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FACULTE DES SCIENCES

Synthesis of new chiral ligands and their application in catalytic enantioselective reactions

Thèse présentée à la Faculté des Sciences par:

KEDAR SHANKAR KARMARKAR
Master of Science de l'Université de Bombay

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Institut de Chimie
de l'Université
de Neuchatel

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IMPRIMATUR POUR LA THÈSE

Synthèse de nouveaux ligands chiraux et leurs applications dans les réactions énantiosélectives.

de M. Kedar Karmarkar

UNIVERSITÉ DE NEUCHÂTEL

FACULTÉ DES SCIENCES

La Faculté des sciences de l'Université de Neuchâtel sur le rapport des membres du jury,

Messieurs R. Neier, R. Deschenaux,
G. Sedelmeier (Bâle) et M. Studer (Bâle).

autorise l'impression de la présente thèse.

Neuchâtel, le 5 juin 1996

Le doyen:

R. Dändliker

SUMMARY

In the literature, many diols are known which function well in building a chiral catalysts which transfer the chirality to the product molecule. Starting from optically pure *(R)*-2-hydroxy-4-phenyl-butyric acid (60 kg of this intermediate was available) the goal was to synthesize optically active chiral ligands which can be used to prepare catalyst for different enantioselective reactions.

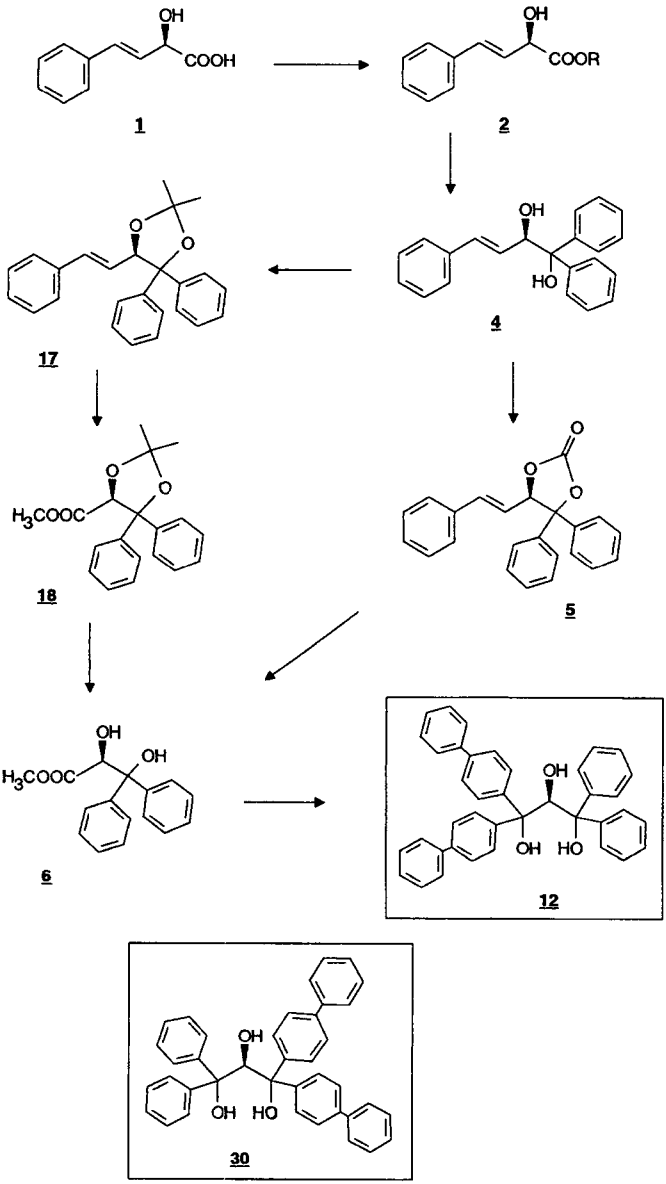
Keeping that in mind we proposed to synthesize tetra aryl glycerols. The beauty of the synthetic sequence was just by reversing the Grignard addition sequence we proposed to synthesize both the enantiomers from the same starting material (please refer to the chapter 2.0, The Theme).

First we prepared methyl ester **2** of the acid **1**. Grignard reaction with PhMgCl gave the styryl diol **4**. Before the oxidative cleavage of the styryl double bond, the diol was protected by preparing it's acetonide **17**. Cleavage of the double bond gave mixture of benzoic acid and acid **37**. Their corresponding methyl esters were prepared and the mixture was separated. The second Grignard reaction of the ester **18** with biphenyl MgBr gave **19** but unfortunately it's protecting group could not be cleaved to convert it to the *(S)* enantiomer of glycerol **12**. it was possible to cleave the acetonide ot **18** to get **6**. The second Grignard with the diol ester **6** gave the *(S)* enantiomer **12**. In a similar way the *(R)* enantiomer **30** was prepared. In this sequence the biphenyl MgBr was reacted first and the second Grignard with PhMgCl.

Since synthesis was tedious we looked for different protecting groups and finally carbonate protecting group **5** was found to be the best as it could be synthesized easily, survived the oxidative cleavage and could be easily removed. Unfortunately, the yield of the glycerols were very low by both the routes. Therefore it was impossible to use them as ligand in the enantioselective reactions.

As all the intermediates are also chiral, in principle each one could be used to prepare the catalyst. By comparing the structures of the intermediate ligands with the ligands known in the literature two reactions were selected namely Katsuki - Sharpless epoxidation and glyoxyl - ene reaction.

- In the Katsuki - Sharpless epoxidation the diol esters **6**, **9** and **10** were successful in transferring the chirality to the product epoxide. The product ee were upto 70% and could be improved upto 94% by recrystallization. Different effects such as ester substituent of ligand, oxidizing reagent, solvent, temperature, substrate on the ee of the product epoxide were studied.
- The diols **4** and **32** and diol ester **6** used as ligands were successful to some extent in increasing the reaction rate, in glyoxylate ene reaction but were unsuccessful to transfer the chirality to the product.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RÉSUMÉ

L'utilisation de diols comme catalyseurs chiraux transférant la chiralité au produit de réaction a été plusieurs fois rapporté dans la littérature. Dans ce contexte, nous nous sommes proposé de synthétiser des ligands chiraux optiquement actifs à partir de l'acide *(R)*-hydroxy-2-phényl-4-butyrique, disponible en grande quantité (environ 60 kg).

Ces ligands, des glycérols tétrasubstitués (restes aryls), devraient par la suite catalyser différentes réactions énantiosélectives. Le choix de ce type de composés repose sur le fait que les deux énantiomères peuvent être obtenus à partir du même produit de départ par inversion des séquences synthétiques impliquant deux additions de Grignard (se référer au chapitre 2.0).

