DEVELOPMENT OF SYNTHETIC METHODOLOGIES EMPLOYING PHOSPHORUS YLIDES AND SYNTHETIC STUDIES TOWARDS AAL-TOXIN, 3-HYDROXYPIPECOLIC ACID AND RELATED COMPOUNDS

A THESIS SUBMITTED TO THE

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IN

CHEMISTRY

BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled "**DEVELOPMENT OF SYNTHETIC METHODOLOGIES EMPLOYING PHOSPHORUS YLIDES AND SYNTHETIC STUDIES TOWARDS AAL-TOXIN, 3-HYDROXYPIPECOLIC ACID AND RELATED COMPOUNDS"** submitted by **Mandar S. Bodas** was carried out by the candidate at the National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Pradeep Kumar)

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Pune 411 008, INDIA **July 2004**

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**DEVELOPMENT OF SYNTHETIC METHODOLOGIES EMPLOYING PHOSPHORUS YLIDES AND SYNTHETIC STUDIES TOWARDS AAL-TOXIN, 3-HYDROXYPIPECOLIC ACID AND RELATED COMPOUNDS"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other University or Institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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July 2004

DEDICATED
TO
ALMIGHTY
&
MY
BELOVED PARENTS

ACKNOWLEDGEMENTS

It gives me great strength and belief in the presence of Almighty, because of whom it was possible to bring the completion of my research endeavour in the best possible way I might have achieved. I bow to the abstract strength and wish it dwells throughout my life.

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MANDAR S. BODAS
July 2004

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CHAPTER 2:
ASYMMETRIC DIHYDROXYLATION, ASYMMETRIC EPOXIDATION AND CYLCI SULFITES / CYCLIC SULFATES AS SYNTHETIC INTERMEDIATES

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
AD	Asymmetric dihydroxylation
Bn	Benzyl
Bu	Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
calcd.	Calculated
cat.	Catalytic/ Catalyst
$CDCl_3$	Deuterated chloroform
conc.	Concentrated
DET	Diethyltartrate
D_2O	Deuterium oxide
de	Diastereomeric excess
ds	Diastereoselectivity
DHP	Dihydropyran
$(DHQ)_2PHAL$	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	1,4-Bis(dihydroquinidin-9-*O*-yl)phthalazine
DIBAL-H	Diisobutyl aluminium hydride
DMAP	N,N-(Dimethylamino)pyridine
DMF	N,N-Dimethyl formamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EIMS	Electron impact mass spectrum
eq. or equiv	Equivalents
Et	Ethyl
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
g	Grams
GLC	Gas liquid chromatography
h	Hours
HLADH	Horse liver alcohol dehydrogenase
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
M^+	Molecular ion
m-CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
mg	Milligram
min	Minutes
mL	Millilitre

mmol	Millimole
M.p.	Melting point
Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
NMO	N-Methyl morpholine N-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PFL	*Pseudomonas fluorescens* lipase
Piv	Pivaloyl
PhH	Benzene
PhMe	Toluene
PLE	Pig liver esterase
PMB	*p*-Methoxybenzyl
PPL	Porcine pancreatic lipase
ppm	Parts per million
PPTS	Pyridinium *p*-toluene sulfonate
p-TsOH	*p*-Toluene sulfonic acid
Pyr	Pyridine
rt	Room temperature
Rf	Retention factor
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
satd.	Saturated
TBAF	Tetrabutyl ammonium fluoride
TBAI	Tetrabutyl ammonium iodide
TBDMS	*tert*-Butyl dimethylsilyl
TBDPS	*tert*-Butyl diphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Tetramethylsilyl
Tr	Trityl
Ts	*p*-Toluene sulfonyl

ABSTRACT

The thesis entitled "**DEVELOPMENT OF SYNTHETIC METHODOLOGIES EMPLOYING PHOSPHORUS YLIDES AND SYNTHETIC STUDIES TOWARDS AAL-TOXIN, 3-HYDROXY PIPECOLIC ACID AND RELATED COMPOUNDS** " is divided into five chapters.

Chapter 1: constitutes the synthesis of (trimethylsilyl)methylenetriphyenylphosphorane and its application towards the synthesis of 4*H*-chromen-4-ones and 4*H*-1-benzothiopyran-4-ones *via* intramolecular Wittig reaction.

Chapter 2: describes a brief introduction to Sharpless asymmetric dihydroxylation, asymmetric epoxidation and cyclic sulfites/sulfates as synthetic intermediates.

Chapter 3: deals with the enantioselective synthesis of 3-hydroxypipecolic acid.

Chapter 4: covers the application of α-amino aldehydes as synthons in the syntheses of aza building blocks for 3-piperidinol alkaloids.

Chapter 5: deals with the studies directed towards the synthesis of AAL-toxin.

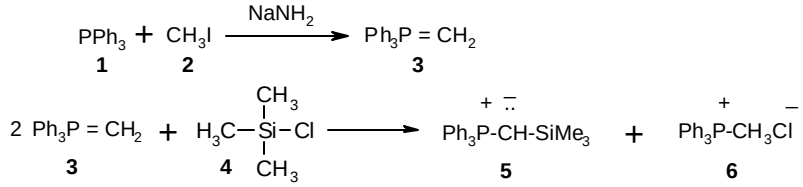
Chapter 1:

Synthesis of (trimethylsilyl)methylenetriphenylphosphorane: Application towards the synthesis of 4*H*-chromen-4-ones and 4*H*-1-benzothiopyran-4-ones *via* intramolecular Wittig reaction

The intramolecular Wittig reaction has been extensively employed as an excellent method for the C-C bond forming process in the synthesis of natural products. In this regard, the phosphacumulene ylides as intramolecular Wittig synthon have been exploited to a large extent for a variety of organic synthetic reactions. However, the synthetic potential of mono- and bis-(trimethylsilyl)methylenetriphenylphosphoranes, one of the recent arrivals in the series of organophosphorus reagents has not been fully realized. As a part of our on going program for developing methodologies using phosphacumulenes[1] and their subsequent application to biologically useful compounds, the (trimethylsilyl)methylenetriphenylphosphorane is envisaged as a versatile reagent offering considerable opportunities for synthetic manipulations.[2]

The (trimethylsilyl)methylenetriphenylphosphorane was prepared from the reaction of triphenylphosphine **1** with methyl iodide **2** and sodamide to yield methylenetriphenylphosphorane **3** which was subsequently reacted with trimethylsilyl chloride **4** to afford the desired (trimethylsilyl)methylenetriphenylphosphorane **5** in good yield (**scheme 1**).

Scheme 1

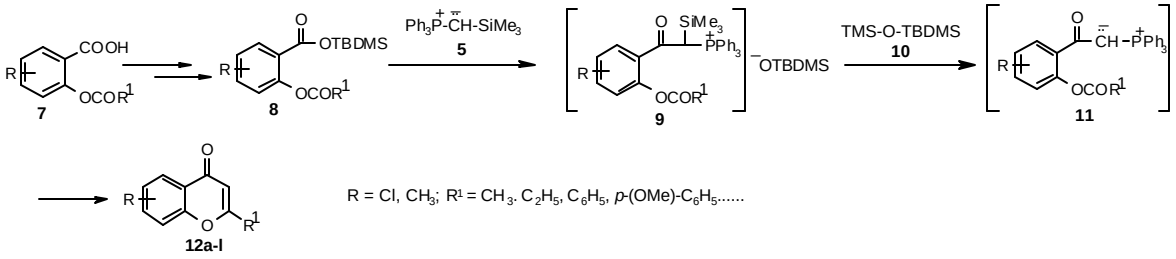


This chapter is further divided into two sections.

Section A: Synthesis of 4*H*-chromen-4-ones

Chromones constitute one of the major class of naturally occurring compounds and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[3] While a variety of synthetic methodologies for chromones have been developed,[4] the literature describing novel one-pot cyclisation method based on consecutive process is rather scarce. We have now developed a new and simple route to 4*H*-chromen-4-ones *via* intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane.

Scheme 2



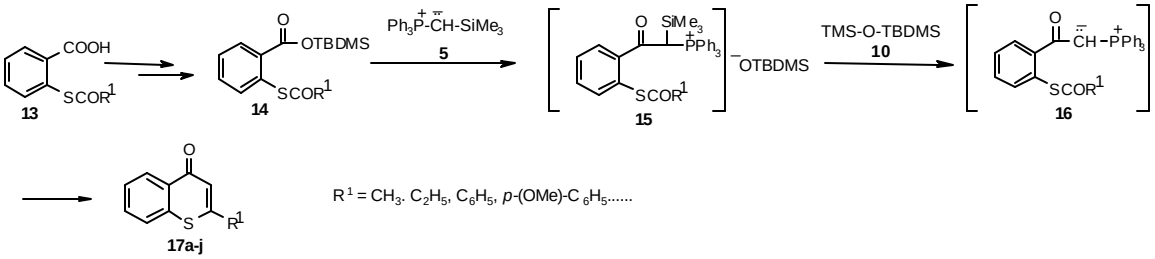
Salicylic acid **7** or its substituted derivative underwent esterification and acylation to afford compound **8**, which on reaction with the ylide, (trimethylsilyl)methylenetriphenylphosphorane **5** underwent ring closure *via* intramolecular Wittig reaction to yield chromones **12** (**scheme 2**). The generality of this reaction has been established with number of examples.

Section B: Synthesis of 4*H*-1-benzothiopyran-4-ones

1-Benzothiopyran-4-ones are an important class of heterocycles. They serve as key intermediates for the synthesis of biologically active compounds.[5] While chromones (4*H*-1-benzopyran-4-ones) have been extensively investigated regarding their synthesis, their isolation as secondary metabolites, and their potential for broad spectrum biological activity,[6] a little attention has been paid towards the synthesis and biological evaluation of thiochromones (4*H*-1-benzothiopyran-4-ones).[7]

In continuation of our earlier work, we have further studied and extended the scope of the above methodology for the construction of other heterocycles as well. Thus, we have developed a convenient and efficient route to 1-benzothiopyran-4-ones *via* intramolecular thiolester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane as illustrated in **scheme 3**.

Scheme 3



Thiosalicylic acid **13** or its substituted derivative underwent esterification and acylation to afford compound **14**, which on reaction with, (trimethylsilyl)methylenetriphenylphosphorane **5** underwent ring closure *via* intramolecular Wittig reaction to give thiochromones **17** (scheme 3). The generality of this reaction has been established with number of examples.

Chapter 2:

Asymmetric Dihydroxylation, Asymmetric Epoxidation and Cyclic Sulfites/Sulfates as Synthetic Intermediates

This chapter gives a brief introduction to Sharpless asymmetric dihydroxylation (AD) reaction, asymmetric epoxidation and cyclic sulfites/sulfates as synthetic intermediates. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. The AD reaction is one such reaction developed by Sharpless in early 1990.[8] It has evolved as one of the most powerful methods for enantioselective oxidation of olefins to optically active vicinal diols that are versatile and convenient building blocks in the synthesis of bioactive molecules.

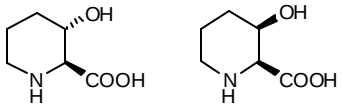
In this chapter the development of AD reaction from stoichiometric to catalytic version, the mechanism, reaction conditions and varied ligands used along with recent applications has been covered. In our synthetic endeavors we have employed the chiral diol compounds obtained by AD reaction towards the synthesis of 3-hydroxy pipecolic acid, 2,6-disubstituted-3-piperidinol alkaloids, and AAL-toxin. To bring about the functional group changes we have also employed the chemistry

of cyclic sulfites/sulfates and epoxides as intermediates.[9] This chapter covers the synthesis, reactivity and applications of cyclic sulfites/sulfates and epoxides as synthetic intermediates.

Chapter 3:

Enantioselective Synthesis of 3-hydroxypipecolic acid

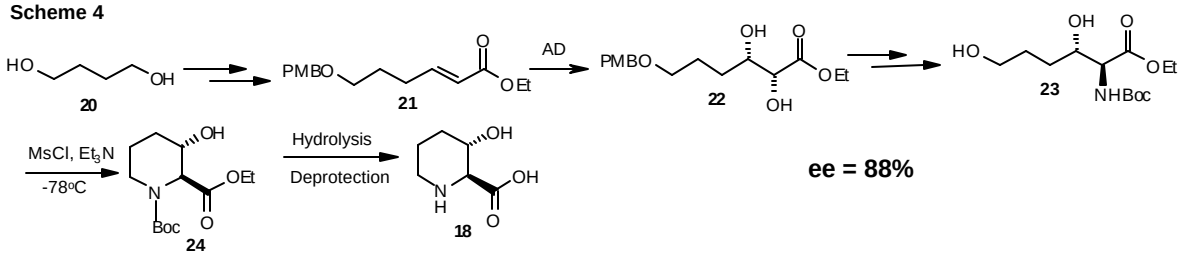
3-Hydroxypipecolic acid, a six-membered cyclic α-amino acid, is an interesting target molecule since it may be seen as a conformationally constrained serine derivative or a hydroxylated homoproline,[10] and may affect the physiological and pathological processes.[11] Moreover, this piperidine unit is found in a number of biologically important products. For example, the *cis*-isomer **19** forms a part of the stucture of tetrazomine, an anititumor antibiotic,[12] while the *trans*-isomer **18** is a precursor of (-)-swainsonine, which has showed a potent and specific α-D-mannosidase inhibitory activity,[13] and it is also found in the structure of Febrifugine, a potential anti-malarial agent.[14] We have employed Sharpless asymmetric dihydroxylation of α,β-unsaturated ester and allylic alcohol, and Sharpless asymmetric epoxidation as the key steps for the synthesis of β-hydroxy pipecolic acid.



18 **19**

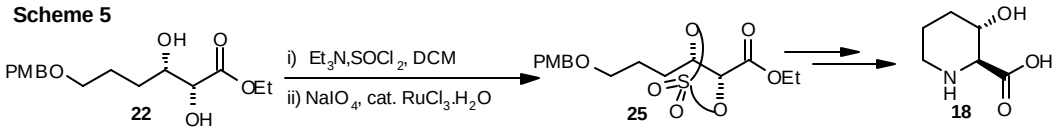
As depicted in **scheme 4**, the diol **22** obtained by Sharpless asymmetric dihydroxylation of the unsaturated ester **21** was converted to Boc-protected amino diol **23,** which in turn was cyclized to piperidine-2-carboxylate **24**, which underwent hydrolysis and deprotection to yield the desired β-hydroxy pipecolic acid **18**.

Scheme 4



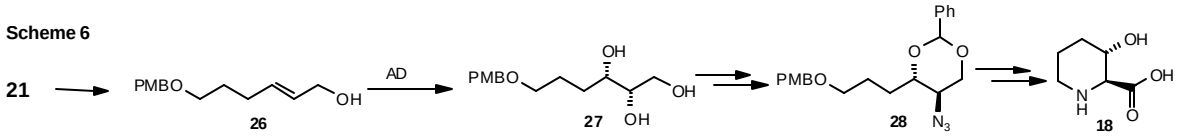
The desired compound **18** was also synthesized by converting diol **22** into the cyclic sulfate **25** (scheme 5). The nucleophilic azide displacement at α-position and subsequent organic transformations as described earlier furnished the target compound **18** in excellent yield.

Scheme 5



As the AD reaction of allylic alcohols is known to give the diol in high enantiomeric excess, we thought of employing the AD reaction on allylic alcohol system. As depicted in **scheme 6**, the triol **27** obtained by the AD reaction of allylic alcohol **26** underwent subsequent organic transformations to yield the desired β-hydroxy pipecolic acid **18** in high ee.

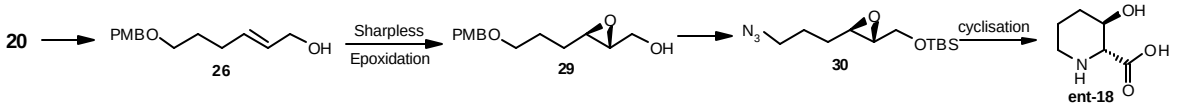
Scheme 6



ee = 92%

It was further planned to employ the Sharpless asymmetric epoxidation of allylic alcohol for the synthesis of β-hydroxypipecolic acid **18**. The epoxide **29** obtained via Sharpless asymmetric epoxidation afforded the azido epoxide **30** by series of reactions (**scheme 7**). The compound **30** was then transformed into the desired β-hydroxypipecolic acid **18**, by regiospecific intramolecular opening of azido epoxide followed by cyclisation.

Scheme 7



ee = 92%

Chapter 4:

a-Amino aldehydes as synthons in the syntheses of aza building blocks for hydroxylated pyrrolidine and piperidine alkaloids

α-Amino aldehydes are versatile building blocks, frequently used in the synthesis of natural products.[15-23] Adducts of α-amino aldehydes and acetylenic compounds are easily transformable to a variety of chiral natural products containing many contiguous stereogenic carbon atoms. Among these products are glycosidic antibiotics,[21] cytostatics,[17] as well as antiviral[23] and anthelmintic compounds.[22] In 1984 Garner published[24] a method for preparing the configurationally stable 1,1-dimethylethyl-4-formyl-2,2-dimethyloxazolidine-3-carboxylate **31**, today called Garner's aldehyde.

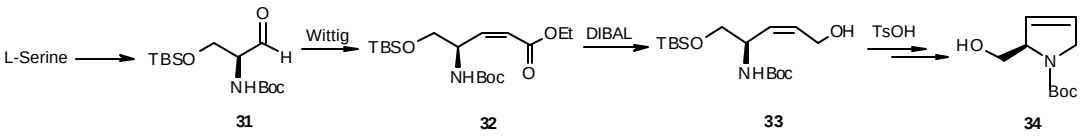
Since that time both enantiomers of **31** have been used extensively as chiral building blocks in asymmetric synthesis. Garner's aldehyde **31** is perhaps one of the most valuable chiral building blocks in recent time, as it has been employed in more than 200 reported studies since its discovery.

This chapter is further divided into three sections.

Section A: Construction of 5-membered aza compounds for the synthesis of hydroxylated pyrrolidine alkaloids

Aldehdye **31**, prepared from L-serine has often been used in the synthesis of important building block, such as compound **34** (**scheme 8**). Compound **32** was converted into allylic alcohol **33** which in turn was cyclized to compound **34**. Compound **34** thus can be transformed easily into biologically active compounds *via* Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation reaction and thus holds lot of synthetic utility as a building block.

Scheme 8

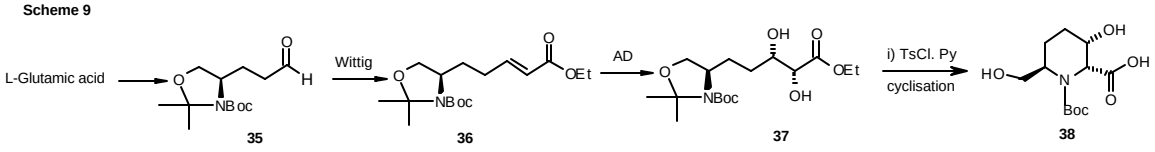


31 **32** **33** **34**

Section B: Construction of 6-membered aza building block for the synthesis of α,α'-3-piperidinol alkaloids

Aldehyde **35**, prepared from L-glutamic acid was used for the synthesis of aza building block **38** which is a key precursor for the synthesis of α,α'-3-piperidinol alkaloids (**scheme 9**). The Sharpless asymmetric dihydroxylation of α,β-unsaturated ester **36** afforded diol **37**, which in turn underwent α-tosylation and cyclisation to afford the aza building block **38**.

Scheme 9



35 **36** **37** **38**

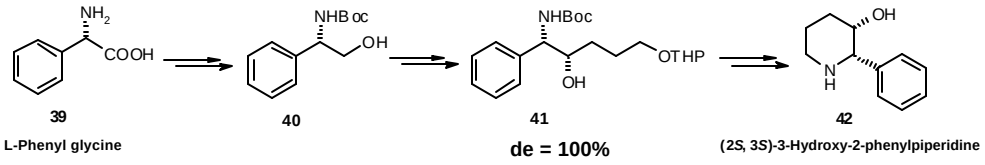
de = 95%

Section C: Synthesis of (2*S*, 3*S*)-3-hydroxy-2-phenylpiperidine

(2*S*, 3*S*)-3-Hydroxy-2-phenylpiperidine **42**, a versatile intermediate for the synthesis of Neurokinin NK1 receptor was synthesized from L-phenyl glycine **39** employing Grignard reaction of compound

40 as the key step (**scheme 10**). The compound **41** was obtained as a single diastereomer, which was further transformed into the desired synthetic intermediate **42**.

Scheme 10



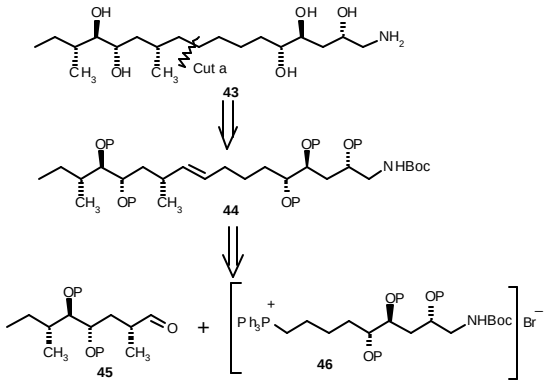
39 L-Phenyl glycine | **40** | **41** de = 100% | **42** (2*S*, 3*S*)-3-Hydroxy-2-phenylpiperidine

Chapter 5:

Studies Directed Towards the Synthesis of AAL-toxin

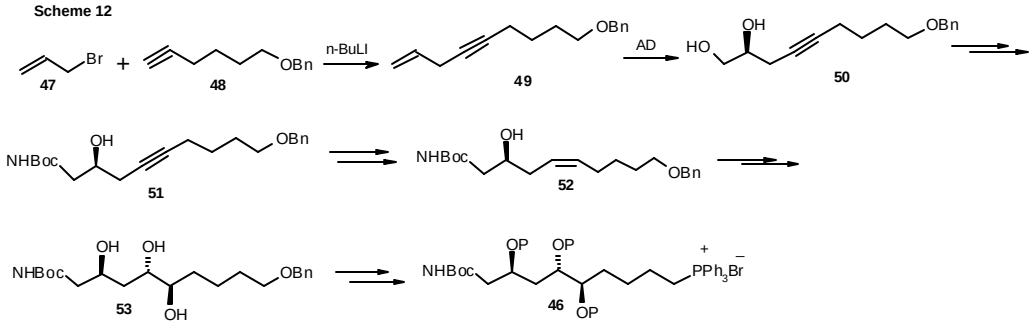
Host-specific toxin (HST) in plant diseases are interesting topics for studying host-parasite interaction. AAL toxins, isolated from *Alternaria alternata f. sp. Lycopersici*, are host-specific phytotoxins responsible for the stem canker diseases of tomato[25]. AAL toxins have been shown to inhibit sphingolipid biosynthesis. It possesses amino alcohol backbones as well as a unique tricaballylic acid moiety similar to fumonisins. Recently the relative configuration and absolute stereochemistry of AAL toxin has been determined by Kishi *et al.*[26] Literature search reveals so far only one report of its total synthesis.

Scheme 11



A convergent approach for the total synthesis of AAL-toxin T_A backbone is planned by the following retrosynthetic route (**scheme 11**). The retrosynthetic analysis of **43** (cut a) shows that the molecule can be divided into two fragments (Scheme 11). It is assumed that two distinct halves would exhibit characteristic spectroscopic properties independent from the remote stereo-centers on the other half of the molecule.

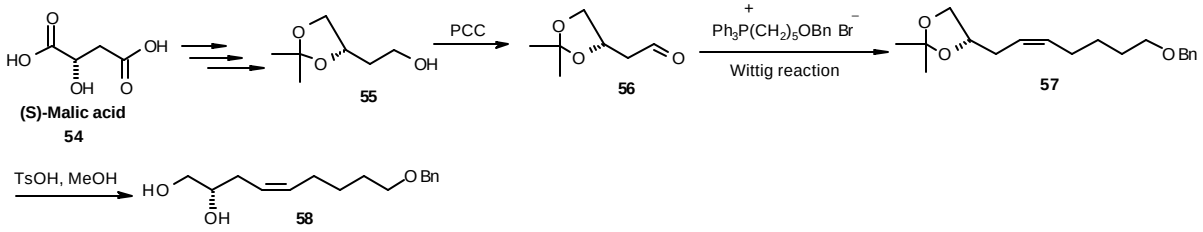
Scheme 12



47 48 49 50 51 52 53 46

The phosphonium salt **46** can be prepared starting from the coupling reaction of allyl bromide **47** with protected 5-hexyn-1-ol **48** to afford compound **49** (**scheme 12**). Sharpless asymmetric dihydroxylation of the terminal olefin **49** led to the formation of diol **50**. The enantiomeric excess of the diol **50** was determined by converting it into its Mosher derivative. Generally the diol formed by Sharpless asymmetric dihydroxylation of terminal olefin leads to the low ee, but in our case we achieved 87% of ee. The primary hydroxyl group of the diol **50** was then converted into Boc protected amine functionality **51** by first converting into the tosyl derivative, then nucleophilic azide displacement of the tosyl and subsequent reduction and protection *in situ* by Boc. The triple bond of **51** was then reduced to *cis* double bond by Lindlar's catalyst to afford the cis olefin **52**. The AD reaction on the *cis* olefin afforded the desired triol **53** with the required stereochemistry. The triol **53** can then be easily transformed into the right half **46** by simple organic transformations.

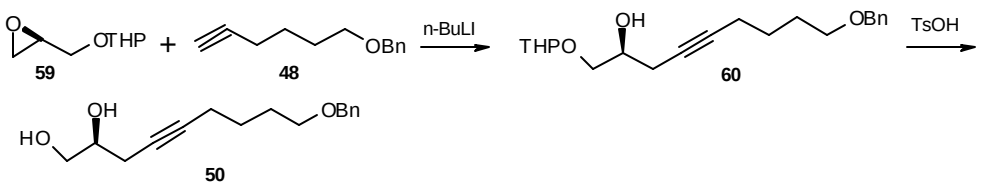
Scheme 13



(S)-Malic acid
54 **55** **56** **57** **58**

The synthesis of right half **46** was also attempted as per the synthetic strategy outlined in **scheme 13**. Thus (S)-malic acid **54** could be converted into **55** through conventional method. The Swern oxidation furnished the aldehyde **56** which underwent Wittig reaction to form the *cis* olefin **57**. The subsequent acetonide deprotection gave compound **58**, which in turn could also be obtained from the reduction of compound **50** (**Scheme 12**).

Scheme 14



59 **48** **60** **50**

Alternatively, the diol **50** could be synthesized starting from optically active tetrahydropyranyl protected (*S*)-glycidol **59** (**scheme 14**). The compound **60** formed by the addition of carbanion of **48** on **58** was subjected to the deprotection of tetrahydropyranyl group to afford the diol **50**.

In summary, the right hand fragment **46** of AAL-toxin was synthesized by three different strategies starting from chiral and achiral substrates.

References

1. a) Kumar, P.; Rao, A. T.; Pandey, B. *J. Chem. Soc., Chem. Commun.* **1992,** 1580. (b) Kumar, P.; Dinesh, C. U.; Pandey, B. *Tetrahedron Lett.* **1994,** *35,* 9228. (c) Kumar, P.; Rao, A. T.; Pandey, B. *Synth. Commun.* **1994,** *24(22),* 3297. (d) Kumar, P.; Saravanan, K. *Tetrahedron* **1998,** *54,* 2161.
2. Bestmann, H. J. Bomhard, A.; Dostalek, R.; Pichl, R.; Riemer, R.; Zimmermann, R. *Synthesis* **1992,** 787.
3. Miao, Z; Yang, S. *Organic Lett.* **2000,** *2,* 1765. and reference therein.
4. a) Ollis, W. D.; Weight, D. *J. Chem. Soc.* **1952,** 3826. (b) Meyer-Dayan, M.; Bodo, B.; Deschamps-Vallet, C.; Molho, D. *Tetrahedron Lett.* **1978,** 3359. (c) Banerji, A.; Goomer, N. C. *Synthesis* **1980,** 874. (d) Babin, P.; Dunoguess, J.; Petraud, M. *Tetrahedron* **1981,** *37,* 1131. (e) Hercouet, A.; Le Corre, M. *Synthesis* **1982,** 597. (f) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* **1990,** *55,* 4349. (g) Nagarathnam, D.; Cushman, M. *Tetrahedron* **1991,** *47* 5071. (h) Nishiraga, A.; Ando, H.; Marugama, K.; Mushino, T. *Synthesis* **1992,** *9,* 839. (i) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. J. *Heterocycl. Chem.* **1996,** *33,* 1887. (j) Riva, C.; Toma, C. D.; Donadel, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. *Synthesis* **1997,** 195. (k) Lokshin, V.; Heynderickx, A.; Samat, A.; Pepe, G.; Guglielmetti, R. *Tetrahedron Lett.* **1999,** *40,* 6761. (l) Dekermendjian, K.; Kahnberg, P.; Witt, M-R.; Sterner, O.; Nielsen, M.; Liljefors, T. *J. Med. Chem.* **1999,** *42,* 4343.
5. (a) Krapcho, J.; Turk, C. F.; Piala, J. J. *J. Med. Chem.* **1968**, *11,* 361. (b) Philipp, A.; Jirkovsky, I.; Martel, R. R; *J. Med. Chem.* **1980**, *23,* 1372. (c) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1985**, *22,* 1593. (d) Malene, C.; Danree, B.; Laubie, M. *Ger. Pat*. **1970**, 2017902; C. A. **1970**, *74*, 22698. (e) Malene, C.; Desnoyers, P. *Br. Pat*. **1969**, 1158473; C. A. **1970**, *72*, 71434. (f) Watanabe, K.; Saito, T.; Niimura, K. *Eur. Pat. Appl*. 1997, EP 758649; C. A. **1997**, *126*, 199456. (g) Tomizawa, K.; Kameo, K.; Saito, H.; Hatayama, K. *Jpn. Kokai Tokkyo Koho* **1990**, JP 02 255676; C. A. **1991**, *114*, 228737. (h) Charris, J.; Dominguez, J.; Lobo, G.; Riggione, F. *Pharm. Pharmacol. Commun*. **1999**, *5(2)*, 107. (i) Sano, T.; Saijo, K.; Tomizawa, K.; Kameo, K.; Yokomori, S.; Hatayama, K. *Jpn. Kokai Tokkyo Koho* **1992**, JP 04082887; C. A. **1992**, *117*, 150893. (j) Jeffery, J. A.;

Outt, P. E.; Randall, J. L.; Johnston, J. N.; Murray, P. D. ; O` Brien, L. M.; Weisshaar, P. S.; Ems, B. L. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 995.

6. (a) Ellis, G. P., *Comprehensive Heterocyclic Chemistry* , Katritzky, A. R. ; Rees, C. W., Eds; Pergamon Press, New York, **1984**, *Vol. 3*, Part 2B , pp 695, 718. (b) Hepworth, J. P., *Comprehensive Heterocyclic Chemistry* , Katritzky, A. R. ; Rees, C. W., Eds.; Pergamon Press, New York, **1984**; Vol. 3, Part 2B, pp 816-830 and 874-883.
7. (a) Hepworth, J. P., *Comprehensive Heterocyclic Chemistry*. , Katritzky, A. R. ; Rees, C. W., Eds; Pergamon Press, New York, **1984**, *Vol. 3*, Part 2B, pp 918-919. (b) Ingall, A. H., *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. ; Rees, C. W., Eds; Pergamon Press, New York, **1984**, *Vol. 3*, Part 2B., pp 941-942.
8. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
9. For reviews on cyclic sulfites/sulfates chemistry, see: (a) Lohray, B. B. Synthesis 1992, 1035. (b) Byun, H-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
10. (a) Wang, C. J.; Wuonola, M. A. *Org. Prep & Proced. Int*. **1992**, *24*, 585. (b) Bailey, P. D.; Millwodd, P. A.; Smith, P. O. *J. Chem. Soc., Chem. Comm.* **1998**, 633.
11. (a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866. (b) Greck, C.; Ferreira, F.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031. (c) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1996**, *37*, 4001. (d) Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron Asymm.* **1997**, *8*, 2957. (e) Scott, J. D.; Tippie, T. N.; Williams R. M. *Tetraheron Lett.* **1998**, *39*, *3659*. (f) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett*. **1999**, *40*, 3843.
12. (a) Saitoh, Y.; Moriyama, Y.; Hirota, H.; takahashi, T.; Khuong-Huu, Q. *Bull. Chem*. *Soc. Jpn.* **1981**, *54*, 488. (b) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K.H.; Byrne, N. E. *J. Am. Chem. Soc*. **1989**, *111*, 3473. (c) Yang, C. H.; Xu, Y. M.; Liao, L. X.; Zhou, W. S. *Tetrahedron Lett.* **1998**, *39*, 9227. (d) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1998**, *39*, 3505. (e) Kadota, L.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 7469. (f) Luker, L..; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3592. (g) Ojima, L.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999. (h) Koulocher, S. D.; Haroutounian, S. A. *Tetrahedron Lett.* **1999**, *40*, 6869. (i) Herdeis, C.; Telser, J. *Eur. J. Org. Chem*. **1999**, 1407.
13. (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175. (b) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814.
14. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron Asymm.* **1997**, *17*, 2975.
15. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*, Wiley, New York **1987**.
16. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

17. Jurczak, J.; Golebiowski, A. From α-amino acids to amino sugars, in *Studies in Natural Products Chemistry*: Atta-ur-Rahman (Ed.), Vol. 4, Stereoselective Synthesis (Part C), Elsevier **1989**.
18. Golebiowski, A.; Jurczak, J. Total synthesis of linocomycin and related chemistry, in *Recent Progress in the Chemical Synthesis of Antibiotics*, Springer, Berlin **1990**.
19. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 11531.
20. Dondoni, A. Carbohydrate synthesis via thiazoles, in *Modern Synthetic Reactions*, Vol. 2, p. 377, Verlag Helvetica Chimica Acta, Basel, VCH, Weinheim **1992**.
21. Jurczak, J.; Golebiowski, A. The synthesis of antibioic amino sugars from α-amino aldehydes, in *Antibiotics and Antiviral Compounds*, Chemical Synthesis and Modification, VCH, Weinheim **1993**.
22. Golebiowski, A. Jurczak, J. *Synlett* **1993**, 241.
23. Kiciak, K.; Jacobsson, U.; Golebiowski, A.; Jurczak, J. *Polish J. Chem*. **1993**, *67*, 685.
24. Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
25. (a) Bottini, A. T.; Gilchrist, D. G. *Tetrahedron Lett*. **1981**, *22*, 2719. (b) Bottini, A. T.; Bowen, J. R.; Gilchrist, D. G. *Tetrahedron Lett*. **1981**, *22, 2723*.
26. Boyle, C. D.; Harmange, J-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995

PUBLICATIONS/CONFERENCES/SYMPOSIA PARTICIPATED/ AWARDS

➢ List of Publications

I) A Novel Synthesis of 4*H*-Chromen-4-ones via Intramolecular Wittig Reaction
Pradeep Kumar* and **Mandar S. Bodas**
Org. Lett. **2000**, *2*, 3821.

II) Yttria-Zirconia Based Lewis Acid: An Efficient and Chemoselective Catalyst for Acylaton Reactions
Pradeep Kumar,* Rajesh Kumar Pandey, **Mandar S. Bodas**, Mohan K. Dongare
Synlett **2001**, 206.

III) A new synthesis of 4*H*-1-benzothiopyran-4-ones using (trimehtylsilyl) methlylene\triphenylphosphorane
Pradeep Kumar* and **Mandar S. Bodas**
Tetrahedron **2001**, *57*, 9755.

IV) Asymmetric dihydroxylation and regioselective C-3 indole coupling routes to the anticoccidial antiobiotic (+)-Diolmycin A2
Rodeny A. Fernandes, **Mandar S. Bodas** and Pradeep Kumar*
Tetrahedron **2002**, *58*, 1223.

V) Acylation of alcohols, thiols and amines with carboxylic acids catalyzed by yttria-zirconia based Lewis acid
Pradeep Kumar,* Rajesh K. Pandey, **Mandar S. Bodas**, Sharda P. Dagade, Mohan K. Dongare, A. V. Ramaswamy
J. Mol. Cat. A. **2002**, *181*, 207.

VI) An efficient stereoselective synthesis of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine
Mandar S. Bodas, Puspesh K. Upadhyay, Pradeep Kumar*
Tetrahedron Lett. **2004**, *45*, 987.

➢ Conferences/Symposia Participated

I) A Novel Synthesis of 4*H*-Chromen-4-ones *via* Intramolecular Wittig Reaction
Mandar S. Bodas, Pradeep Kumar
Presented at Fourth National Symposium in Chemistry, Pune February 1-3, 2002.

II) Enantioselective synthesis of 3-piperidinol alkaloids
Mandar S. Bodas, Pradeep Kumar
Presented at Ramanbhai Foundation 1st International Symposium, Zydus Cadilla, Ahemdabad January 23-25, 2003.

III) Total synthesis of both enantiomers of *trans*-? -hydroxypipecolic acid
Mandar S. Bodas, Pradeep Kumar
Presented at Fifth National Symposium in Chemistry, Pune February 7-9, 2003.

IV) Enantioselective synthesis of 3-piperidinol alkaloids
Nagendra B. Kondekar**, Mandar S. Bodas**, Pradeep Kumar
Presented at Fifth National Symposium in Chemistry, Pune February 7-9, 2003.

VI) Stereoselective synthesis of (2S,3S)-3-hydroxy-2-phenyl piperidine: Application to the synthesis of NK1 receptors
Mandar S. Bodas, Pradeep Kumar
Presented at IUPAC symposium on Biodiversity and Natural Products, New Delhi January 27-31 2004.

CHAPTER 3:
ENANTIOSELECTIVE SYNTHESIS OF 3-HYDROXYPIPECOLIC ACID

CHAPTER 4:
a-AMINO ALDEHYDES AS SYNTHONS IN THE SYNTHESES OF AZA BUILDING BLOCKS FOR HYDROXYLATED PYRROLIDINE AND PIPERIDINE ALKALOIDS

CHAPTER 5:
STUDIES DIRECTED TOWARDS THE SYNTHESIS OF AAL-TOXIN

CHAPTER 1

Synthesis of (trimethylsilyl)methylenetriphenylphosphorane: Application Towards The Synthesis of 4H-chromen-4-ones and 4H-1-benzothiopyran-4-ones via Intramolecular Wittig Reaction

CHAPTER 1

Synthesis of (trimethylsilyl)methylenetriphenyl-phosphorane: Application towards the synthesis of *4H*-chromen-4-ones and *4H*-1-benzothiopyran-4-ones *via* Intramolecular Wittig Reaction

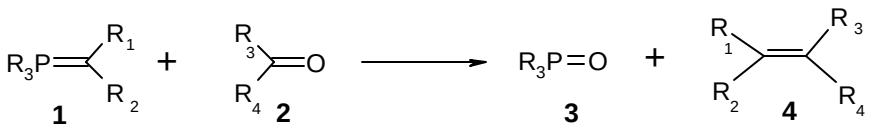
1.1 WITTIG REACTION:

1.1.1. Introduction

There was a time in organic chemistry when the olefination of ketones and aldehydes was faced with some trepidation. Because of limited synthetic methods, as recently as 50 years ago, the chemist had to contend with two isomer problems, that of double-bond position and that of double-bond geometry. Landmark papers[1,2] published by Wittig and co-workers in the early 1950s disclosed a means for the preparation of alkenes with unambiguous positioning of the double bond, based on the reaction of aldehydes or ketones with phosphonium ylides. Because of its effectiveness and generality, the Wittig reaction became widely used and thereby changed the course of olefin synthesis for all time.[3] Indeed, the development of the Wittig reaction helped to usher in the modern era of organic synthesis, wherein positional selectivity, stereoselectivity, and chemoselectivity are of paramount importance to, and under the sensitive and responsive control of, the synthetic practitioner.[4] The 1960s witnessed major advances in the Wittig reaction and in Wittig-style olefinations. The stereochemistry and mechanism of the Wittig reaction were investigated, and a complementary reaction involving phosphoryl-stabilized carbanions

was developed. Several reviews have documented the state of the Wittig and related reactions.[5-17]

In 1953, Wittig and Geissler discovered that the reaction of triphenylmethylenetriphenyl-phosphorane with benzophenone resulted in an almost quantitative yield of 1,1-diphenylethene and triphenylphosphine oxide.[1] Thus the reaction between a phosphorane or phosphonium ylide, and an aldehyde or ketone to form a phosphine oxide and an alkene is known as the Wittig reaction after the German chemist George Wittig, who first showed the value of this procedure in the synthesis of alkenes. This unusual reaction leading to carbon-carbon bonds in one synthetic step was quickly applied to a large variety of different triphenylalkylidene phosphoranes and carbonyl compounds to give alkenes.

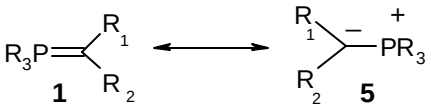


Scheme 1

The valuable feature of Wittig procedure is that, in contrast to the elimination and pyrolytic reactions, it gives rise to alkenes in which the position of the double bond is unambiguous. The reaction generally leads to high yields of di- and tri-substituted alkenes from aldehydes and ketones but because of steric effect, yields of tetra-substituted alkenes from ketones are often poor. The use of Wittig reaction in the synthesis of naturally occurring molecules[18] and as a general method for the preparation of alkenes[17] in a predictable manner has led to it becoming one of the most corner stones of synthetic chemistry.

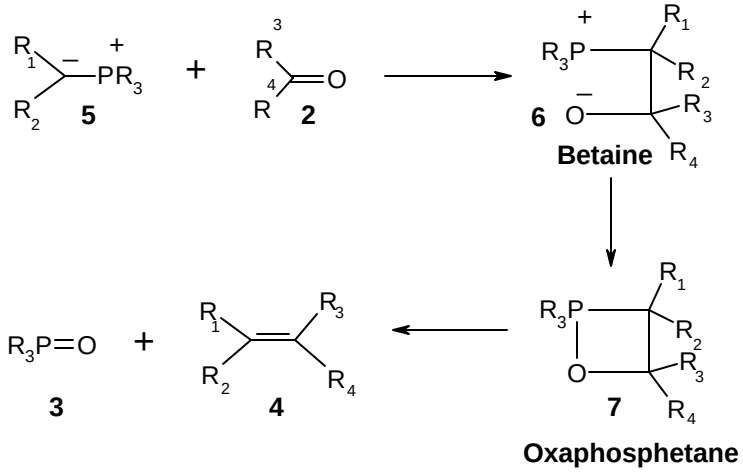
1.1.2 Phosphonium Ylides

Phosphoranes (phosphonium ylide) are resonance stabilized structure in which there is some overlap between the carbon p-orbital and one of the d orbitals of phosphorus as shown in **Scheme 2.**



Scheme 2

Reaction with a carbonyl compound takes place by attack of the carbanionoid carbon of the ylide form on the electrophilic carbon of the carbonyl group with the formation of a



Scheme 3

betaine which collapses to the products by way of a four-membered cyclic transition state (**Scheme 3**), the driving force being provided by formation of the very strong phosphorus oxygen bonds.

Depending on the reactants, either the first or the second step may be rate determining. It has never been observed that the last step is the slowest, and it is uncertain whether the four-membered ring compound is a true intermediate or a transition state. Evidence for the formation is provided by the isolation of compounds of this type in certain cases.

The reactivity of phosphorane depends on the nature of the groups R, R_1 & R_2. In practice, R is nearly always phenyl. Alkylidenetrialkylphosphoranes, in which the formal positive charge on the phosphorus is lessened by the inductive effect of the alkyl groups, are more

reactive than alkylidenetriphenylphosphoranes in the initial addition to a carbonyl group to form a betaine.

In the alkylidene part of the phosphorane, if R_1 or R_2 is an electron withdrawing group (eg. CO or CO_2R), the negative charge in the ylide becomes delocalised into R_1 or R_2 and the nucleophilic character, and reactivity towards carbonyl groups, is decreased. Reagents of this type are much more stable and less reactive than those in which R_1 or R_2 are alkyl groups, and with them the rate determining step in reaction with carbonyl groups is the initial addition to form the betaine. The more electrophilic the carbonyl group the more readily does the reaction proceed.

In the reaction of phosphonate anions and resonance stabilized ylides with aldehydes the *E*-alkene generally predominates. Non-stabilized ylides, on the other hand, usually give more of the *Z*-alkene. High yields of *Z*-1,2-disubstituted alkenes have also been obtained using sodiumhexamethyldisilazide, $NaN[Si(CH_3)]_2$, as base. Varying the reaction conditions can substantially alter the steric course of the reactions, and by proper choice of experimental conditions a high degree of steric control can be achieved at least for reaction leading to disubstituted alkenes. Thus, reaction of stabilized ylides with aldehydes in the presence of protic solvents or lithium salts gives increased amounts of *E*-alkenes. With non-stabilized ylides, salt-free condition and non-polar solvents give high selectivity for *Z*-alkene. These variation in the ratio of *Z*- and *E*-products can be ascribed to the influence of the solvent and additives on the relative stabilities and rates of decomposition of the threo and erythro betaines.[19a-d] Two other variations of the Wittig reaction which overcome the stereochemical limitation to some extent and which can be used for the stereoselective synthesis of *Z*- and *E*-1,2-disubstituted alkenes, are based on the reactivity available with phosphine oxides and phosphonobis-*N,N*-dialkylamides.[20a-b] Reactions employing anions derived from phosphine oxides (the Horner-Wittig reactions) are now finding increasing applications.

1.1.2.1 Stereochemistry and Mechanism

The nonstabilized class of phosphorus ylides is particularly significant mechanistically in that the thermodynamically less stable (*Z*)-alkene is often produced preferentially.[8,11,12,14,21,22] In

fact a certain mystique has persisted with respect to this high preference for contrathermodynamic (*Z*)-alkenes in, for example, reactions of triphenylphosphorus nonstabilized ylides with aldehydes. This characteristic has attracted the curiosity of chemists for decades and stimulated attempts to arrive at a truly satisfying mechanistic explanation. The other two classes of ylides are also interesting from a mechanistic standpoint. For example, one may wonder: Is the strong preference for the (*E*)-alkenes with many stabilized ylides a consequence of kinetic or thermodynamic control. To define the source of such stereocontrol, organic chemists have resorted to mechanistic studies and the pursuit of reaction intermediates.

⇒ 1,2-Oxaphosphetanes and Betaines as Intermediates

Regarding intermediates in the reaction, Wittig first mentioned a four-membered cyclic phosphorane (a 1,2-oxaphosphetane) early on;[1] however, he soon came to favor a zwitterionic phosphorus betaine (**Figure 1**).[2,23] This view gained broad acceptance in the mid 1960s,[5,6,9,24-28] and by 1970. The mechanism of the Wittig reaction was commonly expressed in terms of two steps: (1) nucleophilic addition of the phosphorus ylide to the carbonyl compound to give a betaine species and (2) irreversible decomposition of the betaine to give alkene and phosphine oxide (eq 1).[5-9,24-28] Although the 1,2-oxaphosphetane was widely considered to be a transition state between betaine and final products, rather than a distinct intermediate, two reviews were careful to present the oxaphosphetane as a possible intermediate.[7,9]

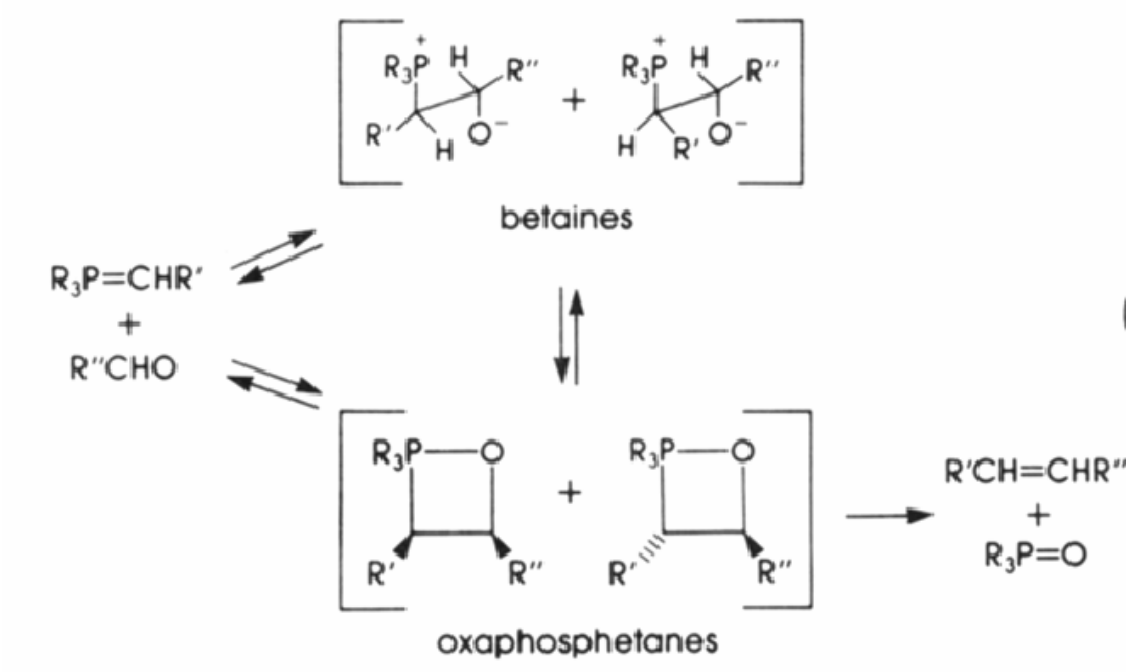
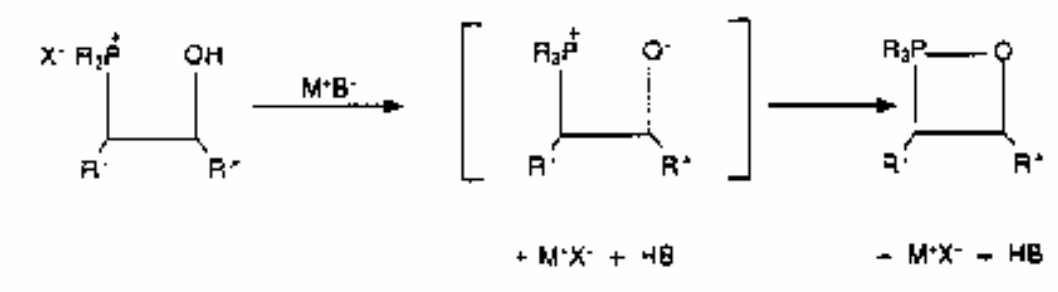


Figure 1

Greater weight had been placed on the dipolar betaine intermediate because of certain experimental observations: (1) the in situ formation of stable adducts between betaines and lithium halide salts, (2) the trapping of betaines as β-hydroxy phosphonium salts by addition of acid at low temperature, and (3) the pronounced effect of lithium salts on alkene stereochemistry.[2,5,6,8,9,26-28] However, in 1973 Vedejs reported for the first time that oxaphosphetanes are the sole observable intermediates by ^{31}P NMR spectroscopy in conventional reactions of nonstabilized ylides at low temperature.[29] Vedejs' positive observations, along with the lack of evidence for uncomplexed betaines, revolutionized impressions about the Wittig reaction mechanism for most organic chemists. Subsequent work by the Vedejs group, reported in 1981[21] established 1,2-oxaphosphetanes as principal intermediates in a variety of reactions involving nonstabilized phosphorus ylides and aldehydes or ketones. In the 1980s, Maryanoff and co-workers extended the oxaphosphetane paradigm by detecting and quantitating the short-lived diastereomeric intermediates in Wittig reactions of nonstabilized ylides and aldehyde.[30-34] In general, the ^{31}P NMR signal for pentacoordinate phosphorus in oxaphosphetanes occurs far upfield (e.g., from -50 to -80 ppm) relative to the reference (at 0 ppm), while the signal for tetracoordinate phosphorus in a betaine would be expected to occur downfield (e.g., from 10 to 50 ppm). The

relative importance of oxaphosphetanes *vs* betaines as intermediates has been a persistent concern. To date, true betaines have never been observed directly in any Wittig reaction. The precipitates formed in certain lithium salt reactions[22] are really betaine-lithium halide adducts, which should not be confused with "salt-free" (i.e., uncomplexed) betaines. Such complexes can arise by the addition of a lithium salt (mild Lewis acid) across the P-O bond of a preformed oxaphosphetane,[22] as opposed to direct formation. By the same token, the production of *O*-hydroxy phosphonium salts on treatment of Wittig reactions with acid at low temperature can be attributed to oxaphosphetanes, which are readily cleaved by addition of HX across the P-O bond.[22,24,33] Even in cases where the betaine must be generated first, such as in deprotonation of a *O*-hydroxy phosphonium salt with base (eq 2), only oxaphosphetane species have been noted by NMR spectroscopy.[33-36]



Equation 2

Since the course of the Wittig reaction virtually demands an oxaphosphetane stage, the question arises: Does a betaine precede the oxaphosphetane stage (Wittig reaction of three distinct steps: ylide + aldehyde - betaine - oxaphosphetane - alkene) or is the oxaphosphetane formed directly from ylide and aldehyde. From the body of experimental data, Vedejs[22,36b] has argued that a four-centered transition state leading directly to oxaphosphetane is more likely. Also, several theoretical studies have strongly favored oxaphosphetanes over betaines.[10b,12,37,38-40]

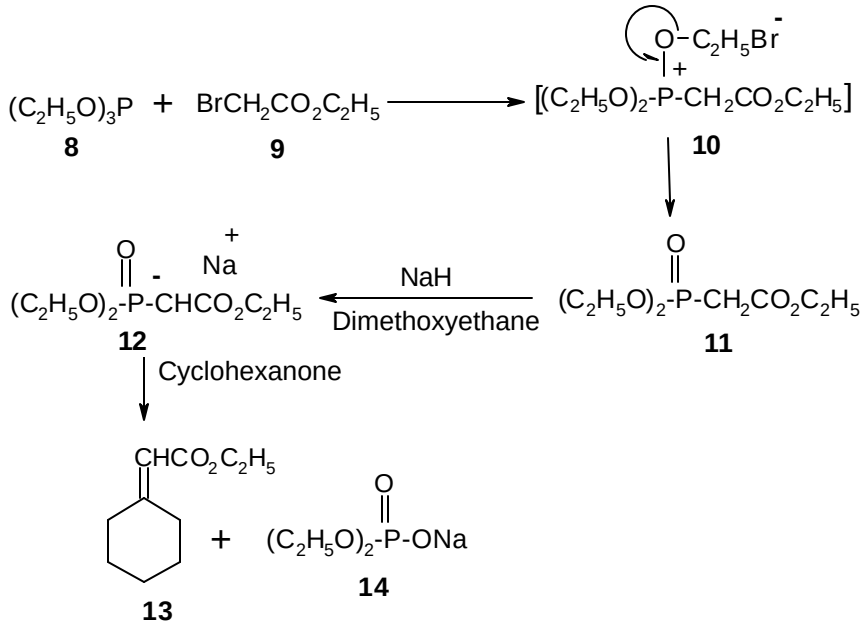
The mechanism of collapse of an oxaphosphetane to ylide and aldehyde is presumably the opposite of direct condensation, given microscopic reversibility. The mechanism for decomposition of an oxaphosphetane to alkene and phosphine oxide is a separate issue of considerable interest. Is this process concerted or stepwise, syn or anti, in nature? Bestmann has proposed the hypothesis of a stepwise path with the concentration of negative charge on carbon and positive charge on phosphorus, in a sort of E2 elimination mechanism. This could

account for the high *E* stereoselectivity of stabilized ylides, where the opportunity for epimerization by bond rotation would be enhanced.

As mentioned above, there has been a mystique associated with the high preference for the contrathermodynamic (*Z*)-alkene in reactions of triphenylphosphonium nonstabilized ylides with aldehydes. For more than two decades, organic chemists have tried to identify the specific factors involved in such stereocontrol. Thus, stereochemistry has served as the premier probe for acquiring mechanistic information on the Wittig reaction and, coincidentally, it has led to a deeper understanding of the mechanism. The pronounced *E* stereoselectivity in reactions of aldehydes with trialkylphosphonium ylides, and with triphenylphosphorus ylides bearing anionic groups, has merited considerable interest as well.

1.1.3 Phosphonate Carbanions

Wittig reactions with stabilized phosphoranes sometimes proceed only slowly. A valuable alternative makes use of phosphonate esters, themselves readily obtained from an alkyl halide and triethylphosphite via an Arbuzov rearrangement[41] or Micharlo-Becker reaction.[42]



Scheme 4

Reaction of the phosphonates with a suitable base gives the corresponding carbanions which are more nucleophilic than the related phosphoranes, since the negative charge is no longer attenuated by delocalisation into d orbitals of the adjacent positively charged phosphorus atom (**Scheme 4**).

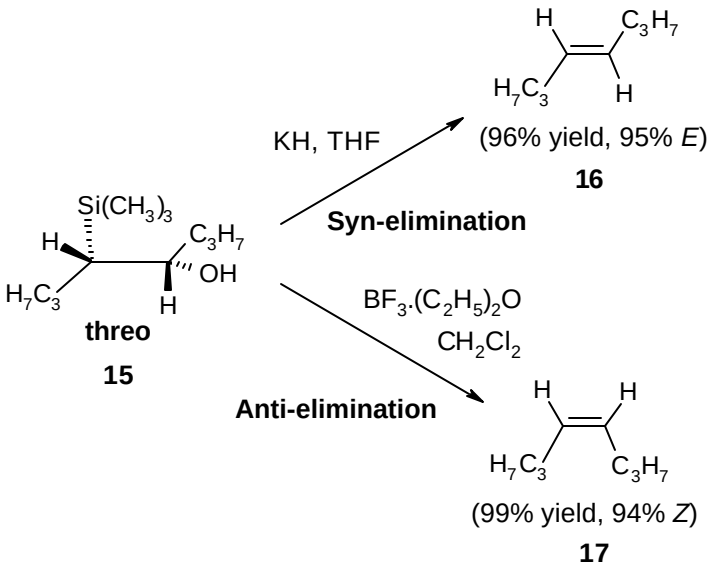
They react readily with the carbonyl group of aldehyde and ketones to form an alkene and a water-soluble phosphate ester. The mechanism of the reaction is analogous to that of Wittig reaction, proceeding by way of *erythro* and *threo* intermediates oxyanions, which undergo *syn* elimination of phosphate, possibly by way of a four membered cyclic intermediate.

Horner and co-workers were the first to react phosphoryl-stabilized carbanions with aldehydes and ketones to produce a olefin.[43,44] This procedure is sometimes also called the Wadsworth Emmons reaction as they serve to popularize this method in the organic synthetic community.[45]

This reaction is superior to Wittig reaction with resonance-stabilized phosphoranes and it is widely employed in the preparation of α,β-unsaturated esters and ketones and other conjugated systems. It gives better yield than Wittig reaction, the useful practical advantage that the phosphate formed as by-product is water soluble and easily removed from the reaction mixture. It is unsuitable for the preparation of alkenes from non-stabilized reagents; in these cases reaction stops at the betaine stage and no alkene is produced.

Several types of phosphonates have been used in synthesis[46] such as nonstabilized phosphonates, phosphonate bearig an α-carbonyl or cyano group, phosphonate bearing both α- and β-carbonyl groups, vinyl and aryl stabilized phosphonates, bisphosphonates and related reagents and heteroatom-stabilized phosphonates.

There is a silicon version of the Wittig reaction, known as the Peterson reaction. It entails the elimination of trimethylsilanol, $(CH_3)_3SiOH$, from a *O*-hydroxy alkyltriethylsilane, and has the practical advantage over the Wittig reaction that the by-product of the reaction, hexamethyldisiloxane, is volatile and much easier to remove from the reaction product than triphenylphosphine oxide. Further the steric course of the reaction is more easily



Scheme 5

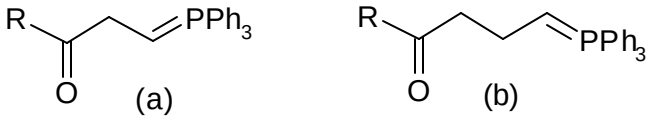
controlled at least for the generation of disubstituted alkenes. Both the *Z*- and *E*-forms of an alkene can be separately obtained from a single stereomer of the hydroxysilane depending on whether the elimination is efficient under basic or acidic conditions (**Scheme 5**).

Table 1: Factors responsible for *E*- and *Z*-Products in the Wittig reaction

Entry	Thermodynamic Control (E-Product)	Kinetic Control (Z-Product)
1.	Elevated temperature	Low Temperature
2.	Non polar, protic solvent	Polar, aprotic solvent
3.	Betain stabilizing salts	Lewis base
	eg. $Li^+BH_4^-$	Salt free solvents
4.	Carbanion stabilization	No carbanion stabilization
5.	Electron rich phosphorus atom	Electrophilic phosphorus atom
6.	Excess base	

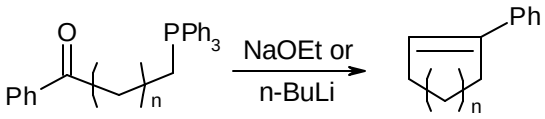
1.1.4 Intramolecular Wittig Reaction

In an intramolecular Wittig reaction, a bicyclic oxaphosphetane must be formed. It is therefore no surprise that cyclopropenes and cyclobutenes are not accessible by this reaction. The corresponding oxaphosphabicyclo[2.1.0]pentanes and [2.2.0]hexanes would be excessively strained, although the P-O bond is much longer than a C-C single bond.[47] The β-carbonyl alkylidenephosphoranes (a) hypothetical precursors of cyclopropenes, are hard to come by, because the corresponding acylethyltriphenyl phosphonium salts undergo Hofmann type elimination of triphenylphosphine on base treatment.[48,49] γ-Carbonyl alkylidenephosphoranes (b) rather give cyclooctadienes by double condensation than cyclobutanes.[50] Triphenylphosphine elimination and formation of a cyclopropyl ketones can also occur.[49]



As expected on the basis of the mechanistic interpretation shown in **Scheme 3**, the common 5-, 6- and 7-membered rings are produced fairly easily by intramolecular Wittig reaction. The formation of medium and large ring cycloalkenes require high dilution techniques, but can be readily accomplished. As long as the carbonyl carbon and the phosphorus ylide carbon can come within reasonable distance from each other and react to give a single bond in a ring with five or more atoms, there are good chances that finally the strained cycloalkene is formed.

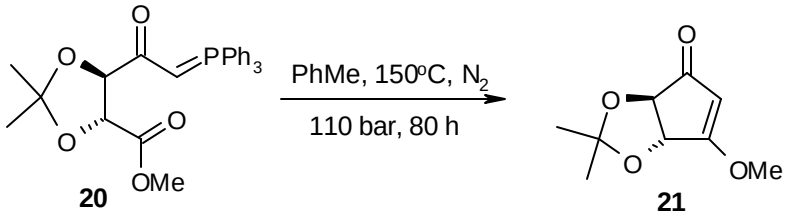
The first example of an intramolecular Wittig reaction with a carbonyl alkyltriphenylphosphonium salt was reported in 1962 and 1964 by two independent groups[49,51] who described the synthesis of 1-phenyl cyclohexene and cyclopentene (**Scheme 6**).



18 **19**

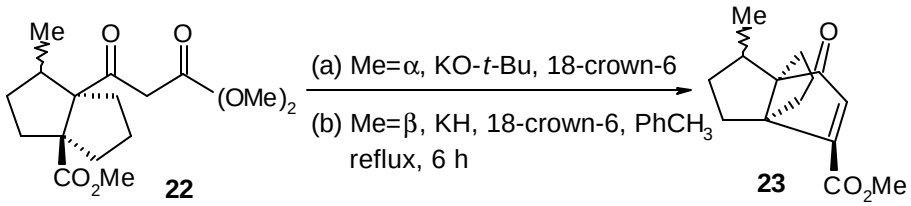
Scheme 6

Simple esters show better reactivity when used in intramolecular reactions, for example Bestmann and co-workers have reported the interesting cyclisation of the tartrate-derived phosphorane, which proceeds in 60% yield to give cyclopentenone, the starting material in



20 **21**

Scheme 7



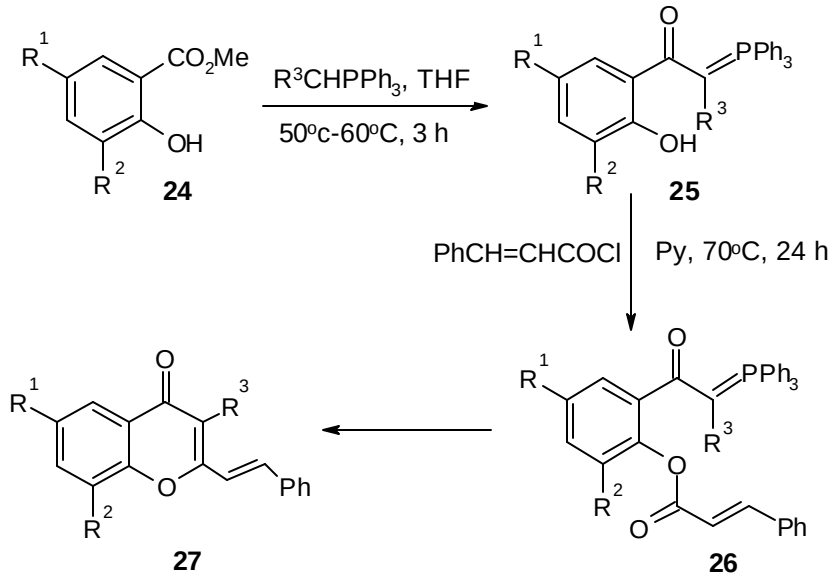
22 **23**

Scheme 8

his synthesis of the carbocyclic nucleoside (-)-neplanocin A. It is however worthy of note that the reaction, which proceeds with epimerisation at C-3, requires highly forcing conditions (**Scheme 7**).[52] In a related process Kraus and Shir reported the synthesis of the tricycles by cyclisation of the phosphonates in modest yield (**Scheme 8**).[53]

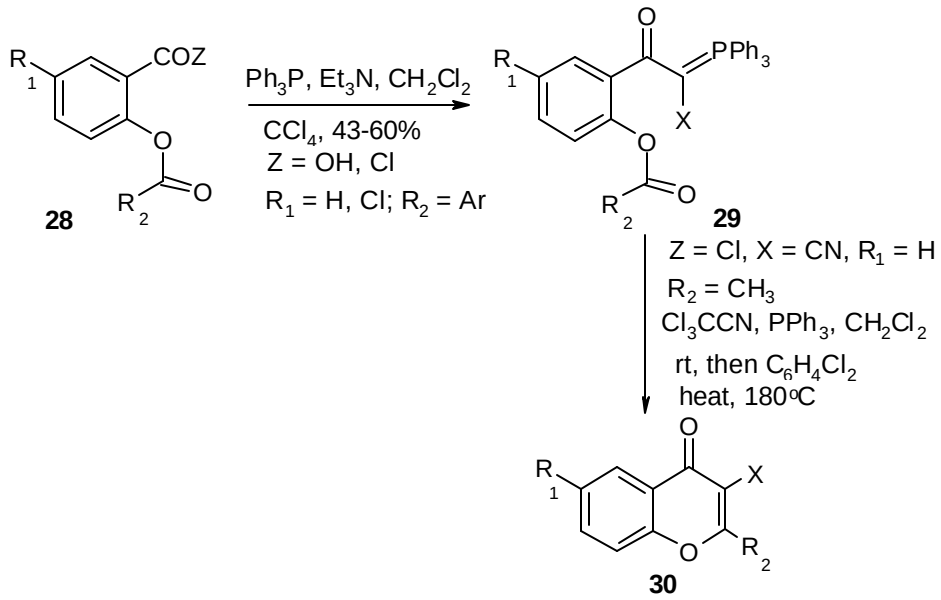
Intramolecular reaction of ester have found considerable application in the synthesis of heterocycles and several examples detailing the formation of benzofurans, chromones, isochromones, dihydrofurans and dihydropyrans have been reported.[54,55]

An example of the synthesis of 2-styryl-4H-[1]benzopyran-4-ones involve the commonly used strategy[56] of reacting the ester function of aromatic ester with non-stabilized ylides



Scheme 9

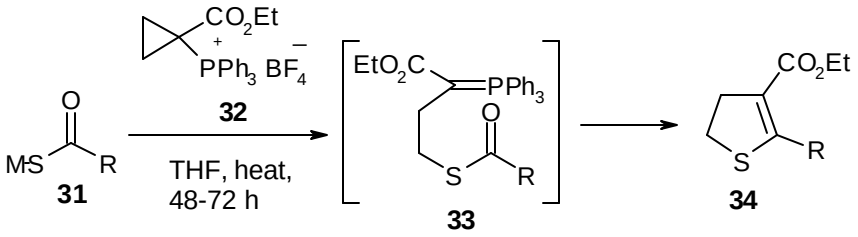
leading to the *O*-ketophosphoranes followed by acylation of the free hydroxy group with an excess of cinnamyl chloride in pyridine to give the intermediate which undergo cyclisation on heating to give the benzopyran-4-one (**Scheme 9**).[57]



Scheme 10

The alternative strategy is to reverse these two steps and begin with an acylsalicylic acid and convert the acid function into a phosphorane.[58] For example the heterocycles (X=Cl) are easily prepared by treatment of the arylcarboxylic acids (Z=OH) with triphenylphosphine in the presence of carbon tetrachloride.[59] This reaction is thought to proceed via an acid chloride and then the intermediate chloro ylide; evidence is offered by the isolation of the cyano ylide (X=CN) prepared from the acid chloride (Z=Cl), which undergoes cyclisation under forcing conditions to give chromones[59] (**Scheme 10**).

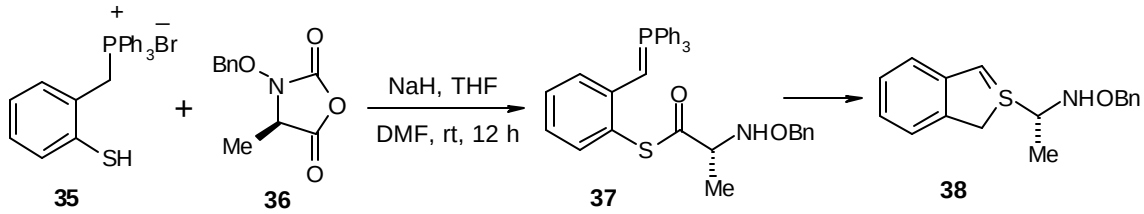
An example of Wittig reaction with thiol esters illustrates the preparation of a series of dihydrothiophenes **34** from the cyclopropane phosphonium salt **32**.[60] Treatment of a thiol acid with **32** in refluxing THF leads to the formation of the dihydrothiophene in high yields, the reaction proceeding *via* the phosphorane **33** (**Scheme 11**).



M = Na, K; R = Me, Ph, OEt, *n*-Pr, *i*-Pr, *t*-Bu, 2-Furyl, CO_2Et

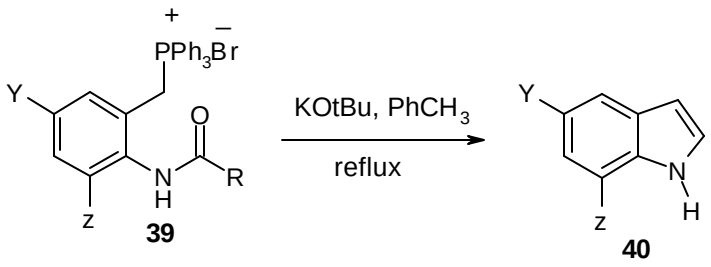
Scheme 11

A similar reaction has been used in the preparation of the benzothiophene **38** where treatment of the anhydride **36** with the sodium thiolate **35** led to the Wittig cyclisation *via* the intermediate **37**[61] (**Scheme 12**).



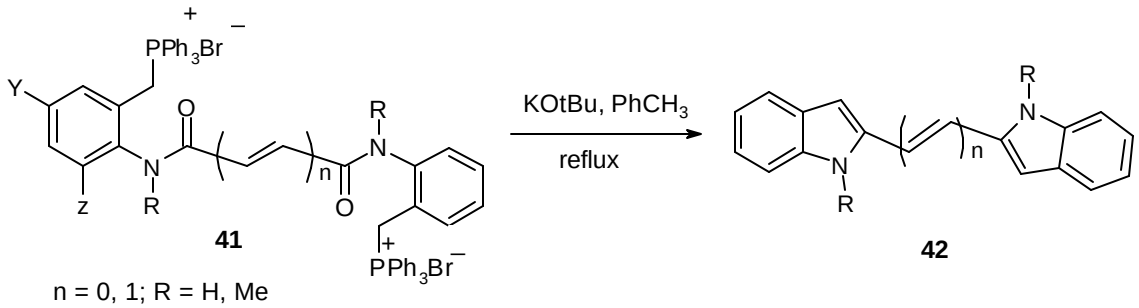
Scheme 12

A useful synthesis of indoles which is applicable to large scale preparations utilizes the intramolecular Wittig reaction of amides. This reaction has continued to be applied to numerous syntheses of indoles **40** from the phosphonium salt **39** on treatment with a base (typically KOtBu) and has become one of the accepted standard routes to this heterocyclic system (**Scheme 13**).[62]



Scheme 13

In addition, Cupuano and co-workers have reported the synthesis of bis-indoles **42** from the corresponding phosphonium salt **41**[63] (**Scheme 14**).



Scheme 14

1.1.5 Conclusion

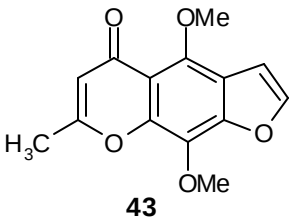
Thus, the Wittig olefination reaction have found widespread prominence in organic synthesis. They have become a powerful technique for the olefination reaction. The scope of the Wittig reaction continues to grow and the methods employed to effect the transformation of a carbonyl species into an alkene are becoming more diverse. When considering the more recent applications of the non classical Wittig reaction it can be seen that a wide range of carbonyls are open to the reaction and the applications in synthesis are significant. These factors will serve to create more interest in the process which will no doubt generate many new synthetic applications in the coming year.

1.2 SECTION A

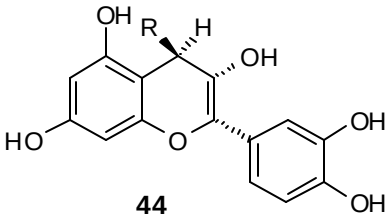
Synthesis of *4H*-Chromen-4-ones

1.2.1 Introduction

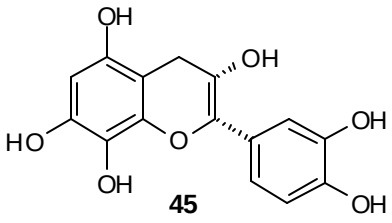
Chromones, flavones and related compounds, which are an important class of oxygenated heterocycles, are widely distributed in nature and have been found to play an important role in a number of biological processes[64-67] and hence intensively studied over the years. In humans naturally occurring chromones and flavones have shown biological effects as well. These are typified by the furochromone khelin **43**, which has exhibited lipid altering capabilities,[68] or hydroxyl flavone which have been shown to possess anti-inflammatory



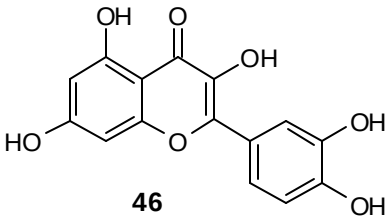
43
Khelin



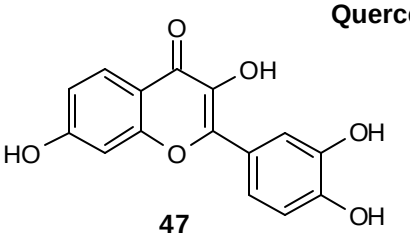
44
(-)-Epicatechin



45
Procyanidin B_2



46
Quercetin



47
Fistein

activity.[69] Other naturally occurring compounds that either are flavone based or flavones have been shown to be capable of mediating DNA strand cleavage in the presence of copper (II) and oxygen, presumably involving intercalation of the flavone.[70-72] These compounds such as (-)-epicatechin **44**, pyrocyanidin B_2 **45**, quercetin **46** and fistein **47**, bear a hydroxyl substituent at C-3 and possess a catechol group at the C-2 position. The presence of the catechol group appears to be critical for DNA strand cleavage since related compounds lacking the catechol moiety do not cleave DNA under the same conditions.[72]

Flavonoids are a group of naturally occurring, low molecular weight compounds that are widely distributed in the plant kingdom and represent a significant part of the average western diet. Many type of compounds comprise the flavonoids, one of the most abundant being the flavones. Members of the flavone class have been associated with a wide variety of biological activities and are endowed with a large number of pharmacological activities; and may be useful in treatment of certain diseases.[71] In particular, they are antioxidants and are able to inhibit ALR2 (Aldose Reductase).[74] An anxiogenic effect is brought about by Sobarin, which is the major flavonoid derivative present in the Brazilian toxic plant *Pseudocalymma elgans*.[75] The recent finding that oral administration of an ethanolic extract of this plant causes central nervous system stimulation, producing an anxiogenic-like effect in rats at low concentrations, and that the acute toxicity of *P. elegans* appears to be unrelated to these CNS actions,[76] might be associated with a possible action of sobarin, presumably derhamnosylated in the gut. Flavones and their regio-isomers; isoflavones provide the color (from pale yellow to orange) in flowers, trees and fruits. They have been of interest in the area of drug development because of their broad spectrum of pharmacological properties.[73,77,78] The chemistry of these compounds has been reviewed repeatedly.[79,80] Furthermore, the flavone molecule contains a C=C bond which bears the electron-accepting oxo and the electron-donating alkoxy group in such a way that conjugation results in a unreactive substrate toward electrophilic as well as nucleophilic agents.

The 2-substituted chroman-4-one (2-substituted 2,3-dihydro-4*H*-1-benzopyran-4-one) skeleton can be found in many natural products, which often show biological activity such as anthelmintic activity and plant growth inhibition activity.[81,82] Furthermore, it has recently been reported that naringenin, one of the representatives of the 2-substituted chroman-4-

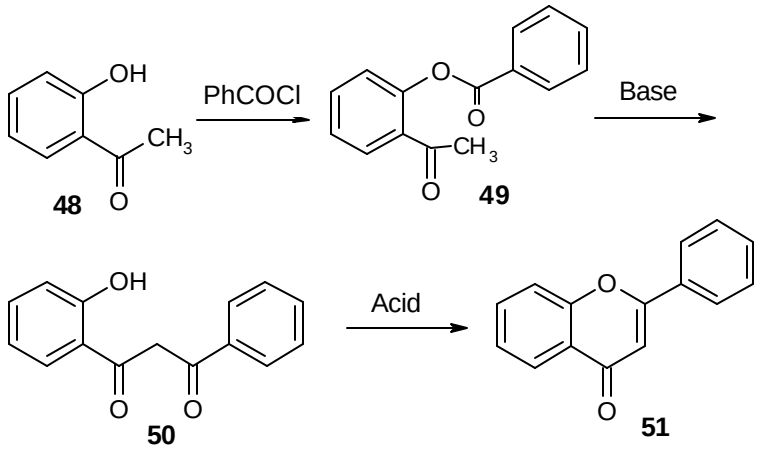
ones, surprisingly enhanced the enantioselectivity in the kinetic resolution of alcohols with an enzyme.[83] Despite this interesting potential of the 2-substituted chroman-4-ones, their synthesis is less developed.

1.2.2 Review of Literature

Currently there are a number of methods available to synthesize flavones,[84] including the Allan-Robinson synthesis,[85] the Baker-Venkataraman method,[86] synthesis from chalcones[83,84] and synthesis via an intramolecular Wittig strategy.[56d,89] At the outset, it appeared the Baker-Venkataraman approach, shown in **Scheme 15**, would be the most convenient route to the synthesis of flavones.

Baker-Venkataraman *et al.* (1933, 1934)[86] Scheme 15

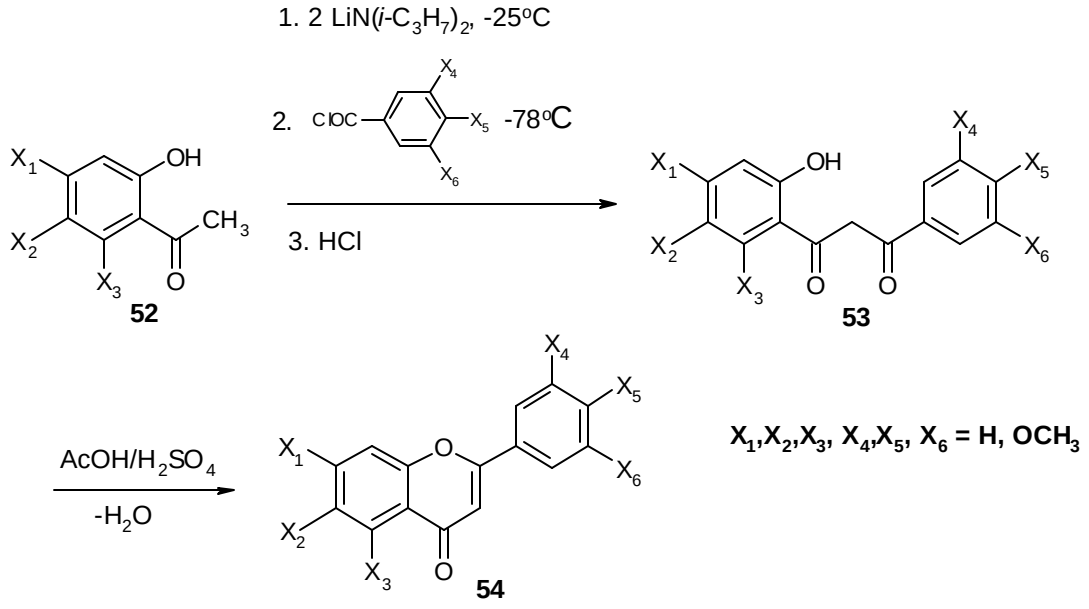
In this process, 2-hydroxyacetophenone **48** is first converted into a benzoyl ester **49**. This species is then isolated and treated with a base (usually potassium hydroxide or potassium carbonate) to effect an intramolecular Claisen condensation, forming a 1,3-diketone **50**. Acid treatment induces a dehydrative cyclization to the flavone **51**.



Scheme 15

Banerji *et al.* (1980)[90] Scheme 16

Banerji *et al.*[90] reported a method for the direct aroylation of *o*-hydroxyacetophenones **52** to β-diketones **53** and the subsequent cyclization to the corresponding flavones **54** (**Scheme 16**). In the Baker-Venkataraman synthesis, rearrangement (internal Claisen condensation) of *o*-acyloxy- or *o*-aroyloxyacetophenones to β-diketones is utilized, which was overcome by the Banerji approach by obtaining good yield and high purity.

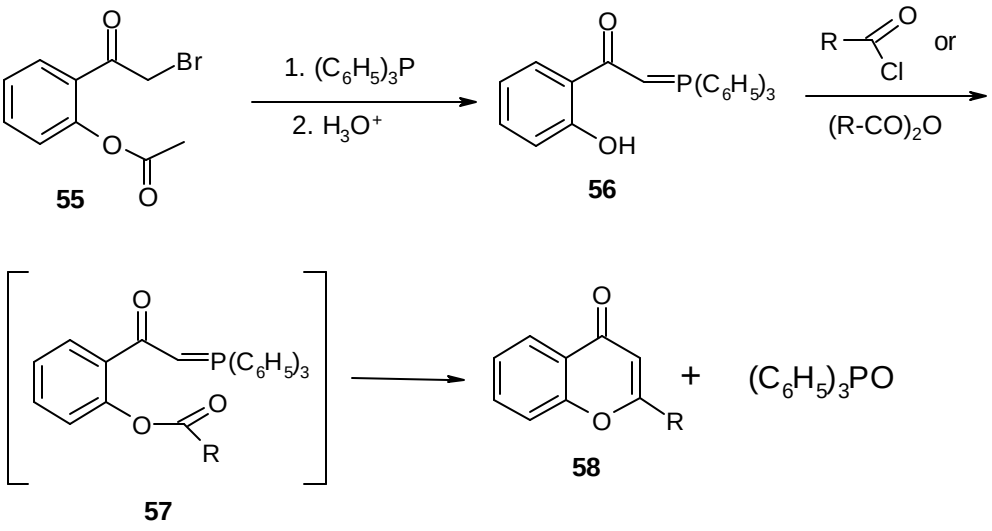


Scheme 16

Hercouet *et al.* (1980)[89a] Scheme 17

Hercouet *et al.*[89a] synthesized chromones **58** from *o*-hydroxyphenacylidenetriphenyl-phosphorane **56** under mild conditions. In **Scheme 17**, the phosphorane **56** was readily obtained from the reaction of triphenylphosphine with *o*-acetoxyphenacyl bromide **55**, followed by acid hydrolysis and treatment of the reaction mixture with sodium carbonate. Reaction of phosphorane **56** with carboxylic acid chlorides or anhydrides in boiling toluene

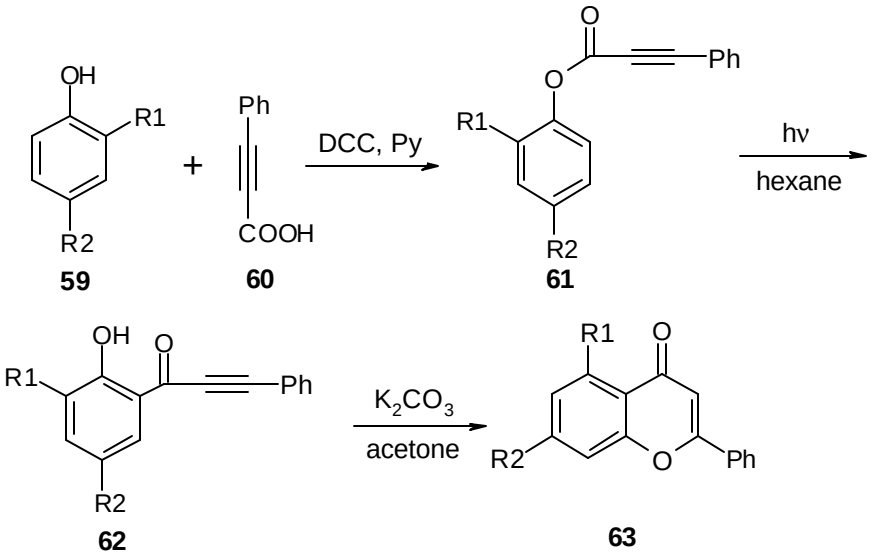
in the presence of pyridine gives the unstable phosphorane **57** which undergoes intramolecular olefination of its ester carbonyl group to afford the chromone **58**.



Scheme 17

Miranda *et al.* (1986)[91] Scheme 18

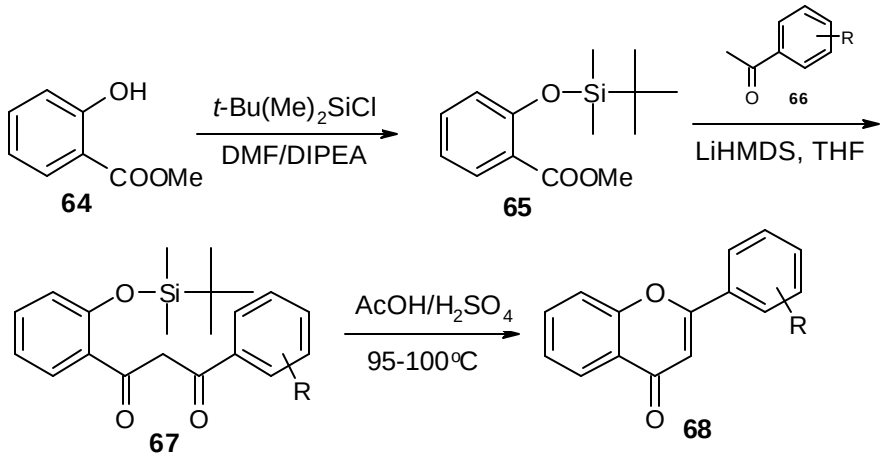
Miranda *et al.*[91] prepared the flavones **63** by irradiation of aryl phenylpropynoates **61** to give *o*-hydroxy arylethynyl ketones **62** *via* a photo-Fries rearrangement (**Scheme 18**). The aryl phenylpropynoates **61** were prepared by esterification of phenylpropynoic acid **60** with the correspoinding phenols **59**, by means of *N,N'*-dicyclohexylcarbodiimide.



Scheme 18

Cushman *et al.* (1991)[92] Scheme 19

Cushman *et al.*[92] developed a facile synthetic method for the conversion of methyl salicylate **64** into flavones **68** in high yields. As shown in **Scheme 19**, compound **64** on

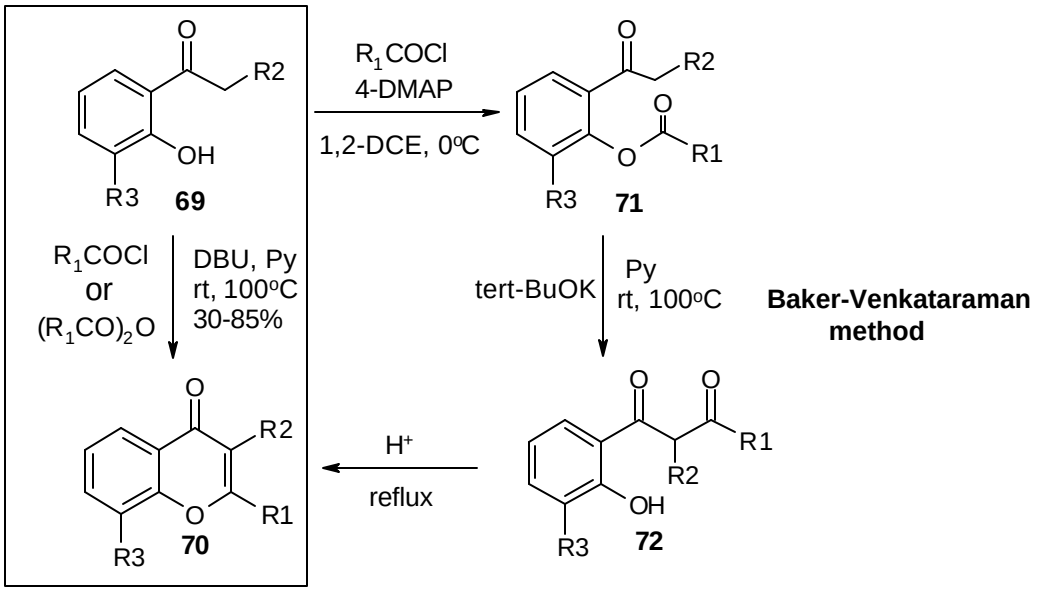


Scheme 19

treatment with *t*-butyldimethylsilyl chloride gave the *O*-silyl protected ester **65**. Condensation of this ester **65** with the lithium anion generated from acetophenones **66** yielded the 1,3-diarylpropane-1,3-diones **67**, which on treatment with glacial acetic acid containing 0.5% H_2SO_4 for 3 h at 95-100°C provided the desired flavones **68** in 83-94% yield.

Riva *et al.* (1997)[93] Scheme 20

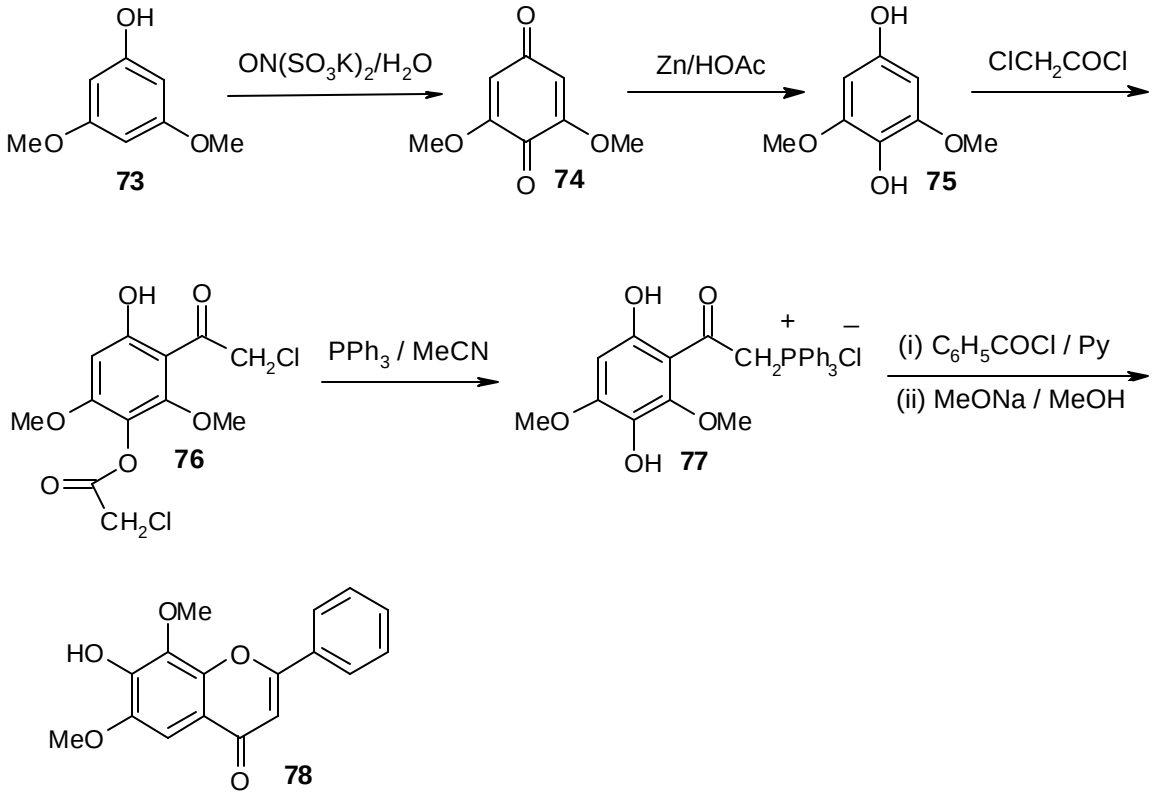
Riva *et al.*[93] modified the Baker-Venkataraman approach by removing the step wise process and directly converting the 2-hydroxy-3-(alkoxycarbonyl or prop-1-enyl)phenyl alkyl ketones **69** into 2,8-disubstituted (3-methyl)-4H-1-benzopyran-4-ones **70** through a DBU assisted one pot process.



Scheme 20

Cassels *et al.* (1999)[94] Scheme 21

Cassels *et al.*[94] synthesized 5,6-dimethoxy-6-hydroxyflavone **78** by using the cyclization of an intermediate phosphorane **77** as the key step. A Friedel-Crafts acylation of **75** with chloroacetyl chloride gave the compound **76**, which was converted into the triphenylphosphonium chloride **77** in 67% yield. Esterification of **77** with benzoyl chloride, followed by treatment of the resulting benzoate with base led to the target flavone **78**, which was obtained in 77% yield.



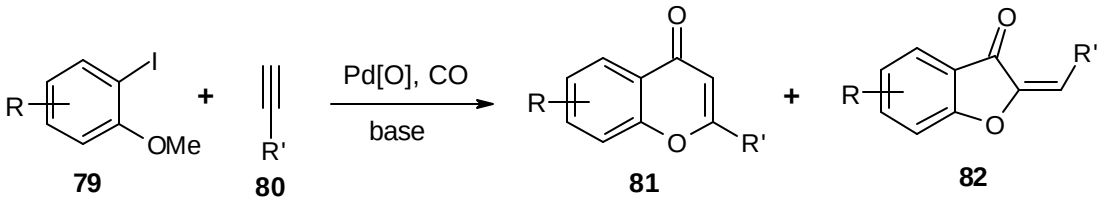
5,7-Dimethoxy-6-hydroxyflavone

Scheme 21

Yang *et al.* (2000)[95] Scheme 22

Yang *et al.*[95] synthesized diversified flavones **81** by applying regioselective carbonylation of *o*-iodophenol acetates **79** and acetylenes **80** mediated by palladium-thiourea-dppp complex

in the presence of base at 40°C under a balloon pressure of CO. The drawback of this reaction was that it led to a mixture with five-membered aurones **82**.

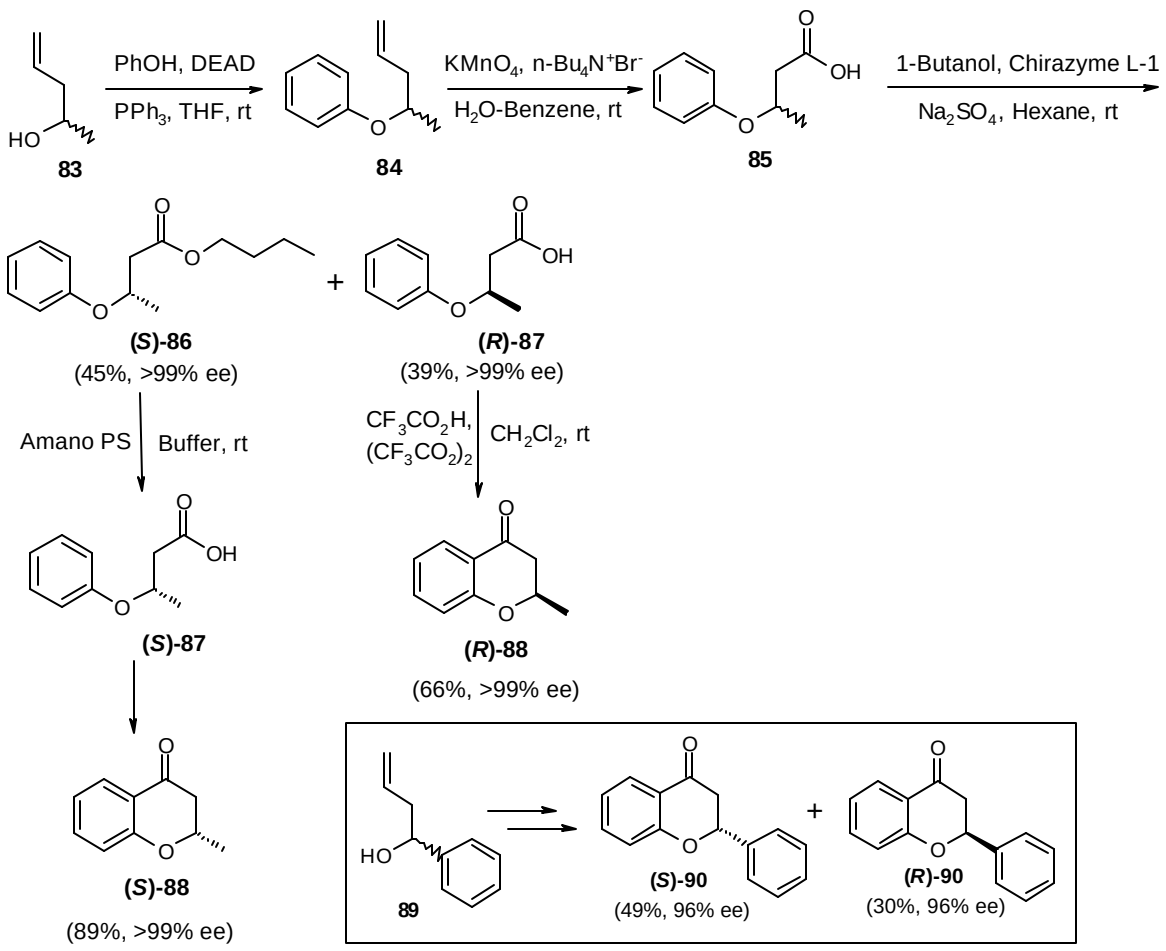


79 **80** **81** **82**

Scheme 22

Kawasaki *et al.* 2003[96] (Scheme 23)

The synthesis of 2-substituted chroman-4-ones is very less developed instead of their interesting potential exhibiting biological activity such as anthelmintic activity and plant growth inhibition activity. They also were found to enhance the enantioselectivity in kinetic resolution. Keeping this point in mind, Kawasaki et al.[96] synthesized 2-substituted chroman-4-ones; 2-methylchroman-4-one **88** and 2-phenylchroman-4-one **90** in optically active form (**Scheme 23**).


PhOH, DEAD
PPh3, THF, rt
KMnO4, n-Bu4N+Br-
H2O-Benzene, rt
1-Butanol, Chirazyme L-1
Na2SO4, Hexane, rt
83
84
85
(S)-86
(45%, >99% ee)
(R)-87
(39%, >99% ee)
Amano PS
Buffer, rt
CF3CO2H,
(CF3CO2)2
CH2Cl2, rt
(S)-87
(R)-88
(66%, >99% ee)
(S)-88
(89%, >99% ee)
89
(S)-90
(49%, 96% ee)
(R)-90
(30%, 96% ee)

Scheme 23

1.2.3 Present Work

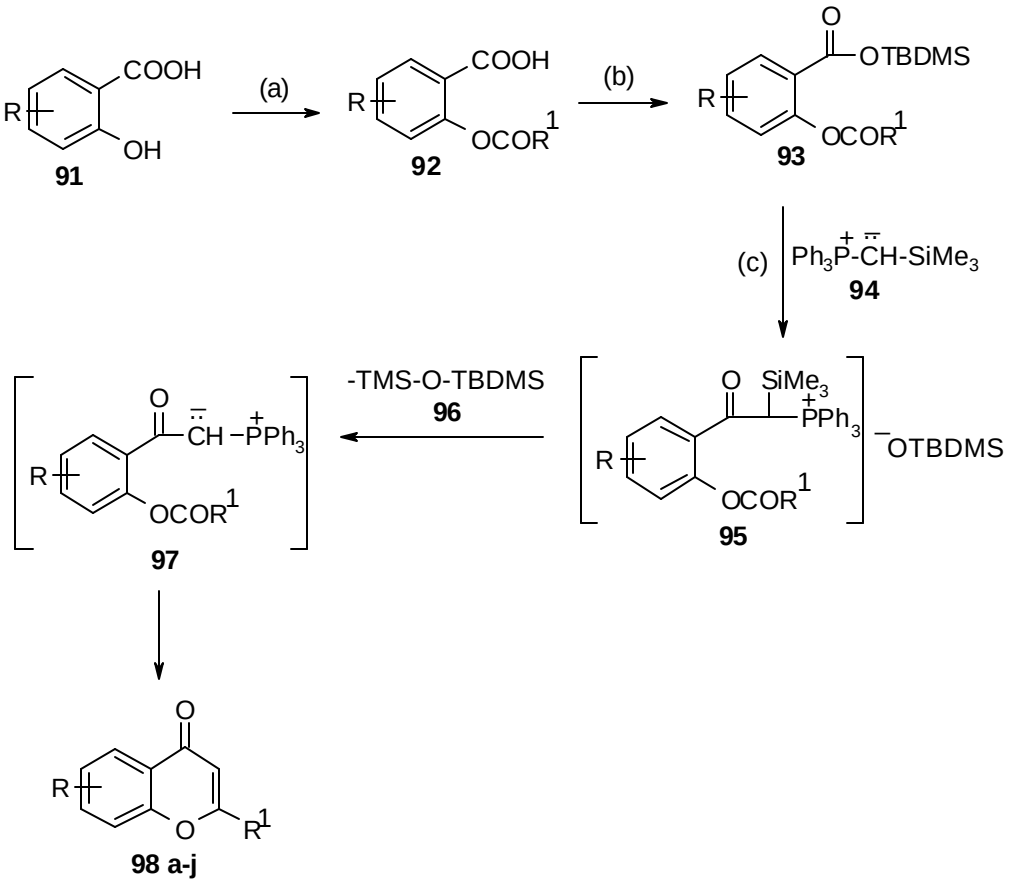
Objective:

Chromones, flavones and related compounds, which are an important class of oxygenated heterocycles, are widely distributed in nature and have been found to play an important role in a number of biological processes and interest in their chemistry continues unabated because of their usefulness as biologically active agents. As a part of our on going program for developing methodologies using phosphacumulene ylides[97] and their subsequent application to biologically useful compounds, the trimethylsilyl (methylenetriphenylphosphorane) is envisaged as a versatile reagent offering considerable opportunities for synthetic manipulations.[98] While a variety of synthetic methodologies for chromones have been developed,[99] the literature describing novel one pot cyclization methods based on a consecutive process is rather scarce. Also, most of these methods suffer either from harsh reaction conditions, poor substituent tolerance, or low chemical yields. We have now developed a new and simple route to 4*H*-chromen-4-ones *via* intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane.

1.2.4 Results and Discussion

Salicylic acid or its substituted derivative **91** was converted into its *O*-acyl(aroyl) derivatives by reaction with the corresponding acid chloride or anhydride. Compound **92** was then treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole to furnish the corresponding silyl ester **93** in excellent yields. When a mixture of compound **93** and (trimethylsilyl)methylenetriphenylphosphorane[98] **94** was heated in refluxing THF, the desired chromones **98** were obtained in 55-80% yields (**Table 2**). The formation of product **98** could be explained by a sequence of reaction as depicted in **Scheme 24**. A possible reaction pathway for the conversion of **93** into **98** involves acylation of (trimethylsilyl)methylenetriphenylphosphorane **94** by **93** to the resulting phosphonium salt **95**. There is then migration of the trimethylsilyl group from C to O, followed by the extrusion of silyl ether **96** and ultimately leading to the acylphosphorane **97**, which

subsequently undergoes ring closure via the intramolecular Wittig reaction on the ester carbonyl to afford the desired chromones **98**. To support our suggested mechanism, the intermediacy of compound **97** has been established by spectroscopic means. Although the treatment of **93b** with **94** in THF at room temperature did not show any progress of

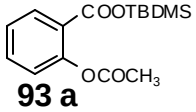
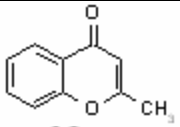
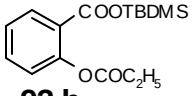
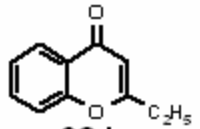
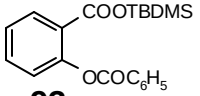
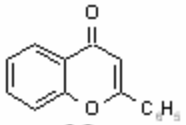
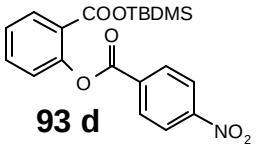
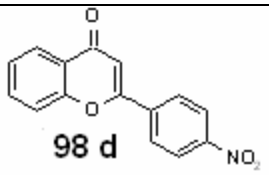
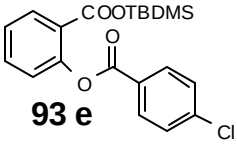
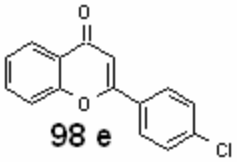
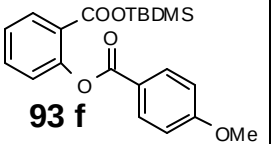
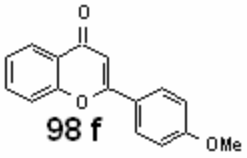


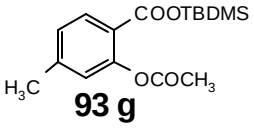
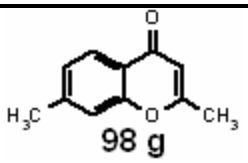
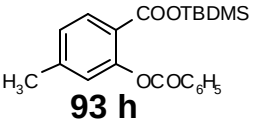
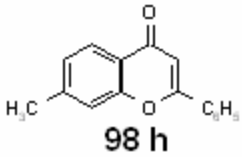
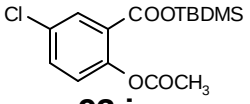
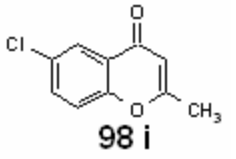
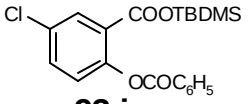
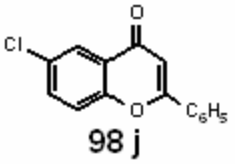
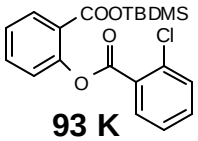
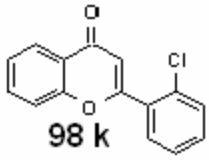
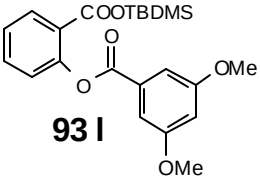
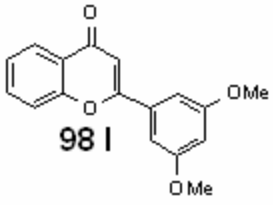
Scheme 24 Reagent and Conditions: (a) $(R_1CO)_2O$, conc. H_2SO_4 (5 drops) or (R_1COCl, aq. KOH, 0^oC-rt, 0.5 h, 75-80% (b) TBDMSCl, imidazole, CH_2Cl_2, 0^oC-rt, 7-8 h, 65-70% (c) 14-45 h, THF, reflux, 55-80%

reaction, the extrusion of silyl ether **96** and formation of acylphosphorane **97** could be observed when the reaction was performed at higher temperature (50 °C). Interestingly, compound **97b** was found to be stable enough to be isolated and was further identified by its spectral data. The ^{1}H NMR spectrum of acylphosphorane **97b** showed the carbanion protons at δ 2.6 as a doublet and the absence of silyl group protons confirming the extrusion of silyl ether **96** and the formation of compound **97b**. Compound **97b**, on heating

in refluxing THF, gave the desired chromone **98b**. The ^{1}H NMR spectrum of chromone **98b** showed the presence of CH protons of the pyran ring at δ 6.9. Also there was the absence of protons of triphenylphosphine group at δ7.3-8.1 and the absence of doublet at δ 2.6 of the carbanion of acylphosphorane **97b** confirming its formation. Even though we

Table 2 : One-pot synthesis of 4*H*-1-chromen-4-ones **98** from **93** and **94** *via* intramolecular Wittig cyclization.

Entry	Substrate	Product[a]	Reaction time(h)	Yield (%)[b]
1.	 **93 a**	 **98 a**	**14**	**75**
2.	 **93 b**	 **98 b**	**16**	**75**
3.	 **93 c**	 **98 c**	**18**	**76**
4.	 **93 d**	 **98 d**	**28**	**60**
5.	 **93 e**	 **98 e**	**22**	**74**
6.	 **93 f**	 **98 f**	**20**	**80**

7.	 **93 g**	 **98 g**	**16**	**72**
8.	 **93 h**	 **98 h**	**18**	**71**
9.	 **93 i**	 **98 i**	**21**	**73**
10.	 **93 j**	 **98 j**	**23**	**73**
11.	 **93 K**	 **98 k**	**45**	**55**
12.	 **93 l**	 **98 l**	**40**	**57**

[a] All products were characterized by their satisfactory IR, ^{1}HNMR, mass spectral data and also by comparison with literature data; [b] Products were purified by silica gel column chromatography using petroleum ether: ethylacetate 98:2 as eluent. Yields refer to isolated pure products.

could not isolate the phosphonium salt **95b**, presumably as a result of its fast rearrangement into the acylphosphorane, the above finding indicates that compound **97b**,

which results from **95b** after the cleavage of silyl ether **96**, is one of the intermediates that undergoes subsequent intramolecular Wittig cyclization at reflux temperature to furnish the desired product **98b**. As is apparent from **Table 2**, the intramolecular Wittig cyclization involving phosphorus ylide and ester carbonyl is general for the preparation of a variety of chromone derivatives. However, steric effect during the Wittig cyclization resulting from the substitution in aroyl group appears to be significant. Thus an *ortho*-substituent such as the chloro group in **93k** and *meta*-substituent such as the methoxy group in **93l** have pronounced steric hindrance due to their close proximity to the carbonyl group, and hence a longer time is required to complete the reaction, affording relatively low yield of the products **98k** and **98l**, respectively (**Table 2**, entries 11 and 12). It may be mentioned that for the synthesis of 2-alkyl chromones, the utilization of a large excess of esters as acylating reagent is reported to be the only acceptable method.[100] Also, the conventional methods employing *o*-hydroxy acetophenone as starting material failed to give the substituted flavones, particularly with methoxy substituents.[101] Similarly, few reports employing palladium-catalyzed carbonylative coupling of 2-hydroxyaryliodides with ethynylarenes are known to give a mixture of flavones and aurones.[95,102] In this connection, the present methodology for the synthesis of chromones is noteworthy.

1.2.5 Conclusion

In summary, an efficient annulation protocol for a variety of chromones has been developed. To the best of our knowledge, this is the first report of chromone synthesis *via* intramolecular Wittig ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane.

