PIG LIVER ACETONE POWDER (PLAP) MEDIATED ENANTIOSELECTIVE SYNTHESIS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

PEDDINTI RAMA KRISHNA

SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD - 500 134.
INDIA

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To
My Parents

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STATEMENT

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

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

P.Rama Krishna

Hyderabad **P.RAMA KRISHNA**

February, 1994

CERTIFICATE

Certified that the work contained in this thesis entitled **"Pig Liver Acetone Powder (PLAP) Mediated Enantioselective Synthesis"** has been carried out by Mr. P.Rama Krishna, under my supervision and the same has not been submitted elsewhere for a degree.

DEAN
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

D. BASAVAIAH
(THESIS SUPERVISOR)

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I thank all my friends in the School for their help. I gratefully acknowledge the help provided by technical and non-teaching staff.

I take this opportunity to convey my deepfelt love and regards to all the members of my family for thier love, encouragement and support.

Financial assistance by CSIR, New Delhi, is gratefully acknowledged.

P.Rama Krishna

ABBREVIATIONS

Ac	acetyl
bp	boiling point
Bu	butyl
^{i}Bu	*iso*-butyl
^{t}Bu	*tert*-butyl
Bn	benzyl
Conf.	(absolute) configuration
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
Et	ethyl
Eu(hfc)$_3$	tris[3-(heptafluoropropylhydroxymethylene)-(-)-camphorato], europium(III) derivative
LAH	lithium aluminum hydride
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
mp	melting point
MTPACl	α-methoxy-α-(trifluoromethyl)phenylacetyl chloride
Np	naphthyl
PCC	pyridinium chlorochromate
Ph	phenyl
PLAP	pig liver acetone powder
Pr	propyl
^{i}Pr	*iso*-propyl
PTC	phase transfer catalyst
Py	pyridine
THF	tetrahydrofuran
p-TsOH	*p*-toluenesulfonic acid

ABSTRACT

Synthesis of enantiomerically pure molecules is one of the fascinating and challenging areas in organic chemistry. Application of biocatalysis for this purpose has become increasingly important in recent years. Hydrolases (esterases, lipases and proteases) are of particular interest, since these enzymes can be used as such and do not require expensive or unstable cofactors. Inspite of biotransformations being widely used, apprehension still haunts synthetic organic chemists regarding the experimental techniques. Apart from this, inaccessibility of required enzyme hinders one to choose biotransformations in preference to conventional reaction methods.

With a view to provide an easy means of handling enzymatic reactions, we have undertaken the project "Pig liver acetone powder (PLAP) mediated enantioselective synthesis". This thesis deals with the utilization of esterase from crude pig liver acetone powder for the synthesis of optically active compounds. The thesis consists of three chapters (i) Introduction, (ii) Objectives, Results and Discussion and (iii) Experimental. In the introduction chapter, literature concerning some important biotransformations has been presented.

The second chapter comprises of objectives, results and discussion. The main objective of our work was to synthesize enantiomerically enriched molecules such as *trans*-2-aryloxycyclohexan-1-ols

(**80-91**) and *trans*-2-alkoxycyclohexan-1-ols (**98-103**), chiral α-hydroxy acids **109-112**, chiral diols **114**, **118**, **122** and **123**, chiral α-substituted ketones **125-129**, **132** and **133**, epoxy alcohol **134** and axially dissymmetric molecule **135** by utilizing PLAP.

The cyclohexyl based chiral auxiliaries such as menthol, Corey's 8-phenylmenthol, Whitesell's *trans*-2-phenylcyclohexanol are some of the commonly used chiral auxiliaries in asymmetric transformations. With a view that structurally related *trans*-2-aryloxycyclohexan-1-ols would be of interest as chiral auxiliaries in organic synthesis, we have undertaken the synthesis of enantiomerically pure *trans*-2-aryloxy-cyclohexan-1-ols. We have prepared a representative class of racemic *trans*-2-aryloxycyclohexan-1-ols {Ar = phenyl (**80**); 4-methylphenyl (**83**); 2-methoxyphenyl (**84**); 4-phenylphenyl (**88**); 4-*tert*-butylphenyl (**89**); 2,4-dimethylphenyl (**91**)} and converted them to the corresponding acetates. These racemic acetates were subjected to PLAP catalyzed enantioselective hydrolysis in biphasic medium (ether/phosphate buffer, pH 8.0). The resulting (-)-alcohols were obtained in 90->99% optical purities.

It was noticed that the optical purities of *trans*-2-aryloxy-cyclohexan-1-ols with *ortho*-substituted aryloxy groups were inferior to that of *para*-substituted ones. This observation has led us to examine the effect of *ortho*-, *meta*-, *para*-substituents in the aromatic ring of the *trans*-2-aryloxycyclohexyl acetate, on the enantiomeric purity of the product (-)-*trans*-2-aryloxycyclohexan-1-ol. For this

purpose we have prepared some more *trans*-2-aryloxycyclohexan-1-ols {Ar = 2-methylphenyl (**81**); 3-methylphenyl (**82**); 3-methoxyphenyl (**85**); 4-methoxyphenyl (**86**); 2-phenylphenyl (**87**); 4-bromophenyl (**90**)} with *ortho*-, *meta*- and *para*-substitutions in the aromatic ring. PLAP hydrolysis of the corresponding acetates produced the desired (-)-alcohols in 13-96% ee. These results also indicate that *para*-substituted aryloxy groups provide better selectivities.

Absolute configuration of (-)-*trans*-2-phenoxycyclohexan-1-ol (**80**) was determined to be (R,R) by synthesizing the same molecule *via* monophenylation of (R,R)-cyclohexane-1,2-diol. With a view to determine the absolute configuration and study the potential in enantioselective synthesis, we have used (-)-*trans*-2-(4-phenylphenoxy)cyclohexanl-ol (**88**) and (-)-*trans*-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (**89**) as chiral auxiliaries for the synthesis of chiral α-hydroxy acids. The resulting α-hydroxy acids were obtained in 76-96% ee with (R)-configuration.

It was reported that the reaction of RZnCl with (R,R)-2-phenoxycyclohex-1-yl phenylglyoxylate produced (R)-α-hydroxy acids. On the basis of sense of asymmetric induction in the above reaction, the absolute configurations of (-)-*trans*-2-(4-phenylphenoxy)cyclohexan-1-ol (**88**) and (-)-*trans*-2-(4-*tert*-butylphenoxy)cyclohexanl-ol (**89**) were assigned as (R,R). In analogy the absolute configurations of all other (-)-*trans*-2-aryloxycyclohexan-1-ols were tentatively assigned as (R,R).

We have provided a possible explanation for the (R,R) selectivity in the hydrolysis of *trans*-2-aryloxycyclohexyl acetates and for the variation in enantiomeric purities (due to the effect of *ortho*-, *meta*-, *para*-substitutions in the aromatic ring of *trans*-2-aryloxy-cyclohexanols) of the alcohols on the basis of three dimensional (cubic) active-site model of PLE proposed by Jones.

After achieving reasonable success in the preparation of chiral *trans*-2-aryloxycyclohexan-1-ols, we have directed our studies toward the synthesis of chiral *trans*-2-alkoxycyclohexan-1-ols (**98-103**). The racemic alcohols were prepared from cyclohexene oxide. The PLAP catalyzed hydrolysis of the corresponding racemic acetates **98a-103a** produced the chiral alcohols (-)-**98-103** in 61-82% enantiomeric purities.

Chiral α-hydroxy acids are important molecules of biological interest. Therefore we focused our attention towards the synthesis of chiral α-hydroxy acids. For this purpose we have first selected mandelic acid as target molecule. Accordingly a variety of alkyl O-acetylmandelates **104a-108a** were prepared and subjected to PLAP catalyzed hydrolysis. The resulting alkyl (S)-mandelates **104-108** were obtained in 23-81% ee.

Since methyl mandelate **104** was obtained in reasonably good enantiomeric purity (75%), we have examined hydroysis of representative methyl esters of α-acetoxy-α-arylacetic acids **109b-112b** with PLAP. The resulting chiral methyl (S)-α-aryl-α-hydroxyacetates

109a-112a were obtained in 26-57% enantiomeric purities.

Chiral 1,2-diols play an important role in asymmetric synthesis. We have selected a representative class of diols **114, 118, 122** and **123** for the resolution with PLAP. The resulting diols were produced upto 97% ee.

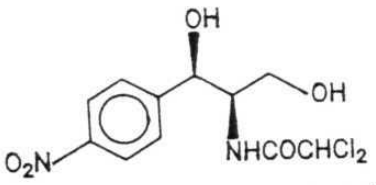
With a view to study the potentiality of PLAP for the enantioface-differentiating hydrolysis of enol acetates, we have prepared a variety of enol acetates **125a-129a, 132a** and **133a,** subjected them to PLAP catalyzed hydrolysis. The resulting ketones were obtained in 10-40% enantiomeric purities . No hydrolysis was observed when longer chain substitutions were present.

We have prepared (2R,3R)-epoxy alcohol **134** and axially dissymmetric alcohol (R)-**135** in 20% and 50% enantiomeric purities respectively *via* PLAP mediated hydrolysis of the corresponding racemic acetates.

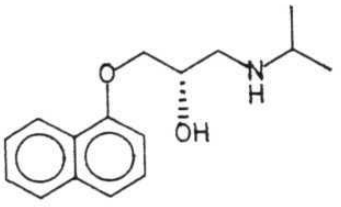
The third chapter provides experimental procedures in detail along with spectral data and physical constants (mp, bp and optical rotations). Determination of optical purities of several compounds is also described in detail.

INTRODUCTION

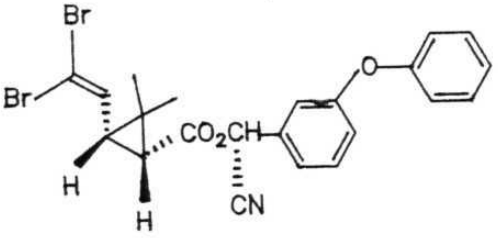
The development of methods for obtaining enantiomerically enriched molecules has become one of the most important goals in the fields of organic and bioorganic chemistry.[1] The importance of enantiomerically pure molecules stems from the central role of enantiomer recognition in biological activity.[2-4] For example (R,R)-chloramphenicol (1) is antibacterial while the corresponding (S,S)-isomer is inactive. (S)-Propranolol (2) is 100 times more active as β-blocking agent than the corresponding (R)-isomer. (R,R,S)-Deltamethrin (3) is a potent insecticide while the (S,S,R)-isomer is inactive.[3]



(R,R)–Chloramphenicol (1)



(S)–Propranolol (2)



(R,R,S)–Deltamethrin (3)

The dependence of biological activity of several chemical products on the enantiomeric purity of these molecules has led to the

development of a number of chiral reagents, chiral catalysts and synthetic strategies for synthesis of optically active molecules. Now the arsenal of synthetic organic chemists has become impressively very rich in methods for the preparation of enantiomerically enriched molecules.[1]

The application of biocatalysis to a variety of organic transformations has become increasingly important in recent years and the synthesis of enantiomerically pure molecules using chemico-enzymatic methodology is at present a well defined area of research which is evidenced by several monographs[5-7], reviews[8-16] and conferences[17-20] in the area. Due to high efficiency and substrate specificity of enzyme catalysis, applications of enzymes have become increasingly attractive to the organic chemists. Recent work of Klibanov[16] on the biotransformations of organic molecules in organic solvents has reduced the gap between the enzymes and organic chemistry thus making enzymes closer to organic chemists.

The available enzymes are traditionally classified into six groups: Oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases on the basis of the specific type of reaction that they catalyze.

Most of the work reported in the literature regarding biotransformations of organic molecules makes use of enzymes from the group hydrolases. The major advantage which make them (hydrolases) useful and attractive for organic chemists is the ready availability

and the non-requirement of added cofactor. Several hydrolytic enzymes (lipases and esterases) are now commercially available and some important ones are mentioned below.

Pig liver esterase	(PLE)	*Pseudomonas* Ak lipase	(lipase Ak)
Horse liver esterase	(HLE)	*Pseudomonas capacia* lipase	(PCL)
Asperigillus niger lipase	(ANL)	*Pseudomonas* sp. lipase	(PSL)
Bacillus subtilis lipase		*Pseudomonas* sp. SAM II lipase	
Candida cylindracea lipase	(CCL)	Porcine pancreas lipase	(PPL)

Since the thesis deals mainly with the enantioselective hydrolysis of racemic acetates, emphasis has been laid on the hydrolysis of esters and related systems.

During the last 15 years the literature is flooded with papers dealing with the preparation of enantiomerically enriched molecules *via* hydrolytic enzyme mediated reactions. As the literature is very vast we have selected some important examples for the synthesis of enantiomerically enriched molecules mediated by esterhydrolases. Literature covering the following aspects has been described.

1. Hydrolysis of alkyl esters
2. Hydrolysis of acyl alcohols
3. Esterification and transesterification
4. Miscellaneous transformations.

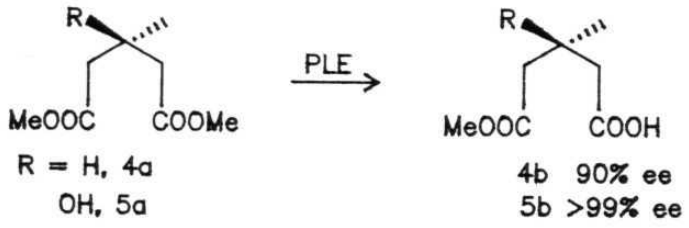
Enantioselective synthesis *via* hydrolysis:

One of the most exploited chapters in biocatalysis is the

enzymatic hydrolysis of a racemate or desymmetrization of *meso* or prochiral substrate to achieve the enantioselective preparation of chiral compounds. Several commercially available esterases, lipases and proteases have been employed for this purpose.

Hydrolysis of prochiral diesters:

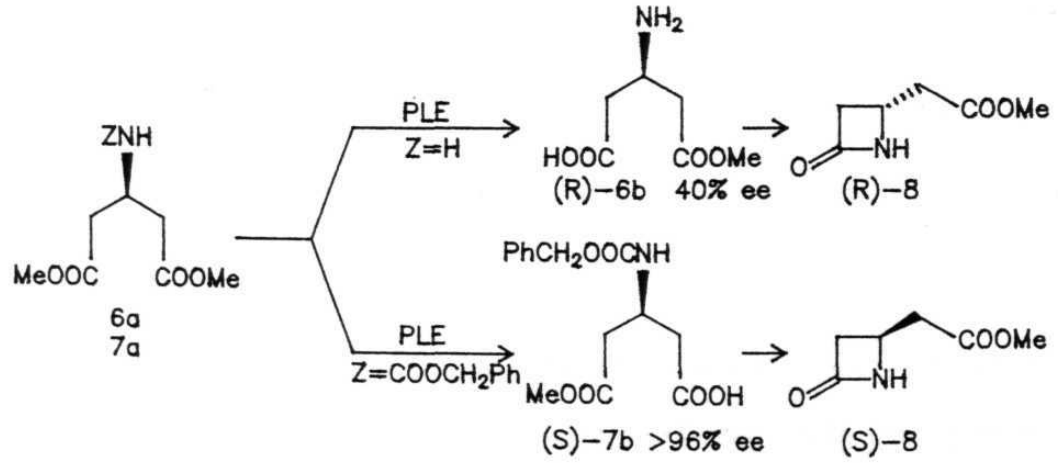
Desymmetrization of the prochiral diesters **4a** and **5a** was described by Tamm and co-workers[21] with PLE. The resulting half-esters **4b, 5b** have been obtained in high enantiomeric purities (Eq.1).



(1)

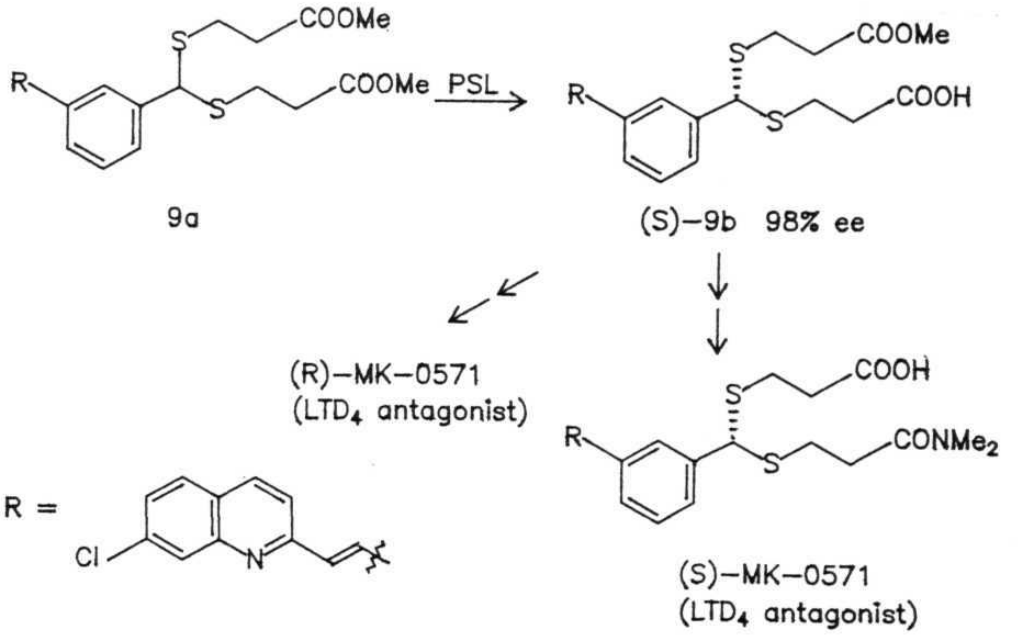
Ohno *et al.*[22] reported an efficient chemico-enzymatic methodology for the preparation of (R)- and (S)-2-azetidiones (8) *via* PLE catalyzed hydrolysis of diesters **6a** and **7a** (Scheme 1).

SCHEME 1:



Recently Huges *et al.*[23] used *Pseudomonas* sp. lipase (PSL) for selective hydrolysis of prochiral diester **9a** where the prochiral center lies four bonds away from the ester group (to be hydrolyzed) to provide desired chiral half-ester **9b** in >98% e.e. Half-ester **9b** can be converted into both enantiomers of potent LTD_4 antagonists. They have also found that if the prochiral centre lies three or five bonds away from the ester groups the resulting enantiomeric purities are inferior (Scheme 2).

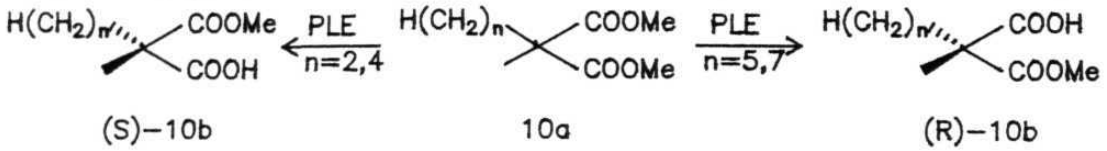
SCHEME 2:



Norin and co-workers[24] described remarkable reversal of enantio-selectivity with length of carbon chain in PLE catalyzed hydrolysis of dialkylated propionic acid diesters. Substrates with a methyl substituent and a short alkyl chain gave (S)-enantiomer in 73% ee whereas substrates with a methyl substituent and longer alkyl chain

produced (R)-enantiomer in 90% ee (Scheme 3).

SCHEME 3:

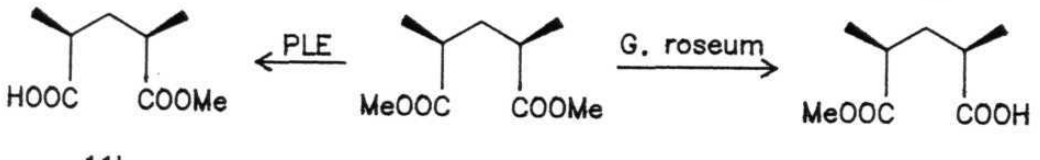


(S)−10b 10a (R)−10b

Hydrolysis of *meso*-diesters:

Sih and co-workers[25] reported chiral synthesis of bifunctional chiral synthons **11b** and **11c**. Hydrolysis of diester **11a** with PLE produced the half ester **11b** in 64% ee whereas microorganism *Gliocladium roseum* mediated hydrolysis produced other isomer **11c** in 98% ee (Scheme 4).

SCHEME 4:

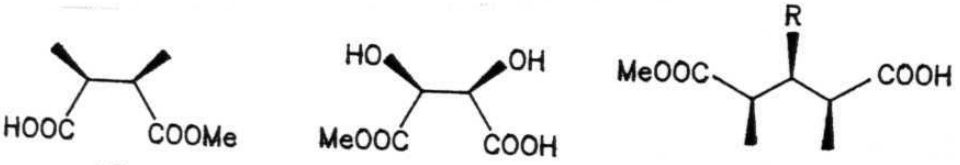


11b
64% ee

11a

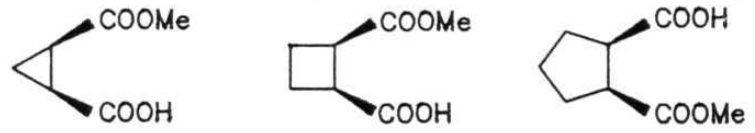
11c
98% ee

Straight chain *meso*-diesters have been enantioselectively hydrolyzed with PLE,[21] to produce half-esters **12-15** in 18-98% ee.



12 13 R = H, 14
OH, 15

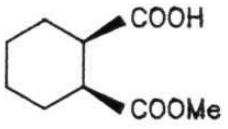
A wide range of monocyclic *meso*-diesters have been enantioselectively hydrolyzed by PLE producing the required half-esters **16-20** in high optical purities (97-100% ee) (except **18**, which was obtained in 17% ee). Ring size induced reversal of stereospecificity was observed in the hydrolysis of monocyclic *meso*-diesters by Tamm,[21] Jones[26] and Schneider.[27] Recently Crout[28] prepared monoester **21** in 86% ee by hydrolyzing the corresponding *meso*-diester with PLE.



16

17

18



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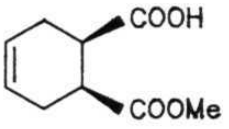

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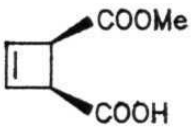
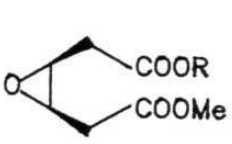
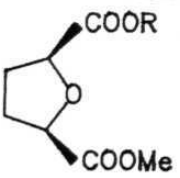


21

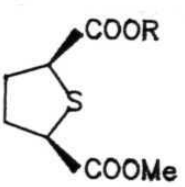
Heterocyclic *meso*-diesters **22a-24a** (R = Me) have been hydrolyzed[29,30] enantioselectively with PLE to produce the desired optically active acid esters **22b-24b** (R = H).



R = H 22b
99% ee



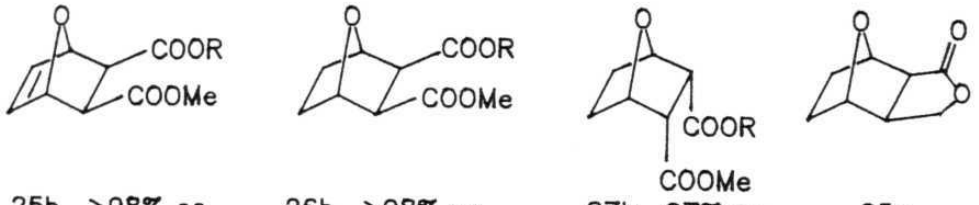
23b
42% ee



24b
46% ee

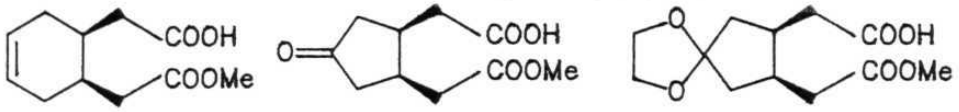
Bloch *et al.*[31] found that the bicyclic *meso*-diesters **25a-27a** (R =

Me) were good substrates for PLE catalyzed hydrolysis, thus producing the desired half-esters **25b-27b** in high enantiomeric purities. The chiral half ester **25b** (R = H) has been converted to tricyclic lactone **25c** which is a potential synthon for natural product synthesis.



R = H **25b** >98% ee **26b** >98% ee **27b** 97% ee **25c**

Recently Nagao *et al.*[32] have used PLE for the preparation of chiral half-esters **28-30**, which are useful synthons for (+)-carbacyclin.

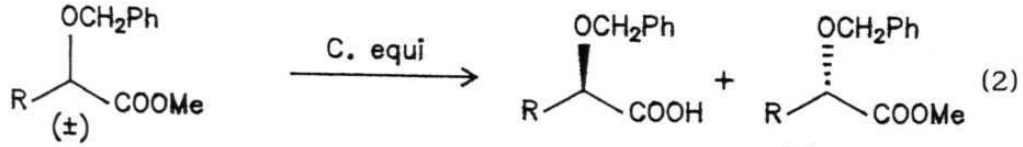


28 **29** **30**

76% ee **88% ee** **90% ee**

Hydrolysis of racemic esters:

Ohta *et al.*[33] synthesized chiral α-benzyloxycarboxylic esters in high optical purities *via* incubation of their racemic methyl esters



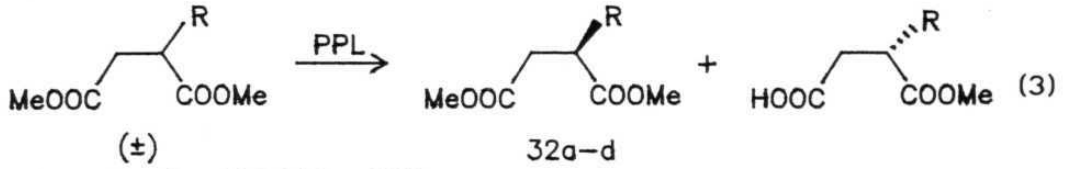
(2)

R = Et, n-Pr, n-Bu, Allyl

(S)-31
>99% ee

with grown cells of a bacterium, *Corynebacterium equi* IFO 3730 (Eq.2).

Racemic dimethyl succinates, aspartates and glutamate were hydrolyzed[34] with PPL to produce optically active dimethyl esters **32a-d** in 95-100% ee (Eq.3).

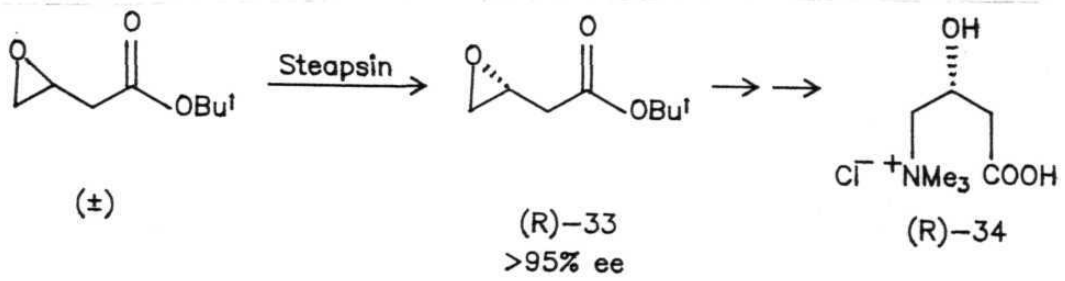


(±) 32a–d

R = Me, Bn, NHCOOBn, NHAc

Francalanci and co-workers[35] reported enantioselective hydrolysis of alkyl 3,4-epoxybutyrates with steapsin to obtain unreacted esters in high optical purities. *iso*-Butyl epoxybutyrate **33** which was obtained in >95% ee has been converted into (-)-(R)-carnitine chloride (**34**), a therapeutic agent in the treatment of myocardia ischaemia (Scheme 5).

SCHEME 5:

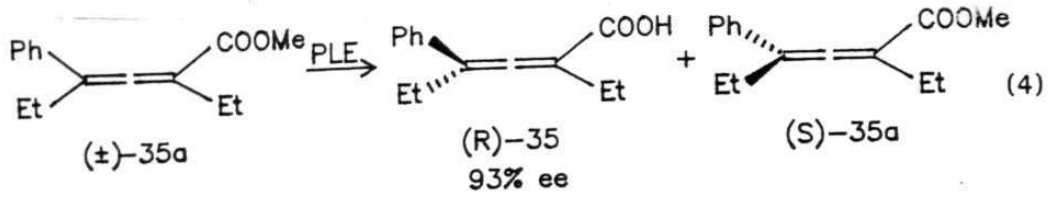


(±)

(R)–33
>95% ee

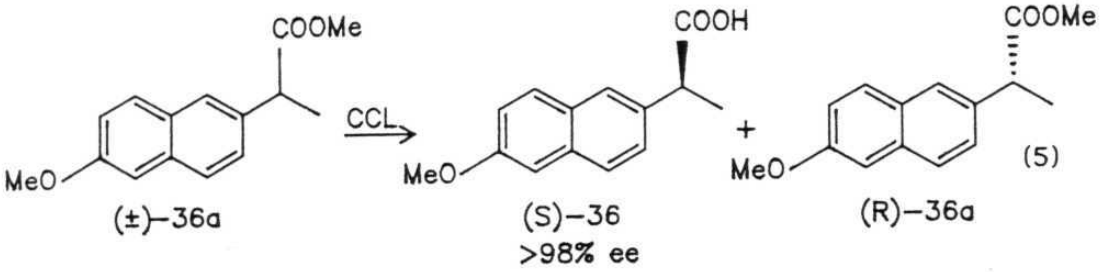
(R)–34

Jones and co-workers[36] employed PLE in the hydrolysis of various substituted racemic allenic esters. Highly substituted substrates proceed with high enantioselectivites (Eq. 4).



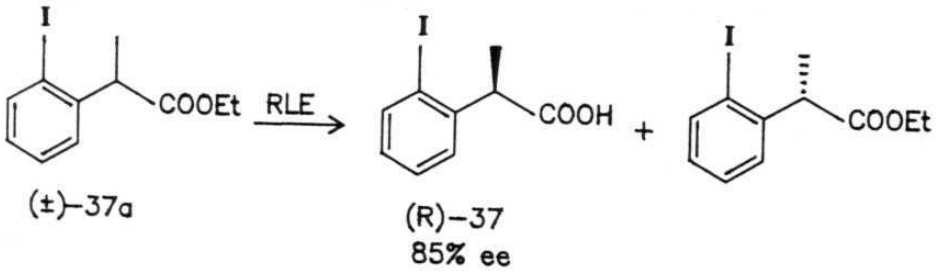
(4)

Sih and co-workers[37] subjected methyl ester of racemic naproxen (36a) to CCL catalyzed hydrolysis to obtain (S)-naproxen in >98% optical purity (Eq.5).



(5)

Rabbit liver esterase (RLE) mediated resolution of *ortho*-substituted 2-arylpropanoic acids was described by Senanayake *et al.*[38] They obtained (R)-acid in 85% ee in the hydrolysis of racemic ester (Eq.6).



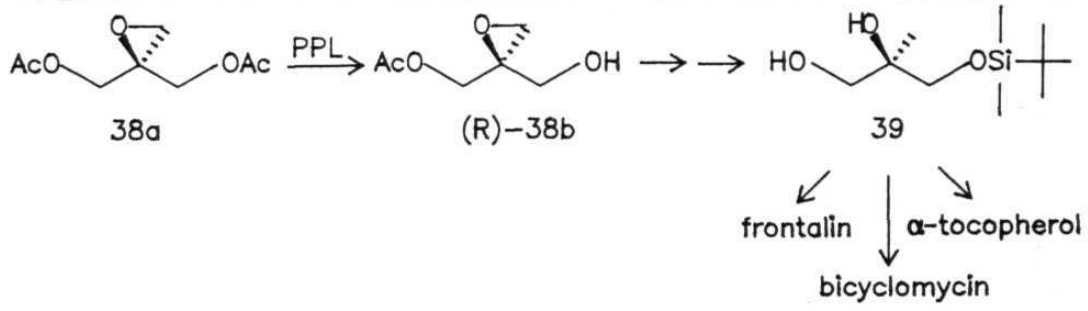
(6)

Hydrolysis of prochiral diacyl alcohols:

Recently Seu *et al.*[39] reported PPL catalyzed enantioselective

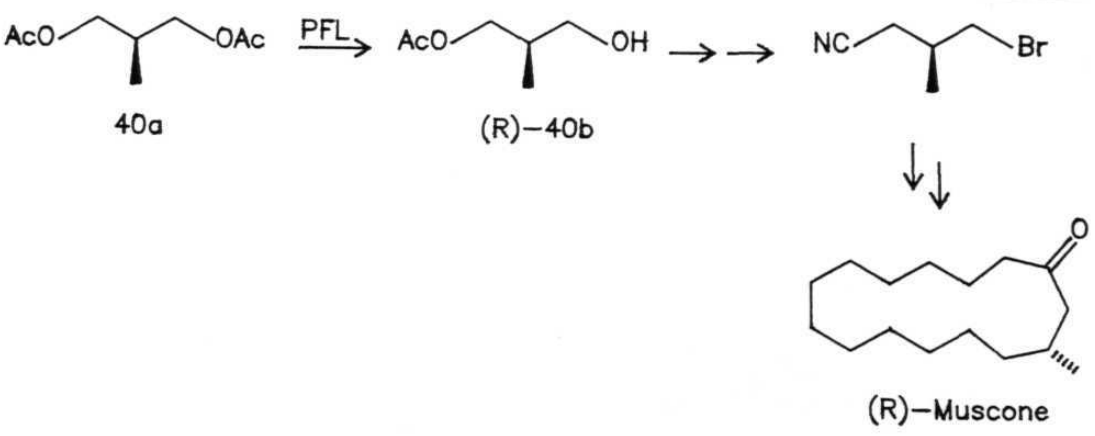
hydrolysis of diacetate **38a** producing (R)-2-acetoxymethylglycidol (**38b**). Its reductive product *tert*-carbinol, **39** is a useful chiral building block for the chiral syntheses of frontalin, bicyclomycin and α-tocopherol (Scheme 6).

SCHEME 6:



Sakai and co-workers[40] employed a chemico-enzymatic route to (R)-muscone. They subjected prochiral diacetate **40a** to PFL catalysis to get the chiral synthon **40b** which was subsequently converted to (R)-muscone (Scheme 7).

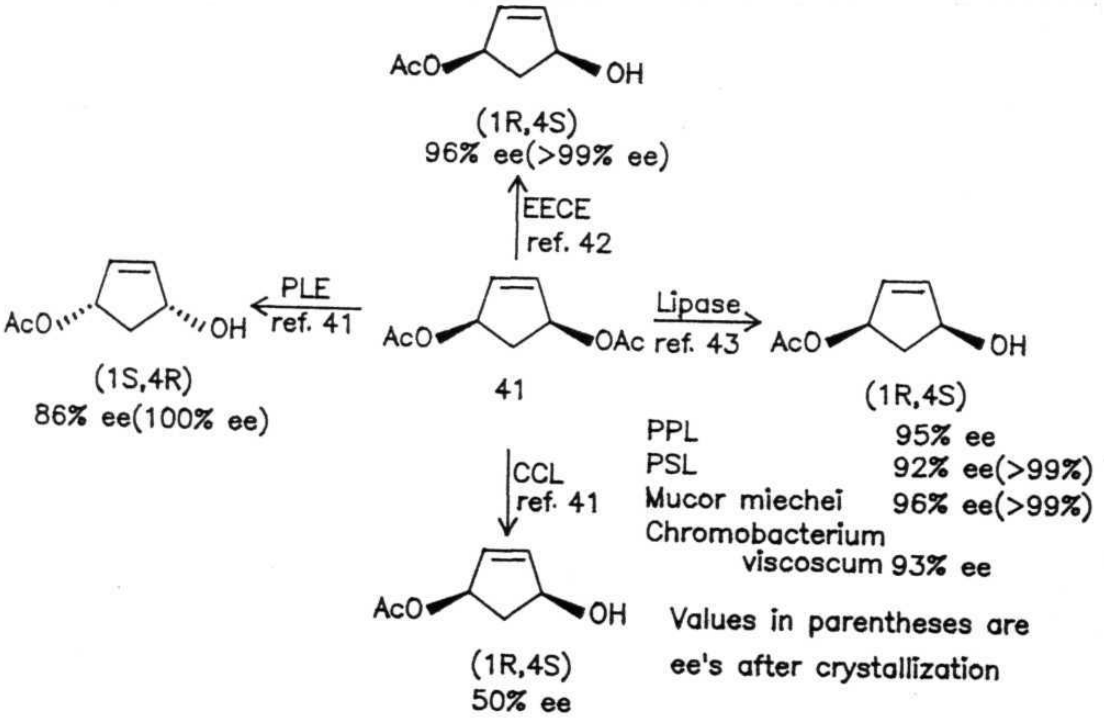
SCHEME 7:



Hydrolysis of *meso*-diacetyl alcohols:

Several enzymatic methods are known for the preparation of the chiral prostaglandin precursor from the corresponding *meso*-1,4-diacetoxycyclopent-2-ene (**41**). PLE provided the (1S,4R)-isomer in 86% ee whereas the (1R,4S)-enantiomer was obtained using CCL only in 50% ee.[41] The use of electric eel cholinesterase (EECE) produced (1R,4S)-isomer in 96% optical purity.[42] Lipases such as PPL, PSL, *Mucor miechei*, *etc.*, gave (1R,4S)-isomer in very high optical purities[43] (Scheme 8).

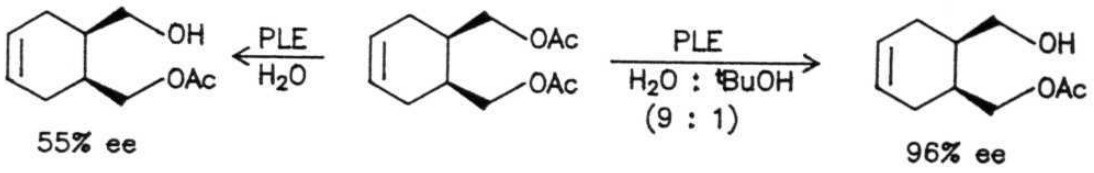
SCHEME 8:



Guanti *et al.*[44] reported PLE catalyzed hydrolysis of *meso*-diacetates and diesters and studied the influence of cosolvents. They

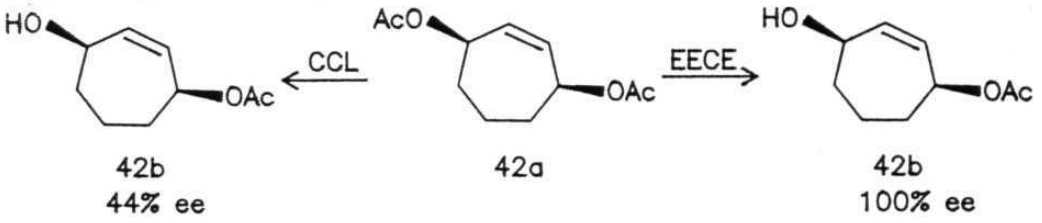
found 10% *tert*-butyl alcohol in water as the best cosolvent in terms of both chemical and optical yields (Scheme.9).

SCHEME 9:

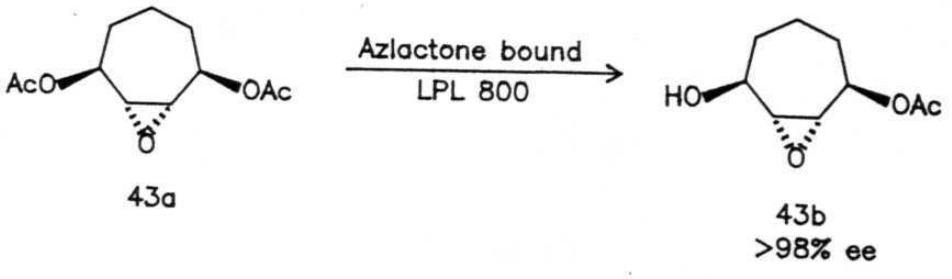


Electric eel cholinesterase (EECE) was employed to desymmetrize the diacetate **42a** to provide (R)-alcohol. The use of CCL for this purpose proved less effective[45] (Scheme 10).

SCHEME 10:



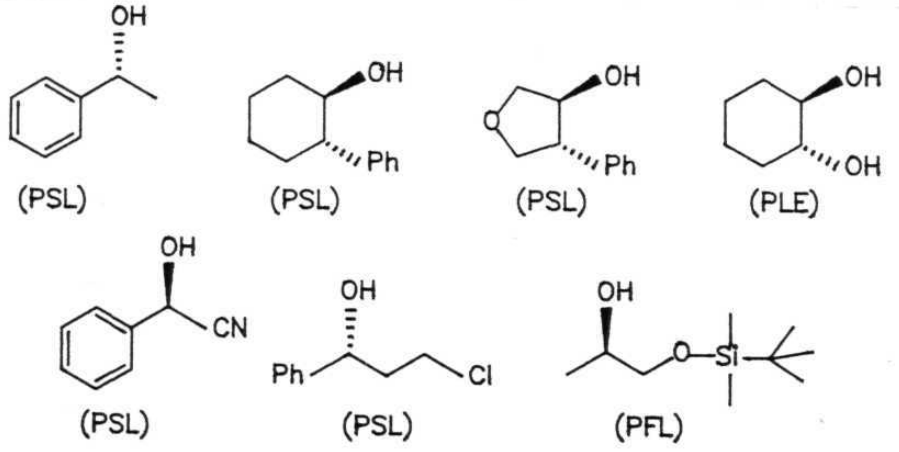
Quite recently asymmetrization of *cis*-3,7-dihydroxycycloheptane derivatives was reported.[46] Diacetate of *trans*-epoxide, **43a** was hydrolyzed with azlactone bound LPL-800 to give monoacetate **43b** in >98% optical purity (Eq.7).



(7)

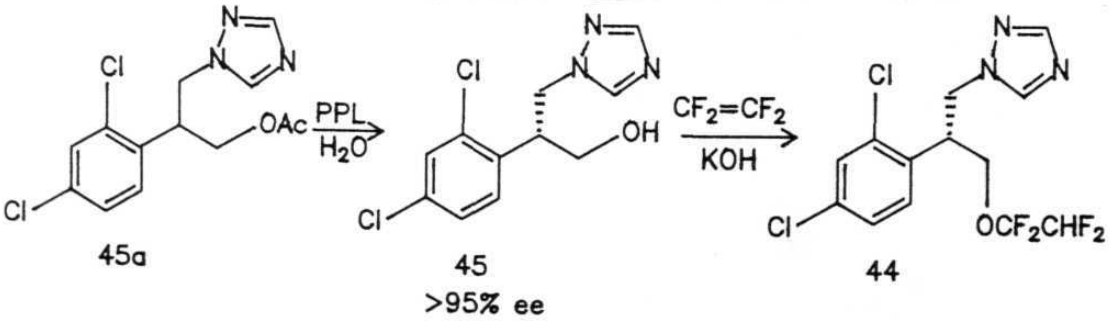
Hydrolysis of racemic acyl alcohols:

Schneider and co-workers[47] have used enzymatic methodology for the preparation of numerous acyclic and alicyclic secondary alcohols in very high enantiomeric purities *via* hydrolysis of the corresponding racemic acetates.

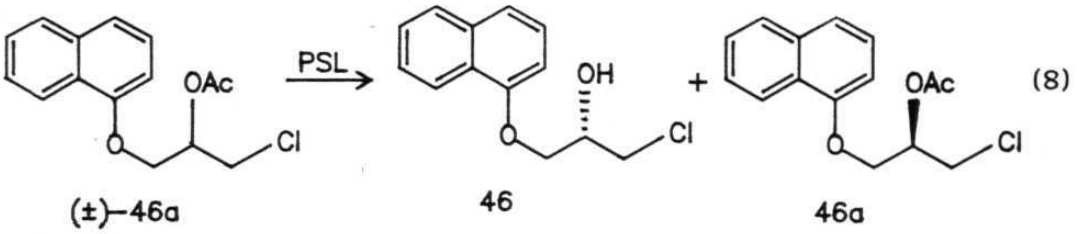


Recently Bianchi *et al.*[48] described the preparation of triazole fungicide **44** in high optical purities using optically active precursor **45** which was prepared *via* enzymatic route (Scheme 11).

