SYNTHESIS AND APPLICATIONS OF A NEW C_2-SYMMETRIC CHIRAL 1,3-DIOL

A THESIS

SUBMITTED FOR THE DEGREE OF

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BY

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MAY 2005

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. N. N. Joshi**, Division of Organic Synthesis, National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled "**Synthesis and Applications of a New C_2-Symmetric Chiral 1,3-Diol**" has been carried out under my supervision and is a bonafide work of **Mr. Kartick Chandra Bhowmick**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune
May 2005

(Dr. N. N. Joshi)
Research Guide

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Kartick Chandra Bhowmick

CONTENTS

ABBREVIATIONS

Ac	-	Acetyl
BINOL	-	2,2′-Dihydroxy-1,1′-binaphthol
Bn	-	Benzyl
Bz	-	Benzoyl
BnBr	-	Benzyl bromide
^{n}BuLi	-	*n*-Butyl lithium

CH_2Cl_2	-	Dichloromethane
$CHCl_3$	-	Chloroform
$CDCl_3$	-	Deuterated chloroform
CSA	-	Camphorsulphonic acid
d-	-	dextrorotatory
DIBAL	-	Diisobutylaluminium hydride
DIPEA	-	Diisopropylethyl amine
DMF	-	*N*,*N*-Dimethylformamide
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
Et	-	Ethyl
Et_3N	-	Triethylamine
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
HMPA	-	Hexamethylphosphoric triamide
l-	-	laevorotatory
LAH	-	Lithium aluminium hydride
Me	-	Methyl
MeI	-	Methyl iodide
MeOH	-	Methanol

mp.	-	Melting point
bp.	-	Boiling point
EtOH	-	Ethanol
NMO	-	*N*-Methylmorpholine *N*-oxide
Pd/C	-	Palladium on Carbon
Ph	-	Phenyl
PPTs	-	Pyridinium para-toluene sulphonate
Py	-	Pyridine
rac-	-	Racemic
RT	-	Room temperature
TBME	-	*tert*-Butylmethyl ether
TEBA	-	Triethylbenzylammonium chloride
THF	-	Tetrahydrofuran
*p*TSA	-	*p*-Toluenesulfonic acid
TsCl	-	*p*-Toluenesulfonyl chloride
$Eu(hfc)_3$	-	tris-[3-(heftafluoropropyl hydroxymethylene)-(-)-camphoroto] europium derivative

GENERAL REMARKS

– ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Chemical shifts have been expressed in parts per million (ppm) on δ scale downfield from TMS. The abbreviations

s, d, t, q and m refer to the singlet, doublet, triplet, quartet and multiplet respectively. Coupling constants wherever mentioned, have been given in Hz.

- ^{13}C NMR spectra were recorded at 50 MHz and 75 MHz with $CDCl_3$ (δ = 77 ppm) as the reference.
- Infrared spectra were scanned on Shimadzu FTIR-8400 spectrophotometer with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured on Bellingham+Stanley ADP220 digital polarimeter.
- Melting points were recorded on Yamaco micro melting point apparatus and are uncorrected.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates ($60F_{254}$) with UV light / I_2 / anisaldehyde as viewing methods.
- All solvents and reagents were purified and dried according to procedures given in D. D. Perin's "*Purification of Laboratory Reagents*" All reactions were carried out under Argon atmosphere using freshly distilled solvents under anhydrous conditions, unless otherwise specified. Yields refer to isolated product, purified by chromatography or distillation.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.

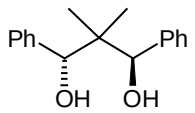
ABSTRACT

Synthesis and Applications of a New C_2-Symmetric Chiral 1,3-Diol

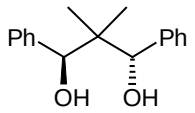
It might appear obvious that the introduction of a symmetry element within a chiral auxiliary would be enough for achieving asymmetric induction in a chemical transformation. In fact in the majority of scenarios, the presence of a C_2-symmetry axis within the chiral auxiliary can serve the very important function of reducing the number of possible competing diastereomeric transition states. This theory enjoys the credibility when we see several C_2-symmetric chiral 1,2-, 1,3-, and 1,4- bidentate ligands, which are known in the literature as efficient chiral auxiliaries in various asymmetric transformations. Although a few C_2-symmetric chiral 1,3-diols are known in the literature, none have proved to be good sources of chirality. Moreover backbone rigidity is very much essential for a 1,3-diol to be an effective chiral auxiliary/ ligand.

Thus rational design and synthesis of sterically constrained chiral 1,3-diol auxiliaries containing backbone rigidity, is an important endeavor. The present work deals with synthesis of homochiral (*R, R*)-/(*S, S*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol (**1**) and its synthetic applications.

Figure 1.



(*R,R*)-**1**



(*S,S*)-**1**

Chapter-1:

Introduction: "Synthesis and applications of C_2-symmetric chiral diols"

This chapter provides background to the present work by reviewing the literature on synthesis and applications of several C_2-symmetric chiral diols in various asymmetric transformations.

Chapter-2:

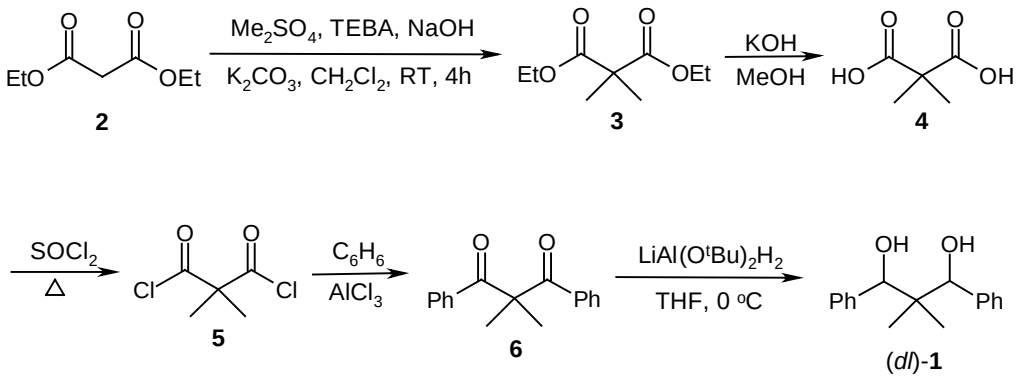
Synthesis and resolution of 2,2-dimethyl-1,3-diphenyl-1,3-propanediol

This chapter has been divided into three sections. Section-2A describes a highly diastereoselective reduction process towards the synthesis of *dl*-**1** starting from the dione **2**. Section-2B describes the employment of aldol-Tishchenko reaction to access *dl*-**1** with absolute diastereoselectivity. Section-2C deals with the successful resolution of *dl*-**1** to obtain both the enantiomers.

Section-2A: Diastereoselective reduction

Four known steps have been employed to obtain the diketone **6** starting from diethylmalonate (**2**), a cheap and commercially available compound (Scheme 1). It was first dimethylated at C-2 position using dimethylsulfate under phase-transfer condition to provide 2,2-dimethyl diethylmalonate. Saponification followed by thionyl chloride treatment provided the corresponding acid chloride **3**. Friedel-Craft reaction between **5** and benzene produced the diketone **6** in high overall yield.

Scheme 1

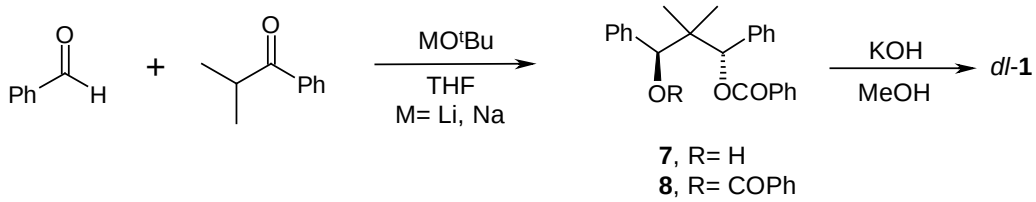


Prior to our work, Mair et al. had described the reduction of diketone **6** with lithium aluminium hydride (LAH) in moderate diastereoselectivity. In order to enhance the selectivity, we examined various reducing agents including $NaBH_4$, $LiBH_4$, $Zn(BH_4)_2$ and a few modified reagents derived from LAH. It was found that lithium di-*tert*-butoxyaluminium hydride reduces **6** with very high diastereoselectivity, providing *dl*-**1** in almost quantitative yield (Scheme 1).

Section-2B: aldol-Tishchenko reaction

This section starts with an introduction providing detailed literature information on stereoselective aldol-Tishchenko reaction. Metal alkoxides of Li, Na, Ca etc. are known to be good promoters of aldol-Tishchenko reaction to furnish monoester of 1,3-glycol with high diastereoselectivity. We explored this reaction for the synthesis of the *dl*-**1** as shown in Scheme 2. Metal alkoxides of Na and Li have been examined in both catalytic and stoichiometric quantity taking benzaldehyde and isobutyrophenone as the reactants.

Scheme 2

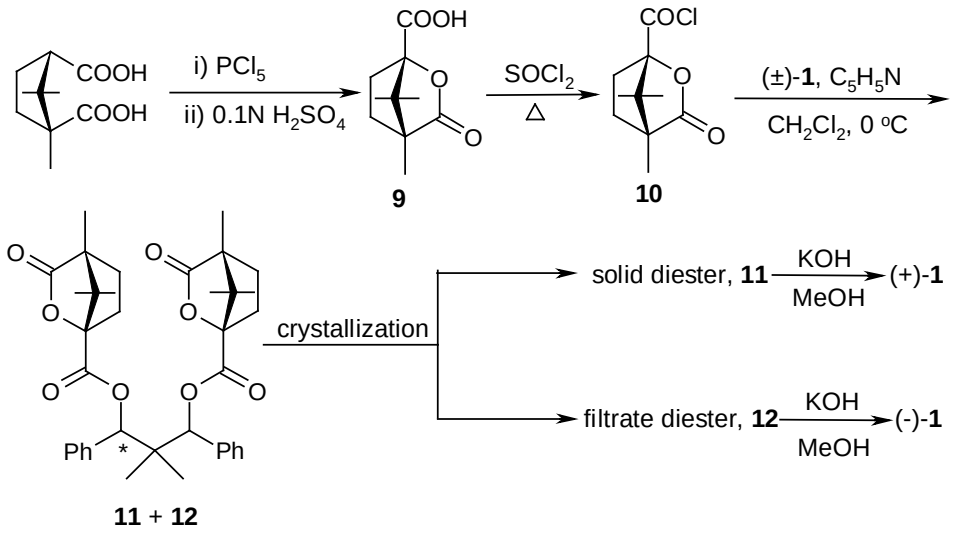


We were pleased to observe that only 1,3-anti glycol was obtained as a mixture of mono- and di-benzoate esters (**7** and **8** respectively) which were saponified to obtain *dl*-**1**. We thus accomplished a very short and practical synthesis of *dl*-**1** in good yield.

Section-2C: Resolution of the diol

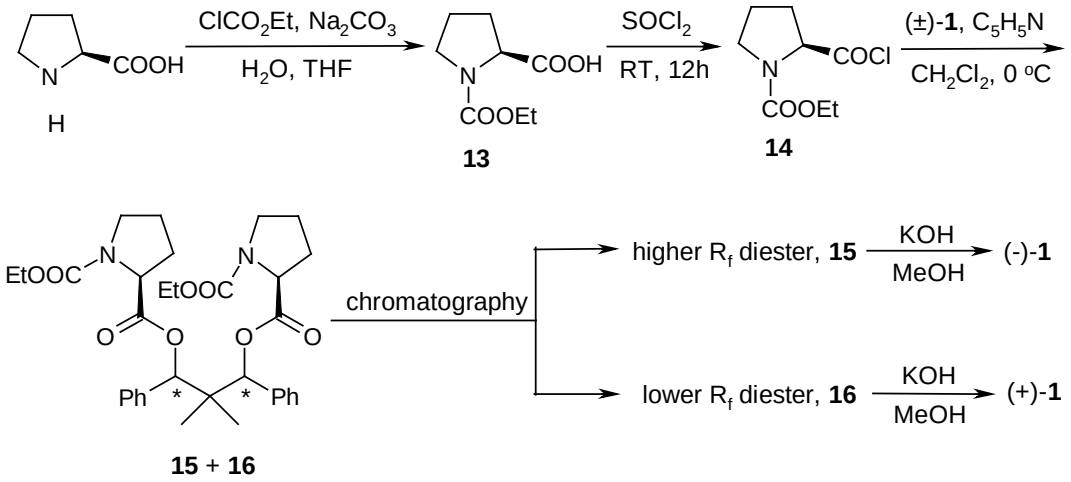
Two different procedures have been described to resolve the *dl*-**1**. The first procedure involves (-)-camphanic acid (**9**) as the resolving agent. It was found that the diesters **11** and **12**, which were synthesized from *dl*-**1** and (-)-camphanoyl chloride (**10**), could be easily separated by crystallization from toluene. The solid diester **11** was obtained in >99% *de* whereas the diester **12** obtained from the mother liquor was of 66% *de*. These were saponified to obtain (+)-**1** (>99% *ee*) and (-)-**1** (66% *ee*) respectively (Scheme 3).

Scheme 3.



Since (-)-camphanic acid is an expensive resolving agent, we examined the possibility of using N-carbethoxy-L-proline (**13**), a cheap alternative. Esterification of *dl*-**1** with 2.5 equiv. of acid chloride **14** gave the diastereomeric diesters **15** and **16** which could not be separated by crystallization, but were separable by flash chromatography on silica gel. Subsequent saponification of the diesters provided (-)-**1** (40% yield, >99%*ee*) from less polar diester **15** and (+)-**1** (33% yield, >99%*ee*) from more polar diester **16** as depicted in Scheme 4.

Scheme 4.



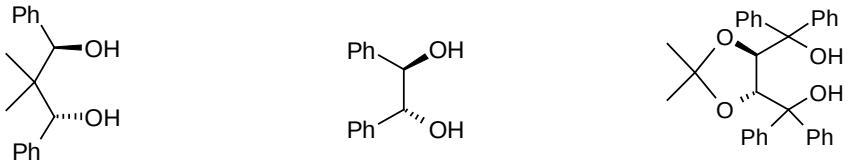
Finally the absolute configuration of (-)-**1** was determined by X-ray crystallography using anomalous dispersion method and found to be (*R,R*).

Chapter-3:

Applications of homochiral 2,2-dimethyl-1,3-diphenyl-1,3-propanediol

This chapter deals with a comparison of enantioselectivity obtained for a few reactions using the present diol **1**, chiral hydrobenzoin (**17**) and chiral TADDOL (**18**). The idea was to compare the effect of 1,2- *vs.* 1,3- *vs.* 1,4-substitution. This chapter contains three sections. Section-3A describes a comparative study of the three diols in asymmetric Diels-Alder reaction. Section-3B provides a detailed study on the application of chiral diol **1** in stereoselective reduction of acetophenone. Section-3C focuses on the application of chiral diol **1** in enantioselective addition of diethylzinc to benzaldehyde.

Figure 2.



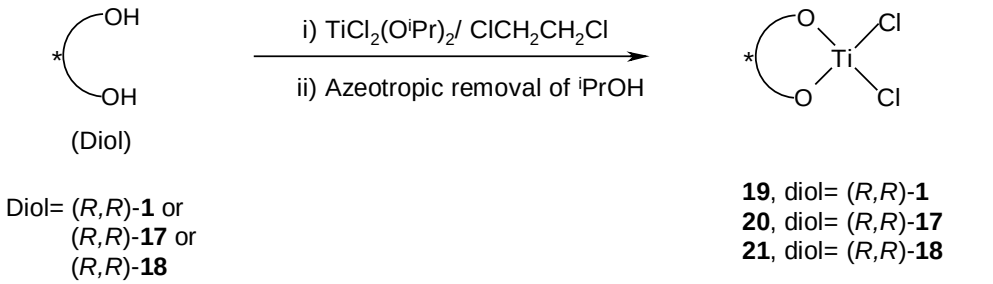
(*R*,*R*)-(-)-**1** (*R*,*R*)-(+)-**17** (*R*,*R*)-(-)-**18**

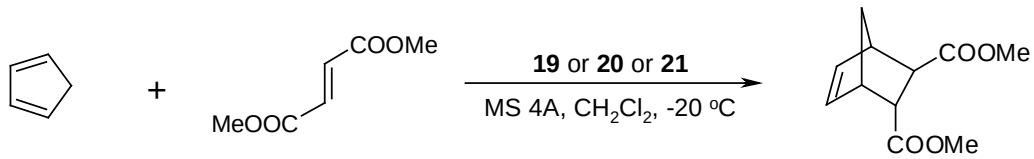
Section-3A: Diels-Alder reaction

To date very limited number of chiral Lewis acid catalysts have been used in the Diels-Alder reaction employing symmetrical α,*β*-unsaturated ester dienophiles. For these dienophiles, exceptionally strong binding between the Lewis acid and carbonyl group is essential to achieve good selectivity. To address this problem, we have examined few chiral titanate complexes synthesized from new chiral 1, 3-diol (**1**), 1,2-diol (**17**) and 1,4-diol (**18**) for enantioselective Diels-Alder reaction between cyclopentadiene and dimethylfumerate.

The titanate complexes from these three diols have been synthesized and used in catalytic as well as stoichiometric quantity for the model reaction (Scheme 5). All the complexes were found to be excellent promoter of the reaction affording high yield (93-99%). It was observed that the ring size of the titanate complexes does not significantly influene the reactivity and yield. However, the cycloadduct was obtained in almost racemic form (2-6% *ee*).

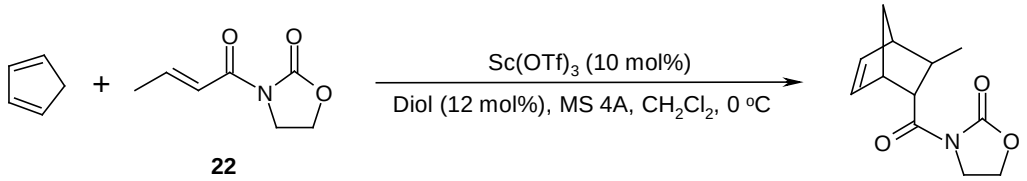
Scheme 5





Additionally, (*R*,*R*)-**1** has been examined as chiral ligand in $Sc(OTf)_3$ catalyzed Diels-Alder reaction between cyclopentadiene and oxazolidinone based dienophile **22** (Scheme 6). Moderate enantioselectivity (45%) was observed using 12 mol% of (*R*,*R*)-**1**.

Scheme 6

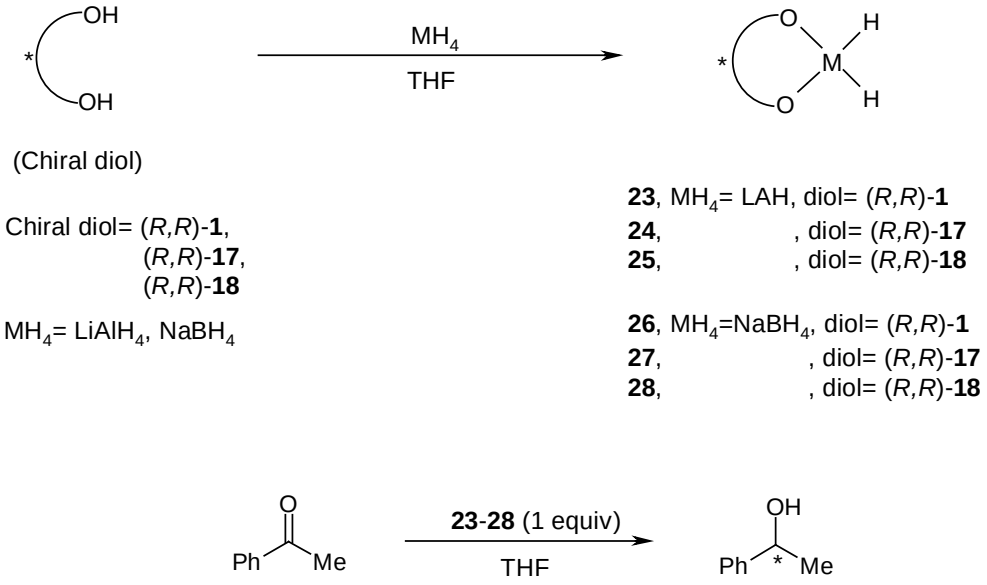


It was interesting to observe that (*R*,*R*)-**17** and (*R*,*R*)-**18** for the similar reaction afforded very low yield and selectivity compare to (-)-**1**.

Section-3B: Reduction of acetophenone

Over the years, there have been many attempts to effect asymmetric induction with alkoxy modified aluminium and boron hydride reagents derived from C_2-symmetric chiral glycols. In our present study, we have prepared few chiral aluminium and boron hydrides from C_2-symmetric chiral **17**, **1** and **18** (Scheme 7). The enantiomeric excess was in the range of 2-40% for the reduction of acetophenone. The highest enantioselectivity was observed for (*R*,*R*)-**18**.

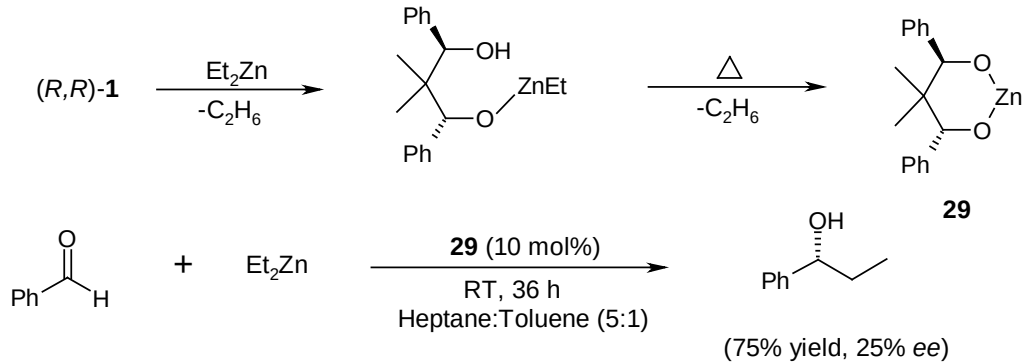
Scheme 7



Section-3C: Addition of diethylzinc to benzaldehyde

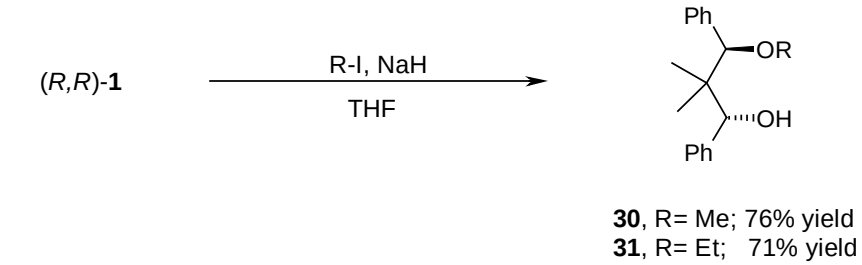
The asymmetric addition of diethylzinc to aromatic aldehydes is one of the most reliable methods for the construction of C-C bond affording chiral hydroxy compounds. Several highly efficient catalysts based on amino alcohols and diols with or without extra metals such as Ti(IV) have been found for this reaction. To date only one C_2-symmetric 1,3-diol, 1,3-diphenylpropanediol has been examined as a ligand, although without exhibiting any catalytic effect. Interestingly, zinc dialkoxide derived from (-)-**1** catalyzed the reaction providing 75% yield with a moderate(25%*ee*) enantioselectivity (Scheme 8).

Scheme 8

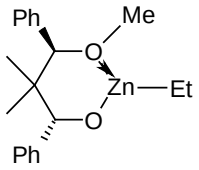


We also prepared monomethyl and monoethyl ether derivatives of (*R,R*)-(-)-**1** following the procedure outlined in Scheme 9. Zinc monoalkoxides **32** and **33** derived from **30** and **31** respectively, were found to be superior catalysts than the parent diol **1** (Scheme 9).

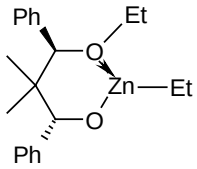
Scheme 9



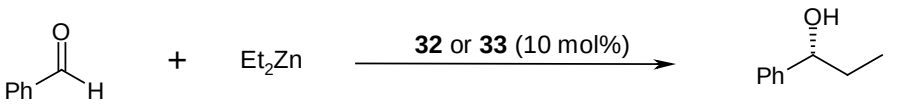
30, R= Me; 76% yield
31, R= Et; 71% yield



32



33



(upto 91% yield
and 72% *ee*)

CHAPTER-1

Synthesis and Applications of C_2-Symmetric Chiral Diols

Introduction

Chirality is one of the most visible phenomenon in nature and today's science & technology is deeply connected to the world of asymmetry.[1] Inevitably the first question glitters in mind is how might we obtain optically active compounds? Historically, the best answer to that question has been to isolate them from natural sources. However the dependence on natural product isolation for production of enantiomerically pure compounds is unacceptable and therefore the synthesis of optically active compounds has been a subject of keen interest. Until the early 1970's the resolution of racemates by classical methods was the primary tool to obtain optically active compounds.[2] Asymmetric synthesis, the selective generation of new chirality elements, is now considered to be a standard laboratory methodology. This development has taken place exponentially in the last two decades, triggered by a number of factors. Pharmaceuticals, vitamin, and agro chemicals need to be produced in enantiopure, rather than nonracemic active compounds because desired activity resides in only one stereoisomer. It is obvious from the fact that the molecules of life are chiral !

The term pervasively associated with asymmetric synthesis is "chiral inducer" i.e. chiral auxiliary/ligand which is truly a basic need for asymmetric synthesis. Thus synthesis of varieties of new chiral auxiliary/ligands and their structural optimization for better results are of interest to the synthetic chemists. Amongst chiral auxiliaries/ligands compounds with C_2 symmetry elements provide higher levels of absolute stereochemical control as compared to those lacking any symmetry.[3] C_2-symmetric diols, diamines and diphosphines account for more than 90% of all chiral inducers. Amongst these, diols have constituted the major part not only because many of them can be derived from natural sources, but also for the fact that these prove to be synthons for diamines and diphosphines. Chiral diols thus remain to be most sought after molecules in the area of asymmetric synthesis.

This chapter provides the background to the present work by reviewing the literature on synthesis and applications of optically pure diols with C_2 symmetry.

1. Synthesis of C_2-symmetric chiral diols

Varieties of C_2-symmetric chiral 1,2-, 1,3- and 1,4-diols have been found to be excellent chiral inducer in different types of asymmetric transformations. Few long chain C_2-symmetric chiral diols also showed their efficacy to induce good level of asymmetric induction during a

chemical transformation. Thus an easy access to these chiral diols is an important task. Synthesis of the C_2-symmetric diols is conveniently accomplished by two basic synthetic strategies, one enzymatic and the other chemical.

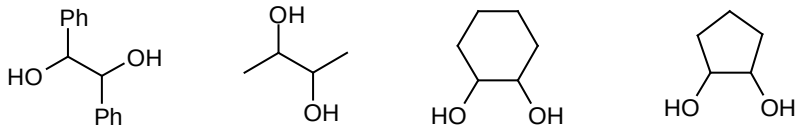
1.1. Enzymatic methods

Parallel to the explosive growth of non-biological processes, the enzymatic processes also have created a visible existance in asymmetric synthesis. 'Necessity', 'convenience' and 'opportunity' are the three advantageous factors for the gradual increase in interest for using enzymes in organic synthesis. Active sites of enzymes are substrate specific and chiral, and hence can show high degree enantiodifferentiation. Moreover, enzymes are intrinsically environment friendly materials that operate best in water. Thus enzymatic methods have been an efficient tool to obtain optically pure compounds including several C_2-symmetric chiral diols.

1.1.1. 1,2-Diols

C_2-symmetric 1,2-diols are the simplest variety of chiral diols. The most popular and useful C_2-symmetric chiral 1,2-diol has been chiral hydrobenzoin (**1**). The preparation of crystals of the enantiomers of *rac*-**1** and resolution by mechanical separation has even been made the basis of an experiment in an introductory course of organic chemistry.[4] The crystal morphologies of *rac*-**1** permitted optical resolution by hand-separation of the two enantiomers.[5] Other diols like chiral 2,3-butanediol (**2**), 1,2-cyclohexanediol (**3**), 1,2-cyclopentanediol (**4**) etc. have enriched this class of compounds. Since early 20th century, several enzymatic approaches have been directed to access these diols in optically pure form.

Figure 1.



1 **2** **3** **4**

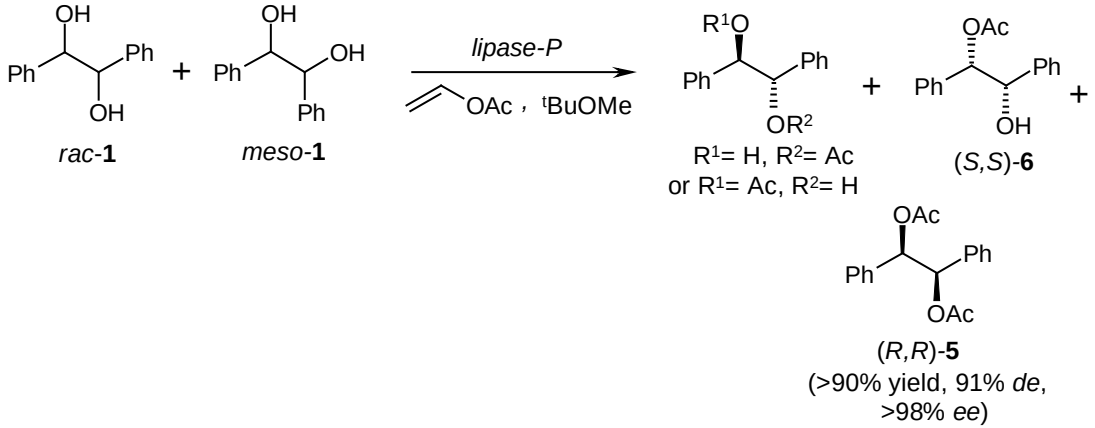
1.1.1.1. Reduction

A series of *para*-substituted symmetrical benzils and benzoins were reduced using *C. macerans* enzyme to yield the (*R*,*R*)-hydrobenzoins of high optical purity in 6-59% yield.[6] Buisson et. al. reported the double reduction of benzils by different yeast strains with varying enantio- and diastereoselectivity.[7] With *S. uvarum* and *S. montanus*, it was possible to obtain nearly pure (*R*,*R*)- and (*S*,*S*)-hydrobenzoins in reasonable yields.

1.1.1.2. Resolution

Basavaiah et. al. obtained (*R,R*)-**1** in 98% *ee* using chicken liver acetone powder (CLAP) *via* the resolution of the corresponding racemic diacetate.[8] Parmar et. al. reported an efficient enzymatic kinetic resolution to obtain the diacetate (2*R*,3*R*)-**5** with high optical purity from a commercial mixture of *meso*- and *rac*-**1**.[9] The monoacetate **6** of the chiral diol **1** was clearly confirmed as (2*S*,3*S*)-enantiomer (Scheme 1).

Scheme 1



rac-**1**

meso-**1**

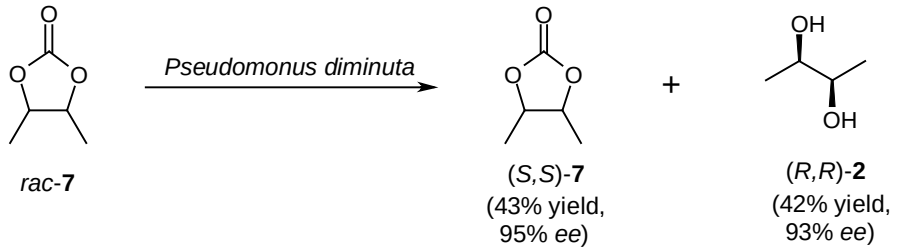
R¹= H, R²= Ac
or R¹= Ac, R²= H

(*S,S*)-**6**

(*R,R*)-**5**
(>90% yield, 91% *de*,
>98% *ee*)

Similarly, lipase from *Pseudomonas cepacia* (PCL, Amano PS) catalyzed the enantioselective diacetylation of *rac*-**2** in vinylacetate.[10] In this synthetic scale sequential kinetic resolution starting from 2.7 g of *rac*-**2**, yielded the corresponding diacetate with 96% *ee* (1.6 g, 30% yield) and (2*S*,3*S*)-**2** with 99% *ee* (0.63 g, 23% yield). Recently Matsumoto et. al. demonstrated the first example of highly enantioselective preparation of optically active both (*R,R*)- and (*S,S*)-**2** *via* the microbial hydrolysis of the corresponding racemic cyclic carbonates **7** (Scheme 2).[11]

Scheme 2



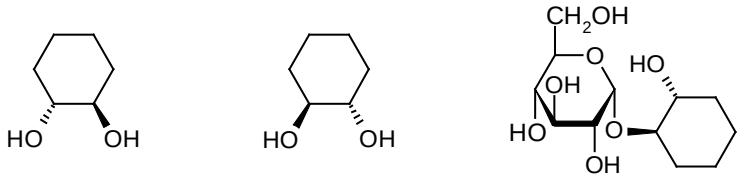
rac-**7**

(*S,S*)-**7**
(43% yield,
95% *ee*)

(*R,R*)-**2**
(42% yield,
93% *ee*)

Derx et. al. for the first time separated the enantiomer of 1,2-cyclohaxanediol (**3**) by optical resolution method.[12] Itano et. al. demonstrated a kinetic resolution process to separate the two enantiomer of *rac*-**3** (Figure 2).[13] A racemic mixture of **3** was incubated with *Takadiastase* and maltose (donor), to give exclusively one D-glucoside **8**. The acid hydrolysis of **8** yielded (*R,R*)-**3** with >99% *ee*.

Figure 2.



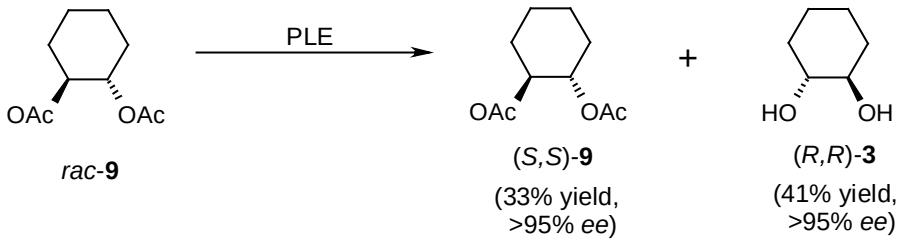
(*R,R*)-**3**

(*S,S*)-**3**

8

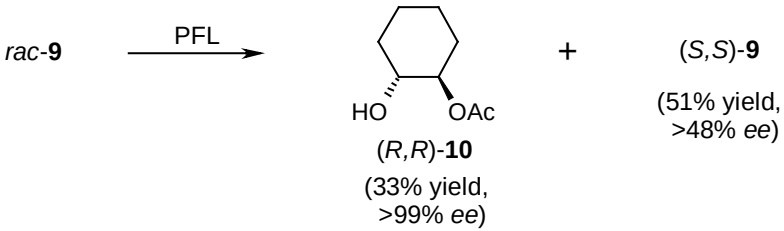
The enzymatic hydrolysis of the racemic diacetate **9** in the presence of porcine liver esterase (PLE), a simple and facile preparative route to optically active diol **3**, was reported by Crout et. al (Scheme 3).[14]

Scheme 3



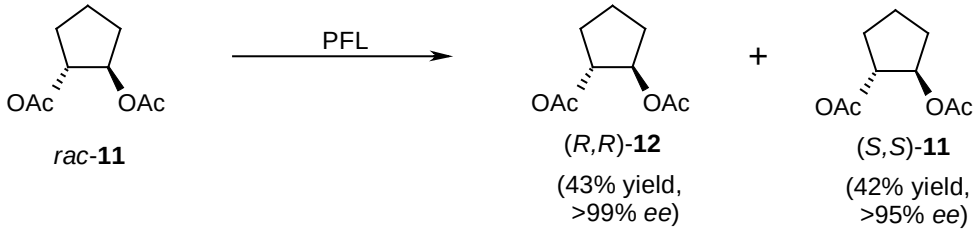
Sakai et. al. described an enzymatic kinetic resolution where *Pseudomonus fluorescens* lipase (PFL) hydrolyzed *rac*-**9** selectively to the monoacetate (*R,R*)-**10** in 33% yield (Scheme 4).[15]

Scheme 4



1,2-Cyclopentanediol (**4**) is another useful chiral ligand/auxiliary in asymmetric synthesis. Derx initiated the preparation of **4** in optically pure form by resolving the stryquinine salt of the bis-hydrogensulfate of *rac*-**4**.[12] Later the racemic di-acetates **11** of *rac*-**4** were successively resolved into the optically active alcohols with high optical purities by PFL. Sakai et. al. obtained the monoacetate (*R,R*)-**12** in >99% *ee* (Scheme 5).[16]

Scheme 5

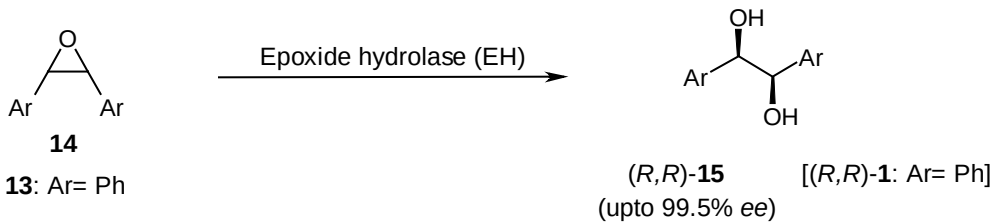


Schneider and co-workers also demonstrated an efficient method where (*R*,*R*)-**12** and (*S*,*S*)-**11** with 97% *ee* and ≥98% *ee* were prepared respectively by enzymatic kinetic hydrolysis of (±)-**11**.[17]

1.1.1.3. Epoxide ring opening

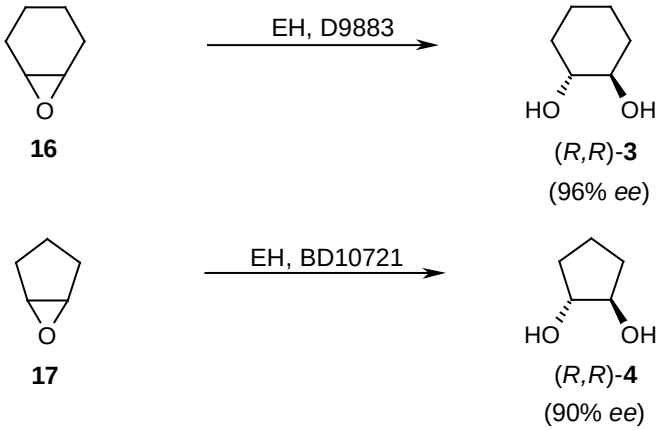
Simultaneous construction of two contiguous stereogenic centers *via* desymmetrization of *meso*-epoxides is an attractive route for catalytic production of chiral 1,2-diol derivatives with 100% theoretical yield. Bellucci et. al. reported the microsomal epoxide hydrolase catalyzed ring opening of *meso*-stilbene oxide **13** to furnish (*R*,*R*)-**1** with 87% optical purity.[18] They also reported enantioselective ring opening of **13** to (*R*,*R*)-**1** by both the microsomal and the cytosolic epoxides hydrolase of rabbit liver.[19] The former enzyme provided higher enantioselectivity (88% *ee*). Very recently Zhao et. al. identified certain epoxide hydrolases (EHs) which provide access to both substituted (*R*,*R*)- and (*S*,*S*)-hydrobenzoins **15** with high enantioselectivity from epoxides **14** (Scheme 6).[20] They have also reported the first example of (*S*,*S*)-selective enzymes for desymmetrization of **2**.

Scheme 6



Jerina et. al. reported a moderate enantioselective process where epoxide hydrase converted *meso*-cyclohexane oxide (**16**) to (*R*,*R*)-**3** with 70% *ee*.[21] Recently Chang et. al. demonstrated an efficient hydrolysis of **16** with epoxide hydrolase (EH) of HXN-200 giving the diol (*R*,*R*)-**3** in 99% yield and 87% *ee*.[22] According to Zhao et. al., (*R*,*R*)-**3** was synthesized in very high enantioselectivity from **16**.[20] (*R*,*R*)-**4** was also synthesized from epoxide **17** using this method (Scheme 7).

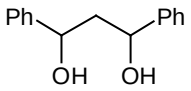
Scheme 7



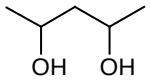
1.1.2. 1,3-Diols

Amongst C_2-symmetric 1,3-diols, 1,3-di-phenylpropane-1,3-diol (**18**) and 2,4-pentanediol (**19**) are the most popular representatives. Several enzymatic methods have been reported for the synthesis of this class of compounds.

Figure 3.



18

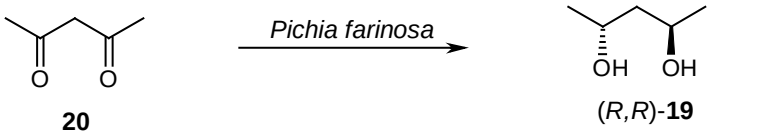


19

1.1.2.1. Reduction

(*R*,*R*)-**19** was obtained by the enantioselective reduction of acetylacetone (**20**) with the yeast *Candida boidinii* KK 912 (IFO 10574).[23] A practical synthesis of optically pure diol **19** was reported by Ikeda et. al.[24] This highly efficient preparative method for (*R*,*R*)-**19** was based on the reduction of the ketone **20** by *Pichia farinose* IAM 4682 (Scheme 8).

Scheme 8



20

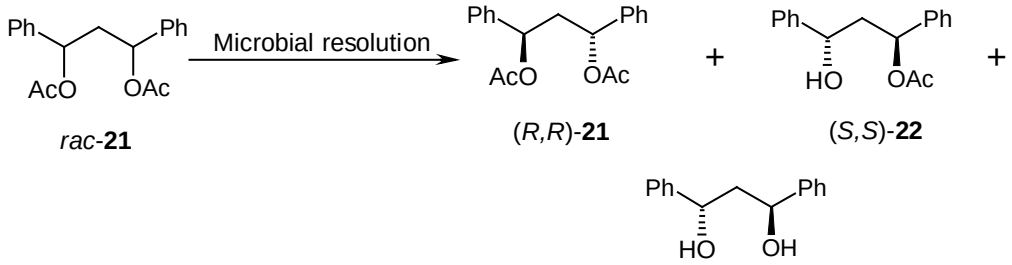
(*R*,*R*)-**19**

(94% yield, 98% *de*
>99% *ee*)

1.1.2.2. Resolution

An efficient microbial synthesis of optically pure **18** has been achieved by exposing the corresponding racemic diacetate **21** to *Trichoderma viride*. Optically pure (*R*,*R*)-**21** and monoacetate (*S*,*S*)-**22** were obtained alongwith the diol (*S*,*S*)-**18** (Scheme 9).[25]

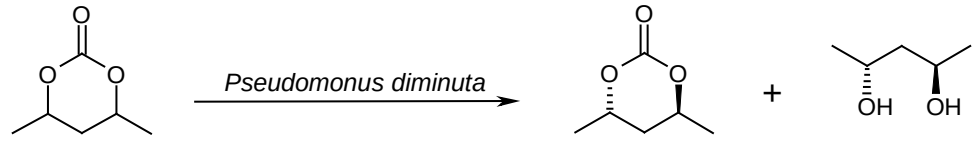
Scheme 9



rac-**21** (*R,R*)-**21** (*S,S*)-**22** (*S,S*)-**18**

Quantitative expressions that govern sequential kinetic resolutions have been developed for calculation of the relative kinetic constants to allow optimization of chemical and optical yields. Guo et. al. prepared enantiomerically pure (*R,R*)- and (*S,S*)-**19** by biocatalytic sequential enantioselective esterification.[26] Recently Matsumoto et. al. demonstrated the first example of highly enantioselective preparation of optically active **19** *via* the microbial hydrolysis of the corresponding racemic cyclic carbonates (Scheme 10).[11]

Scheme 10



rac-carbonates (36% yield, 94% *ee*) (*R,R*)-**19** (26% yield, 91% *ee*)

1.2. Chemical methods

The characteristics of instability, high cost, and narrow substrate specificity have been considered to be the most serious drawbacks of enzymes for use as synthetic catalysts. As a result, application of enzymes has been focused primarily on small scale procedures yielding specific chemicals. Non-biochemical processes with wider applicability are therefore preferred substitute for enzymatic processes. Various

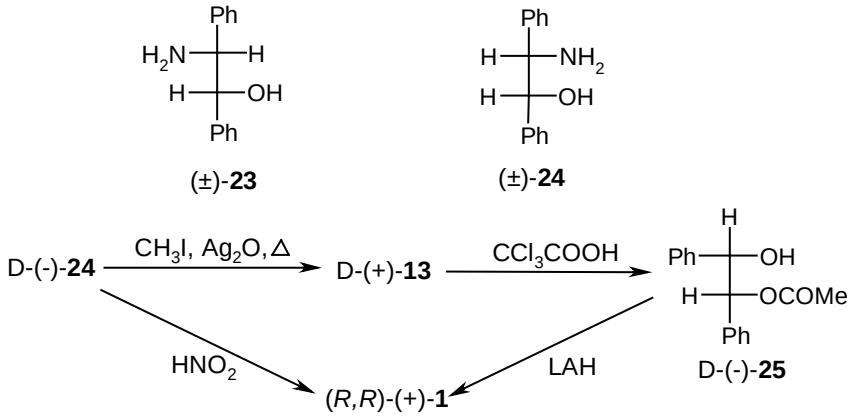
established chemical methods are available in literature for the large scale synthesis of C_2-symmetric diols. These methods include synthetic transformation, resolution, epoxide ring opening, reduction etc. have been found to be all in all for the synthesis of several C_2-symmetric chiral 1,2-, 1,3- and 1,4-diols.

1.2.1. 1,2-Diols

1.2.1.1. Synthetic transformation

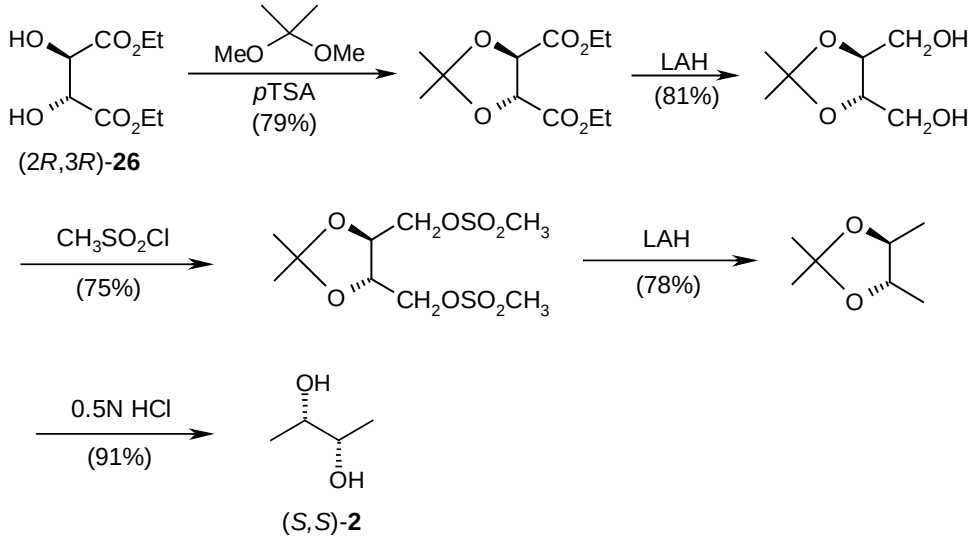
As early as 1899, D-Tartaric acid has been used to resolve (±)-isodiphenylhydroxyethylamine (**23**).[27] Read and Steele demonstrated the resolution of (±)-*erythro*-1,2-diphenyl-2-aminoethanol (**24**) by condensation with *d*-oxymethylene camphor. Upon treating the *N*-hydrochloride salt of D-(-)-**24** with nitrous acid, optically pure *d*-**1** was obtained in low yield after recrystallization (Scheme 11).[28] They also reported the synthesis of optically active *trans*-**13** from (+)- and (-)-**24**.[29] Berti et. al. proposed a simple synthetic route to obtain (+)- or (-)-**1** starting from the optically pure amino alcohol **24** *via* epoxide **13** and hydroxyester **25**. They also determined the configuration of (+)- and (-)-**1**.[30]

Scheme 11



There are many examples of the synthesis of optically pure diol **2** from diethyltartarate (**26**) as the starting material. Simple chemical transformations have been designed to access the diol **2** in high optical purity. Plattner et. al. described a simple strategy to yield (*S*,*S*)-**2** (Scheme 12).[31a]

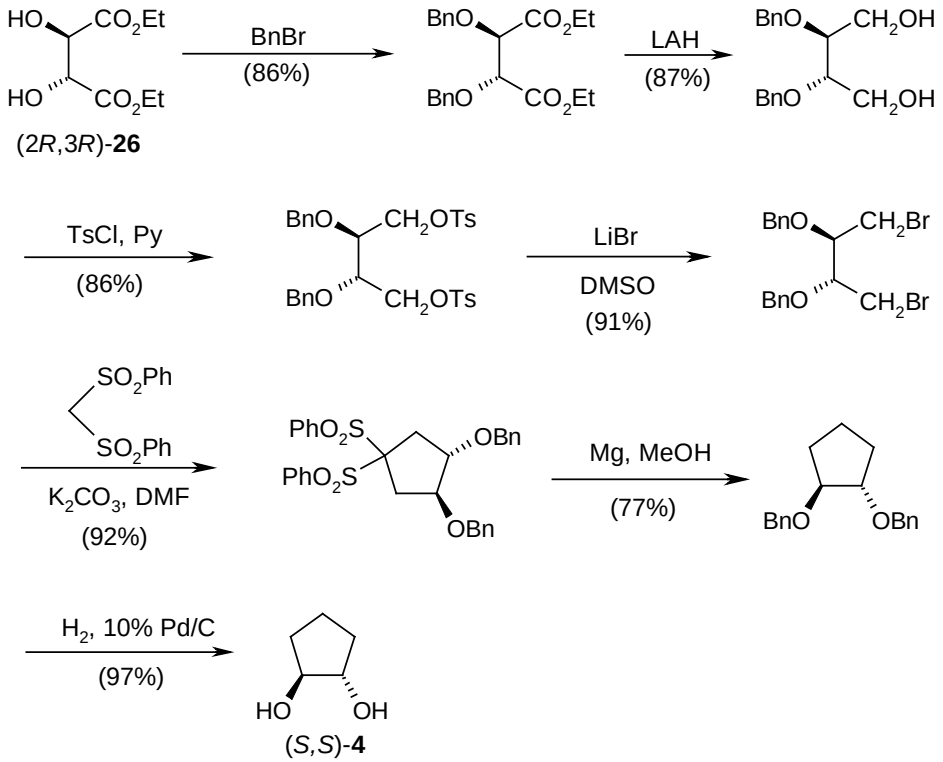
Scheme 12



Mori et. al. demonstrated a similar approach to synthesize both the enantiomer of **2** starting from either enantiomer of **26**.[31b]

Cunningham et. al. presented an efficient and short synthesis of enantiomerically pure (*S*,*S*)-**4** starting from (*R*,*R*)-**26** (Scheme 13).[32]

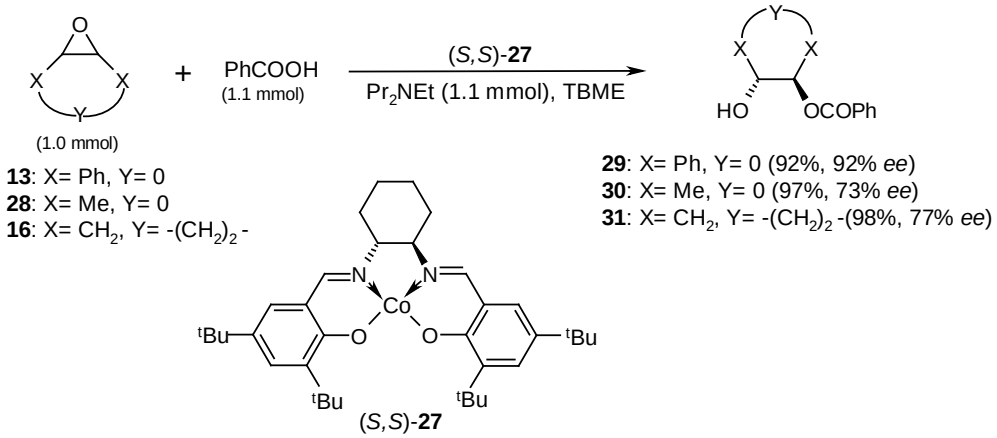
Scheme 13



1.2.1.2. Epoxide ring opening

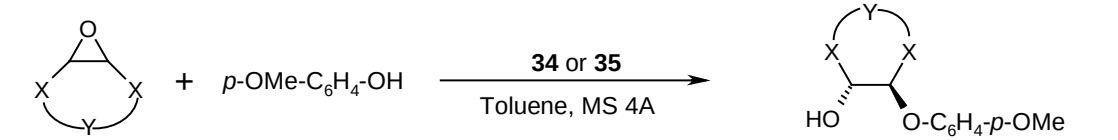
Jacobsen et. al. demonstrated chiral Co-salen complex **27** as an effective catalyst for the enantioselective ring opening of several epoxides like **13**, **28** and **16** in presence of benzoic acid as nucleophile.[33] Corresponding (*R,R*)-diols **29**, **30** and **31** were obtained with very high yield and enantioselectivity (Scheme 14).

