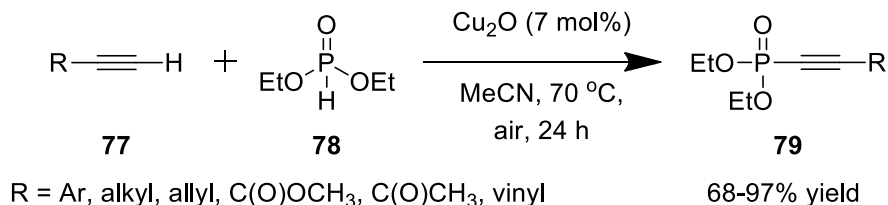
Scheme 31. Cu$_2$O-catalyzed cross-coupling of terminal alkynes with diethyl phosphite

A couple of the most recent synthetic pathways to prepare α-alkynylphosphonates do not employ transition metals to mediate chemistry such as: Cs$_2$CO$_3$-promoted phosphorylation of 1,1-dibromo-1-alkenes with trialkylphosphites to prepare aryl functionalized alkynylphosphonates under metal-free conditions in good to excellent yields (**Scheme 32**) [19].
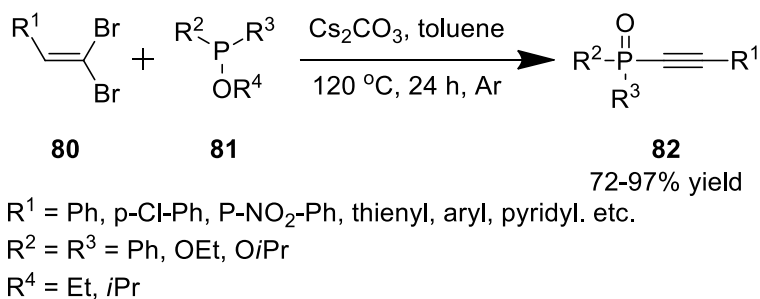
Scheme 32. Cs$_2$CO$_3$-promoted phosphorylation of 1,1-dibromo-1-alkenes

Upon a more thorough literature search, it was noted that only one method was similar and analogous to the method developed in our lab to prepare α-alkynylphosphonates by base-catalyzed β-elmination. The bromodecarboxylation of (*E*)-3-aryl-2-(diethoxyphosphoryl)acrylic acids **83** have been show to prepare α-phosphonovinyl bromides **84** and subsequent base-catalyzed β-elimination to prepare

arylethynylphosphonates **85** in moderate to good yields. (**Scheme 33**) [20]. Although this is a very similar synthetic route to obtain α-alkynylphosphonates as the methodology devised, there are a couple drawbacks of the method described. The 3-aryl-2-(diethoxyphosphoryl)acrylic acids **83** are prepared by the Knoevenagel reaction of diethylphosphonoacetic acid and aryl functionalized aldehydes to prepare a mixture of *E,Z*-isomers of diethyl arylvinylphosphonates [21]. A subsequent reaction involving (*c*-Hex)$_2$NH in benzene isomerizes the substrate and provides the *E*-isomer of diethyl arylvinylphosphonates as an amine salt which is purified and converted to the carboxylic acid via ion-exchange chromatography [21]. Therefore, this is not a convenient way to quickly prepare the starting materials for subsequent use, and additional steps are incorporated in the synthetic pathway to provide diethyl arylvinylphosphonates **85**.
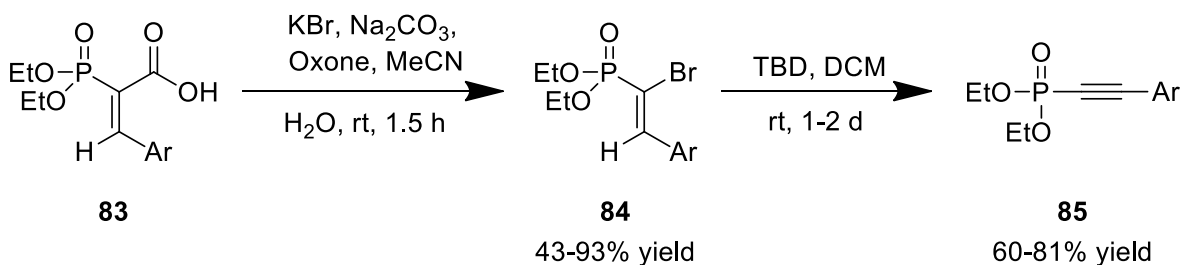
Ar = 4-MeO-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 3,4-(MeO)$_2$-C$_6$H$_4$, 3,4-(OCH$_2$O)-C$_6$H$_4$, 5-methylfuran-2-yl

Scheme 33. Bromodecarboxylation of aryl-2-(diethoxyphosphoryl)acrylic acids and subsequent base-catalyzed elimination to prepare arylethenylphosphonates

To our advantage, these methods lack substrate scope, require multiple reaction steps, use high temperatures, the need of excess additives, expend low atom-economy, use of oxidants, starting materials are not readily available from chemical suppliers, and lastly, they require the use of transition metals that produce hazardous heavy metal waste

and are toxic, therefore, the metals must be carefully removed from the product, especially for the drug and pharmaceutical industry. Therefore, better methods for the synthesis of alkynylphosphonates are highly desired.

5.3 Chemistry of α-Alkynylphosphonates

α-Phosphono-functionalized alkynes have a broad range of synthetic utility, and there are several published literature reviews describing their synthesis and chemistry [9]. A few general synthetic applications of phosphorus-functionalized alkynes include synthetic intermediates and substrates for a variety of chemical reactions to prepare phosphono-functionalized compounds, e.g., addition reactions to prepare β-aminophosphonates (isosteres of β-amino acids) [22], cyclization reactions to prepare fluorinated quinolinylphosphonates [23] and fluorinated arylphosphonates [24], addition and subsequent cyclization reactions to prepare phosphorus 2-pyrones [25], phosphorylated 5-thiotetrazoles [26], and phosphorylated azirines [27], [2+2+2] rhodium-catalyzed cycloadditions to prepare pyridiylphosphonates [28], rhodium-catalyzed oxidative annulations to form complex phosphono-functionalized 7-azaindole derivatives [29], phosphono-functionalized aza-fused heterocycles [30], [4+2] cycloadditions (Diels-Alder reactions) to prepare arylphosphonates [31] and phosphorylated naphthalene derivatives [32], and hydroacylation reactions to prepare phosphonyl heterocycles [33].

In organic synthesis, α-phosphono-functionalized alkynes provide convenient outlets to functionalized α-vinylphosphonates, which is a class of compounds highly sought after due to their commercial, industrial, and pharmaceutical applications. Functionalized α-vinyl phosphonates have shown applications in polymers [34], flame

retardant materials [35], fuel cell applications [36], additives to cement/concrete [37], and biomedical uses [38], and potential therapeutic applications (e.g., anti-viral activity [39], anti-fungal activity [40], anti-cancer activity [41], anti-malarial [42], and anti-influenza [43]). Functionalized α-vinyl phosphonates have been reported as substrates for Diels-Alder/cycloaddition reactions [44], Michael additions [45], selective reductions [46], addition of organolithium and organocopper reagents to alkynylphosphonates [47], group (IV) metal-mediated reactions [48], and hydroboration/Suzuki couplings [49]. These are just a few representative examples of various methods to synthesize functionalized α-vinyl phosphonates from α-alkynylphosphonate precursors.

5.4   Synthesis and Chemistry of α-Phosphonovinyl Sulfonates

Vinyl enol sulfonate functional groups are good, stable leaving groups and are referred to by "pseudohalides" because of the similar reactivity and properties to halides. They participate in a variety of reactions such as nucleophilic substitution reactions, elimination reactions, and they undergo a variety of organometallic coupling reactions. α-Ketophosphonates have been converted to their corresponding α-phosphonovinyl sulfonate counterparts in the literature. A couple of publications describe the synthesis of α-phosphonovinyl *p*-tosylate **88** in 83% yield by treatment of diethyl acetylphosphonate **86** and *p*-toluenesulfonyl chloride **87** in the presence of DBU in acetonitrile (**Scheme 34**) [50]. Also, α-phosphonovinyl nonaflates **91** have been prepared in moderate to good yields by treatment of diethyl phosphonates **89** and nonafluorobutane sulfonyl fluoride **90** in the presence of DBU in THF (**Scheme 35**) [51].
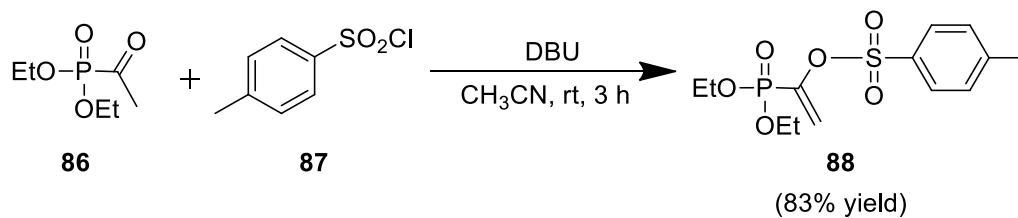
Scheme 34. Preparation of α-phosphonovinyl *p*-tosylate
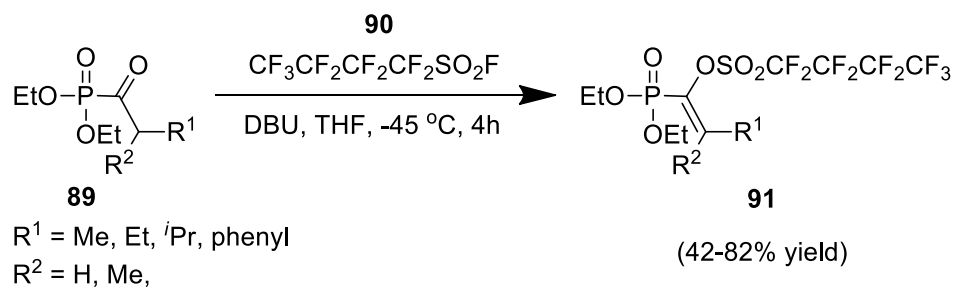
Scheme 35. Preparation of α-phosphonovinyl nonaflates

The α-phosphonovinyl *p*-tosylates **92** were used as substrates with primary amines **93** in a Gabriel-Cromwell reaction to make aziridinyl phosphonates **94** (**Scheme 36**) [52].
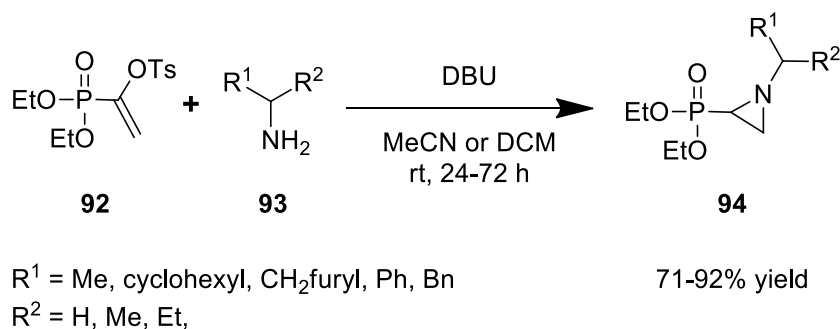
Scheme 36. Synthesis of aziridines from α-tosylated vinyl phosphonate

α-Phosphonovinyl enol sulfonates, α-phosphonovinyl tosylates and α-phosphonovinyl nonaflates have only been employed in the preparation of functionalized

α-vinyl phosphonates via organometallic cross-coupling reactions. A recent publication cited the use of α-phosphonovinyl *p*-tosylates **95** coupled with aryl boronic acids **96** in the presence of a palladium catalyst to afford aryl functionalized α-vinylphosphonates **97** (**Scheme 37**) [50].

R^1 = H, Me, OMe, F, Cl, Br, Ph, CN, OH, etc

(74-99% yield)
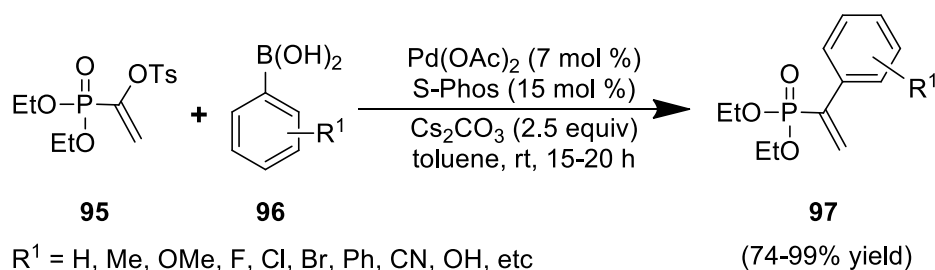
Scheme 37. Suzuki-Miyaura cross-coupling of α-phosphonovinyl *p*-tosylates

The α-phosphonovinyl nonaflates **98** have been demonstrated to couple with alkynes **99** in the presence of a palladium catalyst in a Sonogashira cross-coupling to provide α-alkynyl functionalized α-vinylphosphonates **100** (**Scheme 38**) [51]. In addition, α-phosphonovinyl nonaflates **101** have been demonstrated to couple with vinyl stannanes **102** in the presence of a palladium catalyst in a Stille cross-coupling to afford α-vinyl functionalized α-vinylphosphonates **103** (**Scheme 39**) [51].

R^1 = H, Me
R^2 = H, Me
R^3 = ^{n}Bu, Ph, SiMe$_3$

(71-95% yield)
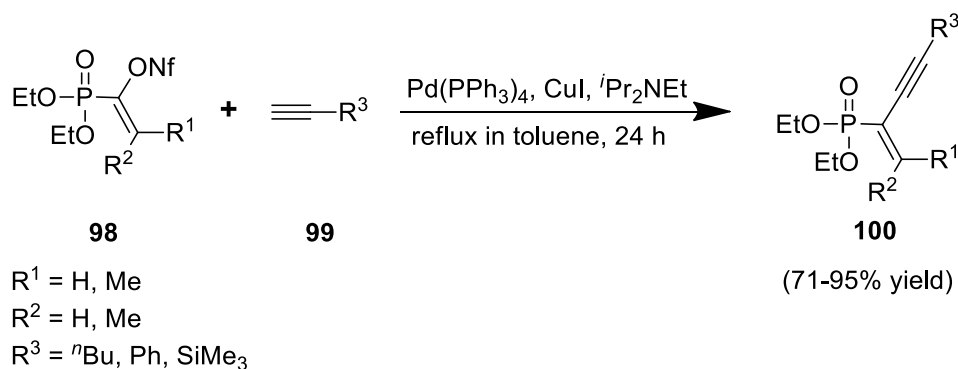
Scheme 38. Sonogashira cross-coupling of α-phosphonovinyl nonaflates
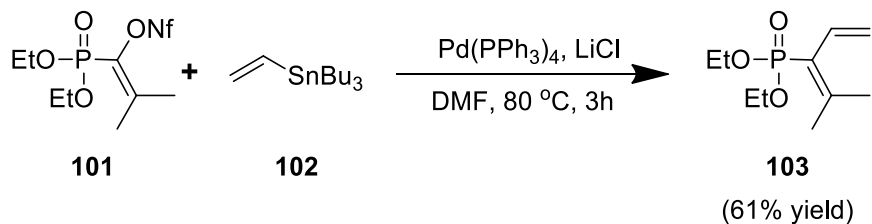
Scheme 39. Stille cross-coupling of α-phosphonovinyl nonaflates

α-Phosphonovinyl acetates were used to study the α-keto phosphonate keto-enol tautomerism and in [3,3]-sigmatropic rearrangements [53]. Aryloxy and phenyloxyacetyloxy vinyl phosphonates have been used as substrates in asymmetric, Rh-catalyzed hydrogenation reactions affording chiral esters that could be hydrolyzed to afford chiral α-hydroxy phosphonates [54]. Note that only two of the α-phosphonovinyl enol sulfonate derivatives, α-phosphonovinyl enol *p*-tosylate and α-phosphonovinyl nonaflates, have been prepared in acceptable yields. α-Phosphonovinyl triflates have been prepared, but only low yields were obtained (0–34%) and, consequently, they were not used or explored any further [51].

Additional representative examples of various methods used to synthesize α-vinyl phosphonates from α-phosphonovinyl enol sulfonates are: Heck coupling [55], cross-coupling reactions of phosphonate derivatives with vinyl halides and aryl halides [56], and cross-coupling reactions of α-bromoalkenyl phosphonates with alkenyl boronates and aryl boronic acids [56]. The literature lacks reports displaying the full potential and synthetic utility of α-phosphonovinyl enol sulfonates, which have not been used as intermediates to prepare functionalized alkynylphosphonates.

The conversion of ketone systems into alkynes via vinyl enol sulfonates can be done by generating the soft enolate with base, trapping the enolate ion with a sulfonating

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agent to form a vinyl enol sulfonate, and subsequent base-promoted β-elimination [50, 51, 52]. By utility of α-phosphonvinyl triflates, this method can be applied and used to prepare functionalized alkynylphosphonates. Using reported methods, the enolate of α-ketophosphonates can be generated by treatment with DBU or Et$_3$N (and other bases) and then trapped with *p*-toluenesulfonyl chloride [50], diethyl chlorophosphate [55] or nonafluorobutanesulfonyl fluoride (nonaflyl fluoride, NfF) [51]. Even though α-phosphonovinyl nonaflates have been shown to be good substrates in organometallic cross-coupling reactions, the authors did not use the triflate (-OSO$_2$CF$_3$) counterparts because of low synthetic yields (0-34%) [51]. The stereochemistry for the majority of α-phosphonovinyl enol derivatives reported appears to be the *E*-isomer [53]. Further confirmation of the *E*-geometry was supported by Kobayashi and Williams, who performed Suzuki-Miyaura cross-coupling of α-phosphonovinyl bromides and performed in-depth NMR studies on the coupling constants between phosphorus–hydrogen atoms to address the stereochemistry [57].

We have been successful in preparing 1-(diethoxyphosphoryl)vinyl trifluoromethanesulfonates **4a-i** in an optimized 18-91% yield [four various methods depending on the substituent on the β position: α-ketophosphonate **3a-i**, Et$_3$N, catalytic DMAP (used in Method A), triflic anhydride (Tf$_2$O), CH$_2$Cl$_2$, -78 °C, then warming to room temperature 12-25 h, purified via column chromatography] (**Scheme 40**). The corresponding 1-(diethoxyphosphoryl)vinyltrifluoromethanesulfonates **4a-i** have a simple structure, which provides facile data interpretations and, in addition, the starting materials to prepare α-phosphonovinyl enol triflates are relatively inexpensive and very stable.
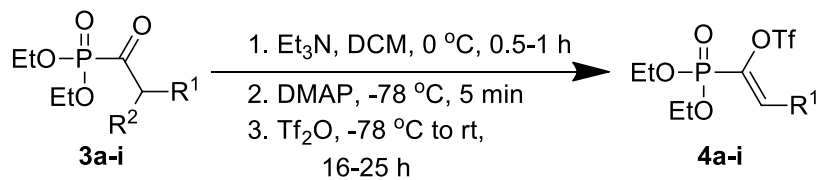
3a $R^1 = R^2 = H$

3b $R^1 = CH_3$, $R^2 = H$

3c $R^1 = CH_2CH_2CH_3$, $R^2 = H$

3d $R^1 = R^2 = -CH_2(CH_2)CH_2-$ (cyclobutyl)

3e $R^1 = Ph$ $R^2 = H$

3f $R^1 = p\text{-}F\text{-}Ph$, $R^2 = H$

3g $R^1 = C(O)OEt$, $R^2 = H$

3h $R^1 = Cl$, $R^2 = H$

3i $R^1 = CF_3$, $R^2 = H$

Scheme 40. Preparation of 1-(diethoxyphosphoryl)vinyl trifluoromethanesulfonates **4a-i**

CHAPTER 6

RESULTS AND DISCUSSION FOR THE SYNTHESIS OF α-PHOSPHONOVINYL TRIFLATES

6.1   Synthetic Methodology for α-Phosphonovinyl Triflates

In this study, novel β-substituted α-phosphonovinyl triflates were prepared in good to moderate yields by taking advantage of soft enolate chemistry of the corresponding β-substituted α-ketophosphonate starting materials. In order to prepare β-substituted α-triflated vinyl phosphonates, optimization of the reaction conditions for the synthesis of the simplest α-phosphonovinyl triflate was examined.

6.2   Synthesis of α-Ketophosphonates

Synthesis of the novel α-phosphonovinyl triflates required the synthesis of α-ketophosphonate starting materials. The literature contains well-established procedures on the preparation of α-ketophosphonates. The majority of the starting materials were obtained by using the Michaelis-Arbuzov reaction. In addition to the Michaelis-Arbuzov reaction, the Abramov reaction was used to obtain troublesome α-ketophosphonate starting materials.

The typical reaction procedure for the Michaelis-Arbuzov reaction is treatment of triethylphosphite with acid halide under dry conditions, nitrogen gas at 0 °C. The reaction was allowed to gradually warm to room temperature and stirred for six hours, and was subsequently placed under high vacuum to rid it of volatile residual by-products and unreacted starting material. α-Ketophosphonates were obtained in high yield and high purity after distillation. The Michaelis-Arbuzov reaction is summarized in **Scheme 41** and will be referred to as Method "M-A."
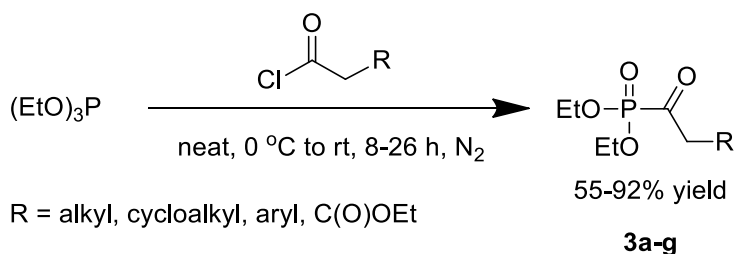
Scheme 41. Synthesis of α-ketophosphonates via Michaelis-Arbuzov reaction

The Abramov reaction makes use of a more reactive phosphite, diethyl (trimethylsilyl)phosphite, which was prepared by treatment of diethyl phosphite with triethylamine, followed by the dropwise addition of trimethylsilylchloride [58]. The typical reaction procedure for the Abramov reaction is treatment of the acid halide under dry conditions, nitrogen gas at 0 °C, followed by the dropwise addition of diethyl (trimethylsilyl)phosphite. The reaction is allowed to gradually warm to room temperature and stirred for four hours. The reaction is subsequently placed on high vacuum to rid it of volatile residual by-products and unreacted starting materials. The Abramov reaction is summarized in **Scheme 42** and will be referred to as Method "A."
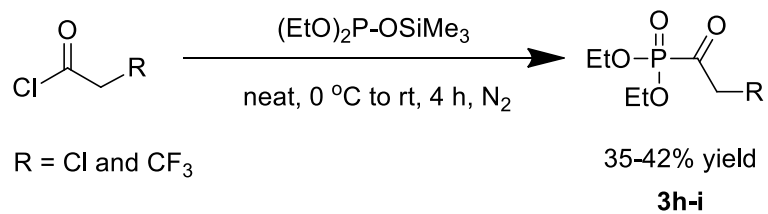
Scheme 42. Synthesis of α-ketophosphonates via Abramov reaction

Our results with these methods are shown in **Table 5**. In general, we obtained acceptable

yields of purified products.

Table 5. Synthesis of α-ketophosphonates

Entry	Method	Time (h)	Yield (%)	α-Ketophosphonate	
1	M-A	24	92[a]	3a	
2	M-A	24	77[a]	3b	
3	M-A	26	83[a]	3c	
4	M-A	8	58[a]	3d	
5	M-A	18	86[a]	3e	
6	M-A	12	57[a]	3f	
7	M-A	24	78[b]	3g	
8	A	4	35[c]	3h	
9	A	4	61[c]	3i	

[a] Represents isolated yield after short-path vacuum distillation
[b] Represents isolated yield after column chromatography
[c] Represents isolated yield after bulb-to-bulb distillation

6.3   Synthesis of α-Phosphonovinyl Triflates

Only a handful of procedures for generating the enolate of α-ketophosphonates via deprotonation by non-nucleophilic amine bases, DBU and Et_3N, at 0 °C are known. It was noted in the literature that DBU commonly gives high yields when the enolate is trapped by electrophiles such as TsCl or NfCl in the solvents THF and CH_3CN [50-52].

In the case of this research study, trifluoromethanesulfonic anhydride (Tf_2O) was heavily employed with catalytic amounts of 4-(dimethylamino)pyridine (DMAP), which is used to hypothetically "activate" trifluoromethanesulfonic anhydride to form a more reactive triflating agent, and it also believed to potentially participate as a co-base.
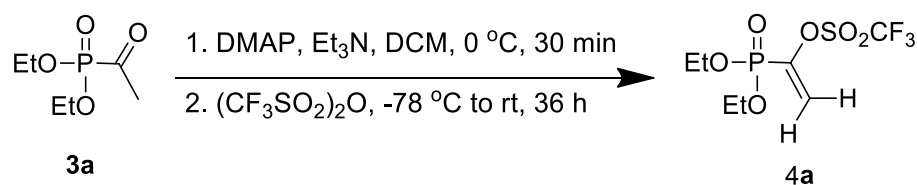
Scheme 43. Pilot reaction conditions

In order to develop a general methodology to prepare novel α-phosphonovinyl triflates bearing substituents at the β-carbon, the simplest α-ketophosphonate, diethyl acetylphosphonate **3a** was used as the model substrate. A pilot experiment was conducted for the synthesis of α-phosphonovinyl triflate **4a** and the reaction conditions are shown in **Scheme 43**. Firstly, diethyl acetylphosphonate **3a** was dissolved in DCM in the presence of DMAP in a 0 °C ice/water bath, followed by the addition of Et_3N, and allowed to stir for 30 minutes. The reaction mixture was then cooled to -78 °C in a dry ice/acetone bath, treated with the dropwise addition of Tf_2O, and allowed to gradually warm to room

temperature and stirred for 36 hours. Analysis of the[1]H NMR spectra of the unpurified reaction material showed desired triflate along with evidence of decomposition products and side-reactions. This preliminary reaction afforded α-triflated vinyl phosphonate **4a** as a yellow liquid in 35% yield after column chromatography.

The pilot experiment was repeated. Close attention was paid to color changes as a qualitative assessment of reaction behavior and product formation. Even though many factors can contribute to color changes, it was a key factor in reaction optimization. When diethyl acetylphosphonate **3a** was dissolved in DCM, a colorless, homogenous solution resulted. DMAP was added to reaction mixture and placed in 0 °C ice bath to cool. During the cooling of the reaction mixture to 0 °C (allowed ~15 minutes to cool), it was noted that the colorless, homogenous solution slowly turned to a light or pale yellow color. Then, Et_3N was added and the solution color intensified to a mild yellow. After 30 minutes, the reaction appeared a strongly yellow colored solution, which was believed at the time to signal the formation of an enolate species in solution. The reaction was cooled to -78 °C for ~15 minutes. Then, Tf_2O was added dropwise; the yellow, homogenous solution turned to a cloudy, light pink that darkened over time. After gradually warming to room temperature and stirring for a total of 36 hours, the reaction appearance was a whiskey brown, homogenous solution. After reaction work-up, compound **4a** was isolated as a yellow liquid in 41% yield after column chromatography.

6.3.1 Triflate Synthesis and Optimization Studies: Method A

Delighted by the reproduction of the initial results with a slightly improved yield, the next step was to increase the reaction yield by performing optimization studies. The solvent, DCM, remained constant throughout the study, but concentration, equivalents of reactants, temperature, amount of DMAP, and order of reagent addition were explored. Results of the study are summarized in **Table 6**.

When executing the initial optimization study, it was unclear of the chemical role of DMAP. Therefore, the next experiment performed, shown in **Scheme 44**, omitted the use of DMAP and triflate **4a** was furnished as a colorless liquid in 54% yield after column chromatography.
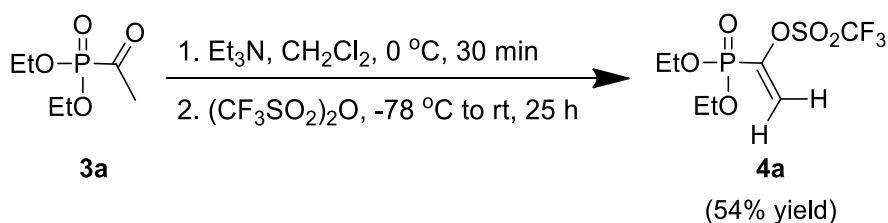
Scheme 44. Pilot reaction conditions excluding DMAP

A noteworthy observation was made in the appearance of the reaction mixture when diethyl acetylphosphonate **3a** was dissolved in DCM cooled to 0 °C, treated with Et$_3$N, and allowed to stir for 30 minutes. The reaction remained a colorless, homogenous solution the whole time; no yellowing was observed. Once treated with Tf$_2$O, the colorless, homogenous solution turned to a cloudy yellow color that darkened. The reaction was allowed to run for 25 hours and the ending reaction color was purple. When the reaction was quenched, the solution changed from purple to a green-blue to blue and

ended in a dark yellow/light brown color. ^{1}H NMR analysis of the unpurified (crude) sample revealed a clean reaction outcome that indicated the desired product, along with starting material present and less decomposition products/side-products as compared to the pilot experiments. After column chromatography, compound **4a** was isolated as a colorless liquid in 54% yield (**Entry 1**, **Table 6**).

Excluding DMAP from the reaction, progress was made toward reaching the optimal reaction conditions. Perhaps the yellowing observed in the previous reactions was not at all enolate formation, but decomposition of diethyl acetylphosphonate to diethylphosphite. This assumption would support the undesired compounds and decomposition products being observed in the NMR spectra of the unpurified sample for the pilot reactions and may contribute to the observed low yields.

Table 6. Method A – Optimization Table

Entry	Scale (mmol)	Et$_3$N (Equiv.)	Tf$_2$O (Equiv.)	DMAP (Equiv.)	Molarity [M]	Time (h)	Yield[a] (%)
1	1.0	1.1	1.1	-----	0.33	25	**54**
2	1.0	2.1	1.1	0.1	0.2	18.5	**61**
3	1.0	1.1	1.1	0.1	0.2	27	**38[b]**
4	1.0	1.1	1.1	0.1	0.33	25	**70[c]**
5	23.0	1.1	1.1	0.1	0.33	25	**87[c]**

[a] Isolated yield after column chromatography.
[b] Incomplete reaction based on 1H NMR; α-ketophosphonate recovered.
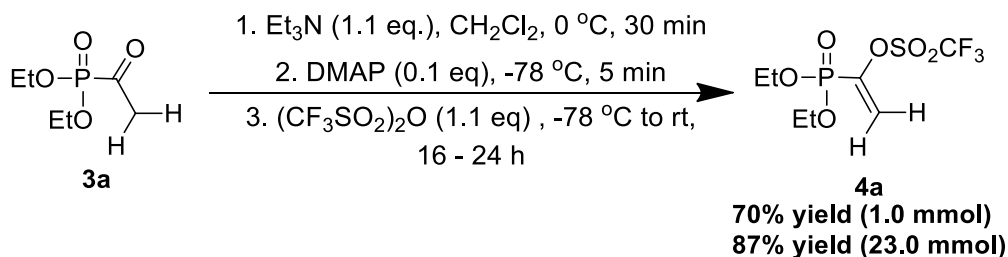[c] Optimized reaction conditions.

With these two factors in mind, the next trial reintroduced the use of DMAP, an increased amount of Et$_3$N, and a decrease in concentration. In this particular experiment, DMAP was not dissolved in the presence of diethyl acetylphosphonate **3a**, but instead it was dissolved by itself in DCM in a vial. After 30 minutes of stirring **3a** with Et$_3$N, the reaction was a homogenous, colorless solution. The reaction was cooled to -78 °C and then the DMAP/DCM solution was cannulated into the reaction flask and allowed to stir for a minute. Then, Tf$_2$O was added dropwise and the reaction mixture slowly turned to a cloudy light pink that darkened in pink over time to a brown/pink color. The reaction was determined complete after 18.5 hours by TLC and the ending reaction mixture that was a homogenous, mild whiskey brown solution. After flash column chromatography, compound **4a** was obtained as a pale or light yellow liquid in 61% yield (**Entry 2**, **Table 6**).

It was noted that when 10% excess Et$_3$N (1.1 equiv.) was used, a colorless oil was obtained after purification, but the reaction did not go to completion. Conversely, when using 110% excess Et$_3$N (2.1 equiv.), a light yellow colored oil was obtained and all starting material was consumed. To understand if 2.1 equivalents of Et$_3$N was necessary for reaction completion or causing a dirtier reaction, the amount of Et$_3$N was decreased to 1.1 equivalents and repeated. After letting the reaction stir for 27 hours, the ending solution was a purple color. ^{1}H NMR analysis of an unpurified sample revealed desired triflate along with unreacted starting material. Compound **4a** was obtained in 38% yield as colorless oil after column chromatography (**Entry 3**, **Table 6**).

According to these results, it seemed as though the use of 2.1 equivalents of Et$_3$N ensured reaction completion, but based off of the ^{1}H NMR spectra, it caused a dirtier

reaction with more side products. On the other hand, when using 10% excess of base, the reaction tended to be sluggish towards the end and did not go to completion. To overcome this problem, a more concentrated reaction mixture appeared to be necessary. To overcome the potential for a problematic exotherm due to a higher reaction concentration, Tf_2O was slowly added dropwise.

After determining the optimal order of addition of reagents, reagent equivalents, and times, the best results were achieved when the concentration was increased. The optimum conditions were determined to be: Et_3N (1.1 equiv.), Tf_2O (1.1 equiv.), DMAP (0.1 equiv., addition at -78 °C and stirred for a minute), and overall reaction concentration (0.33 M), which will be referred to as Method A and is shown in **Scheme 45**. On applying Method A on small reaction scale (1 mmol) to compound **4a**, a colorless oil was obtained in 70% yield as purified by flash column chromatography (**Entry 4**, **Table 6**). In a reaction scale up (23 mmol), the crude isolate was purified by short-path vacuum distillation and compound **4a** was observed as a colorless oil in 87% yield (**Entry 5**, **Table 6**).
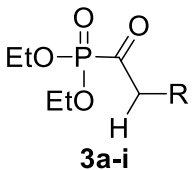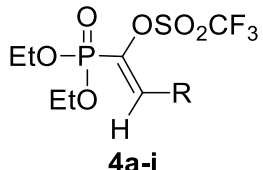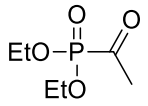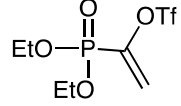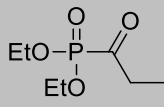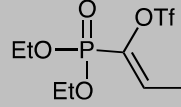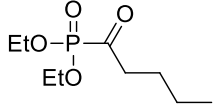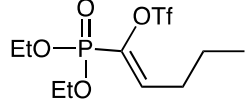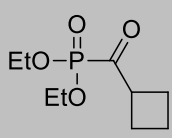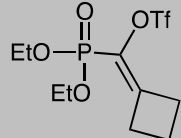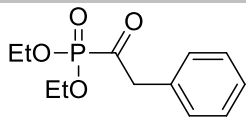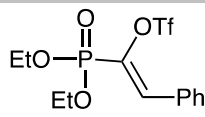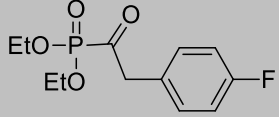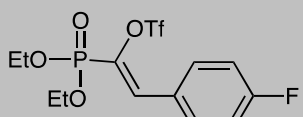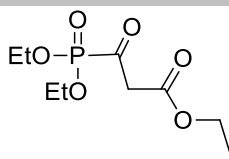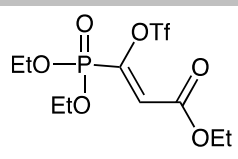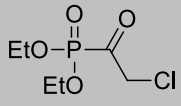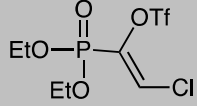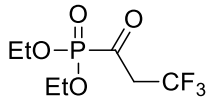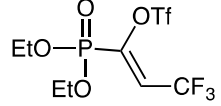

Scheme 45. Optimized conditions for simplest α-phosphonovinyl triflate **4a**

6.3.2 Synthesis of α-Phosphonovinyl Triflates via Method A

After fine-tuning the reaction conditions for the simplest α-phosphonovinyl triflate **4a**, it was time to test Method A with other substrates. In order to investigate the scope and limitations of the newly developed α-triflation procedure, a series of β-substituted α-ketophosphonates were synthesized via the Michaelis-Arbuzov method or Abramov method as stated above in Section 6.2 (**Compounds 3a–3i**, **Table 5**). Method A was applied to eight α-ketophosphonates having substituents on the β carbon, and the results are summarized in **Table 7**.

For β-substituted aliphatic α-ketophosphonates (**3a–3i**), Method A was employed to prepare α-phosphonovinyl triflates (**4a–4i**). In the case of **4b**, an increase in reaction yield of 78% yield was obtained (where the alkyl chain was increased by one carbon). Method A also proved to be tolerable of reaction scale up (27.0 mmol), affording **4b** in 91% yield after short-path vacuum distillation (**Entry 2**, **Table 7**). Surprisingly, using **3a**, a three carbon homolog, resulted in an incomplete reaction and a substantial drop in reaction yield was observed, giving **4c** in 18% yield (**Entry 3**, **Table 7**). Further difficulty was encountered when applying Method A to the cyclobutyl analog **3d**, no triflate, **4d**, was formed and unreacted starting material was recovered (**Entry 4**, **Table 7**). Based on these initial results, it appeared that Method A may not be optimal for preparing **4c** and **4d** and appeared to be sensitive to moderate steric interactions and further method development is required (See section 6.3.3).

Table 7. Synthesis of α-phosphonovinyl triflates via Method A

Reaction scheme:

3a-i → [1. Et₃N (1.1 eq.), DCM, 0 °C, 30 min; 2. DMAP (0.1 eq), -78 °C, 5 min; 3. (CF₃SO₂)₂O (1.1 eq), -78 °C to rt, 16 - 96 h] → 4a-i

$$\text{(EtO)}_2\text{P(O)-CH(R)-C(O)-} \xrightarrow{\text{1. Et}_3\text{N (1.1 eq.), DCM, 0 °C, 30 min; 2. DMAP (0.1 eq), -78 °C, 5 min; 3. (CF}_3\text{SO}_2)_2\text{O (1.1 eq), -78 °C to rt, 16 - 96 h}} \text{(EtO)}_2\text{P(O)-C(OSO}_2\text{CF}_3)=\text{CH-R}$$

Entry	α-Ketophosphonate	Time (h)	Yield[a] (%)	α-Phosphonovinyl Triflate
1	3a	25	70, 87[b]	4a
2	3b	25	78, 91[b]	4b
3	3c	96	18[c]	4c
4	3d	96	0[d]	4d
5	3e	24	68	4e
6	3f	24	71	4f
7	3g	24	0[e]	4g
8	3h	24	0[e]	4h
9	3i	18	46	4i

[a] Isolated yields after column chromatography.
[b] Reaction scale-up (20.0 - 24.0 mmols), purified via short-path vacuum distillation.
[c] Incomplete reaction based on ¹H NMR; α-ketophosphonate recovered.
[d] No reaction. α-ketophosphonate recovered.
[e] Decomposition of α-ketophosphonate observed.

For the α-triflation of aryl β-substituted α-ketophosphonates **3e–3f**, using Method A, the results were analogous to the simplest α-phosphonovinyl triflate **4a**. When a phenyl ring was present on the β carbon, the desired triflate **4e** was afforded in 68% yield after column chromatography (**Entry 5**, **Table 7**). Additional functionality was tested by using a 4-fluorophenyl substituent on the β carbon; triflate product **4f** being obtained in 71% yield after purification via column chromatography (**Entry 6**, **Table 7**). α-Triflation by Method A yielded aryl β-substituted α-phosphonovinyl triflates **4e** and **4f** and does not appear to be affected by the size of the phenyl ring and/or an electron-withdrawing group on the *para* position of the phenyl ring.

The remaining α-ketophosphonates, **3g–3i**, possess electron-withdrawing groups at the β carbon which, in turn, makes the α-hydrogen to the keto functionality of the α-ketophosphonates more acidic. When the methyl group on the β-carbon in compound **3b** is substituted with the electron-withdrawing group CF_3, a decrease in triflate yield was observed and **4i** is afforded in a 46% yield after column chromatography (**Entry 8**, **Table 7**). Upon attempted α-triflation of α-ketophosphonates bearing moderate steric bulk and/or electron-withdrawing groups, such as **4g** and **4h**, the corresponding α-triflated vinyl phosphonate products were not formed and decomposition of starting material was observed by TLC and ^{1}H NMR (**Entries 7** and **9**, **Table 7**).

6.3.3 Triflate Synthesis and Optimization: Method B

As reviewed in Section 6.3.2, when Method A was applied to prepare triflates **4c** and **4d**, poor results were obtained (**Entry 1**, **Table 8**). It appears that Method A is not able to tolerate moderate steric interactions. In the case of longer alkyl chains, such as **4c**, it may be that the free rotation around the β-carbon and γ-carbon obstructs the ability of Et$_3$N to deprotonate the β-carbon due to steric interactions. For highly strained ring systems like **4d**, the hydrogen bonded to the β-carbon is shielded by the cyclobutyl moiety and hindered the bases ability to deprotonate the β-carbon. Hypothetically, if difficulty in deprotonation of the β-carbon due to steric factors is responsible for poor reaction yields, at least three options are evident without substituting Et$_3$N:i) increase the amount of base, ii) increase reaction concentration, or iii) both. The logic behind the proposed solutions are simple; by increasing the amount of base and/or concentrating the reaction, Et$_3$N has an increased rate of interaction with substrate and, in turn, has an increased rate of deprotonating the β-carbon. In order to increase reaction yields for sterically hindered aliphatic α-ketophosphonates, further optimization is necessary. To address these complications and solve the problem, optimization studies were performed. **Table 9** summarizes the results for the synthesis of β-substituted α-phosphonovinyl triflates.

The first change in Method A was that Et$_3$N was increased by 15%, affording **4c** in an increased yield of 26% and no reaction took place for **4d** (**Entry 2**, **Table 8**). Encouraged by the result observed for compound **4c**, Et$_3$N was increased to 4.0 equivalents, Tf$_2$O was increased to 1.5 equivalents, DMAP was removed (yellowing was noted in **Entry 2**, **Table 8** for compound **4c** upon addition of DMAP and decomposition

products were observed in the NMR spectrum of the unpurified sample, along with a significant amount of starting material), and the reaction was diluted slightly by 40% to account for exotherm produced. A significant increase in yield was observed for both aliphatic systems, compound **4c** being isolated in 63% yield and compound **4d** being isolated in 55% yield after column chromatography (**Entry 3**, **Table 8**). In an attempt to increase reaction yields further and provide a cleaner reaction, Tf_2O was decreased to 1.15 equivalents, resulting in a slight increase in yield to 64% for compound **4c** (**Entry 4**, **Table 8**). The optimized reaction conditions were determined to be: Et_3N (4.0 equiv.), Tf_2O (1.15 equiv.), and molarity (0.20 M); and will be referred to as Method B.

Table 8. Method B – Optimization Table

3c R^1 = $CH_2CH_2CH_3$, R^2 = H   **3d** R^1 = R^2 = -$CH_2CH_2CH_2$- (cyclobutyl)

Entry	Et_3N (Equiv.)	Tf_2O (Equiv.)	DMAP (Equiv.)	Molarity [M]	Time (h)	Yield (%)[a] 4c	4d
1	1.1	1.1	0.1	0.33	38	**18**[b]	**0**[c]
2	1.25	1.1	0.1	0.33	38	**26**[b]	**0**[c]
3	4.0	1.5	-----	0.20	19	**63**	**55**
4	4.0	1.15	-----	0.20	20	**64**	-----
5	4.0	1.15	0.1	0.20	19	-----	**50**

[a] Isolated yields after column chromatography.
[b] Incomplete reaction based on ^1H NMR; α-ketophosphonate recovered.
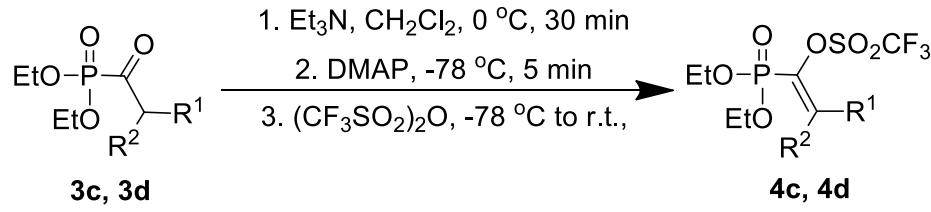[c] No reaction. α-ketophosphonate recovered.

6.3.4 Triflate Synthesis and Optimization: Method C

As reviewed in Section 6.3.2, when Method A was used to prepare **4g**, **4h**, and **4i**, poor results were obtained. By performing the optimization studies reviewed in Section 6.3.3, it is evident that Method A is not optimized to a degree to tolerate moderate steric interactions. In addition, Method A is clearly not well suited for electron-withdrawing substituents either, which was noted in Section 6.3.2. Since these specific α-ketophosphonates, **3g**, **3h**, and **3i**, have both steric factors and electron-withdrawing groups at the β-carbon, it is difficult to speculate exactly where the complication is arising. In order to gain more understanding and increase reaction yields for α-ketophosphonates bearing moderate steric interactions and/or electron-withdrawing groups at the β-carbon, further optimization studies were conducted. **Table 9** summarizes the optimization study used to develop Method C.

When Method A was applied to α-ketophosphonates **3g**, **3h**, and **3i**, the reaction solution began yellowing immediately after the addition of DMAP and decomposition products were noted in the unpurified sample by NMR. Decomposition is most likely due to the fact that these systems are more reactive phosphonate species relative to the previous α-ketophosphonates encountered. The electron-withdrawing groups present on the β-carbon have two influences on the chemical and physical properties of the α-ketophosphonates at hand: 1) the acidity of the hydrogen atom present on the β-carbon has significantly increased and 2) the P–C bond appears more labile relative to simple α-ketophosphonates bearing aliphatic and aryl β-substituents. As a result, these properties are likely responsible for the higher reactivity observed in these particular α-ketophosphonates.

Table 9. Method C – Optimization Table

$$\text{EtO}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle H}{|}}{\overset{|}{\text{P}}}}\text{—}\overset{O}{\overset{\|}{\text{C}}}\text{—R}^1 \quad \xrightarrow[\text{3. (CF}_3\text{SO}_2)_2\text{O, -78 }^\circ\text{C to rt}]{\substack{\text{1. Et}_3\text{N, CH}_2\text{Cl}_2\text{, 0 }^\circ\text{C, 30 min} \\ \text{2. DMAP, -78 }^\circ\text{C, 5 min}}} \quad \text{EtO}-\overset{O}{\overset{\|}{\text{P}}}\text{—C(OSO}_2\text{CF}_3)=\text{CH—R}^1$$

3g-3i → **4g-4i**

3g R^1 = C(O)OEt, **3h** R^1 = Cl, **3i** R^1 = CF$_3$

Entry	Et$_3$N (Equiv)	Tf$_2$O (Equiv.)	DMAP (Equiv.)	Molarity [M]	Time (h)	Yield (%)^a 4g	4h	4i
1	1.1	1.1	0.1	0.33	38	0^b	0^b	39
2	1.1	1.1	-----	0.20	16	56	18	46
3	1.1	1.1	-----	0.10	16	54	17	60
4*	1.1	1.1	-----	0.10	17	58	-----	63

^{a} Isolated yields after column chromatography.
^{b} Decomposition of starting material.
* All reaction steps carried out at -78 °C.

With these factors in mind, the changes made to Method A consisted of the exclusion of DMAP and slight dilution of the reaction mixture to account for potential exotherms. By making these two simple changes in the reaction conditions, an increase in reaction yield was noted for **4i**, which was obtained in 46% yield after purification (**Entry 2**, **Table 9**). Furthermore, α-triflation was successful for compounds **4g** and **4h**, affording triflates in 56% and 18% yields, respectively, after column chromatography (**Entry 2**, **Table 9**). Delighted by these results, additional reaction conditions were explored to minimize decomposition products which were observed in the NMR spectrum of the unpurified sample for compounds **4g, 4h,** and **4i**. A significant increase in reaction yield was observed for triflate **4i**; a 60% yield was obtained after column

chromatography when the reaction concentration was diluted by 50% (**Entry 3**, **Table 9**). These reaction conditions did not have a significant effect on the yield of **4g** or **4h**, yielding similar results to the previous reaction conditions being obtained in 54% yield and 17% yield, respectively (**Entry 3**, **Table 9**). In an attempt to further increase reactions yields and minimize decomposition, the entire reaction process was carried out at -78 °C, affording α-phosphonovinyl triflates **4g** and **4i**, in slightly increased yields of 58% and 63%, respectively, after column chromatography (**Entry 4**, **Table 9**). After completion of this study, the optimized reaction conditions were determined to be: Et_3N (1.15 equiv.), Tf_2O (1.15 equiv.), entire reaction run at -78 °C, and molarity (0.10 M), and these conditions will be referred to as Method C.

In the case of triflate **4h**, the low yields obtained are likely due to impure starting material. Diethyl chloroacetylphosphonate, **3h**, is very difficult to purify due to its high moisture sensitivity and a rapid rate of hydrolysis. In addition, it is also thermally labile and decomposes at about 95 °C; therefore, distillation of **3h** proved to be challenging (0.403 mm Hg, where distillate was caught at about 90 °C). The purity of **3h** was roughly evaluated by ^{1}H NMR and was estimated to be ~50% purity. If **3h** could be obtained in higher purity, we are confident the triflate **4h** would be obtained in a higher yield.

6.4 Characterization of α-Phosphonovinyl Triflates

All of the α-phosphonovinyl triflates prepared are novel and their properties are unknown in the literature. All α-phosphonovinyl triflates were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, FT-IR, LRMS, and HRMS. The following sections describe critical ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectral data. All spectral data can be found in Appendix D.

6.4.1 ^{1}H NMR Characterization of α-Phosphonovinyl Triflates

The α-triflation of α-ketophosphonates can be easily monitored by ^{1}H NMR by the disappearance of the signal for the α-proton adjacent to the carbonyl functionality. The formation of α-phosphonovinyl triflates can be verified by the emergence of the β-vinylic proton signal. In general, the vinylic protons resonate between 6.04–7.48 ppm and have spin-spin splitting patterns arising from [1]H–[31]P nuclei coupling and [1]H–[1]H nuclei coupling (in addition to [1]H–[19]F nuclei coupling for triflate **4i**). Generally, the methylene protons (CH_2) of the ethoxy groups resonate in the range of 4.08–4.34 ppm as complex multiplets and the methyl protons (CH_3) of the ethoxy groups resonate in the range of 1.34–1.40 ppm as apparent triplets with coupling constants of about 7 Hz.

Table 10 summarizes the ^{1}H NMR spectral data for α-phosphonovinyl triflates having vinylic hydrogen(s) with complex splitting patterns. For aliphatic β-substituted α-phosphonovinyl triflates, the simplest α-triflated α-vinylphosphonate **4a** contains two vinylic protons that resonate at 6.04 ppm and 6.23 ppm as a doublet of doublets having coupling constants of $J = 3.9$ Hz and $J_{P-H} = 9.9$ Hz. In the cases of increased alkyl chain length **4b** and **4c**, each has one vinylic proton that resonates as multiplets between 6.77–

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6.87 ppm and 6.69–6.77 ppm, respectively. The splitting pattern for **4b** is a doublet of quartets due to hydrogen–hydrogen coupling and phosphorus–hydrogen coupling. The splitting pattern for **4c** is a doublet of triplets due to hydrogen–hydrogen coupling and phosphorus-hydrogen coupling as well. In the case of tetra-substituted α-phosphonovinyl triflates such as **4d**, slight chemical shifts and a change in multiplicity of the CH_2 signals of the cyclobutyl group are observed. For the α-phosphonovinyl triflate having a $-CF_3$ functionality on the β-carbon, the vinylic proton signal is a doublet of quartets between 6.97 – 6.80 ppm. The observed complex splitting pattern for compound **4i** is due to phosphorus–hydrogen coupling and fluorine–hydrogen coupling. The vinylic proton signals for compounds **4b**, **4c**, and **4i** were not resolved enough using a 300 MHz NMR to give specific chemical shifts or the coupling constants for the splitting patterns observed.

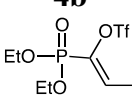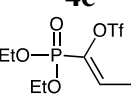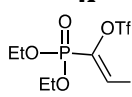**Table 10. ^{1}H NMR data of vinylic hydrogen of α-phosphonovinyl triflates (multiplet splitting patterns)**
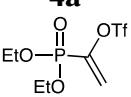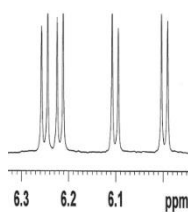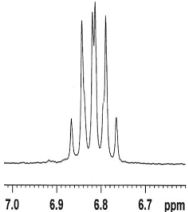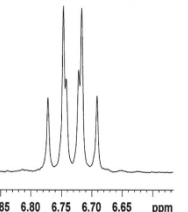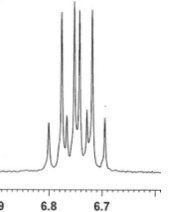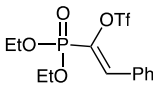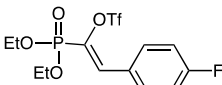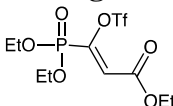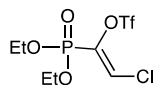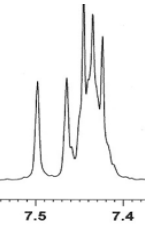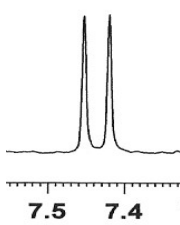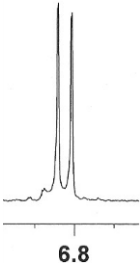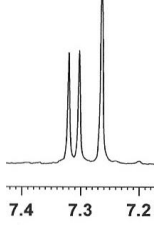
α-Phosphonovinyl Triflate	4a	4b	4c	4i
Vinylic Hydrogen (ppm)	6.04, 6.23	6.77 – 6.87	6.69 – 6.77	6.97 – 6.80
Splitting	*dd*	*dq*	*dt*	*dq*
J_{H-H} $\quad$ (Hz) J_{P-H}	3.9, 3.9 31.2, 9.9	-------------	-------------	-------------
Vinylic Hydrogen Splitting Patterns (^{1}H NMR Spectrum)				

Table 11 summarizes the ^{1}H NMR spectral data for α-phosphonovinyl triflates having vinylic hydrogen(s) with doublet splitting patterns. For the aryl β-substituted α-phosphonovinyl triflates **4e** and **4f**, the vinylic proton resonates at 7.48 ppm and 7.44 ppm, respectively. Both systems have a doublet splitting pattern with a coupling constant of $J_{P\text{-}H}$ = 9.9 Hz. The ester β-substituted α-phosphonovinyl triflate **4g** has one vinylic proton resonating as a doublet splitting pattern with a coupling constant of $J_{P\text{-}H}$ = 10.5 Hz at 6.82 ppm. In the case of the α-phosphonovinyl triflate having a chloro β-substituent, compound **4i**, one vinylic proton resonates at 7.31 ppm and has a doublet splitting pattern with a coupling constant of $J_{P\text{-}H}$ = 5.4 Hz.

Table 11. ^{1}H NMR data of vinylic hydrogen of α-phosphonovinyl triflates (doublet splitting patterns)

α-Phosphonovinyl Triflate	4e	4f	4g	4h
Vinylic Hydrogen (ppm)	7.48	7.44	6.82	7.31
Splitting	*d*	*d*	*d*	*d*
$J_{P\text{-}H}$ (Hz)	9.9	9.9	5.4	10.5
Vinylic Hydrogen Splitting Patterns (^{1}H NMR Spectrum)				

6.4.2 ^{13}C NMR Characterization of α-Phosphonovinyl Triflates

Formation of α-phosphonovinyl triflates can be easily verified by ^{13}C NMR by the presence of a carbon signal given by the –OSO$_2$CF$_3$ functionality and the presence of two carbon signals belonging to the vinylic functionality. In general, the carbon atom of the –OSO$_2$CF$_3$ functional group resonates in the chemical shift range of 118.17 – 118.35 ppm and has a quartet splitting pattern arising from carbon–fluorine coupling with coupling constants ranging from 318 – 320 Hz. The vinyl functionality has two carbon signals that fall within a broad chemical shift range. The α-carbon of the vinyl group falls within a chemical shift range between 129.81 – 146.53 ppm and has a doublet splitting pattern due to carbon–phosphorus coupling with a coupling constant that ranges from 215 – 235 Hz. The β-carbon signal of the vinyl group falls within a chemical shift range of 121.91 – 161.18 ppm and has a doublet splitting pattern arising from carbon–phosphorus coupling with a coupling constant ranging from 18 – 39 Hz. Generally, the methylene carbon of the ethoxy groups resonates in the chemical shift range of 15.94 – 16.00 ppm as doublets due to carbon–phosphorus coupling and displays coupling constants ranging from 6.0 – 6.8 Hz. The methyl carbons of the ethoxy groups resonate in the chemical shift range of 62.90 – 64.65 ppm as doublets with coupling constants ranging from 5.2 – 6.0 Hz. **Table 12** and **Table 13** summarize key ^{13}C NMR spectral data for the carbon signal given by the –OSO$_2$CF$_3$ functionality and the two carbon signals in the vinylic functional group for each α-phosphonvinyl triflate prepared.

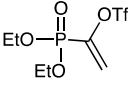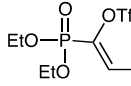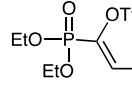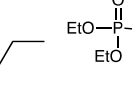**Table 12. ^{13}C NMR spectral data for α-phosphonovinyl triflates 4a-d and 4i**
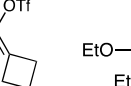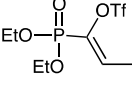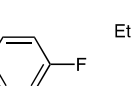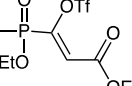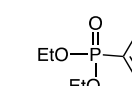
α-Phosphonovinyl Triflate	4a	4b	4c	4d	4e
−OSO$_2$CF$_3$ (ppm)	118.24	118.34	118.35	118.30	118.17
Splitting	q	q	q	q	q
J$_{C-F}$ (Hz)	320	318	318	318	319
Vinylic C$_α$ (ppm)	146.53	139.39	138.11	129.81	136.69
Splitting	d	d	d	d	d
J$_{C-P}$ (Hz)	229	232	230	235	230
Vinylic C$_β$ (ppm)	121.91	138.28	143.19	159.25	138.35
Splitting	d	d	d	d	d
J$_{C-P}$ (Hz)	22.5	25.5	24	25	25.5

Table 13. ^{13}C NMR spectral data for α-phosphonovinyl triflates 4e-h

α-Phosphonovinyl Triflate	4f	4g	4h	4i
−OSO$_2$CF$_3$ (ppm)	118.23	118.28	118.30	118.21
Splitting	q	q	q	q
J$_{C-F}$ (Hz)	312	319	319	319
Vinylic C$_α$ (ppm)	136.52	146.52	140.53	145.60
Splitting	d	d	d	dq
J$_{C-P}$ / J$_{C-F}$ (Hz)	227	220	220	215 / 5.25
Vinylic C$_β$ (ppm)	137.15	126.75	131.15	125.60
Splitting	d	d	d	dd
J$_{C-P}$ / J$_{C-F}$ (Hz)	27	25	39	26 / 10.5

6.5 Stereochemistry of α-Phosphonovinyl Triflates

The olefinic geometries of alkenylphosphonates were reported by Afarinkia et al. in 1997, who studied the enolization of α-ketophosphonates [53]. They found that not all α-ketophosphonates auto-enolize, but they can, nevertheless, be easily enolized fully under basic conditions (Et$_3$N, DCM, r.t.) and can be trapped with acetic anhydride [53]. In all cases, they found that the enol derivative is formed in the *E*-geometry as this places the two bulkiest substituents in the *trans* relationship to the phosphonate moiety. Several α-acetoxyvinylphosphonates were prepared by the Afarinkia group and the phosphorus atom and β-vinylic hydrogen nuclei coupling constant values of all the α-acetoxyvinylphosphonate derivatives were determined to have the *E*-geometry, with phosphorus-vinylic hydrogen nuclei coupling constants ranging from 10.4 – 11.8 Hz [53]. Furthermore, they provided an X-ray crystal structure of dimethyl (phenylacetyl)phosphonate in the enol form that shows the molecule to be present as the hydrogen-bonded dimer, in which the enol –OH of one molecule is bridged to the oxygen atom of the P=O of the phosphonate moiety [53].

In addition to the Afarinkia paper, reports made by Kobayashi and Williams in 2002 further confirmed the *E*-geometry of the olefinic functionality of α-vinylphosphonates. They performed in-depth ^{1}H NMR studies of carefully prepared α-vinylphosphonates, which were afforded by the cross-coupling of α-bromoalkenyl phosphonates with aryl boronic acids and alkenyl borates in the presence of a palladium catalyst. In this study, they prepared α-vinylphosphonates having both *Z* and *E* geometry and provided the coupling constants for each isomer [57]. **Figure 5** and **Figure 6** list a few α-phosphonovinyl bromides that were studied to determine the stereochemistry [57].
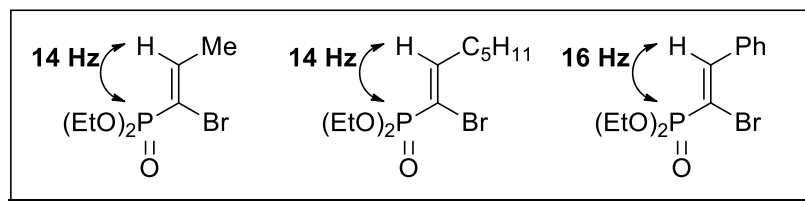
Figure 5. Phosphorus–β-vinylic hydrogen Z-geometry ^{1}H – ^{31}P coupling constants [57]
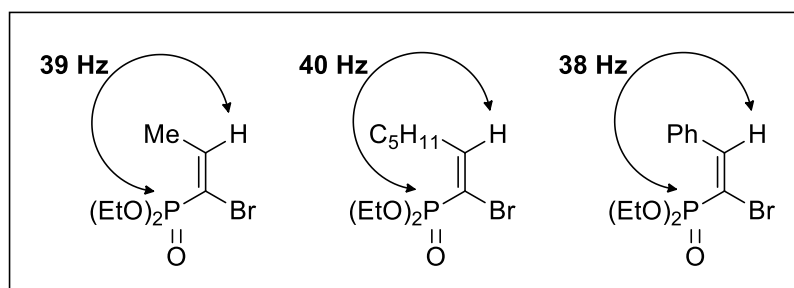
Figure 6. Phosphorus–β-vinylic hydrogen E-geometry ^{1}H – ^{31}P coupling constants [57]

These specific examples were extracted from the literature publication because they are closely related to the α-phosphonovinyl triflate counterparts prepared in this study. **Figure 5** displays the coupling constants for phosphorus–hydrogen nuclei coupling for α-phosphonovinyl bromides that have a Z-geometry relationship. The measured coupling constants are 14 – 16 Hz for the phosphorus-β-vinylic hydrogen nuclei relationship having Z-geometry. **Figure 6** displays the coupling constants for phosphorus–hydrogen nuclei coupling for α-phosphonovinyl bromides that have an E-geometry relationship. The measured coupling constants are 38 – 40 Hz for the phosphorus-β-vinylic hydrogen nuclei relationship having E-geometry. In summary, they were able to determine that the phosphorus–β-vinylic hydrogen coupling constants for the Z-isomers of α-vinylphosphonates, based on the spectral data of the coupling constants, can be 2 – 2.5 times greater than the value of the E isomer [57].

