Gold-Catalyzed Activation of Epoxides and Hydration of Alkynes and Their Synthetic Applications

A Thesis
Submitted for the degree of

DOCTOR OF PHILOSOPHY

by

GANESH KUMAR THOTA

SCHOOL OF CHEMISRY
UNIVERSITY OF HYDERABAD
HYDERABAD, INDIA – 500046
April, 2014

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INDIA

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Dr. Rengarajan Balamurugan**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

Ganesh Kumar Thota

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CERTIFICATE

Certified that the work contained in the thesis entitled ***"Gold-Catalyzed Activation of Epoxides and Hydration of Alkynes and Their Synthetic Applications"*** has been carried out by **Mr. Ganesh Kumar Thota** under my supervision and the same has not been submitted elsewhere for a degree.

Dr. R. Balamurugan
(Thesis Supervisor)

Dean
School of Chemistry

.....Dedicated to

My Beloved Parents

Sri. Thota Anjaneyulu

Smt. Thota Savithree

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Ganesh Kumar Thota

University of Hyderabad

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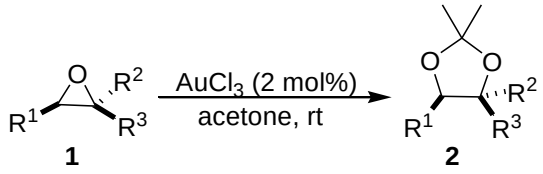
Part-II: Gold-Catalyzed Hydration of Enynediester: Application in the Synthesis of γ-Lactam and Pyrrolidine Derivatives

SYNOPSIS

The thesis entitled **"Gold-Catalyzed Activation of Epoxides and Hydration of Alkynes and Their Synthetic Applications"** is divided into two parts. Each part is subdivided into four sections namely **Introduction**, **Results and discussion**, **Conclusion Experimental section** and **References**. The work described in this thesis is exploratory in nature.

The first part describes the gold catalyzed activation of epoxides and its application in the synthesis of cyclic acetals *via* acetonide formation. A brief review on gold catalysis, methods available for the acetonide formation and synthesis of cyclic acetals is presented in the introductory section. Unlike other early transition metals, gold has poor oxophilicity as evident from the poor stability of gold oxides. The oxophilicity of gold catalyst has not been much explored till date. Hence a study on the ring-opening of epoxides using gold catalyst was undertaken. It was expected that theoxyanion of the ring-opened system will be more nucleophilic. We have found that the reaction of epoxides **1** with acetone in the presence of 2 mol% of $AuCl_3$ was smooth and resulted in the formation of acetonides **2** in high yields (Scheme 1). The efficiency of this method was evaluated with a series of epoxides under gold catalysis. Corresponding acetonide derivatives were obtained in good to excellent yields. As an extension, we have successfully cyclised the acetonide on a suitably placed triple bond intramolecularly under gold catalysis. Corresponding bicyclic acetals were obtained in moderate to good yields.

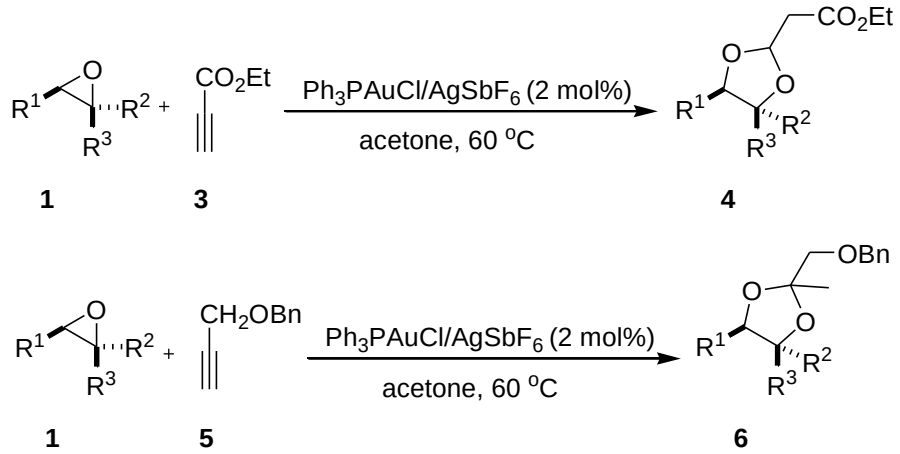


1 **2**

Scheme 1. $AuCl_3$-catalyzed acetonide formation

We have developed a gold(I)-catalyzed synthesis of cyclic acetals by an intermolecular reaction of epoxide and terminal alkynes. This reaction proceeds *via* the formation of acetonide from epoxide which subsequently cyclises on the alkyne activated by gold (Scheme 2). This study is restricted to terminal alkynes only as the internal counter parts are unreactive. A series of epoxides were prepared, and reacted with terminal alkynes **3** and **5** in acetone using 2 mol% $Ph_3PAuCl/AgSbF_6$. Corresponding cyclic acetals were obtained in

good to excellent yields. The synthesized cyclic acetals of type **4** can be deprotected into diols using base. Enantioenriched epoxides were employed to study the regioselectivity of acetonide ring-opening.

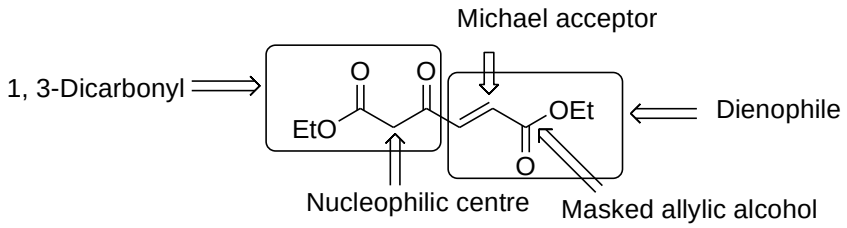


1 **3** **4**

1 **5** **6**

Scheme 2. Gold(I)-catalyzed synthesis of cyclic acetals from epoxides and alkynes

The second part of this thesis describes the gold-catalysed hydration of enynediester obtained from ethyl propiolate and application of the hydrated product **7** in the synthesis of γ-lactam and pyrrolidine derivatives. A brief review on the hydration of alkynes, methods available for the gold catalyzed hydration of alkynes, γ-lactam and pyrrolidine derivatives is presented in the introductory section.

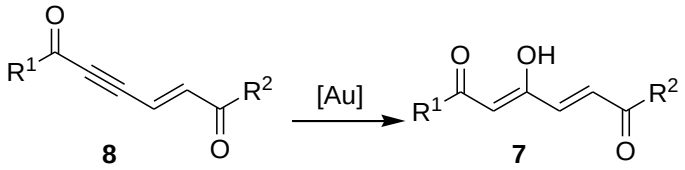


7

Figure 1. Reactive sites of (*E*)-diethyl 4-oxohex-2-enedioate **7**

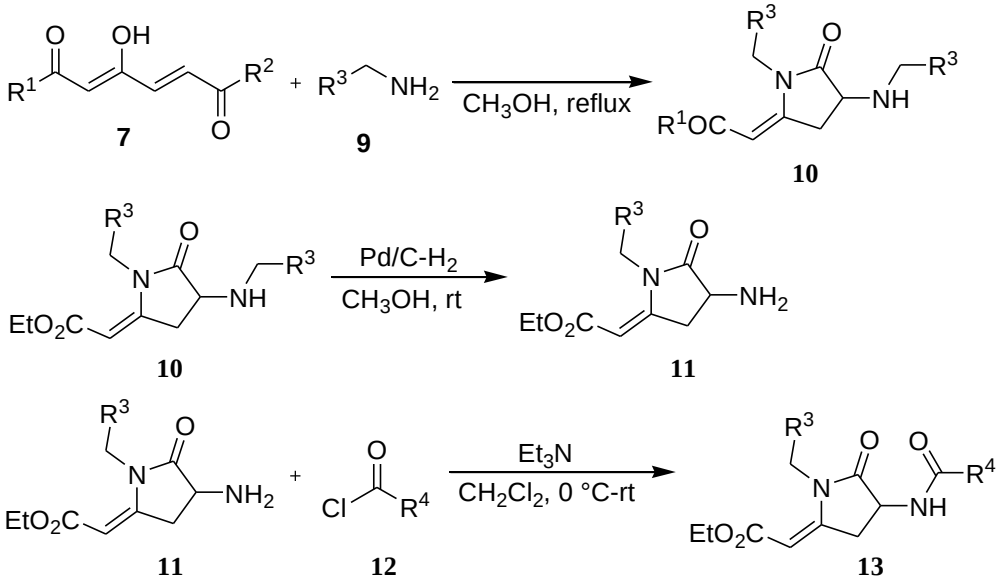
(*E*)-Diethyl 4-oxohex-2-enedioate **7** has an intriguing structure as it has different functionalities. The most interesting aspect of this six carbon compound is that each carbon can selectively be reacted. It has a 1,3-dicarbonyl, carbonyl, two different esters, Michael acceptor carbons and dienophilic portion in it as shown in Figure 1. Hence it can serve as a versatile synthon to make interesting compounds. We have developed a simple method for the synthesis of targeted compound **7** by hydration of easily accessible enyne diester **8** using gold catalyst (Scheme 3). The substrate **8** was subjected to gold-catalysed hydration under

different conditions to assertain the best reaction condition. Also we checked the reactivity of enyne diester **8** with few alcohols as well to make enol ethers. Further to evaluate the application of this hydration stratagy, we synthesized few other subatrates containing alkynyl ketones and alkynyl esters. These substrates were subjected to hydration using gold(I) catalyst in acetone and/or 1,4-dioxane:water solvent systems separately. The hydration product of enyne diester has been utilized in the synthesis of hexane-1,3,6-triol.



Scheme 3. Gold-catalyzed hydration of enyne diethylester

Since the substrate **7** has ketone and Michael acceptor functionalities, we subjected it to react with primary amines. These reactions resulted in the formation of γ-lactam derivatives **10** in moderate to good yields (Scheme 4).

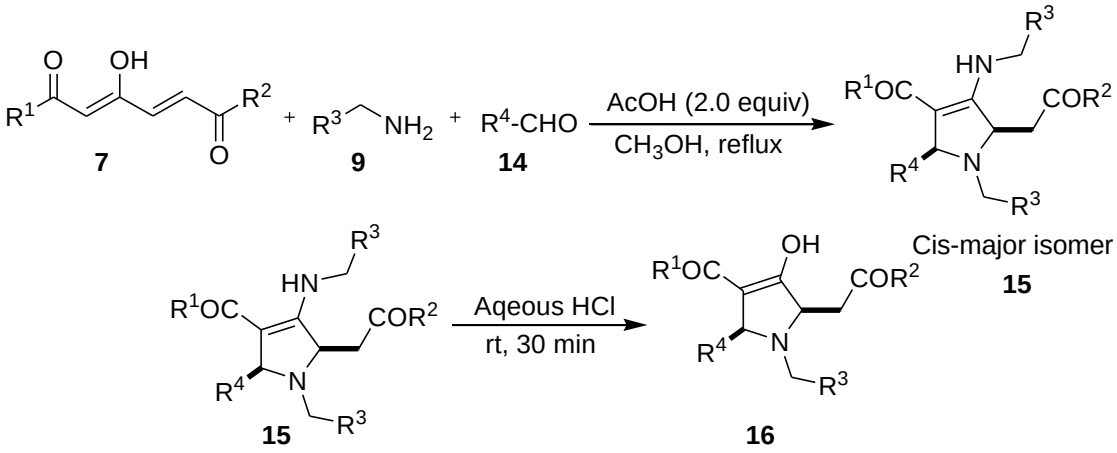


Scheme 4. Synthesis of γ-lactam derivatives

Selective debenzylation of the benzyl group at the amine nitrogen is achievable using Pd/C-H_2. The product could be N-acylated to get compounds having similar structure as that of homoserine lactone (bacterial quorum sensing compounds)

Further, we developed a method for the synthesis of highly functionalized pyrrolidine derivatives **15** by utilising the hydration product **7**. The scope of this reaction was explored

using different aldehydes **14** and benzyl amine derivatives **9** with 2 equivalents of AcOH in methanol solvent at reflux. The resulting pyrrolidine derivatives **16** were obtained in moderate to good yields with good diastereomeric ratio. The *cis*-isomer was found to be the major isomer from NOESY experiments. The synthesized pyrrolidine derivatives **15** were hydrolyzed with aqueous HCl to get the corresponding 1,3-dicarbonyl derivative **16** in quantitative yield (Scheme 5).



Scheme 5. Synthesis of pyrrolidine derivatives

Note: Scheme numbers and compound numbers given in this abstract are different from those given in part-I and II.

LIST OF ACRONYMS USED

AcOH	Acetic acid
Aq.	Aqueous
Bn	Benzyl
br s	Broad singlet (spectral)
Bu	Butyl
t-Bu	*ter*-Butyl
CAN	Ceric ammonium nitrate
^{o}C	Degree Celsius
Cat.	Catalyst
conc.	Concentrated
cm^{-1}	Wavenumber(s)
δ	Chemical shift in parts per million downfield from tetramethyl silane
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
dil.	Diluted
DMF	N,N-Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
ESI	Electron spin ionisation
Et	Ethyl
EtOH	Ethyl alcohol
equiv	Equivalent
g	Gram (s)
h	Hour (s)
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant (in NMR Spectrometry)

LA	Lewis acid
LDA	Lithium diisopropylamide
lit.	Literature
LCMS	Liquid chromatography-mass spectrometry
m	Multiplet (spectral)
Me	Methyl
mg	Milligram (s)
MeCN	Acetonitrile
MHz	Megahertz
min	Minute(s)
mmol	Millimolar
mp	Melting point
MS	Molecular sieves
NMR	Nuclear magnetic resonance
Nu	Nucleophile
OTf	Trifluoromethanesulfonate
Pent	Pentet
PMA	Phosphomolybdic acid
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
q	Quartet (in spectroscopy)
RT	Room temperature
s	Singlet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TFA	Trifluoroacetic acid

PART-I

Gold-Catalyzed Activation of Epoxides: Applications in the Synthesis of Cyclic Acetals via Acetonide Formation

1.1 Introduction to gold catalysis

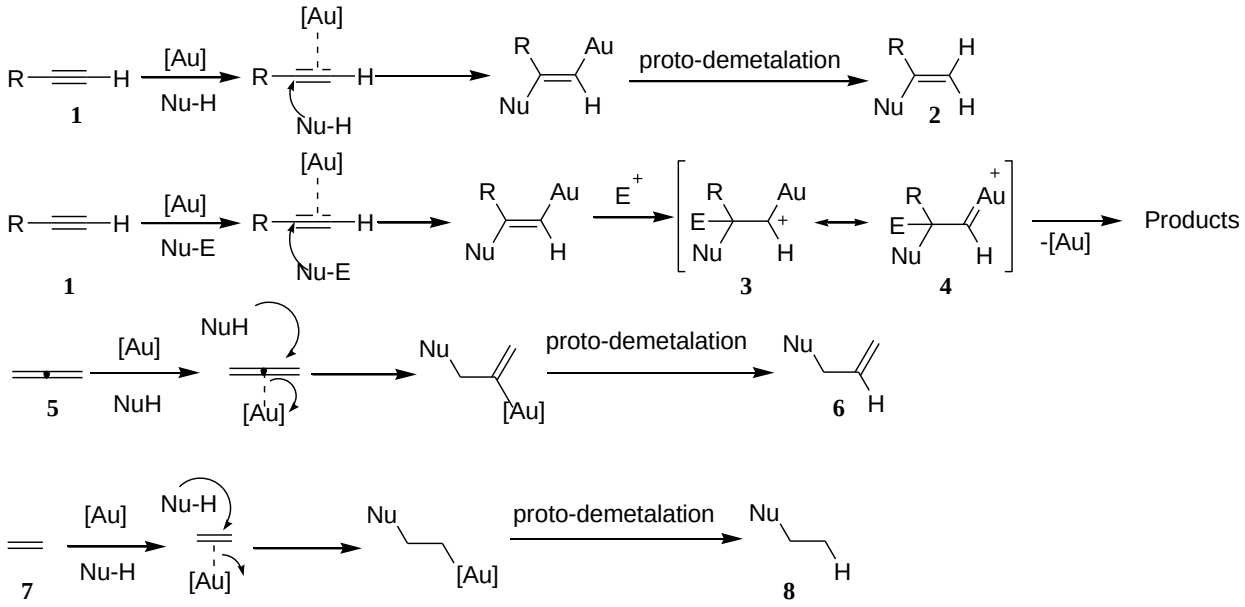
Gold, being one of the precious metals, had been considered as catalytically inactive and its application in catalysis were not explored although other more expensive precious metals like platinum, rhodium etc. have good history in catalysis. Towards the end of the last millennium it was realized that ionic form of gold is active to catalyze organic reactions while metallic gold is inactive. During the last decade catalytic properties of gold compounds have been unearthed to the core. In homogeneous gold catalysis, gold compounds in (I) and (III) oxidation states have been used. Both proved to be very effective in large number organic transformations. Since gold is a soft transition metal, it activates the carbon-carbon multiple bonds (alkyne, allene and alkene) for the attack of different nucleophiles to form C-C, C-O, and C-N bonds. The alkynophilicity of gold catalysts has been well explored and utilized aspect. Gold is expected to have poor oxophilicity as the metallic gold does not get oxidized and gold oxides are unstable. Thus the oxophilicity of gold catalysts have not been explored much. Generally gold catalyzed reactions are faster than other metal catalyzed reactions and the reactions occur under mild conditions and completes in reasonably shorter reaction times. Gold is an environmentally friendly catalyst which adds more application value to its catalysis.[1] The general reactivity pattern of gold catalysts is presented below.

1.2 Gold-catalyzed organic transformations

1.2.1 Carbophilicity of gold compounds

Gold is a $5d^{10}$ $6s^{1}$ system and is influenced heavily by relativistic effect. Because of this, the 6s orbital which is close to the nucleus is contracted on the other hand the 5d orbital, due to heavy shielding of inner orbitals, is expanded. The contraction of 6s orbital is reflected in strong electronegativity which in turn increases its Lewis acidity. Being a softer metal it has strong affinity towards C-C multiple bonds. The expansion of 5d orbital makes the gold to stabilize a carbocationic center next to it by back donation through 5d orbital.[2] The typical reactions catalyzed by gold catalysts are shown in Scheme 1. Due to the exceptional alkynophilicity gold can activate an alkyne bond for the the attack of nucleophiles. The nucleophile could be oxygen, sulfur, nitrogen and carbon based. After the attack of nucleophile the intermediate will undergo protodemetalation to generate an olefin. Another intriguing property of gold is its nature to stabilize a positive charge next to it. If the

nucleophile has a leaving group gold will assist, by back donation, the departure of the leaving group to generate a gold carbene species which is used in further reactions.[3] Gold can activate allene for similar nucleophilic attack to make alkenes of kind **6**. Activation of an alkene by gold is not as efficient as that of an alkyne. Only few reports are there where the reactions of alkenes involve activation by gold and the products are alkanes generally.



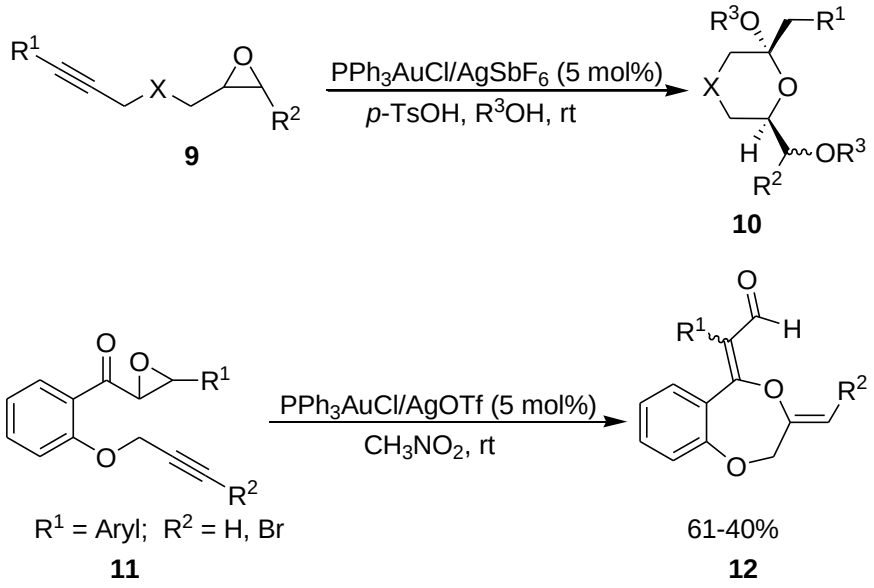
Scheme 1. Gold catalyzed activation of alkynes **1**, allenes **3** and alkenes **5**

1.2.2 Oxophilicity of gold compounds

In most of the gold catalyzed reactions developed in recent years, its carbophilicity has been exploited. It is believed that the oxophilicity of gold is poor as evident from the fact that it does not get oxidized readily and the gold oxides are unstable.[4] Yamamoto has recently shown, from the computed heats of formation values, that both gold(I) and gold(III) possess considerable oxophilicity.[5] However the oxophilicity of the gold catalysts is not well utilized as evident from the limited literature. Most of these reports involve the activation of carbonyl function.[6] When compared with the trivial oxophilic Lewis acids, gold is advantageous because it will not be bound strongly to the oxyanion generated in the reactions involving carbonyls and epoxides. Hence its catalytic efficiency is expected to be high.

1.2.3 Gold-catalyzed activation of epoxides and alkynes/allenes

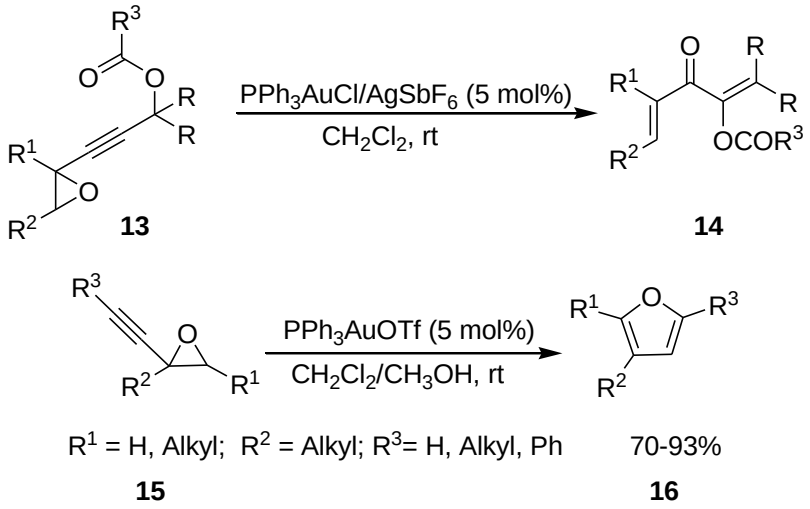
Epoxides are attractive building blocks to construct interesting molecular skeletons.[7] Using gold catalysts, transformations of α- and β-alkynyl epoxides have been reported.[8] In these reactions, considering the alkynophilicity of gold catalysts, intramolecular nucleophilic attack of the oxirane oxygen on the gold-activated alkyne *via* an oxonium ion intermediate has been proposed. In 2008, Shi and co-workers developed a gold catalyzed syntheis of cyclic acetals **10** from epoxyalkynes **9** using water and alcohols as nuleophiles.[9a] In this reaction gold activates the epoxide first for the attack of water/alcohol. The resulting alcohol then cycloisomerizes on the gold activated triple bond. Ultimately, this reaction results in bicyclic acetals and cyclic acetals with water and alcohol respectively.



Scheme 2. Gold (I)-catalyzed reactions of epoxyalkynes

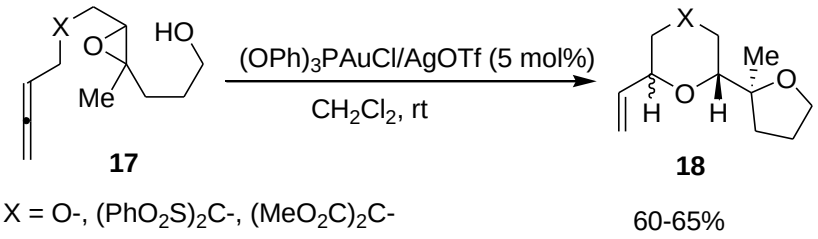
Same research group developed an intramolecular cycloisomerization of **11** to get six- or seven membered heterocyclic compounds **12** using gold(I)- catalyst (Scheme 2).[9b] Pale group investigated the behavior of various alkynyl oxiranes under gold catalysis. These reactions proceed by double activation of the alkyne and the oxirane oxygen atom by gold catalyst which led to the rearranged divinyl ketones **14**.[10a] The same group developed a gold(I)-catalyzed synthesis of highly substituted furans **16** from alkynyl oxiranes **15**.[10b] Based on the mechanistic studies carried out, it was proposed that this reaction takes place

through a cascade opening of epoxide by alcohol, then cyclization of corresponding intermediate followed by alcohol elimination (Scheme 3).



Scheme 3. Gold(I)-catalyzed rearrangement of alkynyl oxiranes

Oxo and carbophilicities of gold was nicely utilized in the gold(I)-catalyzed cyclization of allenyl epoxides developed by Gagne and Lee.[11] This reaction led to the formation of polyether skeletons in moderate yields. This reaction proceeds through gold catalyzed activation of epoxide for the intramolecular attack of hydroxyl function followed by intramolecular hydroalkoxylation on gold-activated allenes (Scheme 4).



Scheme 4. Gold(I)-catalyzed cascade cyclisation of allenyl epoxides **17**

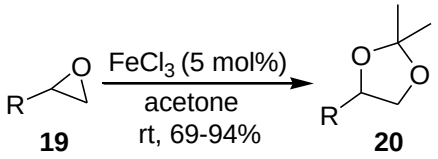
Our research group has contributed in the gold catalyzed substituted naphthalenes synthesis, epoxide rearrangement, transglycosylation on per-*O*-acetylglycals and methylene-bridged bis-1,3-dicarbonyl compounds synthesis by utilizing its oxo and alkynophilicities.[12]

1.3 Gold-catalyzed activation of epoxides for acetonide formation

Epoxides are important and versatile intermediates in organic synthesis.[13] Nuleophilic addition to an epoxide can be promoted by acid or base and diverse nuleophiles could be employed. In acidic condition the epoxide ring opens up at the most substituted carbon for nucleophilic attack. On the other hand, it opens at the less substituted carbon of the ring under basic conditions.

1.3.1 Background

Acetonides are widely used as protecting groups of 1,2 and 1,3-diols in organic synthesis. Apart from the straight forward conversion of diols into acetonides by the reaction with acetone/dimethoxyacetone in the presence of acids,[14] epoxides can be opened with acetone to form acetonides. Lewis acid catalysts find good application to achieve this task. Differnet Lewis acid catalysts such as anhydrous $CuSO_4$,[15] $Er(OTf)_3$,[16] $Cu(OTf)_2$,[17] Bi(III)-salt,[18] $Fe(OTf)_3$,[19] $RuCl_3$,[20] $TiCl_4$,[21] $TiO(TFA)_2$[22] can be employed. In 2007, Roy and co-workers reported a mild and efficient method for the preparation of acetonides **20** from epoxides **19** catalyzed by $FeCl_3$ (Scheme 5).[23] The resulting acetonides were obtained in the range of 69-94% yield at rt from a wide range of epoxides.



19 **20**

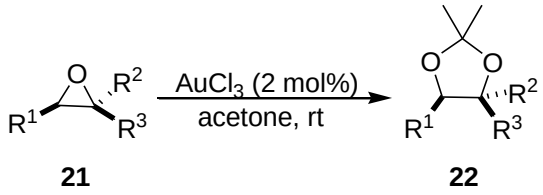
Scheme 5. $FeCl_3$-catalyzed acetonide formation

In 2003, Vyvyan *et al.* reported that anhydrous $SnCl_2$ as an efficient catalyst for the conversion of mono-, di-, and trisubstituted epoxides directly to corresponding acetonide derivatives in good to excellent yields.[24] Optically pure styrene oxide resulted significant loss of optical purity in the corresponding acetonide. $TiCl_3(OTf)$ was found to be a good catalyst at -78 $^{\circ}$C for the conversion of R-(+)-styrene oxide to corresponding acetonide in highly stereospecific fashion with inversion of configuration.[22] In 2006, Lupattelli *et al.* reported Amberlyst 15 as an efficient catalyst for the reaction of aryl substituted oxiranes with acetone to corresponding acetonides in high yields.[25] *trans*-2,3-Diaryloxiranes afford *trans*-acetonides enantiospecifically at room temperature. *trans*-Stilbene epoxide gave a mixture of

syn/anti acetonides along with rearranged product ie., diphenyl acetaldehyde. Other systems such as 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO),[26] tetracyanoethylene (TCNE),[27] $LiBF_4$,[28] Zeolite,[29] CH_3ReO_3,[30] and electro-generated acids[31] have also been reported for acetonide formation. Many of these reported methods require higher reaction temperatures, suffer from long reaction times, functional group in tolerance and the use of expensive and toxic catalysts.

1.4 Results and discussion

We considered the gold catalyzed ring-opening of epoxides with acetone for the following reasons. This will provide a chance to access the oxophilicity of gold catalyst and the products can be reacted with an alkyne utilizing the alkynophilicity of gold in tandem. Unlike other early transition metals gold has poor oxophilicity as evident from the poor stability of gold oxides.[4] We wished to utilize this character in the ring-opening of epoxides **21** as the oxyanion of the ring-opened system will be more nucleophilic. With weak nucloephile such as acetone which can assist the ring opening of epoxide activated by gold catalyst, we expected the acetonide formation. We found that the reaction of epoxides **21** with acetone in the presence of 2 mol% of $AuCl_3$ was smooth and resulted in the acetonides **22** in high yields (Scheme 6).



21 **22**

Scheme 6. $AuCl_3$-catalyzed acetonide formation from epoxides

To study the scope of the reaction a wide variety epoxides **21a–21q** were prepared by standard procedure. Optically pure epoxide **21r** was prepared by Sharpless asymmetric epoxidation from its corresponding alkene. The epoxides listed in the Figure **1** (**21a**-**21r)** were treated with 2 mol% $AuCl_3$ in acetone. Epoxides **21a**-**21m** resulted in their corresponding acetonide derivatives in good to excellent yields. The results of reactions of epoxides **21a**-**21k** are summarized in Table 1.

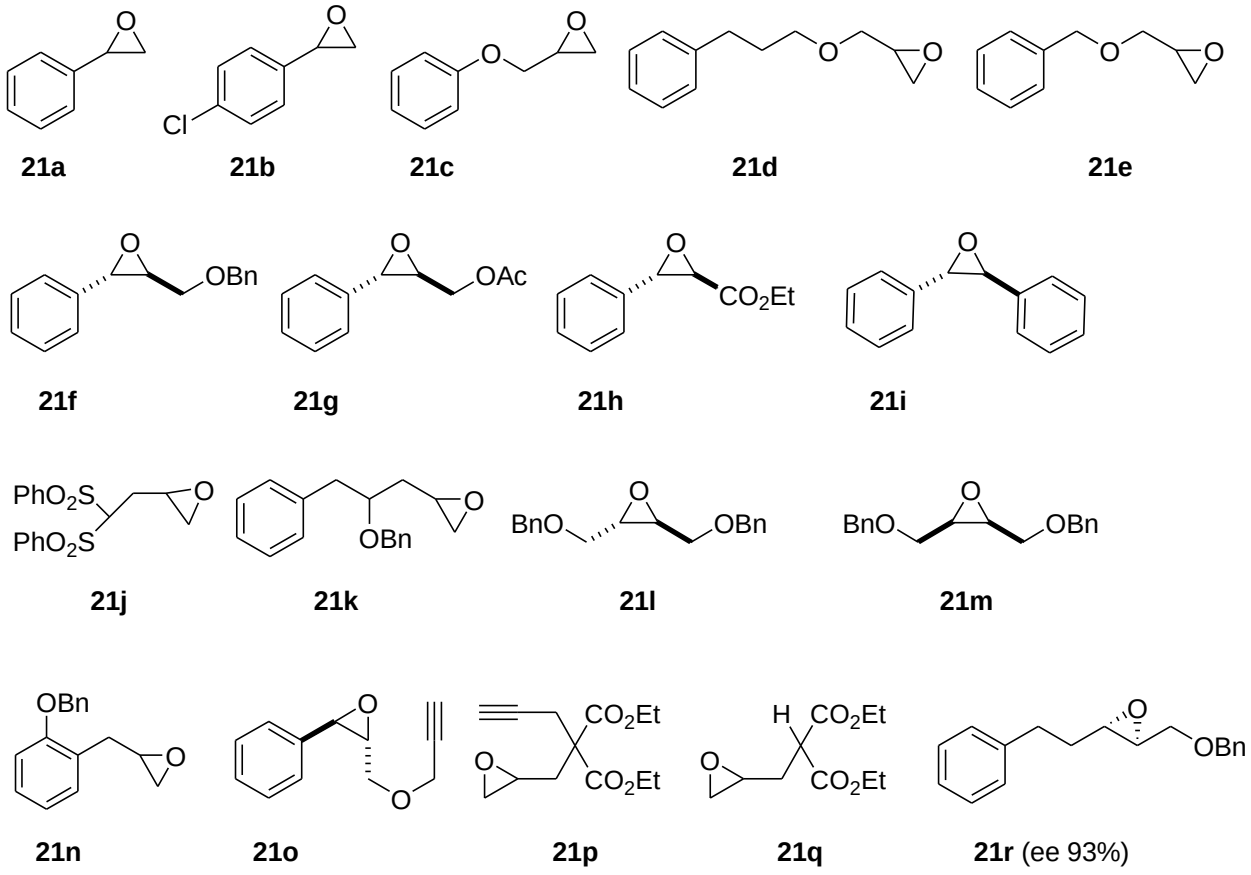
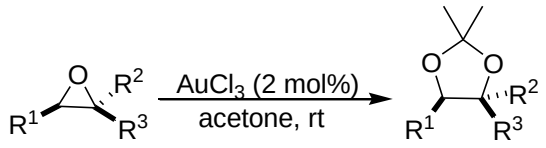


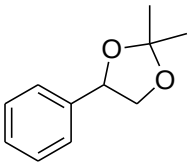
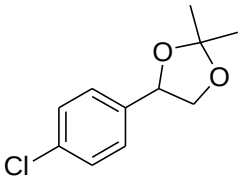
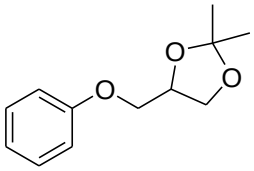
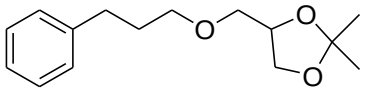
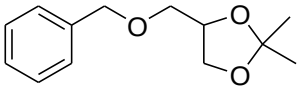
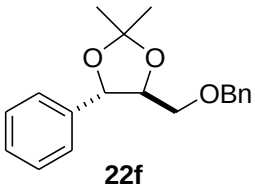
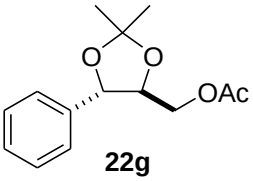
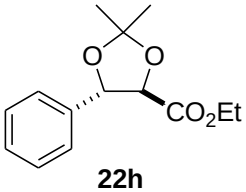
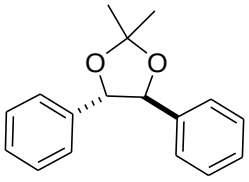
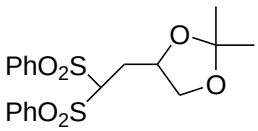
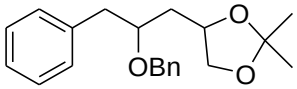
Figure 1. List of epoxides employed in the gold catalyzed acetonide formation

Although same conversion is possible with different Lewis acid catalysts, more than half of them require heating. The reactions were exceptionally smooth and completed quickly at room temperature. Another advantage of $AuCl_3$ is that strict anhydrous condition, which is required for many sensitive Lewis acids, is not necessary as the reactions could be carried out with distilled acetone. Reactions of both mono and vicinally di-substituted epoxides were studied. Di-substituted epoxides with aryl as the substituent gave a mixture of *syn* and *anti* dioxolane derivatives **22f-22i**.

Table 1. $AuCl_3$-catalyzed formation of acetonide derivatives from epoxides

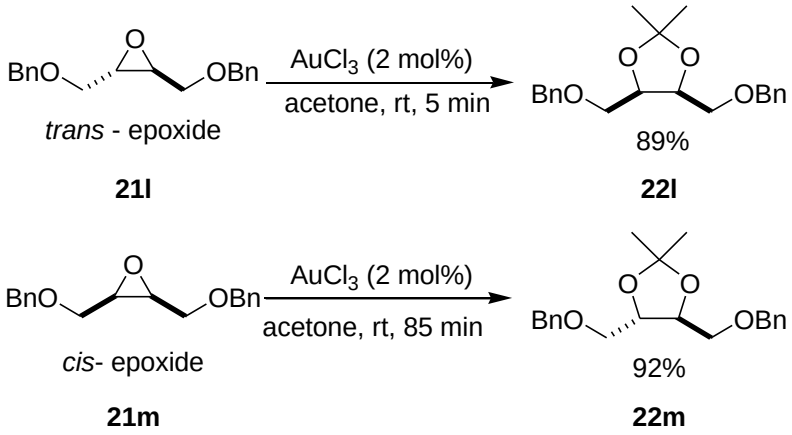


21a-21k **22a-22k**

 **22a**	 **22b**	 **22c**	 **22d**
15 min, 73%[a]	5 min, 87%[a]	40 min, 78%[a]	90 min, 84%[a]
 **22e**	 **22f**	 **22g**	 **22h**
5 min, 83%[a]	15 min, 82%[a] (1:1)[b]	20 min, 74%[a] (2.5:1)[b]	20 min, 92%[a] (1.8:1)[b]
 **22i**	 **22j**	 **22k**	
25 min, 77%[a, c] (1:4.9)[b]	75 min, 52%[a]	10 min, 81%[a] (1:1)[b, d]	

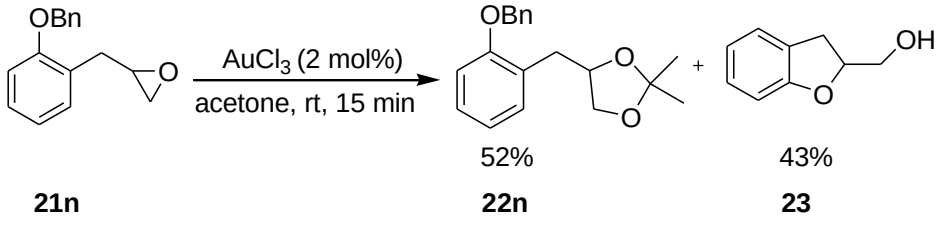
[a] Isolated yield. [b] Values in the paranthesis refer the syn/anti ratio based on integrations in ^{1}H NMR spectrum. [c] Diphenylacetaldehyde also formed in 14% yield. [d] 1:1 Diastereomeric mixture of starting material.

Whereas, dialkyl substituted epoxides **21l** and **21m** gave the corresponding dioxolane derivatives in a complete stereospecific manner **22l** and **22m**. While the *syn*-epoxide gave *anti*-acetonide derivative, *anti*-epoxide gave *syn*-acetonide by S_N2 attack of the solvent acetone on the gold-activated epoxide ring (Scheme 7).



Scheme 7. Reactions with dialkyl substituted epoxides **21l** and **21m**

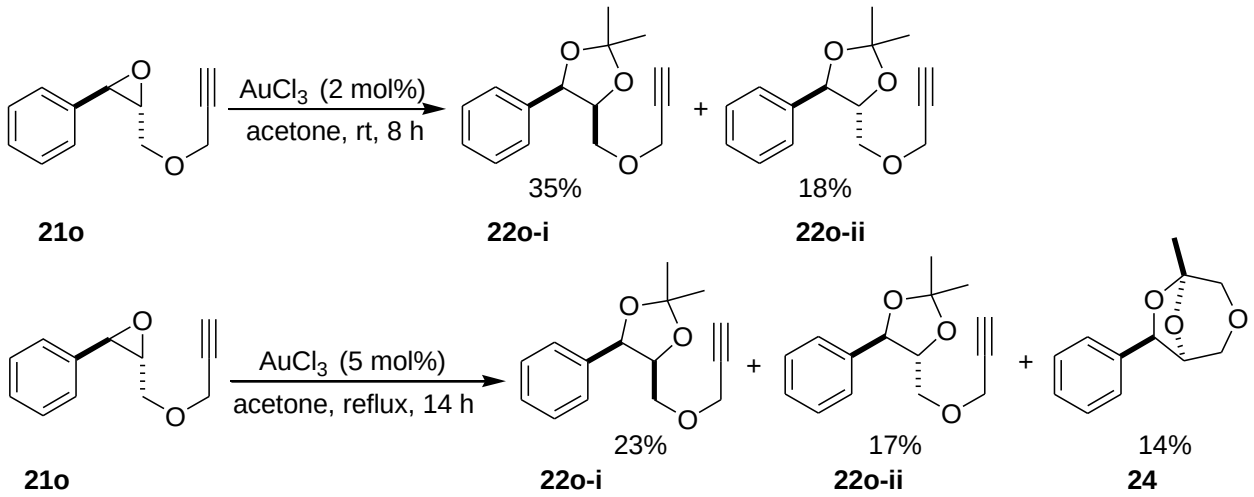
This kind of nucleophilic assistance from the solvent acetone is required to open the epoxide ring. In aryl-substituted epoxides, the generated carbocation is stabilized by the aryl group (see the mechanism). This leads to the scrambling of stereochemistry as the acetone can approach from either side of the carbocation. Under the reaction condition, only stilbene oxide showed some carbocationic rearrangement to result in 14% of diphenylacetaldehyde along with the expected mixture of *syn* and *anti* acetonides. Interestingly, with substrate **21n**, we noticed the formation of 2,3-dihydro-2-hydroxymethylbenzofuran **23** in significant amount along with corresponding acetonide product **22n** (Scheme 8). This product might have formed by the initial gold-catalyzed debenzylation of aryl benzyl ether followed by the attack phenolic hydroxyl group on the epoxide ring. This result is not surprising as certain Lewis acids have already been known to debenzylate aryl benzyl ethers.[32]



Scheme 8. Debenzylation followed by cyclisation of **21n**

Once achieving acetonide formation under gold catalysis we wished to cyclize intramolecularly on a suitably placed triple bond. For this purpose, we made the epoxyalkyne **21o** by treating epoxy alcohol with propargyl bromide using NaH as base. The epoxyalkyne **21o,** when treated with 2 mol% of $AuCl_3$ in acetone at room temperature, resulted in the

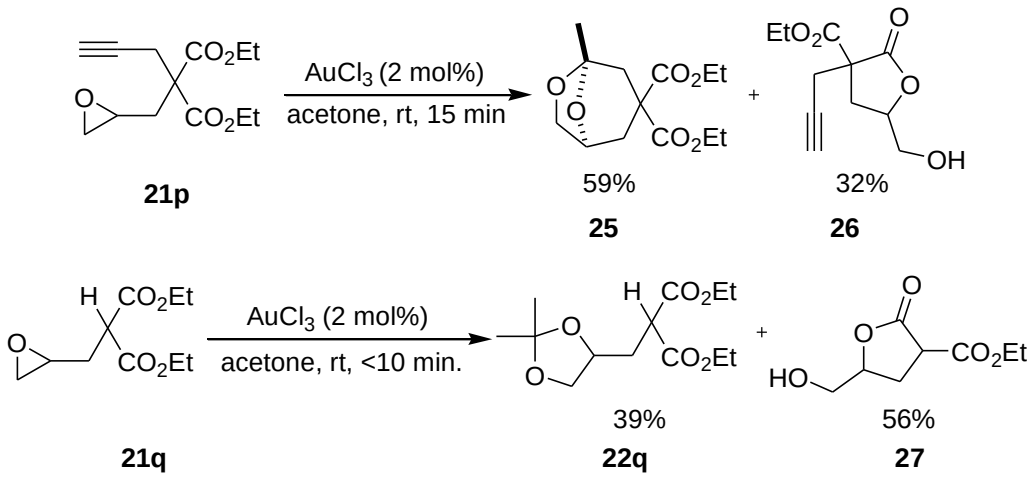
acetonides **22o-i** and **22o-ii** only in 35% and 18% yields respectively. Whereas the reaction under reflux condition gave the bicyclic acetal **24** in 14% yield along with the mixture of acetonide derivatives **22o-i** and **22o-ii** in 23% and 17% yields repectively (Scheme 9).



Scheme 9. Synthesis of bicyclic acetal *via* acetonide from epoxy alkyne **21o**

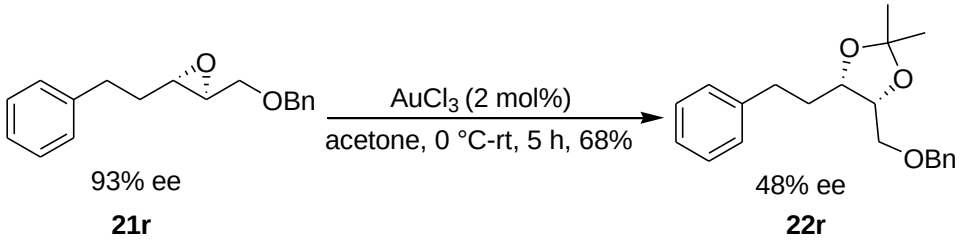
We prepared the epoxyalkyne substrate **21p** from diethyl malonate. When the epoxyalkyne **21p** was treated with 2 mol% $AuCl_3$ in acetone solvent at room temperature, we obtained the bicyclic acetal **25** in 59% yield along with the corresponding γ-lactone product **26** in 32% yield (Scheme 10). When the same substrate **21p** was treated with PPh_3AuCl (2 mol%)/$AgSbF_6$ (2 mol%) in acetone at reflux it resulted 59% yield of bicylic acetal **25**. The bicyclic acetals **24** and **25** were formed from acetonide intermediate. Initially, the gold activates the oxirane ring of epoxyalkyne by coordinating to the oxygen, which is opened by solvent acetone to form acetonide. This acetonide reacts intramolecularly with gold activated alkyne moiety to give bicyclic acetal. The gold(I) catalyzed conversion of epoxyalkyne into bicyclic acetals was carried out by Babu of our research group.[33]

In the case of substrate **21q**, we obtained the corresponding γ-lactone **27** in 56% yield along with the expected acetonide product **22q** in 39% yield. The γ-lactone **26** and **27** might have formed intramolecular ring opening of gold-activated epoxide ring by ester carbonyl group (Scheme 10). Although acetone is present as solvent, intramolecular reaction is preferred over acetonide formation.



Scheme 10. Gold catalyzed epoxide ring opening in **21p** & **21q**

We made optically pure epoxide **21r** (93% ee) using Sharpless asymmetric epoxidation and subjected it to acetonide formation using 2 mol% $AuCl_3$ in acetone to study the regioselectivity of ring opening. The corresponding acetonide **22r** was obtained in 68% yield (Scheme 11). But enantiomeric excess dropped to 48% in the acetonide product **22r** from 93% of the starting epoxide. This could be due to the ring-opening at both carbons of the epoxide.

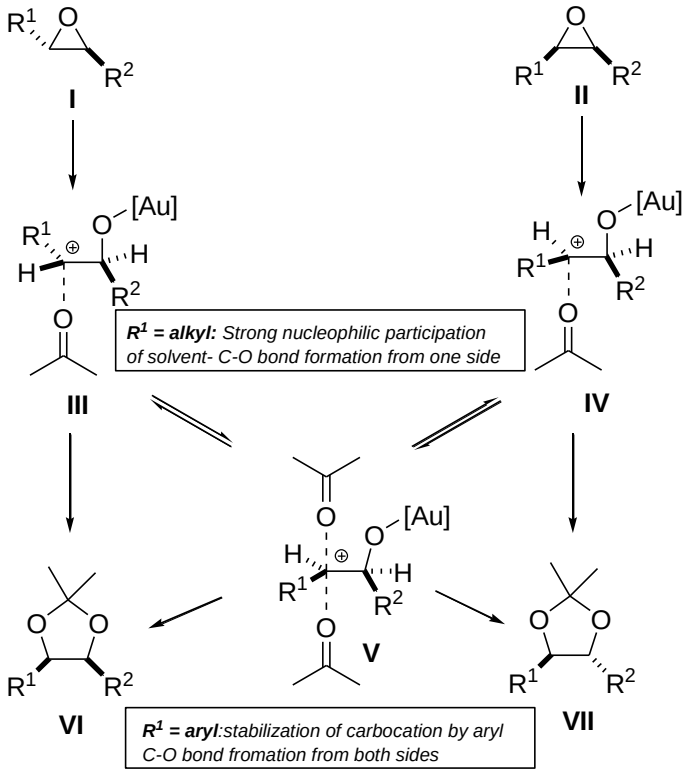


Scheme 11. Acetonide formation from optically pure epoxide **21r**

1.4.1 Mechanism for the gold catalyzed acetonide formation

Initially the gold activated oxirane ring is opened from the back side by the nucleophilic assistance drawn from the solvent acetone. In the case of alkyl substituted epoxides the nucleophilic assistance is strong so that C-O bond between acetone and ring-opened epoxide is formed as the oxirane ring is opened. Hence the aliphatic group substituted *trans* epoxide gives *cis* acetonide **VI** and *cis* epoxide gives *trans* acetonide **VII** via ring-opened species **III** and **IV** respectively **(**Scheme 12**).** On the other hand, aryl substituent can effectively stabilize the carbocation formed upon the ring-opening of epoxide. Hence a

mixture of *cis* and *trans* acetonides are formed as acetone can approach from either side of the carbocation as in **V**.



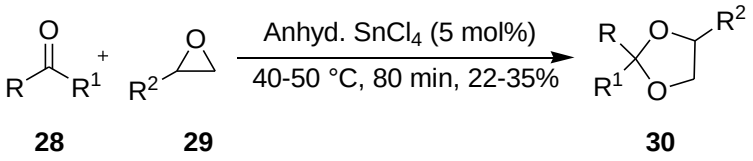
Scheme 12. Proposed mechanism for the gold catalyzed acetonide formation

1.5 Gold-catalyzed cyclic acetals formation

1.5.1 Back ground

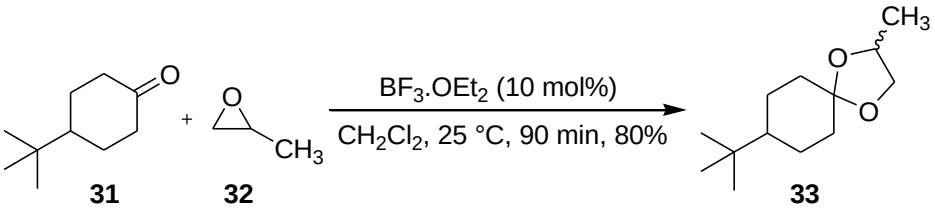
Acetals are important and commonly encountered protecting groups in multistep organic synthesis. In particular the cyclic acetals, being more stable and easily accessible than acyclic counterparts, find regular applications.[34] Apart from their usefulness in protection chemistry,[35] acetals are used in asymmetric synthesis as chiral auxiliaries, constituent of perfumes, polymers and pharmaceuticals.[36] Importantly cyclic acetals are key structural motifs of several biologically active marine natural products.[37] Treatment of a carbonyl compound with diols under Brϕnsted acidic/Lewis acidic condition is a trivial way of obtaining cyclic acetals.[38] However there are only a few reports available in the literature for the formation of cyclic acetals with a variety of functional groups using starting materials other than carbonyls and diols.[39] In 1933, Roblin Jr *et al.* reported the formation of cyclic

acetals **30** from aldehydes or ketones **28** and epoxides **29** by using anhydrous $SnCl_4$ (Scheme 13).[40] In this reaction ethylene oxide reacts with various aldehydes and ketones in the presence of metallic chlorides gave cyclic acetals.



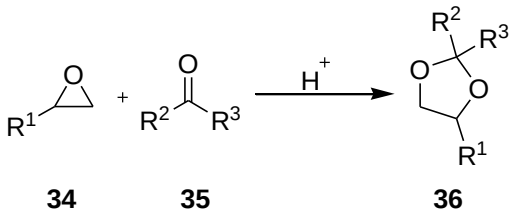
Scheme 13. Anhydrous $SnCl_4$-catalyzed acetonide formation

Scott and co-workers reported a BF_3-mediated reaction of epoxides with cyclic ketones and enones for acetal formation **33**.[41] The approach is applicable to both small and large scale reactions. The resulting acetals were obtained in very good yields (Scheme 14).



Scheme 14. $BF_3.Et_2O$-catalyzed acetal formation

Suo and co-workers reported the synthesis of 1,3-dioxolanes **36** from various epoxides **34** and ketones **35** in presence of acids such as heteropoly acids, Nafion-H, methanesulfonic acid, trifluoroacetic acid and *p*-toluenesulfonic acid (Scheme 15).[42] But the yields were low due to their high ability to catalyze side reactions such as polymerization of oxiranes and diol formation



Scheme 15. Brϕnsted acid catalyzed acetonide formation

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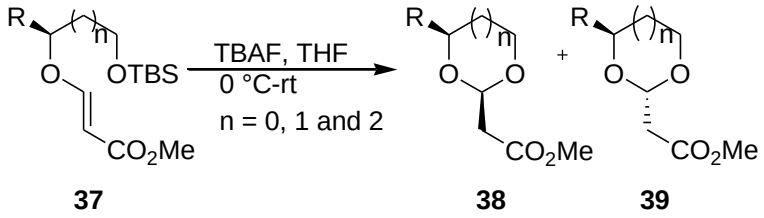
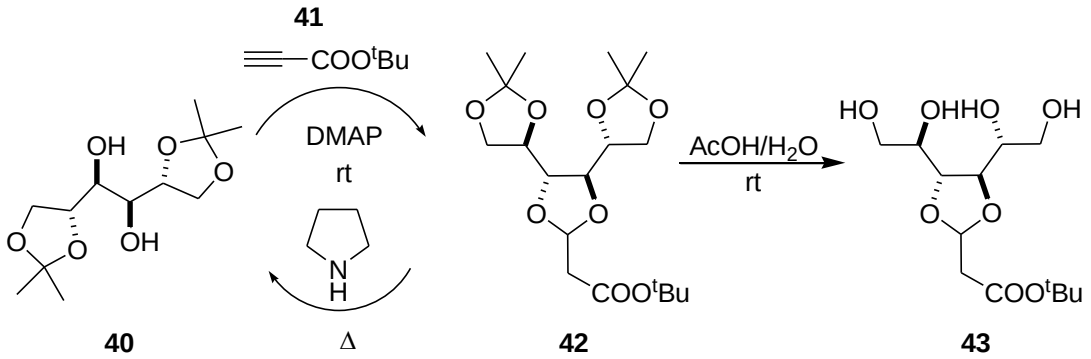
In 1996, Evans and co-workers developed a new method for the synthesis of *cis*-2,4-disubstituted 5-, 6- and 7-membered cyclic acetals with excellent diasteroselectivity. This reaction takes place *via* desilylative intramolecular fluoride-catalyzed hetero-Michael reaction (Scheme 16).[43]



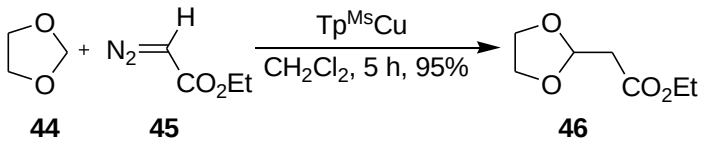
Scheme 16. Intramolecular fluoride-catalyzed hetero-Michael reaction of **37**

In 2000, Vilarrasa and co-workers reported a DMAP assisted formation of cyclic acetals **42** from 1, 2-diols **40** and *t*-butyl propiolate **41**. The interesting aspect of these acetals is that they can be deprotected under basic conditions to give diols (Scheme 17).[44]



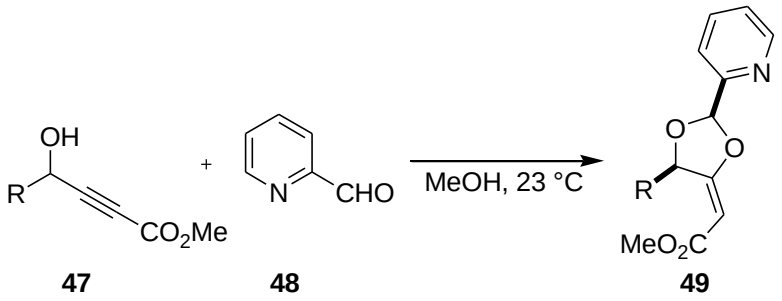
Scheme 17. New base labile protecting groups for 1,2-diols

In 2002, Pérez and co-workers reported the formation of cyclic acetals **46** by intermolecular C-H activation of dioxolane **44** using copper carbene **45** (Scheme 18).[45] The carbene inserts on the C-H bond leading the substitution in the dioxolane ring.



Scheme 18. Cu(I)-complexes catalyzed functionalisation cyclic acetal **44**

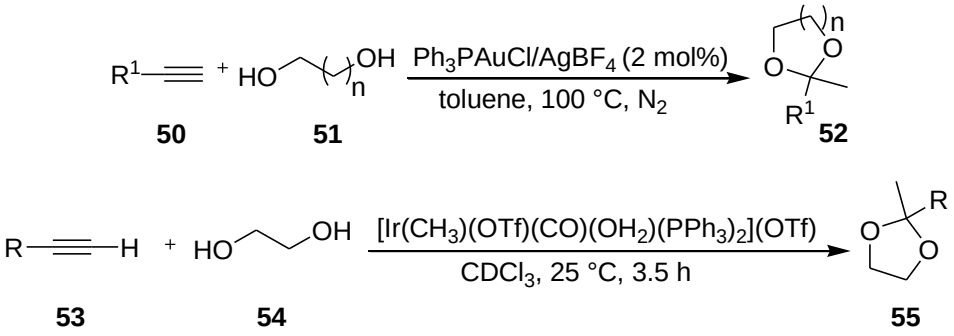
Allylic hydroxyphosphonates have been used to prepare cyclic acetals by intramolecular oxymercuration reaction.[46] Formation of fully functionalized cyclic acetals **49** has been achieved by the reaction of pyridine-2-carboxaldehyde **48** and γ-hydroxy-α-β-acetylenic esters **47** in the absence of any promoters.[47] In fact, this reaction is promoted by the basic nature of the pyridine ring itself (Scheme 19).



47 **48** **49**

Scheme 19. Synthesis of highly functionalized cyclic acetals from pyridine-2-carboxaldehyde

Addition of alcohol to alkynes using transition metal catalysts based on platinum, palladium, mercury and gold has gained attention in recent times. Particularly, gold salts owing to their remarkable alkynophilicity, have found to assist the formation of dimethyl acetals and ketones from alkynes on reaction with methanol and water respectively.[48] Corma and co-workers reported cyclic acetals formation **52** by the reaction of diols **51** and terminal alkynes **50** such as phenylacetylene derivatives and aliphatic alkynes by using gold catalyst.[49] Similarly, Chin and co-workers reported formation of cyclic acetals **55** from diols **54** and terminal alkynes **53** in the presence of cationic iridium complex (Scheme 20).[50]



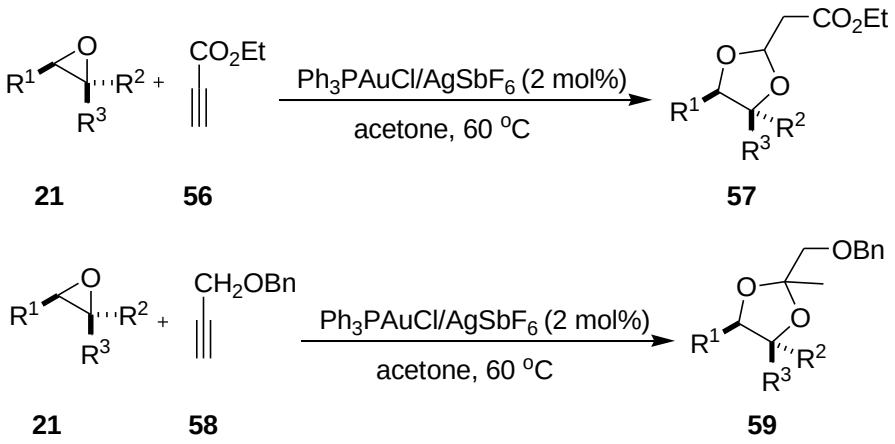
50 **51** **52**

53 **54** **55**

Scheme 20. Addition of diols to terminal alkynes

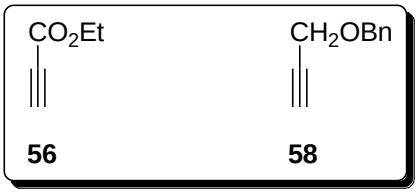
1.5.2 Results and discussion

During our efforts to activate and react epoxides using gold catalysts, we have found the conversion of epoxyalkynes into bicyclic acetals when the reaction was carried out in acetone (*vide supra*).[33] This observation prompted us to study the gold-catalyzed intermolecular reaction of epoxides with alkynes. The reaction resulted in cyclic acetals and the oxo-and alkynophilicities of gold catalyst are crucial in effecting this reaction (Scheme 21). This reaction proceeds *via* the formation of acetonide from epoxide which subsequently cyclizes on the alkyne activated by gold.



Scheme 21. Au(I)-catalyzed synthesis of cyclic acetals

The reaction of epoxides was carried out with terminal alkynes in refluxing acetone using 2 mol% of $Ph_3PAuCl/AgSbF_6$ catalyst system. The study is restricted to terminal alkynes only as the internal counterparts were unreactive. Hence ethyl propiolate **56** and benzyl protected propargyl alcohol **58** were chosen for the study.



A series of epoxides (**21a-21c, 21e, 21l-21m, 21r-21y**) were reacted with **56** and **58** separately and the results are presented in Tables **2** and **3** respectively. The dioxolane products were formed as inseparable mixture of diastereomers. Both the alkynes **56** and **58** showed difference in their reactives. While in ethyl propiolate **56**, the terminal carbon of the alkyne involved in the dioxolane formation, it was the internal carbon of the alkyne that

involved in the cyclic ketal formation in benzyl protected propargyl alcohol **58**. This reactivity difference is understandable from the polarization of the alkyne bonds in these two systems.

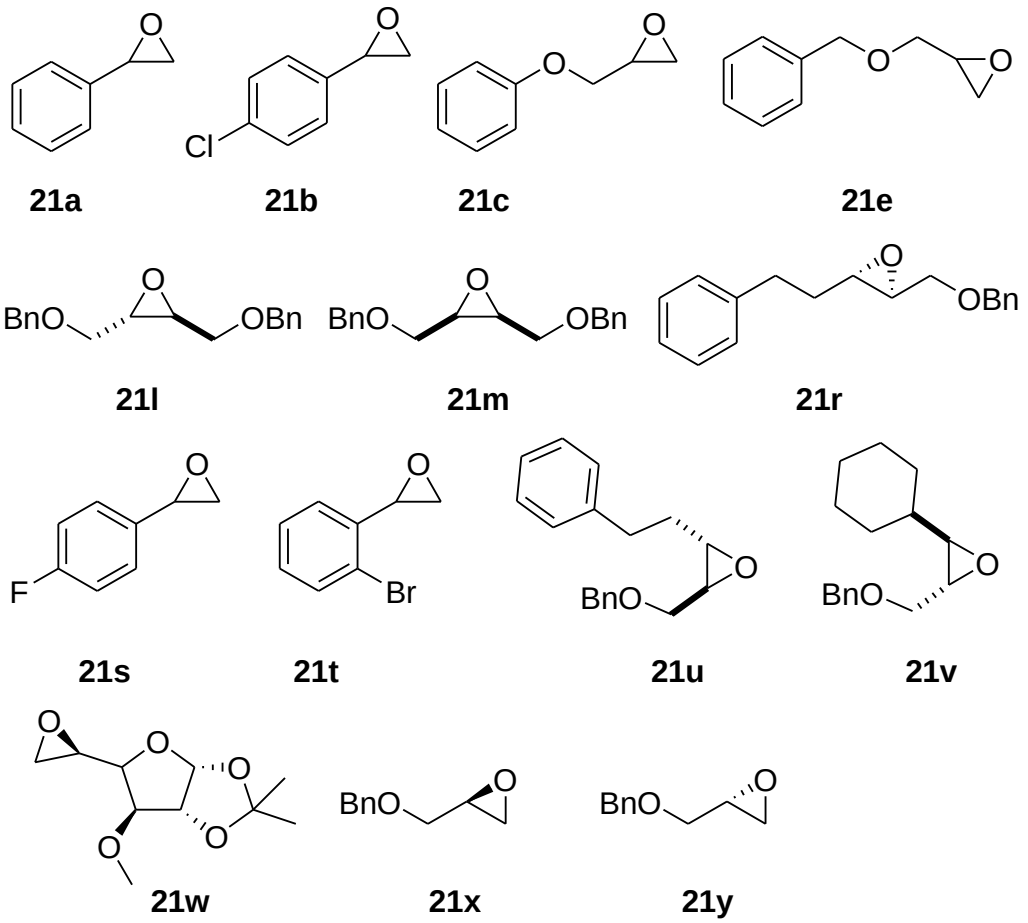
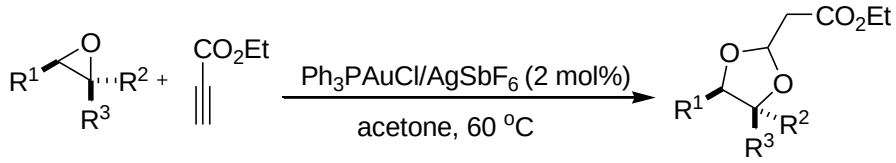


Figure 2. List of epoxides employed in the gold catalyzed cyclic acetal formation

The reactions with ethyl propiolate **56** were comparatively efficient than that with benzyl protected propargyl alcohol **58**. The dioxolanes formed from ethyl propiolate **56** are particularly interesting as they can be deprotected to diols under basic conditions unlike simple acetals which are deprotected under acidic condition. In this reaction, formation of cyclic acetal is expected to happen *via* the formation of acetonide from epoxide as found in the intramolecular bicyclic acetal formation reaction. Some amount of corresponding acetonides was also isolated along with the dioxalone products.

Table 2. Formation of cyclic acetals from epoxides and ethyl propiolate



21 **56** **57**

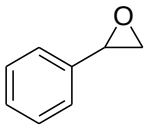
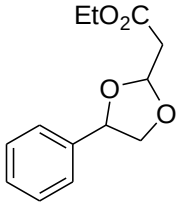
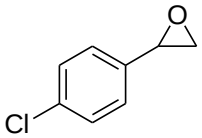
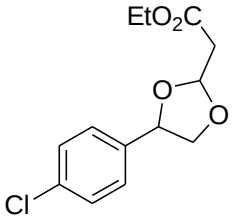
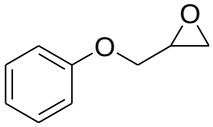
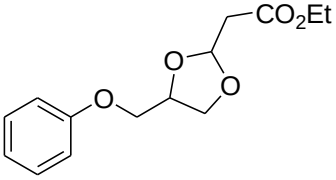
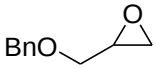
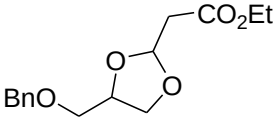
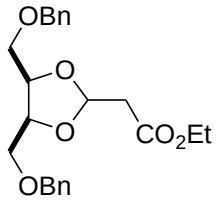
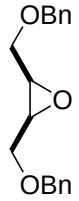
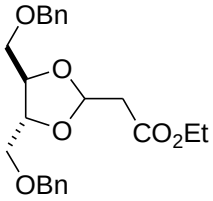
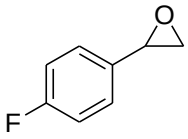
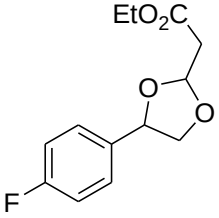
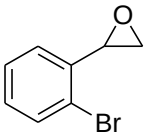
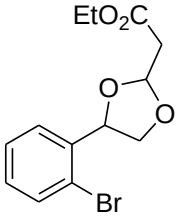
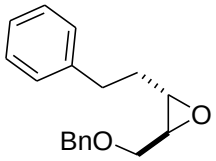
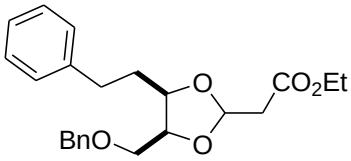
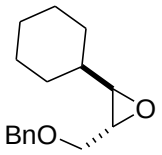
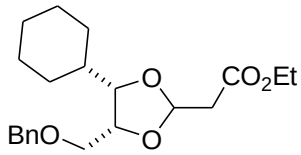
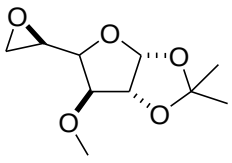
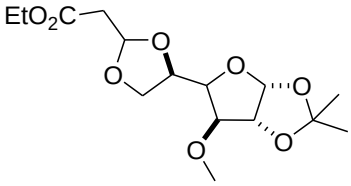
Entry	Epoxide	Time (h)	Product	Yield (%)[a]	dr [b]
1	 **21a**	24	 **57a**	73	1.0:1.2
2	 **21b**	10	 **57b**	82	1.0:1.3
3	 **21c**	24	 **57c**	68	1.0:1.1
4	 **21e**	10	 **57d**	88	1.0:1.2
5	 **21l**	24	 **57e**	82	1.0:3.5

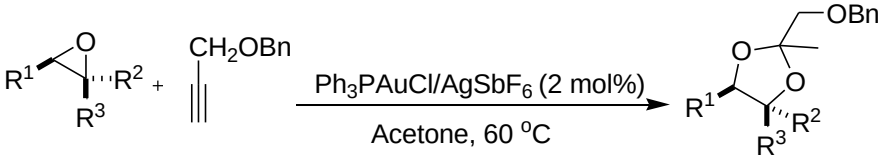
Table 2. Contd…

Entry	Epoxide	Time (h)	Product	Yield (%)[a]	dr [b]
6	 **21m**	24	 **57f**	80	---
7	 **21s**	18	 **57g**	76	1.0:1.4
8	 **21t**	25	 **57h**	75	1.0:1.6
9	 **21u**	24	 **57i**	94	1.0:2.6
10	 **21v**	24	 **57j**	86	1.0:3.3
11	 **21w**	24	 **57k**	43	1.0:1.2

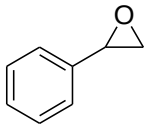
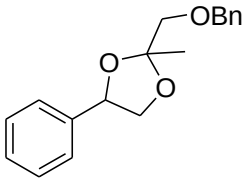
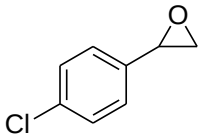
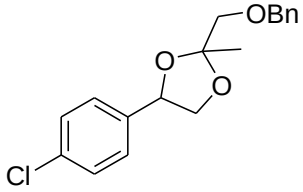
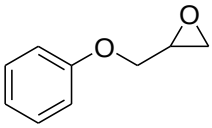
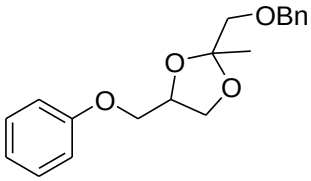
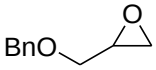
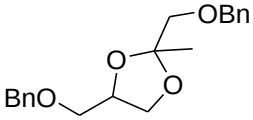
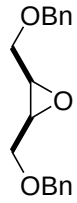
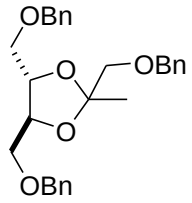
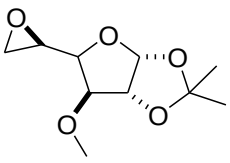
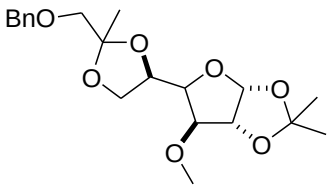
[a] Isolated yield.[b] Diastereomeric ratio was determined from the ^{1}H-NMR spectra of the column purified material.