Scheme 14



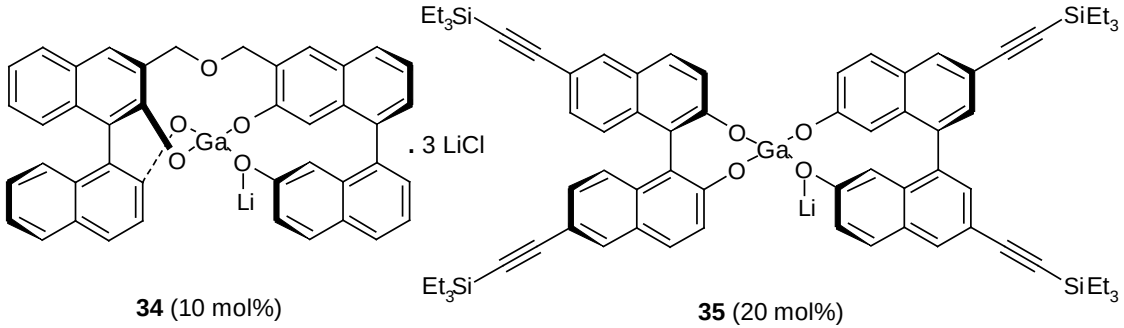
In another catalytic enantioselective ring opening approach by Shibasaki, the *meso*-epoxide **28** and **16** was converted to **32** and **33** respectively with 4-methoxyphenol promoted by Ga-Li-BINOL complex **34** and **35** respectively (Scheme 15).

Scheme 15



28: X= Ph, Y= 0
16: X= CH_2, Y= -$(CH_2)_2$-

32: X= Me, Y= 0 (72%, 91% *ee*)
33: X= CH_2, Y= -$(CH_2)_2$- (60%, 94% *ee*)

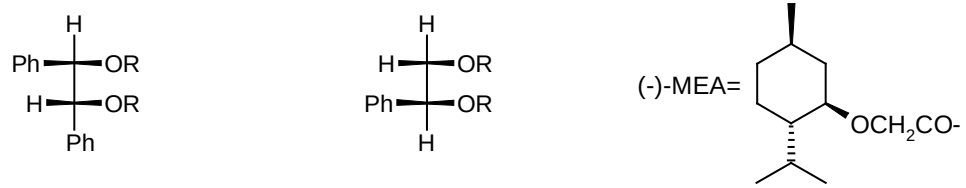


34 (10 mol%) **35** (20 mol%)

1.2.1.3. Resolution

Unlike enantiomers, diastereomeric pairs may have significantly different physical properties which is the basis of their separation from one another in multigram quantity. The first practical resolution of *rac*-**1** was reported by Dietl in 1982.[35] The diastereomeric bis-(-)-menthoxyacetates **36a** and **36b** were easily separated by fractional crystallization from ethanol (Figure 4). Optically pure (*R*,*R*)- and (*S*,*S*)-**1** were obtained after saponification of the diester **36a** and **36b** respectively in very high yield.

Figure 4.

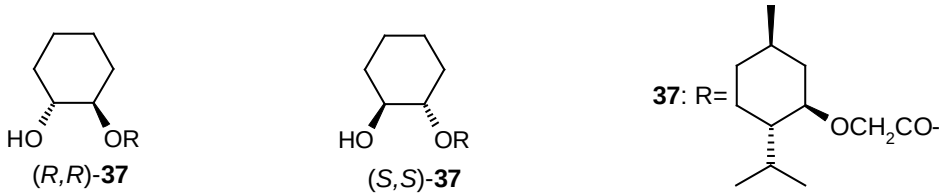


36a : R= (-)-MEA
(*R*,*R*)-**1**: R= H

36b : R= (-)-MEA
(*S*,*S*)-**1**: R= H

In another example, *rac*-**1** was resolved through an addition compound with (1*R*,2*R*)-cyclohexanediamine in 62% yield and 91% *ee*.[36] In the early 1930's Read et. al. resolved the two enantiomers of diol **3** using *l*-menthoxyacetic acid as the resolving reagent. The diastereomeric acetates **37a** and **37b** were separated by fractional crystallization from aqueous methanol (Figure 5).[37] Saponification of monoesters **37** provided optically pure (*R*,*R*)- and (*S*,*S*)-**3**.

Figure 5.



(*R*,*R*)-**37**

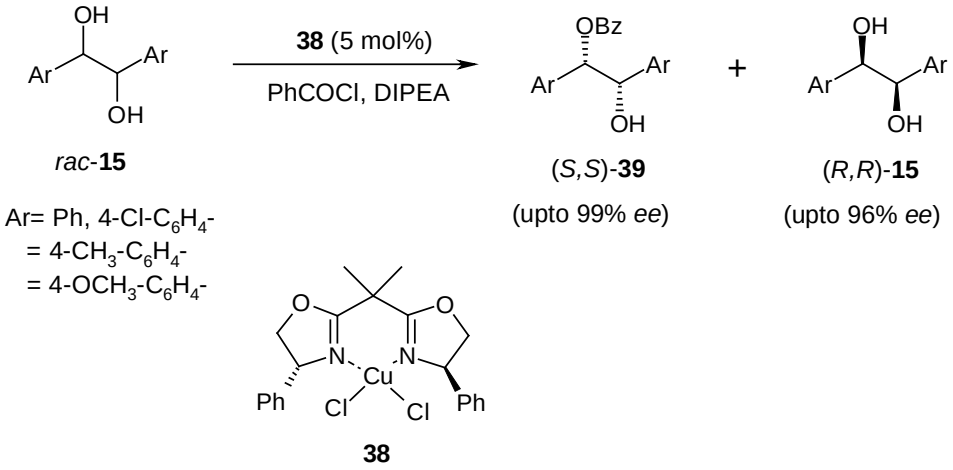
(*S*,*S*)-**37**

3: R= H

Periasamy et. al. resolved *rac*-**1** to obtain (*S*,*S*)-**1** in 99% *ee* through complexation with boric acid and (*S*)-proline.[38] The overall yield of pure (*S*,*S*)-**1** was poor.

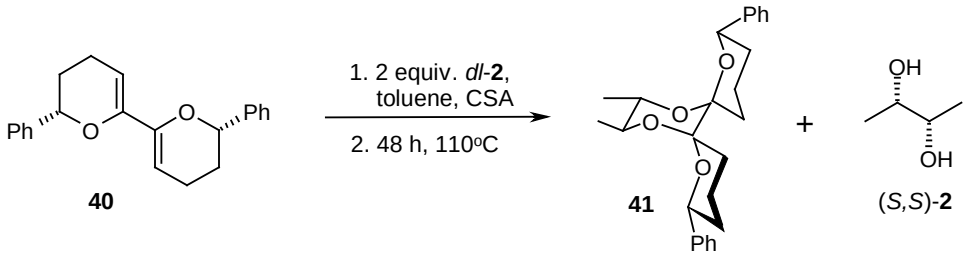
Matsumura et. al. reported an excellent kinetic resolution of *rac*-**15** using catalytic amount of chiral Cu(II) complex **38**. The monobenzoate (*S*,*S*)-**39** and unreacted diol (*R*,*R*)-**15** were obtained in very high enantiomerically pure form (Scheme 16).[39]

Scheme 16



Edwards et. al. described a kinetic resolution of *rac*-**2** using (2S,2′S)-2,2′-diphenyl-3,3′,4,4′-tetrahydro-6,6′-bi-2H-pyran (PDHP) (**40**).[40] The dispiroketal **41** was obtained as the single isomer in 91% yield, leaving (*S,S*)-**2** unreacted (Scheme 17).

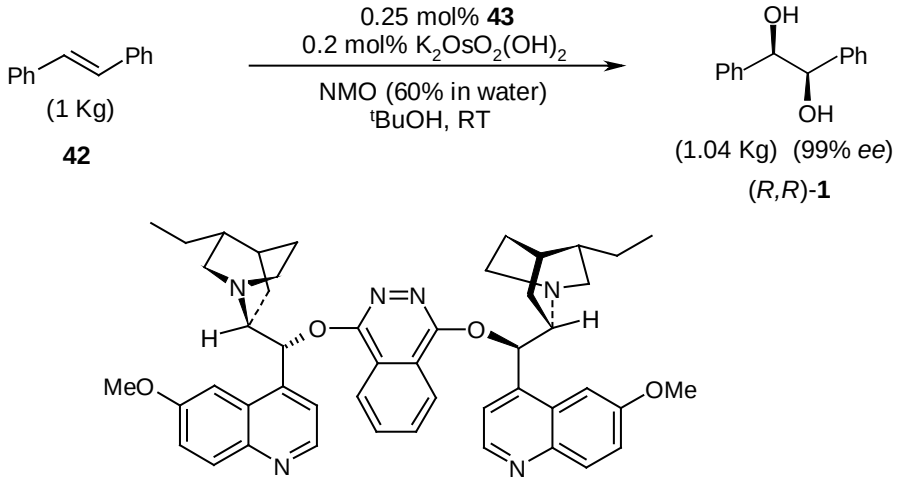
Scheme 17



1.2.1.4. Asymmetric dihydroxylation (ADH)

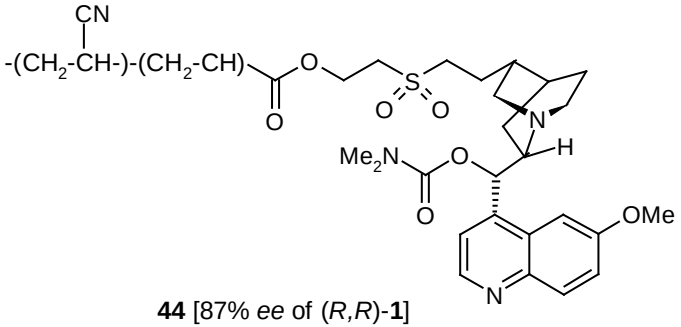
Catalytic asymmetric dihydroxylation has proved to be the best procedure to produce optically pure 1,2-diols particularly hydrobenzoins.[41,42] To remove all ambiguities regarding the efficiency of ADH, Sharpless demonstrated a process for the production of (*R*,*R*)-**1** (99% *ee*) on a kilogram scale, which was performed at room temperature in a 5-L flask and the insoluble solid diol product was isolated by simple filtration of the reaction mixture (Scheme 18).[43]

Scheme 18

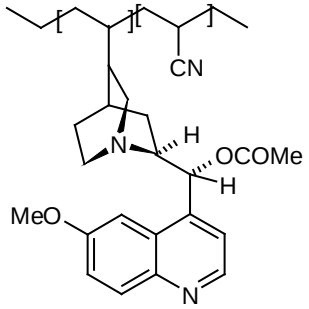


The osmium catalyzed ADH of **42** using molecular oxyzen or air as the stoichiometric oxidant was reported by Beller et. al. providing (*R*,*R*)-**1** with 93% *ee*.[44] Catalytic ADH of **42** using both soluble polymer bound (SPB)[45,46] and insoluble polymer bound (IPB) cinchona alkaloids is a potential industrial process for the synthesis of optically pure diol **1**. A range of chiral polymeric systems like **44**[46a], **45**[46b], **46**[46c], **47**[46d], **48**[46e], **49**[46f], **50**[46g], **51**[46h] and **52**[48] were reported (Figure 6).

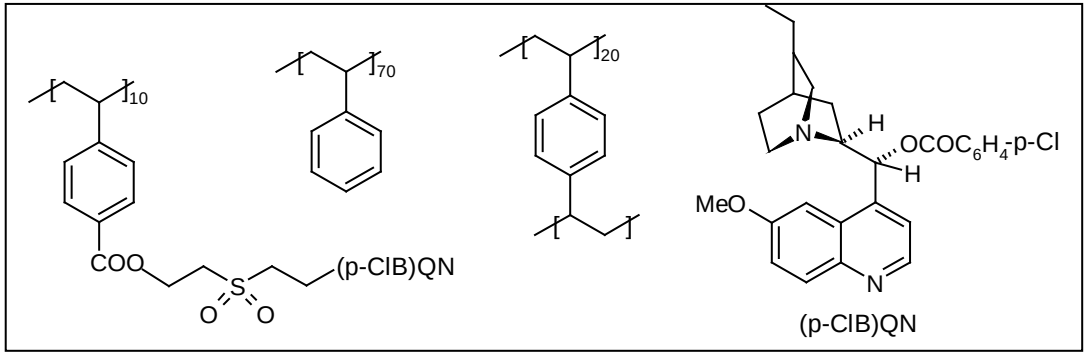
Figure 6.



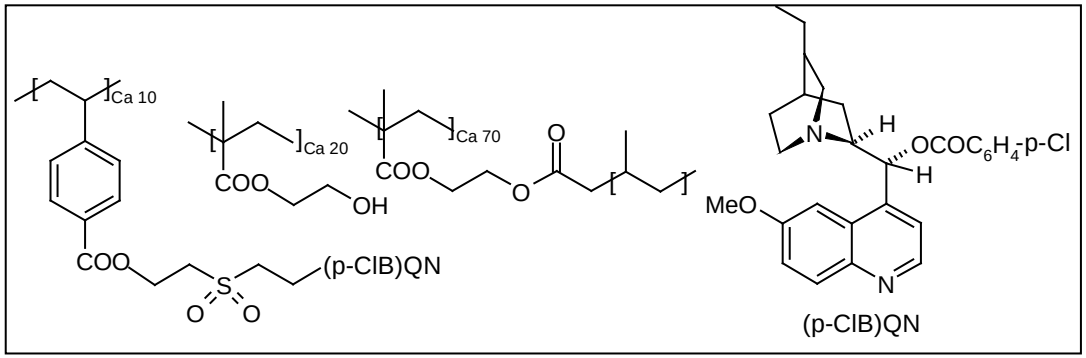
44 [87% *ee* of (*R*,*R*)-**1**]



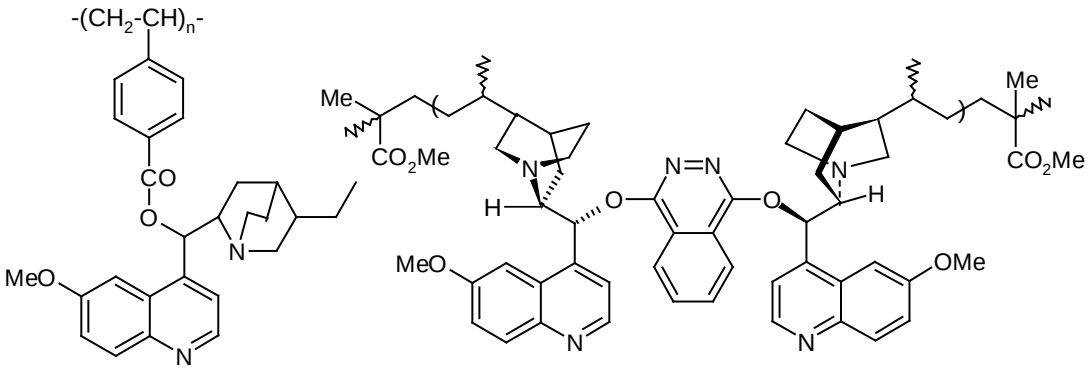
45 [46% *ee* of (*R*,*R*)-**1**]



46 [87% *ee* of (*S*,*S*)-**1**]

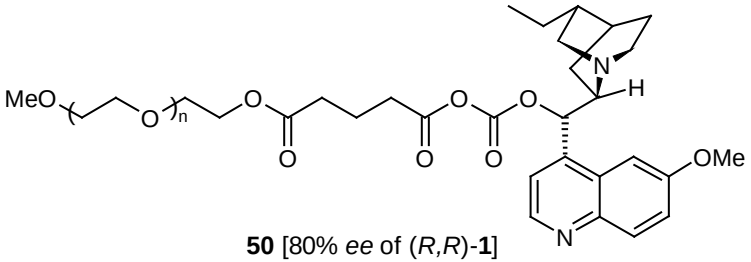


47 [95% *ee* of (*S*,*S*)-**1**]

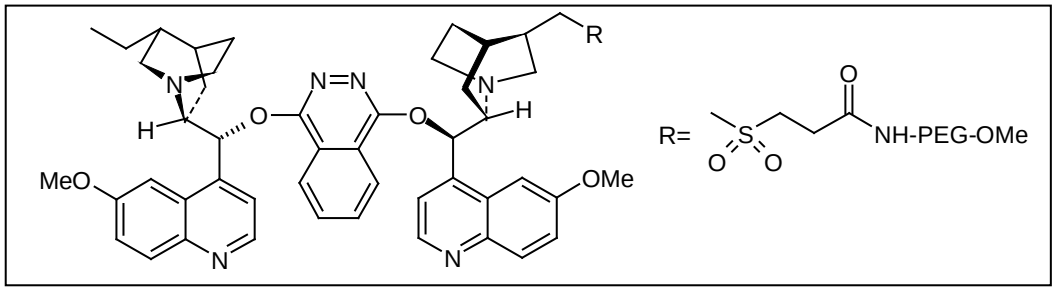


48 [93% *ee* of (*S*,*S*)-**1**]

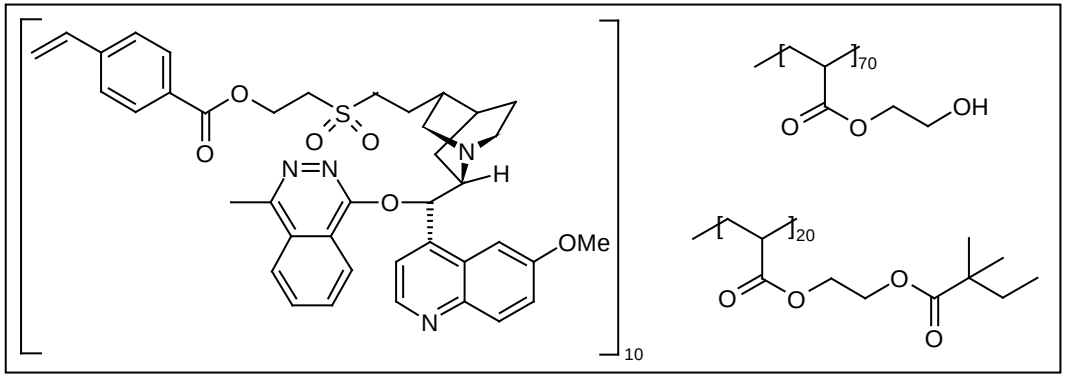
49 [>99% *ee* of (*S*,*S*)-**1**]



50 [80% *ee* of (*R*,*R*)-**1**]



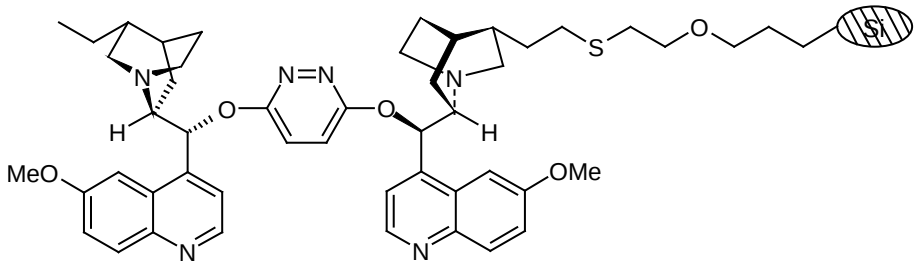
51 [>99% *ee* of (*R*,*R*)-**1**]



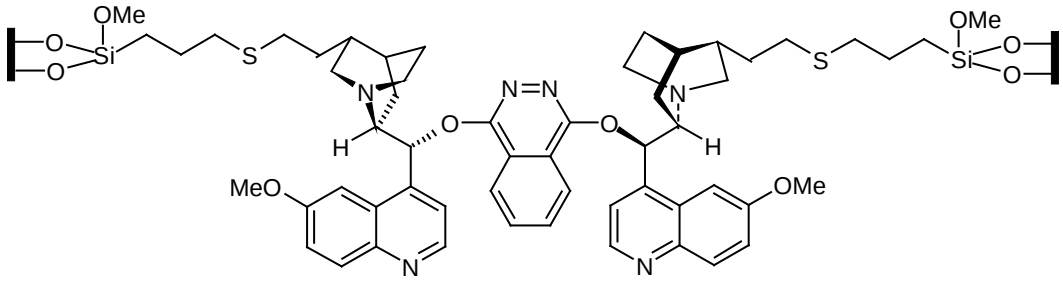
52 [>99% *ee* of (*R*,*R*)-**1**]

Recently many groups have demonstrated very efficient catalytic ADH of **42** using immobilized chiral alkaloids on an inorganic support such as silica[47] or modified resin[48]. Varieties of catalytic systems of this type e.g. **53**[49a], **54**[49b], **55**[49c], **56**[50] have shown their usefulness in ADH (Figure 7).

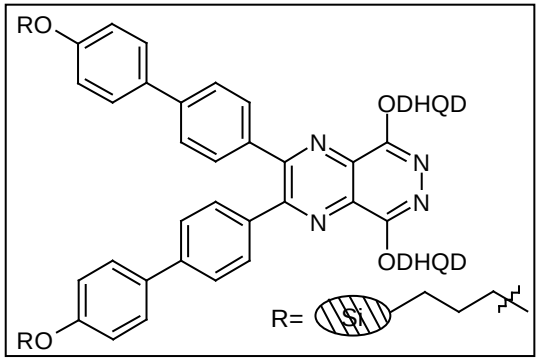
Figure 7.



53 [80% *ee* of (*S*,*S*)-**1**]



54 [>99% *ee* of (*S*,*S*)-**1**]



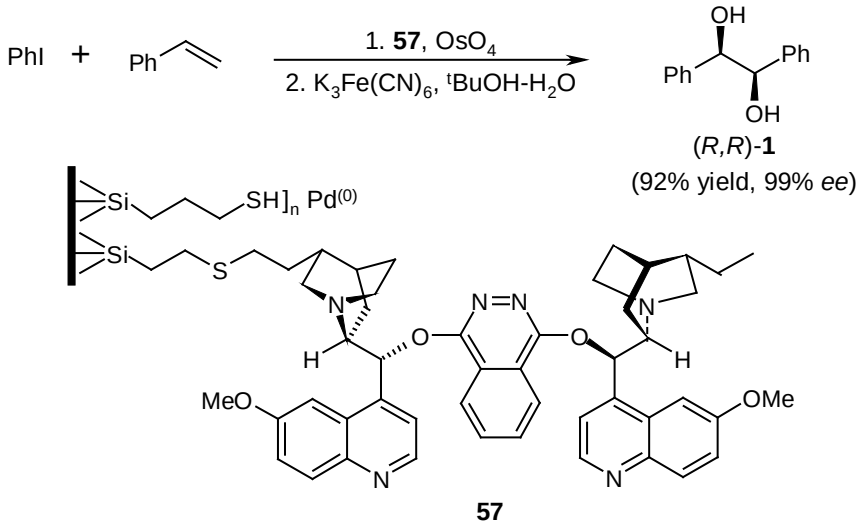
55 [99% *ee* of (*R*,*R*)-**1**]

LHD-OsO_4
$(DHQD)_2$-PHAL
LHD= Layered double hydroxide

56 [97% *ee* of (*R*,*R*)-**1**]

Choudary et. al. very recently reported a new bifunctional heterogeneous system **57** as highly effective catalyst for tandem Heck-AD of styrene to afford the (*R*,*R*)-**1** with high yields and % *ee* (Scheme 19).[51]

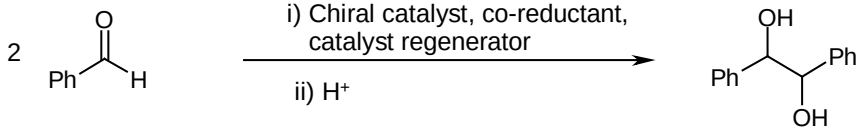
Scheme 19



1.2.1.5. Pinacol coupling

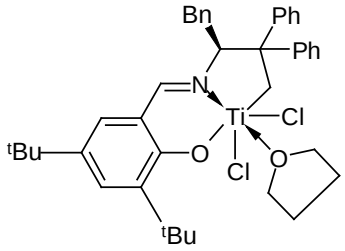
Apart from the AD processes, pinacol coupling of benzaldehyde has been one of the most promising method for preparing optically pure hydrobenzoin (Scheme 20).[52,53]

Scheme 20

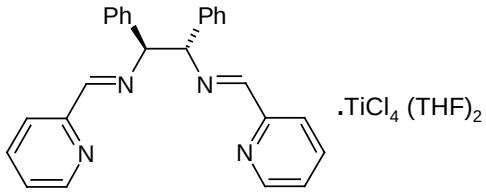


To date, efforts toward synthesis of optically pure **1** employing this reaction have focused on the use of chiral low-valent titanium catalysts e.g. **58**[52a], **59**[52b] (Figure 8).

Figure 8.



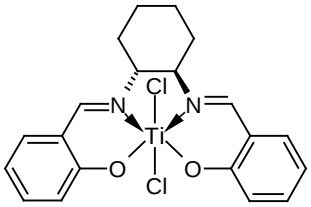
58 [98:2 (*dl:meso*), 77% *ee* of (*S,S*)-**1**]



59 [95:5 (*dl:meso*), 90% *ee* of (*S,S*)-**1**]

Recently our group reported a truly catalytic pinacol coupling reaction using titanium-schiff base complex **60** (Figure 9).[53] Useful synthesis of (*R,R*)-**1** with very high diastereo- as well as enantioselectivity was accomplished.

Figure 9.

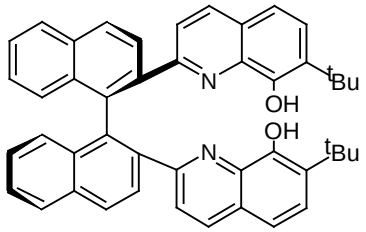


60 [98:2 (*dl:meso*), 97% *ee* of (*R,R*)-**1**]

TBOxCrCl

61

[98:2 (*dl:meso*), 97% *ee* of (*R,R*)-**1**]



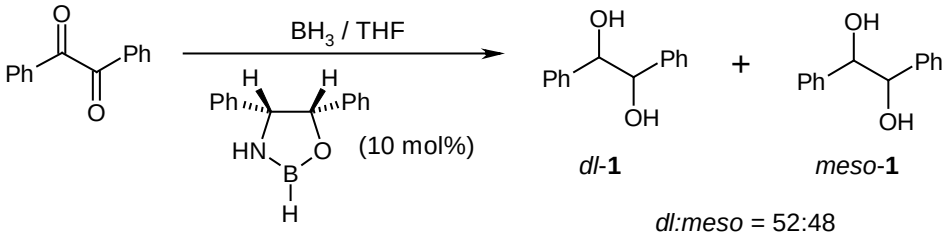
TBOxH

More recently, Yamamoto and co-workers developed a chiral tethered bis(8-quinolinato)(TBOx) chromium catalyst **61** which conferred the highest stereoselectivity reported so far in this reaction (Figure 9).[54]

1.2.1.6. Enantioselective reduction

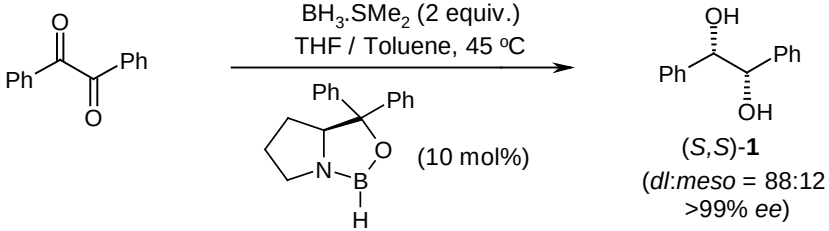
The boron reductions of benzils had an inherent preference for the *meso*-isomers.[55] A chiral oxazaborolidine catalyzed reductions managed to override this preference yielding *dl*-**1** as the major product with moderate enantioselectivity (Scheme 21).[56]

Scheme 21



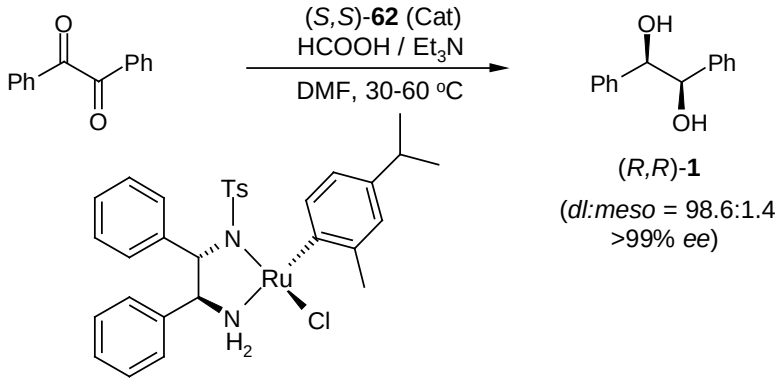
Our group established a convenient oxazaborolidine catalyzed enantioselective route to optically pure (*S*,*S*)-hydrobenzoins.[57] The chiral (*S*,*S*)-**1** was synthesized with high stereochemical control (Scheme 22).

Scheme 22



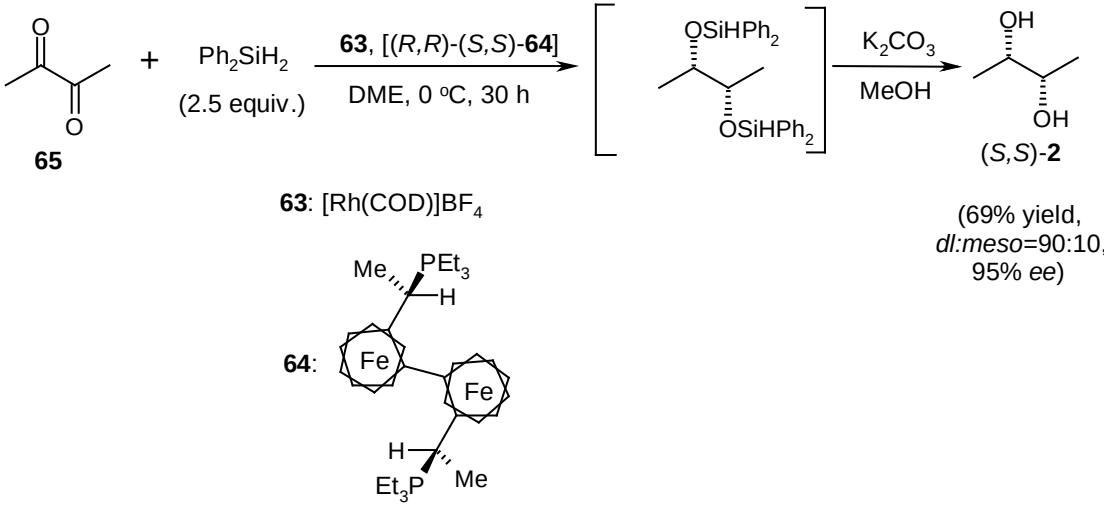
The true breakthrough for the reduction protocol came from Noyori et. al.. They demonstrated a practical asymmetric reduction of benzil to chiral hydrobenzoins using a well-defined chiral Ru(II) catalyst **62** with HCOOH/Et_3N mixture as hydrogen source (Scheme 23).[58]

Scheme 23



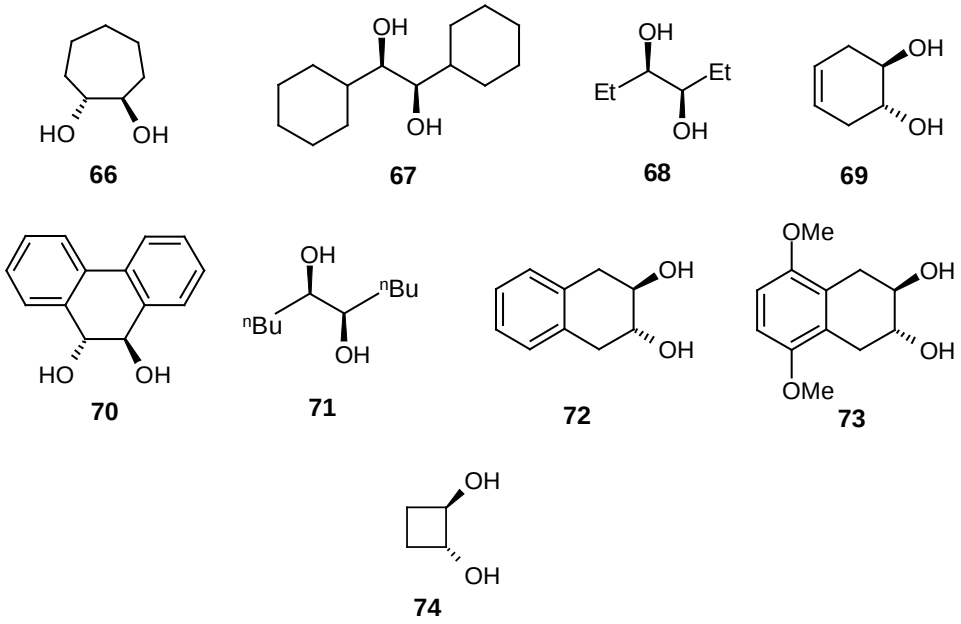
Enantioselective reduction through asymmetric hydrosilylation of symmetrical diketone **65** with diphenylsilane in the presence of catalytic amount of Rh-complex **63** complexed with *trans*-chelating chiral phosphine ligand EtTRAP **64** gave optically active diol **2** with high *ee* (Scheme 24).[59]

Scheme 24



There are many others C_2-symmetric 1,2-diols known in the literature. The synthesis of diols e.g. **66**[15,17,33,34,37], **67**[60], **68**[39], **69**[20,33,34], **70**[33], **71**[44,46h,61-63], **72**[64], **73**[34], **74**[14] have been accomplished by several groups (Figure 10).

Figure 10.

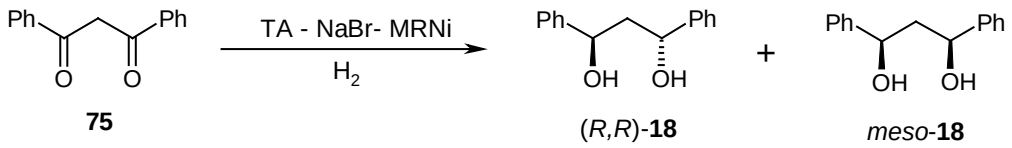


1.2.2. 1,3-Diols

1.2.2.1. Reduction

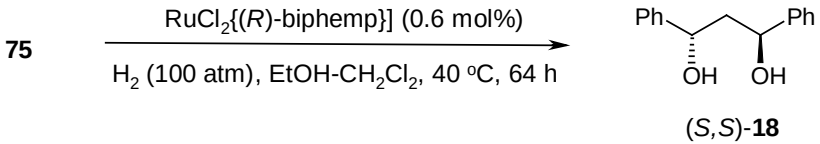
Ito et. al. presented the first synthesis of optically pure diol **18** from the corresponding *β*-diketone **75**.[65] Hydrogenation of **75** over Raney Ni catalyst modified with a mixture of tartaric acid and NaBr (TA-NaBr-MRNi) gave (*R,R*)-**18**. After three consecutive recrystallization from ether/ethylacetate mixture, optically pure (*R,R*)-**18** was obtained in 20% overall yield (Scheme 25).

Scheme 25



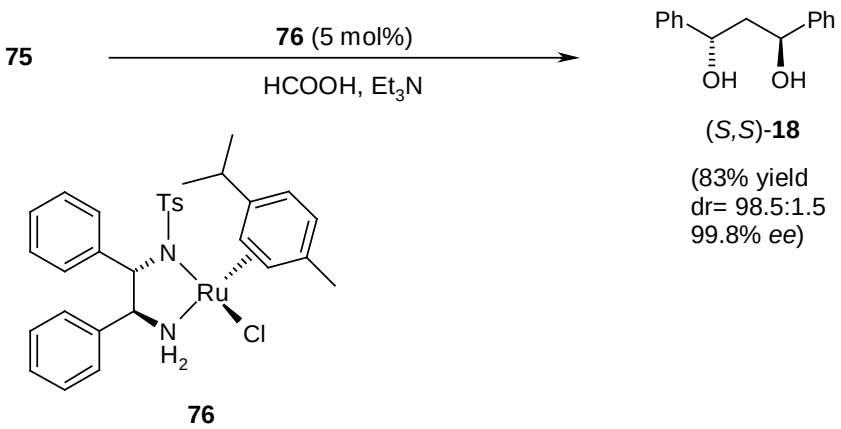
A highly stereoselective hydrogenation of **75** in the presence of [$RuCl_2$\{(R)-biphemp\}][biphemp= 2,2′-bis(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl] was reported by Salvadori et. al. (Scheme 26).[66]

Scheme 26



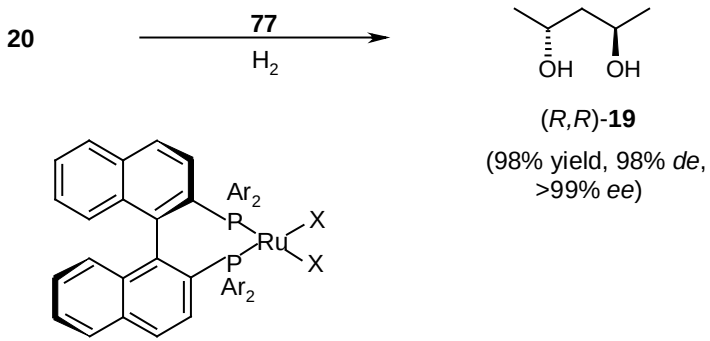
Recently Cossy et. al. reduced **75** using a chiral diamine-based Ru(II) catalyst **76** furnishing optically pure(*S*,*S*)-**18** (Scheme 27).[67] This is the best method reported so far for the synthesis of chiral diol **18**.

Scheme 27



A facile method for the preparation of optically pure (*R,R*)- and (*S,S*)-**19** was described by Ito et. al.[68] Their method involved asymmetric hydrogenation followed by recrystallization of the resulting product from ether. Ru(II)-BINAP **77** catalyzed stereoselective homogeneous hydrogenation of diketone **20** provided extremely high stereoselectivity (Scheme 28).

Scheme 28



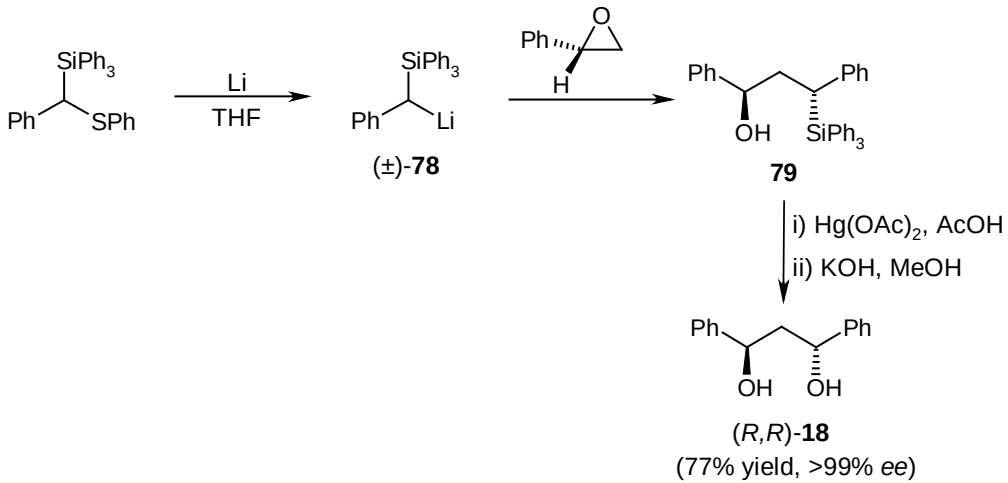
Following Kawano's communication, Noyori and co-workers revealed a similar Ru(II)-BINAP complex for the reduction of **20**. Absolute stereoselection was observed for the reduction process.[70] Mezzetti synthesized another Ru(II) complex which reduced **20** with >99% *ee*.[71]

Quallich's oxazaborolidine catalyst reduced the diketone **20** to produce (*S*,*S*)-**19** with high enantioselectivity (92%).[56]

1.2.2.2. Synthetic transformation

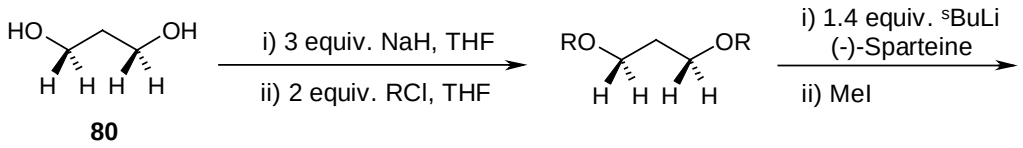
Corey et. al. have described a synthetic route to obtain (*R*,*R*)-**18**.[72] The racemic α-silyl-organolithium reagent **78** reacted with (*R*)-styrene oxide to produce the chiral γ-hydroxysilane **79** which gave (*R*,*R*)-**18** after mercuricacetate treatment (Scheme 29).

Scheme 29

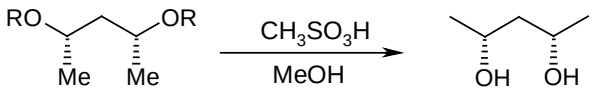


Stereoselective generation of 1,3-carbanions by sparteine-assisted deprotonation of 1,3-propane diol **80** is a novel method for the synthesis of (*S*,*S*)-**19** (Scheme 30).[73]

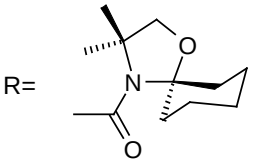
Scheme 30



80



(*S,S*)-**19**
(85% overall yield)

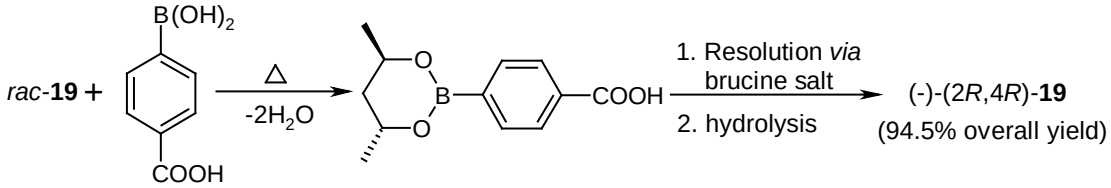


(Cbx)

1.2.2.3. Resolution

Fry et. al. had resolved the *rac*-**19** by repeated fractional crystallization of the diastereomeric salt prepared from the racemic boronic ester **81** and brucine (Scheme 31).[74]

Scheme 31

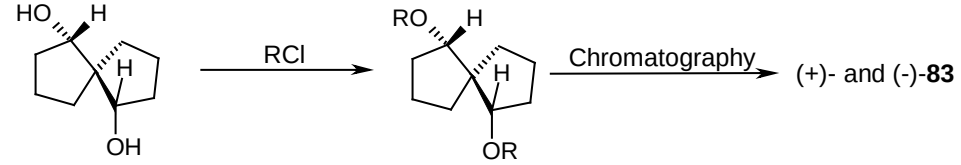


(±)-**81**

Two resolution procedures are available for the synthesis of optically pure spiro[4.4]nonane-1,6-diol (**82**), a conformationally rigid molecule.

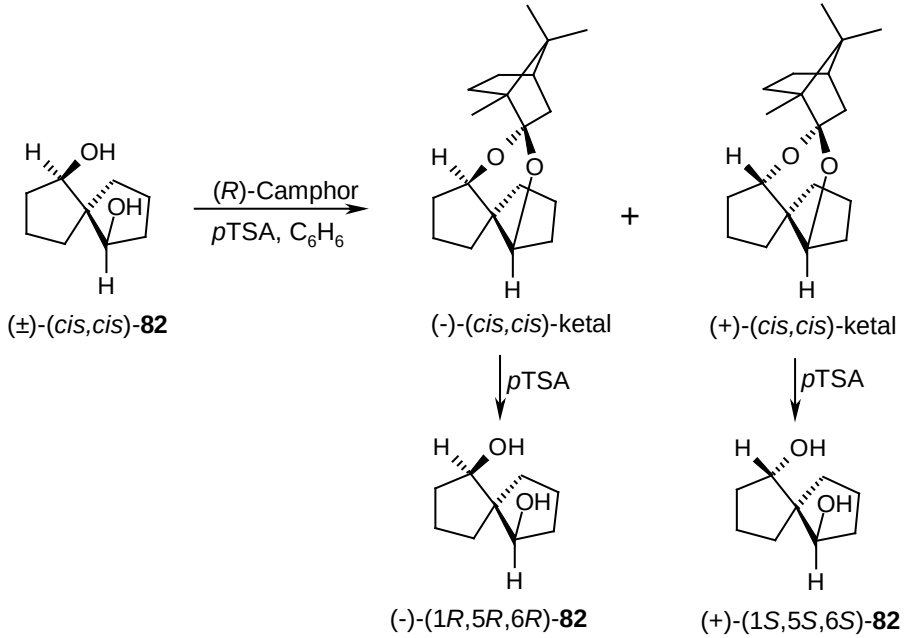
Gerlach resolved the (*trans,trans*)-**82** by preparing its diastereomeric esters **83** from (-)-camphanic acid followed by separation on a silica gel column (Scheme 32).[75] Subsequent saponification of the ester provided optically pure (*S,S*)- and (*R,R*)-**82**.

Scheme 32



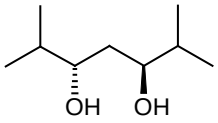
(±)-(*cis,cis*)-**82** Was resolved through diastereomeric ketals with (1*R*)-(+)-camphor (Scheme 33).[76]

Scheme 33

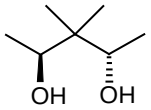


There are many other useful C_2-symmetric 1,3-diols known in the literature e.g. **84**[77,78,79b], **85**[59], **86**[79a], **87**[69] (Figure 11).

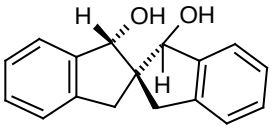
Figure 11.



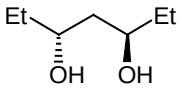
84



85



86



87

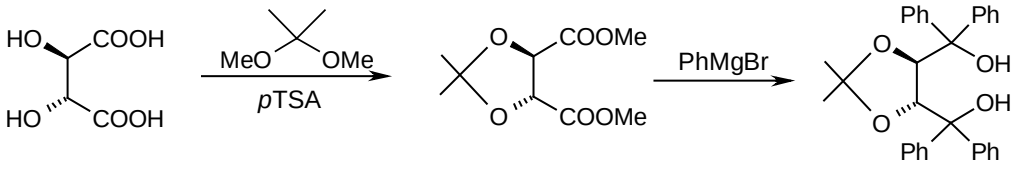
1.2.3. 1,4-Diols

There are not many C_2-symmetric 1,4-diols which have been used as chiral auxiliary/ligand in asymmetric synthesis. The most disadvantageous factor of this class of compounds to use as 'chiral inducer' is the rotational flexibility of the molecule. Seebach for the first time could solve this problem and prepared an useful C_2-symmetric 1,4-diol *viz.* TADDOL (**88**).

1.2.3.1. α,α,α′,α′-Tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol (TADDOL):

TADDOL (**88**) is a C_2-symmetric chiral 1,4-diol. It is a sterically hindered, conformationally rigid, and extraordinarily versatile chiral auxiliary/ligand. It has been prepared from tartaric acid using simple sequence of reactions as shown in Scheme 34.[80-82]

Scheme 34



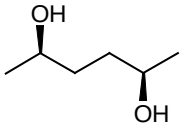
(+)-Tartaric acid

88

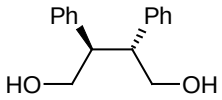
1.2.3.2. Other 1,4-diols

Chiral 2,5-hexanediol (**89**) is another useful C_2-symmetric diol which was obtained by several methods.[24,73,83] Diols **90**[84], **91**[56,83d,84d] were also synthesized by different groups (Figure 12).

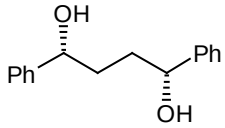
Figure 12.



89



90

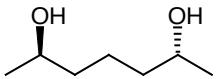


91

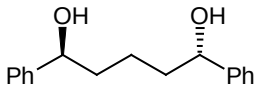
1.2.4. Other diols

Few C_2-symmetric long chain chiral diols are known in the literature. These include **92**[83g], **93**[56,85,86], and **94**[84,86] (Figure 13).

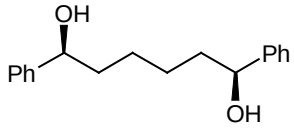
Figure 13.



92



93



94

2. Applications of C_2-symmetric chiral diols

Optically pure C_2-symmetric chiral 1,2-, 1,3-, 1,4- and some long chain diols have found a variety of uses in asymmetric synthesis as chiral ligand, as chiral auxiliaries and as chiral building blocks. Presence of C_2 symmetry and appropriate steric and tunable electronic properties have widened their application. Easy availability of these chiral diols according to the methods discussed earlier is another advantageous crieteria. Herein the applications of various C_2-symmetric chiral diols have been discussed with special emphasis on **1** (a 1,2-diol), **19** (a 1,3-diol) and **88** (a 1,4-diol) in different asymmetric transformations. These include stereoselective addition to carbonyls or imines, protonation, Michael addition reaction, nucleophilic substitution, Diels-Alder reaction etc.