L'acide **1** est converti dans un premier temps en ester méthylique **2**. Une addition de Grignard avec du chlorure de phénylmagnésium donne le diol **4**; après protection des groupements hydroxyles par formation de l'acétonide **17** , la double liaison du reste styryl est clivée par oxydation. Les deux acides benzoïque et **37** sont séparés après formation des esters méthyliques correspondants. Une seconde addition de Grignard sur l'ester **18** avec du bromure de biphénylmagnésium permet d'obtenir le composé **19**. Une tentative de déprotection pour libérer l'énantiomère *(S)* du glycérol **12** n'a pas donné de résultats, mais cette impasse est contournée en produisant le diol ester **6** par clivage de l'acétonide **18**, et en faisant alors seulement la deuxième addition de Grignard.

L'énantiomère *(R)* est produit de façon similaire, mais en inversant l'ordre des deux additions de Grignard.

Afin d'améliorer les conditions de synthèse, nous avons étudié plusieurs protections; il s'avère que la meilleure est le carbonate **5**, qui s'obtient facilement, qui supporte les conditions du clivage oxydatif, et dont la déprotection ne pose pas de problèmes. Le rendement en glycérol reste malheureusement faible, et il n'a pas été possible de l'utiliser comme ligand dans différentes réactions énantiosélectives.

Cependant, tous les intermédiaires étant chiraux, il est en principe possible de les utiliser pour la préparation de catalyseurs; en comparant leurs structures avec celles de ligands connus dans la littérature, nous avons choisi de les tester sur deux réactions: l'époxydation de Katsuki-Sharpless, et une réaction de type ène.

- Pour l'époxydation de Katsuki-Sharpless, les diols esters **6**, **9** et **10** ont été utilisés avec succès et ont permis le transfert de chiralité dans la synthèse d'époxydes. Le produit ee est de 70 %, et atteint 94 % après recristallisation. Plusieurs facteurs tels que les substituants sur le ligand, la nature de l'agent d'oxydation, le solvant, la température ou le substrat ont été étudiés.
- Les diols **4** et **32**, de même que le diol ester **6** utilisés comme ligands ont permis d'augmenter la vitesse de la réaction de type ène-glyoxylate, mais n'ont eu aucune influence sur le transfert de chiralité.

Dedicated
to my parents!

This work was carried out from May 1993 till May 1996 in Catalysis Research Group of of CIBA-GEIGY AG, Basel.

I owe a lot to Dr. G. Sedelmeier as he gave me the opportunity to work in this interesting field and his guidance during this time. I thank him very much for investing his time for this project and encouraging me from time to time. I also thank Prof. R. Neier as this work would not have come to reality without his support and guidance. Dr. M. Studer also invested his time and gave me encouragement and guidance. I also thank him very much.

This work was possible because of help from many people and I wish to thank everybody of them.

I thank Dr. H. U. Blaser for his helpful discussions and suggestions. I thank him and Mr.R. Bader and Mr. P. Baumeister for providing me lab space and facilities in CIBA.

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I always had the help and suggestions from the chemists of the catalyst research and services group where I worked during this project. I sincerely thank all the members of this group. In particular I would like to thank Drs. B. Siebenhaar, A. Indolese, F. Spindler, B. Pugin, M. Müller, U. Siegrist and H. Steiner.

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Curriculum Vitae

Date of Birth	7. April 1964
Native Place	Bombay, INDIA
Parents	Dr. Shankar S. Karmarkar (Chemist) Mrs. Shalini S. Karmarkar (M.A., Hausewife)
Schooling	Primary and secondary school (1969-1979) in Parle Tilak Vidyalaya, Vile-Parle.
	Higher secondary school in Parle College, Vile-Parle.
	Bachelor of Science (B.Sc.) from the University of Bombay (1985).
	Master of Science (M.Sc.) from Department of Chemical Technology, University of Bombay (1988). Thesis work with Dr.S.D.Samant with the title: The Diels-Alder reaction of Lactones.
	From June-November 1989 worked as a trainee in the Pharma Chemical Development of CIBA-GEIGY AG, Basel.
	Worked as a research fellow at the Institute of Organic Chemistry Basel University in the research group of Prof. Ch. Tamm (Dec. 1989 to Nov. 1992).
	From May 1993 till May 1996 worked on this dissertation project in CIBA-GEIGY which was a collaborative project between CIBA-GEIGY AG, Basel and Prof.R.Neier, University of Neuchatel.
Viva examination	10. May 1996
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EP 96810282.2

Date: 5.May 96

1.0 Introduction

1.1 History :

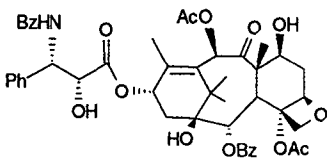
Chemistry has a history of at least a few hundred years and organic chemistry is recognized as a science since the first acknowledged synthesis of urea by Wöhler about 160 years ago. Since that time the challenges to the synthetic chemists have steadily increased in complexity. The tasks during these periods constantly changed in character e.g. before the development of chemistry as a science, the old philosophers were analyzing properties of different substances. They slowly realized that matter is made up of basic elements. In the 18th century it became clear that atoms were basic building blocks. e.g. water is made up of the two elements hydrogen and oxygen in the ratio of 2 :1. Starting from this knowledge the concept of valency was developed and chemists started wondering about the structure of compounds. An important step was made by Kekülé, when he proposed the cyclic structure of the benzene molecule developed from his famous dream. Based on this structural proposal the theory of resonance and aromaticity was developed. D. Mendelejew and L. Meyer proposed the periodic table of the elements simultaneously in 1869. Soon different functional groups were known and different test reactions were developed to identify them. Then the chemists were busy determining the structures of natural products with degradation methods. Since this time chemistry was more or less divided into three main branches: organic, inorganic and physical chemistry.

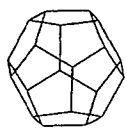
The very important concept of asymmetry and chirality was recognized in the last century first by Malus (1808), Biot (1815), Liebig (1840) and later by Louis Pasteur, when he physically separated two different types of sodium ammonium tartrate·$4H_2O$ crystals in 1848, which were mirror images of each other [1]. Le Bel and Van't Hoff (1874) independently proposed the theory of the tetrahedral nature of carbon 26 years later [2], which was the theoretical explanation of the discovery by Pasteur. From the beginning until the middle of our century the main task of organic chemists was the structure determination of natural products by degradation as well as by synthesis. As a result of these efforts, the so called *name reactions* were discovered. e. g. Diels-Alder reaction, Grignard reaction, Friedel-Crafts reaction to mention a few. Similarly different synthetic reagents were developed to perform a particular transformation e. g. different oxidation and reduction reagents.

