CHIRAL AUXILIARY MEDIATED ASYMMETRIC SYNTHESIS OF α-AND β-HYDROXY ACIDS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

By

T. K. BHARATHI

SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

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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.

Hyderabad

December, 1991

T.K.BHARATHI

CERTIFICATE

Certified that the work contained in this thesis entitled **"Chiral Auxiliary mediated Asymmetric Synthesis of α- and β-Hydroxy acids"** has been carried out by Ms. T.K. Bharathi, under my supervision and the same has not been submitted elsewhere for any degree.

D.BASAVAIAH

(THESIS SUPERVISOR)

DEAN

SCHOOL OF CHEMISTRY

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I would like to thank all my family members and friends for their kind cooperation and encouragement throughout my career.

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T.K. BHARATHI

ABBREVIATIONS

Ac	acetyl
Bu	butyl
n-BuLi	n-butyl lithium
DHP	3,4-dihydro-2H-pyran
DIBAL	diisobutylaluminium hydride
e.e	enantiomeric excess
Et	ethyl
$Eu(hfc)_3$	tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III) derivative
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
MCPBA	m-chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
Ph	phenyl
p-TsOH	p-toluenesulfonic acid
TBDMS	t-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMSCl	trimethylchlorosilane

ABSTRACT

Synthesis of enantiomerically pure molecules is one of the fascinating and challenging areas in organic chemistry. Chiral auxiliary mediated asymmetric synthesis has become one of the most useful methods for obtaining enantiomerically enriched molecules and represents a forefront of research in synthetic organic chemistry. This thesis deals with our studies on chiral auxiliary mediated asymmetric synthesis of α- and β-hydroxy acids.

The thesis consists of three chapters (i) Introduction, (ii) Objectives, Results and Discussion, (iii) Experimental. In the introduction chapter some of the important literature methods describing the synthesis of α- and β-hydroxy acids, which are chiral building blocks for the synthesis of biologically active molecules, have been presented. The second chapter deals with the objectives, results and discussion. A number of synthetic strategies have been reported for the preparation of optically active α- and β-hydroxy acids. However, application of the well known Reformatsky reaction for the preparation of β-hydroxy acids in high enantiomeric purities has not been studied in great detail. We have, therefore, undertaken this research program with the main aim of developing suitable chiral Reformatsky reagents using easily accessible chiral auxiliaries to provide a simple

synthesis of β-hydroxy acids in high optical purities. For this purpose, we have planned

1. to utilize abundantly available lactic acid derivatives as chiral auxiliaries for the preparation of β-hydroxy acids,
2. to employ trans-2-phenylcyclohexan-1-ol and structurally similar trans-2-phenoxycyclohexan-1-ol as chiral auxiliaries for the preparation of β-hydroxy acids.

Our objectives also include the study of possible applications of trans-2-phenylcyclohexan-1-ol and trans-2-phenoxy cyclohexan-1-ol as chiral auxiliaries for the synthesis of chiral α-hydroxy acids.

With the above objectives in mind, we have first selected the easily available lactic acid derived chiral auxiliary, (S)-2-benzyloxypropan-1-ol (**79**). Reaction of the corresponding Reformatsky reagent [2-benzyloxyprop-1-yl] bromoacetate (**81**) with benzaldehyde followed by hydrolysis, provided 3-hydroxy-3-phenyl propionic acid (**77a**) in optically inactive form. We reasoned that this may be due to the fact that chiral centre is far from the reaction site.

Next, we have selected, (S)-1-benzyloxypropan-2-ol (**83**) as the chiral auxiliary, which has the chiral centre near to the reaction site. The zinc Reformatsky reaction of [1-benzyloxyprop-2-yl] bromoacetate (**87**), with benzaldehyde and acetophenone provided the β-hydroxy acids **77a, 77b** in 25 and 12%

optical purities respectively.

We have, then, used (S)-methyl lactate (**89**) as chiral auxiliary. The corresponding Reformatsky reagent (S)-methyl 2-(bromoacetoxy)propionate (**90**) on treatment with benzaldehyde provided, after hydrolysis, β-hydroxy acid **77a** in 100% optical purity but in low chemical yield. The same reaction when extended to other carbonyl compounds provided the β-hydroxy acids **77b-77d** in 11-24% optical purities.

We have, then, used (S)-1-aryloxypropan-2-ols **92, 93, 104, 106** as the chiral auxiliaries. The Reformatsky reaction of the corresponding bromoacetates **98, 100, 102, 111** provided the β-hydroxy acids in low optical purities (0-57%).

We have also utilized (1S,2R)-2-phenylcyclohexan-1-ol (**(+)-5**) as the chiral auxiliary. The Refomatsky reaction of the corresponding bromoacetate **114** with carbonyl compounds after hydrolysis provided the β-hydroxy acids **77a-77g** in 16-89% optical purities. Structurally similar (1S,2S)-2-phenoxycyclohexan-1-ol (**(+)-118**) was next employed as chiral auxiliary. Reformatsky reaction of the corresponding bromoacetate **121** with benzaldehyde, followed by hydrolysis provided the β-hydroxy acid **77a** in 15% optical purity.

We have also investigated the application of (1R,2S)-2-phenylcyclohexan-1-ol (**(-)-5**) and (1R,2R)-2-phenoxycyclohexan-1-ol (**(-)-118**) as chiral auxiliaries for the preparation of chiral

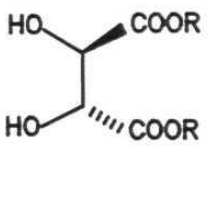
α-hydroxy acids. The reaction of (1R,2S)-2-phenylcyclohex-1-yl phenylglyoxalate (**129**) with a variety of alkylzinc chlorides provided the corresponding α-hydroxy esters, which on hydrolysis gave the desired α-hydroxy acids **78a-e** in 84-99% optical purities. The utilization of (1R,2R)-2-phenoxycyclohexan-1-ol (**(-)-118**) as chiral auxiliary provided the desired α-hydroxy acids **78a-e** in high optical purities (80-93%).

We have also prepared (-) frontalin (**63**), the pheromone,[4] in 70% optical purity using (1R,2R)-2-phenoxycyclohexan-1-ol (**(-)-118**) as chiral auxiliary.

The third chapter deals with the experimental procedures along with the spectral data and physical constants (m.p., b.p. and optical rotations). Determination of enantiomeric excess of some of the hydroxy acids is also described in detail.

INTRODUCTION

Synthesis of enantiomerically pure molecules is one of the fascinating and challenging areas in organic chemistry. Chiral auxiliary mediated asymmetric synthesis[1-5] has become one of the most useful methods for obtaining enantiomerically enriched molecules and represents a forefront of research in synthetic organic chemistry. Several chiral auxiliaries and chiral reagents have been developed in recent years and their applications have been well studied. Some important chiral auxiliaries and chiral reagents whose applications have been well documented are listed below.



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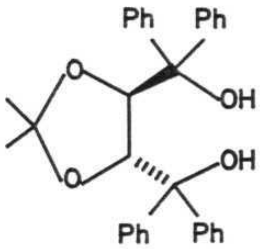

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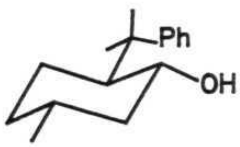

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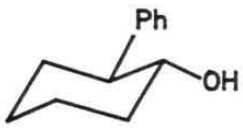

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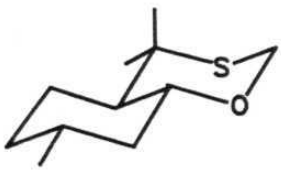

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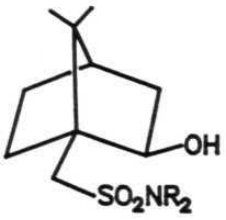

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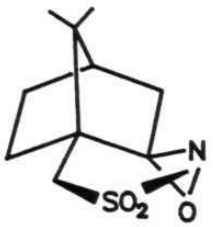

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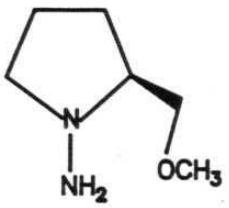

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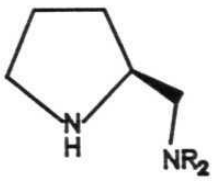

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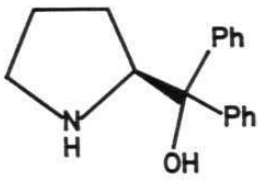

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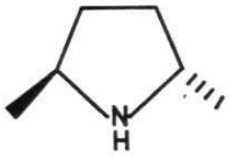

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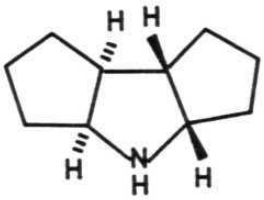

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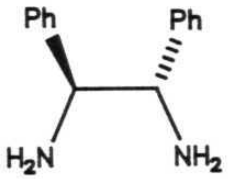

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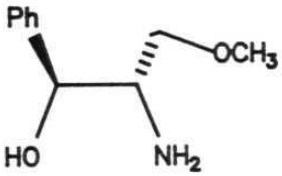

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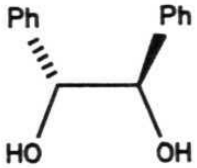

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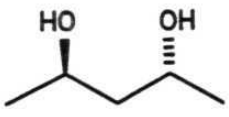

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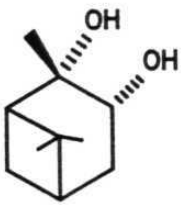

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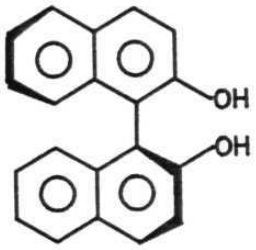

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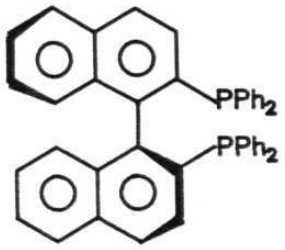

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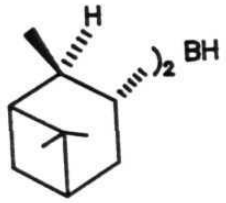

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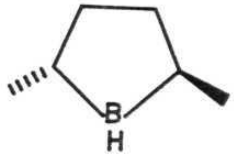


22[30]

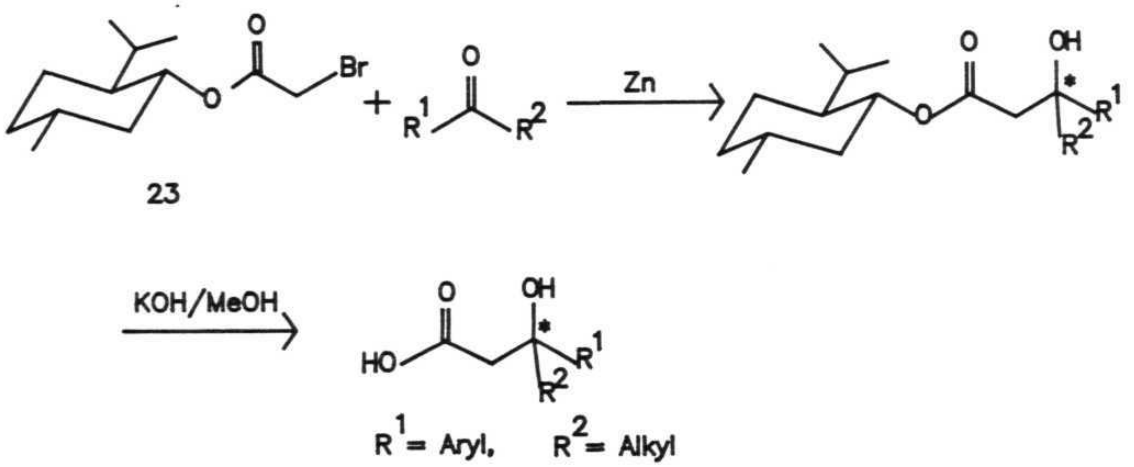
Optically pure α- and β-hydroxy acids are very important synthetic intermediates for the preparation of biologically active molecules.[31-35] Several chiral auxiliaries have been employed and several synthetic strategies have been developed for the preparation of chiral α- and β-hydroxy acids. Some of the important synthetic methods have been described in the following..

Synthesis of β-hydroxy acids:

Using Reformatsky reaction:

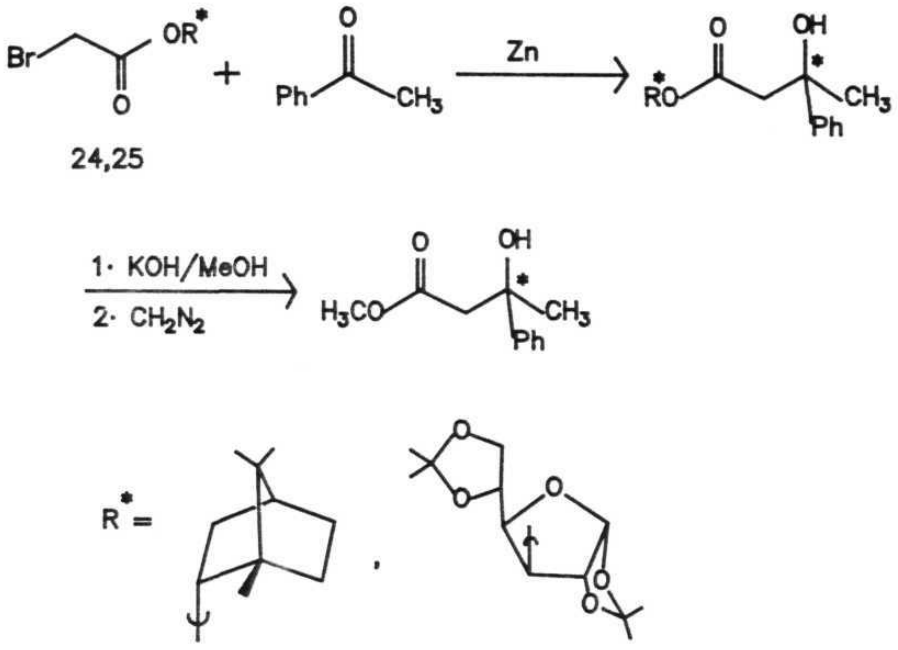
Reformatsky reaction is one of the oldest and the most useful reactions for the preparation of β-hydroxy acids.[36,37] In 1949, Reid[38,39] studied the application of (-)-menthyl bromoacetate (**23**) as Reformatsky reagent for the preparation of chiral β-hydroxy acids (Scheme 1).

SCHEME 1

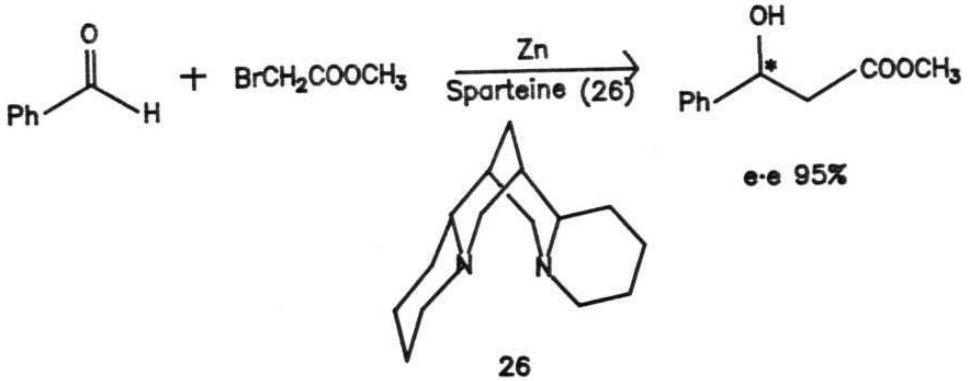


Chiral bromoacetates **24, 25** derived from (-)-borneol and 1,2:5,6-di-O-isopropylidene-α,D-glucofuranose were employed by Brandange *et al.*[40] in the Reformatsky reaction. The resulting β-hydroxy acids were obtained in low optical purities (Scheme 2).

SCHEME 2

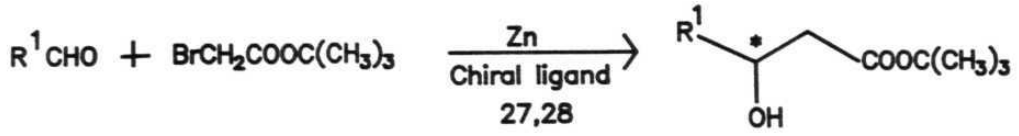


Asymmetric synthesis of β-hydroxy esters by the Reformatsky reaction in the presence of chiral ligand, sparteine (26) was investigated by Guette and co-workers.[41,42] Only in the case of benzaldehyde the resulting β-hydroxy ester (eq.1) was obtained in high enantiomeric purity, whereas other carbonyl compounds furnished the corresponding β-hydroxy esters in low optical purities.



(1)

Recently, Soai and Kawase[43] reported the asymmetric synthesis of β-hydroxy esters by the enantioselective Reformatsky reaction in the presence of chiral amino alcohols **27**, **28** (eq.2) in good optical purities.



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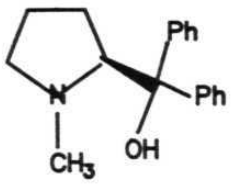

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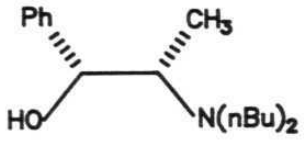
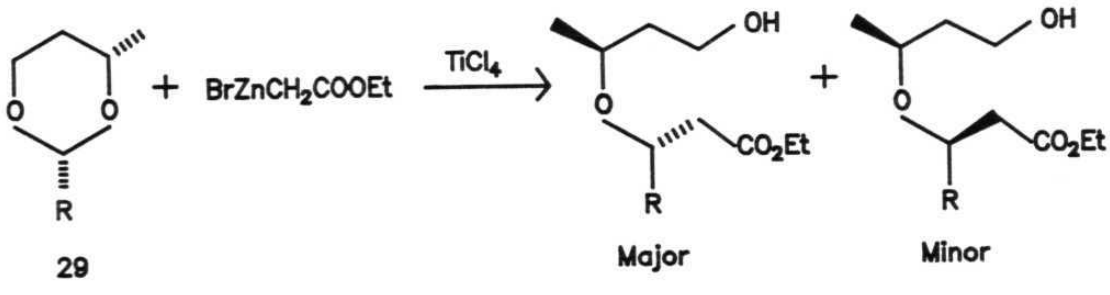


28

R^1 = Aryl, Alkyl

Tagliavini and co-workers [44] reported a novel synthesis of β-hydroxy esters in good enantiomeric purities by the reaction of Reformatsky reagent with chiral acetals **29** in the presence of $TiCl_4$ (Scheme 3).

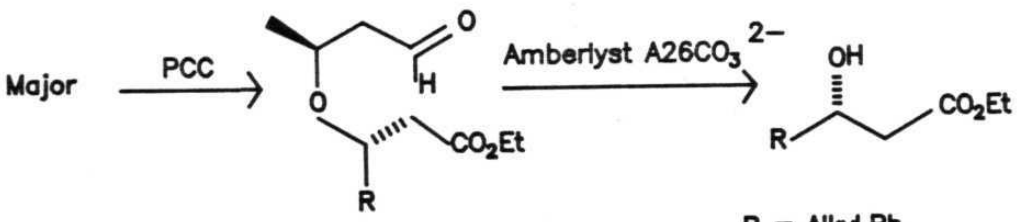
SCHEME 3



29

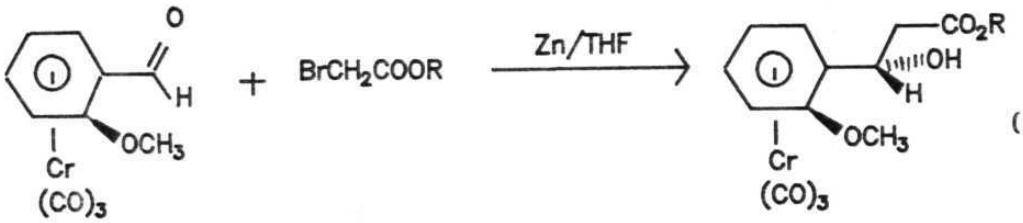
Major

Minor



R = Alkyl,Ph

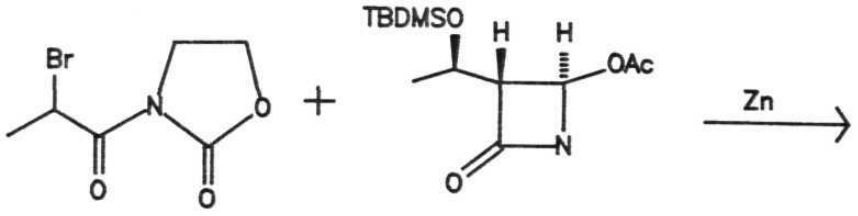
Transition metal complex of aryl carbonyl compound **30** was used in the Reformatsky reaction by Brocard and co-workers[45] to obtain optically pure β-hydroxy esters (eq.3).



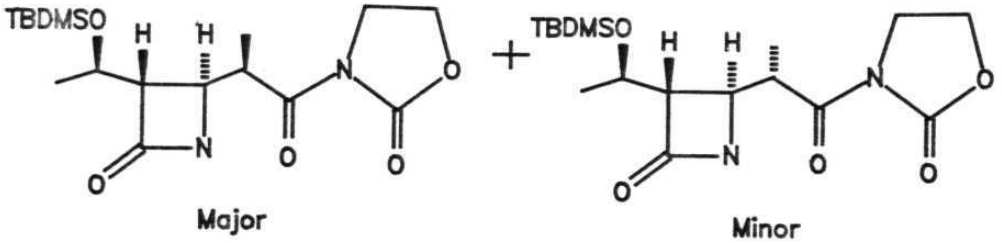
30 (3)

R = Alkyl

Recently, the reaction of 3-(2-bromopropionyl)-2-oxazolidone (**31**) with chiral acetate **32** in the presence of zinc was reported[46] to provide 2,3-syn aldol **33a,b** in high stereoselectivities (eq.4).



31 **32** (4)



Major

33a

Minor

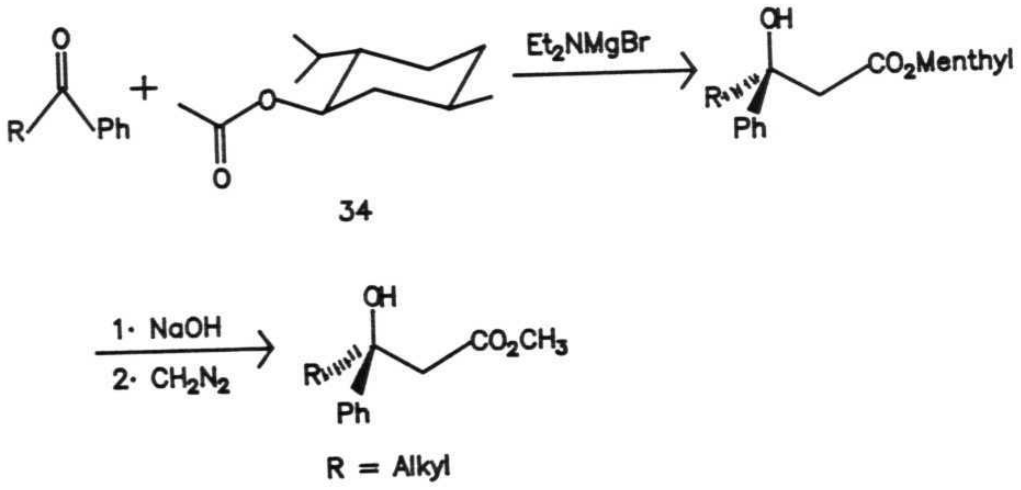
33b

Using aldol addition reaction:

Classical aldol reaction has seen a rapid development for stereoselective preparations during the last two decades[47,48] and has been used for synthesis of optically active β-hydroxy acids.

Solladie *et al.*[49] reported the aldol addition of (-)-menthyl acetate (**34**) with aromatic ketones in the presence of a base to afford β-hydroxy esters in moderate enantiomeric purities (Scheme 4).

SCHEME 4



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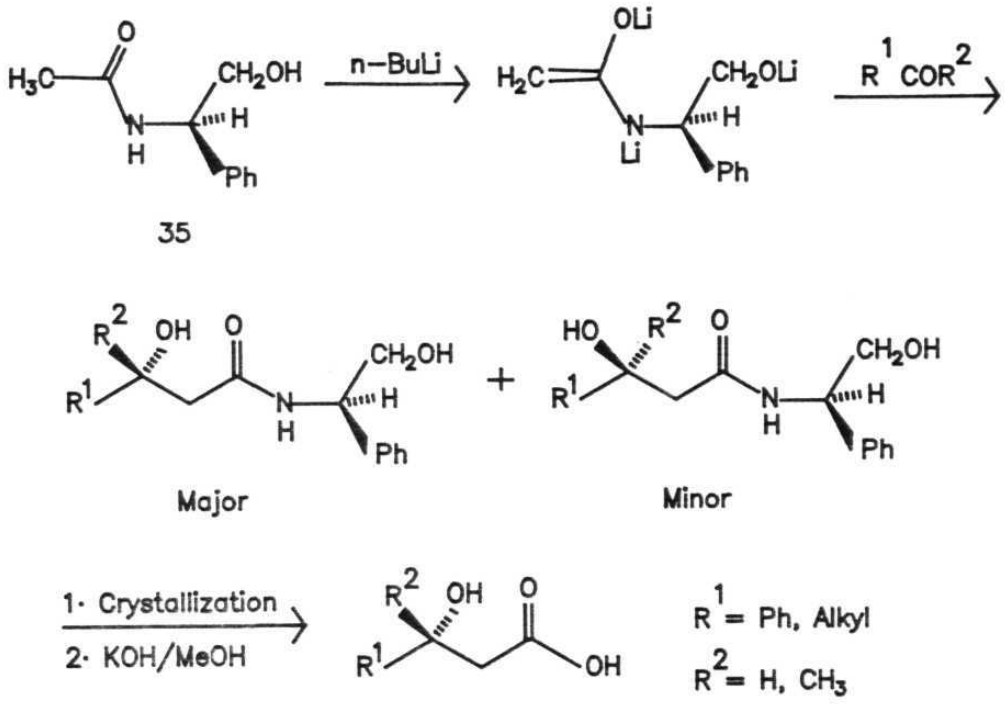
Stereoselective aldol addition reaction with chiral secondary acetamides **35** was reported by Devant and Braun for obtaining β-hydroxy acids in excellent optical purities[50,51] (Scheme 5).

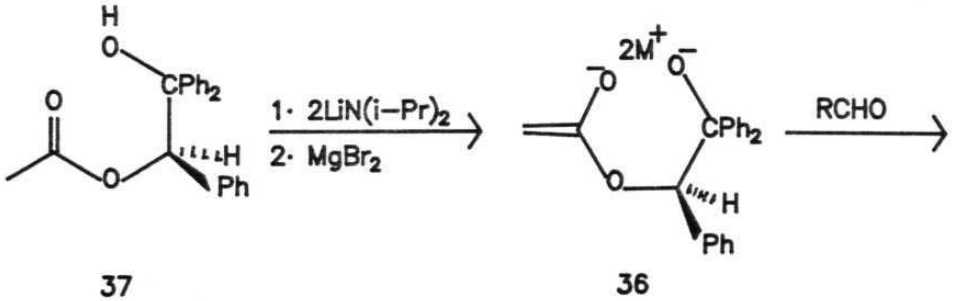
SCHEME 5



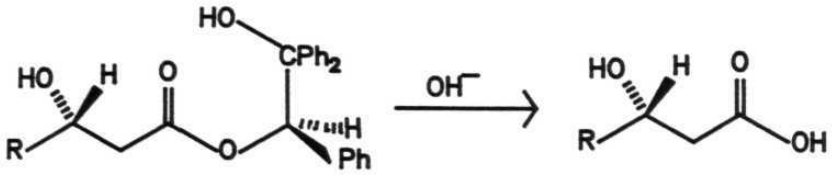
35

Braun and Devant[52] also reported the synthesis of β-hydroxy acids in high enantiomeric purities *via* the addition of the enolate **36**, derived from double deprotonation of 2-acetoxy-1,1,2-triphenylethanol (**37**), to aldehydes (Scheme 6).

SCHEME 6



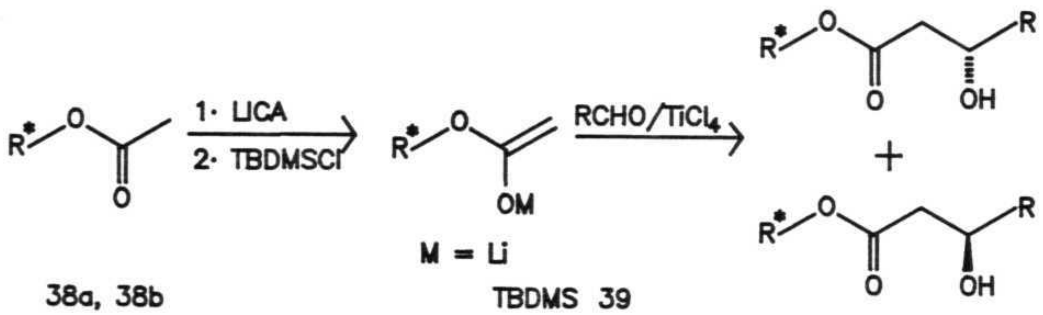
37 **36**



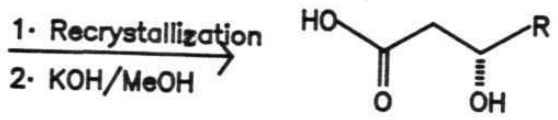
R = Alkyl,Ph

Helmchen *et al.*[53] used camphor derived chiral acetates **38a,b** in the aldol reaction *via* O-silyl ketene acetal **39** to afford β-hydroxy acids in high enantiomeric purities (Scheme 7).

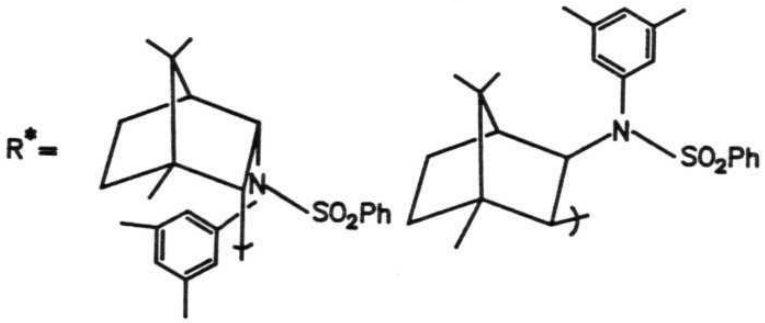
SCHEME 7



38a, 38b TBDMS 39

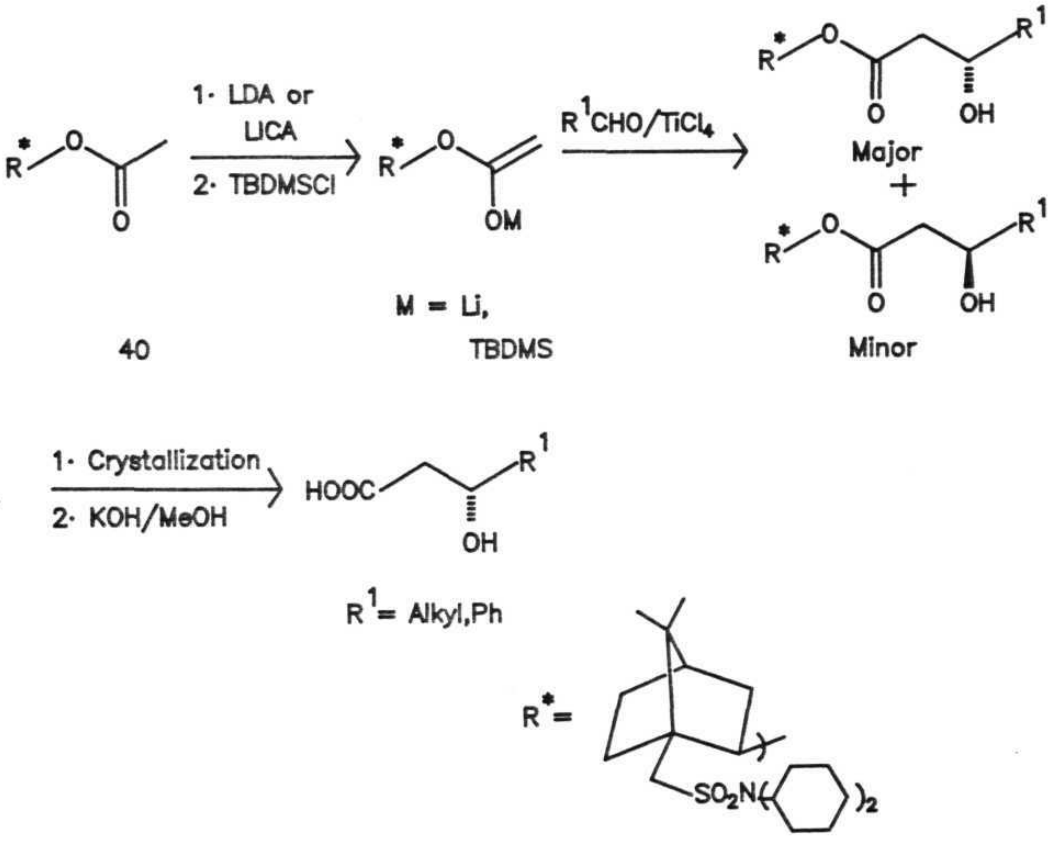


R = Alkyl, Ph



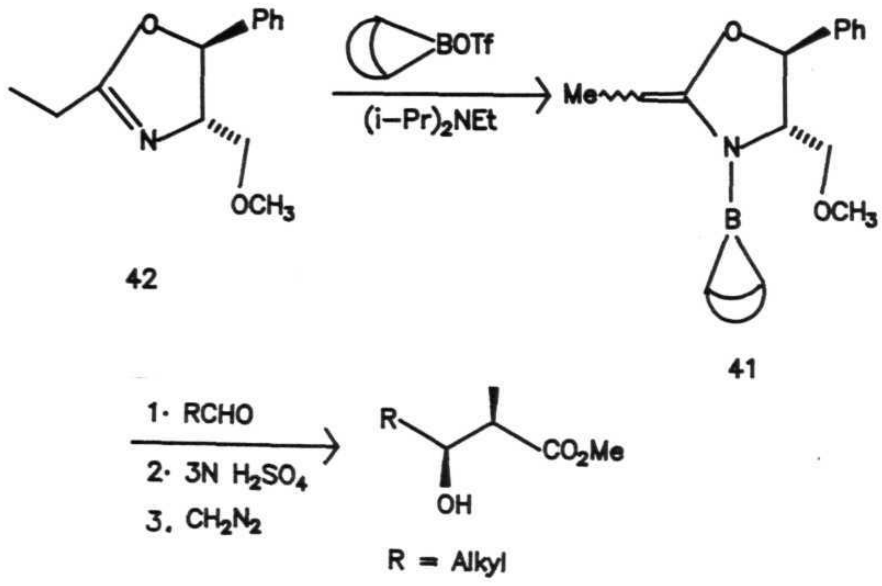
Camphor sulphonamide derived acetate **40** was utilized by Oppolzer and Contelles[54] for the preparation of chiral β-hydroxy acids by an aldol type addition reaction (Scheme 8).

SCHEME 8



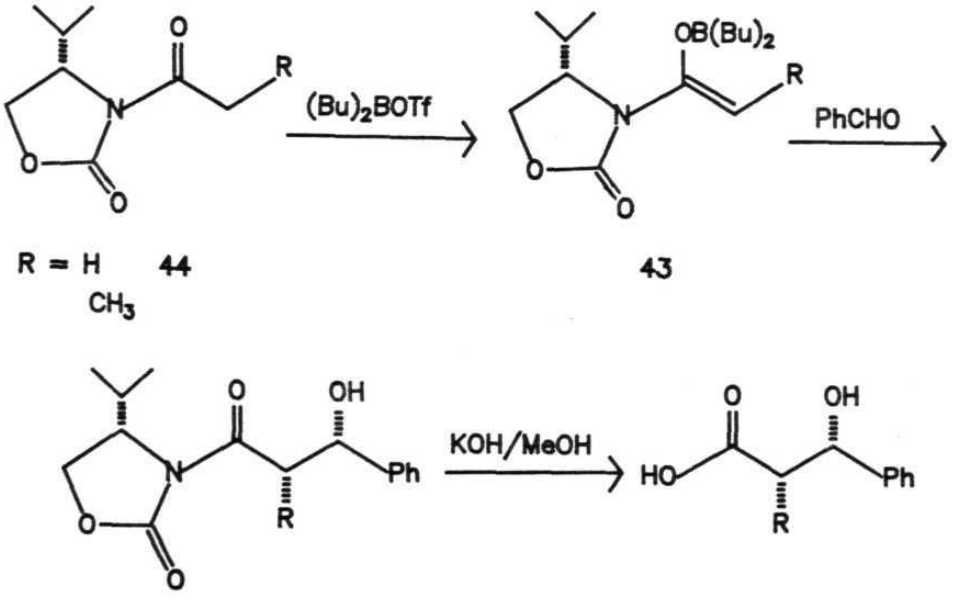
Boron azaenolate **41**, obtained from chiral oxazoline[55] **42**, was utilized in aldol reaction for the preparation of chiral α-substituted β-hydroxy esters in high diastereoselectivity and in moderate enantioselectivity (Scheme 9).

SCHEME 9



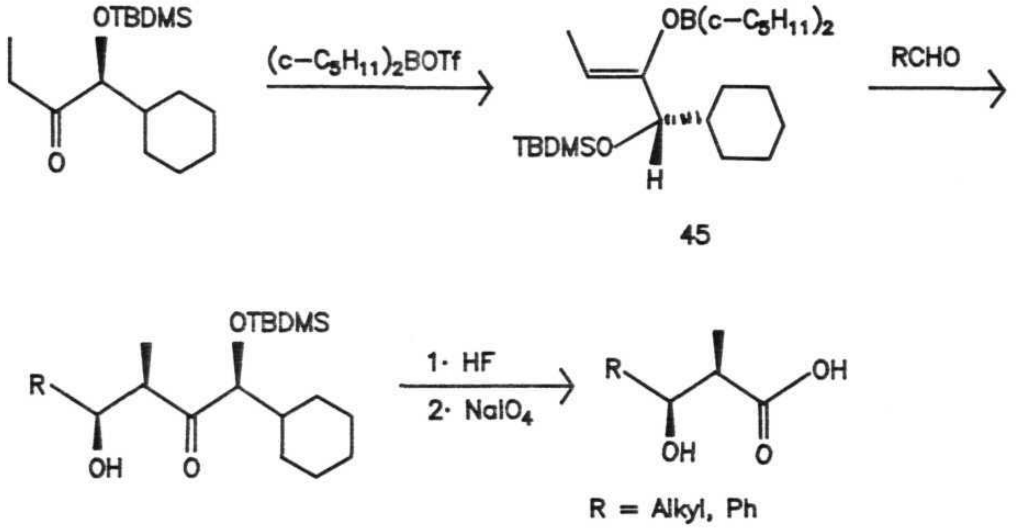
Addition of boron enolates[56] **43**, derived from chiral N-acetyloxazolidone **44**, to aldehydes provided α- substituted β-hydroxy acids in high enantioselectivities (Scheme 10).

SCHEME 10



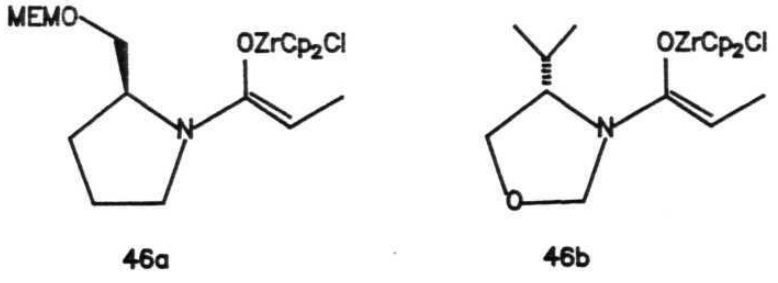
Masamune and co-workers[57] reported the preparation of α-substituted β-hydroxy acids in high enantioselectivities *via* the aldol reaction of chiral boron enolate **45** with aldehydes (Scheme 11).

SCHEME 11

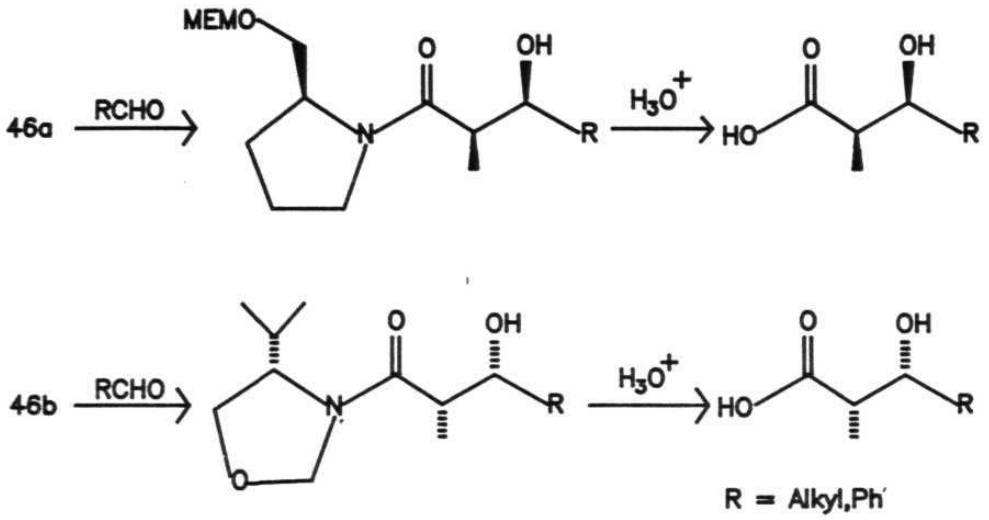


Chiral amide zirconium enolates **46a,b** were utilized by Evans and co-workers in aldol reaction to obtain α- substituted β-hydroxy acids in high selectivities [58] (Scheme 12).