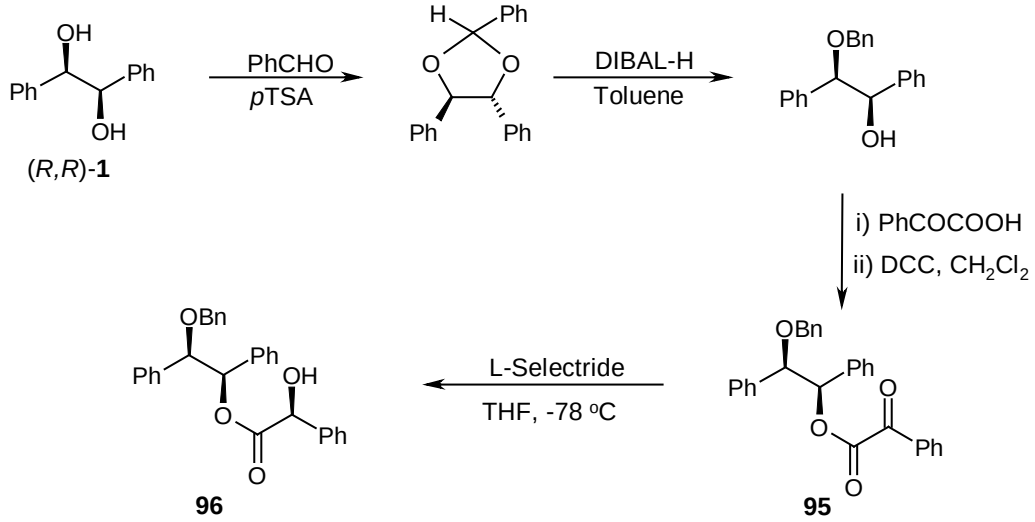
2.1. As chiral auxiliary

Much attention has been paid on different types of diastereo-differentiating reactions of prochiral substrates carrying C_2-symmetric chiral diols as an auxiliary.[87a]

2.1.1. Stereoselective addition to C=O or C=N

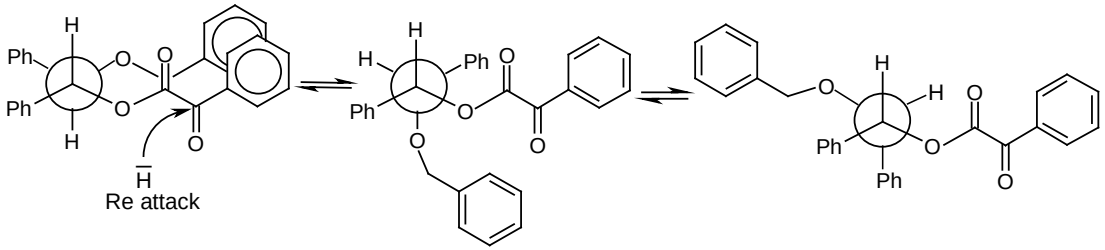
The α-ketoester **95** prepared in 3 steps from (*R*,*R*)-**1** was reduced with L-selectride providing the corresponding *α*-hydroxyester **96** with diastereoselectivities upto 56% (Scheme 35).[88]

Scheme 35



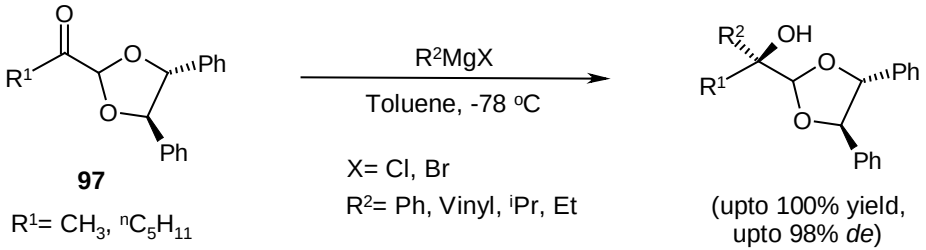
This selectivity has been interpretated as due to carbonyl face-shielding by the stacked –O-CH_2-Ph moiety of **95** (Figure 14).

Figure 14.



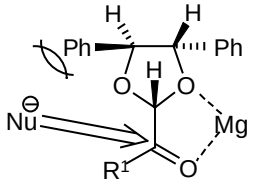
The use of chiral **1** for the preparation of chiral acetals has been investigated in several laboratories.[89] Myler's group described a highly diastereoselective addition reaction to chiral α-ketoacetals **97** (Scheme 36).[90]

Scheme 36

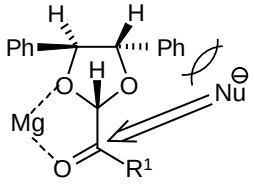


An explanation for the asymmetric induction was also given by the same group (Figure 15).

Figure 15.



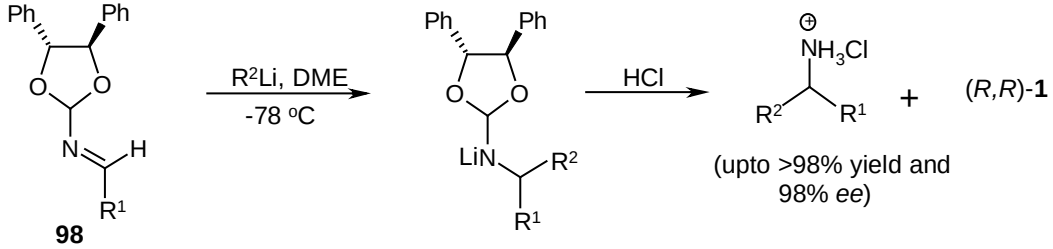
endo trajectory hindered by H
exo trajectory hindered by Ph
Result: Lower selectivity



endo trajectory hindered by Ph
exo trajectory hindered by H
Result: Higher selectivity

Very recently, Boezio et. al. studied a novel class of chiral auxiliaries **97** derived from (*R*,*R*)-**1** for the nucleophilic addition to imines.[91] The main advantage of their method was the ease of recovery of the chiral auxiliary after the addition and mild cleavage condition (Scheme 37).

Scheme 37



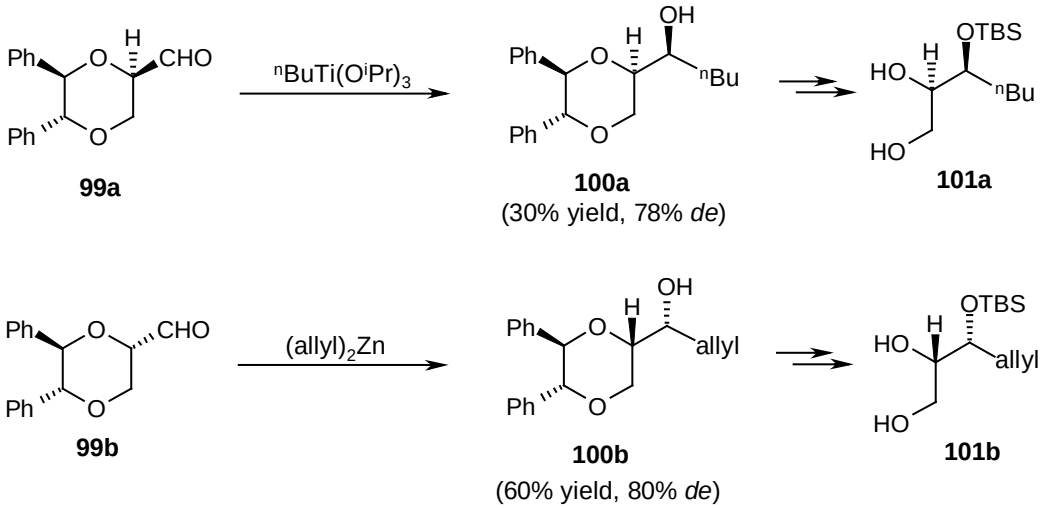
98

R^1= Ph, ^{t}Bu, Furan

R^2= Me, Ph, ^{n}Bu

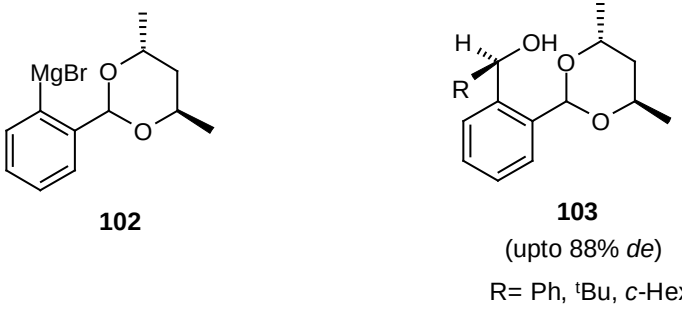
Aube et. al. prepared (2*R*,3*R*,5*S*)- and (2*R*,3*R*,5*R*)-5-carboxaldehyde-2,3-diphenyl-1,4-dioxane (**99**) from (*R*,*R*)-**1** as surrogates for optically 2,3-O-isopropylidine glyceraldehydes in asymmetric synthesis.[92] Several organometallic reagents were added to **99** and the resulting adducts **100** treated with TBSOTf followed by hydrogenolysis to give diastereo- and enantiomerically enriched 1,2,3-triol **101** (Scheme 38).

Scheme 38



Chiral aryl Grignard reagents **102** derived from (*R*,*R*)-**19** was added to aldehydes to provide product **103** with high diastereoselectivity (Figure 16).[93]

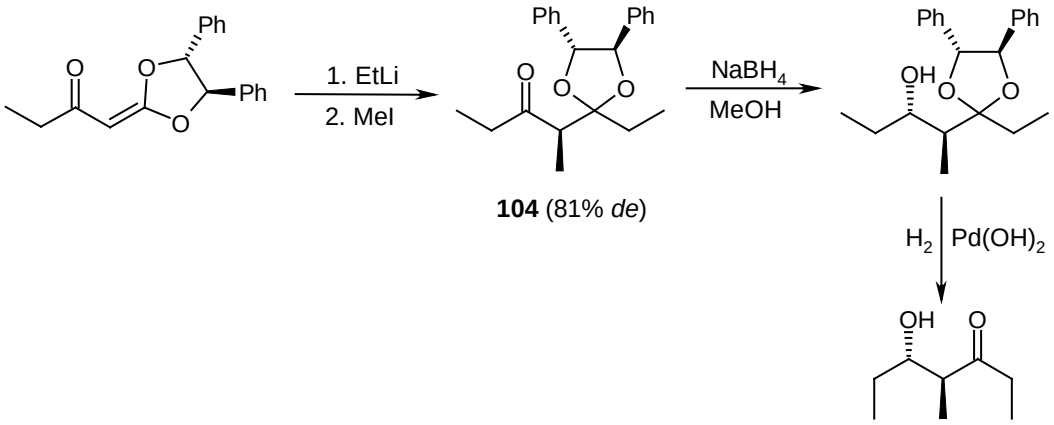
Figure 16.



2.1.2. Acyl ketene acetal

Enantiomerically pure acylketene acetals derived from (*R*,*R*)-**1** were employed to generate a homochiral *β*-ketoketal **104** through a highly diastereoselctive lithium enolate quench. The *β*-ketoketal **104** which was also prepared through desymmetrization ketalization reaction on a *meso*-dione, was employed in the synthesis of the insect pheromone Sitophilure **105** (Scheme 39).[94,95]

Scheme 39

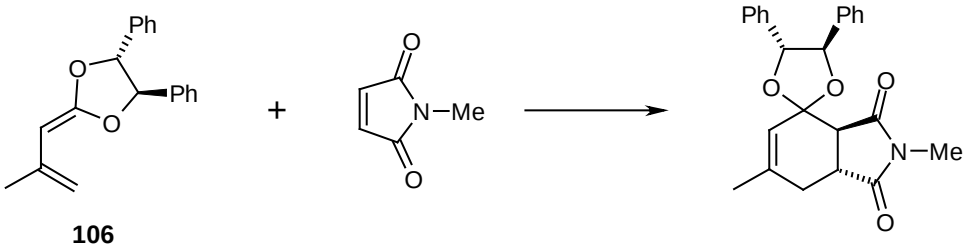


104 (81% *de*)

105

Enantiomerically pure vinylketene acetals **106** derived from optically pure (*R*,*R*)-**1** was employed in asymmetric Diels-Alder reaction (Scheme 40).[96]

Scheme 40

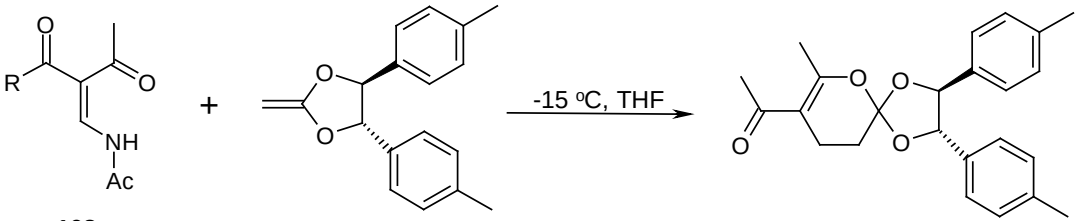


106

(95% yield, 96% *de*)

Heterodiene cycloaddition of (*S*,*S*)-4,5-bis(o-tolyl)-2-methylene-1,3-dioxolane **107** with a series of substituted *β*-amido-α,*β*-unsaturated carbonyl compounds **108** has been found to be diastereoselective (Scheme 41).[97]

Scheme 41



108
R= Me, OMe, OBn

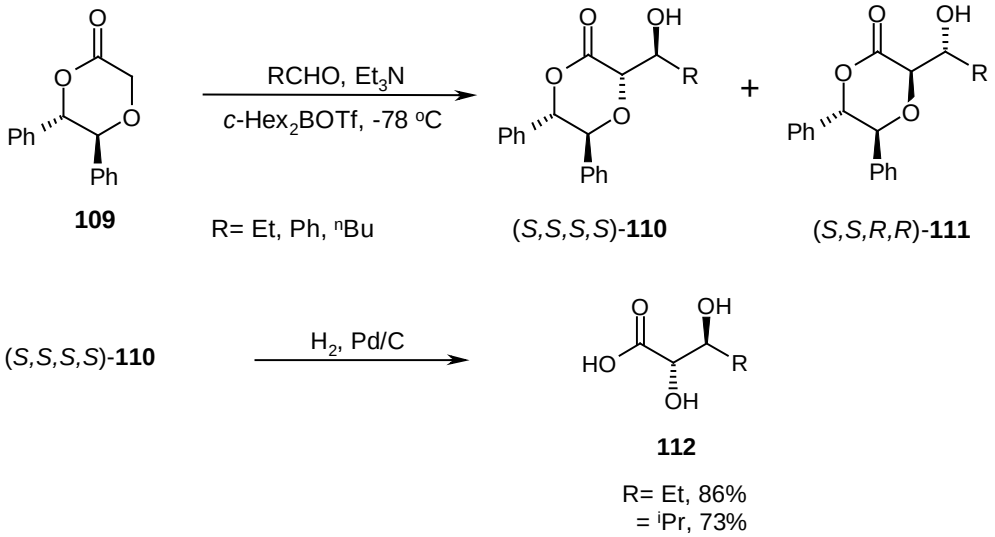
107
(1 equiv.)

(upto 90% *de* and 67% yield)

2.1.3. Aldol reaction

The boron enolate of pyrone **109** undergoes asymmetric aldol reactions with aldehydes to give protected *anti*-1,2-diols **110** and **111**. The pyrone **109** was readily obtained from *trans*-stilbene in two steps. Yields for the aldol reaction ranged 62-92% and the stereoselectivities 70-90% for the *anti*-isomers.[98] Product **110** was subjected to hydrogenolysis to give enantiomerically enriched α,*β*-dihydroxy acids **112** (Scheme 42).

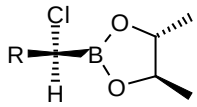
Scheme 42



2.1.4. α-*Chloro boronic ester*

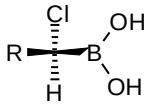
(*R*,*R*)-2,3-Butane diol **2** was used as chiral directing group in the synthesis of (*αS*)-*α*-chloroboronic esters **113** providing 91-96% *de*.[99a] The esters **113** were easily hydrolyzed to crystalline boronic acids **114** (Figure 17).

Figure 17.

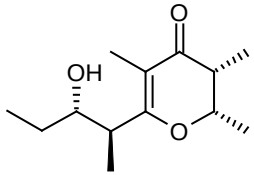


113

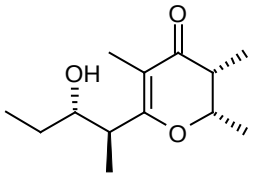
R= Me, ^{i}Pr, ^{n}Bu, Ph



114



115

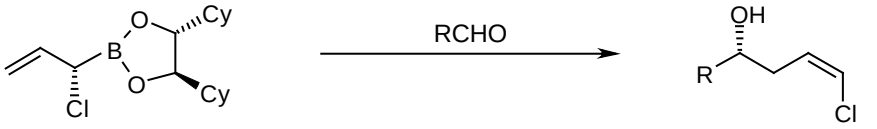


116

Highly stereoselective boronic ester chemistry has been used to synthesize the drugstore beetle pheromone Stegobiol **115** and Stegobinone **116** (Figure 17).[99b] Hoffman and co-workers synthesized Denticulatins A and B[99c] and Mycinolide V[99d] using same boronic ester chemistry.

The generation of enantiomerically pure homoallyl alcohols by allylmetallation of aldehydes using chiral reagents has been in constant development over last two decades. In continuation of the effort, a highly enantioselective allylboration of aldehydes was accomplished by Hoffman's group (Scheme 43).[99e]

Scheme 43



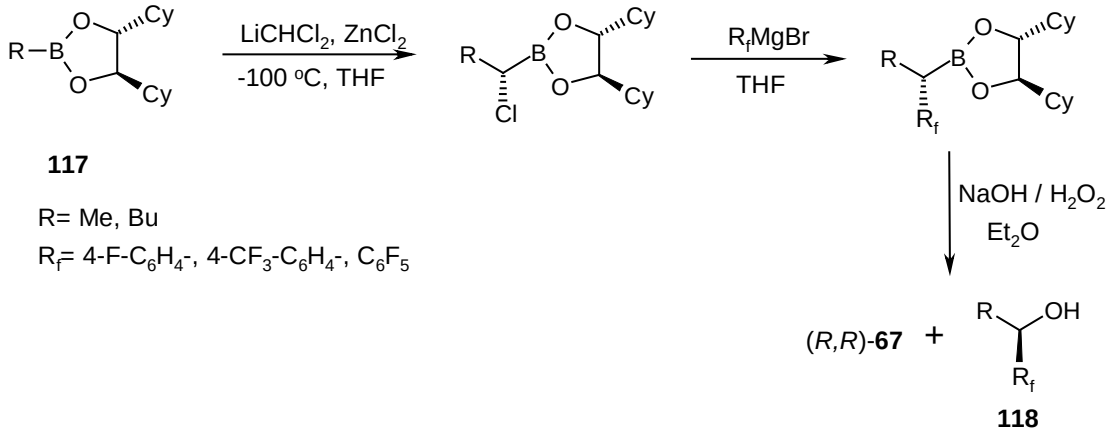
117

R= Me, Et, Ph, ^{i}Pr, isobutyrophenone

(76-89% yield, upto >99% *ee*)

Recently Shreeve et. al. reported a highly stereocontrolled boronic ester chemistry to prepare several fluorinated aryl alcohols **118** (Scheme 44).[99f]

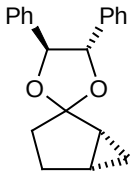
Scheme 44



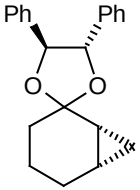
2.1.5. Cyclopropanation

Application of asymmetric Simmons-Smith cyclopropanation reaction is an attractive procedure to prepare optically active cyclopropane derivatives from prochiral alkenes. Highly diastereoselective cyclopropanation of α,β-unsaturated homochiral ketals derived from (*S,S*)-**1** was reported by Mash et. al. (Figure 18).[100]

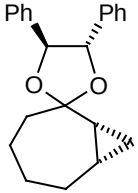
Figure 18.



(86% *de*)



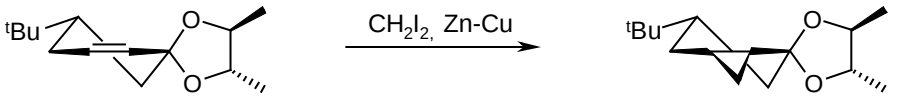
(90% *de*)



(88% *de*)

Since hydrobenzoin is available in both enantiomeric forms, either enantiomer of a particular cyclopropyl ketone can be prepared *via* this methodology. Mash et. al. again reported the effect of cyclohexane ring conformation on the diastereoselctivity observed for Simmons-Smith cyclopropanation of 2-cyclohexene-1-ethylene ketals using (*R*,*R*)-**2** as chiral auxiliary (Scheme 45).[87b]

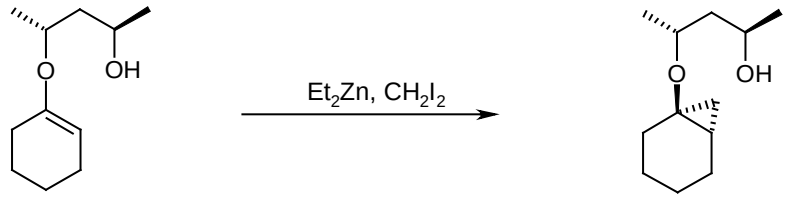
Scheme 45



119 **120** (80% *de*)

Sugimura et. al. reported a highly effective diastereo-differentiating Simmons-Smith reaction employing (*R*,*R*)-**19** as auxiliary (Scheme 46).[101]

Scheme 46



(*R,R*)-**121**

122

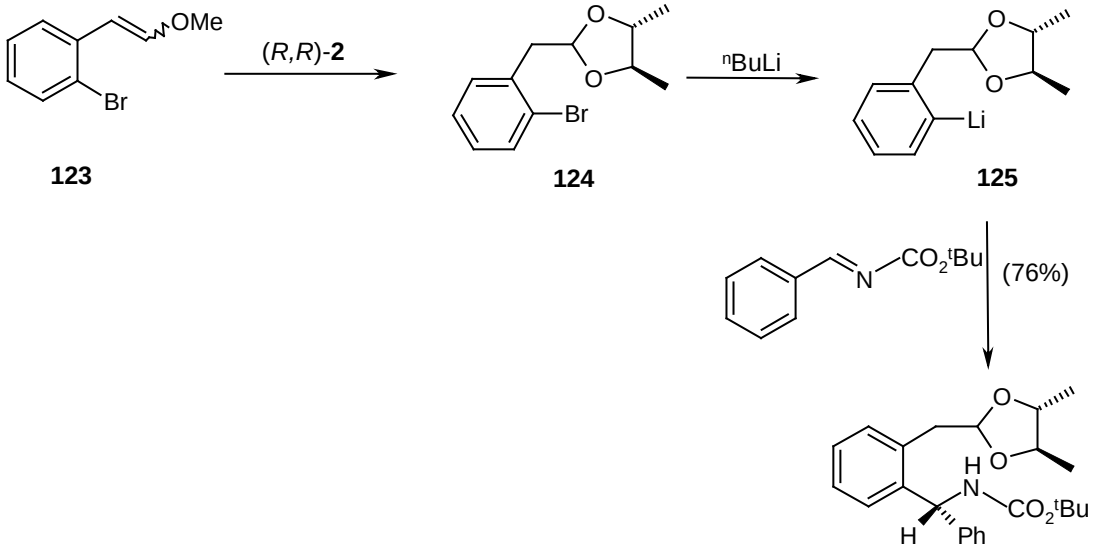
(77% yield, 95.2% *de*)

Enol ether carrying (*R,R*)-**19** as the chiral auxiliary were subjected to cyclopropanation with methyl carbenoid too.[102]

2.1.6. Michael addition reaction

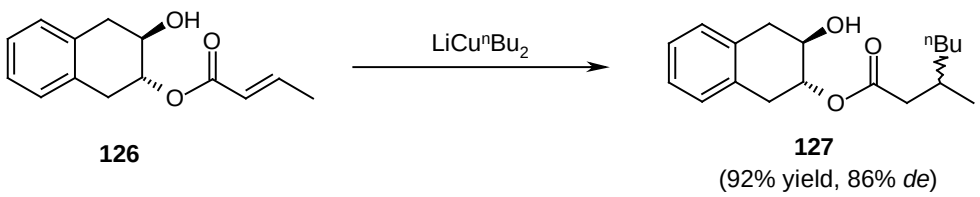
A series of enantiomerically pure 2-(2-bromobenzyl)-1,3-dioxolane **124** has been prepared by transacetalization of the enol ether **123** with enantiomerically pure (*R,R*)-**2** and then the ability of the chiral 1,3-dioxolane moiety to control the diastereoselectivity during the 1,4-addition of aryllithium intermediate **125** to the acylimines were investigated (Scheme 47).[87c]

Scheme 47



The chiral diol **72** was examined in a conjugate addition of lithium dibutylcuprate to the monocrotonate **126** to give the product **127** with 86% *de* (Scheme 48).[64]

Scheme 48



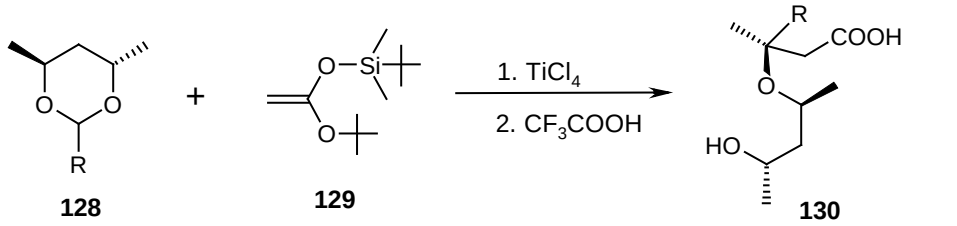
126

127
(92% yield, 86% *de*)

2.1.7. Miscellaneous reactions

$TiCl_4$ catalyzed the coupling of chiral acetals **128** with the silyl enol ether **129** providing excellent diastereoselection for the product **130** (Scheme 49).[103] This procedure was followed towards the synthesis of (*R*)-(+)-α-Lipoic acid **131** (Figure 19).

Scheme 49



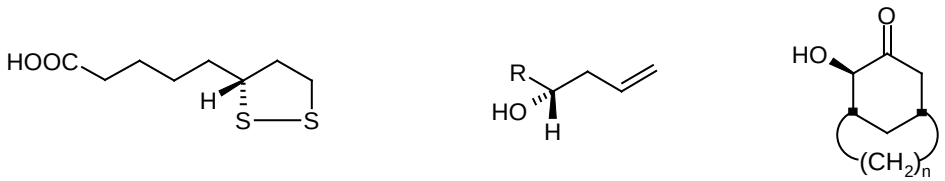
128 **129** **130**

R= *c*-C_6H_{11}, *n*-Octyl, $(CH_2)_4CO_2{}^iPr$

(upto 98% yield and 96% *de*)

Homoallylic alcohols **132** were also synthesized from chiral acetal templates derived from (*R,R*)-**19** (Figure 19).[104] A tandem acetal cleavage-epoxidation reaction providing **133** with 100% diastereoselectivity using (*R,R*)-**19** as auxiliary was reported by Paquette et. al. (Figure 19).[105]

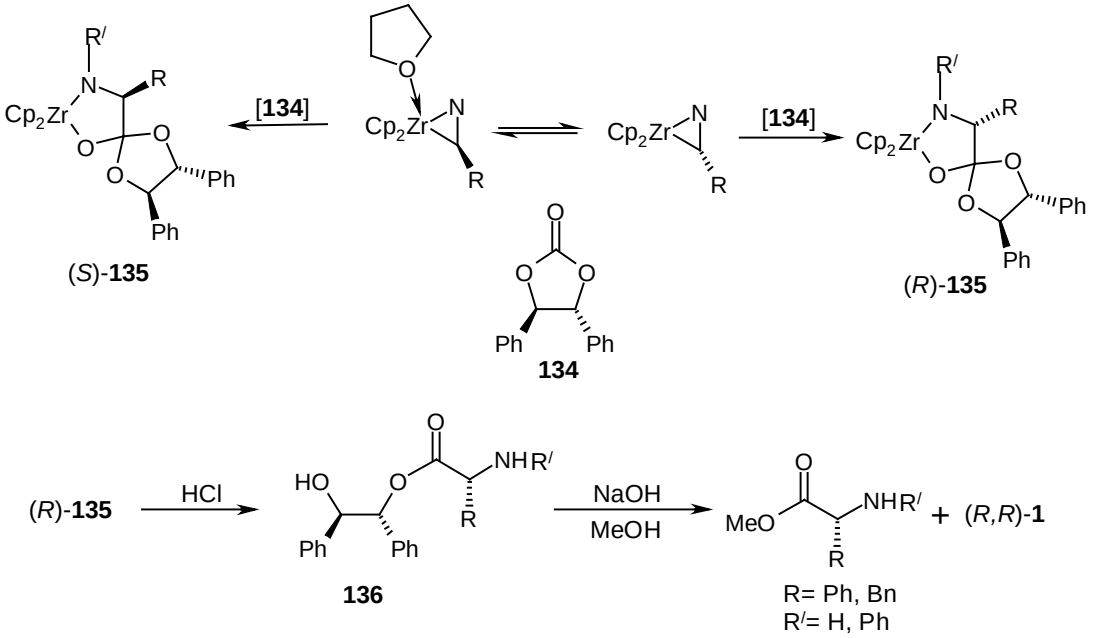
Figure 19.



131 **132** **133**

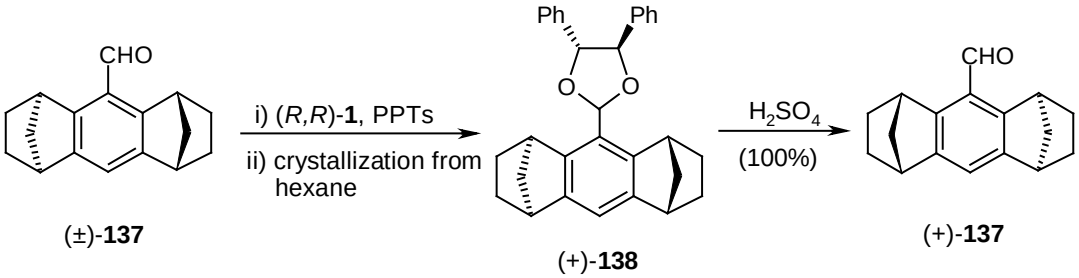
Direct asymmetric carboxylation of the α-position of an amine with an optically active CO_2 equivalent **134** derived from (*R,R*)-**1** was demonstrated by Tunge et. al.[106] The α-amine esters **136** (upto 99.1%) were obtained through a dynamic kinetic resolution of **135** (Scheme 50).

Scheme 50



Halterman used (*R,R*)-**1** as resolving reagent for separation of a racemic aromatic aldehyde **137** *via* the formation of the acetal **138** (Scheme 51).[107]

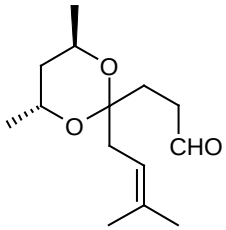
Scheme 51



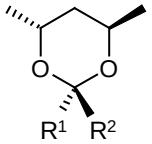
(±)-**137** (+)-**138** (+)-**137**

Epoxidation on **121**[108], ene reaction on **139**[109], stereoselective cleavage of acetal **140**[110] provided the corresponding products **141**, **142** and **143** respectively with very high selectivity (Figure 20).

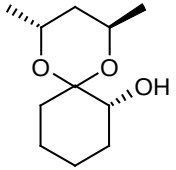
Figure 20.



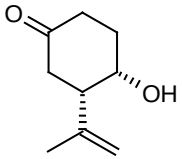
139



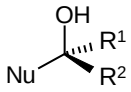
140
R^1= H
R^2= Pr, Ph, *n*-C_6H_{13},
c-C_6H_{11}, Bu-C≡C-



141 (100% *de*)



142 (80% *ee*)



143 (upto 98% *ee*)

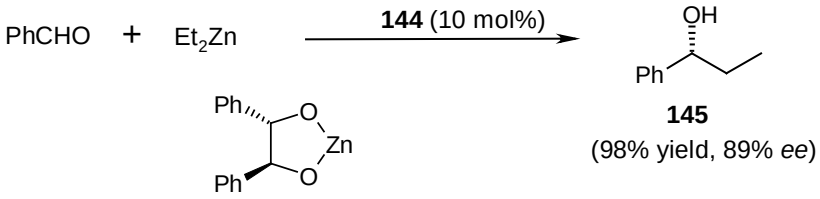
2.2. As chiral ligand

Number of excellent results were demonstrated by several groups applying optically pure C_2-symmetric diol as ligand in various asymmetric transformations.

2.2.1. Nucleophilic addition

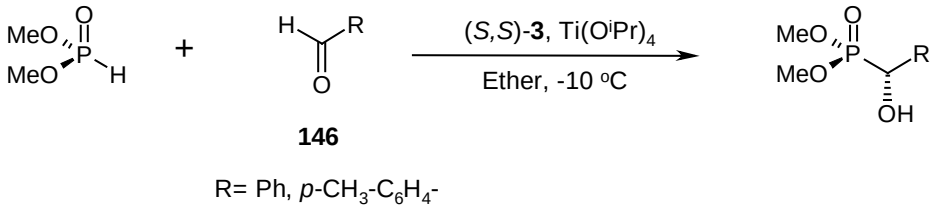
Enantioselective addition of diethylzinc to aldehydes has emerged as a prominent reaction in recent times.[111] The majority of the catalysts employed for this reaction were based on amino alcohols. Rosini et. al. for the first time used a C_2-symmetric diol ligand (*S*,*S*)-**1** for this reaction, though their procedure involved long reaction time and large excess of diethylzinc.[112] Our group examined various dialkoxides derived from Zn/Mg/B and (*S*,*S*)-**1**. It was found that the chiral zinc-dialkoxide **144** proved to be the best catalyst providing 89% *ee* of the product **145** (Scheme 52).[113]

Scheme 52



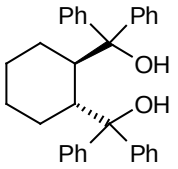
The diol (*S*,*S*)-**3** was identified as effective ligand for titaniumalkoxide catalyzed asymmetric phosphonylation of aldehydes **146** (Scheme 53).[114]

Scheme 53



1,4-diol **147**, a structural analogue of TADDOL, also has been used as a ligand for the addition of Me_3Al to aldehydes (Figure 21).[115]

Figure 21.

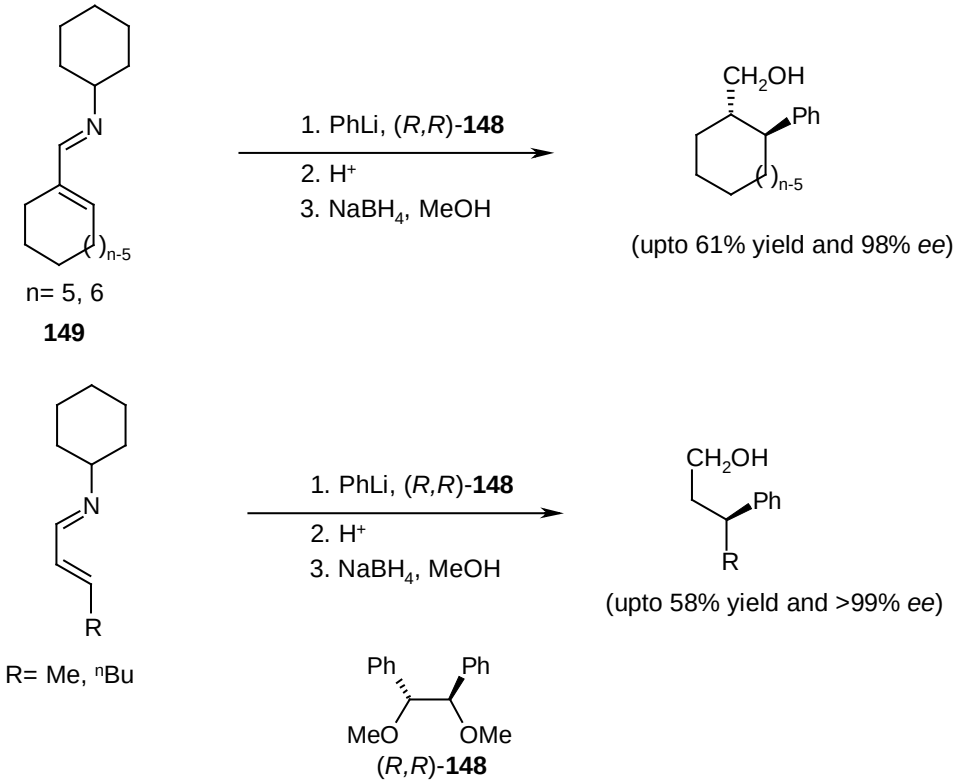


147

2.2.2. 1,4-Conjugate addition reaction

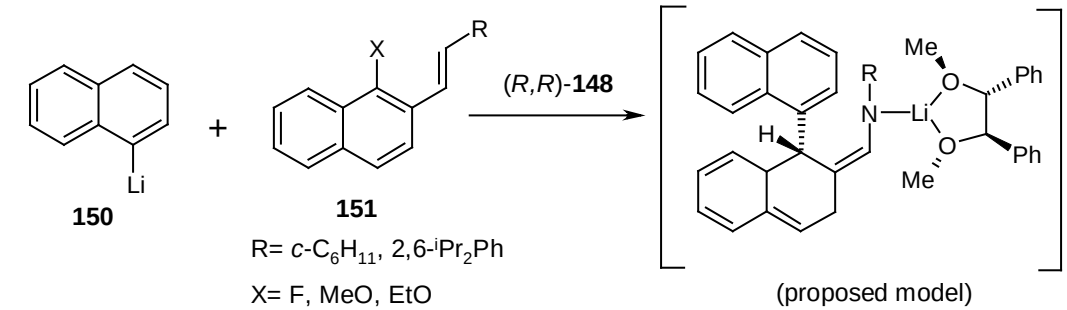
The addition of organometallics to the C-C double bond of α,*β*-unsaturated carbonyl or aldimine compounds, a process known as 1,4-conjugate addition or Michael addition reaction, is a versatile method. Application of this process to asymmetric synthesis is a focused and exciting area of current investigations.[116] Variety of chiral ligand showed their extraordinary contributions to generate chiral adducts with moderate to very high asymmetric induction.[116] Tomioka and co-workers extensively explored a chiral diether ligand **148** derived from (*R*,*R*)-**1** for Michael reaction.[117] The group reported a prototype of enantioselective conjugate addition of an organolithium to an achiral α,*β*-unsaturated aldimine **149** using C_2-symmetric (*R*,*R*)-**148** as a stereocontrol catalyst (Scheme 54).[117a]

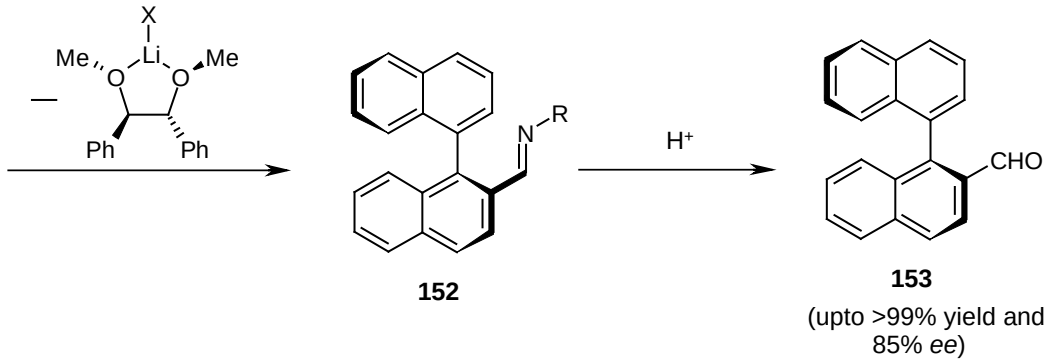
Scheme 54



Soon after the earlier report[117a], the same authors described a process wherein the reaction of napthyllithium **150** with naphthylamine **151** containing a leaving group at C-1, was catalyzed by (*R*,*R*)-**148** leading to the corresponding chiral binaphthyl imine **152** which upon acid treatment provided the binaphthaldehyde **153** in high enantiomeric excess (Scheme 55).[117b]

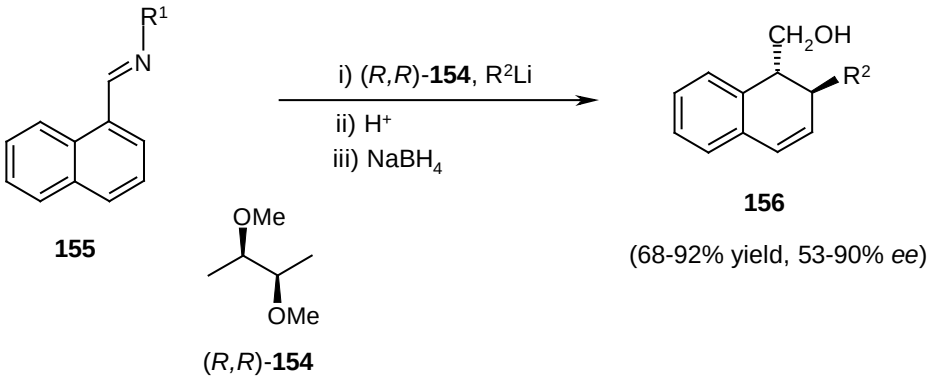
Scheme 55





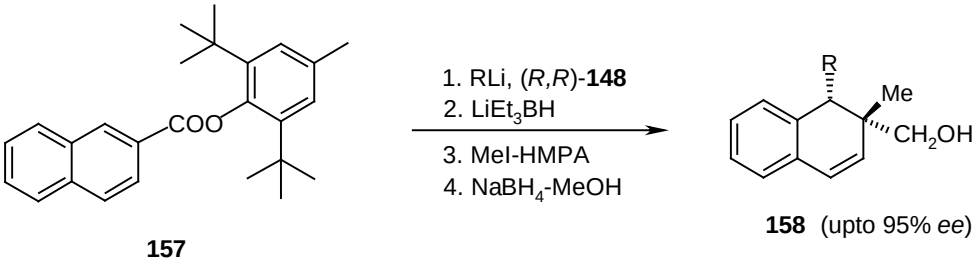
A C_2-symmetric chiral diether ligand **154** was designed and synthesized on the basis of the concept of an asymmetric oxygen atom. Mediated by the chiral diether **154**, high enantioselectivities for the products **156** were achieved in conjugate addition of organolithiums to naphthaldehyde imine **155** (Scheme 56).[118]

Scheme 56



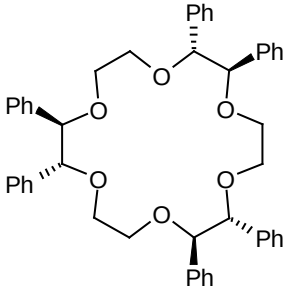
A catalytic asymmetric addition of aryllithiums to naphthalene 2,6-di-tert-butyl-4-methoxyphenyl (BHA)-esters **157** using the chiral mediator (*R,R*)-**148** was also demonstrated.[117c] The product **158** was obtained with 95% *ee* (Scheme 57).

Scheme 57

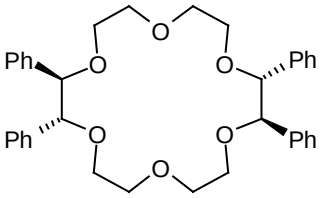


Crosby et. al. synthesized various chiral crown ether (CCE) e.g. **159**, **160** and **161** (Figure 22) from (*R,R*)-**1**.

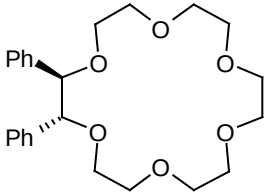
Figure 22.



159



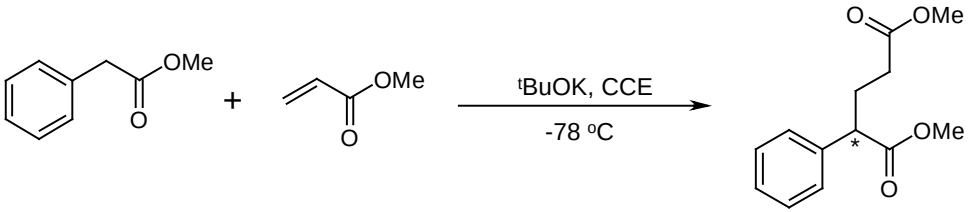
160



161

They used those as a chiral solid-liquid phase transfer catalyst for asymmetric Michael addition reaction (Scheme 58).[119]

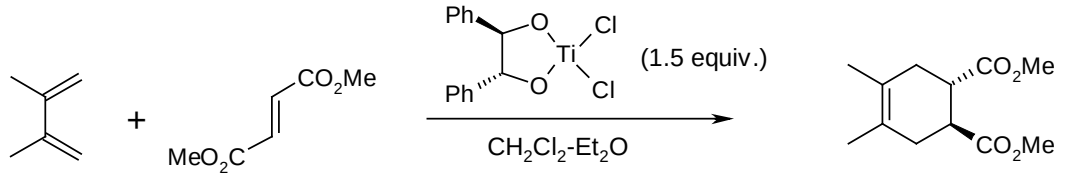
Scheme 58



2.2.3. Diels-Alder reaction

Chiral Lewis acids are excellent catalyst for asymmetric Diels-Alder reaction. Variety of chiral ligands are known to induce absolute stereoselectivity in this concerted six-membered ring forming reaction. Optically pure diol **1** also has been used as a chiral inducer in this reaction with particular success. Devine et. al. showed that the chiral titanium Lewis acid derived from (*R,R*)-**1** and $TiCl_4$ effectively promotes the Diels-Alder reaction of less reactive carboxylic ester dienophiles (Scheme 59).[120]

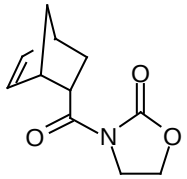
Scheme 59



(79% yield, 92% *ee*)

The diol **19** has not been used much as chiral ligand. An asymmetric Diels-Alder reaction was perfomed to furnish the product **162** using (*R*,*R*)-**19** as chiral ligand (Figure 23).[121]

Figure 23.

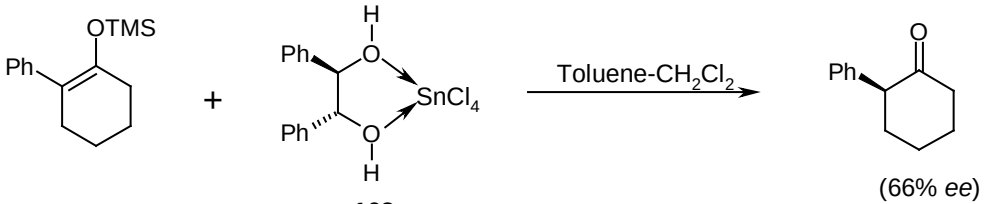


162 (*Exo*:*Endo*= 86:14, upto 83% *ee*)

2.2.4. Enantioselective protonation

The control of enantioselectivity in the protonation of silyl enol ethers with Bronsted acids is very much different, mainly due to bond flexibility between the proton and its chiral connection, the orientational flexibility of the proton, and the fact that the proton sources available are limited to acidic compounds such as carboxylic acids. Yamamoto et. al. developed a Lewis acid-assisted chiral Bronsted acid (LBA) system to overcome these difficulties.[122] Very recently the author described (*R*,*R*)-**1**.$SnCl_4$ complex **163** as a new type of LBA for the enantioselective protonation of silyl enol ethers (Scheme 60).[123] Few other derivatives of (*R*,*R*)-**1** provided the enantioselectivity upto 96% for the same reaction.

Scheme 60



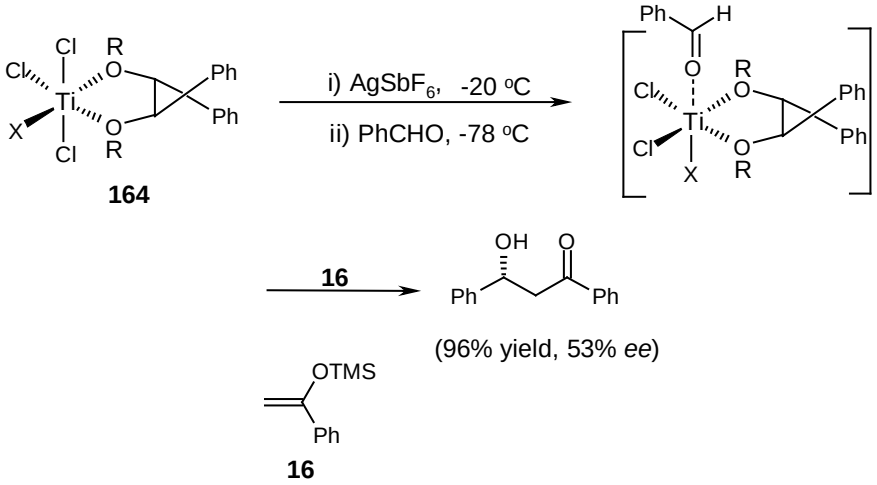
163

(66% *ee*)

2.2.5. Aldol reaction

Few novel cationic Lewis acid complexes were generated by the addition of silver hexafluoro antimonate to titanium complexes **164**. Asymmetric Mukaiyama aldol reaction of benzaldehyde with silyl enol ether **165** was conducted using the *in situ* generated Lewis acid complexes with moderate enantioselectivity (Scheme 61).[124]

Scheme 61



164

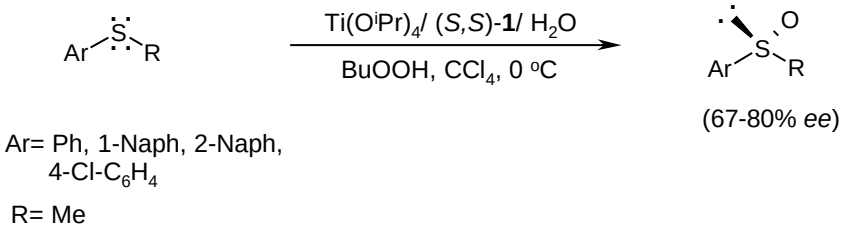
(96% yield, 53% *ee*)

16

2.2.6. Oxidation of sulfides

The asymmetric oxidation of aryl methyl sulfides with hydroperoxides has been achieved using catalytic amounts of $Ti(O^iPr)_4$, (*S,S*)-**1** complex and water. The sulfoxides were thus obtained in 67-80% *ee* by Superchi et. al. (Scheme 62).[125a]

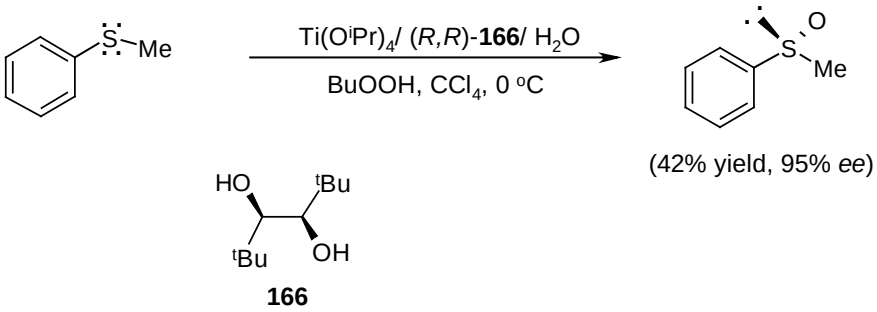
Scheme 62



The same group also optimized the reaction conditions in order to reach the higher enantioselectivity and avoid the intervention of a kinetic resolution process.[125b] The oxidation protocol described was quite versatile and also the values of chemical yields (60-73%) and of enantioselectivity (70-80%) achieved for aryl alkyl sulfides were almost independent of the nature of the aryl substituent and of the size of alkyl group. Notably aryl benzyl sulfides which were poor substrates for the titanium/diethyltartarate catalyzed oxidation[126], afforded very high *ee*'s (92-99%) with this oxidizing system.