Intially, the gold activated epoxide is opened by solvent acetone and the oxyanion generated subsequently cyclizes to form the acetonide. The acetonide then attacks the alkyne activated by gold to form the corresponding dioxolane derivative. While the epoxide **21l** gave a mixture (1.0:3.5) of diastereomers, epoxide **21m** resulted in a single diastereomer. The ring-opening by acetone takes place in a S_N2 fashion when the epoxide ring is attached to alkyl groups. This can easily be understood from the results presented in the entries 5 and 6 of Table 2**.** When the diastereomeric mixture of **57i** and **57j** were treated separately with pyrrolidine resulted in corresponding *trans*-diol as exclusive products. Hence the diastereomers are actually due to different orientation of estermethylene substituent. Monosubstituted epoxides gave diastereomeric mixtures of corresponding cyclic acetal derivatives with diastereomeric ratios close to 1:1. The diastereomeric ratios were determined from the ^{1}H-NMR spectra of the column purified mixture. The susbstrate **21w** was prepared according to literature procedure.[51] It was reacted with alkyne substrates **56** and **58** separately in the presence of 2 mol% of $Ph_3PAuCl/AgSbF_6$ in acetone at 60 $^{\circ}$C. The reactions resulted in the corresponding cyclic acetals derivatives **57k** (Table 2, entry 11) and **59f** (Table 3, entry 6). The stereochemistry of the internal carbon of the dioxolane was assigned based on the stereochemistry of acetonide isolated along with it.[52] From the stereochemistry of acetonide, it is learnt that the stereochemistry of the internal carbon of the epoxide was unaltered. Hence the epoxide ring is opened up by acetone at the less substituted epoxide carbon which resulted in retention of stereochemistry.

Table 3. Results of cyclic acetals formation from epoxides and benzyl protected propargyl alcohol 58

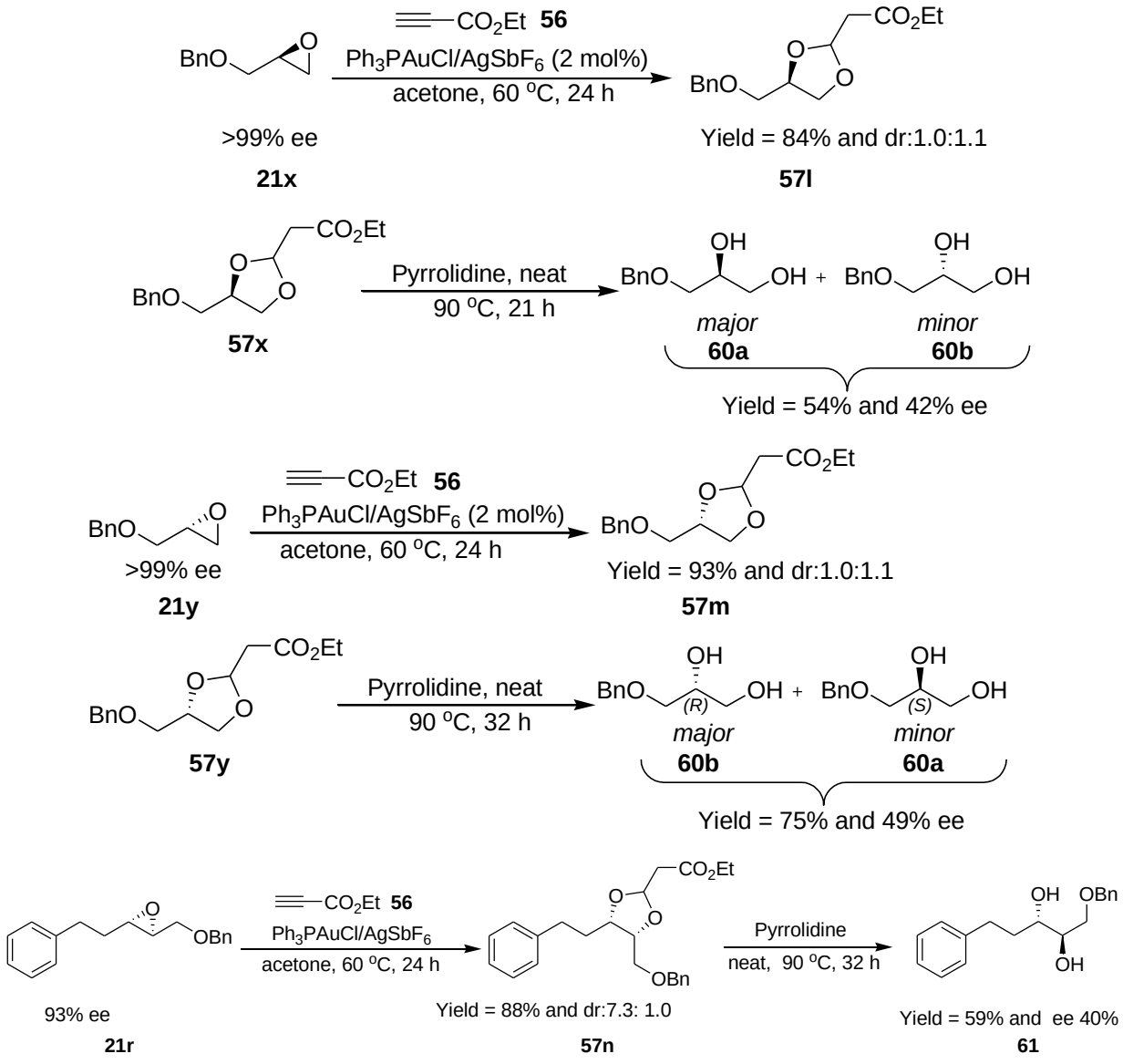


21 **58** **59**

Entry	Epoxide	Time (h)	Product	Yield(%)[a]	dr[b]
1	 **21a**	4	 **59a**	33	1.0:1.0
2	 **21b**	23	 **59b**	61	1.0:1.8
3	 **21c**	15	 **59c**	76	1.0:1.0
4	 **21e**	27	 **59d**	88	1.0:1.2
5	 **21m**	26	 **59e**	82	1.0:1.3
6	 **21w**	24	 **59f**	49	1.0:1.1

[a] Isolated yield.[b] Diastereomeric ratio was determined from ^{1}H-NMR of the column purified material.

Since the terminal epoxide in **21w** is opened up at the less hindered carbon site, we made optically pure epoxides **21x**, **21y**, **21r**. Commecially available (*S*)- and (*R*)-glycidols were benzylated to make **21x** and **21y** respectively. Sharpless asymmetric epoxidation was used to make **21r** from its corresponding alkene. Optically pure epoxides **21x**, **21y** and **21r** generated the corresponding cyclic acetals **57l**, **57m** and **57n** in excellent yields under standard conditions.



Scheme 22. Synthesis of optically active cyclic acetals and deprotection with base

These acetals **57l**, **57m** and **57n** were deprotected with pyrrolidine to check the enantiomeric excess of the products. The ee dropped in all cases to around 40-50%. This

might be due to attack of acetone at both carbons of the epoxide ring (Scheme 22). Still, attack at the less hindred carbon is preferred.

The relative stereochemistries of major and minor diastereomers of **57b** were assigned based on the NOESY spectra of compound **57b**. The aryl and the estermethylene substituents are *cis* and *trans* to each other in major and minor isomers respectively (Figure 3).

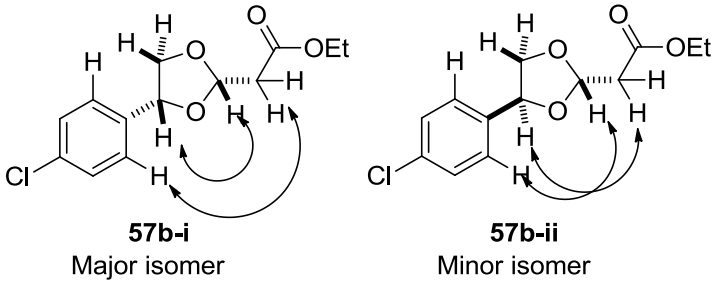
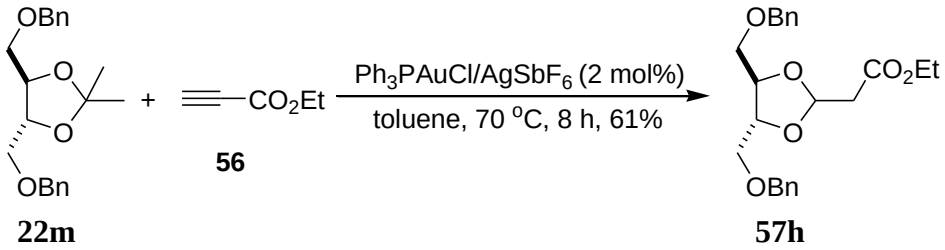


Figure 3. Assignment of relative stereochemistries of major and minor isomers of **57b** based on NOESY correlations

For mechanistic study, we performed the reaction with acetonide derivative **22m** with ethyl propiolate **56** in the presence of 2 mol% $Ph_3PAuCl/AgSbF_6$ and toluene at 70 °C. The reaction gave the corresponding cyclic acetal derivative **57h** in 61% yield (Scheme 23). This indicates that acetonide is formed first which underwent intermolecular cyclization to generate cyclic acetal.



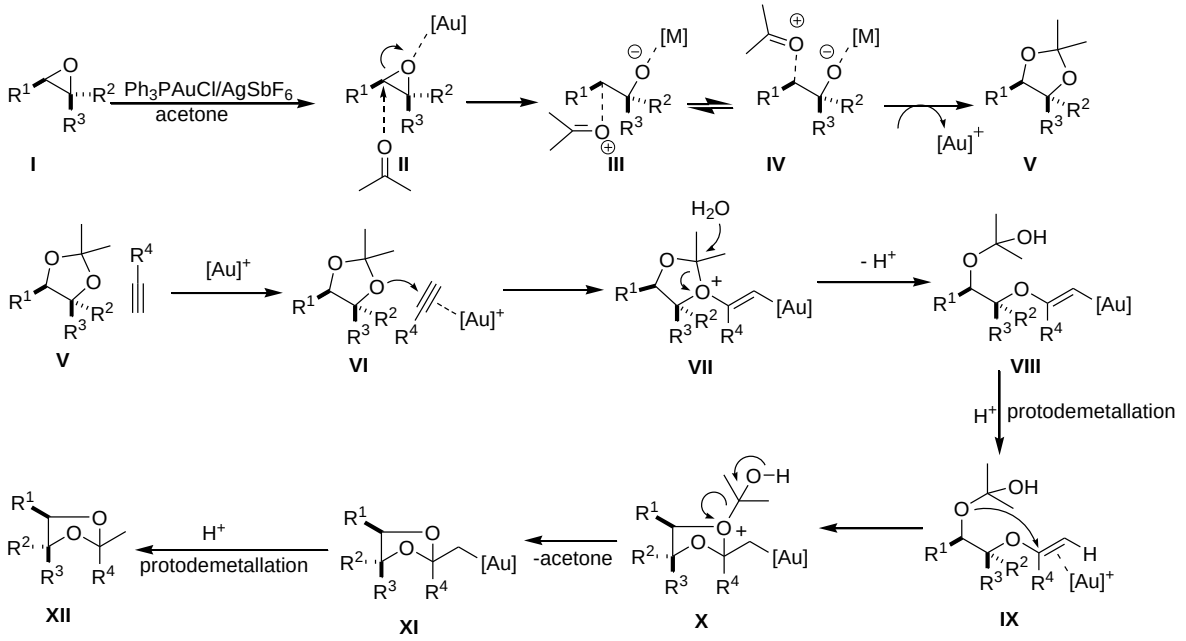
Scheme 23. Formation of cyclic acetal from acetonide substrate **22m** and ethyl propiolate **56**

1.5.3 Mechanism for cyclic acetal formation

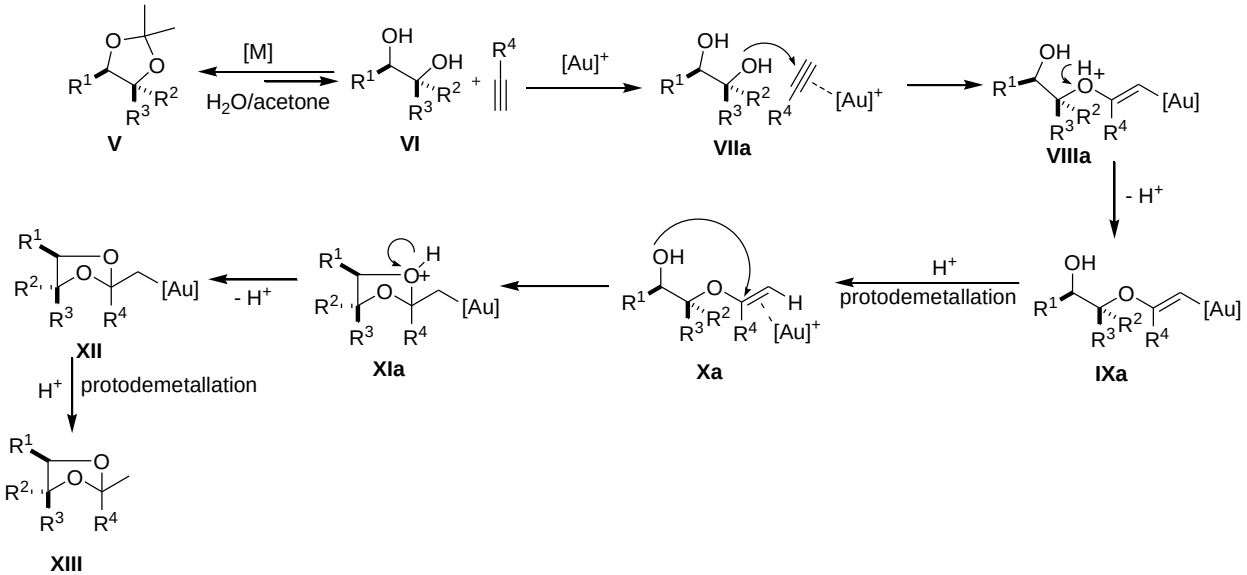
From the studies carried out during our investigation in the bicyclic acetal formation, it was found out that the epoxide is initially converted into its corresponding acetonide derivative by the attack of solvent acetone on the gold-activated epoxide ring.[33] Then the acetonide oxygen can attack the gold-activated alkyne bond. Else the acetonide could be in quilibrium with the corresponding diol which is formed by the attack of water generated by

the aldol self condensation of solvent acetone under the strong Lewis acidic condition. It was found out that the latter pathway is preferred. Hence it is believed that the intermolecular cyclic acetal formation is expected to follow a similar mechanism (Scheme 24).

Pathway – I from acetonide



Pathway- II from diol



Scheme 24. Plausible mechanism for the formation of cyclic acetal

1.6 Conclusions

In conclusion, we have found out that epoxides can be converted into acetonides, which can serve as diol equivalent for further transformation under gold catalysis in acetone. This has been successfully applied to synthesize bicyclic/cyclic acetals. It has been found that the water formed under the reaction condition plays a crucial role in the cyclization of the acetonide on the triple bond. The regioselectivity of epoxide opening is moderate and the less substituted carbon is preferred in general.

1.7 Experimental section

1.7.1 General Information

Chemicals and solvents were obtained from various commercial sources. All starting materials were prepared by following known literature procedures. Ph_3PAuCl, $AgSbF_6$, *n*-BuLi (1.6 M in Hexanes), NaH (60% dispersed in mineral oil) and *m*-CPBA (75%) were purchased from Aldrich Chemical Co. Acetone was dried over $KMnO_4$, and stored over 4 Å type molecular sieves. THF was dried over sodium benzophenone and freshly distilled from a still before use. ^1H and ^{13}C spectra were recorded on a Bruker Avance 500 MHz, 400 MHz and 200 MHz machines using solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on JASCO FT/IR-5300 spectrometer. Elemental (C, H, N) analysis were done using Thermo Finnigan Flash EA 1112 analyser. For TLC, silica gel plates 60 F254 were used and compounds were visualized by UV light and/or by treatment with Seebach solution (phosphomolibdic acid (2.5 g), $Ce(SO_4)_2$ (1 g), Conc. H_2SO_4 (6 mL), H_2O (94 mL)) followed by heating. HPLC analyses of the compounds were done using chiralcel OD-H column, hexanes and isopropanol as eluent. Column chromatography was performed on silica gel 100-200 mesh, using ethyl acetate and hexanes mixture as eluent.

1.7.2 Experimental procedures, spectral and analytical data

I. General procedure for epoxidation with *m*-CPBA (GP-I)

To a solution of alkene/allylic alcohol (1.0 equiv) in CH_2Cl_2 (4 mL/mmol), *m*-CPBA (1.5 equiv) was added slowly and the reaction was allowed to stir at room temperature. After completion of the reaction, saturated Na_2SO_3 solution was added and stirred for 30 min. Then the reaction mixture was taken in a separating funnel and washed two times each with saturated aqueous $NaHCO_3$ solution and brine solution, dried over anhydrous Na_2SO_4 and

concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes) to get the pure product.

II. General procedure for *O*-benzylation (GP-II)

To the epoxy alcohol/alcohol (1.0 equiv) dissolved in dry THF (5 mL/mmol), NaH (60% dispersed in mineral oil, 1.5 equiv) was added slowly at 0 ^{o}C under N_2 atmosphere and stirred for 45 min. At the same temperature benzyl bromide (1.2 equiv) was added slowly and the stirring was continued at room temperature. After completion of the reaction, saturated aqueous NH_4Cl solution was added to quench the reaction. Solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, brine solutions. The resulting organic solution was dried over anhydrous Na_2SO_4 and concentrated. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product.

III. General procedure for DIBAL-H reduction (GP-III)

To a solution of the ester compound (1.0 equiv) in dry CH_2Cl_2 was added DIBAL-H (2.2 equiv) dropwise at –78 °C. After stirring for 45 min at –78 °C, H_2O (20.0 equiv) and NaF (20.0 equiv) were added to the solution. The resulting mixture was stirred at rt for 30 min and filtered through a pad of Celite 545. The filtrate was concentrated to get a residue, which was loaded on silica gel column. It was eluted with ethyl acetate/hexanes mixture to get pure product.

IV. General procedure for asymmetric epoxidation (GP-IV)

To a suspension of Ti(O-*i*-Pr)$_4$ (1.0 equiv) and MS 4 Å (powder, 1.0 mg/1.0 mg w/w) in CH_2Cl_2 was added L-(+)-DIPT (1.2 equiv) at –20 °C. The mixture was stirred at –20 °C for 20 min and cooled to –40 °C. A solution of the alcohol (2.0 equiv) dissolved in CH_2Cl_2 and *t*-BuOOH (3.0 equiv, 5.0-6.0 M in decane) were added to the solution successively. After 4 h at –20 °C, the reaction was quenched by addition of H_2O (20.0 equiv) and NaF (20.3 equiv). The mixture was stirred at rt for 30 min and filtered through a pad of Celite. To the filtrate was added 1 M NaOH, and the mixture was stirred at rt for 30 min. The resulting mixture was extracted with CH_2Cl_2. The resulting organic solution was dried over anhydrous sodium

sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product.

V. General procedure for the $AuCl_3$-catalyzed acetonide formation (GP-V)

To a solution of epoxide (0.5 mmol) in acetone (5 mL), $AuCl_3$ (0.01 mmol) was added. The reaction mixture was stirred at room temperature. After stirring for the specified time, solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure acetonide.

VI. General Procedure for the Au(I)/$AgSbF_6$-catalyzed cyclic acetals formation (GP-VI)

To a stirred solution of epoxide (1.0 equiv) and alkyne substrate (1.5-2.0 equiv) in distilled acetone, $[(C_6H_5)_3P]AuCl$ (0.02 equiv) and $AgSbF_6$ (0.02 equiv) were added consecutively. The reaction mixture was stirred and heated to 60 °C. After stirring for the specified time, solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure cyclic acetal.

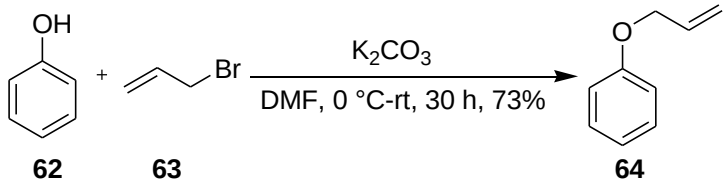
VII. General procedure for cyclic acetals deprotection (GP-VII)

A solution of cyclic acetal (50 mg) in pyrrolidine (2.0 mL) was heated to 90 °C. After completion of the reaction, pyrrolidine was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product.

Typical procedure for cyclic acetals formation from acetonide and ethylpropiolate 56

To a stirred solution of acetonide substarte **22m** (1.0 equiv) and ethylpropiolate **56** (1.5-2.0 equiv) in toluene, $[(C_6H_5)_3P]AuCl$ (0.02 equiv) and $AgSbF_6$ (0.02 equiv) were added consecutively. The reaction mixture was stirred and heated to 60 °C. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure cyclic acetal.

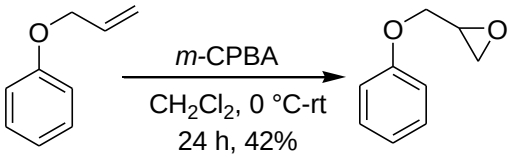
Allyloxybenzene (64):[53]



62 **63** **64**

To a stirred solution of phenol (2.0 g, 21.25 mmol) in dry DMF (20 mL), K_2CO_3 (5.87 g, 42.50 mmol) was added slowly at rt under N_2 atmosphere and stirred at the same temperature for 30 min. Then allyl bromide (2.2 mL, 22.50 mmol) was added slowly and it was allowed to stir at room temperature. After completion of the reaction, it was extracted with EtOAc and washed with brine solution. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **64**. Yield = 2.08 g (73%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.27 (m, 2H), 6.97-6.92 (m, 3H), 6.12-6.02 (m, 1H), 5.45-5.39 (m, 1H), 5.31-5.27 (m, 1H), 4.55-4.54 (m, 2H).

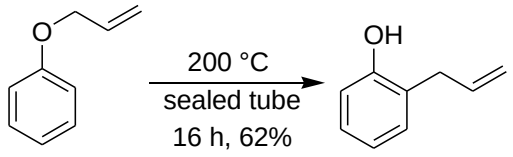
2-(Phenoxymethyl)oxirane (21c):[54]



64 **21c**

Prepared from **64** using GP-I; Yield = 42%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.27 (m, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 4.22 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.98 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.39-3.35 (m, 1H), 2.91 (t, *J* = 4.8 Hz, 1H), 2.77 (dd, *J* = 4.8, 2.8 Hz, 1H).

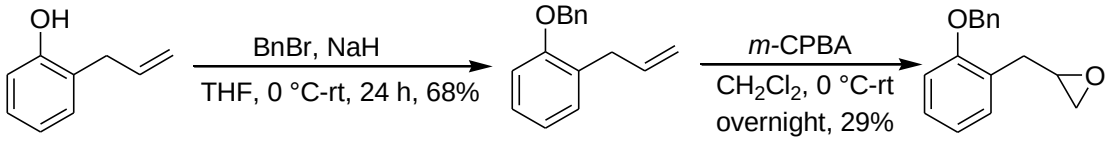
2-Allylphenol (65):[55]



64 **65**

Neat allyloxybenzene **64** (1.13 g, 8.40 mmol) was placed in a sealed tube and heated at 200 °C using oil bath. After 16 h, the reaction mixture was allowed to cool and the crude reaction mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **65**. Yield = 692 mg (62%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15-7.11 (m, 2H), 6.91-6.81 (m, 2H), 6.08-5.98 (m, 1H), 5.18-5.17 (m, 1H), 5.15-5.14 (m, 1H), 4.95 (br s, 1H), 3.42 (d, *J* = 6.4 Hz, 2H).

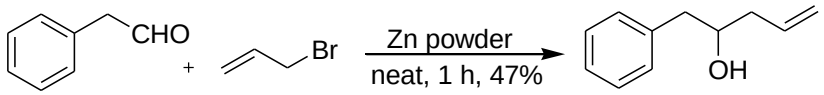
2-(2-(Benzyloxy)benzyl)oxirane (21n):[56]



65 **66** **21n**

Prepared from **65** using GP-II&I; Yield = 62%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.34 (m, 5H), 7.25-7.21 (m, 2H), 6.96-6.92 (m, 2H), 5.10 (s, 2H), 3.25-3.20 (m, 1H), 3.03 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.85 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.75 (t, *J* = 4.4 Hz, 1H), 2.54 (dd, *J* = 4.8, 2.8 Hz, 1H).

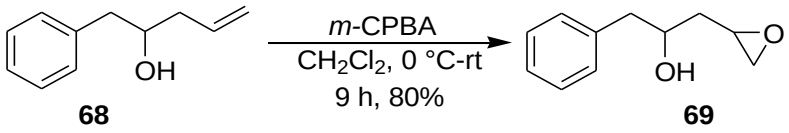
1-Phenylpent-4-en-2-ol (68):[57]



67 **63** **68**

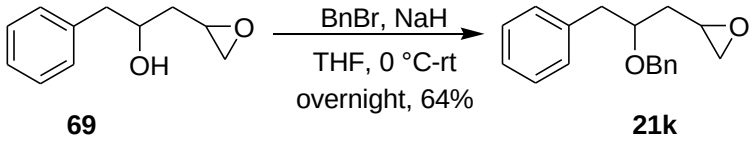
Neat phenylacetaldehyde (1.0 g, 8.32 mmol), allyl bromide (1.21 g, 9.99 mmol) and zinc powder (652 mg, 9.99 mmol) were placed in a RB flask and stirred at rt for 1 h. Then the residue was taken in EtOAc and washed with saturated NH_4Cl solution and brine solution. The organic solution was dried over anhydrous $NaSO_4$ and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **68.** Yield = 47%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 5.93-5.82 (m, 1H), 5.19-5.15 (m, 2H), 3.93-3.86 (m, 1H), 2.86-2.71 (m, 2H), 2.38-2.20 (m, 2H), 1.71 (br s, 1H).

1-(Oxiran-2-yl)-3-phenylpropan-2-ol (69):[58]



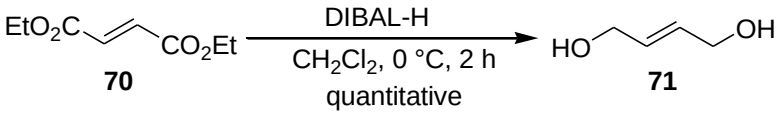
Prepared from **68** using GP-I; Yield = 80%; dr = 1.0:1.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.22 (m, 10H), 4.09-4.07 (m, 2H), 3.18-3.107 (m, 1H), 3.12-3.10 (m, 1H), 2.88-2.72 (m, 6H), 2.61-2.60 (m, 1H), 2.52-2.51 (m, 1H), 2.13-2.05 (m, 2H), 1.93-1.88 (m, 2H), 1.64 (br s, 2H).

2-(2-(Benzyloxy)-3-phenylpropyl)oxirane (21k):



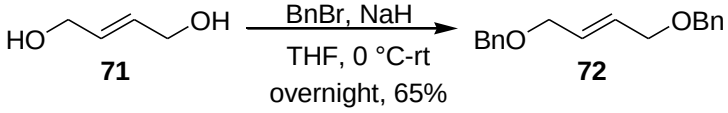
Prepared from **69** using GP-II; Yield = 64%; dr = 1.0:1.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.19 (m, 20H), 4.51 (s, 2H), 4.49 (s, 2H), 3.89-3.85 (m, 1H), 3.81-3.75 (m, 1H), 3.10-3.04 (m, 2H), 3.03-2.98 (m, 1H), 2.98-2.93 (m, 1H), 2.89-2.84 (m, 1H), 2.84-2.80 (m, 1H), 2.77 (t, *J* = 4.4 Hz, 1H), 2.70 (t, *J* = 4.4 Hz, 1H), 2.46 (dd, *J* = 5.2, 2.4 Hz, 1H), 2.40 (dd, *J* = 5.2, 2.4 Hz, 1H), 1.83-1.71 (m, 3H), 1.59-1.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 138.3, 138.3, 129.5, 128.3, 127.8, 127.7, 127.6, 127.5, 126.3, 126.2, 78.2, 78.1, 72.0, 71.2, 49.7, 49.5, 47.6, 46.6, 41.1, 40.7, 37.7, 36.6.

(*E*)-But-2-ene-1,4-diol (71):[59]



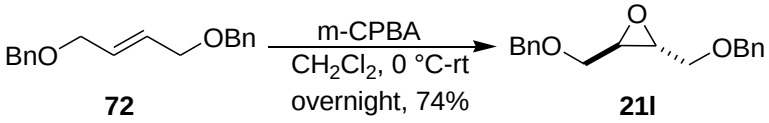
Prepared from fumarate using GP-III; Yield = quantitative; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (m, 2H), 4.17 (m, 4H), 1.85 (br s, 2H).

(*E*)-1,4-Bis(benzyloxy)but-2-ene (72):[60]



Prepared from **71** using GP-II; Yield = 65%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.27 (m, 10H), 5.89-5.88 (m, 2H), 4.53 (s, 4H), 4.06-4.05 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 129.6, 128.4, 127.8, 127.7, 72.3, 70.2.

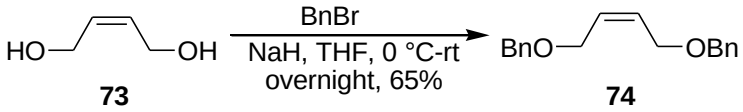
2,3-Bis(benzyloxymethyl)oxirane (21l):[60]



72 **21l**

Prepared from **72** using GP-I; Yield = 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 4.61 (d, *J* = 12.0 Hz, 2H), 4.56 (d, *J* = 11.6 Hz, 2H), 3.76 (dd, *J* = 11.6, 2.4 Hz, 2H), 3.51 (dd, *J* = 11.6, 5.2 Hz, 2H), 3.14-3.12 (m, 2H).

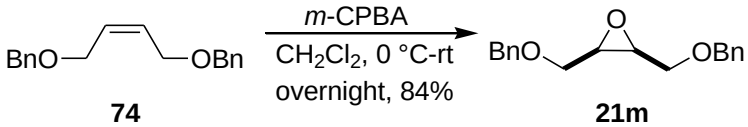
(*Z*)-1,4-Bis(benzyloxy)but-2-ene (74):[61]



73 **74**

Prepared from *cis*-2-butene-1,4-diol **73** using GP-II; Yield = 49%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.29 (m, 10H), 5.84-5.76 (m, 2H), 4.50 (s, 4H), 4.08-4.07 (m, 4H).

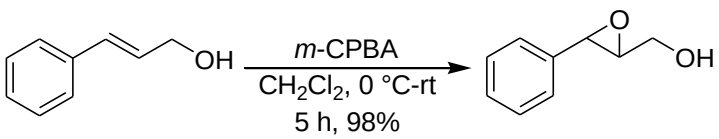
2,3-Bis(benzyloxymethyl)oxirane (21m):[61]



74 **21m**

Prepared from **74** using GP-I; Yield = 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.30 (m, 10H), 4.62 (d, *J* = 12.0 Hz, 2H), 4.52 (d, *J* = 11.6 Hz, 2H), 3.70-3.67 (m, 2H), 3.56-3.52 (m, 2H), 3.27-3.25 (m, 2H).

(3-Phenyloxiran-2-yl)methanol (76):[62]

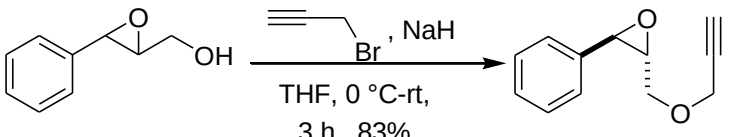


75 **76**

Prepared from cinnamyl alcohol using GP-I; Yield = 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.04 (dd, *J* = 12.8, 2.4 Hz, 1H), 3.93 (s, 1H), 3.82-3.76 (m, 1H), 3.23 (br

d, *J* = 1.6 Hz, 1H), 2.16 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 128.5, 128.3, 125.7, 62.5, 61.2, 55.6.

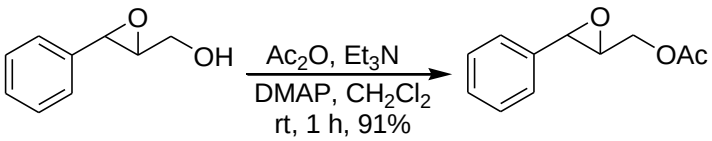
2-Phenyl-3-((prop-2-ynyloxy)methyl)oxirane (21o):



76 **21o**

To the epoxy alcohol **76** (1.5 g, 9.98 mmol) dissolved in dry THF (40 mL), NaH (60% dispersed in mineral oil, 0.6 g, 14.97 mmol) was added slowly at 0 ^{o}C under N_2 atmosphere and stirred for 30 min. At the same temperature propargyl bromide (80% in toluene, 1.3 mL, and 10.98 mmol) was added slowly and it was brought to room temperature. After completion of the reaction, saturated aqueous NH_4Cl solution was added to quench the reaction. Solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, brine solution, dried over anhydrous Na_2SO_4, concentrated and was purified by column chromatography using silica gel (eluent: EtOAc/hexanes) to get the pure **21o**; Colorless liquid; Yield = 83%; R_f = 0.52 in 1:10 EtOAc/hexanes (double elution); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 4.27 (s, 2H), 3.93 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.83 (s, 1H), 3.71 (dd, *J* =11.2, 5.2 Hz, 1H), 3.25- 3.24 (m, 1H), 2.48 (br d, *J* = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 128.1, 127.9, 125.4, 79.1, 74.9, 69.0, 60.3, 58.1, 55.4; IR (neat): υ 3287, 2920, 2118, 1721, 1454, 1099 cm^{-1}; Anal calc'd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; found: C, 76.65; H, 6.48.

(3-Phenyloxiran-2-yl) methyl acetate (21g):[63]

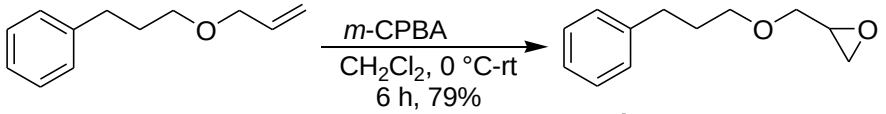


76 **21g**

To a stirred solution of epoxy cinnamyl alcohol **76** (0.5 g, 3.33 mmol) in CH_2Cl_2 (15 mL) were added DMAP (0.041 g, 0.33 mmol) and Et_3N (1.86 mL, 13.32 mmol). The reaction was cooled to 0 °C and Ac_2O (1.60 mL, 16.64 mmol) was added slowly. The resultant reaction mixture was stirred at rt. After 1 h, it was quenched with sat. NH_4Cl solution then extracted

with CH_2Cl_2 and washed with brine solution. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **21g**. Yield = 0.55 mg (86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 4.48 (dd, *J* = 12.4, 3.2 Hz, 1H), 4.10 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.81 (s, 1H), 3.27-3.25 (m, 1H), 2.12 (s, 3H).

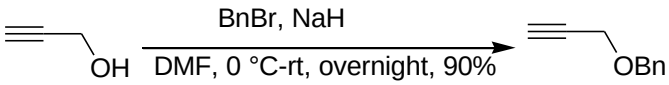
2-((3-Phenylpropoxy)methyl)oxirane (21d):



77 **21d**

Prepared from **77** using GP-I; Yield = 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.19-7.17 (m, 3H), 3.70 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.54-3.44 (m, 2H), 3.36 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.16-3.12 (m, 1H), 2.78 (dd, *J* = 4.8, 4.4 Hz, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.59 (dd, *J* = 5.2, 2.8 Hz, 1H), 1.94-1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 128.4, 128.2, 125.7, 71.4, 70.5, 50.8, 44.2, 32.1, 31.2; IR (neat): υ 2930, 2864, 1602, 1497, 1454, 1111, 912, 700 cm^{-1}; Anal.Calcd for $C_{12}H_{16}O_2$: C 74.97; H 8.39; Found: C 75.11; H 8.32.

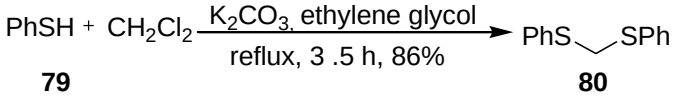
((Prop-2-ynyloxy)methyl)benzene (58):[64]



78 **58**

Prepared from propargyl alcohol and benzyl bromide using GP-II; Colourless oily liquid; Yield = 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.63 (s, 2H), 4.19-4.18 (m, 2H), 2.48-2.47 (m, 1H).

Bis(phenylthio)methane (80):[65]

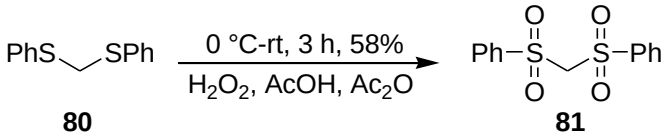


79 **80**

A mixture of anhydrous potassium carbonate (15 g), ethylene glycol (50 mL), CH_2Cl_2 (12.5 mL), and thiophenol (11.0 mL) was stirred and heated to reflux for 3.5 h. Then the reaction mixture was poured into a beaker containing 250 mL of water, and extracted with benzene

(75 mL). The resulting benzene solution was dried over $MgSO_4$ and concentrated in vacuo to obtain crude product, which on distillation under reduced pressure afforded pure **80**. Yield = 10.72 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (m, 4H), 7.34-7.31 (m, 4H), 7.28-7.24 (m, 2H), 4.36 (s, 2H).

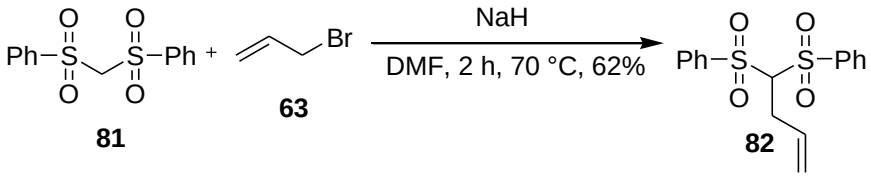
Bis(phenylsulfonyl)methane (81):[66]



80 **81**

Yield = 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 4H), 7.73 (t, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 8.0 Hz, 4H), 4.74 (s, 2H).

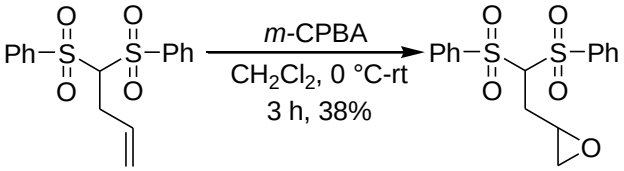
Allylbis(phenylsulfonyl)methane (82):[67]



81 **63** **82**

To the bis(phenylsulfonyl)methane (1.5 g, 5.06 mmol) dissolved in dry DMF (20 mL), NaH (60% dispersed in mineral oil, 0.222 g, 5.57 mmol) was added slowly at room temperature under N_2 atmosphere and stirred at room temperature for 30 min. At the same temperature allyl bromide (0.47 mL, 5.57 mmol) was added slowly and the reaction temperature was raised to 70 ^{o}C. After completion of the reaction, saturated aqueous NH_4Cl solution was added to quench the reaction. Solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine solution. The resulting organic solution was dried over anhydrous Na_2SO_4 and concentrated. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **82**. Yield = 1.05 g (62%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.2 Hz, 4H), 7.71 (t, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 4H), 5.87-5.76 (m, 1H), 5.09-5.02 (m, 2H), 4.47 (t, *J* = 5.6 Hz, 1H), 2.96-2.89 (m, 2H).

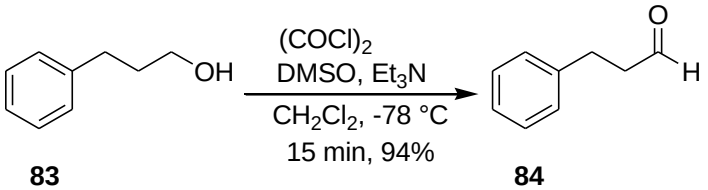
2-(2,2-Bis(phenylsulfonyl)ethyl)oxirane (21j):



82 **21j**

Prepared from **82** using GP-I.; Yield = 38%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.88 (m, 4H), 7.68-7.65 (m, 2H), 7.56-7.51 (m, 4H), 4.70 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.26 (m, 1H), 2.78 (t, *J* = 4.4 Hz, 1H), 2.50-2.44 (m, 2H), 2.36-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 137.1, 134.6, 129.5, 129.3, 129.1, 80.5, 60.2, 49.2, 48.3, 28.9.

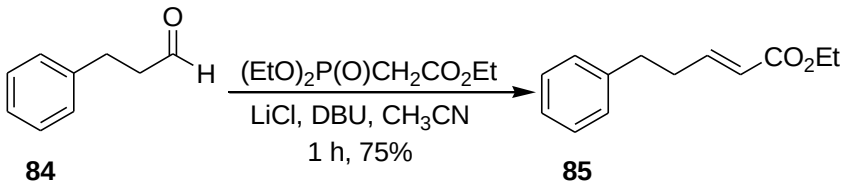
Preparation of 3-phenylpropanal (84):[68]



83 **84**

To a solution of oxalyl chloride (1.4 mL, 16.2 mmol) in CH_2Cl_2 was added dropwise DMSO (2.3 mL, 32.3 mmol) at –78 ^{o}C. After 20 min, a solution of 3-phenyl-1-propanol **83** (2.0 g, 14.7 mmol) in CH_2Cl_2 was added and it was allowed to stir for 30 min. After then triethylamine (10.0 mL, 73.4 mmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature. After completion of the reaction, it was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **84**. Yield = 1.85 g (94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.33-7.20 (m, 5H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H).

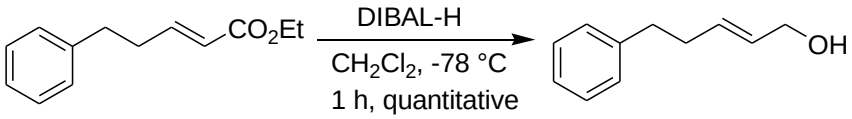
Preparation of (E)-ethyl 5-phenylpent-2-enoate (85):[69]



84 **85**

To a suspension of LiCl (0.442 g, 10.4 mmol) in MeCN were added DBU (1.45 mL, 9.7 mmol) and triethyl phosphonoacetate (1.8 mL, 8.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and a solution of aldehyde **84** (1.0 g, 7.4 mmol) in MeCN was added. The reaction was carried out first at 0 °C for 30 min and then at rt for 30 min, and was quenched by addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **85**. Yield = 1.14 g (75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 7.22-7.18 (m, 3H), 7.01 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.86 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 5.07 (q, *J* = 6.8 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

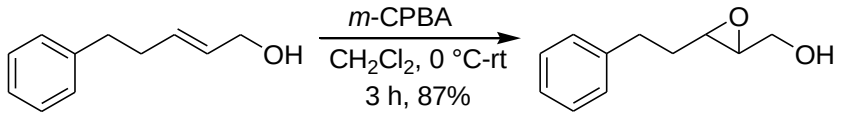
Preparation of (*E*)-5-phenylpent-2-en-1-ol (86):[69]



85 **86**

Prepared from **85** using GP-III; Yield = quantitative; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.21-7.18 (m, 3H), 5.79-5.64 (m, 2H), 4.09 (d, *J* = 5.2 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.39 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 132.1, 129.5, 128.4, 128.3, 125.8, 63.6, 35.5, 33.9.

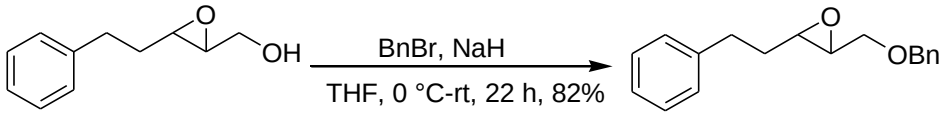
(3-Phenethyloxiran-2-yl)methanol (87):[69b]



86 **87**

Prepared from **86** using GP-I; Yield = 87%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 7.23-7.20 (m, 3H), 3.86-3.83 (m, 1H), 3.59-3.54 (m, 1H), 3.01-2.98 (m, 1H), 2.86-2.81 (m, 2H), 2.78-2.70 (m, 1H), 1.94-1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 128.4, 128.3, 126.1, 61.6, 58.6, 55.3, 33.3, 32.1.

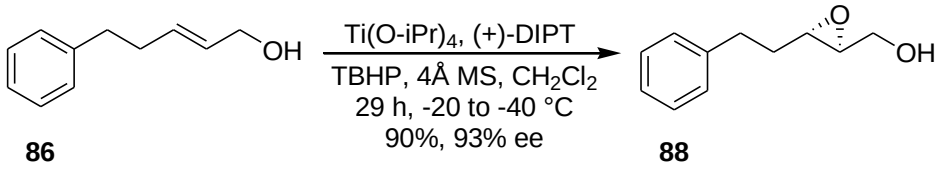
2-(Benzyloxymethyl)-3-phenethyloxirane (21u):[70]



87 **21u**

Prepared from **87** using GP-II; Yield = 82%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.36 (m, 4H), 7.33-7.29 (m, 3H), 7.22-7.21 (m, 3H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 3.68 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.45 (dd, *J* = 11.6, 5.6 Hz, 1H), 2.94-2.86 (m, 2H), 2.84-2.71 (m, 2H), 1.91 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 137.9, 128.4, 128.4, 127.7, 126.0, 73.2, 70.2, 57.2, 55.4, 33.4, 32.1.

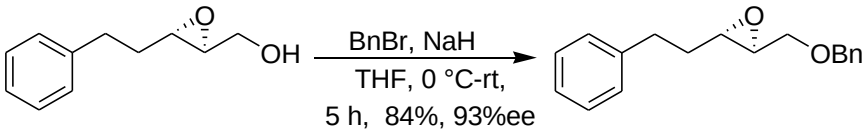
Preparation of ((2S, 3S)-3-phenethyloxiran-2-yl)methanol (88):[71]



86 **88**

To a suspension of Ti(O-*i*-Pr)$_4$ (0.45 mL, 1.54 mmol) and MS 4Å (powder, 600 mg) in CH_2Cl_2 was added L-(+)-DIPT (0.39 mL, 1.85 mmol) at –20 °C. The mixture was stirred at –20 °C for 20 min and cooled further to –40 °C. A solution of the alcohol **86** (500 mg, 3.08 mmol) dissolved in CH_2Cl_2 and *t*-BuOOH (0.84 mL, 5.0-6.0 M in decane, 4.62 mmol) were added to the solution successively. After 4 h at –20 °C, the reaction was quenched by adding H_2O (0.55 mL, 30.82 mmol) and NaF (1.3 g, 31.28 mmol). The mixture was stirred at rt for 30 min and filtered through a pad of celite. To the filtrate was added 1 M NaOH, and the mixture was stirred at rt for 30 min. The resulting mixture was extracted with CH_2Cl_2. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **88.** Yield = 493 mg (90%); ee = 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 7.22-7.19 (m, 3H), 3.87-3.84 (m, 1H), 3.60-3.54 (m, 1H), 3.01-2.98 (m, 1H), 2.86-2.81 (m, 2H), 2.78-2.70 (m, 1H), 1.95-1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 128.6, 128.5, 126.2, 61.7, 58.7, 55.4, 33.4, 32.3. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm).

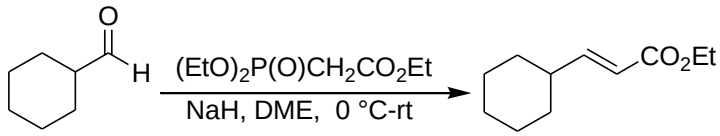
(2S,3S)-2-(Benzyloxymethyl)-3-phenethyloxirane (21r):[70]



88 **21r**

Prepared from **88** using GP-II; Yield = 84%; ee = 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.18 (m, 10H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 3.65 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.42 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.94-2.83 (m, 2H), 2.81-2.68 (m, 2H), 1.88 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 137.9, 128.4, 128.4, 127.7, 126.0, 73.2, 70.2, 57.2, 55.4, 33.5, 32.2. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm).

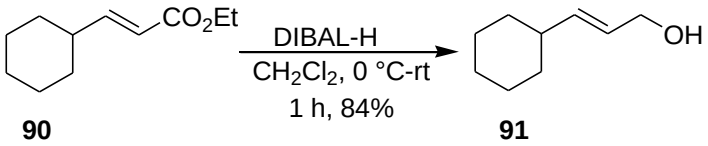
Preparation of (*E*)-ethyl 3-cyclohexylpropenoate (90):[72a]



89 **90**

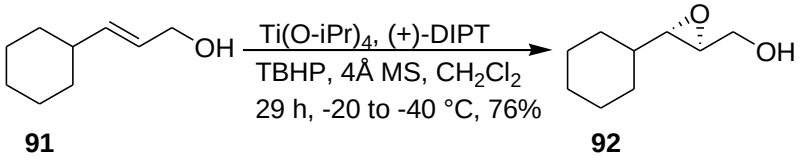
Triethyl phosphonoacetate (2.1 mL, 10.7 mmol) was added dropwise to a cooled (0 ^{o}C) suspension of NaH (535 mg, 13.4 mmol) in dimethoxyethane (15 mL). The reaction mixture was stirred at 0 ^{o}C for 40 min and then allowed to warm to room temperature. Cyclohexanecarboxaldehyde **89** (1.0 g, 8.9 mmol) was added and the mixture was stirred at rt. After completion of the reaction, it was quenched with water and extracted with EtOAc. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **90**. Yield = 950 mg (58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.76 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.14-2.12 (m, 1H), 1.78-1.66 (m, 5H), 1.29 (t *J* = 7.2 Hz, 3H), 1.23-1.10 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 154.3, 118.9, 60.1, 40.4, 31.7, 25.9, 25.7, 14.3.

(*E*)-3-Cyclohexylprop-2-en-1-ol (91):[72b]



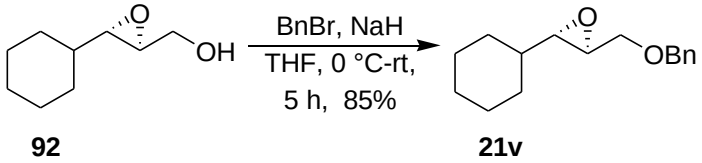
Prepared from **90** using GP-III; Yield = 86%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67-5.55 (m, 2H), 4.08 (d, *J* = 5.2 Hz, 2H), 2.14-2.12 (m, 1H), 1.97-1.96 (m, 1H), 1.73-1.63 (m, 5H), 1.47 (br s, 1H), 1.31-1.03 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 126.3, 64.0, 40.3, 32.7, 26.1, 26.0.

((2S, 3S)-3-Cyclohexyloxiran-2-yl)methanol (92):[72c]



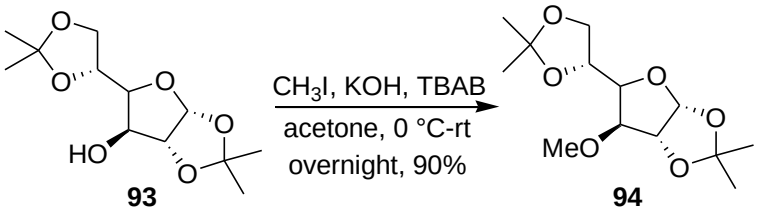
Prepared from **91** using GP-IV; Yield = 76%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92-3.89 (m, 1H), 3.62-3.59 (m, 1H), 2.99-2.98 (m, 1H), 2.76 (dd, *J* = 6.8, 2.4 Hz, 1H), 1.86-1.84 (m, 1H), 1.76-1.66 (m, 4H), 1.31-1.21 (m, 4H), 1.15-1.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 60.2, 57.2, 39.5, 29.6, 28.9, 26.2, 25.6, 25.5.

(2R,3S)-2-(Benzyloxymethyl)-3-cyclohexyloxirane (21v):



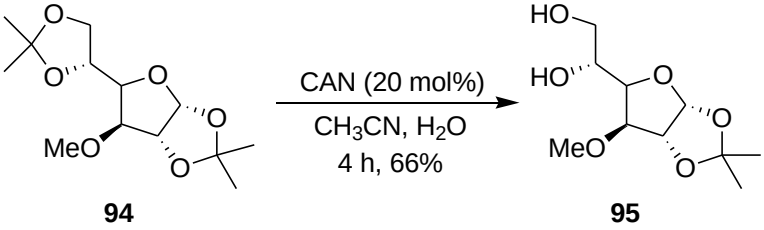
Prepared from **92** using GP-II; Colourless liquid; R_f = 0.58 in 1:3 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.39 (m, 5H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 3.72 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.46 (dd, *J* = 11.2, 6.0 Hz,1H), 3.03-3.01 (m, 1H), 2.64 (dd, *J* = 6.4, 1.9 Hz, 1H), 1.87-1.63 (m, 5H), 1.26-1.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 128.4, 127.7, 73.2, 70.7, 60.4, 55.8, 39.6, 29.6, 29.0, 26.3, 25.7, 25.5; IR (neat): υ 2926, 2853, 1452, 1101, 737, 698 cm^{-1}; Anal.Calc'd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; Found: C, 78.01; H, 9.08.

Preparation of 1,2; 5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (94):[51a]



To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **93** (3.0 g, 11.52 mmol) in 30 mL acetone were added freshly powdered KOH (0.844 g) and tetrabutylammonium bromide (0.137 g), the mixture was cooled to 0 ^{o}C and CH_3I (2.45 g) was added and the reaction was allowed to stirred at room temperature. After 20 min, acetone was removed in a rotovap. Then water was added to the reaction mixture and was extracted with CH_2Cl_2, washed with saturated NH_4Cl solution. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get pure **94** (3.18 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (d, *J* = 3.60 Hz, 1H), 4.56 (d, *J* = 3.6 Hz, 1H), 4.32-4.27 (m, 1H), 4.12-4.06 (m, 2H), 4.00 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.77 (d, *J* = 3.2 Hz, 1H), 3.45 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.7, 109.0, 105.1, 83.6, 81.8, 81.0, 72.3, 67.2, 58.1, 26.8, 26.8, 26.2, 25.3.

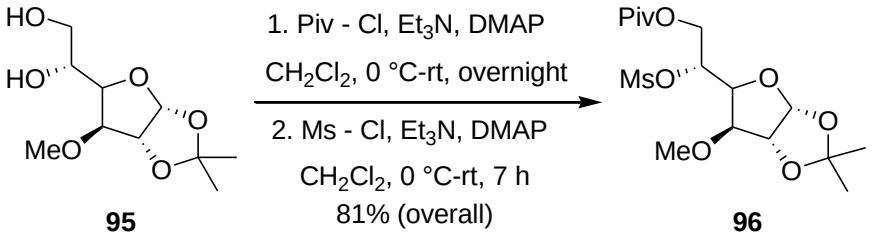
1, 2-*O*-Isopropylidene-3-*O*-methyl-α-D-glucofuranose (95):[51b]



To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **94** (3.18 g, 11.6 mmol) dissolved in water (few drops) and acetonitrile was added ceric ammonium nitrate (CAN) (1.27 g, 2.3 mmol). The resulting solution was stirred at room temperature for 2 h. After that, saturated NH_4OH solution was added and the resulting yellow-orange suspension was filtered over Celigel (celite/silica-gel: 9/1 w/w) and washed with MeOH. The solvents were removed in vacuo and the residue was dried overnight at room temperature to obtain corresponding diol **95**. Yield = quantitative; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (d, *J*

= 3.20 Hz, 1H), 4.60 (d, *J* = 3.2 Hz, 1H), 4.14-4.23 (m, 1H), 4.04-4.00 (m, 1H), 3.90-3.83 (m, 2H), 3.75-3.71 (m, 1H), 3.47 (s, 3H), 1.50 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.7, 105.0, 84.6, 81.3, 79.7, 69.5, 64.4, 57.8, 26.7, 26.2.

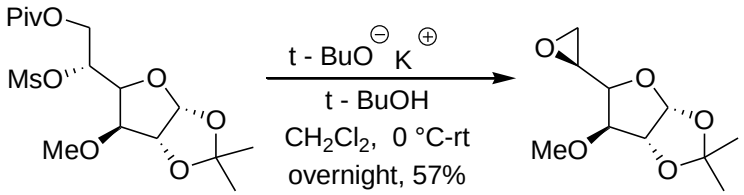
(R)-2-((3aR,6S,6aR)-6-Methoxy-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-(methylsulfonyloxy)ethyl pivalate (96):[51c]



95 **96**

To a stirred solution of 1, 2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **95** (0.8 g, 3.4 mmol) in CH_2Cl_2 were added Et_3N (1.43 mL, 10.2 mmol) and DMAP (0.033 g, 0.27 mmol) successively at rt. The resulting mixture was stirred for 30 min and was cooled to 0 ^oC. Pivaloyl chloride (0.46 mL, 3.76 mmol) was added. After completion of the reaction (primary alcohol protection), the resulting mixture was cooled to 0 ^oC and methane sulfonyl chloride (0.30 mL, 3.76 mmol) was added followed by stirring at rt. After completion of the reaction (secondary alcohol protection), it was extracted with CH_2Cl_2 and washed with saturated NH_4Cl and brine solutions. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **96**. Yield = 81% (over two steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (d, *J* = 3.60 Hz, 1H), 5.18-5.15 (m, 1H), 4.70 (dd, *J* = 12.8, 1.6 Hz, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.35 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.19 (dd, *J* = 12.8, 4.8 Hz, 1H), 3.84 (d, *J* = 2.8 Hz, 1H), 3.45 (s, 3H), 3.06 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 112.1, 105.3, 82.5, 80.8, 77.4, 75.1, 63.2, 57.5, 39.0, 38.9, 27.1, 26.8, 26.2.

(3aR,6S,6aR)-6-Methoxy-2,2-dimethyl-5-((S)-oxiran-2-yl)-tetrahydrofuro[2,3-d][1,3]dioxole (21w):[51c]

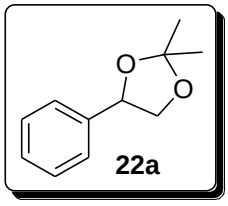


96 **21w**

To a stirred solution of (R)-2-((3aR,6S,6aR)-6-methoxy-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-(methylsulfonyloxy)ethyl pivalate **96** (0.709 g, 1.79 mmol) in CH_2Cl_2 were added *t*-BuOK (0.301 g, 2.68 mmol) and *t*-BuOH (0.34 mL, 3.58 mmol) successively at 0 ^oC. The resulting mixture was stirred at rt. After completion of the reaction, the solvent was removed in a rotovap. The crude reaction mixture was extracted with CH_2Cl_2 and washed with brine solution. The resulting organic solution was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude mixture was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure **21w**. Yield = 57%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (d, *J* = 3.6 Hz, 1H), 4.61 (d, *J* = 3.6 Hz, 1H), 3.85 (dd, *J* = 5.6, 3.6 Hz, 1H), 3.78 (d, *J* = 3.2 Hz, 1H), 3.45 (s, 3H), 3.24-3.21 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 1H), 2.69-2.67 (m, 1H), 1.47 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.8, 105.3, 85.5, 81.7, 81.7, 58.0, 49.9, 43.3, 26.8, 26.3.

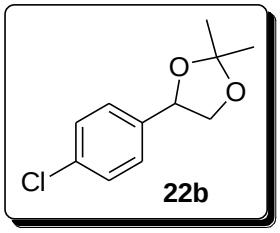
2,2-Dimethyl-4-phenyl-1,3-dioxolane (22a):[24]

Prepared from styrene oxide using GP-V; Yield = 73%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39-7.32 (m, 5H), 5.08 (dd, *J* = 7.8, 5.8 Hz, 1H), 4.32 (dd, *J* = 7.8, 5.8 Hz, 1H), 3.72 (t, *J* = 7.8 Hz, 1H), 1.56 (s, 3H), 1.50 (s, 3H).

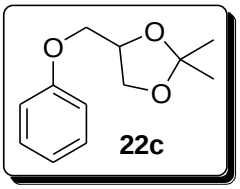


4-(4-Chlorophenyl)-2,2-dimethyl-1,3-dioxolane (22b):[23]

Prepared from 4-chlorostyrene oxide using GP-V; Yield: 87%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34-7.28 (m, 4H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.30 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.66 (t, *J* = 8.0 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H).



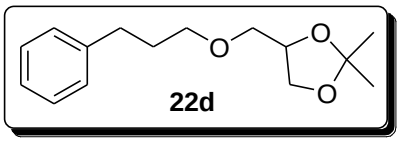
2,2-Dimethyl-4-(phenoxymethyl)-1,3-dioxolane (22c):[23]



Prepared from **21c** using GP-V; Yield = 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 2H), 6.99-6.92 (m, 3H), 4.49 (pent, *J* = 6.0 Hz, 1H), 4.18 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.08 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.97-3.90 (m, 2H), 1.48 (s, 3H), 1.42 (s, 3H).

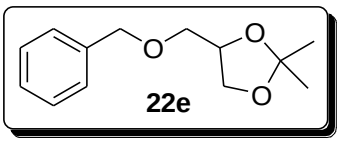
2,2-Dimethyl-4-((3-phenylpropoxy)methyl)-1,3-dioxolane (22d):

Prepared from **21d** using GP-V; Yield = 84%; Colorless liquid; R_f = 0.50 in 1:5 EtOAc/hexanes (double elution); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.19-7.17 (m, 3H), 4.30-4.24 (m, 1H), 4.06 (dd, *J* = 7.6, 6.8 Hz, 1H), 3.74 (dd, *J* = 7.6, 7.2 Hz, 1H), 3.53-3.40 (m, 4H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.94-1.87 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 128.4, 128.3, 125.7, 109.3, 74.7, 71.8, 70.7, 66.8, 32.2, 31.0, 26.7, 25.4; IR (neat): υ 2934, 2865, 1603, 1454, 1371, 1118, 847 cm^{-1}; Anal. Calc′d for $C_{15}H_{22}O_3$: C, 71.97 ; H, 8.86; Found: C, 71.85; H, 8.91.



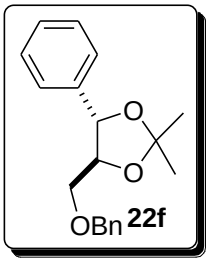
4-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane (22e):[24]

Prepared from **21e** using GP-V; Yield = 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.31 (pent, *J* = 6.4 Hz, 1H), 4.06 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.74 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.56 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.48 (dd, *J* = 10.0, 5.6 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H).



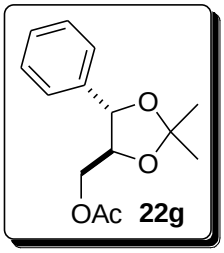
4-(Benzyloxymethyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane (22f):[23]

Prepared from **21f** using GP-V; Yield = 82%; (syn/anti 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.14 (m, 20H), 5.27 (d, *J* = 7.1 Hz, 1H), 4.85 (d, *J* = 8.6 Hz, 1H), 4.65-4.54 (m, 3H), 4.30 (d, *J* = 11.8 Hz, 1H), 4.16 (d, *J* = 11.9 Hz, 1H), 4.02-3.99 (m, 1H), 3.68 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.63 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.20 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.00 (dd, *J* = 10.0, 4.8 Hz, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H); Anal calc'd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43; found: C, 76.45; H, 7.48.



(2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)methyl acetate (22g):[23]

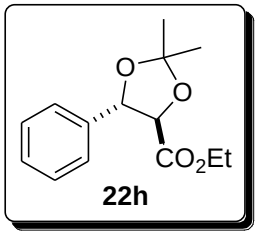
Prepared from **21g** using GP-V; Yield = 74%; (syn/anti 2.5:1); *anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 5H), 4.77 (d, *J* = 8.8 Hz, 1H), 4.35 (dd, *J* = 11.6, 3.2 Hz, 1H), 4.14 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.04-4.00 (m, 1H) , 2.06 (s, 3H), 1.59 (s, 3H), 1.53 (s, 3H); syn isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 5.32 (d, *J* = 7.2 Hz, 1H), 4.59-4.55 (m, 1H), 3.71 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.62 (d, *J* = 11.6, 8.0 Hz, 1H), 1.91 (s, 3H), 1.65 (s, 3H), 1.49 (s, 3H); Anal calc'd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; found: C, 67.32; H, 7.31.



22g

Ethyl 2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (22h):[73]

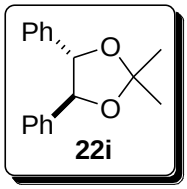
Prepared by following GP-V; Yield = 92%; (syn/anti 1.8:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.29 (m, 10H), 5.44 (d, *J* = 7.6 Hz, 1H), 5.16 (d, *J* = 7.6 Hz, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 4.34 (d, *J* = 7.6 Hz, 1H), 4.29-4.21 (m, 2H), 3.76-3.72 (m, 1H), 3.58-3.54 (m, 1H), 1.80 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.51 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.4, 137.7, 135.7, 128.6, 128.5, 128.4, 128.1, 126.8, 126.5, 111.6, 111.1, 81.4, 80.8, 79.9, 79.0, 61.4, 60.6, 26.9, 26.6, 25.8, 25.3, 14.1, 13.5; Anal calc'd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; found: C, 67.33; H, 7.16.



22h

2,2-Dimethyl-4,5-diphenyl-1,3-dioxolane (22i):[23]

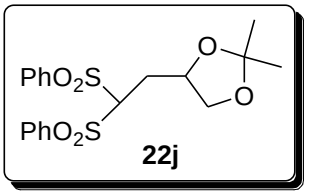
Prepared from *trans*-stilbene epoxide using GP-V; Yield = 77%; (syn/anti 1:4.9); anti isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.22 (m, 10H), 4.75 (s, 2H), 1.68 (s, 6H); syn isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 10H), 5.50 (s, 2H), 1.83 (s, 3H), 1.62 (s, 3H).



22i

4-(2,2-Bis(phenylsulfonyl)ethyl)-2,2-dimethyl-1,3-dioxolane (22j):

Prepared from **21j** using GP-V; Yield = 52%; Yellow solid; melting point: 139-141 ºC; R_f = 0.42 in 1:1 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.40-7.54 (m, 6H), 4.85 (dd, *J* = 6.4, 4.8 Hz, 1H), 4.54 (pent, *J* = 6.0 Hz, 1H), 4.08 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.62 (dd, *J* = 8.8, 4.4 Hz, 1H), 2.36 (t, *J* =

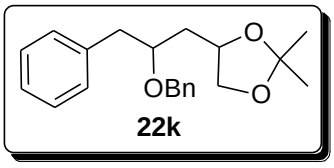


22j

5.6 Hz, 2H), 1.28 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 137.4, 134.5, 129.6, 129.4, 129.1, 109.7, 79.9, 72.6, 68.9, 31.1, 26.8, 25.2; IR (KBr): υ 2988, 2920, 1732, 1585, 1379, 1147, 829 cm^{-1}; Anal.Calc′d for $C_{19}H_{22}O_6S_2$: C, 55.59; H, 5.40; Found: C, 55.68; H, 5.36.

4-(2-(Benzyloxy)-3-phenylpropyl)-2,2-dimethyl-1,3-dioxolane (22k):

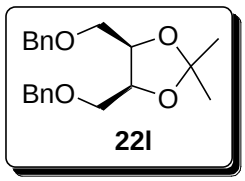
Prepared from **21k** using GP-V; Yield = 81%; (dr: 1:1); Colorless liquid; R_f = 0.58 in 1:5 EtOAc/hexanes (double elution); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.21 (m, 20H), 4.54-4.41 (m, 4H), 4.27-4.19 (m, 2H), 4.02 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.91 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.88-3.81 (m, 1H), 3.69 (pent, *J* = 6.0 Hz, 1H), 3.49 (t, *J* = 8.0 Hz, 1H), 3.42 (t, *J* = 8.0 Hz, 1H), 2.99-2.92 (m, 2H), 2.86 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.80 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.97 (dt, *J* = 14.0, 6.4 Hz, 1H), 1.78 (ddd, *J* = 14.0, 8.0, 2.8 Hz, 1H), 1.72-1.61 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 138.4, 129.7, 128.4, 128.0, 127.9, 127.7, 126.3, 108.6, 108.4, 77.8, 73.6, 73.1, 72.1, 71.3, 70.1, 69.6, 41.2, 40.6, 38.9, 37.5, 27.0, 25.9; IR (neat): υ 2932, 2870, 1602, 1454, 1369, 1157, 870 cm^{-1}; Anal. Calc′d for $C_{21}H_{26}O_3$: C, 77.27 ; H, 8.03; Found: C, 77.35; H, 8.12.



22k

***syn*-4,5-Bis(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane (22l):**

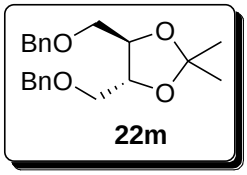
Prepared from **21l** using GP-V; Yield = 89%; Colorless liquid; R_f = 0.63 in 1:1 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 4.57 (d, *J* = 12.0 Hz, 2H), 4.48 (d, *J* = 12.0 Hz, 2H), 4.36 (t, *J* = 4.0 Hz, 2H), 3.60 (dd, *J* = 9.6, 4.8 Hz, 2H), 3.50 (dd, *J* = 10.0, 6.0 Hz, 2H), 1.46 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.4, 127.8, 127.7, 108.9, 75.9, 73.5, 68.7, 27.9, 25.4; Anal.Calc′d for $C_{21}H_{26}O_4$: C, 73.66 ; H, 7.65; Found: C, 73.45; H, 7.61.



22l

***anti*-4,5-Bis(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane (22m):**[74]

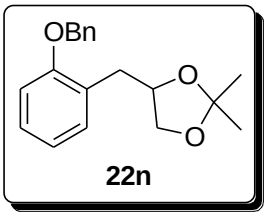
Prepared from **21m** using GP-V; Yield = 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.20 (m, 10H), 4.53 (br s, 4H), 4.00 (br s, 2H), 3.56 (br s, 4H), 1.38 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 128.4, 127.8,



22m

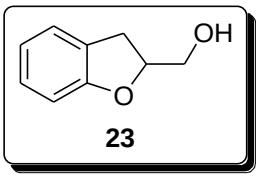
127.7, 109.7, 77.6, 73.6, 70.7, 27.1.

4-(2-(Benzyloxy)benzyl)-2,2-dimethyl-1,3-dioxolane (22n):[23]



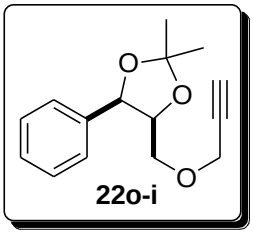
Prepared from **21n** using GP-V; Yield = 52%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.32 (m, 5H), 7.23-7.20 (m, 2H), 6.94-6.90 (m, 2H), 5.10 (s, 2H), 4.42 (pent, *J* = 6.4 Hz, 1H), 3.94 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.66 (t, *J* = 8.0 Hz, 1H), 3.08 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.90 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H).

(2,3-Dihydrobenzofuran-2-yl)methanol (23):[56]



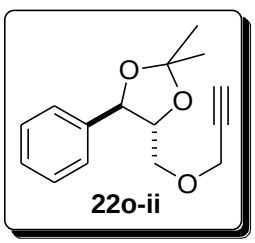
Obatined from **21n** using GP-V; Yield = 43%; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.18 (d, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.95-4.89 (m, 1H), 3.86 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.74 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.26 (dd, *J* = 15.6, 9.6 Hz, 1H), 3.02 (dd, *J* = 15.6, 7.6 Hz, 1H).

(*syn*)-2,2-Dimethyl-4-phenyl-5-((prop-2-ynyloxy)methyl)-1,3-dioxolane (22o-i):



Prepared from **21o** using GP-V; Colorless liquid; Yield = 35%; R_f = 0.41 in 1:10 EtOAc/hexanes (double elution); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 5.26 (d, *J* = 7.2 Hz, 1H), 4.57 (dt, *J* = 10.8, 4.4 Hz, 1H), 3.92 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.86 (dd, *J* = 16.0, 2.4 Hz, 1H), 3.16 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.00 (dd, *J* = 10.4, 4.4 Hz, 1H), 2.32 (t, *J* = 2.4 Hz, 1H), 1.66 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 128.2, 128.0, 126.7, 109.0, 79.3, 78.6, 77.4, 74.5, 70.0, 58.3, 27.2, 24.7; IR (neat): υ 3287, 2861, 2118, 1721, 1462, 1101, 879 cm^{-1}; Anal calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Found: C, 73.17; H, 7.42.