SCHEME 12

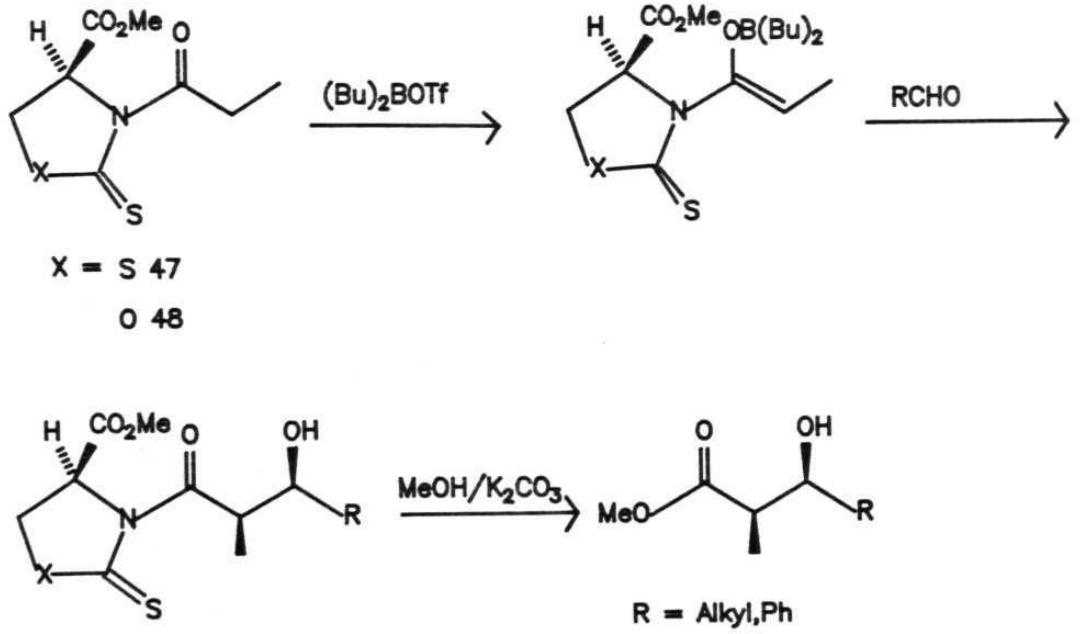


46a **46b**



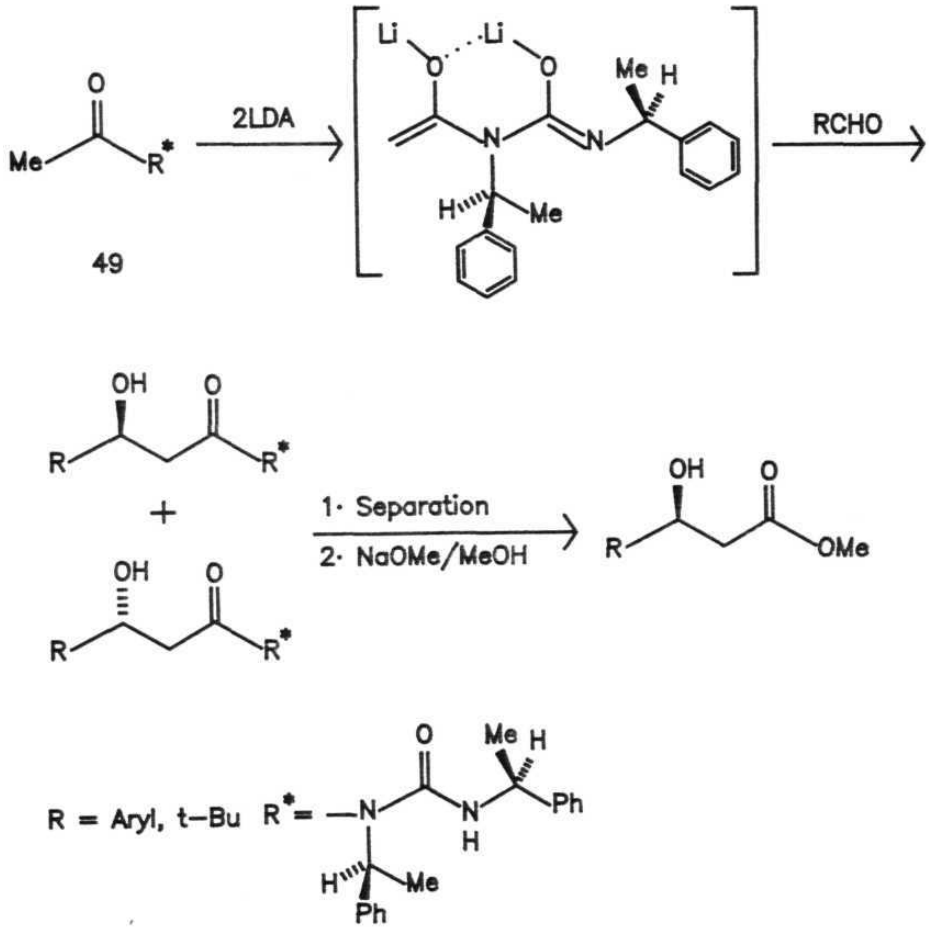
Hsiao and co-workers[59] employed cysteine derived thiazolidinethiones **47** and serine derived oxazolidinethiones **48** in boron triflate mediated aldol addition reaction to provide α-substituted β-hydroxy esters in high optical purities (Scheme 13).

SCHEME 13



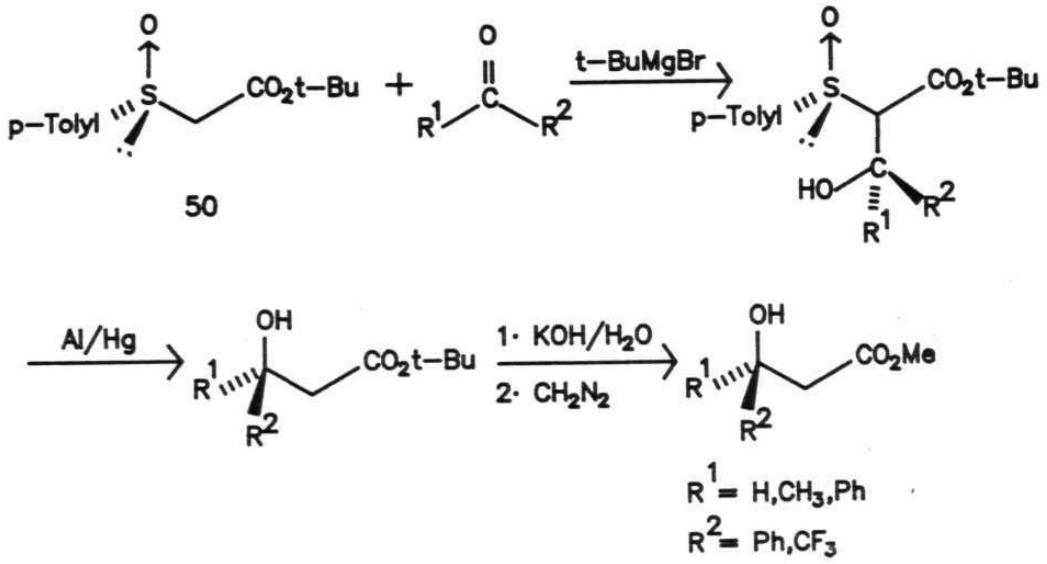
Enantioselective synthesis of β-hydroxy esters was reported by Yamada *et al.*[60] *via* the aldol addition reaction of the chiral acetyl urea **49** with aldehydes (Scheme 14).

SCHEME 14



Mioskowski and Solladie[61,62] reported the aldol reaction of chiral α-sulfinyl ester **50** with carbonyl compounds leading to the formation of chiral β-hydroxy esters (Scheme 15).

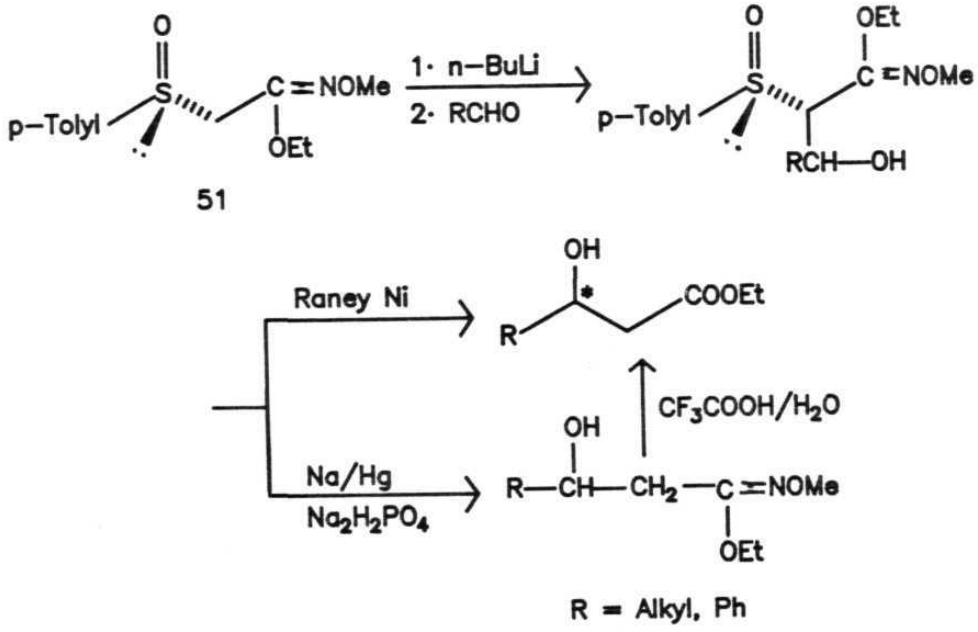
SCHEME 15



50

Colombo and co-workers[63] used R-(4-methylphenylsulfinyl)-ethyl N-methoxyacetimidate (**51**) as chiral acetate equivalent in an aldol type reaction with aldehydes for obtaining β-hydroxy esters in good optical purities (Scheme 16).

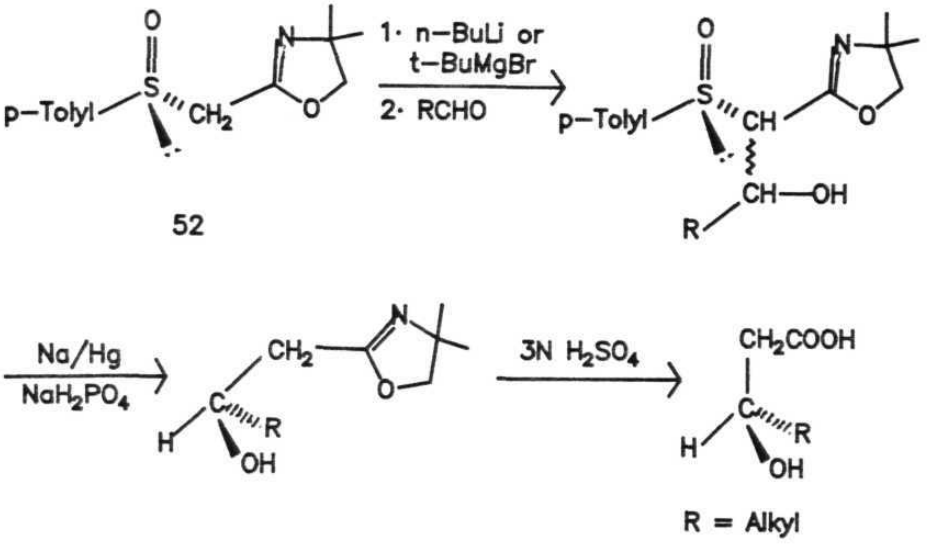
SCHEME 16



51

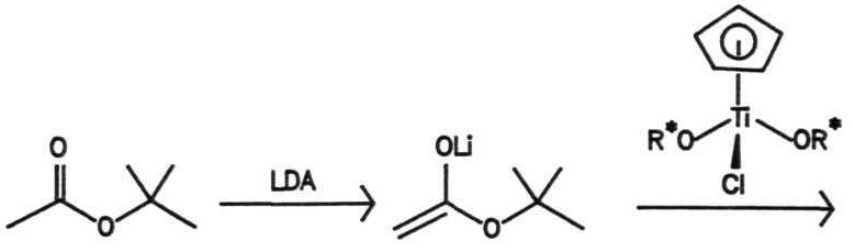
The use of 2-(arylsulfinylmethyl)oxazoline **52** in the stereoselective aldol type reaction was reported by Annunziata *et al.* for the preparation of chiral β-hydroxy acids[64] (Scheme 17).

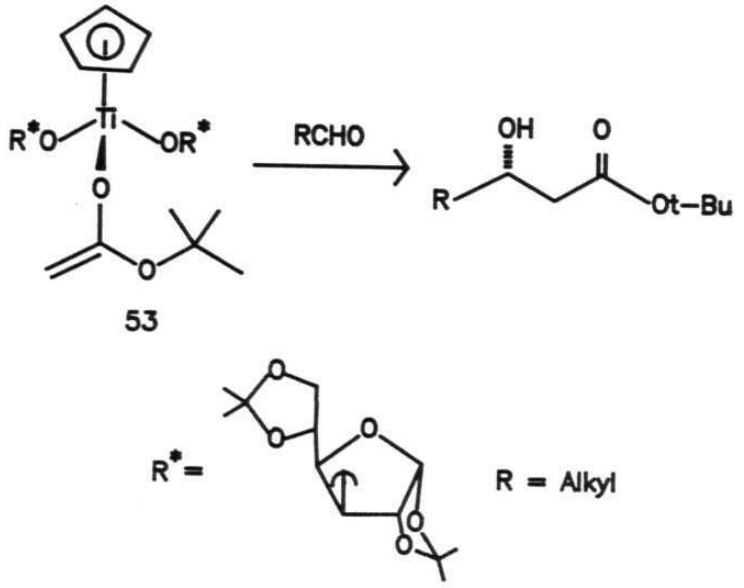
SCHEME 17



Enantioselective aldol reaction of aldehydes with the chiral titanium enolate **53** was reported by Duthaler *et al.*[65] to obtain the corresponding β-hydroxy esters (Scheme 18).

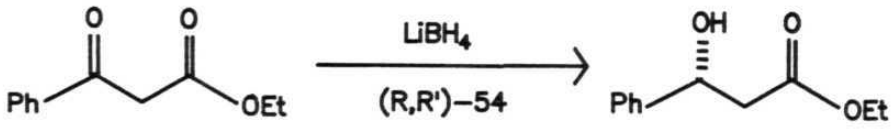
SCHEME 18





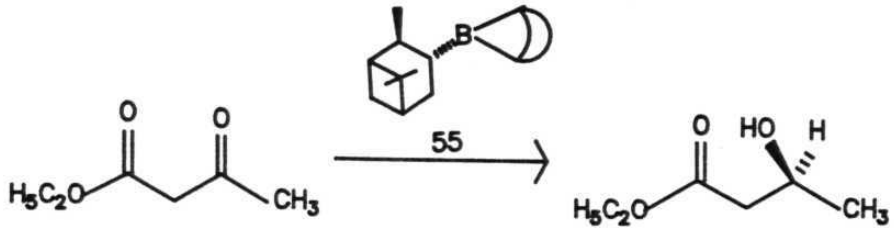
Reduction of β-keto acid derivatives:

Chiral β-hydroxy esters are also prepared by enantioselective reduction of β-keto esters. Soai and co-workers[66] used chirally modified $LiBH_4$ with N,N'-dibenzoylcystine (**54**) for the reduction of β-keto esters to furnish β-hydroxy esters in high enantiomeric purities (eq.5).



(5)

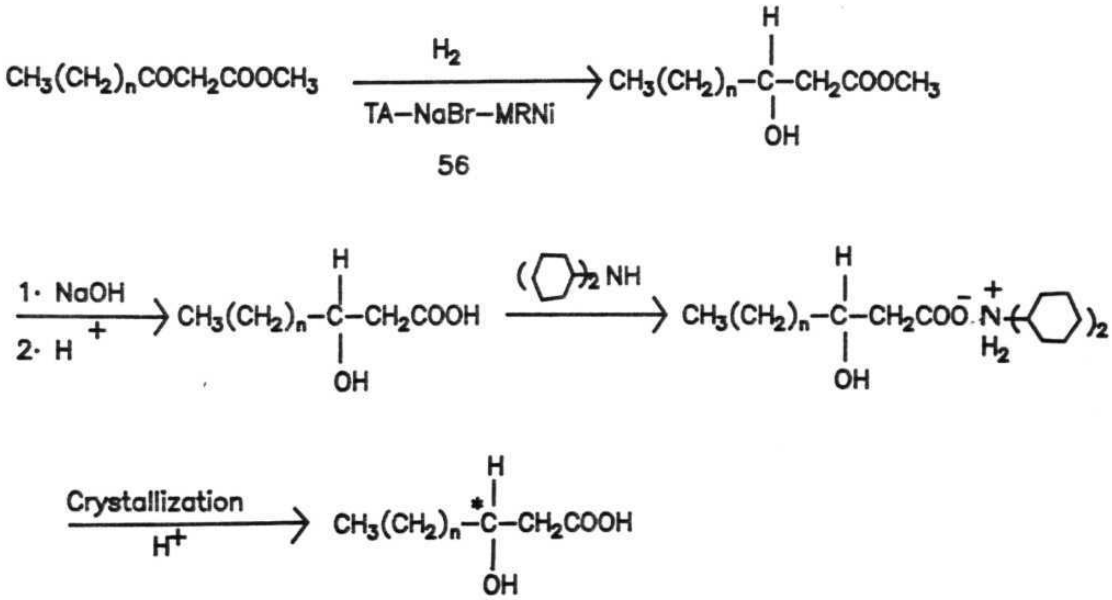
Brown and Pai[67] reduced ethyl acetoacetate with B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (**55**) to obtain the corresponding β-hydroxy ester in 50% enantiomeric purity (eq.6).



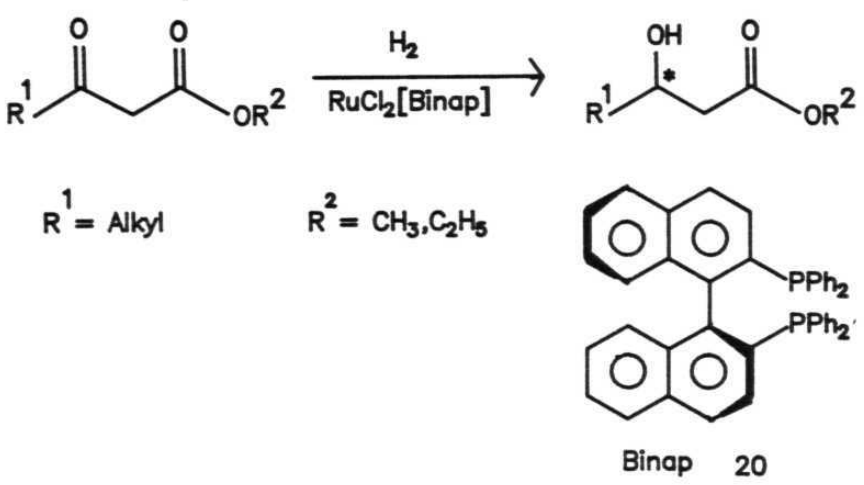
(6)

Tai *et al.*[68] reported the synthesis of optically active 3-hydroxyalkanoic acids *via* hydrogenation of the methyl 3-oxo alkanoates with (R,R)-tartaric acid-NaBr-modified Raney nickel (**56**) catalyst. Crystallization of dicyclohexylammonium salts of these 3-hydroxyalkanoic acids followed by hydrolysis gave 3-hydroxyalkanoic acids in >98% optical purity (Scheme 19).

SCHEME 19



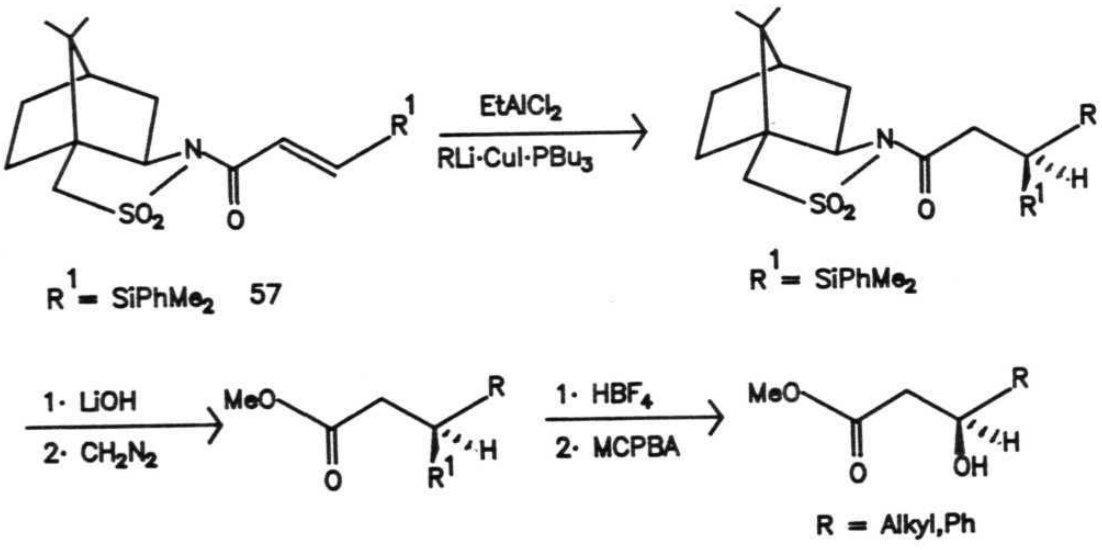
Noyori *et al.*[69] reported a novel asymmetric hydrogenation of β-keto carboxylic esters with chiral catalyst $RuCl_2$(binap) to provide β-hydroxy esters in high enantiomeric purities (eq.7).



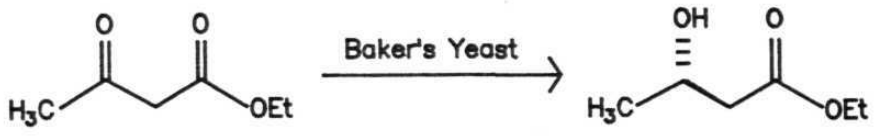
(7)

N-[β-(Silyl)enoyl]sultam **57** was utilized by Oppolzer *et al.*[70] to provide β-hydroxy esters in high enantiomeric purities (Scheme 20).

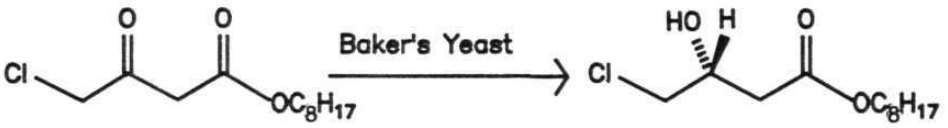
SCHEME 20



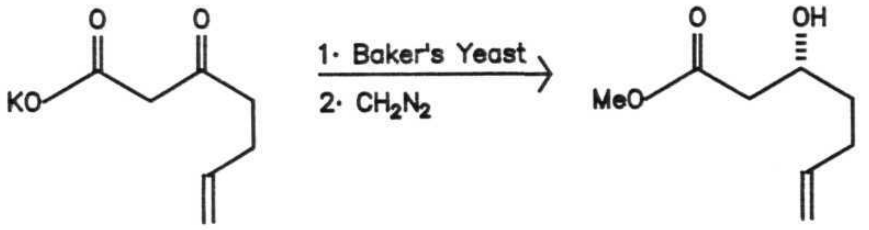
Baker's Yeast[71] has been extensively used for the reduction of β-keto esters to provide the corresponding chiral β-hydroxy esters in good enantiomeric excess (eq.8-11).



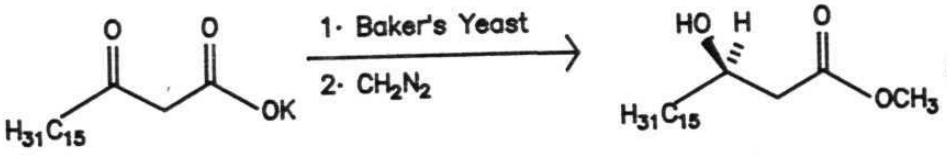
(8)[72]



(9)[73]



(10)[74]



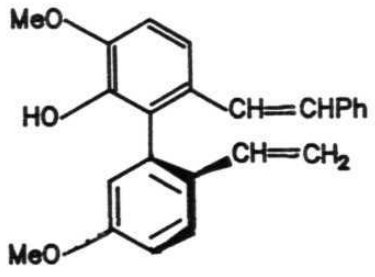
(11)[75]

Synthesis of α-hydroxy acids:

Addition reactions to α-keto acid derivatives:

The first asymmetric synthesis of α-hydroxy acids was studied by Mckenzie[76] in 1904, *via* the newly discovered Grignard addition reaction to chiral α-keto esters. Later this was developed by Prelog and others and the well known Prelog rule was the result of these studies.[77,78] Before 1970, several studies were carried out for obtaining chiral α-hydroxy acids, but almost all these methods, except the single example of Berson and Greenbaum[79], were less effective as the desired α-hydroxy acids were obtained in low optical purities.

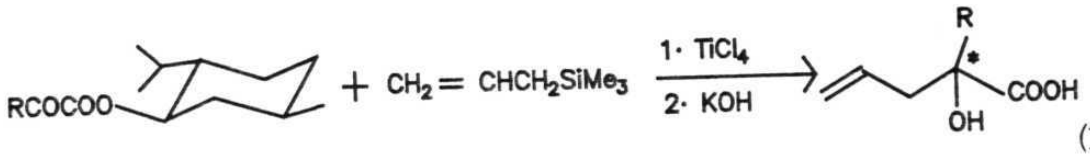
Berson and Greenbaum[79] prepared atrolactic acid in >98% optical purity by using the (+)-biphenyl derivative **58**.



58

In 1976, Ojima and co-workers[80] reported the alkylation of (-)-menthyl phenylglyoxalate (**59**) and (-)-menthyl pyruvate (**60**)

with allyltrimethylsilane to provide the γ,δ-unsaturated-α-hydroxy acids in low enantiomeric purities (eq.12).

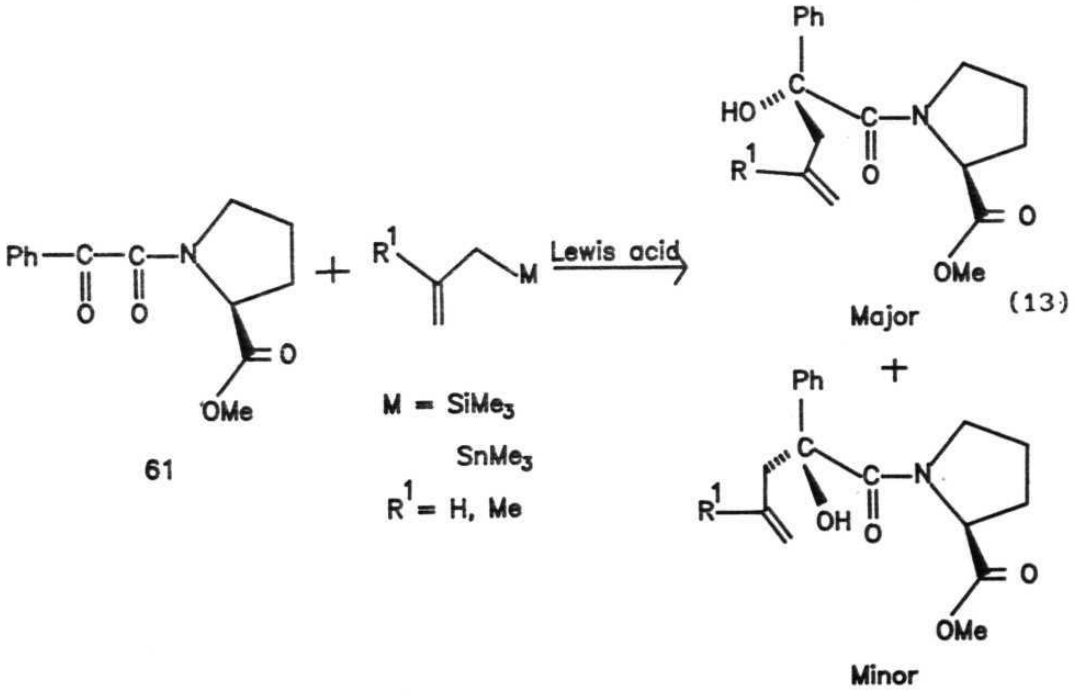


(12)

R = Ph 59

Me 60

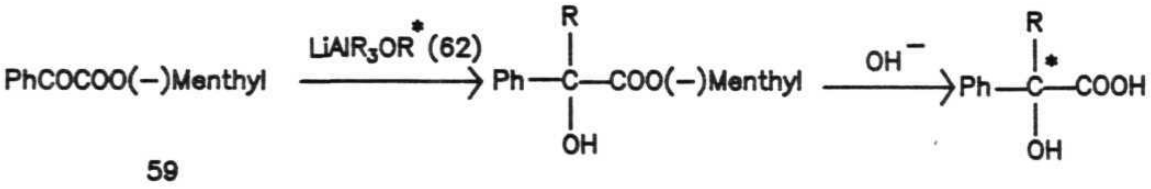
α-Keto amide **61**, derived from (S)-proline, was alkylated with allylsilanes and allylstannanes by Soai and Ishizaki[81] to obtain the corresponding α- substituted α-hydroxy amides in high enantiomeric purities (eq.13).



(13)

Abenhaim *et al.*[82-85] prepared α-alkylmandelic acids in high optical purities by the action of chiral lithium alkoxytrialkylaluminates (**62**) on (-)-menthyl phenylglyoxalate (**59**) (Scheme 21).

SCHEME 21



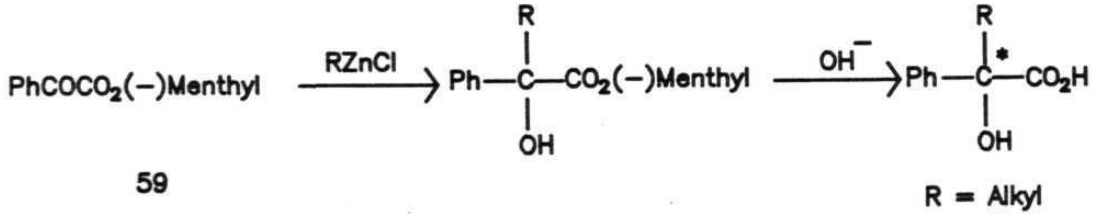
59

R = Alkyl

R*OH = (−)/(+)−N−Me epihedrine

Later Abenhaim *et al.*[86,87] reported the addition of alkyl zinc chlorides to (-)-menthyl phenylglyoxalate (**59**) leading to the formation of α-alkylmandelic acids in high optical purities (Scheme 22).

SCHEME 22

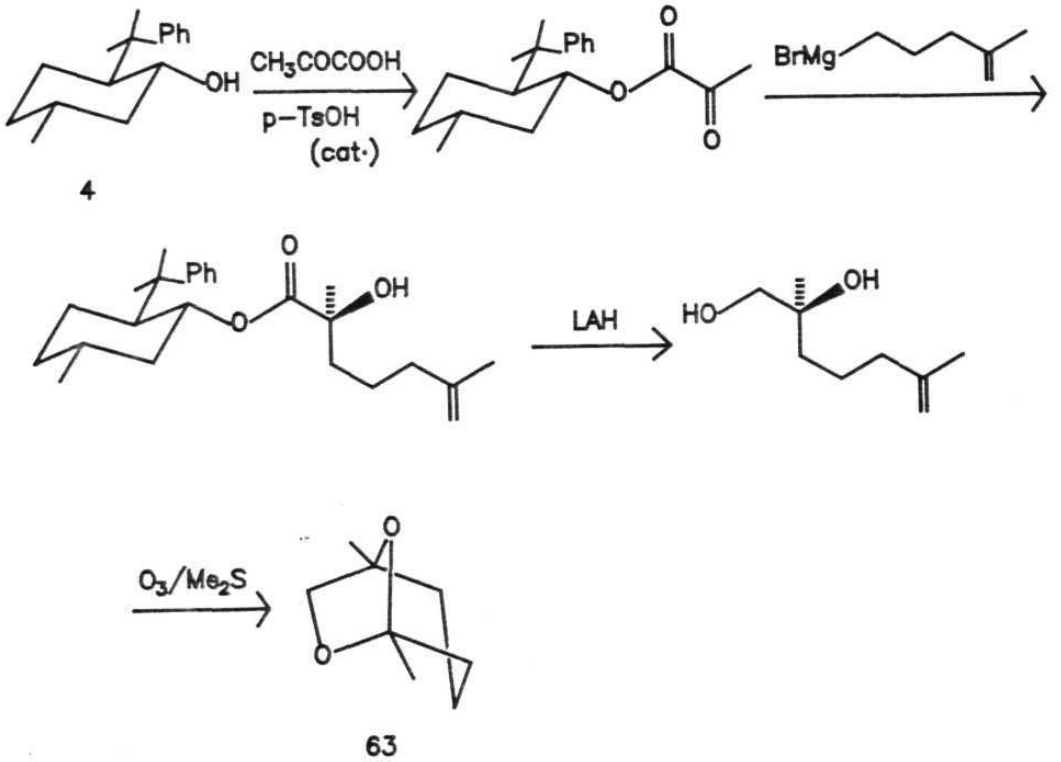


59

R = Alkyl

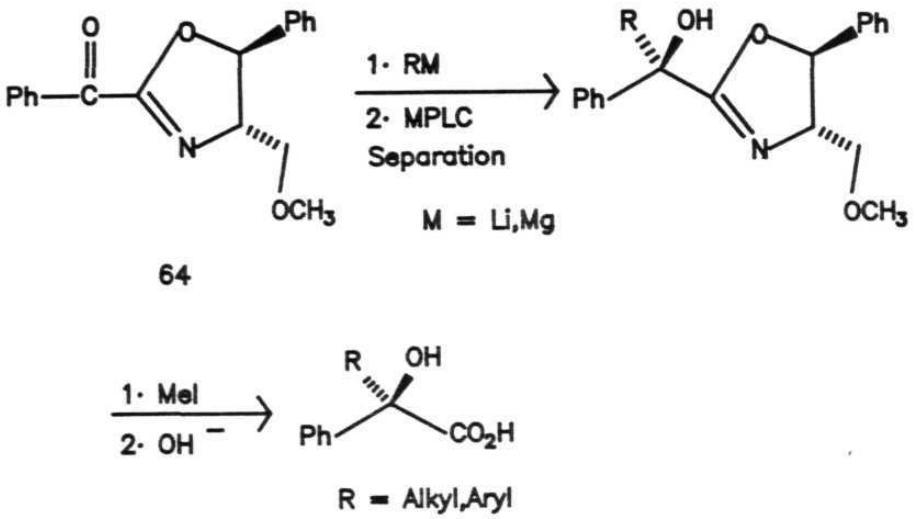
Whitesell *et al*[88] employed 8-phenylmenthol (**4**) as the chiral auxiliary for obtaining optically active α-hydroxy esters. Using this method, the pheromone, Frontalin (**63**) was obtained in optically pure form (Scheme 23).

SCHEME 23



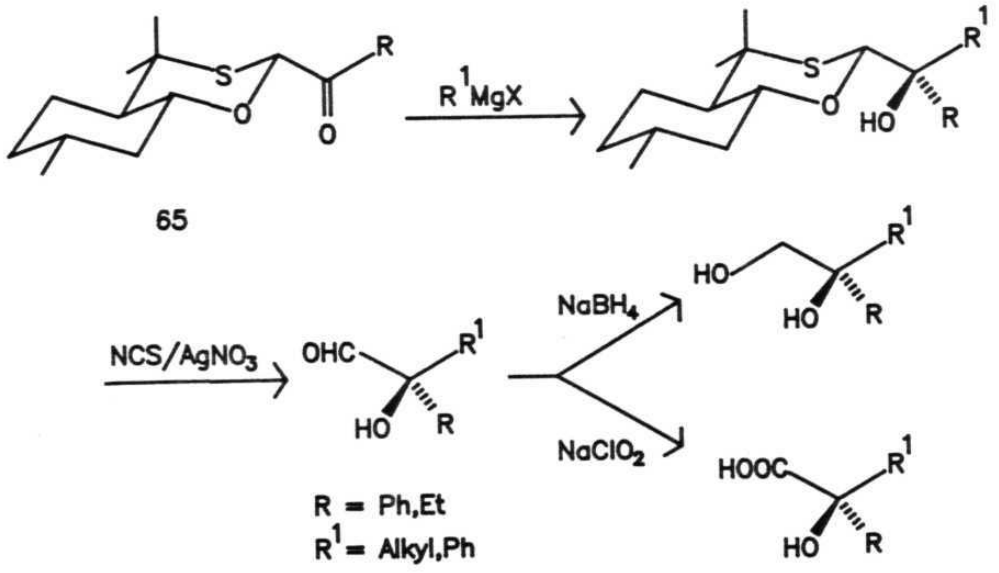
The addition of organometallic reagents to chiral α-ketooxazoline **64** was reported by Meyers *et al.* to provide α-hydroxy acids in high optical purities[89-91] (Scheme 24).

SCHEME 24

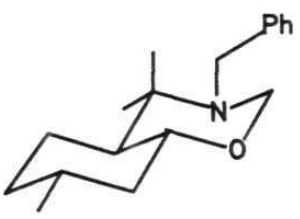


A highly conformationally locked α-keto 1,3-oxathianes[11] 65, prepared from readily available pulegone, were utilized by Eliel and co-workers for the preparation of α-hydroxy derivatives in high enantiomeric purities (Scheme 25).

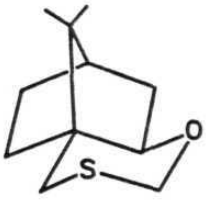
SCHEME 25



Eliel also utilized a nitrogen analog[92] **66**, derived from pulegone, and 1,3-oxathiane[93] **67** derived from (+)-10-camphor sulfonic acid for the preparation of chiral α-hydroxy acids following the similar strategy as in Scheme 25.



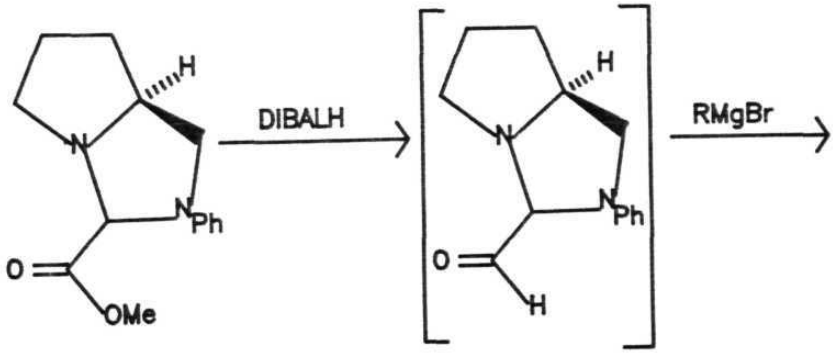
66



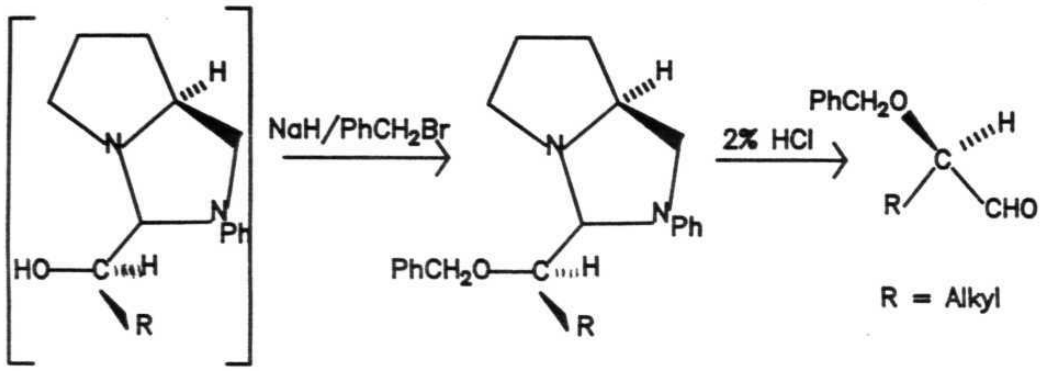
67

Optically active α-benzyloxy aldehydes[94] were synthesized by Mukaiyama *et al.* in high enantiomeric purities *via* the Grignard addition to 2-methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0] octane (**68**) (Scheme 26).

SCHEME 26

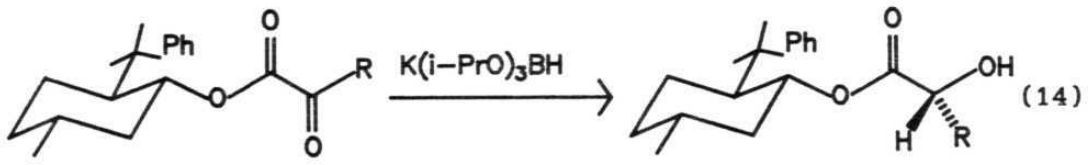


68



Reduction of α-keto esters:

Optically active α-hydroxy esters/acids are also synthesized by enantioselective reduction of α-keto esters. Whitesell *et al.*[95] reported the preparation of α-hydroxy esters in high diastereoselectivity *via* the reduction of α-keto esters **69,70** by metal hydrides (eq.14).

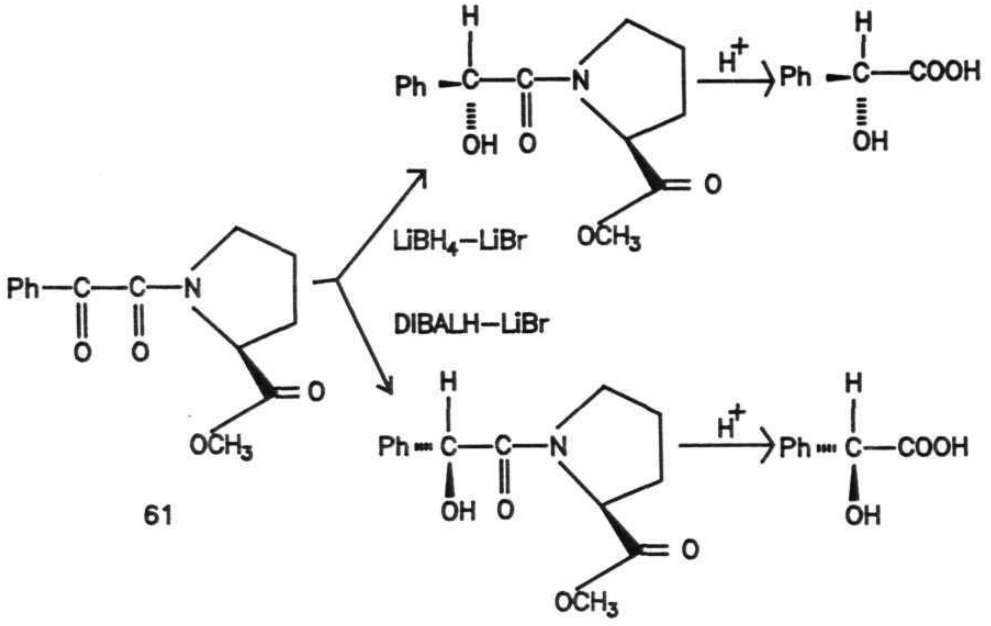


(14)

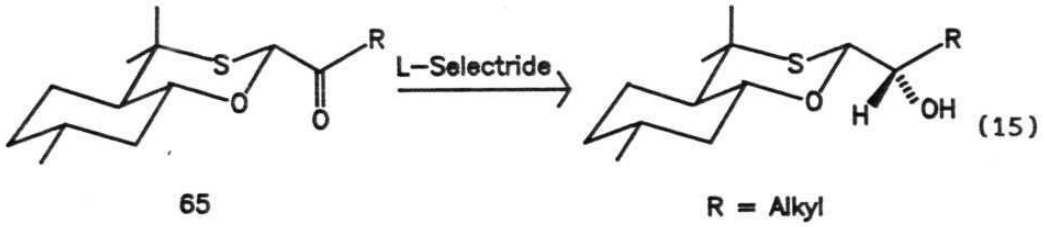
R = Ph 69
CH_3 70

α-Keto amide **61**, derived from (S)-proline,[96] was reduced diastereoselectively to provide α-hydroxy acid in good optical purity (Scheme 27).

SCHEME 27



Reduction of α-keto 1,3-oxathianes[97] **65** with metal hydrides provides α-hydroxy derivatives in high enantiomeric purities (eq.15).