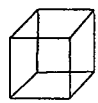
Even now the challenge of natural product synthesis is not over. A recent example is *Taxol* [3]. It is a product isolated from plant extracts containing 11 asymmetric centers. It is giving new hopes for cancer treatment and is a great challenge for synthetic chemists.

The new target for chemists is synthesis of unnatural molecules. Molecules which were attractive because of their special structure, have been synthesized by the chemists. e.g. cubane and dodecahedran (figure 1) [4].

Figure 1







Taxol (natural) **Dodecahedran** **Cuban** (unnatural)

At the middle of this century for the first time UV spectroscopy was applied in organic chemistry as an analytical method. Soon new different methods such as IR, NMR, MS, GC, HPLC, and X-ray were introduced for structure determination and analytical chemistry emerged as the new branch of chemistry [4]. In NMR spectroscopy, with the help of computers, various pulse techniques and fourier transform technique now not only proton NMR but many more nuclei such as ^{13}C, ^{17}O, ^{31}P, ^{15}N and 2D and 3D spectroscopy one can measured. Using chiral shift reagents in NMR spectroscopy, one can directly determine the enantiomeric excess (ee%) of mixtures of enantiomers. With the introduction of chiral column materials in GC and HPLC it is now possible to separate the two enantiomers and determine the ee. Tremendous progress has been made in this area. With an appropriate crystal, one can determine the structure and the absolute configuration of a molecule. The other direction in which the chemists are active in recent years is molecular recognition and the supramolecular chemistry [5].

As a result of these developments the broad division of chemistry into subbranches as organic, physical, inorganic is no more realistic. Now very often we see that chemistry is overlapping with the other branches of science such as biology, medicine, and physics. As a result, chemists often work

together with biologists and medical doctors on a pharmaceutical project or with a physicist on a material research project.

1.2 Challenges for the twenty first century chemists :

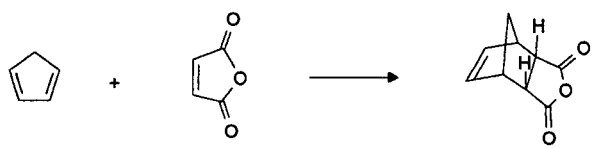
In spite of the progress made, the challenge for the synthetic chemists is not over. On the other hand the tasks are becoming more difficult and complicated. The two main tasks to be solved by chemists in the near future are :

1.2.1 New methods and technologies :

Not long ago the aim of the chemist was to synthesize the desired molecule by the shortest and the cheapest route. The last decade changed the course of the chemistry and especially the chemical industry. While planning the synthetic strategy, chemists started also thinking about the environmental impact along with the cost-profit ratio. Movements like Greenpeace got public sympathy because of the visible effects of the damaged environment increased the public pressure on the governing bodies and as a result, the government regulatory agencies have strengthened the laws. As a result chemists have to design the synthetic strategies in which the desired molecule is synthesized by a route in which the minimum amount of hazardous or toxic chemicals are used and the side products produced in the reaction are easily converted into environmentally acceptable waste.

The best example of an environmentally friendly reaction is the Diels-Alder reaction, because it does not produce any side products. This is ideal because the two starting materials react to form only the product.

Figure 2



Starting material

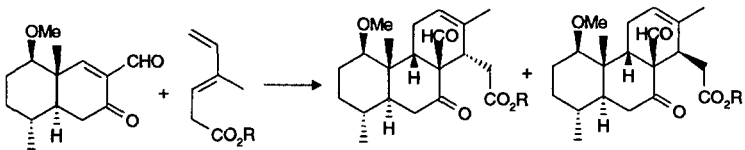
Product

This is not a simple and easy task to achieve and hence chemists are always looking for new reagents and methods that are chemo-, regio-, diastereo-, enantioselective and at the same time economical [6].

The best way of reducing the amount of toxic and hazardous reagents used is to minimize the use of environmentally dangerous materials or not to use them at all. An ideal synthesis from this stand point uses water as the solvent, solar energy as the light source, performing the reaction at ambient temperature producing high valued chemicals in 100% chemical and optical yield. At the moment it sounds like a dream but efforts are already being made in this direction.

An article in a recent *Chemistry & Industry* reviews the use of water as a solvent in chemical reactions [7]. Many different types of reactions, including pericyclic, nucleophilic addition, oxidation and even organometallic reactions, are reported to be carried out in water giving better results than the conventional organic solvents. Figure 3 shows an example of a Diels-Alder reaction.

Figure 3



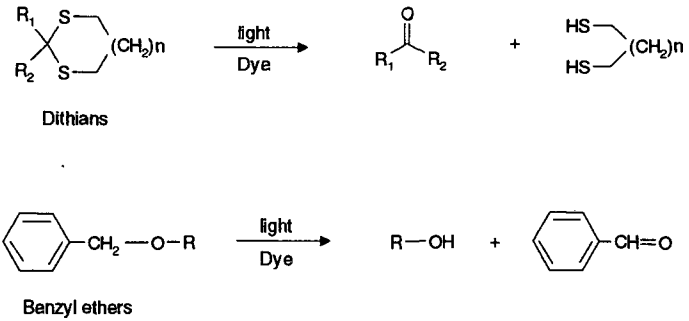
A **B**

R (conditions)	**Yield (A:B)**
Et (toluene, rt, 288h)	52% (0.85:1)
H (H_2O, rt, 17h)	85% (1.5:1)
Na (H_2O, rt, 5h)	100% (3:1)

Diels-Alder reaction in water as a solvent

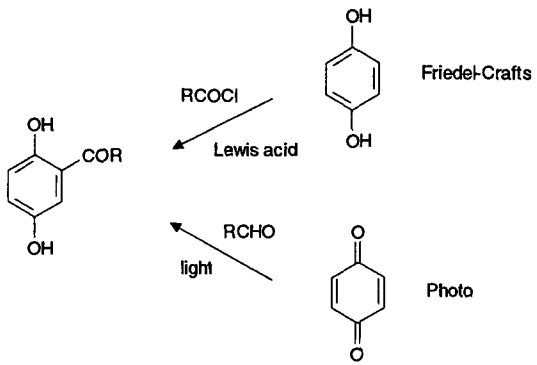
Oxidation is one of the basic transformations which uses toxic metal compounds as the oxidation reagent. The group of Prof. G. A. Epling has successfully used light energy to oxidize dithians to aldehydes or ketones using non toxic tood dyes as catalyst [8]. Figure 4 shows one example.

Figure 4



The Friedel-Crafts reaction is another important reaction which uses toxic reagents and solvents such as Lewis acids, $AlCl_3$, acid chlorides and nitro benzene. G. A. Kraus *et al* have used light energy to carry out the same transformation [8]. Figure 5 shows the transformations.