SCHEME 11:



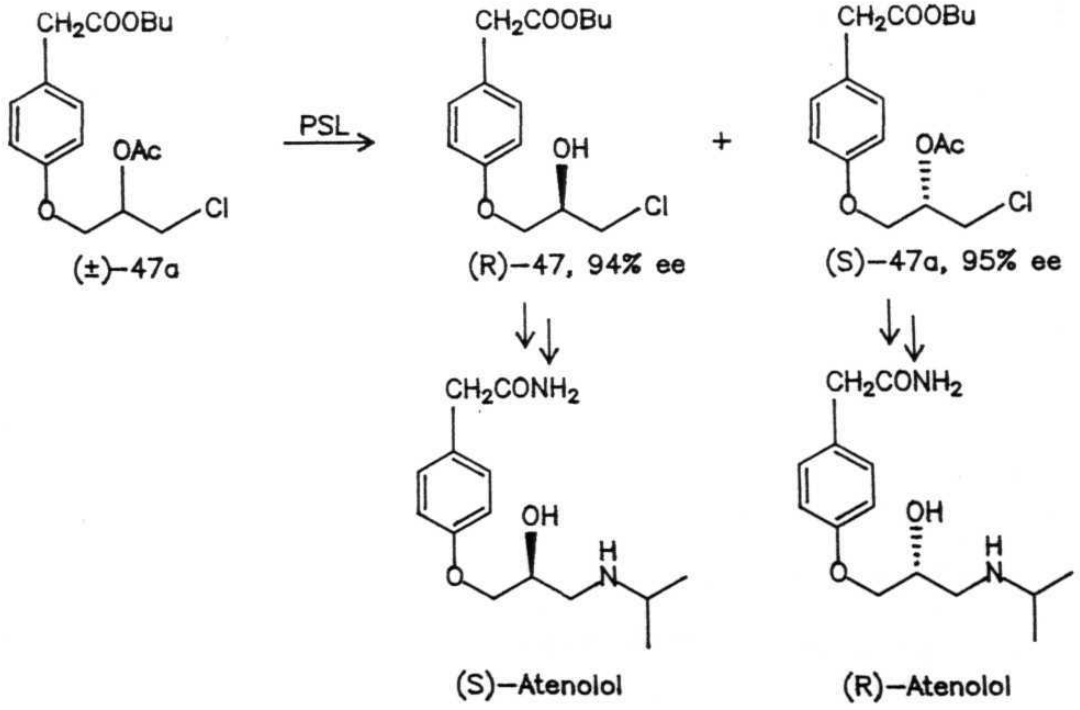
The key intermediates **46** and **46a** of (S)- and (R)-propranolol (**2**) were obtained by the hydrolysis of racemic acetate **46a** using lipase PS in high optical and chemical yields[49] (Eq 8).



(±)–46a 46 46a (8)

Lipase Amano PS catalyzed hydrolysis of racemic ester **47a** produces the resulting alcohol (R)-**47** and acetate (S)-**47a** in high optical purities. These molecules were subsequently converted into (S)- or (R)-atenolol[50] (Scheme 12).

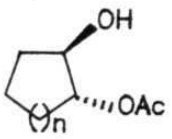
SCHEME 12:



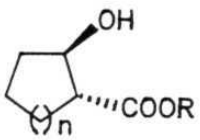
(±)–47a (R)–47, 94% ee (S)–47a, 95% ee

(S)–Atenolol (R)–Atenolol

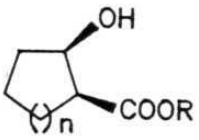
Sakai and co-workers utilized PFL for enantioselective hydrolysis of acetates of 2-substituted cycloalkanols to produce corresponding alcohols in high optical purities.[51,52]



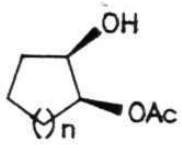
>99% ee
n = 1, 2, 3
R = Me, Et



>99% ee



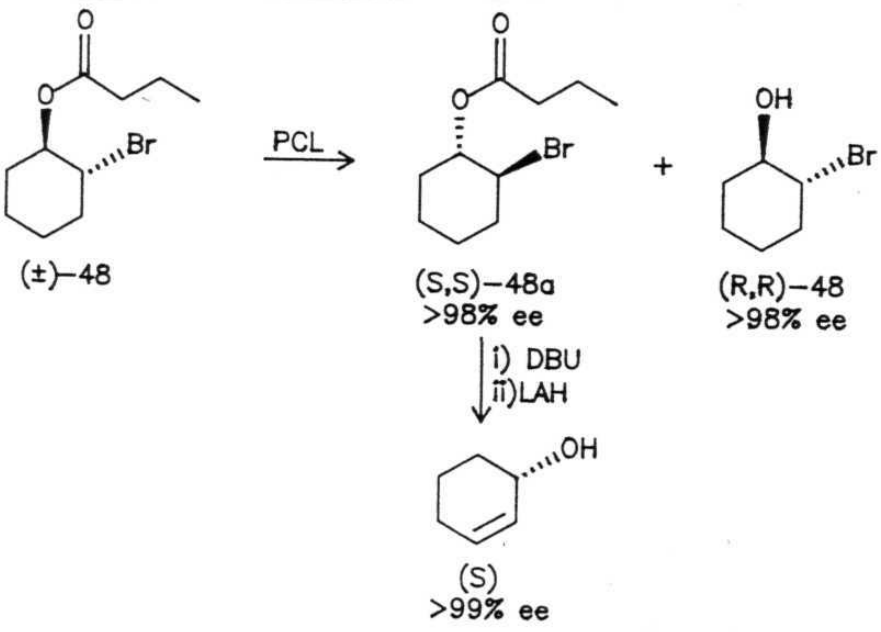
>99% ee



n = 1&3>99% ee
n = 2 70% ee

Very recently Gupta and Kazlauskas[53] described an efficient resolution of *trans*-2-bromocycloalkanols and their conversion to allylic alcohols. Direct resolution of cyclic allylic acetates was inefficient because both the substituents at stereocentre (CH_2CH_2 *vs* CH=CH) were similar in size. 2-Bromocycloalkyl acetates had a larger

SCHEME 13:



(±)–48

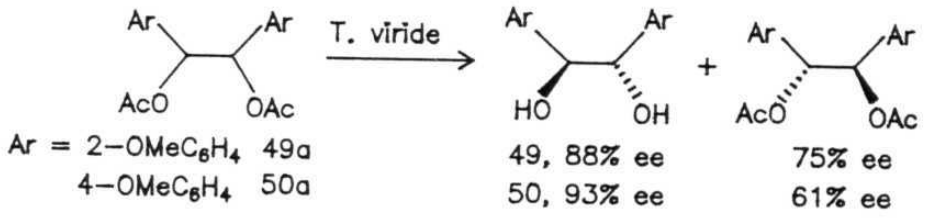
(S,S)–48a
>98% ee

(R,R)–48
>98% ee

(S)
>99% ee

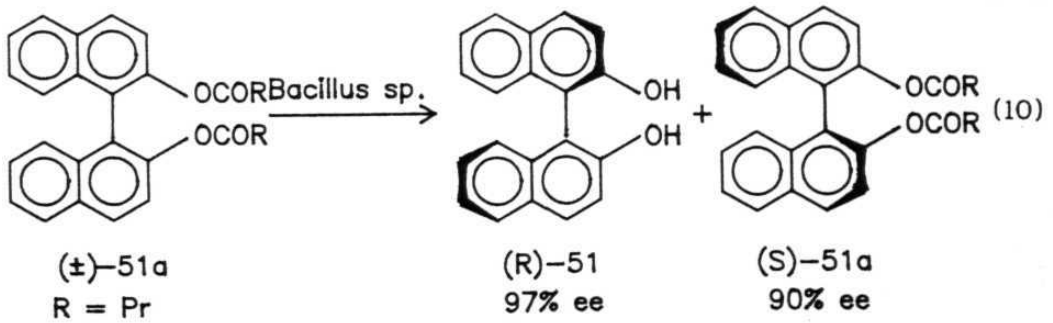
difference in size of the two substituents (CH_2 *vs* CHBr). Thus increasing the difference in size of the substituent helps the hydrolase in distinguishing the enantiomers (Scheme 13).

Microbial (*Trichoderma viride* IFO 9065) resolution of racemic diacetates **49a** and **50a** produced 1,2-bis(methoxyphenyl)ethane-1,2-diols **49** and **50** in high enantiomeric purities[54] (Eq 9).



(9)

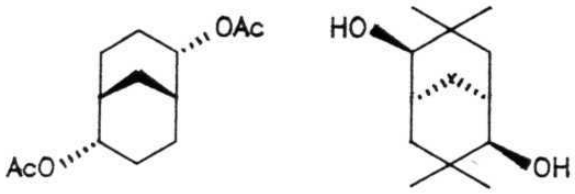
The first example of enzymatic preparation of axially dissymmetric molecule was reported by Ikekawa and co-workers.[55] They have subjected the diester (±)-**51a** for microbial (*Bacillus sp.* L-75) resolution to produce the chiral binaphthol (R)-**51** upto 97% ee (Eq 10).



(10)

Naemura *et al.*[56] obtained the optically active diacetate (-)-**52** (using CCL) and optically active diol (+)-**53** (using PLE) in high optical purities *via* enzymatic hydrolysis of the corresponding racemic

diesters. They prepared optically active crown ethers utilizing these optically active molecules.



(−)−52
95% ee

(+)−53
96% ee

Esterification and transesterification:

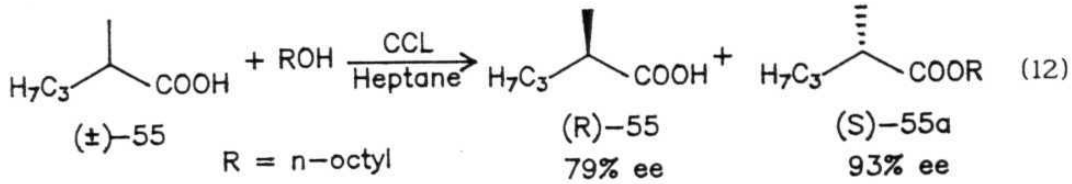
Hydrolytic enzymes such as esterases, lipases and proteases generally catalyze the reverse reaction (esterification) too. Low water concentration is required to minimize hydrolysis. The undesired hydrolysis has to be restrained to carry out esterification of preparative significance. The discovery of enzymatic catalysis in organic solvents by Klibanov paved way to esterification and transesterification.[16]

Klibanov and co-workers[57] described esterification of racemic α-haloacids **54** with *n*-butanol using CCL to produce (R)-esters **54a** and (S)-acids **54** in high enantiomeric purities (Eq.11).

$$\underset{\substack{(\pm)-54\\ R = Me, Bu, Ph\\ X = Br, Cl}}{RCHXCOOH} + n\text{-}BuOH \xrightarrow{CCL} \underset{(R)-54a}{RCHXCOOBu^{n}} + \underset{(S)-54}{RCHXCOOH} \qquad (11)$$

CCL catalyzed enantioselective esterification of α-methyl-

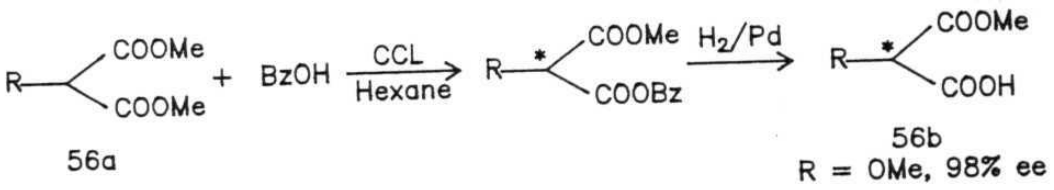
alkanoic acids in heptane was reported by Engel.[58] The resulting (R)-acids **55** and (S)-esters **55a** were obtained in moderate to high enantiomeric excesses (Eq.12).



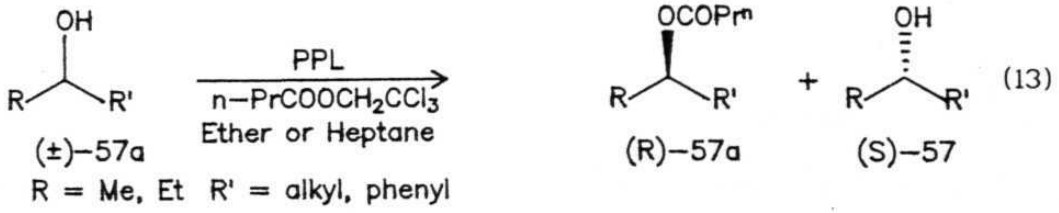
(12)

Recently Gutman *et al.*[59] described the first synthetic route to chiral monosubstituted malonates **56b** by transesterification of prochiral symmetrical dimethylmalonates **56a** with benzyl alcohol using CCL as biocatalyst (Scheme 14).

SCHEME 14:

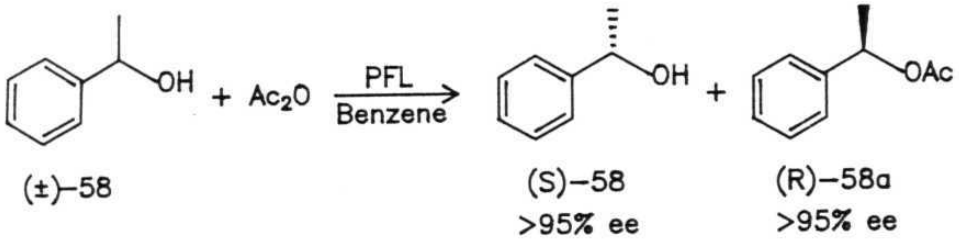


Klibanov and co-workers[57] reported transesterification of racemic alcohols **57** with trichloroethyl butyrate by PPL producing optically active alcohols (S)-**57** and esters (R)-**57a** in moderate to high enantiomeric purities (Eq.13).



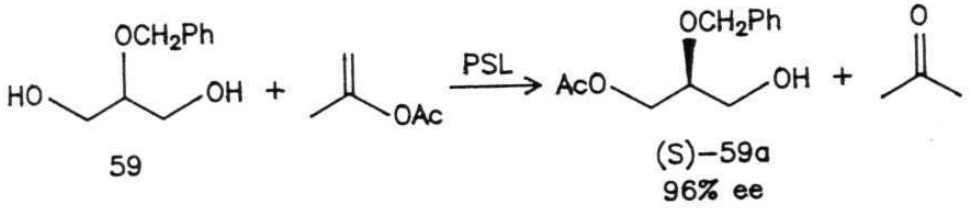
(13)

PFL catalyzed synthesis of optically active alcohols from the racemates was reported by Cesti and co-workers.[60] A number of primary alcohols and secondary alcohols were acylated in organic solvents with acid anhydride as acylating agent to produce esters in high optical purity. *sec*-Phenethyl alcohol (S)-**58** and its O-acetyl derivative (R)-**58a** were obtained in >95% ee by this procedure (Eq.14).



(±)–58 (S)–58 >95% ee (R)–58a >95% ee (14)

Recently Wang *et al.*[61] described isopropenyl and vinyl esters as acylating reagents in lipase-catalyzed irreversible transesterification. The enol freed on transesterification rapidly tautomerizes to



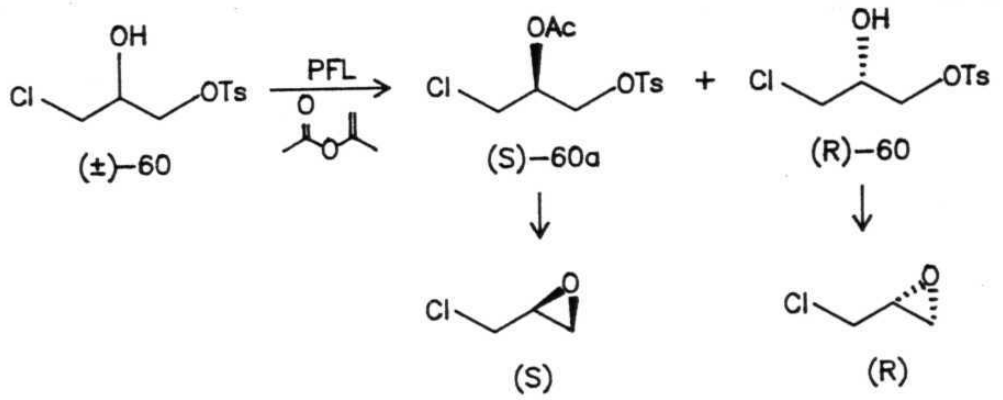
59 (S)–59a 96% ee (15)

the corresponding volatile acetaldehyde or acetone making the process irreversible and simpler for product isolation (Eq.15).

Chen and Liu[62] employed α-hydroxy tosylate **60** for lipase catalyzed transacylation in hexane to produce optically active α-hydroxy tosylate (R)-**60** and its O-acyl derivative (S)-**60a**. These

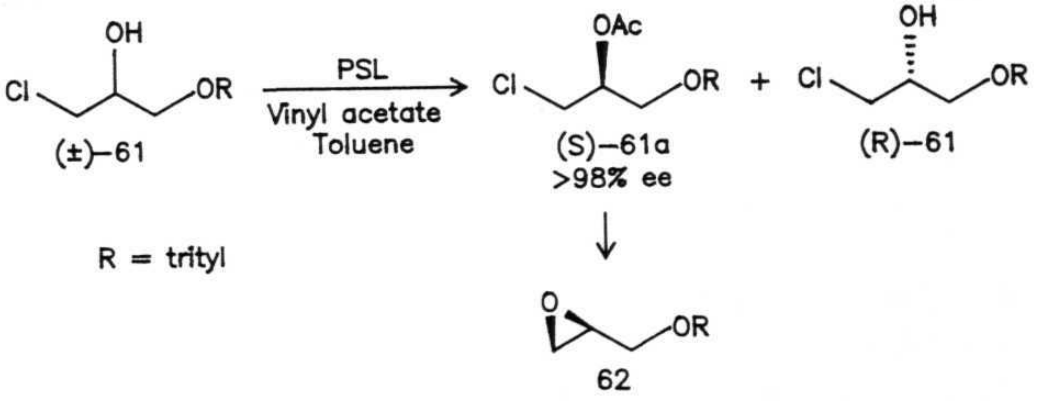
were subsequently converted into the corresponding 1,2-epoxides with high optical purities (Scheme 15).

SCHEME 15:



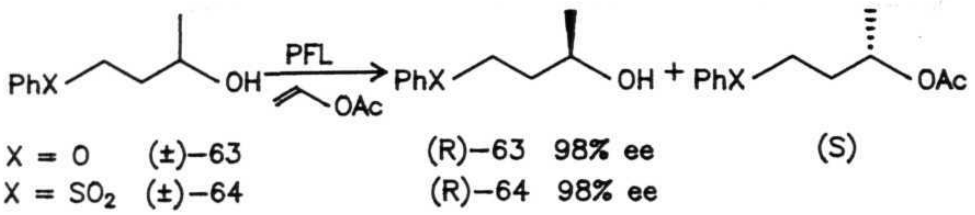
Lipase PS catalyzed enantioselective transesterification of O-trityl diol **61** in presence of vinyl acetate produced its O-acyl derivative (S)-**61a** in >98% ee which was subsequently transformed into (R)-tritylglycidol (**62**) a versatile C_3-synthon[63] (Scheme 16).

SCHEME 16:

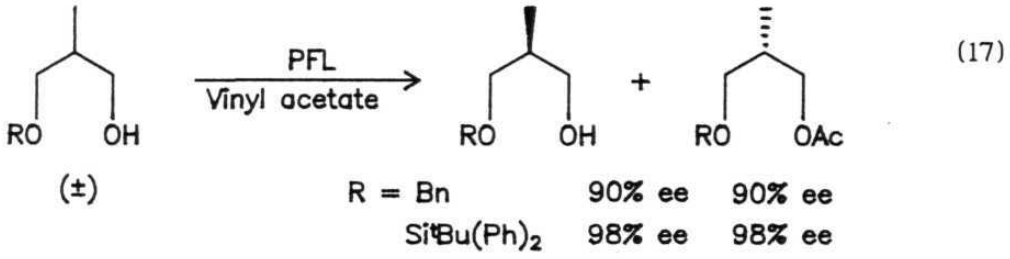


Santaniello and co-workers[64] produced chiral C_5 isoprenoid synthons **63, 64** in high optical purities *via* transesterification of

the corresponding racemic alcohols in chloroform in presence of PFL (Eq.16).

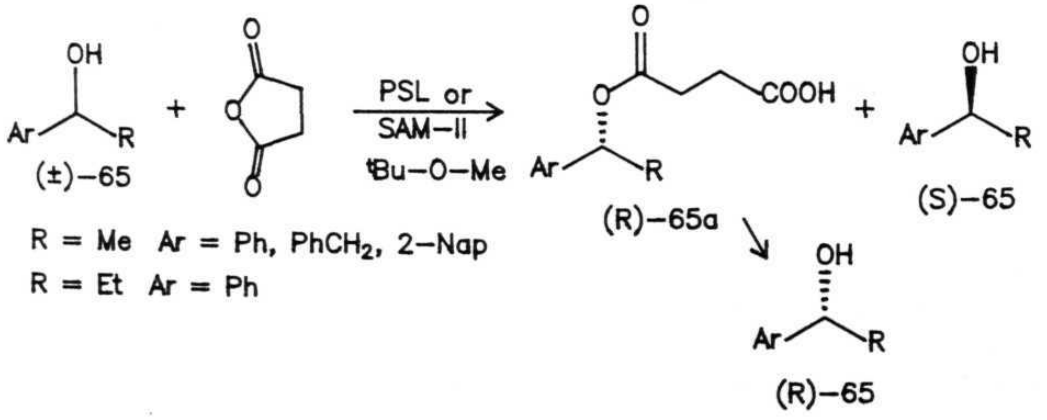


Santaniello and co-workers[65] described irreversible trans-esterification of racemic 2-methyl-1,3-propanediol derivatives in the presence of PFL (Eq 17).



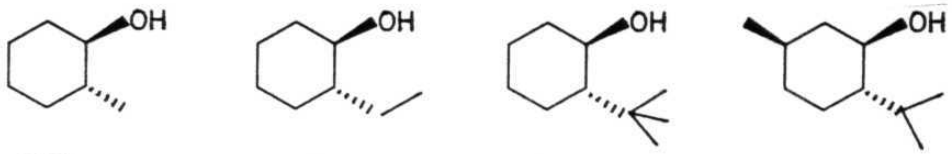
Racemic alkyl-aryl alcohols were resolved in high optical purities by enzymatic acylation with succinic anhydride in organic

SCHEME 17:



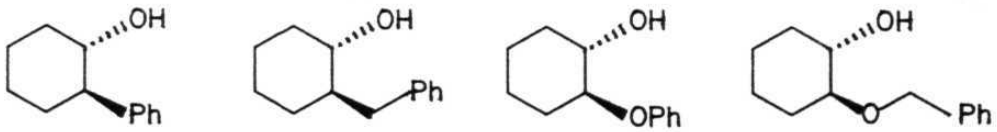
solvents.[66] A major advantage of this method is the ease of separating the ester from the unreacted alcohol (Scheme 17).

2-Alkylcyclohexanols were prepared in high optical purities *via* esterification with lauric acid in hexane using lipase MY (crude form of CCL).[67]



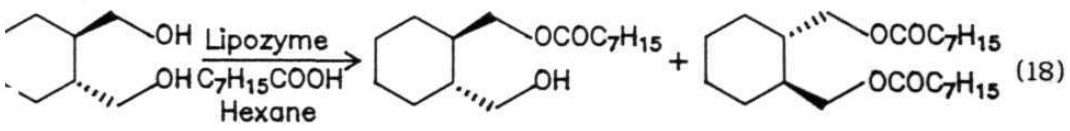
98% ee 96% ee 100% ee 95% ee

Recently Schneider and co-workers synthesized 2-substituted cyclohexanols, which are potential chiral auxiliaries, in high optical purities *via* irreversible transesterification in *tert*-butyl methyl ether with lipase SAM II.[68]



>95% ee >95% ee >95% ee >95% ee

Very recently enzyme catalyzed esterification of racemic *trans*-cyclohexane-1,2-dimethanol was reported by Roberts *et al.*[69] The diol



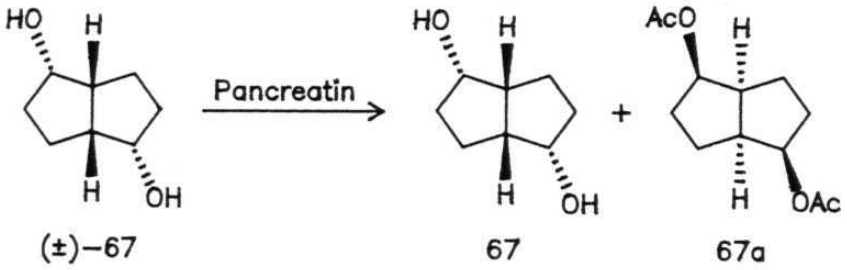
(18)

(±)–66 (R,R)–66a (S,S)–66b

38% ee 83% ee

66 was esterified using different acyl donors and enzyme catalysts to produce optically active monoester **66a** and diester **66b** (Eq.18).

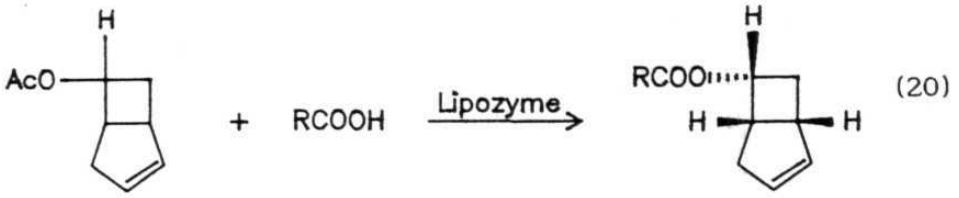
Pancreatin catalyzed esterification of racemic diol **67** with 2,2,2-trichloroethyl acetate in THF was reported. The diacetate **67a** was obtained in 97% ee. The enantiomeric purity of the remaining unreacted alcohol {(+)-**67**, 68% ee} was enhanced to 90% by subjecting



(±)–67 67 67a (19)

to the second *pancreatin* catalysis. Acylation of the unreacted diol followed by recrystallization produced the diacetate in 99% ee (Eq.19).[70]

The inter-esterification reaction is considerably more enantioselective than either the corresponding hydrolysis reaction or the equivalent esterification reaction. Roberts and co-workers[71] described enzyme catalyzed inter-esterification procedure for the preparation of esters of racemic secondary alcohols in high enantiomeric purities. The racemic ester **68a** was subjected to lipozyme catalyzed interesterification with cyclohexanecarboxylic acid to produce optically active ester (-)-**68b** in 99.4% ee. The reason for the higher selectivity is that the bicyclic molecule must visit the enzyme active site twice during the process first to undergo



(20)

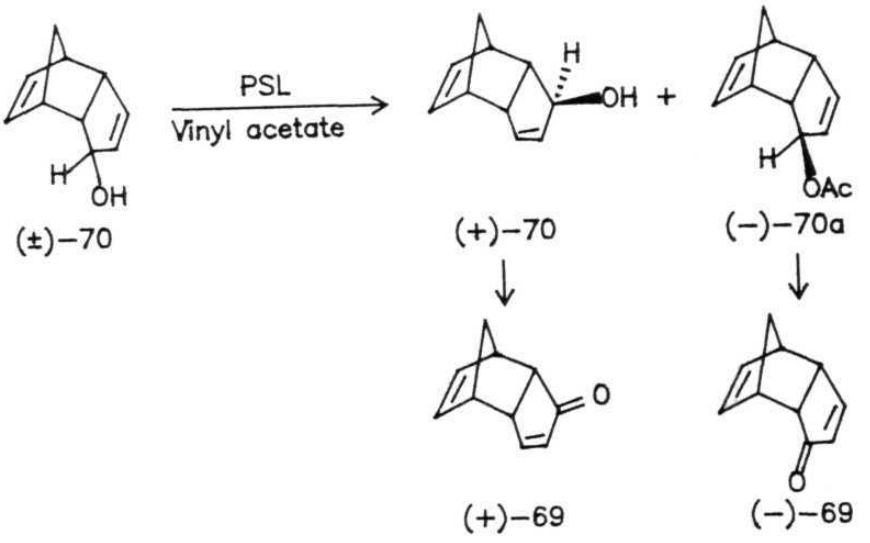
(±)–68a
R = Cyclohexyl

(–)–68b
99.4% ee

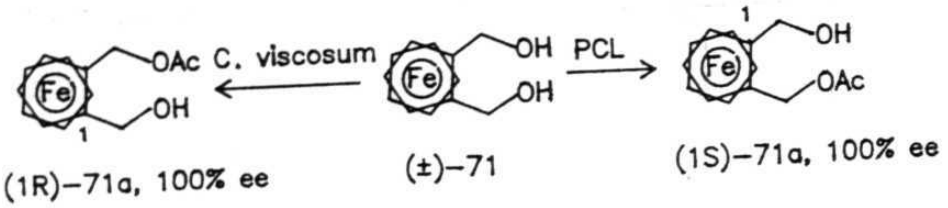
deacylation and then to pick up the cyclohexanoate moiety from the acylated enzyme (Eq.20).

Takano *et al.*[72] described the preparation of optically pure (+)- and (-)- dicyclopentadienone 69 *via* resolution of the corresponding dienol (±)-70 mediated by lipase PS (Scheme 18).

SCHEME 18:



Nicolosi *et al.*[73] obtained both enantiomers of 2-acetoxymethyl 1-hydroxymethylferrocene **71a** *via* enantiotoposelective irreversible acylation of 1,2-bis(hydroxymethyl)ferrocene using vinyl acetate with lipase (*Chromobacterium viscosum* or PCL) as a biocatalyst (Eq.21).



(21)

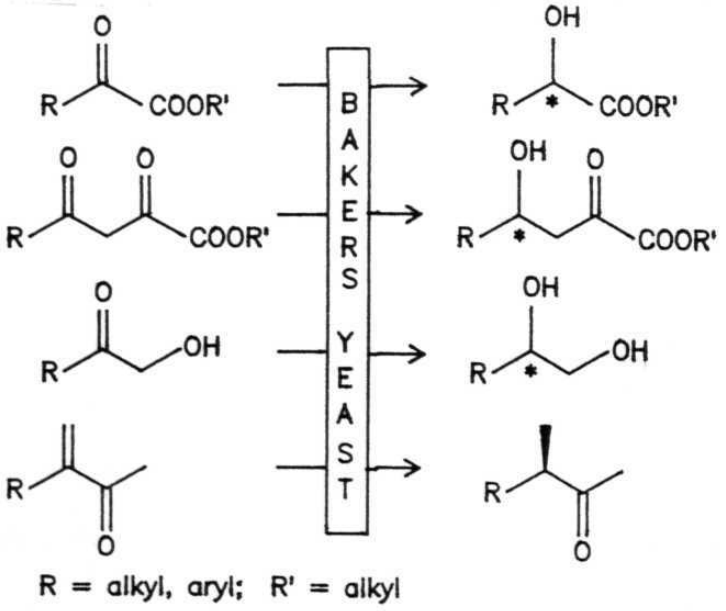
Miscellaneous transformations:

Several important transformations such as reductions, oxidations and reactions involving C-C bond formations and C-C bond cleavage using enzymes leading to enantiomerically enriched molecules have been reported. Very brief description of these transformations is given below.

Biocatalytic reductions:

The enantioselective reductions have been catalyzed by several purified enzymes and microorganisms. Baker's yeast (BY, *Saccharomyces*

SCHEME 19:

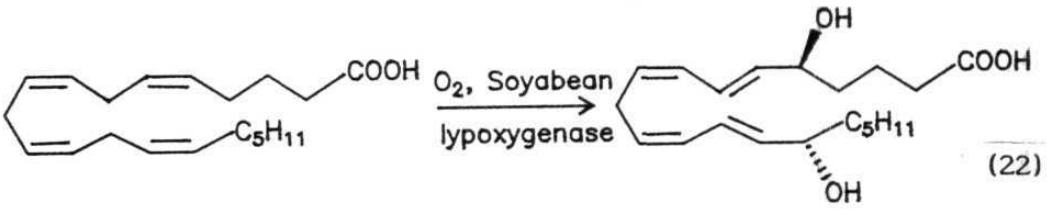


cerevisiae), an inexpensive and easily accessible biocatalyst has been extensively used for the preparation of chiral molecules[74,75] (Scheme 19).

Biocatalytic oxidations:

Oxidation reactions such as hydroxylation, epoxidation, Baeyer-Villiger oxidation, *etc.* have been catalyzed by enzymes to produce the correspondig enantiomerically enriched molecules. Some selected examples are given below (Eq.22-25 and Scheme 20).

Hydroxylation of alkenes:[76]



(22)

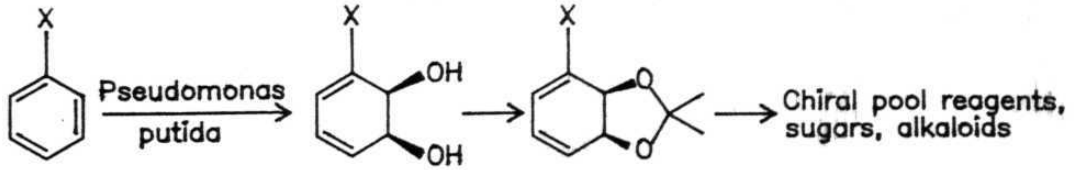
Epoxidation:[77]

n = 3–5

(23)

Arene oxidation:

SCHEME 20:



X = H, CH_3, Cl, Br, $CHCH_2$, OEt, CN, Ph

(Ref. 78)

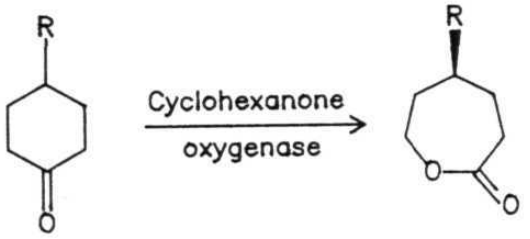
Oxidation of hydroxylated compounds:

(24)

(Ref. 79)

HLADH = Horse liver alcohol dehydrogenase

Baeyer-Villiger oxidation:



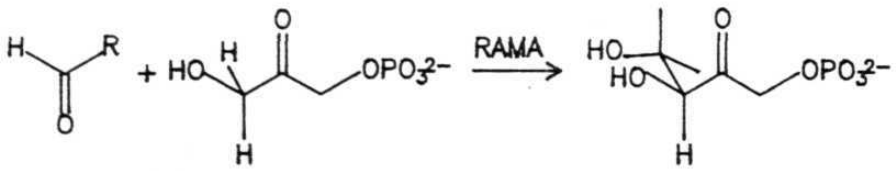
(25)

R = Et, n–Pr, t–Bu (Ref. 80)

Biocatalytic C-C bond formation:

Aldol condensation,[81,82] cyanohydrin formation[83] and Michael addition[84] are among the C-C bond forming reactions catalyzed by enzymes (Eq.26-28).

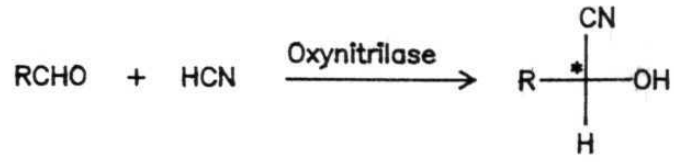
Aldol condensation:



(26)

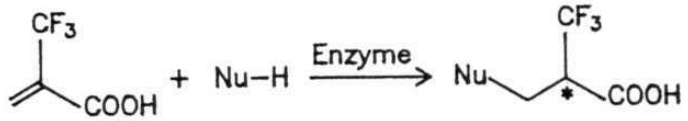
RAMA = Rabbit muscle aldolase

Cyanohydrin formation:



(27)

Michael addition:

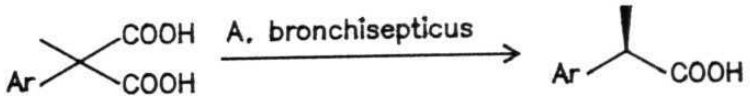


(28)

Nu–H	CCL	PLE
H_2O	70% ee	60% ee
Et_2NH	71% ee	69% ee

Biocatalytic C-C bond cleavage:

Enzymatic cleavage of carbon-carbon bond is also known. Recently *Alacaligenes bronchisepticus* mediated asymmetric decarboxylation of α-disubstituted malonic acids was reported[85] (Eq.29).



(29)

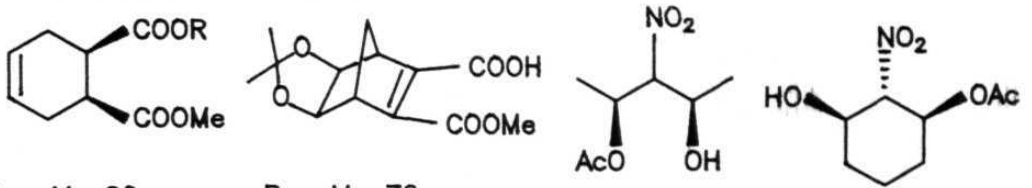
OBJECTIVES, RESULTS AND DISCUSSION

The development of simple methods for the production of optically active compounds has been the goal of our group for the past few years. The prologue evinces that hydrolytic enzymes have been extensively used for the synthesis of enantiomerically enriched molecules.

Inspite of biotransformations being widely used, apprehension still haunts synthetic organic chemists regarding the experimental techniques. Apart from this, inaccessibility of required enzyme hinders one to choose biotransformations in preference to conventional reactions. Using a single pure enzyme is an expensive task. This can possibly be overcome by using crude preparations of certain enzymes if unrequired enzymes present in the crude preparation do not interfere. Literature survey reveals that there are very few reports on the applications of crude enzyme preparations in enantioselective synthesis.

Ohno and co-workers[86] used pig liver acetone powder (PLAP) for the enantioselective hydrolysis of *meso*-dimethylesters **20a** and **72a** (R = Me) to produce chiral half-esters **20** (R = H) and **72** (R = H). Seebach *et al.*[87] reported preparation of chiral monoacetates **73, 74** *via* enantioselective hydrolysis of the corresponding *meso*-nitrodiol

diacetates using pig liver acetone methylene chloride powder (PLAMP).

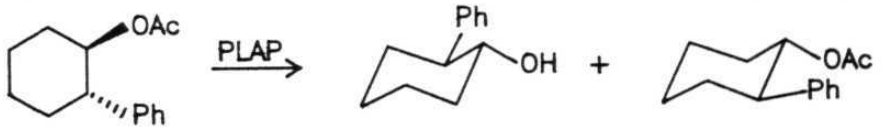


R = Me 20a R = Me 72a

H 20 H 72

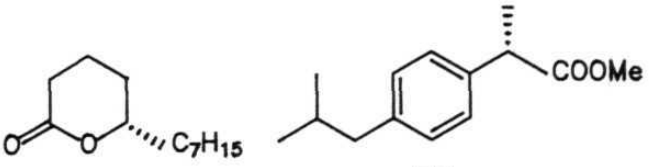
73 74

Whitesell[88] reported an efficient synthesis of both the enantiomers of *trans*-2-phenylcyclohexanol **75** using PLAP (Eq.30).



(±)–75a (R,S)–75 98% ee (S,R)–75a 98% ee (30)

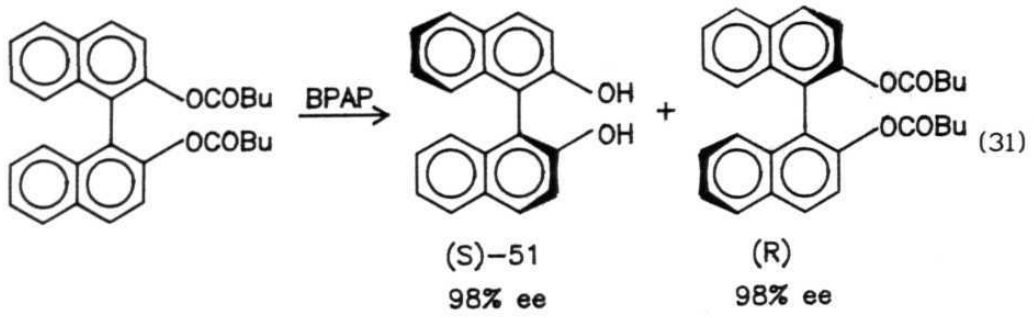
A crude preparation of horse liver esterase (HLE) was utilized in the preparation of lactones[89] (*e.g.***76**) and α-arylpropionic acids and their methyl esters[90] (*e.g.***77**) in high enantiomeric purities.



76 92% ee 77 >96% ee

An efficient resolution of binaphthol using bovine pancreas

acetone powder (BPAP) was reported by Kazlauskas[91] (Eq.31).



Objectives:

It occurred to us that PLAP, an easily available and inexpensive crude preparation will be an useful enzyme for enantioselective synthesis. We have therefore undertaken the project "Pig liver acetone powder (PLAP) mediated enantioselective synthesis" with the following objectives.

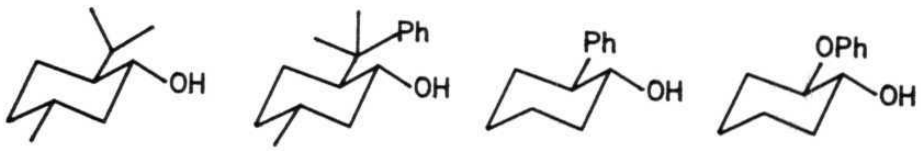
To Provide

1. enantioselective synthesis of *trans*-2-aryloxycyclohexan-1-ols
2. enantioselective synthesis of *trans*-2-alkoxycyclohexan-1-ols
3. simple synthesis of chiral α-hydroxy acids
4. simple synthesis of chiral 1,2-diols
5. simple synthesis of chiral α-substituted ketones

Results and Discussion:

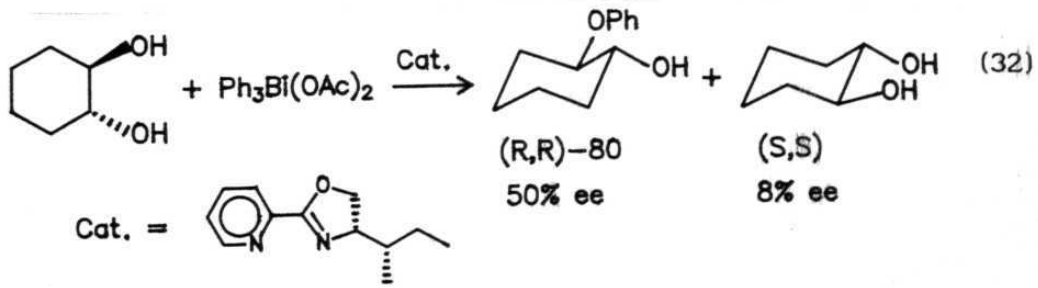
Recent efforts directed towards the synthesis of biologically

active molecules have pointed out the need for a variety of chiral auxiliaries that are easy to synthesize. Among the various chiral auxiliaries, the cyclohexyl-based chiral auxiliaries[92] such as (+)/(-)-menthol[93] (78), (-)-8-phenylmenthol[94] (79), (+)/(-)-*trans*-2-phenylcyclohexanol[95] (75) are some of the commonly used chiral auxiliaries for asymmetric transformations. With a view that structurally related *trans*-2-aryloxycyclohexan-1-ol derivatives would be of interest as chiral auxiliaries in organic synthesis, we have undertaken the synthesis of enantiomerically pure *trans*-2-aryloxy-cyclohexanols.



78 79 75 80

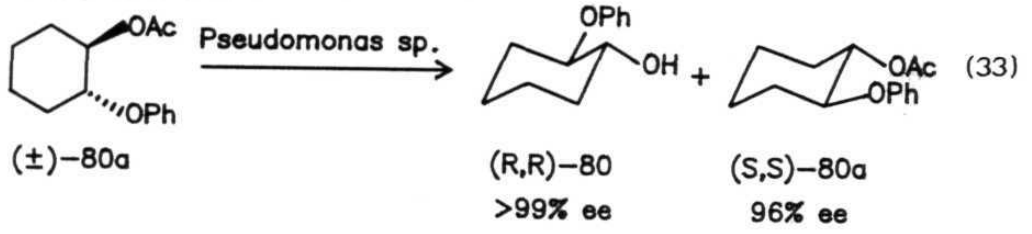
First we have selected chiral *trans*-2-phenoxycyclohexan-1-ol (80) as a target molecule. To the best of our knowledge, only two reports are available in the literature for the synthesis of chiral *trans*-2-phenoxycyclohexan-1-ol (80). Brunner and co-workers[96] prepared



(32)

(R,R)-2-phenoxycyclohexan-1-ol in 50% ee by monophenylation of (±)-*trans*-cyclohexane-1,2-diol in presence of a chiral catalyst (Eq.32).

Schneider and co-workers obtained (R,R)-2-phenoxycyclohexan-1-ol in >99% ee using *pseudomonas* sp. as biocatalyst in the hydrolysis of the corresponding racemic acetate[97] (Eq.33).

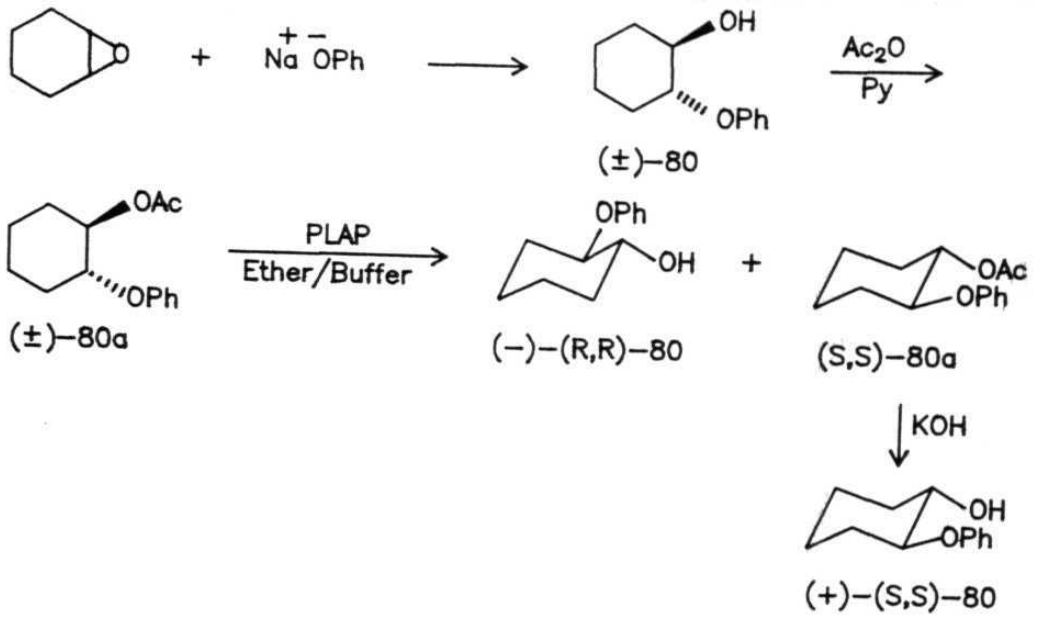


(±)–80a (R,R)–80 >99% ee (S,S)–80a 96% ee (33)

We planned to synthesize *trans*-2-phenoxycyclohexan-1-ol (80) in optically pure form *via* kinetic resolution of racemic *trans*-2-phenoxycyclohexyl acetate (80a) with PLAP. The required racemic alcohol 80 was prepared by the opening of cyclohexene oxide with sodium phenoxide. The structure of the alcohol 80 was established by IR, ^{1}H & ^{13}C NMR (Fig.1 & 2) and mass spectral data. This was converted to its acetate by the treatment with acetic anhydride in the presence of pyridine (Scheme 21).