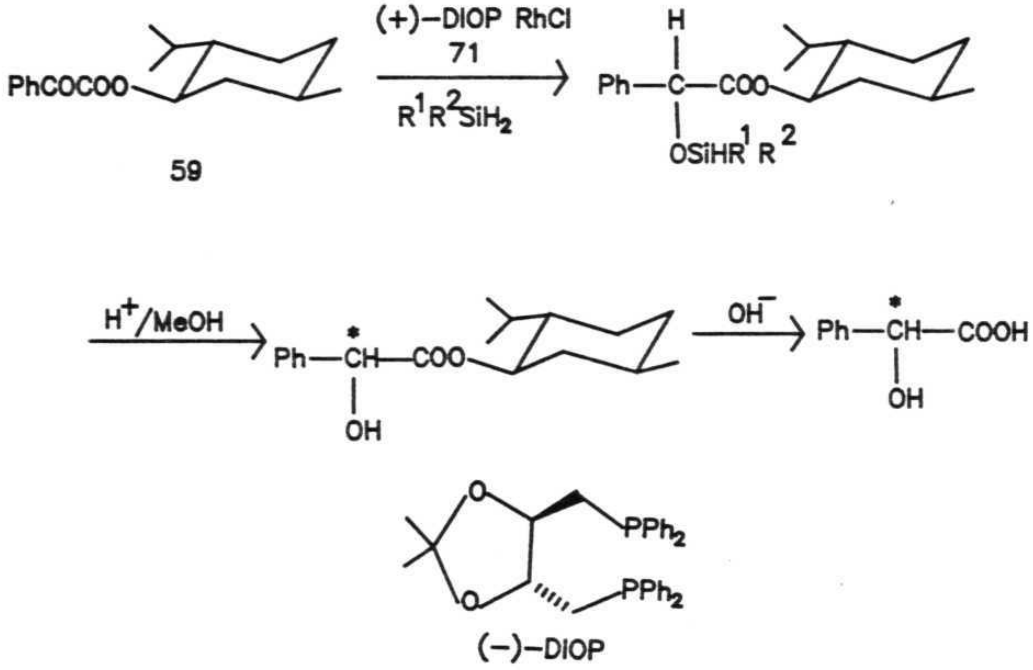


(15)

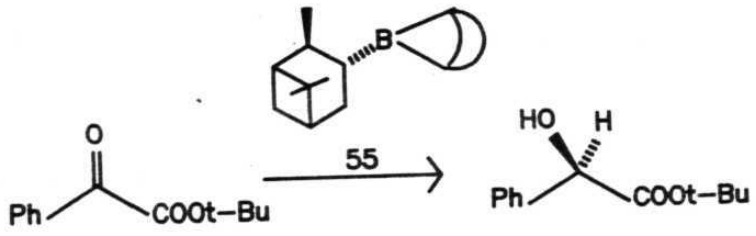
Rhodium complexes of chiral phosphine (**71**) catalyzes hydrosilylation of α-keto ester to provide α-hydroxy acids in good

enantiomeric purities[98]. The use of menthol as a chiral directing group in the double asymmetric induction facilitates the reaction to provide α-hydroxy acids in high optical purities (Scheme 28).

SCHEME 28.



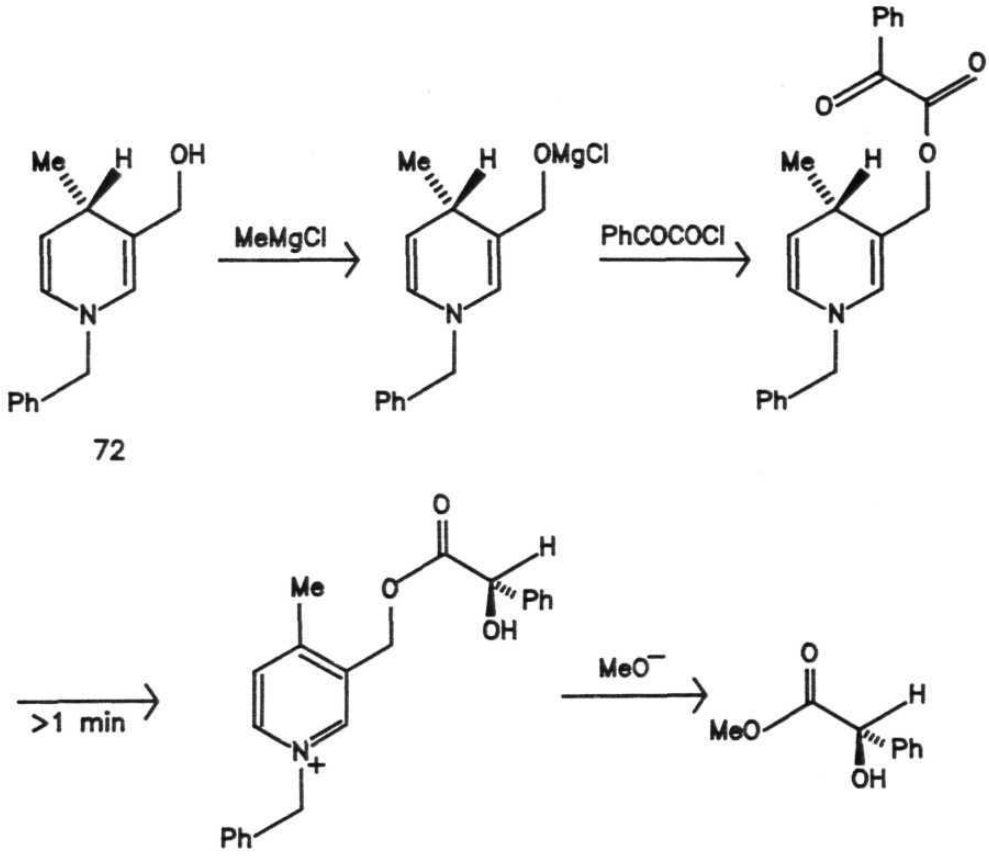
Brown *et al.*[99] reported a convenient synthesis of optically pure α-hydroxy ester *via* reduction of α-keto ester with B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (**55**) (eq.16).



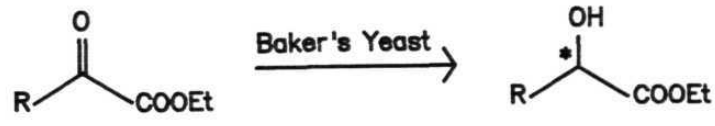
(16)

Meyers *et al.*[100] reported an elegant synthesis of methyl mandelate in 99% optical purity by utilizing an NADH mimic reagent **72** (Scheme 29).

SCHEME 29



Reduction of α-keto esters with Baker's yeast[71,101] provides α-hydroxy esters in high enantiomeric purities (eq.17).

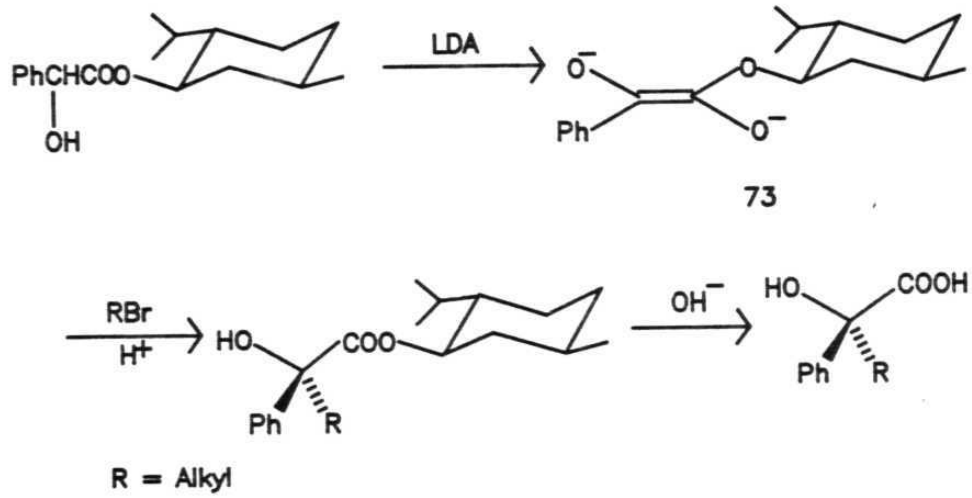


(17)

R = Aryl

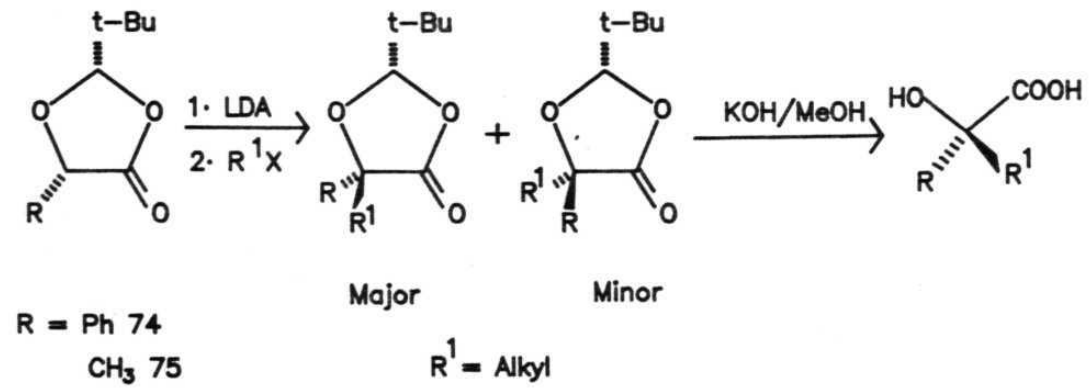
α-Alkylmandelic acids[102] were obtained in moderate stereoselectivities by alkylation of (-)-menthyloxyenediolates (**73**) (Scheme 30).

SCHEME 30



α-Alkylation of 2-substituted 1,3-dioxolan-4-ones[103] **74,75** derived from mandelic acid and lactic acid provides α-hydroxy acids in moderate enantiomeric purities (Scheme 31).

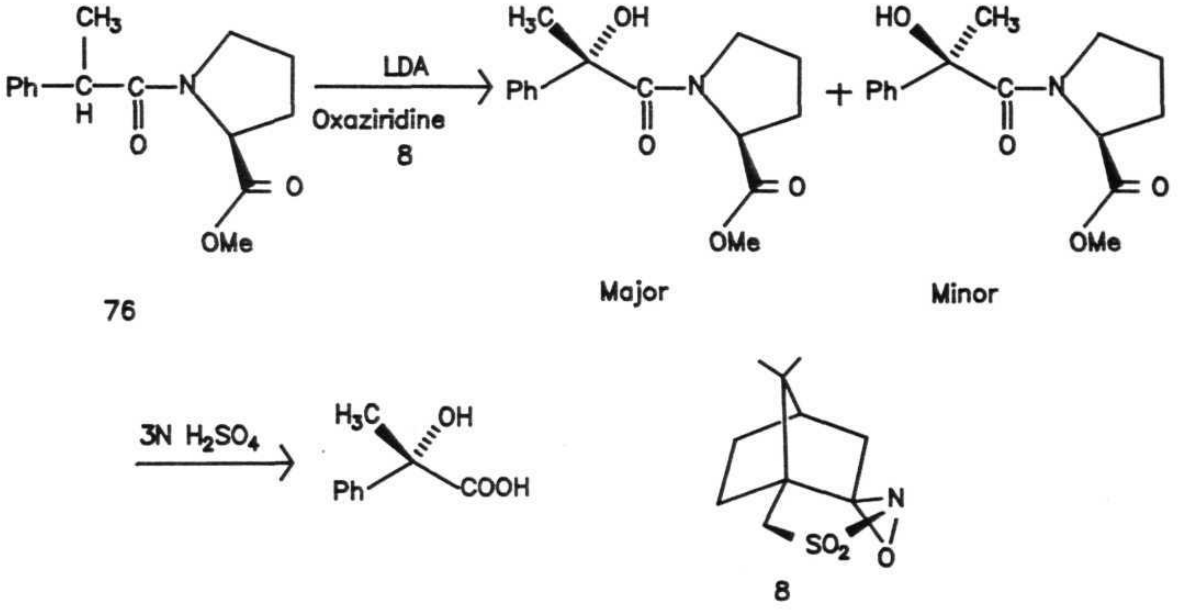
SCHEME 31



Other methods:

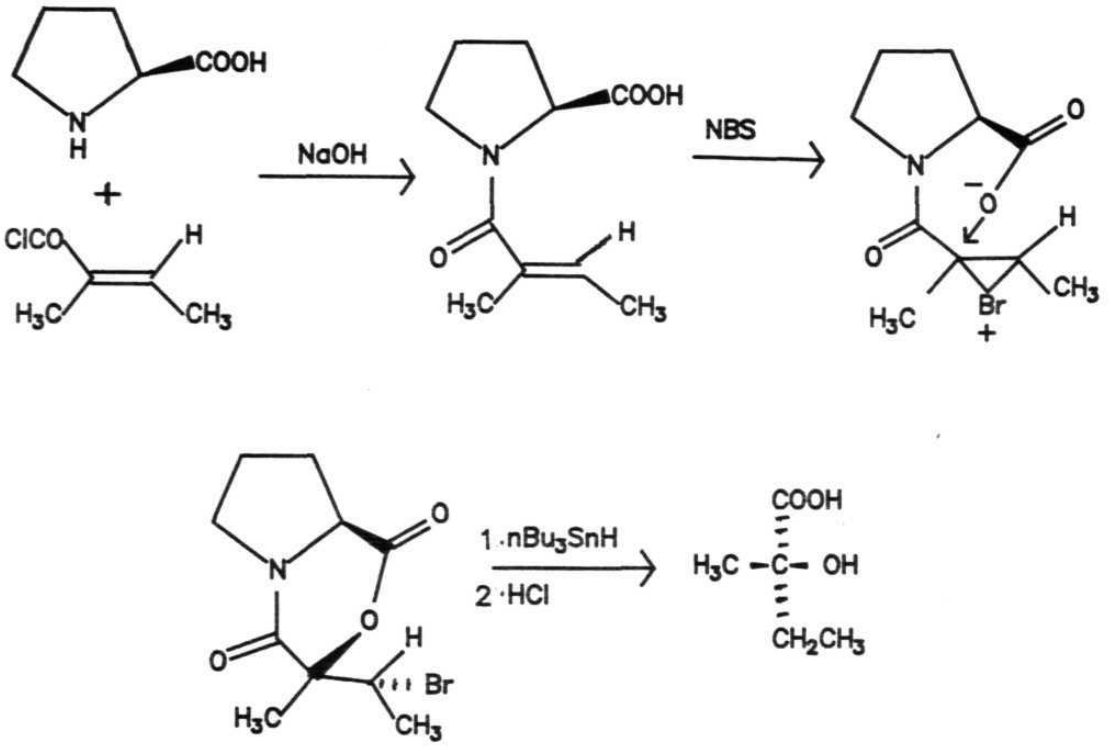
Davis *et al.*[13,104] obtained the atrolactic acid in high optical purity by the direct oxidation of chiral amide **76** enolates using oxaziridine **8** (Scheme 32).

SCHEME 32



Halolactonization[105] method was efficiently used for synthesizing chiral α-hydroxy acids by Terashima and co-workers using (S)-proline as the chiral auxiliary (Scheme 33).

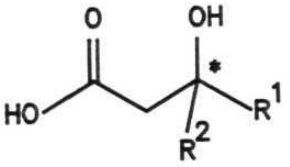
SCHEME 33


COOH
N
H
+
ClCO
H
H3C
CH3
NaOH
COOH
N
O
H
H3C
CH3
NBS
O
N
O
H
O
H3C
Br
CH3
+
O
N
O
O
H
O
H3C
Br
CH3
1 ·nBu3SnH
2 ·HCl
COOH
H3C
C
OH
CH2CH3

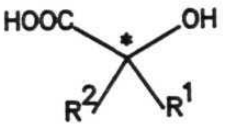
OBJECTIVES, RESULTS AND DISCUSSION

OBJECTIVES:

From the preceeding section it is quite clear that several chiral auxiliaries and chiral reagents have been developed for the synthesis of enantiomerically pure molecules. A number of synthetic strategies have been reported for the preparation of optically active α- and β-hydroxy acids which are chiral building blocks for the synthesis of biologically active molecules. However, application of the well known Reformatsky reaction for the preparation of β-hydroxy acids in high enantiomeric purity has not been studied in great detail. Very few reports are



77



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available on the utilization of Reformatsky reaction for the preparation of chiral β-hydroxy acids. We have, therefore, undertaken this research program with the main aim of developing suitable chiral zinc Reformatsky reagents using easily accessible chiral auxiliaries to provide a simple synthesis of β-hydroxy

acids in high optical purities. For this purpose, we have planned

1. to utilize easily and abundantly available lactic acid derivatives as chiral auxiliaries for the preparation of β-hydroxy acids,
2. to employ trans-2-phenylcyclohexan-1-ol and structurally similar trans-2-phenoxycyclohexan-1-ol as chiral auxiliaries for the preparation of β-hydroxy acids.

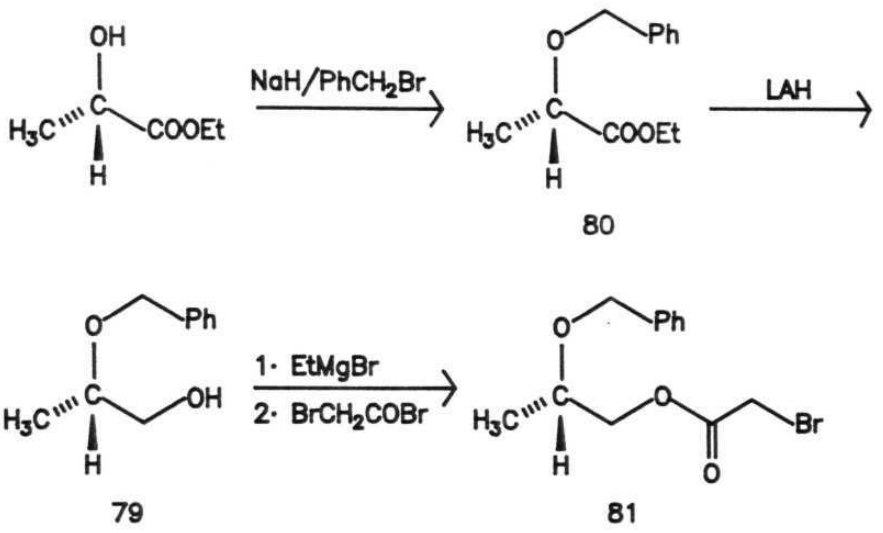
Our objective also includes the study of the possible applications of trans-2-phenylcyclohexan-1-ol and trans-2-phenoxy-cyclohexan-1-ol as chiral auxiliaries for the synthesis of chiral α-hydroxy acids.

RESULTS AND DISCUSSION:

β-Hydroxy acids : Towards chiral Reformatsky reagents:

With the above objectives in mind, we first selected, lactic acid derivative, (S)-2-benzyloxypropan-1-ol (**79**) as chiral auxiliary for the preparation of optically active β-hydroxy acids. (S)-2-Benzyloxypropan-1-ol (**79**) was prepared according to the Scheme 34. Benzylation of (S)-ethyl lactate was carried out with benzyl bromide in the presence of NaH to provide the ethyl 2-O-benzyl-(S)-lactate (**80**), subsequent reduction with lithium aluminium hydride gave (S)-2-benzyloxypropan-1-ol (**79**), $[\alpha]_D^{24}$ = + 41.36 (c 1.85,$CHCl_3$), e.e 90% [Lit.[106] $[\alpha]_D$ = + 45.86 (c 6.4,

SCHEME 34

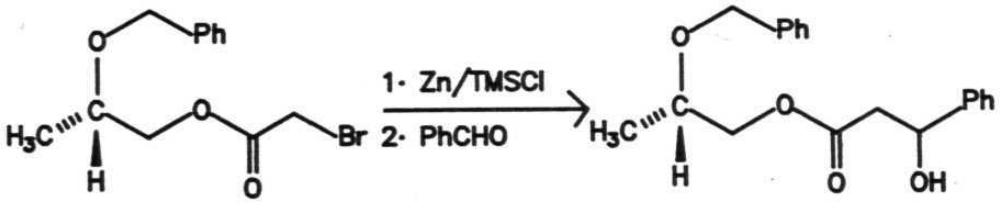


$CHCl_3$), e.e 99%, conf.S]. The structure of the compound **79** was confirmed by IR, ^1H NMR and ^{13}C NMR spectral data. Treatment of **79** with ethylmagnesium bromide followed by bromoacetyl bromide furnished the required chiral Reformatsky reagent (2-benzyloxy prop-1-yl) bromoacetate (**81**). The structure of this molecule **81** was established by IR, ^1H NMR and ^{13}C NMR data.

We carried out the reaction of (2-benzyloxyprop-1-yl) bromoacetate (**81**) with benzaldehyde in the presence of zinc, activated by trimethylchlorosilane,[107] to give the β-hydroxy ester **82**, which on hydrolysis with 2.5 N KOH/MeOH afforded 3-hydroxy-3-phenylpropionic acid (**77a**) (Scheme 35). The β-hydroxy acid **77a**, obtained, was found to be almost racemic indicating that there is

no chiral induction in this reaction. We reasoned that this may be due to the fact that the asymmetric centre is far off from the reaction site. A mention should be made here that the alcohol **79** prepared was only 90% optically pure. Since the chiral Reformatsky reaction provided the β-hydroxy acid in racemic form, we have not attempted to prepare this molecule in optically pure form.

SCHEME 35

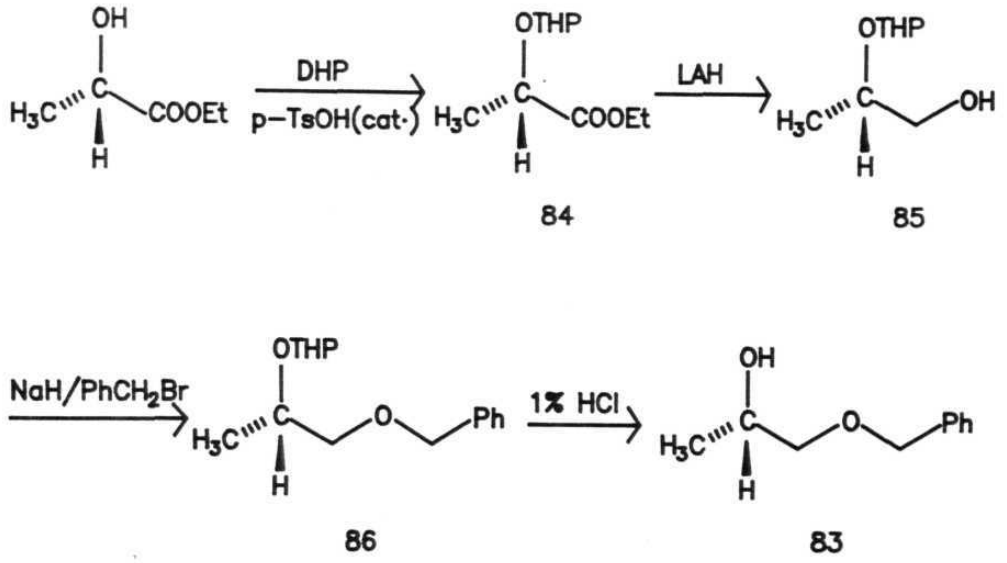


81 **82**

77a (±)

We, then selected the (S)-1-benzyloxypropan-2-ol (**83**), as a chiral auxiliary, where the chiral centre is relatively near to the reaction site. The chiral auxiliary, (S)-1-benzyloxypropan-2-ol (**83**) was prepared according to the Scheme 36.

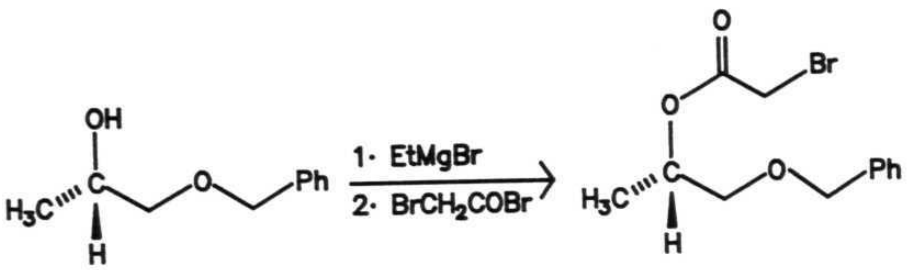
SCHEME 36



Hydroxy group of the (S)-ethyl lactate was protected as THP ether **84** by treatment with dihydropyran in the presence of cat. amount of p-TsOH. Ethyl O-tetrahydropyranyl-(S)-lactate (**84**) was reduced with LAH to provide 2-O-tetrahydropyranyl-(S)-propane-1,2-diol (**85**). Benzylation of **85** was carried out with benzyl bromide in the presence of NaH to give 1-O-benzyl-2-O-tetrahydro-pyranyl-(S)-propane-1,2-diol (**86**). Subsequent cleavage of **86** with dil.HCl afforded (S)-1-benzyloxypropan-2-ol (**83**), $[\alpha]_D^{24}$ = + 12.16 (c 9.38, $CHCl_3$), e.e 99% [Lit.[108] $[\alpha]_D^{25}$ = + 11.0 (c 2, $CHCl_3$), e.e 90%, conf.S]. The structure of this molecule **83** was confirmed by IR, ^1H NMR and ^{13}C NMR spectral data.

The corresponding bromoacetate, (1-benzyloxyprop-2-yl)

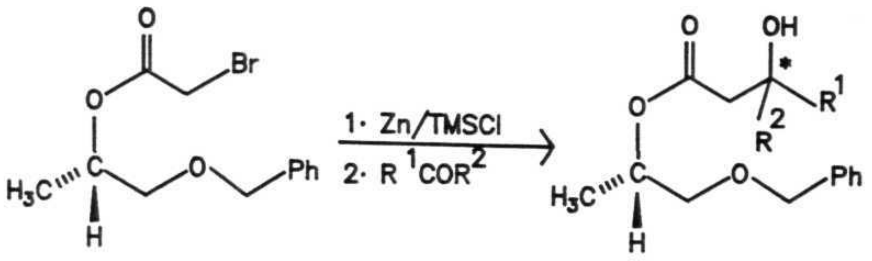
bromoacetate (**87**) was prepared by the action of bromoacetyl bromide on (S)-1-benzyloxypropan-2-ol (**83**) (eq.18). The structure of **87** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.



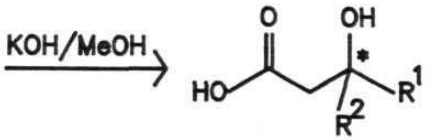
83 **87** (18)

Subsequent zinc Reformatsky reaction of (1-benzyloxyprop-2-yl) bromoacetate (**87**) with benzaldehyde provided the corresponding β-hydroxy ester **88** (R^1 = Ph, R^2 = H), which on hydrolysis with KOH/MeOH furnished the 3-hydroxy-3-phenylpropionic acid (**77a**) (Scheme 37) in 25% optical purity, $[\alpha]_D^{24}$ = + 4.38 (c 3.68, EtOH), conf.R [Lit.[53] $[\alpha]_D^{25}$ = + 17.9 (c 2.3, EtOH), e.e 100%, conf.R]. This result was encouraging. Therefore, the same reaction was extended to acetophenone. The corresponding 3-hydroxy-3-phenyl butanoic acid (**77b**) (Scheme 37) was obtained in 12% optical purity, $[\alpha]_D^{24}$ = - 1.2 (c 6.6, EtOH), conf.R [Lit.[49] $[\alpha]_D^{23}$ = + 6.0 (c 3, EtOH), e.e 58%, conf.S]. Though these results are encouraging, still the optical purities are not satisfactory.

SCHEME 37



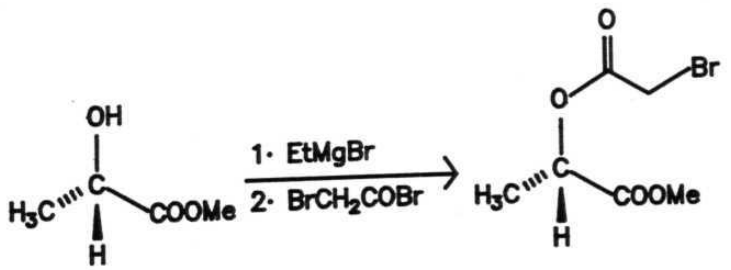
87 88



77a,77b

R^1	R^2	e·e %
Ph	H	25
Ph	CH_3	12

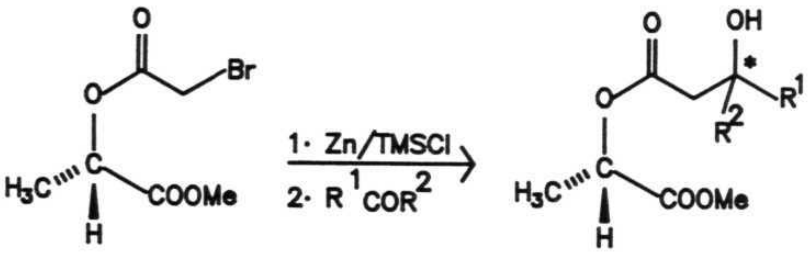
At this stage, we thought of directly using (S)-methyl lactate (89) as chiral auxiliary. The required chiral Reformatsky reagent, (S)-methyl 2-(bromoacetoxy)propionate (90) was easily prepared by the action of bromoacetyl bromide on (S)-methyl lactate (eq.19). The structure of the compound 90 was confirmed by IR, ^1H NMR (Fig.1) and ^{13}C NMR (Fig.2) spectral data.



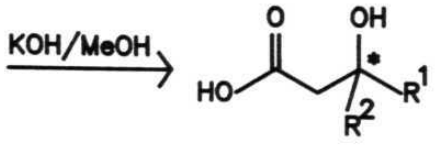
89 90 (19)

Reaction of **90**, with benzaldehyde in the presence of activated zinc (using trimethylchlorosilane) provided the corresponding β-hydroxy ester **91** (R^1 = Ph, R^2 = H), which on hydrolysis with 2.5 N KOH/MeOH furnished (R)-3-hydroxy-3-phenyl propionic acid (**77a**), after two crytallizations from hexane-ether mixture, in 100% optical purity, $[\alpha]_D^{24}$ = + 18 (c 0.5, EtOH) [Lit.[53] $[\alpha]_D^{25}$ = + 17.9 (c 2.3, EtOH), e.e 100%, conf.R] and in 16% overall chemical yield (Scheme 38). We also carried out experiments with activated zinc obtained by other methods such as 1. Zn-Cu couple[109], 2. Rieke zinc[110] (reduction of $ZnCl_2$ with potassium), but there was no improvement in the chemical yield, however, the optical purity remains the same (100%).

SCHEME 38



90 **91**



77a–d

R^1	R^2	e·e %
Ph	H	100
Ph	CH_3	24
Ph	C_2H_5	11
$C_{11}H_{23}$	H	16

After obtaining 100% optical purity, with benzaldehyde as substrate, we have extended this reaction to acetophenone. The required 3-hydroxy-3-phenylbutanoic acid **77b**, was obtained in 24% optical purity, $[\alpha]_D^{24}$ = - 2.45 (c 3.5, EtOH), conf.R [Lit.[49] $[\alpha]_D^{23}$ = + 6.0 (c 3, EtOH), e.e 58%, conf.S] and the chemical yield was also very low (13%). The same reaction when applied to propiophenone, the corresponding β-hydroxy acid, 3-hydroxy-3-phenylpentanoic acid (**77c**) was obtained in 11% optical purity, $[\alpha]_D^{24}$ = - 2.85 (c 1.05, EtOH), conf.R [Lit.[49] $[\alpha]_D^{23}$ = + 15.0 (c 3, EtOH), e.e 58%, conf.S]. We have also studied the reaction of an aliphatic aldehyde i.e., dodecanal with the chiral Reformatsky reagent **90**. Here again the desired 3-hydroxytetradecanoic acid (**77d**) was obtained in 16% optical purity, $[\alpha]_D^{24}$ = - 2.6 (c 2.3, $CHCl_3$), conf.R [Lit.[68] $[\alpha]_D^{20}$ = - 16.2 (c 1, $CHCl_3$), e.e 100%, conf.R] and in very low chemical yield (6%). It appeared to us that the **reagent 90** may be more specific to benzaldehyde. All these results were tabulated in Table 1 (Scheme 38).

Since the (S)-1-benzyloxypropan-2-ol (**83**) gave some encouraging results, we thought that structural modification of the chiral auxiliary in the Reformatsky reaction may provide better optical induction. Accordingly, we have selected (S)-1-phenoxypropan-2-ol (**92**) and (S)-1-(2-naphthyloxy)propan-2-ol (**93**) as the chiral auxiliaries.

Table 1 : Preparation of β-hydroxy acids *via* Reformatsky reaction using derivatives of lactic acid.[a,b]

Reagent	Carbonyl compound	Time hrs	Product	Overall Yield(%)[c]	$[\alpha]_D^{24}$ (c,EtOH)	E.e % Abs conf
81	Benzaldehyde	4	**77a**	25	negligible	almost racemic
87	Benzaldehyde	4	**77a**	30	+ 4.38(3.68)	25(R)[d]
87	Acetophenone	5	**77b**	39	- 1.2(6.6)	12(R)[e]
90	Benzaldehyde	2	**77a**	16	+ 18(0.5)	100(R)[d]
90	Acetophenone	4	**77b**	13	- 2.45(3.5)	24(R)[e]
90	Propiophenone	7	**77c**	7	- 2.85(1.05)	11(R)[f]
90	Dodecanal	5	**77d**	6	- 2.6(2.3, $CHCl_3$)	16(R)[g]

a. All reactions were carried out on 15 mM scale in refluxing benzene.

b. All products were identified spectroscopically by IR, ^1H NMR and ^{13}C NMR.

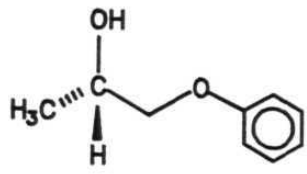
c. Overall yields of the pure crystallized product based on the carbonyl compound.

d. Based on $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R (Ref.53).

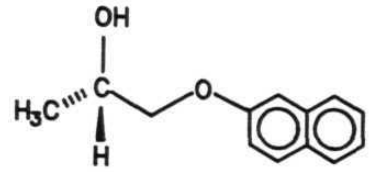
e. Based on $[\alpha]_D^{23}$ + 6.0 (c 3, EtOH), e.e 58%, conf.S (Ref.49).

f. Based on $[\alpha]_D^{23}$ + 15.0 (c 3, EtOH), e.e 58%, conf.S (Ref.49).

g. Based on $[\alpha]_D^{20}$ - 16.2 (c 1, $CHCl)_3$, e.e 100%, conf.R (Ref.68).



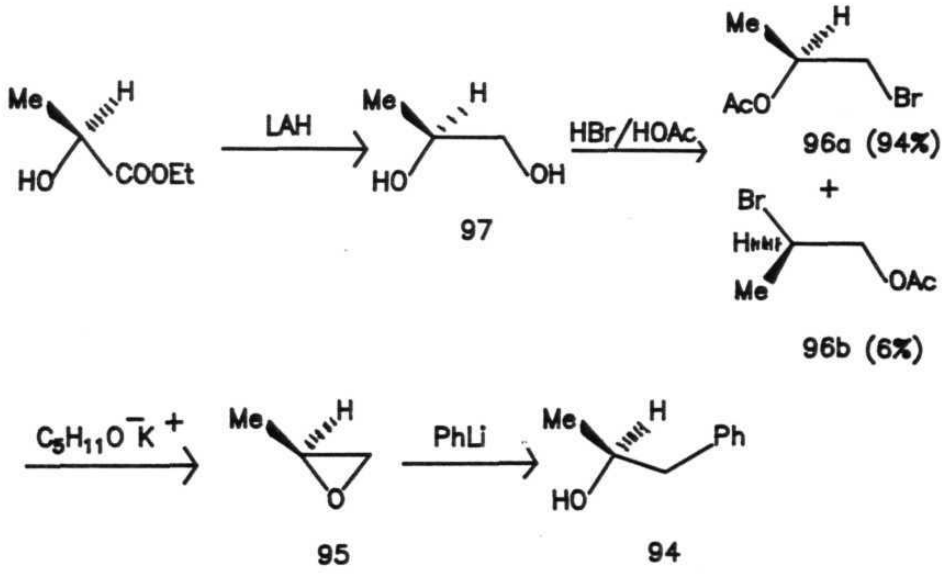
92



93

Golding and co-workers[111] reported the synthesis of (S)-1-phenylpropan-2-ol (**94**) by the action of phenyl lithium on (S)-propylene oxide (**95**), according to the Scheme 39.

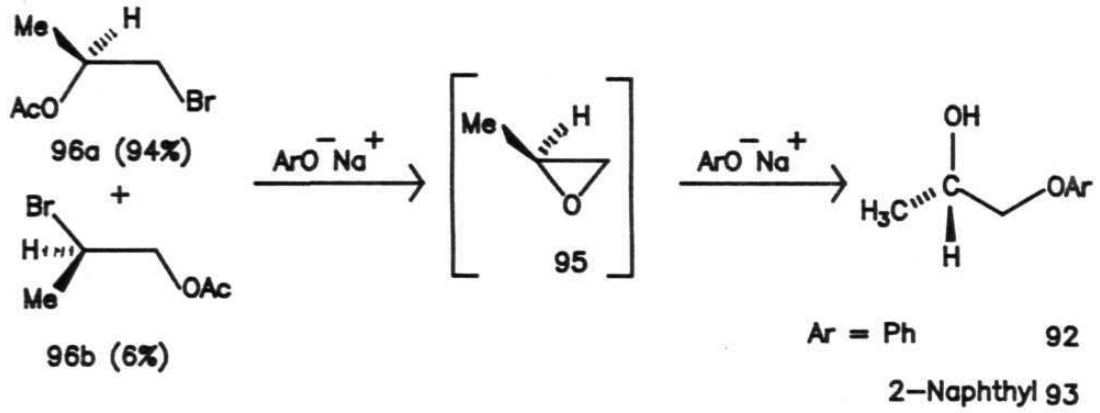
SCHEME 39



It appeared to us that treatment of the (S)-2-acetoxy-1-bromopropane (**96a**) (along with 6% isomeric impurity **96b**) with sodium aryloxides may provide directly the required 1-aryloxy-

propan-2-ols *via* propylene oxide (**95**) as shown in Scheme 40.

SCHEME 40

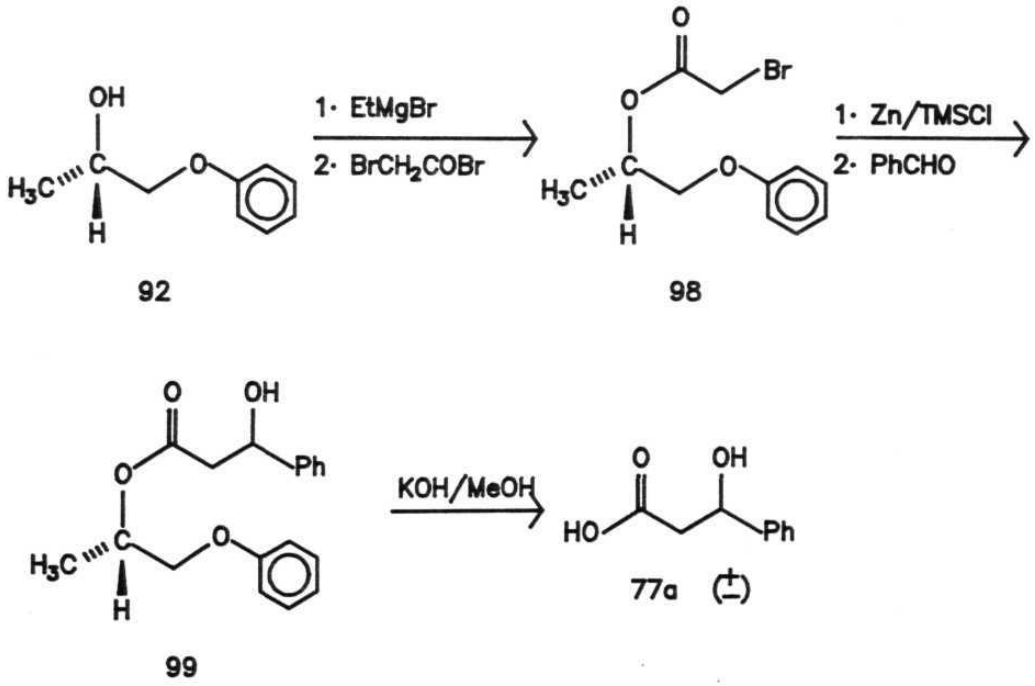


Accordingly, reduction of (S)-ethyl lactate with LAH was carried to furnish (S)-propane-1,2-diol (**97**), $[\alpha]_D^{24}$ = + 20.5 (c 0.96, H_2O) [Lit.[111] $[\alpha]_D^{20}$ = + 20.7 (c 7.5, H_2O), e.e >99%, conf.S]. The diol **97** on treatment with HBr/HOAc gave (S)-2-acetoxy-1-bromo-propane (**96a**), after distillation (b.p 74-76°C/20 mm), as liquid $[\alpha]_D^{24}$ = - 13.50 (c 0.81, $CHCl_3$) [Lit.[111] $[\alpha]_D^{23}$ = - 13.55 (c 5.8, $CHCl_3$), conf.S] (Scheme 39). Treatment of (S)-2-acetoxy-1-bromo propane (**96a**) with two equivalents of sodium phenoxide (prepared insitu from phenol and NaOH) furnished the desired alcohol, (S)-1-phenoxypropan-2-ol (**92**) $[\alpha]_D^{24}$ = + 22.66 (c 1.5, $CHCl_3$) as a colourless liquid in 32% chemical yield. Our attempts to improve the chemical yield by using excess sodium phenoxide did not result in success. The structure of the compound **92** was established by

IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.

The required bromoacetate, (1-phenoxyprop-2-yl) bromoacetate (**98**) was prepared by the action of bromoacetyl bromide on (S)-1-phenoxypropan-2-ol (**92**) (Scheme 41). The structure of the compound **98** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. The Reformatsky reaction of **98** with benzaldehyde in the presence of activated zinc furnished β-hydroxy ester **99**, which on hydrolysis afforded 3-hydroxy-3-phenylpropionic acid (**77a**) in racemic form (Scheme 41).