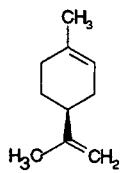
Figure 5



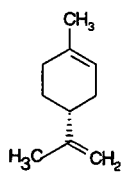
1.2.2 Enantiomerically pure compounds (EPC) :

In the last century L. Pasteur recognized that a compound exists as a pair of enantiomers which are related to each other as mirror images [9]. The 1:1 mixtures of enantiomers are called racemates. It was also known that the two enantiomers have the same physical and chemical properties except that they rotate the plane of linearly polarized light to the same extent but in the opposite directions. The discrimination between the two enantiomers can be made only in a chiral environment. Emil Fischer

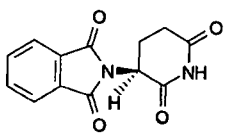
had recognized this and in 1894 postulated the *lock and key* principle [10]. Biological systems are built from chiral receptors which are able to differentiate between the two enantiomeric forms of a simple organic molecule. As a result the two enantiomers are recognized as two different substances and may react differently. For example the chiral structure in our nose can differentiate between the two enantiomers of limonene. The (+)-limonene has orange smell while the (-)- limonene has lemon smell. The importance of having the EPC is evident by the tragic example of thalidomide, where the *(R)* enantiomer is a very effective sedative while the *(S)* enantiomer is teratogenic. The use of the racemate as a drug led to the birth of thousands of disabled children in the sixties [11]. Figure 6 shows the structures of the enantiomers. A very recent publication describes the enantioselective synthesis of both *(R)* and *(S)* -Thalidomide from *(R)* and *(S)* glutamic acid [12].



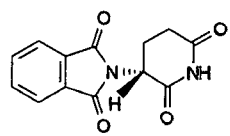
(+)-Limonene
orange smell



(-)-Limonene
lemon smell



S-Thalidomide
teratogenic



R-Thalidomide
sedative

Figure 6

This was the starting point for the health authorities to impose regulations on a national and supranational level in respect to medicinal products to primarily protect the citizens by requiring "quality, safety and efficacy". This gave an enormous shift from the development of racemic pharmaceuticals to chiral one's [11,13]. The following chart in figure 7 shows the 1990 position of chiral drugs in the pharma industry. The market for chiral drugs in 1989 was $ 465 million and was expected to reach $ 1,300 by 1995 [14,15]. Figure 7 shows the division in different categories.

Chiral Drug Sales (1990)

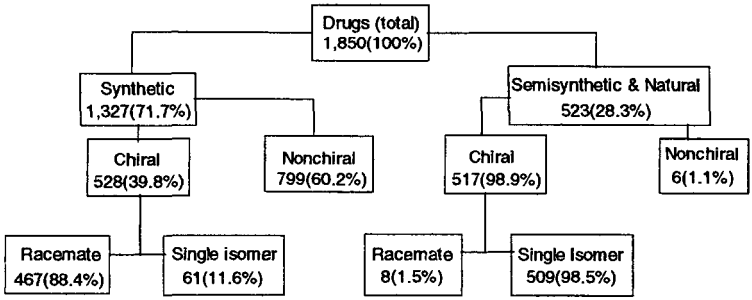


Figure 7

To obtain EPC's is not an easy task. The classical method is the separation of a racemate though it is tedious, and sometimes difficult as well. As the EPC's started gaining more and more importance in natural product synthesis, the pharmaceutical and agrochemical industry as well as in the academics, various methods to achieve enantiomerically pure substances were explored [16].

One can obtain the desired chiral molecule by different methodologies:

A. Start the synthesis with a naturally occurring starting material, from the so called *"Chiral Pool"*. e.g. D-sugars, L-amino acids, terpenoids, alkaloids [16a].

B. Resolve the racemate into the two enantiomers by choosing one of the different methods available e.g. selective crystallization or by chromatographic separation.

C. By enantioselective asymmetric synthesis with the help of "chiral ligand - metal complex" or with the help of a suitable micro organism or an enzyme from prochiral starting material.

Figure 8 shows the different ways to obtain enantiopure compounds.

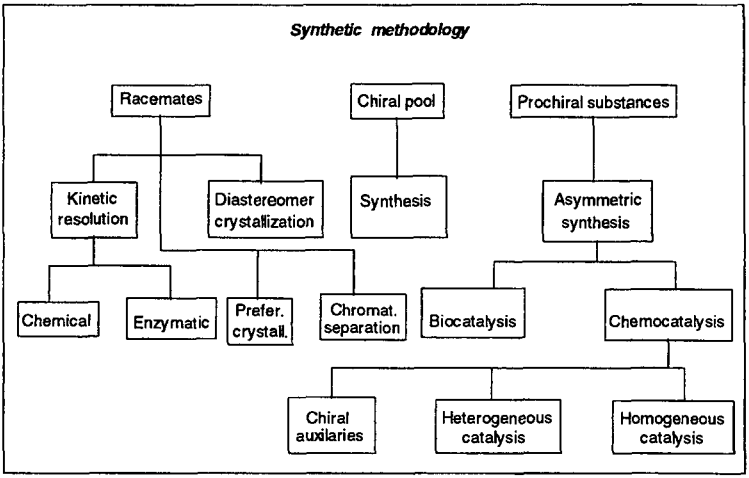


Figure 8

Each method has it's advantages and disadvantages over the other methods. Starting with a substance from the chiral pool, it may not always be possible to synthesize the desired molecule. The chiral pool is a limited choice of chiral starting substances and hence a limited collection of functionalities.

To resolve a racemate by recrystallization of a diastereomeric derivative, it is necessary that only one diastereomer crystallizes while the other remains in the solution. To achieve a good separation requires a lot of empirical experiments modifying the solvents and temperature (trial and error).

The chromatographic separation using a chiral column is at the moment quite popular and widely used analytical method [15]. The advantage is that both enantiomers are available in pure form which is often required as the regulatory agencies require studies of the biological activity of both the enantiomers. But the disadvantage is that one cannot isolate the desired enantiomer on a ton scale but is limited to a few kilograms. In addition, the second enantiomer (50% of the valuable starting substance) is wasted or a suitable method must be found to racemize and separate the enantiomers once again.

With microorganisms or enzymes most of the reactions take place at ambient temperature and narrow pH ranges, typically between 6- 8. In some cases this requires large investments. The selectivity to syntheses of both enantiomers takes a long while till one finds the right organism e.g.

(R)- Oxynitrilase was known since 30 years [17a-d] but enzymes which synthesize the *(S)* enantiomer were only recently applied in organic synthesis [17f,g].