Hydrolysis of racemic acetate 80a was carried out with PLAP under a variety of conditions. The best results were obtained when the hydrolysis was carried out in a biphasic medium (ether/phosphate buffer) producing the desired (-)-*trans*-2-phenoxycyclohexan-1-ol in 22 h (conversion ratio 46:54). It is important to note that the

SCHEME 21:

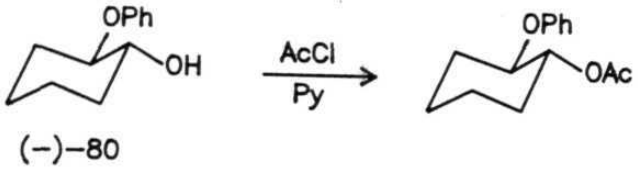


hydrolysis of racemic *trans*-2-phenylcyclohexyl acetate (**75a**) with PLAP took 10 days (for conversion ratio 45:55) to produce (-)-(1R,2S)-2-phenylcyclohexan-1-ol[88] (**75**).

Determination of enantiomeric purity of (-)-*trans*-2-phenoxycyclohexan-1-ol (80):

Examination of ^{1}H NMR spectrum of racemic *trans*-1-acetoxy-2-phenoxycyclohexane (**80a**) in the presence of chiral shift reagent, $Eu(hfc)_3$ showed two distinct peaks for acetoxy methyl protons in equal intensity arising from both the enantiomers. The optically active alcohol (-)-**80** was converted to the corresponding acetate by treatment with acetyl chloride in the presence of pyridine (Eq.34). This acetate was subjected to ^{1}H NMR analysis in the presence of chiral

shift reagent, $Eu(hfc)_3$ and the enantiomeric purity of the (-)-*trans*-



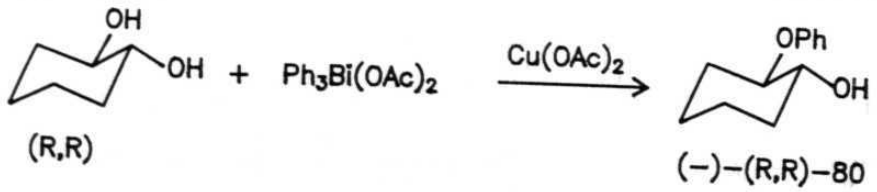
(34)

2-phenoxycyclohexan-1-ol was found to be 98%. Similarly ^1H NMR analysis of the recovered acetate in presence of $Eu(hfc)_3$ showed that its enantiomeric purity is 85%.

The enantiomeric purity of (-)-alcohol was further confirmed by HPLC analysis. Analysis of racemic alcohol 80 on chiral column CHIRALCEL OD showed two peaks arising from both the enantiomers. Similar analysis of alcohol (-)-80 showed only one peak indicating the enantiomeric purity of the alcohol to be >99%.

Determination of absolute configuration of (-)-80:

Absolute configuration of (-)-*trans*-2-phenoxycyclohexan-1-ol was determined as follows. Monophenylation of (-)-(R,R)-cyclohexane-1,2-diol (70% ee, prepared *via* enzymatic resolution, see page No.162) with triphenylbismuth diacetate in the presence of copper(II) acetate according to literature procedure[96,98] provided (-)-*trans*-2-phenoxycy-



(35)

clohexan-1-ol (Eq.35). This indicates that the absolute configuration of (-)-**80** is (R,R).

This encouraging result has led us to study the resolution of other *trans*-2-aryloxycyclohexanols with PLAP with a view to provide a general method for the preparation of enantiomerically pure *trans*-2-aryloxycyclohexan-1-ols. Accordingly representative examples of racemic *trans*-2-aryloxycyclohexan-1-ols (**83, 84, 88, 89** and **91**)* were made *via* opening of cyclohexene oxide with the corresponding aryloxides (Scheme 22). The structure of these alcohols were established by IR, ^{1}H & ^{13}C NMR, mass spectral data and elemental analysis. These alcohols were converted into the corresponding acetates. The enantioselective hydrolysis of these acetates **83a, 84a, 88a, 89a, 91a** with PLAP in a biphasic medium provided the desired (-)-*trans*-2- aryloxycyclohexan-1-ols in 90->99% enantiomeric purities. The recovered acetates were saponified to provide optically active (+)-alcohols (Table 1).

Determination of enantiomeric purity:

The enantiomeric purities of the optically active alcohols (-)-**83**, (-)-**84**, (-)-**88** (Fig.3) and (-)-**89** were determined by the ^{1}H NMR analysis of their acetates in the presence of chiral shift reagent $Eu(hfc)_3$, following similar method as described for (-)-2-phenoxycy-

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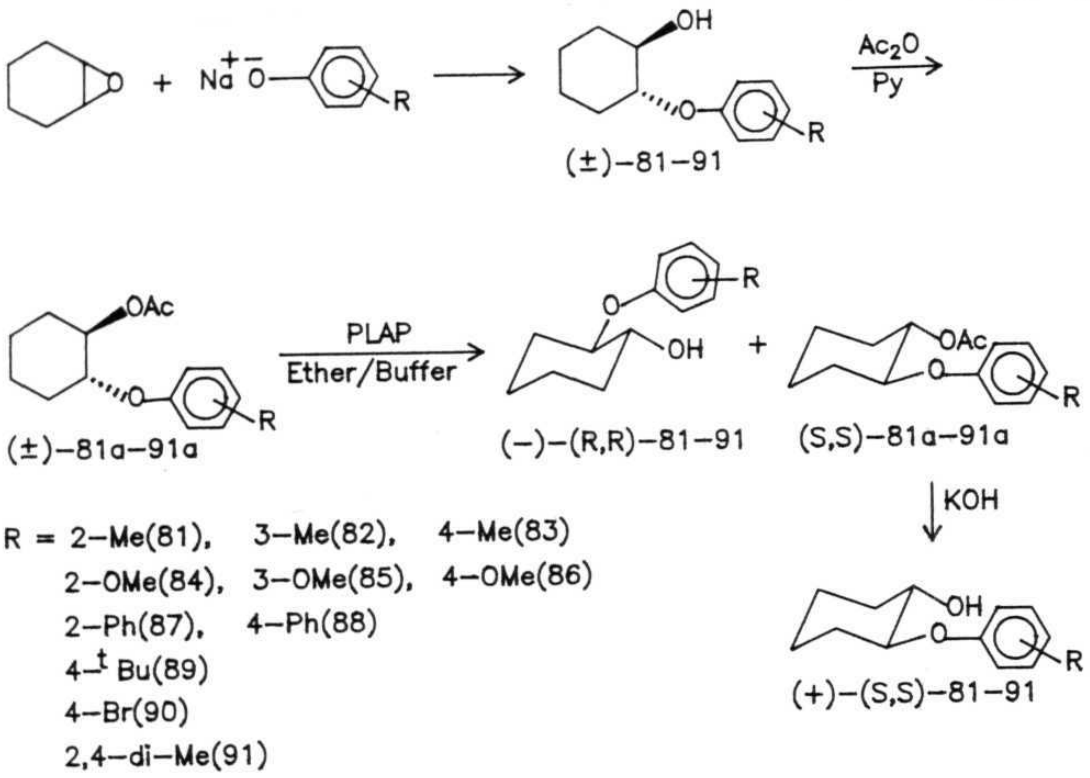
*This numbering is given in order to facilitate the discussion in this chapter.

SCHEME 22:



R = 2–Me(81), 3–Me(82), 4–Me(83)
2–OMe(84), 3–OMe(85), 4–OMe(86)
2–Ph(87), 4–Ph(88)
4–^{t}Bu(89)
4–Br(90)
2,4–di–Me(91)

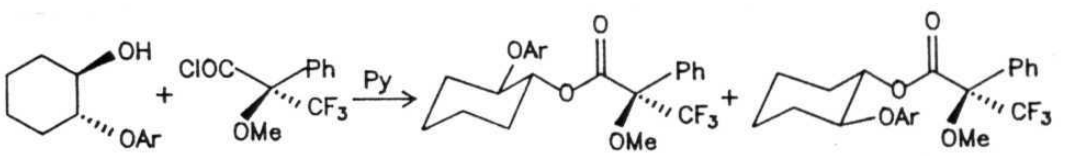
cyclohexan-1-ol and the enantiomeric purities were found to be >99%, 92%, >99%, and >99% respectively. The recovered acetates were also subjected for ^{1}H NMR analysis in presence of $Eu(hfc)_3$ to determine their enantiomeric purities and the values are tabulated (Table 1).

The enantiomeric purities of *para*-substituted alcohols (-)-**83**, (-)-**88** and (-)-**89** were further confirmed by HPLC analysis. Analysis of racemic alcohol **83** on HPLC using chiral column, CHIRALCEL OD showed two peaks arising from both the enantiomers. Similar analysis of alcohol (-)-**83** showed only one peak revealing the absence of the other

enantiomer. Similarly HPLC analysis of chiral alcohols (-)-**88** (Fig.4) and (-)-**89** showed that their enantiomeric purity is >99%.

Determination of enantiomeric purity of (-)-91:

^{1}H NMR analysis of acetate of (±)-*trans*-2-(2,4-dimethylphenoxy)-cyclohexan-1-ol (**91**) in the presence of Eu(hfc)$_3$ was not helpful in determination of enantiomeric purity. Therefore we prepared the Mosher's ester[99] of (±)-**91** with (+)-(S)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (Eq.36) to determine its enantiomeric purity.

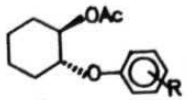


(±)–91 (+)–(S)–MTPACl 1 : 1 (36)

Ar = 2,4–dimethylphenyl

^{1}H NMR spectrum of this Mosher's ester was also not indicative of enantiomeric purity. However, ^{1}H NMR spectrum in the presence of chiral shift reagent, Eu(hfc)$_3$ showed two distinct singlets of equal integration for OMe protons due to both enantiomers. Similar analysis of the Mosher's ester of (-)-alcohol (**91**) was carried out and the enantiomeric excess was found to be 90%. The recovered acetate was saponified and converted into Mosher's ester. ^{1}H NMR analysis of this Mosher's ester in the presence of Eu(hfc)$_3$ indicated that the enantiomeric purity of (+)-**91** is 60%.

Table 1: Enantioselective hydrolysis of *trans*-2-aryloxycyclohex-1-yl acetates 80a-91a with PLAP.[a]

Substrate  R =		Hydrolysis time (h)	Conversion ratio[b]	(-)-Alcohol (80-91) Yield[c] (%)	$[\alpha]_D^{20}$	ee[d] (%)	Conf.	Recovered acetate Yield[c] (%)	ee[e] (%)
H	**80a**	22	44:56	73	-79.16(c 0.86, MeOH)	98[f]	(R,R)	75	85
2-Me	**81a**	60	40:60	72	-44.28(c 1.67, Acetone)	71	(R,R)	92	48
3-Me	**82a**	45	41:59	78	-48.20(c 1.39, Acetone)	90	(R,R)	92	53
4-Me	**83a**	40	41:59	72	-57.15(c 1.54, Acetone)	>99[f]	(R,R)	70	70
2-OMe	**84a**	96	45:55	76	-50.22(c 1.35, MeOH)	92	(R,R)	75	77
3-OMe	**85a**	23	47:53	96	-69.76(c 1.29, MeOH)	94	(R,R)	88	90
4-OMe	**86a**	11	48:52	92	-58.73(c 1.29, MeOH)	95	(R,R)	96	83
2-Ph	**87a**	96	37:63	95	- 8.26(c 0.48, Acetone)	13	(R,R)	93	4[g]
4-Ph	**88a**	96	47:53	72	-28.60(c 1.05, Acetone)	>99[f]	(R,R)	69	88
4-^{t}Bu	**89a**	84	47:53	70	-45.33(c 1.06, Acetone)	>99[f]	(R,R)	68	90
4-Br	**90a**	36	48:52	89	-29.54(c 1.35, Acetone)	96	(R,R)	89	89
2,4-di-Me	**91a**	50	37:63	65	-44.24(c 1.22, Acetone)	90[h]	(R,R)	60	60[h]

a) All reactions were carried out in 30 mM scale with 6 g of PLAP. b) Conversion ratio was determined by HPLC. c) Yields of pure isolated products and are based on conversion ratio. d) Determined by ^{1}H NMR analysis of corresponding acetate in the presence of $Eu(hfc)_3$ unless otherwise noted. e) Determined by ^{1}H NMR analysis in the presence of $Eu(hfc)_3$. f) Also confirmed by HPLC analysis with chiral column, CHIRALCEL OD. g) Comparing the optical rotation of (+)-alcohol with that of (-)-alcohol. h) Determined by ^{1}H NMR analysis of corresponding (+)-MTPA derivative in the presence of $Eu(hfc)_3$.

Effect of *ortho/meta/para* substituents in aryloxy group on enantioselectivity:

(-)-*trans*-2-(2-Methoxyphenoxy)cyclohexan-1-ol (**84**) and (-)-*trans*-2-(2,4-dimethylphenoxy)cyclohexan-1-ol (**91**) were obtained in 92% and 90% enantiomeric purities respectively, while all *para*-substituted alcohols (-)-**83**, (-)-**88**, (-)-**89** were obtained in >99% ee. From these results, it seems logical to assume that the extent of stereochemical outcome depends on the position of the substituent in the aromatic ring of 2-aryloxycyclohexanol.

The above observation has led us to examine the effect of the substitution on aryloxy group on the outcome of enantioselectivity. For this purpose, we have made racemic *trans*-2-(2-methylphenoxy)-cyclohexan-1-ol (**81**), racemic *trans*-2-(3-methylphenoxy)cyclohexan-1-ol (**82**) according to Scheme 22. The structures of these alcohols were established by IR, ^{1}H & ^{13}C NMR spectral data and elemental analysis. These alcohols were converted into the corresponding acetates **81a** and **82a** by treatment with acetic anhydride. PLAP catalyzed hydrolysis of the racemic acetates **81a** and **82a** provided the alcohols (-)-**81** and (-)-**82** in 71% and 90% enantiomeric purities respectively. The enantiomeric purities were determined by ^{1}H NMR analysis of the acetates in the presence of chiral shift reagent, $Eu(hfc)_3$ as described for (-)-*trans*-2-phenoxycyclohexan-1-ol. This result indicates that enantioselectivity decreases significantly from *para*-derivative (>99%)

to *meta*-derivative (90%) to *ortho*-derivative (71%).

Next we planned to study the effect of methoxy substituent on aryloxy group. Accordingly we prepared racemic *trans*-2-(3-methoxyphenoxy)cyclohexan-1-ol (**85**) and racemic *trans*-2-(4-methoxyphenoxy)cyclohexan-1-ol (**86**) (Scheme 22). The structures were confirmed by IR, ^{1}H & ^{13}C NMR spectral data and elemental analysis. Enantioselective hydrolysis of the racemic acetates **85a** and **86a** with PLAP provided (-)-**85** and (-)-**86** in 94% and 95% enantiomeric purities respectively. These results showed that methoxy substitution on aryloxy ring did not have any significant influence on the enantioselectivity.

Next we examined the effect of phenyl substitution on aryloxy ring. We made the desired racemic *trans*-2-(2-phenylphenoxy)cyclohexan-1-ol (**87**) (Scheme 22). The structure was in accordance with IR, ^{1}H & ^{13}C NMR spectral data and elemental analysis. The enantioselective hydrolysis of the acetate **87a** was carried out with PLAP in ether/phosphate buffer. The desired optically active alcohol (-)-**87** was obtained in 13% ee as determined by ^{1}H NMR analysis of its acetate in the presence of $Eu(hfc)_3$.

In order to examine the halogen effect on *para*-position of aromatic ring we have prepared racemic *trans*-2-(4-bromophenoxy)cyclohexan-1-ol (**90**). The enzymatic hydrolysis of its acetate **90a** with PLAP produced optically active alcohol (-)-**90** in 96% ee.

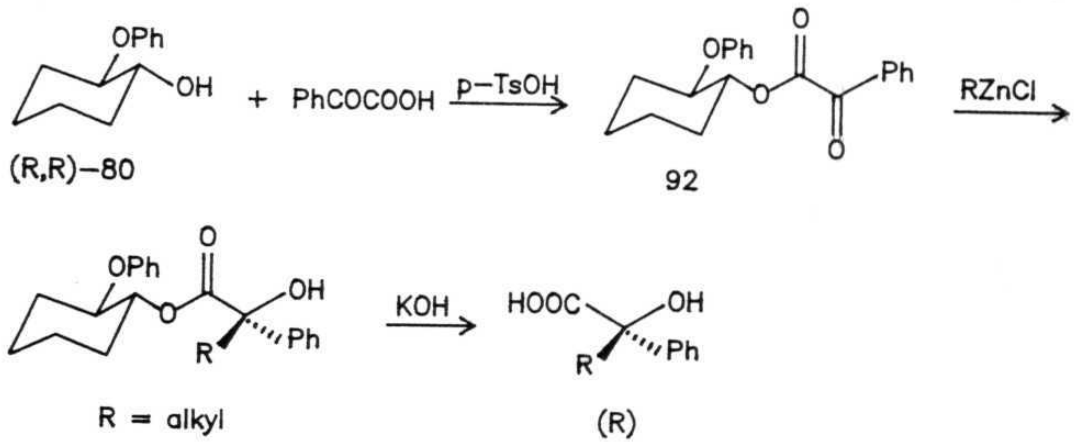
The above studies indicate that *para*-substituted derivatives provide better selectivity than *ortho*-substituted ones.

Determination of absolute configuration

Synthesis of α-hydroxy acids:

In our laboratory (R,R)-2-phenoxycyclohexan-1-ol was used as chiral auxiliary[100] for the preparation of α-hydroxy acids in 80-93% ee *via* alkylzinc chloride addition to the chiral α-keto ester **92** (Scheme 23).

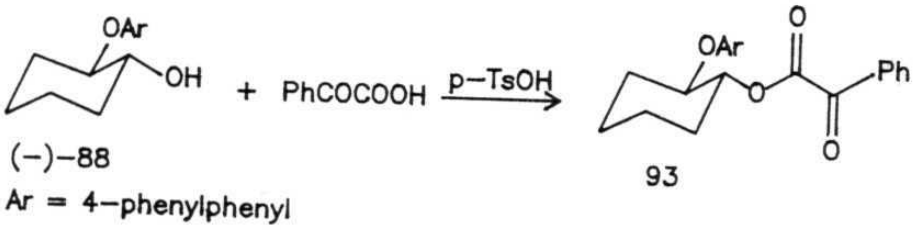
SCHEME 23:



It occurred to us that (i) (-)-*trans*-2-(4-phenylphenoxy)cyclohexan-1-ol and (-)-*trans*-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol would be suitable chiral auxiliaries for the preparation of chiral α-hydroxy acids. (ii) the stereochemistry of the resulting acids would be useful in establishing the absolute configuration of these auxiliaries.

(-)-*trans*-2-(4-Phenylphenoxy)cyclohexan-1-ol as chiral auxiliary:

(-)-*trans*-2-(4-Phenylphenoxy)cyclohexan-1-ol (**88**) was converted to [2-(4-phenylphenoxy)cyclohex-1-yl] phenylglyoxylate (**93**) by the treatment with benzoylformic acid in the presence of p-TsOH (Eq.37). The structure of the glyoxylate **93** was confirmed by IR, ^{1}H & ^{13}C NMR, mass spectral data and elemental analysis.



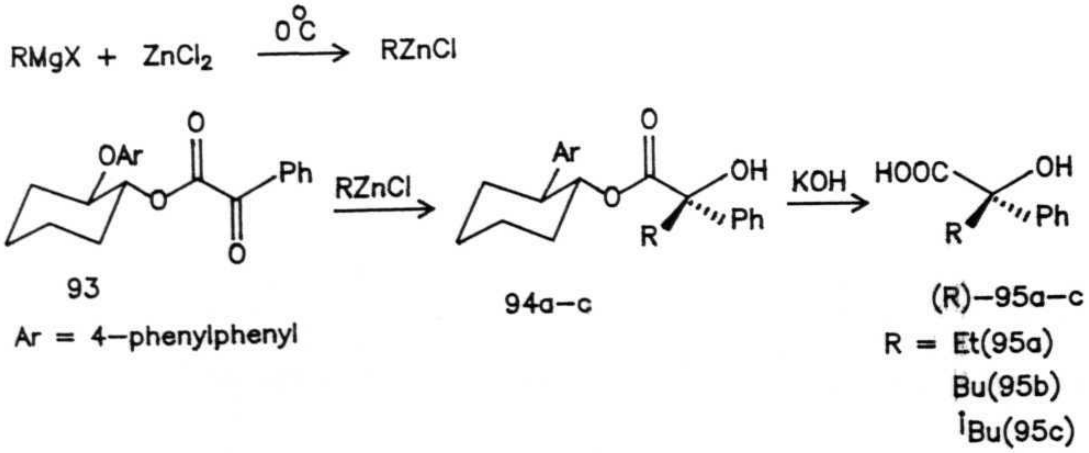
(-)-88
Ar = 4-phenylphenyl

93

(37)

The addition of ethylzinc chloride to the glyoxylate **93** at -78°C provided α-hydroxy ester **94a** (R = Et). The structure of **94a** was confirmed by IR, and ^{1}H NMR spectral data. Saponification of **94a** produced (-)-(R)-2-hydroxy-2-phenylbutanoic acid (**95a**, R = Et) in 81%

SCHEME 24:



93
Ar = 4-phenylphenyl

94a-c

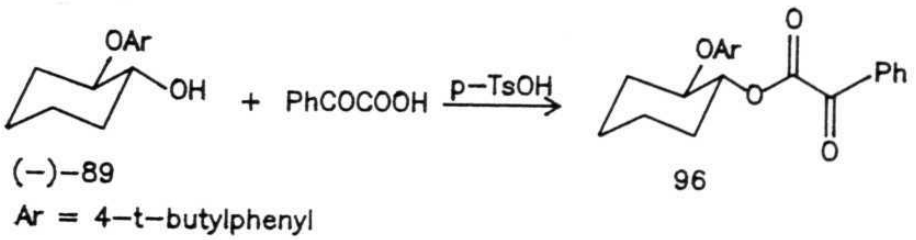
(R)-95a-c
R = Et(95a)
Bu(95b)
tBu(95c)

ee (Scheme 24). The structure of the acid was in accordance with IR, ^{1}H and ^{13}C NMR spectral data. The enantiomeric excess of α-hydroxy acid **95a** was determined by comparing its optical rotation with literature value. (R)-Configuration was assigned on the basis of sign of optical rotation.

We have also employed *n*-butyl and *iso*-butylzinc chlorides for this reaction. The resulting α-hydroxy acids **95b** and **95c** were obtained in 76% and 88% optical purities and have (R)-configuration (Table 2).

(-)-*trans*-2-(4-*ter*-Butylphenoxy)cyclohexan-1-ol as chiral auxiliary:

The chiral alcohol (-)-89 was treated with benzoylformic acid in presence of p-TsOH to provide [2-(4-*tert*-butylphenoxy)cyclohex-1-yl] phenylglyoxylate (96) as a crystalline solid (Eq.38). The structure of this molecule was established by IR, ^{1}H & ^{13}C NMR (Fig.5 & 6), mass spectral data and elemental analysis.



(−)−89 96 (38)

Ar = 4−t−butylphenyl

The reaction of α-keto ester 96 with ethylzinc chloride afforded chiral α-hydroxy ester **97a** (R = Et) (Scheme 25). Subsequent saponification provided chiral 2-hydroxy-2-phenylbutanoic acid (**95a** R = Et) in 96% ee with (R)-configuration.

Table 2. Preparation of chiral substituted α-hydroxy acids from RZnCl and glyoxylates 93 and 96[a].

R in RZnCl	Glyoxylate	Product	Over-all yield[b] (%)	$[\alpha]_D^{24}$ (c, EtOH)	ee[c] (%)	Conf.
Et	**93**	**95a**	77	-27.16 (1.75)	81	(R)
Et	**96**	**95a**	75	-32.05 (1.77)	96	(R)
^{n}Bu	**93**	**95b**	76	-17.61 (2.18)	76	(R)
^{n}Bu	**96**	**95b**	73	-20.50 (1.98)	88	(R)
^{i}Bu	**93**	**95c**	71	-17.87 (1.97)	88	(R)
^{i}Bu	**96**	**95c**	79	-17.38 (1.90)	86	(R)

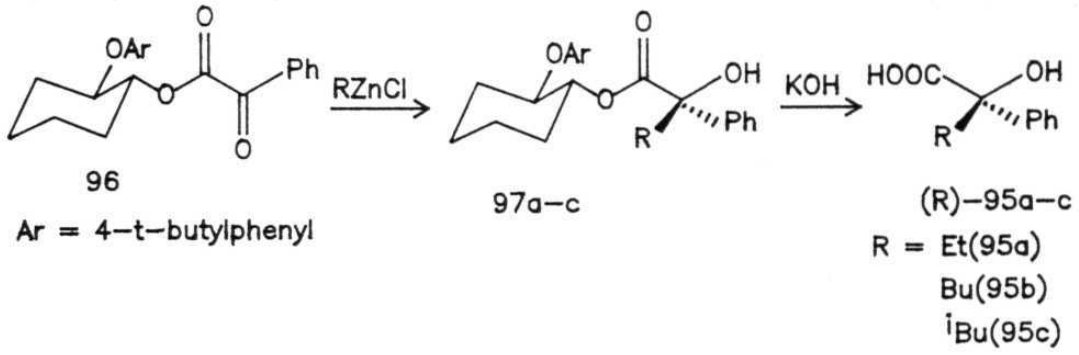
a) All reactions were carried out with 2.5 mM of keto ester and 12.5 mM of RZnCl in dry ether for 2 h at -78°C and 3 h at room temperature.

b) Over-all yields of pure crystallized products based on keto ester.

c) Enantiomeric purities were based on reported rotations: **95a**: $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH), ee >99%, Conf. (S), (Ref. 101); **95b**: $[\alpha]_D^{22}$ -19 (c 2.2, EtOH), ee 82%, Conf. (R), (Ref. 102); **95c**: $[\alpha]_D^{25}$ +20 (c 2, EtOH), ee >99%, Conf. (S), (Ref. 101).

We have also used *n*-butyl and *iso*-butylzinc chlorides in this addition reaction. The resulting chiral α-hydroxy acids **95b** and **95c** were obtained in 88% and 86% enantiomeric purities respectively with (R)-configuration (Table 2).

SCHEME 25:



96

Ar = 4–t–butylphenyl

97a–c

(R)–95a–c

R = Et(95a)

Bu(95b)

^{i}Bu(95c)

On the basis of sense of asymmetric induction {in comparision with (R,R)-2-phenoxycyclohexan-1-ol (80) (Scheme 23)[100]} obtained by the auxiliaries (-)-88, (-)-89 in this reaction, the absolute configurations of (-)-*trans*-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol and (-)-*trans*-2-(4-phenylphenoxy)cyclohexan-1-ol were assigned as (R,R). In analogy, absolute configuration of all other (-)-*trans*-2-aryloxy-cyclohexan-1-ols can be tentatively assigned as (R,R).

Effect of the substitution on phenyl ring in enzymatic hydrolysis of acetates 80a-91a:

Examination of Table 1 led to the following conclusions in the hydrolysis of racemic *trans*-2-aryloxycyclohexyl acetates with PLAP.

1. The (R,R)-enantiomer is hydrolyzed faster.
2. The hydrolysis of *ortho/meta*-substituted compounds is slower than that of *para*-substituted ones.
3. The alcohol with phenyl group in *para*-position of the phenoxy ring was obtained in >99% enantiomeric purity, whereas the phenyl substitution in *ortho*-position of phenoxy group reduced the optical purity to 13% (Fig.A).

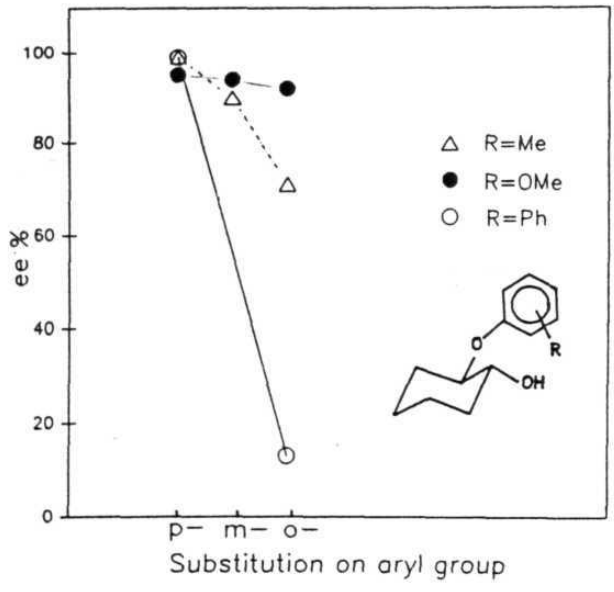


Fig.A: Variation in enantioselectivity with respect to substitution in phenyl ring of *trans*-2-aryloxycyclohexan-1-ol.

Possible explanation for the results:

These results can possibly be explained on the basis of three dimensional (cubic) active site model of PLE (Fig.B) proposed by Jones and co-workers.[103-105] The enzyme responsible for the enantioselective hydrolysis of *trans*-2-aryloxycyclohexyl acetates is

PLE present in PLAP. Since all isoenzymes present in PLE act in a more or less equivalent manner, PLE can be used as a single species for preparative purposes.

Active-site Model of PLE:

The top perspective view and size of the model are shown in Fig.C. The catalytically more important region which is denoted by a circle, contains a serine moiety which initiates the hydrolysis by attacking the carboxyl group of the acetate to be hydrolyzed. This model has four binding regions one large (H_L) and one small (H_S) hydrophobic pockets and two polar cavities on the front (P_F) and back (P_B) of the active-site.

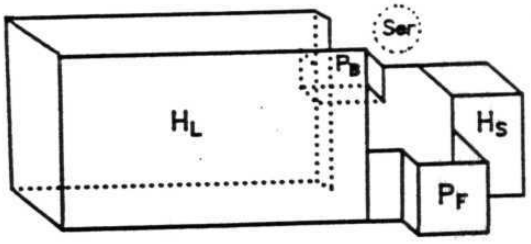


Fig.B: Three dimensional (cubic) active-site model

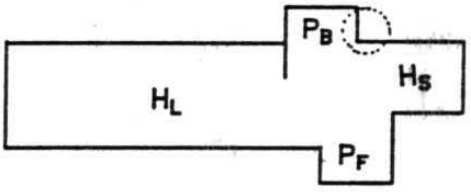


Fig.C: Top perspective view of active-site model

Jones' active-site model is successfully utilized for explaining the results in the hydrolysis of bicyclic esters[106] with PLE; and the hydrolysis of *trans*-2-*tert*-butylcyclohexyl acetate[107] with PLAP which produced (1R,2S)-2-*tert*-butylcyclohexan-1-ol in 99% optical purity.

(R,R)-Selectivity in *trans*-2-aryloxycyclohexan-1-ols:

Tamm's original active-site model[21] and Jones' work[108] unequivocally established that the ester functions at equatorial position in cyclohexyl derivatives are preferentially hydrolyzed with PLE. Hydrolysis of an ester group can only occur when it is in proximity with the catalytically active serine function. Top perspective view of the active-site model is used to illustrate the binding mode selections for *trans*-2-aryloxycyclohexyl acetates. The binding depicted in Fig.D shows the preferred ES complex (enzyme-substrate complex) for hydrolysis of the (R,R)-ester to produce the (R,R)-alcohol. In this case aryloxy group fits comfortably in H_L pocket. The hydrolysis of (S,S)-ester would require the orientation shown in Fig.E. This is clearly precluded since the H_S pocket is too small to accommodate aryloxy group.

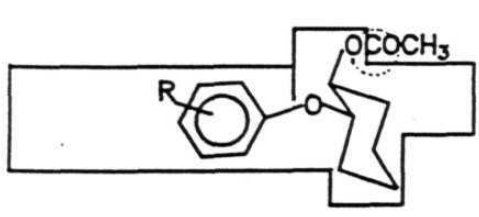


Fig.D: Binding mode for (R,R)-acetate (Favourable binding mode)

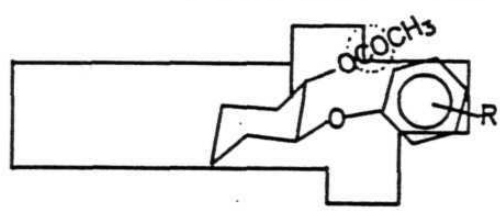


Fig.E: Binding mode for (S,S)-acetate (Unfavourable binding mode)

The hydrolysis of *ortho/meta*-substituted aryloxycyclohexyl acetates is slower than that of *para*-substituted (or unsubstituted) ones probably due to better accommodation for *para*-substituted (or un-

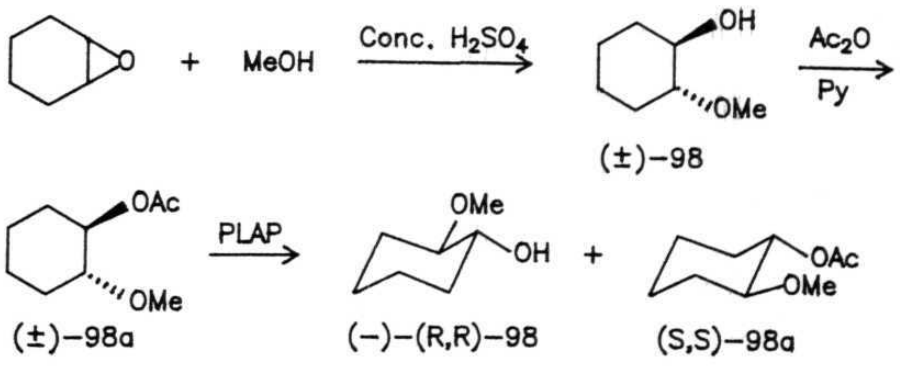
substituted) aryloxy moiety in H_L pocket than the corresponding *ortho/meta*-substituted ones. The bulky phenyl substitution in *ortho*-position of phenoxy group can not be accommodated in the enzyme pocket, thus resulting in slow hydrolysis and low selectivity (13% ee).

trans-2-Alkoxycyclohexan-1-ols:

After obtaining reasonable success in the synthesis of chiral *trans*-2-aryloxycyclohexanols, we directed our studies toward the synthesis of chiral *trans*-2-alkoxycyclohexanols. First we have selected *trans*-2-methoxycyclohexan-1-ol (98), the simplest 2-alkoxycyclohexanol as a target molecule. The racemic alcohol 98 was prepared by sulfuric acid catalyzed[109] opening of cyclohexene oxide with methanol (Scheme 26). The structure of the alcohol was established by IR, ^1H & ^{13}C NMR spectral data.

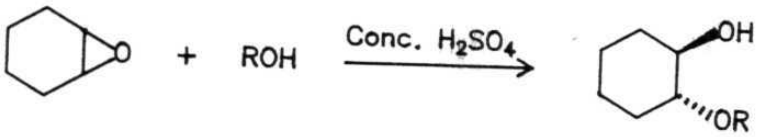
The alcohol 98 was acylated with acetic anhydride. The acetate

SCHEME 26:



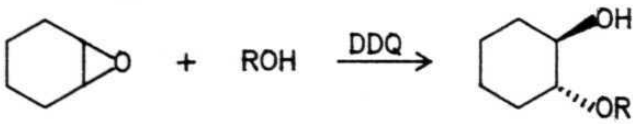
98a was subjected to PLAP catalyzed hydrolysis in a biphasic medium (ether/phosphate buffer) (Scheme 26). The desired (-)-alcohol (**98**) was obtained in 80% ee with (R,R)-configuration as determined by comparing optical rotation with the literature value.[110] The recovered acetate was hydrolyzed with KOH/MeOH to produce (+)-alcohol in 75% ee.

With a view to examine the effect of variation of alkoxy group in cyclohexyl ring, we prepared representative *trans*-2-alkoxycyclohexan-1-ols **99-102**. Racemic alcohols **99** and **100** were prepared by the ring opening of cyclohexene oxide with the corresponding alcohol in the presence of conc. H_2SO_4 (Eq.39). The structures of these alcohols were confirmed by IR, ^1H & ^{13}C NMR spectral data.



(±)–99,100
R = Et(99), ^{i}Pr(100) (39)

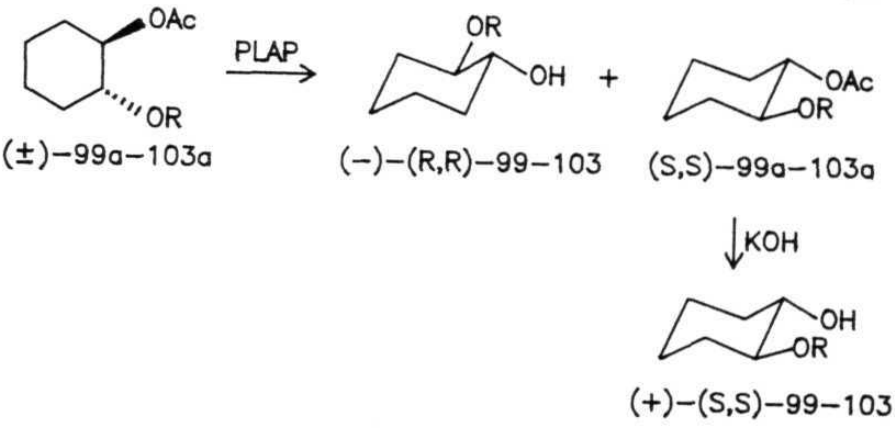
The other alcohols **101** and **102** were prepared by the opening of cyclohexene oxide with the corresponding alcohol in the presence of DDQ[111] (Eq.40). The structure of these alcohols were in agreement with IR, ^1H & ^{13}C NMR spectral data.



(±)–101–103
R = ^{i} Bu(101), Bn(102)
$-CH_2CH_2OCH_2CH_2OCH_3$(103) (40)

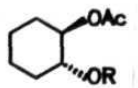
The alcohols 99-102 were converted into the corresponding acetates **99a-102a** by treating them with acetic anhydride in the presence of pyridine. The enantioselective hydrolysis of the acetates **99a-102a** using PLAP in biphasic medium provided the corresponding (-)-alcohols in 76%, 79%, 61% and 79% enantiomeric purities respectively (Scheme 27) (Table 3).

SCHEME 27:



The enantiomeric purity and configuration (R,R) of (-)-**99** and (-)-**100** were determined by comparing optical rotations with literature values.[110] The enantiomeric purity of (-)-*trans*-2-*iso*-butyloxy-cyclohexan-1-ol (**101**) was determined in the following way. The ^{1}H NMR spectrum of the racemic acetate **101a** in the presence of chiral shift reagent, Eu(hfc)$_3$ showed two peaks for acetoxy methyl protons in equal integration arising from both the enantiomers. ^{1}H NMR analysis of optically active acetate (derived from (-)-**101**) in the presence of Eu(hfc)$_3$ showed two peaks for acetoxy methyl protons in the ratio

Table 3: Enantioselective hydrolysis of *trans*-2-alkoxycyclohex-1-yl acetates 98a-103a using PLAP.[a]

Substrate  R =		Hydrolysis time (h)	Conversion[b] ratio	(-)-Alcohol (98-103) Yield[c] (%)	$[\alpha]_D^{20}$	ee[d] (%)	Conf.	Recovered acetate Yield[c] (%)	ee[e] (%)
Me	**98a**	8	47:53	57	-56.58(c 1.34, CH_2Cl_2)	80	(R,R)	79	75
Et	**99a**	26	46:54	73	-61.14(c 1.93, CH_2Cl_2)	76	(R,R)	90	60
i-Pr	**100a**	70	39:61	56	-68.83(c 1.60, CH_2Cl_2)	79	(R,R)	73	39
i-Bu	**101a**	24	44:56	58	-40.70(c 1.37, CH_2Cl_2)	61[f]	(R,R)	50	57
CH_2Ph	**102a**	17	44:56	90	-68.75(c 1.76, CH_2Cl_2)	79[g]	(R,R)	83	69
$CH_2CH_2OCH_3$	**103a**	16	48:52	63	-39.37(c 1.52, CH_2Cl_2)	82[f]	(R,R)	71	79

a) All reactions were carried out in 20 mM scale with 5 g of PLAP.

b) Conversion ratio was determined by GC.

c) Yields of pure isolated products and are based on conversion ratio.

d) Comparing the optical rotation with the literature values unless otherwise noted: **98**: $[\alpha]_D^{20}$ -69.3 (c 2.0, CH_2Cl_2), ee 98%, Conf. (R,R), (Ref. 110); **99**: $[\alpha]_D^{20}$ -75.3 (c 2.0, CH_2Cl_2), ee 94%, Conf. (R,R), (Ref. 110); **100**: $[\alpha]_D^{20}$ -85.6 (c 2.0, CH_2Cl_2), ee 98% Conf. (R,R), (Ref. 110).

e) Comparing the optical rotation of (+)-alcohol with that of corresponding (-)-alcohol.

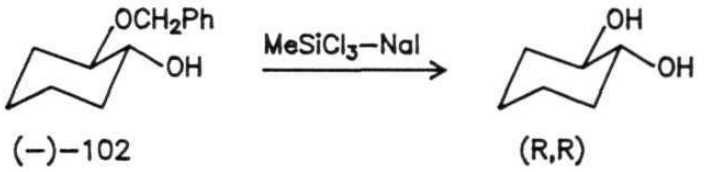
f) Determined by ^1H NMR analysis of corresponding acetate in the presence of $Eu(hfc)_3$.

g) Comparing the optical rotation of diol (obtained after ether cleavage) with literature value.

8.0:1.9 indicating that its enantiomeric purity is 61%.

Determination of optical purity of 2-benzyloxycyclohexan-1-ol:

The chemical degradation of (-)-*trans*-2-benzyloxycyclohexan-1-ol (102) with methyltrichlorosilane/ sodium iodide[112] provided (-)-(R,R)-cyclohexane-1,2-diol {$[\alpha]_D$ -31.5 (0.58, $CHCl_3$)} in 79% ee (Eq.41), thus indicating the enantiomeric purity of the alcohol to be 79% with (R,R)-configuration.



(–)–102 (R,R) (41)

We have also prepared *trans*-2-[2-(2-methoxyethoxy)ethoxy]cyclohexan-1-ol (103) in order to examine the effect of ether grouping on the alkoxy substitution. This compound was prepared by the ring opening of cyclohexene oxide with the corresponding alcohol in the presence of DDQ (Eq.40). The structure of the racemic alcohol **103** was established with IR, ^1H & ^{13}C NMR (Fig.7), mass spectral data and elemental analysis. The alcohol **103** was converted into the corresponding acetate **103a** and subsequent enantioselective hydrolysis with PLAP provided (-)-alcohol {(-)-**103**, $[\alpha]_D^{24}$ -39.37 (c 1.52, CH_2Cl_2} in 82% ee. The optical purity was determined by the ^1H NMR analysis of acetates {of racemic and (-)-alcohols} in the presence of chiral shift reagent, $Eu(hfc)_3$. (R,R)-Configuration was assigned for both (-)-**101**

and (-)-**103** in analogy with (-)-**98**, (-)-**99**, (-)-**100** and (-)-**102**.

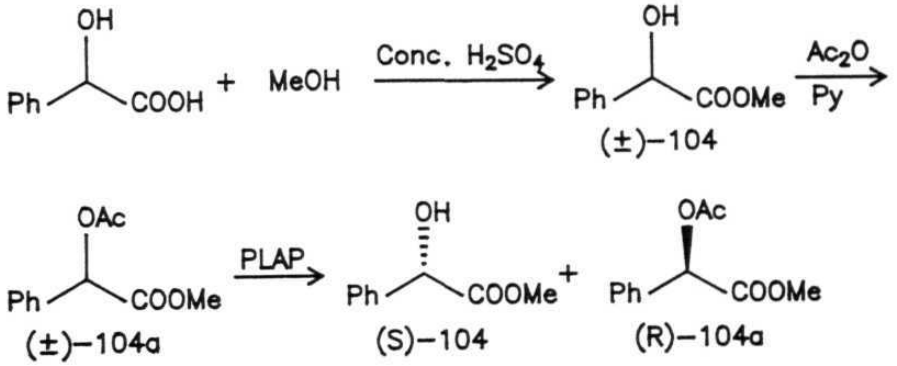
The (R,R) selectivity in the hydrolysis of *trans*-1-acetoxy-2-alkoxycyclohexanes (**98a-103a**) was consistent with that of *trans*-1-acetoxy-2-aryloxy-cyclohexanes. This (R,R) selectivity can possibly be explained on the basis of Tamm's and Jones' active-site model as described for 2-aryloxycyclohexanols (**80-91**). In the case of aryl substituents which possess rigid conformation the hydrolysis by PLAP provided better selectivities. Alkyl groups do not show any rigidity, hence stereochemical outcome is inferior in alkoxycyclohexanols in comparison with aryloxycyclohexanols. However, it is possible to obtain enantiomerically pure (-)-alcohols by again subjecting the acetates of enantiomerically enriched alcohols through enzymatic hydrolysis with PLAP.