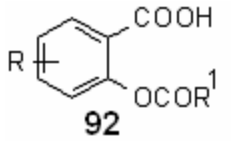
1.2.6 Experimental

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on Bruker AC-200

MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

General procedure for synthesis of *O*-Acyl(aroyl)salicylic acid, 92

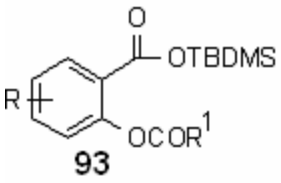


92

⇒ Dry salicylic acid or its substituted derivative **91** (50mmol) and acid anhydride (100mmol) were placed in a small conical flask; 5 drops of conc. sulfuric acid was added and the flask was rotated in order to secure thorough mixing. The mixture was warmed on a water bath to about 50-60°C, and then stirred for about 15 minutes. The mixture was allowed to cool and stirred occasionally. Water was added to the reaction mixture and solid thus obtained was filtered. The solid was then dissolved in about 30ml of hot ethanol and the solution was poured into 75ml of warm water. Solid separated out at this point; the mixture was warmed until it is clear solution and then the solution was cooled slowly. Beautiful needle like crystals separated out. The air dried crude product **92** was recrystallised from pet-ether / ethyl acetate, or hexane.

⇒ 10g of ice followed by freshly distilled acid chloride (10mmol) were added to an ice-cold solution of salicylic acid or its substituted derivative **91** (7mmol) and potassium hydroxide (18mmol) in water (12ml). The mixture was stirred for 0.5 h at room temperature, acidified with dil.HCl; and the material which precipitated out was filtered and washed with water. The air dried crude product **92** was recrystallised from pet-ether / ethyl acetate, or hexane.
Yield:- 75-80%

General procedure for synthesis of *tert*-butyldimethylsilyl ester of *O*-Acyl(aroyl)salicylic acid, 93

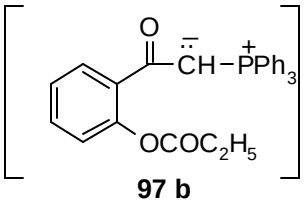


93

A solution of compound **92** (10mmol) and imidazole (15mmol) in dichloromethane (5ml) was cooled to 0°C, and mixture was stirred under nitrogen atmosphere. To the above solution, was added *tert*-butyldimethylsilyl chloride (13 mmol) at 0°C and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 7-8 hours. After the reaction was complete, the reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the product **93**.

yield . 65-70%

Procedure for the synthesis of acylphosphorane 97b



97 b

Compound **93b** was prepared in 68% yield from **92b** following the general experimental procedure as described for **93**.

The (trimethylsilyl)methylenetriphenylphosphorane **94** was prepared following the literature procedure[98] from methylenetriphenylphosphorane and trimethylsilyl chloride.

To a solution of **93b** (1 g, 3.2 mmol) dissolved in absolute THF (5 ml) was added the equimolar amount of silylated ylide **94** (1.13 g, 3.2 mmol) in THF (5 ml). The reaction mixture was heated at 50°C for 8 hours. The reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under reduced pressure and residue thus obtained was washed several times with petroleum ether to afford 1.25 g (85%) of

sufficiently pure acylphosphorane **97b** as an oil which was fully characterized by spectroscopic data.

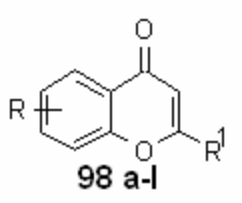
Yield:- 1.25 g, 85%

IR ($CHCl_3$, cm^{-1}): ν_{max} 1730, 1625, 1580, 1525, 1243, 1215

^{1}H NMR ($CDCl_3$, 200 MHz): *d* 1.25 (t, *J*=8Hz, 3H), 2.10 (q, *J*=8Hz, 2H), 2.60 (d, *J*=4Hz, 1H), 6.80-7.25 (m, 2H), 7.30-8.10 (m, 15H), 8.30-8.75 (m, 2H).

Mass (EI), m/z(%): M^+ 452(5), 215(85), 201(70), 138 (60), 120 (100).

General procedure for the synthesis of Chromones, 98

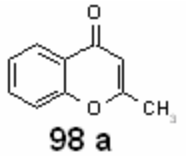


98 a-l

To a solution of compound **93** (50mmol) in absolute THF (5ml) was added under stirring the equimolar amount of silylated ylide **94** (50mmol) in THF (5ml), Then the reaction mixture was refluxed for the indicated length of time (**Table 2**). The reaction was monitored by TLC. After completion of reaction, the solvent was evaporated and the residue was purified by column chromatography (pet.ether:ethyl acetate, 98:2), to afford the product **98**.

Yield:- 55-80%

2-Methyl-4*H*-chromen-4-one



98 a

Physical State: Solid

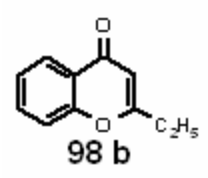
M.P.:- 72°-73°C (Lit.[99j] 70°-71°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1661

^{1}H NMR ($CDCl_3$, 200 MHz): *d* 2.36 (s,3H), 6.92-7.02 (m, 1H), 7.46-7.74 (m, 3H), 7.75-7.95 (m, 1H).

Mass (EI), m/z(%): M^+ 160 (100), 145 (10), 138 (55), 120 (87).

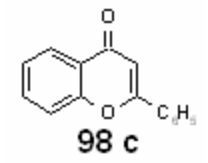
2-Ethyl-4*H*-chromen-4-one



98 b

Physical State: Oil
IR ($CHCl_3$, cm^{-1}): ν_{max} 1676
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 1.29 (t, *J*=8Hz, 3H), 2.66 (q, *J*=8Hz, 2H), 6.9-7.0 (m, 1H), 7.30-7.60 (m, 3H), 7.90-8.20 (m, 1H)
Mass (EI), m/z(%): M^+ 174 (100), 138 (57), 120 (85)

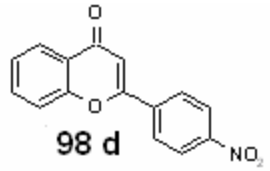
2-Phenyl-4*H*-chromen-4-one



98 c

Physical State: Solid
M.P.:- 96°C (Lit. [99j] 94°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1673
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 6.98 (s, 1H), 7.46-8.13 (m, 9H)
Mass (EI), m/z(%): M^+ 222 (15), 194 (90), 138 (40), 120 (100), 77 (36)

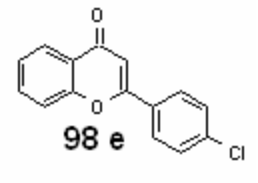
2-(4'-Nitrophenyl)-4*H*-chromen-4-one



98 d

Physical State: Solid
M.P.:- 242°-244°C(Lit. [99j] 240°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1664
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 6.92-7.05 (m, 3H), 7.50-7.59 (m, 2H), 7.91-7.98 (m, 2H), 8.32-8.36(m, 2H)
Mass (EI), m/z(%): M^+ 267 (20), 163 (100), 138 (45), 120 (50)
.

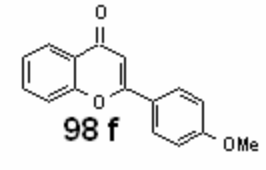
2-(4'-Chlorophenyl)-4*H*-chromen-4-one



98 e

Physical State: Solid
M.P.:-186°-188°C(Lit. [99j] 189°-190°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1687
^{1}H NMR ($CDCl_3$): *d* 6.90 (m, 1H), 7.43-8.05 (m, 8H).
Mass (EI), m/z(%): M^+ 256 (20), 228 (40), 138 (60), 120 (100)

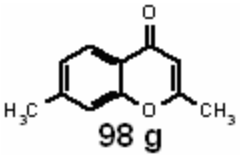
2-(4'-Methoxyphenyl)-4*H*-chromen-4-one



98 f

Physical State: Solid
M.P.:- 156°-157°C (Lit.[99j] 157°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1663
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 3.90 (s,3H), 6.92-7.02 (m, 3H), 7.50-7.56 (m, 2H), 7.94 (m, 2H), 8.06(m, 2H)
Mass (EI), m/z(%): M^+ 252 (25), 224 (100), 209 (22), 120 (87)

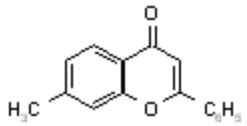
2,7-Dimethyl-4*H*-chromen-4-one



98 g

Physical State: Solid
M.P.:-. 98°-100°C(Lit.[101] 100°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1661
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 2.35 (s,3H), 2.43 (s, 3H), 6.73-6.82 (m, 1H), 6.96 (s, 1H), 7.80 (d, 1H, *J* = 8 Hz), 8.02 (d, 1H, *J* = 8Hz).
Mass (EI), m/z(%): M^+ 174 (100), 154 (80), 105 (36)

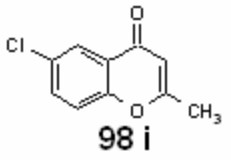
2-Phenyl-7-methyl-4*H*-chromen-4-one



98 h

Physical State: Solid
M.P.:- 128°-130°C (Lit. [99j] 130°-132°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1660
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 2.38 (s,3H), 6.74-7.83 (m, 3H), 7.46-7.65 (m, 5H), 8.13 (m, 1H)
Mass (EI), m/z(%): M^+ 236 (100), 134(86), 105 (30), 77 (24)

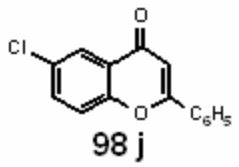
2-Methyl-6-chloro-4*H*-chromen-4-one



98 i

Physical State: Solid
M.P.:-114°-115°C (Lit.[99d] 115°-116°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1661
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 2.35 (s,3H), 6.88-7.02 (m, 1H), 7.46-7.55 (m, 2H), 7.68-7.91 (m, 1H)
Mass (EI), m/z(%): M^+ 194 (100), 173 (40), 155 (80).

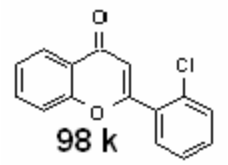
2-Phenyl-6-chloro-4*H*-chromen-4-one



98 j

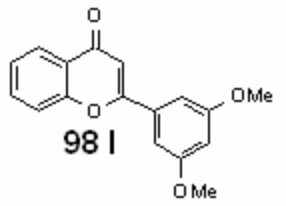
Physical State: Solid
M.P.:-181°-183°C (Lit. [99d] 183°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1685
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 6.95 (s, 1H), 7.44-7.65 (m, 5H), 7.89-7.90 (m, 2H), 8.11-8.15 (m, 1H)
Mass (EI), m/z(%): M^+ 256 (100), 155 (70), 77 (40)

2-(2'-Chlorophenyl)-4*H*-chromen-4-one



Physical State: Solid
M.P.:-192°-193°C(Lit. [99c] 194°-195°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1677
^{1}H NMR ($CDCl_3$, 200 MHz): *d* 6.90 (m,2H), 7.43-8.10 (m, 8H)
Mass (EI), m/z(%): M^+ 256 (20), 228 (40), 138 (60), 120 (100).

2-(3', 5'-Dimethoxyphenyl)-4*H*-chromen-4-one

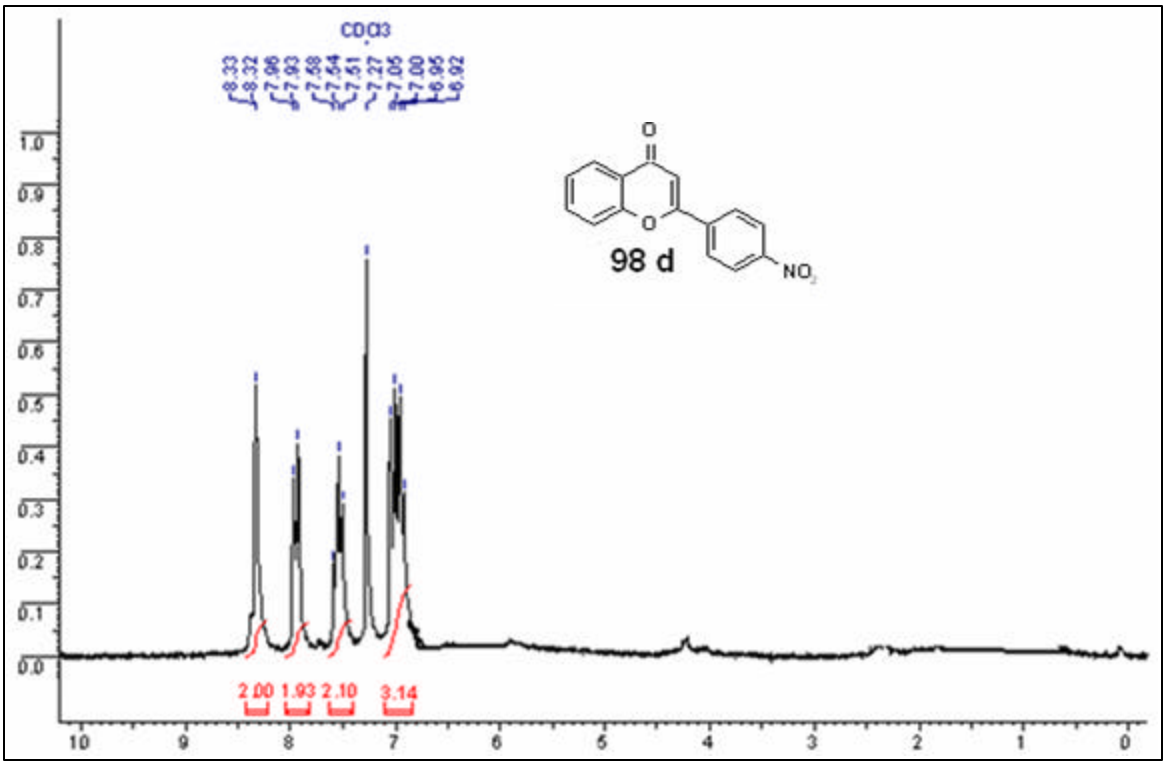


Physical State: Solid
M.P.:-226°-228°C (Lit.[99c] 229°C)
IR ($CHCl_3$, cm^{-1}): ν_{max} 1667
^{1}H NMR($CDCl_3$, 200 MHz): *d* 3.90 (s,6H), 6.92-7.02(m, 2H), 7.50-7.56 (m, 2H), 7.94 (m, 2H), 8.06 (m, 2H)
Mass (EI), m/z(%): M^+ 282 (25), 264 (100), 240 (22), 120 (87).

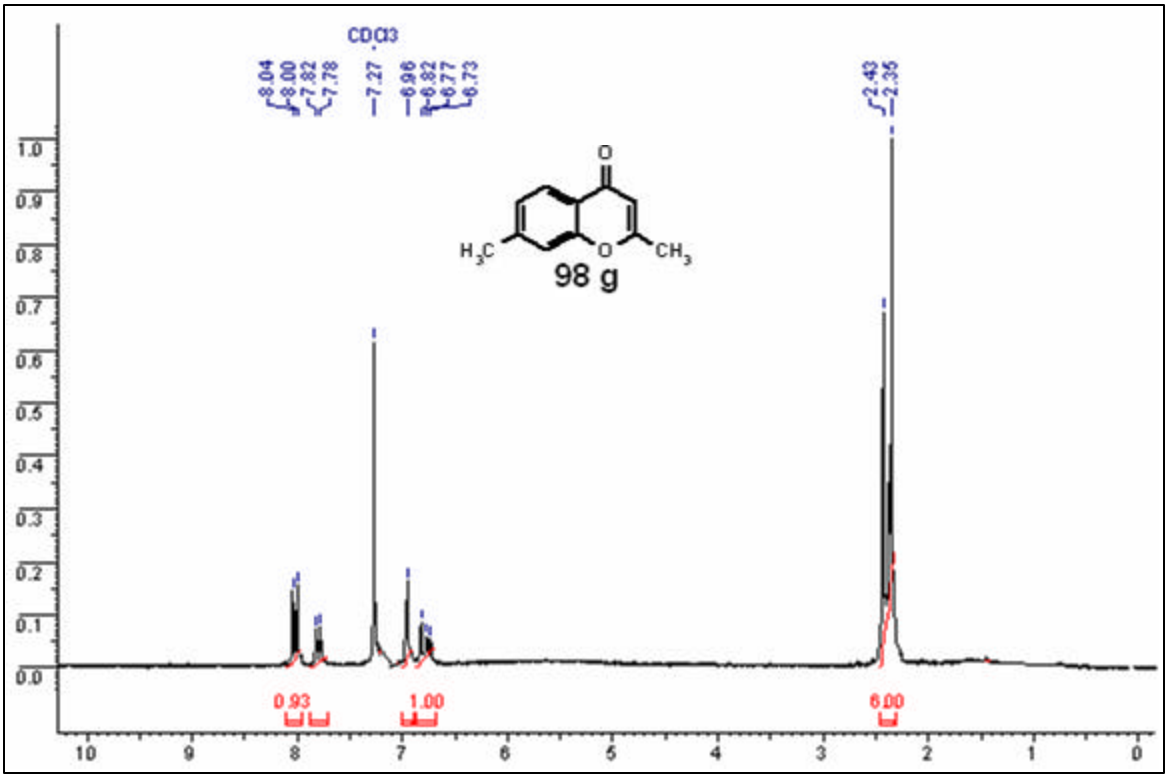
1.2.7 Spectra

1. ^{1}H NMR spectrum of **98d**
2. ^{1}H NMR spectrum of **98g**
3. ^{1}H NMR spectrum of **98h**
4. ^{1}H NMR spectrum of **98j**

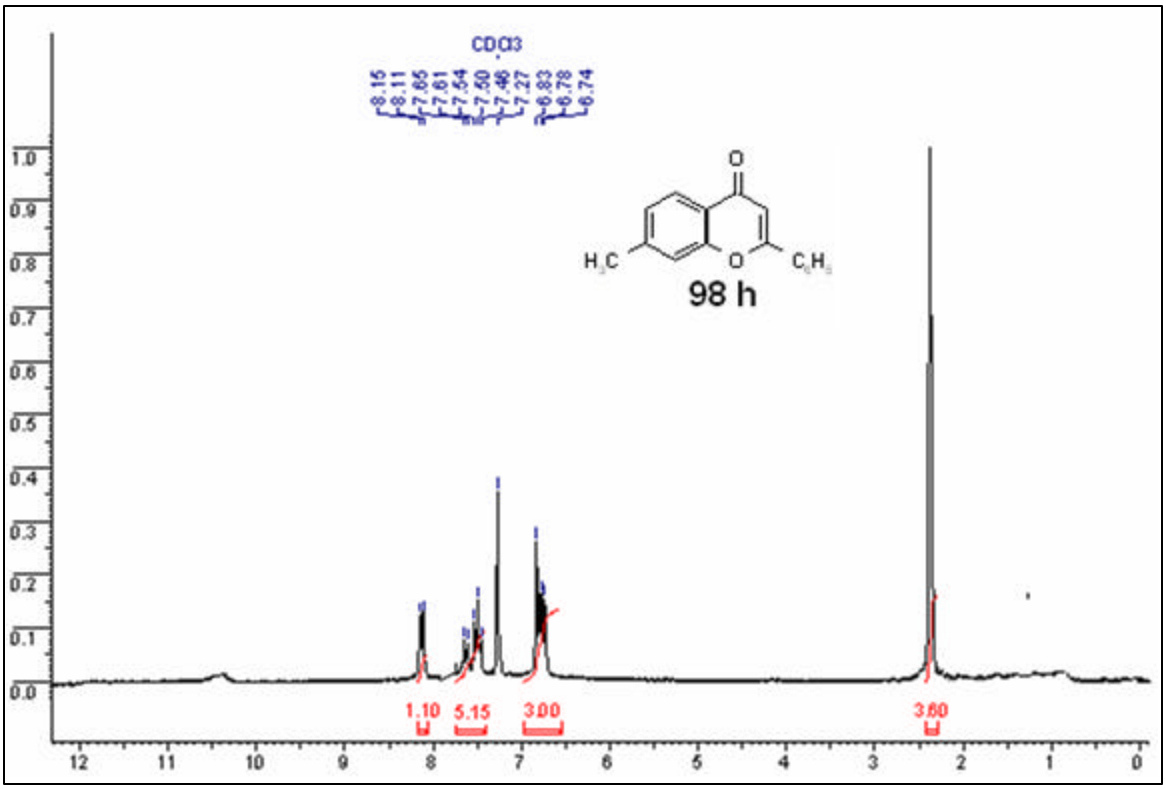
➢ ^{1}H NMR of **98d**



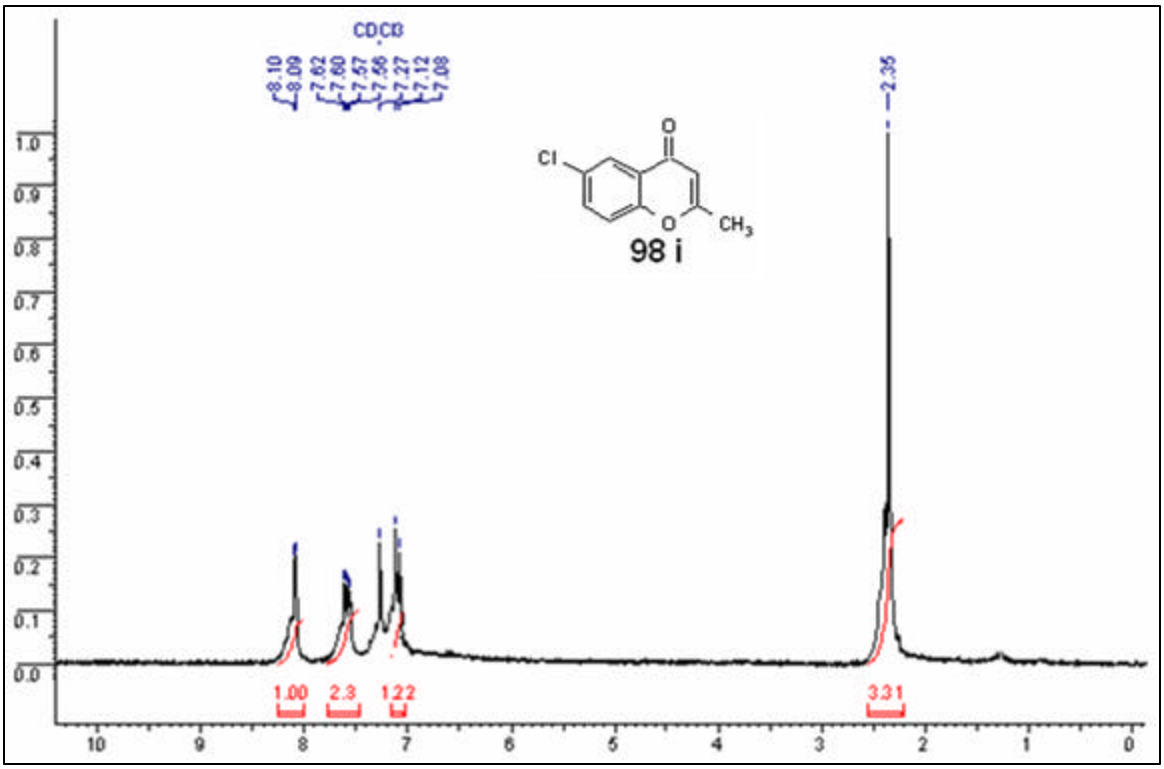
➢ ^{1}H NMR of **98g**



➢ ^{1}H NMR of **98h**



➢ ^{1}H NMR of **98i**



1.3 SECTION B

Synthesis of 4*H*-1-Benzothiopyran-4-ones

1.3.1 Introduction

1-Benzothiopyran-4-ones are an important class of heterocycles. They serve as key intermediates for the synthesis of biologically active compounds.[103] While chromones (4*H*-1-benzopyran-4-ones) have been extensively investigated regarding their synthesis, their isolation as secondary metabolites, and their potential for broad spectrum biological activity,[104] a little attention has been paid towards the synthesis and biological evaluation of thiochromones (4*H*-1-benzothiopyran-4-ones).[105] To obtain more potent derivatives possessing important bioactivities than flavones, quite a large variety of their chemical transformations have been performed. However, their conversion into 4-thioflavones has hitherto received less attention, although such sulfur-containing flavones may be useful intermediates for further transformations and/or may offer new and advantageous bioactivities as well. These compounds have been prepared and studied for their biological potential, especially as bacteriocides and anticancer agents.[106]

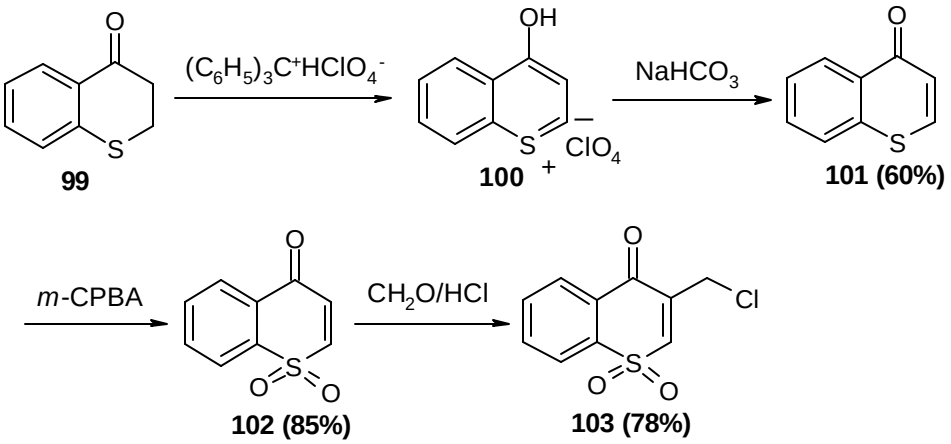
1.3.2 Review of Literature

While chromones have been extensively investigated regarding their synthesis, a little attention has been paid towards the synthesis and biological evaluation of thiochromones (1-benzothiopyran-4-ones). In general, 1-benzothiopyran-4-ones are synthesized either by the condensation of a β-keto ester with a thiophenol in polyphosphoric acid [107] or by the cyclization of a β-substituted cinnamate, derived from the constituent thiophenol and an appropriate propiolate.[108] Recently 4*H*-1-benzothiopyran-4-ones were prepared by the

condensation and subsequent acid-induced cyclization of lithiated intermediates derived either from acetoacetanilide[109], C(α),*N*-benzoylhydrazones or C(α),*N*-carboalkoxy hydrazones[110] with methylthiosalicylate. However, most of these methods suffer either from harsh reaction conditions, poor substituent tolerance or low chemical yields. Also, some of these methods could not be applied for the synthesis of many target molecules,[111] in particular methoxy-substituted thioflavone.[112]

Holshouser *et al.* (1981)[113] Scheme 25

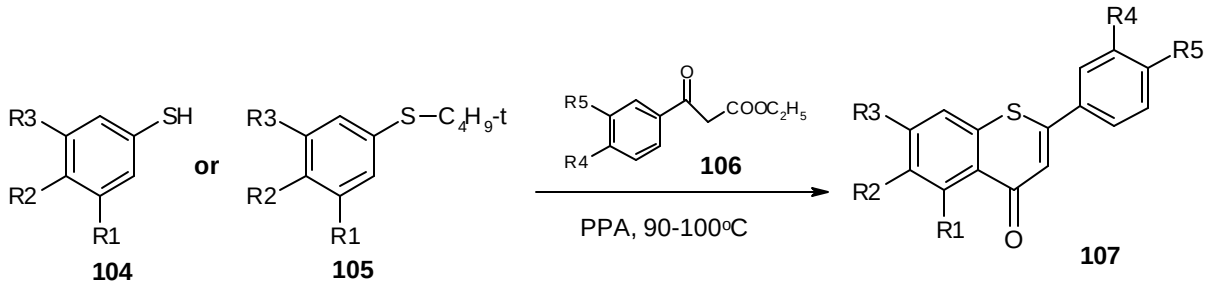
Holshouser *et al.*[113] synthesized thiochromone **103** by the method of Chauhan and Still using hydride abstraction from position 2 of thiochroman-4-one **99** *via* triphenylmethyl perchlorate and subsequent neutralization of the sulfenium salt.[114] *m*-Chloroperbenzoic acid oxidation by the method of Bass and Evans[115] gave thiochromone 1,1-dioxide **102** in 85% yield. Compound **102** was chloromethylated by treatment with formaldehyde (37%) and hydrogen chloride gas, affording **103** in 78% yield. They prepared this dioxide analogues to study the difference in antitumor activity with the thiochromone compounds.



Scheme 25

Nakazumi *et al.* (1983)[116] Scheme 26

Nakazumi *et al.*[116] synthesized some 2-phenyl-4*H*-benzothiopyran-4-ones **107** which exhibit antimicrobial activity by the well known procedure of cyclization of benzenethiols **104** with β-keto esters **106** to 4*H*-benzothiopyran-4-ones (thiochromones) **107** using polyphosphoric acid

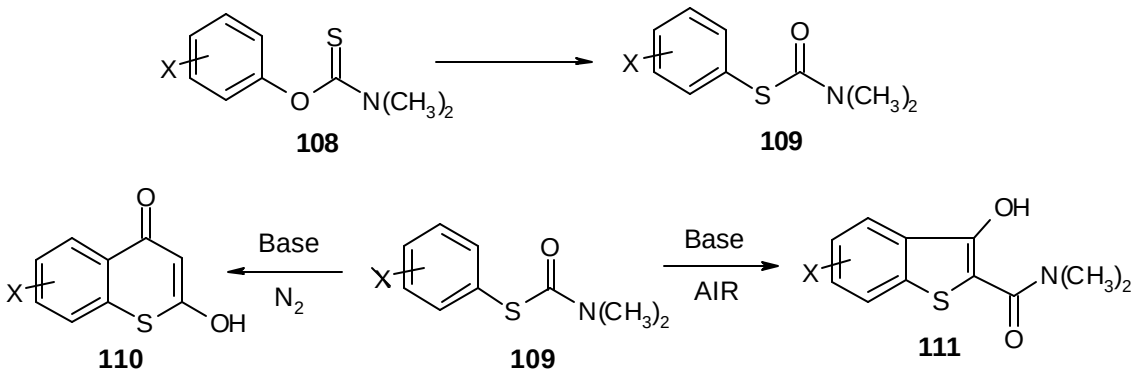


Scheme 26

which promotes the cyclizaiton. They reported an improved synthesis of methoxy-substituted thioflavones from t-butylthiobenzenes **105**, and compared the results with the known preparations of compound **107** from the corresponding benzenethiols **104**.

Lau *et al.* (1987)[117] Scheme 27

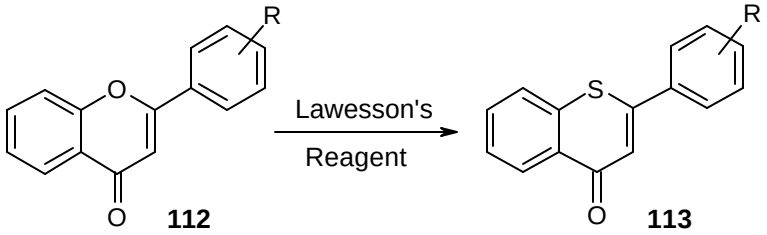
Lau *et al.*[117] synthesized 2-hydroxythiochromones **110** by the treatment of *S*-(*o*-acetylaryl) dimethylthiocarbamates **109** with base in the presence of nitrogen. They also obtained substituted *N, N*-dimethyl-3-hydroxybenzothiophene-2-carboxamides **111** when they used air instead on nitrogen. The *S*-(*o*-acetylaryl) dimethylthiocarbamates **109** were prepared by the Newman-Kwart rearrangement of *O*-(*o*-acetylaryl) dimethylthiocarbamates **108**.



Scheme 27

Levai (1999)[118] Scheme 28

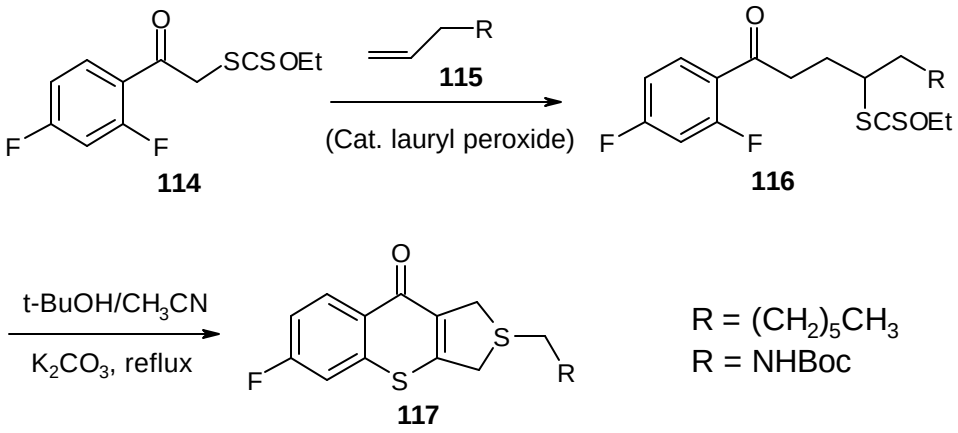
Levai[118] converted flavones **112** into 4-thioflavones **113** with the utilization of Lawesson's reagent as the thiation agent. His aim was to find out an effective thiation agent which acts under simple and convenient reaction conditions and offers beneficial yields irrespective of the substitution pattern of the starting flavone.



Scheme 28

Zard *et al.* (1999)[119] Scheme 29

Zard *et al.*[119] synthesized Dihydrothieno[2,3-b]-benzothiopyran-4-ones **117** by an intermolecular radical addition to an unactivated olefin **115** using an *S*-*o*-fluorophenacyl xanthate **114** followed by a base induced domino cyclization.


O
SCSOEt
F
F
R
115
(Cat. lauryl peroxide)
O
R
SCSOEt
F
F
114
116
t-BuOH/CH3CN
K2CO3, reflux
O
S
F
S
R
117
R = (CH2)5CH3
R = NHBoc

Scheme 29

1.3.3 Present Work

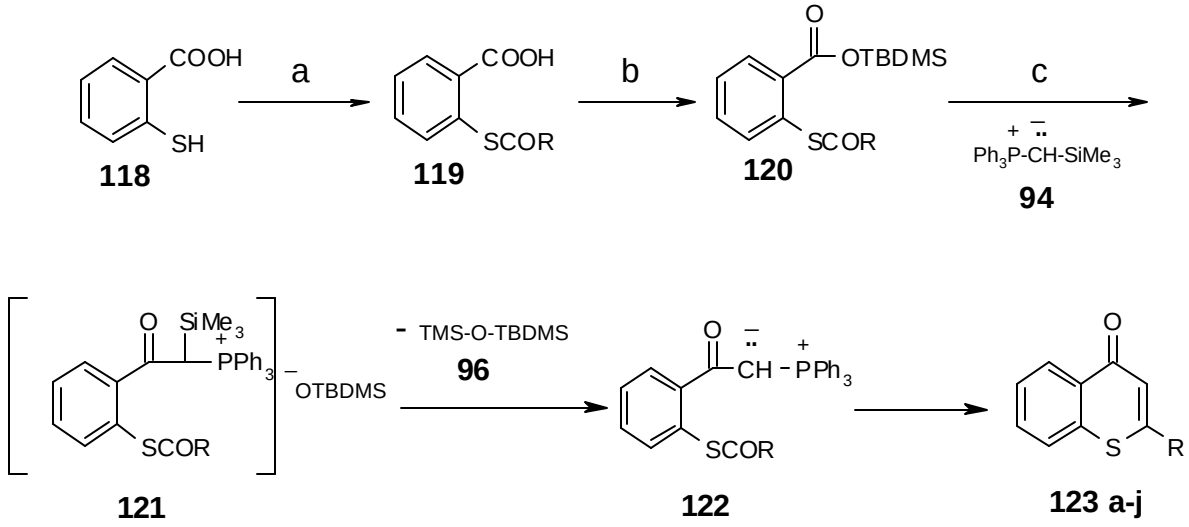
Objective:

1-Benzothiopyran-4-ones are an important class of heterocycles and interest in their chemistry continues unabated because of their usefulness as synthons and / or as biologically active compounds. The trimethylsilyl (methylenetriphenylphosphorane) is envisaged as a versatile reagent offering considerable opportunities for synthetic manipulations. In connection with our studies on biologically active compounds possessing benzothiopyran and benzothiazepine skeletons, we became interested in developing a suitable methodology for the synthesis of 1-benzothiopyran-4-ones. While a variety of synthetic methodologies for thiochromones have been developed as described in preceding section, the literature describing novel one pot cyclization methods based on a consecutive process for thiochromones (4*H*-1-benzothiopyran-4-ones) is rather scarce. Also, most of these methods suffer either from harsh reaction conditions, poor substituent tolerance, or low chemical yields. We have now extrapolated the methodology developed for chromones towards the synthesis of 4*H*-1-benzothiopyran-4-ones *via* intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane.

1.3.4 Results and Discussion

Thiosalicylic acid **118** was converted into its *S*-acyl(aroyl) derivatives **119** by reaction with corresponding acid chloride or anhydride. Compound **119** was then treated with *tert*-butyldimethylsilyl chloride in presence of imidazole to furnish the corresponding silyl ester **120** in good yields. When a mixture of compound **120** and (trimethylsilyl) methylenetriphenylphosphorane[98] **94** was heated in refluxing THF, the desired 2-substituted, 4*H*-1-benzothiopyran-4-ones **123** were obtained in 58-90% yields (**Table 3**). The conversion of **120** into **123** could be explained by a sequence of reaction as depicted in **Scheme 30**. The plausible mechanism can be visualized as initial acylation of (trimethylsilyl)methylenetriphenylphosphorane **94** by **120** to the resulting phosphonium salt **121**. There is then migration of the trimethylsilyl group from C to O followed by the extrusion of silyl ether **96** leading to the acylphosphorane **122** which subsequently

undergoes ring closure *via* the intramolecular Wittig reaction on the thiolester carbonyl to afford the desired thiochromones **123**.

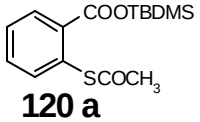
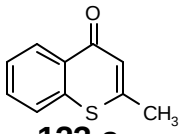
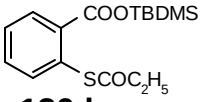
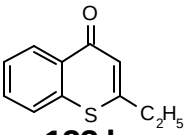
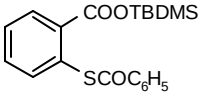
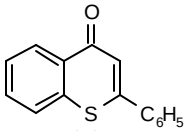
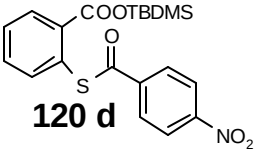
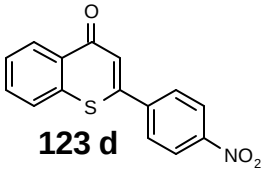


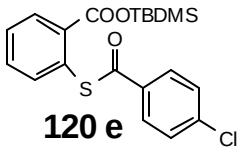
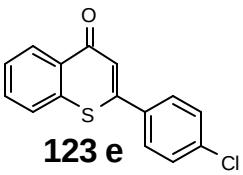
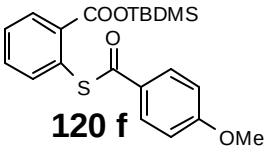
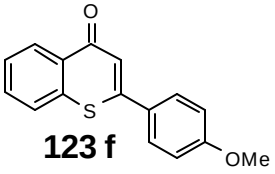
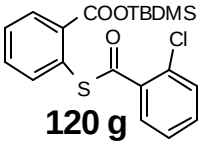
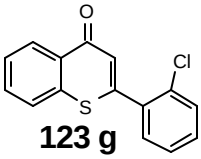
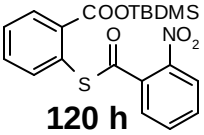
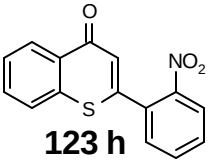
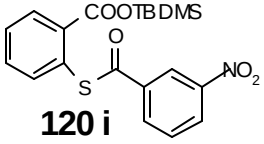
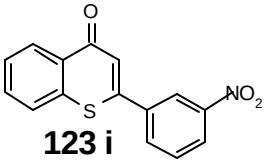
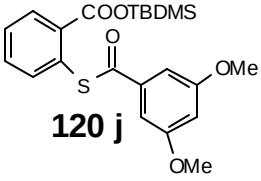
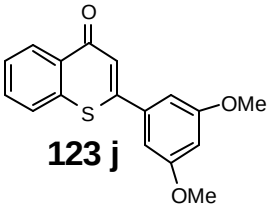
Scheme 30. Reagents and conditions: (a) RCOCl or $(RCO)_2O$, aq. KOH, 0°C-room temp., 0.5 h, 75-80%; (b) TBDMS-Cl, imidazole (1.5 eq), CH_2Cl_2, 0°C-room temp., 7-8 h, 65-70%; (c) 16-38 h in THF, reflux, 58-90%.

With a view to ascertaining the reaction pathway, the reaction of the silyl ester of *S*-acetylthiosalicylic acid **120a** with **94** was carried out at different temperature in order to trap the intermediates formed during reaction. Although the treatment of **120a** with **94** in THF at room temperature did not show any progress of reaction, the extrusion of silyl ether **96** and formation of the acylphosphorane **122a** could be observed when the reaction was performed at higher temperature (55°C). Interestingly, the acylphosphorane **122a** was found to be stable enough to be isolated and was further characterized by its satisfactory IR, ^{1}H NMR and MS spectroscopic data. The ^{1}H NMR spectrum of acylphsophorane **122a** showed the presence of carbanion proton at δ 2.04 as doublet with the absence of silyl group protons. Also there was presence of the protons at δ 7.27-7.77 corresponding to the triphenylphosphine moiety confirming the structure of compound **122a**. Compound **122a** on heating in refluxing THF gave the desired 2-methyl-1-benzothiopyran-4-one **123a**. ^{1}H NMR spectrum of 2-methyl thiochromone **123a** showed the presence of olefinic proton at δ 8.09-8.39 as multiplet corresponding to the thiopyran ring. Also the absence of protons of carabanion of acylphosphorane **122a** at δ 2.04 and the triphenylphosphine at δ 7.27-7.77 confirmed the formation of compound **123a**. The phosphonium salt **121a** could not be

isolated presumably due to its fast rearrangement into the acylphosphorane **122a**. However, the above finding indicates that compound **122a** which results from **121a** after the cleavage of silyl ether **96**, is one of the intermediates which undergoes subsequent intramolecular Wittig cyclization at reflux temperature to afford the desired product **123a**.

Table 3: One-pot synthesis of 2-substituted, 4*H*-1- benzothiopyran-4-ones **123a-j** from **120** and **94**

Entry No.	Substrate	Product[a]	r.t. (h)	Yield (%)
1	 **120 a**	 **123 a**	**16**	**80**
2	 **120 b**	 **123 b**	**17**	**76**
3	 **120 c**	 **123 c**	**18**	**90**
4	 **120 d**	 **123 d**	**22**	**68**

5	 **120 e**	 **123 e**	**21**	**69**
6	 **120 f**	 **123 f**	**25**	**60**
7	 **120 g**	 **123 g**	**35**	**62**
8	 **120 h**	 **123 h**	**38**	**63**
9	 **120 i**	 **123 i**	**30**	**65**
10	 **120 j**	 **123 j**	**33**	**58**

[a] All products were characterized by their satisfactory spectroscopic data. [b] Yields refer to isolated pure products.

The intramolecular Wittig cyclization involving phosphorus ylide and thiolester carbonyl is general for the preparation of a variety of thiochromone derivatives. Further, an electron donating substituent in **120f** reduces the rate of intramolecular Wittig reaction (**Table 3**, entry 6) and hence a little longer time is required to complete the reaction affording relatively low yield of the product **123f**. As it can be seen from **Table 3**, the steric effect during the Wittig cyclization resulting from the substitution in aroyl group appears to be more significant than the electronic factor. Thus, an *ortho*-substituents such as the chloro and nitro group in **120g** and **120h** respectively and *meta* substituents such as the nitro and methoxy group in **120i** and **120j** have pronounced steric hindrance due to their close proximity to the carbonyl group and hence a longer time is required to complete the reaction affording relatively low yields of products **123g-j** (**Table 3**, entries 7-10). It may be mentioned that the cyclization of cinnamate with an electron donating substituent such as methoxy by a usual process led to the formation of the corresponding coumarin instead of thiochromone.[112] Also, the reaction of methoxy substituted benzenethiol with ethylbenzoylacetate by a conventional method has been found to give a mixture of the corresponding thioflavone and isomeric thiocoumarin or only the thiocoumarin in very low yield.[116] In this connection, the present methodology for **123f** and **123j** is noteworthy. Some of the synthesized compounds are precursors for thiochroman-4-ones, which serve as key intermediates in the syntheses of a variety of compounds of biological interest.[122]

1.3.5 Conclusion

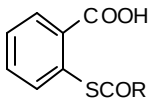
In summary, we have developed an efficient annulation protocol for a variety of thiochromones *via* intramolecular Wittig thiolester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane. This method offers a more general and one-pot synthesis of 1-benzothiopyran-4-one. The protocol developed could be useful particularly in the synthesis of methoxy-substituted benzothiopyranones.

1.3.6 Experimental

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on a Bruker AC-200 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

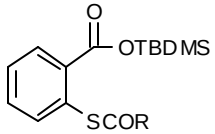
General procedure for the synthesis of *S*-Acyl(aroyl)thiosalicylic acid, 119



119

10g of ice followed by freshly distilled acid chloride or acid anhydride (10mmol) were added to an ice-cold solution of thiosalicylic acid **118** (8mmol) and potassium hydroxide (20mmol) in water (12ml). The resulting mixture was stirred vigorously for 0.5 h at room temperature. After the reaction was complete, the solution was acidified with dil. HCl and the material, which precipitated out, was filtered and washed with water. Recrystallization of the crude product from pet-ether/ethyl acetate or hexane gave the product **119** in 75-80% yield.

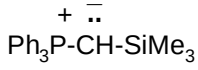
General procedure for the synthesis of *tert*-butyldimethylsilyl ester of *S*-acyl(aroyl)thiosalicylic acid, 120



120

A solution of compound **119** (10mmol) and imidazole (15mmol) in dichloromethane (5ml) was cooled to 0°C, and mixture was stirred under nitrogen atmosphere. To the above solution, was added *tert*-butyldimethylsilyl chloride (13mmol) at 0°C and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 7-8 hours. After the reaction was complete, the reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the product **120** in 65-70% yield, which was used as such for the next reaction without further purification.

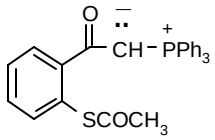
Synthesis of (trimethylsilyl)methylenetriphenylphosphorane, **94**



94

The (trimethylsilyl)methylenetriphenylphosphorane **94** was prepared following the literature procedure[98] from methylenetriphenylphosphorane and trimethylsilyl chloride.

Procedure for the synthesis of 122a



122 a

To a solution of **120a** (1 g, 3.25 mmol) dissolved in absolute THF (5 ml) was added an equimolar amount of silylated ylide **94** (1.325 g, 3.25 mmol) in THF (5 ml). The reaction mixture was heated at 55°C for 8 hours. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure and residue thus obtained was washed several times with petroleum ether to afford 1.25 g (85%) of sufficiently pure acylphosphorane **122a**, which was fully characterized by spectroscopic and analytical data.

Physical State:- oil

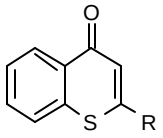
IR ($CHCl_3$, cm^{-1}): ν_{max} 1294, 1437, 1480, 1540, 1610, 1705

^{1}H NMR (200 MHz,$CDCl_3$) δ: 0.89 (s, 3H), 2.04 (d, 1H, *J* = 14 Hz), 7.27-7.77 (m, 19H)

Mass (EI), m/z (%): M^+ 454 (1), 440 (1), 277 (10), 224 (3), 215(40), 201 (78), 152 (35), 107 (25), 75 (100)

Anal. Calcd for $C_{28}H_{23}O_2PS$: C, 74.00; H, 5.10; S 7.04. Found C, 73. 76; H, 5.34; S, 7.34.

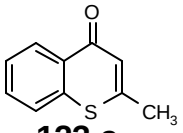
General procedure for the synthesis of 4*H*-1-Benzothiopyran-4-ones, 123



123 a-j

To a solution of compound **120** (50mmol) in absolute THF (5ml) was added under stirring the equimolar amount of silylated ylide **94** (50mmol) in THF (5ml). The reaction mixture was refluxed for the indicated length of time (**Table 3**). The reaction was monitored by TLC. After completion of reaction, the solvent was evaporated and the residue was purified by column chromatography (pet.ether:ethyl acetate, 98:2), to afford the product **123**, in 58-90% yields.

2-Methyl-4*H*-1-benzothiopyran-4-one, 123a



123 a

Physical State:- Colorless solid

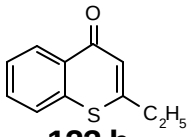
M.P.:- 100°-101°C (Lit.[107a] 103°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1400, 1600, 1703

^{1}H NMR(200 MHz,$CDCl_3$) δ: 2.48 (s, 3H), 6.85 (s, 1H), 7.55-7.65 (m, 3H), 8.09-8.39 (m, 1H)

Mass (EI), m/z (%): M^+ 176 (100), 147 (85), 136 (87).

2-Ethyl-4*H*-1-benzothiopyran-4-one, 123b



123 b

Physical State:- Oil

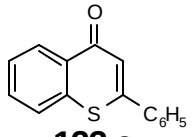
IR ($CHCl_3$, cm^{-1}): ν_{max} 1676

^{1}H NMR(200 MHz,$CDCl_3$) δ: 1.15 (t, 3H, J = 8 Hz), 2.62 (q, 2H, J = 8 Hz), 6.90 (s, 1H), 7.32-7.52 (m, 3H), 7.6-8.0 (m, 1H)

Mass (EI), m/z(%): M^+ 190 (20), 167 (40), 149 (100), 136 (35)

Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85. Found C, 69.68; H, 5.57; S, 17.13.

2-Phenyl-4*H*-1-benzothiopyran-4-one, 123c



123 c

Physical State:- Colorless solid

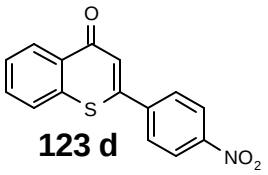
M.P.:- 126°C (Lit. [108a] 122-123°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1600, 1688 1445

^{1}H NMR(200 MHz,$CDCl_3$) δ: 7.12 (s, 1H), 7.49-7.67 (m, 6H), 8.03-8.07 (m, 3H)

Mass (EI), m/z (%): M^+ 238 (40), 215 (100), 136 (50), 107 (60), 77 (45).

2-(4'-Nitrophenyl)-4*H*-1-benzothiopyran-4-one, 123d



123 d

Physical State:- Colorless solid

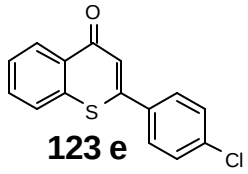
M.P.:- 252°C (Lit. [120] 250-252°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1690, 1532, 1215

^{1}H NMR(200 MHz,$CDCl_3$) *d*: 6.92-7.05 (m, 3H), 7.51-7.58 (m, 2H), 7.93-8.33 (m, 4H)

Mass (EI), m/z (%): M^+ 283 (40),

2-(4'-Chlorophenyl)-4*H*-1-benzothiopyran-4-one, 123e



123 e

Physical State:- Colorless solid

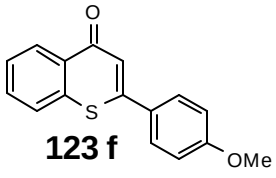
M.P.:- 187-189°C (Lit. [111] 189-190°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1692, 1540, 1215

^{1}H NMR (200 MHz,$CDCl_3$) *d*: 7.21-7.50 (m, 5H), 7.84-7.97 (m, 4H)

Mass (EI), m/z (%): M^+ 272 (30), 244 (35), 139 (100).

2-(4'-Methoxyphenyl)-4*H*-1-benzothiopyran-4-one, 123f



123 f

Physical State:- Colorless solid

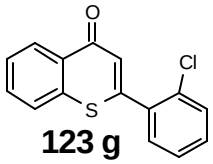
M.P.:- 126-127°C (Lit. [110] 126-127°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1666, 1540, 1243

^{1}H NMR (200 MHz,$CDCl_3$) *d*: 3.90 (s, 3H), 6.9-7.03 (m, 5H), 7.5-7.56 (m, 2H), 7.94 (d, 1H, *J* = 4 Hz), 8.08 (d, 1H, *J* = 6 Hz)

Mass (EI), m/z (%): M^+ 268 (80), 240 (40), 225 (22).

2-(2'-Chlorophenyl)-4*H*-1-benzothiopyran-4-one, 123g



123 g

Physical State:- Colorless solid

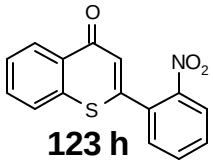
M.P.:- 201°C (Lit. [118]204°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1694,1213

^{1}H NMR (200 MHz,$CDCl_3$) *d*: 6.95-7.00 (m, 1H), 7.44-7.90 (m, 4H), 8.11-8.15 (m, 4H)

Mass (EI), m/z (%) M^+ 272 (35), 244 (28), 139 (95).

2-(2'-Nitrophenyl)-4*H*-1-benzothiopyran-4-one, 123h



123 h

Physical State:- Colorless solid

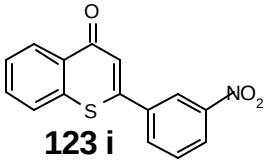
M.P.:- 284°C (Lit. [118] 282°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1694, 1540, 1224;

^{1}H NMR (200 MHz, $CDCl_3$) *d*: 6.89-7.04 (m, 2H), 7.43-7.57 (m, 4H), 7.91-8.09 (m, 3H).

Mass **(EI), m/z (%):** M^+ 283 (80), 139 (76), 123 (38).

2-(3'-Nitrophenyl)-4*H*-1-benzothiopyran-4-one, 123i[121]:



123 i

Physical State:- Colorless solid

M.P.:- 215-216°C

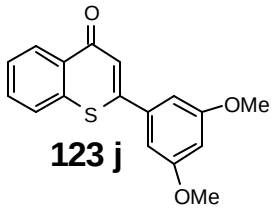
IR ($CHCl_3$, cm^{-1}): ν_{max} 1692, 1530, 1243

^{1}H NMR (200 MHz,$CDCl_3$) *d*: 6.9-7.1 (m, 3H), 7.48-8.01 (m, 6H)

Mass (EI), m/z (%): M^+ 283 (80), 139 (95), 123 (25)

Anal. Calcd for $C_{15}H_9NO_3S$: C, 63.59; H, 3.20; N, 4.94; S, 11.32. Found C, 63.40; H, 3.52; N, 5.14; S, 11.60.

2-(3', 5'-Dimethoxyphenyl)-4*H*-1-benzothiopyran-4-one, 123j



123 j

Physical State:- Colorless solid

M.P.:- 234-236°C (Lit. [111] 236°C)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1686, 1534, 1215

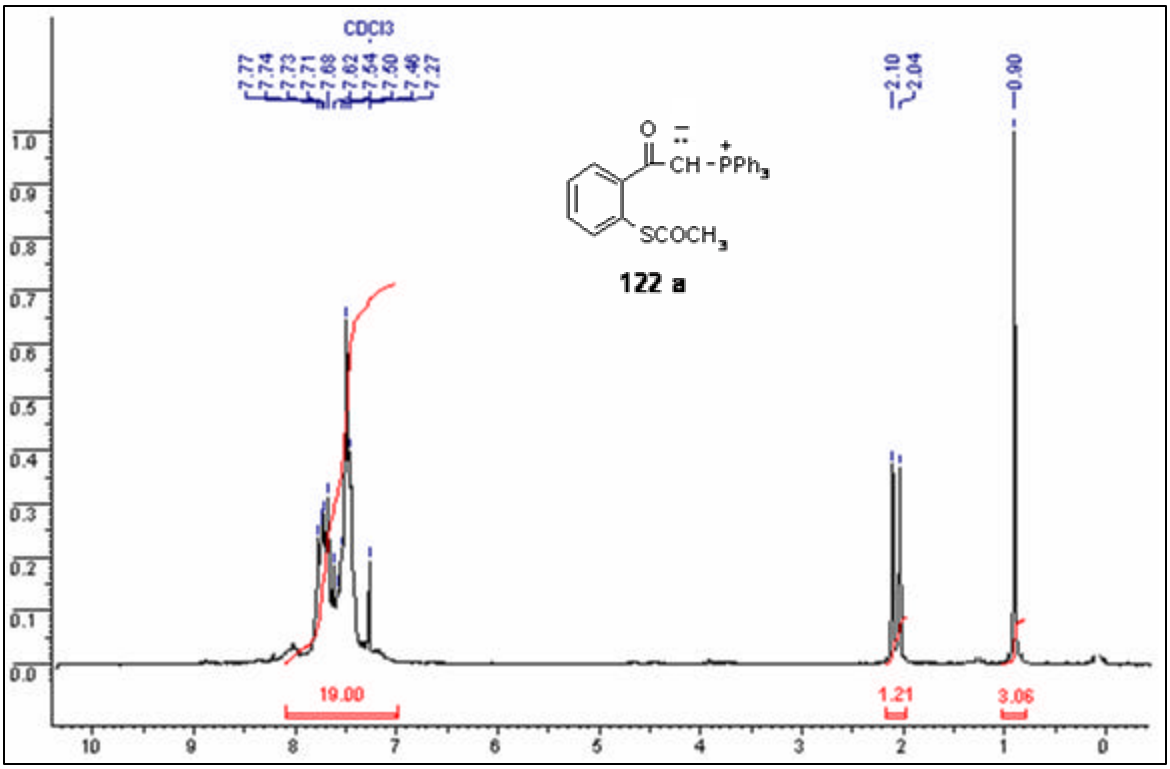
^{1}H NMR (200 MHz,$CDCl_3$) *d*: 3.90 (s, 6H), 7.25-7.42 (m, 4H), 7.87-8.09 (m, 4H)

Mass (EI), m/z (%): M^+ 298 (80), 137 (85), 139 (88), 77 (38).

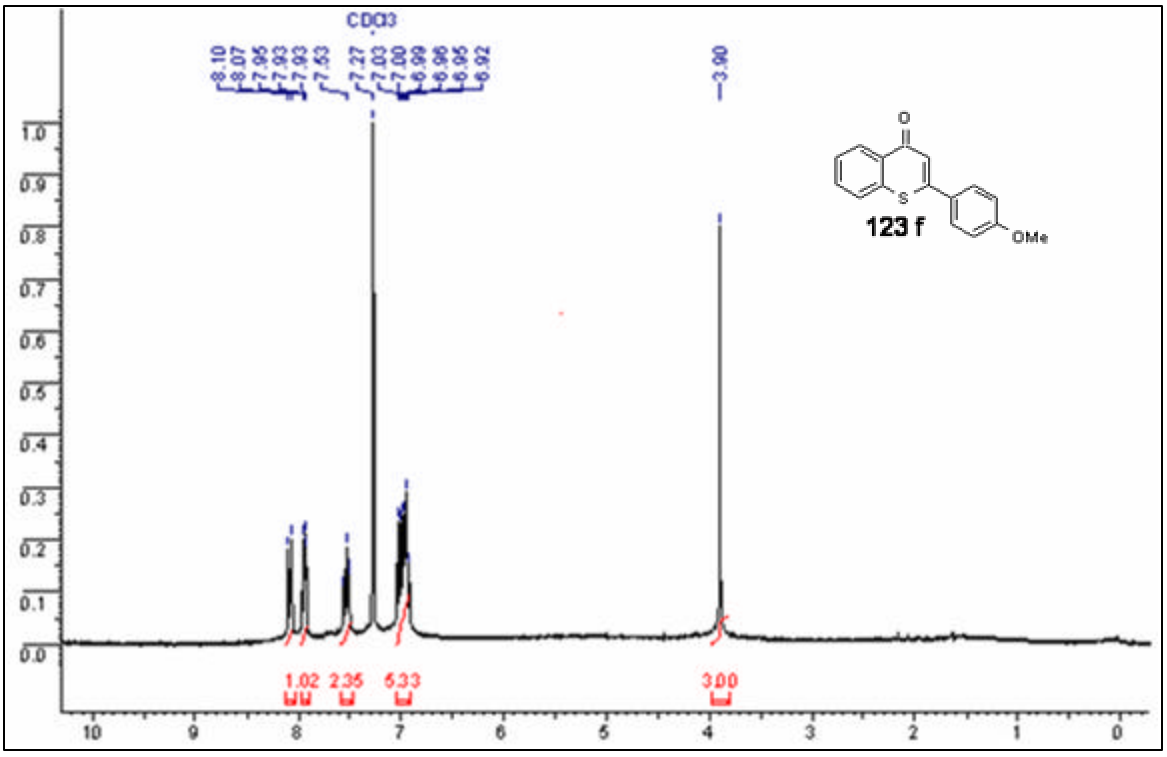
1.3.6 Spectra

1. ^{1}H NMR spectrum of **122a**
2. ^{1}H NMR spectrum of **123f**
3. ^{1}H NMR spectrum of **123g**
4. 1H NMR spectrum of **123h**

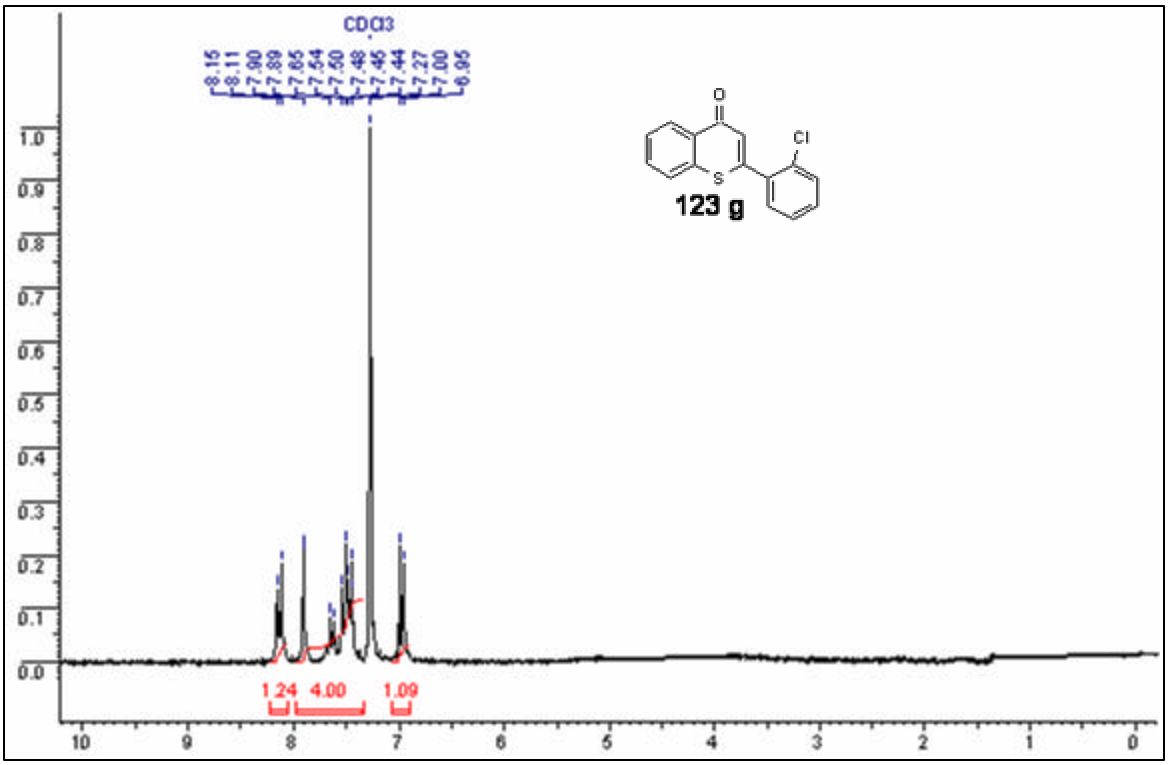
➢ ^{1}H NMR Spectrum of **122a**



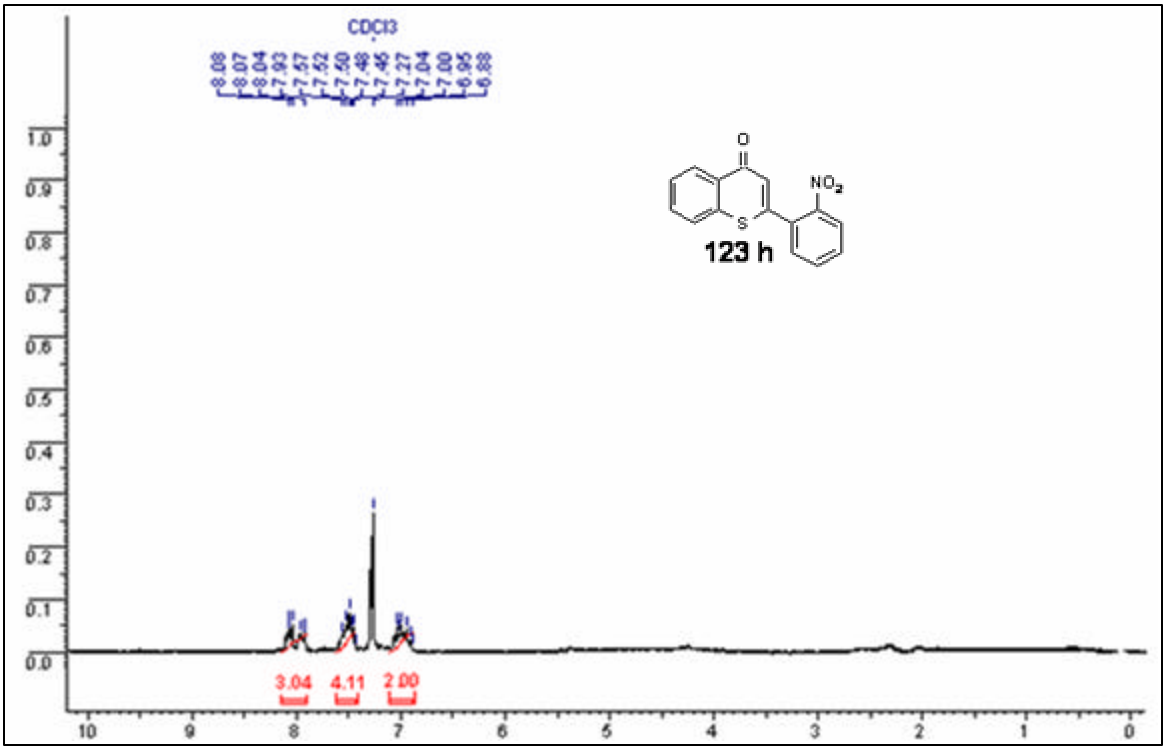
➢ ^{1}H NMR Spectrum of **123f**



➢ ^{1}H NMR Spectrum of **123g**



➢ 1H NMR Spectrum of **123h**



1.4 References:

1. Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem*. **1953**, *580*, 44.
2. Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318.
3. For work in this and other areas, Wittig received the Nobel Prize in Chemistry in 1979 Wittig, G. *Science* (*Washington, D.C*.) **1980**, *210*, 600.
4. For a review of the modern state of organic chemistry, see: Trost, B. M. *Science* (*Washington, D.C.*) **1985**, *227*, 908.
5. Trippett, S. Q. *Rev*. *Chem. Soc*. **1963**, *17*, 406.
6. Johnson, A. W. *Ylide Chemistry*; Academic Press: New York. **1966**.
7. Maercker, A. *Org. React.* **1965**, *14*, 270.
8. Schlosser, M. *Top. Stereochem*. **1970**, *5*, I.
9. Reucroft, J.; Sammes, P. G. Q. *Rev. Chem. Soc*. **1971**, *25*,135.
10. (a) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*,515. (b) *Ibid*. **1980**. *52*. 771.
11. Gosney, I.; Rowley, A. G. *In Organo Phosphorus Reagents in Organic Synthesis*; Cadogan, J. I. &., Ed.; Academic Press: New York, **1979**; pp 17-153.
12. Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem*. **1983**,*109*, 85.
13. McEwen, W. E.; Beaver, B. D.; Cooney, J. V. *Phosphorus Sulfur* **1985**,*25*, 255.
14. (a) Le Bigot, Y.; Delmas, M.; Gaset, A. *Inform. Chim.* **1984**, *251*,123. (b) Pommer, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*. 423. (c) Pommer. H.; Thieme. P. C. *Top. Curr. Chem.* **1983**, *109*; 165.
15. Wadsworth, W. S., Jr. *Org. React*. **1977**, *25*, 73.
16. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.
17. For a review of Wittig reactions of carbonyl compounds other than aldehydes and ketones, see: Murphy, P. J.; Brennan, *J. Chem. Soc. Rev*. **1988**, *17*, 1.
18. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
19. For a review of stereochemistry, see: (a) Revcroft, J.; Sammes, P. G. *Rev. Chem. Soc.* **1971**, *25*, 135. (b) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (c) Bergelson, L. D.; Shemyakin, M. M. *Tetrahedron* **1963**, *19*, 149. (d) Wadsworth, D. H.; Schupp, O.E.; Seus, E. J.; Ford, J. A. *J. Org. Chem.* **1965**, *30*, 680.
20. (a) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1968**, *90*, 6814. (b) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1969**, *34*, 3053.
21. (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, **1972**; pp 682-709. (b) March, J. *Advanced Organic Chemistry:*

Reactions, Mechanism, and Structure, 3rd ed.; McGraw-Hill: New York, **1985**; pp 845-854.

22. Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J . Am. Chem. Soc*. **1981**, *103*, 2823.
23. Wittig, G.; Haa, W. *Chem. Ber.* 1955, **88**, 1654.
24. Schlosser, M.; Thristmann, K. F. *Liebigs Ann. Chem.* **1967**, *708*, 1.
25. Jones, M. E.; Trippett, S. *J. Chem. Soc. C* **1966**, 1090.
26. Lowe, P. A. *Chem. Ind. (London)* **1970**, 1070.
27. Wittig, G.; Weigmann, H.-D.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 676.
28. Schneider, W. P. *Chem. Commun.* **1969**, 785.
29. Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778.
30. Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J . Am. Chem. Soc.* **1985**, *107*, 217.
31. Reitz, A. B.; Mutter, M. S.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1984**,*106*, 1873.
32. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond. H. R.. Jr. *J. Am. Chem. Soc*. **1985**, *107*, 1068.
33. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr.; Whittle, R. R.; Olofson, R. A. *J . Am. Chem. Soc*. **1986**,*108*, 7664.
34. Reitz, A. B.; Nortey, S. 0.; Jordan, A. D., Jr.; Mutter, M. S.; Maryanoff, B. E. *J. Org. Chem*. **1986**, *51*, 3302.
35. Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, .*38*, 118.
36. (a) Vedejs, E.; Marth, C.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940. (b) Vedejs, E.; Marth, C. F. *Ibid*. **1988**, *110*, 3948. (c) Vedeis. E.: Fleck. T. J. *Ibid*., **1989**, *111*, 3654.
37. (a) Volatron, F.; Eisenstein, O. *J . Am. Chem. Soc.* **1987**, *109*, 1. (b) Ibid. **1984**, *106*, 6117.
38. Holler, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, 102, 4632.
39. Schlosser, M.; Muller, G.; Christman, K. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *5*, 667.
40. Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963**, *85*, 3878.
41. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.
42. Worms, K. H.; Schmidst-Dunker, M. *In Organic Phosphorus Compounds*; Kosolapoff, G. M.; Maier, L., Ed.; Wiley: New York, **1976**, *vol. 7*, p. 27.
43. (a) For reviews, see: Dombrovskii, A. V.; Dombrovskii, V. A. *Russ. Chem. Rev.* **1966**, *35*, 733. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

44. (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499.
45. Wadsworth, W. S.; Jr. Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733.
46. Burri, K. F.; Cardune, R. A.; Chen. W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.
47. Chioccola, G.; Daly, J. J. *J. Chem. Soc., A* **1968**, 568.
48. (a) Bestmann, H. J.; Seng, F.; Schulz, H. *Chem. Ber.* **1963**, *96*, 465. (b) Christav, H. J.; Vors, J. P.; Christol, H. *Synthesis* **1979**, 538.
49. Griffin, C. E.; Witschard, G. *J. Org. Chem.* **1964**, *29*, 1001.
50. (a) Berenguer, H. J.; Castells, J.; Galard, R. M.; Morenu-Manas, M. *Tetrahedron Lett.* **1971**, 495. (b) Brown, C. Sargent, M. V. *J. Chem. Soc., C* **1969**, 1818.
51. (a) Bieber, T. L.; Eisman, E. H. *J. Org. Chem.* **1962**, *27*, 678. (b) Griffin, C.E.; Witschard, G. *J. Org. Chem.* **1962**, *27*, 3334.
52. (a) Bestmann, H. J.; Roth, D. *Angew Chem. Int. Ed. Eng*. **1990**, *29*, 99. (b) Bestmann, H. J.; Moenius, T. *Angew Chem. Int. Ed. Eng.* **1986**, *25*, 994.
53. (a) Kraus, G. A.; Shir, J. *J. Org. Chem.* **1991**, *56*, 4147. (b) Akiba, K.; Negishi Y.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2188.
54. Murphy, P. J.; Brenan, J. *Chem. Soc. Rev.* **1988**, *17*, 1.
55. Heron, B. M. *Heterocycles* **1995**, *41*, 2357.
56. (a) Orjales, A.; Bercia, A.; Alonso-Cires, L. *Indian J. Chem. Sect. B* **1994**, *33*, 27. (b) Zammaito, F.; Brion, J. D.; Belachami, L.; Le Baut, G. *J. Heterocycl. Chem.* **1991**, *28*, 2013. (c) Kim, K-J.; Kim, S.; Park, H. *Bull. Korean Chem. Soc.* **1991**, *12*, 120. (d) Le Floc'h, Y.; Lefeuvre, M. *Tetrahedron Lett.* **1986**, *27*, 2751.
57. Zammaito, F.; Brion, J. D.; Ducrey, P.; Le Baut, D. *Synthesis* **1992**, 375.
58. (a) Babin, P.; Dunogues, J.; Duboudin, F.; Petraud, M. *Bull. Soc. Chim. Fr*. **1982**, 125. (b) Bestmann, H. J.; Schade, G. *Chem. Lett.* **1983**, 997.
59. Vorbruggen, M.; Bohn, B. D.; Krolikiewicz, K. *Tetrahedron* **1990**, *46*, 3489.
60. Chattergee, P.; Murphy, P. J.; Pee, R.; Shaw, M *J. Chem. Soc., Perkin Trans 1* **1994**, 2403.
61. Hsiao, C. N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629.
62. (a) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313. (b) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Silvani, A. *Tetrahedron* **1994**, *50*, 6941. (c) Li, J. P.; Newlander, K. A.; Yellin, T. O. *Synthesis* **1988**, 73. (d) Prasitpan, N.; Patel, J. N.; De Cross, P. Z.; Stockwell, B. L.;

Manavalan, P.; Kar, L.; Johnson, M. E. *J. Heterocycl. Chem.* **1992**, *29*, 335. (e) Cirrincione, G.; Almerico, A. M.; Diana, P.; Grimaudo, S. Dattolo, G.; Aiello, E.; Barraja, P.; Mingoia, F. *Farmaco* **1995**, *50*, 849. (f) Arcari, M. ; Aveta, R.; Brandt, A.; Cecchetelli, L.; Corsi, G. B.; Di Rella, M. *Gazz. Chim. Ital.* **1991**, *121*, 499. (g) Capuano, L.; Ahlhelm, A.; Hartmann, H. *Chem. Ber.* **1986**, *119*, 2069. (h) Eitel, M.; Pindur, U. *Synthesis* **1989**, 364. (i) Pindur, U.; Eitel, M. *Helv. Chim. Acta* **1988**, *71*, 1060. (j) Coulton, S.; Gilchrist, T. L.; Graham, K. *J. Chem. Soc*., *Perkin Trans. 1* **1998**, 1193. (k) Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034. (l) Freund, R.; Martinovic, S.; Bernauer, K. *Helv. Chim. Acta* **1992**, *75*, 282.

63. Cupuano, L.; Dreschler, S.; Hammerer, V.; Hanisch, M. *Chem. Ber.* **1988**, *121*, 282.
64. (a) Dean, F. M.; *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, **1963**. (b) Heterocyclic Compounds: Chromenes, Chromanones and Chromones; Ellis, G. P.; Ed.; Wiley: New York, 1977. (c) Swain, T. *In Chemistry and Biochemistry of Plant pigments*; Goodwin, T. W.; Ed.; Academic: London **1976**.
65. For growth regulation: Mandava, N. B. *In Plant Growth Substances*; Mandava, N. B.; Ed.; ACS Symposium Series 136; American Chemical Society: Washington DC, **1979**; p. 135.
66. For indoleacetic acid oxidation: Thiman, K. V. *In Plant Physiology*; Steard, F. C.; Ed.; Academic: New York, **1972**, vol. VI b
67. For dormancy inhibition: Isogi, Y.; Komada, Y.; Okamoto, T. *Chem. Pharm. Bull.* **1970**, 18, 1872.
68. (a) Gamill, R. D.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672. (b) Yamashita, A. *J. Am. Chem. Soc.* **1985**, 105, 5823.
69. (a) Gabor, M. *Prog. Clin. Bio. Res.* **1986**, 213, 471. (b) Fourie, T. G.; Snyckers, F. O. *J. Nat. Prod.* **1984**, 47, 1057.
70. (a) Weinges, K.; Bahr, W.; Ebert, W.; Goritz, K.; Marr, H. D. *In Forschritte Chemie Organische Naturstuffe*; Zechmeister, L.; Ed.; Springer-Verlag: New York, **1969**; p. 159. (b) Freudenberg, K.; Weinger, K. *In The Chemistry of Flavanoid Compounds*; Gesman, T. A.; Ed.; Pergamon: Oxford **1952**; p. 197.
71. (a) Roux, D. G. *Phytochemistry* 1972, *11*, 1219. (b) Thompson, R. S.; Jacquer, D.; Haslam, G.; Tanner, R. J. N. *J. Chem. Soc., Perkin Trans 1* **1972**, 1387. (c) Fletcher, A. C.; Porter, C. J.; Haslam, E.; Gupta, K. *J. Chem. Soc., Perkin Trans 1* **1977**, 1628. (d) Kolodziej, H. *Phytochemistry* **1986**, *25*, 1209.

72. Chrisey, L. A.; Bonjar, G. H. S.; Hecht, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 644.
73. Havsteen, B. *Biochem. Pharmacol.* **1983**, *32*, 1141.
74. Middleton, E.; Kandaswami, C. The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation and cancer. *In The Flavonoids, Advances in Research since **1986***; Harborne, J. B., Ed.; Chapman and Hall: London, **1994**; pp. 619.
75. Krebs, H. C. *Naturforsch*, **1987**, *42b*, 1361.
76. Schutz, R. A.; Schutz, M.T. B; Angelucci, M. E. M.; Munoz, E. M.A.; Da Cunha, C. *Brazil. J. Vet. Res. Animal Sci.* **1996**, *33*, 182.
77. Cassady, J. M.; Baird, W. H.; Chang, C.-J. *J. Nat. Prod.* **1990**, 53, 22.
78. Hodnick, W. F.; Roetttger, W. J.; Kung, F. S.; Bohmant, C. W.; Pardini, R. S. *In Plant Flavonoids in Biology and Medicine*; Liss, A. R.; Ed.; **1986**; pp. 249.
79. Gripenberg, J. *In Chemistry of the Flavonoid Compounds*; Geissman, T. A.; Ed.; Pergamon Press: Oxford, **1962**; pp. 409.
80. Wagner, H.; Farke\as, L. *In The Flavonoids*; Harborne, J. B.; Mabry, T. J.; Mabry, H.; Ed.; Chapman and Hall: New York, **1975**; pp. 214.
81. Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, 465.
82. Ellis, G. P. *Chromenes, Chromanones and Chromones*; John Wiley & Sons: New York, **1977**.
83. Nakamura, K.; Takenaka, K. *Tetrahedron: Asymmetry* **2002**, *13*, 415.
84. For review, see (a) Gripenberg, J. *In The Chemistry of Flavonoid Compounds*; Geissman, T. A., Ed.; MacMillan: New York, **1962**; p. 409. (b) Wagner, H.; Farkas, L. *In The Flavonoids*; Harborne, J. B.; Mabry, T. J.; Mabry, H., Eds.; Academic Press: New York, **1975**; p. 127. (c) Wang, L. *Zhorggue Yiyao Gongye Zazhi* **1990**, *21*, 423.
85. Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, 2192.
86. (a) Baker, W. *J. Chem. Soc*. **1933**, 1381. (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767.
87. (a) Inuma, M.; Iwashima, K.; Matsaura, S. *Chem. Pharm. Bull.* **1984**, *32*, 4395. (b) Hoshino, Y.; Oohinuta, T.; Takeno, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2351.
88. (a) Inuma, M.; Tanaka, T.; Matsaura, S. *Chem. Pharm. Bull.* **1984**, *32*, 3354. (b) Matsaura, S.; Inuma, M.; Ishikawa, K. *Chem. Pharm. Bull*. **1978**, *26*, 305.
89. (a) Hercouet, A.; Le Corre, M.; Le Floc'h, Y. *Synthesis* **1982**, 597. (b) Le Floc'h, Y.; Le Feuvre, M. *Tetrahedron Lett.* **1986**, 5503.

90. Banerji, A.; Goomer, N. C. *Synthesis* **1980**, 874.
91. Hermeneglido, G.; Iborra, S.; Primo, J.; Miranda, M.A. *J. Org. Chem.* **1986**, *51*, 4432.
92. Nagarathnam, D.; Cushman, M. *Tetrahedron* **1991**, *47*, 5071.
93. Riva, C.; De Toma, C.; Donadel, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. *Synthesis* **1997**, 195.
94. Osorio-Olivares, M.; Cassels,B. K.; Sepulveda-Boza, S.; Resende, M.C. *Synth. Commun*. **1999**, *29*, 815.
95. Mioa, H.; Yang, Z. *Organic Lett.* **2000**, *2*, 1765.
96. Kawasaki, M.; Kakuda, H.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron: Asymmetry* **2003**, *14*, 1529.
97. a) Kumar, P.; Rao, A. T.; Pandey, B. *J. Chem. Soc.*, *Chem. Commun.* **1992**, 1580. (b) Kumar, P.; Dinesh, C. U.; Pandey, B. *Tetrahedron Lett.* **1994**, *35*, 9228. (c) Kumar, P.; Rao, A. T.; Pandey, B. *Synth. Commun.* **1994**, *24*, 3297. (d) Kumar, P.; Saravanan, K. *Tetrahedron* **1998**, *54*, 2161.
98. Bestmann, H. J.; Bomhard, A.; Dostalek, R.; Pichl, R.; Riemer, R.; Zimmermann, R. *Synthesis* **1992**, 787.
99. (a) Ollis, W. D.; Weight, D. *J. Chem. Soc.* **1952**, 3826. (b) Meyer-Dayan, M.; Bodo, B.; Deschamps-Vallet, C.; Molho, D. *Tetrahedron Lett.* **1978**, 3359. (c) Banerji, A.; Goomer, N. C. *Synthesis* **1980**, 874. (d) Babin, P.; Dunoguess, J.; Petraud, M. *Tetrahedron* **1981**, *37*, 1131. (e) Hercouet, A.; Le Corre, M. *Synthesis* **1982**, 597. (f) Bestmann, H. J.; Schade, G. *Chem*. *Lett*. **1983**, 997. (g) LeFloch, Y.; Lefeuvre, M. *Tetrahedron Lett.* **1986**, *27*, 2751. (h) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* **1990**, *55*, 4349. (i) Nagarathnam, D.; Cushman, M. *Tetrahedron* **1991**, *47*, 5071. (j) Nishiraga, A.; Ando, H.; Marugama, K.; Mushino, T. *Synthesis* **1992**, *9*, 839. (k) Zammattio, F.; Brion, J. D.; Ducrey, P.; LeBaut, G. *Synthesis* **1992**, *4*, 375. (l) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Heterocycl. Chem.* **1996**, *33*, 1887. (m) Riva, C.; Toma, C. D.; Donadel, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. *Synthesis* **1997**, 195. (n) Lokshin, V.; Heynderickx, A.; Samat, A.; Pepe, G.; Guglielmetti, R. *Tetrahedron Lett.* **1999**, *40*, 6761. (o) Dekermendjian, K.; Kahnberg, P.; Witt, M.-R.; Sterner, O.; Nielsen, M.; Liljefors, T. *J. Med. Chem.* **1999**, *42*, 4343. (p) Osorio-Olivares, M.; Cassels, B. K.; Sepulveda-Boza, S.; Rezende, C. *Synth. Commun*. **1999**, *29*, 815.

100. (a) Heilbron, I. M.; Hey, D. H.; Lowe, A. *J. Chem. Soc.* **1934**, 1311. (b) Geissman, T. A. *J. Am. Chem. Soc.* **1951**, *73*, 3514.
101. Gupta, V. N.; Seshadri, T. R. *J*. *Sci*. *Ind*. *Res*. **1957**, *16*, 116.
102. Ciattini, P. G.; Morera, E.; Ortar, G.; Rossi, S. S. *Tetrahedron* **1991**, *47*, 6449.
103. (a) Krapcho, J.; Turk, C. F.; Piala, J. J. *J. Med. Chem.* **1968**, *11*, 361. (b) Philipp, A.; Jirkovsky, I.; Martel, R. R; *J. Med. Chem.* **1980**, *23*, 1372. (c) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1985**, *22*, 1593. (d) Malene, C.; Danree, B.; Laubie, M. *Ger*. *Pat*. **1970**, 2017902; C. A. **1970**, *74*, 22698. (e) Malene, C.; Desnoyers, P. *Br*. *Pat*. **1969**, 1158473; C. A. **1970**, *72*, 71434. (f) Watanabe, K.; Saito, T.; Niimura, K. *Eur. Pat. Appl*. **1997**, EP 758649; C. A. 1997, *126*, 199456. (g) Tomizawa, K.; Kameo, K.; Saito, H.; Hatayama, K. *Jpn. Kokai Tokkyo Koho* **1990**, JP 02255676; C. A. **1991**, *114*, 228737. (h) Charris, J.; Dominguez, J.; Lobo, G.; Riggione, F. *Pharm. Pharmacol. Commun*. **1999**, *5(2)*, 107. (i) Sano, T.; Saijo, K.; Tomizawa, K.; Kameo, K.; Yokomori, S.; Hatayama, K. *Jpn. Kokai Tokkyo Koho* **1992**, JP 04082887; C. A. **1992**, *117*, 150893. (j) Jeffery, J. A.; Outt, P. E.; Randall, J. L.; Johnston, J. N.; Murray, P. D.; O` Brien, L. M.; Weisshaar, P. S.; Ems, B. L. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 995.
104. (a) Ellis, G. P., *Comprehensive Heterocyclic Chemistry* , Katritzky, A. R. ; Rees, C. W., Eds; Pergamon Press, New York, **1984**, *Vol. 3*, Part 2B , pp 695, 718. (b) Hepworth, J. P., *Comprehensive Heterocyclic Chemistry* , Katritzky, A. R. ; Rees, C. W., Eds.; Pergamon Press, New York, **1984**; Vol. 3, Part 2B, pp 816-830 and 874-883.
105. (a) Hepworth, J. P., *Comprehensive Heterocyclic Chemistry*. , Katritzky, A. R. ; Rees, C. W., Eds; Pergamon Press, New York, **1984**, *Vol. 3*, Part 2B, pp 918-919. (b) Ingall, A. H., *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. ; Rees, C. W., Eds; Pergamon Press, New York, **1984**, *Vol. 3*, Part 2B., pp 941-942.
106. (a) Nakazumi, H.; Ueyama, T.; Kitao, T. *J*. *Heterocycl*. *Chem*. **1984**, *21*, 193. (b) Wang, H.-K.; Bastow, K. F.; Cosentino, L. M.; Lee, K-H. *J*. *Med*. *Chem*. **1996**, *39*, 1975. (c) Holshouser, M. H.; Loeffler, L. J.; Hall, I. H. *J. Med*. *Chem*. **1981**, *24*, 853.
107. (a) Bossert, F. *Liebigs Ann. Chem.* **1964**, *680*, 40. (b) Schneller, S. W. *Adv*. *Heterocycl*. *Chem*. **1975**, *18*, 60. (c) Nakazumi, H.; Watanabe, S.; Kitaguchi, T.; Kitao, T. *Bull. Chem. Soc. Japan* **1990**, *63*, 847.

108. (a) Truce, W. E.; Goldhamer, D. L. *J. Am. Chem. Soc*. **1959**, *81*, 5795. (b) Yu, X.; Liu, J.; Li, X.; Zhang, G.g; Fang, L. *Huaxi Yaoxue Zazhi* **1997**,*12(4)*, 230; C. A. **1998**, *128*, 48115. (c) Razdan, R. K.; Bruni, R. J.; Mehta, A. C.; Weinhardt, K. K.; Papanastassiou, Z. B. *J. Med. Chem*. **1978**, *21(7)*, 643. (d) Buggle, K.; Delahunty, J. J.; Philbin, E. M.; Ryan, N. D. *J. Chem. Soc*. (C) **1971**, 3168.
109. Angel, A. J.; Finefrock, A. E.; French, K. L.; Hurst, D. R.; Williams, A. R.; Rampey, M. E.; Studer-Martinez, S. L.; Beam, C. F. *Can. J. Chem*. **1999**, *77(1)*, 94.
110. French, K. L.; Angel, A. J.; Williams, A. R.; Hurst, D. R.; Beam, C. F. *J. Heterocycl. Chem*. **1998**, *35(1)*, 45 and references therein.
111. Taylor, A. W.; Dean, D. K. *Tetrahedron Lett*. **1988**, *29*, 1845.
112. Wadsworth, D. H.; Detty, M. R. *J. Org. Chem*. **1980**, *45*, 4611.
113. Holshouser, M.H.; Loeffler, L. J.; Hall, I.H. *J. Med. Chem.* **1981**, *24*, 353.
114. Chauhan, M.S.; Still, W. W. J. *Can. J. Chem.* **1975**, *53*, 2880
115. Bass, S. W.; Jr., Evans, S. A. *J. Org. Chem.* **1980**, *45*, 710.
116. Nakazumi, H.; Kitaguchi, T.; Ueyama, T.; Kitao, T. *Synthesis* **1983**, 518.
117. Lau, C. K.; Belanger, P.C.; Dufresne, C.; Scheigetz, J. *J. Org. Chem.* **1987**, *52*, 1670.
118. Levai, A. *Heterocyclic Commun*. **1999**, *5*, 419.
119. Boivin, J.; Boutillier, P.; Zard, Z. *Tetrahedron Lett*. **1999**, *40*, 2529
120. Nakazumi, H.; Ueyama, T.; Sonoda, H.; Kitao, T. *Bull. Chem. Soc., Jpn*. **1984**, *57*, 2323.
121. Dekermendjian, K.; Kahnberg, P.; Witt, M.-R.; Sterner, O.; Nielsen, M.; Liljefors, T. *J. Med. Chem*. **1999**, *42*,. 4343.
122. (a) Dike, S.Y.; Ner, D. H.; Kumar, A. *Synlett* **1991**, *13*, 443. (b) Krapcho, J.; Spitzmiller, E. R.; Turk, C. F. *J. Med. Chem*. **1963**, *6*, 544. (c) Krapcho, J.; Turk, C. F. *J. Med. Chem*. **1966**, *9*, 191. (d) Clarke, P. D.; Fitton, A. O.; Suschitzky, H.; Wallace, T. W.; Dowlatshahi, H. A.; Suschitzky, J. L. *Tetrahedron Lett*. **1986**, *27(1*), 91.

CHAPTER 2

Asymmetric Dihydroxylation, Asymmetric Epoxidation And Cyclic sulfites/sulfates As Synthetic Intermediates

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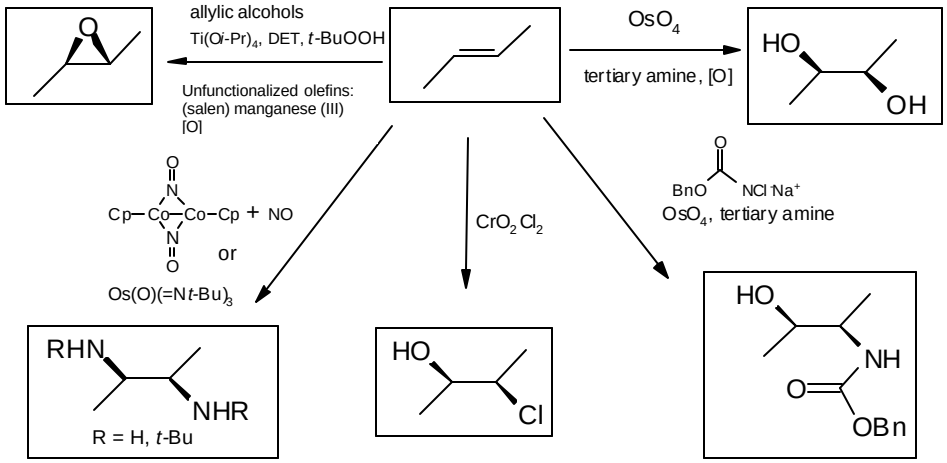
2.1 Asymmetric Dihydroxylation

2.1.1 Introduction

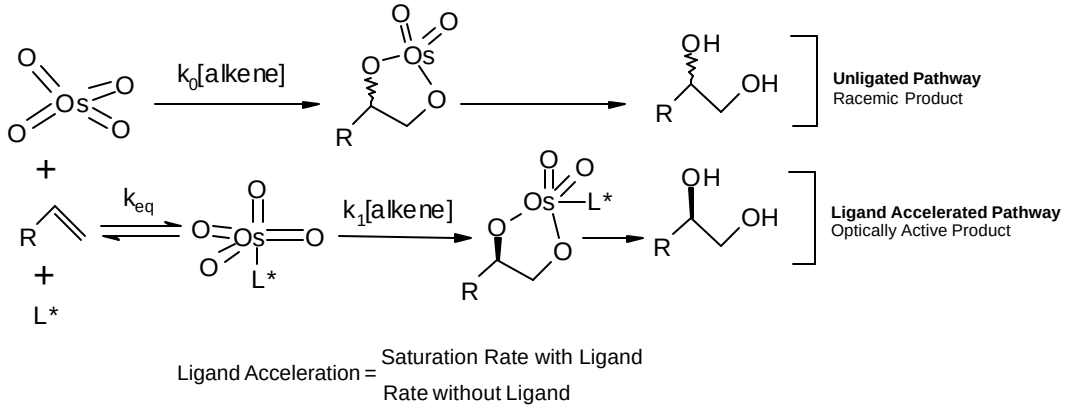
The synthetic organic chemist has obtained a variety of powerful tools in recent years due to the development of many new asymmetric processes. In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical



Scheme 1. Transition metal mediated suprafacial 1,2-difunctionalization of olefins.

use of asymmetric inducing agents.[1] Especially useful are the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. In addition, bonds to heteroatom are much easier to form than carbon-carbon bonds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years (**Scheme 1**).

A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of *ligand acceleration*,[7] wherein a metal-catalyzed process turns over faster in the presence of a co-ordinating ligand (**Scheme 2**). This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way since ligand acceleration ensures that the unligated pathway moves into the background.



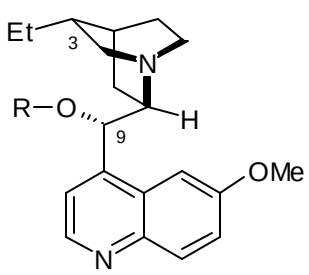
Scheme 2. Ligand accelerated catalysis-dihydroxylation of olefins.[7]

One of the process that greatly benefits from ligand acceleration is the asymmetric dihydroxylation of olefins by osmium (VIII) complexes. In his pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee[8] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[5b] Inorganic co-oxidants such as sodium or potassium chlorate[9a] or hydrogen peroxide,[9b,c] were among the first to be introduced, but in some

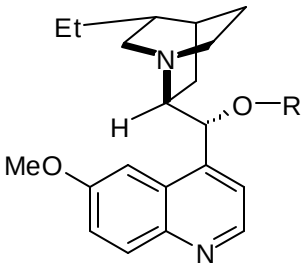
cases diminished yields resulted due to over- oxidation. Much better results were obtained with alkaline *t*-BuOOH, introduced by Sharpless and Akashi,[10] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[11] Tsuji *et al*.[12] demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[13] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of

(a) Cinchona Alkaloid Ligands for AD under *Catalytic* Conditions[13,17,19,20]

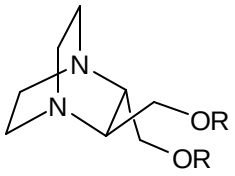


Dihydroquinidine (R = H)
DHQD

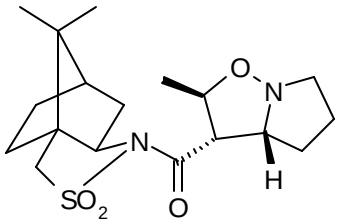


Dihydroquinine (R = H)
DHQ

(b) Monodentate Ligands for AD under *Catalytic* Conditions



R = *t*-BuPh$_2$Si
Hirama *et al.*[15]



Murahashi *et al.* [16n]

(c) Chiral Diamine Ligands for AD under *Stoichiometric* Conditions

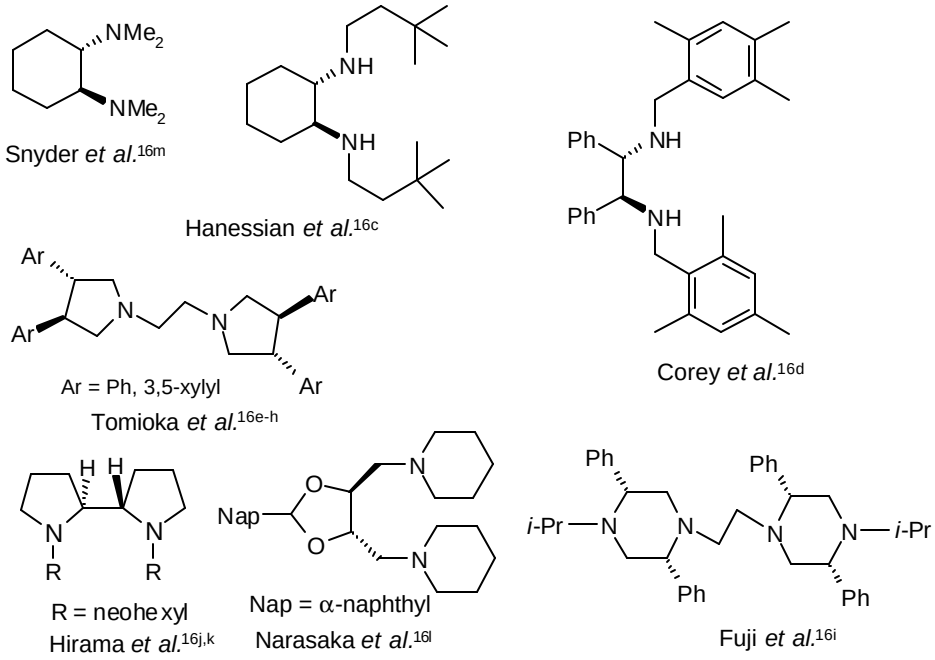


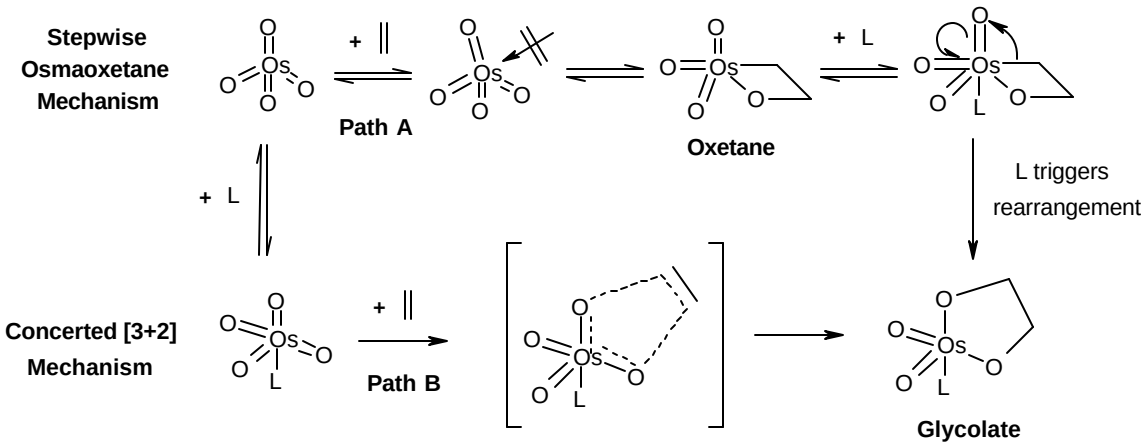
Figure 1. Some ligands for AD reaction.[13,16]

pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[14] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[13] A number of recent methods employ chiral monodentate[15] and bidentate diamine ligands[16] for the asymmetric osmylation of olefins. Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os (VI) glycolate products and as a consequence prevent *in situ* recycling of the Os and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand[16] (**Figure 1**).

2.1.2 Mechanism of Asymmetric Dihydroxylation

The popular mechanism for the osmylation had already been proposed by Boseken in 1922.[21a] Sharpless et al.[21b] and Jorgensen et al.[21c] suggested a stepwise reaction which is

initiated by a [2+2] like addition of the olefin across an Os=O bond (**Path A**) followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product. Boseken[21a] noticed the similarity between the osmylation and permanganate oxidation of alkenes, leading to diols, and suggested a direct transfer of the oxo groups of OsO_4 to the olefin (**Scheme 3, Path B**). This [3+2] mechanism was also adopted by Crigee[8] and has since been favored by most organic chemists, probably due to its similarity to well known organic cycloaddition reactions not involving metals.



Scheme 3. Schematic presentation of the stepwise osmaoxetane mechanism (Path A).[21b,c] and the concerted [3+2] mechanism[21a] (Path B)

Ligand acceleration in the stepwise osmaoxetane mechanism would be explained if coordination of the ligand to the oxetane triggered its rearrangement to glycolate.[22-26] The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature[27] is consistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps having different importance according to temperatures owing to their different activation parameters, ΔH and ΔS. Hence, this observation suggests that the stepwise [2+2]-like mechanism is operative. High level *ab initio* calculations have indeed shown that there are energetically accessible minima on the potential energy surface.[28]

2.1.3 Development of the Asymmetric Dihydroxylation

2.1.3.1 Process Optimization

An important measure for the value of any catalytic process is its turnover rate. Mechanistic investigations are invaluable for the optimization of a catalytic process with respect to both catalytic turnover and enantioselectivity. The asymmetric dihydroxylation is one of the examples where this interplay between mechanistic investigation and optimization has led to a very successful process. The first catalytic version of the asymmetric dihydroxylation was based on the Upjohn process, using *N*-morpholine-*N*-oxide (NMO) as the stoichiometric re-oxidant. It was found, however, by Marko and Sharpless[29] in 1987 that the enantioselectivities in the catalytic version were almost always inferior to those obtained under stoichiometric conditions. Mechanistic studies revealed that the culprit is a second catalytic dihydroxylation cycle.[18] (**Figure 2**), which proceeds with poor-to-no face selectivity, since it does not involve the chiral ligand.[30] This mechanistic insight enabled Wai and Sharpless[18] to develop an optimized version of the asymmetric Upjohn process based on slow addition of the olefin. Kwong[19] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (**Figure 3**).

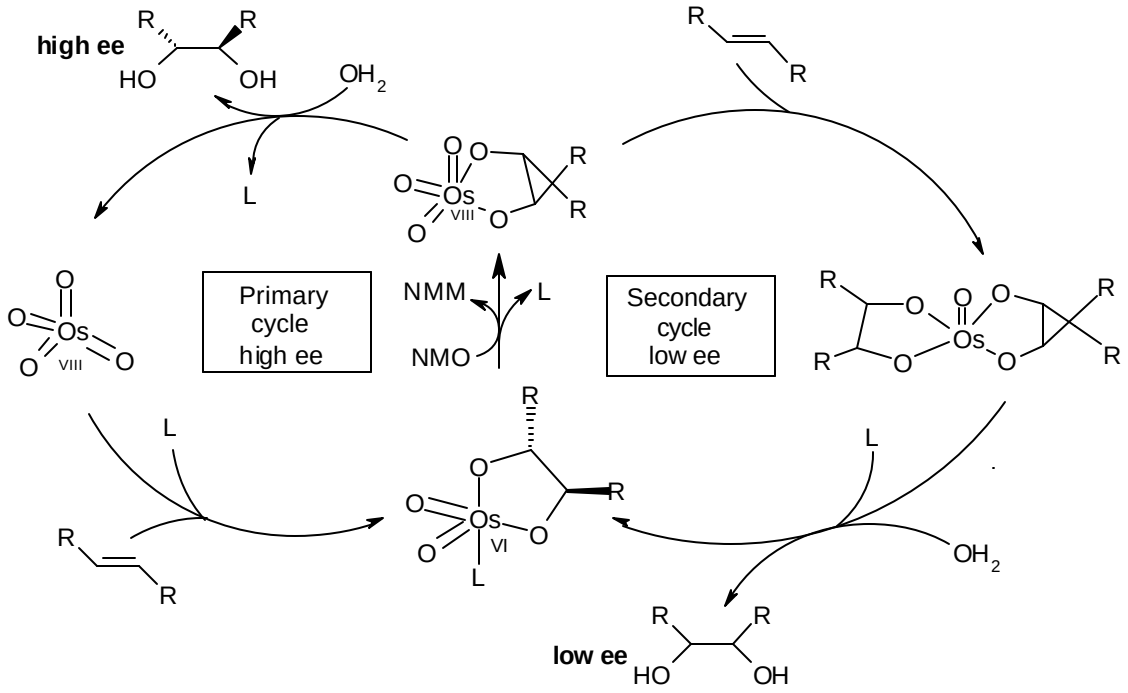


Figure 2. Two Catalytic Cycles for the AD Reaction using NMO as the Co-oxidant.[18]

Sharpless *et al*.[20] found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial influence on the selectivity.[21] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

The above explanation suggested how the catalytic variant of the dihydroxylation might be influenced by the events that take place after the olefin osmylation step. In actuality, for virtually all cases of catalytic dihydroxylation, hydrolysis of the osmium (VI) glycolate products is the turnover limiting step. This is especially true for sterically hindered olefins, and a key goal for improving these catalytic processes has been, and remains facilitation of glycolate hydrolysis.

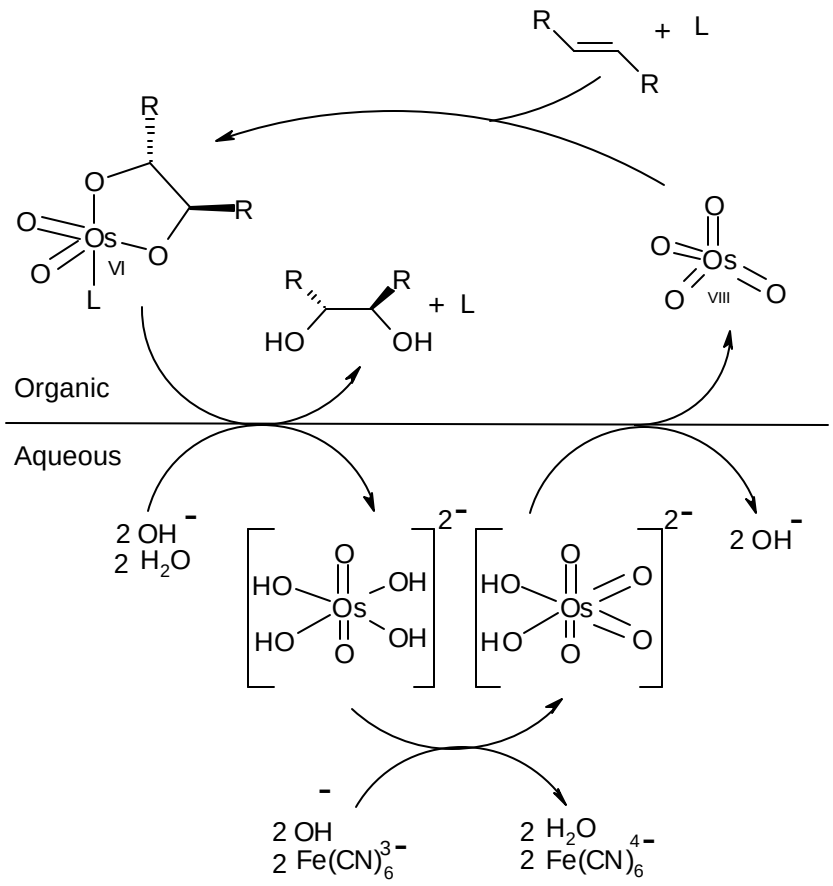


Figure 3. Catalytic Cycle of the AD Reaction with $K_3Fe(CN)_6$ as the Co-oxidant.[19]

2.1.3.2 Ligand Optimization

Since the initial discovery of the cinchona alkaloid system a large number of derivatives have been screened as chiral ligands for the asymmetric dihydroxylation. This systematic structure activity study has revealed that the cinchona molecule is ideally set-up for the asymmetric dihydroxylation, providing the basis both for high ligand acceleration and for high asymmetric induction. The most significant improvements in ligand performance were achieved by optimizing the O(9) substituent. In contrast, modifications to the cinchona core were rarely beneficial.

All of the most successful lingands have one structural feature in common-an aromatic group in the O(9) substituent. The beneficial effect of an aromatic group at O(9) can be

understood in terms of stacking interactions with the substituents of the substrate in the transition state of the selectivity determining step. The discovery of ligands with two independent cinchona alkaloid units by Hartung[20] (phthalazine core) and Crispino[31] (diphenylpyrimidine core) attached to a heterocylic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Figure 4**).

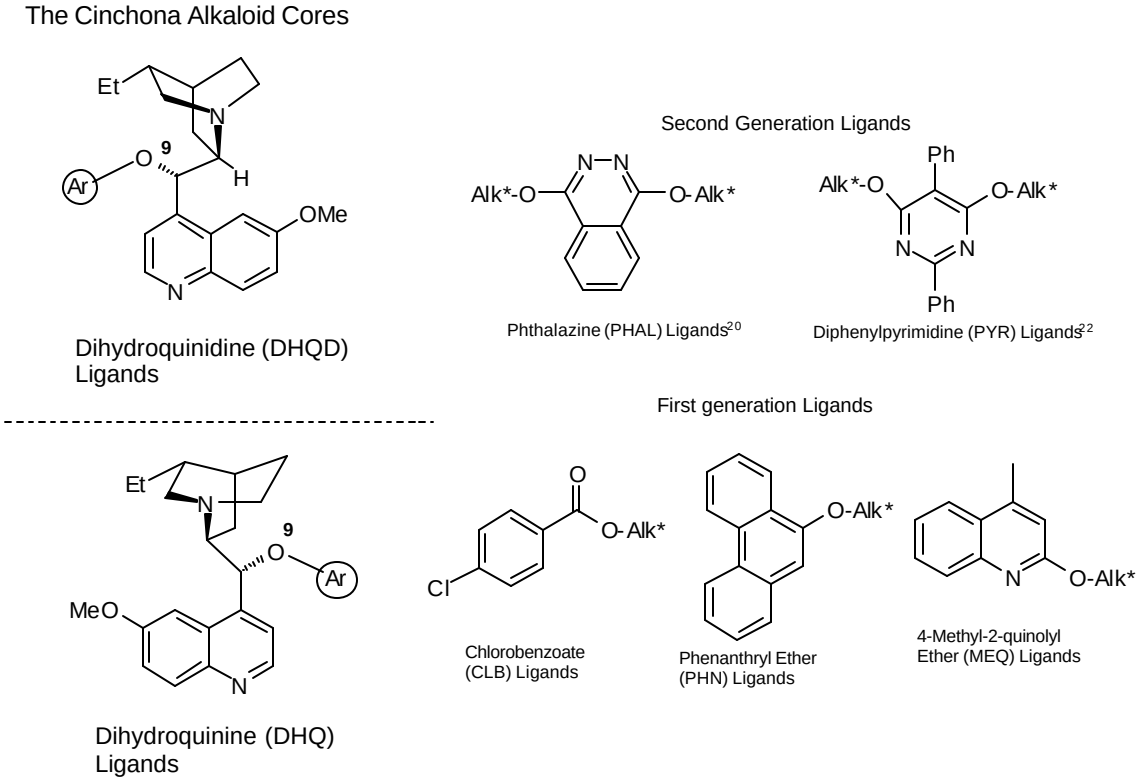
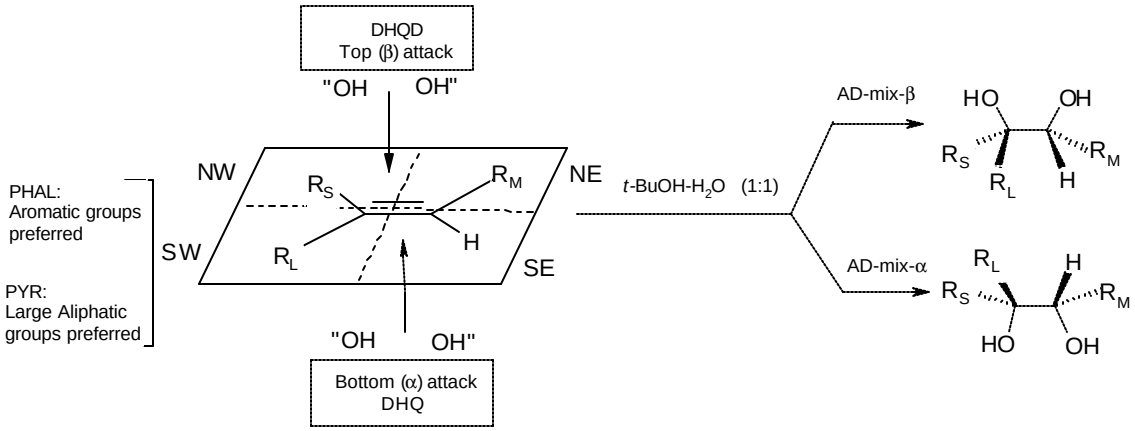


Figure 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 1a)

2.1.3.3 Emperical Rules for Predicting the Face Selectivity

Despite the mechanistic uncertainties, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (**Scheme 4**).[32] The plane of the olefin is divided into four quadrants and the substituents are placed into three quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant,

lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand-dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[32c] An olefin, which is placed into this plane according to the above constraints, receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives.