Inamoto et. al. reported a new preparation of enantiopure diol **166** and its application as a chiral ligand in Ti(IV)-catalyzed enantioselective oxidation of sulfides (Scheme 63).[127]

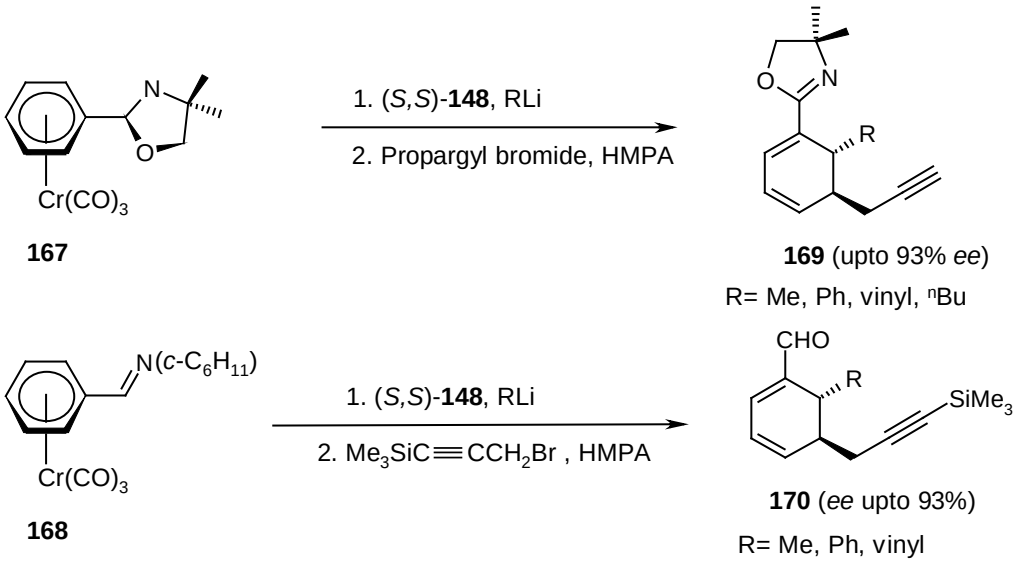
Scheme 63



2.2.7. Addition to aromatic double bond

Methods of asymmetric C-C bond formation in the transformation of benzene and substituted benzenes remained scarce[128] despite of the obvious synthetic potential of the transformation of an arena into a chiral non racemic alicyclic compounds. Kundig et. al. studied this methodology with a greater deal, and put effort to understand both regio- and enantioselective outcome of this reaction. They reported the addition of various nucleophiles e.g. alkyl-, vinyl- and aryllithiums to two different prochiral arene-$Cr(CO)_3$ complexes **167** and **168** in presence of an external chiral ligand (*S*,*S*)-**148** to provide **169** and **170** respectively with very high *ee* (Scheme 64).[129]

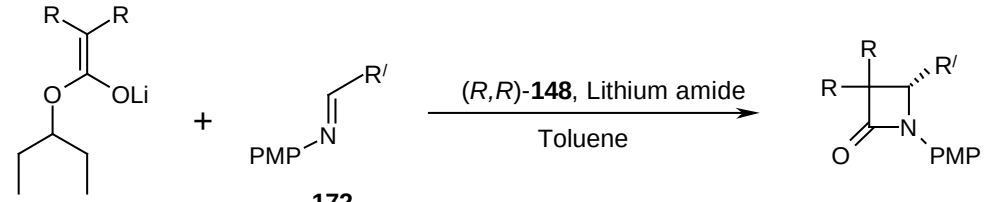
Scheme 64



2.2.8. Miscellaneous reactions

The chiral ligand **148** found its application as external ligand in several asymmetric transformations.[117] The asymmetric addition of the lithium ester enolate to the azomethine group in the presence of an external chiral ligand has not been much studied. Tomioka et. al. described the stoichiometric and catalytic asymmetric reactions of lithium ester enolates **171** with imines **172** based on a ternary complex reagent which comprises three compounds: a chiral ether ligand (*R*,*R*)-**148**, an achiral lithium amide, and **171** giving the corresponding lactams **173** in high *ee* (Scheme 65).[130]

Scheme 65



171

R= Me, -$(CH_2)_5$-

172

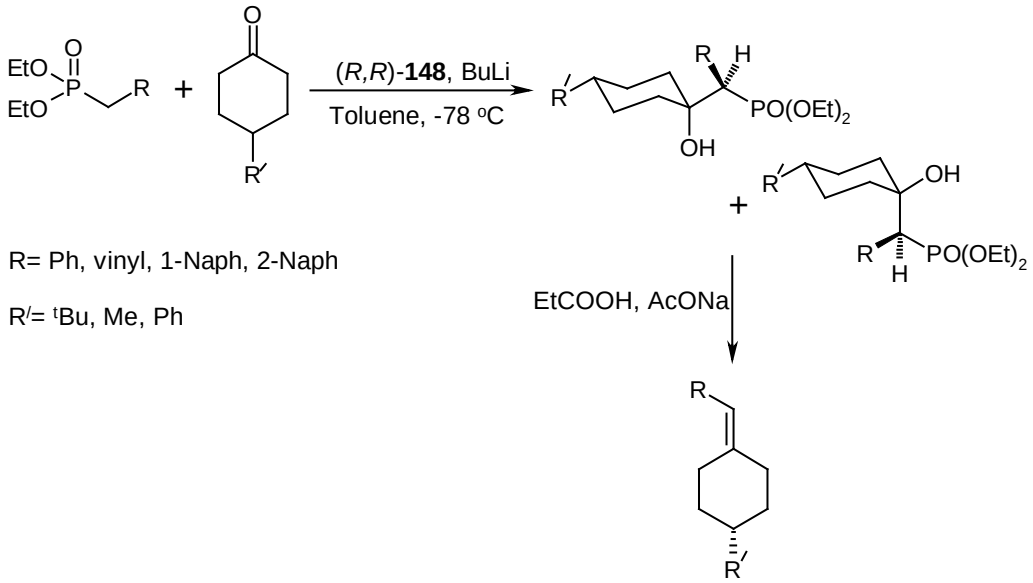
R/= Ph, PMP, 1-Naph

173

(12-99% yield, 26-90% *ee*)

Tomioka et. al. also presented an asymmetric Horner-Wadsworth-Emmons reaction mediated by (*R*,*R*)-**148** (Scheme 66).[131]

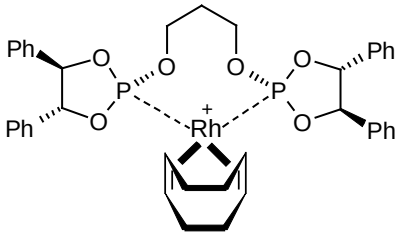
Scheme 66.



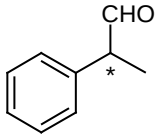
(71-99% yield, 54-90% *ee*)

A chiral Rh-complex **175** was synthesized from (*R*,*R*)-**1** for asymmetric hydrogenation and hydroformylation reaction (Figure 24).[132] The hydroformylated product **176** was obtained with very high enantioselectivity using (*R*,*R*)-**19** as chiral ligand (Figure 24).[133]

Figure 24.



175

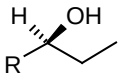


176 (upto 91% *ee*)

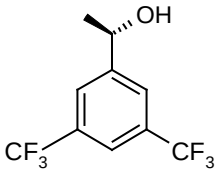
Several other 1,3-diols e.g. **18**[25,91], **82**[134], **84**[102a,135] also have been used as effective chiral ligand in variety of asymmetric reactions.

The application of TADDOL (**88**) as a chiral ligand in asymmetric synthesis is extraordinarily broad. A detailed review on the synthesis and applications of TADDOL and its structural analogues have been discussed recently by Seebach.[82] In the years following this review, TADDOL has been employed in enantioselective additions of $AlEt_3$ to aldehydes,[136] methylation to aldehydes,[137] cyclohexadienyl addition to aldehydes,[138] asymmetric fluorination reaction,[139] asymmetric phospha-analogous Michael addition reaction,[140] and asymmetric Heck reaction[141] to provide varieties of chiral products **177**, **178**, **179**, **180**, **181** and **182** respectively with very high asymmetric induction (Figure 25).

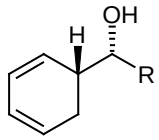
Figure 25.



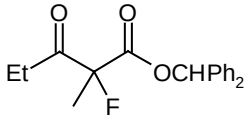
177
(upto 99% *ee*)
R= Ph, 1-Naph, 2-Naph



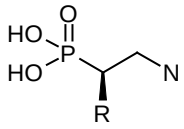
178
(upto 100% *ee*)



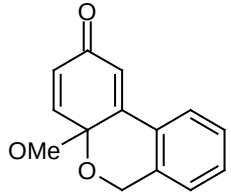
179
(upto 98% *ee*)
R= Ph, Et, *c*-C_5H_{11}



180 (81%*ee*)



181
(upto 95% *ee*)
R= Ph, Me



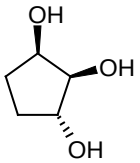
182
(upto 96% *ee*)

2.3. As chiral building blocks

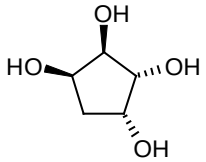
Use of optically pure C_2-symmetric chiral diols as chiral building blocks is not much explored, but opportunities exist since chiral diols are easily available by simple methods discussed in the first part.

Kim et. al. synthesized several enantiopure cyclopentitols **183**, **184**, **185** and amino cyclopentitol **186** employing oxyselemenylation of cyclopentene with (*R,R*)-**1** (Figure 26).[142]

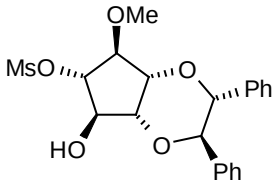
Figure 26.



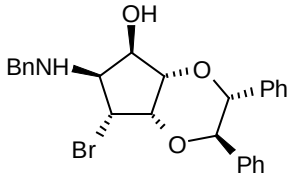
183



184



185



186

Conclusion

Considerable attention has been focused on the synthesis of a broad range of optically pure C_2-symmetric diols. The synthesis includes both enzymatic and chemical strategies. An ideal classical resolution is always desirable method since both the enantiomers would be available in multigram quantity. Other synthetic procedures e.g. synthetic transformations, enantioselective reduction, asymmetric epoxidation and dihydroxylation etc. are adopted considering the structure of the diol ligand to be prepared. The ligands having genetic structure to a naturally occurring and inexpensive chiral source are very much popular e.g. TADDOL which is synthesized by only two steps from (+)-Tartaric acid. 'Synthesis' and 'Application' of a ligand are symbiotically related terms. Simple and cost effective synthesis enhances the application opportunities of a chiral ligand in asymmetric synthesis. Chiral hydrobenzoin and chiral TADDOL are examples to be noted in this regard. This discussion enlightened the applications of chiral C_2-symmetric diols in various classical organic reactions e.g. Diels-Alder reaction, nucleophilic addition to carbonyls and imines, Michael addition reaction, aldol reaction etc. It is clear that a single chiral diol is unable to provide high asymmetric induction for different types of reactants. Better understanding in structure-reactivity-selectivity relationship of C_2-symmetric chiral diols could open up an opportunity for designing new efficient and versatile ligands.

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CHAPTER-2

Synthesis and Resolution of 2,2-Dimethyl-1,3-Diphenyl-1,3-Propanediol

Introduction

The symmetry axis is a line about which rotation through a given angle brings the structure into coincidence with itself. If the rotation operation is repeated several times, the structure must eventually be brought to a position which is identical with its original position, i.e. the structure will have gone full circle to its starting point. If the number of repeatitions is the integer *n*, then

$$n\theta = 2\pi$$

and $$n = 2\pi/\theta$$

The integer *n* is termed the order of the axis, and the axis is given the symbol C_n. In addition the values of θ are restricted to values given as 2π divided by an integer.

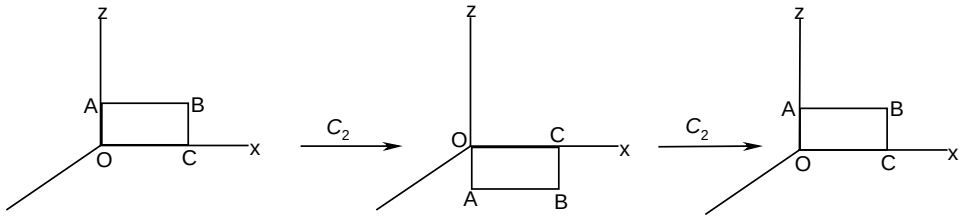
Depending upon the order of the axis, a symmetry may generate several operations. In the case of the two fold axis two operations are generated : (1) a rotation of $2\pi/2 = 180^o$ and (2) a rotation of 360^o. The symbol C_n^m is used for the operation of rotation in which the angle of rotation is given as *m* ($360^o/n$). Thus, the symbols for the two operations generated by a two fold axis are

$$C_2\{\ C_2^1$$
$$\{\ C_2^2$$

Since the C_2^2 operation (rotation through 360^o) produces the same effect as the identity operation (E), the C_2^2 operation is equivalent to the identity operation E, and we may write the two fold operations as

$$C_2\{\ C_2^1$$
$$\{\ C_2^2 = E$$

Figure 1. *Effect of C_2 on a rectangle (ABCO)*



This is the reason why presence of C_2 symmetry axis within the chiral auxiliary is advantageous serving the very important function of reducing the number of possible competing diastereomeric transition states to achieve high level of asymmetric induction. Consequently synthesis of C_2-symmetric chiral 1,2-; 1,3- and 1,4-diols has been of deep interest. Moreover, these diols have found broad applications as chiral auxiliaries or ligands in various asymmetric transformations.[1] Unlike 1,2- & 1,4-diols, number of successful C_2-symmetric chiral 1,3-diols are limited in literature, because most of them lack sufficient conformational rigidity. 1,3-Diphenylpropanediol is one representative example of

such diols. To address this point of concern, we decided to synthesize a conformationally restricted C_2-symmetric chiral 1,3-diol *viz.* (*R,R*)-/(*S,S*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol, a gem dimethylated derivative of 1,3-Diphenylpropanediol. According to Thorpe-Ingold theory, dialkylation at C-2 eventually removes the rotational flexibility from a 1,3-diol making it conformationally rigid molecule.[2]

This chapter deals with the diastereoselective synthesis and resolution of 2,2-dimethyl-1,3-diphenyl-1,3-propanediol. It has been divided into three sections.

a) **Section 2A** : Diastereoselective reduction.

b) **Section 2B** : Aldol-Tishchenko reaction.

c) **Section 2C** : Resolution of the diol.

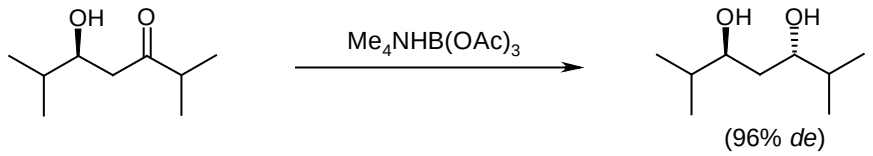
Section 2A

Diastereoselective reduction

Introduction

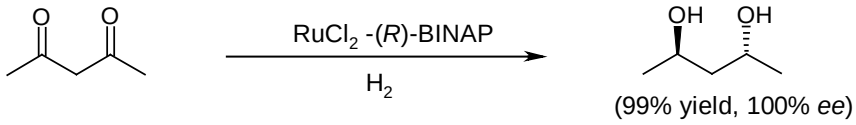
Chiral 1,3-diols can be obtained *via* the following three methods,

a) Diastereoselective reduction of chiral β-hydroxy ketones,[3] (eq 1)



(1)

b) Enantioselective reduction of β-diketones,[4] (eq 2)

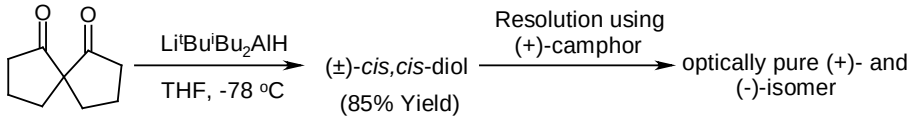


(2)

c) Diastereoselective reduction of *β*-diketones followed by resolution of the resulting diol,[5]

(Scheme 1)

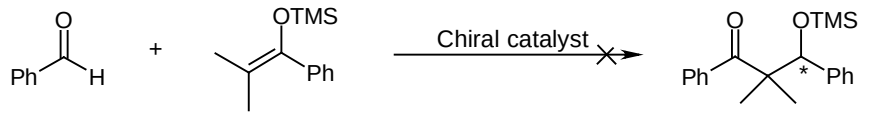
Scheme 1



This section deals with the synthesis of (*dl*)-**1** following the third methodology.

Results and discussion

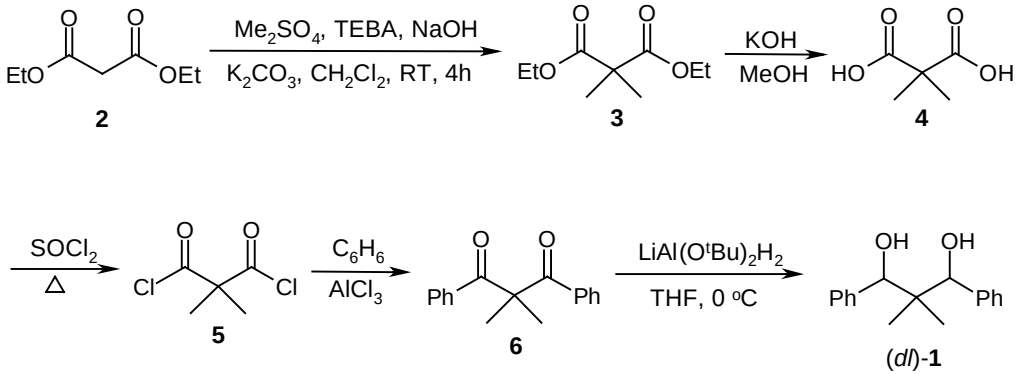
For synthesis of the title diol **1**, the first two methodologies failed. We were unable to bring about an enantioselective Mukaiyama aldol condensation between benzaldehyde and the silyl enol ether of isobutyrophenone (eq 3).[6]



(3)

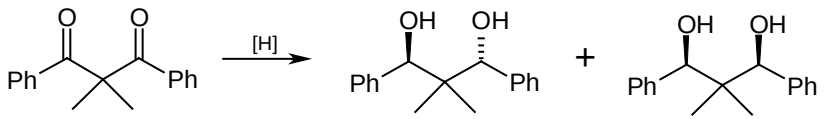
Also, attempts at enantioselective reduction using either BH_3 in the presence of a chiral oxazaborolidine catalyst[7] or Ipc_2BCl[8] failed to reduce the dione **6**. We therefore resorted to the third option, that is reduction followed by resolution. The synthesis of the required dione **6** was started from diethylmalonate (**2**), a cheap and commercially available compound. Four simple steps were employed to accomplish the synthesis of **6** (Scheme 2).[9,10] It was first dimethylated at C-2 position using dimethylsulfate under phase-transfer condition to provide 2,2-dimethyl diethylmalonate (**3**). Saponification followed by thionyl chloride treatment provided the corresponding acid chloride **5**. Friedel-Craft reaction between **5** and benzene produced the diketone **6**.

Scheme 2



Prior to our work, Mair et.al. had described the reduction of diketone **6** with LAH in moderate diastereoselectivity (76% *de*).[10a] In order to enhance the selectivity, we examined various reducing agents including $LiBH_4$, $Zn(BH_4)_2$ and a few modified reagents derived from LAH. We observed lithium tri-*tert*-butoxyaluminium hydride, $LiAl(O^tBu)_3H$ reduces the *β*-dione **6** with exclusive formation of (*dl*)-**1** in good yield (70%). However, the reaction rate was found to be sluggish since it took 15 h at room temperature . The reaction rate was improved significantly employing comparatively less hindered reagent lithium di-*tert*-butoxyaluminium hydride, $LiAl(O^tBu)_2H_2$. This reagent too furnished exclusively (*dl*)-**1** with very high yield (90%) in 1.5 h at 0 ^oC. The diastereoselectivity was determined by ^1H NMR, since the benzylic proton for *meso*-**1** and (*dl*)-**1** appears at 4.73 and 4.59 ppm respectively.

Table 1: *Reduction of β-dione* **6** *using various hydride reducing agents.*



6 (*dl*)-**1** *meso*-**1**

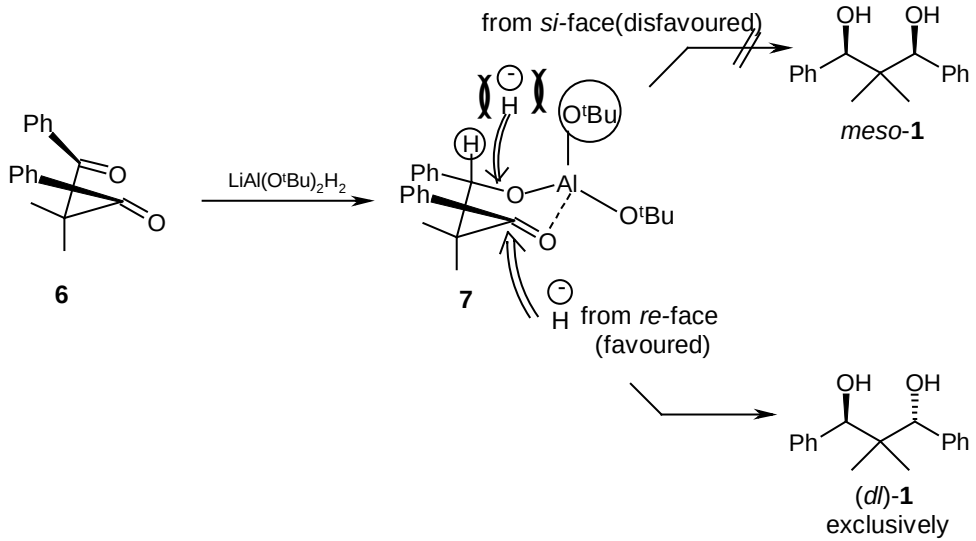
Entry	[H]	Solvent	Temp (^{o}C)	Time (h)	Yield (%)	**1** (*dl*:*meso*)[a]
1	$NaBH_4$	MeOH	25	5	90	58:42
2	$Zn(BH_4)_2$	THF	80	8	b	-
3	$LiBH_4$	THF	25	48	65	82:18
4	LAH	THF	25	0.5	90	88:12
5	$LiAl(O^tBu)_3H$	THF	25	15	70	100:0
6	$LiAl(O^tBu)_2H_2$	THF	0	1.5	90	100:0

[a]Diastereomeric ratio was determined by ^{1}H NMR ; [b]Incomplete reaction

Mechanism :

In presence of $LiAl(O^tBu)_2H_2$, the reduction of *β*-dione **6** is believed to undergo *via β*-hydroxy ketone intermediate **7** (in Figure 2) which attains a stable six-membered chair like conformation and force the incoming hydride reagents to approach from the lower side to attack the less sterically hindered *re*-face of the carbonyl providing exclusively *anti*-diol **1**. This observation is just opposite for 1,2- and 1,4-dione which always give *syn*-diol as the major product under the similar situation.

Figure 2.



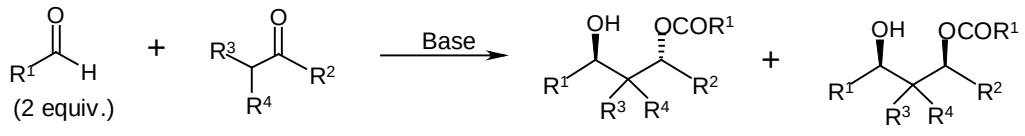
Section 2B

Aldol-Tishchenko reaction

Introduction

Aldol-Tishchenko reaction is a tandem sequential process of aldol reaction followed by Tishchenko reaction, primarily generating 1,3-glycol monoester (Scheme 3). The aldol-Tishchenko reaction has received much attention as a means to couple unactivated carbonyl compounds.

Scheme 3: *General representation of aldol-Tishchenko reaction*.



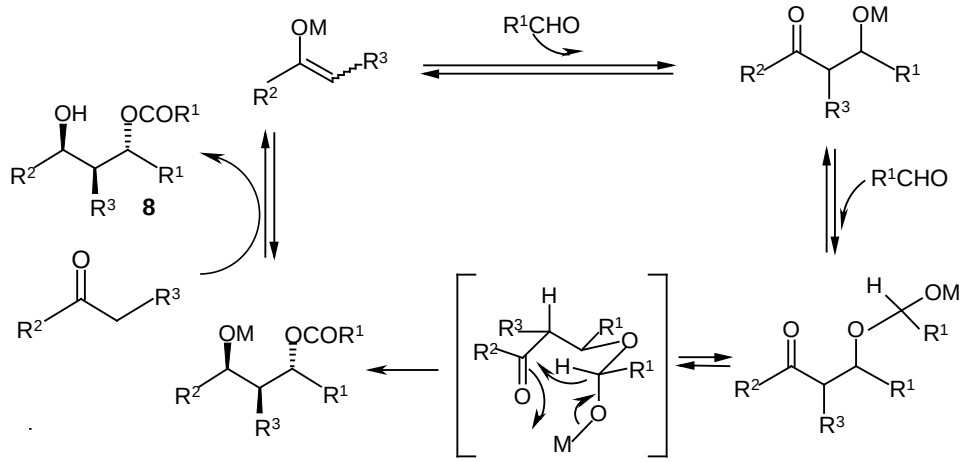
R^1= alkyl or aryl
R^2= H, alkyl or aryl
R^3= H, alkyl or aryl
R^4= H, alkyl or aryl

anti (major) *syn* (minor)

(1,3-glycol monoester)

Several types of base including metal alkoxides, lithium amides etc. in stoichiometric[11] and catalytic quantity[12] are known to be good promoters of aldol-Tishchenko reaction. Mechanistic studies on stereoselective aldol-Tishchenko reactions suggest that the reaction occurs by the mechanism depicted in Scheme 4.[11a, d, e, 12a]

Scheme 4: *Cycle for catalytic aldol-Tishchenko reactions*.



9

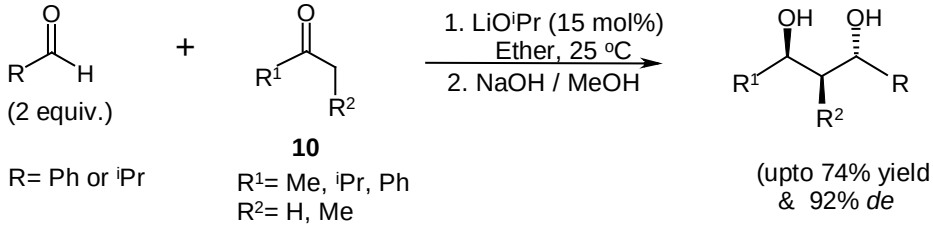
After generation of the enolate, a reversible aldolization step is thought to precede a rate-determining reduction *via* transition state **9**. Bodner et.al. previously confirmed that intramolecular hydride transfer step is the rate-determining step being slower than aldol addition.[11d] The major product stereoisomer **8** is formed from the stereoisomer of structure **9** wherein all substituents at the six-membered ring occupy equatorial positions.

The mild reaction condition and high *anti*-selectivity of the 1,3-glycol monoesters renders the methodology very useful. Aldol-Tishchenko reaction is a fascinating reaction in organic synthesis since many biologically important compounds possess 1,3-*anti*-diol skeleton. This section deals with the synthesis of (*dl*)-**1** using aldol-Tishchenko reaction.

Results and discussion

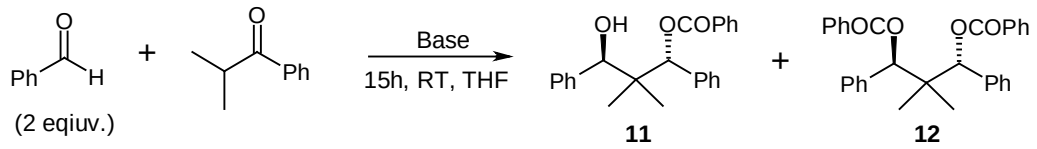
Morken and co-workers very recently have shown $LiO^{i}Pr$ as an efficient catalyst for highly diastereoselective (92% *de*) hetero aldol-Tishchenko reaction.[13] The lithium enolates were generated from the carbonyl compounds **10** containing either secondary or primary α-hydrogen (Scheme 5).

Scheme 5: *Alkoxide-catalyzed aldol-Tishchenko reaction*.



We observed that lithium alkoxides derived from ethanol and isopropanol were unable to promote the reaction between isobutyrophenone and benzaldehyde even with stoichiometric quantity (entry 1 and 2 in Table 2). The basic difference between our's and Morken's substrate is the acidity of α-H in isobutyrophenone and in structure **10** respectively. Thus $LiO^{i}Pr$ which could promote the reaction for ketones like **10**, was inefficient for isobutyrophenone. To prove this, we used stronger base like $LiO^{t}Bu$ which according to the expectation, was found to provide the 1,3-glycol monoester **11**. We were satisfied to note the exclusive formation of *anti*-isomer (by X-ray crystallography). Unlike Morken's observation, $LiO^{t}Bu$ was required in stoichiometric quantity to obtain **11** in satisfactory yield (71%) (entry 5 in Table 2). Using the concentration of $LiO^{t}Bu$ in 10 mol% and 20 mol% diminished the yield to 17% and 32% respectively (entry 3 and 4 in Table 2). Higher benzaldehyde and isobutyrophenone ratio (4:1) in presence of stoichiometric quantity of $LiO^{t}Bu$ enhanced the yield of **11** to 79% (entry 6 in Table 2).

Table 2 : *Various base mediated aldol-Tishchenko reaction*.



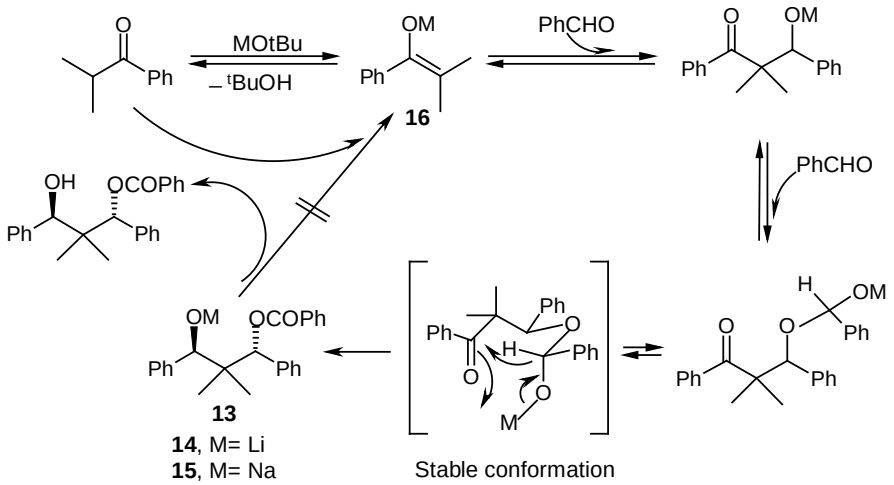
Entry	Base	Mol (%)	Ketone:aldehyde	*anti*-**11** yield (%)	*anti*-**12** yield (%)
1	LiOEt	100	1 : 2.5	-	-
2	$LiO^{i}Pr$	100	1 : 2.5	-	-
3	$LiO^{t}Bu$	10	1 : 2.5	17	-

4	LiO^tBu	20	1 : 2.5	32	-
5	LiO^tBu	100	1 : 2.5	71	-
6	LiO^tBu	100	1 : 4	79	b
7	NaO^iPr	100	1 : 2.5	13	b
8	NaO^tBu	20	1 : 2.5	5	8
9	NaO^tBu	100	1 : 2.5	28	34
10	NaO^tBu	100	1 : 4	39	48
11[a]	KOH	100	1 : 2.5	-	-

[a]At reflux temperature; [b]Very negligible.

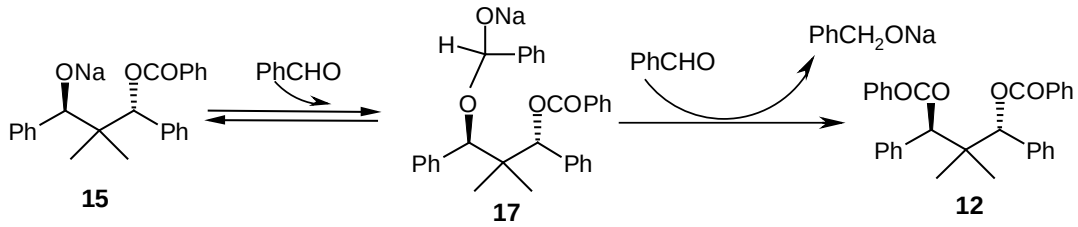
We have also examined the effect of different alkali metals in the alkoxides. The increase in basicity from LiO^{i}Pr to NaO^{i}Pr also couldn't promote the reaction under catalytic (20 mol%) condition but 13% yield of **11** was obtained using 1 equiv. of NaO^{i}Pr from 2.5:1 ratio of benzaldehyde and isobutyrophenone (entry 7 in Table 2). To our surprise, dibenzoate ester **12** was obtained as the major product alongwith desired monoester **11** in the presence of 1 equiv. of NaO^{t}Bu. The ratio of benzaldehyde and isobutyrophenone from 2.5:1 to 4:1 increased the diester yield from 34 to 48% and monoester yield from 28 to 39% under the identical reaction condition (entry 9 and 10 in Table 2). A plausible mechanism has been depicted in Scheme 6 to explain the stereoselective formation of 1,3-glycol monoester **11** and non-catalytic behaviour of the metal-alkoxides.

Scheme 6



In Scheme 6, the catalytic cycle is breaking between the intermediate **13** and metal enolate **16**. Since the intermediate **13** is a secondary metal alkoxide, neither can abstract the less acidic proton from isobutyrophenone nor can equilibrate with *tert*-butanol to keep the cycle on and ultimately make this process stoichiometric. So the nature of the substrate is very much important for this reaction to be catalytic, which was observed in Morken's case. The intermediate **15** which is a better nucleophile too than **14** explains the formation of diester when NaO^tBu was used as base. The intermediate **15** in Scheme 6 behaves like nucleophile rather than act as a base and consequently takes up another benzaldehyde molecule to form intermediate **17** which undergoes intermolecular Tishchenko reduction with benzaldehyde resulting diester **13** and benzylalcohol (Scheme 7).

Scheme 7



In a typical experiment, taking pure monoester **11** in presence of NaO^tBu in THF, didn't generate any diester **12** and diol **1**, and it clearly nullifying the possibility of diester formation from two molecules of monoester **11** *via* disproportionation type reaction. We have also performed one experiment taking KOH as the base but no product corresponding to the monoester **11** and diester **12** were observed even after refluxing the reaction mixture for several hours (entry 11 in Table 2).

Here for the first time we have shown the formation of diester in an aldol-Tishchenko reaction. X-ray study of the single crystal of monoester **11** confirmed *anti* configuration and existance of dimeric arrangement of **11** through an extremely strong H- bonding (Figure 3). The *anti* configuration and moreover presence of C-H···O interaction was confirmed in the dimeric architecture construction for the diester **12** by X-ray crystallography (Figure 4).

Figure 3. *ORTEP diagram of monoester* **11**

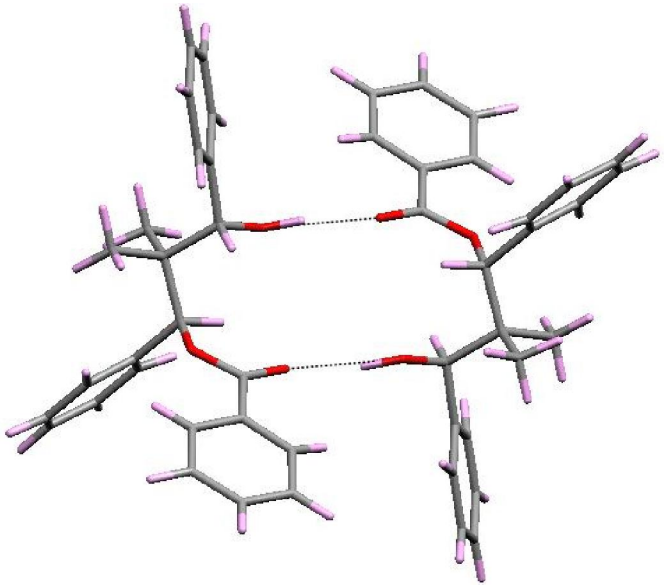
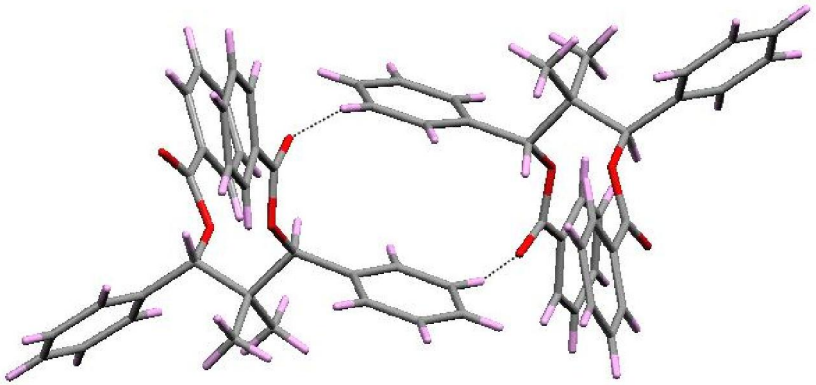


Figure 4. *ORTEP diagram of diester* **12**



Finally, saponification of compound **11** and **12** provided almost quantitative yield of *dl*-diol **1** (eq. 3).

11 + **12** $\xrightarrow{\text{KOH/ MeOH}}$ (*dl*)-diol **1** (3)

Section 2C

Resolution of the diol

Introduction

A resolution is a separation whose point of departure is a racemate and whose conclusion at least one of the enantiomers present in the initial mixture, is recovered. Several resolution techniques are available, including

a) Resolution by direct crystallization

b) Resolution through formation and separation of diastereomers (dissociable diastereomers or covalent diastereomers)

c) Crystallization-induced asymmetric transformations leading to total formation of the initial racemate into a single enantiomer.

Even if it is difficult to predict with certainity how the resolution of a racemate should be undertaken in order to achieve success, a number of elements must be taken into consideration quite early in the design: (a) the quantity and (b) the structure of the compound to be resolved.

It must be evident that on a milligram scale, a resolution using crystallization techniques may be achieved, but rarely without difficulty. Chromatographic resolution techniques are more suitable here. The choice to be made is that of a covalent diastereomeric derivative from which regeneration of the enantiomers is easy and attended by little risk of racemization. Structure of the substrate is at least as much important in the choice of the resolution method as does the scale. Use of covalent derivatives in the resolution of chiral acids and bases is relatively rare. Salts are easy to prepare, and their components are easy to regenerate on virtually any scale. In contrast resolutions with covalent diastereomers is accompanied by additional risks (racemization, low yields). Such derivatives are preffered in the resolution of alcohols, phenols, ketones and so on. Moreover, an advantage of covalent diastereomers is that they may frequently be separated either by chromatography or by crystallization. The application of fractional crystallization methods for the separation of solid solutions has been described numbers of times.[14] The enantiomers after the fractional crystallization are finally obtained only following the cleavage of the diastereomers. Cleavage of diastereomers can take place under a wide variety of conditions. Nevertheless, these reactions must aim to satisfy the following requirements : (a) they must be

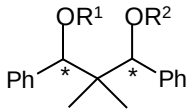
simple, selective, and occur in high yield; (b) they must be non-racemizing; and (c) they should allow the resolving agent to be recovered, especially when the latter is expensive.

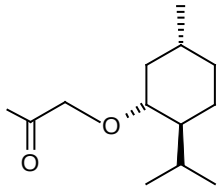
Probably more so than for any other reason, covalent derivatives of alcohols are convenient mediators of resolutions. Diastereomeric esters have figured prominently in the resolution of organic compounds containing hydroxyl groups.

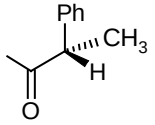
Results and discussion

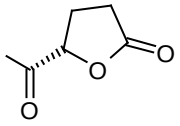
After successful synthesis of *dl*-**1**, we then examined various procedures known for the resolution of the diols. These included the diastereomeric ketals derivatives of (+)-camphor[5] and resolution with boric acid/ L-proline.[15] However both the methods failed to resolve *dl*-**1**. We then turned our attention to the most convenient method of resolution for alcohols. Several diastereomeric esters e.g. **24**, **25**, **26** and **27** were synthesized using popular chiral resolving acids like (-)-menthoxyacetic acid (**18**)[16], (+)-hydratropic acid (**19**)[17], and (-)-5-oxo-2-tetrahydrofuran carboxylic acid (**20**)[18] respectively. For the synthesis of esters, the acids e.g. **18**, **19** and **20** were first converted to the corresponding acid chlorides **21**, **22** and **23** respectively by treating with $SOCl_2$ and then the esterification reaction with (*dl*)-**1** provided the diastereomeric esters. Unfortunately none could be separated either by crystallization or chromatography (Figure 5).

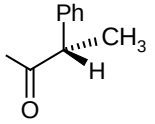
Figure 5. *Various diastereomeric diesters.*



24, $R^1=R^2=$ 

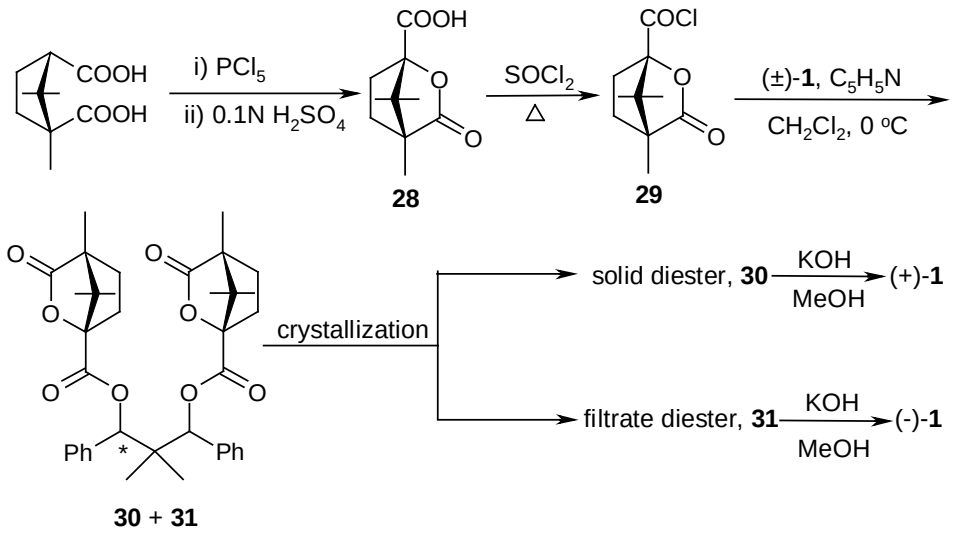
25, $R^1=$ H; $R^2=$ 

27, $R^1=R^2=$ 

26, $R^1=R^2=$ 

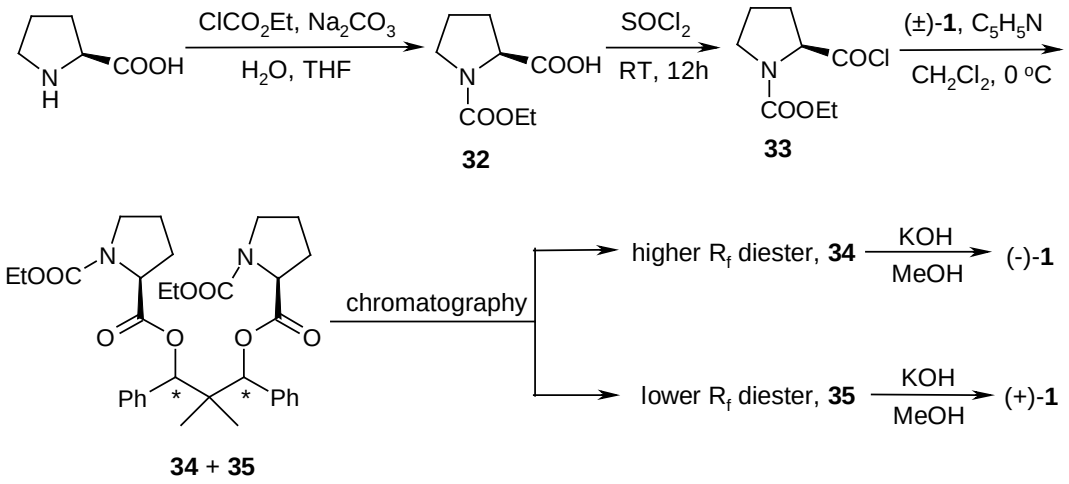
We were eventually successful with esters of (-)-camphanic acid **28**.[19] It was found that the diesters **30** and **31** could be easily separated by crystallization from toluene. The diastereomeric purity could be monitored by TLC and established by ^{1}H NMR (benzylic protons appears at 6.05 and 5.99 δ for **30** and **31** respectively). The solid diester **30** was obtained in >99% *de*, whereas the diester **31** obtained from the mother liquor was of 66% *de*. These were saponified with methanolic KOH to obtain (+)-**1** (>99% *ee*) and (-)-**1** (66% *ee*) respectively (Scheme 8). The enantiomeric purity was further confirmed by chiral HPLC analysis on a chiracel-OD® column.

Scheme 8



Since (-)-camphanic acid is an expensive resolving reagent, we examined the possibility of using N-carbethoxy-L-proline **32**, a cheap alternative. To the best of our knowledge, this acid has never been used as a resolving agent for alcohols or amines. It was obtained in almost quantitative yield by reacting sodium L-prolinate with ethyl chloroformate in aqueous THF. The acid **32** was converted to the corresponding acid chloride **33** by treatment with $SOCl_2$ at room temperature for 12 h (heating resulted in decomposition of acid chloride). Esterification of *dl*-**1** with 2.5 equiv. of **33** gave the diastereomeric diesters **34** and **35**. These could not be separated by crystallization, but were separated by flash chromatography on silica gel. Subsequent saponification of the diesters provided (-)-**1** (40% yield, >99% *ee*) from the less polar diester **34**, and (+)-**1** (33% yield, >99% *ee*) from more polar diester **35** as depicted in Scheme 9.

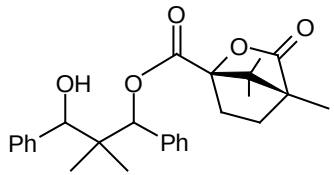
Scheme 9


ClCO2Et, Na2CO3
H2O, THF
SOCl2
RT, 12h
(±)-1, C5H5N
CH2Cl2, 0 oC
COOH
COOEt
COCl
32
33
EtOOC
chromatography
higher Rf diester, 34
lower Rf diester, 35
KOH
MeOH
(-)-1
(+)-1
Ph
34 + 35

Both the resolution procedures described above were optimized at 20 mmol of the diol.[20] The crystallization method can be adopted for procuring multigram quantities of enantiomerically pure (+)-**1**. On the other hand, when both enantiomers are required in relatively small amounts, the second procedures (separation by chromatography) can be taken into consideration.

We also observed a kinetic resolution between monoester **36** (Figure 6) and diester **35** when exactly 2 equiv. of acid chloride **33** was used for esterification. These two esters could be easily separated by flash chromatography. Subsequent saponification provided (-)-**1** from monoester **36** and (+)-**1** from diester **35**.

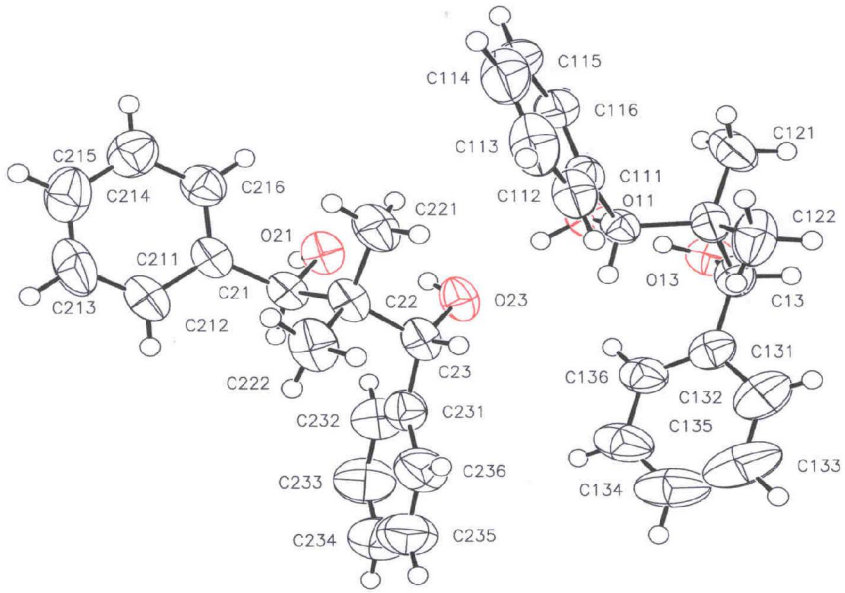
Figure 6.



36

Finally, the absolute configuration of the diol was determined by X-ray crystallography using anomalous dispersion method. It was found that (-)-**1** has (*R*,*R*)-configuration. The ORTEP diagram reveals there are two molecules in the asymmetric unit (Figure 7).

Figure 7. *ORTEP diagram of (-)*-**1**



Conclusions

1. The required non-enolizable dione, dimethyldibenzoyl methane was synthesized starting from diethyl malonate.
2. Various boron and aluminium based reducing agents were examined. Modified aluminium hydride reagent, lithium di-*tert*-butoxyaluminium hydride reduced 2,2-dimethyl-1,3-diphenyl-1,3-propanedione with exclusive formation of (±)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol.

3. (±)-2,2-Dimethyl-1,3-diphenyl-1,3-propanediol was also obtained through aldol-Tischenko reaction in reasonable yield and *anti*-selectivity.
4. Several chiral acids e.g. (-)-menthoxyacetic acid, (-)-5-oxo-2-tetrahydrofurancarboxylic acid, (+)-hydratropic acid, (-)-camphanic acid and N-carbethoxy-L-proline were exemined for resolution. Eventually (-)-camphanic acid and N-carbethoxy-L-proline were successful to resolve the (±)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol.
5. The absolute configuration of (-)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol was determined to be (*R*,*R*)- by X-ray crystallography.