α-Hydroxy acids:

One of the most important classes of chiral pool is α-hydroxy carboxylic acids.[113] Enantiomers of mandelic acid were used for the resolution of alcohols,[114] amines[115] and for the stereoselective synthesis of aldols.[116,117] They were also used as chiral derivatizing reagents useful for determination of enantiomeric purities of chiral molecules.[114,118,119] We have already reported the applications of both alcohols (-)-**88** and (-)-**89** as chiral auxiliaries

for the enantioselective preparation of α-hydroxy acids. We felt that chiral α-hydroxy acids can be synthesized *via* enantioselective hydrolysis of corresponding acetates using PLAP. Accordingly we have first selected methyl O-acetylmandelate **104a** as substrate for enantioselective hydrolysis using PLAP. The required racemic acetate **104a** was prepared according to Scheme 28. Esterification of mandelic acid with methanol in presence of conc. H_2SO_4 followed by acylation provided desired acetate 104a.

SCHEME 28:



Hydrolysis of acetate **104a** was carried out with PLAP in biphasic medium to produce the desired (+)-(S)-hydroxy ester **104** with 75% optical purity as determined by comparing its optical rotation with that of literature value[120] (Scheme 28). We also noticed that the methyl ester functionality was completely intact. The recovered acetate on saponification produced (R)-mandelic acid in 70% optical purity.

At this stage it occurred to us that the variation of ester group

Table 4: Enantioselective hydrolysis of alkyl O-acetylmandelates 104a-108a with PLAP.[a]

Substrate R =	Hydrolysis time (h)	Conversion ratio[b]	(+)-Alcohol (104-108) Yield[c] (%)	$[\alpha]_D^{24}$	ee[d] (%)	Conf.	Recovered diester Yield[c] (%)	ee[e] (%)
Me(104a)	5	48:52	83	+ 87.00(c 1.05, Acetone)	75	(S)	96	70
Et(105a)	8	41:59	65	+ 59.28(c 1.91, $CHCl_3$)	47	(S)	67	35
^{i}Pr(106a)	17	47:53	71	+ 62.25(c 1.01, $CHCl_3$)	55	(S)	95	50
^{t}Bu(107a)	17	34:66	66	+103.84(c 1.10, CCl_4)	80	(S)	80	49
Cyclohexyl (108a)	60	31:69	74	+ 16.78(c 1.13,EtOH)	23	(S)	71	15

a) All reactions were carried out in 5 mM scale with 2 g PLAP.

b) Conversion ratio was determined by HPLC.

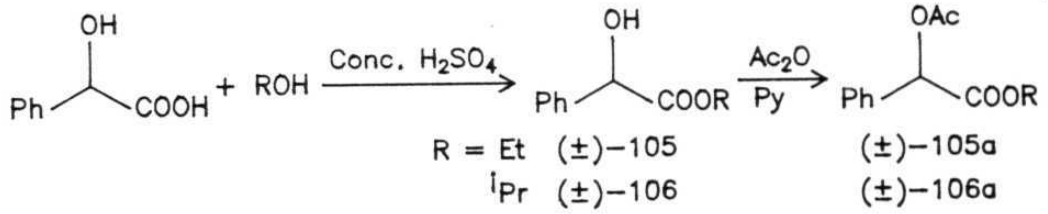
c) Yields of pure isolated products and are based on conversion ratio

d) Ee's were determined based on optical rotation reported in literature: **104**: $[\alpha]_D^{25}$ -115.4 (c 1.0, Acetone), ee >99%, Conf. (R), (Ref. 120); **105**: $[\alpha]_D^{25}$ -126.2 (c 2.01, $CHCl_3$), ee >99%, Conf. (R), (Ref. 121); **106**: $[\alpha]_D^{25}$ -98.9 (c 1.00, $CHCl_3$), ee 88%, Conf. (R), (Ref. 122); **107**: $[\alpha]_D^{27}$ -119.1 (c 1.05, CCl_4), ee 92%, Conf. (R), (Ref. 122); **108**: $[\alpha]_D^{20}$ +71.97 (c 2.04, EtOH), ee 98%, Conf. (S), (Ref. 124).

e) Ee's were determined after KOH/MeOH hydrolysis to (R)-mandelic acid.

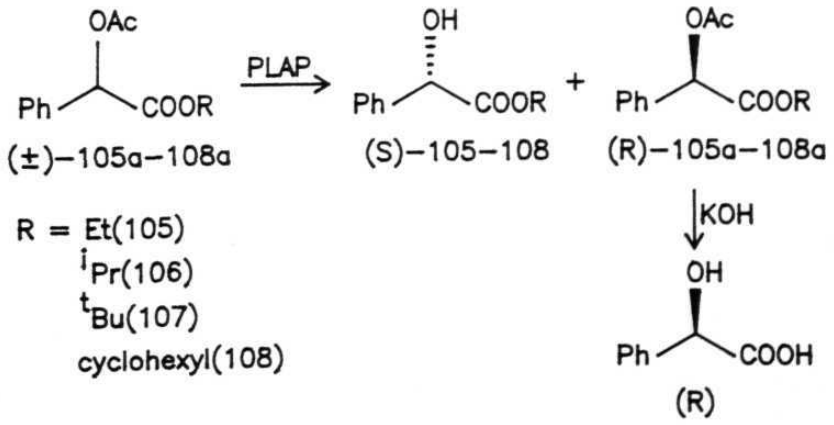
might provide better optical purities in the hydrolysis. We therefore have prepared a variety of mandelic acid esters **105-108**. The esters **105** and **106** were prepared by the esterification of mandelic acid and they were converted to the corresponding acetates **105a, 106a** (Scheme 29). The structures of the compounds were confirmed by IR, ^{1}H & ^{13}C NMR spectral data.

SCHEME 29:



Hydrolysis of these racemic esters (**105a, 106a**) was carried out in biphasic medium which produced the desired (+)-(S)-alcohols **105** and **106** in 47% and 55% optical purities respectively (Scheme 30). The optical purities and (S)-configuration were determined by

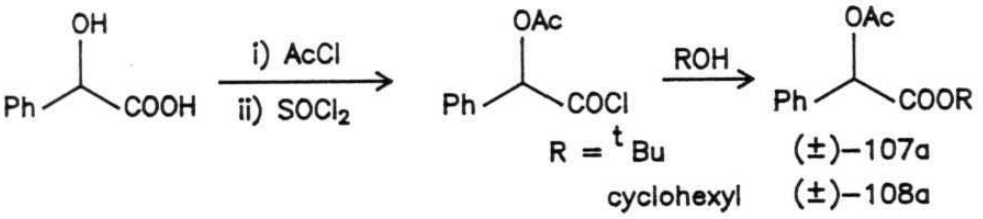
SCHEME 30:



comparing the optical rotations of these alcohols with that of literature values.[121,122]

Because these optical purities are not satisfactory we have directed our studies toward *tert*-butyl ester **107** and cyclohexyl ester **108** expecting that the steric bulk may influence the enantioselectivity. Accordingly the desired acetates **107a** and **108a** were prepared. Treatment of mandelic acid with acetyl chloride according to known procedure[123] gave O-acetylmandelic acid which was converted into O-acetylmandelyl chloride by treatment with thionyl chloride. This acid chloride on treatment with *tert*-butanol and cyclohexanol provided

SCHEME 31:



the required *tert*-butyl ester **107a** and cyclohexyl ester **108a** respectively (Scheme 31). The structures of these esters were in full agreement with IR, ^{1}H & ^{13}C NMR spectral data.

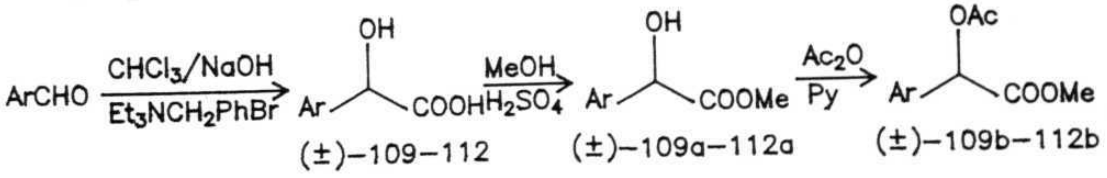
Hydrolysis of **107a** with PLAP was carried out in biphasic medium to produce the desired (+)-(S)-hydroxy ester **107** $[\alpha]_D^{24}$ +103.84 (c 1.10, CCl_4) {Lit.[122] $[\alpha]_D^{27}$ -119.1 (c 1.05, CCl_4), 92% ee, Conf. (R)} with 80% optical purity.

Similarly hydrolysis of cyclohexyl ester **108a** with PLAP produced

the desired (+)-(S)-alcohol in 23% optical purity $[\alpha]_D^{24}$ +16.78 (c 1.13, EtOH) {Lit.[124] $[\alpha]_D^{20}$ +71.97 (c 2.04, EtOH), 98% ee, Conf. (S)}. All these results are summarized in Table 4.

From these results it is clear that methyl and *tert*-butyl esters of mandelic acid provided better results. With a view to provide a general synthesis of chiral α-hydroxy acids and to examine the effect of substituent in the aromatic ring on enantioselectivity, we have directed our studies toward the hydrolysis of a variety of α-acetoxy-α-arylacetic acid methyl esters. The required α-acetoxy-α-arylacetic acid methyl esters **109b-112b** were prepared according to Scheme 32. Treatment of aromatic aldehydes with chloroform in the presence of NaOH and benzyltriethylammonium chloride (PTC) provided[125] the

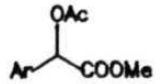
SCHEME 32:



Ar = 2–OMeC$_6$H$_4$(109)
4–MeC$_6$H$_4$(110)
4–OMeC$_6$H$_4$(111)
1–Nap(112)

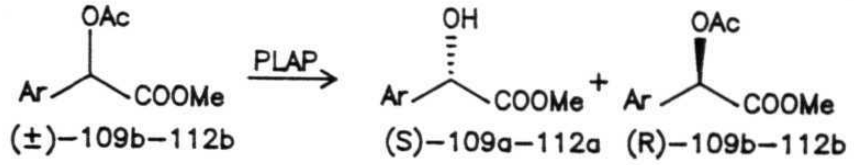
α-hydroxy acids 109-112 which were transformed into the desired acetates **109b-112b** according to Scheme 32. The structures of these esters were in full agreement with IR, ^{1}H & ^{13}C NMR spectral data.

Table 5: Enantioselective hydrolysis of methyl α-acetoxy-α-arylacetates 109b-112b with PLAP.[a]

Substrate  R =	Hydroly-sis time (h)	Conver-sion ratio[b]	Product	Yield[c] (%)	$[\alpha]_D^{24}$	ee[d] (%)	Conf.
2-OMeC$_6$H$_4$ **(109b)**	2	43:57	(+)-**109a**	84	+ 70.15(c 0.98, EtOH)	55	(S)[e]
			(-)-**109b**	80	- 75.24(c 0.61, EtOH)	43	(R)[e]
4-MeC$_6$H$_4$ **(110b)**	4	45:55	(+)-**110a**	65	+ 29.28(c 0.85, EtOH)	26	(S)[e]
			(-)-**110b**	70	- 50.75(c 0.75, EtOH)	20[f]	(R)[e]
4-OMeC$_6$H$_4$ **(111b)**	3	44:56	(+)-**111a**	78	+ 80.68(c 1.02, EtOH)	57	(S)[g]
			(-)-**111b**	87	-117.14(c 0.91, EtOH)	44[f]	(R)[e]
1-Np **(112b)**	4	57:43	(+)-**112a**	64	+ 56.10(c 0.75, EtOH)	30[h]	(S)[i]
			(-)-**112b**	67	-153.26(c 0.89, EtOH)	53	(R)[i]

a) All reactions were carried out in 5 mM scale with 2 g of PLAP.
b) Conversion ratio was determined by HPLC.
c) Yields of pure isolated products and are based on conversion ratio.
d) Determined by HPLC analysis using chiral column, CHIRALCEL OD unless otherwise noted.
e) Absolute configuration was assigned by comparing the sign of optical rotation of the corresponding α-hydroxy acid (after KOH/MeOH hydrolysis) with that of reported one.
f) Determined by comparing the optical rotation of α-hydroxy acid (after KOH/MeOH hydrolysis) with that of literature value.
g) Absolute configuration was assigned by comparing the sign of optical rotation with that of literature value (ref. 127).
h) Determined by HPLC analysis of its acetate using chiral column, CHIRALCEL OD.
i) Tentatively assigned.

First we have examined the hydrolysis of racemic acetate **109b** (Ar = 2-OMeC_6H_4) with PLAP which produced the (+)-alcohol (+)-**109a** (Ar = 2-OMeC_6H_4) in 55% enantiomeric purity (Eq.42).



(±)–109b–112b (S)–109a–112a (R)–109b–112b (42)

Determination of optical purity of (+)-109a and (-)-109b:

The racemic alcohol **109a was** analyzed on HPLC using chiral column CHIRALCEL OD (eluent : hexane/i-PrOH : 95:5) which showed two peaks arising from both enantiomers. We have then subjected the optically active alcohol to similar HPLC analysis which showed two peaks in the ratio 7.77:2.23 indicating that optical purity of this compound is 55% (Fig.8). Similar HPLC analysis of the recovered diester (-)-**109b** with reference to (±)-**109b** showed 43% enantiomeric purity. The absolute configurations of (+)-**109a** & (-)-**109b** were found to be (S) & (R) respectively by comparing the sign of optical rotation of their hydroxy acids with that of literature value.[126]

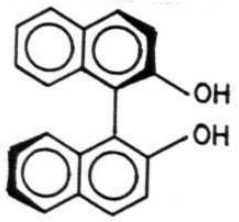
The racemic acetates **110b-112b** were also subjected to enantioselective hydrolysis with PLAP in biphasic system. The desired (+)-alcohols **110a-112a** were obtained in 26%, 57% and 30% optical purities respectively. We have determined the enantiomeric purities of (+)-**110a** & (+)-**111a** by HPLC analysis using chiral column CHIRALCEL OD following the same procedure as described for (+)-**109a**. The recovered

diesters (-)-**110b** & (-)-**111b** were saponified with KOH/MeOH to the known[128] acids (-)-(R)-110 & (-)-(R)-111. The results have been summarized in Table 5.

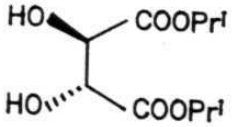
HPLC analysis of (±)-**112a** with chiral column, CHIRALCEL OD was not indicative of enantiomeric purity. Then we subjected its acetate (±)-**112b** to HPLC analysis which showed two peaks due to two enantiomers. Similar HPLC analysis of the acetate of (+)-**112a** and the recovered diester (-)-**112b** showed 30% and 53% *ee*'s respectively. These results have been summarized in Table 5. From this Table it is clear that the optical purities of α-hydroxy acids are not upto satisfactory levels. Then we directed our studies towards the synthesis of chiral diols.

Synthesis of chiral 1,2-diols:

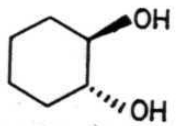
Chiral 1,2-diols play an important role in asymmetric synthesis. These molecules have been utilized as chiral directors in a number of asymmetric reactions.[129] Some important chiral diols **51, 113-115** have been mentioned below.



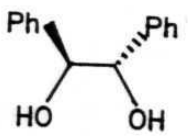
51[130]



113[131]

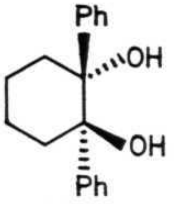


114[132]

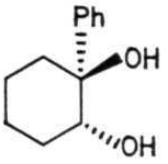


115[133]

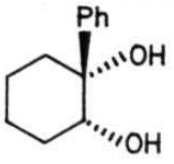
Recently chiral diols **116-118** were used[134] in the preparation of crown ethers **119-121**.



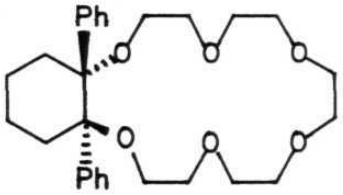
116



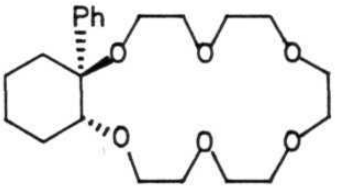
117



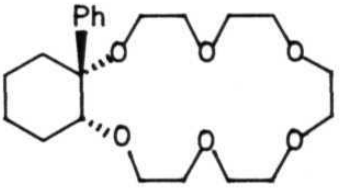
118



119

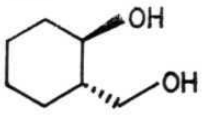


120

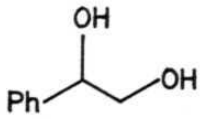


121

Fascinated by the importance of chiral diols, we have next focussed our studies on the synthesis of optically active diols **51, 114, 115, 118, 122, 123** *via* PLAP catalyzed resolution. First we have undertaken the resolution of racemic diol **118**. The required starting molecule was prepared according to known procedure[135] (Scheme 33). The reaction of phenylcyclohexene with formic acid and H_2O_2 produced the *cis*-diol **118**. Subsequent treatment with acetyl chloride produced the racemic monoacetate **118a**. The structures of these compounds were consistent with IR, ^1H & ^{13}C NMR spectral data.



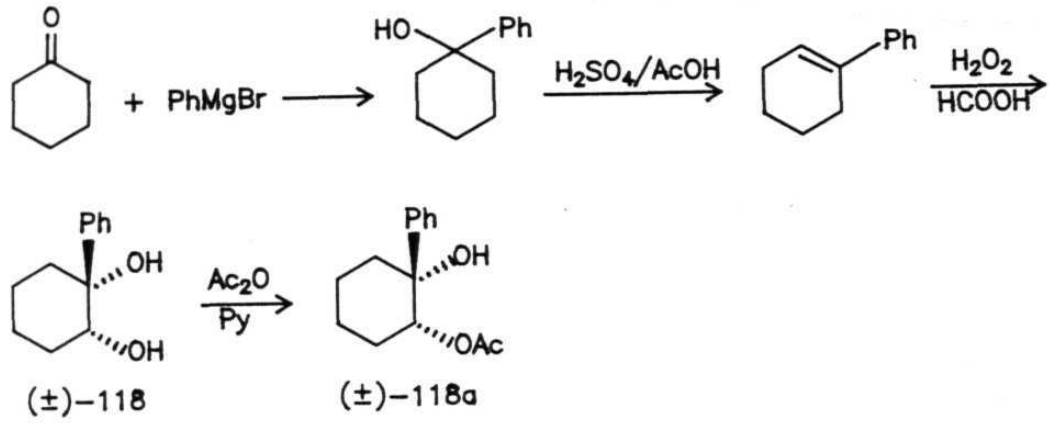
122



123

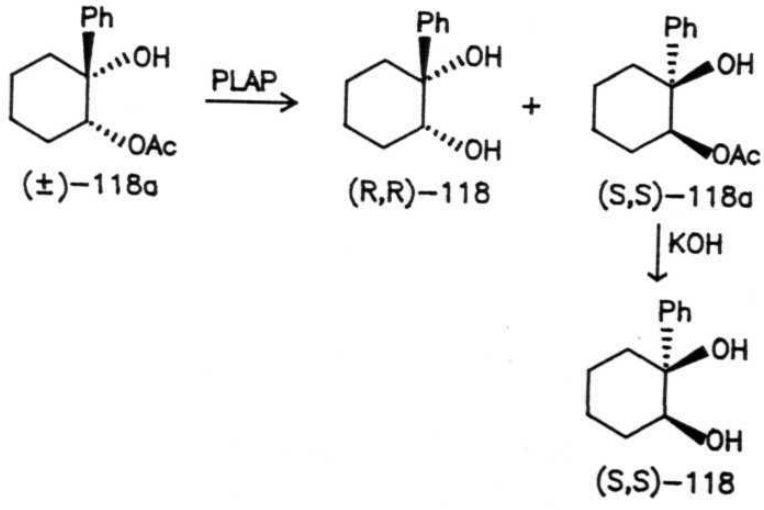
Hydrolysis of the monoacetate **118a** with PLAP in biphasic medium provided the desired (+)-(R,R)-diol **118** in 97% ee, $[\alpha]_D^{24}$ +18.99 (c

SCHEME 33:



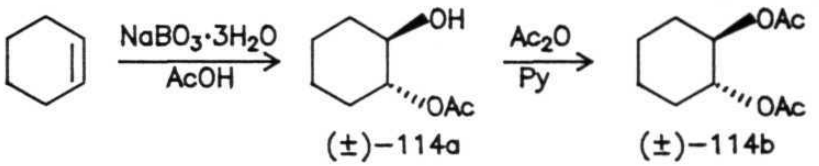
0.76, C_6H_6) {Lit.[134] $[\alpha]_D^{22}$ +19.2 (c 0.33, C_6H_6) ≥98% ee, Conf. (R,R)} (Scheme 34). The recovered monoacetate was saponified with KOH/MeOH to produce (S,S)-diol in 67% ee.

SCHEME 34:



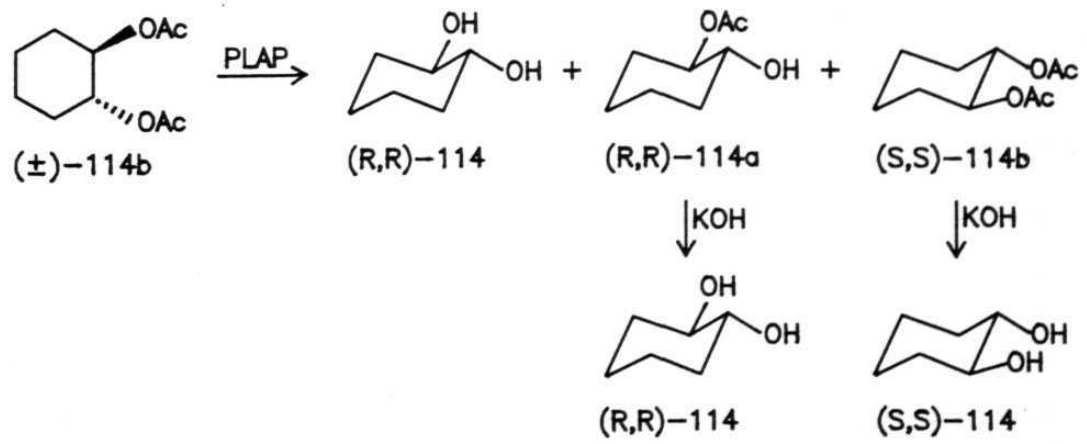
Encouraged by this successful result, we have next undertaken the synthesis of optically active 1,2-cyclohexanediol. The required racemic diacetate **114b** was prepared according to the known procedure[136] (Scheme 35). The reaction of cyclohexene with sodium perborate in acetic acid afforded monoacetate **114a**, which on treatment

SCHEME 35:



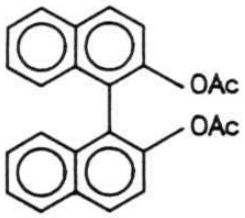
with acetic anhydride provided racemic *trans*-1,2-diacetoxycyclohexane (**114b**). PLAP catalyzed hydrolysis of the racemic diacetate **114b** produced three products (i) (R,R)-1,2-diol in 70% ee, $[\alpha]_D^{24}$ -28.35(c 0.67, $CHCl_3$) {Lit.[137] $[\alpha]_D^{20}$ -40 (c 0.32, $CHCl_3$), Conf. (R,R)} (ii) (R,R)-monoacetate and (iii) (S,S)-diacetate. The optically active monoacetate was saponified to produce (R,R)-diol in 68% ee. The

SCHEME 36:



recovered diacetate on saponification with KOH/MeOH provided (S,S)-diol in 52% ee (Scheme 36).

Next we attempted the resolution of binaphthyl diacetate **51b** with PLAP. However, no hydrolysis was observed (Eq.43).

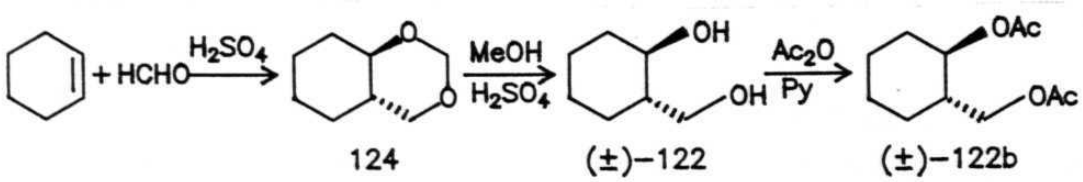


PLAP → No reaction (43)

(±)–51b

Since cyclohexanediol derivatives provided satisfactory results, we have extended our studies for the preparation of *trans*-2-hydroxy-methylcyclohexan-1-ol (**122**) in optically active form. The racemic diacetate **122b** was prepared according to Scheme 37. The Prins reaction of cyclohexene with formaldehyde provided the *trans*-1,3-dioxadecalin[138] (**124**). The cyclic acetal **124** was cleaved with methanol in presence of H_2SO_4 to produce corresponding *trans*-diol **122** which was converted into diacetate **122b** with acetic anhydride. The structures of these molecules are in full agreement with IR, ^1H & ^{13}C NMR (**122** Fig.9) spectral data.

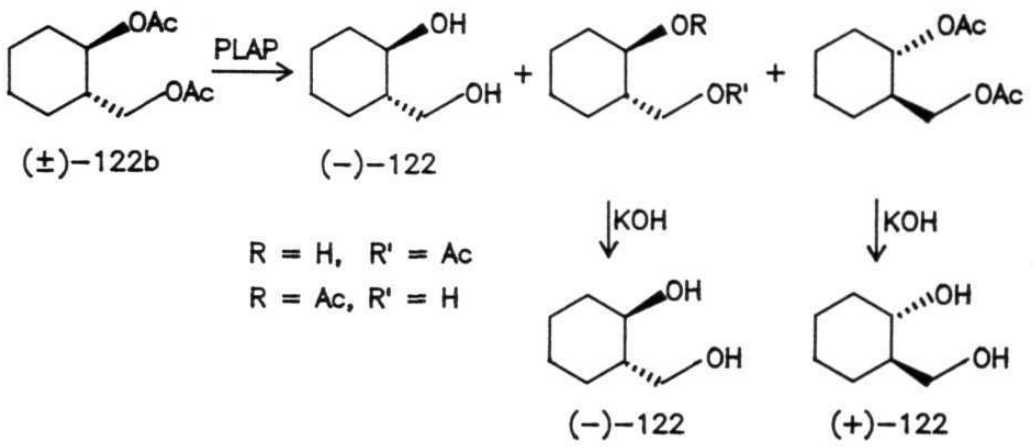
SCHEME 37:



124 (±)–122 (±)–122b

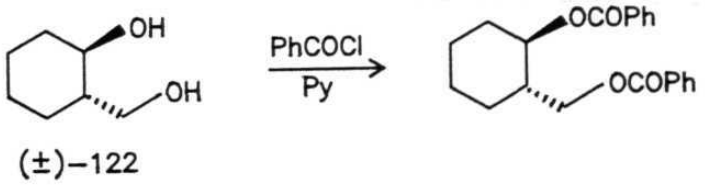
The enantioselective hydrolysis of diacetate **122b** with PLAP in ether/phosphate buffer provided optically active diol, mixed monoacetates and diacetate (Scheme 38).

SCHEME 38:



Determination of enantiomeric excess of (-)-122:

The racemic diol **122** was converted to dibenzoate by treatment with benzoyl chloride in pyridine (Eq.44). The analysis of this



(44)

dibenzoate with HPLC on chiral column, CHIRALCEL OD (eluent: hexane : i-PrOH / 98:2) showed two peaks of equal intensity corresponding to the two enantiomers. Then we converted the optically active diol (-)-**122** to the corresponding dibenzoate. HPLC analysis of this

Table 6: Enantioselective synthesis of diols using PLAP.[a]

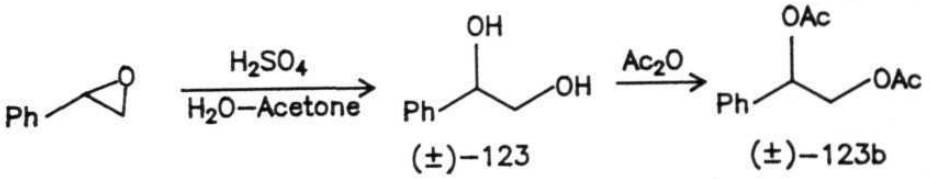
Substrate	Hydroly-sis time	Diol				Monoacetate (Diacetate)[d]		
		Yield[b] (%)	$[\alpha]_D^{24}$	ee[c] (%)	Conf.	Yield[b] (%)	ee (%)	Conf.
118a	10d	33	+18.99(c 0.76, C_6H_6)	97	(R,R)	61	67	(S,S)
114b	84h	5	-28.35(c 0.67, $CHCl_3$)	70	(R,R)	33(42)	68(52)	(R,R){(S,S)}
122b	24h	20	- 9.29(c 0.85, CH_2Cl_2)	46[e]	(R,S)[f]	27(35)	24(17)[g]	(R,S){(S,R)}[f]
123b	12h	20	+ 6.57(c 2.58, H_2O)	16	(S)	25(35)		

a) All reactions were carried out in 20 mM scale with 3 g of PLAP. b) Yields of pure isolated products. c) Determined by comparing optical rotation with that of literature value unless otherwise noted: **118**: $[\alpha]_D^{22}$ +19.2 (c 0.33, C_6H_6), ee 98%, Conf. (R,R), (Ref. 134); **114**: $[\alpha]_D^{20}$ -40.0 (c 0.32, $CHCl_3$), Conf. (R,R), (Ref. 137); **123**: $[\alpha]_D$ +40.6 (c 3.23, H_2O), Conf. (S), (Ref. 140); d) Values in parentheses are of recovered diacetates. e) Determined by HPLC analysis of the corresponding dibenzoate using chiral coloumn, CHIRALCEL OD f) Tentatively assigned. g) Determined by comparing the optical rotation of the corresponding diol with that of (-)-diol **122**.

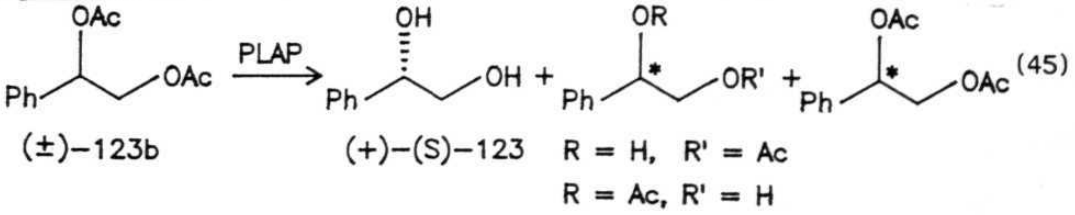
optically active dibenzoate showed two peaks in the ratio 7.32 : 2.67 indicating that the optical purity is 46%. Hydrolysis of the monoester with KOH/MeOH provided the diol in 24% ee. The recovered diacetate on saponification with KOH/MeOH produced the (+)-diol in 17% ee.

Afterwards we directed our studies toward the resolution of acyclic diols. Accordingly we selected 1-phenyl-1,2-diacetoxyethane (**123b**) for resolution. The required diol **123** was synthesized[139] according to Scheme 39. The structure was confirmed by IR, ^{1}H & ^{13}C NMR spectral data. The enantioselective hydrolysis of racemic **123b**

SCHEME 39:

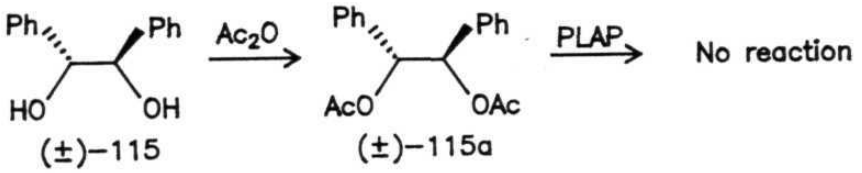


with PLAP provided the optically active diol **123** in 16% ee $[\alpha]_D^{24}$ +6.57 (c 2.58, H_2O) {Lit.[140] $[\alpha]_D^{20}$ +40.6 (c 3.23, H_2O), Conf. (S)} with (S)-configuration (Eq.45). No attempt was made to determine the optical purities of mixed monoacetates and diacetate as their ee's will not be appreciable. All these results are summarized in Table 6.



We have also attempted the hydrolysis of racemic 1,2-diphenyl-ethane-1,2-diol diacetate with PLAP expecting that the presence of two phenyl rings may influence the enantioselectivity. However we found that there was no hydrolysis even after several days.

SCHEME 40:



(±)–115 (±)–115a

As acyclic diols did not provide any encouraging results we did not proceed further.

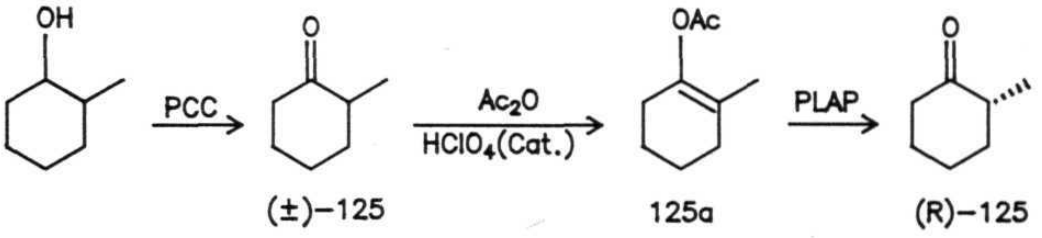
Synthesis of Chiral Ketones:

Synthesis of optically active cyclic ketones has been an interesting area in organic chemistry. A number of methods have been reported in literature for synthesis of chiral ketones.[141] Also chiral ketones have been synthesized from racemic ketones by deprotonation with chiral base followed by protonation.[142] In principle it is quite possible to hydrolyze enol acetates with enantioface differentiation to produce the corresponding ketones in optically active form. Very few reports[143] are available for enantioface differentiating hydrolysis of the corresponding enol esters using enzymes.

We thought that PLAP might hydrolyze enol acetates with

enantioface discrimination to produce the desired ketones in optically active form. Accordingly we have first aimed at the preparation of optically active 2-methylcyclohexanone (125) *via* enantioface differentiating hydrolysis of corresponding enol acetate **125a**. The required enol acetate **125a** was prepared according to Scheme 41. The

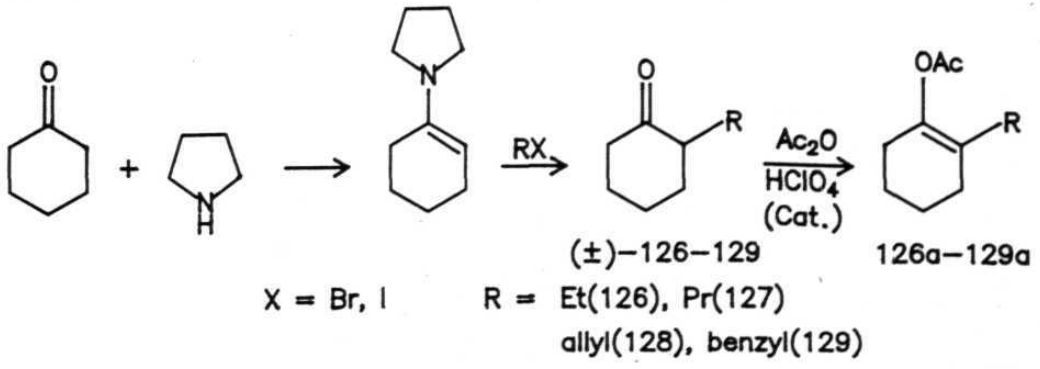
SCHEME 41:



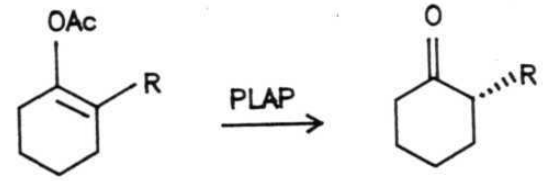
structure of the compound was confirmed by IR, ^{1}H & ^{13}C NMR spectral data. Hydrolysis of enol acetate **125a** with PLAP in ether/phosphate buffer produced the desired (R)-ketone in 20% optical purity.

In order to examine the effect of variation of alkyl group in

SCHEME 42:



cyclohexane ring, we have prepared representative enol acetates **126a-129a** according to Scheme 42. All the structures were in accordance with IR, ^{1}H & ^{13}C NMR spectral data. Hydrolysis of these enol acetates **126a-129a** with PLAP produced the desired optically active ketones in 10%, 40%, 11% and 12% enantiomeric purities respectively (Eq 46) (Table 7).



126a–129a **(–)–126–129** (46)

With a view to synthesize 5-hexadecanolide **130**, pheromone of the oriental hornet, *Vespa orientalis*,[144] we have planned the synthesis of precursor ketone **131** according to the Scheme 43, the key step being the hydrolysis of enol acetate **131a** with enzyme. However PLAP failed

130 **(±)–131**

to hydrolyze **131a** even after several days. This failure may be attributed to the fact that longer chain may not be suitable for the enzyme hydrolysis.

Table 7. PLAP catalyzed enantioface differentiating hydrolysis of enol acetates.[a]

Substrate	Reaction time (h)	(-)-ketone			
		Yield[b] (%)	$[\alpha]^{24}_D$	ee[c] (%)	Conf.
125a	24	69	- 2.88(c 1.04, MeOH)	20	(R)
126a	16	81	- 2.57(c 3.00, MeOH)	10	(R)
127a	24	75	-11.76(c 2.12, MeOH)	40	(R)
128a	12	88	- 1.76(c 1.90, MeOH)	11	(S)
129a	6	71	- 5.67(c 1.29, MeOH)	12	(S)
132a	5	74	-39.06(c 0.64, C_6H_6)	34	(S)
133a	15	72	-48.92(c 1.66, $CHCl_3$)	31	(S)[d]

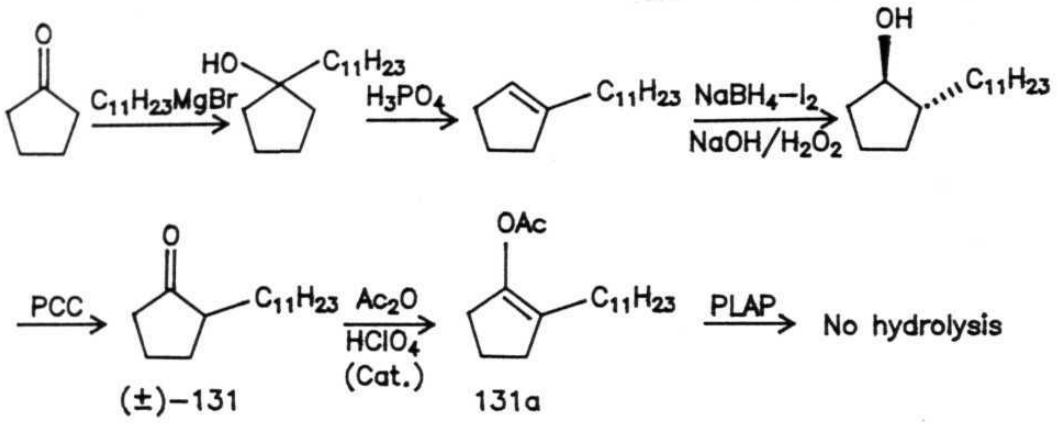
a) All reactions were carried out in 5 mM scale with 2.5 g of PLAP in 40 mL of 0.2 M, pH 6.5 phosphate buffer and 10 mL of ether.

b) Yields of pure isolated products.

c) Optical purities were based on reported optical rotations: **125**: $[\alpha]^{24}_D$ +12.2 (c 4, MeOH), ee 87%, Conf. (S), (Ref. 145); **126**: $[\alpha]^{24}_D$ +24.1 (c 4, MeOH), ee 94%, Conf. (S), (Ref. 145); **127**: $[\alpha]^{24}_D$ +27.9 (c 4, MeOH), ee 99%, Conf. (S), (Ref. 145); **128**: $[\alpha]^{24}_D$ +15.8 (c 3, MeOH), ee 99%, Conf. (R), (Ref. 145); **129**: $[\alpha]^{24}_D$ +41.4 (c 5, MeOH), ee 88%, Conf. (R), (Ref. 145); **132**: $[\alpha]^{24}_D$ -113.5 (c 0.60, C_6H_6), Conf. (S), (Ref. 146); **133**: $[\alpha]^{24}_D$ +158 (c 0.9, $CHCl_3$), (Ref. 147).

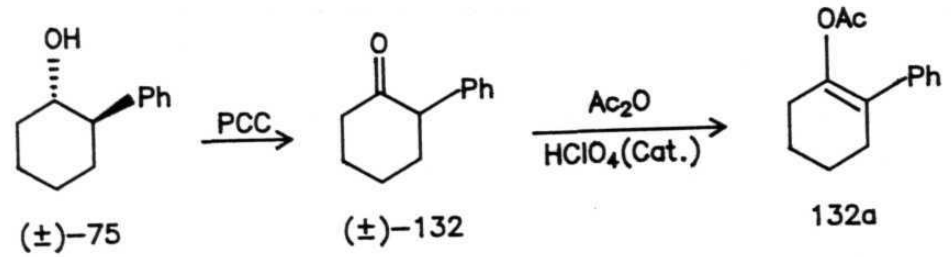
d) Tentatively assigned.

SCHEME 43:



At this stage we thought that the aromatic substitution on cyclic ketones might provide better selectivities. Accordingly we have selected 2-phenylcyclohexanone (**132**) as a substrate for our studies and the required enol acetate **132a** was prepared starting from *trans*-2-phenylcyclohexan-1-ol (**75**) (Scheme 44). The PLAP hydrolysis was carried out in biphasic medium (Eq.47). The reaction was reasonably

SCHEME 44:



faster in ether/phosphate buffer and complete in 4 h. The required (S)-ketone was produced in 34% ee, $[\alpha]_D^{24}$ -39.06(c 0.64, C_6H_6), {Lit.[146]

Table 8. PLAP catalyzed enantioface differentiating hydrolysis of 1-acetoxy-2-phenylcyclohexene (132a) - effect of solvent.[a]

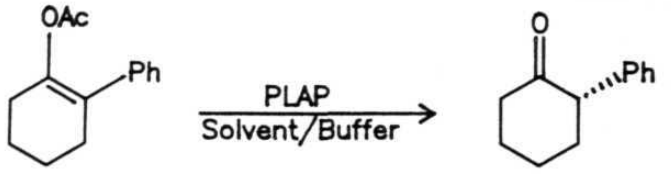
PLAP	System	Time (h)	ketone 132			
			Yield[b] (%)	$[\alpha]_D^{24}$ (c, C_6H_6)	ee[c] (%)	Conf.[d]
1 g	hexane/buffer	48	65	-17.85 (0.62)	15	(S)
1 g	acetone/buffer	60	63	-	0	-
1 g	benzene/buffer	96	59	-	0	-
1 g	ether/buffer	5	74	-39.06 (0.64)	34	(S)
2.5 g	ether/buffer	4	70	-41.95 (0.98)	37	(S)

a) All reaction were carried out in 2.3 mM of enol acetate **132a** in 10 mL of solvent and 20 mL of 0.25 M, pH 6.5 phosphate buffer.

b) Yields of pure isolated products.

c) Determined by comparing the optical rotation with literature value: $[\alpha]_D^{24}$ -113.5 (c 0.60, C_6H_6), Conf. (S), (Ref. 146).

d) Comparing the sign of optical rotation with literature value.



(47)

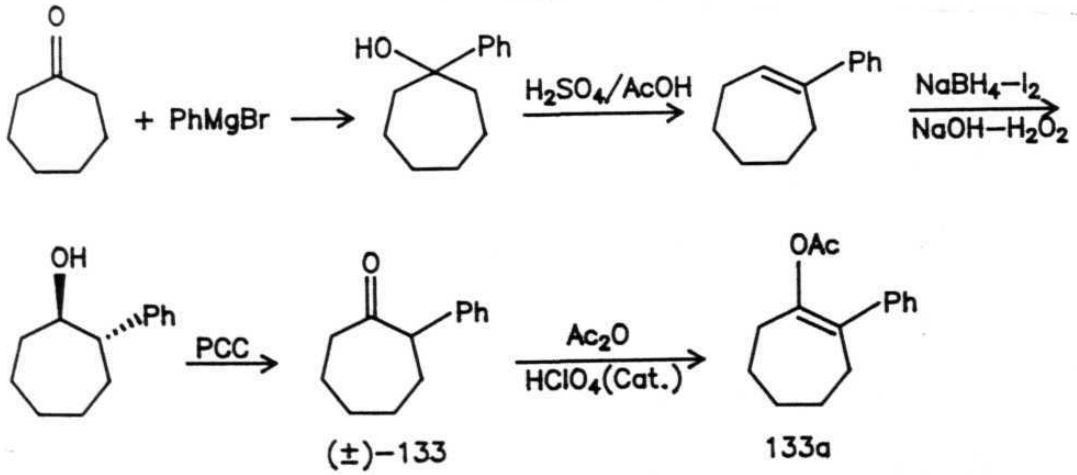
132a (S)−132
0−37% ee

$[\alpha]_D^{24}$ -113.5 (c 0.6, C_6H_6), Conf. (S)}.