In catalytic asymmetric synthesis, an enantiopure catalyst is used to carry out the reaction on the substrate to produce only one enantiomer. By using the other enantiomer of the catalyst the second enantiomer is also achieved. This method utilizes enantiopure reagents in catalytic amount, hence is more elegant and economical.

The use of microorganisms and enzymes is widespread but even then the exact mechanism is not yet clearly understood. On the other hand the mechanism of chiral ligands in the reaction producing EPC's is much more clear. E. J. Corey has coined the term *Chemzymes* for these tiny molecular catalysts [18]. *Chemzymes* are small soluble organic molecules that can catalyze certain reactions in much the same way that natural enzymes catalyze biochemical reactions. It stands for the word chemical enzymes. The advantage of *Chemzymes* over enzymes is that one can rationally design the ligand molecules to perform certain reactions.

Another advantage of asymmetric synthesis catalyzed by chiral ligands is these are catalytic processes in which one chiral catalyst molecule produces thousands of product molecules of definite configuration (amplification). In recent years there are a number of examples where this approach has been applied commercially [19]. Figure 9 shows the industrial applications in the recent years.

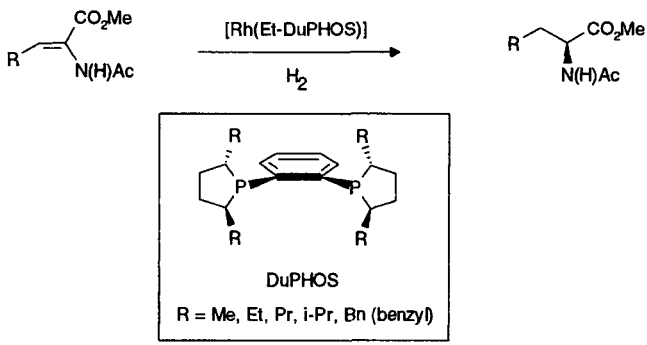
Commercial applications of enantioselective catalysis using metal complexes

Company	Metal	Reaction type	Product
Monsanto	Rh	Hydrogenation	L-Dopa
Sumitomo	Cu	Cyclopropanation	Cilastatin
Anic, Enichem	Rh	Hydrogenation	L-Phenylalanine
J. T. Baker	Ti	Epoxidation	Disparlure
ARCO	Ti	Epoxidation	Glycidols
Takasago	Rh	Rearrangement	L-Menthol
Merck	B	C=O reduction	MK-417 (opthalmic)
E. Merck	Mn	Epoxidation	Antihypertensive
Takasago	Ru	Hydrogenation	Carbapenem

Figure 9

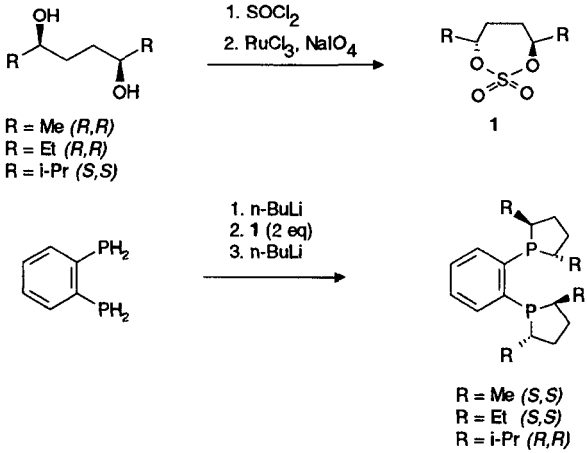
Till recently one had to depend on the chiral pool for the chiral material. e.g. D-Glucose, L-anino acids, terpenoids, and alkaloids were the main source for obtaining chiral substances. So the choice was limited. Even this restriction of chiral pool to provide the α-amino acids in enantiomerically pure form is no more valid with the DuPHOS-Rh catalyst. e.g. access to both the enantiomers of α-amino acids in enantioselectivities approaching 100% is possible by asymmetric rhodium catalyzed hydrogenation of various N-acetamidoacrylate esters (Figure 10).

Figure 10



The various DuPHOS can be obtained in a simple reaction sequence as shown below. Starting from the same material, both enantiomers of DuPHOS can be obtained [20]. The chiral 2,5-dihydroxy hexane can be obtained in both the enantiomeric forms by reduction of the β-keto ester by Ru-BINAP catalyst. Figure 11 shows the reaction sequence.

Synthesis of DuPHOS



The chiral diol preparation

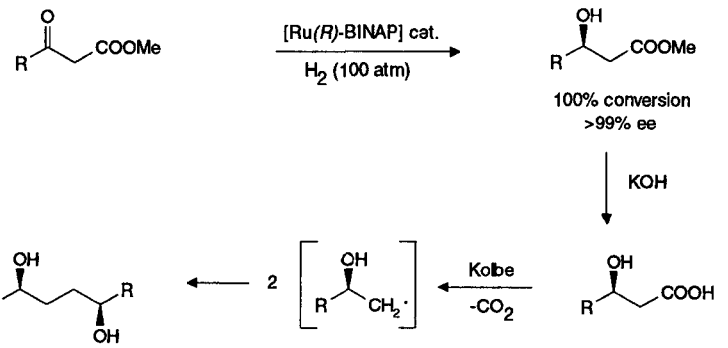


Figure 11

Metal complexes are not only used in nature and by the chemical industry but have also found application as drugs. The case in point is of Desferal. The molecule of *Desferrioxamine B*, which is obtained as a metabolite in the fermentation of a microorganism forms a complex with Fe(III) ion. This is at present the drug of choice for the treatment of transfusional iron overload (Desferal, *CIBA*) in β-thalassemic patients [21]. This ligand forms a complex with the excessive Fe(III) ions in the blood

of the patient. It is then excreted from the body as it's Fe complex giving relief to the patient. Figure 12 shows the complex with Fe ion.

Desferrioxamine B + Fe(III)

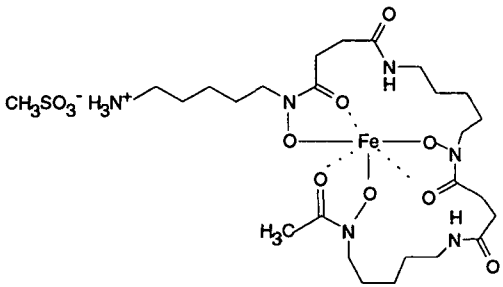


Figure 12

2.0 The Theme

In the last decade the use of enantiomerically pure compounds has increased dramatically and so have the different ways to obtain them [4,22]. Asymmetric synthesis, that is synthesis which produces just one enantiomer is on the forefront and homogeneous catalysis is one of the most popular methods. In this method one uses in the reaction a chiral complex as a catalyst, which induces chirality in the product.