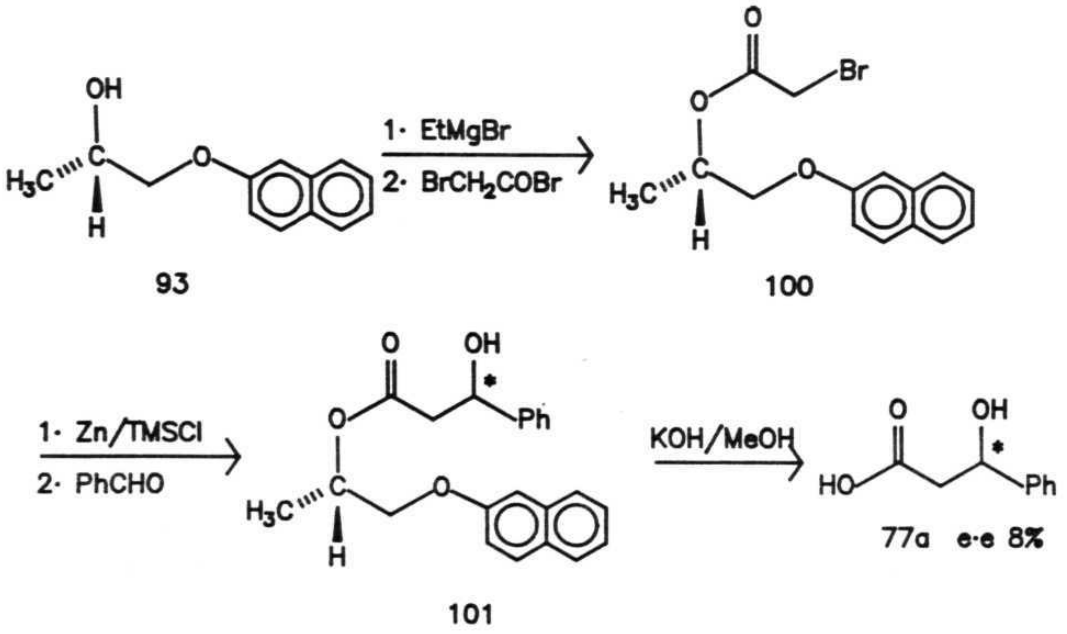
SCHEME 41



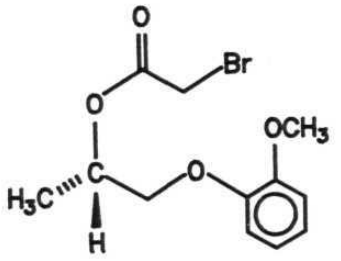
The reaction of two equivalents of sodium 2-naphthoxide

(prepared insitu from 2-naphthol and NaOH) with (S)-2-acetoxy-1-bromopropane (**96a**) provided (S)-1-(2-naphthyloxy)propan-2-ol (**93**) in 33% chemical yield as a crystalline solid, m.p. 84-86°C, $[\alpha]_D^{24}$ = + 17.12 (c 1.46, $CHCl_3$) (Scheme 40). The structure of this molecule **93** was in agreement with IR, ^1H NMR, ^{13}C NMR (Fig.3) spectral data and elemental analysis. The Reformatsky reagent [1-(2-naphthyloxy)prop-2-yl] bromoacetate (**100**) was prepared by treating the alcohol **93** with bromoacetyl bromide (Scheme 42). The structure of the compound **100** was confirmed by IR, ^1H NMR and ^{13}C NMR spectral data. We have subjected the bromoacetate **100**, to zinc Reformatsky reaction with benzaldehyde (Scheme 42). The β-hydroxy ester **101**, obtained, was hydrolyzed to provide 3-hydroxy-3-phenylpropionic acid (**77a**) in 8% optical purity.

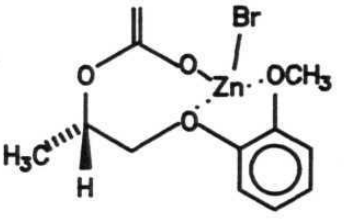
SCHEME 42



The chiral auxiliaries **92** and **93** fail to provide satisfactory levels of chiral induction. At this stage it appeared to us that the introduction of oxygen atom in the phenyl group, may help in obtaining good optical induction in the Reformatsky reaction of bromo ester **102** *via* its coordination with zinc as shown in **103**.

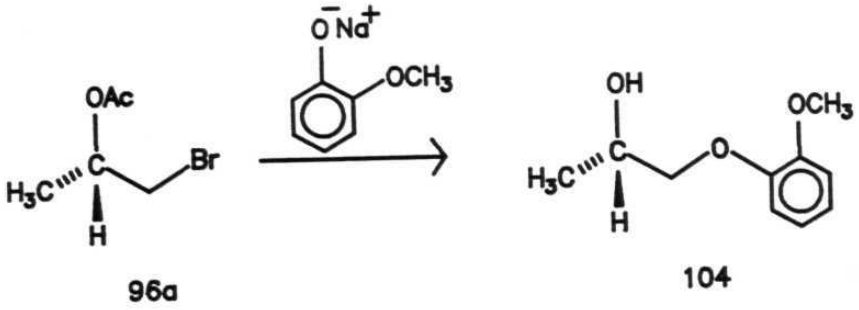


102



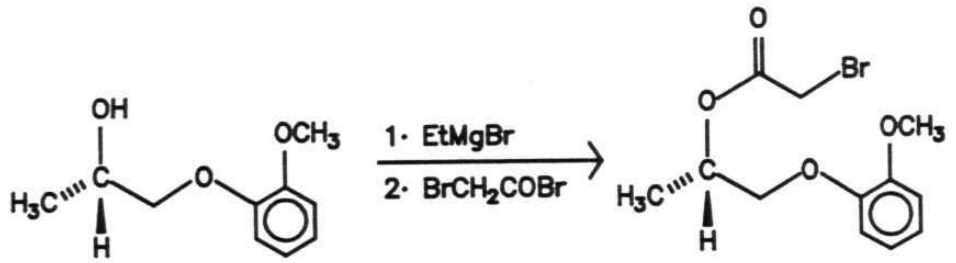
103

Accordingly, we have utilized (S)-1-(2-methoxyphenoxy)-propan-2-ol (**104**) as chiral auxiliary. The alcohol **104** was prepared following the similar strategy as shown in the Scheme 40. Treament of (S)-2-acetoxy-1-bromopropane (**96a**) with two equivalents of sodium 2-methoxyphenoxide (prepared insitu from 2-methoxyphenol and NaOH) furnished the alcohol in 30% chemical yield (eq.20) as a colourless liquid, $[\alpha]_D^{24}$ = + 29.16 (c 1.2, $CHCl_3$). The structure of the compound **104** was confirmed by IR, ^1H NMR (Fig.4), ^{13}C NMR spectral data and elemental analysis.



96a 104 (20)

The Reformatsky reagent [1-(2-methoxyphenoxy)prop-2-yl] bromoacetate (**102**) was prepared by treating the alcohol **104**, with bromoacetyl bromide (eq.21). The structure of the compound **102** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

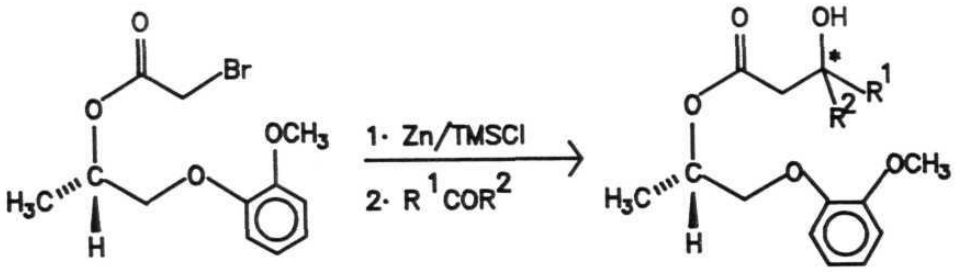


104 102 (21)

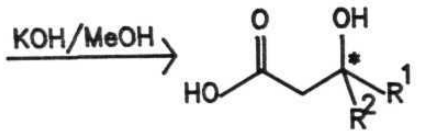
The subsequent zinc Reformatsky reaction of **102** with benzaldehyde furnished the β-hydroxy ester **105** (R^1 = Ph, R^2 = H), which on hydrolysis afforded the 3-hydroxy-3-phenylpropionic acid (**77a**) in 57% optical purity, $[\alpha]_D^{24}$ = + 10.32 (c 1.55, EtOH), conf.R [Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R] (Scheme 43). This reaction was encouraging. Therefore, the same reaction was extended to acetophenone. The resulting 3-hydroxy-3-phenylbutanoic acid (**77b**) (Scheme 43) was obtained in 12%

optical purity, $[\alpha]_D^{24}$ = - 1.25 (c 3.8, EtOH), conf.R [Lit.[49] $[\alpha]_D^{23}$ = + 6.0 (c 3, EtOH), e.e 58%, conf.S]

SCHEME 43



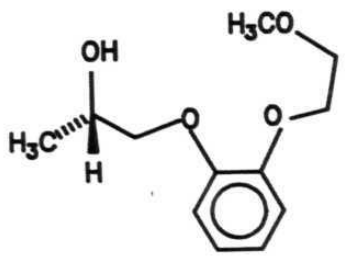
102 105



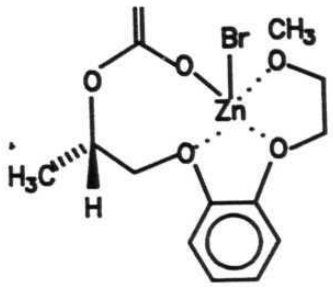
77a,77b

R^1	R^2	e·e %
Ph	H	57
Ph	CH_3	12

Next we have selected (S)-1-[o-(2-methoxyethoxy)phenoxy] propan-2-ol (**106**) as a chiral auxiliary with a view to study the effect of coordination of more oxygen atoms with zinc as shown in **107**. This alcohol **106** was prepared according to Scheme 44.

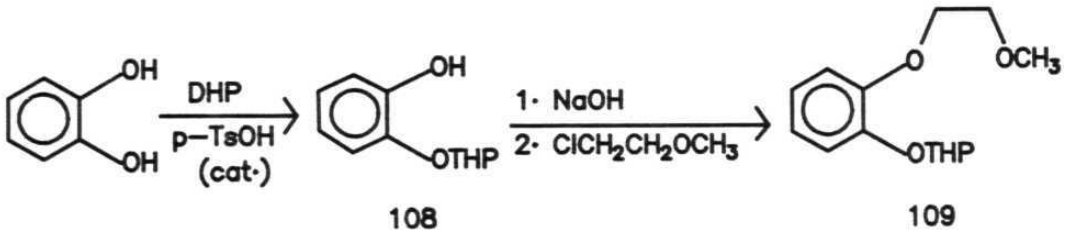


106

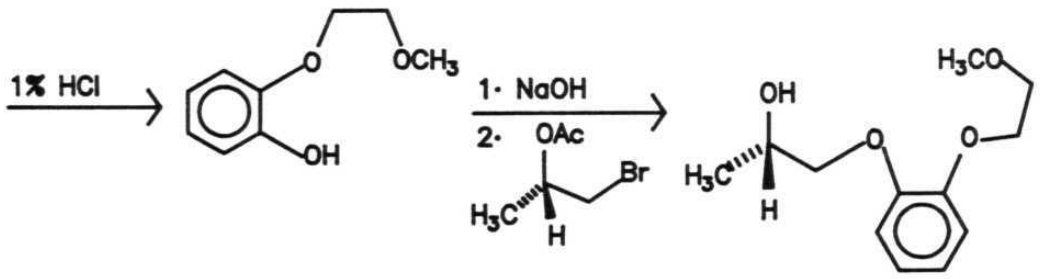


107

SCHEME 44



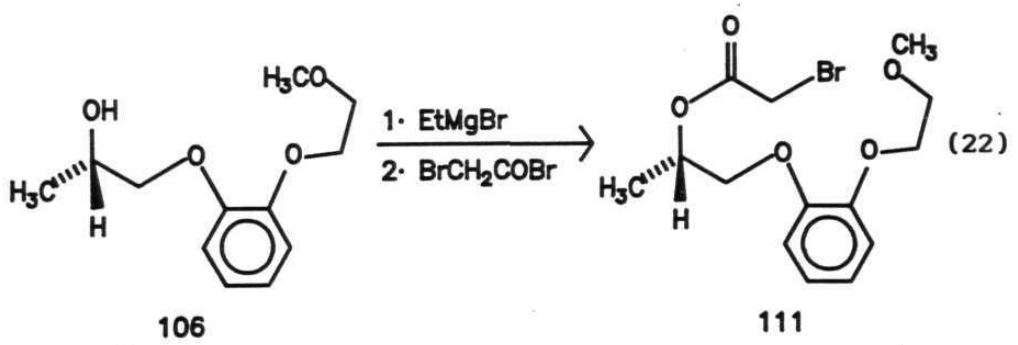
108 109



110 106

Catechol mono THP ether **108** was prepared by treating catechol with dihydropyran in the presence of cat. amount of p-TsOH. Alkylation of o-(tetrahydropyran-2-yloxy)phenol (**108**) with 2-methoxyethyl chloride in the presence of NaOH afforded

1-(2-methoxyethoxy)-2-(tetrahydropyran-2'-yloxy)benzene (**109**). Subsequent acid cleavage of **109** with dil.HCl furnished o-(2-methoxyethoxy)phenol (**110**). The structure of the compound **110** was confirmed by IR, ^{1}H NMR, ^{13}C NMR (Fig. 5) spectral data. The chiral moiety was introduced by treating two equivalents of sodium o-(2-methoxyethoxy)phenoxide with (S)-2-acetoxy-1-bromopropane (**96a**) to provide (S)-1-[o-(2-methoxyethoxy)phenoxy]propan-2-ol (**106**) in 22% chemical yield, $[\alpha]_D^{24}$ = + 10.9 (c 1.1, MeOH). The structure of the compound **106** was confirmed by IR, ^{1}H NMR (Fig. 6), ^{13}C NMR spectral data and elemental analysis. The bromoacetate **111** was prepared by the action of bromoacetyl bromide on the alcohol **106** (eq.22). The structure of the molecule **111** was confirmed by IR, ^{1}H NMR and ^{13}C NMR (Fig. 7) spectral data.

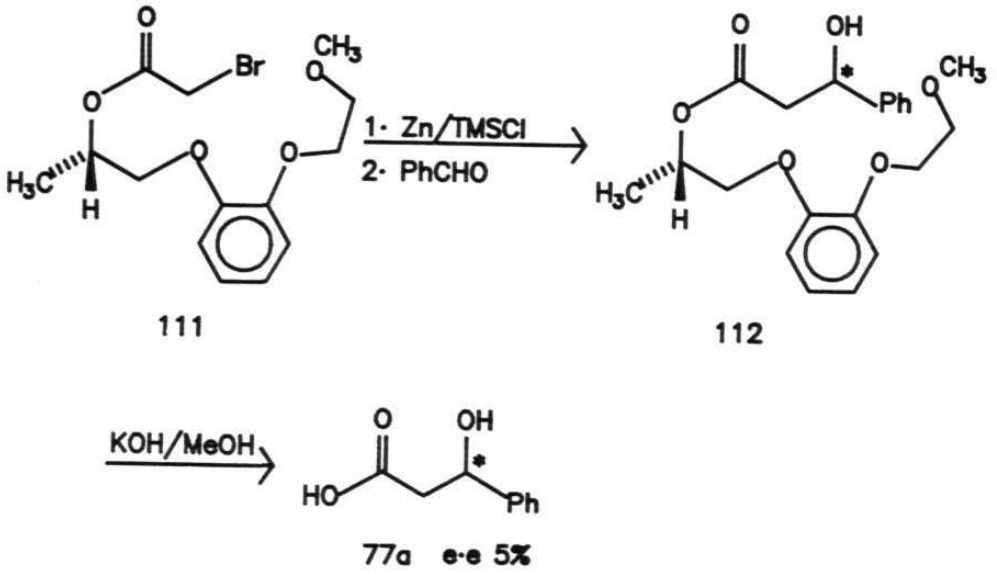


106 **111** (22)

The zinc Reformatsky reaction of bromoacetate **111** with benzaldehyde provided the β-hydroxy ester **112** which on hydrolysis

gave 3-hydroxy-3-phenylpropionic acid **77a** in 5% optical purity and

SCHEME 45



111 112

77a e·e 5%

in low chemical yield (Scheme 45) (Table 2). The failure of this reaction indicates that more oxygen atoms coordination with zinc fail to provide satisfactory chiral induction. Since the chiral auxiliaries **92, 93, 104, 106** did not offer satisfactory results for the preparation of β-hydroxy acids, we did not attempt to synthesize these chiral auxiliaries in good chemical yields.

After attempting the synthesis of chiral β-hydroxy acids with lactic acid derivatives as chiral auxiliaries, we have then turned our attention towards utilization of trans-2-phenylcyclo hexanol as chiral auxiliary.

Table 2: Preparation of β-hydroxy acids *via* Reformatsky reaction using 1-aryloxyprop-2-yl bromoacetates.[a,b]

Reagent	Carbonyl compound	Time hrs	Product	Overall yield[c]%	$[\alpha]_D^{24}$ (c EtOH)	E.e% Abs Conf.
98	Benzaldehyde	2	**77a**	45	--	racemic
100	Benzaldehyde	2	**77a**	30	+1.42 (2.1)	8(R)[d]
102	Benzaldehyde	2	**77a**	35	+10.32(1.55)	57(R)[d]
102	Acetophenone	2	**77b**	25	-1.25(3.8)	12(R)[e]
111	Benzaldehyde	2	**77a**	10	+0.9 (1.95)	5(R)[d]

a. All reactions were carried out on 15 mM scale in refluxing benzene.

b. All products were identified spectroscopically by IR, ^{1}H NMR and ^{13}C NMR.

c. Overall yields of the pure crystallized product based on the carbonyl compound.

d. Based on $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R) (Ref.53).

e. Based on $[\alpha]_D^{23}$ + 6.0 (c 3, EtOH), e.e 58%, conf. S) (Ref. 49).

trans-2-Phenylcyclohexan-1-ol as chiral auxiliary:

Preparation of β-hydroxy acids:

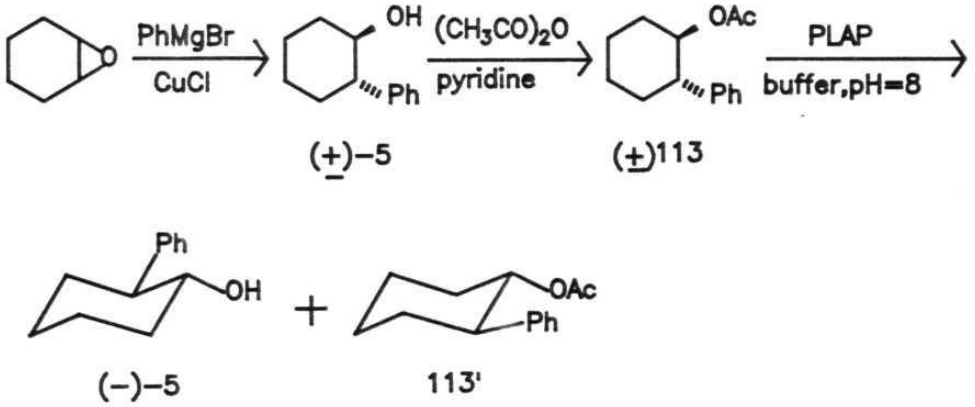
trans-2-Phenylcyclohexanol, the Whitesell auxiliary, has shown to provide exceptional levels of asymmetric induction in a number of reactions such as ene reaction,[112] asymmetric cycloaddition,[113] in the resolution of racemic hydroperoxides[114] and in Pauson-Khand cyclization[115].

Whitesell[10] has demonstrated that this molecule trans-2-phenylcyclohexan-1-ol (**5**) with its diastereoselective face discriminating phenyl group is as effective as 8-phenylmenthol (**4**). With a view to achieve high induction in Reformatsky reaction, we planned to use trans-2-phenylcyclohexan-1-ol (**5**) as a chiral auxiliary in the Reformatsky reaction. Accordingly, we have prepared the chiral trans-2-phenylcyclohexan-1-ol in both (-) and (+) forms (**(-)-5, (+)-5**) according to the Whitesell procedure[116] as shown in the Scheme 46 and Scheme 47.

Addition of phenylmagnesium bromide on cyclohexene oxide in the presence of catalytic amount of CuCl furnished racemic trans-2 phenylcyclohexan-1-ol (**(±)-5**). Acetylation of alcohol **(±)-5** with acetic anhydride afforded racemic trans-2-phenylcyclohex-1-yl acetate (**113**). Structures of both alcohol and acetate were

confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. The racemic trans-2-phenylcyclohexyl acetate (**113**) was subjected to enzymatic hydrolysis with crude pig liver acetone powder (PLAP)[117] in 0.5 M, pH = 8, aqueous KH_2PO_4/K_2HPO_4 buffer for 10 days (conversion ratio 35:65 determined by HPLC) to afford the optically pure (-) alcohol (-)-5, after column purification followed by two crystallizations from pentane as a crystalline solid, m.p. 63-65°C [Lit.[116] m.p 64-65°C] $[\alpha]_D^{24}$ = - 58.2 (c 0.84, MeOH), e.e >99% [Lit.[116] $[\alpha]_D^{27}$ = - 58.4 (c 10, MeOH), e.e 100%].

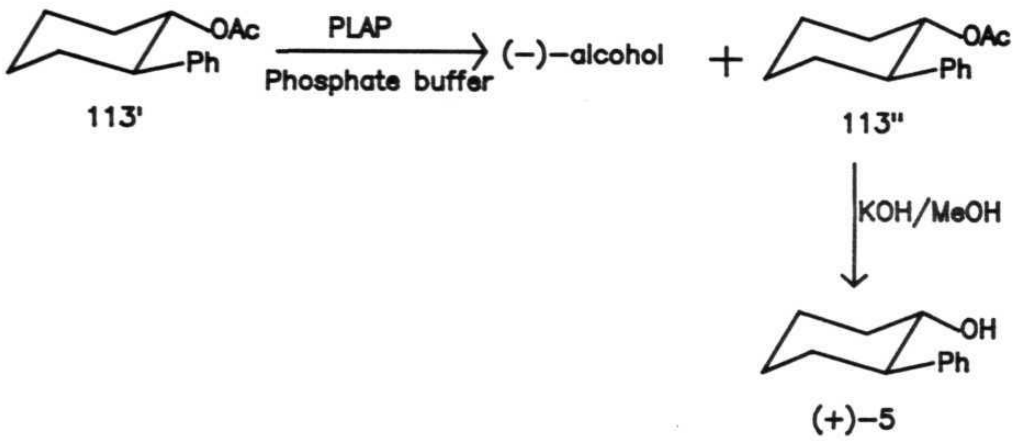
SCHEME 46



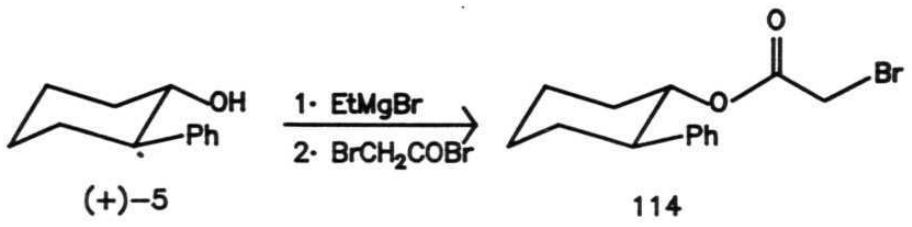
In order to obtain the pure (+)-trans-2-phenylcyclo hexan-1-ol ((+)-5), the recovered acetate of the (+) alcohol **113'** (obtained in Scheme 46) was again subjected to enzymatic hydrolysis with PLAP (Scheme 47). The acetate of the optically pure (+) alcohol **113''** thus obtained was hydrolyzed with KOH/MeOH

to furnish pure (+) alcohol **(+)-5**, after two crystallizations from pentane, m.p 63-65°C [Lit[116]. m.p 64-65°C] $[\alpha]_D^{24}$ = + 58.2 (c 0.95, MeOH), e.e >99% [Lit.[116] $[\alpha]_D^{27}$ = + 58.3 (c 10, MeOH), e.e 100%].

SCHEME 47



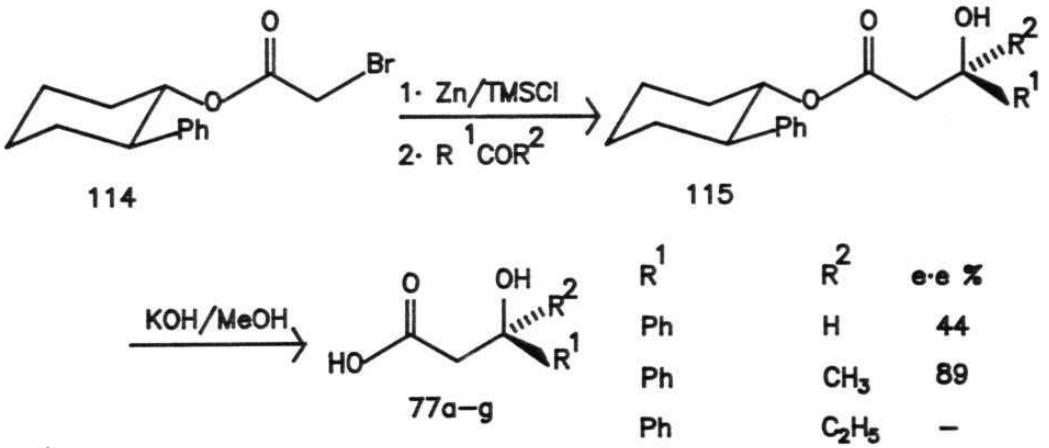
The required [(1S,2R)-2-phenylcyclohex-1-yl] bromoacetate (**114**) was prepared by treatment of (1S,2R)-2-phenylcyclo hexan-1-ol (**(+)-5**) with ethylmagnesium bromide and bromoacetyl bromide (eq.23). The compound **114** was obtained as a colourless liquid and the structure of the compound **114** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data and elemental analysis.



(23)

The zinc Reformatsky reaction of bromoacetate **114** with benzaldehyde afforded the β-hydroxy ester **115** (R^1 = Ph, R^2 = H), which on hydrolysis with KOH/MeOH gave (R)-3-hydroxy-3-phenyl propionic acid (**77a**) in 44% optical purity, $[\alpha]_D^{24}$ = + 7.87 (c 4.5, EtOH), conf.R [Lit.[53] $[\alpha]_D^{25}$ = + 17.9 (c 2.3, EtOH), e.e 100%, conf.R] (Scheme 48). We have extended the same sequence to acetophenone which provided the corresponding 3-hydroxy-3-phenyl butanoic acid (**77b**) in 89% optical purity, $[\alpha]_D^{24}$ = - 9.2 (c 5.18, EtOH), conf.R [Lit.[49] $[\alpha]_D^{23}$ = + 6.0 (c 3, EtOH), e.e 58%, conf.S]. We also employed propiophenone and dodecanal as substrates. The corresponding β-hydroxy acids **77c, 77d** were obtained in racemic form.

SCHEME 48



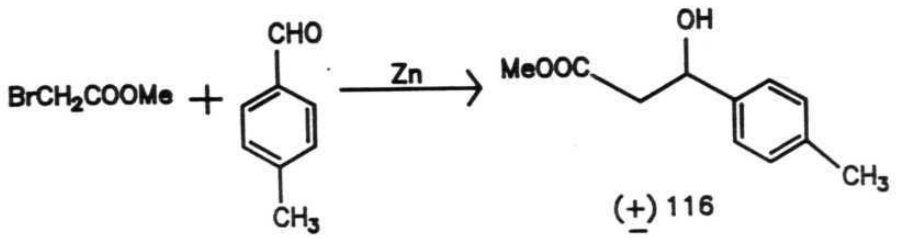
114 115 77a–g

R^1	R^2	e·e %
Ph	H	44
Ph	CH_3	89
Ph	C_2H_5	–
$C_{11}H_{23}$	H	–
p–Tolyl	H	31
1–Naphthyl	H	22
i–Pr	H	11

We, then selected two more aromatic aldehydes, p-tolualdehyde and 1-naphthaldehyde for the study. The resulting β-hydroxy acids i.e., 3-hydroxy-3-(p-tolyl)propionic acid (**77e**) and 3-hydroxy-3-(1-naphthyl)propionic acid (**77f**) were obtained in 31% and 22% optical purities respectively (Scheme 48). The optical rotations of these acids **77e, 77f** are not reported in literature, we have therefore determined their optical purities in the following manner.

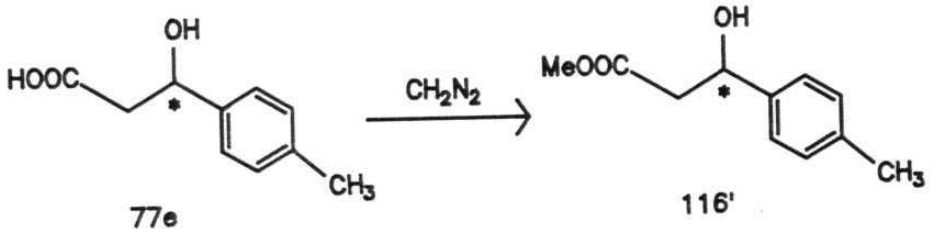
Determination of optical purity:

Racemic methyl 3-hydroxy-3-(p-tolyl)propionate (**116**) was prepared *via* the reaction of methyl bromoacetate with p-tolualdehyde in the presence of zinc (eq.24). Examination of the ^{1}H NMR spectrum shows a singlet for -$COOCH_3$ protons at δ 3.64. The same singlet appeared as two singlets of equal intensities in ^{1}H NMR spectrum of **116** in the presence of chiral shift reagent, $Eu(hfc)_3$, thus indicating that the two singlets arise from two enantiomers.



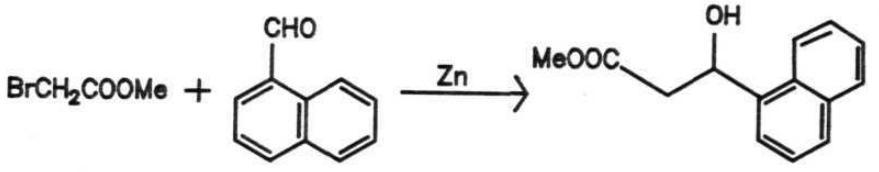
(24)

We have then converted the chiral β-hydroxy acid i.e., 3-hydroxy-3-(p-tolyl)propionic acid (**77e**) to methyl ester **116'** by treating with diazomethane (eq.25). ^1H NMR spectrum of chiral methyl 3-hydroxy-3-(p-tolyl)propionate (**116'**) in the presence of shift reagent, $Eu(hfc)_3$, showed two singlets for $-COOCH_3$ protons in the ratio of 7.6:4.0, indicating that the product is 31% optically pure.

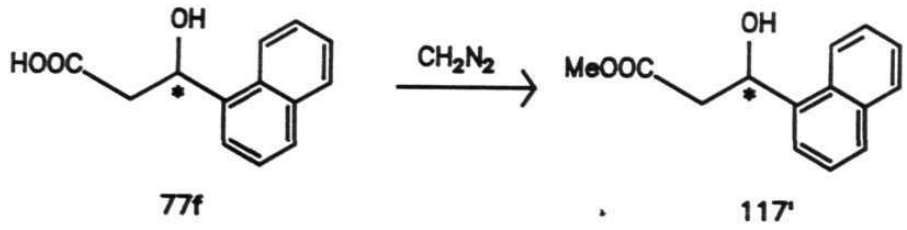


77e 116' (25)

Racemic methyl 3-hydroxy-3-(1-naphthyl)propionate **117** and chiral methyl 3-hydroxy-3-(1-naphthyl)propionate **117'** were prepared according to the eq.26 and eq.27 respectively. The optical purity was determined following the same strategy as in the case of **77e** and was found to be 22% optically pure.



(±) 117 (26)



77f 117' (27)

We have employed another aliphatic aldehyde ie., isobutyraldehyde for this study and found that the corresponding 3-hydroxy-4-methylpentanoic acid (**77g**) was obtained in 11% optical purity, $[\alpha]_D^{24}$ = + 4.13 (c 6.62, $CHCl_3$), conf.R [Lit.[54] $[\alpha]_D^{25}$ = + 36.9 (c 1.59, $CHCl_3$), e.e 98%, conf.R] (Scheme 48). All these results were summarized in Table 3.

After achieving reasonable success using (1S,2R)-2-phenyl-cyclohexan-1-ol (**(+)-5**) as chiral auxiliary in the Reformatsky reaction, we, then turned our attention to utilize structurally similar trans-2-phenoxycyclohexan-1-ol as chiral auxiliary in the Reformatsky reaction. This new chiral auxiliary was prepared in both (-) and (+) forms (**(-)-118, (+)-118**) recently in our laboratory[118] as shown in Scheme 49 and Scheme 50.

Ring opening of cyclohexene oxide with sodium phenoxide furnished racemic trans-2-phenoxycyclohexan-1-ol (**(±)-118**), as a crystalline solid with m.p. 81-82°C (Lit.[119] m.p. 82°C). The structure of the compound **(±)-118** was confirmed by IR, ^1H NMR, ^{13}C

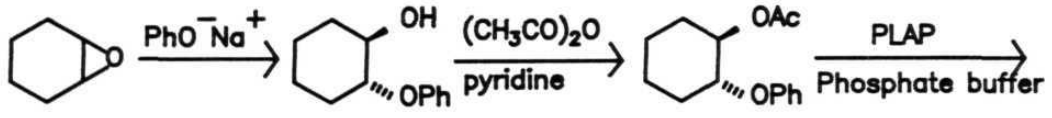
Table 3: Preparation of β-hydroxy acids *via* Reformatsky reaction using [(+)-trans-2-phenylcyclohex-1-yl] bromoacetate (114) and carbonyl compounds.[a,b]

Carbonyl Compd	Product	Overall Yield[c]%	Rotation $[\alpha]_D^{24}$ (c,EtOH)	E.e[d] %	Abs Conf
Benzaldehyde	**77a**	51	+7.87(4.5)	44	R
Acetophenone	**77b**	50	-9.2 (5.18)	89	R
Propiophenone	**77c**	45	-	-	-
Dodecanal	**77d**	35	-	-	-
p-Tolualdehyde	**77e**	47	-3.46(6.64)	31[e]	-
1-Naphthaldehyde	**77f**	63	-6.8 (1.9)	22[e]	-
i-Butyraldehyde	**77g**	45	+4.13(6.62, $CHCl_3$)	11	R

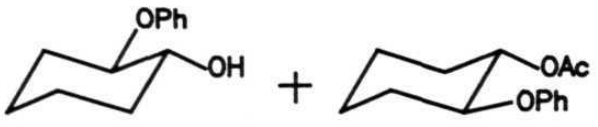
a. All reactions were carried out on 10 mM scale using activated Zn (with TMSCl) in dry benzene, under nitrogen, refluxed for 3 h. b. All products were identified spectroscopically by IR, ^1H NMR and ^{13}C NMR. C. Overall yield of the pure crystallized products based on the carbonyl compound. d. Enantiomeric excess was based on reported rotations : **77a**: $[\alpha]_D^{25}$ +17.9 (c 2.3, EtOH) conf.R, e.e. 100% (Ref.53). **77b**: $[\alpha]_D^{23}$ +6.0 (c 3, EtOH) conf.S, e.e. 58% (Ref.49). **77g**: $[\alpha]_D^{25}$ +36.9 (c 1.59, $CHCl_3$) conf.R, e.e. 98% (Ref.54). e. Enantiomeric excess was determined by ^1H NMR (100 MHz) of the corresponding methyl ester in the presence of shift reagent $Eu(hfc)_3$.

NMR, spectral data and elemental analysis. Acetylation of alcohol **(±)-118** with acetic anhydride provided racemic trans-2-phenoxycyclohex-1-yl acetate (**119**) as a colourless liquid. The structure of the molecule **119** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data. Enzymatic hydrolysis of the racemic acetate **119**, with PLAP in 0.5 M, pH = 8, aqueous KH_2PO_4/K_2HPO_4 buffer after 3 days (conversion ratio 40:60 determined by HPLC) gave optically pure (-)-trans-2-phenoxycyclohexan-1-ol (**(-)-118**), after two crystallizations from hexane, as a crystalline solid, m.p. 94-95°C in 98% optical purity $[\alpha]_D^{24}$ = - 79.2 (c 0.96, MeOH) [Lit.[118] $[\alpha]_D^{23}$ = - 79.1 (c 0.86, MeOH), e.e 98%].

SCHEME 49



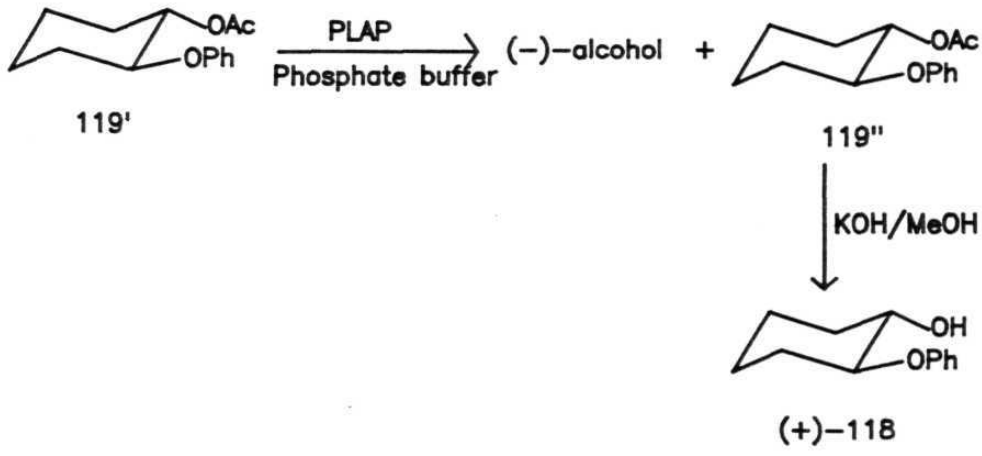
(±)-118 (±) 119



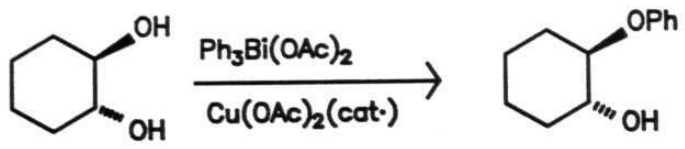
(-)-118 119'

In order to obtain optically pure (+) alcohol **(+)-118**, the recovered acetate of the (+) alcohol **119'** (obtained in the enzymatic hydrolysis) (Scheme 49) was again subjected to enzymatic hydrolysis with PLAP. The acetate of the pure (+) alcohol **119''**, thus obtained, was hydrolyzed with KOH/MeOH to furnish the (+)-trans-2-phenoxycyclohexan-1-ol (**(+)-118**) in 98% optical purity, $[\alpha]_D^{24}$ = + 79.4 (c 0.9, MeOH) (Scheme 50).

SCHEME 50



Recently, we have determined[120] the absolute configuration of the (-)-trans-2-phenoxycyclohexanol (**(-)-118**) to be (1R,2R) by synthesizing the same molecule *via* the monophenylation of (1R,2R)-(-)-cyclohexane-1,2-diol (**120**) with triphenylbismuth diacetate (eq.28) according to the literature method[121].

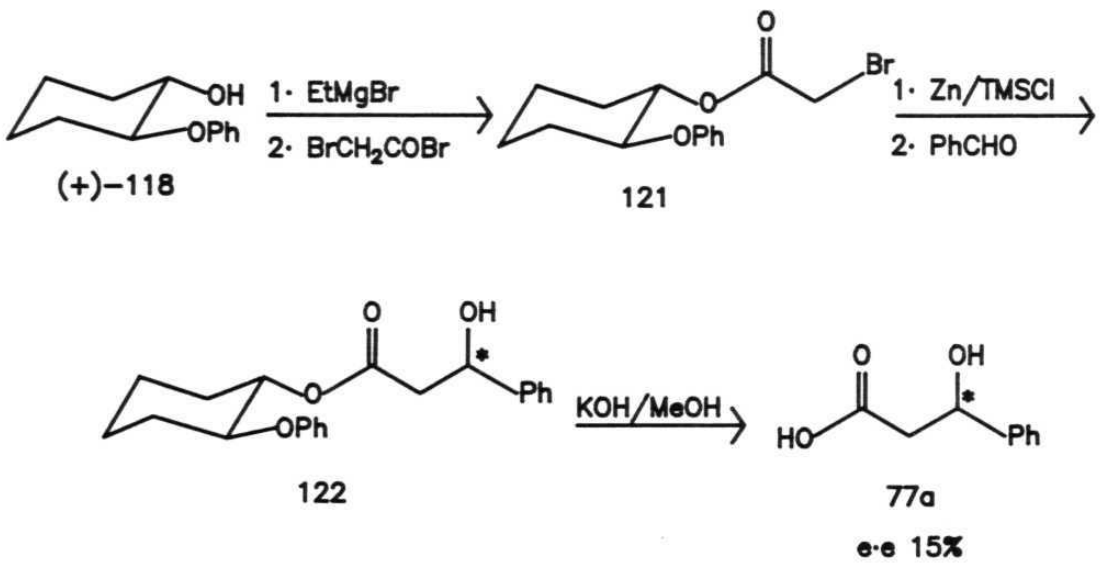


(28)

120 (−)−118

The chiral Reformatsky reagent (1S,2S)-2-phenoxycyclohex-1-yl] bromoacetate (**121**) was prepared by the action of bromoacetyl bromide on (1S,2S)-2-phenoxycyclohexan-1-ol (**(+)-118**) as shown in the Scheme 51. The structure of the compound **121** was confirmed by IR, ^{1}H NMR and ^{13}C NMR (Fig. 8) spectral data.

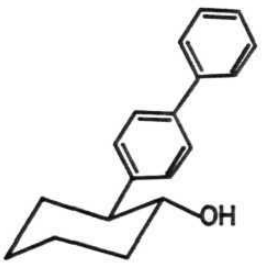
SCHEME 51



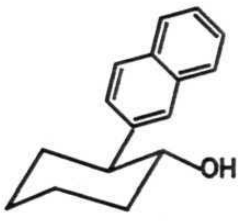
We, then subjected the bromoacetate **121** to zinc Reformatsky reaction with benzaldehyde, which after hydrolysis, provided 3-hydroxy-3-phenylpropionic acid (**77a**) in 15% optical purity,

$[\alpha]_D^{24}$ = + 2.68 (c 7.6, EtOH), conf.R [Lit.[53] $[\alpha]_D^{25}$ = + 17.9 (c 2.3, EtOH), e.e 100%, conf. R].(Scheme 51). Since benzaldehyde failed to provide the corresponding β-hydroxy acid **77a** in satisfactory optical purity, we did not proceed further with this reagent.

Our studies on lactic acid derivatives clearly demonstrate that lactic acid is not suitable chiral source for the preparation of β-hydroxy acids. trans-2-Phenylcyclohexan-1-ol having diastereofacial discriminating phenyl group also fails to provide satisfactory chiral induction. Probably, trans-2-(4-phenyl)phenyl cyclohexan-1-ol (**123**) and trans-2-(2-naphthyl)cyclohexan-1-ol (**124**) would be better chiral auxiliaries for preparing chiral Reformatsky reagents. Work in this direction is in progress in our laboratory.



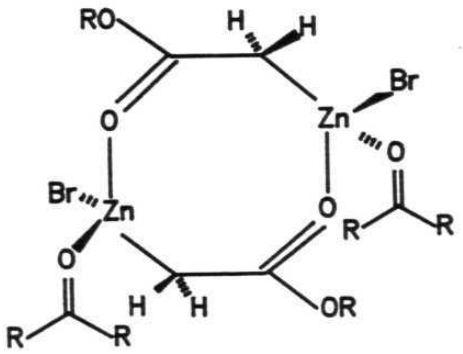
123



124

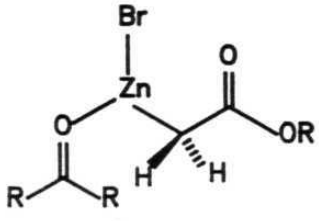
It is worthwhile to mention here the recent literature report on the structure of the Reformatsky reagent. Boersma and

co-workers[122] have reported that the structure of the Reformatsky reagent to be dimeric unit (**125**) in THF in which the zinc is almost tetrahedrally surrounded by two oxygens, one bromine and one carbon atom.