Experimental

General:

Tetrahydrofuran was freshly distilled from benzophenone ketyl. Dichloromethane, toluene, benzene were distilled from calcium hydride and stored over molecular sieves. After azeotropic removal of water, DMSO was distilled under reduced pressure from calcium hydride.

2,2-Dimethyl diethylmalonate (**3**) :

To a vigorously stirred heterogeneous mixture of K_2CO_3 (41.4 g, 300 mmol), NaOH (12 g, 300 mmol) and tryethylbenzylammonium chloride (1.14 g, 5 mmol) in dichloromethane (200 mL), a mixture of diethylmalonate(16.0 g, 100 mmol) and dimethylsulphate (31.5 g, 250 mmol) was added dropwise over 1.5 h at room temparature. After 5 additional hours of stirring at room temparature, the inorganic materials were removed by filtration and washed with dichloromethane (200 mL). All the organic filtrates were combined, washed with water (2 x 50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure on a rotary evaporator. The crude oily residue was fractionated under reduced pressure to yield the pure **3**.

Yield 17.7 g (95%)

bp. 118 ^oC (55 mm Hg) (lit.[9a] bp. 83 ^oC/18 mm Hg)

^1H NMR ($CDCl_3$) δ 1.25 (t, *J* 7.1 Hz, 6H, -C**H**$_3$), 1.43 (s, 6H, -OCH$_2$C**H**$_3$), 4.19

(q, *J* 7.1 Hz, 4H, -OC**H**$_2$)

2,2-Dimethyl malonic acid (**4**) :

A mixture of the compound **3** (18.8 g, 100 mmol) and KOH (19.7 g, 300 mmol) in 50% aq. MeOH (100 mL) was refluxed for 3 h. MeOH then was removed on a rotary evaporator. The solid residue was dissolved in water and acidified to pH~2 with conc. HCl. The aqueous layer was evaporated to dryness. The residue was extracted with acetone (2 x 100 mL). Removal of acetone provided the compound **4** as a white solid.

Yield 13 g (99%)

mp. 190-192 ^{o}C (lit.[9b] 193-194 ^{o}C)

^{1}H NMR (D_2O) δ 1.34 (s, 6H, C**H**$_3$).

2,2-Dimethyl malonoyl chloride (**5**) :

A mixture of acid **4** (13.2 g, 100 mmol) and thionyl chloride (59.5 g, 500 mmol) was refluxed for 5 h. Excess thionyl chloride was distilled from the reaction mixture and the crude acid chloride was distilled under reduced pressure to obtain a light yellow liquid.

Yield 14.6 g (87%)

bp. 90-92 ^{o}C (50 mm Hg) (lit.[9b] bp. 165 ^{o}C)

2,2-Dimethyl-1,3-diphenyl-1,3-propanedione (**6**)

To an well stirred suspension of anhydrous $AlCl_3$ (18.8 g, 141 mmol) in freshly dried benzene (125 mL), the acid chloride **5** (10.8 g, 64 mmol) was added over 1.5 h at 0 ^{o}C. After 4 additional hours of stirring at room temparature, the reaction mixture was poured into an

ice (300 g) and conc.HCl (12 mL) mixture with continuous stirring. It was extracted with ethyl acetate (2 x 100 mL). The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was crystallized from petroleum ether to obtain **6** as white solid.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (**6**) = 0.7]

Yield 11.8 g (74%)

mp. 101-103 ^oC (lit.[10b] 95-97 ^oC)

^1H NMR ($CDCl_3$) δ 1.62 (s, 6H, -C**H**$_3$), 7.25-7.45 (m, 6H, -**H**$_{Ar.}$), 7.81-7.90 (m, 4H, -**H**$_{Ar.}$).

2,2-Dimethyl-1,3-diphenyl-1,3-propanediol (**1**) :

To a stirred suspension of LAH (3.42 g, 90 mmol) in anhydrous THF (30 mL), *t*-butyl alcohol (17.2 mL, 180 mmol) was added dropwise. The resulting solution was cooled to 0 ^oC and treated with a solution of the diketone **6** (7.56 g, 30 mmol) dissolved in THF (30 mL). After the addition, stirring at 0 ^oC was continued for 2 h. The reaction was quenched by the addition of MeOH (5 mL) followed by water (5 mL). The resulting mixture was filtered and the solid was repeatedly washed with EtOAc. Combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was crystallized from aqueous MeOH to obtain pure *dl*-**1**. The stereochemical purity was judged by benzylic proton signals in ^1H NMR.

TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (**6**) = 0.7, R_f (**1**) = 0.21

Yield 6.9 g (90%)

de >99% (by ^1H NMR)

mp. 110-112 ^oC

IR (Nujol) cm^{-1} 3288 (O-H str.)

^1H NMR ($CDCl_3$) δ 0.81 (s, 6H, -C**H**$_3$), 1.85 (br.s, 2H, -O**H**), 4.62 (s, 2H, -C**H**Ph),

7.25-7.35 (m, 10H, -$\mathbf{H}_{Ar.}$).

^{13}C NMR ($CDCl_3$) δ 21.3, 41.1, 80.8, 127.2, 127.5, 127.8, 141.4.

Analysis for $C_{17}H_{20}O_2$

Calculated (%) C, 79.65; H, 7.86

Found (%) C, 79.75; H, 7.96.

Representative procedure for lithium alkoxide mediated aldol-Tishchenko reaction (**Table 2**) :

A 25 mL flame-dried flask was charged with freshly dried *tert*-butanol (0.22 g, 3 mmol) and 2 mL dry THF under argon atmosphere. To the solution was dropwise added 1.3M cyclohexane solution of ^{n}BuLi (2.3 mL, 3 mmol), with stirring. Isobutyrophenone (0.44 g, 3 mmol) was then added and the mixture allowed to stir for 10 minutes. Benzaldehyde (1.27 g, 12 mmol) dissolved in anhydrous THF (5 mL) was added dropwise over a period of 20 minutes. The mixture was allowed to stir for 15 hours, then quenched by the addition of 25 mL 0.5N HCl and extracted with ethylacetate (1 x 60 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethylacetate-petroleum ether as the eluent to obtain **11** as a white solid.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (isobutyrophenone) = 0.7, R_f (**11**) = 0.32]

anti-3-hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate (**11**)

Yield 0.85 g (79%)

de >99% (by ^{1}H NMR)

mp. 138-139 ^{o}C

IR ($CHCl_3$) cm^{-1} 3610 (O-H str.), 1720 (>C=O str.)

^{1}H NMR ($CDCl_3$)	δ 0.80 (s, 3H, -C**H**$_3$), 0.87 (s, 3H, -C**H**$_3$), 2.97 (d, *J* 3.41Hz, 1H, -O**H**), 4.755 (d, 3.29 Hz, 1H, -C**H**Ph), 6.37 (s, 1H, -C**H**Ph), 7.22-7.64 (m, 13H, -**H**$_{Ar.}$), 8.10-8.18 (m, 2H, -**H**$_{Ar.}$)
^{13}C NMR ($CDCl_3$)	δ 17.8, 19.2, 42.9, 76.9, 80.0, 127.3, 127.4, 127.7, 128.1, 128.2, 128.5, 129.6, 130.2, 133.1, 137.9, 141.1, 166.0.
Analysis for	$C_{24}H_{24}O_3$
Calculated (%)	C, 79.97; H, 6.71
Found (%)	C, 80.13; H, 6.56.

Preparation of stock solution of 1M sodium alkoxides in THF :

To a suspension of NaH (0.48 g, 20 mmol) in anhydrous THF (20 mL), 20 mmol freshly dried alcohol (EtOH or ^{i}PrOH or ^{t}BuOH) was added and stirred till hydrogen evolution ceased. The heterogeneous mixture was allowed to settle. The clear supernatant solution of sodium alkoxides were estimated by acidimetry and used for aldol-Tishchenko reaction.

Representative procedure for sodium alkoxide mediated aldol-Tishchenko reaction (**Table 2**) :

A 25 mL flame-dried flask was charged with 1M NaO^{t}Bu (3 mL) under argon atmosphere. Isobutyrophenone (0.44 g, 3 mmol) was then added dropwise and the mixture allowed to stir for 10 minutes. Next, benzaldehyde (1.27 g, 12 mmol) dissolved in anhydrous THF (10 mL) was added dropwise over a period of 20 minutes. The mixture was allowed to stir overnight (16 hours), quenched by the addition of 25 mL 0.5N HCl and extracted with ethylacetate (1 x 60 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethyl acetate-petroleum ether as the eluent to obtain the monoester **11** and the diester **12** separately as white solids.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (isobutyrophenone) = 0.7, R_f (**11**) = 0.32, R_f (**12**) = 0.44]

anti-3-hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate (**11**)

Yield 0.42 g (39%)

de >99.9% (by ^{1}H NMR)

anti-2,2-dimethyl-1,3-diphenylpropyl-1,3-dibenzoate (**12**)

Yield 0.67 g (48%)

de >99.9% (by ^{1}H NMR)

mp. 226-228 ^oC

IR ($CHCl_3$) cm^{-1} 1722 (>C=O str.)

^{1}H NMR ($CDCl_3$) δ 1.05 (s, 6H, -C**H**$_3$), 6.15 (s, 2H, -C**H**Ph), 7.23-7.54 (m, 16H, **H**$_{Ar.}$), 7.99-8.11 (m, 4H, **H**$_{Ar.}$)

^{13}C NMR ($CDCl_3$) δ 19.6, 42.3, 79.3, 127.8, 128.0, 128.3, 129.6, 130.4, 132.9, 137.9, 165.2.

Analysis for $C_{31}H_{28}O_4$

Calculated (%) C, 80.15; H, 6.07

Found (%) C, 80.15; H, 5.81.

***Crystallographic analysis of* 11** :

Empirical formula $C_{24}H_{24}O_3$

Formula weight	360.43
Temperature	566(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.450(8) Å α = 86.48(2)°.
	b = 10.638(10)Å β = 77.402(18)°.
	c = 11.608(10)Å γ = 74.363(16)°.
Volume	980.6(16) $Å^3$
Z, Calculated density	2, 1.221 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	384
Crystal size	0.20 x 0.13 x 0.04 mm
Theta range for data collection	1.99 to 25.00 deg.
Limiting indices	-10<=h<=10, -12<=k<=12, -13<=l<=13
Reflections collected / unique	7088 / 3425 [R(int) = 0.0885]
Completeness to theta = 25.00	99.0 %
Max. and min. transmission	0.9968 and 0.9843
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3425 / 0 / 340
Goodness-of-fit on F^2	0.835
Final R indices [I>2sigma(I)]	R1 = 0.0562, wR2 = 0.0962

R indices (all data)	R1 = 0.1962, wR2 = 0.1330
Largest diff. peak and hole	0.163 and -0.157 e.Å^{-3}

***Crystallographic analysis of* 12** :

Empirical formula	C24.80 H22.40 O3.20
Formula weight	371.63
Temperature	566(2) K
Wavelength	0.71073 Å
Crystal system, space group	TRICLINIC, P-1
Unit cell dimensions	a = 9.1460(11) Å α = 95.472(2)°.
	b = 16.193(2) Å β = 90.034(2)°.
	c = 17.679(2) A γ = 104.379(2)°.
Volume	2523.9(5) Å^3
Z, Calculated density	5, 1.223 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	984

Crystal size	0.34 x 0.24 x 0.09 mm
Theta range for data collection	1.30 to 25.00 deg.
Limiting indices	-10<=h<=10, -19<=k<=19, -21<=l<=21
Reflections collected / unique	36726 / 8865 [R(int) = 0.0569]

Completeness to theta = 25.00	99.7 %
Max. and min. transmission	0.9928 and 0.9734
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8865 / 0 / 635
Goodness-of-fit on F^2	1.221
Final R indices [I>2sigma(I)]	R1 = 0.0963, wR2 = 0.1970
R indices (all data)	R1 = 0.1401, wR2 = 0.2163
Largest diff. peak and hole	0.229 and -0.165 e. $Å^{-3}$

***Saponification of* 11 *and* 12** :

A mixture of the compound **11** and **12** (1 equiv.) and KOH (3 equiv.) in 50% aq. MeOH was refluxed for 2 h. Then MeOH was removed on a rotary evaporator. Water was added and the reaction mixture was extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was crystallized from petroleum ether-ethylacetate mixture to obtain (±)-diol **1** as a white solid.

[TLC data:	Solvent = Petroleum ether : EtOAc (9:1), R_f (**11**) = 0.32, R_f (**12**) = 0.44, R_f (**1**) = 0.21]
mp.	110-112 ^oC
de	>99.9% (by ^1H NMR)

Synthesis of (-)-menthoxyacetic acid (**18**) :

To a suspension of NaH (2.64 g, 110 mmol) in anhydrous THF (100 mL), a solution of (-)-menthol (15.63 g, 100 mmol) in anhydrous THF (50 mL) and DMSO (200 mL) was added dropwise. After 2 hours of stirring, catalytic amount of NaI (1.5 mmol, 0.22 g) was added followed by portionwise addition of $ClCH_2COONa$ (13.98 g, 120 mmol) and the mixture was refluxed for 24 hours. Sufficient cold water was added to quench the reaction followed by removal of unreacted organic impurity from water layer by CH_2Cl_2 extraction. The water layer was acidified upto pH~2 using *conc.*HCl. Major portion of water was evaporated under reduced pressure. The concentrated solution was extracted several times by CH_2Cl_2. The organic layer was washed by brine and dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude acid was purified by distillation to obtain a colorless liquid which upon freezing gave a white solid **18**.

Yield	18.2 g (85%)	
mp.	54-55 ^oC	(lit.[21] 54-55 ^oC)
bp.	142-144 ^oC(4 mm Hg)	(lit.[16] 163-164 ^oC/10 mm Hg)
$[\alpha]_D$	-90 (*c* 1, EtOH)	[lit.[16] –91 (*c* 1, EtOH)]
^1H NMR ($CDCl_3$)	δ 0.75-0.95 (m, 12H, -C**H** and –C**H**$_3$), 1.25-1.45 (m, 2H, -C**H**$_2$), 1.55-1.75 (m, 2H, -C**H**$_2$), 1.95-2.35 (m, 2H, -C**H**$_2$), 3.15-3.30 (m, 1H, -OC**H**), 4.05 (d, *J* 16.88 Hz, 1H, -OC**H**$_2$CO), 4.18 (d, *J* 16Hz, 1H, -OC**H**$_2$CO), 10.51 (br. s, 1H, -O**H**).	

(-)-5-Oxo-2-tetrahydrofurancarboxylic acid (**19**) :

L-Glutamic acid (14.71 g, 100 mmol) was suspended in 160 mL water. $NaNO_2$ (~9 g) Was added all at once. The temparature rose by about 5 ^oC, and the presence of HNO_2 was noted and some N_2 evolution occurred. The temparature was lowered to 15-18 ^oC, and 60 mL of 2N HCl was added dropwise over half an hour. The clear solution was stirred at room temparature overnight. Water was removed under reduced pressure at 40-50 ^oC, and the oily solid was extracted with 100-140 mL of hot acetone and filtered. The acetone filtrate

was dried over Na_2SO_4 and concentrated. After removal of last traces of acetone using pump vacuum, addition of a few seed crystals induced crystallization. The solid was taken up in about 320 mL of hot ethanol free chloroform. A gummy, insoluble oil present was best removed by stirring the mixture with Na_2SO_4 while it was allowed to cool to room temperature. The drying agent was removed by filtration, and $CHCl_3$ volume was reduced to about 60 mL, and the solution was chilled in the freezer (-10 ^oC) to obtain a white solid acid **19**.

Yield	3.54 g (27%)	
mp.	46 ^oC	(lit.[18] 71-72 ^oC)
$[\alpha]_D$	+15.39 (*c* 4.6, MeOH)	[lit.[18] +16.02 (*c* 4.6, MeOH)]
^1H NMR ($CDCl_3$)	δ 2.20-2.40 (m, 1H, -C**H**$_2$), 2.55-2.70 (m, 3H, -C**H**$_2$), 5.02-5.15 (m, 1H, -OC**H**COO-).	

(-)-camphanic acid (**28**) :

To the solid PCl_5 (62 g, 298 mmol) in a 250 mL round bottom flask fitted with a $CaCl_2$-guard tube, (+)-camphoric acid (17 g, 85 mmol) was added portionwise over a period of 20 minutes with constant shaking at 0 ^oC. The reaction mixture was heated for 14 hours at 125 ^oC. Then some volatile materials were removed using rotavapor at 50 ^oC. The residual liquid was then added to mechanically stirred mixture of 300 g ice and 17 mL DMF and the stirring was continued until all the ice has melted. The resulting white waxy solid was extracted by $CHCl_3$ and the organic layer was washed 2-3 times by water and dried over Na_2SO_4 and concentrated in *vacuo* to obtain a white solid. This finely powdered solid was added portionwise over a period of 5 minutes to 160 mL of hot 0.1N H_2SO_4 and the resulting solution was refluxed for 7 hours. After reflux the reaction mixture was allowed to cool to room temperature overnight with constant stirring. The offwhite solid was collected by vacuum filtration and washed with water. The remaining camphanic acid was obtained by extraction of the aqueous filtrate with $CHCl_3$ (2 x 20 mL). The combined camphanic acid was then refluxed over a period of 4-5 hours in toluene (160 mL). The volume of toluene

was reduced to 40 mL and allowed to cool to room temperature overnight. The offwhite camphanic acid crystals were filtered and dried under vacuum.

Yield	12 g (72%)	
mp.	200-203 ^{o}C	(lit.[19] 197-201 ^{o}C)
$[\alpha]_D$	-19.9 (*c* 1.71, dioxan)	[lit.[19] –20.4 (*c* 1.71, dioxan)]
^{1}H NMR ($CDCl_3$)	δ 1.02 (s, 3H, -C**H**$_3$), 1.11 (s, 3H, -C**H**$_3$), 1.14 (s, 3H, -C**H**$_3$), 1.62-1.84 (m, 1H, -C**H**$_2$), 1.87-2.21 (m, 2H, -C**H**$_2$), 2.37-2.59 (m, 1H, -C**H**$_2$), 8.19 (br. s, 1H, -COO**H**).	

Preparation of N-carbethoxy-L-proline (**32**) :

A solution of L-proline (6.9 g, 60 mmol) in water (60 mL) at 0 °C, was treated with sodium carbonate (7.63 g, 72 mmol) and the resulting solution was stirred for 30 min. To this mixture, a solution of ethylchloroformate (6.9 mL, 72 mmol) in THF (15 mL) was added dropwise at 0 °C. After the addition, stirring was continued for 2 h. The reaction mixture was brought to ambient temperature and washed with $CHCl_3$ (30 mL). The aqueous portion was acidified to pH~3 and extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and concentrated to obtain N-carbethoxy-L-proline as a viscous liquid which solidifies upon trituration with cold petroleum ether.

Yield	11 g (quantitative)	
mp.	65 ^{o}C	(lit.[25] 62-63 ^{o}C)
$[\alpha]_D$	-98.2 (*c* 1, $CHCl_3$)	
IR ($CHCl_3$) cm^{-1}	1740 (>C=O str.), 1664 (>C=O str.)	
^{1}H NMR ($CDCl_3$)	δ 1.08-1.50 (m, 3H, -C**H**$_3$), 1.75-2.44 (m, 4H, -C**H**$_2$), 3.29-3.83	

(m, 2H, -NC**H**$_2$), 3.96-4.58 (m, 3H, -OC**H**$_2$ and –NC**H**) 10.53 (br. s, 1H, -O**H**)

^{13}C NMR ($CDCl_3$) δ 14.2, 23.1, 23.9, 29.4, 30.5, 46.2, 46.4, 58.4, 58.7, 61.3, 61.4, 154.7, 155.5, 176.0, 176.5.

Analysis for $C_8H_{13}NO_4$

Calculated (%) C, 51.33; H, 7.00; N, 7.48

Found (%) C, 51.38; H, 7.17; N, 7.29

***General procedure of making acid chlorides* 21, 22 *and* 23** :

A mixture of acid (**18** or **19** or **20**) (20 mmol) and $SOCl_2$ (4.76 g, 40 mmol) was refluxed for 3 hours and then excess $SOCl_2$ was distilled out. The residue was distilled under reduced pressure to obtain acid chloride **21** or **22** or **23** respectively.

(-)-Menthoxyacetyl chloride (**21**) :

Yield 3.72 g (80%)

bp. 126 ^{o}C(10 mm Hg) (lit.[22] 117-120 ^{o}C/3 mm Hg)

(S)-2-Phenylpropanoyl chloride (**22**) :

Yield 2.79 g (83%)

bp. 118 ^{o}C(20 mm Hg) (lit.[17] 97-98 ^{o}C/12.5 mm Hg)

(-)-5-Oxo-2-tetrahydrofuranoyl chloride (**23**) :

Yield 2.23 g (75%)

bp. 122 ^{o}C(10 mm Hg) (lit.[23] 117.1 ^{o}C/10 mm Hg)

All the acid chlorides were dissolved in CH_2Cl_2 to obtain 1M stock solution of each.

(-)-camphanoyl chloride (**29**) :

The literature procedure was slightly modified as follows. A mixture of (-)-camphanic acid (9.9 g, 50 mmol) and thionyl chloride (30 mL) was heated under reflux for 3 h. Excess thionyl chloride was distilled off and the remaining traces were removed under vaccum to obtain a solid of **29**.

Yield 9.4 g (98%)

mp. 72-73 ^{o}C (lit.[24] 69-71 ^{o}C)

It was dissolved in CH_2Cl_2 to obtain a 1M stock solution.

Preparation of the acid chloride **33** :

N-Carbethoxy-L-proline (9.35 g, 50 mmol), thionyl chloride (10 mL) and CH_2Cl_2 (10 mL) were stirred at room temperature for 12 h (reaction monitored by the

rate of HCl and SO_2 evolution). Excess thionyl chloride and CH_2Cl_2 were removed under reduced pressure using a rotavapor. The light yellow residue was almost pure **33** in quantitative yield. It was dissolved in CH_2Cl_2 to obtain a 1M solution, which can be kept for several days with gradual decomposition.

Preparation of (dl)-3-hydroxy-2,2-dimethyl-1,3-diphenylpropyl-(S)- phenylpropanoate (**25**) :

To a solution of (±)-**1** (5.12 g, 20 mmol) in anhydrous pyridine (6.45 mL, 80 mmol) and 30 mL CH_2Cl_2, 1M CH_2Cl_2 solution of **22** (20 mL, 20 mmol) was added dropwise at 0 ^oC. The progress of the reaction was monitored by TLC. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water and saturated aqueous $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethyl acetate-petroleum ether as the eluent to obtain **25** as pure white solid.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (**1**) = 0.21, R_f (**25**) = 0.32]

Yield 5.07 g (65%)

mp. 109 ^oC

$[\alpha]_D$ +9.8 (*c* 1, $CHCl_3$)

IR (Nujol) cm^{-1} 3506 (O-H str.), 3445 (O-H str.), 1713 (>C=O str.), 1699 (>C=O str.)

^1H NMR ($CDCl_3$) δ 0.48, 0.58, 0.60 and 0.71 (s, 6H, -C**H**$_3$), 1.50-1.61 (m, 3H, -C**H**$_3$), 2.53 and 2.65 (d, *J* 3.52 Hz, 1H, -O**H**), 3.83 and 3.84 (q, *J* 7.0 Hz, 1H, -C**H**), 4.02 and 4.40 (d, *J* 3.13 Hz, 1H, -C**H**Ph), 5.98 and 6.04 (s, 1H, -C**H**Ph), 6.97-7.46 (m, 15H, -**H**$_{Ar.}$)

^{13}C NMR ($CDCl_3$) δ 17.3, 17.5, 17.9, 18.7, 19.2, 42.3, 42.7, 45.8, 76.1, 76.7, 79.4, 80.0, 127.1, 127.2, 127.4, 127.5, 127.6, 127.8, 128.0, 128.1, 128.6, 128.8, 137.4, 137.7, 139.9, 140.7, 140.9, 141.0, 141.1, 173.3, 173.8.

Analysis for $C_{26}H_{28}O_3$

Calculated (%) C, 79.97; H, 7.74

Found (%) C, 80.17; H, 7.52.

***General preparation of diesters* 24 *or* 26 *or* 27** :

To 1M CH_2Cl_2 solution of **21** or **22** or **23** (50 mL, 50 mmol), a solution of (±)-**1** (5.12 g, 20 mmol) in anhydrous pyridine (12.9 mL, 160 mmol) was added dropwise at 0 ^oC. The progress of the reaction was monitored by TLC. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water and saturated aqueous $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethyl acetate-petroleum ether as the eluent to obtain the diesters **24** or **26** or **27**.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (**1**) = 0.21, R_f (**24**) = 0.35,
R_f (**26**) = 0.34, R_f (**27**) = 0.03]

(dl)-2,2-dimethyl-1,3-diphenylpropyl-1,3--bis-menthoxyacetate (**24**) :

White solid

Yield 5.07 g (65%)

mp. 132-133 ^oC

$[\alpha]_D$ -61.4 (*c* 1, $CHCl_3$)

IR ($CHCl_3$) cm^{-1} 1765 (>C=O str.), 1745 (>C=O str.)

^1H NMR ($CDCl_3$) δ 0.77-2.14 (m, 42H, -C**H** and –C**H**$_2$ and –C**H**$_3$), 3.04-3.26 (m, 2H, -OC**H**), 4.14 (d, *J* 3.7 Hz, 2H, -OC**H**$_2$COO-), 4.16 (d, *J* 3.7 Hz, 2H, -OC**H**$_2$COO-), 5.94 (s, 2H, -C**H**Ph), 7.27-7.33 (m, 10H, -**H**$_{Ar.}$)

^{13}C NMR ($CDCl_3$) δ 16.3, 18.7, 21.0, 22.3, 23.2, 25.4, 31.3, 31.4, 34.4, 40.1, 41.7, 48.2, 78.0, 80.2, 80.5, 127.7, 128.2, 137.5, 169.9.

Analysis for	$C_{41}H_{60}O_6$
Calculated (%)	C, 75.88; H, 9.32
Found (%)	C, 75.99; H, 9.11.

(dl)-2,2-dimethyl-1,3-diphenylpropyl-1,3-bis-2-phenylpropanoate (**26**) :

	Semi-solid
Yield	9.98 g (96%)
$[\alpha]_D$	+37 (*c* 1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	1738 (>C=O str.)
^{1}H NMR ($CDCl_3$)	δ 0.56 (s, 6H, -C**H**$_3$), 1.49 (d, *J* 7.08Hz, 6H, -C**H**$_3$), 3.79-3.93 (m, 2H, -C**H**Ph), 5.78 (s, 2H, -C**H**Ph), 7.12-7.41 (m, 20H, -**H**$_{Ar.}$)
^{13}C NMR ($CDCl_3$)	δ 17.5, 17.8, 18.2, 18.6, 41.6, 41.7, 45.4, 45.5, 46.0, 78.0, 126.9, 127.4, 127.9, 128.1, 128.5, 128.6, 129.1, 137.3, 140.4, 172.9.
Analysis for	$C_{35}H_{36}O_4$
Calculated (%)	C, 80.74; H, 6.97
Found (%)	C, 80.58; H, 6.73.

(dl)-2,2-dimethyl-1,3-diphenylpropyl-1,3-bis-5-oxo-2-tetrahydrofuranoate (**27**) :

	White solid
Yield	9.4 g (98%)
mp.	165 ^oC

$[\alpha]_D$	+36 (*c* 1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	1788 (>C=O str.), 1747 (>C=O str.)
^1H NMR ($CDCl_3$)	δ 0.84 (s, 6H, -C**H**$_3$), 2.25-2.80 (m, 8H, -C**H**$_2$), 4.85-5.15 (m, 2H, -OC**H**COO), 5.89 (s, 1H, -C**H**Ph), 5.95 (s, 1H, -C**H**Ph), 7.15-7.50 (m, 10H, -**H**$_{Ar.}$)
^{13}C NMR ($CDCl_3$)	δ 18.3, 18.4, 25.2, 25.5, 26.6, 41.9, 42.1, 75.9, 79.0, 79.3, 128.0, 128.3, 136.0, 168.9, 169.1, 176.0, 176.3.
Analysis for	$C_{27}H_{28}O_8$
Calculated (%)	C, 67.50; H, 5.87
Found (%)	C, 67.39; H, 5.68.

***Preparation and resolution of diesters* 30 *and* 31** :

To the above described solution of **29** (50 mL, 50 mmol), a solution of (±)-**1** (5.12 g, 20 mmol) in anhydrous pyridine (12.9 mL, 160 mmol) was added dropwise at 0 ^oC. The progress of the reaction was monitored by TLC. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water and saturated aqueous $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of the diesters **30** and **31** (12 g, 98% crude yield). The above crude mixture was dissolved in the minimum volume of hot toluene and cooled gradually to 0 ^oC over a period of 24 h. The crystals were separated from the mother liquor and recrystallized from toluene to obtain pure **30**.

[TLC data:	Solvent = Petroleum ether : EtOAc (7:3), R_f (**1**) = 0.52,
	R_f (**30** + **31**) = 0.38]
Yield	5.2 g (43% overall)

mp.	234-235 ^{o}C
$[\alpha]_D$	+1.6 (*c* 1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	1794 (>C=O str.), 1747 (>C=O str.)
^{1}H NMR ($CDCl_3$)	δ 0.86 (s, 6H, -C**H**$_3$), 0.88 (s, 6H, -C**H**$_3$), 1.03 (s, 6H, -C**H**$_3$), 1.12 (s, 6H, -C**H**$_3$), 1.49-2.61 (m, 8H, -C**H**$_2$), 6.05 (s, 2H, -C**H**), 7.30-7.40 (m, 10H, -**H**$_{Ar.}$)
^{13}C NMR ($CDCl_3$)	δ 9.5, 16.4, 18.1, 28.8, 30.9, 42.0, 54.2, 54.8, 78.6, 90.9, 127.6, 128.2, 136.5, 166.5, 178.3.

Analysis for	$C_{37}H_{44}O_8$
Calculated (%)	C, 72.06; H, 7.19
Found (%)	C, 71.93; H, 7.54.

Preparation and resolution of diesters *34* and *35* :

To the above described solution of **34** (50 mL, 50 mmol), a solution of (±)-**1** (5.12 g, 20 mmol) in anhydrous pyridine (12.9 mL, 160 mmol) was added dropwise at 0 ℃. The progress of the reaction was monitored by TLC. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water and saturated aqueous $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of the diesters **34** and **35** as a viscous liquid (11.4 g, 96% crude yield). Since the two diesters were easily separable on TLC, they were purified by flash chromatography on silica gel (300–400 mesh) using petroleum ether–ethyl acetate (4:1) as the eluent. The diester **34** (R_f = 0.37) eluted first. The diester **35** (R_f = 0.28) eluted next.

[TLC data: Solvent = Petroleum ether : EtOAc (4:1), R_f (**1**) = 0.41, R_f (**34**) = 0.37, R_f (**35**) = 0.28]

Diester **34** :

White solid

Yield	4.78 g (42% overall)
mp.	62 ^{o}C
$[\alpha]_D$	-84.3 (*c* 1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	1742 (>C=O str.), 1707 (>C=O str.)
^{1}H NMR ($CDCl_3$)	δ 0.67-1.1 (m, 10H, -C**H**$_3$ and –NCH$_2$C**H**$_2$), 1.21-1.49 (m, 2H, -NCHC**H**$_2$), 1.71-2.41 (m, 8H, -OCH$_2$C**H**$_3$ and -NCHC**H**$_2$), 3.43-4.62 (m, 10H, -NC**H** and –NC**H**$_2$ and –OC**H**$_2$CH$_3$), 5.66-5.93 (m, 2H, -C**H**Ph), 7.17-7.44 (m, 10H, -**H**$_{Ar.}$).
^{13}C NMR ($CDCl_3$)	δ 14.2, 14.9, 18.4, 23.7, 24.2, 29.1, 29.3, 30.4, 41.9, 46.3, 46.8, 59.5, 61.4, 78.2, 127.8, 128.2, 137.0, 137.3, 154.7, 155.1, 171.4.
Analysis for	$C_{33}H_{42}N_2O_8$
Calculated (%)	C, 66.65; H, 7.12; N, 4.71
Found (%)	C, 66.56; H, 7.55; N, 4.56.

Diester **35** :

White solid

Yield	4.1 g (36% overall)
mp.	68 ^{o}C
$[\alpha]_D$	+15.1 (*c* 1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	1749 (>C=O str.), 1715 (>C=O str.)
^{1}H NMR ($CDCl_3$)	δ 0.73-0.99 (m, 10H, -C**H**$_3$ and –NCH$_2$C**H**$_2$), 1.18-1.36 (m, 2H, -NCHC**H**$_2$), 1.82-2.41 (m, 8H, -OCH$_2$C**H**$_3$ and -NCHC**H**$_2$), 3.37-4.64 (m, 10H, -NC**H** and –NC**H**$_2$ and –OC**H**$_2$CH$_3$), 5.76-5.96 (m, 2H, -C**H**Ph), 7.22-7.47 (m, 10H, -**H**$_{Ar.}$)
^{13}C NMR ($CDCl_3$)	δ 14.3, 14.7, 18.3, 23.5, 24.3, 41.9, 46.3, 46.7, 59.0, 59.3, 61.2, 78.3, 127.7, 128.2, 137.4, 154.6, 155.0, 171.5.
Analysis for	$C_{33}H_{42}N_2O_8$
Calculated (%)	C, 66.65; H, 7.12; N, 4.71
Found (%)	C, 66.21; H, 7.01; N, 4.68.

***Preparation of* (+)-1** :

The diester **30** or **35** (4 g) was heated under reflux with 1N KOH in methanol (20 mL) for 1 h. Excess solvent was removed on a rotavapor, water (20 mL) was added and the reaction mixture was extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue of the diol (+)-**1** was crystallized from hexane–THF (10:1); mp 125–126 °C; $[\alpha]_D$ +8.0 (*c* 1, $CHCl_3$). The spectral data of the product was identical to that of the racemate. The enantiomeric excess was found to be >99% by HPLC analysis on DIACEL Chiralcel-OD® column using hexane–isopropyl alcohol as the solvent.

***Preparation of* (-)-1** :

Saponification of the diester **34** as described above provided (-)-**1** which was also crystallized from hexane –THF (10:1) to obtain white needles; mp 125– 126 °C; $[\alpha]_D$ -8.0 (*c* 1, $CHCl_3$). Absolute configuration of the enantiomer was found to be (*R*,*R*) by X-ray crystallography.

***Crystallographic analysis of* (-)-1** :

Colourless, needle-like crystals were grown from hexane –THF (10:1), $C_{17}H_{20}O_2$, *M*=256.35, *a*=11.8587 (6), *b*=10.0497 (3), *c*=12.3563 (11) A, *v*=1472.4 (3) A_ , *T*=299 K, *Z*=4, *D*calcd=1.16 g/cm3. Final goodness of fit=1.045, *R*=0.031, *wR*=0.088. Absolute structure determination was completed using the Flack parameter.18 Crystallographic data (excluding structure factors) for (*R*,*R*)-(-)-**1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 179858.

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CHAPTER-3

Applications of homochiral 2,2-Dimethyl-1,3-Diphenyl-1,3-Propanediol

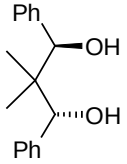
Introduction

C_2-Symmetric chiral diols are versatile ligand/auxiliary in asymmetric synthesis. The diol ligands have the superiority over other such as amino alcohol or diamine regarding its binding ability to form bond with a range of metal atoms generating varieties of complexes. Since a particular reaction is being promoted by a specific metal, the property of broad complexation ability of diol ligands to many metals is advantageous. Many C_2-Symmetric chiral diols have been rationally designed and synthesized and found to be successful as chiral inducers. We have discussed in chapter-1 the synthesis and various applications of this class of ligands known to date.

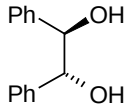
Chiral hydrobenzoin (**2**), an example of C_2-Symmetric 1,2-diols and TADDOL (**3**), a representative of C_2-Symmetric 1,4-diols, are notable in this context. Both the diols are conformationally rigid and can form chiral complexes with a defined stereodifferentiating environment around the metal center. Many synthetically useful C-C bond forming reaction e.g. Diels-Alder reaction, Michael reaction, aldol reaction, addition of diethylzinc to aldehydes etc. have been promoted with high stereoselectivity employing those chiral complexes. Although, a few C_2-Symmetric chiral 1,3-diols are known in the literature (discussed in chapter-1), none have proved to be very useful. Backbone rigidity which is

essential for a 1,3-diol to be an effective chiral auxiliary/ligand, is lacking in all known examples. The C_2-Symmetric 1,3- diol **1** developed by us, is likely to have such required rigidity.

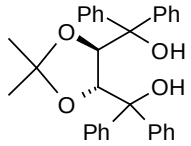
Figure 1.



(*R*,*R*)-(-)-**1**



(*R*,*R*)-(+)-**2**



(*R*,*R*)-(-)-**3**

This chapter deals with a comparison of enantioselectivity obtained for the reactions like Diels-Alder reaction, stereoselective reduction of acetophenone and addition of diethylzinc to benzaldehyde using the present diol **1**, chiral hydrobenzoin (**2**) and chiral TADDOL (**3**). The idea was to compare the effect of 1,2- vs 1,3- vs 1,4-substitution. The chiral diol **2**[1] and **3**[2] were synthesized according to literature procedure with little modification wherever required. This chapter contains three sections.

d) **Section 3A** : Diels-Alder reaction.

e) **Section 3B** : Reduction of acetophenone.

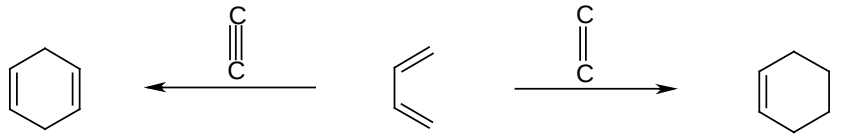
f) **Section 3C** : Addition of diethylzinc to benzaldehyde.

Section 3A

Diels-Alder reaction

Introduction

Diels-Alder cycloaddition is one of the best known organic reaction that is widely used to construct, in a regio- and stereocontrolled way, a six-membered ring upto four stereogenic centers. With the potential of forming carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds, the reaction is a versatile synthetic tool for constructing simple and complex molecules. Since its discovery in 1928[3], thousands of articles have been published concerning synthetic, mechanistic and theoretical aspects of the reaction. The classical Diels-Alder reaction is a cycloaddition between a conjugated diene and a second component, called dienophile, which has at least a π bond (eq 1). When one or more heteroatoms are present in the diene and / a dienophile framework, the cycloaddition is called a hetero-Diels-Alder reaction.

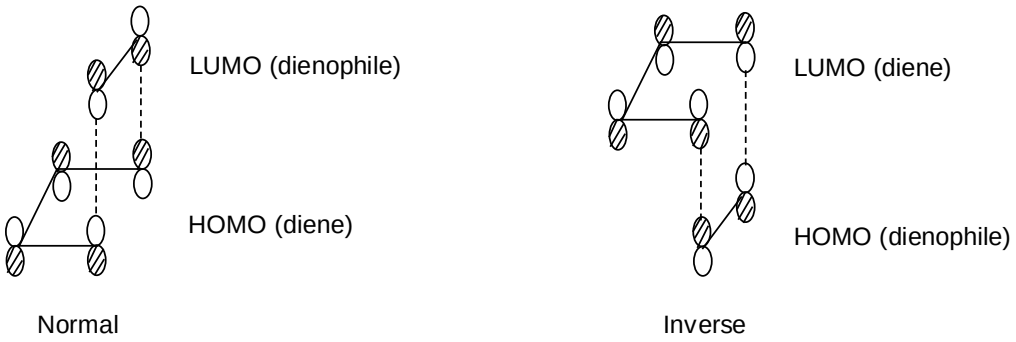


(1)

The reaction is classified as a [$\pi_s^4 + \pi_s^2$] cycloaddition. 4 and 2 identify both the number of π electrons involved in the electronic rearrangement and the number of atoms originating in the unsaturated six-membered ring. The subscript *s* indicates that the reaction takes place suprafacially on both components. A great variety of conjugated dienes and dienophiles have been used.

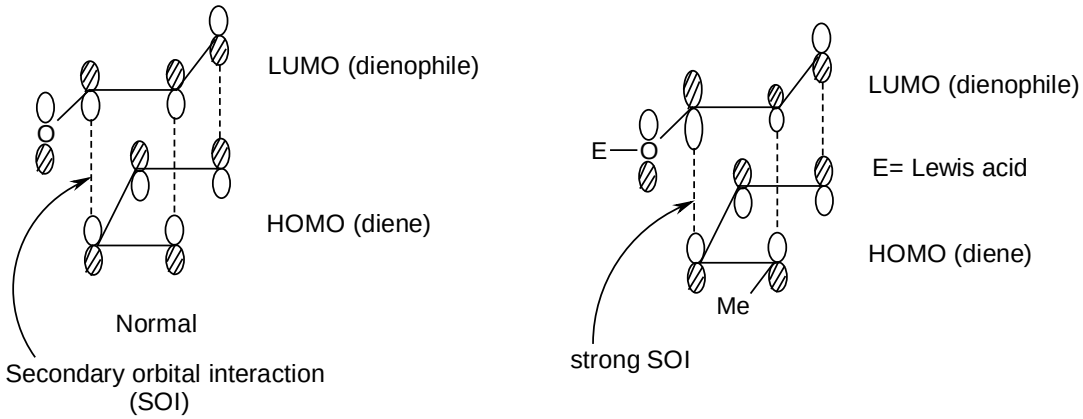
According to frontier molecular orbital theory (FMO), the reactivity, regiochemistry and stereochemistry of the Diels-Alder reactions are controlled by the suprafacial *inphase* interaction of the highest occupied molecular orbital (HOMO) of one component and lowest unoccupied molecular orbital (LUMO) of the other. The reactivity of a Diels-Alder reaction depends on the HOMO-LUMO energy separation of components. The lower is the energy difference, the lower is the transition state energy of the reaction (Scheme 1).

Scheme 1: *FMO model for Diels-Alder raction*



The FMO theory explains the kinetically favored *endo* approach considering an additional non-bonding interaction i.e. secondary orbital interaction. The complexation of dienophile with a Lewis acid increases the possibility of secondary orbital interaction (Scheme 2).

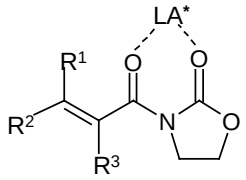
Scheme 2: *FMO model for Lewis acid assisted Diels-Alder reaction*



Yates and Eaton first reported the remarkable acceleration of the reactions of anthracene with maleic anhydride, 1,4-benzoquinone and dimethylfumarate catalyzed by aluminium chloride.[4] The presence of the Lewis-acid catalyst allows the cycloadditions to be carried out under mild conditions. The stereoselectivity, regioselectivity and site selectivity of the cycloaddition reaction can be modified. Indeed high level of asymmetric induction in the intermolecular Diels-Alder reactions have been achieved with suitably designed chiral Lewis-acid catalysts under certain reaction conditions.[5]

There are three basic chelation modes possible between chiral Lewis acid and dienophile.

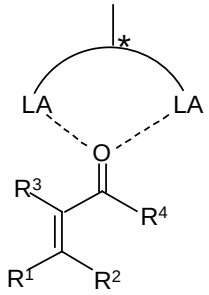
► Chelation of the bidentate dienophile to the chiral Lewis acid complex



(Rigid system)

R^1 , R^2 , R^3 = H, alkyl, aryl

► Chelation of the bidentate chiral Lewis acid to the single carbonyl group

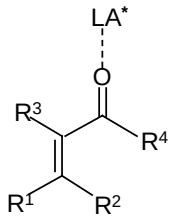


(Rigid system)

R^1 , R^2 , R^3 = H, alkyl, aryl

R^4= OR, NR etc.

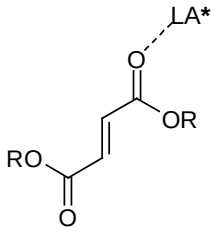
► Monodentate chelation of chiral Lewis acid to the carbonyl group



R^1 , R^2 , R^3 = H, alkyl, aryl

R^4= OR, NR etc.

The selectivity in Diels-Alder reaction employing symmetrical α,*β*-unsaturated ester is supposed to be very much challenging.



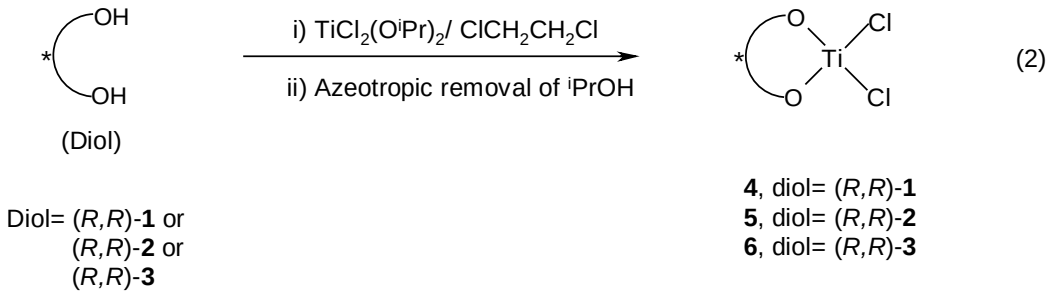
(Symmetrical dienophile complexed to chiral Lewis acid)

To date, very limited number of chiral Lewis acid catalysts have been used in the Diels-Alder reaction employing symmetrical α,*β*-unsaturated ester dienophiles.[6] For these symmetrical α,*β*-unsaturated esters, exceptionally strong binding between the Lewis acid and dienophile's carbonyl group is essential to achieve good selectivity. To address this problem, we have examined few chiral titanate complexes

synthesized from the new chiral 1,3-diol **1**, chiral hydrobenzoin (**2**) and TADDOL (**3**). Cyclopentadiene and dimethylfumarate were selected as the model substrates. This section deals with these results.

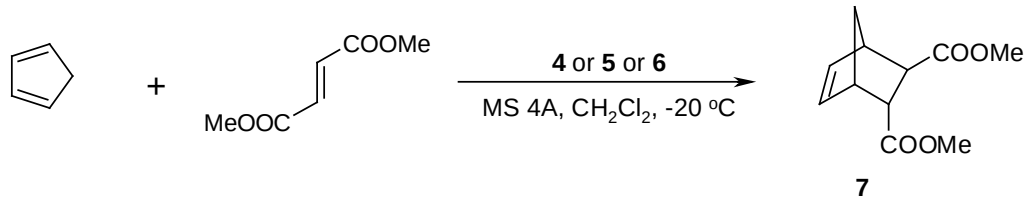
Results and discussion

To begin with, we have first synthesized titanate Lewis acid complexes (**4**-**6**) following the procedure outlined below.



(2)

In situ generated titanate complexes (**4**-**6**) have been used in catalytic as well as stoichiometric quantity for the model reaction (eq 3). All the complexes were found to be excellent promoter of the reaction affording high yield of the cycloadduct **7**. The complex **5** provided lowest yield (86%) under catalytic condition (20 mol%), whereas the highest yield (>99%) was obtained using 1 equiv. of complex **6**. It was observed that the ring size of the titanate complexes do not significantly influence the reactivity and yield. All the reactions were carried out at –20 ^{o}C. Unfortunately all the complexes provided almost racemic product.



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(3)

We concluded that the in situ generated titanate complexes including the new complex **4** were not sufficiently Lewis acidic to complex with the ester group to effect enantioselective cycloaddition. We then moved our attention to a different type of dienophile *viz*. oxazolidinones. These dienophiles **9** have been extensively used in various chiral Lewis acid catalyzed Diels-Alder reaction (Figure 2). It is supposed to give a rigid system due to participation of both carbonyl group during the complexation with Lewis acid.

Table-1: *Titanate complexes* (**4**-**6**) *catalyzed Diels-Alder reaction*

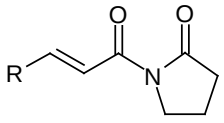
Entry	Titanate complex	mol (%)	Time (h)	Yield[a] (%)	*ee*[b] (%)
1	**4**	20	9	95	2
2	**4**	100	4	95	4
3	**5**	20	7	86	2

4	**5**	100	3	96	6
5	**6**	20	8	93	-
6	**6**	100	3	>99	4

[a]After column chromatography; [b]Using Lanthanide shift reagent [$Eu(hfc)_3$]

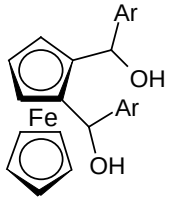
In recent years, rare earth metal based complexes have been used as chiral Lewis acid catalysts.[7] Fukuzawa et. al. reported a $Sc(OTf)_3$/ FERRODIOL **12** system for asymmetric Diels-Alder reaction between cyclopentadiene and oxazolidinone based dienophile.[8]

Figure 2.



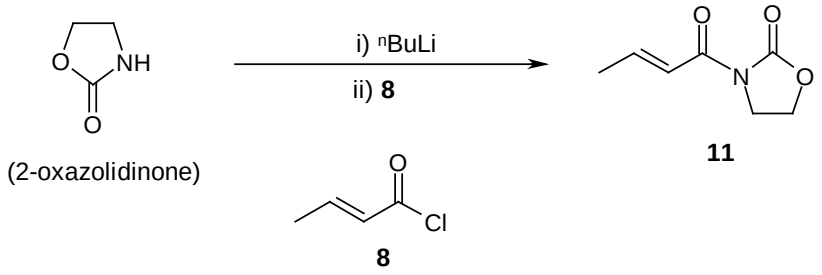
9

10, R= H
11, R= Me



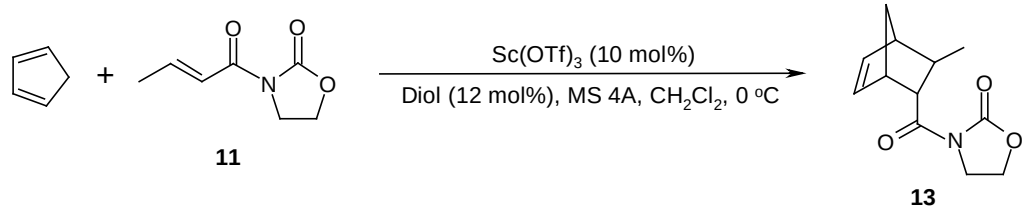
12

This prompted us to investigate the efficiency of chiral diol (**1**-**3**) for the same reaction. The dienophile **11** was synthesized starting from 2-oxazolidinone following the procedure outlined in eq 4.[9a]



(4)

The diol **1** in combination with $Sc(OTf)_3$ and 2,6-lutidine in dichloromethane, generated one interesting catalyst system which efficiently promoted the Diels-Alder reaction between cyclopentadiene and **11** at 0 ^oC (eq 5). Very high yield and high *endo:exo* selectivity was observed but the enantioselectivity (45%) obtained was only moderate (entry 2 in Table 2). A sharp decrease in enantioselectivity (3%) was observed in the absence of 2,6-lutidine additive. That clearly indicated a significant role of the additive to generate an active chiral scandium catalyst.