Depending on the reaction, the chiral complex is synthesized in situ from a suitable metal ion and a suitable chiral ligand or the complex is prepared separately as an isolable compound. To get both enantiomers of the product, both enantiomers of the chiral complex (ligand) must be available in pure form. This is not often easy to achieve, especially when the ligand is derived from chiral pool molecules. e.g. L-amino acids, D-sugars or naturally occurring α - or β - hydroxy acids. For example L-(+)-tartaric acid, L-malic acid or 3-*(R)*-hydroxy butyric acid, monomer of Biopol [22 c,d]. In the case of the unnatural series the corresponding enantiomer is either unavailable or very expensive.

Therefore it would be a fascinating idea to have a synthetic possibility which produces both the enantiomers from the same chiral starting substance !!!

And taking this idea as a working hypothesis we started this work. 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid in 99% optical purity was available in multi kilogram quantities from a pilot plant process in *CIBA* and the ideal starting material for our synthetic endeavors.

Using 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid as starting material we planned to achieve the following goals:

- Synthesize both enantiomers of different tetra aryl glycerols (not reported in the literature until now).
- Use these tetra aryl glycerols and the other intermediates synthesized during our synthesis to prepare chiral metal complex with a suitable metal ion.
- Test these chiral metal complexes in selected reactions as a chiral homogeneous catalyst.

This goal can be achieved at least on paper following the retrosynthetic scheme in figure 13.

Retrosynthesis of Tetra aryl glycerol

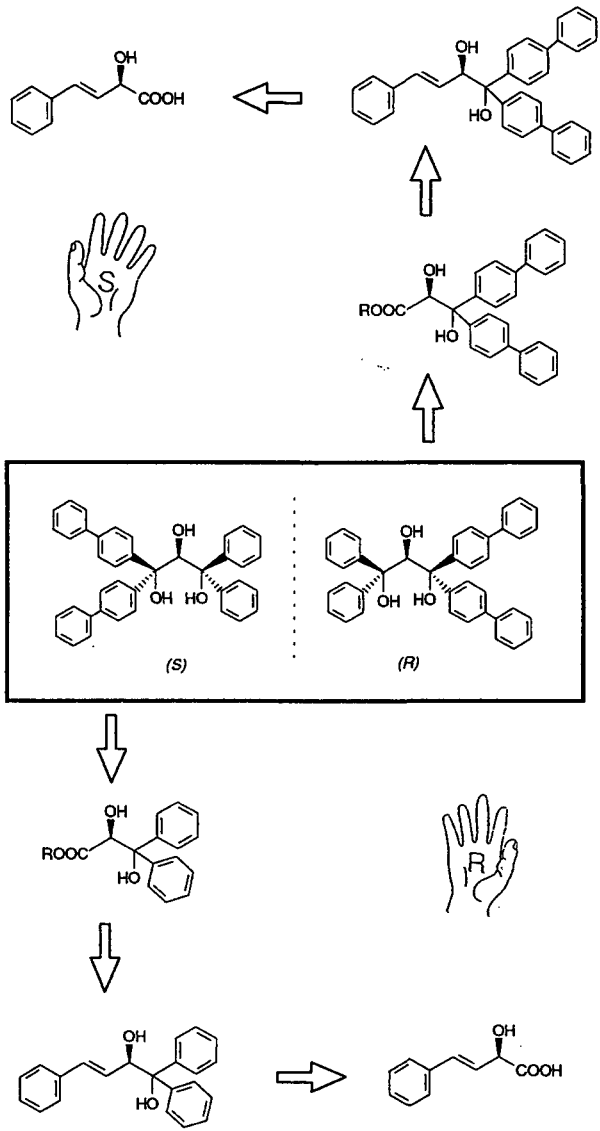


Figure 13

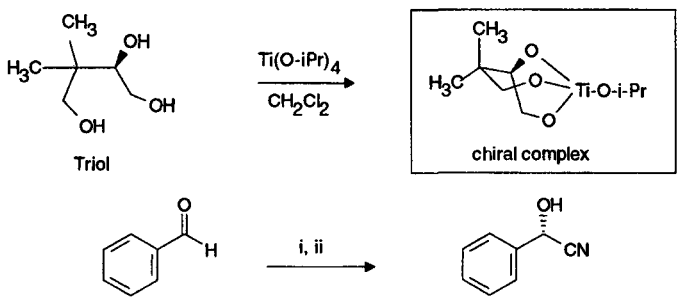
Retrosynthesis of both enantiomers of tetre aryl glycerol from the same chiral starting material by changing the sequence of the Grignard addition.

3.0 SYNTHESIS OF THE LIGANDS :

3.1 Why glycerols as ligands ?

The aim of this work was to synthesize chiral tetra aryl glycerol in their both enantiomeric forms and then use these chiral tetra aryl glycerols and some of the chiral intermediates obtained during the synthesis, as ligands for the synthesis of enantiomerically pure catalysts (See chapter 4.0). e.g. the glycerol can function as a tridentate ligand and hence can form a chiral complex with a suitable metal ions similar to the example shown below. Chiral triol - titanium ion complex [triol obtained from *(R)* Pento lactone] is used as a chirality inducer in the hydroncyanation of benzaldehyde [23]. The ee is up to 76%. The nitrile group can be easily converted to a carboxylic acid. So this is another method to obtain chiral α- hydroxy acids, but unfortunately this process is not catalytic. Figure 14 shows the reaction sequence.

Figure 14



i.TMSCN, chiral complex, solvent
ii. 1N H_2SO_4

TADDOL is a diol ligand whose synthesis was discovered by Toda [24a] and applications developed by D. Seebach and coworkers, starting from tartaric acid. They have prepared a number of different TADDOL ligands and demonstrated that they can be used as efficient chiral inducers in different reactions.

TADDOLs can be used in the reductive addition of dialkyl zinc reagents to aldehydes, a C-C bond forming reaction [24b,c,d]. The product alcohol is obtained with a chemical yield of more than 80% in

most of the cases and optical yields of greater than 90% ee in most cases. In some cases even 99% e.e. is obtained. Figure 15 shows the reaction sequence.

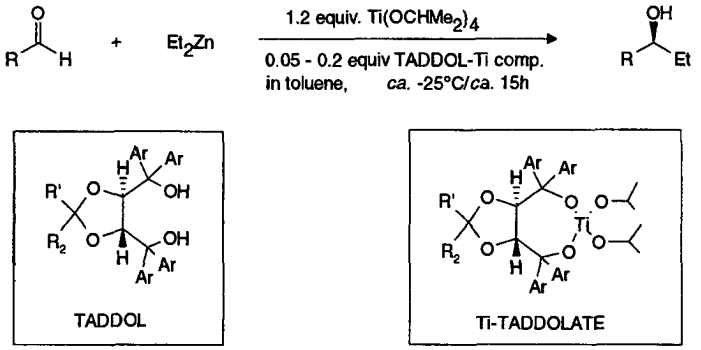


Figure 15

TADDOL is also shown to be a very efficient catalyst in the Diels - Alder reaction. In the example shown below the product is obtained in 89% chemical yield and 91% ee [25]. Figure 16 shows the reaction sequence.