(*anti*)-2,2-Dimethyl-4-phenyl-5-((prop-2-ynyloxy)methyl)-1,3-dioxolane (22o-ii):

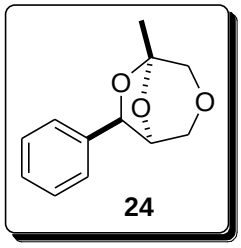


Prepared from **21o** using GP-V; Colorless liquid; Yield = 18%; R_f = 0.54 in 1:10 EtOAc/hexanes (double elution); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.30 (m, 5H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.26 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.20 (dd, *J* = 16.0 , 2.4 Hz, 1H), 3.99 (ddd, *J* = 8.4,

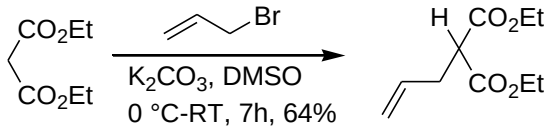
5.2, 2.8 Hz, 1H), 3.74 (dd, *J* = 10.4, 2.8 Hz , 1H), 3.69 (dd, *J* = 10.4, 5.2 Hz, 1H), 2.43 (t, *J* = 2.4 Hz, 1H), 1.58 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 128.6, 128.3, 126.6, 109.6, 82.4, 79.6, 79.4, 74.9, 68.4, 58.8, 27.1; IR (neat): υ 3289, 2986, 2934, 2116, 1604, 1454, 1090, 756 cm^{-1}; Anal calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; found: C, 73.22; H, 7.32.

5-Methyl-7-phenyl-3,6,8-trioxa-bicyclo[3.2.1]octane (24):

Prepared from **21o** using GP-V; Colorless semisolid; Yield = 14%; R_f = 0.46 in 1:10 EtOAc/hexanes (double elution); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 5.29 (d, *J* = 4.8 Hz, 1H), 4.43 (d, *J* = 4.4 Hz, 1H), 3.70 (d, *J* = 12.0 Hz, 1H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.31 (d, *J* = 12.0 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 128.2, 127.5, 126.1, 105.8, 81.1, 78.5, 71.8, 64.3, 20.2; IR (neat): υ 2963, 1494, 1452, 1302, 1233, 1063, 876, 700 cm^{-1}; Anal calc'd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; found: C, 69.95; H, 6.81.



Diethyl 2-allylmalonate (98):[75a]

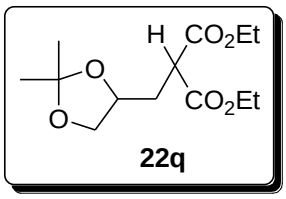


97 **98**

To a solution of diethyl malonate **97** (5 g, 31.25 mmol) in DMSO (50 mL), K_2CO_3 (4.8 g, 35 mmol) added at 0 ºC and stirred for 30 min. Then allyl bromide (3.2 mL, 38 mmol) was added slowly and reaction was continued for 7 h at rt. Ethyl acetate was added to the reaction mixture. It was washed three times with water and brine solution, then dried over anhydrous Na_2SO_4 and concentrated. Pure **98** was obtained by column chromatography using EtOAc/hexanes as eluents. Yield = 64%; Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83-5.73 (m, 1H), 5.14-5.04 (m, 2H), 4.20 (q, *J* = 6.4 Hz, 4H), 3.47-3.36 (m, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 6.4 Hz, 6H).

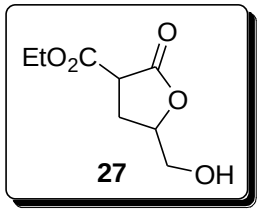
Diethyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)malonate (22q):

Prepared from **21q** using GP-V; Yield = 39%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.20 (q, *J* = 7.2 Hz, 4H), 4.15-4.12 (m, 1H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.60-3.55 (m, 2H), 2.23-2.17 (m, 1H), 2,13-2.06 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.1, 109.2, 73.4, 69.0, 61.5, 48.7, 32.7, 26.8, 25.5, 14.0, 13.9; Anal.Calcd for $C_{13}H_{22}O_6$: C 56.92; H 8.08, Found: C 56.81, H 8.12 .

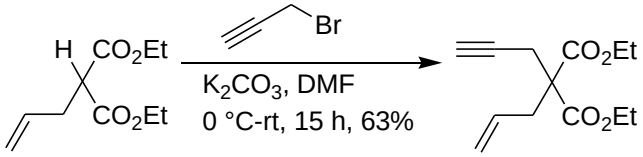


Ethyl 5-(hydroxymethyl)-2-oxo-tetrahydrofuran-3-carboxylate (27):

Prepared from **21q** using GP-V; Yield = 56%, colorless liquid, dr = 1.0:1.1; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of isomers) δ 5.12 (br s, 2H), 4.79-4.74 (m, 1H), 4.65-4.59 (m, 1H), 4.27 (q, *J* = 7.2 Hz, 4H), 3.99-3.91 (m, 2H), 3.77-3.72 (m, 2H), 3.69-3.65 (m, 2H), 2,71-2.67 (m, 1H), 2.59-2.43 (m, 3H), 1.32 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 172.6, 171.9, 168.0, 167.8, 79.7, 79.5, 63.7, 62.4, 62.3, 47.0, 46.9, 27.6, 27.2, 14.0; Anal.Calcd for $C_{18}H_{12}O_5$: C 51.06; H 6.43, Found: C 51.12, H 6.48.



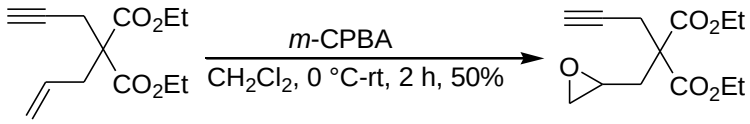
Diethyl 2-allyl-2-(prop-2-ynyl)malonate (99):[75b]



98 **99**

To a solution of mono allylated diethyl malonate **98** (4 g, 20 mmol) in DMF (55 mL), K_2CO_3 (7 g, 50 mmol) was added at 0 ºC and stirred for 1 h. Propargyl bromide (3.3 mL, 30 mmol) was added slowly and reaction continued for 15 h at rt. Then solvent was removed and the crude product was extracted with ethyl acetate, it was washed with aqueous NH_4Cl solution, saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography using EtOAc/hexanes as eluents. Yield = 63%; Pale yellow color liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68-5.58 (m, 1H), 5.21-5.12 (m, 2H), 4.21 (q, *J* = 8.4 Hz, 4H), 2.82-2.79 (m, 4H), 2.02 (t, *J* = 2.8 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 6H).

Diethyl 2-(oxiran-2-ylmethyl)-2-(prop-2-ynyl)malonate (21p):

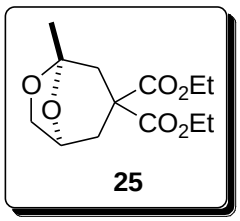


99 **21p**

Prepared from **99** using GP-I; Colorless liquid; Yield = 50%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23-4.14 (m, 4H), 2.96-2.91 (m, 3H), 2.72 (t, *J* = 4.8 Hz, 1H), 2.47 (q, *J* = 2.4 Hz, 1H), 2.36 (dd, *J* = 14.8,4.8 Hz, 1H), 2.11 (dd, *J* = 14.8,7.2 Hz, 1H), 2.02 (t, *J* = 2.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 78.6, 71.8, 61.9, 61.8, 55.6, 48.2, 46.7, 35.6, 23.5, 13.9; IR (neat): υ 3289, 2990, 1732, 1292, 1194, 858 cm^{-1}; Anal.Calcd for $C_{13}H_8O_5$: C 61.40 ; H 7.14; Found: C 61.48; H 7.17.

Diethyl 5-methyl-6,8-dioxa-bicyclo[3.2.1]octane-3,3-dicarboxylate (25):

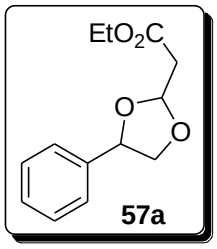
Prepared from **21p** using GP-V; Yield = 59%; Colorless liquid; R_f = 0.68 in 1:3 EtOAc/hexanes; ^{1}H NMR (400 MHz): δ 4.51 (m, 1H), 4.27-4.12 (m, 4H), 4.05 (d, *J* = 6.8 Hz, 1H), 3.66 (t, *J* = 5.2 Hz, 1H), 2.65 (d, *J* = 14.4 Hz, 1H), 2.60 (d, *J* = 14.4, 1H), 2.32 (d, *J* = 14.0 Hz, 1H), 2.04 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.47 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 170.9, 105.3, 73.8, 68.6, 61.85, 61.82, 51.6, 40.5, 31.8, 24.2, 14.0, 13.9; IR (neat): υ 2984, 1734, 1123, 858 cm^{-1}; Anal.Calc'd for $C_{13}H_{20}O_6$: C 57.34, H 7.40 ; Found: C 57.45, H 7.36.



25

Ethyl 2-(4-phenyl-1,3-dioxolan-2-yl)acetate (57a):

Prepared from **21a** and ethyl propiolate **56** by following GP-VI; Yellow liquid; Yield = 73%; R_f = 0.47 in 1:5 EtOAc/hexanes; dr: 1.0:1.2; ^{1}H NMR (400 MHz,$CDCl_3$): (mixture of major and minor isomers) δ 7.36-7.31 (m, 10H), 5.68 (t, *J* = 5.2 Hz, 1H), 5.52 (t, *J* = 5.2 Hz, 1H), 5.10 (t, *J* = 6.8 Hz,, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 4.42 (dd, *J* = 8.0, 6.4 Hz, 1H), 4.24 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 4H), 3.78 (t, *J* = 7.2 Hz, 1H), 3.73 (t, *J* = 7.6 Hz, 1H), 2.86 (t, *J* = 5.2 Hz, 2H), 2.79 (t, *J*= 5.2 Hz, 2H), 1.28 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 139.1, 138.9, 128.6, 128.3, 128.1, 126.3, 126.0, 102.1, 101.8, 78.6,

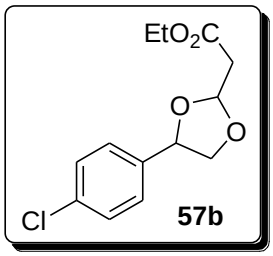


57a

77.7, 72.6, 71.9, 60.8, 40.4, 40.0, 14.2; Anal.Calc'd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; Found: C, 66.15; H, 6.79.

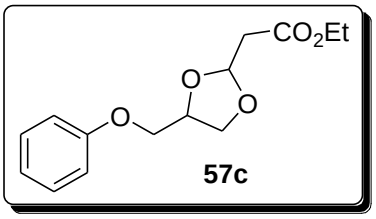
Ethyl 2-(4-(4-chlorophenyl)-1,3-dioxolan-2-yl)acetate (57b):

Prepared from **21b** and ethyl propiolate **56** by following GP-VI; Clear yellow liquid; Yield = 82%; R_f = 0.45 in 1:3 EtOAc/hexanes; dr: 1.0:1.3; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.34-7.28 (m, 8H), 5.65 (t, *J* = 5.2 Hz, 1H), 5.49 (t, *J* = 5.2 Hz, 1H), 5.08-5.01 (m, 2H), 4.41 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.24-4.17 (m, 5H), 3.74 (t, *J* = 7.6 Hz, 1H), 3.67 (t, *J* = 8.0 Hz, 1H), 2.85-2.84 (m, 2H), 2.77-2.76 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 137.6, 134.0, 128.8, 127.7, 127.3, 102.2, 101.9, 77.9, 77.1 72.5, 71.9, 60.9, 40.3, 39.9, 14.2; IR (neat): υ 2984, 2897, 1738, 1136, 825 cm^{-1}; Anal.Calc'd for $C_{13}H_{15}ClO_4$: C, 57.68; H, 5.59; Found: C, 57.61; H, 5.66.



Ethyl 2-(4-(phenoxymethyl)-1,3-dioxolan-2-yl)acetate (57c):

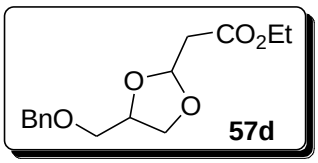
Prepared from **21c** and ethyl propiolate **56** by following GP-VI; Yellow liquid; Yield = 68%; R_f = 0.47 in 1:5 EtOAc/hexanes; dr: 1.0:1.1; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.29 (t, *J* = 8.0 Hz, 4H), 6.97 (t, *J* = 7.2 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 4H), 4.53-4.44 (m, 2H), 4.25 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 4H), 4.11-3.98 (m, 5H), 3.92 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.87 (dd, *J* = 8.4, 6.4 Hz, 1H), 2.75 (dd, *J* = 5.2, 3.8 Hz, 2H), 2.71 (dd, *J* = 7.6, 5.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 158.4, 129.5, 121.2, 114.5, 101.7, 101.5, 74.4, 74.1, 68.3, 67.9, 67.7, 67.6, 60.8, 40.0, 14.2 ; IR (neat): υ 2982, 1738, 1494, 1053, 756 cm^{-1} ; Anal.Calc'd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81; Found: C, 63.25; H, 6.78.



Ethyl 2-(4-(benzyloxymethyl)-1,3-dioxolan-2-yl)acetate (57d):

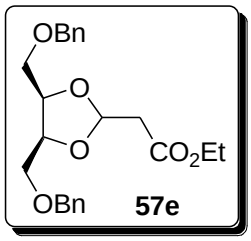
Prepared from **21e** and ethyl propiolate **56** by following GP-VI; Colorless liquid; Yield = 88%; R_f = 0.32 in 1:5 EtOAc/hexanes (double run); dr: 1.0:1.2; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.37-7.27 (m, 10H), 5.42 (t, *J* = 5.2 Hz, 1H), 5.28 (t, *J* = 5.2 Hz, 1H), 4.62-4.53 (m, 4H), 4.33 (quint, *J* = 5.2 Hz, 1H), 4.27 (quint, *J* = 5.6 Hz, 1H),

4.20-4.18 (m, 2 H), 4.16-4.15 (m, 2H), 4.14 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.96 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.84 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.72 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.60-3.54 (m, 2H), 3.53-3.44 (m, 2H), 2.76-2.70 (m, 2H), 2.69-2.62 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 137.7, 128.3, 127.7, 127.6, 101.4, 101.1, 75.1, 74.8, 73.4, 70.5, 70.1, 67.5, 60.6, 40.0, 39.9, 14.0; Anal.Calc'd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; Found: C, 64.35; H, 7.55.



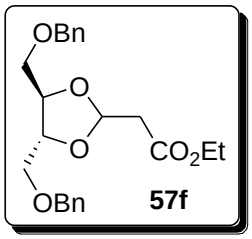
2-Ethyl-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-yl)acetate (57e):

Prepared from **21l** and ethyl propiolate **56** by following GP-VI; Yellow liquid; Yield = 82%; R_f = 0.26 in 1:5 EtOAc/hexanes (double run); dr: 1.0:3.5; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.36-7.29 (m, 20H), 5.67 (t, *J* = 5.2 Hz, 1H), 5.36 (t, *J* = 5.2 Hz, 1H), 4.57-4.53 (m, 4H), 4.50-4.47 (m, 4H), 4.45-4.40 (m, 2H), 4.29-4.26 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 4H), 3.62 (dd, *J* = 10.0, 4.0 Hz, 4H), 3.54 (dd, *J* = 10.0, 5.2 Hz, 4H), 2.73 (d, *J* = 5.2, Hz, 2H), 2.66 (d, *J* = 5.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.4, 137.8, 128.4, 127.9, 127.7, 101.2, 100.8, 76.8, 76.3, 73.5, 68.3, 68.0, 60.8, 40.8, 40.3, 14.1; IR (neat): υ 2918, 1622, 1045, 931, 729 cm^{-1} ; Anal.Calc'd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; Found: C, 68.85; H, 7.12.



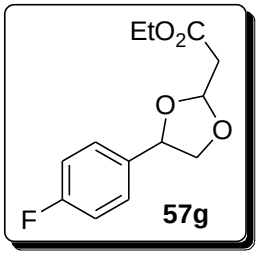
Ethyl 2-4,5-bis(benzyloxymethyl)-1,3-dioxolan-2-yl)acetate (57f):

Prepared from **21m** and ethyl propiolate **56** by following GP-VI; Yield = 80%; ^{1}H NMR (400 MHz, $CDCl_3$): (single isomer) δ 7.36-7.28 (m, 10H), 5.48 (t, *J* = 5.2 Hz, 1H), 4.57 (s, 4H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.12-4.07 (m, 2H), 3.62-3.59 (m, 4H), 2.72 (d, *J* = 5.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, , 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 137.9, 128.4, 127.7, 101.3, 78.1, 73.5, 70.3, 70.1, 60.7, 40.2, 14.1; IR (neat): υ 2912, 2864, 1738, 1255, 1099 cm^{-1}; Anal.Calc'd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; Found: C, 68.81; H, 7.12.



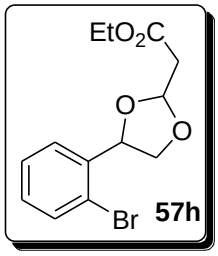
Ethyl 2-(4-(4-fluorophenyl)-1,3-dioxolan-2-yl)acetate (57g):

Prepared from **21s** and ethyl propiolate **56** by following GP-VI; Yellow liquid; Yield = 76%; R_f = 0.47 in 1:5 EtOAc/hexanes; dr: 1.0:1.4; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.34-7.29 (m, 4H), 7.04 (t, *J* = 8.4 Hz, 4H), 5.66 (t, *J* = 4.8 Hz, 1H), 5.48 (t, *J* = 4.8 Hz, 1H), 5.08-5.01 (m, 2H), 4.39 (t, *J* = 8.4 Hz, 1H), 4.23-4.16 (m, 5H), 3.74 (t, *J* = 8.0 Hz, 1H), 3.68 (t, *J* = 7.6 Hz, 1H), 2.84-2.82 (m, 2H), 2.76-2.75 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 162.6 (d, *J* = 236.0 Hz), 134.7, 128.1 (d, *J* = 8.2 Hz), 127.7 (d, *J* = 8.2 Hz), 115.5 (d, *J* = 21.5 Hz), 102.1, 101.8, 78.0, 72.6, 71.9, 60.8, 40.3, 40.0, 14.1; IR (neat): υ 2905, 1738, 1512, 1307, 1134, 837 cm^{-1}; Anal.Calc'd for $C_{13}H_{15}FO_4$: C, 61.41; H, 5.95; Found: C, 61.55; H, 5.87.



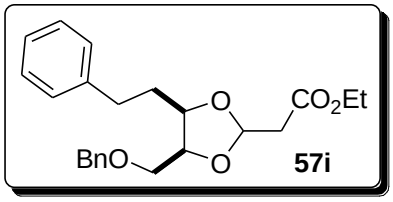
Ethyl 2-(4-(2-bromophenyl)-1,3-dioxolan-2-yl)acetate (57h):

Prepared from **21t** and ethyl propiolate **56** by following GP-VI; Yellow liquid; Yield = 75%; R_f = 0.47 in 1:5 EtOAc/hexanes; dr: 1.0:1.6; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 2H), 5.66 (t, *J* = 5.6 Hz, 1H), 5.50 (t, *J* = 5.2 Hz, 1H), 5.39-5.35 (m, 2H), 4.67 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.41 (t, *J* = 8.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 4H), 3.75 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.62 (dd, *J* = 8.4, 7.2 Hz, 1H), 2.89 (t, *J* = 5.2 Hz, 2H), 2.81 (d, *J* = 5.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 169.3, 139.4, 139.3, 132.7, 132.4, 129.2, 127.8, 127.6, 127.0, 126.6, 121.3, 121.1, 102.0, 101.8, 77.1, 76.9, 71.7, 71.3, 60.9, 40.0, 39.8, 14.2; IR (neat): υ 2984, 1738, 1310, 1179, 1020 cm^{-1}; Anal.Calc'd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80; Found: C, 49.62; H, 4.85.



Ethyl 2-(4-(benzyloxymethyl)-5-phenethyl-1,3-dioxolan-2-yl)acetate (57i):

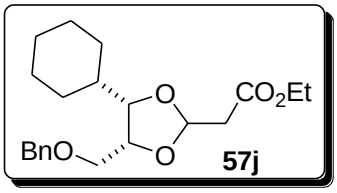
Prepared from **21u** and ethyl propiolate **56** by following GP-VI; Yellow viscous liquid; Yield = 94%; R_f = 0.56 in 1:3 EtOAc/hexanes; dr: 1.0:2.6; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.33-7.26 (m, 14H), 7.21-7.16 (m, 6H), 5.63 (t, *J* = 5.2 Hz, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 4H), 4.17-4.15



(m, 3H), 4.04 (q, *J* = 6.4 Hz, 1H), 3.55-3.51 (m, 2H), 3.48 (dd, *J* = 6.0, 2.4 Hz, 2H), 2.88-2.81 (m, 2H), 2.71 (d, *J* = 5.2 Hz, 2H), 2.67-2.64 (m, 2H), 2.63-2.61 (m, 2H), 1.89-1.80 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 169.3, 141.4, 141.3, 137.6, 128.4, 128.3, 127.7, 127.6, 125.8, 100.1, 77.6, 76.7, 76.5, 73.4, 73.3, 68.6, 67.8, 60.6, 40.7, 40.6, 32.4, 32.3, 30.8, 30.0, 14.1; Anal.Calc'd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; Found: C, 71.68; H, 7.45.

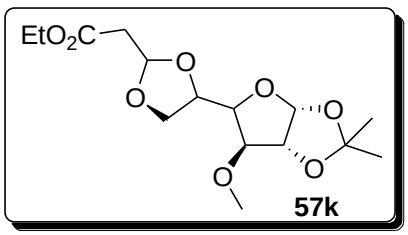
Ethyl 2-((4R,5S)-4-(benzyloxymethyl)-5-cyclohexyl-1,3-dioxolan-2-yl)acetate (57j):

Prepared from **21v** and ethyl propiolate **56** by following GP-VI; Yellow liquid; Yield = 86%; R_f = 0.47 in 1:10 EtOAc/hexanes (triple run); dr: 1.0:3.3; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.35-7.27 (m, 10H), 5.61(t, *J* = 5.2 Hz, 1H), 5.29 (t, *J* = 5.2 Hz, 1H), 4.58-4.55 (m, 4H), 4.32 (q, *J* = 5.2 Hz, 1H), 4.22 (q, *J* = 5.6 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 4H), 3.72 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.66 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.55-3.51 (m, 3H), 3.39 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.71-2.65 (m, 2H), 2.61-2.58(m, 2H), 1.97-1.66 (m, 10H), 1.26 (t, *J* = 7.2Hz, 6H), 1.24-0.97 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 138.0 (2C), 128.4, 127.7, 100.4, 100.2, 83.9, 81.7, 77.1, 76.2, 73.5, 73.4, 69.4, 67.6, 60.7, 60.6, 41.1, 40.8, 37.1, 36.7, 30.3, 29.8, 28.9, 26.3, 25.8, 25.5 (2C), 14.2; IR (neat): υ 2928, 1732, 1447, 1119, 1020, 741, 698 cm^{-1}; Anal.Calc'd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34; Found: C, 69.45; H, 8.26.



Ethyl2-(4-(6-methoxy-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-1,3-dioxolan-2-yl)acetate (57k):

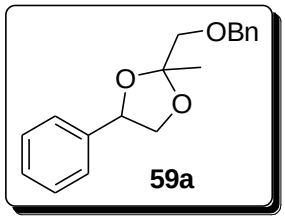
Prepared from **21w** and ethyl propiolate **56** by following GP-VI; Colorless viscous liquid; Yield = 43%; R_f = 0.50 in 1:1 EtOAc/hexanes; dr: 1.0:1.2; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 5.93 (d, *J* = 2.8 Hz, 2H), 5.40 (dd, *J* = 6.4, 4.0 Hz, 1H), 5.28 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.55 (t, *J* = 3.6 Hz, 2H), 4.32 (q, *J* = 7.6 Hz, 1H), 4.27 (q, *J* = 7.6 Hz, 1H), 4.19 (dd, *J* = 8.0, 3.6 Hz, 2H), 4.16 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 4H), 3.99 (t, *J* = 7.2 Hz, 1H), 3.65-3.62 (m, 3H), 3.58 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.33 (s, 6H), 2.79 (dd, *J* = 15.6, 4.0 Hz, 1H), 2.73 (dd, *J* = 15.6, 4.0 Hz, 1H), 2.63 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.59 (dd, *J* = 15.2, 6.4



Hz, 1H), 1.46 (s, 6H), 1.29 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 169.3, 111.8, 105.5, 105.4, 101.7, 101.1, 85.1, 84.7, 81.9, 81.3, 81.2, 80.8, 76.0, 75.4, 66.8, 66.4, 60.7, 57.5, 39.9, 39.8, 26.8, 26.3, 14.1; IR (neat): υ 2986, 2937, 1736, 1373, 1080, 852 cm^{-1} ; Anal.Calc'd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28; Found: C, 54.35; H, 7.19.

2-(Benzyloxymethyl)-2-methyl-4-phenyl-1,3-dioxolane (59a):

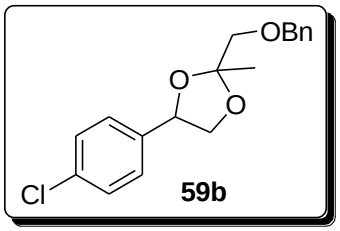
Prepared from **21a** and benzyl protected propargyl alcohol **58** by following GP-VI; Colorless liquid; Yield = 33%; R_f = 0.57 in 1:10 EtOAc/hexanes; dr: 1.0:1.0; ^{1}H NMR (400 MHz,$CDCl_3$): (mixture of isomers) δ 7.38-7.30 (m, 20H), 5.16 (dd, *J* = 7.6, 6.4 Hz, 1H), 5.08 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.71-4.62 (m, 4H), 4.37 (dd, *J* = 8.0, 6.4 Hz, 1H), 4.32 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.76 (q, *J* = 8.4 Hz, 2H), 3.61 (q, *J* = 11.2 Hz, 2H), 3.54 (dd, *J* = 12.8,10.4 Hz, 2H), 1.56 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.3, 128.5, 128.4, 128.2, 128.1, 127.7, 127.6, 126.5, 126.3, 109.8, 109.7, 78.8, 78.1, 74.1, 73.8, 73.6, 73.5, 72.3, 72.1, 22.7, 22.5; Anal.Calc'd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09; Found: C, 76.22; H, 7.13.



59a

2-(Benzyloxymethyl)-4-(4-chlorophenyl)-2-methyl-1,3-dioxolane (59b):

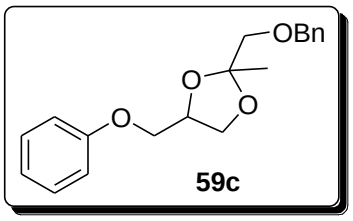
Prepared from **21b** and benzyl protected propargyl alcohol **58** by following GP-VI; Colourless liquid; Yield = 61%; R_f = 0.28 in 1:10 EtOAc/hexanes (double run); dr: 1.0:1.8; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.36-7.34 (d, *J* = 4.4 Hz, 8H), 7.33-7.28 (m, 10H), 5.13 (t, *J* = 7.2 Hz, 1H), 5.06 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.69-4.66 (m, 2H), 4.64-4.61 (m, 2H), 4.35 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.32 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.75-3.67 (m, 2H), 3.63-3.57 (m, 2H), 3.54-3.51 (m, 2H), 1.54 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.5, 136.8, 133.8, 128.7, 128.4, 127.6, 110.0, 109.8, 78.2, 74.2, 73.8, 73.6, 72.1, 22.7; IR (neat): υ 2874, 1601, 1493, 1373, 1103, 1057, 954 cm^{-1}; Anal.Calc'd for $C_{18}H_{19}ClO_3$: C, 67.82; H, 6.01; Found: C, 67.95; H, 5.93.



59b

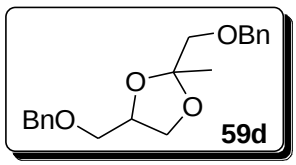
2-(Benzyloxymethyl)-2-methyl-4-(phenoxymethyl)-1,3-dioxolane (59c):

Prepared from **21c** and benzyl protected propargyl alcohol **58** by following GP-VI; Colourless liquid; Yield = 76%; R_f = 0.39 in 1:10 (double run) EtOAc/hexanes; dr: 1.0:1.0; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of isomers) δ 7.38-7.35 (m, 8H), 7.33-7.29 (m, 6H), 7.01-6.93 (m, 4H), 6.88-6.86 (m, 2H), 4.64 (d, *J* = 3.2 Hz, 4H), 4.59-4.53 (m, 2H), 4.27-4.21 (m, 2H), 4.12-4.07 (m, 2H), 3.99-3.95 (m, 4H), 3.56-3.49 (m, 4H), 1.49 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 138.2, 129.5, 128.4, 127.6, 121.2, 121.1, 114.5, 109.9, 109.8, 74.9, 74.5, 74.0, 73.6, 68.7, 68.3, 67.8, 67.5, 22.9, 22.1; IR (neat): υ 2984, 1599, 1495, 1242, 1047 cm^{-1}; Anal.Calc'd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05; Found: C, 72.45; H, 7.15.



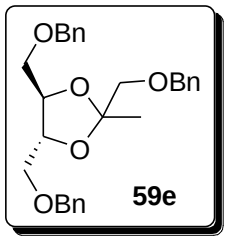
2,4-Bis(benzyloxymethyl)-2-methyl-1,3-dioxolane (59d):

Prepared from **21e** and benzyl protected propargyl alcohol **58** by following GP-VI; Colourless liquid; Yield = 88%; R_f = 0.53 in 1:5 EtOAc/hexanes; dr: 1.0:1.2; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.35-7.28 (m, 20H), 4.63-4.54 (m, 8H), 4.41-4.33 (m, 2H), 4.17-4.09 (m, 2H), 3.83-3.77 (m, 2H), 3.61-3.57 (m, 2H), 3.52-3.42 (m, 3H), 1.44-1.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 138.0, 128.4, 128.3, 127.7, 127.6 , 109.6, 109.5, 75.6, 75.1, 74.1, 73.5, 71.1, 70.7, 67.7, 67.5, 22.9, 22.0; IR (neat): υ 2986, 2864, 1724, 1496, 1101, 856 cm^{-1}; Anal.Calc'd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37; Found: C, 73.24; H, 7.34



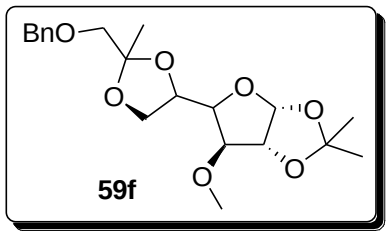
2,4,5-Tris(benzyloxymethyl)-2-methyl-1,3-dioxolane (59e):

Prepared from **21l** and benzyl protected propargyl alcohol **58** by following GP-VI; Colourless liquid; Yield = 82%; R_f = 0.32 in 1:5 EtOAc/hexanes; dr: 1.0:1.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 15H), 4.62-4.53 (m, 6H), 4.13-4.08 (m, 2H), 3.64 (dd, *J* = 8.8, 3.6 Hz, 4H), 3.48 (q, *J* = 10.4 Hz, 2H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.0, 128.4, 128.3, 127.7, 127.6, 109.8, 78.2, 77.8, 74.2, 73.6, 73.5, 70.5, 70.4, 23.2; IR (neat): υ 3030, 2984, 2918, 1371, 1248, 1101, 738 cm^{-1}; Anal.Calc'd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19; Found: C, 74.85; H, 7.26.



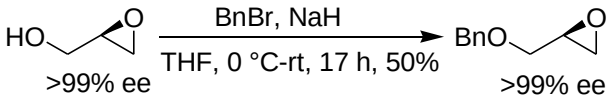
5-(2-(Benzyloxymethyl)-2-methyl-1,3-dioxolan-4-yl)-6-methoxy-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxole (59f):

Prepared from **21w** and benzyl protected propargyl alcohol **58** by following GP-VI; Colourless viscous liquid; Yield = 49%; R_f = 0.53 in 1:1 EtOAc/hexanes; dr: 1.0:1.1; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.33 (t, *J* = 3.2 Hz, 8H), 7.27 (t, *J* = 3.6 Hz, 2H), 5.97-5.96 (m, 2H), 4.65-4.56 (m, 6H), 4.42 (q, *J* = 7.6 Hz, 1H), 4.36 (t, *J* = 8.0 Hz, 1H), 4.24-4.12 (m, 4H), 3.72-3.67 (m, 2H), 3.65 (d, *J* = 3.6 Hz, 1H), 3.60 (d, *J* = 3.6 Hz, 1H), 3.49 (s, 2H), 3.44 (s, 2H), 3.34 (s, 6H), 1.49 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 128.3, 127.5, 111.8, 110.0, 105.5, 84.9, 84.8, 82.3, 81.9, 81.3, 76.2, 75.6, 74.2, 73.5, 73.4, 66.7, 66.6, 57.5, 26.9, 26.8, 22.9, 22.1; IR (neat): υ 2912, 1454, 1379, 1020, 738 cm^{-1}; Anal.Calc'd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42; Found: C, 63.22; H, 7.37.



59f

(S)-2-(Benzyloxymethyl)oxirane (21x):[76a]

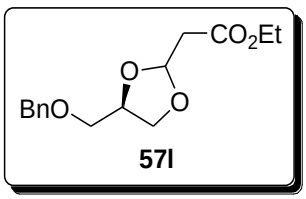


>99% ee **100** >99% ee **21x**

Prepared from (R)-glycidol using GP-II; Yield = 50% and >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.34 (m, 4H), 7.31-7.25 (m, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 3.76 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.44 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.20-3.16 (m, 1H), 2.79 (dd, *J* = 5.2, 4.4 Hz, 1H), 2.63 (dd, *J* = 5.2, 2.8 Hz, 1H).

Ethyl 2-((4R)-4-(benzyloxymethyl)-1,3-dioxolan-2-yl)acetate (57l):

Prepared from **21x** and ethyl propiolate **56** using GP-VI; Yield = 84%; Yellow liquid; R_f = 0.42 in 1:5 EtOAc/hexanes; dr: 1.0:1.1; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.37-7.28 (m, 10H), 5.42 (t, *J* = 5.2 Hz, 1H), 5.31 (t, *J* = 5.2, 1H), 4.60-4.54 (m, 4H), 4.36-4.25 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.14-4.12 (m, 1H), 3.96 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.83 (dd, *J* = 8.4, 5.2 Hz, 1H),

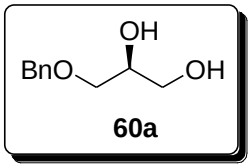


57l

3.72 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.58 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.56 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.51 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.46 (dd, *J* = 9.6, 5.6 Hz, 1H), 2.74 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.71 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.67 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.64 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 137.8, 128.4, 127.7, 101.4, 101.2, 75.1, 74.8, 73.5, 70.6, 70.1, 67.5, 60.7, 40.0, 14.1; IR (neat): υ 2895, 1738, 1370, 1312, 1256, 1181, 1138, 849, 741, 698 cm^{-1}; Anal.Calc'd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; Found: C, 64.38; H, 7.15.

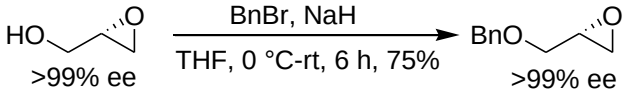
(S)-3-(Benzyloxy)propane-1,2-diol (60a):[77]

Prepared from **57l** using GP-VII; Yield = 54% and ee = 42%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.33 (m, 5H), 4.55 (s, 2H), 3.91-3.87 (m, 1H), 3.72-3.69 (m, 1H), 3.65-3.52 (m, 3H), 2.74 (br s, 1H), 2.27 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 128.5, 127.9, 127.8, 73.6, 71.8, 70.6, 64.1.



60a

(R)-2-(Benzyloxymethyl)oxirane (21y):[76b]

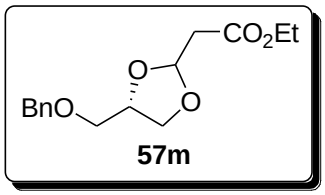


101 **21y**

Prepared from (S)-glycidol using GP-II; Yiled = 75% and >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.35 (m, 4H), 7.32-7.27 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 3.77 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.44 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.21-3.18 (m, 1H), 2.81 (dd, *J* = 4.8, 4.4 Hz, 1H), 2.62 (dd, *J* = 4.8, 2.8 Hz, 1H).

Ethyl 2-((4S)-4-(benzyloxymethyl)-1,3-dioxolan-2-yl)acetate (57m):

Prepared from **21y** and ethylpropiolate **56** using GP-VI; Yield = 93%; Yellow liquid; R_f = 0.39 in 1:10 EtOAc/hexanes; dr: 1.0:1.1; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.37-7.28 (m, 10H), 5.42 (t, *J* = 5.2 Hz, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.61-4.53 (m, 4H), 4.36-4.25 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.14-4.12 (m, 1H), 3.96 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.83 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.72 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.59 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.56 (dd, *J* = 8.0, 5.6 Hz, 1H),

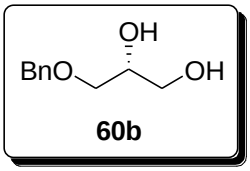


57m

3.51 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.46 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.74 (dd, *J* = 11.2, 5.2 Hz, 1H), 2.71 (dd, *J* = 6.8, 5.2 Hz, 1H), 2.67 (dd, *J* = 10.4, 6.0 Hz, 1H), 2.64 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 137.8, 128.4, 127.8, 127.7, 101.5, 101.2, 75.2, 74.9, 73.6, 73.5, 70.6, 70.2, 67.6, 60.8, 60.7, 40.1, 40.0, 14.2; IR (neat): υ 2895, 1738, 1370, 1310, 1254, 1184, 849, 741, 700 cm^{-1}; Anal.Calc'd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; Found: C, 64.15; H, 7.23.

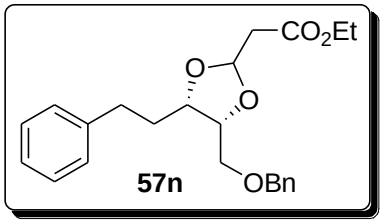
(R)-3-(Benzyloxy)propane-1,2-diol (60b):[77]

Prepared from **57m** using GP-VII; Yield = 75%; and ee = 49%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.31 (m, 5H), 4.57 (s, 2H), 3.93-3.89 (m, 1H), 3.72 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.64 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.60 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.56 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.87 (br s, 1H), 2.42 (br, s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.7, 128.5, 127.9, 127.8, 73.6, 71.8, 70.6, 64.1.



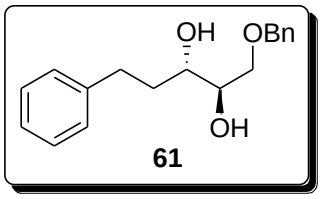
Ethyl 2-((4R,5S)-4-(benzyloxymethyl)-5-phenethyl-1,3-dioxolan-2-yl)acetate (57n):

Prepared from **21r** and ethyl propiolate **56** by following GP-VI; Yield = 88%; Yellow viscous liquid; R_f = 0.52 in 1:5 EtOAc/hexanes (double run); dr: 7.3:1.0; ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of major and minor isomers) δ 7.33-7.23 (m, 14H), 7.21-7.15 (m, 6H), 5.63 (t, *J* = 5.2 Hz, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 2H), 4.48 (d, *J* = 12.0 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 4H), 4.17-4.16 (m, 3H), 4.03 (q, *J* = 6.4 Hz, 1H), 3.57-3.54 (m, 2H), 3.50 (dd, *J* = 6.0, 2.4 Hz, 2H), 2.88-2.81 (m, 2H), 2.71 (d, *J* = 4.8 Hz, 2H), 2.69-2.67 (m, 2H), 2.67-2.62 (m, 2H), 1.85-1.80 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 141.4, 137.7, 128.4, 128.3, 127.7(2C), 125.9, 100.2, 77.7, 76.7, 76.6, 73.4, 68.6, 67.8, 60.6, 40.7, 40.6, 32.4, 30.9, 30.0, 14.1; IR (neat): υ 3443, 2930, 1952, 1877, 1738, 1603, 1369, 1109, 849, 744, 700 cm^{-1}; Anal.Calc'd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; Found: C, 71.96; H, 7.28.



(2R,3S)-1-(Benzyloxy)-5-phenylpentane-2,3-diol (**61**)**:**

Prepared from **57n** by following GP-VII; Colourless viscous liquid; Yield = 59% and ee = 40%; R_f = 0.53 in 1:1 EtOAc/hexanes (double run); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 7H), 7.20-7.18 (m, 3H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 3.76-3.71 (m, 2H), 3.65-3.64 (m, 2H), 2.93-2.86 (m, 1H), 2.79-2.78 (m, 1H), 2.71-2.64 (m, 1H), 2.43-2.42 (m, 1H), 1.80-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 137.5, 128.6, 128.5, 128.4, 128.0, 127.9, 125.9, 73.7, 72.5 (2C), 71.0, 34.6, 32.2; IR (neat): υ 3354, 3028, 1454, 1368, 1310, 1113, 1061, 744, 696 cm^{-1}; Anal.Calc'd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; Found: C, 75.61; H, 7.63.



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1.9 *Representative spectra - I*

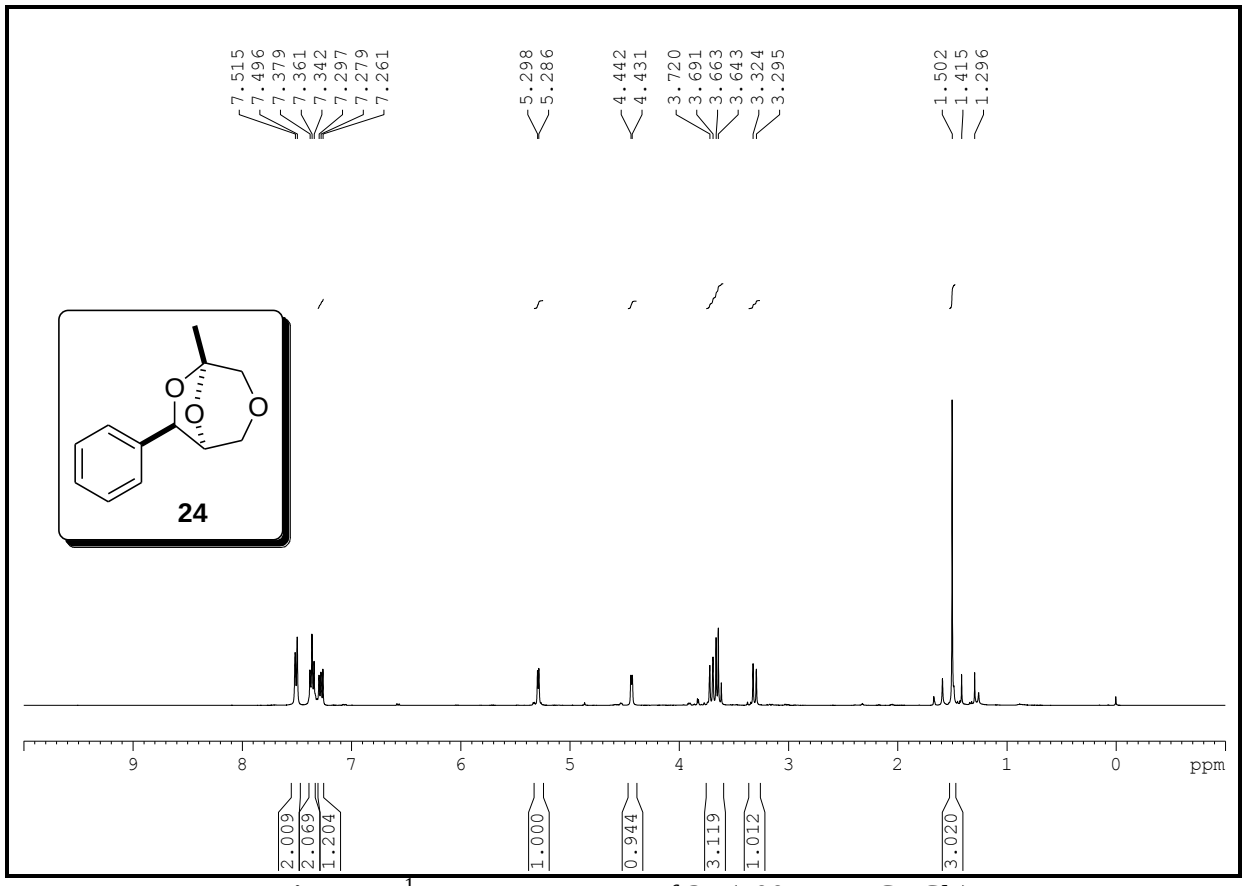


Figure 4. ^{1}H NMR spectrum of **24** (400 MHz, $CDCl_3$)

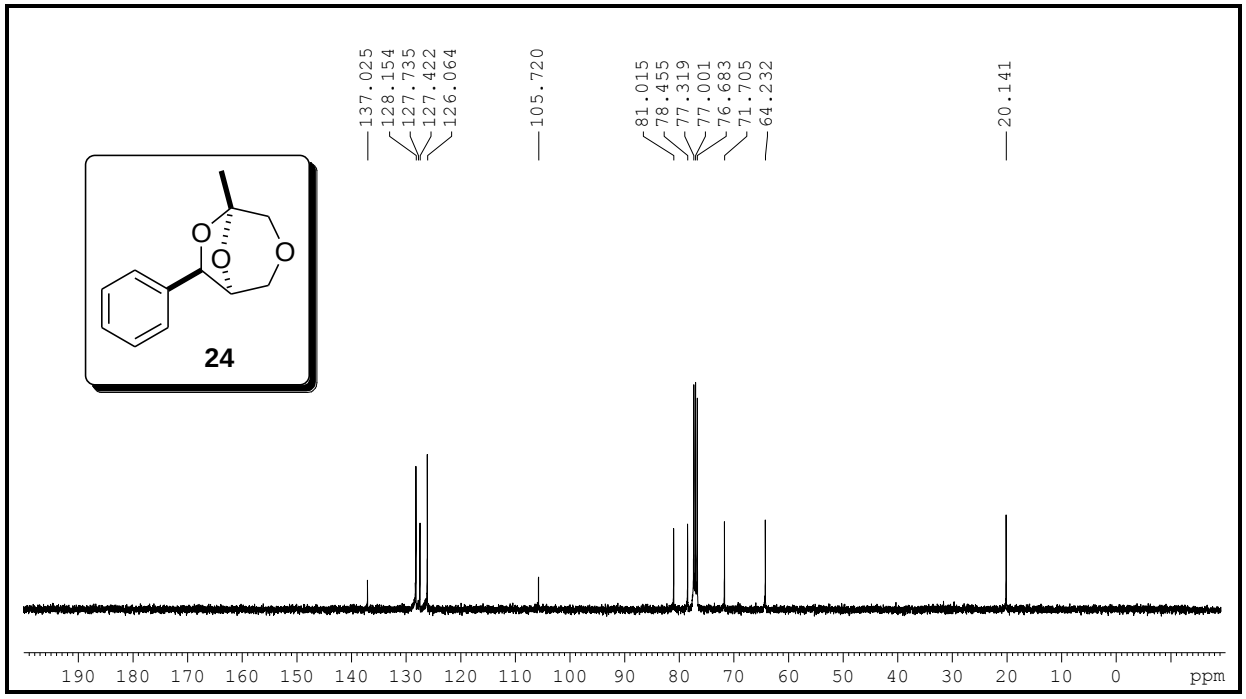


Figure 5. ^{13}C NMR spectrum of **24** (100 MHz, $CDCl_3$)

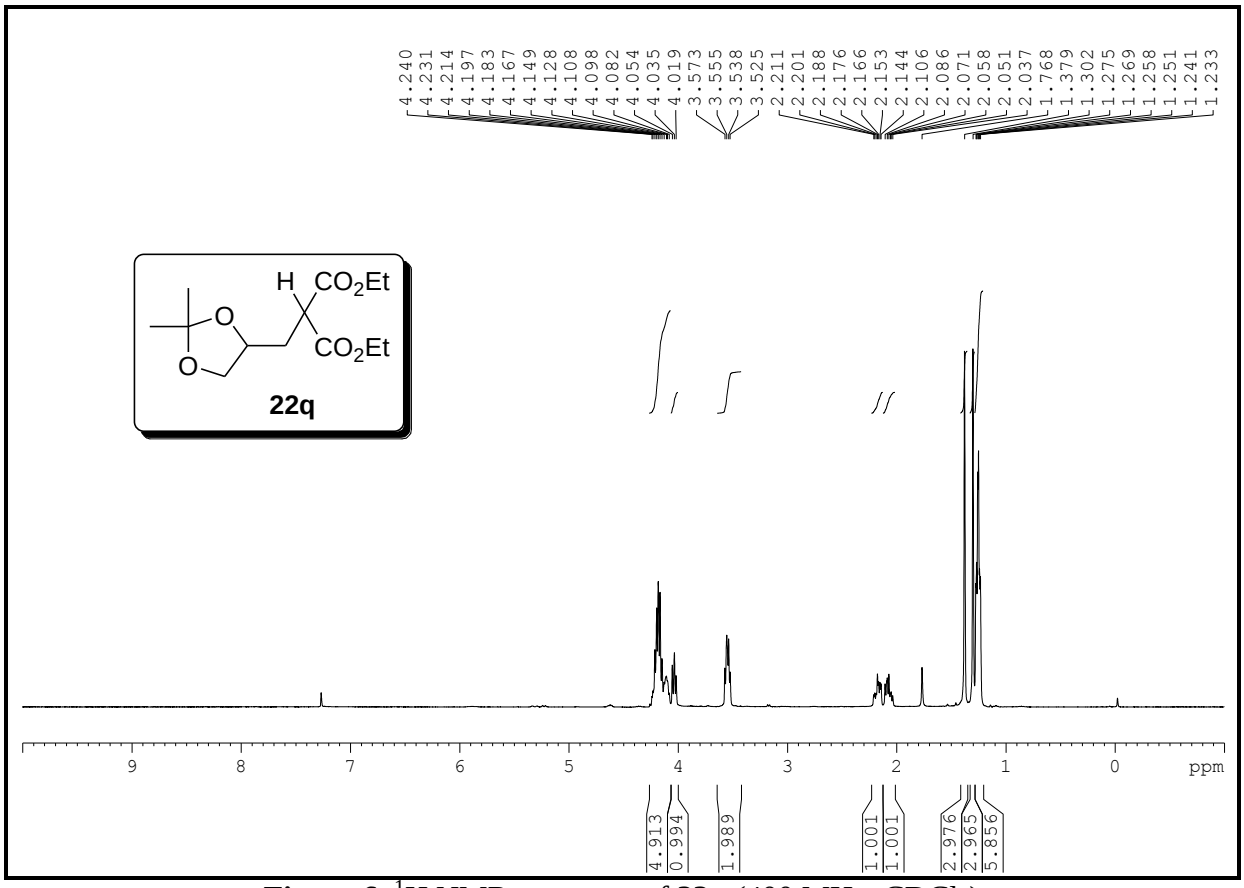


Figure 6. ^{1}H NMR spectrum of **22q** (400 MHz, $CDCl_3$)

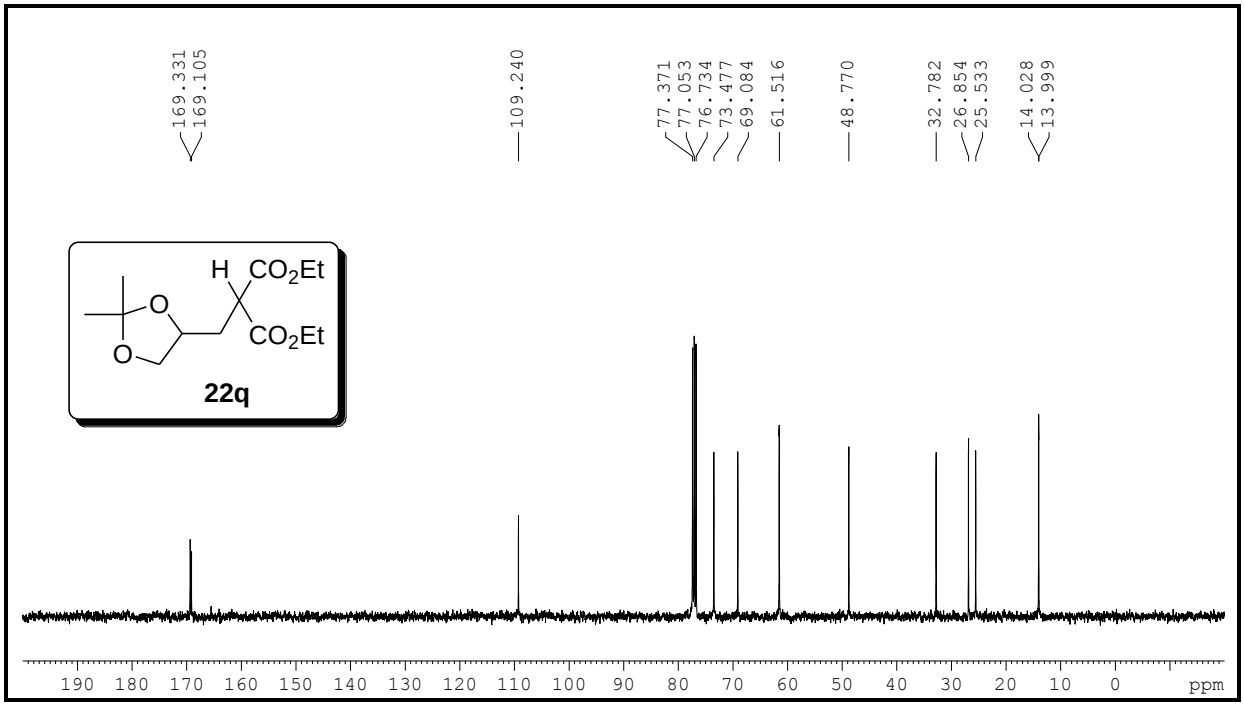


Figure 7. ^{13}C NMR spectrum of **22q** (100 MHz, $CDCl_3$)

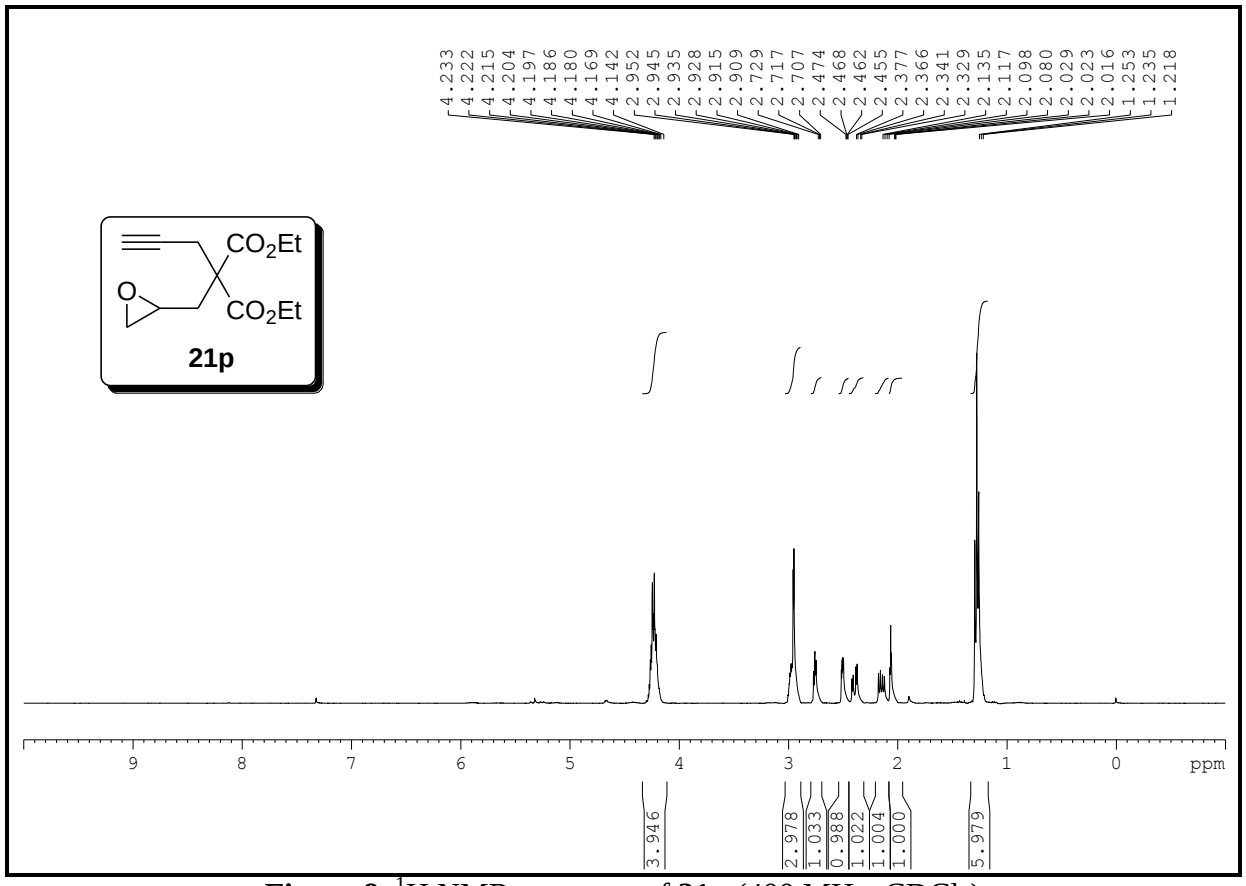


Figure 8. ^{1}H NMR spectrum of **21p** (400 MHz, $CDCl_3$)

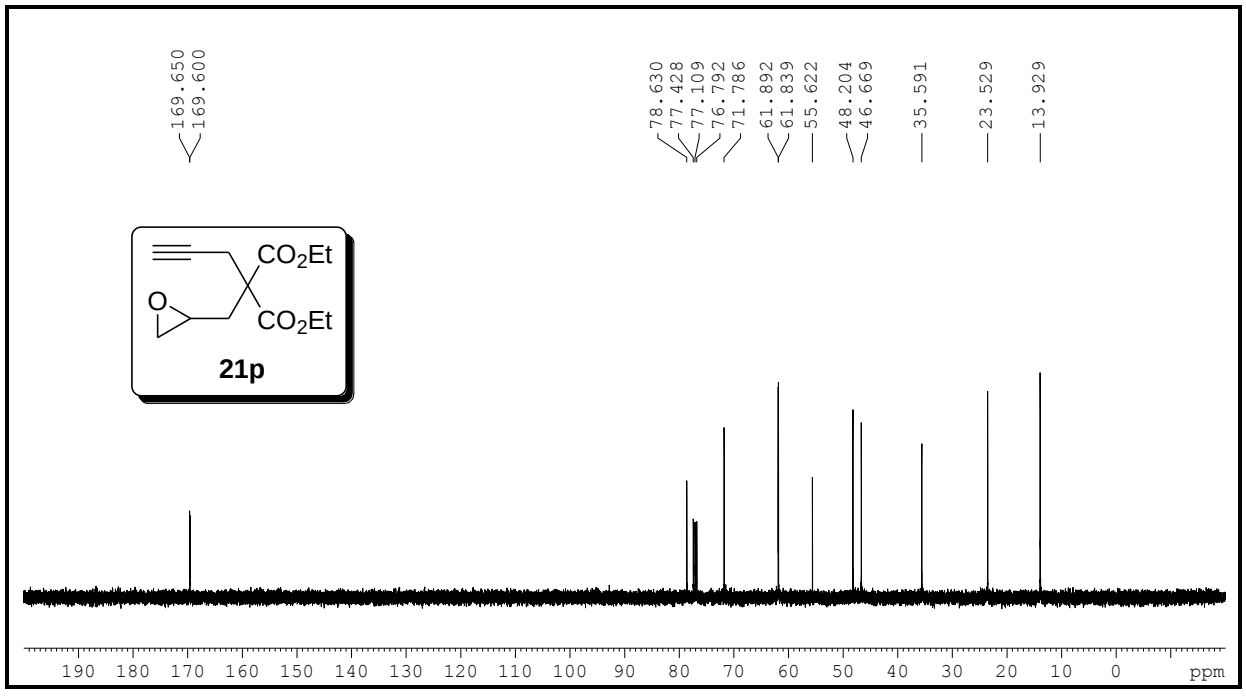


Figure 9. ^{13}C NMR spectrum of **21p** (100 MHz, $CDCl_3$)

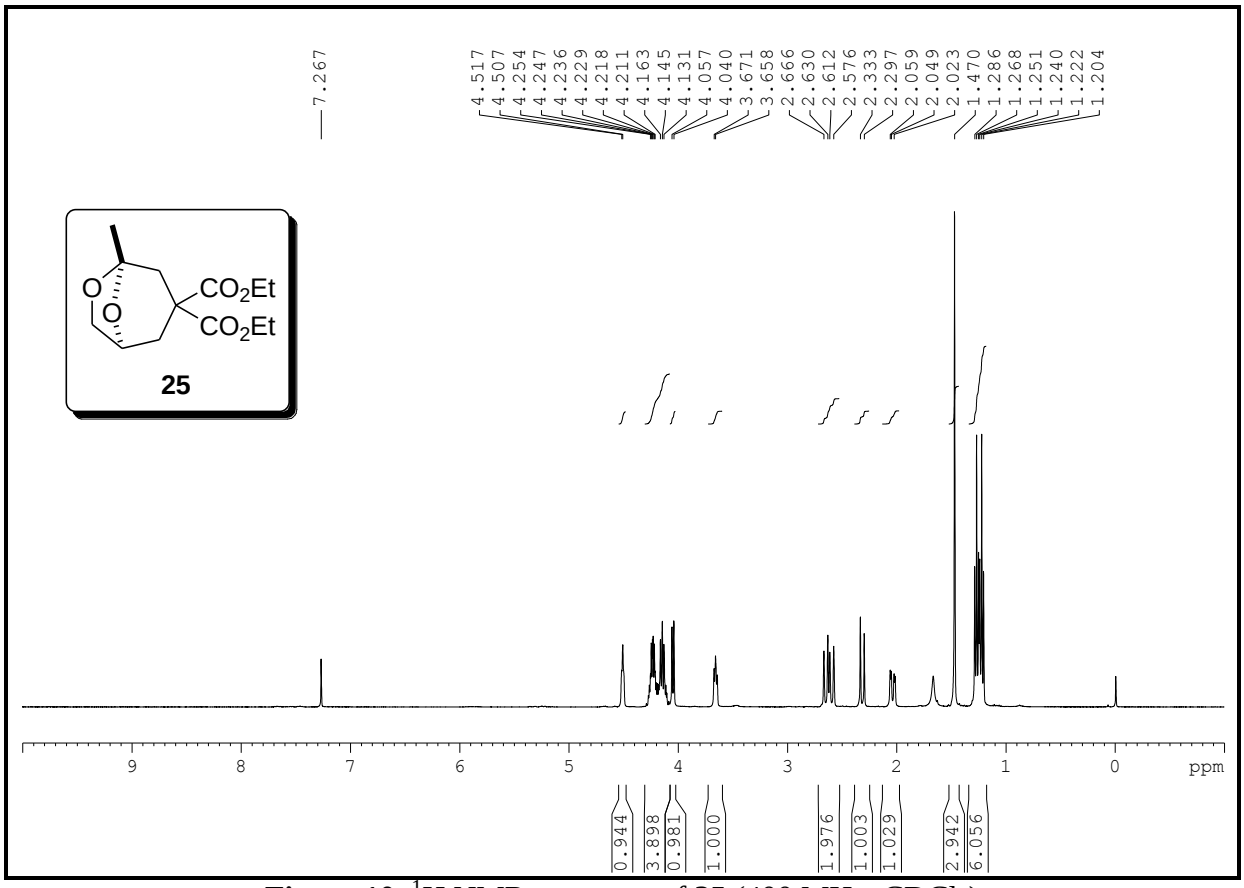


Figure 10. ^{1}H NMR spectrum of **25** (400 MHz, $CDCl_3$)

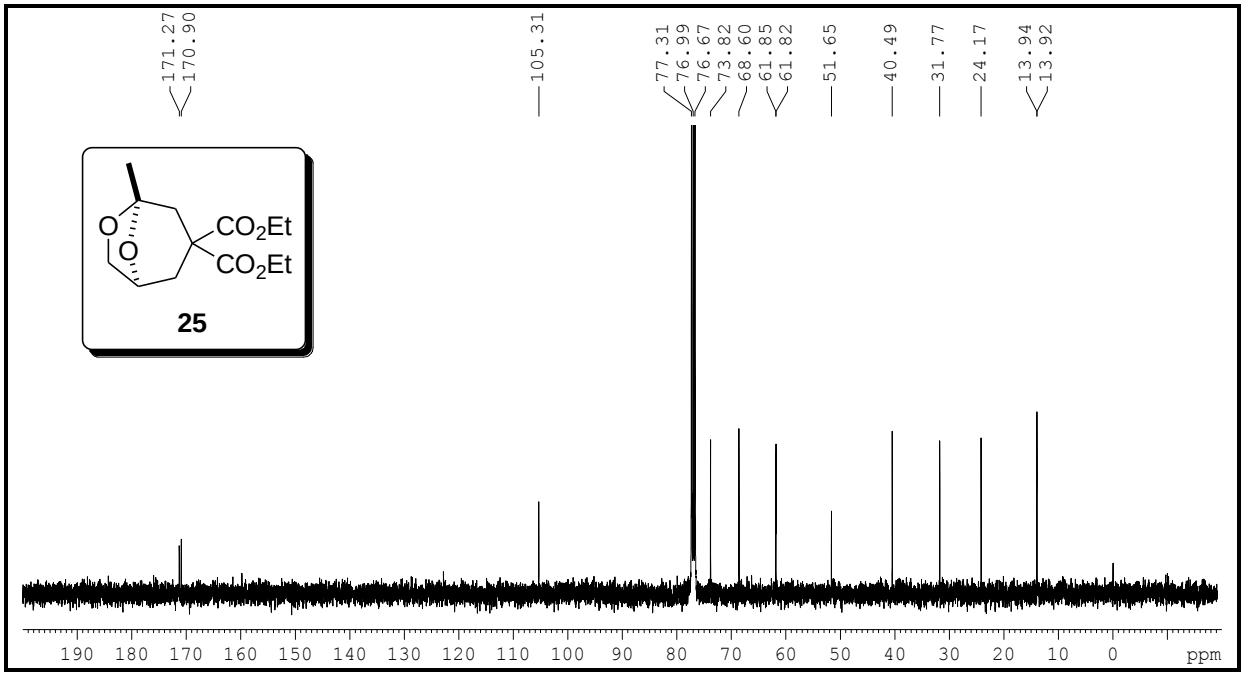


Figure 11. ^{13}C NMR spectrum of **25** (100 MHz, $CDCl_3$)

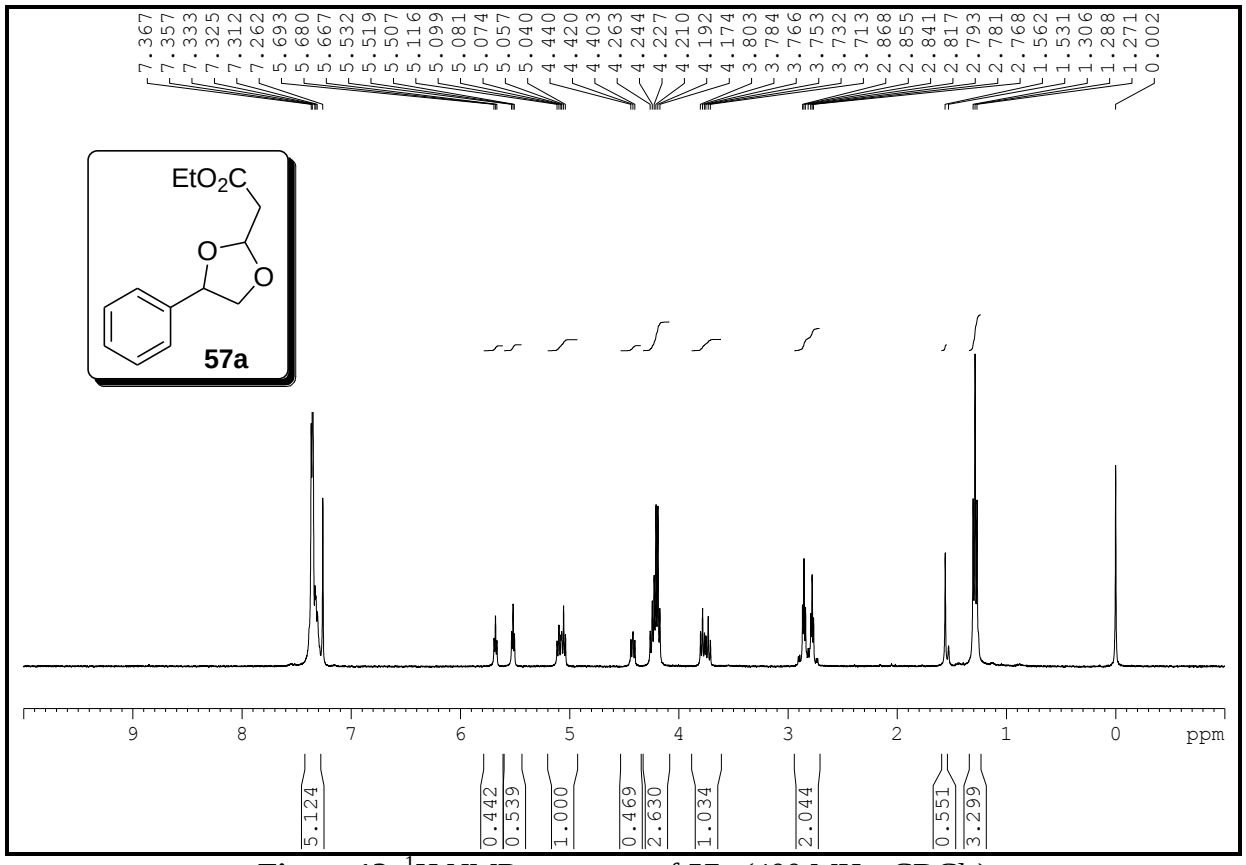


Figure 12. ^{1}H NMR spectrum of **57a** (400 MHz, $CDCl_3$)

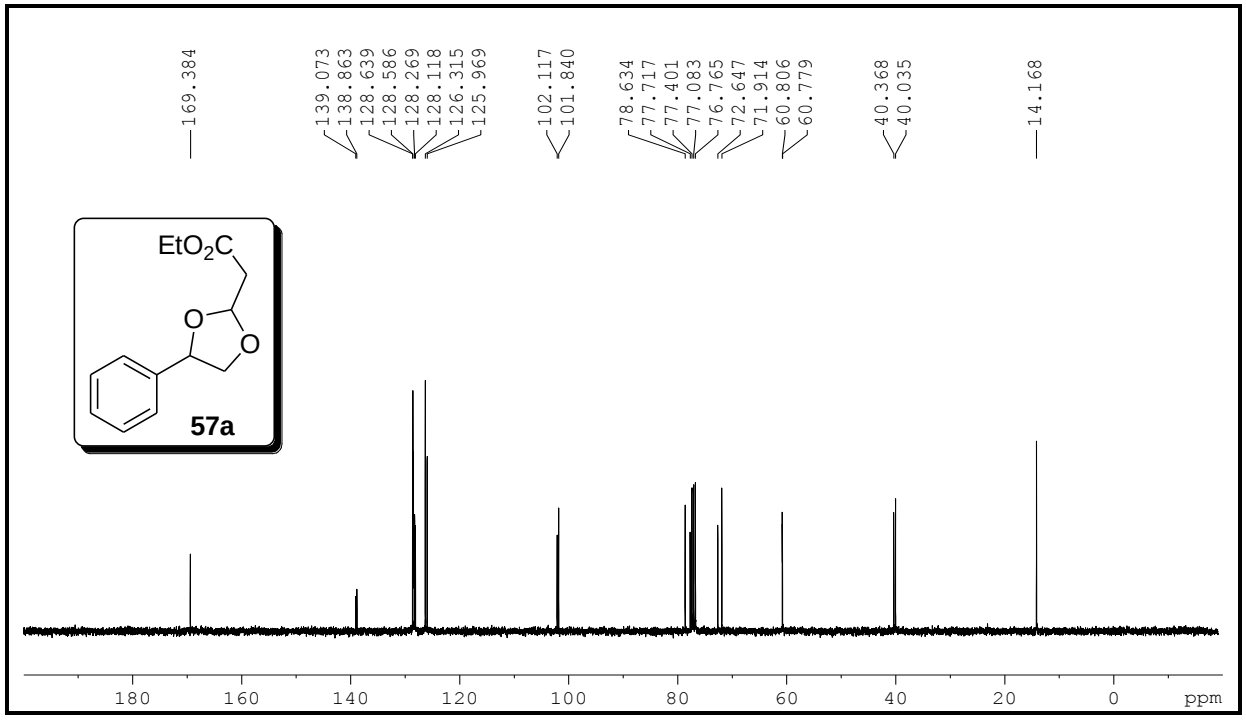


Figure 13. ^{13}C NMR spectrum of **57a** (100 MHz, $CDCl_3$)