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For the simplest α-triflated vinlyphosphonate **4a**, the coupling constant for the β-vinylic hydrogen (**H$_a$**) resonating at 6.04 ppm has a coupling constant of $J_{P-Ha} = 31.2$ Hz and the β-vinylic hydrogen (**H$_b$**) resonating at 6.23 ppm has a coupling constant of $J_{P-Hb} = 9.9$ Hz. Based on the data by Afarinkia et al. and Kobayashi et al., it was concluded that the coupling constant $J_{P-Hb} = 9.9$ Hz belongs to the vinylic hydrogen with *cis*/Z-geometry relative to the phosphonate moiety and the coupling constant $J_{P-Ha} = 31.2$ Hz belongs to the vinylic hydrogen with a *trans*/E-geometry relative to the phosphonate moiety (**Figure 7**).
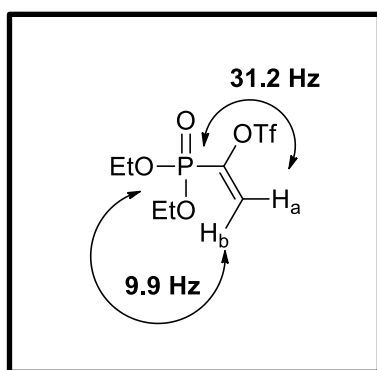
Figure 7. Vinylic hydrogen coupling constants for α-phosphonovinyl triflate **4a**

The stereochemistry for α-phosphonovinyl triflates having a β-substituent present appears to be exclusively the *E*-geometry as determined by ^{1}H NMR through the analysis of the doublet spin-spin coupling constants of β-vinylic hydrogen – phosphorus nuclei. The coupling constants of α-phosphonovinyl triflates having doublet splitting patterns are summarized in **Table 14** and they all have small values except for the simplest α-triflated vinlyphosphonate **4a**, in which the coupling constant $J_{P-Ha} = 31.2$ Hz belonged to the vinylic hydrogen *trans*/E-geometry relative to the phosphonate moiety. In the case of aryl

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β-substituted α-phosphonovinyl triflates **4e** and **4f**, the coupling constant was observed to be $J_{P\text{-}H} = 9.9$ Hz, which is consistent with the Afarinkia et al. data and is consistent with compound **4a**. In addition, for compound **4g**, a coupling constant of the coupling constant $J_{P\text{-}H} = 10.5$ Hz was observed and corresponds to the vinylic hydrogen having *cis/Z*-geometry relative to the phosphonate moiety. Also, for the β-chloro α-phosphonovinyl triflate **4h**, a small coupling constant of $J_{P\text{-}H} = 5.4$ Hz was observed.

Table 14. Analysis of doublet coupling constants of phosphorus–β-vinylic hydrogen atoms for α-phosphonovinyl triflates

Triflate	4a	4e	4f	4g	4h
Vinylic H (ppm)	6.04, 6.23	7.48	7.44	6.82	7.31
Splitting	*dd*	*d*	*d*	*d*	*d*
$J_{H\text{-}H}$ $J_{P\text{-}H}$ **(Hz)**	3.9, 3.9 31.2, 9.9	9.9	9.9	5.4	10.5
Vinylic Hydrogen Splitting Patterns					

Further confirmation of the *E*-geometry was supported by triflate **4g**. Triflate **4g** had a coupling constant of $J_{P\text{-}H} = 10.5$ Hz and was the only α-phosphonovinyl triflate that was a solid at ambient temperature (M.P. = 36 °C). Luckily, X-ray crystallographic data could be obtained on triflate **4g**. The X-ray crystal structure and ORTEP diagram is

shown in **Table 15**, along with key X-ray crystallography data that supports the (*E*) geometry of the corresponding α-phosphonovinyl triflate [59]. The X-ray crystallography reported the torsion angle for dihedron P1-C5-C7-C8 is 177.31(15)° and the torsion angle for dihedron O7-C8-C7-C5 is 2.0(3) °. Further confirmation of the (*E*) geometry is noted by the presence of a hydrogen bond donor/acceptor pair between H7 and O1 having a distance of 3.207(2) Å and a bond angle of 141.2°.

Table 15. X-ray crystallography report supporting *E* stereochemistry

Torsion Angle (°)		Hydrogen Bond Donor/Acceptor	
		C7–H7··········O1	
P1-C5-C7-C8	**O7-C8-C7-C5**	**Distance (Å)**	**Angles (°)**
177.31(15)	2.0(3)	3.207(2)	141.2
ORTEP DIAGRAM			

CHAPTER 7

RESULTS AND DISCUSSION FOR THE SYNTHESIS OF α-ALKYNYLPHOSPHONATES

7.1   Synthetic Methodology for α-Alkynylphosphonates

As stated earlier, the synthetic route to prepare α-alkynylphosphonates (or 1-alkynylphosphonates) was discovered serendipitously while attempting to prepare α-functionalized vinylphosphonates in a previous research project. Herein, a two reaction pathway is described, in which α-alkynylphosphonates are prepared by the base-promoted β-elimination of α-phosphonovinyl triflates prepared from α-ketophosphonates. The following sections describe the methodology and briefly examine its scope and limitations.

7.2   Synthesis of α-Phosphonovinyl Triflates

Synthetic methodology to prepare α-phosphonovinyl triflates was discussed in section 6.3.1 – 6.3.4. Synthetic procedures can be found in the Materials and Methods chapter, Section 9.2 and spectral data can be found in Appendix D.

7.3 Synthesis of α-Alkynylphosphonates

The synthetic methodology described for the facile preparation of α-alkynylphosphonates from α-ketophosphonates via α-phosphonovinyl triflate intermediates involves mild reaction conditions and consists of one synthetic method, but two bases are utilized to furnish β-substituted α-alkynylphosphonates. The procedure employs DBU for α-phosphonovinyl triflates having aliphatic or aryl substitutents at the β-carbon position. DIPEA was used as an alternative to DBU in the case of more acidic α-phosphonovinyl triflates bearing electron-withdrawing groups at the β-carbon position.

7.3.1 Synthesis and Optimization Studies

In order to establish the synthetic methodology to prepare β-substituted α-alkynylphosphonates, it seemed appropriate to start with the simplest α-triflated vinylphosphonate, **4a**. A pilot experiment was conducted by treating **4a**, dissolved in THF, with MeLi at 0 °C, and it was allowed to react for 30 min. Compound **5a** was isolated as a colorless liquid in 41% yield after column chromatography (**Entry 1**, **Table 16**). Encouraged by this result, optimization studies were performed to increase the yield, and the results are summarized in **Table 16**.

Seeking milder reaction conditions, a weaker base was sought first. Amberlyst-26, a resin-supported tertiary amine, was explored initially because it would provide a simple, mild reaction procedure accompanied by a simple work-up. When employing Amberlyst 26 as base in DCM in the presence of **4a** at r.t., no reaction took place within 24 hours (**Entry 2**, **Table 16**). The reaction was heated to reflux and allowed an additional 48 hours, but still no reaction occurred and starting material was recovered.

The next base explored was diisopropylethyl amine (DIPEA). When using DIPEA, the reaction was allowed to run at r.t. for 24 hour and no reaction took place. The reaction was then heated to reflux and allowed to run for an additional 48 hours, and still no β-elimination took place and starting material was recovered (**Entry 3**, **Table 16**). When substituting DBU as the base, positive results were obtained. For the reaction of **4a** in the presence of DBU in DCM at r.t. for 20 hours, **5a** was obtained as a colorless oil in 45% yield after purification via column chromatography (**Entry 4**, **Table 16**).

Table 16. **Optimization table for the preparation of simplest α-alkynylphosphonate**

Entry	Base	Equiv.	Solvent	Temp. (°C)	Molarity	Time (h)	Yield (%)
1	MeLi	2	THF	0	0.15	0.5	**41**[a]
2	A26	2.1	DCM	r.t. → reflux	0.15	72	**0**[b]
3	DIPEA	2.1	DCM	r.t. → reflux	0.15	72	**0**[b]
4	DBU	2.1	DCM	r.t.	0.15	20	**45**[a]

[a]Isolated yield after column chromatography.
[b]No reaction. Starting material recovered.

Now that an appropriate base was found, several α-phosphonovinyl triflates (**4a–4i**, excluding **4d**) were treated with DBU to afford the corresponding α-phosphono-alkynes and the results are summarized in **Table 17**. Upon further optimization, the amount of DBU was decreased to 1.5 equivalents, and several α-phosphonovinyl triflates having aliphatic, aryl, and electron-withdrawing groups substituted on the β-carbon were

utilized. In the case of aliphatic α-phosphonovinyl triflates, increasing the alkyl chain length gave higher yields. The β-elimination of **4b** and **4c** took place within 24 hours at r.t. to furnish **5b** and **5c** as colorless oils in 57% yield and 67% yield, respectively, after column chromatography purification (**Entries 2** and **3**, **Table 17**). High yields of alkynes were observed on aryl β-substituted α-phosphonovinyl triflates were used as substrates. In the case of the simplest aryl α-triflated vinylphosphonate **4e**, the desired product **5e** was afforded in 95% yield after being purified via silica plug (**Entry 4**, **Table 17**). The reaction conditions were also tolerant of the presence of a *para*-fluoro substituent on the phenyl group substituted on the β-carbon, producing **5f** in 94% yield after being purified via silica plug (**Entry 5**, **Table 17**). When the reaction conditions were tested on substrates bearing electron-withdrawing groups on the β-carbon of α-phosphonovinyl triflates, the reaction gave little to no α-alkynylphosphonate product. In the case of **5g** and **5i**, the desired alkynyl product was not found at all (**Entries 6** and **8**, **Table 17**). No starting material was recovered and decomposition products were observed in the unpurified sample when analyzed by ^{1}H NMR. On the other hand, alkyne **5h** was isolated as a colorless liquid in 34% yield after purification via column chromatography (**Entry 7**, **Table 17**).

Table 17. Summary of results for synthesizing α-alkynylphosphonates with DBU

R = H, methyl, propyl, Ph, *p*-F-Ph, C(O)OEt, Cl, CF$_3$

Entry	α-Phosphonovinyl Triflate		Yield (%)[a]	Time (h)	α-Alkynylphosphonate	
1	4a		45	24	5a	
2	4b		57	24	5b	
3	4c		67	24	5c	
4	4e		95[b]	18	5e	
5	4f		94[b]	16	5f	
6	4g		0[c]	12	5g	
7	4h		34	16	5h	
8	4i		0[c]	12	5i	

[a] Isolated yield after column chromatography.
[b] Isolated yield. Purified via silica plug.
[c] Decomposition of α-phosphonvinyl triflates observed.

The reaction conditions needed to be optimized for triflates **4g** and **4i** due to the ester and trifluoro groups on the β-carbon. These systems appear more reactive and have more acidic hydrogen atoms on the β-vinylic carbon. The P–C bond is more labile than

the corresponding aliphatic and aryl β-substituted α-phosphonovinyl triflates due to the electron-withdrawing properties of the -CF$_3$, -Cl, and -COOEt groups. Going by this logic, it seemed appropriate to switch to a milder base like DIPEA and the results are summarized in **Table 18**. When DIPEA was employed as the base for substrate **4g**, a clean β-elimination took place to provide compound **5g** as colorless oil in 91% yield after purification via silica plug (**Entry 1**, **Table 18**). In the case of **4h** and **4i**, desired α-alkynylphosphonates **5h** and **5i**, were obtained as colorless oils in 46% yield and 40% yield, respectively, after purification via column chromatography (**Entries 2** and **3**, **Table 18**).

Table 18. Summary of results for synthesizing α-alkynylphosphonates with DIPEA

R = C(O)OEt, Cl, CF$_3$

Entry	α-Phosphonovinyl Triflate	Yield (%)[a]	Time (h)		α-Alkynylphosphonate
1	4g	94[b]	3	5g	
2	4h	48	24	5h	
3	4i	40	18	5i	

[a] Isolated yield after column chromatography.
[b] Isolated yield. Purified via silica plug.

CHAPTER 8

CONCLUSION

In summary, a convenient method was developed and described for the synthesis of β-substituted α-phosphonovinyl triflates from their corresponding β-substituted α-ketophosphonates. The β-substituted α-phosphonovinyl triflates synthesized were used to prepare β-substituted α-alkynylphosphonates in a convenient, facile base-promoted β-elimination reaction. The synthetic protocol developed to prepare β-substituted α-phosphonovinyl triflates and β-substituted α-alkynylphosphonates is centered around α-ketophosphonate precursors, which are prepared in high yield and purity by the Michaelis-Arbuzov reaction or the Abramov reaction. The starting materials to prepare α-ketophosphonates are cheap and commercially available or can be made simply in the lab. The conversion of α-ketophosphonates to α-phosphonovinyl triflates is achieved by treatment with Et_3N and Tf_2O and is organized into three sets of reaction conditions based on the substrates bearing various groups at the β-carbon of the α-ketophosphonates. The preparation of α-alkynylphosphonates was then achieved by treatment of α-phosphonovinyl triflates with DBU or DIPEA under a base-induced β-elimination.

8.1 Summary of α-Phosphonovinyl Triflates

In retrospect, this research study addressed the issue of synthesizing novel α-phosphonovinyl triflates which was reported to be challenging and could not be accomplished in synthetically usefule yields by previous methods. In direct comparison to the literature methods reported for the synthesis of α-phosphonovinyl tosylates and α-phosphonovinyl nonaflates, the triflate publications lack substrate scope and only moderate yields are obtained. Our methodology for the synthesis of α-phosphonovinyl triflates includes a range of groups on the β-carbon which vary in electronics, sterics/ring strain, and electron donating/withdrawing groups. In direct comparison to α-phosphonovinyl tosylates, the trifluoromethanesulfonate has increased reactivity due to a strong electron-withdrawing effect of the trifluoro group that reduces electron density at the adjacent carbon atom. This is a desirable property in transition-metal mediated reactions. Even though α-phosphonovinyl nonaflates known and nonaflates, in general, maybe more reactive than triflates, the α-phosphonovinyl triflates are novel and their chemistry has not been explored.

Based on this research, a new, facile, and convenient synthesis of novel β-substituted α-phosphonovinyl triflates was developed. The synthetic methodology takes advantage of enolate chemistry of α-ketophosphonates by treatment with Et_3N, followed by enolate trapping with Tf_2O in moderate to good yields. Nine novel β-substituted α-phosphonovinyl triflates were prepared and fully characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, FT-IR, LRMS, and HRMS. Characterization of the α-phosphonovinyl triflates can be found in Appendix D.

Table 19 summarizes the results obtained to prepare α-phosphonovinyl triflates via three methods. Method A is optimized for small, not sterically-demanding aliphatic β-substituted α-ketophosphonates and aryl β-substituted α-ketophosphonates. Method A furnished the corresponding α-triflated vinylphosphonates **4a**, **4b**, **4e**, and **4f**, as colorless oils in 68-91% yield. Method B is optimized for aliphatic β-substituted α-ketophosphonates having longer alkyl chains and strained ring systems. Method B afforded compounds **4c** and **4d** as mild yellow oils in 63% yield and 54% yield, respectively. For α-ketophosphonates bearing electron-withdrawing β-substituents, Method C was developed to afford **4g** and **4i** and was obtained as colorless oils in 58% yield and 63% yield, respectively. Method C also used yielded **4h**, as a colorless oil in 18% yield, but the low yield is assumed to be primarily due to impure starting material. Overall, excluding compound **4h**, desired β-substituted α-phosphonovinyl triflates were prepared in 55-91% yield.

Table 19. Summary of results for α-phosphonovinyl triflates via Method A, B, or C

3a-i → 4a-i
Method A, B, or C
18-91% yield

Entry	α-Ketophosphonates		% Yield[a] Method			α-Phosphonovinyl Triflates	
			A[b]	B[c]	C[d]		
1		3a	70, 85[f]	--	--	4a	
2		3b	78, 91[f]	--	--	4b	
3		3c	18[g]	64	--	4c	
4		3d	0[g]	55	--	4d	
5		3e	68	--	--	4e	
6		3f	71	--	--	4f	
7		3g	0[h]	--	58	4g	
8		3h	0[h]	--	18	4h	
9		3i	46	--	63	4i	

[a]Isolated yield (column chromatography, silica gel).
[b]Method A: [anhydrous reaction conditions and under N_2 atm] 1) Et_3N (1.1 equiv), CH_2Cl_2 (3 mL/mmol), 0 °C, 30 min 2) DMAP (0.1 equiv), -78 °C, 2 min 3) Tf_2O (1.1 equiv), -78 °C to rt, 18 h.
[c]Method B: [anhydrous reaction conditions and under N_2 atm] 1) Et_3N (4 equiv), CH_2Cl_2 (5 mL/mmol), 0 °C, 1 h 2) Tf_2O (1.5 equiv), -78 °C to rt, 19 h.
[d]Method C: [anhydrous reaction conditions and under N_2 atm] 1) Et_3N (1.1 equiv), CH_2Cl_2 (8 mL/mmol), -78 °C, 30 min 2) Tf_2O (1.1 equiv), -78 °C to rt, 18 h.
[f]Reaction scale-up. Purified by short-path vacuum distillation.
[g]Incomplete reaction based on ^{1}H NMR; α-ketophosphonate recovered.
[h]Decomposition of α-ketophosphonate observed by ^{1}H NMR.

8.2   Summary of α-Alkynylphosphonates

To display synthetic utility of the β-substituted α-phosphonovinyl triflates, they were used as substrates for the convenient synthesis of β-substituted α-alkynylphosphonates. The synthetic methodology proceeds through a base-promoted β-elimination of α-phosphonovinyl triflates to afford β-substituted α-alkynylphosphonates in moderate to excellent yields using DBU or DIPEA. Overall, a convenient two reaction pathway was described to prepare α-alkynylphosphonates starting from α-ketophosphonates.   There are no reports in the literature that make use of α-ketophosphonates as a direct or indirect substrates to synthesize functionalized alkynylphosphonates. The method developed is advantageous because functionalized α-ketophosphonates can be easily prepared in high yields from starting materials that are cheap and readily available from chemical suppliers.

Procedures found in the literature often lack substrate scope, require multiple reactions, sometimes require high temperatures, or rely on the need for catalysts or additives or oxidants. Often times starting materials are not readily available from chemical suppliers, and lastly, they may require the use of transition metals which produce hazardous heavy metal waste and are toxic, therefore, they must be carefully removed from the product, especially for the drug and pharmaceutical industry. Therefore, the method developed for the synthesis of substituted alkynylphosphonates is highly desired and advantageous. In addition, the method is inexpensive and easy to carry out.

In total, eight β-substituted α-alkynylphosphonates were prepared and were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and FT-IR. Representative spectra of the

α-alkynylphosphonates can be found in Appendix E. **Table 20** summarizes the results obtained for the synthesis of alkynylphosphonates via base-promoted β-elimination of α-phosphonovinyl triflates.

In summary, aliphatic β-substituted α-alkynylphosphonates **5a**, **5b**, and **5c** were furnished in 45–67% yield and aryl β-functionalized α-alkynylphosphonates **5e** and **5f** were afforded in 95% yield and 94% yield, respectively, using DBU as the base. In the case of electron-withdrawing groups on the β-carbon of α-phosphonovinyl triflates, compounds **5g**, **5h**, and **5i** were obtained in 40-91% yield when using DIPEA as the base. Overall, α-alkynylphosphonates were afforded in 40-95% yield.

Table 20: Summary of results for the synthesis of α-alkynylphosphonates

Entry		α-Phosphonovinyl Triflates	% Yield[a] Method		α-Alkynylphosphonates	
			DBU	**DIPEA**		
1	4a		45		5a	
2	4b		57		5b	
3	4c		67		5c	
4	4e		95		5e	
5	4f		94		5f	
6	4g		0[b]	94	5g	
7	4h		34	48	5h	
8	4i		0[b]	40	5i	

[a]Isolated yield after column chromatography.
[b]Decomposition of α-phosphonvinyl triflates observed.

CHAPTER 9

MATERIALS AND METHODS

<u>GENERAL</u>

All reactions utilizing moisture sensitive reagents were carried out using anhydrous solvents under a dry nitrogen atmosphere. All glassware necessary for sensitive reactions was kept in a 160°C oven and cooled to room temperature under nitrogen gas prior to use. Reagent grade dichloromethane was dried and stored over 3Å molecular sieves. Triethylamine was distilled over calcium hydride under nitrogen atmosphere and stored under argon gas. Diisopropylethylamine (DIPEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled under nitrogen atmosphere. Diethyl (trimethylsilyl) phosphite was prepared using literature [58]. Trifluoromethanesulfonate anhydride (Tf$_2$O) was purchased from Oakwood Chemicals and used without further purification. All acid chlorides used in this study were commercially available and used without further purification. Reactions were monitored by silicagel thin layer chromatography (Sorbent Technologies) using ethyl acetate/hexane eluents. Visualization of compounds was accomplished with UV light and/or potassium permanganate stain and/or vanillin stain followed by heating. α-Ketophosphonates were prepared according to routine procedures and purified by vacuum distillation (unless noted otherwise). Purification of α-

phosphonovinyl triflates and α-alkynylphosphonates was carried out by flash column chromatography (using analytical grade silica gel 60, Sorbent Technologies, with ethyl acetate/hexane eluents) and/or vacuum distillation. All NMR spectra were taken using a Bruker DPX 300 MHz. ^{1}H-NMR spectra are reported in ppm with the sample dissolved in deuterated chloroform spiked with tetramethylsilane as an internal standard (TMS δ = 0.00 ppm). Data are reported as splitting pattern, coupling constant, and integration [s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintet, sex = sextet, b = broad; coupling constant(s) in Hz]. Proton-decoupled ^{13}C-NMR spectra are reported in ppm for samples dissolved in deuterated chloroform and using residual chloroform as internal standard (CHCl$_3$ δ = 77.0 ppm). Proton-decoupled ^{31}P-NMR spectra were recorded on a 300 MHz (121 MHz) spectrometer and are reported in ppm for samples dissolved in deuterated chloroform as solvent and using 85% phosphoric acid as an external standard (δ = 0.00 ppm).

9.1   Experimental for α-Ketophophonates

The experimental methods provided for the synthesis of the following α-ketophosphonates is separated into two synthetic protocols: Michaelis-Arbuzov reaction and Abramov reaction. The synthetic protocols for the preparation of α-ketophosphonates are given as general reaction procedures and are indicated by "M-A method" for the Michealis-Arbuzov procedure and by "Abr. method" for the Abramov procedure.

General Michaelis-Arbuzov Reaction Procedure

In a round-bottomed flask (oven-dried and cooled to r.t. under N_2 gas), triethylphosphite was loaded and cooled in a 0 °C ice water bath. Once the reaction flask was cooled to 0 °C, the corresponding acid chloride (1.0 eq.) was added dropwise by addition funnel slowly to maintain a temperature of approximately 0 °C. The reaction was allowed to gradually come to room temperature and stirred neat for 6 – 18 hours. After 6 – 18 hours stirring at room temperature, the reaction was placed under high vacuum with stirring to rid the reaction of ethyl chloride and volatile unreacted starting materials. Isolated crude product was purified via short-path vacuum distillation or column chromatography to afford the corresponding α-ketophosphonate. All of the α-ketophosphonates prepared by this method are known compounds and correspond to the ^{1}H NMR data reported in the literature.

General Abramov Reaction Procedure

In a round-bottomed flask (oven-dried and cooled to r.t. under N_2 gas), acid chloride was loaded and cooled in a 0 °C ice water bath. Once the reaction flask was cooled to 0 °C, diethyl (trimethylsilyl)phosphite (1.0 eq.) was added dropwise slowly to maintain a temperature of approximately 0 °C. The reaction was gradually warmed to room temperature and stirred neat for 4 – 6 hours. After 4 – 6 hours stirring at room temperature, the reaction was placed under high vacuum with stirring to rid the reaction of trimethylsilylchloride and to remove volatile, unreacted starting materials. The isolated crude product was purified via bulb-to-bulb vacuum distillation to afford the corresponding α-ketophosphonate.

Synthetic Procedure for:

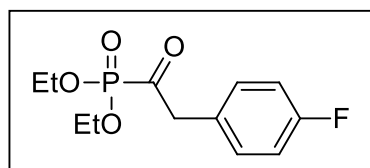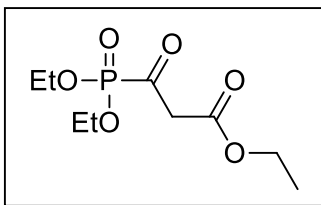**diethyl acetylphosphonate (3a)**
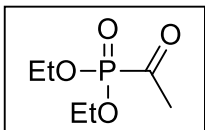
According to the general Michealis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (6.86 mL, 40.0 mmol) and acetyl chloride (2.84 mL, 40.0 mmol) was used to furnish **3a** (6.63 g, 92% yield) as a colorless liquid after short-path vacuum distillation (distillate came over between 54–58 °C under a vacuum of 0.384 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.38 (t, 6H, J = 7.2 Hz), 2.49 (d, 3H, J_{P-H} = 5.1 Hz), 4.18 - 4.28 (m, 4H). See Appendix C for structural data. [60]

Synthetic Procedure for:

diethyl propionylphosphonate (3b)
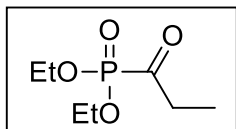
According to the general Michealis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (5.15 mL, 30.0 mmol) and propanoyl chloride (2.60 mL, 30.0 mmol) was used to furnish **3b** (4.43 g, 77% yield) as a colorless liquid after short-path vacuum distillation (distillate came over between 64–69 °C under a vacuum of 0.403 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.11 (t, 3H, 6.8 Hz), 1.38 (t, 6H, J = 7.2 Hz), 2.88 (dq, 2H, J_{P-H} = 5.1 Hz, J_{H-H} = 6.9 Hz), 4.20-4.28 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) -2.92; FT-IR (ATR, neat) v_{max}/cm[-1]: 3059, 2988, 2939, 2912, 1721, 1440, 1394, 1251, 1214, 1164, 1019, 972, 793, 733, 701. See Appendix C for structural data. [61]

Synthetic Procedure for:

diethyl pentanoylphosphonate (3c)
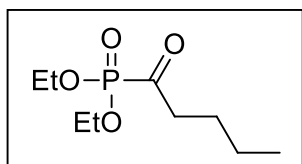
According to the general Michealis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (4.19 mL, 25.2 mmol) and valeryl chloride (3.04 mL, 25.2 mmol) was used to furnish **3c** (4.64 g, 83% yield) as a colorless liquid after short-path vacuum distillation (distillate came over between 82–86 °C under a vacuum of 0.457 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 0.94 (t, 3H, J = 7.5 Hz), 1.38 (t, 6H, J = 6.2 Hz), 1.63 (quin, 2H, J_{H-H} = 7.3 Hz), 4.18-4.27 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) -2.71; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2961, 2934, 2874, 1694, 1445, 1393, 1253, 1163, 1097, 1012, 968, 792, 742. See Appendix C for structural data. [62]

Synthetic Procedure for:

diethyl cyclobutanecarbonylphosphonate (3d)
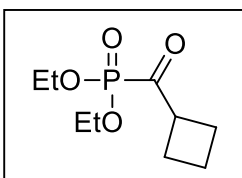
According to the general Michealis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (2.06 mL, 12.0 mmol) and (cyclobutyl)carbonyl chloride (1.37 mL, 12.0 mmol) was used to furnish **3d** (1.53 g, 58% yield) as a colorless liquid after short-path vacuum distillation (distillate came over between 75–78 °C under a vacuum of 0.401 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.37 (t, 6H, J = 7.2 Hz), 1.78-1.94 (m, 1H), 1.95-2.11(m, 1H), 2.17-2.42 (m, 4H), 3.78 (quin, 1H, J_{H-H} = 8.2 Hz), 4.16-4.26 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) 8.89; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2985, 295, 2875, 1703, 1393, 1372, 1183, 1011, 982, 774. See Appendix C for structural data. [63]

Synthetic Procedure for:

diethyl (2-phenylacetyl)phosphonate (3e)
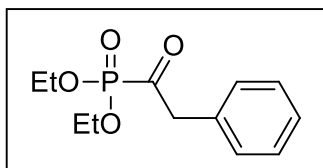
According to the general Miche“alis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (6.00 mL, 35.0 mmol) and phenylacetyl chloride (4.63 mL, 35.0 mmol) was used to furnish **3e** (7.71 g, 86% yield) as a colorless liquid after short-path vacuum distillation (distillate came over between 124–127 °C under a vacuum of 0.414 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.32 (t, 6H, J = 7.2 Hz), 4.09-4.20 (m, 6H), 7.20-7.23 (m, 2H), 7.28-7.37 (m, 3H); FT-IR (ATR, neat) v_{max}/cm^{-1}: 3062, 3032, 2985, 2932, 2905, 1704, 1449, 1390, 1221, 1203, 1164, 1014, 968, 796, 749, 695. See Appendix C for structural data. [64]

Synthetic Procedure for:

diethyl (2-(4-fluorophenyl)acetyl)phosphonate (3f)

According to the general Miche“alis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (3.43 mL, 20.0 mmol) and (4-fluorophenyl)acetyl chloride (2.74 mL, 20.0 mmol) was used to furnish **3f** (3.11 g, 57% yield) as a colorless liquid after short-path vacuum distillation (distillate came over between 114–120 °C under a vacuum of 0.890 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.36 (t, 6H, J = 5.4 Hz), 4.10-4.22 (m, 6H), 6.99-7.07 (m, 2H), 7.16-7.20 (m, 2H); ^{31}P-NMR (121 MHz, CDCl$_3$) 12.73; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3072, 2985, 2939, 2912, 1601, 1507, 1390, 1218, 1159, 1116, 1013, 970, 857, 828, 769. Appendix C for structural data.

Synthetic Procedure for:

ethyl 3-(diethoxyphosphoryl)-3-oxopropanoate (3g)

According to the general Michealis-Arbuzov reaction procedure shown above, a mixture of triethyl phosphite (1.71 mL, 10.0 mmol) and ethyl 3-chloro-3-oxopropanoate (1.23 mL, 10.0 mmol) was used to furnish **3g** (1.98 g, 78% yield) as a colorless liquid after flash column chromatography (50% EtoAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.30-1.40 (m, 9H), 4.15-4.29 (m, 6H), 5.88 (d, 1H, J_{P-H} = 10.2 Hz), 11.68 (d, 1H, J_{P-H} = 29.4 Hz). See Appendix C for structural data. [65]

Synthetic Procedure for:

diethyl (2-chloroacetyl)phosphonate (3h)
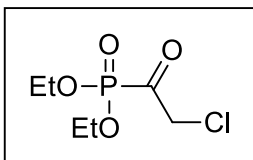
According to the general Abramov reaction procedure shown above, a mixture of diethyl (trimethylsilyl)phosphite (1.53 mL, 6.94 mmol) and chloroacetyl chloride (0.48 mL, 6.0 mmol) was used to furnish **3h** (0.4547 g, 35% yield) as a colorless liquid after bulb-to-bulb distillation (distillate came over between 84–90 °C under a vacuum of 0.401 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.40 (t, 6H, J = 7.2 Hz), 4.23-4.33 (m, 4H), 4.62 (d, 2H, J_{P-H} = 2.1 Hz, keto), 6.22 (d, 0.1H, J_{P-H} = 6.3 Hz, enol); ^{31}P-NMR (121 MHz, CDCl$_3$) δ -3.64. See Appendix C for structural data. This compound is known. [66]

Synthetic Procedure for:

diethyl (3,3,3-trifluoropropanoyl)phosphonate (3i)
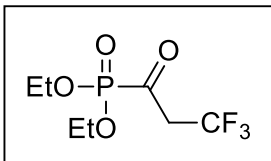
According to the general Abramov reaction procedure shown above, a mixture of diethyl (trimethylsilyl)phosphite (1.53 mL, 6.92 mmol) and 3,3,3-trifluoropropanoyl chloride (0.62 mL, 6.0 mmol) was used to furnish **3i** (0.9157 g, 61% yield) as a colorless liquid after bulb-to-bulb distillation (distillate came over between 70–76 °C under a vacuum of 0.403 mm Hg). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.38 (t, 6H, J = 6.9 Hz), 3.68 (dq, 2H, $J_{P\text{-}H}$ = 0.9 Hz, $J_{F\text{-}H}$ = 9.2 Hz) , 4.21-4.31 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) δ -4.19 (q, $J_{F\text{-}C}$ = 8.8 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) -4.91; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2982, 2939, 2915, 1711, 1366, 1252, 1155, 1098, 101, 976, 893, 792. See Appendix C for structural data.

9.2 Experimental for α-Phosphonovinyl Triflates

The experimental provided for the synthesis of the following α-phosphonovinyl triflates is separated into four synthetic procedures (Labeled: Method A, Method B, and Method C) based on substrate type of the corresponding α-ketophosphonate. See Appendix D for spectral data (^{1}H NMR, ^{13}C NMR, ^{31}P NMR, LRMS, HRMS, and IR).

<u>Method A</u>

In a round-bottomed flask, corresponding α-ketophosphonate was dissolved in anhydrous DCM (3 mL/mmol calculated based on starting material; 85% of total volume calculated was used to dissolve the α-ketophosphonate starting material) and cooled in a

0 °C ice/water bath. To this chilled solution, distilled Et_3N (1.1 eq.) was added and allowed to stir at 0 °C for 30 minutes; the reaction mixture remained as a colorless, homogenous solution. After 30 minutes, the reaction was cooled to -78 °C in a dry ice/acetone bath for 15 minutes. Then, a solution of DMAP (0.1 eq.) in anhydrous DCM (15% of total volume calculated was used to dissolved the 4-dimethylaminopyridine) was cannulated using an argon balloon into the reaction flask and allowed to stir for 5 minutes. After 5 minutes, Tf_2O (1.1 eq.) was added dropwise by syringe (turning the colorless solution to a pink color and then darkening to a light brown/pink over time for the alkyl substituents and turning the colorless solution to a mild yellow color for the aryl substituents). The reaction was allowed to gradually come to room temperature and determined complete by TLC after 25 hours for cases of alkyl substituents and 19 hours for cases of aryl substituents. The reaction was terminated by the addition of $DI-H_2O$ (~3x the total solvent volume) and extracted with DCM (5x ~15-20 mL). All the organic layers were combined and then washed with brine (1x ~20-25 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude isolate was purified by flash column chromatography on silica to give the desired product.

Method B

In a round-bottomed flask, corresponding α-ketophosphonate was dissolved in anhydrous DCM (5 mL/mmol calculated based on α-ketophosphonate) and cooled in a 0 °C ice/water bath. To this chilled solution, distilled Et_3N (4.0 eq.) was added and allowed to stir at 0 °C for 1 hour; the reaction mixture remained as a colorless, homogenous solution. After an hour, the reaction was cooled to -78 °C in a dry ice/acetone bath for 15

minutes. Then, Tf$_2$O (1.5 eq.) was added dropwise slowly by syringe, turning the colorless, homogenous solution to a yellow solution that darkened to a dark brown solution over time. The reaction mixture was allowed to gradually come to room temperature and determined by TLC to be complete after 16 hours. The reaction was terminated by the addition of DI-H$_2$O (~3x the total solvent volume) and extracted with DCM (5x ~15-20 mL). All the organic layers were combined and washed with brine (1x ~20-25 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude isolate was purified by flash column chromatography on silica to give the desired product.

Method C

In a round-bottomed flask, corresponding α-ketophosphonate was dissolved in anhydrous DCM (4 mL/mmol based on α-ketophosphonate) and cooled in a 0 °C ice/water bath. To this chilled solution, distilled Et$_3$N (1.1 eq.) was added and allowed to stir at 0 °C for 30 minutes; the reaction mixture remained as a colorless, homogenous solution. After a half hour, the reaction was cooled to -78 °C in a dry ice/acetone bath and allowed to cool for 15 minutes. Then, Tf$_2$O (1.1 eq.) was added dropwise slowly by syringe, turning the colorless, homogenous solution to a yellow/orange color that deepened in color over time. The reaction mixture was allowed to gradually come to room temperature and determined by TLC to be complete after 18 hours. The reaction was terminated by the addition of DI-H$_2$O (~3x the total solvent volume) and extracted with DCM (5x ~15-20 mL). All the organic layers were combined and washed with brine (1x ~20-25 mL), dried over anhydrous sodium sulfate, and concentrated under reduced

pressure. The crude isolate was purified by flash column chromatography on silica to give the desired product.

Synthetic Procedure for:

1-(diethoxyphosphoryl)vinyl trifluoromethanesulfonate (4a).
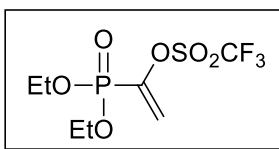
According to the procedure pertaining to Method A shown above, a mixture of diethyl acetylphosphonate (0.1950 g, 1.08 mmol), Et$_3$N (0.17 mL, 1.2 mmol), DMAP (0.0131 g, 0.108 mmol), Tf$_2$O (0.20 mL, 1.2 mmol) in dichloromethane (3.25 mL) afforded **4a** (0.2195 g, 65%) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.38 (t, 6H, J = 6.6 Hz), 4.13 - 4.27 (m, 4H), 6.04 (dd, 1H, J = 3.6 Hz, J_{P-H} = 31.2 Hz), 6.23 (dd, 1H, J = 3.9 Hz, J_{P-H} = 9.9 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 16.00 (d, J_{P-C} = 6.8 Hz), 63.78 (d, J_{P-C} = 6.0 Hz), 118.24 (q, J_{F-C} = 320 Hz), 121.91 (d, J_{P-C} = 22.6), 146.53 (d, J_{P-C} = 228.6 Hz) ^{31}P-NMR (124 MHz, CDCl$_3$) δ 3.01; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3035, 2989, 2945, 2912, 1628, 1422, 1249, 1208, 1137, 1014, 933, 799, 732; HRMS (Direct Probe: Methane Chem Ion) calculated for [C$_{10}$H$_{16}$F$_3$O$_6$PS + H] ([M + H]) 313.0123, observed 313.0111. See Appendix D for structural data.

Synthetic Procedure for:

**(*E*)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate (4b).**
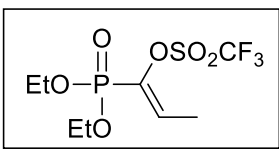
According to the procedure pertaining to Method A shown above, a mixture of diethyl propanoylphosphonate (2.0824 g,

10.7 mmol), Et$_3$N (1.64 mL, 11.8 mmol), DMAP (0.1316 g, 1.07 mmol), Tf$_2$O (1.98 mL, 11.8 mmol) in DCM (40 mL) afforded **4b** (2.7580 g, 78%) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.35 (t, 6H, J = 7 Hz), 1.97 (dd, 3H, J_{P-H} = 2.7 Hz, J = 7.2 Hz), 4.08 – 4.22 (m, 4H), 6.77 – 6.87 (m, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 12.60 (d, J_{P-C} = 11.3 Hz), 15.95 (d, J_{P-C} = 6.7 Hz), 63.24 (d, J_{P-C} = 5.2 Hz), 118.34 (q, J_{F-C} = 318 Hz), 138.28 (d, J_{P-C} = 25.5 Hz), 139.39 (d, J_{P-C} = 232 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 5.40; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2986 , 2936, 1657, 1413, 1263, 1207, 1137, 1055, 1014, 969, 839, 796, 733; HRMS (Direct Probe: Methane Chem Ion) calculated for [C$_8$H$_{14}$F$_3$O$_6$PS + H] ([M + H]) 327.0279, observed 327.0278. See Appendix D for structural data.

Synthetic Procedure for:

(*E*)-1-(diethoxyphosphoryl)pent-1-en-1-yl trifluoromethanesulfonate (4c).
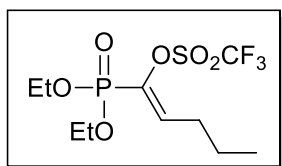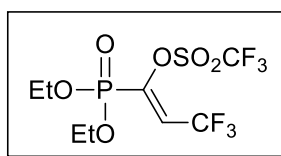

According to the procedure pertaining to Method B shown above, a mixture of diethyl pentanoylphosphonate (0.1379 g, 0.62 mmol), Et$_3$N (0.34 mL, 2.5 mmol), Tf$_2$O (0.16 mL g, 0.94 mmol) in DCM (3 mL) gave **4c** (0.1781 g, 62%) as a pale yellow liquid after flash column chromatography (50% EtOAc/50% Hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 0.98 (t, 3H, J = 7.5 Hz), 1.36 (t, 6H, J_{P-C} = 7.2 Hz, J_{P-C} = 6.9 Hz), 1.54 (sex, 2H, J = 7.2 Hz), 2.35 (dq, 2H, J_{P-H} = 2.7 Hz, J = 7.5 Hz), 4.08 – 4.23 (m, 4H), 6.69 – 6.77 (m, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.57 (s), 15.94 (d, J_{P-C} = 6.7 Hz), 21.17 (d, J_{P-C} = 0.75), 28.80 (d, J_{P-C} = 9.7 Hz), 63.19 (d, J_{P-C} = 5.2 Hz), 118.35 (q, J_{F-C} = 318 Hz), 138.11 (d, J_{P-C} = 230 Hz), 143.19 (d, J_{P-C} = 24 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 4.96;

FT-IR (ATR, neat) v_{max}/cm^{-1}: 2967, 2936, 2915, 2877, 1651, 1412, 1267, 1207, 1136, 1059, 1013, 976, 901, 840, 795; HRMS (Direct Probe: Methane Chem Ion) calculated for [$C_{10}H_{18}F_3O_6PS$ + H] ([M + H]) 355.0592, observed 355.0584. See Appendix D for structural data.

Synthetic Procedure for:

cyclobutylidene(diethoxyphosphoryl)methyl trifluoromethanesulfonate (4d).
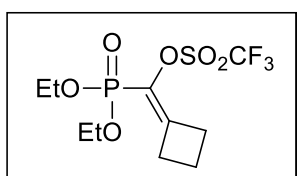
According to the procedure pertaining to Method B shown above, a mixture of diethyl (cyclobutylcarbonyl)phosphonate (0.1434 g, 0.65 mmol), Et$_3$N (0.36 mL, 2.6 mmol), Tf$_2$O (0.16 mL, 0.98 mmol) in DCM (3.5 mL) gave **4d** (0.1256 g, 54%) as a yellow liquid after flash column chromatography (40% EtOAc/60% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.36 (t, 6H, J_{P-H} = 7.2 Hz, J_{P-H} = 6.9 Hz), 2.14 (quin, 2H, J_{P-H} = 7.8 Hz, J_{P-H} = 8.1 Hz), 2.98 – 3.04 (m, 2H), 3.15 – 3.20 (m, 2H), 4.08 – 4.22 (m, 4H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 15.96 (d, J_{P-C} = 6 Hz), 16.56 (s), 30.17 (d, J_{P-C} = 12 Hz), 30.50 (d, J_{P-C} = 3 Hz), 62.90 (d, J_{P-C} = 5.2 Hz), 118.3 (q, J_{F-C} = 318 Hz), 129.81 (d, J_{P-C} = 235 Hz), 159.25 (d, J_{P-C} = 25 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 3.98; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2986, 2935, 2912, 1670, 1410, 1269, 1205, 1135, 1056, 1012, 975, 900, 847, 815, 764; HRMS (Direct Probe: Methane Chem Ion) calculated for [$C_{10}H_{16}F_3O_6PS$ + H] ([M + H]) 353.0436, observed 353.0444. See Appendix D for structural data.

Synthetic Procedure for:

(*E*)-1-(diethoxyphosphoryl)-2-phenylvinyl trifluoromethanesulfonate (4e).
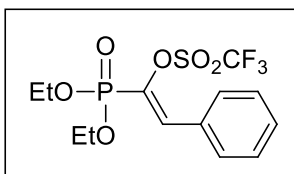
According to the procedure pertaining to Method A shown above, a mixture of diethyl (phenylacetyl)phosphonate (1.2866 g, 5.02 mmol), Et_3N (0.73 mL, 5.2 mmol), DMAP (0.0636 g, 0.52 mmol), Tf_2O (0.88 mL, 5.2 mmol) in DCM (15 mL) yielded **4e** (1.3072 g, 67%) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.40 (t, 6H, *J* = 7 Hz), 4.14 – 4.33 (m, 4H), 7.42 – 7.60 (m, 3H), 7.48 (d, 1H, J_{P-H} = 9.9 Hz), 7.57 – 7.62 (m, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 15.99 (d, J_{P-C} = 6.7 Hz), 63.42 (d, J_{P-C} = 5.2 Hz), 118.17 (q, J_{F-C} = 319 Hz), 128.83 (s, aryl), 129.83 (s, aryl), 130.83 (s, aryl), 130.02 (s, aryl), 136.69 (d, J_{P-C} = 230 Hz), 138.35 (d, J_{P-C} = 25.5 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 6.00; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3062, 3029, 2987, 2936, 2910, 1638, 1418, 1261, 1208, 1135, 1080, 1063, 1015, 979, 875, 729, 692; HRMS (Direct Probe) calculated for [C$_{13}$H$_{16}$F$_3$O$_6$PS] ([M+) 388.0357, observed 388.0352. See Appendix D for structural data.

Synthetic Procedure for:

(*E*)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)vinyl trifluoromethanesulfonate (4f).
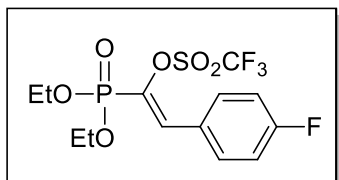
According to the procedure pertaining to Method A shown above, a mixture of diethyl [(4-fluorophenyl)acetyl]phosphonate (1.3771 g, 5.02 mmol), Et_3N (0.77 mL, 5.5 mmol), DMAP (0.0629 g, 0.514 mmol), Tf_2O (0.93 mL, 5.5 mmol) in DCM (15 mL) yieleded**4f** (1.4467 g, 71%) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.40

(t, 6H, J = 7.2 Hz), 4.15 – 4.30 (m, 4H), 7.09 – 7.17 (m, 2H), 7.44 (d, 1H, J_{P-H} = 9.9 Hz), 7.60 – 7.65 (m, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 16.01 (d, J_{P-C} = 6 Hz), 63.47 (d, J_{P-C} = 6 Hz), 116.16 (d, J_{F-C} = 21.7 Hz), 118.23 (q, J_{F-C} = 312 Hz), 126.13 (dq, J_{F-C} = 122 Hz, J_{P-C} = 3 Hz), 132.33 (d, J_{F-C} = 9 Hz), 136.52 (d, J_{F-C} = 227 Hz), 137.15 (d, J_{F-C} = 27 Hz), 163.86 (d, J_{P-C} = 252 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 5.87; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3032, 2988, 2942, 2912, 1642, 1603, 1509, 1417, 1263, 1207, 1163, 1134, 1012, 978, 878, 832, 774; HRMS (Direct Probe) calculated for [C$_{13}$H$_{15}$F$_4$O$_6$PS] ([M+]) 406.0263, observed 406.0263. See Appendix D for structural data.

Synthetic Procedure for:

(*E*)-ethyl 3-(diethoxyphosphoryl)-3-((((trifluoromethyl)sulfonyl)oxy)acrylate (4g).
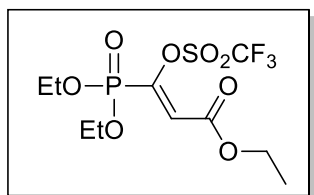
According to the procedure pertaining to Method C shown above, a mixture of ethyl 3-(diethoxyphosphoryl)-3-oxopropanoate (1.3539 g, 5.34 mmol), Et$_3$N (0.82 mL, 5.9 mmol), Tf$_2$O (0.99 mL, 5.9 mmol) in DCM (20 mL) gave **4g** (1.1530 g, 56%) as a white solid after flash column chromatography (50% EtOAc/50% hexanes). Melting point: 34-36 °C; ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.34 (t, 3H, J = 7.2 Hz), 1.38 (t, 6H, J_{P-H} = 7.2 Hz, J_{P-H} = 7.0 Hz) 4.11 – 4.28 (m, 4H), 4.32 (q, 2H, J = 7.2 Hz), 6.82 (d, 1H, J_{P-H} = 10.5 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.85 (s), 15.99 (d, J_{P-C} = 6.7 Hz), 62.23 (s), 64.11 (d, J_{P-C} = 6 Hz), 118.28 (q, J_{F-C} = 319 Hz), 126.75 (d, J_{P-C} = 24.7 Hz), 146.52 (d, J_{P-C} = 220 Hz), 161.18 (d, J_{P-C} = 18 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 3.17; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3061, 2995, 2949, 2914, 1725, 1650, 1427, 1267, 1246, 1197, 1138, 1072, 1012, 987, 964, 906, 847, 778, 754, 719; HRMS (Direct Probe: Methane

Chem Ion) calculated for [$C_{10}H_{16}F_3O_8PS$ + H] ([M + H]) 385.0334, found 385.0333. See

Appendix D and Appendix F for structural data.

Synthetic Procedure for:

(*E*)-2-chloro-1-(diethoxyphosphoryl)vinyl trifluoromethanesulfonate (4h).
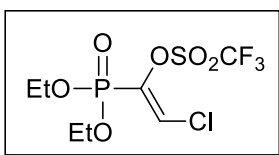
According to the procedure pertaining to Method C shown above, a mixture of diethyl (chloroacetyl)phosphonate (0.1748 g, 0.8140 mmol), (*about 50% pure estimated by ^{1}H NMR), Et$_3$N (0.13 mL, 0.93 mmol), and Tf$_2$O (0.16 mL, 0.93 mmol) in DCM (7 mL) afforded **4h** (0.0495 g, 18%) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.38 (t, 6H, J_{P-H} = 7.2 Hz, J_{P-H} = 6.9 Hz), 4.10 − 4.30 (m, 4H), 7.31 (d, 1H, J_{P-H} = 5.4 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 15.99 (d, J_{P-C} = 6.7 Hz), 64.03 (d, J_{P-C} = 5.2 Hz), 118.30 (q, J_{F-C} = 319 Hz), 131.15 (d, J_{P-C} = 39 Hz), 140.53 (d, J_{P-C} = 220 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 2.38; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3082, 3052, 2990, 2945, 2915, 1607, 1422, 1272, 1209, 1134, 1076, 1010, 981, 870, 838, 723; HRMS (Direct Probe: Methane Chem Ion) calculated for [$C_7H_{11}ClF_3O_6PS$ + H] ([M + H]) 346.9655, observed 346.9661. See Appendix D for structural data.

Synthetic Procedure for:

(*E*)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate (4i).

According to the procedure pertaining to Method D shown above, a mixture of diethyl (3,3,3-

trifluoropropanoyl)phosphonate (0.2421 g, 0.9756 mmol), Et$_3$N (0.16 mL, 1.1 mmol), Tf$_2$O (0.19 mL, 1.1 mmol) in DCM (9 mL) yielded **4i** (0.2325 g, 62%) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.40 (dt, 6H, J_{H-H} = 7.2 Hz, J_{P-H} = 0.6 Hz), 4.15 – 4.34 (m, 4H), 6.97 – 6.80 (m, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 15.94 (d, J_{P-C} = 6 Hz), 64.65 (d, J_{P-C} = 6 Hz), 118.21 (q, J_{F-C} = 319 Hz), 119.65 (dq, J_{F-C} = 271 Hz, J_{P-C} = 19 Hz), 125.60 (dq, J_{P-C} = 26.25 Hz, J_{F-C} = 10.5 Hz) 145.60 (dd, J_{P-C} = 215 Hz, J_{F-C} = 5.25); ^{31}P-NMR (121 MHz, CDCl$_3$) δ 1.63; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3075, 3052, 2991, 2942, 2915, 1668, 1427, 1306, 1262, 1216, 1150, 1132, 1062, 1012, 985, 887, 841, 781, 732, 663; HRMS (Direct Probe: Methane Chem Ion) calculated for [C$_8$H$_{11}$F$_6$O$_6$PS + H] ([M + H]) 380.9996, observed 380.9997. See Appendix D for structural data.

9.3   Experimental for α-Alkynylphosphonates

GENERAL REACTION PROCEDURE

In a round-bottomed flask, the corresponding α-phosphonovinyl triflate was dissolved in reagent grade dichloromethane (0.15 M or 6 mL/mmol of starting material), followed by the dropwise addition of base (DBU or DIPEA, 1.5 – 2.1 eq.) at room temperature. The reaction mixture was allowed to stir at r.t. and monitored by TLC using UV light and KMnO$_4$ stain. When the reaction was determined to be complete, it was diluted with ethyl acetate, followed by the addition of DI-H$_2$O, and extracted with ethyl acetate (3x ~15-20 mL), washed with brine (1x ~15-20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude isolate was subjected to purification by flash column

chromatography to give the desired α-alkynylphosphonate product. All of the α-alkynylphosphonates are known compounds and references are given within. See Appendix E for spectral data (^{1}H NMR and IR).

Synthetic Procedure for:

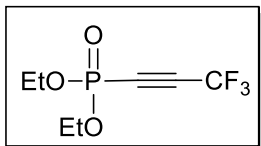**diethyl ethynylphosphonate (5a)**
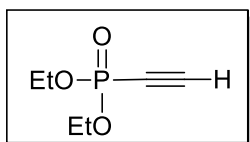
According to the general reaction procedure shown above, a mixture of 1-(diethoxyphosphoryl)vinyl trifluoromethanesulfonate (0.2357 g, 0.7549 mmol) and DBU (0.17 mL, 1.1 mmol) in DCM (4 mL) yielded **5a** (0.0582 g, 48% yield) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.39 (t, 6H, J = 6.9 Hz), 2.91 (d, 1H, J_{P-H} = 13.2 Hz), 4.15 – 4.25 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) -8.36; FT-IR (ATR, neat) v_{max}/cm^{-1}: 3172 (C≡C–H stretch), 2987, 2064 (C≡C stretch), 1394, 1253, 1164, 1099, 1014, 977, 772, 683. See Appendix E for structural data. [7]

Synthetic Procedure for:

diethyl prop-1-yn-1-ylphosphonate (5b).
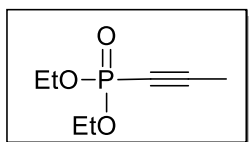
According to the general reaction procedure shown above, a mixture of (*E*)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate (0.2949 g, 0.9040 mmol) and DBU (0.27 mL, 1.8 mmol) in DCM (5 mL) yielded **5b** (0.0826 g, 56% yield) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300

MHz, CDCl$_3$/TMS) δ 1.37 (t, 6H, J = 7.2 Hz), 2.02 (d, 3H, J_{P-H} = 4.8 Hz), 4.10 – 4.20 (m,

4H); ^{31}P-NMR (121 MHz, CDCl$_3$) -6.31FT-IR (ATR, neat) v_{max}/cm^{-1}: 2985, 2919, 2213

(C̀≡C stretch), 1256, 1164, 1050, 1016, 972, 925, 797, 760, 728. See Appendix E for

structural data. [67]

Synthetic Procedure for:

diethyl pent-1-yn-1-ylphosphonate (5c).
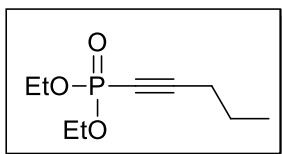
According to the general reaction procedure shown above, a mixture of (*E*)-1-(diethoxyphosphoryl)pent-1-en-1-yl trifluoromethanesulfonate (0.1289 g, 0.3638 mmol) and DBU

(0.08 mL, 0.5 mmol) in DCM (4 mL) gave **5c** (0.0497 g, 67% yield) as a pale yellow

liquid after flash column chromatography (30% EtOAc/70% hexanes). ^{1}H-NMR (300

MHz, CDCl$_3$/TMS) δ 1.02 (t, 3H, J = 7.3 Hz), 1.37 (t, 6H, J = 7.1 Hz), 1.62 (sex, 2H, J =

7.2 Hz), 2.33(dt, 2H, J_{P-H} = 4.5 Hz, J_{H-H} = 7.2 Hz), 4.08 – 4.20 (m, 4H); ^{31}P-NMR (121

MHz, CDCl$_3$) -6.10; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2969, 2934, 2907, 2874, 2204 (C̀≡C

stretch), 1257, 1164, 1098, 1017, 994, 970, 791, 757. See Appendix E for structural data.

[11]

Synthetic Procedure for:

diethyl (phenylethynyl)phosphonate (5e).
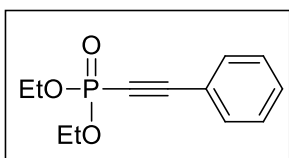
According to the general reaction procedure shown above, a mixture of (*E*)-1-(diethoxyphosphoryl)-2-phenylvinyl trifluoromethanesulfonate (0.1335 g, 0.3438 mmol) and DBU

(0.08 mL, 0.5 mmol) in DCM (5 mL) gave **5e** (0.0785g, 95% yield) as a pale yellow liquid after silica plug purification. ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.41 (t, 6H, J = 7.1 Hz), 4.19 – 4.29 (m, 4H), 7.35 – 7.41 (m, 2H), 7.43 – 7.46 (m, 1H), 7.55 – 7.58 (m, 2H); ^{31}P-NMR (121 MHz, CDCl$_3$) -5.96; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2982, 2185 (C≡C stretch), 1258, 1226, 1163, 1014, 972, 853, 797, 756, 689. See Appendix E for structural data. [16]

Synthetic Procedure for:

diethyl ((4-fluorophenyl)ethynyl)phosphonate (5f).
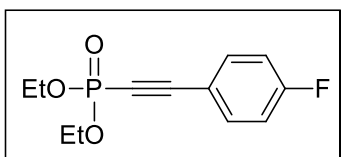
According to the general reaction procedure shown above, a mixture of (*E*)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)vinyl trifluoromethanesulfonate (0.1290 g, 0.3175 mmol) and DBU (0.07 mL, 0.5mmol) in DCM (5 mL) gave **5f** (0.0763g, 94% yield) as a pale yellow liquid after silica plug purification. ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.41 (t, 6H, J = 7.1 Hz), 4.18 – 4.29 (m, 4H), 7.05 – 7.12 (m, 2H), 7.55 – 7.59 (m, 2H); ^{31}P-NMR (121 MHz, CDCl$_3$) -6.14; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2989, 2939, 2905, 2187(C≡C stretch), 1506, 1262, 1235, 1016, 866, 838, 795, 728. See Appendix E for structural data. [19]

Synthetic Procedure for:

ethyl 3-(diethoxyphosphoryl)propiolate (5g).
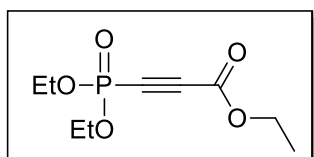
According to the general reaction procedure shown above, a mixture of ethyl (*E*)-ethyl 3-(diethoxyphosphoryl)-3-

((((trifluoromethyl)sulfonyl)oxy)acrylate (0.1390 g, 0.3617 mmol) and DIPEA (0.13 mL, 0.72 mmol) in DCM (3.5 mL) afforded **5g** (0.0803 g, 94% yield) as a pale yellow liquid after silica plug purification. ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.31 − 1.43 (m, 9H), 4.18 − 4.34 (m, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$/TMS) δ 13.76, 15.91 (d, J_{P-C} = 6.7 Hz), 62.98, 64.00 (d, J_{P-C} = 5.2 Hz), 74.65 (d, J_{P-C} = 278 Hz), 86.63 (d, J_{P-C} = 46 Hz), 151.42 (d, J_{P-C} = 6 Hz); ^{31}P-NMR (121 MHz, CDCl$_3$) δ -9.62. FT-IR (ATR, neat) v_{max}/cm^{-1}: 2994, 1717, 1235, 1164, 1011, 962, 856, 802, 771, 748, 724. See Appendix E for structural data. [67]

Synthetic Procedure for:

diethyl (chloroethynyl)phosphonate (5h).
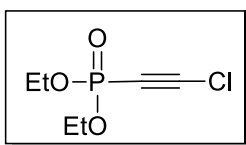
According to the general reaction procedure shown above, a mixture of (*E*)-2-chloro-1-(diethoxyphosphoryl)vinyl trifluoromethanesulfonate (0.0338 g, 0.0975 mmol) and DIPEA 0.04 mL, 0.2 mmol) in DCM (2.5 mL) gave **5h** (0.0092 g, 48% yield) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.38 (t, 6H, J = 7.2 Hz), 4.12 − 4.23 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) -8.40; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2986, 2174 (C̀≡C stretch), 1394, 1260, 1163, 1098, 1012, 961, 796, 752. See Appendix E for structural data. [68]

Synthetic Procedure for:

diethyl (3,3,3-trifluoroprop-1-yn-1-yl)phosphonate (5i).

