ASYMMETRIC SYNTHESIS USING NOVEL CHIRAL AUXILIARIES AND THE SYNTHESIS OF NOVEL HOST MOLECULES

THESIS SUBMITTED
TO THE UNIVERSITY OF KERALA
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN CHEMISTRY
UNDER THE FACULTY OF SCIENCE

BY

JAYA P.

ORGANIC CHEMISTRY DIVISION
REGIONAL RESEARCH LABORATORY (CSIR)
TRIVANDRUM-695 019, KERALA, INDIA

DECEMBER, 1995

ASYMMETRIC SYNTHESIS USING NOVEL CHIRAL AUXILIARIES AND THE SYNTHESIS OF NOVEL HOST MOLECULES

THESIS SUBMITTED
TO THE UNIVERSITY OF KERALA
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN CHEMISTRY
UNDER THE FACULTY OF SCIENCE

BY

JAYA P.

ORGANIC CHEMISTRY DIVISION
REGIONAL RESEARCH LABORATORY (CSIR)
TRIVANDRUM-695 019, KERALA, INDIA

DECEMBER, 1995

DEDICATED

TO

AMMA

DECLARATION

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me at the Organic Chemistry Division of the Regional Research Laboratory, Trivandrum, under the supervision of ***Dr. G. VIJAY NAIR*** *and the same has not been submitted elsewhere for a degree.*

Jaya

JAYA P.

DIVISION OF ORGANIC CHEMISTRY
REGIONAL RESEARCH LABORATORY (CSIR)
TRIVANDRUM-695 019, INDIA

Dr. VIJAY NAIR
DEPUTY DIRECTOR

Phone : 91-471-490406 (O), 341707 (R) Fax : 91-471-490186
E-Mail : rrlt@sirnetm.ernet.in.

CERTIFICATE

Certified that the work described in this thesis entitled ***ASYMMETRIC SYNTHESIS USING NOVEL CHIRAL AUXILIARIES AND THE SYNTHESIS OF NOVEL HOST MOLECULES*** *has been carried out by Miss. JAYA P, under my supervision and the same has not been submitted elsewhere for a degree.*

G. Vijay Nair

G. VIJAY NAIR
THESIS SUPERVISOR

ACKNOWLEDGEMENTS

It is a great pleasure to express my sense of appreciation and gratitude to my research supervisor ***Dr. G. Vijay Nair*** *for his constant encouragement, enthusiastic support and valuable criticism during the course of my work.*

My thanks are due to Dr. J. M. Rao, Scientist, Organic Chemistry Division, Regional Research Laboratory, Trivandrum for optical rotation measurements and Professor G. M. Sharma, Paterson College, New Jersey, U. S. A., Professor T. V. RajanBabu, Ohio State University, Columbus, Ohio, Professor G. Mehta, University of Hyderabad, Professor S. Chandrasekaran, IISc, Bangalore and Mr. V. Manojkumar, Biochemistry Division, RRL, Trivandrum for spectral and analytical data.

I express my sincere thanks to Dr. Kanakamma, Dr. Jessy Mathew, Mr. T. K. Sasikumar and Mr. G. Anilkumar for their help during various stages of my work. Thanks are also due to my other colleagues for their courtesy and cooperation which made my tenure as a research student an enjoyable event.

I would like to thank Dr. Mangalam S. Nair, Scientist, Organic Chemistry Division, Regional Research Laboratory, Trivandrum for her valuable suggestions and Mr. P. Shanmugam, for his useful criticism.

I thank Professor M. V. George and his associates in the Photochemistry Research Unit, RRL, Trivandrum for their help and cooperation.

I wish to thank Dr. A. D. Damodaran, Director, RRL, Trivandrum for providing the available facilities during the entire course of my Ph. D.

I am grateful to CSIR, New Delhi for financial support by the award of Junior and Senior Research Fellowships.

Finally, I am deeply indebted to my family members for their encouragement and support during the tenure of my doctoral programme.

Trivandrum ***Jaya P***
December, 1995

CONTENTS

PREFACE

From its relatively humble origins organic synthesis has developed in to an activity that pervades all our endeavours; its impact on human health and welfare is particularly striking. The progress in organic synthesis is directly attributable to the advances made in the controlled carbon-carbon bond-forming reactions and the manipulation of functional groups achieved during the past fifty years. The synthesis of homochiral or chirally enriched compounds, however, remained a major problem. With the introduction of efficient catalysts and chiral auxiliaries, progress has been achieved in this area also. In spite of this, much remains to be done and asymmetric synthesis using novel chiral auxiliaries continues to be an area of enormous topical interest. The auxiliaries that have attracted the most attention are those derived from natural amino acids and monoterpenes. Bile acids and carbohydrates, although abundant and inexpensive have found very little application as chiral auxiliaries; therefore we have carried out some investigations in this area and the results are embodied in this thesis entitled **ASYMMETRIC SYNTHESIS USING NOVEL CHIRAL AUXILIARIES AND THE SYNTHESIS OF NOVEL HOST MOLECULES.**

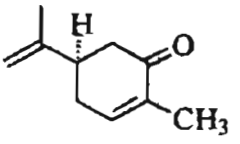
The literature on asymmetric synthesis is enormous and a comprehensive review of the field is not within the scope of this thesis. The introductory chapter, therefore has attempted to highlight only some of the more commonly used methods for the synthesis of optically active compounds. A brief description of the classical methods of asymmetric syntheses is followed by a more detailed account of selected chiral catalysts and auxiliaries. The following chapter describes the use of chiral auxiliaries derived from bile acids such as cholic acid and deoxycholic acid for the synthesis of optically active lactones. The third chapter deals with applications of anhydrofuranosides derived from D-glucose as chiral auxiliaries; special attention being given to γ- and δ-lactones. The last chapter is concerned with the synthesis of novel crown ethers derived from deoxycholic acid. This chapter also includes the complexation studies of these crown ethers with unipositive cations. A summary of the work is given at the end of the thesis.

CHAPTER 1

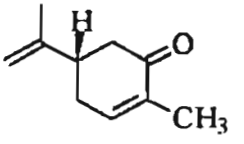
RECENT DEVELOPMENTS IN ASYMMETRIC SYNTHESIS - AN OVERVIEW

1.1 Introduction

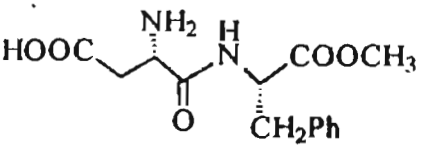
The optical activity of organic compounds in Nature arises from the inherent chirality of the enzymes that are responsible for their production. The optically active receptor sites in biological systems have the ability to differentiate between the enantiomers of a specific molecule. It is noteworthy that the difference in spatial orientation of a single functional group of a chiral molecule drastically affects the biological properties of the compound. A classic illustration is our olfactory response to the enantiomers of carvone. *R*-carvone **1a** has the odour of spearmint, whereas *S*-carvone **1b** smells like caraway[1-3].



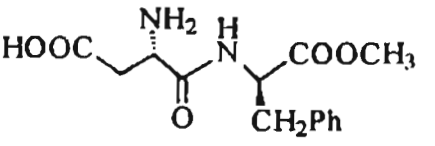
1a *R*-Carvone



1b *S*-Carvone



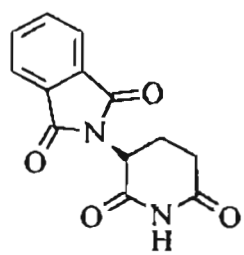
2a (Sweet)



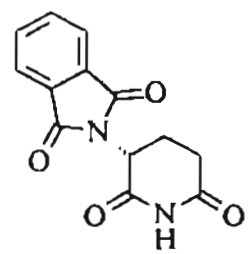
2b (Bitter)

The difference in taste response of the two enantiomers of aspartame **2a** and **2b** is another example[4]; **2a** is sweet, while **2b** is bitter in taste.

The dramatic differences in pharmacological properties of the enantiomers of thalidomide will be the most demonstrative. Foetal death and malformation in children were the tragic consequences brought about by the use of this drug[5]. The teratogenicity has been found to be a property of only the *S*-enantiomer[6].



3a *S*-Thalidomide
Teratogen



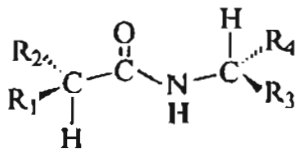
3b *R*-Thalidomide
Sedative

These are only a few of the hundreds of examples in which biological systems respond differently to enantiomers of a chiral molecule. It is thus highly desirable to synthesize molecules in enantiomerically pure form for meaningful studies of their physical or biological properties.

The synthesis of a chiral molecule usually results in the formation of racemic mixture, unless the synthesis is carried out in a chiral environment. This is because the free energy of formation of both the enantiomers is identical. For the synthesis of enantiomerically homogeneous compounds, the chemist has two options: either to synthesize the compound in racemic form and then resolve it into optical antipodes or to perform the synthesis in an enantioselective or preferably enantiospecific fashion so as to produce homochiral compounds.

Ever since the mechanical separation of crystals of the enantiomers of sodium ammonium tartrate by Louis Pasteur in 1848 the technique of resolution to separate enantiomers has been used for nearly hundred and fifty years. Obviously this method is rarely practical and therefore it cannot be considered as a general technique of resolution. However, the formation of diastereomeric quaternary ammonium salts and the selective crystallization of the desired enantiomer is still used as a method of resolution for acids.

Some methods of resolution involve the formation of a covalent bond between the racemic substrate and a chirally pure molecule. The resulting pair of diastereomers can be separated by chromatographic techniques and the desired enantiomer is regenerated from the appropriate diastereomer by chemical manipulations. This again requires that the substrate should possess the appropriate functional groups that are capable of reacting with the resolving agent. Resolution has also been achieved by chromatographic techniques that make use of chiral derivatizing agents (CDA)[7]. The CDA chosen should be enantiomerically pure and react nonselectively with both substrate enantiomers to afford chromatographically separable diastereomers. Helmchen and co-workers have separated a variety of diastereomeric amides **4** by this technique[8]. Even though it is applicable to a wide range of compounds, the method is expensive and it is useful mainly for analytical purposes.



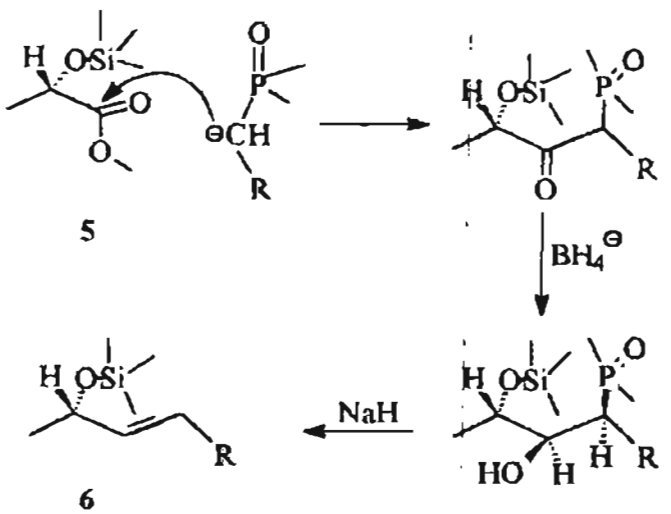
4

R_1	R_2	R_3	R_4
Et	Ph	Me	Ph
Me	Ph	Me	Ph

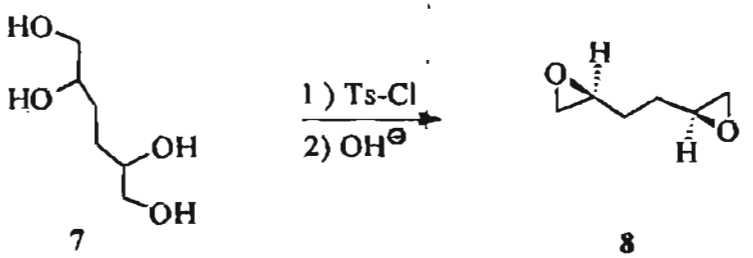
The methods of resolution described above invariably suffer from the disadvantage that half of the mixture will be the wrong enantiomer; which in many cases should be discarded. Additionally, the undesired enantiomer can be poisonous and therefore hazardous to the environment. In the case of compounds with more than one chiral centre the number of diastereomers will also be greater (for n chiral centre, 2^n diastereomers) making resolution tedious and impractical.

The other option for obtaining chiral compounds is to synthesize molecules in optically active form, rather than resolve the racemic mixture. One method of achieving this goal is to transform easily available and inexpensive homochiral natural products such as sugars, amino acids, alkaloids and terpenes into configurationally well-defined intermediates for the synthesis of pure enantiomers. Illustrative examples are the conversion of silyl protected lactic acid ester **5** to the allylic alcohol **6** (scheme-1)[9] and the formation of the bis-epoxide **8** from the mannitol derived alcohol **7** (scheme-2)[10].

But the number of steps involved in such strategies are unacceptably large in most cases. Therefore, one has to look for those compounds that are structurally very close to the target molecule. Another drawback which makes the aforementioned technique impractical is that the starting material of only one absolute configuration will be readily available and hence only one enantiomer of the target molecule can be prepared.



Scheme-1



Scheme-2

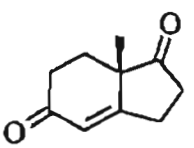
Methods of asymmetric synthesis using chiral catalysts and auxiliaries are consistently more reliable techniques for obtaining optically active compounds. While chiral catalysts are used in substoichiometric amounts as external reagents, chiral auxiliaries are used in stoichiometric amounts as part of the substrate.

A comprehensive review of chiral catalysts and auxiliaries is outside the scope of this chapter. Our discussion in the following sections will be limited to some of the most impressive chiral catalysts and chiral auxiliaries. A brief description of the important chiral catalysts including enzymes is given in section 1.2 of this chapter. Section 1.3 enumerates the applications of some of

the major chiral auxiliaries. A description of the use of crown ethers in chiral recognition is briefly dealt with in section 1.4.

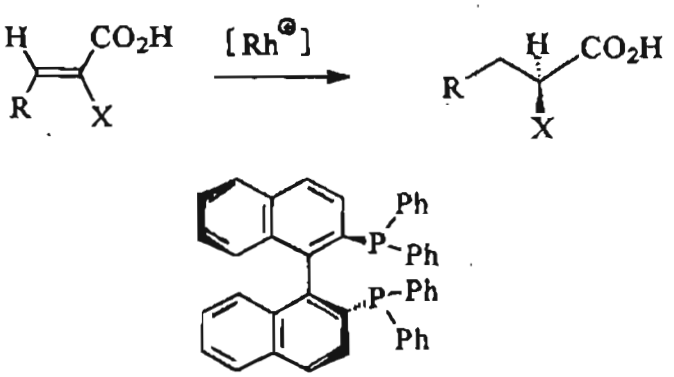
1.2 Chiral catalysts in asymmetric synthesis

Intermolecular transfer of asymmetry can be achieved using optically active catalysts. An early example of the use of homochiral catalyst is the proline catalyzed Robinson annulation for the enantioselective synthesis[11] of the Hajos-Wiechert ketone 9.



9

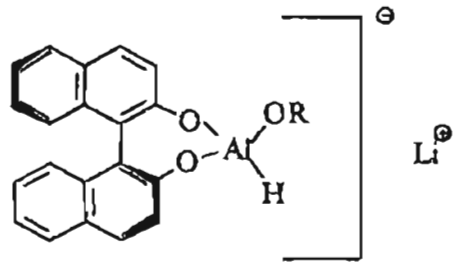
Almost at the same time, another important breakthrough was achieved with the discovery of an asymmetric hydrogenation catalyst. The rhodium complex formed with chiral phosphine ligands, *eg.* 10, efficiently catalyzes the hydrogenation of α,β-unsaturated acids[12] (scheme-3).



10 (+) BINAP; Ligand for Rhodium

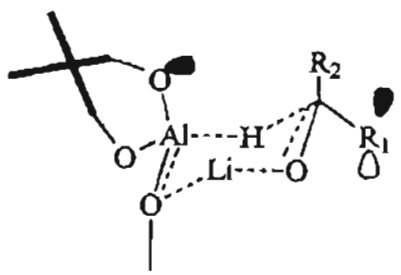
Scheme-3

Among the number of catalysts developed for the asymmetric reduction of carbonyl group, chirally modified lithium aluminium hydrides deserve special mention. Of these, the binaphthyl derivative BINAL-H 11 (BINAL is the complex formed from equimolar amounts of lithium aluminium hydride, 2-2'-dihydroxy-1,1'-binaphthyl and ethanol) is the most promising one.



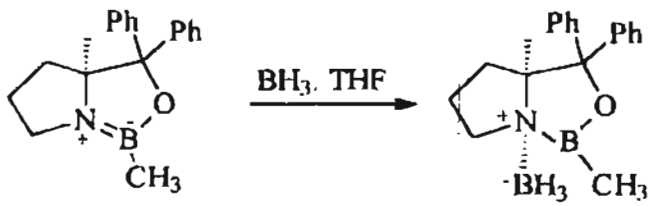
11 *S*-BINAL-H; R = CH_3, Et

BINAL-H is available in both enantiomeric forms[13] and due to the C_2-symmetry of the 1,1'-binaphthyl moiety, the number of possible isomers in the reaction medium is reduced. Enantiomeric excesses ranging from 95-100% have been obtained for the reduction of a range of ketones. The most favourable transition state[14] suggested for the reaction is as shown below and this accounts for the enantioselective formation of the *S*-carbinol.



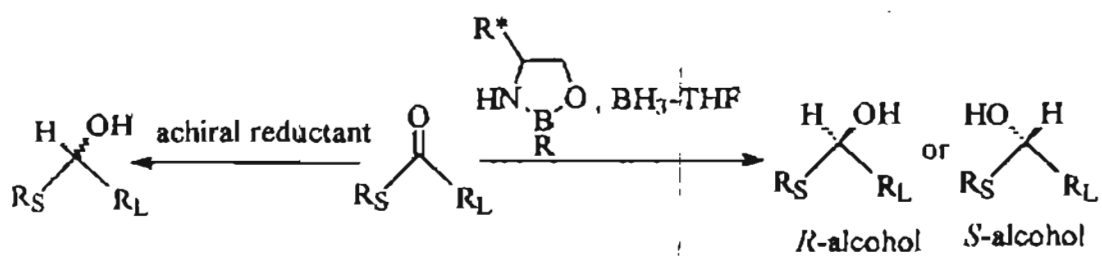
Transition state supporting the *S*-carbinol formation

A second generation of homochiral catalysts was developed from 1,3,2-oxazaborolidines[15,16] (*eg.* **13**).



12 **13**

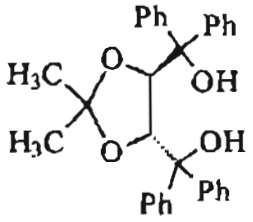
These have been used in the enantioselective reduction of prochiral ketones. In contrast to $NaBH_4$, the chirally modified reagent delivers hydride ion preferentially from a single face of the carbonyl group. Thus the modification of borane with homochiral compounds containing a 1,3,2-oxazaborolidine moiety will lead to chiral products[16] as shown in scheme-4.



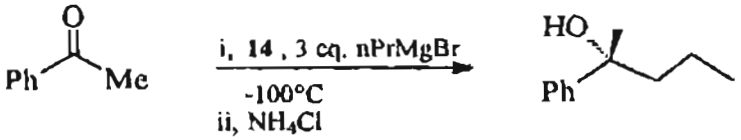
Scheme-4

A characteristic feature of the reduction is that it usually occurs in a predictable manner depending on the absolute configuration of the catalyst used. A wide variety of prochiral ketones can be reduced by borane-THF and in the presence of 5-10 mol% of the catalyst, the secondary alcohols are formed in 83-98% *ee* and in high chemical yields.

Asymmetric catalysts have been used in organometallic reactions also. Seebach[17] has used the tartrate derived TADDOL (α, α, α', α'-Tetraaryl-2,2-dimethyl-1,3-dioxalan-4,5-dimethanol) **14** as a catalyst to make the Grignard reaction diastereoselective.



14

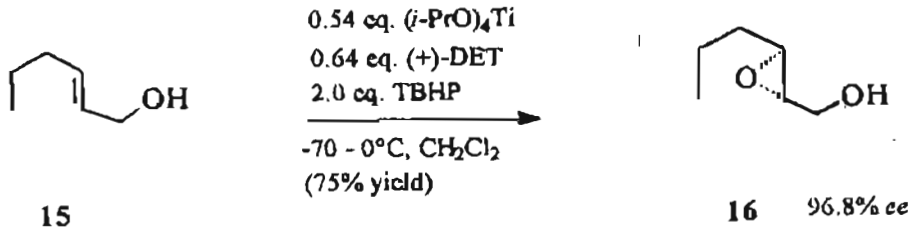


84%, 98% *ee*

Scheme-5

In presence of **14** Grignard reagents add to aryl, vinyl and alkynyl ketones with high stereoselectivity (*eg.* scheme-5).

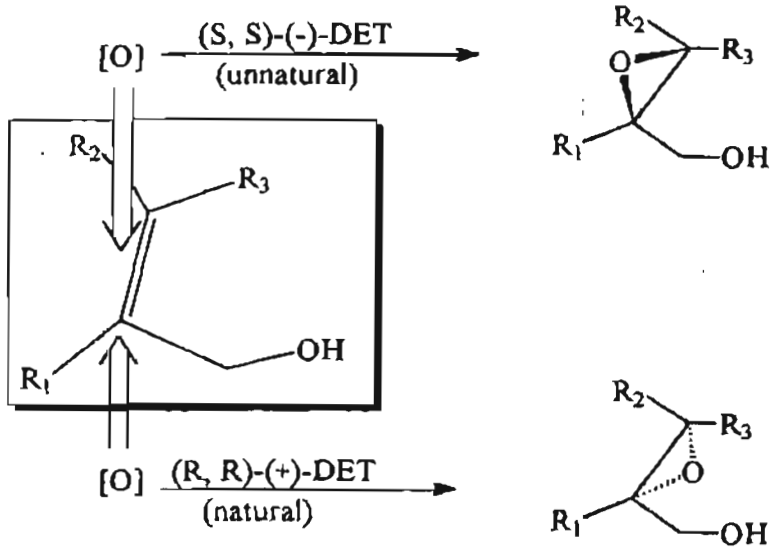
The asymmetric catalysts used in the epoxidation reaction[18] are particularly valuable and a more recent development in this area is the introduction of Mn(III)salen catalysts by Jacobsen[18c,18d]. Various dialkyl tartrates and titanium tetra alkoxides have been developed by Sharpless[18a] to effect the formation of epoxides enantioselectively from primary allylic alcohols. The process has been applied to a wide range of multistep synthesis[18] and the epoxidation of *E*-2-hexene-1-ol (scheme-6) is illustrative.



15 16 96.8% *ee*

Scheme-6

An important feature of the reaction is that the configuration of the major epoxide enantiomer is dependent on the absolute configuration of the tartrate ester. A schematic representation of the transition state suggested for the prediction of absolute configuration of epoxides is given in scheme-7.



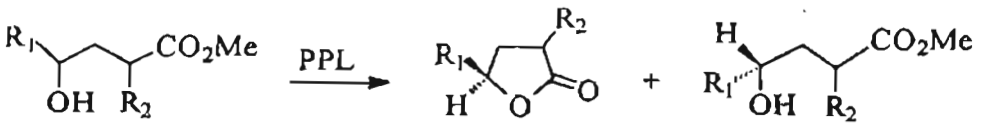
DET = Diethyl tartrate

Scheme-7

The above examples are illustrative of the importance of catalysts in asymmetric induction. The efficiency of a catalyst increases with its ability to coordinate with the substrate and the presence of metals in the catalyst enhances this possibility. In spite of the excellent results obtained in many

cases, practical difficulties associated with the use of chiral catalysts preclude their application in many transformations. Besides, useful catalysts are not yet available for a variety of reactions.

Before concluding this section, it is appropriate to mention briefly the role of enzymes in asymmetric synthesis. Enzymes are widely used as catalysts in asymmetric synthesis and in resolution[19]. They not only provide excellent stereoselectivity in reactions, but are chemoselective and have the ability to induce chemical transformations which are not amenable to other methods. *Among the enzymatic reactions, the lipase and protease catalyzed esterification* and transesterification have found extensive use in the preparative resolution of acids and alcohols. The porcine pancreatic lipase (PPL) catalyzed asymmetric resolution of lactones *via* hydrolysis is illustrative of the use of enzymes in asymmetric synthesis[20] (scheme-8); the *R*-lactone **18** was obtained in >98% *ee*.



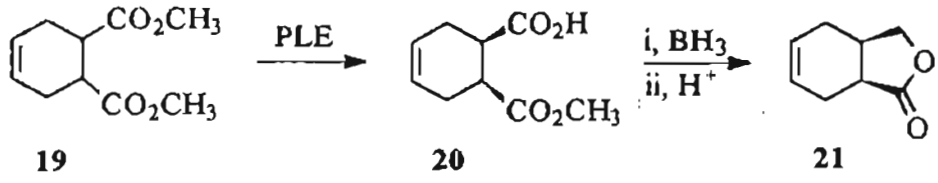
17 **18**

$R_1 = CH_3$, $R_2 = H$

$R_1 = Ph$, $R_2 = H$

Scheme-8

Pig liver esterase (PLE) catalyzed hydrolysis of the diester **19** followed by reduction and lactonization afforded the optically pure lactone **21** in 99% yield[21] (scheme-9).



19 20 21

Scheme-9

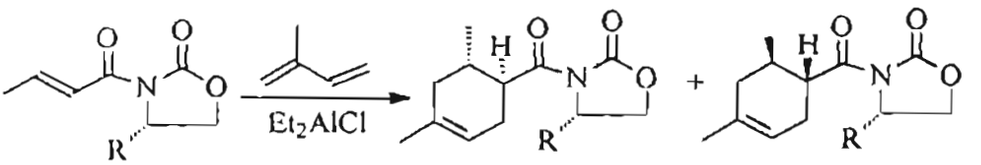
The high specificity of enzymes, however, precludes their use as general catalysts to achieve a particular transformation. Most of the enzyme catalyzed reactions require expensive cofactors like NAD(P)H or ATP. Also, the activity of enzymes will be diminished by exposure to air, adsorption, organic solvents and so on, and hence they find only limited applicaton in large scale reactions.

A consistently reliable strategy for achieving asymmetric synthesis involves the incorporation of a chiral auxiliary and this technique is discussed in some detail in the following section.

1.3 Chiral auxiliaries in asymmetric synthesis

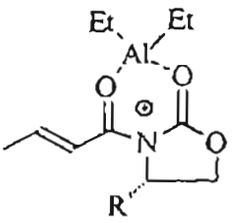
During the past two decades, there has been great interest in developing new chiral auxiliaries to accomplish synthetic transformations with a high degree of asymmetric induction[22]. Usually chiral auxiliary is a compound taken from Nature's chiral pool (*eg.* terpenes[23], amino acids[24] and α-hydroxy acids[25]). The auxiliary makes the transition state diastereoselective and is ultimately removed after the required transformation. An ideal chiral auxiliary should be easily available in optically pure form and should have functional groups to tether prochiral groups. Another major requirement is that the auxiliary should be easily removable without racemization of the newly created asymmetric centres and should be recoverable. During the last few years a number of chiral auxiliaries have been introduced with varying degrees of

success. Some of the examples of the more efficient auxiliaries will be described in this section. Perhaps the most important among the known auxiliaries is the Evans auxiliary derived from α-amino acids[26]. A combination of chelation and restricted rotation inherent in a cyclic system with a bulky directing substituent accounts for the success of these auxiliaries. In the [4+2] cycloaddition reactions, enantiomeric excess of upto 95% was obtained in presence of the auxiliary (scheme-10)[24b].



