β Activation of α, β- unsaturated esters for -C-C- bond formation reactions: Applications in the Synthesis of biological active compounds

THESIS

Submitted To The

UNIVERSITY OF PUNE

For The Degree Of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

By

GAIKWAD AMRUT LAXMANRAO

Research Supervisor

Dr. GANESH PANDEY

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE – 411008

December 2011

Dedicated

To My

Family

National Chemical Laboratory

NCL

Division of Organic Chemistry
Pune – 411 008, INDIA

Dr. Ganesh Pandey
FNA, FNASc, FASc

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"β Activation of α , β- unsaturated esters for -C-C- bond formation reactions: Applications in the Synthesis of biological active compounds"** which is being submitted to the University of Pune for the award of Doctor of Philosophy in Chemistry by Mr. Gaikwad Amrut Laxmanrao was carried out by him under my supervision at the National Chemical Laboratory, Pune. A material that has been obtained from other sources has been duly acknowledged in the thesis.

Date:

Dr. Ganesh Pandey

(Research Guide)

Ph. 020-2590 2627(O), 2590 2417 (R), Mobile: 9970171802, Fax: 020-25902629
E-mail: gp.pandey@ncl.res.in

DECLARATION

I hereby declare that the work presented in the thesis entitled **" β-Activation of α, β- unsaturated esters for C-C bond formation reactions:Application in the synthesis of biological active compounds"** submitted for Ph. D. Degree to the **University of Pune**, has been carried out by me at the **National Chemical Laboratory**, **Pune**, under the supervision of **Dr. Ganesh Pandey**. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University/Institute.

Date: (Gaikwad Amrut Laxmanrao)

Division of Organic Chemistry

National Chemical Laboratory

Pune – 411008.

Acknowledgement

The completion of this work would not have been possible without the generous help and encouragement of a number of people. I would like to thank every one of them for the support they have rendered for the accomplishment of the work presented in this dissertation.

First of all, I would like to present my feelings of gratitude to my research guide, ***Dr. Ganesh Pandey****, for accepting me as a Ph.D. student and for his invaluable guidance, endless patience and everything he taught me throughout this study. I sincerely thank him for teaching me finest skills of synthetic organic chemistry.*

I am thankful to Dr. (Mrs.) S. R. Gadre and my senior colleagues Dr. Manmohan Kapur, Dr. Prabal Banerjee, Dr. Sanjay Raikar, Dr. S. G. Dumbre Dr. Balakrishna, Dr. Kishore Bharadwas, Dr. Kesarinath Tiwari, Dr.Nishant Gupta, Dr. Debasish grahacharya, Dr. Ravindra Kumar, Dr. Prasanna kumara Chikkade, Shrikant, Swaroop, Rajender, Dharmendra, Sujit, Deepak, Debashis Day, Priyanka, Rajesh, Binoy, Animesh, Durgaprasad, Shiva kumar, Janakiram, Jagadish, Vineet, Ramkrishna, Pradip, Akash and Rushil for maintaining a warm and very cheerful atmosphere in the lab and always helping me with valuable scientific suggestions. Special thanks to Rajesh for his help during the writing of this thesis.

Help from the Spectroscopy and CMC group is gratefully acknowledged. Special thanks are due to Dr. P. R. Rajmohan and Dr. Rajesh Gonade, who went out of their way in helping me out whenever I needed an urgent analysis.

I would like to extend my thanks to my friends Dr. Ankush Biradar, Dr. Ganpat Dahe, Dinesh Pawar, Bhagyesh Kulkarni, Koteshwar Rao, Sachin Gawali, Sudnyan Daware, Arvind Korwar, Amit Sadani, Shankar Jadhav and Chandrakant Sangurde for their constant help and encouragement. Special thanks to Dinesh and Bhagyesh for their support and encouragement.

Whatever I am and whatever I intend to be in future is because of goodwill, unstinted support and constant love that I have received during my study and doctoral thesis from my parents, sisters, father-in law, mother-in-law, brother-in-law my maternal uncle and relatives. I have no words to thank my wife Pratima for her permanent help, love and understanding and making me happy during the period of stress.

Finally I thank ***CSIR, New Delhi****, for the award of Senior Research Fellowship and* ***Director, N. C. L.****., for the infra-structural facilities.*

Gaikwad Amrut Laxmanrao.

Contents

List of abbreviations

aq.	aqueous
bp	boiling point
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DMF	N, N-dimethyl formamide
DMSO	dimethylsulfoxide
COSY	correlated spectroscopy
g	gram
GC	Gas Chromatography
h	hour
Hz	Hertz
M	Molarity (molar)
Mg	Milligram
Min	Minute(s)
mL	Milliliter
mmol	Millimole
mp	Melting Point
N	Normality
MS	Mass Spectrum
MsCl	Methanesulfonyl chloride
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect/enhancement
NOESY	Nuclear Overhauser

	Enhancement Spectroscopy
ORTEP	Orthogonal thermal ellipsoid plots
p-TSA	*p*-Toluenesulfonic acid
rt	Room temperature
TBS	*t*-Butyldimethylsilyl
TEA	Triethyl amine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
$CuSO_4$	Copper (II) sulfate
DCA	9, 10- Diacyanoanthracene
DMN	1,5- Dimethoxynaphthalene
PET	Photoinduced electron transfer
AIBN	α,α'–Azo bis(isobutyronitrile)
Bu_3SnH	Tributyltin hydride

Research student	**Gaikwad Amrut Laxmanrao**
Research Guide	**Dr. Ganesh Pandey**
Title of thesis	**β-Activation of α, β-unsatureted esters for –C-C- bond formation reactions: Application in the synthesis of biological active compounds.**
Registration No.	**E1/231/Ph.D/2007 Dated September3, 2007**
Date of Registration	**04.12.2006**
Place of work	**Division of Organic Chemistry, National Chemical Laboratory,** **Dr. Homi Bhabha Road, Pune-411008, INDIA**

Thesis Abstract

The present dissertation is divided into three chapters.

Chapter One: A brief account of β-activation of α , β- unsaturated esters or ketones for carbon- carbon bond forming reactions

The first chapter deals with the brief account of β-activation of α , β-unsaturated esters or ketones for carbon-carbon bond forming reactions.

Developing new strategies for carbon-carbon bond forming reactions are a great challenge in organic chemistry research. Among the several strategies known for carbon-carbon bond forming reactions, radical based strategy occupies an important position. Beside classical approach of carbon centered radical generation, reductive β-activation of α , β- unsaturated esters or ketones has emerged an attractive strategy for radical generation and has been explored by many research groups. On the basis of different strategies utilized for β-activation reactions, these strategies have been broadly classified into four categories.

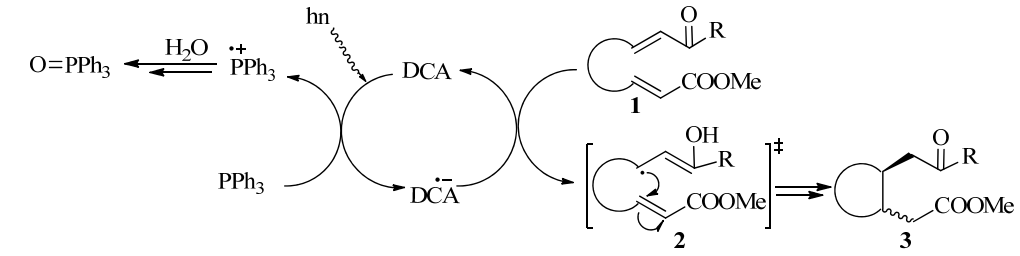
(I) β-activation by electrolytic cathodic cell.

(II) β-activation by activated metals such as Mg, Yb in dry methanol.

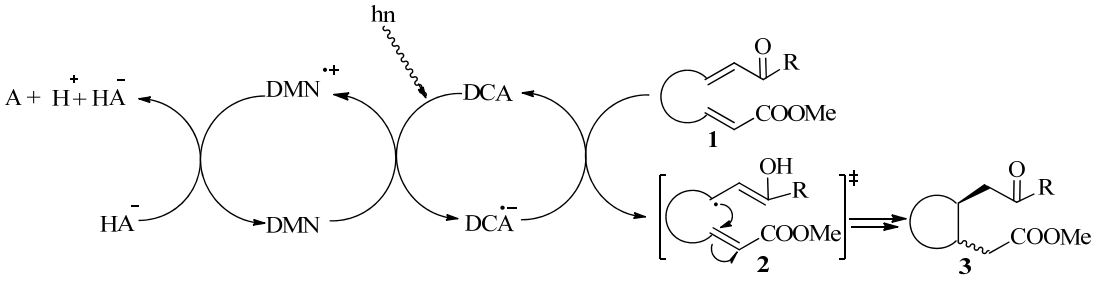
(III) β-activation by radical initiator.

(IV) β-activation by photoinduced electron transfer reactions.

Among all these broadly classified four strategies, the first three approaches suffer from various limitations such as use of toxic reagents and metals (e. g. Bu_3SnH, $HgCl_2$, Yb, Pb) which also require dry reaction conditions resulting into low yield along with low stereoselectivity. In the context of these limitations, β-activation by photoinduced electron transfer (PET), developed previously from our group, overcomes all the above mentioned drawbacks associated with earlier strategies. The PET based strategy employing either photosystem-A or photosystem-B is shown in Figure 1.



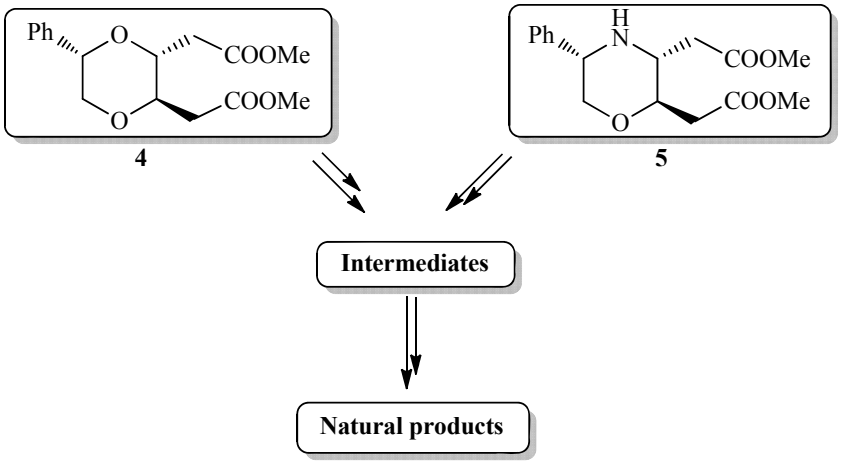
(PS-A)



(PS-B)

Figure -1: Catalytic cycle of photosystem-A and photosystem-B.

With these successful backgrounds on β-activation of α, β-unsaturated carbonyl moieties for radical generation, we envisaged extending the versatility of this methodology for preparing multitalented synthons **4** and **5,** envisaged for synthesizing various natural products intermediates (Scheme 1).



Scheme-1: Multi-talented designer synthons.

In chapter two, we have comprehensively discussed the synthesis of multi-talented synthons **4** and **5** and their transformations to few important natural products intermediates.

Chapter two:

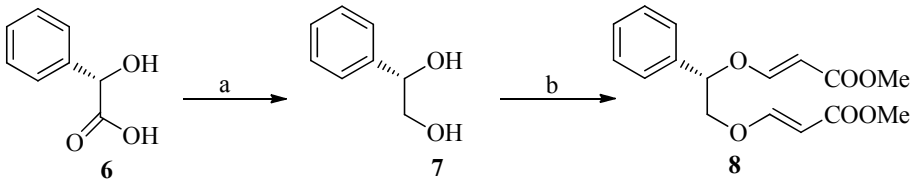
This chapter is divided in two sections

Section A:

(I) Stereoselective synthesis of chiral 6-phenyl -2, 3-bis methylenemethoxycarbonyl-[1,4]-dioxane 4:

Designing a multitalented synthon from which a number of important biologically active molecule precursors could be obtained by simple functional group transformations have always been the attempt of synthetic organic chemist. In this

context, we have explored the utility of our strategy of *β*-activation of *α, β*-unsaturated carbonyl compounds employing either photosystems PS-A or PS-B to design a multitalented synthon **4** by PET cyclization of **8.** Irradiation precursor **8** was obtained in 91 % yield by oxa-Michael reaction of **7** with methyl propiolate-N-methyl morpholine complex at 0 °C. Compound **7** was prepared in 88 % yield by LAH reduction of commercially available *R*-(+) mandelic acid **(6)**, (Scheme 2).



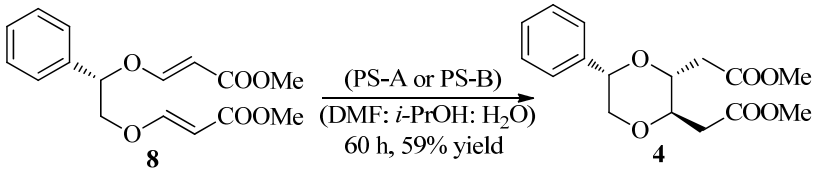
6 **7** **8**

Scheme-2: Synthesis of irradiation precursor **8.**

Reagents and conditions:

(a) LAH , dry THF, reflux 8 h 88 % (b) NMM, Methyl propiolate, dry DCM, 0 $^0C \rightarrow$ rt, 6 h, 91 % yield.

PET activation of **8** utilizing either PS-A or PS-B provided **4** in 59% yield (Scheme 3)



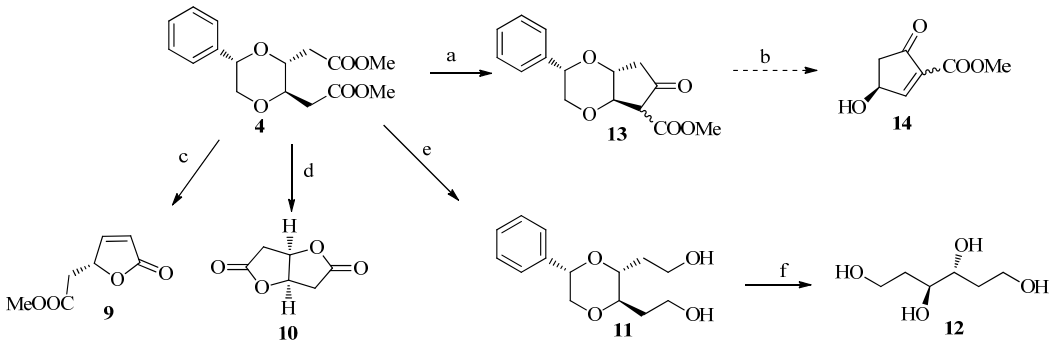
8 **4**

Scheme-3: Synthesis of compound **4** through **PET** cyclization.

which was transformed further into few important biologically active natural product intermediates.

(II) Stereoselective synthesis of optically pure bislactone, dialkylated-1,2-*trans*-diol and *α,β*-unsaturated-γ-substituted butyrolactone utilizing chiral 6-phenyl-2-bis methylenemethoxycarbonyl-[1,4]-dioxan 4:

After successful synthesis of chiral substituted 1, 4-dioxane **4**, its versatility was explored by transforming into a number of important natural products / intermediates such as optically pure bislactone **10**, 1,2-*trans*-diol **12** and *α,β*-unsaturated-*γ*-substituted butyrolactone **9** by simple functional group transformations as shown in Scheme 4.



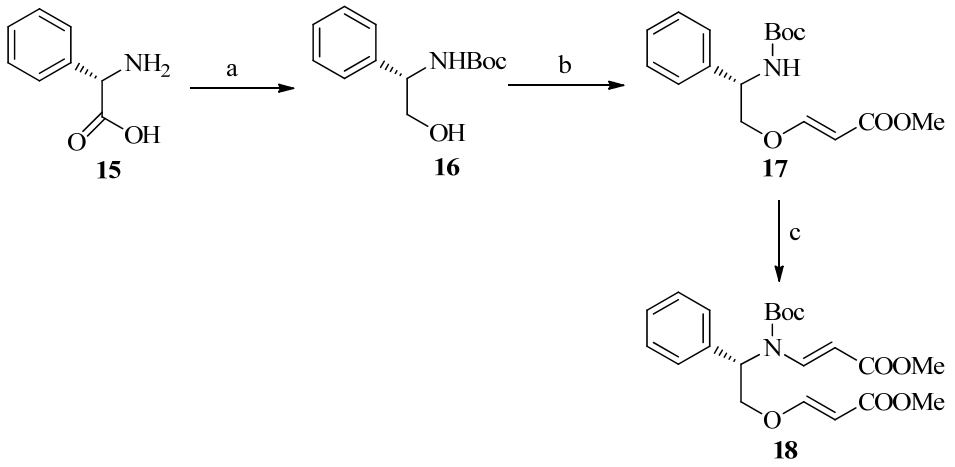
Scheme-4: Synthetic sequence of important intermediates.

Reagents and conditions: (a) NaH, dry THF, reflux 4 h, 38 % (b) BBr_3, dry DCM, -78 ^{0}C → –20 ^{0}C , 20 min, then at 0^{0}C for 2 h (c) $Pd(OH)_2$/C in AcOH, 60 psi 24 h, 86 % (d) BBr_3, dry DCM, -78 ^{0}C → -20 ^{0}C for 20 min, then at 0 ^{0}C for 2 h, 98 % (e) $LiAlH_4$, dry THF reflux for 6 h, 73 % (f) $Pd(OH)_2$/C in AcOH, 60 psi 24 h, 68 %

Section B:

(I) Stereoselective synthesis of chiral 6-phenyl-2,3-bis methylenemethoxycarbonyl morpholine 5.

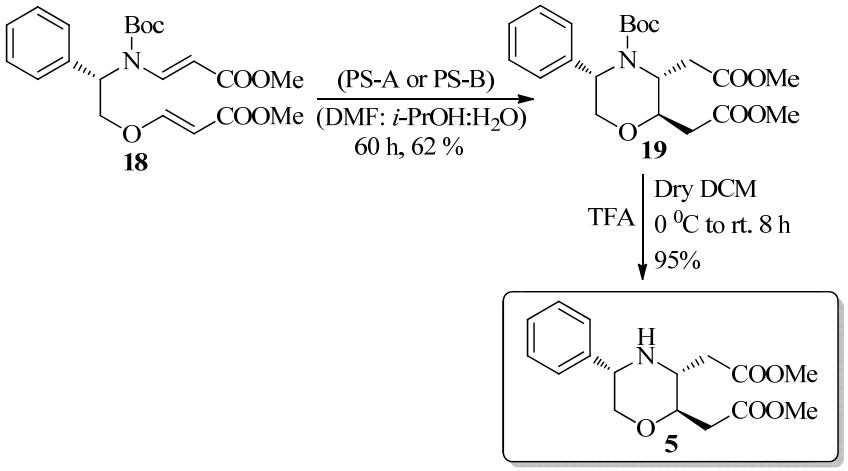
The successful results in the previous section was extended to design another versatile multi-talented synthon **5**, by PET cyclization of **18**, obtained by sequential oxa Michael addition of N- methyl morpholine-methyl propiolate complex in dry DCM at 0° on *R*-(+)-phenyl glycine derivative **16** as shown in Scheme 5.



Scheme-5: Synthesis of irradiation precursor **18.**

Reagents and conditions: (a) $NaBH_4/I_2$, dry THF 18 h reflux, Et_3N, $(Boc)_2O$, $0^0C \rightarrow$ rt for 3 hr 78% yield (b)) NMM, Methyl propiolate, dry DCM 0 ^0C to rt, 6 hr, 91 % (c) NaH, dry THF. Methyl-3-iodoacrylat $0^0C \rightarrow$ rt, 3 h, 80% yield.

PET activation of **18** utilizing either PS-A or PS-B provided **19** in 62% yield (Scheme 6)

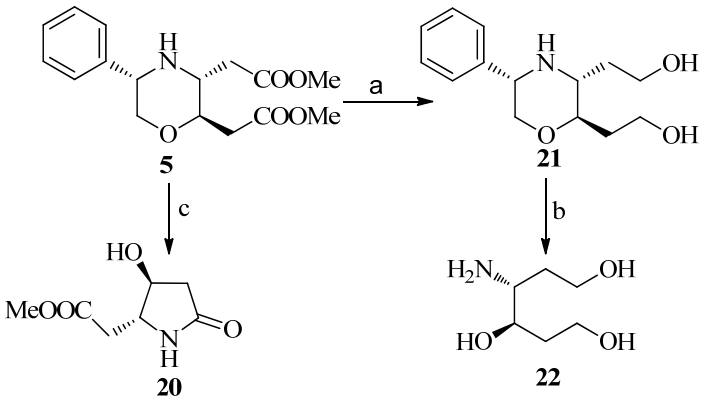


Scheme-6: Synthesis of compound **5,** through PET cyclization.

Compound **5** was transformed further into few important biologically active natural product intermediates.

(II) Stereoselective synthesis of optically pure dialkylated 1,2-*trans*-amino alcohol, *β*-hydroxy-*γ*-substituted butyrolactam, *β*-amino-*γ*-substituted-butyrolactone and 3-amino substituted tetrahydrofuran from multi-talented synthon 5.

Chiral 6-phenyl -2,3-bis methylenemethoxycarbonyl morpholine **5** was transformed to few important intermediates such as dialkylated 1,2-*trans*-aminoalcohol **22** and *β*-hydroxy-*γ*-substituted butyrolactam **20** as shown in Scheme 7.

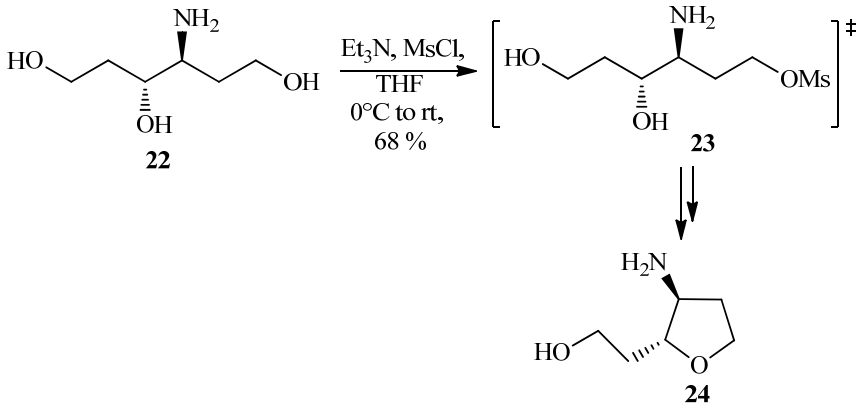


Scheme-7: Synthesis of important intermediates of natural products.

Reagents and conditions:

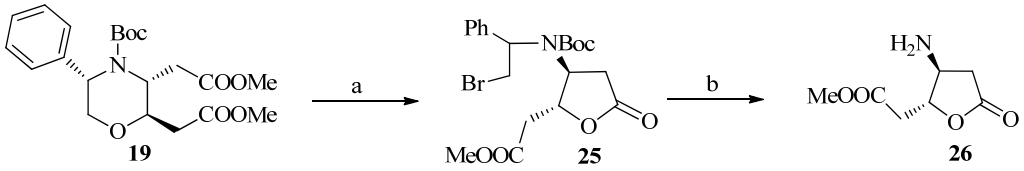
(a) $LiAlH_4$,dry THF, 0^0C to rt , reflux 8 h, 74% (d)H_2, $Pd(OH)_2$/C,60 psi, AcOH, 65 % (c) H_2, $Pd(OH)_2$/C,60 psi, AcOH, 24 h, 86 %.

The utility of Dialkylated-1,2-*trans*-amino alcohol **22** was further demonstrated by synthesizing 2-alkyl-3-amino substituted tetrahydrofuran **24**, an important intermediate for 2,3-dideoxynucleoside (ddN) and aminolignans having potent biological activity as shown in Scheme-8.



Scheme-8: Synthesis of optically pure **24**.

Finally we have also shown utility of Boc-protected morpholine **19** to synthesize optically pure *β*-amino-*γ*-substituted-butyrolactone **26**, an important intermediate used for the synthesis of wide range of compounds including aziridines, oxazolidinones and highly functionalized amino acids (Scheme 9).



Scheme-9: Synthesis of beta amino butyrolactone **26**.

Reagents and conditions:

(a) BBr_3, dry DCM,-78 ^{0}C to -20 ^{0}C , 20 min, then 0^{0}C for 2 h, 86 % .(b) H_2, $Pd(OH)_2$/C,60 psi, AcOH 82 % yield.

Chapter Three:

This chapter describes the detailed experimental procedures, tabulated spectral data and spectra of all new compounds.

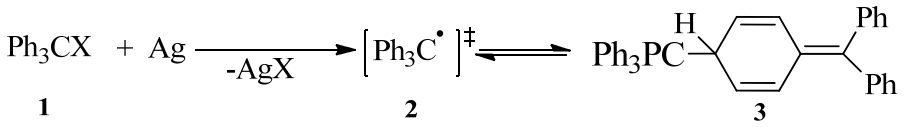
Note: Compound numbers in the abstract are different from those present in the thesis.

CHAPTER 1

β-Activation of α ,β-unsaturated esters or ketones for carbon-carbon bond forming reactions: A brief account

1.1 *Introduction*

Developing strategies for new carbon-carbon bond forming reactions are one of the main activities in organic chemistry research. Although, there exists several carbon-carbon bond forming reactions,[1,2] radical based reactions have gained incredible importance in modern synthetic organic chemistry. Over the last two decades, free-radical reactions have evolved as one the most significant reactive intermediates for C-C bond forming reactions due to their versatility, predictability and functional group tolerance. Although, free radical era can be dated back to 1900 with the discovery of triphenylmethyl radical **2** by Gomberg[3], radical pathway in the organic synthesis began only in 1937 by Hey *et al*.[4] in wherein homolytic phenylation of aromatic substrate to provide **3** (Scheme 1) was reported. In the same year Kharasch[5] recognized the anti-Markovnikov addition of hydrogen bromide to alkenes as a radical chain process.



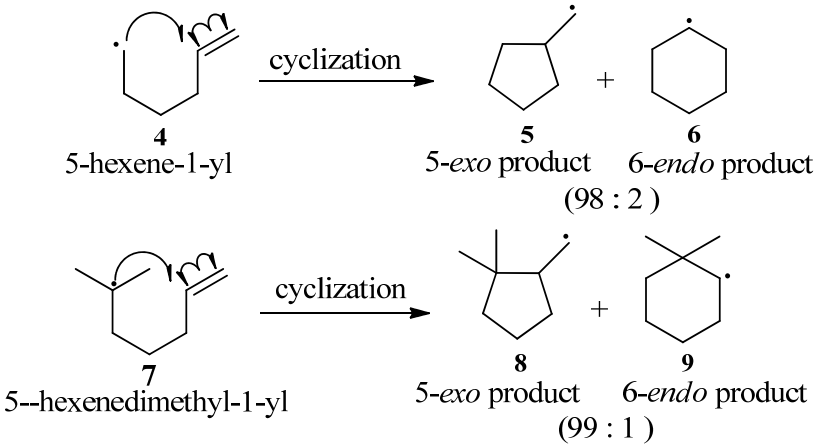
Scheme-1: Gomberg's first radical initiation reaction.

After pioneering research initiated on radical reactions by Gomberg and Kharasch, many strategies for radical reactions were developed.

In free radical reaction, SOMO (singly occupied molecular orbital) interacts with HOMO or LUMO of another molecule where reactivity depends on the potential energy level of the SOMO. For example, an electron-rich free radical having high potential energy behaves as a nucleophile and interacts with LUMO of another

molecule whereas an electron-poor free radical having low potential energy behaves as an electrophile and interacts with HOMO in another molecule. This orbital interaction between SOMO–LUMO or SOMO–HOMO is initial step for carbon-carbon bond formation reaction[6]. In radical initiated carbon-carbon bond forming reactions, the rate of addition of radical to alkene depends largely on the substituents on the radical and the alkene.[7, 8]

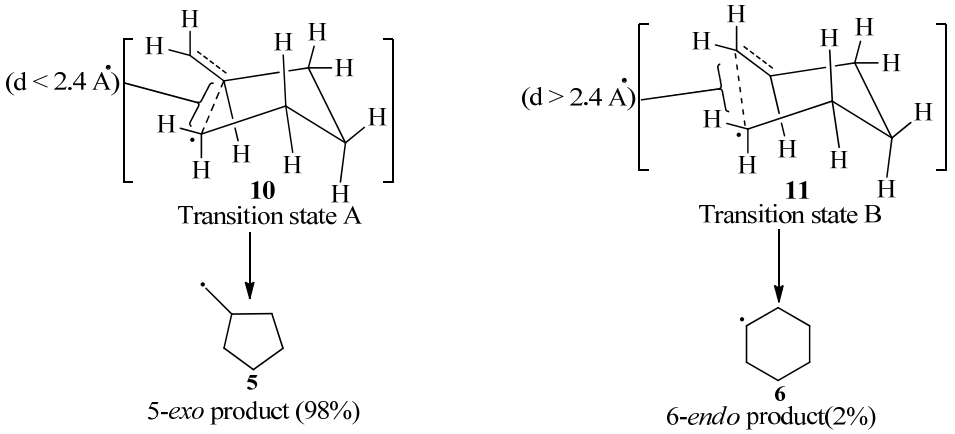
Regioselectivity in radical reactions are generally governed by their substituents and the kinetics of cyclizations. For example, 5-hexene-1-yl **4** radical cyclizes predominantly in an *exo*-mode[9] to give a five membered ring **5** rather than to give an *endo*-cyclized six membered ring **6**. Thus, the less stable primary radicals are formed faster than the more stable secondary radicals as shown in Scheme-2.



Scheme-2: Regioselectivity in radical cyclization.

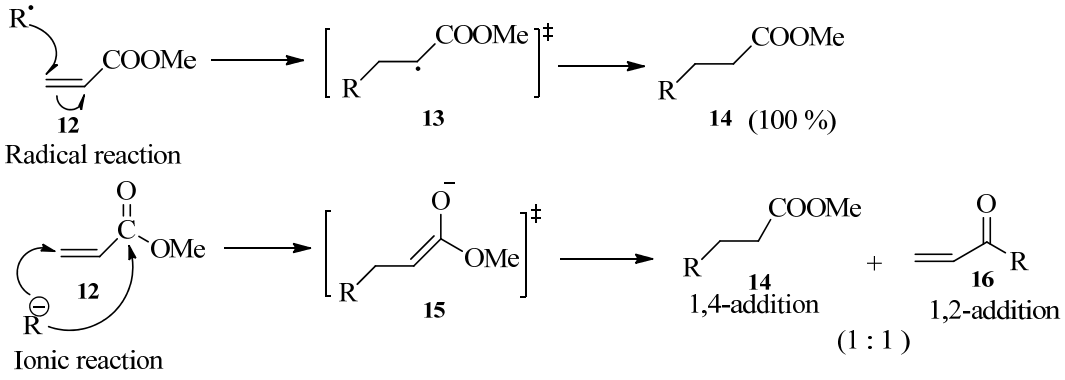
Regioselectivity issue in radical cyclizations is explained by Beckwith *et al.*[10] by considering the stereoelectronic effects in which the distance between the two reacting (carbon) sites play vital role. This concept is explained by considering two unsymmetrical transition states A and B. In transition state A, the distance between the attacking radical carbon and one of the olefinic carbon atoms is less than 2.4 Å.

Thus, it cyclizes very fast and provides five membered ring[11] whereas in transition state B, the distance between the attacking radical and one of the olefinic carbon atom is greater than 2.4 Å, therefore, it cyclizes very slowly to afford six membered ring as shown in Scheme- 3.



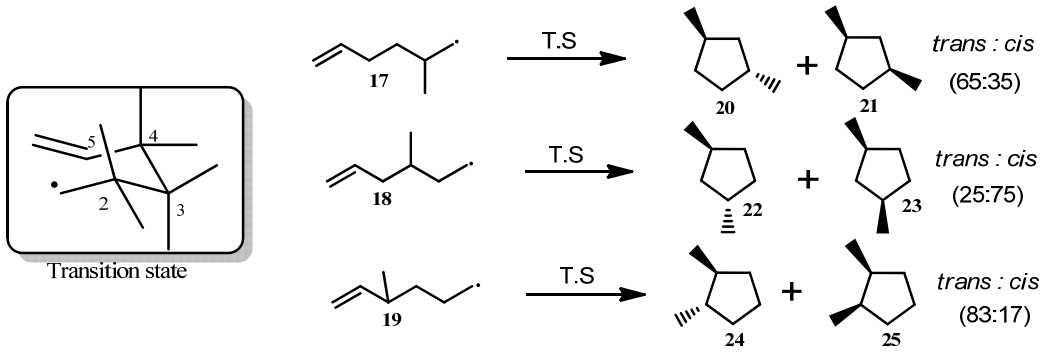
Scheme-3: Stereoelectronic effect in radical cyclization

Particularly, *α,β*-unsaturated esters or ketones **12** are attacked by the carbon centered radicals exclusively at the *β*-position of the olefinic carbon whereas, anionic species, competes for Michael addition at conjugated olefin as well as carbonyl carbon and end up with giving mixture of products **14** and **16** as shown in (Scheme 4).



Scheme-4: Regeoselectivity in radical and ionic reactions.

Stereoselectivity in radical reactions is mainly governed by the substituents present on the olefinic site[12]. According to Beckwith-Houk transition state model[13], during hexyl radical ring closures, 1 or 3 substituted radicals preferentially gives *cis*-disubstituted cyclopentyl product whereas 2 or 4 substituted radicals give *trans*-disubstituted products. The above rule is explained by considering transition state, in which 5-*exo*-cyclization prefers the substituent to be pseudo-equatorial rather than pseudo-axial as shown in Scheme 5.

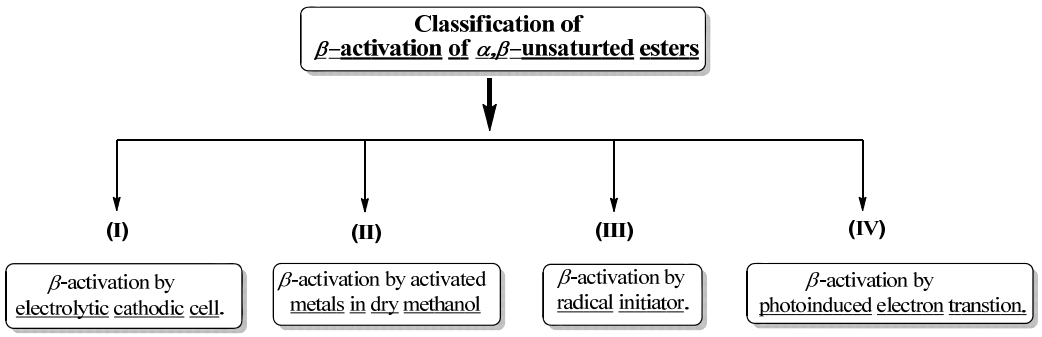


Scheme-5: Stereoselectivity in radical cyclization reaction.

α,β-Unsaturated esters or ketones **12,** apart from being utilized for -C-C- bond formation at its *β*-position through a radical addition, they have also been used as a source of carbon centered radical. These radicals are generated by reductive *β*-activation employing different strategies. Following section would discuss briefly but systematically all the strategies of *β*-activation of *α, β*-unsaturated esters/ketones to put the study under proper perspectives.

1.2 *Classification of β-activation reactions.*

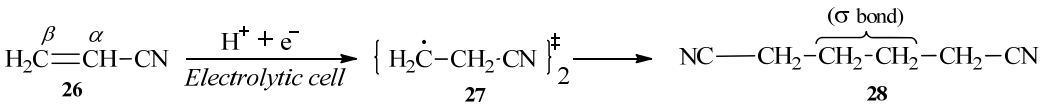
β-Activation of *α*, *β*- unsaturated esters to generate a carbon centered radical and to utilize them for carbon-carbon bond forming reaction have been extensively exploited in organic syntheses. On the basis of different strategies utilized for *β*-activation of *α*, *β*- unsaturated esters, they have been broadly classified into four categories.



I. *β*-Activation by electrolytic cathodic cell.

In this section, we will discuss briefly few reported strategies in the area of organic electrochemistry focusing, particularly, on the use of intramolecular electroreductive cyclization chemistry of *α*, *β*- unsaturated olefins.

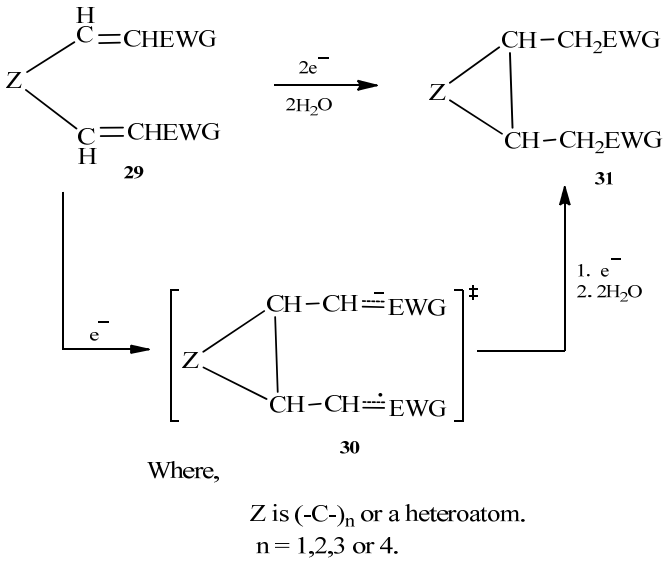
Baizer and co workers[14] in their pioneering studies of electrodimerization and electrocyclization of *α*, *β*-unsaturated nitrile **26** reported the formation of a new σ-bond between two electrophilic carbons and obtained **28,** which was later utilized as a key intermediate in the synthesis of Nylon- 66 as shown in Scheme 6.



Scheme-6: Baizer's approach.

This fundamental concept of *β*-activation via one electron electroreductive dimerization was also explored further utilizing *α, β*-unsaturated esters[15].

One of the very early literature report for intramolecular carbon-carbon bond forming reaction through *β*-activation of *α, β*-unsaturated esters **29** was reported by Petrovich *et al.*[16] at cathodic cell involving transition state **30** to obtain cyclized product **31** in 65% yield (Scheme 7).

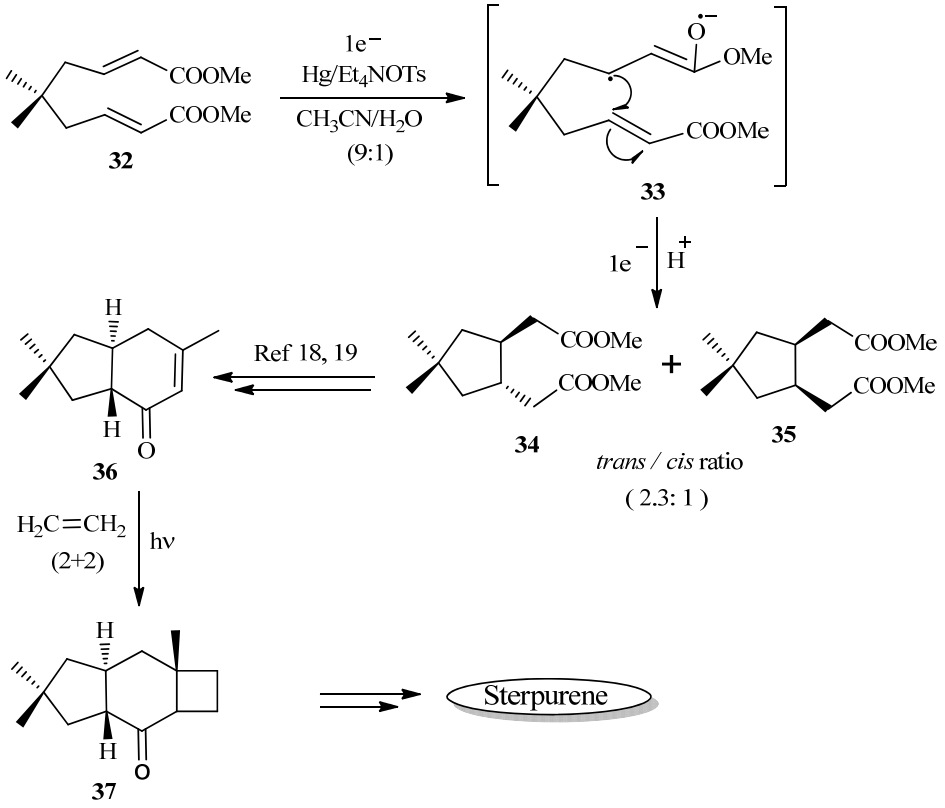


Scheme-7: Petrovich's electroreductive strategy.

Although, it was claimed that the strategy gave excellent results for the construction of three to six membered carbocylic ring system, surprisingly, no further report was seen to explore this strategy for a long time till Little *et al.*[17] in 1986 reported an

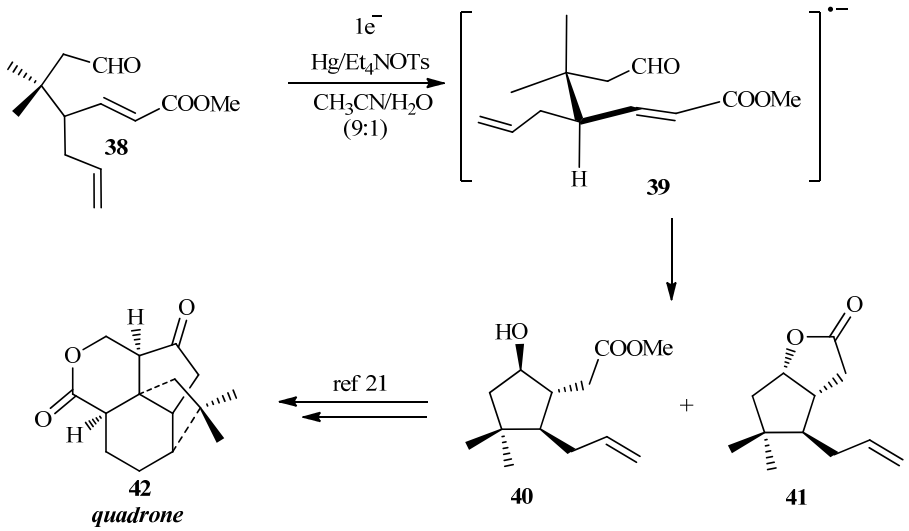
intramolecular electroreductive cyclization of *α, β*-unsaturated esters for the construction of carbocyclic framework.

β-Activation of *α,β*-unsaturated ester **32** using platinum (Pt) foil at anode and a mercury pool at cathode having solution of 0.74 M Et_4NOTs in (9:1) mixture of acetonitrile and water, provided mixture of cyclic products **34** and **35** in 82% yield (2.3:1 *trans*/*cis* ratio). The cyclic compound **34** was further transformed into **37**, used as a precursor in the synthesis of *Sterpurene* class of natural products (Scheme 8).



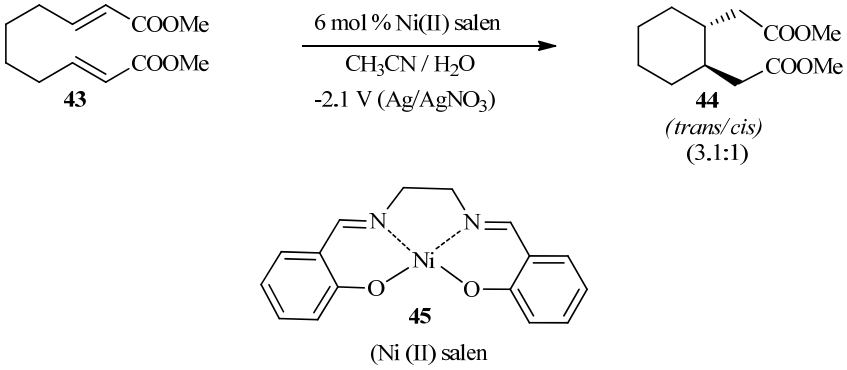
Scheme-8: Little's electroreductive strategy.

The same group[20] further explored this strategy and reported an efficient formal total synthesis of *Quadrone* utilizing one electron reductive electrocyclization of **38** to obtain a mixture of **40** and **41** (89 % yield) through transition state **39** (Scheme 9).



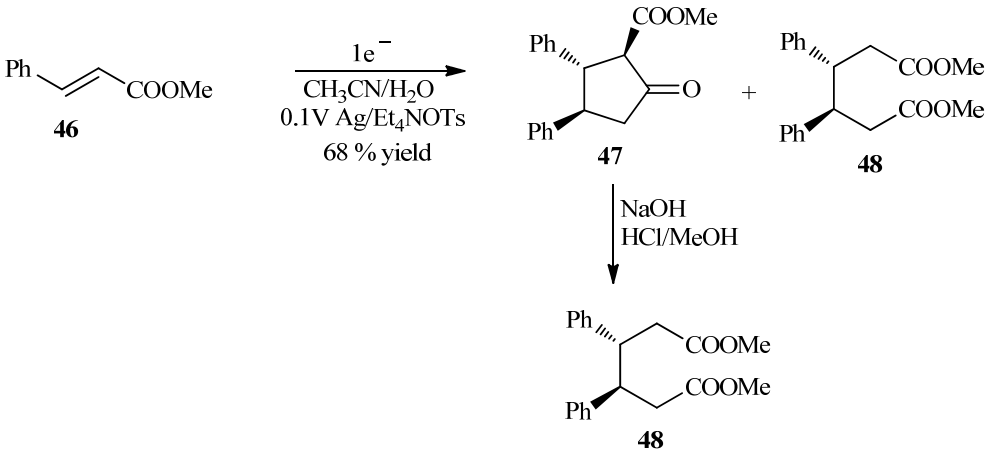
Scheme-9: Quadrone synthesis through electroreductive cyclization.

Very recently the same group[22] has again reported cyclization of **43** using reduced nickel (II) salen catalyst **45** as an electron transferring agent to obtain cyclized product **44** in 73 % yield (3.1:1 *trans/cis* ratio) (Scheme 10).



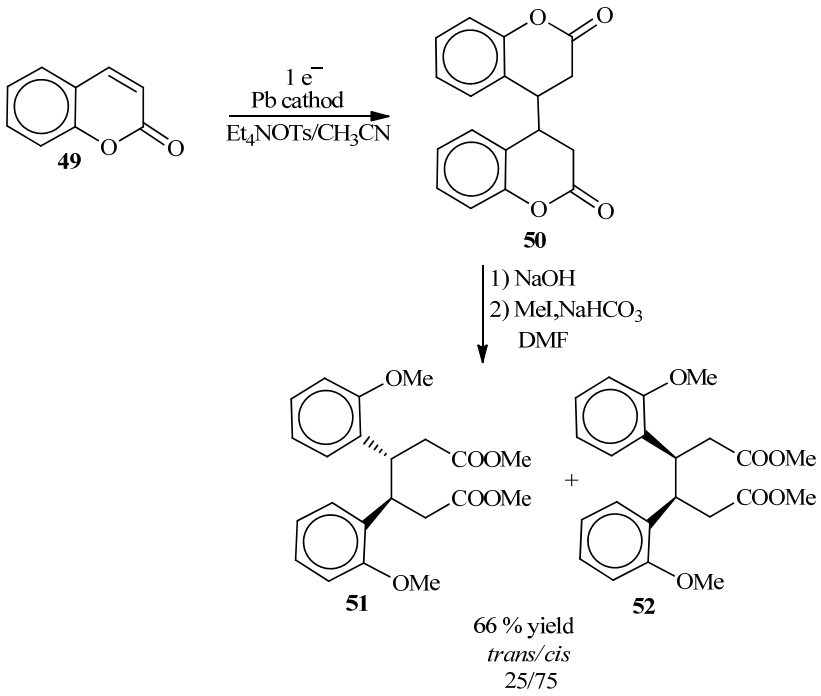
Scheme-10: Little's electroreductive strategy.

Kise *et al.*[23] has reported, recently, electroreductive intermolecular cyclodimerisation of **46** to obtain **47** (68 % yield) and *β-β-* coupled dimerized **48** (11% yield) (Scheme 11), respectively.



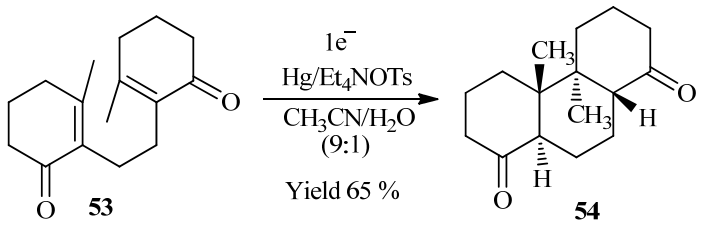
Scheme-11: Kise's cyclodimerization strategy.

Furthermore, utility of this strategy was demonstrated[23] by synthesizing important dimerized products **51** and **52** in 66% yield (2.5:7.5 *trans/cis* ratio), (Scheme 12).



Scheme-12: Kise's electroreductive strategy.

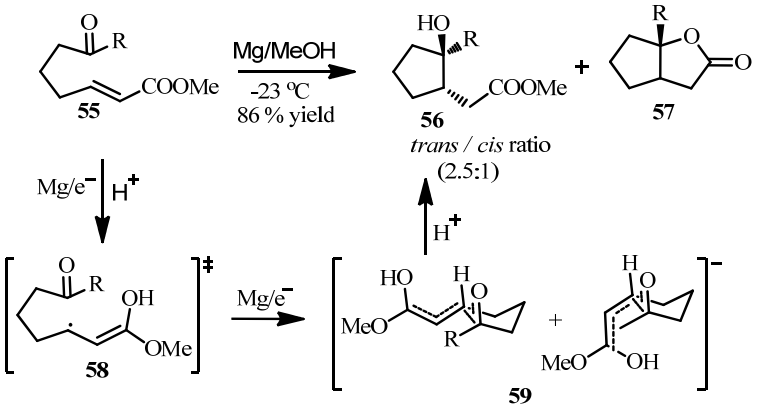
Mandell and co-workers[24], under controlled electroreductive conditions have converted bis-cyclic enone **53** into tricyclic **54** as a single diastereomer in 65% yield (Scheme 13).



Scheme-13: Mandell's electroreductive cyclization.

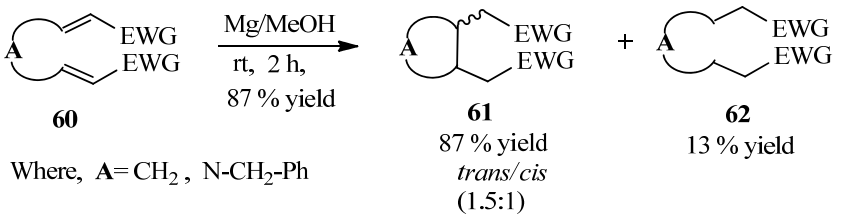
II. *β*-Activation *α, β*-unsaturated esters by activated metals.

Another strategy of *β*-activation of *α, β*-unsaturated esters has been achieved by using activated metals such as magnesium and ytterbium. For example, Lee *et al*.[25] utilized magnesium in methanol for one electron reductive *β*-activation of *α,β*-unsaturated esters **55** to obtain **56** and **57** in 86 % yield (2.5:1 *trans/cis* ratio). Mechanistically, this transformation was explained by the addition of *β*-ketyl radical **58** to carbonyl moiety involving transition state **59** as shown in Scheme 14.



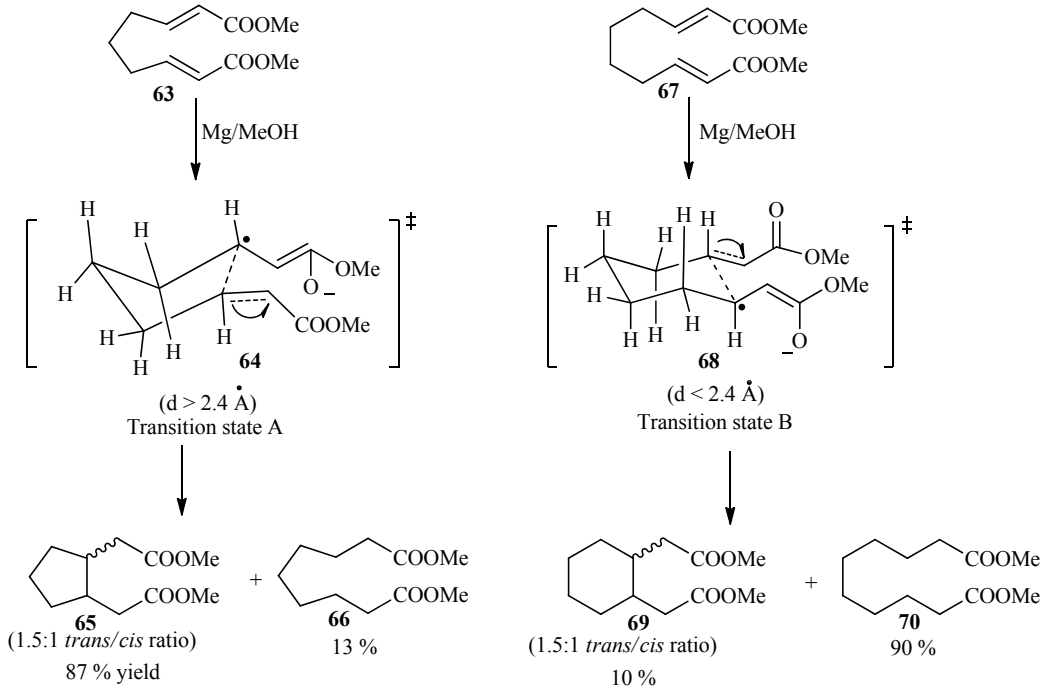
Scheme-14: Lee's strategy for *β*-activation.

Chavan *et al.*[26] have used Mg / MeOH for a facile intramolecular cyclization of **60** to **61** in 87 % yield. Although, this methodology was successful in the synthesis of three to five membered carbocycles and heterocycles, it failed for the construction of six membered rings (Scheme 15).



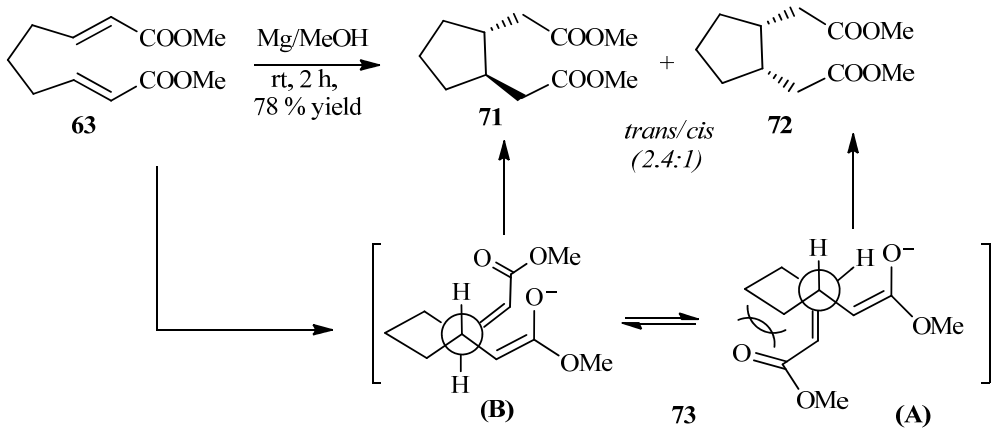
Scheme-15: Chavan's Mg/MeOH strategy

The failure to construct six membered ring through this approach was explained through Beckwith's transition states **64** and **68**. In transition state **64**, the distance between the two reacting carbon centers is less than 2.4 Å, thus, it cyclizes very fast to provide five membered ring **65** as a major compound and reduced product **66** as a minor compound whereas in transition state **68**, the distance between the two reacting carbon centers are greater than 2.4 Å, therefore, cyclizes very slowly and leads to reduced product **70** along with minor six membered cyclized product **69** (Scheme 16).