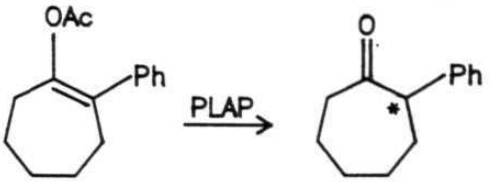
We have also studied the effect of variation of solvent system in the hydrolysis of enol acetate **132a** (Table 8). However, ether/buffer system offers better results. We have also noticed that the use of excess PLAP did not have any effect on the optical purity of the product.

In order to examine the effect of ring size we have next prepared racemic 2-phenylcycloheptanone (**133**). The required ketone **133** was prepared according to Scheme 45. The structure was confirmed by IR,

SCHEME 45:



^{1}H & ^{13}C NMR spectral analysis. The enol acetate **133a** was hydrolyzed with PLAP in ether/phosphate buffer. The hydrolysis took 15 h to



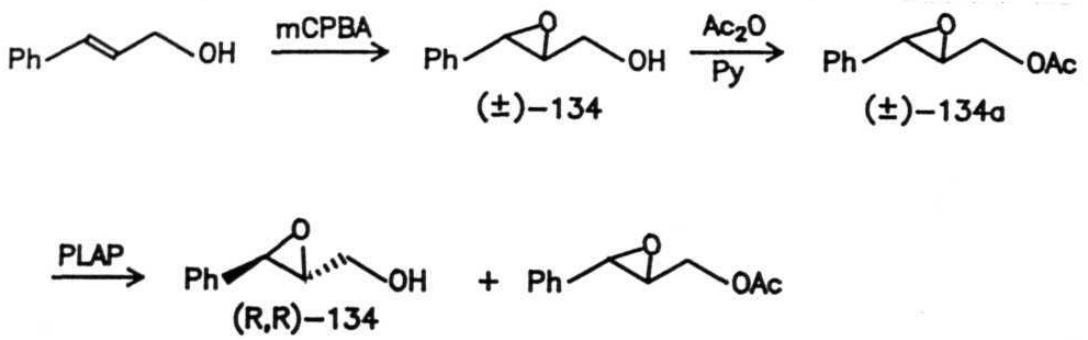
133a **(−)−133** (48)

produce optically active ketone, (-)-**133** in 31% enantiomeric purity, $[\alpha]_D^{24}$ -48.92 (c, 1.66, $CHCl_3$) {Lit.[147] $[\alpha]_D^{25}$ +158 (c 0.9, $CHCl_3$)} (Eq.48).

Epoxycinnamyl alcohol:

Sharpless asymmetric epoxidation produces epoxy alcohols in high optical purities.[148] The epoxy alcohols are very important synthetic units and building blocks for a variety of biological molecules.[149] It occurred to us that PLAP can be used for the preparation of chiral epoxy alcohols *via* the enzymatic hydrolysis of racemic acetates of epoxy alcohols. Therefore we have selected epoxycinnamyl alcohol (**134**) for resolution. The epoxy alcohol **134** was prepared[150] according to Scheme 46. Cinnamyl alcohol was converted to epoxy alcohol **134** with mCPBA which was converted to acetate with acetic anhydride. Enzymatic hydrolysis was carried out with PLAP in biphasic medium. The resulting epoxy alcohol was produced in 20% optical purity (at 10%

SCHEME 46:

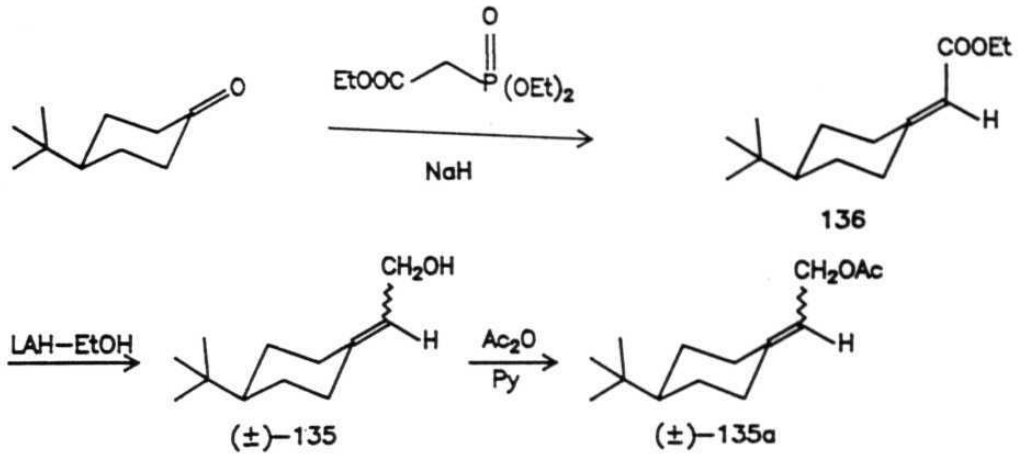


conversion), $[\alpha]_D^{24}$ +9.23 (c 0.65, EtOH) with (2R,3R)- configuration {Lit.[150] $[\alpha]_D^{20}$ +45.9 (c 1.50, EtOH), Conf. (2R,3R). Since this result is not encouraging we did not proceed for the other epoxy alcohols.

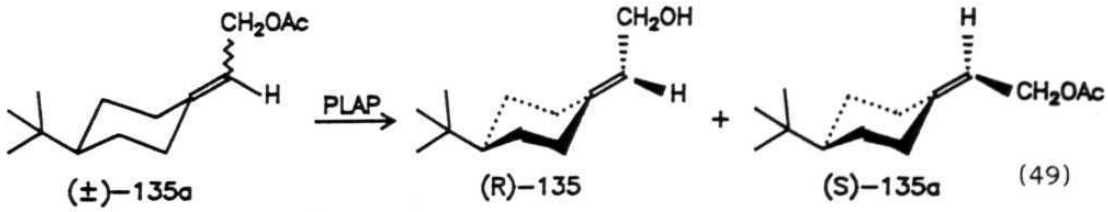
(4-*tert*-Butylcyclohexylidene)ethanol:

Till now we have used PLAP for the resolution of molecules having chiral centre(s). It occurred to us that PLAP can also be applicable for the resolution of molecules which are having axial dissymmetry. Therefore we have selected (4-*tert*-butylcyclohexylidene)ethanol as target molecule (**135**). The molecule was prepared according to Scheme 47. Wittig-Horner reaction of triethyl phosphonoacetate with 4-*tert*-butylcyclohexanone produced ethyl (4-*tert*-butylcyclohexylidene)acetate (136). Subsequent treatment with LAH:EtOH provided the desired racemic alcohol **135** which was acylated with acetic anhydride.

SCHEME 47:



The racemic acetate 135a was subjected to the PLAP catalyzed hydrolysis (Eq.49). The hydrolysis took 18 h for 39% conversion to produce optically active alcohol in 50% enantiomeric purity, $[\alpha]_D^{24}$ -4.68 (1.89, EtOH) with (R)-configuration {Lit.[151] $[\alpha]_D^{25}$ +6.5(c 2.94, EtOH), 70% ee, Conf. (S)}. The recovered acetate was shown to possess



(49)

26% ee as determined by comparing its optical rotation with literature value. It is worth mentioning that 135 has been resolved[152] recently in 58% ee through PFL catalyzed acylation with succinic anhydride.

Conclusions:

Our objective to use pig liver acetone powder (PLAP), an easily available and inexpensive crude preparation in the enantioselective synthesis has met with considerable success. We have developed a convenient methodology for the preparation of *trans*-2-aryloxycyclohexan-1-ols in high enantiomeric purities. Some of these molecules {(-)-**88** & (-)-**89**} have been successfully used as chiral auxiliaries for enantioselective synthesis of α-hydroxy acids. We have also synthesized *trans*-2-alkoxycyclohexan-1-ols in good optical purities. Our attempts to synthesize chiral α-hydroxy acids and diols using PLAP have shown some encouraging results. PLAP also shows some potential for the enantioface differentiating hydrolysis of enol acetates to produce optically active α-substituted ketones. Our studies demonstrate that PLAP is an useful crude enzyme for the preparation of optically active molecules.

EXPERIMENTAL

Melting points: All melting points were recorded on a Buchi 510 capillary melting point apparatus and are uncorrected.

Boiling points: Boiling points refer to the temperatures measured using short path distillation units and are uncorrected.

Elemental analysis: Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyzer.

Infrared spectra: Infrared spectra were recorded on Perkin-Elmer model 1310 or 297 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 $cm.^{-1}$ Solid samples were recorded as KBr wafers and liquid samples as film between NaCl plates.

Nuclear magnetic resonance spectra: Proton magnetic resonance spectra (100 or 200 MHz) and carbon-13 magnetic resonance spectra (25 or 50 MHz) were recorded either on JEOL-FX-100 or BRUKER-AC-200 spectrometer. Spectra for all the samples were measured in deuterochloroform with tetramethylsilane (δ = 0 ppm) as internal standard. Spectral assignments are as follows: (1) Chemical shifts are expressed on δ scale downfield from the signal for internal standard, (2) Standard abbreviation for multiplicity, i.e., s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, br =

broad, (3) Number of hydrogens integrated for the signal, (4) Coupling constant J in Hertz.

Mass spectral analysis: Mass spectra were recorded on Finnigon MAT instrument (70 ev, 100 A, 180^{o}C).

Optical rotations: Optical rotations were measured either on Autopol II automatic polarimeter or Jasco DIP 370 digital polarimeter at the wavelength of the sodium D-line (589 nm) and at ambient temperatures.

Chromatography: Analytical thin layer chromatography (TLC) was performed on glass plates (7x2 cm) coated with Acme's silica gel G or GF 254 (250 mμ) containing 13% calcium sulphate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using Acme's silica gel (100-200 mesh). High pressure liquid chromatography (HPLC) analysis was carried out either on Waters Associates Liquid Chromatograph equipped with model-440 absorbance detector (for conversion ratio determination) or Shimadzu LC-10AD Chromatopac equipped with SPD-10A UV-VIS detector (for conversion ratio determination and ee determinations) using special grade solvents. Enantiomeric purities were determined using chiral column, CHIRALCEL OD (25 cm), supplied by Daicel, Jpn. Gas chromatography analyses were carried out on a CHEMITO model-2800 Gas Chromatograph equipped with a flame ionization detector on SE-30 or

carbowax column using nitrogen as carrier gas.

General: All the solvents used were dried and distilled using suitable drying agents before use. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All reactions were monitored by TLC while enzymatic reactions were monitored by HPLC/GC. The yields of products of enzymatic hydrolyses are based on conversion ratios except for diols where direct yields are reported.

(±)-*trans*-2-Aryloxycyclohexan-1-ols:

(±)-*trans*-2-Aryloxycyclohexan-1-ols were prepared according to literature procedure[153] reported for 2-(2-naphthyloxy)cyclohexan-1-ol.

The following procedure for the preparation of (±)-*trans*-2-phenoxycyclohexan-1-ol is representative.

(±)-*trans*-2-Phenoxycyclohexan-1-ol (80):

To a solution of sodium phenoxide (150 mM) in water (40 mL) [prepared from sodium hydroxide (6 g, 150 mM) and phenol (14.11 g, 150 mM)] was added cyclohexene oxide (5.1 mL, 50 mM) dropwise with stirring at reflux temperature. After refluxing for 2 h, the mixture was cooled to room temperature. Thus obtained solid was filtered, washed thoroughly with water. The dried product was crystallized from hexane to furnish **80** as white crystalline solid.

Yield : 7.59 g (79%)

mp : 81-82°C [Lit.[98] mp 82°C]

IR (KBr) ν_{max} : 3400 cm^{-1}

^1H NMR (100 MHz) : δ 1.00-2.28 (m, 8H), 2.56 (s, 1H, D_2O washable), 3.68 (m, 1H), 3.96 (m, 1H), 6.81-7.40 (m, 5H).

^{13}C NMR (25 MHz) : δ 23.94, 29.17, 32.06, 73.41, 82.24, 116.48, 121.36, 129.65, 158.00.

Mass (m/e) : 192 (M^+)

The following procedure for the preparation of (±)-*trans*-1-acetoxy-2-phenoxycyclohexane (**80a**) is representative.

(±)-*trans*-1-Acetoxy-2-phenoxycyclohexane (80a):

To a solution of racemic *trans*-2-phenoxycyclohexan-1-ol (**80**) (7.61 g, 40 mM) in dry dichloromethane (40 mL) were added pyridine 6.9 mL, 85 mM) and DMAP (0.060 g, 0.5 mM). To this mixture acetic anhydride (7.5 mL, 80 mM) was added dropwise with stirring at room temperature. After 2 h the reaction mixture was poured in ice cold 2N HCl (60 mL) and extracted with ether (3 x 40 mL). The organic layer was washed with saturated K_2CO_3 solution and dried over anhydrous Na_2SO_4. The ethereal extract was concentrated and the product was distilled under reduced pressure.

Yield : 8.9 g (95%)

bp : 126-28°C/1.5 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.08-2.26 (m, 11H), 4.18 (m, 1H), 4.96 (m, 1H), 6.92 (m, 3H), 7.20 (m, 2H).

^{13}C NMR (25 MHz) : δ 21.06, 23.00, 29.70, 74.24, 77.70, 116.41, 121.12, 129.53, 158.47, 170.50.

(±)-*trans*-2-(2-Methylphenoxy)cyclohexan-1-ol (81):

Reaction time : 2 h

Yield : 76%

mp : 112-14°C/2 mm

IR (neat) ν_{max} : 3405 cm^{-1}

^1H NMR (100 MHz) : δ 1.08-2.32 (m, 11H), 2.56 (s, 1H, D_2O washable), 3.84 (m, 2H), 6.81-7.23 (m, 4H)

^{13}C NMR (25 MHz) : δ 16.41, 23.82, 29.35, 32.00, 73.24, 82.24, 114.12, 121.06, 126.88, 128.12, 131.06, 156.12.

Analysis : Calcd. : C, 75.69; H, 8.78

for $C_{13}H_{18}O_2$

Found : C, 75.50; H, 8.78.

(±)-*trans*-1-Acetoxy-2-(2-methylphenoxy)cyclohexane (81a):

Yield : 91%

bp : 112-14°C/ 2 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.16-2.20 (m, 14H), 4.22 (m, 1H), 5.02 (m, 1H), 6.78-7.18 (m, 4H)

^{13}C NMR (25 MHz) : δ 15.76, 20.35, 22.41, 22.53, 29.06, 29.17, 73.35, 76.71, 112.83, 120.24, 126.30, 127.18, 130.48, 156.01, 169.66.

(±)-*trans*-2-(3-Methylphenoxy)cyclohexan-1-ol (82):

Reaction time : 2 h

Yield : 75%

mp : 62-63°C

IR (KBr) ν_{max} : 3415 cm^{-1}

^1H NMR (100 MHz) : δ 1.04-2.28 (m, 11H), 2.52 (s, 1H, D_2O washable), 3.81 (m, 2H), 6.60-7.18 (m, 4H)

^{13}C NMR (25 MHz) : δ 21.41, 23.94, 29.23, 32.06, 73.35, 82.18, 113.42, 117.42, 122.18, 129.36, 139.71, 158.06.

Analysis : Calcd. : C, 75.69; H, 8.79

for $C_{13}H_{18}O_2$

Found : C, 75.55; H, 8.80.

(±)-*trans*-1-Acetoxy-2-(3-methylphenoxy)cyclohexane (82a):

Yield : 92%

bp : 130-32°C/3 mm

IR (KBr) ν_{max} : 1735 cm^{-1}

^1H NMR (100 MHz) : δ 1.08-2.28 (m, 14H), 4.12 (m, 1H), 4.88 (m, 1H), 6.68 (m, 3H), 7.08 (m, 1H)

^{13}C NMR (25 MHz) : δ 20.47, 20.94, 22.41, 22.59, 29.17, 73.53, 76.82, 112.77, 116.83, 121.53, 128.83, 138.95, 158.06, 169.88.

(±)-*trans*-2-(4-Methylphenoxy)cyclohexan-1-ol (83):

Reaction time : 2 h

Yield : 80%

mp : 82-83°C

IR (KBr) ν_{max} : 3450 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.04-2.36 (m, 11H), 2.68 (br s, 1H, D_2O washable), 3.44-4.04 (m, 2H), 6.84 (d, 2H, J = 8 Hz), 7.04 (d, 2H, J = 8 Hz)

^{13}C NMR (25 MHz) : δ 20.41, 23.88, 29.18, 32.00, 73.36, 82.53, 116.60, 130.06, 130.65, 155.83.

Mass (m/e) : 206 (M^+)

Analysis : Calcd. : C, 75.69; H, 8.79

for $C_{13}H_{18}O_2$

Found : C, 75.89; H, 8.83.

(±)-*trans*-1-Acetoxy-2-(4-methylphenoxy)cyclohexane (83a):

Yield : 96%

bp : 112-14°C/3 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.20-2.28 (m, 14H), 4.12 (m, 1H), 4.92 (m, 1H), 6.78 (d, 2H, J = 8 Hz), 7.02 (d, 2H, J = 8 Hz)

^{13}C NMR (25 MHz) : δ 20.12, 20.70, 22.64, 22.76, 29.29, 29.41, 73.83, 77.59, 116.18, 129.65, 130.06, 156.06, 170.13.

(±)-*trans*-2-(2-Methoxyphenoxy)cyclohexan-1-ol (84):

Reaction time : 4 h

Yield : 72%

bp : 130-32°C/0.9 mm

IR (neat) ν_{max} : 3500 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.04-2.28 (m, 8H), 3.48-3.80 (m, 6H, 1H D_2O washable), 6.72-7.12 (m, 4H).

^{13}C NMR (25 MHz) : δ 23.76, 24.12, 30.41, 32.17, 55.65, 73.53, 86.94, 112.12, 119.89, 121.12, 123.34, 147.77, 151.12.

Mass (m/e) : 222 (M^+)

Analysis : Calcd. : C, 70.24; H, 8.16

for $C_{13}H_{18}O_3$

Found : C, 70.11; H, 8.12.

(±)-*trans*-1-Acetoxy-2-(2-methoxyphenoxy)cyclohexane (84a):

Yield : 92%

bp : 150-52°C/3.5-4 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.00-2.24 (m, 11H), 3.80 (s, 3H), 4.08 (m, 1H), 4.96 (m, 1H), 6.88 (m, 4H).

^{13}C NMR (25 MHz) : δ 21.07, 23.19, 29.82, 30.23, 55.95, 74.67, 79.85, 112.66, 118.06, 120.82, 122.17, 146.60, 150.82, 170.26.

(±)-*trans*-2-(3-Methoxyphenoxy)cyclohexan-1-ol (85):

Reaction time : 4 h

Yield : 70%

mp : 72-73°C

IR (neat) ν_{max} : 3415 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.00-2.20 (m, 8H), 2.64 (s, 1H, D_2O washable), 3.24-4.08 (m, 5H), 6.58 (m, 3H), 7.12 (m, 1H).

^{13}C NMR (25 MHz) : δ 23.70, 29.00, 31.94, 55.12, 73.12, 82.00, 102.77, 106.65, 108.41, 129.89, 159.18, 160.88.

Analysis : Calcd. : C, 70.24; H, 8.16

for $C_{13}H_{18}O_3$

Found : C, 70.42; H, 8.14.

(±)-*trans*-1-Acetoxy-2-(3-methoxyphenoxy)cyclohexane (85a):

Yield : 93%

bp : 142-44°C/3 mm

IR (neat) ν_{max} : 1735 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.00-2.24 (m, 11H), 3.76 (s, 3H), 4.16 (m, 1H), 4.98 (m, 1H), 6.50 (m, 3H), 7.18 (m, 1H).

^{13}C NMR (25 MHz) : δ 20.17, 22.17, 22.29, 28.88, 54.35, 73.12, 76.53, 102.06, 106.12, 107.77, 129.30, 159.12, 160.54, 169.53.

(±)-*trans*-2-(4-Methoxyphenoxy)cyclohexan-1-ol (86):

Reaction time : 4 h

Yield : 77%

mp : 75-76°C

IR (neat) ν_{max} : 3400 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.96-2.36 (m, 8H), 2.80 (br, 1H, D_2O washable), 3.28-4.04 (m, 5H), 6. 92 (m, 4H)

^{13}C NMR (25 MHz) : δ 23.82, 29.17, 32.00, 55.59, 73.01, 83.59, 114.65, 118.18, 151.83, 154.47.

Analysis : Calcd. : C, 70.24; H, 8.16

for $C_{13}H_{18}O_3$

Found : C, 70.45; H, 8.18.

(±)-*trans*-1-Acetoxy-2-(4-methoxyphenoxy)cyclohexane (86a):

Yield : 96%

bp : 126-28°C/1 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.06-2.24 (m, 11H), 3.76 (s, 3H), 4.04 (m, 1H), 4.96 (m, 1H), 6.82 (m, 4H).

^{13}C NMR (25 MHz) : δ 21.12, 23.06, 29.65, 29.82, 55.65, 74.35, 79.06, 114.59, 118.01, 152.53, 154.36, 170.62.

(±)-*trans*-2-(2-Phenylphenoxy)cyclohexan-1-ol (87):

Reaction time : 4 h

Yield : 62%

mp : 70-71°C

IR (KBr) ν_{max} : 3455 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.00-2.36 (m, 9H, 1H D_2O washable), 3.54 (m, 1H), 3.81 (m, 1H), 6.82-7.58 (m, 9H)

^{13}C NMR (25 MHz) : δ 23.83, 24.01, 29.64, 31.93, 73.33, 84.01, 116.01, 121.82, 126.98, 128.04, 128.63, 129.63, 131.04,

132.95, 138.53, 154.89.

Analysis : Calcd. : C, 80.56; H, 7.51

for $C_{18}H_{20}O_2$

Found : C, 80.45; H, 7.50.

(±)-*trans*-1-Acetoxy-2-(2-phenylphenoxy)cyclohexane (87a):

Yield : 90%

mp : 76-77°C

IR (KBr) ν_{max} : 1735 cm^{-1}

^1H NMR (100 MHz) : δ 1.12-2.08 (m, 11H), 4.16 (m, 1H), 4.84 (m, 1H), 6.92-7.58 (m, 9H)

^{13}C NMR (25 MHz) : δ 21.11, 22.63, 22.70, 29.24, 29.30, 73.68, 77.59, 114.86, 121.32, 126.80, 127.78, 128.46, 129.65, 131.01, 132.01, 138.63, 155.08,170.30.

(±)-*trans*-2-(4-Phenylphenoxy)cyclohexan-1-ol (88):

Reaction time : 2 h

Yield : 63%

mp : 115-16°C

IR (KBr) ν_{max} : 3420 cm^{-1}

^1H NMR (100 MHz) : δ 1.08-2.32 (m, 8H), 2.64 (s, 1H, D_2O washable), 3.76 (m, 1H), 4.04 (m, 1H), 6.92-7.62 (m, 9H)

^{13}C NMR (25 MHz) : δ 24.00, 29.23, 32.12, 73.47, 82.41, 116.71, 126.89, 128.36, 128.83, 134.48, 140.89, 157.59.

MS(m/e) 268(M^+)

Analysis : Calcd. : C, 80.56; H, 7.51

for $C_{18}H_{20}O_2$

Found : C, 80.62; H, 7.55.

(±)-*trans*-1-Acetoxy-2-(4-phenylphenoxy)cyclohexane (88a):

Yield : 94%

mp : 76-77°C

IR (KBr) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.16-2.24 (m, 11H), 4.20 (m, 1H), 4.96 (m, 1H), 6.92-7.62 (m, 9H)

^{13}C NMR (25 MHz) : δ 21.06, 23.00, 29.65, 74.12, 77.65, 116.59, 126.71, 128.12, 128.77, 134.12, 140.83, 158.00, 170.53.

(±)-*trans*-2-(4-*tert*-Butylphenoxy)cyclohexan-1-ol (89):

Reaction time : 2 h

Yield : 64%

mp : 91-92°C

IR (KBr) ν_{max} : 3350 cm^{-1}

^1H NMR (100 MHz) : δ 1.00-2.20 (m, 17H), 2.56 (s, 1H, D_2O washable), 3.44-4.08 (m, 2H), 6.84 (d, 2H, J = 8 Hz), 7.24 (d, 2H, J = 8 Hz)

^{13}C NMR (25 MHz) : δ 23.88, 29.23, 31.47, 32.00, 34.00, 73.35, 82.29, 115.84, 126.36, 144.01, 155.71.

Mass (m/e) : 248 (M^+)

Analysis : Calcd. : C, 77.37; H, 9.74

for $C_{16}H_{24}O_2$

Found : C, 77.21; H, 9.69.

(±)-*trans*-1-Acetoxy-2-(4-*tert*-butylphenoxy)cyclohexane (89a):

Yield : 92%

bp : 136-38°C/1.5 mm

IR (neat) ν_{max} : 1735 cm^{-1}

^1H NMR (100 MHz) : δ 1.08-2.20 (m, 20H), 4.14 (m, 1H), 4.96 (m, 1H), 6.84 (d, 2H, J = 8 Hz), 7.24 (d, 2H, J = 8 Hz)

^{13}C NMR (25 MHz) : δ 20.59, 22.48, 22.64, 29.17, 31.18, 33.59, 73.59, 77.18, 115.53, 125.83, 143.30, 155.83, 169.95.

(±)-*trans*-2-(4-Bromophenoxy)cyclohexan-1-ol (90):

Reaction time : 3 h

Yield : 68%

mp : 87-88°C

IR (neat) ν_{max} : 3450 cm^{-1}

^1H NMR (200 MHz) : δ 1.14-1.90 (m, 6H), 1.98-2.22 (m, 2H), 2.54 (s, 1H, D_2O washable), 3.71 (m, 1H), 3.92 (m, 1H), 6.81 (m, 2H), 7.37 (m, 2H)

^{13}C NMR (50 MHz) : δ 23.76, 29.00, 32.09, 73.03, 82.42, 113.23, 118.14, 132.23, 156.96.

Mass (m/e) : 271 (M^+)

Analysis : Calcd. : C, 53.13; H, 5.57

for $C_{12}H_{15}O_2Br$

Found : C, 53.15; H, 5.62.

(±)-*trans*-1-Acetoxy-2-(4-bromophenoxy)cyclohexane (90a):

Yield : 93%

bp : 140-42°C/3 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.04-2.24 (m, 11H), 4.12 (m, 1H), 4.88 (m, 1H), 6.78 (m, 2H), 7.32 (m, 2H)

^{13}C NMR (25 MHz) : δ 20.29, 22.23, 28.88, 73.12, 77.00, 112.48, 117.59, 131.71, 157.01, 169.42.

(±)-*trans*-2-(2,4-Dimethylphenoxy)cyclohexan-1-ol (91):

Reaction time : 5 h

Yield : 63%

bp : 126-28°C/4 mm

IR (neat) ν_{max} : 3400 cm^{-1}

^1H NMR (100 MHz) : δ 1.04-2.28 (m, 14H), 2.60 (br, 1H, D_2O washable), 3.60-4.01 (m, 2H), 6.84 (m, 3H)

^{13}C NMR (25 MHz) : δ 16.30, 20.41, 23.87, 29.34, 31.93, 73.48, 82.81, 114.45, 127.15, 127.97, 130.41, 131.83, 157.80.

MS (m/e) : 220(M^+)

Analysis : Calcd. : C, 76.32; H, 9.15

for $C_{14}H_{20}O_2$

Found : C, 76.25; H, 9.11.

(±)-*trans*-1-Acetoxy-2-(2,4-dimethylphenoxy)cyclohexane (91a):

Yield : 89%

bp : 118-20°C/0.5 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.08-2.36 (m, 17H), 4.12 (m, 1H), 4.98 (m, 1H), 6.84 (m, 3H)

^{13}C NMR (25 MHz) : δ 15.88, 20.00, 20.47, 22.53, 22.64, 29.17, 29.35, 73.53, 77.12, 113.18, 126.71, 127.12, 129.42, 131.36, 154.01, 169.77.

Resolution of (±)-*trans*-2-aryloxycyclohexan-1-ols:

Pig liver acetone powder (PLAP):

This was prepared according to the procedure reported by Ohno *et al.*[86]

Fresh pig liver (1 kg) was homogenized in 4 L of chilled acetone by using a kitchen juicer. The homogenized parts were collected by filtration and further washed with chilled acetone (4 L). Thus obtained residue was air dried at room temperature and powdered by using juicer. The fibrous material was removed by sieving to get about 200 g of PLAP as fine powder. This powder can be stored upto 3 months in refrigerator without any significant loss of activity.

General procedure for PLAP-catalyzed hydrolysis of racemic acetates:

To 0.5 M, pH 8.0, KH_2PO_4/K_2HPO_4 buffer (240 mL), racemic acetate (30 mM) in ether (45 mL) was added with rapid stirring at room temperature. After 15 min, 6 g of PLAP was added and the stirring was continued. The progress of the hydrolysis was monitored by HPLC. When an appropriate degree of hydrolysis was accomplished, the reaction was quenched by acidification to pH 4.0 with 2N HCl. To this sodium chloride (25 g) and dichloromethane (75 mL) were added and the mixture was stirred for 30 min. The PLAP residue was removed by filtration with suction and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (silica gel, 10% ethyl acetate in hexane) to get optically active alcohol and unhydrolyzed acetate.

General procedure for the hydrolysis of recovered acetates:

To a solution of 85% KOH (1.68 g, 30 mM) in MeOH (20 mL) recovered acetate (10 mM) was added and stirred for 3 h at room temperature. Then methanol was distilled off under reduced pressure. Residue was diluted with water (20 mL) and extracted with ether (3 x 20 mL). The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated. The crude liquid was purified by column chromatography

(silica gel, 10% ethyl acetate in hexane) to afford (+)-alcohol.

Both (-)-alcohol and (+)-alcohol have IR, ^{1}H & ^{13}C NMR data identical with that of the corresponding racemic alcohol.

General procedure for preparation of acetate of (-)-*trans*-2-aryloxy-cyclohexan-1-ols:

To a stirred solution of (-)-*trans*-2-aryloxycyclohexan-1-ol (0.15 mM) and pyridine (0.1 mL) in benzene (3 mL) was added acetyl chloride (0.1 mL), stirred for 2 h at room temperature. Then the reaction mixture was taken in ether (10 mL), washed successively with dil. HCl, saturated K_2CO_3 solution and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated and passed through silica gel column to afford pure acetate.

General procedure for determination of enantiomeric purities:

^{1}H NMR analysis of acetates in presence of Eu(hfc)$_3$:

The ^{1}H NMR spectrum of racemic acetate (5 mg) was recorded in the presence of $Eu(hfc)_3$. The original singlet of acetoxy-methyl protons shifts and splits into two distinct singlets of equal integration due to both enantiomers. Similarly the acetate of (-)-alcohol was subjected to ^{1}H NMR analysis in the presence of $Eu(hfc)_3$. Enantiomeric purity was determined by the integeration of the two separated $-COCH_3$ signals.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-phenoxycyclohexane (80a):

Hydrolysis of racemic acetate **80a** (7.03 g, 30 mM) with PLAP (6 g) afforded (-)-alcohol **80** and unhydrolyzed acetate in 44:56 ratio.

Reaction time : 22 h

Yield of (-)-alcohol : 1.85 g (73%)

mp : 84-85°C

Optical rotation : $[\alpha]_D^{20}$ -79.16 (c 0.86, MeOH), 98% ee

Yield of recovered acetate : 2.95 g (75%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.30 g (95%)

mp : 83-84°C

Optical rotation : $[\alpha]_D^{20}$ +67.18 (c 1.26, MeOH)

Determination of enantiomeric purity:

^1H NMR analysis in presence of Eu(hfc)$_3$:

The ^1H NMR of racemic acetate (5 mg) was recorded in the presence of Eu(hfc)$_3$ (15 mg). It was observed that the original singlet at δ 1.92 (mixed with multiplet) due to -COCH$_3$ group shifts and splits into two distinct singlets of equal integration indicating that they arise from two enantiomers. Similarly acetate of (-)-alcohol was subjected to ^1H NMR analysis in presence of Eu(hfc)$_3$. The singlet due to -COCH$_3$ group shifts into two distinct singlets in the ratio 20.8:0.2 indicating that (-)-alcohol is 98% enantiomerically pure. The

recovered acetate after the same analysis showed 85% optical purity.

HPLC analysis using chiral column (CHIRALCEL OD):

HPLC analysis of racemic alcohol **80** showed two peaks in 1:1 ratio (eluent:i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 18.72 & 21.64 min) due to (R,R) & (S,S) enantiomers. Similar analysis of chiral alcohol (-)-**80** showed only one peak (retention time: 19.43 min) indicating that its enantiomeric purity is >99%.

Determination of absolute configuration:

Preparation of triphenylbismuth diacetate:

This was prepared according to known procedure.[96]

To a solution of AgOAc (1.66 g, 10 mM) in water (100 mL), was added Ph_3BiCl_2 (2.56 g, 5 mM) (obtained from the reaction of Ph_3Bi with $SOCl_2$) in CH_2Cl_2 (30 mL) and stirred for 5 min at room temperature. The AgCl formed was filtered off, washed with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$) and concentrated. The reagent thus obtained was used directly without purification for the following reaction.

Yield : 1.96 g (71%)

Monophenylation of (-)-(1R,2R)-cyclohexanediol:

This was carried out according to known procedure reported for the preparation of racemic molecule.[98]

A mixture of $Ph_3Bi(OAc)_2$ (1.68 g, 3 mM), (-)-(1R,2R)-cyclohexane-diol (70% ee, see page No.162) (0.35 g, 3 mM) and $Cu(OAc)_2$ (0.0163 g,

0.09 mM) was dissolved in 50 mL of dichloromethane and stirred for 5 h at room temperature. The reaction mixture was passed through silica gel column to afford pure (-)-*trans*-2-phenoxycyclohexan-1-ol.

Yield : 0.476 g (82%)

mp : 82-83°C

Optical rotation : $[\alpha]_D^{20}$ -58.48 (c 0.34, MeOH), 72% ee

Thus the absolute configuration of (-)-*trans*-2-phenoxycyclohexan-1-ol is assigned as (1R,2R).

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(2-methylphenoxy)cyclohexane (81a):

Hydrolysis of racemic acetate **81a** (7.45 g, 30 mM) with PLAP (6 g) furnished (-)-alcohol and unhydrolyzed acetate in 40:60 ratio.

Reaction time : 60 h

Yield of (-)-alcohol : 1.78 g (72%)

Optical rotation : $[\alpha]_D^{20}$ -44.28 (c 1.67, acetone), 71% ee

Yield of recovered acetate : 4.11 g (92%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 3.07 g (90%)

Optical rotation : $[\alpha]_D^{20}$ +30.44 (c 1.25, acetone)

Determination of enantiomeric excess:

^1H NMR analysis in presence of $Eu(hfc)_3$:

^1H NMR spectrum of (±)-**81a** (5 mg) was recorded in presence of Eu(hfc)$_3$ (20 mg). The -COCH$_3$ group shifts and splits into two distinct singlets of equal integration indicating that they arise from two enantiomers. Similarly acetate of (-)-**81** in presence of shift reagent showed two peaks in 15.6:2.6 ratio indicating that the enantiomeric excess of (-)-alcohol is 71%. Similarly recovered acetate was found to be 48% enantiomerically pure.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(3-methylphenoxy)cyclohexane (82a):

Hydrolysis of racemic acetate **82a** (7.45 g, 30 mM) with PLAP (6 g) afforded (-)-alcohol and unhydrolyzed acetate in 41:59 ratio.

Reaction time : 45 h

Yield of (-)-alcohol : 1.98 g (78%)

mp : 71-72°C

Optical rotation : $[\alpha]_D^{20}$ -48.20 (c 1.39, Acetone), 90% ee

Yield of recovered acetate : 4.04 g (92%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol.

Yield of (+)-alcohol : 3.06 g (91%)

mp : 68-69°C

Optical rotation : $[\alpha]_D^{20}$ +27.99 (c 1.28, Acetone)

Determination of enantiomeric excess:

^{1}H NMR analysis in presence of Eu(hfc)$_3$:

^{1}H NMR analysis of (±)-**82a** and acetate of (-)-**82** in presence of shift reagent [acetate (5 mg), Eu(hfc)$_3$ (15 mg)] indicated that the optical purity of (-)-alcohol is 90%. Similarly optical purity of recovered acetate was found to be 53%.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(4-methylphenoxy)cyclohexane (83a):

Hydrolysis of racemic acetate **83a** (7.45 g, 30 mM) with PLAP (6 g) afforded (-)-alcohol and unhydrolyzed acetate in 41:59 ratio.

Reaction time : 40 h

Yield of (-)-alcohol : 1.83 g (72%)

mp : 83-84°C

Optical rotation : $[\alpha]_D^{20}$ -57.15 (c 1.54, acetone), >99% ee

Yield of recovered acetate : 3.07 g (70%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.40 g (94%)

mp : 81-82°C

Optical rotation : $[\alpha]_D^{20}$ +40.62 (c 0.98, acetone)

Determination of enantiomeric excess:

^{1}H NMR analysis in presence of Eu(hfc)$_3$:

^{1}H NMR analysis of (±)-**83a** and acetate of (-)-**83** in presence of

shift reagent [acetate (5 mg), $Eu(hfc)_3$ (10 mg)] indicated that (-)-alcohol is >99% enantiomerically pure. Similarly enantiomeric purity of recovered acetate was found to be 70%.

HPLC analysis using chiral column (CHIRALCEL OD):

HPLC analysis of racemic alcohol **83** showed two peaks in 1:1 ratio (eluent:i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 17.07 & 21.20 min). Similar analysis of chiral alcohol (-)-**83** showed only one peak (retention time: 18.08 min) indicating that its enantiomeric purity is >99%.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-(2-methoxyphenoxy)cyclohexane (84a):

Hydrolysis of racemic acetate **84a** (7.93 g, 30 mM) with PLAP (6 g) afforded (-)-alcohol and unhydrolyzed acetate in 45:55 ratio.

Reaction time : 96 h

Yield of (-)-alcohol : 2.28 g (76%)

Optical rotation : $[\alpha]_D^{20}$ -50.22 (c 1.35, MeOH), 92% ee

Yield of recovered acetate : 3.27 g (75%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.59 g (94%)

Optical rotation : $[\alpha]_D^{20}$ +42.42 (c 1.11, MeOH)

Determination of enantiomeric excess:

^1H NMR analysis in presence of $Eu(hfc)_3$:

^1H NMR analysis of (±)-**84a** and acetate of (-)-**84** in the presence of shift reagent [acetate (5 mg), $Eu(hfc)_3$ (20 mg)] indicated that the optical purity of (-)-alcohol is 92%. Similarly optical purity of unhydrolyzed acetate was found to be 77%.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-(3-methoxyphenoxy)cyclohexane (85a):

Hydrolysis of racemic acetate **85a** (7.93 g, 30 mM) with PLAP (6 g) produced (-)-alcohol and unhydrolyzed ester in 47:53 ratio.

Reaction time : 23 h

Yield of (-)-alcohol : 3.01 g (96%)

mp : 99-100°C

Optical rotation : $[\alpha]_D^{20}$ -69.76 (c 1.29 MeOH), 94% ee

Yield of recovered acetate : 3.70 g (88%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.89 g (93%)

mp : 96-98°C

Optical rotation : $[\alpha]_D^{20}$ +67.26 (c 1.23, MeOH)

Determination of enantiomeric excess:

^1H NMR analysis in presence of $Eu(hfc)_3$:

^1H NMR analysis of (±)-**85a** and acetate of (-)-**85** in presence of

shift reagent [acetate (5 mg), $Eu(hfc)_3$ (20 mg)] indicated that the optical purity of (-)-alcohol is 94%. Similarly optical purity of recovered acetate was found to be 90%.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-(4-methoxyphenoxy)cyclohexane (86a):

Hydrolysis of racemic acetate **86a** (7.93 g, 30 mM) with PLAP (6 g) produced (-)-alcohol and unhydrolyzed acetate in 48:52 ratio.

Reaction time : 11 h

Yield of (-)-alcohol : 2.95 g (92%)

mp : 89-90°C

Optical rotation : $[\alpha]_D^{20}$ -58.73 (c 1.29, MeOH), 95% ee

Yield of recovered acetate : 3.96 g (96%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 3.06 g (92%)

mp : 81-82°C

Optical rotation : $[\alpha]_D^{20}$ +50.16 (c 1.06, MeOH)

Determination of enantiomeric excess:

^1H NMR analysis in presence of $Eu(hfc)_3$:

^1H NMR analysis of (±)-**86a** and acetate of (-)-**86** in presence of shift reagent [acetate (5 mg), $Eu(hfc)_3$ (20 mg)] indicated that the optical purity of (-)-alcohol is 95%. Similarly enantiomeric excess

of recovered acetate was found to be 83%.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(2-phenylphenoxy)cyclohexane (87a):

Hydrolysis of racemic acetate **87a** (9.30 g, 30 mM) of with PLAP (6 g) furnished (-)-alcohol and unhydrolyzed acetate in 37:63 ratio.

Reaction time : 96 h

Yield of (-)-alcohol : 2.83 g (95%)

mp : 78-79°C

Optical rotation : $[\alpha]_D^{20}$ -8.26 (c 0.48, acetone), 13% ee

Yield of recovered acetate : 5.45 g (93%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 4.38 g (93%)

mp : 77-78°C

Optical rotation : $[\alpha]_D^{20}$ +2.23 (c 2.24, acetone), 4 % ee.

Determination of enantiomeric excess:

^1H NMR analysis in presence of $Eu(hfc)_3$:

^1H NMR analysis of (±)-**87a** and acetate of (-)-**87** in presence of shift reagent [acetate (5 mg), $Eu(hfc)_3$ (15 mg)] indicated that the optical purity of (-)-alcohol is 13%. The enantiomeric purity of recovered acetate was found to be 4% by hydrolyzing this acetate into (+)-alcohol and comparing its optical rotation with that of

(-)-alcohol.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(4-phenylphenoxy)cyclohexane (88a):

Hydrolysis of racemic acetate **88a** (9.30 g, 30 mM) with PLAP (6 g) produced (-)-alcohol and unhydrolyzed acetate in 47:53 ratio.

Reaction time : 96 h

Yield of (-)-alcohol : 2.74 g (72%)

mp : 112-13°C

Optical rotation : $[\alpha]_D^{20}$ -28.60 (c 1.05, acetone), >99% ee

Yield of recovered acetate : 3.40 g (69%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.82 g (96%)

mp : 110-11°C

Optical rotation : $[\alpha]_D^{20}$ +25.28 (c 1.23, acetone)

Determination of enantiomeric excess:

^{1}H NMR analysis in presence of Eu(hfc)$_3$:

^{1}H NMR analysis of (±)-**88a** and acetate of (-)-**88** in presence of shift reagent [acetate (5 mg), Eu(hfc)$_3$ (15 mg)] indicated that the optical purity of (-)-alcohol is >99%. Similarly the enantiomeric excess of recovered acetate was found to be 88%.

HPLC analysis using chiral column (CHIRALCEL OD):

HPLC analysis of racemic alcohol **88** showed two peaks in 1:1 ratio (eluent:i-PrOH/hexane: 10:90; flow rate: 0.5 mL/min; retention times: 16.24 & 19.66 min). Similar analysis of chiral alcohol (-)-**88** showed only one peak (retention time: 19.54 min) indicating that its enantiomeric purity is >99%.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(4-*tert*-butylphenoxy)cyclohexane (89a):

Hydrolysis of racemic acetate **89a** (8.71 g, 30 mM) with PLAP (6 g) produced (-)-alcohol and unhydrolyzed acetate in 47:53 ratio.

Reaction time : 84 h

Yield of (-)-alcohol : 2.45 g (70%)

mp : 96-98°C

Optical rotation : $[\alpha]_D^{20}$ -45.33 (c 1.06, acetone), >99% ee

Yield of recovered acetate : 3.14 g (68%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.55 g (95%)

mp : 96-97°C

Optical rotation : $[\alpha]_D^{20}$ +41.25 (c 0.99, acetone)

Determination of enantiomeric excess:

^1H NMR analysis in presence of $Eu(hfc)_3$:

^1H NMR analysis of (±)-**89a** and acetate of (-)-**89** in presence of

shift reagent [acetate (5 mg), $Eu(hfc)_3$ (15 mg)] indicated that the optical purity of (-)-alcohol is >99%. Similarly the enantiomeric excess of unhydrolyzed acetate was determined to be 90%.

HPLC analysis using chiral column (CHIRALCEL OD):

HPLC analysis of racemic alcohol **89** showed two peaks in 1:1 ratio (eluent:i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 12.83 & 13.91 min). Similar analysis of chiral alcohol (-)-**89** showed only one peak (retention time: 12.62 min) indicating that its enantiomeric purity is >99%.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(4-bromophenoxy)cyclohexane (90a):

Hydrolysis of racemic acetate **90a** (9.39 g, 30 mM) with PLAP (6 g) produced (-)-alcohol and recovered acetate in 48:52 ratio.