22 **23** **24**

eg; R = $CH_2C_6H_5$; **23**:**24** = 9:68

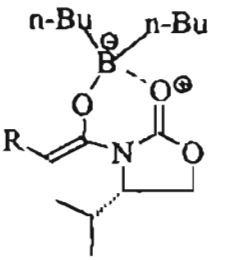


25

Scheme-10

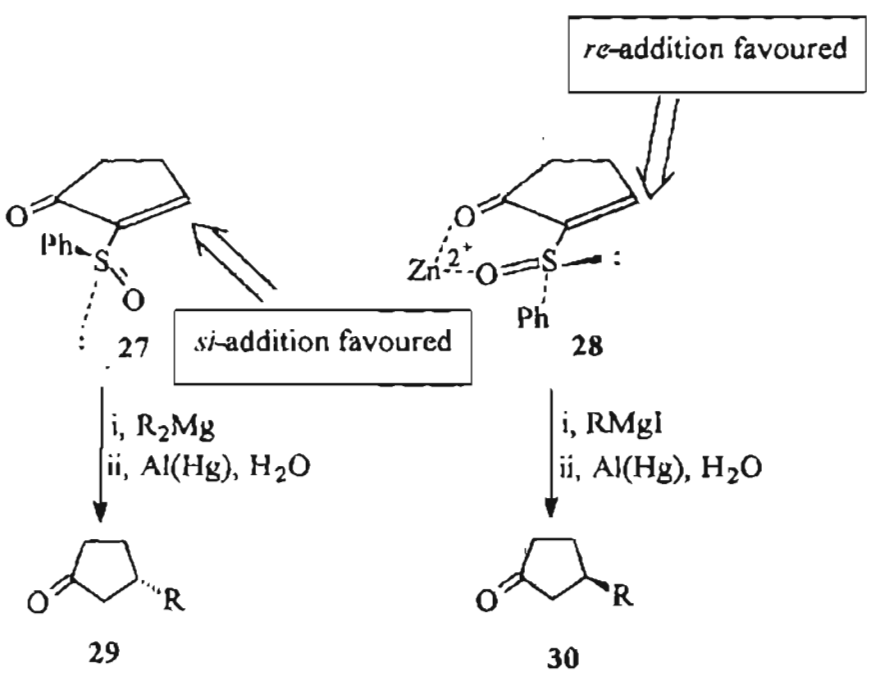
The intervention of a Lewis acid-dienophile complex **25** was put forward to explain the results. In the chelated intermediate **25**, the dienophile is locked through complexation of the two carbonyl groups with the Lewis acid so that the free rotation of the dienophile moiety is prevented. In such a chelated intermediate the substituent at position 4 offers steric repulsion in addition to the π-stacking interaction with the dienophile, if R is aryl, making the approach of the diene from the β-face favourable.

Evans chiral enolates are reported to undergo aldol condensaton with acetophenone[27] with excellent diastereoselectivities. For example, both diastereofacial selectivity and *syn* selectivity have been obtained with the boryl enolate 26.



26

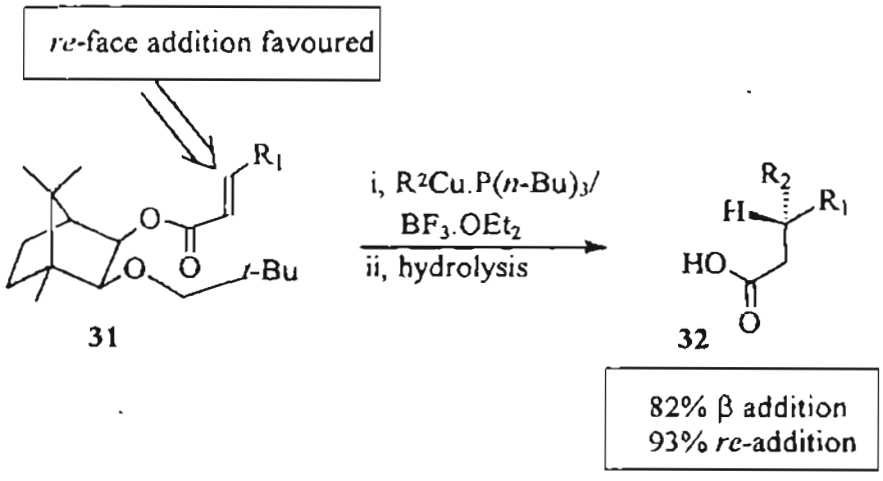
The sulfoxide auxiliaries, although not investigated extensively, are also worth mentioning. In the conjugate addition of nucleophiles to enone sulfoxides, in the absence of a catalyst, *si*-face addition is favoured whereas in the presence of a catalyst, *re*-face addition is preferred[28] (scheme-11).



Scheme-11

This is because the non-chelated conformation **27** is at a minimum energy when the >C=O and sulfinyl oxygen dipoles are oriented in opposite directions rendering the lower face of the enone function as the sterically less hindered face for the depicted isomer, while in the chelated substrate **28** the upper face is less encumbered.

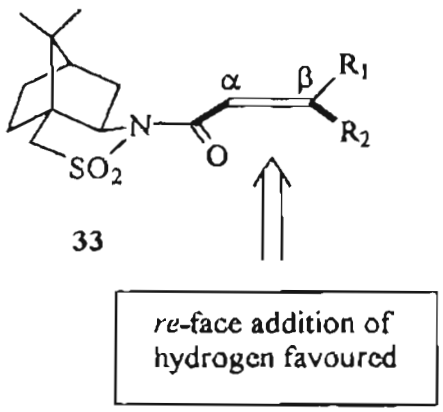
The camphor derived auxiliaries have attracted much attention due to their easy availability and crystalline nature. Moreover, their inherent chirality and sterically enriched carbocyclic skeleton render them suitable as chiral auxiliaries. A few examples showing the efficiency of camphor derived chiral auxiliaries are included here. In the conjugate addition to crotonate esters tethered to the camphor derived auxiliary, adducts were obtained in excellent diastereoselectivity[29] and the reaction is illustrated in scheme-12.



Scheme-12

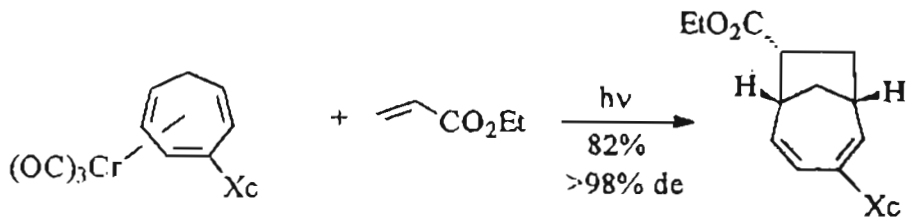
Camphorsultam has proven to be a very good chiral auxiliary. An example of its use is the hydrogenation of α,β-unsaturated amide **33** which proceeded in greater than 90% diastereoselectivity[30]. Analysis of the product

suggested that the catalyst was coordinated with the *syn* oriented sulfonyl group, carbonyl group, and the olefinic bond, thus facilitating the delivery of the hydrogen atom from the *re*-face. Very recently Rigby has obtained >98% *de* in a transition metal mediated higher order cycloaddition of cycloheptatriene using camphorsultam (bornane-10,2-sultam) as the chiral auxiliary[31] (scheme-13).



33

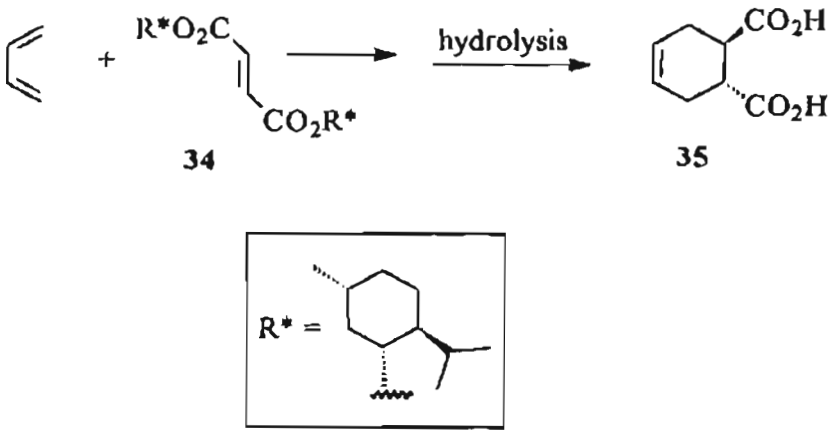
re-face addition of hydrogen favoured



XcH = Camphorsultam

Scheme-13

Other terpene derived chiral auxiliaries also have given impressive results in asymmetric reactions. For example the [4+2] cycloaddition of butadiene with (-) dimenthyl fumarate in presence of $TiCl_4$ as the catalyst, followed by removal of the auxiliary afforded **35** in 78% *ee*. The *ee* value was raised to 90% in presence of diisobutyl aluminium chloride catalyst[32] (scheme-14).



34 35

Scheme-14

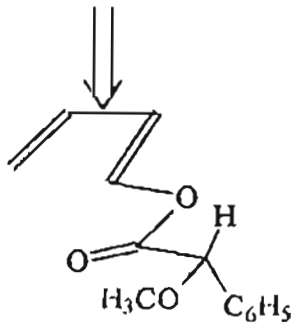
The result has been rationalized by invoking the transition state model **36**, where the diene approaches the *s-trans* conformer of the dienophile from the side away from the isopropyl group. 8-phenyl menthol **37** was found to be superior to menthol itself[33].

36 **37**

si-face addition favoured

In the [4+2] cycloaddition of acrolein, mandelic acid derived diene afforded adducts with 94% diastereoselectivity[34], and the outcome is explained on the basis of a transition state model involving **38**. In a conformation where

the methoxy and carbonyl groups are eclipsed, the approach of the dienophile occurs from the face opposite to the bulky phenyl group.



38

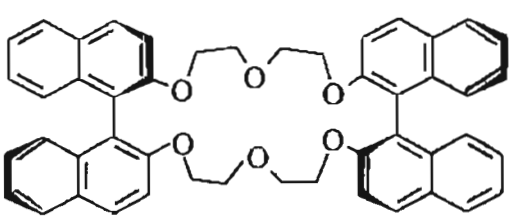
Many of the above illustrations reveal that metal ion chelation also plays a crucial role in asymmetric reactions using chiral auxiliaries. The chelation establishes a fixed stereochemical relationship between stereogenic centres and reaction sites. Often the diastereoselectivity is reversed in the absence of a catalyst. In most of the examples cited, the products were obtained in excellent *ee* values, suggesting that chiral auxiliaries can give results comparable to enzymatic reactions. The chiral auxiliaries are readily available and the experimental conditions are simple. Thus the auxiliary mediated asymmetric synthesis is a valuable and practical method for the synthesis of enantiomerically pure compounds.

Although considerable progress has been made during the last few years much remains to be done and asymmetric synthesis continues to be a very active area of research. In this context, it was of interest to synthesize chiral auxiliaries and host molecules from readily availabe natural products such as bile acids and carbohydrates and the results of our investigations are embodied in this thesis.

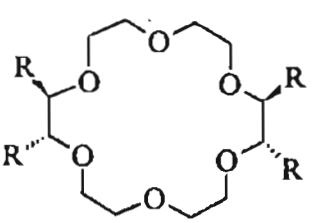
A part of this thesis is concerned with the design and synthesis of crown ethers derived from steroids. Therefore, before concluding this chapter it is appropriate to give a brief description of the use of crown ethers in the recognition of chiral molecules.

1.4 Crown ethers in chiral recognition process.

Most of the biochemical reactions of Nature are catalyzed by enzymes and synthetic chiral receptors are considered as "enzyme-mimics". During the past two decades considerable progress has been made towards the design, synthesis and evaluation of these and other artificial receptors[35]. The efficient binding of alkylammonium ions including amino acids has been achieved by different types of crown ethers. The 22-crown-6-derivative **39**, synthesized by Cram[36], is the first compound of this type that exhibits chiral recognition.



39

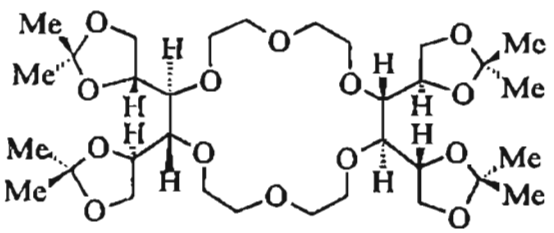


$R = CH_2OCPh_3$

40

Compound **39** showed selectivity towards the *R*-enantiomer of racemic phenylethylammonium hexafluorophosphate. Another chiral crown ether which was used for this purpose is the carbohydrate derived[37] 18-crown-6 ether **40**. The earliest reports on synthetic receptors from carbohydrates were concerned with those derived from D-ribose[38]. Derivatives of D-mannitol, L-threitol and L-iditol have been used for the synthesis of various substituted[37]

as well as fused ring crown ethers[39]. The first example of a crown ether synthesized by this strategy[37] is **41**. Resolution of several amino acid salts was also carried out by chromatographic means, where the receptor used as adsorbant was immobilized by attachment to resins[40]. In these methods, the separation of enantiomers is aided by hydrogen bonding and dipole-dipole attractions as well as charge transfer interactions.



41

A more detailed description of crown ethers and chiral receptors incorporating carbohydrates and steroids is given in chapter 4 of this thesis.

1.5 References

1. Windholz, M. (Ed.), *The Merck Index, 9th ed.*, Merck, Rahway, NJ. **1976**, p. 239.
2. Russel, G. F.; Hills, J. I. *Science* **1971**, *172*, 1043.
3. Friedman, L.; Miller, J. G. *Science* **1971**, *172*, 1044.
4. Mazur, R. H.; Schlatter, J. M.; Goldkamp, A. H. *J. Am. Chem. Soc.* **1969**, *91*, 2684.
5. Mellin, G. W.; Katzenstein, K. *New Engl. J. Med.* **1962**, *267*, 1184.
6. Von Blaschke, G.; Kraft, H. P.; Finkentscher, K.; Kohler, F. *Arzneim-Forsch/Drug Res.* **1979**, *29*, 1640.
7. (a) Buss, P.; Vermeulen, T. *Ind. Eng. Chem.* **1968**, *60*, 12.
   (b) Lochmuller, C.; Souter, R. *J. Chromatogr.* **1975**, *113*, 283.
   (c) Davanakov, C. *Adv. Chromatogr.* **1980**, *18*, 139.
8. (a) Helmchen, G.; Otto, R.; Sauber, K. *Tetrahedron Lett.* **1972**, 3873.
   (b) Helmchen, G.; Volter, H.; Schuhle, W. *Tetrahedron Lett.* **1977**, 1417. (c) Helmchen, G.; Nill, G.; Flockerzi, D.; Schuhle, W.; Youssef, S. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 62.
9. Beckmann, M.; Hildebrandt, H.; Winterfeldt, E. *Tetrahedron Asymmetry* **1990**, *1*, 335.
10. Machinaga, N.; Kibayashi, Ch. *Tetrahedron Lett.* **1990**, *31*, 3637.
11. (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492.
    (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612.
12. Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauf, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 1975.
13. (a) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Noyori, R. *Pure Appl. Chem.* **1981**, *53*, 2316.

14. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

15. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469.

16. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. -P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

17. Weber, B.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84.

18. (a) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Synth.* **1984**, *63*, 66. (b) Adam, W.; Jeko, J.; Levai, A.; Nemes, C.; Patonay, T.; Sebok, P. *Tetrahedron Lett.* **1995**, *36*, 3669. (c) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (d) Lee, N. H.; Muci, A. R.; Jacobsen, E. N.; *Tetrahedron Lett.* **1991**, *32*, 5055. (e) Jacobsen's salenCr(III) complexes in highly enantioselective ring opening of epoxides, see: Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.

19. For reviews on enzymes in Organic Synthesis, see; (a) Whitesides, G. M.; Wong, C. H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 217. (b) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.

20. Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546.

21. Gais, H. -J.; Lukas, K. L. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 142.

22. (a) Caplan, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, 85.
(b) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1974**, *35*, 2797.
(c) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 275.
(d) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157.
(e) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165. (f) Wynberg, H. *Top.*

Stereochem. **1986**, *16*, 87. (g) Brunner, H. *Synthesis* **1988**, 645. (h) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (i) Brigmann, G.; Walter, R.; Weirich, R. *Angew. Chem.* **1990**, *102*, 1006; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977.

23. (a) Walborsky, H. M.; Barash, L.; Davis, T.C. *J. Org. Chem.* **1961**, *26*, 477; *Tetrahedron* **1963**, *19*, 2333. (b) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (c) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3026. (d) Palomo, C.; Berree, F.; Linden, A.; Villalgordo, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1861.

24. (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *Tetrahedron Lett.* **1984**, *25*, 4071. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (c) Bueno, M. P.; Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Charro, P.; Roy, M. A.; Andres, J. M. *Can. J. Chem.* **1991**, *56*, 6551.

25. Helmchen, G.; Karge, R.; Weetman, J. "*Modern Synth. Methods*", Springer Verlag, Heidelberg 1986, Vol. 4, p. 262. (b) Poll, T.; Abdel Hady. A. F.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5595.

26. Evans, D. A. "Studies in Asymmetric Synthesis, The Development of Practical Chiral Enolate Synthones", *Aldrichim. Acta.* **1982**, *15*, 23.

27. Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876.

28. Posner, G. H. *Chem. Scr.* **1985**, 25, NS157. Special Nobel Symposium 60 issue.

29. Oppolzer, W. *Tetrahedron* **1969**, *25*, 43.

30. Oppolzer, W.; Mills, R. J.; Reglier, M. *Tetrahedron Lett.* **1986**, *27*, 183.

31. Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851.

32. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*,183.

33. (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta.* **1980**, *63*, 2015.

34. Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722.

35. (a) Galan, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; Mendoza, J. de. *J. Am. Chem. Soc.* **1992**, *114*, 1511. (b) Nakajaki, M.; Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 787. (c) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4941.

36. Kyba, E. P.; Siegel, M. G.; Sousa, L. R.; Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2691.

37. Curtis, W. D.; Laidler, D. A.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Chem. Commun.* **1975**, 835.

38. Stoddart, J. F.; Szarek, W. A. *Can. J. Chem.* **1968**, *46*, 3061.

39. (a) Haslegrave, J. A.; Stoddart, J. F.; Thompson, D. J. *Tetrahedron Lett.* **1979**, 2279. (b) Metcalfe, J. C.; Stoddart, J. F.; Jones, G.; Crawshaw, T. H.; Quick, A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1981**, 430.

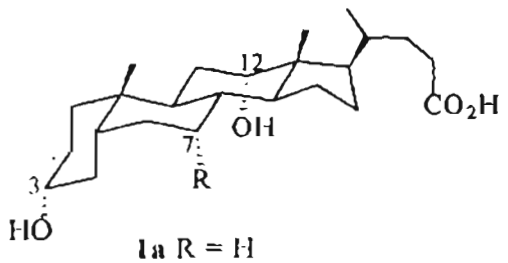
40. Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035.

CHAPTER 2

ASYMMETRIC SYNTHESIS USING BILE ACIDS AS CHIRAL AUXILIARIES

2.1 Introduction

The use of chiral auxiliaries in asymmetric synthesis is an area of active research in organic chemistry[1] (see chapter 1, section 1.3). The most promising auxiliaries are those derived from natural amino acids[2] and terpenes[3]. Even though steroids are relatively abundant and are potentially capable of providing asymmetric environment for organic transformations, they have received only very little attention as chiral auxiliaries[4]. Therefore, it was interesting to undertake some investigations in this area. In particular, we have been interested in the application of the bile acids, deoxycholic acid **1a** and cholic acid **1b** as chiral auxiliaries.



1a R = H
1b R = OH

These bile acids are inexpensive, readily available in optically pure form and are endowed with suitably oriented functional groups in a rigid back-skeleton amenable to the attachment of prochiral moieties. It is

reasonable to assume that the rigid polycyclic steroid ring system can provide "chiral shielding" for the prochiral moiety so that the approach of the reagents would take place only from one face of the functional group. Another advantage is that the hydroxyl groups of **1a** and **1b** exhibit differential chemical reactivity[5]. The C-3 hydroxyl group of cholic acid is more reactive towards acylation than the C-7 hydroxyl, which in turn is more reactive than the one at position 12. The higher reactivity of the C-3 hydroxyl is attributed to its equatorial orientation with respect to ring A. In spite of all these advantages there have been only few reports on the use of bile acids as chiral auxiliaries. These include the asymmetric synthesis of a Troger's base analogue[6] and 1,1'-binaphthol[7] using deoxycholic acid as the chiral template and the use of chiral auxiliaries derived from cholic acid in asymmetric Diels-Alder reactions[8] and α-ketoester reductions[9].

We have now undertaken a detailed study exploring the use of **1a** and **1b** as auxiliaries for the synthesis of γ- and δ-lactones in optically active form. Lactone functionality is present in a large variety of important natural products including pheromones of different insects[10], plant growth regulators[11] and other biologically active compounds. Lactone derivatives are among common flavour components[12] used in perfumery and food industry. They also serve as intermediates in the synthesis of a number of natural products. Most of them are chiral and their physiological activity depends on the absolute configuration[13]; often the optical purity of the substance determines the biological activity[14]. In view of the importance of this class of compounds, many optically active lactones have been synthesized in recent years. Their synthesis in chiral form often relies on complex multi-step transformations involving chiral natural products[15], or enzymatic[16,17] methods. In several cases it has been possible to induce chirality by the use of a chemical reagent[18].

Recently the lipase catalyzed asymmetric resolution of lactones *via* hydrolysis was reported[19a]. While all these methods are useful for the synthesis of chiral lactones, they generally suffer from serious drawbacks. Synthesis from a natural optically active compound is often very inefficient. Enzymatic reduction involves an expensive cofactor (NADH) which has to be regenerated during the reaction and the procedure is very costly and difficult to scale-up. Microbial reduction is restricted to specific compounds which happen to be utilized as growth substrates and therefore the substrate specificity and stereochemical outcome are unpredictable. Use of chiral reagents[18] require critical control of the reaction conditions and have given products of relatively low optical purity. The resolution *via* enzymatic hydrolysis leads to compounds with modest *ee* values. Often such resolutions proceed with difficulty due to the inhibition of the enzymes by the resulting hydroxy acid.

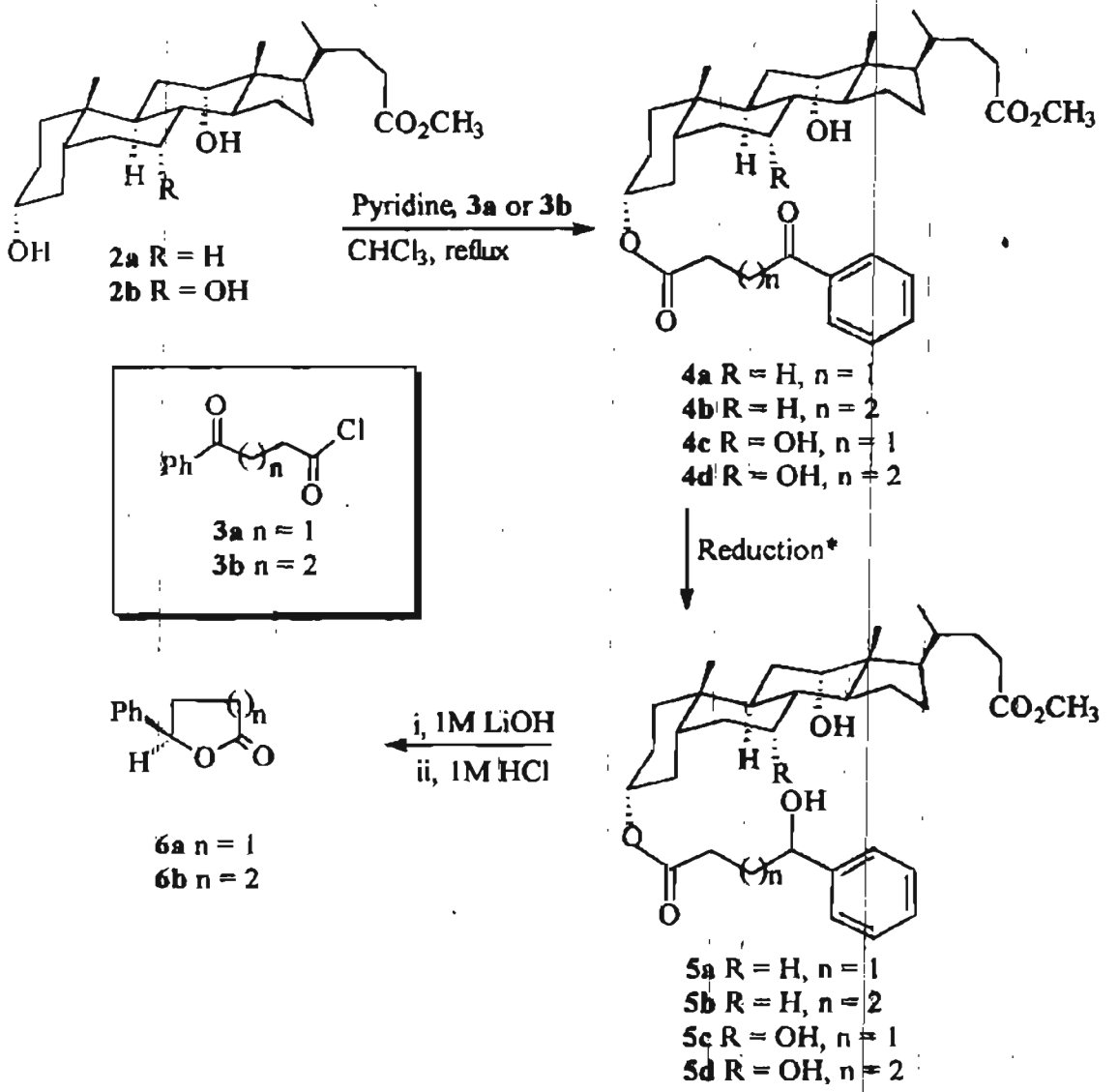
This chapter describes a facile synthesis of a γ-butyrolactone and δ-valerolactone in optically active form using deoxycholic acid and cholic acid as auxiliaries and the results are given in section 2.2.1.