Scheme 4. The mnemonic device for predicting the face selectivity.

Predictions for 1,1-disubstituted olefins using the empirical mnemonic device are not always unambiguous,[33] since it may be difficult to judge which of the two substituents prefer the attractive, SW quadrant. Along with steric size, the properties of the substituents have also to be taken into account and compared with the ligand-specific preferences for the SW quadrant. PHAL ligands show the following preferences for the SW quadrant.[32c,33,34]

Aromatic groups >> *n*-alkyl > branched alkyl > oxygenated residues

Recent studies have revealed that oxygenated residues[33,35] have very small preferences for ligands binding pocket (SW quadrant). Studies with 1,1-disubstituted olefins have shown that pyrimidine (PYR) ligands have very different preferences for SW quadrant[32c,34] and the steric size of a substituent is much more important than in the PHAL system.

Thus, the following preference is observed:

Branched alkyl > long *n*-alkyl (length ≥3) > aromatic residues > short *n*-alkyl

A few exceptions mostly for terminal olefins have appeared in recent years. The AD of certain *ortho*-substituted allyl benzenes in the presence of PHAL ligands have been shown to give facial selectivities opposite to those predicted by the mnemonic device.[36] Furthermore, *trans*-olefins in the same series react with the expected face selectivity even with the PHAL ligands; thereby demonstrating that exceptions are so far limited to the class of terminal olefins. Thus, the mnemonic device is a simple tool for predicting the facial selectivity of the AD reaction. However, reliable predictions require the intrinsic preference of each ligand to be taken into account. Thus, the SW quadrant is especially attractive for aromatic groups in the PHAL systems, while aliphatic groups are preferred in the PYR systems. PYR ligands are, therefore the ligands of choice for aliphatic and/or sterically congested olefins, while PHAL ligands are better for aromatic substrates. These simple rules allow the prediction of the face selectivities even in difficult cases and very few exceptions are known.

2.1.3.4 Reaction Conditions

Catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH. The olefin concentration in the *t*-BuOH/water mixture is usually 0.1M.[20] While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aq. layer),[37] it is possible to buffer the system with 3 equivalents of $NaHCO_3$ (pH 10.3, aq. layer). Buffering of the reaction has a beneficial effect on the yield when base-sensitive substrates are used or base-sensitive products are formed. Normally the reaction is performed with 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant. The key reagents used are the Os reagent and the ligands. Only 0.2 to 0.4 mol% of Os reagent, either OsO_4 or the nonvolatile $K_2OsO_2(OH)_4$ is added. The ligand concentration is 1 mol%. However it can be dropped in some cases without much loss in enantioselectivity. For e.g. stilbene still gives 96% ee when 1/100 of 1 mol% of $(DHQD)_2$-PHAL is used as compared to the 99.8% ee obtained under normal conditions.[20] Alternatively, the amount of OsO_4 can be increased to 1 mol% for accelerating the reaction rate of relatively unreactive olefins. Additionally, the ligand can

be recovered especially when large-scale reactions are carried out. For the PHAL ligands, the combined organic layers are extracted with 3% aq. H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1 g of ligand), followed by a second extraction of the organic solution with saturated K_2SO_4 (ca. 40 mL/1 g of ligand). The ligand enters the aqueous phase as the hydrogen sulfate salt and the solution can be reused directly for the subsequent AD reactions without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base. Additionally, the amount of water should be decreased by the volume of aqueous ligand solution added to the reaction mixture.

Since most substrates require very similar reaction condition, it is possible to use premix of all reactants. These are available commercially as 'AD-mixes' such as AD-mix-β [$(DHQD)_2PHAL$] and AD-mix-α [$(DHQ)_2PHAL$]. 1 kg of AD-mix contains $K_3Fe(CN)_6$ (699.6 g), K_2CO_3 (293.9 g), ligand (5.52 g) and $K_2OsO_2(OH)_4$ (1.04 g). The standard AD procedure calls for 1.4 g of this AD-mix per mmol of olefin. One equivalent of $MeSO_2NH_2$ should be added for all substrates other than terminal olefins to enhance hydrolysis of the osmate (VI) ester and hence the rate of catalytic turnover.

2.1.4 The Cinchona Alkaloid Ligands and their Substrate Preferences

Phthalazine (PHAL) ligands

The phthalazine ligands are most widely used, due to their ready availability and their broad substrate scope.[32b] This ligand class is used in the AD-mix formulation. PHAL ligands react especially well when aromatic groups are present, and remarkably high enantioselectivities are observed when the aromatic substituents appear in certain optimal locations/patterns.[32a] One such case is *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[38] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Recent developments have provided ligands with even broader scope than that of the PHAL derivatives.

Anthraquinone (AQN) ligands

The anthraquinone ligands are especially well suited for almost all olefins having aliphatic substituents.[39] Even diols derived from allyl halides or allyl alcohols can now be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[31]

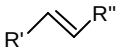
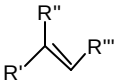
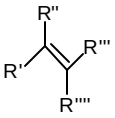
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PYR ligands.[40] Even *cis*-1,2-disubstituted olefins give improved face selectivities with these ligands. The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[41] However, in certain cases better results are obtained with the new second generation ligands.[39,40,42]

Table 1. Recommended ligands for each olefin class.

Olefin Class						
Preferred Ligand	R = Aromatic DPP, PHAL R = Aliphatic AQN R= Branched PYR	R′, R″ = Aromatic DPP, PHAL R′, R″ = Aliphatic AQN R′, R″ = Branched PYR	Acyclic IND Cyclic PYR, DPP, AQN	R′, R″ = Aromatic DPP, PHAL R′, R″ = Aliphatic AQN	PHAL, DPP, AQN	PYR, PHAL

2.1.5 Recent Applications of Sharpless Asymmetric Dihydroxylation (AD) Reaction in Organic Synthesis

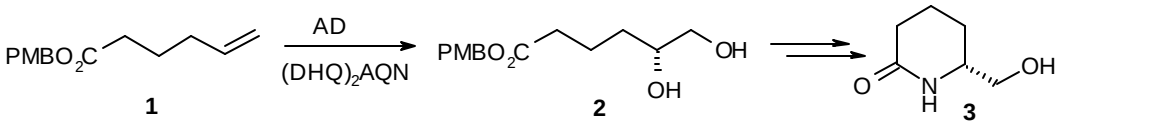
The Sharpless asymmetric dihydroxylation is ideally suited for the preparation of chiral building blocks for asymmetric synthesis, due to its wide scope and normally excellent enantioselectivity. A large number of chiral synthons have been prepared *via* the AD reaction in recent years. Polyols play an important role not only in biological systems, they have also found frequent use as starting materials for the enantiospecific synthesis of natural products.[43] However, the AD reaction offers some important advantages over the use of sugars as chiral building blocks in enantioselective synthesis.

1. AD, catalytic in both OsO_4 and the chiral ligand, provides either enantiomer of the product.
2. AD is not limited to a certain number of standard starting materials (e.g. carbohydrates, tartrates, etc.), since virtually any olefin can be regarded as a substrate. Thus, the synthetic strategy is left almost entirely to the imagination of the chemist and not restricted by the availability of certain starting materials.

3. Third, most enantiospecific syntheses from the chiral pool require an elaborate protecting group strategy. However with AD, the diol can be carried through the synthesis "masked" as an olefin, ready to be released at any point.

In most instances, diols are not the final products and their synthetic elaboration requires some further transformations. Commonly, these involve the selective manipulation of one of the two OH groups either by protecting it or by converting it into a leaving group, suitable for displacement by a nucleophile. Over the last decade, several applications of AD reaction in the syntheses of bioactive molecules and natural products have been documented in the literature. While most synthetic applications of AD are covered in the review article by Sharpless *et al*.,[5a] a few recent applications are documented below.

1. A practical asymmetric synthesis of 6-(hydroxymethyl)piperidine-2-one **3**[43] is achieved employing the AD reaction to alkenyl ester **1** (**Scheme 5**),

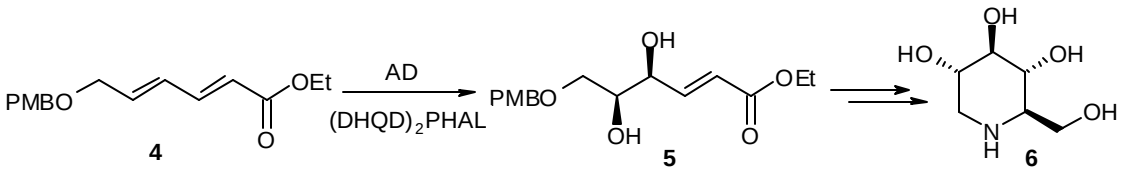


1 **2** **3**

6-(Hydroxymethyl)piperidine-2-one

Scheme 5

2. An asymmetric synthesis of (+)-1-deoxynojirimycin **6**[44] is achieved through the regioselective AD reaction of the diene **4** (**Scheme 6**).

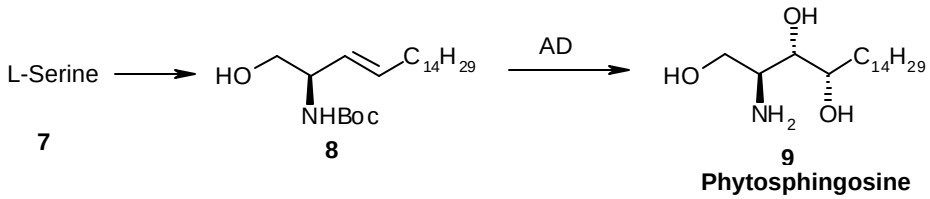


4 **5** **6**

(+)-1-Deoxynojirimycin

Scheme 6

3. A short synthesis of phytosphingosine **9**[45] was achieved by employing AD of the optically active olefin **8** derived from L-serine **7** (**Scheme 7**).

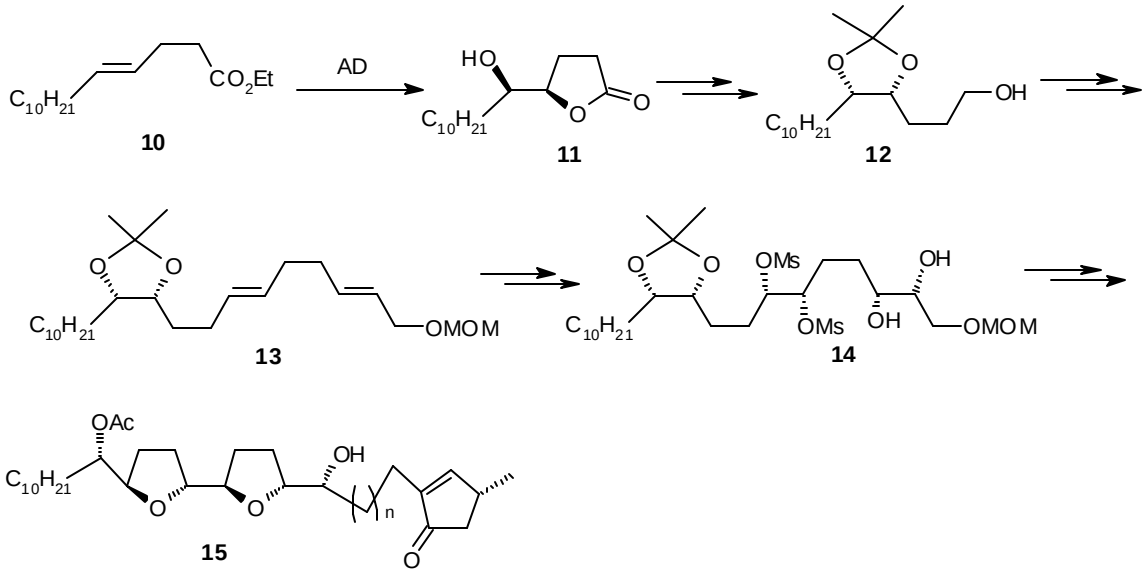


7 **8** **9**

Phytosphingosine

Scheme 7

4. The first total synthesis of naturally occurring (+)-uvaricin **15**[46] is achieved using three consecutive AD reactions to place the necessary oxygen functions on a naked carbon skeleton in a regio- and enantiocontrolled manner (**Scheme 8**).

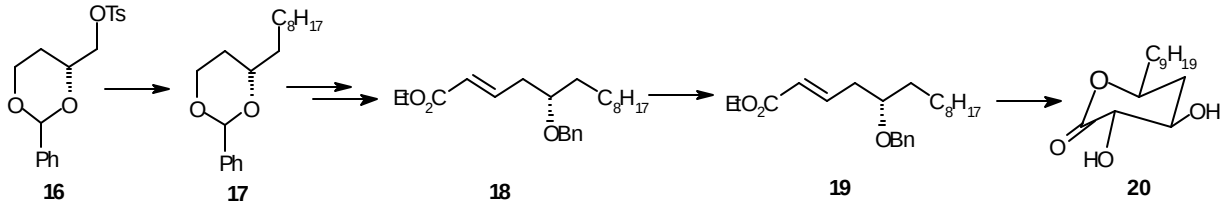


10 **11** **12** **13** **14** **15**

n = 11, (+)-Uvaricin

Scheme 8

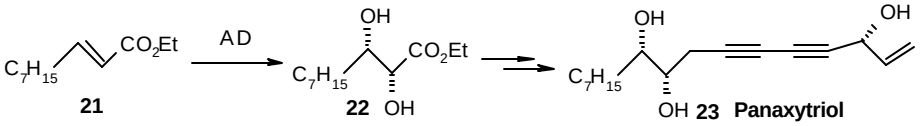
5. The first synthesis of (2*S*,3*R*,5*S*)-(–)-2,3-dihydroxytetradecan-5-olide **20**,[47] a new biologically active δ-lactone produced by *Seiridium unicorne* is accomplished using (*R*)-malic acid and employing the AD reaction (**Scheme 9**).



16 **17** **18** **19** **20**

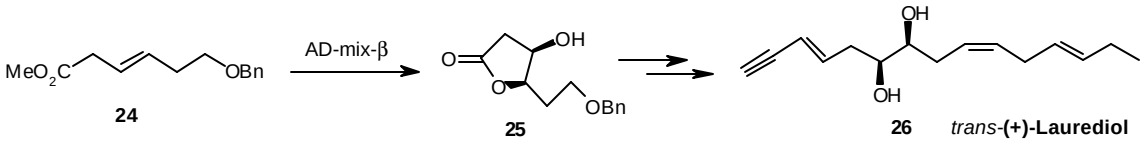
Scheme 9

6. AD is successfully employed in the synthesis of antitumor agent panaxytriol **23** and its diastereomers[48] from olefin **21** (**Scheme 10**).



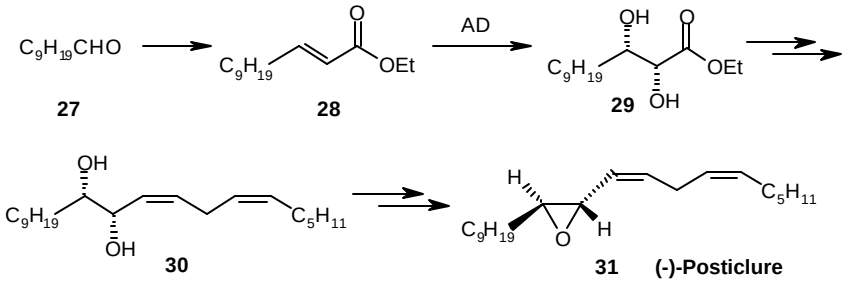
Scheme 10

7. An efficient synthesis of trans-(+)-laurediol **26**[49] has been achieved by AD reaction of olefin **24** to give the intermediate β-hydroxy-γ-lactone **25** which is then extrapolated to **26** (**Scheme 11**).



Scheme 11

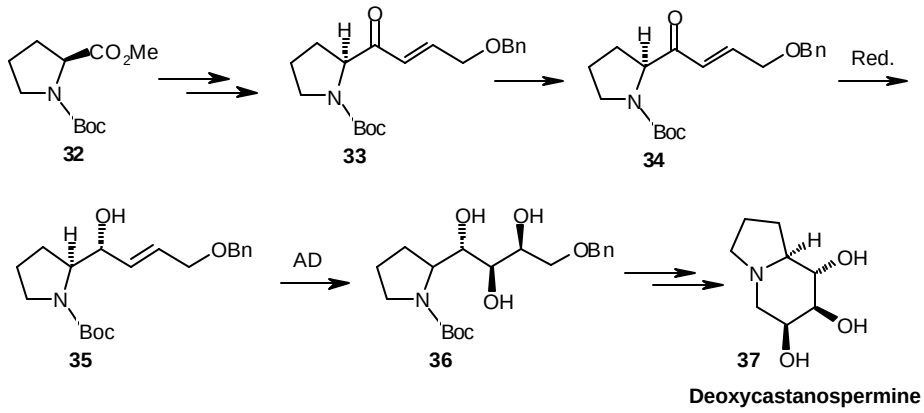
8. A highly enantioselective synthesis of (+)- and (-)-posticlure **31**[50] has been achieved by AD reaction of olefin **28** to give the intermediate diol **29**, which was then converted into the diene **30**. The diene **30** was then easily transformed into the desired compound **31** (**Scheme 12)**.



Scheme 12

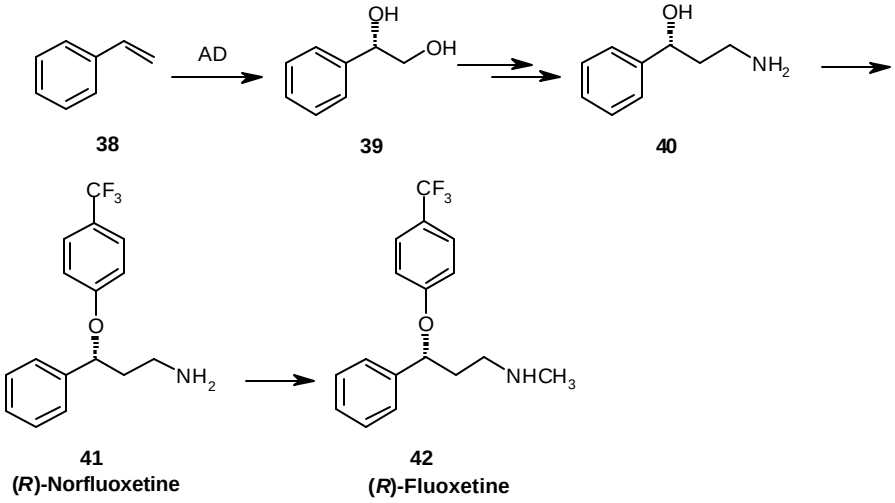
9. An efficient enantioselective synthesis of deoxycastanospermine derivative **37**[51] has been achieved by AD reaction of olefin **35** obtained from *N*-Boc-protected L-proline **32**.

The diol **36** thus obtained by AD reaction was transformed into the title compound **37** (**Scheme 13**).



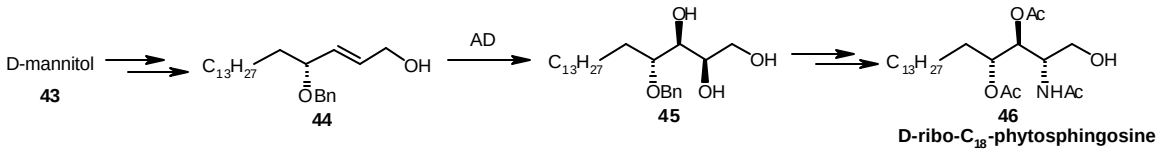
Scheme 13

10. An efficient synthesis of (R)-norfluoxetine **41** and (R)-fluoxetine **42**[52] was achieved by AD reaction of styrene **38** (**Scheme 14**).



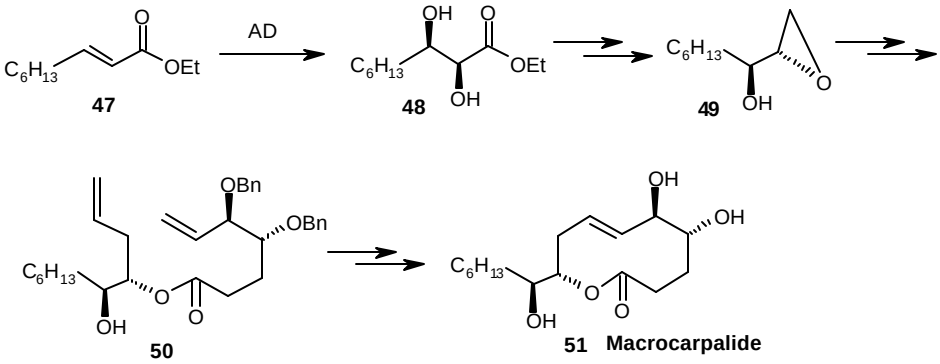
Scheme 14

11. An enantioselective synthesis of D-ribo-C_{18}-phytosphingosine as its tetraacetate derivative **46**[53] was achieved by AD reaction of allylic alcohol **44**. The allylic alcohol **44** obtained from D-mannitol **43** was converted into its diol derivative **45** which subsequently was transformed into the title compound **46** (**Scheme 15**).



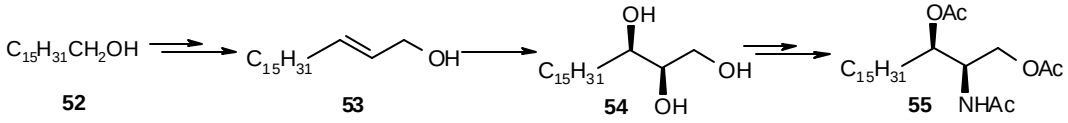
Scheme 15

12. A total synthesis of natural product macrocarpalide **51**[54] has been achieved employing AD reaction and ring closing metathesis as the key step. The diol **48** obtained by AD reaction of olefin **47** was converted into the diene ester **50**. The diene **50** then underwent ring closing metathesis to afford the desired macrocarpalide **51** (**Scheme 16**).



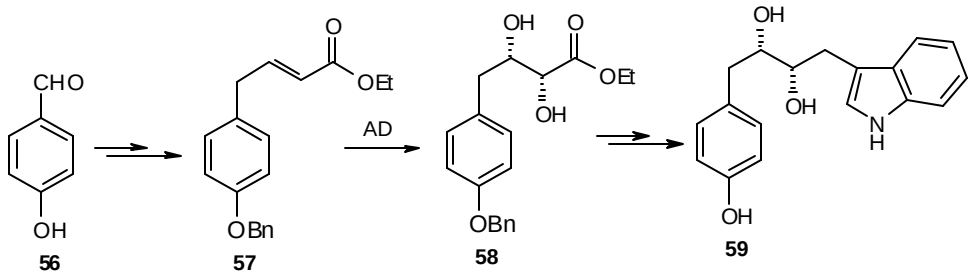
Scheme 16

13. A stereoselective synthesis of D-(+)-*erythro*-dihydrosphingosine as its triacetate derivative **55**[55] has been achieved employing AD reaction as the key step starting from palmityl alcohol **52** (**Scheme 17**).



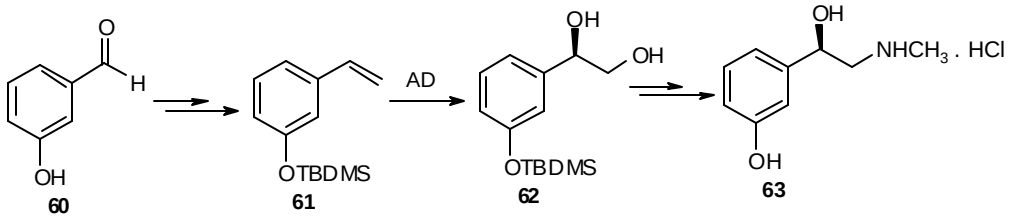
Scheme 17

14. A highly enantioselective synthesis of (+)-diolmycin A2 **59**[56] has been achieved employing AD reaction and CH_3NO_2 solvent assisted regioselective C-3 coupling of indole as the key step starting from 4-hydroxy benzaldehyde **56** (**Scheme 18**).



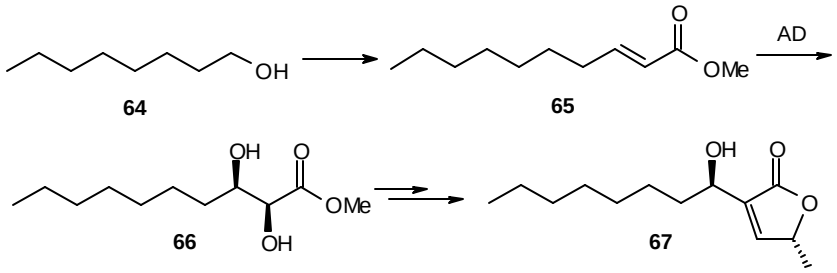
Scheme 18

15. An efficient method for the synthesis of enantiomerically pure (*R*)-phenylephrine hydrochloride **63**[57] has been achieved employing AD reaction as the key step (**Scheme 19**).



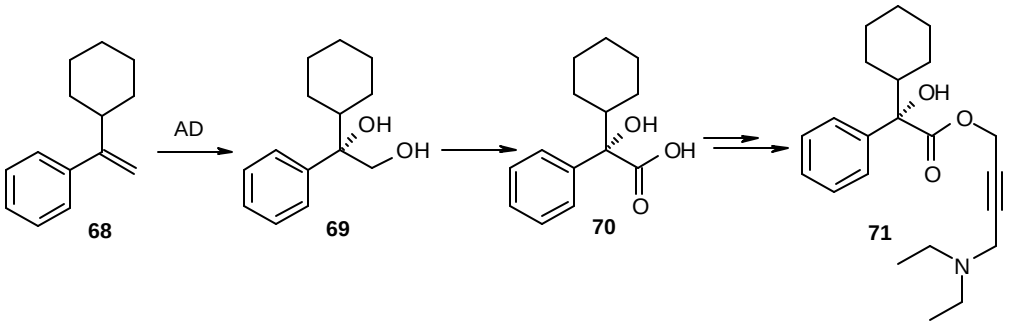
Scheme 19

16. An asymmetric synthesis of (-)-acaterin **67**,[58] an inhibitor of acyl-CoA cholesterol acyl transferase has been achieved employing AD reaction as the key step starting from commercially available octan-1ol **64** (**Scheme 20**).



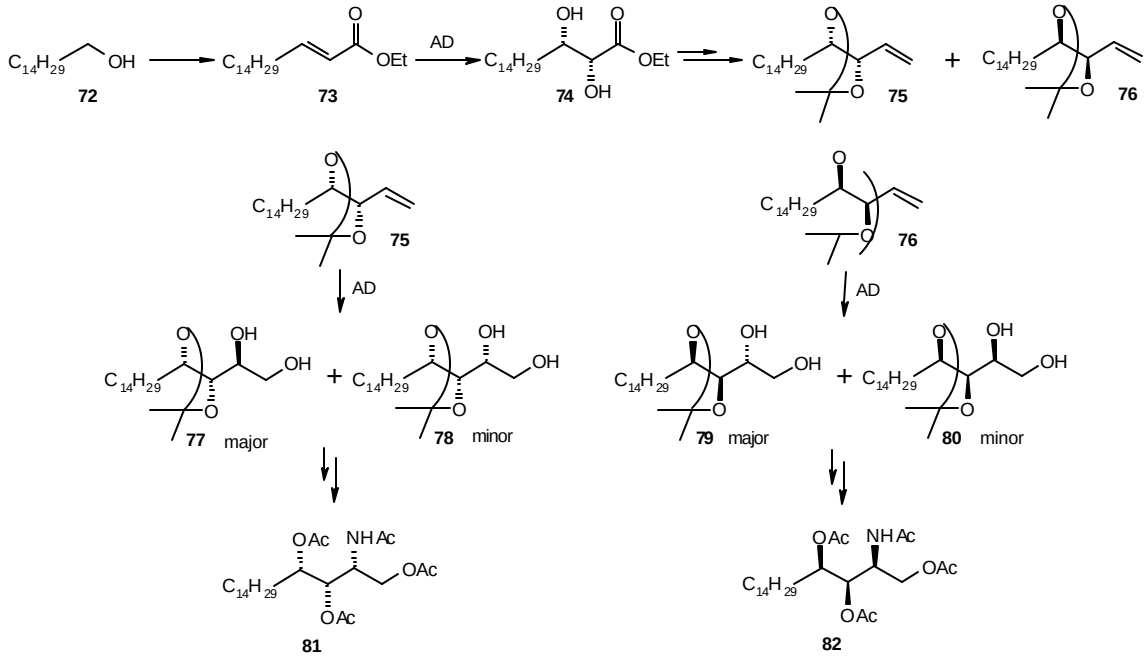
Scheme 20

17. An asymmetric synthesis of (*S*)-oxybutynin **71**[59] has been achieved employing AD reaction of α-cyclohexylstyrene **68** as the key step (**Scheme 21**).



Scheme 21

18. An asymmetric synthesis of L-xylo-(2*R*,3*S*,4*S*)-C_{18}- and D-xylo-(2*S*,3*R*,4*R*)-C_{18}-phytosphingosines as their tetraacetate derivatives **81** & **82**[60] in diastereomerically pure form has been achieved employing AD reaction as the key step and using the concept of double stereodifferentiation in Sharpless asymmetric dihydroxylation (**Scheme 22**).



Scheme 22

2.1.6 Conclusion

Thus, Sharpless asymmetric dihydroxylation has become a powerful tool for catalytic oxidation reaction. With the optimization of ligands and the amount of primary oxidant, the catalytic oxidation reaction leading to chiral diols has proved very promising in terms of both yields and enantioselectivities. It has contributed to rapid advances in synthetic organic chemistry giving access to new molecules needed to investigate hitherto unexplained and undiscovered phenomena in the molecular world.

2.2. CYCLIC SULFITES/SULFATES AS SYNTHETIC INTERMEDIATES

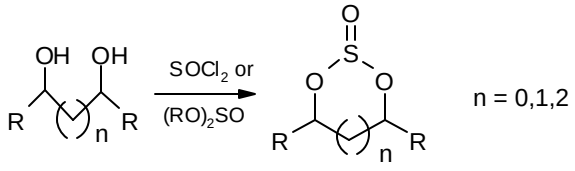
2.2.1. Introduction

Cyclic sulfate esters have been known since 1932.[61] However, the lack of an efficient method for their preparation limited their applications in the repertoire of main line of organic synthesis. But the improved process of converting the diol into cyclic sulfite with thionyl chloride, followed by oxidation of cyclic sulfite with $NaIO_4$ catalyzed by RuO_4[62] (generated *in situ*, using $RuCl_3.3H_2O$) represents an important development that broadened the use of cyclic sulfates as important synthetic intermediates. The advent of AD reaction provided a route to chiral 1,2-diols from a wide spectrum of olefins, which can further be elaborated to cyclic sulfates.[63] Cyclic sulfites/sulfates have the following important features.

1] They have high reactivity toward various nucleophiles and are more reactive than epoxides.
2] They can activate nucleophilic attack at one position while serving as a protecting group at a second position; under vigorous conditions they can serve as an activator for two sequential reactions. 3] Reactions of five-membered cyclic sulfates with nucleophiles provide two contiguous stereocentres; moreover, a remote stereocenter can be controlled by cyclic sulfates of 1,3- and 1,4-diols. 4] The intermediate of substitution is generally a salt of monosulfate ester, probably enabling separation of the product from the non-salt by-product.

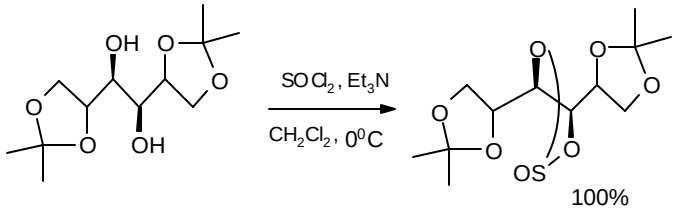
2.2.2. Preparation of Cyclic Sulfites/Sulfates

While several methods for preparation of cyclic sulfite are known, the most efficient synthesis involves the reaction of diol with thionyl chloride[64] or transesterification of a dialkyl sulfite with a diol[65] (**Scheme 23**).



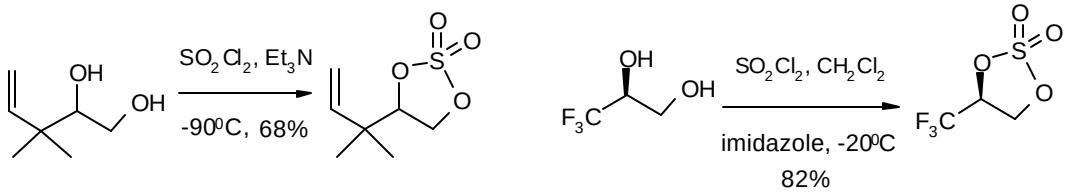
Scheme 23

In most reactions, expelling of hydrogen chloride by either refluxing[66] or using a stream of nitrogen improves the yield. In case of substrates with an acid-labile functionality, a base such as Et_3N, imidazole or pyridine is used to scavenge the hydrogen chloride generated during the reaction[67] (**Scheme 24**).



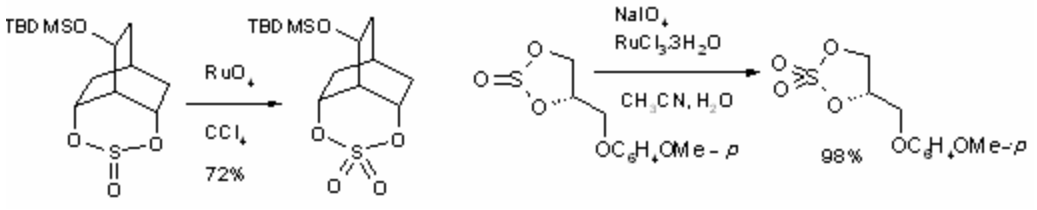
Scheme 24

Cyclic sulfate can be prepared directly by reaction of diol with sulfuryl chloride (SO_2Cl_2), but this gives only moderate yields due to the chlorinating nature of SO_2Cl_2[68] (**Scheme 25**).



Scheme 25

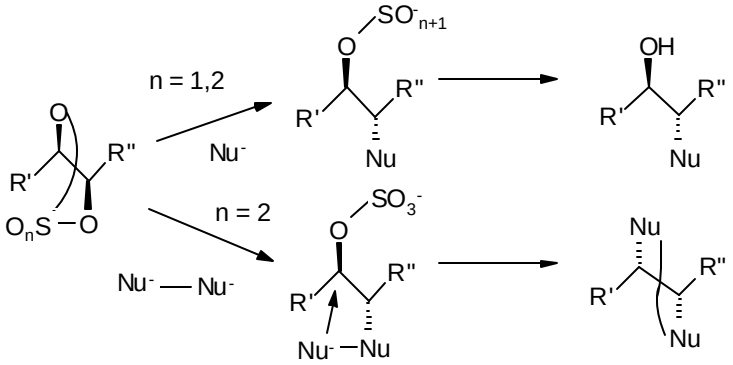
Oxidation of cyclic sulfites to sulfates is another alternative. Use of stoichiometric amount of RuO_4 gave cyclic sulfates in satisfactory yield.[69] However, this procedure is limited to small-scale preparations due to the expensive RuO_4. The discovery that a catalytic amount of RuO_4 is generated *in situ* by the reaction of $RuCl_3$ or RuO_2 with $NaIO_4$ made available an expedited route for the oxidation of cyclic sulfites to sulfates[62] (**Scheme 26**).



Scheme 26

2.2.3. Reactions of Cyclic Sulfites/Sulfates

Analogous to epoxides, cyclic sulfites/sulfates can be opened by attack of a nucleophile at either carbon center giving a sulfite/sulfate monoester. These monoesters allow some interesting transformations, which make the chemistry of cyclic sulfites/sulfates more versatile than of epoxides. Hydrolysis of the monoesters leads to hydroxy compounds that parallel those obtained from oxiranes.[62] However, the sulfate monoester can function as a leaving group, leading to disubstitution products[62] (**Scheme 27**).

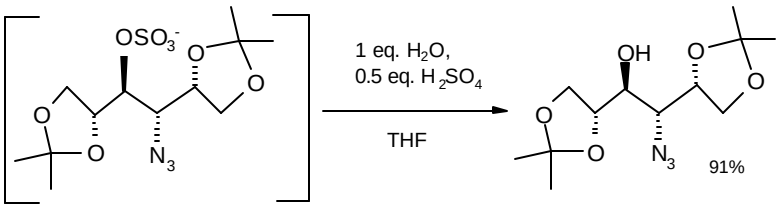


Scheme 27

Cyclic sulfites and especially sulfates react with a variety of nucleophiles and a few examples are Cl^- (LiCl),[64] Br^- (NH_4Br),[64] F^- ($Et_4NF.2H_2O$, *n*-Bu_4NF),[70,71] N_3^- (LiN_3, NaN_3),[62,69,71,72,73,74] RNH_2,[72,75] $PhCO_2^-$ ($PhCO_2NH_4$),[62,69,71] ROH,[76] NO_3^- (*n*-Bu_4NNO_3),[62] SCN^- (NH_4SCN),[62,70] PhS^- (PhSNa),[77] AcS^-,[78] H^- ($NaBH_4$, $NaBH_3CN$),[62] $PhCH_2^-$

($PhCH_2MgBr$, Li_2CuCl_4),[62] $RC{\equiv}C^-$, ($RC{\equiv}CSiMe_3$ + MeLi),[79] $(RS)_2CH^-$ (with 1,4-cyclic sulfates).[80]

The hydrolysis of sulfate monoesters is carried out with an equal volume of 20% aq. H_2SO_4 and ether.[6] However, a chemoselective hydrolysis of sulfate ester in presence of acid-labile groups (acetonide and silyloxy) is carried out with a catalytic amount of H_2SO_4 and 0.5-1.0 equivalents of H_2O in THF[73] (**Scheme 28**). The use of a minimum of water is crucial to achieve the desired chemoselectivity.[73]

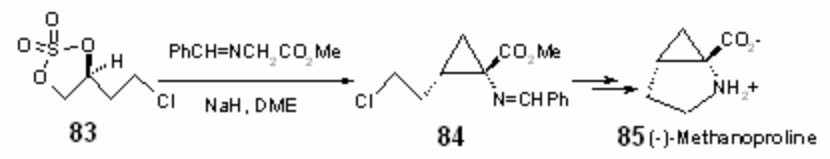


Scheme 28

2.2.4. Recent Applications of Cyclic Sulfites/Sulfates

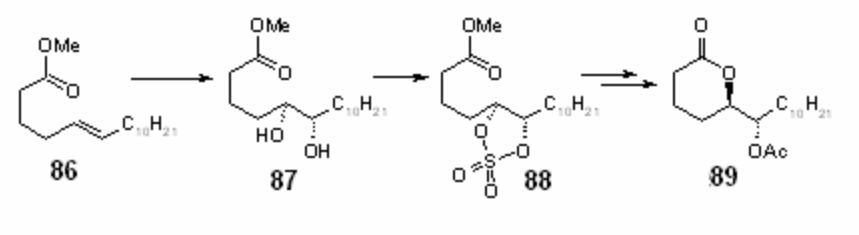
Several applications of cyclic sulfites/sulfates have been documented in the literature in the recent years. A few of them are described below.

1. The first asymmetric synthesis of (2*S*,3*R*)-(–)-methanoproline **85**[81] was achieved by condensation of cyclic sulfate **83** with methylbenzylidene glycinate (**Scheme 29**).



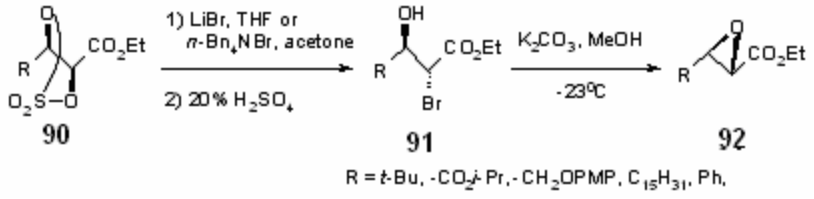
Scheme 29

2. Intramolecular S_N^2 ring opening of a cyclic sulfate **88** has been employed in the synthesis of *erythro*-(–)-6-acetoxy-5-hexadecanolide **89**,[82] a major component of mosquito oviposition attractant pheromone (**Scheme 30**).



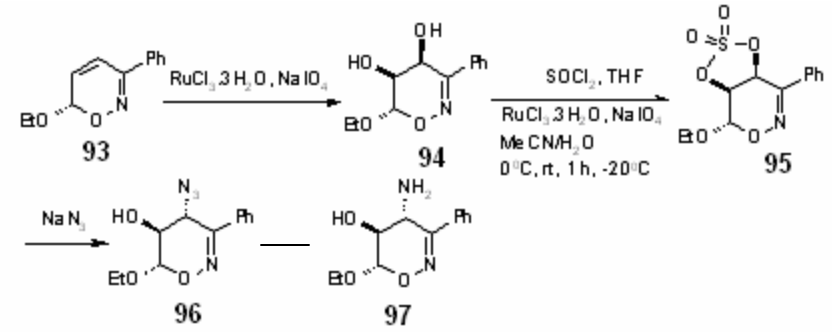
Scheme 30

3. α,β-Epoxyesters **92**[83] have been synthesized from cyclic sulfate **90** with the intermediate formation of 2-bromo-3-hydroxyesters **91** (**Scheme 31**).



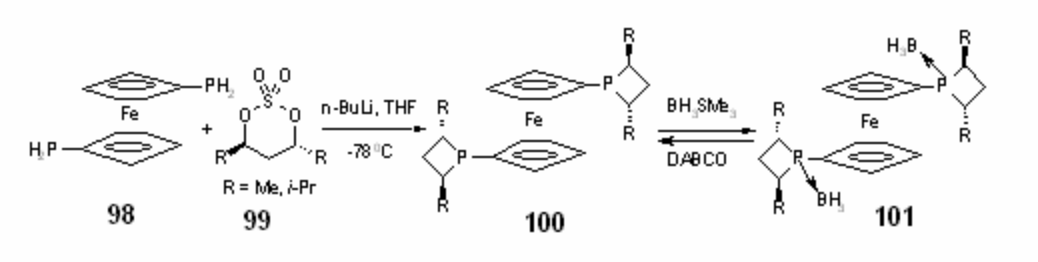
Scheme 31

4. 4-Amino-5-hydroxy substituted 1,2-oxazines **97**[84] are synthesized readily from 6*H*-1,2-oxazines **93** by *cis*-dihydroxylation and regioselective opening of cyclic sulfate **95** with azide (**Scheme 32**).



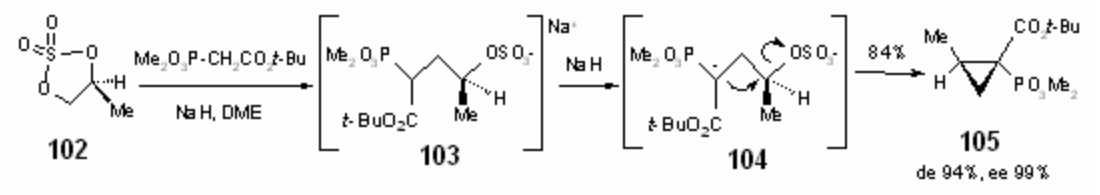
Scheme 32

5. The C_2-symmetric, chiral 1,1′-bis (phosphetano)ferrocenes **100**, **101**[85] have been prepared from the 1,3-diol cyclic sulfates **99** (**Scheme 33**). These have been tested in the rhodium-catalyzed hydrogenation of unsaturated substrates.



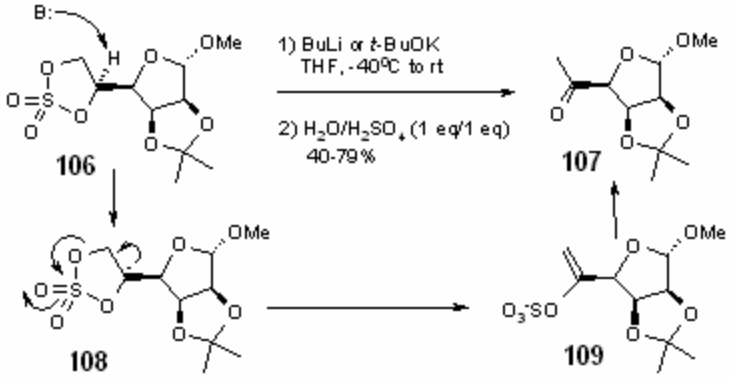
Scheme 33

6. (–)-(1*R*,2*R*)-1-Amino-2-methylcyclopropanephosphonic acid **105**[86] has been synthesized from (+)-(*S*)-1,2-propanediol cyclic sulfate **102** and dimethyl *t*-butoxycarbonyl methyl phosphonate (**Scheme 34**).



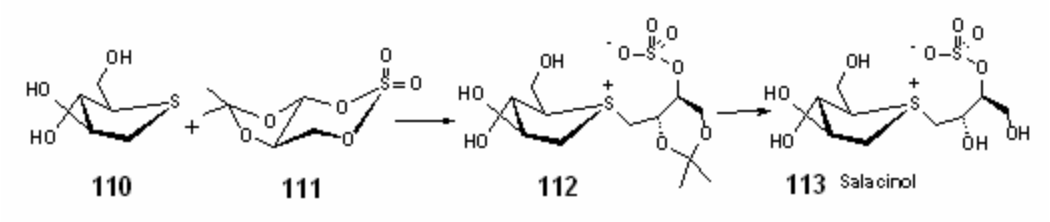
Scheme 34

7. Treatment of 5,6-cyclic sulfates **106** derived from glycofuranoses with strong bases resulted in 6-deoxy-hexofurano-5-ulose **109** derivatives[87] (**Scheme 35**).



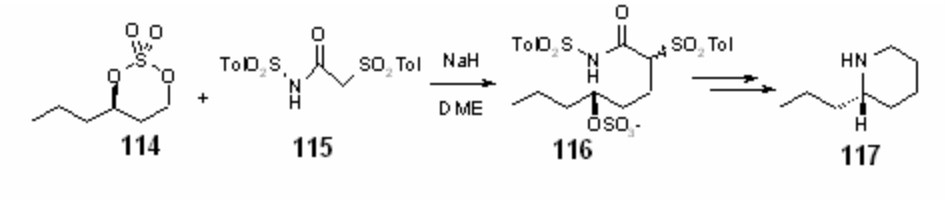
Scheme 35

8. Salacinol **113**[88] has been synthesized by using the cyclic sulfate of 1,3-*O*-isopropylidene-D-erythritol **111** and 1,4-epithio-D-arabinitol **110** (**Scheme 36**).



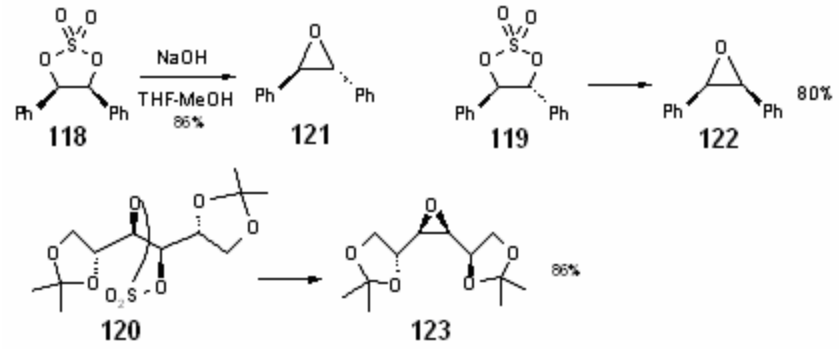
Scheme 36

9. Cyclic sulfate **114** undergoes double alkylation with stabilized C,N-dianions of **115** to provide the piperidine ring of (*S*)-coniine **117**[89] (**Scheme 37**).



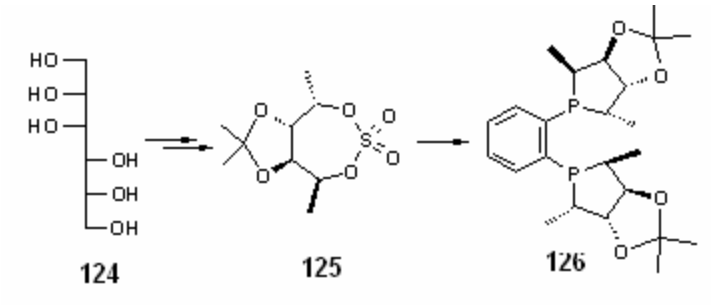
Scheme 37

10. Reaction of cyclic sulfates of *vic*-diols (**118**-**120**) with NaOH in THF-MeOH produced the corresponding epoxides (**121**-**123**) respectively in excellent yields[90] (**Scheme 38**).



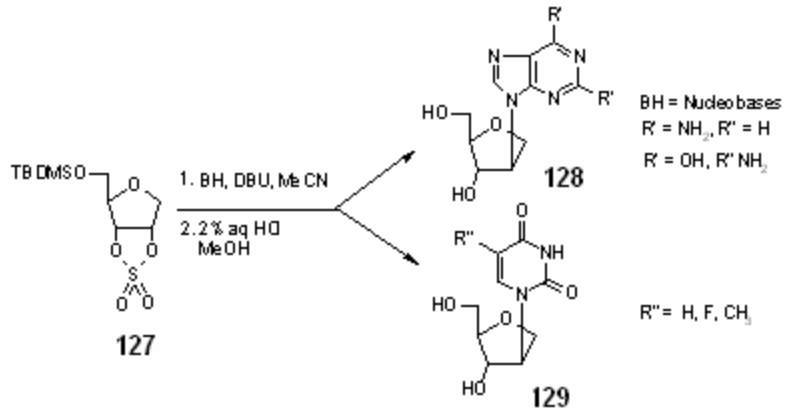
Scheme 38

11. Cyclic sulfate **125** derived from D-mannitol **124** has been employed in the synthesis of diphosphine ligands **126**[91] (**Scheme 39**).



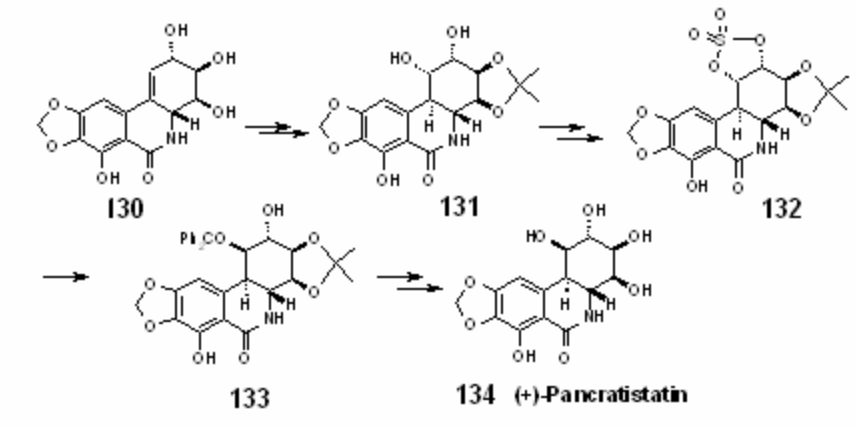
Scheme 39

12. Direct coupling of purine and pyrimidine bases with the cyclic sulfate **127** derived from carbohydrate intermediate gave access to isonucleosides (**128** and **129**)[92] as potential antiviral agents (**Scheme 40**).



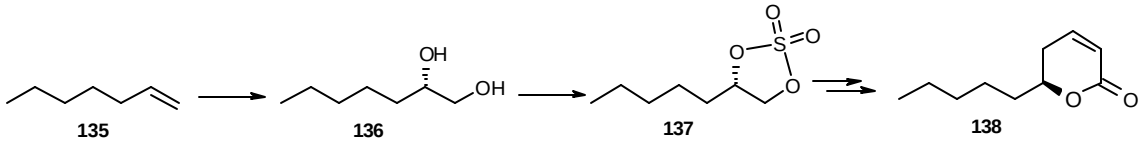
Scheme 40

13. Synthesis of (+)-pancratistatin **134**[93] has been achieved from (+)-narciclasine **130** by employing the cyclic sulfate intermediate **132** (**Scheme 41**).



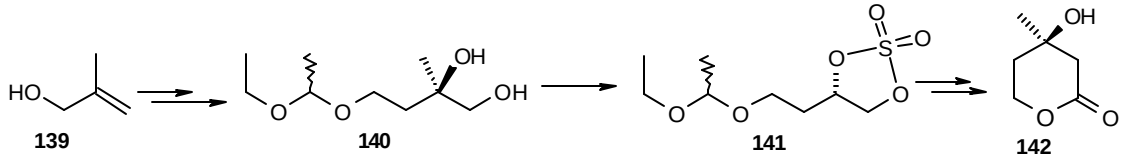
Scheme 41

14. An asymmetric synthesis of (*S*)-(+)-massoialactone **138**[94] has been achieved by employing the cyclic sulfate intermediate **137** (**Scheme 42**).



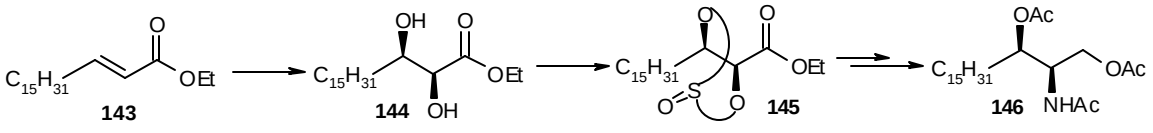
Scheme 42

15. An asymmetric synthesis of (*R*)-(-)-mevalonolactone **142**[95] has been achieved by employing the cyclic sulfate intermediate **141** (**Scheme 43**).



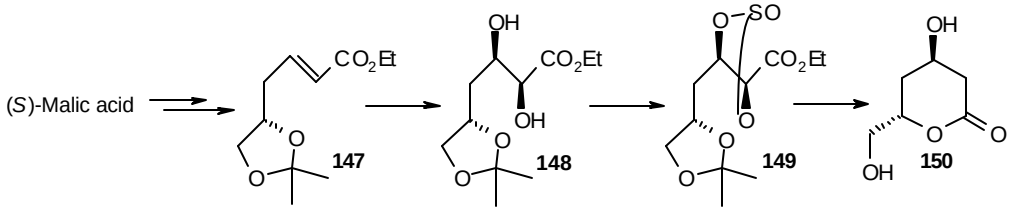
Scheme 43

16. A highly stereocontrolled synthesis of D-(+)-*erythro*-dihydrosphingosine triacetate **146**[96] has been achieved by employing the cyclic sulfite intermediate **145** (**Scheme 44**).



Scheme 44

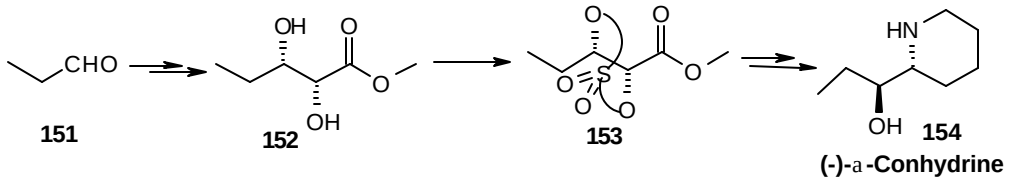
17. A concise enantioselective synthesis of (+)-compactin lactone **150**[97] has been achieved by employing the cyclic sulfite intermediate **149** (**Scheme 45**).



Scheme 45

18. Synthesis of (-)-α-conhydrine **154**[98] has been achieved from propionaldehyde **151** *via* cyclic sulfate intermediate **153** (**Scheme 46**).

.



Scheme 46

2.2.5 Conclusion

Thus, given the vast chemistry associated with synthetic applications of epoxides, exploration of the chemistry of 1,2-cyclic sulfites/sulfates their hitherto neglected cousins in organic synthesis is proving fruitful today. The initial realization that these intermediates are epoxide- like, but generally much more reactive has given synthetic chemists many ideas as to where they might be useful.

2.3. EPOXIDES AS SYNTHETIC INTERMEDIATES

2.3.1. Introduction

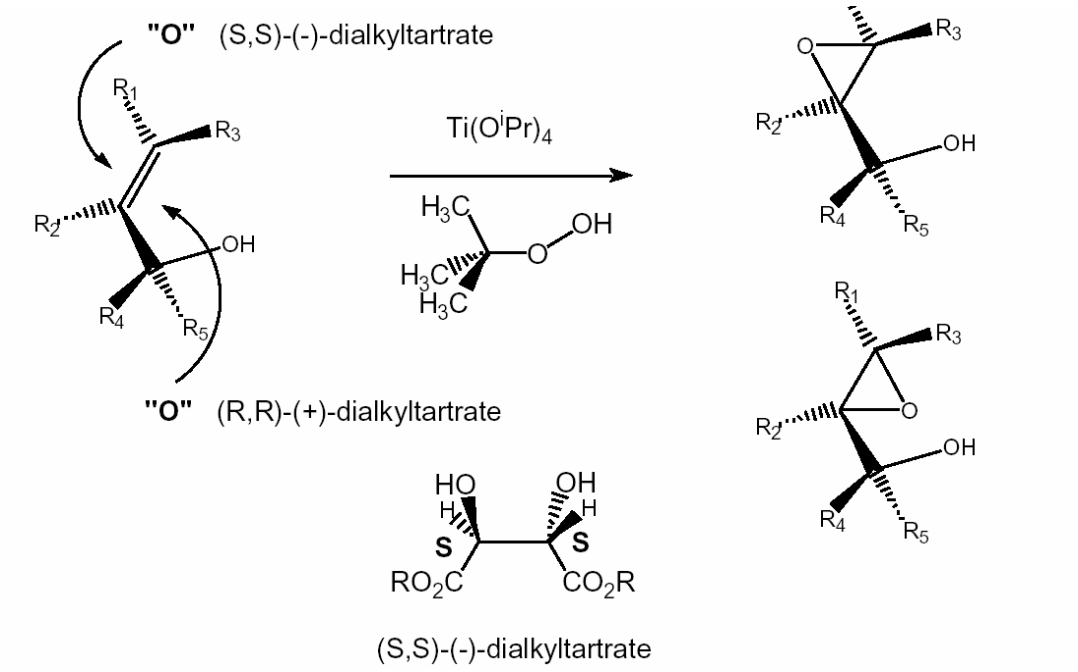
Since the beginning of his independent academic career in 1970, Prof. K. Barry Sharpless has made numerous contributions to the field of synthetic organic chemistry. However, he is rightly famous for his discovery of several asymmetric catalytic oxidation reactions of substituted alkenes. The first of these reactions, developed in the early 80s, employs an optically active titanium alkoxide/tartrate ester catalyst to facilitate the enantioselective epoxidation of prochiral allylic alcohols with *tert*-butylhydroperoxide (TBHP) as the oxidant[99]. The reaction gives high yields and enantiomeric excesses, and its stereochemical outcome is predictable based on simple empirical rules. The one remaining constraint, namely the alcohol functionality necessary for binding the substrate to the catalyst, was eliminated in the next reaction; ''asymmetric dihydroxylation'' which transforms a wide variety of olefins into optically active 1,2-diols which is already discussed earlier in this chapter.

In 1980, Sharpless and Katsuki discovered a system for the asymmetric epoxidation of primary allylic alcohols that utilizes Ti(OPr-*i*)$_4$, a dialkyl tartrate as a chiral ligand, and *tert*-butyl hydroperoxide as the oxidant.[100] Notably, this reaction exhibits high levels of enantioselectivity (usually ee > 90%). Like other metal catalyzed epoxidations, this reaction also proceeds under mild conditions with good chemical yield and with high regio- and chemoselectivity.

2.3.1.1 Asymmetric Epoxidation With The Titanium (IV)-Tartrate Catalyst

The combination of Ti(OPr-*i*)$_4$, a dialkyl tartrate, and *tert*-butyl hydroperoxide epoxidizes most allylic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in **Scheme 47**. An empirical rule predicts without fail the stereochemical outcome of the reaction, which is very general in

scope (R_1-R_5 are all variables).[101] It is notable that the substrate, the oxidant, and the chiral constituent of the catalyst all feature hydroxy groups, which will react with the titanium alkoxide and form a highly ordered transition state. This close interaction of all the ingredients engendered by the transition metal is surely responsible for the high enantioselectivity of the reaction. Of course, it also limits the substrates to allylic alcohols.

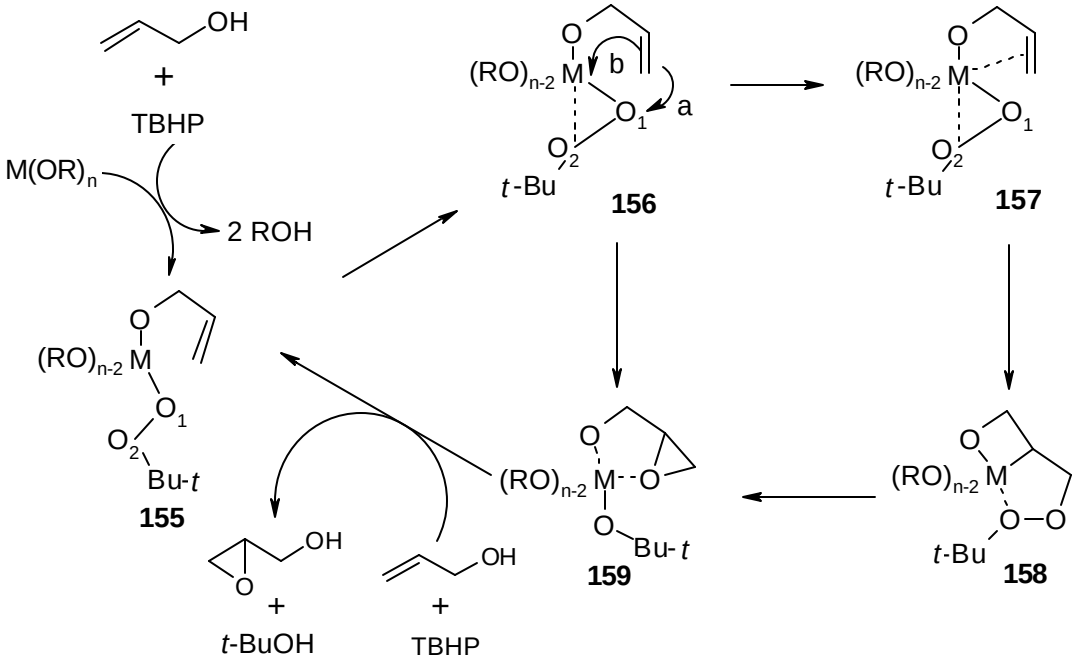


Scheme 47

When an allylic alcohol (R^4, R^5 = H) is drawn in a plane with the hydroxymethyl group at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2*S*)-epoxide; if an (*R*, *R*)-dialkly tartrate is used as the chiral auxiliary. Of course, when an (*S*, *S*)-dialkyl tartrate is used, oxygen is delivered from the top side. The enantiofacial selectivity of the reaction is > 90% ee (usually > 95% ee) for substrates without a *Z* olefinic substituent (R^3 = H). The degree of facial selectivity for a *Z* allylic alcohol depends on the nature of the *Z* substituent R^3. The enantioselectiivity for substrates with unbranched R^3 substituents ranges from 80 to 94% ee, but that for substrates with a branched substituent is lower.[102]

2.3.2 Mechanism of Asymmetric Epoxidation

The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in **Scheme 48**.[103-106]

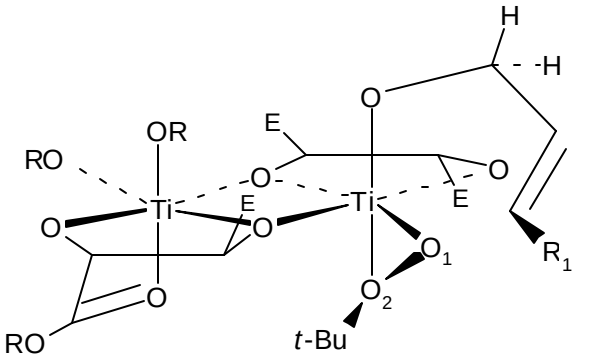


Scheme 48

Metal alkoxides generally undergo rapid ligand exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes $M(OR)_{n-x-y}$-$(OCH_2CH{=}CH2)_x(OOR)_y$. Among them, only species such as **155**, bearing both allylic alkoxide and alkyl hydroperoxide is thought to be further activated by coordination of the second oxygen atom (O_2) to the metal center (see structures **156** and **157**).That the ensuing transfer of O_1 to the double bond of the allylic alcohol occurs in an intramolecular fashion is supported by comparison of the epoxidation rate of allyl alcohol with that of allyl methyl ether.[107] However, controversy still surrounds the oxygen transfer process (**156**-**159**). One suggestion is that the double bond first coordinates to the metal center and then inserts into the μ-2 alkyl hydroperoxide ligand to give an epoxide *via* the peroxometallocycle intermediate **158**.[108-110] An alternative proposal

is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken.[106,111-116] Frontier molecular orbital treatment of peroxometal complexes also suggest that *d* transition metal complexes of ROO- exhibit electrophilic behaviour.[117] Finally, exchange of *tert*-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle.

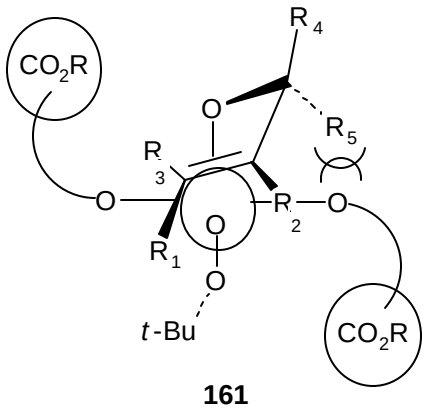
The titanium-tartrate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of **Scheme 48**. Therefore, the remaining mechanistic query is how oxygen is transferred enantioselectively to substrates. The answer to the query is, structures of titanium-dialyl tartrate complexes,[112-113,118-122] as well as those prepared from $Ti(OPr\text{-}i)_4$ and (*R*, *R*)-*N*,*N*'-dibenzyltartramide and from $Ti(OEt)_4$, (*R*, *R*)-diethyl tartrate, and PhC(O)-N(OH)Ph were determined.[123-125] Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst has been proposed as **160** (**Figure 5**).



160 E = CO_2R

Figure 5

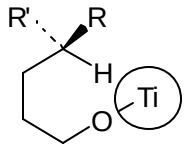
When structure **160** is viewed down the distal peroxide oxygen-titanium bond axis (O_1-Ti), the symmetry of the tartrate "windmill arms" becomes apparent. Within this model, conformer **161** (**Figure 6**), in which the allylic alcohol and the TBHP-ligand align meridionally and the TiO-C-C=C dihedral angle is as small as 30°, has been suggested as a transition state.[116] This conformer experiences severe steric interactions only when $R_5 \neq$ H. This explains the high efficiency of kinetic resolution of racemic secondary allylic alcohols where one enantiomer (R_4 = alkyl, R_5 = H) reacts much faster than the other isomer (R_4 = H, R_5 = alkyl). The poor reactivity of tertiary allylic alcohols (R_4 & R_5 = alkyl) is rationalized analogously. We also see that the Z olefinic substituent (R_3) is close to the hydroxymethyl group bound to titanium because of the small O-C-C=C dihedral angle.



161

Figure 6

These interactions destabilizes conformer **162** (**Figure 7**) and lower the reactivity of this complexes. The C-2 substituent (R_2) in **161** is also in the vicinity of the titanium complex, and only the E-olefinic substituent (R_1) projects toward an open quadrant.



162

Figure 7

2.3.3 Catalytic Asymmetric Epoxidation

Since the principal difficulties (isolation of unstable and/or water-soluble epoxy alcohols) with the stoichiometric reaction are mainly attributed to the mild Lewis acidity of titatnium alkoxide and the aqueous workup required for hydrolysis of the stoichiometric catalyst, it is not surprising that these problems are minimized when the reaction is conducted in a catalytic manner. In 1986, it was discovered that addition of molecular sieves to the reaction mixture allows epoxidation to proceed to completion in the presence of only 5-10% of the Ti(IV)-tartrate complex.[126,127] A catalyst with 5 mol% Ti(OPr-*i*)$_4$ and 6 mol% tartrate has been recommended as the most widely applicable system for asymmetric epoxidation. Below the 5 mol% level, the enantioselectivity of the reaction decreases

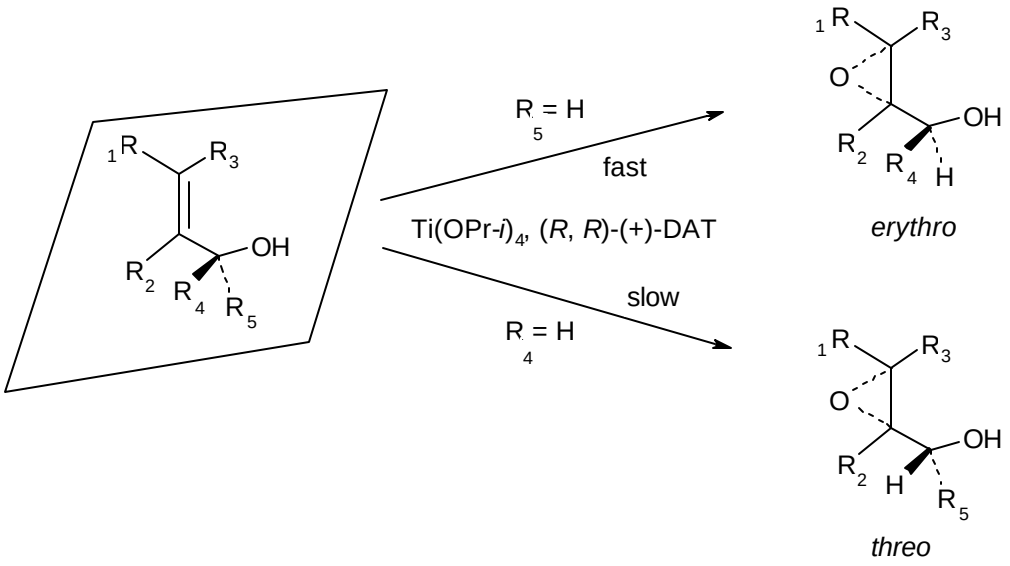
remarkably. The amount of tartrate ester must be carefully controlled, because a large excess of tartrate (>100% excess) decreases the reaction rate [the titanium-tartrate (1:2) complex is inactive], while with too little tartrate (<10% excess) the enantioselectivity may suffer.

Furthermore, epoxy alcohols produced by the catalytic procedure can be coverted *in situ* into *p*-nitrobenzoates or *p*-toluensulfonates, which are more easily isolated than the parent epoxy alcohols and can serve as versatile intermediates for further transformations. The combination of asymmetric epoxidation an *in situ* titanium-mediated epoxide-opening reactions also provides access to diol derivatives without isolating unstable and/or water-soluble epoxy alcohols.

Another advantage of the catalytic process is high substrate concentrations. In the stoichiometric reaction, the substrate concentration must be kept low (0.1-0.3 M) to avoid undesired side reactions like epoxide opening, while the catalytic process can be performed at concentrations up to 0.5-1.0 M. Even with the catalytic procedure, the epoxidation of a sensitive substrate like cinnamyl alcohol should be carried out at around 0.1 M concentration.

2.3.4 Kinetic Resolution of Secondary Allylic Alcohols

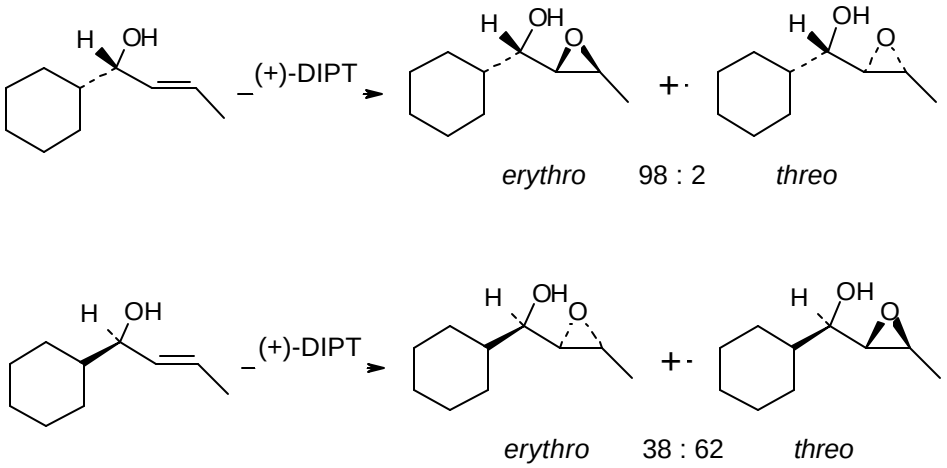
The Kinetic resolution of secondary allylic alcohols was first reported in 1981 (**Scheme 49**),[128] wherein some examples were performed with as little as 13-25% catalyst. Although



Scheme 49

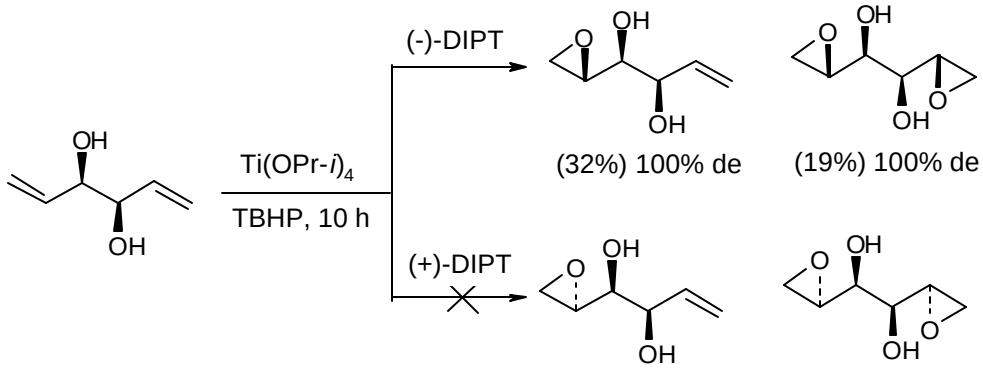
this catalytic procedure has been used by other researchers,[129-132] only recently there has been a report to accomplish kinetic resolution in a truly catalytic manner with selectivity only slightly lower (0-4%) than that achieved in the stoichiometric reaction.[127] The key feature of this catalytic procedure is the use of molecular sieves (zeolites).

With cyclohexyl (*E*)-1-propenyl carbinol as the model ($R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, $R_5 = C_6H_{11}$, and $R_1 = CH_3$, $R_2 = R_3 = R_5 = H$, $R_4 = C_6H_{11}$ in **Scheme 49**), it was found that the *S* enantiomer reacts 74 times faster than the *R* enantiomer at 0° when (*R*, *R*)-(+)-diisopropyl tartrate is used as the chiral auxiliary.[120] As in the epoxidation of primary allylic alcohols,[99] the stereochemical course of the kinetic resolution process has been highly predictable. When the secondary allylic alcohol is drawn so that the hydroxyl group lies in the lower right corner of the plane (**Scheme 49**), the enantiomer that reacts rapidly with (*R*, *R*)-(+)-dialkyl tartrates is the one in which the substituent (R_4) on C-1 is located above the plane. Epoxidation occurs from the underside to give the usual 2S epoxide (*erythro* selectivity, 98:2). The slow reacting enantiomer is the one in which the C-1 substituent (R_5) is located on the underside, interfering with the "normal" delivery of the oxygen atom.



Scheme 50

This interference reduces the expected *threo* selectivity for the slow reacting enantiomer (38 *erythro* : 62 *threo*, **Scheme 50**). This enantioselection rule has consistently been observed for all secondary allylic alcohols except for those with bulky Z-substituents and 1,2-divinylethylene glycols. Kinetic resoulution is very poor for allylic alcohols with bulky Z substituents,[128] and reversed but high enantioselectivity is observed in the kinetic resolution of 1,2-vinylethylene glycols (**Scheme 51**).



Scheme 51

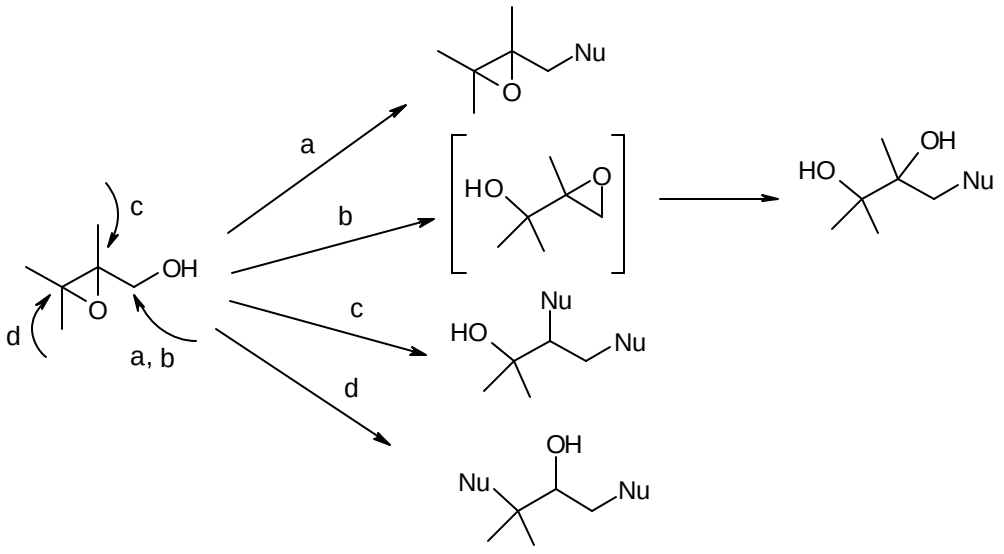
The most important parameters in kinetic resolution are the relative rates of reaction of the two allylic alcohol enantiomers. Three variables influence solutions to the percent ee of the remaining substrate, the percent conversion of the racemic material, and the relative rate (k_{rel}) of reaction of the two enantiomers. Knowledge of any two allows specification of the third. The maximum effectiveness of a kinetic resolution procedure is, of course, when k_{rel}

= ∞, but a value of 50-100 is almost as effective. Actual values are in the range of 15 to 700.[127,133-142]

The kinetic resolution of the racemic secondary allylic alcohols has almost the same substituent effects as the normal asymmetric epoxidation of primary allylic alcohols, excepting, of course, the substituents labeled R_4 (or R_5) in **Scheme 49**.[127] Bulky R_1 groups (**Scheme 49**) increase the rate of epoxidation of the fast-reacting enantiomer and decrease the rate of the slow-reacting enantiomer, thus increasing k_{rel}. It should be recalled that *E*-substituted primary alcohols, even with very bulky groups, are the best substrates for asymmetric epoxidation in terms of rate, yield, and enantioselectivity. The most effectively resolved substrates to date are those in which the *E*-substituent R_1 is trimethylsilyl, iodo, or tri-*n*-butylstanyl: at 50% conversion of the racemic substrate, both the recovered allylic alcohol and the *erythro*-epoxy alcohol have more than 99% ee.[133-139]

2.3.5. Recent Applications of Epoxides

The great utility of the titanium-mediated asymmetric epoxidation in organic synthesis is attributed to its enantioselectivity and to the numerous applications of epoxy alcohols as precursors to diversely functionalized compounds. However, since epoxy alcohols have

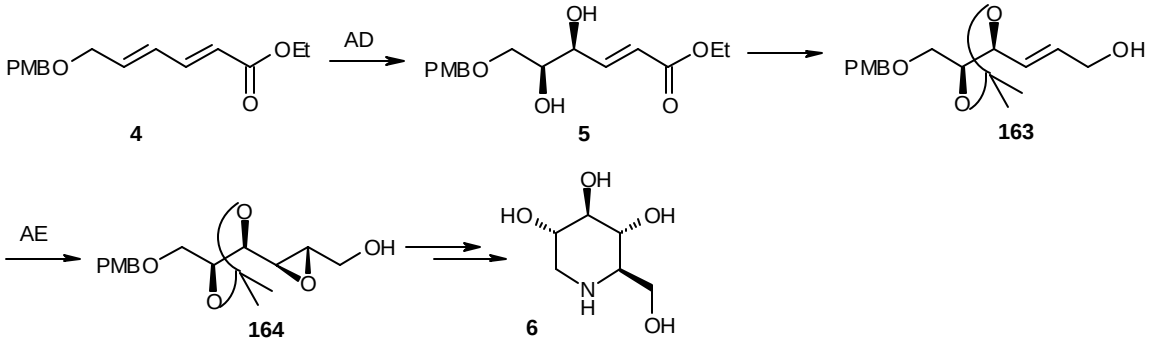


Scheme 52

three reactive sites (**Scheme 52**), regio- and stereoselective reactions are essential for their use, and many studies have been directed toward developing regioselective transformations of epoxy alcohols.

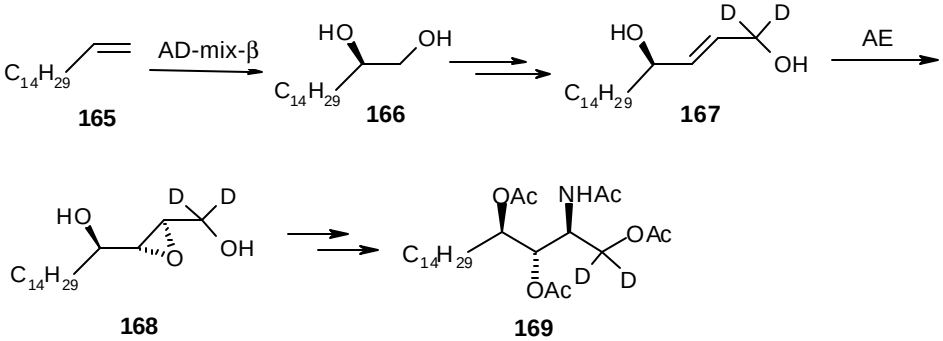
Several applications of epoxides have been documented in the literature in the recent years. A few of them are described below.

1. An asymmetric synthesis of (+)-1-deoxynojirimycin **6**[44] starting from diene **4** is described. employing the Sharpless dihydroxylation and epoxidation (**Scheme 53**).



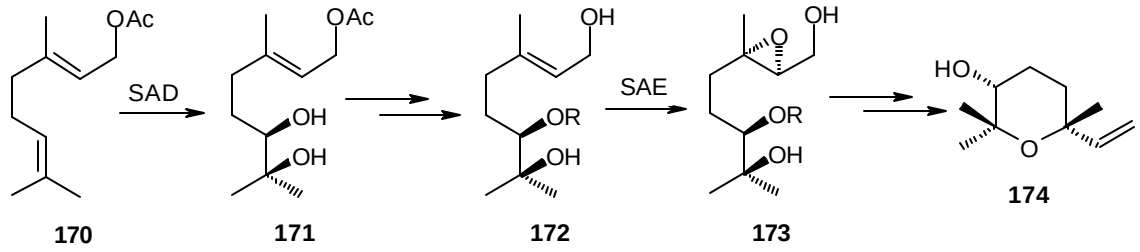
Scheme 53

2. The stereoselective total synthesis of D-*ribo*-[1,1-^{2}H-1,2-^{13}C]phytosphingosine **169**[143] was achieved employing Sharpless asymmetric dihydroxylation and epoxidation (**Scheme 54**). Chirality at the incipient C-4 position was derived from asymmetric dihydroxylation of 1-hexadecene **165**. The remaining chiral centers were formed by Sharpless epoxidation of an allylic alcohol **167**.



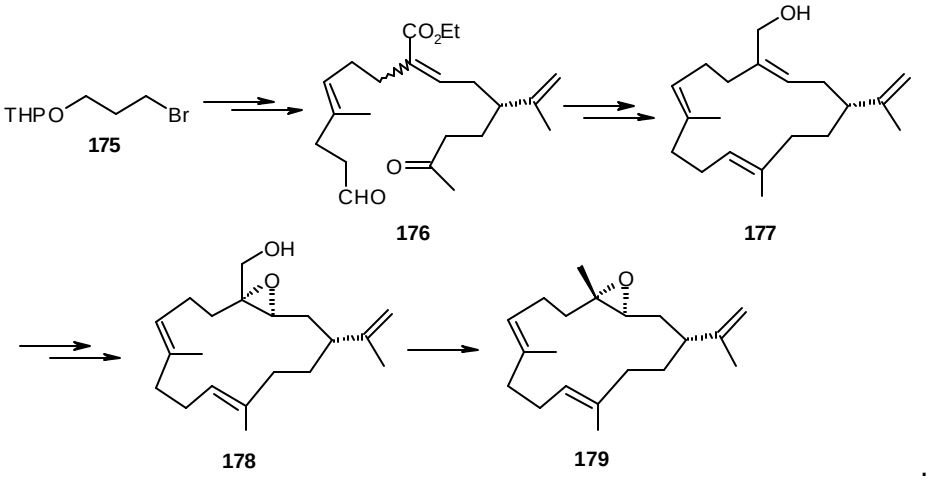
Scheme 54

3. The enantioselective synthesis of tetrahydropyran linalool oxide **174**[144] was achieved by acid catalyzed cyclization of appropriate epoxy alcohol **173** obtained by consecutive Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation of geraniol derivative **170** (**Scheme 55**).



Scheme 55

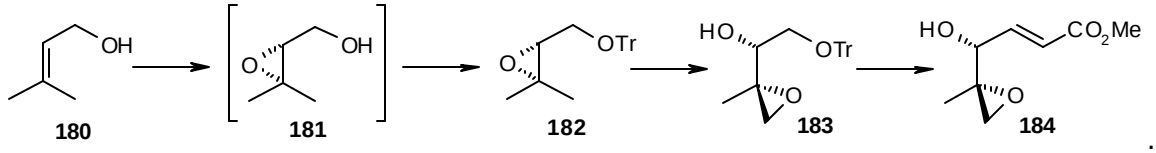
4. An enantioselective 3,4-(+)-epoxycembrene-A **179**[145] was achieved by employing McMurry coupling and Sharpless asymmetric epoxidation as the key steps (**Scheme 56**).



Scheme 56

5. A highly stereoselective synthesis of (2*R*,3*S*)-3,4-epoxy-3-methyl-1-(triphenylmethyl) oxybutan-2-ol **184**[146], which is a substructure found in some naturally-occurring bioactive compounds, was achieved starting from commercially available 3-methyl-2-buten-1-ol **180**

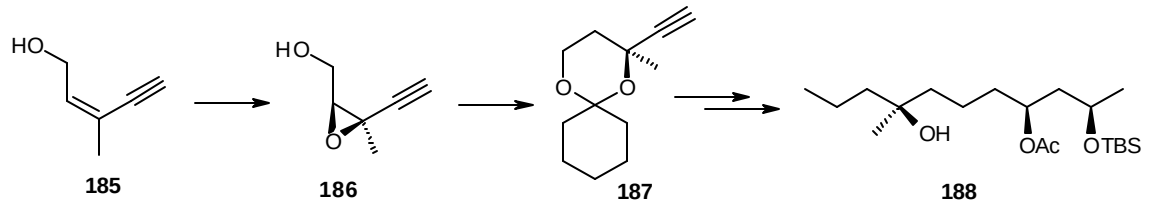
in three steps, using two applications of the Sharpless asymmetric epoxidation as the key stereochemistry establishing reactions (**Scheme 57**).



180 **181** **182** **183** **184**

Scheme 57

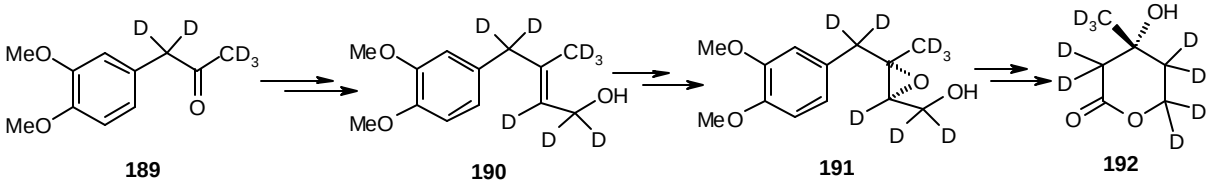
6. A formal synthesis of taurospongin A[147] was achieved using Sharpless asymmetric epoxidation as the key step (**Scheme 58**).



185 **186** **187** **188**

Scheme 58

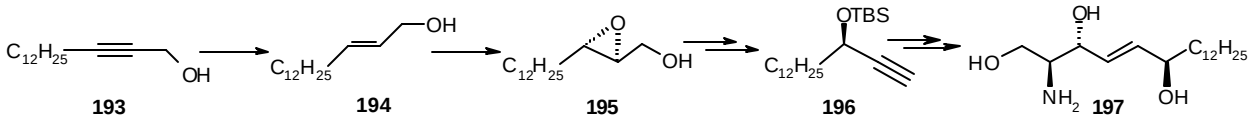
7. Practical enantioselective synthetic method of fully deuterated (*R*)-mevalonolactone **192**[148] has been developed based upon Sharpless asymmetric epoxidation (**Scheme 59**).



189 **190** **191** **192**

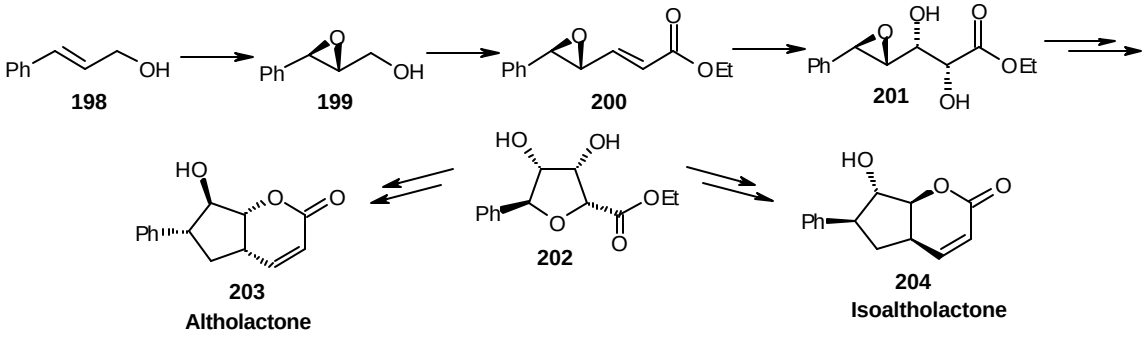
Scheme 59

8. Total synthesis of 6-hydroxy-4*E*-sphinganine **197**[149] was achieved using the Sharpless asymmetric epoxidation as the key step (**Scheme 60**).



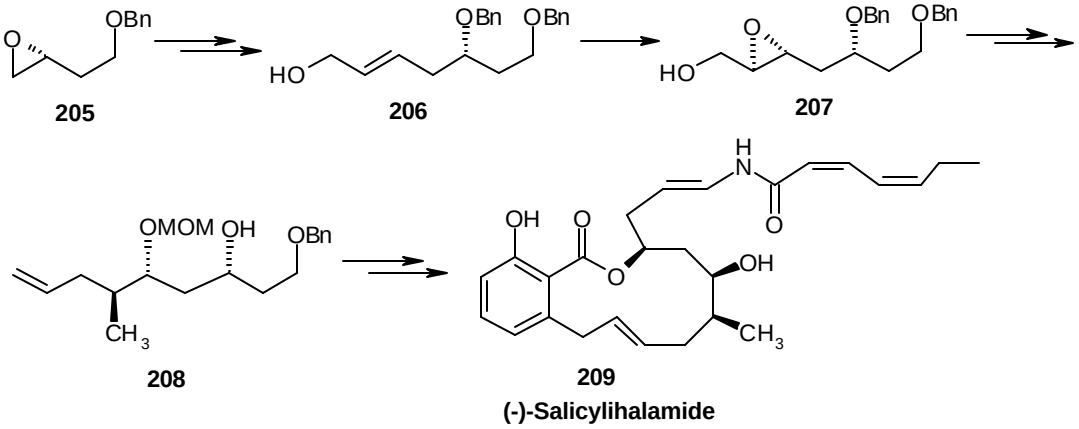
Scheme 60

9. A concise and flexible stereoselective route to altholactone **203**[150] and isoaltholactone **204**[150] was achieved by using Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation as the asymmetric induction process, starting from cinnamyl alcohol **198** (**Scheme 61**).



Scheme 61

10. A Formal total synthesis of (-)-Salicylihalamide **209**[151] was achieved using Sharpless asymmetric epoxidation (**Scheme 62**).



Scheme 62

2.3.6 Conclusion

Thus, Sharpless asymmetric epoxidation reaction has become a powerful oxidation reaction. The versatility of epoxidation reaction provides the advantage of epoxide being a classical intermediate towards bioactive molecule and thus, has contributed to rapid advances in synthetic organic chemistry giving access to new molecules.

2.4 References

1. For recent reviews, see: *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**.
2. (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (b) Katsuki, T. *J. Mol. Catal. A: Chem*. **1996**, *113*, 87. For a recent review, see: Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 101-158.
3. McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995***, 60*, 5750. (b) Kennedy, R. M.; Tang. S. *Tetrahedron Lett.* **1992***, 33*, 3729. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5299. (d) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5303. (e) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett*. **1994**, *35*, 5133.
4. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc*. **1977**, *99*, 3120.
5. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483. (b) Schroder, M. *Chem*. *Rev*. **1980**, *80*, 187.
6. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem*., *Int. Ed. Engl*. **1996**, *35*, 451. (b) Li, G.; Sharpless, K. B. *Acta Chem. Scand*. **1996**, *50*, 649. (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem*., *Int. Ed. Engl*. **1996**, *35*, 2810. (d) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem*., *Int*. *Ed*. *Engl*. **1996**, *35*, 2813. (e) Angelaud, R.; Landais, Y.; Schenk, K. *Tetrahedron Lett*. **1997**, *38*, 1407.
7. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1059.

8. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936***, 522*, 75. (b) Criegee, R. *Angew. Chem*. **1937***, 50,* 153. (c) Criegee, R. *Angew. Chem.* **1938**, *51*, 519. (d) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liebigs Ann*. *Chem*. **1942**, *550*, 99.
9. (a) Hofmann, K. A. *Chem. Ber*. **1912**, *45*, 3329. (b) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936***, 58,* 1302. (c) Milas, N. A.; Trepagnier, J. H.; Nolan, J. T., Jr.; Iliopulos, M. I. *J. Am. Chem. Soc*. **1959**, *81*, 4730.
10. Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc*. **1976**, *98*, 1986.
11. (a) Schneider, W. P.; McIntosh, A. V. US Patent 2,769,824 Nov. 6, 1956. (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, 1973.
12. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*. **1990**, *55*, 766.
13. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980***, 102*, 4263.
14. (a) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans*. **1977**, 941. (b) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413.
15. Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992***, 33*, 639.
16. (a) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Dihydroxylation*. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 227. (b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317. (c) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J.-Y.; Bennani, Y. L. *J. Org. Chem*. **1993**, *58*, 1991. (d) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yeun, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989***, 111*, 9243. (e) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987***, 109*, 6213. (f) Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988***, 29*, 573. (g) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990***, 31*, 1741. (h) Nakajima, M. Tomioka, K.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1993***, 49*, 10793. (i) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Lett.* **1992***, 33*, 4021. (j) Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665. (k) Oishi, T.; Hirama, M *J. Org. Chem.* **1989***, 54*, 5834. (l) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131. (m) Tokles, M.; Snyder, J. K. *Tetrahedron Lett*. **1986**, *27*, 3951. (n) Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* **1992***, 33,* 5081.
17. Jacobsen, E. N.; Marko, I; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988***, 110*, 1968.
18. Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989***, 111*, 1123.

19. Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990***, 31*, 2999.
20. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992***, 57*, 2768.
21. The [3+2] mechanism was originally proposed by Boseken: (a) Boseken, J. *Recl. Trav. Chim.* **1922***, 41*, 199. For the [2+2] mechanism, see: (b) Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **1977***, 99*, 3120. (c) Jorgensen, K. A.; Schiott, B. *Chem. Rev*. **1990**, *90*, 1483.
22. Nelson, D. W.; Gypser, A.; Ho, P. T.; Kolb, H. C.; Kondo,T.; Kwong, H.-L.; McGrath, D.; Rubin, A. E.; Norrby, P.-O.; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840.
23. Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840.
24. Veldkamp, A.; Frenking, G.; *J. Am. Chem. Soc.* **1994**, *116*, 4937.
25. (a) Dapprich, S.; Ujaque, G.; Maseras, F.; Lledos, A.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1996**, *118*, 11660. (b) Torrent, M.; Deng, L.; Sola, M.; Ziegler, T. *Organometallics* **1997**, *16*, 13. (c) Pidun, U.; Boehme, C.; Frenking, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2817.
26. Norrby, P.-O.; Gable, K. P. *J. Chem. Soc., Perkin Trans. 2* **1996**, 171.
27. Gobel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1329.
28. Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *Organometallics* **1994***, 13*, 344. (b) Veldkamp, A.; Frenking, G. *J. Am. Chem. Soc*. **1994**, *116*, 4937.
29. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
30. Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
31. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
32. (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994***, 116*, 1278. (b) Sharpless, K. B.; Amberg, W; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (c) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996***, 61*, 7978.
33. Hale, K. J.; Manaviazar, S.; Peak, S. A. *Tetrahedron Lett.* **1994***, 35*, 425.

34. Krysan, D. J. *Tetrahedron Lett.* **1996***, 37*, 1375.
35. O'Brien, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2129.
36. (a) Salvadori, P.; Superchi, S.; Minutolo, F. *J. Org. Chem.* **1996**, *61,* 4190. (b) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1996***, 118*, 2301. (c) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997***, 119,* 311.
37. Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1993**, *4*, 133. (b) Arrington, M. P.; Bennani, Y. L.; Gobel, T.; Walsh, P. J.; Zhao, S.-H; Sharpless, K. B. *Tetrahedron Lett.* **1993***, 34*, 7375. (c) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994***, 35*, 3469.
38. Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993***, 259*, 64.
39. Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996***, 35,* 448.
40. Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995***, 60,* 3940.
41. Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992***, 114,* 7568.
42. (a) Yoshimitsu, T.; Ogasawara, K. *Synlett* **1995**, 257. (b) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem*. **1994**, *59*, 54. (c) Xie, L.; Crimmins, M. T.; Lee, K.-H. *Tetrahedron Lett*. **1995**, *36*, 4529. (d) Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*, 6895.
43. Hodgkinson, T.; Shipman, M. *Synthesis* **1998**, 1141
44. Lindstrom, U. M.;Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173.
45. Imashiro, R.; Sakurai, O.; Yamashita, Y.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657.
46. Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998***, 63*, 5863.
47. Toshima, H.; Sato, H.; Ichihara, A. *Tetrahedron* **1999**, *55*, 2581.
48. Gurjar, M. K.; Kumar, V. S.; Rao, B. V. *Tetrahedron* **1999***, 55,* 12563.
49. Garcia, C.; Martin, T.; Martin, V. S. *J. Org. Chem*. **2001**, *66*, 1420.
50. Fernandes, R. A.; Kumar, P. *Tetrahedron* **2002**, *58*, 6685.
51. Koskinen, A. M. P.; Kallasta, O. A. *Tetrahedron* **2003**, *59*, 6947.
52. Pandey R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425.
53. Naidu, S. V., Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035.
54. Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873.
55. Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447
56. Fernandes, R. A.; Bodas, M. S.; Kumar, P. *Tetrahedron* **2002**, *58*, 1223.

57. Pandey R. K.; Upadhyay, P. K.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6245.
58. Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149.
59. Fernandes, R. A.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231.
60. Fernandes, R. A.; Kumar, P. *Synthesis* **2003**, 129
61. (a) Baker, W.; Field, F. B. *J. Chem. Soc.* **1932**, 86. (b) Carlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* **1947***, 69,* 1952.
62. Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988***, 110,* 7538.
63. For reviews of cyclic sulfites and sulfates, see: a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Lohray, B. B.; Bhushan, V. *Adv. Heterocycl. Chem.* **1997***, 68*, 89. (c) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
64. Van Woerden, H. F. *Chem. Rev*. **1963**, *63*, 557.
65. King, S. A.; Pipik, B.; Conlon, D. A.; Bhupamy, M. *Synth. Commun.* **1997***, 27*, 701.
66. Burgess, K.; Ho, K.-K.; Ke, C.-Y. *J. Org. Chem.* **1993***, 58*, 3767.
67. Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989***, 30*, 655.
68. (a) Jones, J. K. N.; Perry, M. B.; Turner, J. C. *Can. J. Chem.* **1960***, 38*, 1122. (b) Bragg, P. D.; Jones, J. K. N.; Turner, J. C. *Can. J. Chem*. **1959**, *37*, 1412. (c) Hoffmann, R. W.; Stiasny, H. C. *Tetrahedron Lett.* **1995***, 36*, 4595.
69. (a) Denmark, S. E. *J. Org. Chem.* **1981***, 46*, 3144. (b) Lowe, G.; Salamone, S. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1392.
70. Gao, Y.; Zepp, C. M. *Tetrahedron Lett*. **1991**, *32*, 3155.
71. Vanhessche, K.; Van der Eycken, E.; Vandewalle, M.; Roper, H. *Tetrahedron Lett*. **1990**, *31*, 2337.
72. Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett*. **1989**, *30*, 2623.
73. Lohray, B. B.; Ahuja, J. R. *J. Chem. Soc., Chem. Commun*. **1991**, 95.
74. Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **l990***, 31,* 4317.
75. Hirsenkorn, R. *Tetrahedron Lett.* **1990**, *31*, 7591.
76. Kalantar, T. H.; Sharpless, K. B. *Acta Chem. Scand.* **1993***, 47*, 307.
77. Tomalia, D. A.; Falk, J. C. *J. Heterocycl. Chem.* **1972***, 9*, 891.
78. Pilkington, M.; Wallis, J. D. *J. Chem. Soc., Chem. Commun*. **1993**, 1857.
79. Bates, R. W.; Fernandez-Moro, R.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 2651.
80. Van der Klein, P. A. M.; de Nooy, A. E. J.; van der Marel, G. A.; van Boom, J. H. *Synthesis* **1991**, 347.

81. Hercouet, A.; Bessieres, B.; Corre, M. L. *Tetrahedron: Asymm*etry **1996**, *7*, 1267. Also, see: Hercouet, A.; Bessieres, B.; Corre, M. L. *Tetrahedron: Asymmetry* **1996***, 7*, 283.
82. Lohray, B. B.; Vankateswarlu, S. *Tetrahedron: Asymmetry* **1997**, *7*, 633.
83. He, L.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett*. **1998**, *39*, 2071.
84. Zimmer, R.; Homann, K.; Angermann, J.; Reissig, H.-V. *Synthesis* **1999**, 1223.
85. Marinetti, A.; Labrue, F.; Genet, J.-P. *Synlett* **1999**, 1975.
86. Hercouet, A.; Corre, M. L.; Carboni, B. *Tetrahedron Lett.* **2000**, *41*, 197.
87. Gourlain, T.; Wadouachi, A.; Beaupere, D. *Tetrahedron Lett.* **2000**, *41*, 659.
88. Yuasa, H.; Takada, J.; Hashimoto, H. *Tetrahedron Lett.* **2000**, *41*, 6615.
89. Eskici, M.; Gallagher, T. *Synlett* **2000**, 1360.
90. Jang, D. O.; Joo, Y. H.; Cho, D. H. *Synth. Commun*. **2000**, *30*, 4489.
91. Yan, Y.-Y.; Rajanbabu, T. V. *J. Org. Chem.* **2000***, 65*, 900.
92. Bera, S.; Nair, V. *Tetrahedron Lett.* **2001**, *42*, 5813.
93. Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001***, 66*, 2583.
94. Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445.
95. Fernandes, R. A.; Kumar, P. *Tetrahedron Asymm.* **1999**, *10*, 4349.
96. Fernandes, R. A.; Kumar, P. *Tetrahedron Asymm.* **1999**, *10*, 4797.
97. Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921
98. Kandula, S.V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957.
99. Sharpless, K. B. *Chemtech* **1985**, *15*, 692.
100. Katsuki, T.; Sharpless, K. B. *J. Am. Chem.Soc.*, **1980**, *102*, 5974.
101. Johnson, R. A.; Sharpless, K. B. in: I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*, VCH Publishers, New York, **1993**, p. 103.
102. Finn, M. G.; Sharpless, K.B. in *Asymmetric Synthesis*, Morrison, J. D., Ed., Academic Press, Orlando, FL, **1985**, Vol. 5, pp. 247.
103. Parker, R. E.; Issacs, N. S. *Chem. Rev.* **1959**, 737.
104. Swern, D. in *Organic Peroxides*, D. Swern, Ed., Wiley-Interscience, New York, **1971**, Vol.2. CH.5.
105. Rao, A. S.; Paknikar, S. K.; Kirtane, J.G. *Tetrahedron* **1983**, *39*, 2323.
106. Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.
107. Sharpless, K. B. *Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research XXVII*, Houston, Texas, **1983**, pp. 59-89.

108. Chaumette, P.; Minoun, H.; Saussine, L.; Fisher, J.; Mitschler, A. *J. Organnomet. Chem.* **1983**, *250*, 291.
109. Mimoun, H.; Charpentier, R.; Mitschler, A.; Fisher, J.; Weiss, R. *J. Am. Chem. Soc.* **1980** *102*, 10478.
110. Mimoun, H . *Angew. Chem. Int. Ed. Engl.* **1982** *21*, 734.
111. Sharpless, K. B.; Woodward, S. S.; Finn, M.G. *Pure & Appl. Chem.* **1983**, *55*, 1823.
112. Woodward, S. S.; Finn, M. G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991**, *113*, 106.
113. Finn, M.G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.
114. Mckee, B. H.; Kalantar, T. H.; Sharpless, K. B. *J.Org. Chem.* **1991**, *56*, 6966.
115. Narula, A. S. *Tetrahedron Lett.* **1982**, *23*, 5579.
116. Finn, M. G.; Sharpless, K. B. in *Asymmetric Synthesis*, Morrison, J. D.,Ed., Academic Press, Orlando, FL, **1985**, pp. 247-348.
117. Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6098.
118. Rossiter, B. E.; Sharpless, K. B. The Scripps Research Institute, La Jolla, CA, unpublished results.
119. Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. *J. Am. Chem. Soc.* **1986**, *108*, 2353.
120. Woodward, S. S. Ph.D Dissertation, Stanford University, Stanford, California, 1981.
121. Brugess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1990**, *112*, 7434.
122. Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 4016.
123. Williams, L. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430.
124. Sharpless, K. B. *Chem. Scripta* **1987**, *27*, 521.
125. Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279.
126. Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
127. Gao, Y.; Hanson, R. M.; Kluder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
128. Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

129. Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983**, *48*, 5093.
130. Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1983**, *24*, 3693.
131. Page, P.C. B.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535.
132. Page, P.C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans 1* **1990**, 2403.
133. Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 6351.
134. Kitano, Y.; Matsumoto, T.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1986**, 1323.
135. Kitano, Y.; Matsumoto, T.; Takeda, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1986**, 1732.
136. Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 2033.
137. Kobayashi, Y.; Shimazaki, T.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 5849.
138. Kusakabe, M.; Kato,H.; Sato, F. *Chem. Lett.* **1987**, 2163.
139. Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1988**, 1785.
140. Kobayashi, Y.; Kusakaba, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1587.
141. Matsumoto, Y.; Kitano, Y.; Sato, F. *Tetrahedron Lett.* **1988**, *29*, 5685.
142. Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615.
143. Li, S.; Pang, J.; Wilson, W. K.; Jr. Schroepfer, G. J. *Tetrahedron Asymm.* **1999**, *10*, 1697.
144. Vidari, G.; Di Rosa, A.; Castronovo, F.; Zanoni, G. *Tetrahedron Asymm.* **2000**, *11*, 981.
145. Liu, Z.; Li, W. Z.; Li, Y. *Tetrahedron Asymm.* **2001**, *12*, 95.
146. Uemura, I.; Yamada, K.; Sugiura, K. Miyagawa, H.; Ueno, T. *Tetrahedron Asymm.* **2001**, *12*, 943.
147. Ghosh, A. K.; Lei, H. *Tetrahedron Asymm.* **2003**, *14*, 629.
148. Eguchi, T.; Watanabe, E.; Kakinuma, K. *Tetrahedron* **2003**, *59*, 6035.
149. Yadav, J. S.; Geetha, V.; Raju, A. K.; Gnaneshwar, D.; Chandarsekhar, S. *Tetrahedron Lett.* **2003**, *44*, 2983.
150. Yadav, J. S.; Rajaiah, G.; Raju, A. K. *Tetrahedron Lett.* **2003**, *44*, 5831.

151. Yadav, J. S.; Shrihari, P. *Tetrahedron Asymm.* **2004**, *15*,

CHAPTER 3

Enantioselective Synthesis of 3-hydroxypipecolic acid

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3.1 Introduction

The field of amino acids has gained enormous popularity and relevance in recent years, particularly with the emergence of unnatural analogues as components of molecules with therapeutic potential.[1] The need to replace natural amino acids in peptides with non-proteinogenic counterparts in order to obtain drug-like target molecules has stimulated a great deal of innovation on several fronts.[2] Different areas of expertise have come together to allow a better understanding of interactions of small molecules with biological targets such as enzymes or receptors.[3] These efforts have led to the design of molecules as potential useful medicinal agents often based on intriguing biological rationales and hypotheses. A scenario in which a clinically important enzyme is co-crystallized with its natural substrate, then providing crucial and "visual" information for realistic drug design through common occurrence today.[4] The availability of such strategies is that the original intended constrained motif can also be considered as a scaffold for chemical and functional diversity. In essence, the deployment of other functional groups that can be manipulated at will, and independently of each other, can enhance the utility of the original motif by making it a spatially defined chemical platform. The application of combinatorial methods of diversification could lead to libraries of compounds based on a constrained dipeptide scaffold, and related heteroatom analogs or ring size variants. The judicious choice of orthogonally manipulatable functional group will provide useful scaffolds for combinatorial chemistry.