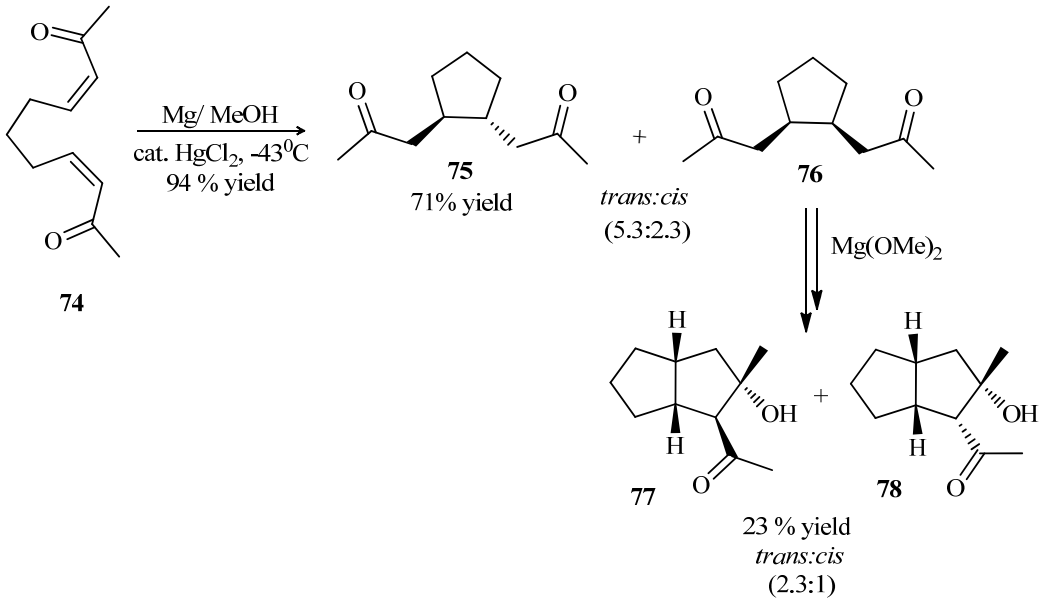
Scheme-16: Transition state in Mg/MeOH strategy.

Pak *et al.*[27] has explored this reaction in intramolecular cyclization of **63** affording a mixture of **71** and **72** in 78 % yield (*trans / cis*, 2.4:1 ratio). Author have also proposed a possible reaction mechanism for its stereochemical outcome involving transition state **73** in which conformer (A), due to steric hindrance, gets converted into more favored stable conformer (B) providing **64** as the major product (Scheme 17).



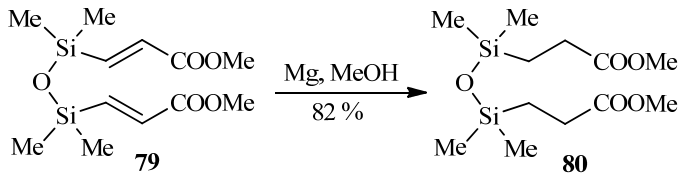
Scheme-17: Pak's Mg/MeOH strategy.

Same author has further reported the cyclization of **74** at lower temperature (-43 °C) using magnesium powder in absolute methanol in the presence of catalytic amount mercuric chloride and have reported enhancement in the overall yield of cyclized products **75** and **76** in 94 % yield (5.3:2.3 *trans*/*cis* ratio). Compound **76** with *cis*-geometry was found to undergo further aldol condensation affording stereoisomeric mixture of bicyclic compounds **77** and **78** in 23 % yield (2.3:1 *trans/cis* ratio) (Scheme 18).



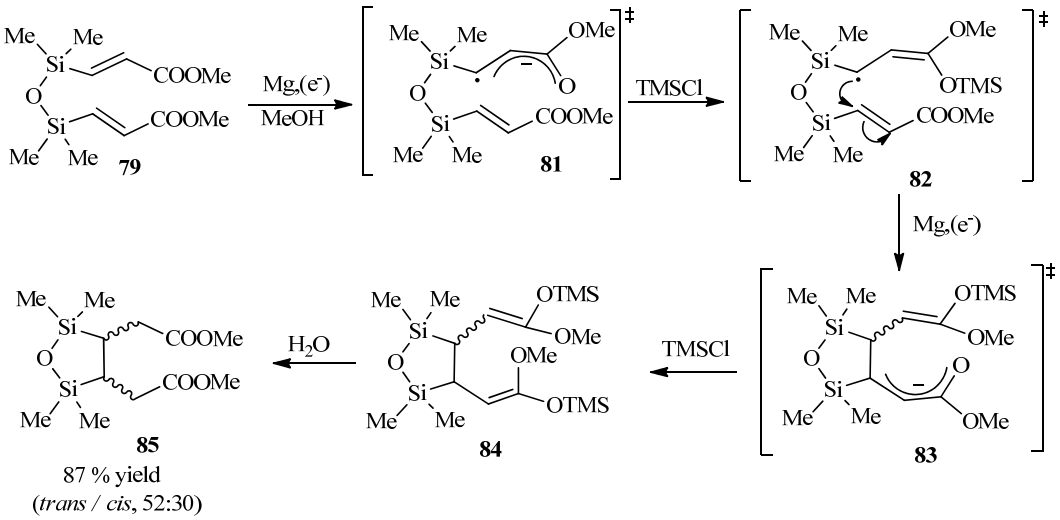
Scheme-18: Pak's strategy in presence of $HgCl_2$.

Reductive cyclization of disiloxane **79,** using activated magnesium metal in absolute methanol at room temperature, was recently attempted by Ghosh *et al*.[28] however, surprisingly they obtained completely reduced product **80** in 82 % yield (Scheme 19). To overcome the problem,



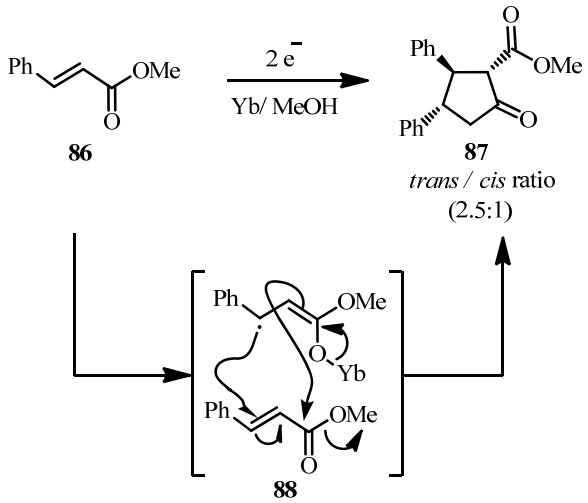
Scheme-19: Ghosh's Mg/MeOH strategy.

author used trimethylsilyl chloride (TMSCl) as an additive and succeeded in obtaining **85** in 87 % yield (*trans / cis*, 52:30 ratio) along with minor amount of **80 (**13% yield). The role of trimethylsilyl chloride in this reaction is explained in Scheme 20.



Scheme-20: Reaction mechanism in Ghosh's strategy.

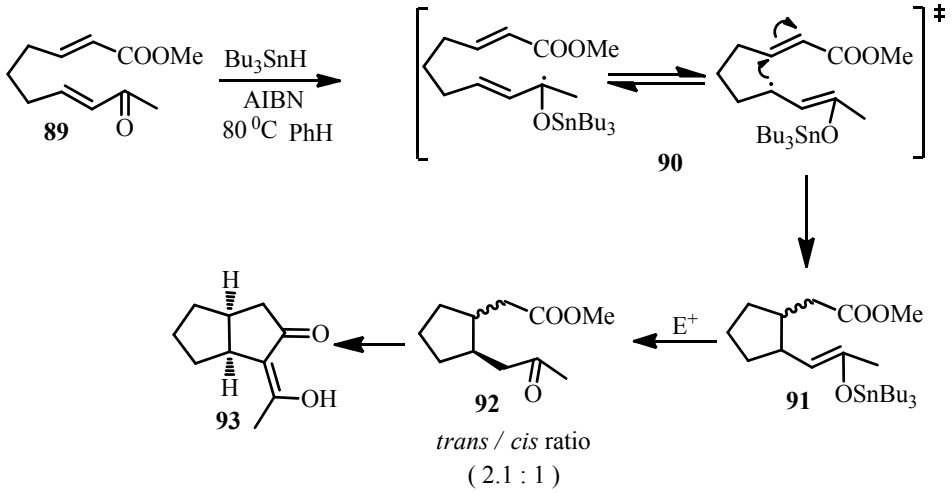
Beside Mg / MeOH as one electron reductant, Fujiwara[29] and co-workers have discovered that PhYbI or Yb in methanol also have the same ability and subsequently Takaki *et al.*[30] utilized Yb/MeOH for cyclodimerization of **86** to obtain **87** in 73% yield, (2.5:1 *trans/cis* ratio) (Scheme 21).



Scheme-21: Takaki's Yb/MeOH strategy.

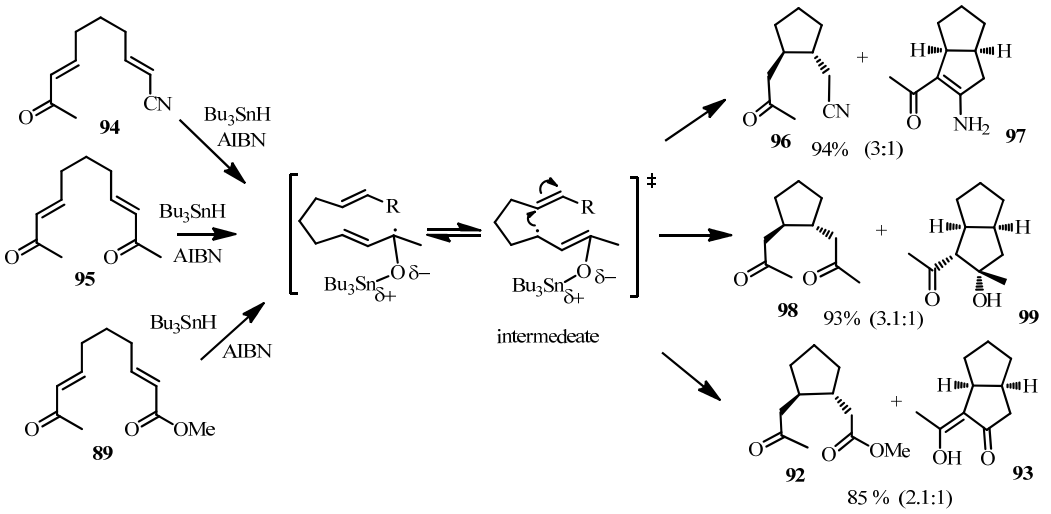
III. *β*-Activation by radical initiator.

In this class of *β*-activation, radical initiator such as tributyl tin radical, formed by the reaction of tributyl tin hydride in the presence of AIBN, adds to a carbonyl moiety of *α, β*-unsaturated esters generating a free radical at *β*-carbon via *O*-stanyl ketyl radical which adds to a tethered olefin to provide cyclic compounds. Enholm *et al*.[31] have used this strategy for intramolecular cyclization of **89** to obtain **92** and **93** in 85 % yield involving transition state **90** with an excellent diastereoselectivity (> 50:1) (Scheme 22).



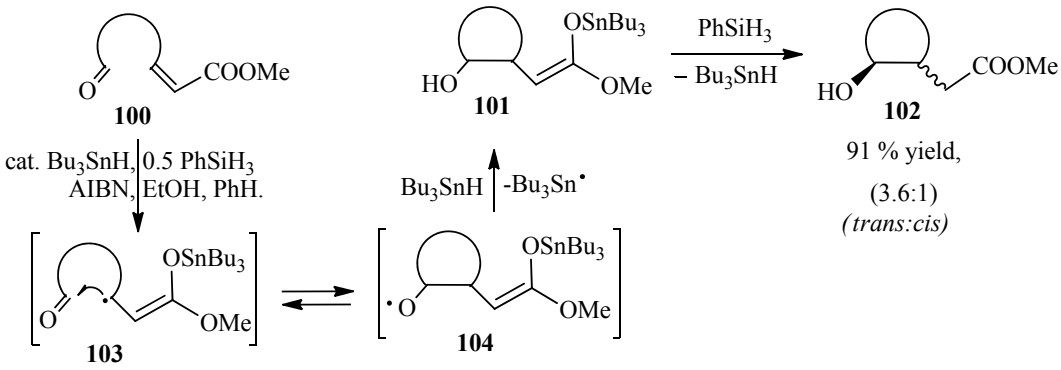
Scheme-22: Enholm's intramolecular reductive strategy

This group[32] has further explored the generality of this reaction using other electron deficient olefins (e. g. esters, nitriles and ketone) and have obtained *trans* substituted cyclopentanes **96**, **98** and **92** along with bicyclic products **97, 99** and **93,** respectively, in each case (Scheme 23).



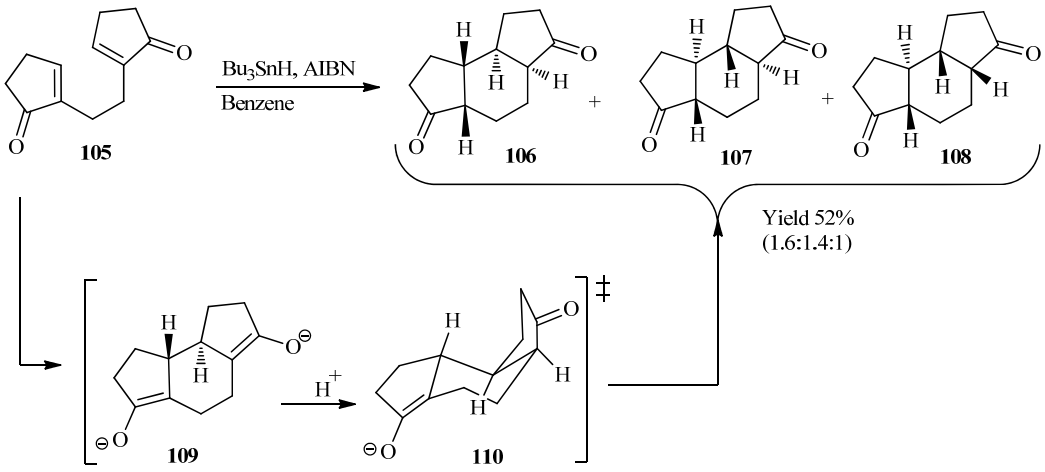
Scheme-23: Enholm's strategy.

In all these initial studies, tributyl tin hydride was used in stoichiometric quantities[33, 34]. Subsequently, to reduce the toxic tributyl tin byproduct from the reaction mixture, Fu *et al*.[35] developed a protocol to use organotin hydrides in catalytic amount employing phenylsilyl hydride ($PhSiH_3$) as hydride donor to regenerate tributyltin hydride (Bu_3SnH) from tributyltin alkoxide[36, 37] and reported reductive cyclization of **100** to **102** in 91 % yield (3.6:1 *trans/cis* ratio) (Scheme 24).



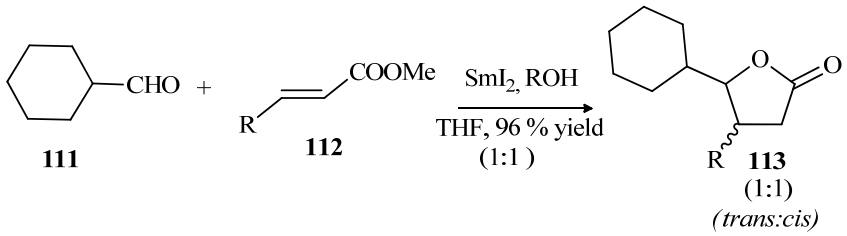
Scheme-24: Fu's catalytic strategy.

Recently Handy *et al.*[38] have used this strategy in the reductive cyclization of cyclic bis-enone **105** to obtain mixture of tricyclic compounds **106**, **107** and **108** in 52 % yield (1.6:1.4:1 ratio) through the transition state **110** (Scheme 25).



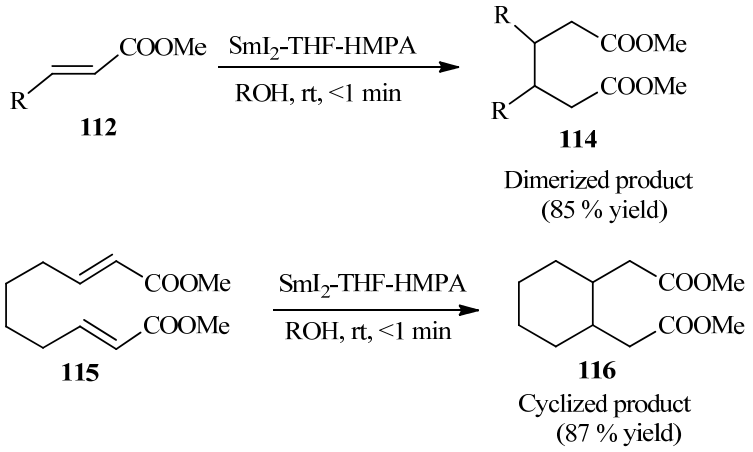
Scheme-25: Handy's strategy for cyclic enone.

Apart from tributyltin hydride (Bu_3SnH/AIBN) as radical initiator, samarium diiodide (SmI_2) was also shown to act as a homogeneous one-electron reducing reagent first by Kagan and co-workers[39] in 1977 but surprisingly, no effort was made to utilize this reagent for *β*-activation of *α, β*-unstaurated esters till Inanaga *et al.*[40] reported reductive cross coupling between **111** and **112** to obtain **113** in 96 % yield (1:1 *trans/cis* ratio) (Scheme 26).



Scheme-26: Inanaga's cross coupling strategy.

Same author has further reported[41] reductive dimerization of **112** to **114** in 85 % yield and intramolecular reductive cyclization of **115** to obtain **116** in 87 % yield. However, no effort was made by this group to determine the diastereomeric ratio of **116** (Scheme 27).



Scheme-27: Inanaga's samarium diiodide strategy.

All these above discussed strategies of *β*-activation from different groups for reductive dimerization or intramolecular cyclization of *α,β*-unsaturated esters or ketones, involves toxic reagents and metals (e. g. Bu_3SnH, $HgCl_2$, Yb, Pb) and also require dry reaction conditions to carry out the experiments resulting into low yield along with low selectivity. In spite of having great potential in synthesis through these strategies, not much effort has been made to develop stable and non hazardous environmental friendly reagents to affect such cyclization.

IV. *β*-Activation by photoinduced electron transfer reactions.

In the context of above limitations of the strategies discussed so far for *β*-activation of *α,β*-unsaturated esters or ketones, a photoinduced electron transfer based strategy was

developed which overcame all the problems associated with earlier strategies. Initially, our group developed a new concept and reaction cycle (PS-A)[42a] of *β*-activation of activated esters or ketones to generate *β*–ketyl radical for cyclization purposes using an electron rich triphenylphospine (PPh_3) as a sacrificial electron donor and 1,9-dicyanoantharacene (DCA) as a visible light harvesting electron acceptor in deoxygenated atmosphere (Figure 1).

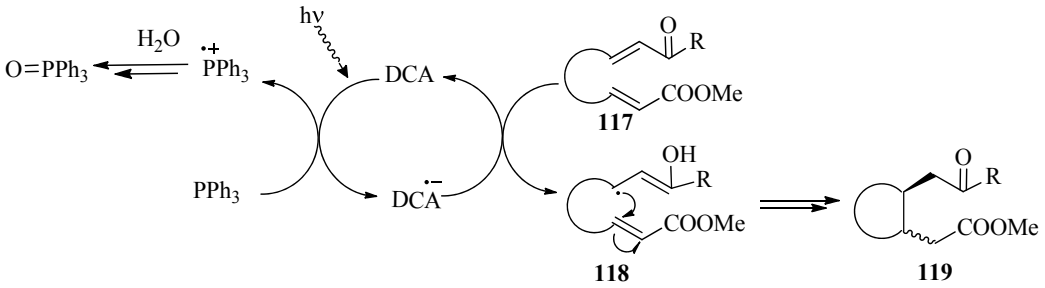
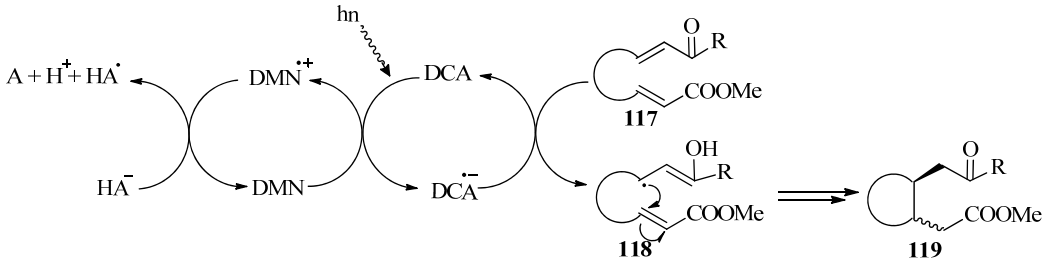


Figure-1: Photosystem-A (PS-A)

Although, the photosystem-A as shown in the Fig-2, represented the success of our basic concept of initiating one electron reductive *β*-activation of *α, β*-unsaturated esters or ketones for carbon-carbon bond formation reactions, it was soon realized that photosystem- A may not be considered ideal for synthetic purposes due to continuously build up of triphenylphospine oxide ($Ph_3P=O$) in the reaction mixture. Therefore, an alternative photosystem, (photosystem-B) was designed [42b] (Fig. 2) which consisted of 1, 9-dicyanoantracene (DCA) as a visible-light absorbing electron acceptor and electron rich 1, 5-dimethoxynaphthaline (DMN) as a primary electron donor while ascorbic acid as a sacrificial electron donor (Figure 2).



(PS-B)

Where,

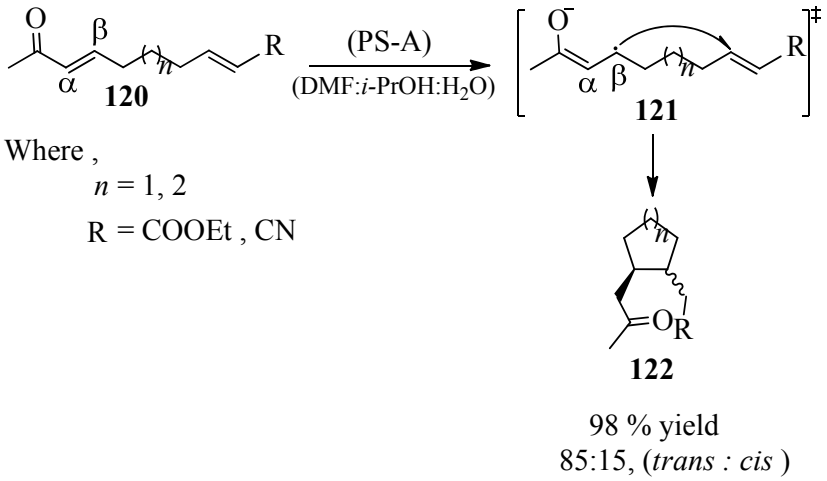
(HA^-) = Ascorbate ion

DMN = 1,5-dimethoxynaphthaline.

DCA = 1,9-dicyanoanthracene.

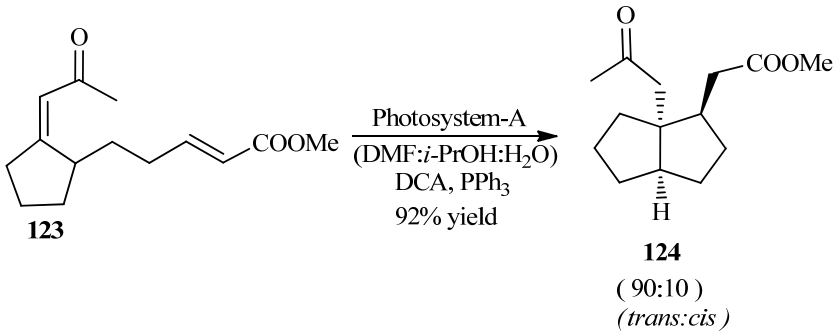
Figure-2: Photosystem-B (PS-B)

In 1992, our group successfully implemented photosystem-A for the construction of five to six membered substituted carbocyclic ring through *β*-activation of **120** followed by its intramolecular addition to the tethered olefin to obtain **122** in 98 % yield (85:15 *trans:cis* ratio) (Scheme 28).



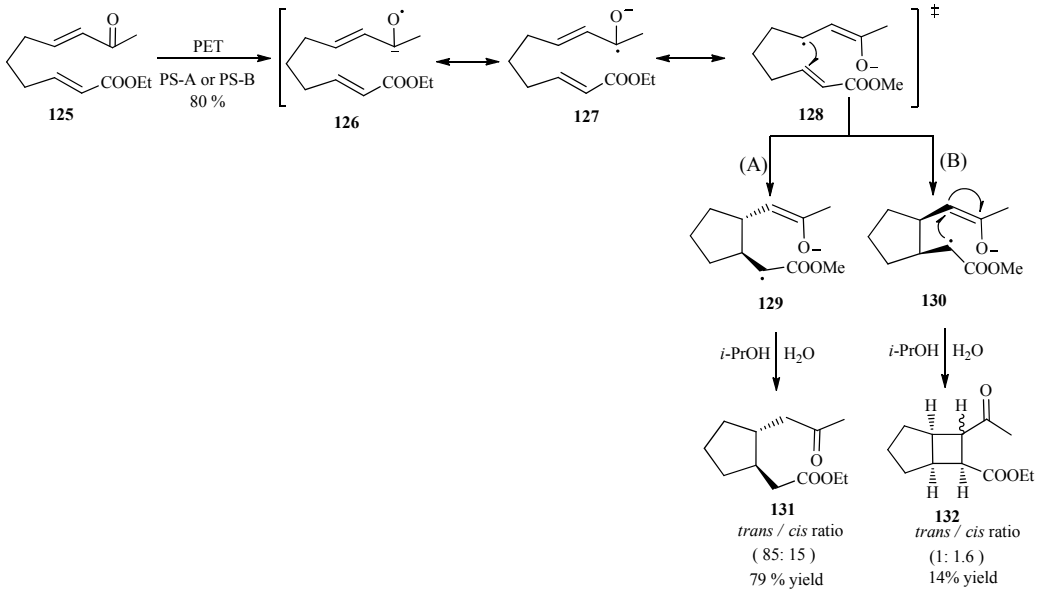
Scheme-28: Pandey's strategy for carbocyclic ring.

This strategy was further extended for the construction of synthetically challenging bicyclic compounds **124 (**92 % yield, 90:10 *trans:cis* ratio)[43] by one electron intramolecular reductive cyclization of **123** (Scheme 29).



Scheme-29: Pandey's strategy for bicyclic compounds.

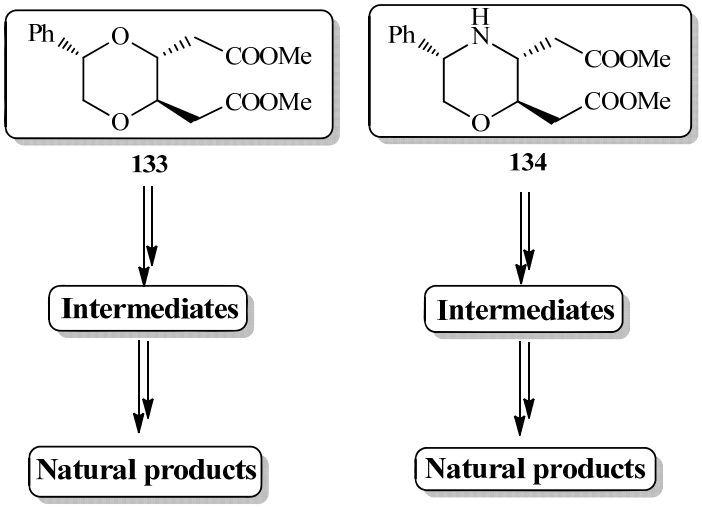
Furthermore, construction of five to six membered carbocyclic rings was demonstrated by reductive cyclization of **125** to obtain **131** in 79 % yield (85:15 *trans:cis* ratio) along with bicyclic compound **132** in 14 % yield (Scheme 30).



Scheme-30: proposed reaction mechanism in PS-B

1.3 *Summary:*

With these successful backgrounds on *β*-activation of *α, β*-unsaturated carbonyl moieties for radical reaction, we envisaged extending the versatility of this methodology by synthesizing the multitalented synthons **133** and **134** for obtaining natural products intermediates (Scheme 31).



Scheme-31: Multi-talented desiner synthons.

In the proceeding chapter, we would comprehensively describe the synthesis of multi-talented synthons **133** and **134** and its potential applications for the synthesis of few important natural products intermediates.

1.4 *References:*

1. Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, U.K., **2000**.
2. Fairlamb, I. J. S. *Tetrahedron* **2005**, *61*, 9661.
3. (a) Gomberg, M. *J. Am. Chem. Soc.* **1900**, *21*, 757. (b) Gomberg, M. *Chem. Ber*. **1900**, *33*, 3150.
4. Hey, D. H.; Waters, W. A. *Chem. Rev*. **1937**, *21*, 169.
5. Kharasch, M. S.; Margolis, E. T.; Mayo, F. R. *J. Org. Chem*. **1937**, *2*, 393.
6. Togo, H. *Advanced free radical reactions fot organic synthesis*, Elsevier, **2004**, p-21.
7. Giese, B. *Angew. Chem. Int. Ed. Engl*. **1983**, *22*, 771.
8. Fleming, I.; *Frontier Orbitals and Organic Chemical Reactions,* Wiley, London, **1976**.
9. Baldwin, J. E. *J. Chem. Soc. Chem. Commun*. **1976**, 734.
10. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron*, **1985**, *41*, 3925. (b) Beckwith, A. L. J.; Lawrence, T. *Perkin Trans*. 2. **1979**, 1535.
11. (a) Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205. (b) Giese, B. *Angew. Chem. Int. Ed. Engl*. **1983**, *22*, 753.
12. (a) Julia, M. *Acc. Chem. Res*. **1971**, *4*, 386. (b) Julia, M. *Pure Appl. Chem*. **1974**, *40*, 553.
13. (a) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K.; *Aus. J. Chem*., **1983**, *36*, 545. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc. Chem. Commun*. **1980**, 482. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem*. **1987**, *52*, 959.

14. (a) Baizer, M.M. *Tetrahedron Lett.***1963,** *15*, 973. (b) Baizer, M.M. *J. Electrochem. Soc.*, **1964**, *2*, 215. (c) M. M. Baizer and J. D. Anderson, *J. Electrochem. Soc.*, **1964**, *111*, 223.

15. Amderson, J. D.; Baizer, M. M. *Tetrahedron Lett.* **1966***, 5*, 511.

16. Petrovich, J. P.; Anderson, J. D. and Baizer, M. M. *J. Org. Chem*. **1966,** *31*, 3897.

17. Little, R. D.; Moens, L.; Baizer, M. M. *J. Org. Chem.* **1986,** *51***,** 4497

18. Ruhlmann, K. *Synthesis* **1971**, 236.

19. Dauben, W. G**.;** Michno, D. M. *J. Org. Chem.* **1977**, *42,* 682.

20. Little, R. D.; Sowell, C. G.; Wolin, R. D. *Tetrahedron Lett.* **1990,** *31*, 485.

21. Kende, A. S.; Roth, B.; Sanfilippo, P. G. G.; Blacklock, T. **J.** *J. Am. Chem. Soc.,* **1982,** *104*, 5808.

22. Miranda, J. A.; Wade, C. J. and Little, R. D. *J. Org. Chem.* **2005,** *70***,** 8017.

23. Kise, N.; Litaka, S.; Iwasaki, S. and Ueda, N. *J. Org. Chem.* **2002,** *67***,** 8305.

24. Mandell, L.; Daley, R. F.; Day, R. A., Jr. *J. Org. Chem.* **1976**, *26*, 4087.

25. Lee, G.H.; Choi, E. B.; Lee, E. and Pak, C. S. *J. Org. Chem.* **1994,** *59***,** 1428.

26. Chavan, S. P.; Ethiraj, K. S. *Tetrahedron Lett.* **1995,** *36,* 2281

27. Lee, G. H.; Lee, H. K; Choi, E. B. and Pak, C. S. *Bull. Korean. Chem. Soc.* **1995**, *16*, 1141.

28. Ghosh, S. K.; Kundu, P.K. *Org. Biomol. Chem.* **2009**, *7*, 4611.

29. Hou, Z**.;** Taniguchi, H. and Fujiwara, Y**.** *Chem. Lett.,* **1987**, 305

30. Takaki, K.; Beppu, F.; Tanaka, S.; Tsubaki, Y.; Jintoku, T. and Fujiwara, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 516.

31. Enholm, E. J. and Kinter, K. S. *J. Am. Chem. Soc.* **1991,** *113***,** 7784.

32. Enholm, E. J. and Kinter, K. S. *J. Org. Chem.* **1995,** *60*, 4850.

33. (a) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939-4942 (b) Enholm, E. J.; Burroff, J. A. *Tetrahedron Lett.* **1992**, *33*, 1835-1838.

34. (a) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.(b) Ardisson, J.; Ferezou, J. P.; Julia, M.; Pancrazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001. (c) Sugawara, T.; Otter, B. A.; Ueda, T. *Tetrahedron Lett.* **1988**, *29*, 75-78.

35. Fu, G. C. and Hays, D. S. *J. Org. Chem.* **1996,** *61*, 4.

36. (a) Nitzsche, S.; Wick, M. *Angew. Chem.* **1957**, *69*, 96.(b) Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1.

37. (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303

38. Handy, S. T. and Omune, D. *Tetrahedron*. **2007**, *63*, 1366.

39. (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5.(b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

40. Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763.

41. Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, K.; Yamaguchi, M. and Hanamoto, T. *Tetrahedron Lett.* **1991**, *32*, 6557.

42. (a) Pandey, G.; Hajra, S. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1169 (b) Pandey, G.; Hajra, S.; Ghorai, M. K.; Ravikumar, K. *J. Am. Chem. Soc.* **1997,** *119*, 8777.

43. Pandey, G.; Hajra, S.; Ghorai, M. K. *Tetrahedron Lett.* **1994***, 35*, 7837

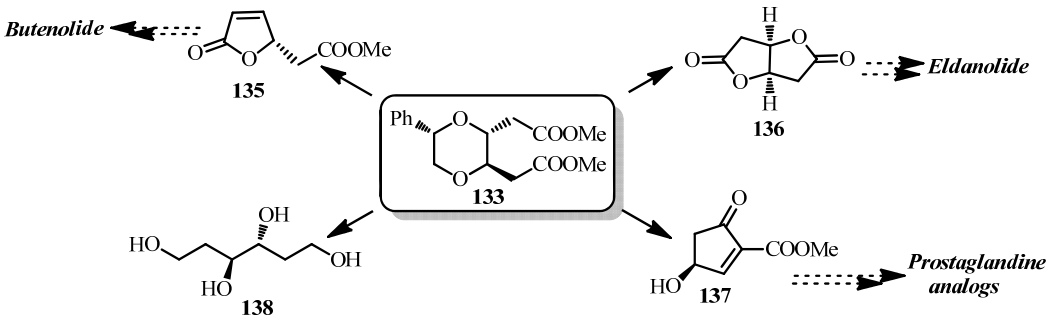
CHAPTER 2: SECTION A

Stereoselective synthesis of chiral 6-phenyl -2, 3-bis methylenemethoxy-carbonyl-[1,4]-dioxane and its application.

Section-A

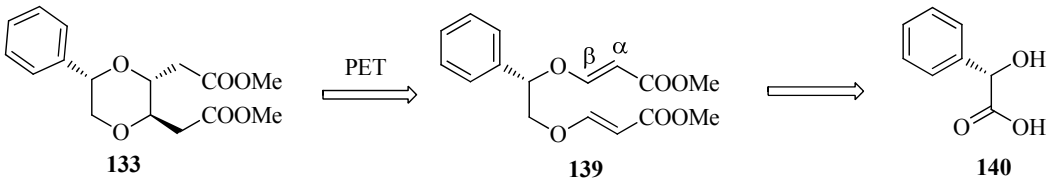
2A.1 *Introduction:*

Designing a multitalented synthon from which a number of important biologically active molecule precursors can be obtained by simple functional group transformations have always attracted the attention of synthetic organic chemist[1]. In this context, we were also inspired to explore the utility of our strategy of *β*-activation of *α, β*-unsaturated carbonyl compounds employing either photosystems PS-A or PS-B to design a multitalented synthon **133** having labile 1,4-dioxane moiety. This synthon was designed keeping in mind its unique structural features which could be transformed into a number of important natural products / intermediates such as bislactone **136**, a precursor for eldanolide[2], *trans* 1,2-diol **138**, as a sub-structural unit of carbasugars[3] and **137** as a prostaglandin precursor[4] along with γ-substituted *α, β*-unsaturated butyrolactone **135** a precursor for butenolide[5] by simple functional group transformation reactions (Scheme-1).



Scheme-1: Versatility of multi-talented synthon **133**.

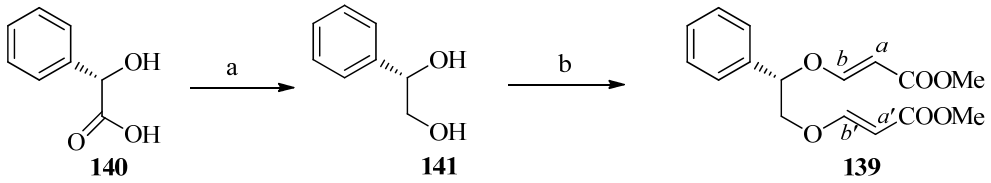
We devised a single step strategy to synthesize all these important intermediates from our designed synthon **133** whose retrosynthesis is outlined in Scheme 2.



Scheme-2: Retrosynthetic analysis of **133**.

2A.2 Result and Discussion:

2A.2.1 Synthesis of (2*E*, 2'*E*)-dimethyl 3,3'-((*S*)-1-phenylethane-1,2-diyl)bis(oxy)diacrylate (140):



Scheme-3: Synthesis of irradiation precursor **139**.

Reagent and conditions:

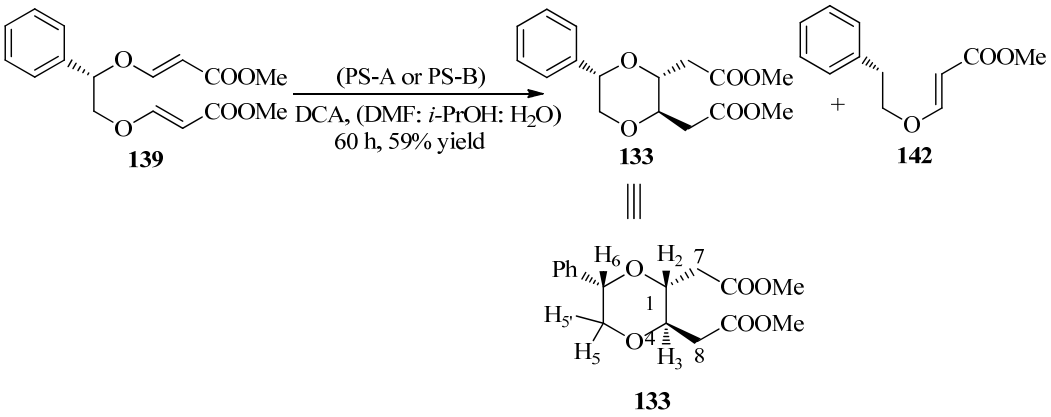
(a) LAH, dry THF, reflux 8 h, 88 % (b) NMM, Methyl propiolate, dry DCM 0 °C→ rt. 6 h, 91 %

Compound **141,** obtained in 88 % yield by LAH reduction of commercially available *R*-(+)-mandelic acid (**140)** on reaction with methyl propiolate in the presence of N-methy morpholine at 0°C, afforded **188** in 91% yield. The structural elucidation of **139** was carried out by detailed ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

The ^{1}H NMR spectrum displayed four sets of doublets (d, J = 11.8 Hz) at δ 7.65 ($1H_b$), 7.55 ($1H_{b'}$), δ 5.28 ($1H_a$) and 5.25 ($1H_{a'}$) for the olefinic protons. While benzylic proton appeared as a doublet of doublet at δ 5.21(dd, J = 10.8, 5.4 Hz, 1H), two methyl protons of the ester moiety appeared as two singlets at δ 3.72 and 3.68 (2s, 6H), respectively. In ^{13}C NMR spectrum the most down field signal at δ 167.74 was

assigned to carbonyl carbon of ester moiety (-C=O-OMe). The two olefinic methine carbons (C_b and $C_{b'}$) appeared at δ 161.85 and 160.92 while the remaining two olefinic carbons (C_a and $C_{a'}$) appeared at δ 99.10 and 97.24, respectively. Two sharp carbon signals appearing at δ 51.18 and 51.11 were assigned to two methyl carbon of ester moiety. Mass spectrum confirmed the structure of **139** by exhibiting molecular ion peak at 307.21 (M+1) and another peak 329.11 at $(M+Na)^+$ respectively.

2A.2.2 Stereoselective synthesis of chiral 6-phenyl -2,3-bis mthylenemethoxycarbonyl-[1,4]-dioxan 133:



Scheme-4: Synthesis of multitalented synthon **133.**

PET activation of **139** involved irradiation (λ = 405 nm) of a solution of **139** (1.64 mmol) containing 1,9-dicyanoanthracene (DCA, 0.71mmol), 1,5-dimethoxy naphthalene (DMN, 0.25mmol) and ascorbic acid (4.24 mmol) in 700 mL solvent [DMF: *i*-PrOH: H_2O, (88:10:2)] in a specially designed photoreactor which consisted of three chambers. The first and outermost chamber contained irradiation solution and the second one was charged with $CuSO_4.5H_2O$: NH_3 filter solution.[6] A 450-W Hanovia medium pressure mercury lamp was housed into a water cooled double jacketed chamber which was immersed into the second one. The whole photoreactor

was made-up of Pyrex glass. The *i*-PrOH functioned as a hydrogen donor. The 405nm wavelength light was obtained by using $CuSO_4.5H_2O$: NH_3 filter solution[6] from 450 W Hannovia medium pressure mercury lamp. All the light under this experimental set up was absorbed by DCA only. Before the irradiation, the solution was deoxygenated by bubbling argon for 2 h. After 60 h of irradiation when **139** was almost consumed (80%; monitored by GC), the solvents were removed under vacuum and the concentrate was purified by column chromatography over silica gel using petroleum-ether/ethylacetate as an eluent which gave **133** in 59% yield as a single diastereomer. Minor amount of cleavage product **142 (**15 %) was also observed during its activation. Un-reacted **139** was recovered in about 20% yield along with DCA and DMN quantitatively.

The ^{1}H NMR spectrum of **133** displayed a doublet of doublet (dd, J = 10.57, 2.74 Hz) at δ 4.68, integrating for one proton, attributed to (H_6) the benzylic proton. A bunch of multiplets appearing between δ 4.03-3.49, integrating for four protons, were assigned to the two methine protons (H_2 and H_3) and two methylene protons (H_5 and $H_{5'}$) of dioxane ring. Other multiplets appearing between δ 2.64-2.53, integrating for four protons, were assigned to methylene protons (H_7 and H_8) ,respectively. The ^{13}C NMR of **133** showed only one set of carbon signals indicating single diastereomer of **133**. A set of four carbon signals appearing at δ 77.57, 75.80, 75.29 and 72.31 were attributed to benzylic carbon (C_6), two methine carbons (C_2 and C_3) and mthylene carbon (C_5) of [1,4]-dioxane ring, respectively. Other carbon signals appearing at δ 37.15 and 36.88 were assigned to two methylene carbons (C_7 and C_8)**,** respectively. ESI-Mass spectrum confirmed the structure of **133** by exhibiting 309.38 $(M+1)^+$ and 332.37 $(M+Na)^+$.

Based on the extensive 2D NMR techniques, such as COSY and NOESY experiments, the stereochemical assignments of H_2, H_3, and H_6 protons were suggested. The illustrated NOSEY interactions between bridged H_6/H_2 and H_5/H_3 confirmed the *cis*-diaxial relationship whereas the protons H_6/H_5 and H_2/H_3 did not show any NOSEY cross peaks indicating the *trans*-diaxial orientation (Figure 5).

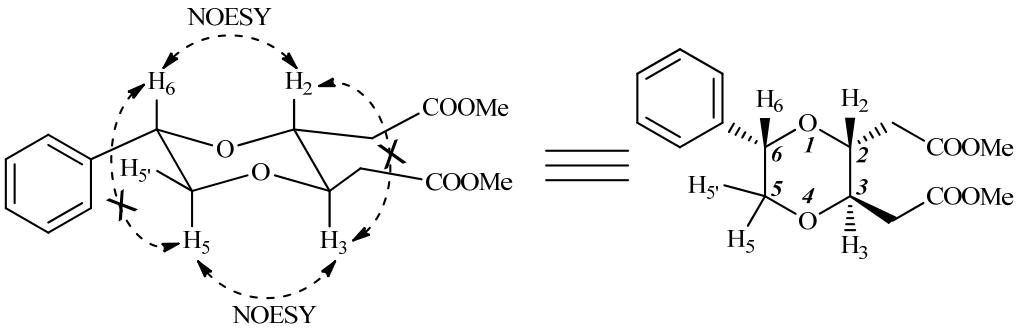
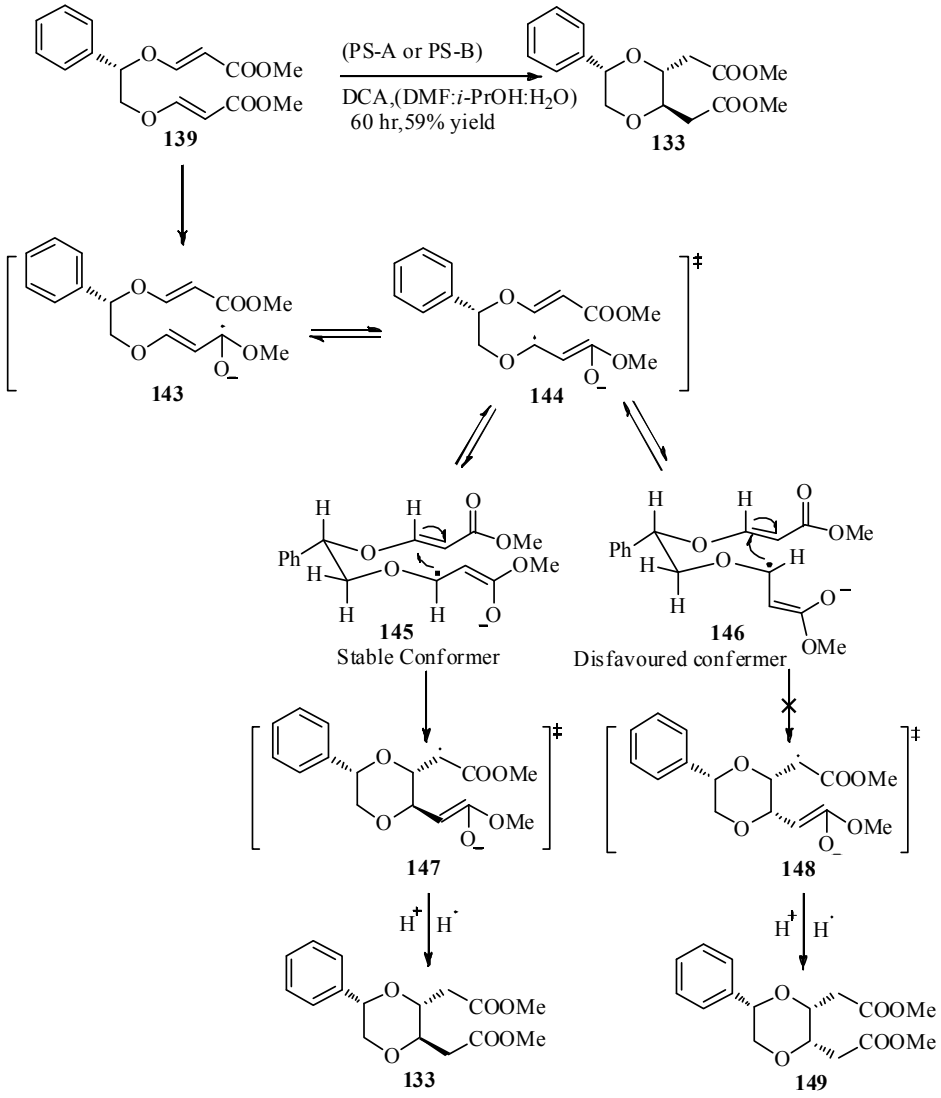


Figure-5: selected NOESY cross peaks in **133.**

2A.2.3 Stereochemical and mechanistic interpretations for the formation of 133:

The observed *anti*-stereochemistry of **133** appeared to be in close agreement with the general trend of *anti*-stereochemistry observed in enone-olefin radical cyclizations. Beckwith's model[7] suggests that under kinetic control, the cyclization of intermediate **148** should give cyclized compound with *syn*-appendages (**149**). However, the predominant *trans*-diastereoselectivity in the formation of **133** led us to postulate that initially produced *syn*-intermediate **148** is less stable which gets transformed to thermodynamically more stable *anti*-intermediate **147** due to the resonance stabilization of ester enolate ketyl radical **144**. Moreover, this argument also draws rationale provided by Bounce *et al*.[8] by considering the dominant secondary orbital interaction and overlap involving HOMO of the enolate and LUMO of the α-alkoxy-

α,β-unsaturated ester carbonyl in the transition state **145** making it more stable transition state for the formation of **133** (Scheme 5).



Scheme-5: Reaction mechanism and stereochemical outcome in PET cyclization.

2A.3. Synthetic Explorations of 133:

Having devised a strategy to obtain **133** in sufficient quantities, we set our goal in evaluating its transformation to **135**, **136**, **137** and **138,** respectively. However, before discussing actual synthetic details of these important intermediates, it would be

appropriate to highlight briefly recent developments in each area to showcase the importance of our strategy.

2A.3.I. Stereoselective synthesis of 1,2-*trans* diols

1,2-*trans*-Diols represent privileged structural motifs that can be found in numerous natural products and other molecules relevant for the life science industry such as sugars, carbasugars and macrolides.[9] (Figure 6).

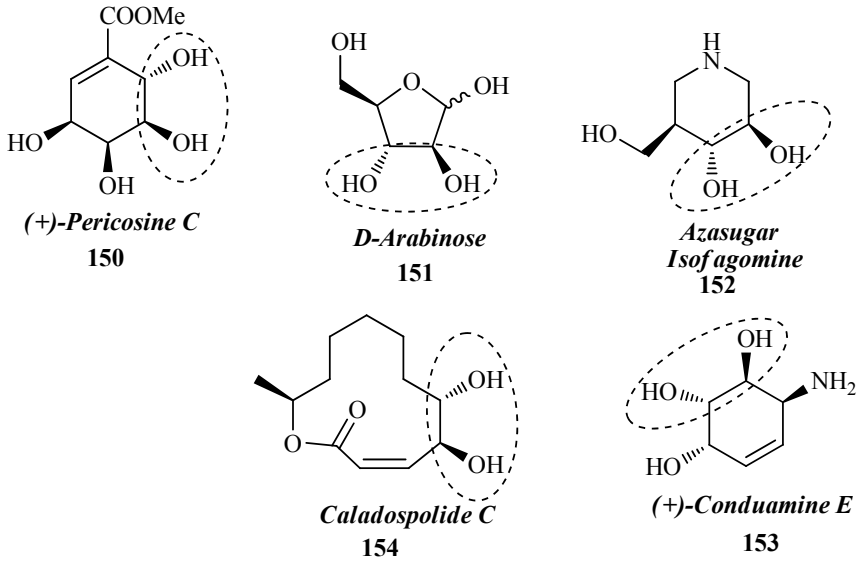
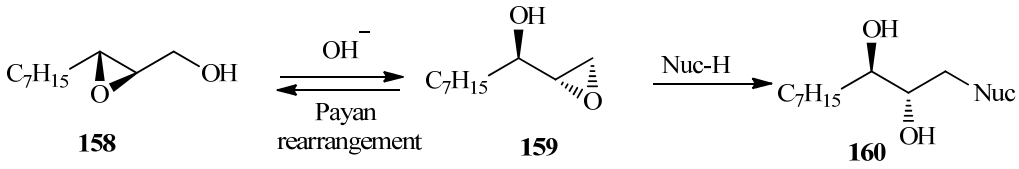


Figure-6: Natural products bearing trans-diols

Apart from 1,2-*trans* diols being a sub-structural unit in natural products, they also serve as an intermediates in asymmetric synthesis.

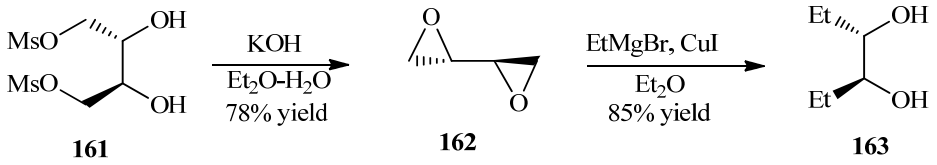
Due to their vast importance, stereoselective synthesis of optically pure 1,2-*trans*-diol continues to be a fascinating area in organic synthesis[11]. There are many strategies available for the asymmetric synthesis of these diols. Among known strategies, nucleophilic ring opening of terminal chiral epoxide **159** with a variety of nucleophiles, reported first time by Behrine *et al*.[12] to obtain chiral 1,2-*trans*-diols of

type **160** (95 % *ee*) is important one. Terminal chiral epoxides **169** were obtained through Payan rearrangement[13] of **158** as shown in Scheme 12.