2.2 Results and Discussion

2.2.1 Synthesis of optically active lactones using deoxycholic acid and cholic acid as auxiliaries

The readily available bile acids, deoxycholic acid **1a** and cholic acid **1b** were esterified with methanol to afford **2a** and **2b** respectively. Compound **2a** on reaction with benzoylpropionyl chloride **3a** and benzoylbutyryl chloride **3b** afforded the ketoesters **4a** and **4b**. Similarly methyl cholate **2b** was converted to the ketoesters **4c** and **4d**. Reduction of these ketoesters under different conditions provided the hydroxy esters **5a-5d** in good chemical yields. The hydroxy esters **5a-5d** were saponified using 1M LiOH to remove the auxiliary

and acidification of the reaction mixture afforded the optically active lactones 6a and 6b in 78-82% yields. The auxiliaries were also recovered from the reaction mixture almost quantitatively (scheme-1).



* See Table 1 for conditions

Scheme-1

The structures of all the compounds described were established by spectral and analytical data. The IR spectrum of compound **4a** exhibited hydroxyl absorption at 3450 cm^{-1} and carbonyl absorptions at 1735 and 1718 cm^{-1}. In the ^1H NMR spectrum the aromatic protons resonated as multiplets centred at δ 7.9 (2H) and δ 7.5 (3H). The singlet at δ 3.6 integrating for the OCH_3 protons and the multiplet at δ 2.9 integrating for the six COCH protons are in agreement with the assigned structure. In the ^{13}C NMR spectrum signals appeared at δ 180.5 and 176.0 for the >C=O carbon atoms and the aromatic carbons resonated at δ 134.1, 129.0 and 128.2. For the hydroxy ester **5a**, the IR spectrum showed hydroxyl absorption at 3460 cm^{-1} and carbonyl absorption at 1740 cm^{-1}. The ^1H NMR spectrum displayed a singlet at δ 7.3 (5H) corresponding to the aromatic protons. ^{13}C NMR spectrum showed a signal at δ 171.5 for the carbonyl carbon and signals at δ 127.0 and 126.2 revealed the presence of aromatic carbon atoms. The mass spectrum (EI) revealed the M^+ peak at *m/z* 568 further confirming the assigned structure.

The spectroscopic and analytical data obtained for the lactones synthesized were consistent with the literature data[19]. The yields obtained under different conditions used for the reduction of ketoesters and the *ee* values obtained for the lactones are given in Table 1.

It is noteworthy that higher *ee* values are obtained when the reduction was carried out with $NaBH_4$ in presence of $ZnCl_2$ irrespective of the temperature. The observed results may be attributed to a transient chelation of Zn^{2+} with the C-12 hydroxyl group of the auxiliary and the carbonyl as shown in figure 1.

Table 1

Entry	Keto ester	Reduction conditions	Lactone (R)	*ee* (%)*	Yield** (%)
1	**4a**	$NaBH_4$, -5°C	**6a**	10	82
2	**4b**	"	**6b**	6	79
3	**4a**	$ZnCl_2$, $NaBH_4$, -5°C	**6a**	42	80
4	**4b**	"	**6b**	32	78
5	**4a**	$ZnCl_2$, $NaBH_4$, -78°C	**6a**	47	80
6	**4b**	"	**6b**	33	77
7	**4c**	$NaBH_4$, -5°C	**6a**	9	80
8	**4d**	"	**6b**	8	78
9	**4c**	$ZnCl_2$, $NaBH_4$, -5°C	**6a**	40	81
10	**4d**	"	**6b**	31	78
11	**4c**	$ZnCl_2$, $NaBH_4$, -78°C	**6a**	42	80
12	**4d**	"	**6b**	30	78

* *ee* values were obtained by comparing optical rotations with those reported in the literature. ** Isolated yield.

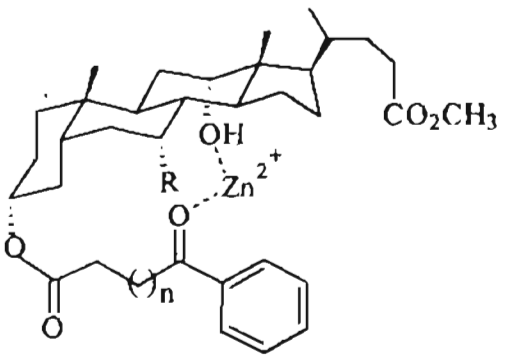


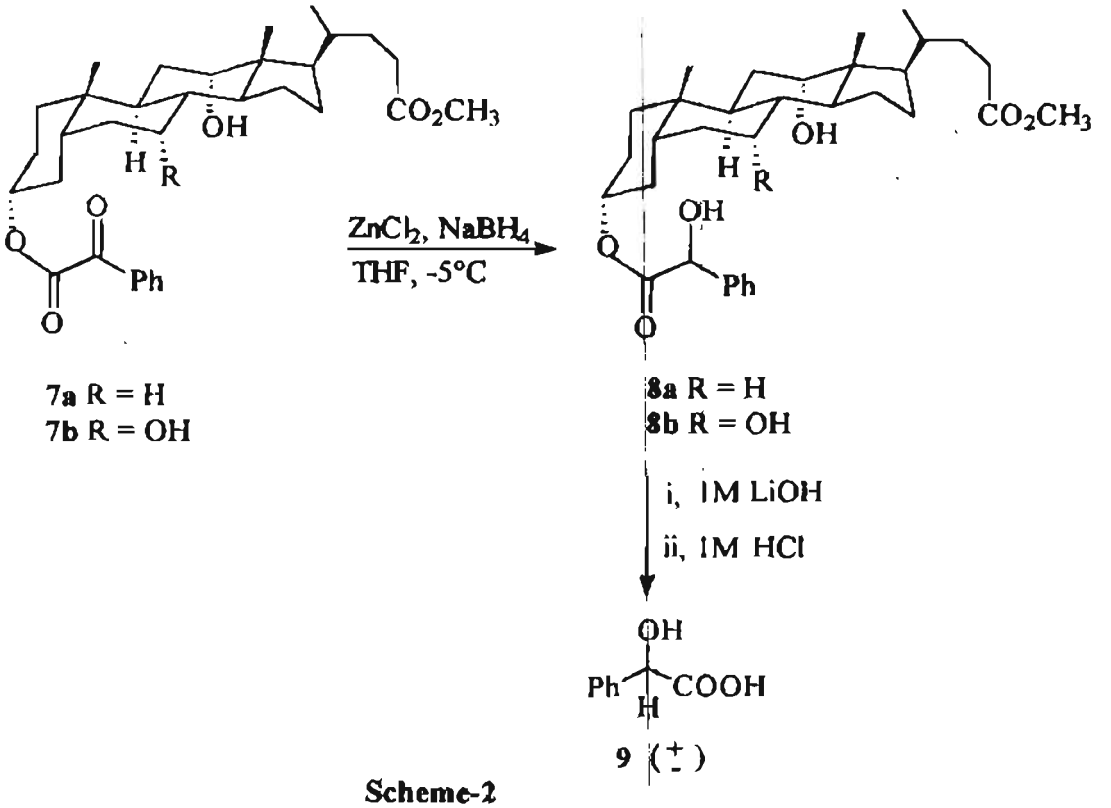
Fig. 1

In such a chelated intermediate which involves the α-hydroxyl group in the steroid ring system, hydride ion delivery takes place from the α-face of the

carbonyl group leading to the product having *R*-configuration. The negligible optical rotation obtained when the reduction was carried out with sodium borohydride is consistent with the argument in favour of a transient chelation. Carbonyl reduction of the ketoesters was also done in the presence of the more "oxophilic" Ce^{3+} ions. The *ee* values were comparable with those of the lactones obtained in the $NaBH_4$ reduction.

The ketoesters **7a** and **7b** were synthesized by condensing benzoylformyl chloride with methyl deoxycholate and methyl cholate respectively in presence of pyridine. Their reduction using $NaBH_4$ in presence of $ZnCl_2$ afforded the hydroxy esters **8a** and **8b**. Saponification followed by acidification afforded the product, mandelic acid **9** in the racemic form (scheme-2). The lack of chiral induction in this case may be due to the absence of transient chelation suggesting that the keto group is too far for coordination. In this situation the carbonyl reduction can take place from both faces leading to the formation of the racemic product.

The ketoesters **7a** and **7b** were characterized spectroscopically. The IR spectrum of compound **7a** showed absorbance at 3460 cm^{-1} for the hydroxyl group. Absorbances at 1735 and 1718 cm^{-1} revealed the presence of carbonyl groups. The ^1H NMR spectrum showed multiplets for the aromatic hydrogens at δ 7.85 (2H) and at δ 7.50 (3H). The ^{13}C NMR signals at δ 178.0, 175.2 and 172.1 supported the existence of carbonyl groups and the aromatic carbons resonated at δ 135.5, 129.2 and 128.5. The disappearence of the peaks corresponding to the benzoyl protons in the ^1H NMR spectrum is diagnostic for the reduced product **8a**. All other spectroscopic data were in agreement with the suggested structure.



7a R = H
7b R = OH

8a R = H
8b R = OH

9 (±)

Scheme-2

2.3 Experimental

General

Melting points were recorded on a Buchi-530 melting point apparatus and are uncorrected. Optical rotations were measured using a JASCO DIP 370 digital polarime ter at ambient temperature (24-27°C). Infrared (IR) spectra were recorded on a Perkin-Elmer model 882 spectrophotometer. Proton NMR were recorded on JEOL EX-90 MHz, Bruker 200, GE 300 (QE PLUS) or Varian 200 MHz NMR spectrometers. NMR spectra were obtained using chloroform-*d* as the solvent unless otherwise mentioned. Chemical shifts are in parts per million (δ) using tetramethylsilane (TMS) as internal standard. Abbreviations used in proton NMR data are s : singlet, brs: broad singlet, d: doublet, t: triplet, dd: doublet of doublet, m: multiplet. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyser. Mass spectral analyses were obtained from Finnigan MAT Model 8430.

Analytical thin layer chromatography was performed on glass plates coated with silica gel (E. Merck) containing 13% calcium sulfate as binder. Visualization of the spots was achieved by exposure to iodine vapour or by methanolic sulfuric acid spray. Silica gel (100-200 mesh, ACME s.d. fine or SRL) was used for column chromatography. Moisture sensitive reactions were carried out by syringe-septum technique and conducted under nitrogen atmosphere. Solvents were dried and distilled according to literature procedure prior to use. Petroleum ether refers to the fraction boiling between 60-80°C. Solvents were removed using a Buchi-EL rotary evaporator. Benzoylpropionyl chloride and benzoylbutyryl chloride were prepared by reacting the corresponding acids with thionyl chloride in $CHCl_3$. Benzoylformyl chloride was obtained by the reaction of benzoylformic acid with oxalyl chloride at room temperature.

Methyl deoxycholate 2a

Deoxycholic acid (0.785 g, 2 mmol) in methanol (15 mL) was stirred at room temperature in presence of conc. H_2SO_4 (2 drops) for 4h. The reaction mixture was neutralized with $NaHCO_3$ and the solvent was removed *in vacuo*. The product was extracted into CH_2Cl_2 (30 mL) and then washed with brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed by distillation. The product was purified on silica gel column using 30% EtOAc in hexane as the eluent to afford **2a** as a colourless solid (0.79 g, 97%). Crystallization from ethyl acetate-hexane mixture afforded colourless crystals of **2a**; m p. 178-179°C.

IR (KBr)	: 3460, 2955, 1735, 1176 cm^{-1}
^1H NMR (60 MHz, $CDCl_3$)	: δ 3.6 (m, 2H, OCH), 3.4 (s, 3H, OCH_3), 2.2 (brs, 2H, OH), 1.8-1.0 (m, steroidal CH_2 and CH), 0.85 (s, 3H, CH_3)

Methyl cholate 2b

Cholic acid (0.82 g, 2 mmol) in dry methanol (15 mL) was stirred in presence of 2 drops of conc. H_2SO_4 for 4h. The reaction mixture was worked up as described for compound **2a**, and the product purified by silica gel column chromatography using 35% EtOAc in hexane as the eluent. Compound **2b** was obtained as a colourless solid (0.8 g, 94%) which was crystallized from a mixture of ethyl acetate and hexane to afford colourless crystals; m p.182-183°C.

IR (KBr) : 3510, 2960, 1728, 1182 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 3.7 (m, 3H, OCH), 3.5 (s, 3H, OCH_3), 2.0 (brs, 3H, OH), 1.8-0.9 (m, steroidal CH and CH_2), 0.85 (s, CH_3)

Benzoylpropionate of methyl deoxycholate 4a

Methyl deoxycholate **2a** (3.0 g, 7.38 mmol) in $CHCl_3$ (30 mL) was treated with pyridine (0.9 mL, 11.07 mmol). To this solution benzoylpropionyl chloride (1.69 g, 8.86 mmol) in dry $CHCl_3$ (15 mL) was added slowly and the mixture was stirred for 3h at reflux temperature. The reaction mixture was diluted with $CHCl_3$ (30 mL), washed successively with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, water and then with saturated brine. The organic layer was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate:hexane (15:85) as the eluent. The product **4a** was obtained as a colourless solid (3.02 g, 93%) and crystallized from ethyl acetate-hexane mixture; m p. 179-180°C.

IR (CH_2Cl_2 film) : 3450, 2958, 1735, 1718, 1435 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 7.90 (m, 2H, Ar-H), 7.5 (m, 3H, Ar-H), 3.8 (m, 2H, OCH), 3.6 (s, 3H, OCH_3), 2.9 (m, 6H, $COCH_2$), 1.8-1.2 (m, steroidal CH_2 and CH), 0.86 (s, 3H, CH_3)

^{13}C NMR (50.2 MHz, $CDCl_3$) : δ 180.5, 176.0, 174.2, 134.1, 129.0, 128.2, 116.5, 75.2, 73.0, 52.0, 49.1, 47.0, 42.2, 36.0, 32.2, 29.0, 28.1, 24.1, 18.2, 14.0.

Anal. calcd. for $C_{35}H_{50}O_6$: C, 74.16; H, 8.90

Found : C, 74.13; H, 8.87

Hydroxy ester 5a

$ZnCl_2$ (0.41 g, 3 mmol) was added to a solution of the ketoester **4a** (1.13 g, 2 mmol) in THF (20 mL) and the mixture was cooled to -5°C with stirring. After 15 min. $NaBH_4$ (0.227 g, 6 mmol) was added and stirred for 10 min. Excess $NaBH_4$ was quenched with dil. HCl and the product was extracted into ethyl acetate (4x20 mL) after diluting the reaction mixture with water. The organic layer was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. Purification of the product by column chromatography on silica gel using 25% ethyl acetate in hexane as the eluent afforded **5a** as a colourless solid (1.07 g, 93 %) and this was crystallized from ethyl acetate-hexane mixture; m p. 181-182°C.

IR (CH_2Cl_2 film) : 3460, 2960, 1740, 1430 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 7.3 (s, 5H, Ar-H), 3.95 (m, 3H, OCH), 3.65 (s, 3H, OCH_3), 2.5 (m, 4H, COCH), 1.9 (brs, 2H, OH), 1.85-1.0 (m, steroidal CH and CH_2), 0.85 (s, 3H, CH_3)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 171.5, 170.0, 127.0, 126.2, 76.9, 53.2, 46.2, 36.0, 34.7, 30.7, 30.6, 28.4, 26.0, 23.6, 22.2, 20.0, 14.

EIMS (*m/z*) : 568 (M^+, 20), 549 (60), 371 (100)

Benzoylbutyrate of methyl deoxycholate 4b

A solution of methyl deoxycholate (2.03 g, 5 mmol) in dry $CHCl_3$ (30 mL) was treated with pyridine (0.70 mL, 7.5 mmol). To this solution benzoylbutyryl chloride (1.25 g, 6.5 mmol) dissolved in $CHCl_3$ (15 mL) was added dropwise and the mixture was stirred at reflux temperature for 3h. Work up by the same procedure described for compound **4a** followed by purification of the product on a silica column using 15% ethyl acetate in hexane as the eluent afforded **4b** (2.09 g, 71%) as a colourless solid. Crystallization from ethyl acetate-hexane afforded the product as colourless crystals; m p. 183-184°C.

IR (KBr)	: 3450, 2958, 1735, 1718 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$)	: δ 7.9-7.8 (m, 2H, Ar-H), 7.51 (m, 3H, Ar-H), 3.80 (m, 2H, OCH), 3.60 (s, 3H, OCH_3), 2.6 (m, 6H), 1.85-1.2 (m, steroidal CH_2 and CH), 0.89 (s, 3H)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 182.1, 175.0, 135.0, 129.0, 128.1, 75.0, 52.0, 49.0, 48.5, 46.2, 39.5, 38.0, 37.0, 36.0, 34.5, 30.0, 29.1, 27.0, 26.0, 24.0, 23.0, 22.0, 19.0, 14.5.
Anal. calcd. for $C_{36}H_{52}O_6$	: C, 74.45; H, 9.02
Found	: C, 74.64; H, 9.21

Hydroxy ester 5b

$ZnCl_2$ (0.409 g, 3 mmol) was added to a solution of the ketoester **4b** (1.16 g, 2 mmol) in THF (20 mL) and the mixture was cooled to -5°C with stirring. After 15 min. $NaBH_4$ (0.227 g, 6 mmol) was added and this was stirred for 10 min. The reaction mixture was processed according to the procedure described

for compound 5a. Purification by column chromatography on silica gel using 25% EtOAc in hexane afforded the product 5b (1.15 g, 98%) as a colourless powder.

IR (KBr) : 3460, 2955, 1740, 1429 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 7.25 (s, 5H, Ar-H), 3.95 (m, 3H, OCH), 3.65 (s, 3H, OCH_3), 2.3 (m, 4H), 2.0 (brs, 2H, OH), 1.86-1.21 (m, steroidal CH_2 and CH), 0.87 (s, 3H, CH_3).

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 170.0, 133.5, 127.1, 126.2, 77.0, 53.0, 46.0, 36.2, 34.6, 30.7, 28.5, 26.1, 23.2, 22.6, 20.0, 19.1, 14.5.

EIMS (*m/z*) : 582 (M^+, 4), 562 (35), 388 (100).

Benzoylpropionate of methyl cholate 4c

Methyl cholate (3.0 g, 7.1 mmol) in dry $CHCl_3$ (30 mL) was treated with pyridine (0.9 mL, 11.07 mmol). Benzoylpropionyl chloride (1.69 g, 8.86 mmol) was added and the mixture stirred at reflux temperature for 3h. The reaction mixture was worked up as described for compound **4a**. Chromatographic purification of the product on silica gel using ethyl acetate:hexane (20:80) as the eluent afforded 4c as a colourless solid (2.85 g, 69%). On crystallization from ethyl acetate-hexane mixture colourless crystals of 4c was obtained; m p. 187-188°C.

IR (KBr) : 3490, 2958, 1730, 1720, 1425, 1172 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.8 (m, 2H, Ar-H), 7.5 (m, 3H, Ar-H), 3.85 (m, 3H, OCH), 3.6 (s, 3H), 2.75

(m, 4H, COCH), 2.0-1.5 (m, steroidal CH_2 and CH), 0.85 (s, 3H, CH_3)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 180.0, 175.5, 172.0, 135.2, 129.0, 128.5, 75.0, 52.0, 48.0, 45.4, 39.5, 38.0, 34.5, 30.0, 29.0, 26.2, 24.3, 23.2, 20.1, 19.0, 14.0.

Anal calcd. for $C_{35}H_{50}O_7$: C, 72.12; H, 8.65

Found : C, 72.18; H, 8.59

Hydroxy ester 5c

$ZnCl_2$ (0.409 g, 3 mmol) was added to a solution of the ketoester **4c** (1.164 g, 2 mmol) in THF (20 mL) and the mixture was cooled to -5°C with stirring for 15 min. followed by the addition of $NaBH_4$ (0.227 g, 6 mmol). The reaction mixture was stirred at -5°C for 10 min. and work up by the usual procedure followed by silica gel column chromatography using 30% ethyl acetate in hexane as the eluent afforded **5c** as a colourless powder (1.05 g, 90%)

IR (KBr) : 3480, 2960, 1725, 1460 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.5 (m, 5H), 3.75 (m, 4H, OCH), 3.65 (s, 3H, OCH_3), 2.6 (m, 2H), 2.0-1.0 (m, steroidal CH and CH_2), 0.85 (s, 3H, CH_3)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 179.0, 175.0, 174.5, 135.2, 128.3, 75.1, 51.5, 48.2, 46.0, 20.0, 14.5, 14.0.

EIMS (*m/z*) : 584 (M^+, 15), 567 (60), 255 (100)

Benzoylbutyrate of methyl cholate 4d

To a solution of methyl cholate (3.0 g, 7.1 mmol) in dry $CHCl_3$ (30 mL), pyridine (0.9 mL, 11.07 mmol) was added. Benzoylbutyryl chloride (1.74 g, 8.52 mmol) dissolved in dry $CHCl_3$ (20 mL) was added to the above solution and stirred for 3h. The reaction mixture was processed as detailed for compound **4b**. Product was purified by silica gel column chromatography using 20% EtOAc in hexane as the eluent. Compound **4d** was obtained as a colourless solid (2.83 g, 67%) and was crystallized from ethyl acetate-hexane mixture to afford colourless crystals of **4d**; m p. 188-189°C.

IR (KBr)	: 3450, 1732, 1720, 1455 cm^{-1}.
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.75 (m, 2H, Ar-H), 7.25 (m, 3H, Ar-H), 3.75 (m, 2H, OCH), 3.65 (s, 3H, OCH_3), 2.7 (m, 6H), 1.8-1.25 (m, steroidal CH and CH_2), 0.85 (s, 3H, CH_3)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 186.0, 178.2, 172.2, 135.5, 128.2, 75.6, 52.4, 49.1, 46.2, 42.5, 39.5, 38.0, 37.0, 36.2, 34.5, 30.5, 28.5, 27.0, 24.5, 22.0, 20.0, 19.0, 14.0.
EIMS (*m/z*)	: 597 (M^+, 5), 579 (60), 388 (100)

Hydroxy ester 5d

$ZnCl_2$ (0.409 g, 3 mmol) was added to a solution of compound **4d** (1.192 g, 2 mmol) in THF (20 mL) and the mixture was cooled to -5°C with stirring. After 15 min. $NaBH_4$ (0.227 g, 6 mmol) was added and the mixture stirred for 10 min. The reaction mixture was worked up as described for compound **5a** and purified by eluting with 30% ethyl acetate in hexane from a silica gel

column. The product **5d** was obtained (1.15 g, 96%) as a colourless solid which on crystallization from ethyl acetate-hexane mixture afforded colourless crystals; m p. 189-190°C.

IR (KBr)	: 3460, 1745, 1455, 1179 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: *δ 7.5 (m, 5H, Ar-H), 3.90 (m, 3H, OCH), 3.6 (s, 3H, OCH_3), 2.2 (m, 4H), 1.7-1.0 (m, steroidal CH and CH_2), 0.86 (s, 3H, CH_3)*
EIMS (*m/z*)	: 598 (M^+, 3), 581 (80), 388 (100)

γ-phenyl-γ-butyrolactone (6a)

Hydroxy ester **5a** (1.136 g, 2 mmol) was dissolved in THF (30 mL), 1M LiOH (10 mL) was added and the solution stirred for 5h at room temperature. *The* reaction mixture was acidified with 1M HCl and the products were extracted into ethyl acetate. *The organic layer was washed with water and dried over* anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the *product purified by silica gel column chromatography using* 10% EtOAc in hexane as the eluent. Compound **6a** was obtained as a colourless viscous liquid *(0.26 g, 81%);* $[\alpha]^{26}_D$ +16°, (c = 1%, $CHCl_3$); lit.[19b] $[\alpha]^{25}_D$ +32.5°, (c = 4.3%, $CHCl_3$)

δ-phenyl-δ-valerolactone (6b)

Hydroxy ester **5b** (1.16 g, 2 mmol) was dissolved in THF (25 mL). To this solution 1M LiOH (10 mL) was added and *stirred for 4h at room temperature.* The reaction mixture was acidified with 1M HCl and the product extracted with

ethyl acetate (4x20 mL). The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by silica gel column chromatography using 10% EtOAc in hexane as the eluent afforded **6b** as a colourless viscous liquid (0.28 g, 80%); $[\alpha]^{26}_D$ +16°, (c = 1%, $CHCl_3$); lit.[19d] $[\alpha]^{26}_D$ +52°, (c = 1%, $CHCl_3$)

Benzoylformate of methyl deoxycholate 7a

Methyl deoxycholate (2.03 g, 5 mmol) in dry $CHCl_3$ (30 mL) was treated with pyridine (0.7 mL, 7.5 mmol). To this solution benzoylformyl chloride (1.01 g, 6 mmol) dissolved in $CHCl_3$ (15 mL) was added and the mixture was stirred at room temperature for 5h. The reaction mixture was worked up by the usual procedure and the product purified by silica gel column chromatography. Elution with 15% EtOAc in hexane afforded **7a** as a colourless solid (2.04 g, 76%).

IR (CH_2Cl_2 film)	: 3460, 2956, 1735, 1718 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.85 (m, 2H), 7.5 (m, 3H), 3.7 (m, 2H, OCH), 3.65 (s, 3H), 1.8-1.0 (m, steroidal CH and CH_2), 0.8 (s, 3H, CH_3)
^{13} C NMR (22.4 MHz, $CDCl_3$)	: δ 178.0, 175.2, 172.1, 135.5, 129.2, 128.5, 75.5, 29.0, 28.2, 27.3, 24.0, 14.0.
EIMS (*m/z*)	: 538 (M^+, 20), 520 (60), 388 (100)

Hydroxy ester 8a

$ZnCl_2$ (0.409 g, 3 mmol) was added to a solution of the ketoester **7a** (1.07 g, 2 mmol) in THF (20 mL) and the mixture was cooled to -5°C with stirring. After 15 min $NaBH_4$ (0.227 g, 6 mmol) was added to the above reaction

mixture and stirred for 10 min. Work up by the usual procedure followed by silica gel column chromatography using 20% EtOAc in hexane as the eluent afforded the product **8a** as a colourless powder (0.96 g, 89%).

IR (KBr)	: 3480, 2960, 1726, 1439 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.4 (m, 5H, Ar-H), 3.7 (m, 3H, OCH), 3.6 (s, 3H, OCH_3), 2.1 (brs, 2H, OH), 1.75-1.0 (m, steroidal CH and CH_2), 0.86 (s, 3H, CH_3).

Mandelic acid 9

Hydroxy ester **8a** (1.08 g, 2 mmol) in THF (20 mL) was stirred with 1M LiOH (8 mL) for 3h. The reaction mixture was acidified with dil. HCl and the solution saturated with NaCl. The product was extracted into EtOAc (5x15 mL) and purified by silica gel column chromatography. Elution with 30% EtOAC in hexane afforded **9** as a colourless solid (0.182 g, 60%): $[\alpha]_D^{26}$ -2°, (c = 1%, MeOH); lit[20]. $[\alpha]_D^{26}$ -153° (c = 2.5, H_2O).