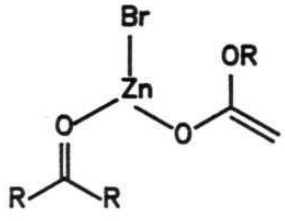


125

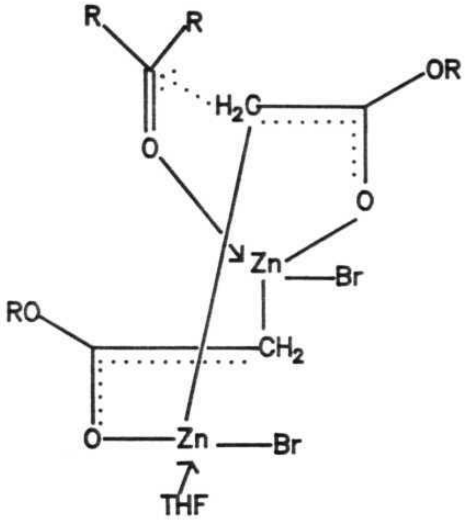
Very recently Dewar *et al.*[123] reported the MNDO theoretical calculations on the Reformatsky reagent. According to these calculations, thermodynamically favoured dimeric complex **125** of the zinc enolates of esters dissociates by the action of carbonyl compound and converts in the rate determining step from the C- to an O- metalated speices(**126**→**127**) which allows the formation of six electron cyclic transition state with the carbonyl compound **128**.



126



127

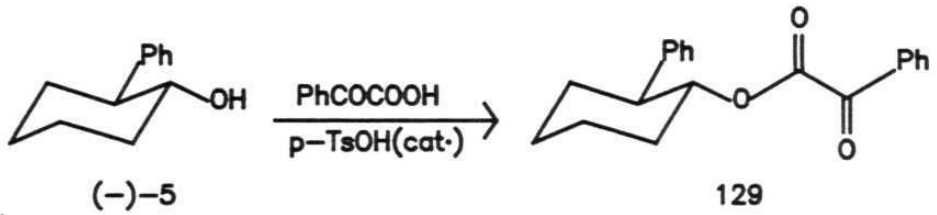


128

Synthesis of α-hydroxy acids:

We have also directed our studies towards possible applications of trans-2-phenylcyclohexan-1-ol (**5**) and trans-2-phenoxycyclohexan-1-ol (**118**) as chiral auxiliaries for the preparation of chiral α-hydroxy acids. Abenhaim and co-workers[86] reported that the reaction of (-)-menthyl phenylglyoxalate (**59**) with a variety of alkylzinc chlorides provided, after hydrolysis, the corresponding α-hydroxy acids in good optical purities (Scheme 23). It occured to us that the reaction of [(1R,2S)-2-phenylcyclo hex-1-yl] phenylglyoxalate (**129**) with alkylzinc chlorides might provide the corresponding α-hydroxy acids in better optical purities as the chiral auxiliary has diastereoface discriminating phenyl group. Accordingly, we have prepared [(1R,2S)-2-

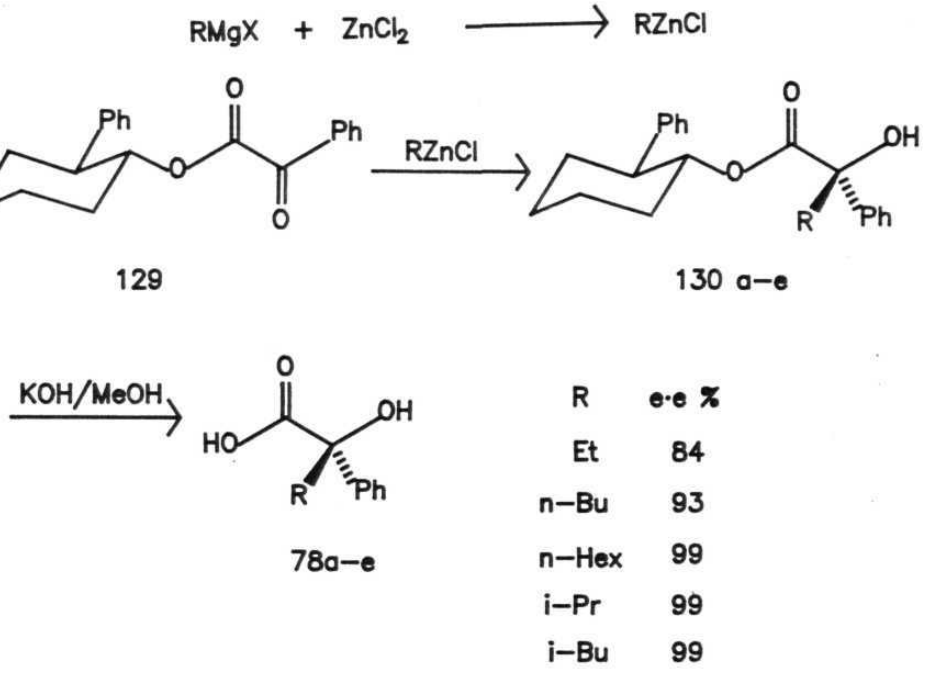
phenylcyclohex-1-yl] phenylglyoxalate (**129**) by treating benzoyl formic acid with (1R,2S)-2-phenylcyclohexan-1-ol (**(-)-5**) in the presence of cat. amount of p-TsOH (eq.29). This was obtained as a crystalline solid, m.p. 66-68°C, $[\alpha]_D^{24}$ = - 14.68 (c 1.97, EtOH). The structure of the compound **129** was confirmed by IR, ^1H NMR (Fig. 9), ^{13}C NMR (Fig. 10) spectral data and elemental analysis.



(-)-5 **129** (29)

First, we have selected ethylzinc chloride for our study. This was prepared[86] by the action of ethylmagnesium bromide on fused $ZnCl_2$ at 0°C. Addition of ethylzinc chloride on [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) was tried first under variety of reaction conditions. The best result was obtained, when the reaction was carried out at -78°C. The required (R)-2-hydroxy-2-phenylbutanoic acid (**78a**) was obtained by the hydrolysis of α-hydroxy ester **130a** (R = Et), as a crystalline solid with 84% optical purity $[\alpha]_D^{24}$ = - 27.97 (c 4.8, EtOH) [Lit.[91] $[\alpha]_D^{25}$ = +33.3 (c 0.87, EtOH), e.e >99%, conf.S] (Scheme 52). The structure of the compound **78a** was confirmed by IR, ^1H NMR and ^{13}C NMR data.

SCHEME 52



R	e.e %
Et	84
n–Bu	93
n–Hex	99
i–Pr	99
i–Bu	99

Then, we have selected n-butyl, n-hexyl, i-propyl and i-butylzinc chlorides for the addition reaction with [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) (Scheme 52). The α-hydroxy acid, 2-hydroxy-2-phenylhexanoic acid (**78b**) was obtained in 93% optical purity, whereas the other three α-hydroxy acids, 2-hydroxy-2-phenyloctanoic acid (**78c**), 2-hydroxy-3-methyl-2-phenylbutanoic acid (**78d**) and 2-hydroxy-4-methyl-2-phenyl-pentanoic acid (**78e**) were obtained in 99% optical purities. All these results were summarized in Table 4. All these optical purities were determined by comparing the specific rotations of these acids **78c-78e** with literature values. In order to have a

Table 4. Preparation of substituted α-hydroxy acids from RZnCl and [(-)-trans-2-phenylcyclohex-1-yl] phenylglyoxalate (129).[a,b]

R in RZnCl	Product	Overall yield[c]%	Rotation $[\alpha]_D^{24}$(c,EtOH)	E.e[d] %	Abs Conf
Ethyl	**78a**	78	-27.97(4.8)	84	R
n-Butyl	**78b**	80	-21.5(4.73)	93	R
n-Hexyl	**78c**	73	-19.3(3.46)	99[e]	R
i-Propyl	**78d**	62	-32.25(2.55)	99[e]	R
i-Butyl	**78e**	50	-20.0(3.5)	99[e]	R

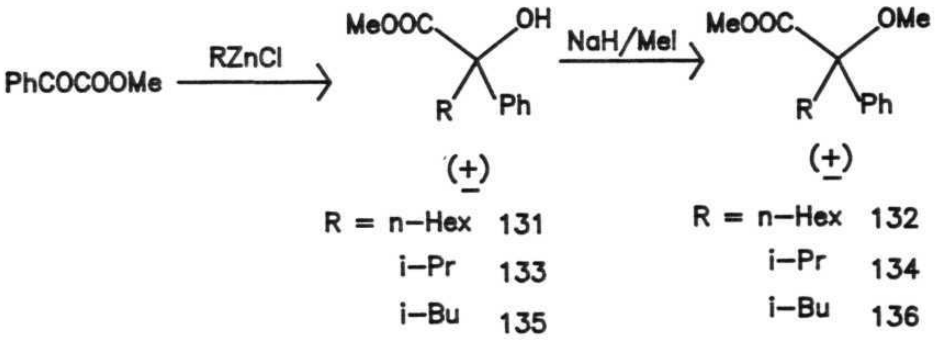
a. Mixture of 2.5 mM of keto ester and 7.5 mM of RZnCl in dry ether was stirred at -78°C for 3 h. b. All products were identified spectroscopically by IR, ^{1}H NMR and ^{13}C NMR. c. Overall yield of the pure crystallized products based on the keto ester. d. Enantiomeric purities were based on reported rotations. **78a**. $[\alpha]_D^{25}$ + 33.3 (c 0.87,EtOH), conf.S, e.e >99%, (Ref.91). **78b**. $[\alpha]_D^{22}$ - 19 (c 2.2, EtOH), conf.R, e.e 82%, (Ref.86). **78c**. $[\alpha]_D^{22}$- 17 (c 2.2, EtOH), conf.R, e.e 88%, (Ref.86). **78d**. $[\alpha]_D^{25}$ + 32.5 (c 2, EtOH), conf.S, e.e >99%, (Ref.91). **78e**. $[\alpha]_D^{25}$ + 20 (c 2 EtOH), conf. S, e.e >99%, (Ref.91) e. Optical purities were also determined by ^{1}H NMR (100 MHz) analysis of the corresponding α-methoxy methyl esters in the presence of shift reagent, $Eu(hfc)_3$.

double check, we have also determined the optical purities of α-hydroxy acids **78c-e** by ^{1}H NMR (100 MHz) shift reagent, Eu(hfc)$_3$, studies in the following way.

Determination of e.e.:

The racemic methyl 2-hydroxy-2-phenyloctanoate (**131**) was prepared by the addition of n-hexylzinc chloride on methyl phenyl glyoxalate. The compound **131** was converted to methyl 2-methoxy-2-phenyloctanoate (**132**) by treating with sodium hydride and methyl iodide, according to the literature method[90] (Scheme 53).

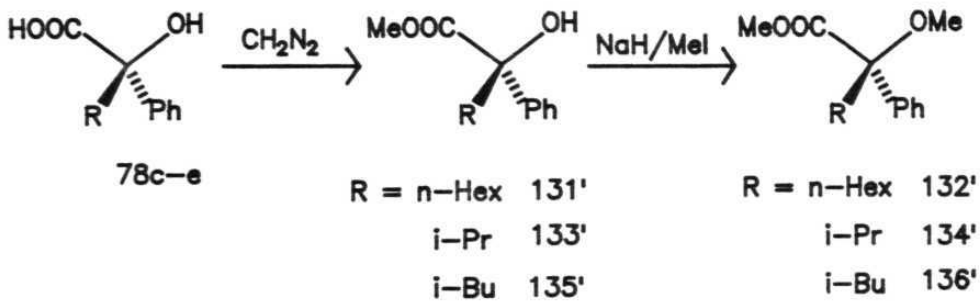
SCHEME 53



^{1}H NMR (Fig. 11) spectrum of the racemic methyl methoxy ester **132** shows a singlet for -COOCH$_3$ protons at δ 3.7. This singlet appeared as two singlets of equal intensities in the presence of shift reagent, Eu(hfc)$_3$, thus indicating that the two singlets arise from two enantiomers.

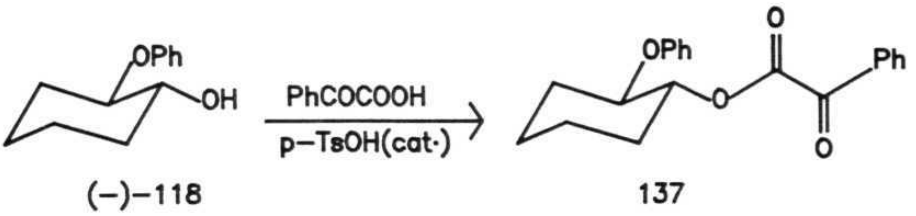
Then, we have converted the chiral (R)-2-hydroxy-2-phenyl octanoic acid (**78c**) to its corresponding methyl ester **131'** by treating with diazomethane. The methyl methoxy ester **132'** was prepared by treatment **131'** with sodium, hydride and methyl iodide as in the case of racemic compound **131** (Scheme 54).

SCHEME 54



Examination of the ^1H NMR (Fig. 11) spectrum of **132'** in the presence of shift reagent, $Eu(hfc)_3$, showed only one singlet for $-COOCH_3$ protons, thus indicating that the optical purity is atleast 99%. The optical purities of the other α-hydroxy acids **78d, 78e** were also determined in the similar manner.

Next, we have undertaken the study of possible application of chiral trans-2-phenoxycyclohexan-1-ol (**118**) as a chiral auxiliary for the preparation of chiral α-hydroxy acids. For this purpose, the required α-keto ester, [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) was prepared according to eq.30.

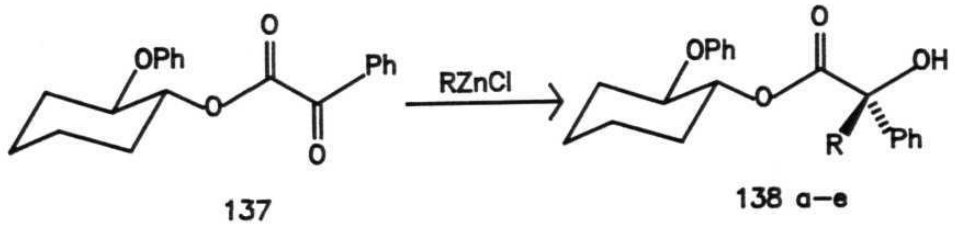


(−)-118 137 (30)

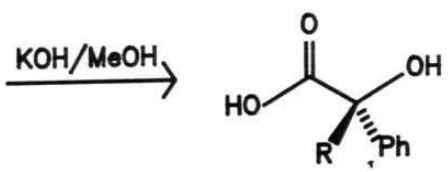
(1R,2R)-2-Phenoxycyclohexan-1-ol ((**-**)-**118**) on treatment with benzoylformic acid in the presence of cat. amount of p-TsOH afforded [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) as a crystalline solid, m.p. 75-76^{o}C, $[\alpha]_{D}^{24}$ = - 50.43 (c 1.125, acetone). The structure of the molecule **137** was established by IR, ^{1}H NMR (Fig. 12), ^{13}C NMR (Fig. 13) spectral data and elemental analysis.

Addition of ethylzinc chloride on **137**, under the same reaction conditions as in the case of **129**, after hydrolysis, provided the (R)-2-hydroxy-2-phenylbutanoic acid **78a** as a solid in

SCHEME 55



137 138 a−e



78a−e

R	e.e %
Et	80
n−Bu	82
n−Hex	91
i−Pr	93
i−Bu	90

80% optical purity $[\alpha]_D^{24}$ = - 26.7 (c 2.8, EtOH) [Lit.[91] $[\alpha]_D^{25}$ = + 33.3 (c 0.87, EtOH), e.e >99%, conf.S] (Scheme 55). Though the optical purity obtained is less in comparision with trans-2-phenylcyclohexanol, the result is encouraging.

We have employed the other alkylzinc chlorides, n-butyl, n-hexyl, i-propyl and i-butylzinc chlorides in the addition reaction. The corresponding α-hydroxy acids **78b-78e** were obtained in 82-93% (corrected values 84-96%) optical purities (Scheme 55). All these results were tabulated in Table 5.

Synthesis of frontalin using (1R,2R)-2-phenoxycyclohexan-1-ol as chiral auxiliary.

Since chiral (1R,2R)-2-phenoxycyclohexan-1-ol (**(-)-118**) provided reasonably satisfactory results for the preparation of chiral alkyl mandelic acid derivatives, we thought of extending its application as a chiral auxiliary for the preparation of optically active frontalin[124] (**63**) which is a component of the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis* Zimmerman, and westren pine beetle, *Dendroctonus brevicomis* Le Conte. Several strategies have been reported for the preparation of chiral frontalin using a variety of chiral auxiliaries such as 8-phenylmenthol,[88] 1,3-oxathiane[125] and (S)-2-(anilinomethyl)pyrrolidine[126].

Table 5. Preparation of substituted α-hydroxy acids from RZnCl and [(-)-trans-2-phenoxycyclohex-1-yl] phenylglyoxalate (137).[a,b]

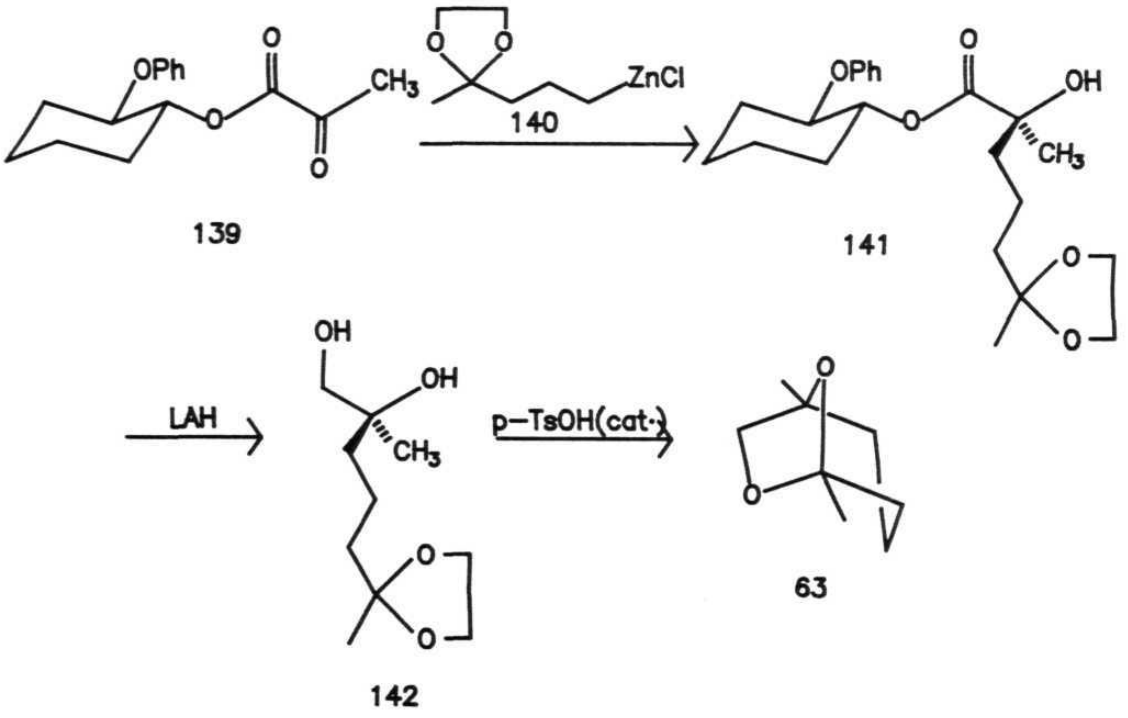
R in RZnCl	Product	Overall yield[c]%	Rotation $[\alpha]_D^{24}$(c,EtOH)	E.e[d] %	Abs Conf
Ethyl	**78a**	71	-26.7(2.8)	80(82)	R
n-Butyl	**78b**	73	-18.97(3.2)	82(84)	R
n-Hexyl	**78c**	74	-17.6(5.2)	91(93)	R
i-Propyl	**78d**	66	-30.14(2.73)	93(95)	R
i-Butyl	**78e**	52	-18.0(1.65)	90(92)	R

a.Mixture of 2 mM of keto ester and 6 mM of RZnCl in dry ether was stirred at -78°C for 3hr. b. All products were identified spectroscopically by IR, ^{1}H NMR and ^{13}C NMR. c. Overall yield of the pure crystallized products based on the keto ester. d. Enantiomeric purities were based on reported rotations. **78a**. $[\alpha]_D^{25}$ + 33.3 (c 0.87,EtOH), conf.S, e.e >99%, (Ref.91). **78b**. $[\alpha]_D^{22}$ - 19 (c 2.2, EtOH), conf.R, e.e 82%, (Ref.86). **78c**. $[\alpha]_D^{22}$ - 17 (c 2.2, EtOH), conf.R, e.e 88%, (Ref.86). **78d**. $[\alpha]_D^{25}$ + 32.5 (c 2, EtOH), conf.S, e.e >99%, (Ref.91). **78e**. $[\alpha]_D^{25}$ + 20 (c 2 EtOH), conf. S, e.e >99%, (Ref. 91) The optical purity of the chiral auxiliary is 98%. Therefore the corrected enantiomeric purities were given in the parenthesis.

63

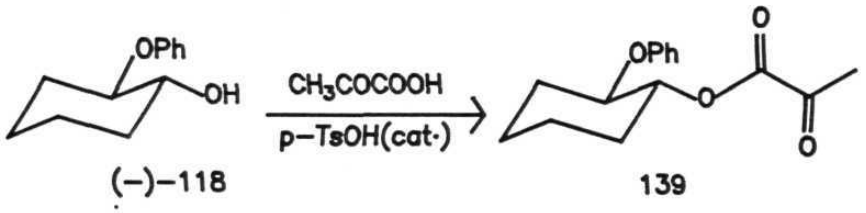
We have planned the synthesis of frontalin (63) according to the Scheme 56.

SCHEME 56



139 141 142 63

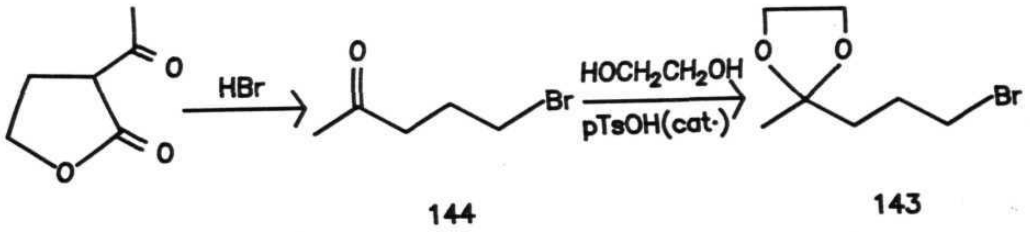
The required [(1R,2R)-2-phenoxycyclohex-1-yl] pyruvate (**139**) was prepared by the action of pyruvic acid on (1R,2R)-2-phenoxy-cyclohexan-1-ol ((-)-**118**) in the presence of catalytic amount of p-TsOH, as a viscous liquid, $[\alpha]_D^{24}$ = - 29.03 (c 3.27, MeOH) (eq.31). The structure of the compound **139** was confirmed by IR, ^1H NMR (Fig.14) , ^{13}C NMR (Fig.15) spectral data and elemental analysis.



(-)-118 139 (31)

The required alkyl bromide, 2-(3-bromoprop-1-yl)-2-methyl-1,3-dioxolone (**143**) was prepared following the literature procedure[127] (Scheme 57). Cleavage of 2-acetylbutyrolactone with HBr provided 5-bromopentan-2-one (**144**). Ketalization of **144** with ethyleneglycol in the presence of catalytic amount of p-TsOH gave **143**, as a colourless liquid.

SCHEME 57



144 143

We, then carried out the addition of alkylzinc chloride **140** with [(1R,2R)-2-phenoxycyclohex-1-yl] pyruvate (**139**) to afford the α-hydroxy ester **141**. Reduction of **141** with LAH furnished the 2-[4-(hydroxymethyl)-4-hydroxypent-1-yl]-2-methyl-1,3-dioxolane (**142**). The diol **142** on treatment with catalytic amount of p-TsOH, as reported in the literature[128a] afforded the (-)-frontalin (**63**) as a colourless liquid in 70% optical purity $[\alpha]_D^{24}$ = - 36.52 (c 2.57, ether) [Lit.[128b] $[\alpha]_D^{25}$ = - 52 (c 2, ether), e.e >99%] (Scheme 56). The structure of the compound **63** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

From all these above studies it is clear that, trans-2-phenoxycyclohexanol is certainly inferior to trans-2-phenylcyclohexanol as chiral auxuliary. This clearly indicates that the oxygen atom present between the phenyl and cyclohexyl rings in trans-2-phenoxycyclohexan-1-ol is playing role in the loss of chiral induction. Further studies are needed to confirm this observation.

CONCLUSION:

We have prepared a variety of chiral auxiliaries from easily and abundantly available lactic acid towards the synthesis of chiral Reformatsky reagents. However, all these chiral auxiliaries fail to provide β-hydroxy acids in satisfactory optical purities.

Our attempts to use chiral trans-2-phenoxycyclohexan-1-ol as a chiral auxiliary for the preparation of chiral β-hydroxy acids also resulted in less satisfactory optical purities. Slight encouraging results with trans-2-phenylcyclohexan-1-ol indicate that the chiral auxiliaries (**123**, **124**) may provide good enantioselectivites. We have made considerable progress in achieving the synthesis of α-hydroxy acids in very high enantiomeric purities particularly with trans-2-phenylcyclohexan-1-ol as chiral auxiliary. Encouraging results in this direction using trans-2-phenoxycyclohexan-1-ol shows the potentiality of this chiral auxiliary.

EXPERIMENTAL

Melting points: Melting points were recorded on a Buchi 510 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 analyser.

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

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra (100 MHz) and carbon-13 magnetic resonance spectra (25 MHz) were recorded on JEOL-FX-100 spectrometer. Spectra for all the samples were measured in chloroform-d solution with tetramethylsilane (δ = 0 ppm) as internal standard. Spectral assignments are as follows: (1) Chemical shift on the δ scale, (2) Standard abbreviations for multiplicity, i.e., s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of a doublet, b = broad, (3) Number of hydrogens integrated for the signal, (4) Coupling constant J in Hertz.

Optical rotations: Optical rotations were measured on a Autopol II

automatic polarimeter at the wavelength of sodium D-line (589 nm) and at the temperature, 24^{o}C.

Chromatography: Analytical thin layer chromatography (TLC) was performed on glass plates (7x2 cm) coated with Acme's silica gel G (250 mμ) containing 13% calcium sulphate as binder. Visualization of spots was achieved by exposure to iodine vapour. Column chromatography was carried out using Acme's silica gel (100-200 mesh). HPLC analyses were performed on Waters Associates model 440 chromatograph.

General: All reactions were followed by TLC, using appropriate solvent system for development. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All the solvents used were dried and distilled using suitable drying agents before use.

Ethyl 2-O-benzyl-(S)-lactate (80):

To a stirred suspension of mineral oil free NaH (55 mM, 1.32 g) in 50 mL of dry THF, (S)-(-)-ethyl lactate (50 mM, 5.66 mL) in 10 mL of dry THF was added dropwise over a period of 10 min at room temperature. After 30 min, benzyl bromide (51 mM, 6.06 mL) was added and stirring was continued for 3 more hours. The reaction mixture was quenched by the addition of 1N HCl solution (15 mL) and extracted with ether (3 x 15 mL). The extracts were dried over anhy. Na_2SO_4. Solvent was evaporated and the residue obtained was distilled under reduced pressure to give ethyl 2-O-benzyl-(S)-lactate (**80**) as a colourless liquid.

Yield : 8.32 g (80%)

b.p. : 115-117^{o}C/10 mm

$[\alpha]_D^{24}$: - 75.4 (c 5.35, $CHCl_3$), conf.S

[Lit.[129] $[\alpha]_D$ - 82.7 (c 1.13, $CHCl_3$), conf.S]

IR (neat): 1730 cm^{-1}

^1H NMR : δ 1.28 (t, 3H, J = 7Hz), 1.42 (d, 3H, J = 7Hz), 3.92-4.28 (m, 3H), 4.4, 4.68 (AB quartet, 2H, J = 10 Hz), 7.28 (s, 5H).

(S)-2-Benzyloxypropan-1-ol (79):

A solution of ethyl 2-O-benzyl-(S)-lactate (**80**) (40 mM, 8.32 g) in 10 mL of dry THF was added slowly to a stirred suspension of

LAH (25 mM, 0.95 g) in 40 mL of dry THF at room temperature. After 2 h, the reaction mixture was quenched by adding 25 mL of 15% KOH solution and stirred for another 30 min. The salts were filtered, the residue was washed with THF. The filtrate and the washings were combined, dried over anhy.Na_2SO_4 and concentrated. The crude material obtained was vacuum distilled to provide pure alcohol **79**, as a liquid.

Yield : 5.0 g (76%)

b.p. : 102-104°C/1.5 mm (Lit.[106] b.p. 95°C/1.0 mm)

$[\alpha]_D^{24}$: + 41.36 (c 1.85, $CHCl_3$), e.e 90%, conf.S

[Lit.[106] $[\alpha]_D$ + 45.86 (c 6.4, $CHCl_3$), e.e 99%, conf.S)

IR (neat): 3450 cm^{-1}

^1H NMR : δ 1.12 (d, 3H, J = 6Hz), 2.68 (b, 1H, -OH), 3.24-3.74 (m, 3H), 4.28-4.68 (m, 2H), 7.26 (m, 5H).

^{13}C NMR : δ 15.82, 66.12, 70.71, 75.59, 127.77, 128.42, 138.53.

(2-Benzyloxyprop-1-yl) bromoacetate (81):

To a stirred solution of ethylmagnesium bromide (45 mM) (prepared from bromoethane and magnesium turnings) in 50 mL of dry ether at 0°C, (S)-2-benzyloxypropan-1-ol (**79**) (45 mM, 7.47 g) was added dropwise at 0°C. After the addition, stirring was continued for one hour at room temperature. Then bromoacetyl bromide (46 mM, **4** mL) was added and stirred for 5 h at room temperature. The

reaction mixture was poured into ice cold water, extracted with ether (3 x 30 mL). The extracts were combined, washed successively with sat.K_2CO_3 solution, water and dried over anhy.Na_2SO_4. Evaporation of the solvent and column chromatography purification (5% ethyl acetate in hexane) afforded **81** as a colourless liquid.

Yield : 9 g (70%)

$[\alpha]_D^{24}$: - 10.67 (c 2.57, $CHCl_3$)

IR (neat): 1730 cm^{-1}

^1H NMR : δ 1.2 (d, 3H, J = 6Hz), 3.48-3.88 (m, 3H), 4.16 (d, 2H, J = 5Hz), 4.56 (s, 2H), 7.28 (s, 5H).

^{13}C NMR : δ 16.29, 25.41, 68.36, 70.53, 71.94, 127.24, 128.01, 138.18, 166.71.

General procedure for β-hydroxy acids:

a. Reformatsky reaction:

Trimethylchlorosilane (0.1 mL) was added to the suspension of zinc (15 mM, 980 mg) in dry benzene (20 mL) with stirring[107] at room temperature. After 15 min, this activated zinc suspension was heated to reflux. To this, bromoacetate (15 mM) in dry benzene (5 mL) and carbonyl compound (15 mM) were added simultaneously but separately dropwise. The reaction mixture was refluxed for appropriate time (as mentioned in that particular experiment). The reaction mixture was allowed to cool to room temperature, quenched

by the addition of sat.NH_4Cl solution and extracted with ether (3 x 20 mL). The ethereal solution was dried over anhy.Na_2SO_4 and concentrated. The crude material was purified by column chromatography (10% ethyl acetate in hexane) to furnish the β-hydroxy ester. (Reformatsky reactions of (1S,2R)-2-phenyl-cyclohex-1-yl bromoacetate (**114**) with carbonyl compounds were carried out on 10 mM scale).

b. Hydrolysis of the β-hydroxy ester:

A mixture of 2.5 N KOH/MeOH and β-hydroxy ester (obtained in the above step) was stirred for 2 h at room temperature. The reaction mixture was diluted with water (5 mL), extracted with ether (3 x 10 mL) to recover the chiral auxiliary. The aqueous layer was neutralized with 2 N HCl solution (5 mL) and extracted with ether (3 x 10 mL). The ether layer was dried over anhy.Na_2SO_4 and evaporated. The crude solid (in case of solid acids) obtained was crystallized from hexane-ether mixture to give β-hydroxy acid as a crystalline solid.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **81**):

This was prepared from (2-benzyloxyprop-1-yl) bromoacetate (**81**) and benzaldehyde (Reformatsky reaction time 4 h).

Yield : 25%

m.p. : 96-97°C [Lit.[130] racemic acid m.p. 96°C)

$[\alpha]_D^{24}$: Nil

IR(CH_2Cl_2): 3600-2700, 1730 cm^{-1}

^1H NMR : (Acetone d_6): δ 2.7 (d, 2H, J = 5Hz), 4.38 (b, 2H, -OH, -COOH, D_2O washable), 5.1 (t, 1H, J = 5Hz) 7.08-7.5 (m, 5H).

^{13}C NMR : (Acetone d_6) : δ 41.06, 67.53, 123.24, 124.71, 125.65, 141.77, 170.24.

Ethyl O-tetrahydropyranyl-(S)-lactate (84):

A mixture of (S)-(-)-ethyl lactate (250 mM, 28.3 mL), dihydropyran (250 mM, 22.65 mL) and 100 mg of p-TsOH in 100 mL of dichloromethane was stirred overnight at room temperature. It was neutralized with sat.$NaHCO_3$ solution and extracted with dichloromethane (3 x 20 mL), dried over anhy.Na_2SO_4. Removal of the solvent, followed by vacuum distillation gave THP ether **84** as a colourless liquid.

Yield : 41 g (81%)

b.p. : 130-134°C/20 mm

IR (neat): no -OH absorption

2-O-Tetrahydropyranyl-(S)-propane-1,2-diol (85):

To a stirred suspension of LAH (60 mM, 2.28 g) in 100 mL of dry THF, ethyl O-tetrahydropyranyl-(S)-lactate (**84**) (100 mM, 20.2 g) in 20 mL of dry THF was added slowly at $0^{o}C$. After stirring the reaction mixture for 2 h at room temperature, the reaction was quenched by adding 30 mL of 15% KOH solution. The salts were filtered and residue was washed with THF. The combined extracts were dried over anhy.Na_2SO_4 and concentrated. The crude compound was distilled under reduced pressure to provide the alcohol **85** as a colourless liquid.

Yield : 11.2 g (70%)

b.p. : 96-98^{o}C/6 mm

IR (neat): 3500 cm^{-1}

1-O-Benzyl-2-O-tetrahydropyranyl-(S)-propane-1,2-diol (86):

A solution of 2-O-tetrahydropyranyl-(S)-propane-1,2-diol (**85**) (50 mM, 8 g) in 15 mL of dry THF was added slowly to a stirred suspension of mineral oil free NaH (60 mM, 1.44 g) in 100 mL of dry THF at room temperature. After stirring for 30 min, benzyl bromide (52 mM, 6.1 mL) was added and stirred for 5 h. Then water (10 mL) was added, extracted with ether (3 x 20 mL). The combined ether layer was dried over anhy.Na_2SO_4. Solvent was evaporated to afford benzyl ether **86** as a colourless oil. This was used without any purification in the next step.

Yield : 12 g (96%)

IR (neat): no -OH absorption

(S)-1-Benzyloxypropan-2-ol (83):

A mixture of THP ether **86** (48 mM, 12 g), 25 mL of methanol and 4 mL of 1 N HCl solution was stirred for 2 h at room temperature. After neutralization with 2 mL of sat.$NaHCO_3$ solution, the solvent was concentrated (to remove methanol) diluted with water, extracted with ether (3 x 20 mL). The ethereal solution was dried over anhy.Na_2SO_4, concentrated and distilled under reduced pressure to furnish the alcohol **83** as a colourless liquid.

Yield : 7.33 g (92%)

b.p. : 106-108^{o}C/5 mm (Lit.[131] b.p. 85^{o}C/0.45 mm)

$[\alpha]_D^{24}$: + 12.16 (c 9.38, $CHCl_3$), e.e 99%, conf.S
[Lit.[108] $[\alpha]_D^{25}$ + 11.0 (c 2, $CHCl_3$), e.e 90%, conf. S]

IR (neat): 3500 cm^{-1}

^1H NMR : δ 1.12 (d, 3H, J = 6Hz), 2.48 (b, 1H, -OH), 3.12-3.52 (m, 2H), 3.92 (m, 1H), 4.52 (s, 2H), 7.28 (s, 5H).

^{13}C NMR : δ 18.70, 66.53, 73,41, 75.94, 127.89, 128.59, 138.18.

[1-Benzyloxyprop-2-yl] bromoacetate (87):

This was prepared from (S)-1-benzyloxypropan-2-ol (**83**) and bromoacetyl bromide following the same procedure as in **81**. This

compound, **87**, was obtained as a liquid.

Yield : 46%

$[\alpha]_D^{24}$: - 2.99 (c 3.67, $CHCl_3$)

IR (neat): 1730 cm^{-1}

^1H NMR : δ 1.24 (d, 3H, J = 6Hz), 3.48 (d, 2H, J = 5Hz), 3.8 (s, 2H), 4.52 (s, 2H), 5.16 (m, 1H), 7.28 (s, 5H).

^{13}C NMR : δ 16.23, 26.11, 71.65, 72.00, 73.12, 127.65, 128.41, 137.94, 166.83.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **87**):

This was prepared from [1-benzyloxyprop-2-yl] bromoacetate (**87**) and benzaldehyde (Reformatsky reaction time 4 h).

Yield : 30%

m.p. : 96-98°C [Lit.[130] racemic acid m.p. 96°C]

$[\alpha]_D^{24}$: + 4.38 (c 3.68, EtOH), e.e 25%, conf. R

[Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R]

This compound has IR, ^1H NMR and ^{13}C NMR data identical with that of the compound prepared using **81**.

3-Hydroxy-3-phenylbutanoic acid (77b):

(Using Reformatsky reagent **87**):

This was prepared from [1-benzyloxyprop-2-yl] bromoacetate

(**87**) and acetophenone (Reformatsky reaction time 5 h).

Yield : 39%

m.p. : 70-73°C [Lit.[38] racemic acid m.p. 71-72°C]

$[\alpha]_D^{24}$: - 1.2 (c 6.6, EtOH), e.e 12%, conf.R

[Lit.[49] $[\alpha]_D^{23}$ + 6.0 (c 3, EtOH), e.e 58%, conf.S]

IR($CHCl_3$): 3600, 3300-2600, 1710 cm^{-1}

^1H NMR : δ 1.52 (s, 3H), 2.76,3.00 (AB quartet, 2H, J = 16Hz), 6.48 (b, 2H, -OH, -COOH), 7.32 (m, 5H).

^{13}C NMR : δ 30.53, 46.06, 73.00, 124.48, 127.30, 128.59, 146.42, 177.42.

(S)-Methyl 2-(bromoacetoxy)propionate (90):

To a stirred solution of (S)-methyl lactate (65 mM, 6.2 mL), ethylmagnesium bromide (65 mM) (prepared from bromoethane and magnesium) was added at 0°C. After stirring for 1 h, bromoacetyl bromide (65 mM, 5.65 mL) was added and stirred for 5 h at room temperature. The reaction mixture was poured into ice-cold water, extracted with ether (3 x 30 mL) . The extracts were combined, washed successively with sat.K_2CO_3 solution, water and dried over anhy.Na_2SO_4. Evaporation of the solvent and purification by column chromatography (5% ethyl acetate in hexane) afforded **90** as a liquid.

Yield : 7.6 g (52%)

$[\alpha]_D^{24}$: - 38.9 (c 7.1, $CHCl_3$)

IR (neat): 1735 cm^{-1}

^1H NMR : δ 1.52 (d, 3H, J = 6Hz), 3.72 (s, 3H), 3.96 (s, 2H), 5.12 (q, 1H, J = 6Hz).

^{13}C NMR : δ 16.94, 25.88, 52.71, 70.35, 167.07, 170.83.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **90**):

This was obtained from (S)-methyl 2-(bromoacetoxy)propionate (**90**) and benzaldehyde (Reformatsky reaction time 2 h).

Yield : 16%

m.p. : 114-116°C [Lit.[130] optically pure acid m.p. 116°C]

$[\alpha]_D^{24}$: + 18.0 (c 0.5, EtOH), e.e 100%, conf. R

[Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf. R]

This compound has the same IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **81**.

3-Hydroxy-3-phenylbutanoic acid (77b):

(Using Reformatsky reagent **90**):

This was prepared from (S)-methyl 2-(bromoacetoxy)propionate (**90**) and acetophenone (Reformatsky reaction time 4 h).

Yield : 13%

m.p. : 71-74°C [Lit.[38] racemic acid m.p 71-72°C]

$[\alpha]_D^{24}$: - 2.45 (c 3.5, EtOH), e.e 24%, conf.R

[Lit.[49] $[\alpha]_D^{23}$ + 6.0 (c 3, EtOH), e.e 58%, conf.S]

This compound has the same IR, ^{1}H NMR and ^{13}C NMR spectral data as that of the compound prepared using **87**.

3-Hydroxy-3-phenylpentanoic acid (77c):

(Using Reformatsky reagent **90**):

This was prepared from (S)-methyl 2-(bromoacetoxy)propionate (**90**) and propiophenone (Reformatsky reaction time 7 h).

Yield : 7%

m.p. : 115-116°C [Lit.[132] optically active acid m.p. 119°C]

$[\alpha]_D^{24}$: - 2.85 (c 1.05, EtOH), e.e 11%, conf. R

[Lit.[49] $[\alpha]_D^{23}$ + 15 (c 3, EtOH), e.e 58%, conf.S]

IR($CHCl_3$): 3600, 3300-2600, 1710 cm^{-1}

^{1}H NMR : δ 0.72, (t, 3H, J = 6Hz), 1.8 (q, 2H, J = 6Hz) 2.8, 3.00 (AB quartet, 2H, J = 16Hz), 6.28 (b, 2H, -OH, -COOH), 7.28 (s, 5H).

^{13}C NMR : δ 7.70, 35.82, 44.59, 75.41, 125.18, 127.12, 128.36, 144.77, 177.59.

3-Hydroxytetradecanoic acid (77d):

(Using Reformatsky reagent **90**):

This was prepared from (S)-methyl 2-(bromoacetoxy)propionate (**90**) and dodecanal (Reformatsky reaction time 5 h).

Yield : 6%

m.p. : 75-76°C [Lit.[68] optically pure acid m.p. 72°C]

$[\alpha]_D^{24}$: - 2.6 (c 2.3, $CHCl_3$), e.e 16%, conf. R

[Lit.[68] $[\alpha]_D^{20}$ - 16.2, (c 1, $CHCl_3$), e.e 100%, conf. R]

IR($CHCl_3$): 3500 - 2800, 1710 cm^{-1}

^1H NMR : δ 0.88 (t, 3H, J = 6Hz), 1.0-1.64 (m, 20H), 2.44 (m, 2H), 4.0 (m, 1H), 5.52 (b, 2H, -OH, -COOH).

(S)-Propane-1,2-diol (97):

This was prepared according to the literature method[111] with some modification.