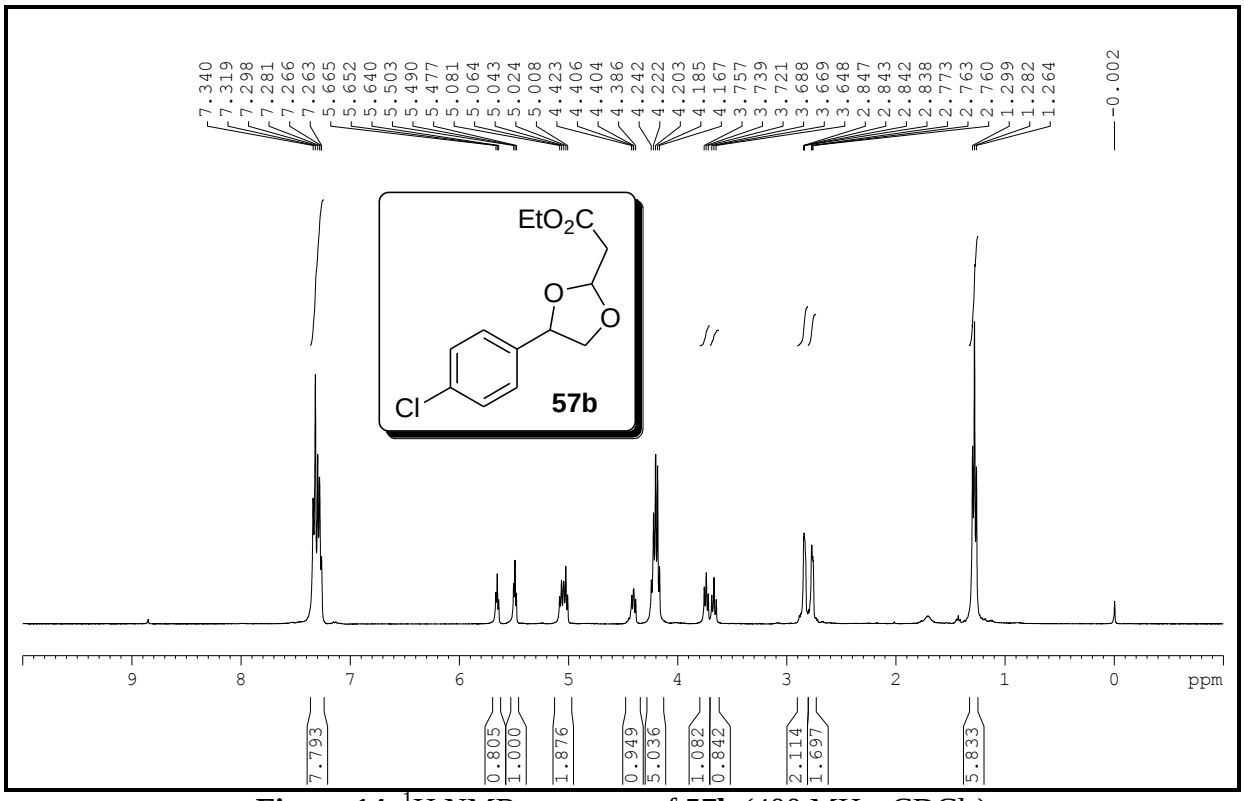


Figure 14. ^{1}H NMR spectrum of **57b** (400 MHz, $CDCl_3$)

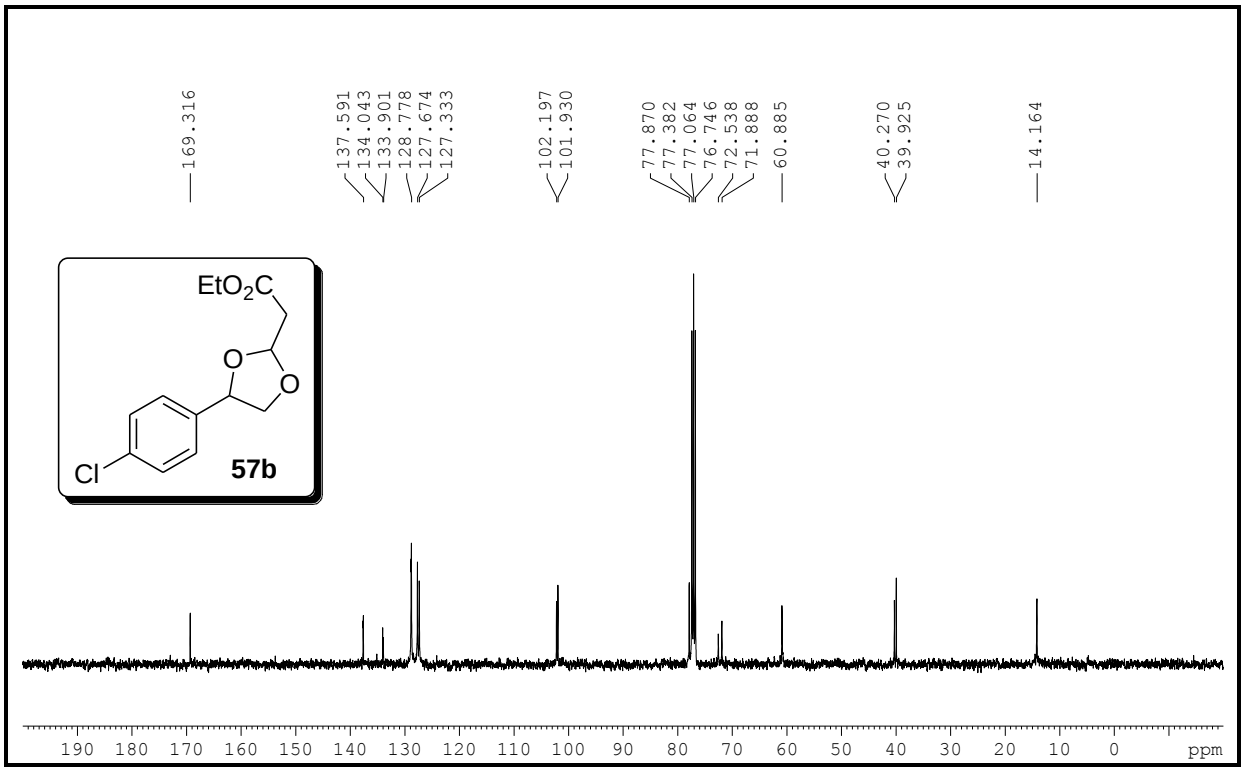


Figure 15. ^{13}C NMR spectrum of **57b** (100 MHz, $CDCl_3$)

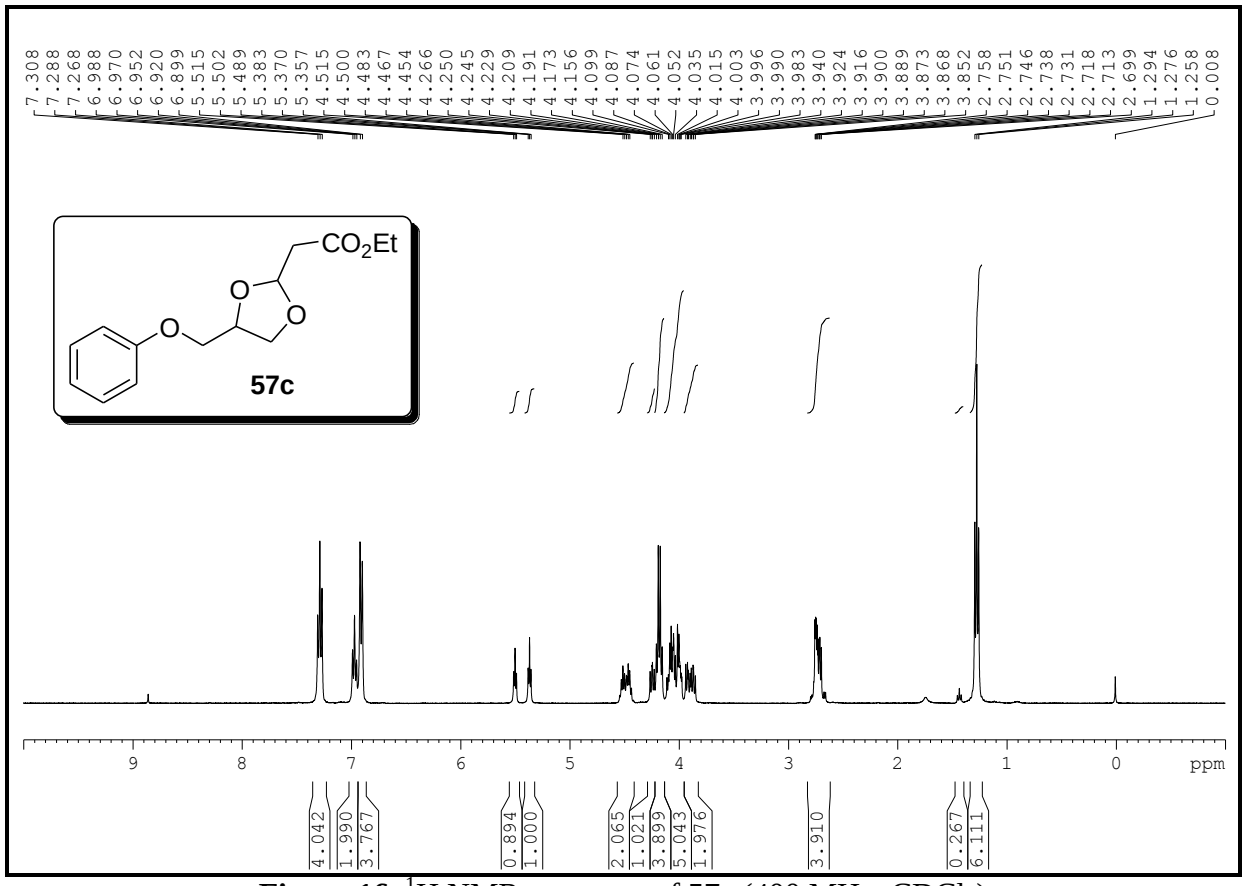


Figure 16. ^{1}H NMR spectrum of **57c** (400 MHz, $CDCl_3$)

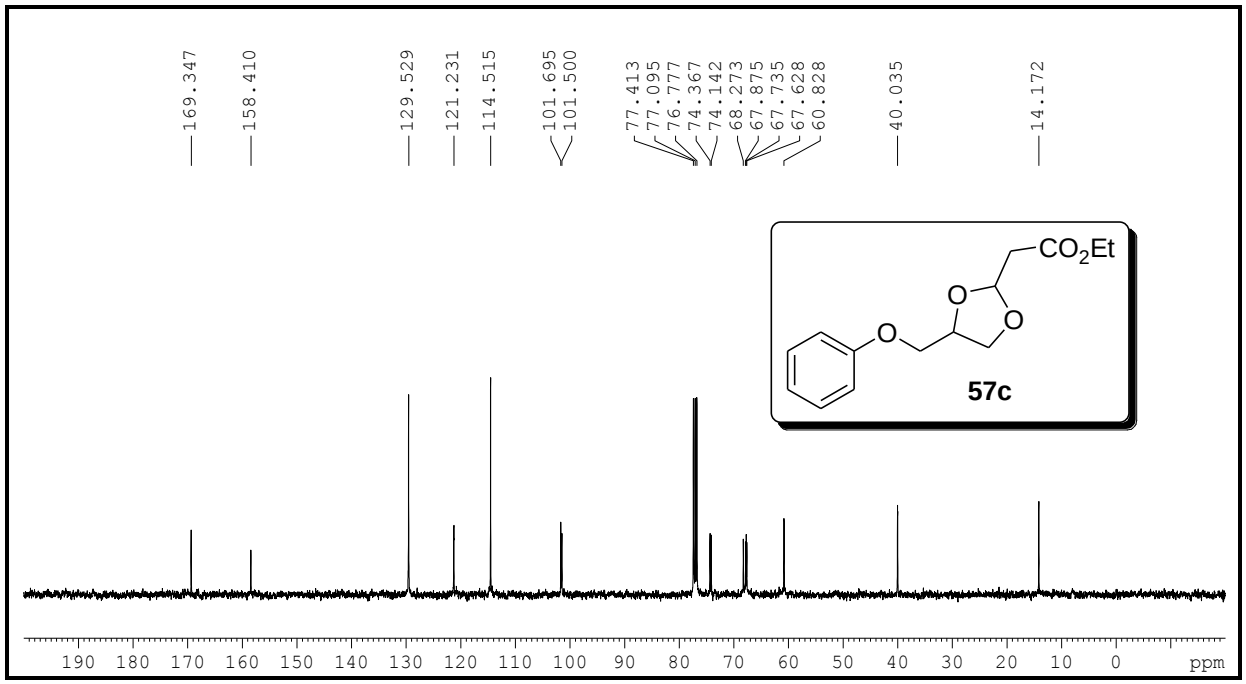


Figure 17. ^{13}C NMR spectrum of **57c** (100 MHz, $CDCl_3$)

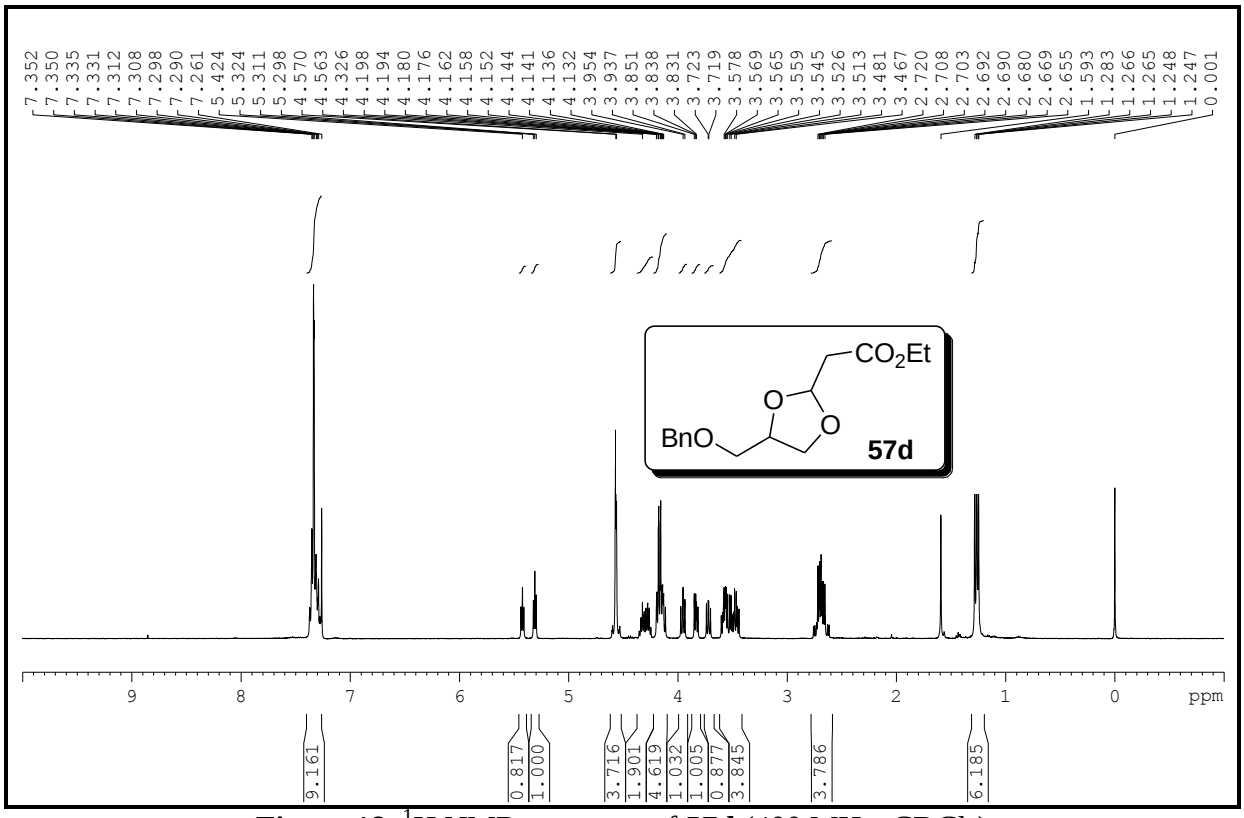


Figure 18. ^{1}H NMR spectrum of **57d** (400 MHz, $CDCl_3$)

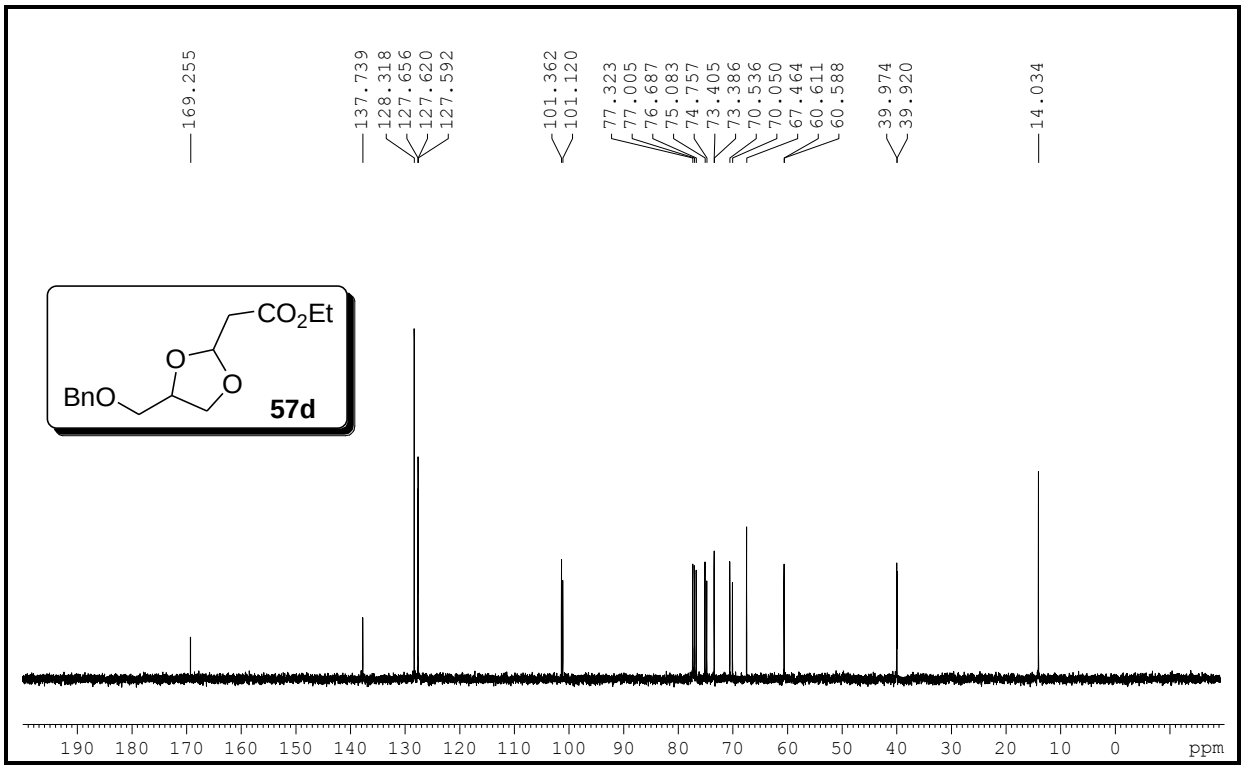


Figure 19. ^{1}H NMR spectrum of **57d** (100 MHz, $CDCl_3$)

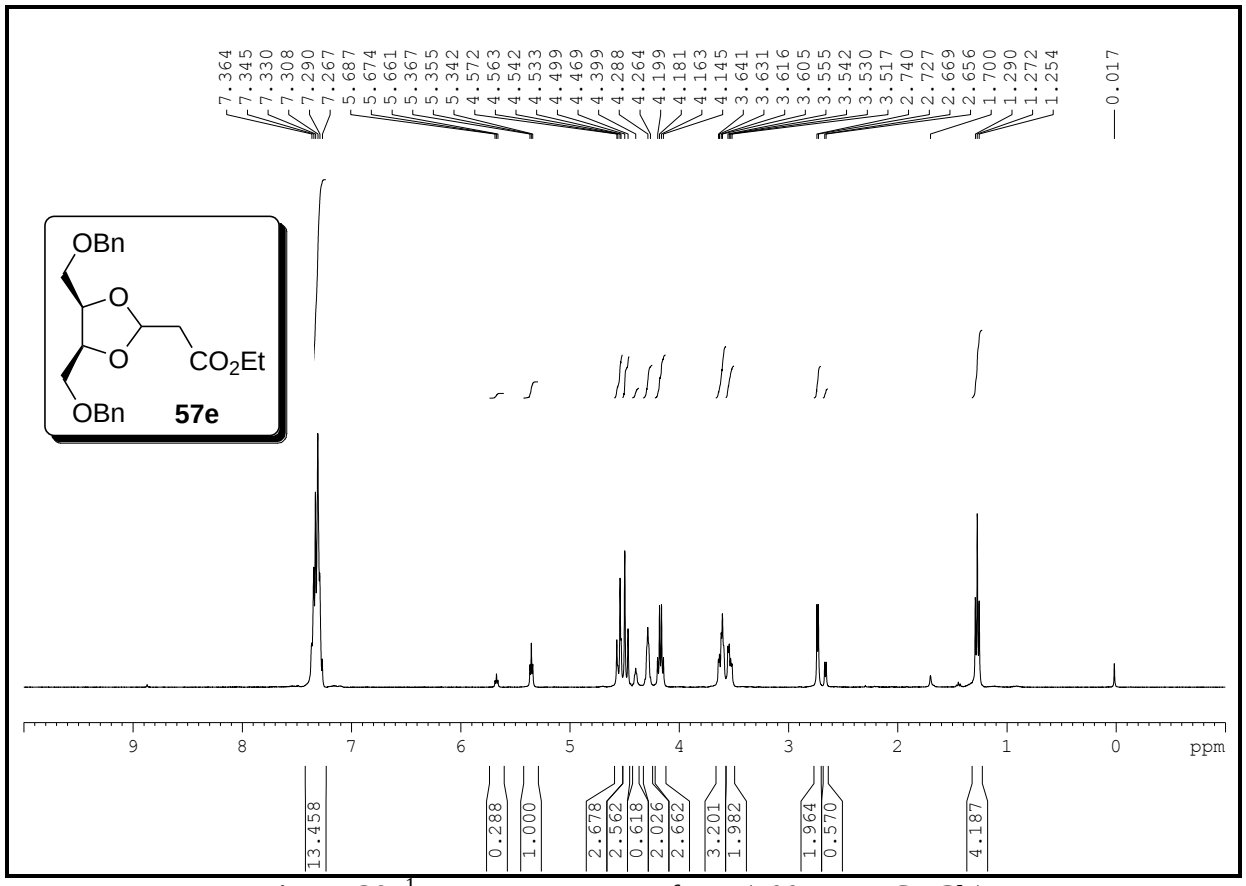


Figure 20. ^{1}H NMR spectrum of **57e** (400 MHz, $CDCl_3$)

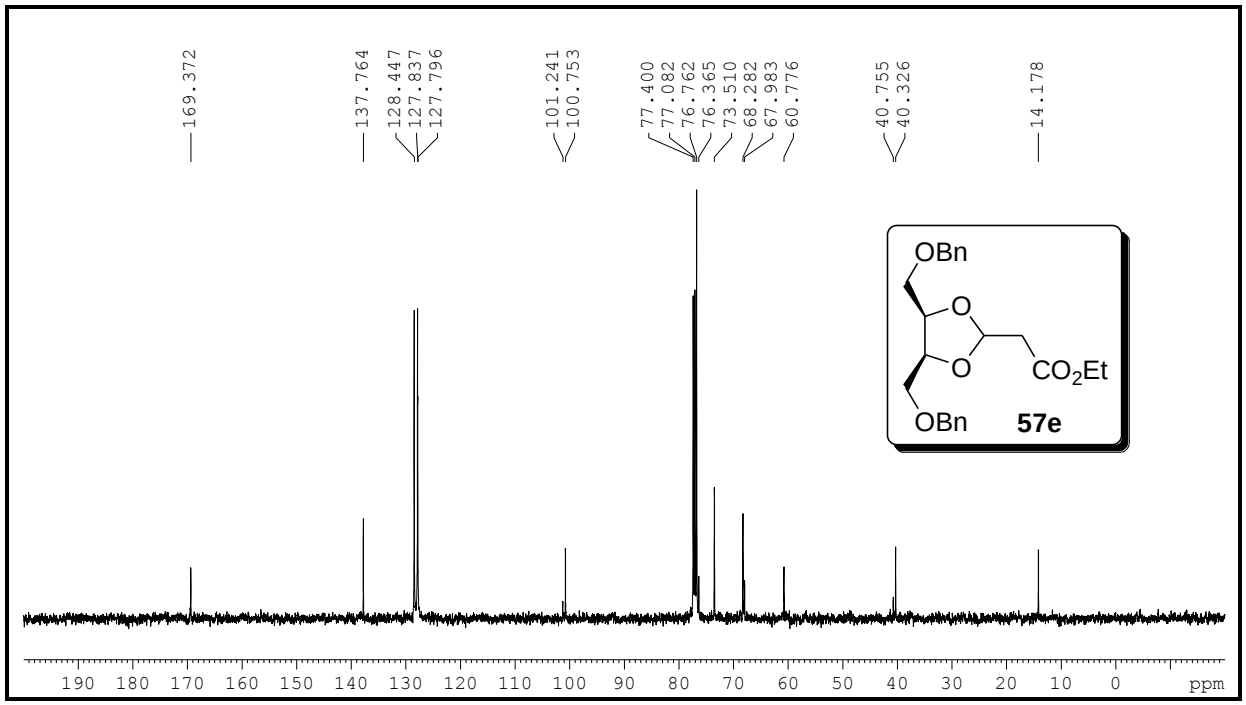


Figure 21. ^{13}C NMR spectrum of **57e** (100 MHz, $CDCl_3$)

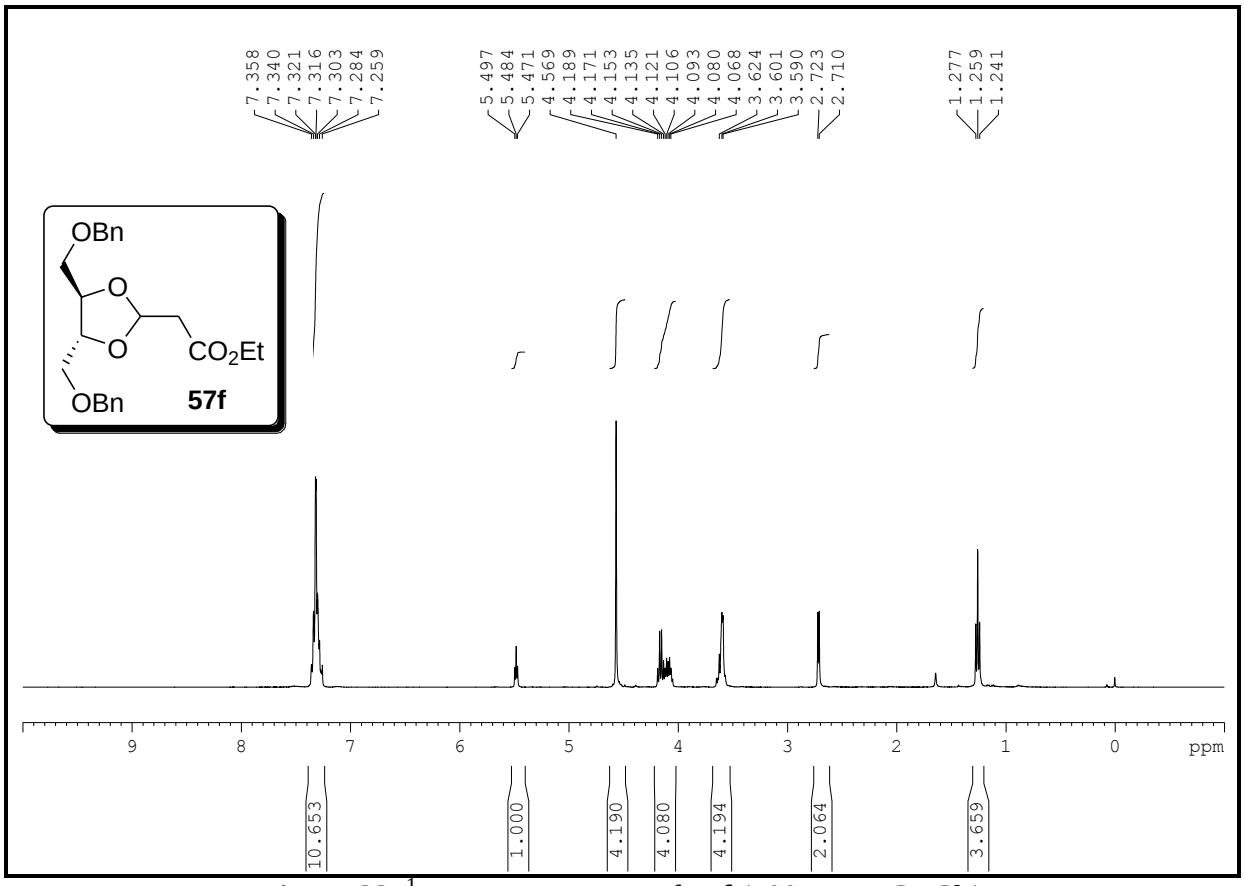


Figure 22. ^{1}H NMR spectrum of **57f** (400 MHz, $CDCl_3$)

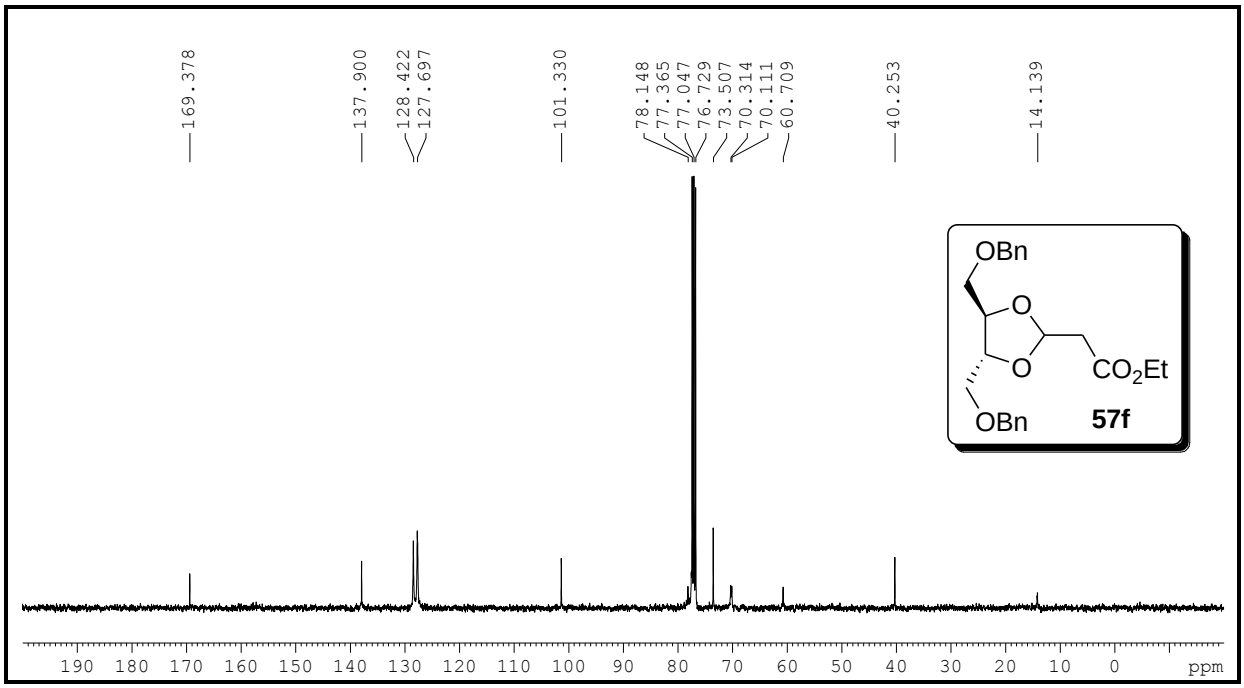


Figure 23. ^{13}C NMR spectrum of **57f** (100 MHz, $CDCl_3$)

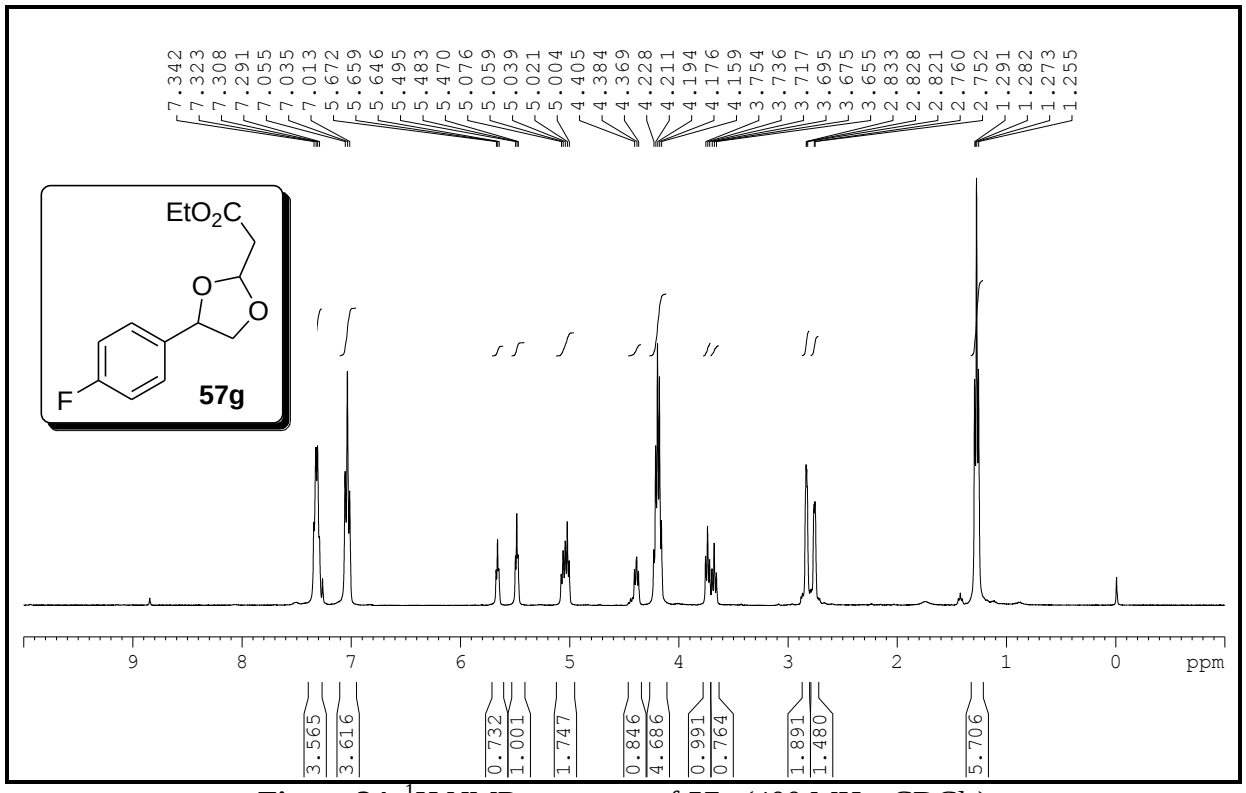


Figure 24. ^{1}H NMR spectrum of **57g** (400 MHz, $CDCl_3$)

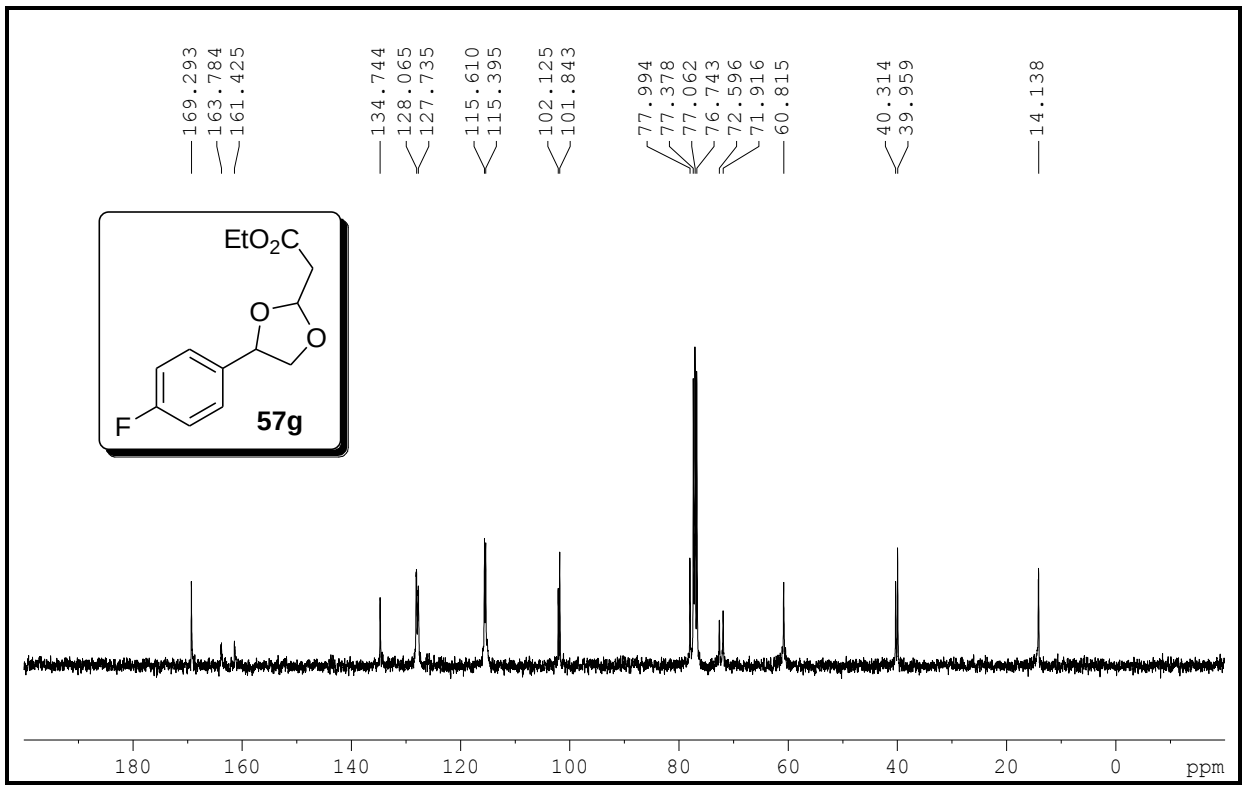


Figure 25. ^{13}C NMR spectrum of **57g** (100 MHz, $CDCl_3$)

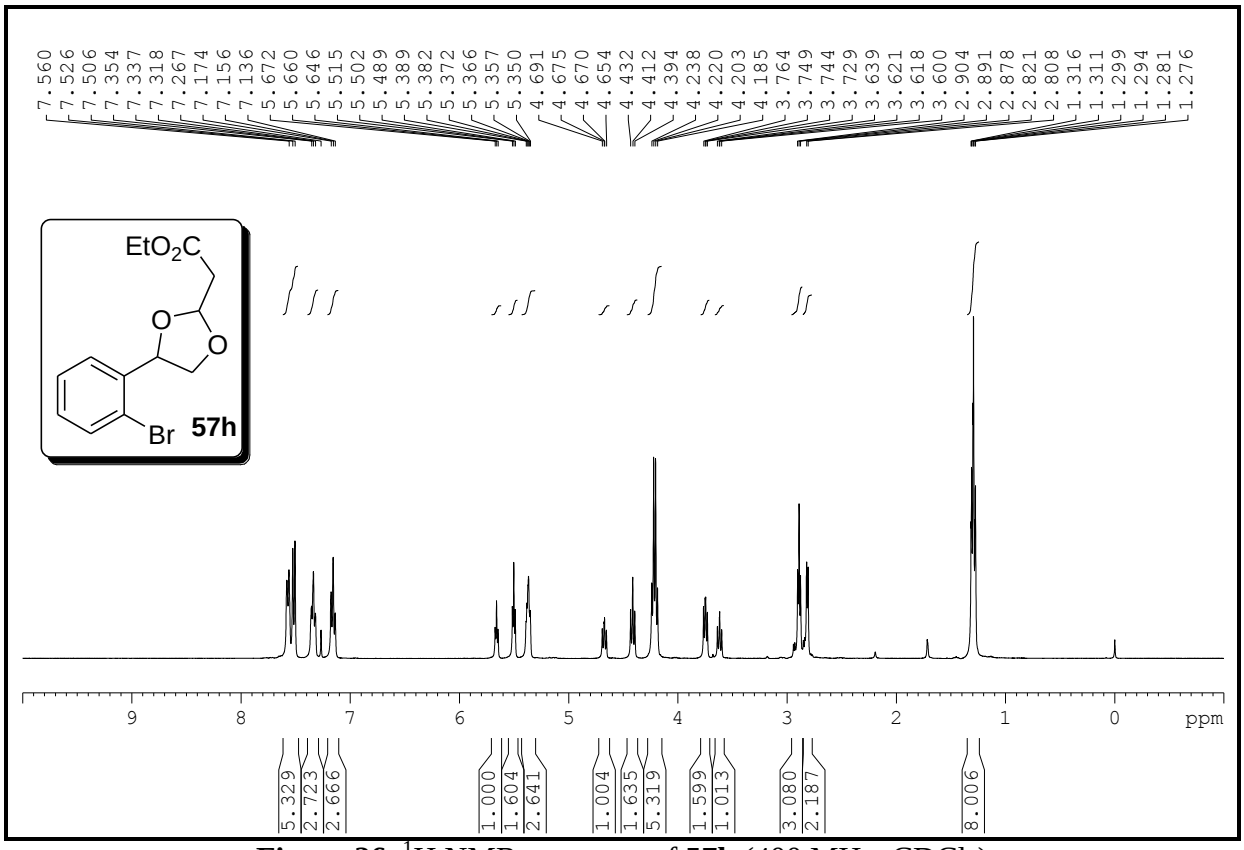


Figure 26. ^{1}H NMR spectrum of **57h** (400 MHz, $CDCl_3$)

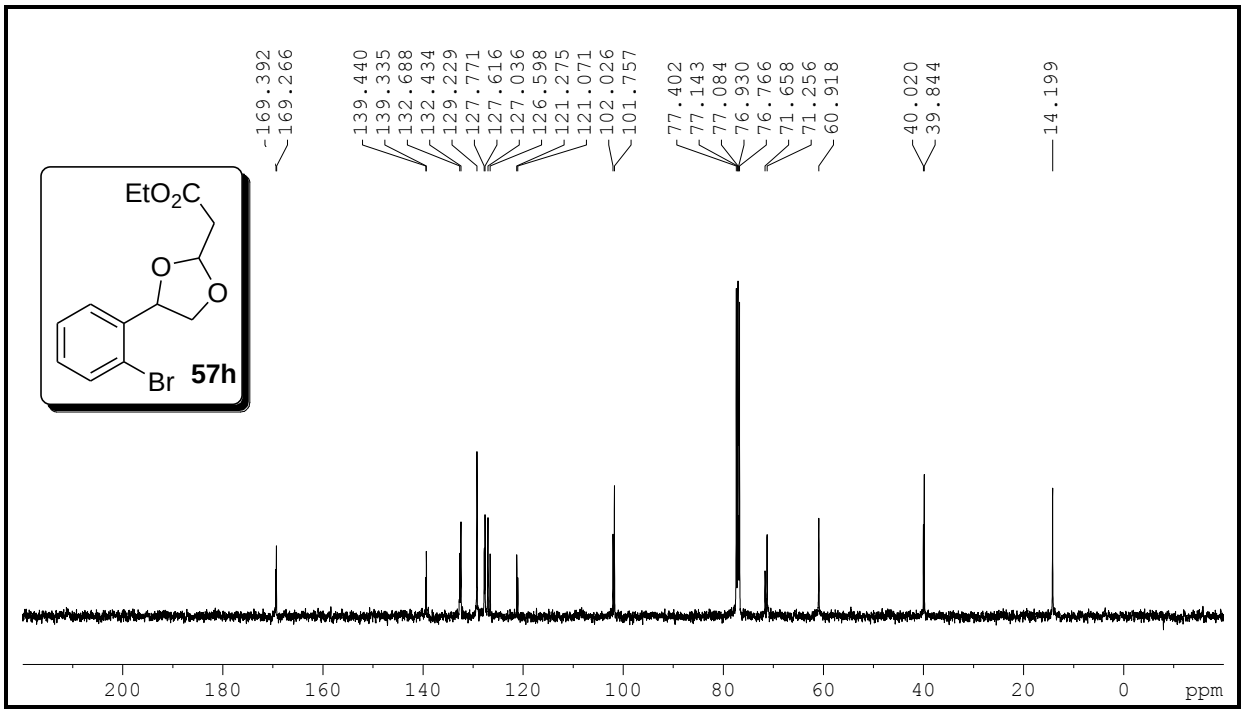


Figure 27. ^{13}C NMR spectrum of **57h** (100 MHz, $CDCl_3$)

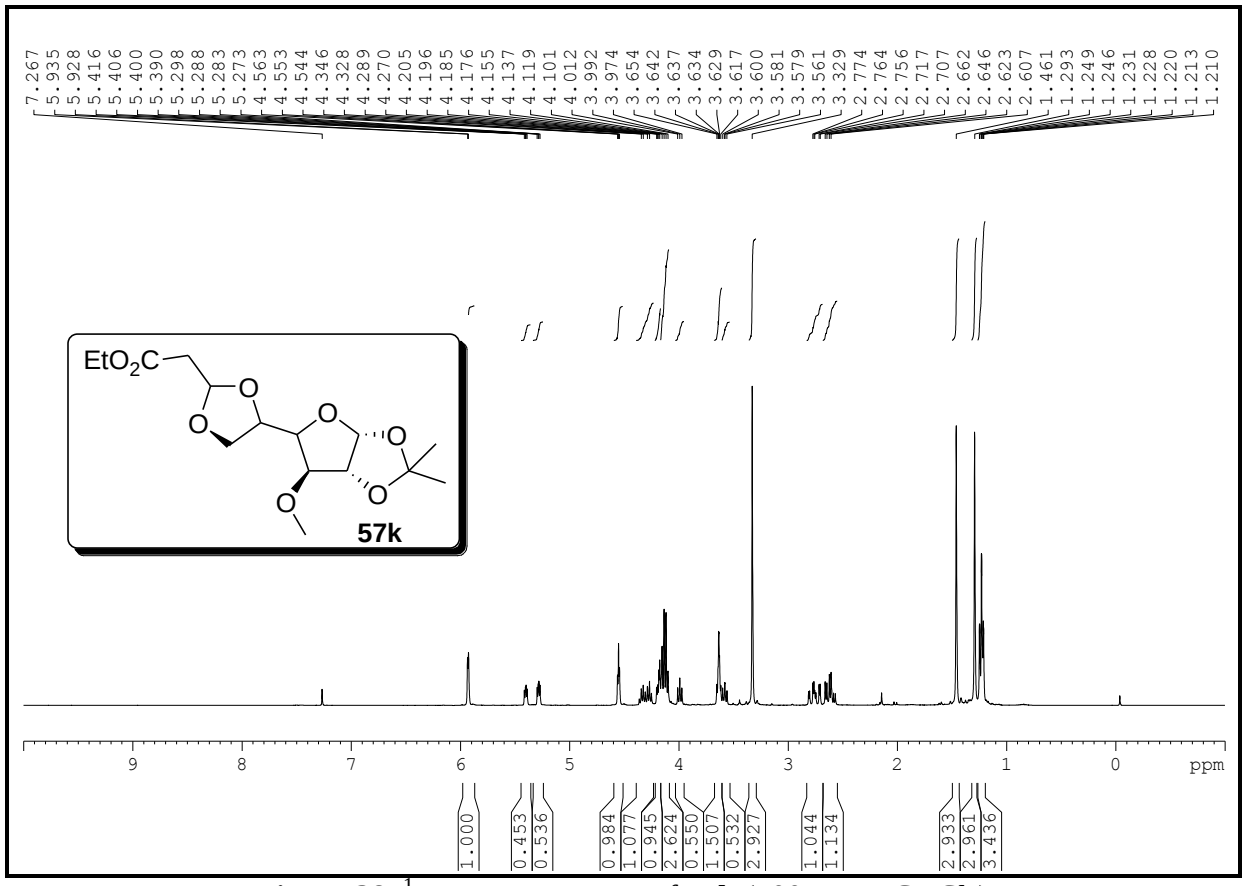


Figure 28. ^{1}H NMR spectrum of **57k** (400 MHz, $CDCl_3$)

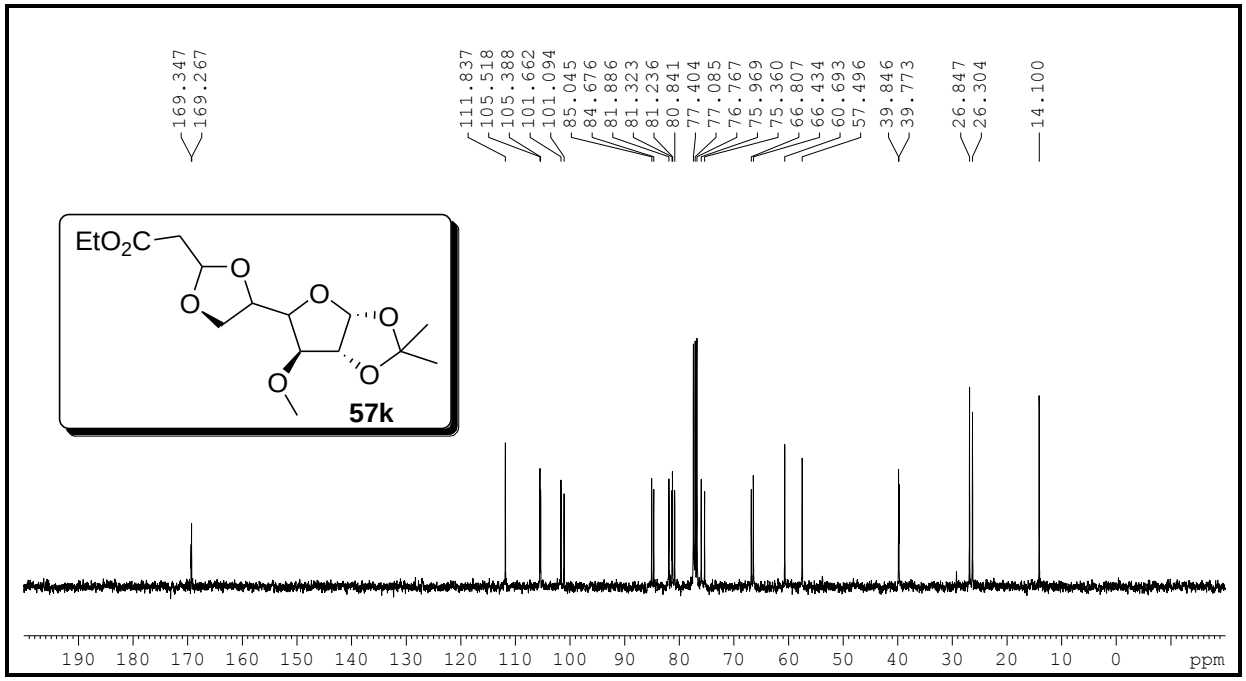


Figure 29. ^{13}C NMR spectrum of **57k** (100 MHz, $CDCl_3$)

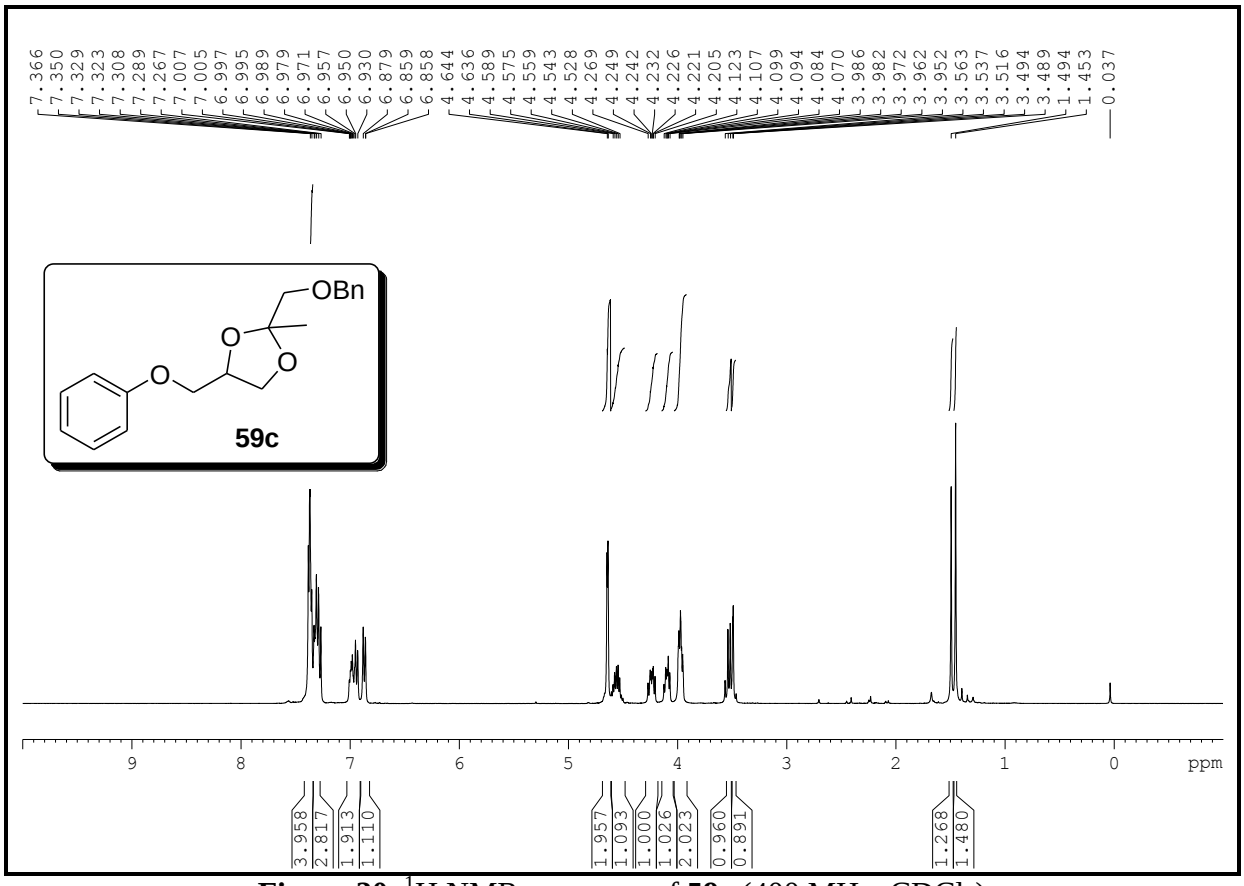


Figure 30. ^{1}H NMR spectrum of **59c** (400 MHz, $CDCl_3$)

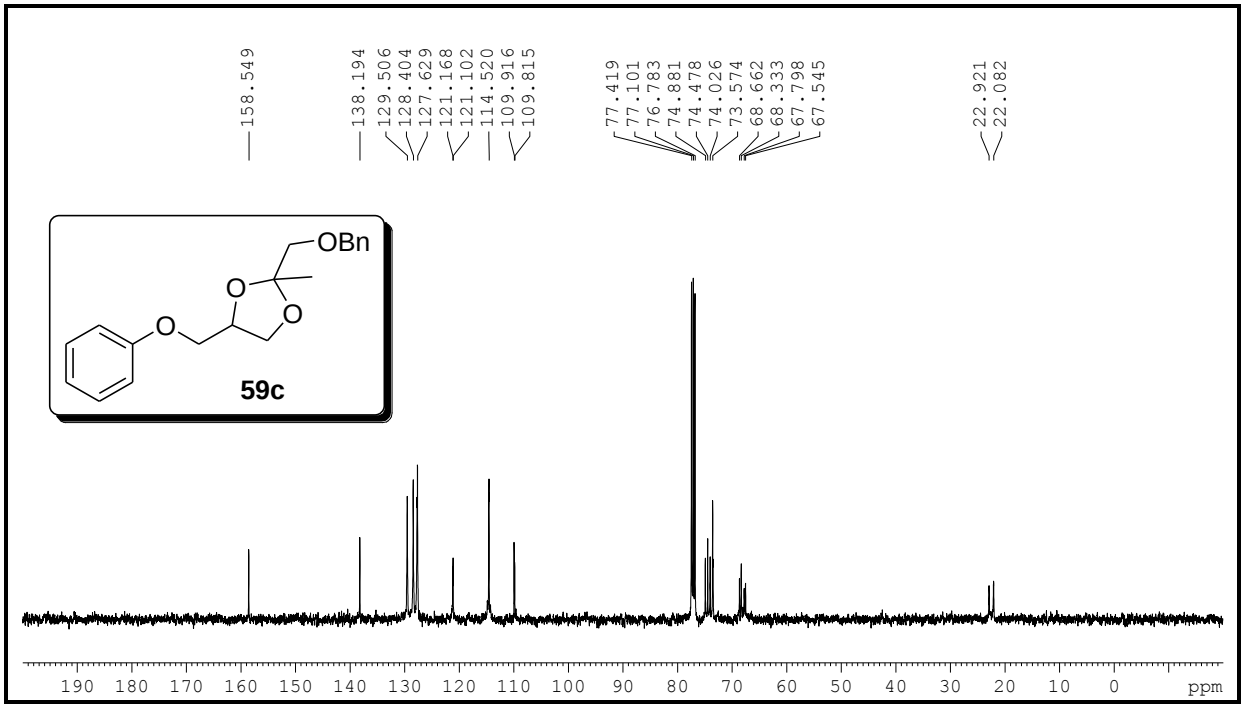


Figure 31. ^{13}C NMR spectrum of **59c** (100 MHz, $CDCl_3$)

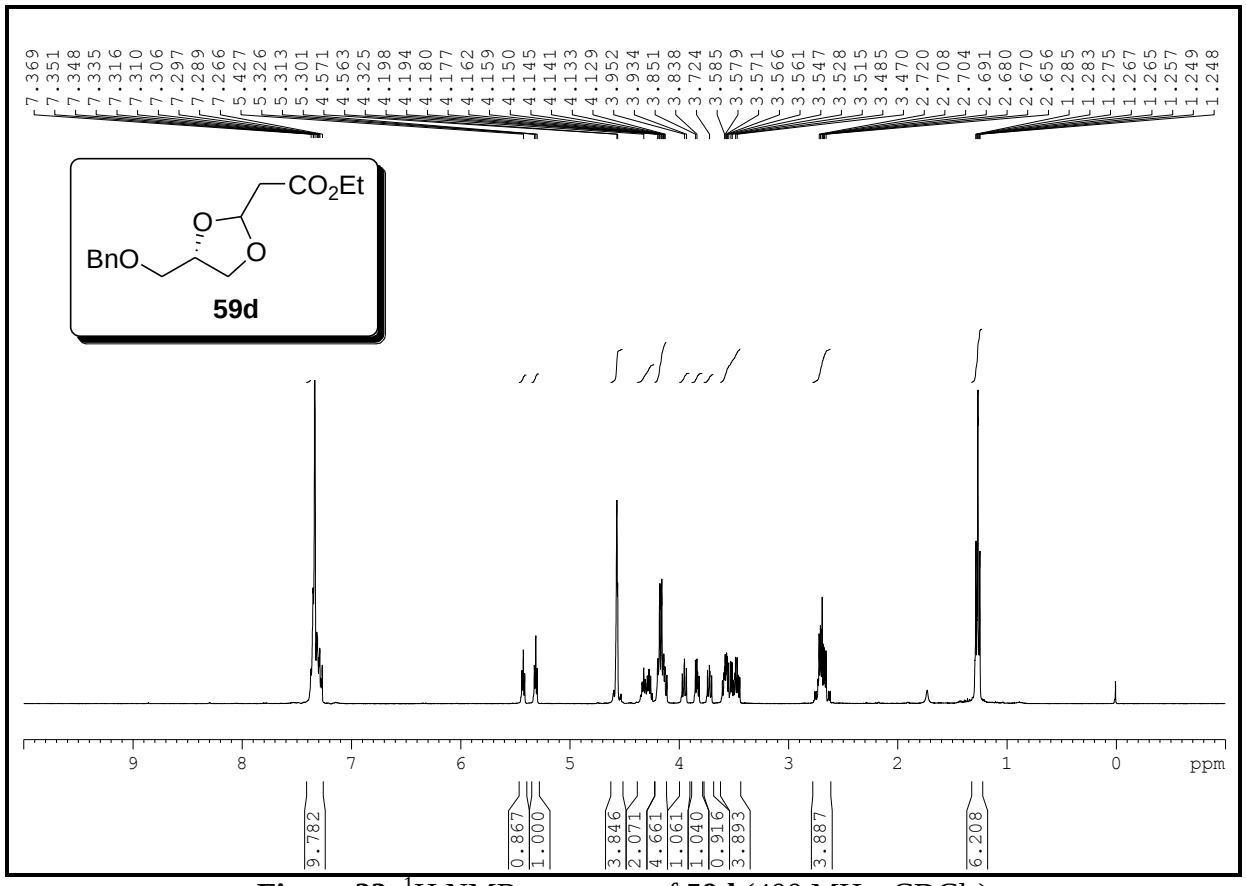


Figure 32. ^{1}H NMR spectrum of **59d** (400 MHz, $CDCl_3$)

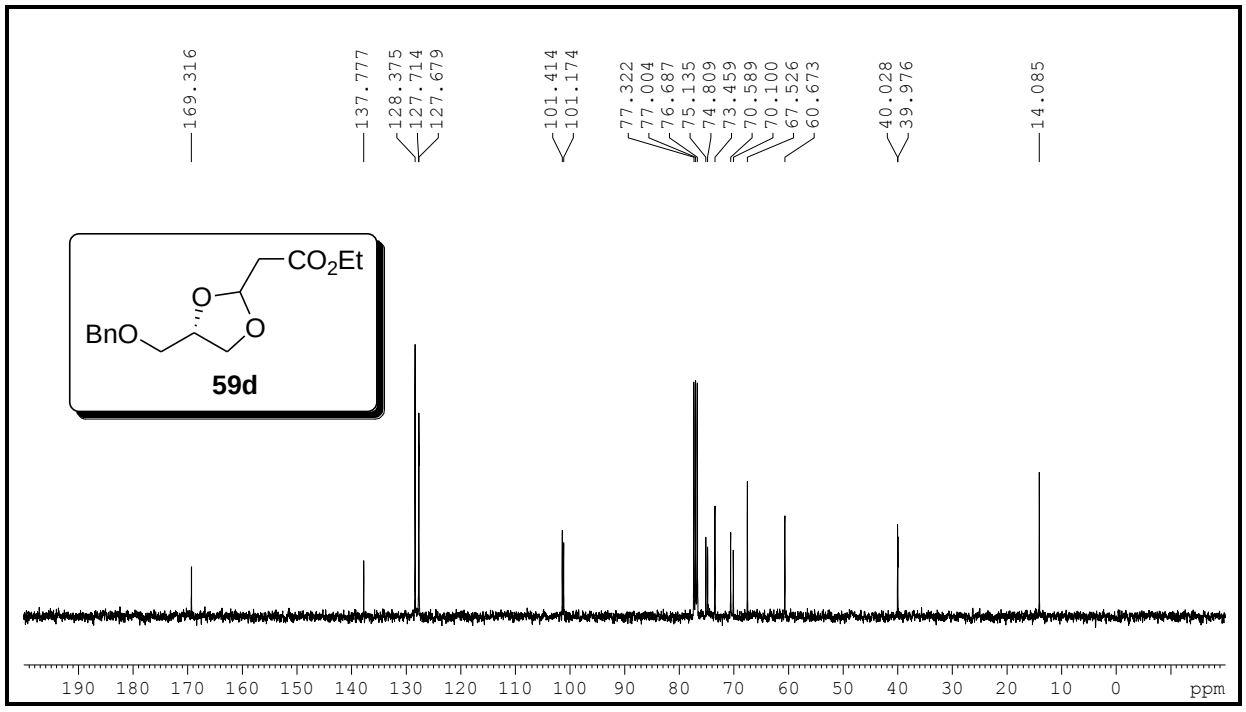


Figure 33. ^{13}C NMR spectrum of **59d** (100 MHz, $CDCl_3$)

Figure 34. ^{1}H NMR spectrum of **59f** (400 MHz, $CDCl_3$)

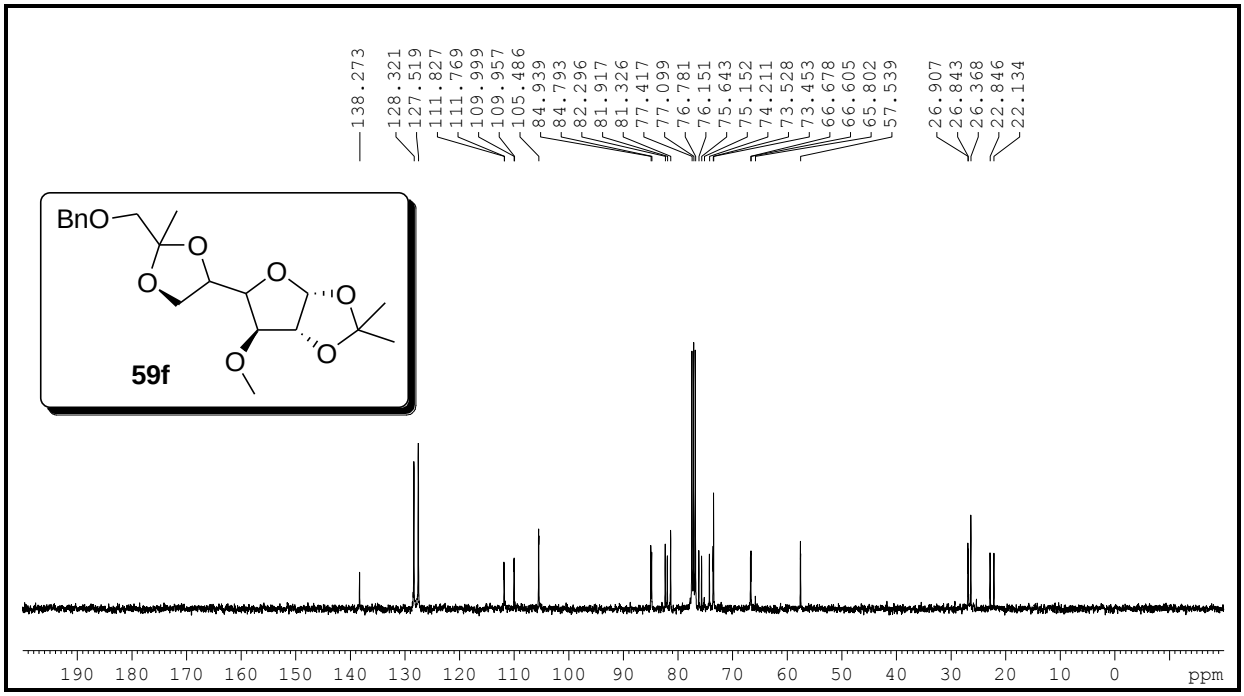


Figure 35. ^{13}C NMR spectrum of **59f** (100 MHz, $CDCl_3$)

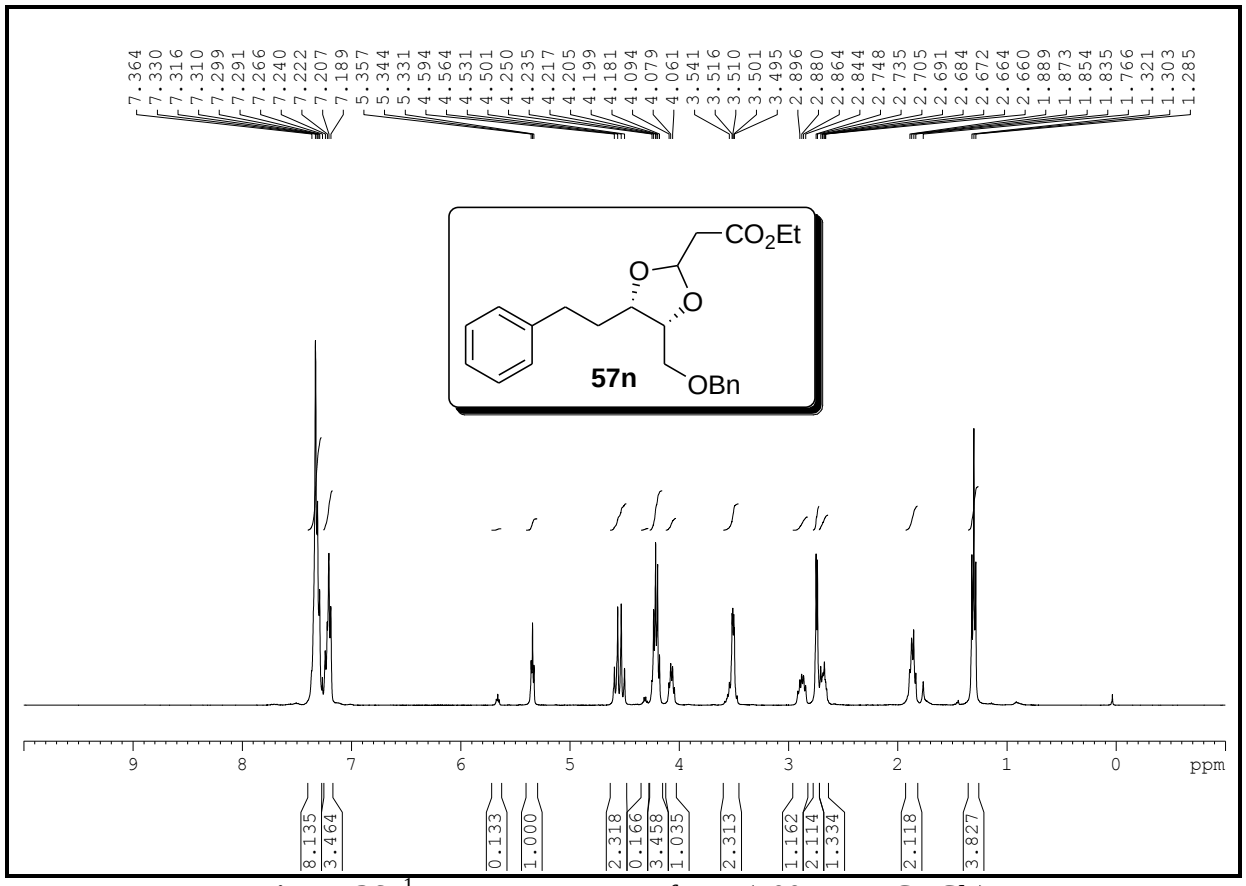


Figure 36. ^{1}H NMR spectrum of **57n** (400 MHz, $CDCl_3$)

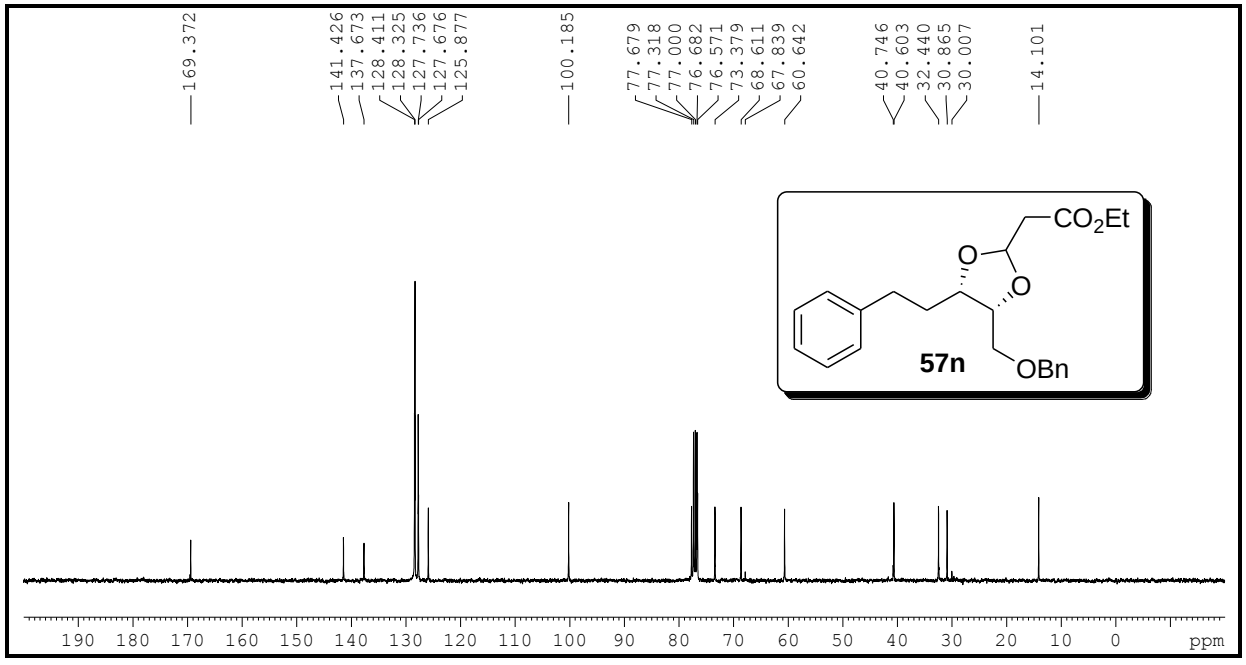


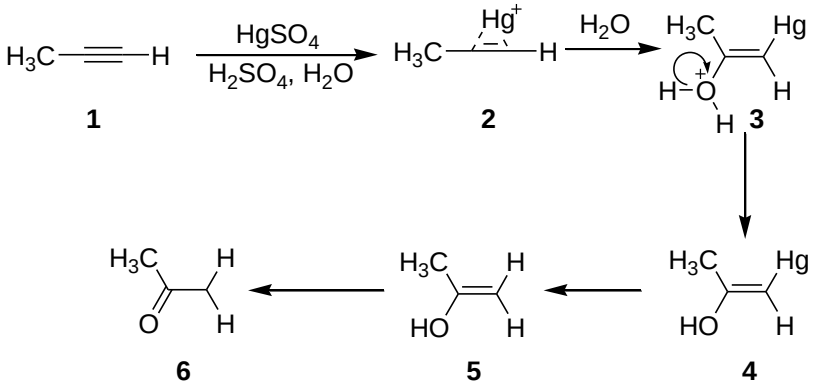
Figure 37. ^{13}C NMR spectrum of **57n** (100 MHz, $CDCl_3$)

PART-II

Gold-Catalyzed Hydration of Enynediester: Application in the Synthesis of γ-Lactam and Pyrrolidine Derivatives

2.1 Introduction to hydration of alkynes

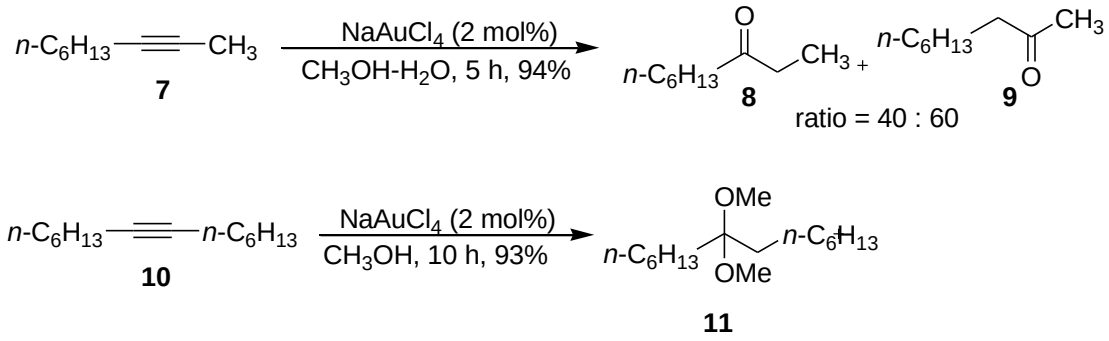
Hydration of alkynes is an important tool to make carbonyl compounds in organic synthesis. It is an atom economical method and has witnessed reasonable success in total synthesis.[1, 2] In 1881, Kucheroff published first report on hydration of acetylene to acetaldehyde using Hg(II) salts as catalysts and the reaction was named as Kucherov reaction.[3] Late transition metal based catalysts have gradually taken prominent place by replacing Hg(II) salts, due to toxicity of mercury salts.[4] Addition of water to alkynes follows Markovnikov's rule. Initially Hg salt coordinates to the π-system of alkyne **1** to form bridged mercurinium intermediate **2** and it reacts with water. Then loss of proton from intermediate **3** to gives organomercury enol **4** and Hg is replaced with proton on acidic workup to give an enol intermediate **5**. This step is known as protodemetallation. The enol intermediate **5** tautomerizes to give hydrated product **6** (Scheme 1).