(5)

Table-2

		Additive	Time	Yield[a]		*ee*[c]	

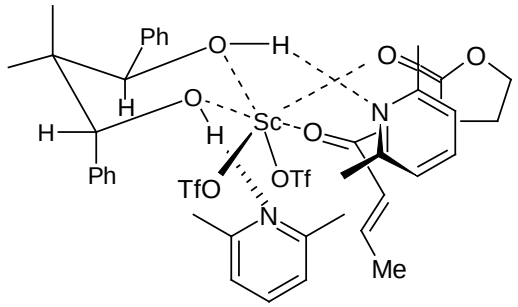
Entry	Diol	(20 mol%)	(h)	(%)	*Endo:Exo*[b]	(%)	*Configuration*[d]
1	(*R*,*R*)-**2**	2,6-lutidine	3	36	72:28	16	$1'R,2'R,3'S,4'S$
2	(*R*,*R*)-**1**	2,6-lutidine	2	74	89:11	45	$1'R,2'R,3'S,4'S$
3	(*R*,*R*)-**1**	-	3	68	87:13	3	$1'R,2'R,3'S,4'S$
4	(*R*,*R*)-**3**	2,6-lutidine	24	23	72:28	-	-

[a]After column chromatography; [b]by ^{1}H NMR; [c]by comparison with literature rotation[9b]; [d]by literature comparison[9b].

It was interesting to observe that (*R*,*R*)-**2** and (*R*,*R*)-**3** for the same reaction afforded very low yield and selectivity compared to (*R*,*R*)-**1** (entry 1 and 4 in Table 2).

Mechanism:

We propose a transition state model for the cycloaddition of cyclopentadiene and dienophile **11** catalyzed by $Sc(OTf)_3$, (*R*,*R*)-**1** and 2,6-lutidine.



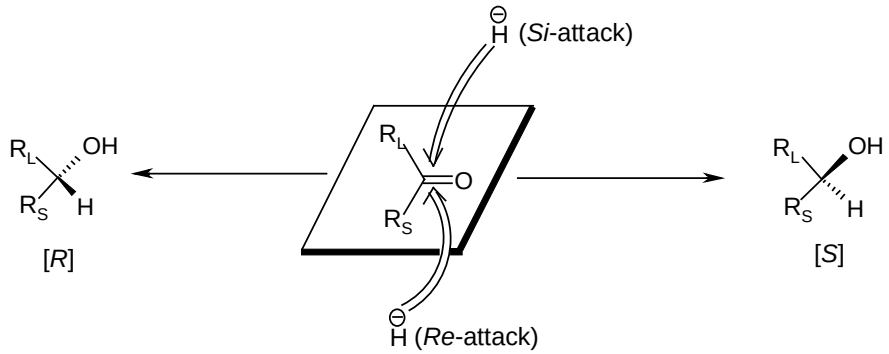
Similar type of transition state model was proposed by Kobayashi in 1994 for BINOL/ $Sc(OTf)_3$ catalyzed Diels-Alder reaction.[10]

Section 3B

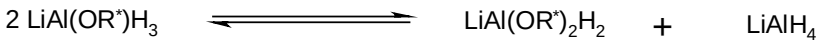
Reduction of acetophenone

Introduction

The reduction of prostereogenic ketones with an optically active reducing agent is a conceptually simple approach to enantiomerically enriched secondary alcohols.



This approach has been studied for a long time now.[11] Although early results were not encouraging , more recent results have provided secondary alcohols in upto 100% *ee*. These reductions can now be used as important steps in the construction of optically active materials. Historically, the LAH based reagents were the first effective reducing agents[12] and borohydride reagents[13] were not as effective. Chiral lithium aluminium alkoxy hydrides have been in use since 1951 when Bothner utilized an LAH/camphor complex.[11] Since then many studies have been directed to determine methods for increasing the stereoselectivity of the reductions. Early work gave poor results since the chiral groups used were alkoxy ligands which were susceptible to disproportionation in solution. This disproportionation gave rise to more than one hydride species in solution.



In the work by McMohon et. al., the reduction of 3,3,5-trimethyl cyclohexanone with tert-butoxyaluminium hydride, mono-tert-butoxyalumino hydride is almost likely the species responsible for the observed streoselectivity.[14] In presence of di- and tri-tert-butoxyalumino hydride, the lithium cation is associated with more than one O-atom and is therefore less selective. In presence of chiral rigid diol ligands the optical yield increases as each hydride is replaced. The use of chiral alkoxy hydrides,[15] namely the bis(alkoxy)aluminium hydride (Figure 3) of primary alcohols, increased due to their stability towards disproportionation. When (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl) cyclopentanone (**14**) was reacted with LAH, two hydrides remain in **15**, one hindered (*syn*) and one unhindered (*anti*) hydride (Figure 3). The effect of replacing the less hindered hydride with an achiral hydride, for the reduction of acetophenone, was studied by Johnson and Klein.[15]

Figure 3.

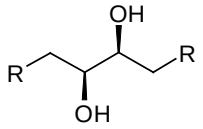
14 **15**

Vigneron et. al. have obtained optical yields of upto 89% in the reduction of aryl alkyl ketones with reagents of the type $LiAlH(OR)(OR')_2$ where R= (-)-N-methylephedrine and R′= 3,5-dimethylphenol.[16]

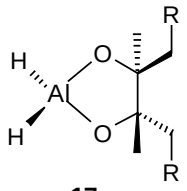
Over the years there have been many attempts to effect asymmetric induction with alkoxy modified aluminium and boron hydride reagents derived from C_2-Symmetric chiral diols. Seebach et. al. found that C_2-Symmetric N- and O-substituted chiral diols $\mathbf{16_{a\text{-}g}}$ (Figure 4) were

effective as chiral ligands in the reduction of aryl alkyl ketones.[17] The diols react with LAH to give complexes, for which a cyclic structure **17** was proposed. The enantiomeric excess were in the range of 0.8-45%.

Figure 4.



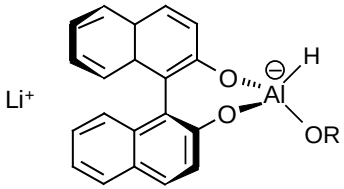
	R
16a	NMe_2
b	Pyrrolidine
c	Piperidine
d	$NMe(C_8H_{17})$
e	NMePh
f	OMe
g	OPh



17

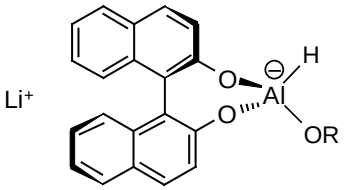
The use of BINAL-H **18** and **19** (Figure 5) in the reduction of aryl alkyl ketones was found to be excellent because of its stability over time and easy availability of the ligand.[18] The optical yields from binal-H were atleast 60% and 100%.

Figure 5.



18

R= alkyl group



19

The asymmetric reductions using trialkyl borohydrides have not seen much success. The enantioselectivity obtained for the reduction of a variety of ketones were in the range of 25-55%. The solubility of $NaBH_4$ in water and its stability to alkali makes it an obvious choice for several attempts at enantioselective reductions in presence of phase-transfer catalysts.

The effect of various parameters like temperature, solvents, substrates and the ligand ratio on the stereoselectivity have been thoroughly studied. Systematic studies on ring size of the lithium or boron complexes of sterically constrained C_2-Symmetric chiral diols would be an important aspect for investigation. This section deals with this aspect.

Results and discussion

In our present study, we have prepared few chiral aluminium (**20**-**22**) and boron hydrides (**23**-**25**) from C_2-Symmetric chiral diols **1**, **2** and **3** (eq 6).

(6)

(Chiral diol)

Chiral diol= (*R*,*R*)-**1**,
(*R*,*R*)-**2**,
(*R*,*R*)-**3**

MH_4= $LiAlH_4$, $NaBH_4$

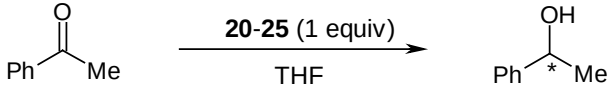
20, MH_4= LAH, diol= (*R*,*R*)-**1**
21, , diol= (*R*,*R*)-**2**
22, , diol= (*R*,*R*)-**3**

23, MH_4=$NaBH_4$, diol= (*R*,*R*)-**1**
24, , diol= (*R*,*R*)-**2**
25, , diol= (*R*,*R*)-**3**

The in situ generated complex hydrides (**20**-**25**) showed different level of asymmetric induction for the reduction of acetophenone. Chiral aluminium hydrides were found to be better reducing agents than boron hydrides.

In the presence of chiral aluminium hydrides, the enantiomeric excess was in the range of 2-40%. The chiral complex **22** derived from TADDOL (**3**) provided highest enantioselectivity (35%) at 0 ^{o}C. Lowering the temperature to –78 ^{o}C did not significantly increase the selectivity (40% *ee*). The five-membered aluminium hydride complex **21** derived from 1,2-diol **2** provided almost racemic (2% *ee*) alcohols whereas the chiral hydride **20** prepared from the new 1,3-diol **1** provided only 5% *ee* under identical reaction condition (entry 1 and 2 in Table 3). As for the reactivity, the complex **21** was most reactive since the reaction was over within 30 minutes yielding 85% product at 0 ^{o}C. The six-membered hydride complex **20** was found to be least reactive giving only 56% yield after 6 h at 0 ^{o}C. Intermediate reactivity was observed for complex **22**. Low temperature (-78 ^{o}C) gave diminished yield for all the complexes. It has been clearly understood that the enantioselectivity is sensitive to the nature of the ligands. The temperature did not have much influence on enantioselectivity for above types of chiral aluminium hydrides. The chiral aluminium complexes **20**, **21** and **22** provided the product alcohol with *R*-, *R*- and *S*-configurations respectively.

Table 3: *Chiral hydride complexes (**20**-**25**) mediated reduction of acetophenone.*



26

Entry	Complex	Temp (^{o}C)	Time (h)	Yield[a] (%)	*ee*[b] (%)	Configuration[c]
1	**20**	0	6	56	5	*R*
2	**21**	0	0.5	85	2	*R*
3	**22**	0	2	72	35	*S*
4	**20**	-78	8	62	8	*R*

5	**21**	-78	3	50	12	*R*
6	**22**	-78	5	45	40	*S*
7	**23**	80	2	86	2	*R*
8	**24**	25	3	95	3	*R*
9	**25**	25	6	92	2	*S*

[a]After distillation; [b]comparison with literature rotation; [c]by literature comparison

Chiral boron reagents (**23**-**25**) were observed to be less reactive as well as selective compared to the aluminium reagents (**20**-**22**) for the reduction of acetophenone. When we performed the reduction of acetophenone at 0^{o}C, the reaction was found to be very slow. Therefore we decided to carry out the comparison study for the chiral boron reagents (**23**-**25**) at room temperature. Significant reactivity difference however, was observed for these chiral boron reagents. The reduction of the ketone using the complex **23** derived from 1,2-diol **2** was extremely sluggish

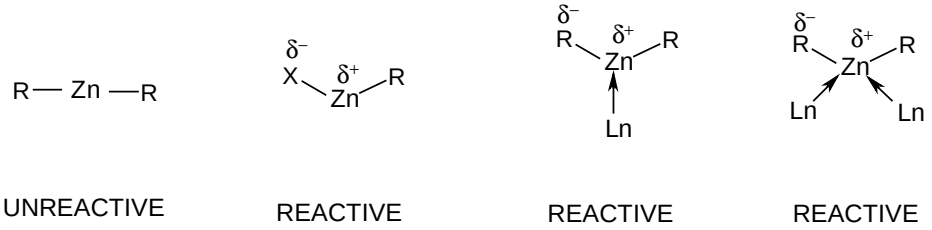
at room temperature but it provided 86% yield after 2 h at 80 ^{o}C whereas **24** and **25** furnished 95% and 92% yields respectively at room temperature itself (Table 3).

Section 3C

Addition of diethylzinc to benzaldehyde

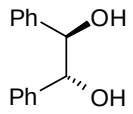
Introduction

The asymmetric addition of diorganozinc to aromatic aldehydes is one of the most reliable methods for the construction of C-C bond affording chiral hydroxy compounds. The reactivity of the diorganozinc can be attributed to the structural deformation through the coordination of an electronegative atom like oxygen or nitrogen. An unreactive linear state to reactive tetrahedral geometry is the driving force.

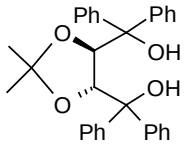


Several highly efficient chiral catalysts based on chiral amino alcohols and diols with or without extra metals such as Ti(IV) have been used for this reaction.[19] Amongst organozinc reagents, the asymmetric addition of diethylzinc to aromatic aldehydes has been most successful and convenient reaction. Without the use of Ti(IV)-coordination, the diols themselves often show lower catalytic activity and selectivity for this reaction.[19] Earlier our group showed that chiral hydrobenzoin (**2**) (a 1,2-diol) is a superior ligand than TADDOL (**3**) (a 1,4-diol) (Figure 6).[20]

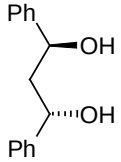
Figure 6.



(*S,S*)-**2**, 89% *ee*



(*R,R*)-**3**, 44% *ee*



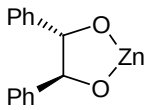
(*S,S*)-**27**, no reaction

To date, only one C_2-Symmetric 1,3-diol, *viz*. 1,3-diphenylpropane diol (**27**) has been examined as a ligand, although without exhibiting any catalytic effect.[20] We asked ourselves whether the C_2-Symmetric 1,3-diols in general are inefficient as catalysts in this reaction. Therefore we decided to investigate the efficacy of our chiral 1,3-diol **1** with respect to other C_2-Symmetric chiral diols showed in Figure 6. In this section we present our results dealing with this aspect.

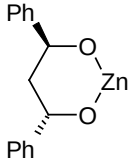
Results and discussion

Ishimori et. al. showed that the reaction of diethylzinc with primary, secondary and tertiary alcohols takes place rapidly to give the corresponding mono-alkoxide. Further reaction of mono-alkoxide with alcohols is very slow.[21] Our group synthesized few chiral zinc-dialkoxides (*S,S*)-**28**, (*S,S*)-**29** and (*R,R*)-**30** by heating equimolar quantity of diethylzinc with the diols (*S,S*)-**2**, (*S,S*)-**27** and (*R,R*)-**3** respectively (Figure 7).

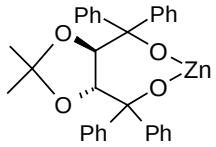
Figure 7.



(*S*,*S*)-**28**



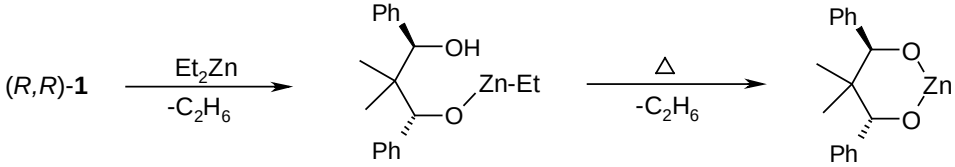
(*S*,*S*)-**29**



(*R*,*R*)-**30**

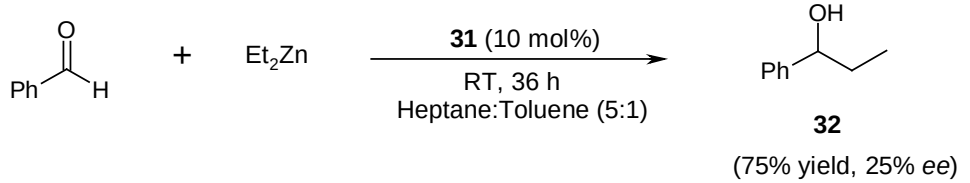
Similarly (*R*,*R*)-**31** was prepared by heating (80 ^{o}C, 30 minutes) equimolar quantity of diethylzinc with the diol (*R*,*R*)-**1** (Scheme 3).

Scheme 3



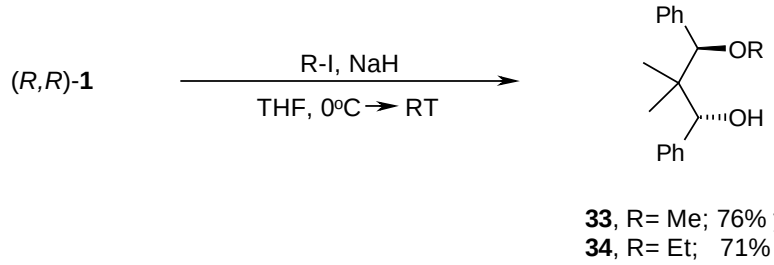
(*R*,*R*)-**31**

We then examined the zinc-alkoxide (*R*,*R*)-**31** as catalyst in addition of diethylzinc to benzaldehyde. **31** Did catalyze the reaction providing 75% yield with a moderate enantioselectivity at room temperature (25% *ee*) (eq 7).



(7)

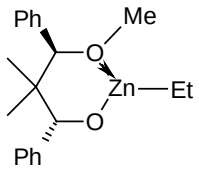
This result prompted us to investigate the effect of other factor like 'basicity' of ligand's oxygen in order to optimize both the yield and enantioselectivity in this reaction. To do so, we synthesized the monomethyl (*R,R*)-**33** and monoethyl ether (*R,R*)-**34** from the diol (*R,R*)-**1** following the procedure outlined in eq 8.



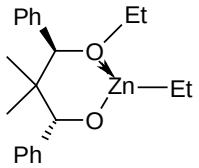
(8)

We then prepared the chiral zinc-alkoxides (*R,R*)-**35** and (*R,R*)-**36** by stirring equimolar quantity of diethylzinc with (*R,R*)-**33** / (*R,R*)-**34** at room temperature for 30 minutes (Figure 8). The enantioselectivity increased substantially to 62% and 70% when (*R,R*)-**35** and (*R,R*)-**36** were used as catalyst respectively at room temperature (entry 4 and 5 in Table 4).

Figure 8.



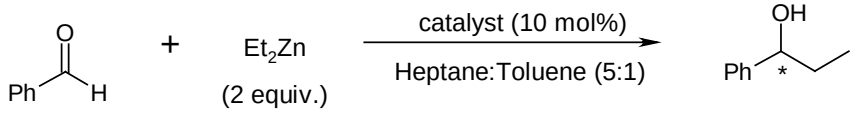
(*R*,*R*)-**35**



(*R*,*R*)-**36**

Lowering the temperature from 25 to 0 ^{o}C diminished both yield (47%) and the enantioselectivity (34%) when **36** was the catalyst. This observation supports oligomerization of the catalyst at low temperature. The polymeric nature of the catalyst **36** was destroyed by raising the temperature to 50 ^{o}C and consequently higher yield (91%) and enantioselectivity (72%) was obtained (entry 7 in Table 4).

Table 4. *Addition of diethylzinc to benzaldehyde*



Entry	catalyst	Temp (^{o}C)	Time (h)	Yield[a] (%)	*ee*[b] (%)	Configuration
1	(*R*,*R*)-**28**	25	18	98	89	*S*
2	(*R*,*R*)-**29**	25	48	c	-	-
3	(*R*,*R*)-**30**	25	48	65	44	*R*
4	(*R*,*R*)-**31**	25	48	75	25	*R*
5	(*R*,*R*)-**35**	25	8	81	62	*R*

6	(*R*,*R*)-**36**	25	4	91	70	*R*
7	(*R*,*R*)-**36**	0	36	47	34	*R*
8	(*R*,*R*)-**36**	50	2	91	72	*R*

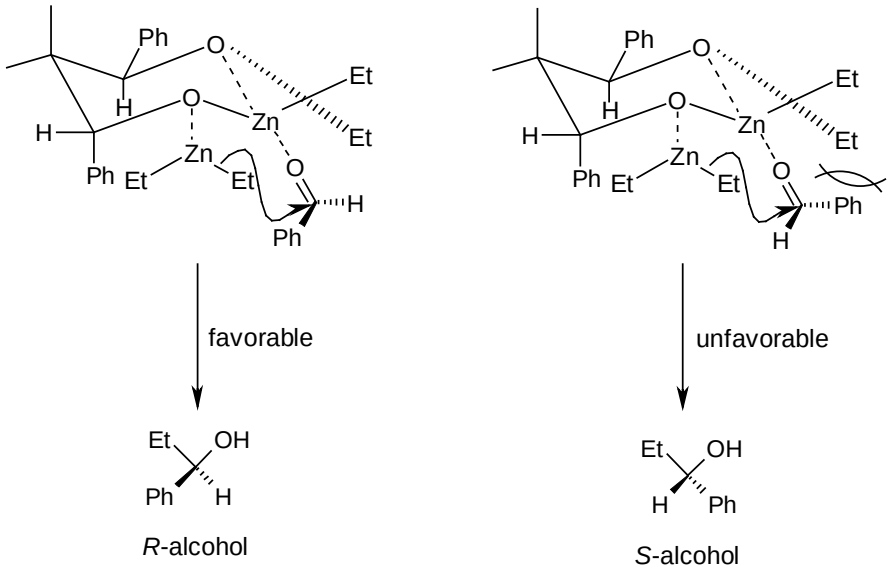
[a]After column chromatography; [b]Comparison with literature rotation; [c]No appreciable reaction

The results obtained from diol **1** and its derivatives may be inferior to 1,2-diol **2**, but much better than that of 1,4-diol **3**, as shown by our group earlier.[20]

Mechanism:

The stereochemical outcome in the product could be explained by the proposed transition state model depicted in Figure 8.

Figure 8.



The ether alkyl group is assumed to play the crucial role for enantioenriched formation of *R*-alcohol as shown in Figure 8. A strong phenyl-alkyl steric interaction is believed to be the driving force for the stereochemical outcome of the reaction.

1. In situ generated chiral titanate complexes derived from (*R*,*R*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol, (*R*,*R*)-hydrobenzoin and (*R*,*R*)-TADDOL promoted the Diels-Alder reaction between cyclopentadiene and dimethylfumarate at –20 ^{o}C. But these complexes failed to induce significant chirality.
2. (*R*,*R*)-2,2-dimethyl-1,3-diphenyl-1,3-propane diol was found to be superior than (*R*,*R*)-hydrobenzoin and (*R*,*R*)-TADDOL in $Sc(OTf)_3$ catalyzed Diels-Alder reaction between cyclopentadiene and 3-crotonoyloxazolidin-2-one.
3. In situ generated chiral aluminium and boron hydride complexes derived from (*R*,*R*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol, (*R*,*R*)-hydrobenzoin and (*R*,*R*)-TADDOL have been examined as chiral inducer for the reduction of acetophenone. (*R*,*R*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol was found to be inferior to TADDOL but better than hydrobenzoin.
4. The new 1,3-diol, (*R*,*R*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol was found to catalyze the addition of diethylzinc to benzaldehyde with good yield but moderate enantioselectivity. Monoethyl derivative improved the reactivity as well as selectivity. These results were inferior to those obtained using hydrobenzoin (a 1,2-diol), but much better than that with TADDOL (a 1,4-diol).

Experimental

General:

Tetrahydrofuran was freshly distilled from benzophenone ketyl. Others anhydrous solvents were obtained following the standard procedure and stored over 4A molecular sieves.[22] Menthoxyacetic acid and its acid chloride was synthesized according to the procedure described in chapter 2. Cyclopentadiene was cracked from dicyclopentadiene and used freshly. Benzaldehyde was purified prior to use by standard procedures.

Preparation of chiral hydrobenzoin (**2**) :

To a 1M CH_2Cl_2 solution of (-)-menthoxyacetyl chloride (13.9 g, 60 mmol), a solution of (±)-**2** (5.35 g, 25 mmol) in pyridine (7.9 g, 100 mmol) and 20 mL CH_2Cl_2 was added at 0 ^oC. Then ice-bath was removed and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water, saturated $NaHCO_3$ and brine. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethylacetate-petroleum ether as the eluent to obtain corresponding

diester (14.3 g, 97%) of (±)-**2** as pure white solid. After three consecutive recrystallization from ethanol diastereomeric diesters were separated. Saponification of solid diester provided optically pure (-)-**2** (40%, >99% *ee*) whereas filtrate diester gave (+)-**2** (42%, 90% *ee*). One crystallization of this optically impure (+)-**2** from aqueous MeOH provided pure (+)-**2** (35%, >99% *ee*).

[TLC data: Solvent = Petroleum ether : EtOAc (4:1), R_f (**2**) = 0.2, R_f (diester) = 0.75]

Optically pure (+)-**2** :

Yield	2.14 g (40%)	
mp.	147-148 ^{o}C	(lit.[23] 148-149 ^{o}C)
$[\alpha]_D$	+94 (*c* 1, EtOH)	[lit.[23] +94.0 (*c* 1, EtOH)
ee	>99%	
^{1}H NMR ($CDCl_3$)	δ 2.90 (br. s, 2H, -O**H**), 4.60 (s, 2H, -C**H**Ph), 7.05 (m, 4H, -$\mathbf{H}_{Ar.}$), 7.15 (m, 6H, -$\mathbf{H}_{Ar.}$).	

Optically pure (-)-**2** :

Yield	1.87 g (35%)	
mp.	148-149 ^{o}C	(lit.[23] 148-149 ^{o}C)
$[\alpha]_D$	-94 (*c* 1, EtOH)	[lit.[23] -94.1 (*c* 1, EtOH)
ee	>99%	

Preparation of (R,R)-TADDOL (**3**) :

In a 1L three-necked flask, equipped with a reflux condenser and a dropping funnel, was placed magnesium turnings (24.3 g, 1 mol) in an argon atmosphere. Dry THF (20 mL) was added to cover the magnesium and the reaction started through addition of 2 mL bromobenzene and heating to reflux. The remaining bromobenzene (78.5 g, 0.5 mol) dissolved in 100 mL of dry THF was added at such a rate that a moderate reflux is maintained. After the addition was complete (1.5 h), the solution was further refluxed for 1 h. The brown Grignard solution was then cooled to room temperature and diluted with 200 mL of THF, and then cooled to 0 ^{o}C. To this mixture, (4*R*, 5*R*)-2,2-dimethyl-1,3-dioxolan-4,5-dicarboxylate-dimethyl ester (10.9 g, 50 mmol) (dissolved in 50 mL THF) was added from the dropping funnel. A vigorous reaction was observed and a yellow solid precipitated out. After the addition was complete (1.5 h), the reaction mixture was refluxed for 2 h and then stirred for an additional 4 h at room temperature. The flask was then placed in an ice-bath and the mixture was hydrolyzed by the slow addition of 300 mL of saturated NH_4Cl solution. The organic layer was separated and the aqueous phase was extracted four times with ether. The combined organic extract was washed twice with brine, dried over Na_2SO_4 and concentrated. The crude product was suspended in petroleum ether (100 mL) and stirred for 1 h at room temperature. The product was filtered and washed with 100 mL petroleum ether. Finally it was recrystallized from aqueous MeOH to obtain a white solid.

[TLC data:	Solvent = Petroleum ether : EtOAc (9:1), R_f (ester) = 0.61, R_f (**3**) = 0.23]	
Yield	12.7 g (55%)	
mp.	199-200 ^{o}C	(lit.[2] 190-192 ^{o}C)
$[\alpha]_D$	-69.1 (*c* 1, $CHCl_3$)	[lit.[2] –68.5 (*c* 1, $CHCl_3$)
^{1}H NMR ($CDCl_3$)	δ 1.06 (s, 6H, -C**H**$_3$), 4.12 (s, 2H, -O**H**), 4.62 (s, 2H, -C**H**), 7.25-7.38 (m, 16H, -**H**$_{Ar.}$), 7.53-7.60 (m, 4H, -**H**$_{Ar.}$).	

***General procedure for cycloaddition reaction using 1 molar equiv. of chiral titanate reagents* 4-6** :

To a 1M CH_2Cl_2 solution of dichlorodiisopropoxy titanium (1 mL, 1 mmol), was added a 1M CH_2Cl_2 solution (1 mL) of the chiral diol **1-3** (1 mmol) and MS 4A (500 mg). The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and CH_2Cl_2 (3 mL) was added. The mixture was cooled to –20 ^oC and then a CH_2Cl_2 solution (2 mL) of dimethyl fumarate (144 mg, 1 mmol) was added to the reaction mixture followed by cyclopentadiene (0.33 g, 5 mmol). After the disappearane of dimethylfumarate, the reaction mixture was quenched with 1N HCl and filtered. The organic layer was separated and washed with brine and dried over Na_2SO_4. Following evaporation of the solvent, the crude product was purified by column chromatography using silica gel (100-200 mesh) and petroleum ether-EtOAc (20:1) as eluent to give the pure cycloadduct **7** as a liquid. Enantiomeric excesses were determined by ^1H NMR using lanthanide shift reagent (LSR), $Eu(hfc)_3$. Satisfactory splitting was observed for methyl of *endo*-ester group at 3.65 ppm). After splitting two signals for two enantiomers, appreared at 3.91 and 3.92 ppm respectively. Integral area of the signals provided us the enantiomeric ratio.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (dimethylfumarate) = 0.27, R_f (**7**) = 0.22]

IR (neat) cm^{-1} 1737 (>C=O)

^1H NMR ($CDCl_3$) (500 MHz) δ 1.46 (ddd, *J* 1.6, 1.8, 8.8 Hz, 1H, -C**H**$_2$), 1.63 (d, *J* 8.7 Hz, 1H, -C**H**$_2$), 2.69 (dd, *J* 1.6, 4.5 Hz, 1H, -C**H**), 3.13 (br.s, 1H, -C**H**), 3.28 (br.s, 1H, -C**H**), 3.38 (t, *J* 4.1 Hz, 1H, -C**H**), 3.65 (s, 3H, -COOC**H**$_3$), 3.72 (s, 3H, -COOC**H**$_3$), 6.07 (dd, *J* 2.8, 5.7 Hz, 1H, =C**H**), 6.28 (dd, *J* 3.2, 5.5 Hz, 1H, =C**H**).

***General procedure for cycloaddition reaction using 0.2 molar equiv. of chiral titanate reagents* 4-6** :

These reactions were performed following the similar procedure described for the above stoichiometric reactions. Instead of 1 mmol, 0.2 mmol of chiral titanium catalysts **4-6** was used.

***Synthesis of 3-crotonoyloxazolidin-2-one* (11)**[9a] :

To a solution of 2-oxazolidinone (3.28 g, 40 mmol) in anhydrous THF (~ 0.3 M) at –78 ^{o}C, was added ^{n}BuLi (1 mol equiv. in hexane solution). After 15 minutes, freshly distilled crotonoyl chloride (4.97 g, 48 mmol) was added. The mixture was stirred at –78 ^{o}C for 30 minutes and at 0 ^{o}C for 15 minutes. The reaction was then quenched with excess saturated NH_4Cl solution and the solvent evaporated under reduced pressure. The resulting slurry was diluted with CH_2Cl_2, and washed with $NaHCO_3$ and brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography using silica gel (100-200 mesh) and petroleum ether-EtOAc as eluent to give a colourless liquid.

[TLC data: Solvent = Petroleum ether : EtOAc (3:2), R_f (2-Oxazolidinone) = 0.04, R_f (**11**) = 0.47]

Yield 4.5 g (73%)

^{1}H NMR ($CDCl_3$) δ 1.97 (d, *J* 5.4 Hz, 3H, -C**H**$_3$), 4.07 (t, *J* 8.3 Hz, 2H, -NC**H**$_2$),

4.44 (t, *J* 8.3 Hz, 2H, -OC**H**$_2$), 6.95-7.40 (m, 2H, =C**H**).

Representative procedure for Diels-Alder reaction with Sc(OTf)$_3$/chiral diol complex (entry 2 in table-2) :

Under an argon atmosphere, Sc(OTf)$_3$ (49 mg, 0.1 mmol) and MS 4A (300 mg) were placed in a 50-mL two necked flask. The flask was heated to 180 ^{o}C under vacuum for 3 h. After cooling to room temperature, a magnetic stirring bar was placed inside the flask, and flushed with argon. CH_2Cl_2 (4 mL) Was introduced through the rubber septum and the flask was cooled to 0 ^{o}C. A CH_2Cl_2 (2 mL) solution of (*R,R*)-**1** (31 mg, 0.12 mmol) and 2,6-lutidine (26 mg, 0.24 mmol) was then introduced, and the mixture was stirred for 0.5 h at the same temperature. 3-Crotonoyloxazolidin-2-one (**11**) (155 mg, 1 mmol) in CH_2Cl_2 (2 mL) and cyclopentadiene (330 mg, 5 mmol) was successively added and the resulting mixture was stirred at 0 ^{o}C. After the disappearance of **11**, the reaction mixture was quenched with water, and the solution was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. A liquid mixture of *endo*- and *exo*-adducts **13** were isolated by column chromatography using silica gel (100-200 mesh) and petroleum ether-EtOAc as eluent. The ratio of *endo*- and *exo*- isomer was determined by ^{1}H NMR. The *endo*-methyl group of *exo*-cycloadduct being more shielded appeared at 0.86 ppm while the *exo*-methyl group of *endo*-cycloadduct at 1.13 ppm. The area of the two signals provided the ratio of *endo*- and *exo*- isomer.

[TLC data: Solvent = Petroleum ether : EtOAc (3:2), R_f (**11**) = 0.47, R_f (**13**) = 0.58]

Yield 164 mg (74%)

$[\alpha]_D$ +92 (*c* 3.5, CCl_4) [lit.[9b] –191 (*c* 3.6, CCl_4) for 92% *ee* of 1*S*$^{/}$,2*S*$^{/}$,3*R*$^{/}$,4*R*$^{/}$]

ee 45% of (1*R*$^{/}$,2*R*$^{/}$,3*S*$^{/}$,4*S*$^{/}$)-isomer

Endo: Exo 89:11 (by ^{1}H NMR)

^{1}H NMR ($CDCl_3$) δ 0.86 (C**H**$_{3\ endo}$), 1.13 (C**H**$_{3\ exo}$), 1.46 (dd, *J* 1.7, 8.5 Hz, 1H, -C**H**$_2$), 1.71 (d, *J* 8.7 Hz, 1H, -C**H**$_2$), 2.05-2.19 (m, 1H, -C**H**), 2.53 (br.s, 1H, -C**H**), 3.28 (br.s, 1H, -C**H**), 3.54 (t, *J* 3.8 Hz, 1H, -C**H**), 3.90-4.10 (m, 2H, -NC**H**$_2$), 4.39 (t, *J* 8.1 Hz, 2H, -OC**H**$_2$), 5.78 (dd, *J* 2.8, 5.6 Hz, 1H, =C**H**), 6.37 (dd, *J* 3.2, 5.6 Hz, 1H, =C**H**).

Representative procedure for chiral aluminium hydride reagents mediated reduction of acetophenone :

To a well stirred suspension of LAH (84 mg, 2.2 mmol) in anhydrous THF (5 ml), was added a solution of diol **3** (1 g, 2.2 mmol) in anhydrous THF (3 ml) at 0 ^{o}C and stirred for 0.5 h. The reaction mixture was cooled to –78 ^{o}C and a solution of acetophenone (240 mg, 2 mmol) in anhydrous THF (1 ml) was added at –78 ^{o}C, and stirring was continued for 8 h. The reaction mixture was quenched successively with MeOH (1 ml) and water (1 ml) at 0 ^{o}C and stirred for 0.5 h at room temperature. Ether was added to dilute the reaction mixture and the organic layer was then separated. The aqueous layer was extracted with ether (10 ml x 2). Usual work-up provided 2-phenylethanol (**26**) which was purified by Kugehl-Rohr distillation.

[TLC data: Solvent = Petroleum ether : EtOAc (4:1), R_f (acetophenone) = 0.78, R_f (**26**) = 0.38]

Yield 110 mg (45%)

bp. 120-125^o (bath temp)/20 mm Hg

$[\alpha]_D$	-17.4 (neat)	[lit.[24] +43.6 (neat) of (*R*)-enantiomer]
ee	40% of (*S*)-enantiomer	
^{1}H NMR ($CDCl_3$)	δ 1.5 (d, *J* 7.2 Hz, 3H, -C**H**$_3$), 2.25 (br.s, 1H, -O**H**), 4.85 (q, *J* 7.2 Hz, 1H, -C**H**Ph), 7.2-7.4 (m, 5H, -**H**$_{Ar.}$).	

Representative procedure for chiral boron hydride reagents mediated reduction of acetophenone :

A mixture of $NaBH_4$ (75 mg, 2 mmol) and (*R*,*R*)-**2** (428 mg, 2 mmol) was stirred in anhydrous THF at room temperature for 1 h and then acetophenone (240 mg, 2 mmol) was added and the mixture stirred for 3 h. The reaction was quenched with successive addition of water (5 mL) and 1N HCl (1 mL) at 0^{o}C and stirred for 15 minutes. It was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (10 mL x 2). Combined organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The product 2-phenyl ethanol (**26**) was distilled using Kugehl-Rohr distillation unit.

Yield	230 mg (95%)	
bp.	120-125^o (bath temp)/20 mm Hg	
$[\alpha]_D$	-1.3 (neat)	[lit.[24] +43.6 (neat) of (*R*)-enantiomer]
ee	3% of (*S*)-enantiomer	

***General procedure for monoalkylation of 1,3-diol* 1** :

To a suspension of NaH (48 mg, 2 mmol) in anhydrous THF (10 mL), was added a solution of (*R,R)*-diol **1** (512 mg, 2 mmol) in anhydrous THF (5 mL) at 0 ^{o}C and stirred it for 0.5 h. Alkyl iodide (2 mmol) was added at the same temperature and then the ice bath was removed. The reaction mixture was allowed to stir at room temperature (8 h for methylation and 36 h for ethylation). Solvent was evaporated and the residue was purified by column chromatography using silica gel (100-200 mesh) and petroleum ether-EtOAc as eluent to obtain the monoalkylated product **33** or **34** as white solid.

[TLC data: Solvent =Petroleum ether : EtOAc (9:1), R_f (**1**) = 0.21, R_f (**33**) = 0.48,

R_f (**34**) = 0.49]

2,2-Dimethyl-1-methoxy-1,3-diphenyl-3-propanol (**33**) :

Yield 0.41 g (76%)

mp. 152-153 ^{o}C

$[\alpha]_D$ -38 (*c* 1, $CHCl_3$)

IR (Nujol) cm^{-1} 3452 (O-H), 3414 (O-H) (one signal for hydrogen-bonded O-H and another for non hydrogen-bonded O-H stretching)

^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H, -C**H**$_3$), 0.84 (s, 3H, -C**H**$_3$), 3.26 (s, 3H, -OC**H**$_3$), 4.13 (s, 1H, -O**H**), 4.64 (d, *J* 5.0 Hz, 1H, -C**H**Ph), 4.73 (d, *J* 5.0

Hz, 1H, -C**H**Ph), 7.15-7.45 (m, 10H, -**H**$_{Ar.}$)

^{13}C NMR ($CDCl_3$)	δ 21.5, 21.6, 41.8, 57.0, 80.2, 90.7, 127.0, 127.4, 127.7, 127.9, 128.5, 137.4, 141.7.
Analysis for	$C_{18}H_{22}O_2$
Calculated (%)	C, 79.96; H, 8.20
Found (%)	C, 80.01; H, 8.47.

2,2-Dimethyl-1-ethoxy-1,3-diphenyl-3-propanol (**34**) :

Yield	0.40 g (71%)
mp.	83 ^{o}C
$[\alpha]_D$	-28 (*c* 1, $CHCl_3$)
IR (Nujol) cm^{-1}	3473 (O-H), 3416 (O-H) (one signal for hydrogen-bonded O-H and another for non hydrogen-bonded O-H stretching)
^{1}H NMR ($CDCl_3$)	δ 0.80 (s, 3H, -C**H**$_3$), 0.88 (s, 3H, -C**H**$_3$), 1.27 (t, *J* 7.0 Hz, 3H, -OCH$_2$C**H**$_3$), 3.20-3.50 (m, 2H, -OC**H**$_2$CH$_3$), 4.21 (s, 1H, -O**H**), 4.64 (d, *J* 4.5 Hz, 1H, -C**H**Ph), 5.02 (d, *J* 4.5 Hz, 1H, -C**H**Ph), 7.15-7.45 (m, 10H, -**H**$_{Ar.}$)

^{13}C NMR ($CDCl_3$)	δ 15.3, 21.4, 22.2, 47.8, 65.0, 79.9, 89.5, 127.0, 127.4, 127.7, 128.0, 128.5, 138.2, 141.8.
Analysis for	$C_{19}H_{24}O_2$
Calculated (%)	C, 80.24; H, 8.50
Found (%)	C, 80.29; H, 8.61.

***General procedure for preparation of zinc di-alkoxides* (28-31)** :

The diol (**2** or **27** or **3** or **1**) (0.5 mmol) in 2 mL toluene was heated (~ 80 ^oC) to dissolve the diol completely and 1M diethylzinc in haptane (0.5 mL, 0.5 mmol) was introduced dropwise at the same temperature. Immediate evolution of ethane was observed. The reaction mixture was kept at 80 ^oC for 0.5 h. A turbid solution of the catalyst (**28** or **29** or **30** or **31** respectively) was obtained which were utilized as it is for alkylation step.

***General procedure for preparation of zinc monoalkoxides* (35-36)** :

To the monoalkylated derivative (**33** or **34**) (0.5 mmol) in 2 mL toluene was added 1M diethyl zinc in haptane (0.5 mL, 0.5 mmol) at room temperature and stirred for 0.5 h to obtain a clear solution of the catalyst (**35** or **36** respectively) which were utilized as it is for alkylation step.

***Addition of diethylzinc to benzaldehyde catalyzed by alkoxide* 31** :

The turbid solution of the catalyst **31** (0.5 mmol) was cooled to 0 ^{o}C and treated with 1M diethylzinc in n-heptane (10 mL, 10 mmol) and benzaldehyde (0.53 g, 5 mmol). The reaction mixture now becomes a clear pale yellow solution. The reaction mixture was gradually allowed to come to room temperature and stirred till TLC indicated the disappearence of benzaldehyde. After 48 h, it was quenched with MeOH (0.5 mL) followed by 1N HCl. The reaction mixture was extracted with ether. The ether extract was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography using silica gel (100-200 mesh) and petroleum ether-EtOAc as eluent to obtain pure product **32** as a liquid.

[TLC data: Solvent = Petroleum ether : EtOAc (9:1), R_f (benzaldehyde) = 0.21,

R_f (**32**) = 0.27]

Yield 510 mg (75%)

$[\alpha]_D$ -11.36 (*c* 5.2, $CHCl_3$) [lit.[25] -45.45 (*c* 5.15, $CHCl_3$)

for the *S*-enantiomer]

ee 25% of (*S*)-enantiomer

^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J* 6.9 Hz, 3H, -C**H**$_3$), 1.85 (m, 2H, -C**H**$_2$), 2.9 (br. s, 1H, -O**H**), 4.6 (t, *J* 6.9, 1H, -C**H**Ph), 7.20-7.50 (m, 5H, -**H**$_{Ar.}$).

***Addition of diethylzinc to benzaldehyde catalyzed by alkoxide* 35 or 36** :

To the clear solution of catalyst (**35** or **36**) (0.5 mmol) was added 1M diethylzinc in n-heptane (10 mL, 10 mmol) and benzaldehyde (0.53 g, 5 mmol) at room temperature. The reaction mixture was stirred at ambient temperature till TLC indicated the

disappearence of benzaldehyde (2-36 h). Thereafter it was quenched with MeOH (0.5 mL) followed by 1N HCl. Usual work-up and purification provided **32**.

Reaction with catalyst **35** at room temperature :

Yield 550 mg (81%)

$[\alpha]_D$ +28.18 (*c* 5.15, $CHCl_3$)

ee 62% of (*R*)-enantiomer.

Reaction with catalyst **36** at room temperature :

Yield 620 mg (91%)

$[\alpha]_D$ +31.81 (*c* 5.15, $CHCl_3$)

ee 70% of (*R*)-enantiomer.

Reaction with catalyst **36** at 0 ^oC :

Yield 320 mg (47%)

$[\alpha]_D$ +15.45 (*c* 5.15, $CHCl_3$)

ee 34% of (*R*)-enantiomer.

Reaction with catalyst **36** at 50 ^{o}C :

Yield	620 mg (91%)
$[\alpha]_D$	+32.72 (*c* 5.15, $CHCl_3$)
ee	72% of (*R*)-enantiomer.