IR (KBr)	: 3480, 3050, 1752 cm^{-1}
^1H NMR (90 MHz, DMSO d_6)	: δ 9.2 (s, 1H, COOH), 7.6 (s, 5H), 4.1 (s, 1H), 2.2 (brs, 1H, OH)

2.4 References

1. Oppolzer, W. *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M.; Fleming, I., Ed.; Pergamon Press: Oxford, 1991, vol. 5, p.363.
2. Amino acid based chiral dienophiles: (a) Evans, D. A.; Chapman, K. T.; Bishaha, J. *Tetrahedron Lett.* **1984**, *25*, 4071. (b) Evans, D. A.; Chapman, K. T.; Bishaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. c) Bueno, M. P.; Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Charro, P.; Roy, M. A.; Andres, J. M. *Can. J. Chem.* **1988**, *66*, 2626. (d) Bueno, M. P.; Cativiela, C.; Mayoral, J. A. *J. Org. Chem.* **1991**, *56*, 6551. (e) Waldmann, H.; Braun, M. *Gazz. Chim. Ital.* **1991**, *121*, 277. (f) Waldmann, H. *Kontakte* (Darmstadt) **1993**, *1*, 58.
3. Terpene derived dienophiles: (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 477. (b) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (c) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta.* **1985**, *68*, 2100. (d) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3026. (d) Palomo, C.; Berree, F.; Linden, A.; Villalgordo, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1861.
4. (a) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhauptand, M.; Moffatt, F. *Helv. Chim. Acta.* **1981**, *64*, 2802. (b) Huang, D. -L.; Draper, R. W. *Tetrahedron Lett.* **1994**, *35*, 661.
5. Baker, J. F.; Bliekenstaff, R. T. *J. Org. Chem.* **1975**, *40*, 1579.
6. Maitra, U.; Bag, B. G. *J. Org. Chem.* **1992**, *57*, 6979.
7. Maitra, U.; Bandyopadhyay, K. B. *Tetrahedron Lett.* **1995**, *36*, 3749.
8. Maitra, U.; Mathivanan, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1469.

9. Maitra, U.; Mathivanan, P. *Tetrahedron Asymm.* **1994**, *5*, 1171.

10. Mori, K. In *Techniques in Pheromone Research*; Hummel, H.; Miller, T., Eds.; Springer Verlag: New York, 1984, Chapter 12.

11. Ino, Y.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1972**, *36*, 2505.

12. (a) Ohloff, G. In *Progress in Organic Chemistry*; Springer Verlag: Wien, 1978; Vol. 35. (b) May, W. A.; Peterson, R. J.; Chang, S. S. *J. Food Sci.* **1978**, *43*, 1248. (c) Kingston, B. H. *Pafai, J.* **1983**, *5*, 11.

13. Silverstein, R. M. In *Semiochemistry, Flavours and Pheromones;* Proceedings ACS Symposium; Acree, T. E., Ed.; W. de Gruyter and Co.; Berlin, 1985; pp 121-140.

14. Tumlinson, J. M.; Klein, M. G.; Dolittle, R. E.; Ladd, T. L.; Proveaux, A. T. *Science* **1977**, *197*, 789.

15. (a) Suzuki, Y.; Mori, W.; Ishizone, H.; Naito, K.; Honda, T. *Tetrahedron Lett.* **1992**, *33*, 4931. (b) Yoda, H.; Shrakawa, K.; Takabe, K. *Chem Lett.* **1991**, 489. (c) Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 3401. (d) Ortuno, R. M.; Merce, R.; Font, J. *Tetrahedron* **1987**, *43*, 2191. (e) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.

16. (a) Robin, S.; Huet, F. *Tetrahedron Lett.* **1993**, *34*, 2945. (b) Aquino, M.; Cardani, S.; Fronza, G.; Fuganti, C.; Fernandez, R. P.; Tagliani, A. *Tetrahedron* **1991**, *47*, 7887. (c) Gopalan, A.; Lucero, R.; Jacobs, H.; Berryman, K. *Synth. Commun.* **1991**, *21*, 1321.

17. (a) Jacobs, H. K.; Muller, B. H.; Gopalan, A. S. *Tetrahedron* **1992**, *48*, 8891. (b) Sibi, M. P.; Gaboury, J. A. *Tetrahedron Lett.* **1992**, *33*, 5681. (c) Sugai, T.; Ohsawa, S.; Yamada, H.; Ohta, H. *Synthesis* **1990**, 1112.

18. (a) Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *48*, 8891. (b) Tamai, Y.; Akiyama, M.; Okamura, A.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 687. (c) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1992**, 728. (d) Keinan, E.; Sinha, S. C.; Bagchi, A.; Wang, Z.; Zhang, X.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6411.

19. (a) Gutman, A. I.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (c) Izumi,T.; Tamura, F.; Akutsu, M. J. *J. Heterocyclic Chem.* **1994**, *31*, 441. (d) Armstrong, D. W.; Stalcup, A. M.; Hilton, M. L.; Duncan, J. D.; Faulkner, J. R. Jr.; Chang, S.-C. *Anal. Chem.* **1990**, *62*, 1610.

20. (a) Weast, R. C., Ed. *CRC Handbook of Chemistry and Physics*, 70th ed.; CRC Press: Boca Raton, FL, 1989-1990. (b) Schwab, G. M.; Baumann, E.; Laevernz, P. *J. Physiol. Chem.* **1933**, *215*, 121.

CHAPTER 3

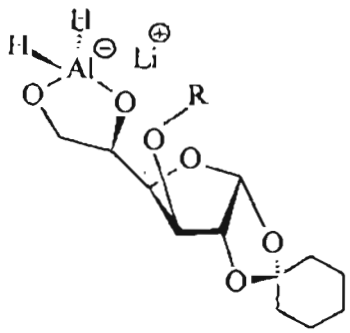
ASYMMETRIC SYNTHESIS USING NOVEL CHIRAL AUXILIARIES DERIVED FROM D-GLUCOSE

3.1 Introduction

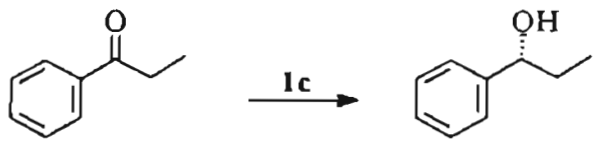
Our investigations using deoxycholic acid and cholic acid as chiral auxiliaries have been discussed in the previous chapter. The chiral induction obtained with these auxiliaries has been modest and therefore we decided to explore the use of carbohydrates as auxiliaries.

Carbohydrates are inexpensive and readily available natural products, endowed with many chiral centres and functional groups. In spite of their availability in optically pure form, they were not used as chiral auxiliaries for a long time. Carbohydrates were considered too complex and it was believed that the chiral information they contain could not be exploited in an organized manner. Later it was recognized that the carbohydrate components of glycoconjugates play a decisive role in biological recognition[1]. For example, selective interaction of carbohydrates with receptors regulate the uptake of serum proteins into cells[2]; they are also involved in immunological processes[3]. These interesting findings made researchers aware that carbohydrates contain considerable amount of regio- and stereochemical information, which can be utilized for the synthesis of chiral products. Since then, carbohydrates have found some use as chiral auxiliaries in stereoselective reactions[4]. The early experiments of Landor[5] are representative of the many reactions in which carbohydrate derivatives provide stereodifferentiation. Lithium alkoxy

aluminium hydrides **1a-1c** prepared from LAH and D-glucose derivatives were employed for the stereoselective reduction of propiophenone to 1-phenyl propanol.

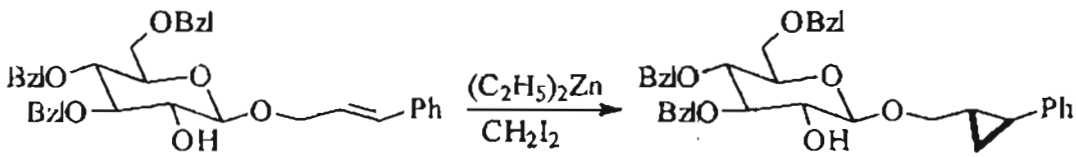


1a R = CH_3
1b R = C_2H_5
1c R = CH_2Ph



(R):(S) = 21:79

Individual examples of the use of carbohydrates as chiral auxiliaries involve aldol condensations[6], Diels-Alder reactions[7,8], [2+2] cycloaddition[9-11], cyclopropanation[12] and Michael addition reactions[13,14]. The most impressive among these is the cyclopropanation[12] by the addition of carbenoids to alkenes using a glucose derivative as the chiral auxiliary (scheme-1).

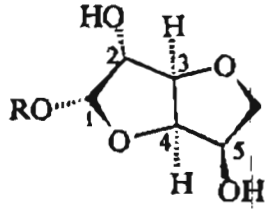


Scheme-1

Excellent diastereoselectivities (*ca.* 100:1) were observed and the products were obtained in high yields.

The literature survey presented above clearly indicates that, although potentially useful, carbohydrates have found only marginal application as chiral auxiliaries. Therefore, it was of interest to undertake some investigations in

this area. We focussed our attention on anhydrosugars readily available from monosaccharides[15]. The anhydrofuranosides **2a** and **2b** appeared particularly attractive and our investigations using **2a** and **2b** as chiral auxiliaries are described in this chapter.



2a R = CH_3
2b R = CH_2Ph

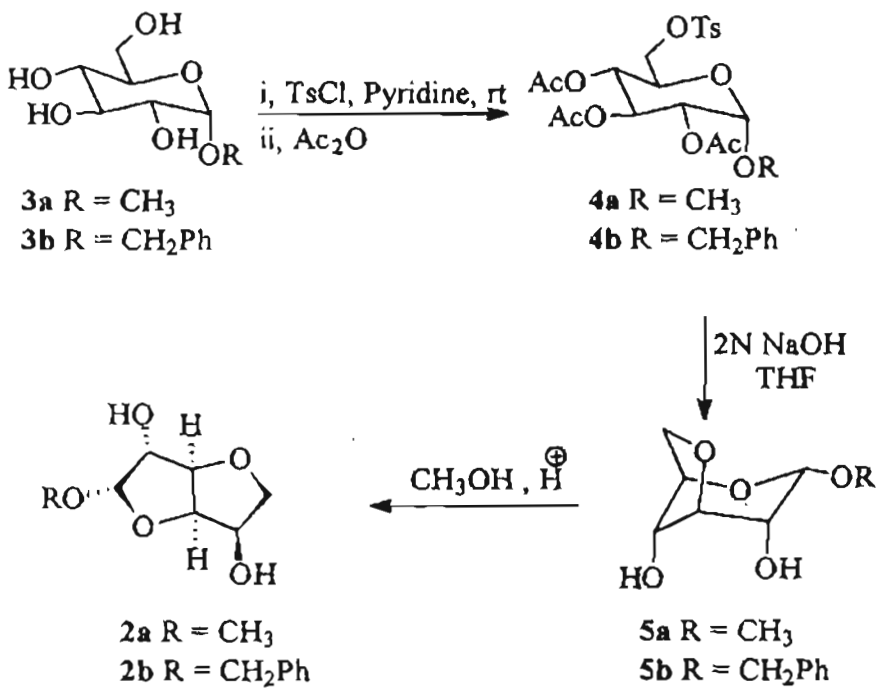
The salient features of these auxiliaries include the presence of a concave and convex face to provide selectivity for attack by the reagent. **2a** and **2b** have five chiral centres, including the two bearing hydroxyl groups that are distinguishable in their reactivitiy. The two *cis* fused five membered rings of **2a** as well as **2b** form a wedge shaped geometry. Since the C-5 hydroxyl is projecting towards the wedge (β) and is hydrogen bonded with the ring oxygen atom, it is less reactive than the α-oriented C-2 hydroxyl group. Prochiral groups can be tethered to the C-2 hydroxyl, preferentially, because it is more reactive than the C-5 hydroxyl group.

Section 3.2.1 of this chapter describes the synthesis of **2a** and **2b**, while 3.2.2 deals with their use as chiral auxiliaries in the synthesis of optically active lactones, and mandelic acid. Their use as chiral auxiliaries in asymmetric Diels-Alder reaction is described in section 3.2.3.

3.2 Results and Discussion

3.2.1 Synthesis of 1-*O*-Methyl-3,6-anhydro-α-D-glucofuranoside (2a) and 1-*O*-Benzyl-3,6-anhydro-α-D-glucofuranoside (2b)

The anhydrofuranosides **2a** and **2b** were synthesized from D-glucose in four steps (scheme-2).



Scheme-2

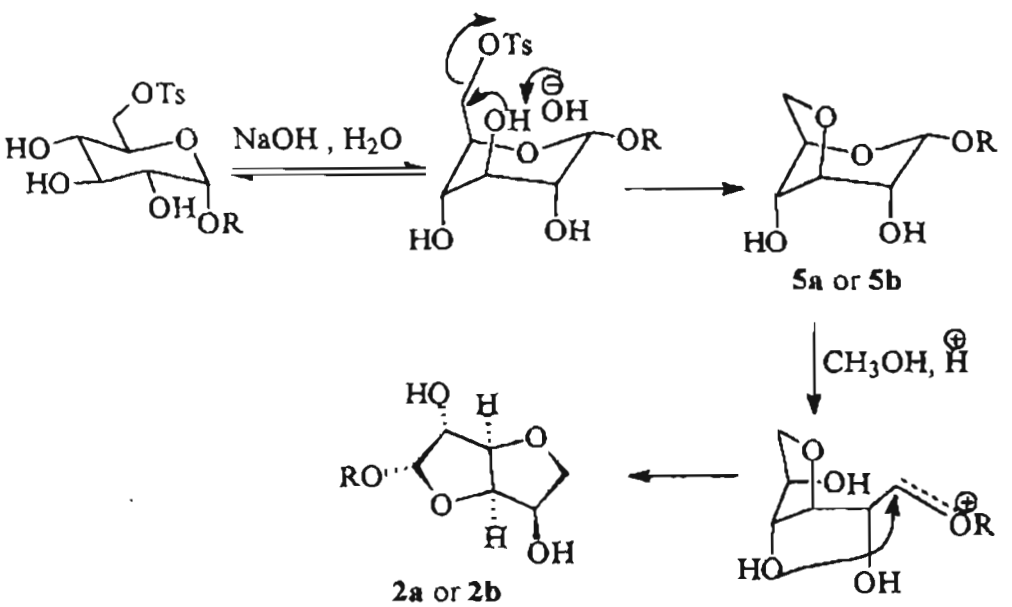
Methyl α-D-glucopyranoside **3a** was synthesized from D-glucose by heating it in methanol with the resin Amberlite IR-120 (H^+). Tosylation of **3a** using tosylchloride in presence of pyridine resulted in the formation of 1-*O*-methyl-6-*O*-tosyl-α-D-glucopyranoside. To facilitate the isolation of this product it was necessary to convert it to the acetate. This was accomplished by the addition of acetic anhydride to the reaction mixture. 1-*O*-methyl-6-*O*-tosyl-3,4,5-tri-*O*-acetyl-α-D-glucopyranoside (**4a**) was isolated in 67% yield.

Deacetylation of **4a** using 2N NaOH resulted in the formation of methyl-3,6-anhydro-α-D-glucopyranoside[17] **5a**. The anhydropyranoside ring system is highly strained and therefore it smoothly rearranges to the more stable furanoside **2a** under acidic conditions. In an analogous manner, benzyl α-D-glucopyranoside **3b** was also converted to the benzyl anhydrofuranoside **2b** *via* the 1-*O*-benzyl-6-*O*-tosyl-3,4,5-tri-*O*-acetyl-α-D-glucopyranoside (**4b**) and the 3,6-anhydro benzyl α-D-glucopyranoside **5b**.

The identity of **3a** was established by comparing its physical constants like melting point and optical rotation to those reported in the literature[16]. For compound **4a** the IR spectrum showed absorbances at 1765 and 1740 cm^{-1}, suggesting the presence of >C=O groups. The aromatic protons resonated as doublets at δ 7.9-7.6 (2H) and at δ 7.4-7.1 (2H) in the ^1H NMR spectrum. The anomeric proton appeared as a doublet at δ 4.8 and the OCH_3 protons resonated as a singlet at δ 3.4. The nine $COCH_3$ protons were visible at δ 2.0 and the Ar-CH_3 protons at δ 1.8. The ^{13}C NMR spectrum exhibited signals at δ 169.9 and 169.3 for the >C=O groups. Signals at δ 132.3, 129.7 and 127.8 were attributed to the aromatic carbons, whereas those at δ 101.2, 78.4 and 68.5 were assigned for the OCH carbons. The 3,6-anhydrofuranoside **2a** yielded satisfactory spectral and analytical data and its physical constants were also comparable with the literature values[18].

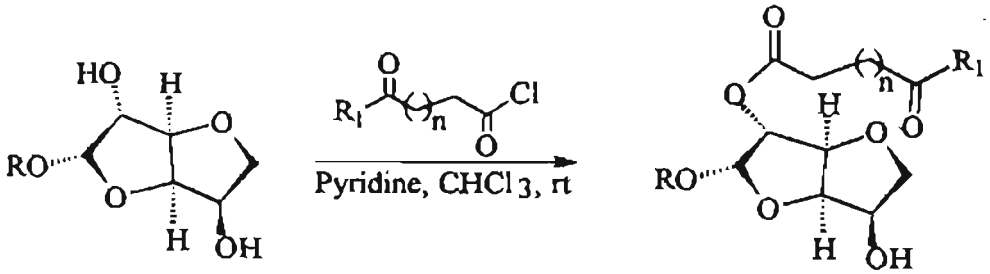
Similarly, compounds **3b**, **4b** and **2b** were characterized spectroscopically. Compound **4b** showed doublets centred at δ 7.65 (2H) and 7.45 (2H) and a multiplet at δ 7.3–7.2 (5H) corresponding the aromatic protons in the ^1H NMR spectrum, in addition to the peaks for the other characteristic protons. The anhydrofuranoside **2b** displayed absorbances at 3510 and 1430 cm^{-1} supporting the presence of a hydroxyl group and C-O bonds in the molecule. Its ^1H NMR spectrum with a singlet at δ 7.25 integrating for five

protons showed the existence of the aromatic moiety. Peaks at δ 4.9 and δ 3.7-3.5 indicated the presence of OCH protons. A broad singlet at δ 2.0 (2H) that disappeared on D_2O exchange proved the presence of the -OH protons. It is noteworthy that the procedure described in scheme-2 is considerably shorter than the literature procedure, which involves eight steps[18]. The following mechanism[19] is suggested for the transformations in scheme-2.



3.2.2 Synthesis of optically active lactones using 2a and 2b as chiral auxiliaries

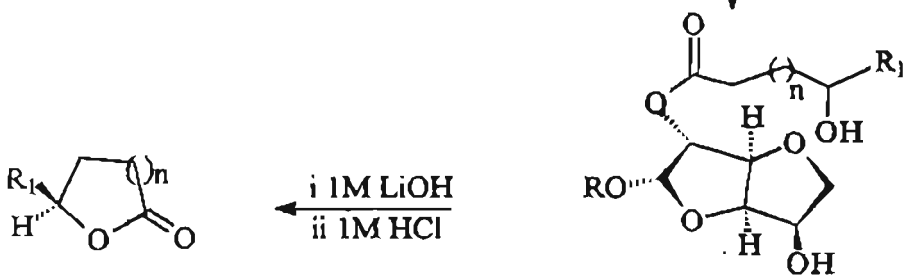
The special structural features of **2a** and **2b** described in section 3.1 render them ideal candidates for use as chiral auxiliaries in asymmetric transformations. Our initial plan for the synthesis of lactones in optically active form envisaged the reduction of prochiral ketones attached to the C-2 hydroxyl group of **2a** and **2b** followed by the removal of the auxiliary (scheme-3).



2a R = CH_3
2b R = CH_2Ph

6a R = CH_3, R_1 = C_6H_5, n = 1
6b R = CH_3, R_1 = C_6H_5, n = 2
6c R = CH_2Ph, R_1 = C_6H_5, n = 1
6d R = CH_2Ph, R_1 = C_6H_5, n = 2
6e R = CH_2Ph, R_1 = CH_3, n = 1
6f R = CH_2Ph, R_1 = CH_3, n = 2

Reduction*



8a n = 1, R_1 = Ph
8b n = 2 R_1 = Ph
8c n = 1 R_1 = CH_3
8d n = 2 R_1 = CH_3

7a R = CH_3, R_1 = C_6H_5, n = 1
7b R = CH_3, R_1 = C_6H_5, n = 2
7c R = CH_2Ph, R_1 = C_6H_5, n = 1
7d R = CH_2Ph, R_1 = C_6H_5, n = 2
7e R = CH_2Ph, R_1 = CH_3, n = 1
7f R = CH_2Ph, R_1 = CH_3, n = 2

*For conditions see Table 1

Scheme-3

The ketoester **6a** was obtained by the reaction of anhydrofuranoside **2a** with benzoylpropionyl chloride in chloroform in presence of pyridine. Benzoyl group of **6a** was reduced under different conditions to obtain the hydroxy ester **7a** and the chiral auxiliary was removed by saponification using 1M LiOH.

Acidification of the reaction mixture afforded the optically active lactone **8a** (*ee*~73%) in 83% yield. Ketoesters **6b-6f** were subjected to the above mentioned operations to afford the corresponding lactones *via* the hydroxy esters **7b-7f**. In all these cases the lactones were obtained in optically active form with *ee* values ranging from 30-93%. The auxiliaries were recovered almost quantitatively.

All the compounds presented in scheme-3 were characterized spectroscopically. The IR spectrum of **6a** showed absorbance at 3510 cm^{-1} indicating the existence of a hydroxyl group. Absorbances at 1740 and 1732 cm^{-1} confirm the presence of the carbonyl groups. The ^1H NMR displayed multiplets centred at δ 7.9 which integrated for 2 protons, and at δ 7.5 for 3 protons indicating the presence of benzoyl group in the molecule. Proton at C-1 appeared as a doublet at δ 4.86. Signals at δ 3.85-3.5 were due to the various -OCH protons and the signal at δ 3.4 was assigned for the $-OCH_3$ while the $COCH_2$ protons resonated at δ 2.9 (4H). In the ^{13}C NMR spectrum, the signals at δ 192.0 and 178.5 were attributed to the carbonyls and those at δ 135.1 and 127.0 were assigned for the aromatic carbon atoms. The -OCH carbon signals were visible at δ 88.2, 82.2 and 75.9. Similarly ketoester **6b** also gave spectral data consistent with its structure. Compound **6c** displayed absorbances at 3520, 1740 and 1735 cm^{-1} in the IR spectrum indicating the existence of hydroxyl group and carbonyl groups in the molecule. ^1H NMR spectrum showed multiplets for the aromatic protons centred at δ 7.75 and δ 7.5 which integrated for two and eight protons respectively. Its EIMS displayed the M^+ peak at *m/z* 412 supporting the assigned structure. Similarly compounds **6d**, **6e** and **6f** were also characterized by their spectral data.

Hydroxy ester **7a** showed strong absorbance in the IR spectrum at 3450 cm^{-1} supporting the presence of OH group and the absorbance at

1745 cm^{-1} is attributed to the ester carbonyl. Its ^1H NMR spectrum exhibited a broad singlet at δ 7.3 which integrated for five protons indicating the presence of the phenyl group. Also the existence of signals at δ 4.8 and 3.5-3.2 proved the presence of various -OCH protons in the molecule. Appearence of the molecular ion at *m/z* 338 confirmed the assigned structure. In a similar manner the structure of the hydroxy esters **7b, 7c, 7d** and **7f** were assigned with the help of their ^1H and ^{13}C NMR and mass spectral data. The analytical and spectral data of the lactones **8a-8d** were in agreement with the literature values[20].

Experimental conditions for the reduction of the ketoesters and the *ee* values obtained for the lactones are shown in Table 1.

Table 1

Entry	Ketoester	Reduction conditions	Lactone	*ee** (%)	Yield (%)**
1	**6a**	$ZnCl_2$, $NaBH_4$, -5°C	**8a**(R)	72	83
2	**6b**	"	**8b**(R)	31	79
3	**6a**	$ZnCl_2$, $NaBH_4$, -78°C	**8a**(R)	73	80
4	**6b**	"	**8b**(R)	30	76
5	**6c**	$ZnCl_2$, $NaBH_4$, -5°C	**8a**(R)	91	82
6	**6d**	"	**8b**(R)	56	77
7	**6c**	$ZnCl_2$, $NaBH_4$, -78°C	**8a**(R)	93	81
8	**6d**	"	**8b**(R)	53	75
9	**6e**	$ZnCl_2$, $NaBH_4$, -5°C	**8c**(S)	82	80
10	**6f**	"	**8d**(S)	48	76

* *ee* values were obtained by comparing optical rotations with those reported in the literature. **Isolated yield.

It is clear from the results that the *ee* values are maximum when **2b** was used as the auxiliary. Surprisingly, temperature does not have any effect on the extent of chiral induction. γ-Lactones **8a** and **8c** showed higher *ee* values than the δ-lactones **8b** and **8d**. To explain the results obtained, a transition state model such as the following (figure 1) may be suggested.