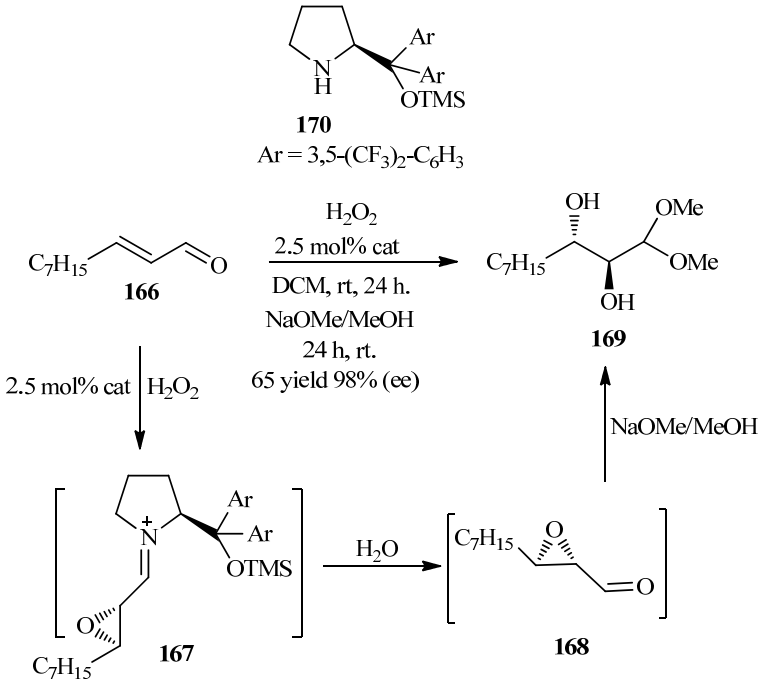
Scheme-12: Behrene's strategy for 1,2 *trans* diol.

The same strategy was further extended by Devine *et el.*[14] for the nucleophilic ring opening of chiral epoxide **162,** obtained from **161** in 78 % yield (95% *ee*), with a Grignard reagent to obtain **163** in 85% yield (Scheme 13).



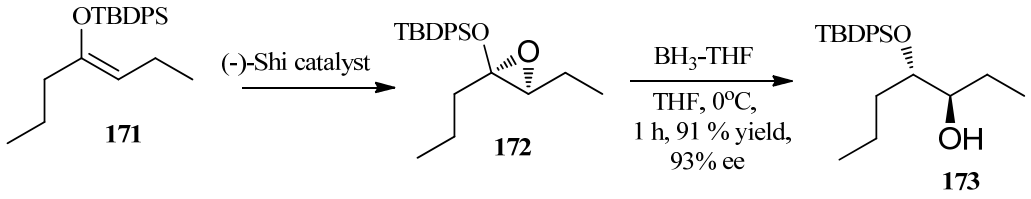
Scheme-13: Devin's approach for 1,2 *trans* diol.

Recently, Jorgensen *et al.*[16] have developed an organocatalytic strategy for the synthesis of iminium-epoxide intermediate **167,** using proline derived catalyst **170,** which upon hydrolysis resulted into *trans* 1,2-diol **169** in 65 % yield (98 % *ee*) (Scheme 10).



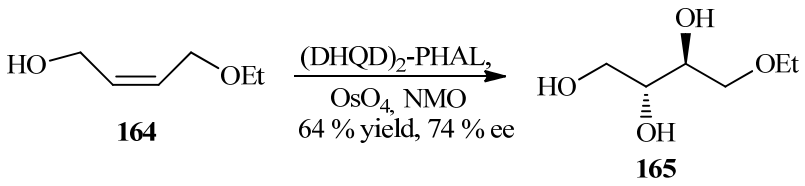
Scheme-10: Jorgensen's organocatalytic strategy for **169.**

Myers *et al.*[17] have utilized silyl enol ether **171** to synthesize epoxide **172** using Shi's epoxidation[18] reagent to obtain chiral epoxide **172** in 77 % yield (91 % *ee*) which on usual ring opening resulted *trans*-1,2-diols **173** in 91 % yield (93 % *ee*) (Scheme 17)



Scheme- 17: Myers's strategy for 1,2-*trans* diol.

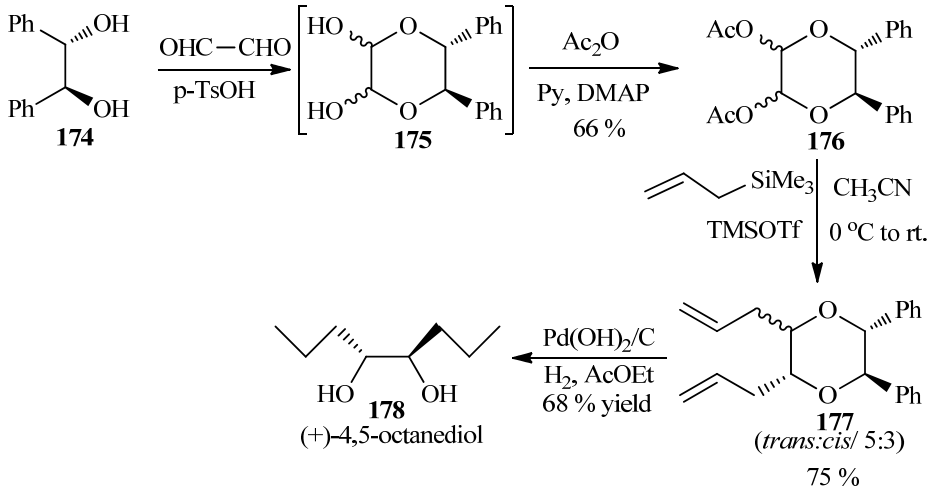
In 1994, the most general and reliable strategy for the synthesis of 1,2-diols was devised by Sharpless *et al.*[15] for the preparation of 1,2-*trans* diol (**165**) in 64 % yield with 74 % *ee* by the dihydroxylation of an un-activated olefin **164** using $(DHQD)_2PHAL$ as a chiral catalyst in presence of OsO_4 (Scheme 7).



Scheme- 7: Sharpless dihydroxylation strategy.

However, due to high cost and toxicity of OsO_4, efforts are continuously made to develop alternative strategies.

Fujioka *et al*.[19] reported a strategy based on exploiting optically active dioxane **177,** prepared in 75 % yield (*dr*: 98:2) by the allylation of hydrobenzoin **174**, to synthesize optically pure 1,2-*trans*-diol **178** in 68 % yield (Scheme 14).

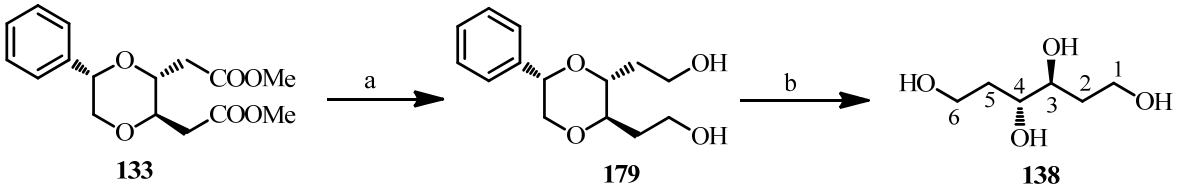


Scheme-14: Fujioka's strategy for dioxane **178**.

It is apparent from the above discussion that all these strategies involve longer reaction sequence with varying degree of enantioselectivity. In this regard, synthesis of dialkyl substituted-1,2-*trans*-diols in high enantioselectivity still remains a great challenge. Therefore, we have devised a novel strategy to obtain optically pure 1,2-*trans*-diol from the designed synthon **133** which is described as follows:

2A.3.I.1 Synthesis of optically pure (3*R*, 4*S*)-hexane-1,3,4,6-tetraol (138):

LAH reduction of **133** produced **179 (**73%) which on subsequent hydrogenation using 20 mol% of $Pd(OH)_2/C$ at 60 psi in acetic acid afforded crude **138** which on further purification by column chromatography produced optically pure **138**, $[\alpha]^{22}_D$= +40.81 (*c* =0.93, MeOH) in 68% yield (Scheme 15).



Scheme-15: Synthesis of disubstituted 1,2-*trans* diol **138**.

Reagents and conditions: (a) LAH, dry THF, reflux 12 hr 73 % (b) H_2 (60 psi), using 20 mol% $Pd(OH)_2/C$, AcOH, 24 h, 68 % yield.

The IR spectrum of **138** showed a broad absorption band at 3518 cm^{-1} corresponding to the hydroxy groups. The ^1H NMR spectrum displayed a bunch of multiplets between δ 3.87-3.64 (m, 6H) which were attributed to methylene protons (H_1 and H_6) and two methine protons (H_3 and H_4) respectively. Another set of multiplets appearing between δ 1.73-1.64 (m, 4H) were attributed to methylene protons (H_2 and H_5), respectively. The ^{13}C NMR displayed three sets of carbon signals at δ 72.44, 62.92 and 32.13 which were attributed to two methine carbons (C_3 and C_4) and four methylene carbons (C_1, C_6 and C_2, C_5), respectively. Finally ESI-Mass spectrum confirmed the structure of **138** by exhibiting peaks at 151.08 $(M+H)^+$ and 173.10 $(M+Na)^+$respectively.

2A.3.II. Stereoselective synthesis of 2,6-dioxabicyclo[3.3.0]octane-3,7-dione (bislactone):

Optically pure bislactones are utilized as a versatile precursor in the synthesis of important biologically active natural products such as eldanolide[20] (**180)** and butenolides[21] (**181** and **182**) (Figure 7).

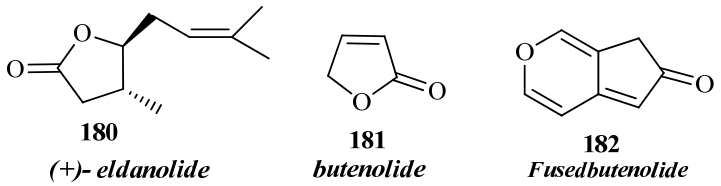
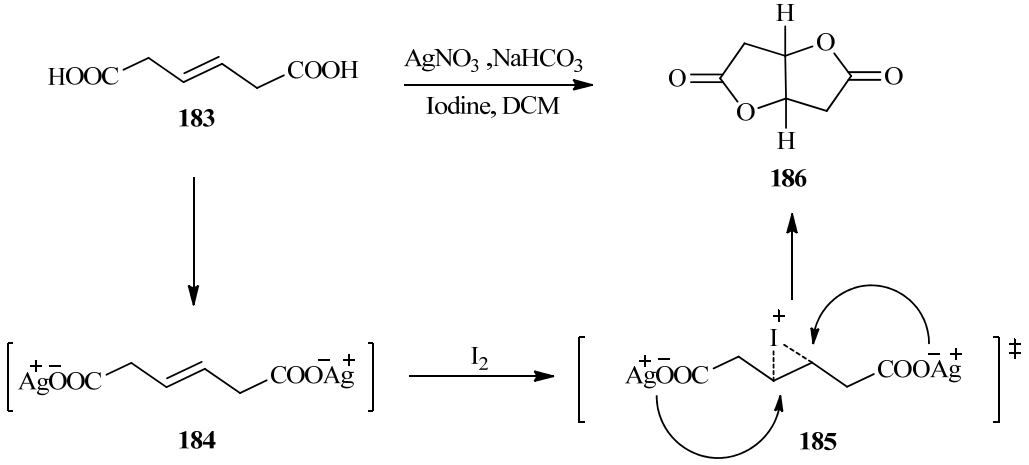


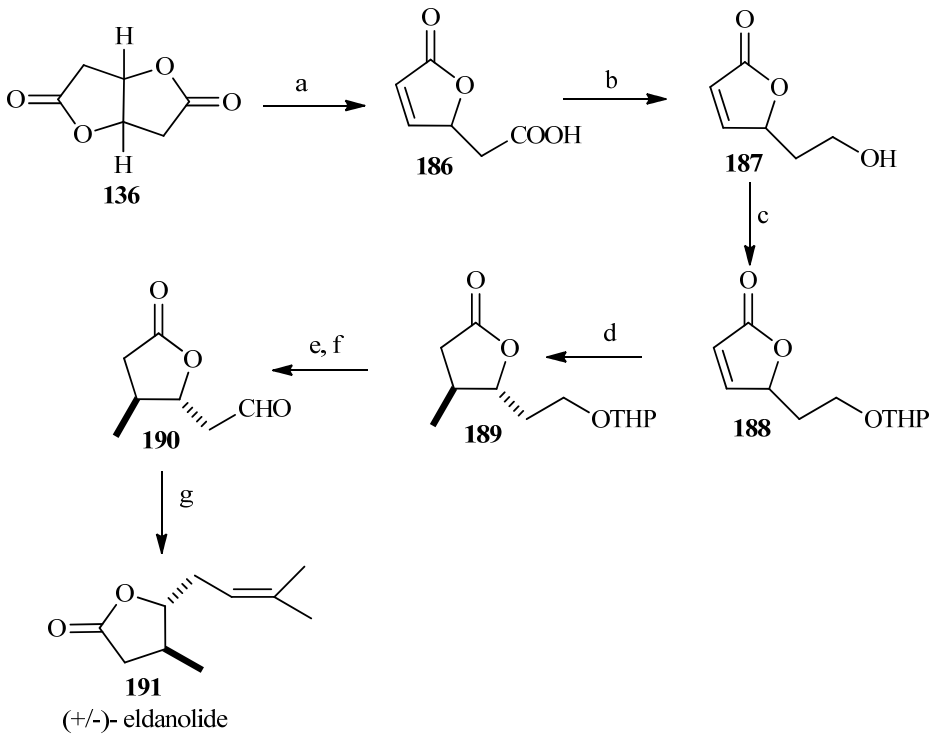
Figure-7: Butenolide class of Natural products

Chiral bislactone have tremendous versatility, however, to our surprise very few strategies are known in literature to synthesize this molecule. In 1988, Sakai *et al.*[22] first time reported the synthesis of **136** (95 % yield) in racemic form through iodolactonization of *trans*-3-hexenedioic acid **183** (Scheme 16).



Scheme-16: Sakai's strategy for bislactone **136**.

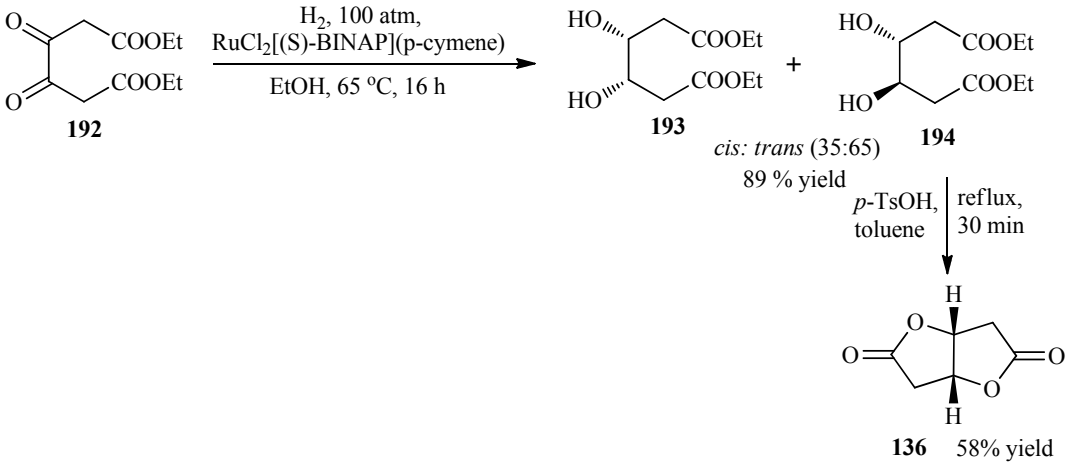
Author also demonstrated its application in the synthesis of (+/-) eldanolide **(191)** as outlined below (Scheme 17).



Scheme- 17: Sakai's approach for eldanolide **(191).**

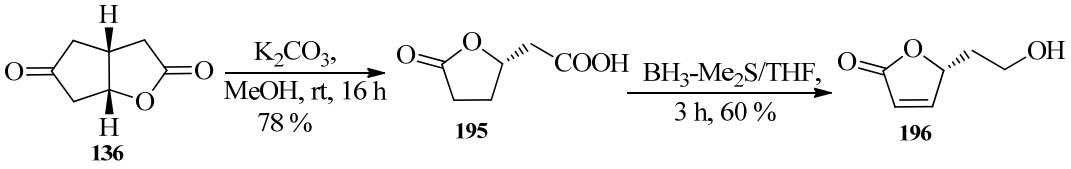
Reagents and conditions: (a) K_2CO_3/MeOH, 20 h, 78 % (b) BH_3-Me_2S/THF, 3 h, 60 % (c) DHP/p-TsOH, DCM, 1 h, 83 % (d) Me_2CuLi, Et_2O, -20 °C, 56 % (e) p-TsOH/MeOH, 12 h, 95 % (f) PCC, DCM, rt, 3h (g) isopropyltriphenylphosponium bromide/ BuLi, -78°C, 2 h, 22 %

After the gap of several years, Kiegiel *et al*.[23] synthesized bislactone **136** (58% yield) in optically pure form by the cyclization of **194,** obtained in 89% yield (*cis:trans* 35:65 ratio) by catalytic asymmetric reduction of **192** using $RuCl_2$[(S)-BINAP](p-cymene) as a chiral catalyst (Scheme 18).



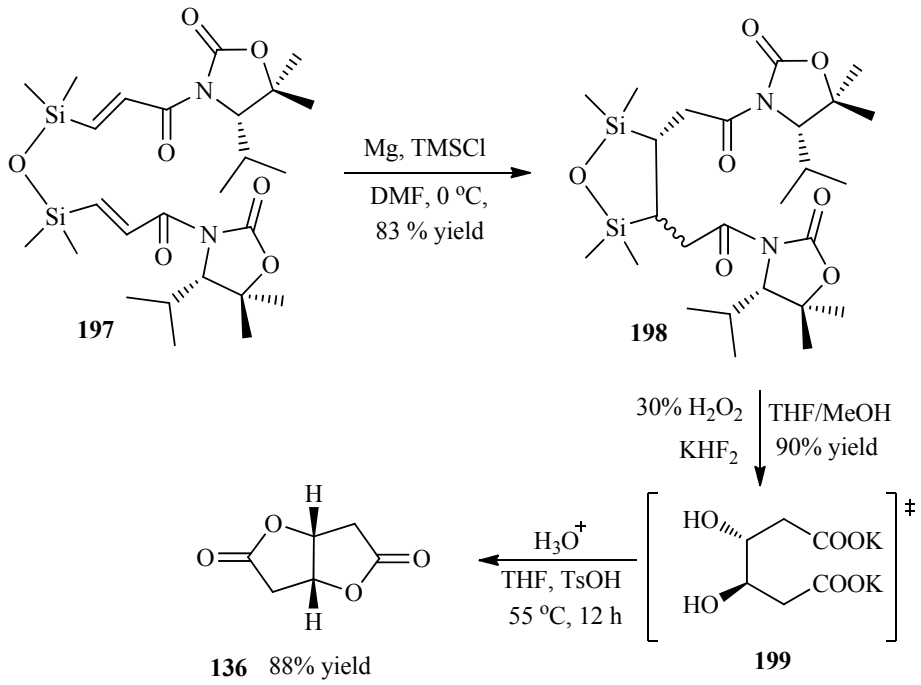
Scheme-18: Kiegiel's strategy for bislactone.

Same author has also shown the utility of their methodology by synthesizing enantiomerically pure butenolide (**196)** in 60 % yield, a sub-structural unit of *Annonaceous Acetogenins*[24] possessing potent biological activity (Scheme 19).



Scheme-19: Application of bislactone **136**.

Recently, Ghosh *et al.*[25] reported magnesium-mediated intramolecular reductive cyclization of **197** to **198** (83% yield, *trans:cis,* 88:12 ratio) which on Fleming–Tamao[26,27] oxidation using KHF_2–H_2O_2 in (1:1) THF–MeOH at 60 °C produced **136** in 88% yield (Scheme 20).

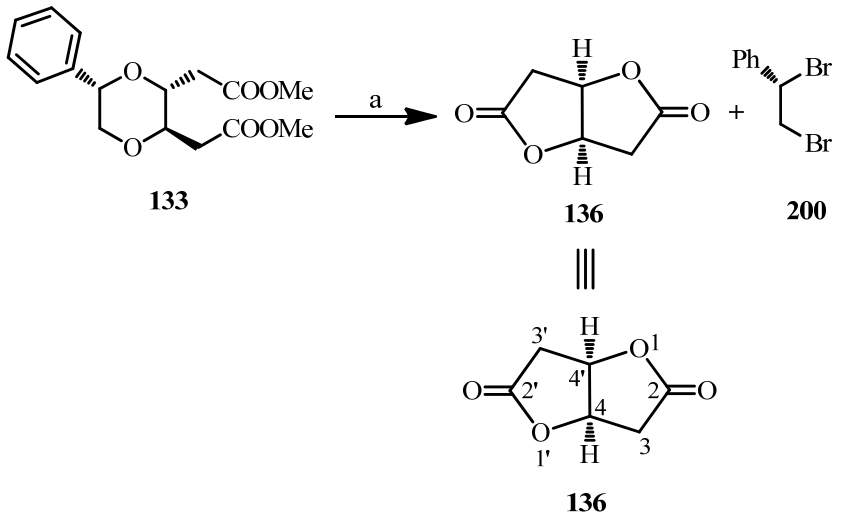


Scheme-20: Ghosh's approach for bislactone **136**.

From all the above discussed strategies, it appears that the synthesis of optical pure bislactones required many steps, resulting into low yield. Therefore, we describe below our strategy for the synthesis of optically pure bislactone **136** from **133**.

2A.3.II.1 Stereoselective synthesis of optically pure 2, 6-dioxabicyclo [3.3.0] octane-3, 7-dione (136):

Optically pure **136** could be obtained in excellent (98%) yield by the cleavage of the labile [1,4]-dioxane ring of **133** by treating it with boron tribromide (BBr_3) at -20 ºC → 0 ºC. The structure of **136** was confirmed by comparing its melting point (mp) and optical rotation [132–133 ºC, $[\alpha]^{22}_D$= +124.48 (*c* =0.21, H_2O) with literature[28] data [m.p. 132 ºC, $[\alpha]^{22}_D$= +143.48 (*c* = 0.21, H_2O), (Scheme 21).



Scheme-21: Synthesis of optically pure bislactone **136.**

Reagents and conditions: (a) BBr_3, (2.1 eq), dry DCM, -78ºC→-20ºC for ½ h,-20ºC→0ºC for 2 h, then 0ºC→rt, 2 h. 98% yield.

The IR spectrum of **136** displayed characteristic strong lactone (C=O) absorption band at 1783 cm^{-1}. The ^1H NMR spectrum showed two sets of multiplets at δ 5.26 (m, 2H) and δ 2.98 (m, 4H) which were assigned to two methine protons (H_4 and $H_{4'}$) and two methylene protons (H_3 and $H_{3'}$), respectively. The ^{13}C NMR (DEPT experiment) confirmed that there are three sets of carbon signals at δ 206.67, 79.06 and 34.94 which were attributed to quaternary carbonyl carbons of the bislacone (-C=O), methine carbons (C_4 and $C_{4'}$) and methylene carbons (C_3 and $C_{3'}$), respectively. ESI-Mass spectrum confirmed the structure of **136** by exhibiting molecular ion peak at 143.02 $(M+H)^+$ and 165.00 $(M+Na)^+$.

Finally, the structure of **136** was also confirmed unambiguously through X-ray crystallographic analysis (see ORTEP drawing figure 8).

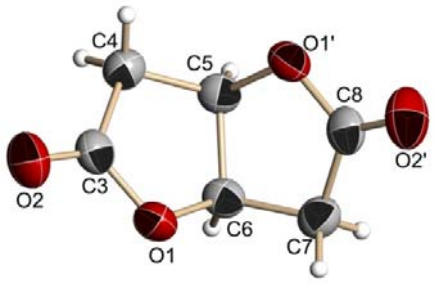
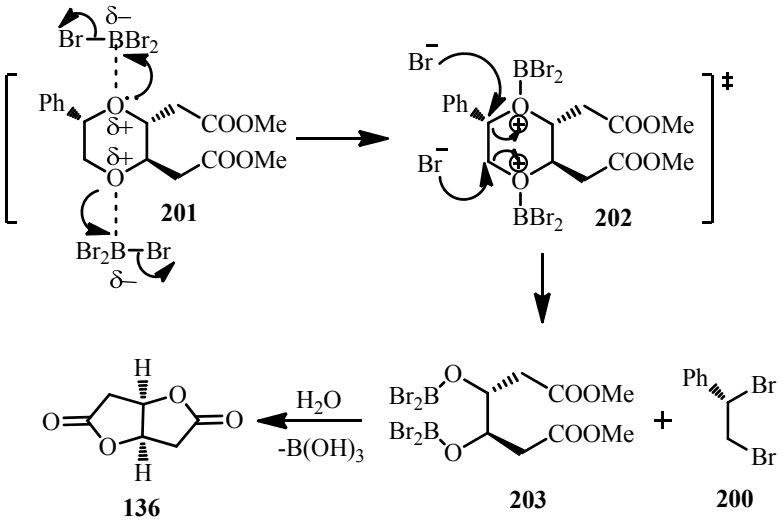


Figure- 8: *ORTEP* diagram of **136**

Plausible mechanism: Plausible mechanism for the formation of **136** is depicted as follows;



Scheme-22: Plausible mechanistic path involved in the synthesis of **136**.

2A.3.III Stereoselective synthesis of *α, β*-unsaturated-γ-substituted butyrolactone:

Chiral *α, β*-unsaturated-γ-substituted butyrolactone are the ubiquitous subunits of antifungal substances and flavor compounds such as (annonacine **207** and uraccine **208**) [29]. These, *α, β*-unsaturated-γ-butyrolactones are also integral part of numerous biologically active natural products[30] such as securinine[31] **(206)** and palinurine B[32] **(205)** (Figure 9) which display diverse pharmacological activities having therapeutic importance.

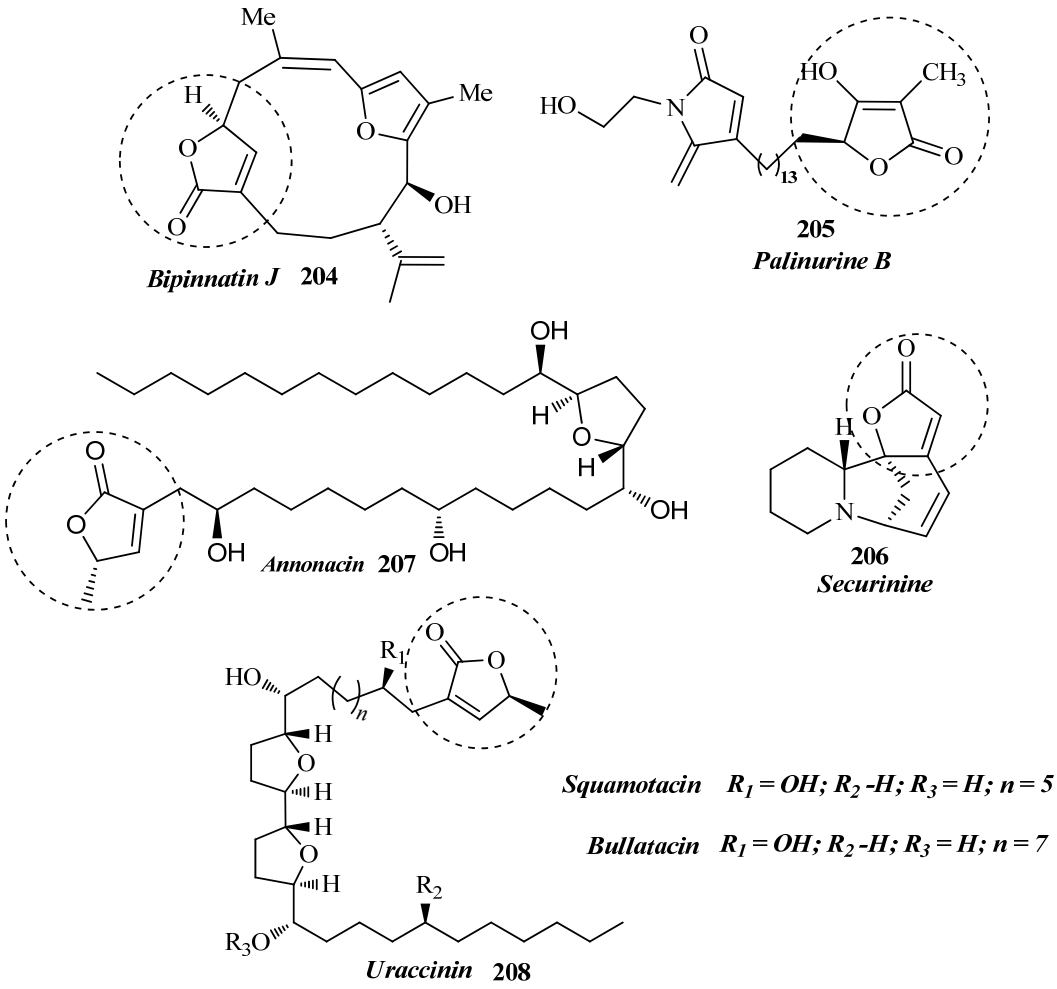
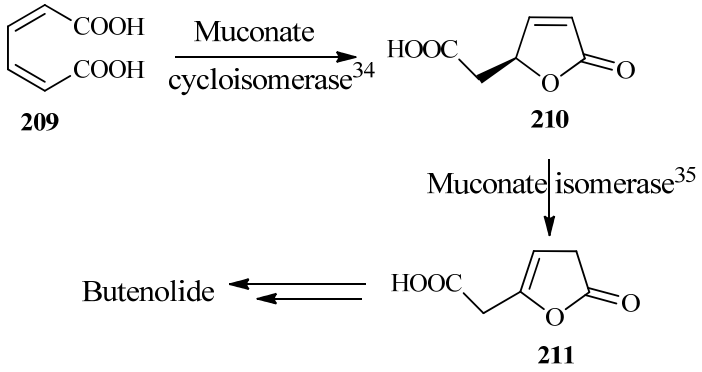


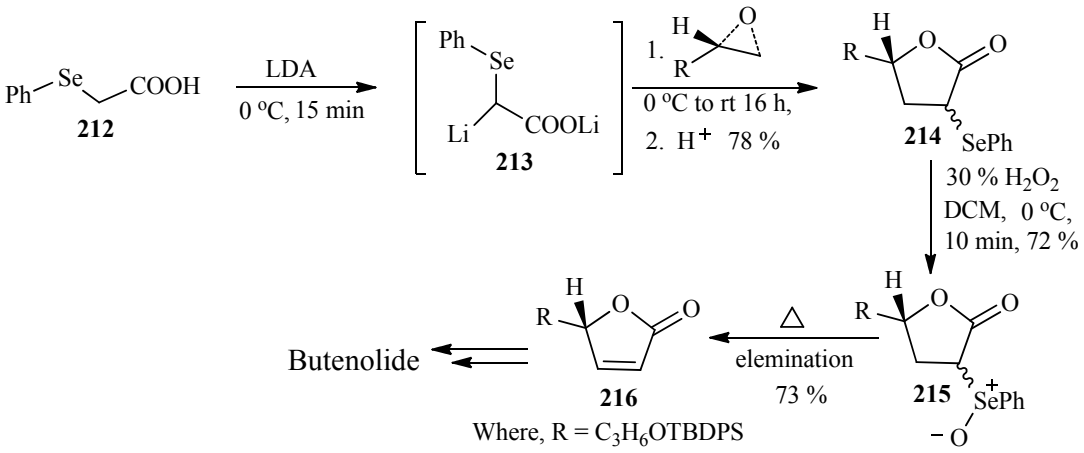
Figure-9: Natural products bearing γ-butyrolactone.

Considering the importance of this substrate in the synthesis of natural products, Sutherland *et al.*[33] has synthesized *α, β*-unsaturated-γ-butyrolactone **210** by enzyme catalyzed cycloisomerization of muconic acid **(209)** leading to the formation of chiral *α, β*-unsaturated-γ-substituted butyrolactone **210** $[\alpha]^{22}_{D}$ = +57.0 (c = 0.51, EtOH) in 97 % yield which was further transformed to **211** using muconate isomerase enzyme (Scheme 24).



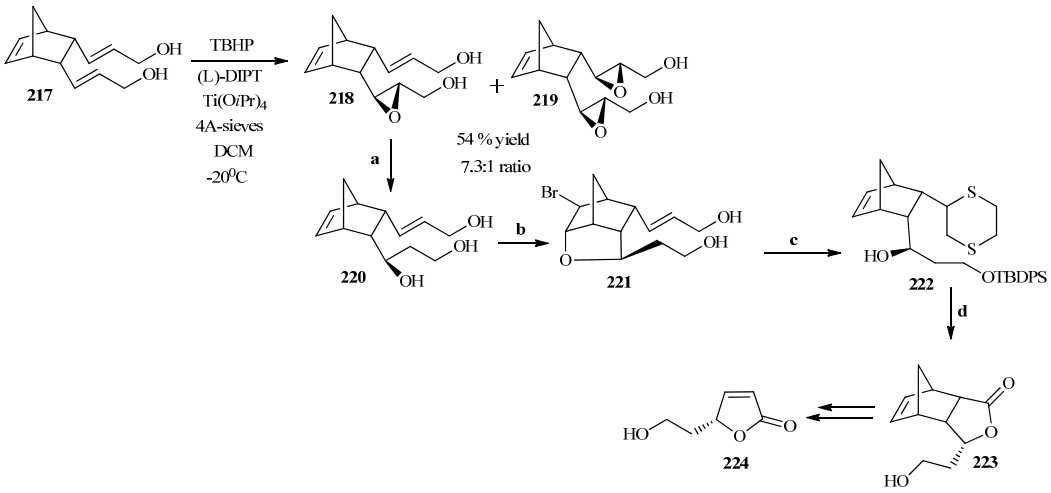
Scheme-24: Sutherland's approach for γ-lactone.

Hanessian *et al.*[36] have reported a mild and efficient strategy for the synthesis of butyrolactone **216** $[\alpha]^{22}_{D}$ = +31.5 (c = 2.0, MeOH, 73% yield) by the nucleophilic ring opening of a chiral epoxide using dilithio derivative of phenylselenoacetic acid **(213)** as shown in Scheme 25.



Scheme-25: Hanessian's strategy for **216**.

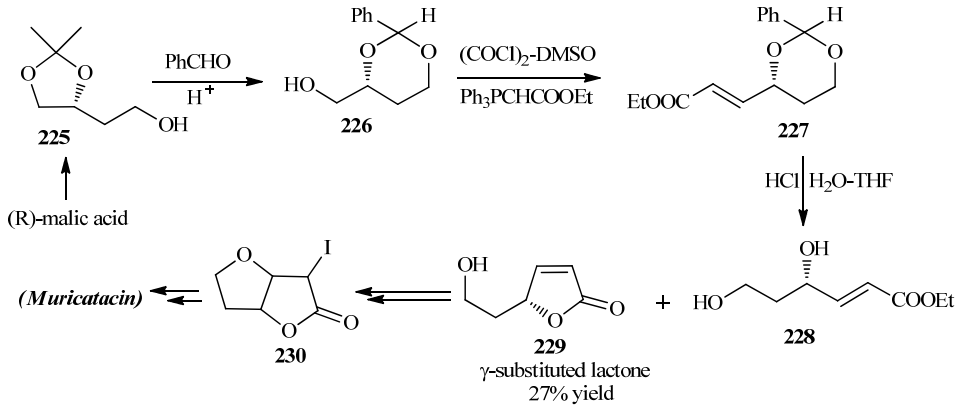
Synthesis of optically pure **224** $[\alpha]^{22}_{D}$= -45.8 (C=0.6, $CHCI_3$) in 68% yield**,** a known butenolide[37], was reported[38] by asymmetric epoxidation of **217** [**(218** and **219** (7.3:1 ratio, 89 % *ee*)] followed by few sequential synthetic steps as shown in Scheme 26.



Scheme-26: Owasagara's strategy for **224**.

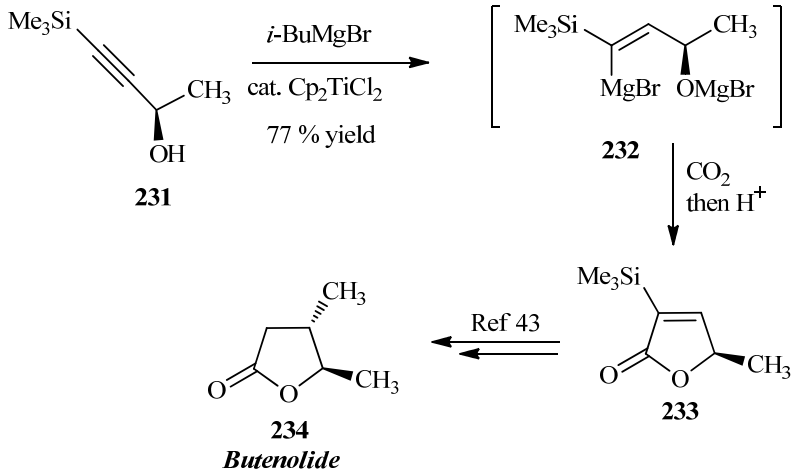
Reagents and conditions: *(a)* Red-AI, THF, 83% yield;*(b)NBS,CH_2Cl_2, 87% yield. (c) (i) OsO_4 (cat.), NMO, acetone-H_2O(1:1), (ii) $NaIO_4$, DCM-H_20 (4:1), (iii) 1,3-propanedithiol, $BF_3.OEt_2$, (iv) tert-butyldiphenyl (TBDPS) chloride, 4-N,N-dimethylaminopyridine (DMAP), (v) Zn, AcOH-EtOH (1:10), 70 °C, 45% overall yield. (d)(i) MeI, $NaHCO_3$, MeCN-H_2O (8:1), (ii) pyridiniumdichlorochromate (PDC),DCM,(iii) Bu_4NF, THF, 68% overall yield.*

Labelle *et al.*[39] have synthesized optically pure **229** $[\alpha]^{22}_{D}$= -45.8 (C=0.6, $CHCl_3$) in 27% yield starting from (*R*)-malic acid employing few conventional synthetic steps as shown in Scheme 27. Butenolide **229** was further utilized in the synthesis of bicyclic lactone **230**, a precursor of Muricatacin.[40]



Scheme-27: Lebelle's strategy for **229**.

Recently, **233** $[\alpha]^{22}_{D}$= -72.8 (*c* = 1.61, $CHCl_3$, 77% yield) is synthesized by Sato *et al.*[41] by the hydromagnesiation[42] of **231** followed by carboxylation of the intermediate **232** with CO_2 in the presence of a proton source . Compound **233** was further transformed to a known butenolide **(234)** as shown in Scheme 28.

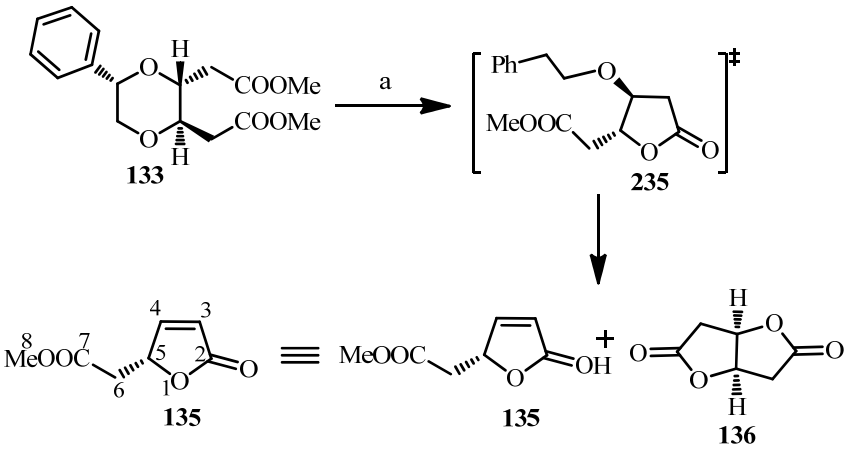


Scheme-28: Sato's strategy for **234.**

From all the above discussions, it is evident that *α,β*-unsaturated-*γ*-substituted-butyrolactones are important constituent of natural products having biological activity. Despite its high importance, very few strategies are available for their syntheses. We describe below our elegant single step strategy to obtain optically pure *α, β*-unsaturated-*γ*-substituted butyrolactone using **133** as a precursor.

2A.3.III.1 Stereoselective synthesis of optically pure (*R*)-methyl 2-(5-oxo-2, 5-dihydrofuran-2-yl) acetate 135:

In order to transform **133** to butenolide **135,** it was hydrogenated using 20 mol % of $Pd(OH)_2$ / C in glacial acetic acid at 60 psi, which led *in situ* cyclization affording **135** $[\alpha]^{22}_D$= +83.21 (*c* =0.48, $CHCl_3$) in 86% yield along with bislactone **136** as a minor product (14% yield). We were delighted to see that both the ether bond of [1,4] dioxane ring cleaved in a single step (Scheme 29).



Scheme-29: synthesis of optically pure γ-substituted γ-lactone **135.**

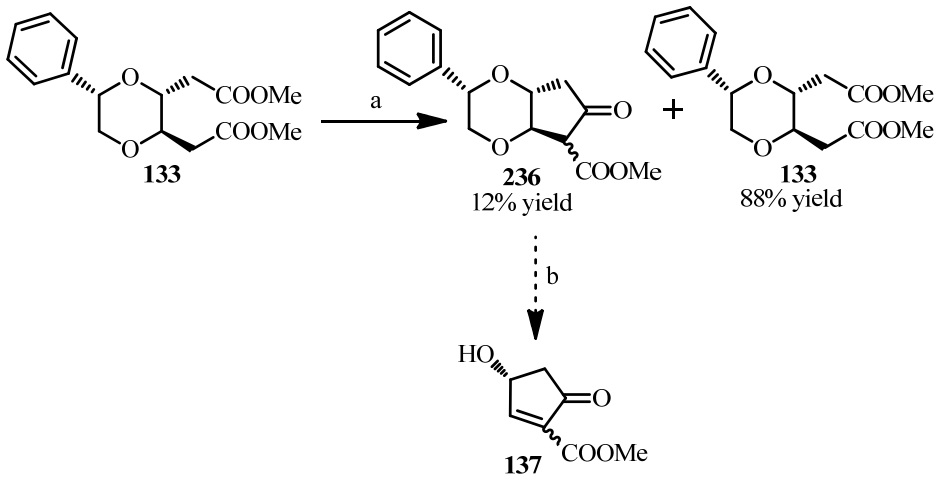
Reagents and conditions: (a) H_2 (60 psi), using 10% w/w Pd $(OH)_2$/C, AcOH, 24 h, 86 % yield.

The IR spectrum of **135** showed a characteristic γ-lactone (-CH_2- C=O-O-) absorption band at 1757 cm^{-1}. The ^{1}H NMR spectrum showed olefinic proton (H_4) as a doublet of

doublet (dd, J = 15.54, 4.30 Hz) at δ 6.85 and another olefinic proton (H_3) appeared as a doublet at δ 6.06 (d, J = 15.6 Hz), respectively. The multiplet appearing at δ 4.67 (m, 1H), integrating for one proton, was assigned to methine proton (H_5) while the methyl protons (-COOC$\underline{H}_3$) of ester moiety appeared as a singlet at δ 3.67 (s, 3H). Another multiplet, observed at δ 2.53 (m, 2H) was attributed to methylene (C_6) protons of **135**. The ^{13}CNMR and DEPT experiments further confirmed the structure of **135** by displaying three carbon signals appearing at δ 148.06 (C_4), 120.65(C_3) and 67.08(C_5), respectively. Carbon signals appearing at δ 51.73 (C_8) and 40.37 (C_6) were attributed to methyl carbon (-COO$\underline{C}H_3$) of ester moiety and methylene carbon (C_6), respectively. ESI-Mass spectrum confirmed the structure of **135** by exhibiting 157.08 $(M+H)^+$ and 179.54 $(M+Na)^+$, respectively.

2A.3.III.2 Attempt towards the synthesis of (*S*)-methyl 3-hydroxy-5-oxocyclopent-1-enecarboxylate (137):

The molecules possessing 2,3-disubstituted cyclopentenone moiety such as jasmone[44] and prostaglandin analogs[45] are very important natural products. Considering the importance of these molecules in human physiological system, many research groups have reported the synthesis of these molecules in recent years[46, 47]. Therefore, we got interested in transforming **133** into such molecular scaffolds by Dieckmann cyclization. Reaction of **133** with sodium hydride in anhydrous THF at 0ºC provided **251** in only in 12% yield. Remaining (88 %) of **133** was recovered back as such. Various reaction conditions were tried to improve the yield of **251** but all our attempts failed. Low yield of **251** can be explained due to the *trans*-geometry of **133** in which enolate generated by sodium hydride is possibly in less proximity with carbonyl functionality of methyl ester. This unforeseen result led us to abandon our further synthetic endeavor towards the synthesis of prostaglandins precursor (Scheme 30).



Scheme-30: Synthesis of prostaglandin precursor **137**.

Reagents and conditions: (a)NaH, dry THF, 0 °C→rt, 3 h, 12 % (b) BBr_3 , (2.1 eq), dry DCM, -78ºC→-20ºC for ½ h,-20ºC→0ºC for 2 h, then 0ºC→rt, 2 h.

2A.4. Summary:

From the above results, it is evident that we have successfully implemented photoinduced electron transfer (PET) reactions in synthesizing a multi-talented synthon **133** and its easy transformation to optically pure bislactone **136**, 1,2-*trans*-diol **138** and γ-substituted butyrolactone **135**. An attempt was also made to synthesize a prostaglandin precursor analogue **137**.

2A.5 References:

1. (a) Meijere, A. D.; Schirmer, H.; Duetsch, M. *Angew. Chem. Int. Ed*. **2000**, *39*, 3964. (b) Granger, B. A.; Kaneda, K.; Martin, S. F. *Org. Lett*., **2011**, *13*, 4542
2. Hizuka, M.; Hayashi, N.; Kamashita, T.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36,* 1550.
3. (a) Ernst, B.; Hart, G. W.; Sinay¨, P., Eds. *Carbohydrates in Chemistry and Biology*; Wiley-VCH: New York, **2000**. (b) Nicolaou, K. C.; Bockovich, N. J. In *Bioorganic Chemistry Carbohydrates*; Hecht, S. M., Ed.; Oxford University Press: New York, **1999**; p 134.
4. Kusuda, S.; Watanabe, Y.; Toru, T. *J. Org. Chem*. **1992**, *57*, 3145.
5. Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett*. **1997**, *38*, 433
6. Calvert, J. G.; Pitts, J. N. *Photochemistry*, Wiley, New York, **1966**, 736.
7. Beeckwith, A. L. J. *Tetrahedron*. **1981**, *37*, 3073.
8. Bounce, R. A.; Dowdy, E. D.; Childress, R. S. and Jones, P. B. *J. Org. Chem.* **1998**, *63*, 144.
9. (a) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons, Inc.: **2001**; pp 195- 266. (b) Yudin, A. K., Ed. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**. (c) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (d) Katsuki, T. *Ad*V. *Synth. Catal.* **2002**, *344*, 131. (e) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599. (f) Wong, O. A.; Shi, Y. *Chem. Re*v. **2008**, *108*, 3958.
10. ko, S. Y.; *Tetrahedron Lett.* **1994**, *35*, 3601.
11. (a) Schroder, M. *Chem. Rev.* **1980**, *80*, 187. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.(c) Johnson, R. A.;

Sharpless, K. B. In *Catalytic Asymmetric Synthesis*,2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, **2000**.

12. Behrens, C. H. and Sharpless, k. B., *Aldrichimica Acta*, **1983**, *16*, 67.
13. (a) Sharpless, K. B. In In *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I., Ed, **1991**, vol, *5*, 389-436, Pergamon, Oxford; (b) Rossiter, B. E.; In *Asymmetric Synthesis*, J, D, morrisio Ed., **1985**, vol *5*, 194-246, Academic Press, new York; (c) Finn, M. J. and Sharpless, K. B., In *Asymmetric Synthesis*, j. D. Morrision Ed., **1985**, vol *5*, 247-308. Academic Press, New York.
14. Devine, P. N. and Oh, T., *Tetrahedron Lett.,* **1991**, *32*, 883.
15. (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.***1976**, *17*, 1973. (b) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.***1991**, *113*, 113. (c) Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993**, *259*, 64. (d) Jacobsen, E. N.; Marko, I.; Mungall, W. S.;Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.(e) Salvador, J. A. R.; Silvestre, S. M.; Moreira, V. M. *Curr. Org. Chem.* **2008**, *12*, 492.
16. Albrecht, L.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2110**, *132*, 9188.
17. Lim, S. M.; Hill, N.; Myers, A. G., *J. Am. Chem. Soc.* **2009**, *131*, 5763.
18. (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am.Chem. Soc.* **1997**, *119*, 11224–11235. (c) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000. (d) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.
19. Fujioka, H.; Matsunaga, N.; Kitagawa, H.; Nagatomi, Y.; Kondo, M.; Kita, Y., *Tetrahedron: Asymmetry*, **1995**, *6*, 2117.

20. Anorbe, B.; Martin, V. S.; Palazone, J. M.; Trujillo, J. M. *Tetrahedron Lett*. **1986**, *27*, 4991.

21. (a) Moustakis, C. A.; Viala, J.; Capdevila, J.; Falk, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 5283; (b) Mosset, F.; Yadagiri, P.; Lumin, S.; Capdevila, J.; Falck, J. R. *Tetrahedron Lett*. **1986**, *27*, 6035. (c) Ennis, M. D.; Base, M. E. *Tetrahedron Lett*. **1986**, *27*, 6031.

22. Hizuka, M.; Hayashi, N.; Kamashita, T.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull*. **1988**, *36*, 1550.

23. Kiegiel, J.; Nowacki, J.; Tarnowska, A.; Stachurska, M.; Jurczak, J. *Tetrahedron Lett.* **2000**, *41*, 4003.

24. Hoye, T. R.; Humpal, P. E.; Jimener, J. I.; Mayer, M. J.; Tan, L.; Ye, Z., *Tetrahedron Lett*. **1994**, *35*, 7517.

25. Ghosh, S. K.; Kundu, P.K. *Org. Biomol. Chem.* **2009**, *7*, 4611.

26. Fleming, I., *Chemtracts-Org. Chem.*, **1996**, *9*, 1.

27. Tamao, K.; Ishida, N.; Ito, Y. and Kumada, M., *Org. Synth.*, **1990**, *69*, 96.

28. Kiegiel, J.; Nowacki, J.; Tarnowska, A.; Stachurska, M.; Jurczak, J. *Tetrahedron Lett*. **2000**, *41*, 4003.

29. (a) Burke, S. D.; Liang, L., *Org. Lett*. **2001**, *3*, 1953. (b) Ohkuma, T.; Kitamura M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509.

30. (a) Figadere, B. *Acc. Chem. Res*. **1995**, 28, 236–359; (b)Knight, D. W. Contemp. *Org. Synth*. **1994**, *1*, 287–315; (c) Freer, A. A.; Kirby, G. W.; Rao, G. V.; Cain, R. B. J. *Chem. Soc., Perkin Trans*. 1 **1996**, 2111–2116.

31. Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett*. **2001**, *3*, 703–706.

32. (a) Liu, Y.; Bae, B. H.; Alam, N.; Hong, J.; Sim, C. J.; Lee, C.-O.; Im, K. S.; Jung, J. H. *J. Nat. Prod*. **2001**, *64*, 1301–1304; (b) Zhang, J.; Blazeeka, P. G.; Bervern, Heidi; Belmant, D. *Tetrahedron Lett*. **2003**, *44*, 5579–5582.

33. Ribbons, D. W. and Sutherland, A. G., *Tetrahedron*, **1994**, *50*, 3587

34. (a) Evans, W.C.; Smith, B.S.W.; Linstead, R.P.; Elvidge, J.A. *Nature* (Lond.), **1951**, *168*, 772, (b) Sistrom, W.R.; Stanier, R.Y. *J. Biol. Chem.,* **1954**, *210*, 821.

35. (a) Ngai, K.-L.; Gmston L.N.; Kallen, R.G. *Biochemistry,* **1983**, *22*, 5223; (b) Ngai K.-L.; Kallen, R.G. *Biochemistry,* **1983**, *22*, 5231.

36. Hanessian, S.; Hodjes, P. J.; Murray, P. j.; Sahoo, S. P., *J. Chem. Soc., Chem. Commun.,* **1986**, 754.

37. Suemune, H.; Hizuka, M.; Kamashita, T.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37,* 1379.

38. Taniguchi, T. and Ogasawara, K., *Tetrahedron Lett*. **1997**, *38*, 433.

39. Labelle, M and Guindon, Y. *J. Am. Chem. Soc*. **1989**, *111*, 2204.

40. Couladouros, E. A. and Mihou, A. P., *Tetrahedron Lett*. **1999**, *40*, 4861.

41. Ito, T.; Okamoto, S.; Sato, E., *Tetrahedron Lett.* **1990**, *31*, 6399-6402.

42. (a) Sato, F.; Watanabe, H.; Tanaka, Y. and Sato, M. *J. Chem, Soc., Chem. Commun*., **1982**, 1126. (b) Sato, F. *J. Organomet. Chem*., **1985**, 53, 285.

43. Ortuiio, R. M.; Merce, R. and Font, J, *Tetrahedron*, **1987**, *43*, 4497.

44. (a) Buchi,G.; Egger, B. *J. Org. Chem*., **1971**, *36*, 2021; (b) Sarkar, T. K.; Ghorai, B. K.; Banerji, A. *Tetrahedron Lett*. **1994**, *35*, 6907.

45. Mitra, A., *The Synthesis of Prostaglandins*; Wiley: New York, **1977**.

46. Bindra, J. S.; Bindra, R., *Prostaglandin Synthesis*, Academic Press: New York, **1977**.

47. Collins, P. W., *Chem. Rev*., **1993**, *93*, 1533.

CHAPTER 2: SECTION B

Stereoselective synthesis of chiral 6-phenyl -2,3-bis methylenemethoxy-carbonyl morpholine and its applications.