According to the general reaction procedure shown above, a mixture of (*E*)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate (0.0560 g, 0.1473 mmol) and DIPEA (0.03 mL, 0.1 mmol) in DCM (2 mL) afforded **5i** (0.0224 g, 40% yield) as a colorless liquid after flash column chromatography (50% EtOAc/50% hexanes). ^{1}H-NMR (300 MHz, CDCl$_3$/TMS) δ 1.42 (t, 6H, *J* = 7 Hz), 4.20 – 4.34 (m, 4H); ^{31}P-NMR (121 MHz, CDCl$_3$) -11.31; FT-IR (ATR, neat) v_{max}/cm^{-1}: 2988, 2943, 2913, 2235 (C≡C stretch), 1628, 1278, 1249, 1220, 1148, 1099, 1013, 984, 880, 797, 761. See Appendix E for structural data. [69]

APPENDIX A

α-OXOKETENE DIMETHYLTHIOACETAL

SPECTRAL DATA
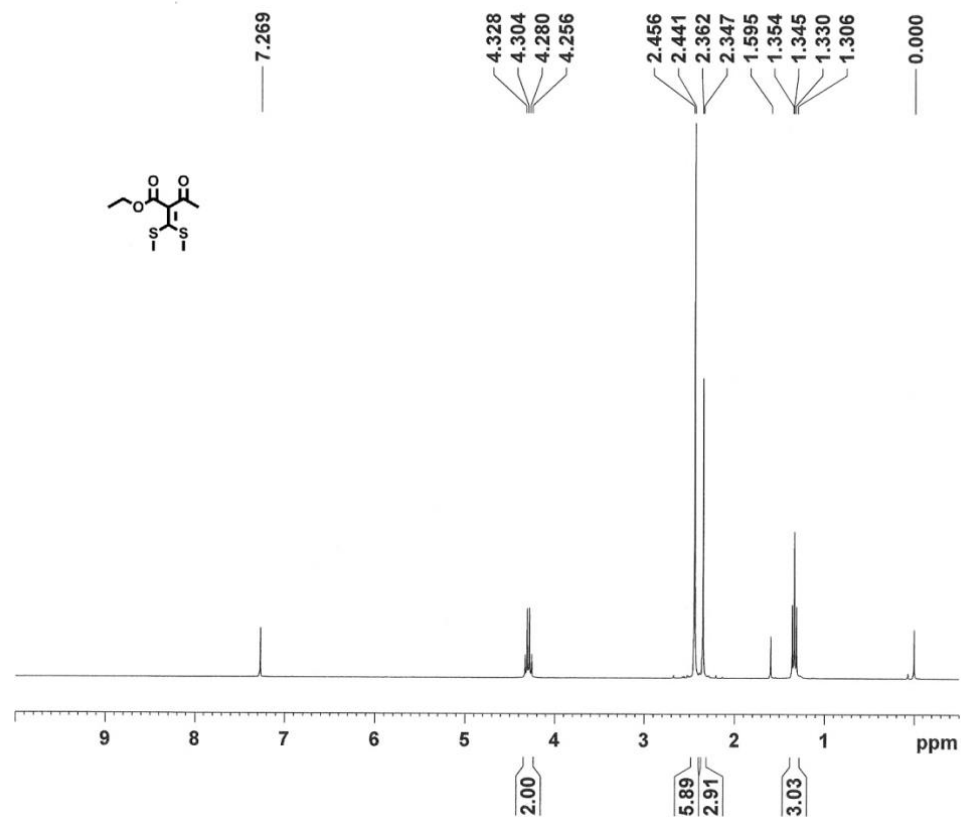
Figure A. 1. ^{1}H NMR spectrum of 1a
ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate
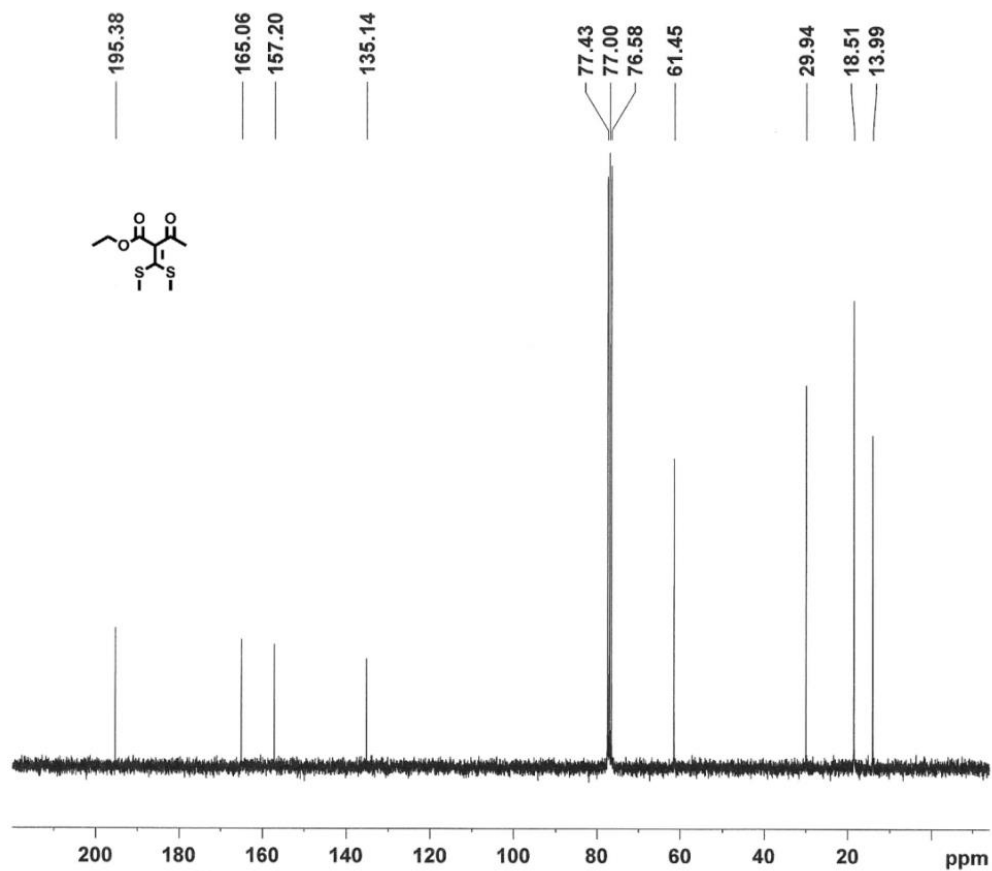
Figure A. 2. ^{13}C NMR spectrum of 1a
ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate
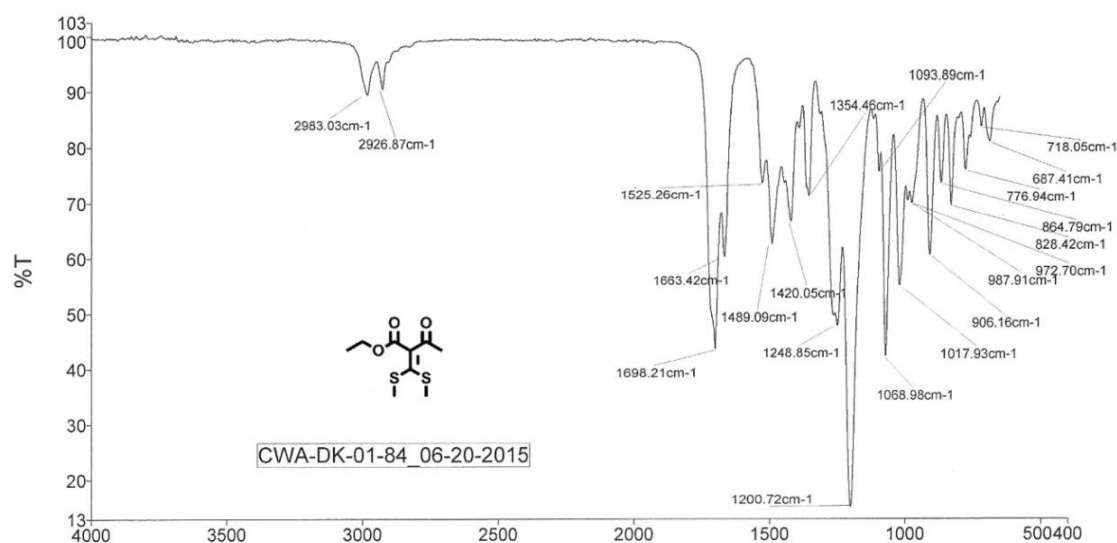
Figure A. 3. FT-IR spectrum of 1a
ethyl 2-[bis(methylsulfanyl)methylidene]-3-oxobutanoate

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Figure A. 4. ¹H NMR spectrum of 1b
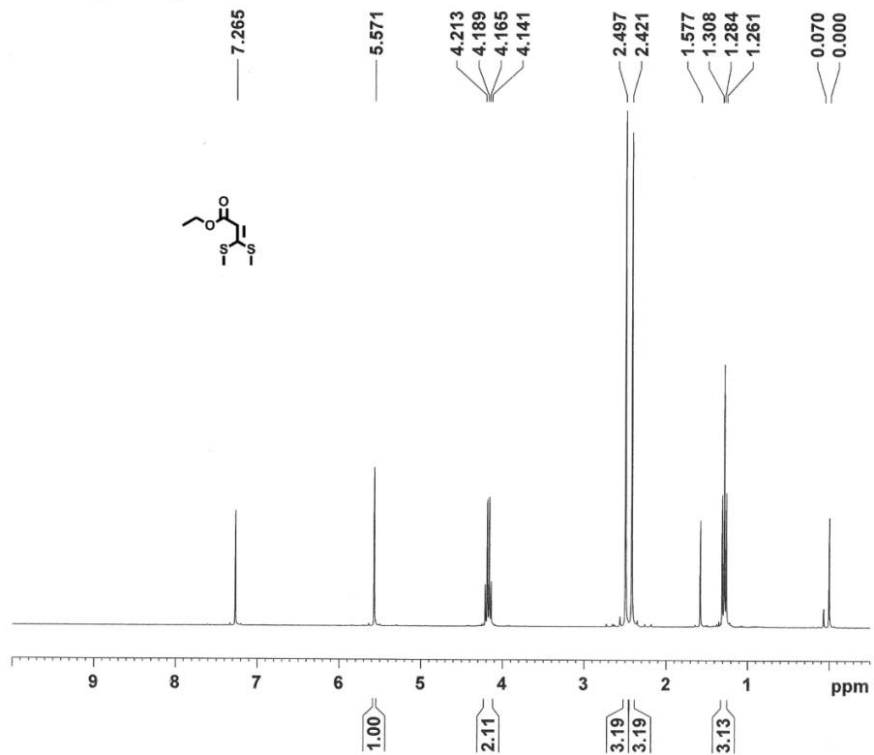
Figure A. 4. ^{1}H NMR spectrum of 1b
Ethyl 3,3-bis(methylsulfanyl)prop-2-enoate
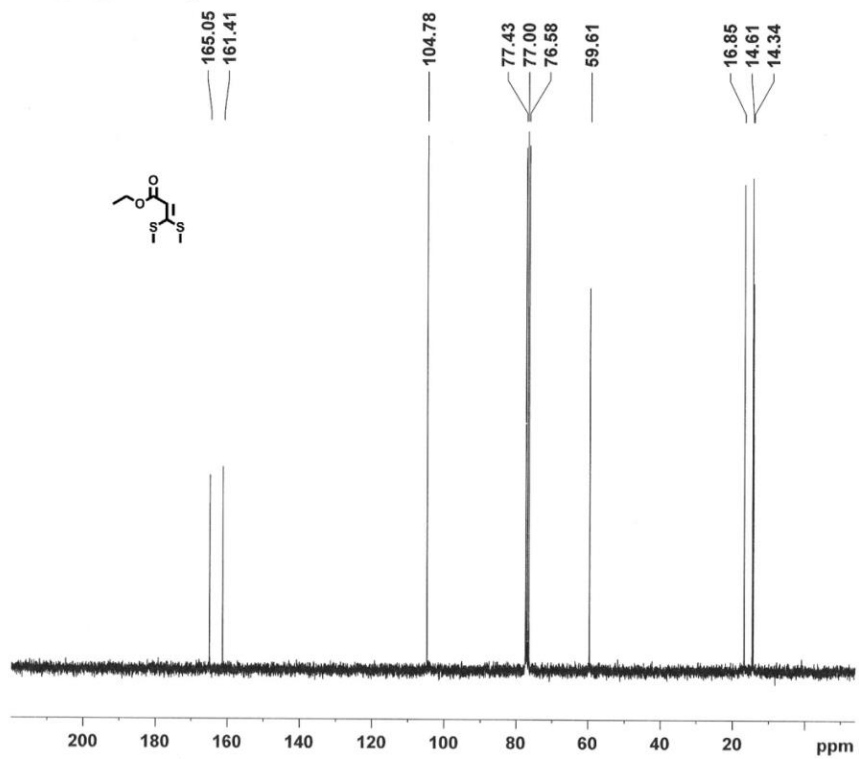
Figure A. 5. ^{13}C NMR spectrum of 1b
Ethyl 3,3-bis(methylsulfanyl)prop-2-enoate

132
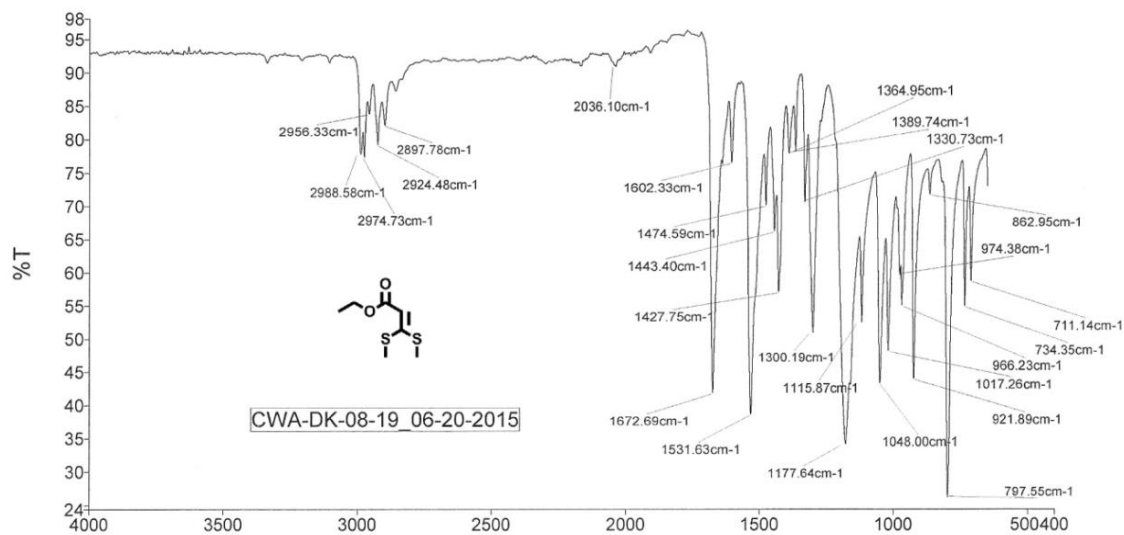
Figure A. 6. FT-IR spectrum of 1b
Ethyl 3,3-bis(methylsulfanyl)prop-2-enoate
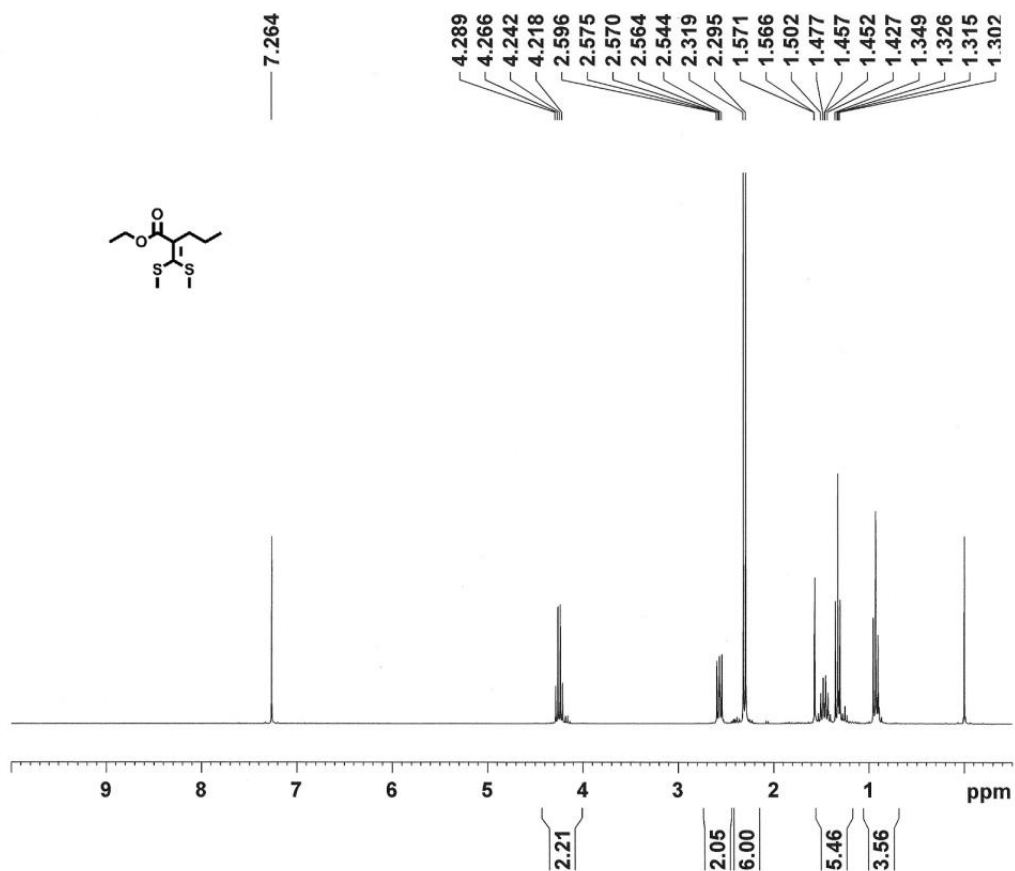
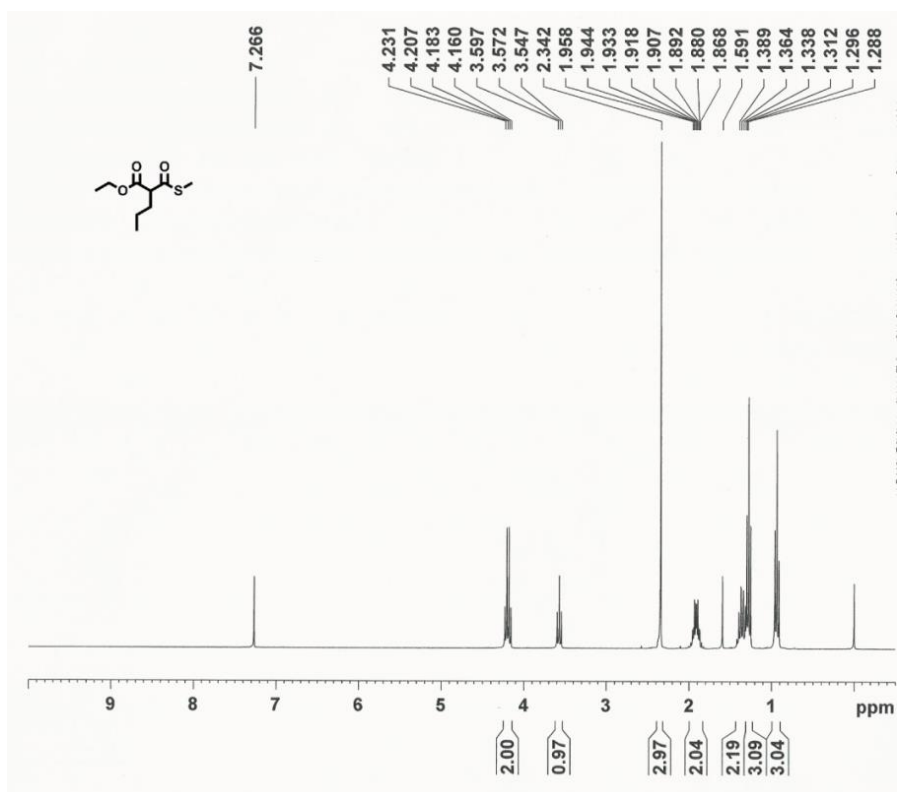**Figure A. 7. ^{1}H NMR spectrum of 1c**
Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate
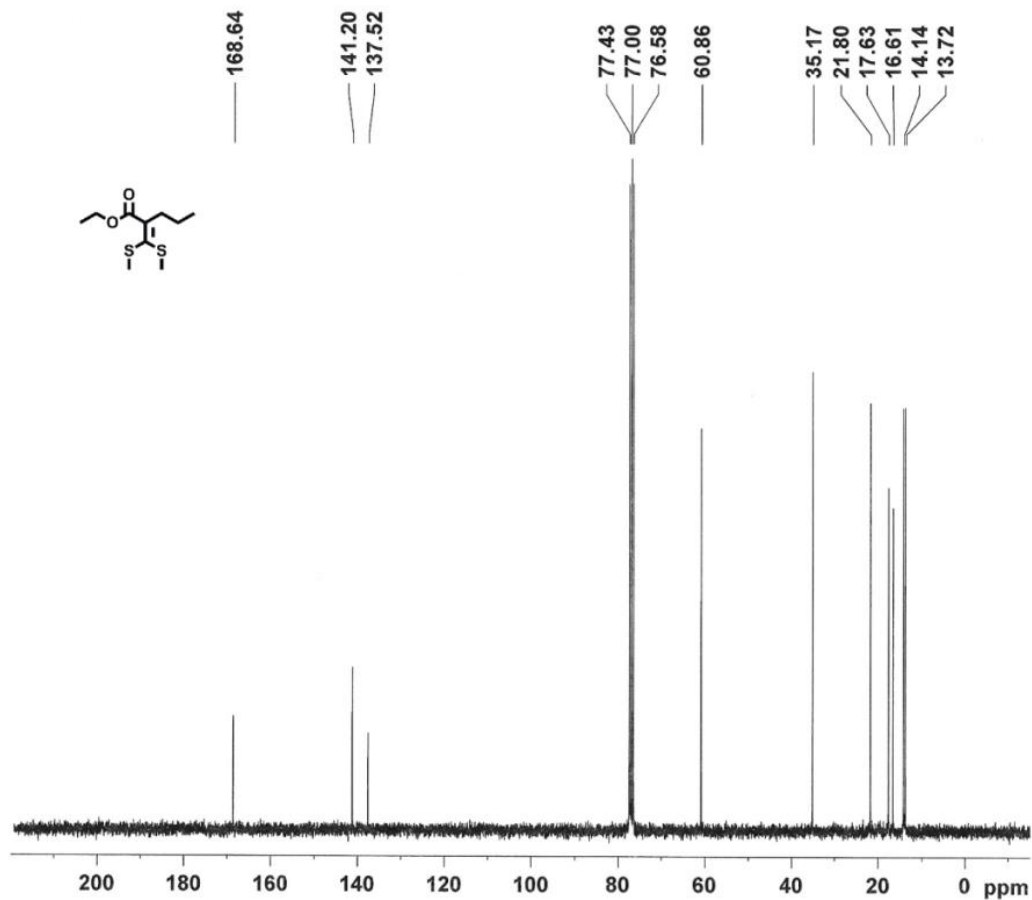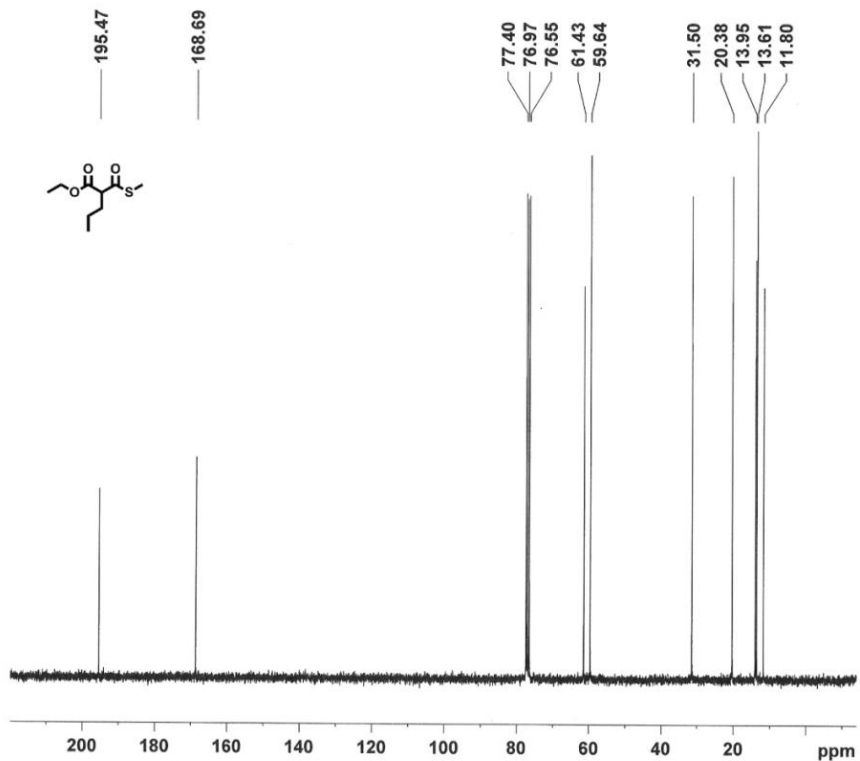
Figure A. 8. ¹³C NMR spectrum of 1c
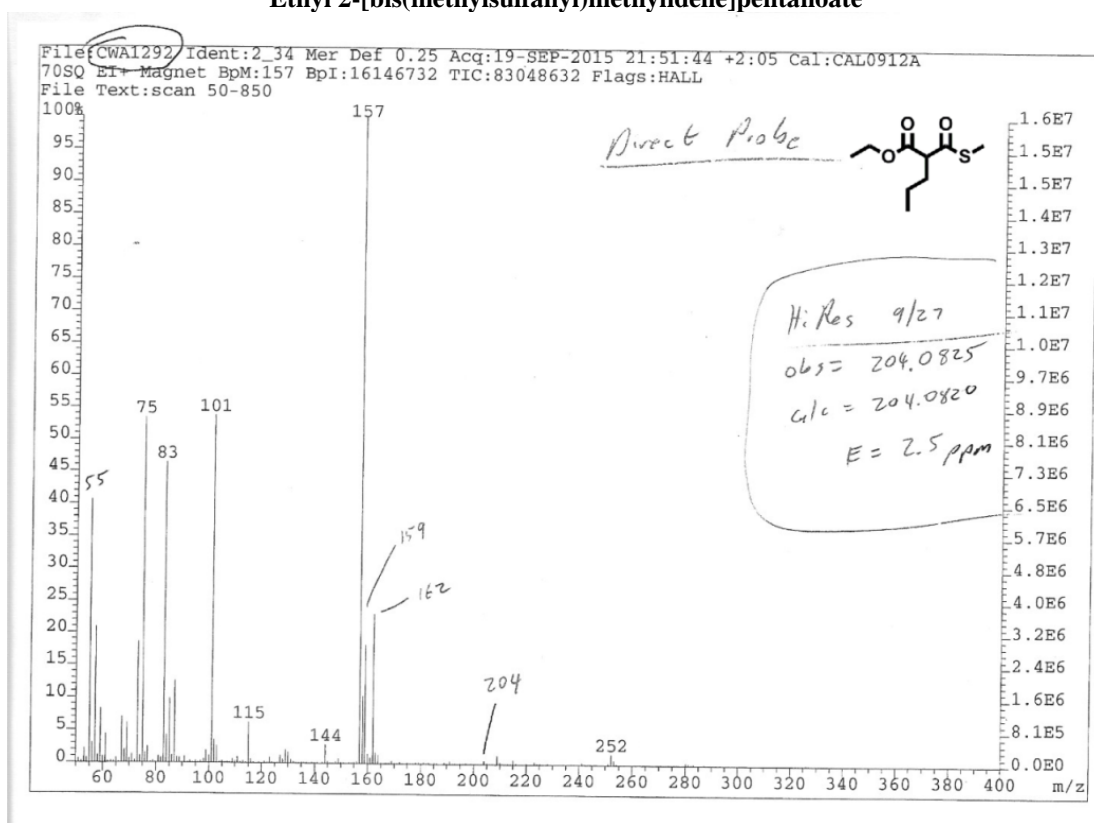**Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate**
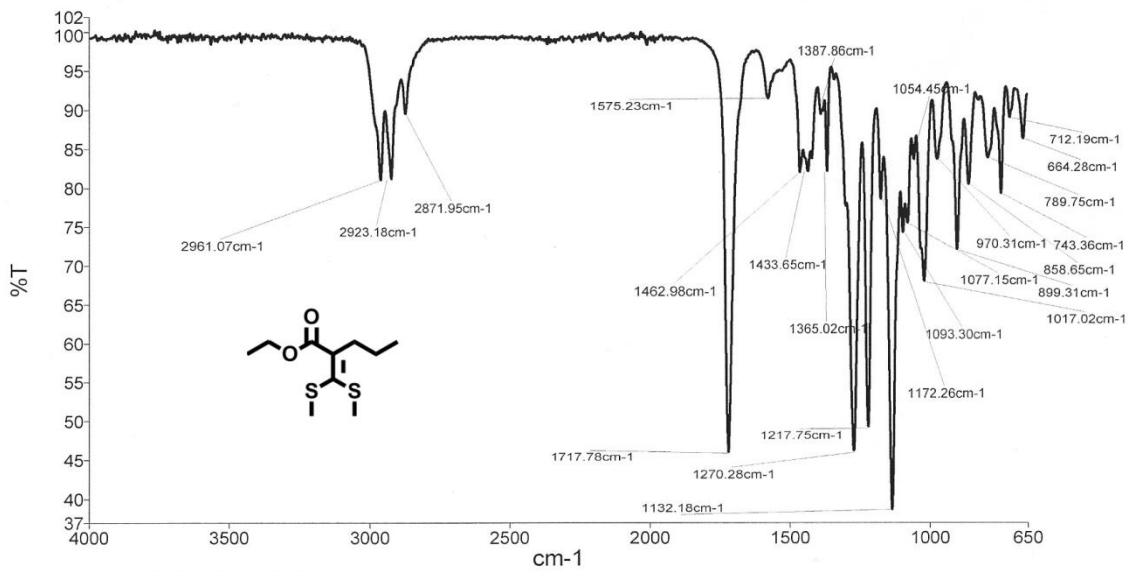
Figure A. 9. FT-IR spectrum of 1c
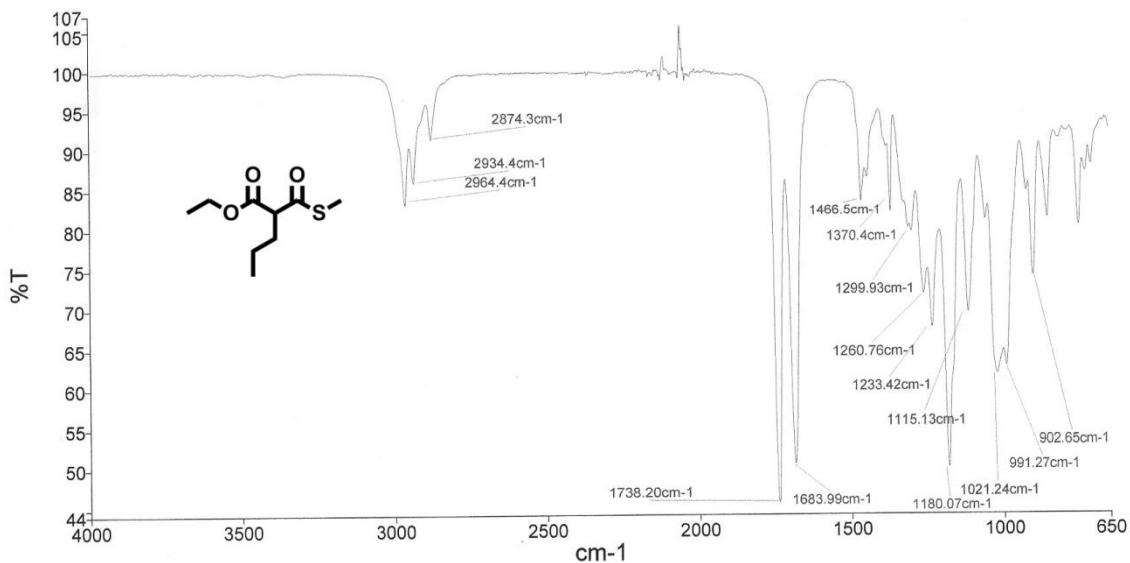**Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate**
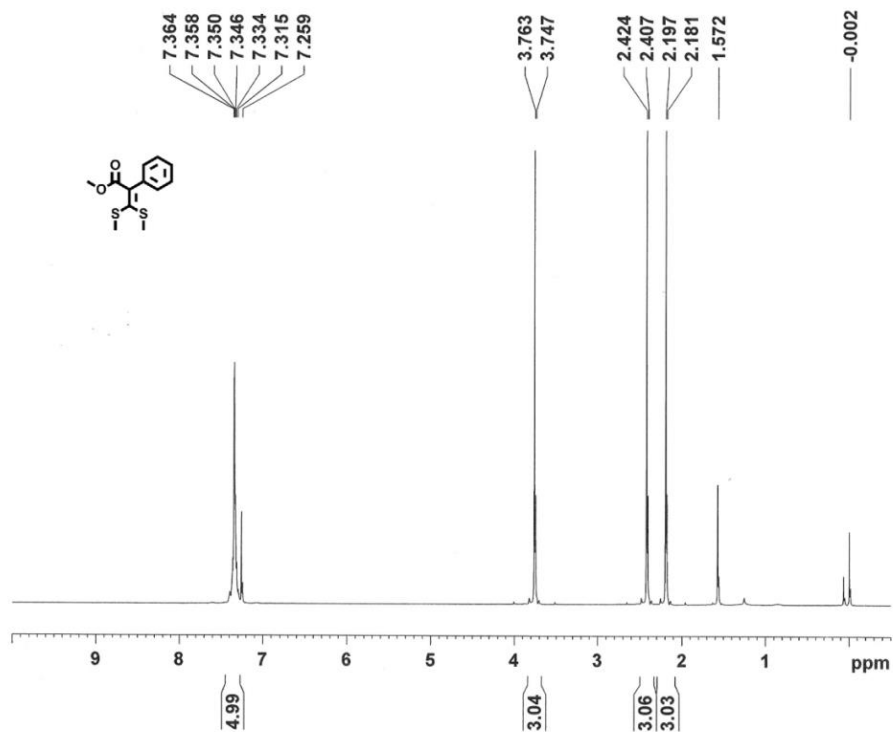
Figure A. 10. ^{1}H NMR spectrum of 1d
Methyl 3,3-bis(methylsulfanyl)-2-phenylprop-2-enoate
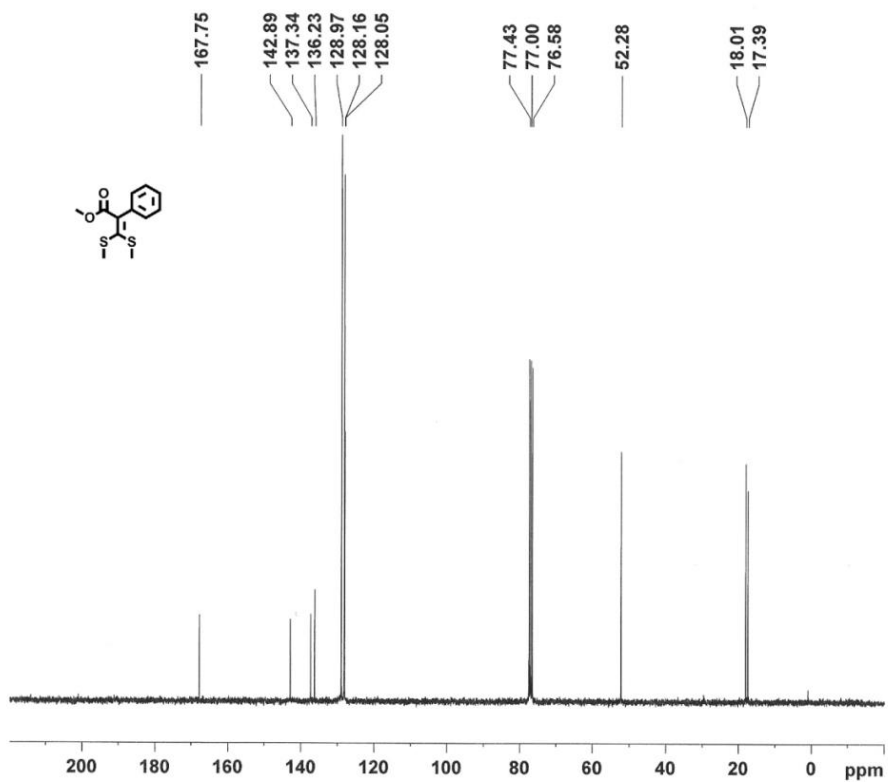
Figure A. 11. ^{13}C NMR spectrum of 1d
Methyl 3,3-bis(methylsulfanyl)-2-phenylprop-2-enoate
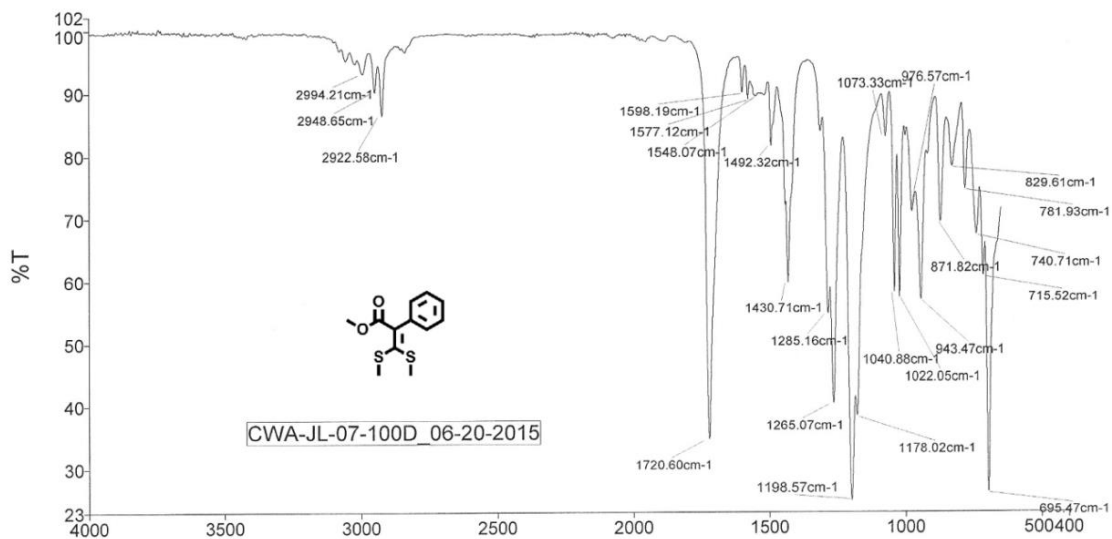
Figure A. 12. FT-IR spectrum of 1d
Methyl 3,3-bis(methylsulfanyl)-2-phenylprop-2-enoate
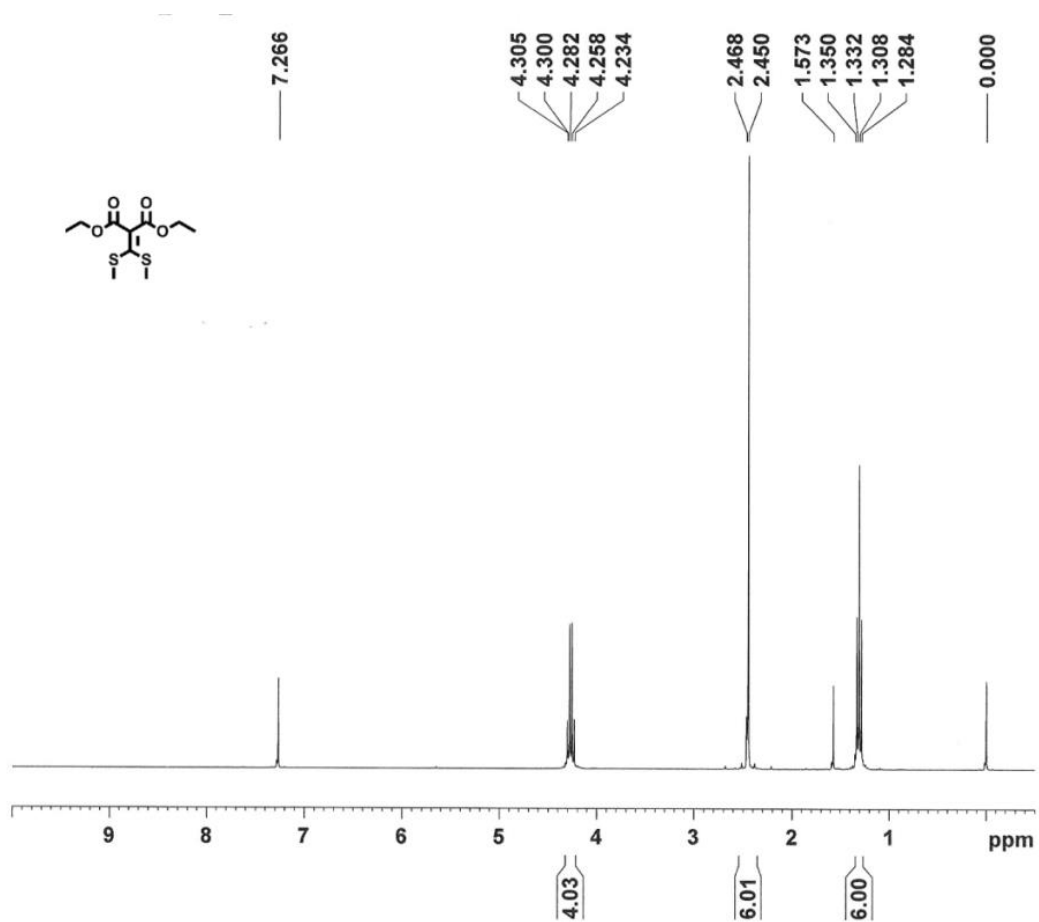
Figure A. 13. ¹H NMR spectrum of 1e
Diethyl [bis(methylsulfanyl)methylidene]propanedioate

136
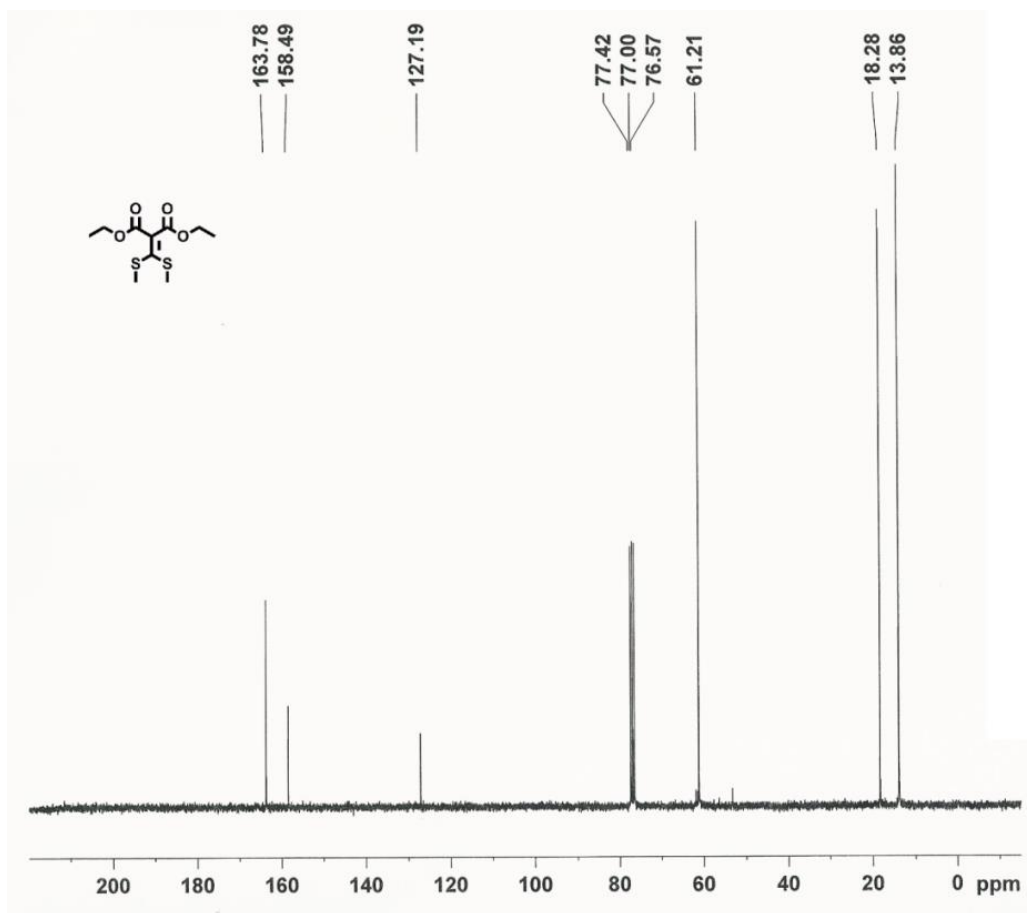
Figure A. 14. ^{13}C NMR spectrum of 1e
Diethyl [bis(methylsulfanyl)methylidene]propanedioate
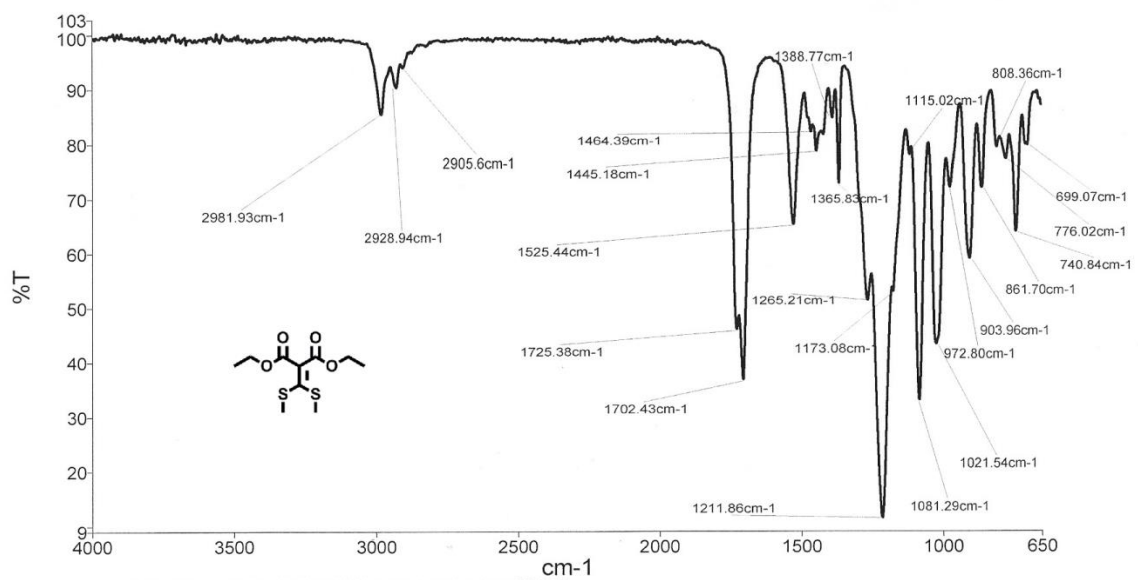
Figure A. 15. FT-IR spectrum of 1e
Diethyl [bis(methylsulfanyl)methylidene]propanedioate

137
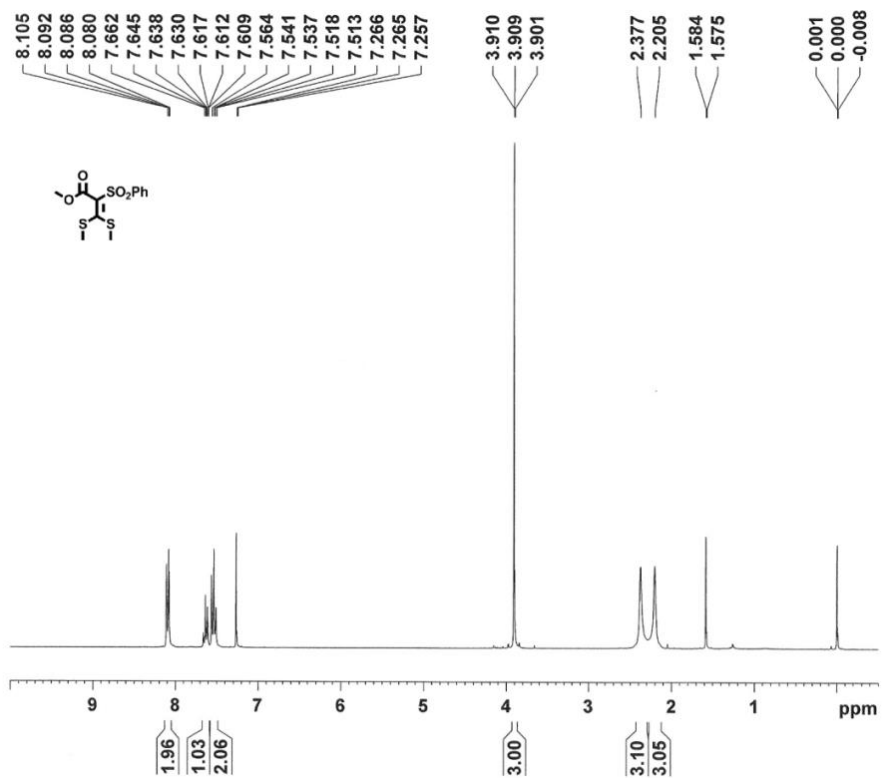
Figure A. 16. ^{1}H NMR spectrum of 1f
Methyl 3,3-bis(methylsulfanyl)-2-(phenylsulfonyl)prop-2-enoate
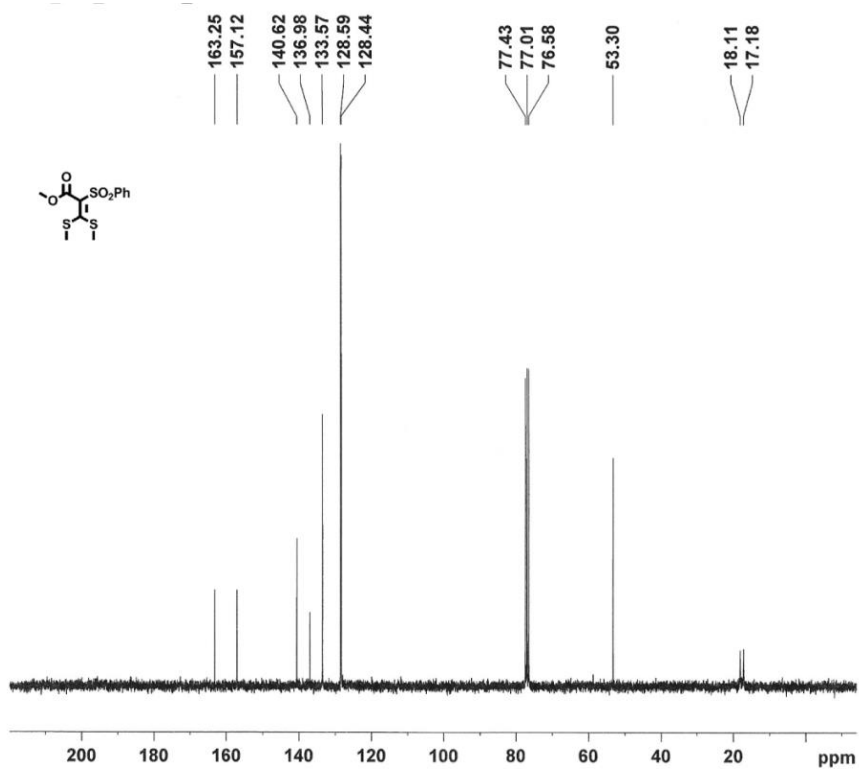
Figure A. 17. ^{13}C NMR spectrum of 1f
Methyl 3,3-bis(methylsulfanyl)-2-(phenylsulfonyl)prop-2-enoate
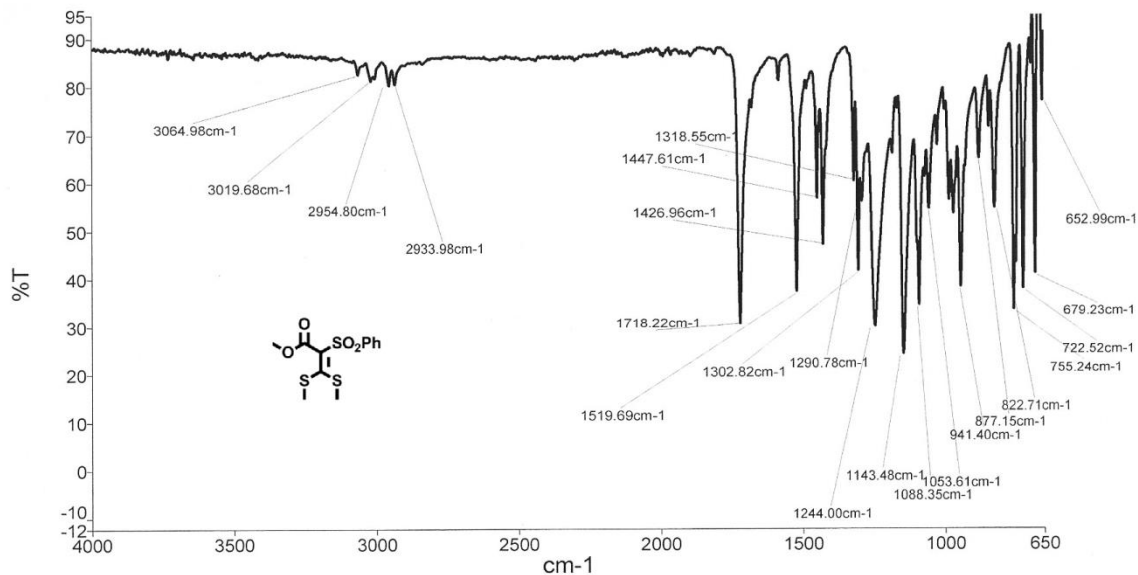
Figure A. 18. FT-IR spectrum of 1f
Methyl 3,3-bis(methylsulfanyl)-2-(phenylsulfonyl)prop-2-enoate
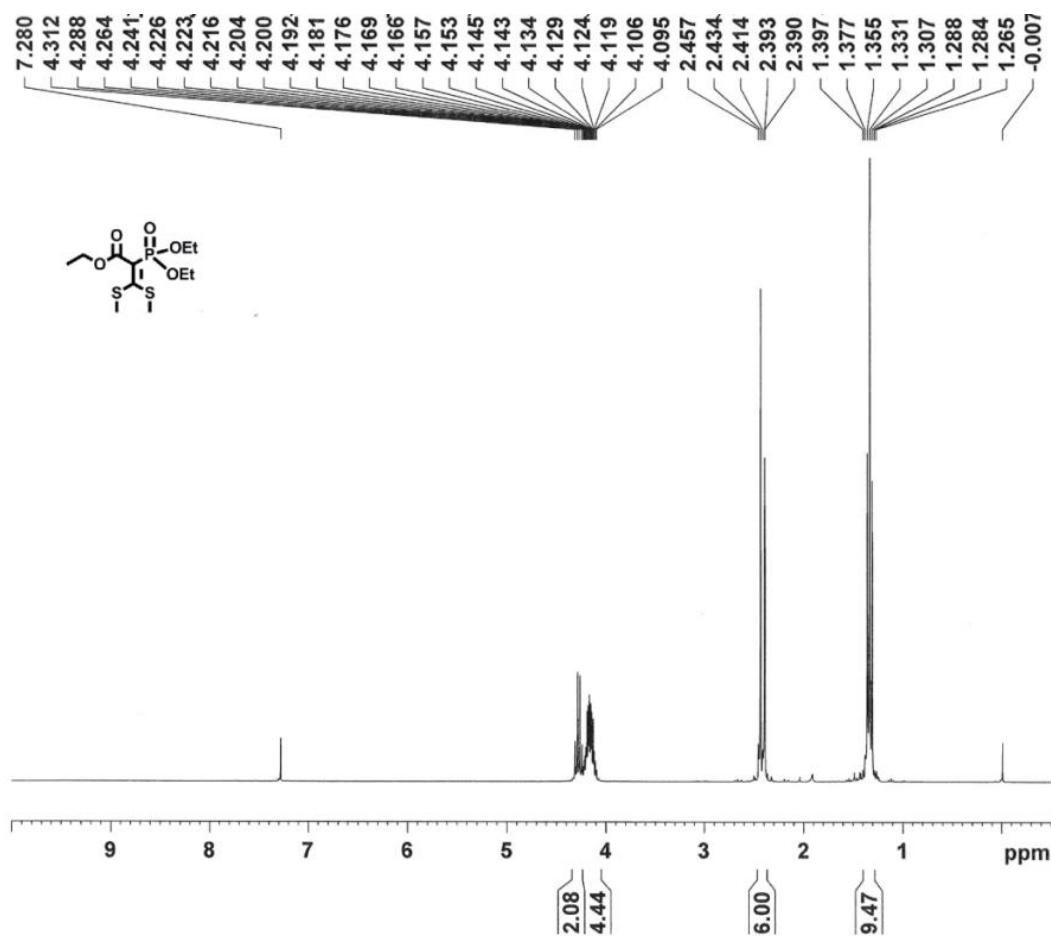
Figure A. 19. ^{1}H NMR spectrum of 1g
Ethyl 3,3-bis(methylsulfanyl)prop-2-(diethylphosphono)acetate
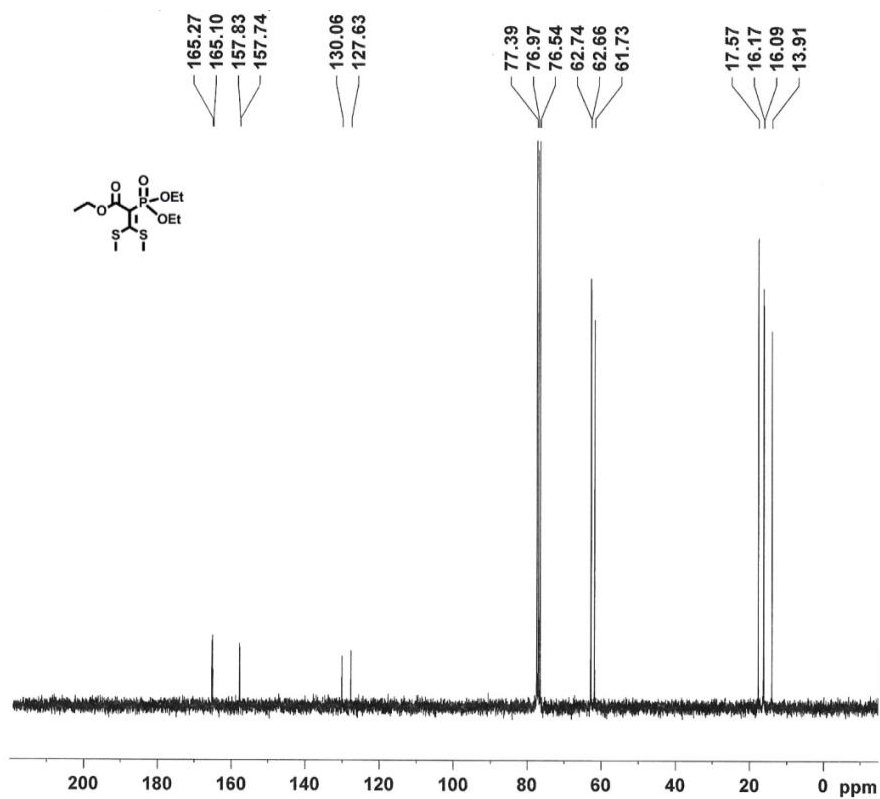
Figure A. 20. ¹³C NMR spectrum of 1g

Figure A. 20. ^{13}C NMR spectrum of 1g
Ethyl 3,3-bis(methylsulfanyl)prop-2-(diethylphosphono)acetate
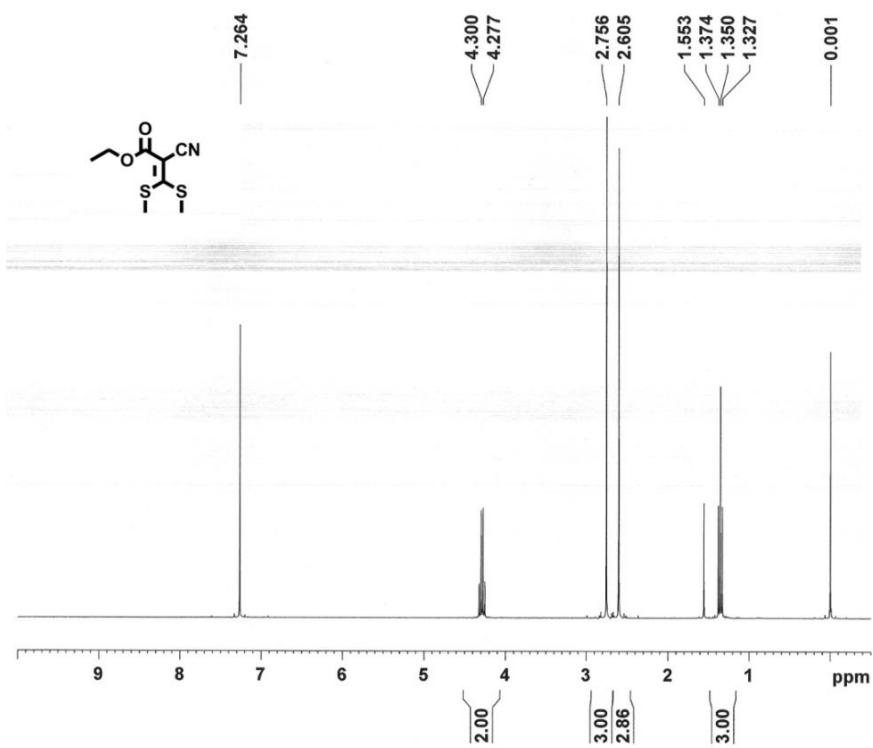
Figure A. 21. ^{1}H NMR spectrum of 1h
Ethyl 3,3-bis(methylsulfanyl)prop-2-cyanoacetate
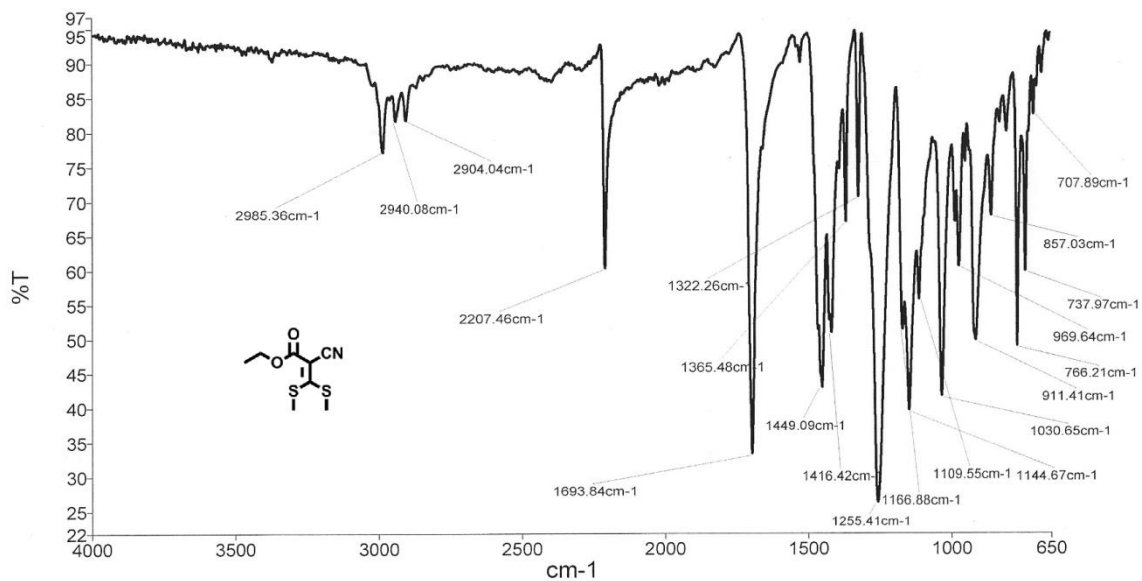
Figure A. 22. FT-IR spectrum of 1h
Ethyl 3,3-bis(methylsulfanyl)prop-2-cyanoacetate
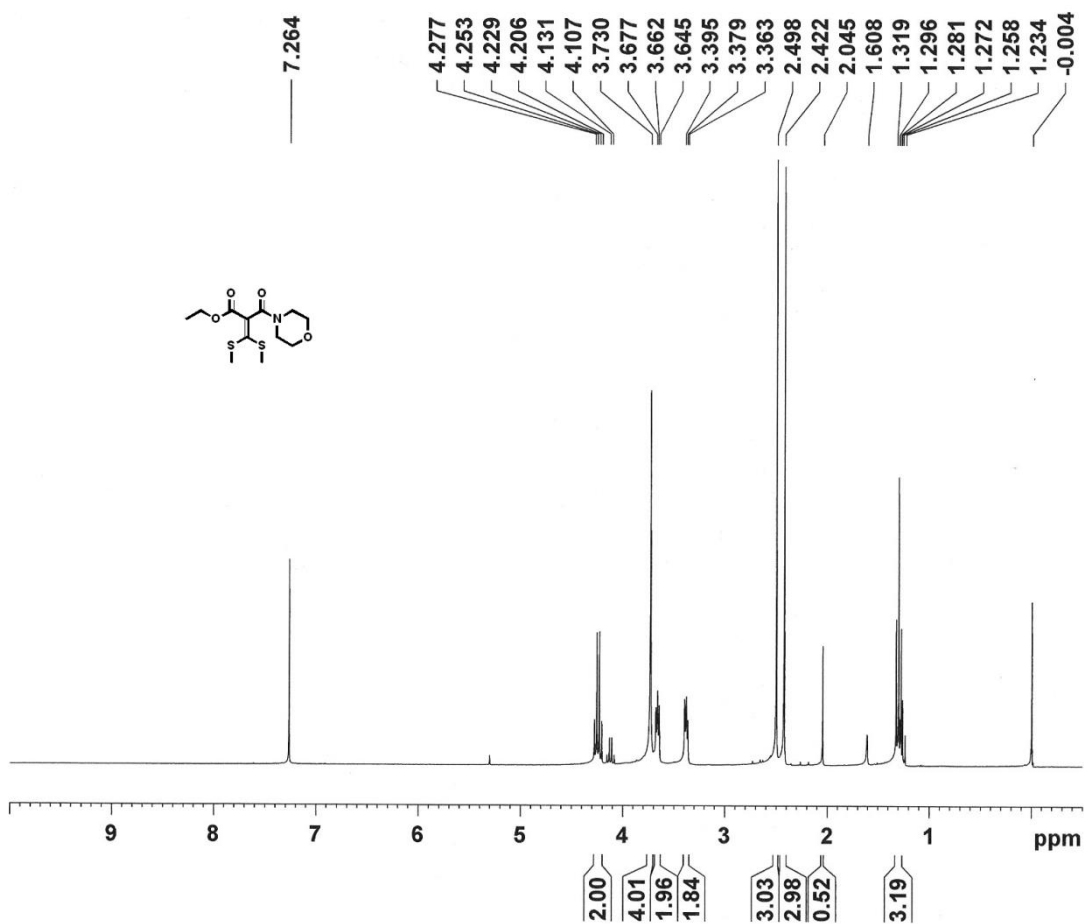
Figure A. 23. ^{1}H NMR spectrum of 1i
Ethyl 3,3-bis(methylsulfanyl)-2-(morpholin-4-yl)propanoate