A solution of (S)-(-)-ethyl lactate (100 mM, 11.33 mL) in dry THF (20 mL) was added dropwise to a stirred suspension of LAH (85 mM, 3.23 g) in dry THF (100 mL) at 0°C. After the addition was complete, the reaction mixture was stirred for 2 h at room temperature. Saturated Na_2SO_4 solution was added carefully and the resulting slurry was refluxed for one hour. The salts were removed by filtration and then the residue was again refluxed for 30 min with 100 mL of THF in order to extract all the diol. The combined organic layer was dried over anhy.Na_2SO_4. Evaporation of the solvent followed by distillation furnished pure diol **97**, as a

colourless liquid.

Yield : 5.0 g (66%)

b.p. : 106-108°C/20 mm (Lit.[111] b.p. 93°C/18 mm)

$[\alpha]_D^{24}$: + 20.5 (c 0.96, H_2O), e.e 99%, conf.S

[Lit.[111] $[\alpha]_D^{20}$ + 20.7 (c 7.5, H_2O), e.e >99%, conf. S]

IR (neat): 3450 cm^{-1}

^1H NMR : δ 1.12 (d, 3H, J = 7Hz), 3.48 (m, 2H), 3.8 (m, 1H), 4.52 (b, 2H, 2-OH).

^{13}C NMR : δ 18.53, 67.71, 68.18.

(S)-2-Acetoxy-1-bromopropane (96a):

This was prepared according to the literature procedure.[111]

A solution of HBr in acetic acid (41 mL, 30% solution) was added slowly to (S)-propane-1,2-diol (**97**) (50 mM, 3.8 g) with stirring at 0°C. After 2h stirring at the same temperature, 100 mL of water was added. The reaction mixture was neutralized by adding solid $NaHCO_3$. The oily layer formed was collected by extracting with ether (3 x 20 mL). The ether extracts were combined, washed with sat.$NaHCO_3$ solution and dried over anhy.Na_2SO_4. Solvent was evaporated and the residue was distilled under reduced pressure to give (S)-2-acetoxy-1-bromopropane (**96a**) as a colourless liquid.

Yield : 7.24 g (80%)

b.p. : 74-76°C/20 mm [Lit.[111] b.p. 57°C/11 mm]

$[\alpha]_D^{24}$: - 13.5 (c 0.81, $CHCl_3$), conf.S

[Lit.[111] $[\alpha]_D^{23}$ - 13.55 (c 5.8, $CHCl_3$), conf.S]

IR (neat): 1720 cm^{-1}

^1H NMR : δ 1.36 (d, 3H, J = 7Hz), 2.08 (s, 3H), 3.44 (d, 2H, J = 5Hz), 5.08 (m, 1H).

^{13}C NMR : δ 18.53, 20.94, 35.12, 69.24, 170.30.

(S)-1-Phenoxypropan-2-ol (92):

(S)-2-Acetoxy-1-bromopropane (**96a**) (25 mM, 4.52 g) was added dropwise to a stirred solution of sodium phenoxide (50 mM) in ethanol [prepared from NaOH (50 mM, 2 g), phenol (50 mM, 4.39 mL) in 15 mL of ethanol] at 0°C over a period of 30 min. After stirring for 4 h at 0°C, the reaction mixture was diluted with water (15 mL) and extracted with ether (3 x 20 mL). The ether extracts were combined, washed with NaOH solution, dil.HCl solution, sat.K_2CO_3 solution and dried over anhy.Na_2SO_4. The solvent was evaporated and the crude material was purified by column chromatography (5% ethyl acetate in hexane) and then distilled under reduced pressure to give (S)-1-phenoxypropan-2-ol (**92**) as a colourless liquid.

Yield : 1.25 g (32%)

b.p. : 92°C/3 mm.

$[\alpha]_D^{24}$: + 22.66 (c 1.5, $CHCl_3$)

IR (neat): 3450 cm^{-1}

^1H NMR : δ 1.28 (d, 3H, J = 7Hz), 2.32 (b, 1H, -OH), 3.6-4.32 (m, 3H), 6.76-7.4 (m, 5H).

^{13}C NMR : δ 18.76, 66.12, 73.18, 114.59, 121.06, 129.53, 158.71.

Analysis calcd. : C, 71.02; H, 7.95;

for $C_9H_{12}O_2$

Found : C, 71.07; H, 7.99.

(1-Phenoxyprop-2-yl) bromoacetate (98):

This compound was prepared from (S)-1-phenoxypropan-2-ol (**92**) and bromoacetyl bromide following the same procedure as in **81**. This compound, **98**, was obtained as a colourless liquid.

Yield : 73%

$[\alpha]_D^{24}$: - 21.47 (c 5.21, $CHCl_3$)

IR (neat): 1725 cm^{-1}

^1H NMR : δ 1.36 (d, 3H, J = 6Hz), 3.76 (s, 2H), 3.96 (d, 2H, J = 6Hz), 5.24 (m, 1H), 6.72-7.32 (m, 5H).

^{13}C NMR : δ 16.35, 26.00, 69.71, 71.12, 114.77, 121.36, 129.65, 158.60, 166.94.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **98**):

This was prepared from (1-phenoxyprop-2-yl) bromoacetate (**98**) and benzaldehyde (Reformatsky reaction time 2 h).

Yield : 45%

m.p. : 96-97°C [Lit.[130] racemic acid m.p. 96°C]

$[\alpha]_D^{24}$: Nil

This compound has IR, ^1H NMR and ^{13}C NMR data identical with that of the compound prepared using **81**.

(S)-1-(2-Naphthyloxy)propan-2-ol (93):

To a stirred solution of NaOH (40 mM, 1.6 g) in ethanol (15 mL), 2-naphthol (40 mM, 5.76 g) was added and stirred for 30 min at room temperature. Then this was cooled to 0°C and (S)-2-acetoxy-1-bromopropane (**96a**) (20 mM, 3.62g) was added slowly. After stirring for 4 h at 0°C, the reaction mixture was diluted with water and extracted with ether (3 x 20 mL). The extracts were combined, washed with NaOH solution, dil.HCl solution and sat.K_2CO_3 solution and dried over anhy.Na_2SO_4. Solvent was evaporated, the residue obtained was purified by column chromatography (5% ethyl acetate in hexane) and then crystallized from pet.ether (40-60°C fraction) to provide the pure alcohol **93** as a crystalline solid.

Yield : 1.33 g (33%)

m.p. : 84-86°C

$[\alpha]_D^{24}$: + 17.12 (c 1.46, $CHCl_3$)

IR (KBr) : 3350 cm^{-1}

^1H NMR : δ 1.32 (d, 3H, J = 7Hz), 2.32 (b, 1H, -OH), 3.82-4.36 (m, 3H), 7.04-7.8 (m, 7H).

^{13}C NMR : δ 18.76, 66.00, 73.12, 106.88, 118.59, 123.71, 126.36, 126.71, 127.59, 129.06, 129.42, 134.48, 156.53.

Analysis Calcd. : C, 77.20; H, 6.98;

for $C_{13}H_{14}O_2$

Found : C, 77.26; H, 7.01.

[1-(2-Naphthyloxy)prop-2-yl] bromoacetate (100):

This compound was prepared (as a crystalline solid) from (S)-1-(2-naphthyloxy)propan-2-ol (**93**) and bromoacetyl bromide following the same procedure as in **81**.

Yield : 62%

m.p. : 50-51°C

$[\alpha]_D^{24}$: - 29.12 (c 5.7, $CHCl_3$)

IR (KBr) : 1730 cm^{-1}

^1H NMR : δ 1.48 (d, 3H, J = 7Hz), 3.84 (s, 2H), 4.12 (d, 2H, J = 6Hz), 5.36 (m, 1H), 7.04-7.8 (m, 7H).

^{13}C NMR : δ 16.25, 25.87, 69.67, 70.89, 106.88, 118.75, 123.82, 126.48, 126.75, 127.63, 129.14, 129.53, 134.37, 156.39, 166.84.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **100**):

This compound was prepared from [1-(2-naphthyloxy)prop-2-yl] bromoacetate (**100**) and benzaldehyde (Reformatsky reaction time 2 h).

Yield : 30%

m.p. : 96-97°C [Lit.[130] racemic acid m.p. 96°C]

$[\alpha]_D^{24}$: + 1.42 (c 2.1, EtOH), e.e 8%

[Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R]

This compound has the same IR, ^{1}H NMR and ^{13}C NMR spectral data as that of the compound prepared using **81**.

(S)-1-(2-Methoxyphenoxy)propan-2-ol (104):

This compound was prepared from (S)-2-acetoxy-1-bromopropane (**96a**) and 2-methoxyphenol following the same procedure as in **92**. This compound, **104**, was obtained as a colourless liquid after column purification (10% ethyl acetate in hexane).

Yield : 30%

b.p. : 142°C/10mm

$[\alpha]_D^{24}$: + 29.16 (c 1.2, $CHCl_3$)

IR (neat): 3500 cm^{-1}

^{1}H NMR : δ 1.24 (d, 3H, J = 7Hz), 3.32-4.32 (m, 7H, 1H D_2O exchangeable), 6.88 (s, 4H).

^{13}C NMR : δ 18.53, 55.76, 65.83, 75.53, 112.00, 114.88, 121.18, 121.94, 148.36, 149.89.

Analysis calcd.: C, 65.91; H, 7.74;

for $C_{10}H_{14}O_3$

Found : C, 66.02; H, 7.77.

[1-(2-Methoxyphenoxy)prop-2-yl] bromoacetate (102):

This was prepared from (S)-1-(2-methoxyphenoxy)propan-2-ol and bromoacetyl bromide following the same procedure as in **81**. This compound, **102**, was obtained as a viscous liquid.

Yield : 60%

$[\alpha]_D^{24}$: - 13.23 (c 5.4, $CHCl_3$)

IR (neat): 1730 cm^{-1}

^1H NMR : δ 1.32 (d, 3H, J = 6Hz), 3.8 (s, 3H), 3.82 (s, 2H), 4.04 (d, 2H, J = 6Hz), 5.28 (m, 1H), 6.88 (s, 4H).

^{13}C NMR : δ 16.29, 26.17, 56.00, 71.29, 71.53, 112.53, 115.35, 121.00, 122.36, 148.18, 150.24, 166.89.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **102**):

This was prepared from [1-(2-methoxyphenoxy)prop-2-yl] bromoacetate (**102**) and benzaldehyde (Reformatsky reaction time

2 h).

Yield : 35%

m.p : 100-105°C [Lit.[130] optically pure acid m.p. 116°C]

$[\alpha]_D^{24}$: + 10.32 (c 1.55, EtOH), e.e 57%, conf.R

[Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R]

This compound has IR, ^1H NMR and ^{13}C NMR spctral data identical with that of the compound prepared using **81**.

3-Hydroxy-3-phenylbutanoic acid (77b):

(Using Reformatsky reagent **102**):

This compound was prepared from [1-(2-methoxyphenoxy) prop-2-yl] bromoacetate (**102**) and acetophenone (Reformatsky reaction time 2 h)

Yield : 25%

m.p : 71-73°C [Lit.[38] racemic acid m.p. 71-72°C]

$[\alpha]_D^{24}$: - 1.25 (c 3.8, EtOH), e.e 12%, conf.R

[Lit.[49] $[\alpha]_D^{23}$ + 6.0 (c 3, EtOH), e.e 58%, conf.S]

This compound has the same IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **87**.

o-(Tetrahydropyran-2-yloxy)phenol (108):

A mixture of catechol (50 mM, 5.5 g), dihydropyran (50 mM, 4.53 mL) and 50 mg of p-toluenesulfonic acid in dichloromethane

(100 mL) was stirred for 4 h at room temperature. The reaction mixture was washed with sat.$NaHCO_3$ solution, several times with water and dried over anhy.Na_2SO_4. Removal of the solvent, followed by column chromatography (5% ethyl acetate in hexane) purification gave the THP ether **108** as a liquid.

Yield : 6 g (62%)

IR (neat): 3500 cm^{-1}

[1-(2-Methoxyethoxy)-2-(tetrahydropyran-2'-yloxy)]benzene (109):

To a stirred solution of NaOH (50 mM, 2 g) in 10 mL of water, o-(tetrahydropyran-2-yloxy)phenol (**108**) (50 mM, 9.71 g) in ethanol (15 mL) was added and stirred for 1 h at room temperature. Then 2-methoxyethyl chloride (50 mM, 4.56 mL) was added at room temperature. After stirring overnight the reaction mixture was diluted with water (20 mL) extracted with hexane (3 x 20 mL). The extracts were combined, washed with NaOH solution (to remove any unreacted phenol) and water. The hexane layer was dried over anhy.Na_2SO_4 and evaporated. The crude material was used in the next step without any purification.

Yield : 12 g (95%)

IR (neat): no -OH absorption

o-(2-Methoxyethoxy)phenol (110):

A mixture of THP ether **109** (47.5 mM, 12 g), methanol (10 mL) and 4 mL of 1N HCl solution was stirred for 2 h at room temperature. After neutralizing the acid with solid $NaHCO_3$, it was diluted with water and extracted with ether (3 x 20 mL). The ether layer was dried over anhy.Na_2SO_4 and concentrated. Purification of the compound by column chromatography (10% ethyl acetate in hexane) furnished phenol **110** as a colourless liquid.

Yield : 7.34 g (92%)

IR (neat): 3500 cm^{-1}

^1H NMR : δ 3.44 (s, 3H), 3.68 (m, 2H), 4.12 (m, 2H), 6.88 (m, 4H).

^{13}C NMR : δ 58.94, 69.94, 70.94, 115.53, 115.65, 120.06, 123.18, 146.06, 147.54.

(S)-1-[o-(2-Methoxyethoxy)phenoxy]propan-2-ol (106):

To a stirred solution of NaOH (20 mM, 800 mg) in ethanol (10 mL), o-(2-methoxyethoxy)phenol (**110**) (20 mM, 3.36 g) in ethanol (5 mL) was added and stirred for 1 h at room temperature. The reaction mixture was cooled to 0°C. (S)-2-Acetoxy-1-bromopropane (**96a**) (10 mM, 1.81 g) in ethanol (10 mL) was added dropwise and stirred for 4 h at 0°C. The reaction mixture was diluted with water and extracted with ether (3 x 20 mL). The ethereal solution

was washed successively with NaOH solution, dil.HCl solution and sat.$NaHCO_3$ solution. After drying over anhy.Na_2SO_4, solvent was evaporated and purification by column chromatography (10% ethyl acetate in hexane) gave the pure alcohol **106** as a colourless oil.

Yield : 500 mg (22%)

$[\alpha]_D^{24}$: + 10.9 (c 1.1, MeOH)

IR (neat): 3500 cm^{-1}

^1H NMR : δ 1.2 (d, 3H, J = 7Hz), 3.4 (s, 3H), 3.64-4.24 (m, 7H, 1H D_2O washable), 6.88 (s, 4H).

^{13}C NMR : δ 18.17, 59.00, 65.71, 69.29, 71.12, 75.82, 115.83, 122.12, 122.36, 149.24, 149.36.

Analysis calcd. : C, 63.70; H, 8.02;

for $C_{12}H_{18}O_4$

Found : C, 63.74; H, 8.04.

1-[o-(2-Methoxyethoxy)phenoxy]prop-2-yl bromoacetate (111):

To a stirred solution of ethylmagnesium bromide (7 mM) (prepared from bromoethane and magnesium) in dry ether (15 mL) at 0°C, alcohol **106** (7 mM, 1.58 g) in dry ether (50 mL) was added dropwise and stirred for 1 h at room temperature. Then bromoacetyl bromide (7 mM, 0.61 mL)was added and stirred for 4 h. The reaction mixture was poured into an ice cold water and extracted with ether (3 x 10 mL). The ether layer was washed with sat.K_2CO_3 solution

and dried over anhy.Na_2SO_4. Removal of the solvent, followed by column chromatography purification (7% ethyl acetate in hexane) gave the pure bromoacetate **111** as a colourless liquid.

Yield : 1 g (41%)

$[\alpha]_D^{24}$: - 15.67 (c 0.5,$CHCl_3$)

IR (neat): 1720 cm^{-1}

^1H NMR : δ 1.4 (d, 3H, J = 7Hz), 3.44 (s, 3H), 3.6-4.16 (m, 8H), 5.32 (m, 1H), 6.92 (s, 4H).

^{13}C NMR : δ 16.17, 26.12, 59.12, 68.82, 71.06, 71.24, 71.47, 115.30, 115.71, 121.77, 122.30, 148.83, 149.30, 166.83.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **111**):

This was prepared from bromoacetate **111** and benzaldehyde (Reformatsky reaction time 2 h).

Yield : 10%

m.p : 96°C [Lit.[130] racemic acid m.p. 96°C]

$[\alpha]_D^{24}$: + 0.9 (c 1.95, EtOH), e.e 5%.

[Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 2.3, EtOH), e.e 100%, conf.R]

This compound has the same IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **81**.

(±)-trans-2-Phenylcyclohexan-1-ol ((±)-5):

This compound was prepared according to the procedure reported by Whitesell *et al*.[116]

To a stirred solution of phenylmagnesium bromide (350 mM), [prepared from bromobenzene (350 mM, 37 mL) and magnesium turnings (350 mM, 8.4 g)] in dry THF (300 mL) at -20°C (ice-salt mixture), copper(I) chloride (15.7 mM, 1.55 g) was added and stirred for 10 min. Then a solution of cyclohexene oxide (250 mM, 25.3 mL) in dry THF (20 mL) was added slowly at the same temperature. The reaction mixture was allowed to warm to 0°C and stirring was continued for 2 h at 0°C. The reaction mixture was quenched by adding sat. $(NH_4)_2SO_4$ solution (100 mL). The organic layer was washed with sat. $(NH_4)_2SO_4$ solution until the aqueous layer was no longer blue. The combined aqueous layers were extracted with ether (3 x 50 mL). The extracts were combined, dried over anhy. Na_2SO_4 and concentrated. The solid obtained was crystallized from pentane to furnish the racemic alcohol **(±)-5** as a crystalline solid.

Yield : 33 g (75%)

m.p. : 55-56°C (Lit.[116] m.p. 56-57°C)

IR (KBr) : 3600 Cm^{-1}

^1H NMR : δ 1.25-2.2 (m, 9H 1H D_2O exchangeable), 2.4 (m, 1H), 3.6 (m, 1H), 7.12-7.3 (m, 5H).

^{13}C NMR : δ 25.00, 26.00, 33.29, 34.41, 53.18, 74.29, 126.83, 128.01, 128.77, 143.47.

(±)-trans-2-Phenylcyclohex-1-yl acetate (113):

A solution of (±)-trans-2-phenylcyclohexan-1-ol **(±)-5** (200 mM, 35.2 g) in dichloromethane (50 mL) was added dropwise to a stirred solution of 4-dimethylaminopyridine (6.8 mM, 840 mg) and pyridine (420 mM, 34 mL) in dichloromethane (100 mL) at $0^{o}C$. After 10 min, acetic anhydride (400 mM, 37.74 mL) was added slowly at the same temperature. After stirring for 2 h at room temperature, the reaction mixture was poured into a mixture of crushed ice and 6 N HCl solution (100 mL) and extracted with ether (3 x 50 mL). The organic layer was washed with 2 N HCl solution, sat.Na HCO_3 solution and dried over anhy.Na_2SO_4. Removal of the solvent gave pure racemic acetate **113** as a liquid.

Yield : 41 g (94%)

IR (neat): 1730 cm^{-1}

^{1}H NMR : δ 1.2-2.2 (m, 11H), 2.6 (m 1H), 4.96 (m, 1H), 7.08-7.28 (m, 5H).

^{13}C NMR : δ 20.76, 24.70, 25.76, 32.39, 33.76, 49.70, 75.82, 126.41, 127.53, 128.30, 143.18, 170.30.

Enzymatic hydrolysis of (±)-trans-2-phenylcyclohex-1-yl acetate: (-)-(1R,2S)-2-Phenylcyclohexan-1-ol ((-)-5):

This reaction was carried out according to Whitesell procedure [116] with some modification.

To 800 mL of 0.5 M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer, (±)-trans-2-phenylcyclohex-1-yl acetate (**113**) (100 mM, 21.8 g) in acetone (100 mL) was added with rapid stirring at room temperature. After 1 h, pig liver acetone powder (PLAP)(4 g) was added and the stirring was continued for 10 days. (35:65 conversion ratio by HPLC). The reaction was quenched by adding 2 N HCl to pH 4.0. Then NaCl solid (10 g) and dichloromethane (200 mL) were added. After 30 min stirring, the residue was allowed to settle, aqueous layer was separated and extracted with dichloromethane (3 x 100 mL). The PLAP residue from the organic layer was filtered and the organic layers were combined, dried over anhy.Na_2SO_4 and concentrated. Column chromatography (10% ethyl acetate in hexane) purification of the crude material furnished 13 g of acetate and 5.5 g of (-) alcohol. The (-) alcohol **(-)-5** obtained was crystallized from pentane as a crystalline solid.

Yield : 5.35 g (89%)

m.p. : 63-65°C [Lit.[116] m.p. 64-65°C]

$[\alpha]_D^{24}$: - 58.2 (c 0.84, MeOH) e.e >99%

[Lit.[116] $[\alpha]_D^{27}$ - 58.4 (c 10, MeOH) e.e 100%]

(+)-(1S,2R)-2-Phenylcyclohexan-1-ol ((+)-5):

The acetate of the (+)-alcohol **113'** (13 g) (recovered

acetate in the above enzymatic hydrolysis) was again subjected to enzymatic hydrolysis with PLAP (3 g) following the above mentioned procedure. After 7 days the reaction mixture was quenched by adding dil.HCl solution and the usual work up gave acetate of pure (+)-alcohol **113''** (8 g) and (-) alcohol (having less rotation) (3.8 g).

To a stirred solution of KOH (73.3 mM, 4.1 g) in methanol (20 mL) trans-2-phenylcyclohex-1-yl acetate (**113''**) (36.7 mM, 8 g) was added and stirred for 2 h at room temperature. Water (20 mL) was added and extracted with ether (3 x 20 mL). The ethereal solution was dried over anhy.Na_2SO_4 and concentrated. The solid obtained was crystallized from pentane as a crystalline solid.

Yield : 6 g (94%)

m.p. : 63-65°C [Lit[116]. m.p. 64-65°C]

$[\alpha]_D^{24}$: + 58.2 (c 0.95, MeOH), e.e >99%

[Lit[116]. $[\alpha]_D^{23}$ + 58.3 (c 10, MeOH) e.e 100%]

[(1S, 2R)-2-Phenylcyclohex-1-yl] bromoacetate (114):

A solution of (1S, 2R)-2-phenylcyclohexan-1-ol **((+)-5)** (45 mM, 7.92 g) in dry ether (20 mL) was added dropwise to a stirred solution of ethylmagnesium bromide (45 mM) [prepared from bromoethane and magnesium turnings] in dry ether (100 mL) at 0°C.

After the addition the reaction was allowed to warm to room temperature and stirring was continued for one hour and then bromoacetyl bromide (45 mM, 3.92 mL) was added and stirred for 7 h at room temperature. The reaction mixture was poured into ice cold water, extracted with ether (3 x 20 mL). The extracts were combined, washed with sat.K_2CO_3 solution, water and dried over anhy.Na_2SO_4. Evaporation of the solvent followed by column chromatography purification (5% ethyl acetate in hexane) gave bromoacetate **114** as a liquid.

Yield : 9.34 g (70%)

$[\alpha]_D^{24}$: + 19.81 (c 4.44, $CHCl_3$)

IR (neat): 1730 cm^{-1}

^1H NMR : δ 1.2-2.2 (m, 8H), 2.64 (m, 1H), 3.48 (s, 2H), 4.96 (m, 1H), 7.1-7.3 (m, 5H).

^{13}C NMR : δ 24.35, 25.41, 25.64, 31.64, 33.47, 49.29, 77.82, 126.61, 127. 36, 128.18, 148.42, 166.24.

Analysis Calcd.: C,56.58; H,5.77;

for $C_{14}H_{17}BrO_2$

Found : C, 56.70; H, 5.74.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **114**):

This was prepared from [(1S,2R)-2-phenylcyclohex-1-yl]

bromoacetate (**114**) and benzaldehyde (Reformatsky reaction time 3h).

Yield : 51%

m.p. : 98-103°C [Lit.[130] optically pure acid m.p. 116°C]

$[\alpha]_D^{24}$: + 7.87 (c 4.5, EtOH), e.e 44%, conf.R

[Lit.[53] $[\alpha]_D^{23}$ + 17.9 (c 1, EtOH), e.e 100%, conf.R]

This compound has IR, ^1H NMR and ^{13}C NMR spectral data identical with that of the compound prepared using **81**.

3-Hydroxy-3-phenylbutanoic acid (77b):

(Using Reformatsky reagent **114**):

This was prepared from [(1S,2R)-2-phenylcyclohex-1-yl] bromoacetate (**114**) and acetophenone (Reformatsky reaction time 3 h).

Yield : 50%

m.p. : 77-80°C [Lit.[133] optically pure acid m.p. 83.4-83.7°C]

$[\alpha]_D^{24}$: - 9.2 (c 5.18, EtOH) e.e 89%, conf.R

[Lit.[49] $[\alpha]_D^{23}$ + 6.0 (c 3, EtOH), e.e 58%, conf.S]

This compound has the same IR, ^1H NMR and ^{13}C NMR data as that of the compound prepared using **87**.

3-Hydroxy-3-phenylpentanoic acid (77c):

(Using Reformatsky reagent **114**):

This was preared from [(1S,2R)-2-phenylcyclohex-1-yl

bromoacetate (**114**) and propiophenone (Reformatsky reaction time 3 h).

Yield : **45%**

m.p. : 114-116°C [Lit.[132] optically pure acid m.p. 122-123°C]

$[\alpha]_D^{24}$: Nil

This compound has IR, ^1H NMR, and ^{13}C NMR spectral data identical with that of the compound prepared using **90**.

3-Hydroxytetradeconoic acid (77d):

(Using Reformatsky reagent **114**):

This compound was obtained from [(1S,2R)-2-phenylcyclohex-1-yl] bromoacetate (**114**) and dodecanal (Reformatsky reaction time 3 h).

Yield : 35%

m.p. : 75-77°C [Lit.[68] optically pure acid m.p. 72°C]

$[\alpha]_D^{24}$: Nil

This has the same IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **90**.

3-Hydroxy-3-(p-tolyl)propionic acid (77e):

(Using Reformatsky reagent **114**):

This was prepared from [(1S,2R)-2-phenylcyclohex-1-yl] bromoacetate (**114**) and p-tolualdehyde (Reformatsky reaction time

3 h).

Yield : 47%

m.p. : 75-76°C

$[\alpha]_D^{24}$: - 3.46 (c 6.64, EtOH), e.e 31%

IR(CH_2Cl_2): 3500-2600, 1710 cm^{-1}

^1H NMR : (Acetone d_6) : δ 2.26 (s, 3H), 2.6 (d, 2H, J = 7Hz), 5.08 (t, 1H, J = 8Hz), 7.1 (d, 2H, J = 6 Hz) 7.4 (d, 2H, J = 6 Hz).

^{13}C NMR : (Acetone d_6) : δ 20.41, 43.82, 70.18, 126.06, 129.12, 136.95, 141.64, 173.12.

Analysis Calcd.: C, 66.65; H, 6.71;

for $C_{10}H_{12}O_3$

Found : C, 66.79; H, 6.73.

The structure of the acid **77e** was further confirmed by its methyl ester.

Methyl 3-hydroxy-3-(p-tolyl)propionate (116'):

To a solution of chiral 3-hydroxy-3-(p-tolyl)propionic acid (**77e**) (0.55 mM, 100 mg) in 10 mL of dry ether, a solution of diazomethane in ether (prepared from N-nitrosomethylurea) was added till a light yellow colour remained. Solvent was removed and crude compound was passed through a column (10% ethyl acetate in hexane) which afforded methyl ester **116'**.

Yield : 96 mg (90%)

IR (neat): 3450, 1720 cm^{-1}

^1H NMR : δ 2.36 (s, 3H), 2.72 (t, 2H, J = 5Hz), 3.2 (b, 1H, -OH), 3.68 (s, 3H), 5.08 (t, 1H, J = 5Hz), 7.4 (q, 4H, J = 7Hz)

Determination of e.e:

Preparation of (±)-methyl 3-hydroxy-3-(p-tolyl)propionate (116):

To a stirred suspension of zinc (10 mM, 653 mg) in dry refluxing benzene (10 mL) p-tolualdehyde (5 mM, 0.59 mL) and methyl bromoacetate (5 mM, 0.47 mL) were added slowly and refluxed for 3 h. The reaction mixture was allowed to cool to room temperature, sat.NH_4Cl solution was added and extracted with ether (3 x 10 mL). The organic layer was dried over anhy.Na_2SO_4 and evaporated. The crude material obtained was purified by column chromatography (10% ethyl acetate in hexane) to furnish **116** as a colourless liquid.

Yield : 600 mg (62%)

The compound has the same IR, ^1H NMR spectral data as that of **116'**.

^1H NMR analysis using chiral shift reagent, $Eu(hfc)_3$:

^1H NMR spectrum of the racemic methyl ester **116** (5 mg) was

recorded in the presence of $Eu(hfc)_3$ (20 mg). The $-COOCH_3$ original singlet at δ 3.68 shifts and spilts into two distinct singlets of equal integration indicating that they arise from two enantiomers. Similarly the chiral methyl ester **116'**, prepared from optically active 3-hydroxy-3-(p-tolyl)propionic acid (**77e**) was analyzed for enantiomeric purity using $Eu(hfc)_3$. The original singlet of $-COOCH_3$ appeared as two distinct singlets in 7.5:4 integration showing that the optical purity is 31%.

3-Hydroxy-3-(1-naphthyl)propionic acid (77f):

(Using Reformatsky reagent **114**):

This compound was prepared (as a white solid) from [(1S,2R)-2-phenylcyclohex-1-yl] bromoacetate (**114**) and 1-naphthaldehyde (Reformatsky reaction time 3 h).

Yield : 63%

m.p. : 162-164°C

$[\alpha]_D^{24}$: - 6.8 (c 1.9, EtOH), e.e 22%

IR(CH_2Cl_2): 3500-2700, 1710 cm^{-1}

^1H NMR : (Acetone d_6) : δ 2.8 (m, 2H, J = 6Hz), 5.92 (dd, 1H, J = 4Hz, 8Hz), 7.4-8.2 (m, 7H).

^{13}C NMR :(Acetone d_6) :δ 41.06, 65.06, 121.00, 123.36, 123.65, 123.94, 125.65, 126.71, 128.06, 128.18, 131.94, 137.94, 170.60.

The structure of the acid **77f** was also confirmed by its methyl ester.

Methyl 3-hydroxy-3-(1-naphthyl)propionate (117'):

This was prepared (as a liquid) from optically active 3-hydroxy-3-(1-naphthyl)propionic acid (**77f**) and diazomethane following the same procedure as in **116'**.

Yield : 92%

IR(neat) : 3500.1720 Cm^{-1}

^1H NMR : δ 2.84 (m, 2H), 3.2 (b, 1H, -OH), 3.72 (s, 3H), 5.88 (t, 1H, J = 4Hz), 7.32 - 8.04 (m, 7H).

Determination of e.e:

Preparation of (±)-methyl 3-hydroxy-3-(1-naphthyl)propionate (117):

This was prepared from 1-naphthaldehyde and methyl bromoacetate following the same procedure as in **116**. This compound, **117**, was obtained as a liquid.

Yield : 60%

This has the same IR, ^1H NMR spectral data as that of **117'**.

^1H NMR analysis using chiral shift reagent $Eu(hfc)_3$:

Racemic methyl ester **117** ^1H NMR spectrum was recorded in the presence of $Eu(hfc)_3$. The original singlet of $-COOCH_3$ at δ 3.72

shifts and splits into two distinct singlets of equal integration indicating that they are arising from two enantiomers. Similarly, the methyl ester of optically active acid **117'** was analyzed for enantiomeric excess using $Eu(hfc)_3$. The singlet of $-COOCH_3$ appeared as two distinct singlets in 7.8:5.0 integration showing that the optical purity is 22%.

3-Hydroxy-4-methylpentanoic acid (77g):

(Using Reformatsky reagent **114**):

This was obtained as a colourless liquid from [(1S,2R)-2-phenylcyclohex-1-yl] bromoacetate (**114**) and isobutyraldehyde (Reformatsky reaction time 3 h).

Yield : 45%

$[\alpha]_D^{24}$: + 4.13 (c 6.62, $CHCl_3$), e.e 11%, conf.R

[Lit.[54] $[\alpha]_D^{25}$ + 36.9 (c 1.59, $CHCl_3$), e.e 98%, conf.R)

IR (neat): 3500-2700, 1720 cm^{-1}

^1H NMR : δ 0.9 (d, 6H, J = 6Hz), 1.68 (m, 1H), 2.48 (m, 2H),3.76 (m, 1H), 6.0 (b, 2H, -OH, -COOH, D_2O exchangeable).

^{13}C NMR : δ 17.58, 18.17, 33.06, 38.41, 73.06, 176.95,

(±)-trans-2-Phenoxycyclohexan-1-ol ((±)-118):

This was prepared according to literature[134] procedure reported for 2-(2-naphthyloxy)phenylcyclohexan-1-ol.

To a stirred solution of sodium phenoxide (300 mM) in H_2O (50 mL) [prepared from NaOH (300 mM, 12 g) and phenol (300 mM, 26.36 mL)] cyclohexene oxide (100 mM, 10.11 mL) was added dropwise at reflux temperature. After refluxing for 2 h, the reaction mixture was allowed to cool to room temperature. The solid obtained was filtered, washed throughly with water and dried under reduced pressure. It was crystallized from hexane as a crystalline white solid.

Yield : 15 g (78%)

m.p. : 81-82°C (Lit.[119] m.p. 82°C)

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

^1H NMR : δ 1.2-2.24 (m, 8H), 2.52 (s, 1H, D_2O exchangeable) 3.72 (m, 1H), 3.96 (m, 1H), 6.92-7.32 (m, 5H).

^{13}C NMR : δ 23.94, 29.17, 32.06, 73.41, 82.24, 116.47, 121.36, 129.65, 158.00.

Analysis cacld. : C, 74.97; H,8.39;

for $C_{12}H_{16}O_2$

Found : C, 74.99; H,8.40.

(±)-trans-2-Phenoxycyclohex-1-yl acetate (119):

The acetylation of (±)-trans-2-phenoxycyclohexan-1-ol (**(±)-118**) was carried out following the same procedure as in **113**

to furnish (±)-trans-2-phenoxycyclohex-1-yl acetate (**119**), as a colourless liquid.

Yield : 93%

b.p. : 126-128°C/1.5 mm

IR (neat): 1740 cm^{-1}

^1H NMR : δ 1.2-2.2 (m, 11H), 4.2 (m, 1H), 4.96 (m, 1H), 6.84-7.4 (m, 5H).

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

Enzymatic hydrolysis of (±)-trans-2-phenoxycyclohex-1-yl acetate (119):

(-)-(1R,2R)-2-Phenoxycyclohexan-1-ol ((-)-118):

The hydrolysis was carried out according to the procedure developed in our laboratory.[118]

To 400 mL of 0.5 M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer, (±) trans-2-phenoxycyclohex-1-yl acetate (**(±)-118**) (100 mM, 23.4 g) in ether (100 mL) was added with rapid stirring at room temperature. After 15 min, Pig Liver Acetone Powder (PLAP) (20 g) was added. After 72 h (conversion ratio 40:60, determined by HPLC analysis), the reaction mixture was quenched with 2 N HCl solution. Then NaCl (10 g) and dichloromethane (200 mL) were added and stirring was continued for 30 min. The PLAP residue was allowed to settle,

aqueous layer was separated and extracted with dichloromethane (3 x 100 mL). The PLAP residue from the organic layer was filtered and the organic layers were combined, dried over anhy. Na_2SO_4 and evaporated. The crude liquid obtained was purified by column chromatography (using 10% ethyl acetate in hexane) to afford 13.5 g of acetate and 7.2 g of (-) alcohol (**(-)-118**), after crystallizing twice from hexane as a crystalline solid.

Yield : 7 g (91%)

m.p. : 94-95°C

$[\alpha]_D^{24}$: - 79.2 (c 0.96, MeOH), e.e 98%

[Lit[118]. $[\alpha]_D^{23}$ - 79.1 (c 0.86, MeOH), e.e 98%]

(1S,2S)-2-Phenoxycyclohexan-1-ol ((+)-118):

The acetate of the (+) alcohol **119'** (13.5 g) (recovered acetate in the enzymatic hydrolysis) obtained was again subjected to enzymatic hydrolysis with PLAP, following the above mentioned procedure. After 48 h, the reaction was quenched and the usual workup gave 8.5 g of acetate of pure (+) alcohol **119''** and 3 g of (-) alcohol (with less rotation).

To a stirred solution of KOH (72.6 mM, 4.06 g) in methanol (20 mL) acetate of (+)alcohol **119''** (36.3 mM, 8.5 g) was added and stirred for 2 h at room temperature. Water (20 mL) was added and

extracted with ether (3 x 20 mL). The ethereal solution was dried over anhy. Na_2SO_4 and concentrated. After two crystallizations from hexane gave a crystalline solid of the (+) alcohol [**(+)-118**].

Yield : 6.5 g (93%)

m.p. : 94-96°C

$[\alpha]_D^{24}$: + 79.4 (c 0.9, MeOH), e.e 98%

[Lit[118]. $[\alpha]_D^{23}$ - 79.1, (c 0.86, MeOH), e.e 98%]

[(1S,2S)-2-Phenoxycyclohex-1-yl] bromoacetate (121):

This was prepared from (1S,2S)-2-phenoxycyclohexan-1-ol (**(+)-118**) and bromoacetyl bromide following the same procedure as in **114**. This compound, **121**, was obtained as a colourless liquid.

Reaction time : 12 h

Yield : 70%

$[\alpha]_D^{24}$: + 12.75 (c 3.68, $CHCl_3$).

IR (neat): 1730 cm^{-1}

^1H NMR : δ 1.2-2.2 (m, 8H), 3.6 (s, 2H), 4.24 (m, 1H), 5.04 (m, 1H), 6.8-7.36 (m, 5H).

^{13}C NMR : δ 22.64, 22.76, 25.82, 29.11, 29.41, 75.65, 78.18, 116.18, 121.12, 129.36, 158.00, 166.60.

3-Hydroxy-3-phenylpropionic acid (77a):

(Using Reformatsky reagent **121**):

This was prepared from (1S,2S)-2-phenoxycyclohex-1-yl bromoacetate (**121**) and benzaldehyde (Reformatsky reaction time 3h).

Yield : 55%

m.p. : 96-99°C [Lit.[130] racemic acid 96°C]

$[\alpha]_D^{24}$: + 2.68 (c 7.6, EtOH), e.e 15%, conf.R

[Lit.[53] $[\alpha]_D^{25}$ + 17.9 (c 1.94, EtOH), e.e 100%, conf.R]

This compound has IR, ^1H NMR and ^{13}C NMR spectral data identical with that of the compound prepared using **81**.

[(1R,2S)-2-Phenylcyclohex-1-yl] phenylglyoxalate (129):

A stirred solution of (1R,2S)-2-phenylcyclohexan-1-ol (**(-)-5**) (25 mM, 4.4 g), benzoylformic acid (27 mM, 4.05 g) and p-toluenesulfonic acid (0.75 mM, 150 mg) in 50 mL of dry benzene was heated under reflux with azeotropic removal of water for 3 h. The reaction mixture was cooled, taken in ether, washed with sat.K_2CO_3 solution and water. The organic layer was dried over anhy.Na_2SO_4 and evaporated. The crude material was passed through a column (5% ethyl acetate in hexane). The solid thus obtained was crystallized from hexane to provide the compound **129**.

Yield : 4.71 g (61%)

m.p. : 66-68°C

$[\alpha]_D^{24}$: - 14.68 (c 1.97, EtOH)

IR($CHCl_3$): 1720, 1700 cm^{-1}

^1H NMR : δ 1.32-2.28 (m, 8H), 2.72 (m, 1H), 5.32 (m, 1H), 7.16-7.6 (m, 10H).

^{13}C NMR : δ 24.82, 25.64, 32.23, 34.17, 49.94, 78.47, 127.06, 128.06, 128.95, 129.89, 132.24, 134.71, 142.95, 164.18, 187.47.

Analysis Calcd. : C, 77.90; H, 6.54;

for $C_{20}H_{20}O_3$

Found : C, 77.99; H, 6.51.

[(1R,2S)-2-Phenylcyclohex-1-yl] 2-hydroxy-2-phenylbutanoate (130a):

To a stirred solution of ethylmagnesium bromide (7.5 mM), [prepared from bromoethane and magnesium] in dry ether (15 mL), anhy.$ZnCl_2$ [7.5 mM, 1.02 g] was added at 0°C. After 2 h stirring at 0°C, it was cooled to -78°C. To this precooled (at -78°C) solution of [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) (2.5 mM, 770 mg) in ether (15 mL) was added. After 3 h stirring at -78°C, the reaction mixture was allowed to warm to 0°C. The reaction mixture was quenched by the addition of sat.NH_4Cl solution (10 mL) and extracted with ether. The ethereal solution was dried over anhy.Na_2SO_4 and evaporated. The compound obtained was used for the next step without any purification.

Yield : 750 mg (89%)

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.7 (t, 3H, J = 7Hz), 1.2-2.32 (m, 10H), 2.68 (m, 1H), 3.44 (s, 1H, -OH, D_2O exchangeable) 5.00 (m, 1H), 6.9-7.16 (m, 10H).

(R)-2-Hydroxy-2-phenylbutanoic acid (78a):

To a stirred solution of KOH (4.49 mM, 250 mg) in methanol (5 mL), α-hydroxy ester **130a** (2.2 mM, 750 mg) was added and stirred for 2 h at room temperature. The reaction mixture was diluted with water (5 mL), extracted with ether (3 x 10 mL) (to recover the chiral auxiliary). The aqueous layer was neutralized by adding 2 N HCl solution and extracted with ether (3 x 10 mL). The ethereal solution was dried over anhy.Na_2SO_4 and evaporated. The solid obtained was crystallized from hexane-ether mixture as a crystalline solid.

Yield : 350 mg (88%)

m.p. : 119-120°C [Lit.[91] optically pure acid m.p. 124-125°C]

$[\alpha]_D^{24}$: - 27.97 (c 4.8, EtOH), e.e 84%, conf.R

[Lit.[91] $[\alpha]_D^{25}$ + 33.3 (c 0.87, EtOH), e.e >99%, conf.S]

IR (KBr) : 3500, 3300-2600, 1710 cm^{-1}

^1H NMR : δ 0.92 (t, 3H, J = 5Hz), 1.8-2.5 (m, 2H), 5.6 (b, 2H, -OH, -COOH, D_2O exchangeable), 7.2-7.7 (m, 5H).

^{13}C NMR : (Acetone d_6): δ 7.70, 32.76, 78.53, 125.94, 127.59, 128.24, 143.00, 176.07

[(1R,2S)-2-Phenylcyclohex-1-yl] 2-hydroxy-2-phenylhexanoate (130b):

This compound was prepared from [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) and n-butylzinc chloride following the same procedure as in **130a**. This compound, **130b**, was obtained as a viscous liquid.

Yield : 87%

IR (neat): 3500, 1720 cm^{-1}

^{1}H NMR : δ 0.84 (t, 3H, J = 5 Hz), 0.96-2.32 (m, 14H), 2.68 (m, 1H), 3.44 (s, 1H, -OH, $-D_2O$ exchangeable), 5.00 (m, 1H) 6.8-7.24 (m, 10H)

(R)-2-Hydroxy-2-phenylhexanoic acid (78b):

This compound was prepared by the hydrolysis of the α-hydroxy ester **130b** following the same procedure as in **78a**. This compound, **78b**, was obtained as a white solid.