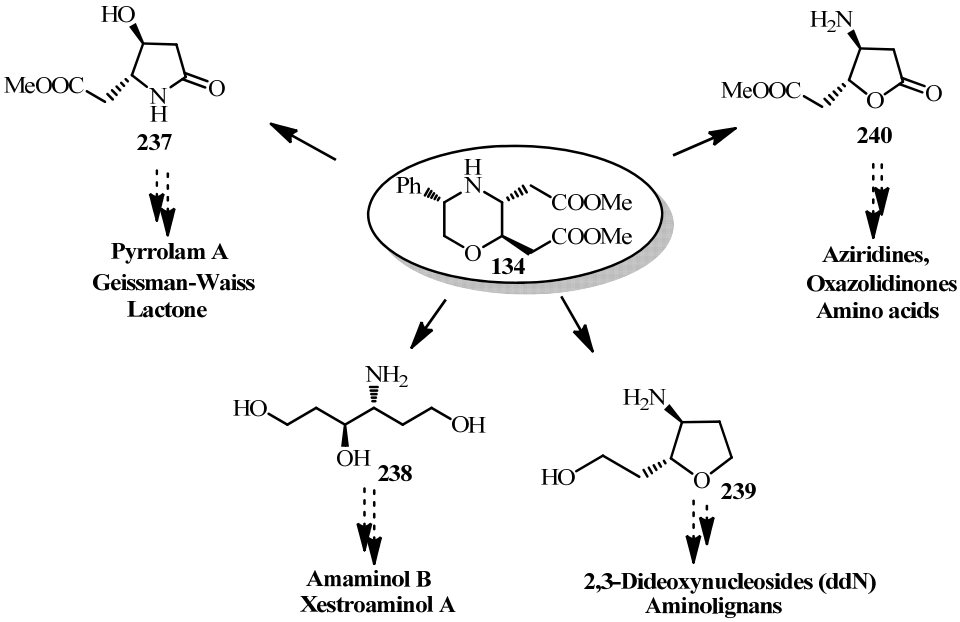
Section B

2B.1 ***Introduction:***

The successful results in the previous section encouraged us to extend further this strategy to design another versatile multi-talented synthon, the optically pure substituted morpholine. Apart from its unique structural framework amenable for various transformations, this structural motif itself has tremendous pharmacological importance[1]. However, despite its importance and potent use in various synthetic transformations, the synthetic access for pure substituted morpholines is rather limited.

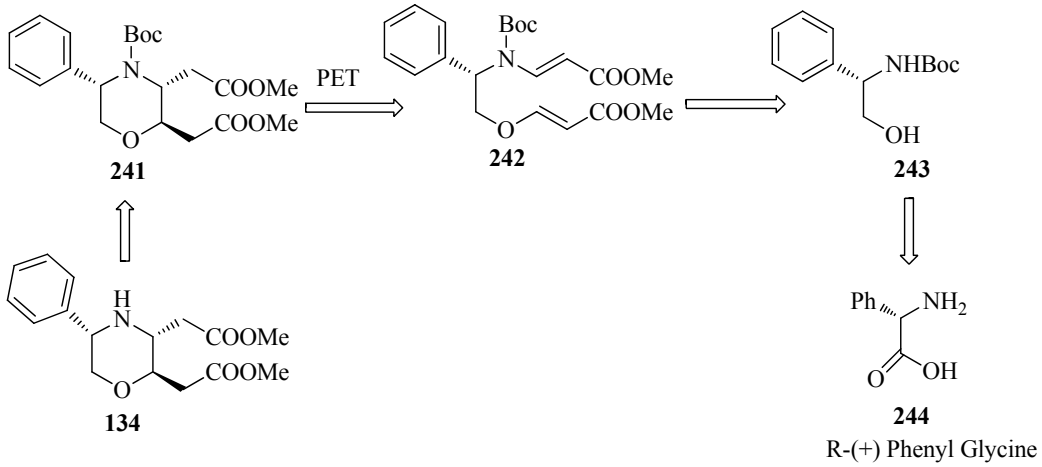
Towards our planned strategy of utilizing chiral substituted morpholine **134** for various other important synthetic precursors, we proposed its synthesis by utilizing the strategy discussed in previous section. The synthetic potential of **134** was also visualized considering its transformation to (a) optically pure *β*-hydroxy-γ-substituted butyrolactam **237**, an important intermediate for pyrrolizidine class of alkoloids[2]; (b) optically pure 1,2-*trans* amino alcohols **238,** a sub-structural unit widely found in bioactive natural products of marine origin[3] such as crusigasterine 277, amaminol B, xestroaminol A; (c) optically pure 2,3-disubstituted tetrahydrofuran **239**, an important sub-structural unit of aminolignans and 2,3-dideoxynucleosides[4] and (d) optically pure *β*- amino-γ-substituted butyrolactone **240,** used as a versatile intermediate for the synthesis of highly functionalized amino acids[5].

We would discuss the synthesis of **134** and its transformation to various synthetic intermediates mentioned in Scheme-31.



Scheme-31: Synthetic versatility of multitalented synthon **134**.

We devised a single step strategy to synthesize designed synthon **134** as shown retrosynthetically in Scheme 32.

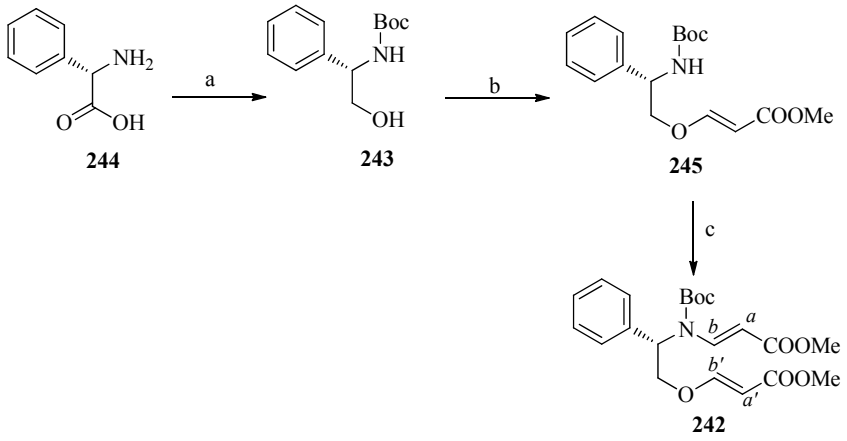


Scheme-32: Retrosynthetic analysis for multitalented synthon **134**.

2B.2 Results and discussion:

2B.2.1 Synthesis of (*E*)-methyl 3-((*S*)-2-((tert-butoxycarbonyl)((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)amino)-2-phenylethoxy)acrylate 242 :

The required irradiation precursor **242** was obtained in 80 % yield by sequential oxa-Michael - aza-Michael addition of methyl propiolate on to **243** as shown in Scheme 33.



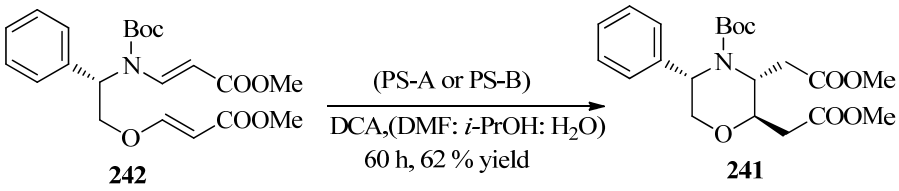
Scheme-33: synthesis of irradiation precursor **242**.

Reagents and conditions: (a) $NaBH_4/I_2$, dry THF 18 h, reflux , $Et_3N/(Boc)_2O$, $0^0C \rightarrow$ r t for 3 h, 78% yield (b) NMM, Methyl propiolate, dry DCM 0 $^0C \rightarrow$ rt, for 6 h, 91 % yield (c) NaH, dry THF, Methyl 3-iodoacrylate, 0 $^0C \rightarrow$ rt, for 3 h, 80% yield.

The ^{1}H NMR spectrum of **242** displayed two sets of doublet at δ 8.30 ($1H_b$) and 5.36 ($1H_a$) with J = 14.40 Hz while another set of two doublets for $1H_{b'}$ and $1H_{a'}$ (d, J = 12.64 Hz) appeared at δ 7.67, and 5.29, respectively. The benzylic proton appeared as a doublet of doublet (dd, J = 13.64, 6.82 Hz) at δ 5.46 and two methyl protons of ester moiety (-COOC$\underline{H}_3$) appeared as two singlets at δ 3.75 and 3.72 (2s, 6H). In ^{13}C NMR spectrum, the most down field carbon signals appearing at δ 167.93 and 167.72 were assigned to carbonyl carbons of ester moiety (-C=O-OMe) and four methine carbons

of olefinic moiety appeared at δ 161.49 ($C_{b'}$), 142.90 (C_b), 98.69 (C_a) and 97.26 ($C_{a'}$), respectively. Remaining three prominent carbon signals appearing at δ 51.30, 51.21 and 27.90 were assigned to two methyl carbon (-COO<u>C</u>H_3) of methyl ester moiety and another methyl carbons of *tert*-butyl dicaboxylate group, respectively. In addition, ESI-Mass spectrum confirmed the structure of **242** by exhibiting 406.41$(M+1)^+$and 428.53 $(M+Na)^+$.

2B.2.2 Stereoselective synthesis of chiral 6-phenyl -2,3-bis mthylenemethoxycarbonyl NBoc-morpholine 241:

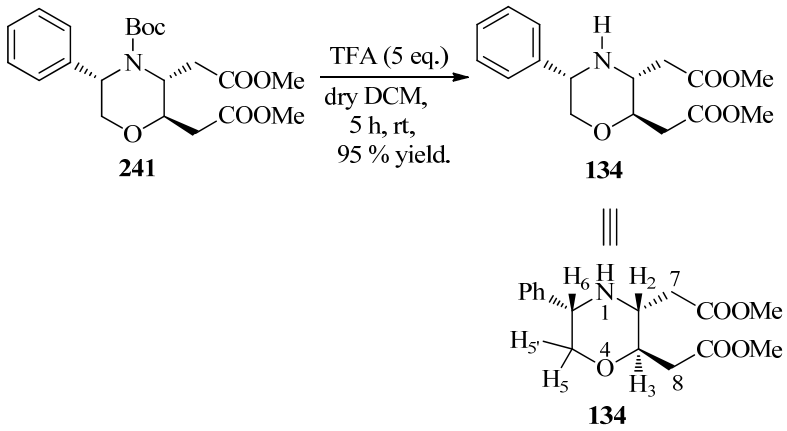


Scheme-34: Synthesis of multitalented synthon **241**.

PET activation of **242** involved irradiation (λ = 405 nm, in a similar photoreactor setup as described in previous section) of a solution of **242** (1.64 mmol) containing 1,9-dicyanoanthracene (DCA, 0.71mmol), 1,5-dimethoxy naphthalene (DMN, 0.25mmol) and ascorbic acid (4.24 mmol) in 700 mL solvent [DMF: *i*-PrOH: H_2O, (88:10:2)]. After 60 h of irradiation, when **242** was almost consumed and no more changes observed (monitored by GC) the solvents were removed under vacuum and the concentrate was purified by column chromatography over silica gel using petroleum-ether/ethylacetate as an eluent to afford **241** in 62% yield along with un-reacted **242** in 32 % yield. DCA and DMN were also recovered back quantitatively.

ESI-Mass spectrum confirmed the formation of **241** by exhibiting two adduct ion peaks at 408.49 $(M+1)^+$ and 430.50 $(M+Na)^+$. However, owing to the existence of

rotamers, due to N-Boc moiety[7], ^{1}H NMR spectra appeared very complex and made it very difficult to interpret**.** Therefore, N-Boc was deprotected using trifluroacetic acid (TFA) in anhydrous dichloromethane (DCM) at ambient temperature which provided **134** $[\alpha]^{22}_D$= +79.173 (*c* = 0.6, $CHCl_3$) in 95 % yield (Scheme 35).



Scheme-35: Synthesis of 2, 3, 6-trisubstituted morpholine **134**.

In the ^{1}H NMR of **134**, the H_2 appeared as a triplet (t, *J* = 18.8, 9.54 Hz) at δ 3.45 and H_3 along with H_5 appeared as a multiplet between δ 3.79-3.65. The $H_{5'}$ appeared as a doublet of doublet (dd, *J* = 9.64, 3.89 Hz) at δ 3.54. The H_6 clearly appeared as a doublet of doublet (dd, *J* = 9.29, 3.77 Hz) at δ 3.95. The methylene protons (H_7 and $H_{7'}$) appeared as a doublet of doublet (dd, *J* = 12.04, 6.77 Hz, 1H) at δ 2.76 and at δ 2.61 (dd, *J* = 12.06, 5.08 Hz, 1H), respectively. Similarly, methylene protons (H_6 and $H_{6'}$) appeared as a doublet of doublet (dd, *J* = 12.55, 6.28 Hz, 1H) at δ 2.72 and (dd, *J* = 12.80, 6.53 Hz, 1H) at δ 2.55 respectively. The ^{13}C NMR displayed four carbon signals appearing at δ 56.37 (C_2), 76.00 (C_3), 75.28 (C_5) and 62.45 (C_6), respectively. Another pair of carbon signals appearing at δ 36.89 and 34.79 was assigned to the two methylene carbons (-C<u>H</u>$_2$-COO-) adjacent to ester moieties, respectively. In addition, ESI-Mass spectrum confirmed the structure of **134** by exhibiting 308.11 $(M+1)^+$ and 330.15 $(M+Na)^+$.

The relative stereochemistry of **134** was suggested based on the analysis of HETCOR, COSY and NOSEY ^{1}HNMR experiments. The illustrated NOSEY interactions between bridged H_6/H_2 and H_5/H_3 confirmed the *cis*-diaxial relationship whereas the protons H_6/H_5 and H_2/H_3 did not show any NOSEY cross peaks indicating the *trans*-diaxial orientation (Figure 10).

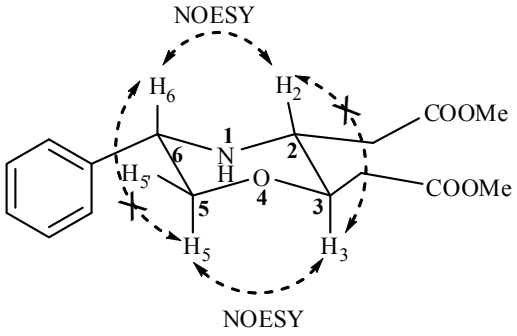
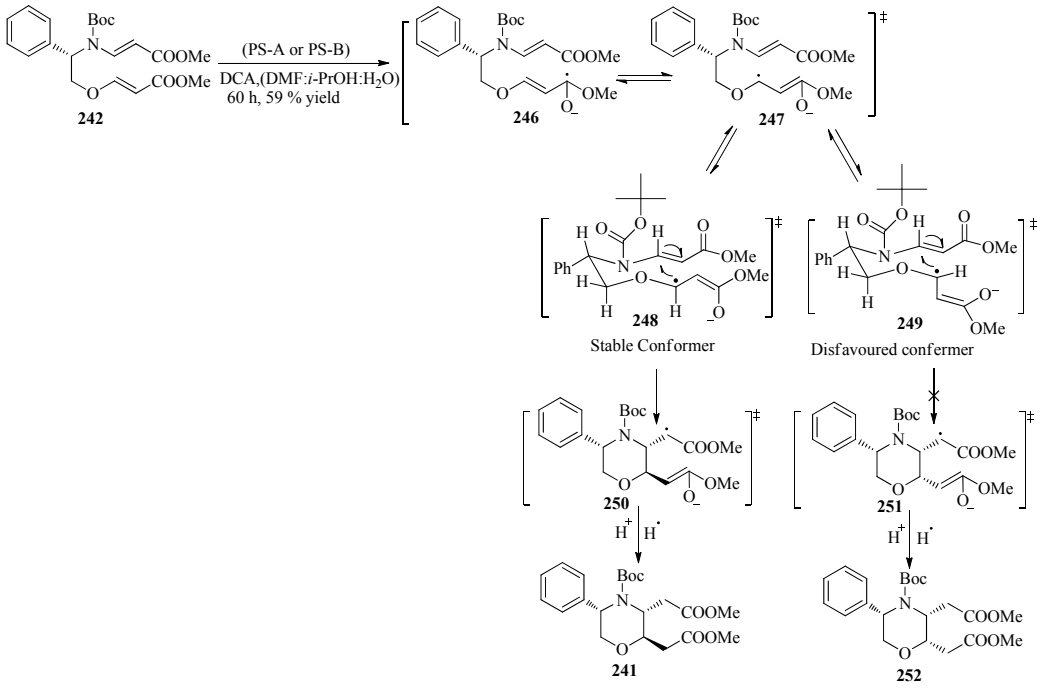


Figure-10: Selected NOESY cross peaks in **134**

2B.2.3 Stereochemical and mechanistic interpretation of 241:

The observed *anti*-stereochemistry of **241** appeared to be in close agreement with the general trend of *anti*-stereochemistry observed in enone-olefin radical cyclizations. Beckwith's model[8] suggests that under kinetic control, the cyclization of intermediate **247** should give cyclized compound with *syn*-appendages (**251**). However, the predominant *trans*-diastereoselectivity in the formation of **241** led us to postulate that initially produced *syn*-intermediate **249** is less stable which gets transformed to thermodynamically more stable *anti*-intermediate **248** due to the resonance stabilization of ester enolate ketyl radical **247**. Moreover, this argument also draws rationale provided by Bounce *et al*.[9] by considering the dominant secondary orbital interaction and overlap involving HOMO of the enolate and LUMO of the α-alkoxy-

α,β-unsaturated ester carbonyl in the transition state **248** making it more stable transition state for the formation of **241** (Scheme 36).



Scheme-36: Reaction mechanism and stereochemical output.

2B.3 Synthetic Explorations of 134:

Having devised a strategy to obtain **134** in sufficient quantities, we set our goal in evaluating its transformation to some important intermediates used in the syntheses of bioactive natural products[10] such as, **237**, **238, 239** and **240**. However, before discussing actual synthetic details of these important intermediates, it would be appropriate to highlight briefly recent developments in each area to showcase the importance of our strategy.

2B.3.I Stereoselective synthesis of *β*-hydroxyl-*γ*-substituted butyrolactams:

β-Hydroxy-*γ*-substituted butyrolactam belongs to pyrrolizidine class of alkaloids such as lycopsamine (**253)**, pyrrolam A (**256)**, Geissman-Waiss lactone (**258)**, alexine (**254)** and casuarine (**257)** (Figure 11)[11] which are widely present in plants and exhibit diverse range of interesting bioactivities[12].

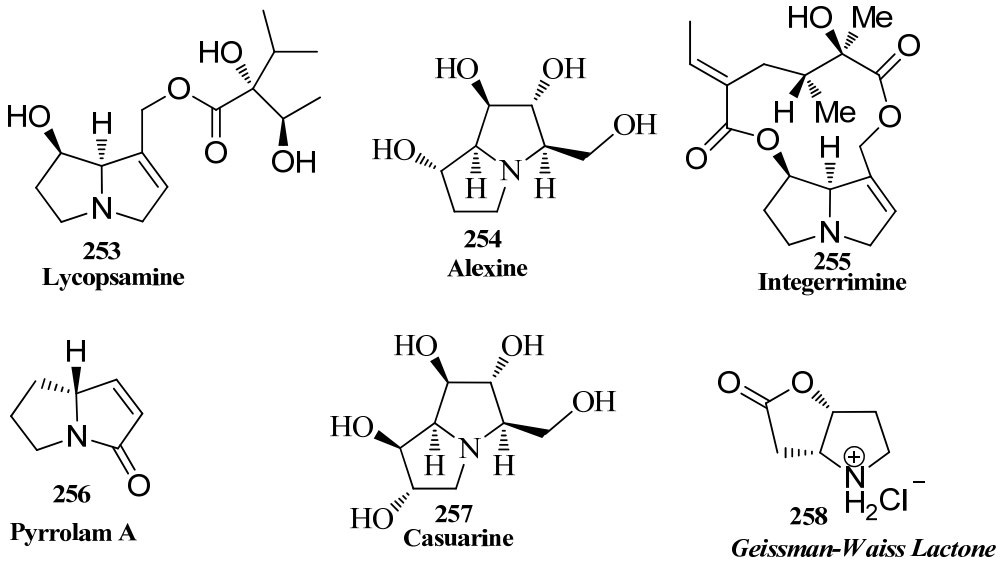
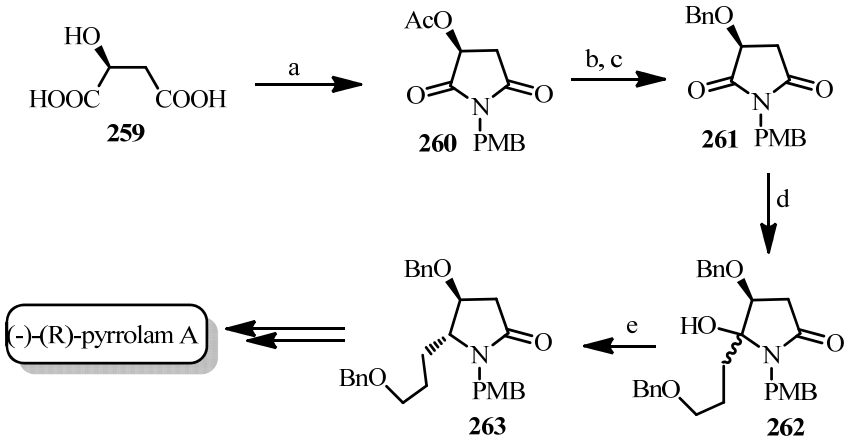


Figure-11: Pyrrolizidine class of alkaloids.

Towards the synthesis of these alkaloids many strategies have been devised. However, all the major strategies for the synthesis of pyrrolizidine class of alkaloids involve *β*-hydroxy-*γ*-substituted butyrolactam **237** as a key intermediate[13]. Therefore much attention has been paid to synthesize **237.** Briefly we would discuss few reported strategies for the synthesis of **237** or its analogue to put the proceeding discussion in proper perspectives:

Huang *et al.*[14] reported the synthesis of optically pure **263** as a key intermediate for the synthesis of (-)-pyrrolam A **(256)**. The synthesis started from commercially available (S)-malic acid **(259)** by reacting it with benzylamine leading to the

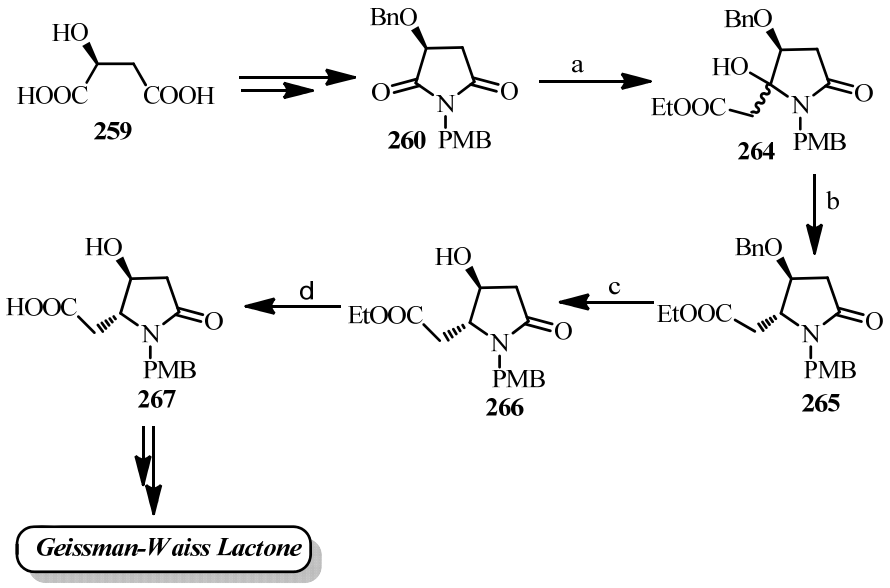
formation of enantiopure pyrrolidine derivative **261**[15] $[\alpha]^{20}_D$= + 70.80 (*c* = 0.94, $CHCl_3$) in 91 % yield. Following few linear synthetic steps as shown in Scheme 37, **263** $[\alpha]^{20}_D$= +19.91. (*c* = 1.00, $CHCl_3$) was obtained in 68 % yield which was further transformed to Pyrrolam A (Scheme 37).



Scheme-37: Huang's strategy for Pyrrolam A.

Reagents and conditions: (a) AcCl (excess), reflux, 2 h; $PhCH_2NH_2$, THF, 4 h: AcCl (excess], reflux, 18 h; 83 % (b) AcCl, EtOH, 50°C, 91%; (c) BnBr, Ag_2O, Et_2O, rt, 94%; (d) $BnO(CH_2)_3MgBr$, THF, 0°C, 90%; (e) Et_3SiH, $BF_3.OEt_2$, CH_2Cl_2, −78°C → rt, 68%.

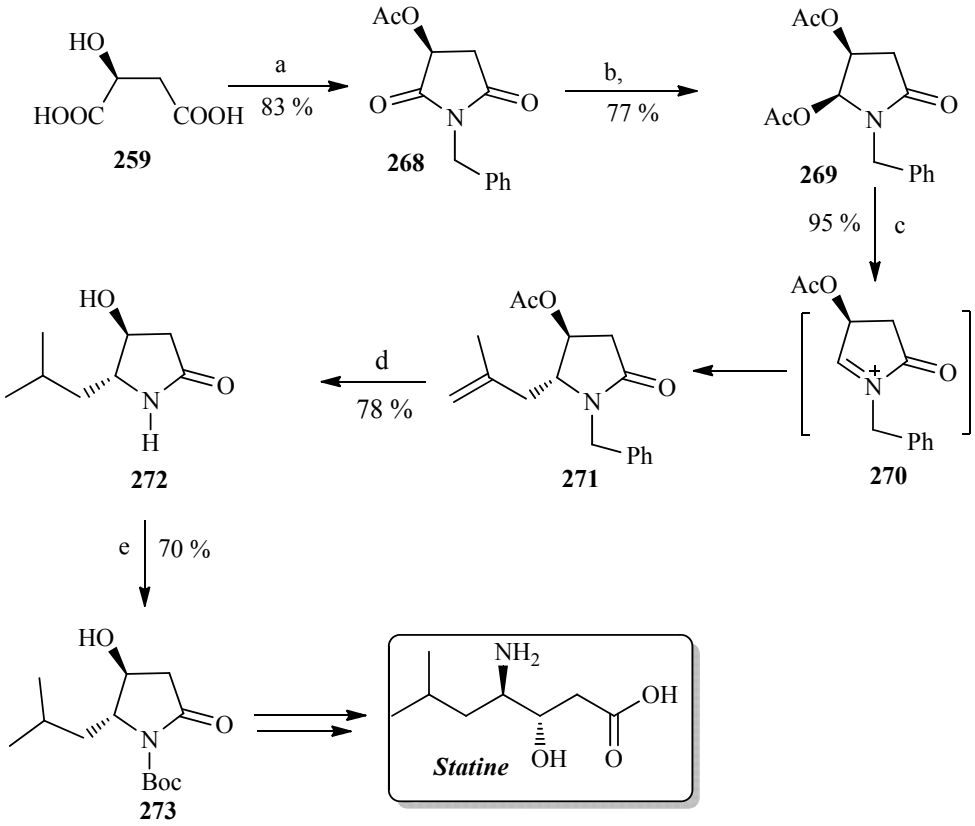
Similar strategy was also utilized for the synthesis of Geissman-Waiss lactone[16] **(258)** in 87 % yield; a precursor of (+)-retronecine[17, 18] from **267** $[\alpha]^{20}_D$= +1.61. (*c* = 1.1, $CHCl_3$) which was obtained from **259** by following the steps as shown in Scheme 38.



Scheme-38: Huang's strategy for **267**.

Reagents and conditions: (a) LiHMDS, AcOEt, THF, -78 °C, 76 % (b) Et_3SiH, F_3B-OEt, DCM, -78 °C→ rt, 86 % (c) H_2, 10 % Pd/C, EtOH, 87 % (d) LiOH, H_2O, rt, 5 h, quantitative

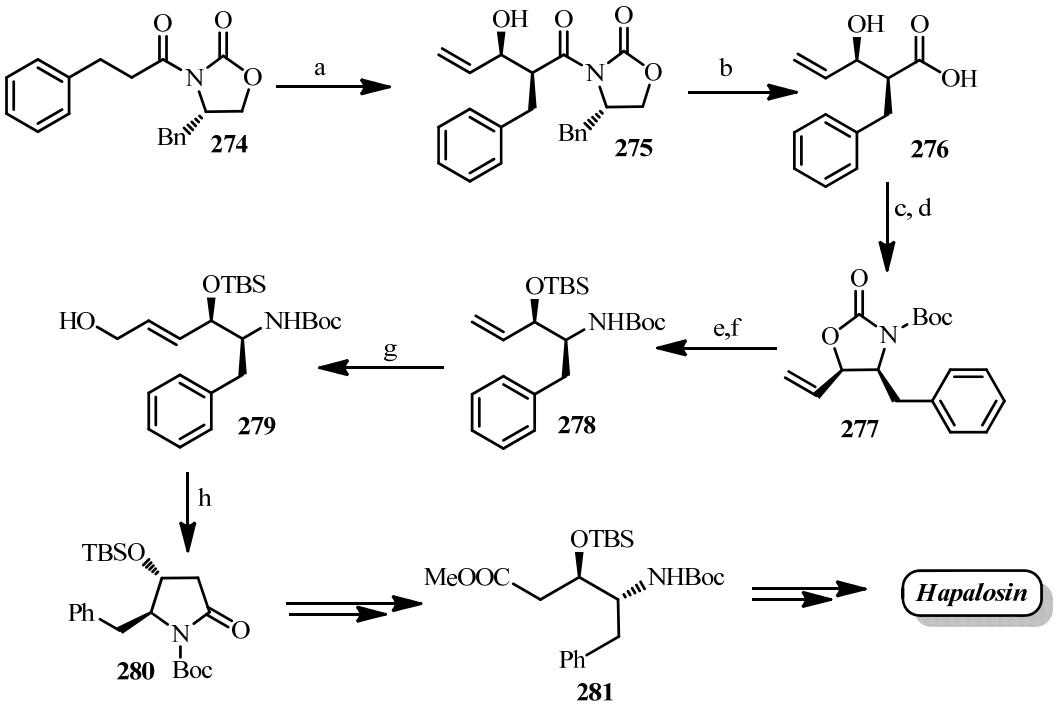
Hiemstra *et al*.[19] reported the synthesis of optically pure **273** as a key intermediate in the synthesis of *β*-hydroxy-γ-amino acids starting from **259** involving the intermediacy of **271** (95 % yield, *trans/cis* 11:1) as shown in Scheme 39.



Scheme-39: Heimstra's strategy for Statine.

Reagents and conditions: *(a)AcCl (excess), reflux, 2 h; $PhCH_2NH_2$, THF, 4 h: AcCl (excess), reflux, 18 h; (b)(i)$NaBH_4$, EtOH, -20 °C, 15 min;(ii) Ac_2O, DMAP, py, 4 h**;** (c) $BF_3.Ei_2O$ (2 equiv), $CH_2=C(Me)CH_2SiMe_3$ (3 equiv), CH_2C1_2, 18 h; (d) (i)MeOH, MeONa (cat), 2 h**;** (ii) H_2, 5% Pd/C (cat), EtOH, 2 h; (iii) Na, NH_3, -78 °C, 1.5 h; (e)(i) TBDMSCI, imidazole**,** DMF, 18 h: (ii) $(BOC)_2O$, Et_3N, DMAP, CH_2C1_2, 18 h; (iii) KF, Bu4NF, THF, 2 h*

Recently, Maier *et al.*[20] have devised an aldol reaction/Curtius rearrangement protocol to obtain a key intermediate **280** in 75 % yield, utilized in the synthesis of sub-structural unit of *Hapalosin* having potent activity for reversing the activity of *P-glycoprotein* in human physiological system[21] starting from **274** (Scheme 40).



Scheme-40: Maier's strategy for **227**.

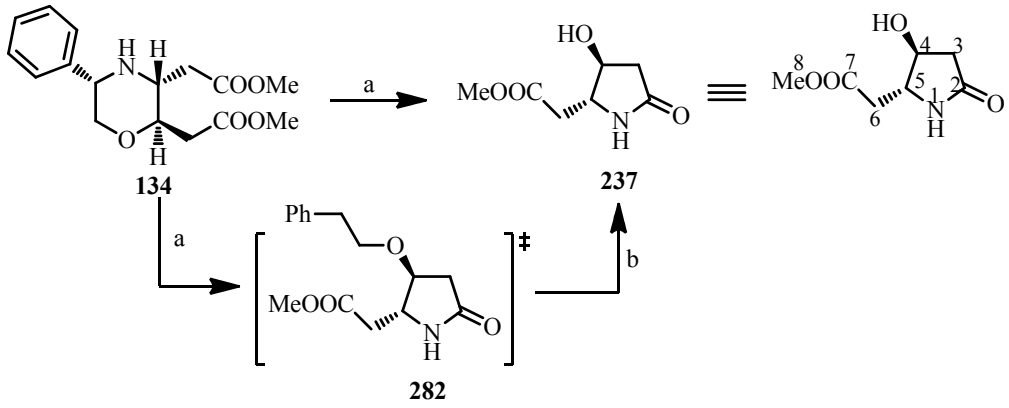
Reagents and conditions: (a) Bu_2BOTf, iPr_2NEt, CH_2=CHCHO, dry DCM, -78ºC→rt, 79% yield (b) LiOH, H_2O_2, THF:H_2O (3:1), 0ºC→rt, 15 h, 85 % yield (c) $(PhO)_2P(O)N_3$, Et_3N, Toulene, reflux, 4 h, 80 % yield. (d) $(Boc)_2O$, Et_3N,DMAP, rt, 5 h, 95% yield. (e) Cs_2CO_3, MeOH, rt 25 h, 76 % yield. (f) TBSCl, Immidazole, DMF, 2 h, rt, 90% yield (g) 9-BBN, 30% H_2O_2, THF, rt, 20 h, 72% yield. (h) PDC, DMF, rt, 15 h, 75% yield.

It is apparent from the above discussion that *β*-hydroxy-*γ*-substituted butyrolactams are important intermediates in the synthesis of pyrrolizidine class of alkaloids and γ-amino acids. However, known strategies for its synthesis have generally utilized chiral (S)-malic acid **(259)** as a starting compound which invariably involved longer reaction sequence with varying degree of enantioselectivity. In this regard, synthesis of optically pure *β*-hydroxy-*γ*-substituted butyrolactam still remains a challenge. Therefore, we have devised a novel strategy to obtain optically pure *β*-hydroxy-*γ*-

substituted butyrolactam **237** in a single step from the designed synthon **134** which is described as follows:

2B.3.I.1 Stereoselective synthesis of optically pure methyl 2-((2*R*,3*S*)-3-hydroxy-5-oxopyrrolidin-2-yl)acetate 237:

Hydrogenation of **134** using 20 mole % of $Pd(OH)_2/C$ at 60 psi (H_2) in glacial acetic acid cleaved the benzylic bond of the labile morpholine ring which subsequently cyclized to provide optically pure *β*-hydroxy-*γ*-substituted *γ*-lactam **237** {$[\alpha]^{22}_D$= +24.71(*c* =0.61, MeOH)}in 86% yield (Scheme 41).



Scheme-41: Synthesis of optically pure γ-lactam **237**.

Reagents and conditions: *(a) H_2 (60 psi), using 20 mol % $Pd(OH)_2/C$, AcOH, 24 h, 86 % yield (b) BBr_3, dry DCM, -78ºC.*

The structure of compound **237** was established by detailed ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

In the ^{1}H NMR spectrum of **237,** the H_4 proton appeared as a doublet of doublet of doublet (ddd, *J* = 10.54, 6.03, 4.51 Hz) at δ 4.68 (1H) whereas H_5 proton appeared as a multiplet at δ 4.29 (m, 1H). A sharp singlet appearing at δ 3.77 (s, 3H) was attributed to methyl protons (-COOC$\underline{H}_3$) of ester moiety and two methylene protons

(H_3 and $H_{3'}$) appeared as a doublet of doublet (dd, *J* = 18.06, 8.08 Hz, 1H) at δ 2.90 and (dd, *J* = 18.06, 5.08 Hz, 1H) δ 2.61, respectively. Similarly, methylene protons (H_6 and $H_{6'}$) appeared as a doublet of doublet (dd, *J* = 13.55, 6.52 Hz, 1H) at δ 2.84 and (dd, *J* = 13.56, 4.52 Hz, 1H) δ 2.74, respectively. In the ^{13}C NMR spectrum, the most down field carbon signals appearing at δ 180.88 (C_2) and 175.53(C_7) were assigned to carbonyl carbons of lactam and ester moiety, respectively and the carbons signals appearing at δ 74.89 (C_4) and 64.01(C_5) were attributed to two methine carbon (C_4 and C_5),respectively. The carbon signal appearing at δ 54.96 (C_8) was attributed to methyl carbon (-COO$\underline{C}H_3$) of ester moiety and other signals appearing at δ 42.64 (C_3) and 41.51(C_6) were assigned to methylene carbons (C_3) and (C_6), respectively. In addition, ESI-Mass spectrum confirmed the structure of **237** by exhibiting 174.10 $(M+H)^+$ and 196.00 $(M+Na)^+$.

2B.3.II Stereoselective synthesis of 1, 2-*trans* amino alcohols:

The 1,2-*trans* amino alcohol moieties represent privileged structural motif of numerous bioactive natural products of marine origin such as (2*R*, 3S)-2-aminotetradeca-5,7-diene-3-ol **(283)**,[22] (2*R*, 3S)-cusigasterine 277 (**284**),[23] amaminol B (**286**)[24] and halaminol A (**285**)[25] (Figure-12).

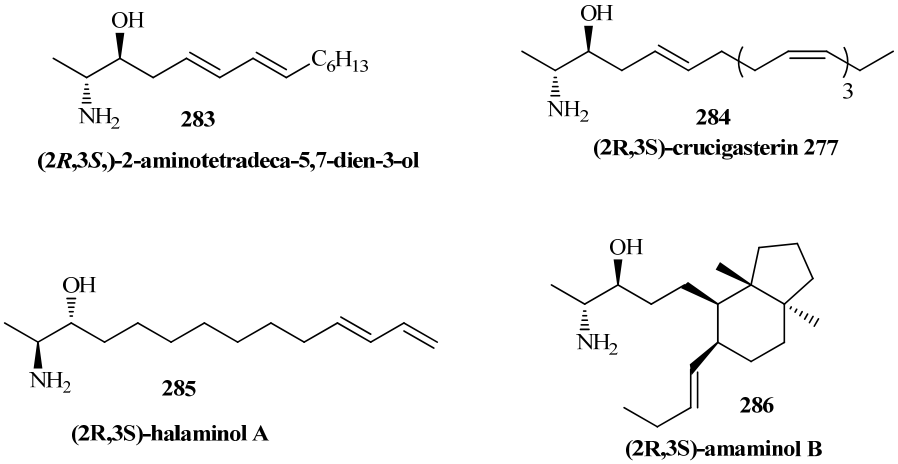


Figure-12: Marine natural products.

Apart from these marine natural products, 1,2-*trans*-amino alcohols are also sub-structural motif in sphingosine (**287)**, sulfobasine B (**288)**, *Saquinavir* (**291)** and polyhydroxy aza-sugars such as *(+)*-castanospermine (**289)** and swainsonine (**290)** (Figure-13).

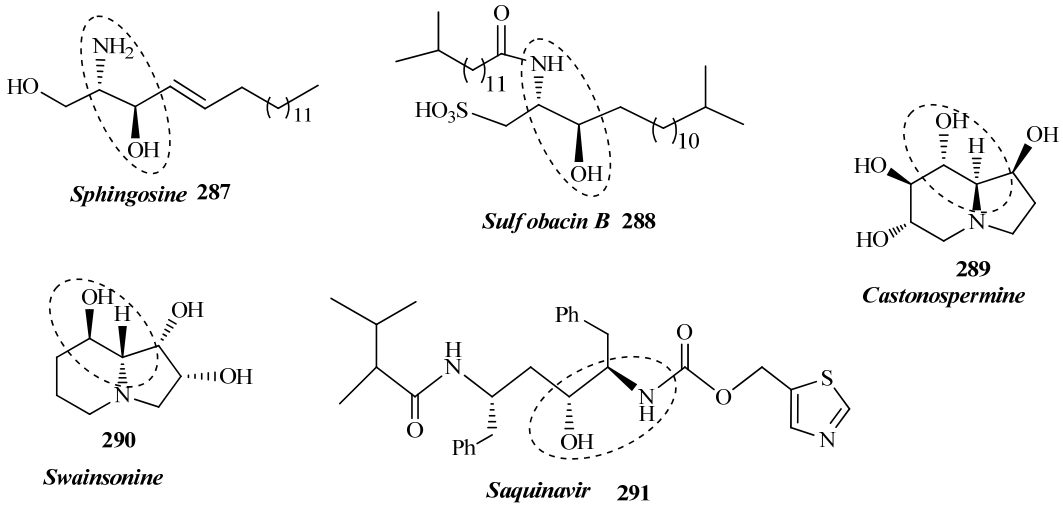
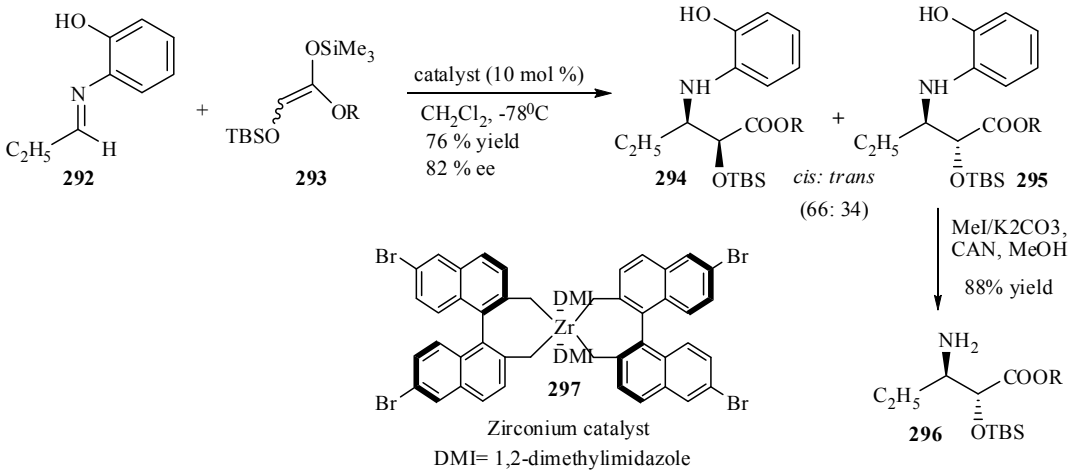


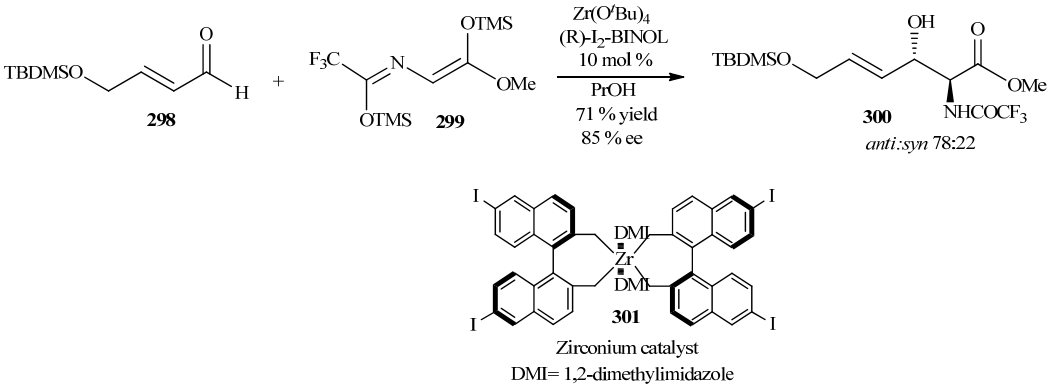
Figure-13: 1,2-*trans*-amino alcohol as sub-unit in natural products.

Among the synthetic strategies known towards the synthesis of enantiopure 1,2-dialkylated-*trans*-amino alcohols, highly stereoselective Mannich-type reaction of α-alkoxy enolates **293** to imines **292** in presence of zirconium based chiral catalyst **297** providing a mixture of **294** and **295** in 76 % yield (82 % *ee*),(*cis:trans*, 66:34 ratio) is interesting one[26,27] (Scheme 42).



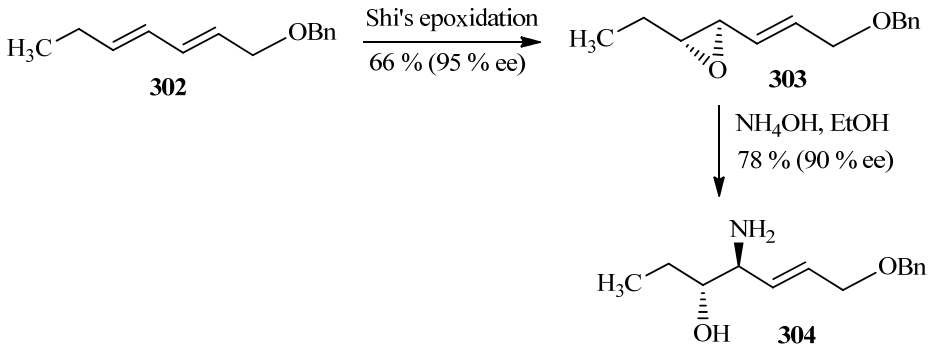
Scheme-42: Kobayashi's mannich type strategy for **296**.

Aldol type reactions strategy[28] is also reported from the same group to obtain chiral 1,2-*trans* amino alcohols **300** in 85 % yield with 97 % *ee* as shown in Scheme 43.



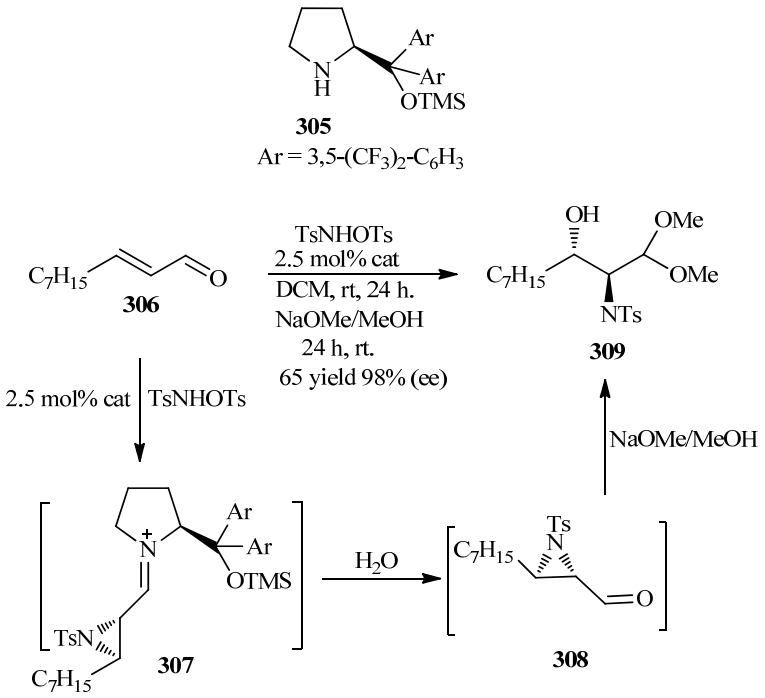
Scheme-43: Kobayashi's aldol reaction type strategy for **300.**

Apart from carbon-carbon bond forming strategy for enantiopure 1,2-*trans* amino alcohols, classical approach[29] of chiral epoxide opening with amine is very well known where chiral 1,2-*trans*-amino alcohol **304** is obtained in 78 % yield (90 % *ee*). The chiral epoxide **303** was obtained in 66 % yield (95% *ee*) by Shi's epoxidation strategy[30] (Scheme-44)



Scheme-44: Somfai's strategy for 1,2-*trans* amino alcohol **304**.

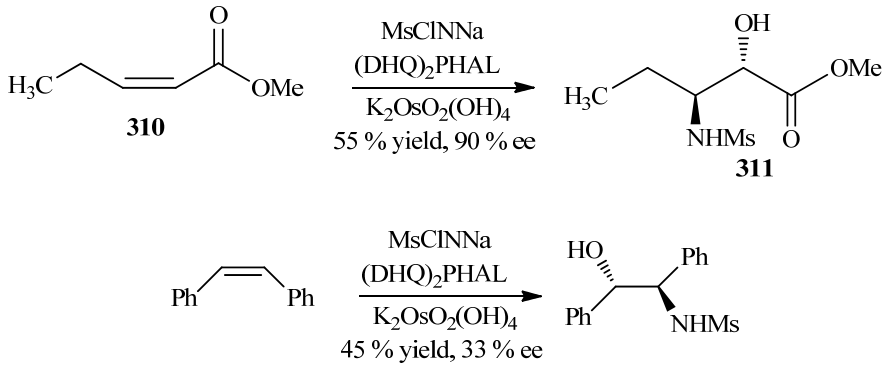
Similarly, chiral aziridine opening with hydroxy nucleophile strategy is also known[31] for the synthesis of *trans* 1,2-amino alcohol **309** in 67 % yield (98 % *ee*) as shown in Scheme 45.



Scheme-45: Jorgensen's organocatalytic strategy for **309.**

The most direct approach toward enantioselective synthesis of 1,2-*trans*-amino alcohols is by Sharpless asymmetric aminohydroxylation[32] of olefins conjugated with esters or ketones using $(DHQD)_2PHAL$ as a chiral catalyst in presence of K_2OsO_2 and

MsClNNa as a reagents to produce **311** in 55 % yield with 90 % *ee* . However, this strategy gave very low yield (45 %) and poor enantioselectivity (33 % *ee*) with isolated olefins (e.g. *cis*-stilbine) (Scheme 46).

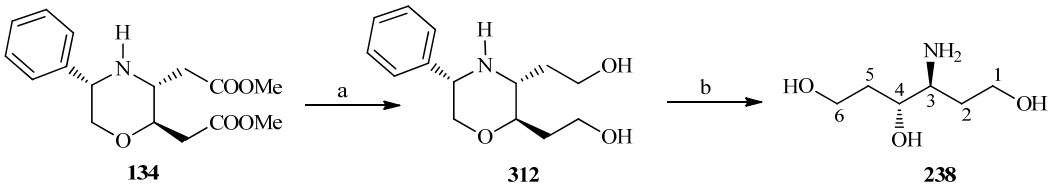


Scheme-46: Sharpless asymmetric aminohydroxylation strategy.

It is apparent from the above discussion that known synthetic strategies towards the synthesis of enantiopure 1,2-dialkylated-*trans*-amino alcohols require many synthetic steps resulting into low yield or many times poor enantioselectivity. Therefore, we devised a novel strategy to obtain optically pure 1,2-*trans*-amino alcohol from the designed synthon **134** in high yield as described below:

2B.3.II.1 Stereoselective synthesis of optically pure (3*R*,4*S*)-4-aminohexane-1,3,6-triol 238:

Compound **312** was obtained in 89 % yield by LAH reduction of **134** which upon hydrogenation using 20 mol% $Pd(OH)_2/C$ under pressure (60 *psi*) in glacial acetic acid, produced crude **238** which was further purified by column chromatography over silica gel using dichloromethane/methanol as an eluent to afford optically pure **238** $[\alpha]^{22}_{D}$= +66.31 (*c* = 0.24, MeOH) in 65 % yield (Scheme 47).



Scheme-47: Synthesis of 1, 2-*trans* amino alcohol.

Reagents and conditions: (a) LAH, dry THF, reflux 8 h, 89 % (b) H_2 (60 psi), using 20 mol % $Pd(OH)_2/C$, AcOH, 30 h, 65 % yield.

The structure of compound **238** was established by detailed ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

In the ^{1}H NMR spectrum of **238,** four methylene protons of H_1, H_6 and one methine proton H_4 appeared together as a bunch of multiplets between δ 3.77-3.47 (m, 5H). The H_3 proton appeared as a doublet of triplet (dt, J = 7.07, 1.64 Hz, 1H) at δ 2.60. Remaining methylene protons H_2 and H_5 appeared together as multiplets between δ 1.73- 1.59 (m, 4H). The ^{13}C NMR and DEPT experiment further confirmed the structure of **238** by displaying two methine carbon signals C_4 and C_3 at δ 73.10 and 51.24, respectively. The carbon signals appearing at δ 61.63 (C_6), 58.88 (C_1), 36.48 (C_2) and 35.98 (C_5) corresponded with the four methylene carbons (-$\underline{C}H_2$-$\underline{C}H_2$-) respectively. Finally ESI-Mass spectrum confirmed the structure of **238** by exhibiting 150.18 $(M+H)^+$ and 172.11 $(M+Na)^+$.

2B.3.III Stereoselective synthesis of *β*- amino γ-substituted butyrolactone:

β-Amino-γ-substituted butyrolactone moiety is present as a sub-structural unit of amicoumacin C[33] (**313)** and AI-77-B (**314)** having potent anti-inflammatory activity and gastroprotective activity respectively. These molecules are isolated from a culture broth of *Bacillus pumilus*[34] (Figure 14).

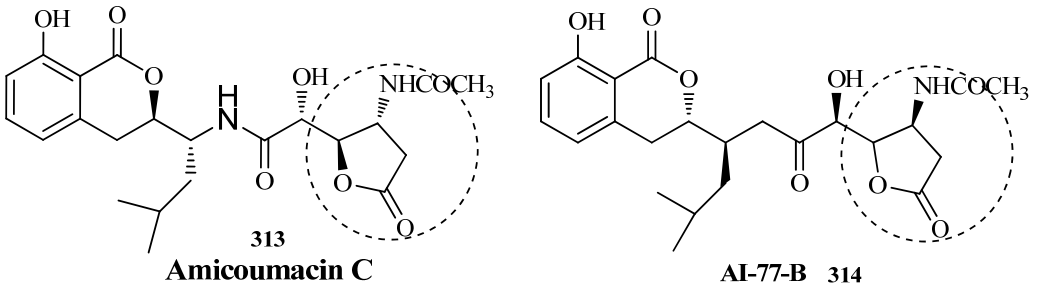
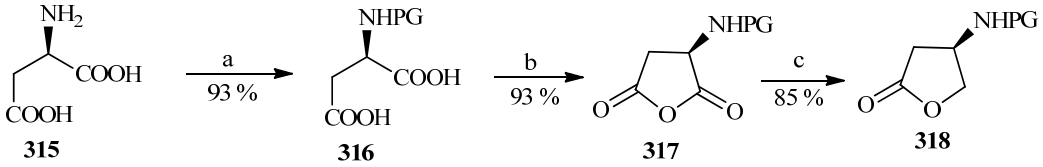


Figure-14: Natural products bearing *β*-amino-γ-substituted butyrolactone.