Reaction time	: 36 h
Yield of (-)-alcohol	: 3.47 g (89%)
mp	: 88-89°C
Optical rotation	: $[\alpha]_D^{20}$ -29.54 (c 1.35, acetone), 96% ee
Yield of recovered acetate	: 4.34 g (89%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol	: 3.50 g (93%)
mp	: 88-89°C

Optical rotation : $[\alpha]_D^{20}$ +27.43 (c 1.46, acetone)

Determination of enantiomeric excess:

^1H NMR analysis in presence of Eu(hfc)$_3$:

^{1}H NMR analysis of (±)-**90a** and acetate of (-)-**90** in presence of shift reagent [acetate (5 mg), Eu(hfc)$_3$ (10 mg)] indicated that the optical purity of (-)-alcohol is 96%. Similar analysis of recovered acetate showed that it is 89% enantiomerically pure.

Enzymatic hydrolysis of *trans*-1-acetoxy-2-(2,4-dimethylphenoxy)cyclohexane (91a):

Hydrolysis of racemic acetate **91a** (7.86 g, 30 mM) with PLAP (6 g) afforded (-)-alcohol and unhydrolyzed acetate in 37:63 ratio.

Reaction time : 50 h

Yield of (-)-alcohol : 1.59 g (65%)

Optical rotation : $[\alpha]_D^{20}$ -44.24 (c 1.22, acetone), 90% ee

Yield of recovered acetate : 2.97 g (60%)

The recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol

Yield of (+)-alcohol : 2.25 g (90%)

Optical rotation : $[\alpha]_D^{20}$ +30.12 (c 0.98, acetone)

Determination of enantiomeric excess:

Preparation of Mosher's ester:

To a mixture of (±)-alcohol (0.022 g) in pyridine (0.2 mL), 0.2 M

solution of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPACl] in dichloromethane (1 mL) was added and stirred for 12 h at room temperature. Water (1 mL) and ether (15 mL) were addded and the ether solution was washed successively with dil. HCl, saturated K_2CO_3 solution and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated and passed through silica gel column (5% ethyl acetate in hexane) to provide Mosher's ester in 92% yield (0.040 g).

^{1}H NMR (100 MHz) : δ 1.16-1.84 (m, 8H), 2.08 (s, 3H), 2.21 (s, 3H), 3.44 (m, 3H), 4.22 (m, 1H), 5.24 (m, 1H), 6.52-7.60 (m, 8H).

^{1}H NMR analysis of Mosher's ester in presence of Eu(hfc)$_3$:

In ^{1}H NMR spectrum of Mosher's ester in the presence of shift reagent [sample:Eu(hfc)$_3$ = 1:2], the peak originally at δ 3.44 due to -OMe group splits into two broad singlets of equal integration due to (R,R) & (S,S) enantiomers. ^{1}H NMR analysis of Mosher's ester from (-)-alcohol in the presence of Eu(hfc)$_3$ showed two broad singlets in 7.9:0.4 ratio, indicating the enantiomeric purity of (-)-alcohol to be 90%. Similar analysis of Mosher's ester of (+)-alcohol showed that the enantiomeric purity of (+)-alcohol is 60%.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] phenylglyoxylate (93):

A solution of (1R,2R)-2-(4-phenylphenoxy)cyclohexan-1-ol **(88)** (8.04 g, 30 mM), benzoylformic acid (4.95 g, 33.5 mM) and *p*-toluene-

sulfonic acid (129 mg, 0.9 mM) in 60 mL of dry benzene was refluxed for 3 h with azeotropic removal of water. The reaction mixture was cooled to room temperature, diluted with ether (40 mL), washed with saturated K_2CO_3 solution followed by water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude material was passed through silica gel. Recrystallization of the crude material from hexane-benzene (5:1) afforded pure glyoxylate **93**.

Yield : 9.97 g (83%)

mp : 105-6°C

Optical rotation : $[\alpha]_D^{24}$ -43.78 (c 0.98, acetone)

IR (KBr) ν_{max} : 1722, 1685 cm^{-1}.

^1H NMR (200 MHz) : δ 1.24-1.94 (m, 6H), 2.25 (m, 2H), 4.35 (m, 1H), 5.34 (m, 1H), 7.05 (m, 2H), 7.49 (m, 10H), 8.90 (m, 2H).

^{13}C NMR (50 MHz) : δ 23.08, 23.41, 29.84, 29.93, 76.50, 77.65, 116.43, 126.70, 126.79, 128.22, 128.79, 129.96, 132.28, 134.34, 134.80, 140.62, 157.18, 163.81, 186.82.

Mass (m/e) : 400 (M^+)

Analysis : Calcd. : C, 77.98; H, 6.04

for $C_{26}H_{24}O_4$

: Found : C, 78.25: H, 6.08.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenylbutanoate (94a):

To a stirred solution of ethylmagnesium bromide (12.5 mM) (prepared from bromoethane and magnesium) in dry ether (25 mL), anhydrous $ZnCl_2$ (1.7 g, 12.5 mM) was added at 0^oC. After 2 h stirring at 0^oC it was cooled to -78^oC. To this a solution of [(1R,2R)-2-(4-phenylphenoxy)cyclohex-1-yl] phenylglyoxylate (93) (1.00 g, 2.5 mM) in ether (30 mL) was added dropwise at -78^oC. After 3 h stirring at the same temperature, it was stirred for 1 h at room temperature. The reaction mixture was cooled to 0^oC, quenched with saturated ammonium chloride solution (15 mL) and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to provide **94a** as colorless solid. The compound thus obtained was used for the next step without purification.

Yield : 1.025 g (95%)

mp : $79-80^oC$

IR (KBr) ν_{max} : 3470, 1710 cm^{-1}

^1H NMR (200 MHz) : δ 0.83 & 0.92 (2 t in 1:9 ratio, 3H, diastereomeric $-CH_3$, J = 7.2 Hz), 1.21-2.36 (m, 10H), 3.71 (s, 1H, D_2O washable), 4.22 (m, 1H), 5.07 (m, 1H), 6.72-7.68 (m, 14H).

(R)-2-Hydroxy-2-phenylbutanoic acid (95a):

To a stirred solution of KOH (0.255 g, 4.5 mM) in methanol (10 mL), α-hydroxy ester **94a** (0.947 g, 2.2 mM) was added and stirred for 2 h at room temperature. The reaction mixture was diluted with water

(10 mL), extracted with ether (3 x 10 mL) (to recover the chiral auxiliary). The aqueous layer was neutralized with 2N HCl, extracted with ether (3 x 10 mL). The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and recrystallized from hexane-ether (3:1) mixture.

Yield : 0.320 g (81%)

mp : 121-23°C [Lit.[101] optically pure acid mp 124-25°C]

Optical rotation : $[\alpha]_D^{24}$ -27.16 (c 1.75, EtOH), 81% ee, Conf. (R)

{Lit.[101] $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH), >99% ee, Conf. (S)}

IR (KBr) ν_{max} : 3400, 3190-2550, 1715 cm^{-1}

^1H NMR (100 MHz) : δ 0.92 (t, 3H, J = 5 Hz), 1.82-2.52 (m, 2H), 5.60 (br, 2H, D_2O washable), 7.21-7.72 (m, 5H)

^{13}C NMR (50 MHz) : δ 7.94, 32.60, 82.24, 125.57, 128.00, 128.36, 140.84, 179.98.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenylhexanoate (94b):

This compound was prepared from [(1R,2R)-2-(4-phenylphenoxy)cyclohex-1-yl] phenylglyoxylate (93) and n-butylzinc chloride as a viscous liquid following the same procedure as described for compound **94a**.

Yield : 96%

IR (neat) ν_{max} : 3450, 1715 cm^{-1}

^{1}H NMR (200 MHz) : δ 0.72 & 0.87 (2 t in 1:9 ratio, 3H, diastereomeric $-CH_3$, J = 6Hz), 1.12-2.24 (m, 14H), 3.74 (s, 1H, D_2O washable), 4.25 (m, 1H), 5.06 (m, 1H), 6.82-7.65 (m, 14H).

(R)-2-Hydroxy-2-phenylhexanoic acid (95b):

This was obtained by the hydrolysis of α-hydroxy ester **94b** (2.2 mM) and was crystallized from hexane-ether (3:1) mixture.

Yield : 0.362 g (79%)

mp : 98-99°C

Optical rotation : $[\alpha]_D^{24}$ -17.61 (c 2.18, EtOH), 76% ee, Conf. (R)

{Lit.[102] $[\alpha]_D^{22}$ -19.00 (c 2.20, EtOH), 82% ee, Conf. (R)}

IR (KBr) ν_{max} : 3400, 3150-2500 (br), 1710 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.91 (distorted t, 3H), 1.06-1.48 (m, 4H), 1.82-2.42 (m, 2H), 5.42 (br, 2H, D_2O washable), 7.23-7.68 (m, 5H)

^{13}C NMR (50 MHz) : δ 13.95, 22.78, 25.77, 39.45, 78.48, 125.56, 128.02, 128.41, 141.11, 180.36.

[(1R,2R)-2-(4-Phenylphenoxy)cyclohex-1-yl] 2-hydroxy-4-methyl-2-phenylpentanoate (94c):

This was prepared from [(1R,2R)-(4-phenylphenoxy)cyclohex-1-yl] phenylglyoxylate **93** and *iso*-butylzinc chloride following the same procedure as described for **94a**.

Yield : 96%

mp : 86-87°C

IR (KBr) ν_{max} : 3455, 1705 cm^{-1}

^1H NMR (200 MHz) : δ 0.79 & 0.90 (m & t in 0.5:9.5 ratio, 6H, diastereomeric $(CH_3)_2$, J = 7.2 Hz), 1.22-2.28 (m, 11H), 3.78 (s, 1H, D_2O washable), 4.24 (m, 1H), 5.08 (m, 1H), 6.74-7.62 (m, 14H).

(R)-2-Hydroxy-4-methyl-2-phenylpentanoic acid (95c):

Hydrolysis of α-hydroxy ester (2.2 mM) followed by recrystallization from hexane-ether mixture produced white solid.

Yield : 0.340 g (74%)

mp : 117-19°C [Lit.[101] optically pure acid mp 118-20°C]

Optical rotation : $[\alpha]_D^{24}$ -17.87 (c 1.97, EtOH), 88% ee, Conf. (R)

{Lit.[101] $[\alpha]_D^{25}$ +20.0 (c 2.00, EtOH), >99% ee, Conf. (S)}

IR (KBr) ν_{max} : 3400, 3140-2550, 1710 cm^{-1}

^1H NMR (100 MHz) : δ 0.92 (t, 6H, J = 5Hz), 1.65-2.21 (m, 3H), 5.53 (br, 2H, D_2O washable), 7.42-7.81 (m, 5H).

^{13}C NMR (50 MHz) : δ 23.32, 24.40, 24.67, 47.84, 78.44, 125.55, 128.00, 128.42, 141.84, 180.92.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] phenylglyoxylate (96):

This was prepared from (1R,2R)-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (**89**) and benzoylformic acid in the presence catalytic amount of

p-TsOH following the same procedure as described for **93**. The product was crystallized from hexane.

Yield : 81%

mp : 61-62°C

Optical rotation : $[\alpha]_D^{24}$ -34.85 (c 1.01, acetone)

IR (KBr) ν_{max} : 1750, 1685 cm^{-1}

^1H NMR (200 MHz) : δ 1.26 (s, 9H), 1.29-1.84 (m, 6H), 2.22 (m, 2H), 4.28 (m, 1H), 5.32 (m, 1H), 6.90 (m, 2H), 7.25 (m, 4H), 7.62 (m, 1H), 7.94 (m, 2H)

^{13}C NMR (50 MHz) : δ 22.62, 22.98, 29.45, 31.11, 33.62, 76.03, 77.15, 115.28, 125.88, 128.34, 129.56, 131.90, 134.26, 143.54, 154.92, 163.34, 186.34.

Mass (m/e) : 380 (M^+)

Analysis : Calcd. : C, 75.76; H, 7.42

for $C_{24}H_{28}O_4$

: Found : C, 75.58; H, 7.39.

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenyl-butanoate (97a):

This was prepared from [(1R,2R)-2-(4-*tert*-butylphenoxy)cyclohex-1-yl] phenylglyoxylate (**96**) and ethylzinc chloride following the same as procedure described for **94a**.

Yield : 96%

mp : 67-68°C

IR (KBr) ν_{max} : 3420, 1715 cm^{-1}

^1H NMR (200 MHz) : δ 0.90 (t, 3H, J = 8Hz), 1.29 (s, 9H), 1.34-2.28 (m, 10H), 3.65 (s, 1H, D_2O washable), 4.18 (m, 1H), 5.06 (m, 1H), 6.54 (m, 2H), 7.08-7.32 (m, 5H), 7.50 (m, 2H).

^{13}C NMR (50 MHz) : δ 7.40, 22.03, 22.32, 28.70, 30.93, 32.14, 33.44, 75.38, 75.64, 78.16, 114.64, 124.86, 125.54, 126.78, 127.41, 141.21, 143.04, 154.58, 174.21.

(R)-2-Hydroxy-2-phenylbutanoic acid (95a):

Hydrolysis of above hydroxy ester (2.2 mM) with KOH/MeOH followed by crystallization from hexane-ether mixture provided **95a** as crystalline solid.

Yield : 0.310 g (78%)

mp : 123-24°C [Lit.[101] optically pure acid mp 124-25°C]

Optical rotation : $[\alpha]_D^{24}$ -32.35 (c 1.77, EtOH), 96% ee, Conf. (R)

{Lit.[101] $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH), >99% ee, Conf. (S)}

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-2-phenyl-hexanoate (97b):

This was prepared from α-keto ester **96** and *n*-butylzinc chloride following the same procedure as described for **94a**.

Yield : 99%

IR (neat) ν_{max} : 3520, 1725 cm^{-1}

^1H NMR (200 MHz) : δ 0.72 & 0.90 (2 t in 1:9 ratio, 3H, diastereomeric $-CH_3$, J = 4 Hz), 1.24-2.28 (m, 23H), 3.68 (s, 1H, D_2O washable), 4.18 (m, 1H), 5.02 (m, 1H), 6.70-7.85 (m, 9H).

(R)-2-Hydroxy-2-phenylhexanoic acid (95b):

Hydrolysis of the above hydroxy ester **97b** (2.2 mM) followed by crystallization from hexane-ether mixture afforded **95b** as crystalline solid.

Yield : 0.340 g (74%)

mp : 98-99°C

Optical rotation : $[\alpha]_D^{24}$ -20.50 (c 1.98, EtOH), 88% ee, Conf. (R)

{Lit.[102] $[\alpha]_D^{22}$ -19.00 (c 2.20, EtOH), 82% ee, Conf. (R)}

[(1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohex-1-yl] 2-hydroxy-4-methyl-2-phenylpentanoate (97c):

This compound was prepared from the glyoxylate **96** (2.5 mM) and *iso*-butylzinc chloride following the same procedure as described for **94a**.

Yield : 97%

IR (neat) ν_{max} : 3350, 1745 cm^{-1}

^1H NMR (200 MHz) : δ 0.68 & 0.82 (2 m in 0.5:9.5 ratio, 6H, diastereomeric $(CH_3)_2$, 1.22 (s, 9H), 1.06-2.18 (m, 11H),

3.64 (s, 1H, D_2O washable), 4.02-4.18 (m, 1H), 4.84-5.02 (m, 1H), 6.54-7.80 (m, 9H).

(R)-2-Hydroxy-4-methyl-2-phenylpentanoic acid (95c):

This acid was obtained by the hydrolysis of above hydroxy ester (2.2 mM) followed by crystallization from hexane-ether mixture as crystalline solid.

Yield : 0.370 g (81%)

mp : 116-18°C [Lit.[101] optically pure acid mp 118-20°C]

Optical rotation : $[\alpha]_D^{24}$ -17.38(c 1.9, EtOH), 86% ee, Conf. (R)

{Lit.[101] $[\alpha]_D^{25}$ +20.0 (c 2.0, EtOH), >99% ee, Conf. (S)}

(±)-*trans*-2-Methoxycyclohexan-1-ol (98):

To a stirred solution of cyclohexene oxide (5.0 mL, 50 mM) in methanol (25 mL), 2 drops of conc. sulfuric acid was added and refluxed gently for 4 h. The excess methanol was distilled off. The residue was taken in ether (30 mL), washed with saturated K_2CO_3 solution followed by brine. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. Distillation under reduced pressure afforded the racemic alcohol 98 as colorless liquid.

Yield : 5.86 (90%)

bp : 116-20°C/30 mm [Lit.[109] bp 72.5-73.2/10 mm]

IR (neat) ν_{max} : 3400 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.96-2.21 (m, 8H), 2.84-3.42 (m, 6H, 1H D_2O washable).

^{13}C NMR (25 MHz) : δ 23.35, 27.83, 31.76, 55.76, 72.71, 84.36.

Mass (m/e) : 130 (M^+)

All *trans*-1-acetoxy-2-alkoxycyclohexanes were prepared from the corresponding alcohols by treatment with acetic anhydride in presence of pyridine following the same procedure as described for **80a**.

(±)-*trans*-1-Acetoxy-2-methoxycyclohexane (98a):

Yield : 90%

bp : 94-96°C/10 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.08-2.04 (m, 11H), 3.11 (m, 1H), 3.14 (s, 3H), 4.70 (m, 1H)

^{13}C NMR (50 MHz) : δ 20.99, 22.87, 22.97, 28.85, 29.43, 56.70, 74.55, 80.12, 170.05.

(±)-*trans*-2-Ethoxycyclohexan-1-ol (99):

This was prepared from cyclohexene oxide and ethanol following the same procedure as described for **98**.

Reaction time : 4 h

Yield : 76%

bp : 96-100°C/10 mm [Lit[110] bp 78-79°C/13 mm]

IR (neat) ν_{max} : 3450 cm^{-1}

^1H NMR (100 MHz) : δ 1.00-2.18 (m, 11H), 2.76-3.12 (m, 2H, 1H D_2O washable), 3.20-3.84 (m, 3H)

^{13}C NMR (25 MHz) : δ 15.17, 23.59, 23.76, 29.00, 32.00, 63.71, 72.88, 82.94.

(±)-*trans*-1-Acetoxy-2-ethoxycyclohexane (99a):

Yield : 92%

bp : 120-22°C/20 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.00-2.16 (m, 14H), 3.14-3.80 (m, 3H), 4.68 (m, 1H)

^{13}C NMR (25 MHz) : δ 15.17, 20.70, 22.82, 29.29, 29.53, 64.47, 74.59, 78.47, 170.00.

(±)-*trans*-2-*iso*-Propyloxycyclohexan-1-ol (100):

This was prepared from cyclohexene oxide and *iso*-propanol following the same procedure as described for **98**.

Reaction time : 4 h

Yield : 75%

bp : 104-6°C/8 mm [Lit.[110] bp 81-83°C/12 mm]

IR (neat) ν_{max} : 3400 cm^{-1}

^1H NMR (100 MHz) : δ 1.00-2.20 (m, 14H), 2.68 (s, 1H, D_2O washable), 2.88-3.48 (m, 2H), 3.80 (m, 1H).

^{13}C NMR (25 MHz) : δ 21.88, 23.35, 23.64, 24.00, 30.06, 31.88, 69.18, 73.18, 80.83.

Mass (m/e) : 158 (M^+)

(±)-*trans*-1-Acetoxy-2-*iso*-propyloxycyclohexane (100a):

Yield : 91%

bp : 112-14°C/10 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.98-2.12 (m, 17H), 3.2 (m, 1H), 3.64 (m, 1H), 4.62 (m, 1H).

^{13}C NMR (25 MHz) : δ 20.70, 22.23, 22.70, 22.94, 29.53, 30.94, 70.89, 75.06, 76.83, 170.00.

(±)-*trans*-2-*iso*-Butyloxycyclohexan-1-ol (101):

A mixture of cyclohexene oxide (5.0 mL, 50 mM), *iso*-butanol (30 mL, 320 mM) and DDQ (0.113 g, 0.5 mM, 1 mole %) was refluxed for 12 h. The excess *iso*-butanol was distilled off under reduced pressure. The residue thus obtained was fractionally distilled to afford the alcohol 101 as a colorless liquid.

Yield : 5.25 (61%)

bp : 56-58°C/1 mm

IR (neat) ν_{max} : 3400 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.75-2.19 (m, 15H), 2.74 (s, 1H, D_2O washable), 2.68-3.58 (m, 4H).

^{13}C NMR (25 MHz) : δ 18.88, 23.47, 23.70, 28.35, 28.65, 31.65, 73.18, 75.30, 83.18.

Mass (m/e) : 178 (M^+)

(±)-*trans*-1-Acetoxy-2-*iso*-butyloxycyclohexane (101a):

Yield : 95%

bp : 84-86°C/3 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.88 (d, 6H, J = 6 Hz), 1.06-2.06 (m, 12H), 3.24 (m, 3H), 4.68 (m, 1H).

(±)-*trans*-2-Benzyloxycyclohexan-1-ol (102):

This was prepared from cyclohexene oxide and benzyl alcohol following the same procedure as described for **101**.

Reaction time : 12 h

Yield : 64%

bp : 118-20°C/1 mm [Lit.[154] bp 110-12°C/0.3 mm]

IR (neat) ν_{max} : 3400 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.88-2.16 (m, 8H), 2.52 (br, 1H, D_2O washable), 2.88-3.56 (m, 2H), 4.40 and 4.64 (AB quartet, 2H, J = 12 Hz), 7.14 (s, 5H).

^{13}C NMR (25 MHz) : δ 23.76, 24.06, 29.11, 32.00, 70.77, 73.65, 83.35, 127.71, 128.41, 138.71.

Analysis : Calcd. : C, 75.69; H, 8.79

for $C_{13}H_{18}O_2$

: Found : C, 75.55; H, 8.75.

(±)-*trans*-1-Acetoxy-2-benzyloxycyclohexane (102a):

Yield : 94%

bp : 138-40°C/30 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.04-2.20 (m, 11H), 3.32 (m, 1H), 4.51-4.98 (m, 3H), 7.28 (s, 5H).

^{13}C NMR (50 MHz) : δ 21.26, 23.26, 29.86, 71.29, 75.09, 78.71, 127.34, 128.26, 139.03, 170.35.

(±)-*trans*-2-[2-(2-Methoxyethoxy)ethoxy]cyclohexan-1-ol (103):

This was prepared from cyclohexene oxide and diethylene glycol monomethyl ether following the same procedure as described for **101**.

Reaction time : 12 h

Yield : 62%

bp : 108-10°C/2 mm

IR (neat) ν_{max} : 3450 cm^{-1}

^1H NMR (100 MHz) : δ 0.84-2.16 (m, 8H), 2.72-3.92 (m, 14H, 1H D_2O washable)

^{13}C NMR (25 MHz) : δ 23.53, 23.88, 29.35, 31.88, 58.41, 68.06, 69.94, 70.35, 71.47, 73.29, 84.06.

Mass (m/e) : 218 (M^+)

Analysis : Calcd. : C, 60.52; H, 10.15

for $C_{11}H_{22}O_4$

Found : C, 60.45; H, 10.09.

(±)-*trans*-1-Acetoxy-2-[2-(2-methoxyethoxy)ethoxy]cyclohexane (103a):

Yield : 96%

bp : 126-28°C/4 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 1.00-2.08 (m, 11H), 3.08-3.76 (m, 12H), 4.62 (m, 1H)

^{13}C NMR (50 MHz) : δ 20.96, 23.04, 29.56, 29.67, 58.63, 68.87, 70.27, 70.62, 71.70, 74.86, 79.41, 170.06.

Resolution of (±)-*trans*-2-alkoxycyclohexan-1-ols:

General procedure for enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-alkoxycyclohexanes:

Enzymatic hydrolysis of *trans*-1-acetoxy-2-alkoxycyclohexanes was carried out in 20 mM scale in phosphate buffer (0.5 M, pH 8.0, 120 mL) and ether (20 mL) with PLAP (3 g). Conversion ratios were determined by GC.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-methyoxycyclohexane (98a):

Hydrolysis of racemic acetate **98a** (3.44 g, 20 mM) with PLAP (3 g)

afforded (-)-alcohol and unhydrolyzed acetate in 47:53 ratio.

Reaction time 8 h

Yield of (-)-alcohol : 0.70 g (57%)

Optical rotation : $[\alpha]_D^{24}$ -56.58(c 1.34, CH_2Cl_2),80% ee, Conf. (R,R)

{Lit.[110] $[\alpha]_D^{20}$ -69.3(c 2.0, CH_2Cl_2), 98% ee, Conf. (R,R)}

Yield of recovered acetate : 1.44 g (79%)

This recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol.

Yield of (+)-alcohol : 0.98 (90%)

Optical rotation : $[\alpha]_D^{24}$ +53.04 (c 2.13, CH_2Cl_2), 75% ee

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-ethoxycyclohexane (99a):

Hydrolysis of racemic acetate **99a** (3.74 g, 20 mM) with PLAP (3 g) afforded (-)-alcohol and unhydrolyzed acetate in 46:54 ratio.

Reaction time : 26 h

Yield of (-)-alcohol : 0.97 g (73%)

Optical rotation : $[\alpha]_D^{24}$ -61.14(c 1.93, CH_2Cl_2),76% ee, Conf. (R,R)

{Lit.[110] $[\alpha]_D^{20}$ -75.3 (c 2.0, CH_2Cl_2),94% ee, Conf. (R,R)}

Yield of recovered acetate : 1.82 g (90%)

This recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol.

Yield of (+)-alcohol : 1.32 (94%)

Optical rotation : $[\alpha]_D^{24}$ +48.39 (c 0.93, CH_2Cl_2), 60% ee.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-*iso*-propyloxycyclohexane (100a):

Hydrolysis of racemic acetate **100a** (4.00 g, 20 mM) with PLAP (3 g) afforded (-)-alcohol and unhydrolyzed acetate in 39:61 ratio.

Reaction time : 70 h

Yield of (-)-alcohol : 0.69 g (56%)

Optical rotation : $[\alpha]_D^{24}$ -68.83 (c 1.6, CH_2Cl_2),79% ee, Conf. (R,R)

{Lit.[110] $[\alpha]_D^{20}$ -85.6 (c 2.0, CH_2Cl_2),98% ee, Conf. (R,R)}

Yield of recovered acetate : 1.83 g (73%)

This recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol.

Yield of (+)-alcohol : 1.33 (92%)

Optical rotation : $[\alpha]_D^{24}$ +33.80 (c 1.83, CH_2Cl_2), 39% ee.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-*iso*-butyloxycyclohexane (101a):

Hydrolysis of racemic acetate **101a** (4.28 g, 20 mM) with PLAP (3 g) afforded (-)-alcohol and unhydrolyzed acetate in 44:56 ratio.

Reaction time : 24 h

Yield of (-)-alcohol : 0.88 g (58%)

Optical rotation : $[\alpha]_D^{24}$ -40.70 (c 1.37, CH_2Cl_2), 61% ee

Yield of recovered acetate : 1.21 g (50%)

This recovered acetate was hydrolyzed with KOH/MeOH to provide

(+)-alcohol.

Yield of (+)-alcohol : 1.29 (91%)

Optical rotation : $[\alpha]_D^{24}$ +38.06 (c 1.14, CH_2Cl_2) 57% ee

Determination of enantiomeric excess:

^1H NMR analysis in presence of Eu(hfc)$_3$:

^1H NMR spectrum of racemic acetate **101a** and acetate of (-)-**101** in presence of shift reagent [acetate (5 mg), Eu(hfc)$_3$ (30 mg)] indicated that the optical purity of (-)-alcohol is 61%.

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-benzyloxycyclohexane (102a):

Hydrolysis of racemic acetate **102a** (4.96 g, 20 mM) with PLAP (3 g) afforded (-)-alcohol and unhydrolyzed acetate in 44:56 ratio.

Reaction time : 17 h

Yield of (-)-alcohol : 1.67 g (90%)

Optical rotation : $[\alpha]_D^{24}$ -68.75 (c 1.76, CH_2Cl_2),79% ee Conf (R,R)

Yield of recovered acetate : 2.27 g (83%)

This recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol.

Yield of (+)-alcohol : 1.79 (95%)

Optical rotation : $[\alpha]_D^{24}$ +60.66 (c 1.76, CH_2Cl_2), 69% ee.

Determination of enantiomeric excess and absolute configuration:

Chemical degradation to (-)-cyclohexane-1,2-diol:

To a solution of NaI (0.720 g, 4.8 mM) in dry acetonitrile (10 mL) were added successively trichloro(methyl)silane (0.5 mL, 4.8 mM) and alcohol (-)-102 (0.825 g, 4 mM) at room temperature under nitrogen. After 5 h, water (10 mL) was added and extracted with ether. The ether layer was washed with aqueous $Na_2S_2O_3$ solution and NaCl. The ethereal extract was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (silica gel, 20% ethyl acetate in hexane) to afford crystalline cyclohexane-1,2-diol.

Yield : 0.206 g (45%)

mp : 109-110°C [Lit.[137] optically pure diol mp 113-14°C]

IR, ^1H & ^{13}C NMR spectral data are in full agreement with those of racemic diol.

Optical rotation : $[\alpha]_D^{24}$ -31.55 (c 0.58, $CHCl_3$), 79% ee, Conf. (R,R)

{Lit.[137] $[\alpha]_D^{25}$ -40 (c 0.32, $CHCl_3$), Conf. (R,R)}

Enzymatic hydrolysis of (±)-*trans*-1-acetoxy-2-[2-(2-methoxyethoxy)-ethoxy]cyclohexane (103a):

Hydrolysis of racemic acetate **103a** (6.01 g, 20 mM) with PLAP (3 g) afforded (-)-alcohol and unhydrolyzed acetate in 48:52 ratio.

Reaction time : 16 h

Yield of (-)-alcohol : 1.56 g (63%)

Optical rotation : $[\alpha]_D^{24}$ -39.37 (c 1.52, CH_2Cl_2), 82% ee

Yield of recovered acetate : 2.22 g (71%)

This recovered acetate was hydrolyzed with KOH/MeOH to provide (+)-alcohol.

Yield of (+)-alcohol : 1.81 (95%)

Optical rotation : $[\alpha]_D^{24}$ +37.96 (c 1.57, CH_2Cl_2), 79% ee.

Determination of enantiomeric purity:

^1H NMR analysis in presence of Eu(hfc)$_3$:

^1H NMR spectrum of racemic acetate **101a** and acetate of (-)-**101** in presence of shift reagent [acetate (5 mg), $Eu(hfc)_3$ (30 mg)] indicated that the optical purity of (-)-alcohol is 82%.

Methyl (±)-mandelate (104):

To a stirred solution of mandelic acid (4.56 g, 30 mM) in methanol (30 mL) 2 drops of conc. H_2SO_4 were added and refluxed for 3 h. Methanol was distilled off and the crude ester was taken in ether (25 mL), washed with aqueous K_2CO_3 solution followed by brine. The organic layer was dried over anhydrous Na_2SO_4, evaporated and distilled under reduced pressure.

Yield : 4.44 g (89%)

bp : 86-88^oC/5 mm

IR (neat) ν_{max} : 3350, 1740 cm^{-1}

^1H NMR (200 MHz) : δ 3.48 (d, 1H, J = 6 Hz, D_2O washable), 3.75 (s, 3H), 5.17 (d, 1H, J = 6 Hz), 7.36 (m, 5H).

^{13}C NMR (25 MHz) : δ 52.41, 72.77, 126.48, 128.21, 128.36, 138.30, 173.89.

Methyl (±)-O-acetylmandelate (104a):

This was prepared by acetylation of methyl mandelate with acetic anhydride and pyridine.

Yield : 96%

bp : 74-76°C/1 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ 2.18 (s, 3H), 3.70 (s, 3H), 5.93 (s, 1H), 7.38 (m, 5H)

^{13}C NMR (25 MHz) : δ 20.23, 52.24, 74.29, 127.54, 128.71, 129.12, 133.77, 169.24, 170.13.

Ethyl (±)-mandelate (105):

This was prepared by the esterification of mandelic acid with ethanol in the presence of conc. H_2SO_4 following the same procedure as described for **104**.

Reaction time : 3 h

Yield : 4.70 g (87%)

bp : 98°C/5 mm

IR (neat) ν_{max} : 3420, 1730 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.18 (t, 3H, J = 6 Hz), 3.72 (d, 1H, J = 4 Hz, D_2O washable), 4.18 (m, 2H), 5.14 (d, 1H, J = 6 Hz), 7.33

(m, 5H).

^{13}C NMR (25 MHz) : 18.64, 61.77, 72.77, 126.48, 128.36, 128.77, 138.48, 173.53.

Ethyl (±)-O-acetylmandelate (105a):

This was prepared by acetylation of ethyl mandelate with acetic anhydride and pyridine.

Yield : 95%

bp : 118-20°C/6.5 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.21 (t, 3H, J = 6 Hz), 2.18 (s, 3H), 4.22 (m, 2H), 5.90 (s, 1H), 7.46 (m, 5H).

^{13}C NMR (25 MHz) : δ 13.47, 20.06, 61.18, 74.29, 127.42, 128.48, 128.89, 133.77, 168.54, 169.89.

***iso*-Propyl (±)-mandelate (106):**

This was prepared by the esterification of mandelic acid with *iso*-propanol in the presence of conc. H_2SO_4 following the same procedure as described for **104**.

Reaction time : 4 h

Yield : 5.13 g (88%)

bp : 96-98°C/5 mm

IR (neat) ν_{max} : 1720, 3430 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.09 (d, 3H, J = 6 Hz), 1.26 (d, 3H, J = 6 Hz), 3.72 (d, 1H, J = 4 Hz, D_2O washable), 5.05 (m, 2H), 7.24-7.50 (m, 5H).

^{13}C NMR (25 MHz) : 20.94, 21.23, 69.35, 72.77, 126.30, 127.94, 128.18, 138.59, 172.95.

iso-Propyl (±)-O-acetylmandelate (106a):

This was prepared by acetylation of *iso*-propyl mandelate with acetic anhydride and pyridine.

Yield : 98%

bp : 110-12°C/4.5 mm

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.05 (d, 3H, J = 6 Hz), 1.26 (d, 3H, J = 6 Hz), 2.17 (s, 3H), 5.03 (m, 1H), 5.86 (s, 1H), 7.42 (m, 5H).

^{13}C NMR (25 MHz) : 20.29, 21.06, 21.29, 69.06, 74.59, 127.48, 128.59, 128.95, 133.95, 168.24, 170.06.

O-Acetylmandelic acid:

This was prepared according to the literature procedure.[123] Acetyl chloride (15 mL, 210 mM) was added to mandelic acid (10.5 g, 70 mM) at room temperature with stirring. After the formation of clear solution (15 min), the excess acetyl chloride was distilled off. Traces of acetyl chloride were removed by applying vacuum. Thus

formed acetyl mandelic acid was used for the next reaction without further purification.

Yield : 12.92 g (95%)

α-Acetoxy-α-phenylacetyl chloride:

O-Acetylmandelic acid (12.62 g, 65 mM) was taken in thionyl chloride (30 mL) and refluxed for 4 h. The excess thionyl chloride was distilled off and the product was distilled under reduced pressure.

Yield : 11.19 g (81%)

bp : 116-18°C/6.5 mm [Lit.[123] bp 125-30°C/ 10 mm]

IR (neat) ν_{max} : 1740, 1800 cm^{-1}

***tert*-Butyl (±)-O-acetylmandelate (107a):**

To a stirred solution of pyridine (1.6 mL, 20 mM) in *tert*-butanol (15 mL) α-acetoxy-α-phenylacetyl chloride (4.25 g, 20 mM) was added and stirred over night. The reaction mixture was diluted with ether (15 mL), washed successively with dil. HCl, aqueous K_2CO_3 solution and brine. The organic phase was dried over anhydrous Na_2SO_4, solvent was evaporated and the crude ester was recrystallized from hexane.

Yield : 3.86 g (77%)

mp : 60-61°C

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.40 (s, 9H), 2.18 (s, 3H), 5.79 (s, 1H), 7.38 (m, 5H)

^{13}C NMR (25 MHz) : 20.47, 27.59, 74.88, 82.24, 127.47, 128.59, 128.89, 134.36, 167.83, 170.24.

Cyclohexyl (±)-O-acetylmandelate (108a):

This was prepared by the reaction of α-acetoxy-α-phenylacetyl chloride (4.25 g, 20 mM) and cyclohexanol (2.1 mL, 20 mM) in the presence of pyridine (1.6 mL, 20 mM) in dichloromethane (20 mL) following the same procedure as described for **107a**.

Reaction time : 4 h

Yield : 3.82 g (69%)

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.18-1.92 (m, 10H), 2.18 (s, 3H), 4.75 (br, 1H), 5.88 (s, 1H), 7.36 (m, 5H).

^{13}C NMR (25 MHz) : δ 20.26, 22.88, 23.00, 24.94, 30.65, 30.88, 73.59, 74.53, 127.36, 128.48, 128.89, 134.01, 168.07, 170.06.

Enzymatic hydrolysis of (±)-O-acetylmandelic acid esters:

General procedure for hydrolysis of (±)-O-acetylmandelic acid esters:

Enzymatic hydrolysis of O-acetylmandelic acid esters was carried out in 5 mM scale with phosphate buffer (0.5 M, pH 8.0, 40 mL), ether

(10 mL) and 2 g of PLAP. In all these reactions only the hydrolysis of acetate had taken place and the methyl ester functionality was completely intact. Conversion ratios were determined by HPLC. Optical purities were determined based on optical rotations reported in literature.

Enzymatic hydrolysis of methyl (±)-O-acetylmandelate (104a):

Hydrolysis of racemic diester **104a** (1.04 g, 5 mM) with PLAP (2 g) afforded (+)-methyl mandelate and unhydrolyzed diester in 48:52 ratio.

Reaction time : 5 h

Yield of (+)-alcohol : 0.331 g (83%)

Optical rotation : $[\alpha]_D^{24}$ + 87.00(c 1.05, acetone),75% ee, Conf. (S)

{Lit.[120] $[\alpha]_D^{25}$ -115.4 (c 1, acetone), >99% ee, Conf. (R)}

Yield of recovered diester : 0.520 g (96%)

Hydrolysis of this diester with KOH/MeOH afforded (-)-(R)-mandelic acid.

Yield of (-)-mandelic acid : 0.342 g (90%)

Optical rotation : $[\alpha]_D^{24}$ -108.06(c 0.54, acetone),70% ee, Conf. (R)

{Lit.[155] $[\alpha]_D^{25}$ -154.3 (c 2.1, acetone), Conf. (R)}

Enzymatic hydrolysis of racemic ethyl (±)-O-acetylmandelate (105a):

Hydrolysis of racemic diester **105a** (1.11 g, 5 mM) with PLAP (2 g) furnished (+)-methyl mandelate and unhydrolyzed diester in 41:59

ratio.

Reaction time : 8 h

Yield of (+)-alcohol : 0.240 g (65%)

Optical rotation : $[\alpha]_D^{24}$ +59.28 (c 1.91, $CHCl_3$), 47% ee, Conf. (S)

{Lit.[121] $[\alpha]_D^{25}$ -126.2 (c 2.01, $CHCl_3$), Conf. (R)}

Yield of recovered diester : 0.439 g (67%).

Hydrolysis of this diester with KOH/MeOH afforded (-)-(R)-mandelic acid.

Yield of (-)-mandelic acid : 0.273 g (91%)

Optical rotation : $[\alpha]_D^{24}$ -54.32 (c 0.99, acetone) 35% ee, Conf. (R)

{Lit.[155] $[\alpha]_D^{25}$ -154.3 (c 2.1, acetone), Conf. (R)}

Enzymatic hydrolysis of *iso*-propyl (±)-O-acetylmandelate (106a):

Hydrolysis of diester **106a** (1.18 g, 5 mM) with PLAP (2 g) afforded (+)-*iso*-propyl mandelate and unhydrolyzed diester in 47:53 ratio.

Reaction time : 17 h

Yield of (+)-alcohol : 0.323 g (71%)

Optical rotation : $[\alpha]_D^{24}$ +62.25 (c 1.01, $CHCl_3$), 55% ee, Conf. (S)

{Lit.[122] $[\alpha]_D^{25}$ -98.9 (c 1.00, $CHCl_3$), 88% ee, Conf. (R)}

Yield of recovered diester : 0.600 g (95%).

Hydrolysis of this diester with KOH/MeOH afforded (-)-(R)-mandelic acid.

Yield of (-)-mandelic acid : 0.344 g (89%)

Optical rotation : $[\alpha]_D^{24}$ -76.92 (c 0.6, acetone), 50% ee, Conf. (R)
{Lit.[155] $[\alpha]_D^{25}$ -154.3 (c 2.1, acetone), Conf. (R)}

Enzymatic hydrolysis of *tert*-butyl (±)-O-acetylmandelate (107a):

Hydrolysis of diester **107a** (1.25 g, 5 mM) with PLAP (2 g) afforded (+)-*tert*-butyl mandelate and unhydrolyzed diester in 34:66 ratio.

Reaction time : 17 h

Yield of (+)-alcohol : 0.234 g (66%)

mp : 71-72°C [Lit.[122] mp 73-75°C for 92% optically pure alcohol]

Optical rotation : $[\alpha]_D^{24}$ +103.84 (c 1.10, CCl_4), 80% ee, Conf. (S)
{Lit.[122] $[\alpha]_D^{27}$ -119.1 (c 1.05, CCl_4), 92% ee, Conf. (R)}

IR(KBr) ν_{max} : 3420, 1720 cm^{-1}

^1H NMR (200 MHz) : δ 1.42 (s, 9H), 3.50 (d, 1H, J = 4 Hz, D_2O washable), 5.01 (d, 1H, J = 4 Hz), 7.38 (m, 5H).

^{13}C NMR (25 MHz) : δ 27.76, 73.06, 83.00, 126.48, 128.18, 128.48 139.12, 173.06.

Yield of recovered diester : 0.660 g (80%)

This diester was subjected to KOH/MeOH hydrolysis to furnish (-)-(R)-mandelic acid.

Yield of (-)-mandelic acid : 0.361 g (90%)

Optical rotation : $[\alpha]_D^{24}$ -75.69(c 1.00, acetone), 49% ee, Conf. (R)

{Lit.[155] $[\alpha]_D^{25}$ -154.3(c 2.1, acetone), Conf. (R)}

Enzymatic hydrolysis of cyclohexyl (±)-O-acetylmandelate (108a):

Hydrolysis of diester 108a (1.38 g, 5 mM) with PLAP (2 g) produced (+)-cyclohexyl mandelate and unhydrolyzed diester in 31:69 ratio.

Reaction time : 60 h

Yield of (+)-alcohol : 0.270 g (74%)

Optical rotation : $[\alpha]_D^{24}$ + 16.78 (c 1.13, EtOH), 23% ee, Conf. (S)

{Lit.[124] $[\alpha]_D^{20}$ +71.97 (c 2.04, EtOH) 98.% ee, Conf. (S)}

IR(neat)ν_{max} : 3400, 1720 cm^{-1}

^1H NMR (200 MHz) : δ 1.18-1.94 (m, 10H), 3.50 (d, 1H, J = 4 Hz, D_2O washable), 4.84 (m, 1H), 5.12 (d, 1H, J = 4 Hz) 7.34 (m, 5H).

^{13}C NMR (25 MHz) : δ 23.06, 23.29, 25.12, 30.94, 31.29, 72.94, 74.65, 126.53, 128.30, 128.53, 138.89, 173.36.

Yield of recovered diester : 0.677 g (71%)

The above diester was hydrolyzed with KOH/MeOH to get (-)-(R)-mandelic acid.

Yield of (-)-mandelic acid : 0.328 g (88%)

Optical rotation : $[\alpha]_D^{24}$ -24.00 (c 1.00, acetone) 15% ee, Conf. (R)

{Lit.[155] $[\alpha]_D^{25}$ -154.3 (c 2.1, acetone), Conf. (R)}

Methyl (±)-α-hydroxy-α-arylacetates:

General procedure for preparation of methyl (+)-α-hydroxy-α-aryl-acetates:

α-Hydroxy acids were prepared according to literature procedure.[125]

To a stirred solution of aromatic aldehyde (20 mM) and triethyl-benzylammonium chloride (0.228 g, 1 mM) in chloroform (3.5 mL), 50% NaOH solution (5 mL) was added dropwise at 55°C. The reaction contents were stirred for 1 h at the same temperature and cooled to room temperature. It was acidified with 50% H_2SO_4 (10 mL) and extracted with ether (3 x 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, evaporated. Thus obtained crude α-hydroxy acids were esterified in methanol in presence of conc. H_2SO_4 (cat.) as described for the preparation of **104**. These methyl esters were converted into the corresponding O-acetyl derivatives with acetic anhydride in the presence of pyridine.

Methyl (±)-α-hydroxy-α-(2-methoxyphenyl)acetate (109a):

Yield : 76%

IR (neat) ν_{max} : 3420, 1730 cm^{-1}

^1H NMR (200 MHz) : δ 3.57 (d, 1H, J = 6 Hz, D_2O washable), 3.73 (s, 3H), 3.84 (s, 3H), 5.28 (d, 1H, J = 6 Hz), 6.95 (m, 2H), 7.32 (m, 2H).

^{13}C NMR (25 MHz) : δ 52.53, 55.53, 69.94, 111.24, 120.89, 127.12, 129.36, 129.94, 157.18, 174.34.