Scheme 1. Hg(II)-catalyzed hydration of alkynes

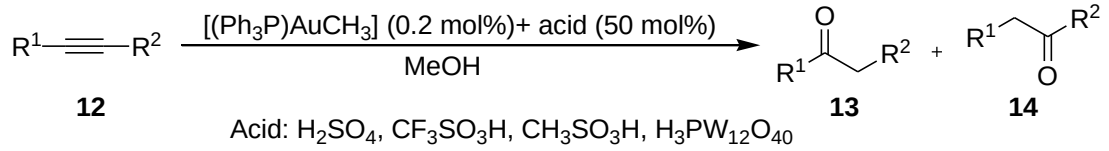
Apart from mercury catalyst, a number of catalysts based on metals have been employed in catalyzing the hydration of alkynes in recent years. Salts of metals such as Au, Pt, Pd, Ir, Fe and Ag made huge success in catalysing hydration of alkynes in the past decade.[5] Among them, gold catalyzed hydration of alkynes took prominent place due to the higher affinity of gold towards carbon-carbon multiple bonds and its non toxicity. Recent years have witnessed publication of several reports on hydration of alkynes using gold catalysts.[6] The advantage of gold catalyst is that it does not need anhydrous solvents and in fact the reactions can be conducted in aqueous solutions.[7a] The catalytic activity of gold halides can be enhanced by generating cationic gold species by exchanging the halide with non-nucleophilic counteranions.[7b] Generally hydration of alkynes in the absence of metal

catalyst requires harsh conditions.[8] Gold salts are excellent catalysts for the hydration of terminal alkynes, but unsymmetrical internal alkynes remain a challenge due to regioselectivity problems. Hydration of terminal alkynes showed good regioselectivity and resulted in excellent yields. However unsymmetrical internal alkynes are non-regioselective. In 1991, Fukuda *et al*. first reported on hydration of alkynes using gold catalyst.[9] Both terminal and internal alkynes gave corresponding ketones in aqueous methanol. The resulting acetal products were obtained in excellent yields at reflux condition in methanol solvent (Scheme 2).



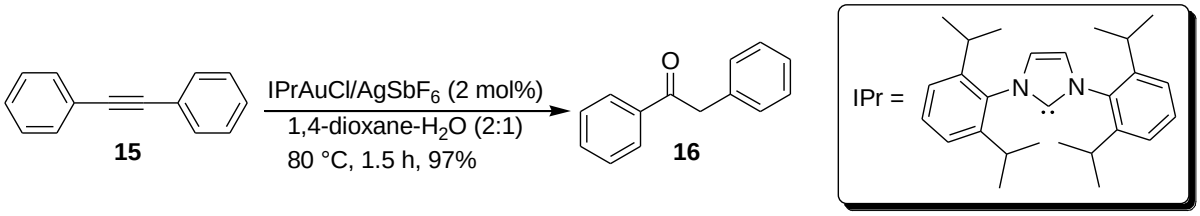
Scheme 2. $NaAuCl_4$- catalyzed hydration of alkynes **7** and **10**

In 2002, Hayashi and Tanaka reported highly efficient [$(Ph_3P)AuCH_3$] catalyzed hydration of alkynes in the presence of acid.[10] In this reaction, Au(I)/acid (H_2SO_4, CF_3SO_3H, CH_3SO_3H, $H_3PW_{12}O_{40}$) system in aqueous methanol serve as powerful catalyst for hydration of alkynes. The corresponding ketones were obtained in good to excellent yields (Scheme 3).



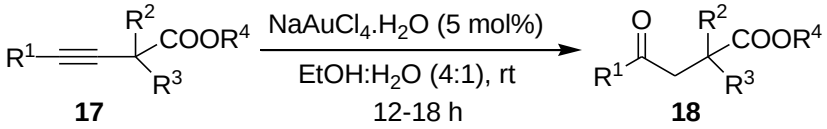
Scheme 3. [$(Ph_3P)AuCH_3$] + acid catalyzed hydration of alkynes

Mostly, gold catalyzed hydration of alkyne required strong acids as co-catalyst and higher temperature.



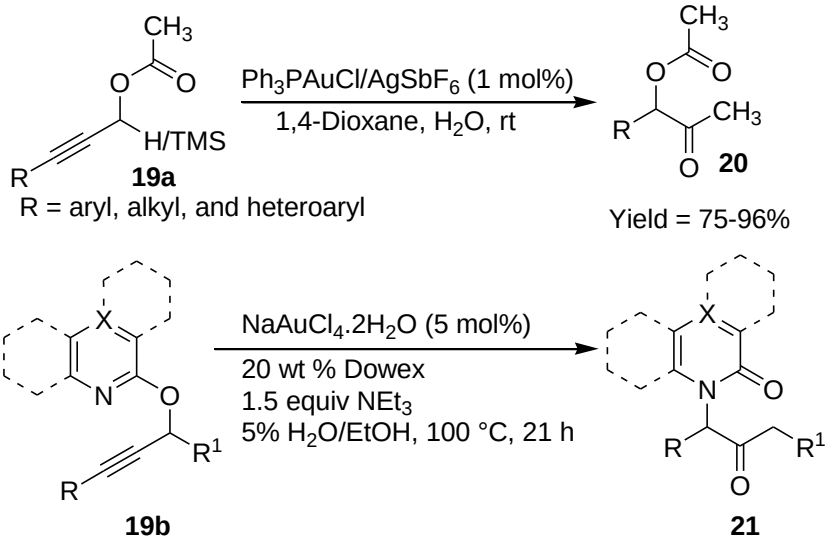
Scheme 4. IPrAuCl/$AgSbF_6$-catalyzed hydration of diphenyl acetylene

In 2009, Nolan and co-workers reported a (NHC)-Au(I) catalyzed acid free alkyne hydration under mild conditions (Scheme 4) at very low catalyst loadings (parts per million level) in 1, 4-dioxane-water (2:1) solvent system.[11] In the same year, Wang *et al*. reported a directed gold catalyzed regioselective hydration of 3-alkynoates (Scheme 5).[12] This reaction takes place through neighbouring carbonyl group assistance and enabled by a favoured 5-*endo dig* cyclization. The resulting *γ*-keto esters were obtained in high yields under mild reaction conditions.



Scheme 5. $NaAuCl_4.2H_2O$-catalyzed hydration of 3-alkynoates

Sahoo and co-workers have used acetoxy group to facilitate hydration.[13a] Romero *et al*. have developed a $NaAuCl_4.2H_2O$ catalyzed tandem amination-hydration of alkynes (Scheme



Scheme 6. Gold catalyzed propargyl alcohol derivatives

6).[13b] In this reaction, nucleophilic addition of sp^2 pyridine nitrogen to a gold-activated alkyne in a 6-*endodig* fashion occurs in the first step. The cationic intermediate undergoes tautomerization followed by rearrangement. α-(*N*-2-Pyridonyl)ketones and hetero cyclic analogues were obtained in good to excellent yields.

2.2 Synthesis of (*E*)-diethyl 4-oxohex-2-enedioate 22

2.2.1 Background

(*E*)-Diethyl 4-oxohex-2-enedioate **22** has an intriguing structure as it has different functionalities. The most interesting aspect of this six carbon compound is each carbon can selectively be reacted. It has a 1,3-dicarbonyl, carbonyl, two different esters, Michael acceptor carbons and dienophilic portion in it. Hence it can serve as a versatile synthon to make interesting compounds. .

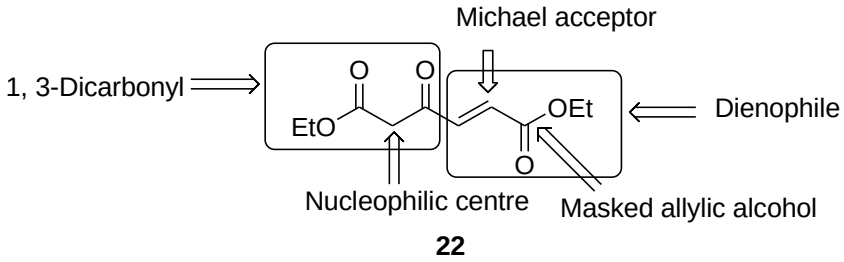
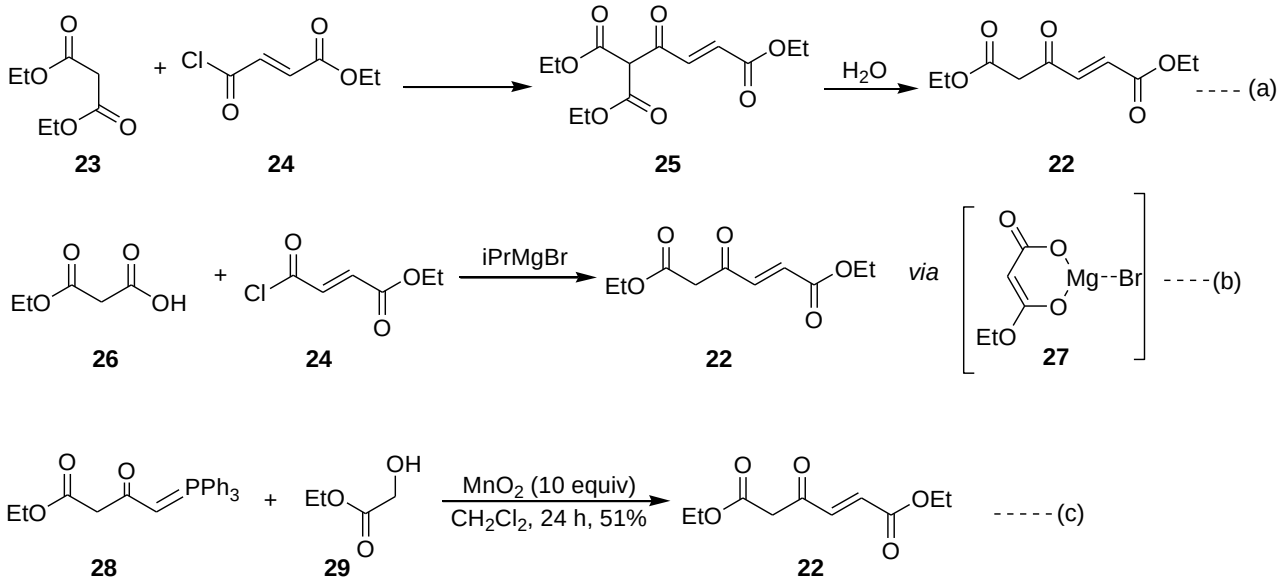


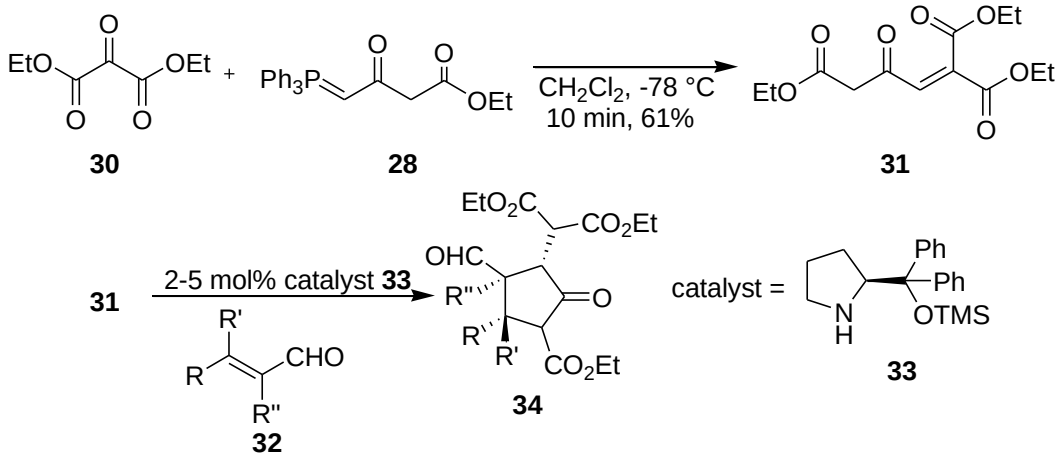
Figure 1. Reactive sites of (*E*)-diethyl 4-oxohex-2-enedioate **22**

There are only a few reports available for the synthesis of (*E*)-diethyl 4-oxohex-2-enedioate **22** from different starting materials (Scheme 7).[14] However none of them are straight forward and generally involve several steps. Gelin and co-workers have reported the synthesis of this compound from the acid chlorides **24** and ethyl hydrogen malonate **26**. This reaction takes place *via* the magnesium complex **27** (equation b, scheme 7). Later, in 2007, Langer and co-workers have reported the synthesis of this compound. In this reaction a phosphorane **28** was reacted with ethyl glyoxylate **29**, which generated *in situ* the required aldehyde for the Wittig olefination. In these methods, the starting material preparation would take more steps.



Scheme 7. Different methods for the synthesis of (*E*)-diethyl 4-oxohex-2-enedioate **22**

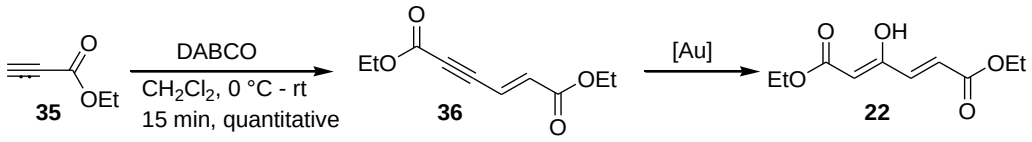
The utility of such system has been demonstrated in few reports. For example, in 2010, Ma and co-workers have utilised β-keto ester **31** in the synthesis of polysusbstituted cyclopentanones. The reaction happens *via* cascade double Michael addition reactions of α, β-unsaturated aldehydes **32** with β-keto ester **31** in presence of catalytic amount of organocatalyst **33** to afford polysubstituted cyclopentanones with excellent enantioselectivity (Scheme 8).[15n]



Scheme 8. Synthesis of poly substituted cyclopentanones

2.2.2 Results and discussions

Since few reports only are available for the preparation of the desired compound **22** and they being multi-step process, we wish to make it in a much simpler way. We anticipated that the target compound could be made by hydration of easily accessible enyne diester **36** whose synthesis from commercially available ethyl propiolate **35** is already reported (Scheme 9).



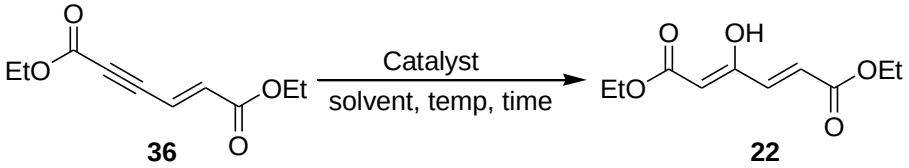
Scheme 9. Gold-catalyzed hydration of enyne diester

The enyne diethyl ester **36** was prepared in quantitative yield from ethyl propiolate **35** using DABCO as catlyst by following literature procedure.[16] The substrate was subjected to gold-catalyzed hydration under different conditions to assertain the best reaction condition. The results of the screening experiments are given in Table 1.

Initially the hydration reaction was attempted with cheaper gold (III) catalysts such as $AuCl_3$ and $NaAuCl_4$ with or without silver based co-catalysts. Poor conversion of the reaction was noticed in these reactions (Table 1, entries 1-6). When the reaction was carried out in distilled acetone in presence of $Ph_3PAuCl/AgSbF_6$ (2 mol%) at reflux condition, the reaction occured with 100% conversion and gave 64% isolated yield after 3 h (Table 1, entry 7). The product of hydration **22** was confirmed by literature data, which was reported by Langer and co-workers.[15c] It exists mainly in its enolic form. Monitoring the completion of the reaction was difficult by TLC analysis as the statrting material and the product have same R_f value although product spot is more iodine active. Brønsted acids are known to facilitate hydration of alkyne.[10] Hence the reaction was attempted with Brønsted acid p-TSA. However decomposed mixture was detected with p-TSA catalyst (Table 1, entry 10). No hydration product was observed from crude NMR spectra, when the reactions were carried out with $PtCl_2$ (Table 1, entry 11) and $Ph_3PAuCl/AgSbF_6$ (1 mol%) in CH_2Cl_2:H_2O (1:1) (Table1, entry 12). The reaction worked smoothly with catalytic amount of $IPrAuCl/AgSbF_6$ in dioxane and water (2:1) at 110 °C. It gave 100% conversion but isolated yields were very

poor (Table 1, entry 15). Good amount of polar material were isolated that might have formed formed by the hydrolysis of the ester function.

Table 1. Results of screening experiments for the hydration of enyne diester



36 **22**

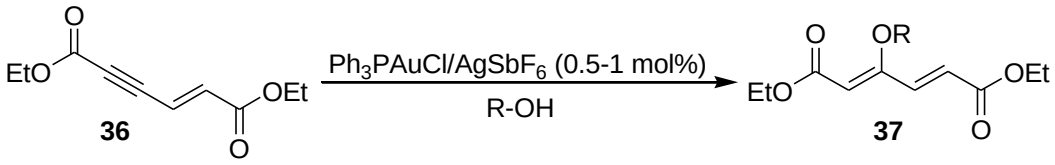
Entrry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Conv (%)[a]
1	$AuCl_3$ (2)	H_2O	80	10	38
2	$NaAuCl_4.2H_2O$ (2)	DCE:H_2O[c]	reflux	17	24
3	$AuCl_3$ (2)	Acetone	rt	48	12
4	$AuCl_3/AgSbF_6$ (2/6)	H_2O	80	24	13
5	$AuCl_3$/AgOTf (2/6)	Acetone:H_2O[c]	60	12	4
6	$AuCl_3/AgSbF_6$ (2/6)	H_2O:Dioxane (1:2)	110	9	21
7	$Ph_3PAuCl/AgSbF_6$ (2)	Acetone	60	3	100 (64)[b]
8	$Ph_3PAuCl/AgSbF_6$ (1)	Acetone	rt	10	90
9	$Ph_3PAuCl/AgSbF_6$ (0.2)	Acetone	rt	72	66
10	p-TSA (50)	H_2O:Dioxane (1:3)	reflux	39	dm
11	$PtCl_2$ (1)	H_2O:Dioxane[c]	110	28	NR
12	$Ph_3PAuCl/AgSbF_6$ (1)	CH_2Cl_2:H_2O (1:1)	reflux	22	nr
13	**(IPr)AuCl/$AgSbF_6$ (0.3)**	**Acetone**	**60**	**24**	**100 (86)[b]**
14	(IPr)AuCl/$AgSbF_6$(0.1)	H_2O:Dioxane (2:1)	80	16	67
15	(IPr)AuCl/$AgSbF_6$ (0.2)	H_2O:Dioxane (1:2)	110	1.5	100
16	(IPr)AuCl/$AgSbF_6$ (0.1)	H_2O:Dioxane (1:2)	110	3	72
17	$Ph_3PAuCl/AgSbF_6$ (0.2)	Acetone	rt	10	42
18	(IPr)AuCl/$AgSbF_6$ (0.1)	Acetone	60	96	100
19	$AgSbF_6$ (5)	H_2O:Dioxane (1:2)	110	19	41

[a] Conversion based on the integration of proton NMR of crude product. [b] Isolated yield. [c] 50µL H_2O was used; NR: no reaction; dm: decomposed mixture.

Using $AgSbF_6$ alone as the catalyst it gave 41% conversion after 19 h under same reaction condition. In presence of IPrAuCl/$AgSbF_6$ (0.1 mol %) in acetone at 60 °C the reaction gave

100% conversion after 4 days (Table 1, entry 18). The best condition was found with IPrAuCl/$AgSbF_6$ (0.3 mol%) at reflux condition in acetone which resulted in 100% conversion and 86% isolated yield (Table 1, entry 13). It is a simple and efficinet method to preapare hydration of enyne diester. Acetone was found to be the best and economic solvent for this reaction. In this reaction, water required for hydration might have been generated by aldol self condensation of acetone under the acidic reaction condition. In this case no need to do workup process. Simply once reaction completed, the crude reaction mixture was filtered through celite 545 to remove the catalyst and solvent was removed in a rotovap. The crude reaction mixture was loaded onto a silicagel column and it was eluted with ethyl acetate/hexanes mixture to get the pure product. In this way we could get good isolated yields. In the case of acetone solvent this kind of polar material is formed in less amount. The reaction when performed at 5 g scale under the optimized reaction conditions it gave the product in 85% yield (Table 1, entry 13).

We checked the reactivity of enyne diester **36** with few alcohols as well (Scheme 10). Substrate **36** resulted methanol adduct **37a** in 68% yield upon treatment with 1 mol% $Ph_3PAuCl/AgSbF_6$, in methanol at room temperature (Table 2, entry 1).

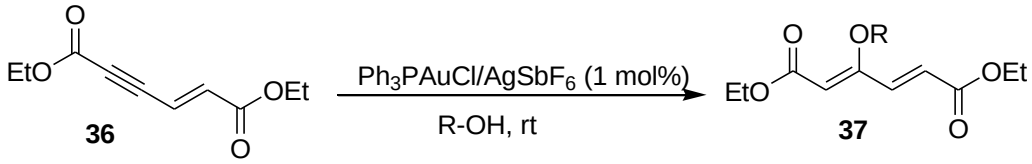


Scheme 10. Gold catalyzed addition of alcohols to enyne diester **36**

It is a protected form of enol of hydration product and could be a useful intermediate organic synthesis. Similarly the reaction in EtOH resulted in corresponding ethyl derivative. It has to be mentioned that alkynes an treatment with alcohols under gold catalysis give corresponding acetal. However in the reaction of enyne diester with alcohol mono addition only happened. Reactions with other alcohols such as benzyl alcohol, allyl alcohol and propargyl alcohol were carried out in dichloroethane. These reactions took more time for completion. While benzyl and allyl alcohols gave their corresponding addition products, propargyl alcohol did not react as gold may coordinate to the electron rich propargyl alcohol triple bond instead of activating the enyne diester **36**. The enyne diester was reacted with but-2-en-1,4-diol under gold-catalyzed conditions. There are two different possible reactions.

One is the cyclic acetal formation by double addition on the C≡C bond. The second possibility is usual addition of one hydroxy to the C≡C bond followed by the Michael addition of the other hydroxy on the α,β-unsaturated ester. However the reaction resulted a complex mixture of products. Later the enynediester was treated with 0.3 mol% $IPrAuCl/AgSbF_6$ in methanol to get the corresponding addition product **37a** in 78% yield at room temperature after 4 h.

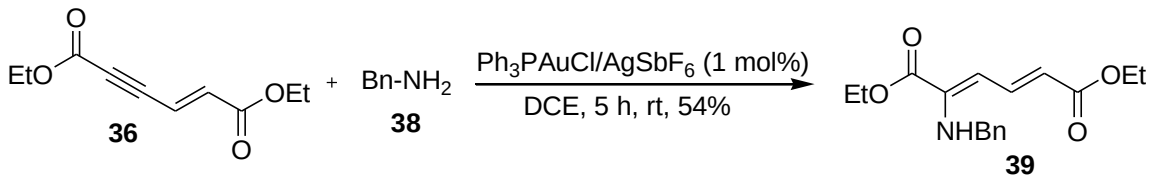
Table 2. Au(I)-catalyzed addition of alcohols to enyne diester **36**



Entry	R-OH	Solvent	Time (h)	Product	Yield % [a]
1	CH_3OH	MeOH	5	**37a**	68
2	EtOH	EtOH	5	**37b**	60
3[b]	BnOH	DCE	17	**37c**	65
4[b]	Allylic alochol	DCE	24	**37d**	35
5[b]	Propargylic alcohol	DCE	29	---	nr
6[b]	Cis-2-butene-1,4-diol	DCE	25	---	Complex mix.

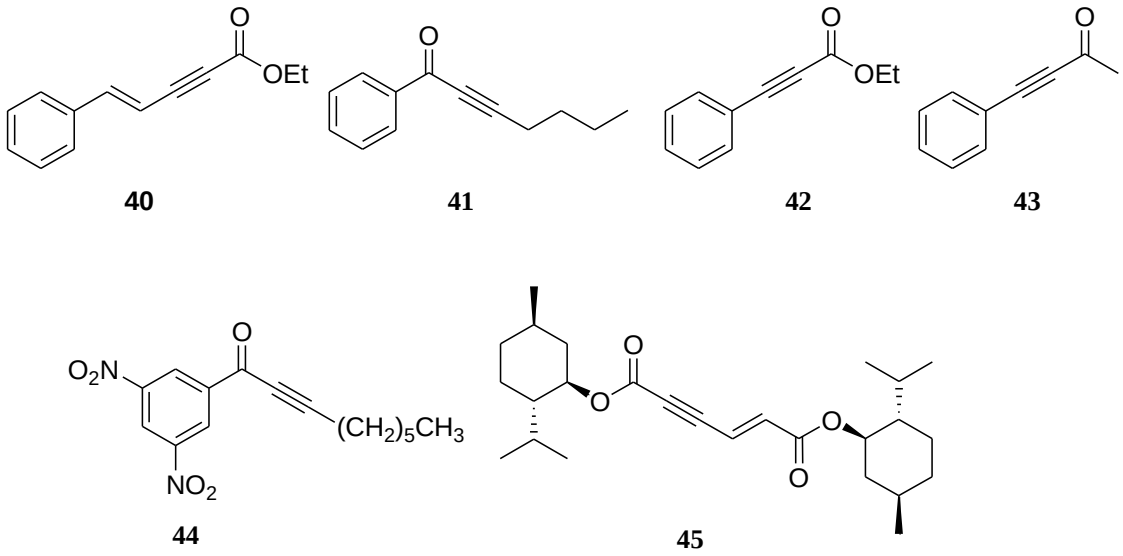
[a] Isolated yield; [b] 2.0 equiv of corresponding alcohol was used.

We then reacted benzylamine with the enyne diester in presence of 1 mol% of $Ph_3PAuCl/AgSbF_6$ catalyst in dichloroethane solvent (Scheme 11). This reaction gave exclusively the α(δ′)-addition product **39** in 54% yield. This type of addition is known without the influence of any catalyst.[17]



Scheme 11. Addition of benzyl amine **38** to enyne diester **36**

To evaluate the application of this hydration stratagy, we synthesized few other subatrates containing alkynyl ketones and alkynyl esters (Figure **2**).[18] These substrates were subjected to hydration by gold catalyst separately in both acetone and 1,4-dioxane:water solvent systems.



40 **41** **42** **43**

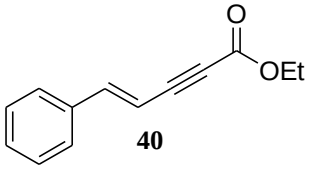
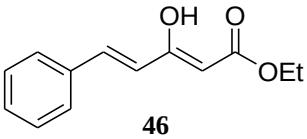
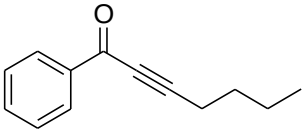
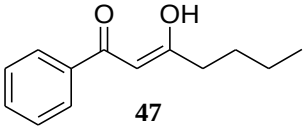
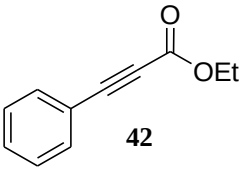
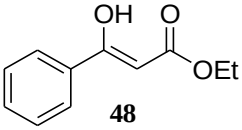
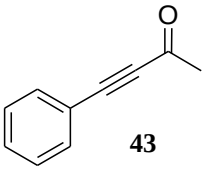
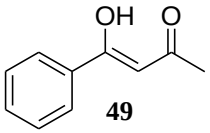
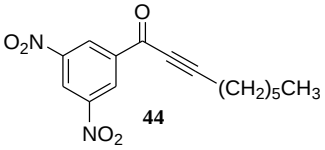
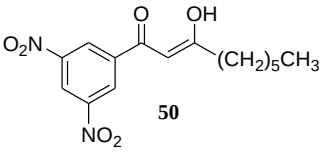
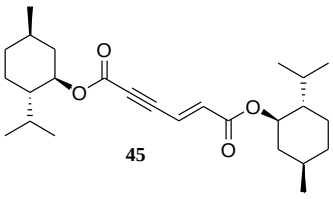
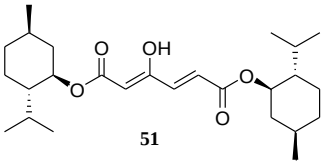
44 **45**

Figure 2. Various alkynyl ketones/esters employed in gold catalyzed hydration

The substrate **40** was prepared in two steps from cinnamaldehyde.[19] Alkynyl ketones **41**, **44** were obtained by palladium catalyzed coupling of alkyne and acyl chloride. The substarte **45** was prepared using literature procedure.[16] The synthesized alkynyl ketone/esters were treated with 0.3 mol% of IPrAuCl/$AgSbF_6$ to get the corresponding hydration products and the results are summarized in table 3. The substrate **40**, which on hydration in acetone solvent gave 76% isolated yield of **46** (Table 3, entry 1). Alkynyl ketone **41** gave 44% isolated yield of hydration product **47** in acetone solvent, however in dioxane:water solvent gave 91% isolated yield (Table 3, entry 2). At higher temprature, alkynyl ester might get hydrolyzed and resulted in poor isolated yields. The substrates **43** and **44** gave hydration products with 84% and 84% isolated yields respectively (Table 3, entry 4 and 5). The substrate **45** gave 27% of corresponding hydration product **51** in dioxane:water system (Table 3, entry 6). From these experiments it is clear that, acetone solvent is good for alkynyl esters and dioxane:water solvent is good for alkynyl ketones.

To check whether $Ph_3PAuCl/AgSbF_6$ in acetone system is uesful for the hydration of simple alkynes, we treated diphenylacetylene with catalytic amount of $Ph_3PAuCl/AgSbF_6$ in acetone solvent at varying conditions. But we could not detect hydration product. No hydration product was obtained, even when the reaction was performed in acetone:water (4:1) at reflux condition.

Table 3. $IPrAuCl/AgSbF_6$ (0.3 mol%) catalyzed hydration of alkynyl ketones/esters

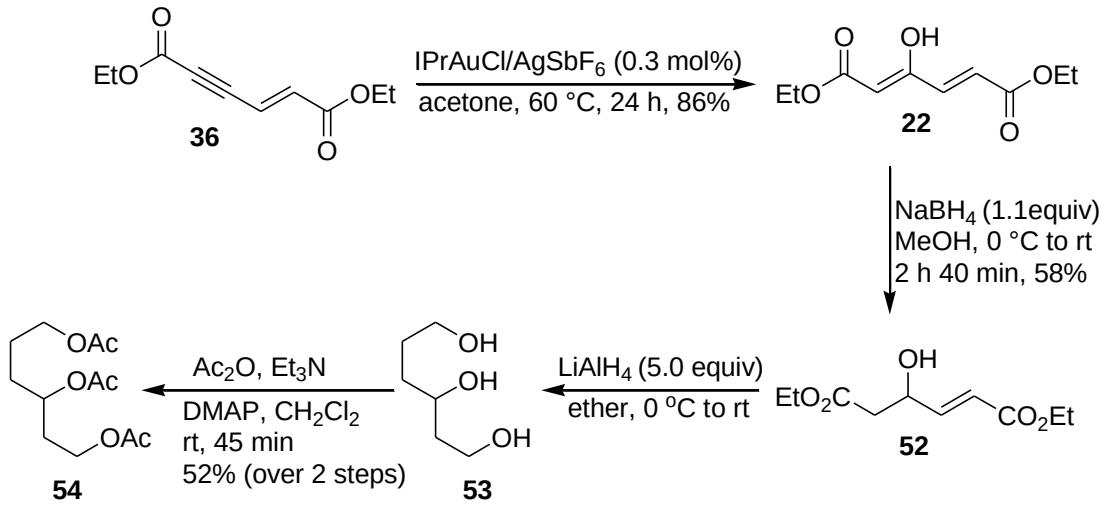
Entry	Substrate	Time (h)	T (°C)	Product	Yield [a]
1	 **40**	4	60	 **46**	76[b]
2	 **41**	6 2.5	60 110	 **47**	44[b] 91[d]
3	 **42**	24	rt	 **48**	85[c]
4	 **43**	2.5	110	 **49**	84[d]
5	 **44**	2.5	110	 **50**	84[d]
6	 **45**	3.5	110	 **51**	27[d]

[a] Isolated yield. [b] Reactions were carried out in acetone solvent. [c] Reaction was carried out in presence of 1 mol% $Ph_3PAuCl/AgSbF_6$ in acetone solvent. [d] Reactions were carried out in dioxane:water (2:1) solvent.

2.3 Applications of hydration product 22

2.3.1 Synthesis of hexane 1,3,6-triol triacetate

We then focused our attention in utilizing the hydration product of enyne diester in different synthetic applications. In this respect conversion, of the hydration product into hexan-1,3,6-triol was attempted using $LiAlH_4$. However all our attempts failed as the reaction resulted in a complex mixture of products. In a modified approach the ketone function of product of hydration **22** was reduced with $NaBH_4$. This compound was reduced with excess of $LiAlH_4$ and the product on subsequent acetylation gave the triacetate **54** in 52% yield over two steps (Scheme 12). This triol is a useful intermediate for the synthesis of γ–butyrolactones by oxidative lactonization.[20]



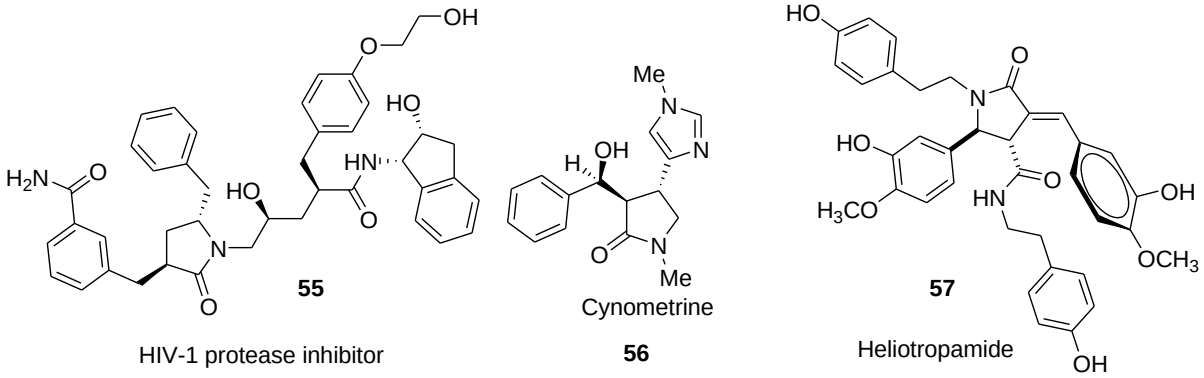
Scheme 12. Synthesis of hexane-1,3,6-triol triacetate

2.3.2 Synthesis of γ-lactam derivatives

2.3.2.1 Introduction to γ-lactam derivatives

γ-Lactam structure is an important subunit often found in many nitrogen containing heterocycles.[21] They find applications in many areas ranging from medicinal chemistry to polymer chemistry. Functionalized γ-lactams are widely distributed among the structures of a large number of biologically active natural products. The prevalence of γ-lactams in biologically significant molecules has led to the development of facile access to them.

N-substituted γ-lactams



N-H γ –lactams

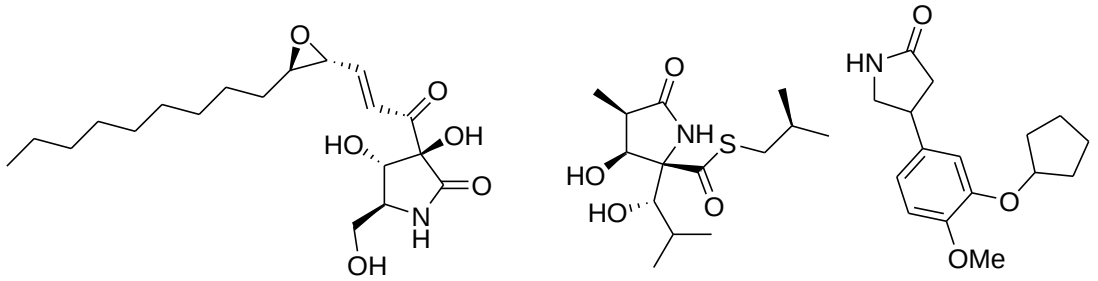
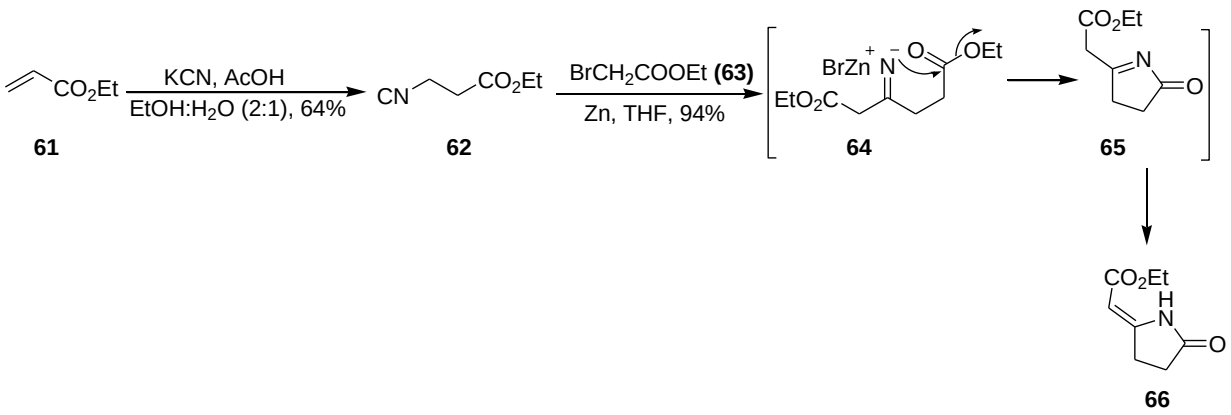


Figure 3. Representative natural products containing γ-lactam unit

Many syntheses of γ-lactams substructure has led to the production of distinct libraries of small molecules for biological evaluation.[22] (+)-Lactacystin **59** (selective inhibitor of the proteasome), (-)-pramanicin **58** (anti-fungal drug**)**, (R)(-)-rolipram **60** (phosphodiesterase-IV inhibitor-PDE-IV), cynometrine **56** and heliotropamide **57** (alkaloid) are few examples γ-lactam unit containing natural products (Figure 3).[23] The *γ*-lactam subunit also forms a series of HIV protease inhibitors **55** developed by GlaxoSmithKline. They also serve as important intermediates for the synthesis of some complex molecules due to their potential reactivity and high stereoselectivity in their transformations.[24]

In 2003, Shrestha-Dawadi *et al*. reported a synthesis of simple N-H γ-lactam from ethyl acrylate.[25] The reaction takes place through 1,4-addition of KCN to ethyl acrylate to give ethyl 3-cyanopropanoate. Then the zinc ester enolate selectively attacks the nitrile function without attacking the ester part (Blaise reaction). Intramolecular attack of imino nitrogen at

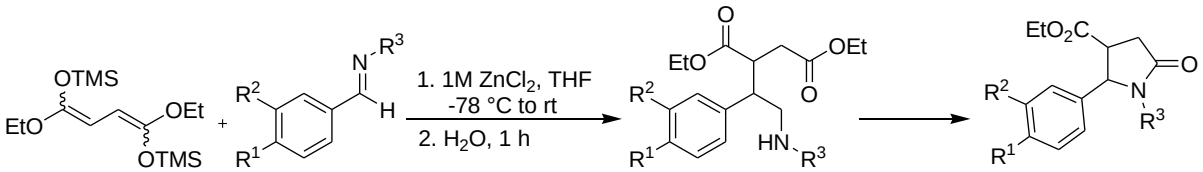
the ester group gives a five-membered ring compound. Further, this is converted into corresponding N-H γ-lactam in good yields (Scheme 13).



61 **62** **64** **65** **66**

Scheme 13. Synthesis of simple N-H γ-lactam

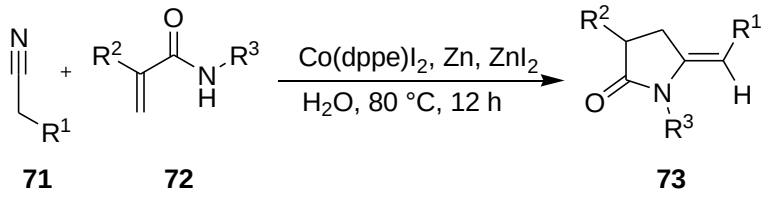
In 2007, Pohmakotr *et al.* have established an efficient synthesis of β-carboethoxy-γ-lactams from (*bis*)trimethylsilyloxy derivative **67** and imine **68** (Scheme 14).[26] This reaction takes place through imino Mukaiyama aldol-type reaction under Lewis acidic conditions. The resulting γ-lactams **70** were obtained in good yields as a mixture of *cis* and *trans* isomers.



67 **68** **69** **70**

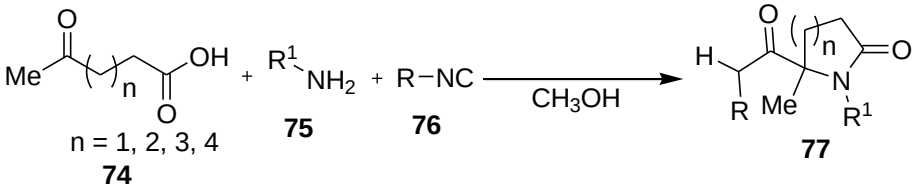
Scheme 14. Synthesis of β-carboethoxy-γ-lactams **70**

In 2009, Wong *et al*. reported a cobalt-catalyzed regioselective synthesis of pyrrolidinones.[27] This reaction takes place through intermolecular reductive coupling of nitriles **71** and acryl amides **72** in one pot. This reaction is believed to be initiated by the reduction of Co(II) to Co(I) by zinc dust, followed by chemoselective cyclometalation of Co(I) with nitrile and acrylamide to form cobalt azacyclopentene intermediate. Protonation followed by hydrolysis gives an intermediate. Which further undergoes keto-amide cyclization and elimination of water to give pyrrolidinone derivative **73** in excellent yields (Scheme 15)



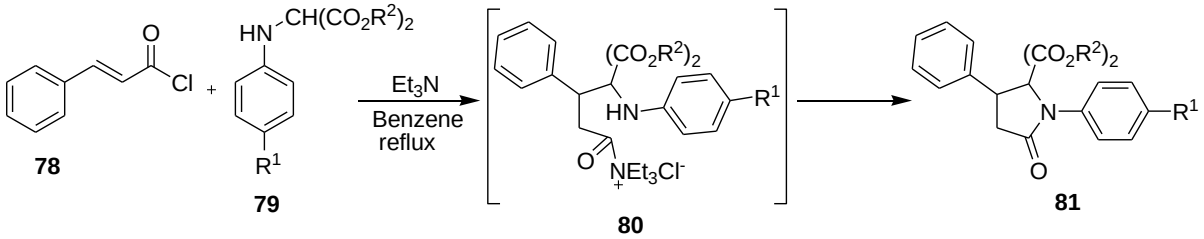
Scheme 15. Cobalt-catalyzed reductive coupling of nitriles **71** and acrylamides **72**

Harriman *et al*. have reported a three component intramolecular Ugi reaction of keto acid **74**, amine **75** and isocyanide **76** for the synthesis of γ-lactams (Scheme 16).[28] The reaction happens through the formation of imine from ketoacid **74** and amine **75** in methanol solvent. Subsequent addition of isocyanide **76** results in the formation of nitrilium intermediate. Intramolecular attack of the carboxylate on the nitrilium carbon results in cyclic intermediate which subsequently give the corresponding lactam derivative **77**.



Scheme 16. Three component reaction for synthesis of substituted γ-lactams

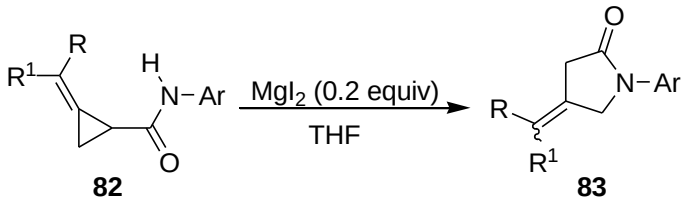
Chatterjee *et al*. have reported a convenient synthesis γ–lactams.[29] This reaction involves intermolecular Michael addition followed by intramolecular amidification. The resulting **γ–**lactam **81** obtained in good yield at reflux in benzene and triethylamine (Scheme 17).



Scheme 17. Synthesis of γ–lactams *via* Michael addition

In 2007, Lautens and co-workers have reported a novel and efficient route for the synthesis of *exo-β, γ*-unsaturated lactams from substituted and non-substituted secondary methylenecyclopropyl amides (Scheme 18).[30] This reaction proceeds by initial ring-opening

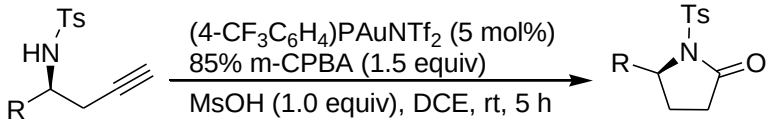
by iodide *via* an S_N2 pathway to generate the corresponding vinylogous enolate intermediate. The enolate gets protonated and its cyclization gives *exo-β, γ*-unsaturated lactam product **83** in excellent yields.



82 **83**

Scheme 18. Synthesis of *exo-β, γ*-unsaturated lactams

Gold-catalyzed tandem cycloisomerization/oxidation of homopropargyl amides **84** has been developed by Ye and co-workers.[31] This reaction takes place through 5-*endo-dig* cyclization of a gold activated homopropargyl amide to form vinyl gold intermediate. In the presence of acid, vinyl gold intermediate is transformed into iminium intermediate which undergoes oxidation by *m*-CPBA. The resulting *γ*-lactams are obtained in good yields. The chirality is maintained if an enantiopure homopropargylamine is used (Scheme 19).

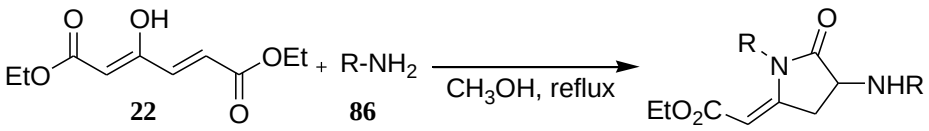


84 **85**

Scheme 19. Gold catalyzed formation of enantioenriched γ-lactams **84**

2.3.2.2 Results and discussion

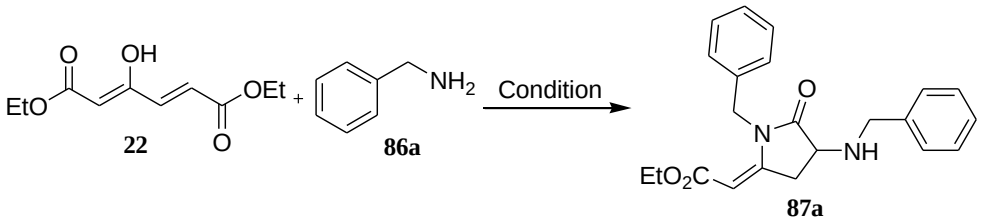
This section mainly deals with the utilization of hydrated product of enyne diester **22** in the synthesis γ-lactam derivatives. Since the substrate **37** has ketone and Michael acceptor functionalities, we subjected it to react with primary amines. These reactions resulted in the efficient formation of γ-lactam derivatives **87** (Scheme 20).



22 **86** **87**

Scheme 20. Synthesis of γ-lactam derivatives

Table 4. Screening results for the formation of γ-lactams

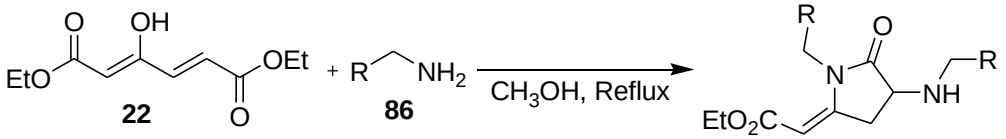


Entry	Solvent	Temp	Time (h)	Yield[a]
1.	CH_3OH	reflux	24	72
2.	CH_2Cl_2	rt	12	trace[b]
3.	CH_2Cl_2	reflux	8	trace[b]
4.	CH_3CN	reflux	10	41

[a] Isolated yield. [b] Determined from crude proton NMR.

Initially the reaction of **22** with benzyl amine was checked in methanol. It resulted in the formation of γ-lactam **87a** in 72% yield after 24 h of reflux in methanol (Table 4, entry 1). The product was confirmed by ^{1}H-NMR, ^{13}C-NMR and DEPT experiments. In dichloromethane the reaction did not happen even under reflux (Table 4, entries 2 and 3). In CH_3CN, under refluxing condition although the reaction completed in 10 h, it resulted in 41% yield (Table 4, entry 4). Since the γ-lactam subunit is present in several biologically important natural products, we treated compound **37** with different aryl amines in methanol under reflux conditions. These reactions resulted in the formation of corresponding γ-lactam derivatives **87** in moderate to good yields. The results are summarized in Table 5.

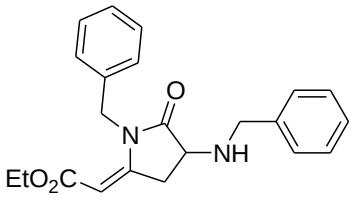
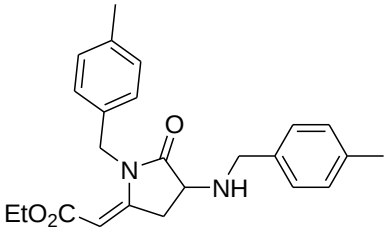
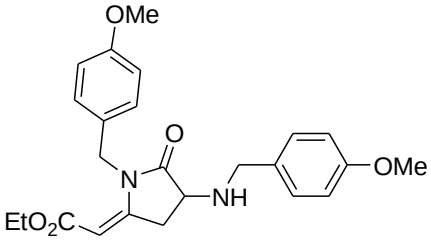
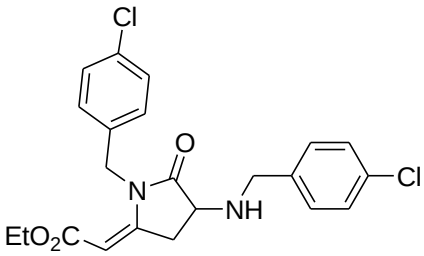
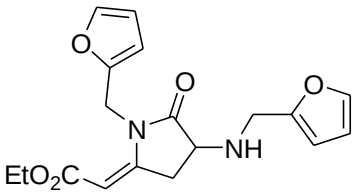
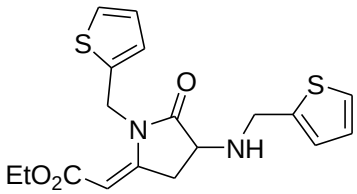
Table 5. Synthesis of γ-lactam derivatives



R = C_6H_5 **86a**; 4-$CH_3C_6H_4$ **86b**; 4-$OMeC_6H_4$ **86c**

4-ClC_6H_4 **86d**; C_4H_3O **86e**; C_4H_3S **86f**

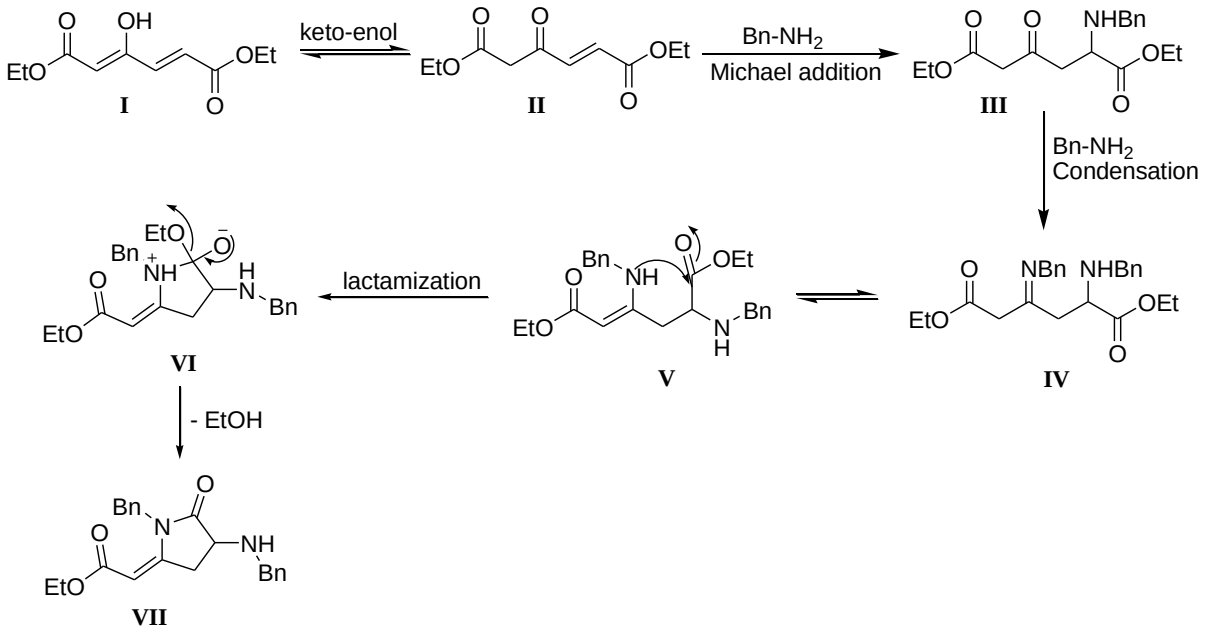
Table 2. Contd…

		
87a	**87b**	**87c**
24 h, 72%[a]	9 h, 55%[a]	9 h, 51%[a]
		
87d	**87e**	**87f**
9 h, 50%[a]	9 h, 48%[a]	8 h, 62%[a]

[a] Isolated yield.

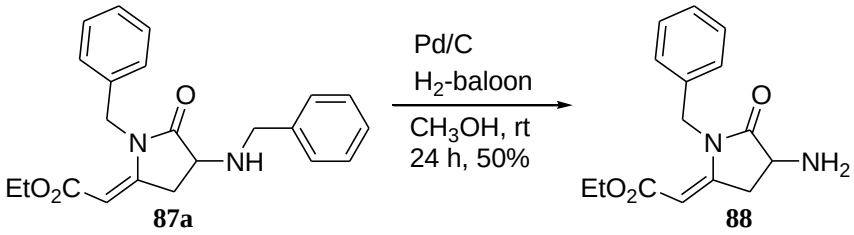
2.3.2.3 Plausible mechanism for the formation of γ-lactam

In the compound **22** there are two Michael acceptor sites available for a nucleophile to attack. In principle, the nucleophile can attack either carbon of the double bond as one is β-to the ester carbon and the other one is β-to the keto function. In the actual reaction, the primary amine attacks the β-carbon of the keto function to form intermediate **III** as shown in Scheme 21. It reacts with another equivalent of amine to form enamine **V**, which subsequently lactamizes to form the γ-lactam **VII**. When the reaction was performed with pyrrolidine (secondary amine) under optimized reaction condition, it resulted in a complex mixture along with a small amount of unreacted starting material.



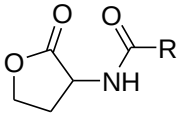
Scheme 21. Plausible mechanism for the formation of γ-lactam

These lactams have similar structure of *N*-acylhomoserine lactones **89** (HSL).[32] These compounds are involved in the bacterial quorum sensing. In this regard, the synthesized γ-lactam **87a** was debenzylated with Pd/C-H_2 in methanol solvent. Selective mono debenzylation occurred at the amine nitrogen site to afford compound **88** in 50% yield.



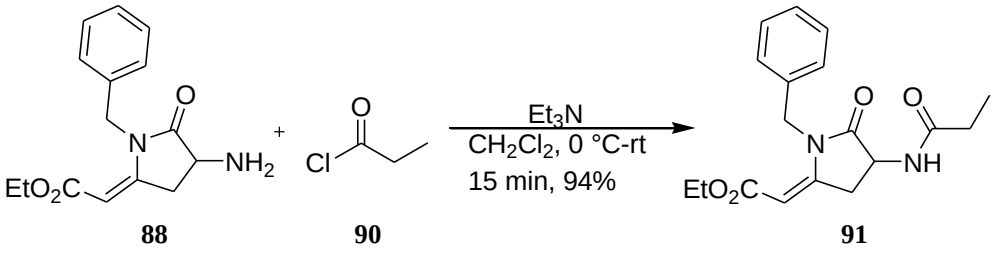
Scheme 22. Debenzylation of compound **87a**

In order to check the biological activity of γ-lactams, we prepared *N*-acyl derivative of compound of **88** by reacting with propanoyl chloride **90** in presence of Et_3N to get the corresponding *N*-acyl product **91** in excellent yield (Scheme 23). The biological studies are yet to be carried out.



N-Acyl homoserine lactone
(R = 4 to 18 carbon atoms)

89



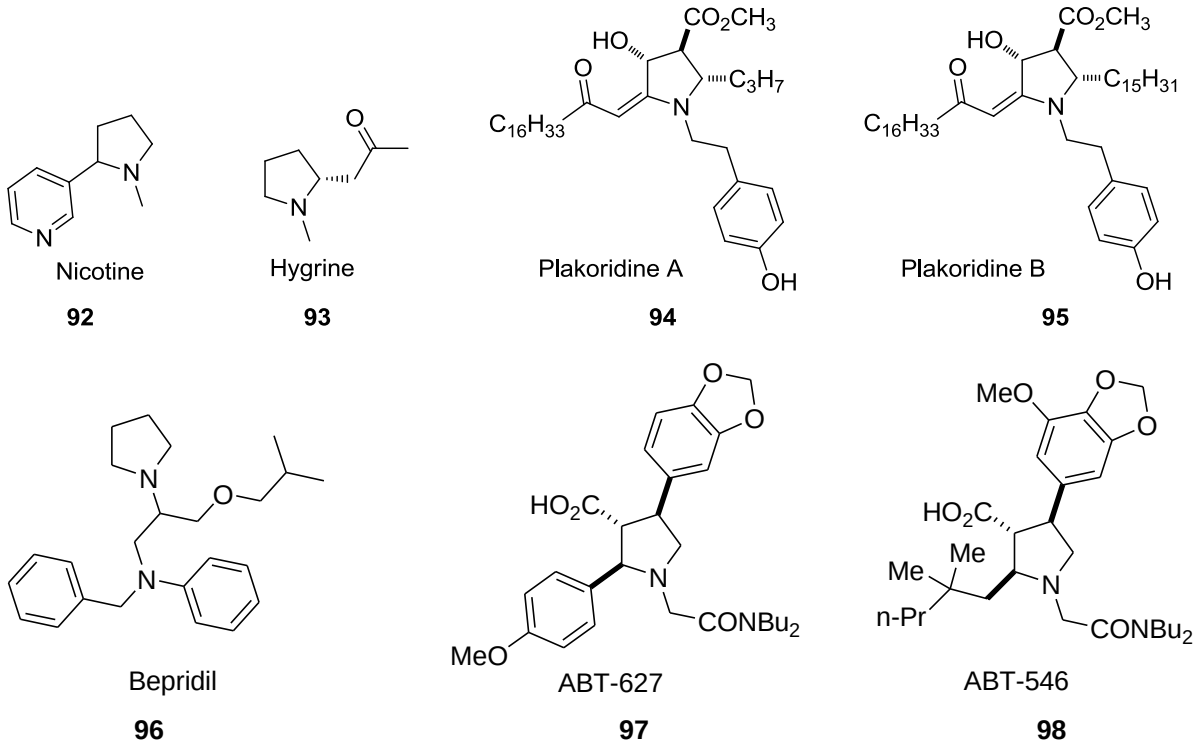
88 **90** **91**

Scheme 23. *N*-Acylation of compound **88**

2.3.3 Synthesis of pyrrolidine derivatives

2.3.3.1 Introduction to pyrrolidines

Pyrrolidine structure is found in various naturally occurring biologically significant compounds. Functionalized pyrrolidines are often found in numerous natural alkaloids and find applications as pharmaceutical drugs. They are used as building blocks in the synthesis of more complex structural motifs.[33]



92 **93** **94** **95**

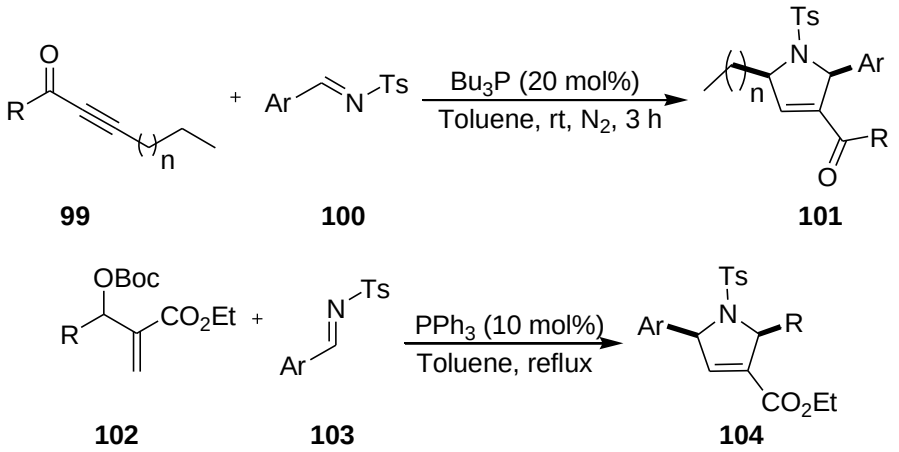
96 **97** **98**

Figure 4. Representative molecules containing pyrrolidine moiety

Few examples of pyrrolidine containing natural products are presented in Figure 4.[34] The pyrrolidine motif having less substituents such as simple nicotine **92**, hygrine **93** (natural alkaloid) and bepridil **96** (to treat angina), and highly substituted ones such as plakoridine A

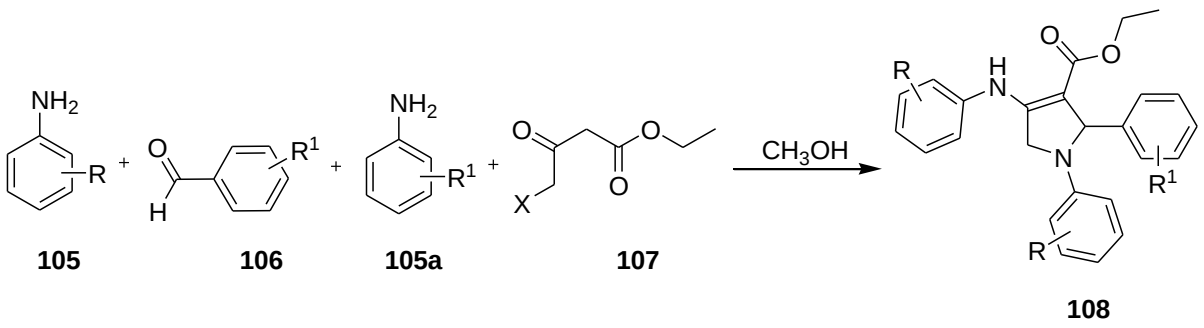
94 (cytotoxic), plakoridine B **95**, ABT-627 **97** and ABT-546 **98** (to treat cancer and congestive heart failure) are known.

Among the numerous known methodologies reported to obtain pyrrolidine derivatives, the ones which are closely related to the structure of the product that we synthesized are presented in this section. Meng *et al.* have reported an interesting [3+2] annulation of alkynyl ketones **99** with *N*-tosylimines **100** catalyzed by Bu_3P. The pyrrolidines formed by this methodology are obtained in good to excellent yields with *cis*-configuration.[35a] The annulation of modified allylic ylides with various aromatic imines catalyzed by tertiary amine was developed by Li and co-workers. It involves reaction of allylic compounds **102** with N-tosylimines **103** to give highly substituted pyrrolidines **104** in moderate to good yields with high stereoselectivity (Scheme 24).[35b]



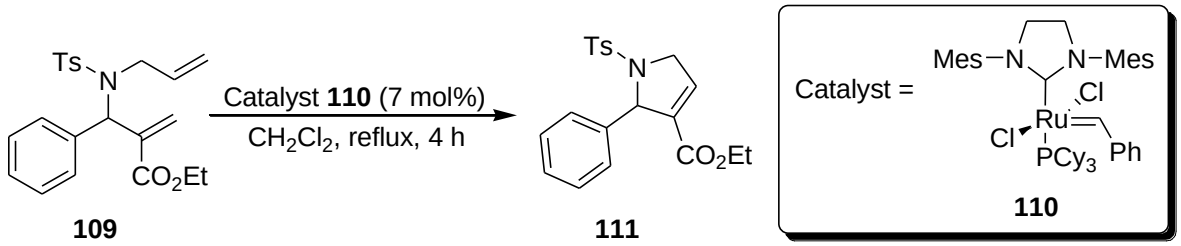
Scheme 24. Synthesis of highly functionalized pyrrolidines from imines

In 2011, Sobolev and co-workers reported a simple method for the synthesis of 1,2,3,4-tetrasubstituted 3-pyrrolines **108** under catalyst free conditions.[36] This reaction takes place *via* cyclisation of γ-halo-β-ketoesters **107** with aromatic amines **105**, **105a** and aldehydes **106** in methanol solvent (Scheme 25). Initially the condensation product (Schiff base) is formed from aromatic amine and aldehyde. This intermediate reacts with the enol form of γ-halo-β-ketoester forming corresponding addition product. Intramolecular cyclization affords 4-oxopyrrolidine derivative. The final step involves the reaction with a second molecule of the aromatic amine to result in 1,2,3,4-substituted 3-pyrrolines **108**. The products were obtained in moderate yields only.



Scheme 25. Synthesis of 1,2,3,4-tetrasubstituted 3-pyrrolines

Kim *et al*. have developed an efficient method for the synthesis of 2,5-dihydropyrrole skeleton.[37] This reaction takes place *via* ring closing metathesis (RCM) reaction of substrates obtained from Baylis–Hillman adducts **109**. The corresponding 2, 5-dihydropyrrole skeletons were obtained in excellent yields (Scheme 26).