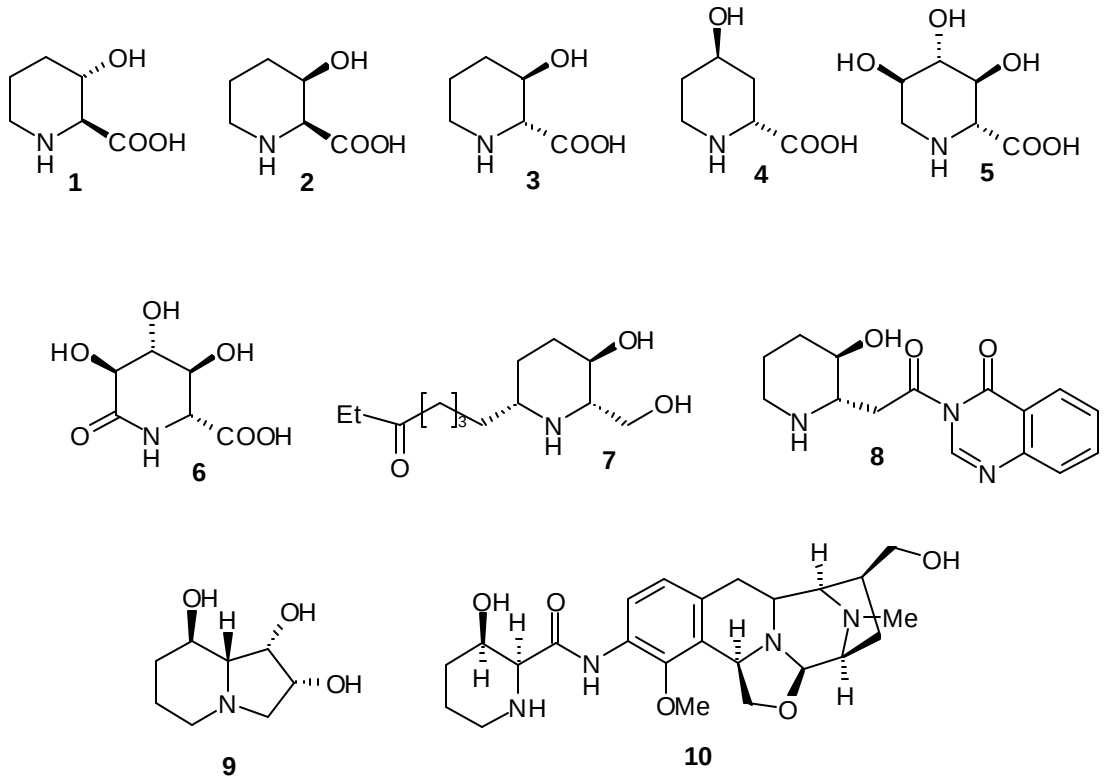
The α-amino-carboxylic acids are one of the five major classes of natural products and they exhibit important and diverse biological functions.[5, 6] Historically, the amino acids have been subdivided into the 20 proteinogenic and the non-proteinogenic

representatives.[7] The number of known naturally occurring unusual, *i.e.* non-proteinogenic, structures is constantly increasing, and had reached 700 when counting was discontinued in 1985.[7c] Besides their role as constituents of peptides, proteins, and peptidoglycans in bacterial cell walls, amino acids have also a function for neuronal signal transduction (glycine, glutamate) and are further metabolized, e.g. to polyamines. The unusual structures are mainly produced by various microorganisms and have evolved to interfere with biochemical pathways of other organisms. In close analogy a large number of man-designed unusual amino acids find pharmaceutical applications or are used to control plant growth and plant diseases, Except for glycine, α-amino acids are chiral structures and most naturally occurring compounds belong to the L-series, which in most cases corresponds to the (*S*)-configuration according to the C.I.P-rules. A lot of effort has therefore been devoted to the preparation of amino acids in enantiomerically pure form of either configuration, a subject already covered by many general reviews[8, 9] and reviews covering selected aspects including their industrial production;[10] specific methods such as chiral glycine templates,[11] kinetic resolution by enzymes,[12] chromium amino carbene complexes,[13] carbohydrates as chiral auxiliaries,[14] partial synthesis from carbohydrates[15] or other amino acids;[16] specific compounds such as α,β-unsaturated,[17] β,γ-unsaturated,[18] and acetylenic amino acids,[19] aryl-glycines,[20] fluorine-containing structures,[21] 1-aminocyclopropane carboxylic acids,[22] and α-amino aldehydes;[23] mechanistic aspects like allylic strain[24] and catalyst structure in asymmetric hydrogenations;[25] and the use of amino acids as chiral starting materials,[23a, 26] auxiliaries and catalysts.[27]

The synthesis of α-amino-β-hydroxy acids has been of great interest owing to their use as chiral building blocks for organic synthesis or as components of biologically active peptides. The α-amino-β-hydroxy acids has also the use as potent enzyme inhibitor[28a-c]. Their utility lies in their two set stereocenters and multifunctionalities, all of which are differentiable. The cyclic amino acids analogues have their importance in physiological and pathological processes[29]. Additionally incorporation of extra functional groups into native α-amino acid structures is a desired feature since it normally affects the biological function of these systems. For example hydroxyprolines are critical for the stability of protocallogen triplex helix, and some ring-substituted prolines have been employed as conformational restrictive elements for the study of bioactive polypeptides.[30]

Chiral non-racemic piperidines are common structural units found in many biologically and medicinally important natural and non-natural products. It is thus not surprising that many new asymmetric methods have been developed.[31]

3-Hydroxy pipecolic acids **1**, **2**, **3**, six membered cyclic α-amino-β-hydroxy acids constitute non natural variants of a structural motif often encountered in a variety of functional molecules e.g. naturally occurring (2*S*,4*R*)-4-hydroxy pipecolic acid **4**, the uronic acid derivative of deoxynojirimycin **5** and potent β-glucuronidase inhibitor D-glucaro-δ-lactam **6** and may be regarded as an "expanded" hydroxylated proline,[32] or a conformationally restricted serine derivative and may affect the physiological and pathological processes.[33] Interestingly, the synthesis of 3-hydroxy piperidine derivatives, such as, 3-hydroxy pipecolic acid **1**, **2**, **3**[34], (+)-prosophylline **7**[35], Febrifugine **8**[36] etc. are less developed and their asymmetric syntheses have been accomplished only very recently.



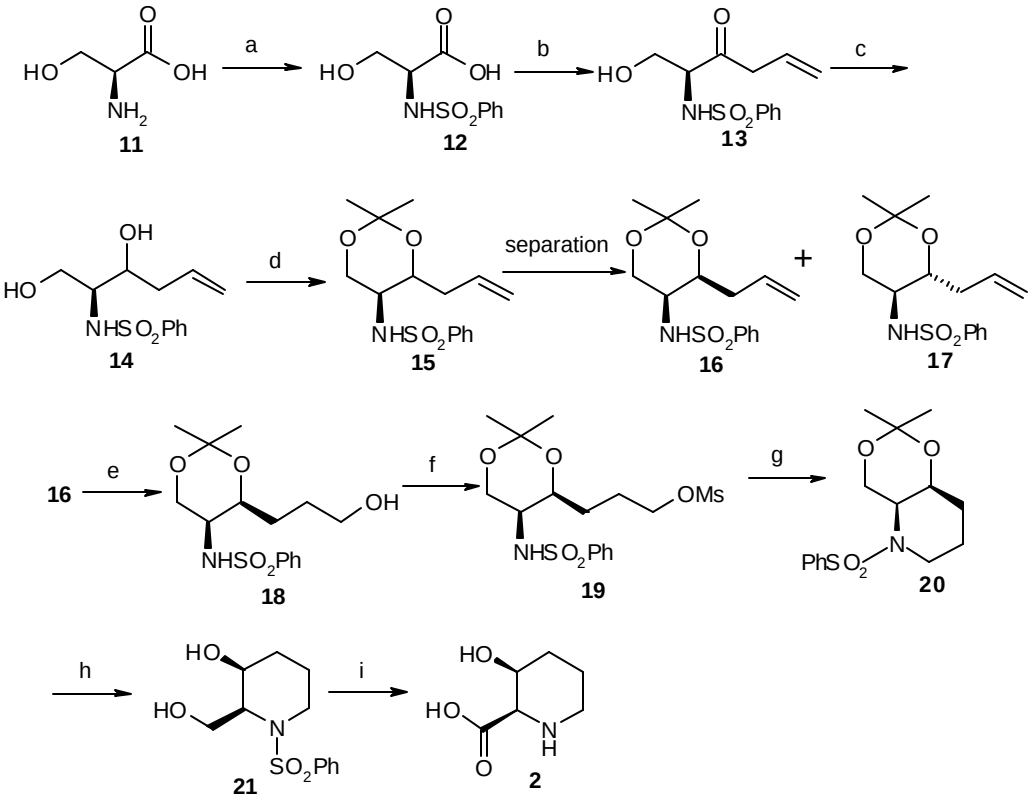
The piperidine unit of 3-hydroxy pipecolic acid is found in a number of biologically important products. For example, the cis-isomer **2** forms a part of the stucture of tetrazomine, an anititumor antibiotic **10**,[37] while the trans-isomer **1** is a precursor of (-)-swainsonine **9**, which has showed a potent and specific α-D-mannosidase inhibitory

activity,[38] and it is also found in the structure of febrifugine **8**, a potent anti-malarial agent.[39]

3.2 Review of Literature:

Rapoport *et al.* (1989)[33a] Scheme 1

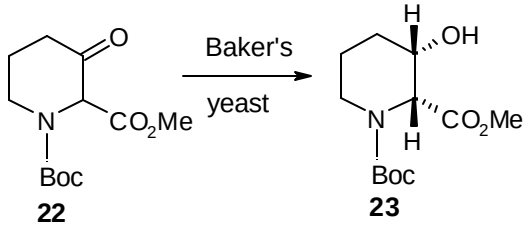
Rapoport *et. al* synthesized β-hydroxypipecolic acid **2** from L-serine **11**. The synthesis proceeds by the ready addition of allylmagnesium bromide and (methylthio)methyllithium to the carboxy group of N-(phenylsulfonyl)serine **12** to give high yields of the corresponding ketone **13**. These particular organometallic reagents were chosen because by further manipulation they allow the introduction of wide scope of functionalities. By judicious choice of reducing agent, either diastereomeric amino alcohol can be obtained with high preference on reduction of the amino ketone. The original serine primary hydroxyl group can then be selectively oxidized to give the amino acid in high overall yield and > 99% ee.



Scheme 1 Reagent and Conditions: (a) $PhSO_2Cl$, K_2CO_3, H_2O (b) *n*-BuLi, CH_2=$CHCH_2MgBr$ (c) K-selectride, $LiBH_4$ (d) 2,2-dimethoxy propane (e) (i) BH_3.THF; (ii) OH-, H_2O_2 (f) MsCl, Et_3N, CH_2Cl_2 (g) K_2CO_3, CH_3OH (h) (i) HCl, CH_3OH; (ii) Pt, O_2, H_2O/EtOAc (i) $2e^-$

Knight *et al.* (1993)[40] Scheme 2

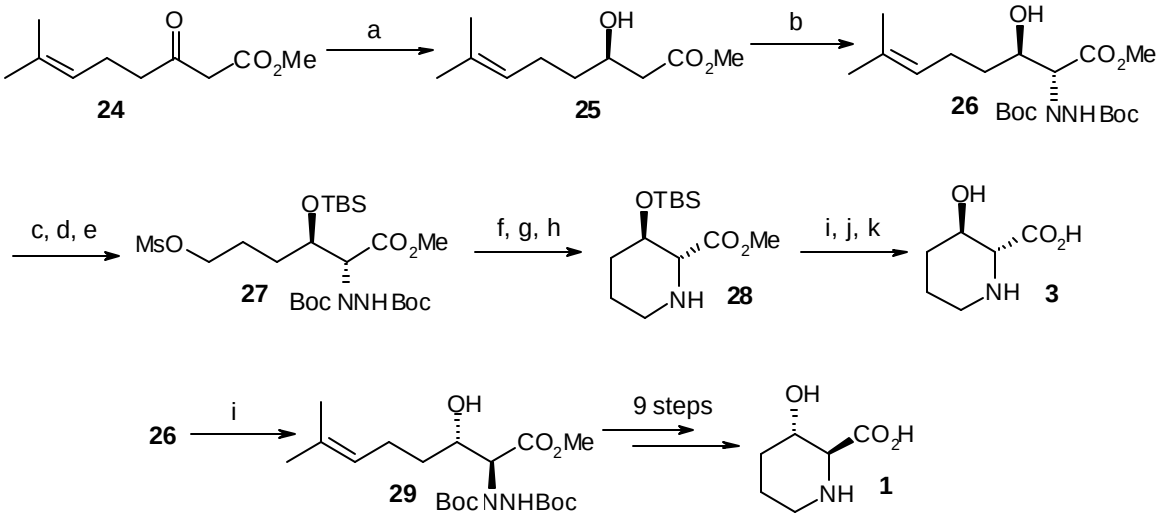
Knight *et al.* carried out Baker's yeast reduction of the ketopiperidine carboxylate **22**, which leads to the corresponding hydroxyl ester in good chemical yields, 93% with > 99% de.



Scheme 2

Greck *et al.* (1996)[41] Scheme 3

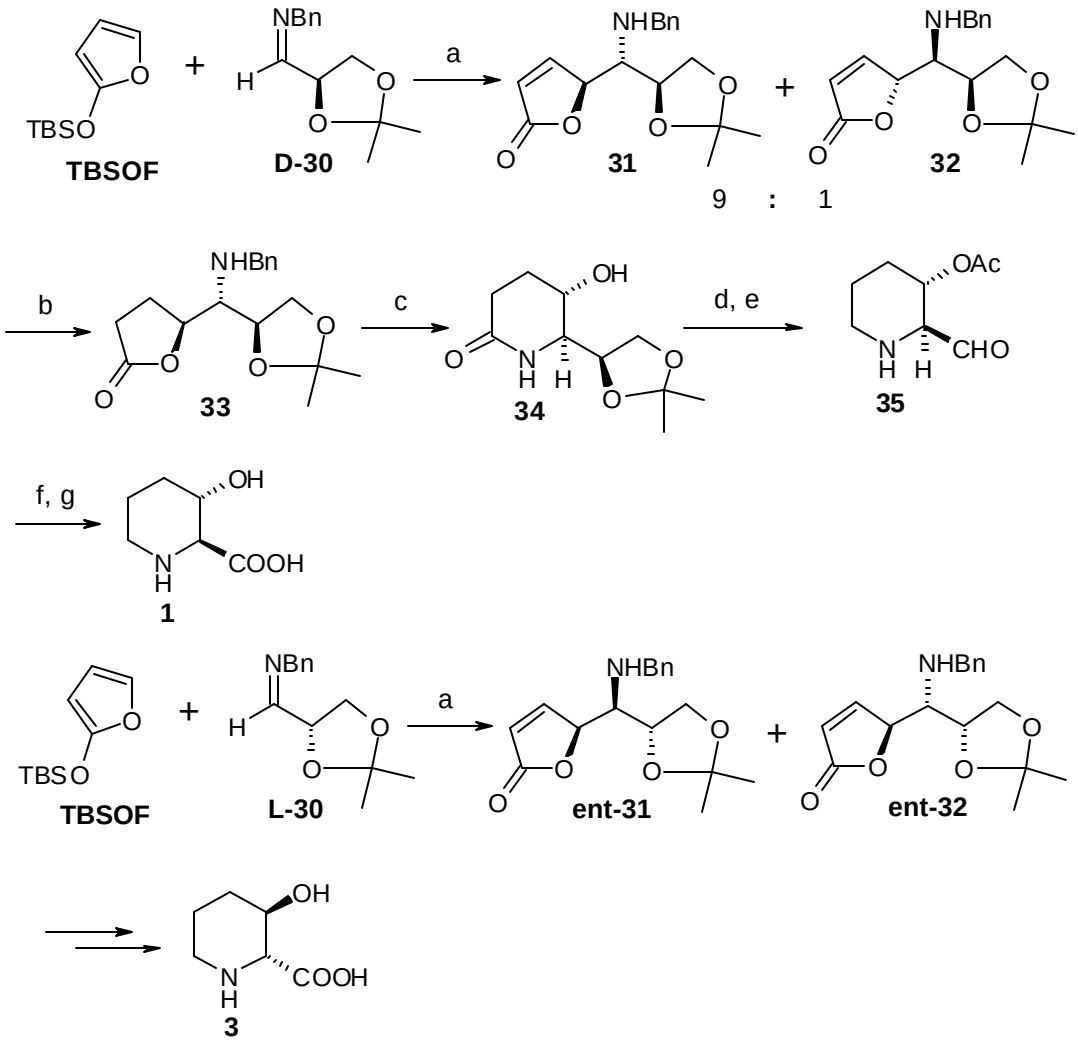
Greck *et al.* achieved the syntheses of enantiomerically pure (2*R*, 3*R*) and (2*S*, 3*S*)-3-hydroxypipecolic acids **3** and **1** respectively from methyl-7-methyl-3-oxo-6-octenoate **24** employing asymmetric hydrogenation and electrophilic amination as the key steps.



Scheme 3 Reagent and Conditions: (a) H_2, 1 atm, $RuBr_2$[(*R*)-Binap] 2%, MeOH, 50°C, 98%, ee-97% (b) MeZnBr 1eq., 0°C, LDA 2eq., DBAD 2eq., -78°C, NH_4Cl, H_2O, 55%, de 98% (c) TBDMSOTf, 2,6-Lutidine, -78°C (d) O_3, CH_2Cl_2, -78°C, $BH_3.Me_2S$ (e) MsCl, Py, 0°C, 65% (f) TFA, CH_2Cl_2 (g) H_2, Raney-Ni, ultrasound (h) Et_3N, CH_2Cl_2, 75% (i) HF, CH_3CN, 50°C (j) K_2CO_3, MeOH, 50°C, 98%, ee-97% (k) Amberlite CG 50, 80% (from **28**)

Casiraghi *et al.* (1997)[32] Scheme 4

trans-β-Hydroxypipecolic acids of both L- and D-series **1** and **3** have been straight forwardly prepared by Casiraghi *et al.* in 14% and 15% yields respectively; starting from glyceraldehydes imines **D-30** and **L-30** as useful three carbon chirons. The key feature of these parallel syntheses lies on the highly diastereoselective character of the initial coupling maneuver between silyloxy furan TBSOF and imines **30**, which ultimately accounts for the relative, and hence absolute configuration of the target pipecolic acid.

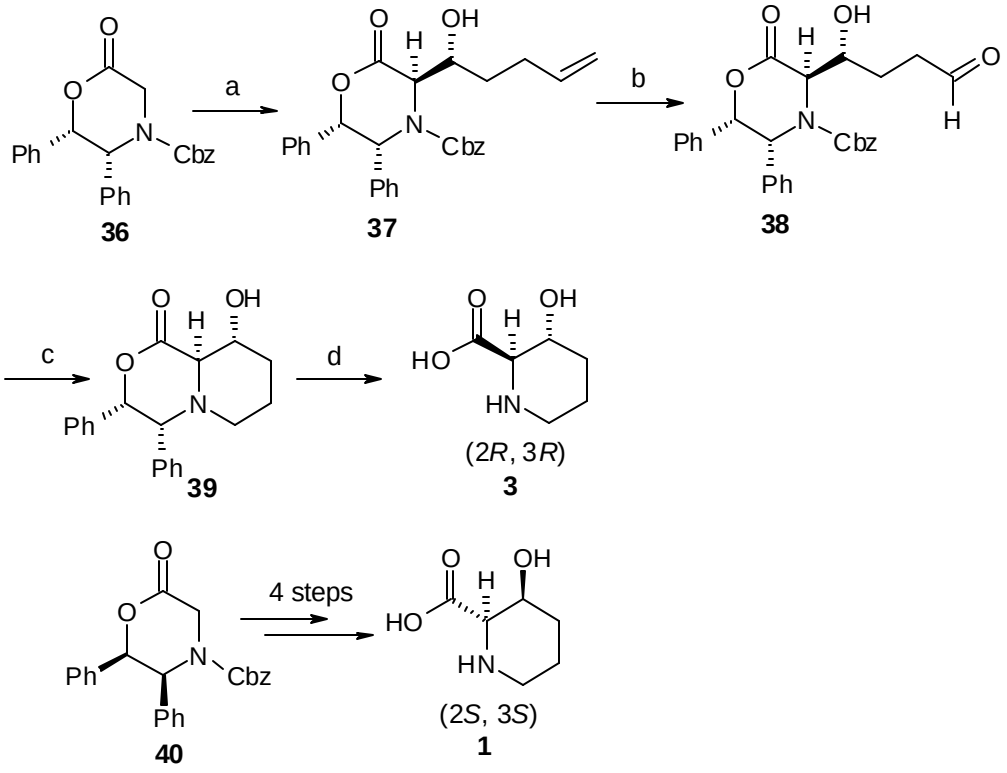


Scheme 4 Reagent and Conditions: (a) TBSOTf, CH_2Cl_2, 80°C, 90% (b) (i) H_2, Pd/C, NaOAc, THF; (ii) flash chromatography, 75% (c) DBU, 80°C, 82 % (d) (i) $LiAlH_4$, $AlCl_3$, THF, -80°C-20°C, 70%; (ii) Ac_2O, Py, DMAP, CH_2Cl_2, 90% (e) (i) 80% aq. AcOH, 80°C; (ii) aq. $NaIO_4$, SiO_2, CH_2Cl_2, 88% (f) $NaIO_4$, $RuO_2.2H_2O$, CCl_4-MeCN-H_2O, acetone, 78% (g) (i) NaOMe, MeOH; (ii) 6 N aq. HCl, 80°C; (iii) purification.

Williams *et al.* (1998)[37] Scheme 5

As shown in **Scheme 5**, Williams *et al.* converted the commercially available lactone **36** into corresponding enolate with di-n-butylboron triflate. Diastereoselective aldol condensation with 4-pentenal provided *anti*-β-hydroxy aldol product which underwent ozonolysis to yield aldehyde **38**. Mild catalytic hydrogenation of aldehyde **38** afforded bicyclic intermediate **39**. Finally the amino acid (2*R*, 3*R*)-β-hydroxypipecolic acid **3** was produced through catalytic hydrogenation over Pd-black.

The corresponding (2*S*, 3*S*)-β-hydroxypipecolic acid **1** was synthesized in the same manner using commercially available lactone **40**.

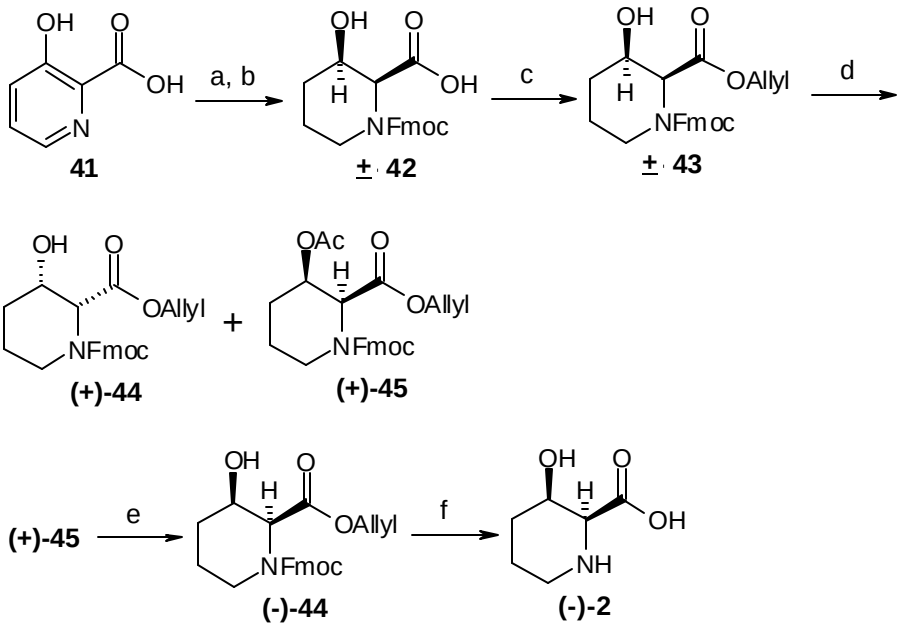


Scheme 5 Reagent and Conditions: (a) (i) BuBOTf, Et_3N; (ii) $CH_2{=}CH(CH_2)_2CHO$, CH_2Cl_2, -78°C (b) (i) O_3, CH_2Cl_2, -78°C; (ii) Me_2S, rt, 69% (c) H_2 (1 atm), 5% Pd/C, CH_2Cl_2, 66% (d) H_2 (50 psi), $PdCl_2$, EtOH, THF, rt, 92%

Williams *et al.* (2000)[42] Scheme 6

Wiiliams *et al.* did the enzymatic resolution of the protected amino acid racemate using Lipase PS (Amano) derived from the reduction of picolinic acid **41** and the amine protected as Fmoc derivative **(±)-42**. The resolution proceeded smoothly forming acetate of (2*S*, 3*R*) isomer, providing **(+)-45** in 46% yield. The (2*R*, 3*S*) amino acid **(+)-44** was recovered in 43% yield.

The acetate **(+)-45** was easily cleaved to form **(-)-44** which was then converted into the free amino acid **(-)-2**.

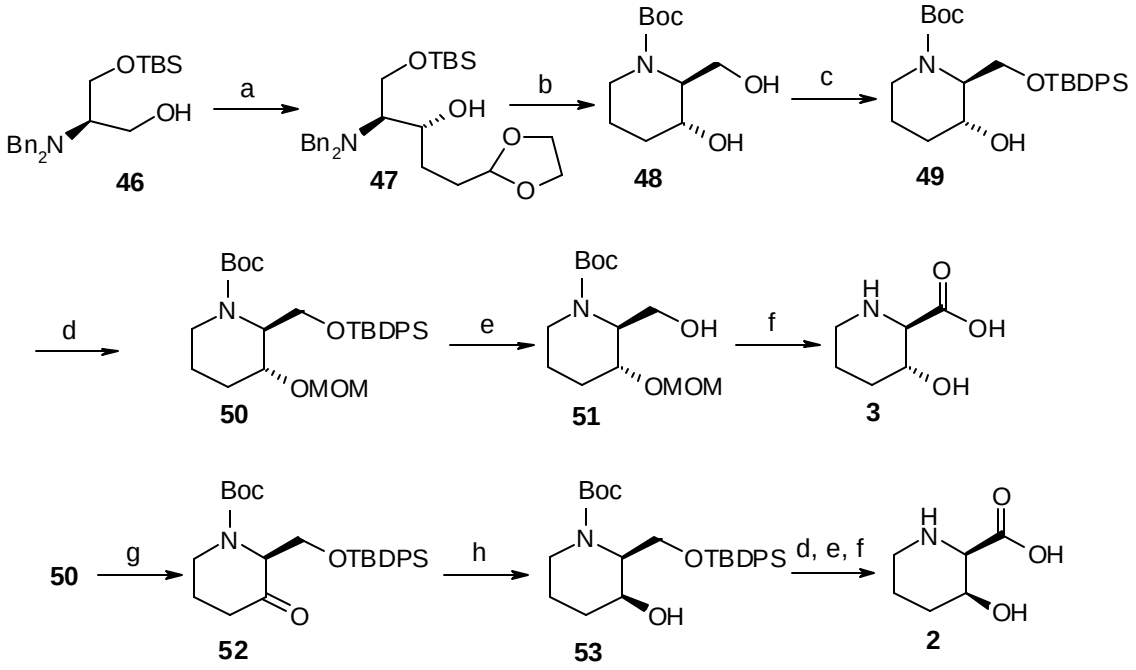


Scheme 6 Reagent and Conditions: (a) H_2 (80 Psi), Rh/C, con. NH_4OH, H_2O (b) Fmoc, Na_2CO_3, dioxane:H_2O (1:1). 0°C-rt, 55% (c) allyl alchohol, TsOH, H_2O, PhH, 68% (d) Lipase PS, vinyl acetate, *i*-Pr_2O, 30°C, 3.5 days, 91% (e) allyl alcohol, H_2SO_4 (cat.) 80°C, 91% (f) (i) 2 M LiOH, EtOH; (ii) Dowex (H^+), 93%

Zhu *et al.* (2000)[39] Scheme 7

Zhu *et al.* achieved the asymmetric syntheses of (2*R*, 3*R*) and (2*R*, 3*S*)-3-hydroxypipecolic acids featuring a key diastereoselective addition of Buchi's Grignard

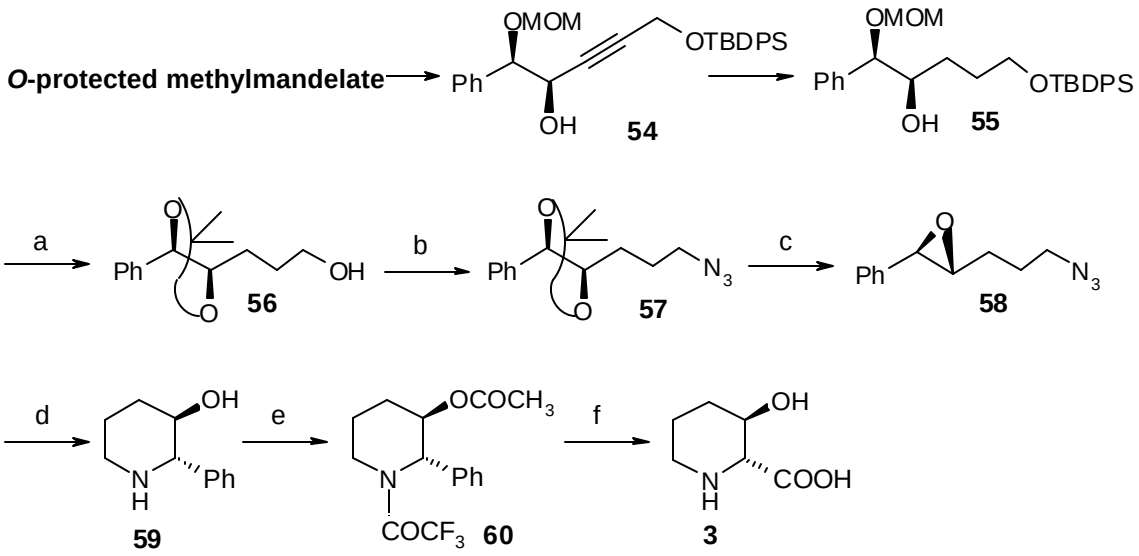
reagent to the chiral serinal obtained from **46**. Based on stereocontrolled analysis, a stereocontrolled reduction of piperidin-3-one **52** to *cis*-2,3-disubstituted piperidine **53** is also described.



Scheme 7 Reagent and Conditions: (a) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, Et_3N; (ii) 2-(2-Bromoethyl)-1,3-dioxolane, Mg, THF, 86% (b) (i) H_2, 10% Pd/C, 3 N HCl, THF : *t*-BuOH (1:1); (ii) Boc_2O, H_2O, dioxane, 1 N NaOH, 80% (c) TBDPSCl, DMF, imidazole (d) MOMCl, Hunig's base, CH_2Cl_2, reflux, 90% (e) HF (48%), Py, THF, 85% (f) (i) CrO_3/H_2SO_4 2.67 M, acetone, 0°C; (ii) 6 N HCl, 80°C, 2 h, 75% (g) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, Et_3N, 96% (h) $NaBH_4$, MeOH, 0°C, 88%

Haddad *et al.* (2001)[43] Scheme 8

Haddad *et al.* used *O*-protected methylmandelate as the starting material as chiral source for the enantioselective synthesis of trans-(2R, 3R)-3-hydroxypipecolic acid **3**. The synthesis involved a regioselective intramolecular nucleophilic substitution of an azido epoxide **58** as the key step.



Scheme 8 Reagent and Conditions: (a) (i) MeOH, HCl, rt, 90%; (ii) $CuSO_4$, acetone, PPTS, 92% (b) MsCl, Et_3N, DMAP; then NaN_3, DMF, 60°C, 82% (c) THF/10% HCl (2/1), reflux (12 h); then $MeC(OMe_3)$, Me_3SiCl (CH_2Cl_2/0°C) (d) PPh_3, H_2O, THF, 48 h, 38% (e) (i) $(CF_3CO)_2O$; (ii) K_2CO_3, THF; (iii) $(CH_3CO)_2$, Et_3N, 80% (f) (i) $RuCl_3.H_2O$, $NaIO_4$; (ii) K_2CO_3, MeOH, 60%

3.3 Present Work

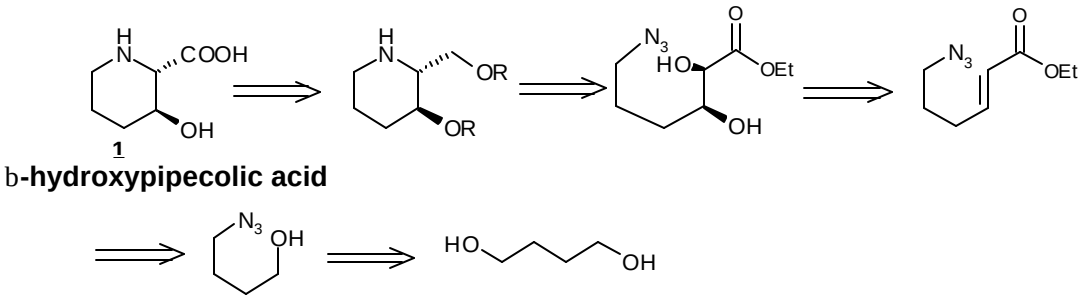
Objective:

3-Hydroxypipecolic acid, a six-membered cyclic α-amino-β-hydroxy acid, is an interesting target molecule since it may be seen as a conformationally constrained serine derivative or a hydroxylated homoproline, and may affect the physiological and pathological processes. Moreover the piperidine unit is found in a number of biologically important products. From a synthetic point of view, only few enantioselective synthesis of **1** or its enantiomer has been reported. Hence interest in newer synthetic methods with fewer steps goes unabated.

As seen from the literature, there are only one or two synthesis reported starting from achiral source, and also where the chirality was achieved by enzymatic resolution. Only one synthesis is reported where they have induced the chiral centre by asymmetric hydrogenation.[41]

Herein we have planned to synthesize the target compound **1**, employing the Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation as the key step and thereby inducing the desired chirality, starting from cheap achiral source.

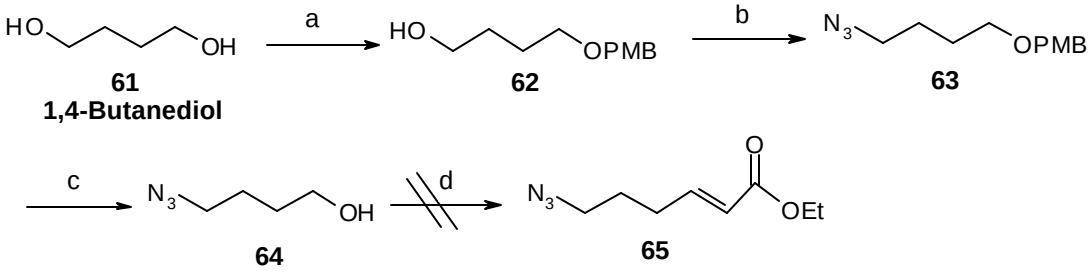
As seen from the retrosynthetic analysis (**Scheme 9**), the diol could be visualized as an important precursor for the syntheses of target molecule **1**, which in turn could be obtained from 1,4-butanediol, a cheap commercially available achiral source.



Scheme 9

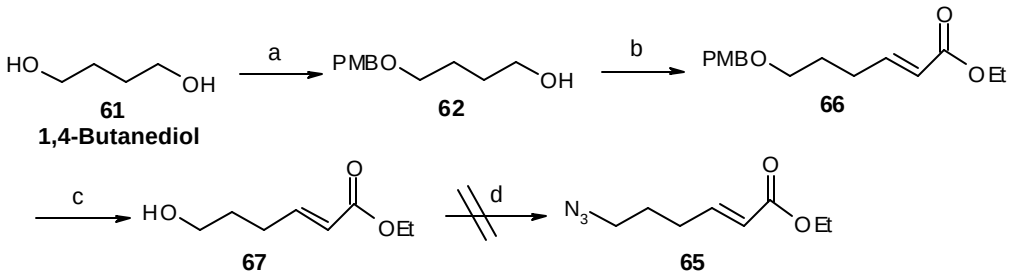
3.4 Results and Discussion

The synthetic approach for the target molecule **1** is depicted in **Scheme 10**. It was planned to synthesize azido olefin, a suitable precursor for the target molecule **1**. The mono protection of 1,4-butanediol **61** by *p*-methoxybenzyl chloride afforded the alcohol **62** in 80% yield. The ^{1}H NMR spectrum showed the singlet at δ 3.80 and δ 4.45 corresponding to the 4-methoxy and benzylic CH_2 group respectively. The primary hydroxyl group was then mesylated and further transformed into azido compound **63** in 82% yield. The IR spectrum showed the stretching at 2100 cm-1 which is characteristic of azide functionality. The p-methoxybenzyl group was then deprotected using DDQ to obtain the azido alcohol **64**. The free hydroxyl group of **64** was then oxidized using Swern oxidation to afford the aldehyde which was subsequently treated with two carbon Wittig ylide, however the desired azido olefin **65** could not be obtained. Instead a complex reaction mixture was obtained. The compound obtained after purification was found to be the addition product resulting through *in situ* 1,3-dipolar addition between the azide and olefin.



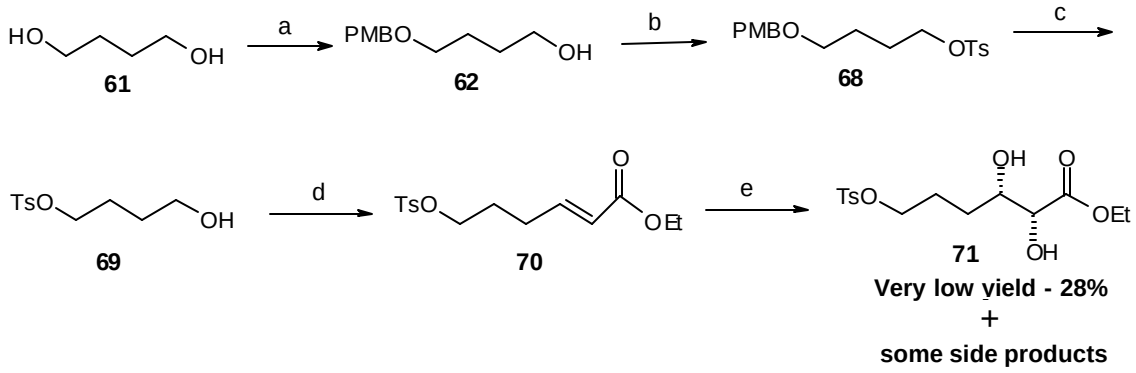
Scheme 10 Reagent and Conditions: (a) DMF, NaH, *p*-$OMeC_6H_4CH_2Br$, 80% (b) (i) MsCl, Et_3N, DMAP; then NaN_3, DMF, 60°C, 82% (c) DDQ, CH_2Cl_2, H_2O, 88% (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; then Et_3N (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux 4 h

In an alternative approach (**Scheme 11**), it was planned to prepare the olefinic ester and then transform the terminal hydroxyl group into azide moiety, but this also resulted into the complex reaction mixture which was thought to be the 1,3-dipolar addition product in accordance with the literature precedence.[44]



Scheme 11 Reagent and Conditions: (a) DMF, NaH, *p*-$OMeC_6H_4CH_2Br$, 80% (b) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; then Et_3N (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux 4 h, 80% (c) DDQ, CH_2Cl_2, H_2O, 88% (d) (i) MsCl, Et_3N, DMAP; then NaN_3, DMF, 60°C

Since we failed in our attempt to obtain the azido olefin **65**, we thought of making the α,β-unsaturated ester **70** with a tosyl functionality which could further be easily manipulated into the target compound.

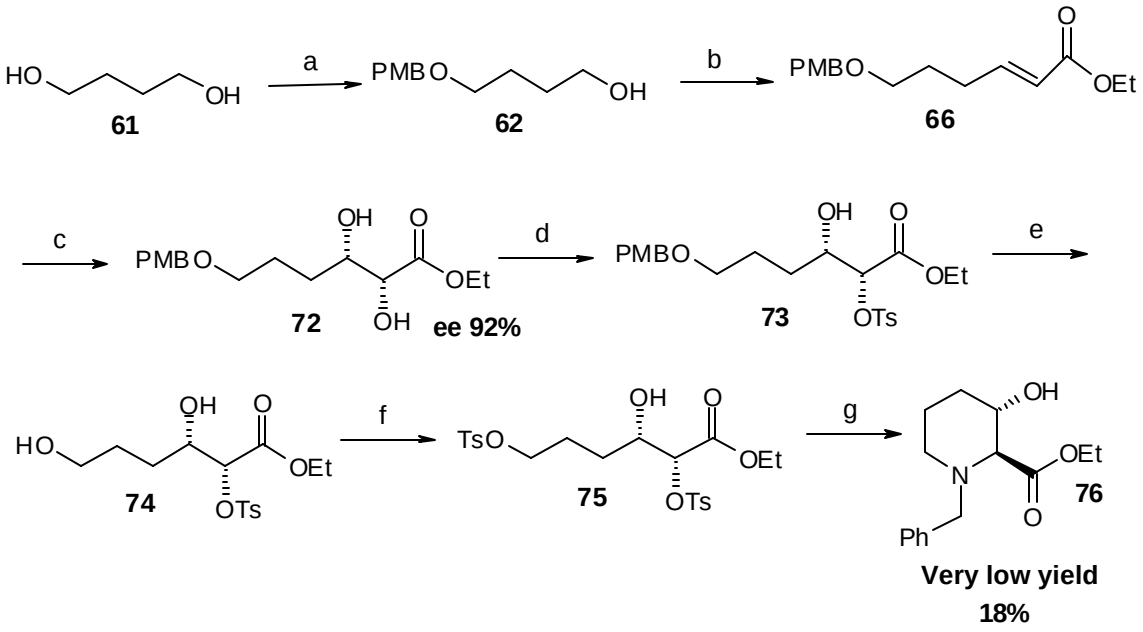


Scheme 12 Reagent and Conditions: (a) DMF, NaH, *p*-$OMeC_6H_4CH_2Br$, 80% (b) *p*-TsCl, Et_3N, CH_2Cl_2, 90% (c) DDQ, CH_2Cl_2, H_2O, 88% (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; then Et_3N (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux 4 h, 80% (e) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.4 mol%), *t*-BuOH:H_2O (1:1)

As depicted in **Scheme 12**, the free hydroxyl group of compound **62** was converted into its tosyl derivative **68** by reaction with *p*-toulenesulfonyl chloride and triethyl amine as base in 90% yield. The IR spectrum showed absence of hydroxyl group. The ^1H NMR spectrum gave the methyl of toluyl group at δ 2.3 (singlet). The *p*-methoxybenzyl group of compound **68** was deprotected to yield alcohol **69** with the tosyl functionality. The alcohol

69 was then subjected to Swern oxidation to afford the aldehyde which was subsequently transformed into α,β-unsaturated olefin **70**. The IR spectrum showed stretching at 1724 cm^{-1} for α,β-unsaturated olefinic ester, the olefin C=C stretch at 1654 cm^{-1} and the absence of hydroxyl absorption at 3400 cm^{-1}. The ^1H NMR spectrum gave the olefinic protons at δ 5.84 (doublet) and 6.98 (doublet of triplet) with a coupling constant *J* = 15 Hz indicating *trans*-olefin. The olefin **70** was then subjected to Sharpless asymmetric dihydroxylation reaction to afford the diol **71** in a low yield (28%) along with side product which was assumed to be the pyran derivative (no proper interpretation by ^1H NMR). Due to the difficulty faced in the main dihydroxylation step, this scheme was further abandoned.

In order to overcome the problem, we thought of subjecting the olefin to AD reaction without an azide or tosyl functionality. As shown in **Scheme 13**, the olefin **66**, obtained from 1,4-butanediol **61** was subjected to Sharpless asymmetric dihydroxylation using $(DHQ)_2PHAL$ ligand to afford the diol **72** in 85% yield and 88% ee. The IR spectrum showed a strong band at 3440 cm^{-1} indicating hydroxyl groups and absence of 1654 cm^{-1} corresponding to C=C stretch. The ^1H NMR spectra showed the absence of olefinic protons and the presence of newly generated two hydroxyl group at δ 3.91 (doublet) and 4.06 (multiplet). The corresponding carbons appeared at δ 72.12 and 73.41 in the ^{13}C NMR spectrum. The diol **72** was then regioselectively tosylated at α-position using *p*-toluenesulfonyl chloride and triethyl amine as base to afford the α-tosylated compound **73** in 70% yield. The ^1H NMR spectrum gave the CH_3 protons of toluyl group at δ 2.43 (singlet) and the orthocoupled doublet at δ 7.32 and δ 7.83 for *p*-toluyl group. The p-methoxybenzyl group of compound **73** was then deprotected using DDQ to afford the diol **74** in 92% yield. The ^1H NMR spectrum showed the absence of protons at δ 4.44 (singlet) corresponding to the benzylic CH_2 group. The primary hydroxyl group of compound **74** was transformed into tosyl derivative to yield the di-tosylated intermediate **75** in 78% yield.

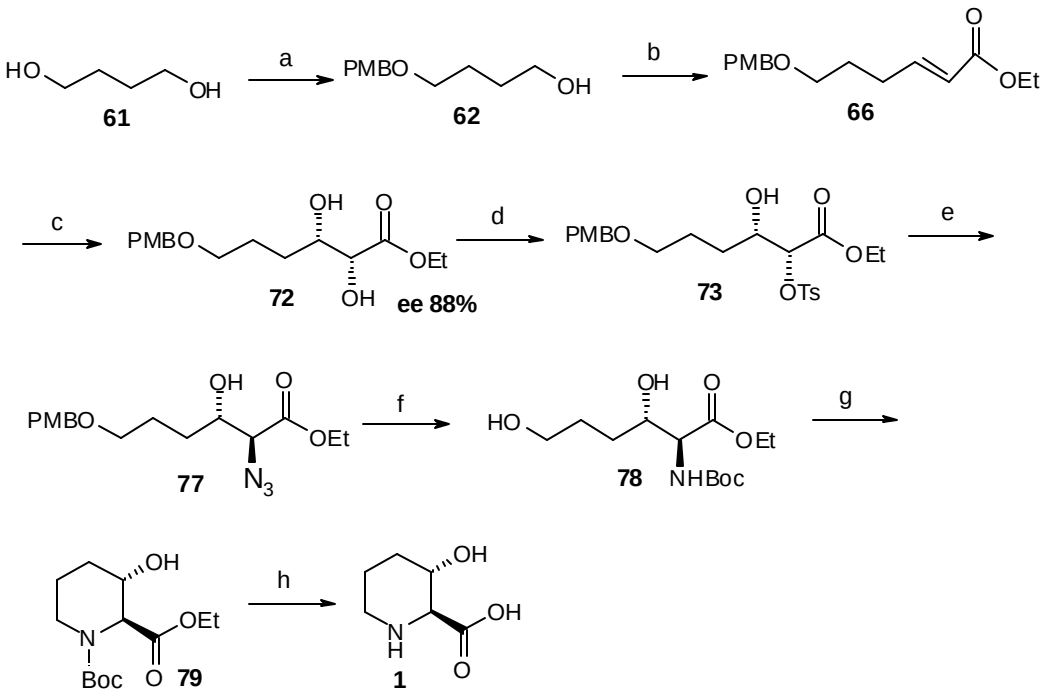


Scheme 13 Reagent and Conditions: a) DMF, NaH, *p*-$OMeC_6H_4CH_2Br$, 80% (b) (i) PCC, NaOAc, celite, CH_2Cl_2, 0°C (ii) $Ph_3P{=}CHCO_2Et$, benzene, rt, 24 h, 80% (c) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.4 mol%), *t*-BuOH:H_2O (1:1), 85% (d) *p*-TsCl, Et_3N, CH_2Cl_2, 0°C, 30 h, 70% (e) DDQ, CH_2Cl_2, H_2O, 92% (f) *p*-TsCl, Et_3N, CH_2Cl_2, 0°C, 8 h, 78% (g) $C_6H_5NH_2$, $C_6H_5CH_3$, HMPA, reflux, 35 h, 18%

Compound **75** was then treated under reflux conditions with benzyl amine in the presence of HMPA (catalytic) in toluene to afford the cyclized intermediate **76** in poor yield (18%). The reason behind the poor yield could perhaps be attributed to the displacement of only one tosyl group by benzyl amine resulting into the monobenzylated intermediate which was less reactive towards the displacement of other tosyl functionality. So to improve the yields, we thought of altering the synthetic sequence and modify the scheme in following manner.

Instead of introducing the amino functionality at the later stage, it would be appropriate to bring in the amino group earlier. We therefore thought of converting the tosyl group of **73** (**Scheme 13**) into azido moiety so as to introduce the amino group early in the synthesis.

So, according to the modified strategy compound **73** was first subjected to the nucleophilic displacement by azide to afford the azido compound **77** in 80% yield (**Scheme 14**).

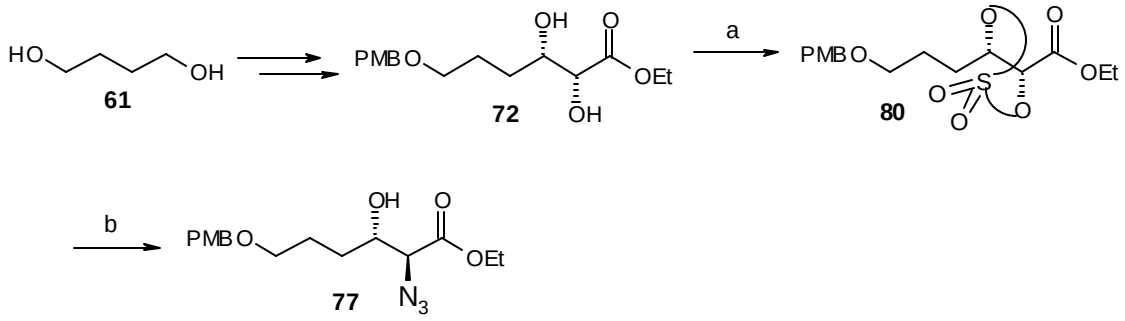


Scheme 14 Reagent and Conditions: a) DMF, NaH, *p*-$OMeC_6H_4CH_2Br$, 80% (b) (i) PCC, NaOAc, celite, CH_2Cl_2, 0°C (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux 4 h, 80% (c) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.4 mol%), *t*-BuOH:H_2O (1:1), 85% (d) *p*-TsCl, Et_3N, CH_2Cl_2, 0°C, 30 h, 70% (e) NaN_3, DMF, 80°C, 80% (f) (i) DDQ, CH_2Cl_2, H_2O; (ii) H_2/Pd-C, Boc_2O, EtOAc, 70% (g) MsCl, Et_3N, CH_2Cl_2, -78°C, 95% (h) (i) $LiOH.H_2O$, THF, MeOH, H_2O, 6 h (ii) TFA: CH_2Cl_2 (1:1), 1.5 h; then Dowex 50, 90%

The IR spectrum showed the N≡N stretch at 2100 cm^{-1}. In the ^1H NMR spectrum there was no protons corresponding to toluyl group at δ 2.43 (singlet) and also there were no orthocoupled doublet corresponding to protons of the aromatic ring of the toluyl group indicating the absence of *p*-tosyl group in the compound **77**. The azide functionality of compound **77** was reduced to amino functionality under hydrogenation conditions on Pd/C and subsequently *in situ* protected with di-*tert*-butyl pyrocarbonate. The *p*-methoxybenzyl group was subsequently deprotected with the help of DDQ in dichloromethane to afford the amino diol **78**. The IR spectrum showed the amide carbonyl stretch at 1722 cm^{-1} and absence of 2100 cm^{-1} peak corresponding to N≡N stretch. The ^1H NMR spectrum showed the presence of CH_3 protons of Boc group at δ 1.44 (singlet) and the absence of benzylic CH_2 protons, the orthocoupled doublet of the p-methoxybenzyl group at δ 4.44 (singlet)

and δ 6.87 & δ 7.25. The main goal now left to be achieved was to cyclize the compound **78** to the desired target compound **1**. The compound **78** was mesylated and *in situ* cyclised in the presence of triethyl amine as base at -78°C to afford the desired compound **79** in 95% yield. Compound **79** was then transformed into the desired target compound, 3-hydroxypipecolic acid **1** by hydrolyzing the ester group with the help of $LiOH.H_2O$, in THF/H_2O followed by deprotection of the Boc group with trifluoroacetic acid. The spectral data for this compound were in agreement with the reported data.[32] Thus, the synthesis of 3-hydroxy pipecolic acid was achieved by employing Sharpless asymmetric dihydroxylation as the key step.

In order to improve the yield of azido compound **77**, we adopted a different approach as illustrated in **Scheme 15**.The synthesis of the azide compound **77** was achieved by means of regioselective opening of cyclic sulfate by azide instead of the nucleophilic displacement of tosyl. Thus, the diol **72** was first converted into its cyclic sulfite derivative **80** in 92% yield by treatment with $SOCl_2$ and Et_3N, which was further oxidized using $NaIO_4$ and a catalytic amount of $RuCl_3.H_2O$ to give the cyclic sulfate **80** in 92% yield.

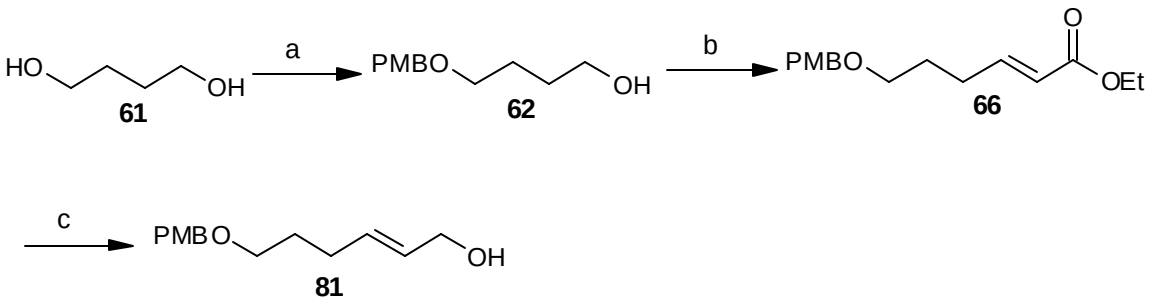


Scheme 15 Reagent and Conditions: a) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 20 min; (ii) $RuCl_3.H_2O$, $NaIO_4$, CCl_4:CH_3CN:H_2O (1:1:1.5), 0°C, 2 h, 92% (b) NaN_3, DMF, 80°C, 94%

The IR spectrum showed the absence of hydroxyl group. The regioslective opening of cyclic sulfate **80** was achieved by treating with NaN_3 in DMF as solvent and heating at 80°C to afford the azide **77** in 94% yield. So there was considerable improvement in the yield of the azido compound **77** with the shorter reaction time (2 h), as compared to the formation of the tosyl compound **73** which took more than 30 h to complete the reaction.

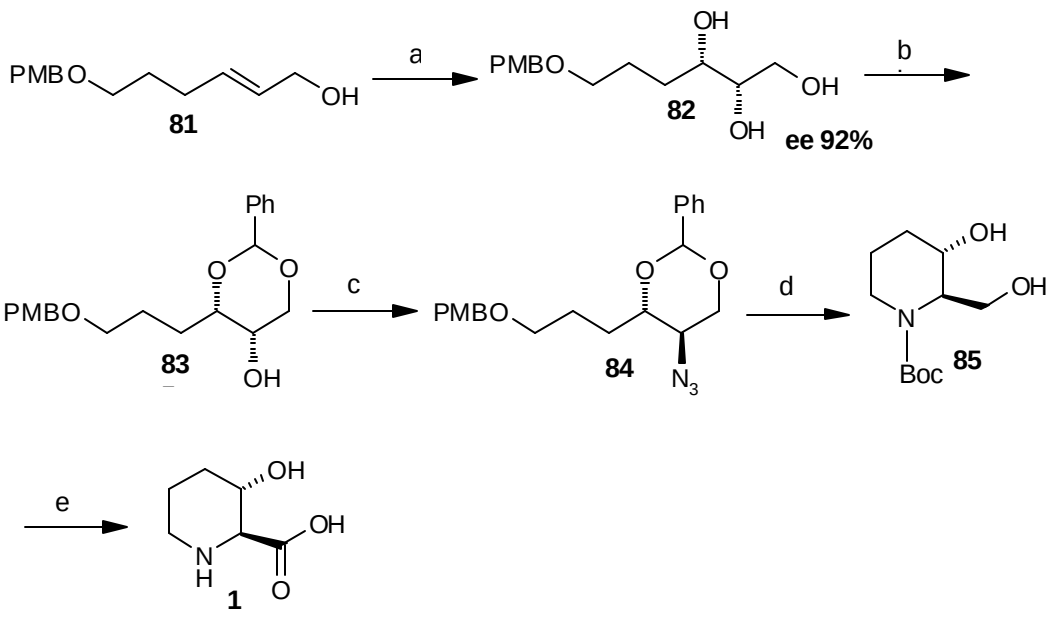
Our next objective was to synthesise 3-hydroxypipecolic acid **1** in pure enantiomerically form by enhancing the enantiomeric excess of the diol resulting from the reaction of Sharpless asymmetric dhihydroxylation. It is well known in literature that the Sharpless asymmetric dhydroxylation on allylic alcohols results in high enantiomeric excess in comparison with α,β-unsaturated esters, therefore we thought of employing the AD reaction on allylic alcohol system for the synthesis of 3-hydroxypipecolic acid.

As depicted in **Scheme 16**, the allylic alcohol **81** was prepared by reduction of the α,β-unsaturated ester **66** by the treatment with DIBAL-H in CH_2Cl_2 at -78°C. The IR spectrum showed the presence of hydroxyl group at 3408 cm^{-1} and the absence of carbonyl functionality at 1724 cm^{-1}. The ^1H NMR spectrum showed the allylic protons at δ 5.67 (multiplet) and the absence of the triplet and quartet corresponding to the ester group.



Scheme 16 Reagent and Conditions: a) (i) a) DMF, NaH, *p*-$OMeC_6H_4CH_2Br$, 80% (b) (i) PCC, NaOAc, celite, CH_2Cl_2, 0°C (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux 4 h, 80% (c) DIBAL-H, CH_2Cl_2, 0°C, 80%

As shown in **Scheme 17**, the Sharpless asymmetric dihydroxylation was then carried out on the allylic alcohol **81** using $(DHQ)_2PHAL$ to afford the triol **82** in 70% yield and 92% ee. The IR spectrum showed intense absorption of hydroxyl group at 3389 cm^{-1}. The ^1H NMR spectrum showed the absence of allylic protons at δ 5.67.



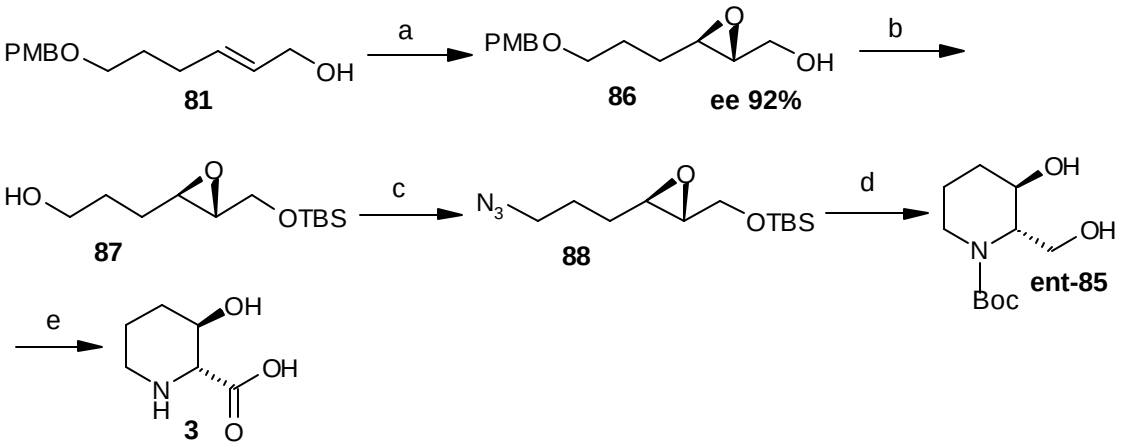
Scheme 17 Reagent and Conditions: a) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.4 mol%), *t*-BuOH:H_2O (1:1), 70% (b) $C_6H_5CH(OMe)_2$, CH_2Cl_2, , TsOH, rt, 85% (c) (i) MsCl, Et_3N, CH_2Cl_2, 0°C; (ii) NaN_3, DMF, 60°C, 80% (d) (i) DDQ, CH_2Cl_2, H_2O; (ii) MsCl, Et_3N, CH_2Cl_2, -78°C (iii) H_2/Pd-C, MeOH, then Boc_2O, 59%, 3 steps (e) Ref. 39

The triol **82** was transformed into 1,3-benzylidene protected alcohol **83** with the use of benzaldehyde dimethylacetal in 85% yield. The ^{1}H NMR spectrum showed the presence of benzylic CH proton at δ 5.56 (singlet). The enantiomeric excess was determined by converting the free secondary hydroxy group of **83** into its Mosher's derivative and thus determining the ee from ^{19}F NMR spectrum which was found to be 92%. The free hydroxy group of **83** was then mesylated, and subjected to nucleophilic azide displacement to afford compound **84** in 80% yield. The IR spectrum showed the azide stretch at 2100 cm^{-1} and the absence of hydroxyl absorption.

The *p*-methoxybenzyl group of **84** was then deprotected, and the free hydroxy group thus obtained was mesylated and subjected to the reductive ring closure, cleavage of benzylidene group and *in situ* Boc protection of the free amine resulted into 4-deoxyfagomine **85** in 59% yield. The IR spectrum showed the hydroxyl absorption at 3478 cm^{-1}. The compound **85** was then transformed into the desired target compound **1**

using the literature method.[39] The physical and spectroscopic data of **1** were in full agreement with the literature.[36]

As illustrated in **Scheme 18**, 3-hydroxypipecolic acid **1** was also prepared employing the Sharpless asymmetric epoxidation of the allylic alcohol **81** as the key step. The ^{1}H NMR spectrum of **86** showed the epoxy protons at δ 3.45 and δ 3.69.



Scheme 18 Reagent and Conditions: a) Ti(*i*-OPr)$_4$, (+)-DIPT, TBHP, CH_2Cl_2, -78^{o}C, 67% (b) (i) TBDMSCl, imidazole, CH_2Cl_2, 0^{o}C; (ii) DDQ, CH_2Cl_2, H_2O, 90% 2 steps (c) (i) MsCl, Et_3N, CH_2Cl_2, 0^{o}C; (ii) NaN_3, DMF, 60^{o}C, 81%, 2 steps (d) Ph_3P, THF:H_2O (1:1), rt, 48 h; then Boc_2O, 48% (e) Ref. 39

The epoxide **86** obtained in 66% yield, and 92% ee[45] as a result of Sharpless asymmetric epoxidation of allylic alcohol **81** was transformed into compound **87** by first TBS protection of the allylic hydroxy group and then subsequent deprotection of the *p*-methoxybenzyl group. The ^{1}H NMR spectrum showed the absence of protons at δ 4.44 (singlet) corresponding to the benzylic CH_2 group and the presence of the protons at δ 0.08 and δ 0.90 corresponding to the *tert*-butyldimethylsilyl chloride. The resultant alcohol **87** was then mesylated and subjected to nucleophilic azide displacement to furnish **88** in 81% yield. The IR spectrum showed the azide stretch at 2100 cm^{-1} and the absence of hydroxyl absorption. The compound **88** was treated with triphenyl phosphine in the presence of water, resulting in the azide reduction followed by subsequent epoxide ring opening by the amine and in situ cyclization and Boc protection to afford the

deoxyfagomine **ent-85** in 48% yield. The subsequent conversion to the target compound **3** is already reported in the literature.[39]

3.5. Conclusion

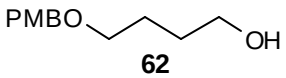
In conclusion, an asymmetric synthesis of both the enantiomers of 3-hydroxypipecolic acid has been realized using the Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation as the source of chirality for the first time. We have successfully employed the chemistry of regioselective α-tosylation, cyclic sulfites/sulfates, the cyclic 1,3-benzylidene or the regioselective intramolecular nucleophilic substitution of an azido epoxide to achieve the required stereochemistry of the C-2 centre of 3-hydroxypipecolic acid. The merits of this synthesis are high-yielding reaction steps, high enantioselectivity and various possibilities available for structural modifications. The other enantiomer could be synthesized via β-dihydroxylation of olefin and following the reaction sequence as discussed above.

3.6. Experimental section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC or otherwise indicated. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

Preparation of 4-(4-methoxybenzyloxy)-butan-1-ol, 62



62

To a solution of 1,4-butanediol **61** (5.0 g, 55.48 mmol) in dry THF (100 mL) was added sodium hydride (50%, 4.80 g, 100 mmol) at 0°C. The reaction mixture was then stirred at room temperature for 1 h after which it was again cooled to 0°C. To this was added slowly *p*-methoxybenzyl bromide (14.5 g, 72.14 mmol). The reaction mixture was then brought to 0°C and quenched with addition of cold water. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether : EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **62** (9.32 g) as a yellow colored oil.

Yield:- 9.32 g, 80%

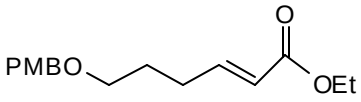
IR ($CHCl_3$, cm^{-1}): ν_{max} 1097, 1174, 1248, 1513, 1612, 2863, 2937, 3400

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64-1.71 (m, 4 H), 3.49 (t, 2 H, *J* = 5 Hz), 3.62 (t, 2 H, *J* = 5 Hz), 3.80 (s, 3 H), 4.45 (s, 2 H), 6.88 (d, 2 H, *J* = 10 Hz), 7.26 (d, 2 H, *J* = 10 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.36, 29.57, 55.17, 62.28, 69.98, 72.54, 113.80, 129.31, 130.34, 159.22

Anal. Calcd. for $C_{12}H_{18}0_3$: C, 68.54; H, 8.63 Found: C, 68.44; H, 8.61.

Synthesis of 6-(4-Methoxybenzyloxy)-hex-2-enoic acid ethyl ester, 66



66

To a ice cold solution of pyridine chlorochromate (15.40 g, 71.44 mmol), sodium acetate (1.953 g, 23.8 mmol) and celite (20 g) in CH_2Cl_2 (100 mL) was added the alcohol **62** (10 g, 47.62 mmol) in CH_2Cl_2 (30 mL) dropwise. The reaction mixture was then stirred for 6 h at room temperature after which it was filtered through sintered funnel. The residue was washed with Et_2O (3 x 100 mL) and the filtrate concentrated in vacuo to give the residual oil. Flash silica gel column chromatography using petroleum ether : EtOAc (9 : 1) as

eluent gave the aldehyde (7.9 g, 70.70%), which was used as such for the next step without purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (12.93 g, 37.152 mmol) in dry benzene (100 mL) was added a solution of the above aldehyde in dry benzene (50 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether : EtOAc (8.5 : 1.5) as eluent to afford the α,β-unsaturated olefin **66** (8.47 g) as a pale yellow liquid.

Yield:- 8.47 g, 80%

IR ($CHCl_3$, cm^{-1}): ν_{max}1038, 1100, 1204, 1300, 1654, 1724, 2858, 2956

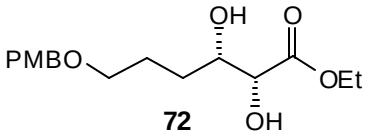
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31(t, 3 H, *J* = 8 Hz), 1.75-181 (m, 2 H), 2.31 (q, 2 H, *J* = 7 Hz), 3.48 (t, 2 H, *J* = 6Hz), 3.83 (s, 3H), 4.22 (q, 2 H, *J* = 8Hz), 4.45 (s, 2 H), 5.84 (d, 1 H, *J* = 15 Hz), 6.90 (d, 2H, *J* = 9 Hz), 7.00 (dt, 1 H, *J* = 10 Hz, 15 Hz), 7.28 (d, 2H, *J* = 9Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.34, 28.23, 28.99, 55.26, 60.19, 69.10, 72.66, 113.84, 121.70, 129.32, 130.55, 148.67. 159.26, 166.67

Mass (ESI): 279 (M+1), 241, 204, 121, 91

Anal. Calcd. for $C_{16}H_{22}0_4$: C, 69.04; H, 7.97, Found: C, 69.10; H, 7.75

Synthesis of (2*R*, 3*S*)-2,3-dihydroxy-6-(4-methoxybenzyloxy)-hexanoic acid ethlyl ester, 72



72

To a mixture of K_3FeCN_6 (17.75 g, 53.95 mmol), K_2CO_3 (7.44 g, 53.91 mmol), $(DHQD)_2PHAL$ (140 mg, 1 mol%, 0.179 mmol) in *t*-butanol / H_2O (1:1, 250 mL) at 0°C was added osmium tetroxide (0.72 mL, 0.4 mol%), followed by methane sulfonamide (1.71 g, 18.00 mmol). After stirring for 2 min at 0°C, the olefin **66** (5.0 g, 17.98 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 16 h. After completion of reaction, the mixture was quenched with sodium sulfite (12 g). The stirring was continued for

additional 30 min and then the solution was extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7:3) as eluent gave **72** (4.38 g) as a thick liquid.

Yield:- 4.38 g, 85%

$[\alpha]_D^{20}$:- -6.74 (c = 1.6, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1032, 1130, 1248, 1513, 1612, 1736, 2864, 2938, 3440

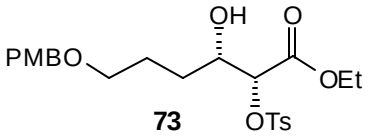
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, 3 H, *J* = 6 Hz), 1.73 (m, 4 H), 2.82 (brs, 2H), 3.49 (t, 2 H, *J* = 6 Hz), 3.80 (s, 3H), 3.91 (d, 1 H, *J* = 5 Hz), 4.06 (m, 1 H), 4.26 (q, 2 H, *J* = 5 Hz), 4.44 (s, 2 H), 6.87 (d, 2 H, *J* = 10 Hz), 7.25 (d, 2 H, *J* = 10 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.77, 25.69, 30.06, 42.58, 54.83, 61.21, 69.51, 72.12, 73.41, 113.48, 128.97, 130.14, 158.87, 173.21

Mass (ESI): 312 (M^+),

Anal. Calcd. for $C_{16}H_{24}0_6$: C, 61.52; H, 7.74 Found: C, 61.66; H, 7.70

Synthesis of (2*R*, 3*S*)-3-hydroxy-6-(4-methoxylbenzyloxy)-2-(toluene-4-sulfonyloxy)-hexanoic acid ethyl ester, 73



73

To a solution of **72** (3.0 g, 9.61 mmol) and Et_3N (1.65 g, 16.35 mmol) in CH_2Cl_2 (100 mL) at 0°C was added *p*-toluenesulfonyl chloride (1.83 g, 9.61 mmol). The reaction mixture was stirred at 0°C for 30 h. After the reaction was complete, water (30 mL) was added and the solution was extracted in CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (4:1) as eluent gave **73** (3.14g) as a pale yellow oil.

Yield:- 3.14 g, 70%

$[\alpha]_D^{20}$:- +2.87 (c = 1.08, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1367, 1722, 2870, 2941, 3441

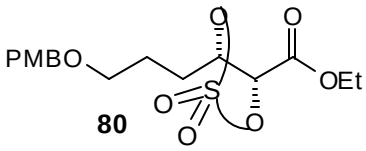
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (t, 3H, *J* = 5 Hz), 1.62-1.75 (m, 4H), 2.43 (s, 3H), 3.41-3.48 (m, 2H), 3.80 (s, 3H), 4.03 (m, 1H), 4.12 (q, 2H, *J* = 5 Hz), 4.44 (s, 2H), 4.83 (d, 1H, *J* = 7 Hz), 6.87 (d, 2H, *J* = 10 Hz), 7.25 (d, 2H, *J* = 10 Hz), 7.32 (d, 2 H, *J* = 8 Hz), 7.83 (d, 2 H, *J* = 8 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.78, 21.42, 25.65, 30.02, 55.11 61.73, 69.44, 71.23, 72.42, 80.19, 113.73, 128.05, 129.16, 129.65, 130.40, 131.55, 145.07, 159.13, 167.22

Mass (ESI): 484 ($M+NH4^+$), 364, 346, 230, 121

Anal. Calcd. for $C_{23}H_{30}0_8S$: C, 59.21; H, 6.48; S, 6.87 Found: C, 59.30; H, 6.50; S, 6.81

Synthesis of 5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dioxo-2λ^6-[1,3,2]-dioxathiiolane-4-carboxylic acid ethyl ester, 80



80

To a stirred solution of diol **72** (0.5 g, 1.60 mmol) in dry CH_2Cl_2 (7 mL) cooled at 0°C were added Et_3N (0.405 g, 0.6 mL, 4.0 mmol) and a solution of $SOCl_2$ (0.286 g, 0.2 mL, 2.40 mmol) in CH_2Cl_2 (7 mL) over a period of 10 min. Stirring was continued for 20 min at 0°C and then the solution was quenched by adding water (5 mL) followed by addition of CH_2Cl_2 (30 mL). The organic layer was separated, washed with cold water (2 × 10 mL), brine (20 mL), dried (Na_2SO_4) and filtered through a pad of silica gel. The filtrate was concentrated to give a yellow liquid. To this was added a cold solution of CCl_4 (4 mL) and CH_3CN (4 mL). The reaction flask was cooled in an ice bath and cold water (5 mL) was added. $RuCl_3.H_2O$ (5 mg) and $NaIO_4$ (0.5 g, 2.33 mmol) were added at once and the reaction mixture was stirred vigorously at 0°C. The progress of reaction was monitored by TLC. After 2 h, ether (20 mL) was added and the layers separated. The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and passed through a silica gel column. The filtrate was concentrated and the crude product was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to give **80** (0.55 g) as a yellow liquid.

Yield:- 0.55g, 92%

[a] $_D^{20}$:- -2.3 (c = 1.1, $CHCl_3$)

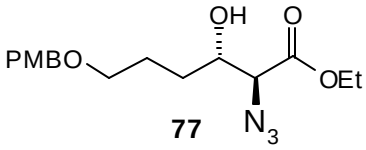
IR ($CHCl_3$) cm^{-1}: ν_{max} 1457, 2980, 3033

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, 3H, *J* = 6 Hz), 1.73-1.91 (m, 2H), 2.06-2.2 (m, 2H), 3.51-3.57 (m, 2H), 3.81 (s, 3H), 4.35 (q, 2H, *J* = 5 Hz), 4.51 (s, 2H), 4.89 (d, 1H, *J* = 8 Hz), 4.98-5.08 (m, 1H) 6.89 (d, 2H, *J* = 10 Hz), 7.27 (d, 2H, *J* = 10 Hz)

Mass (ESI): 392 ($M+NH_4^+$), 374 (M^+), 246, 230

Anal. Calcd. for $C_{16}H_{22}0_8S$: C, 51.33; H, 5.92; S, 8.56 Found: C, 51.30; H, 6.05; S, 8.81

Synthesis of 2-azido-3-hydroxy-6-(4-methoxybenzyloxy)-hexanoic acid ethyl ester, 77



77

A mixture of compound **73** (3.0 g, 6.43 mmol) and NaN_3 (1.674 g, 25.75 mmol) in DMF (20 mL) was heated at 60°C with vigorous stirring. After 6 h, the mixture was cooled to room temp. and the solvent removed in vacuo. To the residue was added water (10 mL), and solution was extracted in ether (3 x 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product with petroleum ether / EtOAc (6:1) as eluent gave **77** (1.736 g) as colorless oil.

Yield:- 1.736 g, 80%

[a] $_D^{20}$:- -24.41 (c = 1.00, $CHCl_3$)

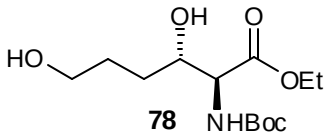
I.R. ($CHCl_3$) cm^{-1}: ν_{max} 1722, 2100, 2870, 2941, 3441

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (t, 3H, *J* = 6 Hz), 1.62-1.75 (m, 4H), 3.43-3.50 (m, 2H), 3.80 (s, 3H), 4.03 (m, 2H), 4.12 (q, 2H, *J* = 6 Hz), 4.44 (s, 2 H), 6.87 (d, 2 H, *J* = 10 Hz), 7.25 (d, 2 H, *J* = 10 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.78, 21.42, 25.65, 30.02, 55.11 61.73, 69.23, 69.44, 72.23, 113.73, 128.05, 130.40, 159.13, 167.22

Anal. Calcd. for $C_{16}H_{23}N_30_5$: C, 56.97; H, 6.82; N, 12.46 Found: C, 57.02; H, 6.90; N, 12.53

Synthesis of (2*S*, 3*S*)-2-tert-butoxycarbonylamino-3,6-dihydroxyhexanoic acid ethyl ester, 78



78

To a solution of compound **77** (1.5 g, 4.45 mmol) in CH_2Cl_2 (30 mL) and H_2O (1.2 mL) at 0^oC was added DDQ (1.11 g, 4.89 mmol) in portions. The resultant mixture was stirred at room temperature for 3 h and then sat. aq. $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (6 : 4) as eluent afforded azido alcohol (0.87 g, 90%) as pale yellow oil.

A mixture of above compound, Boc_2O (0.87 g, 0.40 mmol) and Pd-C (10 %, 80 mg) in 10 mL of EtOAc was hydrogenated (1 atm) for 20 h. The solid was removed by filtration, and the solution was concentrated in vacuo. Silica gel column chromatography of the crude product with petroleum ether / EtOAc (6:4) as eluent gave **80** as a pale yellow oil (0.907 g).

Yield:- 0.907 g, 70% (from **79**)

$[\alpha]_D^{20}$:- -10.74 (c = 1.00, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1711, 1736, 2935, 3431

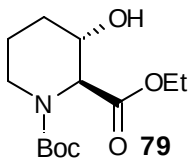
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* = 6 Hz), 1.42 (s, 9H), 1.69 (m, 4H), 3.66-3.75 (m, 3H), 3.94 (brs, 2H), 4.16-4.26 (m, 3H), 5.58 (brs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.08, 28.27, 29.97, 30.33, 58.67, 61.43, 62.16, 72.56, 80.17, 155.93, 170.80

Mass (ESI): 291(M^+), 203, 147

Anal. Calcd. for $C_{13}H_{25}N0_6$: C, 53.59; H, 8.65; N, 4.81 Found: C, 53.52; H, 8.55; N, 4.95

Synthesis of (2*S*, 3*S*)-3-hydroxypiperidine1,2-dicarboxylic acid-1-*tert*-butyl ester-2-ethyl ester, 79



79

To a stirred solution of diol **78** (0.500 g, 1.71 mmol) in CH_2Cl_2 (15 mL) was added MsCl (0.15 mL, 1.97 mmol) at -78°C. Et_3N (0.28 mL, 1.97 mmol) was added slowly over 10 min. After the mixture was stirred at -78°C for 1.5 h, aqueous NH_4Cl (2 mL) was added. The mixture was warmed to room temperature and diluted with CH_2Cl_2 (50 mL), washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product with petroleum ether / EtOAc (6:2) as eluent gave the product **79** as colorless oil (0.445 g).

Yield:- 0.445 g, 95%

$[\alpha]_D^{20}$:- -5.02 (c = 0.90, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1708, 1746, 2930, 2980, 3431

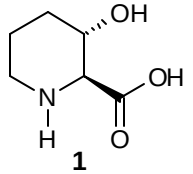
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 6 Hz), 1.46 (s, 9 H), 1.94 (m, 4H), 3.03-3.11 (m, 1 H), 4.23-4.34 (m, 4H), 4.63-4.68 (m, 1 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.16, 25.11, 27.14, 28.28, 52.2, 62.42, 69.11, 71.60, 80.54, 159.86, 168.46

Mass (ESI): 274 (M+1), 199, 129

Anal. Calcd. for $C_{13}H_{23}N0_5$: C, 57.13; H, 8.48; N, 5.12, Found: C, 57.33; H, 8.45; N, 4.96

Preparation of (2*S*, 3S)-3-hydroxypipecolic acid, 1



1

To a stirred solution of compound **79** (0.2 g, 0.73 mmol) in THF (6 mL), MeOH (2 mL) and water (2 mL) was added $LiOH.H_2O$ (0.092 g, 2.19 mmol) at room temperature. After

stirring for 5 h, the mixture was acidified by addition of $NaHSO_4$ (10%) to pH 3 and then extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na_2SO_4. After removal of solvent, the residue was dissolved in CH_2Cl_2 (4 mL) and TFA (4 mL) at 0°C. After the mixture was stirred at room temperature for 1.5 h, the solvent removed in vacuo. The residue was taken up in water (1 mL) and the resulting aqueous solution passed through a column (15 x 1 cm) of a strongly acidic ion exchange resin (Dowex 50 x 2, 100-200 mesh), eluting first with water (100 mL) and then with aqueous ammonium hydroxide (2M, 100 mL). The ammonia fraction was concentrated in vacuo, and the solid residue was recrystallized from EtOAc and EtOH (5:1); giving white solid **1** (0.095 g).

Yield:- 0.095 g, 90%

M.P.:- 232-236°C [Lit. [39] 230-238°C]

$[\alpha]_D^{20}$:- +13.5 (*c* 0.2, 10% aq.HCl) [Lit.[39], $[\alpha]_D^{20}$ = +12.9 (*c* 0.23, 10% aq.HCl)]

IR ($CHCl_3$, cm^{-1}): ν_{max} 2500, 2846, 2983, 3364

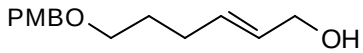
^{1}H NMR (200 MHz, D_2O): δ 1.62-1.66 (m, 2H), 1.89-1.93(m. 2H), 2.84-2.99 (m, 1H), 3.82-3.83 (m, 1H), 4.10-4.15 (m, 1H), 4.32 (brs, 1H)

^{13}C NMR (50 MHz, D_2O): δ 20.11, 29.90, 46.44, 62.01, 66.40, 176.40

Mass (ESI): 147 (M+2)

Anal. Calcd. for $C_6H_{11}N0_3$: C, 49.65; H, 7.64; N, 9.65, Found: C, 49.56; H, 7.61; N, 9.60

Synthesis of 6-(4-methoxybenzyloxy)-hex-en-1-ol, 81



81

To a solution of olefin **66** (3.0 g, 10.8 mmol) in CH_2Cl_2 (30 mL) at 0°C was added DIBAL-H (21.6 mL, 21.6 mmoL). The reaction mixture was then stirred for 1 h at room temperature. After the completion of reaction, the reaction mixture was cooled to 0°C and subsequently quenched with sat. solution of sodium potassium tartrate and stirring was continued for further 1 h. The precipitate formed was filtered and the filtratre concentrated. Silica gel column chromatography using petroleum ether : EtOAc (1:1) as eluent furnished allylic alcohol **81** (2.043 g).

Yield:- 2.043 g, 80%

IR ($CHCl_3$, cm^{-1}): ν_{max} 1612, 2860, 2935, 3408

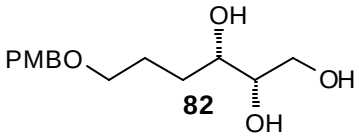
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68-1.74 (m, 2H), 2.15 (q, 2H, *J* = 7 Hz), 3.47 (t, 2H, *J* = 8Hz), 3.82 (s, 3H), 4.07 (d, 2H, *J* = 7 Hz), 4.45 (s, 2H), 5.63-5.72 (m, 2H), 6.90 (d, 2H, *J* = 10 Hz), 7.28 (d, 2H, *J* = 10 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 28.73, 29.07, 55.12 63.12, 69.27, 72.39, 113.70, 129.16, 129.61, 130.54, 131.68, 159.07

Mass (ESI): 237 (M+1), 219, 138, 121

Anal. Calcd. for $C_{14}H_{20}0_3$: C, 71.16; H, 8.53, Found: C, 71.10; H, 8.44

Synthesis of (2*S*, 3*S*)-6-(4-methoxybenzyloxy)-hexane-1,2,3-triol, 82



82

To a mixture of $K_3Fe(CN)_6$ (8.37 g, 25.44 mmol), K_2CO_3 (3.51 g, 25.44 mmol), $(DHQ)_2PHAL$ (66 mg, 1 mol%, 0.085 mmol) in *tert*-butanol / H_2O (1:1, 100 mL) at 0°C was added (0.1 M) OsO_4 (0.64 mL, 0.4 mol%), followed by methanesulfonamide (0.805 g, 8.47 mmol). After stirring for 2 min at 0°C, the allylic alcohol **81** (2.0 g, 8.47 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 18 h and then quenched with sodium sulfite (4 g). The stirring was continued for additional 30 min. and then the solution was extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (3 : 7) as eluent gave the triol **82** (1.6 g) as thick liquid.

Yield:- 1.6 g, 70.67%

$[\alpha]_D^{20}$: -5.39 (*c* 0.84, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 3389

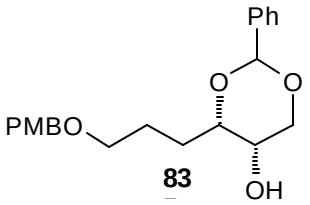
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64-1.78 (m, 4H), 3.07 (brs, 3 H), 3.48-3.54 (m, 2H), 3.67-3.71 (m, 4H), 3.81 (s, 3H), 4.46 (s, 2 H), 6.88 (d, 2H, *J* = 9Hz), 7.26 (d, 2H, *J* = 9 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.76, 30.02, 54.91 63.85, 69.84, 71.42, 72.17, 74.13, 113.49, 129.16, 129.03, 158.87

Mass (ESI): 270 (M^+), 234, 142, 91

Anal. Calcd. for $C_{14}H_{22}0_5$: C, 62.20; H, 8.20, Found: C, 62.28; H, 8.45

Synthesis of (2*S*, 3*S*)-4-[3-(4-methoxybenzyloxy) propyl]-2-phenyl-[1,3]dioxan-5-ol, 83



83

To a solution of triol **82** (1.5 g, 5.55 mmol) in dry CH_2Cl_2 (80 mL) was added p-TsOH (150 mg) and benzaldehyde dimethyl acetal (1.02 g, 6.7 mmol). The reaction mixture was stirred at room temperature overnight. Subsequently, it was neutralized with sat. aq. $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with aq. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (7 : 3) as eluent afforded 1,3-protected alcohol **83**, the major product (1.69 g) as pale yellow thick liquid.

Yield:- 1.69 g, 85%

$[\alpha]_D^{20}$: -7.40 (*c* 0. 4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1247, 1512, 1612, 1713, 2857, 2933, 3452

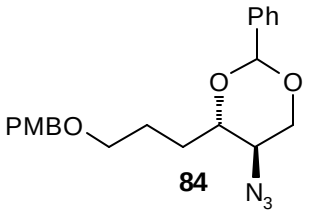
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75-.1.89 (m, 4H), 3.49-3.54 (m, 3H), 3.82 (s, 3H), 3.83 (m, 2H), 3.84-3.88 (m, 1H), 4.04-4.26 (m, 1H), 4.46 (s, 2H), 5.56 (s, 1H), 6.89 (d, 2H, *J* = 9 Hz), 7.28 (d, 2H, *J* = 9Hz), 7.39 (t, 3H, *J* = 8 Hz), 7.51 (d, 2H, *J* = 9Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.01, 25.88, 27.74, 54.92 65.03, 69.59, 72.25, 79.51, 100.93, 113.57, 125.81, 127.90, 128.54, 129.03, 130.08, 158.94

Mass (ESI): 376 ($M+NH_4^+$), 316, 279, 237, 183

Anal. Calcd. for $C_{21}H_{26}0_5$: C, 70.37; H, 7.31, Found: C, 70.31; H, 7.35

Synthesis of (2*R*, 3*S*)-5-azido-4-[3-(4-methoxybenzyloxy)propyl]-2-phenyl-[1,3]dioxane, 84



84

To a solution of 1,3-protected alcohol **83** (1.0 g, 2.79 mmol) in dry CH_2Cl_2 (30 mL) at 0^oC was added methanesulfonylchloride (0.48 g, 4.2 mmol), Et_3N (0.57 g, 5.63 mmol), and DMAP (cat). The reaction mixture was stirred at room temperature overnight and then poured into $Et_2O.H_2O$ mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to a yellow syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (30 mL) was added sodium azide (1.36 g, 20.95 mmol) and the reaction mixture was stirred at 80^oC for 24 h. It was then cooled and poured into water and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (8 : 2) as eluent furnished the azide **84** (0.86 g) as pale yellow oil.

Yield:- 0.86 g, 80.3%

[α]$_D^{20}$: - 6.32 (*c* 1.32, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): ν_{max} 2100, 2882, 2940, 3338

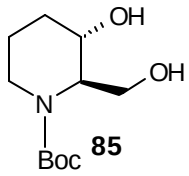
^{1}H NMR (500 MHz, $CDCl_3$): δ1.72-.1.89 (m, 4H), 3.42-3.56 (m, 4H), 3.73 (s, 3H), 3.75-3.98 (m, 1H), 4.18-4.24 (m, 1H), 4.46 (s, 2H), 5.57 (s, 1H), 6.89 (d, 2H, *J* = 9 Hz), 7.26-7.28 (m, 2H), 7.40 (t, 3H, *J* = 9 Hz), 7.50 (d, 2H, *J* = 9Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.23, 27.62, 29.31, 51.64, 54.97, 63.44, 66.78, 69.04, 72.39, 77.99, 103.92, 113.66, 126.28, 128.20, 129.09, 129.29, 130.40

Mass (ESI): 383 (M^+), 370, 356, 279, 234, 204, 161, 149

Anal. Calcd. for $C_{21}H_{25}N_30_4$: C, 65.78; H, 6.57; N, 10.96, Found: C, 65.84; H, 6.55; N, 11.02

Synthesis of (2*R*, 3*S*)-3-hydroxy-2-hydroxymethylpiperidine-1-carboxylic acid *tert*-butyl ester, 85



85

To a solution of azide **84** (1.0 g, 2.61 mmol) in CH_2Cl_2 (30 mL) and H_2O (1.2 mL) at 0°C was added DDQ (0.652 g, 2.87 mmol) in portions. The resultant mixture was stirred at room temperature for 3 h and then sat. aq. $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (6 : 4) as eluent afforded the azido alcohol (0.62 g, 90.37%) as pale yellow oil.

To a solution of azido alcohol (0.5 g, 1.90 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonyl chloride (0.33 g, 2.89 mmol), Et_3N (0.385 g, 3.8 mmol) and DMAP (cat). The reaction mixture was stirred at room temperature overnight and poured into $Et_2O.H_2O$ mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3x 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to a syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in methanol was added 10% Pd/C (10 w/w, 80 mg). The reaction mixture was stirred for 30 h under H_2 (1 atm). *tert*-Butyl dicarbonate (0.54 g, 2.47 mmol) was added to the resultant mixture and stirring was continued for additional 12 h. The reaction mixture was filtered through celite pad and the filtrate concentrated. Silica gel column chromatography of the residue using $CHCl_3$: MeOH (19:1) as eluent furnished deoxyfagomine **85** (0.255 g) as a thick syrupy liquid.

Yield:- 0.255 g, 59 %

$[\alpha]^{25}_D$:- +5.2 (*c* 0.25, MeOH);

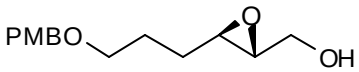
IR ($CHCl_3$, cm^{-1}): ν_{max} 1675, 2854, 2987, 3359, 3478

^{1}H NMR (500 MHz, $CDCl_3$ + $DMSOD_6$): δ 1.46 (s, 9H), 1.73-1.81 (m, 4H), 2.98-3.01 (m, 1H), 3.32-3.38 (m, 1H), 3.45-3.53 (m, 1H), 3.67-3.71 (m, 2H), 3.91-3.95 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$ + $DMSOD_6$): δ 20.11, 28.55, 29.22, 32.62, 42.12, 62.31, 63.99, 80.80, 156.49

Anal. Calcd. for $C_{11}H_{21}N0_4$: C, 57.12; H, 9.15; N, 6.06, Found: C, 57.23; H, 9.18; N, 6.27

Synthesis of (2*R*, 3*R*)-{3-[3-(4-methoxybenzyloxy)-propyl]-oxiranyl}-methanol, 86



86

To a solution of Ti(O-*i*-Pr)$_4$ (4.336 g, 5.25 mmol) in CH_2Cl_2 (40 mL) at –20^{o}C was added (+) DIPT (4.47 g, 19.08 mmol). After stirring for 10 min., the allylic alcohol **81** (3.0 g, 12.71 mmol) was added. After stirring for 20 min. at –20^{o}C, *t*-BuOOH (5.0 M in decane, 5.1 mL, 2.29 g, 25.43 mmol) was added and the reaction mixture was stirred for 20 h at –20^{o}C. The resultant mixture was then quenched by addition of sat. aq. $NaHCO_3$ (40 mL) and Et_2O (80 mL), and stirred for 1 h at room temperature after which it was filtered through a pad of celite. The filtrate was diluted with Et_2O (80 mL) and stirred for 20 min. with 1 M NaOH (50 mL). The phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography using petroleum ether : EtOAc (1:1) as eluent afforded the epoxide **86** (2.11 g) as a colorless oil.

Yield:- 2.11 g, 66.62%

[a] $_D^{20}$: +21.49 (*c* = 1, $CHCl_3$) [Lit.[23] [α] $_D^{29}$ **:** +21 (*c* = 2.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1578, 1684, 2856, 2924, 3458

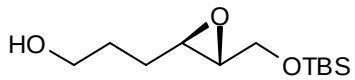
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76-2.05 (m, 4H), 3.47 (q, 1H, *J* = 5 Hz), 3.68-3.78 (m, 3H), 3.81 (s, 3H), 3.86 (q, 2H, *J* = 10 Hz), 3.95 (q, 1H, *J* = 5 Hz), 4.60 (s, 2H), 6.89 (d, 2H, *J* = 10 Hz), 7.28(d, 2H, *J* = 10 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.47, 27.51, 54.83 61.99, 67.87, 72.03, 80.43, 113.70, 129.18, 130.37, 131.68, 158.93

Mass (ESI): 252 (M^+), 230, 200, 121

Anal. Calcd. for $C_{14}H_{20}0_4$: C, 66.65; H, 7.99, Found: C, 66.60; H, 8.00

Synthesis of (2*R*, 3*R*)-3-[3- *(tert*-butyldimethylsilanyloxymethyl) oxiranyl]-propan-1-ol, 87



87

To a ice cold solution of Et_3N (1.45 g, 14.33 mmol) in CH_2Cl_2 (40 mL) was added DMAP (cat) and TBDMSCl (1.8 g, 11.94 mmol). After 5 min., the epoxide **86** (2.0 g, 7.94 mmol) in CH_2Cl_2 (10 mL) was added. The resultant mixture was stirred at room temperature for 10 h, and then poured into sat. aq. $NaHCO_3$ and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography by using using petroleum ether : EtOAc (9:1) furnished TBS protected epoxide (2.61 g, 90%) as a colorless oil.

To a solution of TBS protected epoxide (2.0 g, 5.46 mmol) in CH_2Cl_2 (40 mL) and H_2O (2.0 mL) at 0^oC was added DDQ (1.364 g, 60.08 mmol) in portions. The resultant mixture was stirred at room temperature for 3 h and then sat. aq. $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue by using petroleum ether : EtOAc (3 :1) furnished epoxide alcohol **87** (1.21 g, 90%) as a pale yellow oil.

Yield:- 1.21 g, 90%

$[\alpha]_D^{20}$: +13.97 (c = 0.46, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1604, 1686, 2874, 2932, 3412

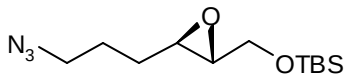
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6 H), 0.90(s, 9 H), 1.89-1.97 (m, 4H), 3.21 (brs, 1H), 3.60-3.85 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.70, 18.00, 25.47, 25.60, 26.78, 64.54, 67.96, 73.04, 78.89

Mass (ESI): 264 ($M+NH4^+$), 254, 230, 200, 121

Anal. Calcd. for $C_{12}H_{26}0_3Si$: C, 58.49; H, 10.63; Si, 11.40 Found: C, 58.52; H, 10.59; Si, 11.30

Synthesis of (2*R*, 3*R*)-[3-(3-azidopropyl)-oxiranyl]methanol, 88



88

To a solution of the epoxide **87** (0.750 g, 3.05 mmol) in CH_2Cl_2 (30 mL) at 0°C was added Et_3N (0.617 g, 6.097 mmol) and methanesulfonyl chloride (0.524 g, 4.574 mmol). The resultant mixture was stirred overnight at room temperature and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to yellow oil which was used as such for the next step.

To the solution of above mesylate in dry DMF (20 mL) was added sodium azide (1.0 g, 15.4 mmol) and the reaction mixture was stirred at 70°C overnight. The solution was then cooled to room temperature and then poured into $Et_2O.H_2O$ (50 mL 1:1). The phases were separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with H_2O, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue by using petroleum ether : EtOAc (7 :3) afforded azido epoxide **88** (0.9 g) as a pale yellow oil.

Yield:- 0.9 g, 81.82%

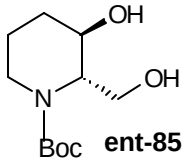
$[\alpha]_D^{20}$:- +11.15 (*c* = 0.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1225, 1347, 2100, 2836, 2953

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.72-2.07 (m, 4H), 3.48-3.49 (m, 2H) 3.79 (m, 4H)

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.70, 18.00, 25.47, 26.17, 28.86, 52.44, 64.46, 68.83, 79.10

Synthesis of (2*S*, 3*R*)-3-hydroxy-2-hydroxymethylpiperidine-1-carboxylic acid *tert*-butyl ester, ent-85



ent-85

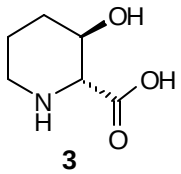
To a solution of azido epoxide **88** (0.500 g, 1.85 mmol) in THF (9 mL) and H_2O (1 mL) was added triphenyl phosphine (0.73 g, 2.783 mmol). The reaction mixture was stirred at room temperature for 48 h after which tert-butyl dicarbonate (0.48 g, 2.21 mmol) and sodium hydroxide (0.09 g, 2.25 mmol) was added and the stirring was continued for additional 12 h The reaction mixture was neutralized by addition of 10% solution of $KHSO_4$ and diluted with CH_2Cl_2. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. To this crude product in THF (10 mL) was added TBAF (0.8 mL, 1.0 M in THF) and the reaction mixture stirred for 1 h at room temperature. TLC analysis at this point indicated the deprotection of the TBDMS group. The reaction was quenched with aq. satd. NH_4Cl (5 mL) and the phases separated. The aqueous phase was extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue using $CHCl_3$: MeOH (19:1) as eluent afforded the cyclized product **ent-85** (0.200 g) as a thick syrupy liquid.

Yield:- 0.200 g, 48 %

[a]$^{25}_{D}$:- -5.2 (*c* 0.25, MeOH);

Spectroscopic data obtained are same as described earlier for 85 (page 155)

Preparation of (2*R*, 3*R*)-3-hydroxypipecolic acid, 3



3

The synthesis of the title compound, **3** was carried out from **ent-85** using the reported procedure[39]

M.P.:- 235-239°C [Lit. [39] 234-239°C]

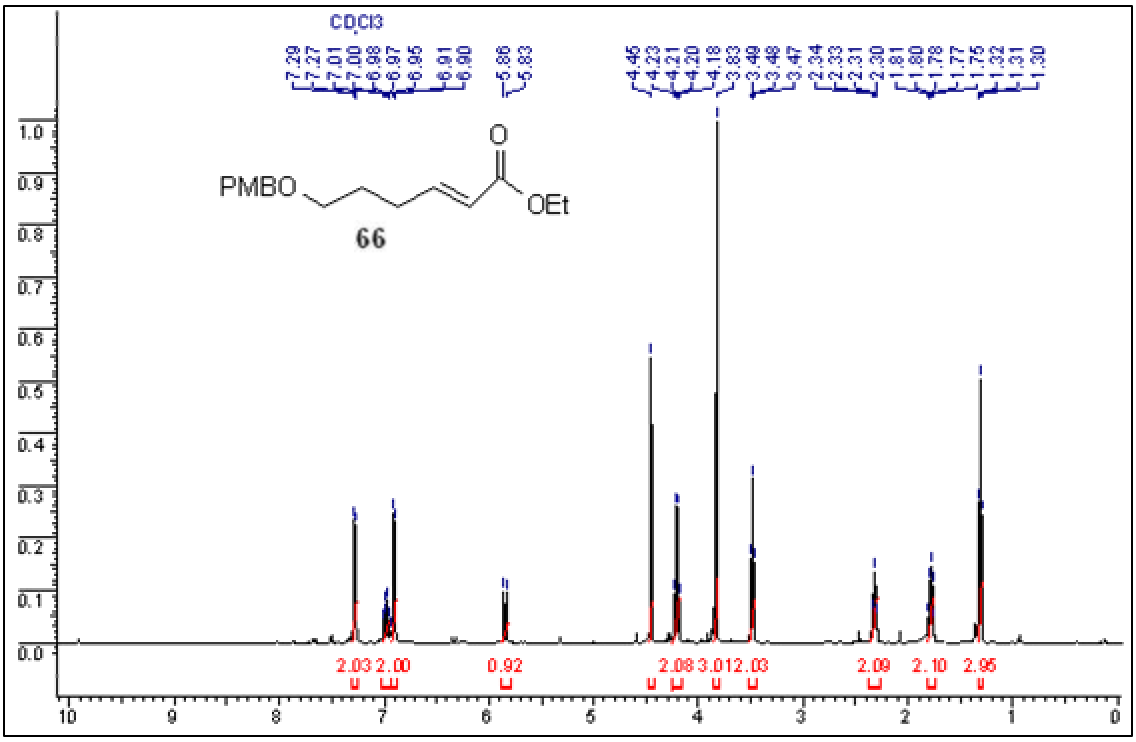
[a] $_D^{20}$:- -13.5 (*c* 0.23, 10% aq.HCl) [Lit.[39], $[\alpha]_D^{20}$ = -13.0 (*c* 0.2, 10% aq.HCl)]

The ^{1}H NMR and ^{13}C NMR spectral data were identical to those reported for its enantiomer **1**.