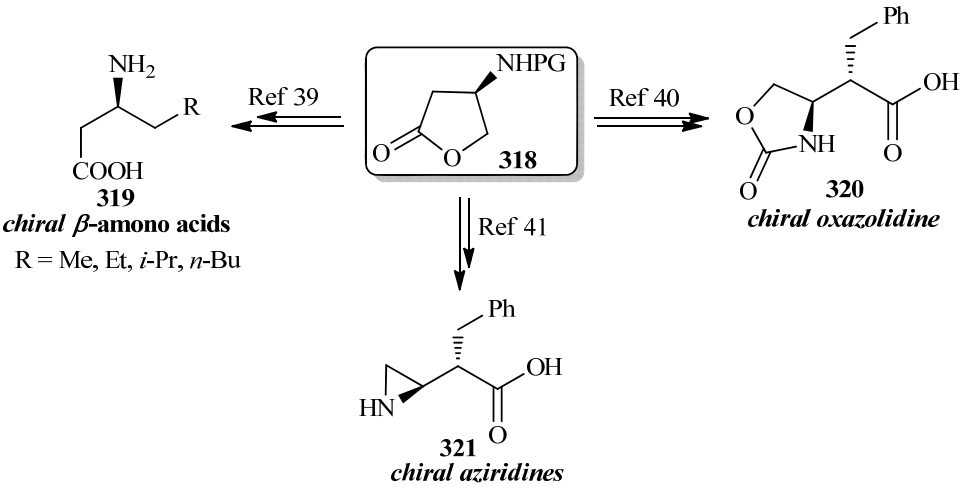
Enantiopure pure *β*-amino-γ-butyrolactones **318** are also recognized as valuable synthetic intermediates for the synthesis of aziridines,[35] oxazolidinones,[36,37] and highly functionalized amino acids.[38] Generally, **318** is synthesized from commercially available D-aspartic acid (**315**) (Scheme 48).



Scheme-48: Synthesis of *β*-amino butyrolactone **318**

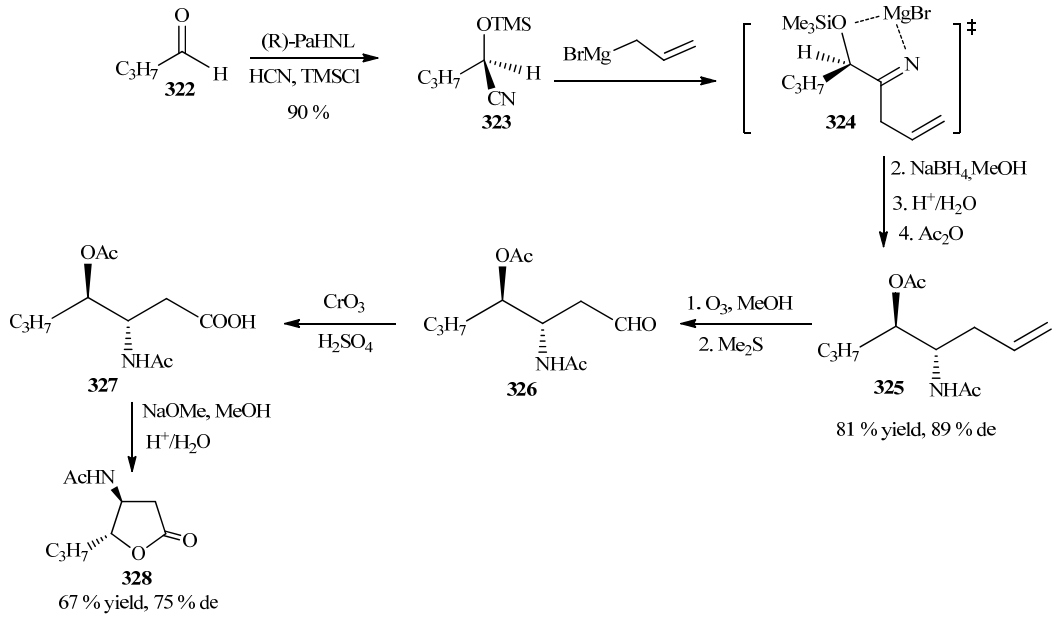
Reagents and conditions: (a) TsCl, NaOH, i-Pr$_2$EtN, 25ºC, 12 h, 93% yield (b) Ac2O, 28ºC, 18 h, 92% yield (c) NaBH$_4$, dry THF, reflux , 8 h, 85 % yield.

Several research groups have utilized **318** as a common key precursor for the synthesis of optically pure aziridine **321**, oxazolidine **320** and *β*-amino acids **319** (Scheme 49).



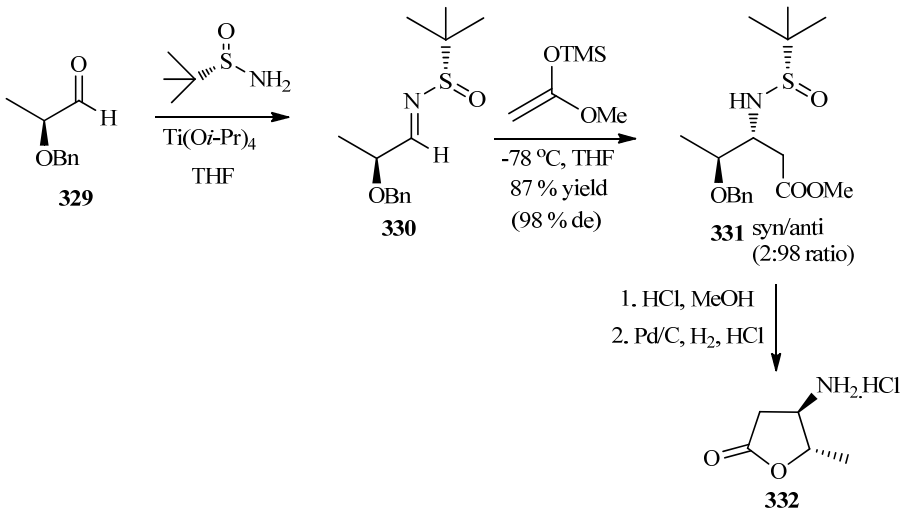
Scheme-49: Applications of *β*-amino butyrolactone.

Apart from chiral aspartic acid as a starting material for the synthesis of such butyrolactones, Effenberger *et al*.[42] have devised strategy to obtain optically pure **328** in 67 % yield (75% *de*) from chiral *trans*-1,2-amino alcohol derivative **327**as shown in Scheme-50.



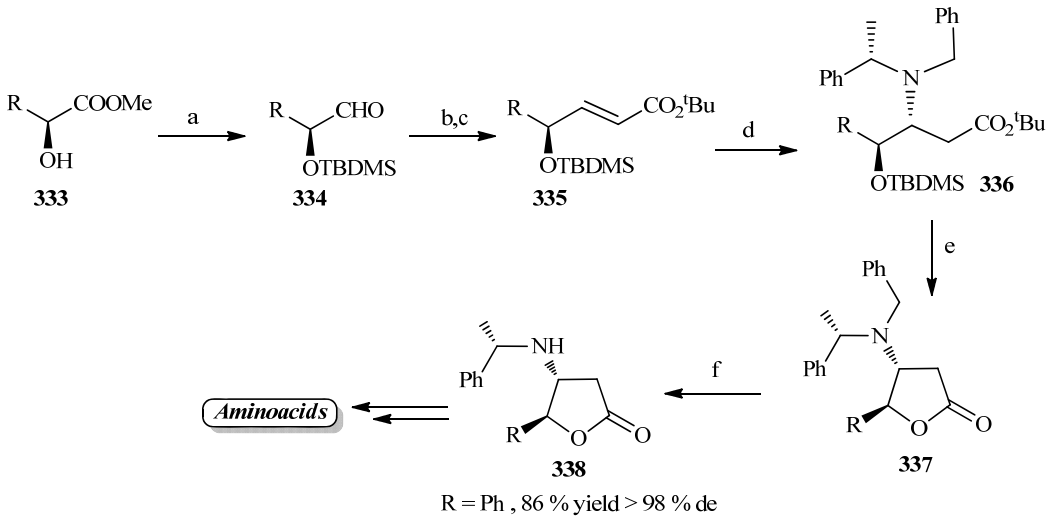
Scheme-50: Effenberger's strategy for **336**.

Similarly, Ellman *et al.*[43] have also reported the synthesis of optically pure *β*-amino-γ-butyrolactone **332** by the cyclization of **331,** obtained **(**87 % yield and 98% *de*) by the diastereoselective addition of enol-TMS to *N*-*tert*-butanesulfinyl-*R*-alkoxyacetaldimines **330** as shown in Scheme-51.



Scheme-51: Ellman's strategy for **332**.

Recently, Davies *et al.*[44] have cyclized **336** to obtain **338 (**86 % yield, 98% *de*) as a key intermediate in the synthesis of amino acids as shown in Scheme 52.



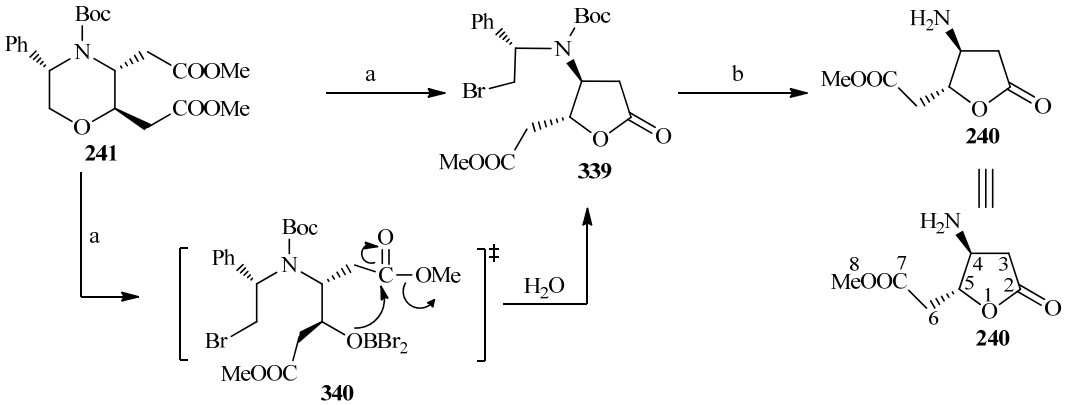
Scheme-52: Davies's strategy for **338**.

Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt; 96 % .(b) DIBAL-H, −78 °C, PhMe; 83% (c) tert-butyl diethylphosphonoacetate, NaH, THF, −78 ºC → rt. 86% (d) lithium (S)-N-benzyl-N-(α-methylbenzyl)amide, THF, −78 °C → −50 ºC, 12 h, 94%; (e) TBAF, THF, 50 °C, then TFA, rt, 66% (f) Pd/C, H_2 (6 bar), EtOH, 60 °C, 86% yield.

From all the above discussions it is evident that optically pure *β*-amino-γ-butyrolactone is an important intermediate but there is no simple strategy to obtain it in optically pure form. In this context, we have devised a novel two step approach for obtaining optically pure *β*-amino-γ-butyrolactone **240** in very high yield from **134** as described below:

2B.3.III.1 Stereoselective synthesis of optically pure methyl 2-((2*R*, 3*S*)-3-amino-5-oxotetrahydrofuran-2-yl)acetate 240:

Compound **339** was obtained in 86 % yield from **241** by cleaving the ether bond (-C-O-C-) of morpholine ring by utilizing boron tribromide (BBr_3) as a Lewis acid at -20 ºC in anhydrous dichloromethane which upon hydrogenation under pressure at 60 psi using 20 mol % of $Pd(OH)_2/C$ in glacial acetic acid afforded crude **240** in 82 % yield. Further purification by column chromatography over silica gel using dichloromethane/methanol as an eluent gave optically pure **206** $[\alpha]^{22}_D$= +53.40 (*c* =0.48, MeOH) (Scheme 53).



Scheme-53: Synthetic strategy towards optically pure **240.**

Reagents and conditions: (a) *BBr_3, dry DCM, -78ºC→0ºC for 2 h, 86% yield (b) H_2 (60 psi), using 20 mol % $Pd(OH)_2/C$, AcOH, 24 h, 82 % yield.*

In the ^{1}H NMR spectrum of **240,** the H_5 proton appeared as a doublet of doublet of doublet (ddd, *J* = 6.10, 3.67, 3.05 Hz) at δ 4.22 (1H) whereas H_4 appeared as a multiplet at δ 3.72 (m, 1H). A sharp singlet appearing at δ 3.70 (s, 3H) was attributed to methyl protons (-COOC$\underline{H}_3$) of ester moiety. Methylene protons H_3 and $H_{3'}$ appeared as a doublet of doublet (dd, *J* = 16.48, 6.71 Hz, 1H) and (dd, *J* = 16.48, 8.24 Hz, 1H) at δ 2.75 and 2.55, respectively. Similarly, H_6 and $H_{6'}$ appeared as a doublet of doublet (dd, *J* = 17.40, 6.72 Hz, 1H) and (dd, *J* = 17.40, 3.38 Hz, 1H) at δ 2.72 and 2.21, respectively. The ^{13}C NMR and DEPT experiments further confirmed the structure of **240** by displaying carbonyl carbon C_2 and C_7 signals at δ 172.71 and 169.27, respectively. The other two carbon signals appearing at δ 80.12 and 60.33 were attributed to two methine carbons C_5 and C_4 and methyl carbon signal C_8 appeared at δ 52.31. The carbon signals appearing at δ 37.37 and 34.36 were assigned to two methylene carbons C_3 and C_6, respectively. ESI-Mass spectrum confirmed the structure of **240** by exhibiting 174.12 $(M+1)^+$ and 196.11 $(M+Na)^+$.

2B.3.IV Stereoselective synthesis of 2-alkyl-3-amino substituted tetrahydrofurans:

Substituted 3-hydroxy tetrahydrofurans are commonly occurring sub-structures in a broad array of natural products and other biologically active molecules[45]. Therefore, many stereoselective strategies for their construction is known in the literature.[46] However, corresponding 3-amino tetrahydrofuran sub-structures are not so common in natural products, albeit, they are found as a part structure of 2,3-dideoxynucleoside(ddN, **341**)[47]**,** aminolignana (**342)**[48]**,** 3-amino-3-deoxyadenosine (**343)**[49] and γ-aminobutyricacid (GABA, **344**)[50] (Figure 15) possessing potent anti-HIV activity.

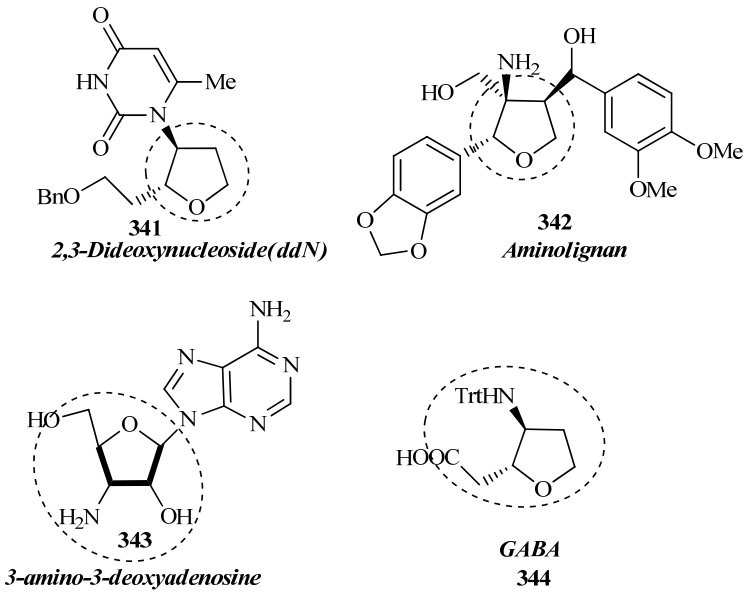
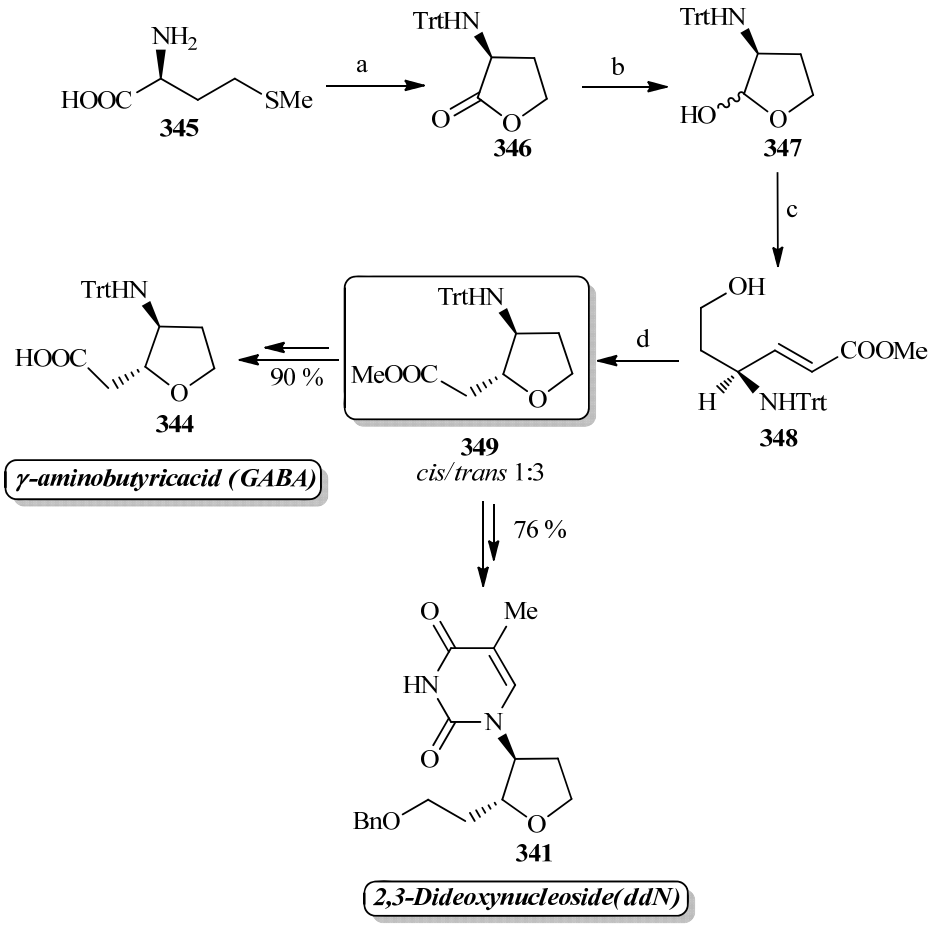


Figure-15: 3-amino tetrahydrofuran bearing natural products.

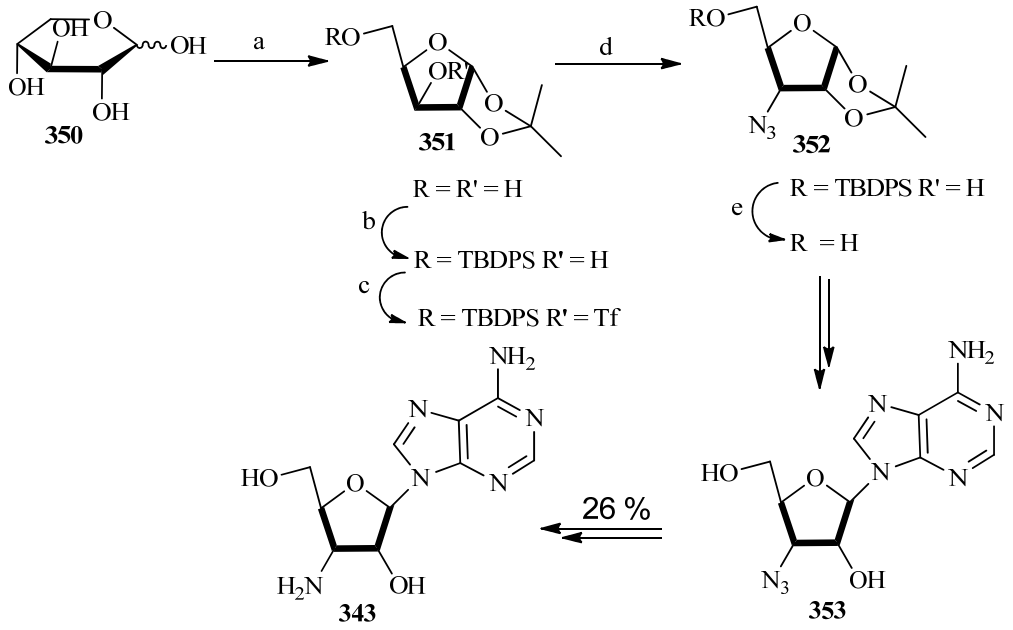
The key intermediates 3-amino tetrahydrofurans are synthesized either by using chiral methionine or by chiral D-xylose. Utilizing commercially available D or L-methionine (**345)**, Papaioannou *et al*.[51] have synthesized **349** in 80 % yield for the preparation of dideoxynucleoside **341** (76 % yield) and γ-aminobutyricacid (GABA, **344,** 90 % yield**)**[52] (Scheme 54).



Scheme-54: Papaioannou's strategy for **344** and **341.**

Reagents and conditions: (a)(i) Me_3SiCl; (ii) Trt-Cl/Et_3N; (iii) MeOH; (iv) MeI; (v) NaOH/H_2O; (vii) DCC (b) DIBAL, - 65 °C, 30 min, 95 % (c) $Ph_3P{=}CHCO_2Me$, DMF, 12 h, 90 % (d) Bu_4NF, THF, 15 min, 80 %

3-Azido-ribofuranose (**352)**, a key intermediate in the synthesis of 3-amino-3-deoxyadenosine (**343)**[53], known to be active against HIV reverse transcriptase,[54] is also obtained (56 % yield) from D-xylose (**350)** by following multistep protocol as shown in Scheme 55.



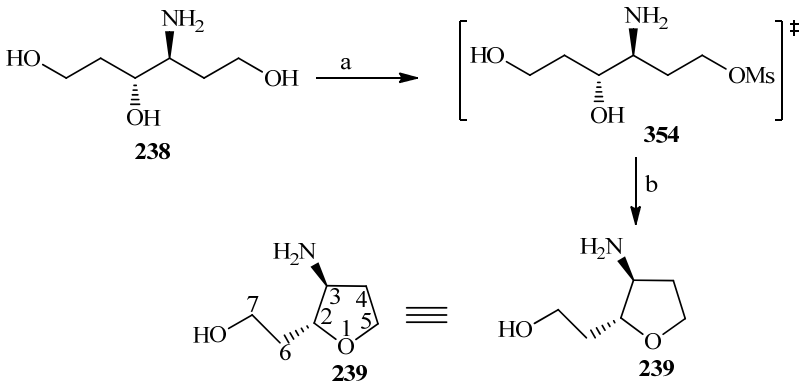
Scheme-56: Synthesis of 3-amino-3-deoxyadenosine **343**.

Reagents and conditions: (a) acetone, cat. H_2SO_4, 70% (b) TBDPSCl, imidazole, DMF, rt,3h, 60% (c) $(F_3CSO_2)_2O$, pyridine, DCM, -10 °C, 15min. (d) NaN_3, pyridine, DMF, rt, 7 days, 56% (e) TBAF, THF; rt, 2h, 95 %.

Our strategy of obtaining optically pure **239** from **238** as described below:

2B.3.IV.1 Stereoselective synthesis of 2-((2*R*,3S)-3-aminotetrahydrofuran-2-yl)ethanol 239:

Monomesylation of **238** using one equivalent of Et_3N/MsCl at 0°C led to *in situ* cyclization providing crude **239** which on purification by column chromatography over silica gel using dichloromethane/methanol as an eluent, afforded optically pure **239** $[\alpha]^{22}_D$= +36.81 (*c* = 0.64, MeOH) in 68 % yield (Scheme 57).



Scheme-57: Strategy towards optically pure **239**.

Reagents and conditions: (a) *Et_3N, MsCl,THF, 0°C (b) 0 →rt 3h 70 %*

In the ^{1}H NMR spectrum of **239,** the H_2 appeared as a doublet of doublet of doublet (ddd, *J* = 9.98, 7.83, 2.05 Hz) at δ 4.02 (1H) while H_3 appeared as a multiplet at δ 2.97 (m, 1H). Methylene protons H_7 appeared as a triplet (t, *J* = 12.26, 6.07 Hz, 2H) at δ 3.80 and H_5 appeared as a bunch of multiplets between δ 3.61-3.50 (m, 2H). Similarly, the H_4 and H_6 all together appeared as multiplets between δ 2.20- 1.57 (m, 4H). The ^{13}C NMR and DEPT experiment further confirmed the structure of **239** by displaying two methine carbon signals (C_5 and C_4) at δ 81.76 and 58.89, respectively. The remaining four methylene carbon signals appeared at δ 68.39 (C_2), 61.42 (C_7), 53.44 (C_3) and 33.70 (C_6), respectively. Finally ESI-Mass spectrum confirmed the structure of **239** by exhibiting molecular ion peaks at 132.18 $(M+1)^+$ and 154.87 $(M+Na)^+$, respectively.

2B.4 Summary:

The work presented and discussed in this section clearly illustrates the success of our strategy for the stereoselective construction of enantiomerically pure substituted morpholine **134** and its successful transformations to **237**, **238, 239** and **240**; important intermediates used in the synthesis of natural products / bioactive molecules.

2B.5 References:

1. (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641. (b) O'Neil, S. V.; Wang, Y.; Laufersweiler, M. C.; Oppong, K. A.;Soper, D. L.; Wos, J. A.; Ellis, C. D.; Baize, M. W.; Bosch, G. K.; Fancher,A. N.; Lu, W.; Suchanek, M. K.; Wang, R. L.; De, B.; Demuth, T. P., Jr. *Bioorg.Med. Chem. Lett.* **2005**, *15*, 5434. (c) Allison, B. D.; Phuong, V. K.; McAtee,L. C.; Rosen, M.; Morton, M.; Prendergast, C.; Barrett, T.; Lagaud, G.; Freedman,J.;Li, L.; Wu, X.; Venkatesan, H.; Pippel, M.; Woods, C.; Rizzolio, M. C.;Hack, M.; Hoey, K.; Deng, X.; King, C.; Shankley, N. P.; Rabinowitz, M. H. *J. Med. Chem.* **2006**, *49*, 6371.
2. Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G. Linney, I. D., *Org. Lett*. **2008**, *10*, 3615.
3. He, B. Y.; Wu, T. J.; Yu, X. Y. and Huang, P. Q., *Tetrahedron Asymmetry*, **2003**, *14*, 2101.
4. Huryn, D. M.; Okabe, M. *Chem. Rev*. **1992**, *92*, 1745-1768; De Clercq, E. AIDS Res. *Human Retrovirus*. **1992**, *8,* 119-134; De Clercq, E. *J. Med. Chem***. 1995**, *38*, 2491-2517; De Clercq, E. *Clin. Microbiol. Rev*. **1997**, *10*, 674-693.
5. Jefford, C. W.; Wang, J. *Tetrahedron Lett.* **1993**, *34*, 1111.
6. Piers, E.; Wong, T.; Coish, P. D.; Rogers, C., *Can. J. Chem.* **1994**, *72*, 1816.
7. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron Asymmetry* **2003**, *14*, 2651.
8. Beeckwith, A. L. J. *Tetrahedron*. **1981**, *37*, 3073.
9. Bounce, R. A.; Dowdy, E. D.; Childress, R. S. and Jones, P. B. *J. Org. Chem.* **1998**, *63*, 144.

10. (a) Belfield, A.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399. (b) Hong, Y.; Senanayake, C. H.; Xiang, T.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 3121. (c) Goodbrand, H. B.; Hu, N. X. *J. Org. Chem.* **1999**, *64*, 670 (c) Kundu, N. G.; Mahanty, J. S.; Chowdhurry, C.; Dasgupta, S. K.; Das, B.; Spears, C. P.; Balzarini, J.; De Clercq, E. *Eur. J. Med. Chem.* **1999**, *34*, 389. (d) McClenaghan, N. D.; Passalacqua, R.; Loiseau, F.; Campagna, S.; Verheyde, B.; Hameurlaine, A.; Dehaen, W. *J. Am. Chem. Soc.* **2003**, *125*, 5356. (e) Paredes, E.; Kneeteman, M.; Gonzalez-Sierra, M.; Mancini, P. M. E. *Tetrahedron Lett*. **2003**, *44*, 2943.

11. Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G. Linney, I. D., *Org. Lett.* **2008**, *10*, 3615.

12. Pereda-Miranda, R. *Phytochemistry of Medicinal Plants*; Arnason, J. T.; Mata, R.; Romeo, J. T., Eds.; Plennum Press: New York, **1995**; Chapter 5, pp 103-108.

13. (a) Liddell, J. R. *Nat. Prod. Rep.* **2001**, *18*, 441–447, and references cited therein; (b) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proc. Int*. **1996**, *28*, 641–690; (c) Dai, W.-M.; Nagao, Y. *Heterocycles* **1990**, *30*, 1231–1261.

14. Huang, P. Q.; Chen, Q. F.; Chen, C. L.; Zhang, H. K., *Tetrahedron Asymmetry* **1999**, *10*, 3827.

15. (a) Hiemstra, H.; Speckamp, W. N. in *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I. Eds;Pergamon Press: Oxford, **1991**; vol. 2, pp. 1047-1082 and references cited therein. (b) Hiemstra, H.; Speckamp, W. N.; in *The Alkaloids;* Brossi, A.; Ed.; Academic Press: New York, **1988**, Vol. 32, p 271.

(c) De Koning, H.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. in *Studies in Natural Product,Chemistry;* Atta-ur-Rahman, Ed.; Bioactive Natural Products (Part A); Elsevier: Amsterdam, **1993**,Vol. 13, pp 473.(d). Koot, W. J.; Van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamlp, *W. N. Tetrahedron Lett.* **1991**, *32,* 401.

16. Du, J. X.; Huang, H. Y.; Huang, P. Q., *Tetrahedron Asymmetry* **2004**, *15*, 3461.
17. (a) Geissman, T. A.; Waiss, A. C. J. Org. Chem. **1962**, *27*, 139.; (b) De Faria, A. R.; Matos, C. R. R.; Correia, C. R. *Tetrahedron Lett*. **1993**, *34*, 27 (c) Tanaka, M.; Murakami, T.; Suemune, H.; Sakai, K. *Heterocycles* **1992**, *33*, 697.
18. (a) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Morimoto, K.; Mukaiyama, T. *Chem. Lett*. **1982**, 455; (b) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans.* 1. **1987**, 2377.; (c) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393.
19. Koot, W. J.; Ginkel, R. V.; Kranenburg, M.; Hiemstra, H., *Tetrahedron Lett.* **1991**, *32*, 401-404.
20. Godwin, C. G.; Maier, M. E. *J. Org. Chem*. **1999**, *64*, 4551.
21. (a) Dinh, T. Q.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem*. **1997**, *62*, 790-791.(b) Dinh, T. Q.; Du, X.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem*. **1997**, *62*, 6773-6783.
22. Gulavita, N. K.; Scheuer, P. J. *J. Org. Chem*. **1989**, *54*, 366.
23. Jares-Erijman, E. A.; Bapat, C. P.; Lithgow-Bertelloni, A.; Rinehart, K. L.; Sakai, R. *J. Org. Chem*. **1993**, *58*, 5732.

24. Sata, N. U.; Fusetani, N. *Tetrahedron Lett*. **2000**, *41*, 489.

25. Jime´nez, C.; Crews, P. *J. Nat. Prod*. **1990**, *53*, 978.

26. List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827-833; Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842-1843; Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338-339; Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712-4713.

27. Kobayashi, S.; Ishitani, H.; Ueno, M., *J. Am. Chem. Soc.* **1998**, *120*, 431.

28. Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192-9193.

29. Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574-8583.

30. (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am.Chem. Soc.* **1997**, *119*, 11224–11235. (c) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000. (d) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.

31. Albrecht, L.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2110**, *132*, 9188.

32. Li, G.; Chang, H.-T.; Sharpless, B. K. *Angew. Chem. Int. Ed.* **1996**, *35*, 451-454.

33. Masaru, E.; Shigefumi, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1144.

34. Shimojima, Y.; Shirai, T.; Baba, T.; Hayashi, H., *J. Med. Chem.* **1985**, *28*, 3-9

35. Park, J.; Tian, G. R.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 3696.

36. Chung, S. J.; Chung, S.; Lee, H. S.; Kim, E.-J.; Oh, K. S.; Choi, H. S.; Kim, K. S.; Kim, Y. J.; Hahn, J. H.; Kim, D. H. *J. Org. Chem*. **2001**, *66*, 6462.

37. Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull*. **1986**, *34*, 3020.

38. Kim, H. Y.; Toogood, P. L. *Tetrahedron Lett*. **1996**, *37*, 2349.

39. Jefford, C. W.; Wang, J. *Tetrahedron Lett.* **1993**, *34*, 1111.

40. Chung, S. J.; Chung, S.; Lee, H. S.; Kim, E.-J.; Oh, K. S.; Choi, H. S.; Kim, K. S.; Kim, Y. J.; Hahn, J. H.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 6462.

41. Park, J.; Tian, G. R.; Kim, D. H. *J. Org. Chem*. **2001**, *66*, 3696.

42. (a)Roos, J.; Effinberger, F., *Tetrahedron Asymmetry*: **2002**, *13*, 1855. (a) Effenberger, F. *Angew*. *Chem*. **1994**, 106, 1609–1619; *Angew*. *Chem*., *Int*. *Ed*. *Engl*. **1994**, 33, 1555–1564; (c) Kruse, C. G. In *Chirality in Industry*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; Wiley: New York, **1992**; pp. 279–299; (d) Effenberger, F. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, **2000**; pp. 321–342.

43. Evans, J. W.; Ellman, J. A., *J. Org. Chem.* **2003**, *68*, 9948-9957.

44. Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; and Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922.

45. Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep*. **2005**, 269–303.

46. (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362; (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408; (c) Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754; (d) Koert, U. Synthesis 1995, 115–132; (e) Miura, K.; Hosomi, A. *Synlett* **2003**, 143–155.

47. Balayiannis, G.; Karigiannis, G.; Gatos, P.; Papaioannou, D.; Clercq, E. D., *Tetrahedron Lett.* **2000**, *41*, 6191

48. Hirao, H.; Yamauchi, S.; Ishibashi, F., *Biosci. Biotechnol. Biochem*., **2007**, *71*, 741.

49. Herdewijn P, Balzarini J, Masanori B, Pauwels R, Van Aerschot A, Janssen G, De Clercq E. *J. Med. Chem.* **1988**, *31*, 2040-2048

50. Krogsgaard-Larsen, P. In: Fonnum, F., Ed., *Amino Acids as Chemical Transmitters*, Plenum, New York **1978**, p. 305.

51. Papaioannou, D.; Stavropoulos, G.; Sivas, M.; Barlos, K.; Francis, G. W.; Aksnes, G. W.; Moe, K. M., *Acta. Chemica. Scandinavica*. **1991**, *45*, 99.

52. Roberts, E.; Chase, T. N.; Tower, D. B., *GABA in Nervous System Function*, Raven Press, New York **1976**.

53. Botta, O.; Moyroud, E.; Lobato, C.; Strazewski, P., *Tetrahedron*, **1998**, *54*, 13529.

54. Herdewijn P, Balzarini J, Masanori B, Pauwels R, Van Aerschot A, Janssen G, De Clercq E. *J. Med. Chem.* **1988**, *31*, 2040-2048.

CHAPTER 3

EXPERIMENTAL

General Remarks:

All the moisture-sensitive reactions were performed under an atmosphere of argon and glass wares were dried in an oven at 110 °C prior to use. Solvents for anhydrous reactions were dried according to Perrin *et al*. [1] Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing through commercially available pre-dried, activated alumina and dried by distillation over sodium/benzophenone and stored over sodium wire. Benzene, dichloromethane (DCM), dimethylformamide (DMF) and triethylamine were distilled over calcium hydride (CaH_2) and stored over 4 Å molecular sieves and KOH respectively. Solvents used for chromatography were distilled at respective boiling points using known procedures. Petroleum ether, used in the column chromatography was distilled in 60-80 °C boiling range.

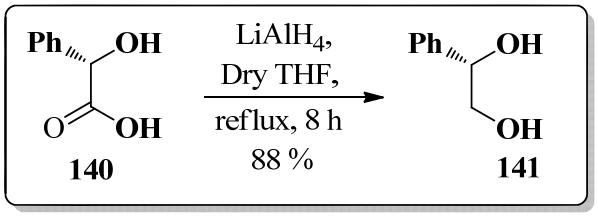
All commercial reagents were obtained from Sigma-Aldrich, Lancaster Chemical Co. (UK) and S. D. Fine Chemical Co. India. *n*-Butyllithium was titrated using diphenylacetic acid as an indicator. Progress of the reactions was monitored by thin layer chromatography (TLC, 0.25mm E. Merck silica gel plates, $60F_{254}$) and visualized by using UV light, followed by heating after dipping in alkaline solution of $KMnO_4$ and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in aqueous H_2SO_4 (250 mL), phospomolybdic acid and iodine. Column chromatography was performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or SRL India. Typical syringe and cannula techniques were used to transfer air and moisture-sensitive reagents.

All melting points were uncorrected in degree Celsius and recorded on Thermonik and Buchi melting point apparatus. IR spectra were recorded on a Perkin – Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX 500 instruments using

deuteriated solvents. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, doublet; t, triplet; dt, doublet of triplet; dd, doublet of a doublet; m, multiplet;). ^{13}C NMR spectra were recorded on Bruker ACF 200, AV 400 and Bruker DRX 500 instruments operating at 50 MHz, 100 MHz and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Mass spectra were recorded on PE SCIEX API QSTAR pulsar (LC-MS), automated GC/MS with solid probe facility mass spectrometer. Optical rotations were measured on a JASCO P-1030 polarimeter. Microanalysis data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyzer at National Chemical Laboratory.

3.1 Experimental procedures and spectral data:

1. (S)-1-phenylethane-1,2-diol (141):



To a stirred solution of lithium aluminum hydride (0.29 g, 7.89 mmol) in anhydrous THF (25 mL) at 0°C was added drop by drop solution of **140** (1 g, 6.56 mmol) in anhydrous THF (18 mL) through syringe. After the addition was over, the ice bath was removed and the resultant reaction mixture was refluxed for 8 h. The reaction mixture was then cooled to room temperature and the resultant reaction mixture was carefully quenched by drop wise addition of 2N NaOH at 0 ºC. The resultant solid was removed by filtration through centered funnel and washed with ethyl acetate (3 X 20 mL). The combined filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified by column chromatography (SiO_2,

ethyl acetate-pet ether 65:35) to get the corresponding diol **141** as a white solid (0.79 g, 88 % yield).

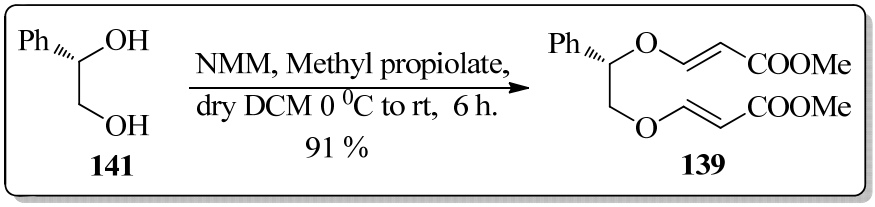
Yield : 88 %

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.37 (m, 5H), 4.11 (dd, *J* = 17.56, 5.50 Hz, 1H), 3.79 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ : 142.39, 128.67, 127.58, 126.77, 80.86, 67.87

Mass (ESI): (*m/z*) : 139.07 (M^++H), 161.11 (M^++Na)

2. (2E,2'E)-dimethyl 3,3'-((S)-1-phenylethane-1,2-diyl)bis(oxy)diacrylate (139) :



To a stirred solution of N-methylmorpholine (NMM) (1.26 g, 12.5 mmol) in 25 mL of anhydrous dichloromethane (DCM) was slowly added methyl propiolate (1.05 g, 12.5 mmol) in DCM (5 mL) at 0°C. The resultant reaction mixture was stirred at 0°C for 10 min. A solution of (S)-1-phenylethane-1,2-diol **141** (0.823 g , 5.97 mmol) in DCM (10 mL) was slowly added to the reaction mixture at 0 °C and further stirred for 10 min at 0 °C and then at room temperature for 10 h. The reaction mixture was then washed with water (3 x 40 mL) and extracted with dichloromethane. The organic layer was separated, dried over anhydrous sodium sulfate and finally concentrated under reduced pressure afforded crude product, which was further purified by column chromatography (SiO2, ethyl acetate-pet ether 15:85) to afford **139** as a colorless thick liquid (1.66 g, 91 % yield).

Yield : 91 %

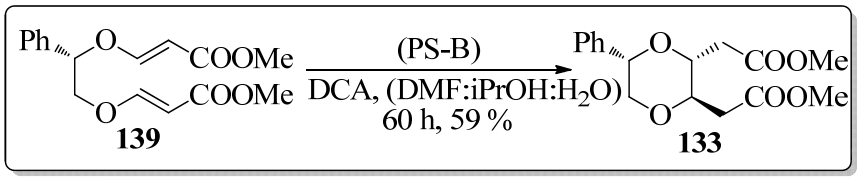
IR (film) γ_{max} cm^{-1} in $CHCl_3$: 1735, 1653, 1281, 1041, 923

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.65 (d, *J* = 11.88 Hz, 1H), 7.55 (d, *J* = 11.88 Hz, 1H), 7.45 (m, 5H), 5.28 (d, *J* = 11.88 Hz, 1H), 5.25 (d, *J* = 11.88 Hz, 1H), 5.21(dd, *J* = 10.8, 5.4 Hz, 1H), 3.72(s, 3H), 3.68(s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 167.74, 167.71, 161.85, 160.92, 135.21, 129.25, 129.09, 126.45, 99.10, 97.24, 81.95, 73.11, 51.18, 51.11

Mass (ESI): (*m/z*) : 307.21 (M^++H), 329.11 (M^++Na)

3. Dimethyl 2,2'-((2R,3R,5S)-5-phenyl-1,4-dioxane-2,3-diyl)diacetate 133 :

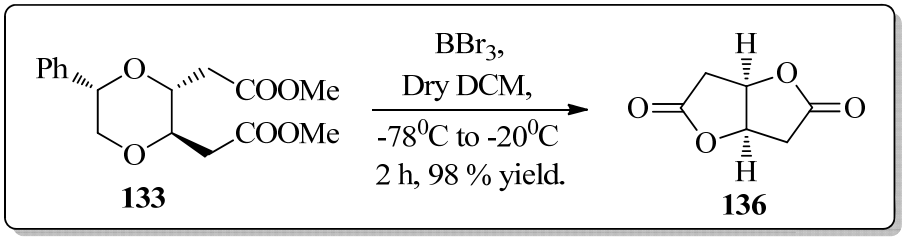


A solution of compound **139** (0.5 g, 1.63 mmol), DCA (0.16 g, 0.71 mmol), DMN (0.046 g, 0.25mmol) and ascorbic acid (0.75 g, 4.24 mmol) dissolved in a mixture of DMF: *i*-PrOH: H_2O (88: 10: 02), (700 mL), solvent was irradiated in a specially designed photoreactor, made-up of Pyrex glass consisted of three chambers. The first and outer most chamber contained the irradiation solution and the middle chamber was filled with filter solution prepared from $CuSO_4.5H_2O$ and 20% aq. solution of NH_3. 450 W Hannovia medium pressure mercury lamp was housed into a water

cooled double jacketed chamber which was immersed into the second one. The whole reaction mixture was deoxygenated by bubbling argon gas for 2 h. The progress of the reaction was monitored by GC, and after 60 h of irradiation, 80 % of **139** was consumed. The solvent was removed under reduced pressure to get crude product. The concentrate was dissolved in ethyl acetate (3 X 50 mL) and washed with water and saturated brine solution. The organic layer was dried over anhydrous sodium sulfate and finally concentrated under reduced pressure and purified by column chromatography (SiO_2, ethyl acetate-pet ether 10:90) to afford **133** as a light yellow thick liquid (0.29 g, 59 % yield).

Yield	:	59 %
$[\alpha]^{29}_D$	:	+ 60.83 (*c* = 2.05, MeOH)
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	2982, 2902, 1736, 1112, 1048, 755
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	7.39-7.31 (m, 5H), 4.68 (dd, *J* = 10.57, 2.74 Hz), 4.03-3.49 (m, 4H), 3.86 (2s, 6H), 2.64-2.53 (m, 4H)
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	171.01, 170.89, 137.11, 128.72, 128.29, 126.86, 126.11, 77.57, 75.80, 75.29, 72.31, 52.02, 51.52, 37.15, 36.88
Mass (ESI): (*m/z*)	:	309.38 (M^++1), 331.37 (M^++Na)

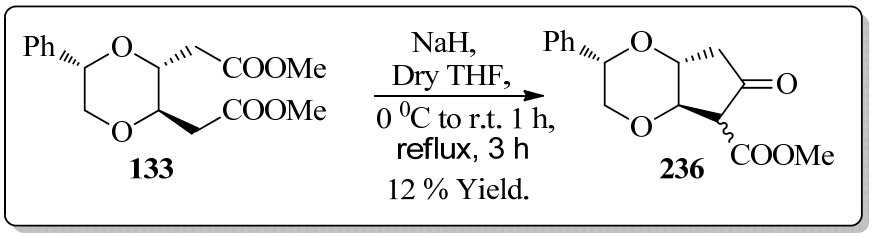
4. 2,6-dioxabicyclo[3.3.0]octane-3,7-dione 136 :



To a stirred solution of **133** (0.1 g, 0.32 mmol) in dry methylene chloride (5 mL) was added boron tribromide (BBr_3) (0.21 g, 0.81 mmol) in dry methelyne chloride (2 mL) dropwise at -78 °C. After completion of addition, the reaction mixture was stirred at -20 °C for 30 min and then at 0 °C for 1 h. Again slowly the temperature was raised to room temperature and stirred for another one hour. The reaction mixture was quenched by addition of (2 mL) of aqueous sodium bicarbonate solution and the reaction mixture was extracted with DCM (3 X 10 mL). The combined ether extracts were washed with brine and dried over anhydrous sodium sulfate and finally concentrated under reduced pressure to get crude product as a white amorphous powder, which was crystallized by using acetone- pet ether afforded colorless crystalline product **136** (mp = 132 °C), (0.045 g, 98 % yield).

Yield	:	98 %
$[\alpha]^{29}_{D}$	:	+ 124.48 (*c* = 0.21, H_2O)
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3023, 2958, 1783, 1401, 1191, 1165, 1051, 927.
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	5.26 (m, *2*H) , 2.98 (m, 2H)
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	206.97, 79.06, 34.94
Mass (ESI): (*m/z*)	:	143.02 (M^++H), 165.00 (M^++Na)

5. (2S,4aR,7aR)-methyl 6-oxo-2-phenylhexahydro-2H-cyclopenta[b][1,4]dioxine-5- carboxylate 236 :



A two necked oven dried 50 mL RB flask, equipped with a magnetic stirring bar and argon balloon, was charged with sodium hydride NaH (60 %) (0.015 g, 0.64 mmol) which was washed with dry pet ether (2 X 15 mL), the suspension was then completely dried by applying high vacuum. To the suspension of NaH, in dry THF (5 mL) was added a solution of **133** (0.2 g, 0.65 mmol) in dry THF (5 mL) dropwise at 0°C. After completion of addition, the reaction mixture was allowed to stir at ambient temperature for one hour, and then it was refluxed for 3 h. Then the reaction mixture was carefully quenched with saturated ammonium chloride solution at 0 ºC. The reaction mixture was then extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and finally concentrated over rotaevaporator and purified by column chromatography (SiO_2, ethyl acetate-pet ether 10:90) to afford the corresponding **236** as a light yellow liquid (0.021 g, 12 % yield).

Yield : 12 %

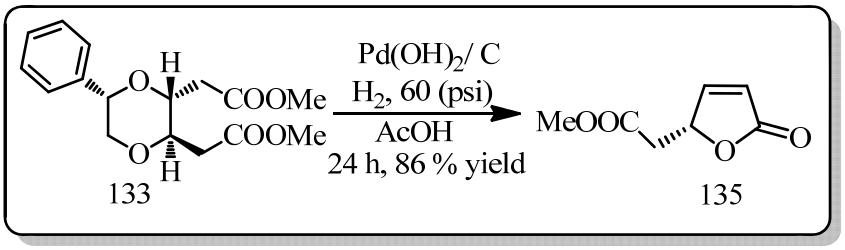
IR (film) γ_{max} cm^{-1} in $CHCl_3$: 2958, 1783, 1715, 1058, 928,

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.25 (m, *5*H), 5.51 (dd, *J* = 10.31, 1.18), 5.00(dd, *J* = 8.9, 1.6 Hz, 1H), 4.51-3.61 (m, 4H), 3.75 (s, 3H), 2.65-2.25 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ : 201.08, 170.78, 136.48, 127.91, 126.76, 126.00, 127.8,127.3, 80.58, 75.19, 72.21, 64.69, 60.27, 50.96, 39.13

Mass (ESI): (*m/z*) : 277.02 (M^++H), 299.23 (M^++Na)

6. (R)-methyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate 135 :



To a solution of **133** (0.2 g, 0.65 mmol) in glacial acetic acid (10 mL) was added $Pd(OH)_2/C$ (0.015 g, 20 mol %). The mixture was then hydrogenated over Parr shaker at 60 Psi for 24 h. The suspension was filtered over celite and concentrared under reduced pressure. The residue was washed with water (2X 10 mL) and extracted with ethyl acetate dried over anhydrous sodium sulfate and finally concentrated over vacuo gave crude product, which was purified by column chromatography (SiO_2, ethyl acetate-pet ether 5:95) to afford the corresponding **135** as a clear liquid (0.10 g, 86% yield).

Yield : 86 %

IR (film) γ_{max} cm^{-1} in $CHCl_3$: 1757, 1735, 1159, 1021, 792

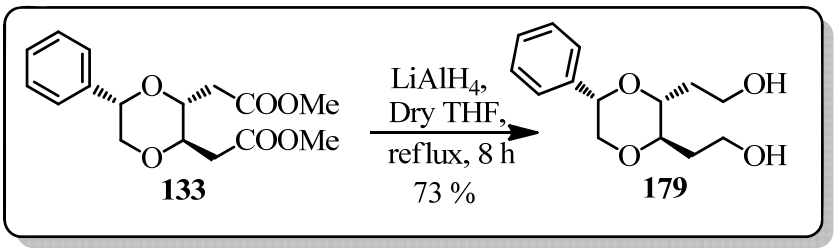
$[\alpha]^{29}_D$: + 83.21 (*c* = 0.48, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ : 6.85 (dd, *J* = 15.54, 4.30 Hz, 1H), 6.06 (d, *J* = 15.60, Hz, 1H), 4.67 (m, 1H), 3.67 (s, 3H), 2.53(m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 172.09, 166.88, 148.06, 120.65, 67.08, 51.73, 40.37

Mass (ESI): (*m/z*) : 157.08 (M^++H), 179.54 (M^++Na)

7. Synthesis of 2,2'-((2R,3R,5S)-5-phenyl-1,4-dioxane-2,3-diyl)diethanol 179 :



To a stirred solution of lithium aluminum hydride (0.11 g, 2.92 mmol) in anhydrous THF (30 mL) at 0°C was added a solution of **133** (0.6 g, 1.94 mmol) in anhydrous THF (10 mL) dropwise. After the addition was over, the reaction mixture was refluxed for 12 h. Then the reaction mixture was carefully quenched with 2N NaOH solution at 0°C. The resultant reaction mixture was filtered through sintered funnel and the solid was washed repeatedly with ethyl acetate (3 X 30 mL). The filtrate was dried over anhydrous sodium sulfate and finally concentrated over vacuo and purified by column chromatography (SiO_2, ethyl acetate-pet ether 65:35) to afford the corresponding diol **179** as a thick liquid (0.43 g, 73 % yield).

Yield : 73 %

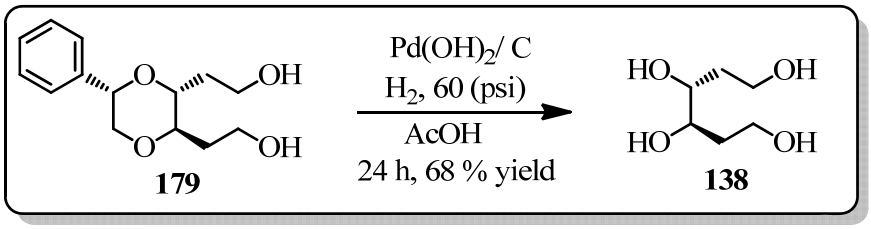
IR (film) γ_{max} cm^{-1} in $CHCl_3$: 3471, 2931, 1148, 1012, 734.

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.37-7.31 (m, 5H), 4.67 (dd, *J* = 10.37, 2.74 Hz, 1H), 3.90-3.48 (m, 8H), 3.10-2.98(brs, 2H), 1.83-1.64(m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 137.86, 128.50, 126.76, 126.13, 79.12, 78.24, 77.76, 72.20, 60.06, 59.96, 33.38, 33.21.

Mass (ESI): (*m/z*) : 253.26 (M^++H), 275.14 (M^++Na)

8. Synthesis of (3R,4R)-hexane-1,3,4,6-tetraol 142 :



To a solution of **179** (0.2 g, 0.79 mmol) in glacial acetic acid (10 mL) was added $Pd(OH)_2/C$ (0.02 g, 20 mol %) and was hydrogenated over Parr shaker at 60 Psi for 24 h. The suspension was filtered over celite and concentrared under reduced pressure. The residue was washed with water (2X 10 mL) and extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO_2, DCM-MeOH 95:05) to afford the corresponding **138** as a thick liquid (0.11 g, 68% yield).

Yield : 68 %

IR (film) γ_{max} cm^{-1} in $CHCl_3$: 3518, 1191, 1165, 1051, 927.

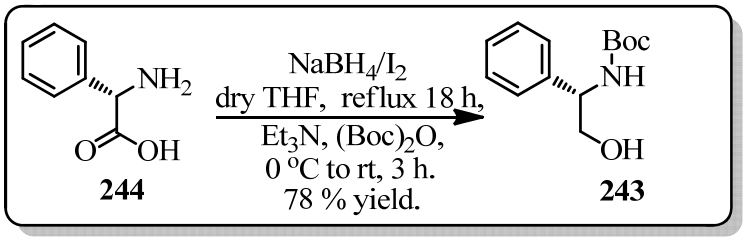
$[\alpha]^{29}_D$: + 40.81 (*c* = 0.93, MeOH)

^{1}H NMR (500 MHz, $CDCl_3$) δ : 3.87-3.64 (m, *6*H), 3.11-2.51 (bs, 4H), 1.73-1.64 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 72.44, 62.92, 32.13

Mass (ESI): (*m/z*) : 151.08 (M^++H), 173.10 (M^++Na)

9. (S)-tert-butyl (2-hydroxy-1-phenylethyl)carbamate 243 :



A oven dried 250 mL two necked round bottom flask equiped with magnetic stirring bar and argon balloon system was charged with sodium borohydride (6 g, 158.7 mmol) in 100 mL of anhydrous THF. The resulting suspension was cooled to 0°C, and with the pressure-equalizing dropping funnel was charged with a previously prepared solution of iodine (16.78 g, 66.15 mmol) in anhydrous THF(30 mL), was added drop by drop to the borohydride-THF suspension over 30 min. Compound **244** (10 g, 66.15 mmol) was added to the reaction mixture in small portions and refluxed for 18 h. The resultant reaction mixture was quenched with methanol cautiously at 0 ºC. It was then diluted with 50 mL of anhydrous THF and triethylamine (7.02 g, 69.45 mmol) was added in one portion with vigorous stirring, Di-*tert*-butyl dicarbonate (14.58 g, 66.81 mmol) was then added dropwise, followed by addition of 50 mL of anhydrous THF. The reaction mixture was then allowed to warm to room temperature and was stirred for another 3 h. The solvents were removed in vacuo and the resulting white solid was dissolved in ethyl acetate 100 mL and water 100 mL. To this stirred solution (1:1) solution of 1.2 N aqueous HCl (50 mL) and brine solution (50 mL) was added and the resultant reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with 50 mL (1:1) solution of saturated sodium hydrogen carbonate and brine solution, and finally with water. The combined organic phase was dried over anhydrous sodium sulfate and the solvent was removed in vacuo to afford crude residue, which was further purified by column

chromatography (SiO_2, ethyl acetate/ pet ether 40:60) to afford the corresponding **243** as white crystalline solid (12.24 g, 78% yield).