141
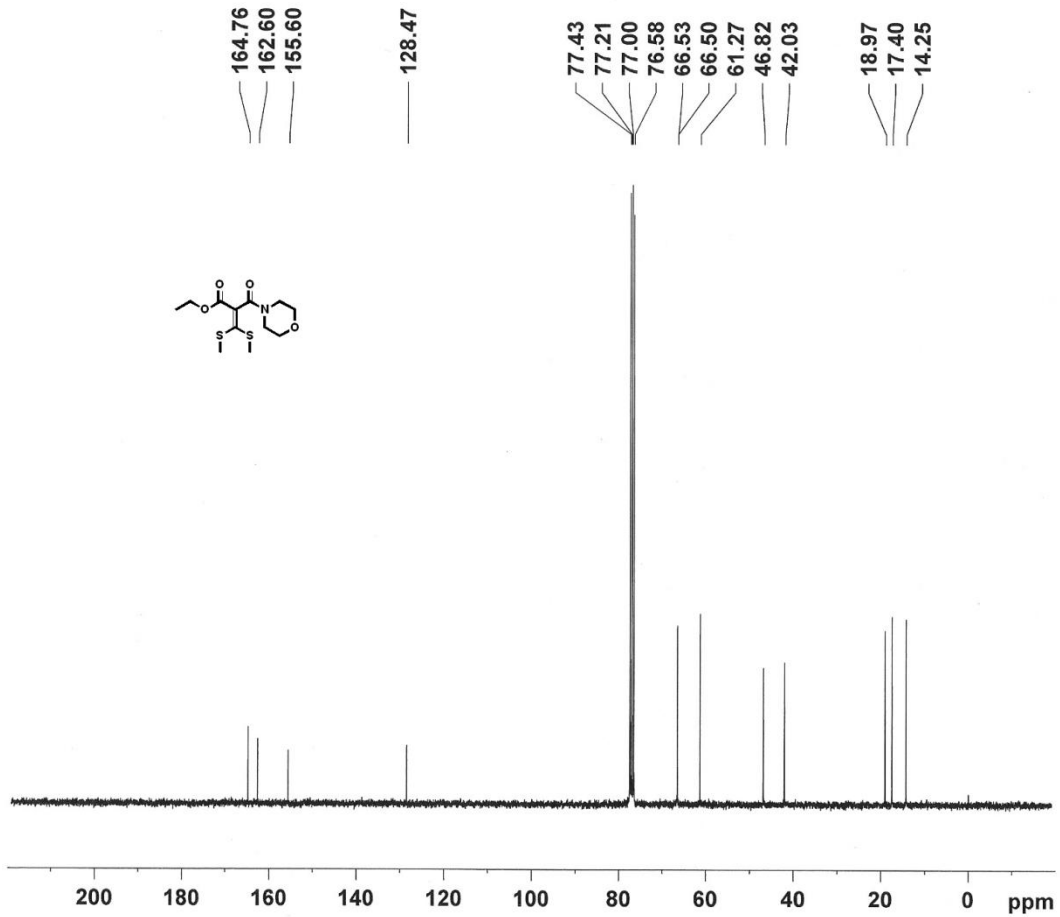
Figure A. 24. ^{13}C NMR spectrum of 1i
Ethyl 3,3-bis(methylsulfanyl)-2-(morpholin-4-yl)propanoate
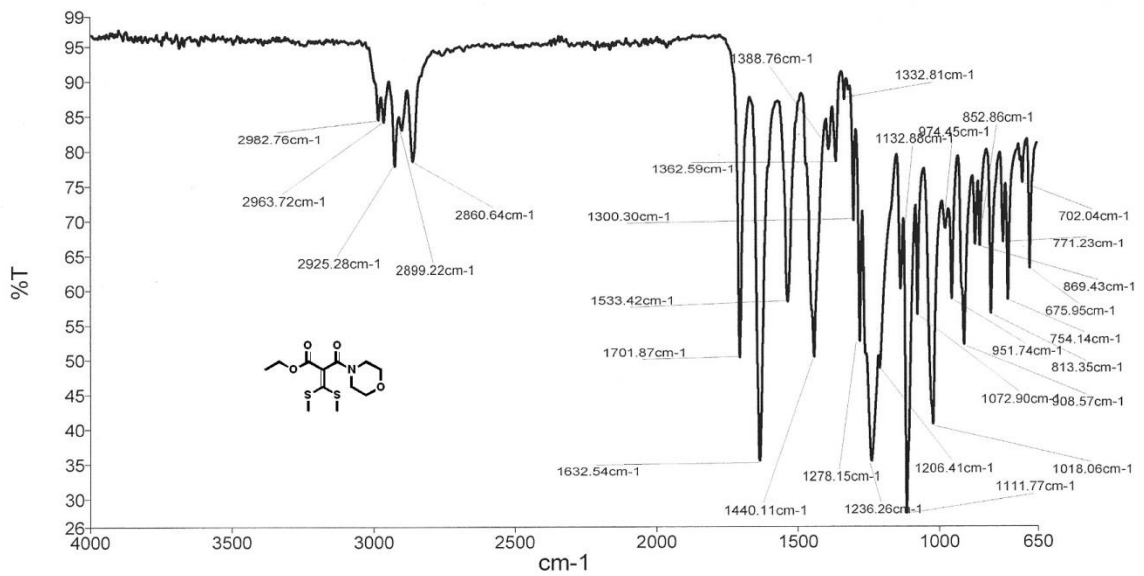
Figure A. 25. FT-IR spectrum of 1i
Ethyl 3,3-bis(methylsulfanyl)-2-(morpholin-4-yl)propanoate
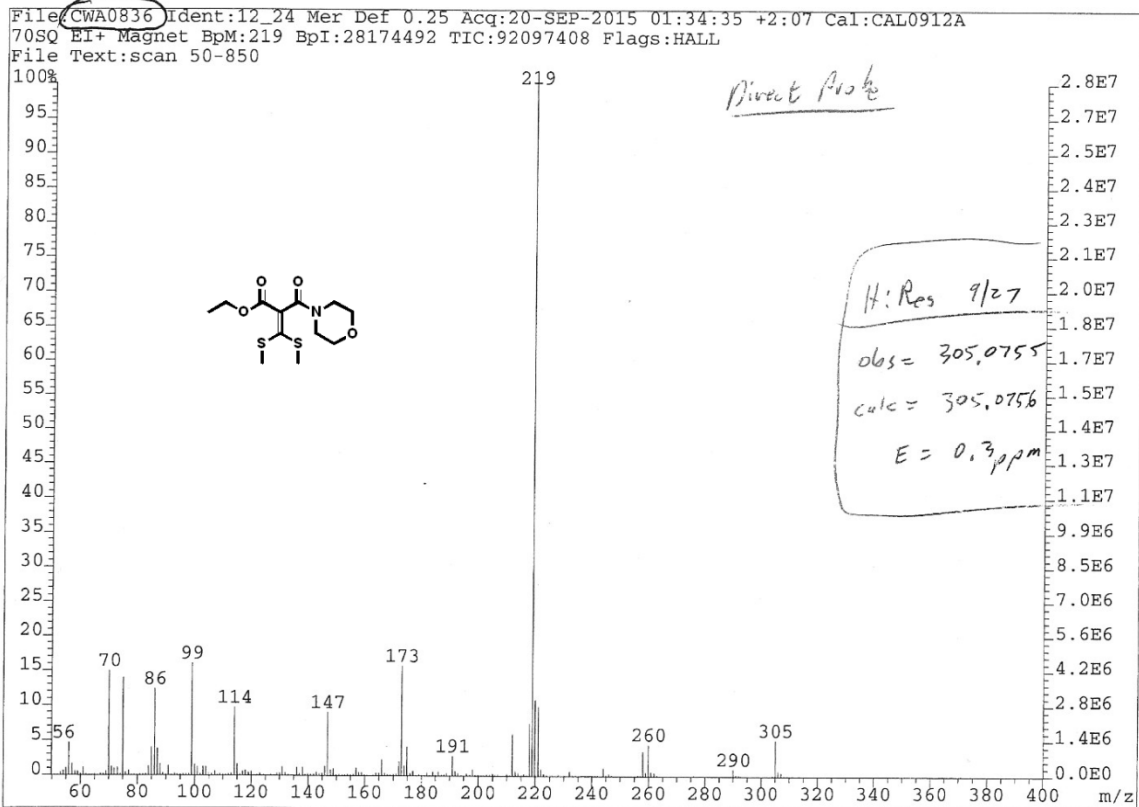
Figure A. 26. LRMS spectrum of 1i
Ethyl 3,3-bis(methylsulfanyl)-2-(morpholin-4-yl)propanoate

APPENDIX B

1,3-*S,O*-ESTER SPECTRAL DATA
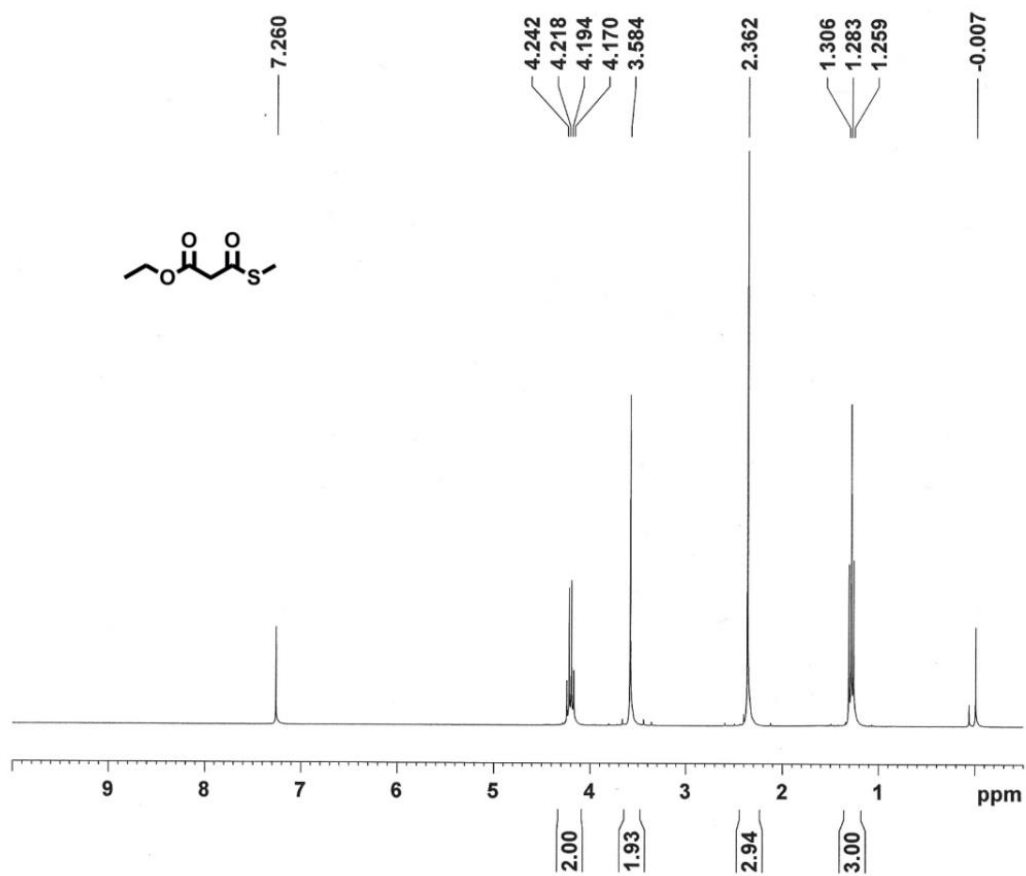
Figure B. 1. ^{1}H NMR spectrum of 2a
Ethyl 3-(methylsulfanyl)-3-oxopropanoate
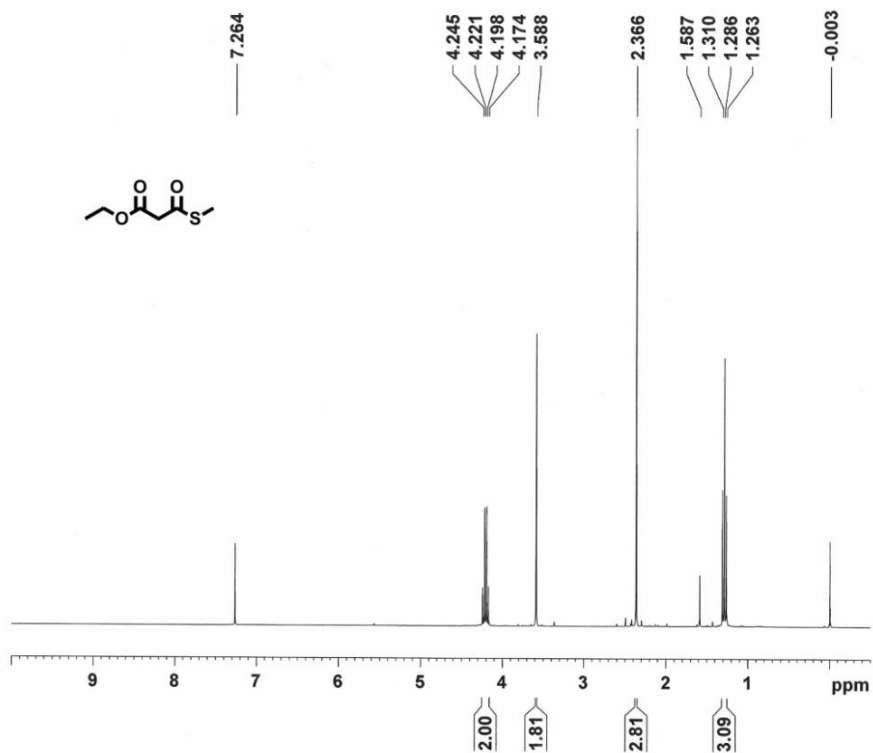
Figure B. 2. ^{1}H NMR spectrum of 2b
Ethyl 3-(methylsulfanyl)-3-oxopropanoate

Figure B. 3. ^{1}H NMR spectrum of 2c
Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate

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Figure B. 4. ^{13}C NMR spectrum of 2c
Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate

Figure B. 5. LRMS spectrum of 2c
Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate

Figure B. 6. FT-IR spectrum of 2c
Ethyl 2-[bis(methylsulfanyl)methylidene]pentanoate
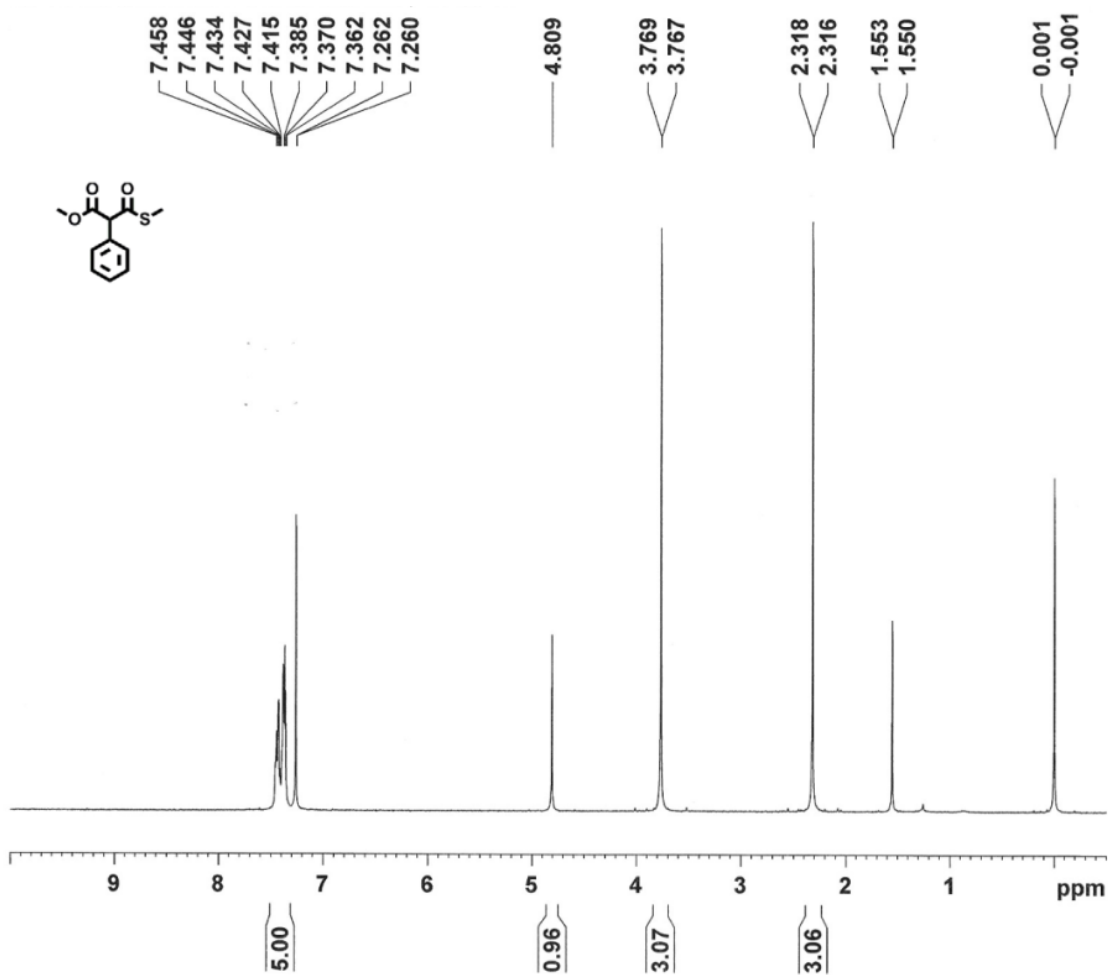
Figure B. 7. ^{1}H NMR spectrum of 2d
Methyl 3-(methylsulfanyl)-3-oxo-2-phenylpropanoate
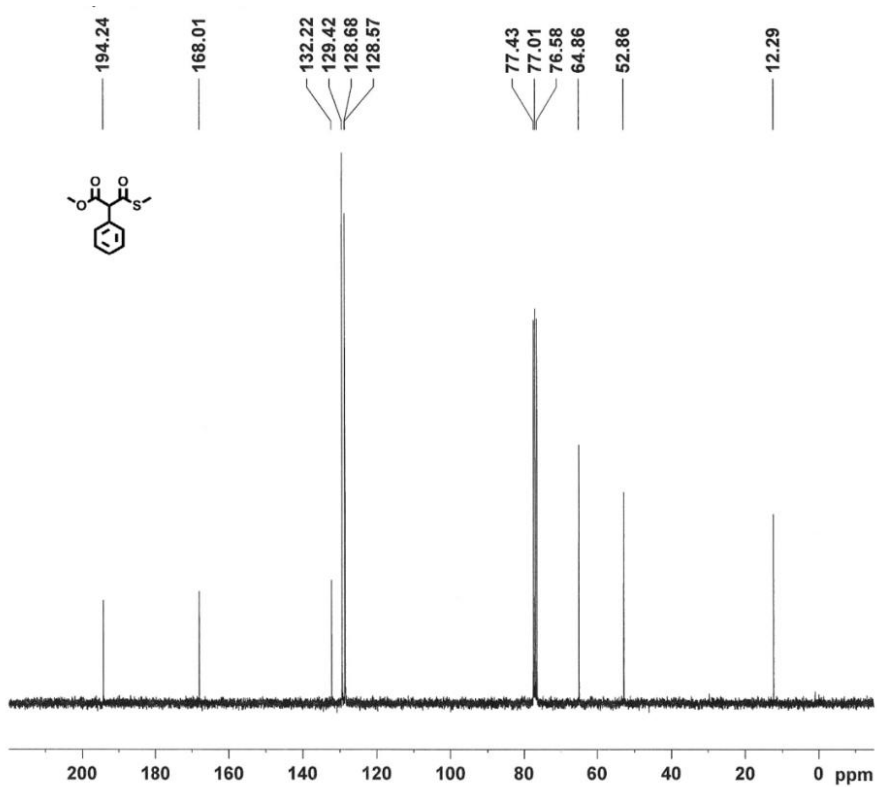
Figure B. 8. ^{13}C NMR spectrum of 2d
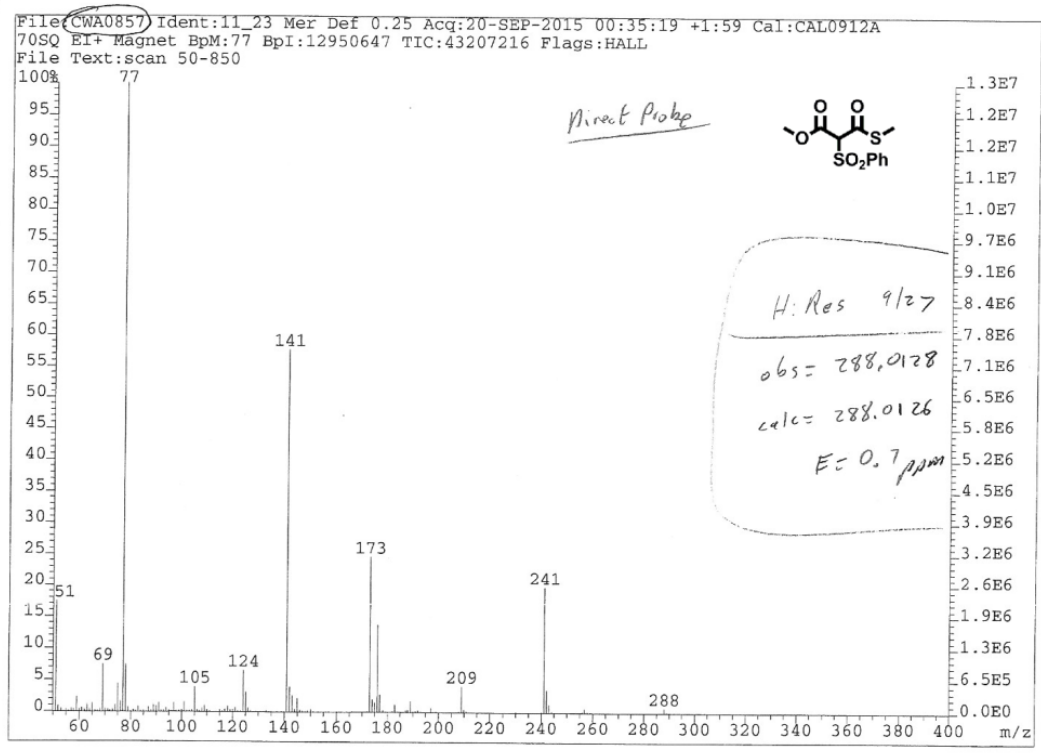**Methyl 3-(methylsulfanyl)-3-oxo-2-phenylpropanoate**
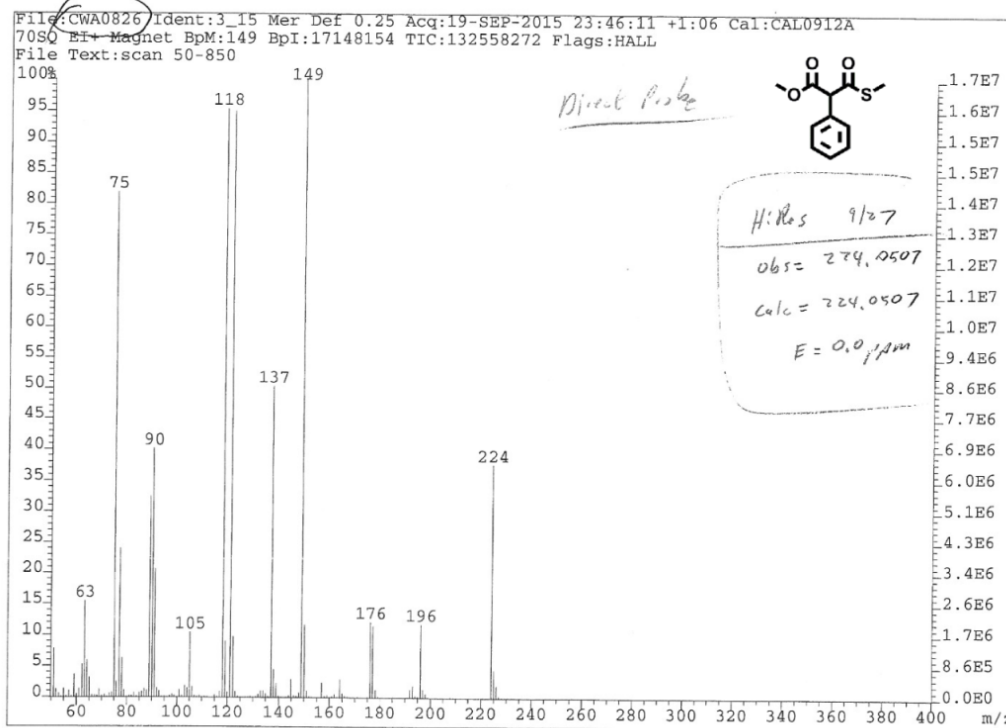
Figure B. 9. LRMS spectrum of 2d
Methyl 3-(methylsulfanyl)-3-oxo-2-phenylpropanoate
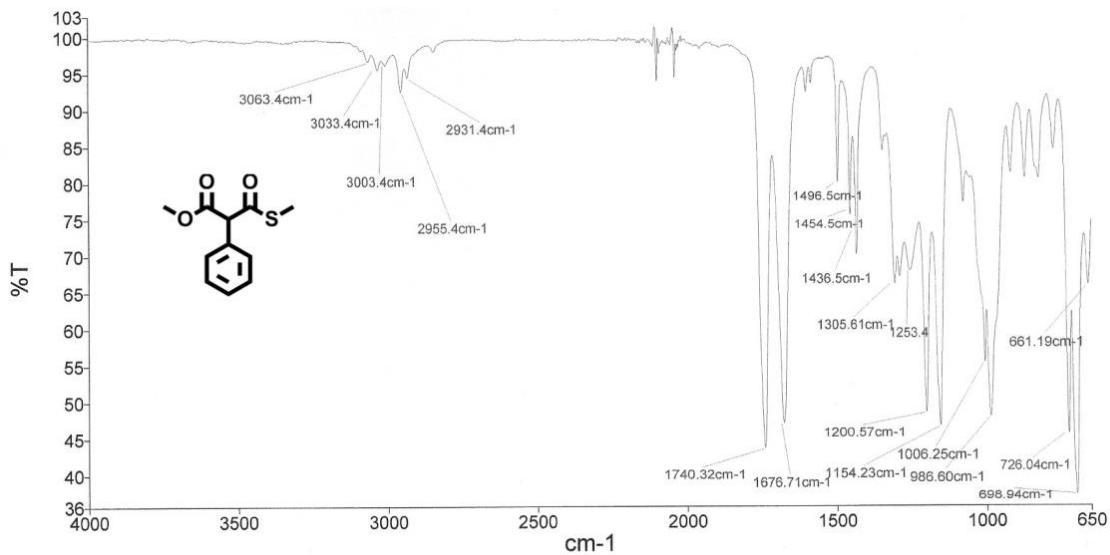
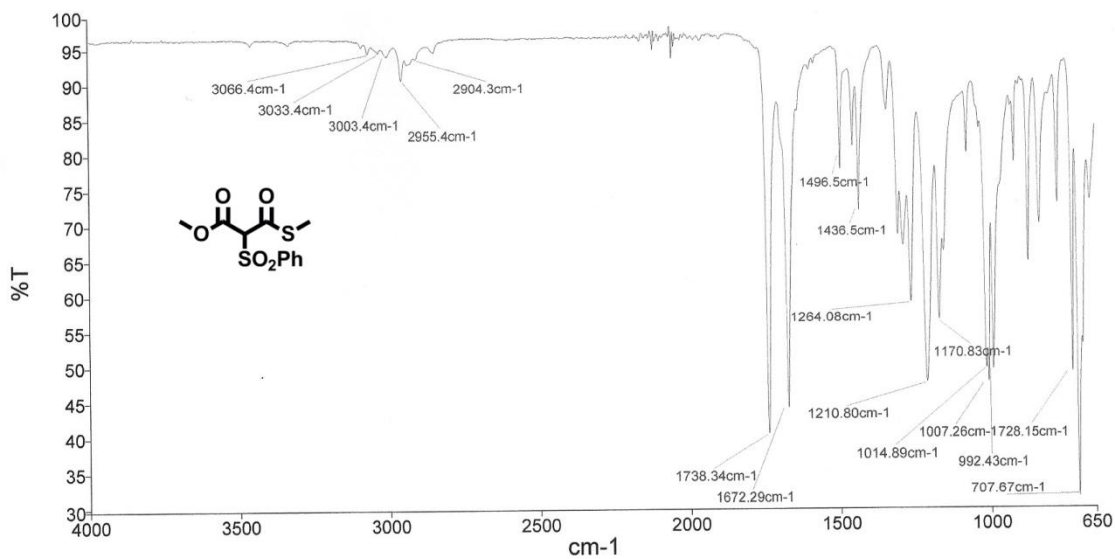**Figure B. 10. FT-IR spectrum of 2d**
Methyl 3-(methylsulfanyl)-3-oxo-2-phenylpropanoate
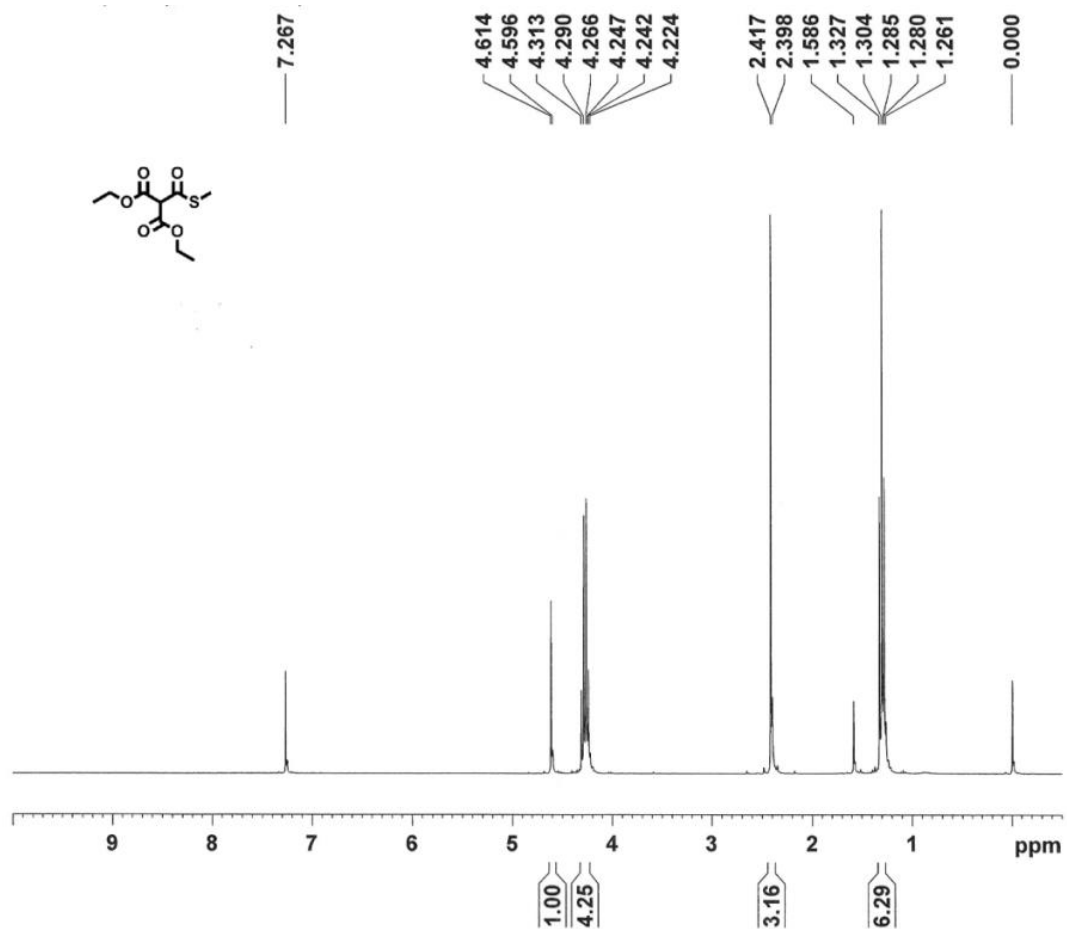
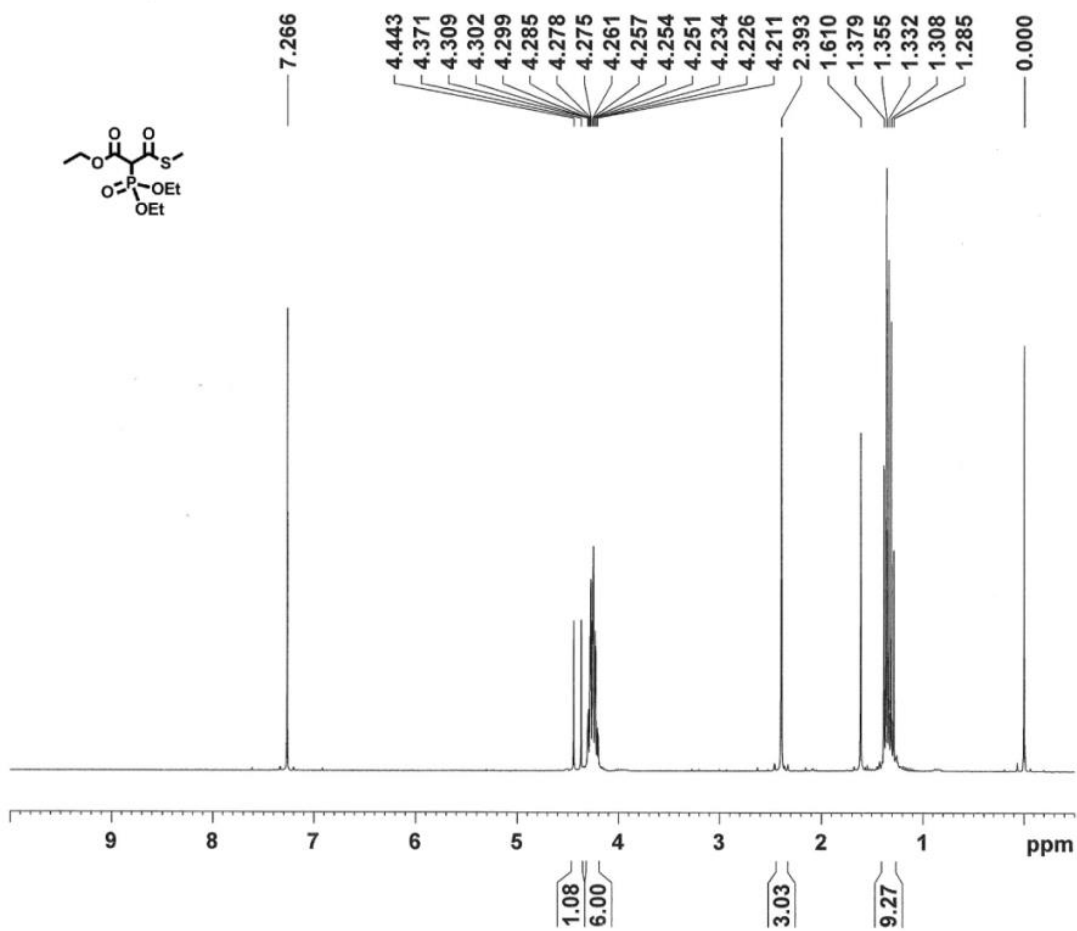**Figure B. 11. ^{1}H NMR spectrum of 2e**
Diethyl [(methylsulfanyl)carbonyl] propanedioate

149
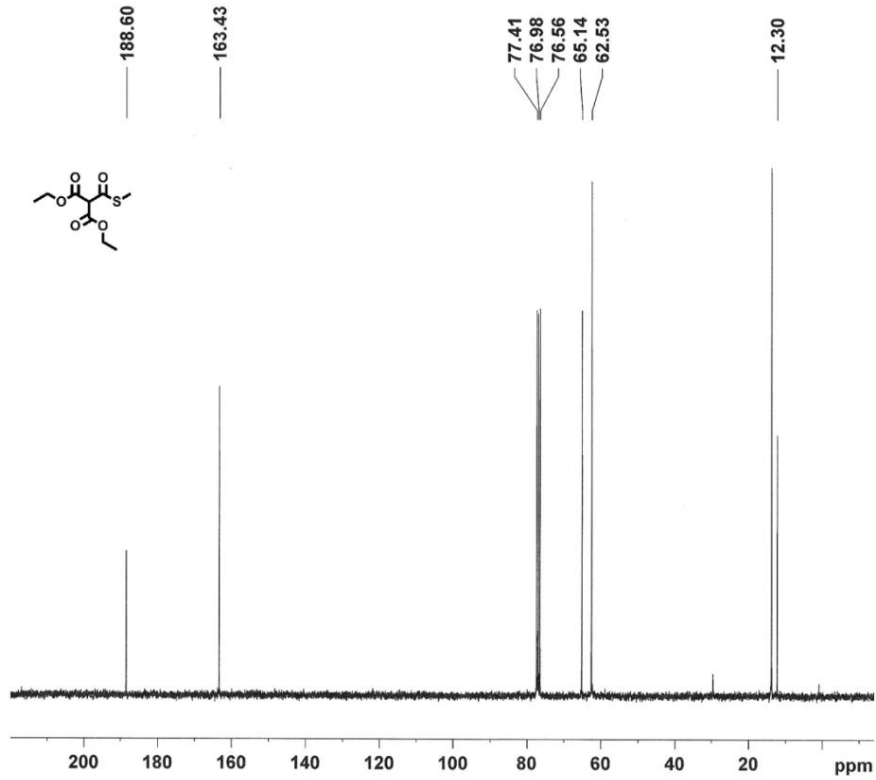
Figure B. 12. ^{13}C NMR spectrum of 2e
Diethyl [(methylsulfanyl)carbonyl] propanedioate
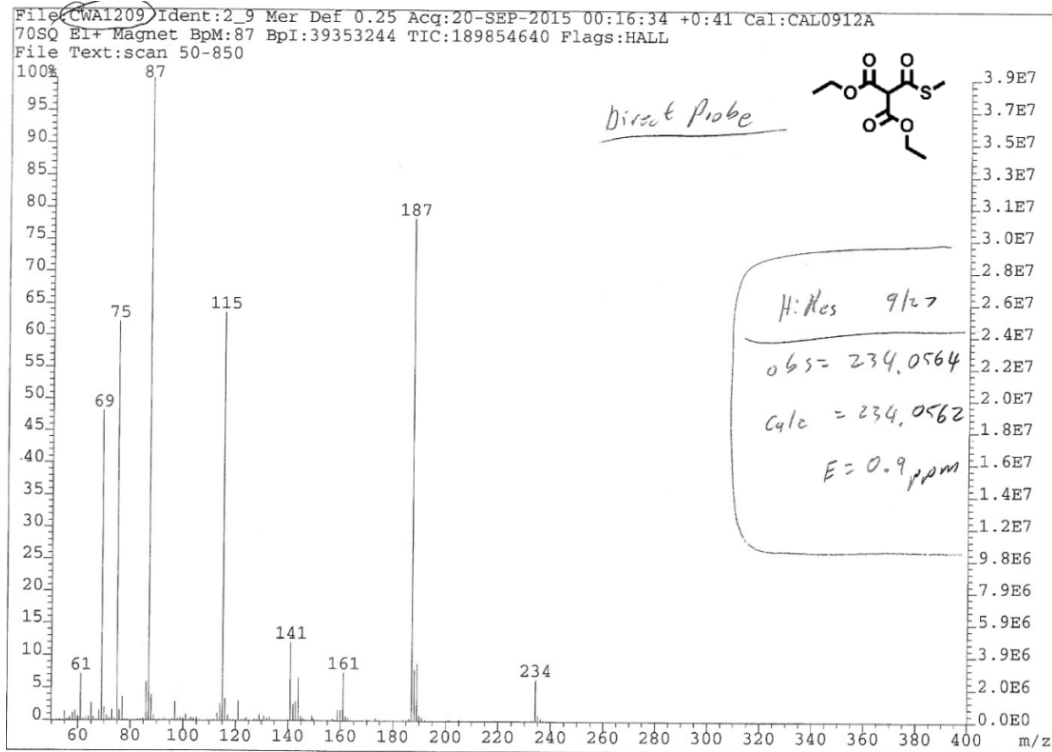
Figure B. 13. LRMS spectrum of 2e
Diethyl [(methylsulfanyl)carbonyl] propanedioate

150
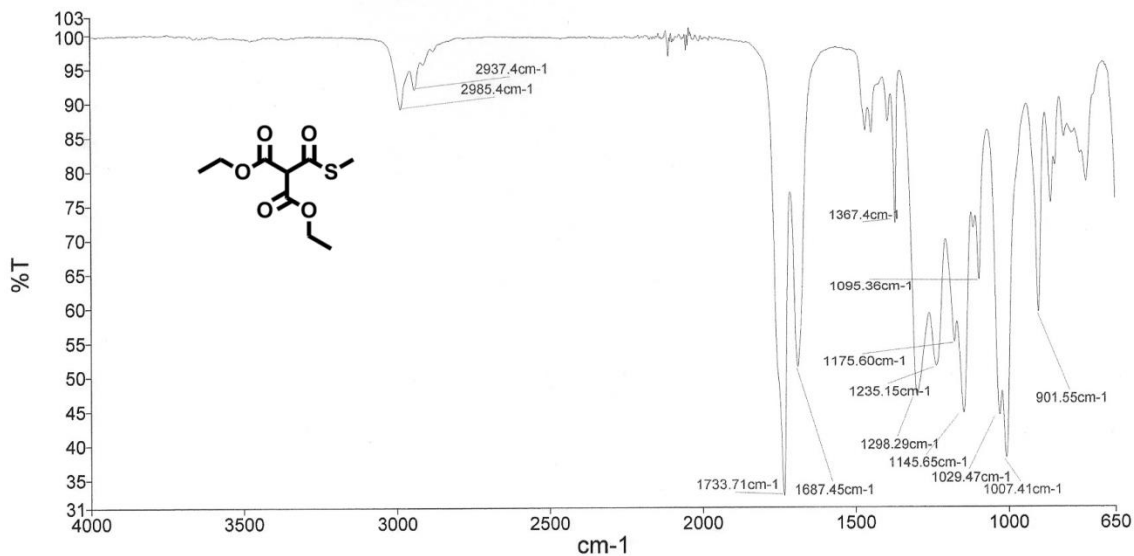
Figure B. 14. FT-IR spectrum of 2e
Diethyl [(methylsulfanyl)carbonyl] propanedioate
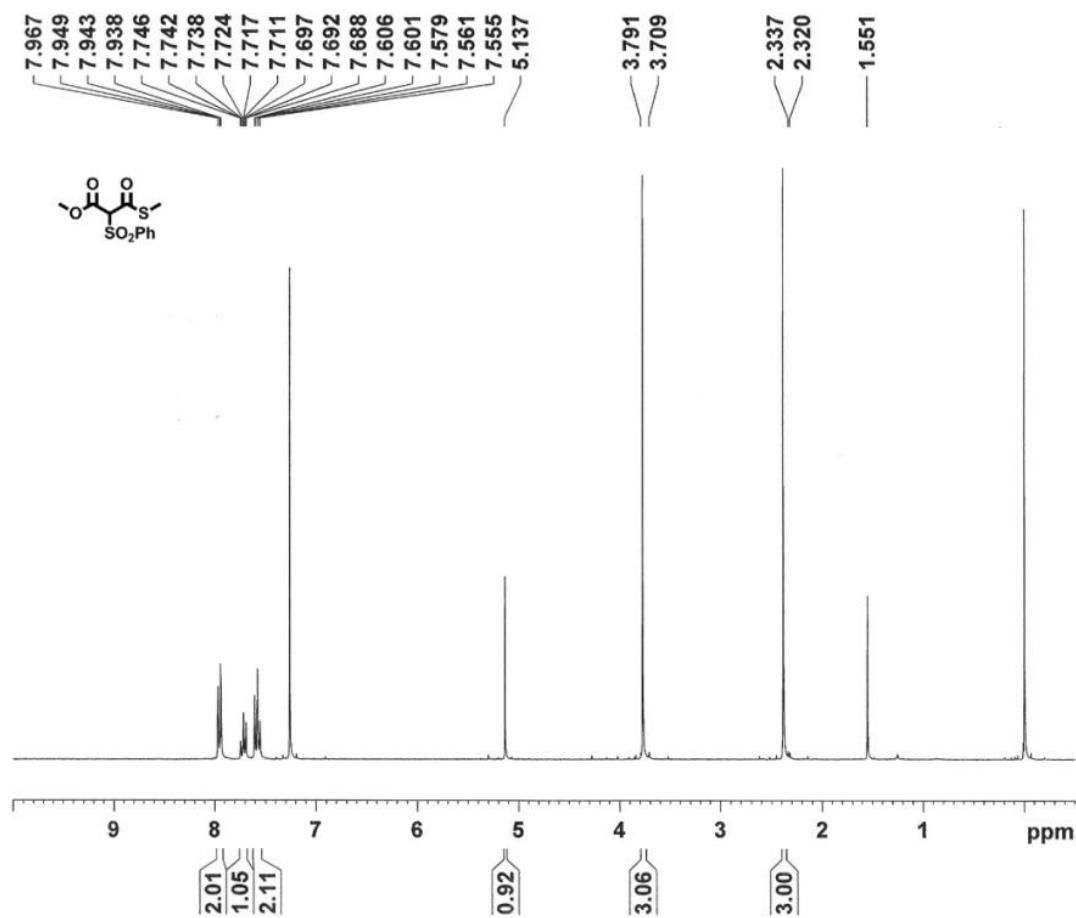
Figure B. 15. ¹H NMR spectrum of 2f
Methyl 3-(methylsulfanyl)-3-oxo-2-(phenylsulfonyl)propanoate
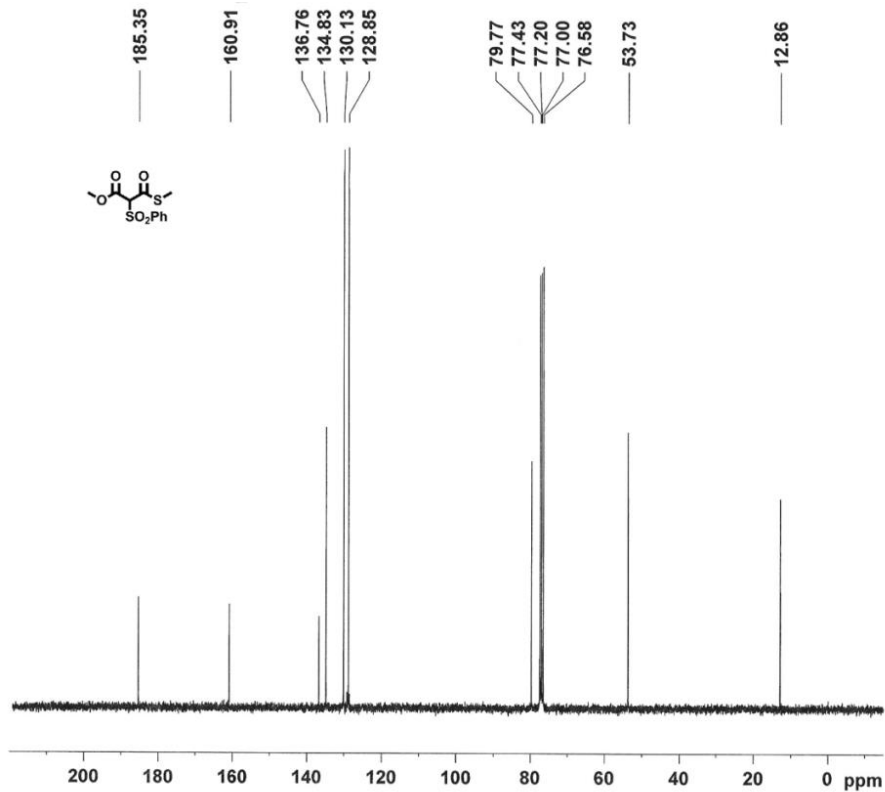
Figure B. 16. ^{13}C NMR spectrum of 2f
Methyl 3-(methylsulfanyl)-3-oxo-2-(phenylsulfonyl)propanoate

Figure B. 17. LMRS spectrum of 2f
Methyl 3-(methylsulfanyl)-3-oxo-2-(phenylsulfonyl)propanoate

152

Figure B. 18. FT-IR spectrum of 2f
Methyl 3-(methylsulfanyl)-3-oxo-2-(phenylsulfonyl)propanoate

Figure B. 19. ^{1}H NMR spectrum of 2g
Ethyl 2-(diethoxyphosphoryl)-3-(methylsulfanyl)-3-oxopropanoate
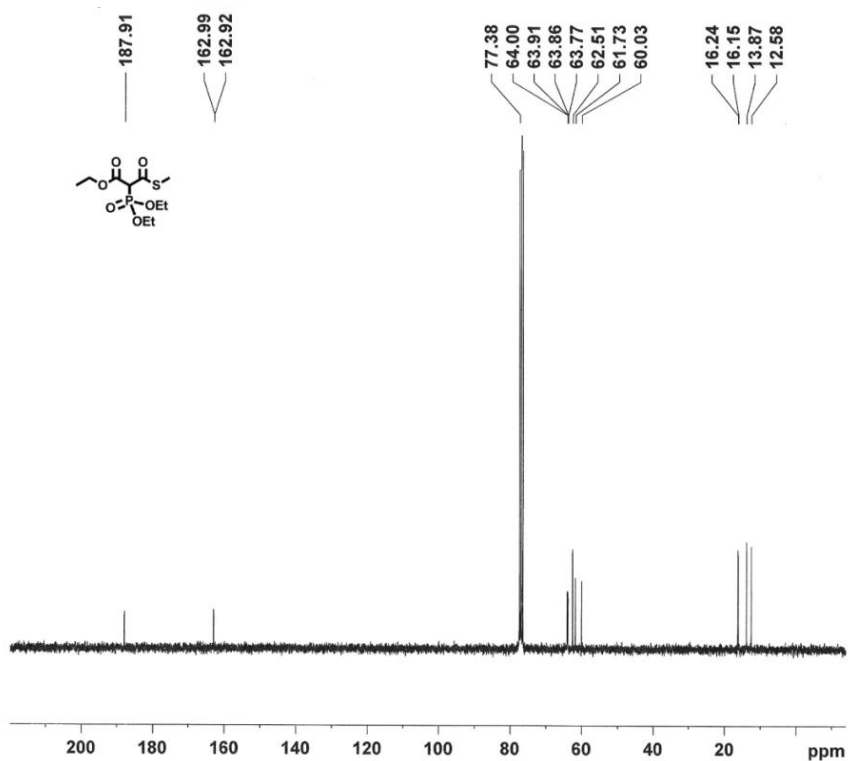
Figure B. 20. ^{13}C NMR spectrum of 2g
Ethyl 2-(diethoxyphosphoryl)-3-(methylsulfanyl)-3-oxopropanoate
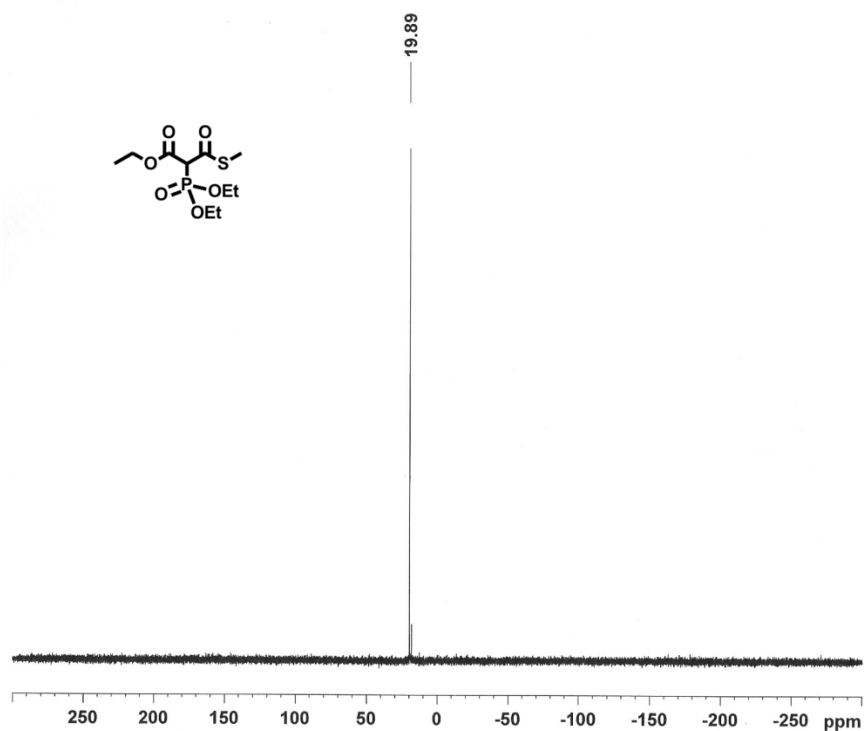
Figure B. 21. ^{31}P NMR spectrum of 2g
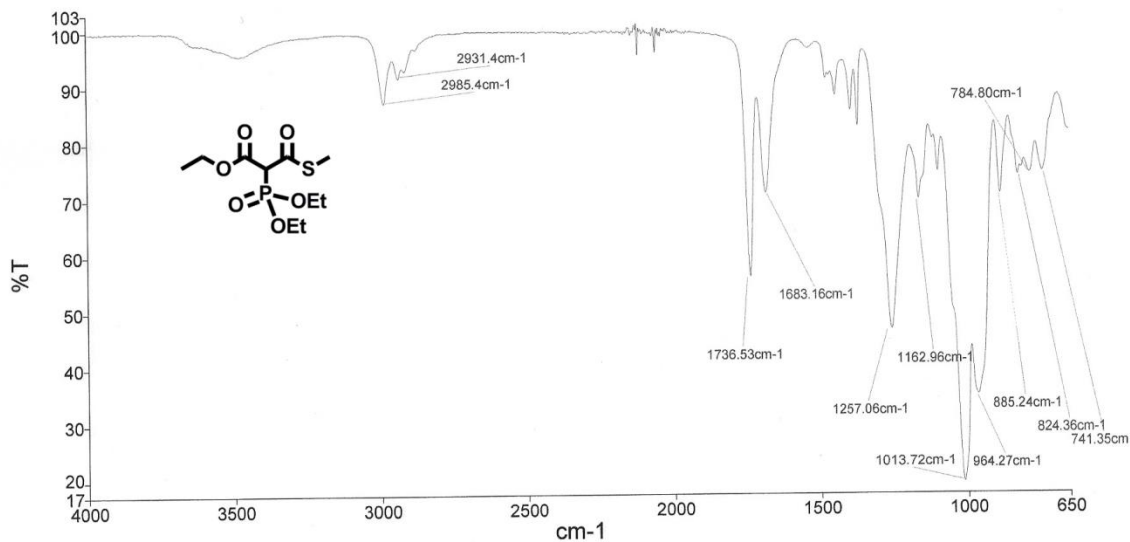**Ethyl 2-(diethoxyphosphoryl)-3-(methylsulfanyl)-3-oxopropanoate**

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Figure B. 22. FT-IR spectrum of 2g
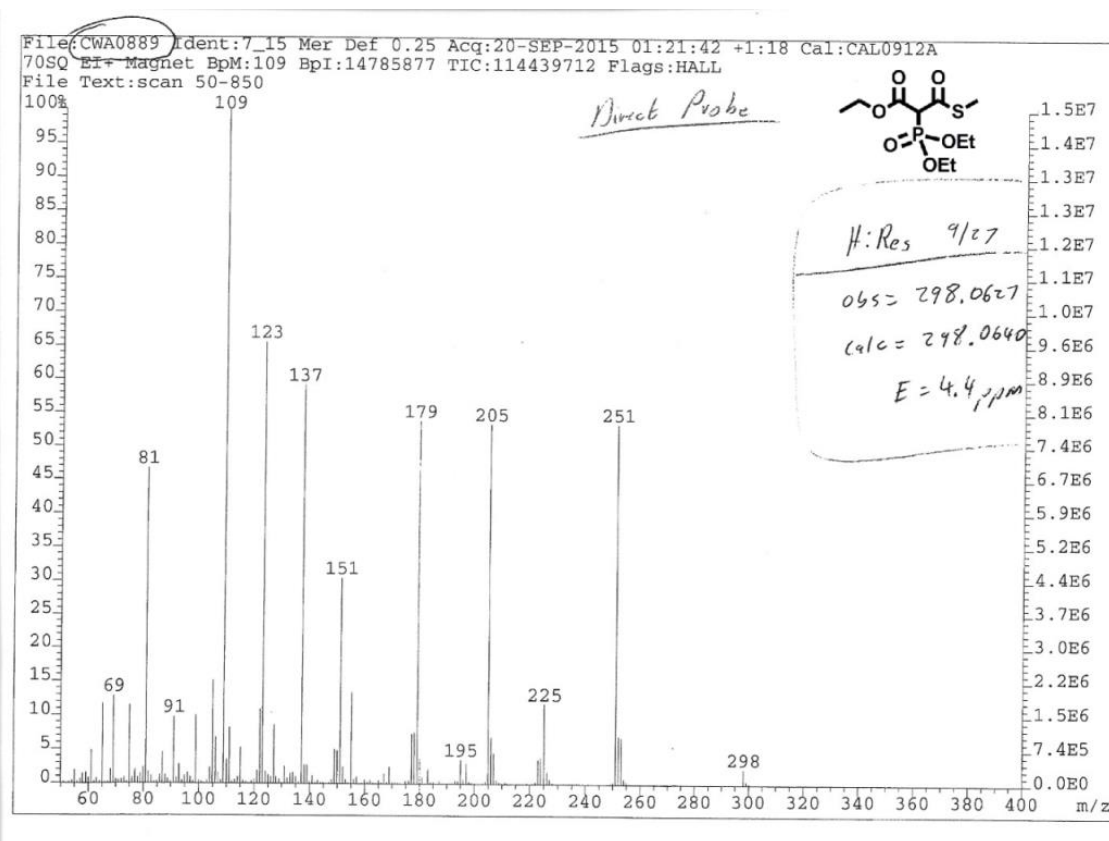**Ethyl 2-(diethoxyphosphoryl)-3-(methylsulfanyl)-3-oxopropanoate**

Figure B. 23. LRMS spectrum of 2g
Ethyl 2-(diethoxyphosphoryl)-3-(methylsulfanyl)-3-oxopropanoate

APPENDIX C

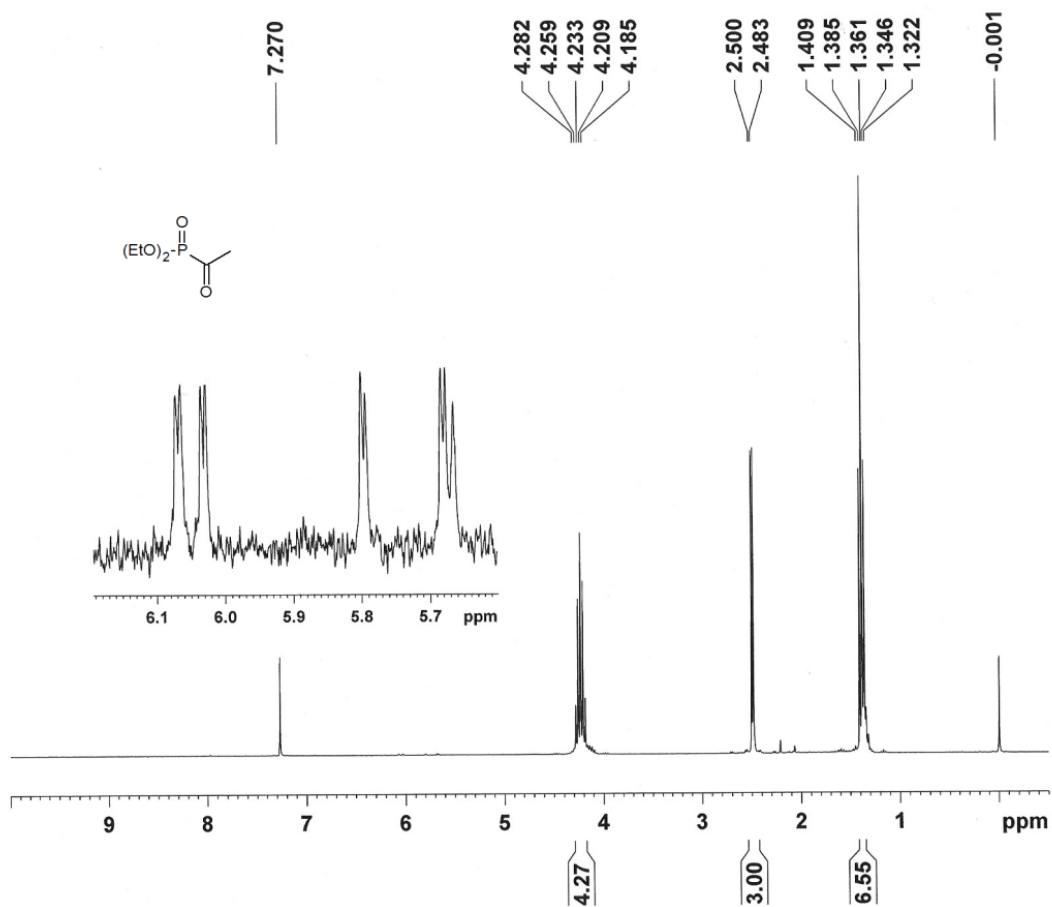## α-KETOPHOSPHONATE SPECTRAL DATA

**Figure C. 1. ^{1}H NMR spectrum of 3a
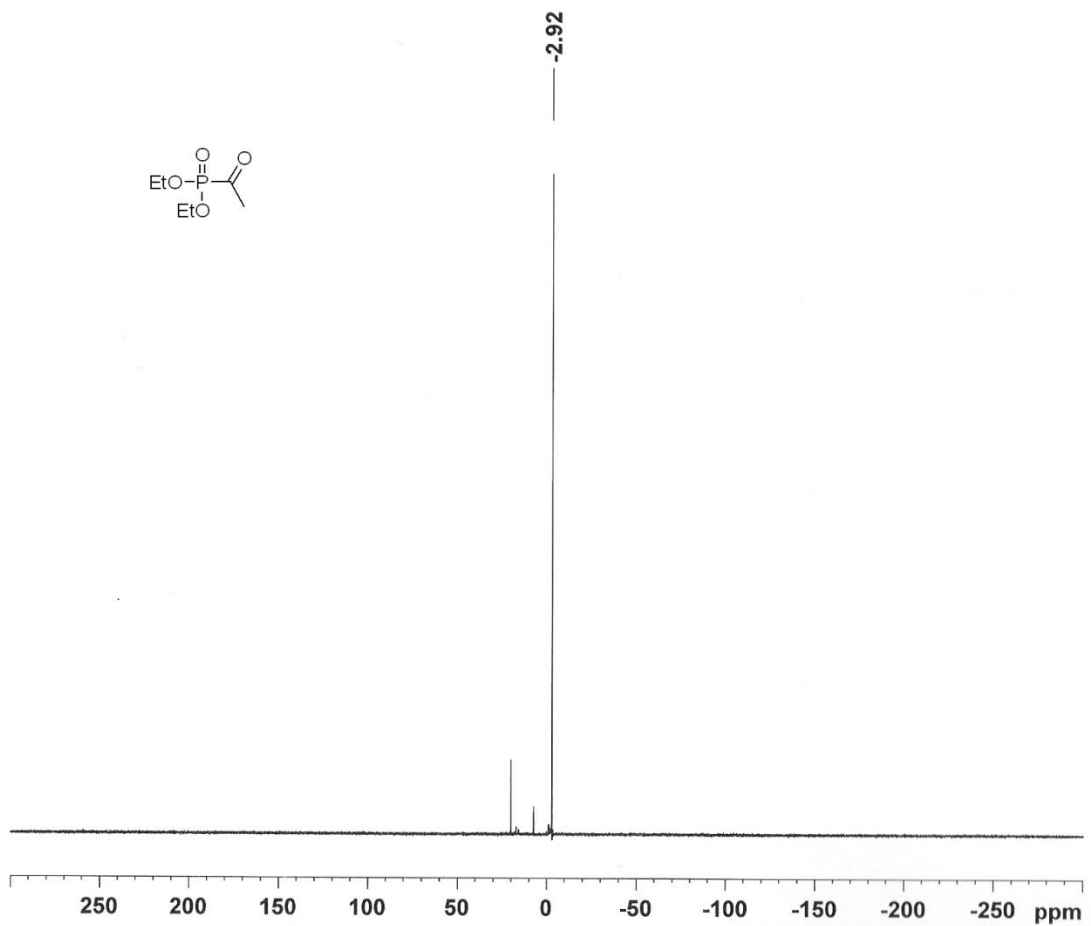diethyl acetylphosphonate**

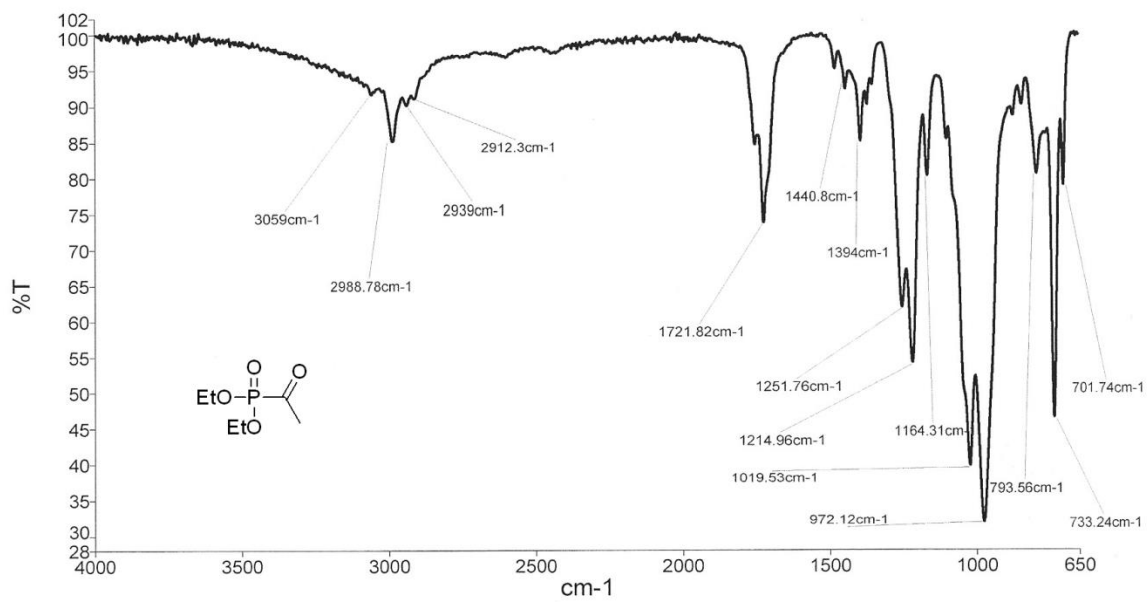**Figure C. 2. ^{31}P NMR spectrum of 3a**
diethyl acetylphosphonate