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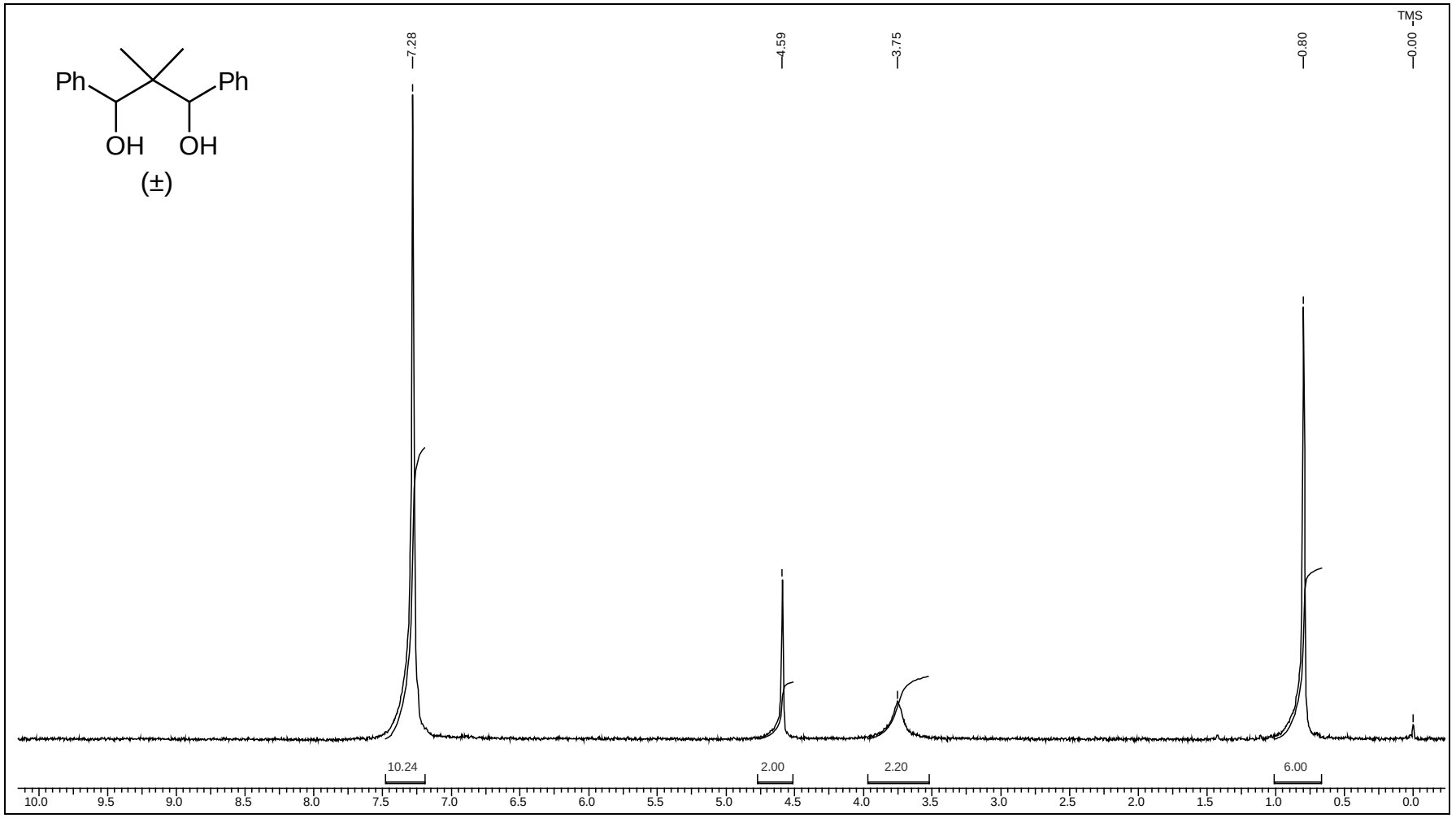
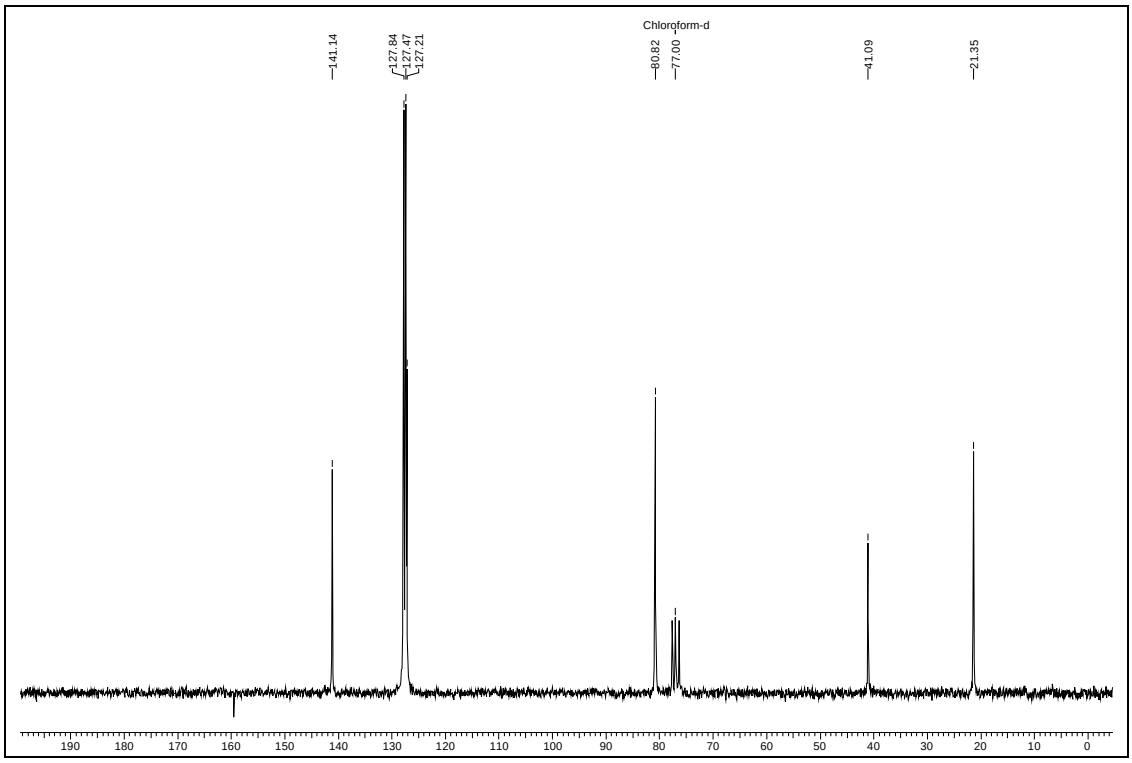
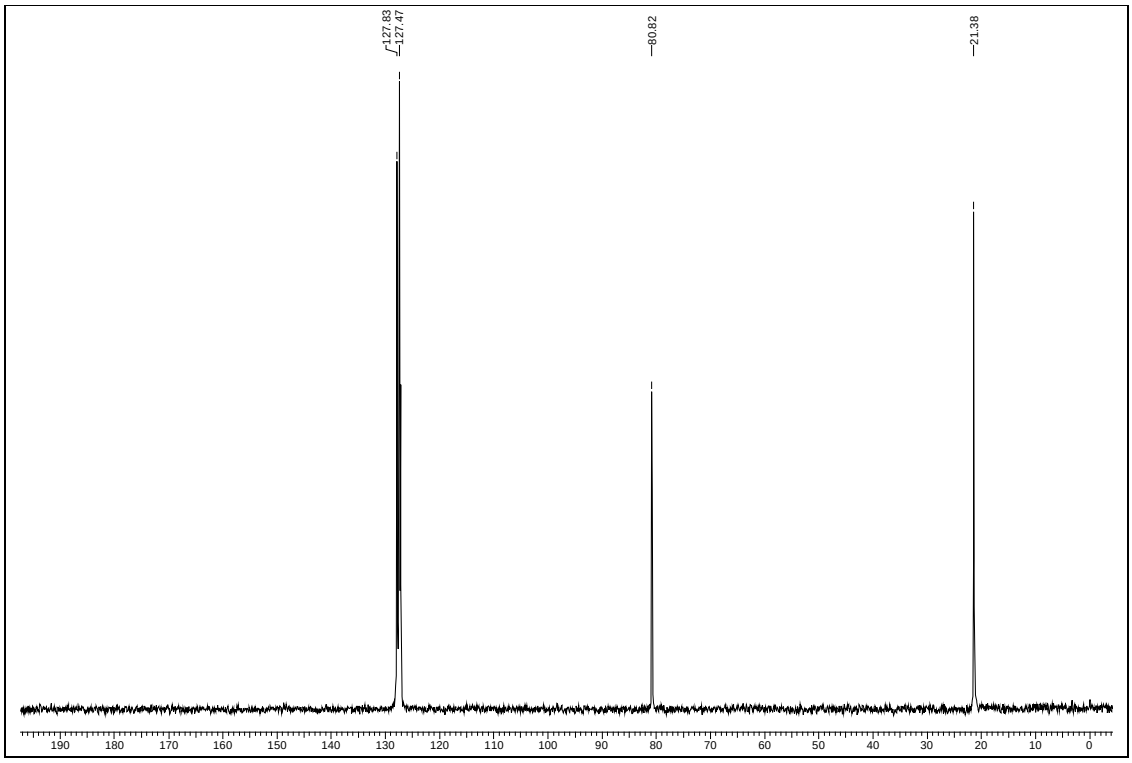