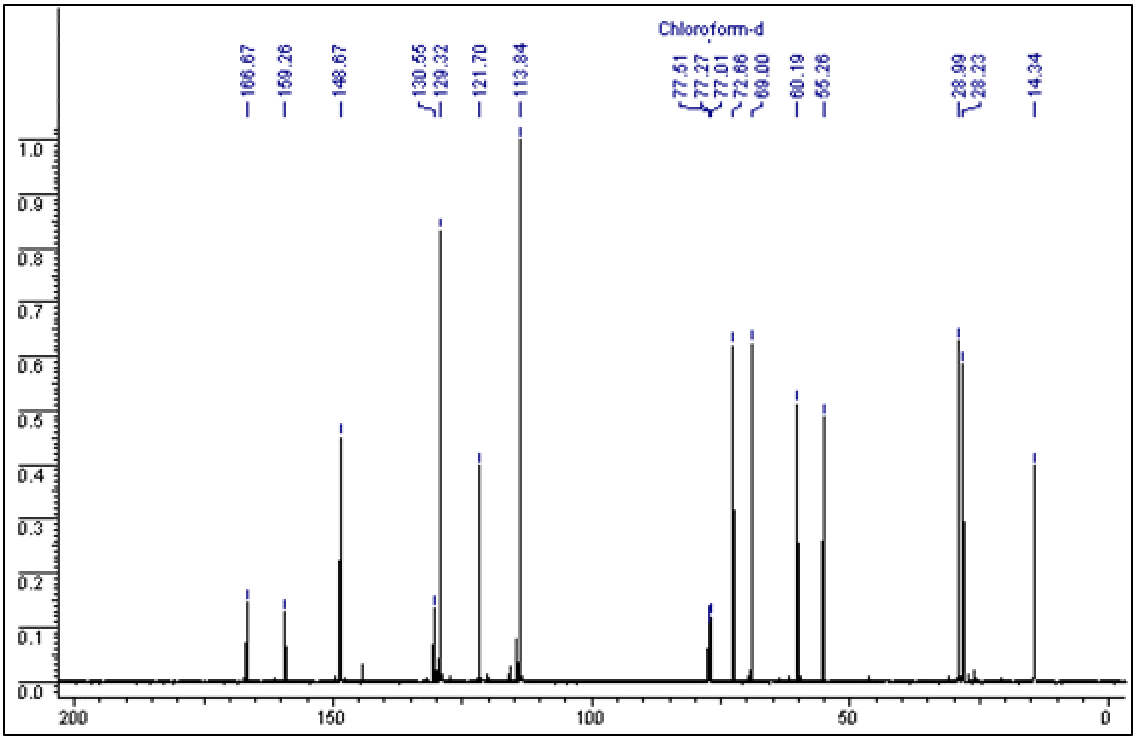
3.7. Spectra

1. ^{1}H NMR spectrum of **66**
2. ^{13}C NMR spectrum of **66**
3. ^{1}H NMR spectrum of **72**
4. ^{13}C NMR spectrum of **72**
5. ^{1}H NMR spectrum of **73**
6. ^{13}C NMR spectrum of **73**
7. ^{1}H NMR spectrum of **78**
8. ^{13}C NMR spectrum of **78**
9. ^{1}H NMR spectrum of **81**
10. ^{13}C NMR spectrum of **81**
11. ^{1}H NMR spectrum of **82**
12. ^{13}C NMR spectrum of **82**
13. ^{1}H NMR spectrum of **85**
14. ^{13}C NMR spectrum of **85**
15. ^{1}H NMR spectrum of **86**
16. ^{13}C NMR spectrum of **86**
17. ^{1}H NMR spectrum of **1**
18. ^{13}C NMR spectrum of **1**

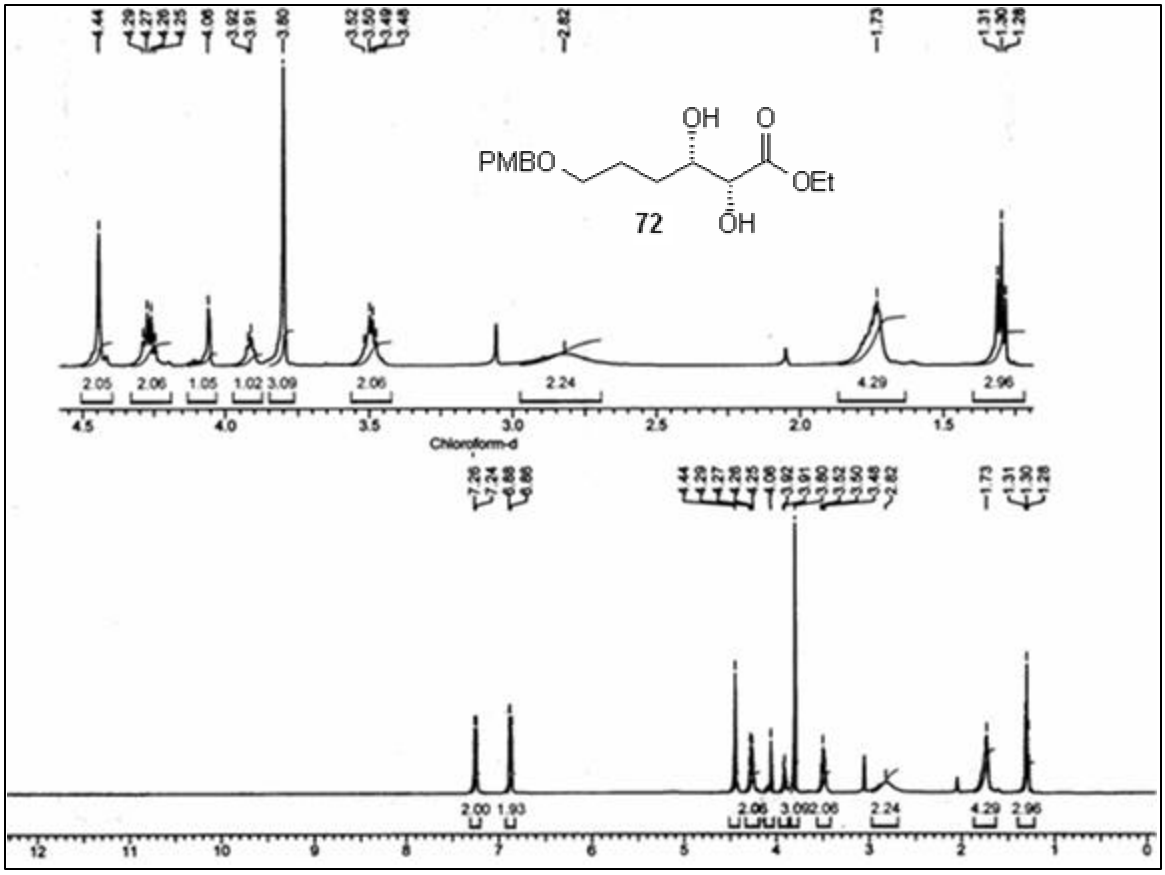
^{1}H NMR spectrum of **66**



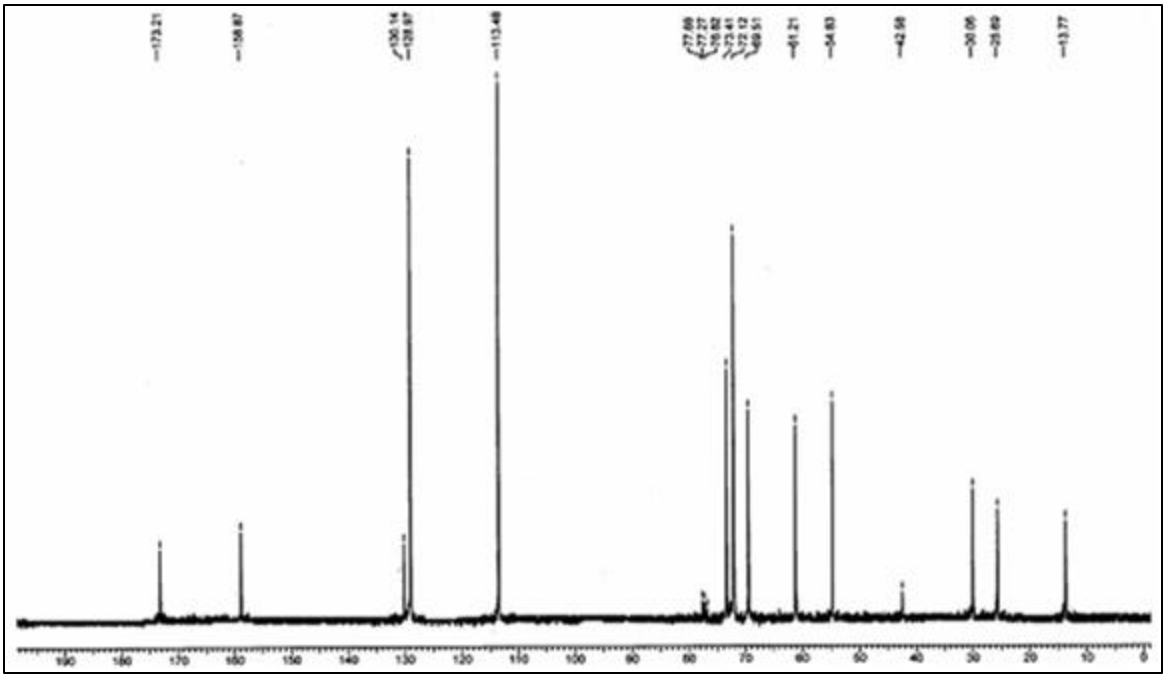
- ^{13}C NMR spectrum of **66**



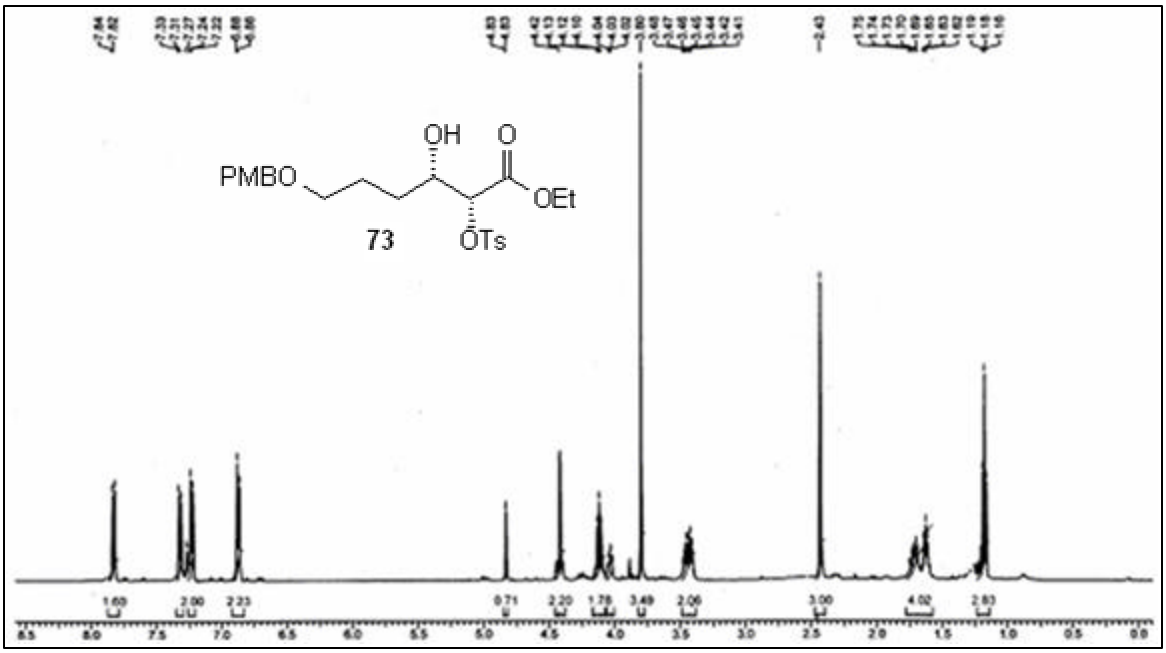
- ^{1}H NMR spectrum of **72**



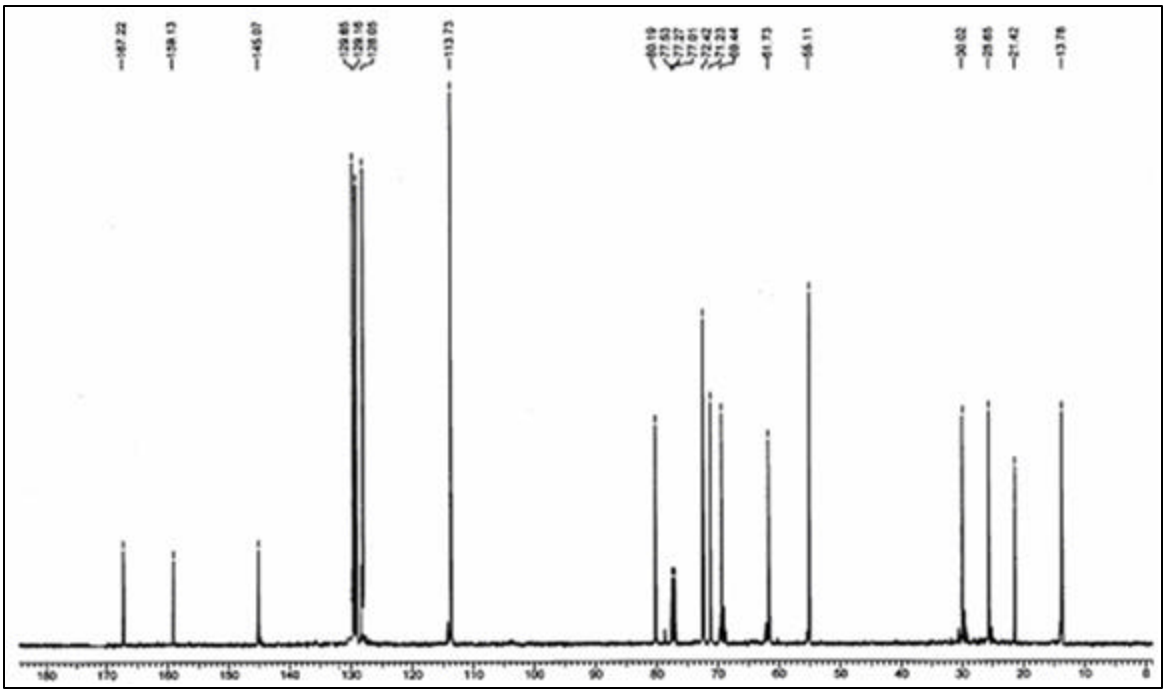
- ^{13}C NMR spectrum of **72**



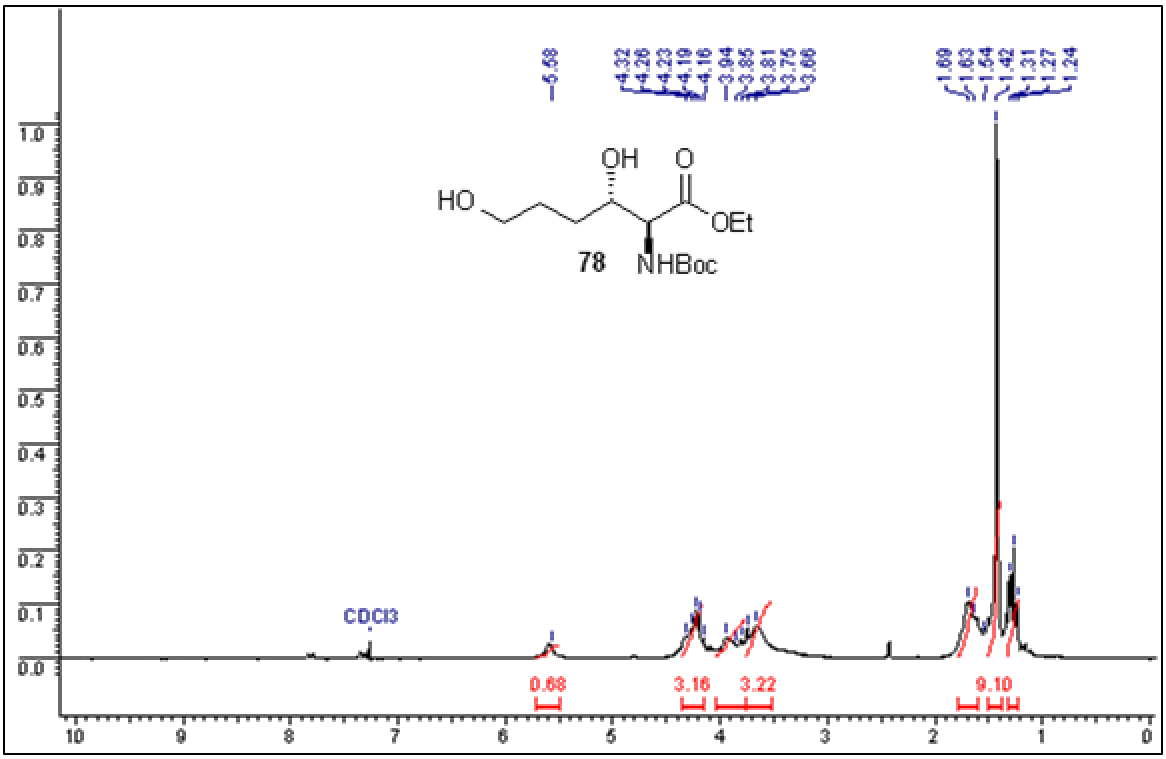
- ^{1}H NMR spectrum of **73**



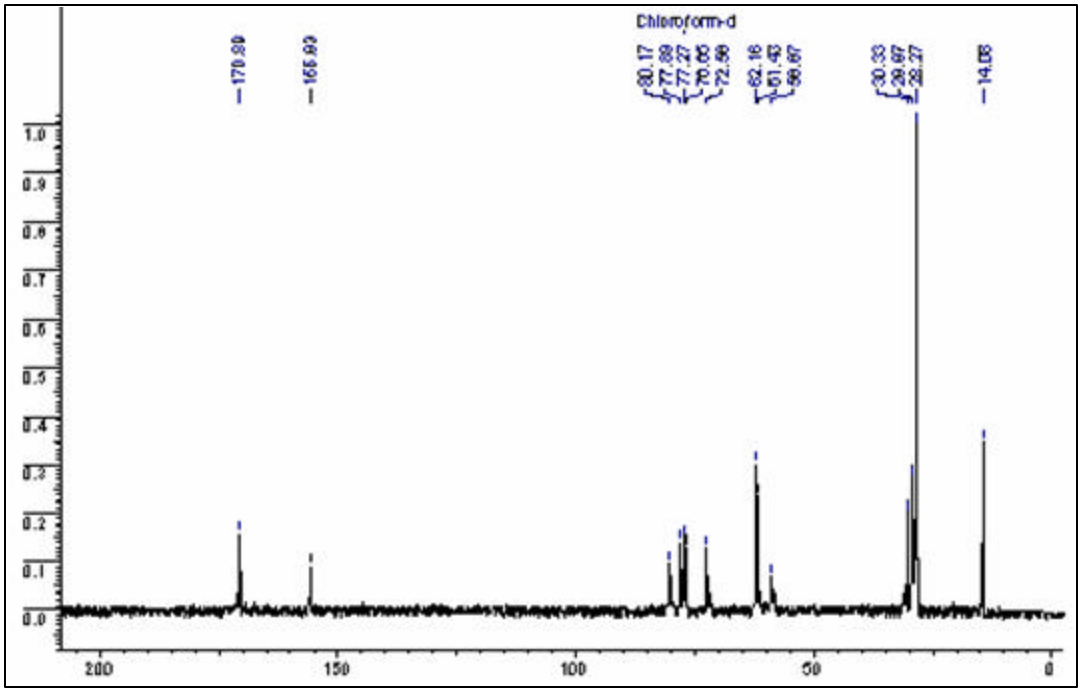
- ^{13}C NMR spectrum of **73**



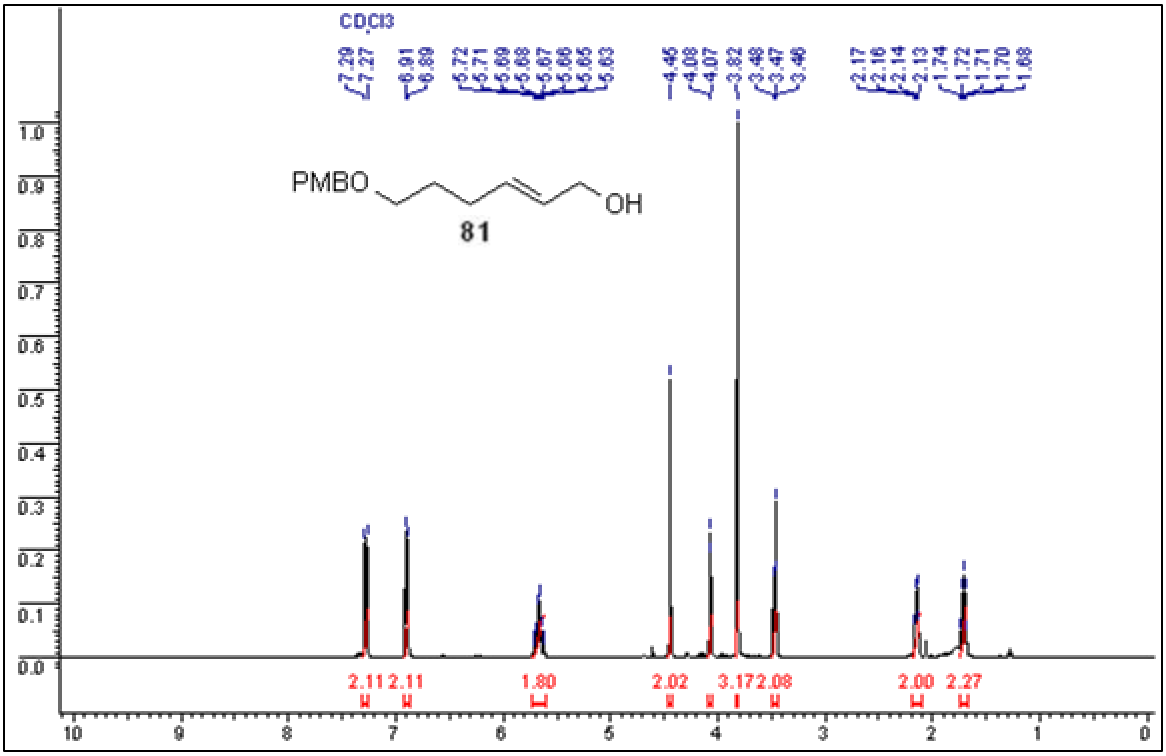
^{1}H NMR spectrum of **78**



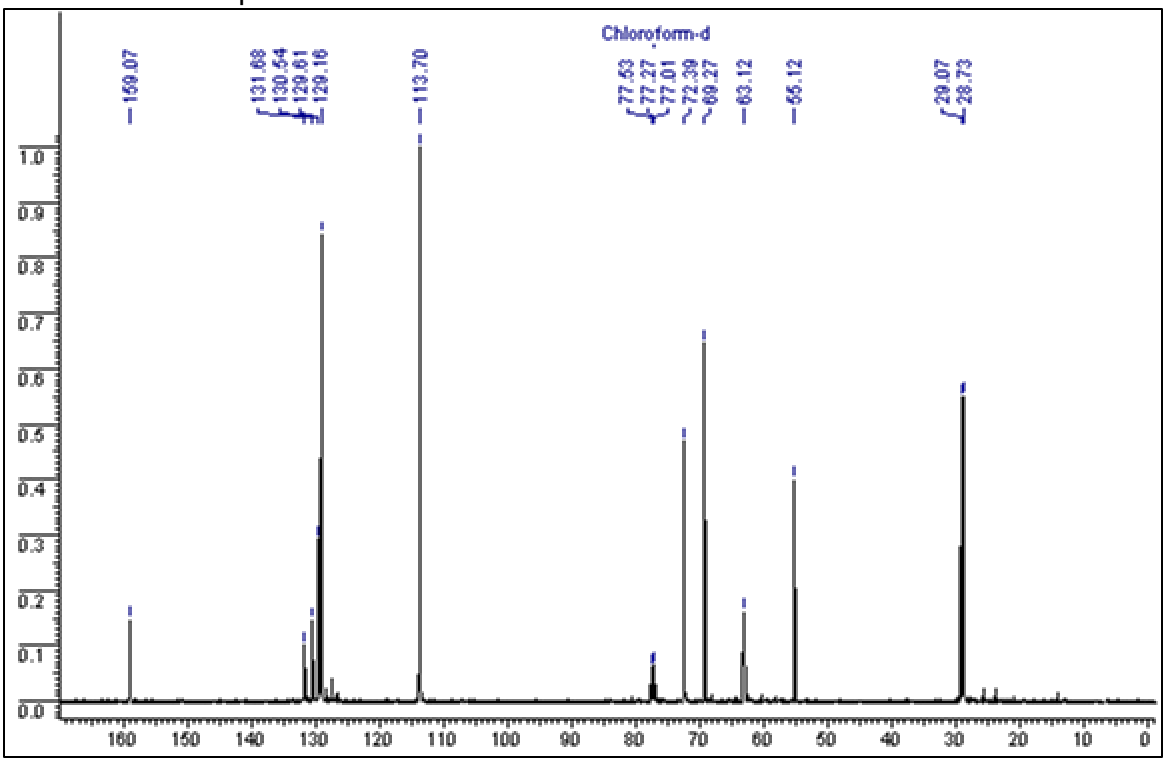
➢ ^{13}C NMR spectrum of **78**



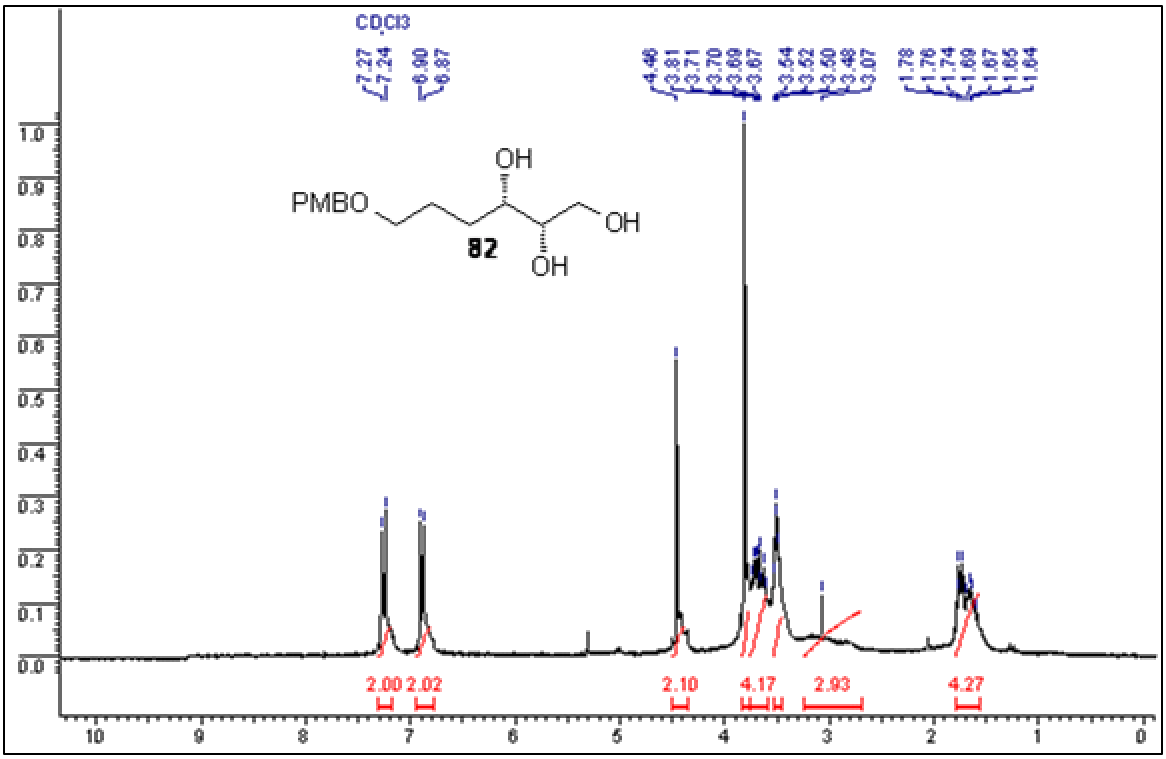
➢ ^{1}H NMR spectrum of **81**



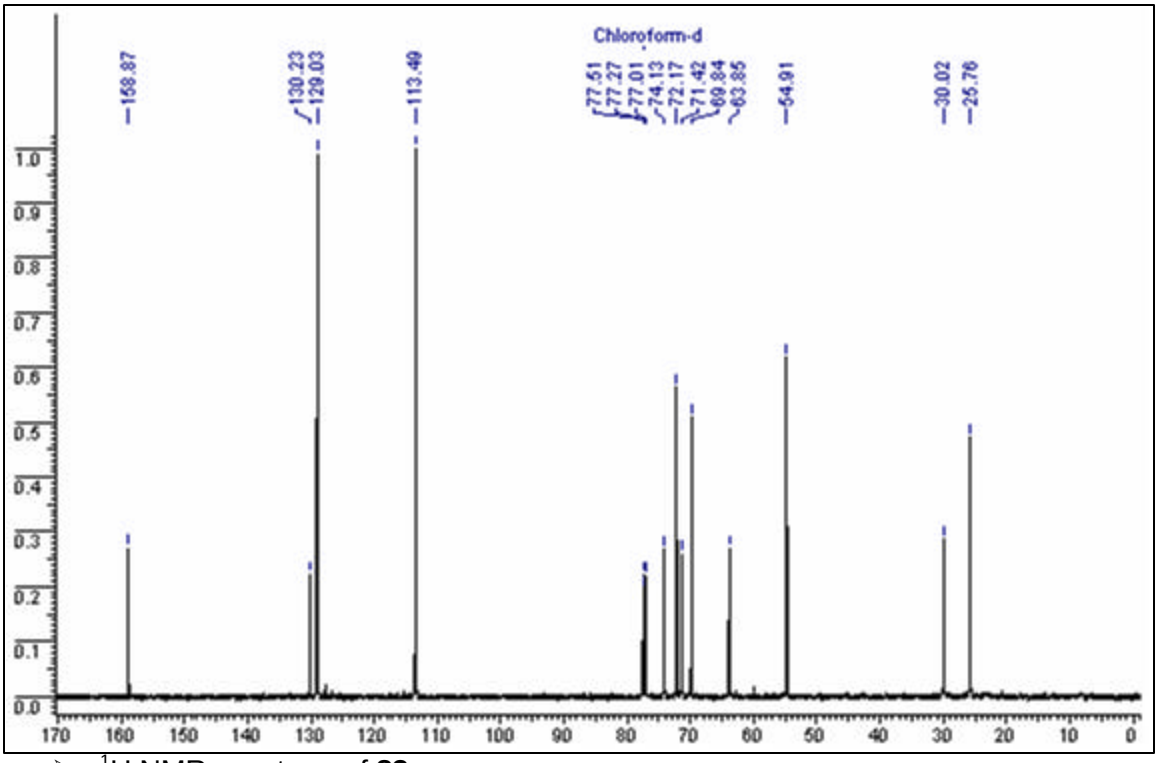
➢ ^{13}C NMR spectrum of **81**



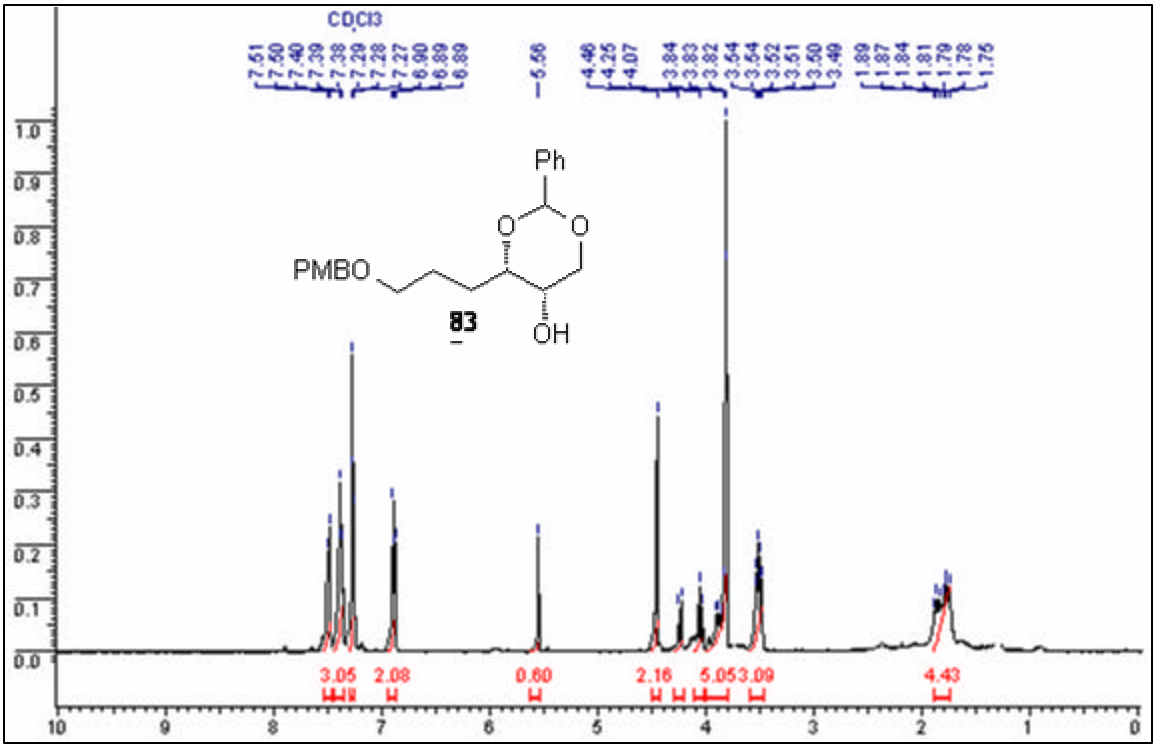
- ^{1}H NMR spectrum of **82**



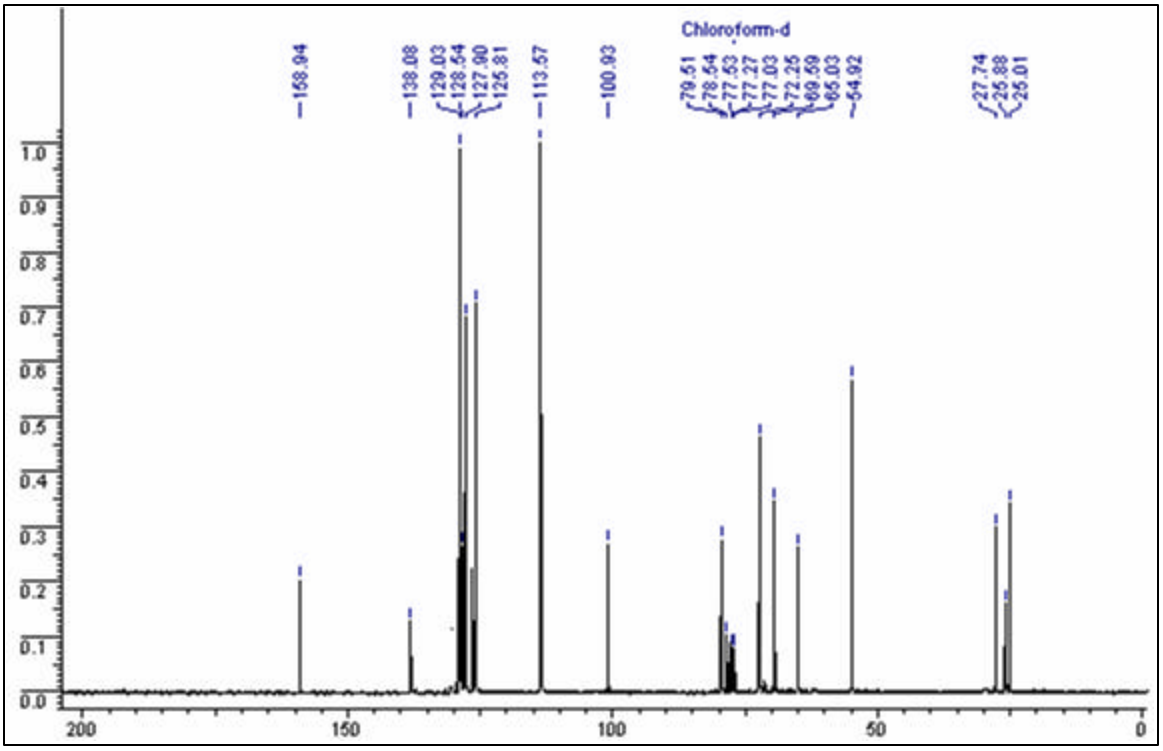
- ^{13}C NMR spectrum of **82**



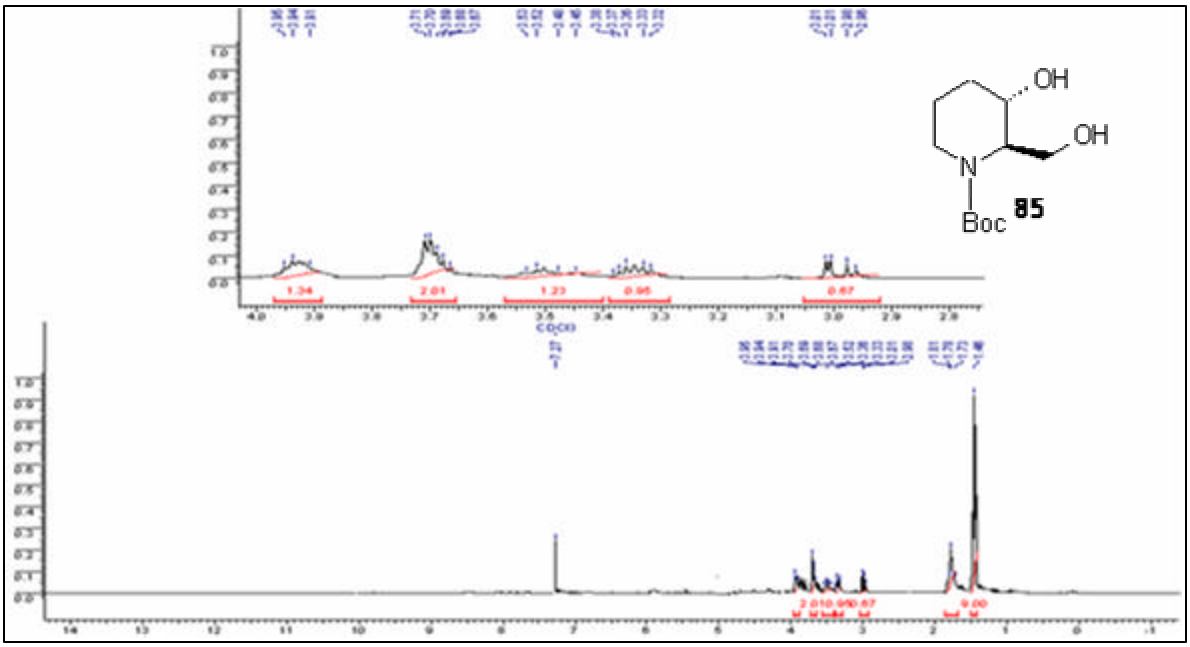
- ^{1}H NMR spectrum of **83**



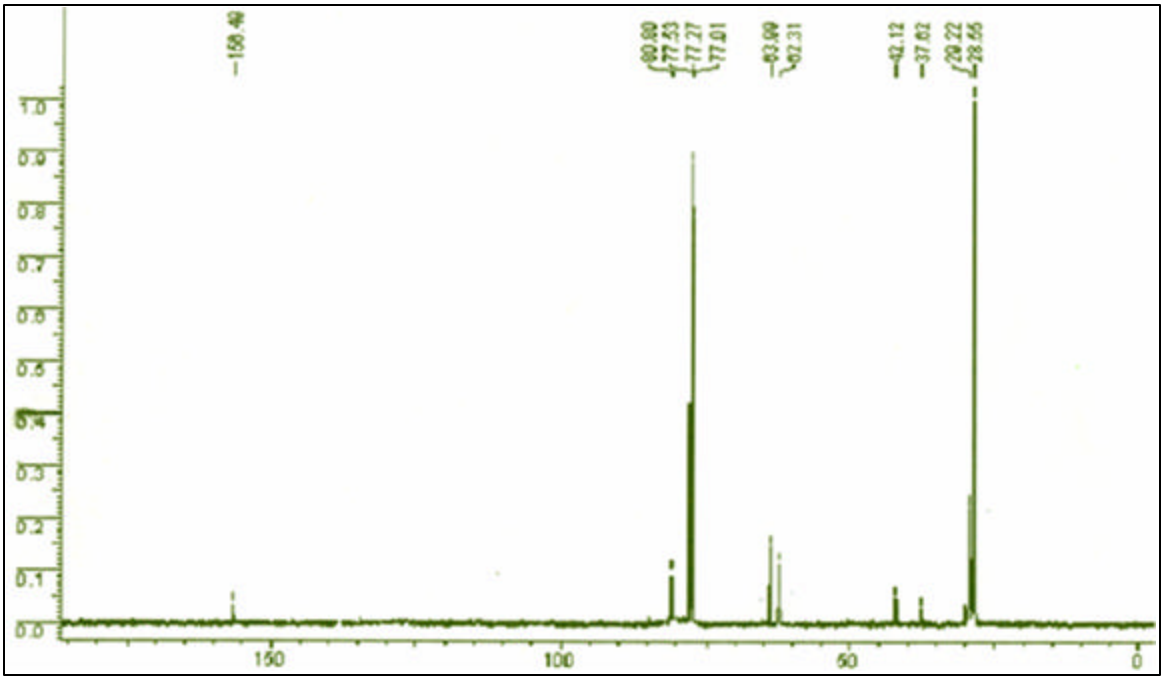
➢ ^{13}C NMR spectrum of **83**



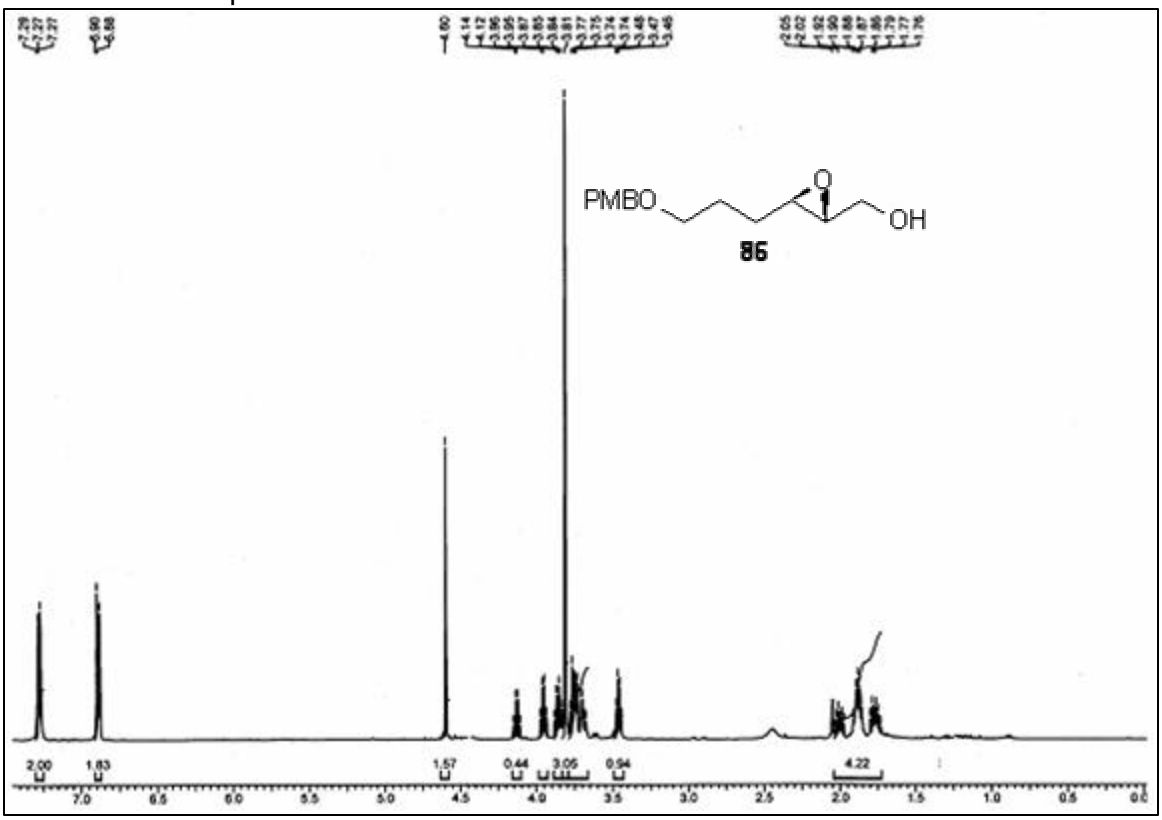
- ^{1}H NMR spectrum of **85**



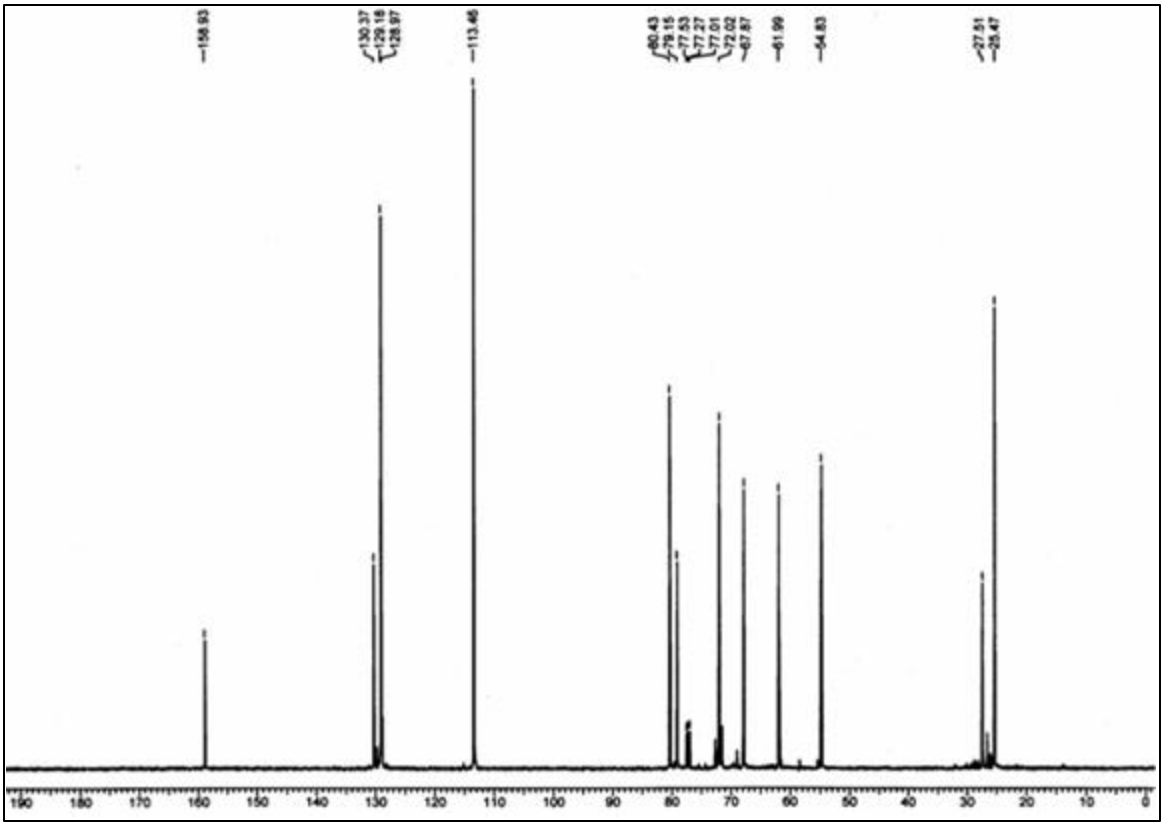
- ^{13}C NMR spectrum of **85**



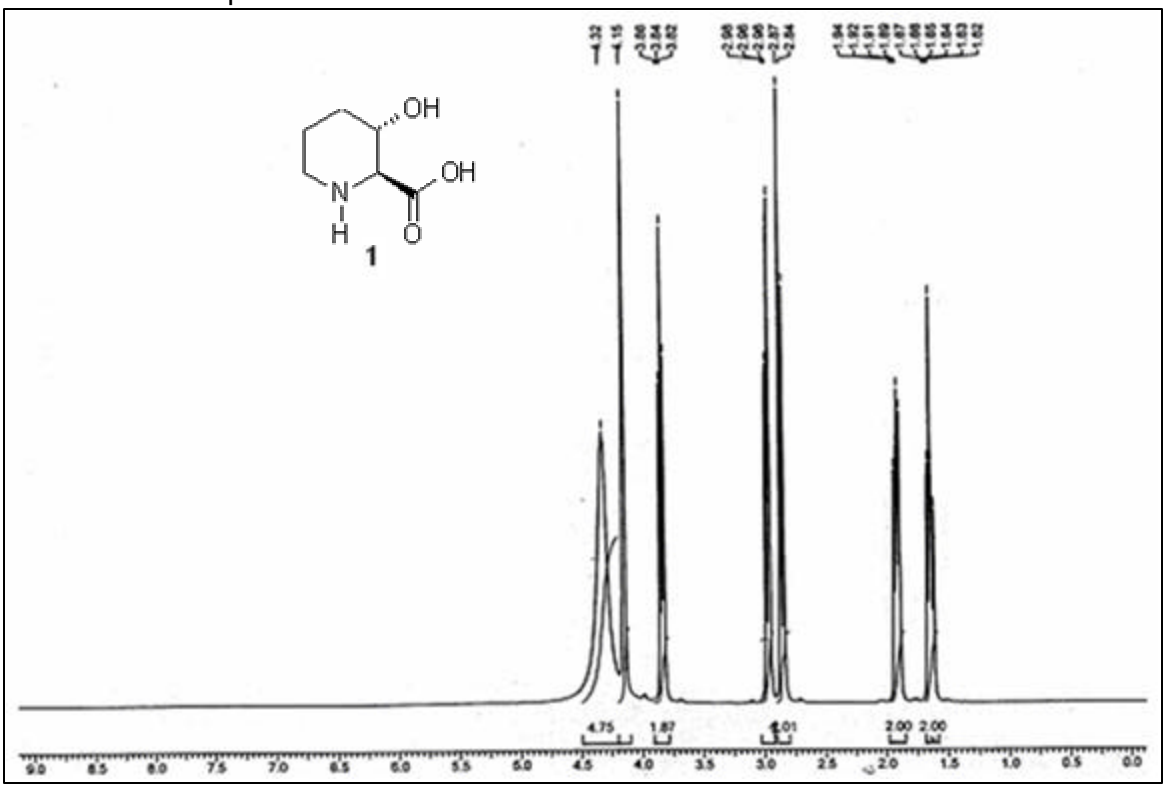
- ^{1}H NMR spectrum of **86**



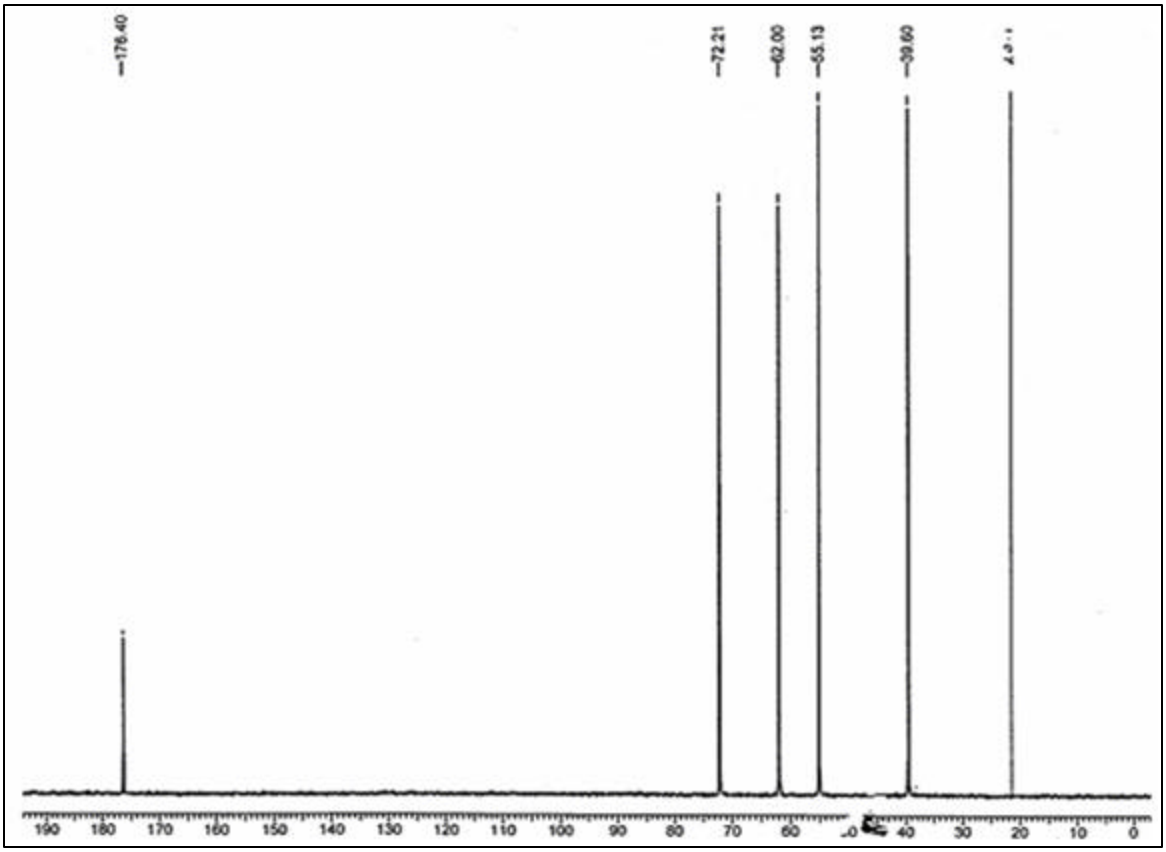
- ^{13}C NMR spectrum of **86**



- ^{1}H NMR spectrum of **1**



- ^{13}C NMR spectrum of **1**



3.7. References

1. For recent reviews on amino acids, see (a) Sardina, F. J.; Rapport, H. "Enantiosepecific Synthesis of Heterocycles from α-Amino Acids", *Chem. Rev.* **1996**, *96*, 1825. (b) Duthaler, R. O. "Recent Developments in the Stereoselective Synthesis of α-Amino Acids", *Tetrahedron* **1994**, *50*, 1539. (c) Ohfune, Y. "Stereoselective Routes Toward the Synthesis of Unusual Amino Acids", *Acc. Chem. Res.* **1992**, *25*, 360. (d) Williams, R. H. "The Synthesis of Optically Active α-Amino Acids". New York, N. Y.; Pegamon, 1989. (e) Coppola, G. M.; Schuster, H.F. "Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids", Wiley, New York, N. Y.; 1987.
2. See for example, (a) Gante, J. "Peptidomimetics – Tailored Enzyme Inhibitors:, *Angew. Chem. Int. Ed. Engl.* **1994,** *33*, 1699. (b) Adang, A. E. P.; Hermkens, P. H. H.; Linders, J. T. M.; Ortenheijm, H. C. J.; van Staveren, C. J. "Case Histories of Peptidomimetics: Progression from Peptides to Drugs", *Rec. Trav. Chim. Pays Ras.* **1994**, *113*, 63. (c) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook,

C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. "Concepts and Progress in the Development of Peptide Mimetics", *J. Med. Chem.* **1993**, *36*, 3039.

3. For selected reviews, see (a) Symposia-in-print No. 5, "Apporoaches to Non-Peptide Lignans for Peptide Receptor Sites", Horwell, D. C.; Guest editor, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 797. (b) Giannis, A.; Kolter., T. "Peptidomimetic for Receptor Ligands – Discovery, Development and Medical Perspectives", *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244. (c) Morgan, B. A.; Gainor, J. A., "Approach to the Discovery of non-Peptide Ligands for Peptide Receptors and Peptidases", *Annu. Rep. Med. Chem.* **1989**, *24*, 243.
4. For a perspective see, Appch, K. and 32 co-authors, "*Design of Enzyme Inhibitors Using Iterative Protein Crystallographic Analysis*", *J. Med. Chem.* **1991**, *34*, 1925.
5. Barrett, G.C. (Ed.) Chemistry and Biochemistry of the *Amino Acid* Chapman and Hall, London **1985**.
6. Jones, J.H (Sen. Reporter) *Amino Acids and Peptides,* Specialist Periodical Report; The Royal Society of Chemistry **1992**; *Volume* 23 (Literature published in 1990), and previous volumes.
7. (a) Bell, E. A. *The Non-protein Amino Acids of Higher Plants* in *Endeavour **1980**, Vol. 4* (New Series),102. (b) Wagner, I.; Musso. H. *Angew. Chem.* **1983**. *95*, 827; *Angew. Chem.; Int. Ed. Engl.* **1983***, 22.* 816. (c) Hunt, S. in *Chemistry and Biochemistry of the Amino Acids;* Barrett, G. C. (Ed.); Chapman and Hall, London **1985**, *Chapter 4,* pp. 55 - 138.
8. (a) Izumi, Y.; Chibata, I.; Itoh, T. *Angew. Chem.* **1978**, *90*, 187*; Angew. Chem. Int. Ed. Engl.* **1978,** *17*, 176**.** (b) Hoppe, D. *Nachr*. *Chem. Tech. Lab.* **1982**, *30*, 782 and 852. (c) Kochetkov, K. A.; Belikov, V. M. *Russian Chem Rev.* **1987**, *56*, 1045. (d) Altenbach, H.-J. *Nachr. Chem. Tech. Lab.* **1988**, *36*, 999. (e) O' Donnell, M. J. (Ed.) *Symposia in-Print No 33; Tetrahedron* **1988**, *44*, 5253. (f) Haemers, A.; Mishra, L.; Van Assche, I.; Bollaert, W. *Die Pharmazie* **1989**, *44*, 97. (g) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights;* Verlag Chemie, Weinheim **1991**, 300. (h) Ogum, K.; Inaba, T.; *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)* **1991,** *49*, 575.

9. Williams, R.M. *Synthesis of optically Active α-Amino Acids, Vo17* of *Organic Chemistry Series;* Baldwin, J. E.; Magnus, P. D. (Eds.); Pergamon Press, Oxford **1989**.
10. (a) Leuchtenberger, W.; Plockner, U. *Chem. tng. Tech* **1988***, 60,* 16. (b) Kamphuis, J.; Boesten, W. H. J.; Broxterman, Q. B.; Hermes, H. F. M.; van Balken, J. A. M.; Meijer, E. M.; Schoemaker, H. E. in *Bioprocesses and Applied Enzymology;* Reiser, J. (Ed.); *Vol42* of *Adv. in Biochem. Engin. J Biotechn.;* Fiechter, A. (Ed.); Springer, Berlin **1990**; 134. (c) Kamphuis, J.; Meijer, E. M.; Boesten, W. H. J.; Sonke, T, van den Tweel, W. J. J.; Schoemaker, H. E. *Ann. New York Acad. Sci*.**1992**, 672 (Enzyme Engineering XI), 510 - 527. (d) Scott, J.W. in *Topics in Stereochemistry,* Eliel, E.L.; Wilen. S. H. (Eds.); J. Wiley & Sons, New York **1989**, *Vol 19,* pp. 209.
11. (a) Schbllkopf, U. *Topics in Current Chemistry;* Boschke, F. L. (Ed.); Springer, Berlin **1983**; Vol. 109. 65. (b) Belokon', Yu. N. *Pure Appl. Chem.* **1992**, *64*, 1917. (c) Williams, R. M. *Aldrichimica Acta* **1992**, *25 (l)*, 11.
12. Verkhovskaya, M. A.; Yamskov, L A. *Russian Chem. Rev.* **1991**, *60*,1163.
13. Schwindt, M.A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143.
14. (a) Cintas, P. *Tetrahedron* **1991,** *47*, 6079. **(**b) Kunz, H.; Ruck, C. *Angew.* Chem. **1993**, *105*, 355.; *Angew. Chem. Int. Ed. Engl*. **1993**. *32*. 336.
15. Kochetkov, K. A.; Sviridov, A. F. *Bioorg. Khim*. **1991**, *17*, 5 and 293.
16. (a) Seebach, D.; Imwinkehied, R.; Weber, T. in *Modern Synthetic Methods;* Scheffold, R. (Ed.); Springer, Berlin **1986**, *Vol 4,* pp. 125. (b) Seebach, D.; Roggo, S.; Zimmermann. J. in *Stereochemistry of Organic and Bioorganic Transformations* (Proceedings of the 17th Workshop Conference Hoechst); Bartmann, W.; Sharpless, K.B. (Eds.); Verlag Chemie, Weinheim **1987**, pp. 85. (c) Ohfune, Y. *Act. Chem. Res.* **1992**, *25*, 360.
17. Schmidt, U.; Lieberknecht. A.; Wild, J. *Synthesis* **1988***,* 159.
18. Havlicek, L.; Hanus, J. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1365.
19. Abdulganeeva, S. A.; Enkanov, K. B. *Russian Chem. Rev.* **1991**, *60*, 676.
20. Williams, R. M**.;** Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
21. (a) Kukhar', V. P.; Soloshonok, V. A. *Russian Chem. Rev.* **1991**, *60*, 850. (b) Kukhar, V. P.; Yagupol'skii, Yu. T.; Gerus, I. I.; Kolycheva, M. T. *Russian Chem. Rev.* **1991**, *150*, 1050.

22. (a) Stammer, C. H. *Tetrahedron* **1998**, *46*, 2231. (b) Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5.
23. (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Fisher, L. E.; Muchowski. J. M.; *Org. Prep. Proc. Int.* **1990,** 22, 399.
24. (a) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon. B.; Hidber. P. C.; Irwin, J. J .; Lecher, R.; Maestro, M.; Maetzke, T.; Mourifio, A.; Pfammatter, E.; Platmer, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G. *Helv. Chim. Acta* **1992**, 75, 913. (b) Lamatsch, B.; Seebach, D.; Ha, T.-K. *Helv. Chim. Acta* **1992**, *75*, 1095.
25. (a) Sakuraba, S.; Morimoto, T.; Achiwa, K. *Tetrahedron Asymm.* **1991**, *2*, 597. (b) Giovannetti, J. S.; Kelly, C. M.; Landis, C. R. *J. Am. Chem. Soc.* **1993**, *115*, 4040.
26. (a) Kleemann, A. *Chem. Zrg.* **1982**, *106*, 151. (b) Coppola, G. M.; Schuster, H. F. *Construction of Chiral Molecules using Amino Acids,* J. Wiley & Sons., New York **1987**. c) Reetz, M. T. *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**. *30*, 1531. d) Yokomatsu, T.; Yuasa. Y.; Shibuya, S. *Heterocycles* **1992**, *33*, 1051. (e) Gdpbiowski, A.; Jurczak, J. *Synlett* **1993**, 241.
27. (a) Dmuz, K.; Kleemann, A.; Martens, J. *Angew.* Chem. **1982**, *94*, 590; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 584. (b) Martens, J. in *Topics in Current Chemistry*; Boschke, F. L. (Ed.); Springer, Heidelberg **1984**, *Vol. 125*, pp. 167. c) Mortreux, A.; Petit, F.; Buono, G.; Pfeiffer, G. *Bull. Soc. Chim. Fr.* **1987**, 631. d) Waldmann, H.; Braun, M. Gazz. *Chim. ital.* **1991**, *121*, 277. e) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935.
28. (a) Walsh, C. *Tetrahedron* **1982**, *38*, 871 (b) Ayi, A. I.; Guedj, R. *J. Chem. Soc., Perkin Trans 1* **1983**, 2045. (c) Khomutov, R. M.; Kovaleva, G. K.; Severin, E. S. *Izv. Akd. Navk SSR Seriya Khim.* **1966**, *11*, 1925.
29. For an excellent review see, Hanessian, S.; M-Smith, G.; Lombart, H-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
30. (a) Sharma, R.; Lubell, W. D.; *J. Org. Chem.* **1996**, *61*, 202. (b) Beausolcil, E.; L' Archevëque, B.; Bèlec, L.; Alfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (c) Mulzer, J.; Meier, A. *J. Org. Chem.* **1996**, *61*, 566. (d) Herdeis, C.; Hubmam, H. P. *Tetrahedron Asymm.* **1993**, *34*, 5455.

31. (a) Wang, C. J.; Wuonota, M. A. *Org. Prep & Proced. Int.* **1992**, *24*, 585. (b) Bailey, P. D.; Millwood, P. A.; Smith, P.D. *J. Chem. Soc., Chem. Commun.* **1998**, 633.
32. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron Asymm.* **1997**, *8*, 2975.
33. (a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866. (b) Greck, C.; Ferreira, F.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031. (c) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1996**, *37*, 4001. (d) Scott, J. D.; Tippie, T. N.; Williams R. M. *Tetrahedron Lett.* **1998**, 39, *3659*. (e) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett*. **1999**, *40*, 3843.
34. Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413.
35. (a) Saitoh, Y.; Moriyama, Y.; Hirota, H.; takahashi, T.; Khuong-Huu, Q. *Bull. Chem*. *Soc. Jpn.* **1981**, *54*, 488. (b) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K.H.; Byrne, N. E. *J. Am. Chem. Soc*. **1989**, *111*, 3473. (c) Yang, C. H.; Xu, Y. M.; Liao, L. X.; Zhou, W. S. *Tetrahedron Lett.* **1998**, *39*, 9227. (d) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1998**, *39*, 3505. (e) Kadota, L.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 7469. (f) Luker, P.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3592. (g) Ojima, L.; Vidal, E. S. *J.Org. Chem.* **1998**, *63*, 7999. (h) Koulocher, S. D.; Haroutounian, S. A. *Tetrahedron Lett.* **1999**, *40*, 6869. (i) Herdeis, C.; Telser, J. *Eur. J. Org. Chem*. **1999**, 1407.
36. (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175. (b) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814.
37. Scott, J. D. Tippie, T. N.; Williams, R. M. *Tetrahedron Lett.* **1998**, *39*, 3659.
38. Ferreira, F. Greck, C.; Genet, *J.* P*. Bull. Soc. Chim. Fr.* **1997**, *134*, 615.
39. Jourdant, A. ; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7033 references cited therein.
40. Knight, e.W.; Lewis, N.; Share, A. *Tetrahedron Asymm.* **1993**, *4*, 625.
41. Greck, C.; Ferreira, F.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031.
42. Scott, J. D.; Williams, R. M. *Tetrahedron Lett.* **2000**, *41*, 8413.
43. Haddad, M.; Larcheveque, M. *Tetrahedron Lett.* **2001**, *42*, 5223.
44. Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469.
45. Lindsay, K.B.; Pyne, S. G. *J. Org. Chem*. **2002**, *67*, 7774.

CHAPTER 4

α-Amino Aldehydes As Synthons In The Syntheses Of Aza Building Blocks For Hydroxylated Pyrrolidine And Piperidine Alkaloids

CHAPTER 4

a-Amino Aldehydes As Synthons In The Syntheses Of Aza Building Blocks For Hydroxylated Pyrrolidine And Piperidine Alkaloids

4.1 a-Amino Aldehydes as Synthons

4.1.1 Introduction

The synthesis of optically active organic compounds is one of the most important problems of contemporary chemistry. Pure enantiomers attain increasing commercial interest, especially in the field of pharmaceutical products. During recent years, asymmetric synthesis has greatly contributed to progress in highly controlled formation of new chiral centers.[1]These processes still remain the basic problems in the total synthesis of natural products. Preparation of the latter in an optically pure form by application of chiral starting materials is very advantageous, enabling precise programming and efficient realization of synthetic pathways. Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules.[2] α-Amino acids are the second important natural source of chiral substrates, useful in stereocontrolled organic synthesis.[2e,3]

Naturally occurring amino acids constitute an attractive source of chiral, non-racemic starting materials for asymmetric synthesis. This is due in part to the commercial availability of these substances, which in many cases involve the unnatural antipode as well. Active esters of amino acid derivatives represent one of the most important classes of activation for peptide coupling.

In nature amino acids are combined to give proteins with hundreds or even thousands of amino acids in each one. Small assemblies of amino acids are know as peptides and the amide bond that links them is called a peptide bond. Longer peptides are called proteins, though where exactly the boundary occurs is difficult to say. Amino sugars one of the class of amino acid derivatives produce structure of remarkable variety and beauty.

Amino acids are particularly useful precursors for the asymmetric synthesis of piperidine alkaloids for several reasons. Firstly, many amino acids are cheap and homochiral; secondly, they already contain the nitrogen of the alkaloid target; thirdly, they usually lead to 2-substituted piperidines, which is the commonest position for substitution. Conformationally constrained α-amino acids have gained significant attention in recent years. This may be due to the observations that incorporation of such amino acids into peptides induces the conformational change and thus may serve as useful means for obtaining information on receptor recognition. It also provides peptide mimetics that can be used as new drugs. This type of amino acids *per se* exhibits interesting biological activities. For designing such amino acids, construction of a proline or piperidine analogue with a functional group at a specific position of the pyrrolidine or piperidine framework has become a major strategy.

Aldehydes are important and versatile compounds, widely used in organic synthesis. In recent years there has been a growing interest in chiral nonracemic aldehydes because of the development of new and effective methods for controlling stereochemistry of several basic organic reactions, such as metalloorganic addition to the carbonyl group,[4] aldol condensation,[5] [4 + 2] cycloaddition with carbonyl heterodienophiles,[6] etc. Protected α-hydroxy aldehydes **I** and α-amino aldehydes **II** (**Figure 1**) are of special interest, owing to their ready availability in both enantiomeric forms from natural sources (sugars and α-amino acids, respectively) and to pronounced versatility due to the presence of both the formyl group and suitably protected hydroxy or amino functionality in the molecule.

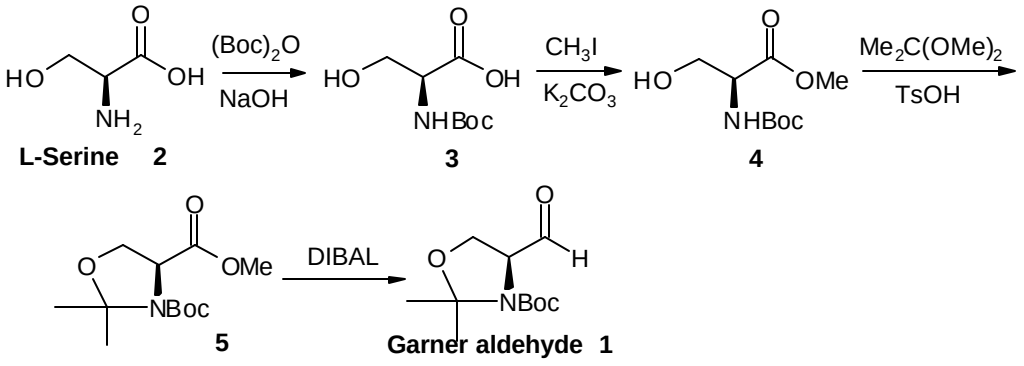
Figure 1

Recently, several extensive reviews on the application of α-hydroxy aldehydes in organic synthesis have been published;[2e, 5a,c] but there is no general survey concerning α-amino aldehyde.[7] On account of the increasing interest of chemists in α-amino aldehydes, reflected by an augmenting number of relevant publications, and in view of our belief that their further potential applications may be very important, we resolved to gather and present the actual knowledge concerning the use of optically pure N-protected α-amino aldehydes in stereocontrolled organic synthesis.

α-Amino aldehydes are versatile building blocks, frequently used in the syntheses of natural products.[8-16] Adducts of α-amino aldehydes and acetylenic compounds are easily transformable to a variety of chiral natural products containing many contiguous stereogenic carbon atoms. Among these products are glycosidic antibiotics[14], cytostatics[10], as well as antiviral[16] and anthelmintic[15] compounds. In 1984 Garner published[17] a method for preparing the configurationally stable 1,1-dimethylethyl-4-formyl-2,2-dimethyloxazolidine-3-carboxylate **1**, today called Garner's aldehyde. Since that time both enantiomers of **1** have been used extensively as chiral building blocks in asymmetric synthesis. Garner's aldehyde **1** is perhaps one of the most valuable chiral building blocks in recent time, as it has been employed in more than 200 reported studies since its discovery.

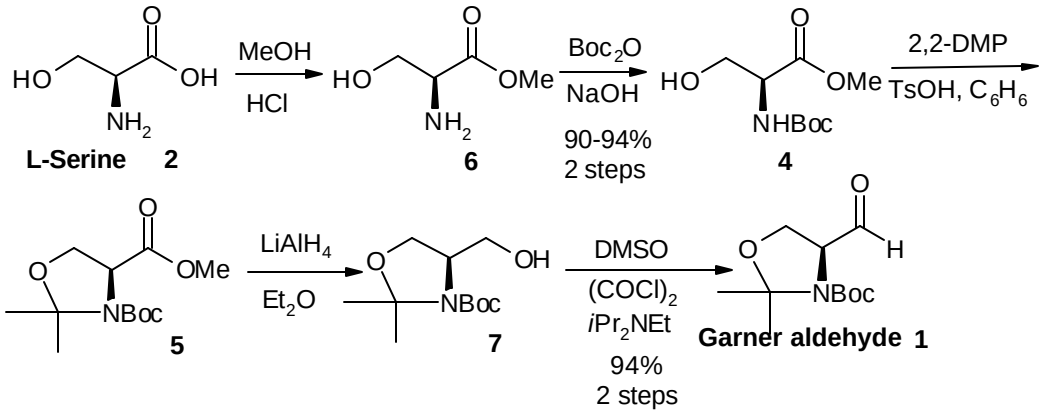
The first synthesis of **1** was, as the compound's name implies, reported by Philip Garner.[8] His synthesis started with Boc protection of the L-serine **2** using di-*tert*-butyl dicarbonate [Boc_2O] at pH ≥ 10 to from N-Boc-serine **3**, which was converted to the methyl ester **4** either by diazomethane[18] or, more conveniently, with MeI and K_2CO_3 (Scheme 1).[19] Compound **4** was then treated with $Me_2C(OMe)_2$, and TsOH to give the oxazolidine ester **5** in 87-89% yield. Direct reduction of ester **5** with DIBAL in toluene then afforded the title Garner's aldehyde **1** in 76% yield.[20]

Garner's original synthesis (**Scheme 1**) has been subject to a number of improvements. The step that has been subjected to most attempts at improvement is the DIBAL reduction of **5** to aldehyde **1**. A more reliable procedure was to reduce the ester to the alcohol **6** and then oxidize it back to **1** under Swern conditions (**scheme 2**)[21-26]. Roush and Hunt noted that not only was the DIBAL reduction tricky, but the enantiomeric excess was also only 86-87% in their hands.[23] The reliability and yield of the synthesis was improved by



Scheme 1

replacing DIBAL with $LiAlH_4$-Swern protocol (**Scheme 2**), but not the enantiomeric purity of **1**. This was confirmed by Marshall *et al*., who also obtained a product with 90% ee after the Swern oxidation.[22] This problem was solved by Dondoni *et al*. by changing the base used in the Swern oxidation from Et_3N to Hünig's base.[25] Hünig's base is more hindered and therefore less likely to facilitate enolisation of **1**. With the modification the enantiomeric purity of **1** was more than 97%.

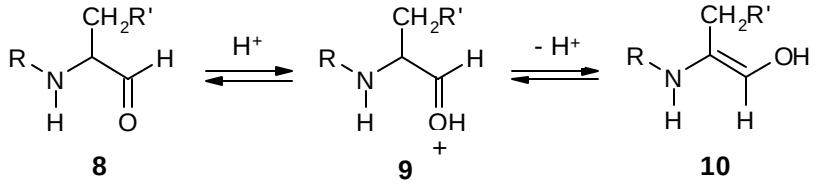


Scheme 2

Both steps of this sequence have also been carried out with other reagents. The reduction of **5** to **7** can be performed by $NaBH_4$-LiCl and proceeds in 96% yield.[27] The oxidation of **7** to **1** can also be performed via TEMPO-catalyzed oxidation, which proceeds in 90% yield and with 100% ee optical purity,[28] or with DMSO-triphosgene which gives 81% yield of a product with an optical purity similar to that reported by Garner.[29]

4.1.2 Physical and Chemical Properties of N-Protected α-Amino Aldehydes

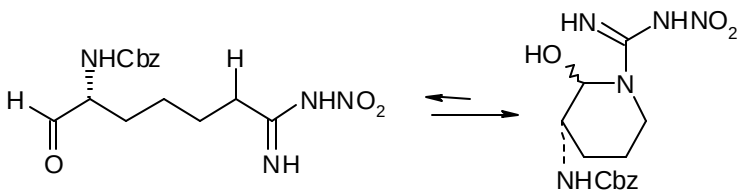
N-Protected α-amino aldehydes are usually colorless crystals or oils, well soluble in typical organic solvents. They are relatively unstable both chemically and configurationally, particularly in solution. For this reason their elemental analysis and optical rotation measurements should be considered as only approximate. Therefore, it is recommended to use these compounds immediately after preparation; however, if purification is necessary, two methods are available: flash chromatography on silica gel[30] or formation of much more stable semicarbazone[31] followed by simple chromatography and subsequent decomposition to return the pure aldehyde. The optical stability of some N-protected α-amino aldehydes during chromatography on silica gel was first studied by Ito et al.[32] (**Table 1**, **Schemes 3** and **4**)**.** As shown in **Table 1**, the order of the extent of



8 **9** **10**

Scheme 3

racemization of Cbz-L-α-amino aldehydes on silica gel was as follows: Cbz-S-Bzl-L-cysteinal >> Cbz-L-phenylalaninal > Cbz-L-leucinal >> Cbz-NG-nitro-L-argininal. The authors[32]proposed a racemization mechanism for compounds **8** involving the protonated form **9** and enol **10** (**Scheme 3**). Aldehydes **8** with an enol-stabilizing R' group, e.g., Cbz-



11 **12**

Scheme 4

S-Bzl-cysteinal, racemize extremely quickly during contact with silica gel. Limited racemization of Cbz-N^G-nitro-*L*-argininal (6) seems to be related to its cyclic carbinolamine structure **12** (**Scheme 4**), which probably prevents the nitroargininal derivative **11** from racemization due to keto-enol tautomerism. Further studies on the

Table 1: Optical Stability of Selected a-Amino Aldehydes on Silica Gel

α-Amino Aldehyde	deg of racemization, %		22 h[a]
	0 h[a]	6 h[a]	
Cbz-N^G-nitor-*L*-argininal	0	5	9
Cbz-*L*-leucinal	0	32	65
Cbz-*L*-phenylalaninal	0	53	85
Cbz-*S*-L-cysteinal	7	99	100

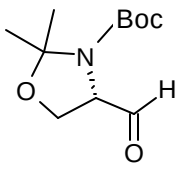
[a] Exposure time

optical stability of N-protected α-amino aldehydes were carried out by Evans and co-workers,[33] who found that the reduction-oxidation procedure (BH_3.THF-CrO_3/Py) generates Boc-α-amino aldehydes with complete retention of chiral integrity (>99.5%). The optical lability of the crude aldehydes depends on their structure. Thus, as expected from previous studies,[32] Boc-*L*-phenylalaninal appeared to be much less stable than Boc-*L*-leucinal. Very illustrative results of optical stability investigations of BOC-*L*-leucinal during storage at various temperatures are shown in **Table 2.** These studies led

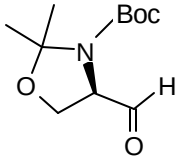
Table 2: Optical Stability of Boc-*L*-Leucinal During Storage

Storage time, day	Storage temp, °C	$[\alpha]^{24}_{D}$, deg	L / L HPLC
0		+ 18.2	100
1	- 30	+ 17.9	99/1
9	- 30	+ 17.4	99/1
9	+ 24	+ 6.9	7/3

to the conclusion that even Boc-*L*-leucinal subjected to any prolonged treatment regimen, including drying, could no longer be regarded as optically pure unless otherwise verified as such.[33] Recently, two important reports on configurational stability of N-protected α-amino aldehydes have appeared. The first one by Lubell and Rapoport[34] describes the synthesis of N-(9-(9-phenylfluorenyl))-*L*-alaninal. Exposure to silica gel or to a non-nucleophilic base caused no detectable racemization. The PhFl N-protecting group also maintains the configurational integrity of *L*-alaninal during C-C bond-forming reactions, affording enantiomerically pure products from Wittig reactions, aldol condensations, and Grignard additions.[34] The second report by Garner and Park[18] describes the synthesis of N,O-diprotected *L*-serinal **1** and *L*-threo-ninal **threo 1** (**Figure 2**). These



1



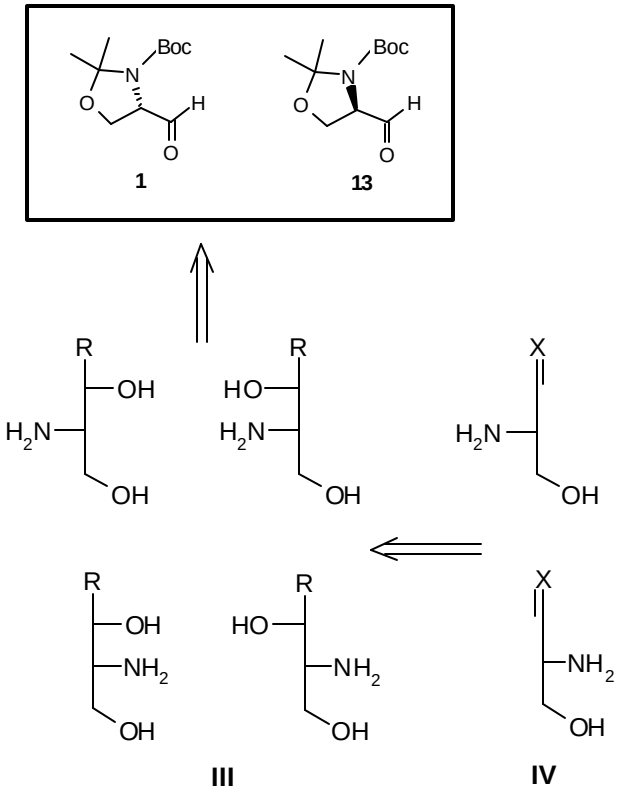
threo-1

Figure 2

differentially protected β-hydroxy-α-amino aldehydes were shown to be produced in a 93-95 % enantiomeric excess. The configurational stability of compounds **1** and **threo 1** during their purification either by vacuum distillation or by flash chromatography was also demonstrated.[18]

4.1.3 Nucleophilic Addition Reactions to Garner's Aldehyde

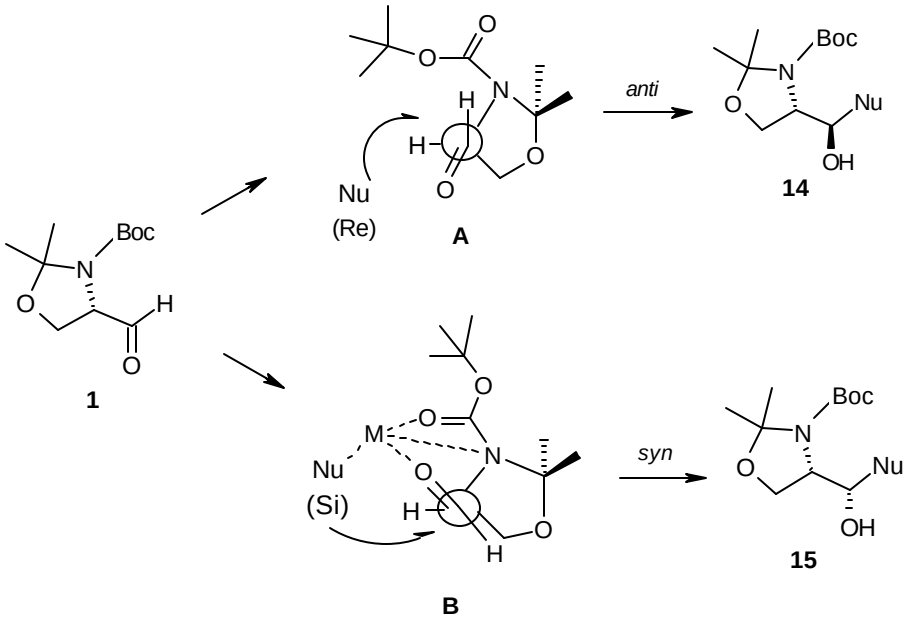
The addition of nucleophilic compounds to Garner's aldehyde **1** opens access to the 2-amino-1,3-dihydroxypropyl structure motif which is widespread in natural products. The synthesis of azasugars, peptide antibiotics and sphingosines can be realized stereoselectively by this means. Nucleophilic additions to **1** lead first to the corresponding 2-amino-1,3-dihydroxypropyl derivatives **III** through the formation of a carbon–carbon or carbon–hetero atom bond (**Scheme 5**). Depending on the reaction conditions, subsequent elimination of water gives access to *D*- and *L*-2-amino-3-hydroxypropyl products **IV**. In most cases, the constitution of **1** prevents racemisation during nucleophilic addition reactions. Therefore, starting from **1** or **13** all four possible isomers of the *D*-, *L*--*threo* and the *D*-, *L*-*erythro* series are selectively available in moderate to excellent yields.[35]



Scheme 5 **1 and 13** are the precursors for the *D*- and *L*-2-aminohydroxypropyl structural element

4.1.3.1 Addition of Organometallic Reagents

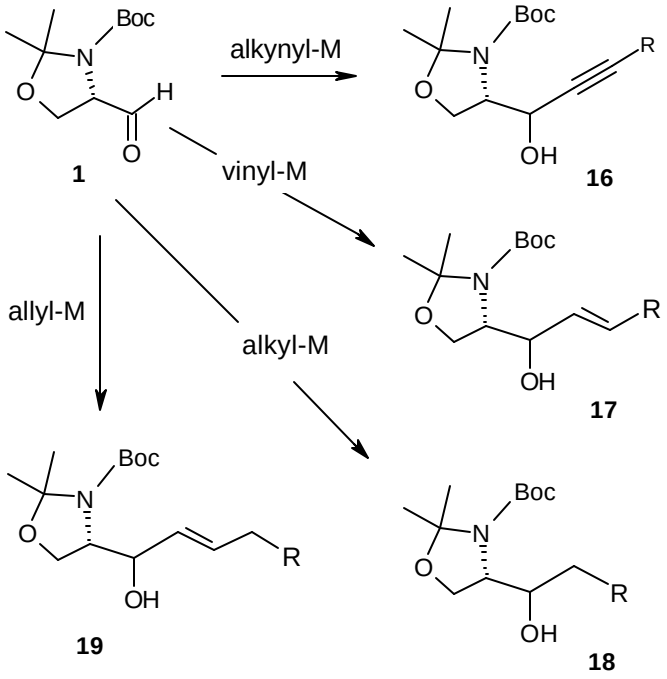
Addition of metal activated carbon nucleophiles to **1** leads, in most cases, to mixtures of two diastereomers, *anti*-addition gives the *erythro*-products, while *syn*-addition leads to the *threo*-products. Herold first reported that high asymmetric induction in both the directions could be achieved using different solvents and additives with chelation effect.[36] The formation of the reaction products is explained either with the Felkin-Ahn model **A** involving a non-chelating transition state and leading to the *anti*-adduct **14**, or with the Cram model **B** having a chelation-controlled transition state and leading to the syn-adduct **15** (**Scheme 6**).[37] Without chelation the formation of *syn*-products is believed to be disfavoured because of repulsion between the electronegative O- and N-atoms. Efficient formation of *syn*-products can also be achieved by simple oxidation of the diastereoisomeric *anti–syn* mixture to the corresponding ketone followed by metallo-



Scheme 6 *L-erythro* (*anti*) or *L-threo* (*syn*) product formation by nucleophilic additions to **1**; **A** *Felkin–Ahn* model, **B** *Cram* model.

hydride reduction (with $NaBH_4$,[38-47] $LiBH_4$,[48] $Zn(BH_4)_2$,[49,50] K-Selectride, DIBAL[51-53] or Bu_3BHK[54]), which is highly biased towards formation of the *syn*-product **15**. It is possible to make almost equal mixtures of **14** and **15**, which might be useful in combinatorial syntheses, since all four isomers of the *D*-, *L-threo* and the *D*-, *L-erythro* 2-amino-1,3-dihydroxypropyl structure element would be obtained by this means. However, it is also

possible to obtain enantiomerically pure compounds even on a solid phase. For instance, ? -aminosphingosine derivatives have been synthesised on a solid phase and used to purify sphingosine kinase, an enzyme involved in a variety of mammalian processes.[55,56] Depending on the carbon nucleophile and the metal counterion different stereoselectivities are observed. One of the most important addition reactions is the alkynylation, which gives selective access to all possible stereoisomers of alkynyl, vinyl and alkyl products **16**–**19** (**Scheme 7**).



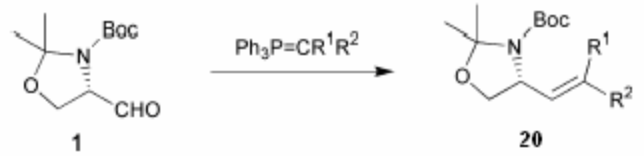
Scheme 7 Addition of alkynyl, vinyl, alkyl and allyl reagents to **1**

4.1.3.2 Witiţg Reactions

4.1.3.2.1 Wittig Reaction of Garner's Aldehyde with Non-Stabilized Ylides

The Wittig reaction of **1** with non-stabilised ylides favours the formation of the corresponding *Z*-olefin. Beaulieu *et al.*[57] investigated such processes in detail. Thus, treatment of **1** with a variety of phosphorus ylides generated from the corresponding phosphonium salts provides alkenes (**Table 3**). In most instances, *Z*-olefins are formed exclusively. Glycosphingolipids and sphingomyelins that are biomembrane components play physiologically important roles in bioorganisms. As a consequence, sphingosines, dihydrosphingosines and phytosphingosines have been independently synthesized by many groups. Very recently, three different types of sphingosine derivative were prepared using **1** as starting material.[58] Wittig olefination of **1** using *n*-BuLi and pentadecyltriphenylphosphonium bromide **21** ($C_{15}H_{31}PPh_3Br$) only resulted in low yields

Table 3



1 **20**

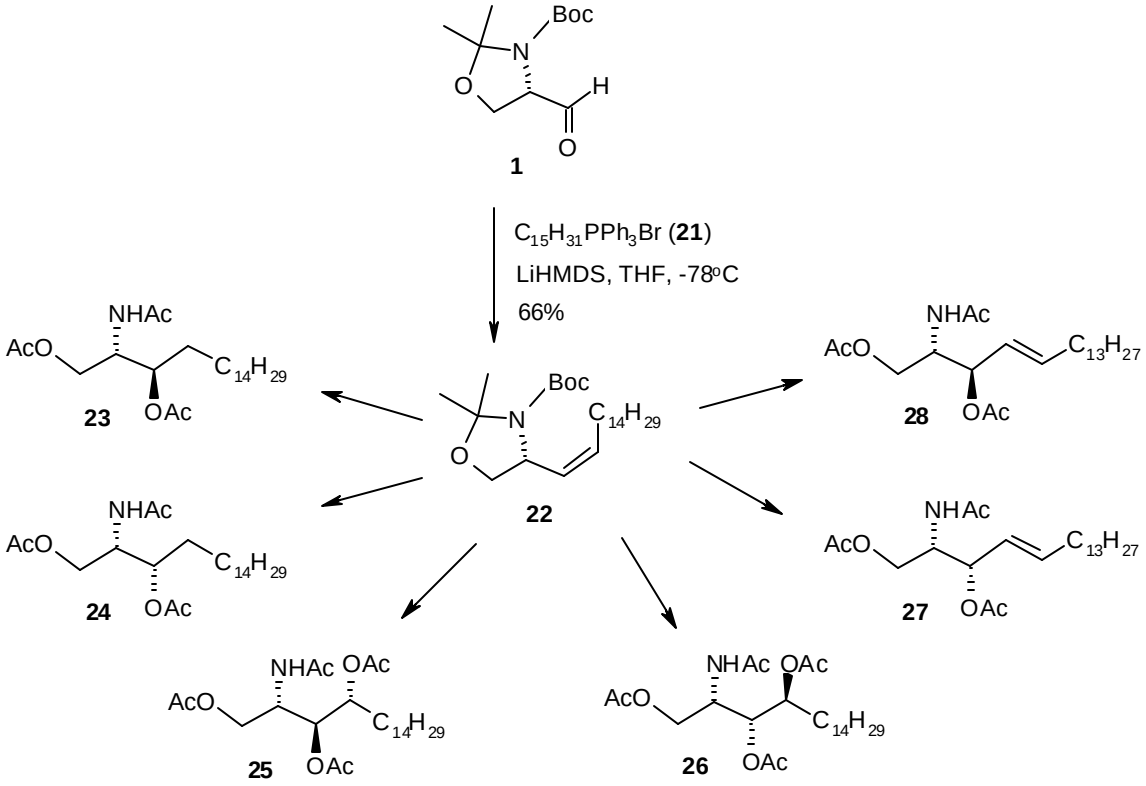
Entry	Compound	R^1	R^2	Yield (%)	*Z*
1	a	Me	H	62[a]	93
2	b	*n*-C_5H_{11}	H	78[a]	>98
3	c	CH_2CH_2Ph	H	96[a]	>98
4	d	$(CH_2)_2CO_2H$	H	73[b]	>98
5	e	Et	Me	50	70

[a] Ylide generated from phosphonium salt using *n*-BuLi.

[b] Ylide generated from phoshonium salt using LiHMDS

of the desired olefin. In contrast, by using $C_{15}H_{31}PPh_3Br$–LiHMDS in combination, a 9 : 1 mixture of (*Z*)- and (*E*)-isomers was obtained in 83% total yield. Use of sodium hexamethyldisilazide (NaHMDS) as a base gave a similar result. Column chromatographic

purification then provided pure (*Z*)-**22**. Further functional group manipulation then afforded dihydrosphingosines **23**–**24**, phytosphingosines **25**–**26** and sphingosines **27**–**28** (**Scheme 8**). A similar approach to phytosphingosines has been described by Horikawa *et al.*[59] Reagent-controlled *cis*-dihydroxylation using AD-mix was investigated in detail.



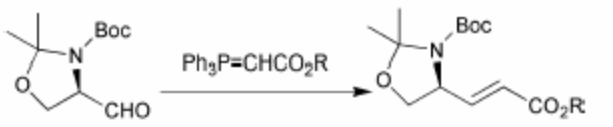
Scheme 8

4.1.3.2.2 Wittig Reaction of Garner's Aldehyde with Stabilized Ylides

Garner's aldehyde **1** has been used often in the synthesis of another important building block, compound **29**, which also offers many possibilities for chemical transformation. This a,ß-unsaturated ester can undergo Michael type addition, cyclopropanation, [2,3]-cycloaddition, Diels–Alder reaction, epoxidation, dihydroxylation *etc*. Further functional group interconversions will pave the way to many other useful building blocks. Here, the preparation of **29** using the Wittig reagent is described and later some uses of this building block will be discussed. Wittig reaction of **1** with commercially available ylides proved to be

a very convenient procedure for preparation of **29**. Both reactants can be simply mixed in a solvent and stirred at room temperature, though the work up does involve chromatography. The stereochemical outcome of this reaction strongly depended on solvents. When the reaction was performed in methanol, poor *E* / *Z* ratios were observed, while in THF or benzene, high stereoselectivity was observed (**Table 4**).[60-67] Taylor and

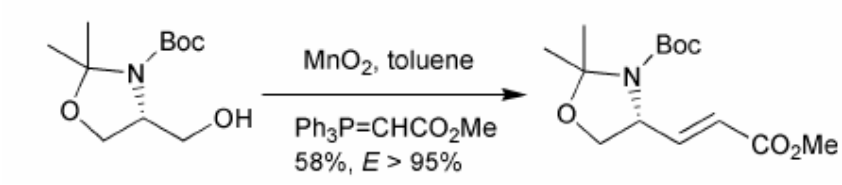
Table 4



13 **29**

Entry	R	Solvent	Yield (%)	*E* : *Z*	Ref.
1	Me	MeOH	93	3 : 2	61
2	Me	MeOH	78	3 : 1	62
3	Et	THF	72	1 : 0	63
4	Et	Benzene	82	1 : 0	60, 64
5	Me	Benzene	86	94 : 6	65
6	Et	Benzene	100	1 : 0	66
7	Me	Benzene	95	1 : 0	67

coworkers have developed a one pot procedure for the preparation of **29**. The corresponding alcohol **7** was oxidised using manganese dioxide in the presence of the



7 **29**

Scheme 9

ylide and the aldehyde **1** so formed was trapped as formed to produce the a,ß-unsaturated ester **29** directly. Even though this *in situ* oxidation–Wittig methodology proceeded in moderate yield, the stereoselectivity was very high (>95% *E*) (**Scheme 9**).[68] Due to the

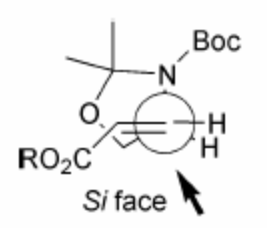


Figure 3 Felkin-Ahn model of the 1,4-nucleophilic addition of metal dialkylcuprates to compound **29**

presence of the chiral oxazolidine moiety, Michael addition of organometallic reagents to compound **29** was expected to be diastereoselective. Yoda *et al.*, C. Wermuth *et al.* and Hanessian *et al.* have systematically investigated the reactivity and stereochemical outcome of this reaction. The reaction conditions are similar in all three cases. Conjungate addition of organocuprates to **29** esters in the presence trimethylsilyl chloride led to faster reaction and higher yield. The diastereoselectivities observed ranged from good to excellent.[69–72] The formation of the favoured *syn*-isomer was rationalised by the Felkin–Ahn model wherein nucleophilic addition takes place preferentially from the *Si*-face (**Fig. 3**).[72]

4.1.4 Conclusion

As can be seen from the above-presented description, N-protected α-amino aldehydes are versatile chirons, widely recognized, inexpensive, and easily accessible from natural sources. However, the degree of stereoselectivity obtained in some reactions shown is not high enough to meet the present requirements, and thus more work has to be done to elucidate the nature of all factors responsible for asymmetric induction. Higher stereoselectivities will surely extend the utility of these valuable chiral synthons.

Garner's aldehyde, one of the major component of α-amino aldehydes has, in a very short time, proven an extremely useful chiral building block in organic synthesis. Its value is due to its simple structure that allows it to be used for many targets and because good methods exist for diastereoselective elaboration of aldehydes. It may be anticipated that similar simple chiral building blocks for alternative purposes are in demand and will develope in the future.

4.2 SECTION A

Construction Of 5-membered Aza Compounds For The Synthesis Of Pyrrolidine Alkaloids

4.2.1 Introduction

Imino sugars are well known as glycosidase inhibitors and many of them are naturally occurring.[73,74] 1,4-Dideoxy-1,4-imino-*D*-arabinose and -*D*-ribose are naturally occurring imino sugars exhibiting activity as glycosidase inhibitors,[74] and hydroxylated pyrrolidines constituted one of the main classes of naturally occurring sugar mimics having nitrogen in the ring.[73] Much attention has been focused on this class of compounds because of their potential for cell-biological and therapeutic applications as a consequence of their role as glycosidase inhibitors.[73,74] A wide range of analogues has been synthesized.[73-75] Because of their sugar-like structures it is not surprising that many syntheses of hydroxylated pyrrolidines utilize carbohydrates as starting materials. There are also strategies that employ inexpensive non-carbohydrates as starting materials. The synthesis of mono- and di-hydroxylated pyrrolidines with a carboxyl or hydroxymethyl group at position 2 of the ring is the subject of the present review. Those having carboxyl groups are named hydroxylated prolines.

A number of hydroxylated prolines and 2-hydroxymethyl pyrrolidines have been isolated from natural sources[76-116] (**Fig. 4**). trans-3-Hydroxyproline **30** was isolated from a dried Mediterranean sponge and from telomycin,[76-78] while its cis isomer **31** was obtained from telomycin only.[79,80] (2*S*,3*S*)-3-Hydroxyproline **32** was found in naturally occurring peptides, namely mucrorin-D,[81] telomycin[82] and in bovine Achilles tendon collagen.[83] (2*S*,4*R*)-4-Hydroxyproline **33** was found in the oligopeptide antibiotics echinocandin B, C, and D, isolated from strains of *Aspergillus ruglosus* and *Aspergillus nidulans*. They are characterized by their high antifungal and anti-yeast activities.[84-86] The (2*S*,*3S*,4*S*) **34** and (2*S*,3*R*,4*R*)-3,4-dihydroxyprolines **35** have been isolated from diatom cell walls[87] and *Amanita vitosa mushrooms*.[88,89] It is believed that dihydroxyprolines act in plants as

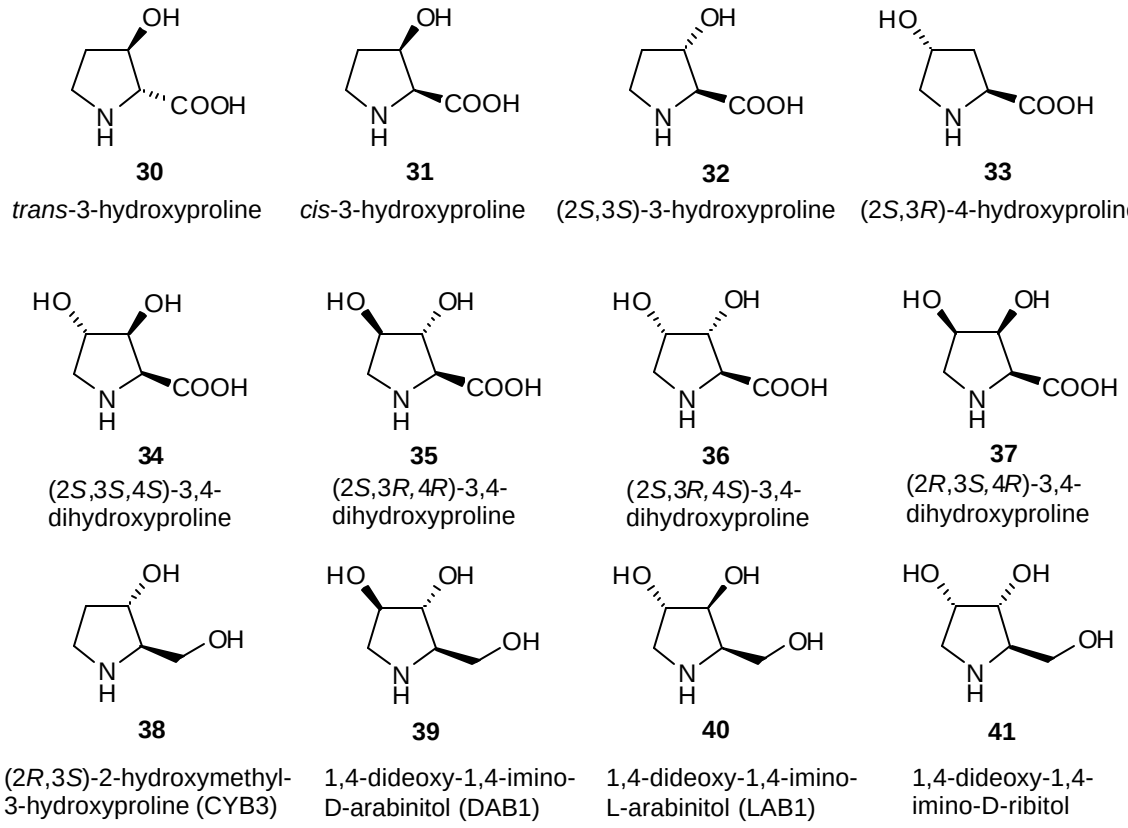


Figure 4

Natural mono- and di-hydroxylated prolines and 2-hydroxymethylpyrrolidines

defense agents against predators and parasites.[90] (2*S*,3*R*,4*S*)-3,4-Dihydroxyproline **36** was isolated from animal adhesive protein (Mefp 1) found in the mussel *Mytilus edulis* .[91-93] (2*R*,3*S*,4*R*)-3,4-Dihydroxyproline **37** was also isolated from natural sources.[94,95]

(2*R*,3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidine **38** (*L*-trans-3-hydroxyprolinol or CYB3) was isolated from the legume *Castanospermum australe*; and it has no significant biological activity.[96] 1,4-Dideoxy-1,4-imino-*D*-arabinitol (10) (DAB1) has been found in both *Arachniodes standishii* [97,98] and *Angylocalyx boutiqueanus*[99] and is a potent inhibitor of yeast α-glucosidase (50% inhibition at 1.8 x 10^{-7} M)[100,101] and different mouse gut disaccharidases to various degrees.[102] DAB1 **39** inhibits the hydrolysis of sinigrin and progoitrin by thioglucosidases from mustard and the cabbage aphid *Brevicoryne brassicae* [103] It also inhibits phloem unloading and/or utilization of sucrose, resulting in insufficient sucrose transport from cotyledons to roots and hypocotyls.[104] The mechanism of insect

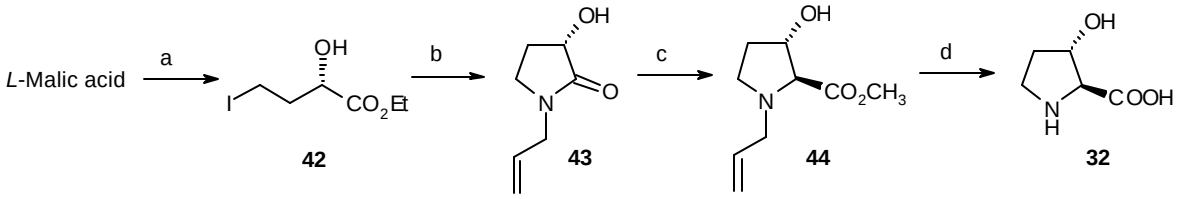
antifeedant activity of DAB1 **39** has been studied[105] and it may be carcinogenic to rodents.[106] The enantiomer LAB1 **40** occurs as a component of bacterial lipopolysaccharides[107,108] but shows a weaker inhibition of α-glucosidase (50% inhibition at 1.0 x 10^{-5} M)[109,110] and exhibits several other biological activities.[111-114] 1,4-Dideoxy-1,4-imino-*D*-ribitol **41** has been isolated from *Morus spp.*[115,116]

4.2.2 Review of Literature

Various synthetic methods for the synthesis of hydroxyprolines and pyrrolidines have been reported from carbohydrates[117-132] and from non-carbohydrates.

Durand *et al.* (1998)[133] Scheme 10

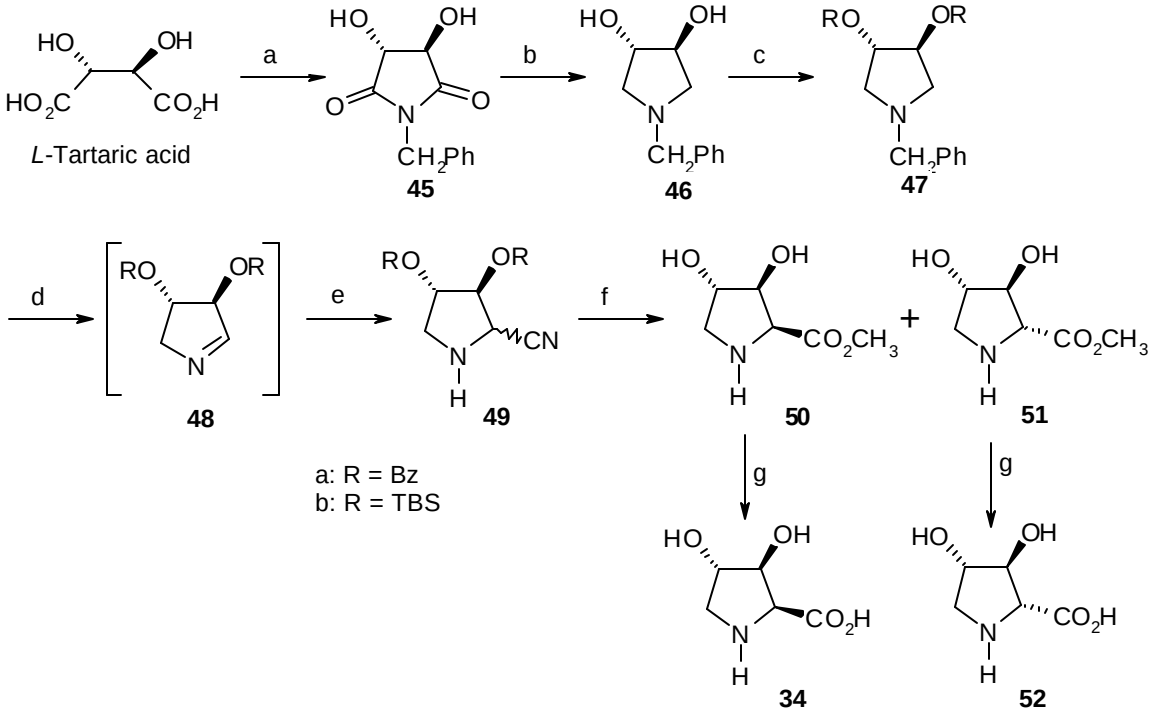
A stereoselective synthesis of (-)-(2*S*, 3*S*)-3-hydroxyproline **32** has been achieved from *L*-malic acid by conversion into ethyl (2*R*)-2-hydroxy-4-iodobutanoate **42**.[133] Cyclization of **42** using allylamine gave the lactone **43**. The lactone was then transformed in **44**. The compound **44** was hydrogenated and saponified to afford the desired (-)-(2*S*, 3*S*)-3-hydroxyproline **32**.



Scheme 10 Reagent and Conditions: (a) CH_2=$CHCH_2NH_2$, THF, rt, 90% (b) (i) TBSCl, imidazole, DMF, rt, 80%; (ii) DIBAL, THF, -35 to -15°C; then KCN, H_2O, -10°C to rt, 93%; (c) (i) HCl, CH_3OH, -20°C; (ii) Amberlyst 15, CH_3OH, 65°C, 83% (d) (i) $Pd(dba)_2$, Dppb, mercaptobenzoic acid, THF, rt; then 1 M HCl, 70% (ii) KOH, CH_3OH, H_2O, rt, 88%.

Arakawa *et al.* (1991)[134] Scheme 11

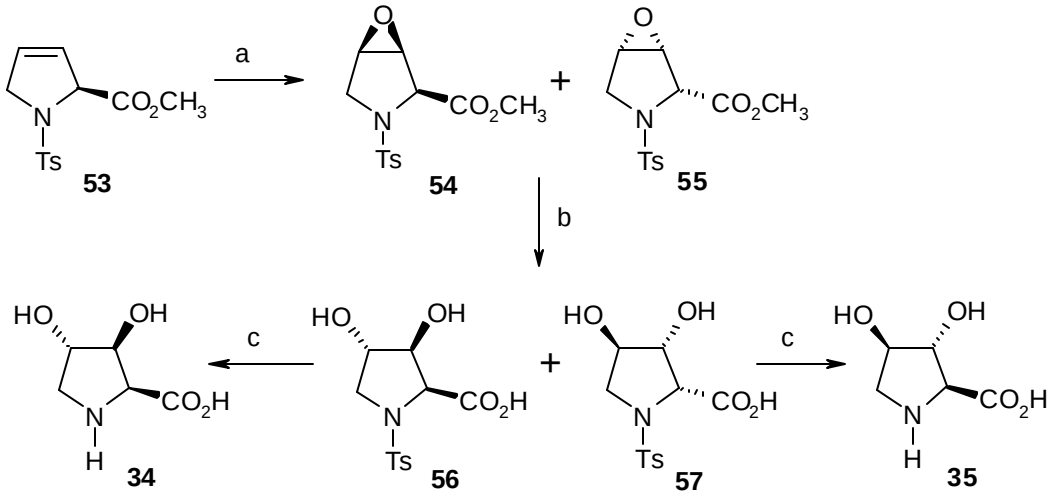
(2*S*,3*S*,4*S*)-3,4-Dihydroxyproline **34** and its (2*R*,3*S*,4*S*) isomer **52** have been synthesized from *L*-tartaric acid by conversion into (3*S*,4*S*)-1-benzyl-3,4-dihydroxypyrrolidine **46** in 42% yield *via* (3*R*,4*R*)-1-benzyl-3,4-dihydroxy-2,5-dioxopyrrolidine **45**.



Scheme 11 Reagent and Conditions: (a) $BnNH_2$, xylene (b) $LiAlH_4$, THF (c) (i) BzCl, aq. Na_2CO_3, CH_2Cl_2, 83% or NaH, TBSCl, 93%; (ii) H_2, $Pd(OH)_2$ on C, AcOH or CH_3OH, **70**, 100% 83% (d) (i) NCS, Et_2O; (ii) DBU, benzene (e) $(CH_3)_3SiCN$, ZnI_2 (f) (i) 6 N HCl, AcOH; (ii) CH_3OH, $SOCl_2$; (iii) CbzCl; (iv) dioxane, aq. $NaHCO_3$ (g) (i) 1 N NaOH, CH_3OH; (ii) Amberlite 20^oC; (iii) H_2, Pd on C, 50% aq. AcOH.

Karl *et al.* (1981)[89] Scheme 12

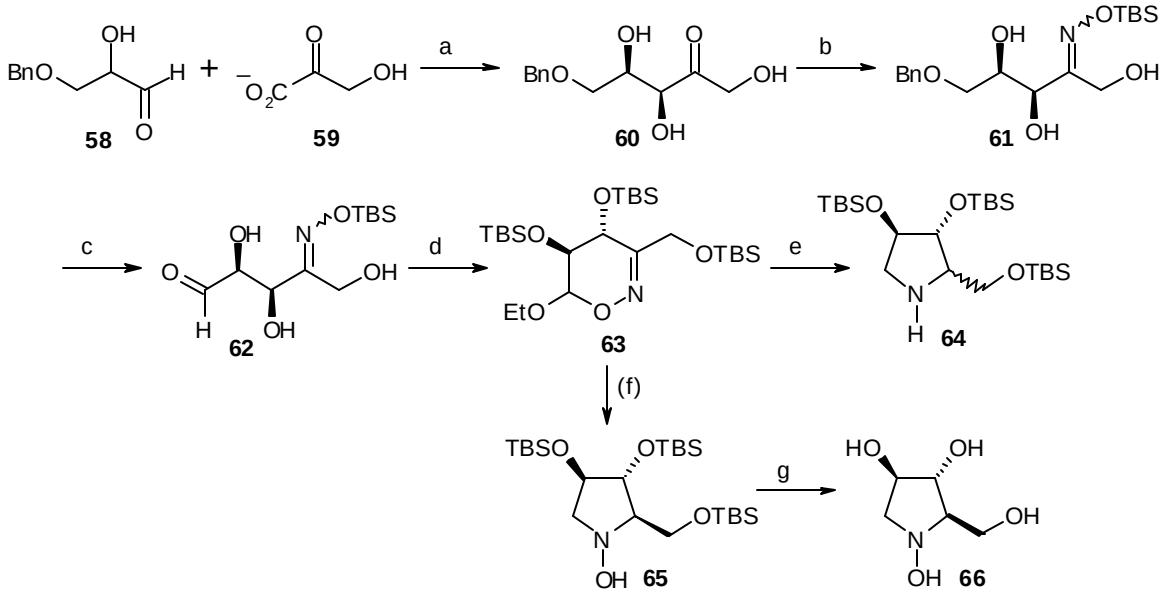
Karl *et al.* converted the N-tosyl-3,4-dehydro-*L*-prolinemethyl ester **53**[89] into 2,3-*trans*-3,4-dihydroxy-*L*-proline **35** and its 2,3-*cis* diastereomer **34** (**Scheme 12**) *via* a *trans* dihydroxylation process.



Scheme 12 Reagent and Conditions : (a) TFAA, CH_2Cl_2, H_2O_2, 92% (b) (i) 2 M H_2SO_4, acetone, 8 h; (ii) 1 M NaOH; (iii) 1 M HCl (c) Na, naphthalene, NH_3

Humphrey *et al.* (2000)[135] Scheme 13

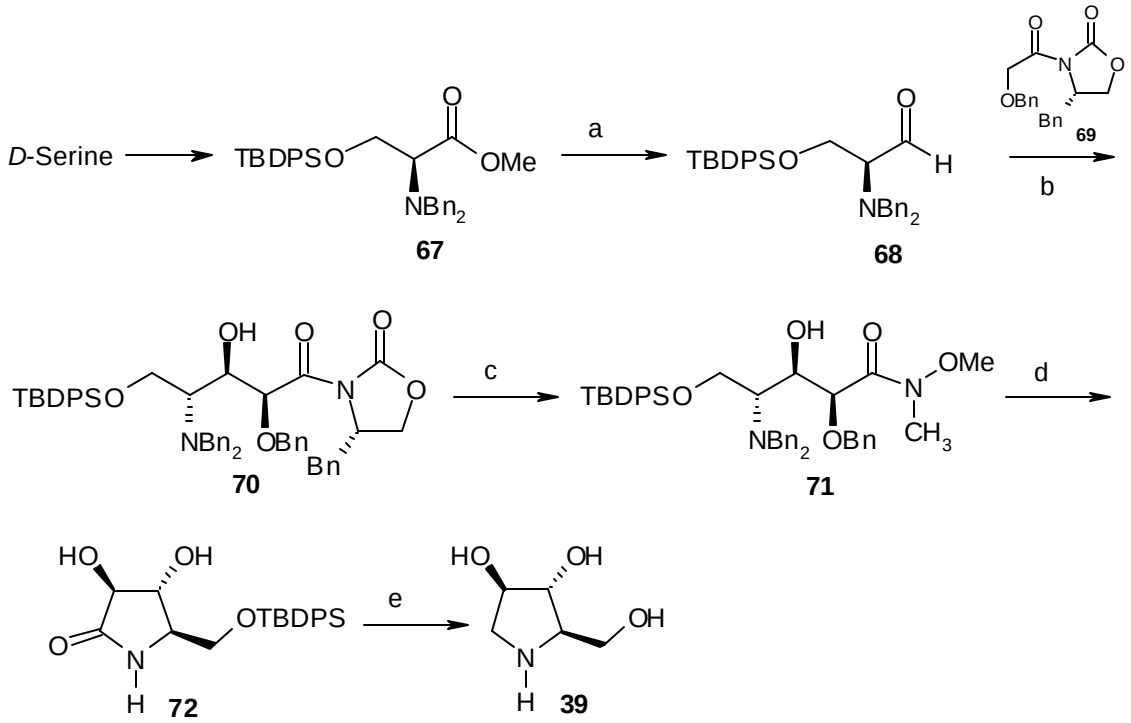
The synthesis of **66**, the *N*-hydroxypyrrolidine analogue of **39**, from racemic 3-*O*-benzylglyceraldehyde **58** *via* its coupling with hydroxypyruvate **59** to give 5-*O*-benzyl-xylulose **60** in 80% yield has been reported by Humphrey *et al*.[135]



Scheme 13 Reagent and Conditions: (a) Transketolase, TPP, Mg^{2+}, P^{H} 7, 80% (b) (i) TBSOTf, Et_3N, 83%; (ii) NH_2OH-HCl, $KHCO_3$, 71%; (iii) TBSOTf, Et_3N, 95% (c) (i) H_2, 10% Pd on C, 100%; (ii) NaOCl, TEMPO, 66% or Swern oxidation, 40-60% (d) $(EtO)_3CH$, *p*-TsOH, EtOH (e) $NaCNBH_3$, acetic acid, 37% (f) aq. HF, (1:1) THF-CH_3CN, 100% (g) H_2, 10% Pd on C, EtOH, 59%

Henderson *et al.* (2000)[136] Scheme 14

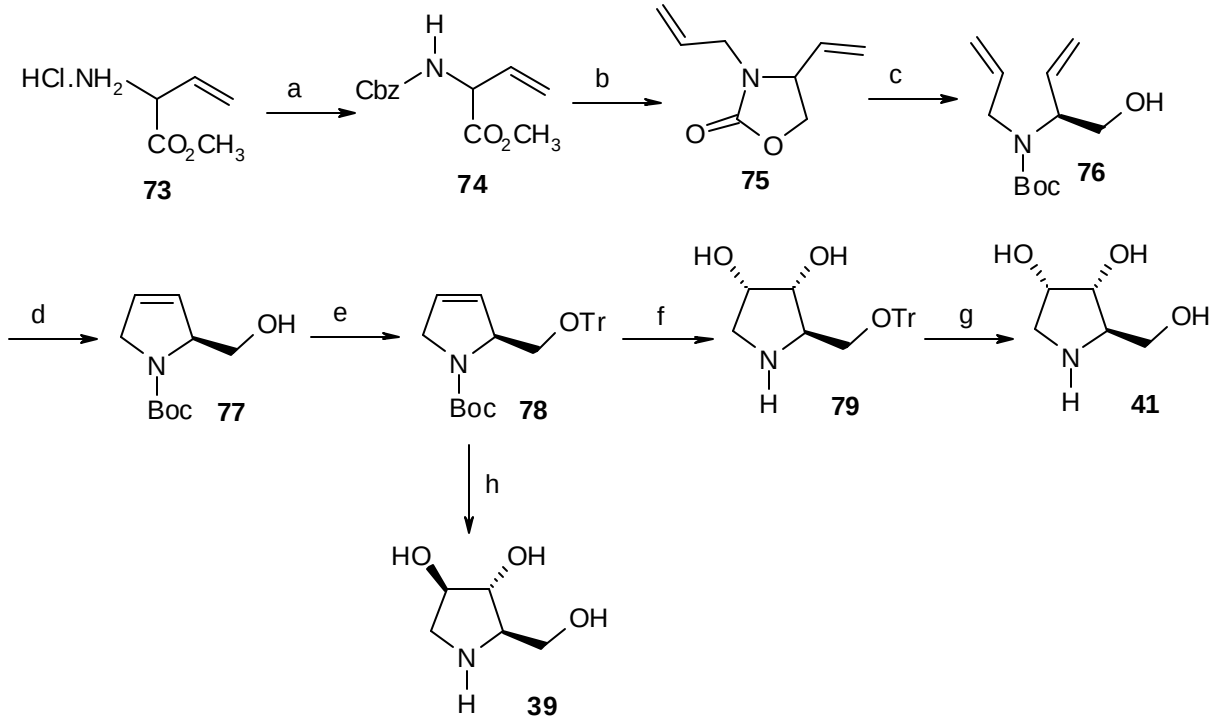
1,4-Dideoxy-1,4-imino-*D*-arabinitol **39** has been synthesized in ten steps from *D*-serine by Henderson *et al.* with an overall yield of 49% (**Scheme 14**).



Scheme 14 Reagent and Conditions: (a) (i) DIBAL-H, toluene, -78°C, 30 min, 93%; (ii) $(COCl)_2$, Me_2SO, CH_2Cl_2, -78°C, 1 h; then Et_3N, 100% (b) Et_3N, *n*-Bu_2BOTf, CH_2Cl_2, -78°C to 0°C, 3 h, 82% (c) $(CH_3O)NHCH_3$-HCl, $(CH3)_3Al$, THF, -30°C to 0°C, 2 h, 100% (d) $Pd(OH)_2$, H_2 (1 atm), CH_3OH, 72 h, 71% (e) (i) BH_3-THF, THF, reflux, 18 h, 100%; (ii) 48% aq. HF, CH_3CN, rt, 15 min; then $CH_3OSi(CH_3)_3$, Dowex OH^-, 100%.

Huwe *et al.* (1997)[137] Scheme 15

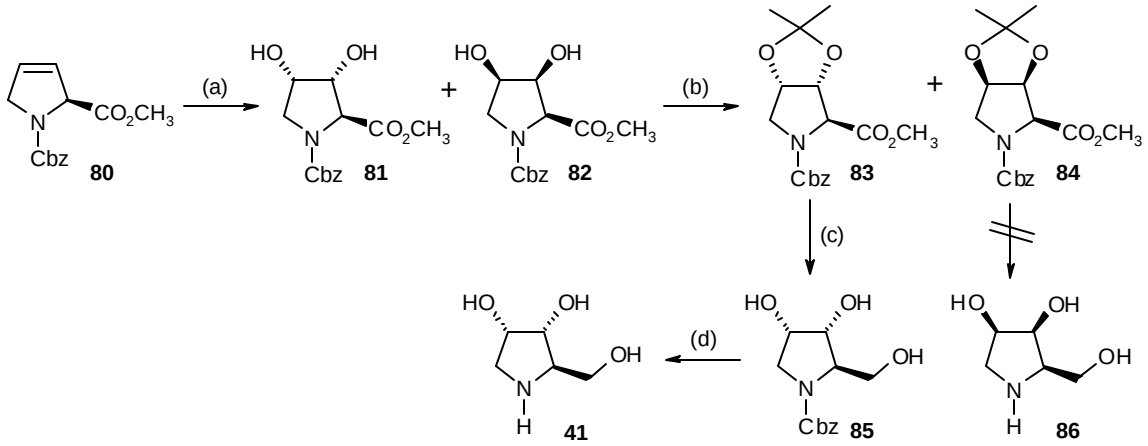
Huwe *et al.* [137] used the vinyl derivative **73** of glycine methyl ester hydrochloride for the synthesis of (2*R*,3*R*,4*R*)-**39** and (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol **41** (**Scheme 15**).[137] Reduction of the *N*-Cbz-vinyl derivative **73** with $LiBH_4$ afforded **74**, which was treated with allyl bromide to afford the *N*-allyl-4-vinyl-oxazolidin-2-one **75**.This was hydroxylated, followed by the treatment with di-*tert*-butyl dicarbonate to give the metathesis precursor **76**, which underwent intramolecular cyclization to afford dehydroprolinol derivative **77**. Subsequent deprotection, hydroxylation, followed by removal of the protecting groups afforded **41** in 78% yield.