Figure C. 3. FT-IR spectrum of 3a
diethyl acetylphosphonate
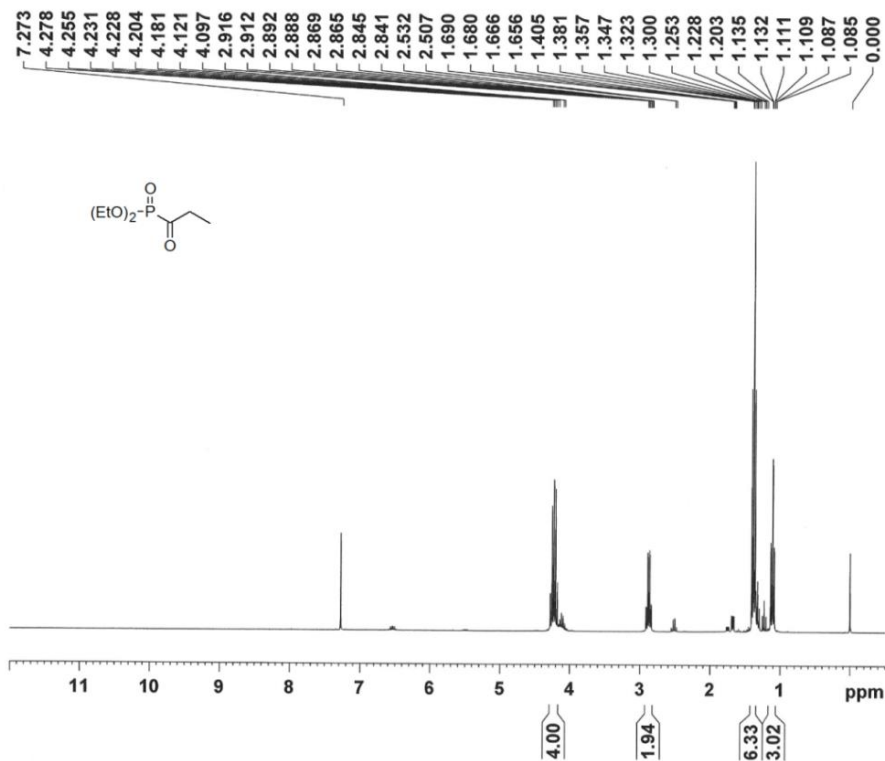
157

Figure C. 4. ^{1}H NMR spectrum of 3b
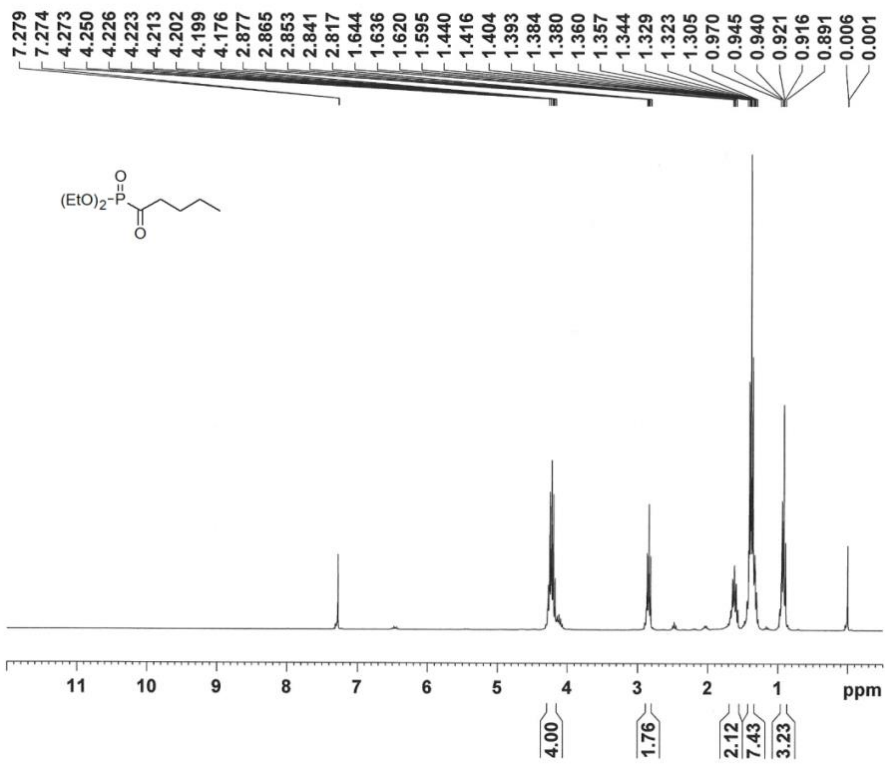**diethyl propanoylphosphonate**

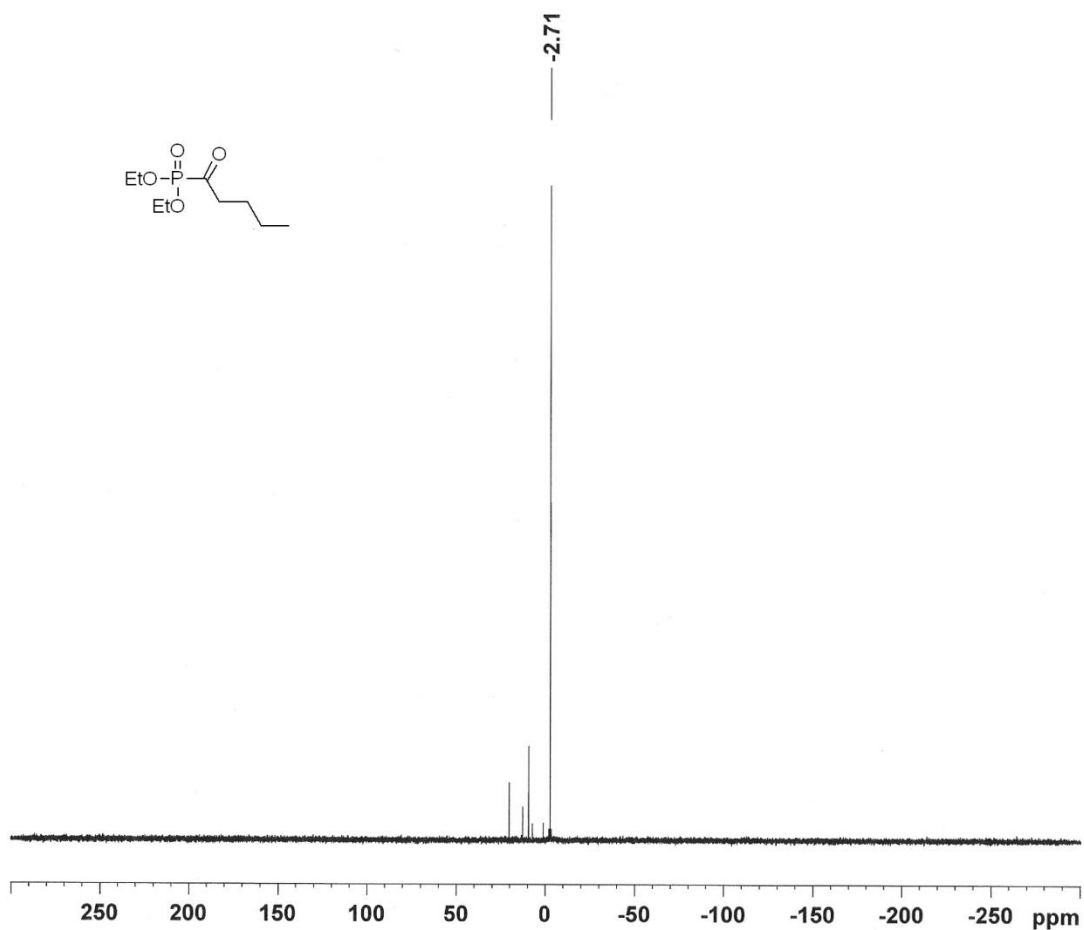**Figure C. 5. ^{1}H NMR spectrum of 3c**
diethyl pentanoylphosphonate

Figure C. 6. ^{31}P NMR spectrum of 3c
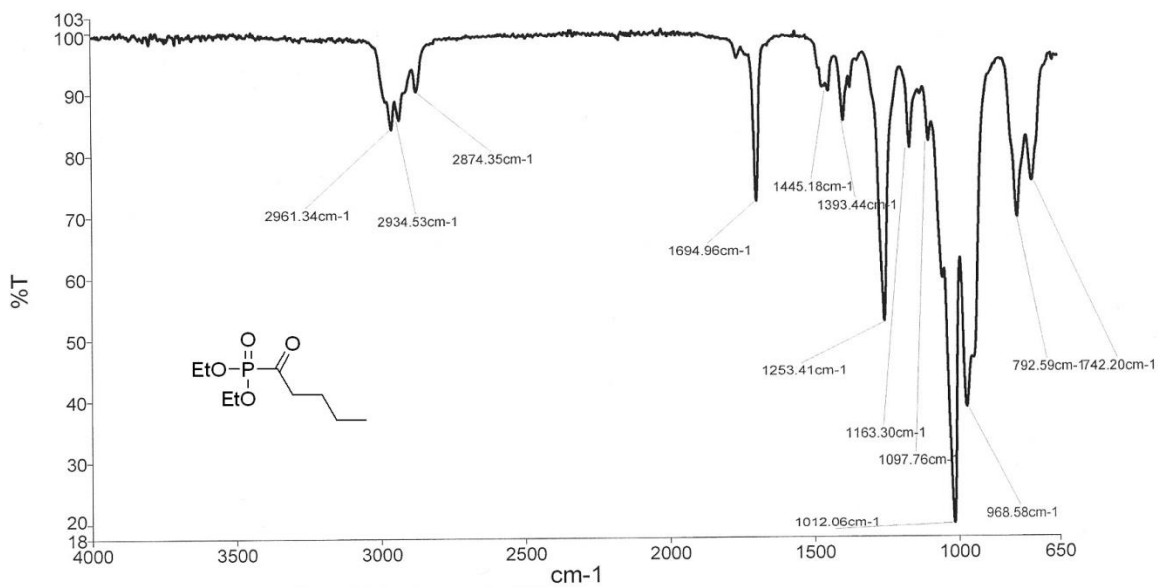**diethyl pentanoylphosphonate**

Figure C. 7. FT-IR spectrum of 3c
diethyl pentanoylphosphonate

159
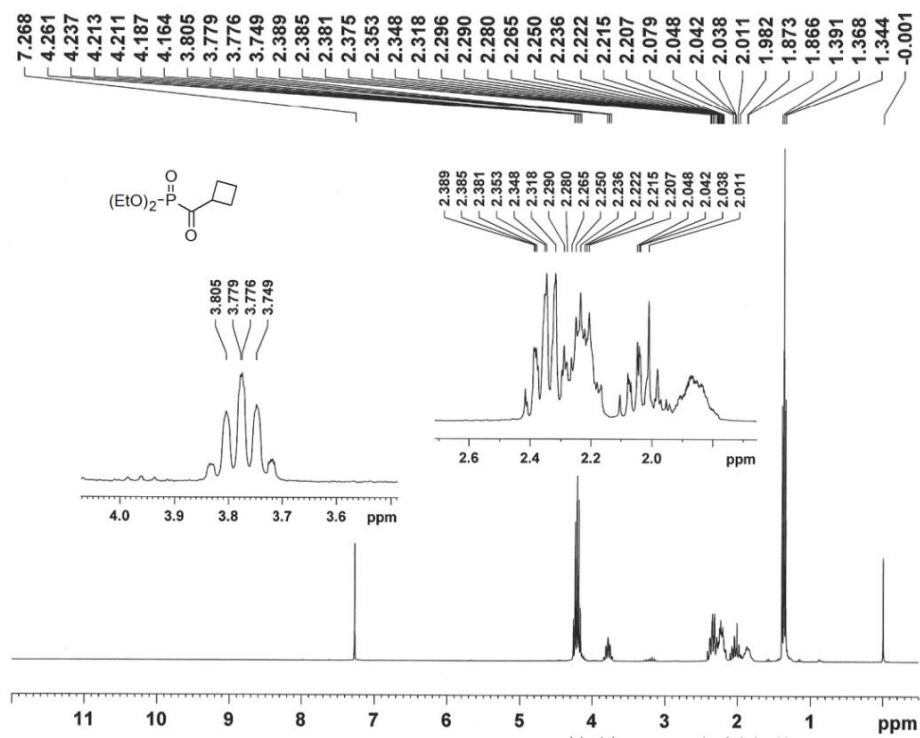
**Figure C. 8. ^{1}H NMR spectrum of 3d
diethyl (cyclobutylcarbonyl)phosphonate**
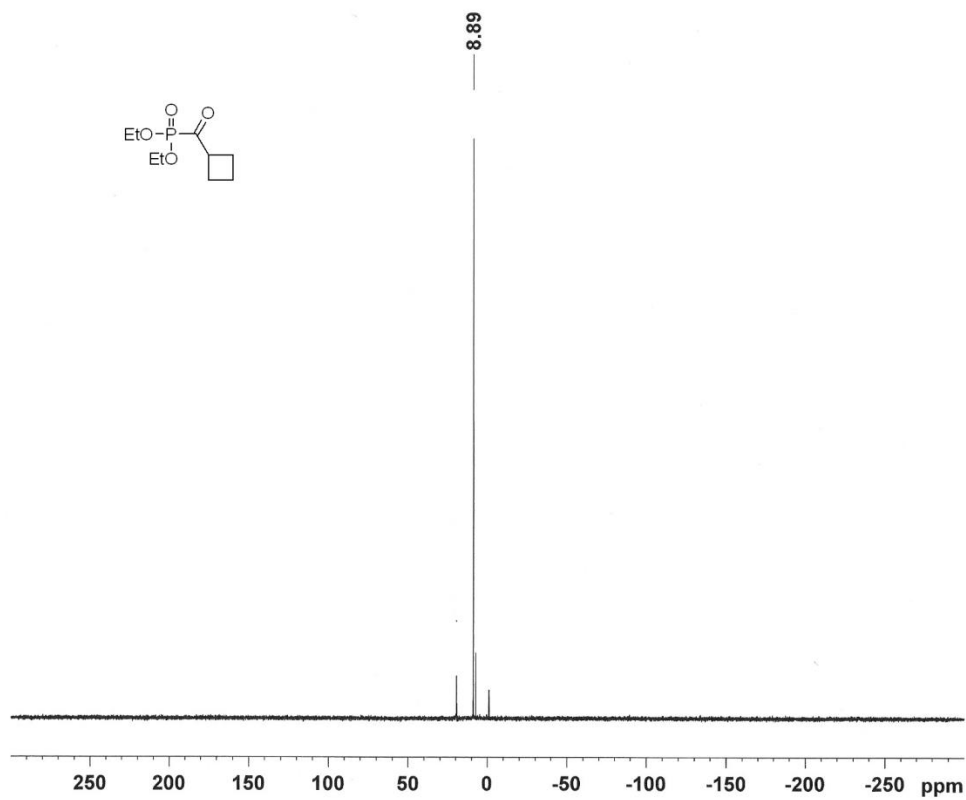
**Figure C. 9. ^{31}P NMR spectrum of 3d
diethyl (cyclobutylcarbonyl)phosphonate**
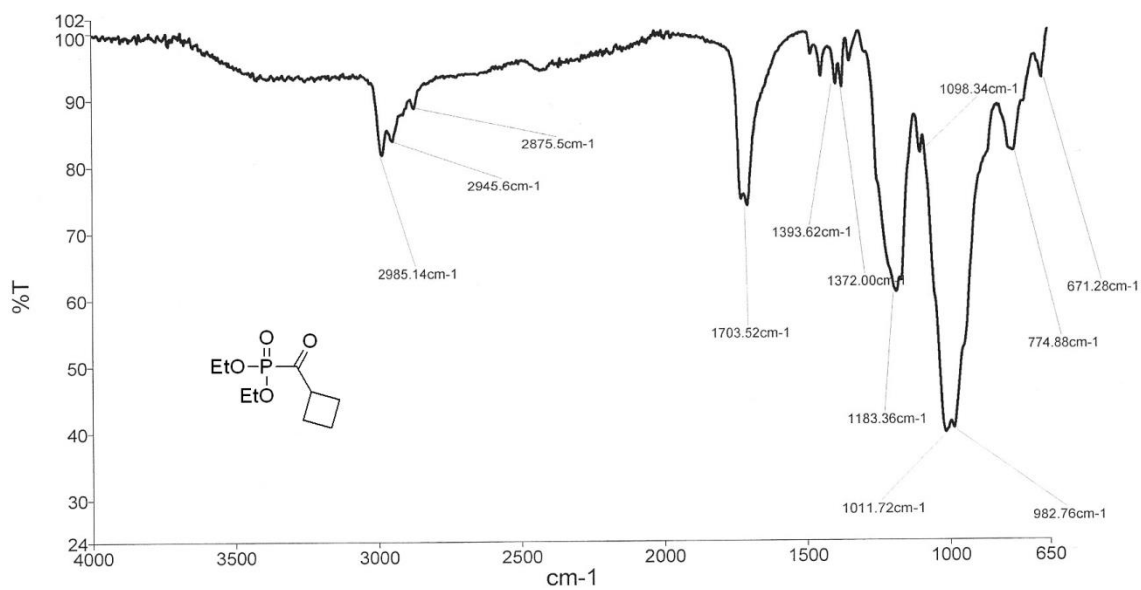
Figure C. 10. FT-IR spectrum of 3d
diethyl (cyclobutylcarbonyl)phosphonate
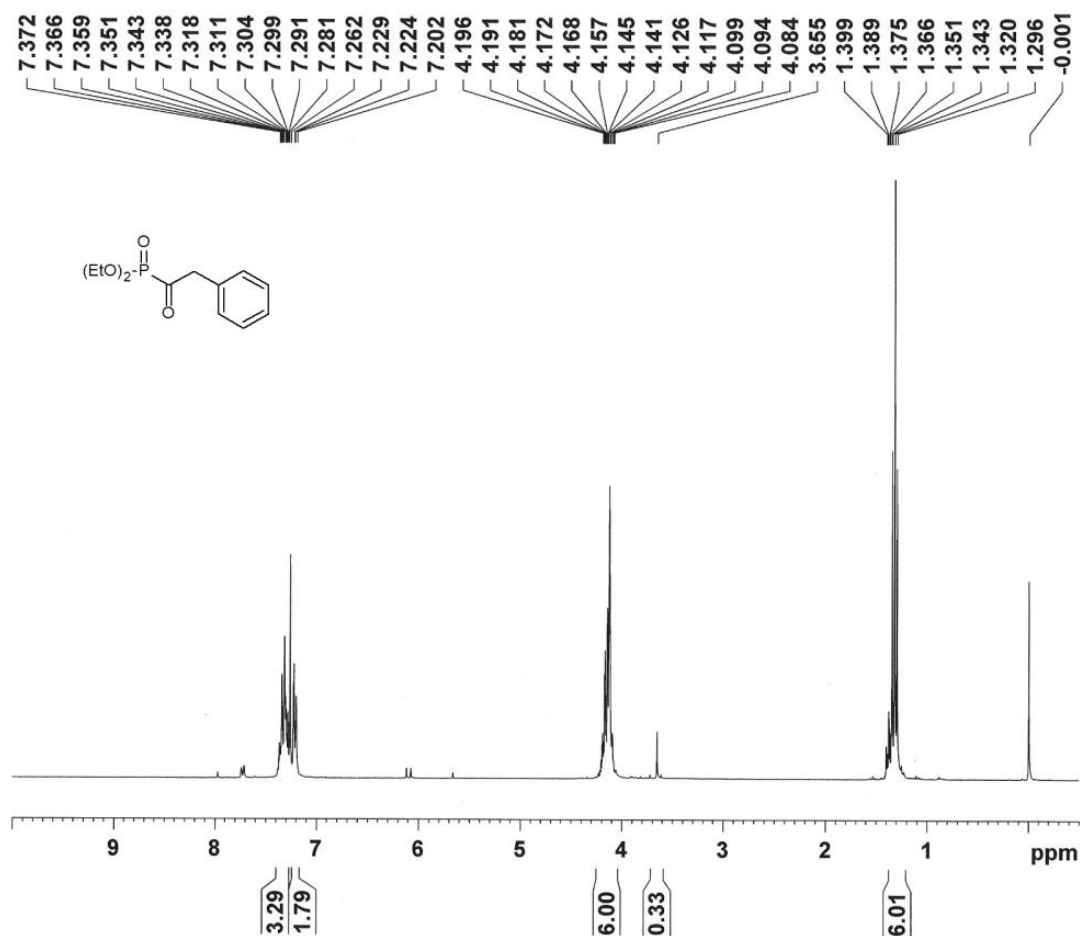
Figure C. 11. ¹H NMR spectrum of 3e
diethyl (phenylacetyl)phosphonate
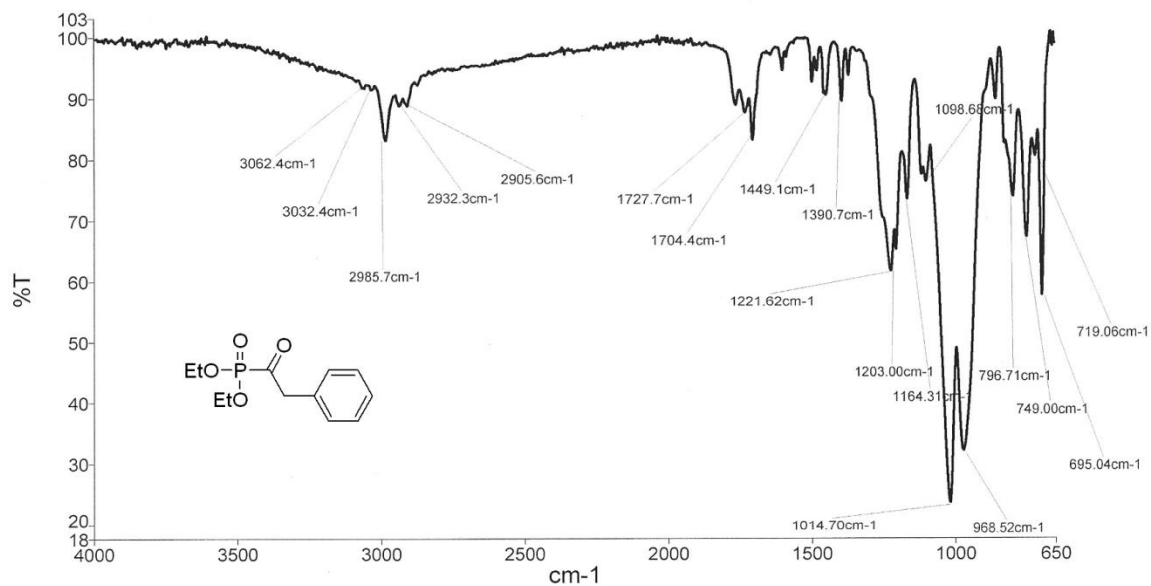
Figure C. 12. FT-IR spectrum of 3e
diethyl (phenylacetyl)phosphonate
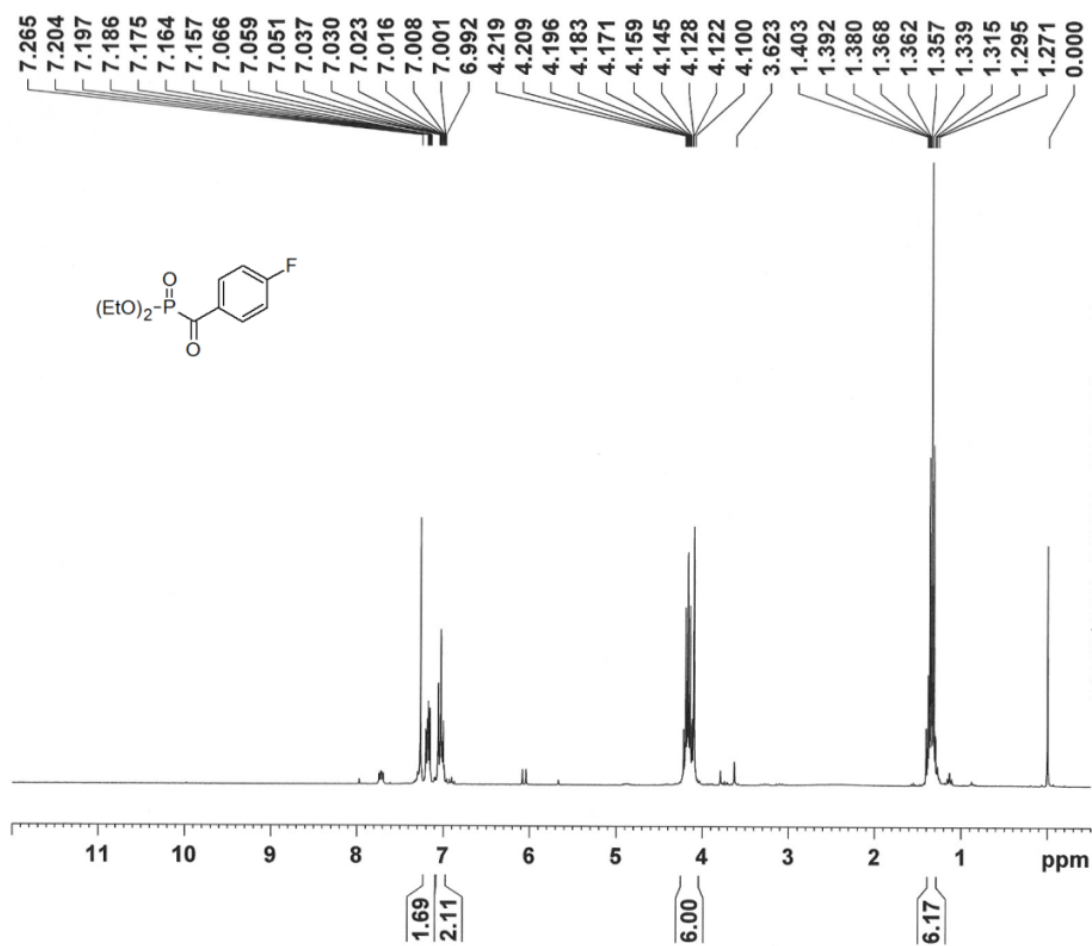
Figure C. 13. ¹H NMR spectrum of 3f
diethyl [(4-fluorophenyl)acetyl]phosphonate

162
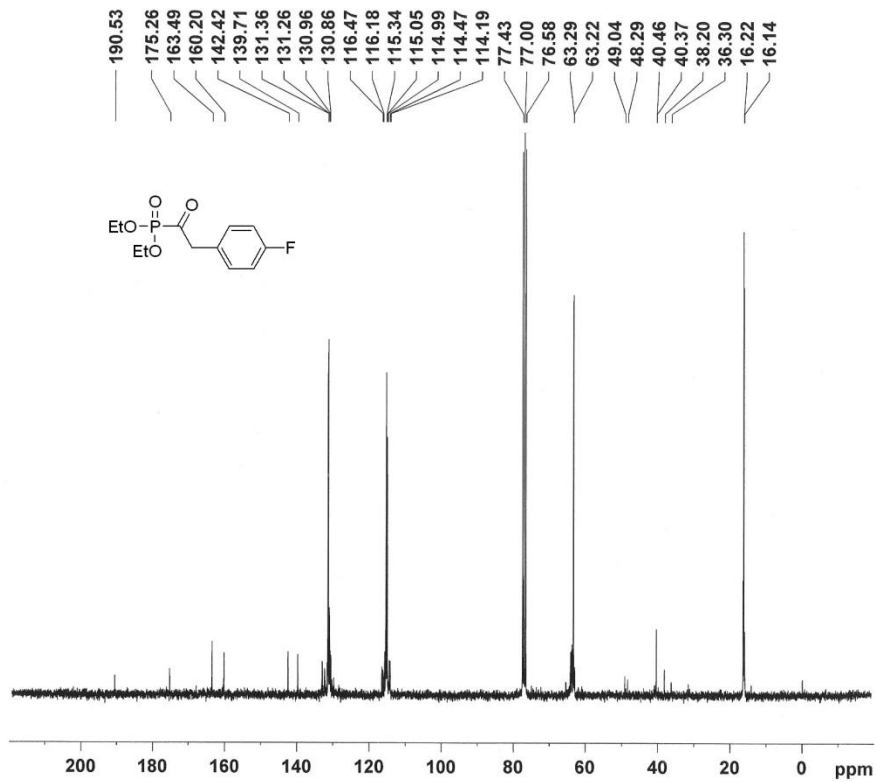
Figure C. 14. ^{13}C NMR spectrum of 3f
diethyl [(4-fluorophenyl)acetyl]phosphonate
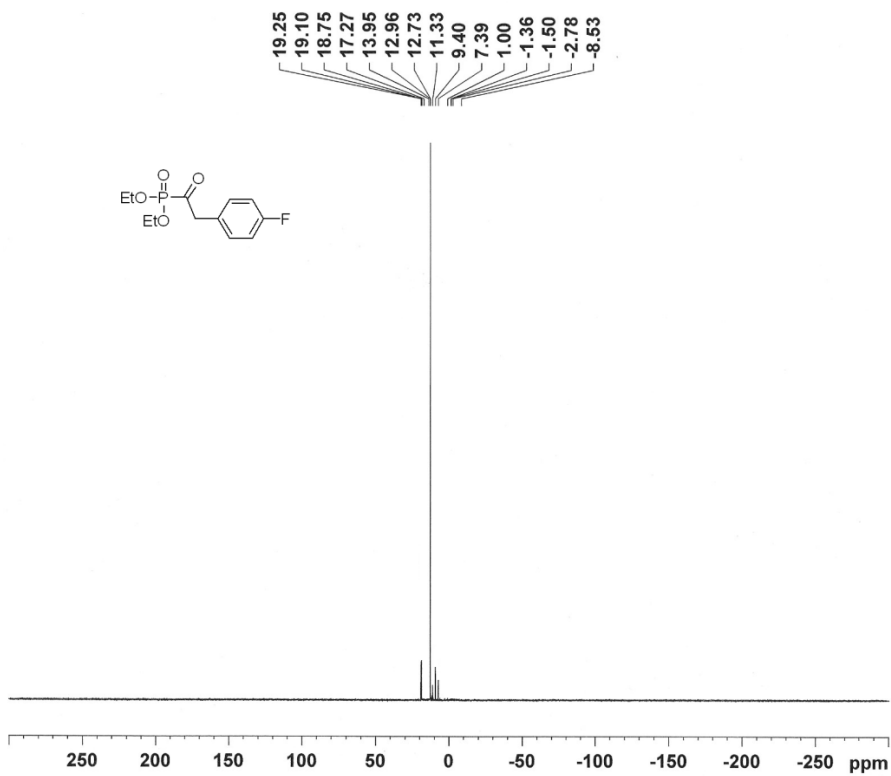
Figure C. 15. ^{31}P NMR spectrum of 3f
diethyl [(4-fluorophenyl)acetyl]phosphonate
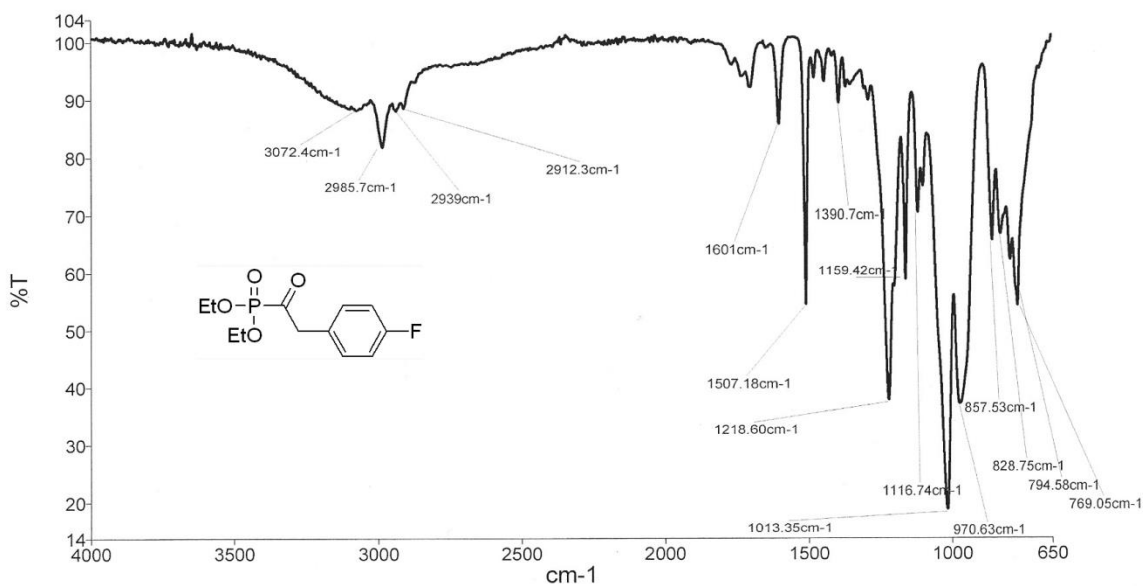
Figure C. 16. FT-IR spectrum of 3f
diethyl [(4-fluorophenyl)acetyl]phosphonate
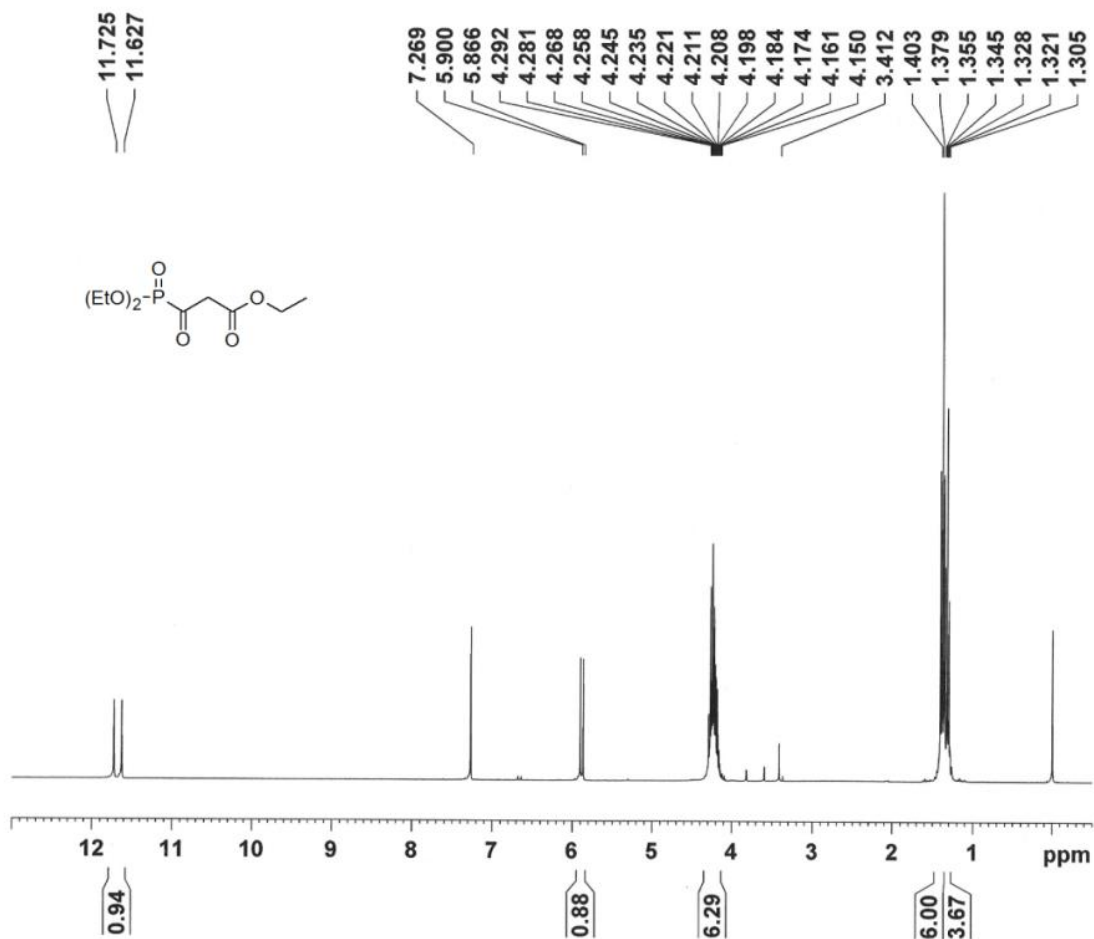
Figure C. 17. ^{1}H NMR spectrum of 3g
ethyl 3-(diethoxyphosphoryl)-3-oxopropanoate

164
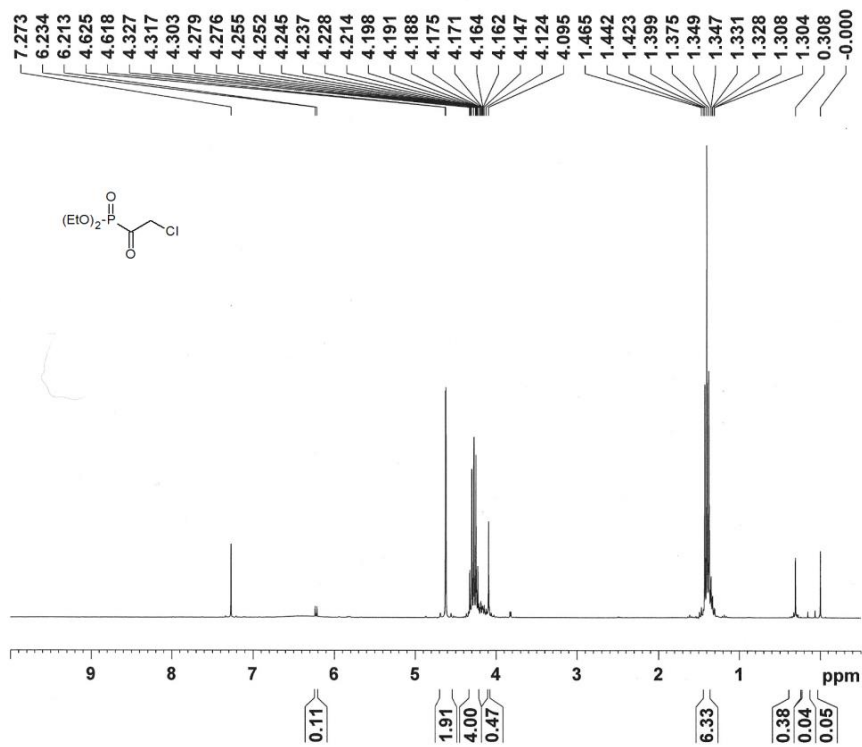
Figure C. 18. ¹H NMR spectrum of 3h
diethyl (chloroacetyl)phosphonate
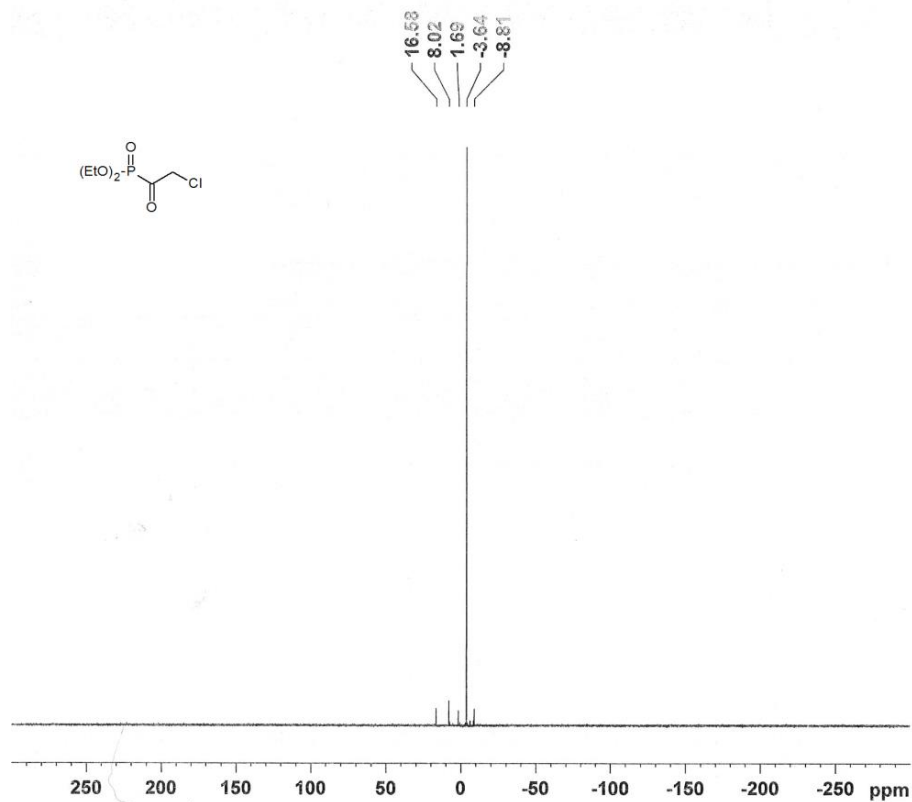
Figure C. 19. ³¹P NMR spectrum of 3h
diethyl (chloroacetyl)phosphonate
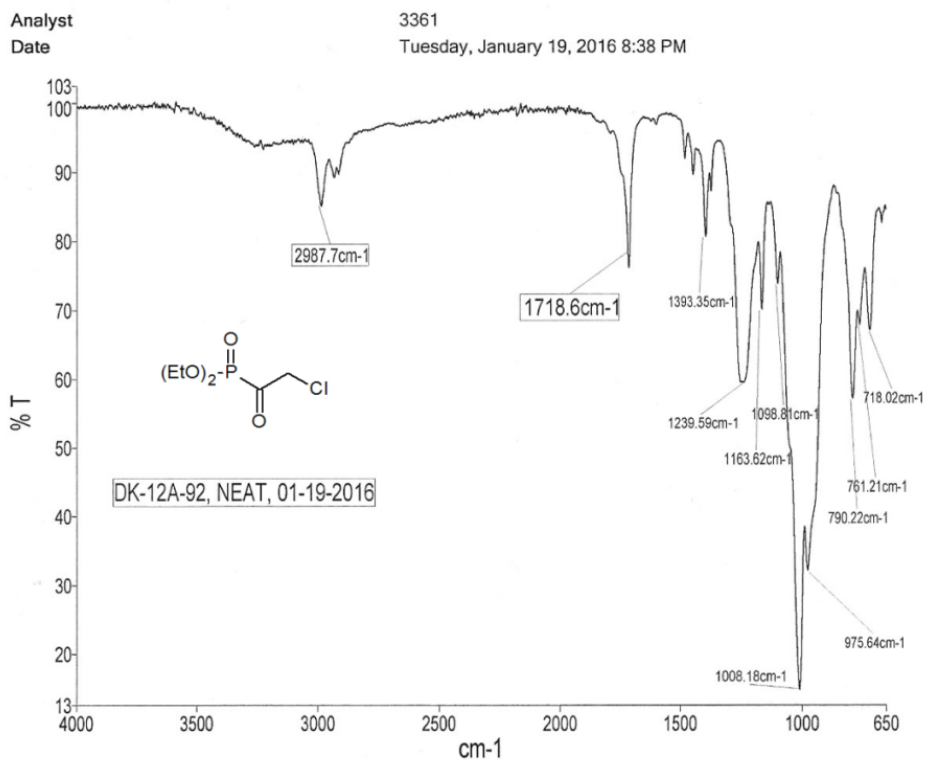
Figure C. 20. FT-IR spectrum of 3h
diethyl (chloroacetyl)phosphonate
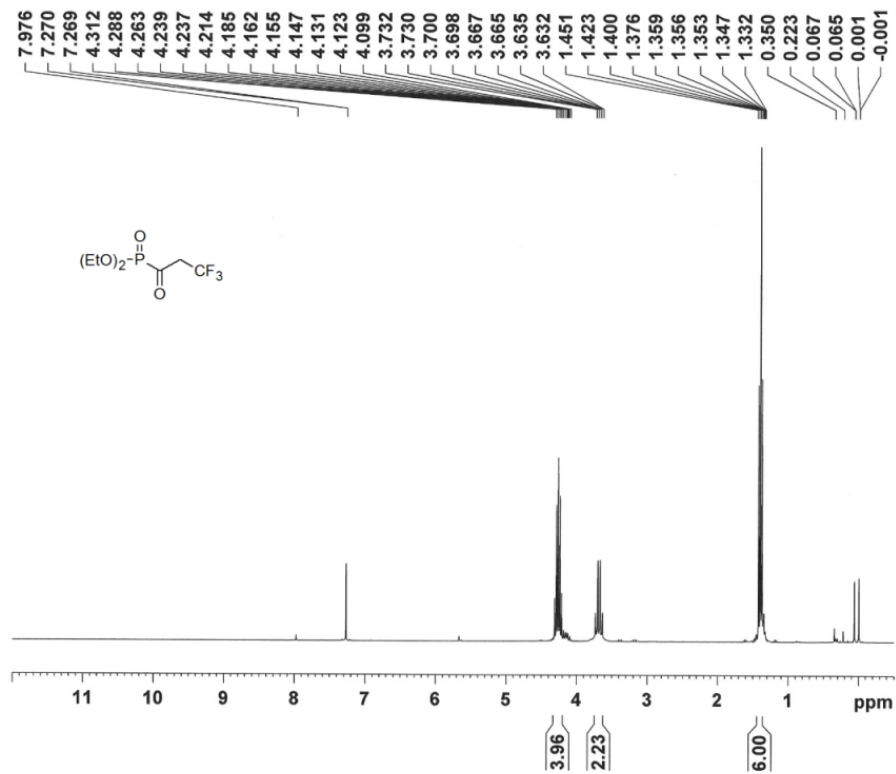
Figure C. 21. ^{1}H NMR spectrum of 3i
diethyl (3,3,3-trifluoropropanoyl)phosphonate

166
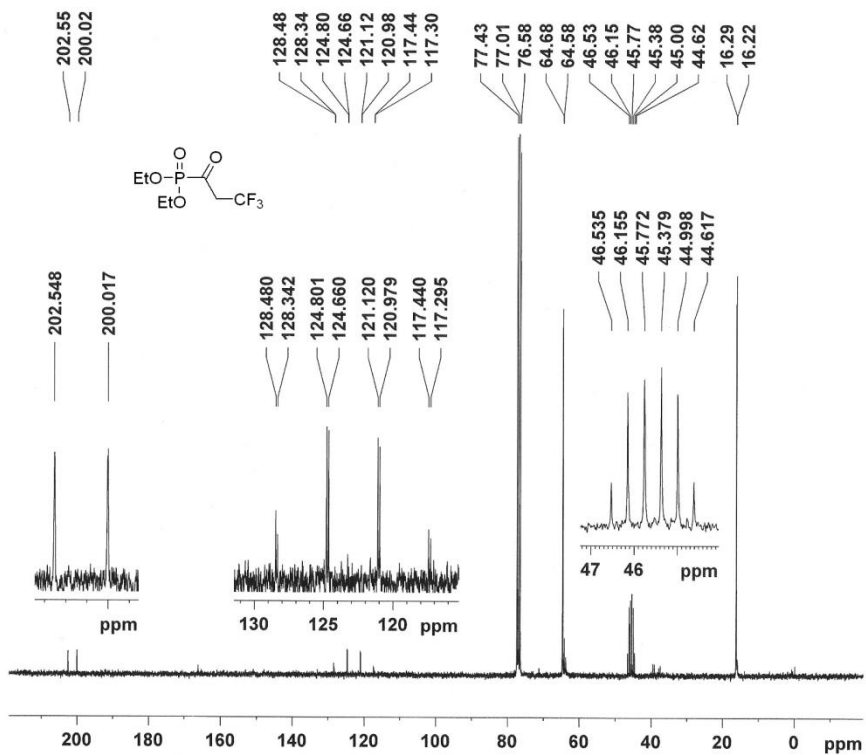
Figure C. 22. ^{13}C NMR spectrum of 3i
diethyl (3,3,3-trifluoropropanoyl)phosphonate
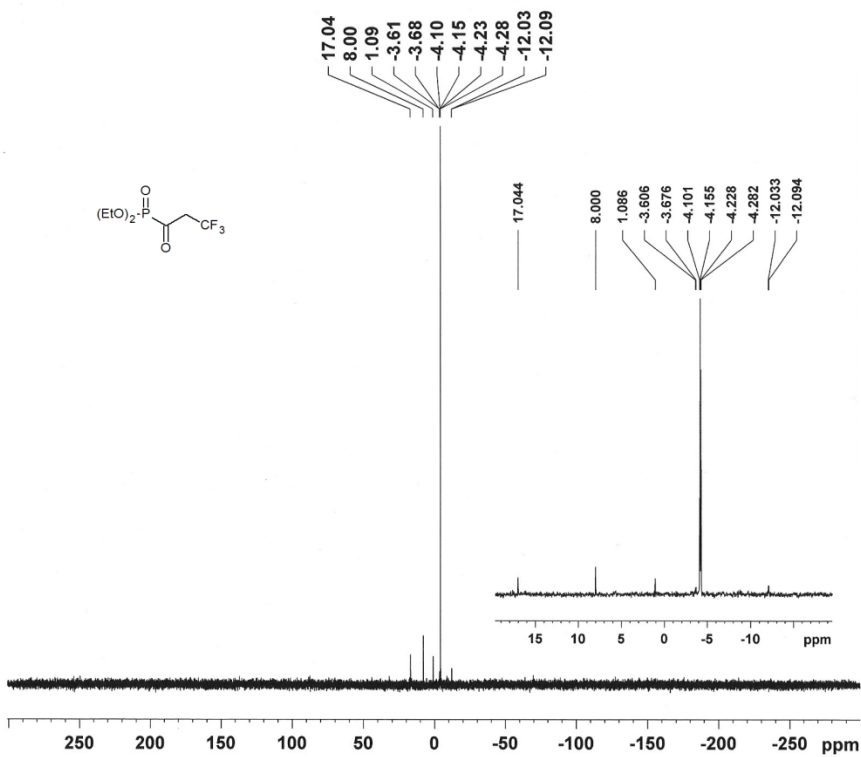
Figure C. 23. ^{31}P NMR spectrum of 3i
diethyl (3,3,3-trifluoropropanoyl)phosphonate
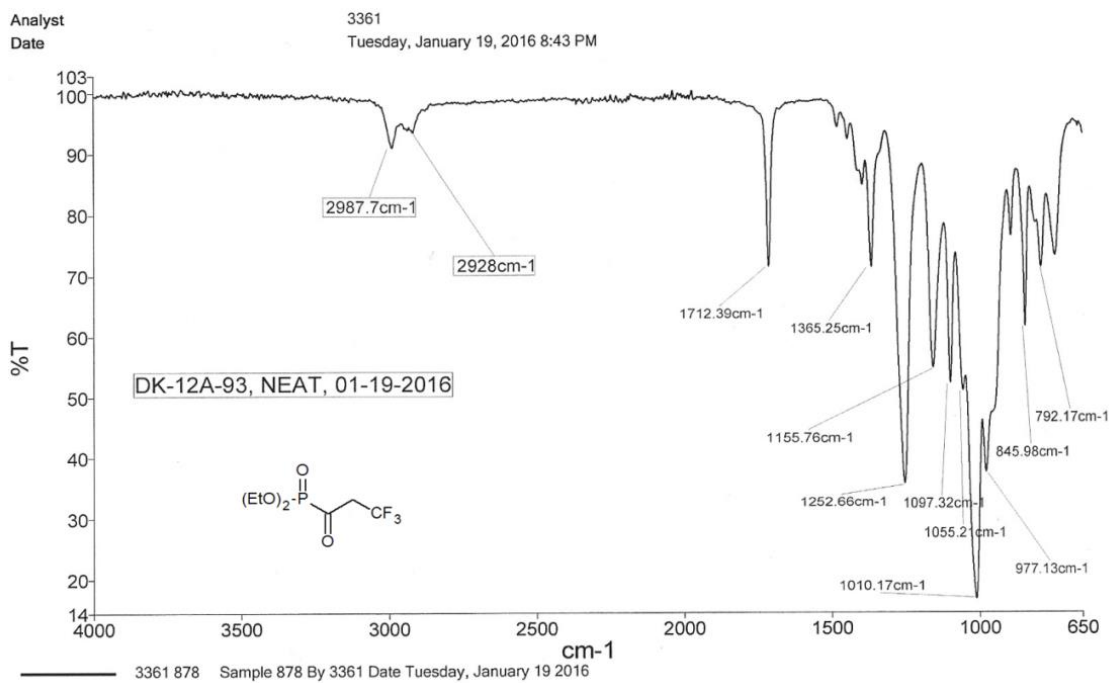
Figure C. 24. FT-IR spectrum of 3i
diethyl (3,3,3-trifluoropropanoyl)phosphonate