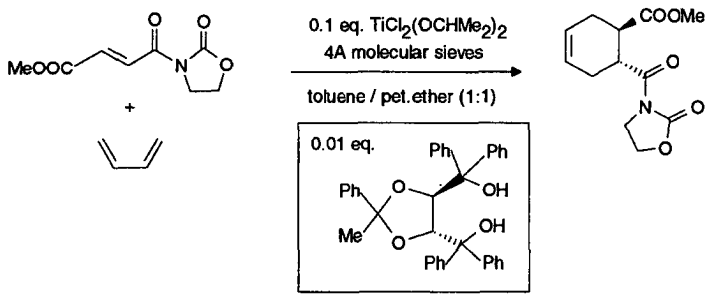
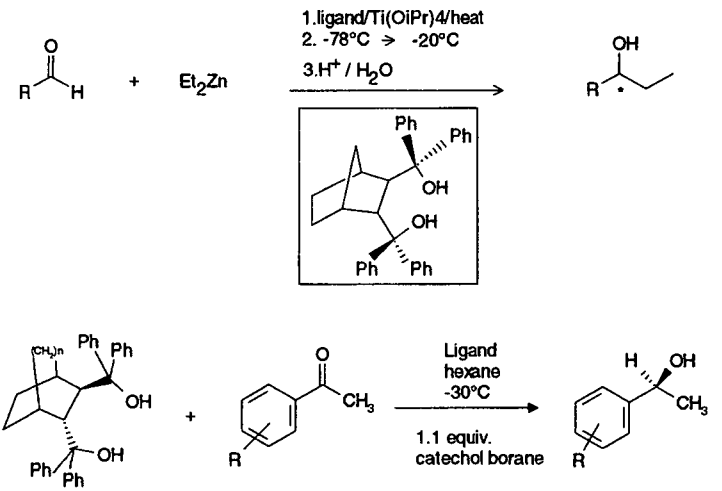


Figure 16

Bicyclic analogs of TADDOL are also shown to be very good chiral inducers for the addition of an ethyl group to an aldehyde utilizing $Zn(C_2H_5)_2$. This provide an optically active alcohol in high ee [26]. Bicyclic analog of TADDOL have also been applied to borane/ titanium alkoxide mediated reductions of aryl alkyl ketones [27]. The chemical yields are reported to be above 95% whereas the

optical yields are in the range of 89-95% ee in the first case and 85-100% conversion with up to 84% ee in the second case. Figure 17 shows the reaction sequence.

Figure 17



Ligand 10 mol%

These are only some examples in which diols and a triol have been successfully used as a chiral ligand. For further examples, refer to chapter 4.0. Using these examples as a starting point we decided to prepare some tetra aryl glycerols and use them as chiral inducers in some enantioselective reactions.

3.2 The starting material

The starting material used for the present project was 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid 1 of 99% (ee). It is a very important enantiomerically pure starting material as it is a chiral building block for the *(S)*-homophenyl alanin pharmacophor of many ACE-inhibitors (Angiotensin Converting Enzyme-inhibitors) sold on the market like Benazepril (*CIBA*), Enalapril (*MSD*), and Cilazapril (*Roche*) [28] (See Figure 18). 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid 1 can be obtained by enantioselective reduction of the keto group of prochiral β,γ-unsaturated α-keto acid followed by the reduction of the double bond [29], by enantioselective reduction of 2-oxo-4-phenylbutyric acid with Rh catalyst [30],

and by microbial reduction with the microorganisms *Proteus mirabilis* or *Proteus vulgaris* [31]. Acid **1** was obtained from the microorganism *Proteus mirabilis*. The saturated analog of **1**, 2-*(R)*-hydroxy-4-phenyl-butyric acid **31** can also be obtained via enzymatic stereoselective reduction of the corresponding α-keto acid using D-Lactate dehydrogenase and NADPH as Co-factor via EMR (Enzyme Membrane Reactor) technology [32], via a chemical approach using homogeneous asymmetric hydrogenation [33] or Pt/Al_2O_3/Cinchonidin as catalyst [34], by lipase induced enzymatic resolution of a racemic derivative [35], by chemical resolution of the racemic acid or by asymmetric catalytic $Ti(OR)_4$- mediated hydrocyanation [36,37].

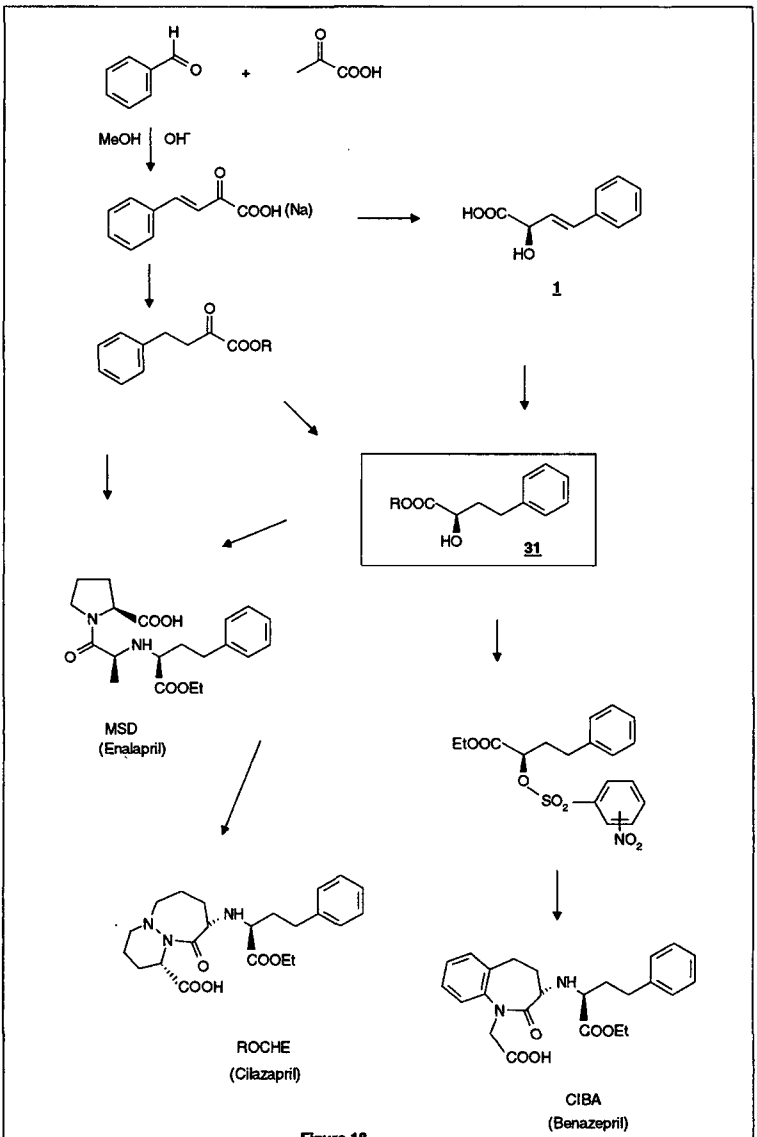
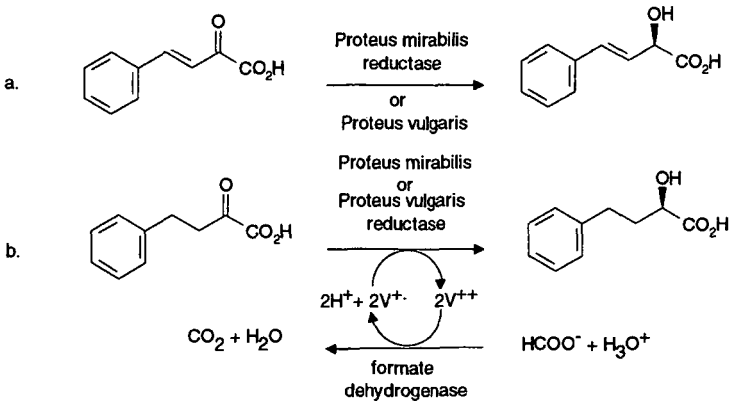