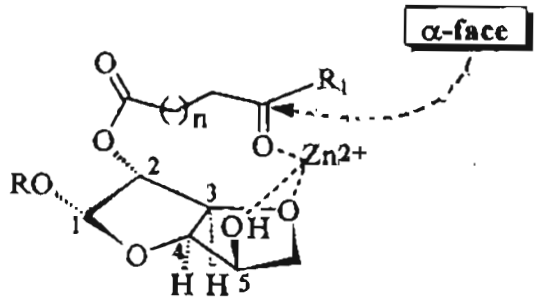


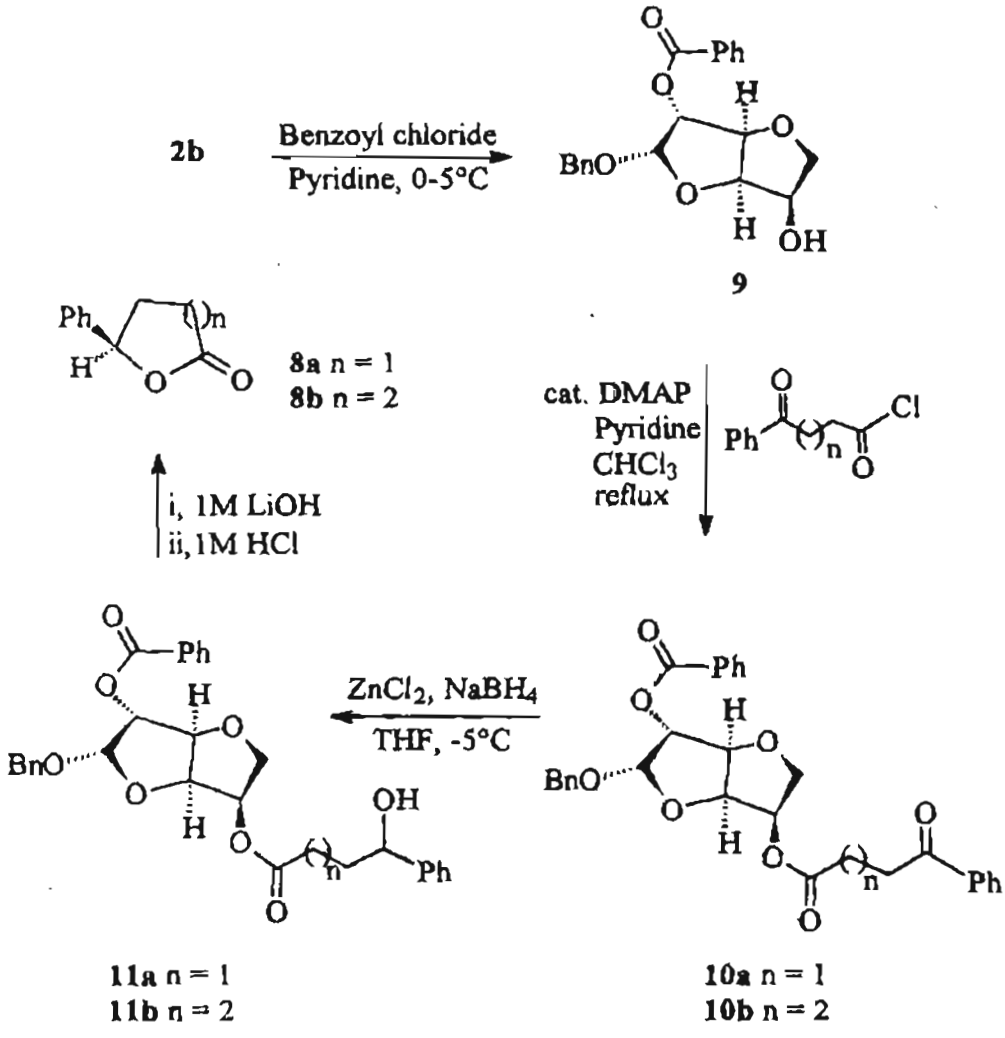
Fig.1

A chelated intermediate with the metal ion, involving the C-5 hydroxyl (β), the prochiral keto group and the ring oxygen, can explain the observed configuration of the product. The role of the -OR group is not clear, but a rationalization along the following lines may be made. To avoid the steric interaction between the substituents at C-1 and C-2, the ketoester moiety (at C-2) is pushed away from the C-1 substituent, enabling it to participate in chelation more efficiently. Between $-OCH_3$ and $-OCH_2Ph$ the latter is sterically more demanding and hence better results are obtained with auxiliary **2b**. It is clear from fig.1 that the β-face of the carbonyl group is shielded by the ring system and the β-hydroxyl group and therefore the reducing species presumably approaches from the α-face more freely. The explanation given above is in accordance with the formation of **8a** and **8b** in *R*-configuration and **8c** and **8d** in *S*-configuration. Thus, both a chelative and a steric effect may be

responsible for the observed results. As the chain length of the ketoester increases, the flexibility of the chelated intermediate also increases and this may account for the lower *ee* values of the valerolactones **8b** and **8d**. The poor *ee* values obtained when $NaBH_4$ alone was used for the reduction provides indirect support for the suggested model. Reduction with $NaBH_4$ in presence of Ce^{3+} ions resulted in the formation of lactones with *ee* values comparable to those obtained when $NaBH_4$ alone was used. Similar was the case when $LiBH_4$ was used as the reducing agent. These results underscore the fact that Zn^{2+} has better chelating ability than the other ions mentioned, thus indirectly suggesting that the stereochemical outcome of the reduction is largely controlled by chelation.

In this context, it was of interest to investigate the extent of chiral induction in the reduction of prochiral ketones tethered to C-5 hydroxyl. With this objective the lactones **8a** and **8b** were synthesized as outlined in scheme-4.

Protection of the C-2 OH of **2b** as the benzoate using benzoyl chloride in presence of pyridine at 0-5°C afforded **9**. The latter was then reacted with benzoylpropionyl chloride using pyridine and catalytic amount of DMAP to obtain **10a** in 65% yield. **10a** on reduction with $NaBH_4$ in presence of $ZnCl_2$ at -5°C led to the hydroxy ester **11a**, which on saponification followed by acidification afforded the lactone **8a** (*R*-configuration) in 75% *ee*. In an analogous manner **11b** was synthesized from **9** using benzoylbutyryl chloride. Reduction of **11b** followed by the removal of the auxiliary afforded the lactone **8b** (*R*-configuration) in 38% *ee*.

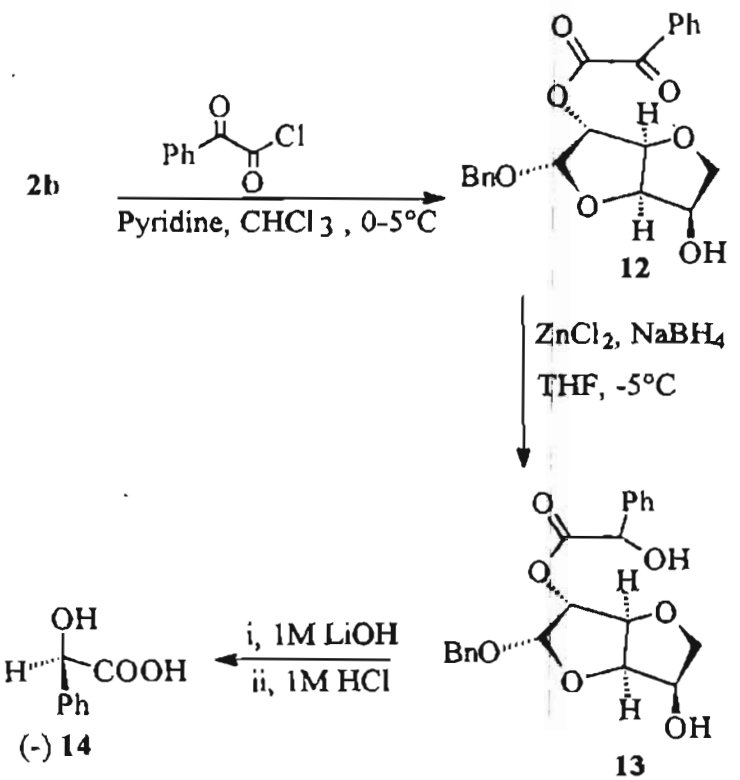


Scheme-4

The IR spectrum of **10a** with absorbances at 1735 and 1720 cm^{-1} revealed the presence of carbonyl groups. Proton NMR spectrum of this compound exhibited multiplets at δ 7.6-7.5 (4H) and at δ 7.4-7.2 (11H) for the aromatic protons. The mass spectrum of **10a** displayed M^+ peak at *m/z* 516. The IR spectrum of **11a** showed a strong band at 3480 cm^{-1} characteristic for hydroxyl group. In the ^1H NMR spectrum, multiplets at δ 7.6 and δ 7.5-7.3 which integrated for 2 and 13 protons respectively confirmed the presence of the benzoyl group and the other aromatic protons in the molecule.

R-configuration of the lactone **8a** obtained by the above sequence may be rationalized as follows. The ketoester moiety attached to the C-5 hydroxyl is inside the wedge formed by the two ring systems. Therefore the β-face of the carbonyl goup is shielded and hence the reducing species can only approach from the α-face. The *ee* value of 75% obtained for **8a** may be due to the shielding effect of the ring system. It may be recalled that under the same reduction conditions ketoester **6c** afforded the lactone **8a** with 91% *ee* (Table 1) which was explained by invoking a steric and chelative effect. In the case of ketoester **10a** the chances for chelation is less compared to **6c** and this may account for the lower *ee* value obtained.

After completing the studies on the synthesis of chiral lactones, we investigated the possibility of using **2b** in the synthesis of optically active mandelic acid and this is outlined in scheme-5.



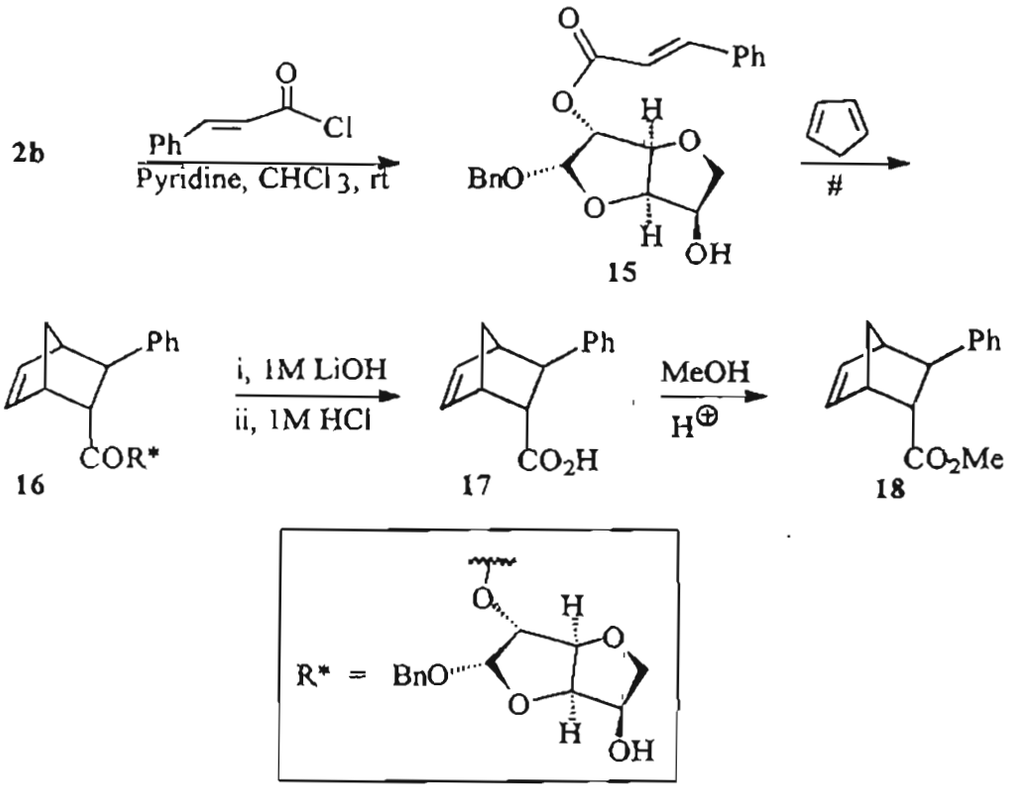
Scheme-5

Benzyl anhydrofuranoside **2b** was converted to the benzoylformate **12** by reacting it with benzoylformyl chloride at 0-5°C using pyridine as the base. The ketoester **12** on reduction with $NaBH_4$ in presence of $ZnCl_2$ at -5°C afforded the hydroxyester **13** which on saponification with 1M LiOH followed by acidification resulted in the formation of (-) mandelic acid **14** (60%) in 32% *ee*. The compounds **12, 13** and **14** were characterized spectroscopically. Ketoester **12** showed absorbances at 3510, 1730 and 1725 cm^{-1} in the IR spectrum for the hydroxyl and the carbonyl groups. Its proton NMR spectrum exhibited multiplets at δ 7.6 (2H) and at δ 7.3-7.1 (8H) for the aromatic protons. The proton at C-1 appeared as a doublet at δ 4.7 and the multiplet at δ 3.8-3.5 for 6 protons suggested the presence of the OCH protons in the molecule. The hydroxy ester **13** and mandelic acid **14** also gave satisfactory spectral data.

3.2.3 Asymmetric Diels-Alder reaction using anhydrofuranoside 2b as chiral auxiliary

The remarkable regioselectivity, generally predictable endoselectivity and syn stereospecificity render the Diels-Alder reaction unequalled in terms of elegance and efficiency in the construction of six membered rings. To achieve absolute stereochemical control in the intermolecular and intramolecular [4+2] cycloaddition processes, new strategies including the use of chiral auxiliaries were developed. Many chiral auxiliaries with varying degrees of success have been reported for Diels-Alder reactions[21-25]. In view of the high *ee* values obtained for the lactones synthesized using **2b** as chiral auxiliary, it was of interest to investigate its usefulness in asymmetric Diels-Alder reactions. With this objective, the Diels-Alder reaction of the cinnamate ester **15** with cyclopentadiene was investigated under different conditions (scheme-6).

The synthesis of the cinnamate **15** was accomplished by treating **2b** with cinnamoyl chloride in presence of pyridine. This on [4+2] cycloaddition with cyclopentadiene afforded the adduct **16**. Saponification of **16** followed by acidification resulted in the formation of **17** and the latter was characterized as its methyl ester **18**.



#For conditions see Table 2

Scheme-6

Cinnamate ester **15** showed absorbances at 3515, 1715 and 1675 cm^{-1} for the hydroxyl and the carbonyl groups in the IR spectrum. The ^1H NMR spectrum of **15** showed a broad singlet at δ 7.3 (10H) for the aromatic protons and a doublet at δ 4.9 which integrated for the two olefinic protons. In addition to this, the characteristic signals for the anhydrofuranoside ring system were

also present in the proton spectrum. ^{13}C NMR of **15** displayed signals at δ 182.0 for the >C=O group, δ 132.0, 129.2 and 126.5 for the aromatic carbons and at δ 98.0, 86.5, 82.0, 80.2 and 75.9 for the various OCH carbon atoms. Adduct **16** showed absorbance at 3510 cm^{-1} for the hydroxyl group and at 1730 cm^{-1} for the carbonyl group in the IR spectrum. The broad singlet at δ 7.4 in the ^{1}H NMR spectrum integrated for the 10 aromatic protons while the doublet at δ 4.3 integrated for the two olefinic protons. The spectral data of **18** was in agreement with those reported in the literature[26]. Experimental conditions for the [4+2] cycloaddition and the results obtained are given in Table 2.

Table 2

Entry	Experimental condition	Yield (%)*	*ee* (%)**
1	no catalyst, rt	59	42
2	$ZnCl_2$, -5°C	55	45
3	$ZnCl_2$, -78°C	49	49

* Isolated yield. ***ee* values were obtained by comparing optical rotations with those reported in the literature.

The adduct **18** was obtained in moderate *ee* values irrespective of the experimental conditions and unlike in the case of carbonyl reduction (section 3.2.2) the influence of Zn^{2+} ion appears to be insignificant.

In conclusion, the anhydrosugars **2a** and **2b** have been found to be very efficient auxiliaries for the asymmetric reduction of prochiral ketones tethered to them. The process has been utilized in a facile synthesis of optically active γ- and δ-lactones. The higher level of chiral induction afforded by **2b** along with its enhanced solubility in organic solvents *vis a vis* **2a** makes it the

auxiliary of choice. It is remarkable that using **2b**, *ee* value of upto 93% was obtained. This is comparable with the results obtained in other chemical[20b] and enzymatic techniques[20a]. It is anticipated that **2b** will be a useful chiral auxiliary in a number of other transformations of synthetic importance.

3.3 Experimental

A general description of the experimental procedure is given in chapter 2 (section 2.3). Amberlite IR-120 H^+ (Sigma) was activated by washing it with dil. HCl followed by drying under vacuum. The acid chlorides were freshly prepared according to the usual procedures. Visualization of t.l.c. spots was done in most cases by spraying methanol:H_2SO_4 (9:1). The experimental procedure for the reduction using $NaBH_4$ in presence of $ZnCl_2$ at -5°C is described in detail. Experimental details for reduction in presence of Ce^{3+} were identical except for the use of $CeCl_3$ instead of $ZnCl_2$; those of the low temperature (-78°C) reduction of the various ketoesters were also similar.

1-O-Methyl-α-D-glucopyranoside (3a)

A mixture of α-D-glucose (10 g, 55.55 mmol) in methanol (30 mL) and 2.5 g of amberlite IR-120 (H^+) was refluxed with vigorous stirring. After 24h the resin was removed by filtration and washed with methanol. The filtrate and washings were combined and concentrated. The glucopyranoside obtained was purified by chromatography on silica gel column using 15% methanol in chloroform as the eluent. **3a** was obtained as a colourless solid (5.71 g, 53%). Crystallization of the product from methanol afforded colourless crystals; m p. 165-166°C, $[\alpha]_D^{26}$ +156° (c = 2, water); lit[16]. m p. 168-169°C, $[\alpha]_D^{25}$ +157° (c = 2, water).

1-O-Methyl-6-O-p-toluenelsulfonyl-3,4,5-tri-O-acetyl-α-D-glucopyranoside (4a)

Methyl α-D-glucopyranoside **3a** (4.85 g, 25 mmol) was dissolved in dry pyridine (20 mL). Tosyl chloride (5.729 g, 30 mmol) was added slowly to the above solution. After stirring for 8h at room temperature, acetic anhydride (8.49 mL, 90 mmol) was added to it, and the stirring continued for 2h. The reaction mixture was dissolved in dichloromethane (100 mL) and successively washed with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, water and then with saturated brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed by distillation. Purification of the resulting product by chromatography on silica gel column using 15% EtOAc in hexane as the eluent afforded **4a** as a colourless solid (6.67 g, 67%). Crystallization from ethyl acetate-hexane mixture afforded colourless crystals; m p.109-110°C.

IR (CH_2Cl_2 film)	: 2950, 2852, 1765, 1740, 1454 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.9-7.6 (d, J = 8 Hz, 2H), 7.4-7.1(d, J = 8 Hz,, 2H), 4.8 (d, 2H, J = 4.1 Hz), 4.4-4.0 (m, 6H), 3.4 (s, 3H, OCH_3), 2.0 (s, 9H, $COCH_3$), 1.8 (s, 3H, $ArCH_3$)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 169.9, 169.3, 169.1, 145.0, 132.3, 129.7, 127.8, 101.2, 78.4, 68.5, 67.6, 56.7, 21.4, 20.4, 20.3.

1-O-Methyl-3,6-anhydro-α-D-glucopyranoside (5a)

A solution of **4a** (9.5 g, 20 mmol) in THF (50 mL) was stirred with 2N NaOH (30 mL) at room temperature for 12h and then at 80°C for 1h. The reaction mixture was concentrated and the product extracted with hot acetone (60 mL). The solvent was evaporated under reduced pressure and the product

crystallized from ethyl acetate (2.464 g, 70%); m p. 89-90°C, $[\alpha]_D^{26}$ +54° (c = 1, methanol); lit[17]. m p. 92-93°C, $[\alpha]_D^{25}$ +56° (c = 1, H_2O).

1-O-Methyl-3,6-anhydro-[α]-D-glucofuranoside (2a)

The anhydropyranoside **5a** (1.76 g, 10 mmol) was dissolved in methanol (10 mL) containing 1N HCl (1 mL) and stirred at room temperature for 4h. Neutralization of the reaction mixture with saturated $NaHCO_3$ followed by removal of the solvent gave a syrupy mixture. The product was purified by crystallization from ethanol to afford colourless crystals of **2a** (1.23 g, 70%); m p. 67-68°C, $[\alpha]_D^{26}$ +168° (c = 0.9, methanol); lit[18]. m p. 70-71°C, $[\alpha]_D^{25}$ +172° (c = 1, H_2O)

1-O-Benzyl-α-D-glucopyranoside (3b)

D-glucose (10 g, 55.55 mmol) in benzyl alcohol (30 mL) was heated at 80°C in presence of 2.5 g of amberlite IR-120 (H^+) for 24h. The reaction mixture was processed as described for compound **3a** and purified by silica gel column chromatography using 25% MeOH in $CHCl_3$. Crystallization of the product from ethanol afforded **3b** as colourless crystals (8 g, 53%); m p. 169-170°C, $[\alpha]_D^{26}$ 198° (c = 1%, water); lit.[16] m p. 172-173°C, $[\alpha]_D^{25}$ 205° (c = 1%, water)

1-O-Benzyl-6-O-p-toluenesulfonyl-3,4,5-tri-O-acetyl-α-D-glucopyranoside (4b)

Benzyl glucopyranoside **3a** (8.10 g, 30 mmol) was dissolved in dry pyridine (30 mL). Tosylchloride (6.86 g, 36 mmol) was added slowly and the mixture was stirred for 8h at room temperature. Acetic anhydride (10.18 mL, 108 mmol) was added to the above mixture and the stirring continued for 2h. The reaction mixture was worked up as described for compound **4a** and the product

was purified by chromatography on silica gel column. Elution with 15% EtOAc in hexane furnished the product **4b** *(11.24 g, 68 %) as a colourless* solid. Crystallization from EtOAc-hexane mixture afforded **4b** as colourless crystals; m p. 112-113°C.

IR (CH_2Cl_2 film)	: 1760, 1745, 1632, 1430 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.7-7.6 (d, J = 8 Hz, 2H, Ar-H), 7.5-7.4 (d, J = 8 Hz, 2H, Ar-H), 7.3-7.2 (m, 5H, Ar-H), 4.7 (d, 2H, J = 4.2 Hz), 4.4-4.0 (m, 8H, OCH), 2.1 (s, 9H, $COCH_3$), 1.9 (s, 3H, $ArCH_3$)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: 170.2, 169.5, 132.7, 127.0, 126.4, 126.0, 101.5, 77.5, 71.2, 70.3, 62.0 20.5.

1-O-Benzyl-3,6-anhydro-α-D-glucopyranoside (5b)

A solution of **4b** (11.04 g, 20 mmol) in THF (60 mL) was treated with 2N NaOH (20 mL) at room temperature for 12h and then at 80°C for 1h. The product was isolated as described for compound **5a** and purified by crystallization from ethyl acetate (3.78 g, 75%), m p. 95-96°C, $[\alpha]_D^{26}$ +62° (c = 1, methanol).

1-O-Benzyl-3,6-anhydro-α-D-glucofuranoside (2b)

Anhydropyranoside **5b** (2.52 g, 10 mmol) was stirred in methanol (15 mL) containing 1N HCl (1 mL) at room temperature. After 5h the reaction mixture was worked up as described for compound **2a** and the product purified by crystallization from ethanol. The compound **2b** was obtained as colourless crystals (1.73 g, 68%); m p. 75-76°C, $[\alpha]_D^{26}$ +135° (c = 1, methanol).

IR (KBr)	: 3510, 2995, 1630, 1430, 1175 cm^{-1}
^{1}HNMR (90 MHz, $CDCl_3$)	: δ 7.25 (s, 5H, Ar-H), 4.9 (brs, 1H), 3.7-3.5 (m, 8H, OCH), 2.0 (s, 2H, OH)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: 127.0, 101.2, 88.2, 75.1, 72.0, 40.5.

1-O-Methyl-3,6-anhydrofuranosyl-2-(2-benzoyl)-propionate (6a)

Benzoylpropionyl chloride (2.34 g, 12 mmol) in $CHCl_3$ (10 mL) was added to a solution of the anhydrofuranoside **2a** (1.76 g, 10 mmol) in $CHCl_3$ (15 mL) containing dry pyridine (0.97 mL, 12 mmol) and the mixture was stirred at room temperature for 3h. The reaction mixture was diluted with $CHCl_3$ (40 mL), washed successively with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, water and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the product by chromatography on silica gel column using 15% EtOAc in hexane afforded **6a** (2.92 g, 87%) as a colourless solid which was crystallized from ethyl acetate-hexane mixture; m p. 77-78°C.

IR (KBr)	: 3510, 1740, 1732, 1629, 1430 cm^{-1}
^{1}H NMR (270 MHz, $CDCl_3$)	: δ 7.9 (m, 2H, Ar-H), 7.5 (m, 3H, Ar-H), 4.86 (d, J = 6.8 Hz, 1H), 3.85-3.50 (m, 6H, OCH), 3.4 (s, 3H, OCH_3), 2.9 (m, 4H, COCH), 2.1 (brs, 1H, OH)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 192.0, 178.5, 135.1, 127.0, 88.2, 82.2, 75.9, 76.3, 71.9, 43.5, 42.5.
Anal. calcd. for $C_{17}H_{20}O_7$	: C, 60.69; H, 6.00
Found	: C, 60.36; H, 5.95

1-O-Methyl-3,6-anhydrofuranosyl-2-(3-benzoyl)-butyrate (6b)

Methyl anhydrofuranoside **2a** (1.76 g, 10 mmol) in $CHCl_3$ (15 mL) was treated with pyridine (0.97 mL, 12 mmol) at room temperature and benzoylbutyryl chloride (2.5 g, 12 mmol) dissolved in $CHCl_3$ (10 mL) was added to the above solution. The mixture was stirred at room temperature for 3h and was processed as described for compound **6a**. Chromatographic purification of the product on silica gel column using 15% EtOAc in hexane furnished **6b** (2.56 g, 73 %) as a colourless solid. Crystallization from ethyl acetate-hexane mixture afforded colourless crystals, m p. 80-81°C.

IR (KBr)	: 3520, 2995, 1735, 1728, 1435 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.8 (m, 2H), 7.5 (m, 3H), 4.8 (brs, 1H), 3.7-3.5 (m, 6H), 3.4, (s, 3H, OCH_3), 2.8 (m, 4H), 2.1 (brs, 1H, OH), 1.9 (m, 2H)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 189.6, 177.2, 136.1, 87.9, 82.3, 75.9, 75.2, 71.8, 44.0, 42.5, 25.5.
Anal Calcd. for $C_{18}H_{22}O_7$	: C, 61.69; H, 6.33
Found	: C, 61.60; H, 6.29

1-O-Benzyl-3,6-anhydrofuranosyl-2-(2-benzoyl)-propionate (6c)

A solution of **2b** (1.26 g, 5 mmol) in $CHCl_3$ (15 mL) containing pyridine (0.81 mL, 10 mmol) was treated with benzoylpropionyl chloride (1.17 g, 6 mmol) in $CHCl_3$ (10 mL) at room temperature. After 3.5h the reaction mixture was processed as described for compound **6a** and the product was purified by chromatography on silica gel column using 10% ethyl acetate in hexane as the eluent. Compound **6c** was obtained as a colourless solid (1.79 g,

87%) which was crystallized from a mixture of ethyl acetate and hexane to afford colourless crystals of 6c; m p. 90-91°C.

IR (CH_2Cl_2 film)	: 3520, 2990, 1740, 1735, 1428 cm^{-1}
^1H NMR (270 MHz, $CDCl_3$)	: δ 7.75 (m, 2H, Ar-H), 7.5 (m, 8H, Ar-H), 4.86 (d, J = 6.8 Hz, 1H), 3.65 (brs, 2H), 3.3-3.2 (m, 6H), 2.9 (m, 4H, COCH), 2.1 (brs, 1H, OH)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 191.5, 176.5, 135.1, 127.0, 88.2, 82.2, 75.9, 76.3, 71.9, 43.5, 42.5, 25.6.
EIMS (*m/z*)	: 412 (M^+, 20), 305 (45), 251 (60), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(3-benzoyl)-butyrate (6d)

A mixture of **2b** (0.504 g, 2 mmol) and pyridine (0.242 mL, 3 mmol) in $CHCl_3$ (15 mL) was treated with benzoylbutyryl chloride (0.502 g, 2.4 mmol) in $CHCl_3$ (10 ml) at room temperature for 3.5h. Work-up of the reaction mixture as described for compound **6a** followed by chromatographic purification of the product on silica gel column using 20% ethyl acetate in hexane afforded **6d** as a colourless solid (0.647 g, 76%). Crystallization from ethyl acetate-hexane mixture afforded colourless crystals, m p. 95-96°C.