APPENDIX D

α-PHOSPHONOVINYL TRIFLATE SPECTRAL

DATA
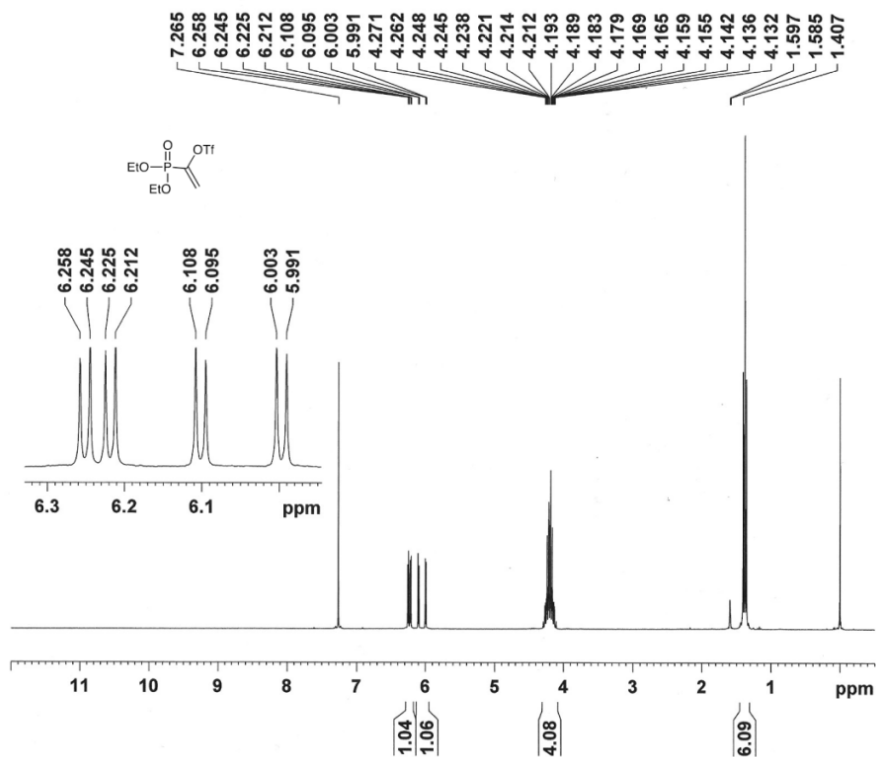
Figure D. 1. ¹H NMR spectrum of 4a
1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
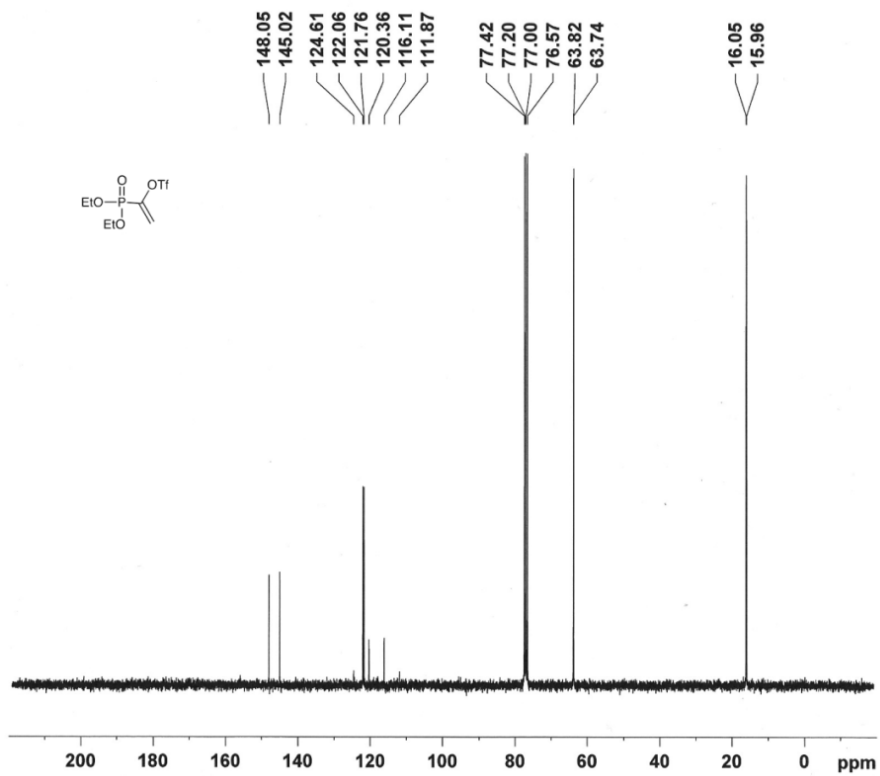
Figure D. 2. ^{13}C NMR spectrum of 4a
1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
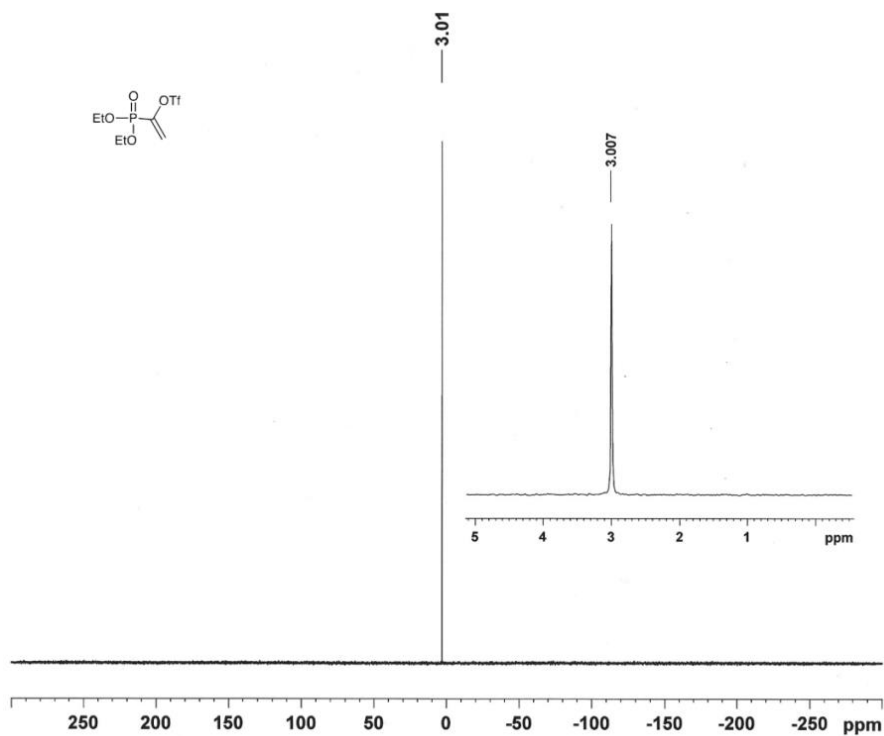
Figure D. 3. ^{31}P NMR spectrum of 4a
1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
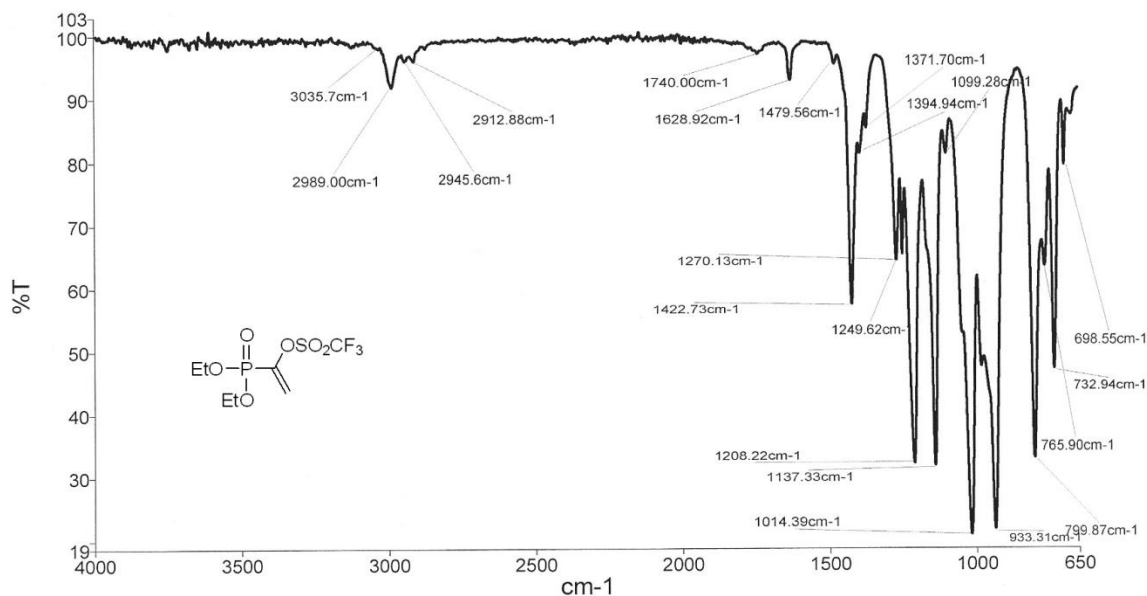
Figure D. 4. FT-IR spectrum of 4a
1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
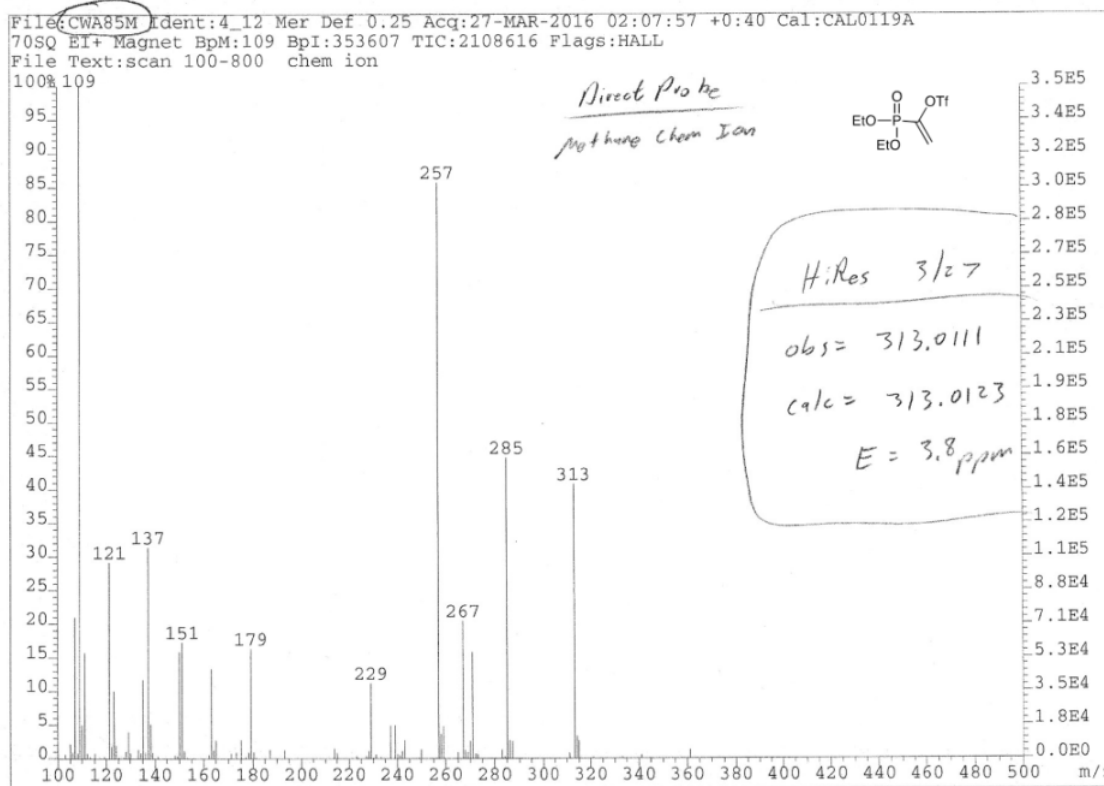
Figure D. 5. LRMS spectrum of 4a
1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
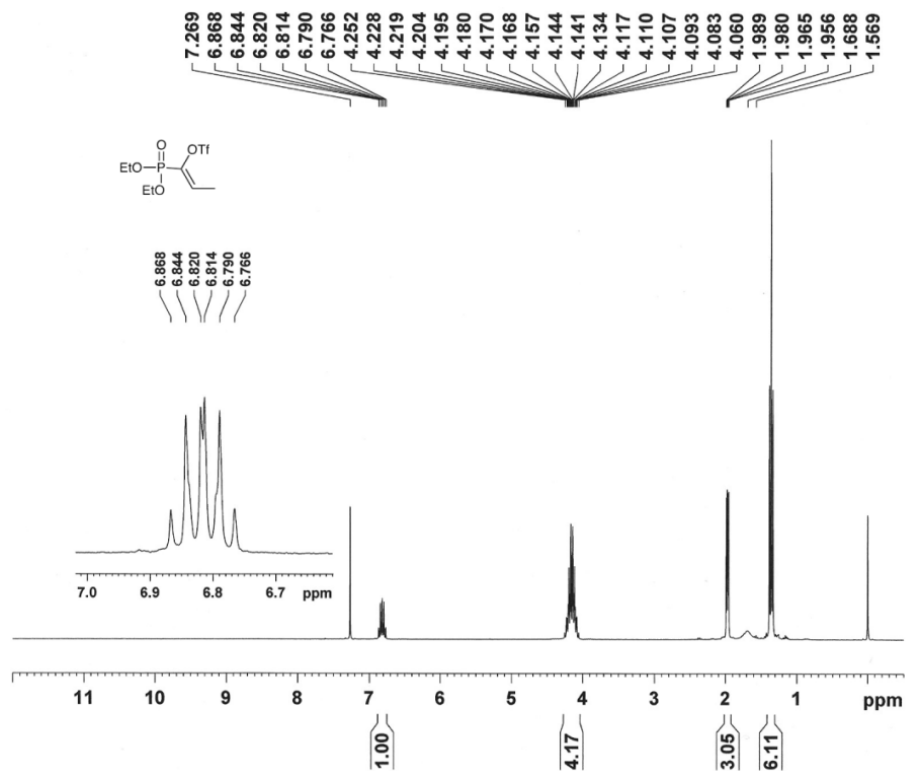
Figure D. 6. ^{1}H NMR spectrum of 4b
(1E)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate
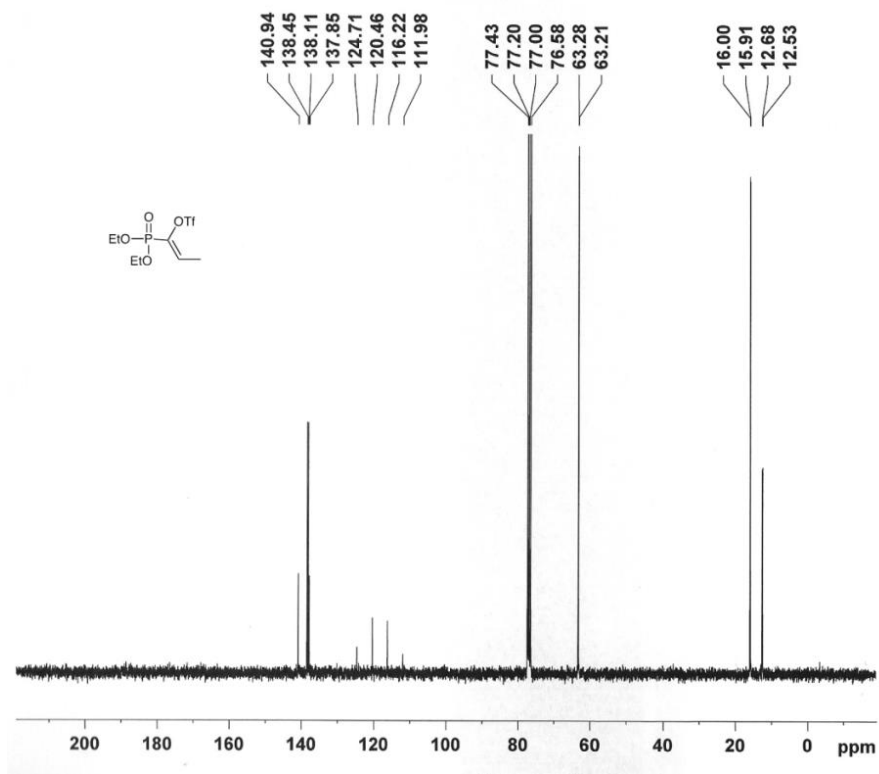
Figure D. 7. ^{13}C NMR spectrum of 4b
(1E)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate
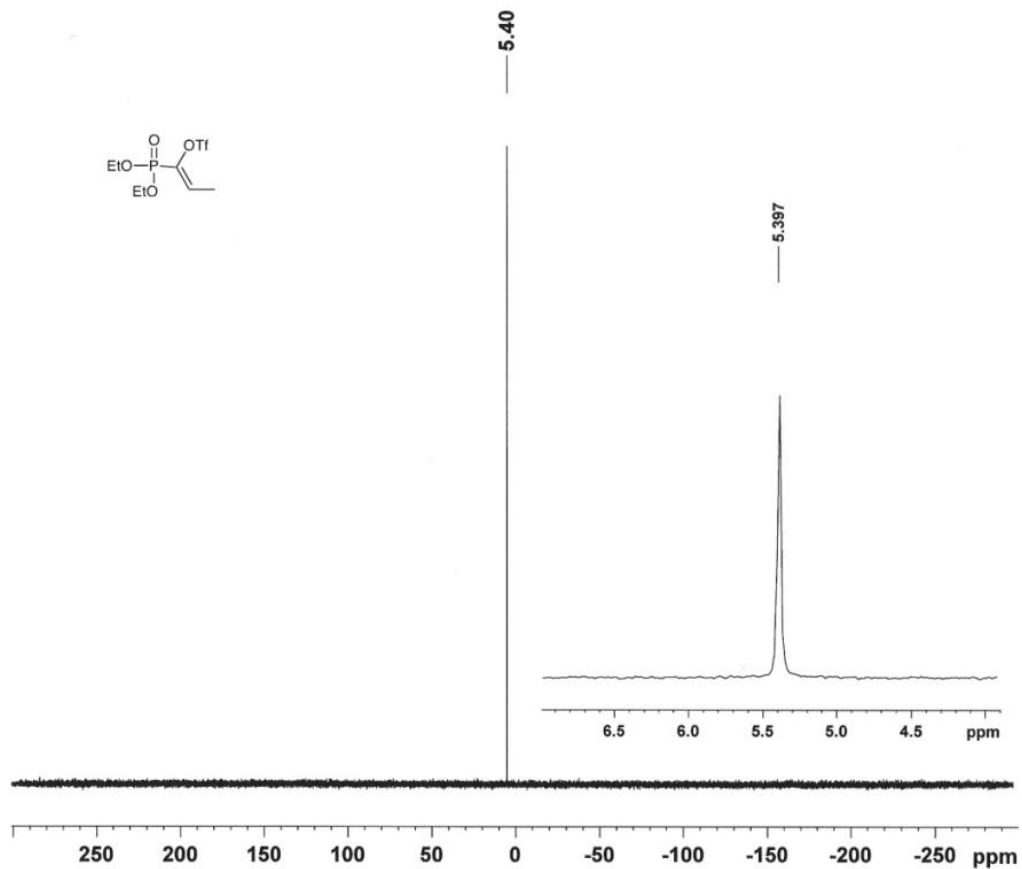
Figure D. 8. ³¹P NMR spectrum of 4b

Figure D. 8. ^{31}P NMR spectrum of 4b
(1E)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate
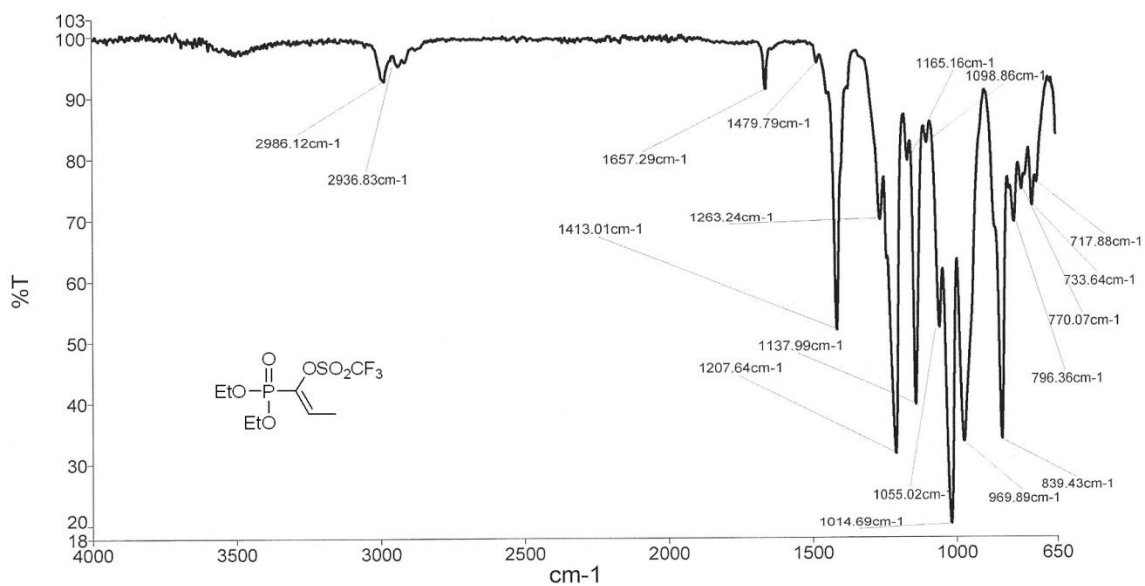
Figure D. 9. FT-IR spectrum of 4b
(1E)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate
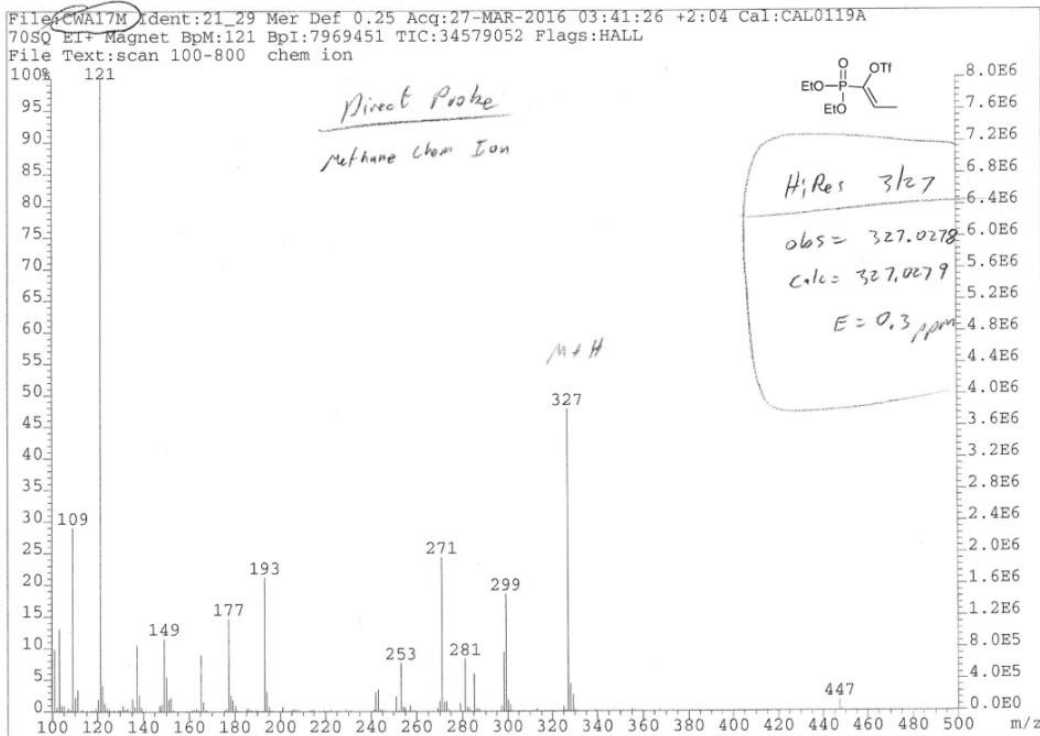
Figure D. 10. LRMS spectrum of 4b
(1E)-1-(diethoxyphosphoryl)prop-1-en-1-yl trifluoromethanesulfonate
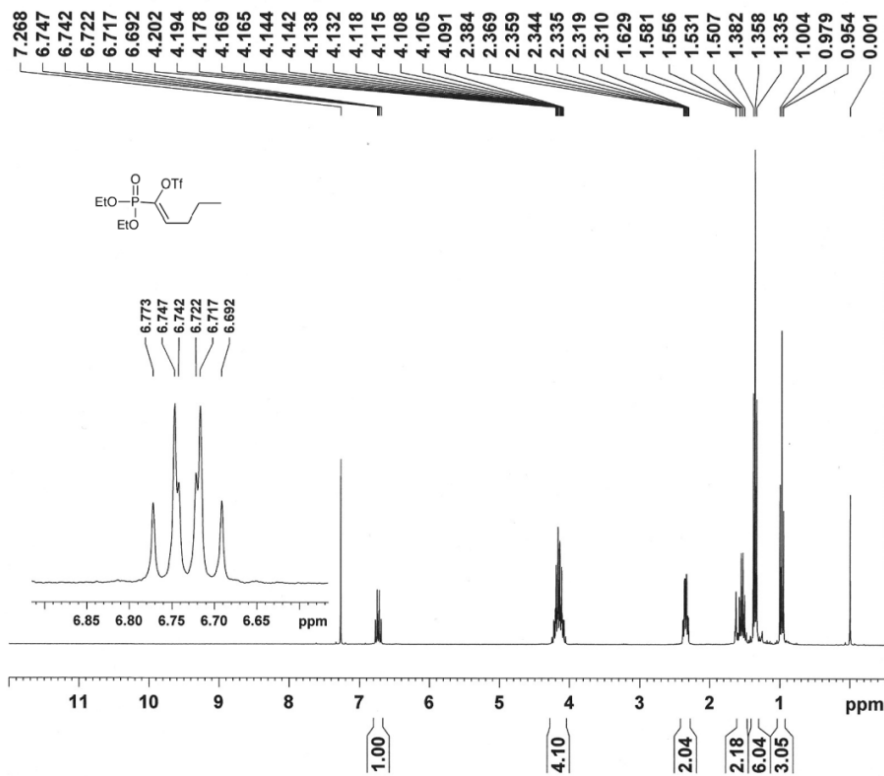
Figure D. 11. ¹H NMR spectrum of 4c
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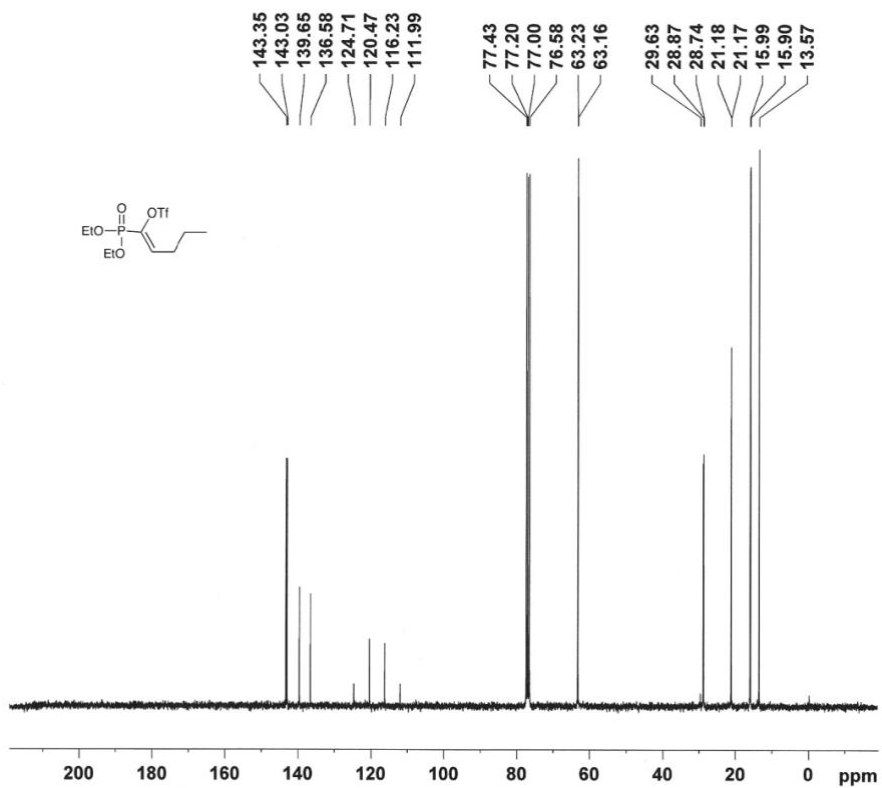
Figure D. 12. ^{13}C NMR spectrum of 4c
(1E)-1-(diethoxyphosphoryl)pent-1-en-1-yl trifluoromethanesulfonate
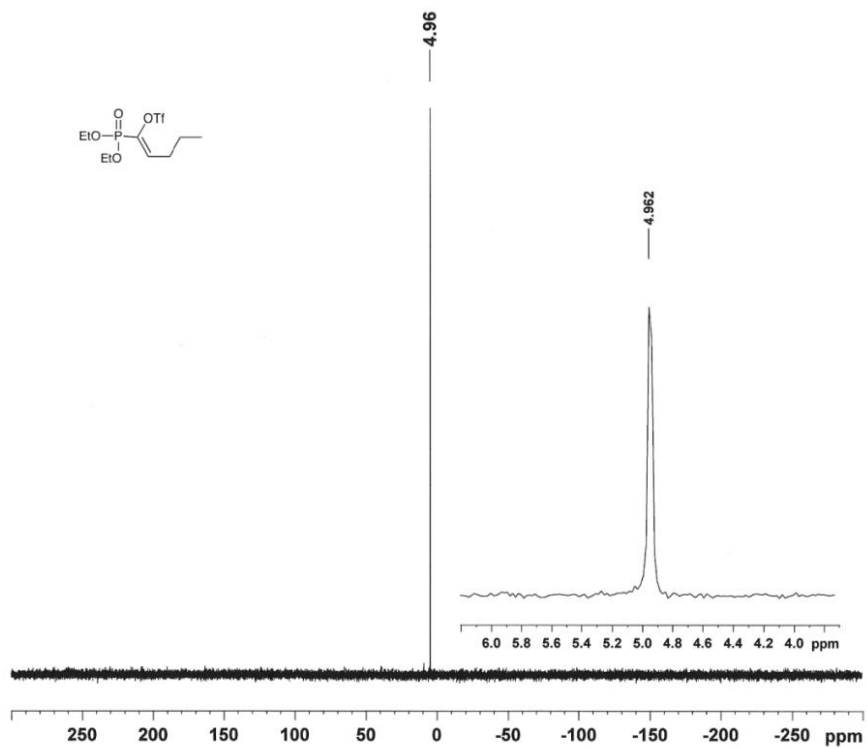
Figure D. 13. ^{31}P NMR spectrum of 4c
(1E)-1-(diethoxyphosphoryl)pent-1-en-1-yl trifluoromethanesulfonate
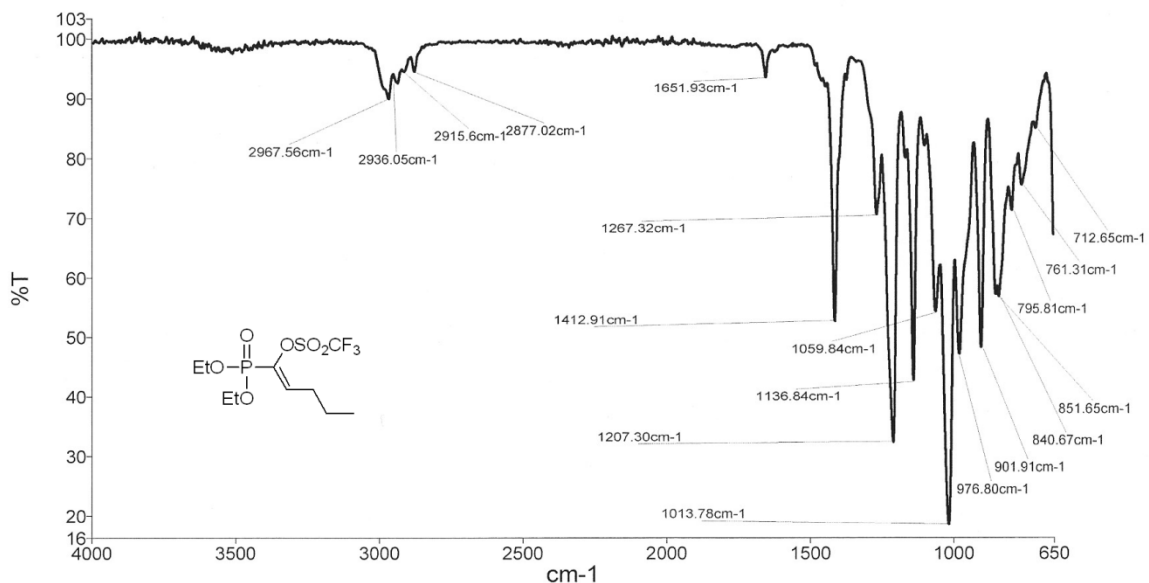
Figure D. 14. FT-IR spectrum of 4c
(1E)-1-(diethoxyphosphoryl)pent-1-en-1-yl trifluoromethanesulfonate
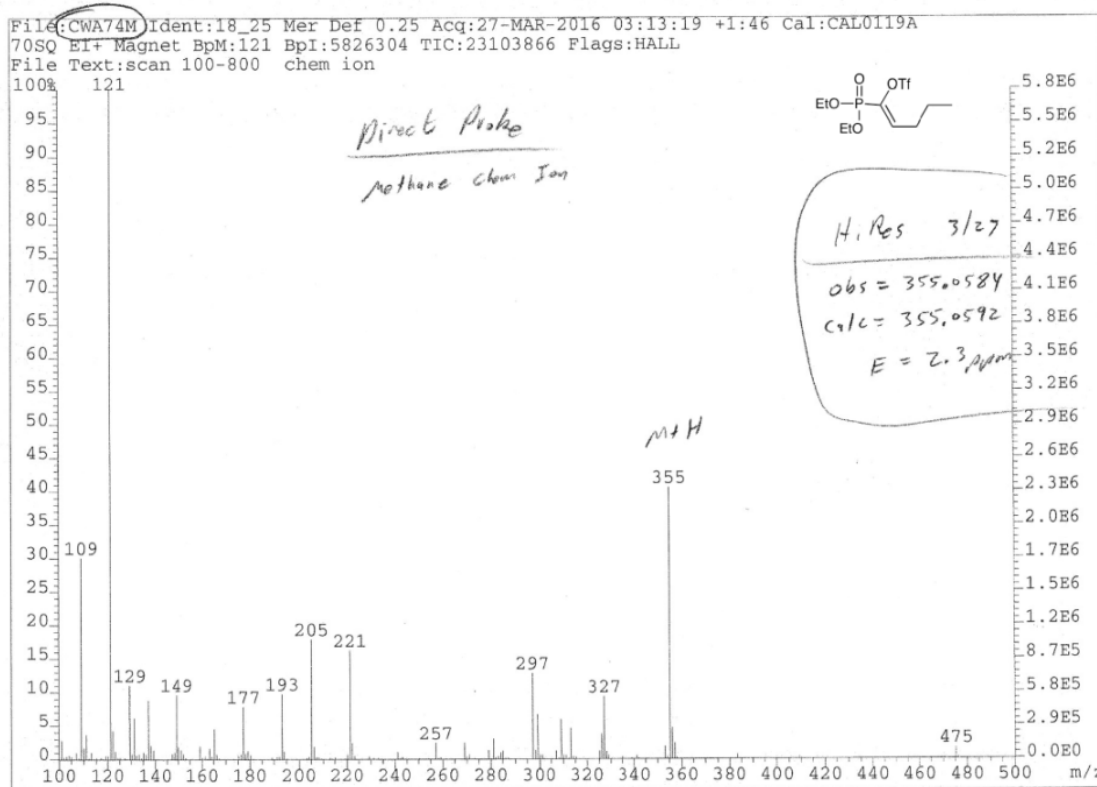
Figure D. 15. LRMS spectrum of 4c
(1E)-1-(diethoxyphosphoryl)pent-1-en-1-yl trifluoromethanesulfonate
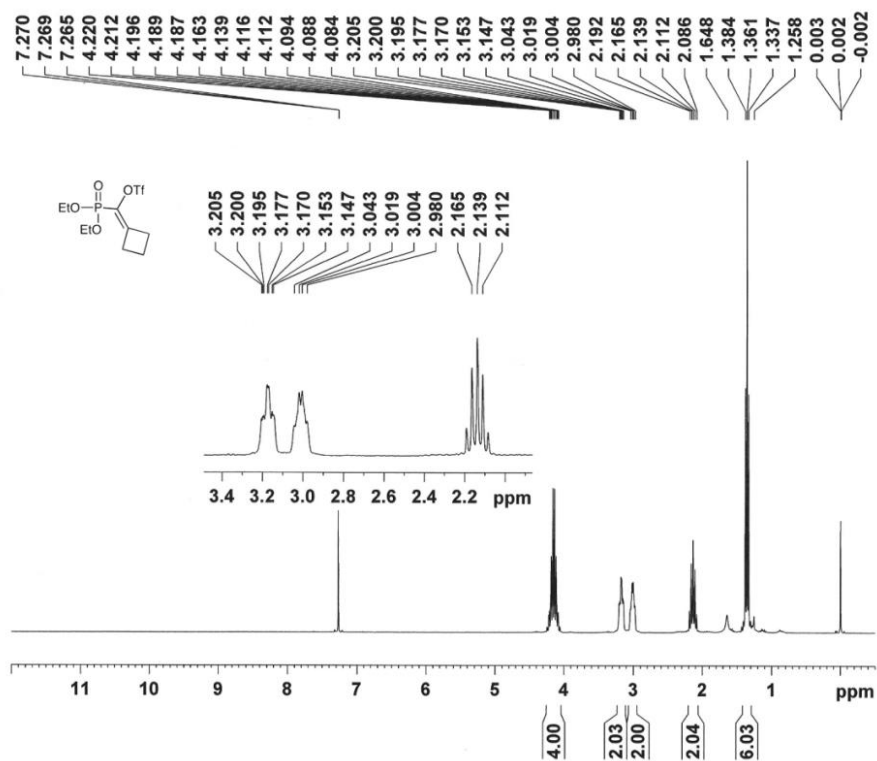
**Figure D. 16. ¹H NMR spectrum of 4d
cyclobutylidene(diethoxyphosphoryl)methyl trifluoromethanesulfonate**
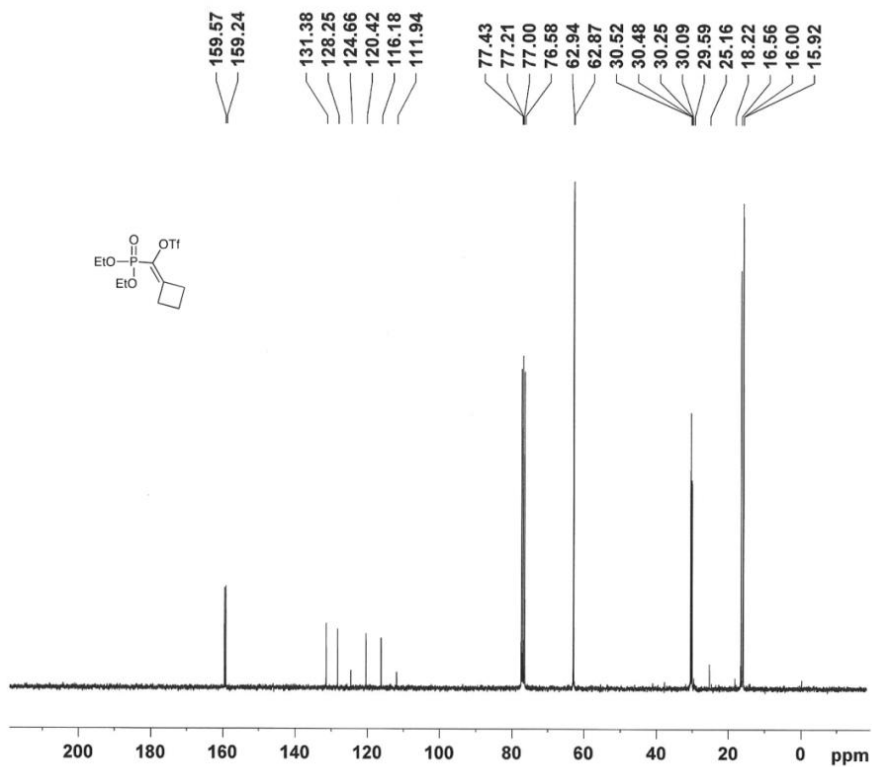
**Figure D. 17. ¹³C NMR spectrum of 4d
cyclobutylidene(diethoxyphosphoryl)methyl trifluoromethanesulfonate**

177
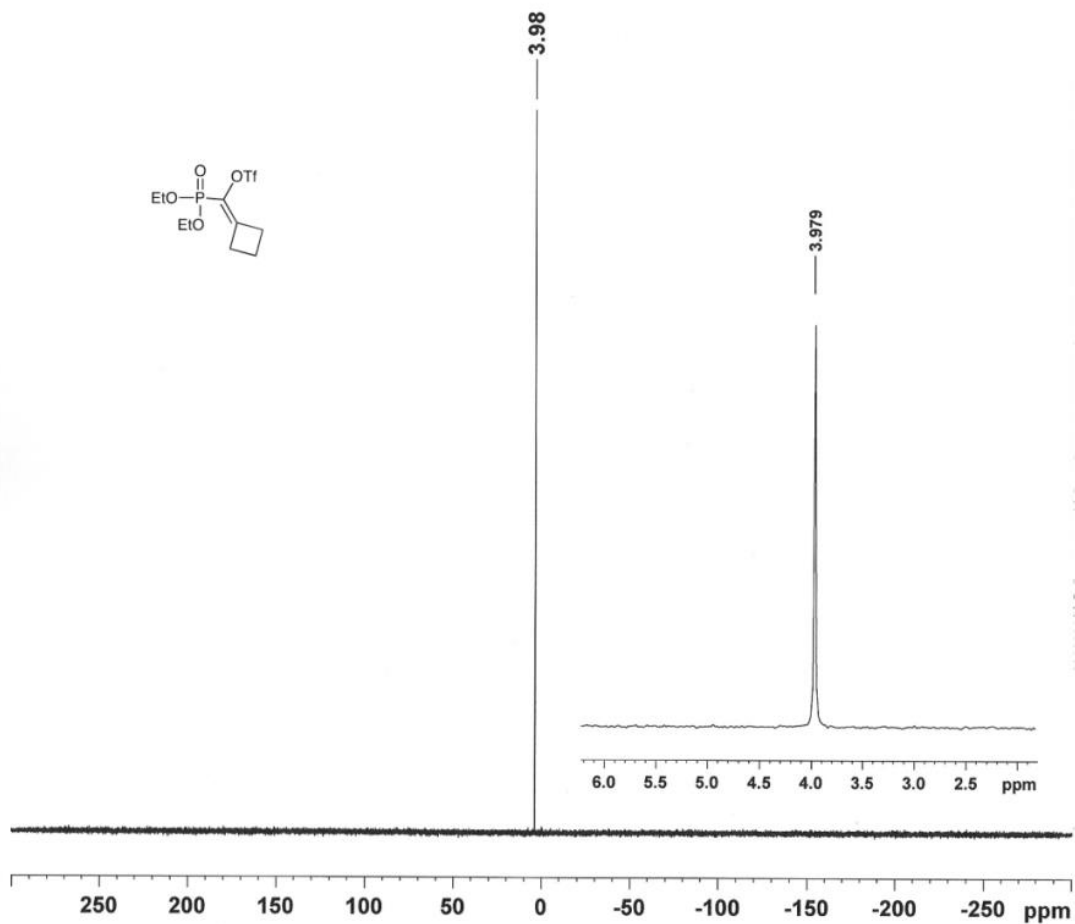
Figure D. 18. ³¹P NMR spectrum of 4d
cyclobutylidene(diethoxyphosphoryl)methyl trifluoromethanesulfonate
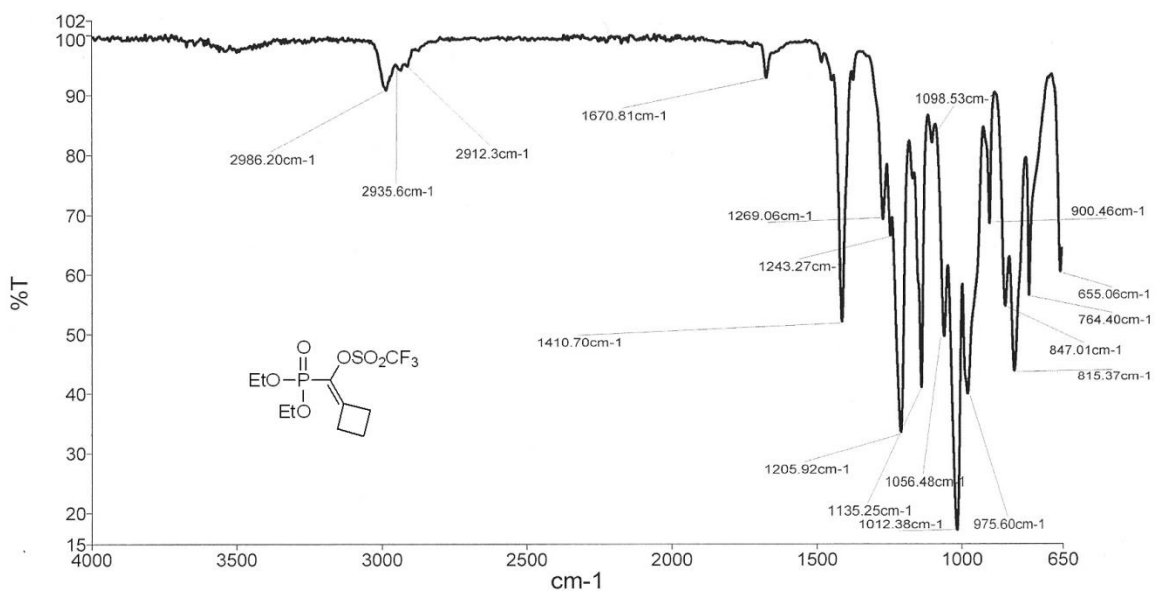
Figure D. 19. FT-IR spectrum of 4d
cyclobutylidene(diethoxyphosphoryl)methyl trifluoromethanesulfonate

178
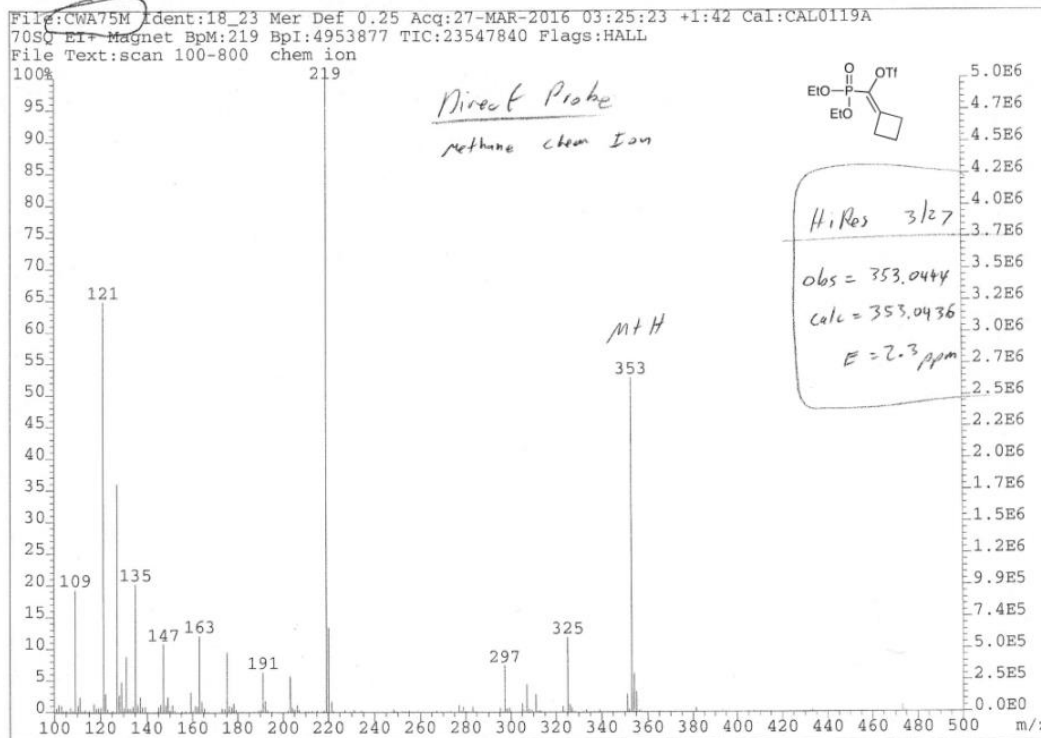
Figure D. 20. LRMS spectrum of 4d
cyclobutylidene(diethoxyphosphoryl)methyl trifluoromethanesulfonate
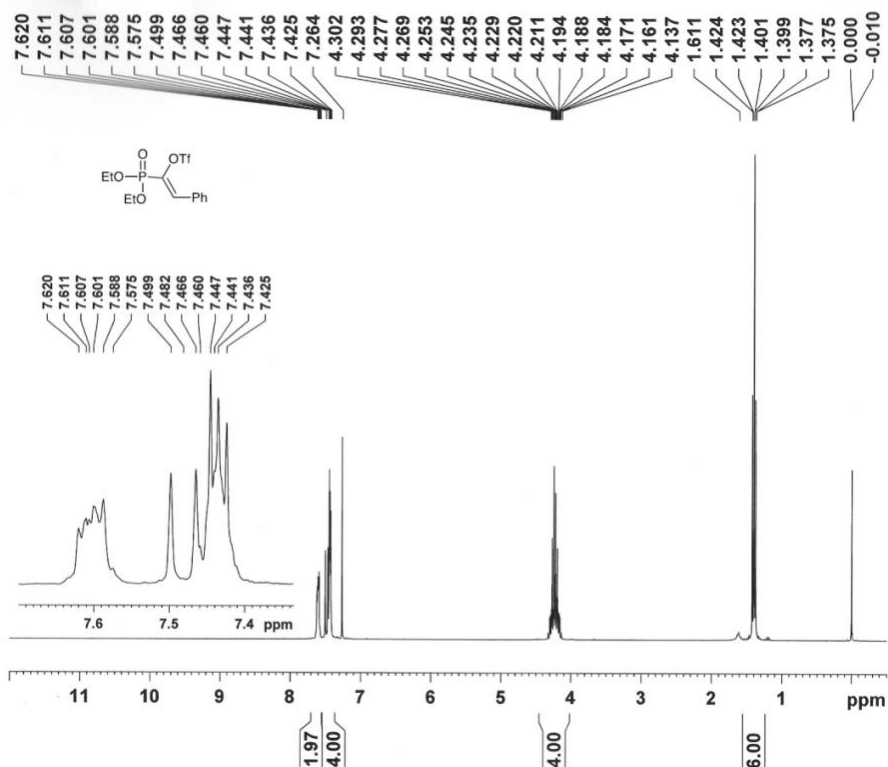
Figure D. 21. ¹H NMR spectrum of 4e
(E)-1-(diethoxyphosphoryl)-2-phenylethenyl trifluoromethanesulfonate
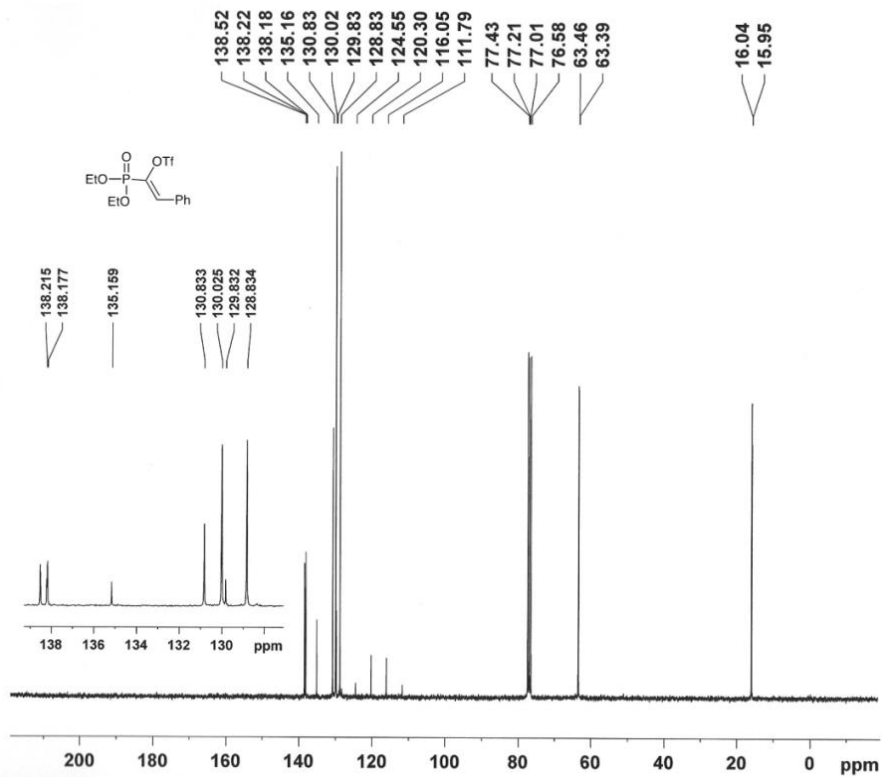
Figure D. 22. ¹³C NMR spectrum of 4e

Figure D. 22. ^{13}C NMR spectrum of 4e
(E)-1-(diethoxyphosphoryl)-2-phenylethenyl trifluoromethanesulfonate
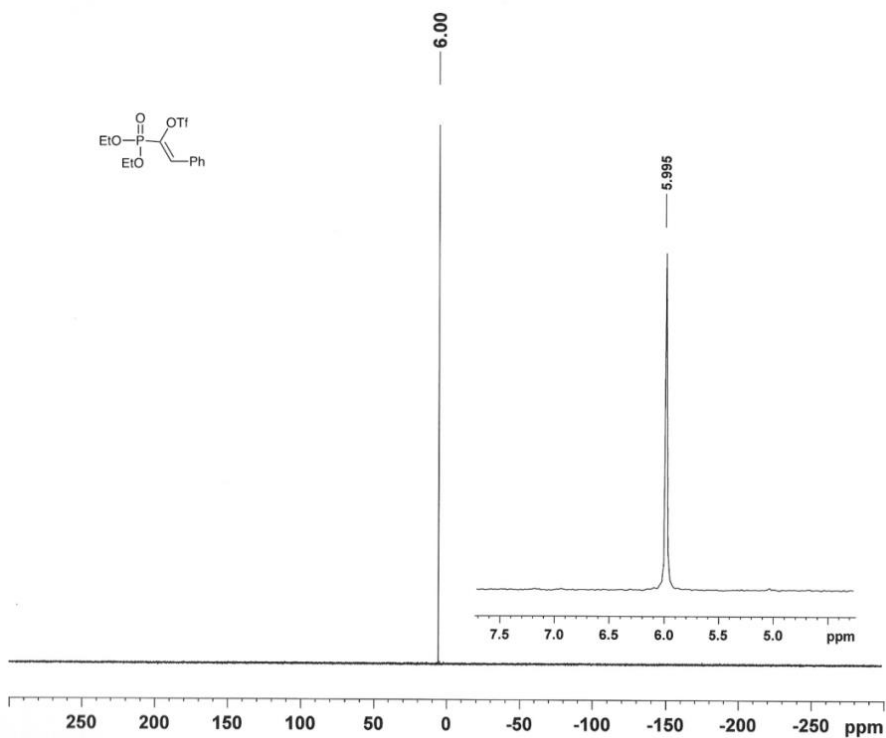
Figure D. 23. ^{31}P NMR spectrum of 4e
(E)-1-(diethoxyphosphoryl)-2-phenylethenyl trifluoromethanesulfonate

180
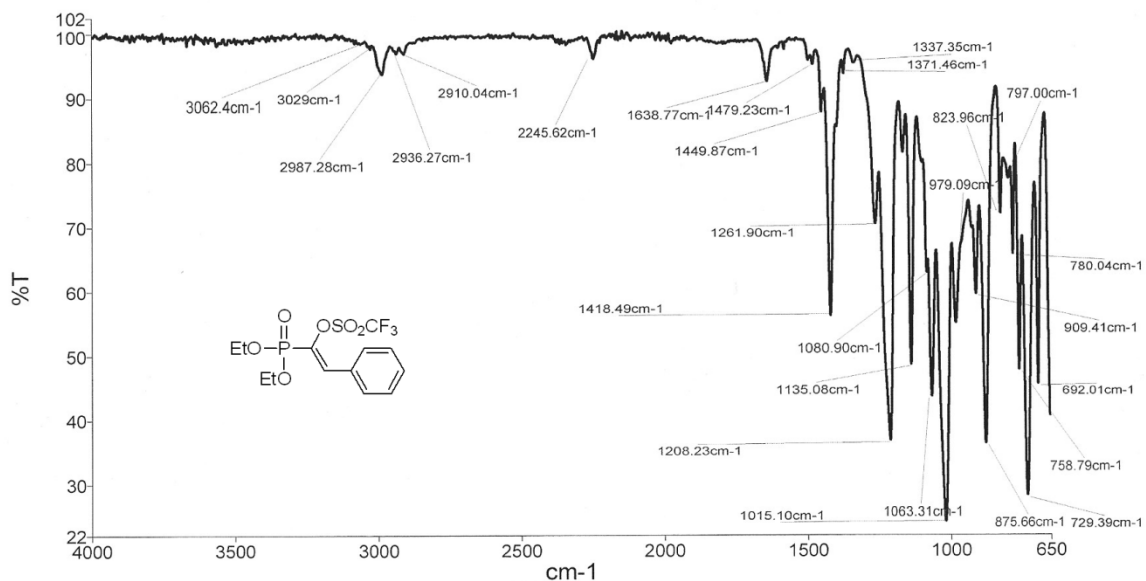
Figure D. 24. FT-IR spectrum of 4e
(E)-1-(diethoxyphosphoryl)-2-phenylethenyl trifluoromethanesulfonate
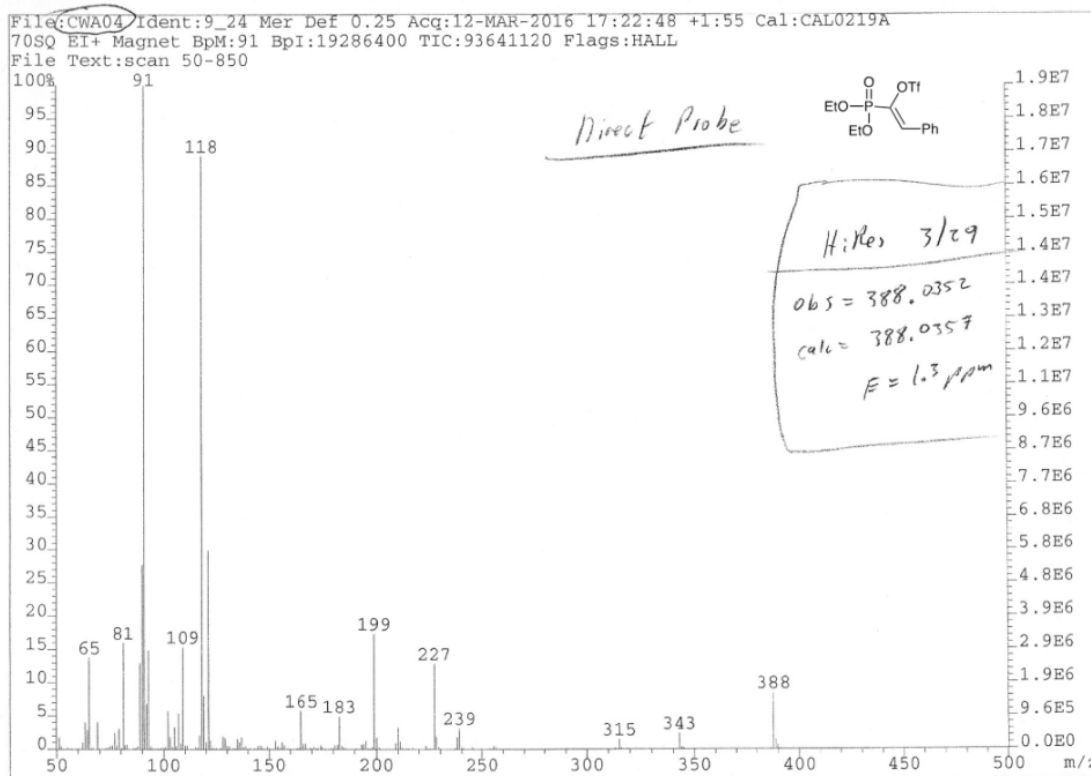
Figure D. 25. LRMS spectrum of 4e
(E)-1-(diethoxyphosphoryl)-2-phenylethenyl trifluoromethanesulfonate
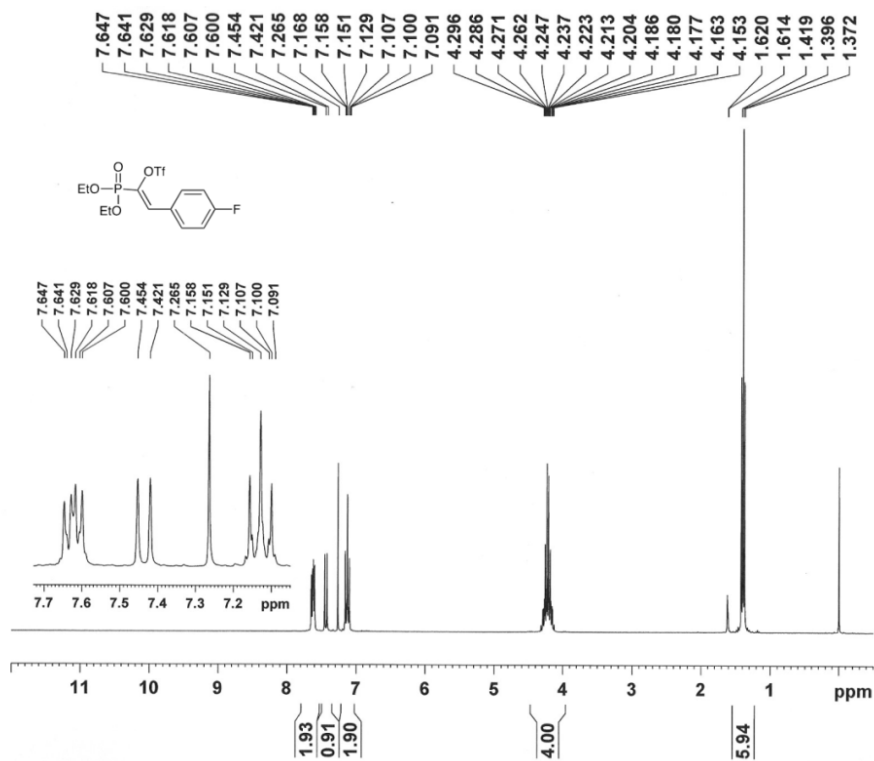
Figure D. 26. ^{1}H NMR spectrum of 4f
(E)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)ethenyl trifluoromethanesulfonate
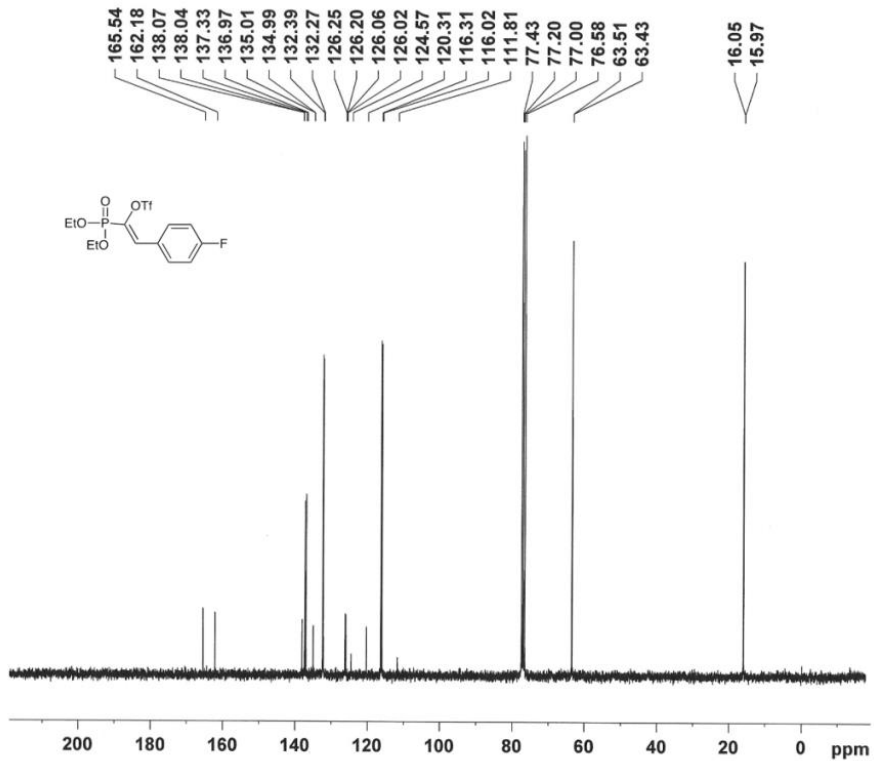
Figure D. 27. ^{13}C NMR spectrum of 4f
(E)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)ethenyl trifluoromethanesulfonate
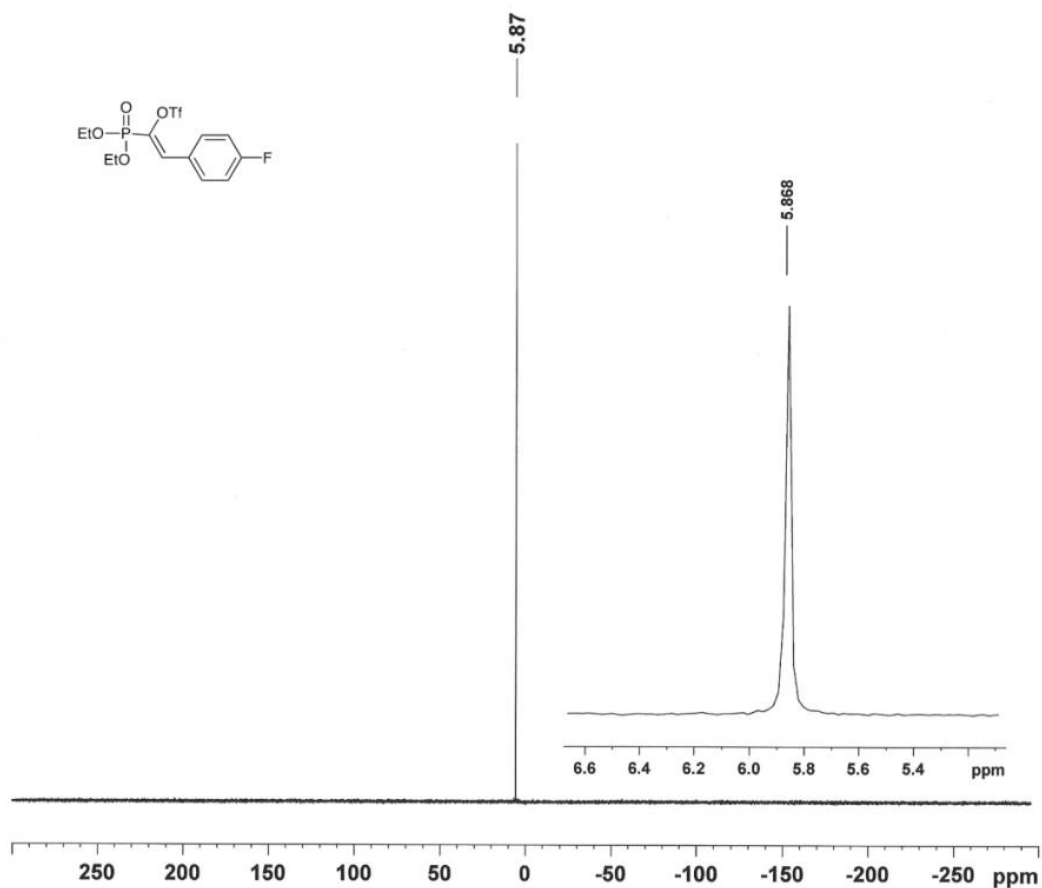
Figure D. 28. ^{31}P NMR spectrum of 4f
(E)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)ethenyl trifluoromethanesulfonate
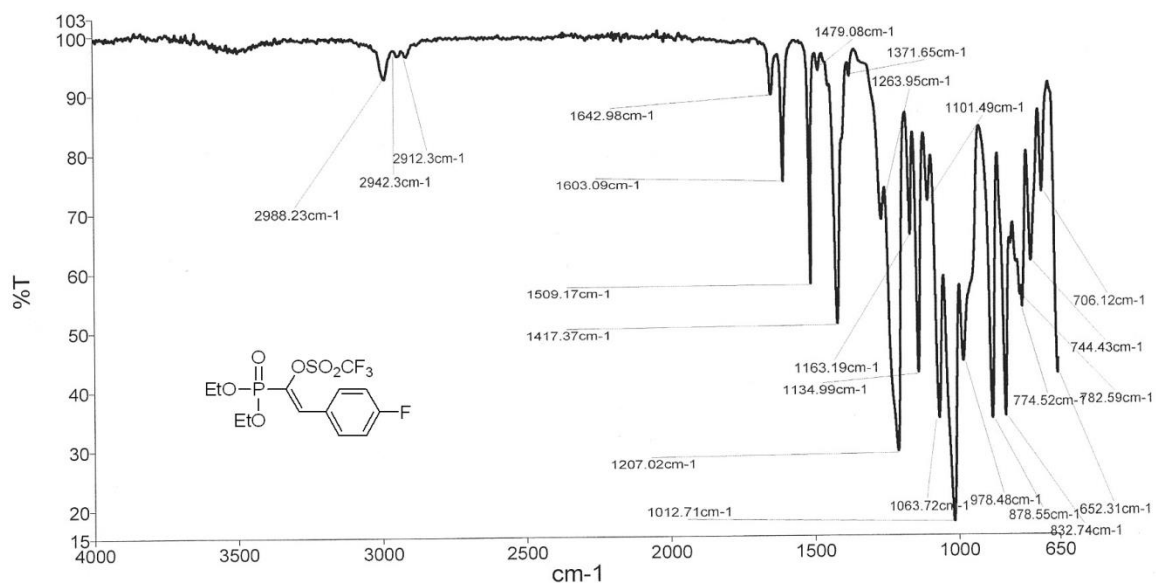
Figure D. 29. FT-IR spectrum of 4f
(E)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)ethenyl trifluoromethanesulfonate