Yield : 78 %

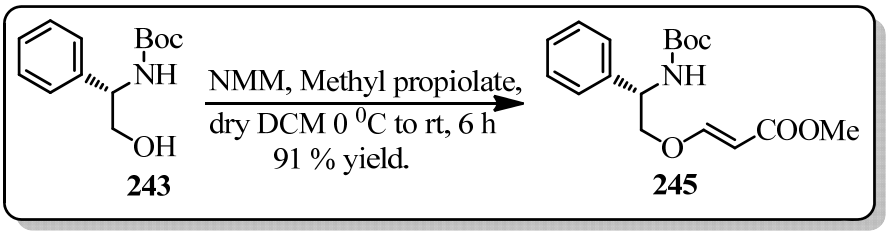
IR (film) γ_{max} cm^{-1} in $CHCl_3$: 3023, 2958, 1783, 1165, 1051, 927.

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.37-7.27 (m, *5*H), 4.77 (t, *J* = 4.92, 9.85 Hz, 1H), 3.89-3.78 (m, *2*H), 2.05 (brs, 1H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 161.92, 138.69, 128.80, 128.01, 126.70, 80.14, 73.05, 59.61, 28.32

Mass (ESI): (*m/z*) : 238.13 (M^++H), 260.63 (M^++Na)

10. (S,E)-methyl 3-(2-((tert-butoxycarbonyl)amino)-2-phenylethoxy)acrylate 245:



To a stirred solution of N-methylmorpholine (NMM) (0.51 g, 5.06 mmol) in anhydrous dichloromethane (DCM) (15 mL), was slowly added methyl propiolate (0.42 g, 5.06 mmol) in DCM (5 mL) at 0°C. The resultant reaction mixture was stirred for 10 min at 0°C, then a solution of **243** (1.0 g, 4.21 mmol) in DCM (10 mL) was slowly added to the reaction mixture at 0 °C, and the reaction mixture was further stirred for another 10 min. The cooling bath was removed and the reaction mixture

stirred at ambient temperature for 10 h. The reaction mixture was then washed with water (3 x 40 mL) and extracted with dichloromethane. The organic layer was separated, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO_2, ethyl acetate-pet ether 20:80) to afford **242** as a light yellow thick liquid (1.23 g, 91 % yield).

Yield : 91 %

IR (film) γ_{max} cm^{-1} in $CHCl_3$: 3041, 2951, 1735, 1653, 1281, 1041, 923

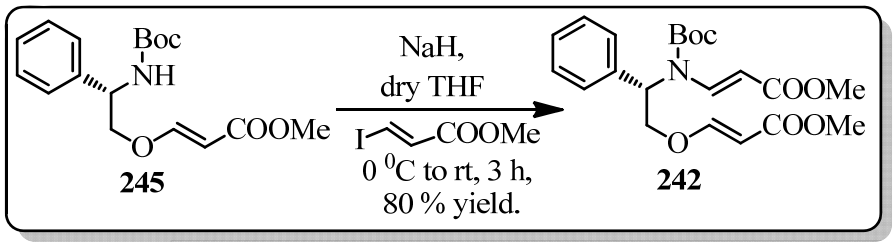
^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.43 (d, *J* = 12.63 Hz, 1H), 7.24-7.12 (m, 5H), 5.09 (d, *J* = 12.63 Hz, 1H), 5.14-5.04 (m, 1H), 4.84 (bs, 1H), 3.99-3.85 (m, 2H), 3.53 (s, 3H), 1.28 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ : 167.90, 161.92, 155.14, 138.69, 128.80, 128.01, 126.70, 96.97, 80.14, 73.05, 51.19, 28.32

Mass (ESI): (*m/z*) : 322.19 (M^++H), 344.30 (M^++Na)

11. (E)-methyl 3-((S)-2-((tert-butoxycarbonyl)((E)-3-methoxy-3-oxoprop-1-en-1-yl)amino)-

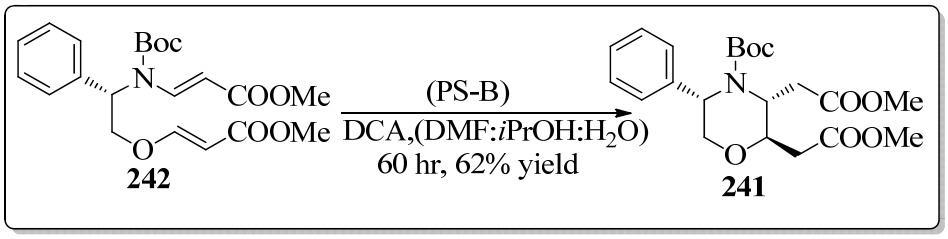
2-phenylethoxy)acrylate 242 :



A oven dried 50 mL two necked RB flask, equipped with a magnetic stirring bar and argon balloon, was charged with sodium hydride NaH (60 %) (0.089 g, 3.73 mmol) and was washed with dry pet ether (2 X 5 mL), and dried by applying high vacuum. To this suspension of NaH in dry THF (10 mL) was added a solution of **245** (1.0 g, 3.11 mmol) in dry THF (10 mL) dropwise at 0°C. After complete addition, the reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was then carefully quenched with saturated ammonium chloride solution at 0 ºC. The reaction mixture was then extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and finally concentrated over vacuo and purified by column chromatography (SiO_2, ethyl acetate-pet ether 10:90) to afford the corresponding **242** as a light yellow liquid (1.09 g, 80 % yield).

Yield	:	80 %
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3044, 1735, 1653, 1281, 1161, 1028, 727
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	8.30 (d, *J* = 14.40 Hz, 1H), 7.67 (d, *J* = 12.64 Hz, 1H), 7.41-7.23 (m, 5H), 5.46 (dd, *J* = 13.64, 6.82 Hz, 1), 5.36 (d, *J* = 14.40 Hz, 1H), 5.29 (d, *J* = 12.64 Hz, 1H), 4.61 (d, *J* = 6.82 Hz, 2H), 3.75(s, 3H), 3.72 (s, 3H), 1.48 (s, 9H)
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	167.93, 167.72, 161.49, 152.01, 142.90, 136.00, 128.88, 128.07, 126.67, 126.15, 98.69, 97.26, 84.07, 70.02, 56.37, 51.30, 52.21, 27.90
Mass (ESI): (*m/z*)	:	406.41 (M^++H), 428.53 (M^++Na)

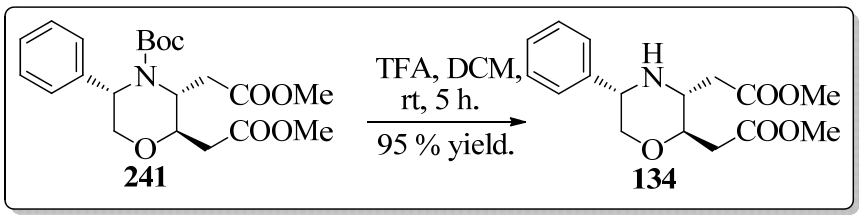
12. Dimethyl 2,2'-((2R,3R,5S)-4-(tert-butoxycarbonyl)-5-phenylmorpholine-2,3-diyl) diyl)diacetate 241 :



A solution of compound **242** (0.6 g, 1.48 mmol), DCA (0.168 g, 0.74 mmol), DMN (0.055 g, 0.29mmol) and ascorbic acid (0.75 g, 4.24 mmol) dissolved in a mixture of DMF: *i*-PrOH: H_2O (700 mL, 88:10:02) solvent, was irradiated in a specially designed photoreactor, made-up of Pyrex glass consisted of three chambers. The first and outer most chamber contained the irradiation solution and the middle chamber was filled with filter solution prepared from $CuSO_4.5H_2O$ and 20% aq. solution of NH_3. 450 W Hannovia medium pressure mercury lamp was housed into a water cooled double jacketed chamber which was immersed into the second one. The whole reaction mixture was deoxygenated by bubbling argon gas for 2 h. The progress of the reaction was monitored by GC. After 60 hours of irradiation, the solvent was removed under reduced pressure. The concentrate was dissolved in ethyl acetate (3 X 50 mL) and washed with water and saturated brine solution. The combined organic layer was separated, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO2, ethyl acetate-pet ether 10:90) to afford **241** as a light yellow thick liquid (0.37 g, 62 % yield).

Yield	:	62 %
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3023, 2958, 1783, 1401, 1343, 1191, 1165, 1051, 927
Mass (ESI): (*m/z*)	:	408.49 (M^++H), 430.50 (M^++Na)

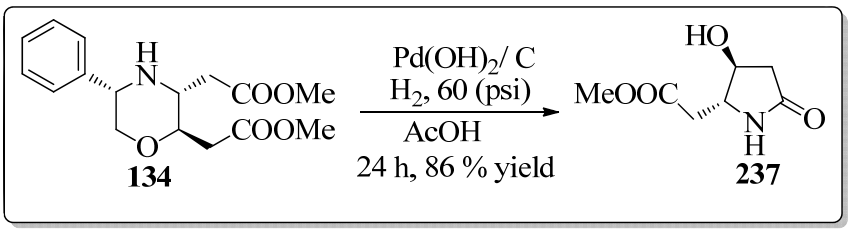
13. Dimethyl 2,2'-((2R,3R,5S)-5-phenylmorpholine-2,3-diyl)diacetate 134 :



To a stirred solution of **241** (0.45 g, 1.11 mmol) in dry dichloromethane (30 mL) was added trifluoroacetic acid (0.42 mL, 5.55 mmol) dropwise. It was then stirred at ambient temperature for 5 h. Then the reaction mixture was concentrated over vacuo, neutralized with satureted aqueous sodium hydrogen carbonate and extracted with dichloromethane (2 X 15 mL). The combined organic layer was washed with brine solution and concentrated under reduced pressure and purified by column chromatography (SiO_2, ethyl acetate-pet ether 70:30) to afford **134** as a clear liquid (0.32 g, 95 % yield).

Yield	:	95 %
$[\alpha]^{29}_D$	:	+ 79.17 (c = 0.61, $CHCl_3$)
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3248, 3023, 2958, 1735, 1585, 910
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	7.37-7.27 (m, 5H), 3.95 (dd, J = 9.64, 3.54 Hz, 1H), 3.79-3.65 (m, 3H), 3.96 (2s, 6H), 3.51 (t, J = 18.1, 9.54 Hz, 1H), 2.76 (dd, J = 12.04, 6.77 Hz, 1H$_7$), 2.61(dd, J =12.06, 5.08 Hz, 1 H$_{7'}$), 2.72 (dd, J = 12.55, 6.80 Hz, 1 H$_6$), 2.55 (dd, J = 12.80, 6.53 Hz, 1 H$_{6'}$), 2.29 (bs, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	173.11, 172.03, 140.35, 129.24, 128.43, 127.56, 76.00, 66.28, 62.45, 56.37, 52.02, 51.52, 36.89, 34.79
Mass (ESI): (*m/z*)	:	308.11 (M^++H), 330.15 (M^++Na)

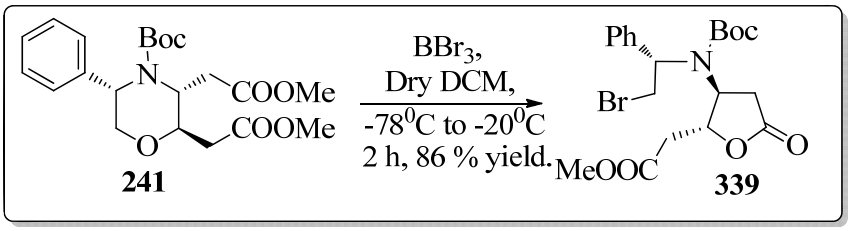
14. Methyl 2-((2R,3S)-3-hydroxy-5-oxopyrrolidin-2-yl)acetate 237 :



To a solution of **134** (0.2 g, 0.65 mmlo) in glacial acetic acid (10 mL) was added $Pd(OH)_2/C$ (0.015 g, 20 mol %) and it was subjected for hydrogenation over Parr shaker at 60 Psi for 24 h. The suspension was filtered over celite and concentrared under reduced pressure. The resultant residue was washed with (2X 10 mL) water and extracted with ethyl acetate. The combined organic layer was subsequently washed with brine and dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO_2, MeOH- DCM, 5:95) to afford the corresponding **237** as a sticky solid (0.096 g, 86% yield).

Yield	:	86%
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3640, 3220, 1677, 1735
$[\alpha]^{29}_D$	:	+ 24.71 (*c* = 0.61, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	4.68 (ddd, *J* = 10.54, 6.03, 4.51 Hz, $1H_5$), 4.29 (m, $1H_4$), 3.77 (s, 3H), 3.7 (bs, 1H), 2.90 (dd, *J* = 18.06, 8.08 Hz, $1H_3$), 2.61(dd, *J* = 18.06, 5.08 Hz, 1 $H_{3'}$), 2.84 (dd, *J* = 13.56, 4.52 Hz, 1 H_6), 2.74 (dd, *J* = 13.56, 4.52 Hz, 1 $H_{6'}$)
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	180.88, 175.53, 74.89, 64.01, 54.96, 42.64, 41.51
Mass (ESI): (*m/z*)	:	174.10(M^++H), 196.00(M^++Na)

15. Methyl 2-((2R,3S)-3-(((S)-2-bromo-1-phenylethyl) (tert-butoxycarbonyl) amino)-5-oxotetrahydrofuran-2-yl)acetate 339:



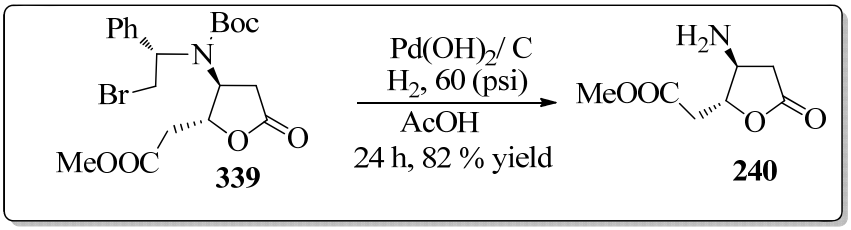
To a stirred solution of **241** (0.3 g, 0.74 mmol) in dry methylene chloride (15 mL) was added boron tribromide (BBr_3) (0.18 g, 0.74 mmol) in dry DCM (2 mL) dropwise at -78 °C. After completion of addition, the reaction mixture was stirred at -20 °C for 30 min and then at 0 °C for 1 h. Again slowly the temperature was raised to room temperature and stirred for another one hour. The reaction mixture was quenched by addition of (2 mL) of aqueous sodium bicarbonate solution and the reaction mixture was extracted with DCM (3 X 10 mL). The combined ether extracts were washed with brine and dried over anhydrous sodium sulfate, concentrated and purified by column chromatography(SiO_2, ethyl acetate-pet ether, 30:70) to afford the corresponding **268** as a light brown liquid (0.2 g, 62% yield).

Yield : 86 %

IR (film) γ_{max} cm^{-1} in $CHCl_3$: 3023, 2958, 1783, 1401, 1343, 1191, 1165, 1051, 927

Mass (ESI): (*m/z*) : 456.09 (M^++H), 478.21 (M^++Na)

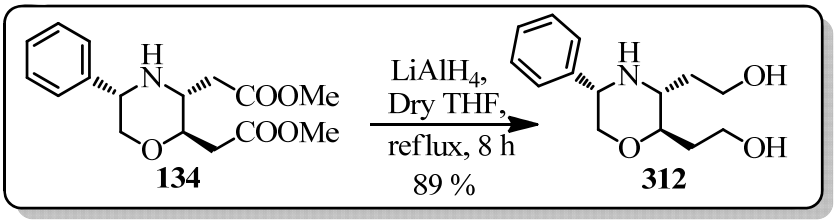
16. Methyl 2-((2R,3S)-3-amino-5-oxotetrahydrofuran-2-yl)acetate 240 :



To a solution of **339** (0.2 g, 0.44 mmlo) in glacial acetic acid (10 mL) was added $Pd(OH)_2/C$ (0.045 g, 20 mol %) and hydrogenated over Parr shaker at 60 Psi for 12 h. The suspension was filtered over celite and concentrared under reduced pressure. The resultant residue was washed with (1:1) mixture of water and brine solution (2X 10 mL) and extracted with ethyl acetate. The combined organic layer was subsequently washed with brine, dried over anhydrous sodium sulfate and finally concentrated over vacuo afforded **240** as a crude product, which was further purified by column chromatography (SiO_2, MeOH- DCM, 5:95) to afford the corresponding **240** as a clear liquid (0.096 g, 82% yield).

Yield	:	82 %
$[\alpha]^{29}_D$	:	+53.40 (c = 0.48, MeOH)
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3442, 3360, 1775, 1735, 1619, 1281
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	4.22 (ddd, *J* = 6.10, 3.67, 3.05 Hz, $1H_5$), 3.72 (m, 1H), 3.70 (s, 3H), 3.77 (bs, 2H), 2.75 (dd, *J* = 16.48, 6.71 Hz, $1H_3$), 2.55(dd, *J* = 16.48, 8.24 Hz, 1 $H_{3'}$), 2.72 (dd, *J* = 17.40, 6.72 Hz, 1 H_6), 2.21 (dd, *J* = 13.40, 3.682 Hz, 1 $H_{6'}$).
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	172.11, 169.27, 80.12, 60.33, 52.31, 37.37, 34.37
Mass (ESI): *(m/z)*	:	174.12 (M^++H), 196.11 (M^++Na).

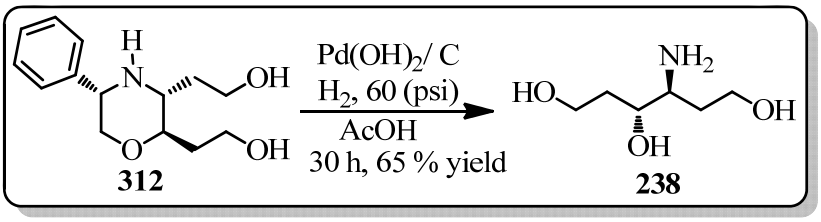
17. Synthesis of 2,2'-((2R,3R,5S)-5-phenylmorpholine-2,3-diyl)diethanol 312 :



The stirred solution of lithium aluminum hydride (0.055 g, 1.45 mmol) in anhydrous THF (30 mL) was added dropwise solution of **134** (0.3 g, 0.97 mmol) in anhydrous THF (10 mL) at 0°C. After the addition was over, the resultant reaction mixture was refluxed for 12 h, then cooled to room temperature. The reaction mixture was then carefully quenched with 2N NaOH solution at 0 ºC. The resultant reaction mixture was filtered through sintered funnel and the solid was washed repeatedly with ethyl acetate (3 X 30 mL). The filtrate was dried over anhydrous sodium sulfate and finally concentrated over vacuo and purified by column chromatography (SiO_2, ethyl acetate-pet ether 95:05) to afford the corresponding diol **312** as a thick liquid (0.21 g, 89 % yield).

Yield	:	89 %
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3540, 3288, 2850, 1585, 1220, 915
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	7.38-7.30 (m, 5H), 3.9-3.48 (m, 9H), 2.85 (m, 1H), 1.83-1.64 (m, 4H).
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	137.86, 128.50, 128.19, 126.13, 80.04, 72.20, 61.03, 60.12, 59.29, 54.63, 33.81, 31.91.
Mass (ESI): (*m/z*)	:	252.16 (M^++H), 274.21 (M^++Na)

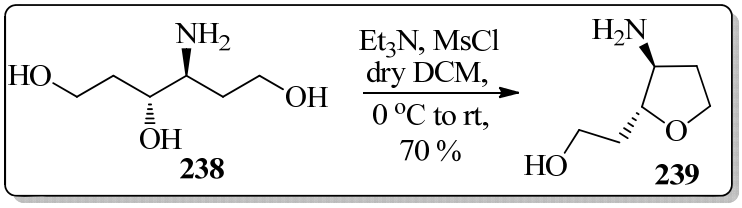
18. Synthesis of (3R,4S)-4-aminohexane-1,3,6-triol 238 :



To a solution of **312** (0.24 g, 0.95 mmlo) in glacial acetic acid (10 mL) was added $Pd(OH)_2/C$ (0.050 g, 20 %) and it was hydrogenated over Parr shaker at 60 Psi for 24 h. The suspension was filtered over celite and concentrared under reduced pressure. The residue was washed with (1:1) mixture of water and brine solution (2X 10 mL) and extracted with ethyl acetate. The combined organic layer was subsequently washed with brine dried over anhydrous sodium sulfate and finally concentrated over vacuo afforded 208 as a crude product, was further purified by column chromatography (SiO_2, MeOH- DCM, 5:95) to afford the corresponding **238** as a clear thick liquid (0.092 g, 65% yield).

Yield	:	65 %
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3600-3518, 2990, 1580, 1470, 1320, 1250, 910
$[\alpha]^{29}_D$	:	+66.31 (*c* = 0.24, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	3.77-3.47 (m, 5H), 2.60 (dt, *J* = 7.07, 1.64 Hz, 1H), 1.73-1.59 (m, 4H)
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	73.10, 61.63, 58.88, 51.24, 36.48, 35.98
Mass (ESI): (*m/z*)	:	150.18 (M^++H), 172.11 (M^++Na)

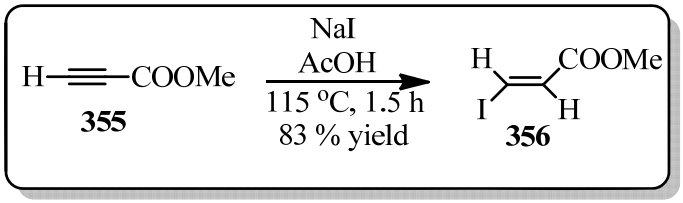
19. 2-((2R,3S)-3-aminotetrahydrofuran-2-yl)ethanol 239 :



To a stirring solution of **238** (0.1 g, 0.67 mmol), in dry DCM (10 mL), was added anhydrous triethyl amine (Et_3N, 0.11 mL, 0.73 mmol) dropwise at 0 °C. After 30 min, mesyl chloride (MsCl) (0.05 mL, 0.73 mmol) was added dropwise and the resulting reaction mixture was stirred for another 3 h at 0 °C. The reaction mixture was stirred at ambient temperature for another 2 h. Then the reaction mixture was quenched with saturated ammonium chloride and the resultant reaction mixture was washed with (1:1) mixture of water and brine solution (2 X 10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was subsequently washed with brine dried over anhydrous sodium sulfate and finally concentrated over vacuo afforded 208 as a crude product, was further purified by column chromatography (SiO_2, MeOH- DCM, 5:95) to afford the corresponding **239** as a clear thick liquid (0.061 g, 70 % yield).

Yield	:	70 %
IR (film) γ_{max} cm^{-1} in $CHCl_3$	:	3200-2300, 2190, 1650, 1610, 1510
$[\alpha]^{29}_D$	:	+36.81 (*c* = 0.64, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	4.02 (ddd, *J* = 9.98, 7.83, 2.05 Hz 1H), 3.80 (t, *J* =12.26, 6.07 Hz, 2H), 3.61- 3.50 (m, 2H), 2.97 (m, 1H), 2.20-1.57 (m, 4H).
^{13}C NMR (125 MHz, $CDCl_3$) δ	:	81.76, 68.39, 61.42, 58.89, 53.44, 33.70.
Mass (ESI): (*m/z*)	:	132.18 (M^++H), 154.87 (M^++Na)

20. Preparation of (E)-methyl 3-iodoacrylate 356 :



A two neck RB flask containing a mixture of methyl propiolate **355** (2.11 ml, 23.78 mmol), sodium iodide (5.7 g, 38.06 mmol) and glacial acetic acid (8.71 mL, 125.25 mmol) was placed in a preheated oil bath. The resultant reaction mixture was stirred at 115 °C for 1.5 h. Then the brown reaction mixture was transferred while hot to a separating funnel containing water (~8 mL per mmol of ester substrate). The reaction flask was washed with a mixture of water and diethyl ether (10:40 mL). The organic phase seperated was collected and the aqueous phase was washed with diethyl ether. The combined organic phases were washed subsiquently with saturated aqueous sodium bicarbonate, 1 M aqueous sodium thiosulfate, brine solution respectively and dried over anhydrous sodium sulfate and concentrated over vacuo. Distillation of the remaining material (40 °C/ 0.03 Torr) from basic alumina (~ 30 mg per mmol of ester substrate) provided the the **356** (4 g, 83 % yield).

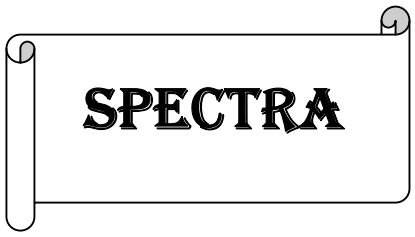
Yield : 83 %

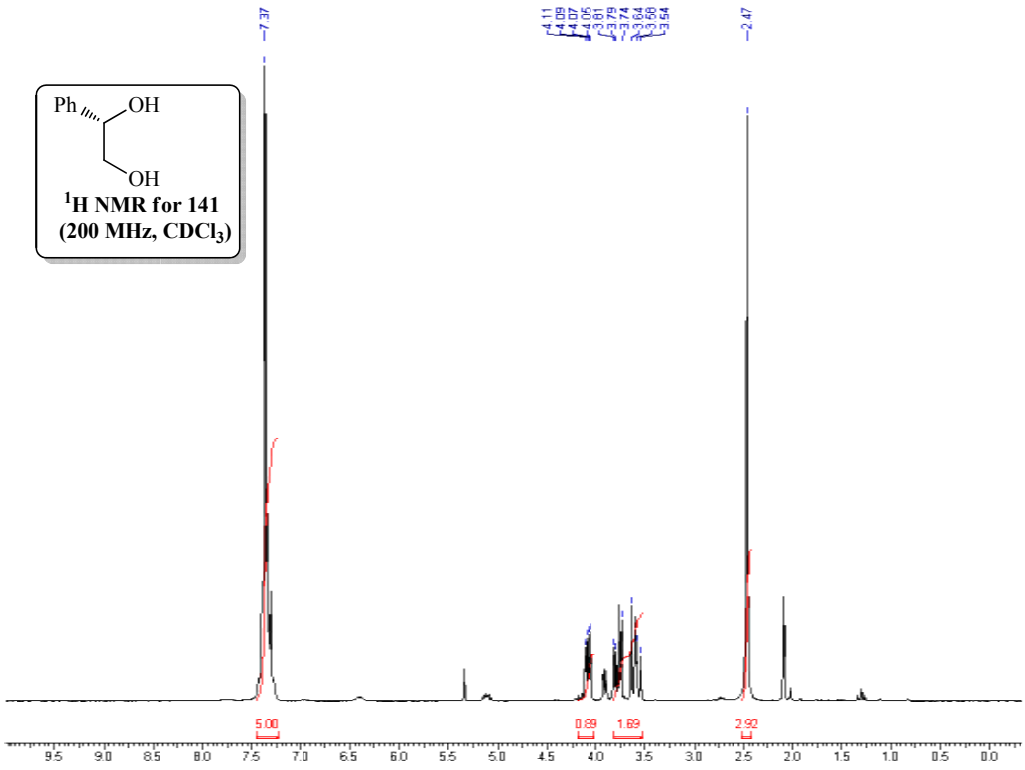
^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.47 (d, *J* = 8.97 Hz, 1H), 6.90 (d, *J* = 8.97 Hz, 1H), 3.75 (s, 3H)

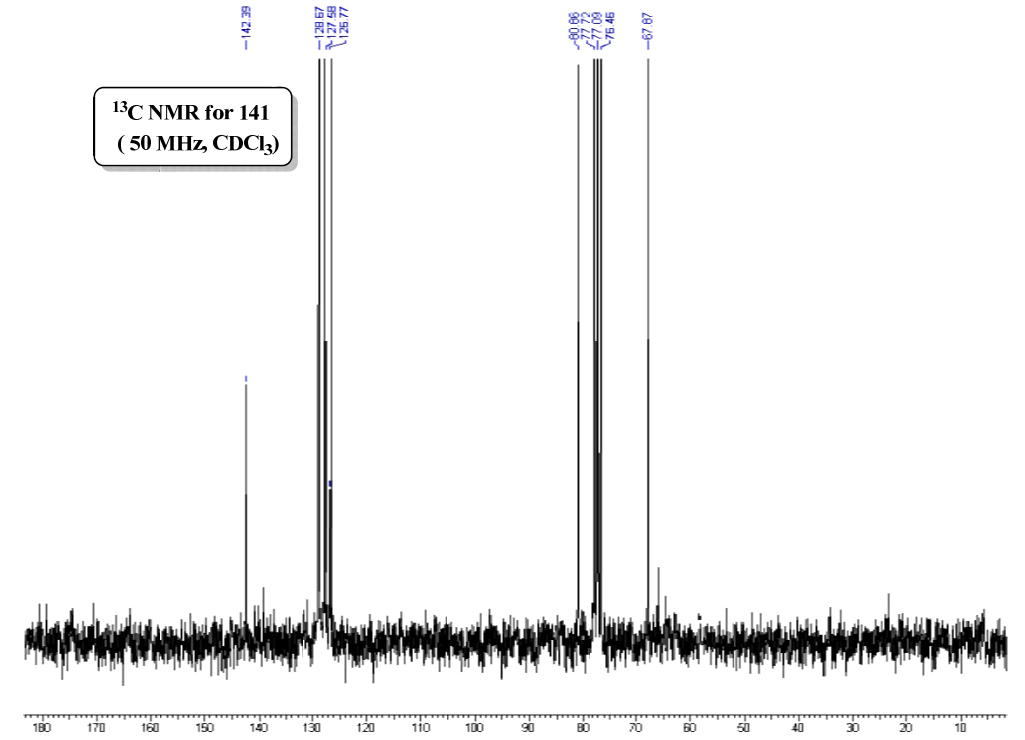
^{13}C NMR (125 MHz, $CDCl_3$) δ : 165.00, 129.58, 95.08, 51.67.

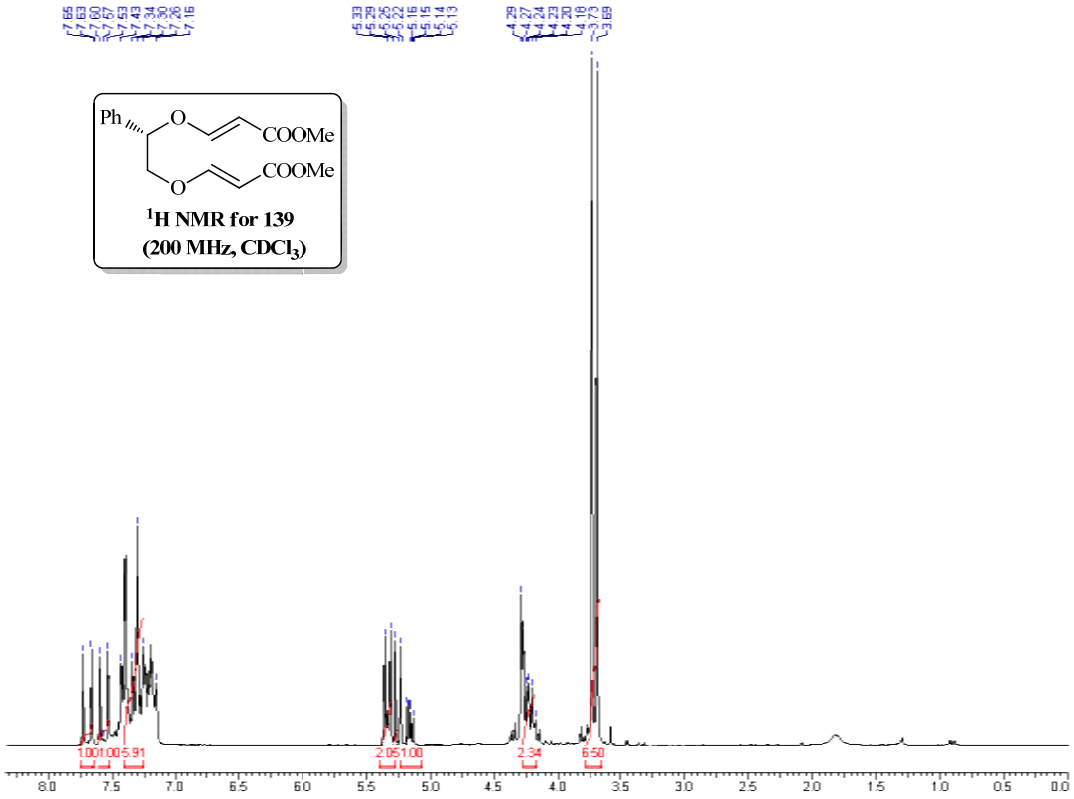
Mass (ESI): (*m/z*) : 212.93 (M^++H), 235.11 (M^++Na)

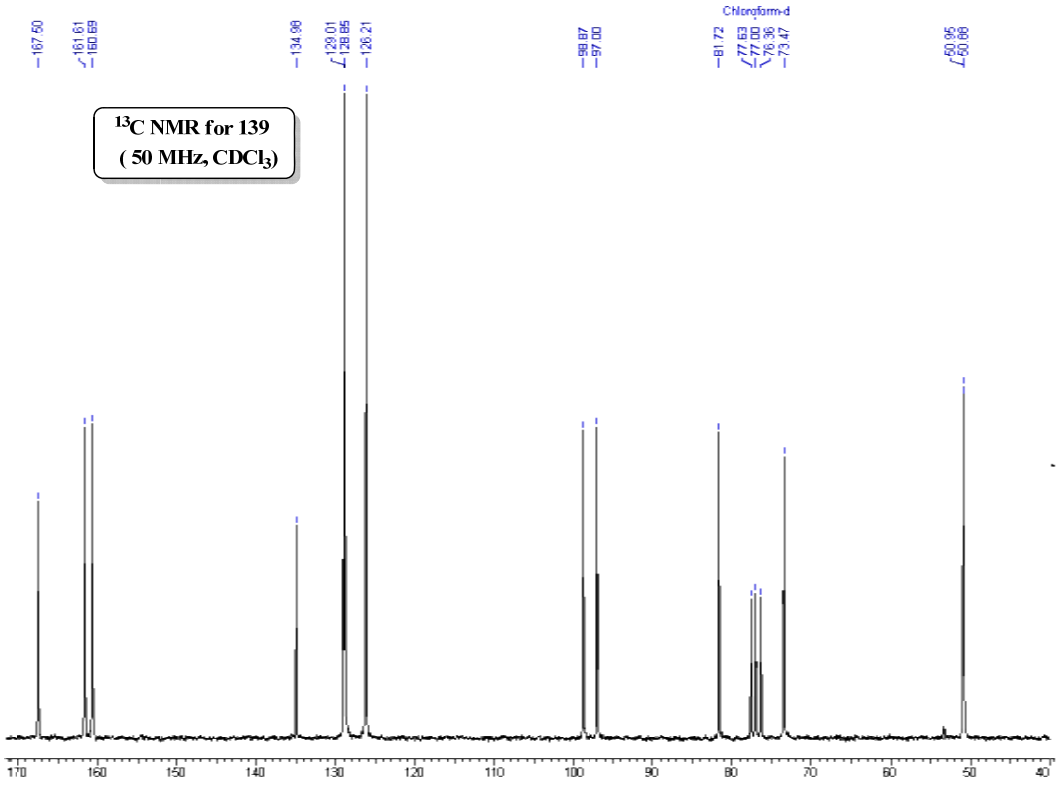
1) Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 4th ed., Butterworth Heinemann, 1999

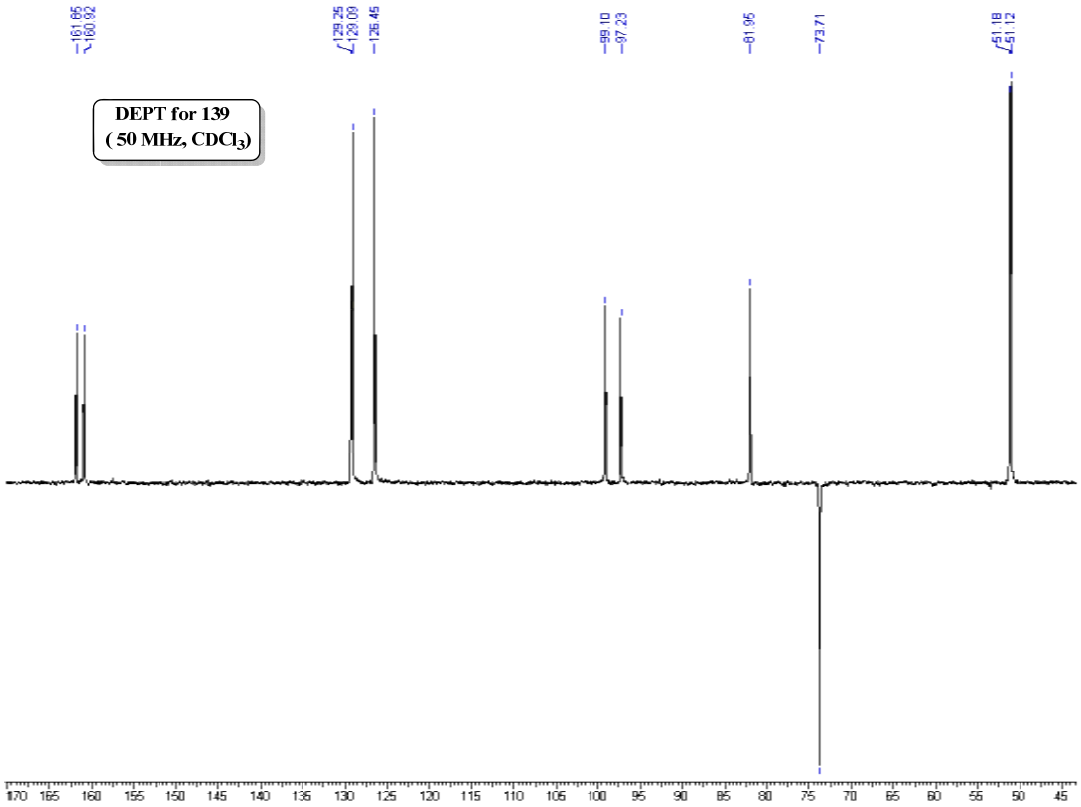

SPECTRA

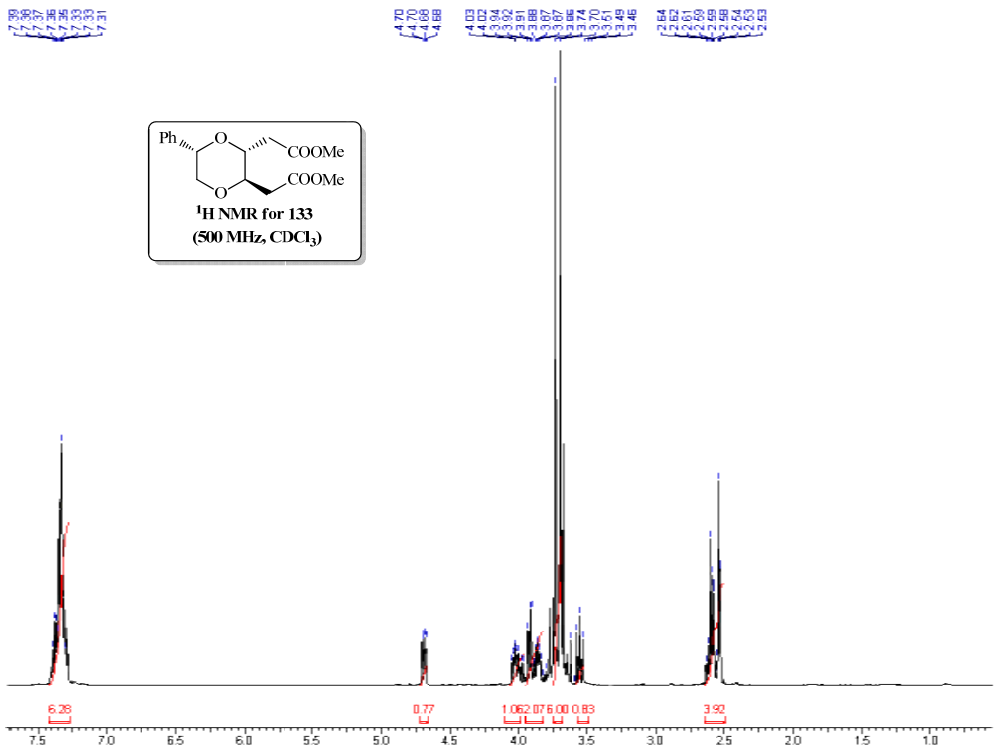

Ph
OH
OH
^{1}H NMR for 141
(200 MHz, CDCl$_3$)
7.37
4.11
4.09
4.07
4.05
4.01
3.79
3.74
3.64
3.56
3.54
2.47
5.00
0.89
1.89
2.92

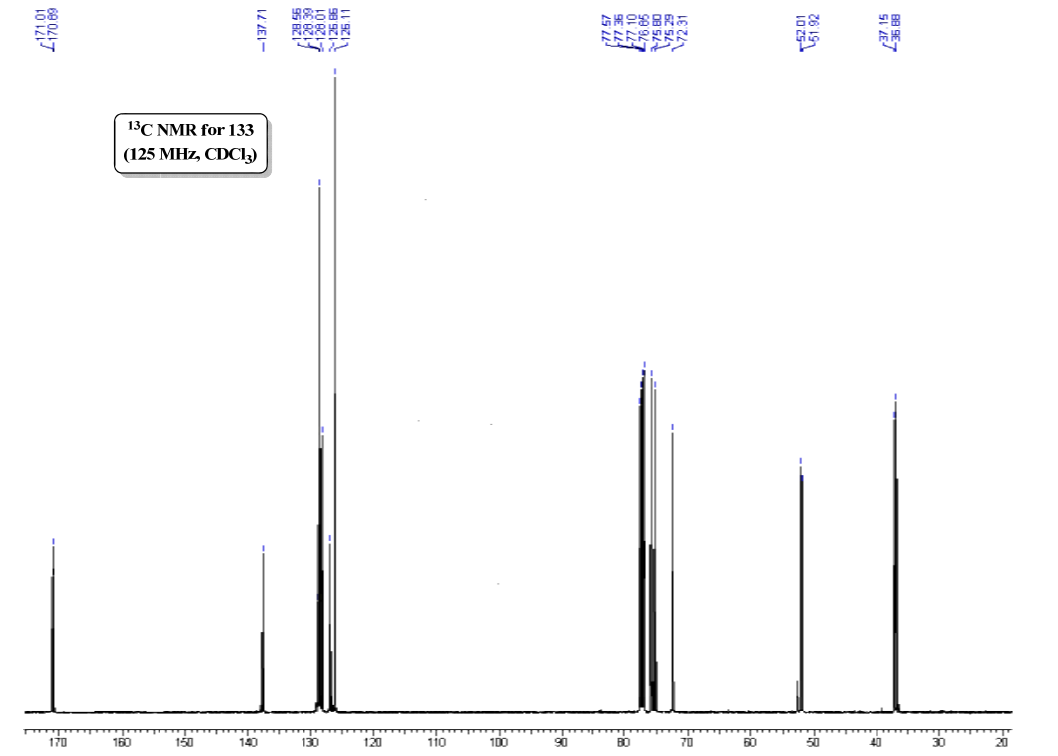

^{13}C NMR for 141
(50 MHz, CDCl$_3$)
142.39
138.67
128.69
127.79
126.77
90.86
77.73
77.09
76.46
67.87

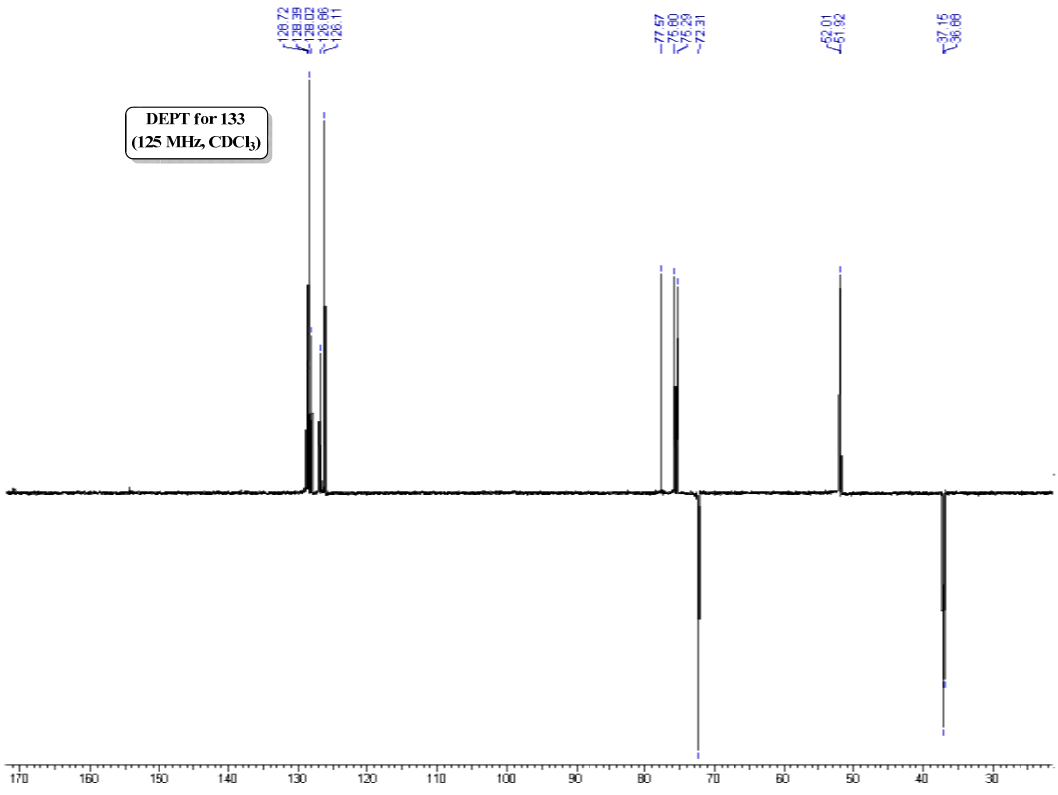

Ph
O
COOMe
COOMe
O
^{1}H NMR for 139
(200 MHz, CDCl$_3$)


Chloroform-d
^{13}C NMR for 139
(50 MHz, CDCl$_3$)

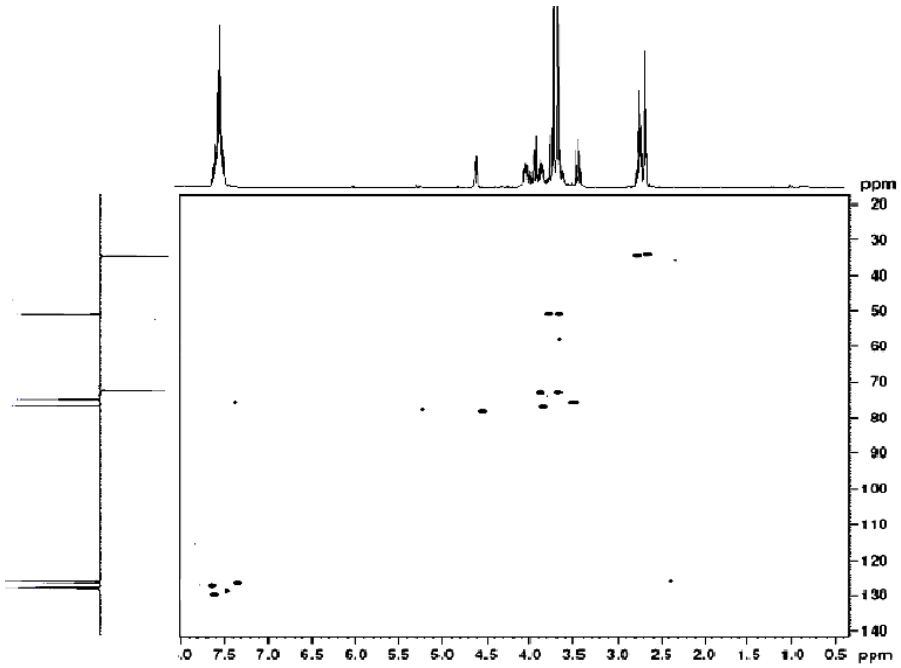

DEPT for 139
(50 MHz, CDCl3)


Ph
O
COOMe
COOMe
O
1H NMR for 133
(500 MHz, CDCl3)

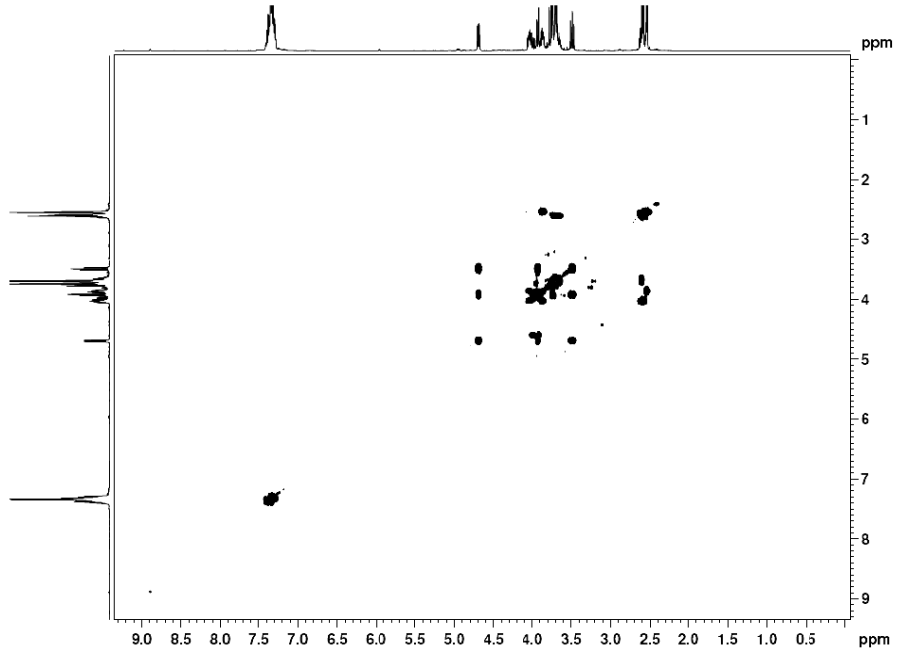

171.01
170.69
137.71
129.56
129.39
129.01
126.86
126.11
77.57
77.36
77.10
76.85
75.60
75.29
72.31
52.01
51.92
37.15
36.88
13C NMR for 133
(125 MHz, CDCl3)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


128.72
129.39
129.02
126.86
126.11
77.57
75.60
75.29
72.31
52.01
51.92
37.15
36.88
DEPT for 133
(125 MHz, CDCl3)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