Scheme 15 Reagent and Conditions: (a) (i) CbzCl, $NaHCO_3$, H_2O, rt, 30 min, 45%; (ii) $LiBH_4$, CH_3OH, Et_2O, rt, 2 h, 81% (b) NaH, DMF, rt, 24 h; then $BrCH_2CH{=}CH_2$, rt, 24 h, 92% (c) (i) NaOH, H_2O, EtOH, 80°C, 4 h,; (ii) Boc_2O, Et_3N, CH_2Cl_2, rt, 6 h, 82% (d) 4 mol% $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$, PhH, rt, 32 h, 95% (e) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 days, 93% (f) OsO_4, $(CH_3)_3NO$, Py, *t*-BuOH, H_2O, 80°C, 42 h, 96%; (g) HCl, CH_3OH, $AcOCH_3$, rt, 1 h, 78%; (h) (i) *m*-CPBA, Et_2O, rt, 21 days, 75%; (ii) KOH, H_2O, Me_2SO, 95°C, 64 h, 87%; (iii) HCl, CH_3OH, $AcOCH_3$, rt, 1 h, 89%.

Hassan *et al.* (1994)[138] Scheme 16

Hassan *et al.*[138] carried out the dihydroxylation of (2*S*)-3,4-dehydroproline derivative **80** to afford **81** and **82** (**Scheme 16**) for the synthesis of **41**. The mixture of diols was treated with DMP to give the separable mixture of **83** and **84**. Reduction of the major isomer **83** afforded the protected pyrrolidine **85**, which was deprotected to give (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol **41**. Compound **84** under similar condition failed to give **86**.



Scheme 16 Reagent and Conditions : (a) OsO_4, *t*-BuOH, H_2O, NMO, THF, 50°C, overnight, 97% (b) DMP, 4 M HCl, 1,4-dioxane, rt, 18 h, 92% (c) $LiBH_4$, THF, rt, 90 min (d) (i) TFA, H_2O, 35°C, 15 min, 96%; (ii) 10% Pd on C, H_2, EtOH, 18 h, 95% or **85** and sodium naphthalenide in THF, -78°C; then 0.1 M HCl, 72%.

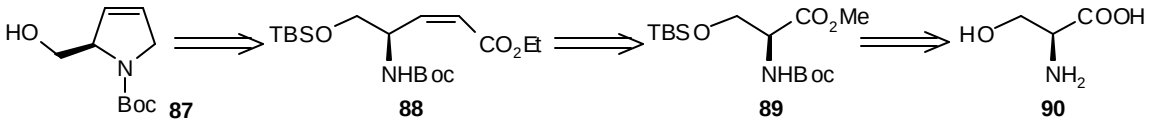
4.2.3 Present Work

Objective:

Imino sugars are well know as glycosidase inhibitors and many of them are naturally occurring. 1,4-Dideoxy-1,4-imino-D-arabinose and D-ribose are naturally occurring and hydroxylated pyrrolidines constitute one of the main class of naturally occurring sugar mimics having nitrogen in the ring. As a consequence, much attention has been focused on their potential application for cell-biological and therapeutic applications.

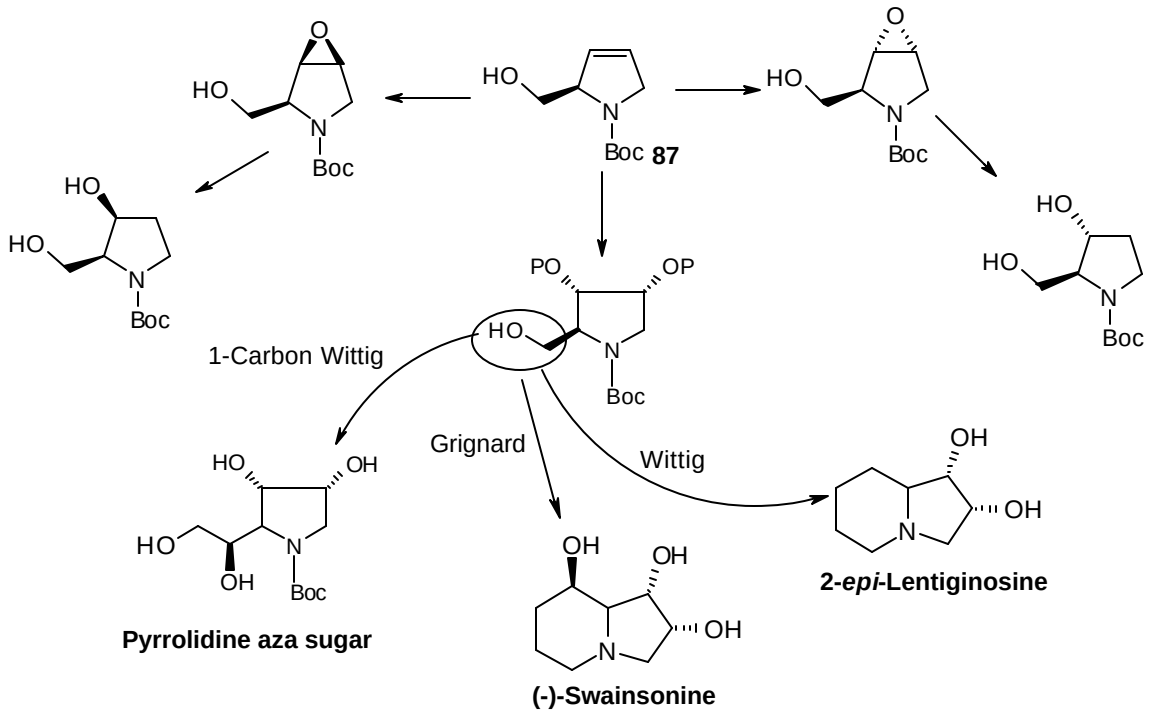
As seen from the literature, there are very few synthesis of hydroxylated pyrrolidine derivatives with the use of α-amino aldehydes as the synthetic precursor. On the above basis of the application of pyrrolidine alkaloids, and the exceptional usage of α-amino aldehydes as a building block, we thought of synthesizing such an intermediate which can be useful in the synthesis of variety of compounds of biological interest.

With above objective in mind, we planned to synthesize the synthetic pyrrolidine intermediate **87**; the enantiomer of compound **78**[137] starting from *L*-serine. As seen from



Scheme 17

the retrosynthetic ananlysis (**Scheme 17**) the desired intermediate **87** could be obtained from L-serine *via* the Wiitig olefination product **88**. The cis-olefin **88** is the important intermediate which could be easily transformed into **87**. This strategy is very

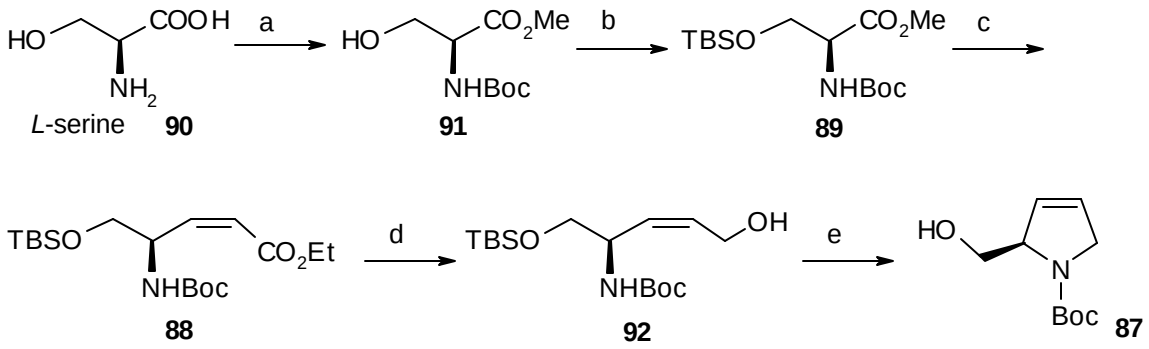


Scheme 18

short and efficient in practicability. The desired intermediate could then be easily transformed into bioactive molecules like swainsonine, lentiginosine and related compounds (**Scheme 18**), which renders our synthetic intermediate **87** a powerful tool for the synthesis of aza sugars.

4.2.4 Results and Discussion

As per our retrosynthetic analysis we started our approach towards the desired synthetic intermediate **87**, with α-amino acid; *L*-serine **90** (**Scheme 19**). Following the literature precedence[18,19,21-28], the amino group of *L*-serine **90** was protected using di-*tert*-butyldicarbonate (Boc_2O), as a Boc derivative and the acid functionality was esterifed using methyl iodide to afford compound **91**, whose spectroscopic data was matched with the literature one[18,19,21-28]. The free hydroxyl group of compound **91** was then protected with the use of TBSCl and Et_3N to furnish the TBS-derivative **89**. The ^1H NMR showed the two group of CH_3 protons linked with the silyl of the TBS group at δ -0.05 and -0.88 confirming the protection. The IR spectrum showed the absence of hydroxy group. The compound **89** was then subjected under reductive conditions with DIBAL-H in toluene to afford the aldehyde which was subsequently reacted without characterization with the two



Scheme 19 Reagent and Conditions : (a) (i) Boc_2O, NaOH, 1,4-dioxane, 0°C-rt; then $KHSO_4$, 4 h; (ii) K_2CO_3, MeI, 0°C-rt, 1 h (b) TBSCl, imidazole, CH_2Cl_2, 0°C-rt, 4 h 95% (c) (i) DIBAL-H, toluene, -78°C, 1.5 h; (ii) $Ph_3P{=}CHCO_2Et$, MeOH, 0°C, overnight, 82% (d) DIBAL-H, CH_2Cl_2, 0°C, 2 h, 75% (e) (i) MsCl, Et_3N, CH_2Cl_2, 0°C-rt, 3 h; (ii) (1:1) TFA-CH_2Cl_2, rt, 1 h; (iii) Et_3N, Boc_2O, CH_2Cl_2, 0.5 h, 65% (3 steps).

carbon Wittig ylide in MeOH at 0°C to afford the α,β-unsaturated-*cis*-olefin **88**. The ^{1}H NMR spectrum of **88** showed the olefinic protons at δ 5.93-6.00 and δ 6.85-6.96. The ^{13}C NMR spectrum showed the presence of olefinic carbons at δ 121.85 & 146.30 and the carbonyl function of the ethyl ester at δ 165.93 . The α,β-unsaturated ester **88** was then reduced to allylic alcohol **92** by DIBAL-H at 0°C. The 1H NMR spectrum of **92** showed the allylic protons at δ 5.68-5.87 with absence of the ethyl ester protons at δ 1.29 (CH_3 protons) and δ 4.19 (CH_2 protons). Also, there was presence of olefinic carbons in the ^{13}C NMR spectrum of **92** at δ128.89 & 130.86; which showed the shift in corresponding compound **88** with the absence of carbonyl carbon of the ethyl ester at δ 165.93. The allylic free hydroxyl group of **92** was mesylated, the protecting groups deprotected and the resultant compound cyclised to the desired synthetic intermediate **87**. The spectroscopic data were in accordance with the literature[137].

4.2.5. Conclusion

In conclusion, we have developed a simple, short and efficient route to the synthetic pyrrolidine aza precursor which can thus be easily transformed into various target molecules of biological interest.

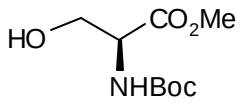
4.2.6. Experimental section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz machine and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan LCMS mass spectrometer. Elemental analyses were carried out on a Carlo Erba

CHNS-O analyzer. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

Preparation of *2-tert*-butoxycarbonylamino-3-hydroxypropionic acid methyl ester, 91



91

A solution of di-*tert*-butyldicarbonate (29.09 g, 133.28 mmol) in dioxane (90 ml) is added to an ice cold solution of L-serine **90** (10.0 g, 95.24 mmol) in 1N NaOH (7.61 g in 190 ml H_2O) by means of an addition funnel. The two phase mixture is stirred at 5^oC for 30 min, then allowed to warm to room temperature over 3.5 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half its original volume at 35^oC, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 150 ml). The combined extracts are dried over Na_2SO_4, filtered and concentrated to give 18.5 g (94% crude yield) of *N*-Boc-L-serine as colorless, sticky foam which is used without further purification.

To a ice cold solution of *N*-Boc-L-serine (18.5 g, 90.24 mmol) in DMF (160 ml) is added solid K_2CO_3 (13.70 g, 99.27 mmol). After stirring for 10 min in an ice bath, methyl iodide (25.63 g, 180.49 mmol) is added to the white suspension and stirring continued at 0^oC for 30 min. Where upon the mixture solidifies. The reaction is warmed to room temperature and stirred for additional 1 h or so at which point TLC analysis indicates complete formation of the methyl ester. The reaction mixture is filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase is washed with brine, dried, filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (3: 7) as eluent gave *N*-Boc-L-serine methyl ester **91** (17.73 g, 85%) as a thick liquid.

Yield: 17.73 g, 85 % (2 steps)

$[\alpha]_D^{20}$: 18.0 (c = 5.0, MeOH) [Lit.[18] $[\alpha]_D^{20}$]: 17.5 (c = 5.0, MeOH).

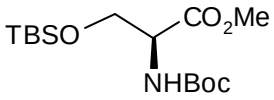
IR ($CHCl_3$ cm^{-1}): ν_{max} 1638, 1735, 3354, 3480

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41(s, 9H), 3.64-3.68 (m, 1H), 3.74 (s, 3H), 3.84-3.95 (m, 2H), 4.34 (brs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.12, 52.31, 55.62, 62.68, 79.95, 155.86, 171.48

Analysis calcd. for $C_9H_{17}NO_5$: C: 49.31; H: 7.82; N: 6.39 Found: C: 49.28; H: 7.80; N: 6.42.

Preparation of, (2*S*)-2-*tert*-butoxycarbonylamino-3-(*tert*-butyldimethylsilanyloxy)-propionic acid methyl ester, 89



89

To ice cooled solution of *N*-Boc-L-serine methyl ester **91** (5.0 g, 22.80 mmol) in CH_2Cl_2 (70 ml) was added imidazole (3.10 g, 45.53 mmol) and *tert*-butyldimethylsilyl chloride (5.16 g, 34.23 mmol). The reaction mixture was allowed to warm at room temperature over 4 h at which TLC analysis shows the reaction to be complete. The reaction was quenched by addition of water (100 ml) and extracted with CH_2Cl_2 (3 x 60 ml). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated. The silica gel column chromatography of the crude product using petroleum ether / EtOAc (9.5:0.5) as eluent gave **89** (7.22 g, 95%) as a colorless oil.

Yield: 7.22 g, 95 %

[a**]$_D^{20}$**: -21.0 (c = 4.0, $CHCl_3$)

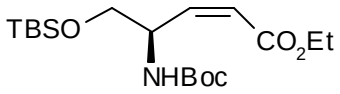
IR ($CHCl_3$ cm^{-1}): ν_{max} 1658, 1750, 3438

^{1}H NMR (200 MHz, $CDCl_3$): δ -0.05 (s, 6H), 0.78 (s, 9H), 1.37 (s, 9H), 3.68 (s, 3H), 3.90-4.04 (m, 2H), 4.26-4.39 (m,1H), 5.31 (brs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ -6.23, 17.59, 25.16, 27.66, 51.19, 55.19, 63.24, 78.35, 154.44, 170.21

Analysis calcd. for $C_{15}H_{31}NO_5Si$: C: 54.02; H: 9.37; N: 4.20, Si: 8.42 Found: C: 54.11; H: 9.40; N: 4.18, Si: 8.40.

Preparation of, (2*S*)-4-*tert*-butoxycarbonylamino-5-(*tert*-butyldimethylsilanyloxy)-pent-2-enoic acid ethyl ester, 88



88

A solution of **89** (7.0 g, 20.98 mmol) in toluene (50 ml) is cooled to -78°C. To this solution is added at -78 °C a solution of 2.0 M DIBAL-H (16.6 ml). The rate of addition is adjusted so as to keep the internal temperature below -65 °C and takes approximately 1 h to complete. The reaction mixture is stirred for an additional 2 h at -78°C. The reaction is quenched by slowly adding 10 ml of cold (-78°C) methanol (evolution of hydrogen occurs) so as to keep the internal temperature below -65 °C. The resulting white emulsion is slowly poured into 75 ml of ice cold 1N HCl with swirling over 15 min, and the aqueous mixture is then extracted with EtOAc (3 x 175 ml). The combined organic layers were washed with brine (150 ml), dried over Na_2SO_4, filtered and concentrated to give 6.05 g of crude product as a colorless oil. The aldehyde was used without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (7.65 g, 21.98 mmol) in dry methanol (60 ml) at 0°C was added a solution of above aldehyde in dry MeOH (30 ml). The reaction mixture was stirred at 0°C overnight. It was then concentrated and purified by silica gel column chromatography using petroleum ether / EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **88** (6.43 g, 82%).

Yield: 6.43 g, 82 %

$[\alpha]_D^{20}$: -15.0 (c = 1.44, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1740, 2830, 2956, 3430

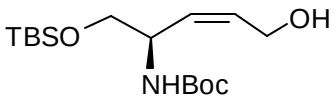
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.05 (s, 6H), 0.88 (s, 9H), 1.28 (t, 3H, *J* = 8Hz), 1.45 (s, 9H), 3.68-3.76 (m, 2H), 4.19 (q, 2H, J=8Hz), 4.30-4.37 (m, 1H), 5.34 (brs, 1H), 5.93-6.00 (m, 1H), 6.90 (dd, 1H, *J* = 6Hz, *J* = 10Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.35, 14.16, 18.16, 25.74, 28.27, 53.08, 60.18, 64.63, 79.48, 121.86, 146.30, 155.16, 165.93

Mass (ESI): 391 (M^++NH_4^+), 374 (M+1), 243

Analysis calcd. for $C_{18}H_{35}NO_5Si$: C: 57.90; H: 9.45; N: 3.75, Si: 7.50 Found: C: 57.98; H: 9.49; N: 3.71, Si: 7.59

Preparation of, (2*S*)-[1-(*tert*-butyldimethylsilanyloxymethyl)4-hydroxy-but-2-enyl]carbamic acid-*tert*-butyl ester, 90



92

To a solution of olefin **88** (5.0 g, 13.38 mmol) in CH_2Cl_2 (50 ml) at 0 ^oC was added DIBAL-H (13.4 ml, 26.79 mmol). The reaction mixture was the stirred for 2 h at 0 ^oC. After completion of reaction, it was quenched with saturated solution of sodium potassium tartrate and stirring was continued for further 1 h. The precipitate formed was filtered and the filtrate concentrated. Silica gel column chromatography using petroleum ether / EtOAc (1:1) as eluent furnished allylic alcohol **92** (3.33 g, 75%) as a thick liquid.

Yield: 3.3 g, 75 %

$[\alpha]_D^{20}$: -11.93 (C=1.24, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1658, 2928, 2936, 3350, 3438

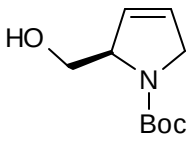
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.05 (s, 6H), 0.88 (s, 9H), 1.44 (s, 9H), 3.24 (brs, 1H), 3.60-3.66 (m, 3H), 4.12-4.15 (m, 2H), 4.93 (brs, 1H), 5.68-5.87 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.47, 18.16, 25.77, 29.31, 53.56, 62.38, 65.29, 77.29, 128.99, 130.83, 155.64

Mass (ESI): 349 (M^++NH_4^+), 331 (M^+)

Analysis calcd. for $C_{16}H_{33}NO_4Si$: C: 57.97; H: 10.03; N: 4.22, Si: 8.47 Found: C: 57.93; H: 10.10; N: 4.26, Si: 8.50.

Preparation of (2*S*)-2-hydroxymethyl-2.5-dihydroxypyrrole-1-carbamic acid-*tert*-butyl ester, 87



87

To a ice cold solution of **92** (3.0 g, 9.05 mmol) in CH_2Cl_2 (30 ml) was added Et_3N (1.83 g, 18.08 mmol) and mesylchloride (1.35 g, 11.78 mmol). The reaction was the stirred for 3 h

at room temperature. After completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (25 ml), washed with brine and dried (Na_2SO_4) and concentrated. To this crude product in CH_2Cl_2 (30 ml) was added TFA (15 ml, excess) and the reaction stirred for 1 h at room temperature. After this the reaction mixture was concentrated to dryness to afford 0.8 g of the cyclized product.

To the solution of crude product CH_2Cl_2 (15 ml) was added Et_3N (1.24 g, 12.25 mmol) and Boc_2O (1.96 g, 8.98 mmol). The reaction was stirred for 0.5 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product with petroleum ether / EtOAc (7:3) as eluent afforded **87** (1.16 g, 65%) as a yellow oil.

Yield: 1.16 g, 65 %

[a **]$_D^{20}$:** 1.6 (C=0.54, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1586, 1680, 2936, 3380

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.97 (brs, 1H), 3.66-3.75 (m, 2H), 4.07 (d, 2H, *J* = 9Hz), 4.28 (brs, 1H), 4.91-4.99 (m, 1H), 5.80-5.89 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 28.58,44.48, 53.66, 65.24, 80.28, 128.22, 132.32, 156.10

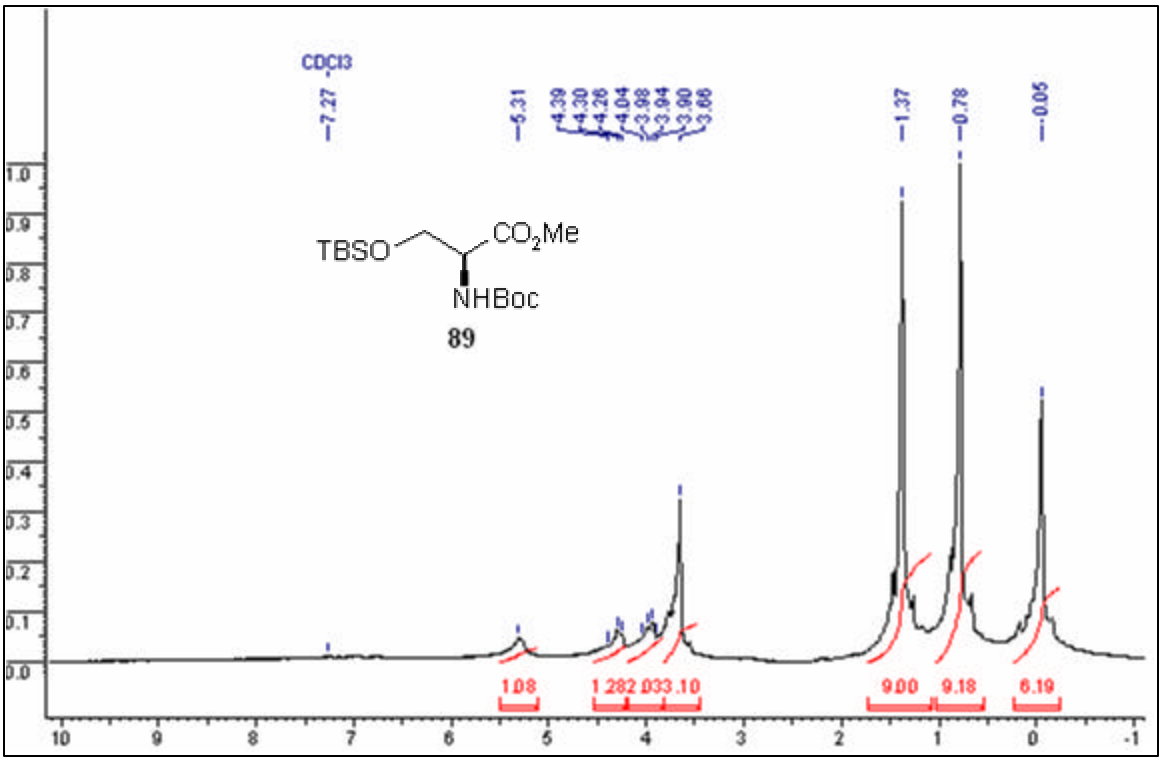
Mass: 199 (M^+), 181, 168, 101, 99

Analysis calcd. for $C_{10}H_{17}NO_3$: C: 60.28; H: 8.60; N: 7.03 Found: C: 60.25; H: 8.62; N: 7.05.

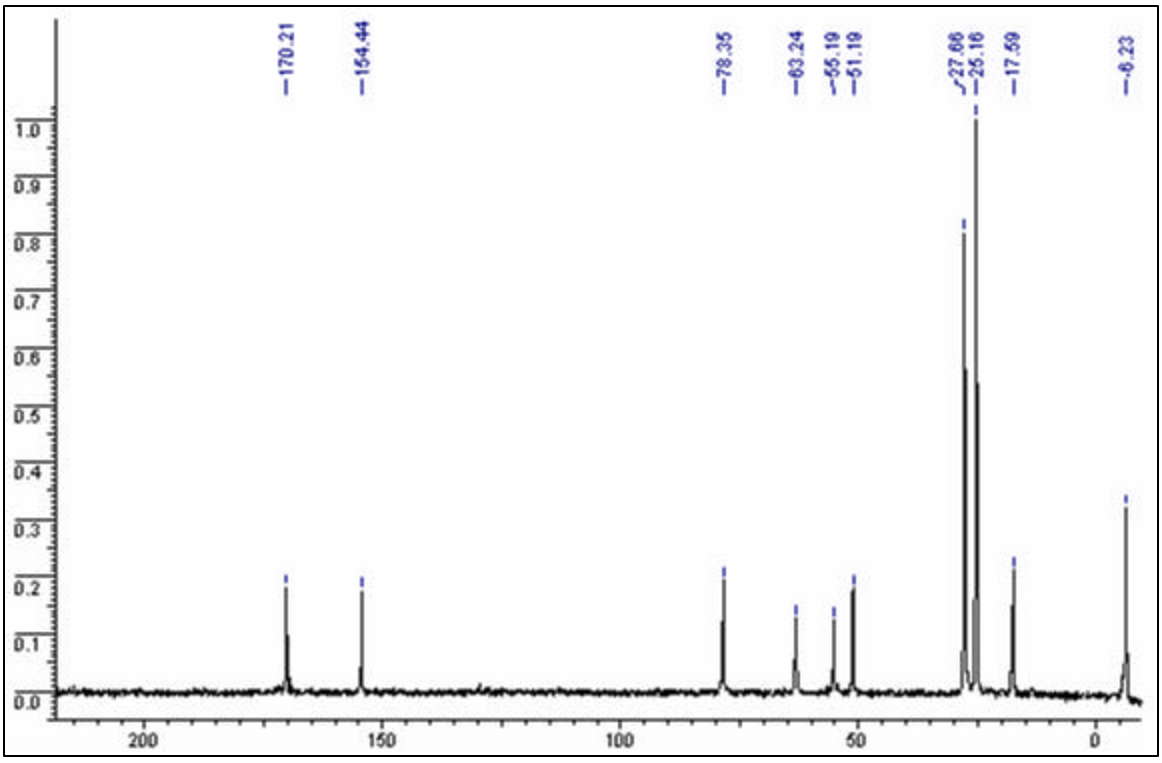
4.2.7. Spectra

1. ^{1}H NMR of **89**
2. ^{13}C NMR of **89**
3. ^{1}H NMR of **88**
4. ^{13}C NMR of **88**
5. ^{1}H NMR of **87**
6. ^{13}C NMR of **87**

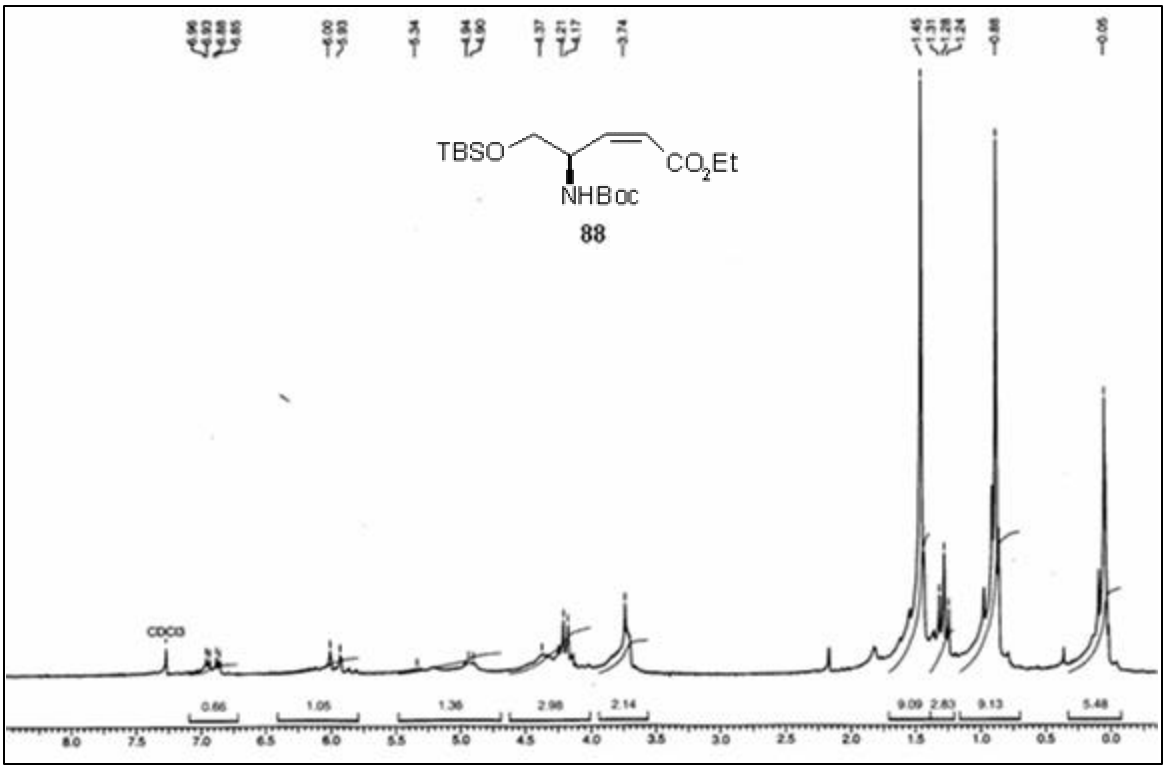
➢ ^{1}H NMR Spectra of **89**



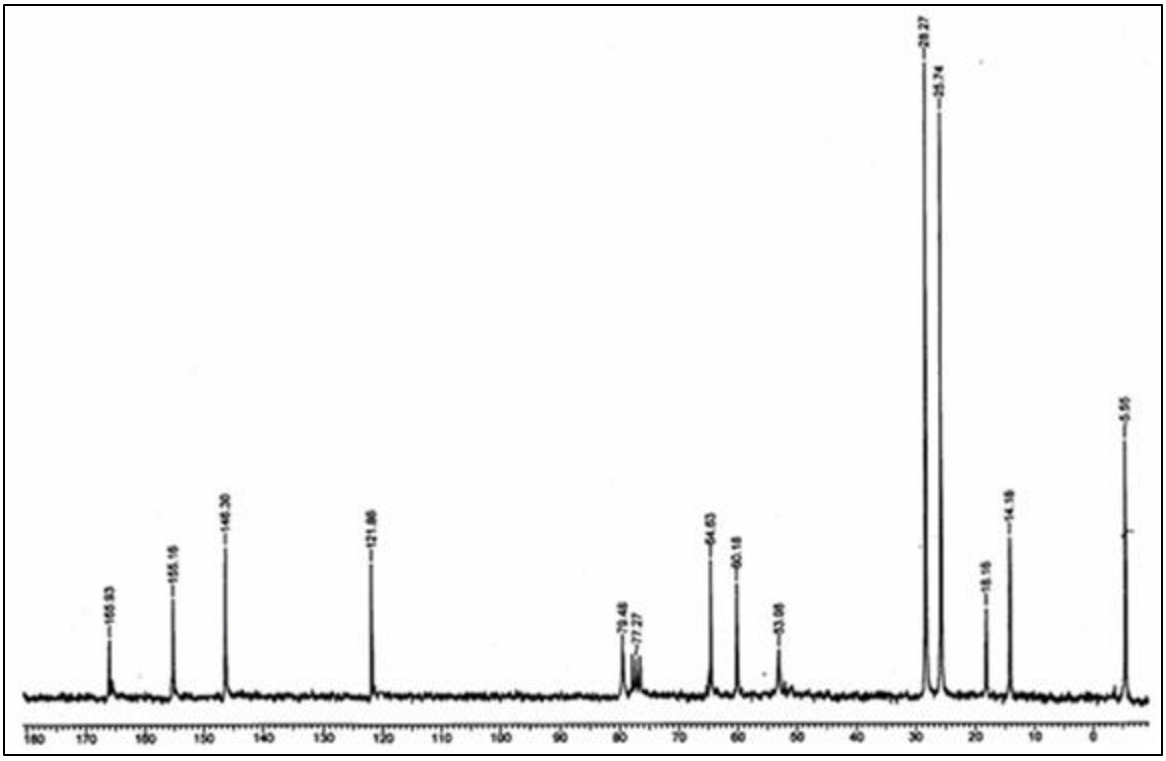
➢ ^{13}C NMR Spectra of **89**



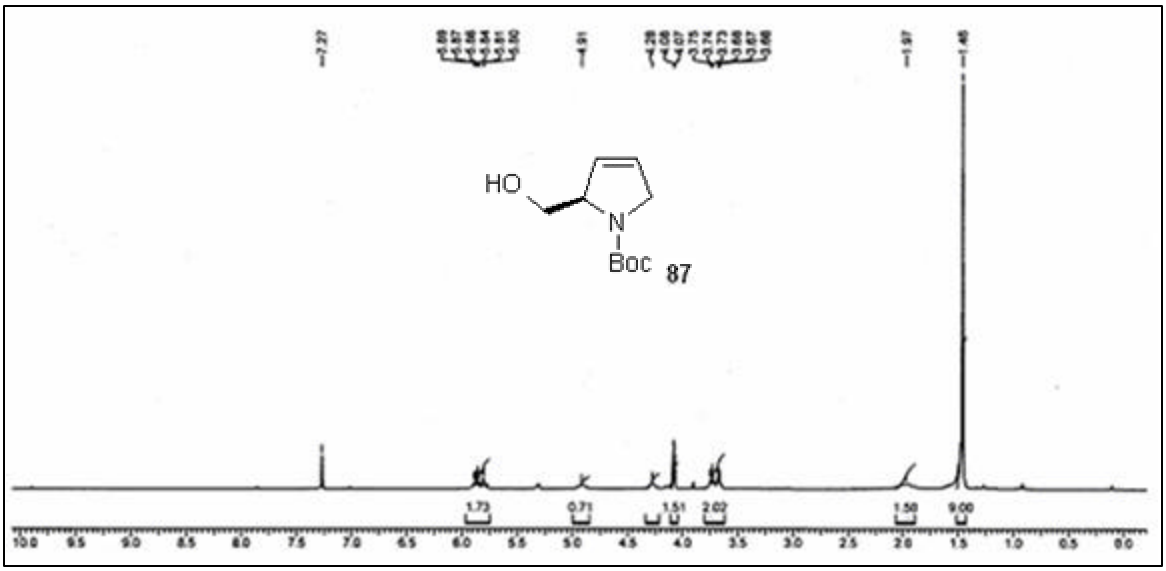
➢ ^{1}H NMR Spectra of **88**



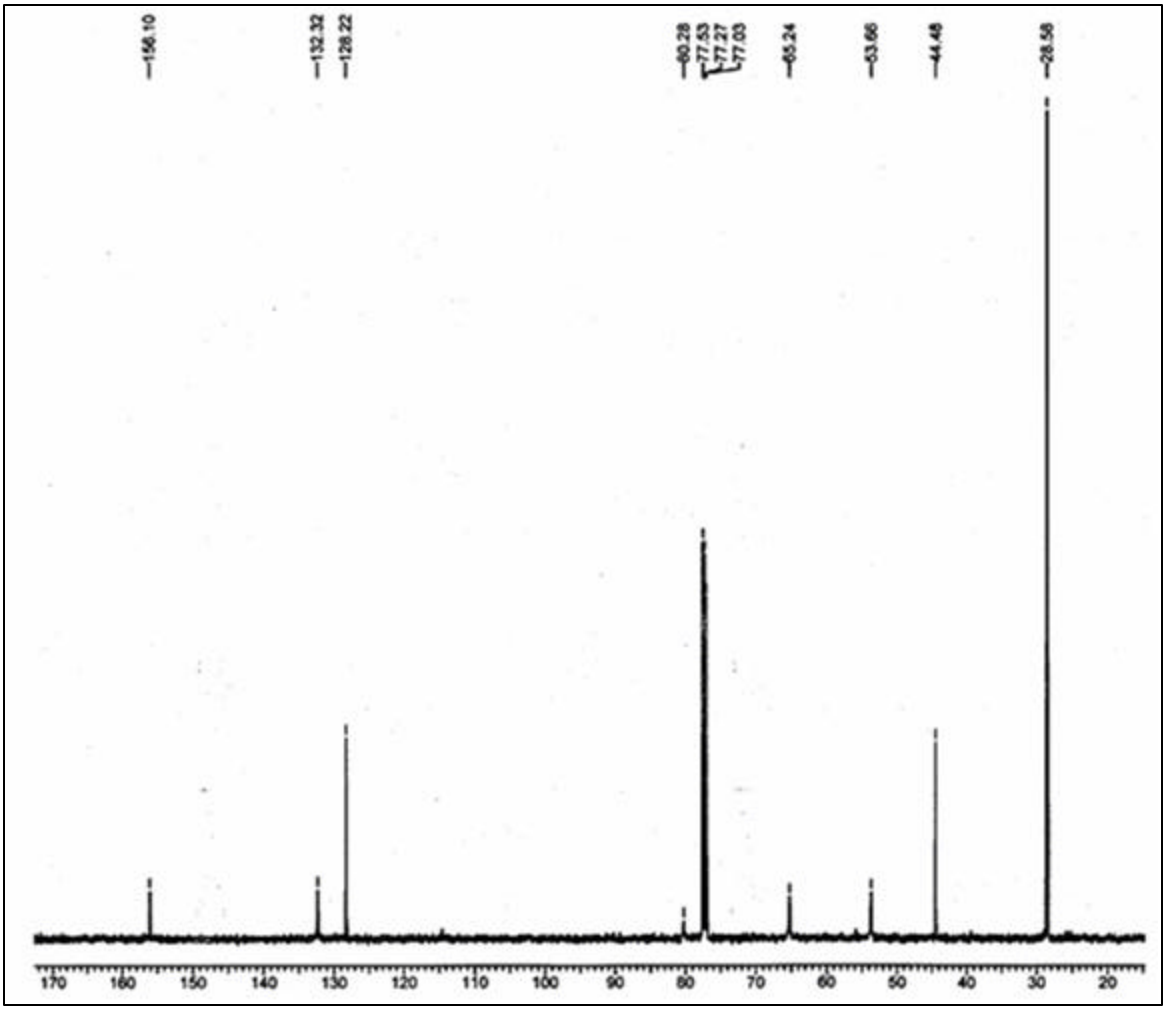
➢ ^{13}C NMR Spectrum of **88**



➢ ^{1}H NMR Spectra of **87**



➢ ^{13}C NMR Spectrum of **87**



4.3 SECTION B

Construction Of 6-membered Aza Building Block For The Synthesis Of a,a¢-Piperidinol Alkaloids

4.3.1 INTRODUCTION

All life is made of molecules, and the chemical reactions common to all living things involve the primary metabolism of nucleic acids, proteins, carbohydrates and lipids. They occur perhaps in just one species, though more commonly in several. They are obviously then, not essential for life, though they usually help survival. These are the products of secondary metabolism. The exploration of compounds produced by the secondary metabolism of plants, microorganisms, fungi, insects, mammals, and every other type of living thing has hardly begun. Even so, the variety and richness of the structures are overwhelming. Without some kind of classification the task of description would be hopeless.

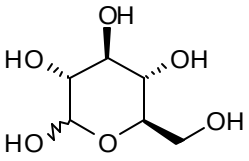
Alkaloids were known in ancient times because they are easy to extract from plants and some of them have powerful and deadly effects. Any plant contains millions of chemical compounds, but some plants like the deadly nightshade, can be mashed up and extracted with aqueous acid to give a few compounds soluble in that medium, which precipitate on neutralization. These compounds were seen to be "**like alkali**" and Meissner, the apothecary from Halle, in 1819 named them "**alkaloids**".

Polyhydroxylated piperidine alkaloids are frequently found in living system, and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes. Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids important tools in the study of biochemical pathways. A number of piperidines and indolizidines bearing carbonaceous substituents at both α and α' positions have been isolated from

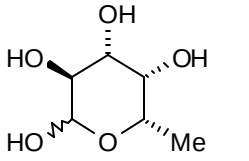
natural sources and many of them have received much attention due to a variety of biological activities. 3-Piperidinol alkaloids having appendages at α and α' positions also have been also isolated from plants. These 3-piperidinol alkaloids also exhibit a variety of pharmacological properties such as anesthetic, analgesic and antibiotic activities. Recently, the alkaloids containing this ring system were isolated form marine species and all of them showed substantial cytotoxic activity against human solid tumor cell lines. These 2,6-dialkylated piperidine alkaloids have been found abundantly in nature and are key structural units in medicinally important compounds.[139]

Prosopis alkaloids, isolated from *Prosopis africanan*, forms a subgroup possessing a characteristic 3-hydroxy function.[140] Structurally these compounds, possessing a polar head group and a hydrophobic aliphatic tail, can be considered as cyclic analogues of membrane lipid sphingosine.[141]

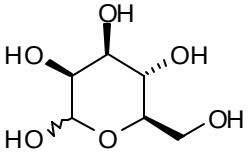
Hydroxylated piperidine alkaloids are found frequently in living system,[140a,142] and the wide range of potent physiological effects stems from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[143] Important structure-activity relationships for these molecules center around the stereochemical configuration of hydroxyl functionality which are β to the nitrogen. Due to the prominence of D-glucose **93** and D-mannose **95** in biological processes, many alkaloids mimic the C-4 and C-6 structural features of these carbohydrates (**Figure 5**). Polyhydroxylated piperidine alkaloids exhibit selective inhibition of a number of biological important pathways including the binding and processing of glycoproteins.[144]



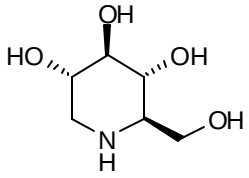
93
1-D-Glucose



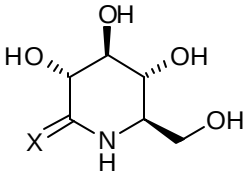
94
Fucose



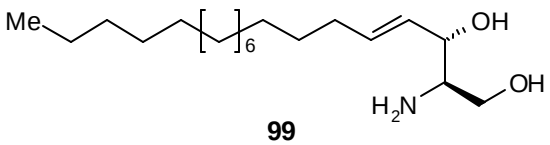
95
D-Mannose



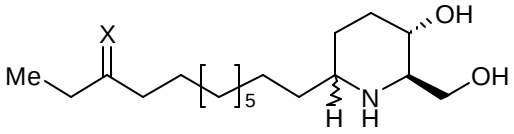
96
Deoxynojirimycin



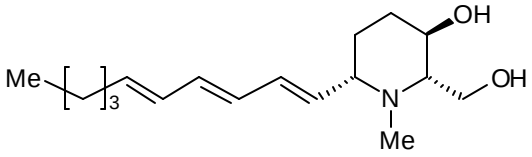
97: X=H,H; Deoxymannojirimycin
98: X=O; D-mannonolactam



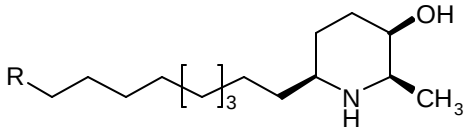
99
Sphingosine



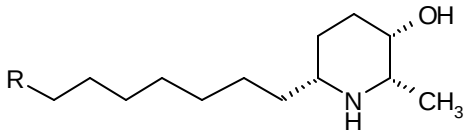
100: X=O; b=H; Prosophine **102: X=H,H; b=H**
101: X=O; a=H; Prosophylline **103: X=H,H; a=H**



104
Micropine



105: R = -COMe; Prosafrinine
106: R = -CH_2COMe; Cassine



107: R = -CO_2H; Carpamic acid
108: R =-$(CH_2)_5$COMe; Spectaline

Figure 5

The construction of versatile chiral building blocks provides us with powerful tools for the efficient syntheses of biologically active natural products. A large number of methods leading to the syntheses of the piperidine,[145,146] decahydroquinoline,[146] indolizidine[146,147a,b] and quinolizidine[146,147b] systems have already been developed. For instances, a piperidin-3-ol bearing appendages with versatile functionality at the 2- and 6-positions would serve as a building block for efficient syntheses of piperidin-3-ols found in natural products,[148] and several methods for their stereoselective construction have been reported. These methods

involve strategies starting with phytooxygenation of pyridine ring system,[149] intramolecular cyclization reactions of a 2-hydroxy-5-ketoamine[150], oxidative cleavage of a 2-azabicyclo [2,2,2] octan-5-one ring system[151], and aza-annulation reaction of an enamine ester with acrylic anhydride[152]. Other methods, which have been investigated, for this chiral construction involve an aza-Achmatowicz rearrangement of a furan derivative[153], an intramolecular double Michael reaction[154] or palladium-catalyzed cyclization[155] of an N-protected amino-olefin, radical cyclization of a 2,3-dihydrooxazolone derivative[156] and a 1,3-dipolar cycloaddition of a nitrone to a dipolar cycloaddition of a nitrone to a dipolarophile.[157]

4.3.2 Review of Literature

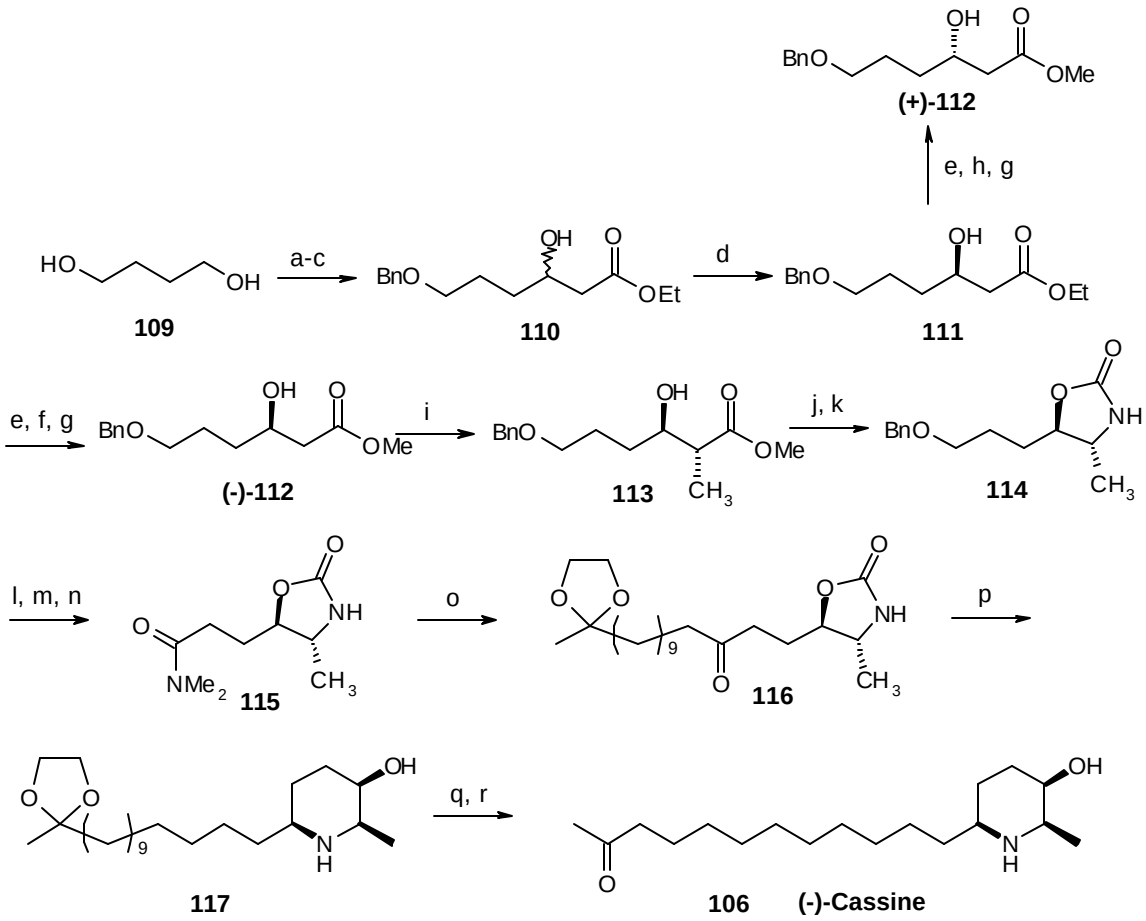
Due to the biological activities presented by 3-piperidinol alkaloids, they have gained a huge attention by the chemists to synthesize these kind of alkaloids. There are various synthetic methods in the literature for the synthesis of α,α′-3-piperidinol alkaloids and we can classify the methods for syntheses as follows:

1. Achiral substrate as a starting source
2. Carbohydrate substrate as a starting source
3. Amino acids or chiral substrate as a starting source

1. Achiral substrate as a starting souce:

Meyer *et al.* (1997)[158] Scheme 20

A efficient and flexible route to (-)-cassine **106** was accomplished by Meyer *et al.*[158] The key component of the synthesis was a chiral-β-hydroxyester **112**, which was obtained by lipase catalyzed kinetic resolution. Based on this starting material, diastereoselective alkylation of its dianion **111**, Curtius rearrangement to a 2-oxazolidinone **114**, Grignard reaction to introduce the side-chain and conversion of the aliphatic-2-oxazolidinone **116** into a 3-piperidinol **117** by imine cyclizaiton lead to the exemplary total synthesis of **106**.

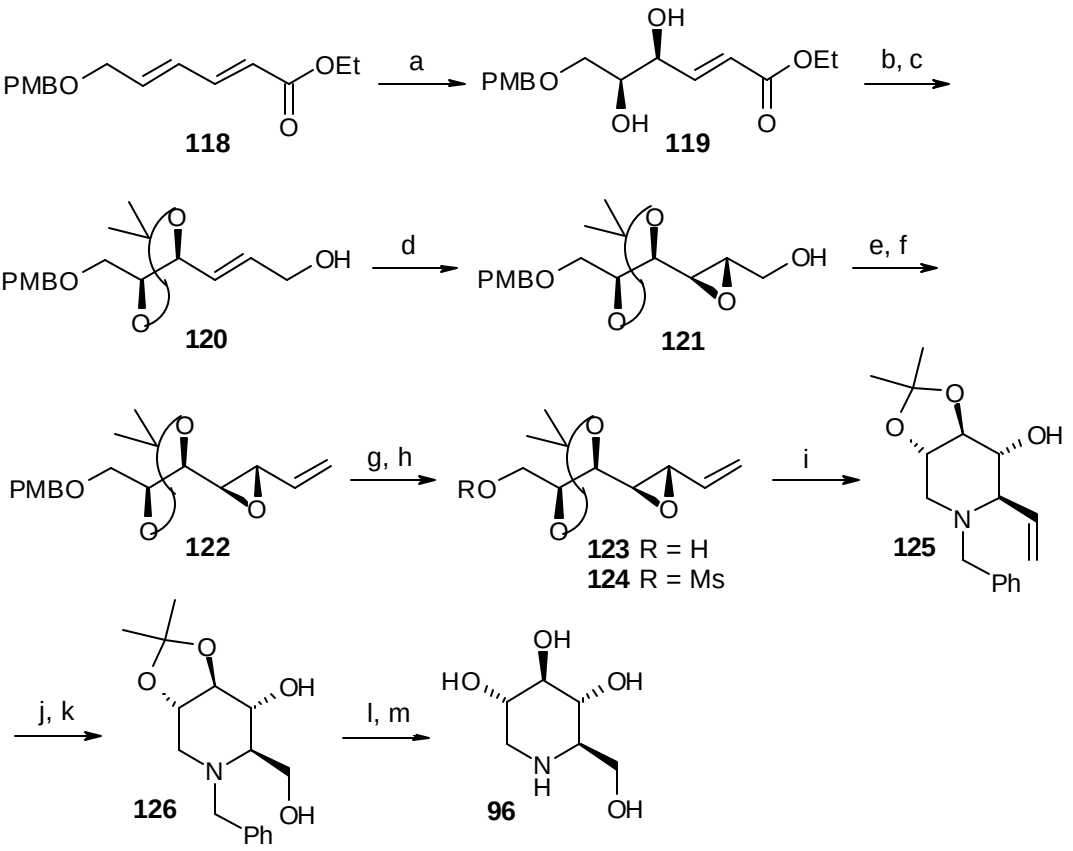


Scheme 20 Reagent and Conditions: (a) KO-*t*-Bu, BnCl, 90-130°C, 85% (b) $(COCl)_2$, Et_3N, DMSO, -78°C-rt, 88% (c) Zn/Cu, $BrCH_2CO_2Et$, THF/Et_2O, reflux, 89%, (d) PPL. Phosphate buffer, rt (e) NaOH, EtOH, 0°C, 100% (f) (1*R*, 2*S*)-ephidrine, EtOAc; then H_2SO_4, Et_2O (g) CH_2N_2, Et_2O, 100% (h) (1*S*, 2*R*)-ephidrine, EtOAc then H_2SO_4 (i) LDA, CH_3I, THF, -78°C-rt (j) N_2H_4, DMAP (cat.), MeOH (k) $NaNO_2$, 6 N HCl, MeOH, 0°C-rt, 66% (l)10% Pd/C, 3.5 bar H_2, MeOH, rt, quantitative (m) Jone's oxidation (n) CDI, CH_2Cl_2, 0°C-rt; then $NHMe_2$, 0°C-rt, 77% (o) Grignard reagent from 12-bromo-2-dodecanon-ethylenacetal, THF, HMPA, reflux, 51% (p) $Ba(OH)_2$, dioxane, reflux (q) 10% Pd/C, H_2, MeOH, 73% (r) 2 N H_2SO_4, MeOH, reflux, 98%.

Somfai *et al.* (1998)[159] Scheme 21

An asymmetric synthesis of (+)-1-deoxynojirymycin **127** in 14 steps starting from diene **118** was executed by Somfai *et al.*[159] The key transformations in the sequence being a

Sharpless dihydroxylation and epoxidation followed by a regio- and stereoselective aminolysis of vinyl epoxide **124** to give piperidine **125**.

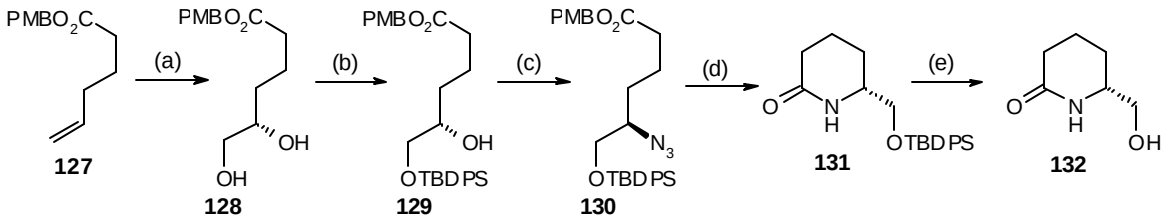


Scheme 21 Reagent and Conditions: (a) AD-mix-α, *t*-BuOH, H_2O, 62%, 97% *ee* (b) 2-methoxypropene, DMF, 97% (c) DIBAL, CH_2Cl_2, -78°C, 93% (d) (+)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, 80%, > 95% *de* (e) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, -78°C-rt, 88% (f) Ph_3PCH_3Br, KHMDS, THF, PhMe, 73% (g) DDQ, CH_2Cl_2, H_2O, 88% (h) MsCl, *i*-Pr_2Net, CH_2Cl_2, 0°C, 88% (i) $BnNH_2$, TsOH, DMSO, 120°C, 76% (j) OsO_4, NMO, *t*-BuOH, THF, H_2O; $NaIO_4$ THF, H_2O (k) $LiAlH_4$, THF, 0°C, 84% (l) TFA, MeOH, 87% (m) H_2, Pd/C,EtOH, 89%.

Shipman *et al.* (1998)[160] Scheme 22

An asymmetric synthesis of 6-(hydroxymethyl)piperidin-2-one **132** is described by Shipman *et al.*[160] Asymmetric dihydroxylation of alkenyl ester **127** using the $(DHQ)_2AQN$

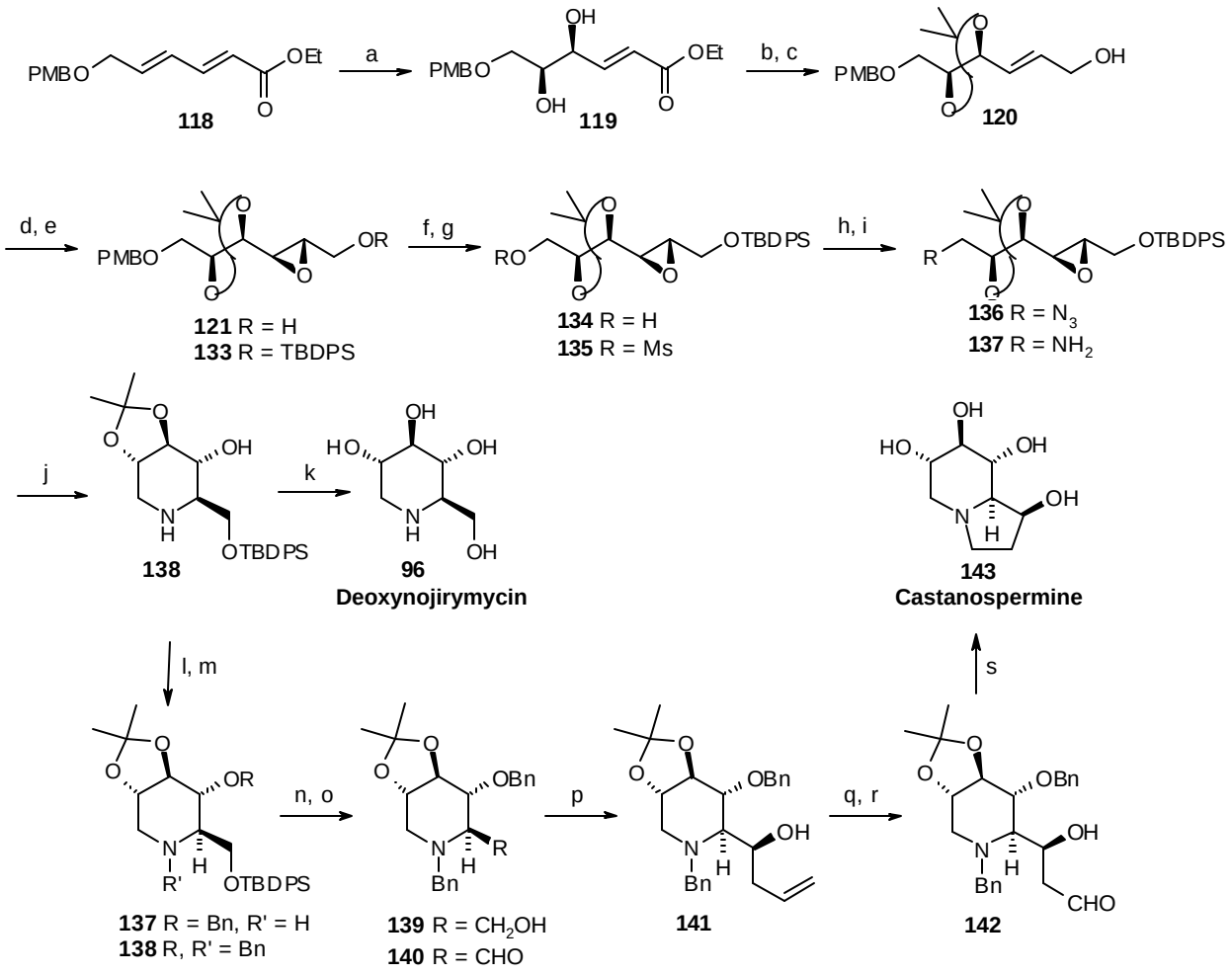
ligand provides diol **128** in >95% ee after recrystallisation. This diol can subsequently be transformed into **132** using a five step reaction sequence.



Scheme 22 Reagent and Conditions: (a) $(DHQ)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, 0^oC, *t*-BuOH, H_2O, 56%, >95% *ee* (b) TBDPSCl, imidazole, DMF, 91% (c) (i) MsCl, Et_3N, CH_2Cl_2, 0^oC, 94%; (ii) NaN_3, DMF, 80^oC, 82% (d) H_2, Pd/C, EtOH, 84% (e) TBAF, THF, 89%.

Somfai *et al.* (2003)[161] Scheme 23

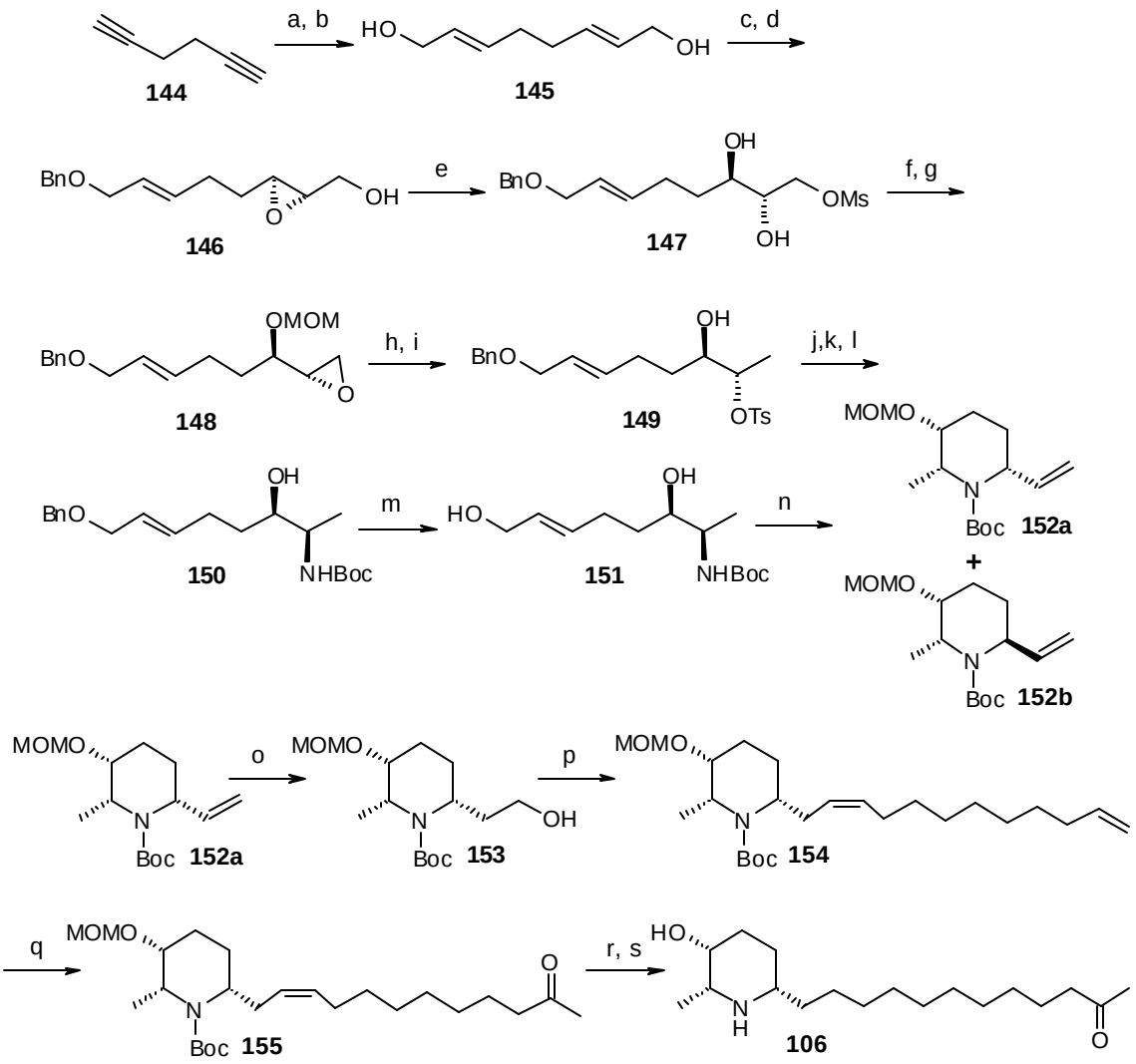
An asymmetric synthesis of deoxynojirimycin **96** and castanospermine **143** is described by Somfai *et al.*[161] starting from diene **118**. The required stereochemistry is introduced by an asymmetric hydroxylation followed by epoxidaiton. An intramolecular cyclization of amine **137** gives access to the corresponding tetra-substituted piperidine, which is a precursor to compound **96** and **143**. This work is a modification and extension of the previous work reported.[157] The problems with this approach resided in the difficulties encountered in preparing the aldehyde from compound **125** (**Scheme 21**) and hence the alternative approach from diene **118** towards alkaloids **96** and **143** was developed.



Scheme 23 Reagent and Conditions: (a) AD-mix-α, *t*-BuOH, H_2O, 62%, 97% *ee* (b) 2-methoxypropene, DMF, 97% (c) DIBAL, CH_2Cl_2, -78°C, 93% (d) (+)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, 80%, > 95% *de* (e) *t*-BuPh$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, 97% (f) DDQ, CH_2Cl_2, H_2O, 92% (g) MsCl, *i*-Pr$_2$NEt, CH_2Cl_2, 0°C, 100% (h) NaN_3, DMF, 70% (i) Ph_3P,THF, H_2O, 83% (j) EtOH, Δ, 100% (k) HCl (37%), MeOH, 100% (l) KHMDS (2.2 equiv.), BnBr (3 equiv.), THF, -78°C, 82% (m) BnBr (1.3 equiv.), K_2CO_3 (2.6 equiv.), CH_3CN, Δ, 97% (n) *n*-Bu_4NF, THF, rt, 100% (o) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, -78°C-rt, 93% (p) $CH_2CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, -65 to -60°C, 71% (q) OsO_4, NMO, *t*-BuOH-THF-H_2O (10:3:1) (r) $NaIO_4$, THF-H_2O (1:1), 84% (2 steps) (s) H_2, Pd/C, then TFA, 81%.

Makabe *et al.* (2003)[162] Scheme 24

An asymmetric synthesis of cassine **106** is described by Makabe *et al.*[162] starting from 1,5-hexadiyne **144**. The $PDCl_2$-catalyzed cyclization of amino allylic alcohol **151** gave the cyclized product **152a** with good diastereoselectivity. The versatility of compound **152a** as the building block for synthesizing *cis*-2,6-disubstituted piperidine alkaloids has been demonstrated by a total synthesis of cassine **106**.

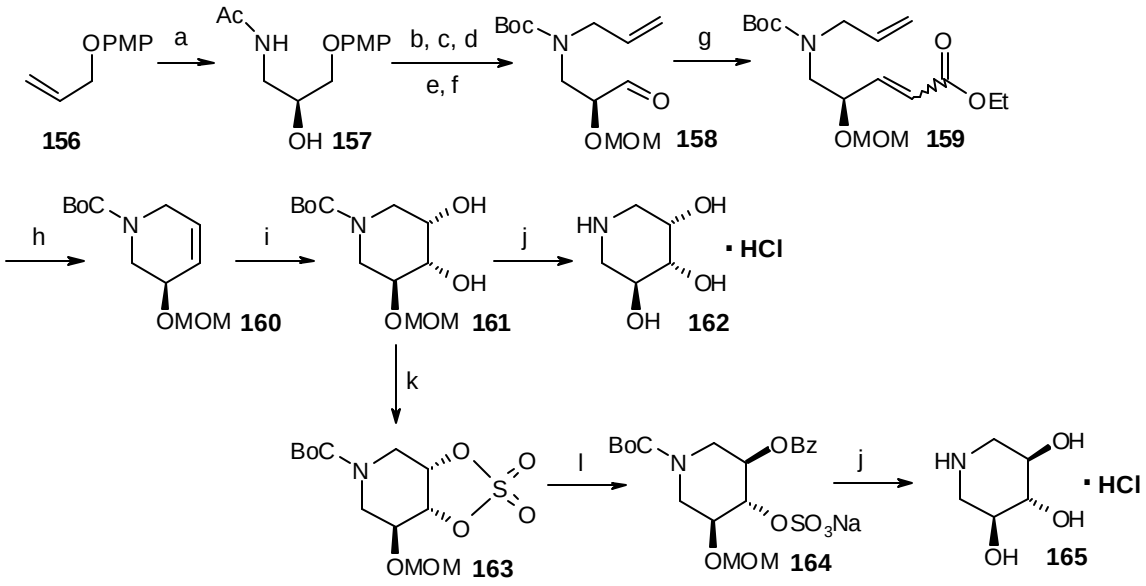


Scheme 24 Reagent and Conditions: (a) *n*-BuLi, $(HCHO)_n$, 71% (b) Na, NH_3, reflux, 76% (c) BnBr (1.5 equiv.), NaH (2.2 equiv.), *n*-Bu_4NI (0.2 equiv.), 56% (d) (+)-DET, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, 90%, > 95% *de* (e) (i) MsCl, Et_3N, CH_2Cl_2; (ii) $HClO_4$, 60^{o}C, 90% (f) K_2CO_3, 89% (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 99% (h) $LiAlH_4$, THF, 50^{o}C, 70% (i) *p*-TsCl, pyridine, 96% (j) NaN_3,

DMF, 50°C, 47% (k) Ph_3P,THF, H_2O, 81% (l) Boc_2O, Et_3N, 81% (m) Na/NH_3, 90% (n) 5 mol% $PdCl_2$, THF, (o) (i) 9-BBN from 0°C-rt; (ii) NaOH, H_2O_2, 96% (p) (i) PCC; (ii) $CH_2=CHCH_2)_8PPh_3^+I^-$, *n*-BuLi, -40°C, 67% (q) O_2, Cu_2Cl_2, $PdCl_2$, 72% (r) H_2, 5% Pd/C, 81%. (s) aq. HCl, MeOH, 100%.

Han (2003)[163] Scheme 25

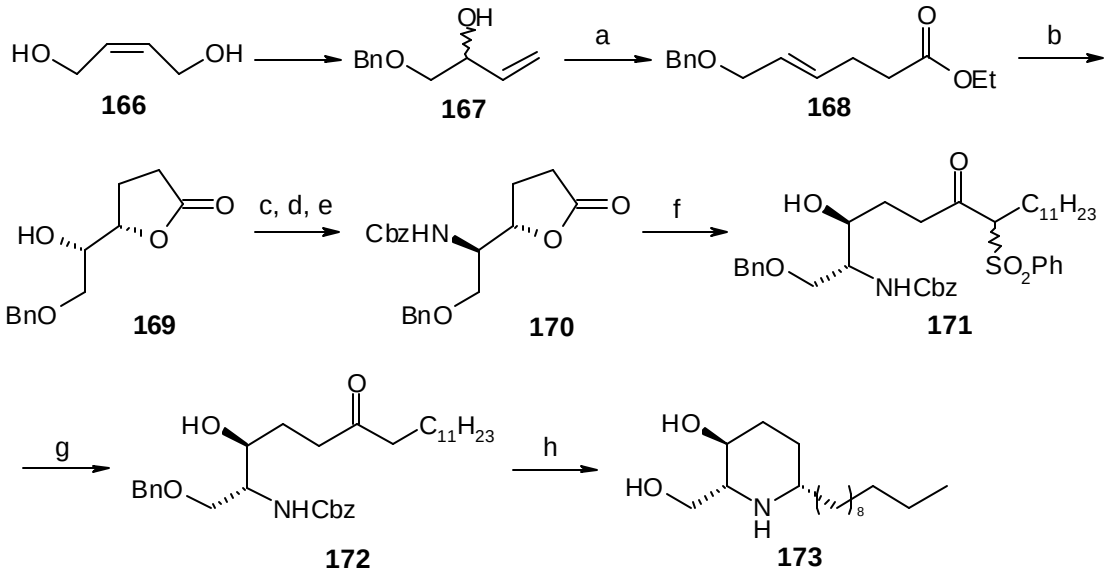
A new methodology for asymmetric synthesis of polyhydroxylated piperidines is described by Han[163] starting from readily available achiral olefin **156**. The olefin **156** was transformed into 5-des(hydroxymethyl)-1-deoxynojirimycin **165** and its mannose analog **162** *via* regioselective aminohydroxylation (AA), ring-closing metathesis (RCM), and diastereoselective dihydroxylation reactions.



Scheme 25 Reagent and Conditions: (a) $(DHQD)_2PHAL$ (6 mol%), potassium osmate (5 mol%), LiOH, AcNHBr, *t*-BuOH-H_2O (1:1), 4°C, 63% (b) MOMBr, DIPEA, CH_2Cl_2, 86% (c) Boc_2O, THF, reflux; then LiOH, 85% (d) allyl bromide, KH, THF, 97% (e) CAN, MeCN-H_2O, (4:1), 0°C, 73% (f) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, -50°C, 73% (g) Triethylphosphonoacetate, LiBr, DBU, THF, 88% (h) Second generation Grubb's catalyst, CH_2Cl_2, 89% (i) OsO_4, NMO, MeCN-H_2O (1:1), 98% (j) 6 N HCl, 80°C, 94% (k) $SOCl_2$, Et_3N, then $NaIO_4$, $RuCl_3$, CH_3CN- CH_2Cl_2-H_2O (1:1:1), 88% (l) NaOBz, DMF, 105°C; then (j), 90%.

Chavan *et al.* (2004)[164] Scheme 26

An efficient synthesis of deoxoprosophylline **173** is described by Chavan *et al.*[164] starting from readily *cis*-2-butene-1,4-diol **166** in which the Sharpless asymmetric dihydroxylation was used as the key step.

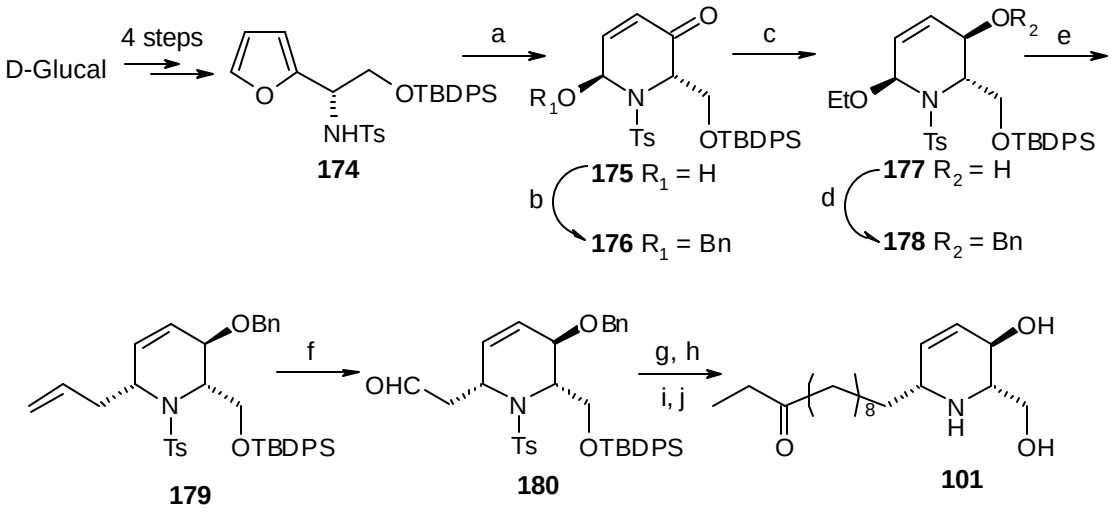


Scheme 26 Reagent and Conditions: (a) $CH_3C(OEt)_3$, cat. Propionic acid, 140°C, 2 h, 94% (b) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH-H_2O (1:1), 0°C, 24 h, 95%, 93% ee (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 92% (d) NaN3, DMF, 90°C, 89% (e) (i) TPP, H_2O, C_6H_6, 8 h; (ii) CbzCl, Et_3N, cat. DMAP, CH_2Cl_2, 75% 2 steps (f) $C_{12}H_{23}SO_2Ph$, *n*-BuLi, THF, -78°C, 24 h, 94% (g) Na-Hg, Na_2HPO_4, MeOH, -10°C, 95% (h) 20% $Pd(OH)_2/C$, H_2, MeOH, rt, 24 h, 76%.

2. Carbohydrate substrate as a starting souce:

Haroutounian *et al.* (1999)[165] Scheme 27

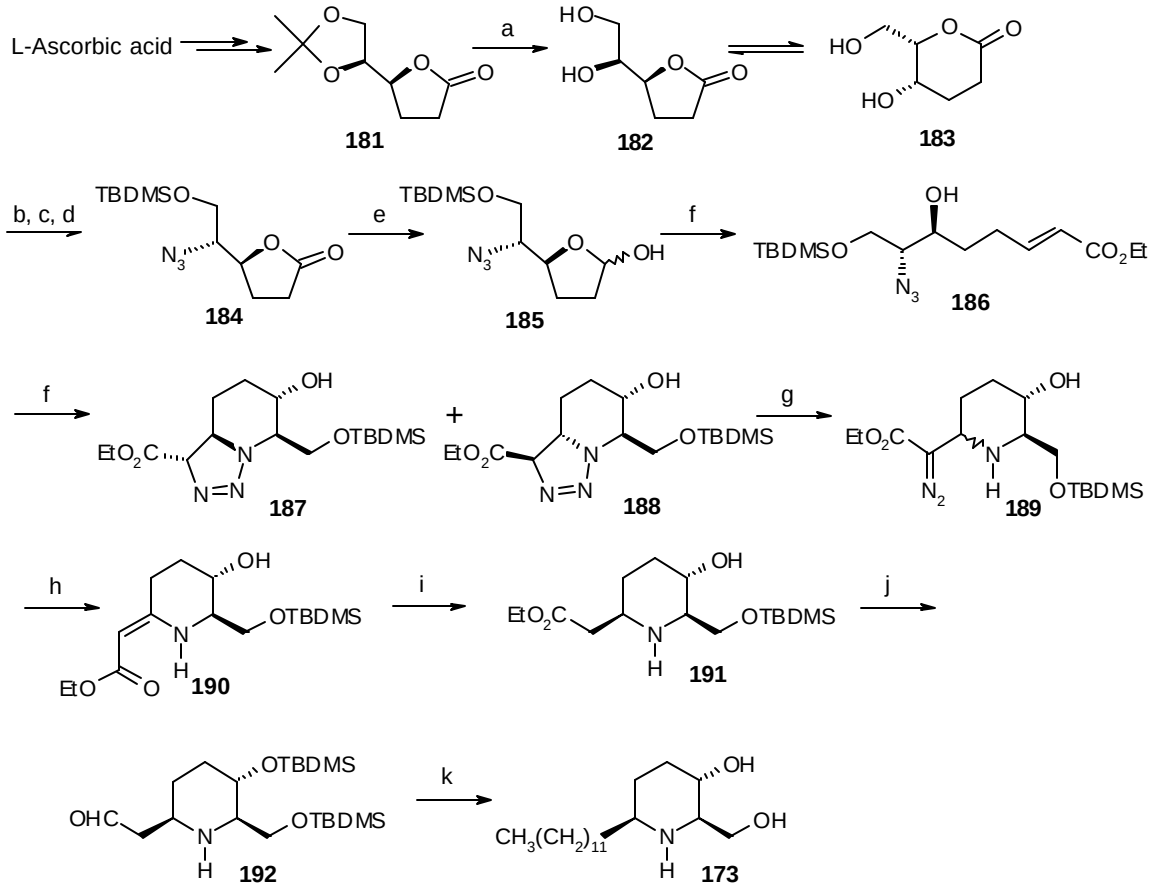
A efficient and flexible route to (-)-prosophylline **101** was accomplished by Haroutounian *et al.*[165] from D-glucal *via* (2*S*)-hydroxymethyl-dihydropyridone **174** by a 17-step synthesis in 12% overall yield.



Scheme 27 Reagent and Conditions: (a) *m*-CPBA, CH_2Cl_2, 91% (b) $HC(OEt)_3$, $BF_3.OEt_2$, 4 Å mol. Sieves, THF, 0°C, 95% (c) (i) H_2, Pd/C, AcOEt, 91%; (ii) $NaBH_3CN$, AcOH, MeOH, 0°C-rt, 85% (d) NaH, BnBr, Bu_4NI, THF, 91% (e) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78°C, 87% (f) (i) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_2$, Na_2SO_3, *t*-BuOH/H_2O (1:1); (ii) $NaIO_4$, H_2O/EtOH (1:1), 96%, two steps (g) PPh_3, $CH_3CH_2C(OCH_2)_2C_7H_{14}Br$, *n*-BuLi, 68% (h) HCl, H_2O (i) H_2, Pd/C, EtOH, 88%, two steps (j) (i) TBAF, THF, 91%; (ii) Na, naphthalene, 64%.

Herdeis *et al* (1999)[166] Scheme 28

An efficient and flexible route to (+)-deoxoprosophylline **173** was accomplished by Herdeis *et al.*[166] from L-ascorbic acid. The synthetic pathway includes the formation of an *O*-protected 5-azido-2,3-dideoxysugar **185** which is subjected to a tandem Wittg [2+3]-cycloaddition reaction, leading to the heterocyclic core unit of (+)-prosophylline **101**. Stereoselective hydrogenation and chain elongation yields the desired alkaloid.

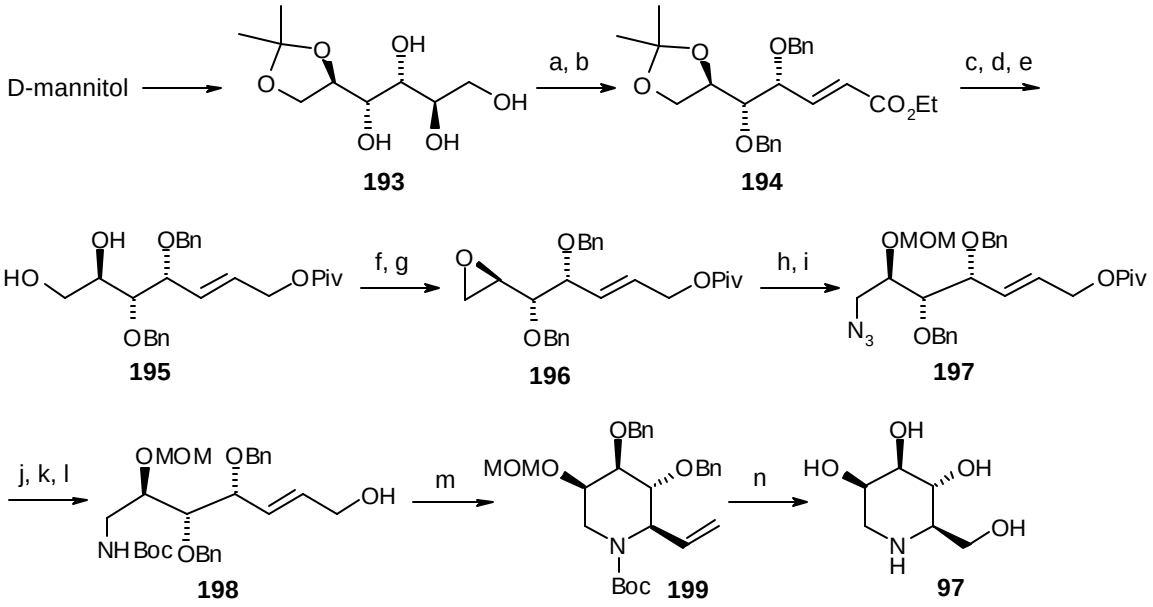


Scheme 28 Reagent and Conditions: (a) con. HCl, *i*-PrOH, 48 h, 96% (b) excess TBDMSCl, Et_3N, DMAP, DMF, 12 min., 99% (c) MsCl, Et_3N, CH_2Cl_2, 20 min., 79% (d) NaN_3, DMPU, 70°C, 24 h, 65% (e) DIBAL-H, THF, -78°C, 4-6 h, 69% (f) $Ph_3PCHCOOEt$, toluene, rt, 1 day (g) toluene, rt, 4 days, 98% (h) (i) Et_3N, CH_2Cl_2, 12 h, 96%; (ii) $Rh(OAc)_4$, 12 h, 97% (i) H_2, 10% Pd/C, EtOH, 48 h, 71% (j) (i) TBDMSCl, imidazole, DMF, 84%; (ii) DIBAL-H, *n*-pentane, -78°C, 25 min., 66% (k) (i) $Ph_3P(CH_2)_9CH_3Br$, $NaN[Si(CH_3)_3]_2$, THF, -40°C-rt, 4 h, 79%; (ii) H_2, 10% Pd/C, EtOH, 12 h, 93%; (iii) HCl, EtOH, 15 min., then 6 N KOH, 87%.

Hirai *et al.* (2000)[167] Scheme 29

A efficient and flexible route to (+)-deoxymannojirimycine **97** was accomplished by Hirai *et al.*[167] from D-mannitol. The synthetic pathway including the palladium(II)-catalyzed cyclization of urethane **198**, derived from D-mannitol, gave the cyclic compound **199** with excellent diastereoselectivity. During these transformations, the Pd(II) species are not

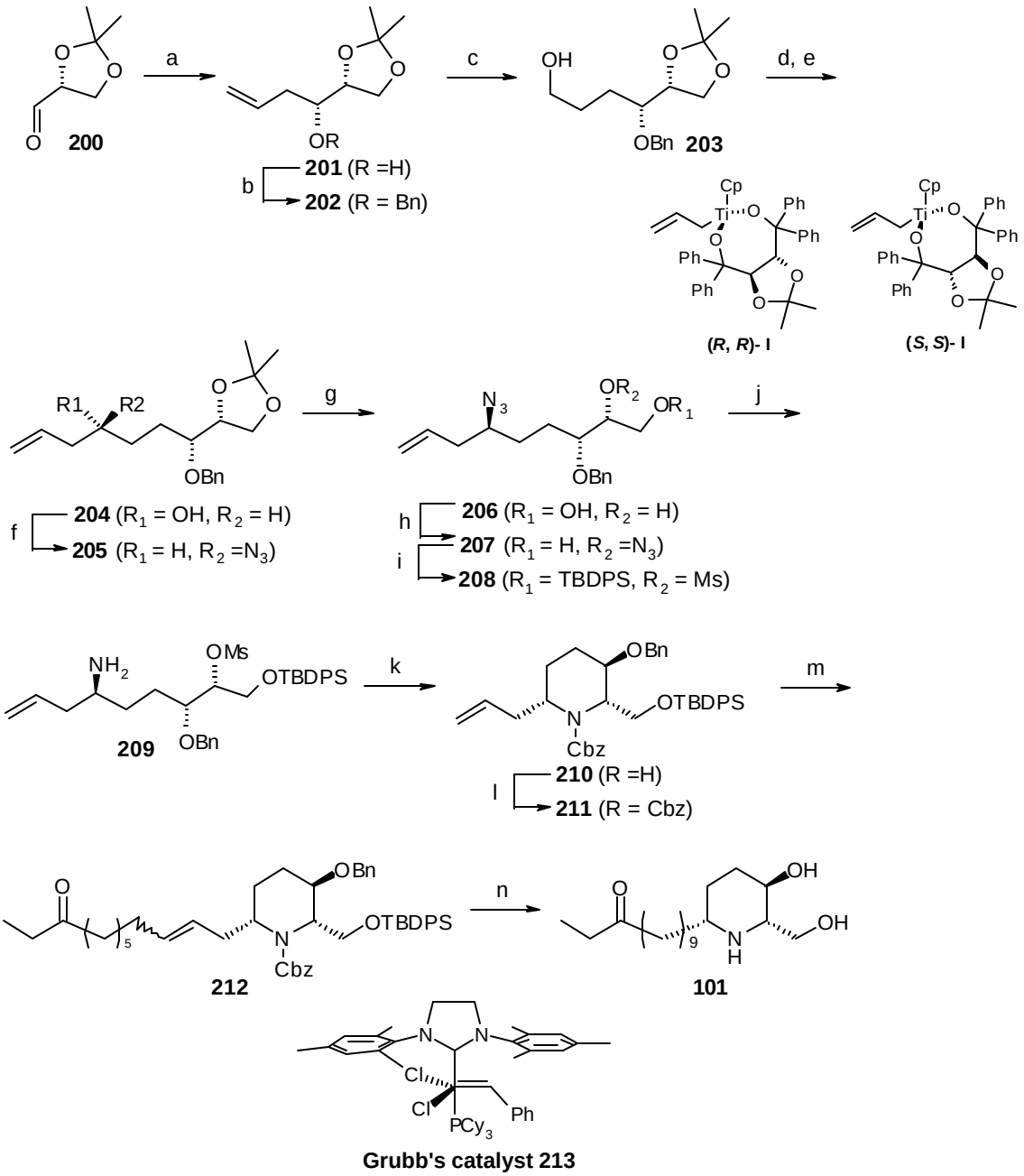
reduced and thus the catalyst can be recycled without its reoxidation. The cycloadduct **199** was converted to the desired compound **97**.



Scheme 29 Reagent and Conditions: (a) $NaIO_4$, H_2O-Et_2O, 0°C, 79% (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C, 89% (c) DIBAL-H, THF, -78°C, 94% (d) PivCl, pyridine, THF, 0°C, 93% (e) 10% aq. HCl, THF, 40°C, 95% (f) TsCl, pyridine, CH_2Cl_2, 0°C, 85% (g) K_2CO_3, MeOH, 0°C, 89% (h) NaN_3, NH_4Cl, 15-crown-5, DMF, rt, 47% (i) MOMCl, *i*-Pr_2NEt, 0°C, 83% (j) PPh_3, THF, rt, 46% (k) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 95% (l) K_2CO_3, MeOH, rt, quantitative yield (m)15 mol% $PdCl_2L_2$, THF, rt, 85% (n) (i) O_3, CH_2Cl_2-MeOH; -78°C, $NaBH_4$, -78°C, 92%; (ii) TFA, CH_2Cl_2, 0°C-rt; (iii) H_2, Pd/C, con. HCl, EtOH, rt, 33%, 2 steps.

Cossy *et al.* (2001)[168] Scheme 30

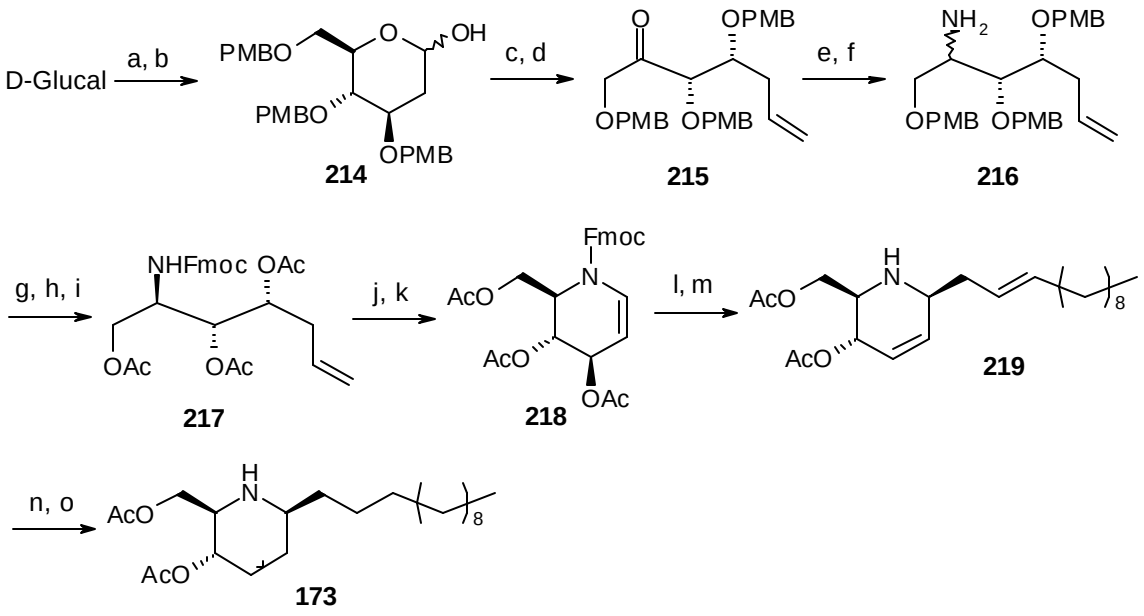
An enantioselective synthesis of (-)-prosophylline **101** was accomplished by Cossy *et al.*[168] from D-glyceraldehyde **200** in 15 steps by using two enantioselective allyltitanations and a cross-metathesis reaction as the key-steps.



Scheme 30 Reagent and Conditions : (a) (*S*, *S*)-I, Et_2O, -78°C, 86% (b) *t*-BuOK, BnBr, THF, 91% (c) (i) BH_3.THF; (ii) H_2O_2, NaOH, H_2O, 83% (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, quantitative yield (e) (*R*, *R*)-I, Et_2O, -78°C, 81% (f) Ph_3P, DEAD, DPPA, THF, 0°C-rt (g) AcOH/H_2O : 80/20, 76% for two steps (h) TBDPSCl, imidazole, CH_2Cl_2, 96% (i) MsCl, DMAP, pyridine, 98% (j) Ph_3P, THF/H_2O, 89% (k) Et_3N, MeOH, reflux, 88% (l) CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, quantitative yield (m) $CH_3CH_2CO(CH_2)_6CH=CH_2$, **213**, CH_2Cl_2, reflux, 58% (n) (i) H_2, 10% Pd/C, MeOH/HCl : 50/1, 60%; (ii) TBAF, THF, 90%

Shipman *et al.* (2002)[169] Scheme 31

An enantioselective synthesis of (+)-deoxoprosophylline **173** was accomplished by Shipman *et al.*[169] from D-glucal. During the course of synthesis the tri-*O*-acetyl imino glucal **218** formed underwent a variety of Lewis acid mediated carbon-carbon bond forming reactions at C-1 of the piperidine nucleus. In all the reactions studied, the β-anomer is predominant outcome, leading to the synthesis of title compound **173**.

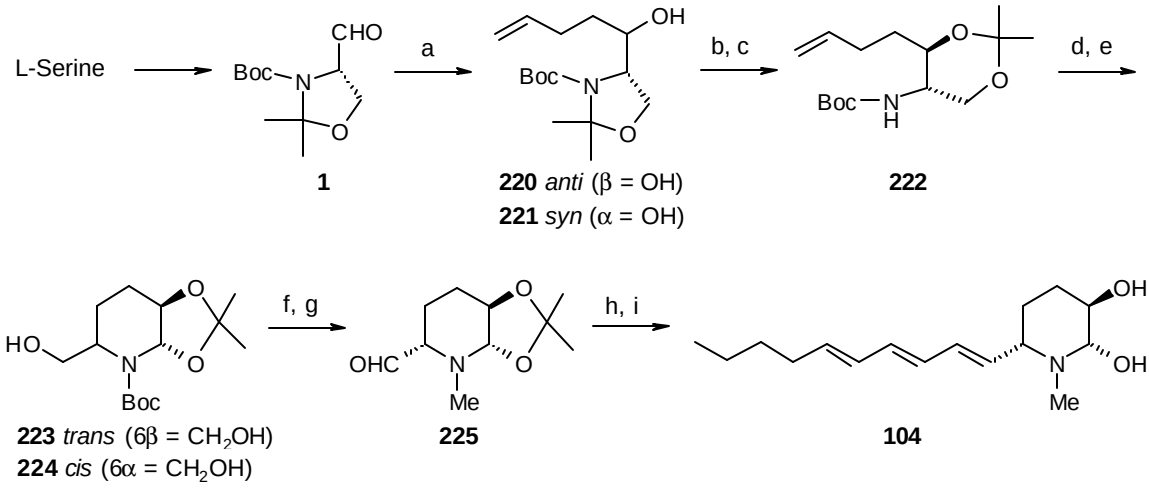


Scheme 31 Reagent and Conditions: (a) NaH, PMBCl, DMF (b) $Hg(OAc)_2$, THF-H_2O then $NaBH_4$, 51%, 2 steps (c) $Ph_3P{=}CH_2$, toluene (d) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 69% 2 steps (e) $HONH_2{\cdot}HCl$, pyridine, EtOH, 60°C (f) $LiAlH_4$, Et_2O, rt (g) FmocCl, K_2CO_3, THF-H_2O (3:1) (h) CF_3CO_2H, CH_2Cl_2, (i) Ac_2O, pyridine, rt, 54% from **215** (j) O_3, -78°C, CH_2Cl_2, then Me_2S, rt (k) $(COCl)_2$, Et_3N, DMF, CH_2Cl_2, 53%, 2 steps (l) $BF_3{\cdot}Et_2O$, CH_2Cl_2, $H_2C{=}CHCH(SiMe_3)(CH_2)_8CH_3$, -60°C-0°C, 3 h (m) piperidine, CH_2Cl_2, rt, 1 h, 78%, 2 steps (n) H_2, Pt/C, EtOH, 1.5 h (o) LiOH, THF-H_2O, 2.5 h, 51%, 2 steps.

3. Amino acid or Chiral substrate as a starting souce:

Read *et al.* (1996)[170] Scheme 32

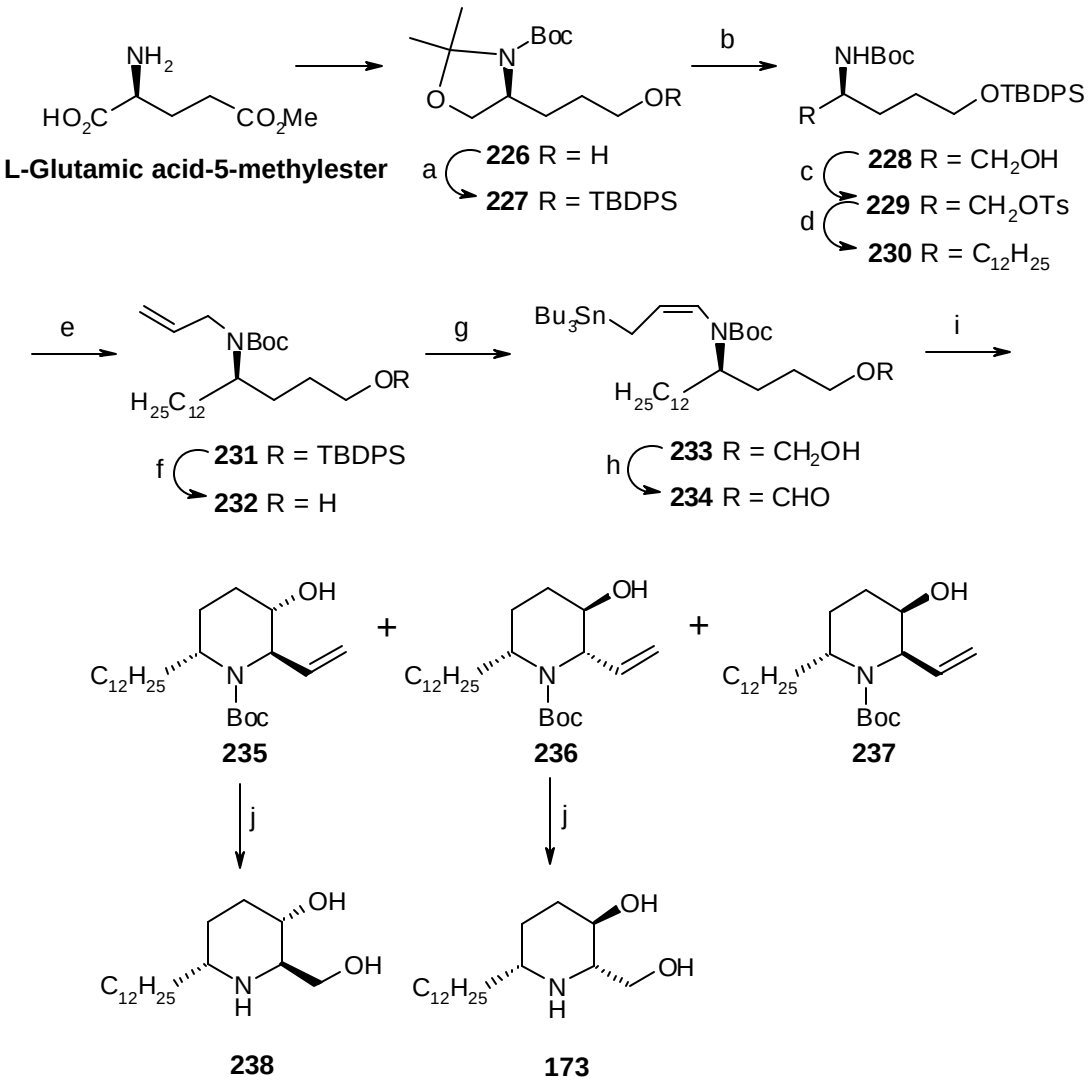
The enantioselective total synthesis of micropine **104**, an unusual 2,6-disubstituted piperidine alkaloid, through mercuric trifluoroacetate-catalysed intramolecular alkenylamide cyclisation is described by Read *et al.*[170] The synthesis proceeds from L-serine and affords material of the same positive sign of optical rotation as the natural product thereby confirming the absolute stereochemistry of micropine **104**.



Scheme 32 Reagent and Conditions : (a) $H_2C{=}CHCH_2CH_2MgBr$, THF (b) Amberlyst 15, MeOH (c) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2 (d) (i) $Hg(OCOCF_3)_2$, THF; (ii) $NaHCO_3$, KBr (e) O_3, $NaBH_4$, DMF (f) $LiAlH_4$, Et_2O (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (h) $CH_3(CH_2)_3(CH_2)_4CH_2P(O)(OEt)_2$, KH, THF (i) H_2SO_4, MeOH.

Yamamoto *et al.* (1997)[171] Scheme 33

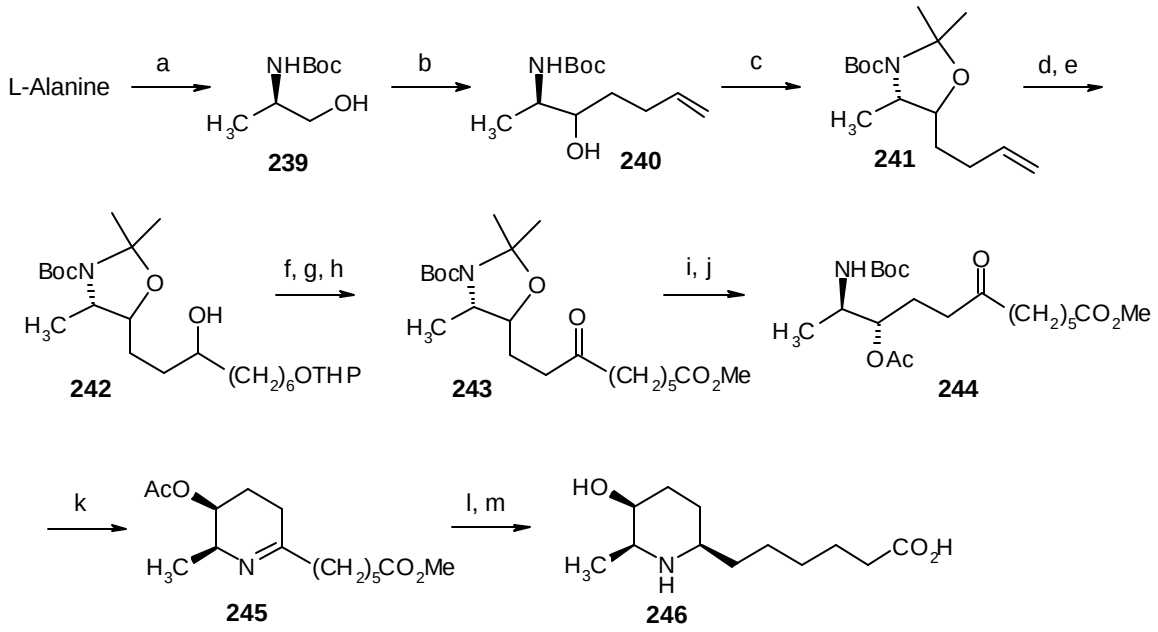
Asymmetric total syntheses of (+)-desoxoprosopinine **238** and (-)-desoxoprosophylline **173** were accomplished using L-glutamic acid as the chiral source by Yamamoto *et al.*[171] in which the intramolecular reaction of a γ-aminoallylstannane with an aldehyde was used as a key step.



Scheme 33 Reagent and Conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 100% (b) $PdCl_2(CH_3CN)_2$, CH_3CN, reflux, 98% (c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 98% (d) $C_{11}H_{23}Li$, CuI, Et_2O, -35°C, 82% (e) allylbromide, KH, THF, 0°C-rt, 92% (f) TBAF, THF, rt, 74% (g) *sec*-BuLi, TMEDA, THF, -78°C, then *n*-Bu_3SnCl, -78°C-rt, 61% (h) SO_3·Py DMSO, Et_3N, CH_2Cl_2, 0°C, 92% (i) $BF_3.Et_2O$ or $TiCl_4$ or $ZrCl_2$ or $SnCl_4$, $MgBr_2{\cdot}OEt_2$ or HCl or CF_3CO_2H, -78°C or 0°C 58%-98% (j) O_3, MeOH, -78°C; then $NaBH_4$, -78°C-rt, 53% for **238** and 43% for **173**.

Datta *et al.* (1999)[172] Scheme 34

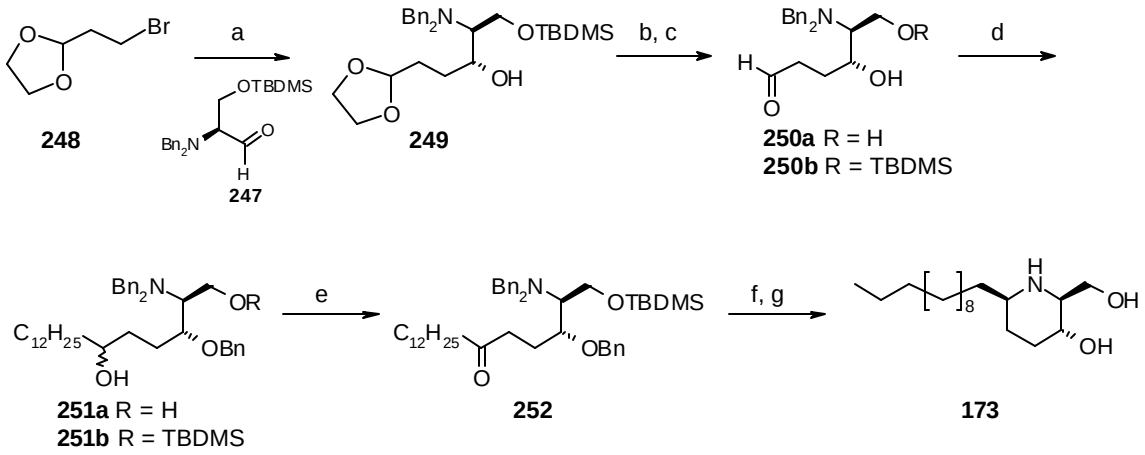
Asymmetric total syntheses of enantiopure (+)-azimic acid **246** was developed using L-alanine as the chiral source by Datta *et al.*[172] The, strategy envisages initial building-up of the functionalized *syn*-1,2-amino alcohol fragment **240** with required stereochemistry, *via* chelation controlled addition of a suitable Grignard reagent to N-Boc-alaninal. The strategically placed terminal alkene group of **240** can then be utilized towards formation of the pivotal ketoester intermediate **244**. Finally, intramolecular cyclodehydration involving the amine and the ketone functionalities followed by stereoselective hydrogenation of the resulting Δ-piperidine completes the intended synthesis.



Scheme 34 Reagent and Conditions: (a) $LiAlH_4$, THF; then Boc_2O, 70% (b) Swern oxidant.; then $H_2C{=}CH(CH_2)_2MgBr$ (c) $Me_2C(OMe)_2$, PPTS (d) OsO_4, NMO; then $NaIO_4$ (impregnated on silica gel), 93% (e) $BrMg(CH_2)_6OTHP$, 79% (f) 2-iodoxybenzoic acid, 88% (g) PTSA, EtOH, 80% (h) $RuCl_3{\cdot}H_2O$, $NaIO_4$; then CH_2N_2, Et_2O, 78% (i) 80% $AcOH{\cdot}H_2O$, 84% (j) Ac_2O, DMAP, 92% (k) HCO_2H, CH_2Cl_2, 72% (l) H_2, Pd/C, 77% (m) $N_2H_4{\cdot}H_2O$, MeOH, 68%.

Zhu *et al.* (2001)[173] Scheme 35

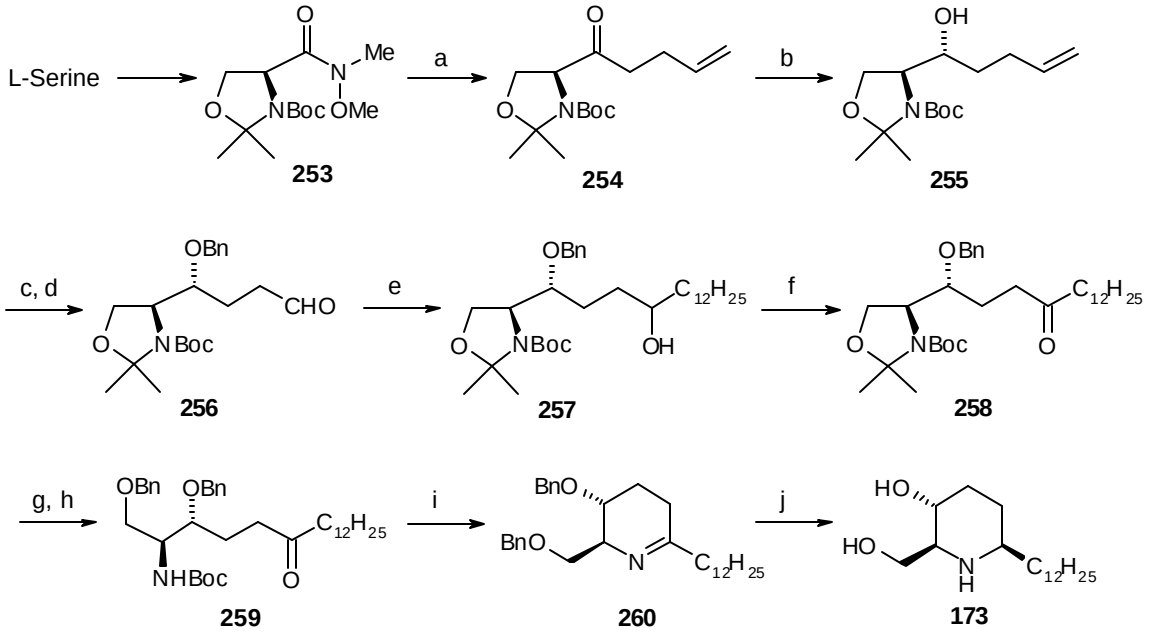
Asymmetric syntheses of (-)-deoxoprosophylline **173** from chiral L-*N*,*N*-dibenzyl serine (TBDMS) aldehyde **247** is reported by Zhu *et al.*[173] A highly diastereoselective intramolecular reductive amination of ω-oxo amino diol **252** is a key step of the synthesis.



Scheme 35 Reagent and Conditions : (a) Mg, THF, rt then **247**, 86% (b) NaH, BnBr, Bu_4NF, 0°C, then rt, 85% (c) (i) 3 N HCl, THF; (ii) TBDMSCl, imidazole, DMF, rt, 90% (d) $C_{12}H_{25}Br$, Mg, dibromoethane, THF, then **250b**, 70°C, 80% (e) DMSO, $(COCl)_2$ then Et_3N, 84% (f) $Pd(OH)_2$, cyclohexene, EtOH, reflux (g) Pd/C, MeOH, 73%.