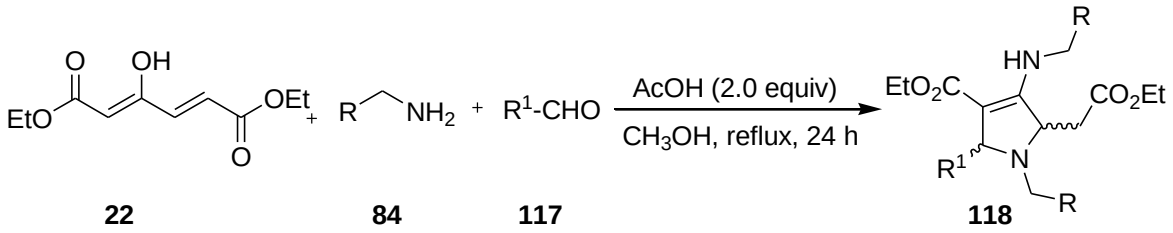
Scheme 26. Synthesis of 2,5-dihydropyrrole **111**

In 2009, Jiang and co-workers reported an acetic acid mediated synthesis of tetra- and penta substituted polyfunctional dihydropyrroles **116** from acetylenedicarboxylates **112**, amines **113**, **114** and aldehydes **115** in one pot.[38] This reaction involves a domino hydroamination/nucleophilic addition/amidation-cyclization process. The resulting tetra substituted dihydropyrroles were obtained in good to excellent yields (Scheme 27).

Scheme 27. Synthesis of tetra substituted polyfunctional dihydropyrroles

2.3.3.2 Results and discussion

The hydrated product **22** can be considered as a 1,3-dipole as it has a strong nucleophilic center at the active methylene carbon and a good Michael acceptor. Hence it was planned to react the hydrated product **22** with an imine. It is expected that after the nucleophilic addition of active methylene carbon on imine, the nitrogen can add in a Michael fashion to the double bond to form the pyrrolidine structure. The required imine can be generated *in situ* by treating aldehyde with amine in the presence of acid. With this idea in mind, we examined the reaction of hydration product **37** with benzaldehyde and benzyl amine in presence of AcOH in methanol solvent. The reaction resulted pyrrolidine derivative **118** (Scheme 27), whose structure was confirmed by ^{1}H, ^{13}C and DEPT-135 NMR.



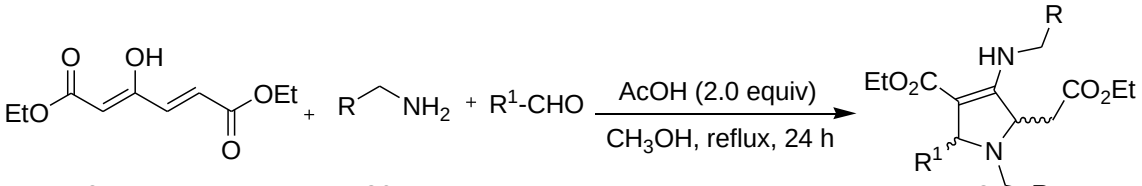
22 **84** **117** **118**

Scheme 28. Synthesis of highly substituted and functionalized pyrrolidine derivatives

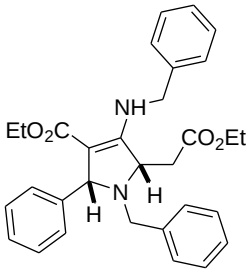
We found that, AcOH (2.0 equiv) in methanol solvent at reflux condition was the best condition for the formation of pyrrolidine derivatives. Also 2 equivalents of amine is required for better yield of the product. Hence, all reactions were carried out in AcOH (2.0 equiv) in methanol solvent at reflux condition. The scope of this reaction was explored by using different aldehydes **117a-117g** and benzyl amine derivatives **86a-86g** with 2 equivalents of AcOH in methanol solvent at reflux. The resultant pyrrolidine derivatives (**118a-118m)** were obtained in moderate to good yields with good diastereomeric ratio. The results are shown in Table 6. The diastereomeric ratios were calculated from the integrations in ^{1}H-NMR spectra of the column purified mixture. In all cases (**118a-118m**) we found that the *syn* isomer was the major isomer. It is important to mention that, in most of the cases γ-lactam was also obtained as a minor side product along with pyrrolidine derivative. The addition order of reactants is important to form pyrrolidine derivative. The addition order of reactants was the mixture of benzyl amine **86** (2.5 equiv), aldehyde **117** (1.0 equiv) and acetic acid (2.0 equiv) in methanol solvent was stirred for 10 minutes at room temperature. To this the hydration product **22** (1.0 equiv) in methanol was added followed by reflux for 24 h. Aromatic

aldehydes only work well as the reaction with aliphatic aldehyde, butyraldehyde resulted **118m** in 18% yield only.

Table 6. Synthesis of highly substituted and functionalized pyrrolidines

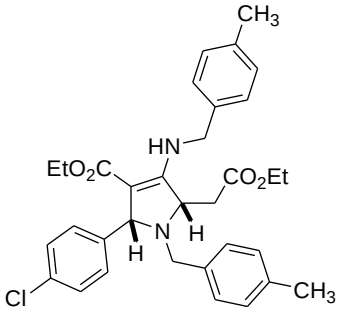


R =	C_6H_5 **86a**	R^1 =	Ph **117a**
	4-$CH_3C_6H_4$ **86b**		4-ClC_6H_4 **117b**
	4-$OCH_3C_6H_4$ **86d**		3-Br-4-FC_6H_3 **117c**
	4-ClC_6H_4 **86c**		4-$MeOC_6H_4$ **117d**
	4-C_4H_3O **86e**		3,4-$(OCH_2O)C_6H_3$ **117e**
	4-FC_6H_4 **86g**		C_4H_3O **117f**
			n-propyl **117g**



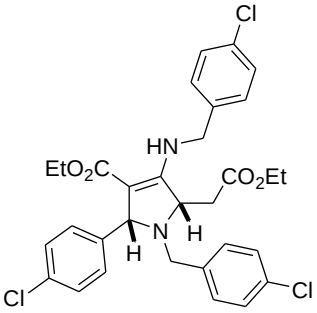
118a

49%[a], dr:11.5:1.0 [b]



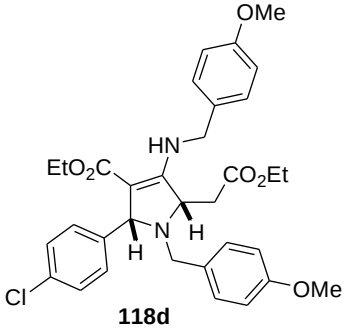
118b

54%[a], dr: 9.0:1.0[b]



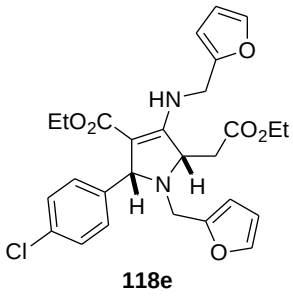
118c

74%[a], dr: 3.8:1[b]



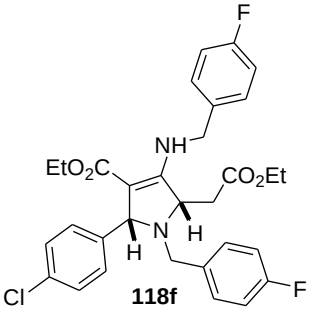
118d

67%[a], dr: 12:1.0[b]



118e

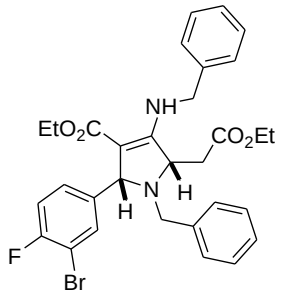
46%[a], dr: 10:1.0[b]



118f

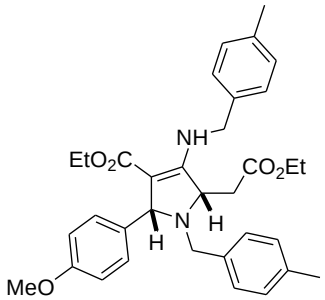
64%[a], dr: 19:1.0[b]

Table 6. Contd…



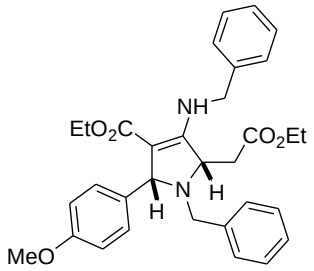
118g

42%[a], dr: 6.7:1.0[b]



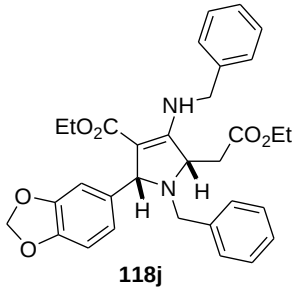
118h

55%[a], dr: 12:1.0[b]



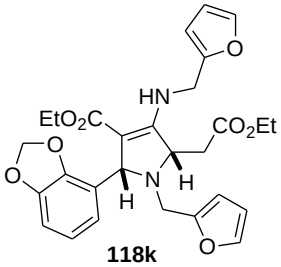
118i

29%[a], dr: 4.9:1.0[b]



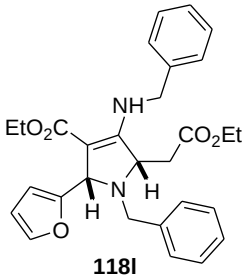
118j

49%[a], dr: 19:1.0[b]



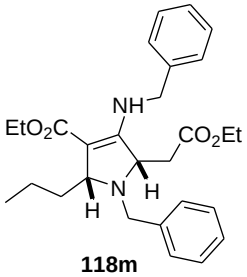
118k

59%[a], dr: 12:1.0[b]



118l

58%[a], dr: 4.3:1.0[b]

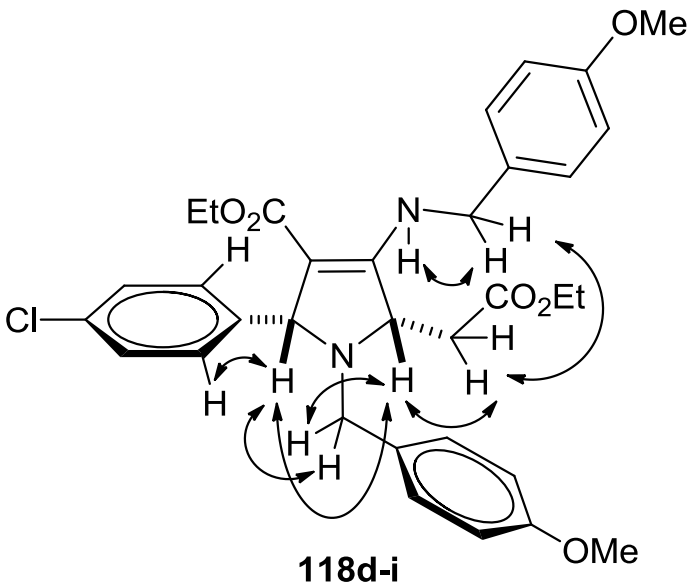


118m

18%[a]dr:13.3:1.0[b]

[a] Isolated yields. [b] Calculated from proton NMR of the column purified material.

2.3.3.3 NOESY experiment on compound 118d



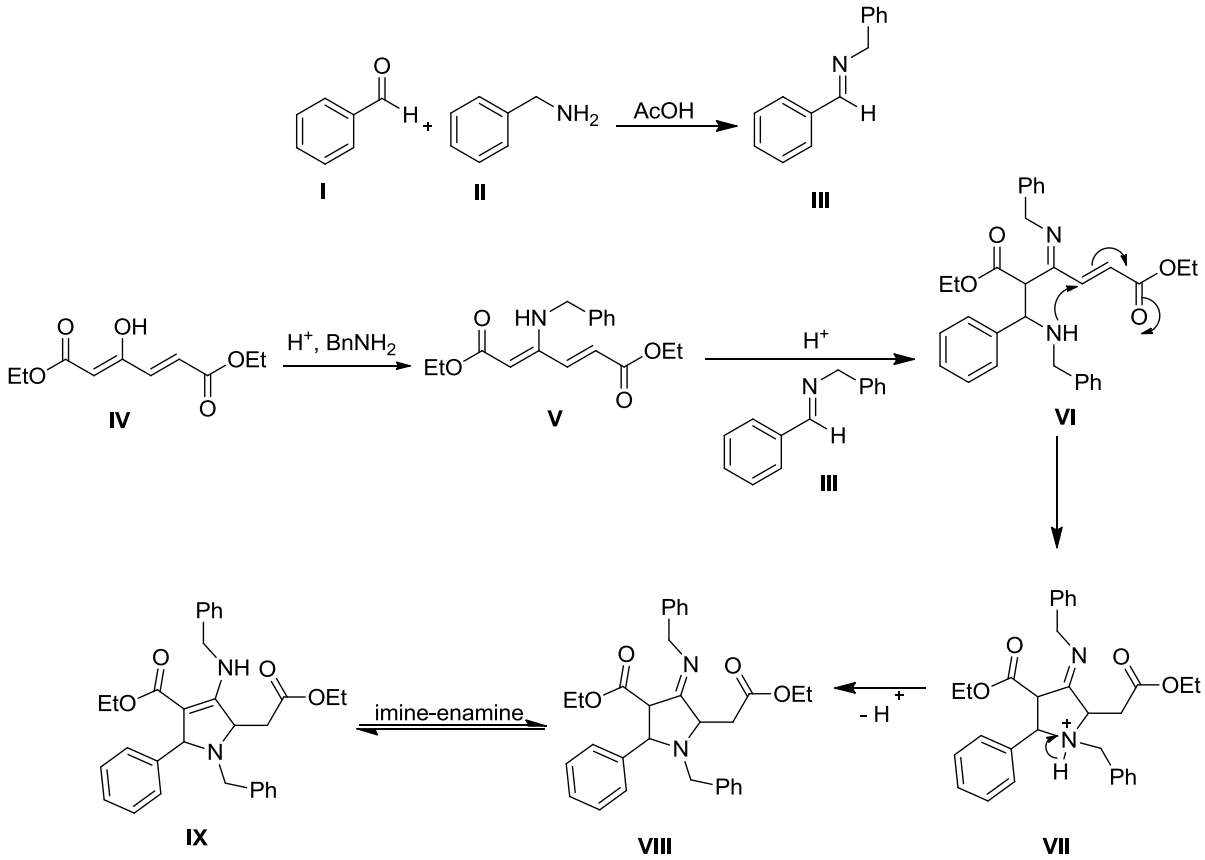
118d-i
major isomer
syn

Figure 5. NOESY experiment of compound **118d**

The relative orientations of substituents in major (*syn*/**118d-i**) diastereomer of **118d** were assigned based on the NOESY spectra of compound **118d**. The aryl and the estermethylene substituents are *cis* and *trans* to each other in major and minor isomers respectively (Figure 5). Key interactions observed in the NOESY spectra of the major isomer was shown in Figure 5.

2.3.3.4 Mechanism for the formation of pyrrolidine derivatives

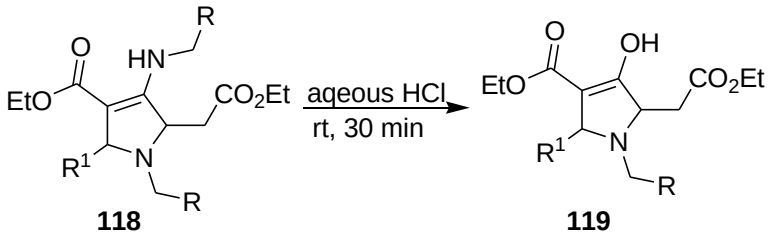
A plausible mechanism for the formation of pyrrolidine derivatives from enyne diester is shown in scheme **29**. In presence of acetic acid, benzaldehyde **I** and benzyl amine **II** form imine intermediate **III**. Reaction of the keto form of hydrated product **IV** with benzyl amine followed by nucleophilic addition on imine intermediate **III** gives the intermediate **VI**. Then the intermediate **VI** reacts intramolecularly *via* aza-Michael addition to give intermediate **VII**, which on deprotonation give intermediate **VIII.** This on tatuomerisation gives the actual pyrrolidine product **IX** (Scheme 29).



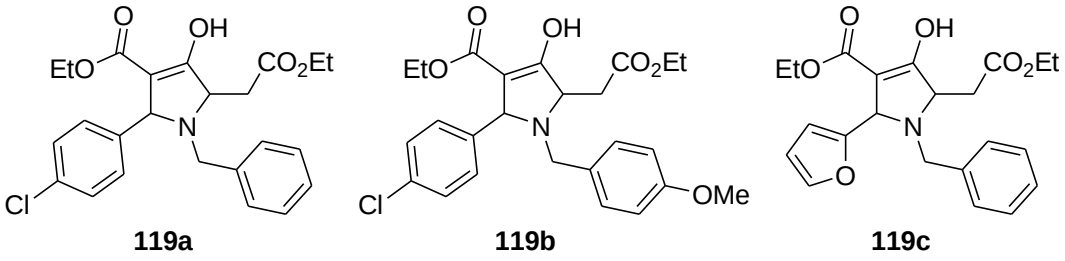
Scheme 29. Mechanism for the formation of pyrrolidine derivatives

2.3.3.5 Hydrolysis of pyrrolidine derivatives

The synthesized pyrrolidine derivatives **118** could be hydrolyzed with aqueous HCl to get the corresponding 1,3-diacrbonyl derivative **119**. The resulting hydrolysed products **119** were obtained in 100% conversion (Scheme 30). Importantly, the diastereomeric ratios of the starting pyrrolidines were maintained in the products as well.



118 **119**

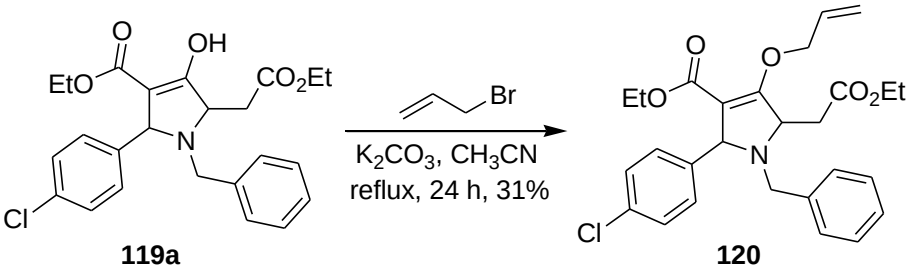


119a **119b** **119c**

100% conversion 100% conversion 100% conversion

Scheme 30. Hydrolysis of pyrrolidine derivatives **118**

Structure of the hydrolysed product was further confirmed by *O*-alkylation of **119a** using K_2CO_3 and allyl bromide (Scheme 31).



119a **120**

Scheme 31. *O*-Allylation of hydrolysed pyrrolidine derivative **119a**

2.4 Conclusions

Gold catalysis can advantageously be used to make useful 1,3-dicarbonyl systems. Cationic gold(I) in dioxane/water mixture is good for the hydration of triple bond in alkynones. Acetone is better solvent for the hydration of alkynes conjugated with esters. We have shown that readily accessible enyne diester **36** could be converted into useful building block **22**. This building block **22** which has multiple functional groups cannot be prepared as straightforward as the method developed by us. Some of the uses of this compound were explored. It can be converted into 1,3,6-hexanetriol.

Functionalized γ-lactam derivatives can be obtained from **22** by simple treatment with benzylamines. One of the benzyl groups in the γ-lactam derivatives (on the free amine substituent) can be selectively deprotected. This product can be acylated. Some of the compounds have been sent to evaluate their ability to act as bacterial quorum sensing inhibitors.

We successfully utilized the diester **22** in the synthesis of highly substituted and functionalized pyrrolidine derivatives in moderate to good yields. This is a three component reaction of aldehyde, benzyl amines and hydrated diester mediated by acetic acid. *Cis*-diastereomer is obtained as the major product in excellent diastereomeric ratio. These products could serve as intermediates for complex natural products synthesis as they have different functionalities.

2.5 Experimental section

2.5.1 General Information

Chemicals and solvents were obtained from various commercial sources. All gold and silver catalysts, *n*-BuLi (1.6 M in Hexanes) and NaH (60% dispersed in mineral oil) were purchased from Aldrich Chemical Co. Acetone dried over $KMnO_4$ and stored over 4Å type molecular sieves. THF dried over sodium and benzophenone and freshly distilled from THF still before use. ^{1}H and ^{13}C spectra were recorded on a Bruker Avance 400 MHz and 500 MHz using solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on JASCO FT/IR-5300 spectrometer. Elemental (C, H, N) analysis were done using Thermo Finnigan Flash EA 1112 analyser. High resolution mass spectra (HRMS) were recorded on micromass ESI-TOF MS. For TLC, silica gel plates 60 F254 were used and

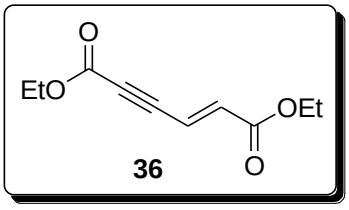
compounds were visualized by UV light and/or by treatment with Seebach solution (phosphomolibdic acid (2.5 g), $Ce(SO_4)_2$ (1 g), Conc. H_2SO_4 (6 mL), H_2O (94 mL)) followed by heating. Column chromatography was performed on silicagel 100-200 mesh, using ethyl acetate and hexanes mixture as eluent.

2.5.2 Experimental procedures, spectral and analytical data

I. General procedure for preparation of enyne diester (GP-I): To a solution of alkynoates (1.0 equiv) in CH_2Cl_2, DABCO (5 mol%) was added at 0 °C. The reaction immediately turned to dark in colour and was allowed to stir for 10-15 min. Then the solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure enynediester.

(*E*)-Diethyl hex-2-en-4-ynedioate (36):[39]

Prepared from ethyl propiolate by following GP-I; Yellow liquid; Yield = quantitative; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 16.0 Hz, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 152.9, 135.2, 121.3, 86.9, 81.3, 62.3, 61.1, 13.9, 13.8.



36

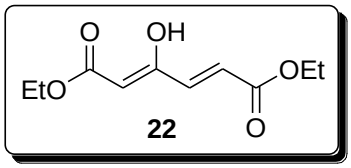
II. General procedure for hydration of enyne diester/alkynyl ketones/esters (GP-II):

To a solution of enynediester/alkynyl ketones/esters (1.0 equiv) in acetone or 1, 4-dioxane: water (2:1), IPrAuCl (0.3 mol%) and $AgSbF_6$ (0.3 mol%) were added consecutively. The reaction mixture was allowed to stir at 110 °C (1,4-dioxane:water) or 60 °C (acetone). The progress of the reaction was monitored by TLC. After completion of the reaction, it was filtered through a pad of celite 545, and then solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product.

(2*Z*,4*E*)-Diethyl 3-hydroxyhexa-2,4-dienedioate (22):[14c]

Prepared by following GP-II; Colourless liquid; Yield = 86%; R_f = 0.58 in 1:5 EtOAc/hexanes; Keto/enol : 7:93; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 6.90 (d, *J* =

15.6 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 5.27 (s, 1H), 4.25-4.20 (m, 4H), 1.31-1.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 165.9, 165.8, 137.2, 125.7, 96.5, 60.9, 60.7, 14.1 (2C).

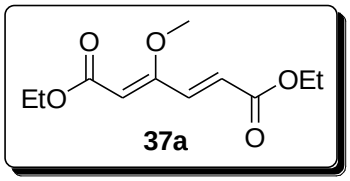


III. General procedure for addition of alcohols to enyne diester 36 (GP-III):

To a stirred solution of enynediester **36** (1.0 equiv) in CH_3OH or EtOH or dichloroethane, was added corresponding nucleophilic substrate (1.5 equiv or excess) followed by consecutive addition of $(Ph_3P)AuCl$ (1 mol%) and $AgSbF_6$ (1 mol%). The mixture was stirred at room temperature. After stirring for the specified time given in table 2, solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure corresponding addition product.

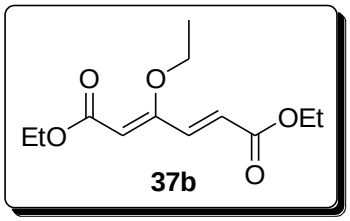
(2*Z*,4*E*)-Diethyl 3-methoxyhexa-2,4-dienedioate (37a):

Prepared from methanol by following GP-III; Colourless liquid; Yield = 68%; R_f = 0.41 in 1:10 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 16.0 Hz, 1H), 6.50 (d, *J* = 15.6 Hz, 1H), 5.29 (s, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 1.33-1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 163.7, 134.8, 124.7, 97.0, 60.7, 60.1, 55.6, 14.2 (2C); HRMS: calcd for $C_{11}H_{16}O_5$ $[M+H]^+$ 229.1077, Found 229.1078.



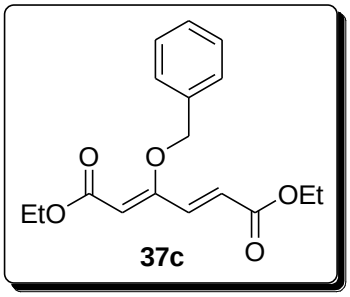
(2*Z*,4*E*)-Diethyl 3-ethoxyhexa-2,4-dienedioate (37b):

Prepared from ethanol by following GP-III; Colourless liquid; Yield = 60%; R_f = 0.61 in 1:10 EtOAc/hexanes (triple run); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 15.6 Hz, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 5.23 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.88 (q, *J* = 6.8 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 2H), 1.31-1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 166.2, 163.0, 135.1, 124.5, 97.2, 64.0, 60.6, 60.0, 14.2, 14.1, 14.0; HRMS: calcd for $C_{12}H_{18}O_5$ $[M+Na]^+$ 265.1052, found 265.1051.



(2*Z*,4*E*)-Diethyl 3-(benzyloxy)hexa-2,4-dienedioate (37c):

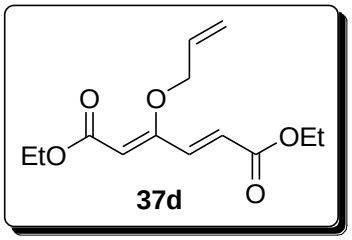
Prepared from benzyl alcohol by following GP-III; Colourless liquid; Yield = 65%; R_f = 0.53 in 1:10 EtOAc/hexanes (double run); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 16.0 Hz, 1H), 7.40-7.36 (m, 5H), 6.55 (d, *J* = 15.6 Hz, 1H), 5.41 (s, 1H), 4.92 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H, 1.31 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 162.7, 135.1, 134.9, 128.7, 128.4, 127.5, 124.8, 98.2, 70.3, 60.8, 60.2, 14.3, 14.2; IR (neat): υ 2984, 1715, 1647, 1588, 1456, 1373, 1146, 829, 743 cm^{-1}; HRMS: calcd for $C_{17}H_{20}O_5$ $[M+H]^+$ 305.1390, Found 305.1390.



37c

(2*Z*,4*E*)-Diethyl 3-(allyloxy)hexa-2,4-dienedioate (37d):

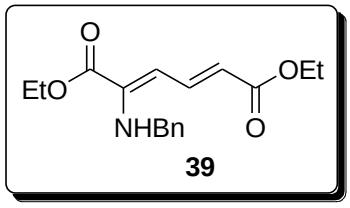
Prepared from allylic alcohol by following GP-III; Colourless liquid; Yield = 35%; R_f = 0.58 in 1:10 EtOAc/hexanes (triple run); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 15.6 Hz, 1H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.02-5.94 (m, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.32(d, *J* = 10.4 Hz, 1H), 5.28 (s, 1H), 4.41 (q, *J* = 5.2 Hz, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 162.5, 134.9, 131.4, 124.7, 118.5, 97.9, 69.0, 60.7, 60.2, 14.3, 14.2; HRMS: calcd for $C_{13}H_{18}O_5$ $[M+H]^+$ 255.1233, Found 255.1232.



37d

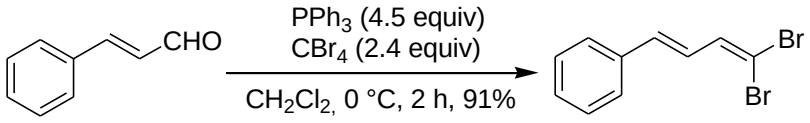
(2*Z*,4*E*)-Diethyl 2-(benzylamino)hexa-2,4-dienedioate (39):[17]

Prepared from benzylamine by following GP-III; Yellow liquid; Yield = 71%; R_f = 0.42 in 1:5 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd *J* = 14.8, 12.0 Hz, 1H), 7.38-7.29 (m, 5H), 5.68 (d, *J* = 14.8 Hz, 1H), 5.52 (d, *J* = 12.0 Hz, 1H), 5.28 (brs, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.24 (d, *J* = 5.2 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 164.2, 142.3, 138.9, 137.0, 128.8, 127.7, 127.6, 116.6, 103.1, 62.4, 59.8, 47.7, 14.4, 14.1.



39

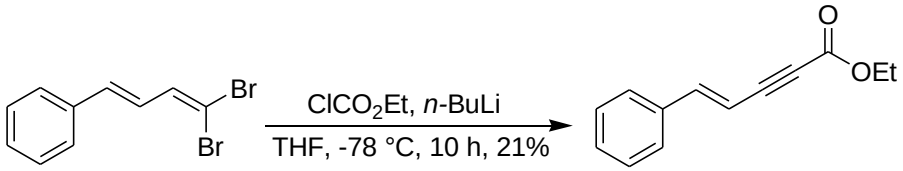
Preparation of (*E*)-(4,4-dibromobuta-1,3-dienyl)benzene (122):[40a]



121 **122**

CBr_4 (3.01 g, 9.08 mmol) was added slowly to a solution of PPh_3 (4.46 g, 17.02 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was allowed to stir at 0 °C over 35 min. To the slurry was added slowly *trans*-cinnamaldehyde (0.5 g, 3.78 mmol) and it was allowed to stir at 0 °C for 1 h. After completion of the reaction, reaction mixture was diluted with diethyl ether and filtered through a pad of celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine solution, dried over anhydrous Na_2SO_4 and evaporated under vacuo. The crude product was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product **122** as yellow liquid; Yield = 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.47 (m, 2H), 7.38-7.30 (m, 3H), 7.12 (d, *J* = 9.6 Hz, 1H), 6.85-6.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 136.3, 135.7, 128.8, 128.6, 126.8, 125.3, 91.3.

Preparation of (*E*)-Ethyl 5-phenylpent-4-en-2-ynoate (40):[40b]



122 **40**

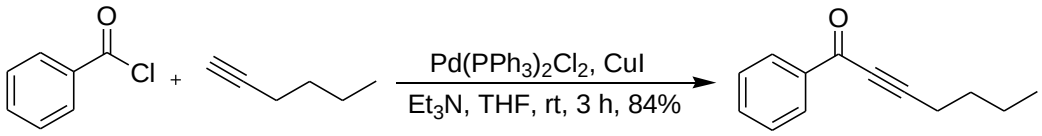
n-BuLi (1.6 M in hexane, 2.82 mL, 4.51 mmol) was added to a solution of dibromoalkene **122** (0.5 g, 1.74 mmol) at -78 °C under nitrogen atmosphere. The resultant reaction mixture was stirred at -78 °C for 1 h and at rt for 1 h. The resultant solution was cooled again to -78 °C and ethyl chloroformate (0.231 mL, 2.43 mmol) was added. The reaction mixture was warmed to rt and maintained the same temperature. After completion of the reaction, it was quenched with sat. NH_4Cl and then extracted with EtOAc. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under vacuo. The crude product was loaded on a silicagel column, it was eluted with EtOAc/hexanes mixture to get the pure **40** as colorless liquid; Yield = 21%; R_f = 0.57 in 1:10 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.38-7.36 (m, 3H), 7.26 (d, *J* = 16.4 Hz, 1H), 6.20

(d, *J* = 16.4 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 147.6, 135.0, 130.0, 128.9, 126.9, 104.7, 85.8, 82.3, 62.0, 14.1; IR (neat): υ 2980, 2204, 1730, 1614, 1366, 1252, 1102, 1014, 962, 750, 688 cm^{-1}; HRMS: calcd for $C_{13}H_{12}O_2$ $[M+H]^+$ 201.0916, Found 201.0915.

IV. General procedure for the preparation of alkynyl ketones (GP-IV):

$PdCl_2(PPh_3)_2$ (0.5 mol%) and Et_3N (1.2 equiv) were added to a solution of acid chloride (1.2 equiv) in dry THF at rt under nitrogen atmosphere. The reaction mixture was allowed to stir for 10 min and then CuI (2 mol %) was added. After stirring for 10 min, 1-alkyne (1.0 equiv) was added. The resultant reaction mixture was allowed to stir at rt. The progress of the reaction was monitored by TLC. After completion of the reaction, 1-2 mL of water was added to the reaction mixture and stirred for 15-30 min. Then the reaction mixture was extracted with EtOAc, washed with saturated NH_4Cl and brine solutions. The resultant organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The crude product was purified by column chromatography using EtOAc/hexanes mixture as eluents and silica gel as stationary phase to get the pure product.

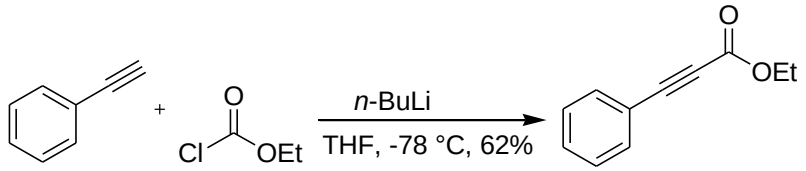
1-Phenylhept-2-yn-1-one (41):[41]



123 **124** **41**

Prepared by following GP-IV; Colorless liquid; Yield = 84%; R_f = 0.43 in 1:10 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.13 (m, 2H), 7.62-7.58 (m, 1H), 7.50-7.46 (m, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.70-1.63 (m, 2H), 1.56-1.46 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 136.9, 133.9, 129.6, 128.5, 96.9, 79.7, 29.8, 22.1, 18.9, 13.5.

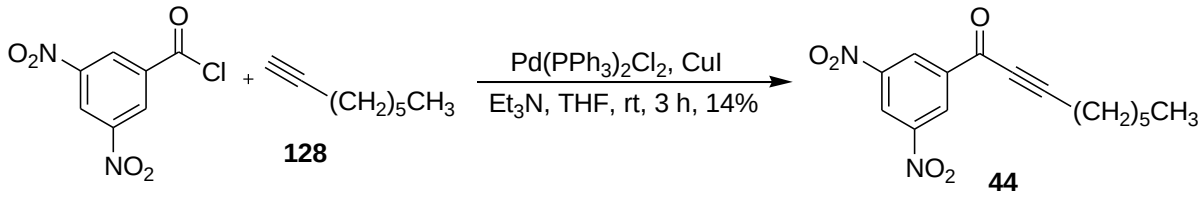
Ethyl 3-phenylpropiolate (42):[42]



125 **126** **42**

n-BuLi (1.6 M in hexane, 15.0 mL, 29.37 mmol) was added to a solution of phenylacetylene (2g, 19.58 mmol) at -78 °C under nitrogen atmosphere. The resultant reaction mixture was stirred at -78 °C for 30 min. Then ethyl chloroformate (2.04 mL, 21.54 mmol) was added. The reaction mixture was stirred at -78 °C. After completion of the reaction, it was quenched with saturated NH_4Cl and then extracted with EtOAc. The resultant organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under vacuo. The crude reaction mixture was loaded on a silicagel column, it was eluted with EtOAc/hexanes mixture to get the pure **42** as colorless liquid; Yield = 62%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

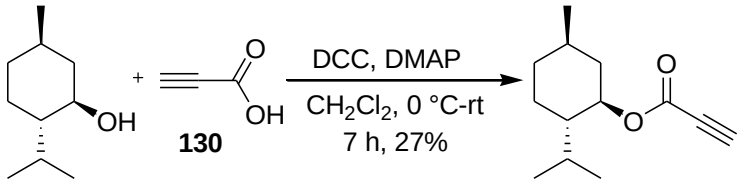
1-(3,5-Dinitrophenyl)non-2-yn-1-one (44):



127 **128** **44**

Prepared by following GP-IV; Yellow liquid; Yield = 14%; R_f = 0.50 in 1:10 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26-9.24 (m, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.75 (m, 2H), 1.56-1.51 (m, 2H), 1.38-1.34 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 148.7, 139.5, 128.8, 122.7, 101.8, 78.6, 31.2, 28.7, 27.5, 22.4, 19.4, 14.0; IR (neat): υ 3099, 2929, 2209, 1661, 1625, 1547, 1345, 1262, 1154, 921, 719 cm^{-1}; HRMS: calcd for $C_{15}H_{16}N_2O_5$ $[M+H]^+$ 305.1138, Found 305.1137.

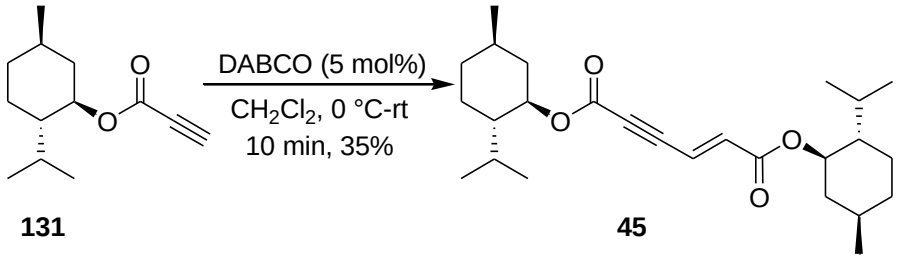
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl propiolate (131):[43]



129 **130** **131**

To a solution of menthol **129** (0.736 g, 4.71 mmol) and propiolic acid **130** (0.3 g, 4.28 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a combined solution of DCC (0.972 g, 4.71 mmol) and DMAP (0.005 g, 0.043 mmol) in CH_2Cl_2 (10 mL) over a period of 15 min. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was filtered and washed with ether and solvents were removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product **131** as colorless liquid; Yield = 27%; R_f = 0.52 in 1:3 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.81 (td, *J* = 10.8, 4.4 Hz, 1H), 2.87 (s, 1H), 2.05-2.021 (m, 1H), 1.94-1.88 (m, 2H), 1.75-1.67 (m, 2H), 1.50-1.45 (m, 2H), 1.34-1.27 (m, 1H), 1.11-1.02 (m, 1H), 0.92 (d, *J* = 3.6 Hz, 3H), 0.90 (d, *J* = 4.0 Hz, 3H), 0.77 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 76.8, 74.2, 55.7, 46.7, 40.4, 34.9, 34.0, 31.4, 26.1, 25.4, 24.7, 23.3, 21.9, 20.7, 16.2.

(*E*)-Bis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) hex-2-en-4-ynedioate (45):[16]

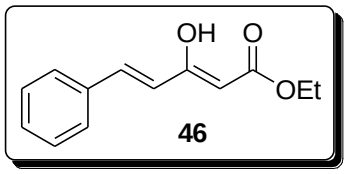


131 **45**

Prepared by following GP-I; Colorless liquid; Yield = 35%; R_f = 0.51 in 1:10 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 16.0 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.81 (td, *J* = 10.8, 4.4 Hz, 1H), 4.74 (td, *J* = 11.2, 4.4 Hz, 1H), 2.04-1.98 (m, 2H), 1.91-1.79 (m, 2H), 1.70-1.66 (m, 4H), 1.52-1.37 (m, 4H), 1.09-0.98 (m, 4H), 0.91-0.86 (m, 14H), 0.76 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 152.8, 135.7, 121.4, 87.2, 81.4, 76.8, 75.3, 46.9, 46.7, 40.7, 40.5, 34.1, 34.0, 31.4, 31.3, 26.3, 26.1, 23.4, 23.3, 21.9 (2C), 20.6, 16.3, 16.1.

(2*Z*,4*E*)-Ethyl 3-hydroxy-5-phenylpenta-2,4-dienoate (46):

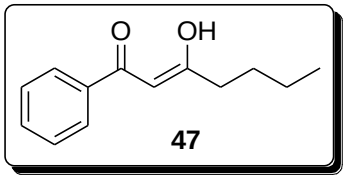
Prepared by following GP-II; Yellow liquid; Yield = 76%; R_f = 0.47 in 1:10 EtOAc/hexanes; Keto/enol : 3:2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.99 (d, *J* = 1.2 Hz, 1H), 7.62 (s, 1H), 7.58-7.55 (m, 3H), 7.51-7.46 (m, 2H), 7.43- 7.39 (m, 4H), 7.37-7.32 (m, 2H), 6.81 (d, *J* = 16.4 Hz, 1H), 6.44 (dd, *J* = 16.0, 1.2 Hz, 1H), 5.17 (s, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 172.9, 169.2, 167.4, 144.7, 136.8, 135.4, 134.1, 131.0, 129.4, 129.0, 128.8, 128.5, 127.6, 125.2, 121.9, 92.0, 61.5, 60.2, 47.7, 14.3, 14.1; IR (neat): υ 3394, 3058, 2934, 1645, 1739, 1418, 1226, 1143, 1045, 802, 734 cm^{-1}; HRMS: calcd for $C_{13}H_{14}O_3$ $[M+H]^+$ 219.1022, Found 219.1023.



46

(*Z*)-3-Hydroxy-1-phenylhept-2-en-1-one (47):

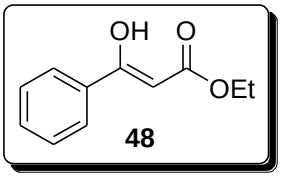
Prepared by following GP-II; Colorless liquid; Yield = 91%; R_f = 0.69 in 1:10 EtOAc/hexanes (double run); Keto:enol = 1:10; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.22 (br s, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.70 (pent, *J* = 7.6 Hz, 2H), 1.43 (sextet, *J* = 7.6 Hz, 2H), 0.97 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 183.5, 132.2, 128.6, 127.0, 96.1, 39.0, 27.9, 22.4, 13.8.



47

(*Z*)-Ethyl 3-hydroxy-3-phenylacrylate (48):[44]

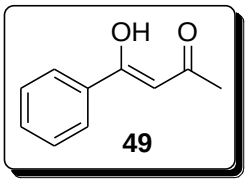
Prepared by following GP-II; Colorless liquid; Yield = 85%; R_f = 0.67 in 1:3 EtOAc/hexanes (double run); Keto/enol: 9:1; ^{1}H NMR (400 MHz, $CDCl_3$): (keto form) δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); and ^{1}H NMR (400 MHz, $CDCl_3$): (enol form) δ 12.59 (s, 1H), 7.77 (d, *J* = 6.8 Hz, 2H), 7.44-7.38 (m, 3H), 5.66 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): (keto+enol) δ 192.6, 173.2, 171.4, 167.5, 136.0, 133.7, 133.4, 131.2, 128.8, 128.5, 126.0, 87.4, 61.5, 60.3, 46.0, 14.3, 14.1.



48

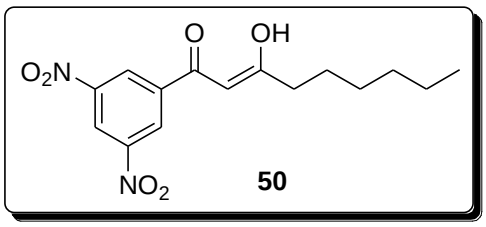
(*Z*)-4-Hydroxy-4-phenylbut-3-en-2-one (49):[45]

Prepared by following GP-II; Colorless liquid; Yield = 84%; R_f = 0.58 in 1:10 EtOAc/hexanes; Keto:enol = 1:11.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.17 (br s, 1H), 7.88-7.86 (m, 2H), 7.53-7.50 (m, 1H), 7.46-7.42 (m, 2H), 6.18 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 183.3, 134.8, 132.2, 128.6, 127.0, 96.7, 25.8.



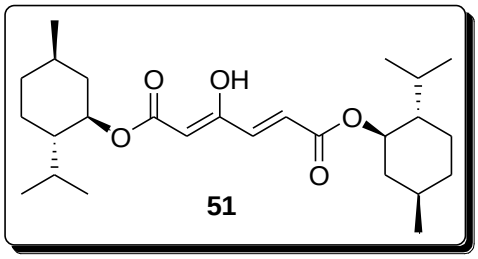
(Z)-1-(3,5-Dinitrophenyl)-3-hydroxynon-2-en-1-one (50):

Prepared by following GP-II; Yellow liquid; Yield = 80%; R_f = 0.50 in 1:10 EtOAc/hexanes; keto:enol = 1:99; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (m, 1H), 9.02-9.01 (m, 2H), 6.34 (s, 1H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.73 (m, 2H), 1.35-1.31 (m, 4H), 1.38-1.34 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 177.4, 148.8, 138.8, 128.8, 126.7, 121.1, 97.0, 39.5, 31.5, 28.9, 25.5, 22.4, 14.0; IR (NEAT): υ 3420, 3105, 2924, 2209, 1625, 1542, 1340, 1257, 1143, 916, 729 cm^{-1}; HRMS: calcd for $C_{15}H_{18}N_2O_6$ $[M+H]^+$ 323.1244, Found 323.1239.



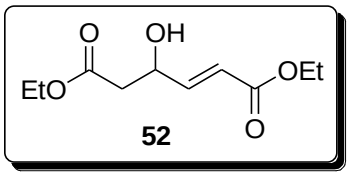
(2*Z*,4*E*)-Bis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 3-hydroxyhexa-2,4-dienedioate (51):

Prepared by following GP-II; Yield = 28%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.7 (d, *J* = 1.6 Hz, 1H), 6.90 (dd, *J* = 15.2, 1.2 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 5.27 (s, 1H), 4.84-4.72 (m, 2H), 2.04-1.99 (m, 2H), 1.93-1.72 (m, 2H), 1.69-1.67 (m, 4H), 1.50-1.37 (m, 4H), 1.10-0.99 (m, 4H), 0.99-0.87 (m, 14H), 0.78-.73 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 152.8, 135.7, 121.4, 87.2, 81.4, 76.8, 75.3, 46.9, 46.7, 40.7, 40.5, 34.1, 34.0, 31.4, 31.3, 26.3, 26.1, 23.4, 23.3, 21.9 (2C), 20.6, 16.3, 16.1; HRMS: calcd for $C_{26}H_{42}O_5Na$ $[M+Na]^+$ 457.2930, Found 457.2934**.**



Preparation of (*E*)-Diethyl 4-hydroxyhex-2-enedioate (52):

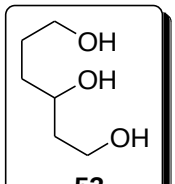
To a stirred solution of hydrated enyne diester **22** (0.395 g, 1.84 mmol) in methanol, was added $NaBH_4$ (0.077 g, 2.03 mmol) at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir. After 2 h 40 min the reaction mixture was quenched with saturated NH_4Cl solution and solvent was removed. The crude reaction mixture was extracted with EtOAc, washed with brine solution. The resultant organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The crude reaction mixture was purified by column chromatography using EtOAc/hexanes mixtures as eluents to get pure **52** as colorless liquid. Yield = 58%; R_f = 0.56 in 1:1 EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (dd, *J* = 15.6, 4.0 Hz, 1H), 6.14 (d, *J* = 15.6 Hz, 1H), 4.72 (br s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.26 (d, *J* = 3.2 Hz, 1H), 2.66 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.52 (dd, *J* = 16.4, 8.8 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 166.3, 147.3, 121.2, 67.1, 61.0, 60.5, 40.3, 14.2 (2C); IR (NEAT): υ 3437, 2982, 1726, 1715, 1269, 1161, 1105, 1034 862 cm^{-1}; HRMS: calcd for $C_{10}H_{16}O_5Na$ $[M+Na]^+$ 239.0896, Found 239.0890



52

Preaparation of Hexane-1,3,6-triol (53):

To a stirred solution of (*E*)-diethyl 4-hydroxyhex-2-enedioate **52** (0.04 g, 0.185 mmol) in dry diethyl ether was added $LiAlH_4$ (0.035 g, 0.925 mmol) at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir at room temperature. After 7 h the reaction mixture was quenched with few drops of water at 0 °C. Reaction mixture was filtered through a pad of celite and washed with EtOAc, The resultant solution was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The resultant crude **53** was used for further reactions without purification. Yield = 20 mg

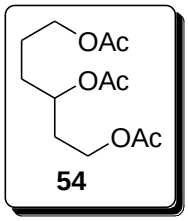


53

Hexane-1,3,6-triyl triacetate (54):

To a stirred solution of hexane-1,3,6-triol **53** (0.02g, 0.149 mmol) in CH_2Cl_2 was added DMAP (0.002g, 0.0149 mmol) and Et_3N (0.166 mL, 1.192 mmol). The reaction was cooled to 0 °C and Ac_2O (0.14 mL, 1.49 mmol, 10.0 equiv) was added slowly. The resultant reaction mixture was stirred at rt. After 45 min, solvent was removed in a rotovap. The residue was

loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure triacetate **54** as colorless liquid. Yield = 52%; R_f = 0.63 in 1:1 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.06-4.99 (m, 1H), 4.11-4.07 (m, 4H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.92-1.87 (m, 2H), 1.67-1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (2C), 170.6, 70.4, 63.9, 60.6, 32.9, 30.7, 24.4, 21.0, 20.9 (2C); IR (neat): υ 2964, 1736, 1439, 1370, 1240, 1042 cm^{-1}; HRMS: calcd for $C_{12}H_{20}O_6Na$ $[M+Na]^+$ 283.1158, Found 283.1156



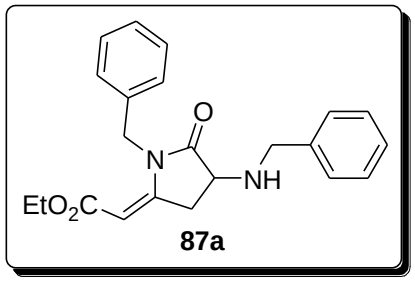
54

V. General procedure for the formation of substituted γ-lactam (GP-V):

To a solution of hydrated product of enyne diester **22** (1.0 equiv) in methanol, arylmethylamine derivative (2.5 equiv) was added. The reaction mixture was allowed to stir at reflux condition. After specified time given in table 5, solvent was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product.

(*Z*)-Ethyl 2-(1-benzyl-4-(benzylamino)-5-oxopyrrolidin-2-ylidene)acetate (87a):

Prepared by following GP-V using **22** and benzylamine; Yellow liquid; R_f = 0.42 in 1:1 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 8H), 7.21-7.19 (m, 2H), 5.22 (t, *J* = 1.6 Hz, 1H), 4.75 (d, *J* = 15.2 Hz, 1H), 4.69(d, *J* = 15.2 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.97 (d, *J* = 12.8 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.70-3.62 (m, 2H), 3.03-2.94 (m, 1H), 2.06 (br s, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 166.9, 156.5, 139.0, 134.5, 128.8, 128.6, 128.3, 127.8, 127.4, 127.1, 93.6, 59.7, 54.9, 51.5, 44.2, 33.1, 14.3; IR (neat): υ 3337, 3055, 2986, 1630, 1265, 1148, 743 cm^{-1}; HRMS: calcd for $C_{22}H_{24}N_2O_3$ $[M+H]^+$ 365.1866, Found 365.1869.

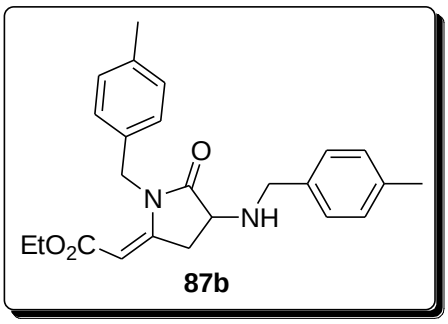


87a

(*Z*)-Ethyl 2-(1-(4-methylbenzyl)-4-((4-methylbenzyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (87b):

Prepared by following GP-V using **22** and 4-methylbenzylamine; Yellow liquid; R_f = 0.15 in 1:1 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 2H), 7.15-7.08 (m, 6H),

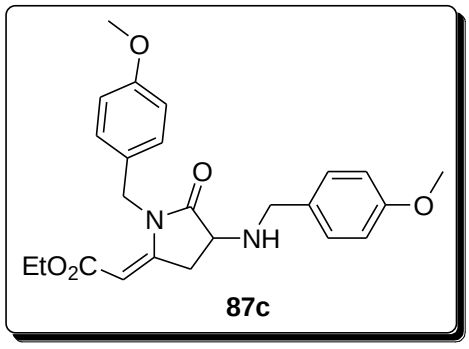
5.22 (s, 1H), 4.70 (d, *J* = 15.6 Hz, 1H), 4.64(d, *J* = 15.6 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.79 (d, *J* = 12.8 Hz, 1H), 3.67-3.59 (m, 2H), 3.01-2.92 (m, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 167.0, 156.6, 137.5, 136.9, 135.9, 131.5, 129.4, 129.2, 128.2, 127.1, 93.4, 59.6, 54.7, 51.1, 44.0, 33.1, 21.0, 14.3; IR (neat): υ 3297, 2984, 2924, 1626, 1312, 1034, 814 cm^{-1}; HRMS: calcd for $C_{24}H_{28}N_2O_3$ $[M+H]^+$ 393.2179, Found 393.2178.



87b

(Z)-Ethyl 2-(1-(4-methoxybenzyl)-4-((4-methoxybenzyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (87c):

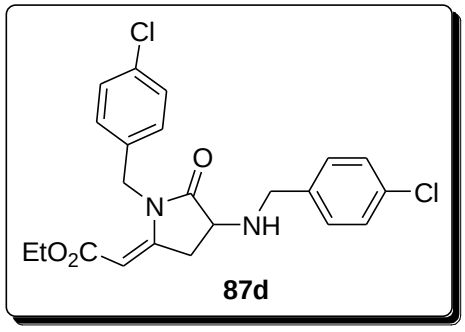
Prepared by following GP-V using **22** and 4-methoxybenzylamine; Yellow liquid; R_f = 0.12 in 1:3 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 1H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.62 (d, *J* = 15.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.89 (d, *J* = 13.2 Hz, 1H), 3.80 (s, 3H), 3.77 (d, *J* = 12.8 Hz, 1H), 3.78 (s, 3H), 3.66-3.59 (m, 2H), 2.99-2.91 (m, 1H), 1.95 (br s, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 167.0, 159.2, 158.9, 156.6, 131.1, 129.5, 128.6, 126.7, 114.2, 114.0, 93.5, 59.7, 55.3, 54.8, 50.9, 43.7, 33.1, 14.4; HRMS: calcd for $C_{24}H_{28}N_2O_5$ $[M+H]^+$ 425.2077, Found 425.2082



87c

(*Z*)-Ethyl 2-(1-(4-chlorobenzyl)-4-((4-chlorobenzyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (87d):

Prepared by following GP-V using **22** and 4-chlorobenzylamine; Yellow liquid; R_f = 0.25 in 1:2 EtOAc/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.27 (m, 6H), 7.16-7.13 (m, 2H), 5.18 (t, *J* = 1.5 Hz, 1H), 4.72-4.65 (m, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.92

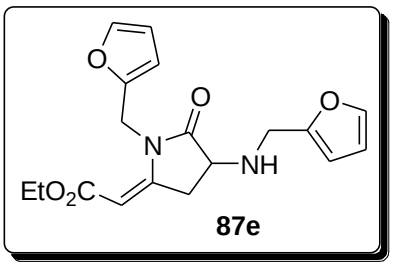


87d

(d, *J* = 13.0 Hz, 1H), 3.84 (d, *J* = 13.5 Hz, 1H), 3.68-3.62 (m, 2H), 2.99-2.93 (m, 1H), 2.96 (ddd, *J* = 21.5, 8.5, 2.5 Hz, 1H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 166.8, 156.0, 137.4, 133.8, 133.2, 133.0, 129.6, 129.1, 128.7, 128.5, 93.8, 59.8, 54.8, 50.8, 43.6, 33.1, 14.3; HRMS: calcd for $C_{22}H_{22}Cl_2N_2O_3$ $[M+H]^+$ 433.1086, Found 433.1082

(*Z*)-Ethyl 2-(1-(furan-2-ylmethyl)-4-((furan-2-ylmethyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (87e):

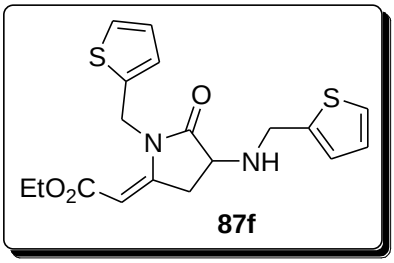
Prepared by following GP-V using **22** and furfurylamine; Yellow liquid; R_f = 0.13 in 1:3 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 14.4, 0.8 Hz, 2H), 6.31-6.28 (m, 3H), 6.22-6.21 (m, 1H), 5.45 (s, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.96 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.8 Hz, 1H), 3.66-3.57 (m, 2H), 2.92-2.88 (m, 1H), 2.13 (br s, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 167.0, 156.1, 152.4, 147.9, 142.6, 142.3, 110.4, 110.1, 108.9, 107.8, 93.4, 59.7, 54.3, 43.8, 37.3, 32.9, 14.4; IR (neat): υ 3327, 3055, 2986, 1630, 1422, 1265, 1148, 748 cm^{-1}; HRMS: calcd for $C_{18}H_{20}N_2O_5$ $[M+H]^+$ 345.1451, found 345.1451.



87e

(*Z*)-Ethyl 2-(5-oxo-1-(thiophen-2-ylmethyl)-4-((thiophen-2-ylmethyl)amino)pyrrolidin-2-ylidene)acetate (87f):

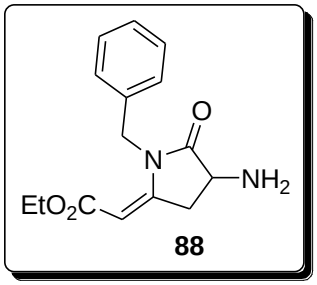
Prepared by following GP-V using **22** and 2-thiophenemethylamine; Yellow liquid; R_f = 0.09 in 1:3 EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.21 (m, 2H), 7.02-7.01 (m, 1H), 6.96-6.93 (m, 3H), 5.39 (s, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.14 (d, *J* = 14.0 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.69-3.60 (m, 2H), 2.98-2.90 (m, 1H), 2.12 (br s, 1H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 166.9, 155.8, 142.3, 136.6, 127.0, 126.9, 126.8, 125.7, 125.6, 125.0, 93.4, 59.8, 54.4, 45.9, 39.1, 33.1, 14.4 ; IR (neat): υ 3412, 3055, 2986, 1630, 1265, 1140, 746 cm^{-1}; HRMS: calcd for $C_{18}H_{20}N_2O_3S_2$ $[M+H]^+$ 377.0994, Found 377.0996.



87f

(*Z*)-Ethyl 2-(4-amino-1-benzyl-5-oxopyrrolidin-2-ylidene)acetate (88):

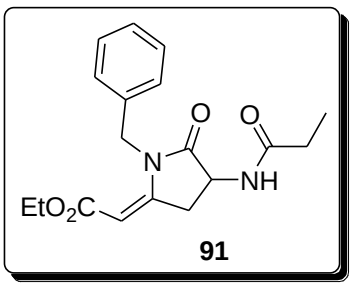
An oven dried round bottom flask was charged with γ-lactam substrate **87a** (1.0 equiv) and 10 mol% of Pd/C (10% Pd) and hydrogen gas was passed through a bladder. Then dry methanol was added. The reaction mixture was allowed to stir at room temperature for 24 h under hydrogen atmosphere baloon, then the reaction mixture was filtered through a pad of celite 545 and washed with ethyl acetate and the solvents were removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure product **88**. Yield = 50%; Colorless gummy liquid; R_f = 0.21 in EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27(m, 3H), 7.22-7.20 (m, 2H), 5.23 (s, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.83-3.75 (m, 2H), 2.87-2.79 (m, 1H), 1.74 (br s, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 166.8, 155.9, 134.6, 128.8, 127.8, 127.1, 93.7, 59.7, 50.1, 44.3, 34.7, 14.3; IR (neat): υ 3364, 2982, 1620, 1416, 1315, 1148, 822 cm^{-1}; HRMS: calcd for $C_{15}H_{18}N_2O_3$ $[M+H]^+$ 275.1396, Found 275.1394.



88

Ethyl 2-(1-benzyl-5-oxo-4-propionamidopyrrolidin-2-ylidene)acetate (91):

To a stirred solution of substrate **88** (0.010 g, 0.036 mmol) in CH_2Cl_2 was added triethylamine (7.3 µL, 0.052 mmol) at 0 ^{o}C. The solution was stirred for 10 min., and then propionyl chloride (4.6 µL, 0.04 mmol) was added. The reaction mixture was allowed to stir at rt. The reaction was monitored by TLC. After completion of the reaction, it was extracted with CH_2Cl_2 and washed with brine solution. The resultant organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The crude residue was subjected into column chromatography and eluted with ethyl acetate/hexanes to get the pure desired product as colorless liquid; Yield = 94%; R_f = 0.43 in EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 7.29-7.25 (m, 3H), 6.36 (d, *J* = 6.8 Hz, 1H), 5.21 (t, *J* = 1.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 16.0 Hz, 1H), 4.32 (dt, *J* = 9.6, 6.8 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.82 (ddd, *J* = 18.4, 9.6, 1.2 Hz, 1H), 3.09 (ddd, *J* = 18.8, 6.8, 2.4 Hz, 1H), 2.28 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 174.1, 166.8, 155.5, 134.4,



91

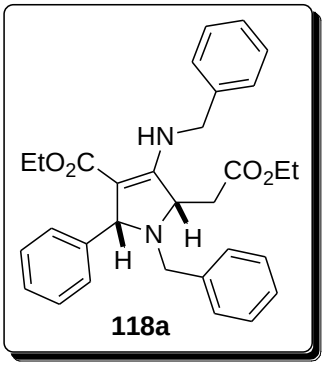
128.8, 127.7, 127.0, 93.9, 59.7, 49.4, 44.6, 32.7, 29.0, 14.3, 9.4; IR (KBr): υ 3282, 3068, 2975, 1654, 1616, 1545, 1156, 827, 701 cm^{-1};

VI. General procedure for synthesis of substituted pyrrolidine derivatives (GP-VI):

To a stirred solution of aromatic/aliphatic aldehyde (1.0 equiv) and aromatic/aliphatic benzyl amine derivative (2.5 equiv) in dry methanol, acetic acid (2.0 equiv) was added and stirred for 10-15 min. at room temperature. To this hydrated enyne diester **22** was added, and the reaction mixture was heated to reflux. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, methanol was removed in a rotovap. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure pyrrolidine dervtive as a mixture of diastereomers.

Ethyl 1-benzyl-4-(benzylamino)-5-(2-ethoxy-2-oxoethyl)-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (118a):

Prepared by following GP-VI; Yellow liquid; Yield = 49%, R_f = 0.50 in 1:3 EtOAc/hexanes; dr: 11.5:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (t, *J* = 5.6 Hz, 1H), 7.40-7.23 (m, 15H), 4.84 (s, 1H), 4.51-4.50 (m, 2H), 4.20-4.15 (m, 1H), 4.08-4.03 (m, 1H), 3.98-3.93 (m, 2H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 14.0 Hz, 1H), 3.64 (t, *J* = 6.8 Hz, 1H), 2.87 (dd, *J* = 17.2, 6.8 Hz, 1H), 2.60 (dd, *J* = 17.2, 5.2 Hz, 1H), 1.22 (t, *J* = 6.8 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 169.7, 156.9, 145.2, 139.5, 138.9, 129.2, 128.9, 128.7, 128.1, 127.4, 127.3, 126.9, 126.7, 126.3, 91.8, 60.5, 60.1, 58.7, 54.0, 53.1, 46.1, 26.7, 14.2, 14.1; HRMS (ESI): calcd for $C_{31}H_{34}N_2O_4$ $[M+H]^+$ 499.2598, Found 499.2596.

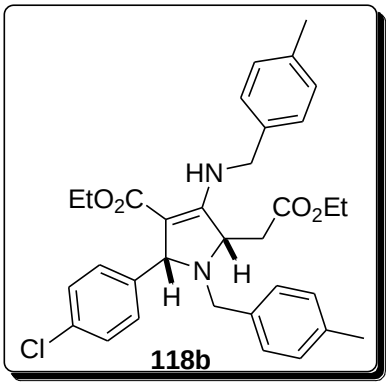


118a

Ethyl 2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-1-(4-methylbenzyl)-4-(4-methylbenzylamino)-2,5-dihydro-1H-pyrrole-3-carboxylate (118b):

Prepared by following GP-VI; Yellow liquid; Yield = 54%, R_f = 0.47 in 1:3 EtOAc/hexanes; dr: 9.0:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (t, *J* = 5.2 Hz, 1H), 7.27-7.12 (m, 10H), 7.09-7.07 (m, 2H), 4.76 (s, 1H), 4.43-4.41 (m, 2H), 4.17-4.11 (m, 1H), 4.06-4.02 (m, 1H), 3.95-3.90 (m, 2H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.58-3.54 (m, 2H), 2.84 (dd,

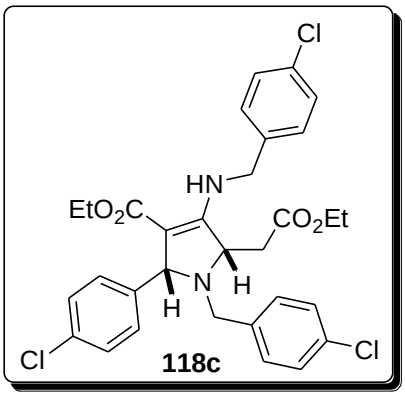
J = 17.2, 6.8 Hz, 1H), 2.54 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 169.5, 157.1, 144.0, 137.0, 136.6, 136.1, 135.7, 131.8, 130.5, 129.4, 128.9, 127.5, 126.7, 91.1, 60.6, 59.5, 58.7, 53.9, 52.8, 46.0, 26.7, 21.1, 21.0, 14.2, 14.1; IR (neat): υ 3271, 2980, 2920, 1731, 1654, 1599, 1227, 1084, 1188, 799 cm^{-1}; HRMS (ESI): calcd for $C_{33}H_{37}ClN_2O_4$ $[M+H]^+$ 561.2521, Found 561.2520.



118b

Ethyl 1-(4-chlorobenzyl)-4-(4-chlorobenzylamino)-2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (118c):

Prepared by following GP-VI; Viscous yellow liquid; Yield = 74%, R_f = 0.50 in 1:3 EtOAc/hexanes; dr: 3.8:1.0; Major isomer (*syn*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.46 (t, *J* = 6.4 Hz, 1H), 7.35-7.32 (m, 2H), 7.26-7.19 (m, 10H), 4.73 (s, 1H), 4.44-4.43 (m, 2H), 4.18-4.13 (m, 1H), 4.08-4.01 (m, 1H), 3.98-3.89 (m, 2H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.55-3.52 (m, 1H), 2.78 (dd, *J* = 17.2, 6.8 Hz, 1H), 2.53 (dd, *J* = 17.2, 5.6 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 169.5, 156.7, 143.5, 137.7, 137.3, 133.2, 132.8, 132.1, 130.4, 130.2, 129.0, 128.4, 128.1, 127.6, 91.7, 60.8, 59.7, 58.9, 53.9, 52.5, 45.6, 26.7, 14.2, 14.1; IR (neat): υ 3271, 2981, 1901, 1732, 1649, 1594, 1490, 1222, 1085, 1019, 811, 734 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{31}Cl_3N_2O_4$ $[M+Na]^+$ 623.1247, Found 623.1304.

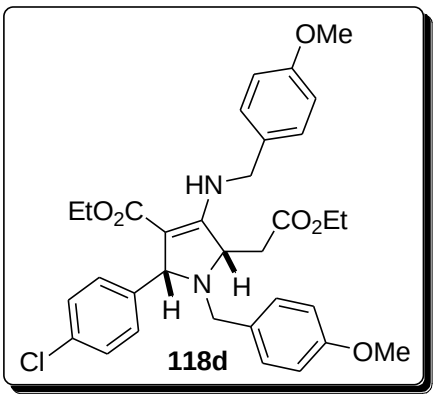


118c

Ethyl 2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-1-(4-methoxybenzyl)-4-(4-methoxybenzylamino)-2,5-dihydro-1H-pyrrole-3-carboxylate (118d):

Prepared by following GP-VI; Viscous yellow liquid; Yield = 67%; R_f = 0.39 in 1:3 EtOAc/hexanes; dr: 12: 1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (br s, 1H), 7.24-7.18 (m, 8H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 7.6 Hz, 2H), 4.75 (s, 1H), 4.41-4.40 (m, 2H), 4.19-4.04 (m, 2H), 3.93 (q, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.69 (d,

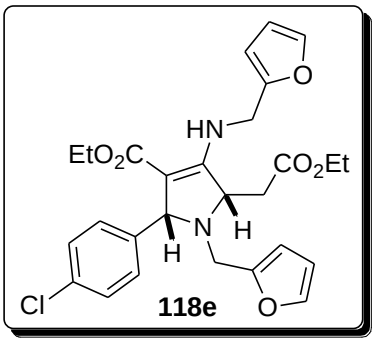
J = 12.8 Hz, 1H), 3.58-3.55 (m, 1H), 3.53 (d, *J* = 12.8 Hz, 1H), 2.85 (dd, *J* = 17.2, 7.2 Hz, 1H), 2.55 (dd, *J* = 17.6, 5.2 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 169.5, 158.9, 158.7, 157.1, 144.0, 131.8, 131.2, 130.7, 130.5, 130.0, 128.1, 127.5, 114.2, 113.6, 91.0, 60.6, 59.3, 58.7, 55.3, 55.2, 53.8, 52.4, 45.7, 26.6, 14.2; IR (neat): υ 3271, 2975, 2833, 1742, 1655, 1594, 1512, 1359, 1249, 1090, 833, 740 cm^{-1}; HRMS (ESI): calcd for $C_{33}H_{37}ClN_2O_6$ $[M+H]^+$ 593.2419, Found 593.2418.



118d

Ethyl 2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-1-(furan-2-ylmethyl)-4-(furan-2-ylmethylamino)-2,5-dihydro-1H-pyrrole-3-carboxylate (118e):

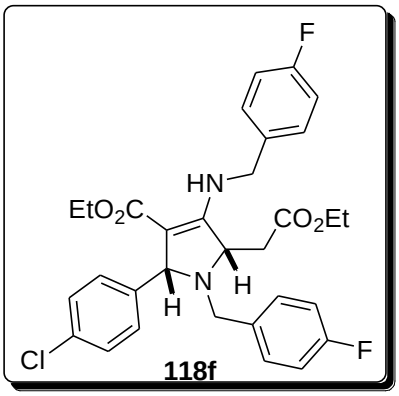
Prepared by following GP-VI; Yellow liquid; Yield = 70%; R_f = 0.58 in 1:3 EtOAc/hexanes; dr: 10:1.0; Major isomer (*syn*) ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (t, *J* = 6.0 Hz, 1H), 7.37 (dd, *J* = 2, 0.8 Hz, 1H), 7.34 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.28-7.18 (m, 4H), 6.32 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.28 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.21 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.15-6.14 (m, 1H), 4.81 (s, 1H), 4.42-4.41 (m, 2H), 4.20-4.08 (m, 2H), 3.96-3.90 (m, 2H), 3.89-3.85 (m, 1H), 3.66-3.60 (m, 2H), 2.95 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.69 (dd, *J* = 17.2, 5.6 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.3, 156.2, 152.6, 151.9, 143.5, 142.2, 142.1, 132.0, 130.5, 127.6, 110.4, 110.1, 108.5, 106.9, 92.1, 60.7, 60.0, 58.9, 54.3, 46.5, 39.5, 26.7, 14.2, 14.1; IR (neat): υ 3271, 2975, 1732, 1655, 1600, 1244, 1014, 734, 597 cm^{-1}; HRMS (ESI): calcd for $C_{27}H_{29}ClN_2O_6$ $[M+H]^+$ 513.1793, Found 513.1793.