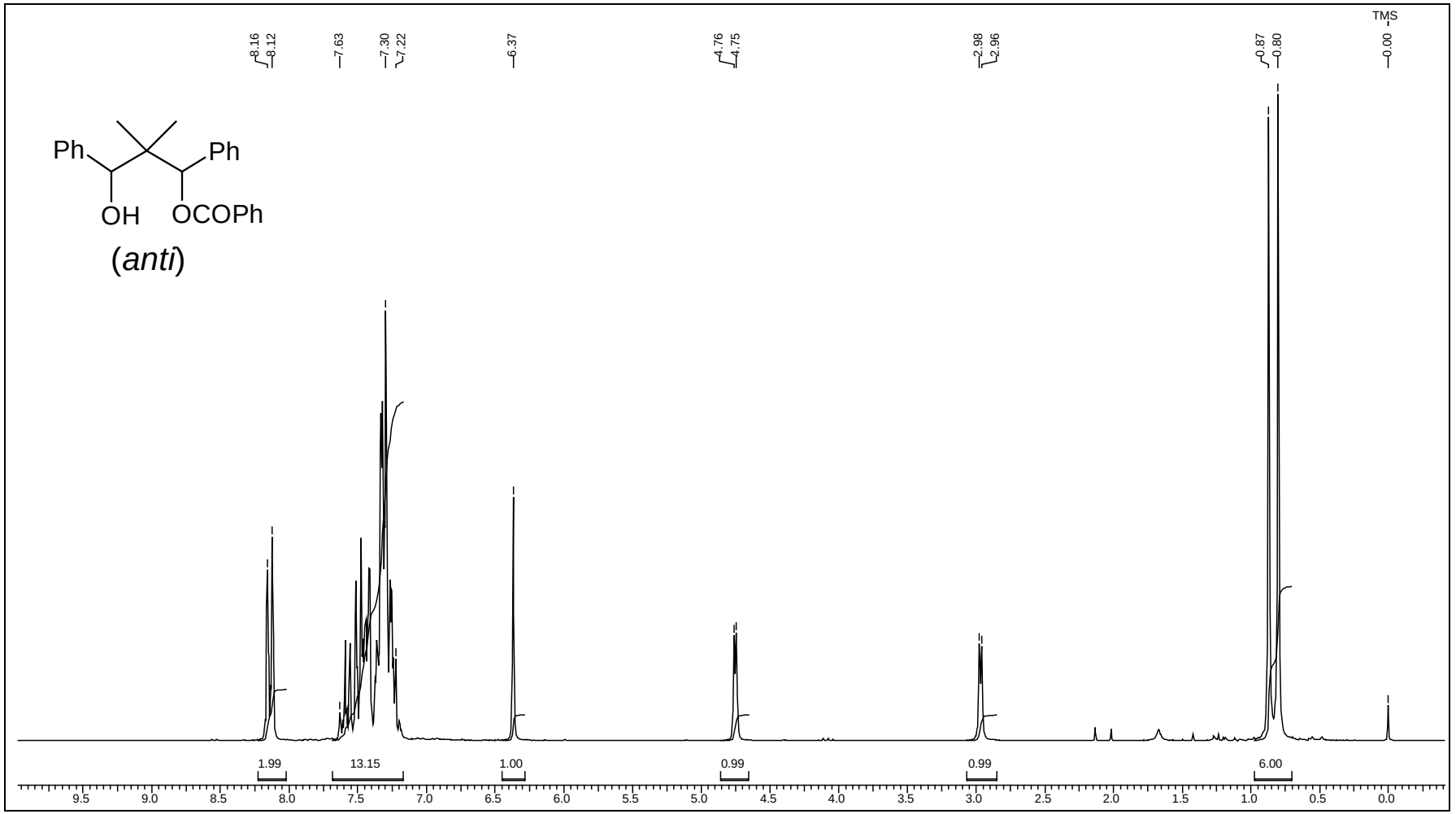
^{1}H NMR spectrum of compound (±)-1



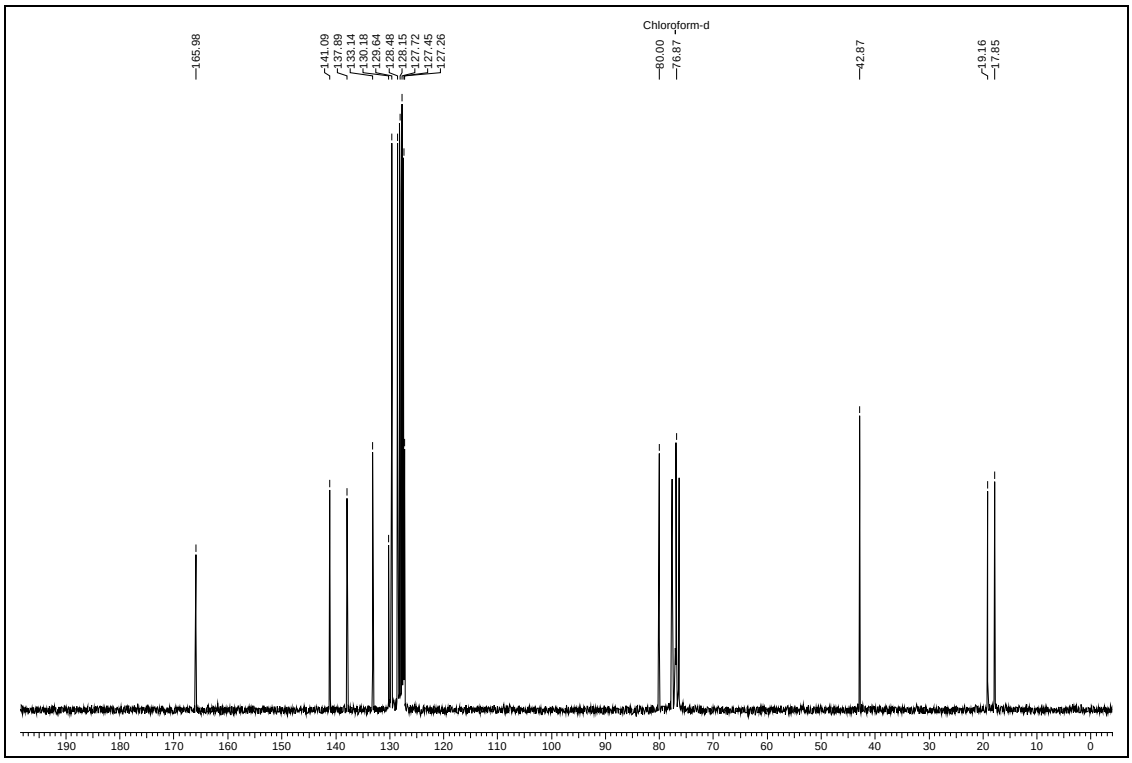
^{13}C NMR spectrum of compound (±)-1



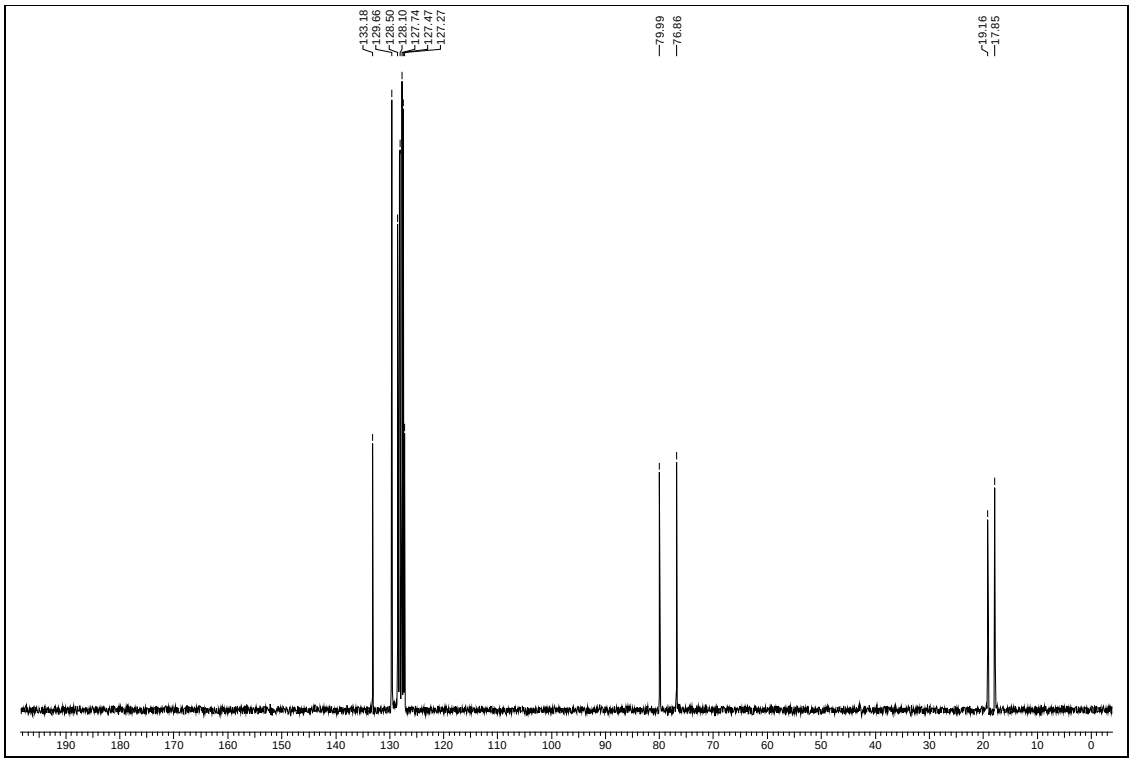
DEPT NMR spectrum of compound (±)-1



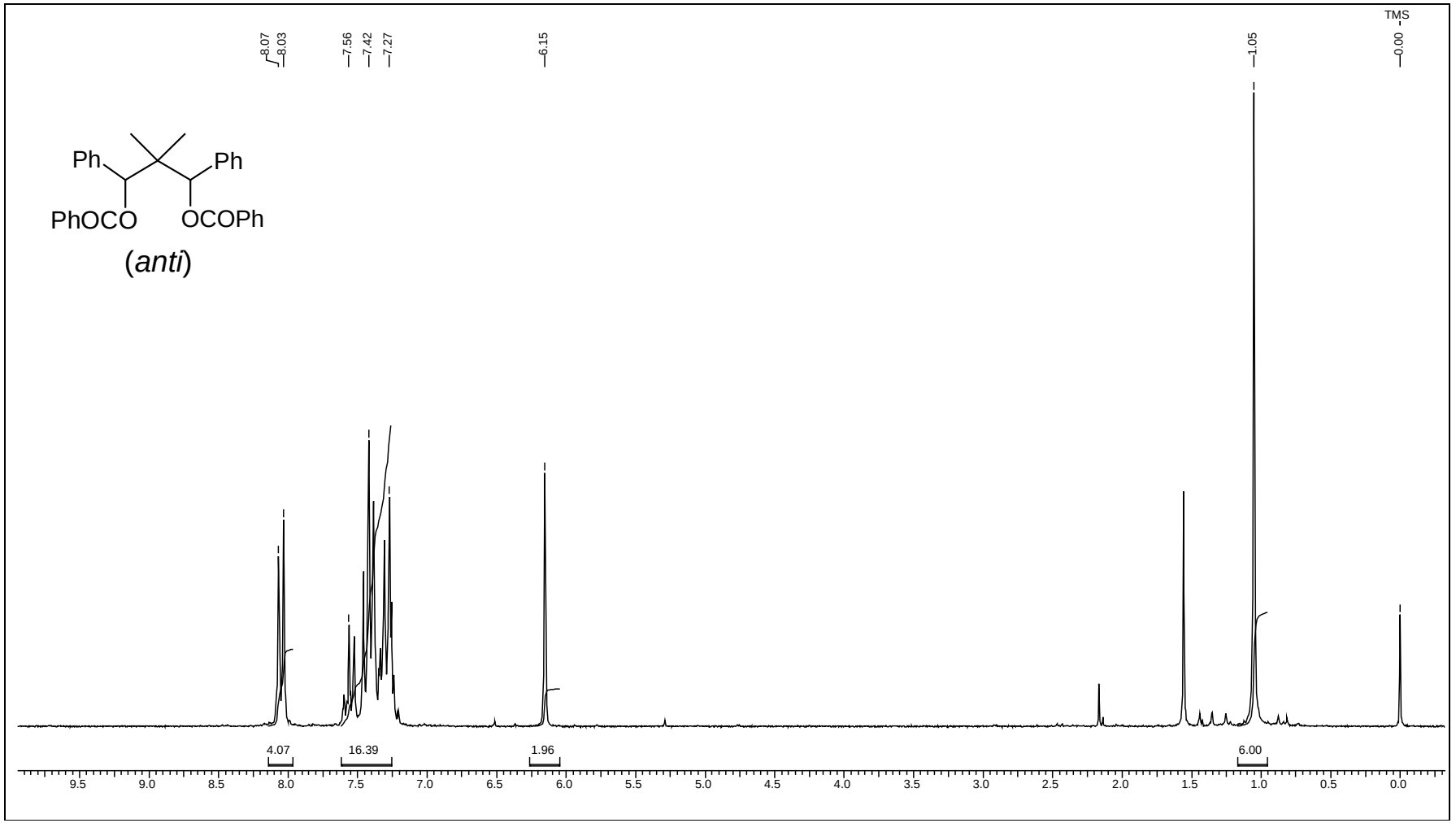
^{1}H NMR spectrum of compound 11



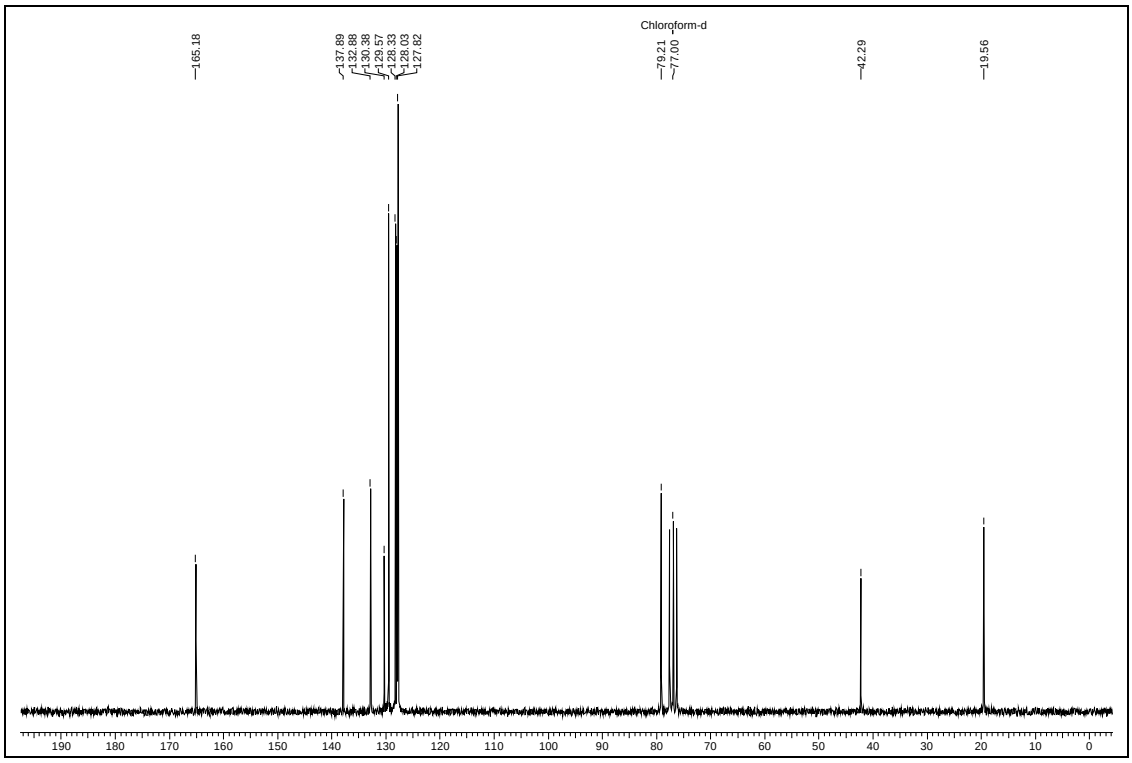
^{13}C NMR spectrum of compound 11



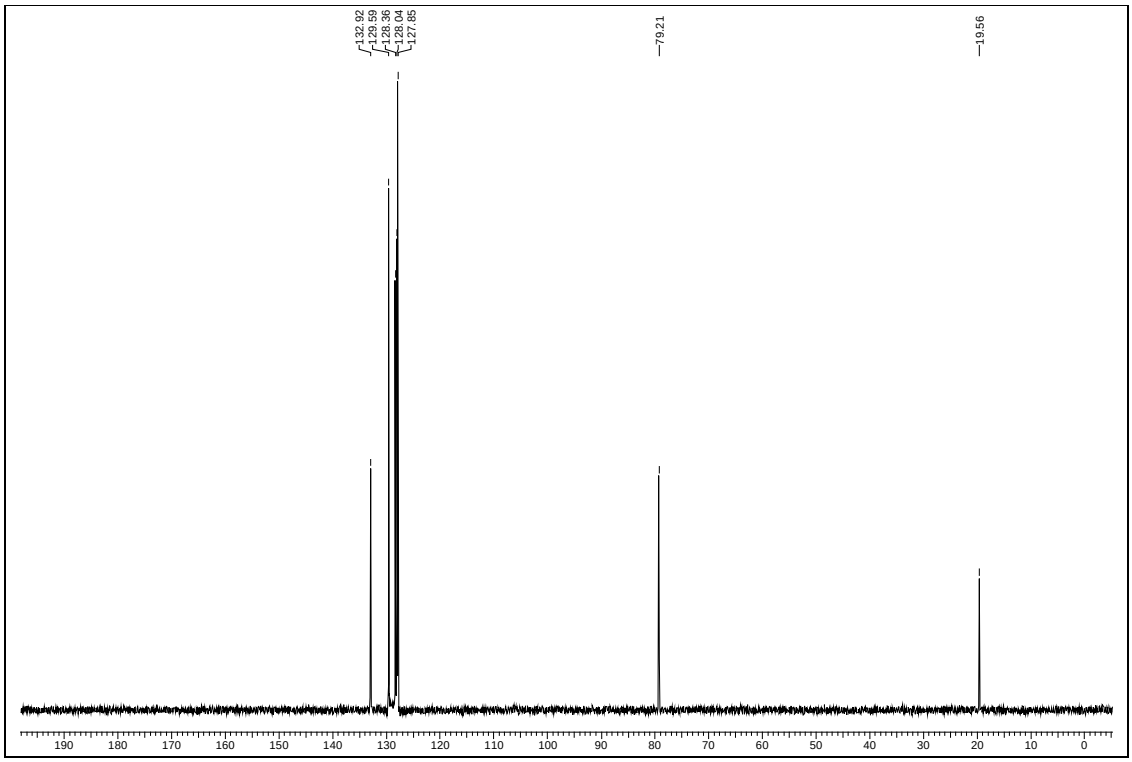
NMR spectrum of compound 11



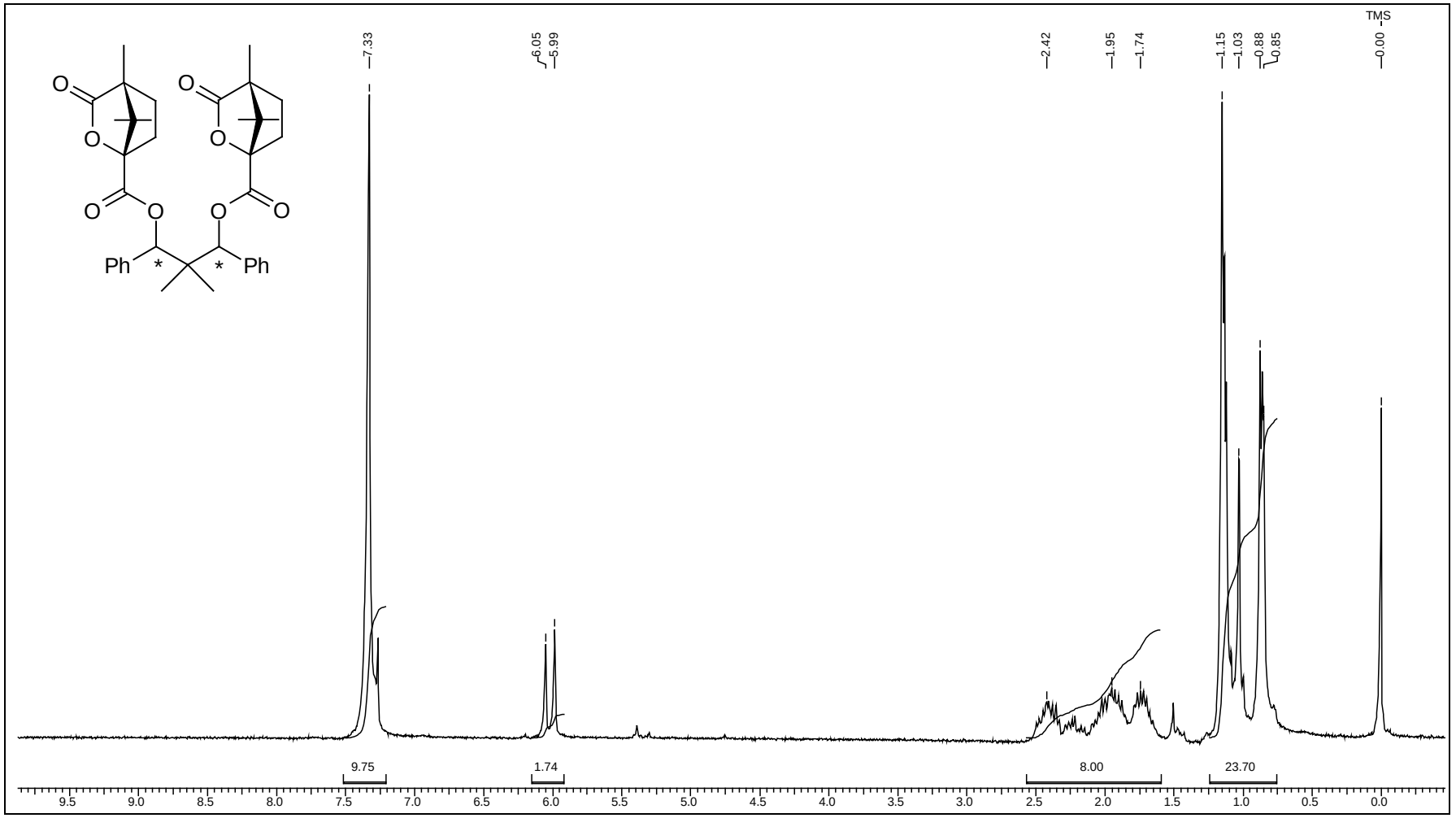
^{1}H NMR spectrum of compound 12



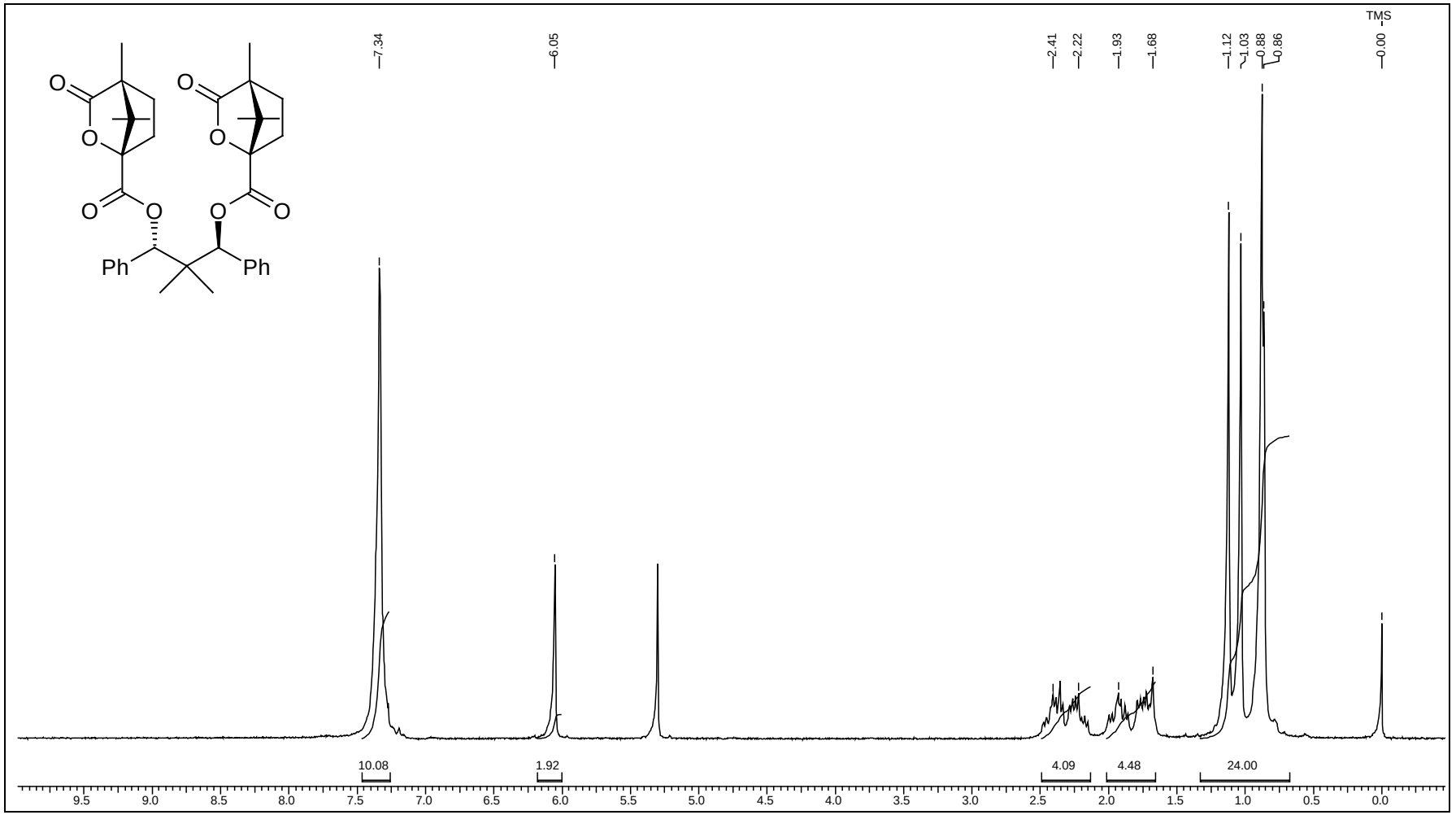
^{13}C NMR spectrum of compound 12



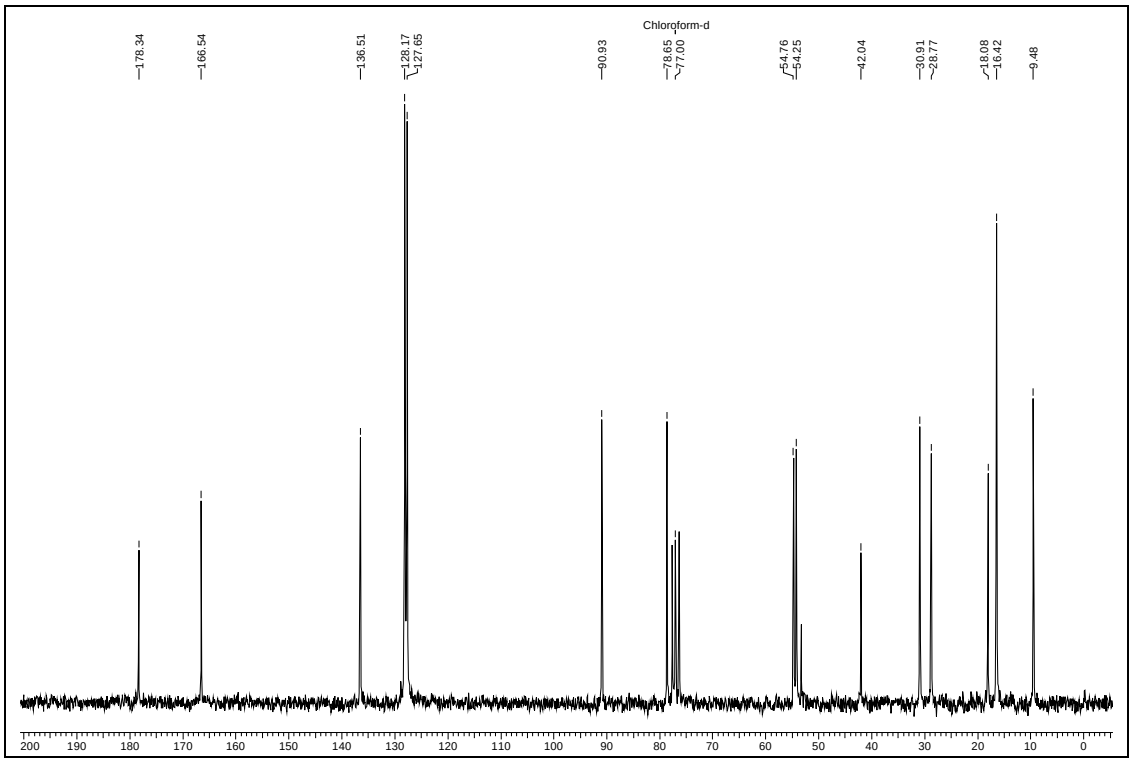
DEPT NMR spectrum of compound 12



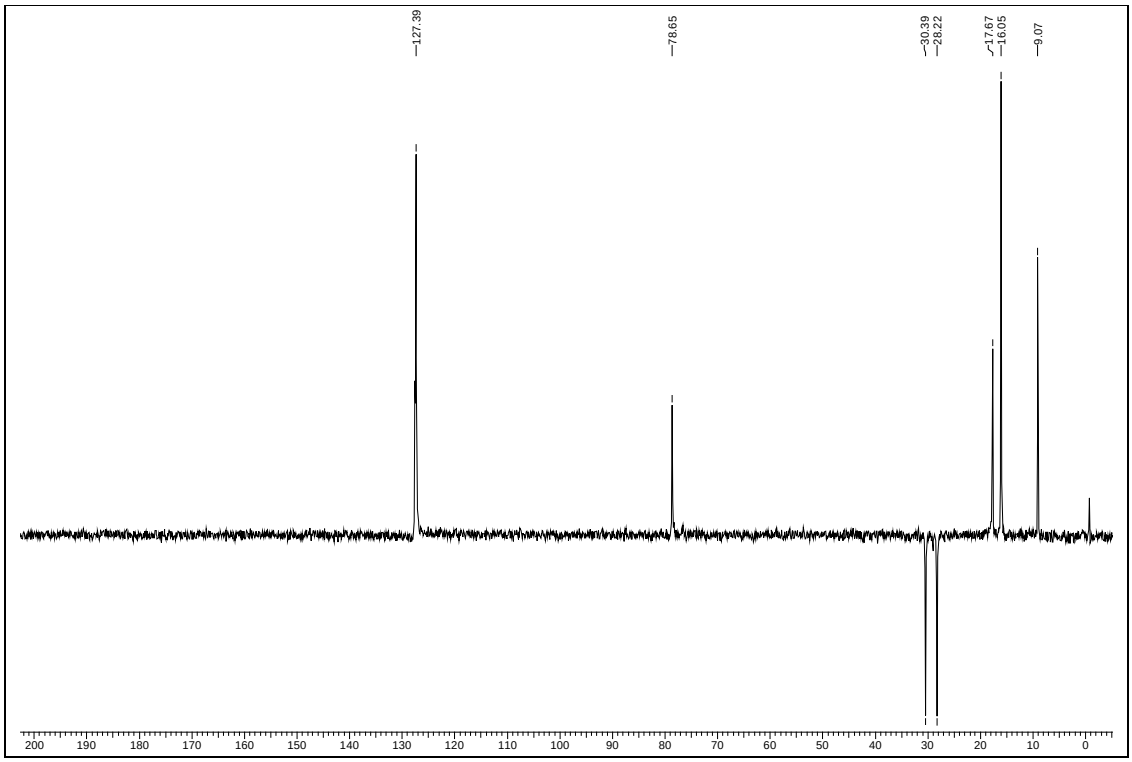
^{1}H NMR spectrum of 30 and 31 mixture



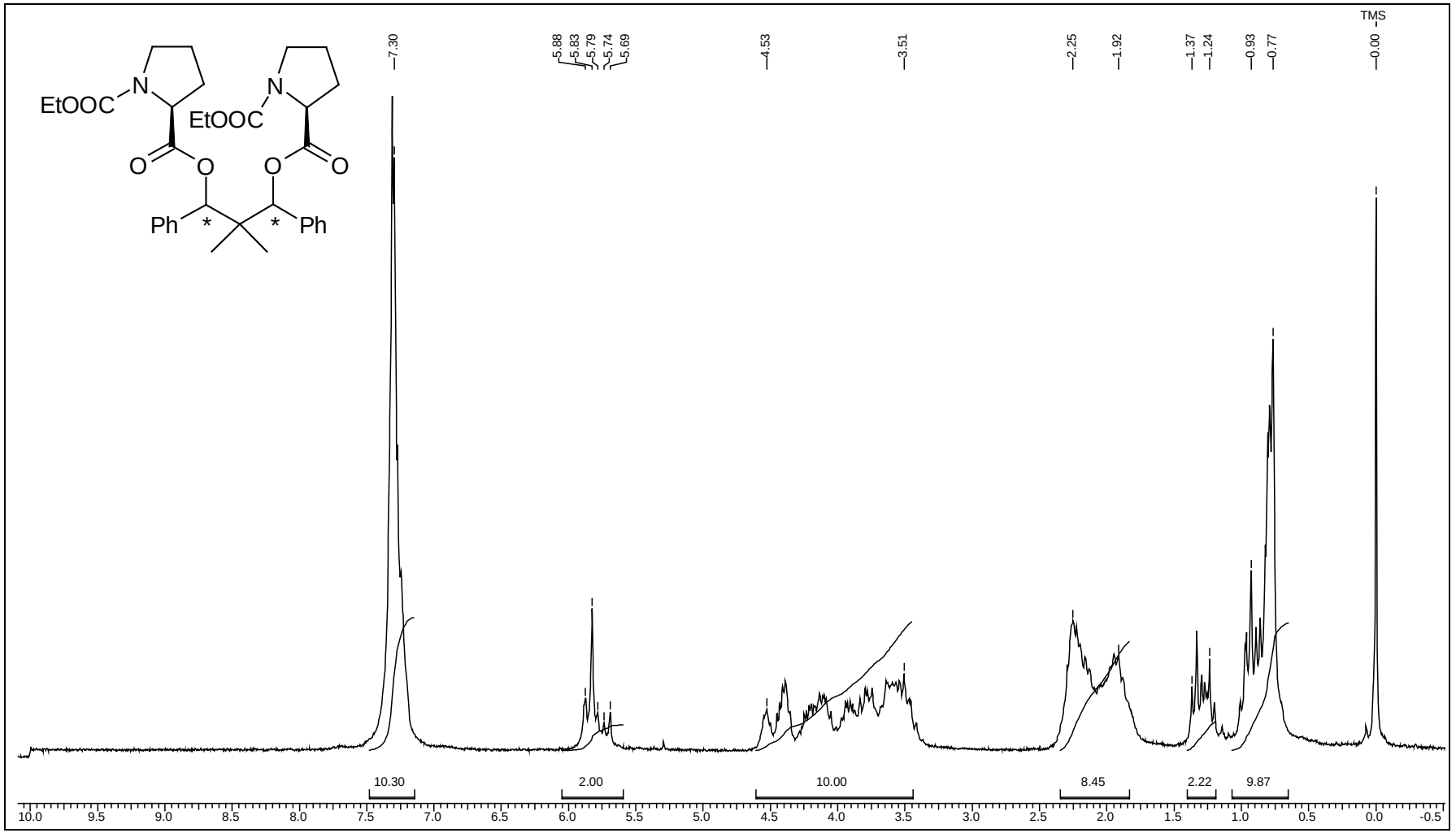
^{1}H NMR spectrum of compound 30



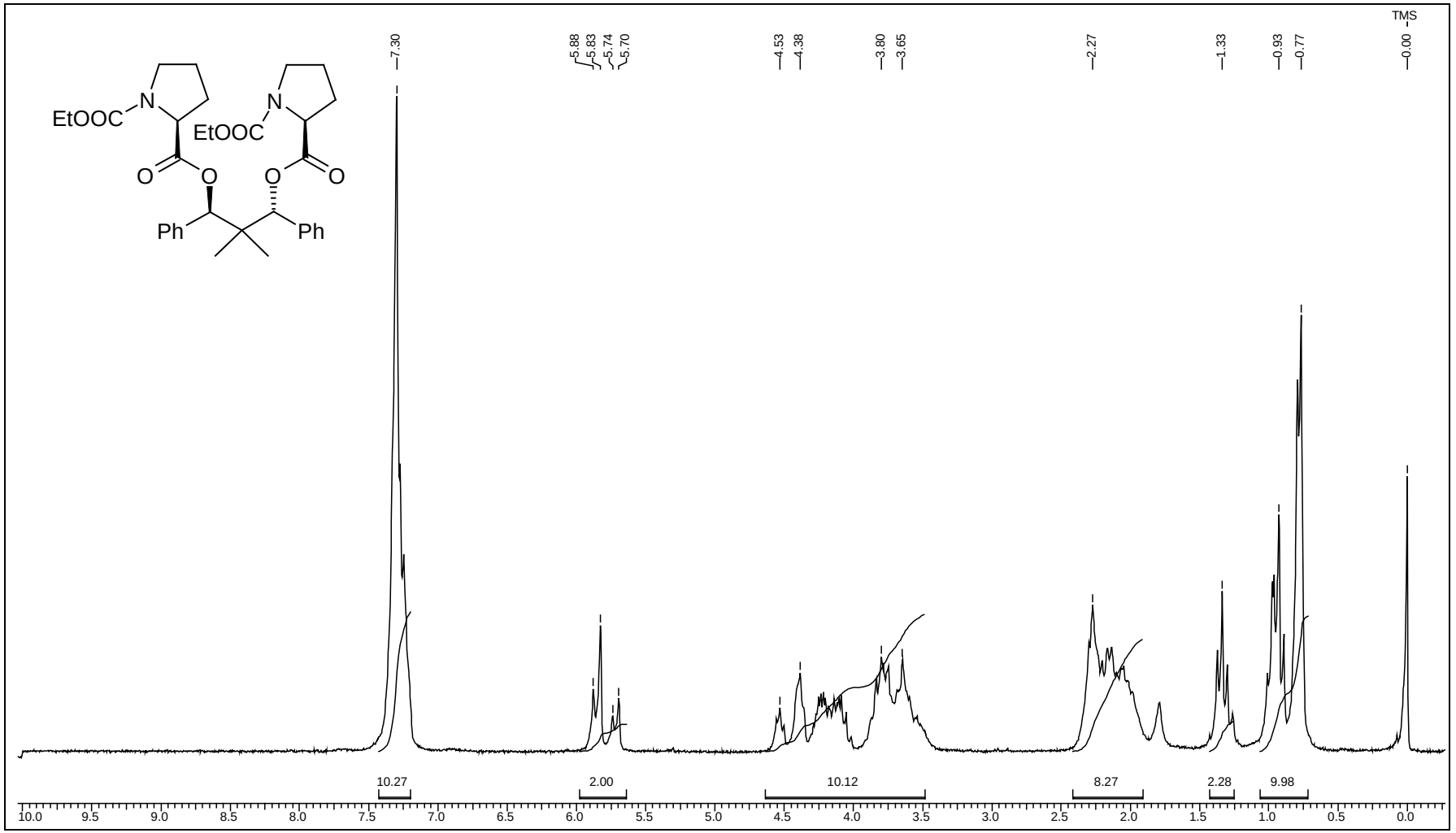
^{13}C NMR spectrum of compound 30



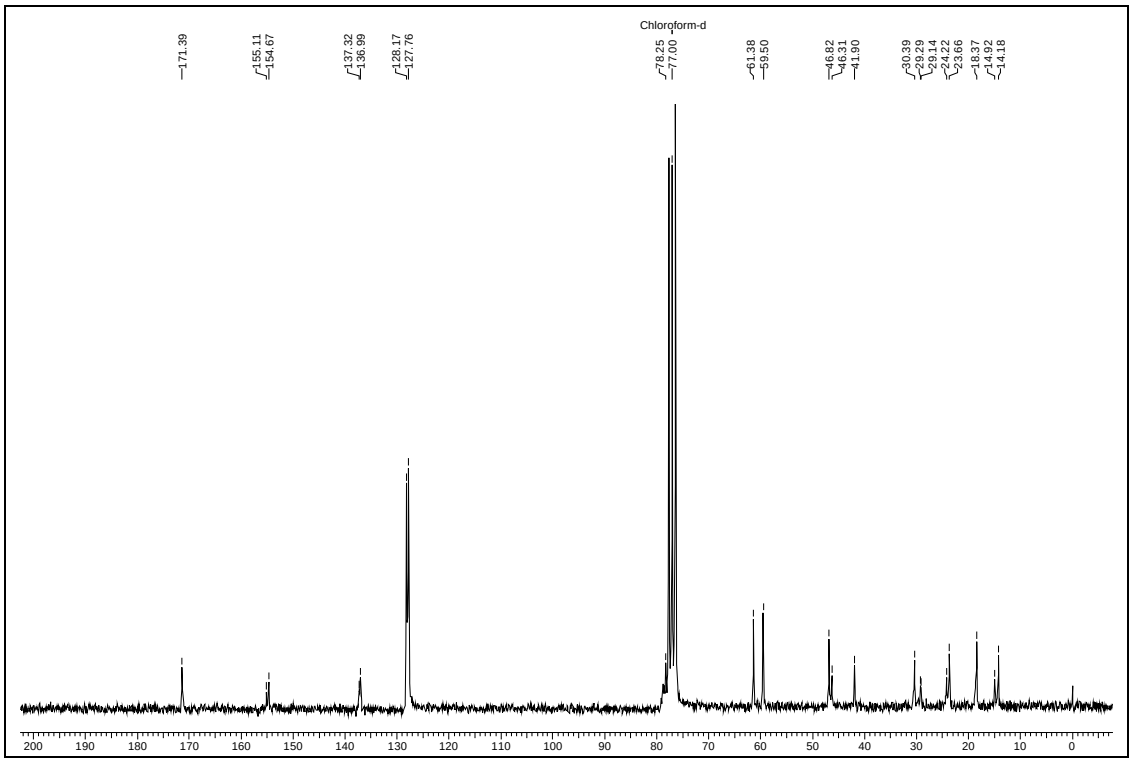
DEPT NMR spectrum of compound 30



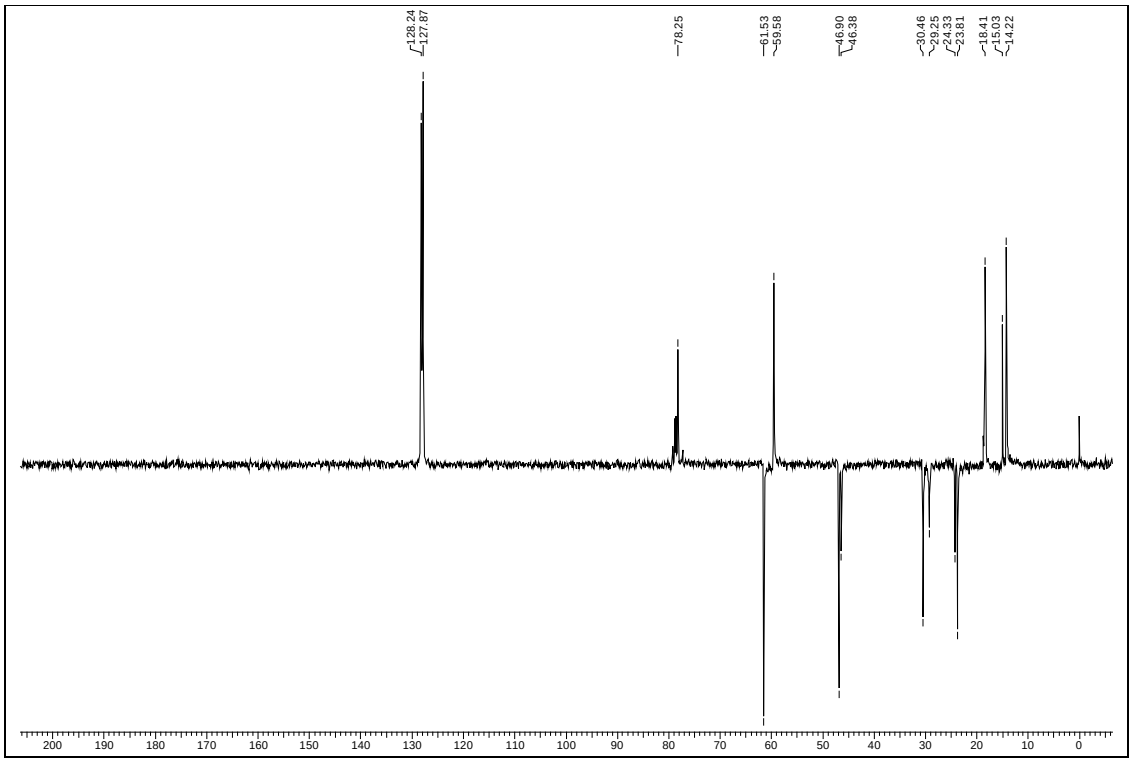
^{1}H NMR spectrum of 34 and 35 mixture



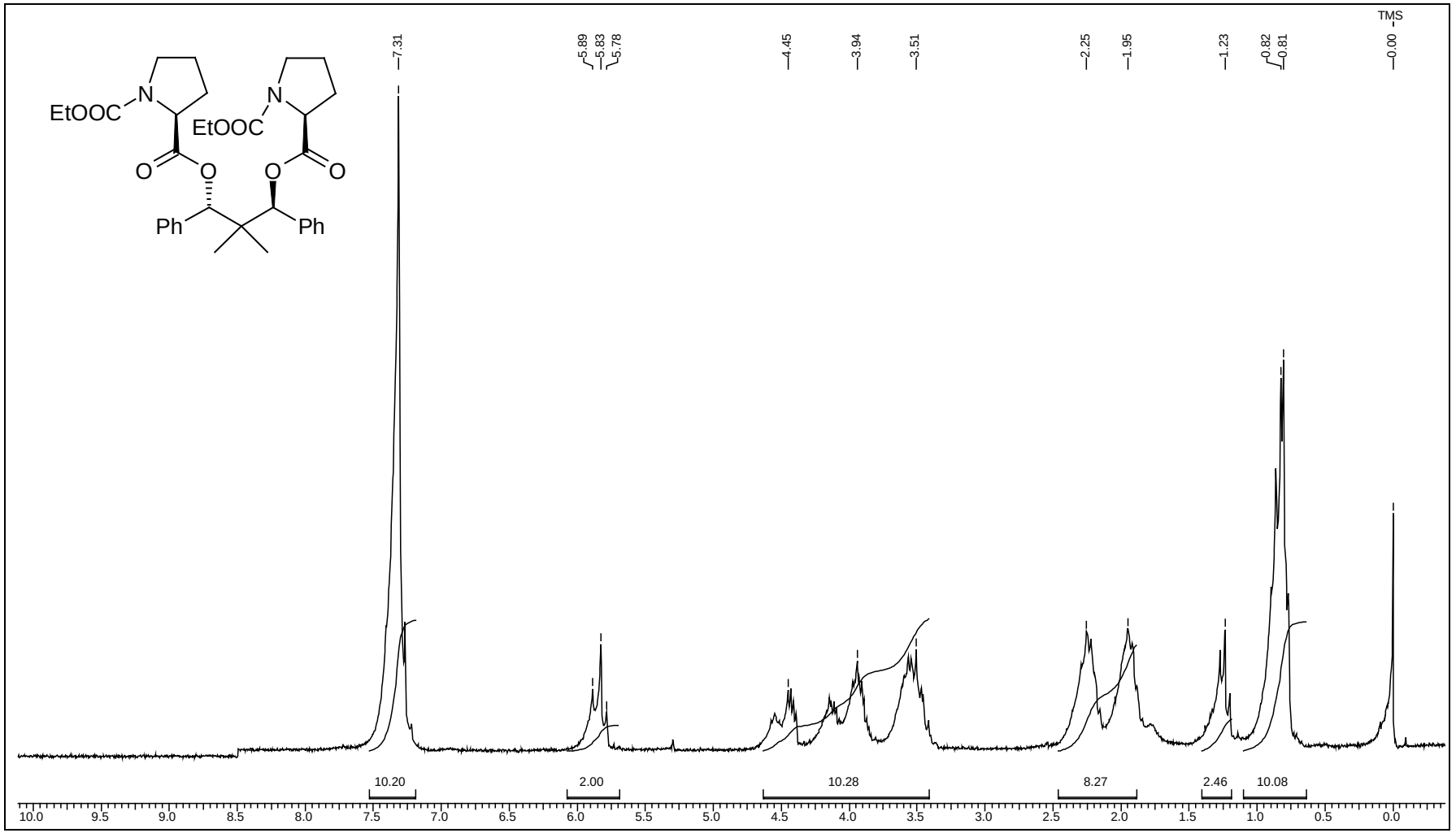
^{1}H NMR spectrum of compound 34



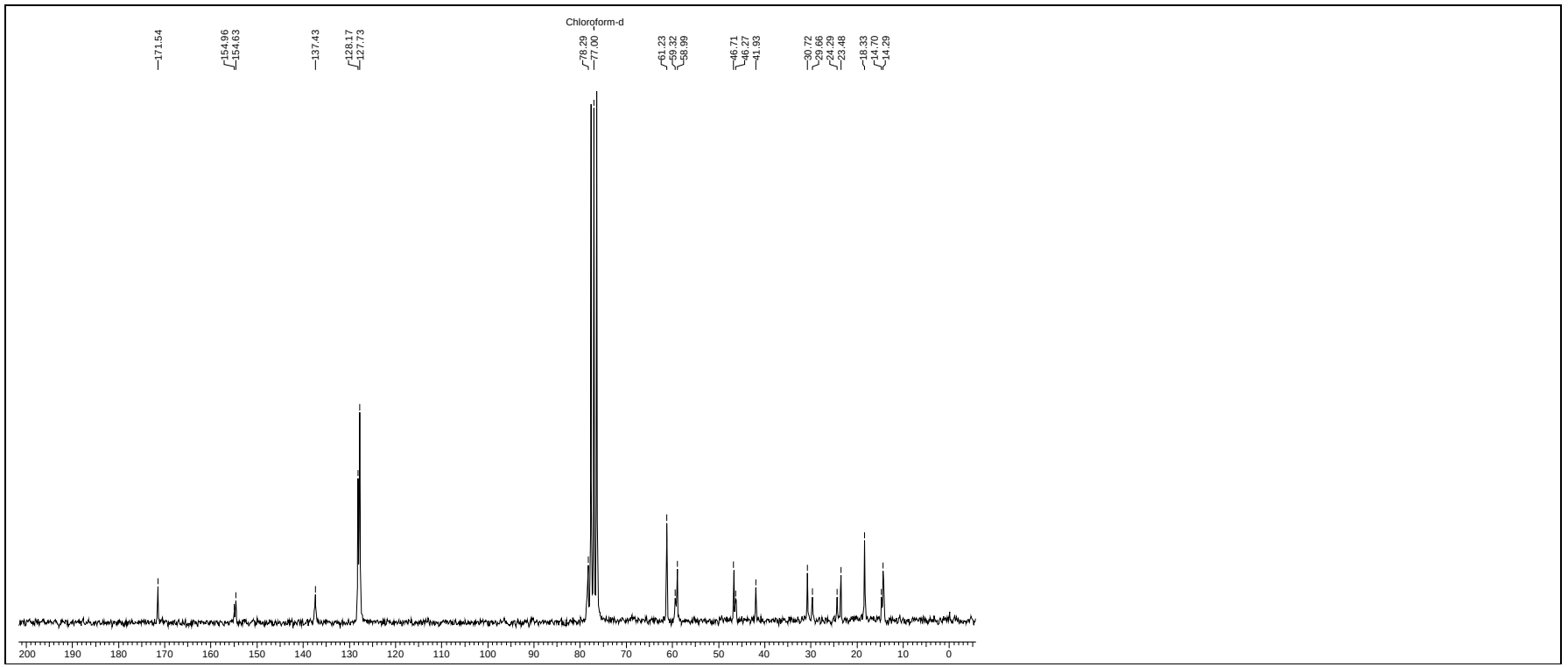
^{13}C NMR spectrum of compound 34



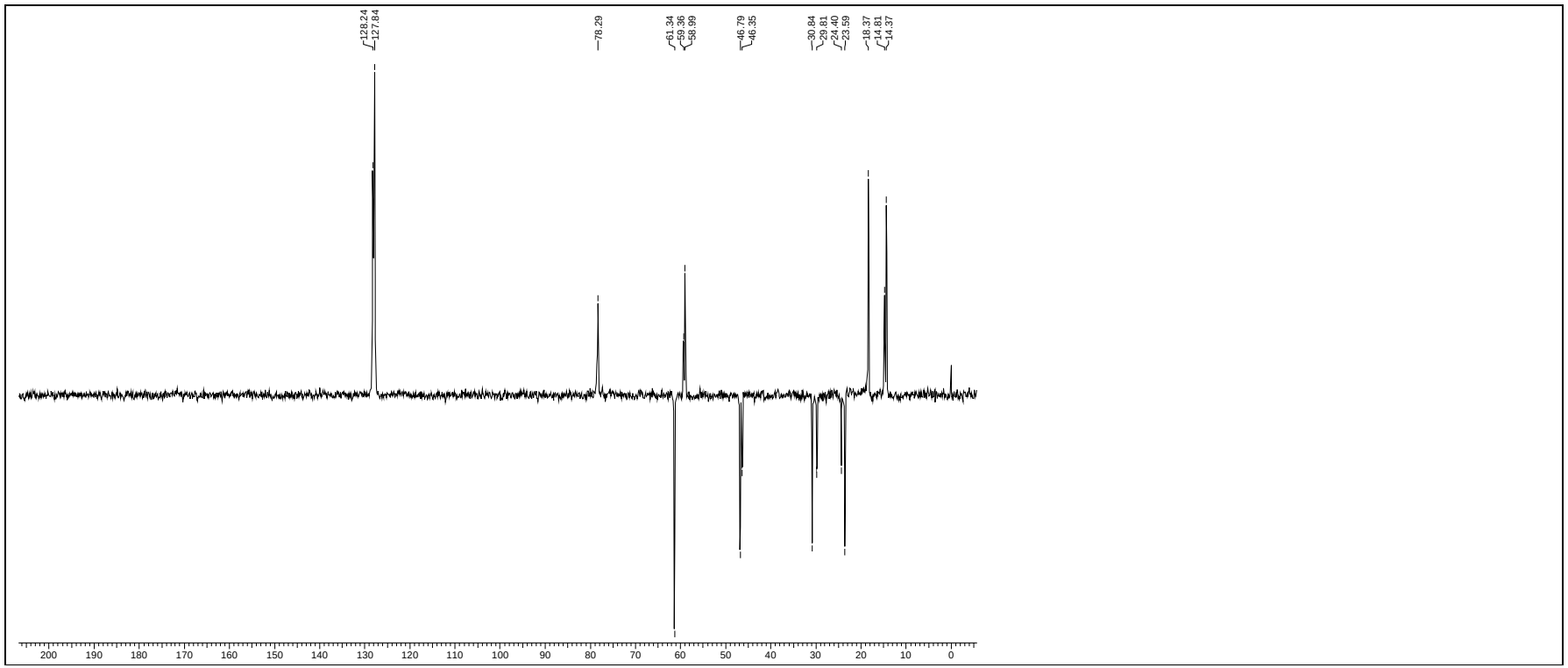
DEPT NMR spectrum of compound 34



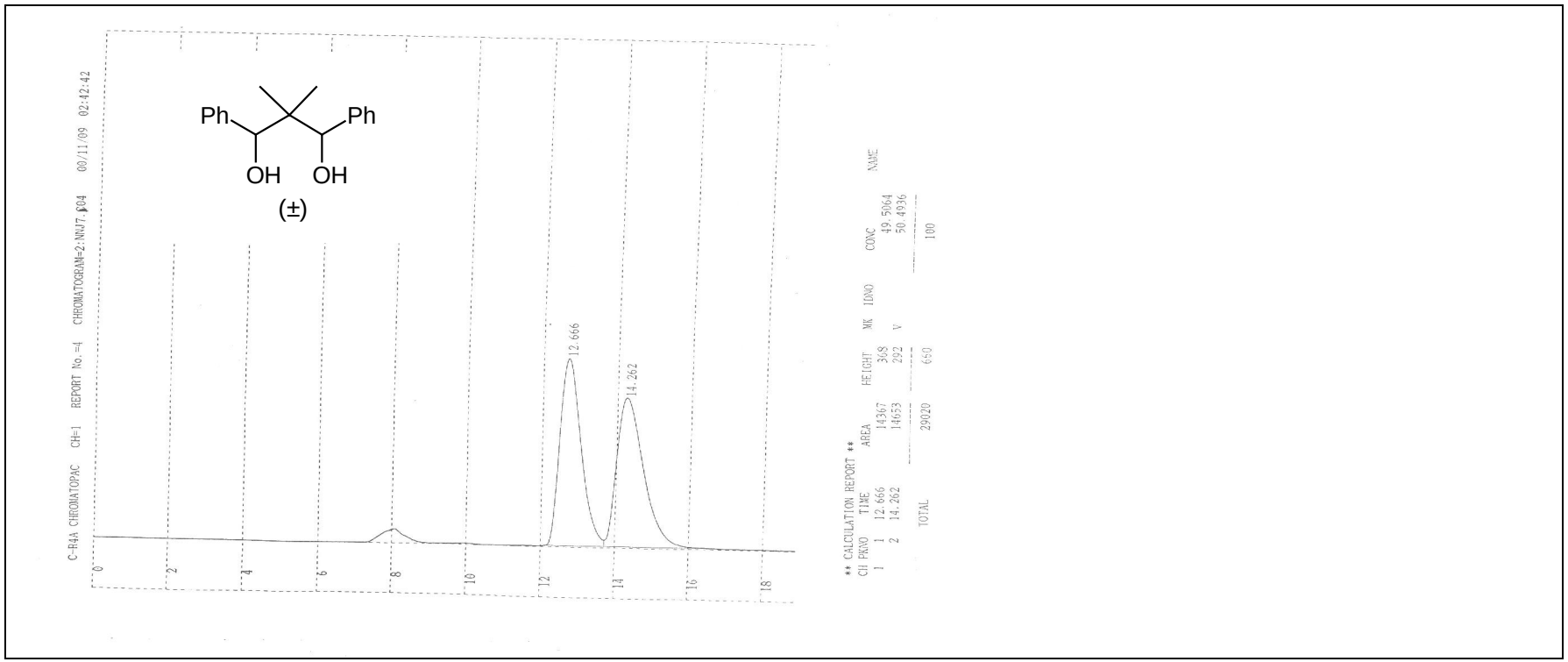
^{1}H NMR spectrum of compound 35



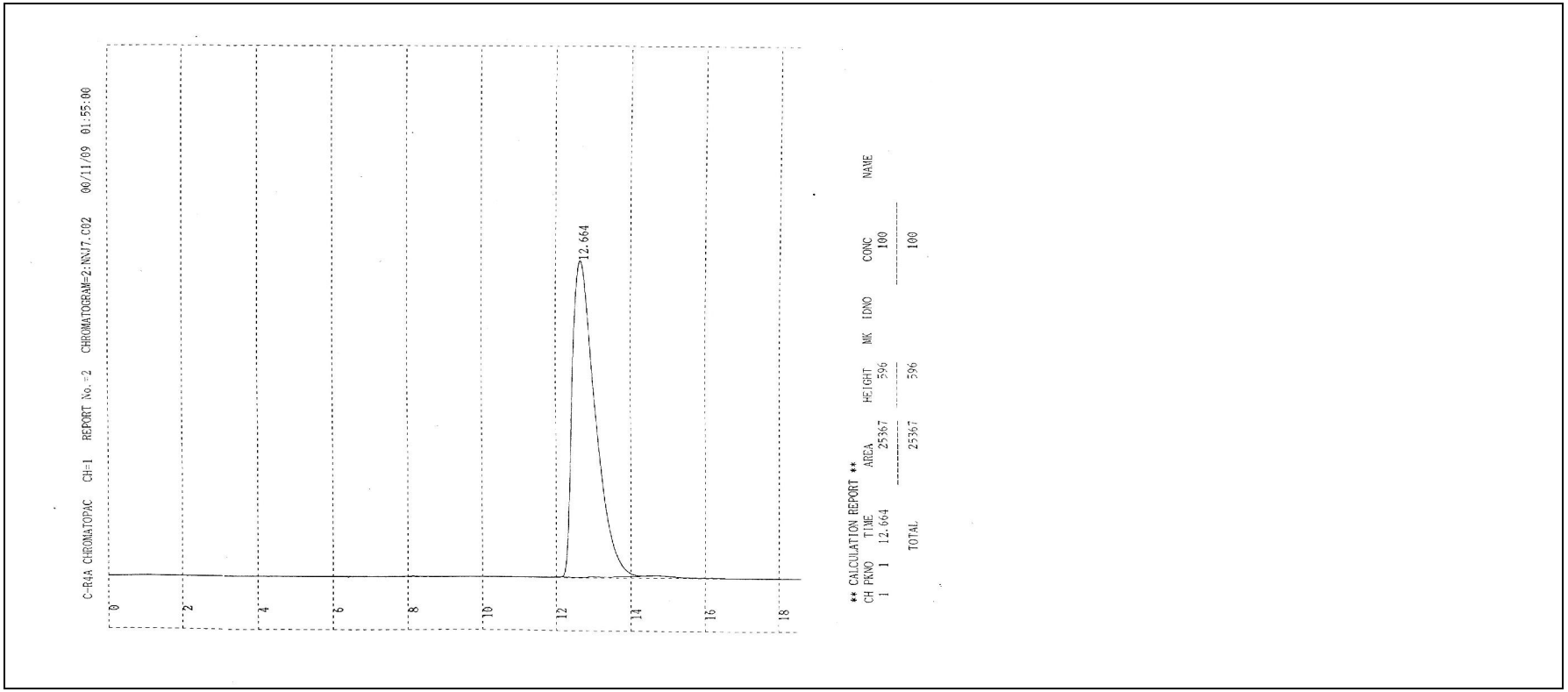
^{13}C NMR spectrum of compound 35



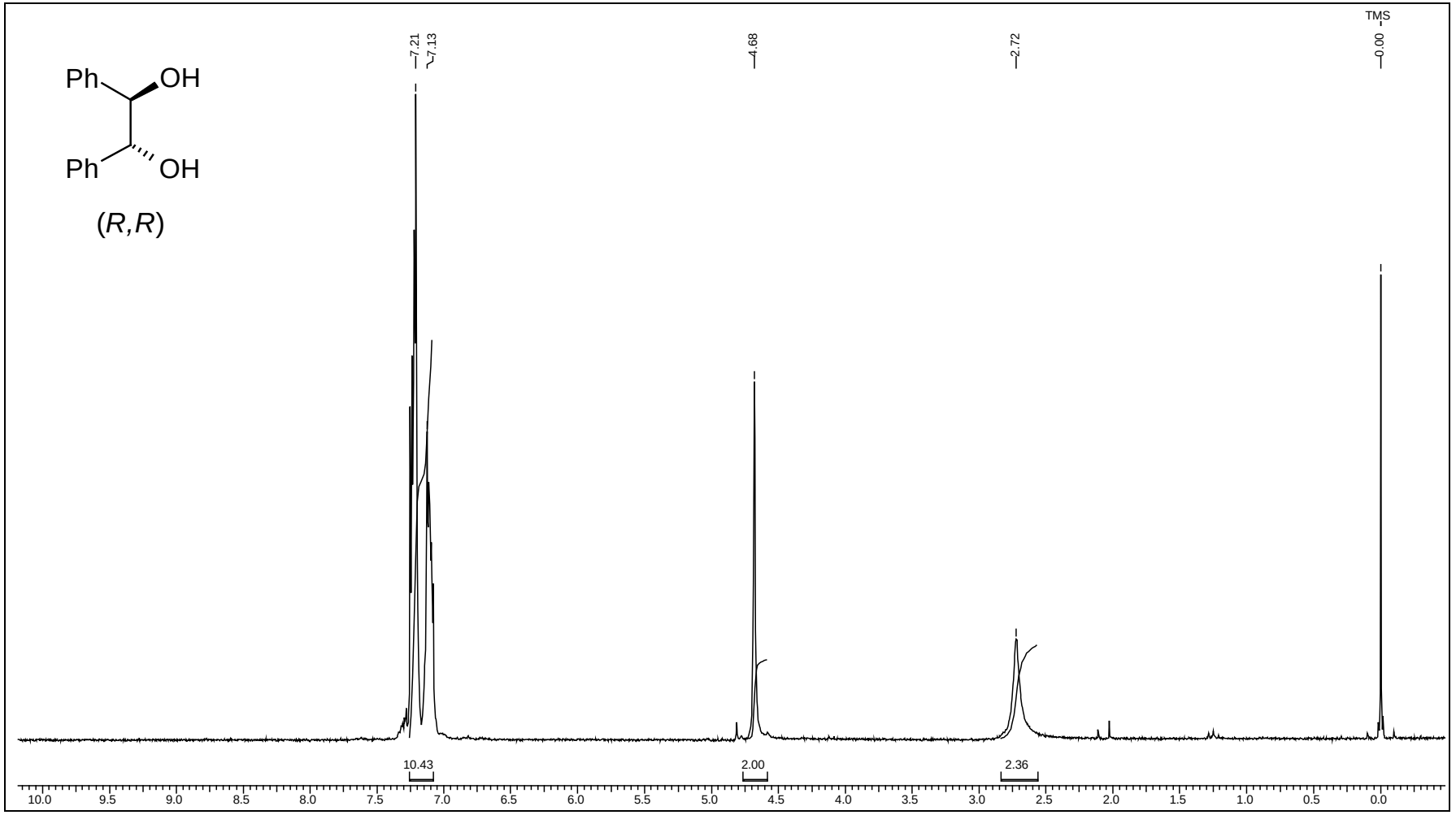
DEPT NMR spectrum of compound 35



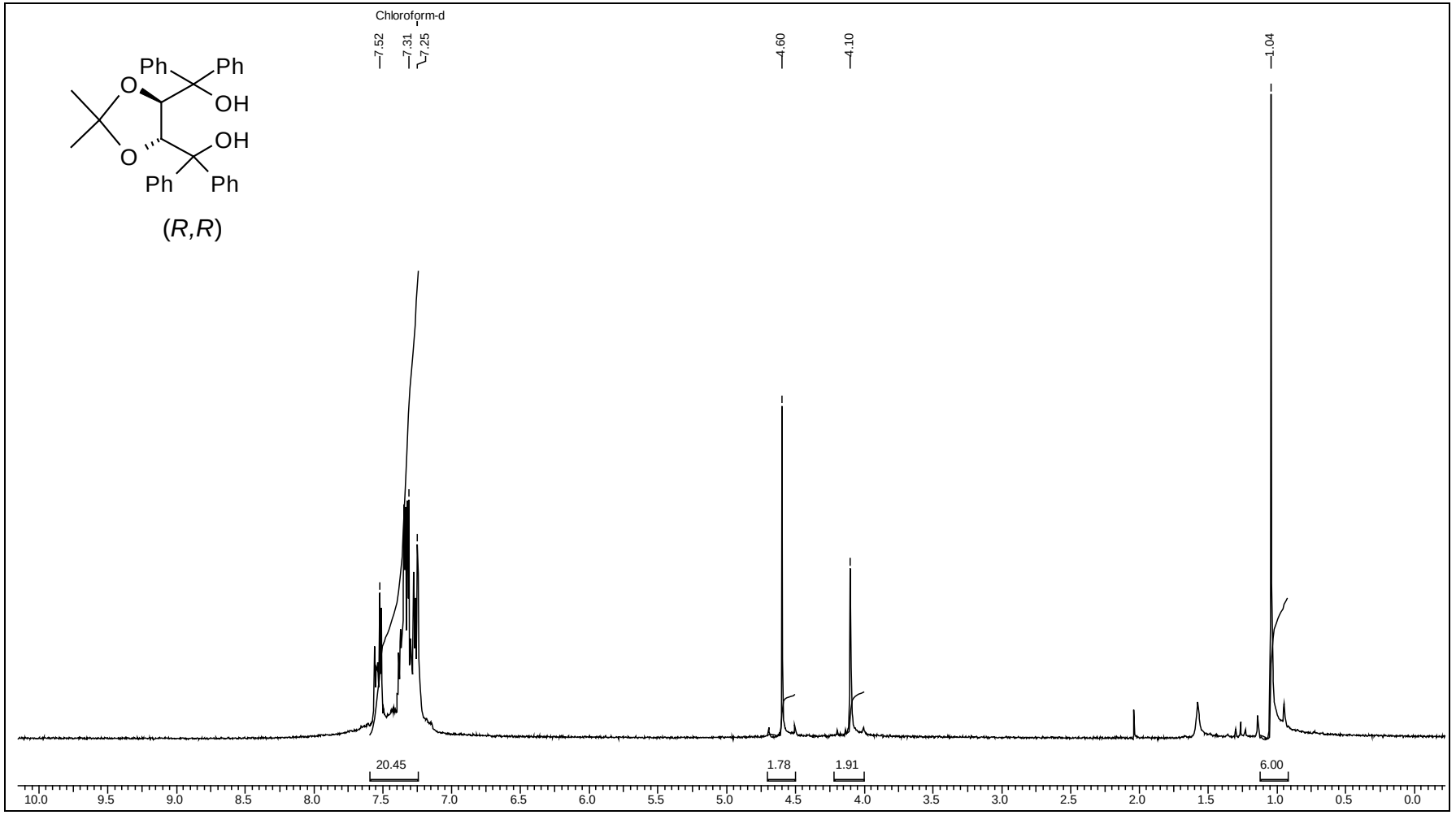
Chiral HPLC of compound (±)-1



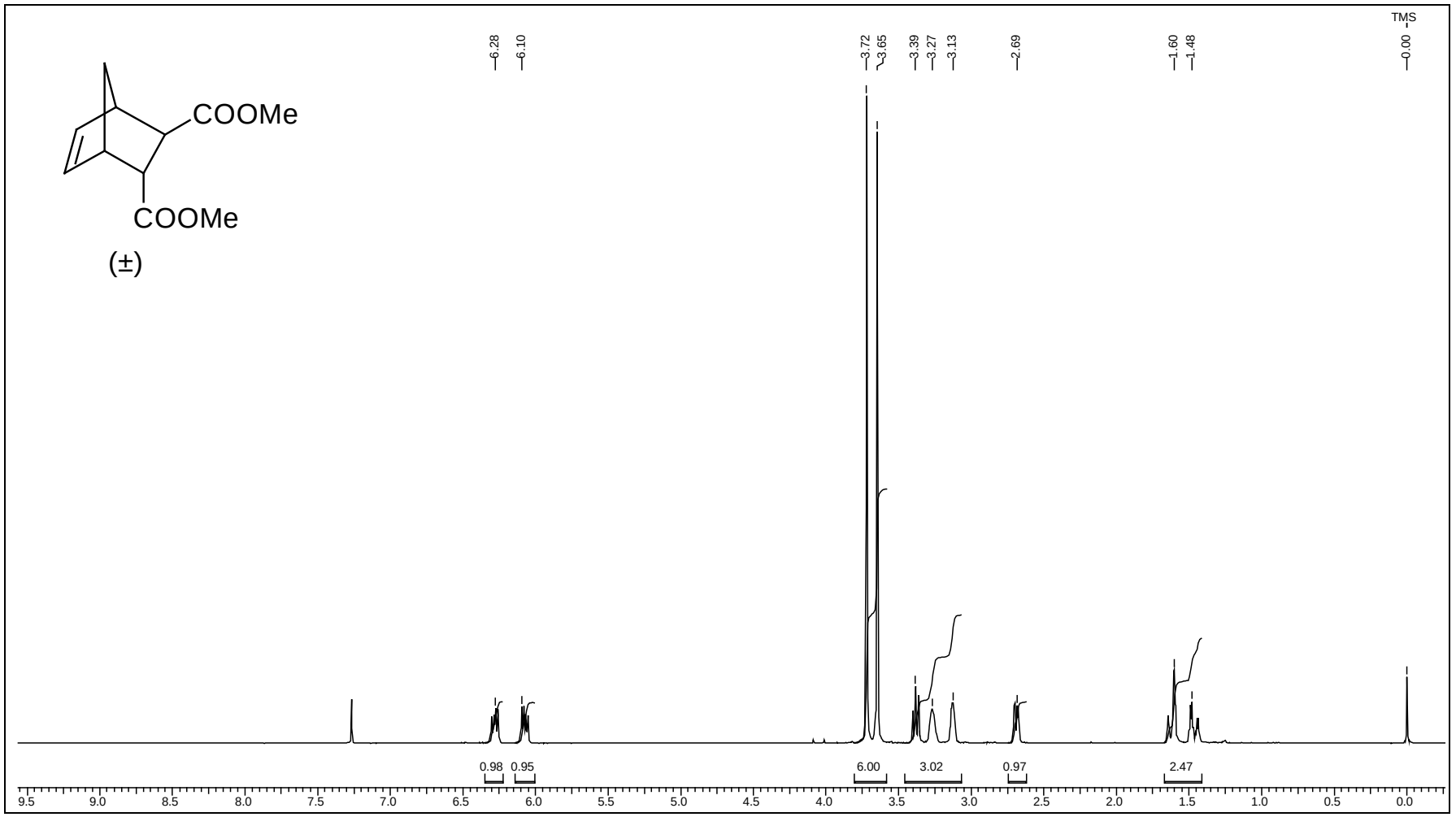
Chiral HPLC of compound (+)-1



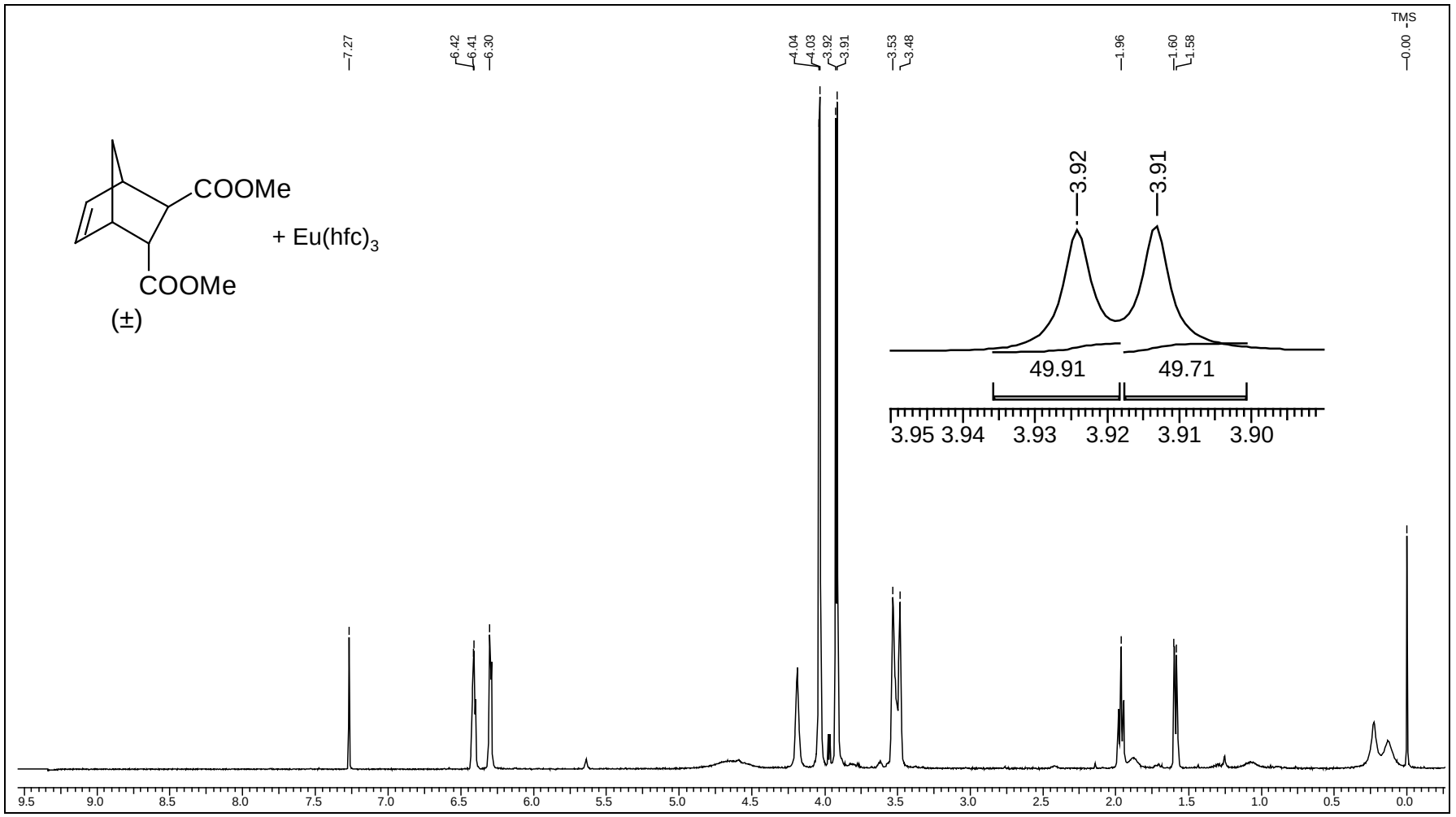
^{1}H NMR spectrum of compound 2



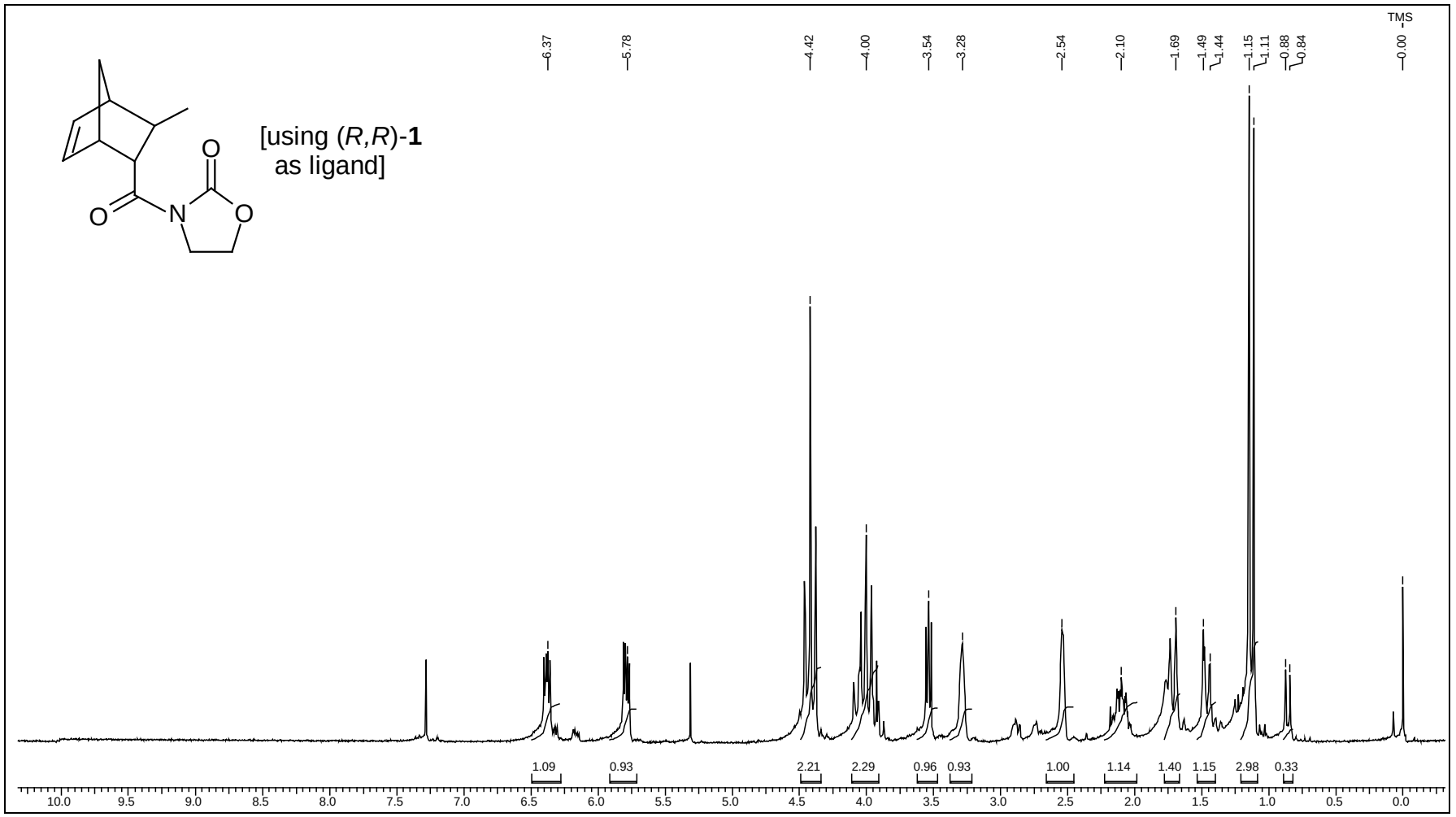
^{1}H NMR spectrum of compound 3



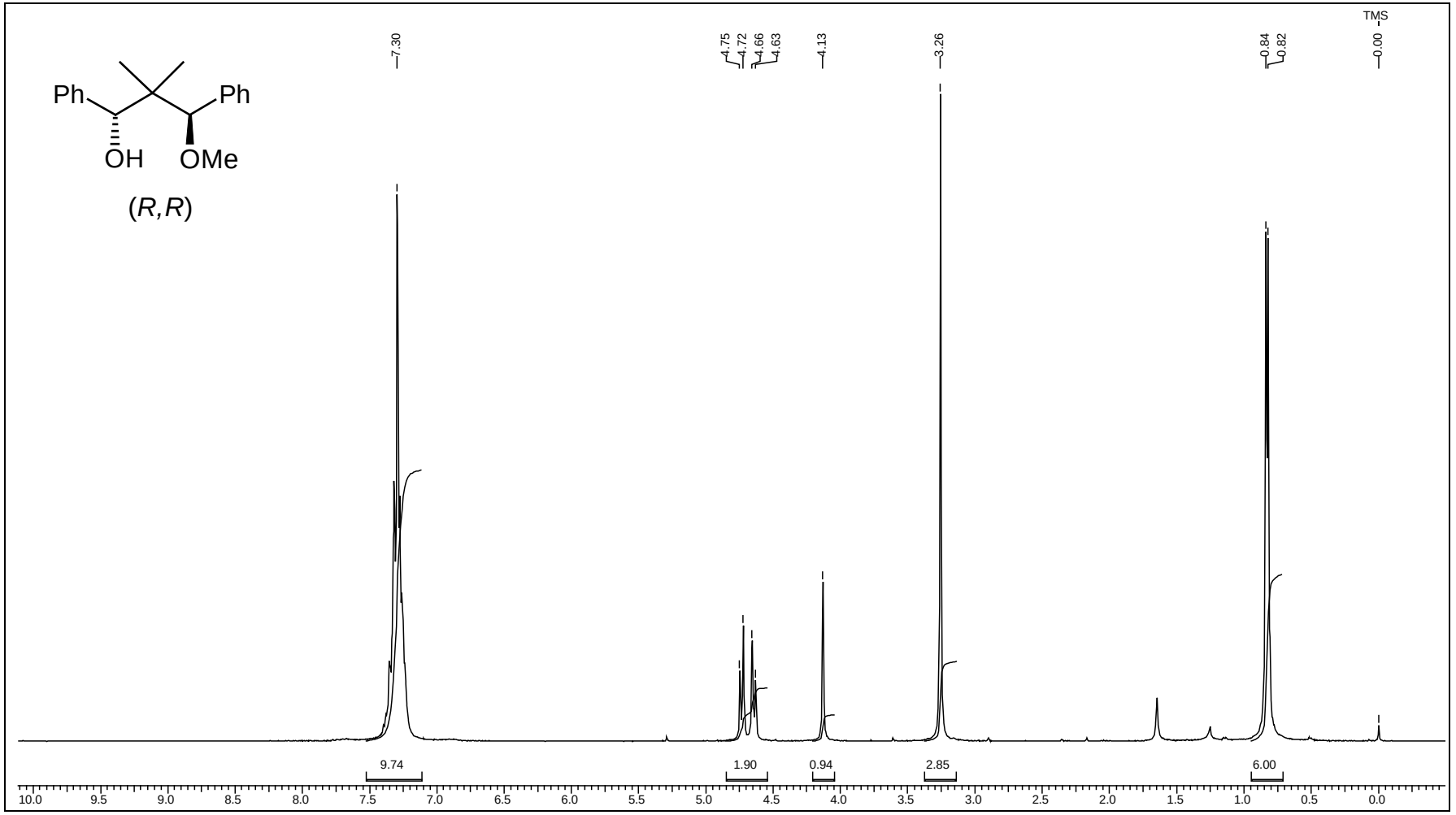
^{1}H NMR spectrum of compound (±)-7



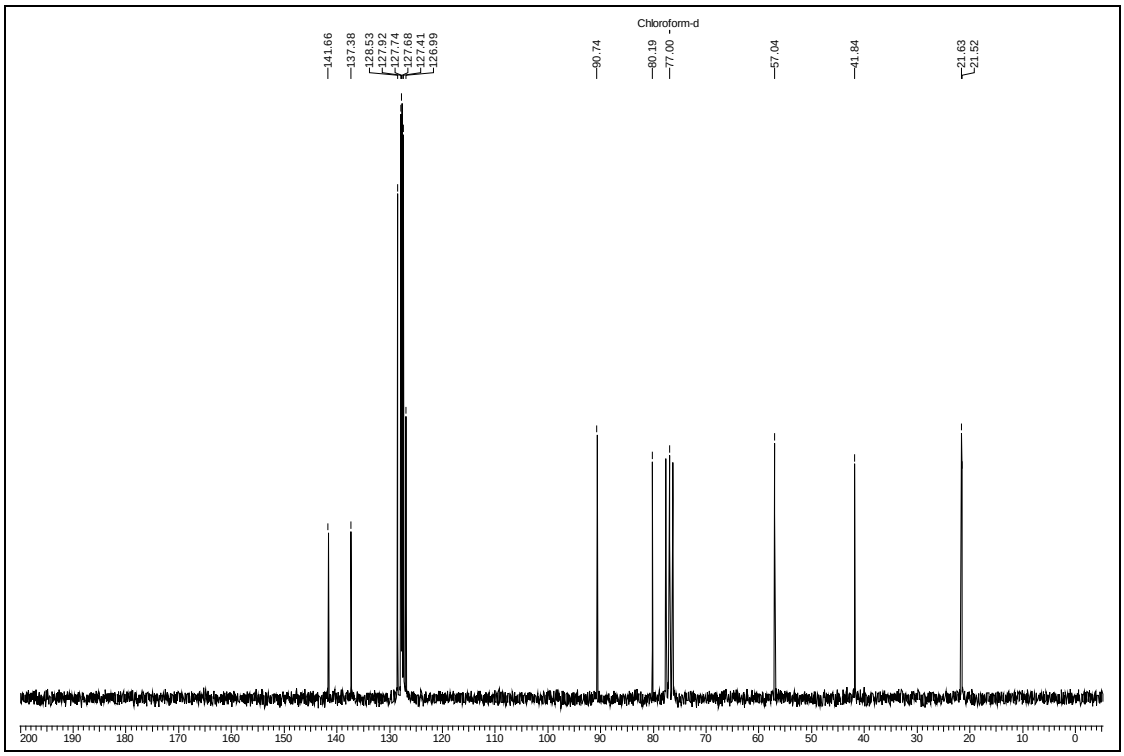
^{1}H NMR spectrum of compound (±)-7 and Eu(hfc)$_3$ for *ee* determination



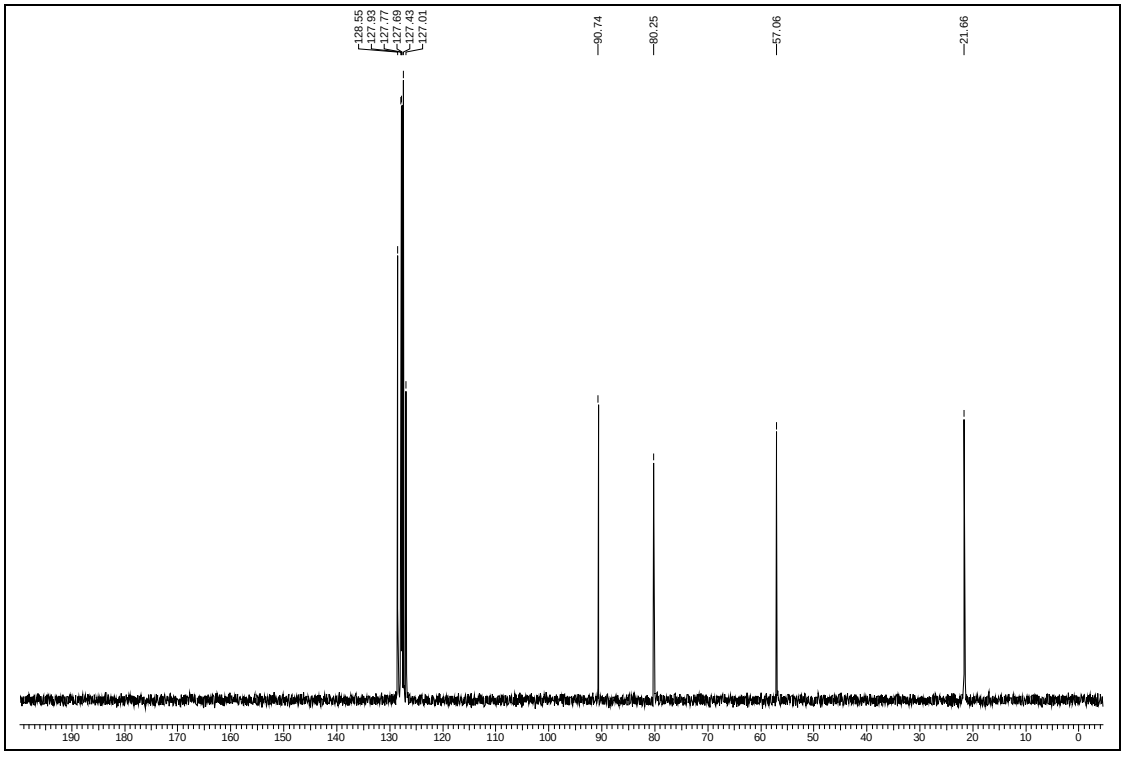
^{1}H NMR spectrum of compound 13



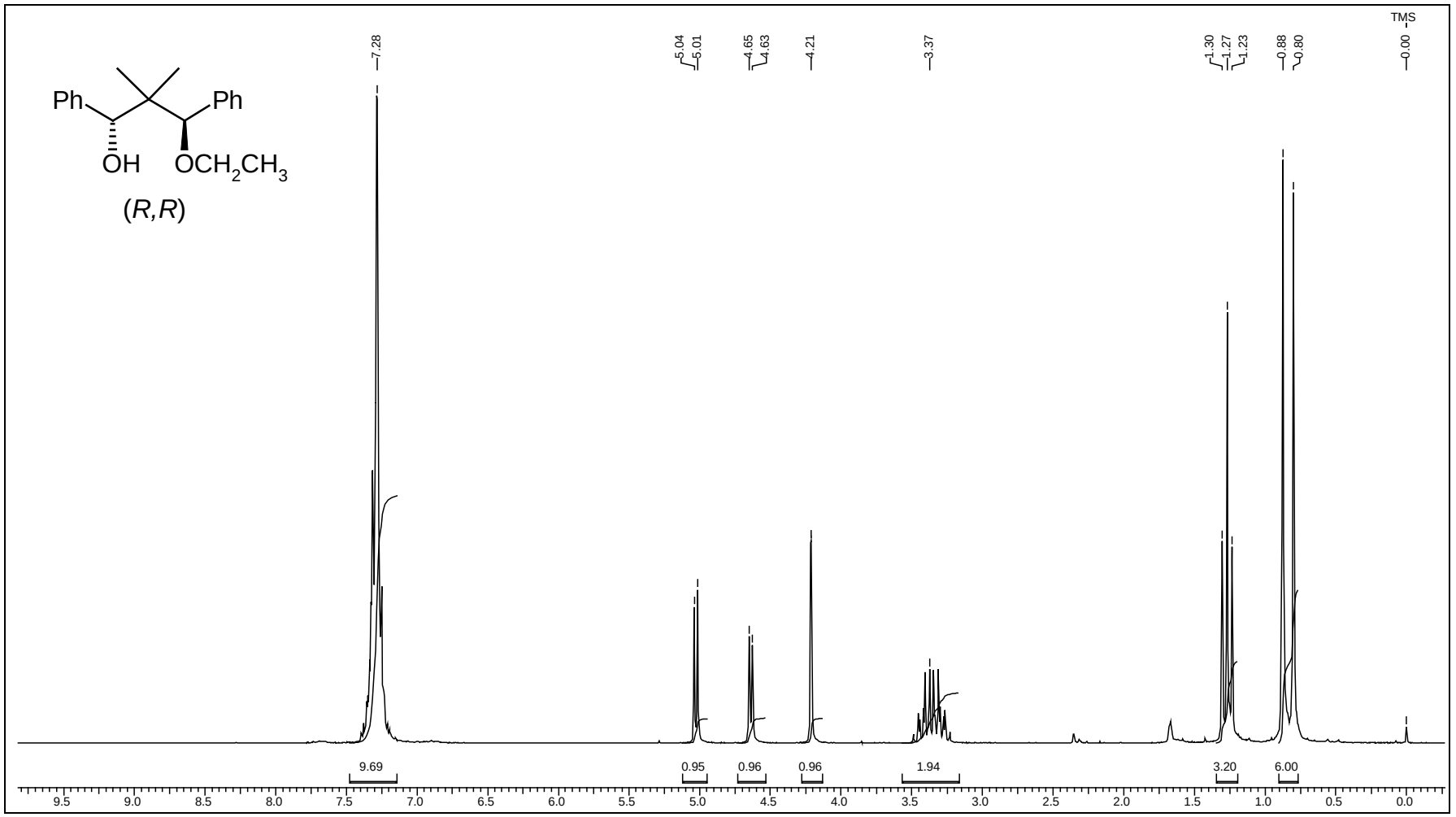
^{1}H NMR spectrum of compound 33



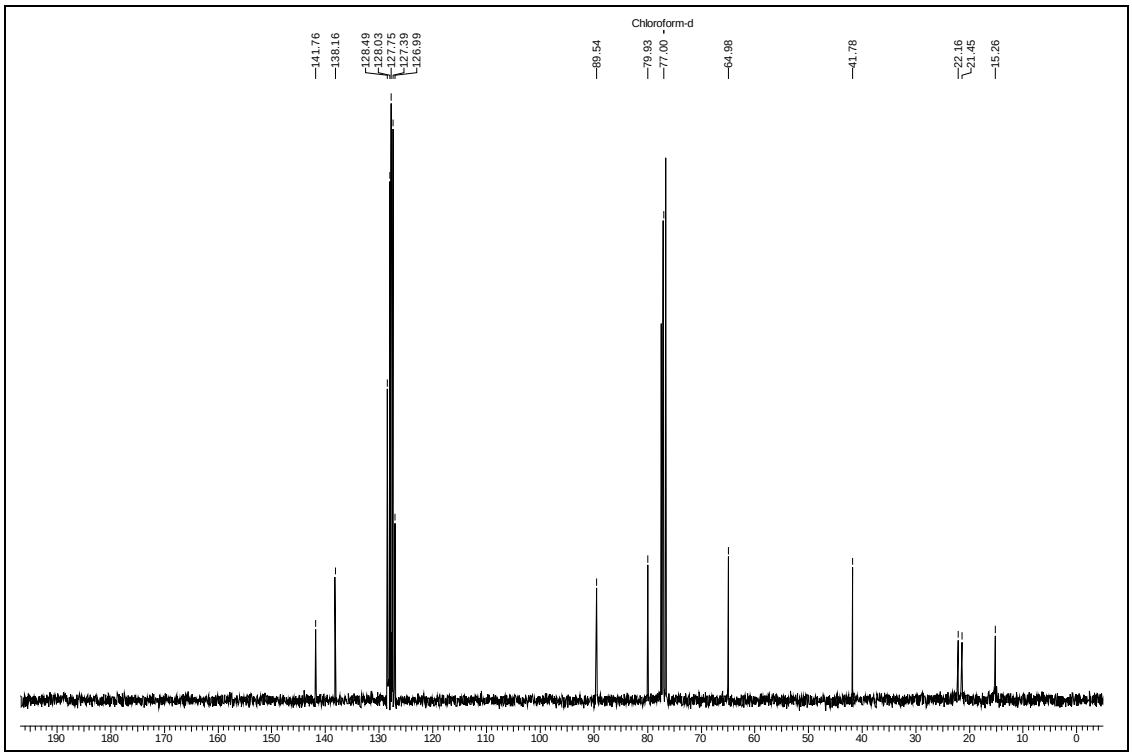
^{13}C NMR spectrum of compound 33



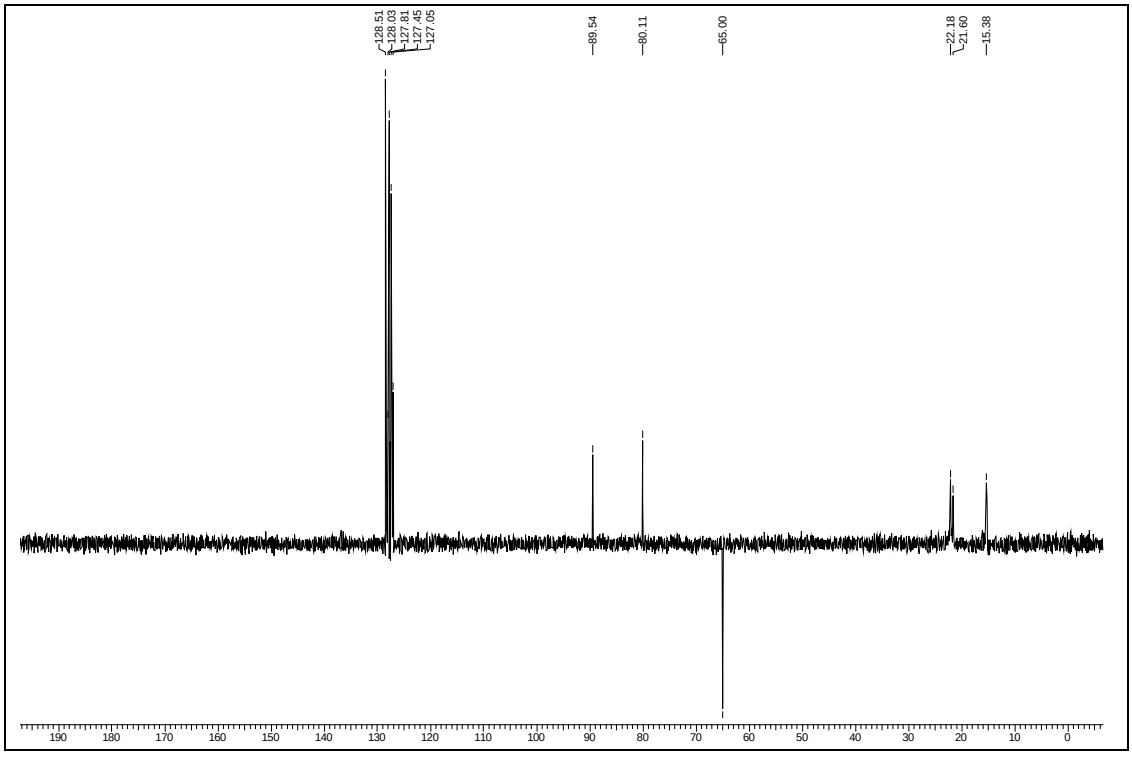
DEPT NMR spectrum of compound 33



^{1}H NMR spectrum of compound 34



^{13}C NMR spectrum of compound 34



DEPT NMR spectrum of compound 34