Methyl (±)-α-acetoxy-α-(2-methoxyphenyl)acetate (109b):

Yield : 93%

mp : 67-69°C

IR (KBr) ν_{max} : 1735 cm^{-1}

^{1}H NMR (200 MHz) : δ 2.15 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 6.44 (s, 1H), 6.96 (m, 2H), 7.36 (m, 2H).

^{13}C NMR (25 MHz) : δ 20.29, 52.00, 55.47, 68.47, 112.12, 120.59, 122.48, 129.18, 130.59, 157.18, 169.59, 170.13.

Methyl (±)-α-hydroxy-α-(4-methylphenyl)acetate (110a):

Yield : 79%

IR (neat) ν_{max} : 3420, 1735 cm^{-1}

^{1}H NMR (200 MHz) : δ 2.32 (s, 3H), 3.60 (br, 1H, D_2O washable), 3.71 (s, 3H), 5.12 (d, 1H, J = 6 Hz), 7.14 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz).

^{13}C NMR (25 MHz) : δ 20.88, 52.59, 72.71, 126.53, 129.24, 135.47, 138.18, 174.18.

Methyl (±)-α-acetoxy-α-(4-methylphenyl)acetate (110b):

Yield : 96%

mp : 66-68°C

IR (KBr) ν_{max} : 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ 2.18 (s, 3H), 2.35 (s, 3H), 3.71 (s, 3H), 5.90 (s, 1H), 7.18 (d, 2H, J = 8 Hz), 7.35 (d, 2H, J = 8 Hz).

^{13}C NMR (25 MHz) : δ 20.29, 20.88, 52.18, 74.18, 127.59, 129.42, 130.89, 139.12, 169.35, 170.18.

Methyl (±)-α-hydroxy-α-(4-methoxyphenyl)acetate (111a):

Yield : 75%

IR (neat) ν_{max} : 3340, 1718 cm^{-1}

^{1}H NMR (200 MHz) : δ 3.55 (br, 1H, D_2O washable), 3.72 (s, 3H), 3.78 (s, 3H), 5.10 (d, 1H, J = 6 Hz), 6.87 (d, 2H, J = 8 Hz), 7.31 (d, 2H, J = 8 Hz).

^{13}C NMR (25 MHz) : δ 52.53, 55.00, 72.41, 113.88, 127.89, 130.59, 159.65, 174.18.

Methyl (±)-α-acetoxy-α-(4-methoxyphenyl)acetate (111b):

Yield : 95%

IR (neat) ν_{max} : 1725 cm^{-1}

^{1}H NMR (200 MHz) : δ 2.17 (s, 3H), 3.71 (s, 3H), 3.80 (s, 3H), 5.87 (s, 1H), 6.90 (d, 2H, J = 8 Hz), 7.37 (d, 2H, J = 8 Hz)

^{13}C NMR (25 MHz) : δ 20.59, 52.40, 55.21, 74.08, 114.18, 125.85, 129.08, 160.33, 169.49, 170.27.

Methyl (±)-α-hydroxy-α-(1-naphthyl)acetate (112a):

Yield : 83%

IR (neat) ν_{max} : 3425, 1728 cm^{-1}

^1H NMR (200 MHz) : δ 3.52 (d, 1H, J = 4 Hz, D_2O washable), 3.71 (s, 3H), 5.80 (d, 1H, J = 4 Hz), 7.49 (m, 4H), 7.81 (m, 2H), 8.14 (m, 1H).

^{13}C NMR (25 MHz) : δ 52.71, 71.29, 123.71, 125.18, 125.83, 126.53, 128.77, 129.36, 131.00, 134.01, 134.12, 174.53.

Methyl (±)-α-acetoxy-α-(1-naphthyl)acetate (112b):

Yield : 95%

IR (neat) ν_{max} : 1735 cm^{-1}

^1H NMR (200 MHz) : δ 2.20 (s, 3H), 3.69 (s, 3H), 6.72 (s, 1H), 7.58 (m, 4H), 7.81 (d, 2H, J = 6 Hz), 8.18 (d, 1H, J = 6 Hz).

^{13}C NMR (25 MHz) : δ 20.47, 52.47, 72.35, 123.71, 125.18, 126.06, 126.95, 127.47, 128.83, 130.01, 131.06, 133.95, 169.66, 170.30.

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-arylacetates:

General procedure for enzymatic hydrolysis of methyl (±)-α-acetoxy-α-arylacetates:

Hydrolysis of methyl α-acetoxy-α-arylacetates was carried out in 5 mM scale with phosphate buffer (0.5 M, pH 8.0, 40 mL), ether (10 mL) and PLAP (2 g). In all these reactions only hydrolysis of acetate had taken place and the methyl ester functionality was completely intact. Conversion ratios were determined by HPLC. Chiral column,

CHIRALCEL OD was used for the determination of enantiomeric purities.

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(2-methoxyphenyl)-acetate (109b):

Hydrolysis of racemic acetate **109b** (1.19 g, 5 mM) with PLAP (2 g) afforded optically active alcohol **(+)-109a** and recovered ester **(-)-109b** in 43:57 ratio.

Reaction time : 2 h

Yield of (+)-alcohol : 0.354 g (84%)

Optical rotation : $[\alpha]_D^{24}$ +70.15 (c 0.98, EtOH), 55% ee

The alcohol **(+)-109a** was saponified with KOH/MeOH to afford optically active acid (+)-109.

Optical rotation : $[\alpha]_D^{24}$ +89.15 (c 1.0, MeOH), Conf. (S)

{Lit.[126] *levo* rotation in MeOH for (R)-acid at 589 nm}

Yield of recovered ester : 0.545 g (80%)

Optical rotation : $[\alpha]_D^{24}$ -75.24 (c 0.61, EtOH)

Determination of enantiomeric excess:

HPLC analysis of racemic alcohol **109a** showed two peaks in 1:1 ratio (eluent: i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 46.75 and 54.20 min) due to (R) & (S) enantiomers. Similar analysis of optically active alcohol (+)-109a showed two peaks in 7.77:2.23 ratio (retention times: 47.30 and 55.61 min respectively) indicating that its optical purity is 55%.

Similarly racemic acetate **109b** showed two peaks in 1:1 ratio (retention times: 19.92 and 22.78 min) due to (R) & (S) enantiomers under the same conditions. The recovered ester (-)-**109b** showed two peaks in 2.82:7.17 ratio (retention times: 19.13 and 21.72 min respectively) indicating that its optical purity is 43%.

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(4-methylphenyl)acetate (110b):

Hydrolysis of racemic acetate **110b** (1.11 g, 5 mM) with PLAP (2 g) produced optically active alcohol (+)-**110a** and recovered ester (-)-**110b** in 45:55 ratio.

Reaction time : 4 h

Yield of (+)-alcohol : 0.265 g (65%)

Optical rotation : $[\alpha]_D^{24}$ +29.28 (c 0.85, EtOH)

This hydroxy ester was subjected to KOH/MeOH hydrolysis to produce (+)-hydroxy acid.

Yield of (+)-hydroxy acid : 93%

Optical rotation : $[\alpha]_D^{24}$ +41.0 (c 0.3, EtOH), 27% ee, Conf. (S)

{Lit.[128] $[\alpha]_D^{25}$ -153 (c 0.3, EtOH), Conf. (R)}

Yield of recovered ester : 0.431 g (70%)

Optical rotation : $[\alpha]_D^{24}$ -50.75 (c 0.75, EtOH)

This diester was hydrolyzed with KOH/MeOH to furnish (-)-hydroxy acid.

Yield of (-)-hydroxy acid : 90%

optical rotation : $[\alpha]_D^{24}$ -30.82 (c 0.29, EtOH), 20% ee, Conf (R)

Enantiomeric purity of (+)-**110a** was further confirmed by HPLC analysis. HPLC analysis of racemic alcohol **110a** showed two peaks in 1:1 ratio (eluent: i-PrOH/hexane: 5:95; flow rate: 0.5 mL/min; retention times: 24.87 and 32.60 min) due to (R) & (S) enantiomers. Similar analysis of optically active alcohol (+)-**110a** showed two peaks in 6.30:3.69 ratio (retention times: 23.74 and 31.44 min respectively) indicating that its optical purity is 26%.

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(4-methoxyphenyl)-acetate (111b):

Hydrolysis of racemic acetate **111b** (1.19 g, 5 mM) with PLAP (2 g) produced optically active alcohol (+)-**111a** and recovered ester (-)-**111b** in 44:56 ratio.

Reaction time : 3 h

Yield of (+)-alcohol : 0.335 g (78%)

Optical rotation : $[\alpha]_D^{24}$ +80.68 (c 1.02, EtOH), 59% ee, Conf. (S)

{Lit.[127] $[\alpha]_D^{18}$ +136.7 (c 2.4, EtOH), Conf. (S)}

This hydroxy ester was subjected to KOH/MeOH hydrolysis to produce (+)-hydroxy acid.

Yield of (+)-hydroxy acid : 92%

Optical rotation : $[\alpha]_D^{24}$ +82.09 (c 0.27, H_2O), 58% ee, Conf. (S)

{Lit.[128] $[\alpha]_D^{25}$ -141 (c 0.3, H_2O) Conf. (R)}

Yield of recovered ester : 0.580 g (87%)

Optical rotation : $[\alpha]_D^{24}$ -117.14 (c 0.91, EtOH)

This ester was hydrolyzed with KOH/MeOH to produce (-)-hydroxy acid.

Yield of (-)-hydroxy acid : 94%

optical rotation : $[\alpha]_D^{24}$ -62.06 (c 0.29, H_2O), 44% ee, Conf. (R)

Enantiomeric purity of (+)-**111a** was further confirmed by HPLC analysis. HPLC analysis of the racemic alcohol **111a** showed two peaks in 1:1 ratio (eluent: i-PrOH/hexane: 10:90; flow rate: 0.5 mL/min; retention times: 24.95 and 38.81 min) due to (R) & (S) enantiomers. Similarly the optically active alcohol (+)-**111a** showed two peaks in 7.87:2.12 ratio (retention times: 24.94 and 39.28 min respectively) indicating that its optical purity is 57%.

Enzymatic hydrolysis of methyl (±)-α-acetoxy-α-(1-naphthyl)acetate (112b):

Hydrolysis of racemic acetate **112b** (1.29 g, 5 mM) with PLAP (2 g) afforded optically active alcohol (+)-**112a** and recovered acetate (-)-**112b** in 57:43 ratio.

Reaction time : 4 h

Yield of (+)-alcohol : 0.395 g (64%)

mp : 67-69°C

Optical rotation : $[\alpha]_D^{24}$ +56.10 (c 0.75, EtOH), 30% ee

Yield of recovered ester : 0.370 g (67%)

mp : 56-58°C

Optical rotation : $[\alpha]_D^{24}$ -153.26 (c 0.89, EtOH), 53% ee

Determination of enantiomeric excess:

HPLC analysis of the racemic acetate **112b** showed two peaks in 1:1 ratio (eluent: i-PrOH/hexane: 1:99; flow rate: 0.5 mL/min; retention times: 37.03 and 39.31 min) due to (R) & (S) enantiomers. Similar analysis of the acetate from optically active alcohol (+)-**112a** showed two peaks in 6.51:3.49 ratio (retention times: 38.95 and 41.82 min respectively) indicating that its optical purity is 30%.

Similar analysis of the recovered ester (-)-**112b** indicated that it is 53% enantiomerically pure.

1-Phenylcyclohexan-1-ol:

To a solution of phenylmagnesium bromide (100 mM) in dry THF (90 mL) (prepared from bromobenzene and magnesium) cyclohexanone (10.4 mL, 100 mM) was added dropwise at 0°C. After stirring for 2 h at room temperature, the reaction was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous phase was extracted with ether (2 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated and distilled under reduced pressure.

Yield : 10.92 g (62%)

bp : 80-84^{o}C/1 mm

IR (neat) ν_{max} : 3325 cm^{-1}

1-Phenylcyclohex-1-ene:

This was prepared according to known method.[156]

To the above *tert*-alcohol (10.57 g, 60 mM) was added 20% H_2SO_4 in acetic acid (10 mL) and stirred for 10 min. Then it was diluted with water (50 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were washed with aqueous K_2CO_3 solution followed by brine and dried over anhydrous $MgSO_4$. Solvent was evaporated and column chromatograpy (silica gel, hexane) provided pure olefin as a colorless liquid.

Yield : 6.49 g (68%)

IR (neat) ν_{max} : 1600 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.2-1.88 (m, 4H), 1.92-2.48 (m, 4H), 6.08 (m, 1H), 7.08-7.44 (m, 5H)

(±)-*cis*-1-Phenylcyclohexane-1,2-diol (118):

This was prepared according to literature procedure.[135b]

To a stirred solution of formic acid (15 mL, 400 mM), H_2O_2 (60%, 3mL) and potassium acetate (400 mg, 4 mM), 1-phenylcyclohexene (6.33 g, 40 mM) in ether (4 mL) was added dropwise at -63^{o}C. After the addition was complete, the reaction was stirred overnight at room temperature. The reaction mixture was neutralized with NaOH solution

and extracted with ether (3 x 20 mL). The combined organic extracts were washed with 2N NaOH, dried over anhydrous Na_2SO_4 and the solvent was evaporated. Thus obtained crude oil was heated under reflux for 30 min. with a solution of KOH (8 g) in H_2O (10 mL) and methanol (20 mL). Methanol was distillied off and the residue was extracted with ether (3 x 30 mL). The combined ethereal layer was washed with 2N NaOH followed by water and dried over anhydrous Na_2SO_4. Solvent was removed and the crude product was recrystallized from hexane.

Yield : 5.00 g (65%)

mp : 93-94°C [Lit.[135b] 94-96°C]

IR (neat) ν_{max} : 3350 cm^{-1}

^1H NMR (200 MHz) : δ 1.30-1.96 (m, 9H, 1H D_2O washable), 2.61 (s, 1H, D_2O washable), 4.02 (dd, 1H, J = 3 Hz, J = 6 Hz), 7.20-7.56 (m, 5H).

(±)-*cis*-1-Phenyl-2-acetoxycyclohexan-1-ol (118a):

To a stirred solution of diol 118 (4.80 g, 25 mM) pyridine (3.2 mL, 40 mM) and DMAP (30 mg) in dichloromethane (20 mL), acetic anhydride (3.7 mL, 40 mM) was added and stirred for 2 h at room temperature. The reaction mixture was diluted with ether (30 mL) and washed successively with 2N HCl, aqueous K_2CO_3 solution and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was recrystallized from hexane.

Yield : 5.27 g (90%)

mp : 118-19°C

IR (neat) ν_{max} : 3520, 1720 cm^{-1}

^1H NMR (200 MHz) : δ 1.32-2.02 (m, 11H), 2.26 (s, 1H, D_2O washable), 5.30 (m, 1H), 7.20-7.52 (m, 5H)

^{13}C NMR (50 MHz) : δ 20.83, 21.04, 24.18, 27.20, 39.72, 75.28, 76.27, 124.67, 126.93, 128.23, 145.97, 169.75.

(±)-*trans*-2-Acetoxycyclohexan-1-ol (114a):

This was prepared according to literature procedure.[136]

A mixture of cyclohexene (5.0 mL, 50 mM) and sodium perborate (30.7 g, 200 mM) in glacial acetic acid (120 mL) was stirred at 50°C for 30 h. The reaction mixture was cooled to room temperature. Water (20 mL) was added and extracted with chloroform (3 x 50 mL). The combined organic layer was repeatedly washed with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solution was concentrated and distilled under reduced pressure.

Yield : 4.30 g (54%)

bp : 90-94°C/1 mm [Lit.[136] bp 70-80°C/0.5 mm]

IR (neat) ν_{max} : 3420, 1720 cm^{-1}

^1H NMR (100 MHz) : δ 1.04-2.12 (m, 11H), 3.02 (br, 1H, D_2O washable), 3.48 (m, 1H), 4.54 (m, 1H)

^{13}C NMR (25 MHz) : δ 20.70, 23.23, 29.41, 32.47, 71.59, 77.35, 171.07.

(±)-1,2-Diacetoxycyclohexane (114b):

This was prepared from **114a** and acetic anhydride in the presence of pyridine in CH_2Cl_2.

Yield : 96%

bp : 102-4°C/2 mm [Lit.[157] bp 120°C/12 mm]

IR (neat) ν_{max} : 1735 cm^{-1}

^1H NMR (100 MHz) : δ 1.37 (m, 4H), 1.72 (m, 2H), 2.02 (m, 8H), 4.80 (m, 2H)

^{13}C NMR (50 MHz) : δ 21.04, 23.34, 30.04, 73.64, 170.36.

(±)-2,2'-Diacetoxy-1-1'-binaphthyl (51b):

This was prepared by the acetylation of [1,1'-binaphthalene]-2,2'-diol with acetic anhydride in dichloromethane in the presence of pyridine.

Yield : 96%

IR (neat) ν_{max} : 1740, 1445 cm^{-1}

^1H NMR (100 MHz) : δ 1.85 (s, 6H), 7.02-7.52 (m, 8H), 7.89 (t, 4H, J = 8 Hz).

***trans*-1,3-Dioxadecalin (124):**

This was prepared according to literature procedure.[138]

Cyclohexene (10.1 mL, 100 mM) was added to a mixture of

formaldehyde solution (300 mL of 37% in H_2O) and conc. H_2SO_4 (2 mL) and stirred for 15 h at 70°C. The reaction contents were cooled to room temperature and layers were separated. The organic layer was taken in ether (50 mL), washed successively with 10% aqueous $NaHCO_3$, 20% aqueous $NaHSO_3$ solution, H_2O and brine. The ethereal solution was dried over anhydrous Na_2SO_4, concentrated and distilled under reduced pressure.

Yield : 8.54 g (60%)

bp : 80-82°C/15 mm [Lit.[138] bp 90-93°C]

IR (neat) ν_{max} : 1450, 1160 cm^{-1}

^1H NMR (200 MHz) : δ 0.82-2.01 (m, 9H), 3.14-3.42 (m, 2H), 3.92 (dd, 1H, J = 3 Hz, 10 Hz), 4.74 (d, 1H, J = 6 Hz), 5.08 (d 1H, J = 6 Hz)

^{13}C NMR (50 MHz) : δ 24.43, 24.89, 26.04, 31.34, 41.63, 71.44, 81.36, 93.95.

(±)-*trans*-2-Hydroxymethylcyclohexan-1-ol (122):

To a stirred solution of 1,3-dioxadecalin (8.53 g, 60 mM), in methanol (10 mL) few drops of conc. H_2SO_4 were added and refluxed for 17 h. Then methanol was distilled off, the residue was taken in ether (50 mL) and washed with saturated Na_2CO_3 solution followed by brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (40% ethyl acetate in hexane).

Yield : 4.06 g (52%)

bp : 96-100°C/1 mm [Lit.[158] bp 111-14°C/3 mm]

IR (neat) ν_{max} : 3550-3150 (br) cm^{-1}

^1H NMR (100 MHz) : δ 0.81-2.08 (m, 9H), 2.92 (m, 2H, D_2O washable), 3.32-3.76 (m, 3H)

^{13}C NMR (25 MHz) : δ 23.47, 24.11, 26.29, 34.17, 45.00, 67.29, 75.06.

(±)-1-Acetoxy-2-acetoxymethylcyclohexane (122b):

This was prepared from the racemic diol **122** (1 equiv.) and acetic anhydride (3 equiv.) in presence of pyridine (3 equiv.) in CH_2Cl_2.

Yield : 94%

bp : 114-16°C/2 mm

IR (neat) ν_{max} : 1735 cm^{-1}

^1H NMR (200 MHz) : δ 1.15-1.42 (m, 4H), 1.68-1.92 (m, 5H), 2.04 (s, 6H), 4.01 (d, 2H, J = 6 Hz), 4.62 (m, 1H)

^{13}C NMR (25 MHz) : δ 20.35, 20.70, 24.06, 24.59, 28.00, 31.41, 41.47, 64.88, 72.88, 170.06, 170.60.

(±)-1-Phenylethane-1,2-diol (123):

To a stirred solution of styrene oxide (5.7 mL, 50 mM) in acetone (40 mL), conc. H_2SO_4 (2-3 drops) in water (40 mL) was added and stirred over night. Acetone was distilled off and the residue was diluted with ether (40 mL), washed with saturated K_2CO_3 solution followed by brine. The ethereal layer was dried over anhydrous $MgSO_4$.

Removal of the solvent and recrystallization from hexane/ethyl acetate (4:1) produced crystalline solid.

Yield : 5.61 g (81%)

mp : 65-67°C [Lit.[139] mp 63-64°C]

IR (neat) ν_{max} : 3400-3080 (br) cm^{-1}

^1H NMR (200 MHz) : δ 2.63 (br, 2H, D_2O washable), 3.67 (m, 2H), 4.79 (m, 1H), 7.36 (m, 5H)

^{13}C NMR (50 MHz) : δ 67.98, 74.75, 126.15, 127.87, 128.48, 140.56.

(±)-1-Phenyl-1,2-diacetoxyethane (123b):

This was prepared from the racemic diol **123** (1 equiv.) and acetic anhydride (3 equiv.) in presence of pyridine (3 equiv.) in CH_2Cl_2.

Yield : 94%

bp : 90-92°C/2 m

IR (neat) ν_{max} : 1740 cm^{-1}

^1H NMR (200 MHz) : δ 1.95 (s, 3H), 2.01 (s, 3H), 4.22 (m, 2H), 5.84 (m, 1H), 7.25 (m, 5H)

^{13}C NMR (50 MHz) : δ 20.45, 20.77, 65.87, 73.13, 126.52, 128.44, 136.43, 169.75, 170.31.

(±)-1,2-Diphenylethane-1,2-diol (115):

This was prepared according to known procedure.[159]

To a solution of benzoin (7.43 g, 35mM) in THF (15 mL) and water

(15 mL) $NaBH_4$ (1.00 g, 26 mM) was added in portions. The reaction mixture was stirred under reflux for 2 h and cooled to room temperature. The excess $NaBH_4$ was destroyed by adding dil. HCl and THF was distilled off. The white solid, thus formed, was filtered and washed with water. This was air dried and recrystallized from benzene.

Yield : 6.15 (82%)

mp : 132-33°C

A mixture of the above hydrobenzoin (6 g) and KOH (50 g) was powdered and moistened with methanol (13 mL). This was heated to 110°C and the pressure was reduced gradually to 20 mm. After complete evaporation of methanol from the reaction mixture, oil bath temperature was increased to 180-190°C. When the effervescence ceased (15-20 min) the reaction mixture was cooled to room temperature under vacuum. Vacuum was released and water was added and the reaction mixture was extracted with ether. The ethereal layer was washed with dil. HCl, dried over anhydrous Na_2SO_4 and concentrated. Recrystallization from methanol water (1:2) afforded (±)-1,2-diphenylethane-1,2-diol as white crystalline solid.

Yield : 4.80 g (80)%

mp : 119-20°C [Lit.[159] mp 121°C]

IR (neat) ν_{max} : 3425 cm^{-1}

^{1}H NMR (100 MHz) : δ 2.96 (s, 2H, D_2O washable), 4.62 (s, 2H), 6.98-7.36 (m, 10H).

^{13}C NMR (25 MHz) : δ 79.18, 127.12, 128.06, 128.30, 140.06.

(±)-*trans*-1,2-Diacetoxy-1,2-diphenylethane (115a):

This was prepared from the racemic diol **115** (1 equiv.) and acetic anhydride (3 equiv.) in presence of pyridine (3 equiv.) in CH_2Cl_2.

Yield : 96%

IR (neat) ν_{max} : 1740 cm^{-1}

^{1}H NMR (100 MHz) : δ 2.04 (s, 6H), 7.02 (s, 2H), 6.84-7.24 (m, 10H).

^{13}C NMR (25 MHz) : δ 20.88, 77.18, 127.65, 128.30 128.47, 136.36, 169.83.

Enzymatic hydrolysis of (±)-*cis*-1-phenyl-2-acetoxycyclohexan-1-ol (118a):

Hydrolysis of racemic acetate **118a** (4.685 g, 20 mM) with PLAP (3 g) furnished optically active alcohol (+)-**118** and recovered acetate in 10 days.

Yield of (+)-alcohol : 1.265 g (33%)

mp : 121-22°C [Lit.[134] mp 121-121.5°C for >95% ee]

Optical rotation : $[\alpha]_D^{24}$ +18.99 (c 0.76, C_6H_6), 97% ee, Conf. (R,R)

{Lit.[134] $[\alpha]_D^{22}$ +19.2 (c 0.33, C_6H_6), 98% ee, Conf. (R,R)}

Yield of recovered ester : 2.923 g (61%)

mp : 112-13°C

This ester was hydrolyzed with KOH/MeOH to furnish optically active diol (-)-**118**.

Yiled of (-)-alcohol : 96%

mp : 113-114°C [Lit.[146] mp 121.5-122°C]

Optical rotation : $[\alpha]_D^{24}$ -13.01 (c 0.84, C_6H_6), 67% ee, Conf. (S,S)

{Lit.[146] $[\alpha]_D^{25}$ -19.4 (c 1.23, C_6H_6), Conf. (S,S)}

Enzymatic hydrolysis of (±)-1,2-diacetoxycyclohexane (114b):

Hydrolysis of racemic diacetate **114b** (4.00 g, 20 mM) with PLAP (3 g) furnished optically active diol (-)-**114**, monoacetate **114a** and unhydrolyzed diacetate **114b** in 84 h.

Yield of (+)-diol : 0.120 g (5%)

mp : 109-110°C [Lit.[137] mp 113-114°C]

Optical rotation : $[\alpha]_D^{24}$ -28.35 (c 0.67, $CHCl_3$) 70% ee, Conf. (R,R)

{Lit.[137] $[\alpha]_D^{20}$ -40 (c 0.32, $CHCl_3$), Conf. (R,R)}

IR (KBr) ν_{max} : 3275 cm^{-1}

^1H NMR (200 MHz) : δ 1.26 (m, 4H), 1.70 (m, 2H), 1.96 (m, 2H), 2.30 (s, 2H, D_2O washable), 3.35 (m, 2H).

^{13}C NMR (25 MHz) : δ 24.35, 32.88, 75.71.

Yield of monoacetate : 1.044 g (33%)

This monoacetate was hydrolyzed with KOH/MeOH to furnish (-)-diol.

Yield of (-)-diol : 94%

mp : 109-110°C

Optical rotation : $[\alpha]_D^{24}$ -27.12 (c 0.59, $CHCl_3$) 68% ee, Conf. (R,R)

Yield of recovered diester : 1.689 g (42%)

This diacetate was hydrolyzed with KOH/MeOH to furnish (+)-diol.

Yield of (+)-diol : 95%

mp : 107-108°C

Optical rotation : $[\alpha]_D^{24}$ +21.05 (c 0.57, $CHCl_3$) 52% ee, Conf. (S,S)

Attempted hydrolysis of (±)-2,2'-diacetoxy-1,1'-binaphthyl (51b):

Hydrolysis of diacetate **51b** (7.406 g, 20 mM) with PLAP (3 g) was carried out for 10 days and no hydrolysis was observed.

Hydrolysis of (±)-1-acetoxy-2-acetoxymethylcyclohexane (122b):

Hydrolysis of racemic diacetate **122b** (4.283 g, 20 mM) with PLAP was (3 g) carried out for 24 h to furnish optically active diol **(-)-122**, monoacetate and unhydrolyzed diester.

Yield of (-)-diol : 0.521 g (20%)

Optical rotation : $[\alpha]_D^{24}$ -9.29 (c 0.85, CH_2Cl_2), 46% ee

Yield of monoacetate : 0.931 g (27)%

This monoacetate was hydrolyzed with KOH/MeOH to produce the optically active diol **(-)-122**.

Yiled of diol : 95%

Optical rotation : $[\alpha]_D^{24}$ -4.84 (c 1.16, CH_2Cl_2), 24% ee

Yield of unhydrolyzed diester : 1.510 g (35%)

The above diester was hydrolyzed with KOH/MeOH to produce optically active diol (+)-**122**.

Yield of (+)-diol : 93%

Optical rotation : $[\alpha]_D^{24}$ +3.43 (c 1.98, CH_2Cl_2), 17% ee

Determination of optical purity:

Preparation of dibenzoate:

A mixture of racemic diol **122** (0.130 g, 1 mM), pyridine (0.25 mL, 3 mM) and benzoyl chloride (0.35 mL, 3 mM) in 5 mL of dichloromethane was stirred for 2 h. Usual work up followed by column chramatography (silica gel, 5% ethyl acetate in hexane) produced pure dibenzoate.

Yield : 0.303 g (88%)

IR (neat)ν_{max} : 1700 cm^{-1}

^1H NMR (100 MHz) : δ 1.05-2.36 (m, 9H), 4.12-4.92 (m, 2H), 4.80-5.16 (m, 1H), 7.16-8.12 (m, 10H).

Chiral column, CHIRALCEL OD was used for the analysis. The racemic dibenzoate showed two peaks in 1:1 ratio (eluent:i-PrOH/hexane 2:98; flow rate: 0.5 mL/min; retention times: 17.43 and 21.94 min). The dibenzoate prepared from optically active diol (-)-**122** showed two peaks in 7.32 : 2.67 ratio (retention times: 17.93 & 22.45 min) under similar conditions indicating that its optical purity is 46%.

Enzymatic hydrolysis of (±)-1,2-diacetoxy-1-phenylethane (123b):

Hydrolysis of racemic diacetate **123b** (4.443 g, 20 mM) with PLAP (3 g) was carried out for 12 h to produce optically active diol, monoacetate and unhydrolyzed diacetate.

Yield of (+)-diol : 0.553 g (20%)

mp : 66-68°C

Optical rotation : $[\alpha]_D^{24}$ +6.57 (c 2.58, H_2O) 16% ee, Conf. (S)

{Lit.[140] $[\alpha]_D^{20}$ +40.6 (c 3.23, H_2O) Conf. (S)}

Yield of monoacetate : 0.900 g (25%)

Yield of recovered diacetate : 1.555 g (35%)

Attempted hydrolysis of (±)-1,2-diacetoxy-1,2-diphenylethane (115a):

Hydrolysis of diacetate 115a (5.965 g, 20 mM) with PLAP (3 g) was carried out for 12 days. But no hydrolysis was observed.

(±)-2-Methylcyclohexanone (125):

To a suspension of PCC (6.47 g, 30 mM) in 40 mL of anhydrous CH_2Cl_2, was added 2-methylcyclohexanol (2.28 g, 20 mM) in CH_2Cl_2 (5 mL). After 2 h stirring at room temperature, dry ether (20 mL) was added and the supernatant was decanted from the black gum. The residue was washed thoroughly with ether (3 x 10 mL) and the combined organic solution was passed through a short pad of florisil. The solvent was evaporated and the residue was distilled.

Yield : 1.90 g (85%)

bp : 160-62°C

IR (neat)ν_{max} : 1710 cm^{-1}

^1H NMR (100 MHz) : δ 1.00 (d, 3H, J = 7 Hz) 1.16-2.56 (m, 9H)

^{13}C NMR (25 MHz) : δ 14.29, 24.82, 27.59, 35.82, 41.41, 44.95, 213.25.

1-Acetoxy-2-methylcyclohexene (125a):

This was prepared according to literature procedure.[143]

To a stirred solution of methyl cyclohexanone (1.12 g, 10 mM), acetic anhydride (1.9 mL, 20 mM) in CCl_4 (10 mL), 60% $HClO_4$ aqueous solution (2-3 drops) was added at 0°C and stirred overnight at room temperature. The solution was diluted with ether (100 mL), washed thoroughly with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography furnished pure enol ester **125a**.

Yield : 1.25 g (81%)

IR (neat)ν_{max} : 1740, 1700 cm^{-1}

^1H NMR (100 MHz) : δ 1.40-1.72 (m, 7H), 1.84-2.12 (m, 7H)

^{13}C NMR (25 MHz) : δ 15.76, 20.53, 22.29, 22.94, 26.94, 29.88, 120.12, 141.89, 169.06.

(1-Pyrrolidino)-1-cyclohexene:

This was prepared following literature procedure.[160]

A mixture of cyclohexanone (9.3 mL, 90 mM) and pyrrolidine (10.5 mL, 126 mM) in benzene (35 mL) was refluxed for 8 h with azeotropic removal of water. The solvent and excess amine were distilled off. The residue was dried under vacuum and used as such for further reactions.

Yield : 12.53 g (92%)

(±)-2-Ethylcyclohexanone (126):

To a solution of 1-pyrrolidino-1-cyclohexene (3.0 g, 20 mM) in acetonitrile (25 mL) ethyl bromide was added dropwise (2.3 mL, 30 mM). After completion of the addition the solution was refluxed for 20 h under nitrogen. Acetonitrile was distilled off and the residue was diluted with water (15 mL) and heated for 10 min at 100°C. The solution thus obtained was cooled and extracted with ether. The ether extract was dried over anhydrous Na_2SO_4 and concentrated. The crude material was used as such for the next step.

IR (neat)ν_{max} : 1710 cm^{-1}

1-Acetoxy-2-ethylcyclohexene (126a):

This was prepared from the ketone **126** and acetic anhydride following the same procedure as described for **125a**.

Yield : 83%

IR (neat)ν_{max} : 1735, 1690 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.92 (t, 3H, J = 7 Hz), 1.08-2.52 (m, 13H)

^{13}C NMR (25 MHz) : δ 11.88, 20.70, 22.53, 23.11, 23.23, 26.94, 27.23, 125.71, 141.65, 169.70

(±)-2-Propylcyclohexanone (127):

This was prepared by the alkylation of 1-pyrrolidino-1-cyclohexene with propyl iodide following the same procedure as described for **126**.

Reaction time : 18 h

Yield : 56%

IR (neat)ν_{max} : 1710 cm^{-1}

^{1}H NMR (200 MHz) : δ 0.87 (t, 3H, J = 7H), 1.14-2.48 (m, 13H)

^{13}C NMR (25 MHz) : δ 14.00, 20.12, 24.64, 27.88, 31.41, 33.70, 41.76, 50.29, 213.54.

1-Acetoxy-2-propylcyclohexene (127a):

This was prepared from the ketone **127** and acetic anhydride following the same procedure as described for **125a**.

Yield : 91%

IR (neat)ν_{max} : 1735, 1680 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.92 (t, 3H, J = 6 Hz), 1.02-2.20 (m, 15H)

^{13}C NMR (25 MHz) : δ 13.94, 20.47, 20.76, 22.53, 23.12, 27.17, 27.82, 32.29, 124.30, 142.42, 169.30.

(±)-2-Allylcyclohexanone (128):

This was prepared by the alkylation of 1-pyrrolidino-1-cyclohexene with allyl bromide following the same procedure as described for **126**.

Reaction time : 13 h

Yield : 71%

bp : 90-96/16 mm (Lit.[160] bp 100-5/18-20 mm)

IR (neat)ν_{max} : 1695, 1640 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.32-2.64 (m, 11H), 4.92-5.12 (m, 2H), 5.75 (m, 1H)

^{13}C NMR (25 MHz) : δ 24.70, 27.64, 33.12, 33.53, 41.70, 50.00, 115.89, 136.42, 211.78.

1-Acetoxy-2-allylcyclohexene (128a):

This was prepared from the ketone **128** and acetic anhydride following the same procedure as described for **125a**.

Yield : 77%

IR (neat)ν_{max} : 1740, 1700 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.32-2.28 (m, 11H), 2.68 (d, 2H, J = 7 Hz), 4.84-5.12 (m, 2H), 5.44-5.88 (m, 1H).

(±)-2-Benzylcyclohexanone (129):

This was prepared by the alkylation of 1-pyrrolidino-1-cyclohexene with benzyl bromide following the same procedure as described for **126**.

Yield : 51%

IR (neat)ν_{max} : 1710, 1600 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.2-2.72 (m, 9H), 3.2 (d, 2H, J = 8 Hz), 7.20 (m, 5H).

^{13}C NMR (25 MHz) : δ 24.70, 27.70, 33.06, 35.18, 41.76, 52.06, 125.71, 128.06, 128.95, 140.18, 211.95.

1-Acetoxy-2-benzylcyclohexene (129a):

This was prepared from the ketone **129** and acetic anhydride following the same procedure as described for **125a**.

Yield : 86%

IR (neat)ν_{max} : 1750, 1700 cm^{-1}

^{1}H NMR (100 MHz) : δ 1.44-2.32 (m, 11H), 3.28 (s, 2H), 7.2 (m, 5H).

^{13}C NMR (25 MHz) : δ 20.76, 22.29, 22.94, 27.12, 27.47, 36.18, 123.30, 126.06, 128.42, 128.83, 139.59, 143.18, 169.42.

1-(n-Undecyl)cyclopentan-1-ol:

This was prepared from cyclopentanone and n-undecylmagnesium bromide following the same procedure as described for 1-phenylcyclohexan-1-ol.

Yield : 52%

IR (neat)ν_{max} : 3400 cm^{-1}

^1H NMR (100 MHz) : δ 0.84 (distorted t, 3H), 1.24-1.60 (m, 29H, 1H D_2O washable).

1-(n-Undecyl)cyclopent-1-ene:

A suspension of 1-(n-undecyl)cyclopentan-1-ol (4.8 g, 20 mM) and phosphoric acid (5 mL) was heated for 1 h at 120°C. The reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with hexane (3 x 10 mL). The combined organic extracts were washed successively with 5% NaOH solution and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated and passed through column (silica gel, hexane) to afford pure olefin as a colorless liquid.

Yield : 80%

IR (neat)ν_{max} : 1645 cm^{-1} (weak)

^1H NMR (100 MHz) : δ 0.88 (distorted t, 3H), 1.00-2.00 (m, 27H), 5.78 (br, 1H).

^{13}C NMR (25 MHz) : δ 13.35, 22.06, 23.82, 27.23, 28.76, 29.06, 30.59, 31.35, 31.41, 34.41, 122.41, 144.48.

(±)-*trans*-2-(n-undecyl)cyclopentan-1-ol:

Hydroboration/oxidation procedure developed by Periasamy[161] was used.

To a suspension of sodium borohydride (0.27 g, 7 mM) in THF (25 mL) under nitrogen atmosphere, was added 1-(n-undecyl)cyclopent-1-ene (3.33 g, 15 mM). Then a solution of iodine (0.9 g, 3.5 mM) in THF (15 mL) was added dropwise at $0^{o}C$. After 3 h stirring at the same temperature, the reaction was quenched with water (1 mL) and added 2.5 N NaOH solution (15 mL). Then 30% aqueous H_2O_2 solution (14 mL) was added dropwise with constant stirring at $0^{o}C$ and the stirring was continued for 4 h at room temperature. The contents were extracted with ether (3 x 30 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, concentrated and column chromatographed on silica gel (5% ethyl acetate in hexane) to afford pure alcohol as a colorless liquid.

Yield : 2.9 g (80%)

IR (neat)ν_{max} : 3350 cm^{-1}

^{1}H NMR (100 MHz) : δ 0.89 (distorted t, 3H), 1.12-2.11 (m, 28H), 3.66-3.93 (m, 1H).

^{13}C NMR (25 MHz) : δ 14.00, 21.88, 22.70, 28.35, 29.41, 29.76, 30.00, 32.00, 34.00, 34.47, 48.23, 79.06.

(±)-2-(n-Undecyl)cyclopentanone (131):

This was prepared by the oxidation of racemic *trans*-2-(n-undecyl)cyclohexan-1-ol with PCC following the same procedure as described for **125**.

Yield : 78%

IR (neat)ν_{max} : 1710 cm^{-1}

^1H NMR (100 MHz) : δ 0.88 (distorted t, 3H), 1.08-2.48 (m, 27H)

^{13}C NMR (25 MHz) : δ 14.00, 20.70, 22.64, 27.53, 29.29, 29.47, 29.59, 29.76, 31.88, 38.06, 49.06, 221.25.

1-Acetoxy-2-(n-undecyl)cyclopentene (131a):

This was prepared from the ketone **131** and acetic anhydride following the same procedure as described for **125a**.

Yield : 80%

IR (neat)ν_{max} : 1735, 1690 cm^{-1}

^1H NMR (100 MHz) : δ 0.88 (distorted t, 3H), 1.98-2.74 (m, 29H).

(±)-2-Phenylcyclohexanone (132):

This was prepared by the oxidation of racemic *trans*-2-phenyl-cyclohexan-1-ol with PCC following the same procedure as described for **125**.

Yield : 89%

mp : 61-62°C [Lit.[162] mp 62°C]

IR (neat)ν_{max} : 1700 cm^{-1}

^1H NMR (100 MHz) : δ 1.42-2.61 (m, 8H), 3.40-3.72 (m, 1H), 6.92-7.56 (m, 5H).

^{13}C NMR (25 MHz) : δ 25.17, 27.65, 35.00, 42.06, 57.24, 126.88, 128.36, 128.53, 138.83, 210.42.

1-Acetoxy-2-phenylcyclohexene (132a):

This was prepared from the ketone **132** and acetic anhydride following the same procedure as described for **125a**.

Yield : 92%

IR (neat)ν_{max} : 1740, 1680 cm^{-1}

^1H NMR (100 MHz) : δ 1.53-2.62 (m, 11H), 7.04-7.48 (m, 5H).

^{13}C NMR (25 MHz) : δ 20.64, 22.70, 22.88, 27.53, 30.12, 125.53, 126.95, 127.65, 128.18, 139.59, 143.59, 169.42.

1-Phenylcycloheptan-1-ol:

This was prepared from cycloheptanone and phenylmagnesium bromide following the same procedure as described for 1-phenylcyclohexan-1-ol.

Yield : 69%

IR (neat)ν_{max} : 3375 cm^{-1}

^1H NMR (200 MHz) : δ 1.52-2.18 (m, 13H, 1H D_2O washable), 7.2-7.4 (m, 3H), 7.46-7.58 (m, 2H)

^{13}C NMR (50 MHz) : δ 22.63, 29.15, 43.22, 76.88, 124.54, 126.51, 128.17, 150.81.

1-Phenylcycloheptene:

This was prepared from 1-phenylcycloheptan-1-ol following the same procedure as described for 1-phenylcyclohexene.

Yield : 72%

IR (neat)ν_{max} : 1605 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.50-1.72 (m, 4H), 1.84 (m, 2H), 2.32 (m, 2H), 2.62 (m, 2H), 6.08 (t, 1H, J = 6 Hz), 7.18-7.34 (m, 5H).

^{13}C NMR (50 MHz) : δ 26.87, 26.99, 28.93, 32.82, 125.68, 126.25, 128.11, 130.32, 145.02.

(±)-*trans*-2-phenylcycloheptan-1-ol:

This was prepared by hydroboration followed by oxidation of 1-phenylcycloheptene following the same procedure as described for *trans*-2-(n-undecyl)cyclopentan-1-ol.

Yield : 82%

IR (neat)ν_{max} : 3350 cm^{-1}

^{1}H NMR (200 MHz) : δ 1.48-2.22 (m, 11H, 1H D_2O washable), 2.58 (m, 1H), 3.82 (m, 1H), 7.32 (m, 5H).

^{13}C NMR (25 MHz) : δ 21.59, 26.53, 27.17, 31.82, 35.12, 55.06, 77.12, 126.24, 127.47, 128.48, 145.95.

(±)-2-Phenylcycloheptanone (133):

This was prepared by the oxidation of *trans*-2-phenylcycloheptan-1-ol with PCC following the same procedure as described for **125**.

Yield : 77%

IR (neat)ν_{max} : 1680 cm^{-1}

^1H NMR (100MHz) : δ 1.24-2.20 (m, 8H), 2.62 (m, 2H), 3.72 (m, 1H), 7.24 (s, 5H).

^{13}C NMR (25 MHz) : δ 25.17, 28.41, 29.82, 31.88, 42.59, 58.65, 126.89, 127.89, 128.53, 140.42, 213.54.

1-Acetoxy-2-phenylcycloheptene (133a):

This was prepared from the ketone **133** and acetic anhydride following the same procedure as described for **125a**.

Yield : 93%

IR (neat)ν_{max} : 1735 cm^{-1}

^1H NMR (100 MHz) : δ 1.52-1.88 (m, 9H), 2.42 (m, 4H), 7.16 (m, 5H).

^{13}C NMR (25 MHz) : δ 20.35, 24.70, 26.41, 31.35, 33.29, 33.59, 126.24, 127.12, 127.77, 129.94, 141.24, 147.89, 169.53.

General procedure for enzymatic hydrolysis of cycloalkanone enol acetates:

To 0.2 M, pH 6.5 phosphate buffer (40 mL) enol ester (5 mM) in ether (10 mL) and PLAP (2.5 g) were added with strring at room temperature. After completion of the reaction (TLC) ether (20 mL) was

added and enzyme was removed by filtration. The layers were separated and aqueous layer was extracted with ether. The combined ether extracts were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (silica gel, 0-5% EtOAc in hexane).

Spectral data (IR, ^1H & ^{13}C NMR) of all chiral ketones were in full agreement with those of racemates.

Enzymatic hydrolysis of 1-acetoxy-2-methylcyclohexene (125a):

Hydrolysis of enol acetate 125a (0.771 g, 5 mM) was carried out with PLAP (2.5 g).

Reaction time : 24 h

Yield : 0.387 (69%)

Optical rotation : $[\alpha]_D^{24}$ -2.88 (c 1.04, MeOH), 20% ee, Conf. (R)

{Lit.[145] $[\alpha]_D^{24}$ +12.2 (c 4, MeOH), 87% ee, Conf. (S)}

Enzymatic hydrolysis of 1-acetoxy-2-ethylcyclohexene (126a):

Hydrolysis of enol acetate 126a (0.841 g, 5 mM) was carried out with PLAP (2.5 g).