IR (CH_2Cl_2 film)	: 3510, 2995, 1735, 1728, 1430 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.7 (m, 2H, Ar-H), 7.5 (m, 8H, Ar-H), 4.8 (d, J = 6.75 Hz, 1H), 3.8-3.4 (m, 8H, OCH), 2.8 (m, 4H, COCH), 2.1 (brs, 1H, OH), 1.85 (m, 2H, $COCHC\underline{H_2}$)

HRMS calcd. for $C_{24}H_{26}O_7$: 426.1678

Found : 426.1654

1-O-Benzyl-3,6-anhydrofuranosyl-2-(2-acetyl)-propionate (6e)

A solution of acetylpropionyl chloride (0.64 g, 4.8 mmol) in $CHCl_3$ (10 mL) was added to a solution of **2b** (1.01 g, 4 mmol) in $CHCl_3$ (15 mL) containing pyridine (0.38 mL, 4.8 mmol) and the mixture was stirred at room temperature for 2.5h. The reaction mixture was worked up as described for **6a** and was purified by chromatography on silica gel column using 20% EtOAc in hexane as the eluent to afford **6e** as a colourless semi solid (1.17 g, 70%).

IR (KBr) : 3515, 1735, 1720, 1428 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$) : δ 7.4 (s, 5H, Ar-H), 4.85 (d, J = 6.5 Hz, 1H), 3.7-3.3 (m, 8H), 2.9 (m, 7H).

GCMS (*m/z*) : 350 (M^+, 20), 251 (30), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2- (3-acetyl)-butyrate (6f)

A solution of **2b** (1.01 g, 4 mmol) in $CHCl_3$ (15 mL) containing pyridine (0.38 mL, 4.8 mmol) was stirred with acetylbutyryl chloride (0.71 g, 4.8 mmol) in $CHCl_3$ (10 mL) at room temperature for 2.5h and was worked up as described for compound **6a**. Purification of the product by chromatography on silica gel column using 20% EtOAC in hexane as the eluent furnished **6f** as a colourless semi solid (1.04 g, 72%).

IR (KBr) : 3510, 2995, 1728, 1720, 1428 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.4 (s, 5H, Ar-H), 4.8 (d, J = 6.6 Hz, 1H), 3.6-3.2 (m, 6H), 2.9 (m, 7H), 1.9 (m, 2H)

GCMS (*m/z*) : 364 (M^+, 25), 251 (40), 144 (100)

1-O-Methyl-3,6-anhydrofuranosyl-2-(3-hydroxy,3-phenyl)-propionate (7a)

A solution of **6a** (3.36 g, 10 mmol) in THF (20 mL) was stirred with $ZnCl_2$ (1.64 g ,12 mmol) at -5°C. After 15 min $NaBH_4$ (0.76 g, 20 mmol) was added and the mixture was stirred for 10 min at -5°C. Excess $NaBH_4$ was quenched with dil. HCl and the reaction mixture was diluted with water (20 mL). The product was extracted into ethyl acetate and the solution washed with water, saturated $NaHCO_3$ solution and finally with saturated brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The product was purified by chromatography on silica gel column using ethyl acetate : hexane (20:80) as the eluent to afford **7a** as colourless solid (3.17 g, 94%) which was crystallized from ethyl acetate-hexane mixture to afford colourless crystals of **7a**; m p. 86-87°C.

IR (KBr) : 3450, 1745, 1432 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.3 (brs, 5H, Ar-H), 4.8 (d, J = 6.9 Hz, 1H), 3.5-3.2 (m, 7H, OCH), 2.4 (m, 2H), 2.2-2.1 (brs, 2H, OH), 1.9 (m, 2H)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 180.0, 130.2, 88.6, 82.1, 76.0, 75.2, 72.1, 44.5, 26.3.

EIMS (*m/z*) : 338 (M^+, 5), 320 (70), 144 (100)

1-O-Methyl-3,6-anhydrofuranosyl-2-(4-hydroxy,4-phenyl)-butyrate (7b)

Benzoylbutyrate **6b** (1.05 g, 3 mmol) was dissolved in THF (15 mL) and $ZnCl_2$ (0.49 g, 3.6 mmol) was added to it. The mixture was cooled to -5°C with stirring; after 15 min. $NaBH_4$ (0.23 g, 6 mmol) was added and stirred for 10

min. The reaction mixture was processed as described for 7a and the product was purified by chromatography on silica gel column. Elution with 20% EtOAc in hexane afforded 7b as a colourless solid (0.982 g, 93%) which was crystallized from ethyl acetate hexane mixture to afford colourless crystals; m p. 92-93°C.

IR (KBr)	: 3470, 1736, 1629, 1430 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.4 (s, 5H, Ar-H), 4.7 (d, J = 6.7 Hz, 1H), 3.6-3.2 (m, 7H, OCH), 2.7 (m, 2H), 2.1 (brs, 2H, OH), 1.9 (m, 4H)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 179.5, 129.0, 88.5, 82.2, 45.5, 44.0.
GCMS (*m/z*)	: 353 (M^+, 5), 336 (60), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(3-hydroxy,3-phenyl)-propionate (7c)

To a solution of 6c (1.65 g, 4 mmol) in THF (20 mL), $ZnCl_2$ (0.33 g, 2.4 mmol) was added and the mixture was stirred at -5°C for 15 min. This was treated with $NaBH_4$ (0.34 g, 6 mmol) for 10 min. Work-up by the usual procedure followed by chromatographic purification on silica gel column using 20% EtOAc in hexane afforded 7c as colourless solid (1.529 g, 92%). Crystallization from a mixture of ethyl acetate in hexane afforded 7c as colourless crystals; m p. 98-99°C.

IR (KBr)	: 3465, 1735, 1632, 1425 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.4 (brs, 10 H, Ar-H), 4.8 (d, J = 6.7 Hz, 1H), 3.8-3.6 (m, 9H, OCH), 2.8 (m, 2H, COCH), 2.0 (brs, 2H, OH), 1.85-1.70 (m, 2H)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 179.5, 135.6, 129.2, 127.0, 126.5, 87.5, 86.0, 82.4, 75.6, 44.6, 44.0, 25.7, 25.0.

GCMS (*m/z*) : 414 (M^+, 5), 396 (40), 307 (60), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(4-hydroxy,4-phenyl)-butyrate (7d)

Ketoester **6d** (0.852 g, 2 mmol) in THF (15 mL) was treated with $NaBH_4$ (0.114 g, 3 mmol) in presence of $ZnCl_2$ (0.326, 2.4 mmol) as described in the above experiments. The reaction mixture was processed as described for **7a**, followed by purification by chromatography on silica gel column using 25% ethyl acetate in hexane furnished **7d** as a colourless solid (0.787 g, 92%). Crystallization from ethyl acetate-hexane mixture afforded colourless crystals; m p. 102-103°C.

IR (KBr) : 3480, 2990, 1635, 1428 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$) : δ 7.45 (brs, 10H, Ar-H), 4.8 (d, J = 6.7 Hz, 1H), 3.75-3.6 (m, 9H, OCH), 2.75 (m, 2H), 1.9 (brs, 2H, OH), 1.8-1.7 (m, 4H)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 179.0, 136.5, 130.0, 127.2, 87.2, 86.5, 81.0, 75.5, 44.5, 44.0, 25.7, 25.5

GCMS (*m/z*) : 428 (M^+, 5), 410 (45), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(3-hydroxy,3-methyl)-propionate (7e)

Acetylpropionate **6e** (1.05 g, 3 mmol) in THF was stirred with $ZnCl_2$ (0.49 g, 3.6 mmol) at -5°C for 15 min. $NaBH_4$ (0.23 g, 6 mmol) was added to the mixture and stirred at -5°C for 15 min. The reaction mixture was worked up by the usual procedure and the product was purified by chromatography on silica

gel column. Elution with 25% EtOAc in hexane afforded 7e as a colourless semi solid (0.97 g, 92%).

IR (KBr)	: 3470, 2998, 1725, 1630, 1432 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.35 (s, 5H, Ar-H), 4.85 (d, J = 6.9 Hz, 1H), 3.7-3.2 (m, 9H, OCH), 2.6 (m, 2H, COCH), 2.0 (brs, 2H, OH), 1.8-1.6 (m, 5H)
^{13} C NMR (22.4 MHz, $CDCl_3$)	: δ 186.0, 135.6, 127.2, 87.5,86.0, 76.3, 26.5, 26.0, 25.2.
GCMS (*m/z*)	: 352 (M^+, 5), 334 (40), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(4-hydroxy,4-methyl)-butyrate (7f)

Ketoester 6f (1.09 g, 3 mmol) in THF (20 mL) was treated with $NaBH_4$ (0.23 g, 6 mmol) in presence of $ZnCl_2$ (0.49 g, 3.6 mmol) as described for compound 7e. Work-up by the usual procedure and purification of the product by chromatography on silica gel column using 25% EtOAc in hexane afforded 7f as a colourless semi solid (1.0 g, 83 %).

IR (KBr)	: 3450, 2995, 1730, 1428 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.3 (s, 5H, Ar-H), 4.7 (d, J = 6.5 Hz, 1H), 3.8-3.4 (m, 8H, OCH), 2.7 (m, 2H), 2.0 (brs, 2H, OH), 1.9 (m, 4H)
^{13}C NMR (22.4 MHZ, $CDCl_3$)	: δ 176.5, 134.0, 127.0, 126.5, 90.2, 87.0, 75.3, 43.0, 25.5, 25.0.
EIMS (*m/z*)	: 366 (M^+, 10), 349 (65), 253 (20), 144 (100).

γ-Phenyl-γ-butyrolactone (8a)

Typical experimental procedure: Hydroxyester **7a** (1.014 g, 3 mmol) in THF (30 mL) was stirred with 1M LiOH at room temperature for 4h. The reaction mixture was acidified using 1M HCl, diluted with water (30 mL). Product was extracted into ethyl acetate and washed with water, saturated $NaHCO_3$ solution and saturated brine. The organic layer was dried over anhydrous Na_2SO_4; removal of the solvent under reduced pressure followed by chromatographic purification of the product on silica gel column using 10% ethyl acetate in hexane as the eluent afforded **8a** as a viscous liquid (0.403 g, 83%); $[\alpha]_D^{26}$ +23° (c = 1.0, $CHCl_3$); lit. +32.5 ° (c = 4.3, $CHCl_3$)[20b].

δ-Phenyl-δ-valerolactone (8b)

Typical experimental procedure: A solution of **7b** (1.06 g, 3 mmol) in THF (25 mL) was reacted with LiOH at room temperature. After 4.5h the reaction mixture was processed as described for compound **8a**. Purification of the product by chromatography on silica gel column using a mixture of ethyl acetate:hexane (10:90) afforded **8b** (0.42 g, 79 %) as a viscous liquid; $[\alpha]_D^{26}$ +16° (c = 1.0, $CHCl_3$); lit.[20d] +52° (c = 1.0, $CHCl_3$).

γ-Methyl-γ-bytyrolactone (8c)

Hydroxyester **7e** (0.70 g, 2 mmol) in THF (25 mL) was saponified using 1M LiOH (10 mL) and the reaction mixture was worked up as described for compound **8a**. The product was purified by chromatography on silica gel column using 10% EtOAc in hexane as the eluent to furnish **8c** (0.16 g, 80%) as a colourless viscous liquid; $[\alpha]_D^{26}$ -30° (c = 1.0, $CHCl_3$); lit.[20b,f] $[\alpha]_D^{26}$ -36.8° (c = 1.44, CH_2Cl_2).

δ-Methyl-δ-valerolactone (8d)

Hydroxyester **7f** (1.10 g, 3 mmol) in THF (25 mL) was treated with 1M LiOH (10 mL) for 4h. The reaction mixture was worked up as detailed for compound **8a** and the product was purified by chromatography on silica gel column. Elution with 10% EtOAc in hexane afforded the product **8d** (0.26 g, 75%); $[\alpha]_D^{26}$ -23° (c = 1.0, $CHCl_3$); lit.[20f,g] $[\alpha]_D^{26}$ -48° (c = 1.0, CH_2Cl_2)

1-O-Benzyl-3,6-anhydrofuranosyl-2-benzoate (9)

Anhydrous pyridine (0.58 mL, 7.2 mmol) was added to a solution of benzyl anhydrofuranoside **2b** (1.512, 6 mmol) in $CHCl_3$ (20 mL). Benzoyl chloride (1.012 g, 7.2 mmol) was added to it and the mixture stirred for 2h. Work-up by the usual procedure followed by chromatographic purification on silica gel column using 20% EtOAc in hexane as the eluent furnished 9 as a colourless solid (1.623 g, 76%). Crystallization from ethyl acetate in hexane afforded colourless crystals; m p. 82-83°C.

IR (KBr)	: 3480, 2998, 1725, 1432 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.7 (m, 2H, Ar-H), 7.5 (m, 8H, Ar-H), 4.86 (d, J = 6.8 Hz, 1H), 3.7-3.4 (m, 6H, OCH), 2.1 (brs, 1H, OH)
GCMS (*m/z*)	: 336 (M^+, 20), 251 (60), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-O-benzoyl-5—(2-benzoyl)-propionate (10a)

Compound 9 (0.712 g, 2 mmol) in $CHCl_3$ (20 mL) was treated with benzoylpropionyl chloride (0.468 g, 2.4 mmol) in $CHCl_3$ (15 mL) in presence of pyridine (0.20 mL, 2.4 mmol) and a catalytic amount of DMAP (0.071 g) and the mixture refluxed for 4h. The reaction mixture was worked up by the usual procedure and the product purified by chromatography on silica gel

column. Elution with 15% ethyl acetate in hexane afforded **10a** as a colourless solid (0.639 g, 63%): this was crystallized from ethyl acetate-hexane mixture to afford colourless crystals; m p. 114-115°C.

IR (CH_2Cl_2 film)	: 2995, 1735, 1720, 1630, 1460 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.6-7.5 (m, 4H), 7.4-7.2 (m, 11H), 4.8 (d, J = 6.8 Hz, 1H), 3.8-3.4 (m, 8H), 2.9-2.8 (m, 4H, COCH)
GCMS (*m/z*)	: 516 (M^+, 20), 408 (25), 251 (60), 144 (100)

1-O-Benzyl-3,6-anhydrfuranosyl-2-O-benzoyl–5-(3-benzoyl)-butyrate (10b)

A solution of 9 (0.712 g, 2 mmol) in $CHCl_3$ (20 mL) was treated with benzoylbutyryl chloride (0.502 g, 2.4 mmol) in $CHCl_3$ (15 mL) in presence of pyridine (0.20 mL, 2.4 mmol) and catalytic amount of DMAP (0.071 g) as described for **10a**. The reaction mixture was processed after 4h as usual and the product purified by chromatography on silica gel column. Elution with a mixture of 20% EtOAc in hexane afforded **10b** as a colourless solid (0.259 g, 80%) which on crystallization from ethyl acetate-hexane mixture afforded colourless crystals; m p. 120-121°C.

IR (CH_2Cl_2 film)	: 2990, 1632, 1730, 1720, 1429 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.7 (m, 4H, Ar-H), 7.4-7.3 (m, 11H), 4.8 (d, J = 6.8 Hz, 1H), 3.7-3.2 (m, 8H), 2.8-2.6 (m, 4H, COCH), 1.85 (m, 2H)
GCMS (*m/z*)	: 530 (M^+, 20), 411 (5), [illegible] (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-O-benzoyl–5-(3-hydroxy,3-phenyl)-propionate (11a)

Ketoester **10a** (1.30 g, 2 mmol) in THF (20 mL) was reduced with $NaBH_4$ (0.15 g, 4 mmol) in presence of $ZnCl_2$ (0.326 g, 2.4 mmol) according to the general procedure. The usual work-up followed by chromatographic purification on silica gel column using 25% EtOAc in hexane as the eluent afforded **11a** (0.929 g, 90 %). This was crystallized from a mixture of ethyl acetate in hexane to afford colourless crystals, m p. 115-116°C.

IR (KBr)	: 3480, 2992, 1730, 1720, 1438 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.6 (m, 2H, Ar-H), 7.5-7.3 (m, 13H Ar-H), 4.8 (d, J = 6.6 Hz, 1H), 3.8-3.2 (m, 9H), 2.6 (m, 2H, COCH), 1.9 (s, 1H, OH), 1.85 (m, 2H)
GCMS (*m/z*)	: 518 (M^+, 5), 500 (30), 355 (45), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-O-benzoyl-5-(4-hydroxy,4-phenyl)-butyrate (11b)

Compound **10b** (1.06 g, 2 mmol) in THF (20 mL) was treated with $NaBH_4$ (0.15 g, 4 mmol) in presence of $ZnCl_2$ (0.326 g, 2.4 mmol) as described for **7a**. The reaction mixture was worked up by the usual procedure and the product was purified by chromatography on silica gel column. Elution with 25% EtOAc in hexane furnished **11b** as a colourless solid (0.978 g, 92 %). This was crystallized from ethyl acetate-hexane mixture to afford colourless crystals; m p. 123-124°C.

IR (KBr)	: 3480, 1730, 1725, 1430 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.5 (m, 2H), 7.4-7.5 (m, 13H), 4.7 (d, J = 6.65 Hz), 3.85-3.55 (m, 6H), 2.6 (m 2H), 2.0 (brs, 1H, OH), 1.8 (m, 4H)
GCMS (*m/z*)	: 532 (M^+, 5), 514 (20), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(1-benzoyl)-formate (12)

Compound **2b** (0.756 g, 3 mmol) in $CHCl_3$ (20 mL) containing pyridine (0.46 mL, 6 mmol) was treated with benzoylformyl chloride (0.605 g, 3.6 mmol) in $CHCl_3$ (10 mL) at 0°C for 2h. The reaction mixture was worked up by the usual procedure and the product purified by chromatography on silica gel column using 15% EtOAC in hexane as the eluent to afford **12** as a colourless solid (0.806 g, 70%). This was crystallized from a mixture of ethyl acetate and hexane to afford colourless crystals; m p. 78-79°C.

IR (KBr)	: 3510, 1730, 1725, 1435 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.6 (m, 2H, Ar-H), 7.3-7.1 (m, 8H, Ar-H), 4.7 (d, J = 6.8 Hz, 1H), 3.8-3.5 (m, 6H), 2.0 (brs, 1H, OH)
GCMS (*m/z*)	: 384 (M^+, 10), 251 (60), 144 (100)

1-O-Benzyl-3,6-anhydrofuranosyl-2-(1-hydroxy,1-phenyl)formate (13)

Ketoester **12** (1.152 g, 3 mmol) in THF (20 mL) containing $ZnCl_2$ (0.489 g, 3.6 mmol) was treated with $NaBH_4$ (0.22 g, 6 mmol) at -5°C for 10 min. Work-up by the usual procedure followed by chromatographic purification on silica gel using 25% EtOAC in hexane afforded **13** (0.104 g, 90 %) as a colourless semi solid.

IR (KBr) : 3505, 1728, 1718, 1430, 1172 cm-1

1H NMR (90 MHz, $CDCl_3$) : δ 7.6 (brs, 10H, ArH), 4.7 (d, J = 6.8 Hz), 3.8-3.5 (m, 7H), 1.9 (brs, 2H, OH)

GCMS (*m/z*) : 386 (M^+, 5), 368 (30), 251 (60), 144 (100)

Mandelic acid 14

Compound **13** (1.158 g, 3 mmol) in THF (25 mL) was reacted with 1M LiOH at room temperature for 4h. The reaction mixture was acidified with 1M HCl and the solution was saturated with NaCl. The product was extracted into ethyl acetate. The extract was processed as usual and purified by chromatography on silica gel column using 30% EtOAc in hexane as the eluent. **14** was obtained as a colourless solid (0.274 g, 60%) and crystallized from methanol; m p. 130-131°C; $[\alpha]_D^{26}$ -49° (c = 1, methanol); lit[27]. m p.132-133°C $[\alpha]_D^{26}$ -153° (c = 2.5, H_2O).

IR (KBr) : 3480, 3050, 1752 cm^{-1}

1H NMR (90 MHz, DMSO d_6) : δ 9.2 (s, 1H, COOH), 7.6 (s, 5H), 4.1 (s, 1H), 2.2 (brs, 1H, OH)

1-O-Benzyl-3,6-anhydrofuranosyl-2-cinnamate (15)

Anhydrofuranoside **2b** (0.756 g, 3 mmol) in $CHCl_3$ (20 mL) was treated with cinnamoylchloride (0.599 g, 3.6 mmol) dissolved in $CHCl_3$ (10 mL) in presence of pyridine (0.48 mL, 6 mmol) at room temperature for 3h. Work-up of the reaction mixture by the usual procedure followed by chromatographic

purification of the product on silica gel column using 15% EtOAc in hexane furnished **15** (0.836 g, 73 %) as a colourless semi solid.

IR (KBr) : 3515, 2995, 1715, 1675, 1629, 1428 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.3 (m, 10H), 4.9 (d, J = 6.85 Hz, 1H), 4.7 (d, J = 12.4 Hz, 2H, CH=CH), 3.9-3.5 (m, 8H)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 182.0, 141.5, 132.0, 129.2, 126.5, 98.0, 86.5, 82.0, 80.2, 75.9, 75.2.

GCMS (*m/z*) : 382 (M^+, 60), 251 (60), 144 (100)

Diels-Alder adduct 16

A solution of the cinnamate **15** (1.146 g, 3 mmol) in toluene (10 mL) containing $ZnCl_2$ (0.816 g, 6 mmol) was stirred with cyclopentadiene (0.79 mL, 12 mmol) at -5°C for 5h. Toluene was evaporated *in vacuo* and the product was dissolved in dichloromethane (50 mL), washed successively with water and saturated brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed by distillation. Purification of the product by chromatography on silica gel column using 12% EtOAc in hexane afforded the adduct **16** as a colourless solid (1.01 g, 75%). Crystallization from ethyl acetate-hexane mixture afforded colourless crystals; m p.108-110°C.

IR (KBr) : 3510, 1730, 1638, 1430 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.4 (brs, 10H, Ar-H), 4.8 (d, J = 6.8 Hz, 1H), 4.3 (d, J = 12.9 Hz, 2H, CH=CH), 3.8-3.5 (m, 8H, OCH), 2.8 (m, 1H, COCH), 1.7-1.6 (m, 5H)

GCMS (*m/z*) : 448 (M^+, 20), 251 (60), 144 (100)

Methyl 3-phenyl-bicyclo[2.2.1]-hept-5-ene-2-carboxylate (18)

The adduct **16** (0.816 g, 6 mmol) in THF (25 mL) was stirred with 1M LiOH (10 mL) at room temperature for 4h. The reaction mixture was acidified using dil. HCl and extracted with ethyl acetate. The extract was processed as usual and the product purified by chromatography on silica gel column using 20% EtOAc in hexane. **17** was obtained as a colourless powder (0.449 g, 70%).

IR (KBr) : 2992, 1735, 1690, 1436 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 9.1 (s, 1H, COOH), 7.70 (s, 5H), 5.8 (dd, 1H, J = 5.6, 2.8 Hz), 5.7 (dd, 1H, J = 5.6, 2.7 Hz), 2.80 (m, 1H), 2.1 (m, 5H)

Adduct **17** was converted into the methyl ester **18** by stirring it with methanol in presence of conc. H_2SO_4 and the reaction mixture was neutralized by stirring it with saturated $NaHCO_3$. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and dried over anhydrous Na_2SO_4. The solvent was removed by distillation and the product purified by chromatography on silica gel column using 5% ethyl acetate in hexane as the eluent to afford **18** as a colourless viscous liquid (0.392 g, 82%); $[\alpha]_D^{26}$ +61° (c = 1%, $CHCl_3$), lit[26]. $[\alpha]_D^{25}$ +136° (c = 1%, $CHCl_3$).

IR (KBr) : 2995, 1730, 1718, 163+ 2, 1430 cm^{-1}

^1H NMR (90 MHz, $CDCl_3$) : δ 7.5 (s, 5H, Ar-H), 5.75 (dd, J = 5.5, 3 Hz), 5.7 (dd, J = 5.5, 3 Hz), 3.6 (s, 3H, OCH_3), 2.7 (m, 1H), 2.0 (m, 5H)

3.4 References

1. For a recent overeview see: Karlsson, K. -A. *Trends Biochem. Sci.* **1991**, *12*, 265.
2. Ashwell, G.; Morell, A. G. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1974**, *41*, 99.
3. For a review see: Karlsson, K. -A. *Amm. Rev. Biochem.* **1989**, *58*, 309.
4. For a review see: Kunz, H.; Ruck, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336.
5. (a) Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. C* **1966**, 1922, 2280 (b) Landor, S. R.; Miller, B. J.; Tatchell, A .R. *ibid.* ***1967***, 197.
6. Heathcock, C. H.; White, C. T.; Morrison, J. J.; Van Derveer, D. *J. Org. Chem.* **1981**, *46*, 1296.
7. Kunz, H.; Muller, B.; Schanzenbach, D. *Angew. Chem.* **1987**, *99*, 269; *Angew. Chem. Int. Ed. Eng.* **1987**, *26*, 267.
8. Shing, T. K.; Lloyd-Williams, P. *J. Chem. Soc. Chem. Commun.* **1987**, 423.
9. (a) Pelzer, R.; Jutten, P.; Scharf, H.-D. *Chem. Ber.* **1989**, 122, 487. (b) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem.* **1991**,103, 480 518; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477, 515.
10. Kaluza, Z.; Fudong, W.; Belzeeki, C.; Chmielewski, M. *Tetrahedron Lett.* **1989**, *38*, 5171.
11. Ganz, I.; Kunz, H. *Synthesis*, **1994**, 1353.

12 (a) Charette, A. B.; Cote, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166. (b) Charette, A. B.; Marcoux, J.-F, Cote, B. *Tetrahedron Lett.* **1991**, *32*, 7215.

13. Kunz, H. In *Selectivities in Lewis Acid Promoted Reactions* Schinzer, D., Ed.; Kluwer, Amsterdam, **1989**, p.189.

14. Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 910.

15. Tamion, R.; Marsais, F.; Ribereau, P.; Queguiner, G. *Tetrahedron Asymmetry* **1993**, *4*, 1879.

16. Bollenback, G. N. *Methods in Carbohydrate Chemistry* Whistler, R. L.; Wolform, M. L.; Ed.; Academic Press New York, 1963; Vol. II, p. 326.

17. Bollenback, G. N. *Methods in Carbohydrate Chemistry* Whistler, R. L.; Wolform, M. L.; Ed.; Academic Press, New York, 1963; Vol. II, p. 182.

18. (a) Chalk, R. C.; Ball, D. H.; Long, L. Jr. *J. Chem. Soc.* **1966**, *31*, 1509. (b) Haworth, W. N.; Owen, L. N.; Smith, F. *J. Chem. Soc.* **1941**, 88,

19. Ferrier, R. J.; Collins, P. M. In *Monosaccharide Chemistry*, Penguin Books Ltd., England, **1972**, p. 152.

20. (a) Gutman, A. I.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (c) Izumi, T.; Tamura, F.; Akutsu, M. J. *J. Heterocyclic. Chem.* **1994**, *31*, 441. (d) Armstrong, D. W.; Stalcup, A. M.; Hilton, M. L.; Duncan, J. D.; Faulkner, J. R. Jr.; Chang, S.-C. *Anal. Chem.* **1990**, *62*, 1610. (e) Mori, K. *Tetrahedron*, **1975**, *31*, 3011. (f) Enders, D.; Grobner, R.; Runsink, J. *Synthesis* **1995**, 949 and the references cited therein (g) Gutman, A. L.; Oren, D.; Boltanski, A. *Tetrahedron Lett.* **1987**, *28*, 3861.