183
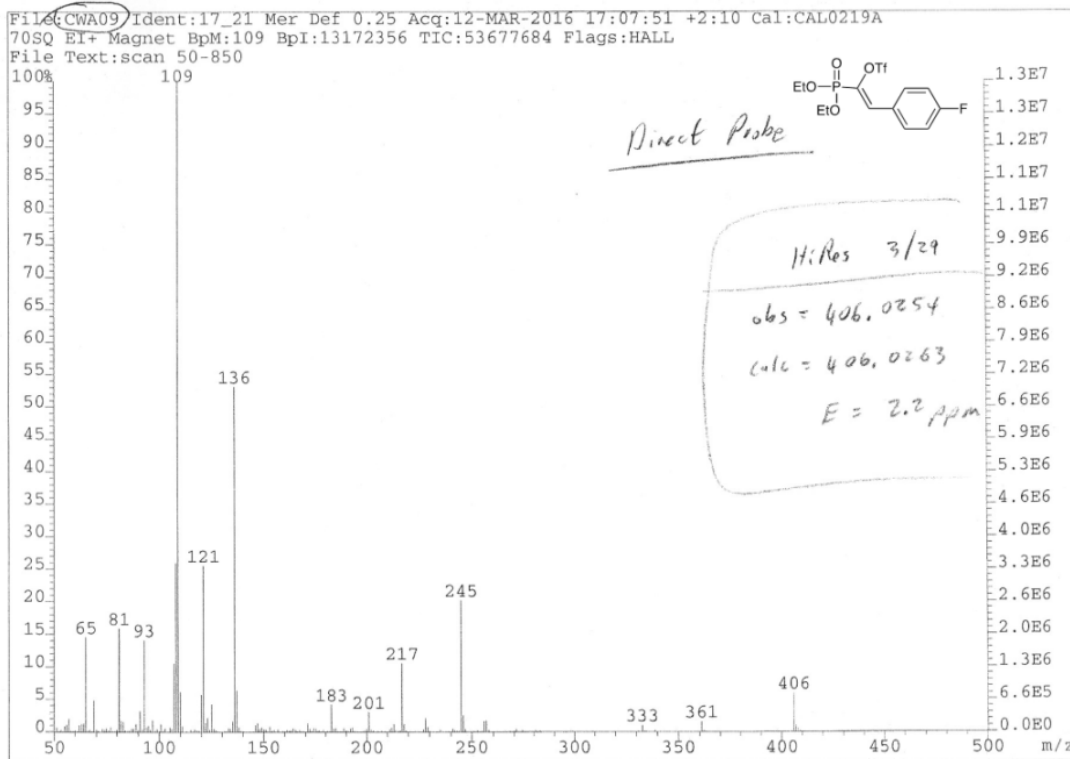
Figure D. 30. LRMS spectrum of 4f
(E)-1-(diethoxyphosphoryl)-2-(4-fluorophenyl)ethenyl trifluoromethanesulfonate
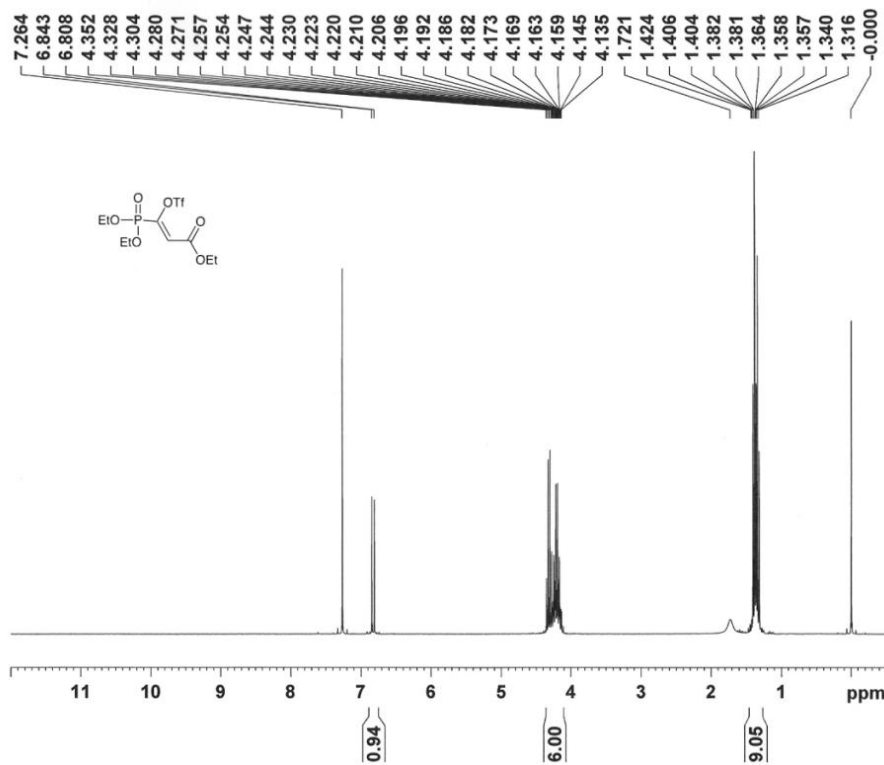
Figure D. 31. ¹H NMR spectrum of 4g
ethyl (2E)-3-(diethoxyphosphoryl)-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate

184
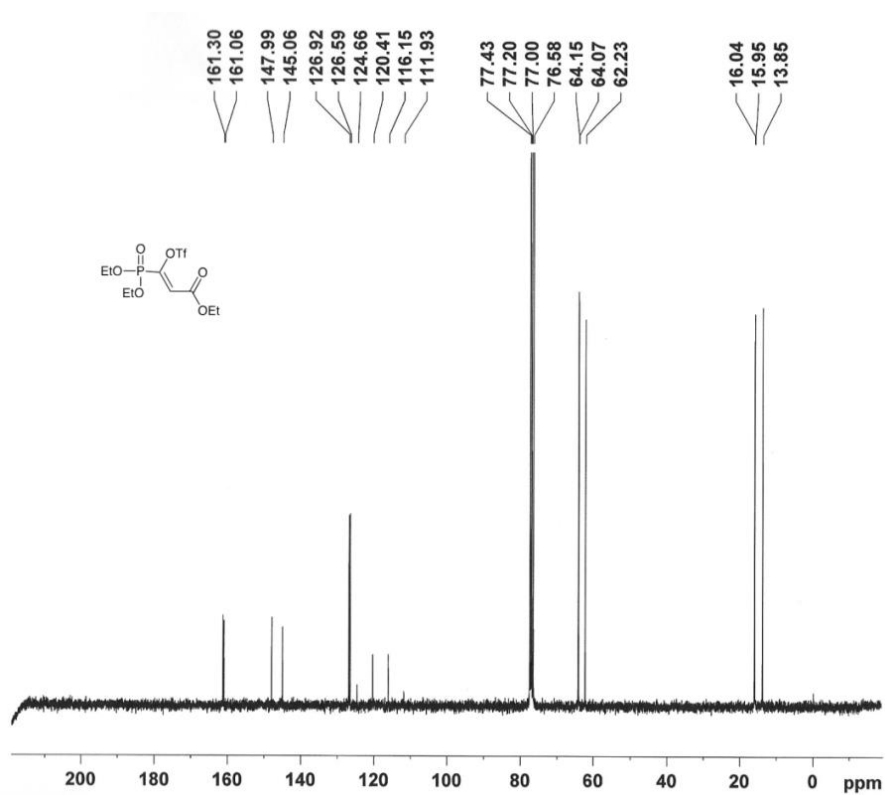
Figure D. 32. ^{13}C NMR spectrum of 4g
ethyl (2E)-3-(diethoxyphosphoryl)-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate
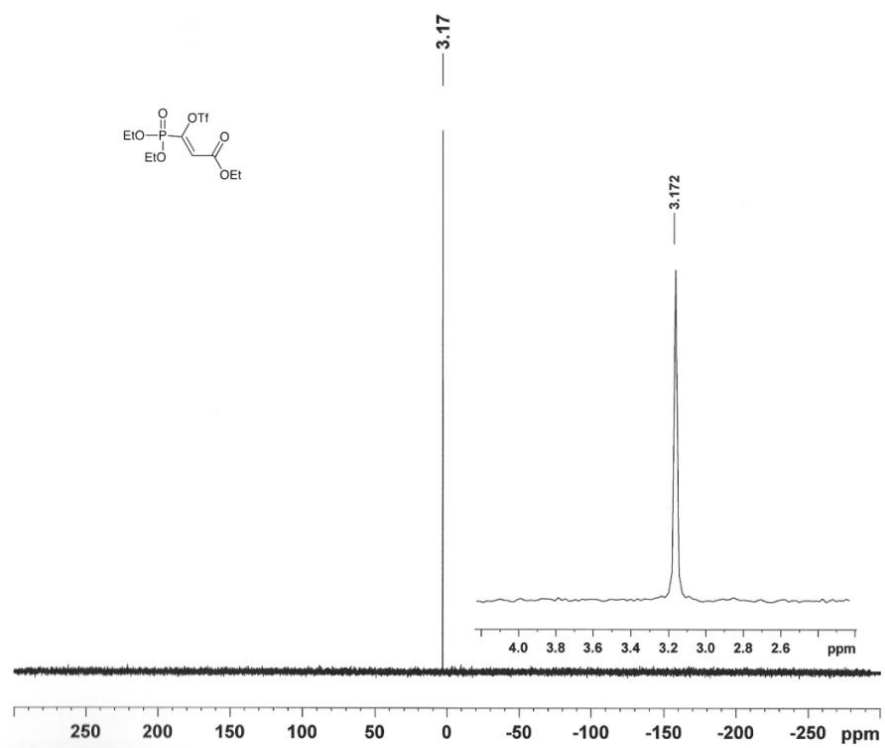
Figure D. 33. ^{31}P NMR spectrum of 4g
ethyl (2E)-3-(diethoxyphosphoryl)-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate

185
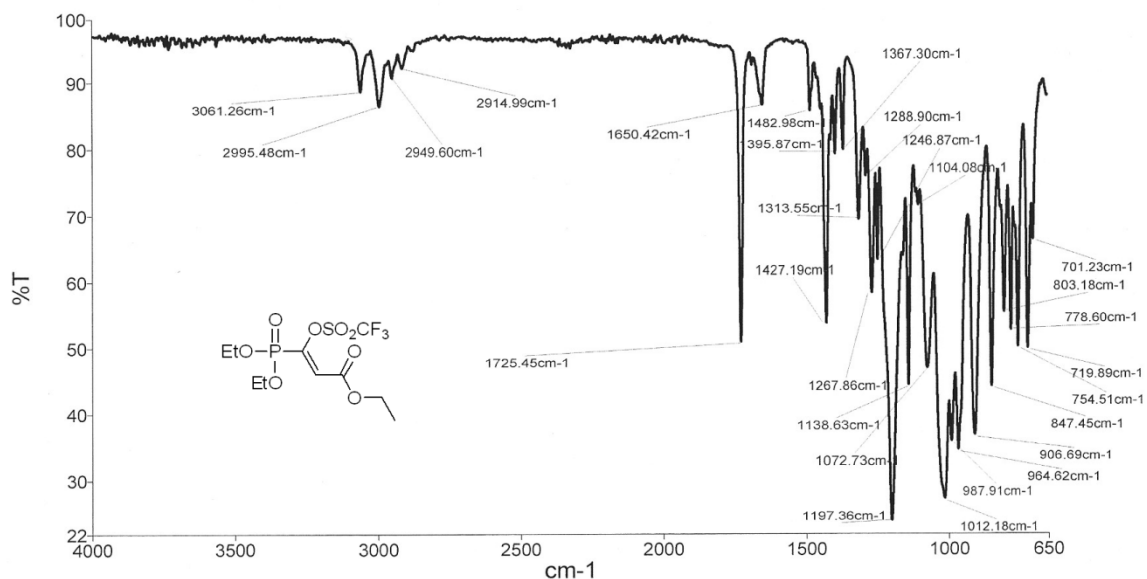
Figure D. 34. FT-IR spectrum of 4g
ethyl (2E)-3-(diethoxyphosphoryl)-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate
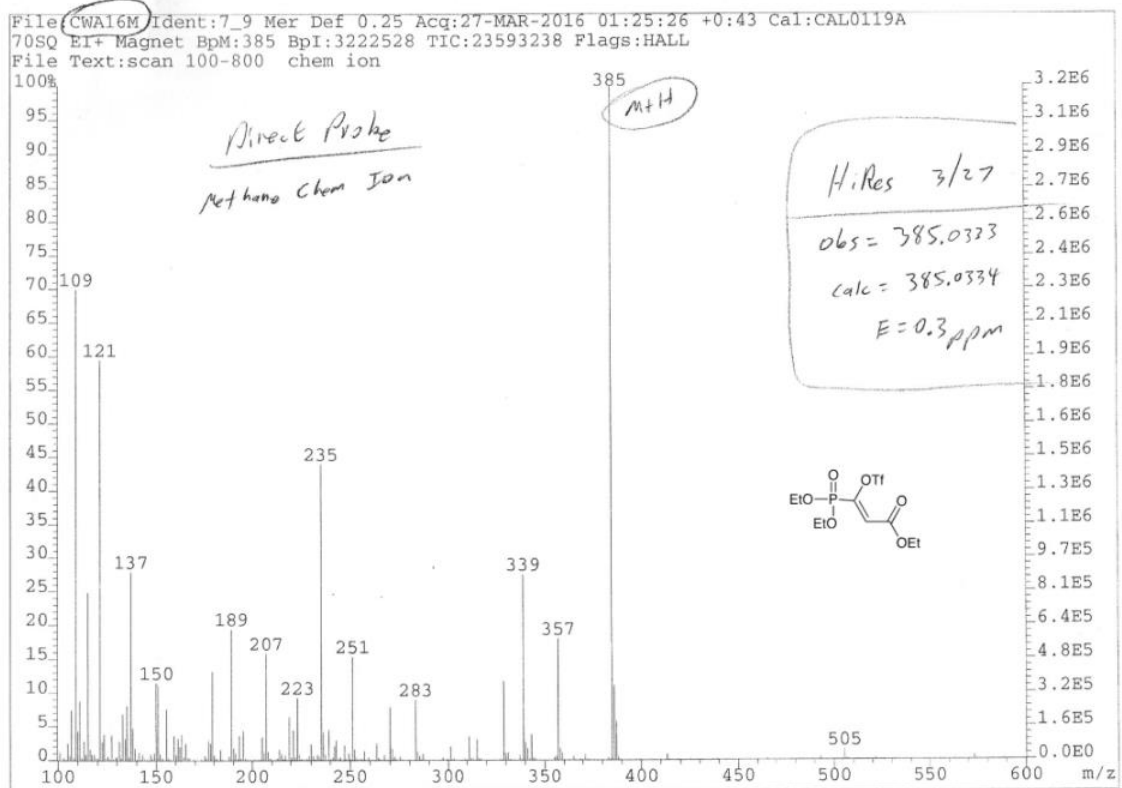
Figure D. 35. LRMS spectrum of 4g
ethyl (2E)-3-(diethoxyphosphoryl)-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate

186
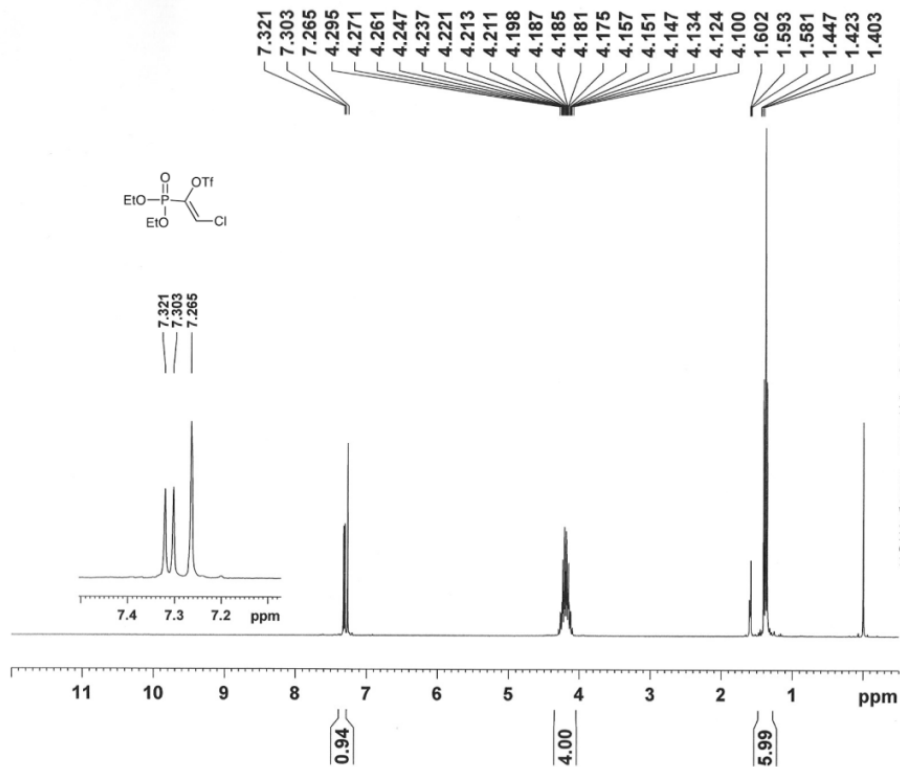
Figure D. 36. ^{1}H NMR spectrum of 4h
(E)-2-chloro-1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
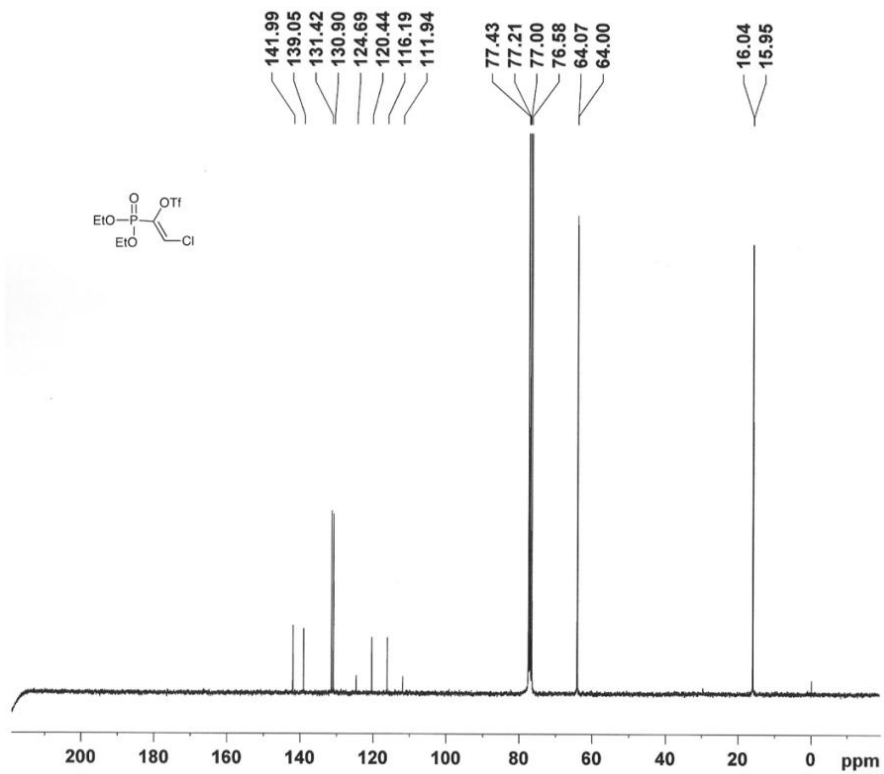
Figure D. 37. ^{13}C NMR spectrum of 4h
(E)-2-chloro-1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate

187
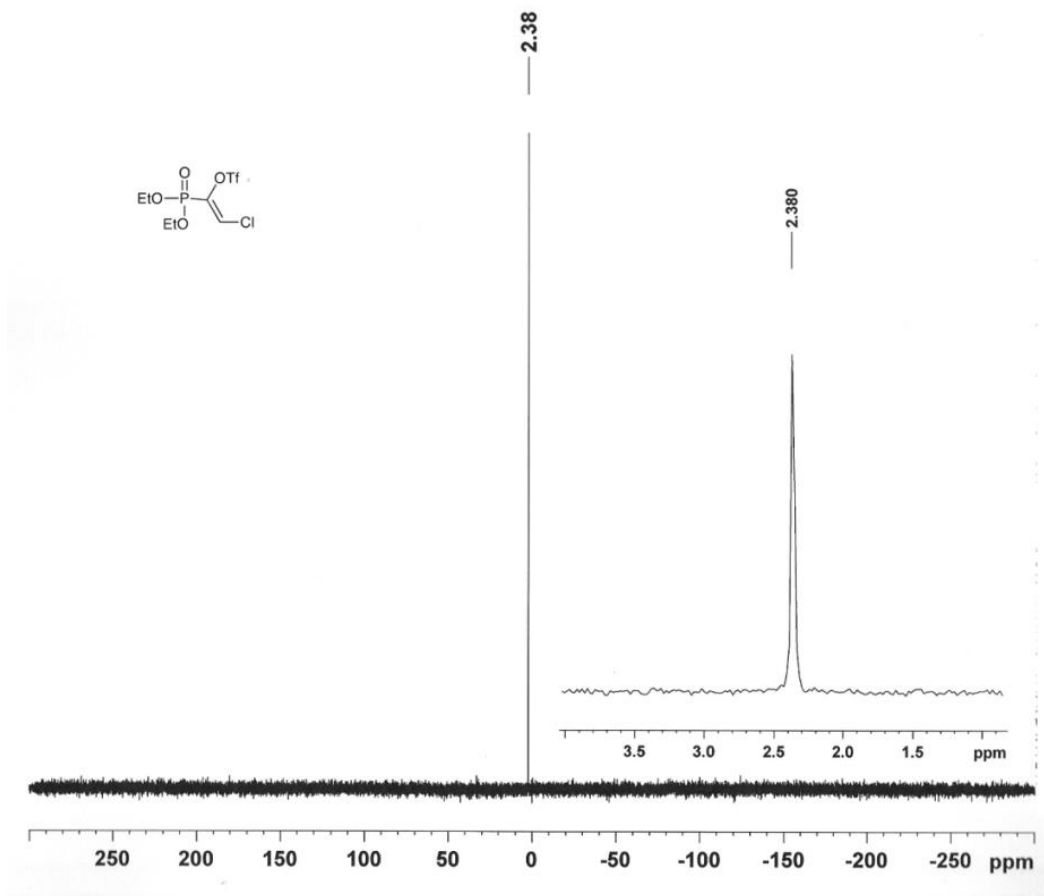
Figure D. 38. ^{31}P NMR spectrum of 4h
(E)-2-chloro-1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
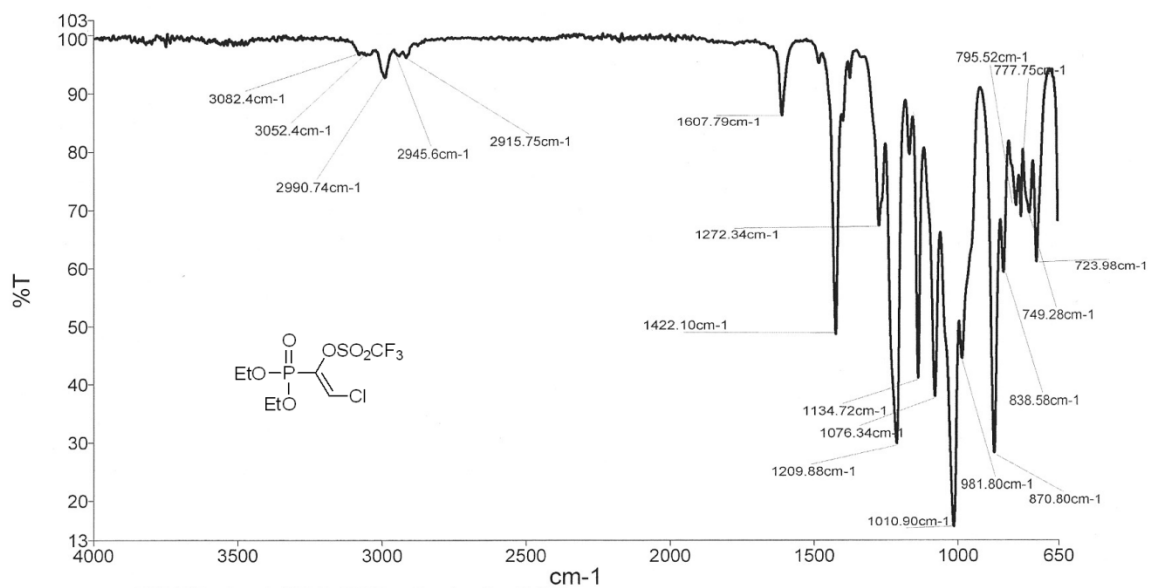
Figure D. 39. FT-IR spectrum of 4h
(E)-2-chloro-1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate

188
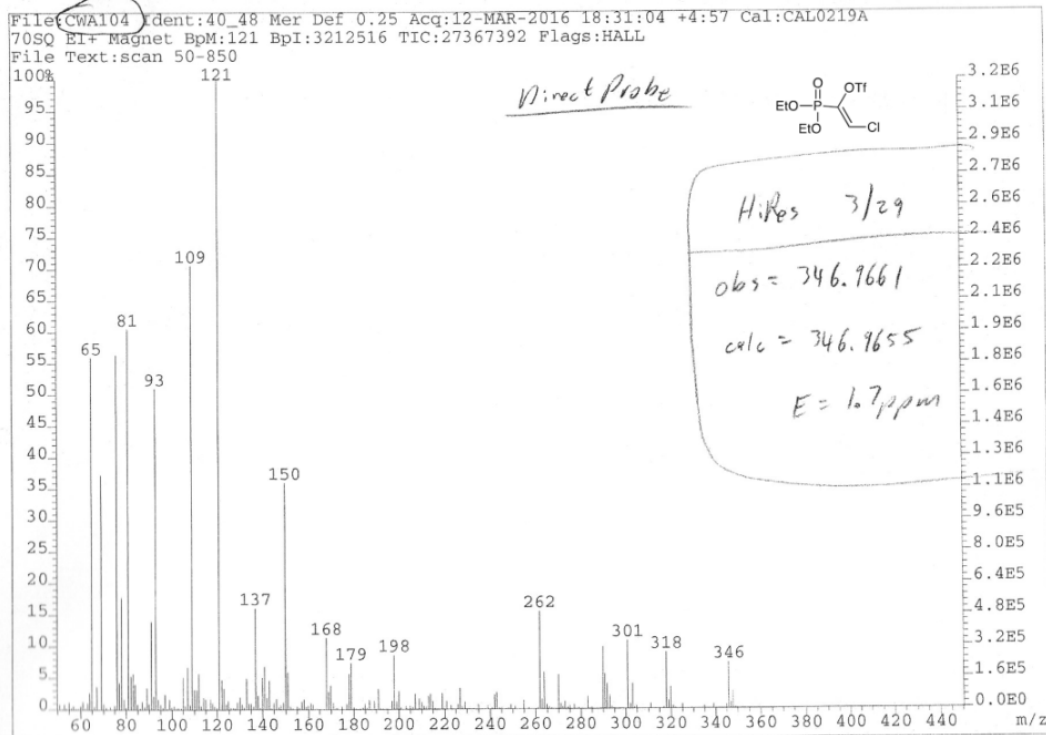
Figure D. 40. LRMS spectrum of 4h
(E)-2-chloro-1-(diethoxyphosphoryl)ethenyl trifluoromethanesulfonate
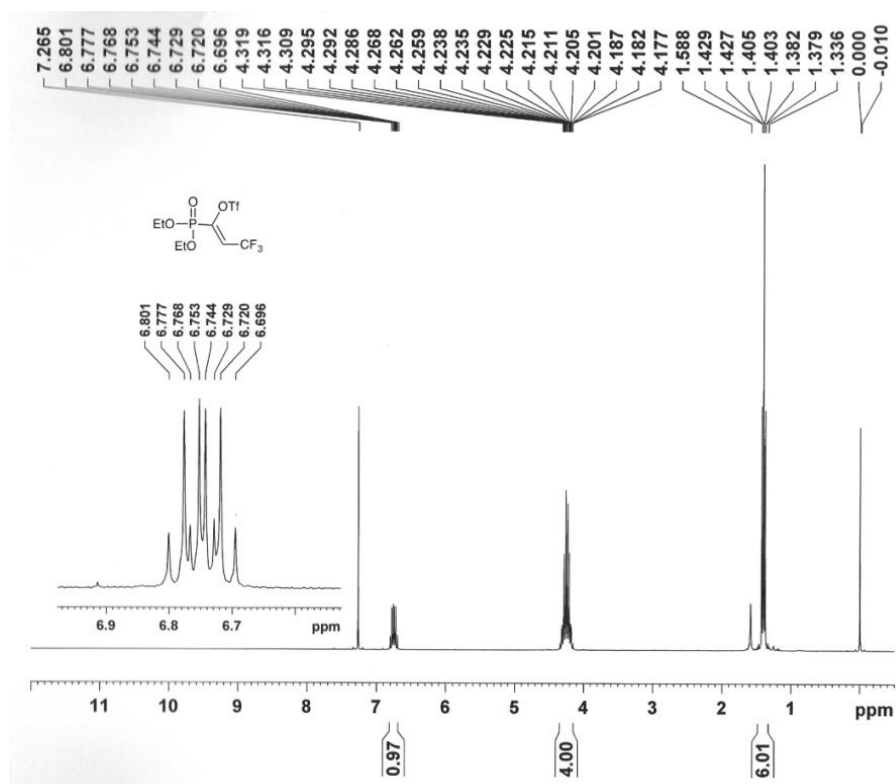
Figure D. 41. ¹H NMR spectrum of 4i
(1E)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate
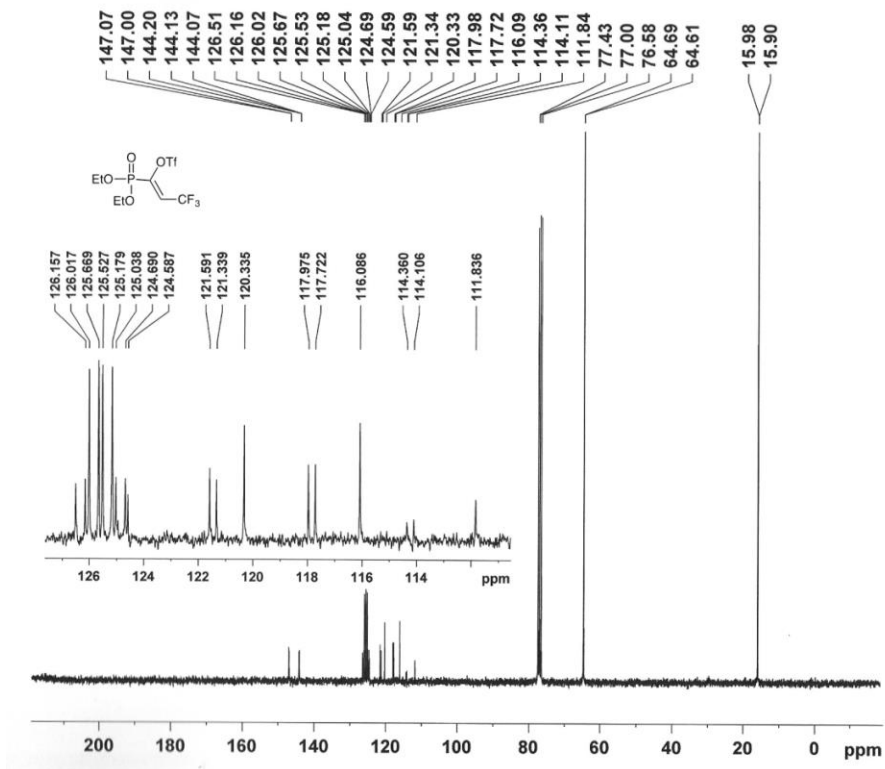
Figure D. 42. ^{13}C NMR spectrum of 4i
(1E)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate
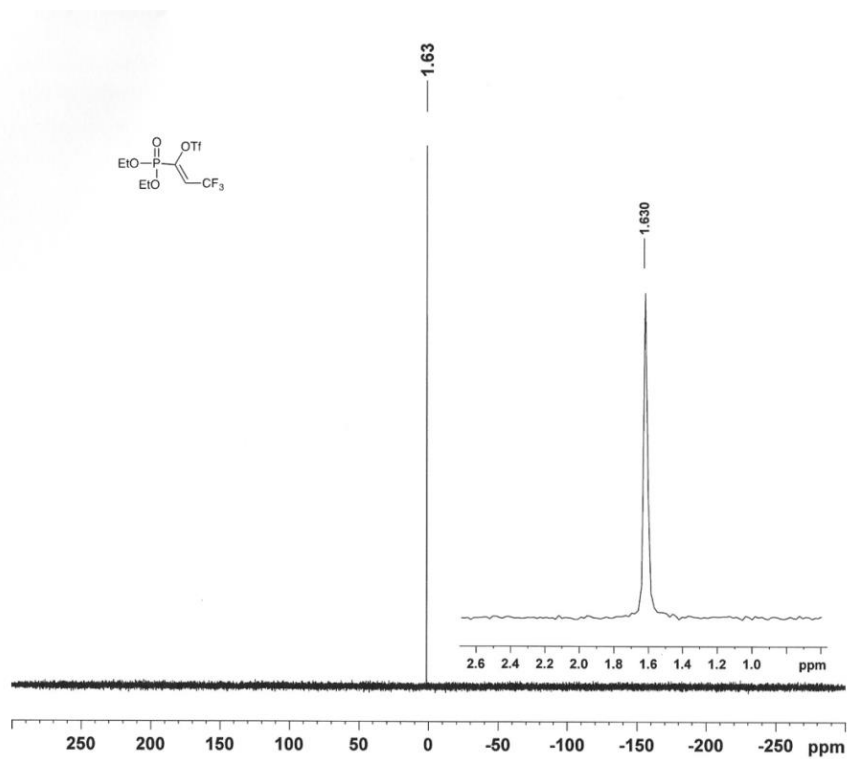
Figure D. 43. ^{31}P NMR spectrum of 4i
(1E)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate

190
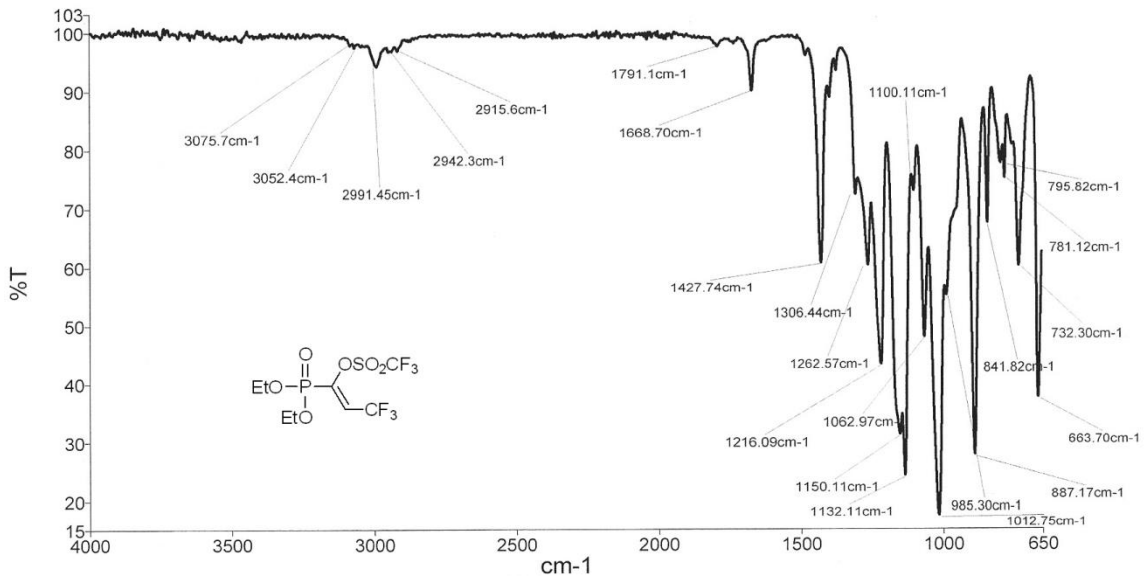
Figure D. 44. FT-IR spectrum of 4i
(1E)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate
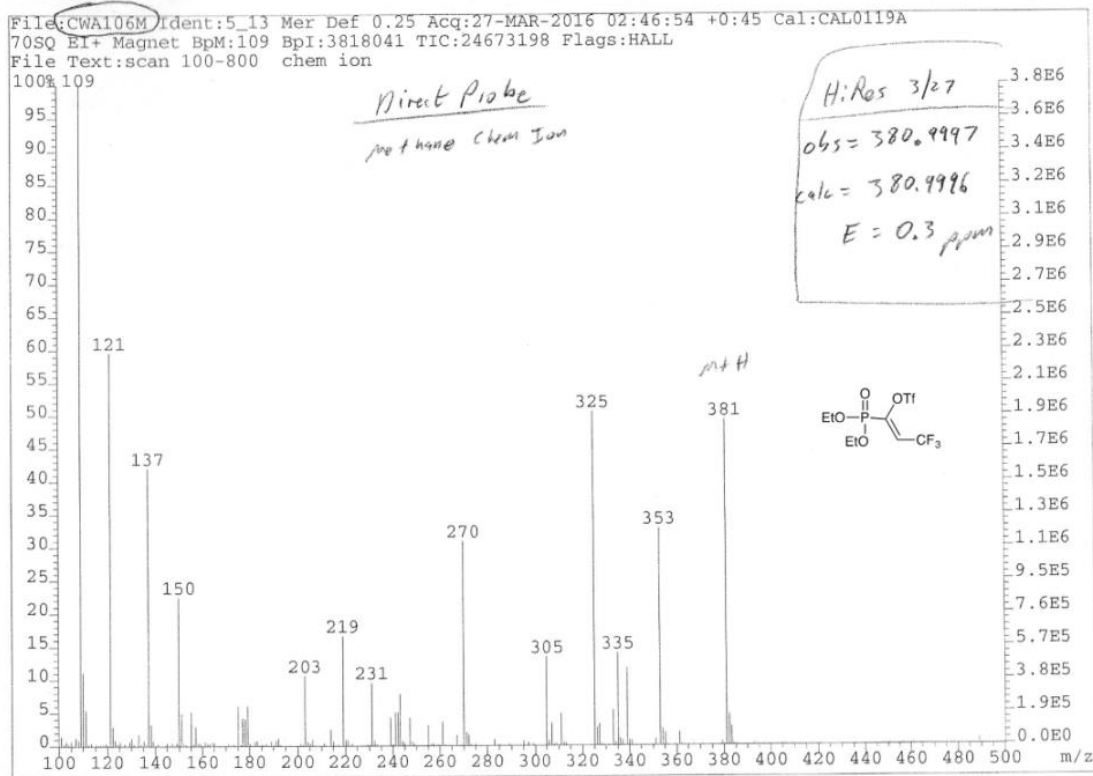
Figure D. 45. LRMS spectrum of 4i
(1E)-1-(diethoxyphosphoryl)-3,3,3-trifluoroprop-1-en-1-yl trifluoromethanesulfonate

APPENDIX E

α-ALKYNYLPHOSPHONATE SPECTRAL DATA
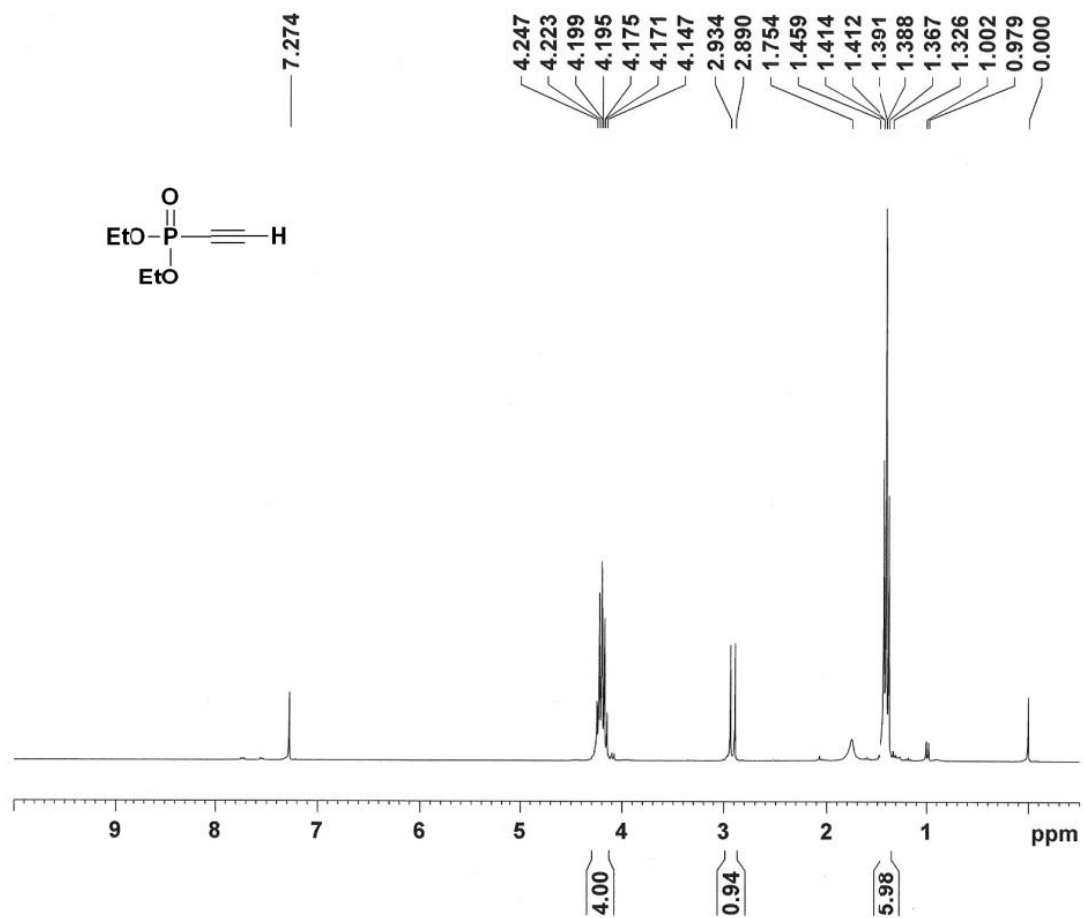
Figure E. 1. ^{1}H NMR spectrum of 5a
diethyl ethynylphosphonate
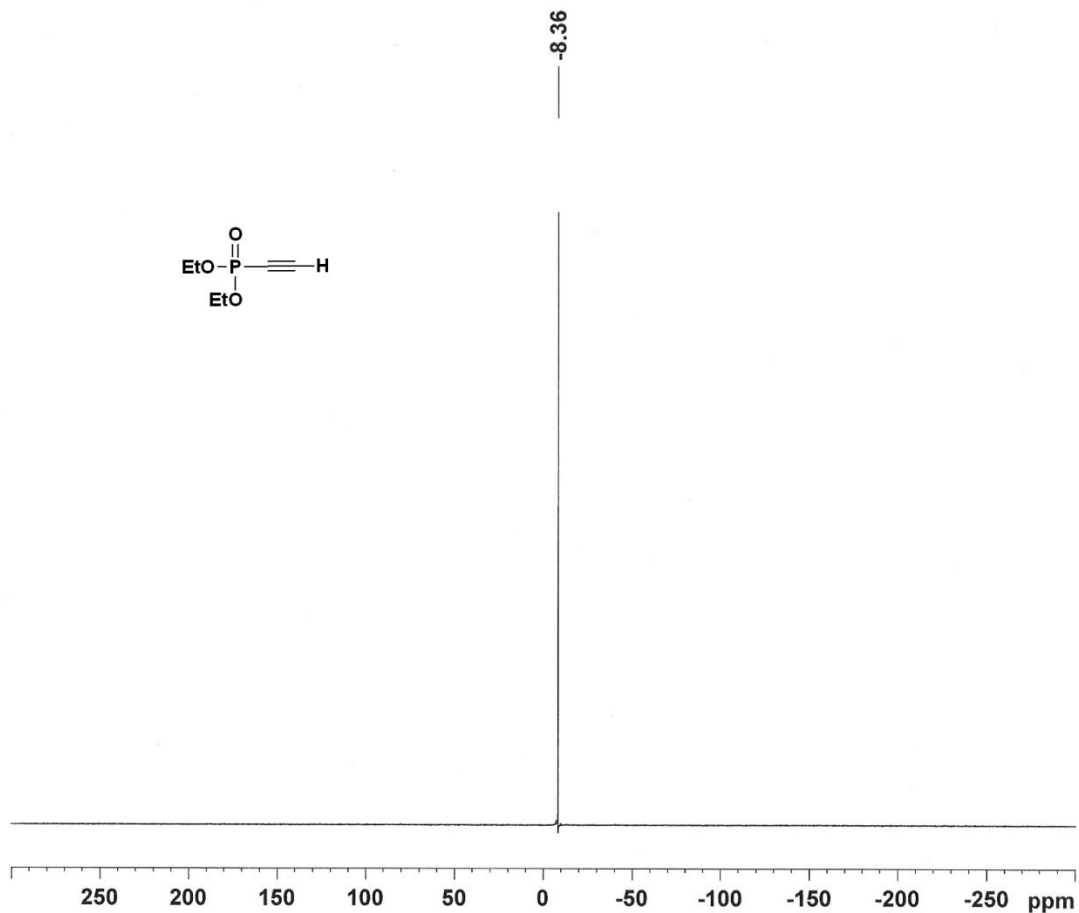
Figure E. 2. ^{31}P NMR spectrum of 5a
diethyl ethynylphosphonate
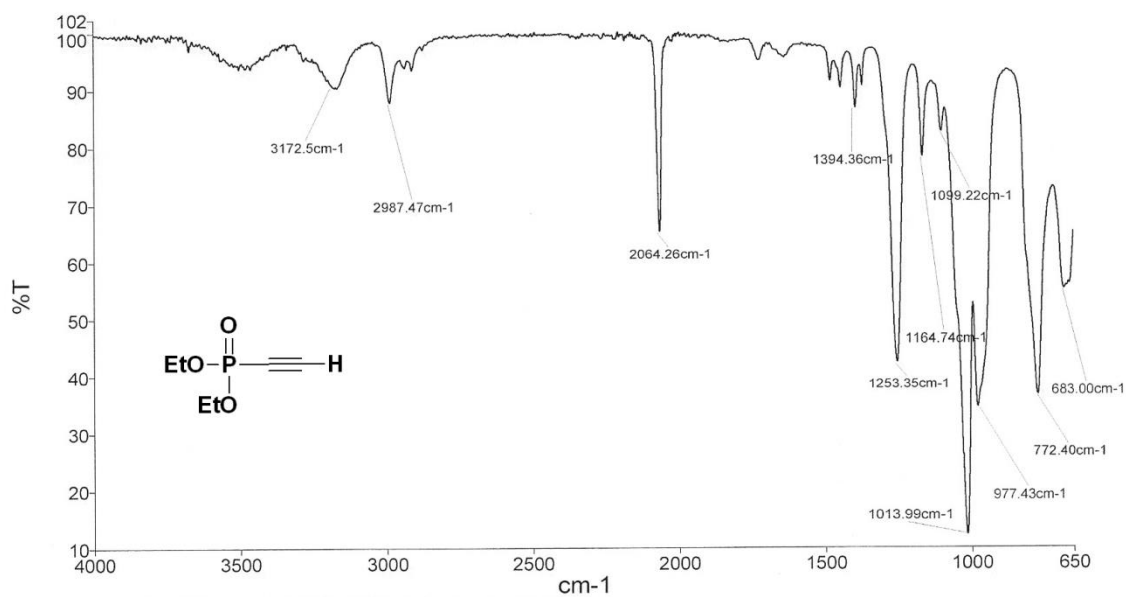
Figure E. 3. FT-IR spectrum of 5a
diethyl ethynylphosphonate

193
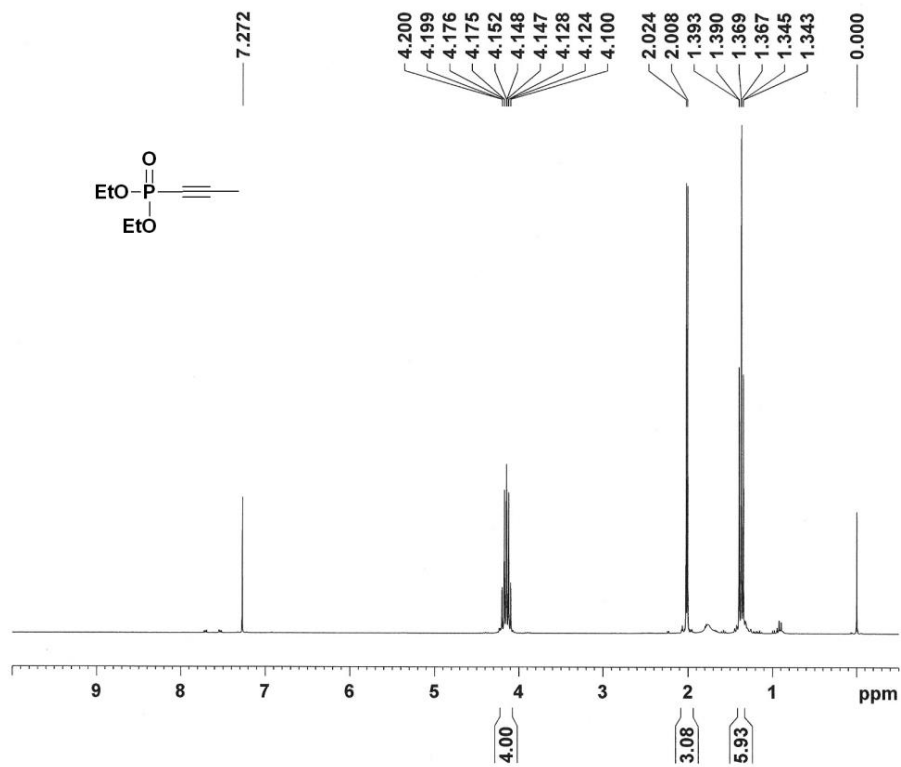
Figure E. 4. ¹H NMR spectrum of 5b
diethyl prop-1-yn-1-ylphosphonate
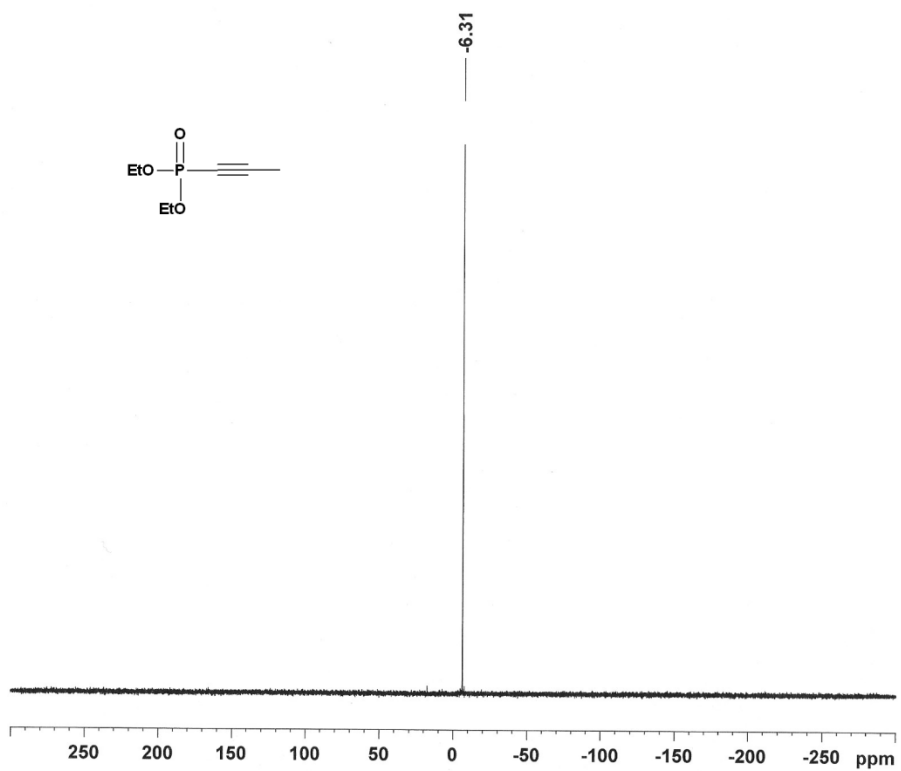
Figure E. 5. ³¹P NMR spectrum of 5b
diethyl prop-1-yn-1-ylphosphonate

194
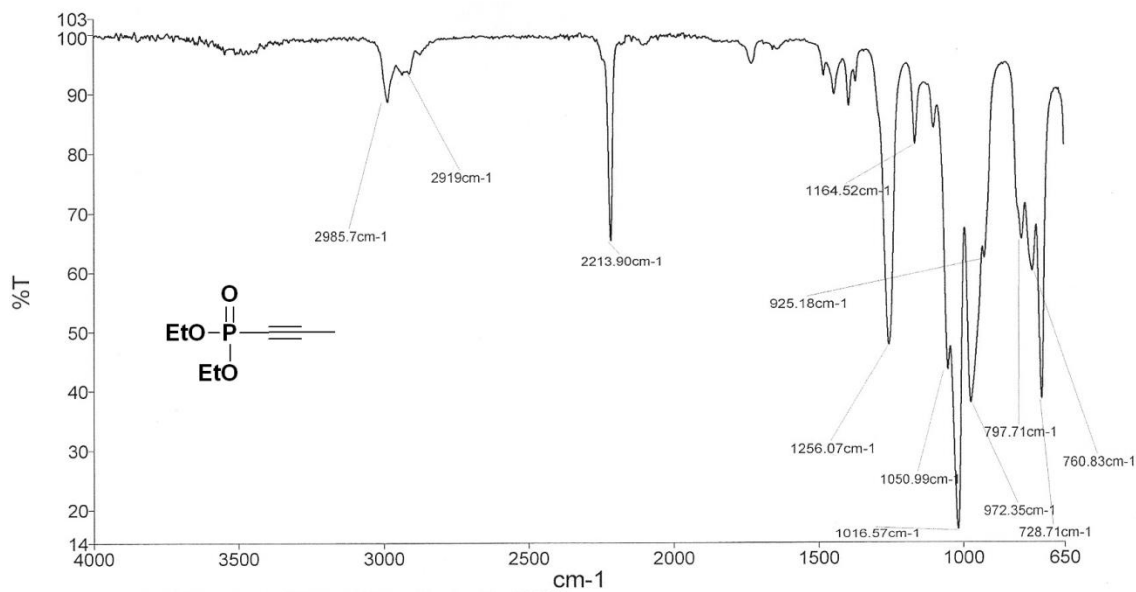
Figure E. 6. FT-IR spectrum of 5b
diethyl prop-1-yn-1-ylphosphonate
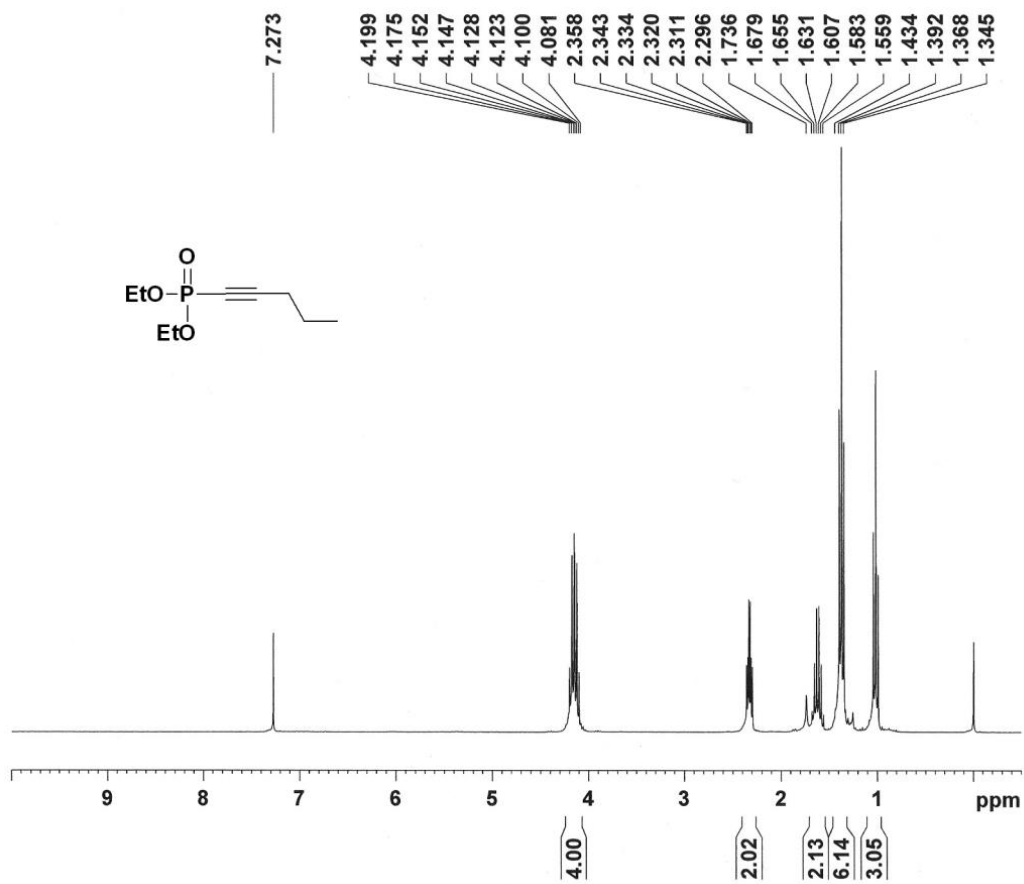
Figure E. 7. ^{1}H NMR spectrum of 5c
diethyl pent-1-yn-1-ylphosphonate
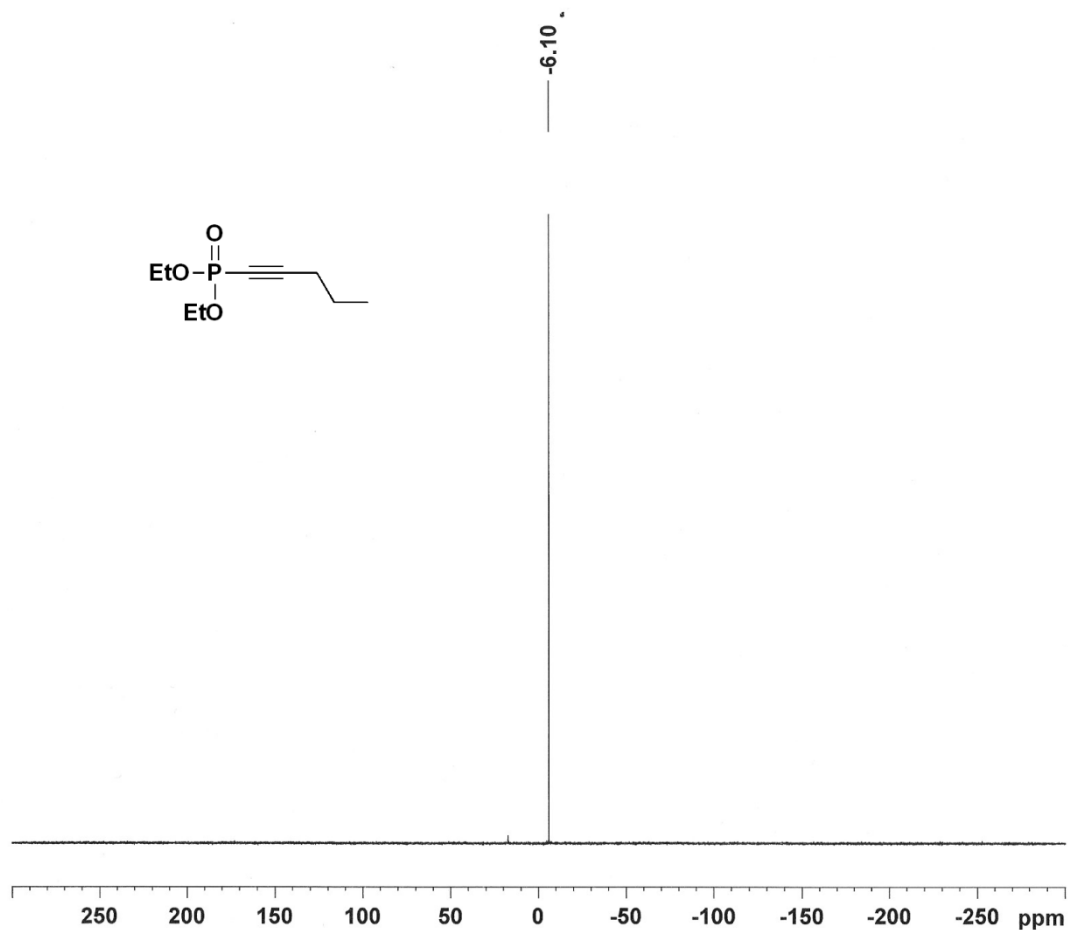
Figure E. 8. ^{31}P NMR spectrum of 5c
diethyl pent-1-yn-1-ylphosphonate
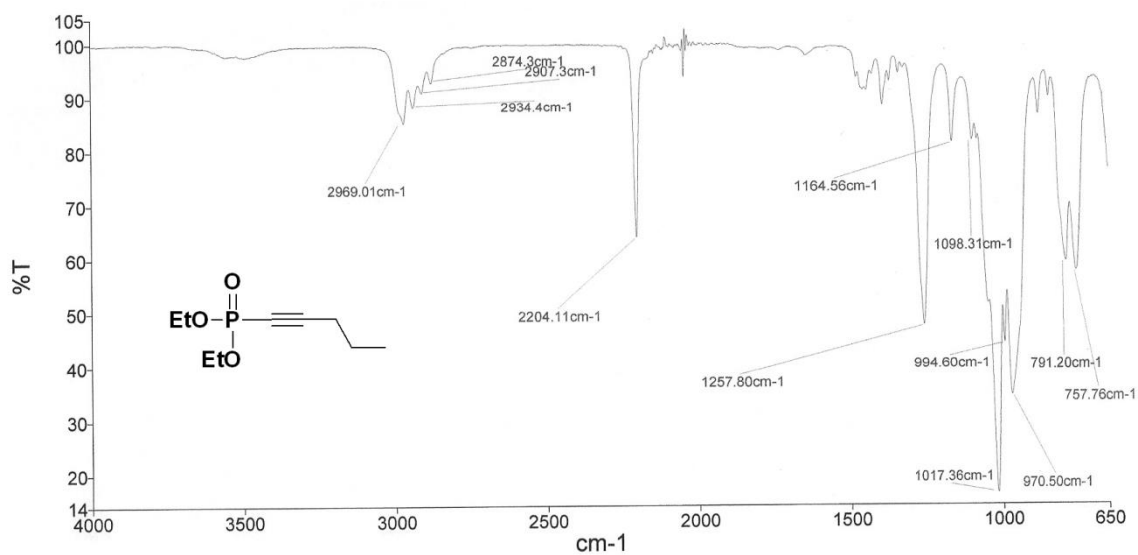
Figure E. 9. FT-IR spectrum of 5c
diethyl pent-1-yn-1-ylphosphonate
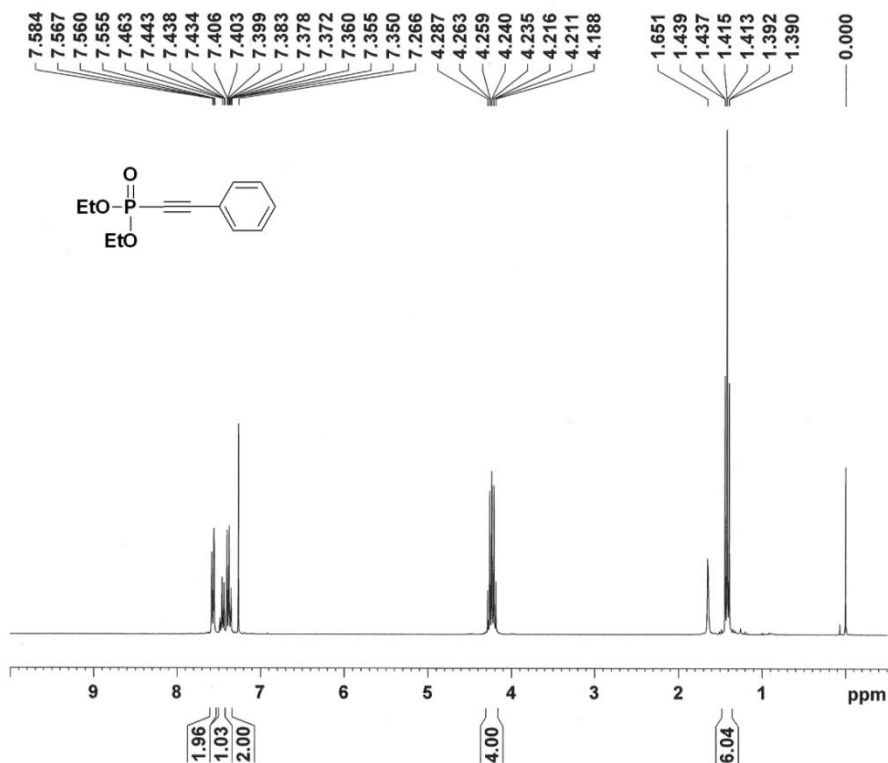
Figure E. 10. ^{1}H NMR spectrum of 5e
diethyl (phenylethynyl)phosphonate
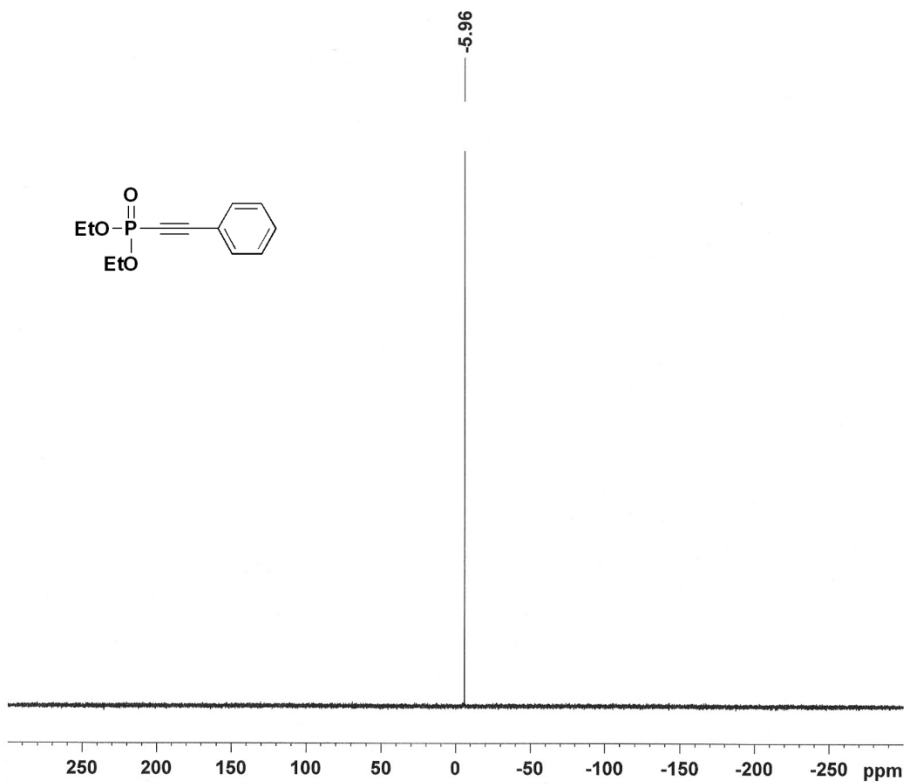
Figure E. 11. ^{31}P NMR spectrum of 5e
diethyl (phenylethynyl)phosphonate
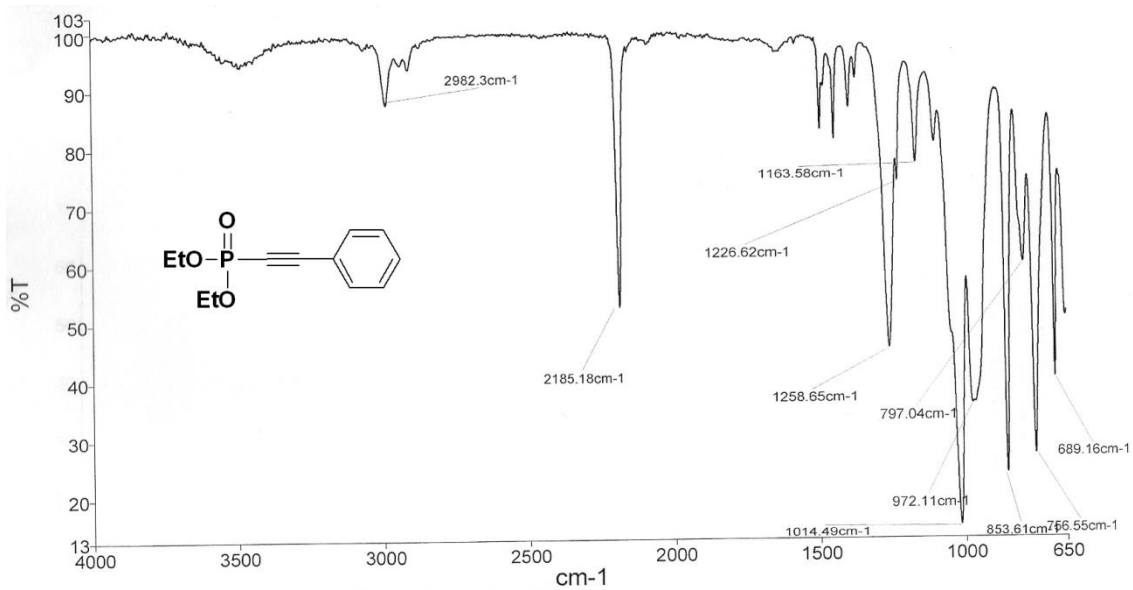
Figure E. 12. FT-IR spectrum of 5e
diethyl (phenylethynyl)phosphonate
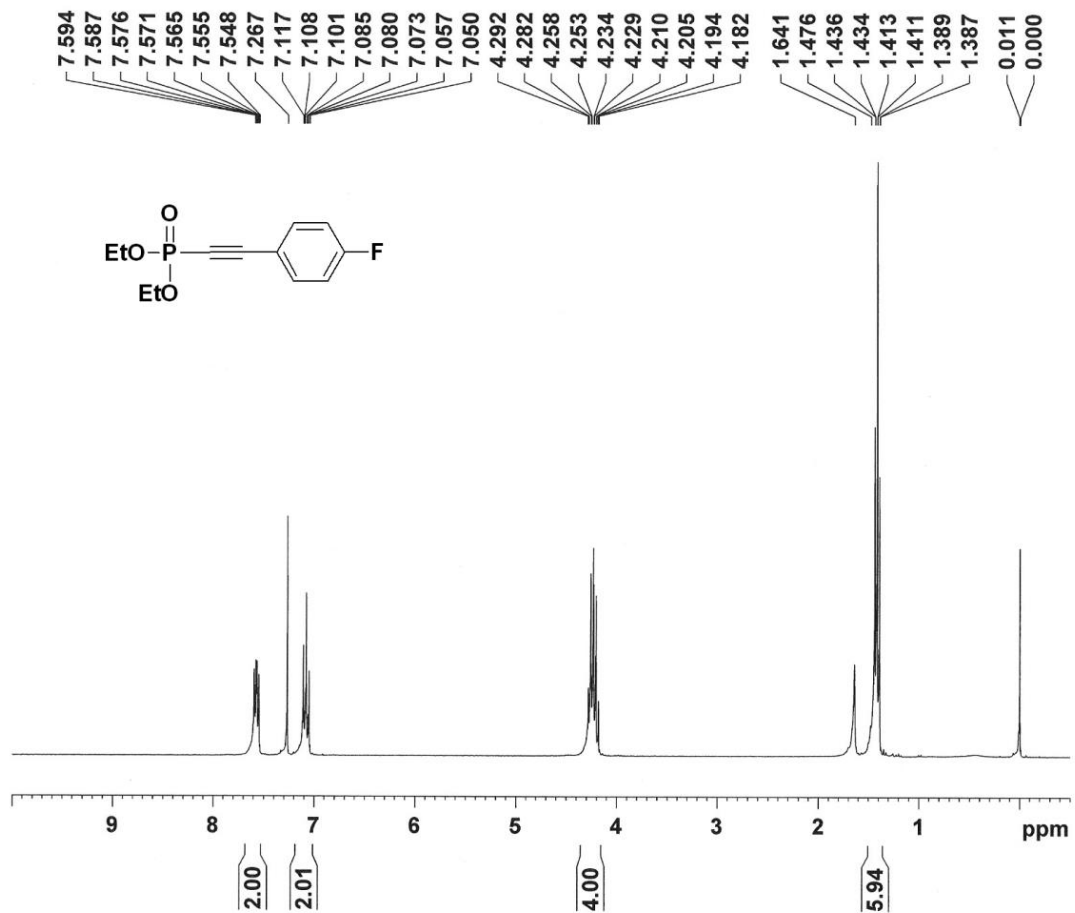
Figure E. 13. ¹H NMR spectrum of 5f
diethyl [(4-fluorophenyl)ethynyl]phosphonate