118e

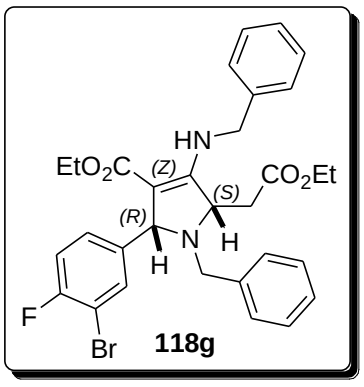
Ethyl 2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-1-(4-fluorobenzyl)-4-(4-fluorobenzylamino)-2,5-dihydro-1H-pyrrole-3-carboxylate (118f):

Prepared by following GP-VI; Yellow liquid; Yield = 64%, R_f = 0.50 in 1:3 EtOAc/hexanes; dr: 19:1.0; Major isomer (*syn*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.44 (t, *J* = 6.0 Hz, 1H), 7.28-7.20 (m, 8H), 7.07-7.03 (m, 2H), 6.99-6.94 (m, 2H), 4.74 (s, 1H), 4.45-4.43 (m, 2H), 4.19-4.12 (m, 1H), 4.09-4.03 (m, 1H), 3.96-3.90 (m, 2H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 12.8 Hz, 1H), 3.56-3.53 (m, 1H), 2.82 (dd, *J* = 17.2, 7.2 Hz, 1H), 2.55 (dd, *J* = 17.2, 5.6 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 169.5, 162.1 (d, *J* = 244.4 Hz), 162.1 (d, *J* = 243.5), 156.8, 143.7, 134.9, 134.9, 134.5, 134.5, 132.1, 130.5, 130.4 (d, *J* = 8.1 Hz), 128.5 (d, *J* = 8.1 Hz), 127.7, 115.7 (d, *J* = 21.6 Hz), 115.0 (d, *J* = 21.2 Hz), 91.5, 60.8, 59.6, 58.9, 53.9, 52.4, 45.6, 26.7, 14.2, 14.2; IR (neat): υ 3271, 2981, 1884, 1726, 1649, 1594, 1512, 1222, 827, 740 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{31}ClF_2N_2O_4$ $[M+H]^+$ 569.2019, Found 569.2019.



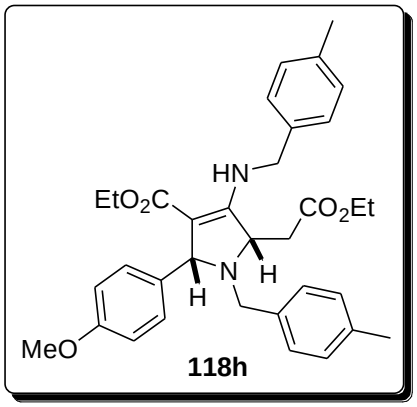
Ethyl 1-benzyl-4-(benzylamino)-2-(3-bromo-4-fluorophenyl)-5-(2-ethoxy-2-oxoethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (118g):

Prepared by following GP-VI; Yellow liquid; Yield = 42%, R_f = 0.61 in 1:3 EtOAc/hexanes; dr: 6.7:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (t, *J* = 6.0 Hz, 1H), 7.40-7.22 (m, 13H), 4.79 (s, 1H), 4.50-4.48 (m, 2H), 4.19-4.13 (m, 1H), 4.10-3.91 (m, 3H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.62 (d, *J* = 13.6 Hz, 1H), 3.57 (t, *J* = 6.0 Hz, 1H), 2.88 (dd, *J* = 17.2, 6.4 Hz, 1H), 2.60 (dd, *J* = 17.2, 5.6 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.3, 157.1, 143.0, 139.0, 138.7, 134.0, 129.5 (d, *J* = 7.57 Hz), 128.8, 128.2, 127.4, 127.1, 126.7, 115.3 (d, *J* = 22.0 Hz), 91.3, 60.6, 59.5, 58.8, 53.9, 53.3, 46.2, 27.1, 14.1; IR (neat): υ 3282, 3036, 2975, 1736, 1649, 1600, 975, 811, 740, 696, 668 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{32}BrFN_2O_4$ $[M+H]^+$ 595.1608, Found 595.1605.



Ethyl 5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-1-(4-methylbenzyl)-4-(4-methylbenzylamino)-2,5-dihydro-1H-pyrrole-3-carboxylate (118h):

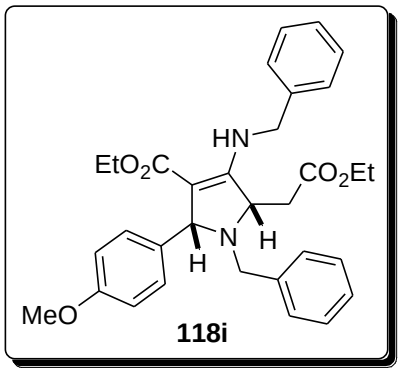
Prepared by following GP-VI; Yellow liquid; Yield = 55%, R_f = 0.48 in 1:3 EtOAc/hexanes; dr: 12:1.0; Major isomer (*syn*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.43 (t, *J* = 6.0 Hz, 1H), 7.28-7.18 (m, 8H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.76 (s, 1H), 4.46-4.45 (m, 2H), 4.18-4.16 (m, 1H), 4.09-4.05 (m, 1H), 3.98-3.93 (m, 2H), 3.80 (s, 3H), 3.71 (d, *J* = 13.0 Hz, 1H), 3.64-62 (m, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 2.84 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.56 (dd, *J* = 17.5, 6.0 Hz, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 169.9, 158.0, 156.9, 137.4, 136.9, 136.6, 136.4, 135.9, 130.1, 129.4, 128.9, 128.8, 126.8, 112.7, 91.6, 60.5, 59.2, 58.6, 55.2, 53.9, 52.6, 45.9, 26.4, 21.1 (2C), 14.2 (2C).



118h

Ethyl 1-benzyl-4-(benzylamino)-5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (118i):

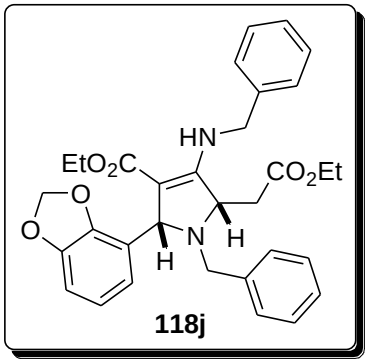
Prepared by following GP-VI; Yellow liquid; Yield = 29%, R_f = 0.44 in 1:3 EtOAc/hexanes; dr: 4.9:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (t, *J* = 6.0 Hz, 1H), 7.39-7.22 (m, 12H), 6.81-6.78 (m, 2H), 4.76 (s, 1H), 4.50-4.48 (m, 2H), 4.18-4.13 (m, 1H), 4.07-4.01 (m, 1H), 3.97-3.90 (m, 2H), 3.78 (s, 3H), 3.75 (d, *J* = 15.2 Hz, 1H), 3.64 (d, *J* = 14.0 Hz, 1H), 3.62(t, *J* = 7.2 Hz, 1H), 2.83 (dd, *J* = 17.2, 7.2 Hz, 1H), 2.56 (dd, *J* = 17.2, 5.6 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 169.8, 158.1, 156.8, 139.6, 138.9, 128.9, 128.7, 128.1, 127.3, 126.9, 126.7, 114.3, 112.7, 91.8, 60.5, 59.3, 58.7, 55.5, 55.1, 53.9, 53.0, 46.1, 26.5, 14.2; HRMS (ESI): calcd for $C_{32}H_{36}N_2O_5$ $[M+H]^+$ 529.2702, Found 529.2701.



118i

Ethyl 2-(benzo[d][1,3]dioxol-4-yl)-1-benzyl-4-(benzylamino)-5-(2-ethoxy-2-oxoethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (118j):

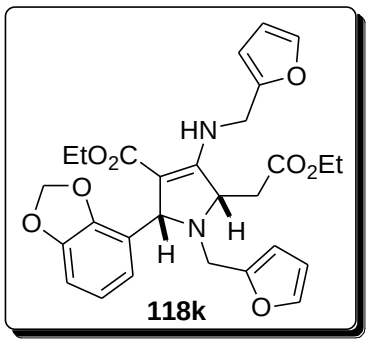
Prepared by following GP-VI; Yellow liquid; Yield = 49%, R_f = 0.47 in 1:3 EtOAc/hexanes; dr: 19:1.0; Major isomer (*syn*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.47 (t, *J* = 6.0 Hz, 1H), 7.40-7.29 (m, 10H), 6.88 (d, *J* = 1.5 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.94-5.93 (m, 2H), 4.75 (s, 1H), 4.51-4.50 (m, 2H), 4.21-4.15 (m, 1H), 4.10-4.04 (m, 1H), 4.00-3.96 (m, 2H), 3.77 (d, *J* = 13.0 Hz, 1H), 3.67 (d, *J* = 13.5 Hz, 1H), 3.65-3.64 (m, 1H), 2.85 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.57 (dd, *J* = 17.0, 5.5 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 169.7, 156.9, 147.0, 146.0, 139.5, 139.3, 138.9, 128.9, 128.8, 128.1, 127.3, 127.0, 126.8, 122.5, 109.3, 106.9, 100.6, 91.7, 60.6, 59.8, 58.7, 53.9, 53.0, 46.2, 26.5, 14.2, 14.2; HRMS (ESI): calcd for $C_{32}H_{34}N_2O_6$ $[M+H]^+$ 543.2496, Found 543.2493.



118j

Ethyl 2-(benzo[d][1,3]dioxol-4-yl)-5-(2-ethoxy-2-oxoethyl)-1-(furan-2-ylmethyl)-4-(furan-2-ylmethylamino)-2,5-dihydro-1H-pyrrole-3-carboxylate (118k):

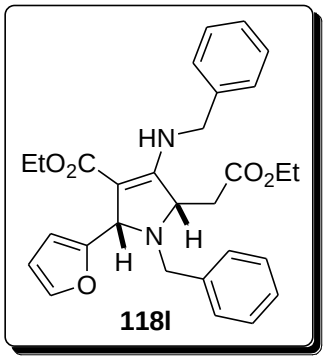
Prepared by following GP-VI; Yellow liquid; Yield = 59%; R_f = 0.32 in 1:3 EtOAc/hexanes; dr: 12:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (br s, 1H), 7.36 (d, *J* = 10.8 Hz, 2H), 6.86-6.84 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.30 (d, *J* = 14.4 Hz, 2H), 6.19 (d, *J* = 20.4 Hz, 2H), 5.90 (s, 2H), 4.76 (s, 1H), 4.42-4.40 (m, 2H), 4.19-4.08 (m, 2H), 3.97-3.93 (m, 2H), 3.85 (d, *J* = 14.0 Hz, 1H), 3.70-3.68 (m, 1H), 3.66 (d, *J* = 14.0 Hz, 1H), 2.92 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.66 (dd, *J* = 17.2, 5.2Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 169.5, 156.0, 152.9, 152.0, 147.0, 146.1, 142.2, 141.9, 138.8, 122.5, 110.3, 110.1, 109.4, 108.3, 106.9, 106.9, 100.6, 92.5, 60.7, 60.3, 58.8, 54.2, 46.4, 39.5, 26.5, 14.2 (2C); IR (neat): υ 3271, 2975, 2904, 1737, 1655, 1600, 1436, 1036, 800, 729 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{30}N_2O_8$ $[M+H]^+$ 523.2081, Found 523.2080.



118k

Ethyl 1-benzyl-4-(benzylamino)-5-(2-ethoxy-2-oxoethyl)-2-(furan-2-yl)-2,5-dihydro-1H-pyrrole-3-carboxylate (118l):

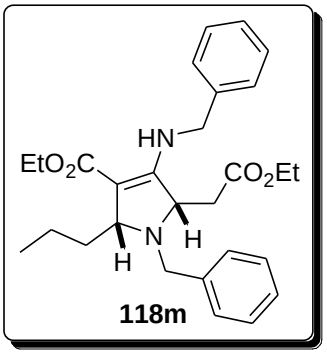
Prepared by following GP-VI; Yellow liquid; Yield = 58%; R_f = 0.45 in 1:3 EtOAc/hexanes; dr: 4.3:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (t, *J* = 6.4 Hz, 1H), 7.46-7.25 (m, 11H), 6.28 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.12-6.11 (m, 1H), 4.87 (s, 1H), 4.52-4.50 (m, 2H), 4.23-4.03 (m, 4H), 3.97-3.93 (m, 1H), 3.88-3.85 (m, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 2.82 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.60 (dd, *J* = 17.2, 5.6 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 169.6, 157.3, 157.1, 141.3, 139.2, 138.7, 128.8, 128.7, 128.1, 127.4, 126.9, 126.8, 109.7, 107.8, 89.3, 60.8, 58.7, 55.2, 54.1, 52.9, 46.1, 25.4, 14.2, 14.1; IR (neat): υ 3288, 3063, 2980, 1726, 1655, 1600, 1233, 734, 701 cm^{-1}; HRMS (ESI): calcd for $C_{29}H_{32}N_2O_5$ $[M+H]^+$ 489.2390, Found 489.2391.



118l

Ethyl 1-benzyl-4-(benzylamino)-5-(2-ethoxy-2-oxoethyl)-2-propyl-2,5-dihydro-1H-pyrrole-3-carboxylate (118m):

Prepared by following GP-VI; Yellow liquid; R_f = 0.68 in 1:3 EtOAc/hexanes; dr: 13.3:1.0; Major isomer (*syn*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (t, *J* = 6.0 Hz, 1H), 7.38-7.22 (m, 10H), 4.49 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.43 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.23-4.02 (m, 4H), 3.94 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.56 (d, *J* = 13.6 Hz, 1H), 3.50 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 2.72 (dd, *J* = 17.6, 11.2 Hz, 1H), 2.42 (dd, *J* = 18.0, 5.2 Hz, 1H), 1.52-1.36 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.68 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 170.2, 156.5, 139.8, 138.9, 129.1, 128.8, 127.8, 127.3, 126.9, 126.7, 92.3, 60.9, 58.7, 55.2, 54.2, 52.8, 46.0, 36.8, 23.1, 19.2, 14.4, 14.2, 13.7; IR (neat): υ 3277, 3068, 2959, 1732, 1644, 1600, 1452, 1216, 729, 701 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{36}N_2O_4$ $[M+H]^+$ 465.2754, Found 465.2753.



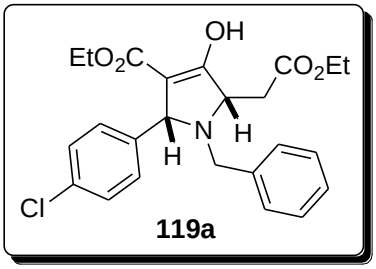
118m

VII. General procedure for hydrolysis of pyrrolidine derivatives (GP-VII):

Pyrrolidine derivative was taken in diluted HCl and allowed to stir at rt. The reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was extracted with EtOAc and washed with brine solution. The resultant organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The crude reaction mixture was purified by column chromatography using EtOAc/hexanes mixtures as eluents to get the pure hydrolyzed product.

Ethyl 1-benzyl-2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-4-hydroxy-2,5-dihydro-1H-pyrrole-3-carboxylate (119a):

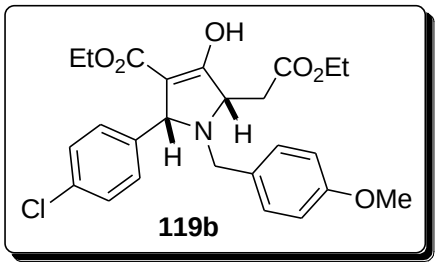
Prepared by following GP-VII; Colorless liquid; Yield = 100% conversion; R_f = 0.61 in 1:3 EtOAc/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.29 (s, 1H), 7.23-7.14 (m, 9H), 4.68 (s, 1H), 4.14-4.06 (m, 2H), 3.98-3.90 (m, 2H), 3.71 (d, *J* = 13.5 Hz, 1H), 3.59-3.56 (m, 2H), 2.72-2.62 (m, 2H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 171.1, 169.4, 142.2, 138.8, 132.6, 130.6, 128.8, 128.3, 127.8, 127.3, 100.0, 60.7, 60.4, 59.1, 54.2, 53.4, 31.0, 14.2, 13.8; IR (neat): υ 3202, 2975, 1733, 1650, 1490, 1061, 1019, 817, 745, 703 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{26}ClNO_5$ $[M+H]^+$ 444.1579, Found 444.1579.



119a

Ethyl 2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-4-hydroxy-1-(4-methoxybenzyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (119b):

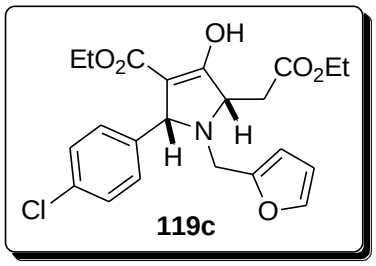
Prepared by following GP-VII; Colorless liquid; Yield = 100% conversion; R_f = 0.50 in 1:3 EtOAc/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.36 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.73 (s, 1H), 4.19-4.16 (m, 2H), 4.04-4.00 (m, 2H), 3.79 (s, 3H), 3.70 (d, *J* = 13.0 Hz, 1H), 3.64 (t, *J* = 5.5 Hz, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 2.72 (d, *J* = 5.5 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 171.1, 169.5, 158.9, 142.3, 132.6, 130.7, 130.6, 129.9, 127.8, 113.7, 99.9, 60.7, 60.4, 58.9, 55.2, 54.0, 52.7, 31.0, 14.3, 13.8; IR (neat): υ 3277, 2975, 2904, 1726, 1649, 1594, 1370, 1238, 1090, 827, 740, 696 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{28}ClNO_6$ $[M+H]^+$ 474.1684, Found 474.1683.



119b

Ethyl 2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-1-(furan-2-ylmethyl)-4-hydroxy-2,5-dihydro-1H-pyrrole-3-carboxylate (119c):

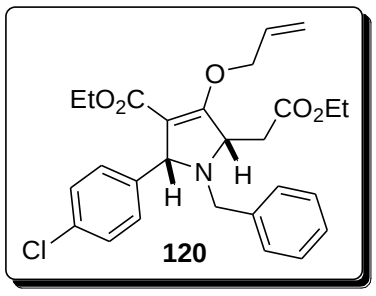
Prepared by following GP-VII; Colorless liquid; Yield = 100% conversion; R_f = 0.50 in 1:3 EtOAc/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.32 (s, 1H), 7.33-7.28 (m, 3H), 7.25-7.23 (m, 2H), 6.27 (dd, *J* = 3.0, 2.0 Hz, 1H), 6.11 (d, *J* = 3.0 Hz, 1H), 4.80 (s, 1H), 4.19-4.12 (m, 2H), 4.06-3.98 (m, 2H), 3.86 (d, *J* = 14.5 Hz, 1H), 3.72-3.70 (m, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 2.87-2.82 (m, 1H), 2.74-2.70 (m, 1H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H; ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 168.9, 152.2, 142.2, 141.9, 132.7, 130.6, 127.8, 110.1, 108.6, 100.3, 60.7, 60.4, 59.2, 54.9, 46.8, 31.5, 14.2, 13.8; HRMS (ESI): calcd for $C_{22}H_{24}ClNO_6$ $[M+H]^+$ 434.1371, Found 434.1370.



119c

Ethyl 4-(allyloxy)-1-benzyl-2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (120):

To a stirred solution of **119a** (0.036 g, 0.0811 mmol) in dry CH_3CN was added K_2CO_3 (0.011 g, 0.0811 mmol) at 0 ^{0}C. The reaction mixture was stirred for 30 min., and then allyl bromide (11 µL, 0.1217 mmol) was added. The resulted reaction mixture was allowed to reflux and it was monitored by TLC. After 17 h, the reaction was stopped and CH_3CN was removed in rotovap. The resulted reaction mixture was extracted with ethyl acetate, washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The crude product was purified by column chromatography using EtOAc/hexanes mixtures as eluents to get the pure **120** as colorless liquid; Yield = 31%; R_f = 0.47 in 1:3 EtOAc/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.24 (m, 9H), 6.04-5.96 (m, 1H), 5.45 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.28 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.87 (s, 1H), 4.55-4.53 (m, 2H), 4.26-4.19 (m, 1H), 4.19-4.12 (m, 1H), 4.04-3.97 (m, 2H), 3.75 (d, *J* = 13.0 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 1H), 3.59 (d, *J* = 13.5 Hz, 1H), 2.81-2.76 (m, 1H), 2.67-2.62 (m, 1H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 165.8, 158.0, 141.1, 138.8, 133.3, 132.9, 130.4, 128.9, 128.3, 128.1, 127.3, 117.6, 69.1, 60.9, 60.9, 59.9,



120

54.8, 53.2, 27.4, 14.3, 14.0; HRMS (ESI): calcd for $C_{27}H_{30}ClNO_5$ $[M+Na]^+$ 506.1711, Found 506.1711.

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2.7 *Representative spectra – II*

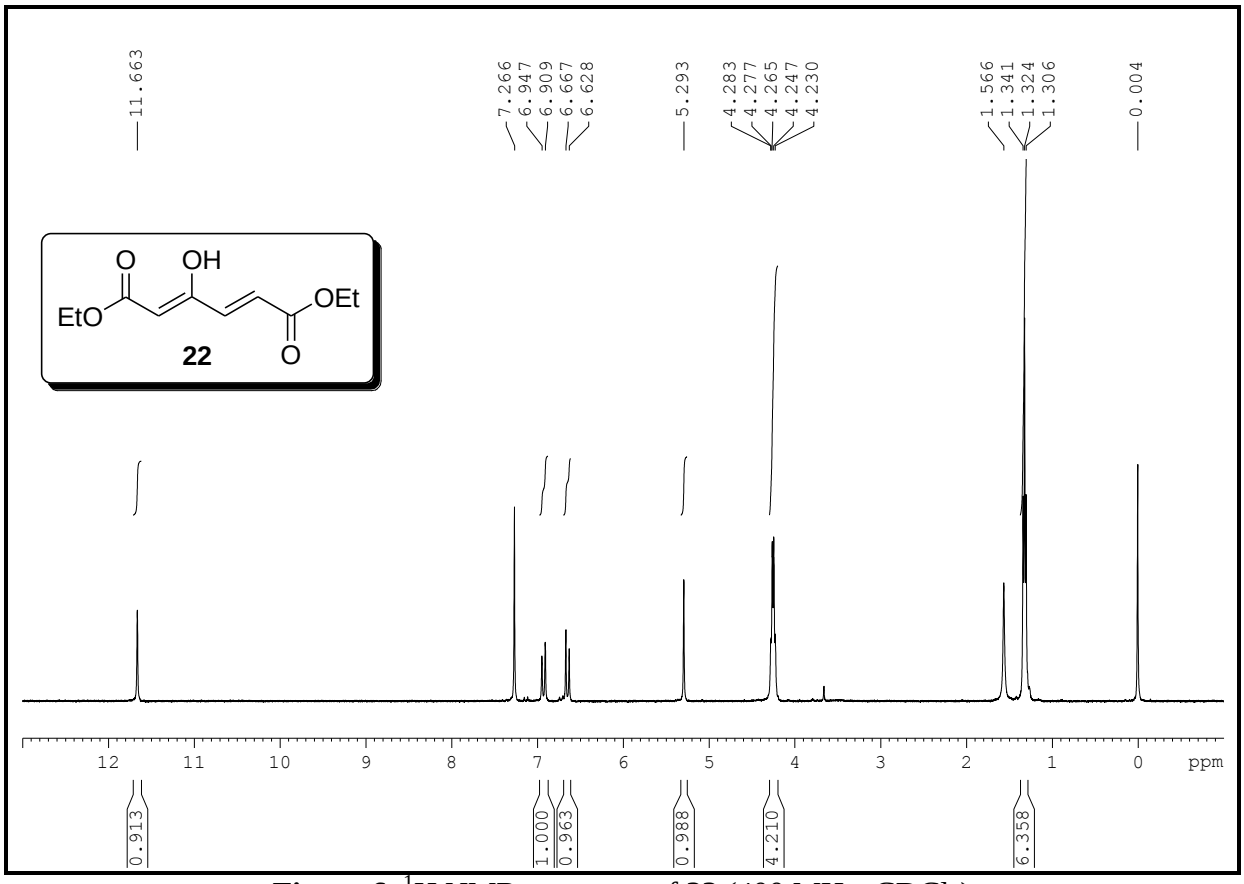

Figure 6. ^{1}H NMR spectrum of **22** (400 MHz, $CDCl_3$)

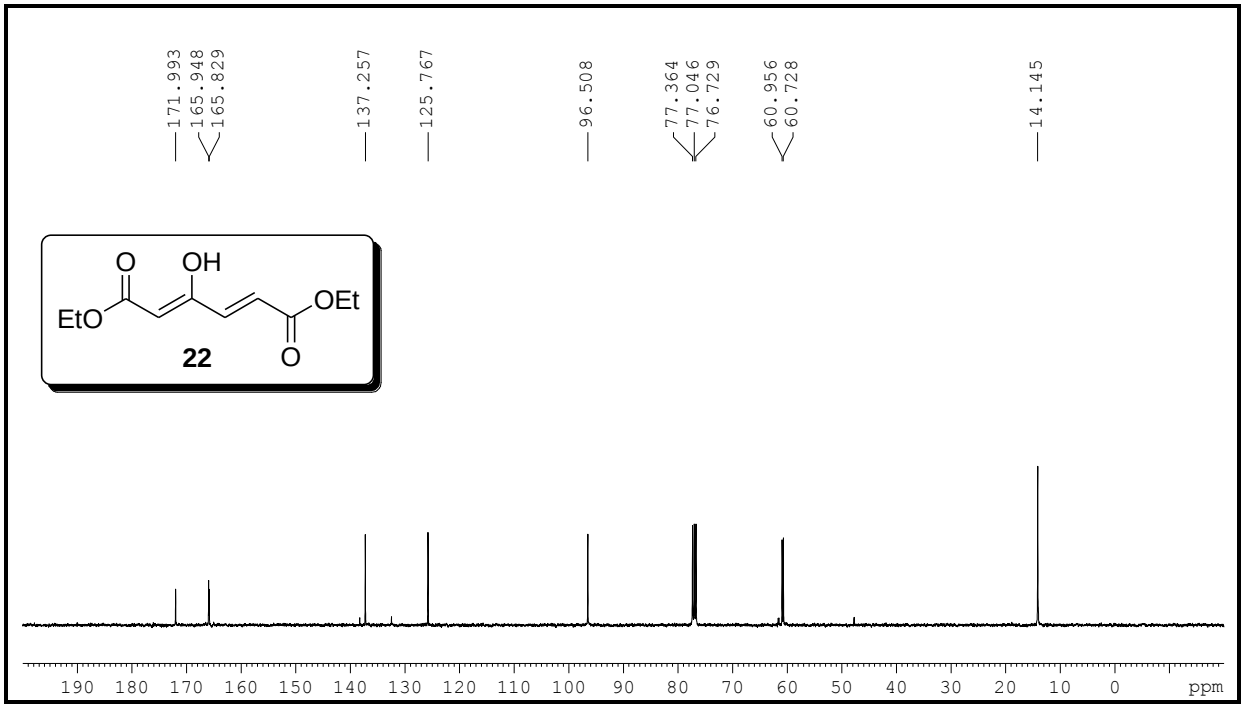

Figure 7. ^{13}C NMR spectrum of **22** (100 MHz, $CDCl_3$)

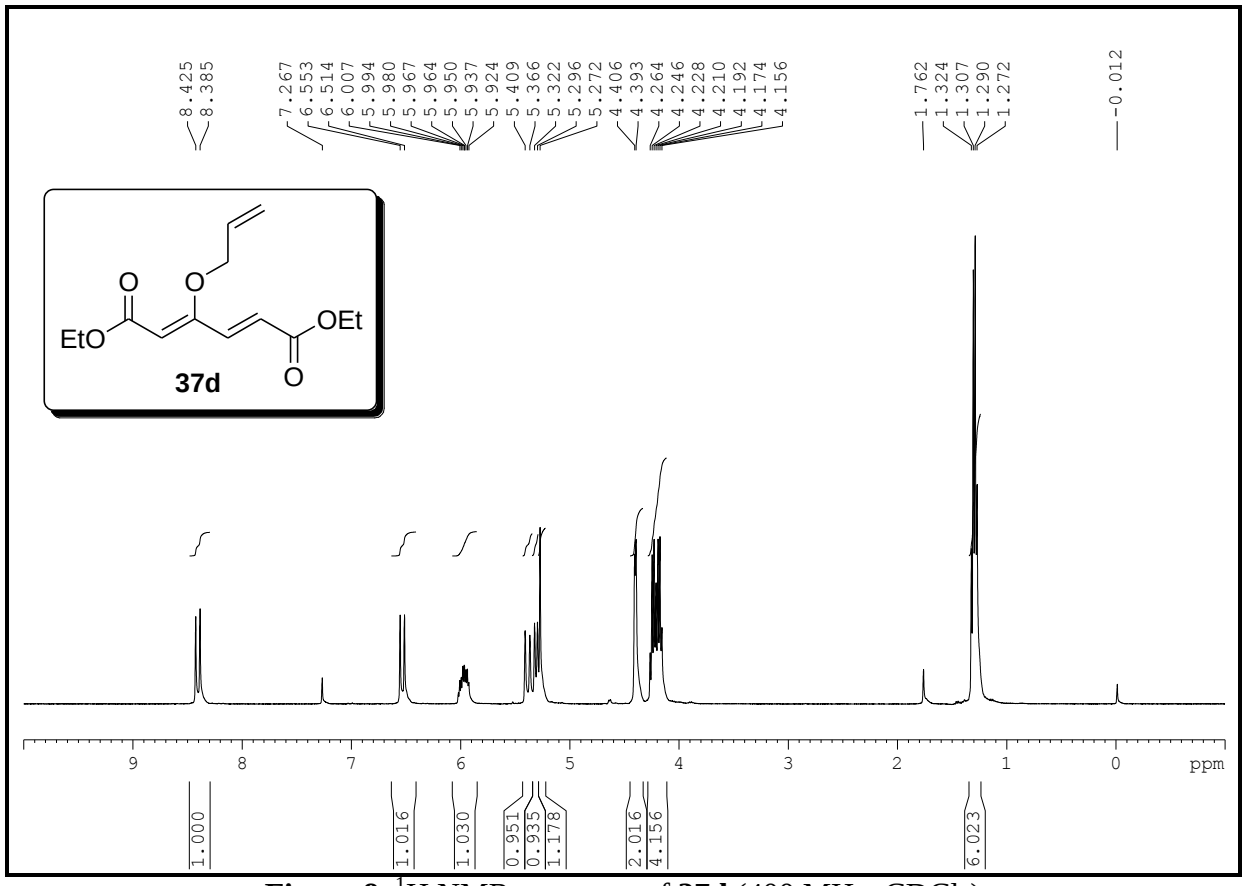

Figure 8. ^{1}H NMR spectrum of **37d** (400 MHz, $CDCl_3$)

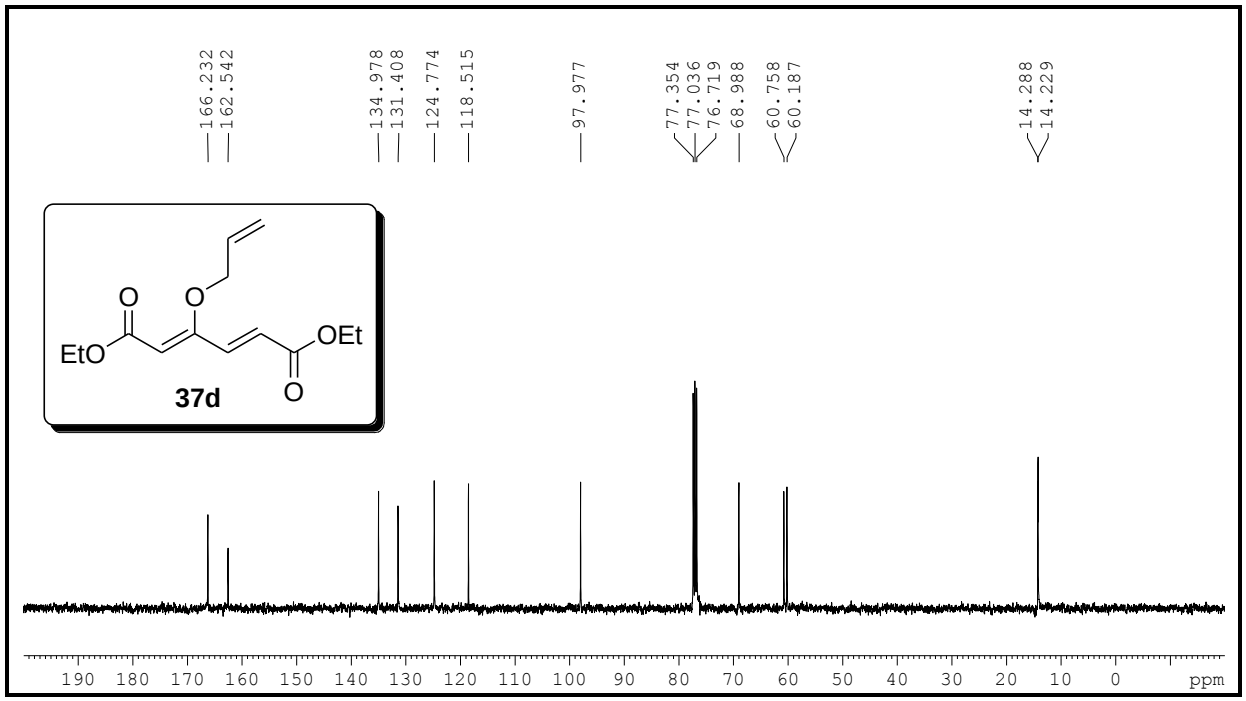

Figure 9. ^{13}C NMR spectrum of **37d** (100 MHz, $CDCl_3$)

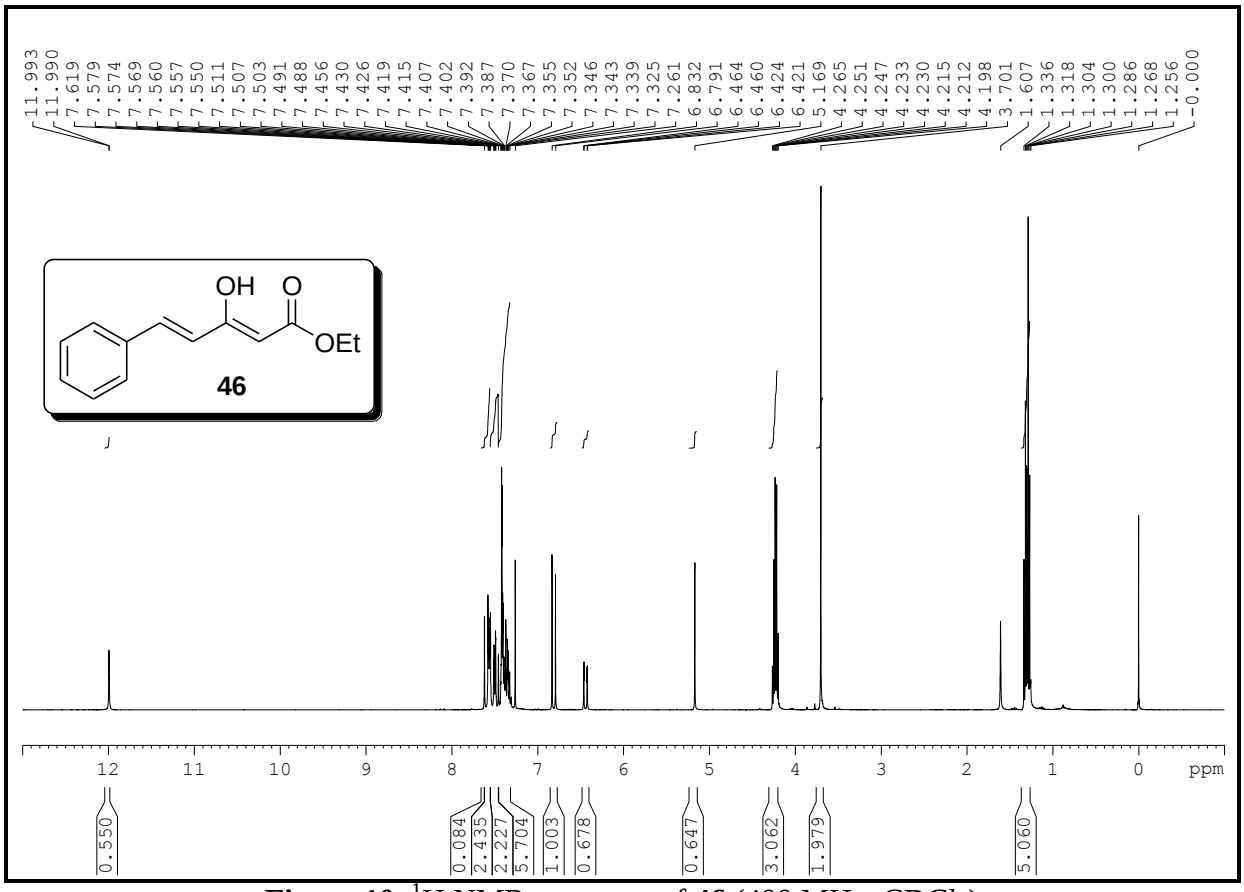

Figure 10. ^{1}H NMR spectrum of **46** (400 MHz, $CDCl_3$)

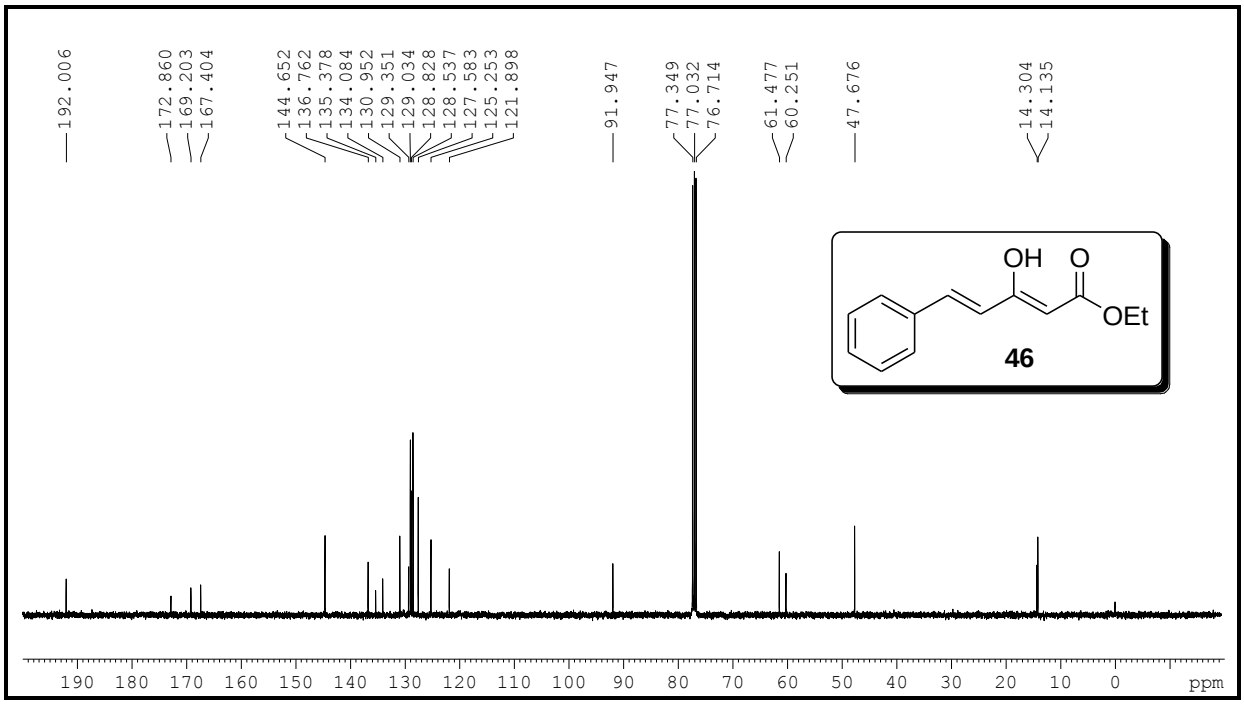

Figure 11. ^{13}C NMR spectrum of **46** (100 MHz, $CDCl_3$)

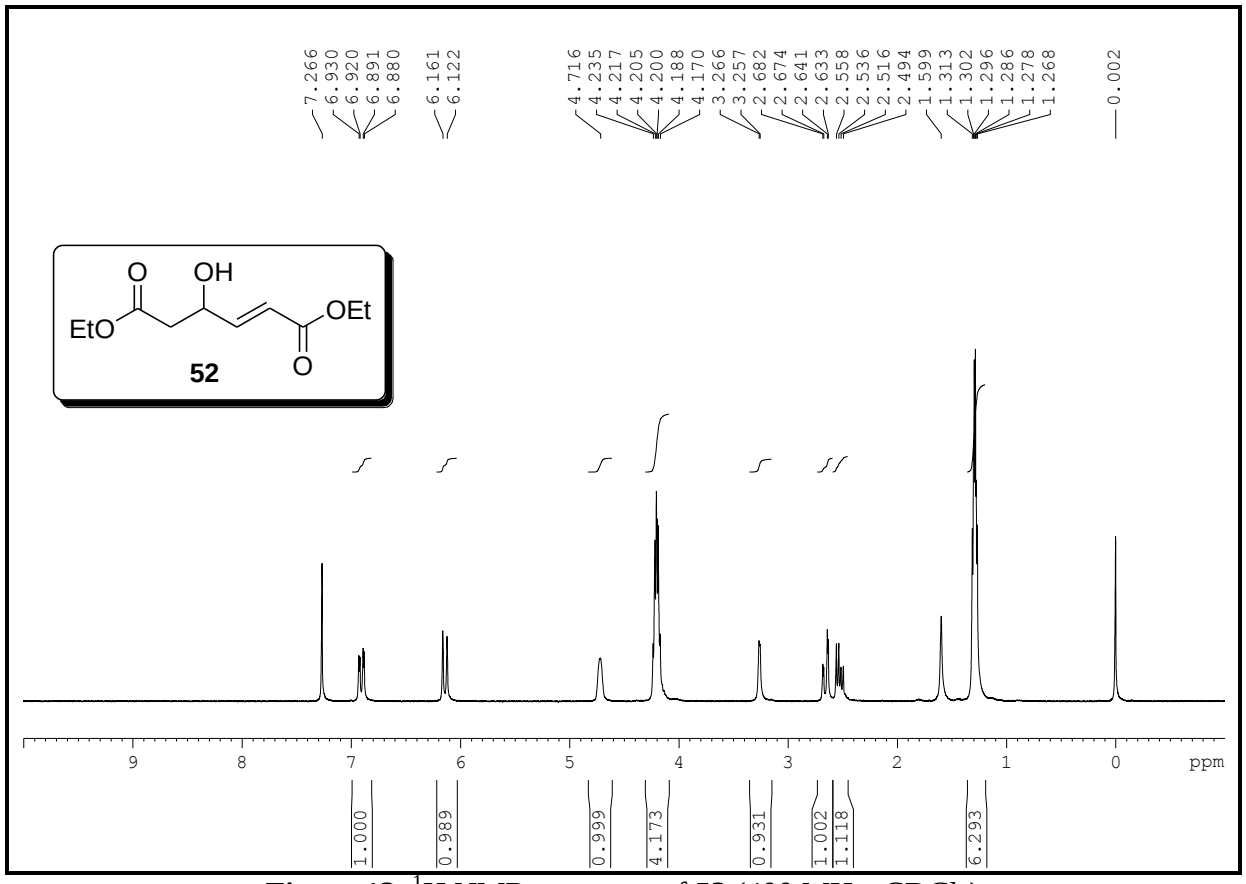

Figure 12. ^{1}H NMR spectrum of **52** (400 MHz, $CDCl_3$)

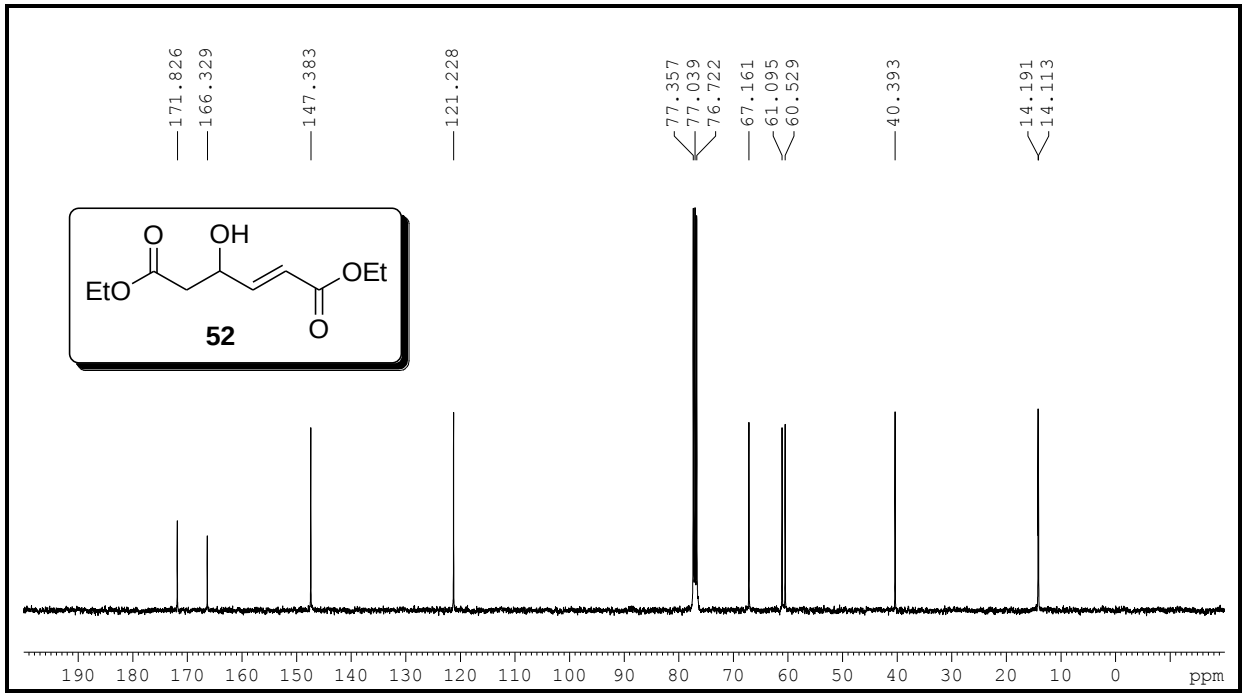

Figure 13. ^{13}C NMR spectrum of **52** (100 MHz, $CDCl_3$)

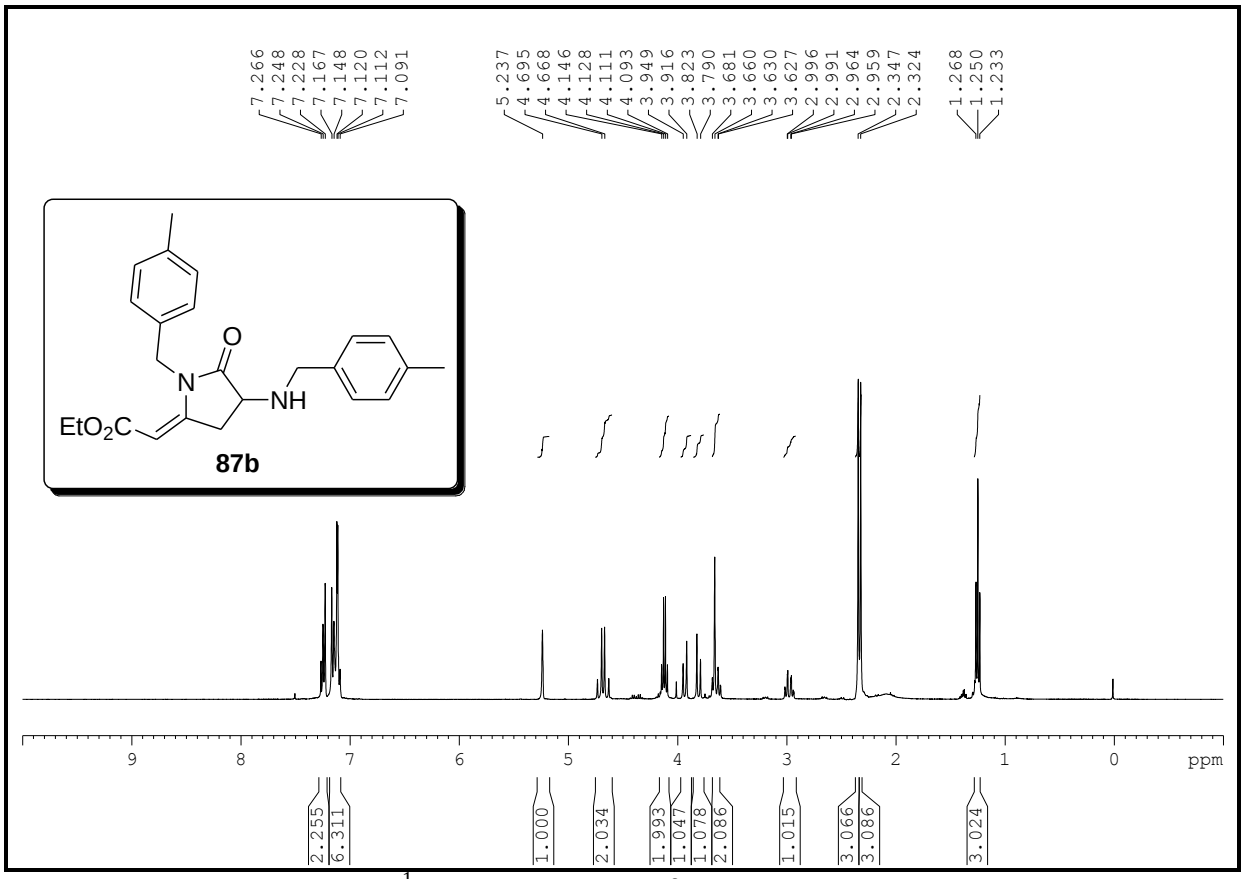

Figure 14. ^{1}H NMR spectrum of **87b** (400 MHz, $CDCl_3$)

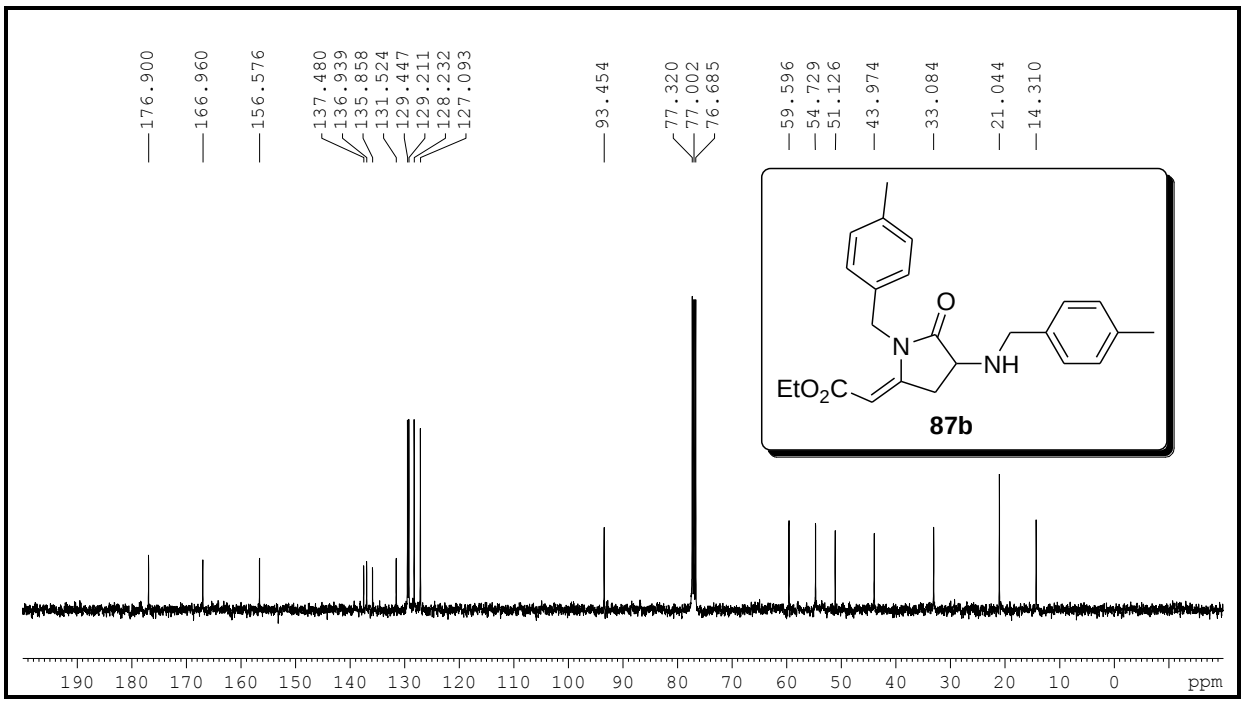

Figure 15. ^{13}C NMR spectrum of **87b** (100 MHz, $CDCl_3$)

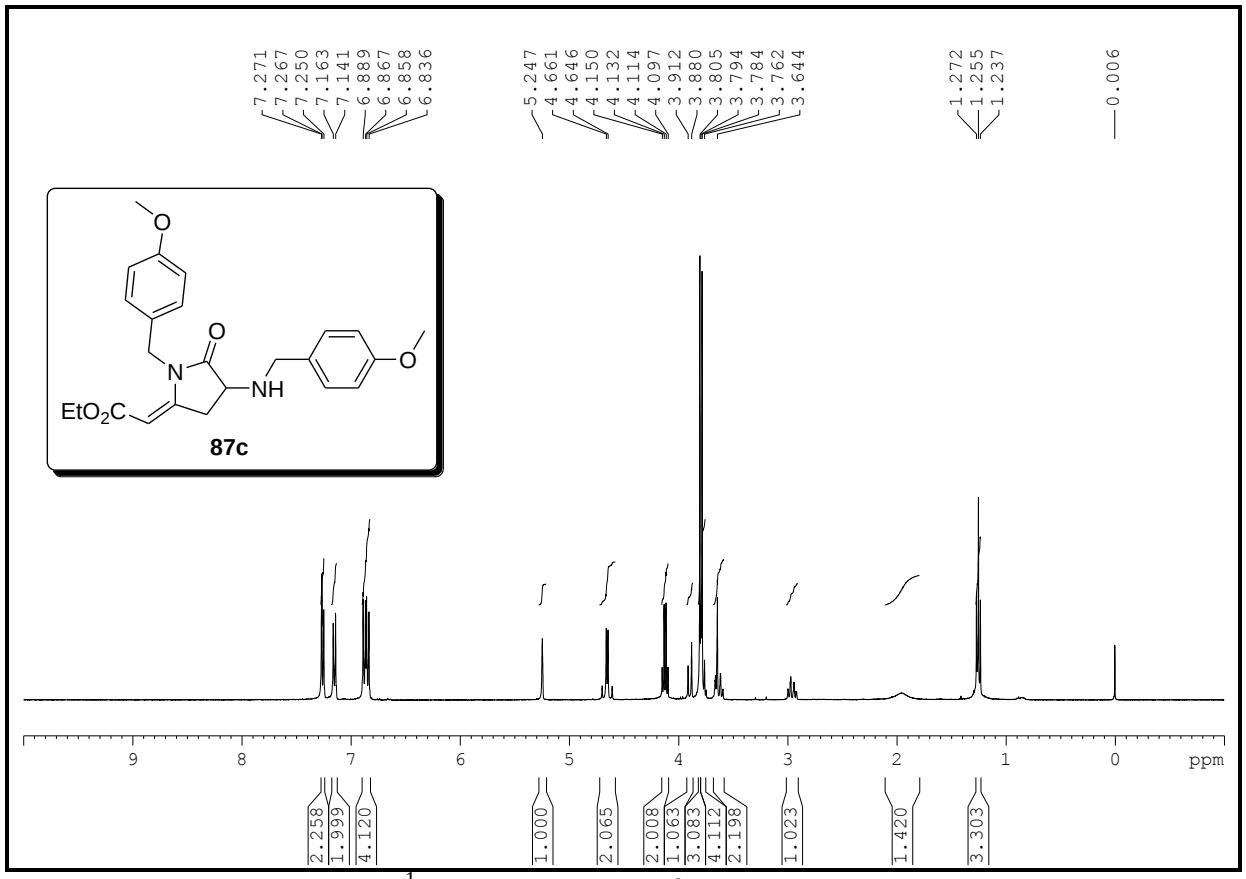

Figure 16. ^{1}H NMR spectrum of **87c** (400 MHz, $CDCl_3$)

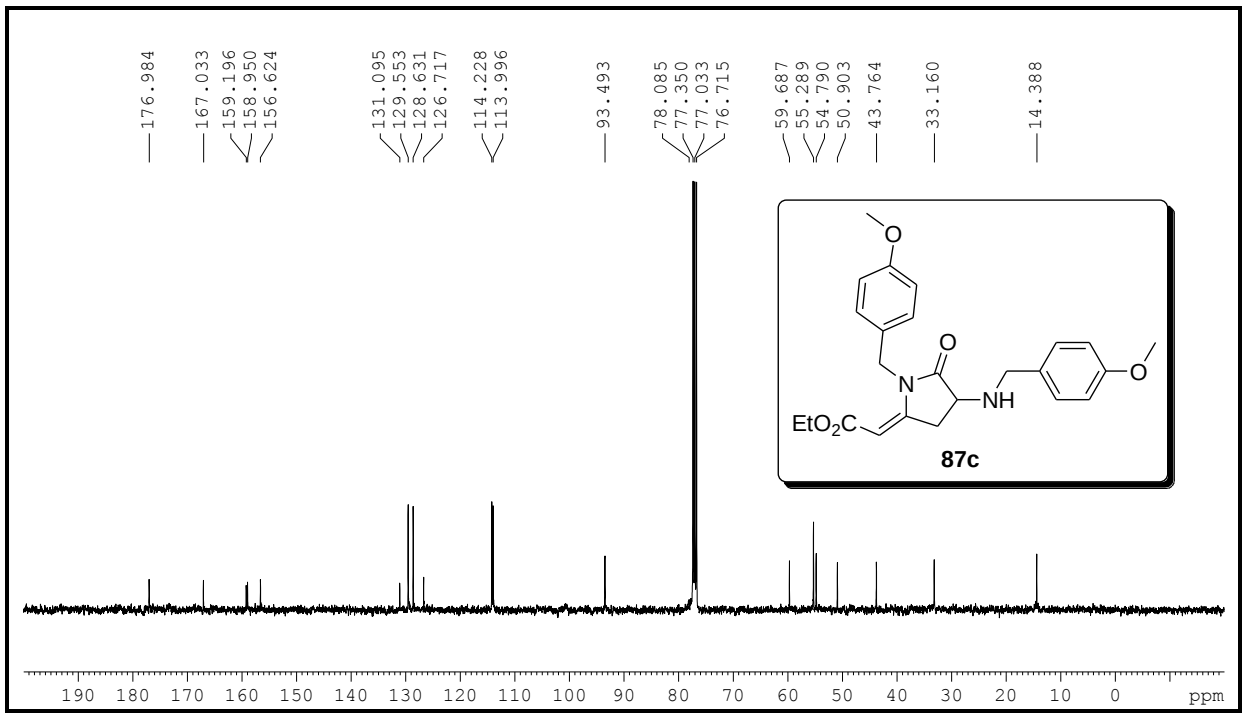

Figure 17. ^{13}C NMR spectrum of **87c** (100 MHz, $CDCl_3$)

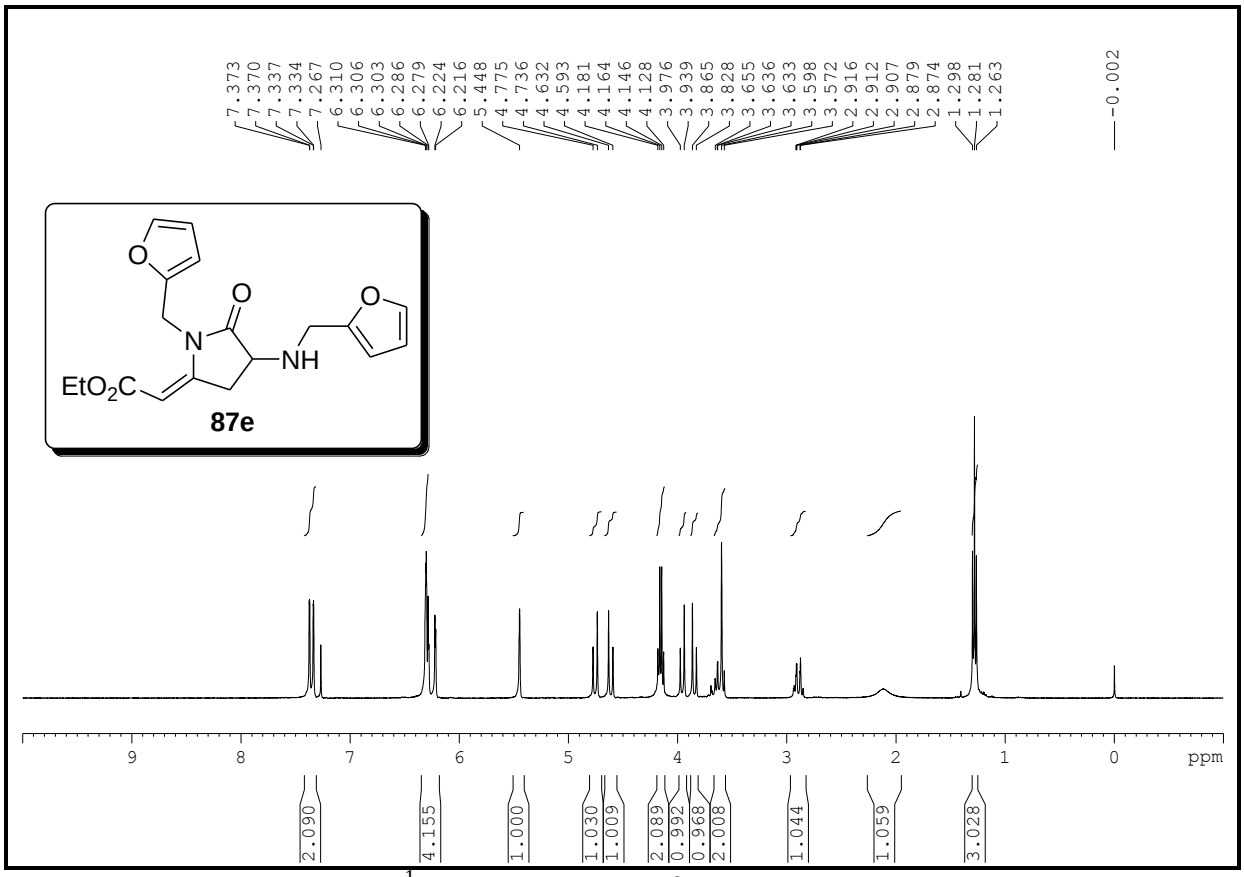

Figure 18. ^{1}H NMR spectrum of **87e** (400 MHz, $CDCl_3$)

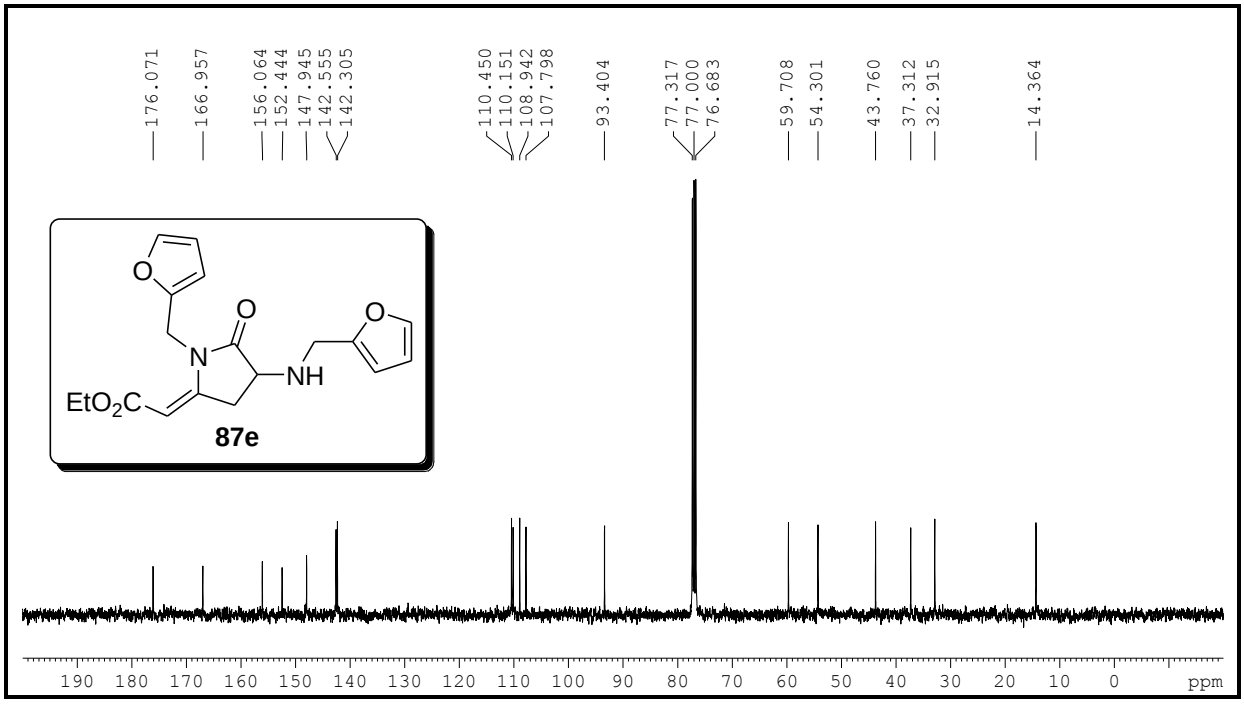

Figure 19. ^{13}C NMR spectrum of **87e** (100 MHz, $CDCl_3$)

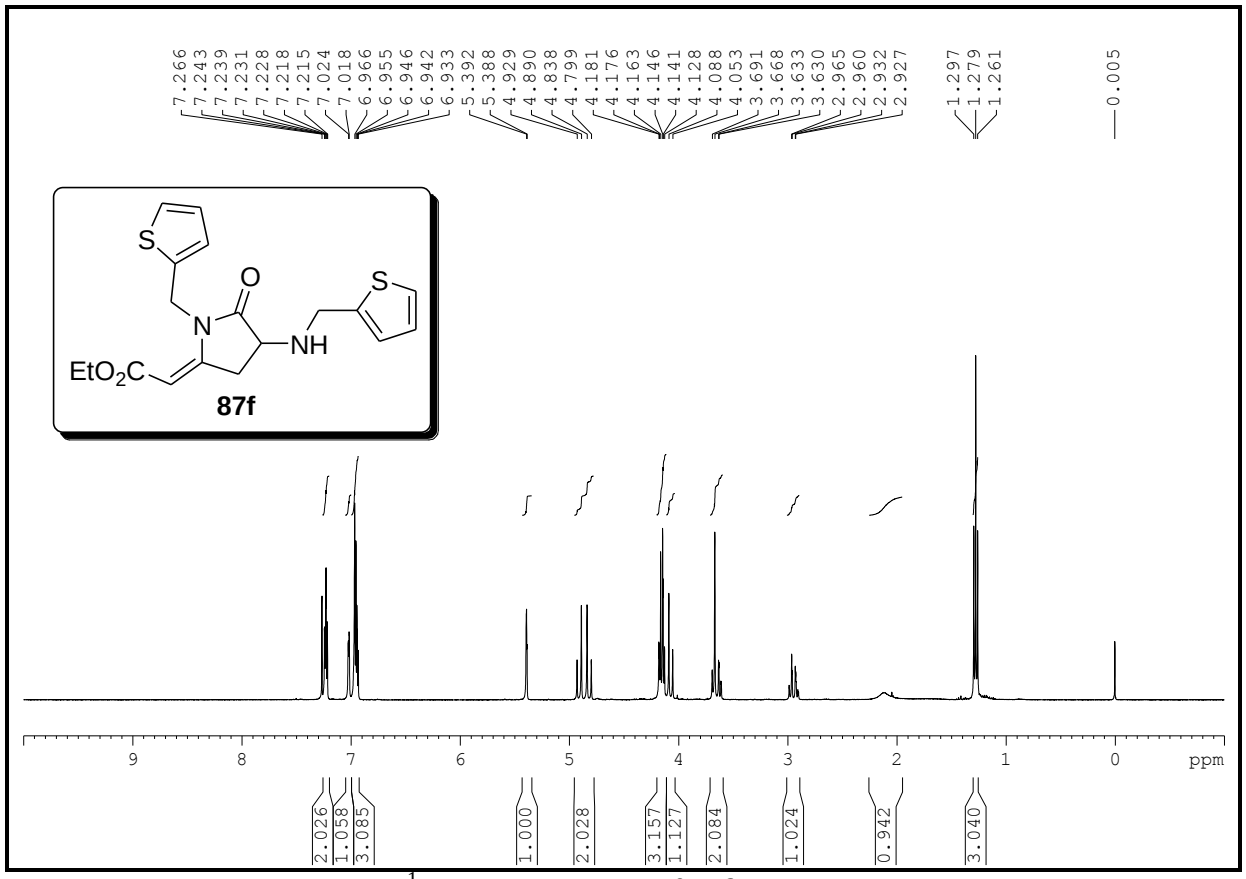

Figure 20. ^{1}H NMR spectrum of **87f** (400 MHz, $CDCl_3$)

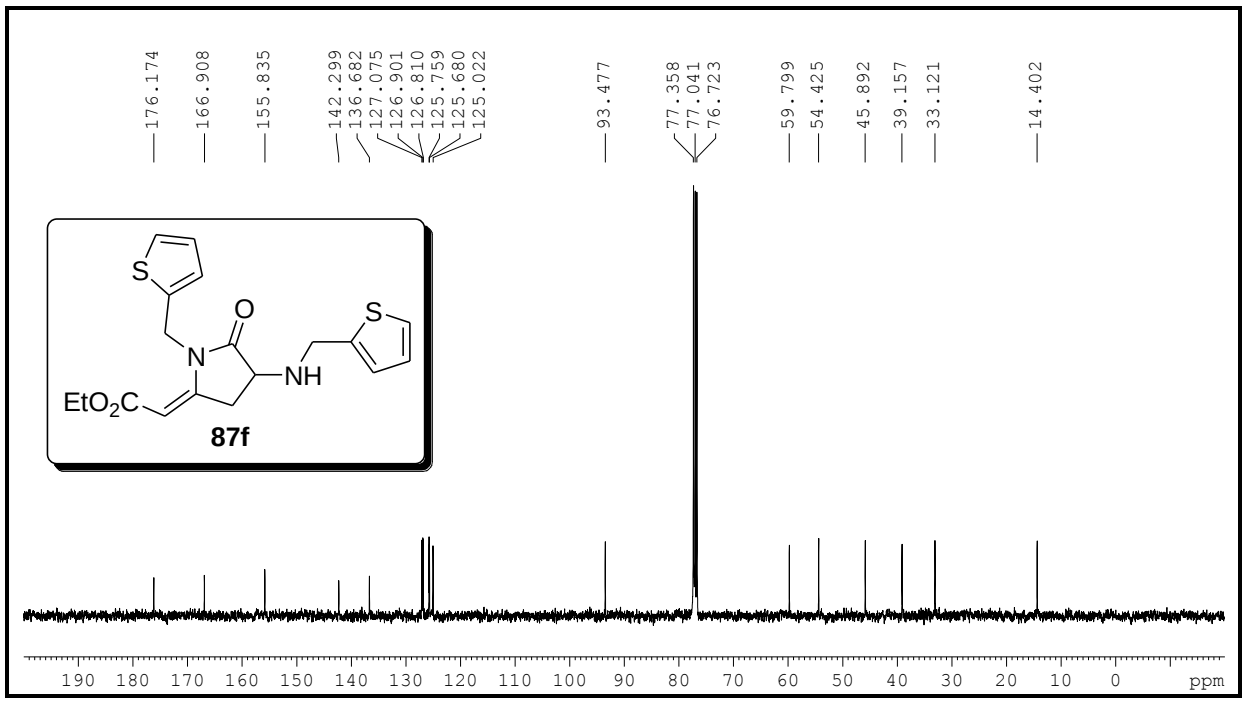

Figure 21. ^{13}C NMR spectrum of **87f** (100 MHz, $CDCl_3$)