21. For a review of Asymmetric Diels-Alder reactions see: Taschner, M. J. *In Organic Synthesis: Theory and application*, JAI press, 1989, Vol. 1, pages 1-101.

22. (a) Amino acid based chiral dienophiles; Evans, D. A.; Chapman, K. T.; Bishaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (c) Bueno, M. P.; Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Charro, P.; Roy, M. A.; Andres, J. M. *Can. J. Chem.* **1988**, *66*, 2626.

23. Carbohydrate-derived chiral auxiliaries; (a) Kunz, H.; Muller, B.; Schanzenbach, D. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 267. (b) Stahle, W.; Kunz, H. *Syn. Lett.* **1991**, 260. (c) Kunz, H.; Ruck, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336.

24. α-hydroxy carboxylic acid derivatives as dienophiles; (a) Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *25*, 2191. (b) Poll, T.; Abdel Hadey, A. F.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5595.

25. Terpene-derived dienophiles; (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 477. (b) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

26. (a) Rao, K. R.; Srinivasan, T. N.; Bhanumathi, B. *Tetrahedron Lett.* **1990**, *31*, 5959. (b) Kishikawa, K.; Horie, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1990**, 1009.

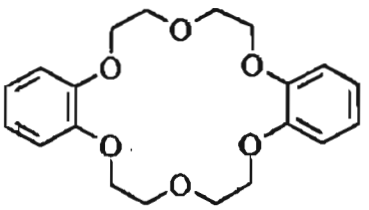
27. (a) Weast, R. C., Ed. *CRC Handbook of Chemistry and Physics*, 70th ed.; CRC Press: Boca Raton, FL, 1989-1990. (b) Schwab, G. M.; Baumann, E.; Laevernz, P. *J. Physiol. Chem.* **1933**, *215*, 121.

CHAPTER 4

SYNTHESIS AND APPLICATIONS OF NOVEL CROWN ETHERS DERIVED FROM DEOXYCHOLIC ACID

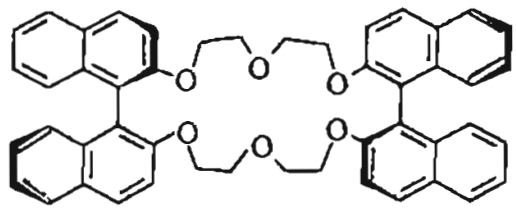
4.1 Introduction

The serendipitous discovery of crown ethers by Pedersen heralded a new era in the chemistry of host-guest molecular interactions. The first crown ether synthesized by Pedersen[1] was the benzo-[18]-crown-6 (1). Since then a large number of molecular receptors of varying sizes and shapes have been synthesized[2], and their properties have been examined thoroughly. Much of the interest invoked by crown ethers is due to their resemblance to naturally occurring ionophores.



1

A major area of interest in crown ether chemistry has been concerned with the synthesis of molecules which can recognize and bind chiral molecules, artificial enzymes which can catalyze organic reactions and systems which can store and process information at the molecular level[3]. In recent years, crown ethers derived from chiral molecules have been evaluated for their enantioselective recognition properties[4]. Chiral crown ethers have been synthesized from a variety of natural products bearing hydroxyl groups[2, 5]. The first compound to show chiral recognition was 2 synthesized by Cram[6].

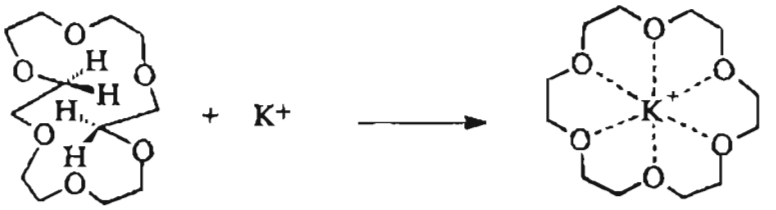


2

Compound 2 was able to complex with *R*-phenylethylammonium hexafluorophosphate selectively from a racemic mixture.

The most extensively studied naturally occurring receptors that possess rigid cavities are cyclodextrins obtained by the enzymatic hydrolysis of starch. The hydrophobic interior cavity of cyclodextrins are of 4-7A° units in diameter. They readily form inclusion complexes with a variety of organic guest molecules including aliphatic and aromatic hydrocarbons, alcohols, phenols, esters, ethers and carboxylic acids which are held inside by hydrophobic interaction.

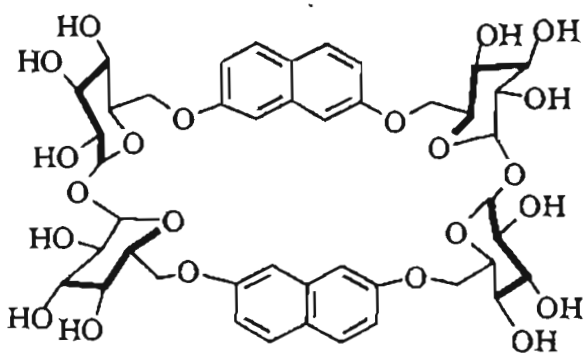
Complexation properties of macrocyclic ligands with metal ions have been studied extensively. For example, compound 1 forms stable complexes with cations like Na^+, K^+, Rb^+, Cs^+, Ca^{2+}, Ba^{2+}, Cd^{2+}, NH_4^+ and substituted ammonium ions. It was confirmed from the X-ray crystal structure of 18-crown-6 (3) that such compounds do not contain cavities in the uncomplexed state and the methylene bridges are turned towards the centre of the molecule to fill the intramolecular voids. On complexation, reorganization occurs to form a cavity for accomodating the guest species which will be held by non-bonded interactions at the centre at a specific interatomic distance, as shown in structure 4.



3 4

One major problem associated with the synthesis of artificial receptors is that most of the organic molecules are too flexible to form receptors of defined geometry. Ideal template molecules should have well-defined geometries in which conformational freedom is kept under control. This can be achieved either by the design of flexible frameworks in which the necessary rigidity is achieved by careful adjustment of non-covalent interactions (*eg.* in proteins) or by choosing rigid molecular units as building blocks.

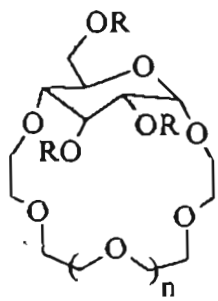
Cyclophanes[7] are a class of rigid macrocyclic compounds in which the backbone of the molecule is entirely made of carbon and hydrogen atoms. The necessary hydrophilicity is incorporated in the molecule by attaching ionic groups. Cyclophanes constituted of sugar units and aromatic units are called glycophanes and a few compounds of this type were synthesized by Wilcox[8]. As expected, these compounds display the properties of cyclodextrins as well as cyclophanes. Penades and co-workers[9] described the synthesis of the glycophane **5** from α-α'-trehalose, which is conformationally more restricted than monosaccharides.



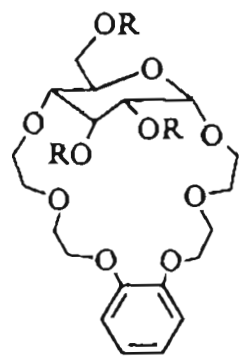
5

These glycophanes showed donor-acceptor interaction with electron deficient aromatic guest molecules in methanol-water mixture and exhibited chiral discrimination towards racemic amino acids.

Very recently, a series of novel crown ethers incorporating D-glucose units has been synthesized in our laboratory[10-12]. These showed binding affinities towards cations and some of them were used as catalysts in asymmetric Michael reaction. For example, crown ethers **6** and **7** synthesized from D-glucose showed appreciable cation binding affinity and **7** catalyzed Michael reaction to produce optically active adducts[12].

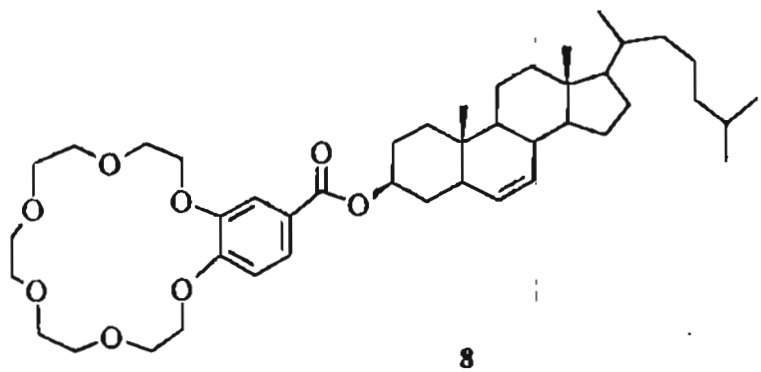


6, n = 2, R = Bn



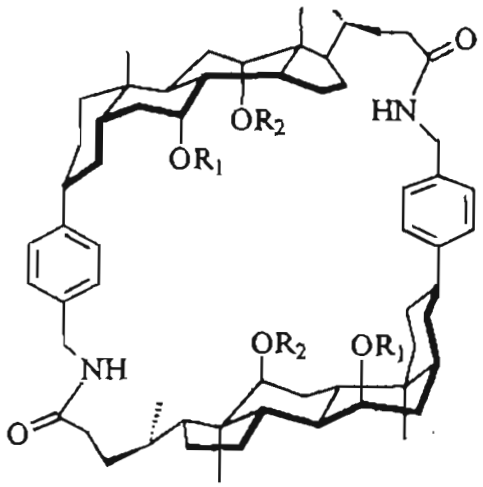
7, R = Bn

As a follow-up of this work, it was of interest to synthesize crown ethers incorporating other natural products, especially steroids. Steroids are the largest rigid systems that are readily available in homochiral form and are endowed with functional groups for substitution. Steroids are valuable in promoting liquid crystallinity and also useful in the study of hydrophobic aggregates such as lipid membranes. Cholesteryl crown ether **8** has been reported to show liquid crystalline properties and has been useful in enantioselectively encapsulating chiral anions[13].



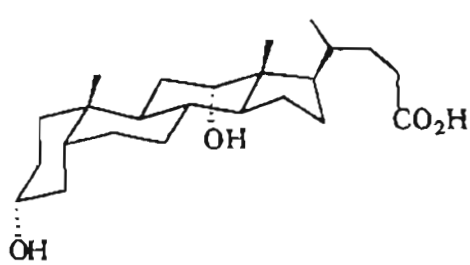
8

Among the many steroids available commercially, bile acids are inexpensive and have fairly evenly disposed functional groups which could be differentiated in terms of their reactivity. Another valuable feature is the inherent asymmetry in these molecules. Very few studies, however, have been undertaken to utilize the uniquely disposed hydroxyl groups of bile acids for the synthesis of molecular receptors. Even though in recent years they have been used as chiral auxiliaries in asymmetric synthesis[14], only a few molecular receptors have been synthesized so far from bile acids. These are illustrated by the cholaphanes **9a** and **9b** synthesized from cholic acid[15].



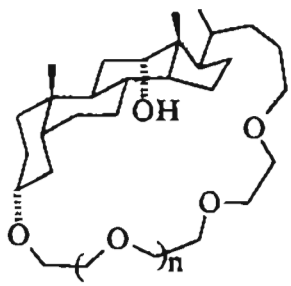
9a $R_1, R_2 = H$
9b $R_1 = H, R_2 = Bn$

Our investigations in this area have been focussed on the use of deoxycholic acid **10** as template to incorporate various crown ether moieties and to study their cation binding affinities[16]. The presence of the rigid steroid skeleton and parallelly oriented hydroxyl groups which can be differentiated in their reactivities[17] are the attributes of this molecule that make it a desirable precursor for the synthesis of various crown ethers.

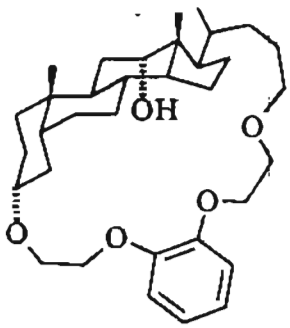


10

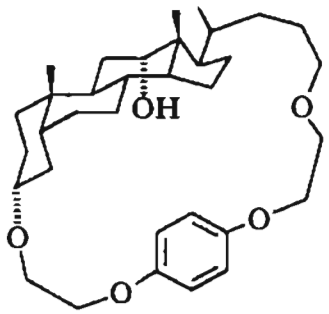
In particular, we have been interested in synthesizing crown ethers such as **13-16** and investigating their complexation properties.



13, n = 1
14, n = 2



15



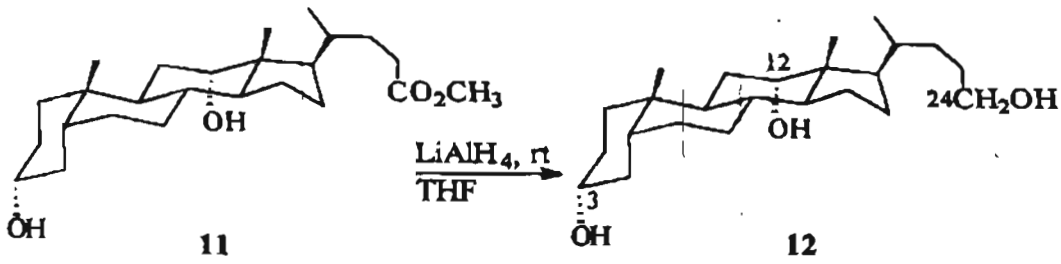
16

Section 4.2.1 of this chapter deals with the synthesis of the crown ethers **13-16** starting from deoxycholic acid **10**. The complexation studies involving them with the cations Li^+, Na^+, K^+, Cs^+ and NH_4^+ as well as their energy minimization calculations are described in section 4.2.2. The catalytic use of the crown ether **13** in an asymmetric Michael reaction is described in section 4.2.3.

4.2 Results and Discussion

4.2.1 Synthesis of crown ethers from deoxycholic acid

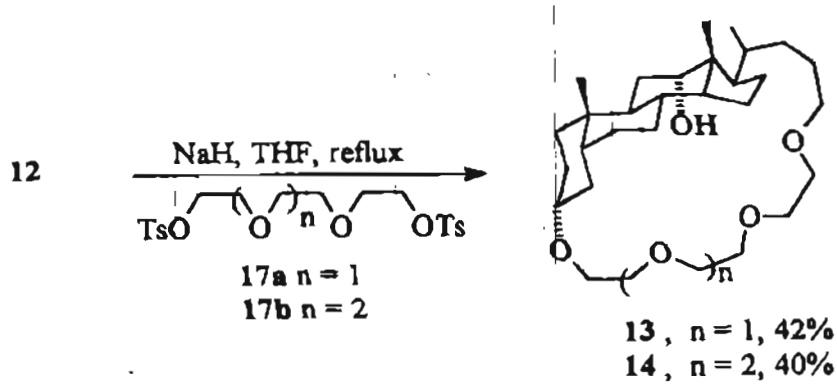
Since deoxycholic acid **10** is relatively inexpensive and is endowed with many attractive features as mentioned in section 4.1, it was chosen as the starting material for the construction of various crown ethers. Esterification of **10** with methanol in presence of conc. H_2SO_4 resulted in the formation of methyl deoxycholate **11** which was reduced to the triol[18] **12** using $LiAlH_4$ (scheme-1).



Scheme-1

Triol **12** was formed in 92% yield, and it was characterized spectroscopically. The IR spectrum of **12** showed a strong absorbance at 3450 cm^{-1} indicating the presence of the hydroxyl groups. A broad singlet in the ^1H NMR at δ 2.1(3H) which disappeared on D_2O exchange supported the presence of the three hydroxyl groups in the molecule. The characteristic steroid protons resonated at δ 1.85-0.90.

Using the triol **12**, crown ethers **13** and **14** were synthesized as illustrated in scheme-2.



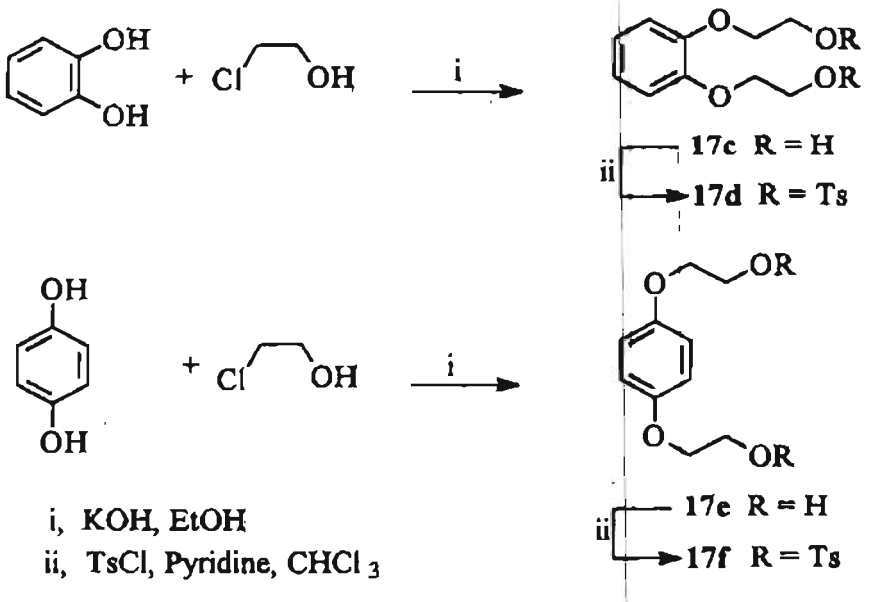
Scheme-2

The triol **12** was condensed with triethyleneglycol ditosylate **17a** in presence of NaH in dry THF to afford the crown ether **13** in 42% yield. Condensation of

12 with tetraethyleneglycol ditosylate 17b under similar experimental conditions resulted in the formation of crown ether 14 in 40% yield.

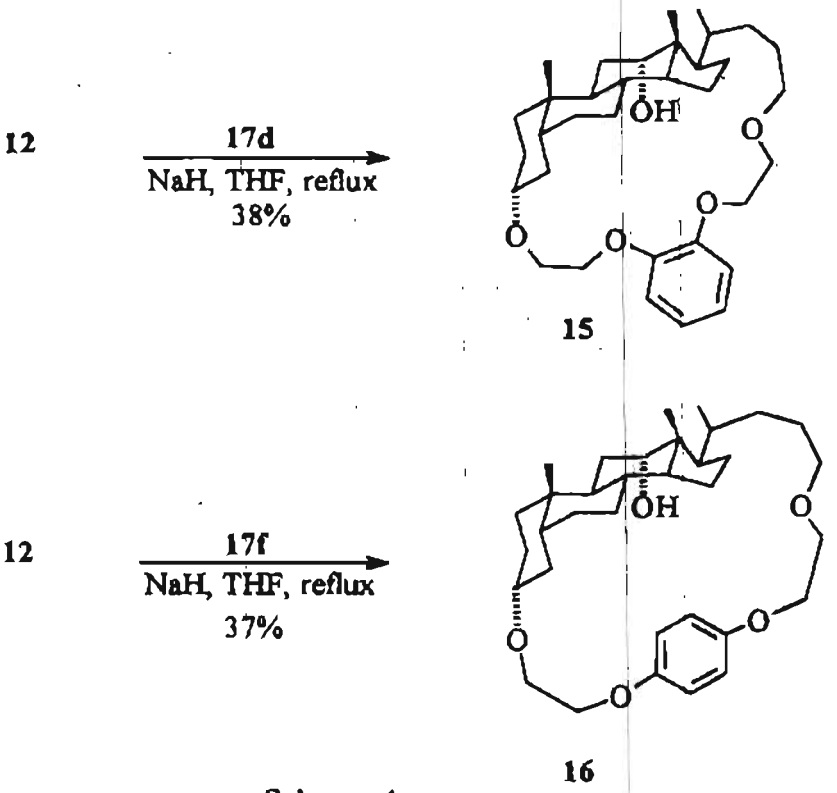
Compound 13 showed absorbance at 3455 cm^{-1} in the IR spectrum indicating the presence of hydroxyl group. Absorbance at 1426 cm^{-1} was suggestive of the presence of the ethylene dioxy units. In the ^1H NMR spectrum, the multiplet at δ 3.75-3.20 integrated for 16 protons revealing the existence of the OCH protons. The multiplet at δ 1.85-1.0 is due to the various protons in the steroid nucleus. Signals at δ 87.6, 82.0, 81.6, 80.0 and 75.5 in the ^{13}C NMR indicated the existence of ethylene dioxy carbon atoms in the molecule. The FABMS of crown ether 13 showed the molecular ion (M^+) peak at *m/z* 492.36. In the IR spectrum of 14, the hydroxyl and C-O absorbances were present at 3450 and 1426 cm^{-1} respectively. The ^1H and ^{13}C NMR spectra also were in agreement with its assigned structure.

To synthesize crown ethers 15 and 16, the ditosylates 17d and 17f were required and these were prepared from the corresponding diols by the conventional procedure[19] (scheme-3). Catechol and hydroquinone were converted to the diols 17c and 17e respectively by reacting them with chloroethanol. These diols on treatment with tosylchloride and pyridine afforded the ditosylates 17d and 17f whose spectral data were in agreement with the literature values[19].



Scheme-3

The crown ethers **15** and **16** were synthesized by condensing the triol **12** with **17d** and **17f** respectively in presence of NaH (scheme-4).



Scheme-4

The presence of the hydroxyl group in crown ether **15** was discerned from the IR absorption at 3460 cm^{-1}. Absorbances at 2990 and 1598 cm^{-1} suggested the presence of the aromatic moiety whereas the absorbance at 1427 cm^{-1} is attributed to the ethylene dioxy units. The four aromatic protons resonated as a multiplet at δ 6.95-6.85 in the ^1H NMR spectrum. A broad multiplet at δ 4.1-3.2 (12H) showed the presence of OCH protons. Signals at δ 136.0 and 129.1 in the ^{13}C NMR proved the presence of aromatic carbon atoms. The ethylene dioxy carbons resonated at δ 88.5, 86.5, 81.0, 80.0 and 75.6 ppm. The EIMS of compound **15** exhibited M^+ peak at *m/z* 540, further confirming the assigned structure of the molecule. Crown ether **16** also showed satisfactory spectral data.

4.2.2 Complexation studies with unipositive cations

With the reasonable assumption that the crown ethers **13-16** are potentially capable of coordinating alkali and/or alkaline earth metal ions, we have carried out some complexation studies. Crown ethers **13** and **15** were chosen as representative examples for complexation studies with the cations, Li^+, Na^+, K^+, Cs^+ and NH_4^+. The binding affinities of the macrocycles with these cations were determined using the Cram's picrate method[20]. The $CDCl_3$ solution of the host was shaken with the picrate solutions of the various cations in distilled water to allow the crown ether to complex with the cations. Molar ratio of the picrate to host was determined by measuring the UV absorbance, at 380 nm of a measured volume of the $CDCl_3$ layer. From this the association constant K_a was determined using equation (1)

$$K_a = \frac{R}{(1-R)\,K_d \left[(G_i)_{H_2O} - R\,(H_i)_{CDCl_3} \frac{V_{CDCl_3}}{V_{H_2O}} \right]^2} \qquad \text{eqn (1)}$$

R, Molar ratio of picrate to host

K_d, Distribution constant of the picrate salt between water and chloroform

$[G_i]_{H_2O}$, Initial picrate concentration

$[H_i]_{CDCl_3}$, Initial host concentration

V_{CDCl_3}, Volume of $CDCl_3$

V_{H_2O}, Volume of water

The picrate salts were prepared according to the reported procedure[21] by neutralizing picric acid with the corresponding metal hydroxides. 0.075 M solution of the hosts in $CDCl_3$ was used to extract the picrate solution (0.015 M) of Li^+, Na^+, K^+, Cs^+ and NH_4^+ ions in distilled water. The UV absorbance of the organic phase was measured at 380 nm.

The distribution constant (K_d) of the picrates between water and chloroform was determined by extracting known concentrations of picrate salts into chloroform layer. From the absorbance values, the concentration of the picrate salt extracted *ie* $[G^+X^-]_{CDCl_3}$ was calculated and K_d was determined using eqation (2).

$$K_d = \frac{[G^+X^-_{CDCl_3}]}{[G^+]_{H_2O}\,[X^-]_{H_2O}} \qquad \text{eqn (2)}$$

The log K_a values obtained for Li^+, Na^+, K^+, Cs^+ and NH_4^+ from the above experiments are given in Table1.

Table 1

Cation	Li^+	Na^+	K^+	Cs^+	NH_4^+
Host **13**	4.04	3.75	5.01	4.02	5.27
Host **15**	3.96	3.73	4.97	3.92	5.06.

Both the hosts **13** and **15** show moderate to good binding affinities for all the cations used. The order of affinity observed was $NH_4^+ > K^+ > Na^+ > Cs^+ > Li^+$. The high affinity for NH_4^+ ion may be explained by the fact that it can interact with the oxygen atoms of the 'crown ether' portion and the C-12 hydroxyl group of the host (figure 1). The lower values obtained for Li^+ and Na^+ may reflect the fact that the cavities of the crown ethers may be too large to hold them tightly.