198
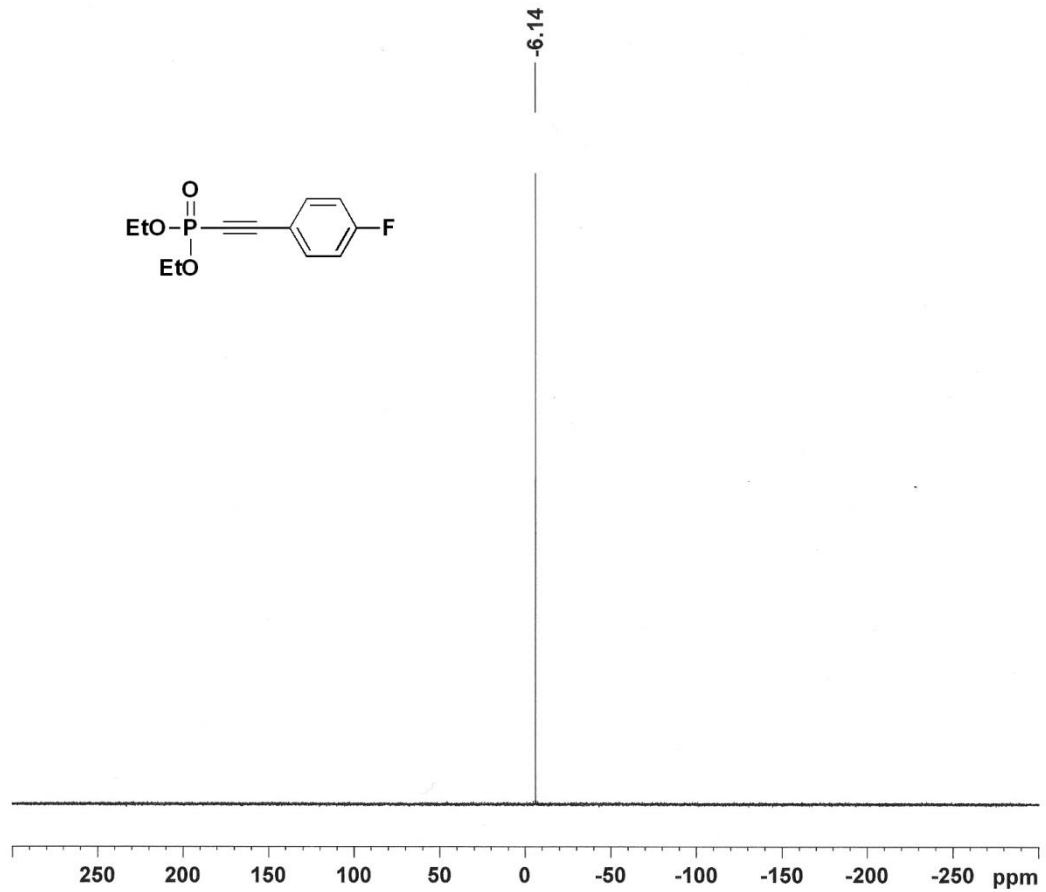
Figure E. 14. ³¹P NMR spectrum of 5f
diethyl [(4-fluorophenyl)ethynyl]phosphonate
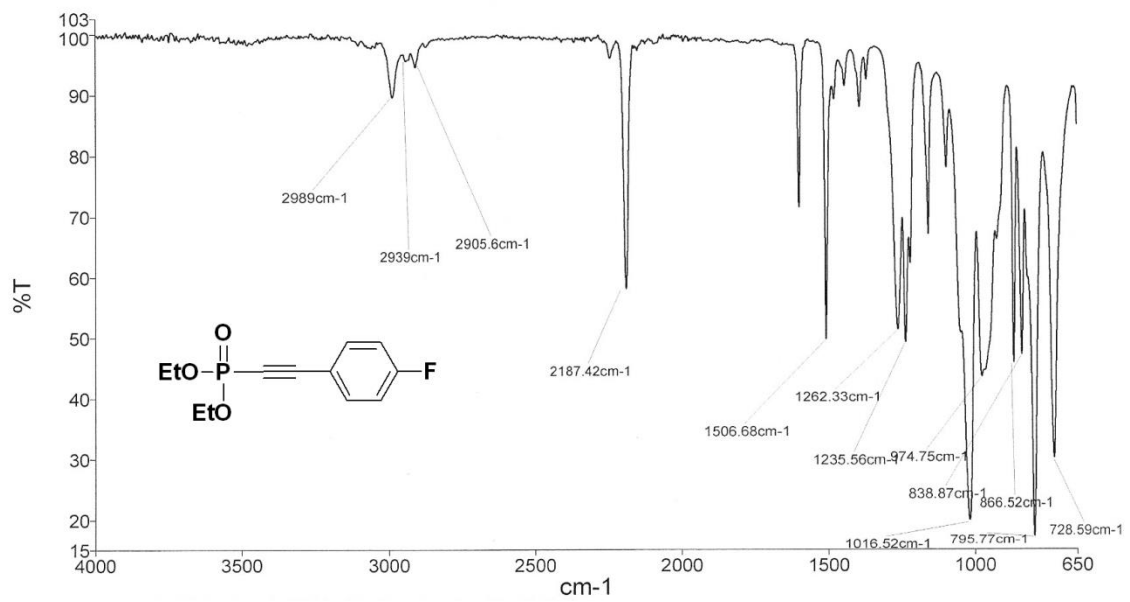
Figure E. 15. FT-IR spectrum of 5f
diethyl [(4-fluorophenyl)ethynyl]phosphonate
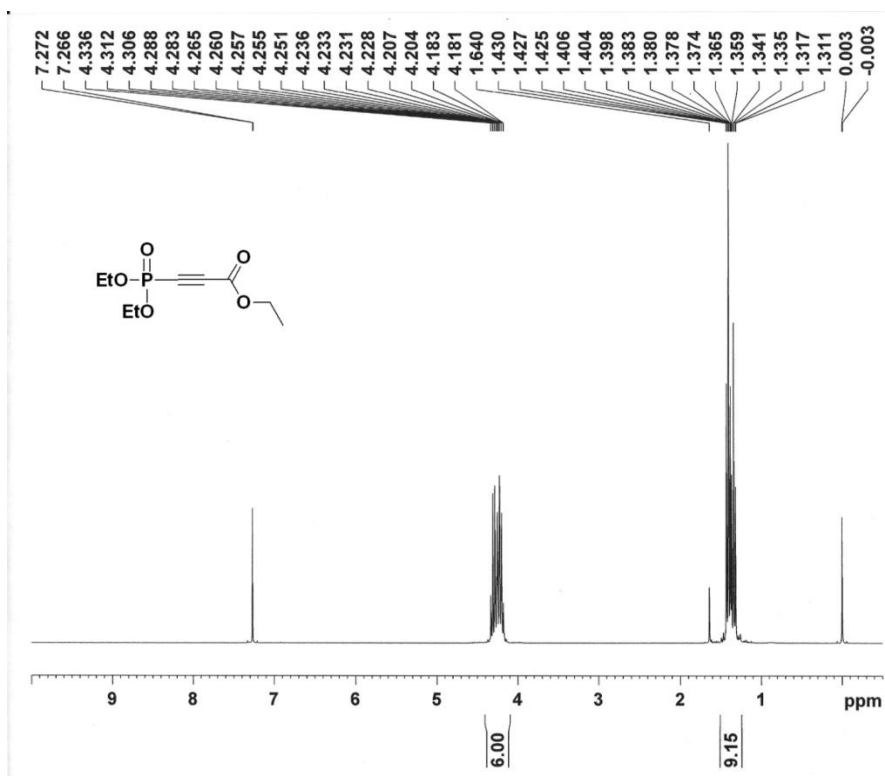
**Figure E. 16. ^{1}H NMR spectrum of 5g
ethyl 3-(diethoxyphosphoryl)prop-2-ynoate**
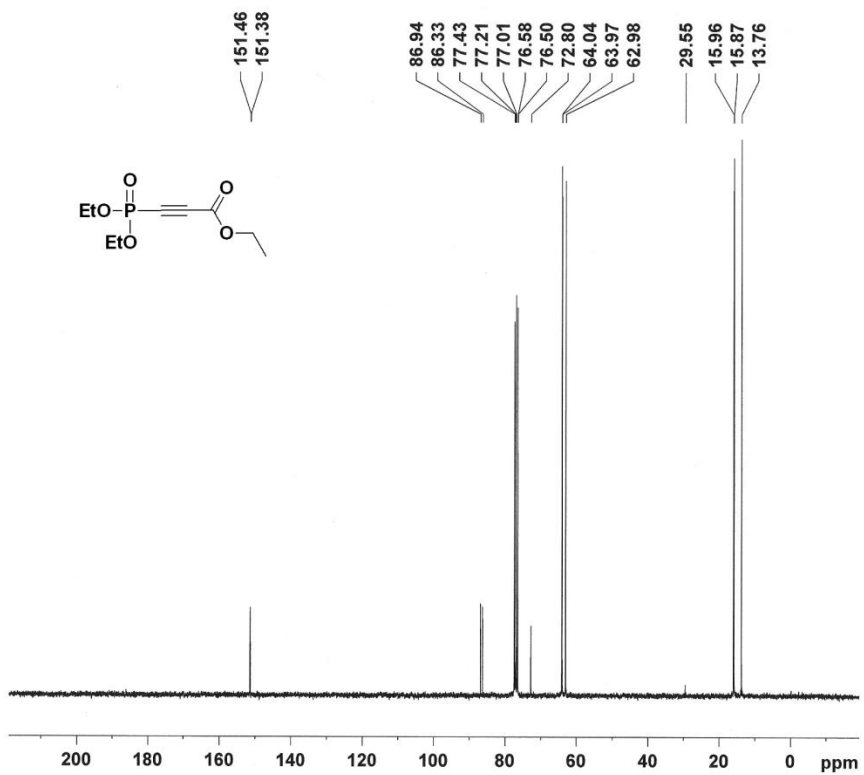
**Figure E. 17. ^{13}C NMR spectrum of 5g
ethyl 3-(diethoxyphosphoryl)prop-2-ynoate**
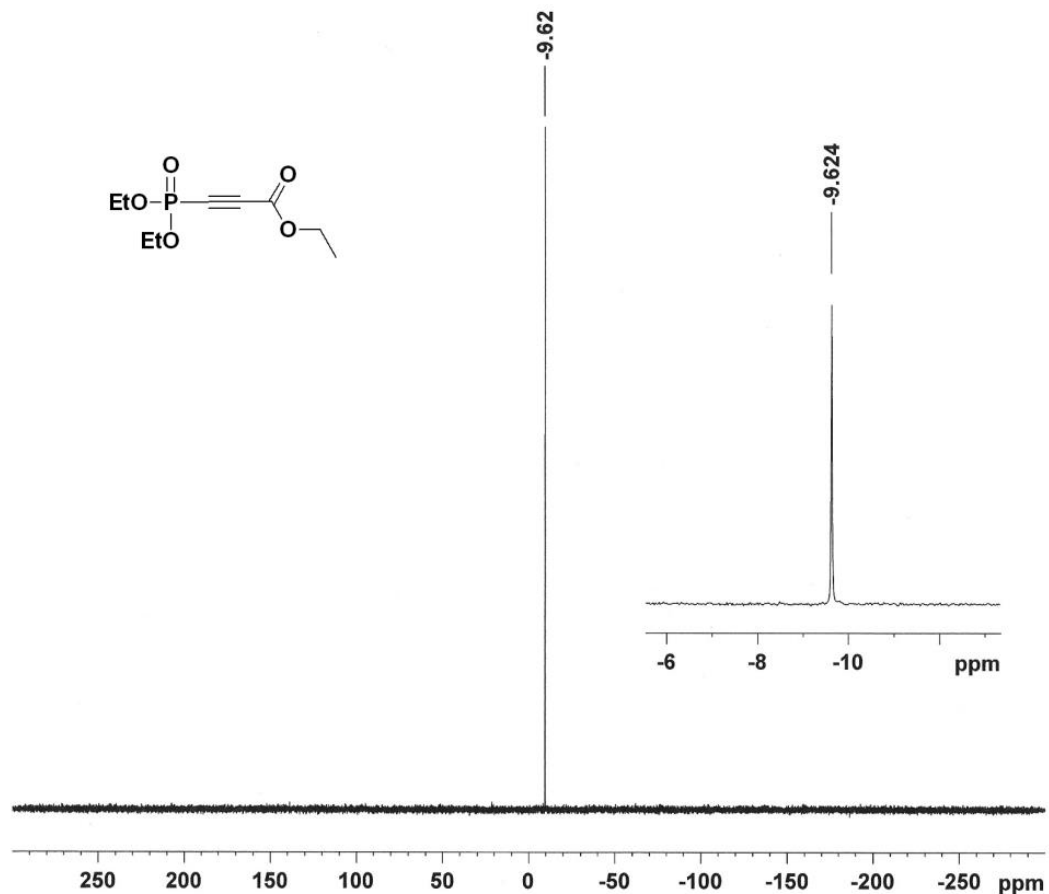
Figure E. 18. ^{31}P NMR spectrum of 5g
ethyl 3-(diethoxyphosphoryl)prop-2-ynoate
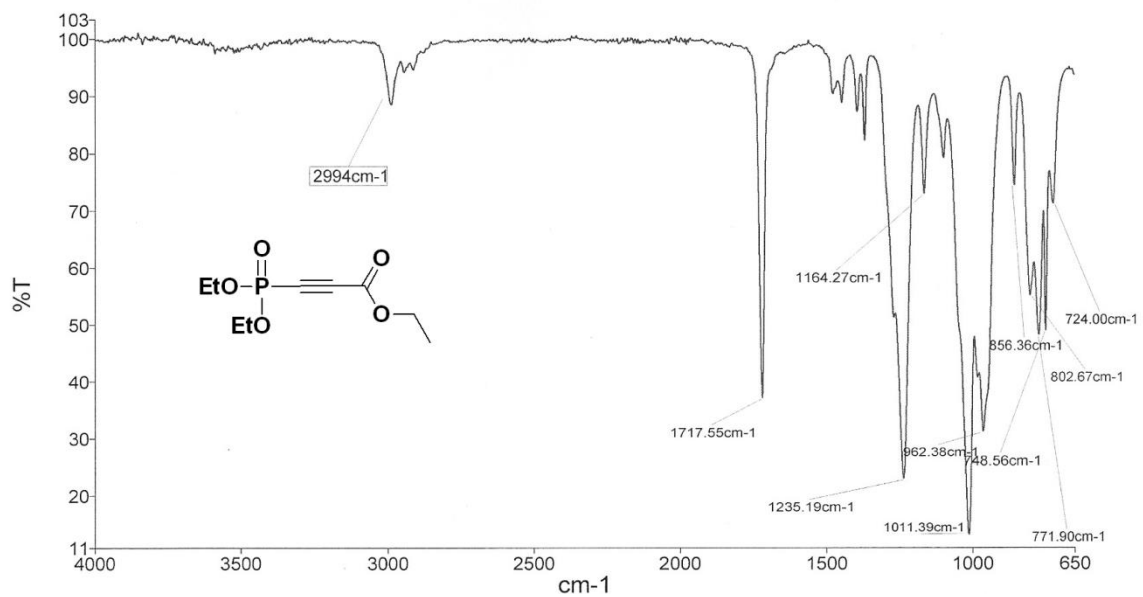
Figure E. 19. FT-IR spectrum of 5g
ethyl 3-(diethoxyphosphoryl)prop-2-ynoate

201
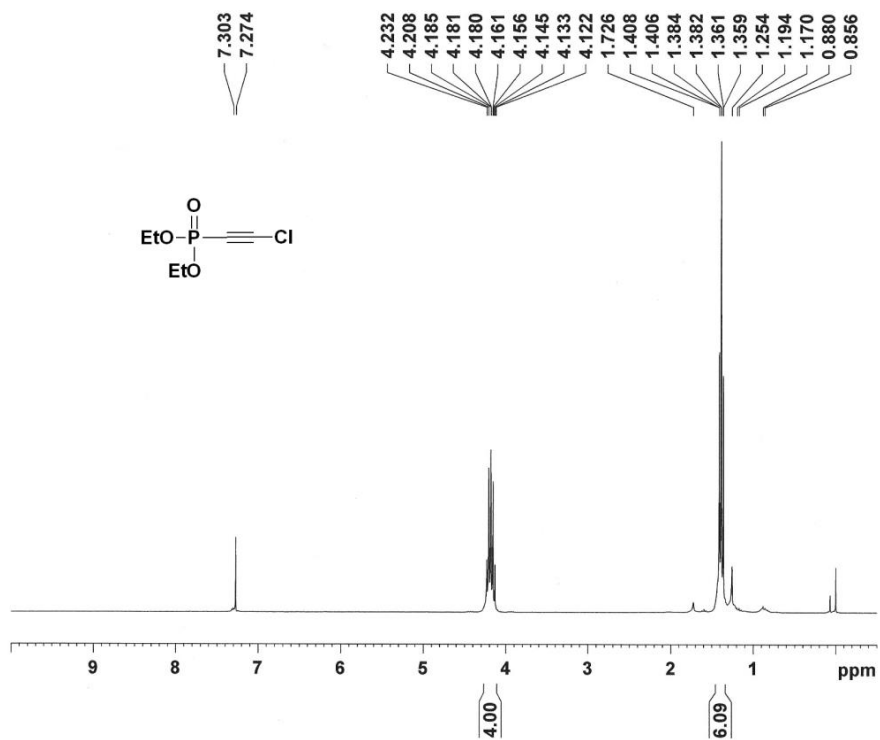
Figure E. 20. ¹H NMR spectrum of 5h
diethyl (chloroethynyl)phosphonate
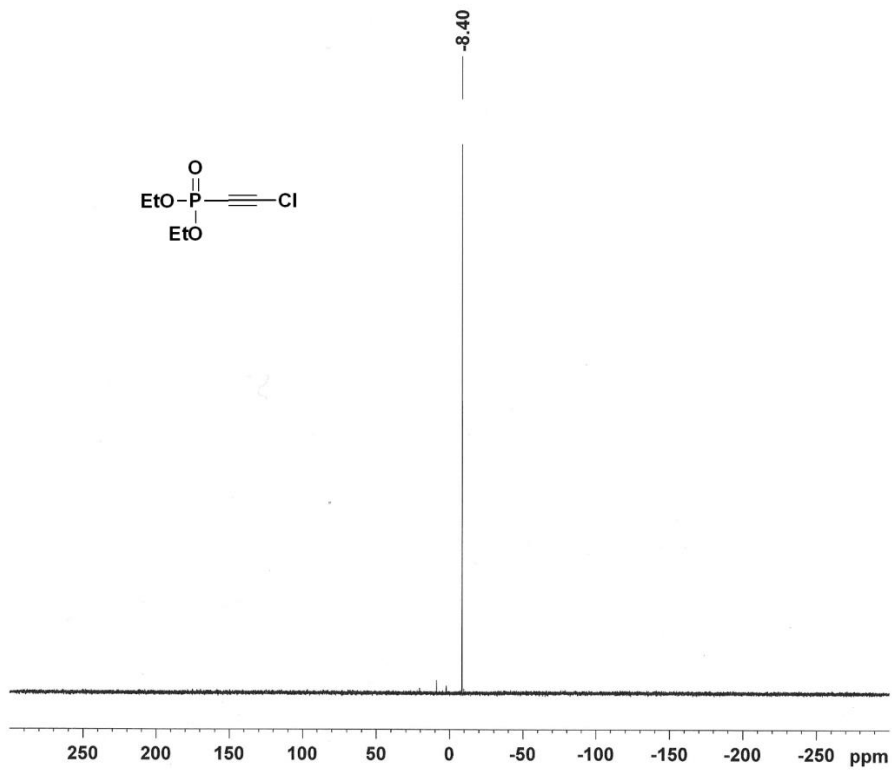
Figure E. 21. ³¹P NMR spectrum of 5h
diethyl (chloroethynyl)phosphonate
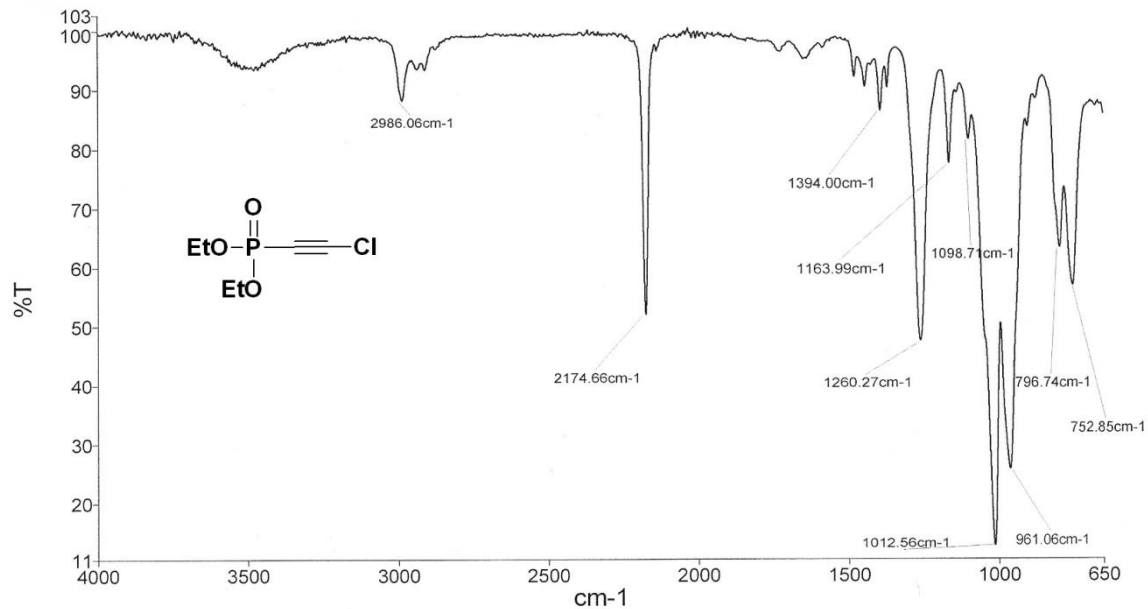
Figure E. 22. FT-IR spectrum of 5h
diethyl (chloroethynyl)phosphonate
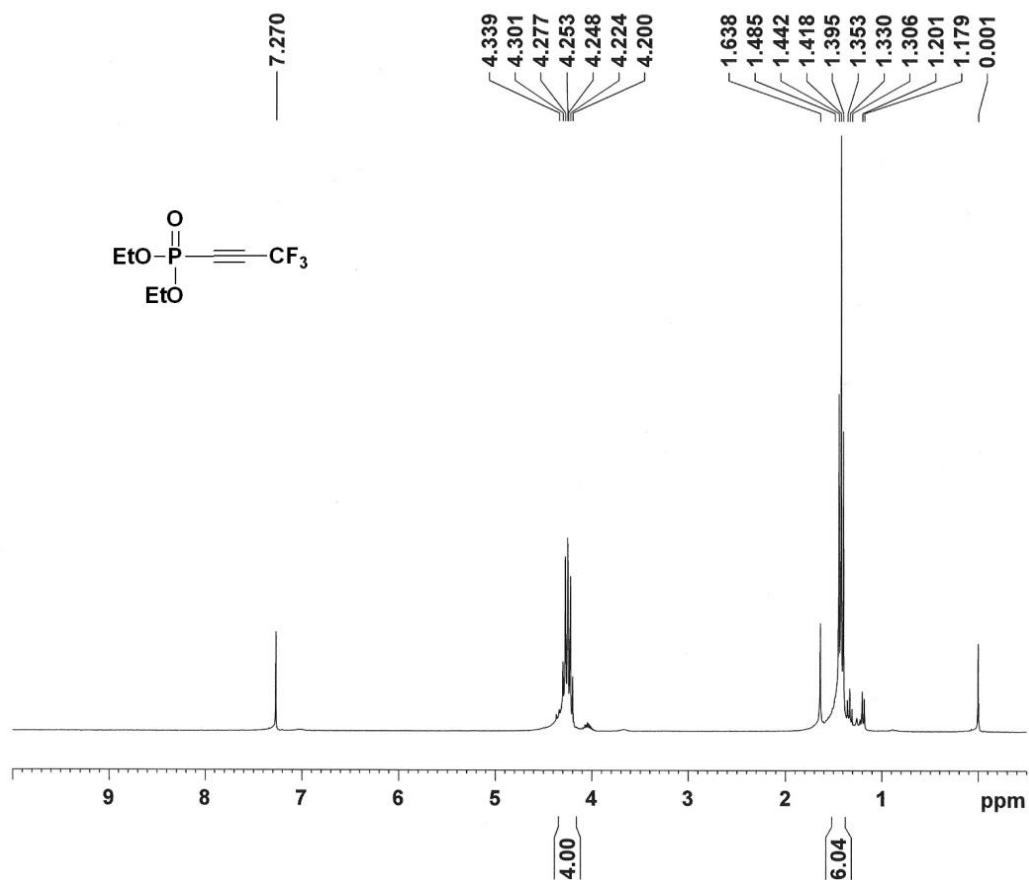
Figure E. 23. ^{1}H NMR spectrum of 5i
diethyl (3,3,3-trifluoroprop-1-yn-1-yl)phosphonate
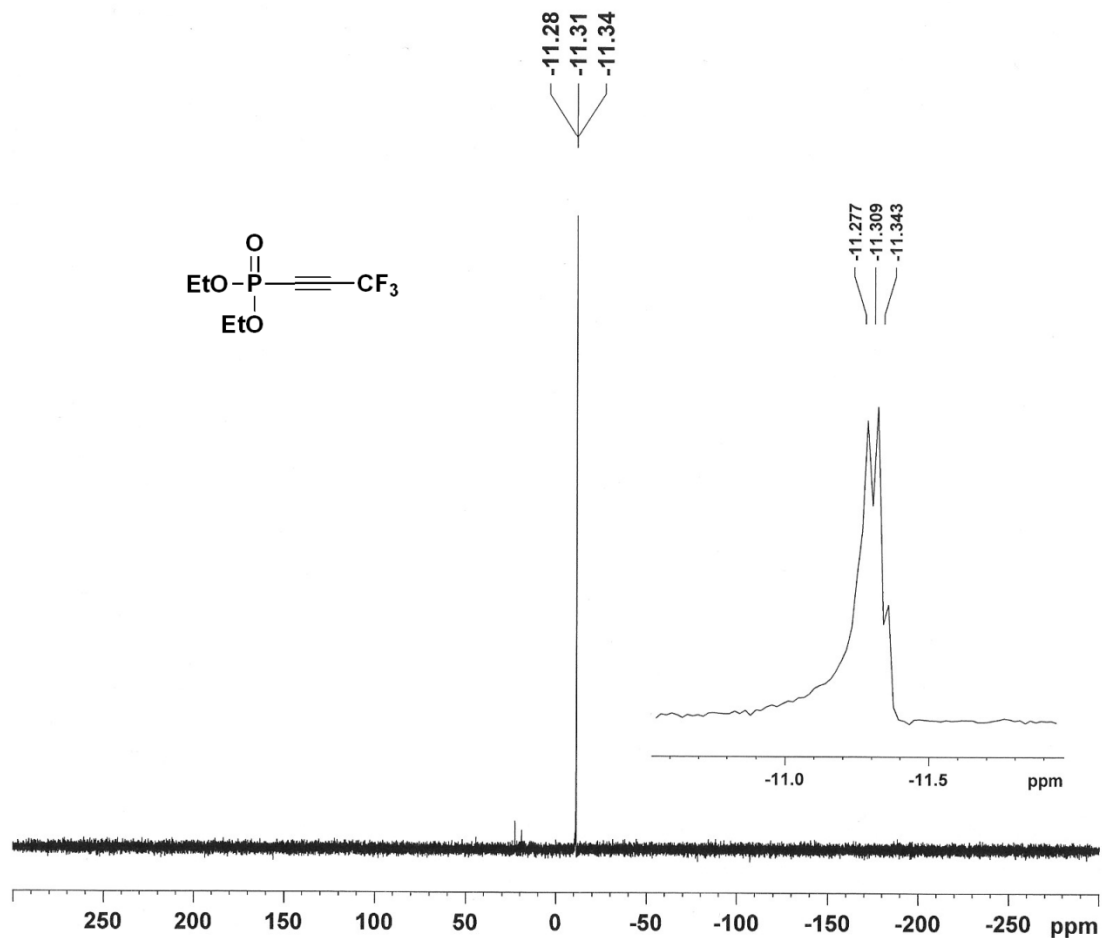
Figure E. 24. ^{31}P NMR spectrum of 5i
diethyl (3,3,3-trifluoroprop-1-yn-1-yl)phosphonate
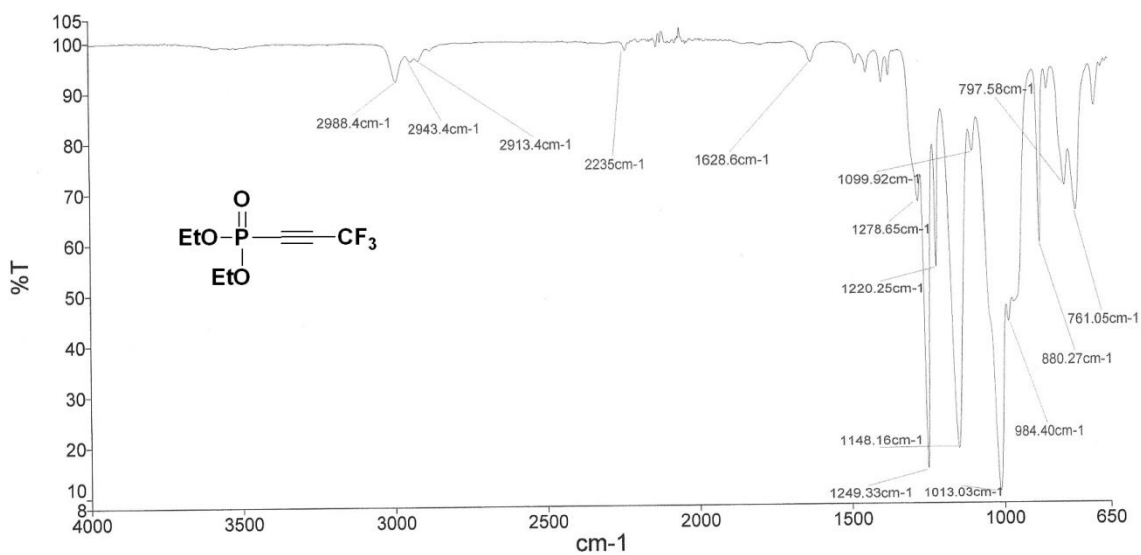
Figure E. 25. FT-IR spectrum of 5i
diethyl (3,3,3-trifluoroprop-1-yn-1-yl)phosphonate

APPENDIX F

X-RAY CRYSTALLOGRAPHY DATA FOR

COMPOUND **4g**

(E)-ethyl 3-(diethoxyphosphoryl)-3-(((trifluoromethyl)sulfonyl)oxy)acrylate

C$_{10}$H$_{16}$F$_3$O$_8$PS

Data and crystal structure report provided by Dr. Collins McMillen at Clemson

University [59]

Crystal Structure Report

A specimen of C$_{10}$H$_{16}$F$_3$O$_8$PS, approximate dimensions 0.076 mm x 0.187 mm x 0.261

mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were

measured.

The integration of the data using a triclinic unit cell yielded a total of 12435 reflections to

a maximum θ angle of 26.48° (0.80 Å resolution), of which 3308 were independent

(average redundancy 3.759, completeness = 98.1%, R$_{int}$ = 3.17%, R$_{sig}$ = 3.26%) and 2768

(83.68%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a} = 9.3367(9)$ Å, $\underline{b} = 9.4958(9)$ Å, $\underline{c} = 11.5343(11)$ Å, $\alpha = 94.649(3)°$, $\beta = 107.891(3)°$, $\gamma = 119.188(3)°$, volume = 816.14(14) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 $\sigma(I)$. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8806 and 1.0000.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 2 for the formula unit, $C_{10}H_{16}F_3O_8PS$. The final anisotropic full-matrix least-squares refinement on F^2 with 208 variables converged at R1 = 3.67%, for the observed data and wR2 = 9.20% for all data. The goodness-of-fit was 1.063. The largest peak in the final difference electron density synthesis was 0.404 e$^-$/Å^3 and the largest hole was -0.419 e$^-$/Å^3 with an RMS deviation of 0.066 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.564 g/cm^3 and F(000), 396 e$^-$.
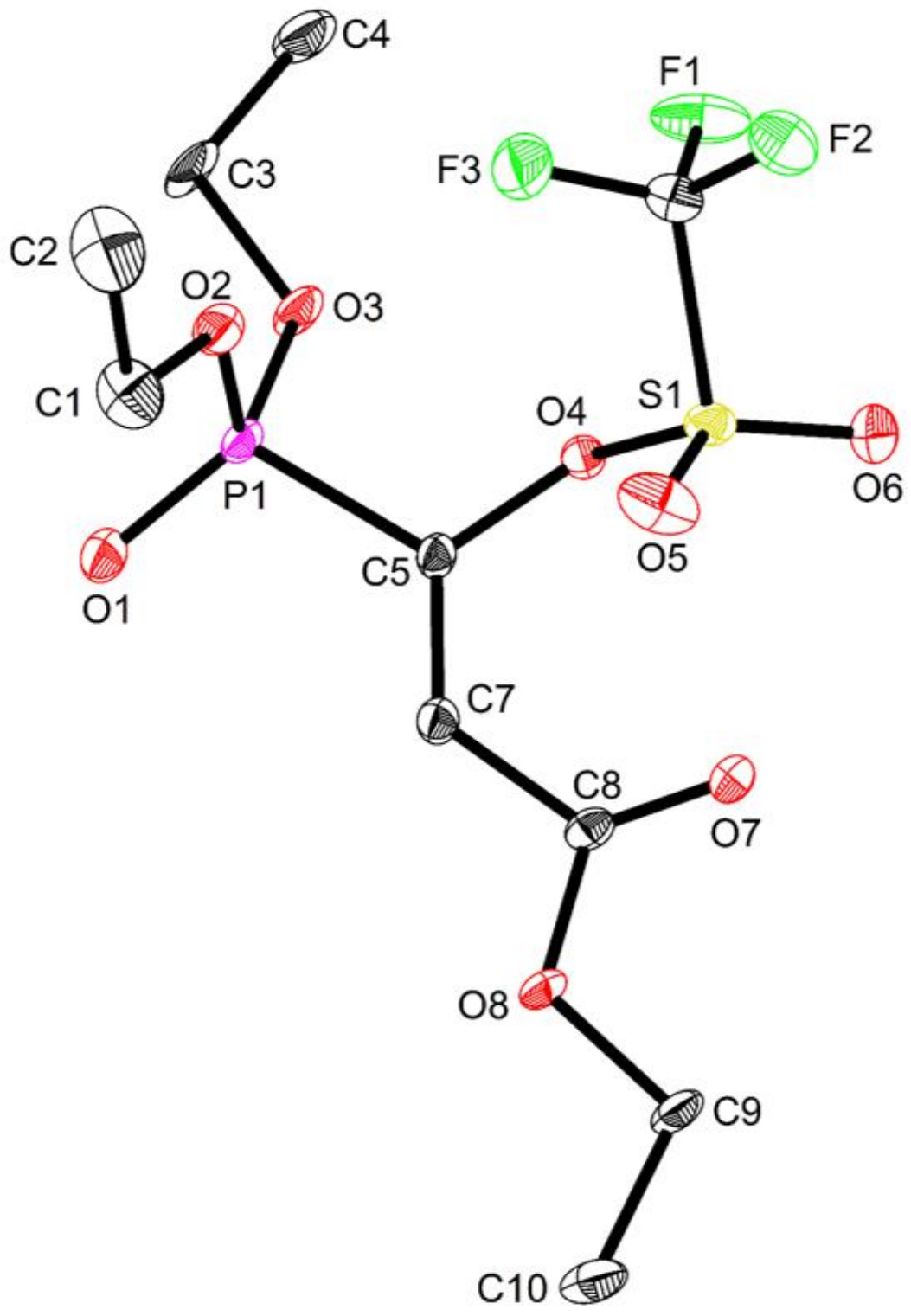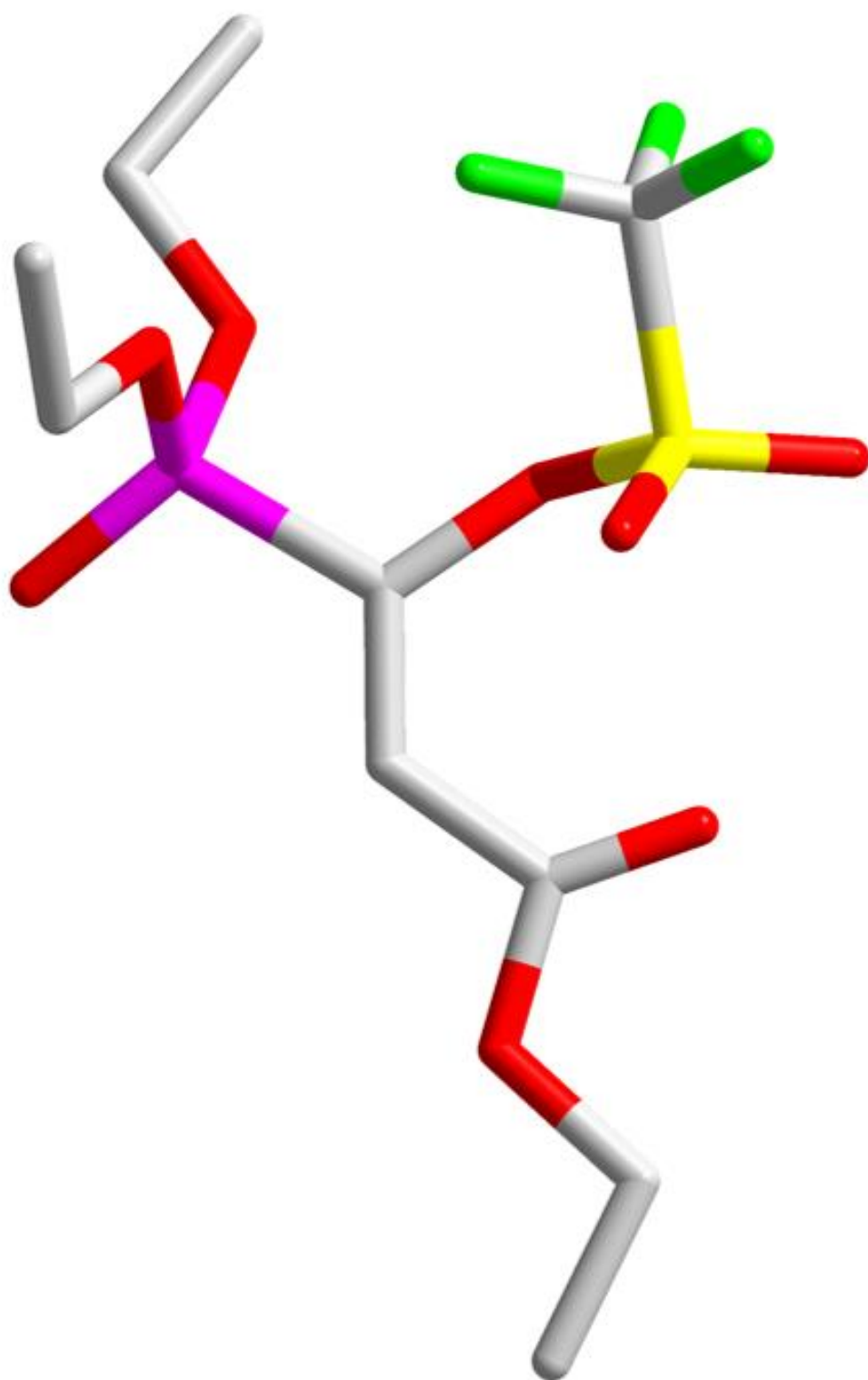
Table 1. Sample and crystal data for

D8_0249_CWA_DK_12a16_all.

Identification code	D8_0249_CWA_DK_12a16_all
Chemical formula	$C_{10}H_{16}F_3O_8PS$
Formula weight	384.26 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.076 x 0.187 x 0.261 mm
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 9.3367(9) Å α = 94.649(3)°
	b = 9.4958(9) Å β = 107.891(3)°
	c = 11.5343(11) Å γ = 119.188(3)°
Volume	816.14(14) Å^3
Z	2
Density (calculated)	1.564 g/cm^3
Absorption coefficient	0.363 mm^{-1}
F(000)	396

Table 2. Data collection and structure refinement for

D8_0249_CWA_DK_12a16_all.

Theta range for data	2.56 to 26.48°

collection

Index ranges	-11<=h<=11, -11<=k<=11, -14<=l<=14
Reflections collected	12435
Independent reflections	3308 [R(int) = 0.0317]
Max. and min. transmission	1.0000 and 0.8806
Structure solution technique	direct methods
Structure solution program	SHELXT-2014 (Sheldrick 2014)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014 (Sheldrick 2014)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3308 / 0 / 208
Goodness-of-fit on F^2	1.063
Final R indices	2768 data; I>2σ(I) R1 = 0.0367, wR2 = 0.0860
	all data R1 = 0.0475, wR2 = 0.0920
Weighting scheme	w=1/[σ^2(F$_o$^{2})+(0.0416P)^2+0.6247P]

<div align="center">

where $P=(F_o^2+2F_c^2)/3$

</div>

Largest diff. peak and

$\qquad$ 0.404 and -0.419 e$\mathring{A}^{-3}$

hole

R.M.S. deviation from

$\qquad$ 0.066 e$\mathring{A}^{-3}$

mean

Table 3. Atomic coordinates and

equivalent isotropic atomic displacement

parameters ($\mathring{A}^2$) for

D8_0249_CWA_DK_12a16_all.

U(eq) is defined as one third of the trace of

the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
S1	0.39007(7)	0.43828(6)	0.19669(5)	0.01669(14)
P1	0.66376(7)	0.92542(6)	0.36036(5)	0.01377(13)
F3	0.3636(2)	0.62471(16)	0.04607(12)	0.0385(4)
O4	0.44481(17)	0.58567(15)	0.30838(12)	0.0129(3)
O7	0.59536(19)	0.41289(16)	0.43501(13)	0.0181(3)
F2	0.18954(19)	0.35838(16)	0.96171(12)	0.0359(4)
O3	0.48018(19)	0.89890(16)	0.34650(14)	0.0190(3)
O8	0.88114(18)	0.58652(16)	0.57560(13)	0.0167(3)
O2	0.66026(19)	0.92892(16)	0.22368(13)	0.0189(3)

	x/a	y/b	z/c	U(eq)
O1	0.82780(19)	0.06181(16)	0.46351(13)	0.0190(3)
F1	0.1321(2)	0.4827(2)	0.08767(14)	0.0422(4)
O6	0.2596(2)	0.28646(17)	0.20779(14)	0.0277(4)
O5	0.5397(2)	0.4607(2)	0.17517(14)	0.0286(4)
C5	0.6235(3)	0.7231(2)	0.37874(18)	0.0124(4)
C8	0.7286(3)	0.5511(2)	0.48621(18)	0.0134(4)
C7	0.7489(3)	0.7095(2)	0.45939(18)	0.0141(4)
C9	0.8875(3)	0.4433(2)	0.60832(19)	0.0175(4)
C10	0.0698(3)	0.5155(3)	0.7114(2)	0.0229(5)
C3	0.4316(3)	0.0200(3)	0.3104(2)	0.0242(5)
C6	0.2620(3)	0.4817(3)	0.0651(2)	0.0230(5)
C4	0.2320(3)	0.9269(3)	0.2536(2)	0.0268(5)
C1	0.8231(3)	0.9890(3)	0.2011(2)	0.0275(5)
C2	0.7803(4)	0.9994(3)	0.0666(2)	0.0380(6)

Table 4. Bond lengths (Å) for

D8_0249_CWA_DK_12a16_all.

S1-O5	1.4110(16)	S1-O6	1.4113(16)
S1-O4	1.5765(13)	S1-C6	1.836(2)
P1-O1	1.4610(15)	P1-O3	1.5592(15)
P1-O2	1.5703(15)	P1-C5	1.8135(18)

F3-C6	1.309(2)	O4-C5	1.420(2)
O7-C8	1.204(2)	F2-C6	1.325(2)
O3-C3	1.473(2)	O8-C8	1.334(2)
O8-C9	1.464(2)	O2-C1	1.458(3)
F1-C6	1.321(3)	C5-C7	1.323(3)
C8-C7	1.493(3)	C7-H7	0.95
C9-C10	1.506(3)	C9-H9A	0.99
C9-H9B	0.99	C10-H10A	0.98
C10-H10B	0.98	C10-H10C	0.98
C3-C4	1.495(3)	C3-H3A	0.99
C3-H3B	0.99	C4-H4A	0.98
C4-H4B	0.98	C4-H4C	0.98
C1-C2	1.503(3)	C1-H1A	0.99
C1-H1B	0.99	C2-H2A	0.98
C2-H2B	0.98	C2-H2C	0.98

Table 5. Bond angles (°) for

D8_0249_CWA_DK_12a16_all.

O5-S1-O6	123.94(10)	O5-S1-O4	111.69(8)
O6-S1-O4	107.97(9)	O5-S1-C6	107.24(10)

O6-S1-C6	104.07(10)	O4-S1-C6	98.67(8)
O1-P1-O3	119.69(8)	O1-P1-O2	115.03(8)
O3-P1-O2	102.74(8)	O1-P1-C5	110.75(8)
O3-P1-C5	99.89(8)	O2-P1-C5	107.08(8)
C5-O4-S1	123.76(12)	C3-O3-P1	122.20(13)
C8-O8-C9	116.46(15)	C1-O2-P1	120.78(13)
C7-C5-O4	123.65(16)	C7-C5-P1	121.59(15)
O4-C5-P1	114.55(13)	O7-C8-O8	125.34(17)
O7-C8-C7	125.27(18)	O8-C8-C7	109.39(16)
C5-C7-C8	126.22(18)	C5-C7-H7	116.9
C8-C7-H7	116.9	O8-C9-C10	106.26(16)
O8-C9-H9A	110.5	C10-C9-H9A	110.5
O8-C9-H9B	110.5	C10-C9-H9B	110.5
H9A-C9-H9B	108.7	C9-C10-H10A	109.5
C9-C10-H10B	109.5	H10A-C10-H10B	109.5
C9-C10-H10C	109.5	H10A-C10-H10C	109.5
H10B-C10-H10C	109.5	O3-C3-C4	107.27(16)
O3-C3-H3A	110.3	C4-C3-H3A	110.3
O3-C3-H3B	110.3	C4-C3-H3B	110.3

H3A-C3-H3B	108.5	F3-C6-F1	109.67(18)
F3-C6-F2	109.15(18)	F1-C6-F2	108.52(18)
F3-C6-S1	111.87(15)	F1-C6-S1	110.03(15)
F2-C6-S1	107.51(14)	C3-C4-H4A	109.5
C3-C4-H4B	109.5	H4A-C4-H4B	109.5
C3-C4-H4C	109.5	H4A-C4-H4C	109.5
H4B-C4-H4C	109.5	O2-C1-C2	107.47(19)
O2-C1-H1A	110.2	C2-C1-H1A	110.2
O2-C1-H1B	110.2	C2-C1-H1B	110.2
H1A-C1-H1B	108.5	C1-C2-H2A	109.5
C1-C2-H2B	109.5	H2A-C2-H2B	109.5
C1-C2-H2C	109.5	H2A-C2-H2C	109.5
H2B-C2-H2C	109.5		

Table 6. Torsion angles (°) for

D8_0249_CWA_DK_12a16_all.

O5-S1-O4-C5	-0.43(16)	O6-S1-O4-C5	139.10(14)
C6-S1-O4-C5	-112.96(15)	O1-P1-O3-C3	68.13(17)
O2-P1-O3-C3	-60.79(16)	C5-P1-O3-C3	-170.98(16)

O1-P1-O2-C1	34.18(17)	O3-P1-O2-C1	165.94(14)
C5-P1-O2-C1	-89.37(16)	S1-O4-C5-C7	-70.0(2)
S1-O4-C5-P1	115.21(12)	O1-P1-C5-C7	-13.4(2)
O3-P1-C5-C7	-140.55(17)	O2-P1-C5-C7	112.72(17)
O1-P1-C5-O4	161.52(12)	O3-P1-C5-O4	34.39(14)
O2-P1-C5-O4	-72.34(14)	C9-O8-C8-O7	3.2(3)
C9-O8-C8-C7	-176.70(15)	O4-C5-C7-C8	2.8(3)
P1-C5-C7-C8	177.31(15)	O7-C8-C7-C5	2.0(3)
O8-C8-C7-C5	178.04(18)	C8-O8-C9-C10	179.08(16)
P1-O3-C3-C4	156.35(15)	O5-S1-C6-F3	-50.21(18)
O6-S1-C6-F3	176.91(15)	O4-S1-C6-F3	65.81(17)
O5-S1-C6-F1	-172.38(14)	O6-S1-C6-F1	54.74(17)
O4-S1-C6-F1	-56.36(16)	O5-S1-C6-F2	69.61(17)

O6-S1-C6-F2 -63.27(17) O4-S1-C6-F2   -174.37(14)

P1-O2-C1-   -

C2   172.12(15)

Table 7. Anisotropic atomic displacement parameters (Å^2)

for D8_0249_CWA_DK_12a16_all.

The anisotropic atomic displacement factor exponent takes the

form: $-2\pi^2[\,h^2\,a^{*2}\,U_{11} + ... + 2\,h\,k\,a^*\,b^*\,U_{12}\,]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	0.0173(3)	0.0158(2)	0.0162(3)	0.00113(18)	0.0020(2)	0.0116(2)
P1	0.0142(3)	0.0111(2)	0.0191(3)	0.00664(19)	0.0066(2)	0.0087(2)
F3	0.0414(9)	0.0253(7)	0.0266(7)	0.0113(6)	0.0012(6)	0.0091(6)
O4	0.0114(7)	0.0123(6)	0.0163(7)	0.0031(5)	0.0051(6)	0.0076(5)
O7	0.0182(8)	0.0124(7)	0.0223(7)	0.0054(6)	0.0045(6)	0.0093(6)
F2	0.0386(8)	0.0293(7)	0.0187(7)	-0.0009(5)	-0.0029(6)	0.0133(6)
O3	0.0185(8)	0.0161(7)	0.0317(8)	0.0126(6)	0.0119(7)	0.0138(6)
O8	0.0157(7)	0.0143(7)	0.0226(7)	0.0088(6)	0.0049(6)	0.0110(6)
O2	0.0189(8)	0.0179(7)	0.0217(7)	0.0093(6)	0.0088(6)	0.0103(6)
O1	0.0194(8)	0.0138(7)	0.0243(8)	0.0060(6)	0.0079(6)	0.0096(6)
F1	0.0321(9)	0.0665(10)	0.0400(8)	0.0168(7)	0.0069(7)	0.0389(8)
O6	0.0262(9)	0.0140(7)	0.0285(8)	0.0030(6)	0.0006(7)	0.0073(7)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O5	0.0254(9)	0.0408(9)	0.0231(8)	-0.0022(7)	0.0070(7)	0.0234(8)
C5	0.0123(10)	0.0097(8)	0.0159(9)	0.0031(7)	0.0056(8)	0.0064(7)
C8	0.0150(10)	0.0156(9)	0.0163(9)	0.0068(8)	0.0080(8)	0.0116(8)
C7	0.0131(10)	0.0116(9)	0.0174(10)	0.0039(7)	0.0057(8)	0.0067(8)
C9	0.0195(11)	0.0180(10)	0.0242(10)	0.0128(8)	0.0101(9)	0.0147(9)
C10	0.0227(12)	0.0309(12)	0.0258(11)	0.0168(9)	0.0106(10)	0.0200(10)
C3	0.0254(12)	0.0177(10)	0.0438(13)	0.0166(9)	0.0158(11)	0.0191(9)
C6	0.0198(12)	0.0224(11)	0.0201(11)	0.0049(8)	0.0016(9)	0.0107(9)
C4	0.0245(12)	0.0272(11)	0.0404(13)	0.0200(10)	0.0140(11)	0.0198(10)
C1	0.0242(12)	0.0312(12)	0.0278(12)	0.0084(10)	0.0149(10)	0.0127(10)
C2	0.0402(16)	0.0386(14)	0.0285(13)	0.0078(11)	0.0196(12)	0.0135(12)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters ($Å^2$) for D8_0249_CWA_DK_12a16_all.

	x/a	y/b	z/c	U(eq)
H7	0.8627	0.8101	0.5045	0.017
H9A	0.8698	0.3681	0.5334	0.021
H9B	0.7929	0.3782	0.6388	0.021
H10A	1.0809	0.4241	0.7369	0.034

	x/a	y/b	z/c	U(eq)
H10B	1.1618	0.5797	0.6798	0.034
H10C	1.0853	0.5897	0.7847	0.034
H3A	0.4800	1.0678	0.2480	0.029
H3B	0.4814	1.1129	0.3859	0.029
H4A	0.1948	1.0040	0.2284	0.04
H4B	0.1844	0.8355	0.1789	0.04
H4C	0.1858	0.8803	0.3162	0.04
H1A	0.8638	0.9106	0.2140	0.033
H1B	0.9194	1.1010	0.2606	0.033
H2A	0.8875	1.0395	0.0484	0.057
H2B	0.6851	0.8878	0.0086	0.057
H2C	0.7405	1.0774	0.0550	0.057

Table 9. Hydrogen bond distances (Å) and angles (°) for D8_0249_CWA_DK_12a16_all.

	Donor-H	Acceptor-H	Donor-Acceptor	Angle
C7-H7···O1	0.95	2.41	3.207(2)	141.2
C9-H9B···O4	0.99	2.64	3.415(3)	135.7
C3-	0.99	2.45	3.247(2)	137.7

	Donor-H	Acceptor-H	Donor-Acceptor	Angle
H3B···O7				
C4-H4A···O6	0.98	2.50	3.394(3)	152.4
C4-H4C···O1	0.98	2.61	3.477(3)	147.5

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