Datta *et al.* (2001)[174] Scheme 36

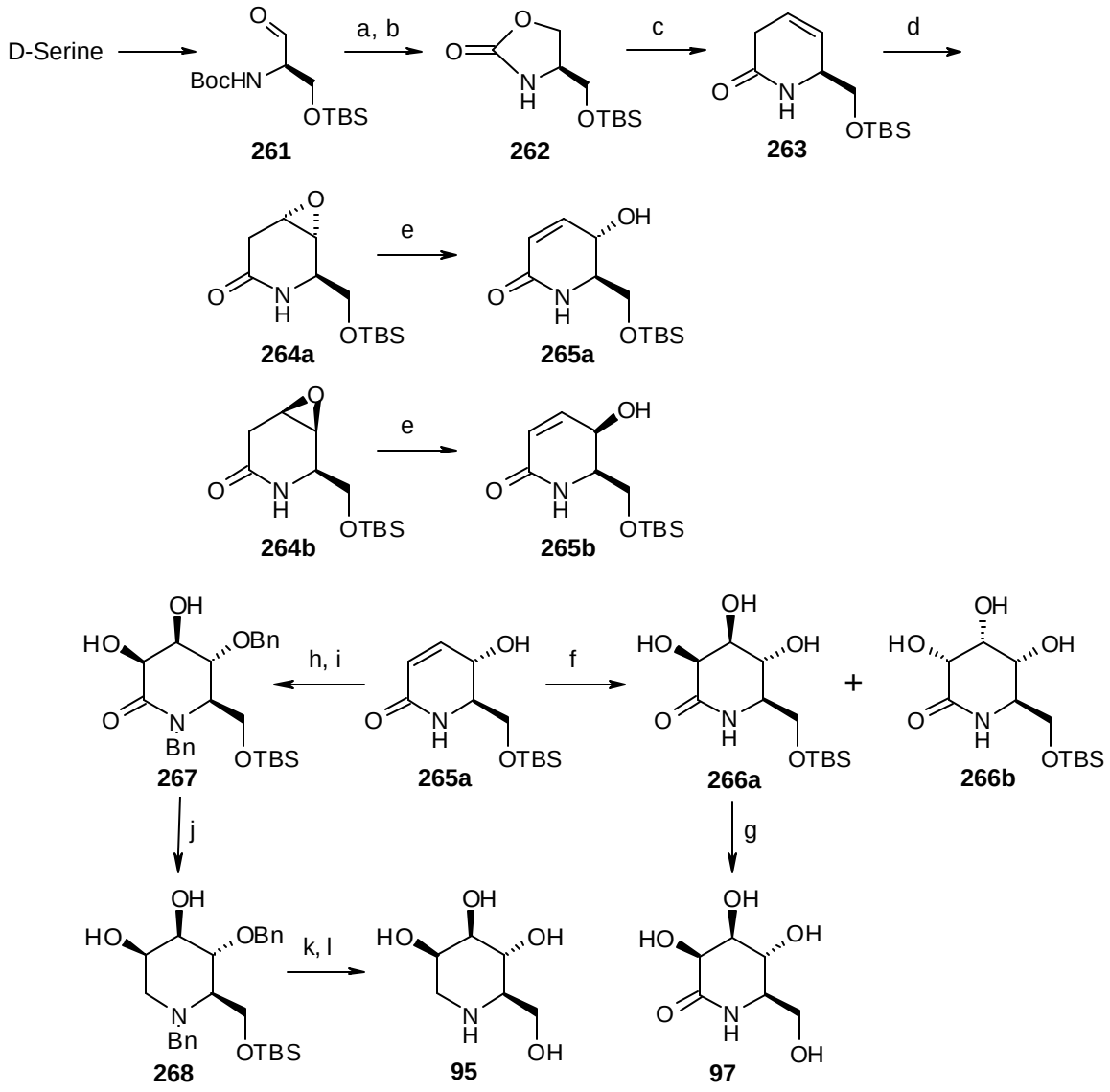
Asymmetric syntheses of prosopis alkaloid (-)-deoxoprosophylline **173** from easily available amino acid L-serine is reported by Datta *et al.*[174] as a chiral pool starting material.



Scheme 36 Reagent and Conditions: (a) $BrMgCH_2CH_2CH{=}CH_2$, THF, 0°C, 76% (b) $Zn(BH_4)_2$, Et_2O-C_6H_6, 76% (c) NaH, BnBr, 70% (d) (i) OsO_4; (ii) $NaIO_4$ (on silica gel), 92% (e) $C_{12}H_{25}MgBr$, 80% (f) 2-Iodoxybenzoic acid, 91% (g) 80% AcOH in H_2O, 83% (h) BnBr, Ag_2O, 85% (i) HCO_2H, 78% (j) EtOH·HCl, 72%.

Knight *et al.* (2003)[175] Scheme 37

The stereoselective synthesis of piperidine alkaloids deoxymannojirimycin **97** and D-mannolactam **98** from D-serine has been achieved by Knight *et al.*[175] The key step involves palladium-catalysed decarboxylative carbonylation of a serine-derived 5-vinyloxazolidin-2-one **262** to give 6-(tertbutyldimethylsilyloxymethyl)-3,6-dihydro-1H-pyridin-2-one **263** which was subsequently converted into the title compounds.



Scheme 37 Reagent and Conditions : (a) $BrMgCH{=}CH_2$ (2.5 equiv.), THF, -78°C-rt, 3 h (b) KO-*t*-Bu, THF, rt, 3 h, 75% from **261** (c) $PdCl_2(PPh_3)_2$ (10 mol%), CO (65 atm), EtOH, 60°C, 32 h, 81% (d) Oxone (5 equiv.), $NaHCO_3$ (15 equiv.), acetone/H_2O, rt, 3 h, 95%, (**264a**/**264b**, 4.1:1) (e) DBU (2 equiv.), CH_2Cl_2, reflux, 3 h, 95% (f) OsO_4 (9 mol%), NMO (3 equiv.), *t*-BuOH, rt, 3 h, 56%, (**266a**/**266b**, 3.2:1) (g) TFA/H_2O (1:1), rt 10 h, 70% (h) NaH (2 equiv.), DMF, BnBr, 0°C-rt, 3 h, 64% (i) HCO_2H, 78% (j) OsO_4 (7 mol%), NMO (3 equiv.), *t*-BuOH, rt, 3 h, 89% (k) $LiAlH_4$ (5 equiv.), Et_2O, rt, 3 h, 89% (l) H_2, Pd/C, EtOH, HCl, rt, 2 h, 68% from **268**.

Koskinen *et al.* (2003)[176] Scheme 38

A new and efficient enantioselective total synthesis of the title deoxycastanospermine derivative **276** has been developed by Koskinen *et al.*[176], based on amino acid and β-ketophosphonate chemistry, as well as employment of internal asymmetric induction for the creation of the new chiral centers proved successful. With proper choice of reaction conditions, the approach can also be applied in selective preparation of several isomers of deoxycastanospermine.

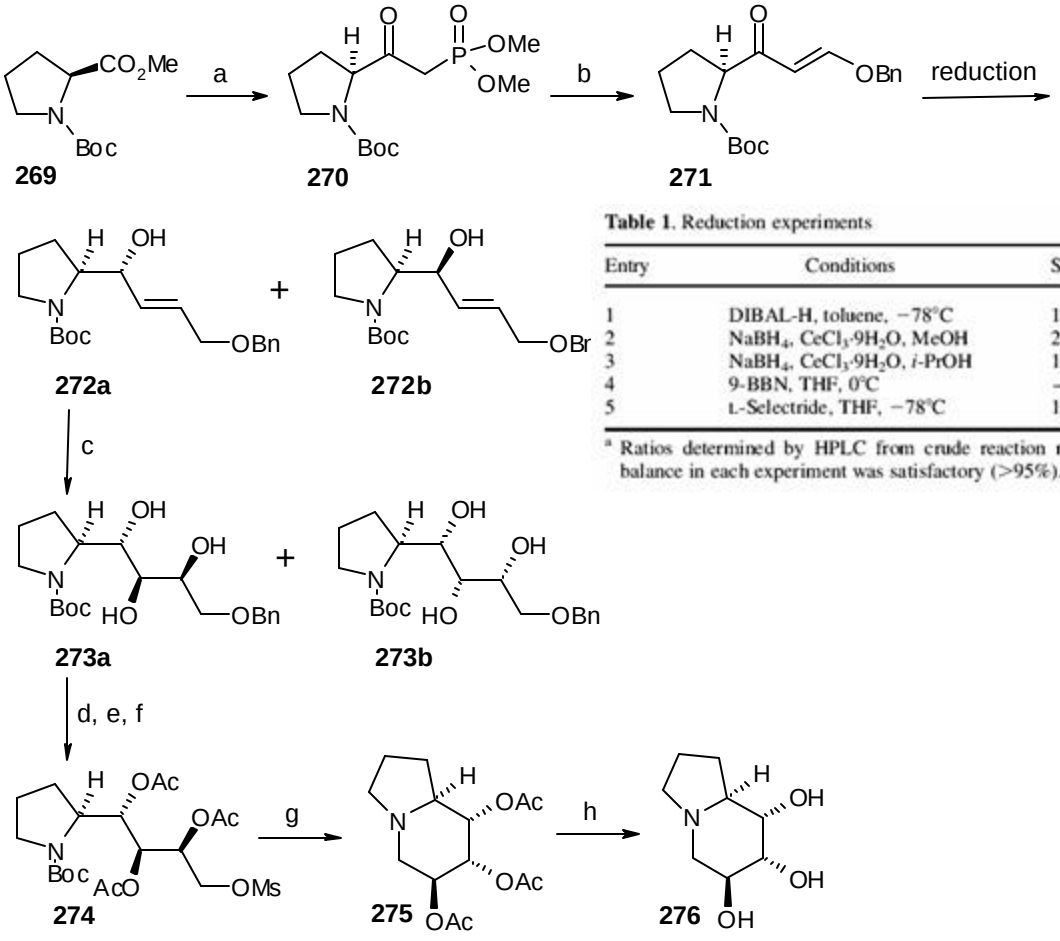


Table 1. Reduction experiments

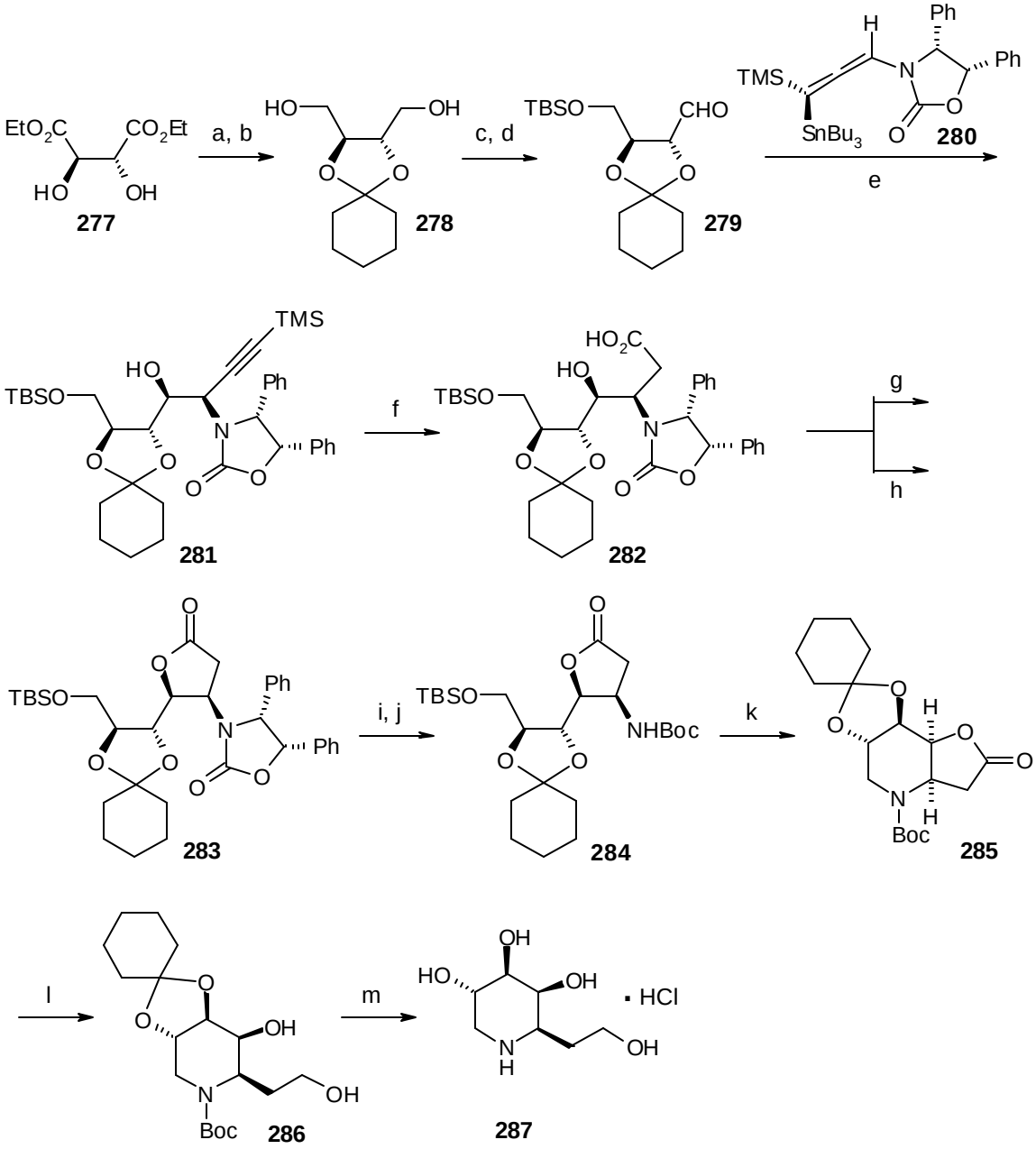
Entry	Conditions	Selectivity *anti*/*syn*[a]
1	DIBAL-H, toluene, −78°C	1.3:1
2	$NaBH_4$, $CeCl_3 \cdot 9H_2O$, MeOH	2.4:1
3	$NaBH_4$, $CeCl_3 \cdot 9H_2O$, *i*-PrOH	1.1:1
4	9-BBN, THF, 0°C	–
5	L-Selectride, THF, −78°C	1:5.3

[a] Ratios determined by HPLC from crude reaction mixture. The mass balance in each experiment was satisfactory (>95%).

Scheme 38 Reagent and Conditions: (a) *n*-BuLi, DMMP, THF, -78°C $BnOCH_2CHO$, K_2CO_3, MeCN (c) OsO_4, NMO (cat.), acetone/H_2O (d) Ac_2O, pyridine, DMAP, CH_2Cl_2 (e) H_2, Pd/C, MeOH (f) MsCl, Et_3N, CH_2Cl_2 (g) (i) TFA, CH_2Cl_2 (ii) Et_3N, MeCN (h) NaOMe, MeOH.

Hegedus *et al.* (2004)[177] Scheme 39

1-Deoxy-D-galactohomonojirimycin **287** was synthesized in seven steps from optically pure allenylstannane **280** and L-lactate-derived aldehyde **279** by Hegedus *et al.*[177] in 48% overall yield. The key step was the Lewis acid catalyzed reaction of **279** and **280** to give the *syn*-amino alcohol in excellent yield and very high diastereoselectivity.



Scheme 39 Reagent and Conditions: (a) cyclohexanone, PhH, TsOH, reflux (b) $LiAlH_4$, THF, reflux (c) NaH, TBSCl, THF, 25°C (d) Dess-Martin periodanane, CH_2Cl_2, 25°C (e) BF_3,OEt_2, CH_2Cl_2, -70 °C (f) Cy_2BH, THF, 0-25°C, and then H_2O_2, aq $NaHCO_3$, 0-25°C (g) Mukaiyama reagent, Et_3N, CH_2Cl_2, 25°C (h) DEAD, Ph_3P, THF, -20 to +25°C; (i) 80 psi H_2, catalyst $Pd(OH)_2$, Boc_2O, THF, 25°C (j) HF,Pyridine, MeCN, 25°C (k) DEAD, Ph_3P, THF, -20 to +25°C (l) $LiAlH_4$, THF, -20°C (m) HCl/MeOH, 25°C.

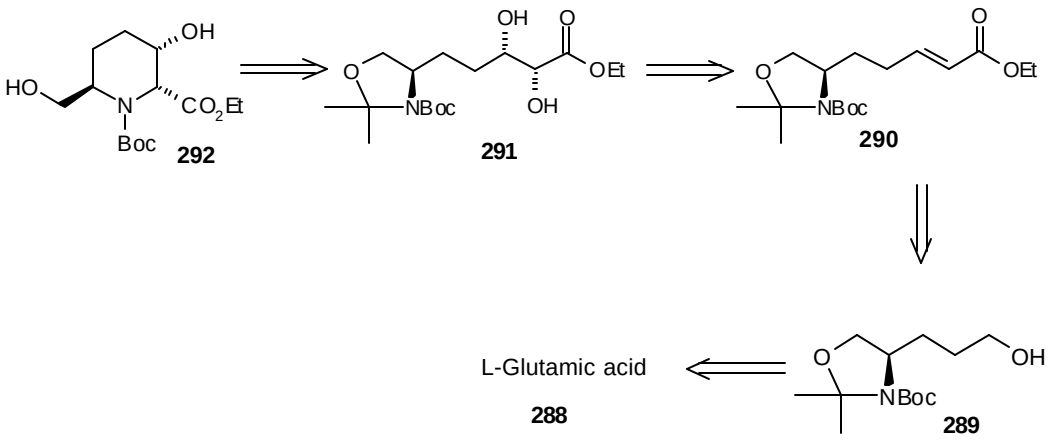
4.3.3 Present Work

Objective:

The hydroxylated piperidine alkaloids exhibit a variety of pharmacological properties such as anesthetic, analgesic and antibiotic activities. On the other hand, construction of a versatile chiral building block for biologically active natural compounds would provide us with powerful tools for the synthesis of target natural products.

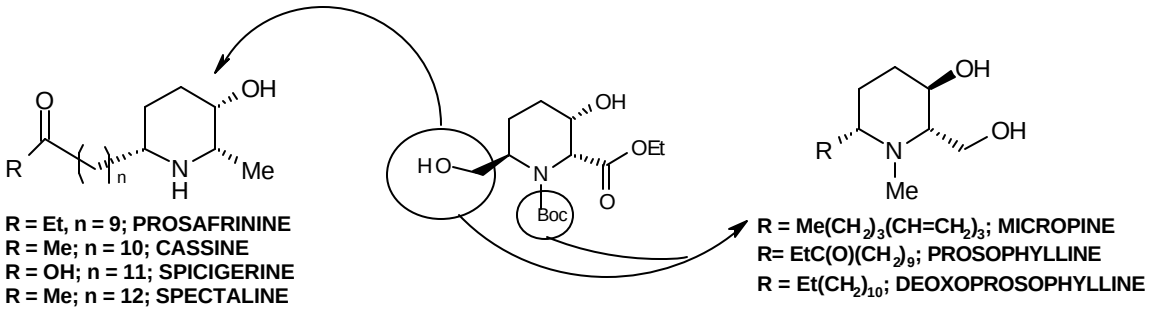
As seen from the literature, there are very few synthesis of hydroxylated piperidine derivatives with the use of α-amino aldehydes as the synthetic precursor and if there are then either they are derived with the use of some specific reagents or suffer from harsh reaction conditions, poor selectivity and low yields of the desired products. Also on the other hand, they are designed to obtain exclusively one desired derivative of hydroxylated piperidine alkaloids without any generalization to obtain a number of derivatives from a single starting amino acid. On the above basis of the application of hydroxylated piperidine alkaloids, and the exceptional usage of α-amino aldehydes as a building block, we thought of synthesizing such an intermediate which can be useful in forming synthesis of variety of derivatives of biological interest.

As seen from **Scheme 40**, the desired building block **292** could be obtained from either L-serine or L-glutamic acid *via* the Wittig olefination product **290**. The dihydroyxlation of the olefin **290** yields the diol **291** which could be easily transformed into the desired building block **292**.



Scheme 40

The synthetic utility and versatility of the building block **292** is such that it can be easily transformed into the various hydroxylated piperidine alkaloids of biological importance (**Scheme 41**).

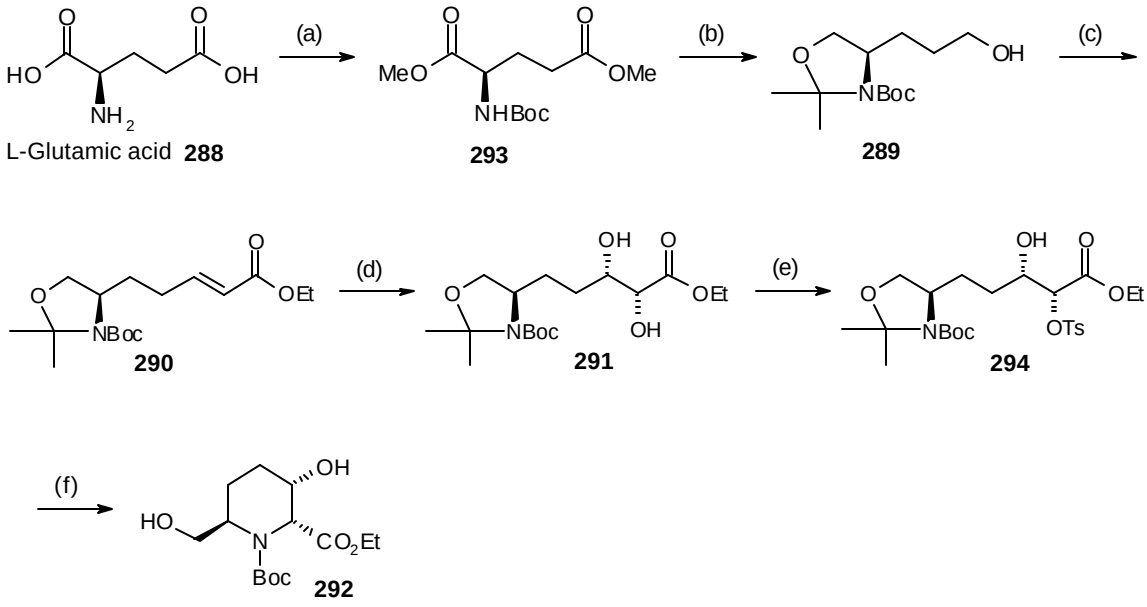


Scheme 41

4.3.4 Results and Discussion

As per our retrosynthetic analysis we started our approach towards the desired synthetic intermediate **292** from L-glutamic acid **288** (**Scheme 42**). L-glutamic acid **288** was converted into the *N*-Boc-(*S*)-glutamic dimethylester **293** in 85% yield by first treating it with Boc_2O and then esterifying the resultant product with CH_3I.The ^1H NMR spectrum of

compound **293** showed the *tert*-butyl protons at δ 1.50 (singlet) and the dimethyl ester protons at δ 3.74 (singlet) and δ 3.81 (singlet). The diester of **293** was then reduced by $LiAlH_4$ to the corresponding alcohol (80%) which was further subjected to oxazolidine formation by 2,2-dimethoxypropane to afford the oxazolidine derivative **289** in 85% yield. The spectroscopic data of compound **289** was in accordance with the literature precedence.[171,178] Compound **289** was then subjected to Swern oxidation and thereafter Wittig olefination conditions with the two carbon Wittig ylide to afford the α,β-unsaturated olefinic ester **290** in 80% yield. The ^{1}H NMR spectrum of **290** showed the two set of olefinic protons at δ 5.78-5.87 (triplet of doublet) and at δ 6.87-7.01 (multiplet). The IR spectrum showed the absence of hydroxyl absorption at ν 3450 cm^{-1} confirming the transformation



Scheme 42 Reagent and Conditions: (a) (i) Boc_2O, NaOH, dioxane, H_2O, 3 h; (ii) K_2CO_3, CH_3I, DMF, 1 h, 85% (2 steps) (b) (i) $LiAlH_4$, THF, 0°C-rt, 6 h, 80%; (ii) 2,2-dimethoxypropane, benzene, TsOH, reflux, 18 h, 85% (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, then *i*-Pr_2NEt, -78°C, 2 h; (ii) $Ph_3P{=}CHCO_2Et$, benzene, overnight, 80% (d) K_2CO_3, $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ OsO_4, *t*-BuOH : H_2O (1:1), 24 h, 74% (e) *p*-TsCl, Et_3N, CH_2Cl_2, 0°C, 40 h, 52% (f) (i) TFA, CH_3CN, 0°C, 2.5 h; (ii) NaH, THF, 0°C-rt, 3 h (iii) Boc_2O, Et_3N, CH_2Cl_2, rt, 1 h, 65% (3 steps).

of compound **289**, and the presence of peak at ν 1750 cm^{-1} corresponding to the α,β-unsaturated olefinic ester. Compound **290** was then transformed into its dihydroxy derivative **291** by Sharpless asymmetric dihydroxylation conditions with the use of $(DHQ)_2PHAL$ ligand in 74% yield. Here the diastereoselectivity of the resultant diol **291** was measured by its ^{13}C NMR spectrum, showing 95% diastereoselectivity (95% de). The ^1H NMR spectrum of diol **291** showed the absence of the olefinic protons at δ 5.78-5.87 (triplet of doublet) and at δ 6.87-7.01 (multiplet). Also it showed the presence of the ester functionality as combination of triplet-quartet at δ 1.32 and δ 4.29 respectively confirming just the absence of olefin function. The IR spectrum showed the presence of hydroxyl function at ν 3400 cm^{-1}. The diol was then regioselectively tosylated at its α-postion to the ester carbonyl with the help of *p*-toluenesulfonyl chloride to afford the tosyl desrivative **294** in 52% yield. The ^1H NMR spectrum of the tosyl derivative **294** showed the CH_3 portons of tolulyl group at δ 2.46 (singlet) and the orthocoupled doublet at δ 7.35 and δ 7.85 for *p*-toluyl group. The oxazolidine part and the Boc group of compound **294** was deprotected by TFA/CH_3CN, and the product thus obtained was further subjected to cyclisation by NaH/THF without purification to obtain the desired versatile intermediate **292** in 65% yield. The ^1H NMR spectrum of compound **292** showed the absence of tosyl group, Boc group and the acetonide group by the absence of protons at δ 2.45, 7.35, 7.85 (tosyl group), δ 1.45 (Boc group) and δ 1.56 (acetonide group) confirming the cyclisation process.

4.3.5. Conclusion

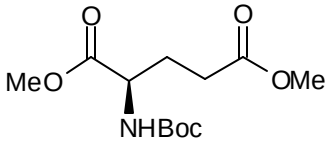
In conclusion, we have developed a simple, short and efficient route to the synthetic piperidine aza precursor which can be easily transformed into various target molecules of biological interest.

4.3.6. Experimental section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz machine and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan LCMS mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

Preparation of (2*S*)-2-*tert*-butoxycarbonylamino-pentanedioic acid dimethyl ester, 293



293

A solution of di-*tert*-butyldicarbonate (17.80 g, 81.56 mmol) in dioxane (90 mL) is added to an ice cold solution of L-glutamic acid **288** (10.0 g, 67.96 mmol) in 1N NaOH (5.44 g in 136 mL H_2O) by means of an addition funnel. The two phase mixture is stirred at 5^{o}C for 30 min, then allowed to warm to room temperature over 3.5 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half its original volume at 35^{o}C, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 150 ml). The combined extracts are dried over Na_2SO_4, filtered and concentrated to give 18.5 g, 98% *N*-Boc-L-glutamic acid as colorless, sticky foam which is used without further purification.

To an ice cold solution of *N*-Boc- L-glutamic acid **293** (15.29 g, 61.50 mmol) in DMF (160 mL) is added solid K_2CO_3 (18.66 g, 135.21 mmol). After stirring for 10 min in an ice bath, methyl iodide (34.90 g, 245.87 mmol) is added to the white suspension and stirring continued at 0°C for 30 min. where upon the mixture solidifies. The reaction is warmed to room temperature and stirred for addition at 1 h or at point when TLC analysis indicates complete formation of the methyl ester. The reaction mixture is filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase is washed with brine, dried, filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (9:1) as eluent gave *N*-Boc-L-glutamic acid methyl ester **293** (15.90 g, 85%) as a thick liquid.

Yield: 15.90 g, 85%

$[\alpha]_D^{20}$: + 14.58 (c = 1.0, $CHCl_3$)

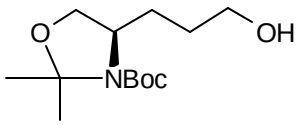
IR ($CHCl_3$ cm^{-1}): ν_{max} 1681, 1723, 1736, 3461

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50(s, 9H), 1.96-2.06 (m, 1H), 2.20-2.33 (m, 1H), 2.44-2.52 (m, 2H), 3.74 (s, 3H), 3.81 (s, 3H), 4.38 (m, 1H), 5.25 (brs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.93, 27.66, 29.50, 51.11, 51.70, 52.36, 80.11, 156.42, 170.62, 170.66

Analysis calcd.for $C_{12}H_{21}NO_6$: C: 52.35; H: 7.69; N: 5.09 Found: C: 52.32; H: 7.66; N: 5.07.

Preparation of (2*S*)-4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carbamicacid dimethyl ester, 289



289

To a stirred suspension of $LiAlH_4$ (6.21 g, 163.42 mmol) in dry THF (350 mL) at 0°C was added a solution of diester **289** (15.0 g, 54.49 mmol) in dry THF (150 mL). The ice bath was removed and the reaction mixture was stirred for 18 h, excess $LiAlH_4$ was quenched by adding water. The whole precipitate obtained was filtered and washed with methanol. The combined filtrate was concentrated to near dryness. The inorganic materials contained in the residual oil were removed by short column chromatography over silica gel

using chloroform / ethanol (3:1) as eluent afforded the diol (9.6 g, 80%) as a syrupy liquid. $[\alpha]_D^{20}$: -11.26 (c=1.12, $CHCl_3$)

To the solution of diol (9.0 g, 41.09 mmol) in dry benzene (150 mL) wad added 2,2-dimethoxy propane (6.47 g, 61.62 mmol) and TsOH (180 mg). The colorless solution is heated under relux temperature (110°C) for 18 h. After completion of reaction, the reaction was cooled down to room temperature, and concentrated to half of its volume, The reaction mixture was then partitioned between saturated $NaHCO_3$ (50 mL) and diethyl ether (150 mL). The organic layer is washed with brine, dried (Na_2SO_4), filtered and concentrated to give the crude product as amber oil. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7:3) as eluent gave **289** (9.06, 85%) as a colorless oil.

Yield: 9.06, 85%

$[\alpha]_D^{20}$: - 3.30 (c = 1.0, $CHCl_3$)

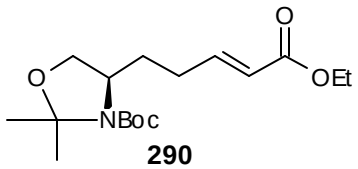
IR ($CHCl_3$ cm^{-1}): ν_{max} 1685, 2836, 2986, 3340

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44(s, 9H), 1.47 (s, 6H), 1.54-1.63 (m, 4H), 2.10 (brs, 1H), 3.55-3.75 (m, 4H), 3.91-3.94 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.52, 27.54, 28.46, 29.15, 29.52, 57.31, 62.16, 69.94, 80.28, 93.30, 152.44

Analysis calcd.for $C_{13}H_{25}NO_4$: C: 60.21; H: 9.71; N: 5.40 Found: C: 60.32; H: 9.66; N: 5.47.

Preparation of (2*S*)-4-(4-ethoxycarbonyl-but-3-enyl)-2,2-dimethyloxazolidine-3-carbamicacid *tert*-butyl ester, 290



290

To a cold (–78 °C) stirred solution of oxalylchloride (6.61 g, 51.99 mmol) in anhyd. CH_2Cl_2 (80 ml) was added DMSO (8.13 g, 14.05 mmol) over 25 min. At the end of the addition the mixture was warmed to –60 °C over a period of 20 min, then a solution of alcohol **289** (9.0 g, 34.70 mmol) was added dropwise over 50 min. The mixture was warmed to –45 °C over 30 min, then a solution of *N*,*N*-diisopropylethyl amine (19.74g,

152.72 mmol) in CH_2Cl_2 (5 mL) was slowly added. The cooling bath was removed and the mixture was allowed to warm to 0°C over 10 min and then transferred to a separating funnel charged with ice cold 1M HCl solution (130 ml). The two phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 30 ml) and the combined organic phases were washed with aqueous phosphate buffer (pH 7.0, 4 x 80 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to give 8.62g, (95% crude yield) of the aldehyde as a clear yellow oil which was used without purification.

To a solution of (ethoxycarbonylmethylene) triphenyl phosphorane (12.66 g, 36.38 mmol) in dry benzene (300 mL) was added the solution of above aldehyde in dry benzene (50 mL). The reaction was stirred at room temperature over night. It was then concentrated and purified by silica gel column chromatography using petroleum ether / EtOAc (8:2) as eluent to give α,β-unsatuarated olefin **290** (9.09 g) as a pale yellow oil.

Yield: 9.09 g, 80 %

[a **]$_D^{20}$:** + 15.61 (c = 1.0, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1674, 1748, 2870, 2931

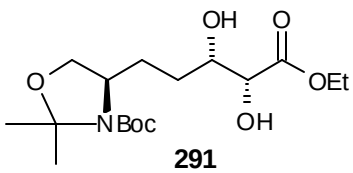
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 8Hz), 1.46 (s, 9H), 1.54 (s, 3H), 1.57 (s, 3H), 1.89-194 (m, 2H), 2.15-2.33 (m, 2H), 3.69 (t, 1H, *J* = 8Hz), 3.89-3.93 (m, 2H), 4.16 (q, 2H, J = 8Hz), 5.78-5.87 (m, 1H), 6.87-7.01 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.30, 24.52, 26.95, 28.53, 30.54, 31.98, 55.64, 59.03, 65.86, 79.77, 93.37, 122.04, 148.07, 152.33, 166.48.

Mass (ESI): 344 (M^++NH_4^+), 328 (M+1)

Analysis calcd.for $C_{17}H_{29}NO_5$: C: 62.36; H: 8.93; N: 4.27 Found: C: 62.32; H: 8.86; N: 4.17.

Preparation of (2*S*,5*R*,6*S*)-4-(4-ethoxycarbonyl-3,4-dihydroxybutyl)-2,2-dimethyloxazolidine-3-carbamicacid *tert*-butyl ester, 291



291

To a mixture of K_3FeCN_6 (15.10 g, 45.89 mmol), K_2CO_3 (6.33 g, 45.89 mmol), $(DHQ)_2PHAL$ (0.012 g, 1 mol%l) in *t*-butanol / H_2O (1:1, 250 mL) at 0°C was added osmium tetroxide (0.63 mL, 0.4 mol%), followed by methane sulfonamide (1.45 g, 15.27 mmol). After stirring for 2 min at 0°C, the olefin **294** (5.0 g, 15.27 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 16 h and after completion of reaction, the mixture was quenched with sodium sulfite (12 g). The stirring was continued for additional 30 min and then the solution was extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7:3) as eluent gave **291** (4.09 g) as a thick liquid.

Yield:- 4.09 g, 74%

$[\alpha]_D^{20}$: + (c = 1.0, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1648, 1730, 2836, 2940, 3380

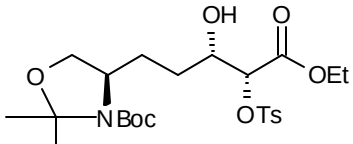
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 8Hz), 1.45 (s, 9H), 1.56 (s, 6H), 1.82 (m, 6H), 3.60-3.75 (m, 1H), 3.92-4.04 (m, 4H), 4.26 (q, 2H, *J* = 8Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.27, 24.60, 27.72, 28.53, 29.67, 30.11, 57.20, 61.87, 67.24, 72.64, 73.93, 80.65, 93.59, 153.60, 172.50.

Mass (ESI): 379(M^++NH_4^+), 362 (M+1), 343, 298, 261

Analysis calcd.for $C_{17}H_{31}NO_7$: C: 56.49; H: 8.65; N: 3.88 Found: C: 56.46; H: 8.68; N: 3.85.

Preparation of (2*S*,5*R*,6*S*)-4-[4-ethoxycarbonyl-3-ihydroxybutyl-4-(toluene-4-sulfonyloxy)-butyl]-2,2-dimethyloxazolidine-3-carbamicacid *tert*-butyl ester, 294



294

To a solution of **291** (3.0 g, 83 mmol) and Et_3N (1.26 g, 12.45 mmol) in CH_2Cl_2 (100 mL) at 0°C was added *p*-toluenesulfonyl chloride (1.58 g, 8.28 mmol). The reaction mixture was stirred at 0°C for 30 h. After the reaction was complete, water (30 mL) was added and the solution was extracted in CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography

of the crude product using petroleum ether / EtOAc (4:1) as eluent gave **294** (2.23 g) as a pale yellow oil.

Yield:- 2.23 g, 52%

[a]$_D^{20}$: + (c = 1.0, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1428, 1536, 1666, 1728, 2836, 2973, 3340

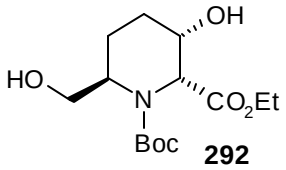
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 8Hz), 1.45 (s, 9H), 1.56 (s, 6H), 1.81 (m, 5H), 2.46 (s, 3H), 3.50-3.68 (m, 2H), 4.07-4.18 (m, 4H), 4.86 (d, 1H, *J* = 4Hz), 7.35 (d, 2H, *J* = 8Hz), 7.85 (d, 2H, *J* = 8Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.30, 24.52, 26.95, 28.53, 30.54, 31.98, 55.64, 59.03, 65.86, 79.77, 93.37, 122.04, 148.07, 152.33, 166.48.

Mass (ESI): 533 (M^++NH_4^+), 516 (M+1)

Analysis calcd.for $C_{24}H_{37}NO_9S$: C: 55.91; H: 7.23; N: 2.72; S, 6.22 Found: C: 55.94; H: 7.25; N: 2.75; S, 6.19.

Preparation of (2*S*,3*S*,6*S*)-3-hydroxy-6-hydroxymethyl piperidine-1,2-dicarboxylic acid-1-*tert*-butyl ester-2-ethyl ester, 292



292

To a ice cold solution of **294** (2.0 g, 3.87 mmol) in CH_3CN (30 ml) was added TFA (10 mL, excess). The reaction was stirred for 2.5 h at room temperature after which the solvent was evaporated to dryness. The resultant residue was dissolved in dry THF (25 mL) and the reaction mixture cooled at 0 ^oC. Sodium hydride (0.14 g, 5.83 mmol) was added and the reaction stirred for 3 h at room temperature. After the reaction was complete, water (10 mL) was added and the solution was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to yield the cyclized compound which was used without purification.

To the above crude product in CH_2Cl_2 (15 mL) was added Et_3N (0.58 g, 5.73 mmol) and Boc_2O (1.0 g, 4.58 mmol). The reaction was stirred at room temperature for 1 h. Water (20 mL) was added after the completion of reaction and the solution extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and

concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (9:6) as a eluent gave **292** (0.75 g) as a colorless oil.

Yield: 0.75 g, 65%

$[\alpha]_D^{20}$: + 2.45 (c = 1.0, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1253. 1648, 1745, 2832, 2946, 3380

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H, J = 6Hz), 1.44 (s, 9H), 1.59-1.75 (m, 4H), 3.59-3.64 (m, 4H), 3.69-3.72 (m, 2H), 3.95-4.35 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.97, 23.84, 28.10, 30.36, 42.69, 61.30, 65.12, 68.86, 78.20, 153.36, 170.11

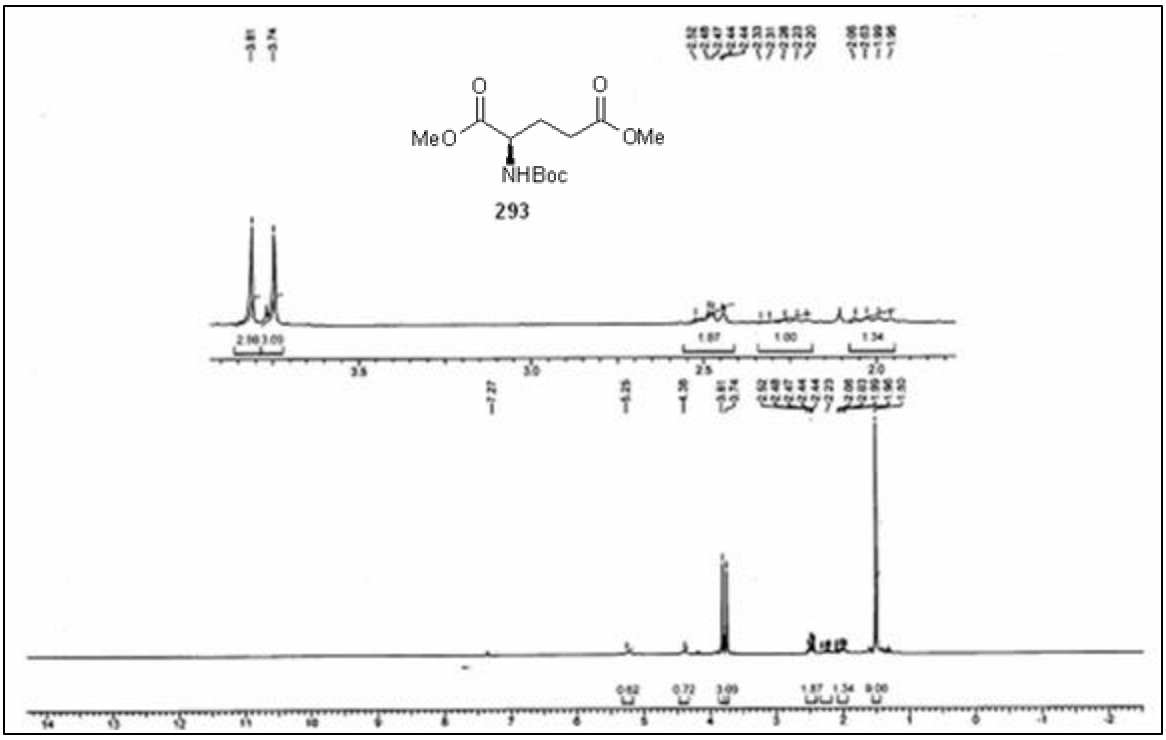
Mass (ESI): 221 (M^++NH_4^+), 204 (M+1)

Analysis calcd.for $C_{14}H_{25}NO_6$: C: 82.70; H: 12.39; N: 6.87 Found: C: 83.70; H: 12.59; N: 6.77

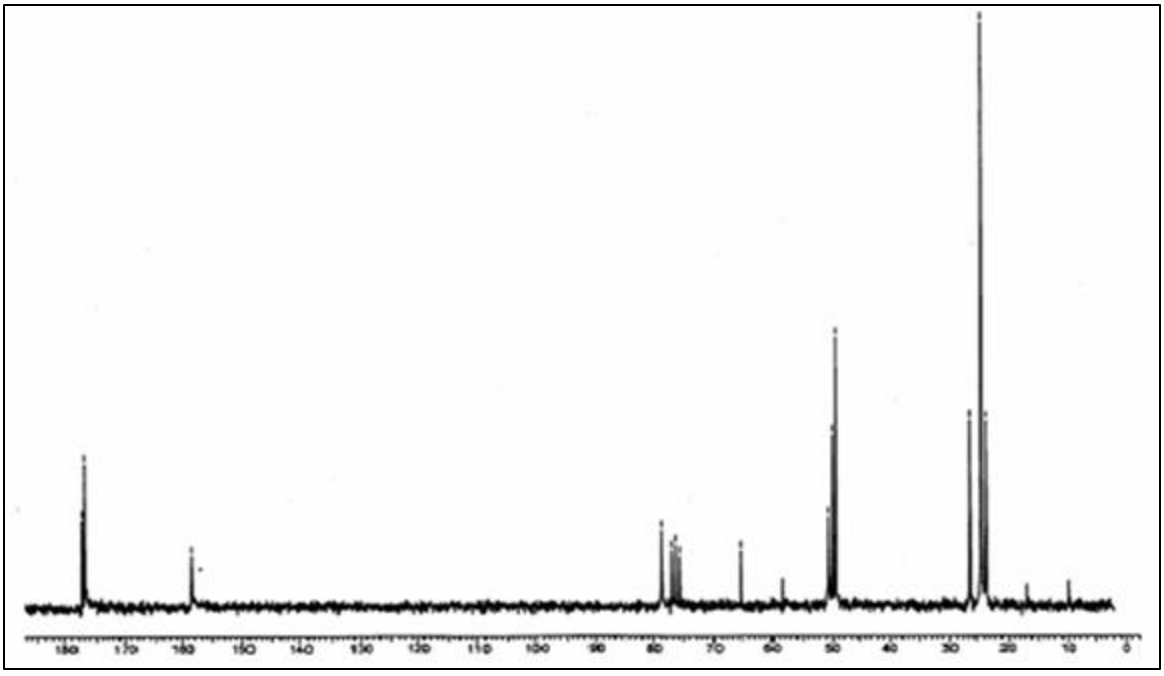
4.3.7. Spectra

1. ^{1}H NMR of 2**93**
2. ^{13}C NMR of **293**
3. ^{1}H NMR of **290**
4. ^{13}C NMR of **290**
5. ^{1}H NMR of **291**
6. ^{13}C NMR of **291**
7. ^{1}H NMR of **292**
8. ^{13}C NMR of **292**

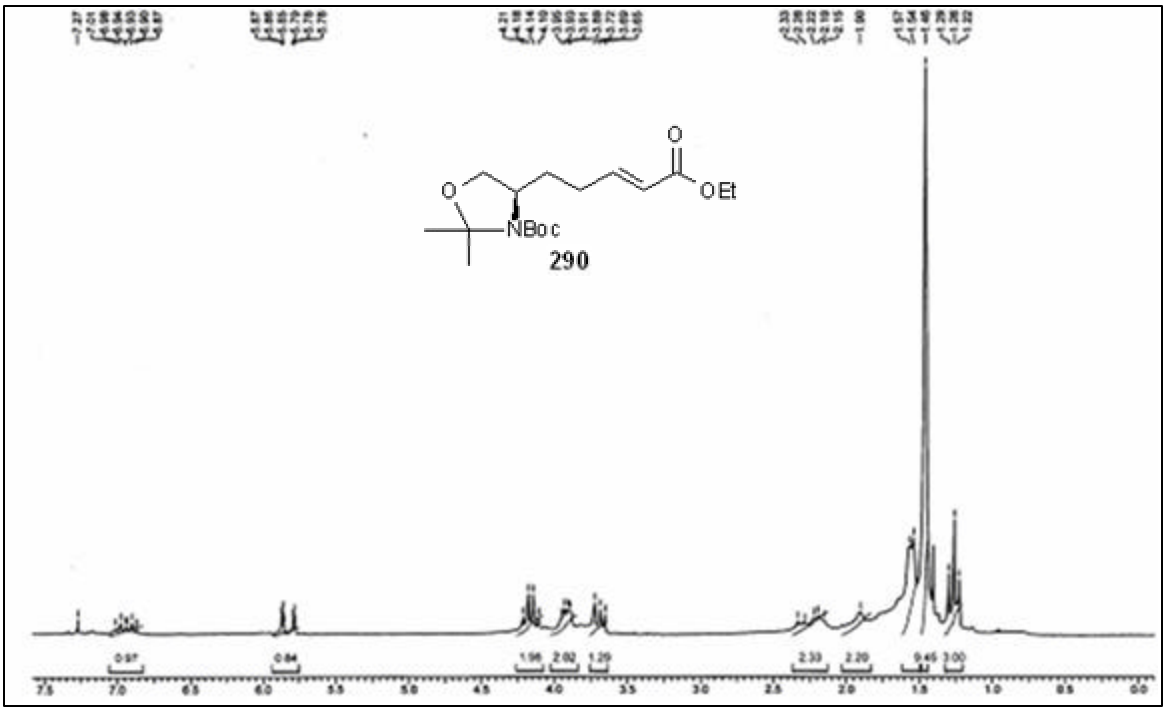
➢ ^{1}H NMR spectrum of **293**



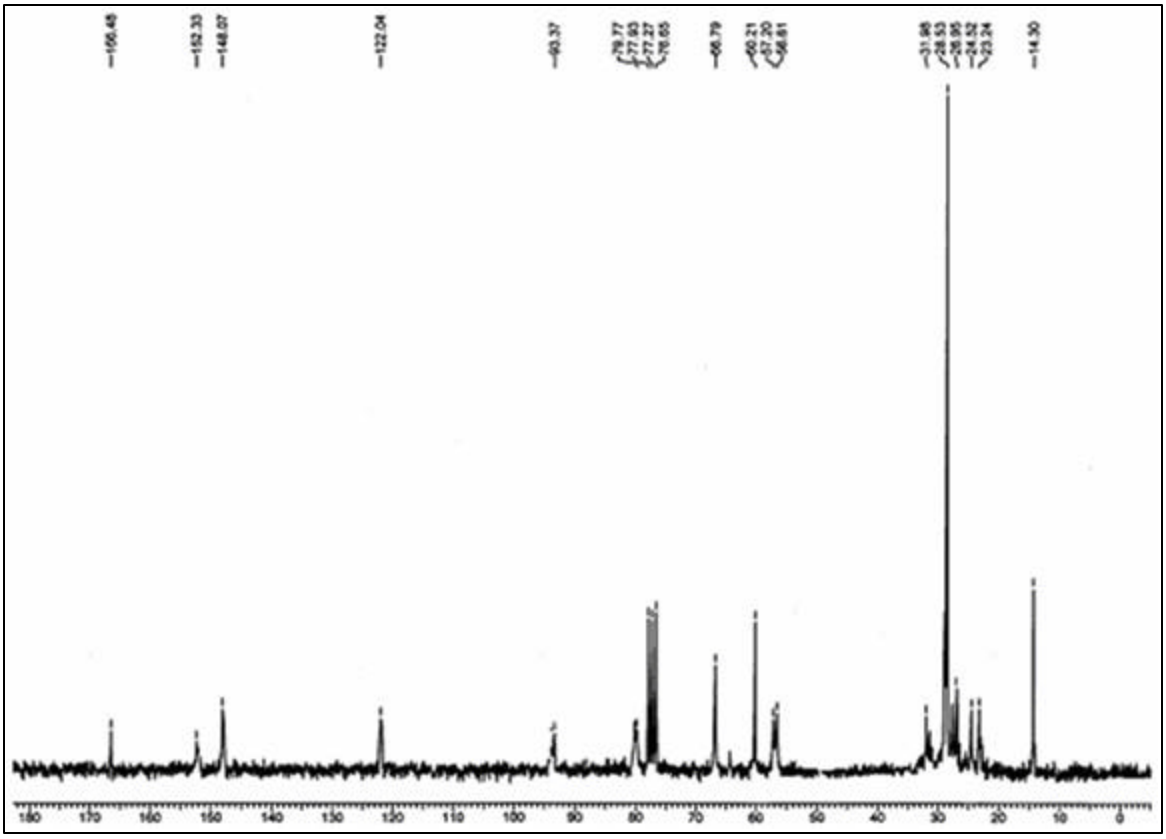
➢ ^{13}C NMR spectrum of **293**



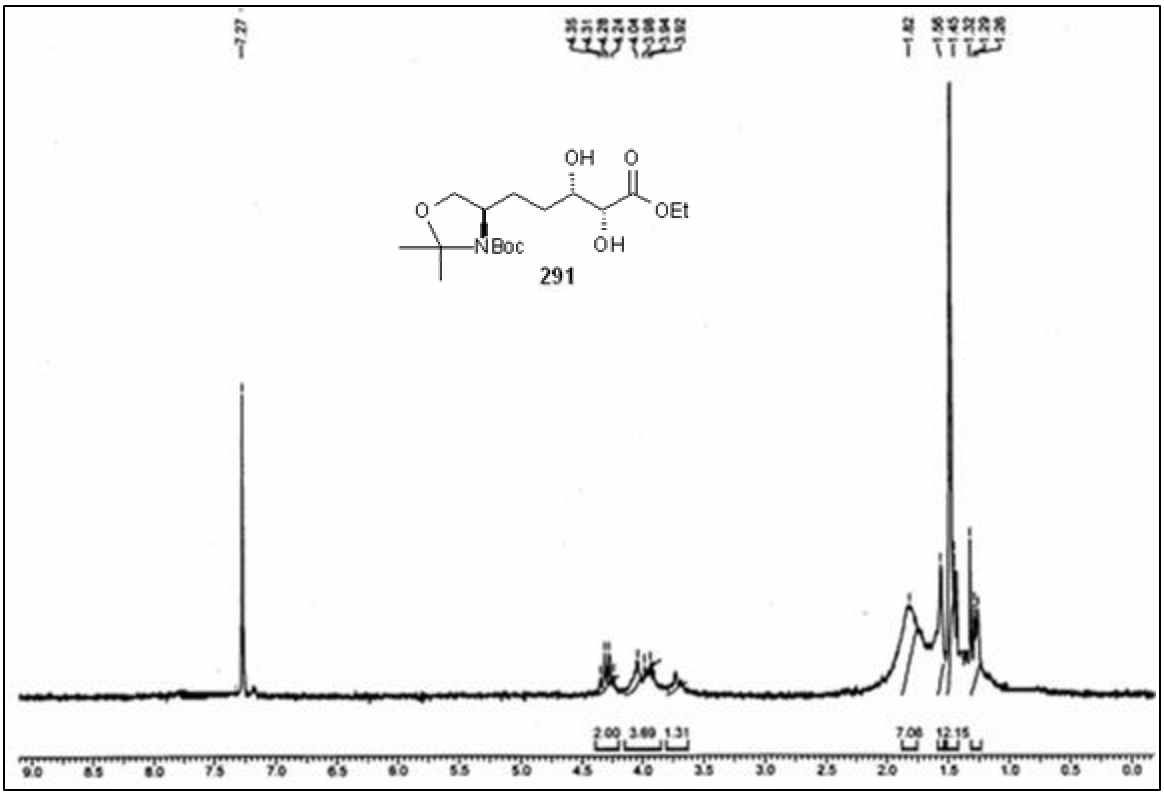
➢ ^{1}H NMR spectrum of **290**



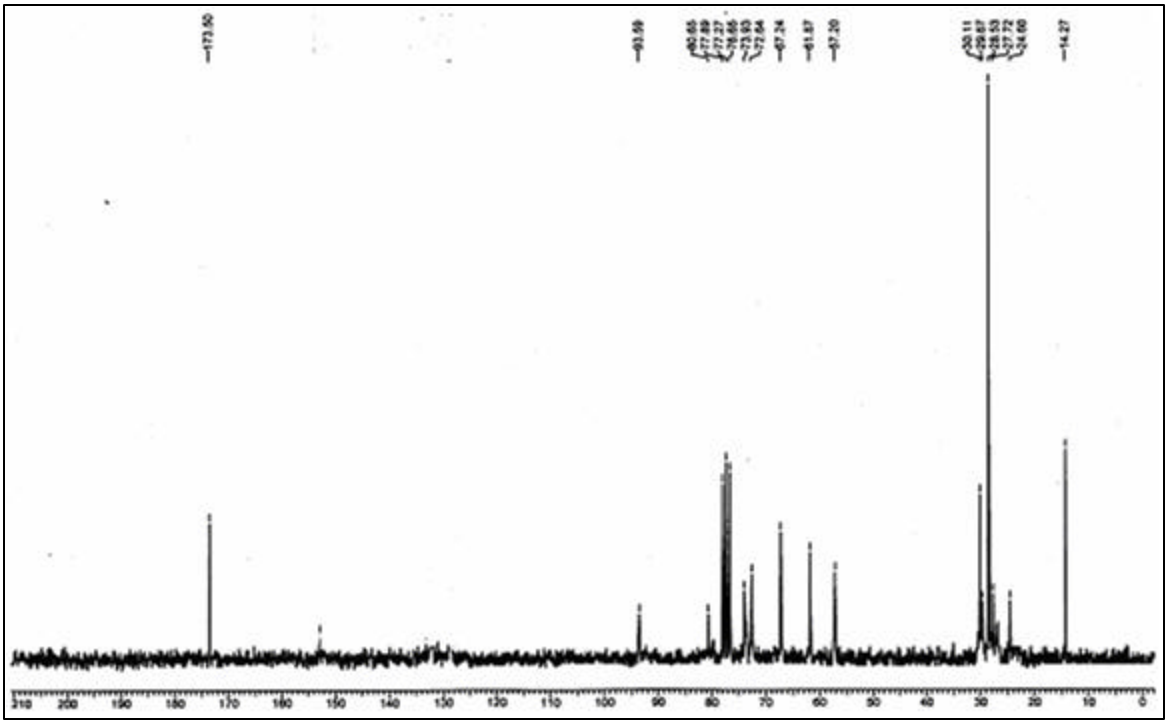
➢ ^{13}C NMR spectrum of **290**



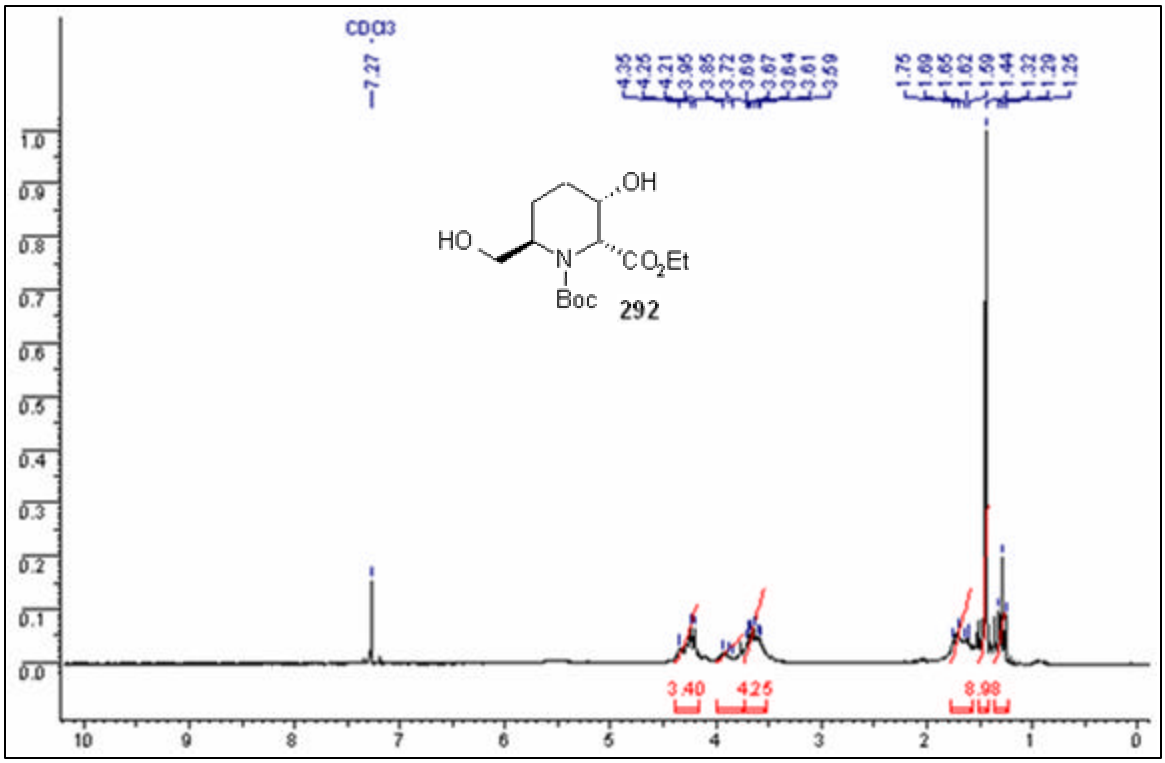
➢ ^{1}H NMR spectrum of **291**



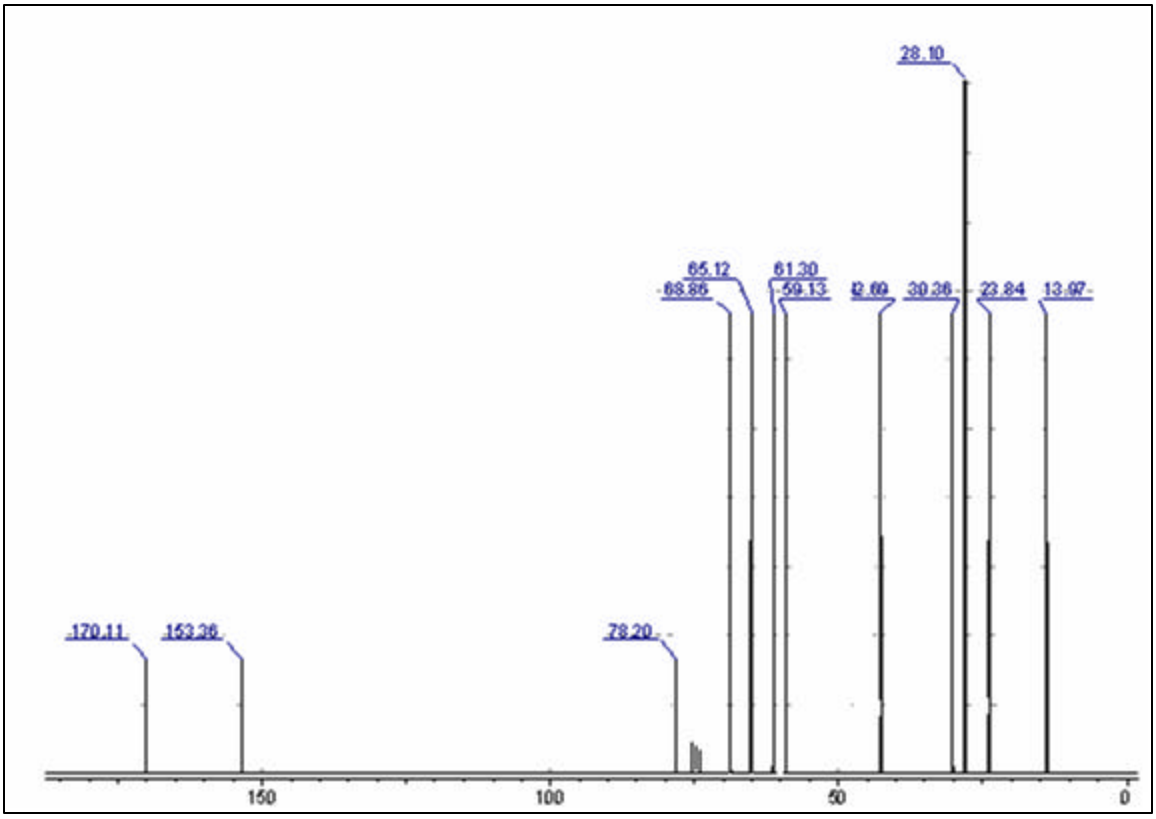
➢ ^{13}C NMR spectrum of **291**



➢ ^{1}H NMR spectrum of **292**



➢ ^{13}C NMR spectrum of **292**



4.4 SECTION C

Synthesis Of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine

4.4.1 INTRODUCTION

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks in natural products and synthetic compounds with important biological activities. Therefore a huge amount of synthetic effort has been spent on the preparation of these systems.[179,180] With respect to biologically active target molecules there is an increasing interest in the diastereo- and enantioselective synthesis of piperidines. The piperidine ring system **295** is one of the most common structural sub-unit in natural compounds as exemplified in the following structures (**Figure 6, 296**-**303**). The importance of this ring system makes short, versatile, stereocontrolled routes to substituted piperidines of tremendous potential value. 2-Alkyl-3-hydroxyl piperidines and 2-alkly-3-aminopiperidines are structural units found in numerous bioactive natural products, drugs, and drug candidates. For example, (+)-CP-99,994 **300** and (+)-L-733,060 **301** are selective and potent neurokinin substance P receptor antagonists, which have been shown to posses potent antiemetic activity.

The peptide substance P is an endogenous mammalian neuromodulator that acts preferentially on tachykinin NK 1 receptors. Substance P is thought to be involved in the perception of pain since it is released in response to tissue damage/injury from sensory nerve terminals in the periphery as well as within the dorsal horn of the spinal cord. Substance P has also been implicated in the pathogenesis of migraine as it is thought to be released from trigeminal sensory nerves which innervate pain producing cranial structures that when activated experimentally can produce neurogenic inflammation within the dura mater. Consequently, the significance of tachykinin NK-1 receptors in some in-vivo anti-nociceptive and anti-inflammatory assays has remained ambiguous. Block of ion

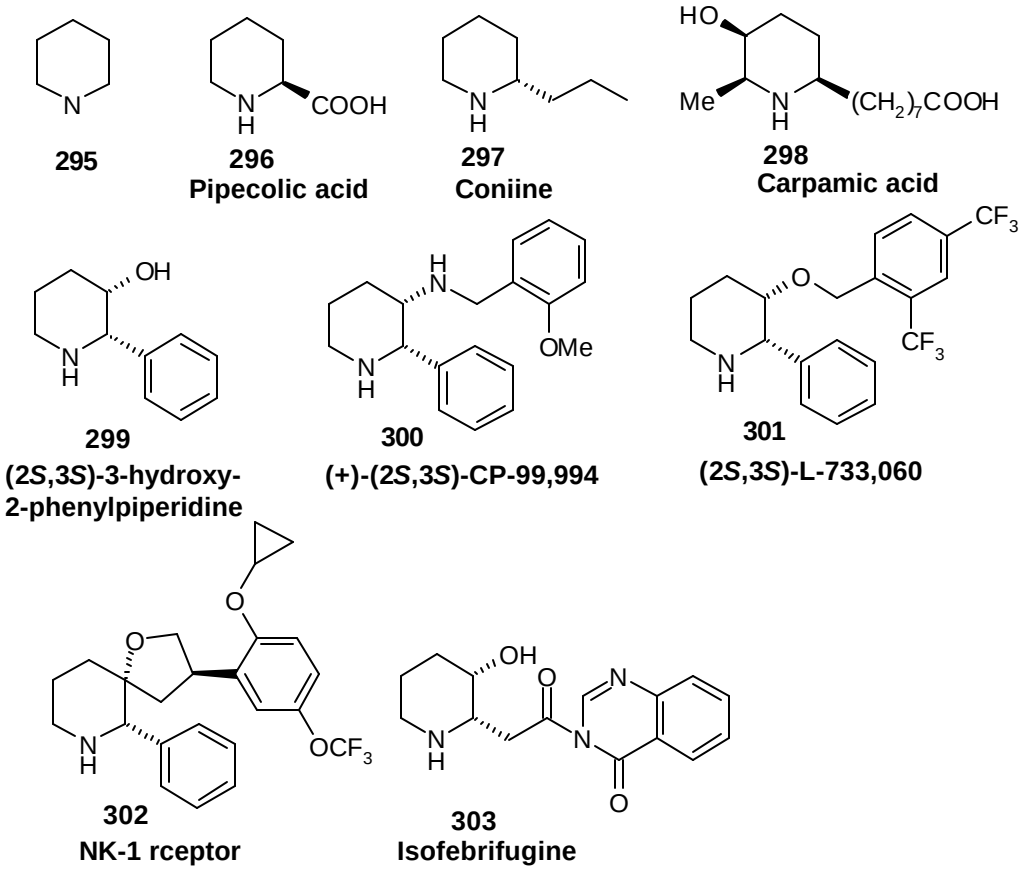


Figure 6

channels by tachykinin NK-1receptor antagonists may also result in adverse cardiovascular side-effects. Extravasation in the dura mater caused by application of exogenous substance P is also blocked by tachykinin NK 1 receptor antagonists. Thus, tachykinin NK-1 receptors may, indeed, have a functional role in some forms of pain and inflammation.

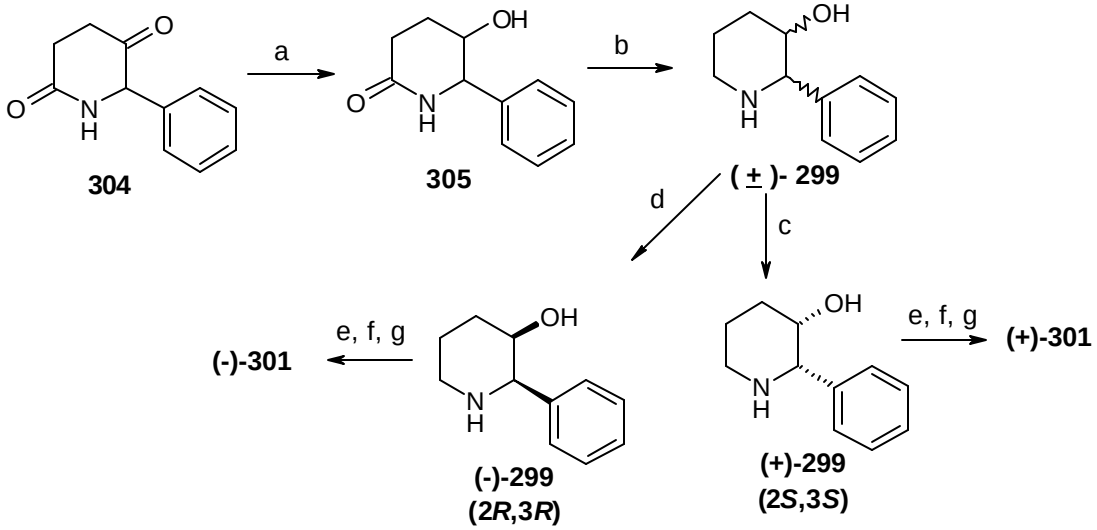
These nonpeptide ligands **300** and **301** are known to exhibit a variety of biological activities including neurogenic inflammation,[183] pain transmission and regulation of the immune response.[184] They have been implicated in a variety of disorders including migraine,[185] rheumatoid arthritis[186] and pain.[187] It has been established that the *cis*-relationship between the two substituents on the piperidine ring and 2*S*,3*S* configurations are essential for high-affinity binding to the human NK1 receptor.[181,182,188]

4.4.2 Review of Literature

N-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **299** is an important intermediate from which nonpeptide neurokinin NK1 receptor antagonists **300** and **301** have been prepared. A few reports have appeared on the asymmetric synthesis of **299**.

Harrison *et al.* (1994)[189] Scheme 43

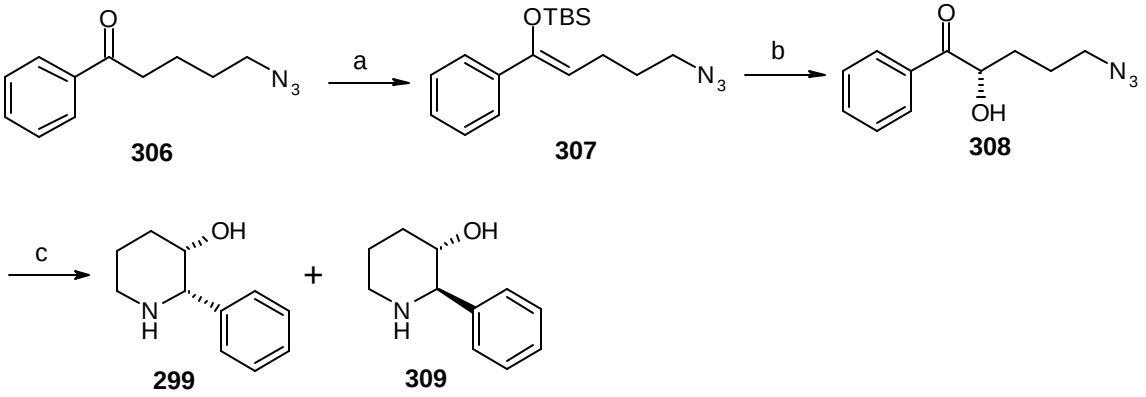
The synthesis of piperidine-based ethers (+)-**301** and (-)-**301** was described by Harrison *et al.*[189] *via* **299**. The key step in the synthesis was the resolution of the racemic mixture of **299**. The compound **299** was obtained with high selectivity by initial reduction of the keto-lactam **304** to provide hydroxyl-lactam **305** followed by reduction of the lactam carbonyl using borane.



Scheme 43 Reagent and Conditions: (a) $NaBH_4$, MeOH, -20°C (b) BH_3.THF, reflux, then *p*-TsOH, 76% (c) Na_2CO_3, (-)-dibenzoyl tartaric acid (d) Na_2CO_3, (+)-dibenzoyl tartaric acid (e) di-*t*-butyldicarbonate, CH_2Cl_2, 99% (f) NaH, DMF, 3,5-bis(trifluoromethyl)benzyl bromide, 82% (g) TFA, 99%.

Stadler *et al.* (1999)[190] Scheme 44

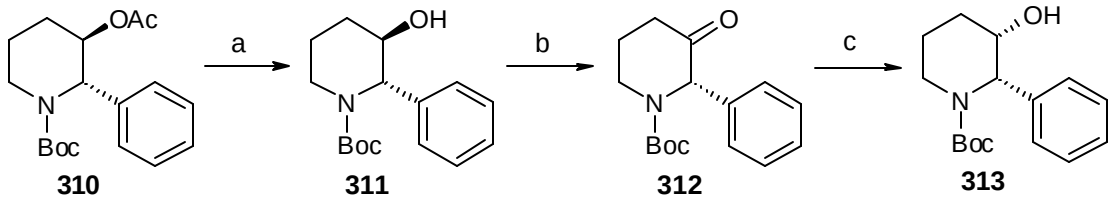
Stadler *et al.* synthesized compound **299** by employing Sharpless asymmetric dihydroxylation of the silyl enol ether **307** (**Scheme 44**). Hydrogenation of the ketone **308** obtained by hydrolysis **307** yielded the desired compound **299** as a diastereomeric mixture.



Scheme 44 Reagent and Conditions: (a) Et_3N, TBDMS, CH_3CN, rt (b) AD-mix-α, *t*-BuOH:H_2O (1:1) (c) H_2, Pd/C.

Langiois *et al.* (1999)[191] Scheme 45

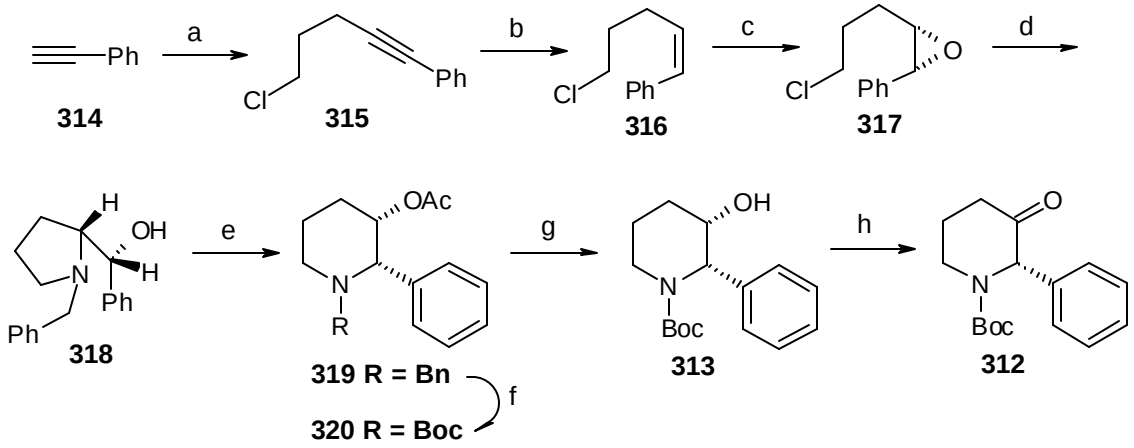
(2*S*)-*N*-Boc-3-oxo-2-phenylpiperidine **312** and (2*S*,3*S*)-*N*-Boc-3-hydroxy-2-phenylpiperidine **313**, known chiral building blocks for the synthesis of non-peptide substance P antagonists, were prepared from *trans*-(2*S*,3*R*)-*N*-Boc-3-acetoxy-2-phenylpiperidine **310** by Lagiois *et al.* (**Scheme 45**).



Scheme 45 Reagent and Conditions: (a) 3N NaOH, 65°C (b) DMSO, $(COCl)_2$, *i*-Pr_2NEt, -20°C (c) L-Selectride, -78°C.

Lee *et al.* (2001)[192] Scheme 46

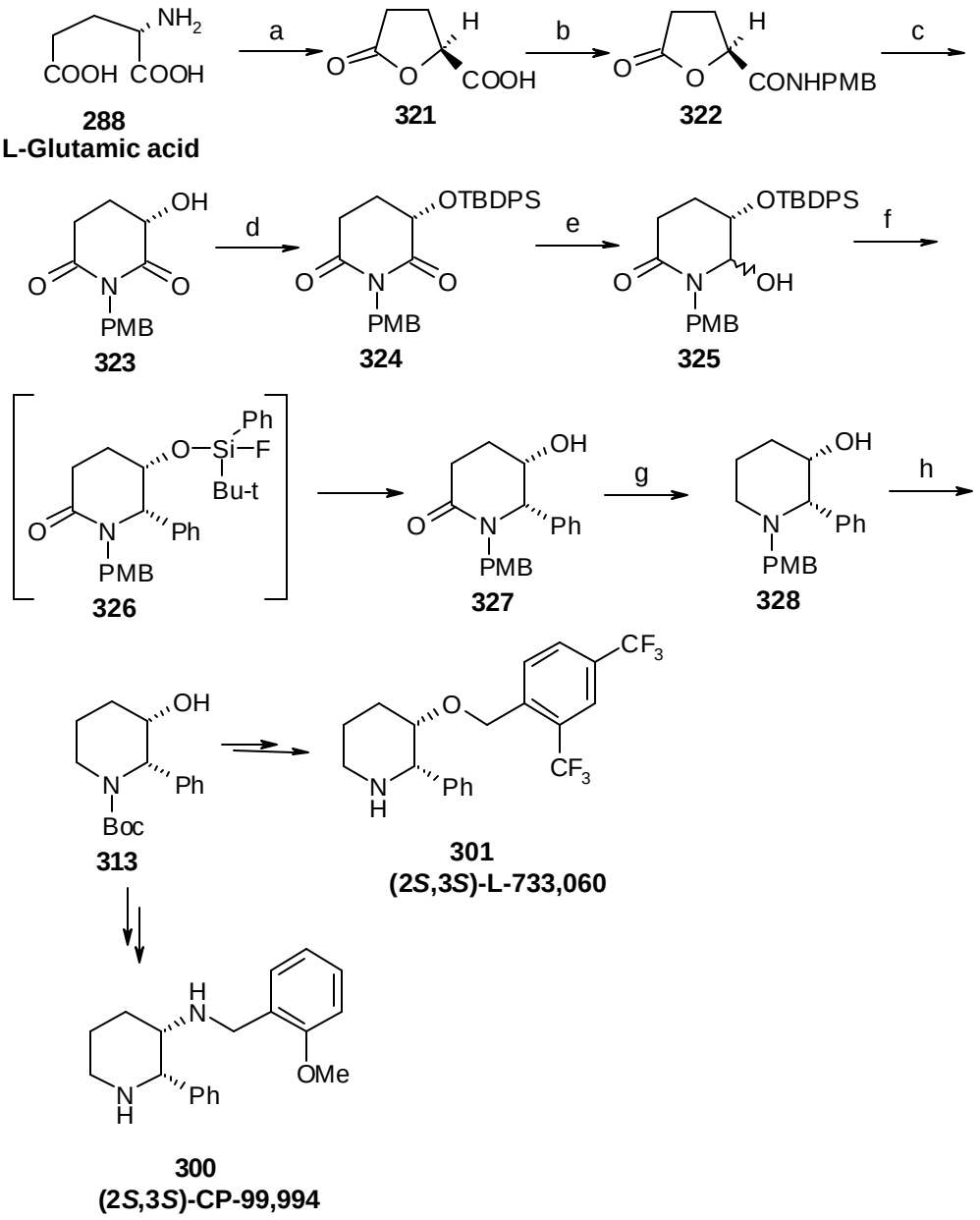
A catalytic highly enantioselective preparation of (2*S*)-*N*-Boc-3-oxo-2-phenylpiperidine **312** and (2*S*,3*S*)-*N*-Boc-3-hydroxy-2-phenylpiperidine **313** was developed using an intramolecular epoxide opening followed by ring expansion. The *cis*-epoxide starting material **317** was available in high ee *via* Jacobsen epoxidation of **316**.



Scheme 46 Reagent and Conditions: (a) *n*-BuLi, $Cl(CH_2)_3Br$ (b) H_2, Lindlar cat., 1-hexene (c) Jacobsen epoxidation (d) $PhCH_2NH_2$, $NaHCO_3$, NaI (e) (i) MsCl, Et_3N; (ii) *n*-Bu_4NOAc (f) Pd/C, Boc_2O (g) NaOH, MeOH (h) Moffat.

Huang *et al.* (2003)[193] Scheme 47

Huang *el al.*[193] synthesized the selective and potent neurokinin substance P receptor antangonist (+)-CP-99,994 **300** and (+)-L-733,060 **301** from a new (3*S*)-piperidinol synthon derived from L-glutamic acid **288**. The method featured a C-2 regioselective reduction of glutarimide **324**, Lewis acid-promoted Si to C-2 phenyl group migration of **325** as the key steps.



288
L-Glutamic acid

321

322

323

324

325

326

327

328

313

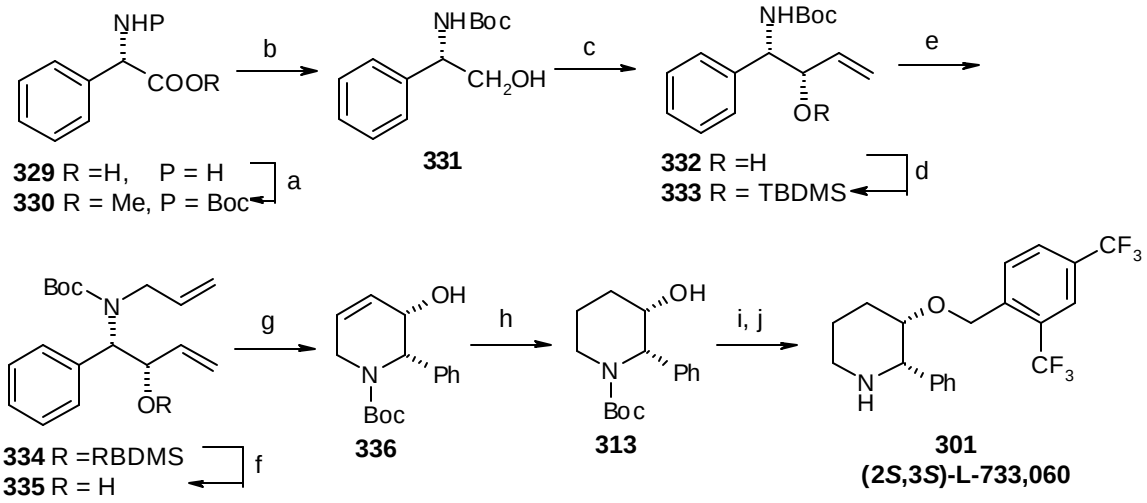
301
(2*S*,3*S*)-L-733,060

300
(2*S*,3*S*)-CP-99,994

Scheme 47 Reagent and Conditions: (a) H_2SO_4, $NaNO_2$ (b) (i) $SOCl_2$, 60°C; (ii) PMB-NH_2, CH_2Cl_2, rt, 70% (2 steps) (c) *t*-BuOK, THF, -78°C to -40°C, 90% (d) TBDPSCl, imidazole, CH_2Cl_2, 94% (e) $NaBH_4$, MeOH, -20°C, 94% (f) BF_3.OEt, CH_2Cl_2, rt, 80% (g) $LiAlH_4$, THF, rt, 81% (h) 20% $Pd(OH)_2/C$, H_2, EtOH, Boc_2O, rt, 88%.

Rao *et al.* (2003)[194] Scheme 48

Rao *el al.*[194] synthesized the non-peptide neurokinin substance P receptor (+)-L-733,060 **301** using ring closing metathesis as the key step., starting from L-phenyl glycine **329**.



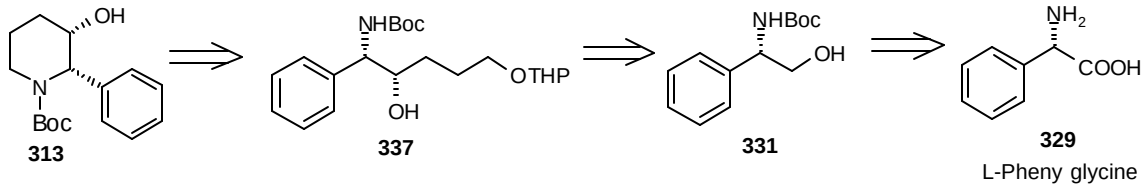
Scheme 48 Reagent and Conditions: (a) AcCl, MeOH then $(Boc)_2O$, Et_3N, THF, 0°C–rt, 8 h, 97% (b) LiCl, $NaBH_4$, EtOH, THF, 0°C–rt, 12 h, 87% (c) DMSO, $(COCl)_2$, CH_2Cl_2, *i*-Pr_2NEt then CH_2=$CHMgBr$, THF, 2 h, rt, 61% (d) TBDMS–Cl, imidazole, CH_2Cl_2, 0°C–rt, 24 h, 90% (e) CH_2=$CHCH_2Br$, NaH, DMF, 0°C–rt, 24 h, 90% (f) TBAF–AcOH, THF, 0°C–rt, 24 h, 85%; (g) Grubbs' catalyst, CH_2Cl_2, rt, 6 h, 82% (h) Pd/C, H_2, EtOH, 4 h, rt, 65% (i) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80°C, 13 h, 80% (j) TFA, rt, 1 h, 79%.

4.4.3 Present Work

Objective:

As part of our research program aimed at developing enantioselective syntheses of naturally occurring piperidine alkaloids we became interested in developing a simple and feasible route to *N*-Boc-3-hydroxy-2-phenylpiperidine **313**, as it is the synthetic precursor to the potent neurokinin substance P receptor antangonist (+)-CP-99,994 **300** and (+)-L-733,060 **301**.

As can be seen from the retrosynthetic analysis (**Scheme 49**), the desired synthetic intermediate *N*-Boc-3-hydroxy-2-phenylpiperidine **313**, could well be obtained from L-phenyl glycine **329**.

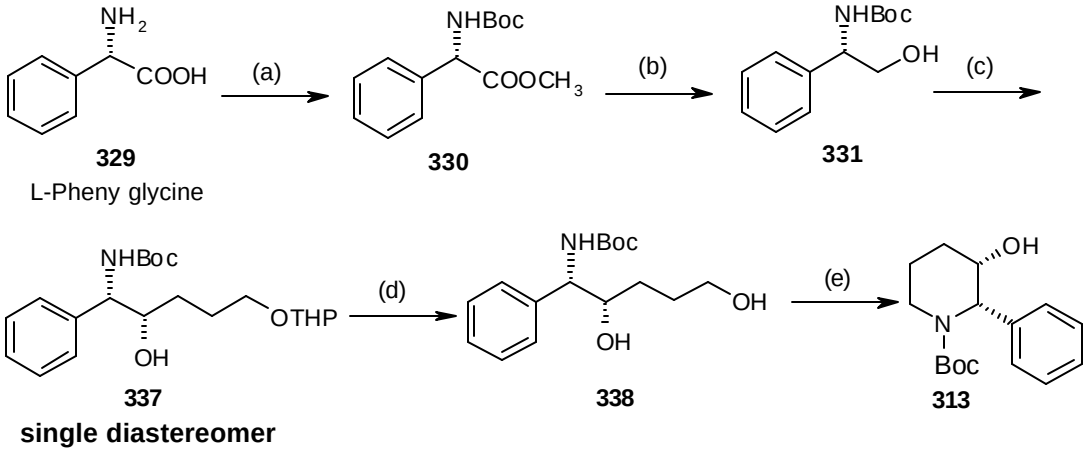


Scheme 49

We thought of employing Grignard reaction of the alcohol **331** obtained from L-phenyl glycine **329** as the key step to obtain the key precursor **337**. The difference here in our approach than the previous one[194] lies in the use of 3-(tetrahydropyran-2-yloxy)propylmagnesium bromide as the Grignard reagent instead of vinylmagnesium bromide to obtain more diastereoselectivity involving a more convenient and economically feasible route for the construction of piperidine ring rather than using the Grubb's catalyst.

4.4.4 Results and Discussion

As per our retrosynthetic analysis we started our approach towards the desired synthetic intermediate **313** from L-phenyl glycine **329** (**Scheme 50**). L-Phenyl glycine **329** was first converted into *N*-Boc derivative and subsequently esterified with methyl iodide to give *N*-Boc methylester **330** in 85% yield. The ^{1}H NMR spectrum of **330** showed protons corresponding to the Boc group at δ 1.44 and the methyl protons of the ester group at δ 3.73. The ester **330** was reduced to alcohol **331** using $LiAlH_4$ in 89% yield. The ^{1}H NMR spectrum of alcohol **331** showed the absence of methyl protons of the ester group at δ 3.73 and the ^{13}C-DEPT spectrum showed the CH_2OH carbon at δ 66.46. The essential feature of our synthetic strategy was the presumption that the aldehyde derived from alcohol **331** would undergo chelation controlled carbonyl addition[195] and provide preferentially the desired *threo* amino alcohol **337** in a stereoselective manner. Thus, Swern oxidation of **331** followed by *in situ* reaction of the resulting aldehyde with 3-(tetrahydropyran-2-yloxy)propylmagnesium bromide afforded the amino alcohol **337** as a **single diastereomer** in favour of the *syn* isomer, which is in accordance with the



Scheme 50 Reagent and Conditions: (a) (i) $(Boc)_2O$, 1 N NaOH, Dioxane, 2 h, 0°C-rt, 95%, (ii) K_2CO_3, DMF, CH_3I, 1 h, 0°C-rt, 85%; (b) $LiAlH_4$, THF, 1 h, 0°C-rt, 89%; (c) DMSO, $(COCl)_2$, -78°C, CH_2Cl_2, 2 h; *i*-Pr_2NEt then BrMg $(CH_2)_3OTHP$, THF, 2 h, rt, 58%; (d) TsOH, MeOH, 2 h, rt, 85%; (e) (i) *p*-MsCl, Et_3N, CH_2Cl_2, 3 h, 0°C-rt, (ii) NaH, THF, rt, 78%.

reported observation.[196] The ^{1}H NMR spectrum of **337** showed the THP group protons at δ 1.52-1.68, showing the inclusion of the aliphatic group by Grignard reaction. Also the ^{13}C-DEPT spectrum of **337** showed the presence of three CH carbon at δ 56.50 (-CHNHBoc), δ 94.36 (-CHOH) and δ 98.60 (-CH of the tetrahydropyranyl group) confirming the success of the Grignard product. Also we confirmed about the single diastereomer after obtaining a single peak in the ^{13}C-DEPT spectrum of **337** corresponding to the secondary OH group introduced. The THP group of **337** was deprotected using *p*-toluenesulfonic acid to give the amino diol **338** in 85% yield. The primary hydroxyl group was then mesylated followed by *in situ* cyclisation using NaH to furnish *N*-Boc-(2*S*, 3*S*)-3-hydroxy-2-phenylpiperidine **313** in 78% yield, $[\alpha]^{20}_{D}$ = + 35.41 (*c* 1.2, $CHCl_3$) [Lit.[194] $[\alpha]^{25}_{D}$ = +38.30 (*c* 1.92, $CHCl_3$)]. The physical and spectroscopic data of **313** were in full agreement with the literature values.[194] The intermediate **313** could easily be transformed into the non-peptidic neurokinin NK1 receptor antagonists **300** and **301** as previously reported.[193, 194]

4.4.5. Conclusion

In summary, a highly enantio- and stereoselective synthesis of N-Boc-(2S,3S)-3-hydroxy-2-phenylpiperidine **313** has been accomplished. The short reaction sequence and high overally yield of the target compound render our strategy a good alternative to the known methods.

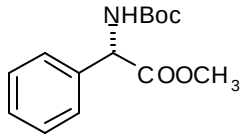
4.4.6. Experimental section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz machine and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and

125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan LCMS mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

Preparation of (2*S*)-*tert*-butoxycarbonylamino phenylacetic acid methyl ester, 330



330

A solution of di-tert-butyldicarbonate (3.47 g, 15.9 mmol) in dioxane (50 mL) is added to an ice cold solution of phenyl glycine **329** (2.0 g, 13.23 mmol) in 1N NaOH (1.06 g in 26 mL H_2O) by means of an addition funnel. The two phase mixture is stirred at 5 ^oC for 30 min, then allowed to warm to room temperature over 2 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half its original volume at 35 ^oC, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 150 mL). The combined extracts are dried over Na_2SO_4, filtered and concentrated to give 18.5 g, 98% N-Boc-L-phenyl glycine (3.15 g, 95% crude yield) as colorless, sticky foam which is used without further purification.

To a ice cold solution of *N*-Boc-L-phenyl glycine (3.15 g, 12.53 mmol) in DMF (30 mL) is added solid K_2CO_3 (1.91 g, 13.84 mmol). After stirring for 10 min in an ice bath, methyl iodide (3.56 g, 28.08 mmol) is added to the white suspension and stirring continued at 0^oC for 30 min. where upon the mixture solidifies. The reaction is warmed to room temperature and stirred for additional 1 h. TLC analysis indicated complete formation of the methyl ester. The reaction mixture is filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase is washed with brine, dried, filtered and concentrated to give *N*-Boc-L- phenyl glycine methyl ester **330** (2.98 g) as a white solid (M.P. 134-135^oC).

Yield: 2.98 g, 85%

$[\alpha]_D^{20}$: + 12.32 (c = 1.0, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1586, 1682, 1736, 2830, 2942, 3430

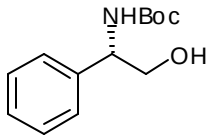
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.73 (s, 3H), 5.32 (d, 1H, *J* = 6Hz), 5.55 (brs, 1H), 7.36 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.31, 52.64, 57.64, 80.10, 127.72, 128.47, 128.91, 136.93, 154.90, 171.30

Mass (ESI): 273 (M^++NH_4^+), 265(M^+)

Analysis calcd.for $C_{14}H_{19}NO_4$: C: 63.38; H: 7.22; N: 5.28 Found: C: 63.40; H: 7.26; N: 5.25.

Preparation of (2*S)*-(2-hydroxy-1-phenylethyl)carbamic acid *tert*- butyl ester, 331



331

To a stirred suspension of $LiAlH_4$ (0.54 g, 14.23mmol) in dry THF (80 mL) at 0 °C was added a solution of **330** (2.5 g, 9.43 mmol) in dry THF (20 mL). The ice bath was removed and the reaction mixture was stirred for 1 h. Excess $LiAlH_4$ was quenched by adding water. The white precipitate obtained was filtered and washed with methanol. The combined filtrate was concentrated to near dryness. The inroganic materials contained in the residual oil were removed by short column chromatography over silica gel using petroleum ether / EtOAc (9:6) as eluent to afford the alcohol **331** (1.99 g) as a white solid (M.P. 113-114°C).

Yield: 1.99 g, 89%

[α]$_D^{20}$: + 28.42 (c = 1.02, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1564, 1685, 2839, 2936, 3364, 3438

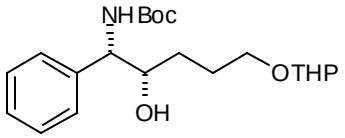
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.10 (brs, 1H), 3.84 (d, 2H, *J* = 5Hz), 4.78 (m, 1H), 5.27 (brs, 1H), 7.277.36 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.46, 56.91, 66.46, 80.06, 126.71, 127.6, 128.73, 139.94, 156.41

Mass (ESI): 237(M^+), 219, 207, 137

Analysis calcd.for $C_{13}H_{19}NO_3$: C: 65.80; H: 8.07; N: 5.90 Found: 65.83; H: 8.11; N: 5.87.

Preparation of (2*S)*-[2-hydroxy-1-phenyl-5-(tetrahydropyran-2-yloxy)pentyl]-carbamic acid *tert*- butyl ester, 337



337

To a stirred solution of oxalyl chloride (0.80 g, 6.30 mmol) in CH_2Cl_2 (25 mL) at –78°C under nitrogen atmosphere was added DMSO (0.66 g, 8.44 mmol) in dropwise manner. After stirring for 30 min, a solution of amino alcohol **331** (1 g, 4.21 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture over 30 min. The mixture was warmed to –35°C and stirred for 30 min; at this temperature, followed by dropwise addition of diisopropyl ethylamine (3.27 g, 2.53 mmol) over 5 min. The reaction mixture was then warmed to 0°C in 15 min and transferred through a cannula to a room temperature solution of [$MgBr(CH_2)_3OTHP$] prepared from Mg (1.42 g, 59.16 mmol) and tetrahydropyranyl protected 1-bromo-3-propanol (6.5 g, 29.50 mmol) in ether (20 mL over 30 min) after stirring for 2 h at room temperature. The reaction mixture was poured into aq. NH_4Cl solution (30 mL) and acidified to pH 4 by adding 10% aqueous HCl solution. The organic layer was separated, aqueous layer extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed sequentially with water and brine. After drying over Na_2SO_4 solvent was removed under vacuo and the residue purified by silica gel column chromatography using petroleum ether / EtOAc (8.5:1.5) to yield the amino alcohol **337** (0.93 g) as a white solid (M.P. 110-112°C).

Yield: 0.93 g, 58 %

$[\alpha]_D^{20}$: + 13.73 (c = 0.82, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}): ν_{max} 1448, 1550, 1680, 2840, 2936, 3350, 3480

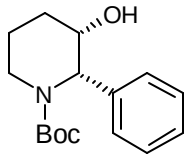
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.54-1.68 (m, 8H), 2.04-2.35 (m, 2H), 3.41-3.65 (m, 2H), 3.74-3.88 (m, 3H), 4.21-4.24 (m, 1H), 4.58 (m, 1H), 5.45 (brs, 1H), 7.30 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.05, 25.08, 28.24, 30.22, 32.50, 34.93, 56.50, 63.82, 65.84, 79.65, 94.36, 98.60, 126.53, 127.26, 128.40, 140.02, 156.23

Mass (ESI): 397(M^++NH_4^+), 380 (M+1), 356, 279, 246

Analysis calcd.for $C_{21}H_{33}NO_5$: C: 66.46; H: 8.76; N: 3.69 Found: 66.45; H: 8.77; N: 3.71.

Preparation of (2*S*,3*S*)-[3-hydroxy-2-phenylpiperidine-1-carbamic acid *tert*- butyl ester, 313



313

To a solution of **337** (0.9 g, 2.37mmol) in methanol (10 mL) was added TsOH (10 mg, cata) and the reaction mixture stirred for 2 h at room temperature. After completion of reaction, solvent was evaporated and water (10 mL) was added to it, extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine, dried and concentrated to give **338** (0.62 g, 89% crude yield). The compound was further used without purification.

To the solution of **338** (0.62 g, 2.09 mmol) and Et_3N (0.32 g, 3.16mmol) in CH_2Cl_2 (10 mL) at 0°C was added MsCl (0.29 g, 2.53mmol). The reaction was brought to room temperature slowly in 3 hours after which the TLC indicated the completion of reaction. Water (10 mL) was added to quench the reaction and the solution extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to dryness to afford the mesyl derivative.

To the suspension of NaH (0.076 g, 3.16 mmol) in dry THF (6ml) was added the above mesyl derivative in dry THF (4 mL) at 0°C. The reaction was then stirred at room temperature for 1 h after which it was quenched by addition of water (5 mL). The solution was extracted with EtOAc (3 x 10 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7 :3) as eluent gave **313** (0.45 g) as a pale yellow oil.

Yield: 0.45 g, 78 % (from **388**)

$[\alpha]_D^{20}$: + 35.41 (c = 1.2, $CHCl_3$) [Lit.[194] $[\alpha]_D^{25}$: + 35.41 (c = 1.92, $CHCl_3$)]

IR ($CHCl_3$ cm^{-1}): ν_{max} 1454, 1675, 2859, 2936, 3444

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.52-1.68 (m, 2H), 2.04-2.35 (m, 2H), 3.71-3.89 (m, 2H), 4.11-4.14 (m, 1H), 4.58 (m, 1H), 7.30 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): 24.11, 27.65, 28.28, 39.50, 59.61, 71.21, 79.95, 127.25, 128.39, 128.65, 139.23, 156.24

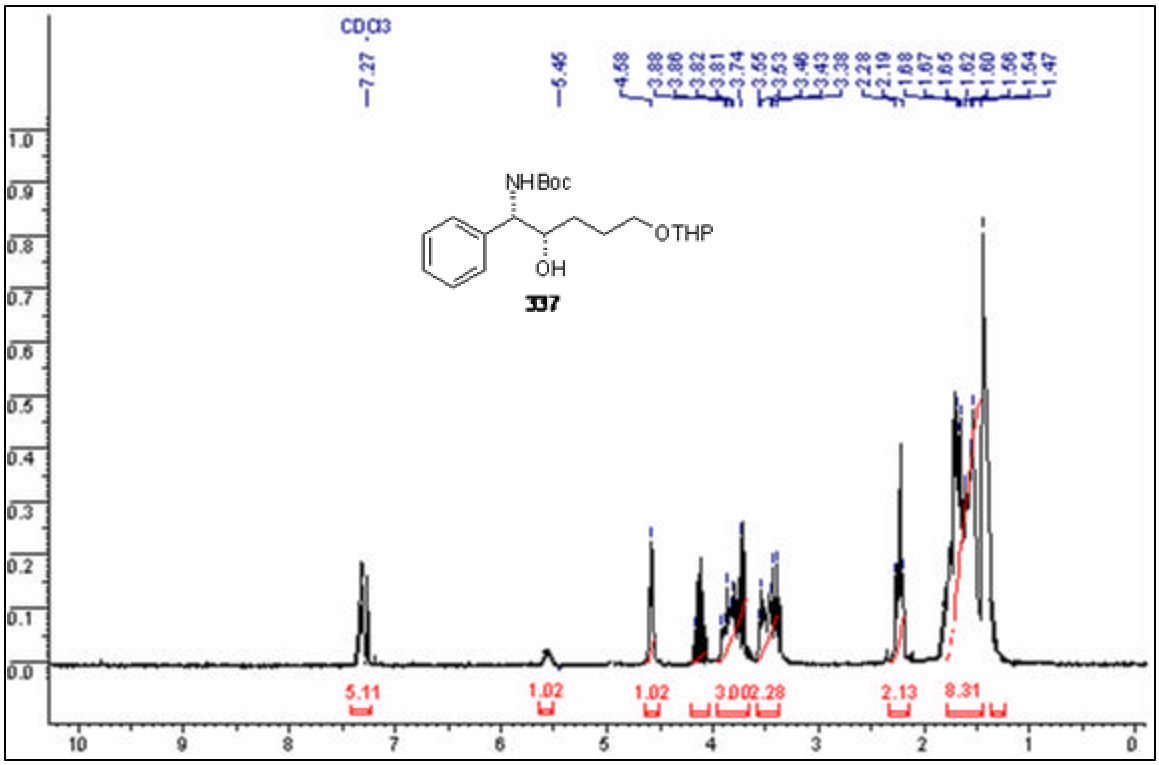
Mass (ESI): 278 (M+1), 260, 201, 183

Analysis calcd.for $C_{16}H_{23}NO_3$: C: 69.29; H: 8.36; N: 5.05 Found: 69.30; H: 8.33; N: 5.07.

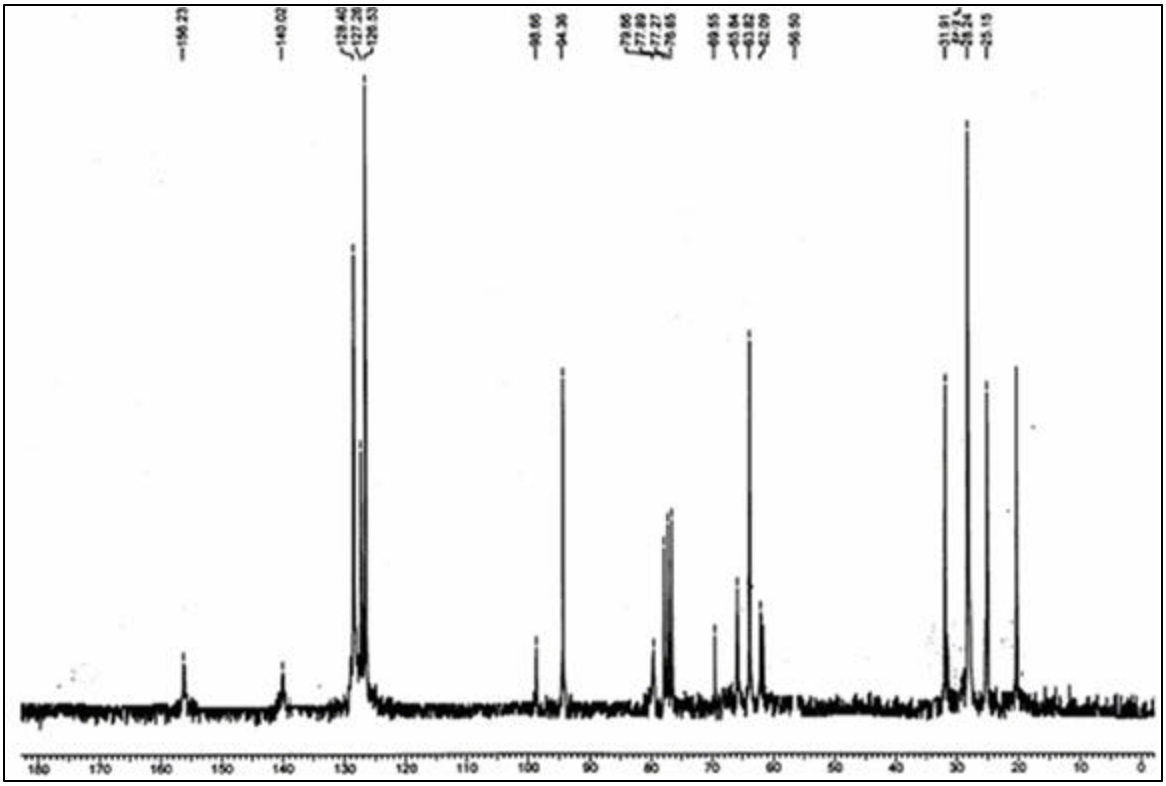
4.4.7. Spectra

1. ^{1}H NMR of **337**
2. ^{13}C NMR of **337**
3. DEPT NMR of **337**
4. ^{1}H NMR of **313**

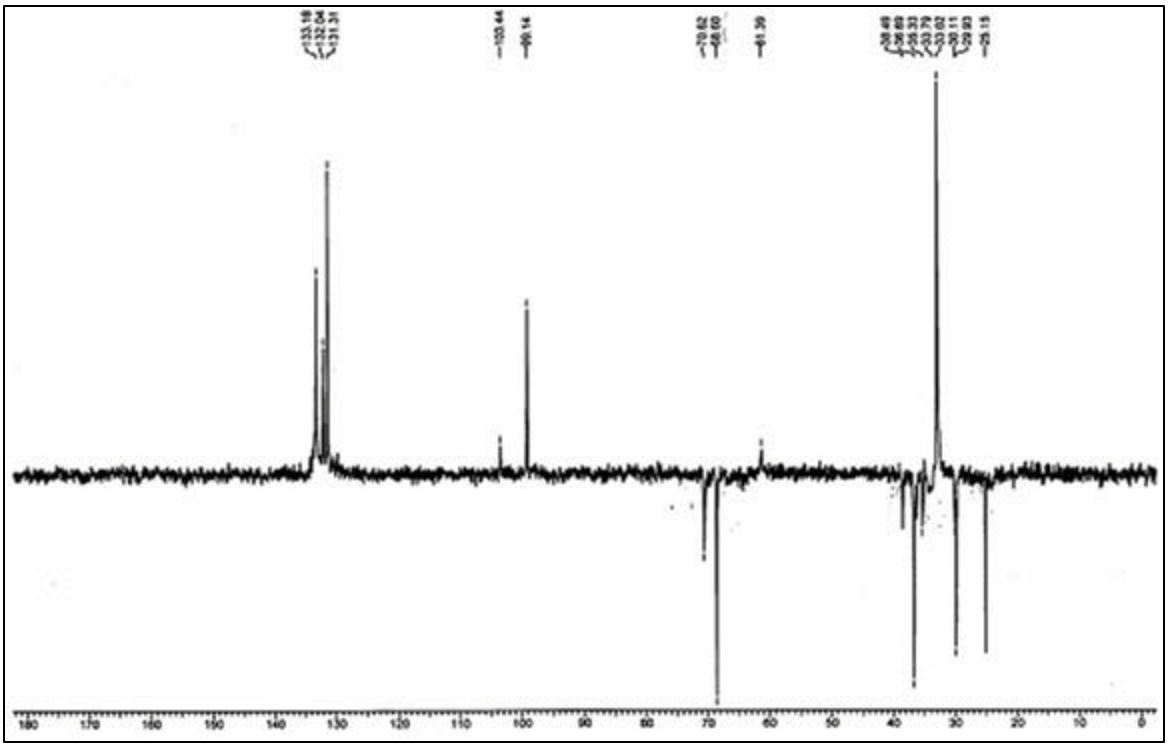
➢ ^{1}H NMR spectrum of **337**



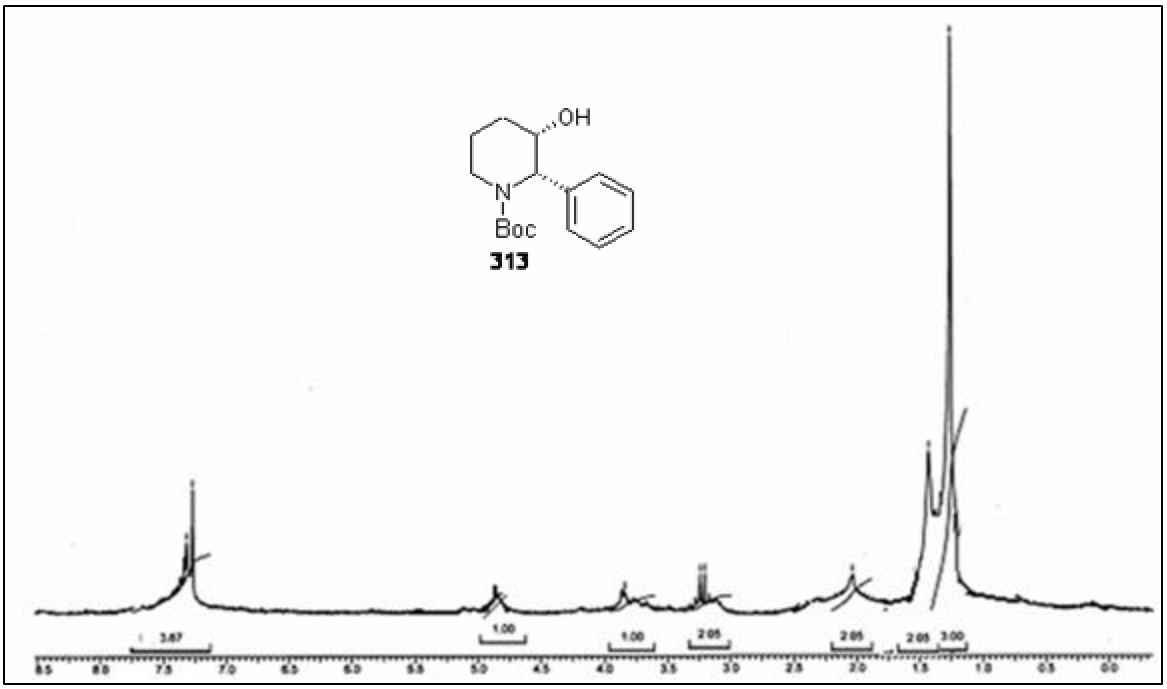
➢ ^{13}C NMR spectrum of **337**



➢ DEPT NMR spectrum of **337**



➢ ^{1}H NMR spectrum of **313**



4.5. References

1. Recent reviews: (a) Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280. (b) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42,* 5157. (c) Morrison, J. D., Ed. *Asymmetric Synthesis,* Academic Press: New York, 1983, **1984**; 5 vols.
2. (a) Vasella, A. In *Modern Synthetic Methods 1980;* Scheffold, R., Ed.; Salle & Sauerhder: Frankfurt, **1980**, p 173. (b) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach;* Pergamon Press**:** Oxford, **1983.** (c) Scott, J. W. *In Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, **1984;** p 1. (d) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161. (e) Jurczak, J.; Pikul, S.; Bauer, T. *Ibid*. **1986**, *42*, 447.
3. Martens, J. *Top. Curr. Chem.* **1984**, *125,* 165.
4. (a) Yamamoto, Y.; Yatagi, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (b) Maed, K.; Macdonald, T. L. *J. Org. Chem*. **1985**, 50, 422. (c) Reetz, M. T.; Kessler, K. Ibid. **1985**, *50*, 5436. (d) Pikul, S.; Raczko, J.; Ankner, K.; Jurczak, J. *J. Am. Chem. Soc*. **1987**, *109*, 3981.
5. (a) Evans, D**.** A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem*. **1983**, *13*, 1. (b) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (c) Heathcock, C. H. *In Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, **1984**, *Vol. 3B***,** p 111. (d) Wuts, P. G. M.; Walters, M. A. *J. Org. Chem*. **1984**, *49*, 4573.
6. (a) Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. (b) Jurczak, J.; Bauer, T. *Tetrahedron* **1986**, *42*, 5045.
7. Tourvê, D. *Janssen Chim. Acta* **1985**, *3*, 3.
8. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*, Wiley, New York **1987**.
9. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
10. Jurczak, J.; Golebiowski, A. From α-amino acids to amino sugars, in *Studies in Natural Products Chemistry*: Atta-ur-Rahman (Ed.), *Vol. 4*, Stereoselective Synthesis (Part C), Elsevier **1989**.
11. Golebiowski, A.; Jurczak, J. Total synthesis of linocomycin and related chemistry, in *Recent Progress in the Chemical Synthesis of Antibiotics*, Springer, Berlin **1990**.
12. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 11531.