Reaction time : 16 h

Yield : 0.511 g (81%)

Optical rotation : $[\alpha]_D^{24}$ -2.57 (c 3.00, MeOH), 10% ee, Conf. (R)

{Lit.[145] $[\alpha]_D^{24}$ +24.1 (c 4, MeOH), 94% ee, Conf. (S)}

Enzymatic hydrolysis of 1-acetoxy-2-propylcyclohexene (127a):

Hydrolysis of enol acetate **127a** (0.911 g, 5 mM) was carried out with PLAP (2.5 g).

Reaction time : 24 h

Yield : 0.526 g (75%)

Optical rotation : $[\alpha]_D^{24}$ -11.76 (c 2.12, MeOH), 40% ee, Conf. (R)

{Lit.[145] $[\alpha]_D^{24}$ +27.9 (c 4, MeOH), 99% ee, Conf. (S)}

Enzymatic hydrolysis of 1-acetoxy-2-allylcyclohexene (128a):

Hydrolysis of enol acetate **128a** (1.142 g, 5 mM) was carried out with PLAP (2.5 g).

Reaction time : 12 h

Yield : 0.608 g (88%)

Optical rotation : $[\alpha]_D^{24}$ -1.76 (c 1.90, MeOH), 11% ee, Conf. (S)

{Lit.[145] $[\alpha]_D^{24}$ +15.8 (c 3, MeOH), 99% ee, Conf. (R)}

Enzymatic hydrolysis of 1-acetoxy-2-benzylcyclohexene (129a):

Hydrolysis of enol acetate **129a** (0.901 g, 5 mM) was carried out with PLAP (2.5 g).

Reaction time : 6 h

Yield : 0.668 g (71%)

Optical rotation : $[\alpha]_D^{24}$ -5.67 (c 1.29, MeOH), 12% ee, Conf. (S)

{Lit.[145] $[\alpha]_D^{24}$ +41.4 (c 5, MeOH), 88% ee, Conf. (R)}

Attempted enzymatic hydrolysis of 1-acetoxy-2-undecylcyclopentene (131a):

Hydrolysis of enol acetate **131a** (1.192 g, 5 mM) was carried out with PLAP (2.5 g) for 6 days. No hydrolysis had taken place.

Enzymatic hydrolysis of 1-acetoxy-2-phenylcyclohexene (132a) in different solvents:

1-Acetoxy-2-phenylcyclohexene (**132a**, 0.5 g, 2.3 mM) was subjected to hydrolysis with PLAP (1 g) in organic solvent (10 mL) and phosphate buffer (0.2 M, pH 6.5, 20 mL).

Buffer/Hexane:

Reaction time : 48 h

Yield : 65%

Optical rotation : $[\alpha]_D^{24}$ -17.85 (c 0.62, C_6H_6), 15% ee, Conf. (S)

{Lit.[146] $[\alpha]_D^{24}$ -113.5 (c 0.60, C_6H_6), Conf. (S)}

Buffer/Acetone:

Reaction time : 60 h

Yield : 63%

The ketone was obtained in racemic form.

Buffer/Benzene:

Reaction time : 96 h

Yield : 59%

The ketone was obtained in racemic form.

Buffer/Ether:

Reaction time : 5 h

Yield : 74%

Optical rotation : $[\alpha]_D^{24}$ -39.06 (c 0.64, C_6H_6), 34% ee, Conf. (S)

The quantity of PLAP was increased from 1 g to 2.5 g and reaction was carried out in ether/buffer system.

Reaction time : 4 h

Yield : 70%

Optical rotation : $[\alpha]_D^{24}$ -41.95 (c 0.98, C_6H_6), 37% ee, Conf. (S)

Enzymatic hydrolysis of 1-acetoxy-2-phenylcycloheptene (133a):

Hydrolysis of enol acetate **133a** (1.15 g, 5 mM) was carried out with PLAP (2.5 g).

Reaction time : 15 h

Yield : 0.670 g (72%)

Optical rotation : $[\alpha]_D^{24}$ -48.92 (c 1.66, $CHCl_3$), 31% ee,

{Lit.[147] $[\alpha]_D^{24}$ +158 (c 0.9, $CHCl_3$)}

Epoxycinnamyl alcohol (134):

Cinnamyl alcohol was epoxidized according to literature procedure.[150]

To a stirred solution of *trans*-cinnamyl alcohol (2.6 mL, 20 mM) in CH_2Cl_2 (15 mL), mCPBA (85%, 30 mM) was added in portions at 0^oC

over a period of 1 h and stirred at room temperature for 24 h. The solid was separated, then filtered. The filtrate was washed with aqueous $NaHSO_3$ solution, aqueous Na_2CO_3 solution and then thoroughly with water. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (silica gel, 20% EtOAc in hexane).

Yield : 1.62 g (54%)

IR (neat)ν_{max} : 3250 cm^{-1}

^1H NMR (100 MHz) : δ 2.08 (br, s, 1H, D_2O washable), 3.22 (m, 2H), 3.72-4.18 (m, 2H), 7.24-7.48 (m, 5H).

^{13}C NMR (25 MHz) : δ 55.71, 61.41, 62.53, 125.83, 128.30, 128.48, 136.77.

Epoxycinnamyl acetate (134a):

Yield : 95%

IR (neat)ν_{max} : 1740 cm^{-1}

^1H NMR (100 MHz) : δ 2.12 (s, 3H), 3.22 (m, 1H), 3.81 (d, 1H, J = 3 Hz), 4.02 and 4.52 (dd, 1H, J = 6 Hz, 4 Hz), 4.12 and 4.22 (dd, 1H, J = 6 Hz, 4 Hz).

^{13}C NMR (25 MHz) : δ 20.53, 56.41, 59.12, 64.12, 125.77, 128.59, 136.42, 170.65.

Enzymatic hydrolysis of 2,3-epoxycinnamyl acetate (134a):

Hydrolysis of acetate **134a** (0.96 g, 5 mM) with PLAP (1.5 g) in

ether (10 mL) and phosphate buffer (0.5 M, pH 8.0, 40 mL) afforded optically active alcohol (+)-**134** and unhydrolyzed acetate in 10:90 ratio.

Reaction time : 4.5 h

Yield of (+)-alcohol : 0.060 g (75%)

Optical rotation : $[\alpha]_D^{24}$ +9.23 (c 0.65, EtOH), 20% ee, Conf. (2R,3R)

{Lit.[150] $[\alpha]_D^{20}$ +45.9 (c 1.50, EtOH), Conf. (2R,3R)}

Yield of recovered acetate : 0.520 g (63%)

Ethyl (4-*tert*-butylcyclohexylidene)acetate (136):

To a stirred suspension of mineral oil free NaH (0.77 g, 30 mM) in DMF (15 mL), triethyl phosphonoacetate (4.4 mL, 22 mM) was slowly added under nitrogen atmosphere. After the evalution of H_2 ceased (half an hour), was added 4-*tert*-butylcyclohexanone (3.085 g, 20 mM) in DMF (10 mL) dropwise at 0^oC and stirring was continued for 3 h at room temperature. The reaction mixture was diluted with ether, successively washed with water and brine. The organic solution was dried over anhydrous Na_2SO_4 and concentrated. The crude ester thus obtained was used as such for the next step.

Yield : 3.23 g (72%)

(4-*tert*-Butylcyclohexylidene)ethanol (135):

To a solution of ester **136** (2.243 g, 10 mM) in ether (8 mL) LAH:EtOH (1:1) reagent (0.5 M, 24 mL, 12 mM) in ether was added at

-78°C. After 1 h strring at room temperature, the reaction mixture was allowed to warm to 0°C and the excess reagent was destroyed by the addition of water (1 mL) and filtered. The residue was washed thoroughly with ether. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (silica gel, 10% ethyl acetate in hexane) to provide pure alcohol.

Yield : 1.35 (74%)

IR (neat)ν_{max} : 3270, 1660 cm^{-1}

^1H NMR (100 MHz) : δ 0.85 (s, 9H), 0.93-2.77 (m, 10H), 4.18 (d, 2H, J = 6 Hz), 5.38 (t, 1H, J = 6 Hz).

^{13}C NMR (25 MHz) : δ 27.59, 28.59, 28.70, 29.12, 32.47, 36.94, 48.41, 58.65, 120.18, 144.43.

(4-*tert*-Butylcyclohexylidene)ethyl acetate (135a):

Yield : 93%

IR (neat)ν_{max} : 1740, 1660 cm^{-1}

^1H NMR (100 MHz) : δ 0.74 (s, 9H), 0.82-2.62 (m, 12H), 4.32-4.54 (d, 2H), 5.02-5.24 (m, 1H).

Enzymatic hydrolysis of (4-*tert*-butylcyclohexylidene)ethyl acetate (135a):

Hydrolysis of acetate 135a (1.12 g, 5 mM) with PLAP (2 g) in ether (10 mL) and phosphate buffer (0.5 M, pH 8, 40 mL) furnished (R)-alcohol and (S)-acetate in 39:61.

Reaction time : 18 h

Yield of (-)-alcohol : 0.26 g (74%)

Optical rotation : $[\alpha]_D^{24}$ -4.68(c 1.89, EtOH), 50% ee, Conf. (R)

{Lit.[151] $[\alpha]_D^{25}$ +6.5 (c 2.94, EtOH), 70% ee, Conf. (S)}

Yield of (+)-acetate : 0.60 g (87%)

Optical rotation : $[\alpha]_D^{24}$ +4.10 (c 3.17, EtOH), 26% ee, Conf. (S)

{Lit.[163] $[\alpha]_D^{20}$ +9.23 (c 1.95, EtOH), 60% ee, Conf. (S)}

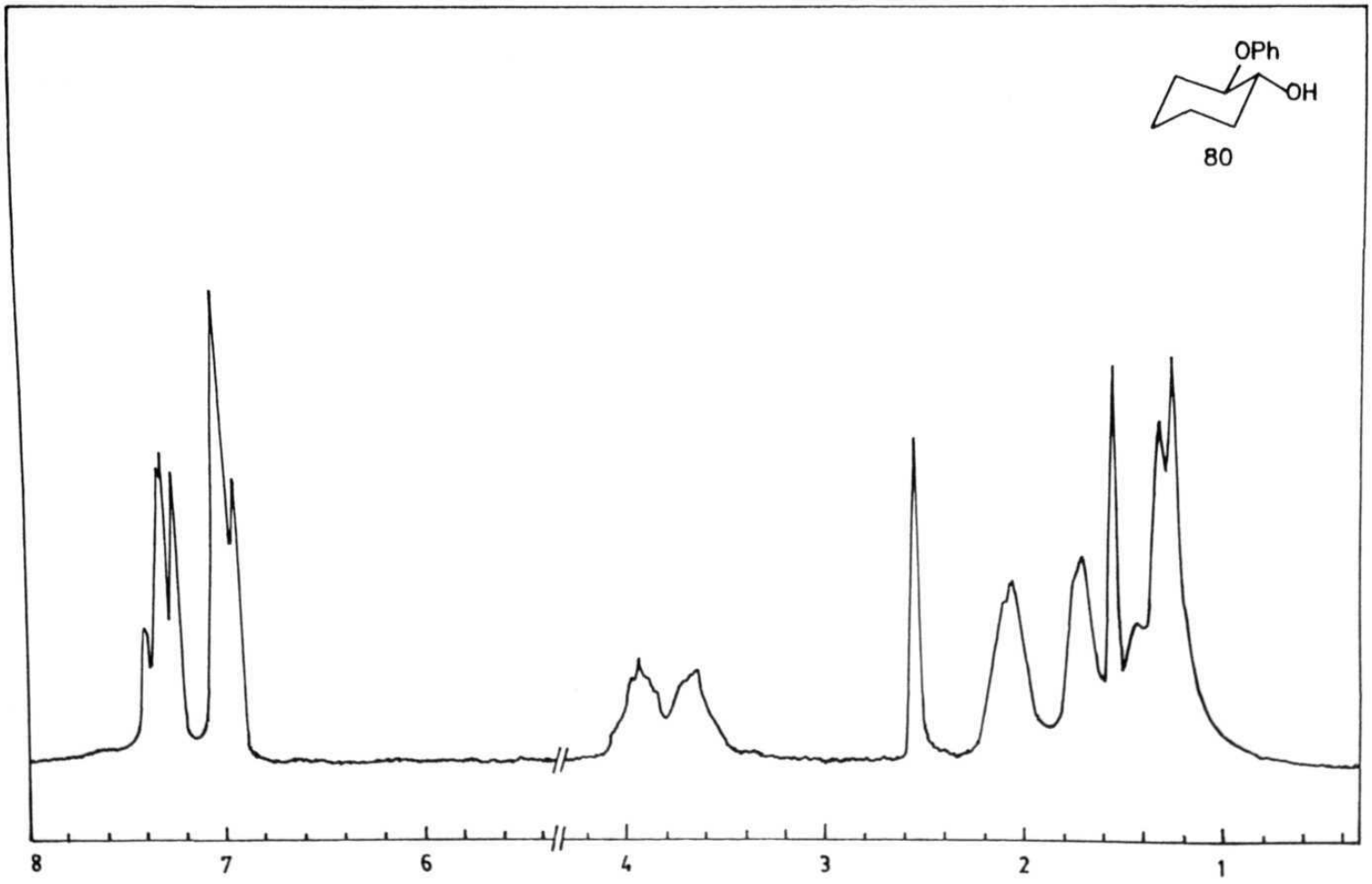


Fig.1 : ^{1}H NMR (100 MHz) Spectrum of 80

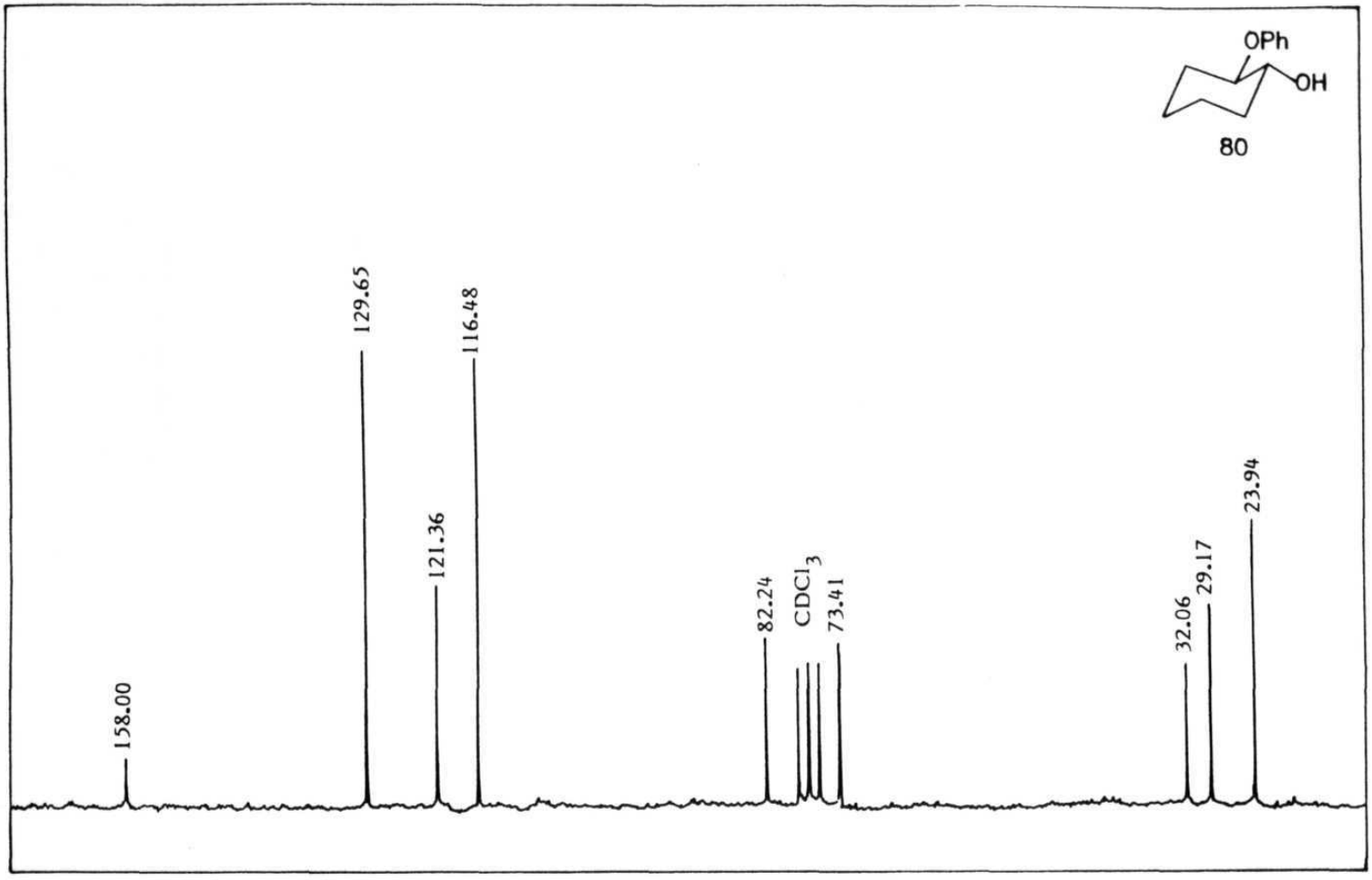


Fig.2 : ^{13}C NMR (25 MHz) Spectrum of 80

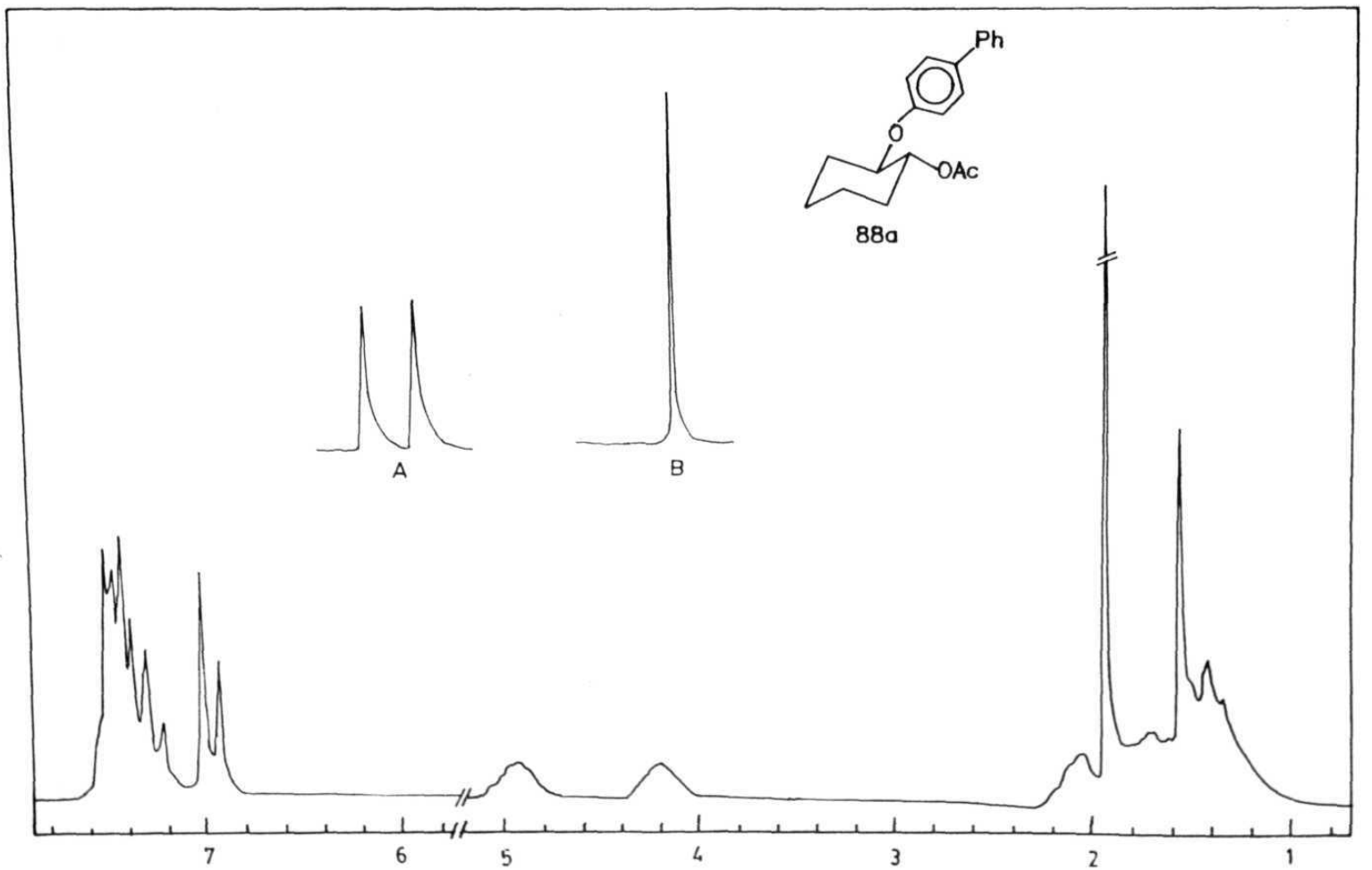


Fig.3 : ^{1}H NMR (100 MHz) Spectrum of 88a in presence of $Eu(hfc)_3$
(A) splitting of $OCOCH_3$ signal of (±) 88a, (B) $OCOCH_3$ signal of (-)-88a, ee >99%.

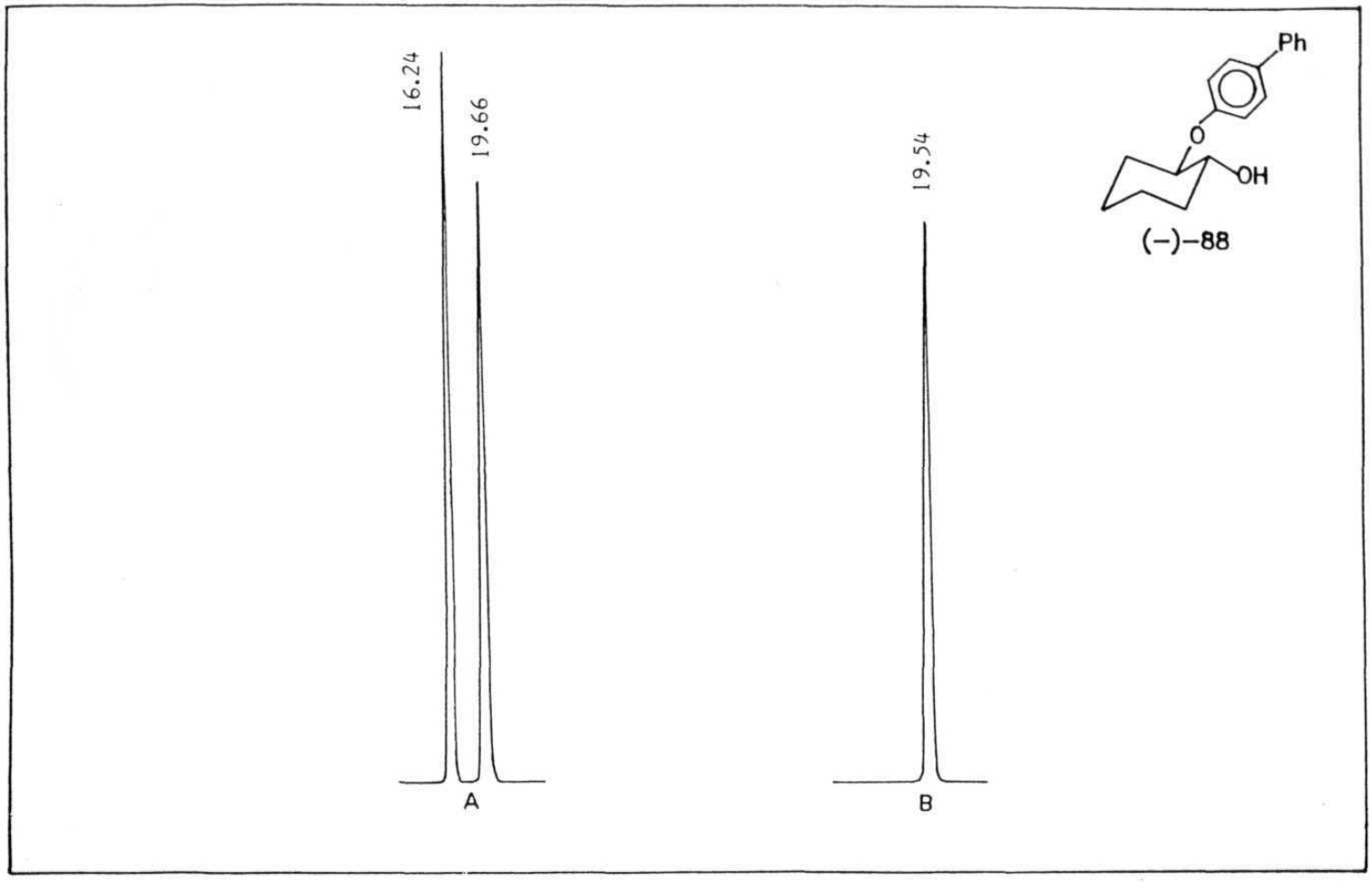


Fig.4 : HPLC analysis of 88 on chiral column, CHIRALCEL OD
(A) chromatogram of (±) 88, (B) chromatogram of (-)-88, ee >99%.

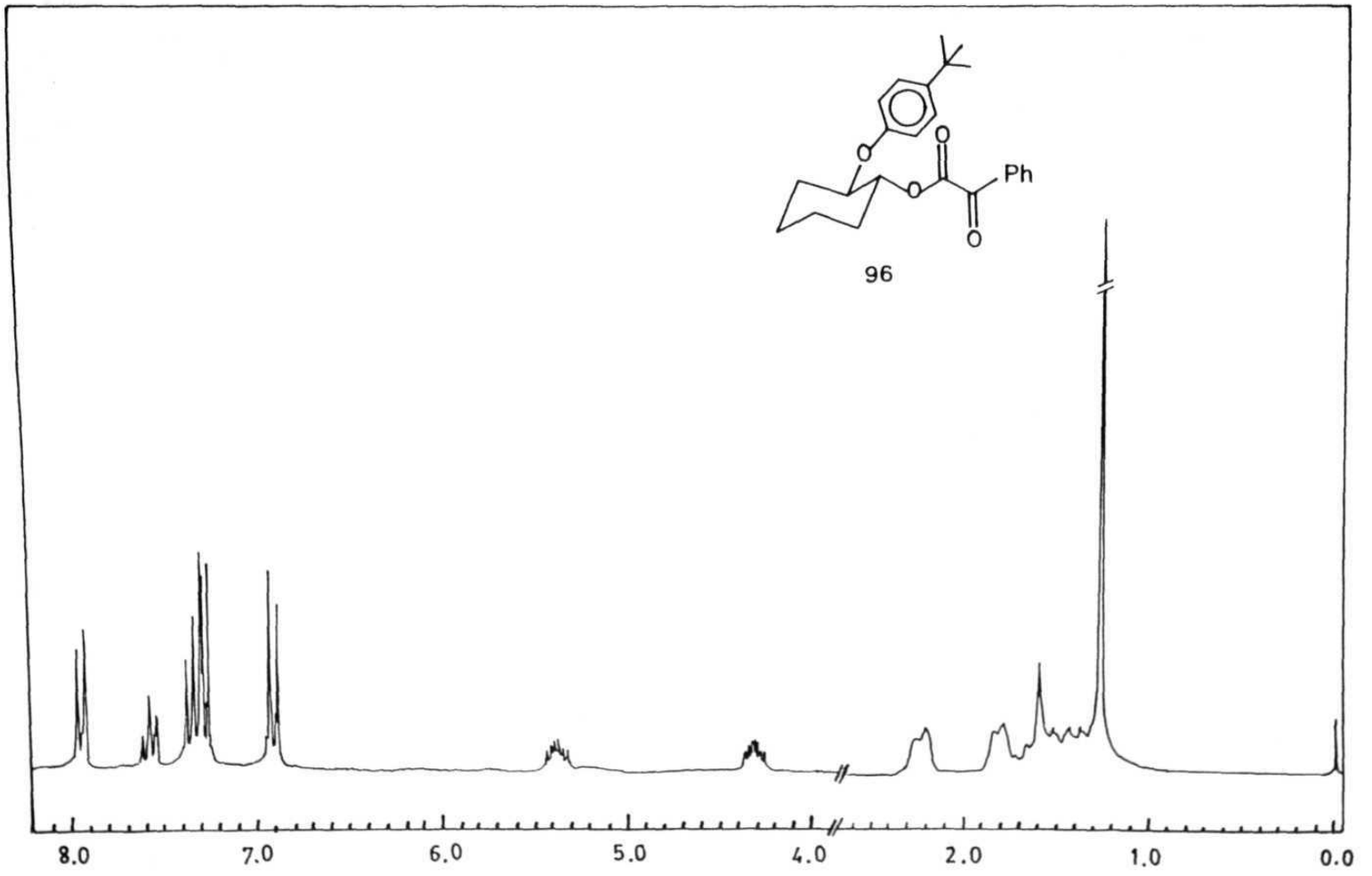


Fig.5 : ^{1}H NMR (200 MHz) Spectrum of 96

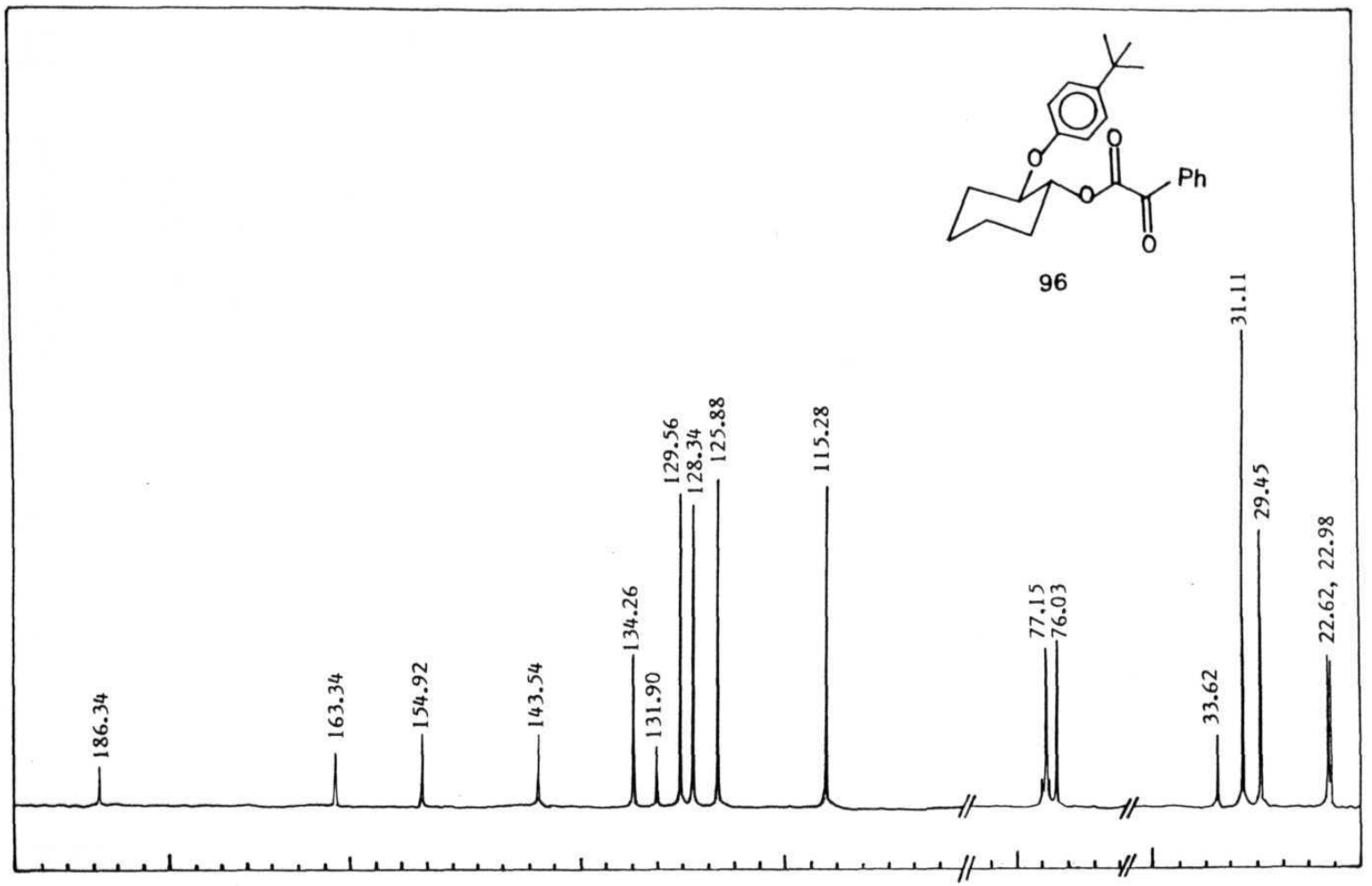


Fig.6 : ^{13}C NMR (50 MHz) Spectrum of 96

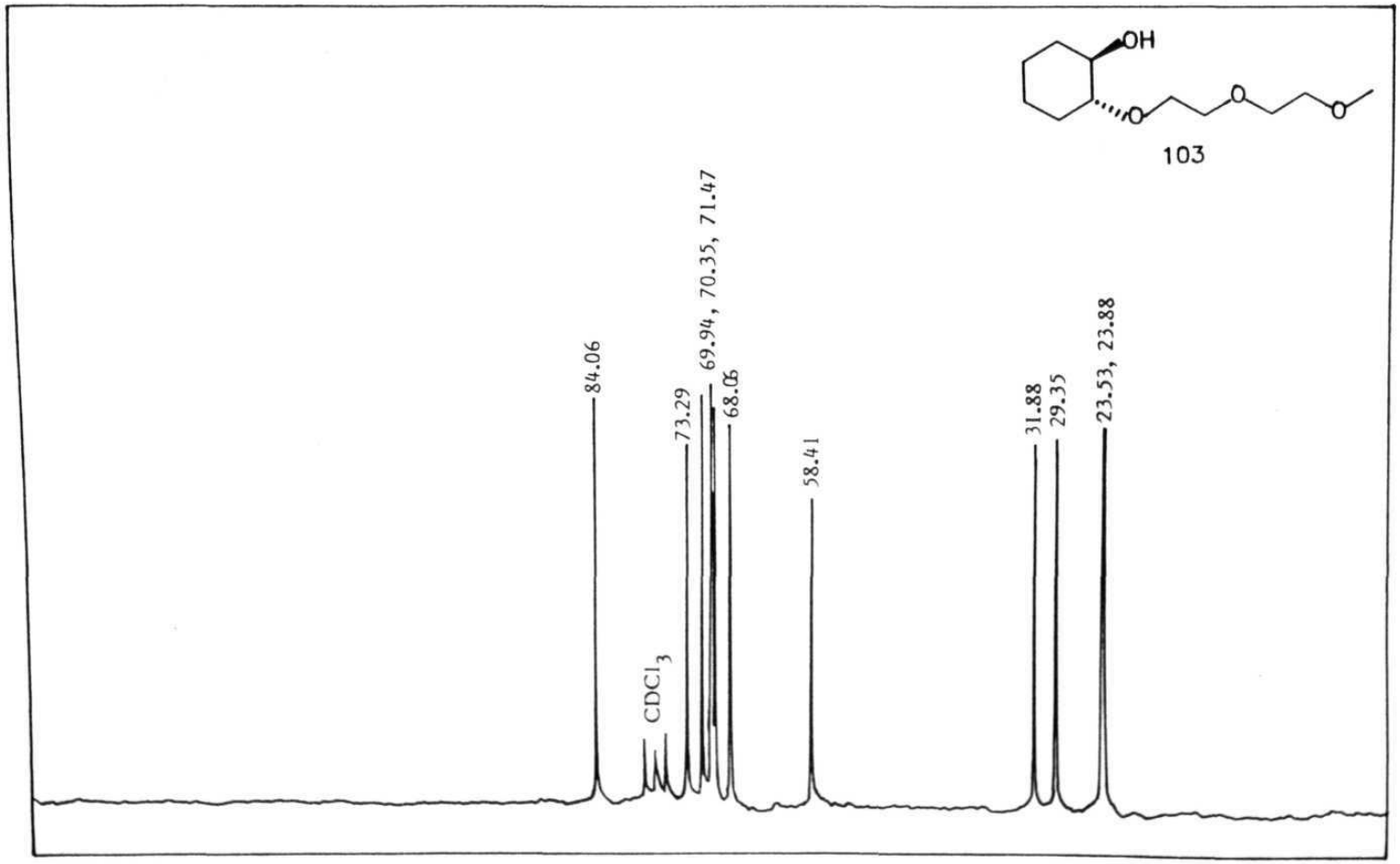


Fig.7 : ^{13}C NMR (25 MHz) Spectrum of 103

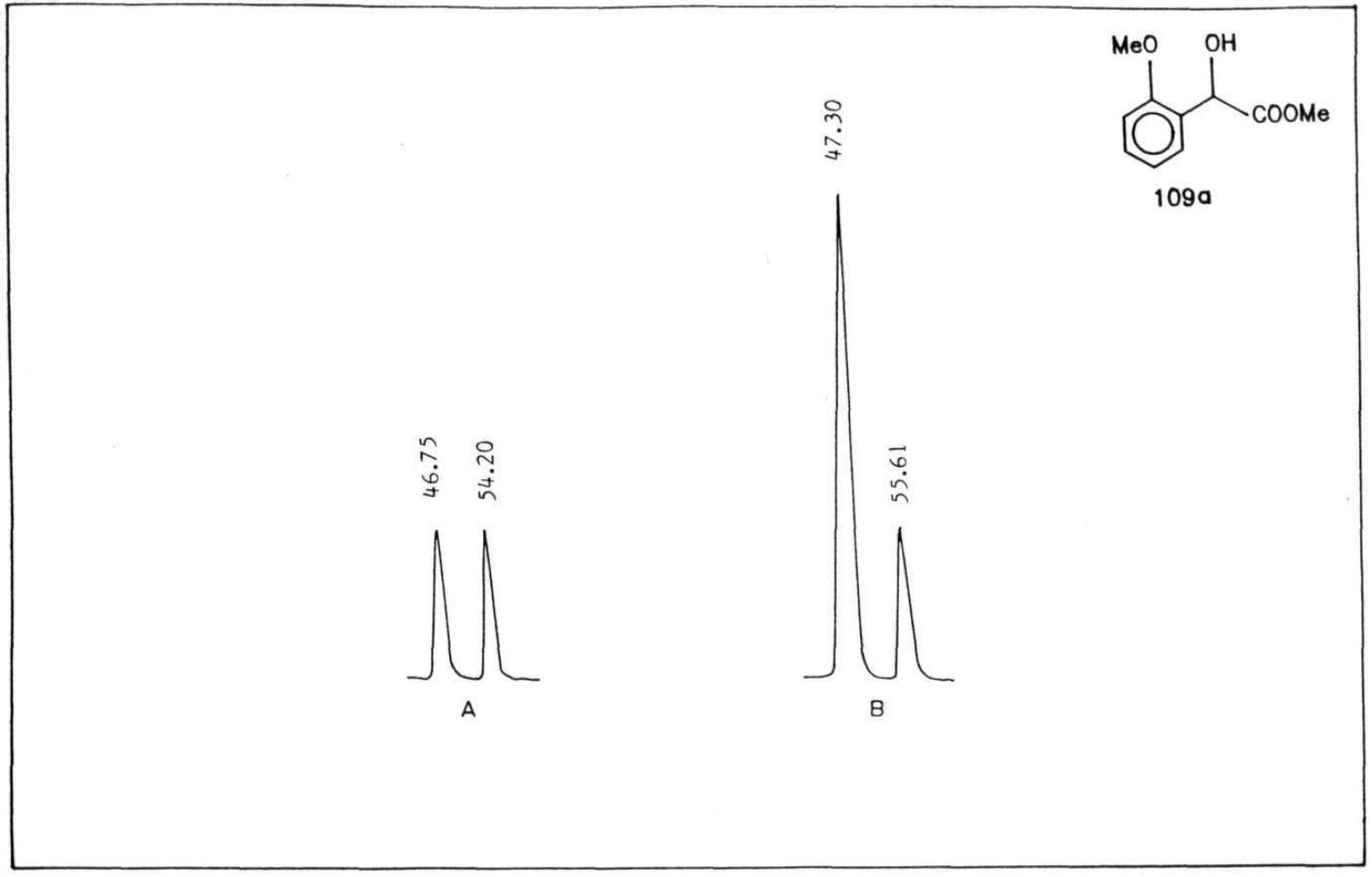


Fig.8 : HPLC analysis of 109a on chiral column, CHIRALCEL OD

(A) chromatogram of (±) 109a, (B) chromatogram of (+)-109a, ee 55%.

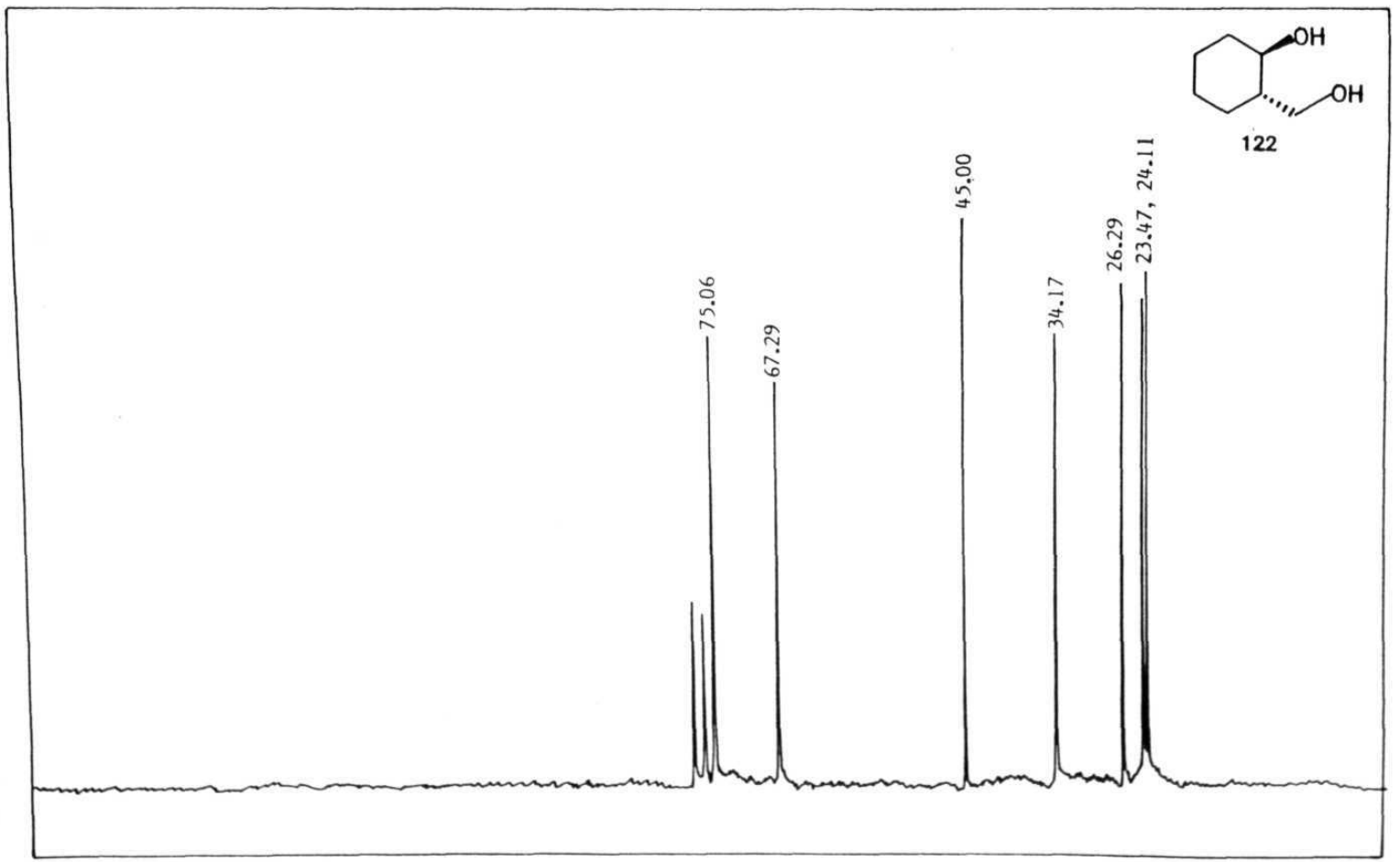


Fig.9: ^{13}C NMR (25 MHz) Spectrum of 122

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VITAE

The author was born on 10th August 1966 at Navuduru, West Godavari, Andhra Pradesh. Following his early education he joined DNR college, Bhimavaram and received his B.Sc degree from Andhra University in 1986. He joined the University of Hyderabad for M.Sc and recieved the degree in 1988 and registered for Ph.D in July 1988. He was awarded JRF and SRF by CSIR, New Delhi.

List of Publications:

1. Convenient enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-aryloxycyclohexanes by crude pig liver acetone powder (PLAP).
   D. Basavaiah, P. Rama Krishna and T.K. Bharathi
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5. (1R,2R)-2-Phenoxycyclohexan-1-ol as chiral auxiliary: Enantio-selective synthesis of Frontalin.
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