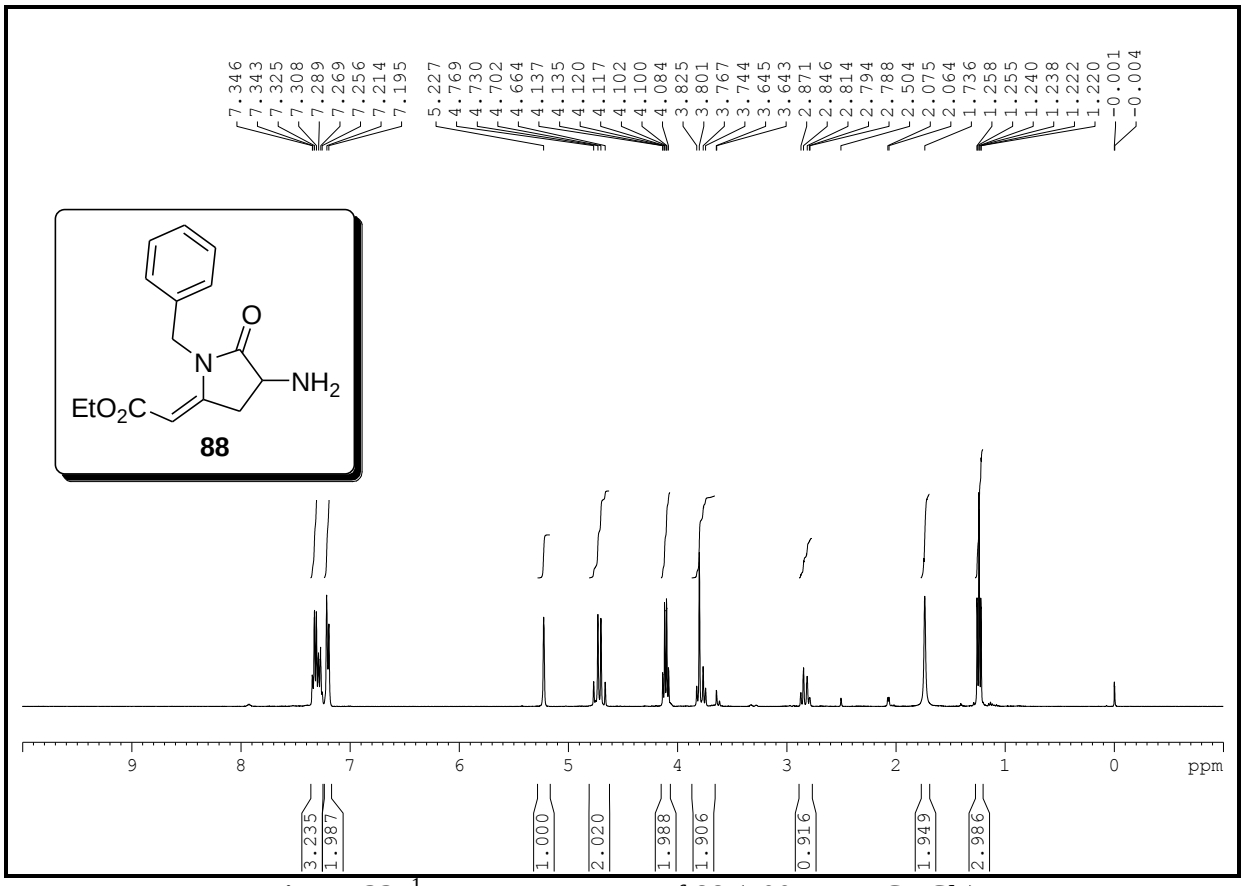

Figure 22. ^{1}H NMR spectrum of **88** (400 MHz, $CDCl_3$)

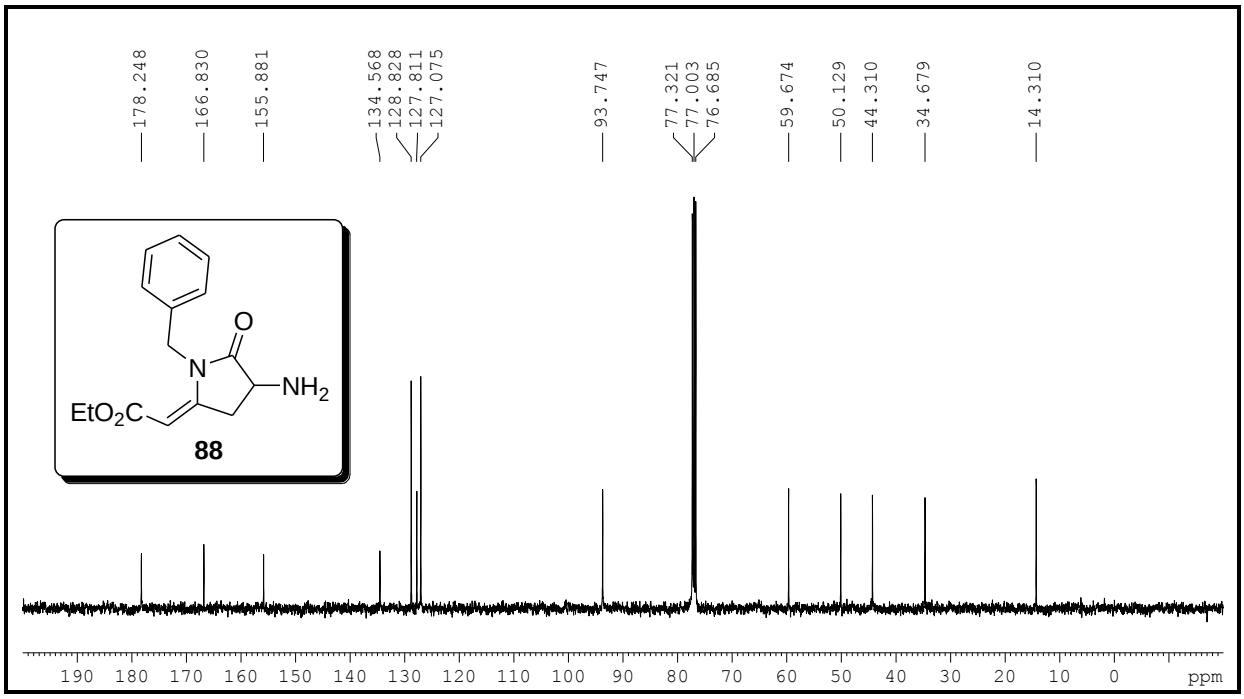

Figure 23. ^{13}C NMR spectrum of **88** (100 MHz, $CDCl_3$)

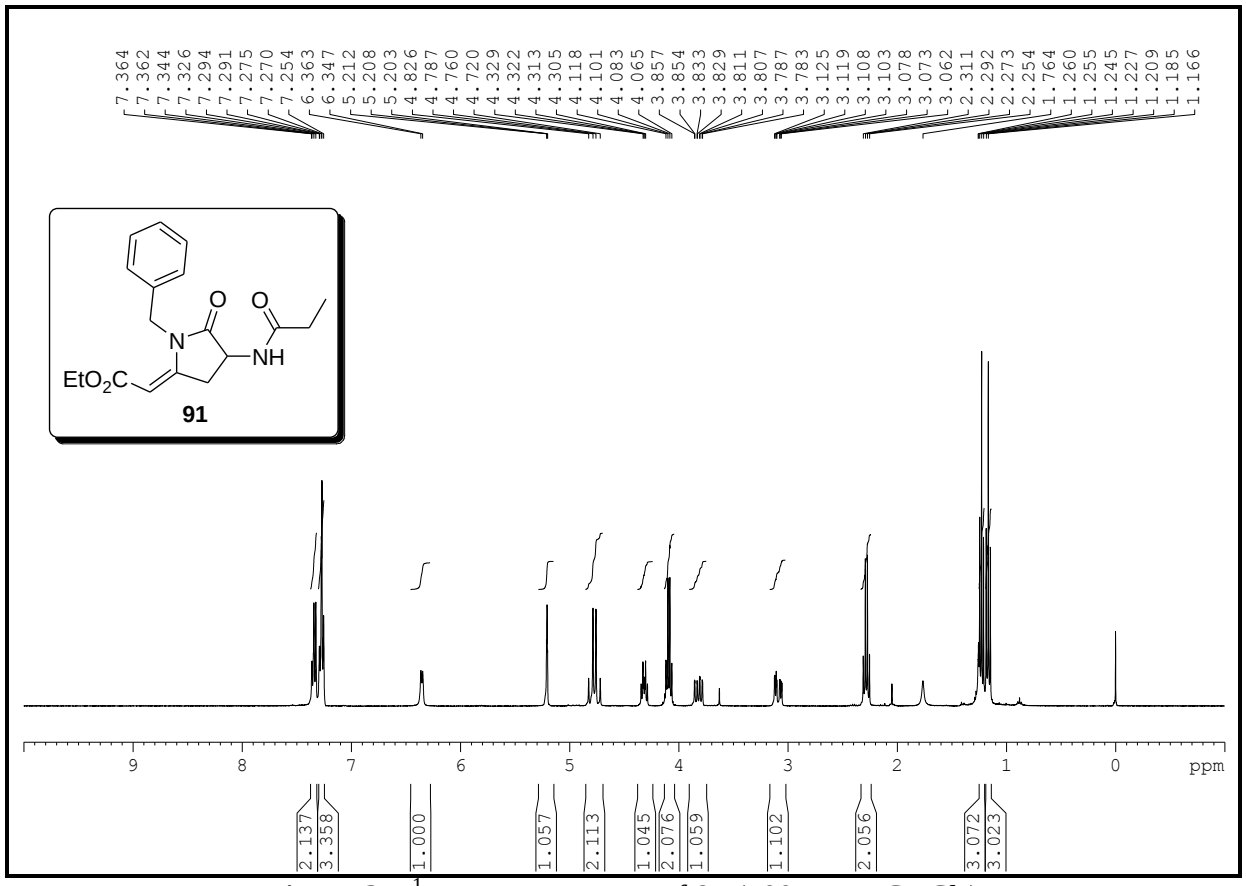

Figure 24. ^{1}H NMR spectrum of **91** (400 MHz, $CDCl_3$)

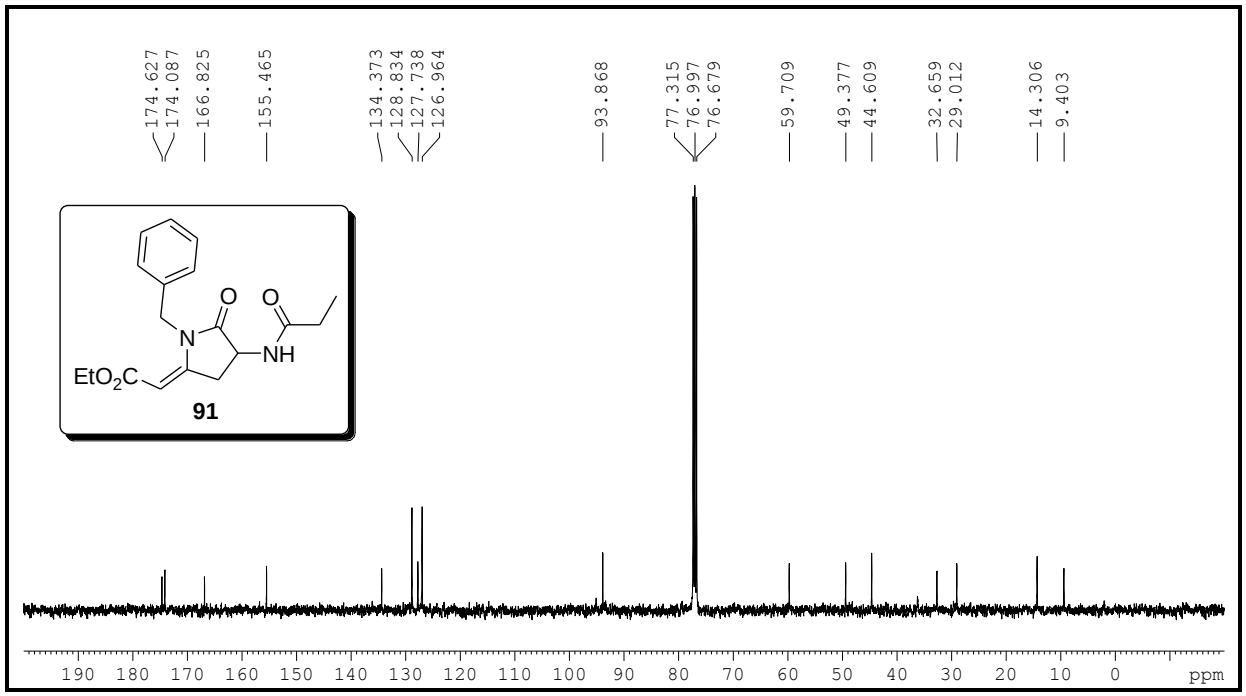

Figure 25. ^{13}C NMR spectrum of **91** (100 MHz, $CDCl_3$)

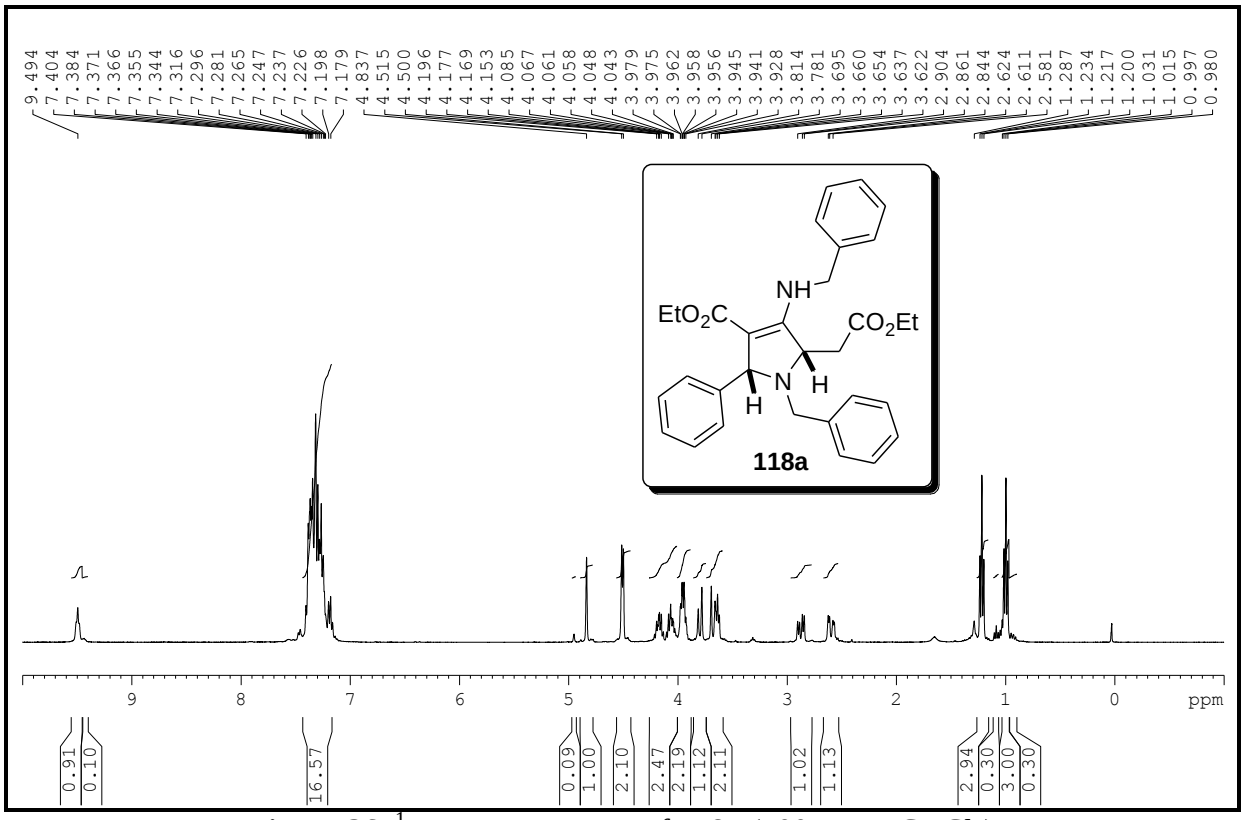

Figure 26. ^{1}H NMR spectrum of **118a** (400 MHz, $CDCl_3$)

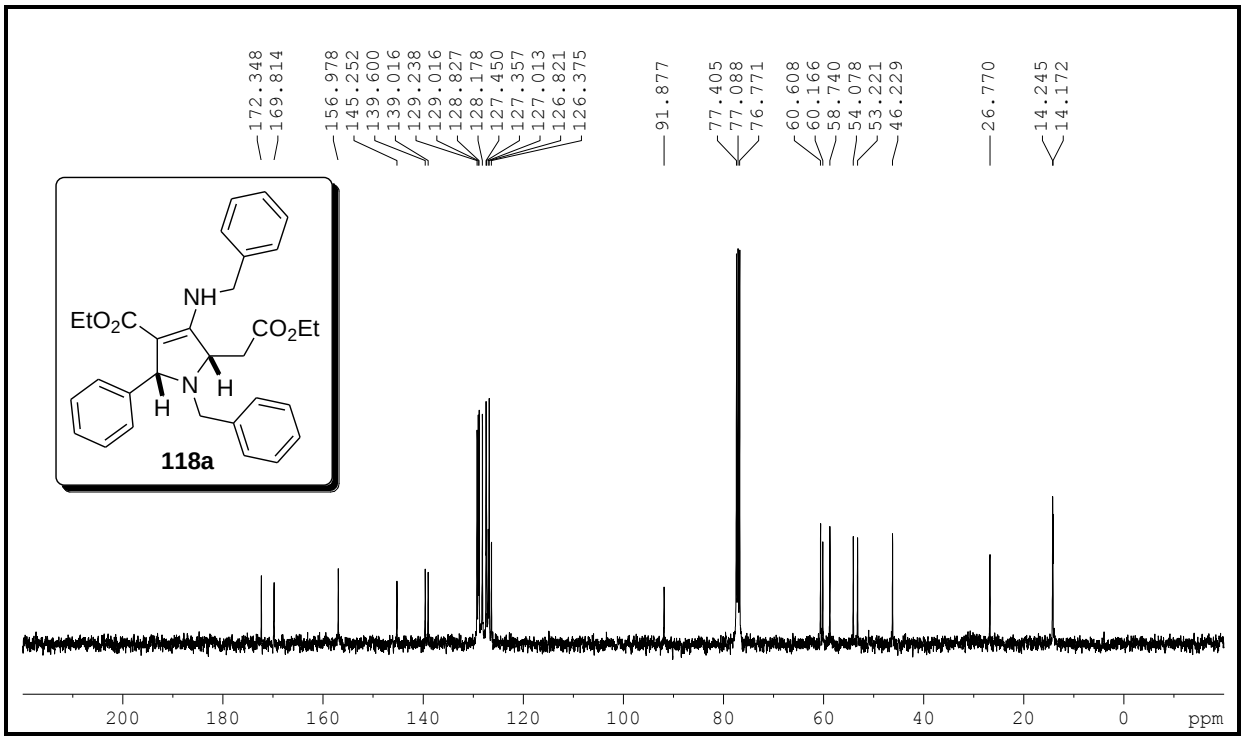

Figure 27. ^{13}C NMR spectrum of **118a** (100 MHz, $CDCl_3$)

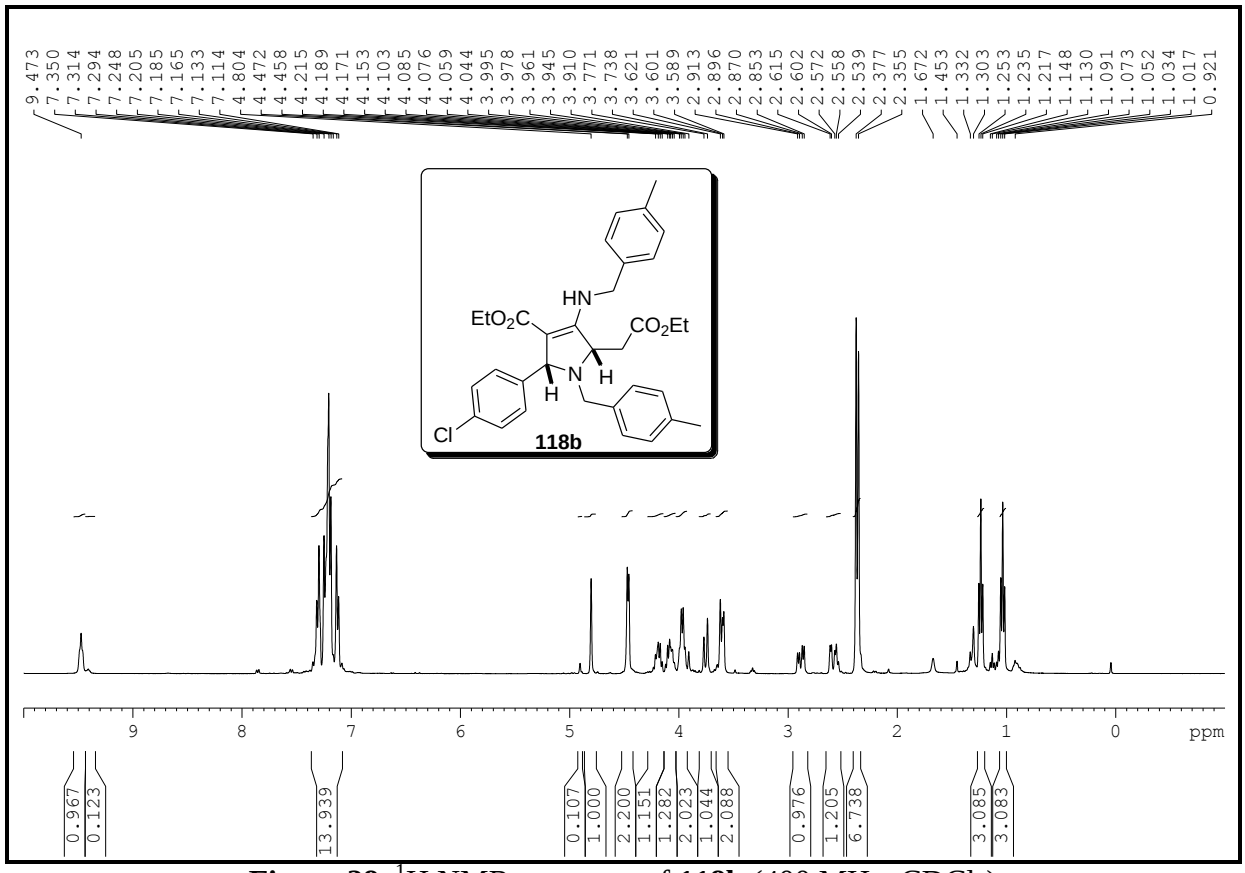

Figure 28. ^{1}H NMR spectrum of **118b** (400 MHz, $CDCl_3$)

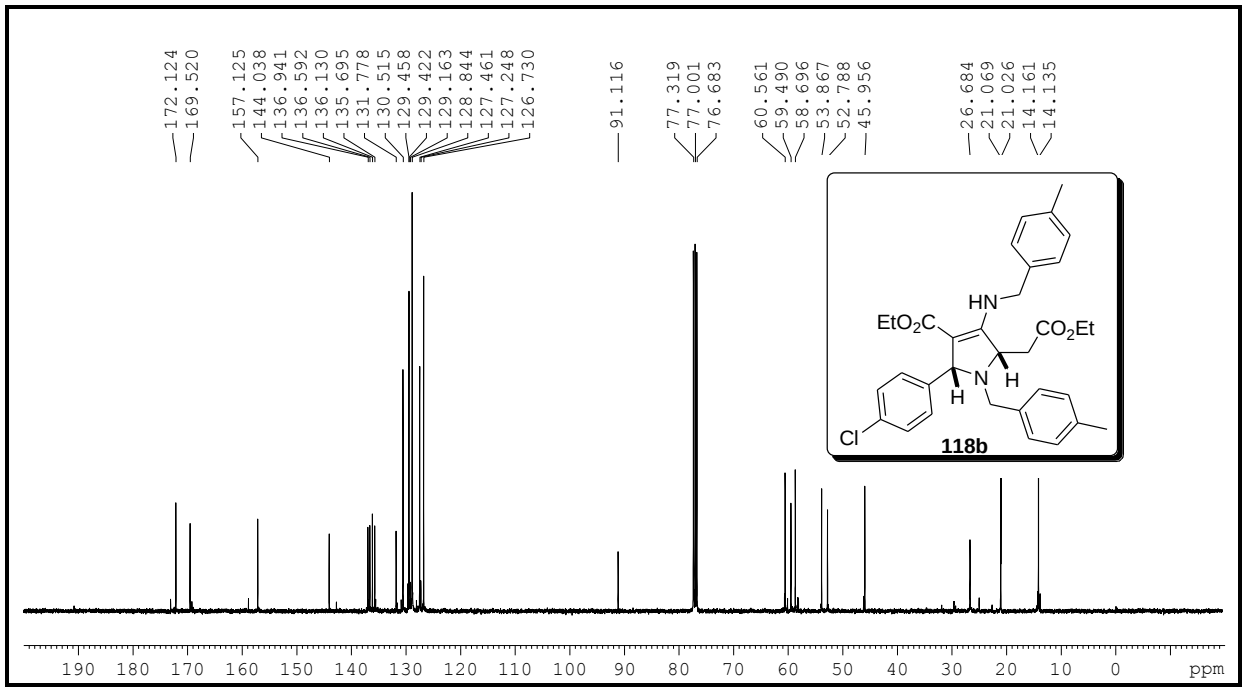

Figure 29. ^{13}C NMR spectrum of **118b** (100 MHz, $CDCl_3$)

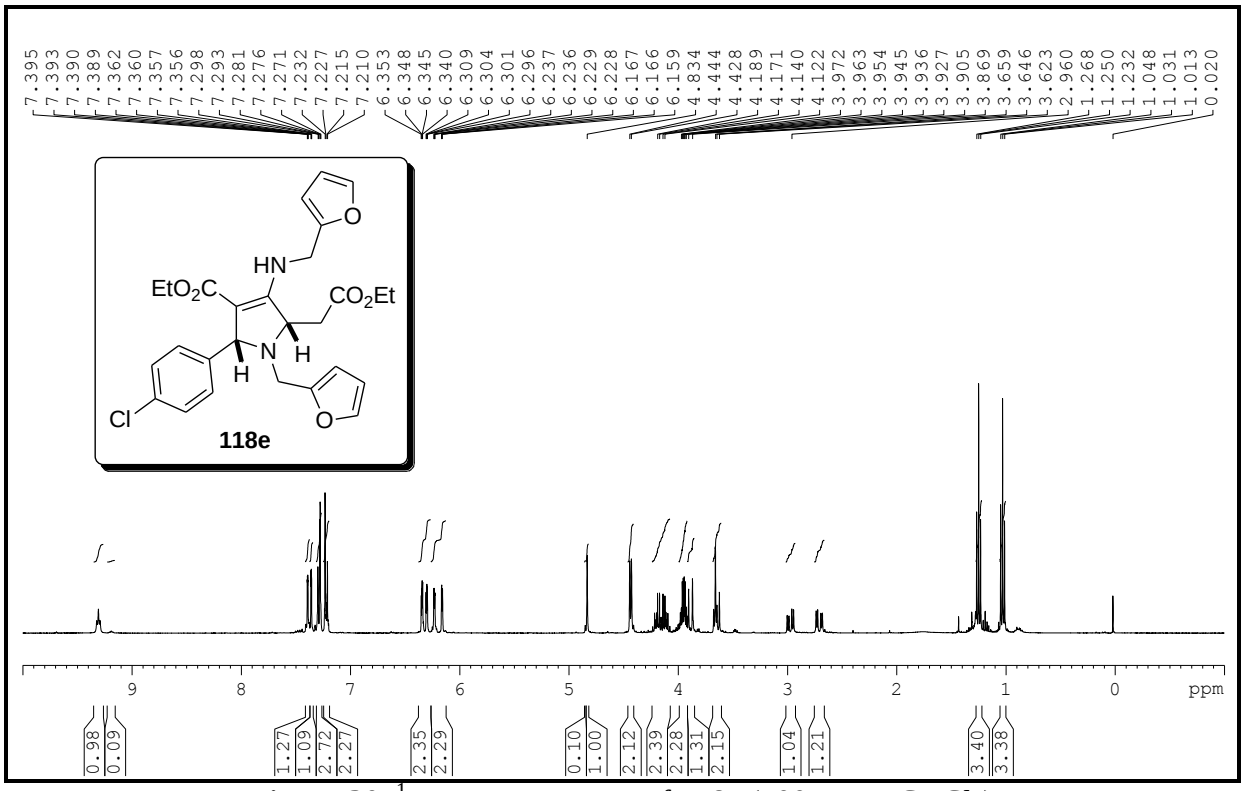

Figure 30. ^{1}H NMR spectrum of **118e** (400 MHz, $CDCl_3$)

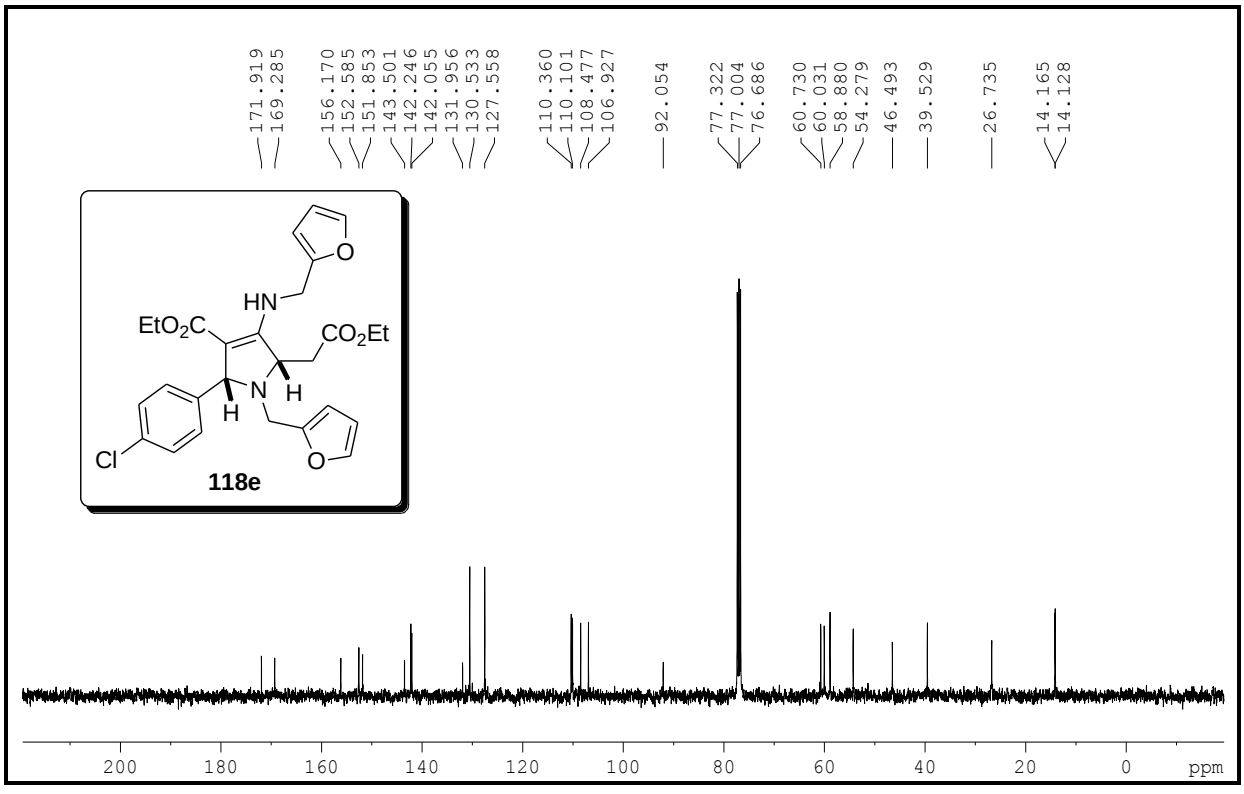

Figure 31. ^{13}C NMR spectrum of **118e** (100 MHz, $CDCl_3$)

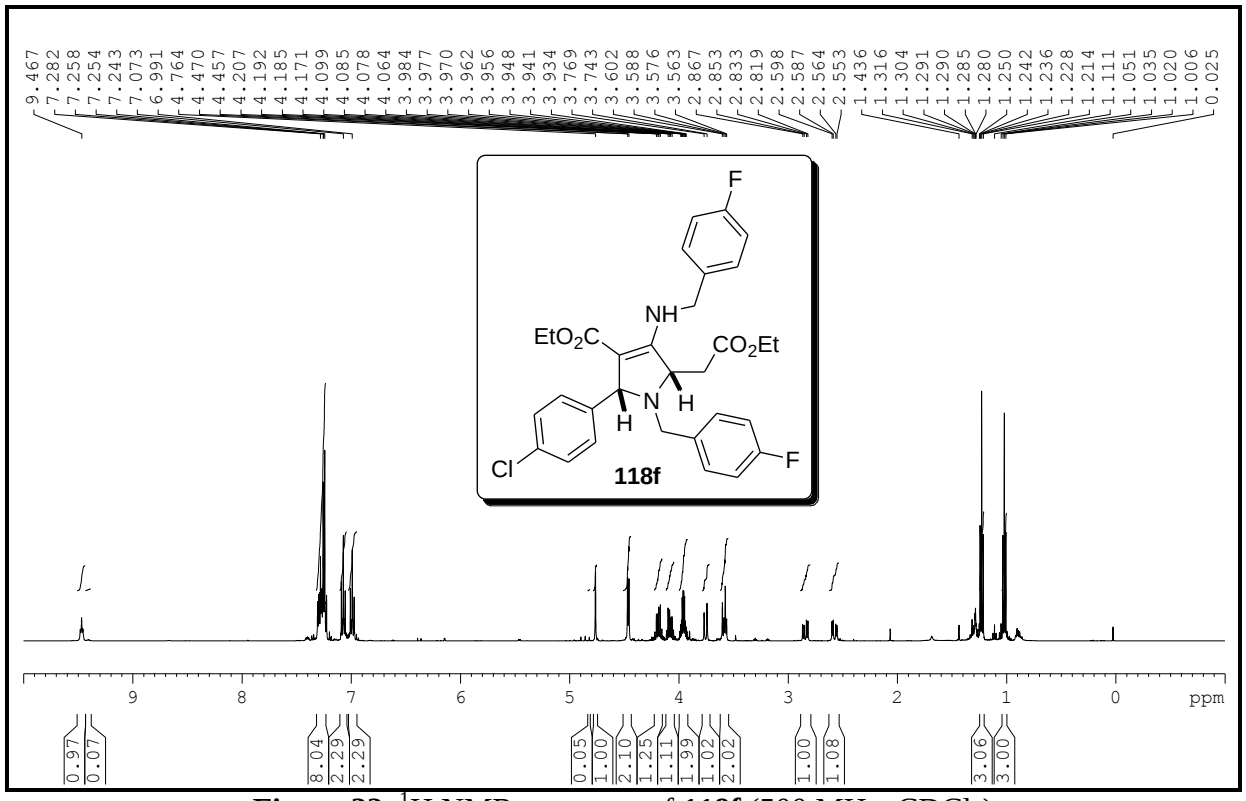

Figure 32. ^{1}H NMR spectrum of **118f** (500 MHz, $CDCl_3$)

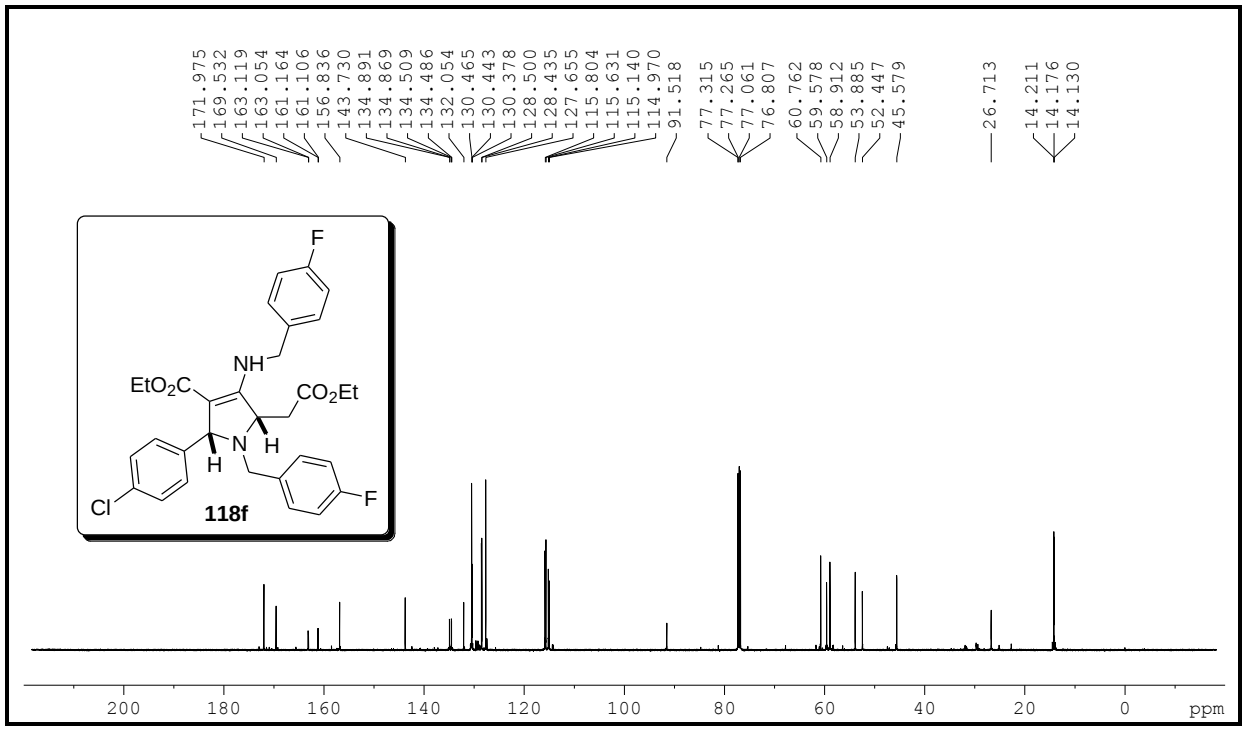

Figure 33. ^{13}C NMR spectrum of **118f** (125 MHz, $CDCl_3$)

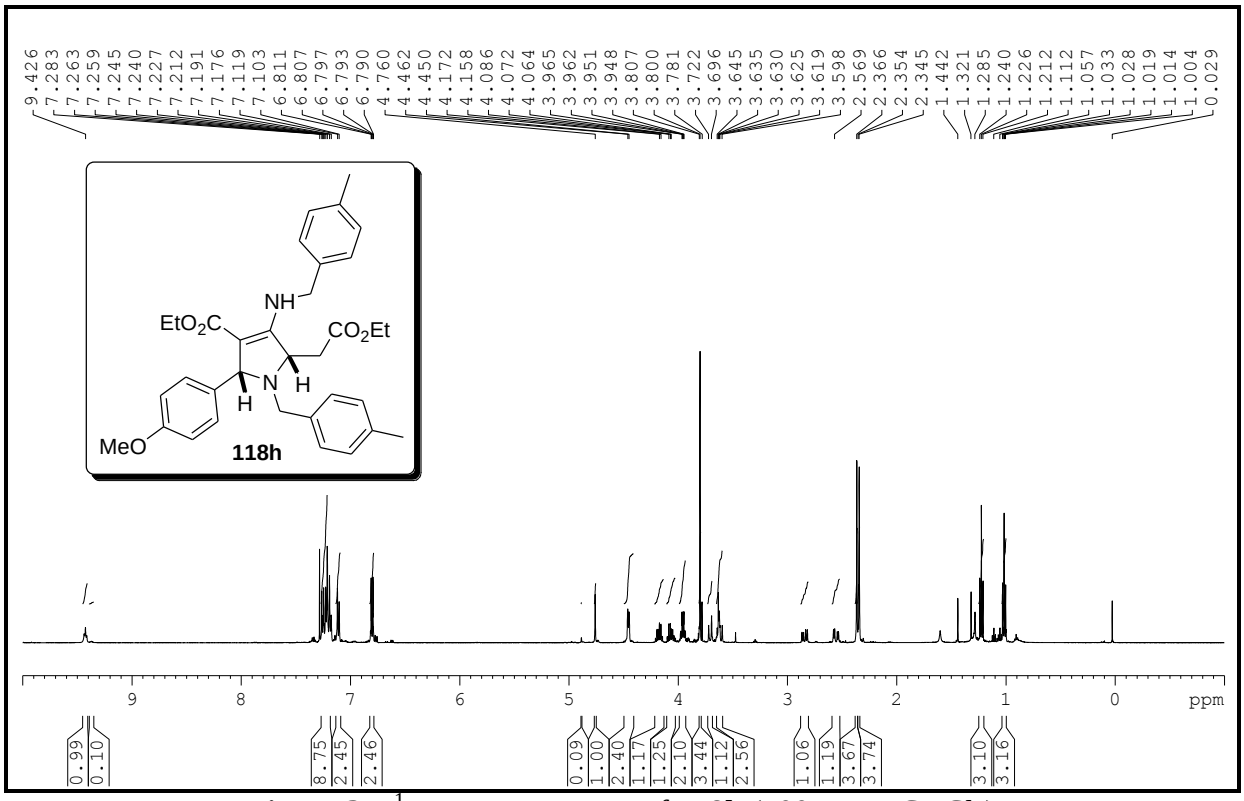

Figure 34. ^{1}H NMR spectrum of **118h** (500 MHz, $CDCl_3$)

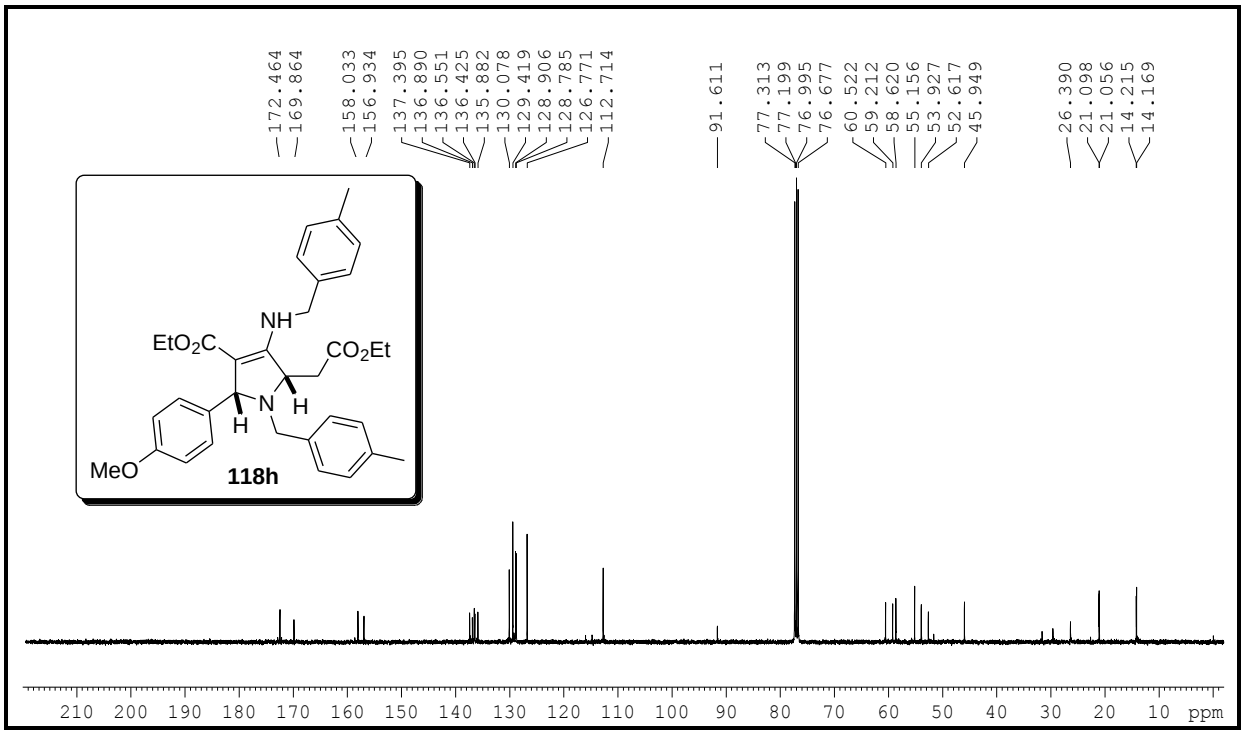

Figure 35. ^{13}C NMR spectrum of **118h** (100 MHz, $CDCl_3$)

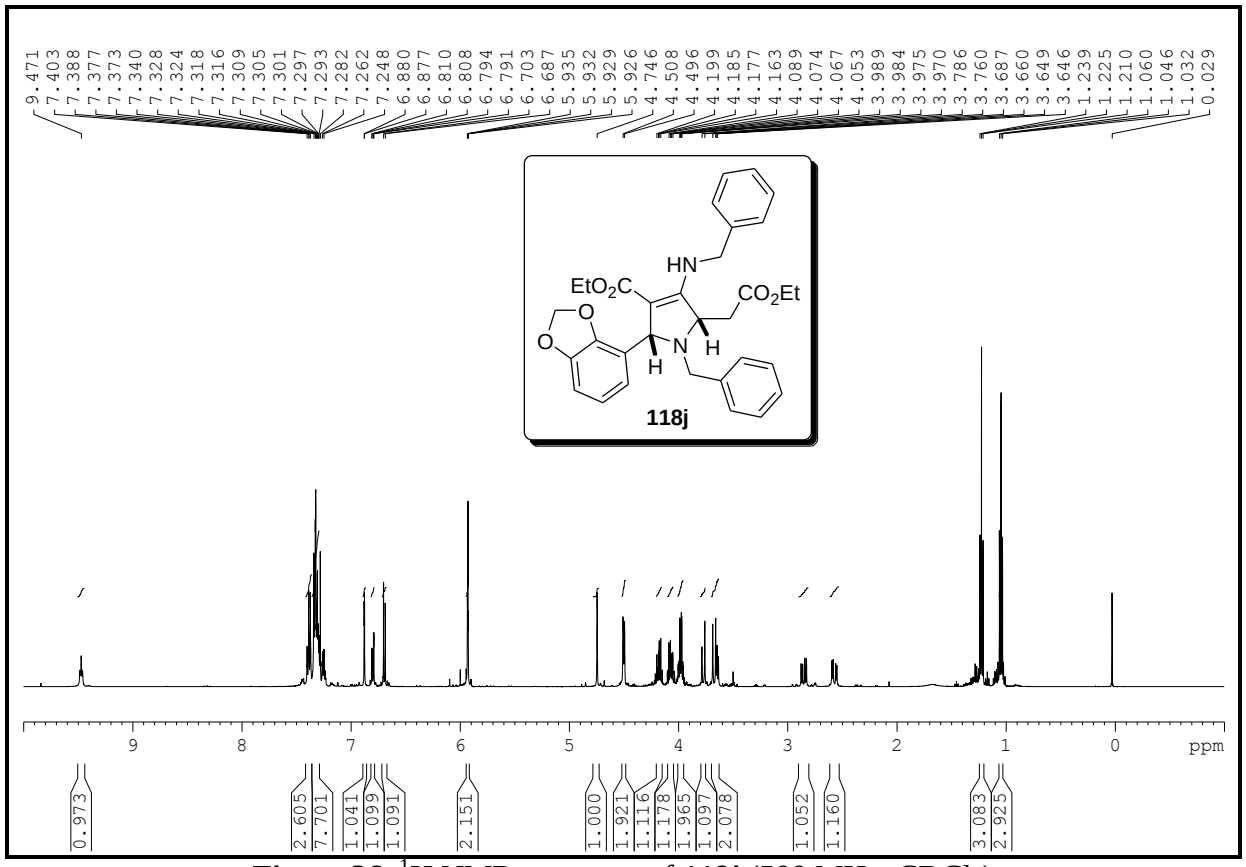

Figure 36. ^{1}H NMR spectrum of **118j** (500 MHz, $CDCl_3$)

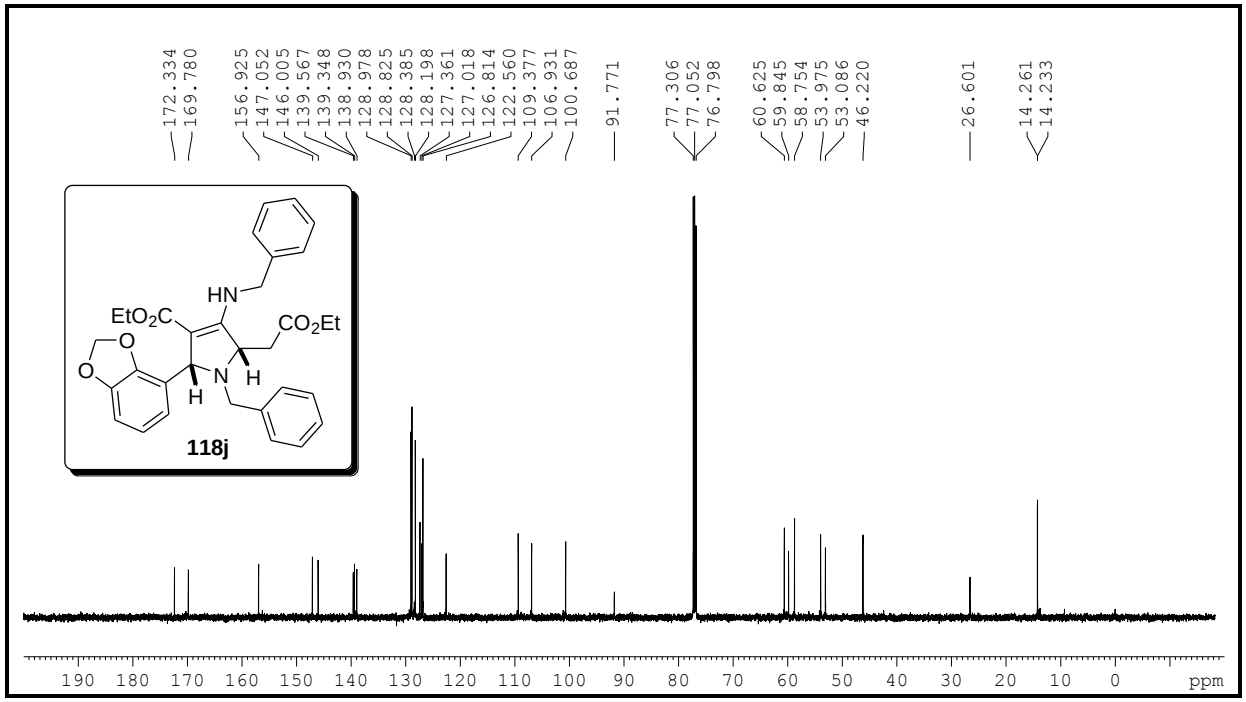

Figure 37. ^{13}C NMR spectrum of **118j** (125 MHz, $CDCl_3$)

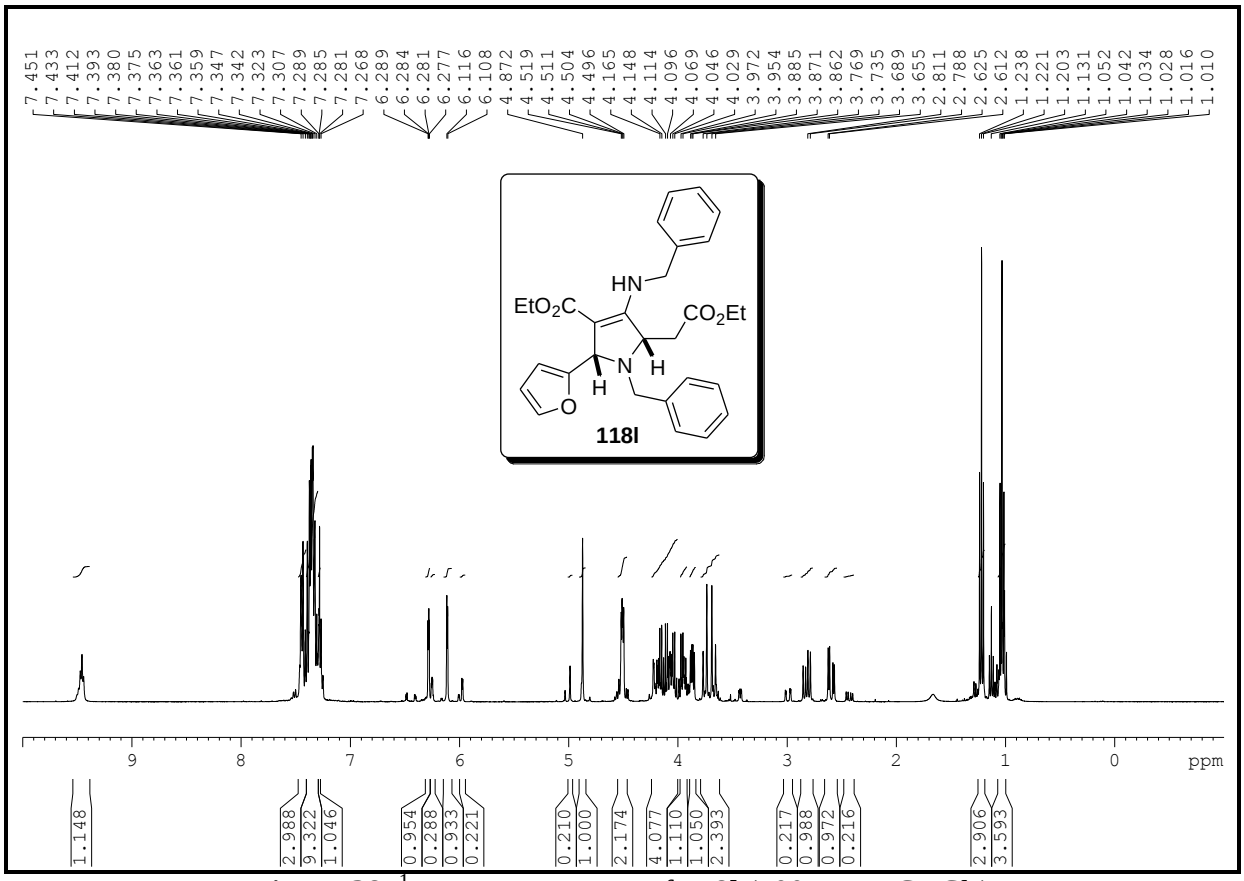

Figure 38. ^{1}H NMR spectrum of **118l** (400 MHz, $CDCl_3$)

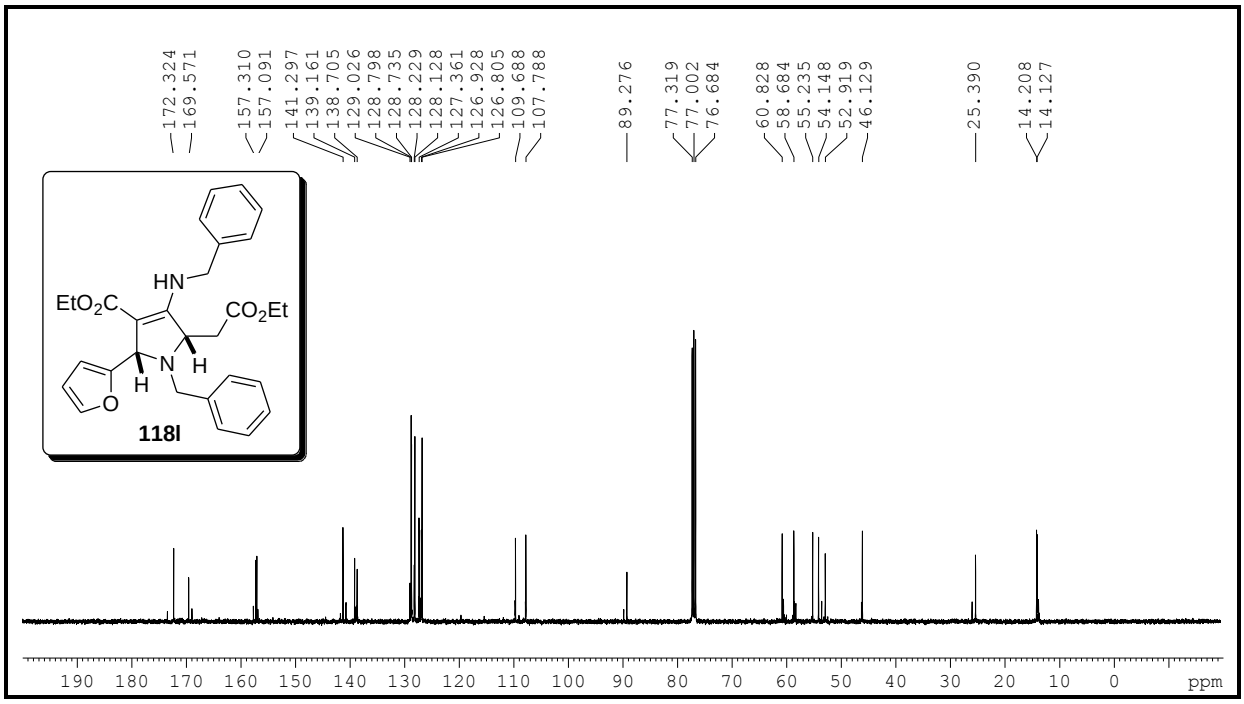

Figure 39. ^{13}C NMR spectrum of **118l** (100 MHz, $CDCl_3$)

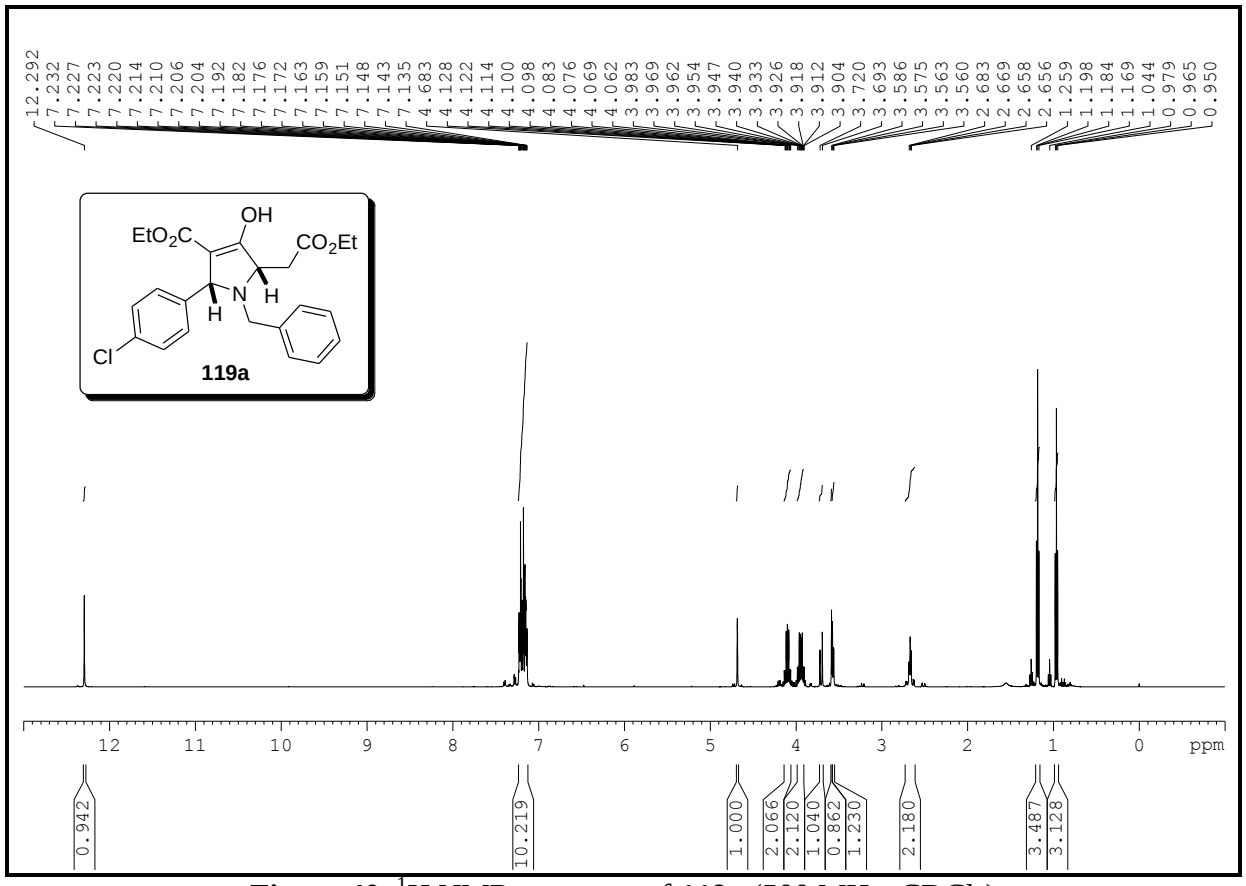

Figure 40. ^{1}H NMR spectrum of **119a** (500 MHz, $CDCl_3$)

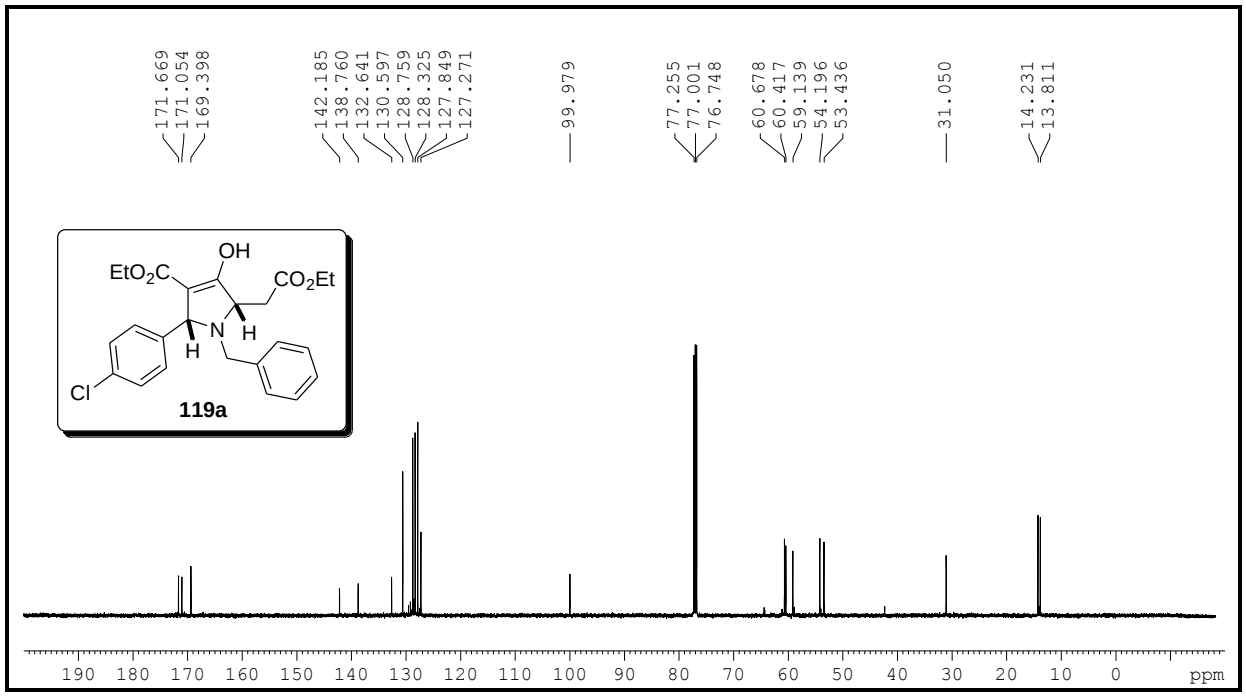

Figure 41. ^{13}C NMR spectrum of **119a** (125 MHz, $CDCl_3$)

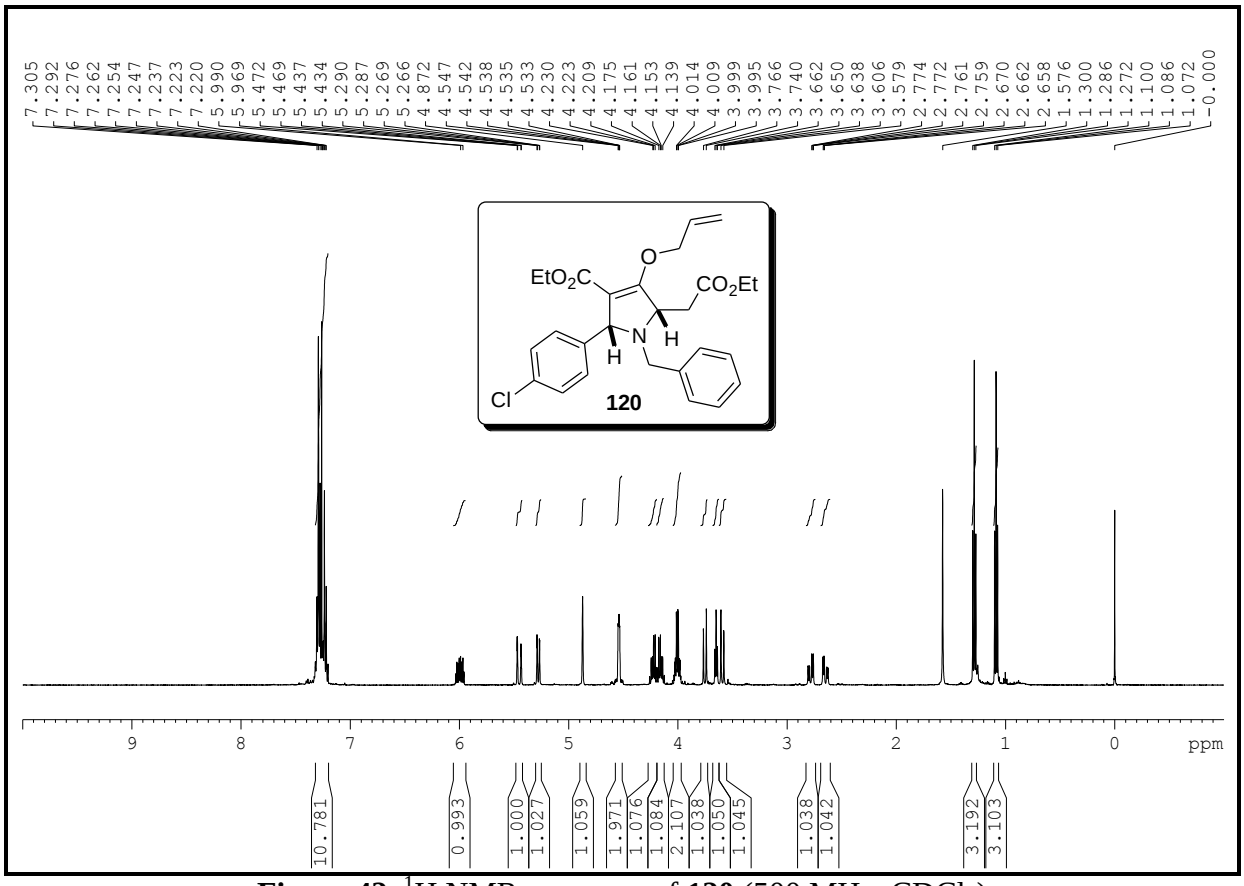

Figure 42. ^{1}H NMR spectrum of **120** (500 MHz, $CDCl_3$)

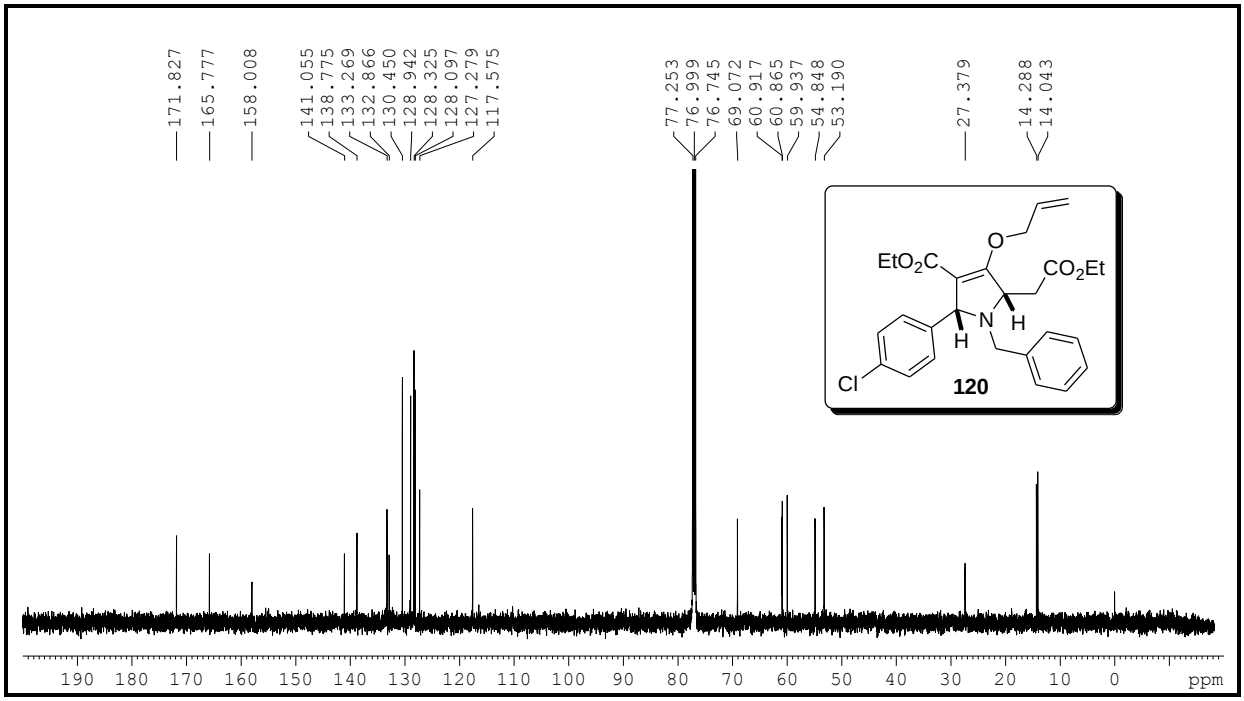

Figure 43. ^{13}C NMR spectrum of **120** (125 MHz, $CDCl_3$)

List of Publications

1. Gold-catalysed activation of epoxides: application in the synthesis of bicyclic ketals. Rengarajan Balamurugan,* Raveendra Babu Kothapalli and **Ganesh Kumar Thota**. *Eur. J. Org. Chem*. **2011**, 1557–1569.

2. Synthesis of cyclic acetals by metal-catalyzed reactions of epoxides and alkynes in acetone. **Ganesh Kumar Thota** and Rengarajan Balamurugan* (*manuscript to be submitted*).

3. Gold-catalyzed hydration of enynediester, alkynyl ketones/esters. **Ganesh Kumar Thota** and Rengarajan Balamurugan* (*manuscript to be submitted*).

4. One-pot synthesis of highly functionalized γ-lactam derivatives. **Ganesh Kumar Thota** and Rengarajan Balamurugan* (*manuscript to be submitted*).

5. Synthesis of highly substituted and functionalized pyrrolidine derivatives. **Ganesh Kumar Thota** and Rengarajan Balamurugan* (*manuscript to be submitted*).

Poster Presentation

1. Presented a poster on "Gold-catalyzed activation of epoxides in the Synthesis of bicyclic/cyclic acetals *via* acetonides*"* in the 7th Junior National Organic Symposium Trust (J-NOST) conference for Research Scholars held at Indian Institute of Science Education and Research (IISER) Mohali, INDIA.