13. Dondoni, A. Carbohydrate synthesis via thiazoles, in *Modern Synthetic Reactions*, *Vol. 2,* p. 377, Verlag Helvetica Chimica Acta, Basel, VCH, Weinheim **1992**.
14. Jurczak, J.; Golebiowski, A. The synthesis of antibiotic amino sugars from α-amino aldehydes, in *Antibiotics and Antiviral Compounds*, Chemical Synthesis and Modification, VCH, Weinheim **1993**.
15. Golebiowski, A. Jurczak, J. *Synlett* **1993**, 241.
16. Kiciak, K.; Jacobsson, U.; Golebiowski, A.; Jurczak, J. *Polish J. Chem*. **1993**, *67*, 685.
17. Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
18. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
19. Garner, P.;Park, J. M. *Org. Synth.* **1991**, *70*, 18.
20. Moriwake, T.; Hamano, S.-I.; Saito, S.; Torii, S. *Chem. Lett.* **1987**, 2085.
21. Yanagida, M.; Hashimoto, K.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Tetrahedron Lett.* **1989**, *30*, 3799.
22. Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org Chem.* **1994**, *59*, 5139.
23. Roush, W. R.; Hunt, J. A. *J. Org Chem.* **1995**, *60*, 798.
24. Dondoni, A.;Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.
25. Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527.
26. Hashimoto, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron* **1996**, *52*, 1931.
27. Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673.
28. J. Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051.
29. Palomo, C.; Cossio, F. P.; Ontoria, J. M. Odriozola, J. M. *J. Org. Chem.* **1991**, *56*, 5948.
30. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
31. Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 307.
32. Ito. A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081.
33. Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem*. **1982**, *47*, 3016.
34. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.
35. Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919.

36. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354.
37. Gruza, H.; Kiciak, K.; Krasiñski, A.; Jurczak, J. *Tetrahedron Asymm.* **1997**, *8*, 2627.
38. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 702.
39. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun.* **1988**, 10.
40. Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162.
41. Dondoni, A.; Merino, P.; Perrone, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1576.
42. Dondoni, A.; Perrone, P. *J. Org. Chem.* **1995**, *60*, 4749.
43. Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1999**, *64*, 933.
44. Dondoni, A.; Marra, A.; Massi, A. *Chem. Commun.* **1998**, 1741.
45. Ho.man, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979.
46. Ho.man, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 3953.
47. Dondoni, A.; Massi, A.; Marra, A. *Tetrahedron Lett*. **1998**, *39*, 6601.
48. Berkowitz, D. B.; Eggen, M.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666.
49. Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 473.
50. Doi, Y.; Ishiba, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573.
51. Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate,T.; Nakagawa, M. *Synlett* **1998**, 389.
52. Nimkar, S.; Menaldino, S.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037.
53. Khiar, N.; Singh, K.; Garcia, M.; Martin-Lomas, M. *Tetrahedron Lett.* **1999**, *40*, 5779.
54. Koskinen, A. M. P.; Koskinen, P. M. *Tetrahedron Lett.* **1993**, *34*, 6765.
55. Ruan, F.; Yamamura, S.; Hakomori, S,-I.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 6615.
56. Kozikowski, A. P.; Ding Q.; Spiegel, S. *Tetrahedron Lett.* **1996**, *37*, 3279.
57. Beaulieu, P. L.; Duceppe, J.-S. Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196.
58. Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem*. **2000**, *65*, 3538.
59. Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657.

60. Dondoni, A.; Merino, P.; Perrone, P. *Tetrahedron* **1993**, *49*, 2939.
61. Priepke, H.; Brückner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 555.
62. Drew, M. G. B.; Harrison, R. J.; Mann, J.; Tench, A. J.; Young, R. J. *Tetrahedron* **1999**, ***55***, 1163.
63. Hon, Y.-S.; Chang and, Y.-C.; Chu, K.-P. *J. Chin. Chem. Soc.* **2000**, *47*, 91.
64. Devel, L.; Vidal-Cros, A.; Thellend, A. *Tetrahedron Lett.* **2000**, *41*, 299.
65. Kozikowski, A. P.; Du, D. Ma, L.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 6666.
66. Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279.
67. Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4049.
68. Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337.
69. Yoda, H.; Shirai, T.; Katagiri, T.; Takabe, K.; Kimata, K.; Hosoya, K. *Chem. Lett.* **1990**, 2037.
70. Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083.
71. Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, *37*, 7477.
72. Jako, I.; Uiber, P.; Mann, A.; Wermuth, C.-G.; Boulanger, T.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729.
73. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron Asymm*. **2000**, *11*, 1645.
74. El Ashry, E. S. H.; Rashed, N.; Shobier, A. H. S. *Pharmazie* **2000**, 55, 331.
75. El Nemr, A. *Tetrahedron* **2000**, *56*, 8579.
76. Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1963**, 8*5*, 2824.
77. Sheehan, J. C.; Whitner, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 3980.
78. Ogle, J. D.; Arlinghaus, R. B.; Logan, M. A. *J. Biol. Chem*. **1962**, *237*, 3667.
79. Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *Biochem. Biophys. Res. Commun.* **1962**, *8*, 453.
80. Irreverre, F.; Morita, K.; Ishii, S.; Witkop, B. *Biochem. Biophys. Res. Commun.* **1963**, *9*, 69.
81. Tschesche, R.; Samuel, T. D.; Uhlendorf, J.; Fehlhaber, H.-W. *Chem. Ber.* **1972**, *105*, 316.
82. Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462.

83. Wolff, J. S.; Ogle, J. D.; Logan, M. A. *J. Biol. Chem.* **1966**, *241*, 1300.
84. Benz, F.; Knu¨ sel, F.; Nu¨esch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459.
85. Keller-Jusle´n, C.; Kuhn, M.; Loosli, H.-R.; Petcher, T. J.; Weber, H. P.; von Wartburg, A. *Tetrahedron Lett.* **1976**, 4147.
86. Wehner, V.; Ja¨ger, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169.
87. Nakajima, T.; Volcani, B. E. *Science* **1969**, *164*, 1400.
88. Buku, A.; Faulstich, H.; Wieland, T.; Dabrowski, J *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 2370.
89. Karl, J.-U.; Wieland, T. *Liebigs Ann. Chem.* **1981**, 1445.
90. Fellows, L. E. *Chem. Ber.* **1987**, 842.
91. Taylor, S. W.; Waite, J. H.; Ross, M. M.; Shabanowitz, J.; Hunt, D. F. *J. Am. Chem. Soc.* **1994**, *116*, 10803.
92. Waite, J. H.; Tanzer, M. L. *Science* **1981**, *212*, 1038.
93. Waite, J. H.; Housley, T. J.; Tanzer, M. L. *Biochemistry* **1985**, *24*, 5010.
94. Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett*. **1985**, *26*, 5307.
95. Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205.
96. Nash, R. J.; Bell, E. A.; Fleet, G. W. J.; Jones, R. H.; Williams, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 738.
97. Furukawa, J.; Okuda, S.; Saito, K.; Hatanaka, S.-I. *Phytochemistry* **1985**, *24*, 593.
98. Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125.
99. Nash, R. J.; Bell, E. A.; Williams, J. M. *Phytochemistry* **1985**, *24*, 1620.
100. Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128.
101. Meng, Q.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 445.
102. Scofield, A. M.; Fellows, L. E.; Fleet, G. W. J.; Nash, R. *J. Life Sci.* **1986**, *39*, 645.
103. Scofield, A. M.; Rossiter, J. T.; Witham, P.; Kite, G. C.; Nash, R. J.; Fellows, L. E. *Phytochemistry* **1990**, *29*, 107.
104. Aoki, T.; Hatanaka, S. *Phytochemistry* **1991**, *30*, 3197.
105. Simmonds, M. S. J.; Blaney, W. M.; Fellows, L. E. *J. Chem. Ecol.* **1990**, *16*, 3167.

106. Rosenkranz, H. S.; Klopman, G. *Carcinogenesis* (*London*) **1990**, *11*, 349.
107. Volk, W. A.; Galanos, C.; Luderitz, O. Eur. *J. Biochem.* **1970**, *17*, 223.
108. Galanos, C.; Lu¨ dertiz, O.; Rietschel, E. T.; Westphal, O. In *Biochemistry of Lipids II* ; Goodwin, T. W., Ed.; *Int. Rev. Biochem*. **1977**, *14*, 239.
109. Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127.
110. Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685.
111. Behling, J. R.; Campbell, A. L.; Babiak, K. A.; Ng, J. S.; Medich, J.; Farid, P.; Fleet, G. W. J. *Tetrahedron* **1993**, *49*, 3359.
112. Axamawaty, M. T. H.; Fleet, G. W. J.; Hannah, K. A.; Namgoong, S. K.; Sinnott, M. L. *Biochem. J.* **1990**, 266,
113. Robinson, K. M.; Rhinehard, B. L.; Ducep, J.-B.; Danzin, C. *Drugs Future* **1992**, *17*, 705.
114. Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoon, S. K.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 229.
115. Asano, N.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res.* **1994**, *253*, 235.
116. Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res.* **1994**, *259*, 243.
117. Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymm*. **1990**, *1*, 119.
118. Hosaka, A.; Ichikawa, S.; Shindo, H.; Sato, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 97.
119. Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500.
120. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4536.
121. Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymm.* **1996**, *7*, 1167.
122. Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637.
123. Weir, C. A.; Taylor, C. M *J. Org. Chem.* **1999**, *64*, 1554.
124. Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *6*, 3125.
125. Naleway, J. J.; Raetz, C. R. H.; Anderson, L. *Carbohydr. Res*. **1988**, *179*, 199.
126. Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127.

127. Dho, J. C.; Fleet, G. W. J.; Peach, J. M.; Prout, K.; Smith, P. W. *Tetrahedron Lett.* **1986**, *27*, 3203.

128. Dho, J. C.; Fleet, G. W. J.; Peach, J. M.; Prout, K.; Smith, P. W. *Tetrahedron Lett.* **1986**, *27*, 5203.

129. Chen, S. Y.; Joullie, M. M. *Tetrahedron Lett.* **1983**, *24*, 5027.

130. Bols, M.; Lundt, I. *Acta Chem. Scand.* **1992**, *46*, 298.

131. Kim, H. J.; Lee, W. S.; Yang, M. S.; Lee, S. G.; Park, K. H. *Synlett* **1999**, 614.

132. Trybulski, E. J.; Kramss, R. H.; Mangano, R. M.; Brabander, H. J.; Francisco, G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 827.

133. Durand, J.-O.; Larcheveˆque, M.; Petit, Y. *Tetrahedron Lett.* **1998**, *39*, 5743.

134. Arakawa, Y.; Yoshifuji, S. *Chem. Pharm. Bull.* **1991**, *39*, 2219.

135. Humphrey, A. J.; Parsons, S. F.; Smith, M. E. B.; Turner, N. J. *Tetrahedron Lett.* **2000**, *41*, 4481.

136. Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J. Chem. Soc., Perkin Trans 1* **2000**, 1837.

137. Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61.

138. Goli, D. M.; Cheesman, B. V.; Hassan, M. E.; Lodaya, R.; Slama, J. T. *Carbohydr. Res.* **1994**, *259*, 219.

139. (a) Strunz, G. M.; Findley, J. A. *In The Alkaloids*; Brossi, A.; Ed., Academic Press **1985**, Vol. 26, pp. 89-183. (b) Schneider, M. J. *In Alkaloids: Chemical and biological Perspectives*; Pelletier, S. W.; Ed.; Pergamon: Oxford, **1996**, Vol. 10, pp. 125-299.

140. (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutrard, R. *Bull. Chem. Soc. Chim. Fr.* **1966**, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutrard, R. *Bull. Soc. Chim. Bel.* **1972**, *81*, 425 & 443.

141. Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1532.

142. For reviews that include piperidine alkaloids, see: (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491. (b) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9,* 17. (c) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 447. (d) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1987**; Vol. 31, Chapter 6. (e) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, **1985**; Vol. 3, Chapter 1.

143. For more specific information on hydroxylated piperidines, see the following articles and the references cited within: (a) van den Broek, L. A. G. M.; Vermaas,

D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A,; Bolscher, J. G. M.; Ploegh, H. L.; van Kemenade, F. J.; de Goede, R. E.Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1995**, *112*, 82. (b) Wincheater, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (c) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (d) Fleet, G. W. J.; Fellows, L. E.; Winchester, B. Plagiarizing Plants: Aminosugars as a Class of Glycosidase Inhibitors In *Bioactive Compounds From Plants*; Wiley:; Chichester (Ciba Foundation Symposium 154), **1990**; pp 112-125. (e) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

144. Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497.
145. Wang, C.-L. J.; Wuonola, M. A. *Org. Prep. Proc. Int*. **1992**, *24*, 585.
146. Daly, J. W.; Garraffu, H. M.; Spande, T. F. in *The Alkaloids*, ed. Brossi, A., Academic Press, New York **1993**, Vol. 44, pp. 18-288
147. (a) Takahata, H.; Momose, T., in *The Alkaloids*, ed. Brossi, A., Academic Press, New York, **1985**, Vol.44, pp. 189-256. (b) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 535.
148. (a) Aguinaldo, A. M.; Read, R. W. *Phytochemistry*, **1990**, *29*, 2309. (b) Bolzani, V. da S.; Gunatilaka, A. A. L.; Kingston, D. G. J. *Tetrahedron* **1995**, *51*, 5929.
149. Natsume, M. *Yuki Gousei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn)* **1986**, *44*, 326 and references therein.
150. Paterne, M.; Brown, E. *J. Chem. Res.* **1985**, 278.
151. Holmer, A. B.; Thompson, J.; Baxter, A. J.; G.; Dixon, J. *J. Chm. Soc., Chem. Commun.* **1985**, 37.
152. Cook, G. R.; Benolz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575.
153. Gufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989,** *111*, 3473.
154. Akiyama, E.; Hirama, M. *Synlett* **1996**, 100.
155. (a) Tadano, K.; Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, J.; Maeda, K.; Ogawa, S. *Synlett* **1993**, 565. (b) Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, J.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681.
156. Yuasa, Y.; Ando, J.; Shibuga, S. *Tetrahedron Asymm.* **1995**, *6*, 1525; *J. Chem. Soc., Perkin Trans 1* **1996**, 793.

157. Kiguchi, T.; Sjoralawa. M.; Ninomiya, J.; Naito, T. *Chem. Pharm. Bull.* **1996**, *44*, 1282.
158. Oettig, J.; Holzkamp, J.; Meyer, H. H.; Pahi, A. *Tetrahedron Asymm.* **1997**, *8*, 477.
159. Lindstorm, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173.
160. Hodgkinson, T. J.; Shipman, M. *Synthesis* **1998**, 1141.
161. Somfai, P.; Marchand, P.; Torsell, S.; Lindstrom, U. M. *Tetrahedron* **2003**, *59*, 1293.
162. Makabe, H.; Long, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27.
163. Han, H. *Tetrahedron Lett.* **2003**, *44*, 1567.
164. Chavan, S. P.; Praveen, C. *Tetrahedron Lett.* **2004**, *45*, 421.
165. Koulocher, S. D.; Haroutounian, S. A. *Tetrahedron Lett.* **1999**, *40*, 6869.
166. Herdeis, C.; Telser, J. *Eur. J. Org. Chem.* **1999**, 1407.
167. Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427.
168. Cossy, J.; Willis, C.; Bellosta, V. *Synlett* **2001**, 1578.
169. Dransfield, P. J.; Gore, P. M.; Shipman, M.; Slawin, A. M. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 150.
170. Bayquen, A. V.; Read, R. W. *Tetrahedron* **1996**, *52*, 13467.
171. Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Asymm.* **1997**, *8*, 3887.
172. Kiran Kumar, K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899.
173. Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2001**, *42*, 3431.
174. Datta, A.; Ravikumar, J. S.; Roy, S. *Tetrahedron* **2001**, *57*, 1169.
175. Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281.
176. Koskinen, A. M. P.; Kallatsa, O. A. *Tetrahedron* **2003**, *59*, 6947.
177. Achmatowiz, M.; Hegedus, L. S. *J. Org. Chem.* **2004**, *69*, 2229.
178. Kotsuki, H.; Kusumi, T.; Inoue, M.; Ushio, Y., Ochi, M. *Tetrahedron Lett.* **1991**, *32,* 4159.
179. Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781.
180. Reviews: (a) Pinder, A. R. *Nat. Prod. Rep.* **1989**, *6*, 67. (b) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine. Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. (c) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17. (d) Pinder, A. R. *Nat. Prod. Rep.* **1992**,

9, 491. (e) Wang, S. J. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 583. (f) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581. (g) Steele, J. *Contemp. Org. Synth.* **1994**, *1*, 95. (h) Angle, S. R.; Breitenbucher, J. G. *Stud. Nat. Prod. Chem.* **1995**, *16*, 453. (i) Hammann, P. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995, p 323. (j) Angle, S. R.; Breitenbucher, J. G. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1995, Vol. 16, p 453. (k) Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Proced. Int.* **1996**, *28*, 501. (l) Enders, D.; Bettray, W. *Pure Appl. Chem.* **1996**, *68*, 569. (m) Wanner, M. J.; Koomen, G. J. *Pure Appl. Chem.* **1996**, *68*, 2051. (n) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023. (o) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637. (p) De Raadt, A.; Ekhart, C. W.; Ebner, M.; Stutz, A. E. *Top. Curr. Chem.* **1997**, *187*, 157. (q) Holmes, A. B.; Bourdin, B.; Collins, I.; Davison, E. C.; Rudge, A. J.; Stork, T. C.; Warner, J. A. *Pure Appl. Chem.* **1997**, *69*, 531. (r) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 387. (s) Gawley, R. E. *Curr. Org. Chem.* **1997**, *1*, 71. (t) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. (u) Kazmaier, U. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 351. (v) Depezay, J.-C. *Carbohydr. Mimics* **1998**, 307. (w) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553. (x) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1. (y) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493.

181. (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. **1993**, EP 528,495 A1; (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. Bioorg. Med. *Chem. Lett.* **1994**, *4*, 2545.
182. Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.
183. Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1988**, *241*, 1218.
184. Perianan, A.; Snyderman, R.; Malfroy, B. *Biochem. Biophys. Res. Commun.* **1989**, *161*, 520.
185. (a) Moskowitz, M. A. *Trends*. *Pharmacol. Sci.* **1992**, *13*, 307. (b) Zaman, S.; Woods, A. J.; Watson, J. W.; Reynolds, D. J. M.; Andrews, P. L. R. *Neuropharmacology* **2000**, *39*, 316.
186. Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1987**, 235, 893–.
187. Otsuka, M.; Yanagisawa, M. *J. Physiol.* (London) **1988**, *395*, 255.

188. (a) Giardina, G. A. M.; Raveglia, L. F.; Grugni, M. *Drugs Future* **1997**, *22*, 1235. (b) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett*. **1999**, *40*, 5071.

189. Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 2545.

190. Stadler, H.; Bos, M. *Heterocycles* **1999**, *5*, 1067.

191. Calvez, O.; Langiois, N. *Tetrahedron Lett.* **1999**, *40*, 7099.

192. Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223.

193. Huang, P-Q.; Liu, L-X.; Wei, B-G.; Ruan, Y-P. *Org. Lett.* **2003**, *5*, 1927.

194. Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915.

195. For stereocontrolled addition of organometallic compound to the optically active *N*-protected α-amino aldehydes see, review: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

196. For related examples, see: Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939 and references therein.

CHAPTER 5

Studies Directed Towards the Synthesis of AAL-Toxin

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5.1 Introduction

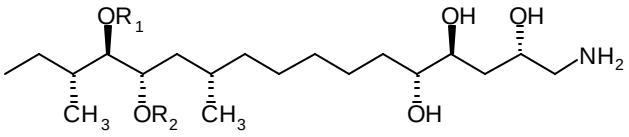
All living creatures are having their own life-time, and humans are no exception. However, the quality and length of life and the incidence of disease depend on the geochemical, climatic and weather conditions in the environment. These conditions, in turn, determine the flora and fauna, the amount and type of food, and the suitability of the food for the requirements of the body. Such external factors affect the internal functioning of the human body.

- **Cell Injury:**

The classical theory of disease attributed all disorders to systematic imbalances or to noxious effect or tumor on specific organs.[1] The basis of all disease is injury to the smallest living unit of the body, namely the cell. If one accepts the premise that a living cell must maintain an organization capable of producing energy, then the most pressing need for a free living cell, whether prokaryotic or eukaryotic, is to establish a structural and functional barrier between its internal milieu and a hostile environment. The plasma membrane serves this purpose. At the same time, in order to survive, the cell must be able to adopt to adverse environmental conditions, such as oxygen supply, the presence of noxious agent and so on. The evolution of multicellular organism eased the hazardous lot of individual cells by establishing a controlled extracellular environment in which temperature, oxygenation, ionic content and nutrient supply are relatively constant. It also permitted the luxury of differentiation cells for such widely divergent functions as nutrient storage, communication contractile activity, synthesis of proteins or peptides for export, absorption and defense against foreign invaders.

➢ Natural Toxins:

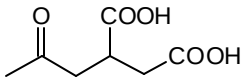
The world consists of diverse assemblage of life forms which occur in environments of extreme variations in pressure, salinity and temperature. Natural products which are the metabolites of this various life forms, are novel and complex in nature that have no counterparts in the terrestrial world. Many of the natural products isolated from marine sources and terrestrial plants have been used for a long time as drugs to cure human diseases. However, certain natural products cause toxic symptoms when they are exposed to humans and animals. Relatively some of the natural toxin play major role in human life and environmental pollution. Therefore, the natural toxins attracted scientist's attention to review their structure and action involved in human intoxication. Attention is also paid to etiological studies, as most natural product chemists are concerned about the origin of natural toxins. Although the majority have been found to be produced by bacteria, the amounts of the toxin produced by the bacteria, however so small that identification of the toxin in bacterial cultures is often made on the basis of rather proof evidence. The small amount of toxins in the natural sources, force the organic chemists to prepare in



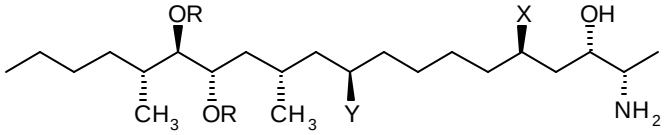
AAL-TOXIN 1

AAL-toxin TA_1: R_1 = H; R_2 = TCA

AAL-toxin TA_2: R_1 = TCA; R_2 = H



Tricarballylic acid (TCA)



FUMONISIN

Fumonisin B_1: X = Y = OH; R = TCA

Fumonisin B_2: X = OH; Y = H; R = TCA

Fumonisin B_3: X = H; Y = OH; R = TCA

Figure 1

considerable quantity through remarkable chemical synthesis to conduct further studies, such as structural elucidation and complete biological activities. It is pertinent to mention that some of the natural toxins are attractive to scientists due to their important biological activity and structure complexity.[2]

AAL-Toxin (**Figure 1**) were isolated from *Alternaia altermata f. sp. lycopersici*, a casual fungus of tomato stem canker.[3] AAL-toxins are characterized as a host-specific toxin because they are selectively toxic only to host of the producing microorganisms. AAL-toxin exhibited biological activities in both mammalian cell and plant cell. The 2D spectrum of AAL-toxin TA_1 was determined by Bottini *et al.*[3] and the complete relative and absolute stereochemistry of AAL-toxin TA_1 has been determined by Kishi *et al.*[4] by a combination of derivatisation, NMR and chiral gas chromatographic methods. Fumonisins, found in the corn fungus *Fusarium moniliforme*, are known to exhibit a variety of biological activities.[5] Notably, they have recently received attention due to their presence in corn products and their association with esophageal cancer.[6] Both the classes of natural products exhibit cross-bioactivity and have been shown to inihibit sphingolipid biosynthesis.[6,7] AAL toxins and fumonisins bear striking structural similarity: they possess similar amino alcohol backbones as well as a unique tricarballylic acid moiety.

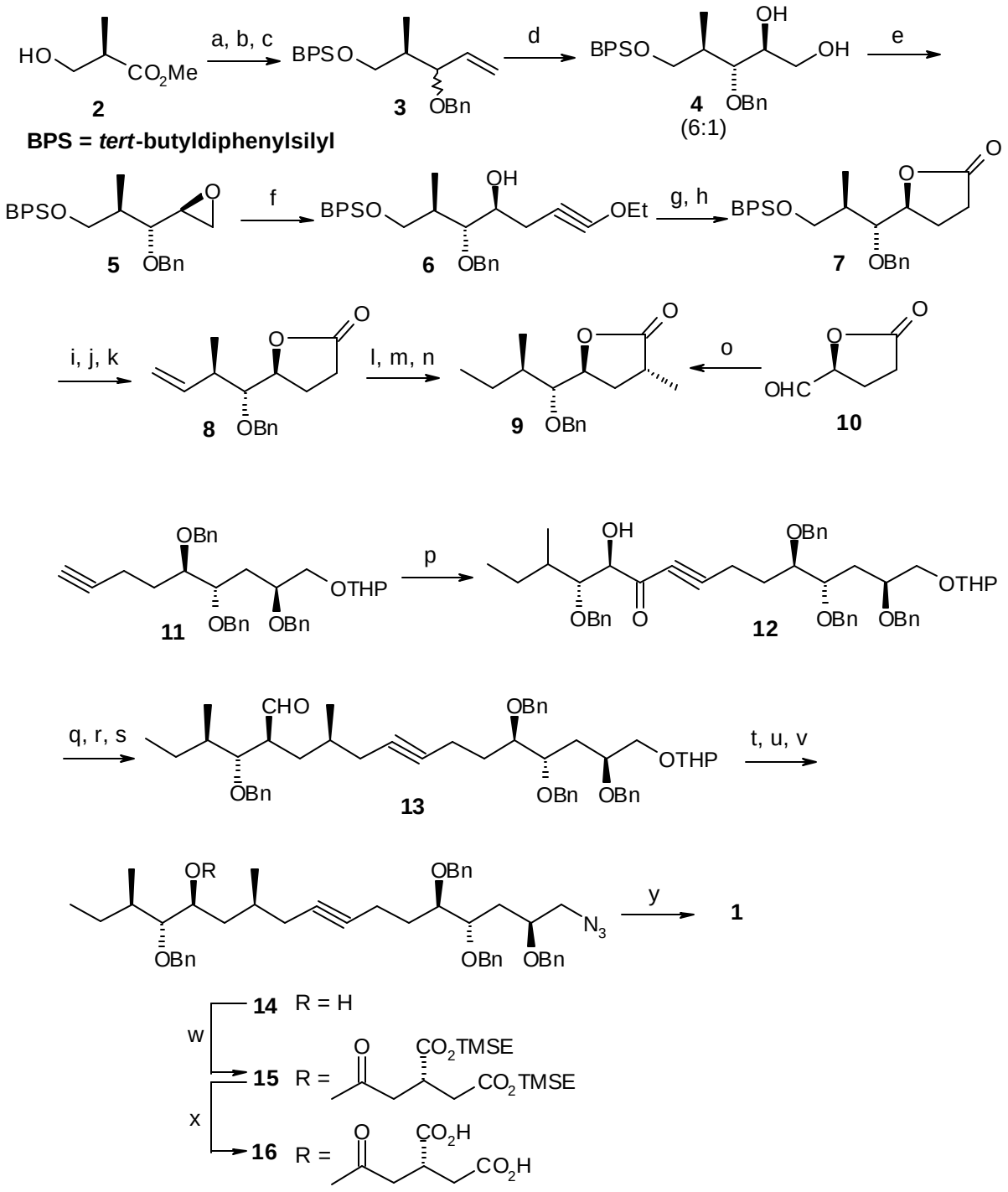
5.2 Review of Literature:

There is only one reports in the literature[8] for the total synthesis of AAL-toxin along with few publications[3,4,9] describing only the relative and absolute stereochemistry of this molecule.

Oikawa *et al.* (1999)[8] Scheme 1

The first total synthesis of AAL-Toxin **1** was developed by Oikawa et al.[8] Two alternative synthetic routes of the left half segment **9** have been developed. Efficient condensation between the left segment **9** and right segment **11**[10] followed by Pd-catalyzed

deoxygenation and further elaboration achieved the first total synthesis of AAL-Toxin TA_1 **1.**



Scheme 1 Reagent and Conditions: (a) BPSCl, imidazole, DMF, quant. (b) DIBAL-H, Et_2O, -78°C, then CH_2=CHMgBr, 77% (c) NaH, BnBr, *n*-Bu_4NI, THF, 91%; chromatographic separation

(d) OsO_4, NMO, acetone:H_2O (8:1), 91% (e) $MeC(OMe)_3$, cat. PPTS, CH_2Cl_2; AcBr, CH_2Cl_2; K_2CO_3, MeOh, 77% (f) ethyl ethynyl ether, *n*-BuLi, $BF_3.Et_2O$, THF, -78°C (g) HgCl, EtOH (h) K_2OC_3, MeOH then 3 M HCl, 59% (3 steps) (i) TBAF, THF, 80% (j) Swern oxid. (k) Ph_3PCH_3Br, *n*-BuLi, THF, 19% (2 steps, recovered aldehyde 70%) (l) H_2. Pd/C, EtOAc (m) $CCl_3C(=NH)OBn$, TfOH, CH_2Cl_2:cyclohexane (1:1), 57% (2 steps) (n) LiHMDS, CH_3I, THF, -78°C, 68% (o) (i) crotylboronate, MS4A, CH_2Cl_2, -78°C; (ii) NaH, BnBr, *n*-Bu_4NI, THF, 90% (p) *n*-BuLi, Et_2O, -20°C, **9**, 72% (q) $NaBH_4$, $CeCl_3$, MeOH, 85% (r) Ac_2O, HCO_2H, Py, 97% (s) $Pd(OAc)_2$, *n*-Bu_3P, THF, 84% (t) $LiAlH_4$, THF (u) PPTS, EtOH, 89% (2 steps) (v) HN_3, Ph_3P, DEAD, toluene, 69% (w) 2,4-$NO_2C_6H_4COCl$, $CH_3COCH_2CH(CO_2TMSE)CH_2CO_2TMSE$, Et_3N, toluene; then **14**, DMAP, 71% (x) TBAF, THF (y) H_2, PD/C, *t*-BuOH-THF-1M HCl (3:1:0.04), 76% (2 steps)

5.3 Present Work

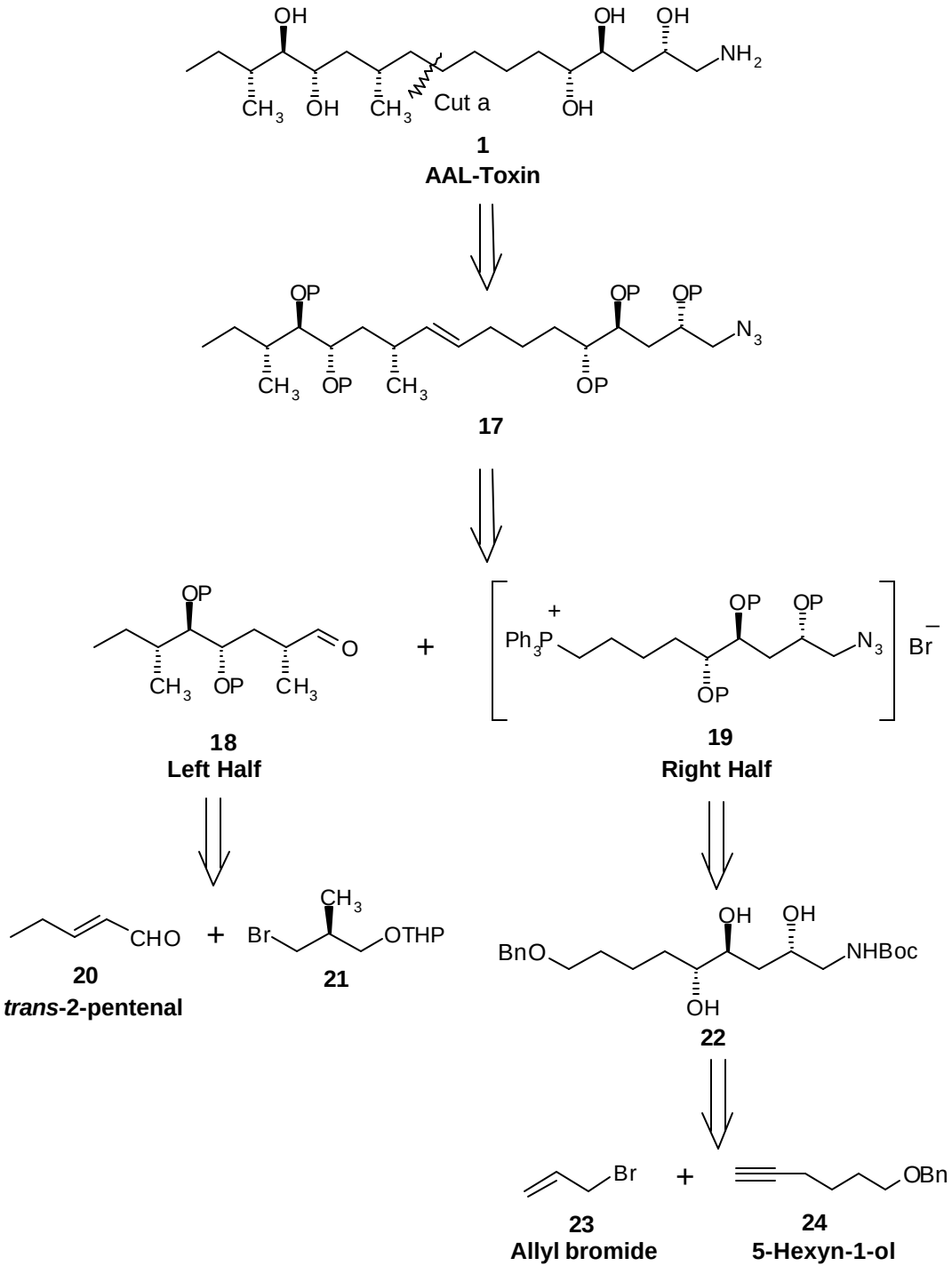
Objective:

Since the host specific AAL-toxins have received negligible attention towards its synthesis apart from achieving its relative and absolute stereochemistry; the exploration in the total synthesis of AAL-toxin would lead towards fruitful success in its chemistry. In the backdrop of the knowledge of absolute stereochemistry; the chemistry to explore the synthesis of AAL-toxin was thought of and initiated.

A convergent approach for the total synthesis of AAL-toxin T_A backbone is planned by the following synthetic routes (**Scheme 2**). The retrosynthetic analysis of **1** (cut a) shows that the molecule can be divided into two fragments (**Scheme 2**). It is assumed that two distinct halves would exhibit characteristic spectroscopic properties independent from the remote stereo-centers on the other half of the molecule.

Thus, the assignment of the relative stereochemistry of AAL toxin could be reduced to determining the relative stereochemistry of the left and right half separately. The left half of the molecule including the diastereomers can be synthesized from trans-2-pentenal **20**, whereas the right half can be derived from the reaction between allyl bromide **8** and protected 5-hexyn-1-ol **24**. AAL toxin can be synthesized *via* Wittig olefination from the

aldehyde **18** of the left half and the phosphonium salt **19** of the right half followed by the subsequent catalytic reduction of **17** (**Scheme 2**).



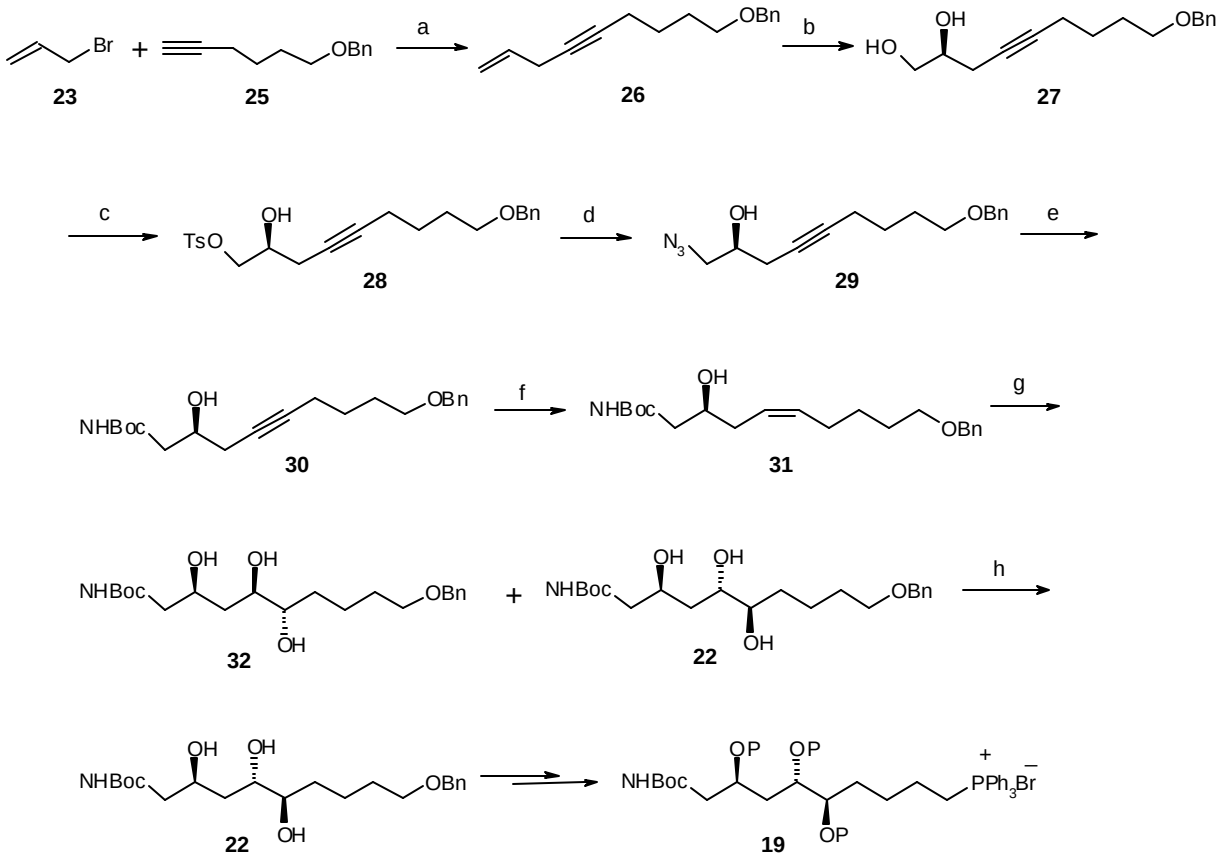
Scheme 2

5.4 Results and Discussion

As per our retrosynthetic ananlysis, the plan was to first synthesize both the half so as to meet to the target molecule. In order to achieve the total synthesis of AAL-toxin we first decided to have a crack at the Right Half of the molecule which has a 9-carbon chain length. The Right Half segment has also longer route to come to its synthesis than the left half, hence the decision to start with the synthesis of Right Half came to our mind.

So, as per the retrosynthetic analysis; to achieve the synthesis of the Right Half we have to start with the coupling of allyl bromide **23** with 5-hexyn-1-ol **24** (**Scheme 3**). This coupling will lead to the desired skeleton of the Right Half keeping in mind the functionalities to be brought into as well as the carbon chain length. For this to happen, the free hydroxyl group of 5-hexyn-1-ol **24** was reacted with benzyl bromide in presence of sodium hydride to obtain the benzyl derivative **25**. The IR spectrum of compound **25** showed the absence of primary hydroxyl group. The ^{1}H NMR spectrum showed the presence of aromatic protons at δ 7.28 and the benzylic CH_2 group at δ 4.44. The coupling between allyl bromide **23** and **25** was carried out with the help of *n*-BuLi at reflux temperature in THF, to furnish the resultant coupled product **26** in 70% yield. ^{1}H NMR spectrum showed the allylic protons to the alkyne group at δ 5.09 and δ 5.30. The CH_2 group adjacent to the alkyne group appeared in a splitting fashion of one proton at δ 3.13 and the other at δ 3.68. The terminal olefin of compound **26** was then subjected to Sharpless asymmetric dihydroxylation conditions to achieve the diol **27** in 65% yield and 87% ee.[11] Generally the AD reaction of the terminal olefin leads to poor ee, but with our substrate we got good results. The ligand used for the catalytic asymmetric dihydroxylation reaction was second generation anthraquinone derivative, $(DHQD)_2AQN$. The IR spectrum of diol **27** showed presence of 3400 cm^{-1} peak which confirmed the presence of hydroxyl group. The ^{1}H NMR spectrum of diol **27** showed the absence of peaks at δ 5.09 and δ 5.30 corresponding to the allylic CH_2 group and the presence of broad peak at δ 3.16 corresponding to the two hydroxyl protons. Now in order to achieve the amine functionality present in the desired side chain, the primary hydroxyl group of diol **27** was selectively transformed into its tosyl derivative **28** in 90% yield with the help of catalytic dibutyltin oxide and *p*-toluenesulfonyl chloride. The ^{1}H NMR spectrum of the tosyl derivative **28**

showed the presence of *p*-toluyl group at δ 2.43 and ortho coupled doublet of two protons at δ 7.80 corresponding to aromatic protons



Scheme 3 Reagent and Conditions : (a) *n*-BuLi, THF, reflux, 24 h, 70% (b) K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2AQN$ (1 mol%), OsO_4 (0.4 mol%), *t*-BuOH : H_2O (1:1), 0^oC, 20 h, 65% (c) *p*-TsCl. Bu_2SnO, Et_3N, CH_2Cl_2, 0^oC, 1 h, 90% (d) NaN_3, DMF, 70^oC, 20 h, 69% (e) (i) Ph_3P, THF, H_2O, rt, 24 h; (ii) Boc_2O, Et_3N, CH_2Cl_2, rt, 12 h, 80% (f) H_2 (1 atm) / Pd-$BaSO_4$, MeOH, 14 h, 90% (g) K_2CO_3, $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol%), OsO_4 (0.4 mol%), *t*-BuOH : H_2O (1:1), 0^oC, 18 h, 70% (h) Chromatographic separation

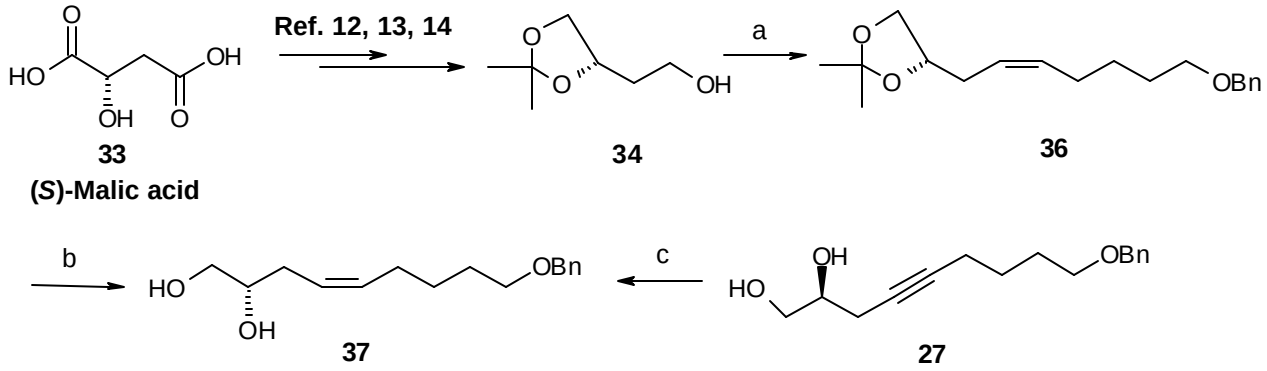
of the tosyl group. The tosylate **28** was swiftly transformed into compound **29** by nucleophilic azide displacement in 70% yield. The ^1H NMR spectrum showed the absence of peak corresponding to the tosyl group δ 2.43 and δ 7.80. The IR spectrum of **29** showed the presence of N=N streching at 2105 cm^{-1} confirming the azide functionality. The azide functionality of compound **29** was subsequently reduced to amine and protected as its Boc derivative to afford the Boc protected amino alcohol **30** in 80% yield. The IR spectrum of

compound **30** showed the stretching at 3582 cm^{-1} showing the presence of -NH group and the presence of amide carbonyl at 1706 cm^{-1} and the absence of N=N stretch at 2108 cm^{--1}. The ^{1}H NMR spectrum showed the presence of nine protons corresponding to the Boc group at δ 1.45. Now once the amine functionality was brought into the side chain, the remaining and the most important thing left was the introduction of another two chiral trans hydroxyl group. For this reason, the alkyne functionality of **30** was reduced to *cis*-olefin by hydrogenation over Lindlar's catalyst to afford the compound **31**. The IR spectrum showed the absence of stretching at 2251 cm^{-1} corresponding to the alkyne group. The ^{1}H NMR spectrum showed *cis*-olefinic protons at δ 5.46 as a multiplet of two protons. The compound **31** was then subjected to Sharpless asymmetric dihydroxylation to afford the desired *trans*-diol **22** with the gem-amino alcohol function. Here a mixture of compound **22** and **32** was obtained which was then column chromatographed to isolate the desired compound **22**. The ^{1}H NMR spectrum of the triol **7** showed the absence of the *cis*-olefinic protons at δ 5.46. The ^{13}C NMR spectrum showed the shifting of *cis*-olefinic protons from δ 133.42 and δ 136.90 to the chiral hydroxyl protons at δ 65.0 and δ 74.81. The stereochemistry of compound **22** was assessed by comparison with the analogous reported observations,[8] in which there is amino group instead of NHBoc and the chain is simple alkyl instead of the terminal protected hydroxyl group. The comparison of the ^{13}C spectrum of **22** indicated that the δ 65.34 and δ 74.94 values of the carbon with the chirality matched with the analogous report confirming the desired stereochemistry in **22**. Compound **22** can be easily transformed into the wittig salt **19** by standard synthetic manipulation.

In an alternative approach to the synthesis of compound **22** leading its way to the synthesis of Right Half, we thought of starting the synthesis with a chiral substrate so that the enantiomeric excess of the diol **27** (**Scheme 3**) could be enhanced and also cross checked.

For this to fulfill, we started our synthetic endeavor with (*S*)-malic acid **23**. (*S*)-malic acid **23** could easily be transformed into acetonide protected alcohol **24** by conventional methods[12,13,14] (**Scheme 4**). The gem-dihydroxy group of compound **34** will now serve our purpose of the dihydroxy part of diol **27.** The compound **34** was oxidized to aldehyde by Swern oxidation and then it was reacted without characterization with the Wittig ylide prepared *in situ* from its corresponding salt **35** to afford the Wittig product **36** bearing *cis*-

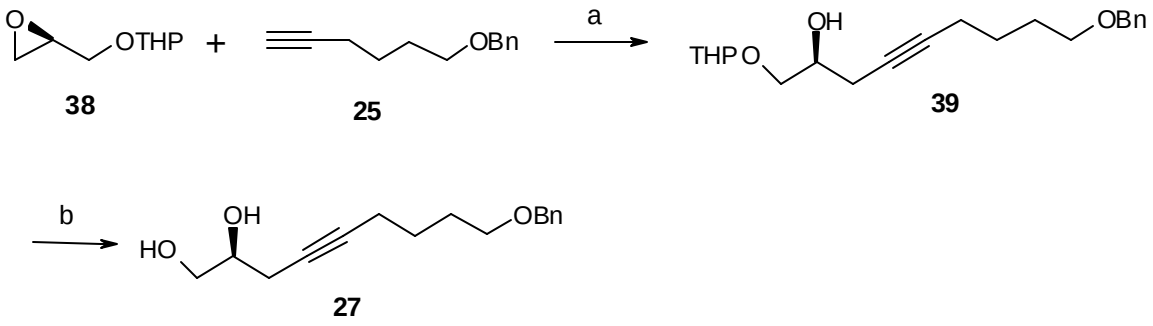
olefin. The ^{1}H NMR spectrum of compound **36** showed the *cis*-olefinic peaks at δ 5.33-5.56.



Scheme 4 Reagent and Conditions: (a) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 2 h; then Et_3N; (ii) $Ph_3P^+[(CH_2)_5OBn]Br^-$ **35**, *n*-BuLi, THF, -78°C, then addition of aldehyde, 8 h, 78% (b) TsOH, MeOH, rt, 4 h, 90% (c) H_2 (1 atm) / Pd-$BaSO_4$, MeOH, 14 h, 80%

Also the peaks at δ 1.36 (singlet) and δ 1.46 (singlet) confirmed the acetonide group and the peak at δ 7.30-7.36 (multiplet) and δ 4.51 (singlet) confirmed the benzylic protection. The acetonide protection of **36** was then deprotected by *p*-toluenesulfonic acid in methanol to afford the diol **37**. The diol **37**can also be prepared by the reduction of diol **27** under hydrogenation conditions with the help of Lindlar catalyst. Thus the unambiguous synthesis of **37** was achieved and also the assessment of the enantiomeric excess of diol **27** could be cross checked by comparison of the optical rotation of diol **37** obtained by both the routes which was matching. The IR spectrum of diol **37** showed the presence of C-OH stretch at 3360 cm^{-1} confirming the hydroxyl functionality. The ^{1}H NMR spectrum showed the disappearance of the acetonide peaks at δ 1.36 and δ 1.46 and the appearance of the broad singlet at δ 1.87 confirming the presence of hydroxyl group.

To devise a new and short synthetic strategy and strengthen our confirmation regarding the enantiomeric excess of the diol **27**, we thought of employing another chiral source such as (*S*)-glycidol. As illustrated in **Scheme 5**, we started with tetrahydropyranyl protected (*S*)-glycidol **38**. The epoxide of compound **38** was opened with protected 5-hexyn-1-ol **25** by generation of anion at the hexyne with *n*-BuLi to afford the compound **39**.



Scheme 5 Reagent and Conditions: (a) *n*-BuLi, THF:HMPA (1:9), 0°C-rt, 80% (b) TsOH, MeOH, rt, 4 h, 88%.

which was then easily transformed to the diol **27** by deprotection of the tetrahydropyranyl protection with the help of *p*-toluenesulfonic acid in methanol. Thus compound **27** could be synthesized in optically active form by employing the synthetic strategies as illustrated in **Scheme 4** and **Scheme 5**.

5.5. Conclusion

In conclusion, an asymmetric synthesis of the Right Half, the major segment of the AAL-toxin molecule was achieved. The enantiomeric excess and optical purity was determined and reconfirmed by synthesizing the compound **27** employing different routes.

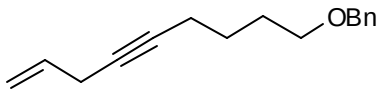
5.6. Experimental section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard, and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ATI

MATTSON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC or otherwise indicated. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

Preparation of non-8-en-5-ynyloxymethylbenzene, 26



26

To a solution of compound **25** (10.0 g, 53.19 mmol) in dry THf (100 mL) at 0^{o}C was added *n*-BuLi (36.2 mL, 5.10 g, 77.68 mmol). The resultant mixture was stirred for 1 h at room temperature after which it was again cooled to 0^{o}C. The solution of allyl bromide **23** (7.7 g, 63.64 mmol) in dry THF (30 mL) was added slowly and the reaction mixture was refluxed for 24 h. The reaction was quenched with addition of sat.aq. NH_4Cl (50 mL) at 0^{o}C. The phases were separated and the aqueous phase extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residual oil using petroleum ether : EtOAc (95 : 5) as eluent afforded compound **26** (8.5 g, 70 %) as a colorless oil.

Yield:- 8.5 g, 70 %

IR ($CHCl_3$) cm^{-1}: ν_{max} 1130, 1216, 1711, 21166, 2857, 2935

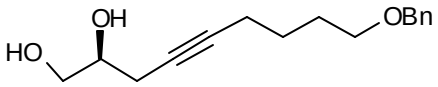
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62-1.78 (m, 4H), 2.21-2.28 (m, 2H), 2.93-2.97 (m, 2H), 3.51 (t, 2H, *J* = 6 Hz), 4.52 (s, 2H), 5.08-5.13 (m, 1H), 5.28-5.37 (m, 1H), 5.77-5.93 (m, 1H), 7.35 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.57, 23.09, 25.74, 28.86, 29.71, 69.77, 72.75, 76.79, 82.42, 115.50, 127.52, 128.29, 133.33, 138.62

Mass (ESI): 229 (M + 1), 179, 147, 128, 91

Anal. Calcd. for $C_{16}H_{20}0$: C, 84.16; H, 8.83 Found: C, 84.25; H, 8.55

Synthesis of (2*S*)-9-benzyloxy-non-4-yne-1,2-diol, 27



27

To a mixture of K_3FeCN_6 (17.303 g, 52.59 mmol), K_2CO_3 (7.26 g, 52.60 mmol), $(DHQD)_2AQN$ (0.151g, 1 mol%, 0.176 mmol) in *t*-butanol / H_2O (1:1, 200 mL) at 0°C was added osmium tetroxide (0.18 mL, 0.4 mol%). After stirring for 2 min at 0°C, the olefin **26** (4.0 g, 17.53 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 20 h. The reaction was quenched with sodium sulfite (34 g). The stirring was continued for additional 30 min. The phases were separated and the aqueous phase extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7:3) as eluent gave **27** (3.0 g, 65%) as a thick liquid.

Yield:- 3.0 g, 65%

[α] $_D^{20}$:- - 4.09 (c = 1, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1722, 2116, 2857, 2925, 3302

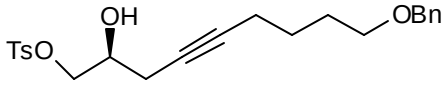
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53-1.76 (m, 4H), 2.16-2.24 (m, 2H), 2.36-2.39 (m, 2H), 3.16 (brs, 2H), 3.46-3.59 (m, 3H), 3.67-3.81 (m, 2H), 4.51 (s, 2H), 7.34 (m, 5H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 18.22, 23.26, 25.28, 28.52, 65.05, 69.54, 70.53, 72.52, 76.01, 81.93, 127.39, 128.09, 138.05

Mass (ESI): 261 (M-1), 243, 225, 207, 179

Anal. Calcd. for $C_{16}H_{22}0_3$: C, 73.25; H, 8.45 Found: C, 73.12; H, 8.40

Synthesis of (2*S*)-toluene-4-sulfonic acid-9-benzyloxy-non-4-ynylester, 28



28

To a solution of alcohol **27** (1.0 g, 3.81 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (0.386 g, 3.81 mmol), Bu_2SnO (2 mol%), *p*-toluenesulfonylchloride (0.728 g, 3.81 mmol). The reaction mixture was stirred until TLC indicated complete consumption of starting material (1 h). The reaction was quenched with H_2O (30 mL) and the layers were separated. The aqueous phase was extracted in CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (8:2) as eluent afforded tosyl derivative **28** (1.42 g, 90%) as a pale yellow oil.

Yield:- 1.42.0 g, 90%

$[\alpha]_D^{20}$:- - 8.34 (c = 2.36, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1483, 2132, 2836, 2954, 3304

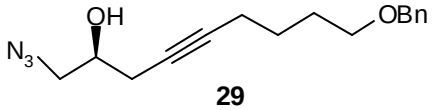
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54-1.71 (m, 4H), 2.00-2.13 (m, 4H), 2.43 (s, 3H), 3.48 (t, 2H, *J* = 6 Hz), 3.92-4.16 (m, 3H), 4.51 (s, 2H), 7.34 (m, 7H), 7.78 (d, 2H, *J* = 10 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): 18.49, 21.66, 23.64, 25.55, 28.86, 67.97, 69.81, 72.31, 72.90, 74.70, 83.30, 127.70, 128.03, 128.40, 129.94, 132.66, 138.55, 145.65

Mass (ESI): 434 (M + NH_4^+), 417 (M +1), 245, 227, 209, 181

Anal. Calcd. for $C_{23}H_{28}0_5S$: C, 66.32; H, 6.78; S, 7.70 Found: C, 66.12; H, 6.69; S, 7.85

Synthesis of (2*S*)-1-azido-9-benzyloxy-non-4-ynyl-2-ol, 29



29

To a solution of tosylate **28** (1.0 g, 2.4 mmol) in dry DMF (20 mL) was added NaN_3 0.94 g, 14.46 mmol). The reaction mixture was stirred at 70°C for 20 h. The mixture was cooled to room temp. and the mixture was poured in Et_2O:H_2O (1:1, 60 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product with petroleum ether / EtOAc (6:1) as eluent gave the azido compound **29** (0.48 g, 69%) as colorless oil

Yield:- 0.48 g, 69%

[a] $_D^{20}$:- - 3.86 (c = 1.34, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1716, 1811, 2105, 2251, 2865, 2937, 3437

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59-1.70 (m, 4H), 2.10-2.23 (m, 2H), 2.41-2.26 (m, 2H), 3.37-3.52 (m, 4H), 3.85-3.91 (m, 1H), 4.51 (s, 2H), 7.34 (m, 5H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 18.42, 24.74, 25.48, 28.71, 55.33, 69.29, 69.70, 72.71, 75.32, 83.00, 127.59, 128.29, 138.36

Mass (ESI): 287 (M^+), 258, 240, 140, 126, 91

Anal. Calcd. for $C_{16}H_{21}N_30_2$: C, 66.88; H, 7.37; N, 14.62 Found: C, 66.91; H, 7.30; N, 14.55

Synthesis of (2*S*)-(9-benzyloxy-2-hydroxy-non-4-ynyl)-carbamic acid *tert*-butylester, 30

29

To a solution of azide **29** (0.4 g, 1.39 mmol) in dry THF (10 mL), H_2O (3 mL) was added Ph_3P (0.42 g, 1.6 mmol) at room temperature, and mixture stirred for 24 h. The mixture was concentrated and the residue was purified by flash silica gel column chromagtography using $CHCl_3$: MeOH (18 :1) as eluent to afford the amine (0.37 g, 85%) as a thick liquid which was used directly into the next reaction without further purification.

To a solution of amine (0.300 g, 1.15 mmol) in CH_2Cl_2 (15 mL) and Et_3N (0.175 g, 1.73 mmol) was added *tert*-butyldicarbonate (0.3 g, 1.37 mmol) at room temperature, and mixture stirred for 12 h. The reaction was quenched with sat. NH_4Cl at 0^oC and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with satd. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue using petroleum ether : EtOAc (2:1) afforded the desired compound **30** (0.332 g, 80%) as a colorless oil.

Yield:- 0.332 g, 80%

[a] $_D^{20}$:- - 5.20 (c = 1.20, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max}, 1716, 1811, 2105, 2251, 2865, 2937, 3437

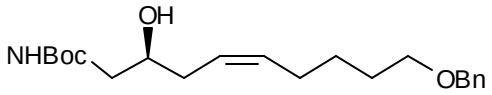
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.58-1.73 (m, 4H), 2.08-2.19 (m, 2H), 2.37-2.41 (m, 2H), 3.39-3.50 (m, 3H), 3.60-3.79 (m, 2H), 4.51 (s, 2H), 4.93 (brs, 1H), 7.34 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.71, 25.22, 25.81, 28.53, 29.04, 45.73, 69.99, 70.18, 73.04, 76.02, 79.88, 83.04, 157.81, 128.55, 138.66, 157.14

Mass (ESI): 391 (M + NH_4^+), 374 (M + 1), 306, 262, 227, 172

Anal. Calcd. for $C_{22}H_{31}N0_4$: C, 70.75; H, 8.66; N, 3.75 Found: C, 70.85; H, 8.50; N, 3.65

Synthesis of (2*S*)-(9-benzyloxy-2-hydroxy-non-4-enyl)-carbamic acid *tert*-butyl ester, 31



31

To a solution of **30** (0.300 g, 0.80 mmol) and quinoline (0.153 g, 1.18 mmol) in 25 mL MeOH was added Pd-$BaSO_4$ (5%, 60 mg). The mixture was stirred for 14 h under hydrogen atmosphere (1 atm.). The reaction mixture was filtered through a pad of celite and concentrated. Flash silica gel column chromatography of the crude product using petroleum ether : EtOAc (7:3) afforded **31** (0.270 g, 90%) as a colorless thick liquid.

Yield:- 0.270 g, 90%

$[\alpha]_D^{20}$:- - 4.63 (c = 1, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1503, 1694, 2860, 2932, 3370

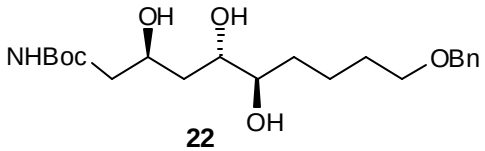
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.55-1.70 (m, 4H), 2.02-2.18 (m, 4H), 2.85-2.98 (m, 2H), 3.38 (t, 2H, *J* = 10 Hz), 3.47-3.75 (m, 2H), 4.50 (s, 2H), 4.85 (brs, 1H), 5.33-5.59 (m, 2H), 7.34 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.45, 27.40, 28.65, 29.57, 33.11, 46.51, 70.53, 71.44, 73.15, 79.86, 115.72, 128.57, 129.95, 133.40, 138.92, 150.27

Mass (ESI): 393 (M + NH_4^+), 376 (M + 1), 308, 264, 227, 160, 130

Anal. Calcd. for $C_{22}H_{33}N0_4$: C, 70.37; H, 8.86; N, 3.73 Found: C, 70.29; H, 8.80; N, 3.69

Synthesis of (2*S*, 4*S*, 5*R*)-(9-benzyloxy-2,4,5-trihydroxynonyl)-carbamic acid *tert*-butyl ester, 22



22

To a mixture of K_2CO_3 (0.23 g, 1.66 mmol), $K_3Fe(CN)_6$ (0.54 g, 1.66 mmol), $(DHQ)_2PHAL$ (0.0004 g, 1 mol% mmol) in *tert*-butanol / H_2O (1:1, 6 mL) at 0°C was added in (0.1 M) OsO_4 (0.0005 g, 0.4 mol%), followed by methanesulfonamide (0.052 g, 0.55 mmol). After stirring for 2 min at 0°C, the compound **31** (0.2 g, 0.55 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 18 h and then quenched with sodium sulfite (1.6 g). The stirring was continued for additional 30 min. and then the solution was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. Both compound **22** and **32** were obtained. Silica gel column chromatography of the crude product using $CHCl_3$: MeOH (18 : 2) as eluent gave triol **22** (0.152 g, 70%) as an oil.

Yield:- 0.152 g, 70%

$[\alpha]_D^{20}$:- - 3.53 (c = 0.2, MeOH)

IR ($CHCl_3$) cm^{-1}: ν_{max} 1169, 1250, 1366, 1503, 1694, 2860, 2932, 3370

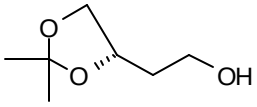
^{1}H NMR (200 MHz, $CHCl_3$ + $DMSOD_6$): δ 1.45 (s, 9H), 1.55-1.70 (m, 4H), 1.81 (brs, 3H), 2.02-2.13 (m, 2H), 2.18-2.25 (m, 2H), 2.95-3.08 (m, 1H), 3.26-3.38 (m, 1H), 3.44-3.47 (m, 3H), 3.51-3.75 (m, 2H), 4.50 (s, 2H), 4.95 (brs, 1H), 7.34 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$ + $DMSOD_6$): δ 25.02, 25.89, 27.76, 29.50, 54.94, 62.43, 65.04, 66.68, 69.44, 72.26, 125.82, 127.91, 129.04, 138.09, 158.96

Mass (ESI): 427 ($M + NH_4^+$), 410 (M + 1), 308, 264, 227

Anal. Calcd. for $C_{22}H_{35}N0_6$: C, 64.53; H, 8.61; N, 3.42 Found: C, 64.42; H, 8.73; N, 3.56

Synthesis of 2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol, 34



34

For experimental procedure from (*S*)-malic acid see references 12, 13, 14.

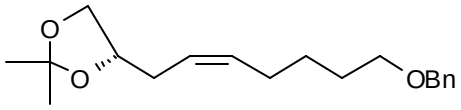
[a]$_D^{20}$: – 3.89 (c = 1, MeOH) [lit. $[\alpha]_D^{20}$ – 2.23 (c = 9.8, MeOH)[14]]

IR (neat, cm^{-1}): n_{max} 3395, 2972, 2930, 2873, 1367, 1212, 1148, 1048, 844

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.40 (s, 3H), 1.80 (q, *J* = 6 Hz, 2H), 2.65 (s, 1H), 3.57 (t, *J* = 8 Hz, 1H), 3.77 (t, *J* = 6 Hz, 2H), 4.07 (dd, *J* = 2, 6 Hz, 1H), 4.28 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.91, 26.09, 35.57, 58.36, 68.69, 73.18, 107.84

Synthesis of (2*S*)-4-(7-benzyloxy-hept-2-enyl)-2,2,-dimethyl-[1,3]-dioxalane, 36



36

To a solution of oxalyl chloride (4.36 g, 3 mL, 34.34 mmol) in CH_2Cl_2 (80 mL) at –78°C was added dropwise dry DMSO (5.37 g, 4.9 mL, 68.70 mmol) in CH_2Cl_2 (20 mL). After 20 min, **34** (3.35 g, 22.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 30 min giving a copious white precipitate. After stirring for 1 h at –60°C, Et_3N (14.4 mL, 103.02 mmol) was added slowly and stirred for 1 h allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into 2N HCl (100 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and passed through a short pad of silica gel. The filtrate was concentrated to give the aldehyde (3.1 g) as pale yellow oil. This was used for the next step without further purification.

IR (neat, cm^{-1}): ν_{max} 3035, 2957, 2805, 1717, 1631, 1374, 950

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.40 (s, 3H), 2.6-2.8 (m, 2H), 3.57 (dd, *J* = 3, 6 Hz, 1H), 4.18 (dd, *J* = 3, 6 Hz, 1H), 4.52 (t, *J* = 7 Hz, 1H), 9.78 (s, 1H)

To a solution of $Ph_3P^+[(CH_2)_5OBn]Br^-$ **35** (21.61 g, 41.6 mmol) in dry THF (60 mL) at -78°C was added 2.2 M *n*-BuLi (23.5 mL, 3.3 g, 51.56 mmol) and the reaction stirred for 1.5 h at the same temperature. After the generation of ylide (change in color of the reaction mixture) was added the solution of aldehyde (3 g, 20.8 mmol) in THF (15 mL) at -78°C.

Stirring was continued for further 8 h at the same temperature. The reaction was quenched by addition of satd. aq. NH_4Cl (50 mL) and the reaction brought to room temperature in 30 min. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to thick syrup. Column chromatography of the crude product on silica gel using petroleum ether / EtOAc (95:5) as eluent gave **36** (4.94 g) as a pale yellow oil.

Yield: 4.94 g, 78% (from **34**)

$[\alpha]_D^{20}$: – 9.02 (c = 0.4, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 1650, 2874, 2929, 2977

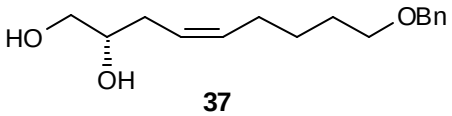
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.43 (s, 3H), 1.45-1.50 (m, 4H), 1.59-1.64 (m, 2H), 1.66-2.09 (m, 2H), 3.48 (t, 2H, *J* = 6Hz), 3.55 (t, 1H, *J* = 6Hz), 4.00-4.12 (m, 2H), 4.51 (s, 2H), 5.35-5.41 (m, 1H), 5.50-5.56 (m, 1H), 7.30-7.36 (m, 5H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 25.82, 26.34, 27.08, 27.39, 29.56, 31.72, 69.23, 70.42, 73.06, 75.84, 109.05, 124.39, 127.64, 127.76, 132.69, 138.87

Mass (ESI): 322 (M^++NH_4^+), 227, 204, 172

Analysis calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.98; H, 9.28.

Synthesis of (2*S*)-9-benzyloxy-non-4-yne-1,2-diol, 37



37

To the solution of **36** (3.0 g, 9.85 mmol) in MeOH (30 mL) at rt was added TsOH (cat.). The reaction mixture was stirred at rt for 4 h. After the completion of reaction, it was quenched with sat. aq. $NaHCO_3$ (5 mL). The solution was extracted in EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7:3) gave **37**(2.34 g) as a colorless oil.

Yield:- 2.34 g, 90%

$[\alpha]_D^{20}$:- - 2.66 (c = 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1634, 2839, 2952, 3360

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45-1.48 (m, 2H), 1.61-1.65 (m, 2H), 1.87 (brs, 2H), 2.06-2.09 (m, 2H), 2.21-2.30 (m, 2H), 3.45-3.50 (m, 3H), 3.65-3.68 (m, 1H), 3.73-3.76 (m, 1H), 4.51 (s, 2H), 5.39-5.44 (m, 1H), 5.54-5.57 (m, 1H), 7.29-7.34 (m, 5H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.20, 27.19, 29.39, 31.34, 66.19, 70.36, 72.16, 72.94, 125.12, 127.62, 127.75, 128.43, 132.43, 138.57

Mass (ESI): 282 (M^++NH_4^+), 227, 204

Analysis calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.70; H, 9.16.

Synthesis of (2*S*)-9-benzyloxy(1-tetrahydropyran-2-yloxy)-non-4-yne-2-ol, 39

39

To a solution of HMPA (1.1 mL, 6.32 mmol) and **25** (1.19 g, 6.32 mmol) in THF (10 mL) at 0°C was added dropwise 2.2 M *n*-BuLi (2.9 mL, 6.32 mmol). The mixture was stirred for 1 h at rt. After cooling at 0°C, a solution of epoxide **38** (0.5 g, 3.16 mmol) in THF (5 mL) was added. The mixture was allowed to warm to rt and stirred for 12 h. After addition of $Na_2SO_4.H_2O$ the mixture was decanted. Concentration and silica gel column chromatography using petroleum ether / EtOAc (8:1) yielded **39** (0.88 g) as a pale yellow oil.

Yield:- 0.88 g, 80%

[α] $_D^{20}$:- - 1.66 (c = 0.7, $CHCl_3$)

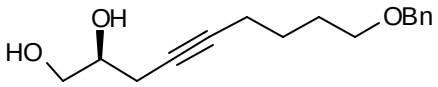
IR ($CHCl_3$ cm^{-1}): ν_{max} 1624, 2837, 2942, 3420

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54-1.63 (m, 10H), 2.05-2.24 (m, 2H), 2.28-2.41 (m, 2H), 2.68-2.73 (m, 2H), 3.44-3.71 (m, 4H), 3.74-3.86 (m, 2H), 4.51 (s, 2H), 4.58 (m, 1H), 7.29-7.36 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.68, 25.56, 26.21, 29.40, 29.62, 29.76, 30.82,62.32, 65.72, 70.06, 70.85, 73.12, 76.14, 82.90, 98.87, 127.78, 128.57, 128.71, 138.64

Analysis calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.83; H, 8.75.

Synthesis of (2*S*)-9-benzyloxy-non-4-yne-1,2-diol, 37 (FROM 39)



27

To a stirred solution of **39** (0.5 g, 1.44 mmol) in MeOH (5 mL) at rt was added TsOH (cat.). The mixture was stirred for 4 h at rt. After the completion of reaction, it was quenched with satd. aq. $NaHCO_3$ (5 mL). The solution was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether / EtOAc (7:3) as eluent gave **27** (0.33 g, 88%) as a syrupy liquid.

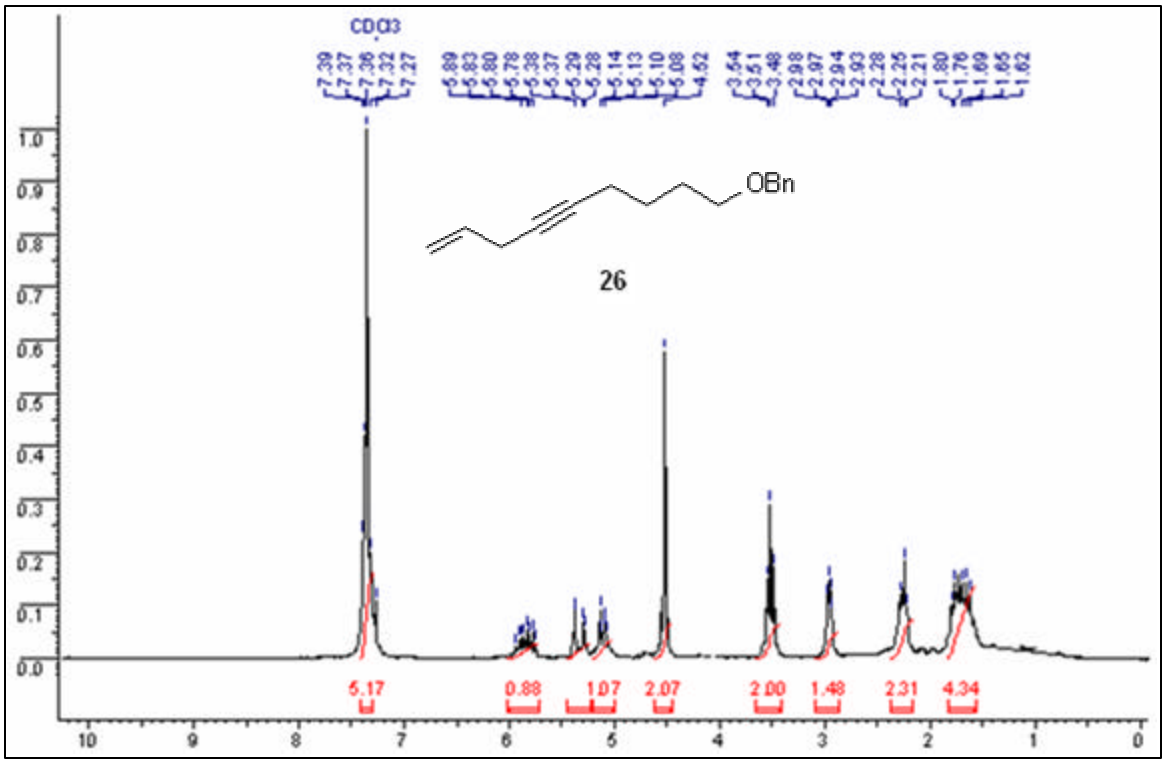
Yield:- 0.33 g, 88%

[α**]** $_D^{20}$**:-** - 4.19 (c = 1.02, $CHCl_3$)

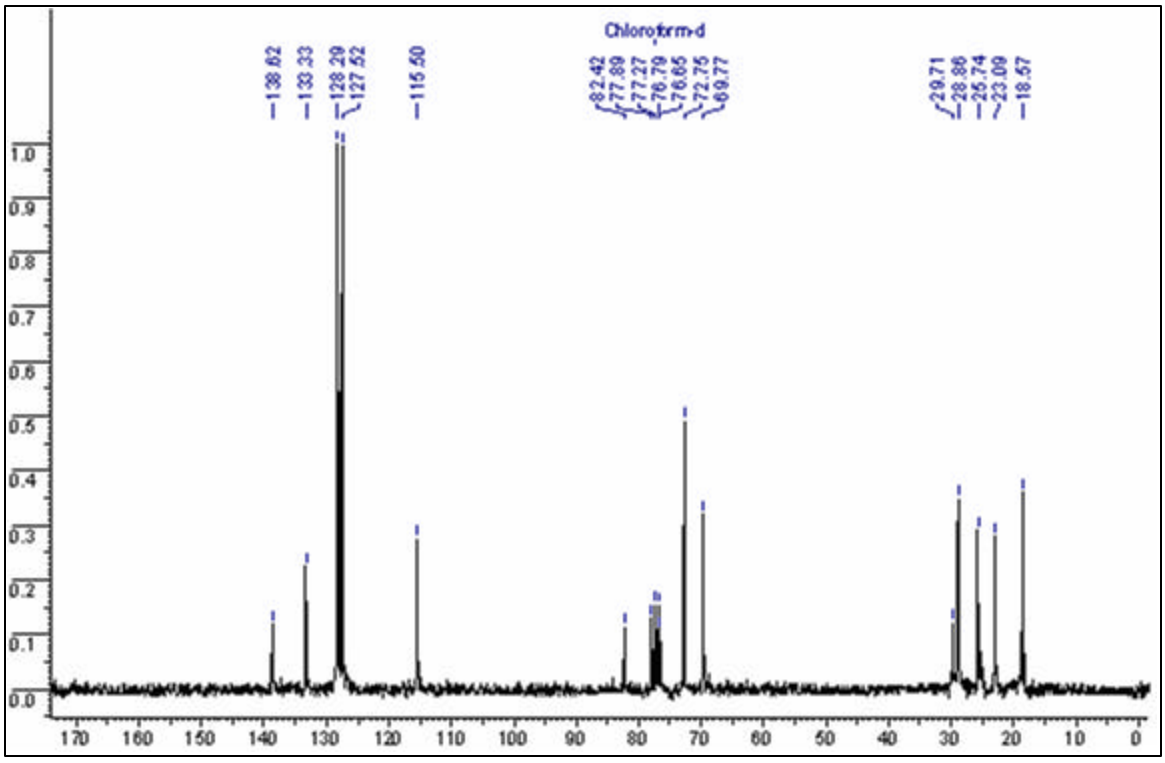
5.7. Spectra

1. ^{1}H NMR of **26**
2. ^{13}C NMR of **26**
3. ^{1}H NMR of **27**
4. ^{13}C NMR of **27**
5. ^{1}H NMR of **29**
6. ^{13}C NMR of **29**
7. ^{1}H NMR of **30**
8. ^{13}C NMR of **30**
9. ^{1}H NMR of **22**
10. ^{13}C NMR of **22**
11. ^{1}H NMR of **36**
12. ^{13}C NMR of **36**
13. ^{1}H NMR of **37**
14. ^{13}C NMR of **37**

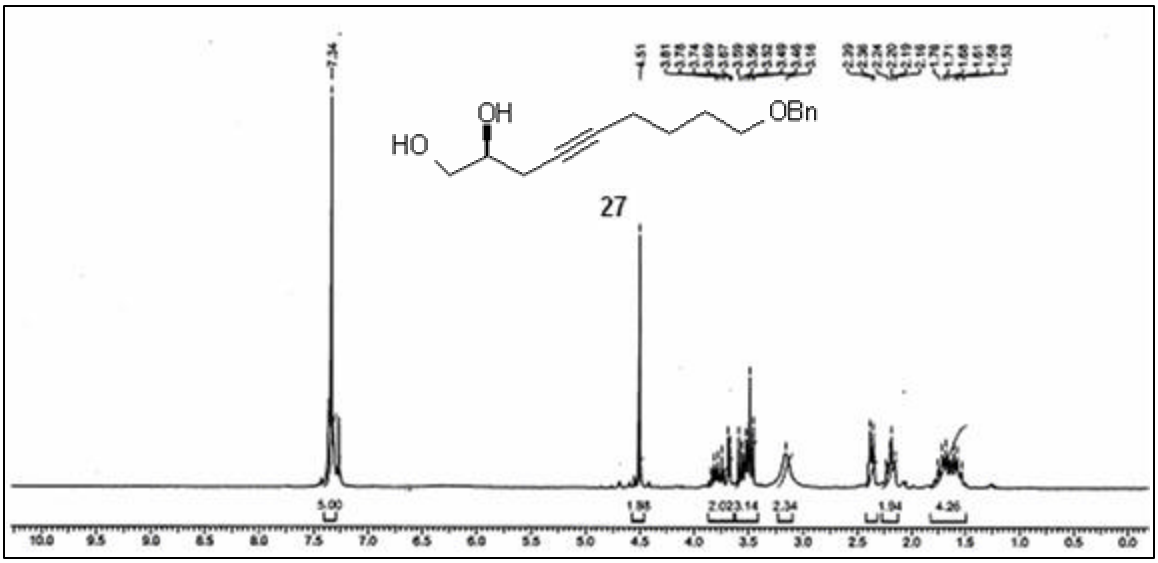
➢ ^{1}H NMR of **26**



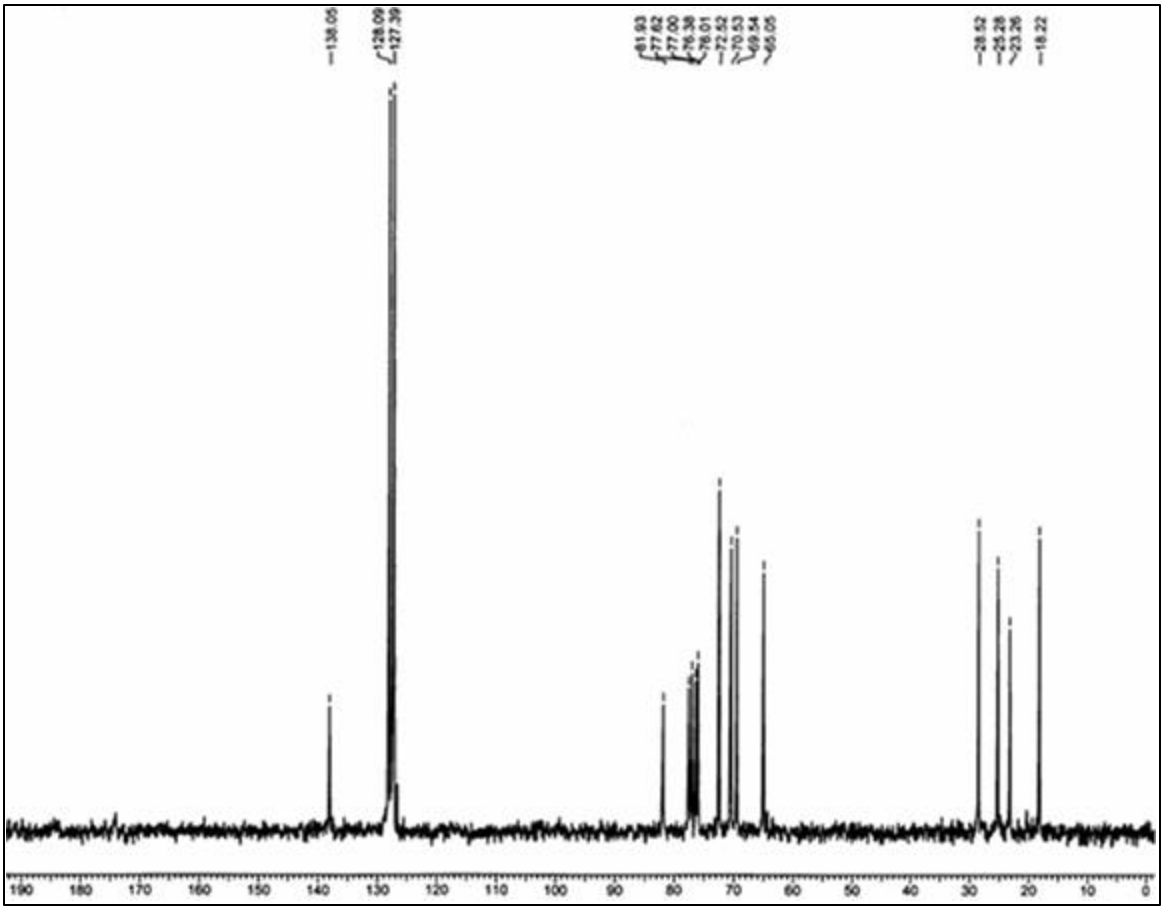
➢ ^{13}C NMR of **26**



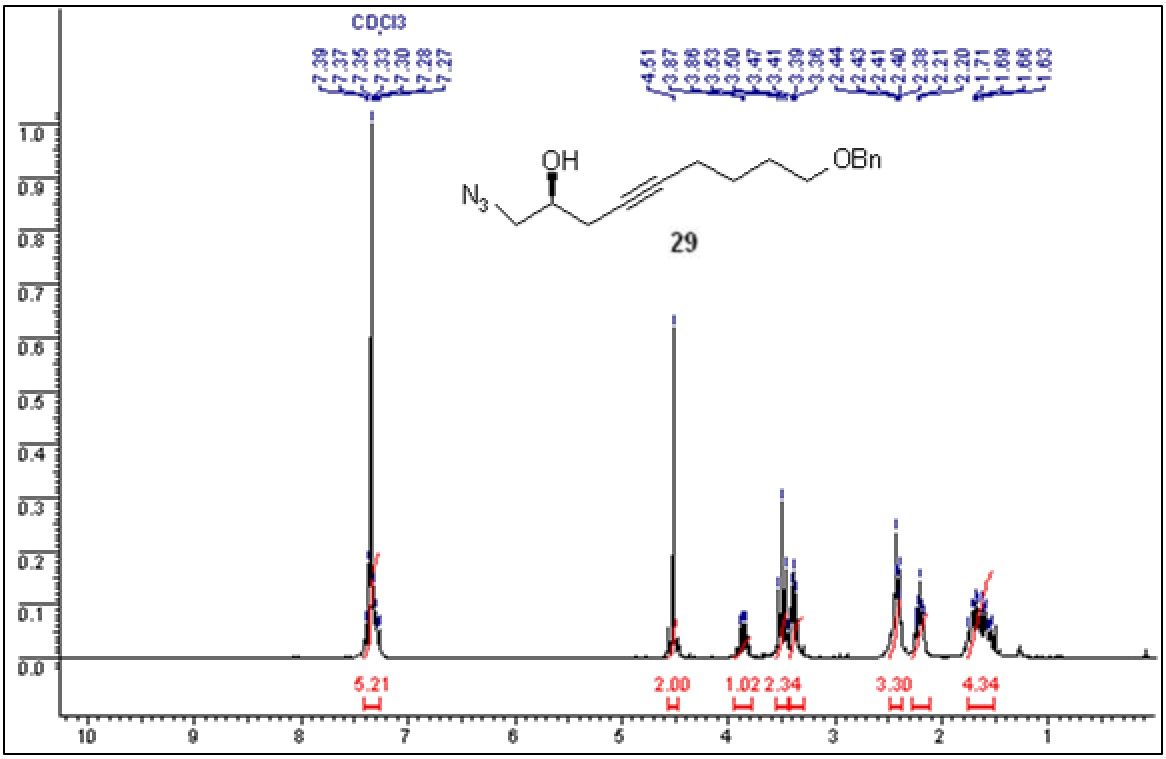
➢ ^{1}H NMR of **27**



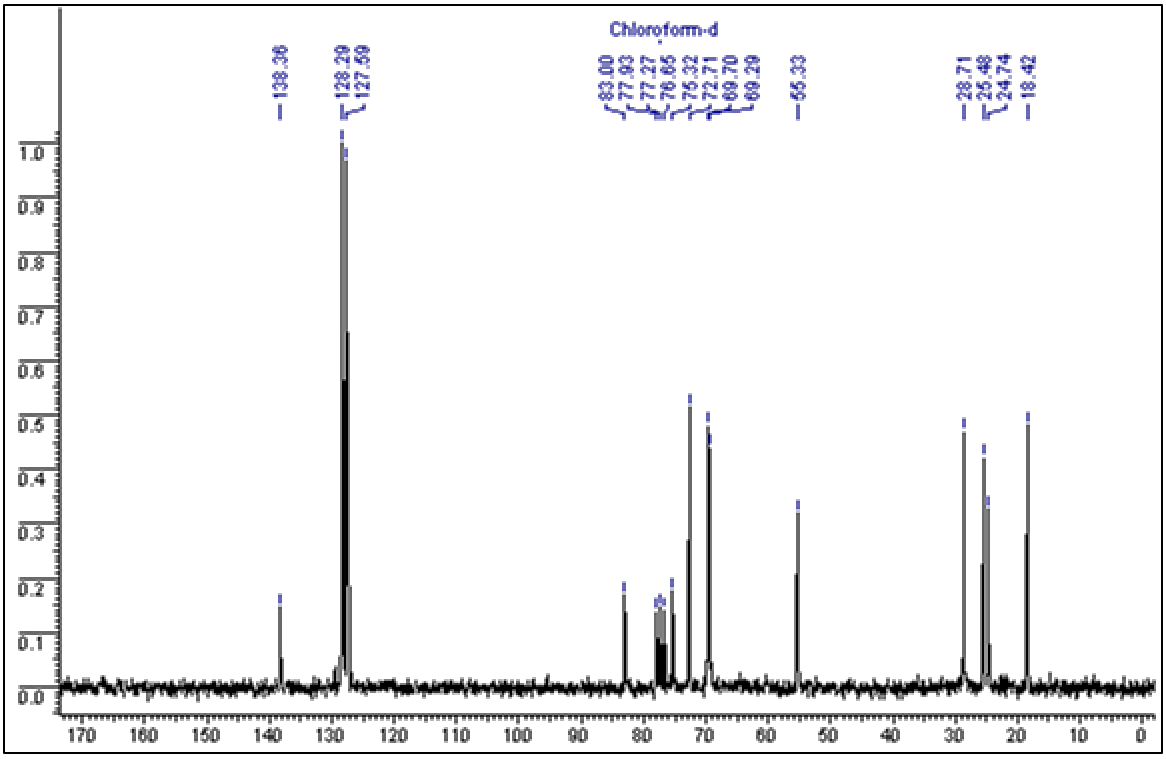
➢ ^{13}C NMR of **27**



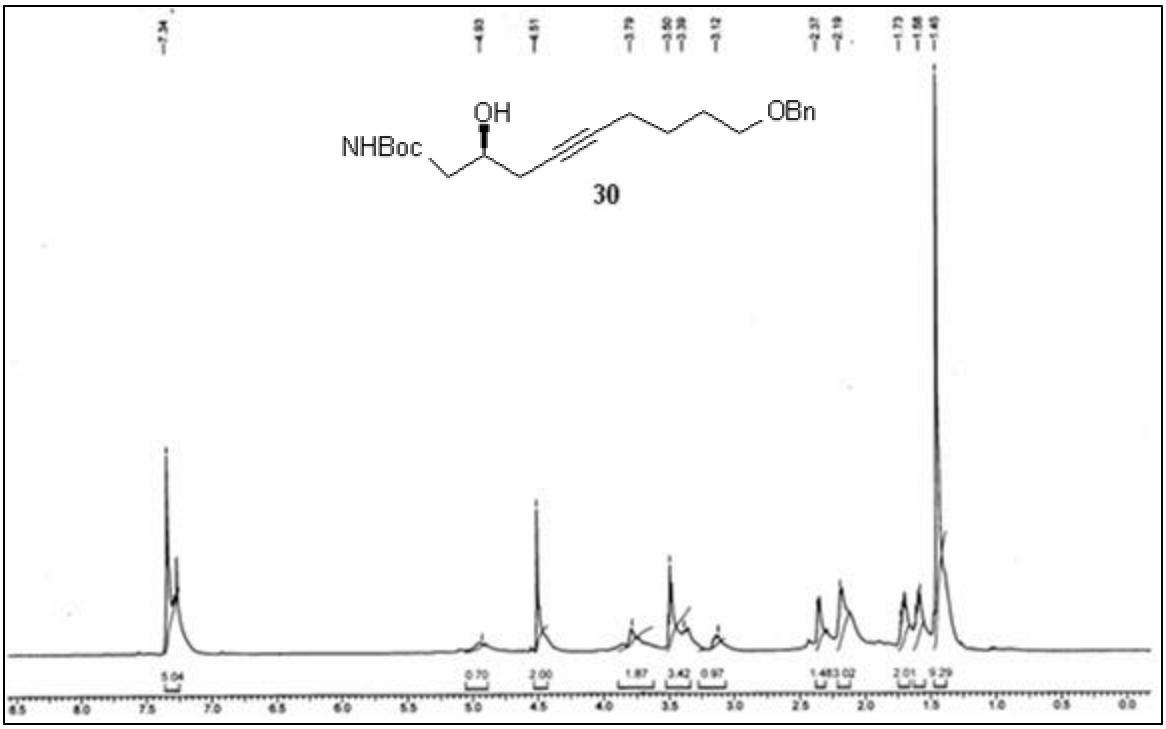
➢ ^{1}H NMR of **29**



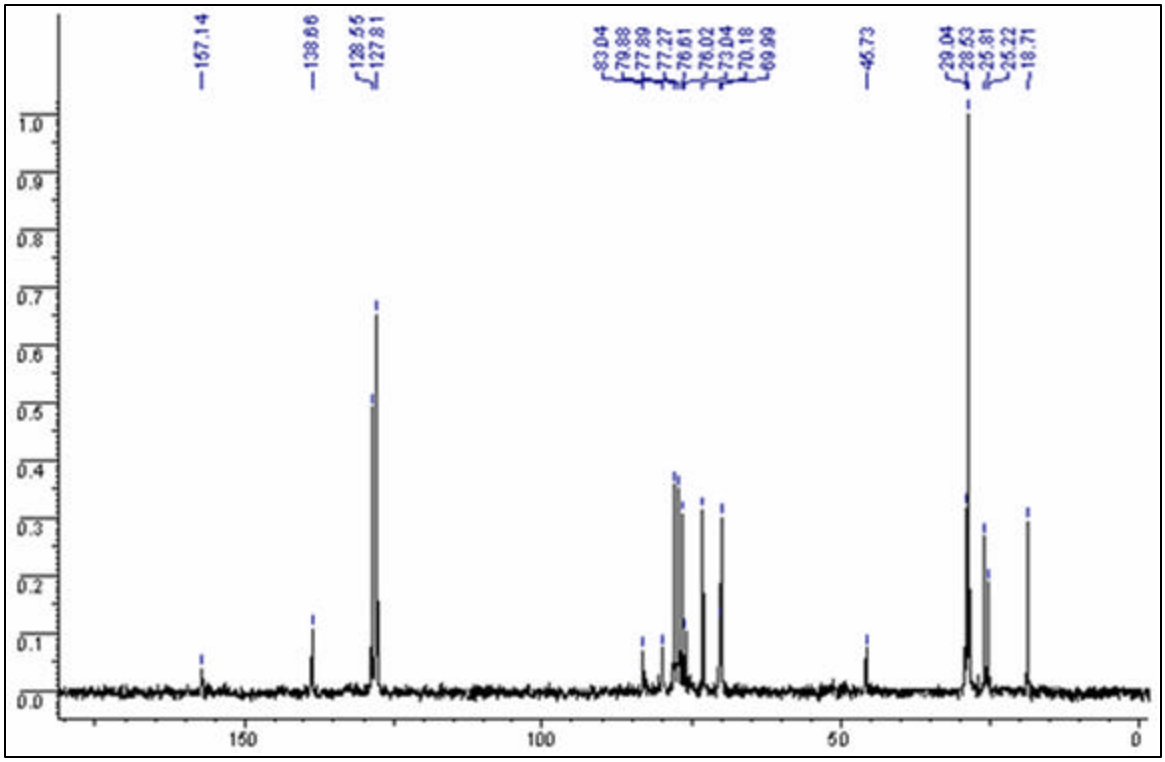
➢ ^{13}C NMR of **29**



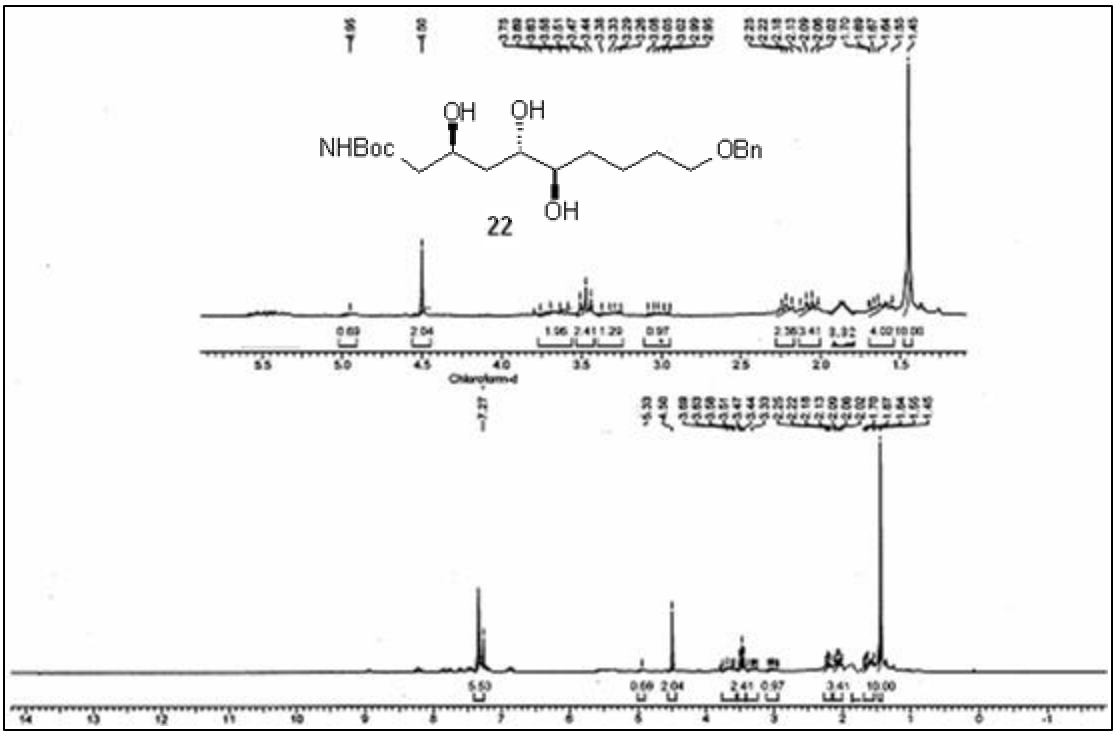
➢ ^{1}H NMR of **30**



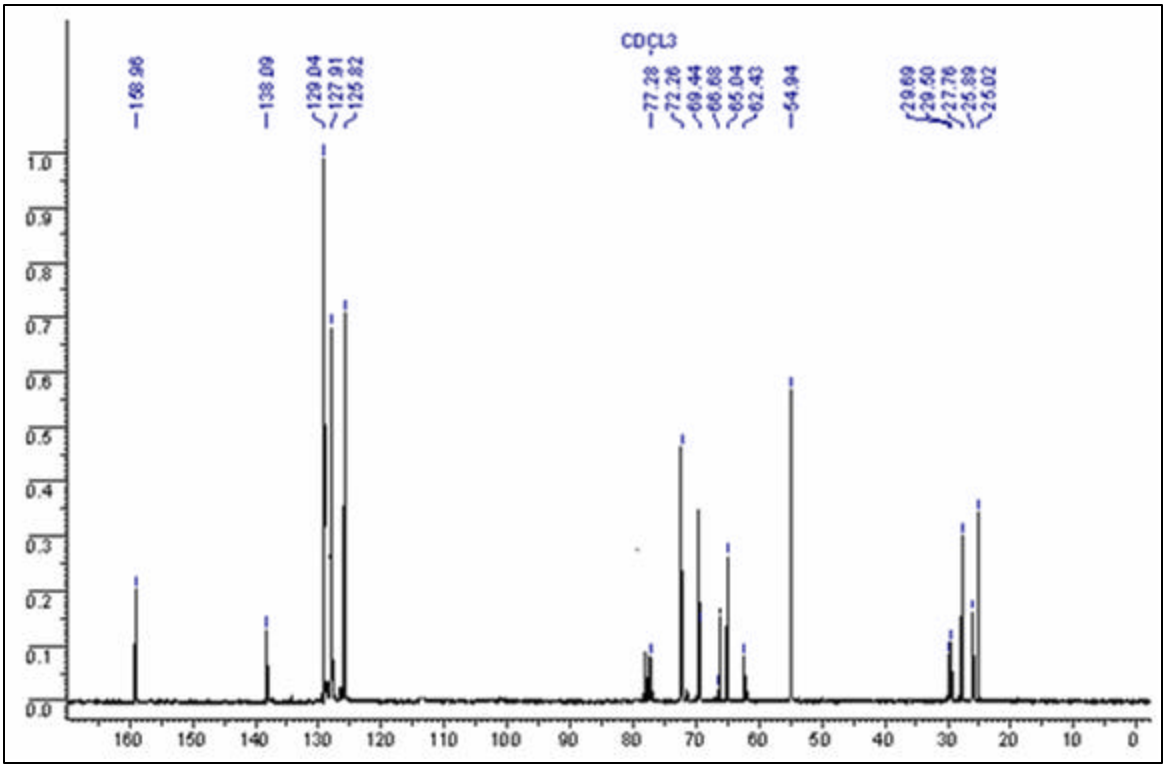
➢ ^{13}C NMR of **30**



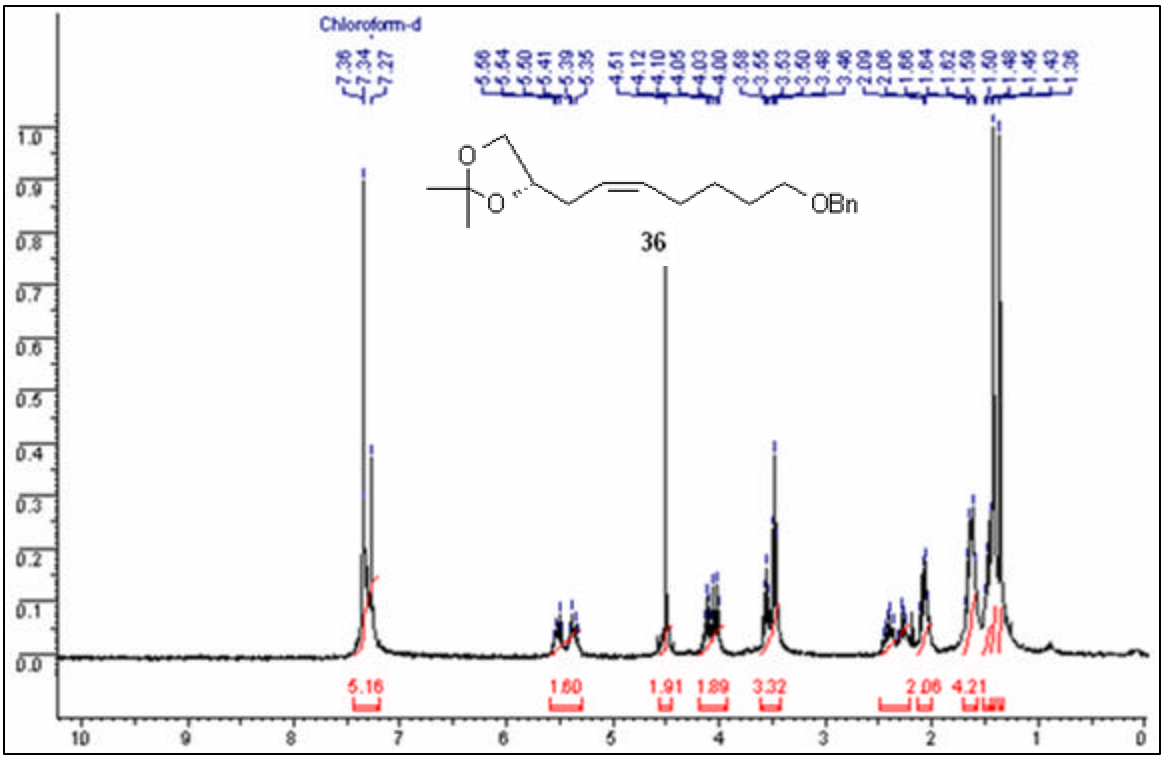
➢ ^{1}H NMR of **22**



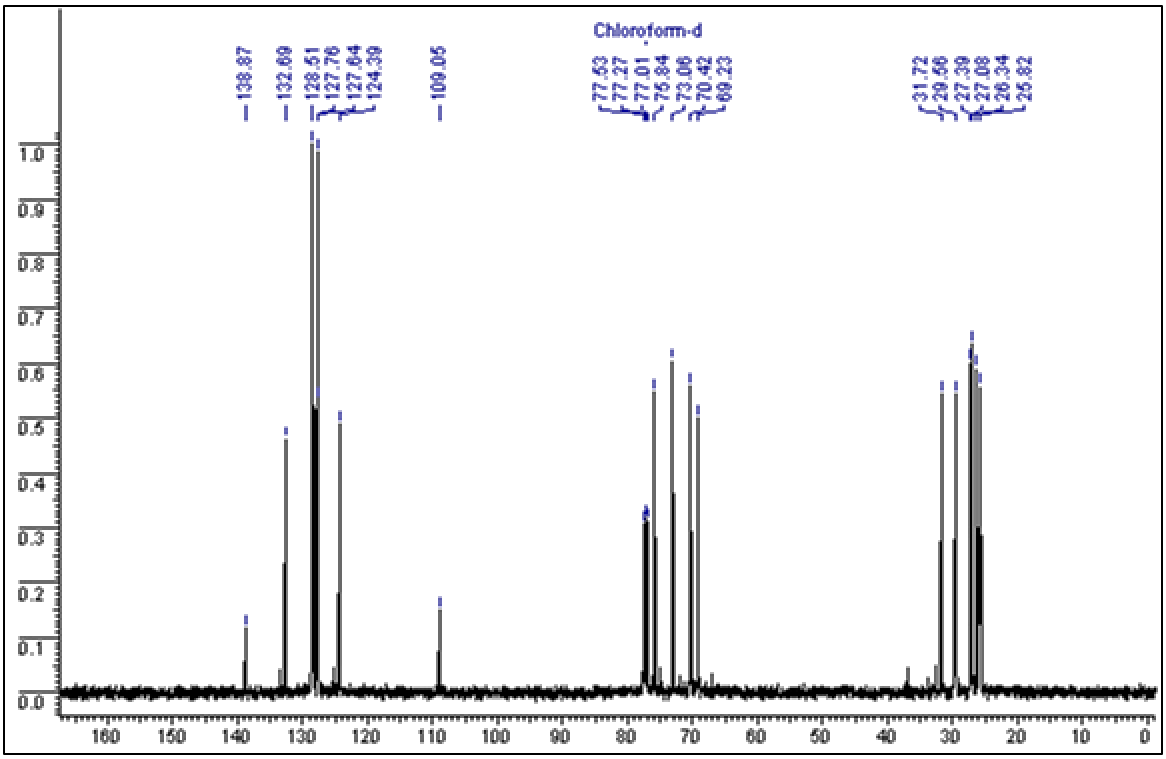
➢ ^{13}C NMR of **22**



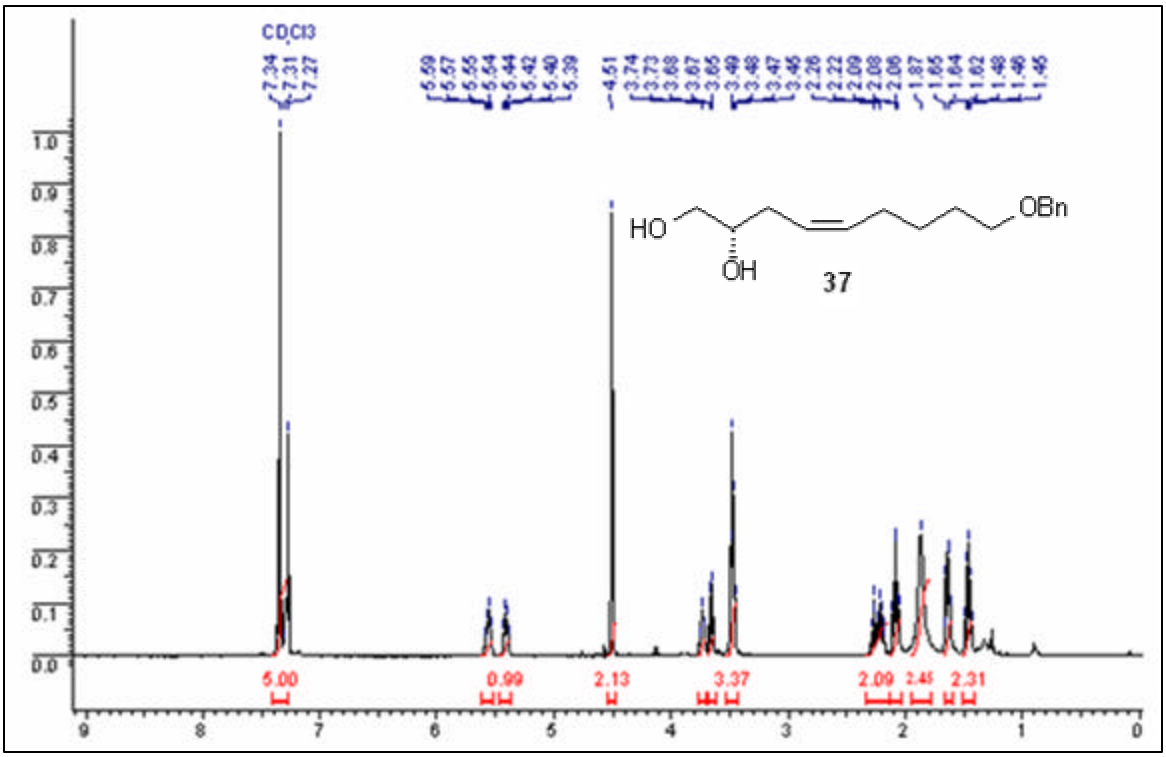
➢ ^{1}H NMR of **36**



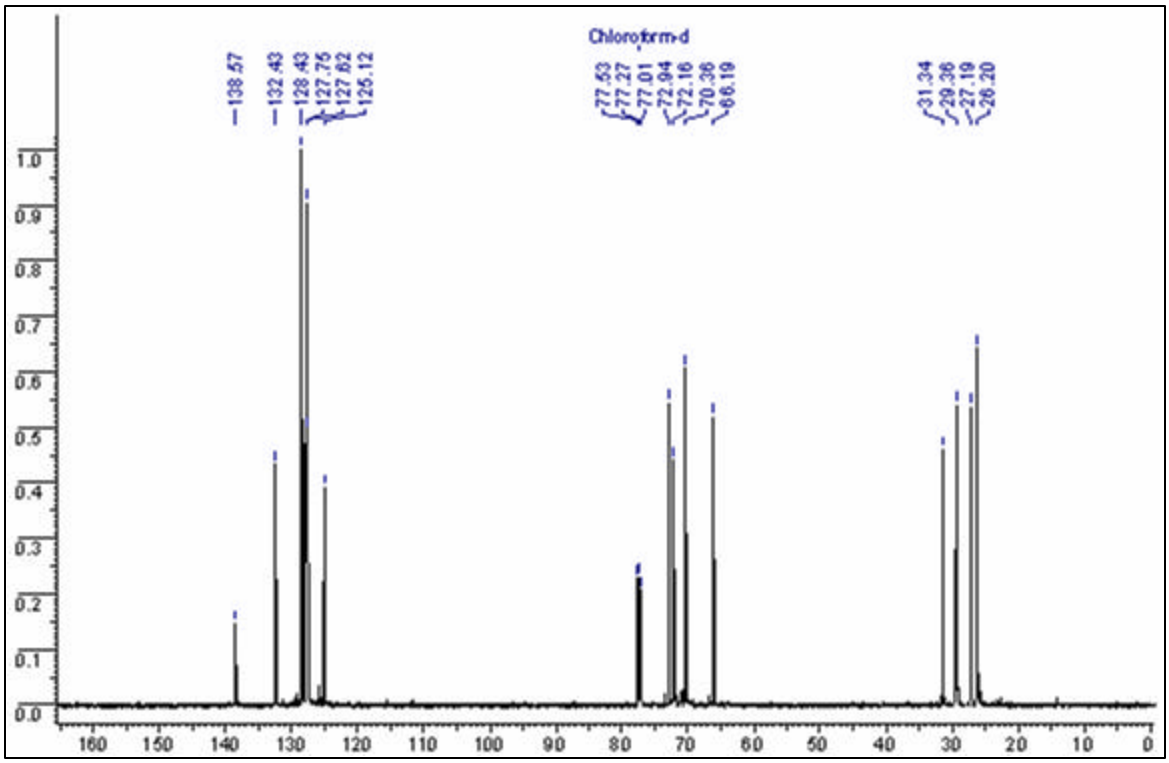
➢ ^{13}C NMR of **36**



➢ ^{1}H NMR of **37**



➢ ^{13}C NMR of **37**



5.8 References

1. Robin, E.; Rarber, J. L.; "*Pathology*" Lippincott, J. B.; Washington: **1988**.
2. Yasumoto, T.; Murata, M. *Chem. Rev*. **1993**, 1897.
3. (a) Bottini, A. T.; Gilchrist, D. G. *Tetrahedron Lett.* **1981**, *22*, 2719. (b) Bottini, A. T.; Bowen, J. R.; Gilchrist, D. G. *Tetrahedron Lett.* **1981**, *22*, 2723.
4. Boyle, C. D.; Harmange, J-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995.
5. Bezuidenhout, S. C.; Gelderblom, W. C. A.; Gorst-Allman, C. P.; Horak, R. M.; Marasas, W. F. O.; Spiteller, G.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1988**, 743.
6. See *Mycopathologia*, **1992**, *117*, 1-124 for 18 reviews regarding various aspects of biological activity of fumonisins and AAL toxins.
7. Merrill, A. H.; Jr.; Wang, E.; Gilchrist, D. G.; Riley, R.T. *Adv. Lipid Res.* **1993**, *26*, 215.
8. Oikawa, H.; Yamawaki, D.; Kagawa, T.; Ichihara, A. *Tetrahedron Lett.* **1999**, *40*, 6621.
9. Oikawa, H.; Matsuda, I.; Kagawa, T.; Ichihara, A.; Kohmoto, K. *Tetrahedron* **1994**, *50*, 13347.
10. Oikawa, H.; Kagawa, T.; Kobayashi, T.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6169.
11. The ee was calculated by converting the free secondary hydroxyl group of tosyl derivative **13** into its (*S*)-MTPA ester [Mosher's derivative] by reacting it with (*S*)-Mosher's acid and then carrying out the ^{19}F spectrum of the resultant ester.
12. Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.
13. (a) Beilstein Handbook of Organic Chemistry, H3, 429, (b) Hungerbuhler, E.; Seebach, D.; Wasmuth, D. *Helv*. *Chim*. *Acta* **1981**, *64*, 1467.
14. Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett*. **1982**, *23*, 4883.