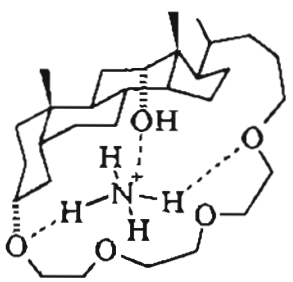
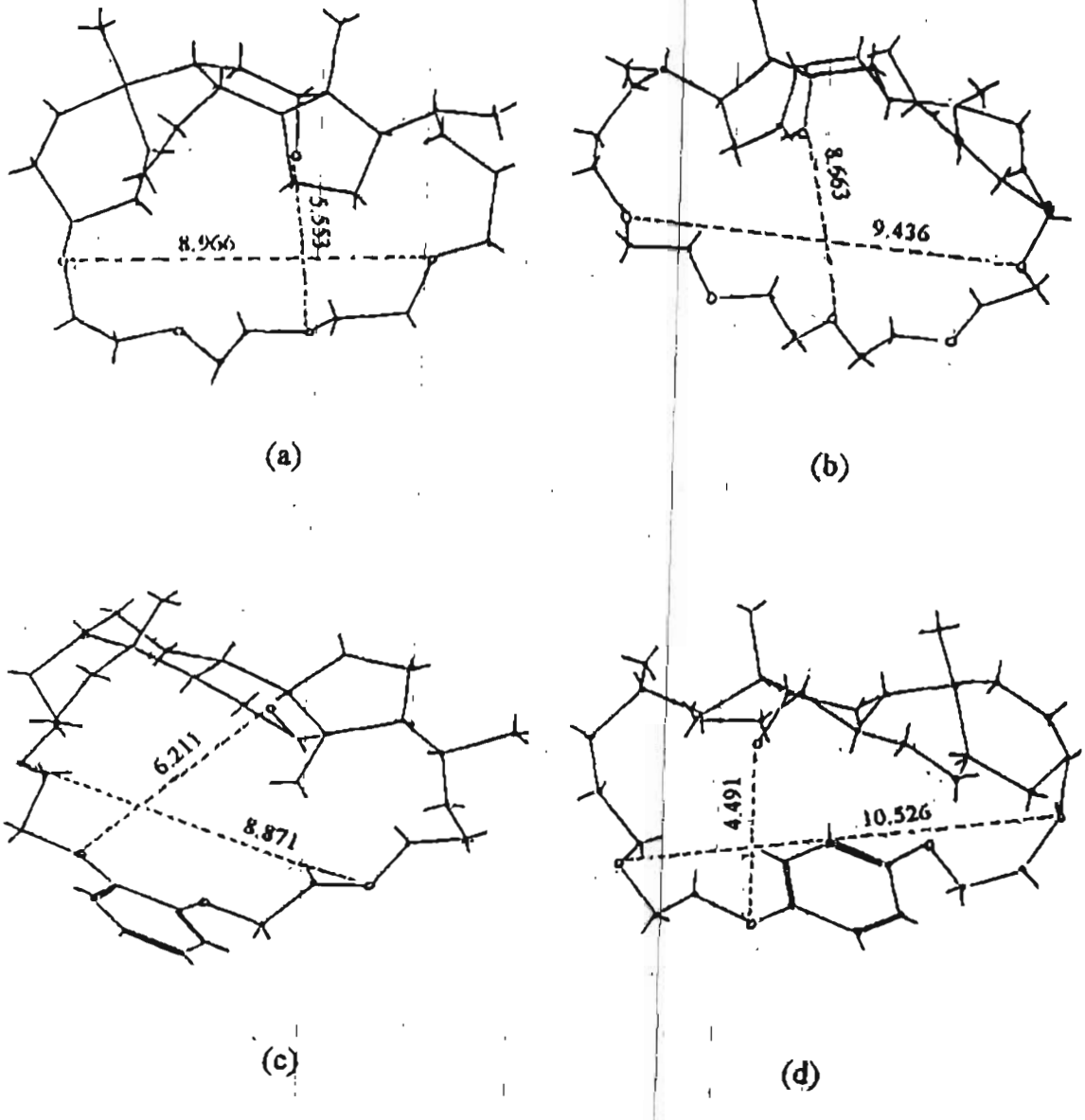


Fig. 1

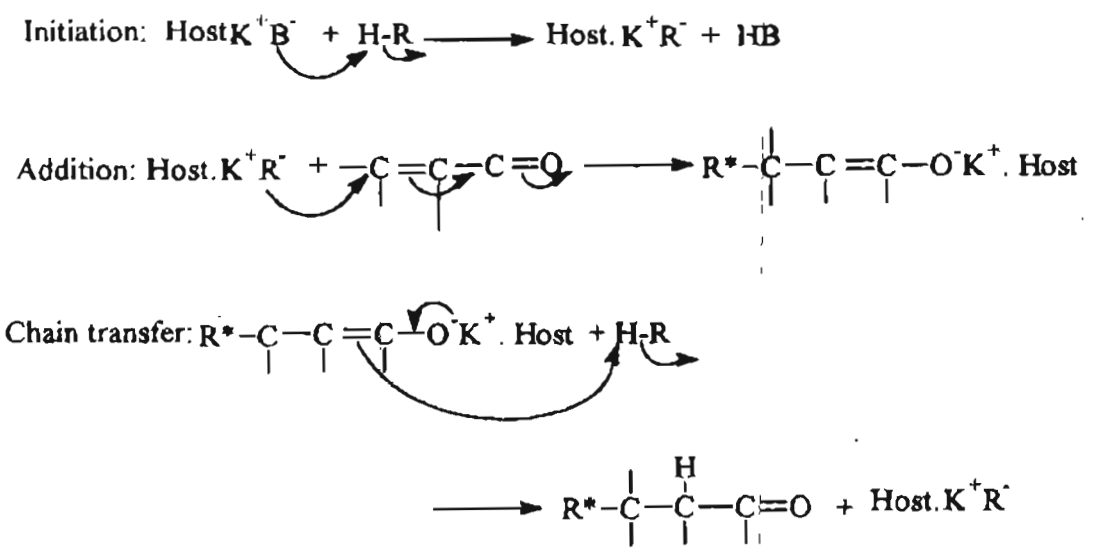
The energy minimized structures of crown ethers **13-16** were determined using PC MODEL software. It was observed that the distance between the diagonal oxygen atoms is in the range of 4-9A° units. The incorporation of the steroid skeleton made a slight distortion to the macrocyclic ring from the normal crown ether structure, with the nonoptimal orientation of the ether oxygen atoms. Figures (a-d) show the energy minimized structures of crown ethers **13-16** respectively.



Energy minimized conformations of crown ethers 13-16 (MMX method)

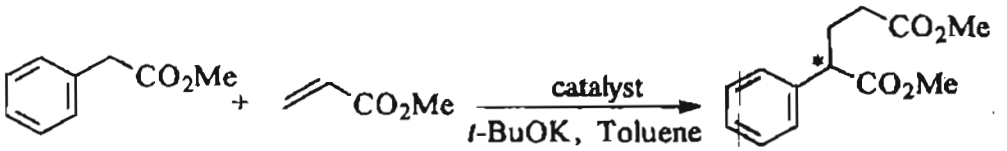
4.2.3 Asymmetric Michael reaction using crown ether 13 as a catalyst

Bergson reported the first example of a chiral catalyst which was used in the Michael reaction[22]. Potassium alkoxides were reported to complex with chiral hosts and catalyze Michael reactions[23] and it was suggested that the following catalytic chain reaction mechanism operates in these reactions (scheme-5).



Scheme-5

The preliminary complexation studies with the cations using crown ether **13** as the host revealed that the binding affinity was appreciable for K^+ ions (log K_a = 5.01). Therefore it was of interest to carry out Michael reactions using **13** as the catalyst. The addition of methyl phenylacetate to methyl acrylate in presence of the host using potassium *t*-butoxide as the base was investigated (scheme-6).



18

Scheme-6

The addition occurred and the product was formed in 28-30% chemical yield. The *ee* values range from 25-28%. The experimental conditions and the ratio of the substrates to the host are shown in Table 2.

Table 2

Entry	Temp °C	Substrate ratio[a]	Reaction period (h)	Yield (%)	$[\alpha]_D$	*ee* (%)[24]
1	-15°C	1:0:40:15	3	28	-	-
2	-5°C	1:1:40:15	3.5	30	24	27
3	-15°C	1:1:40:15	3.5	29	26	30

a) *t*-BuOK : host : methyl phenylacetate : methyl acrylate

In conclusion, the facile synthesis of a class of novel crown ethers has been accomplished. The starting materials are readily available and all the crown ethers are obtained in 38-42% yields. Interestingly the crown ethers **13** and **15** showed excellent binding affinities for various unipositive cations. Because of the appreciable binding affinity observed for K^+ ion, the crown ether **13** was used as a catalyst in an asymmetric Michael reaction. Although only moderate asymmetric induction was observed, it appears that further work will be fruitful in this area.

4.3 Experimental

A general description of the experimental techniques is given in chapter 2 (section 2.3). Tetrahydrofuran (THF) used was freshly distilled out from benzophenone ketyl, and sodium hydride (Spectrochem) was 60% emulsion in mineral oil. UV measurements were done with a Shimadzu UV-2100 spectrophotometer. Picrates of various cations were prepared according to the usual procedure[18].

The experimental procedure for the synthesis of methyl deoxycholate **11** is described in chapter 2 (section 2.3; compound No. **2a**)

3,12,24-cholan triol 12

Methyl deoxycholate **11** (1.218 g, 3 mmol) in dry THF (15 mL) was added dropwise to a suspension of lithium aluminium hydride (0.228 g, 6 mmol) in THF (10 mL) . The mixture was stirred for 30 min. at room temperature. Excess LAH was quenched with ice-cold dil. HCl and the reaction mixture was diluted with water (30 mL). The product was extracted into ethyl acetate (4X15 mL) and the organic layer was washed with saturated $NaHCO_3$ solution, saturated brine and then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the product purified by silica gel column chromatography. Elution with 60% ethyl acetate in hexane afforded **12** (1.01 g, 89 %) as a colourless solid and this was crystallized from ethyl acetate-hexane mixture; m p. 119-120°C[18].

IR (KBr)	: 3450, 3062, 2990, 1170 cm^{-1}.
^1H NMR (60 MHz, $CDCl_3$)	: δ 4.2-4.0 (m, 4H, OCH), 2.1 (brs, 3H, OH), 1.85-0.90 (m, steroidal CH and CH_2), 0.85 (s, 3H, CH_3)

Crown ether 13

A solution of the triol **12** (0.567 g, 1.5 mmol) in THF (25 mL) was added to a suspension of NaH (0.216 g, *ca* 9 mmol) in dry THF (10 mL). The mixture was refluxed for 1h under nitrogen atmosphere. Triethyleneglycol ditosylate **17a** (1.658g, 3.3 mmol) in dry THF (30 mL) was added slowly to the above mixture and stirred for 26h. Excess NaH was destroyed using ice-cold dil. HCl, the reaction mixture diluted with water (50 mL) and extracted into ethyl acetate (5X25 mL). The organic layer was washed successively with saturated $NaHCO_3$ solution, water and finally with saturated brine; dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the product by chromatography on silica gel column using 40% ethyl acetate in hexane as the eluent afforded the crown ether **13** (0.311 g, 42 %) as a colourless viscous liquid.

IR (KBr)	: 3455, 2998, 1426, 1172 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	: δ 3.75-3.20 (m, 16H, OCH), 1.85-1.0 (m, steroidal CH and CH_2), 0.89 (s, 3H, CH_3)
^{13}C NMR (67.8 MHz, $CDCl_3$)	: δ 87.6, 82.0, 81.6, 80.0, 75.5, 73.1, 71.5, 70.2, 67.3, 62.0, 48.7, 47.5, 47.2, 46.5, 45.5, 42.5, 35.5, 35.1, 34.5, 34.2, 33.2, 32.0, 27.5, 26.5, 24.3, 17.5, 12.5.

FABMS (*m/z*) : 492.36 (M^+, 5), 475.38 (30), 325.24 (100), 255.12 (60)

Crown ether 14

Triol **12** (0.567 g, 1.5 mmol) in dry THF (25 mL) was refluxed with NaH (0.216 g, *ca* 9 mmol) for 1h. Tetraethyleneglycol ditosylate **17b** (1.803 g, 3.3 mmol) dissolved in dry THF (30 mL) was added slowly to the above mixture at reflux temperature and stirred for 30h. The reaction mixture was worked up as described for compound **13** and the product purified by chromatography on silica gel column. Elution with 40% ethyl acetate in hexane afforded **14** as a colourless viscous liquid (0.305 g, 38 %).

IR (KBr) : 3450, 2990, 1426, 1175 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) : δ 3.90-3.20 (m, 20H, OCH), 1.85-1.20 (m, steroidal CH and CH_2), 0.85 (s, 3H, CH_3),

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 85.6, 84.2, 82.0, 80.2, 73.5, 72.6, 67.4, 62.0, 48.5, 47.2, 46.5, 35.5, 34.5, 33.4, 33.2, 32.0, 31.1, 27.5, 26.5, 24.3, 17.5, 12.5.

EIMS (*m/z*) : 536 (M^+, 4), 518 (25), 255 (100)

1,2-Bis(2-O-p-toluenesulphonylethoxy)benzene (17d)

Catechol (1.1 g, 10 mmol) was added to a solution of KOH (1.3 g, 23.17 mmol) in absolute ethanol (10 mL), and the resulting dark solution was stirred for 1h at room temperature. 2-Chloroethanol (1.7 g, 21.1 mmol) was added to the above solution and refluxed for 30h with stirring. The reaction mixture was

cooled and the suspension was filtered to remove the insoluble potassium salts. Ethanol was removed under reduced pressure and the residue was purified by chromatography on silica gel column using ethyl acetate as the eluent. The product was obtained (1.55 g, 78%) as a white solid; recrystallization from a mixture of dichloromethane and hexane afforded colourless crystals; m p. 110-111°C. This diol **17c** (1.0 g, 5.04 mmol) was tosylated by the usual procedure using tosylchloride and pyridine to afford the ditosylate **17d** (1.80 g, 70 %) as a colourless solid after chromatographic purification on silica gel column using 30% ethyl acetate in hexane as the eluent. The product was crystallized from a mixture of dichloromethane and hexane to afford colourless crystals; m p. 95-96°C.

IR (KBr)	: 2880, 1600, 1520 cm^{-1}
^1H NMR (60 MHz, $CDCl_3$)	: δ 7.35 9 (m, 8H, Ar-H), 6.8 (s, 4H, Ar-H), 4.1 (m, 8H, OCH), 2.3 (s, 6H, Ar-CH_3)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 148.4, 145.2, 132.6, 129.8, 127.5, 122.7, 115.6, 68.0, 67.3, 21.2.

1,4-Bis(2-hydroxyethoxy)benzene (17e)

Hydroquinone (2 g, 18.16 mmol) was added to a solution of KOH (2 g, 35.6 mmol) in absolute ethanol (20 mL) and stirred for 1h. This was followed by the addition of 2-chloroethanol (3.61 g, 44.83 mmol) and the mixture was refluxed for 30h with stirring. After cooling to room temperature, the suspension was filtered to remove the insoluble salts. Solvent was removed under reduced pressure, and the product was purified by chromatography on silica gel column using a mixture of ethyl acetate and hexane (9:1) as the eluent to afford **17e** as a white solid (3.32 g, 92%). This product was

crystallized from a mixture of chloroform and hexane to afford colourless crystals; m p. 109-110°C.

^{1}H NMR (90 MHz, $CDCl_3$) : δ 6.7 (s, 4H,Ar-H), 4.5-3.3 (m, 10H, OCH)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 148.6, 121.7, 114.3, 71.0, 60.6.

1,4-Bis(2-O-p-toluenesulphonylethoxy)benzene (17f)

A solution of the diol **17e** (1.5 g, 7.56 mmol) in dry $CHCl_3$ (50 mL) was treated with pyridine (4.846 mL, 60 mmol) and was cooled to 0°C. Tosyl chloride (3.6 g, 18.88 mmol) was added in small portions to the above solution while maintaining the temperature below 5°C. The resulting solution was stirred at room temperature for 16h, and then poured into ice-cold water. The product was extracted into ethyl acetate (4x25 mL), washed successively with 2N HCl, water, saturated $NaHCO_3$ solution and then with saturated brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the product by chromatography on silica gel column using 30% ethyl acetate in hexane as the eluent afforded **17f** (3.2 g, 38 %) as a white solid. Recrystallization from ethyl acetate-hexane mixture afforded colourless crystals of **17f**; m p. 141-142°C.

^{1}H NMR (90 MHz, $CDCl_3$) : δ 7.6 (m, 8H, Ar-H), 6.7 (s, 4H, Ar-H), 4.5-4.0 (m, 8H), 2.5 (s, 6H, Ar-CH_3)

^{13}C NMR (22.4 MHz, $CDCl_3$) : δ 152.69, 144.90, 132.94, 129.81, 127.90, 115.73, 68.17, 66.20, 21.58.

Crown ether 15

A suspension of NaH (0.216 g, *ca* 9 mmol) in THF (30 mL) containing the triol **12** (0.567 g, 1.5 mmol) was treated with the ditosylate **17d** (1.66 g, 3.3 mmol) as described for compound **13**. Work-up by the usual procedure followed by purification of the product by chromatography on silica gel column using ethyl acetate:hexane (25:75) afforded **15** (0.307 g, 38 %) as a colourless viscous liquid.

IR (KBr)	: 3460, 2990, 1598, 1427, 1175 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$)	: δ 6.95-6.85 (m, 4H, Ar-H), 4.1-3.2 (m, 12H, OCH_2), 1.22-0.8 (m, steroidal CH and CH_2), 0.85 (s, 3H)
^{13}C NMR (67.8 MHz, $CDCl_3$)	: δ 136.0, 129.1, 88.5, 86.5, 81.0, 80.0, 75.6, 68.3, 61.5, 48.0, 47.5, 47.1, 46.0, 45.5, 38.5, 35.0, 34.4, 33.5, 33.0, 31.0, 27.5, 26.4, 17.5, 12.0.
EIMS (*m/z*)	: 540 (M^+, 10), 522 (10), 342 (5), 255 (100)
Anal. calcd. for $C_{34}H_{52}O_5$	: C, 75.52; H, 9.69
Found	: C, 75.48; H, 9.71

Crown ether 16

NaH (0.216 g, *ca* 9 mmol) was taken in dry THF (15 mL) and a solution of triol **12** (0.567 g, 1.5 mmol) in THF (20 mL) was added to it and the mixture was refluxed for 1h. The ditosylate **17f** (1.658 g, 3.3 mmol) in dry THF (25 mL) was added slowly to the above mixture and refluxed for 28h. Work-up by the usual procedure was followed by chromatographic purification on silica gel

column using 25% ethyl acetate in hexane as the eluent; **16** was obtained as a colourless viscous liquid (0.229 g, 37%).

IR (KBr)	: 3456, 2992, 1598, 1430, 1177 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$)	: δ 7.0-6.9 (d, J = 7.5 Hz, 2H, Ar-H), 6.8-6.7 (d, J = 7.5 Hz, 2H, Ar-H), 4.0-3.5 (m, 12H, OCH), 1.22-0.9 (m, steroidal CH and CH_2), 0.85 (s, 3H, CH_3)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 136.0, 129.5, 126.2, 85.4, 81.5, 81.0, 71.5, 71.0, 68.0, 61.5, 48.0, 47.1, 42.3, 38.5, 35.0, 33.5, 32.2, 27.5, 26.4, 24.5, 17.5, 12.0.
EIMS (*m/z*)	: 540 (M^+, 20), 522 (10), 422 (10), 255 (100)

Determination of association constants

0.015 M picrate salt solutions of Li^+, Na^+, K^+, Cs^+ and NH_4^+ ions were prepared in distilled water. 0.5 mL each of these solutions was transferred into 12 mL centrifuge tubes. 0.5 mL of distilled water was taken in another tube as the blank. 0.2 mL of a solution of the crown ether **13** or **15** in $CDCl_3$ (0.075 M) was added to each of these tubes. The contents of the tubes were mixed by means of a vortex mixture for 5 min. and the solution was separated into two clear layers by centrifugation. 0.05 mL of the $CDCl_3$ layer was transferred to a 5 mL standard flask and made upto the mark with acetonitrile. The absorbance of each 5 mL solution was measured against the blank solution

at 380 nm. The orientation of the cell in the spectrophotometer was always kept constant.

Inorder to determine the extinction coefficient (ε) for each salt in acetonitrile and the distribution constant K_d of the picrates between water and chloroform, the picrate salt solutions ($10x10^{-6}$ M) in distilled water were prepared. Absorbance of each solution against acetonitrile at 380 nm was measured. To determine K_d, picrate salt solutions (0.015 M) in distilled water (20 mL) were shaken with 30 mL of ethanol-free chloroform in a separatory funnel and the layers were allowed to separate. After 18h the chloroform layer was transferred into a flask and was evaporated under vacuum. The residue was quantitatively transferred with acetonitrile to a 5 mL volumetric flask and diluted upto the mark. Keeping the path length constant (1 cm), absorbance at 380 nm was measured.

Michael adduct 18

Methyl phenylacetate (0.6 g, 4 mmol) in dry toluene (1.0 mL) was added slowly to a suspension of potassium *t*-butoxide (0.0112 g, 0.1 mmol) in toluene (1.0 mL) under argon atmosphere and stirred for 15 min. at -15°C. To this, a solution of the host **13** (0.0492 g, 0.1 mmol) in toluene was added and stirred for another 15 min. followed by the addition of methyl acrylate (0.129 g, 1.5 mmol) in toluene (1.0 mL). The product was extracted in to toluene (3x15 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the product was purified by chromatography on silica gel column using 6% ethyl acetate in hexane as the eluent. Adduct **18** was obtained as colurless viscous liquid[24] (0.29 g, 29%); $[\alpha]_D^{26}$ +26°, (c = 1%, $CHCl_3$)

IR (KBr)	: 2992, 1725, 1718, 1620 cm^{-1}
^1H NMR (90 MHz, $CDCl_3$)	: δ 7.5 (s, 5H, Ar-H), 3.5 (s, 6H, $COOCH_3$), 2.3 (m, 3H, -COCH), 1.9 (m, 2H)
^{13}C NMR (22.4 MHz, $CDCl_3$)	: δ 172.0, 171.5, 132.0, 129.5, 45.4, 45.0, 22.5.

Molecular mechanics calculations

Energy minimized structures of the crown ethers **13-16** were determined using PC MODEL Version 4 software available from Serena Software, USA, *on a PC-AT-486 machine. Minimizations were carried out with MMX force* field.

4.4 References

1. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
2. (a) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1991**, *91*, 1721. (b) Izatt, R. M.; Bradshaw, J. S.; Pawlak, K.; Bruening, R. L.; Tarbet, B. J. *Chem. Rev.* **1992**, *92*, 1261.
3. For leading references see; Rebek, J. Jr. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 245; Lehn, J. -M. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304; Diederich, F. N. *'Cyclophanes', Royal Society of Chemistry, Cambridge*, **1991**; Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philip, D.; Pietraszkiewiez, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193; Seel, C.; Vogtle, F. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 528.
4. (a) Galan, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; Mendoza, J. de. *J. Am. Chem. Soc.* **1992**, *114*, 1511. (b) Nakajaki, M.; Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 787. (c) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4941.
5. Anderson, D. W.; Ashton, P. R.; Black, R. M.; Leigh, D. A.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 904.
6. Kyba, E. P.; Siegel, M. G.; Sousa, L. R.; Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2691.

7. Diederich, F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 362.
8. Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463.
9. Coteron, J. M.; Vicent, C.; Bosso, C.; Penades, S. *J. Am. Chem. Soc.* **1993**, *115*, 10066.
10. Kanakamma, P. P.; Mani, N. S.; Nair, V. *Synth. Commun.* **1996**, *25*, 0000.
11. Mani, N. S.; Kanakamma, P. P. *Tetrahedron Lett.* **1994**, *35*, 3629.
12. Kanakamma, P. P.; Mani, N. S.; Maitra, U.; Nair, V. *J. Chem. Soc., Perkin Trans 1.* **1995**, 2339.
13. Shinkai, S.; Nishi, T.; Matsuda, T. *Chem. Lett.* **1991**, 437.
14. (a) Maitra, U.; Bag, B. G. *J. Org. Chem.* **1992**, *57*, 6979. (b) Maitra, U.; Mathivanan, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1469.
15. (a) Davis, A. P.; Orchard, A. M.; Slawin, Z.; William, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 612. (b) Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem. Int. Ed. Engl.* **1990**, 29.
16. After the synthesis of crown ethers **13-16** was completed we became aware of the synthesis of a crown ether from cholic acid, Maitra, U.; Bag, B. G. *J. Org. Chem.* **1994**, *59*, 6114.
17. Baker, J. F.; Blickenstaff, R. T. *J. Org. Chem.* **1975**, *40*, 1579.
18. Spero, G. B.; McIntosh, A. V. Jr.; Levin, R. H. *J. Am. Chem. Soc.* **1948**, *70*, 1907.
19. Kabalka, G. W.; Varma, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.

20. Moore, S. S.; Tarnowsky, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.

21. (a) Copland, M. A.; Fuoss, R. M. *J. Phys. Chem.* **1964**, *68*, 1177.
(b) Silbverrad, O.; Phillips, H. A. *J. Chem. Soc.* **1908**, *93*, 474.
(c) Brown, R.; Jones, W. E. *J. Chem. Soc.* **1946**, 781.

22. Langstrom, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.

23. (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057.
(b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2738.

24. Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625.

SUMMARY

The thesis entitled **ASYMMETRIC SYNTHESIS USING NOVEL CHIRAL AUXILIARIES AND THE SYNTHESIS OF NOVEL HOST MOLECULES** embodies the results of our investigations in the area of asymmetric synthesis.

An introduction to the thesis highlighting the various methods that are commonly employed in the synthesis of optically active compounds is given in the first chapter. This includes a brief description of the classical methods of asymmetric synthesis and a selective but more detailed account of the use of chiral catalysts and auxiliaries.

Chapter 2 deals with the synthesis of optically active γ-phenyl-γ-butyrolactone (**6a**) and δ-phenyl-δ-valerolactone (**6b**) in optically active form using deoxycholic acid **1a** and cholic acid **1b** as chiral auxiliaries. The strategy involves attachment of prochiral moieties containing keto group to the auxiliaries followed by reduction of the keto group under various conditions to afford the hydroxy esters. The auxiliaries are removed by saponification to afford the lactones **6a** and **6b** in optically active form. Modest *ee* values (upto 47%) are obtained when the ketoester derived from **1a** is reduced using $NaBH_4$ in presence of $ZnCl_2$. A transition state model is proposed to explain the results. It is observed that temperature does not have any appreciable effect on the level of chiral induction.

A facile synthesis of the anhydrofuranosides **2a** and **2b** along with their use as auxiliaries in the synthesis of optically active lactones constitutes the subject matter of the third chapter. γ-phenyl-γ-butyrolactone (**8a**), δ-phenyl-δ-

butyrolactone (**8b**), γ-methyl-γ-butyrolactone (**8c**) and δ-methyl-δ-valerolactone (**8d**) are obtained with good *ee* values especially when **2b** is used as the chiral auxiliary. An *ee* value of 93% is obtained for **8a**, when the reduction is carried out using $NaBH_4$ in presence of $ZnCl_2$ and this compares favourably with that obtained by the enzymatic methods. A rationalization of the results in the light of a transition state model is also included in this chapter. A synthesis of (-) mandelic acid, albeit in 32% *ee*, is also described in this chapter. The potential use of **2b** as a chiral auxiliary in Diels-Alder reaction is illustrated by the synthesis of **18** by the cycloaddition of cyclopentadiene to the cinnamate **15** derived from **2b**.

Chapter 4 contains the results of our investigations on the synthesis of crown ethers incorporating steroid moiety. The novel crown ethers **13-16** have been sythesized from deoxycholic acid and their energy minimized structures were obtained using PC MODEL software. The crown ethers **13** and **15** were used as hosts for the compexation of various unipositive cations and the use of **13** as catalyst in an asymmetric Michael reaction was investigatd.

It is evident from the results presented in this thesis that useful chiral auxiliaries can be derived from inexpensive and readily available natural products such as bile acids and D-glucose. The anhydrofuranoside **2b** is found to be a superior auxiliary for the synthesis of chiral lactones; *ee* values >90% are obtained with **2b**.

It is noteworthy that most other methods available for the synthesis of γ- or δ-phenyl lactones lead to racemization. In this context the present method which is efficient and simple is particularly attractive. It is anticipated that auxiliaries such as **2b** will be useful in a number of other transformations of importance in organic synthesis.

List of publications

1. Asymmetric induction using bile acids as chiral auxiliaries; V. Nair and *J. Prabhakaran*, Ind. J. Chem., 1995, 34B, 841
2. Novel crown ethers from 7-deoxycholic acid; V. Nair and *J. Prabhakaran*, Synth. Commun., 1995, 0000
3. Asymmetric induction using novel chiral auxiliaries derived from D-glucose; V. Nair and *J. Prabhakaran*, J. Chem. Soc., Perkin Trans 1 (communicated)
4. Novel chiral auxiliaries in asymmetric synthesis; V. Nair and *J. Prabhakaran*, POST IUPAC-ICOS 10, Trivandrum, December 1994, Abstracts P-21