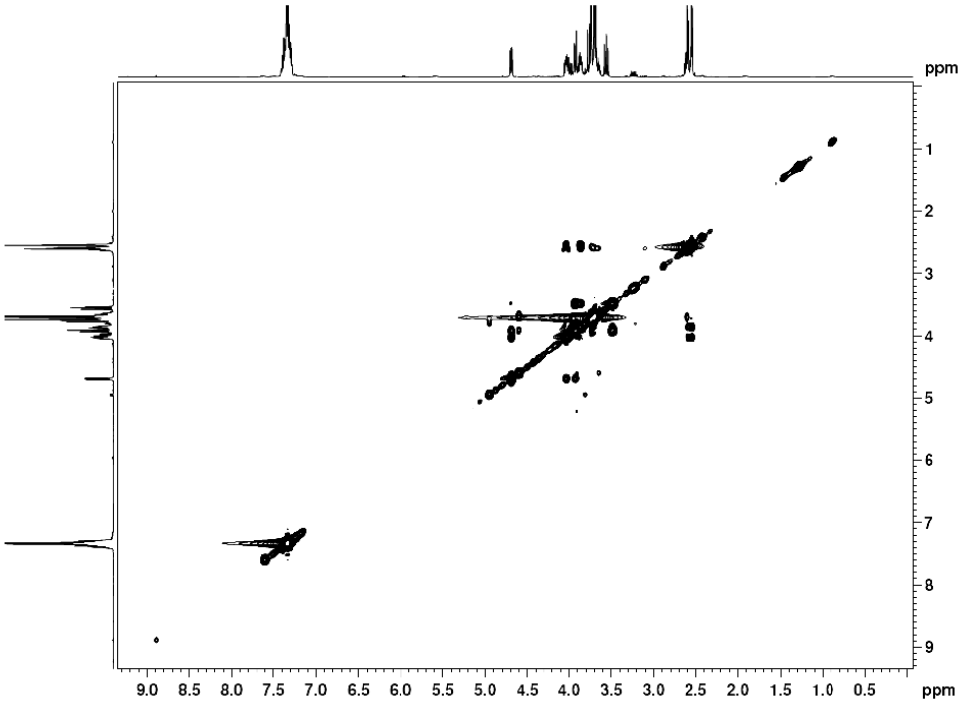
HSQC for **133**

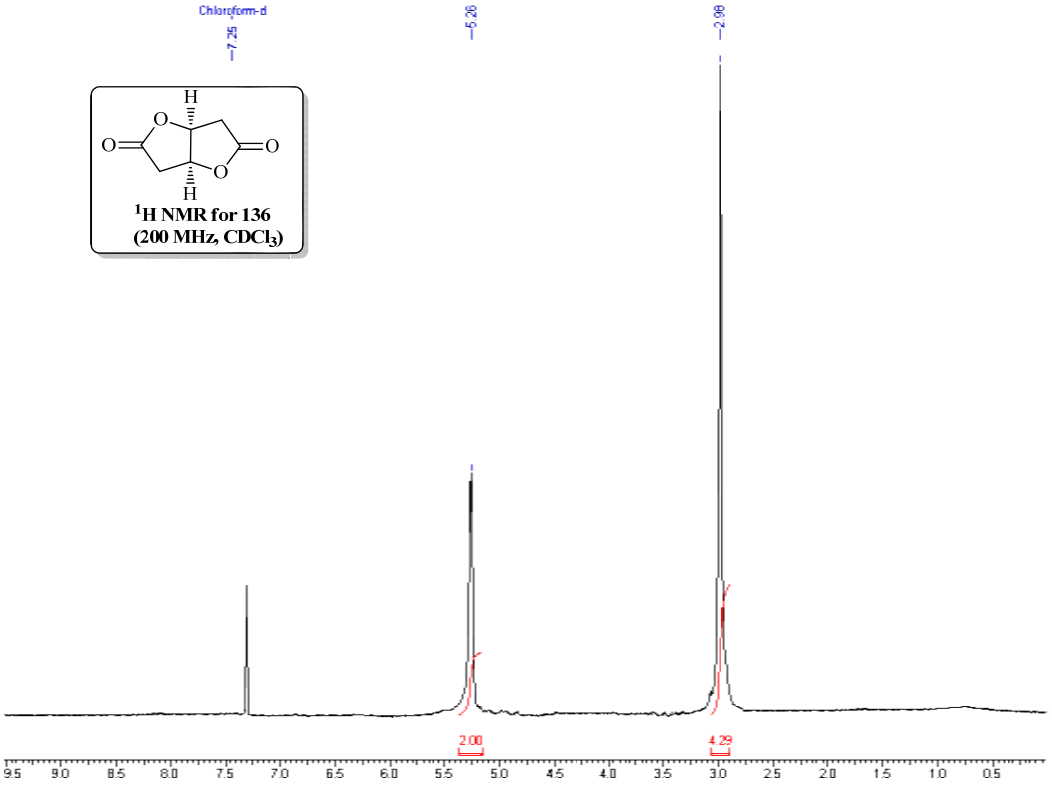


COSY

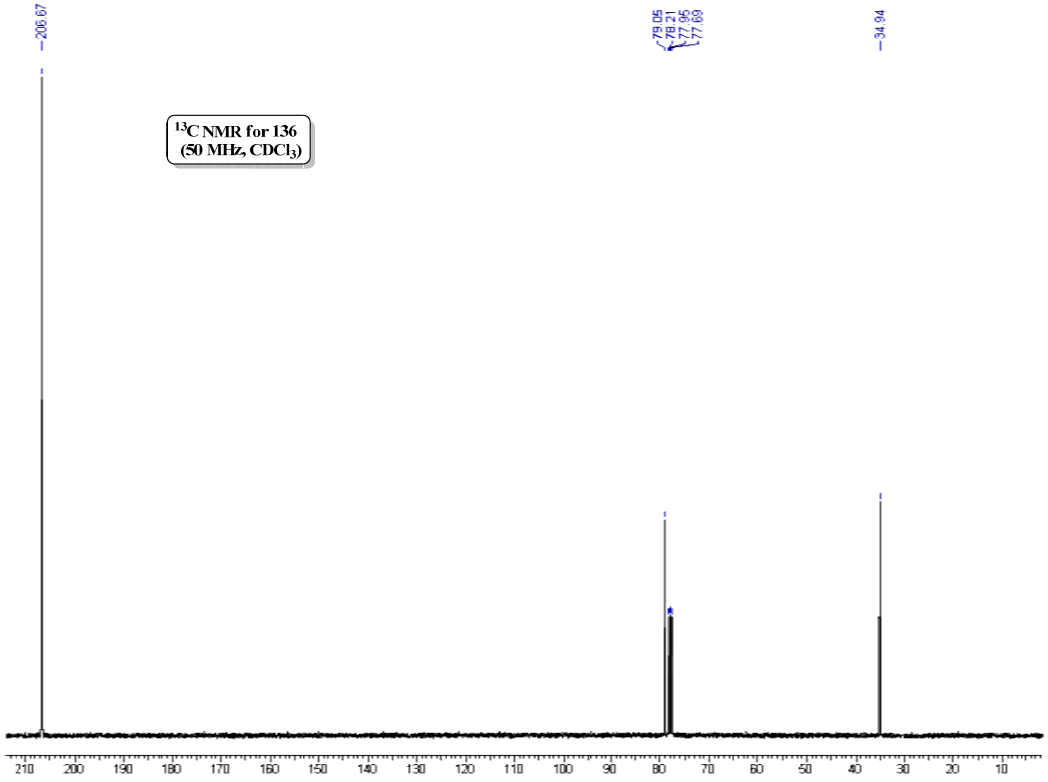


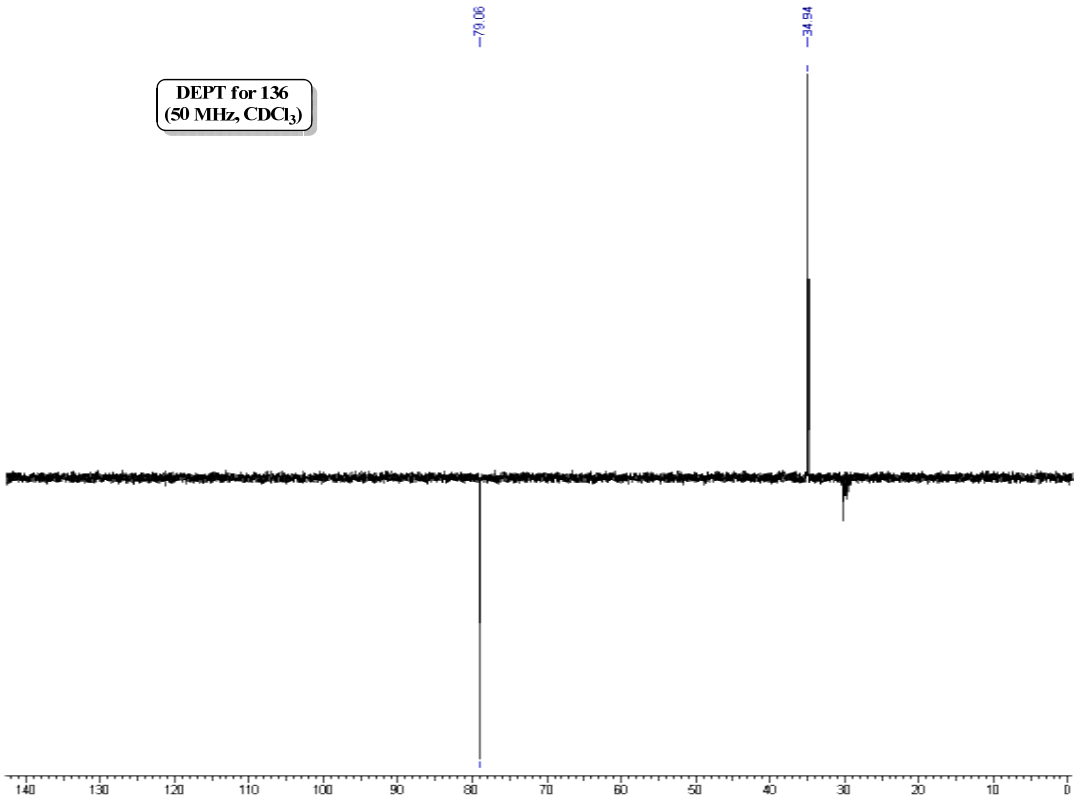
NOESY

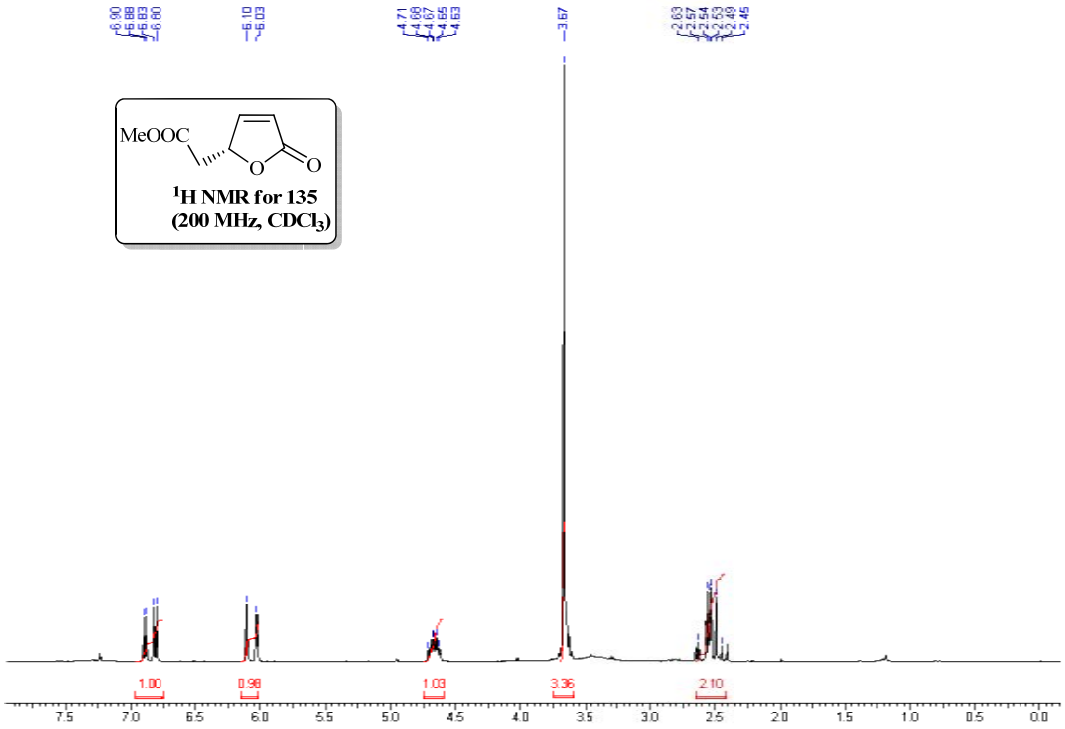


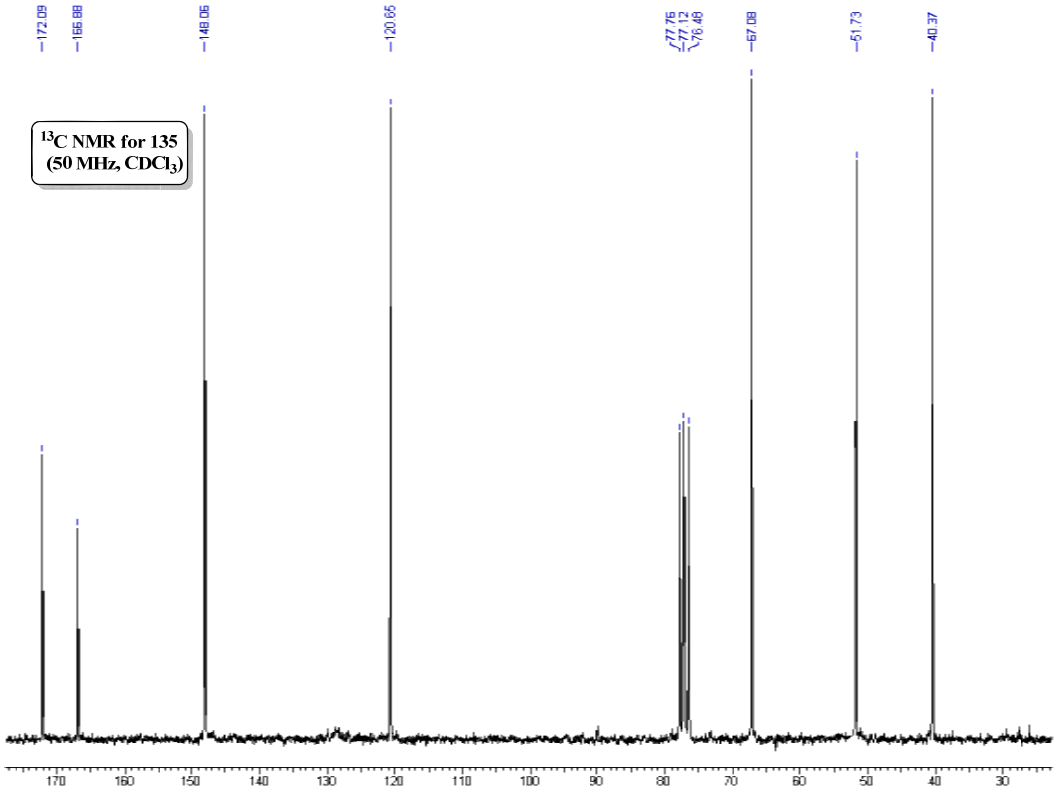


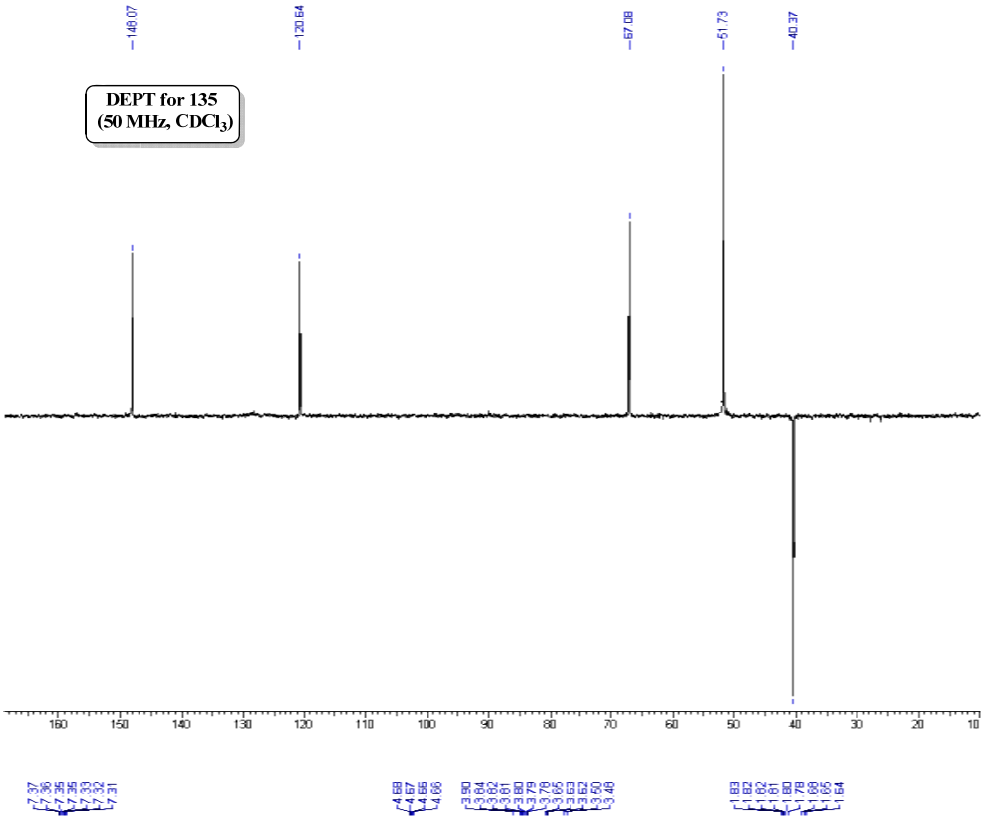
^{1}H NMR for 136
(200 MHz, $CDCl_3$)

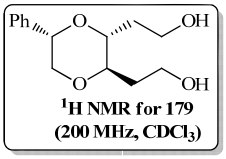

206.67
79.05
79.21
77.95
77.69
34.94
^{13}C NMR for 136
(50 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


79.06
34.94
DEPT for 136
(50 MHz, CDCl$_3$)
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

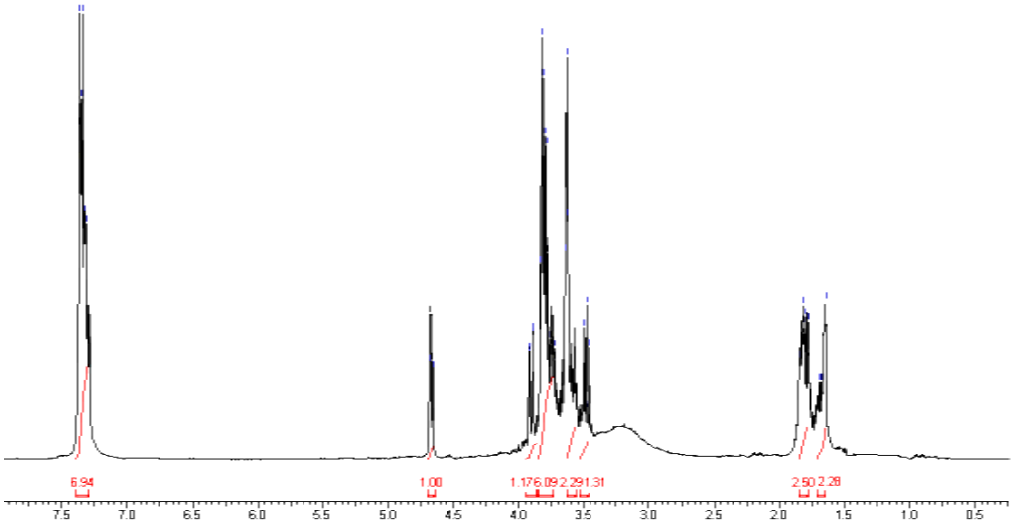

MeOOC
O
O
^{1}H NMR for 135
(200 MHz, CDCl$_3$)

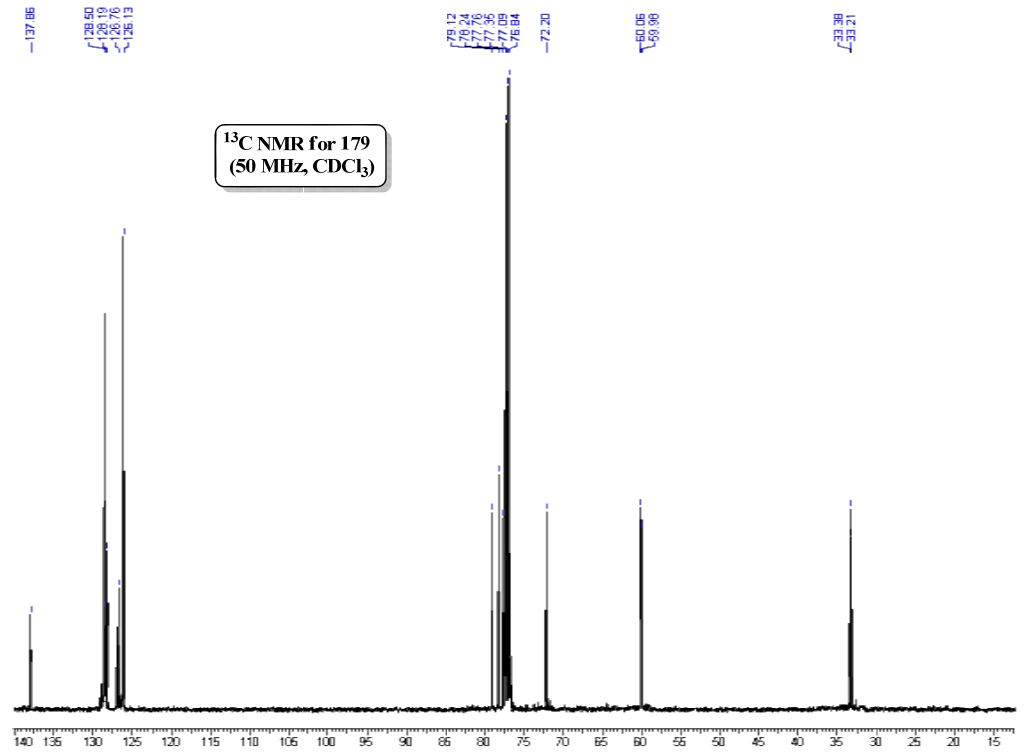

^{13}C NMR for 135
(50 MHz, CDCl$_3$)

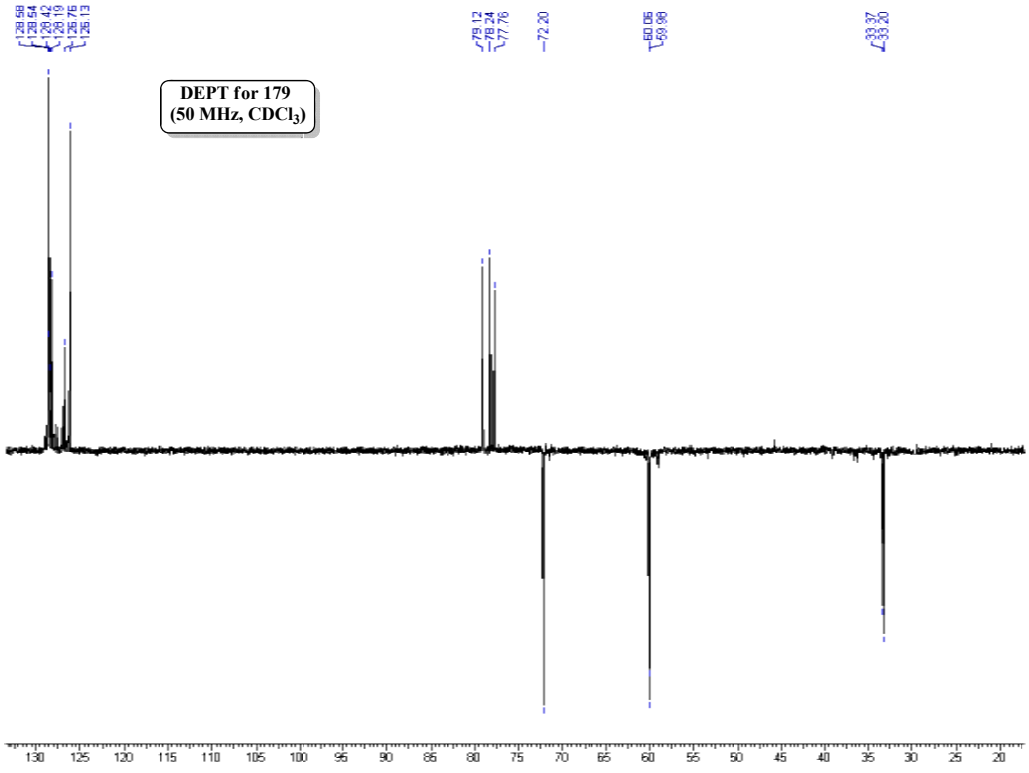


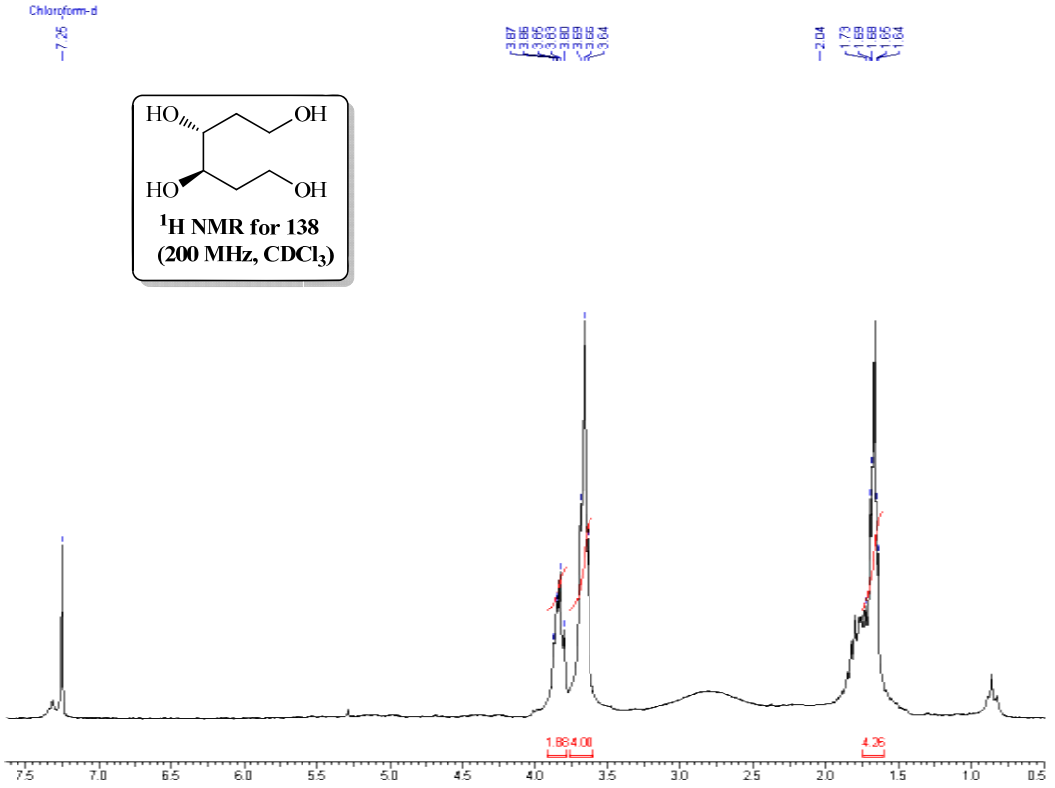


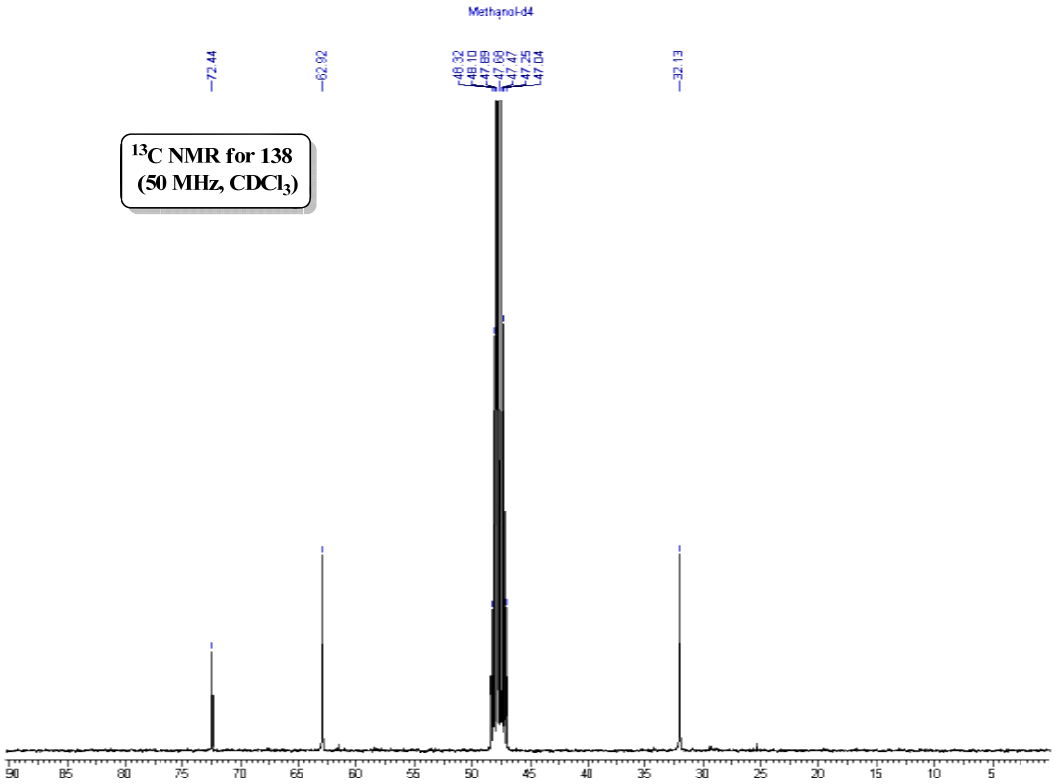
^{1}H NMR for 179
(200 MHz, CDCl$_3$)

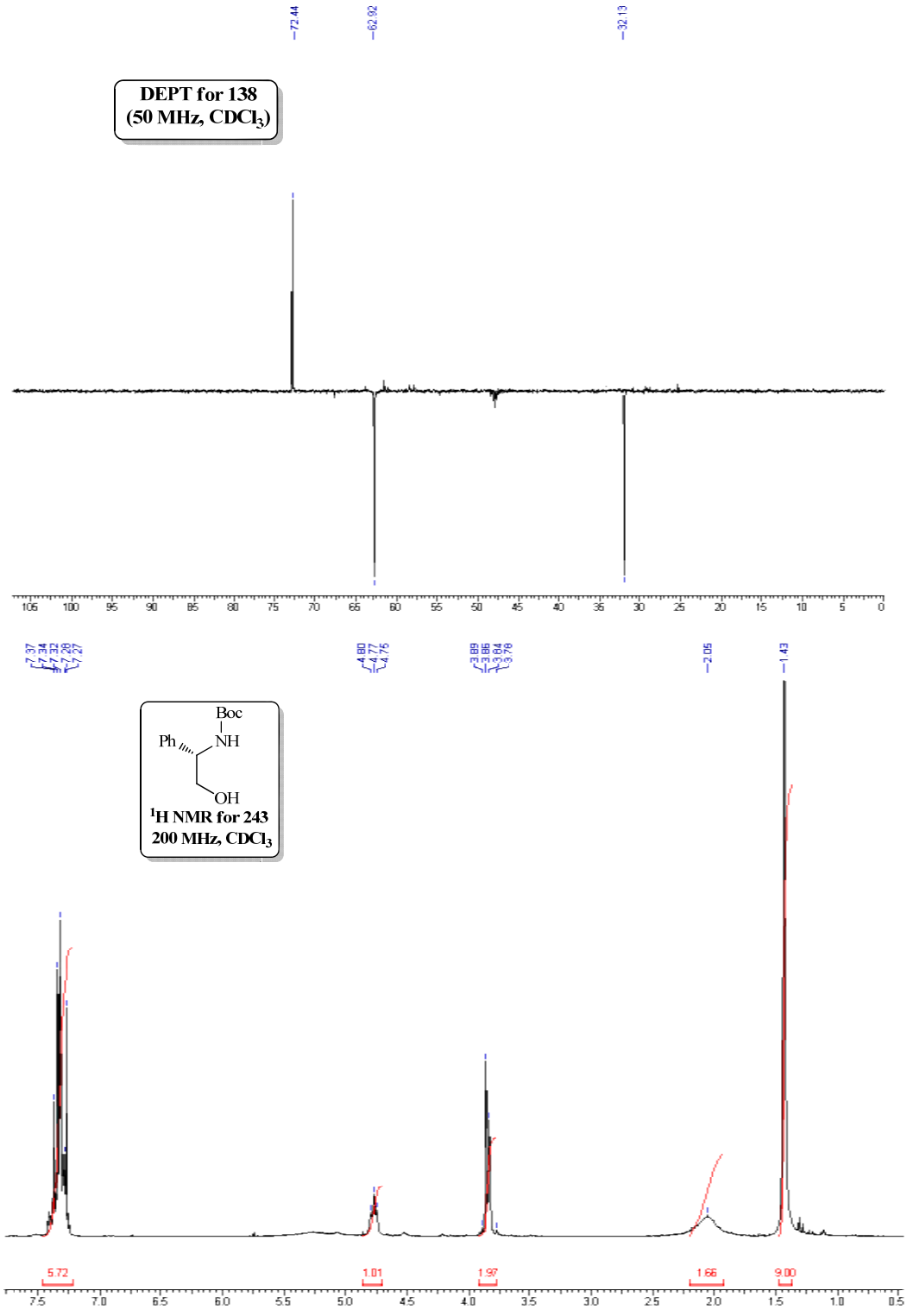


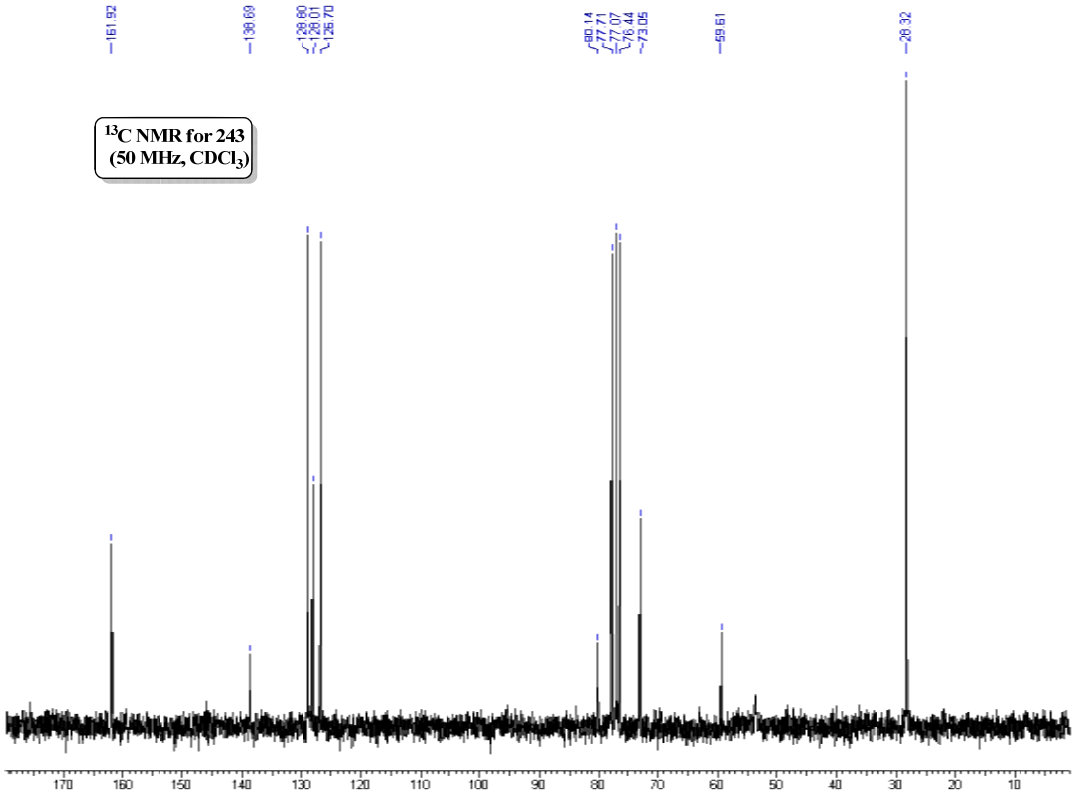

137.86
128.50
128.19
126.76
126.13
79.12
78.24
77.76
77.35
77.09
76.84
72.20
60.06
59.98
33.38
33.21
^{13}C NMR for 179
(50 MHz, CDCl$_3$)

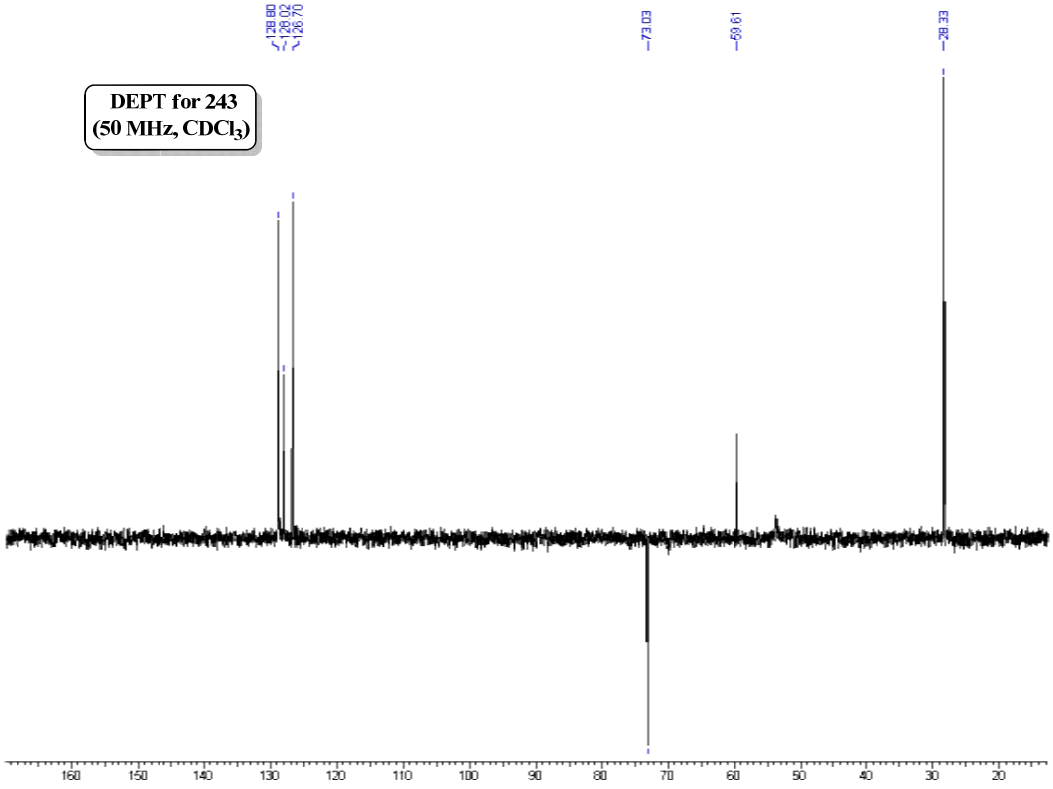

128.59
128.54
126.42
126.19
125.76
125.13
79.12
78.24
77.76
72.20
60.06
59.98
33.37
33.20
DEPT for 179
(50 MHz, CDCl$_3$)

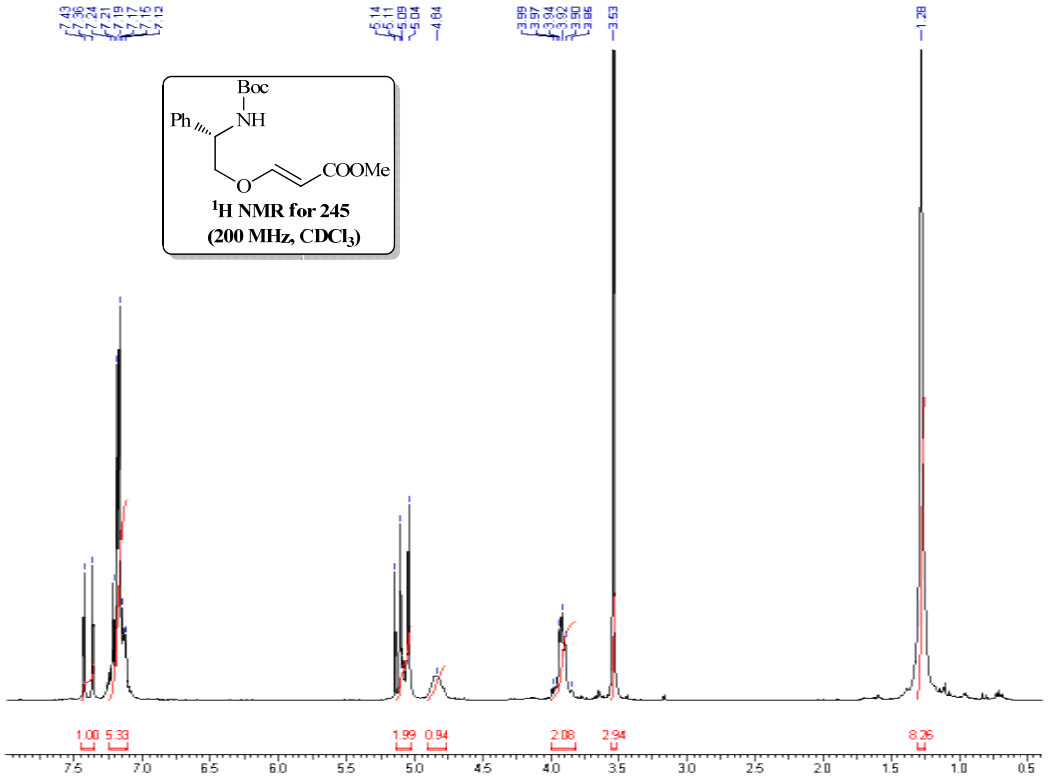

Chloroform-d
7.25
3.87
3.86
3.85
3.83
3.80
3.69
3.66
3.64
2.04
1.73
1.69
1.68
1.65
1.64
HO
OH
HO
OH
1H NMR for 138
(200 MHz, CDCl3)
1.884.00
4.26

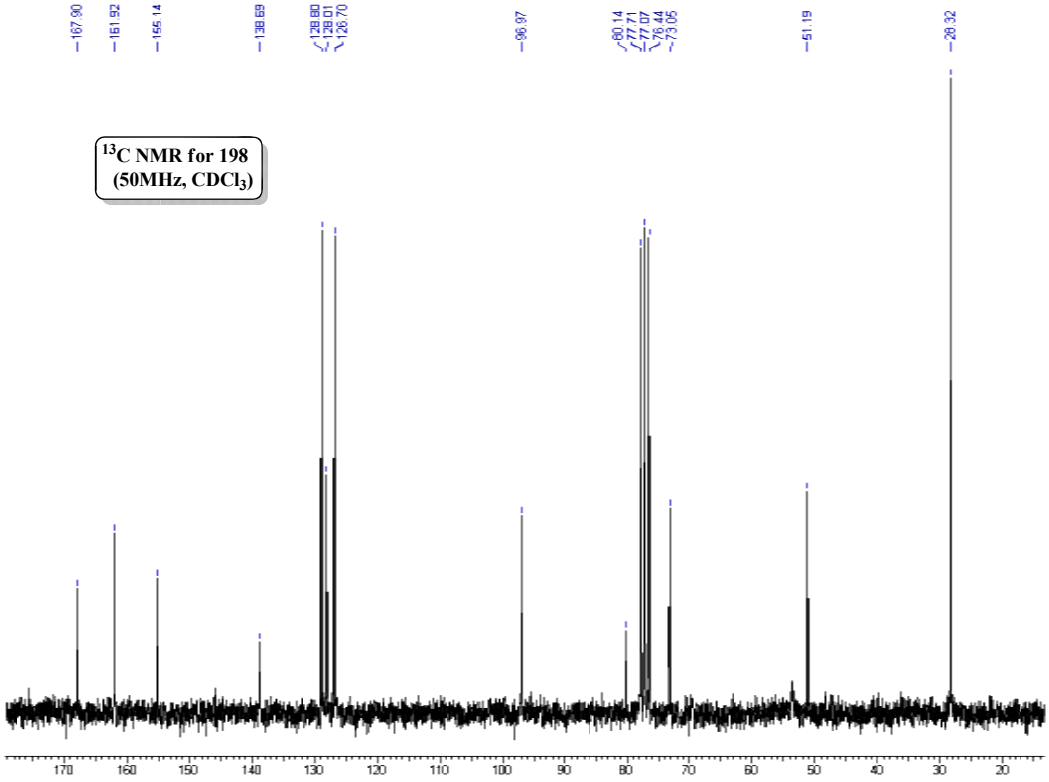

Methanol-d4
72.44
62.92
49.32
49.10
47.88
47.68
47.47
47.25
47.04
32.13
13C NMR for 138
(50 MHz, CDCl3)

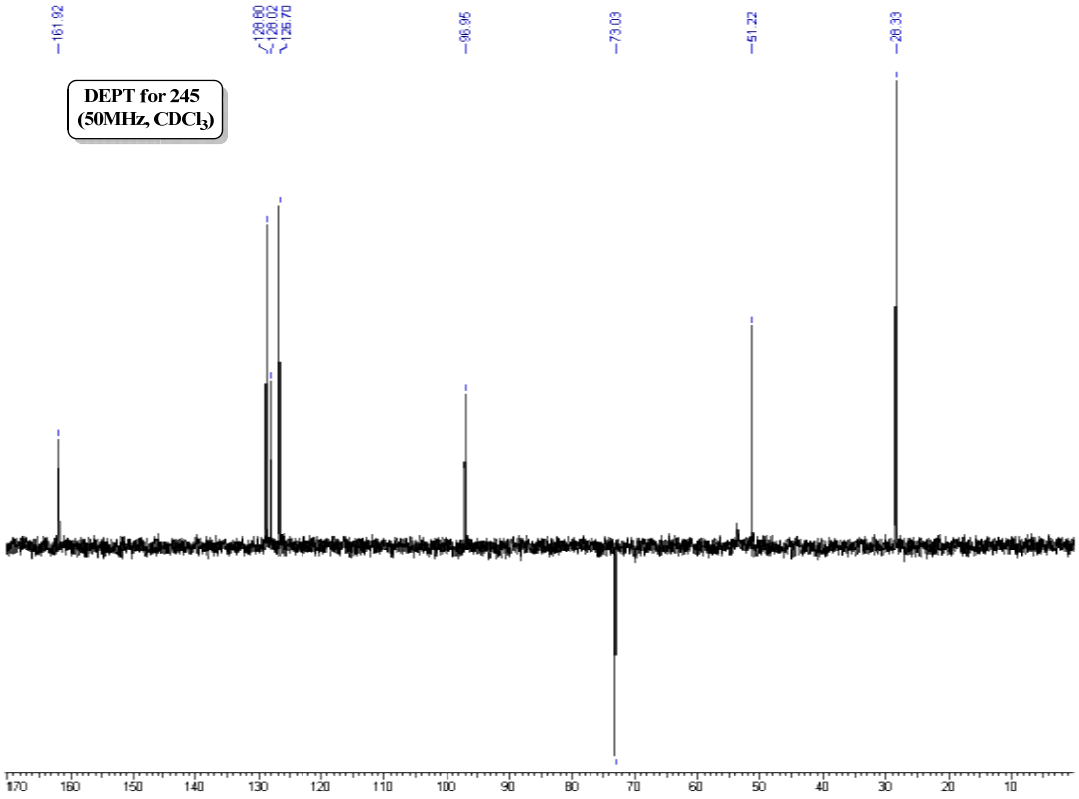

72.44
62.92
32.13
DEPT for 138
(50 MHz, CDCl3)
7.37
7.34
7.32
7.28
7.27
4.80
4.77
4.75
3.89
3.86
3.84
3.78
2.05
1.43
Boc
Ph
NH
OH
1H NMR for 243
200 MHz, CDCl3
5.72
1.01
1.97
1.66
9.00

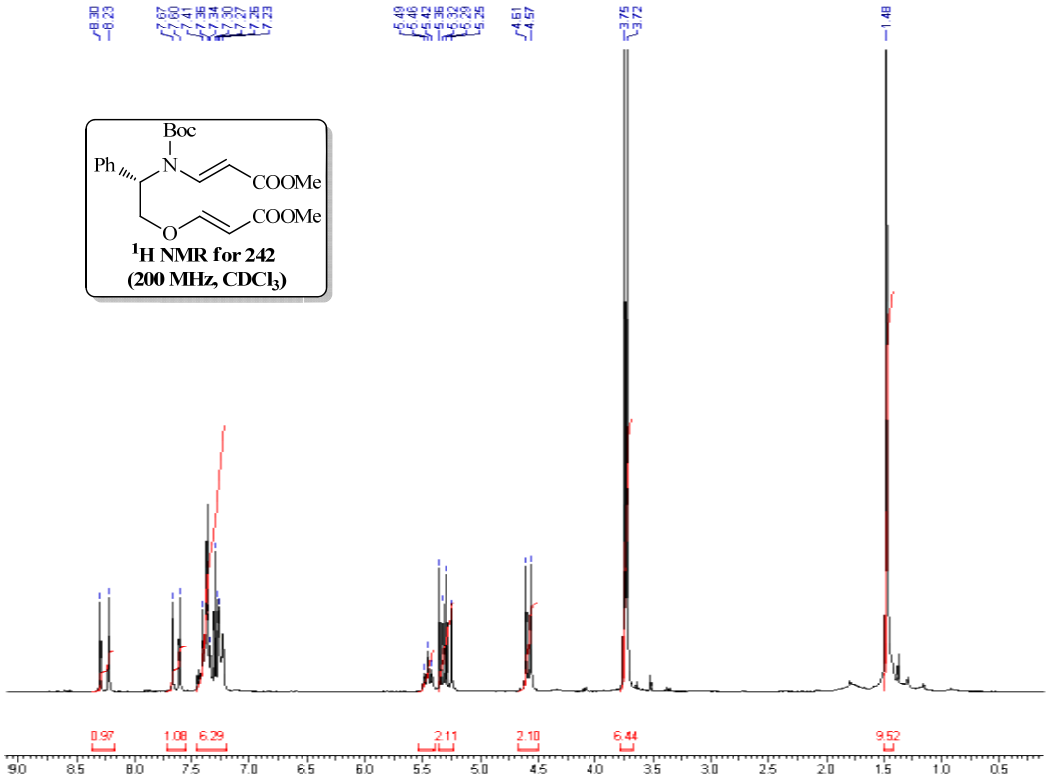

161.92
139.69
128.80
128.01
125.70
80.14
77.71
77.07
76.44
73.05
59.61
28.32
^{13}C NMR for 243
(50 MHz, CDCl$_3$)

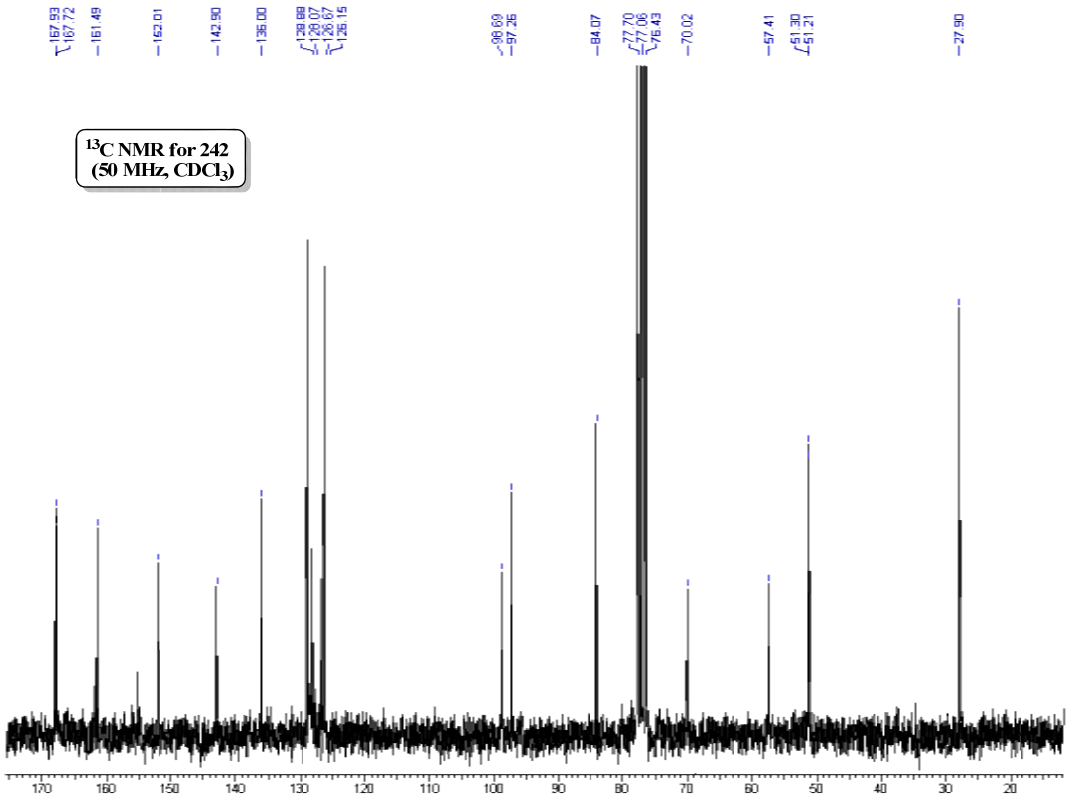

128.80
128.02
125.70
73.03
59.61
28.33
DEPT for 243
(50 MHz, CDCl$_3$)

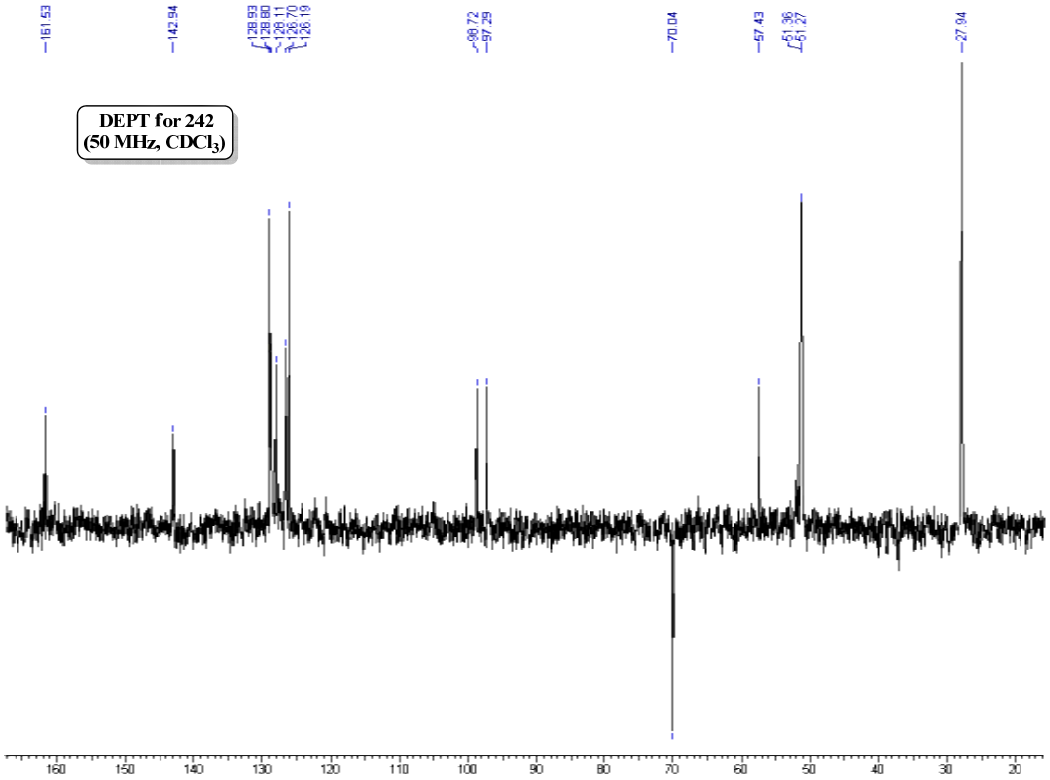

Boc
NH
Ph
O
COOMe
^{1}H NMR for 245
(200 MHz, CDCl$_3$)