Yield : 92%

m.p. : 98-100°C

$[\alpha]_D^{24}$: - 21.5 (c 4.73, EtOH), e.e 93%, conf.R

[Lit.[86] $[\alpha]_D^{22}$ - 19.0 (c 2.2, EtOH), e.e 82%, conf.R]

IR (KBr) : 3550, 3300-2600, 1720 cm^{-1}

^{1}H NMR : δ 0.9 (distorted t, 3H), 1.06-1.46 (m, 4H), 1.82-2.4 (m, 2H), 5.4 (b, 2H, -OH, -COOH, D_2O exchangeable), 7.2-7.68 (m, 5H).

^{13}C NMR : δ 17.88, 22.75, 25.70, 39.01, 78.53, 125.65, 128.12, 128.53, 141.18, 180.59.

[(1R,2S)-2-Phenylcyclohex-1-yl] 2-hydroxy-2-phenyloctanoate (130c):

This compound was prepared from [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) and n-hexylzinc chloride, following the same procedure as in **130a**. This compound, **130c**, was obtained as a viscous liquid.

Yield : 85%

IR (neat): 3500, 1720 cm^{-1}

^{1}H NMR : δ 0.88 (distorted t, 3H), 1.0-2.36 (m, 18H), 2.64 (m, 1H), 3.52 (s, 1H, -OH, D_2O exchangeable), 5.0 (m, 1H), 7.00-7.3 (m, 10H).

^{13}C NMR : δ 14.05, 22.53, 23.41, 24.64, 25.70, 29.35, 31.64, 32.06, 34.35, 39.94, 49.70, 78.41,78.71, 125.12, 126.71, 127.12, 127.42, 128.06, 128.59, 143.18, 143.71, 174.77.

(R)-2-Hydroxy-2-phenyloctanoic acid (78c):

Hydrolysis of the α-hydroxy ester **130c** was carried out

following the same procedure as in **78a** to obtain **78c** as a white solid.

Yield : 86%

m.p. : 95-97^{o}C

$[\alpha]_D^{24}$: - 19.3 (c 3.46, EtOH), e.e > 99%, conf.R

[Lit.[86] $[\alpha]_D^{22}$ - 17 (c 2.2, EtOH), e.e 88%, conf.R]

IR (KBr) : 3550, 3300-2600, 1720 cm^{-1}

^{1}H NMR : δ 0.9 (distorted t, 3H), 1.1-1.48 (m, 8H), 2.1 (m, 2H), 5.2 (b, 2H, -OH, -COOH, D_2O exchangeable), 7.2-7.7 (m, 5H).

^{13}C NMR : δ 14.00, 22.59, 23.53, 29.29, 31.64, 39.59, 78.41, 125.65, 128.12, 128.48, 141.18, 180.54.

Determination of e.e:

Preparation of (±)-methyl 2-hydroxy-2-phenyloctanoate (131):

To a stirred solution of n-hexylmagnesium bromide (7.5 mM) (prepared from n-hexyl bromide and magnesium) in dry ether (10 mL) at 0^{o}C, anhy.$ZnCl_2$ (7.5 mM, 1.02 g) was added and stirred for 2 h at the same temperature. To this, a solution of methyl phenyl-glyoxalate (2.5 mM, 410 mg) in ether (5 mL) was added at 0^{o}C. After 2 h stirring at room temperature, sat.NH_4Cl solution was added and extracted with ether (3 x 10mL). The ethereal solution was dried over anhy.Na_2SO_4 and evaporated. Purification by column chromatography (10% ethyl acetate in hexane) afforded α-hydroxy ester **131** as a colourless liquid.

Yield : 525 mg (84%)

IR (neat): 3500, 1720 cm^{-1}

(±)-Methyl 2-methoxy-2-phenyloctanoate (132):

This was prepared according to the literature procedure[90].

To a stirred suspension of mineral oil free NaH (0.5 mM, 12 mg) in THF (5 mL), methyl 2-hydroxy-2-phenyloctanoate (**131**) (0.5 mM, 125 mg) in THF was added and stirred overnight at room temperature. To this, methyl iodide (1 mM, 0.1 mL) was added and stirred for 24 h at room temperature. A saturated solution of Na_2SO_4 was added and extracted with ether (3 x 10 mL). The ethereal solution was dried over anhy.Na_2SO_4 and evaporated. The compound obtained was purified by passing through a column (10% ethyl acetate in hexane).

Yield : 85 mg (65%)

IR (neat): 1720 cm^{-1}

^1H NMR : δ 0.84 (distorted t, 3H), 1.0-1.4 (m, 8H), 1.92-2.32 (m, 2H), 3.2 (s, 3H), 3.7 (s, 3H), 7.2-7.54 (m, 5H).

Methyl 2-hydroxy-2-phenyloctanoate (131'):

To a solution of optically active 2-hydroxy-2-phenyloctanoic acid (**78c**) (0.42 mM, 100 mg) in ether, a solution of diazomethane (prepared from N-nitrosomethylurea) in ether was added till a

light yellow colour persists. The solvent was removed and the crude compound obtained was directly used in the next step without any purification.

yield : 98 mg (93%)

IR (neat): 3500, 1720 Cm^{-1}

Methyl 2-methoxy-2-phenyloctanoate (132'):

This was prepared (as a liquid) from α-hydroxy ester **131'** and methyl iodide following the same procedure as in **132**.

Yield : 68%

This compound has the same IR, ^1H NMR spectral data as that of **132**.

^1H NMR analysis using chiral shift reagent, $Eu(hfc)_3$:

^1H NMR spectrum of the racemic methoxy ester **132** (5 mg) was recorded in the presence of shift reagent, $Eu(hfc)_3$, (25 mg). The $-COOCH_3$ singlet (at δ 3.7) appeared as two distinct singlets of equal integration indicating that the two singlets arise from two enantiomers. Similarly, the ^1H NMR spectrum of the optically active compound **132'** in the presence of $Eu(hfc)_3$ was recorded. The original singlet of $-COOCH_3$ (at δ 3.7) shifts and was intact as a singlet showing that the optical purity is atleast 99%.

[(1R,2S)-2-Phenylcyclohex-1-yl] 2-hydroxy-3-methyl-2-phenylbutanoate (130d):

This compound was prepared from [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) and i-propylzinc chloride following the same procedure as in **130a**. This comound, **130d**, was obtained as a colourless oil.

Yield : 90%

IR (neat): 3500, 1720 cm^{-1}

^{1}H NMR : δ 0.5 (d, 3H, J = 6Hz), 0.76 (d, 3H, J = 6Hz), 1.12-2.84 (m, 10H), 3.32 (s, 1H, -OH, D_2O exchangeable), 4.92 (m, 1H), 6.8-7.2 (m, 10H).

^{13}C NMR : δ 15.72, 16.79, 24.56, 25.63, 31.93, 34.42, 35.54, 49.65, 78.61, 80.66, 125.53, 126.56, 126.90, 127.19, 127.83, 128.51, 140.96, 142.57, 175.00.

(R)-2-Hydroxy-3-methyl-2-phenylbutanoic acid (78d):

Hydrolysis of the α-hydroxy ester **130d** was carried out following the same procedure as in **78a** to provide **78d** as a crystalline solid.

Yield : 69%

m.p. : 102-103°C [Lit.[91] optically pure acid m.p. 103-105°C]

$[\alpha]_D^{24}$: - 32.25 (c 2.55, EtOH), e.e 99%, conf.R

[Lit.[91] $[\alpha]_D^{25}$ + 32.5 (c 2, EtOH), e.e > 99%, conf.S]

IR (KBr) : 3500, 3300-2600, 1720 cm^{-1}

^{1}H NMR : δ 0.72 (d, 3H, J = 6Hz), 1.08 (d, 3H, J = 6Hz), 2.6 (m, 1H), 7.2-7.76 (m, 5H).

^{13}C NMR : δ 15.70, 17.17, 35.82, 81.30, 126.06, 127.94, 128.36, 140.42, 180.88.

The structure of the acid **78d** was further confirmed by its methyl ester.

Methyl 2-hydroxy-3-methyl-2-phenylbutanoate (133'):

This compound was prepared (as a liquid) from α-hydroxy acid **78d** and diazomethane following the same procedure as in **131'**.

Yield : 89%

IR (neat): 3500, 1720cm^{-1}.

^{1}H (NMR) : 0.68 (d, 3H, J = 6Hz), 0.92 (d, 3H, J = 6Hz), 2.52 (m, 1H), 3.6 (s, 1H, -OH), 3.76 (s, 3H), 7.2-7.64 (m, 5H).

Determination of e.e:

Preparation of (±)-methyl 2-hydroxy-3-methyl-2-phenylbutanoate (133):

This was prepared (as a liquid) from methyl phenylglyoxalate and i-propylzinc chloride following the same procedure as in **131**.

Yield : 85%

IR (neat): 3500, 1720 cm^{-1}.

(±)-Methyl 2-methoxy-3-methyl-2-phenylbutanoate (134):

This compound was prepared (as a liquid) from α-hydroxy ester **133** and methyl iodide following the same procedure as in **132**.

Yield : 60%

IR (neat): 1720 cm^{-1}

^1H NMR : δ 0.8 (d, 3H, J = 6Hz), 0.88 (d, 3H, J = 6Hz), 2.44 (m, 1H), 3.2 (s, 3H), 3.8 (s, 3H), 7.2-7.38 (m, 5H).

Methyl 2-methoxy-3-methyl-2-phenylbutanoate (134'):

This was prepared (as a liquid) from α-hydroxy ester **133'** and methyl iodide following the same procedure as in **132**.

Yield : 55%

This has the IR, ^1H NMR spectral data identical with that of **134**.

^1H NMR analysis using chiral shift reagent, Eu(hfc)$_3$:

Racemic methoxy ester **134** (5 mg) ^1H NMR spectrum was recorded in the presence of Eu(hfc)$_3$ (25 mg) and the -COOCH$_3$ singlet at δ 3.8 appeared as two distinct singlets of equal integration. Similarly, ^1H NMR spectrum of the optically active compound **134'** in the presence of Eu(hfc)$_3$ was recorded. The

original singlet of $-COOCH_3$ (at δ 3.8) shifts and was intact as a singlet showing that the optical purity is atleast 99%.

[(1R,2S)-2-Phenylcyclohex-1-yl] 2-hydroxy-4-methyl-2-methylpentanoate (130e):

This compound was prepared from [(1R,2S)-2-phenylcyclohex-1-yl] phenylglyoxalate (**129**) and i-butylzinc chloride following the same procedure as in **130a**. This compound, **130e**, was obtained as a colourless oil.

Yield : 70%

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.52-0.88 (m, 6H), 1.0-2.8 (m, 12H), 3.4 (b, 1H, -OH, D_2O washable), 4.92 (m, 1H), 6.76-7.4 (m, 10H)

^{13}C NMR : δ 23.78, 24.19, 24.48, 24.60, 25.54, 31.88, 34.89, 47.79, 49.50, 78.32, 78.53, 124.76, 126.29, 126.70, 126.99, 127.64, 128.23, 128.46, 142.37, 142.42, 174.66

(R)-2-Hydroxy-4-methyl-2-phenylpentanoic acid (78e):

Hydrolysis of the α-hydroxy ester **130e** was carried out following the same procedure as in **78a** to give **78e**. This compound, **78e**, was obtained as a white solid.

Yield : 71%

m.p. : 117-119°C [Lit.[91] optically pure acid m.p. 118-120°C]

$[\alpha]_D^{24}$: - 20.0 (c 3.5, EtOH), e.e 99%, conf.R

[Lit.[91] $[\alpha]_D^{25}$ + 20.0 (c 2, EtOH), e.e > 99%, conf.S]

IR (KBr) : 3500, 3300-2600, 1720 cm^{-1} .

^1H NMR : δ 0.9 (t, 6H, J = 5Hz), 1.64-2.2 (m, 3H), 5.5 (b, 2H, -OH, -COOH, D_2O exchangeable), 7.4-7.8 (m, 5H).

Determination of ee

Preparation of (±) methyl 2-hydroxy-4-methyl-2-phenylpentanoate (135):

This was prepared from methyl phenylglyoxalate and i-butylzinc chloride following the same procedure as in **131**.

Yield : 87%

IR (neat): 3500, 1720 cm^{-1}

Methyl 2-methoxy-4-methyl-2-phenylpentanoate (136):

This was prepared from α-hydroxy ester **135** and methyl iodide following the same procedure as in **132**

Yield : 62%

IR (neat): 1720 cm^{-1}

^1H NMR : δ 0.8 (t, 6H, J = 7Hz), 1.52 (m, 1H), 2.08 (dd, 2H, J = 4Hz, 8Hz), 3.08 (s, 3H), 3.6 (s, 3H), 7.16-7.4 (m, 5H).

Methyl 2-hydroxy-4-methyl-2-phenylpentanoate (135'):

This was prepared from α-hydroxy acid **78a** and diazomethane following the same procedure as in **131'**.

Yield : 86%

IR (neat): 3500, 1720 cm^{-1}

Methyl 2-methoxy-4-methyl-2-phenylpentanoate (136'):

This was prepared from α-hydroxy ester **135'** and methyl iodide following the same procedure as in **132**. This compound, **136'**, was obtined as a colourless liquid.

Yield : 64%

This has the same IR, ^1H NMR spctral data as that of the compound **136**.

^1H NMR analysis using chiral shift reagent, Eu(hfc)$_3$:

Racemic methoxy ester **136** (5 mg) ^1H NMR spectrum was recorded in the presence of Eu(hfc)$_3$ (25 mg) and the -$COOCH_3$ singlet at δ 3.6 shifts and splits into two distinct singlets of equal integration. Similarly, ^1H NMR spectrum of the optically active compound **136'** in the presence of Eu(hfc)$_3$ was recorded. The original singlet of -$COOCH_3$ at δ 3.6 shifts and was intact as a singlet showing that the optical purity is atleast 99%.

[(1R,2R)-2-Phenoxycyclohex-1-yl] phenylglyoxalate (137):

This compound was prepared from (1R,2R)-2-phenoxycyclohexan-1-ol (**(-)-118**) and benzoylformic acid in the presence of catalytic amount of p-toluenesulfonic acid, following the same procedure as in **129**. Crystallization from pet.ether (60-80^{o}C fraction) afforded **137** as a crystalline solid.

Yield : 70%

m.p. : 75-76^{o}C

$[\alpha]_D^{24}$: - 50.43 (c 1.125, Acetone).

IR($CHCl_3$) : 1730, 1690 cm^{-1}

^{1}H NMR : δ 1.2-2.4 (m, 8H), 4.24 (m, 1H), 5.26 (m, 1H), 6.6-7.94(m, 10H).

^{13}C NMR : δ 22.88, 23.23, 29.59, 29.76, 76.30, 77.41, 116.21, 121.36, 128.77, 129.59, 129.94, 132.24, 134.77, 157.53, 163.83, 186.89.

Analysis Calcd.: C, 74.05; H,6.21;

for $C_{20}H_{20}O_4$

Found : C, 74.10; H, 6.21.

[1R,2R)-2-Phenoxycyclohex-1-yl] 2-hydroxy-2-phenylbutanoate (138a):

This compound was prepared from [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) and ethylzinc chloride as a viscous liquid following the same procedure as in **130a**. This

reaction was carried out on 2 mM scale. The compound, **138a**, was hydrolyzed without any purification.

Yield : 85%

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.92 (t, 3H, J = 6Hz), 1.2-2.32 (m, 10H), 3.64 (s, 1H, -OH, D_2O exchangeable), 4.2 (m, 1H), 5.0 (m, 1H), 6.68-7.6 (m, 10H).

(R)-2-Hydroxy-2-phenylbutanoic acid (78a):

Hydrolysis of the α-hydroxy ester **138a** was carried out following the same procedure as for the hydrolysis of [(1R,2S)-2-phenylcyclohex-1-yl] 2-hydroxy-2-phenylbutanoate (**130a**) to provide **78a** as a white solid.

Yield : 84%

m.p. : 118-120°C [Lit.[91] optically pure acid m.p. 124-125°C]

$[\alpha]_D^{24}$: - 26.7 (c 2.8, EtOH), e.e 80% (corrected 82%), conf.R [Lit.[91] $[\alpha]_D^{25}$ + 33.3, (c 0.87, EtOH), e.e > 99%, conf.S]

This compound has the IR, ^1H NMR and ^{13}C NMR spectral data identical with that of the compound prepared using **129**.

[(1R,2R)-2-Phenoxycyclohex-1-yl] 2-hydroxy-2-phenylhexanoate (138b):

This compound was prepared from [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) and n-butylzinc chloride following

the same procedure as in **138a**. This compound, **138b**, was obtained as a viscous liquid.

Yield : 88%

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.88 (distorted t, 3H), 1.0-2.2 (m, 14H), 3.6 (s, 1H, -OH, D_2O exchangeable), 4.2 (m, 1H), 5.0 (m, 1H), 6.6-7.6 (m, 10H).

(R)-2-Hydroxy-2-phenylhexanoic acid (78b):

This was obtained as a white solid by the hydrolysis of the α-hydroxy ester **138b** following the same procedure as in **78a**.

Yield : 83%

m.p. : 97-99°C

$[\alpha]_D^{24}$: - 18.97 (c 3.2, EtOH), e.e 82%, (corrected 84), conf.R [Lit.[86] $[\alpha]_D^{22}$ - 19, (c 2.2, EtOH), e.e 82%, conf.R]

This compound has the same IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **129**.

[(1R,2R)-2-Phenoxycyclohex-1-yl] 2-hydroxy-2-phenyloctanoate (138c):

This compound was prepared from [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) and n-hexylzinc chloride following the same procedure as in **138a**. This compound, **138c**, was obtained as a viscous liquid.

Yield : 94%

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.84 (distorted t, 3H), 1.0-2.2 (m, 18H), 3.6 (s, 1H, -OH, D_2O exchangeable), 4.2 (m, 1H), 5.0 (m, 1H), 6.6-7.6 (m, 10H).

(R)-2-Hydroxy-2-phenyloctanoic acid (78c):

Hydrolysis of the α-hydroxy ester **138c** was carried out following the same procedure as in **78a** to provide **78c** as a white solid.

Yield : 79%

m.p. : 94-96°C

$[\alpha]_D^{24}$: - 17.6 (c 5.2, EtOH), e.e 91% (corrected 93%), conf.R [Lit.[86] $[\alpha]_D^{22}$ - 17, (c 2.2, EtOH), e.e 88%, conf.R]

This compound has the same IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **129**.

[(1R,2R)-2-Phenoxycyclohex-1-yl] 2-hydroxy-3-methyl-2-phenylbutanoate (138d):

This compound was prepared (as a viscous liquid) from [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) and i-propylzinc chloride following the same procedure as in **138a**.

Yield : 89%

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.64 (d, 3H, J = 6Hz), 1.00 (d, 3H, J = 6Hz), 1.2-2.2 (m, 8H), 2.6 (m, 1H), 3.6 (s, 1H, -OH, D_2O exchangeable), 4.2 (m, 1H), 5.0(m, 1H), 6.6-7.6 (m, 10H)

(R)-2-Hydroxy-3-methyl-2-phenylbutanoic acid (78d):

Hydrolysis of the α-hydroxy ester **138d** was carried out following the same procedure as in **78a** to provide **78d** as a white solid.

Yield : 74%

m.p. : 102-103°C [Lit.[91] optically pure acid m.p. 103-105°C]

$[\alpha]_D^{24}$: - 30.14 (c 2.73, EtOH), e.e 93% (corrected 95%), conf.R [Lit.[91] $[\alpha]_D^{22}$ + 32.5 (c 2, EtOH), e.e > 99%, conf.S]

This compound has the IR, ^1H NMR and ^{13}C NMR spectral data as that of the compound prepared using **129**.

[(1R,2R)-2-Phenoxycyclohex-1-yl] 2-hydroxy-4-methyl-2-phenyl-pentanoate (138e):

This compound was prepared from [(1R,2R)-2-phenoxycyclohex-1-yl] phenylglyoxalate (**137**) and i-butylzinc chloride following the same procedure as in **138a**. This copound, **138e**, was obtained as a viscous liquid.

Yield : 77%

IR (neat): 3500, 1720 cm^{-1}

^1H NMR : δ 0.8 (m, 6H), 1.0-2.28 (m, 11H) 3.6 (b, 1H, -OH, D_2O exchangeable), 4.2 (m,1H), 5.2 (m,1H) 6.6-7.88 (m, 10H)

(R)-2-Hydroxy-4-methyl-2-phenylbutanoic acid (78e):

Hydrolysis of the α-hydroxy ester **138e** was carried out following the same procedure as in **78a** to provide **78e** as a white solid.

Yield : 68%

m.p. : 116-119°C [Lit.[91] optically pure acid m.p.118-120°C]

$[\alpha]_D^{24}$: - 18.0 (c 1.65, EtOH), e.e 90% (corrected 92%), conf.R [Lit.[91] $[\alpha]_D^{25}$ + 20.0, (c 2, EtOH), e.e > 99%, conf.S]

This has the same IR, ^1H NMR data as that of the compound obtained using **129**.

[(1R,2R)-2-Phenoxycyclohex-1-yl] pyruvate (139):

This was prepared according to the literature procedure reported by Whitesell *et al.* for the preparation of [(1R,2S)-2-phenylcyclohex-1-yl] pyruvate.[112]

To a stirred solution of (1R,2R)-2-phenoxycyclohexan-1-ol (**(-)-118**) (20 mM, 3.84 g) in dry benzene (50 mL), pyruvic acid (50 mM, 3.47 mL) and p-toluenesulfonic acid (1.2 mM, 220 mg) were

added and heated under reflux with azeotropic removal of water for 3 h. The reaction was allowed to cool to room temperature, diluted with ether, washed with sat.K_2CO_3 solution and water. The organic layer was dried over anhy.Na_2SO_4 and the solvent was evaporated. The crude material was distilled under reduced pressure to furnish **139** as a colourless liquid.

Yield : 4.45 g (85%)

b.p. : 154-156^{o}C/1.5 mm

$[\alpha]_D^{24}$: - 29.03 (c 3.27, MeOH)

IR (neat): 1730 cm^{-1}

^{1}H NMR : δ 1.2-2.32 (m, 11H), 4.24 (m, 1H), 5.08 (m, 1H), 6.8-7.38 (m, 5H).

^{13}C NMR : δ 23.06, 23.23, 26.59, 29.59, 29.94, 77.00, 77.77, 116.59, 121.53, 129.65, 158.24, 160.36, 192.07.

Analysis calcd. : C, 68.68; H, 6.92;

for $C_{15}H_{18}O_4$

Found : C, 68.60; H, 6.90

5-Bromopentan-2-one (144):

This was prepared according to the literature procedure.[126]

To a stirred solution of HBr (80 mL of 48% solution in H_2O) in a flask fitted with a Dean-Stark trap, 2-acetylbutyrolactone (250 mM, 26.9 mL) was added dropwise at the reflux temperature

over a period of 3 h. After the addition was complete, refluxing was continued for one more hour. The oily layer collected in Dean-Stark trap was separated by extracting with ether. Ether layer was washed with water, dried over anhy.Na_2SO_4 and evaporated. The crude material was distilled under reduced pressure to furnish 5-bromopentan-2-one (**144**) as a colourless liquid.

Yield : 18.5 g (45%)

IR (neat): 1700 cm^{-1}

^1H NMR : δ 2.2 (m, 5H), 2.68 (t, 2H, J = 6Hz), 3.5 (t, 2H, J = 5Hz).

2-(3-Bromoprop-1-yl)-2-methyl-1,3-dioxolane (143):

This was prepared following the reported procedure.[126]

A mixture of 5-bromopentan-2-one (**144**) (60 mM, 10g), ethyleneglycol (120 mM, 6.7 mL) and p-toluenesulfonic acid (100 mg) in dry benzene (100 mL) was heated under reflux (12h) with azeotropic removal of water. The reaction mixture was cooled to room temperature, poured into 1% $NaHCO_3$ solution and extracted with ether (3 x 20 mL). The organic layer was washed with water and dried over anhy.Na_2SO_4. Removal of the solvent and distillation under reduced pressure gave pure ketal **143** as a colourless liquid.

Yield : 10 g (80%)

b.p. : 80-83°C/10mm [Lit.[126] b.p.103-105°C/2mm]

IR (neat): no carbonyl absorption

^{1}H NMR : δ 1.36 (s, 3H), 1.6-2.2 (m, 4H), 3.44 (t, 2H, J = 5Hz), 3.96 (s, 4H).

2-{4-[(2-phenoxycyclohex-1-yloxy)carboxy]-4-hydroxy}pent-1-yl-2-methyl-1,3-dioxolane (141):

To a stirred solution of Grignard reagent (20 mM) (prepared from 2-(3-bromoprop-1-yl)-2-methyl-1,3-dioxolane (**143**) and magnesium) in dry THF at 0°C anhy.$ZnCl_2$ (20 mM, 2.72 g) was added. After stirring for 2 h at 0°C, the reaction mixture was cooled to -78°C, and a precooled (at -78°C) solution of [(1R,2R)-2-phenoxy cyclohex-1-yl] pyruvate (**139**) (10 mM, 2.62 g) in dry THF (5 mL) was added. After 3 h stirring at -78°C, the reaction mixture was allowed to warm to 0°C, sat.NH_4Cl solution was added and extracted with ether (3 x 20 mL). The ethereal solution was dried over anhy.Na_2SO_4 and evaporated. The crude material was directly used in the next step without any purification.

Yield : 3.6 g (91.8% crude)

IR (neat): 3500, 1720 cm^{-1}

^{1}H NMR : δ 1.00-2.2 (m, 20H), 3.2 (b, 1H, -OH), 3.96 (s, 4H), 4.2 (m, 1H), 5.00 (m, 1H), 6.6-7.2 (m, 5H).

2-[4-(Hydroxymethyl)-4-hydroxypent-1-yl]-2-methyl-1,3-dioxolane (142):

A solution of α-hydroxy ester **141** (9.1 mM, 3.6 g) in dry THF was added dropwise to a stirred suspension of LAH (8.1 mM, 307 mg) in dry THF at room temperature. After 2 h stirring at room temperature, the reaction was quenched by adding sat.Na_2SO_4 solution. The salts were filtered and the residue was washed with THF. The organic layer was dried over anhy.Na_2SO_4 and the solvent was evaporated. The crude material was purified by column chromatography (30% ethyl acetate in hexane) to obtain pure diol **142** as a colourless liquid.

Yield : 745 mg (40%)

IR (neat): 3500 cm^{-1}

^1H NMR : δ 1.18 (s, 3H), 1.32 (s, 3H), 1.4-1.74 (m, 6H), 2.4 (b, 2H, 2-OH, D_2O exchangeable), 3.4 (s, 2H), 3.92 (s, 4H).

^{13}C NMR : δ 18.06, 22.82, 23.53, 38.41, 39.41, 64.41, 69.41, 72.82, 111.00.

(-)-Frontalin (63):

This was prepared according to the literature procedure.[127]

To a stirred solution of diol **142** (400 mg, 2 mM) in 10 mL of dichloromethane, p-toluenesulfonic acid (40 mg) was added at

$0^{o}C$ and stirred for 2 h at the same temperature. The excess acid was neutralized by adding solid $NaHCO_3$ and washed with water. The organic layer was dried over anhy.Na_2SO_4 and evaporated. Purification by column chromatography (using hexane), followed by distillation gave frontalin (**63**) as a colourless liquid.

Yield : 127 mg (45%)

b.p. : 90-92^{o}C/100 mm [Lit.[128a] b.p.91^{o}C/100 mm]

$[\alpha]_D^{24}$: - 36.52 (c 2.57, ether), e.e 70%

[Lit.[128b] $[\alpha]_D^{25}$ - 52 (c 2, ether), e.e > 99%]

IR (neat): 2960, 1380, 1455, 1265, 1030 cm^{-1}

^{1}H NMR : δ 1.34 (s, 3H), 1.44 (s, 3H), 1.48-1.8 (m, 6H), 3.48 (d, 1H, J = 6Hz), 3.88 (d, 1H, J = 6Hz).

^{13}C NMR : δ 17.58, 22.63, 24.17, 33.47, 34.12, 73.77, 79.53, 107.65.

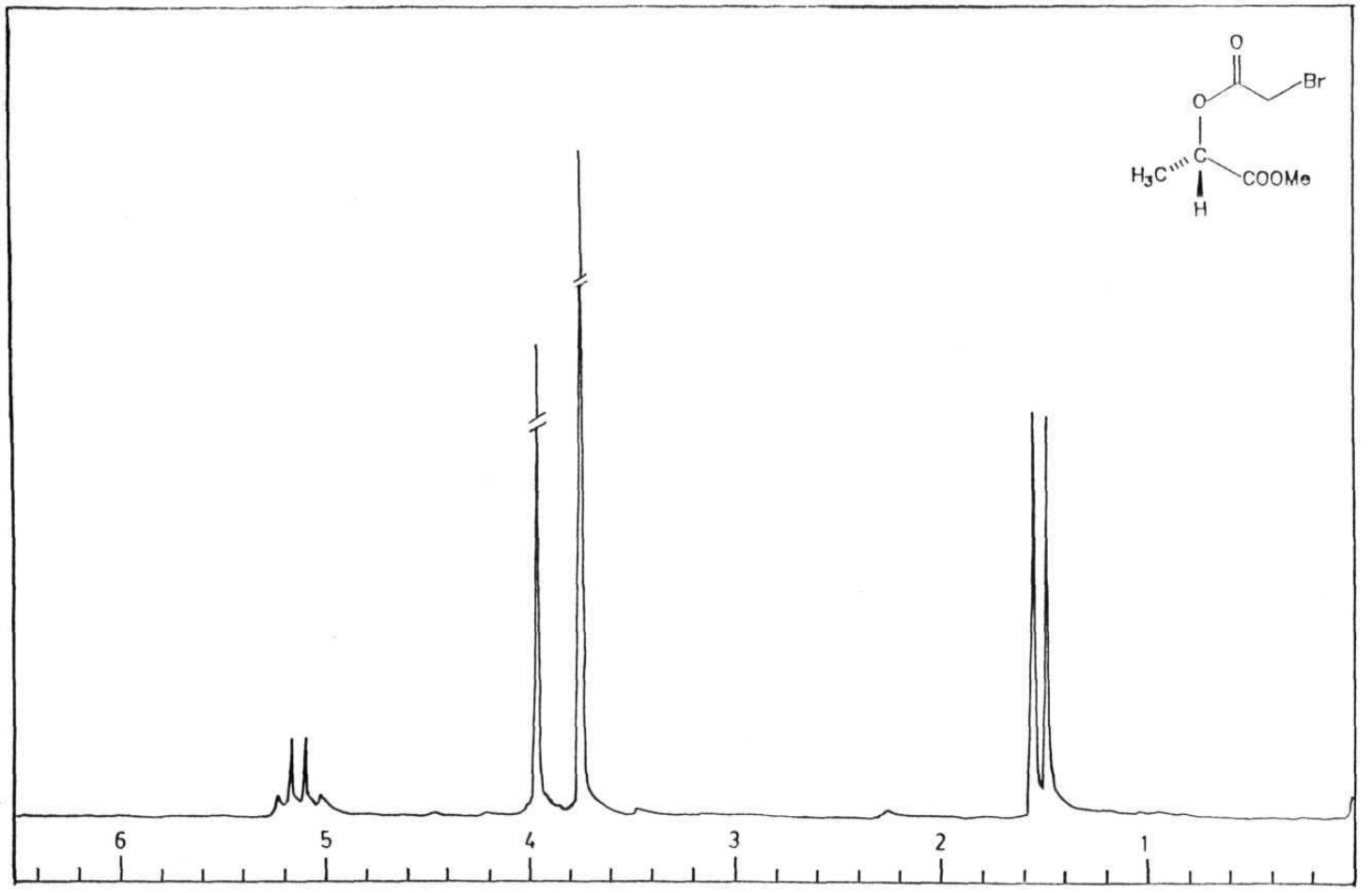


Fig. 1: ^{1}H NMR spectrum of **90**.

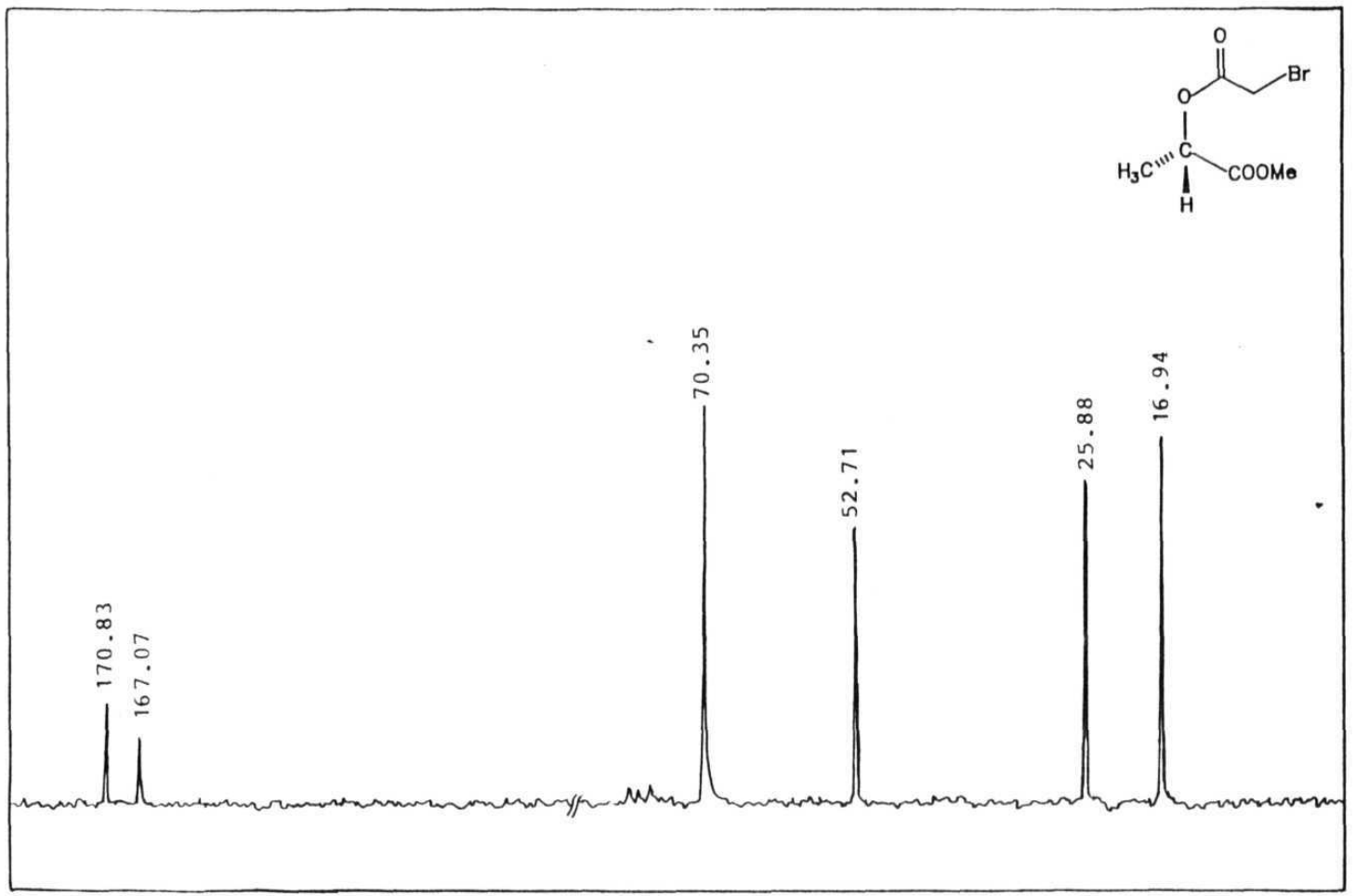


Fig. 2: ^{13}C NMR spectrum of **90**.

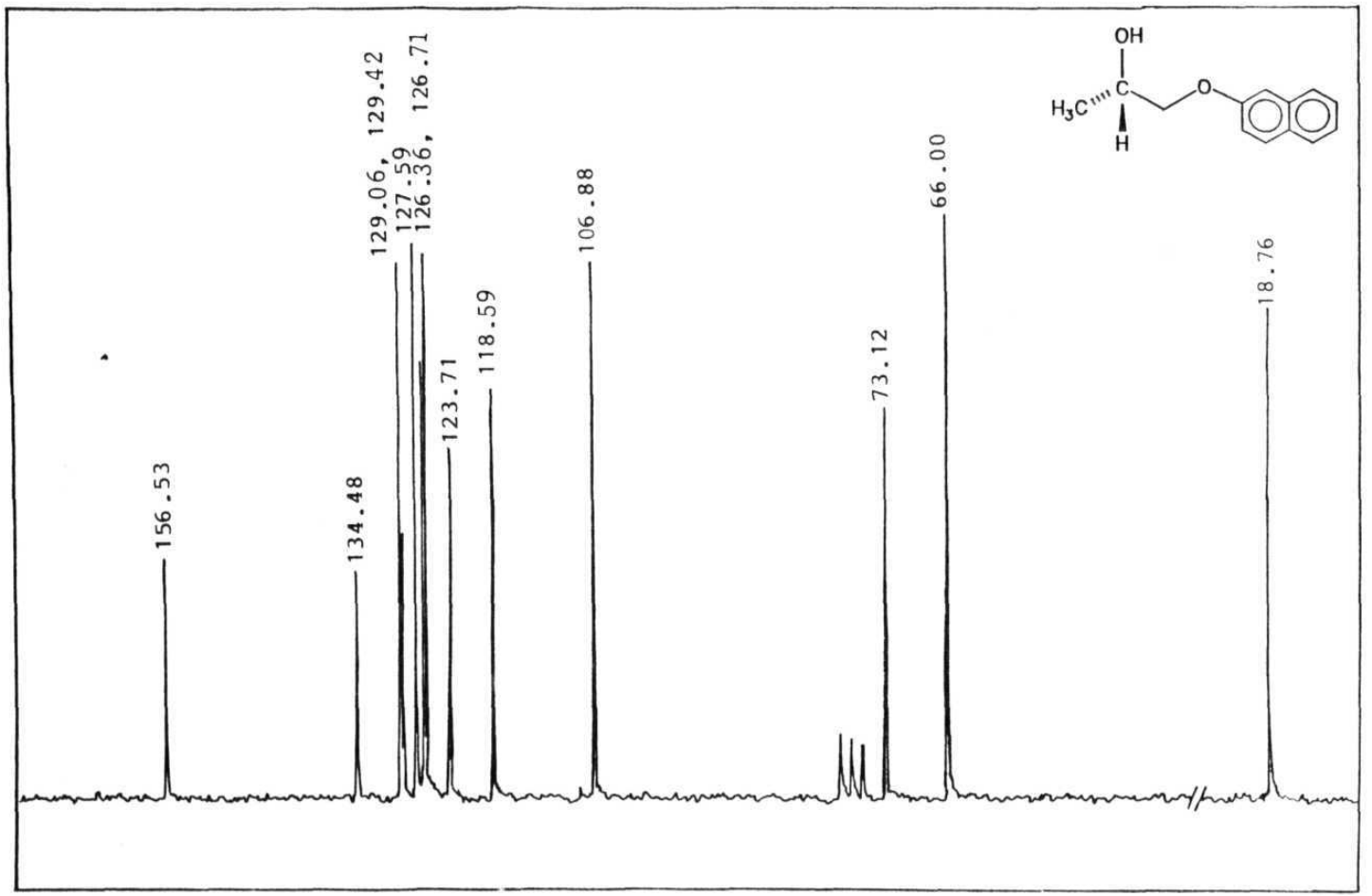


Fig. 3: ^{13}C NMR spectrum of 93.

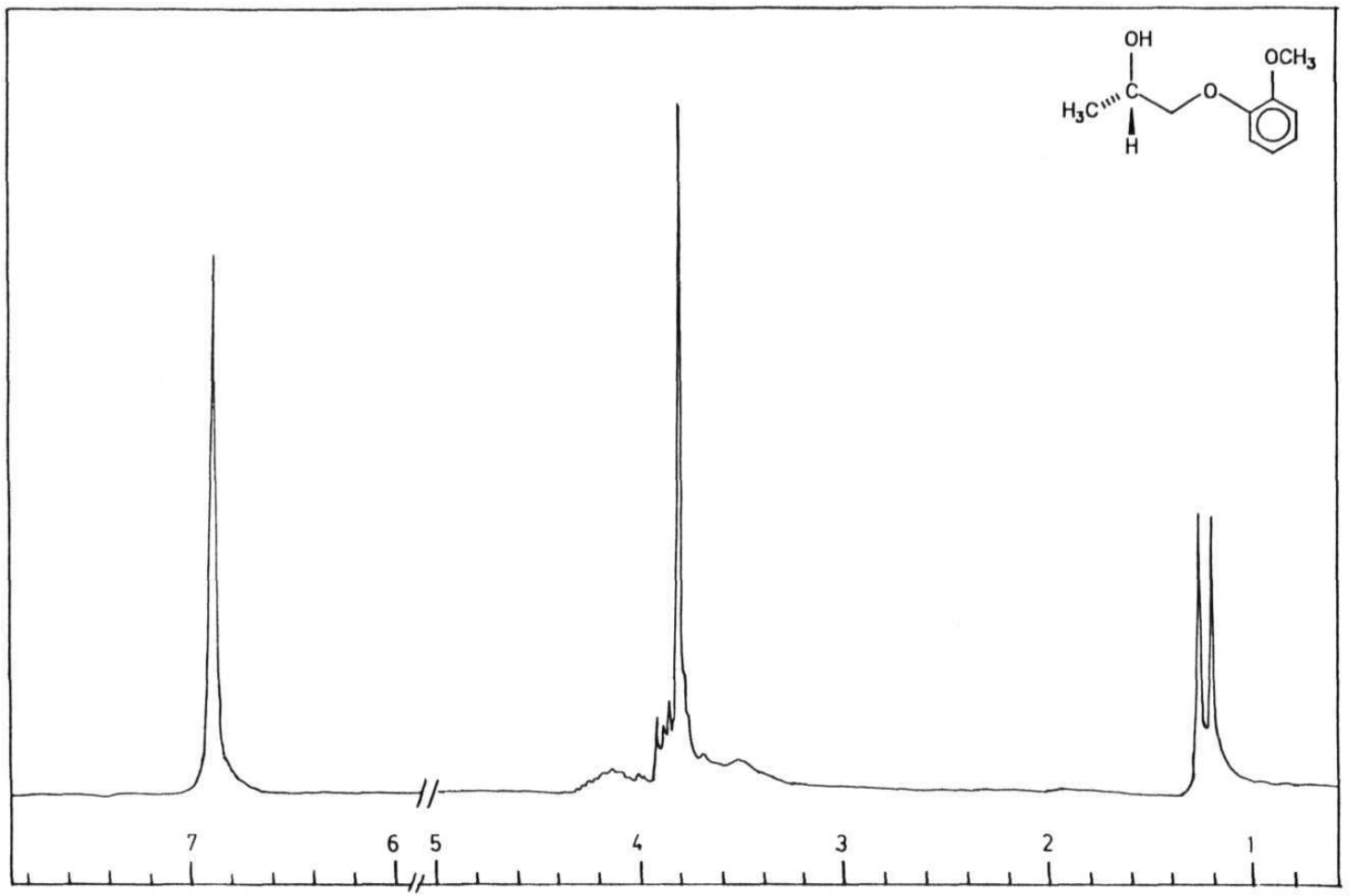


Fig. 4: ^{1}H NMR spectrum of **104**.