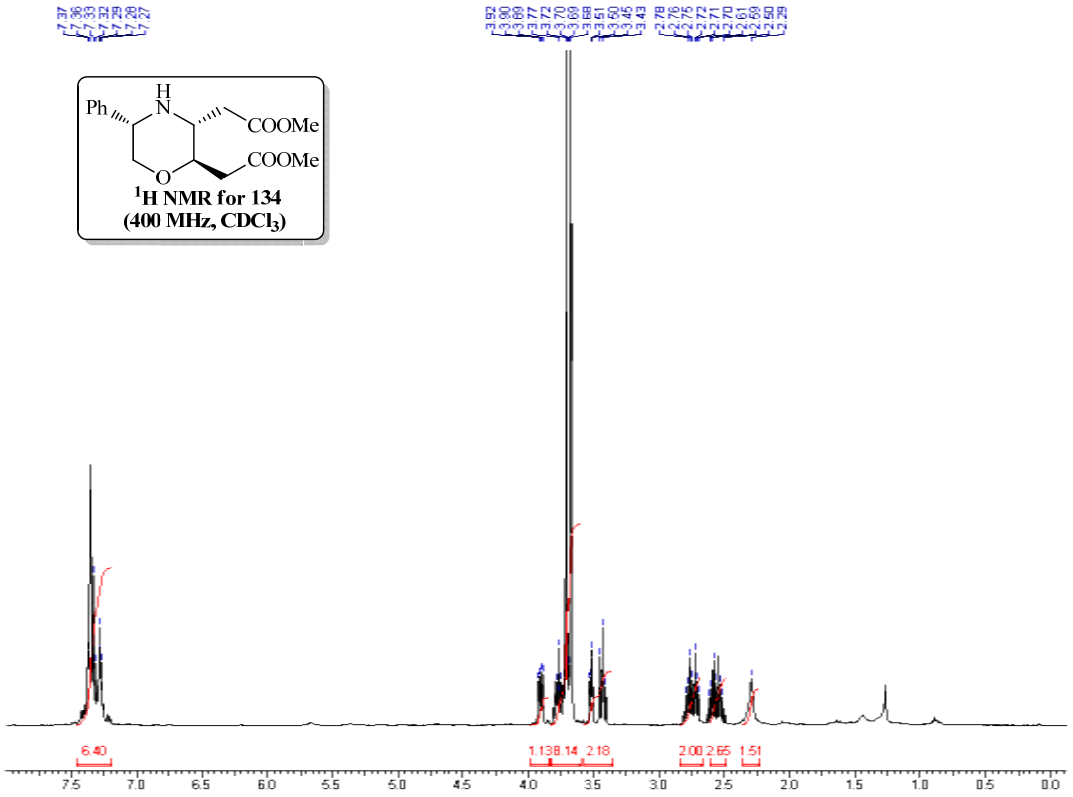

^{13}C NMR for 198
(50MHz, CDCl$_3$)

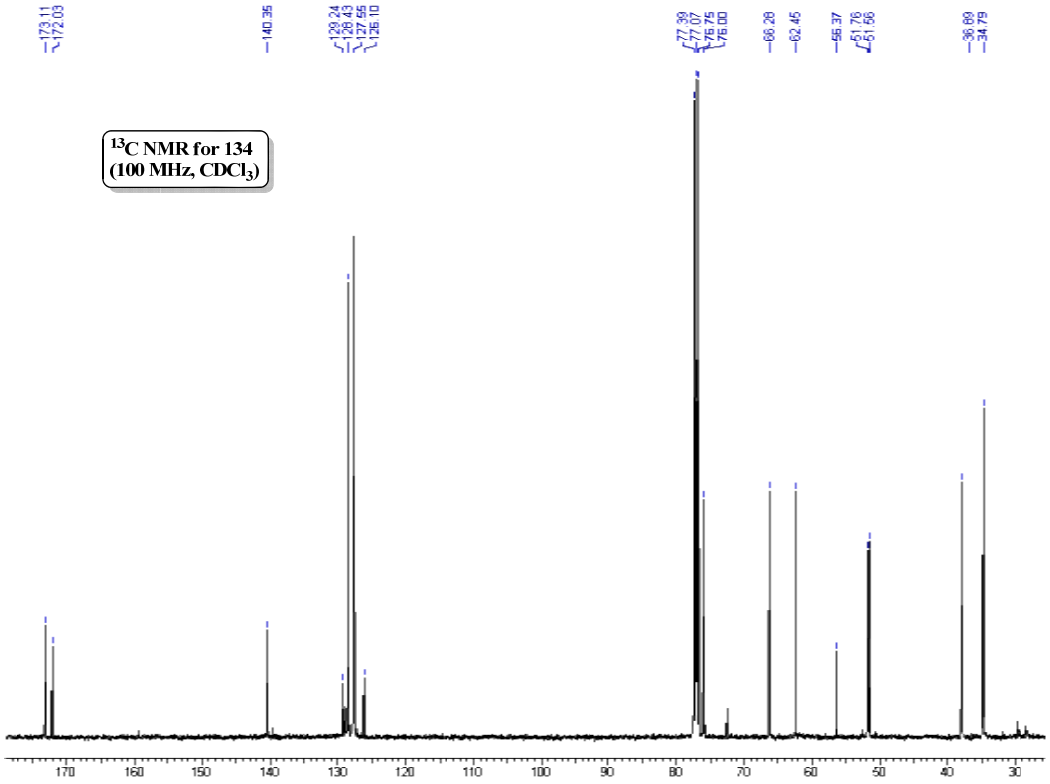

161.92
128.80
128.02
126.70
96.95
73.03
51.22
28.33
DEPT for 245
(50MHz, CDCl3)

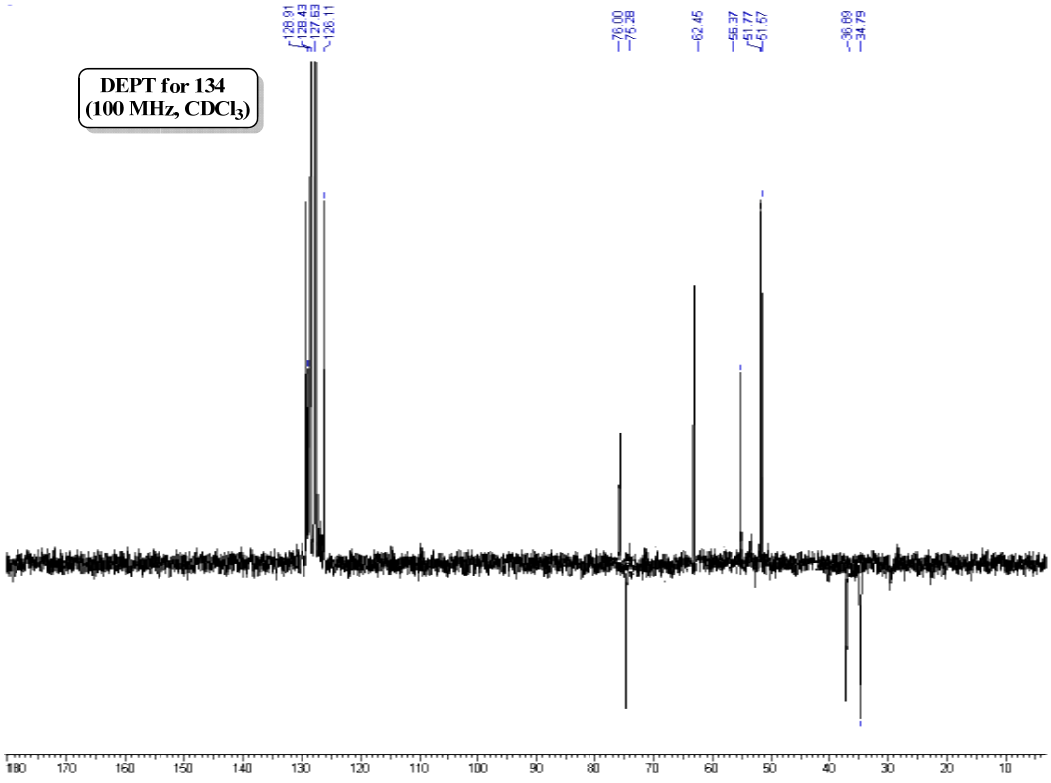

Boc
Ph
N
COOMe
COOMe
O
1H NMR for 242
(200 MHz, CDCl3)
0.97
1.08
6.29
2.11
2.10
6.44
9.52


167.93
167.72
161.49
152.01
142.90
136.00
129.88
129.07
126.67
126.15
99.69
97.25
84.07
77.70
77.06
76.43
70.02
57.41
51.30
51.21
27.90
^{13}C NMR for 242
(50 MHz, CDCl$_3$)

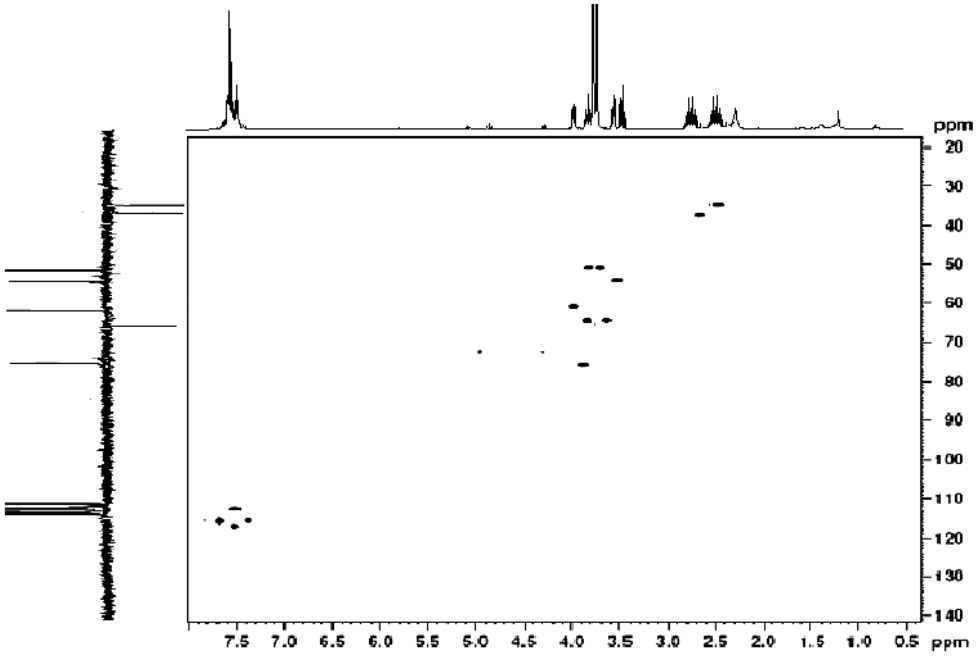

161.53
142.94
129.93
129.80
128.11
126.70
126.19
99.72
97.29
70.04
57.43
51.36
51.27
27.94
DEPT for 242
(50 MHz, CDCl$_3$)


Ph
H
N
O
COOMe
COOMe
^{1}H NMR for 134
(400 MHz, CDCl$_3$)

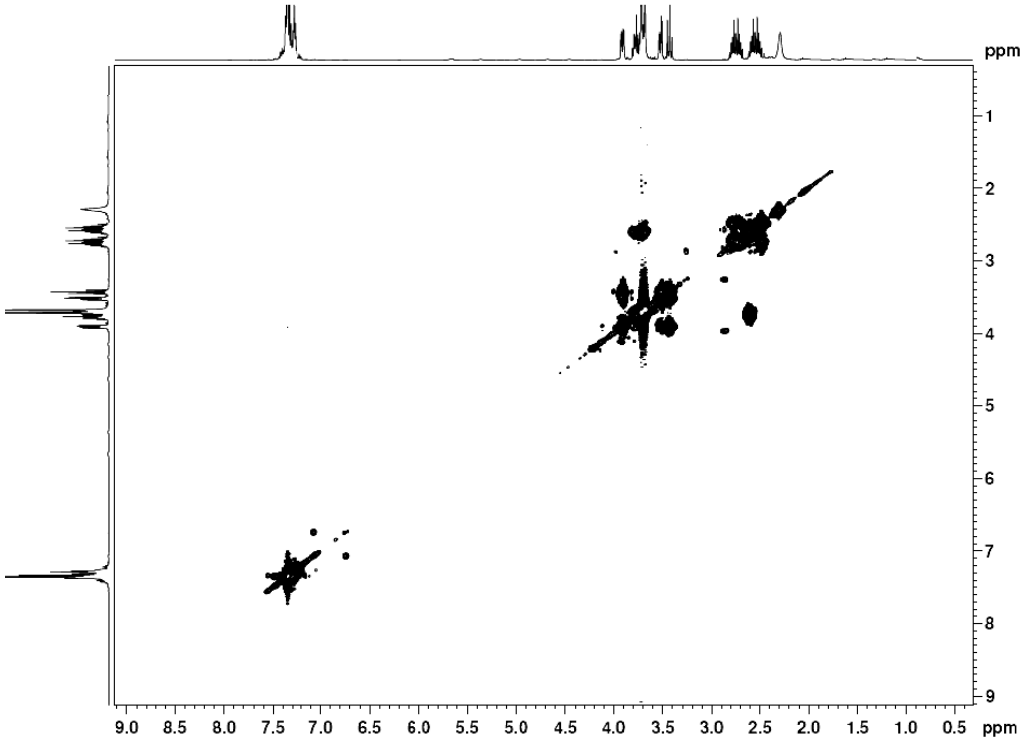

^{13}C NMR for 134
(100 MHz, CDCl$_3$)


DEPT for 134
(100 MHz, CDCl3)
128.91
128.43
127.63
126.11
76.00
75.28
62.45
56.37
51.77
51.57
36.69
34.79
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

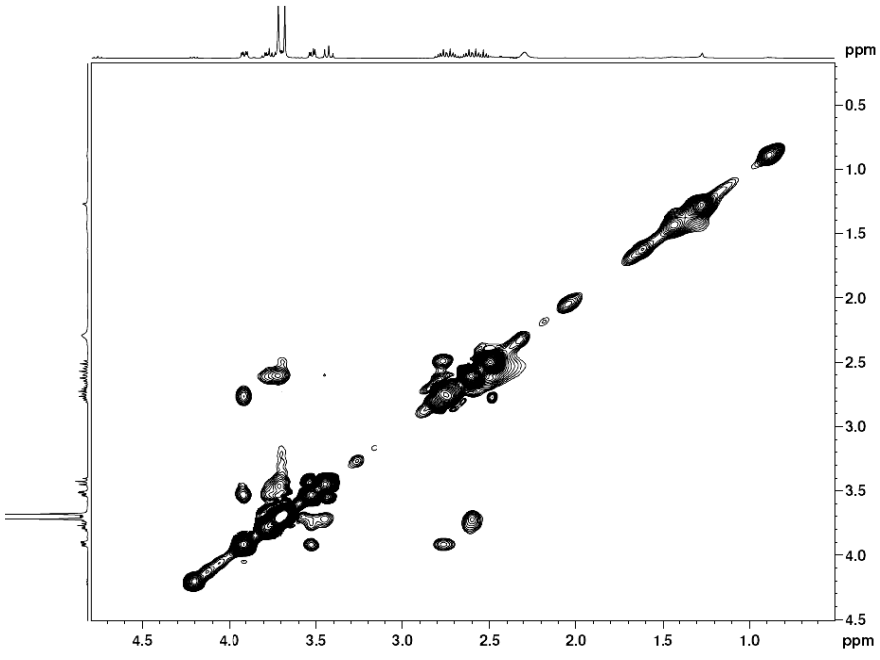
HSQC for **134**

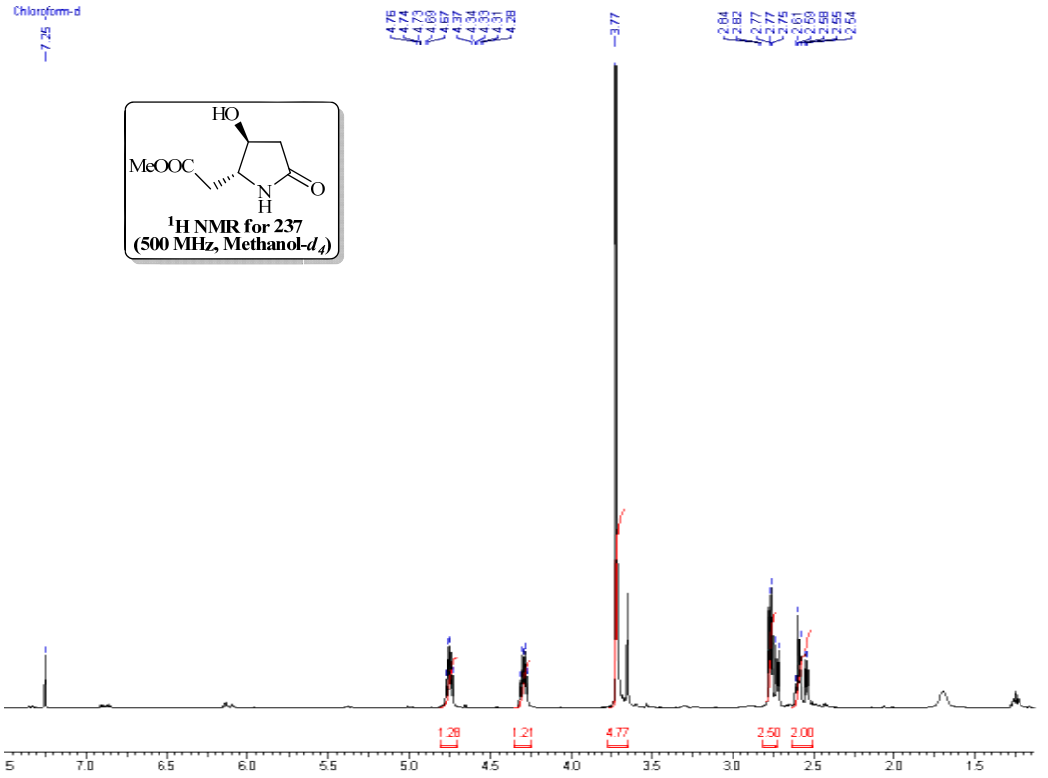

ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

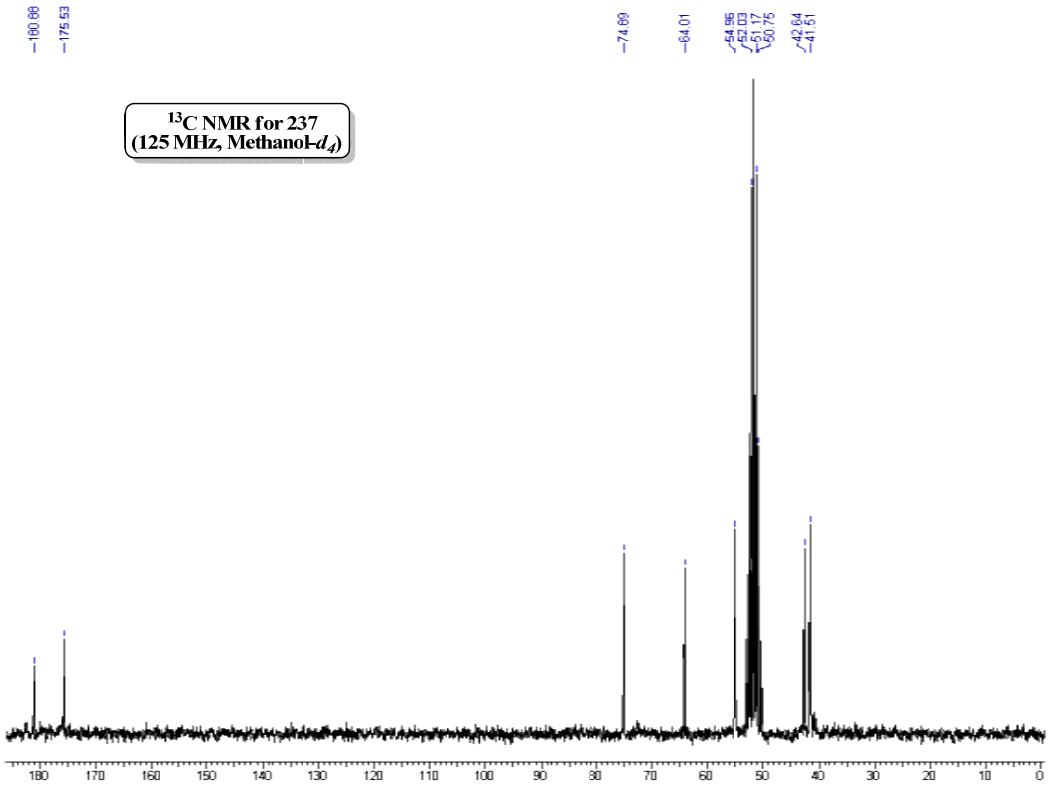
COSY

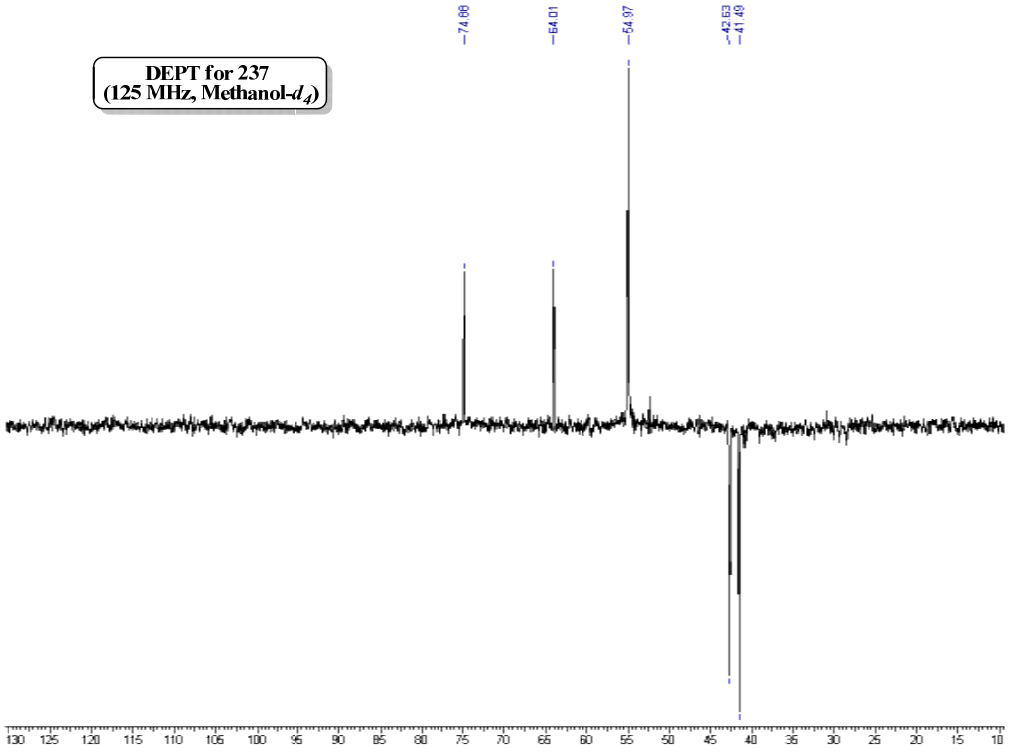

ppm
1
2
3
4
5
6
7
8
9
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

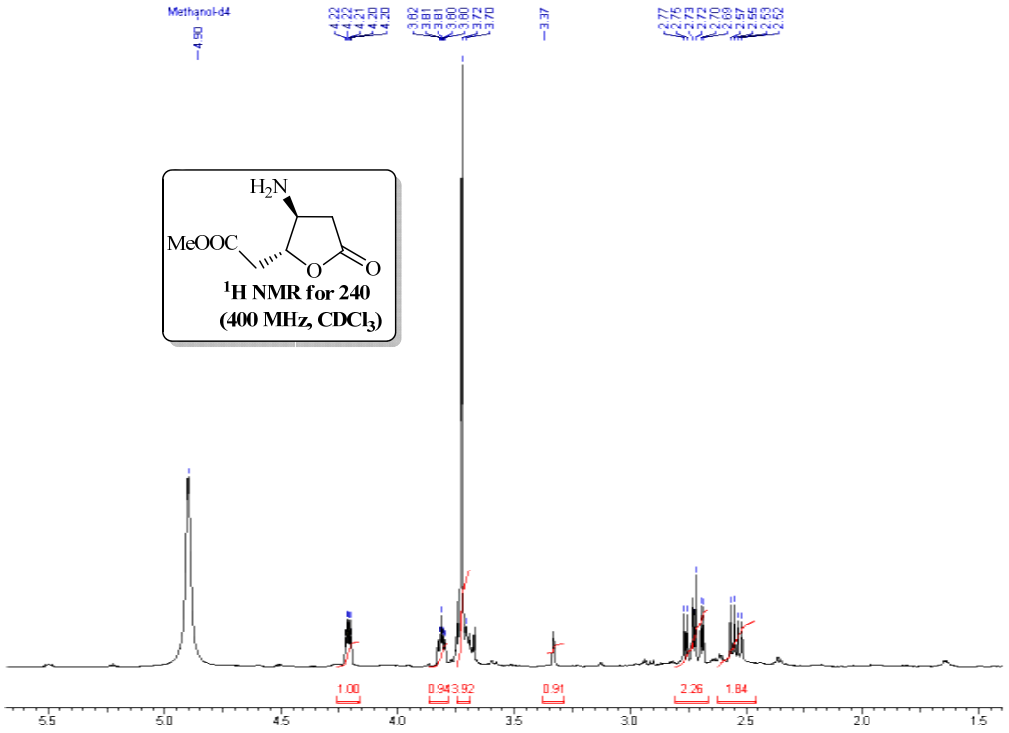
NOESY

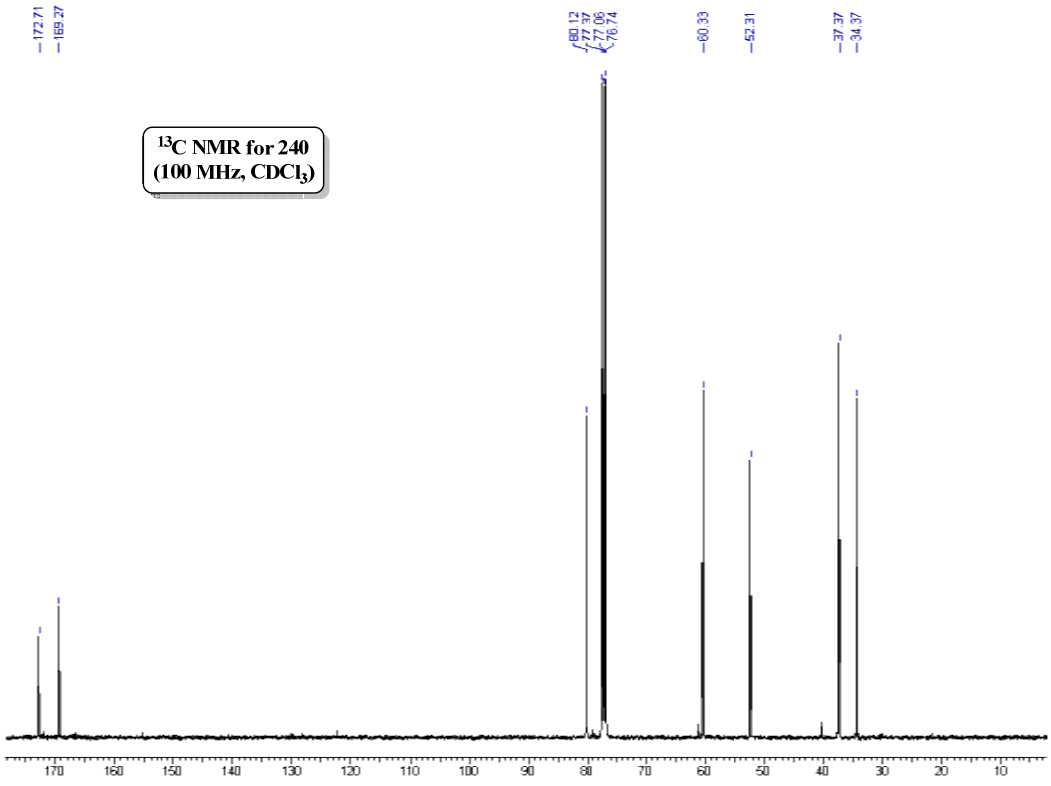

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

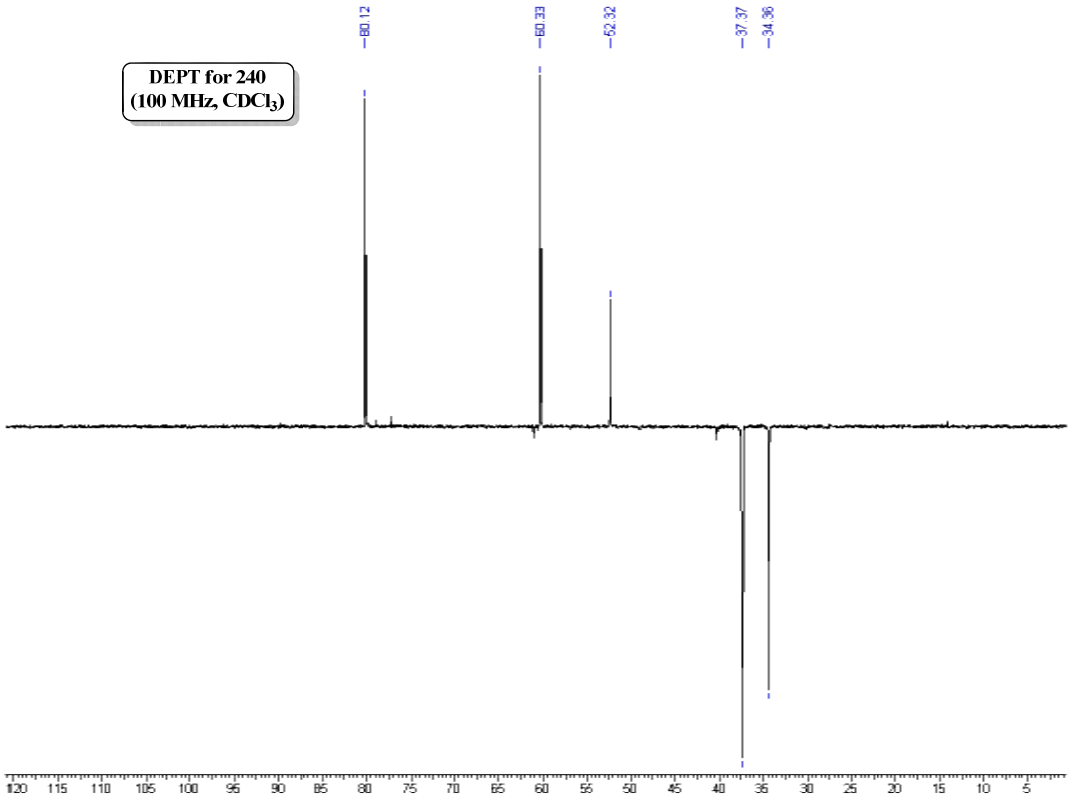

Chloroform-d
7.25
4.76
4.74
4.73
4.69
4.57
4.37
4.34
4.33
4.31
4.28
3.77
2.84
2.82
2.77
2.77
2.75
2.61
2.59
2.58
2.55
2.54
HO
MeOOC
N
H
O
1H NMR for 237
(500 MHz, Methanol-d4)
1.28
1.21
4.77
2.50
2.00
5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

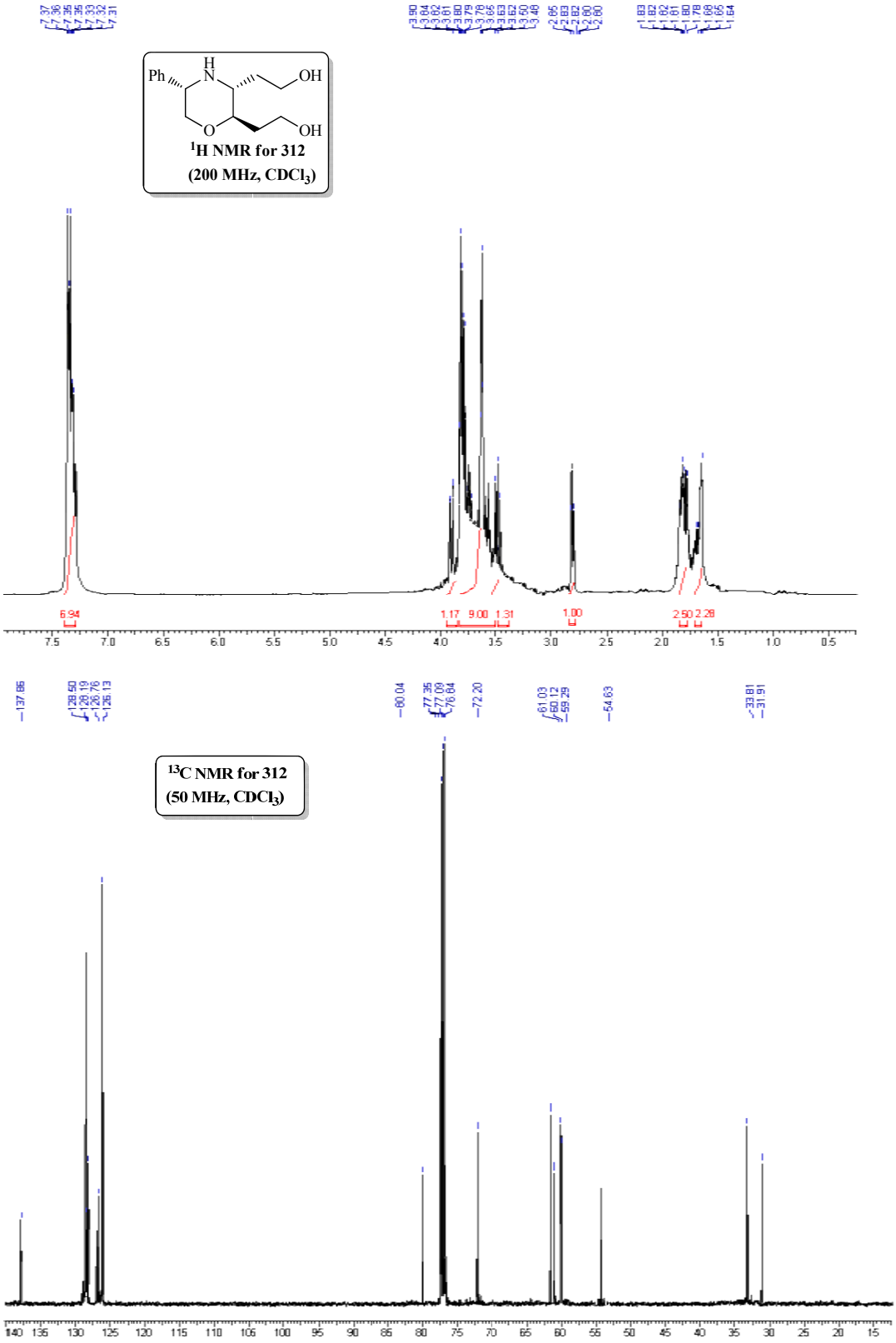

180.88
175.53
74.89
64.01
54.96
52.03
51.17
50.75
42.64
41.51
13C NMR for 237
(125 MHz, Methanol-d4)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

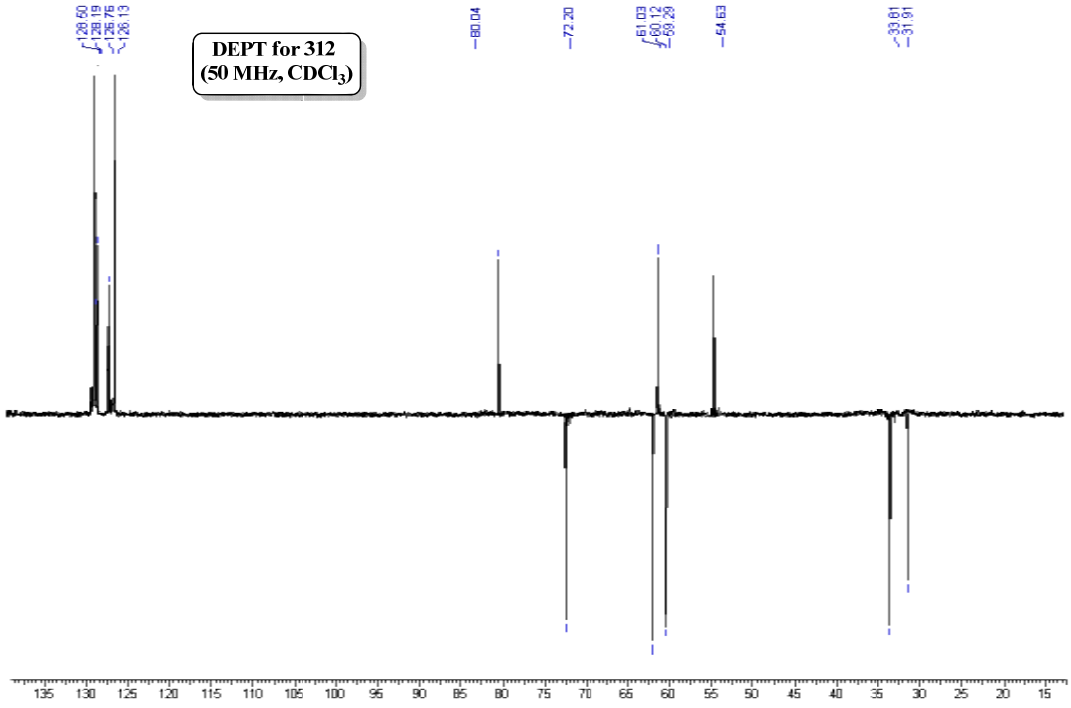

DEPT for 237
(125 MHz, Methanol-d_4)
74.88
64.01
54.97
42.63
41.49

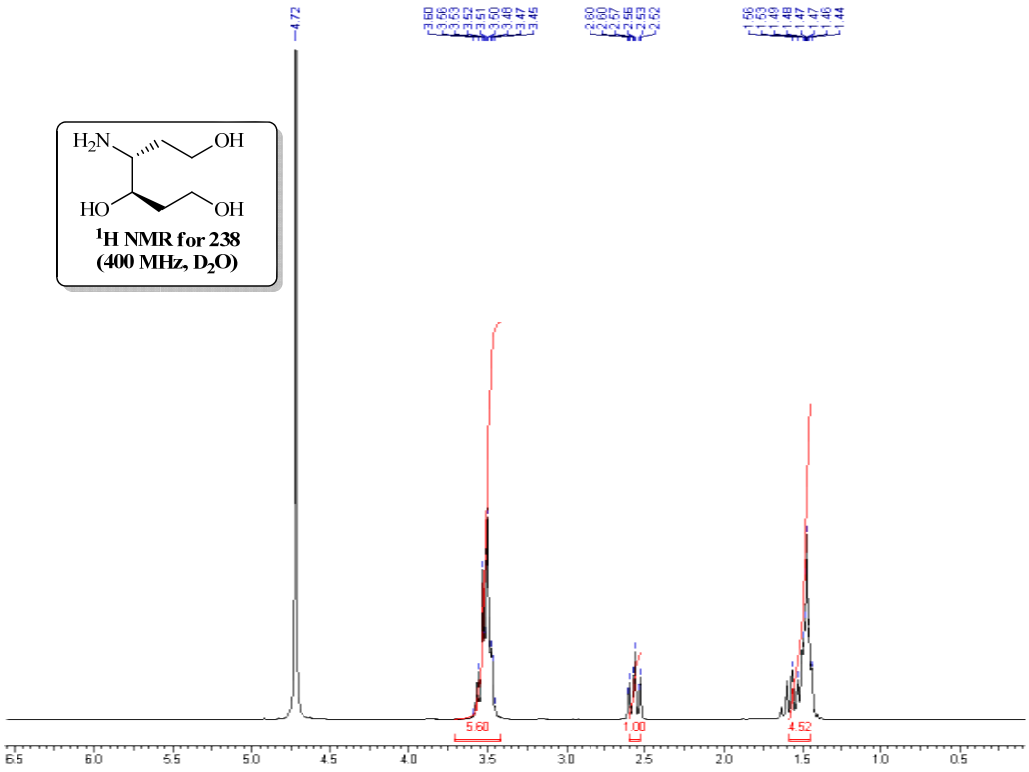

Methanol-d4
4.90
3.37
H_2N
MeOOC
O
O
^{1}H NMR for 240
(400 MHz, $CDCl_3$)


172.71
169.27
80.12
77.97
77.66
76.74
60.33
52.31
37.37
34.37
^{13}C NMR for 240
(100 MHz, CDCl$_3$)

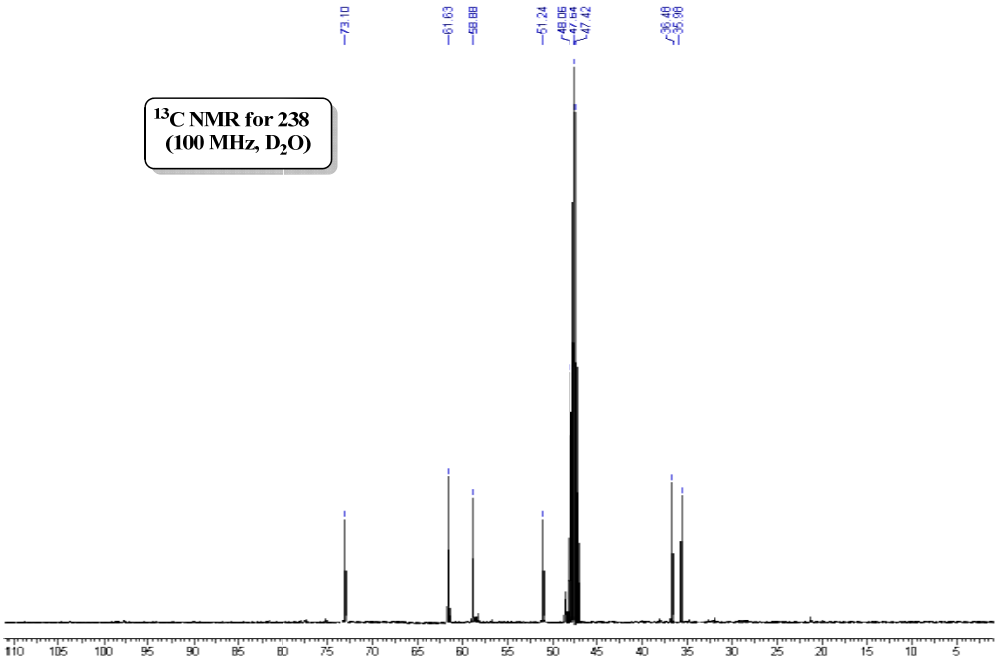

80.12
60.33
52.32
37.37
34.36
DEPT for 240
(100 MHz, CDCl$_3$)


Ph
H
N
OH
O
OH
^{1}H NMR for 312
(200 MHz, CDCl$_3$)
^{13}C NMR for 312
(50 MHz, CDCl$_3$)

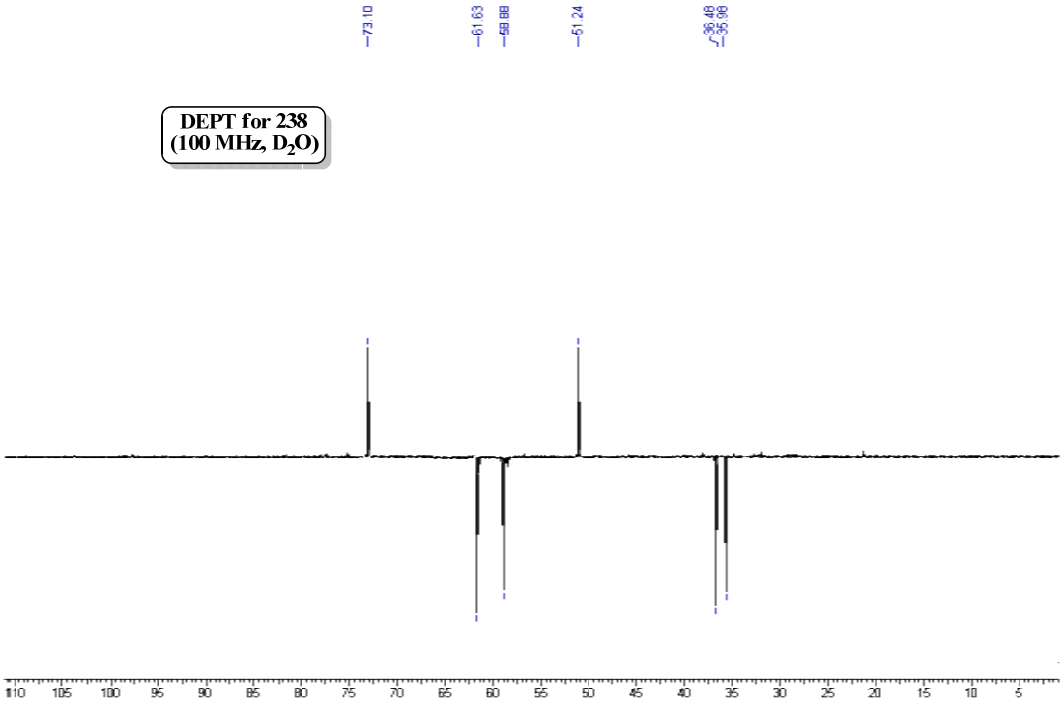

DEPT for 312
(50 MHz, CDCl3)

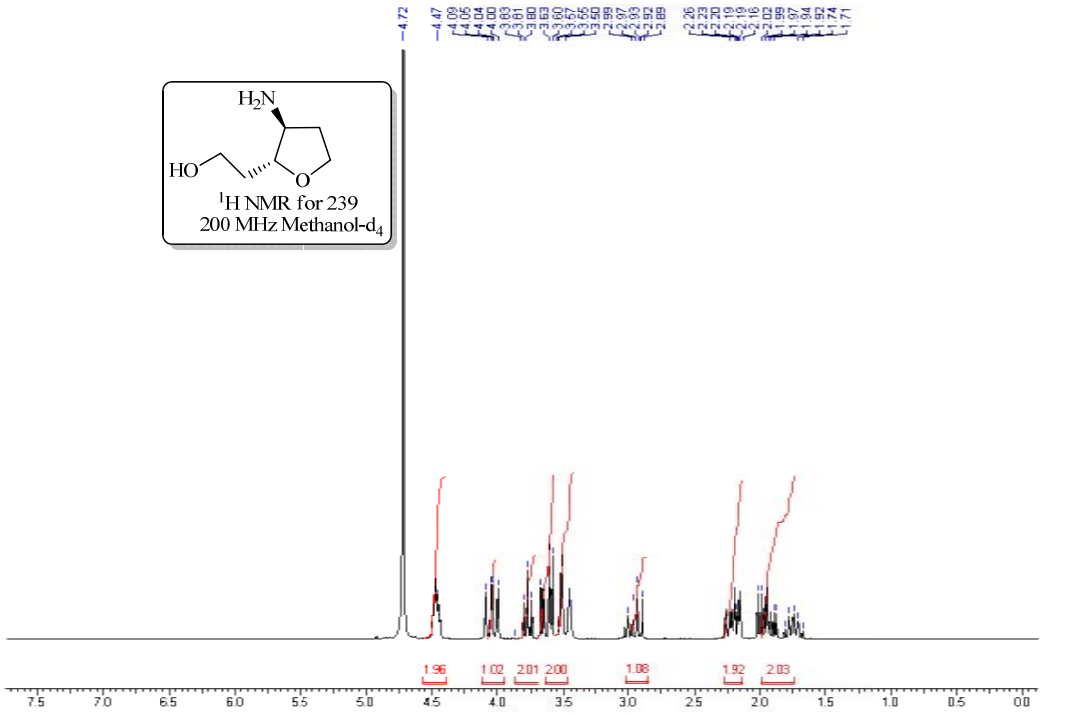

H2N
OH
HO
OH
1H NMR for 238
(400 MHz, D2O)

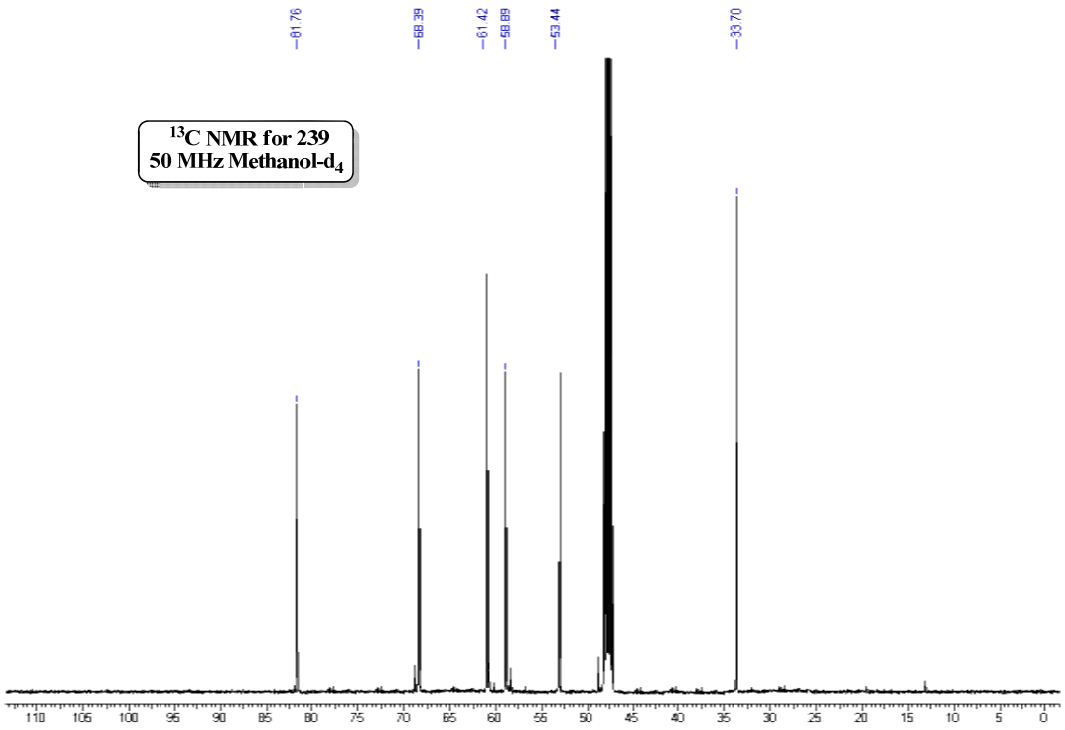
^{13}C NMR for 238 (100 MHz, D_2O)

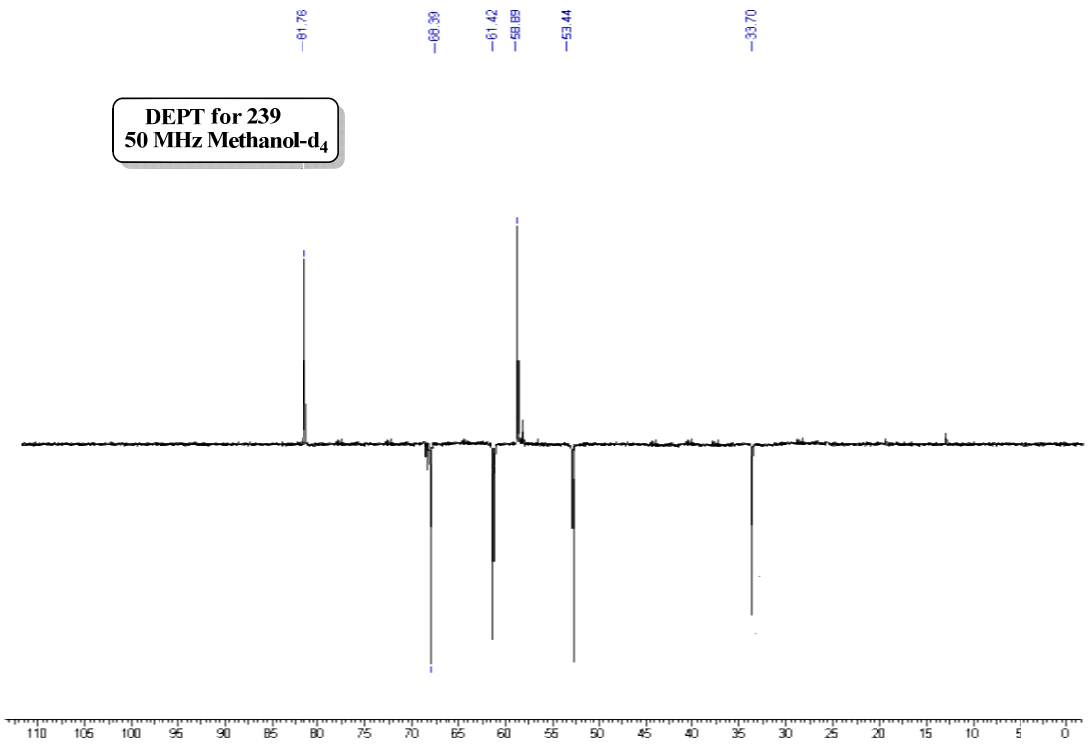


DEPT for 238 (100 MHz, D_2O)



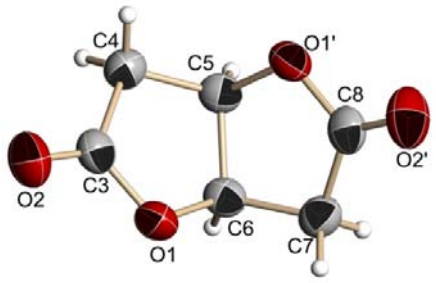

H2N
HO
O
1H NMR for 239
200 MHz Methanol-d4


13C NMR for 239
50 MHz Methanol-d4


81.76
68.39
61.42
59.89
53.44
33.70
DEPT for 239
50 MHz Methanol-d4
110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0

3.3 Apendix:

1) X-ray crystal data and structure refinement values for 136



(*ORTEP* diagram of **136)**

Table 1. Crystal data and structure refinement for algbislactone.

Identification code	algbislactone
Empirical formula	C3 H6 O4
Formula weight	106.08
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 10.0616(16) Å, α = 90° deg.
	b = 6.2249(10) Å, β = 113.595(2)°.
	c = 10.5026(16) Å, γ = 90°.
Volume	602.81(16) $Å^3$
Z, Calculated density	4, 1.169 Mg/m^3
Absorption coefficient	0.112 mm^{-1}
F(000)	224
Crystal size	0.17 x 0.16 x 0.10 mm
Theta range for data collection	2.37 to 25.00°.
Limiting indices	-10<=h<=11, -7<=k<=7, -12<=l<=7
Reflections collected / unique	2890 / 1057 [R(int) = 0.0128]
Completeness to theta = 25.00	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9889 and 0.9813
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1057 / 0 / 92

Goodness-of-fit on F^2	1.113
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0853
R indices (all data)	R1 = 0.0365, wR2 = 0.0860
Extinction coefficient	0.110(11)
Largest diff. peak and hole	0.163 and -0.169 e. $Å^{-3}$

List of publications

(1) Chiral 6-phenyl-2,3-bismethylenemethoxycarbonyl-[1,4]-dioxane as designer synthon for an efficient and short synthesis of optically pure 2,6-dioxabicyclo[3.3.0]octane-3,7-dione

Ganesh Pandey, **Amrut L. Gaikwad** and Smita R. Gadre; *Tetrahedron Letters*, **2006**, *47*, 701-703.

(2) Stereoselective synthesis of *β*-hydroxy-*γ*-lactam, *β*-amino-*γ*-substituted butyrolactone, *trans*-1,2-amino alcohol and 3-amino tetrahydrofuran from chiral substituted morpholine.

Ganesh Pandey, **Amrut L. Gaikwad** (*manuscript under preparation*).

Erratum