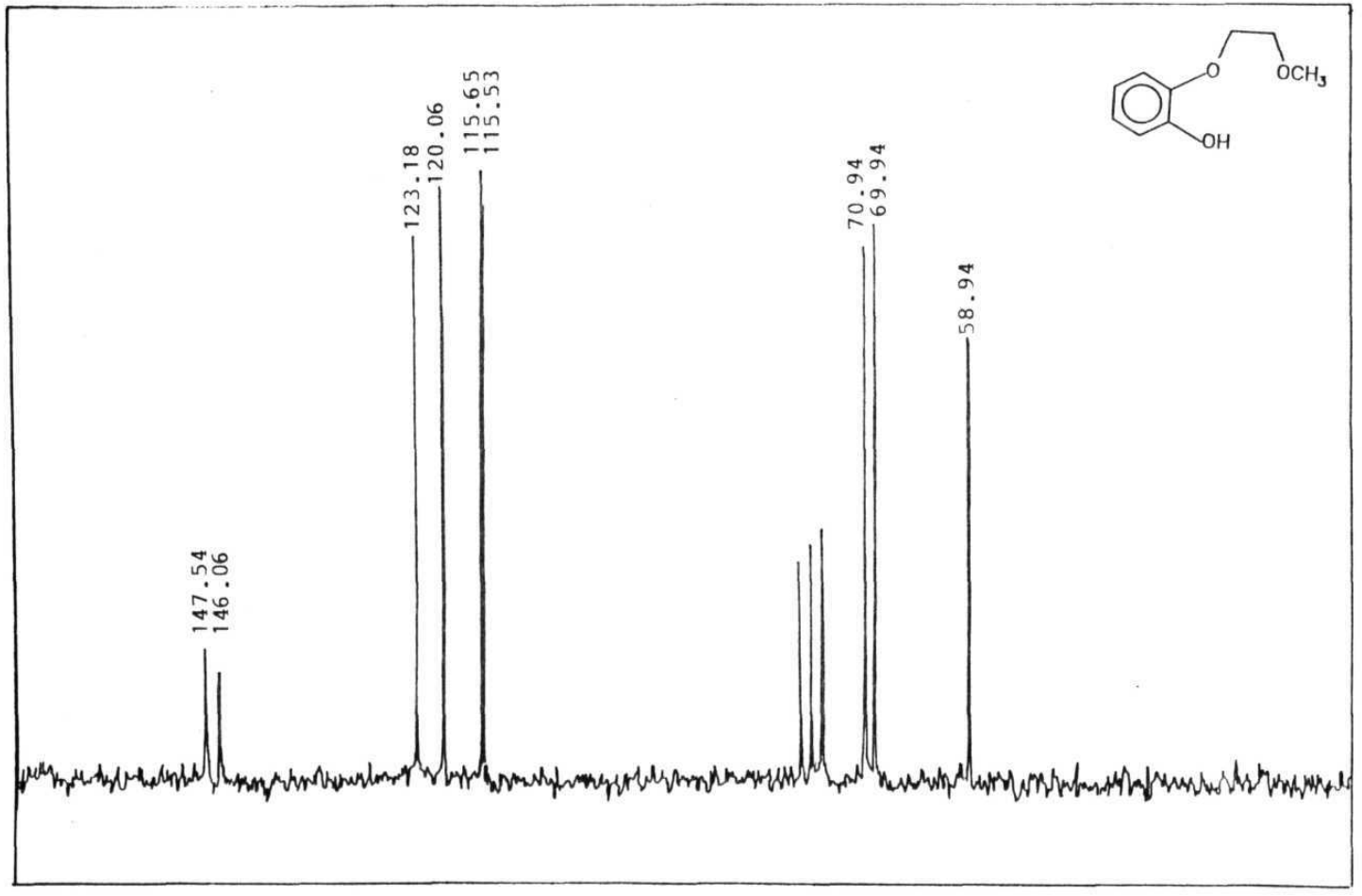


Fig. 5: ^{13}C NMR spectrum of **110**.

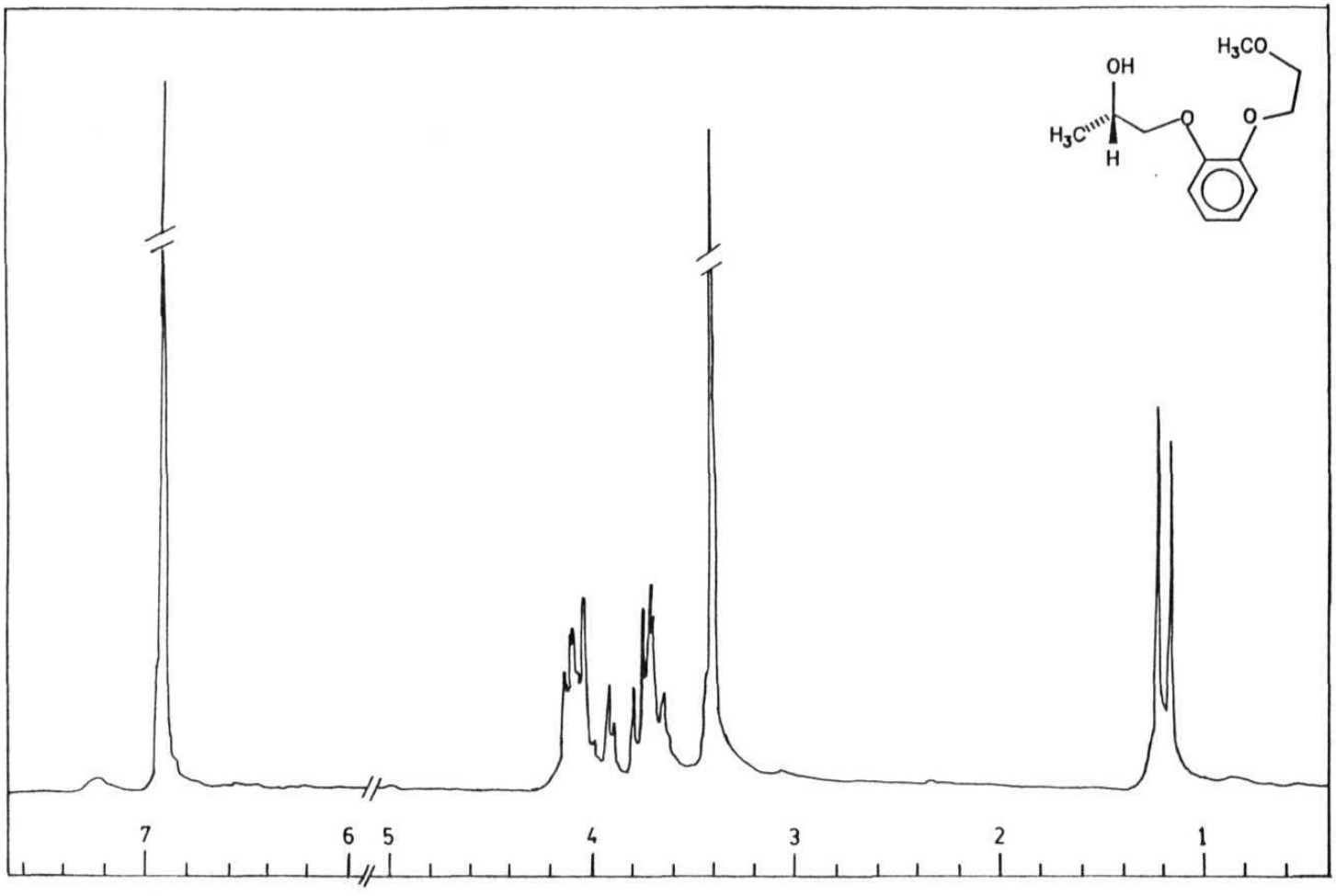


Fig. 6: ^{1}H NMR spectrum of **106**.

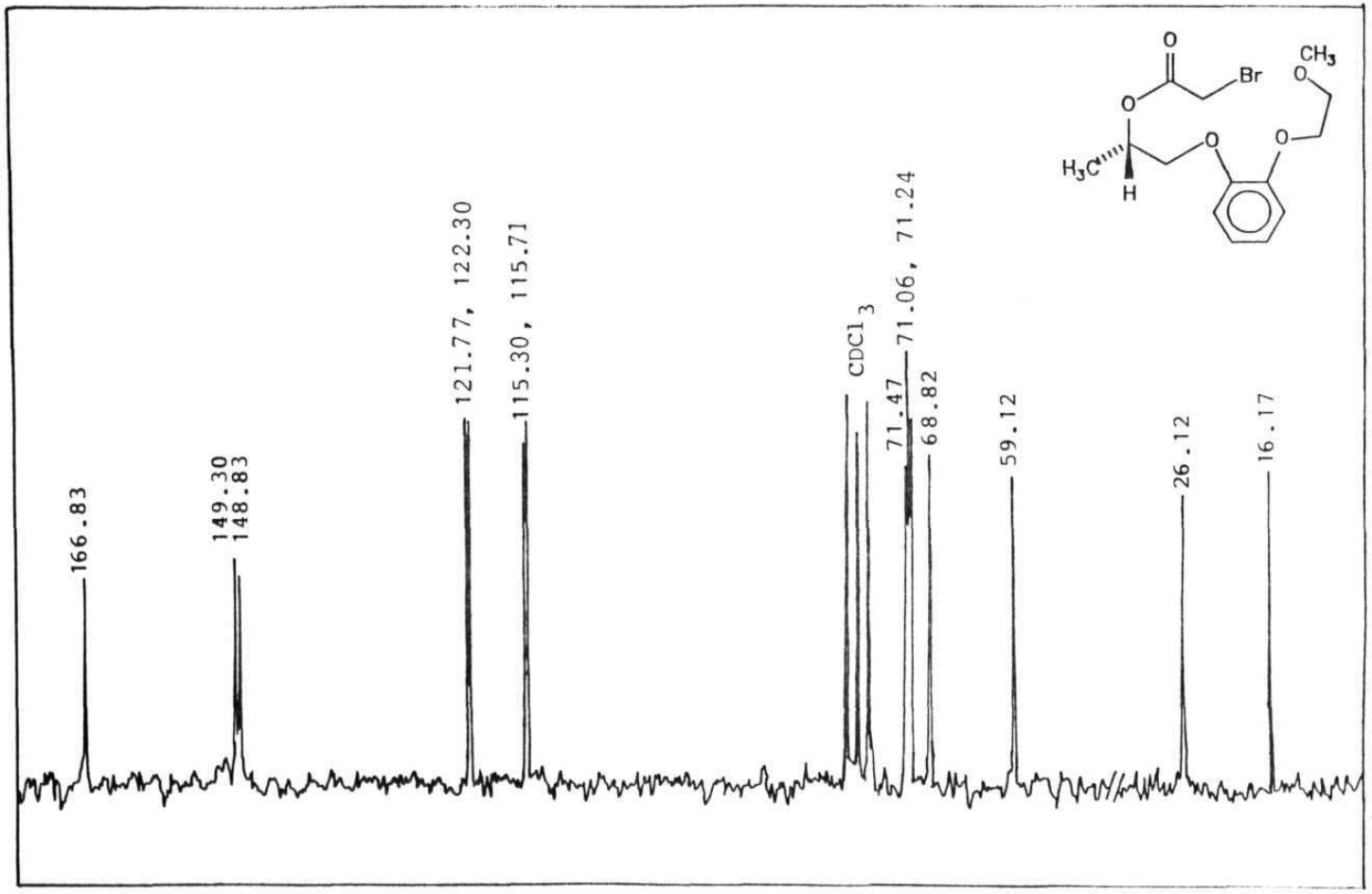


Fig. 7: ^{13}C NMR spectrum of **111**.

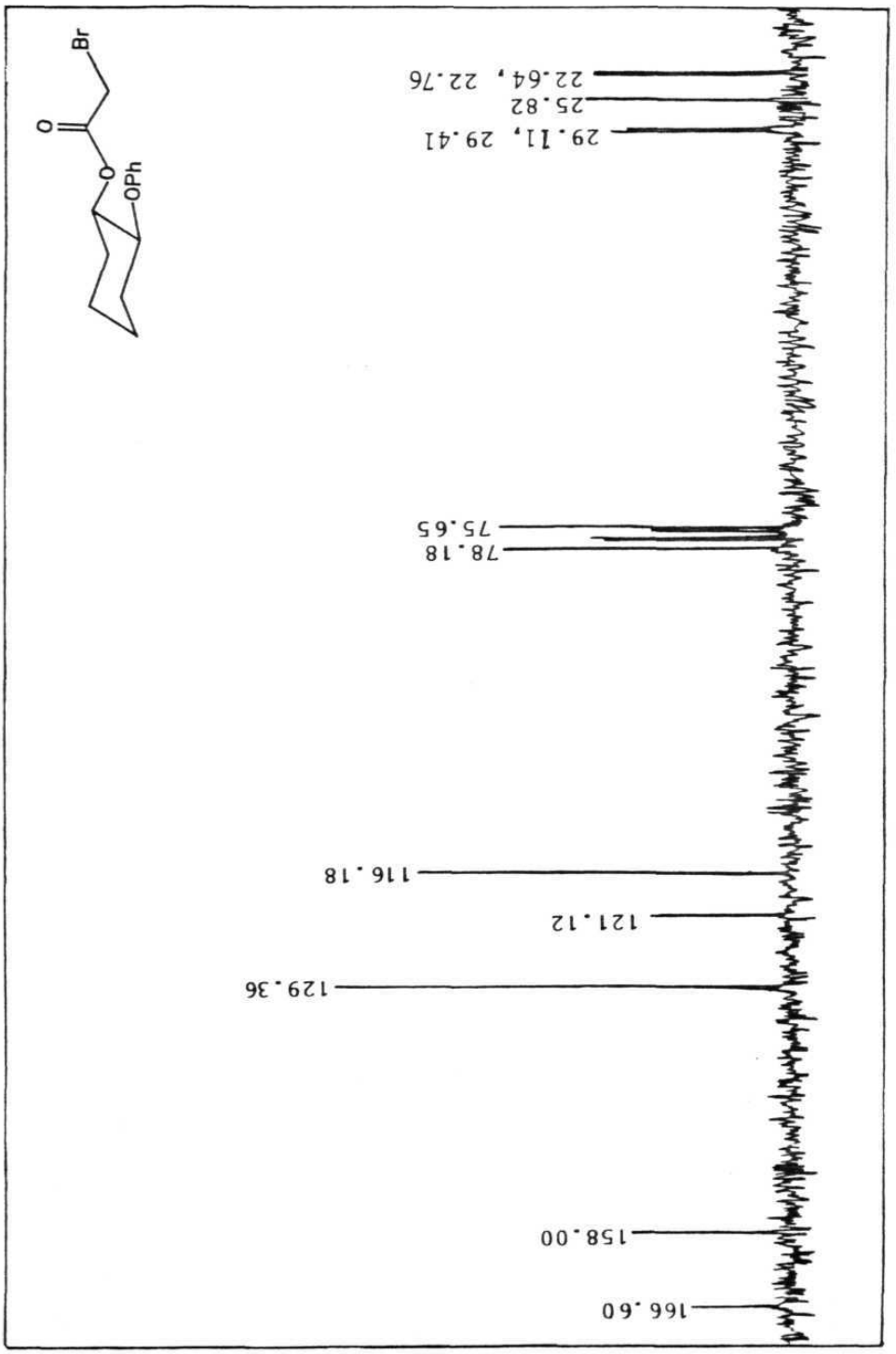


Fig. 8: ^{13}C NMR spectrum of **121**.

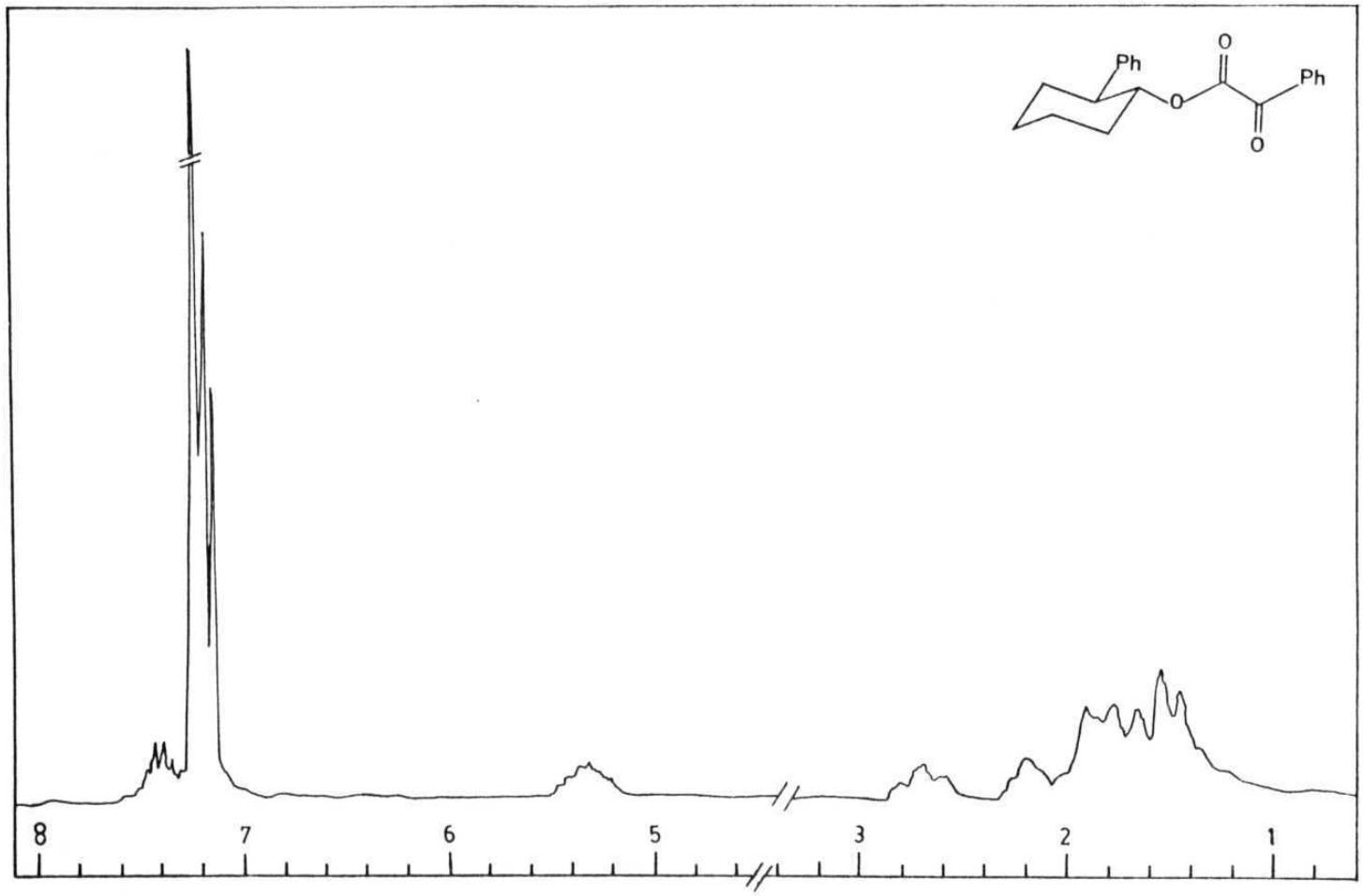


Fig. 9: ^{1}H NMR spectrum of **129**.

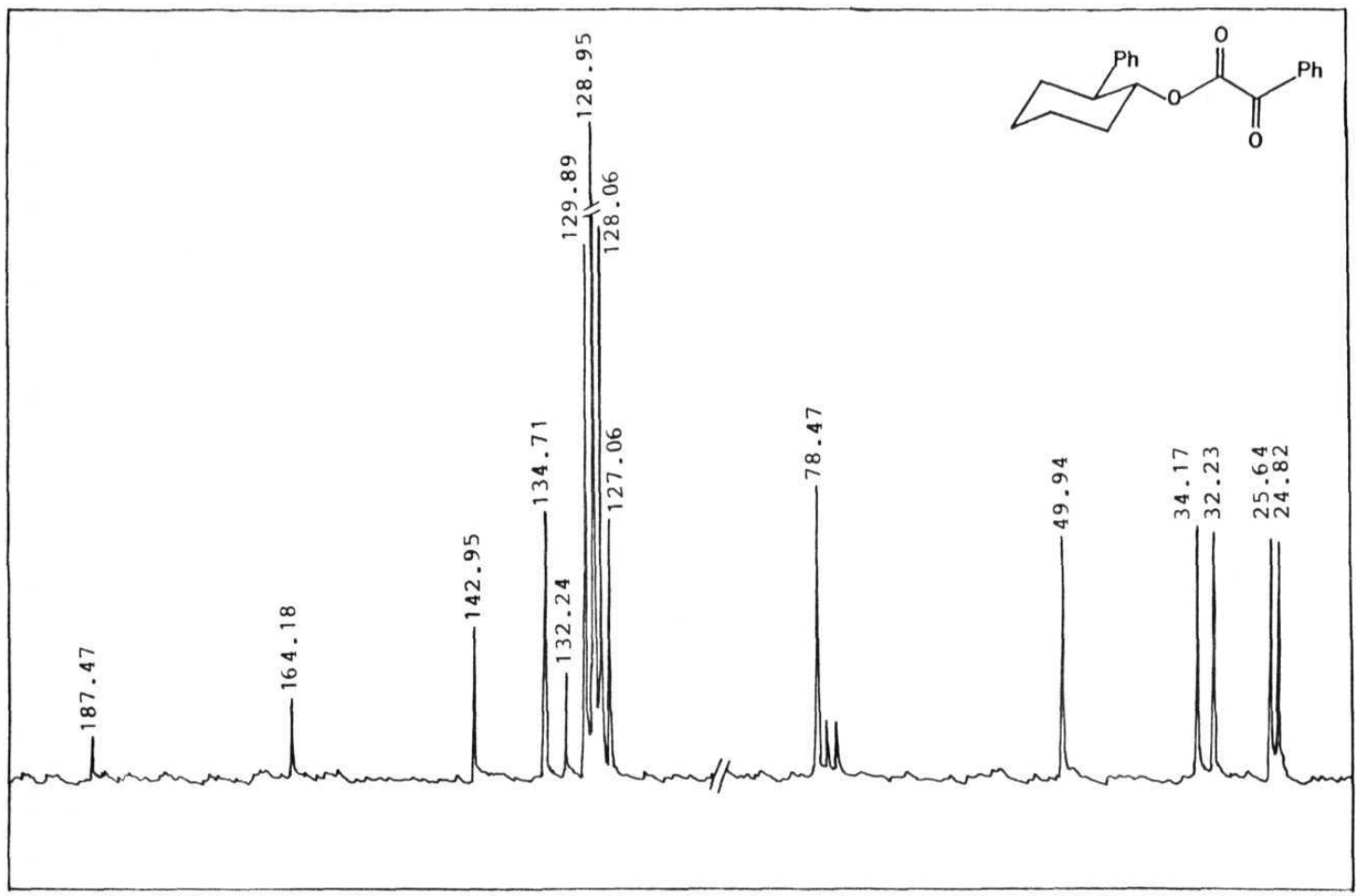


Fig. 10: ^{13}C NMR spectrum of **129**.

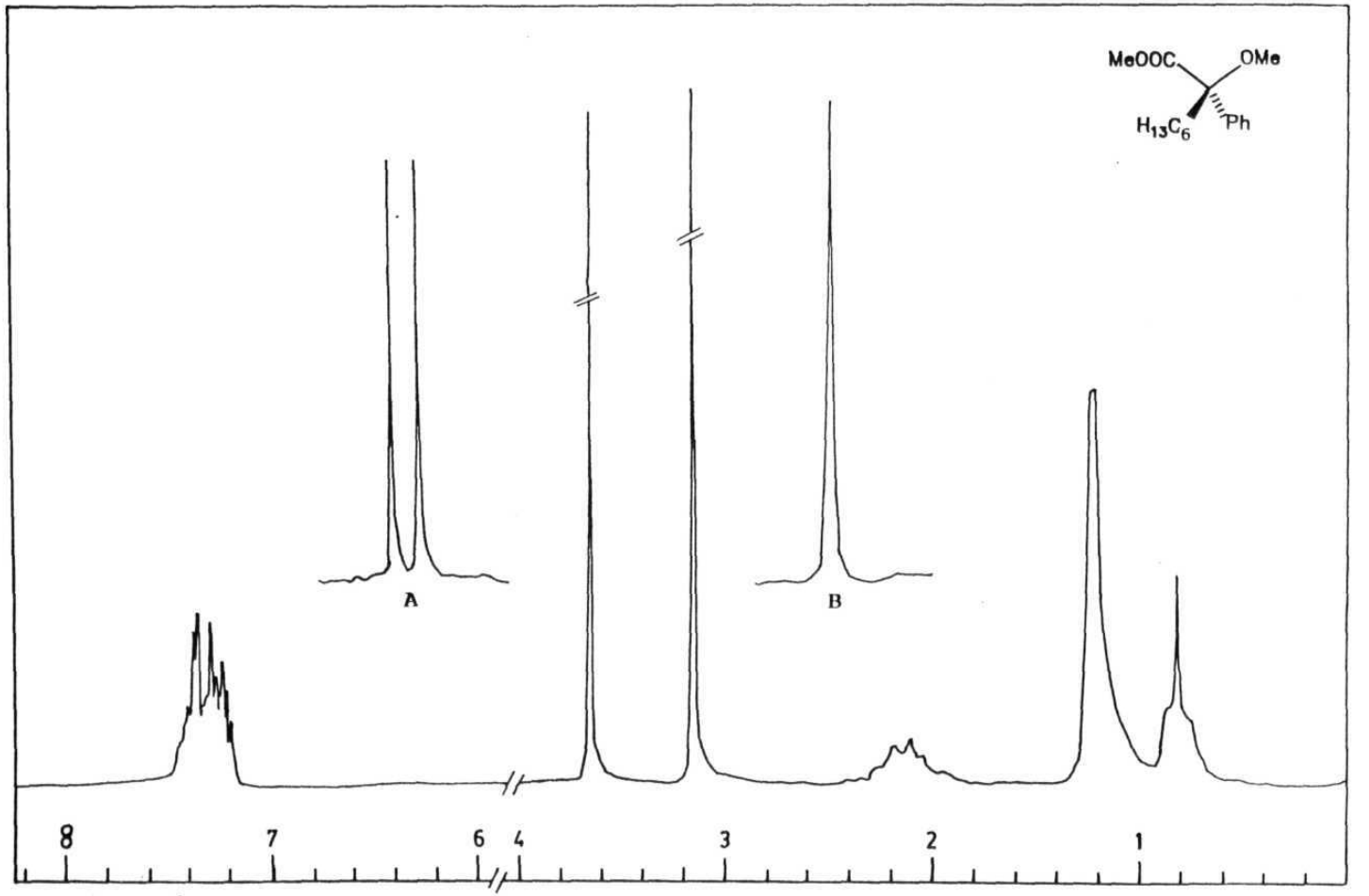


Fig. 11: ^1H NMR spectrum of **132**. A: Splitting of $-COOCH_3$ signal of **132** in the presence of $Eu(hfc)_3$. B: $-COOCH_3$ signal of **132'** in the presence of $Eu(hfc)_3$ (no splitting e.e >99%).

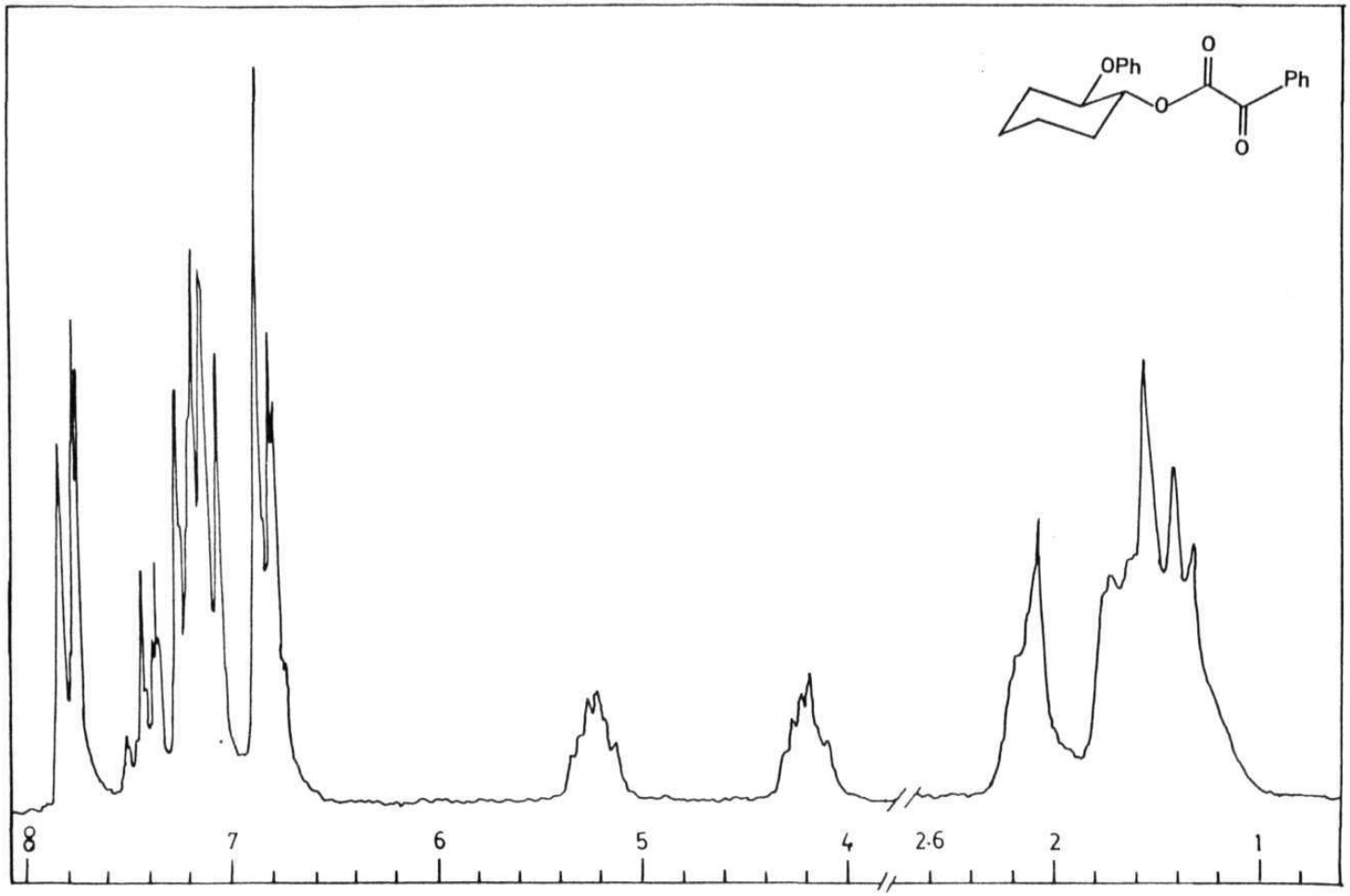


Fig. 12: ^{1}H NMR spectrum of **137**.

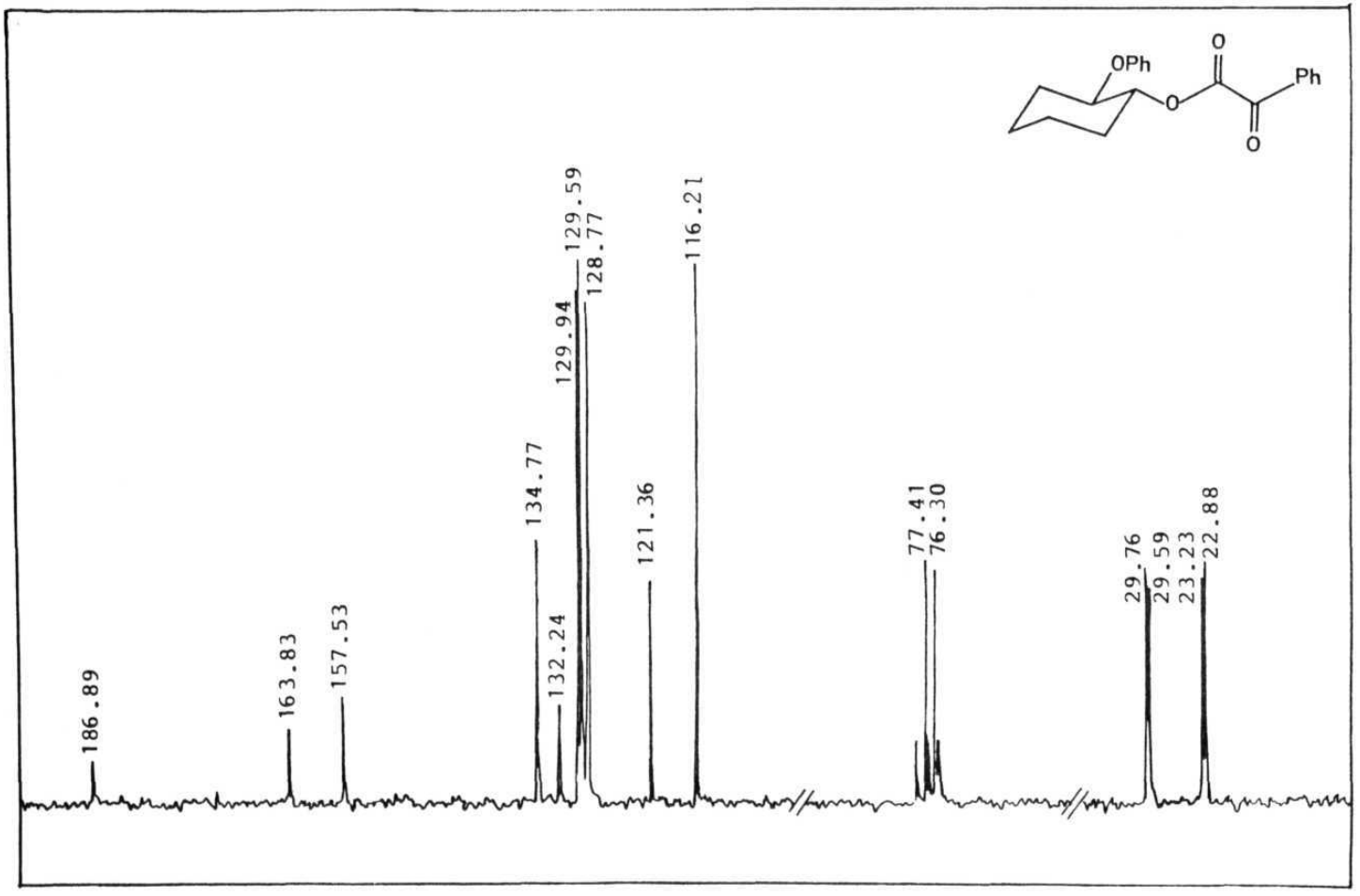


Fig. 13: ^{13}C NMR spectrum of **137**.

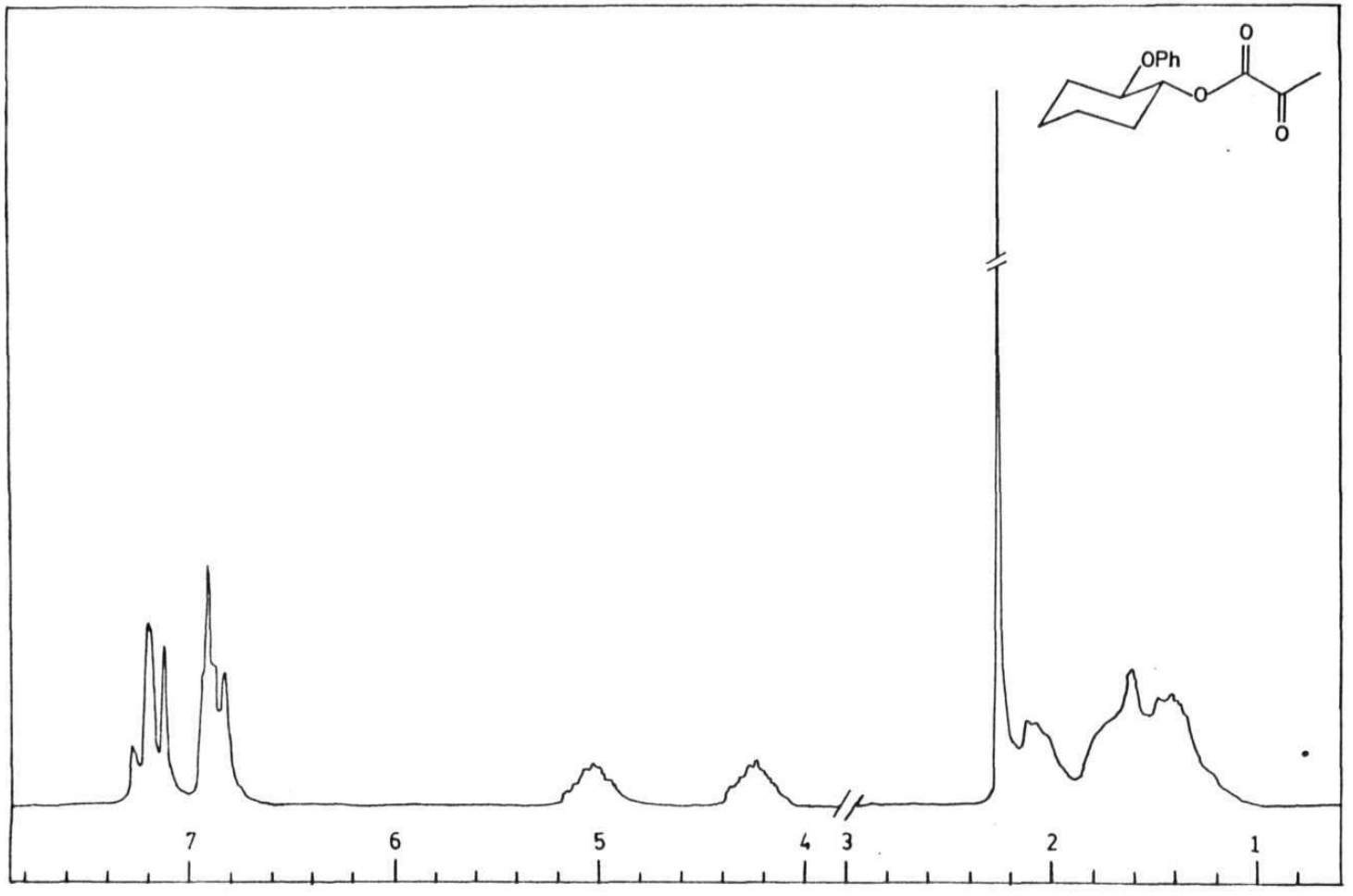


Fig. 14: ^{1}H NMR spectrum of **139**.

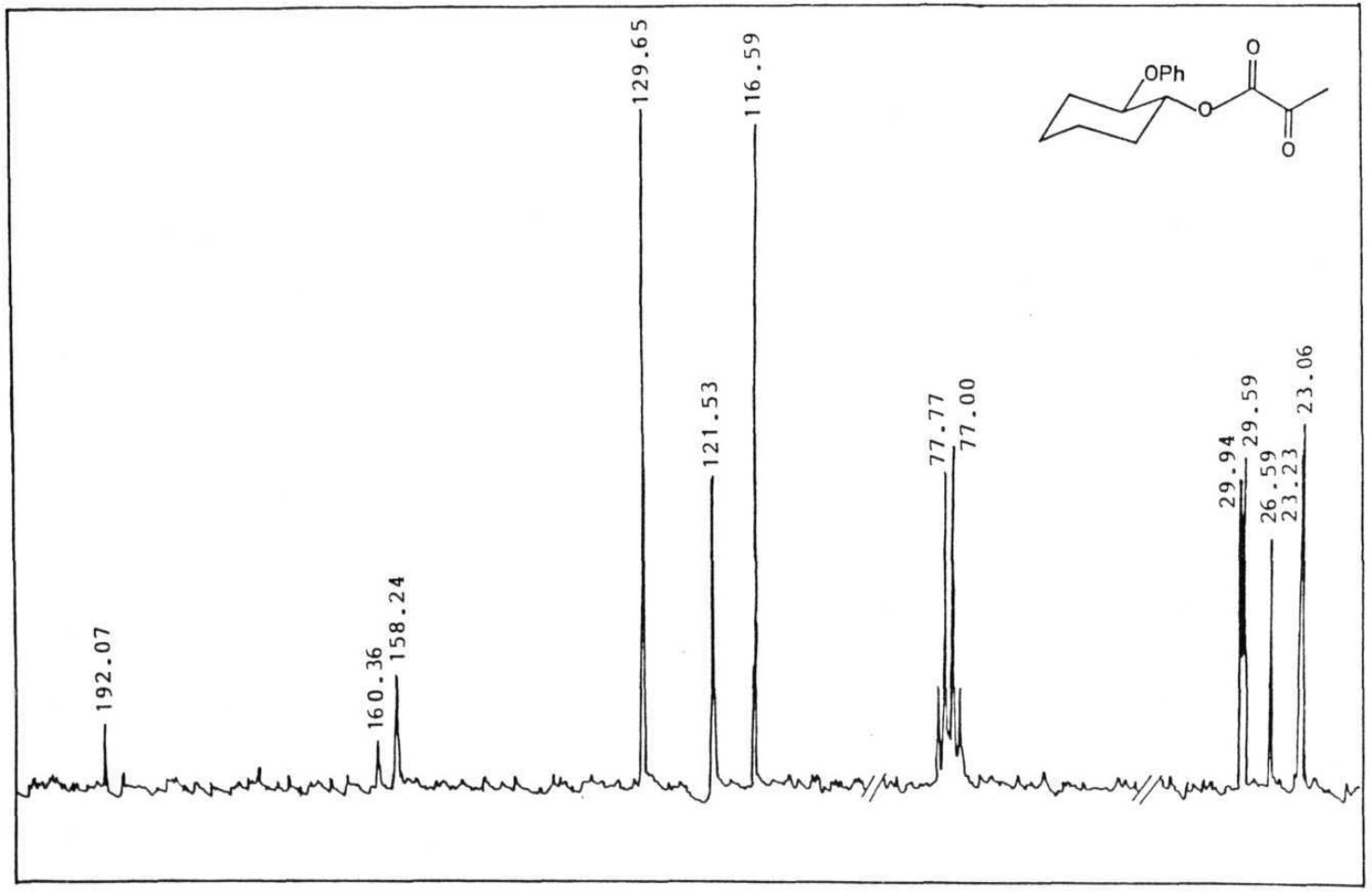


Fig. 15: ^{13}C NMR spectrum of **139**.

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VITAE

The author was born on 28th February 1965 at Mangalagiri, Andhra Pradesh. Following her earlier education, she joined S.P.W.College, Tirupati and obtained B.Sc. degree from S.V.University in 1984. Later, she joined the University of Hyderabad, Hyderabad and received her M.Sc and M.Phil degrees in 1986 and 1987 respectively. She joined the Ph.D programme in August 1987 in School of Chemistry, University of Hyderabad, Hyderabad. She was awarded JRF and SRF by CSIR, New Delhi.

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