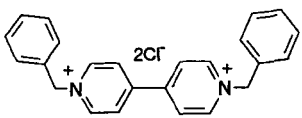
Figure 18

ACE - inhibitors derived from
2-*(R)*-hydroxy-4-phenyl-butyric acid

3.2.1 Preparation of the hydroxy acid 1 and conversion to the ester 2.

The starting material 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid 1 was prepared by stereoselective reduction of the corresponding prochiral β,γ -unsaturated α-keto acid by microbial transformation. Whole cells of *Proteus mirabilis* are used for the transformation and benzylviologen was the electron mediator. The radical cation of benzylviologen is the reduction equivalent normally delivered by a coenzyme, for example NADH or NADPH [28]. Benzylviologen is reduced to the radical cation by formate and formate dehydrogenase as catalyst, which is also present in the organism. The figure 19 shows the process.





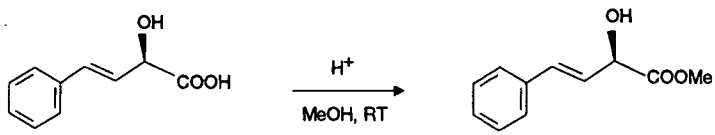
a. V^{++} = benzylviologen

Figure 19

The starting substance 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid 1 has one chiral center bearing an OH function. In order to synthesize a triol two more hydroxy groups have to be introduced. To achieve this, 1 was first converted to an ester. The methyl ester was prepared by dissolving this acid in dry methanol containing 1M HCl gas. A clear orange red colored solution was formed which was stirred overnight. After normal workup, ester 2 was obtained as a viscous oil. This dark red colored oil was

distilled (0.02 mbar, 120° C bath temp.). A faint yellow colored liquid distillate was obtained which slowly solidified into fine, low melting crystals (yield 72%) and some dark substance remained as a 'polymeric' residue . In a similar way the ethyl ester was also prepared but in the further synthesis only the methyl ester was used.

Figure 20



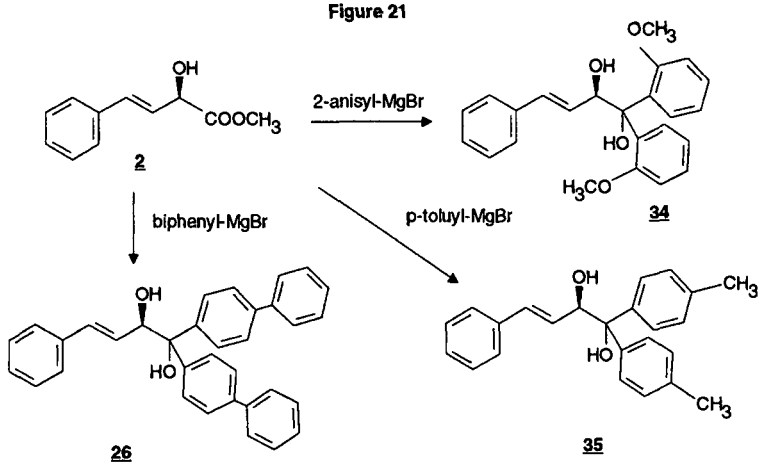
1 2

3.2.2 Protection of the hydroxy group in hydroxy ester 2 and Grignard reaction.

The introduction of the second OH group can be achieved by reacting the ester with either ArLi or with ArMgX, a Grignard reagent. In the literature it was found that the chemical yields by bofh the reactions are in the same range [38]. Hence the Grignard reaction was preferred over lithium reagent as the 'Ar' group can easily be varied using different aryl halides.

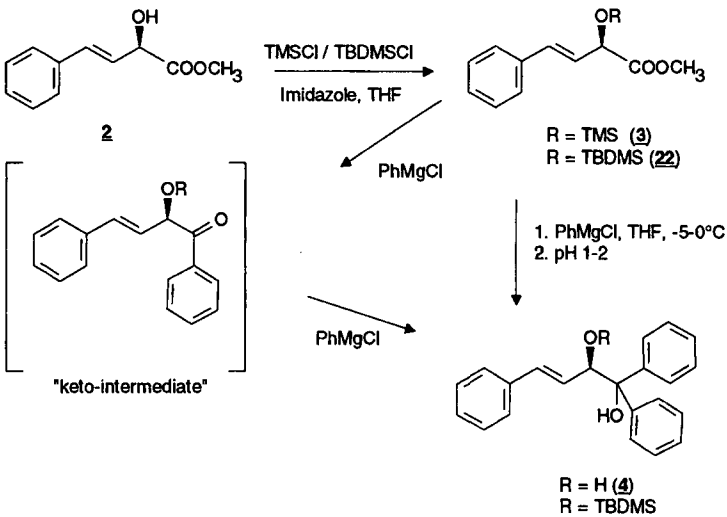
When the free α -hydroxy methyl ester 2 was reacted with four equivalents of phenyl magnesium chloride (PhMgCl), the desired diol 4 was obtained. Even though the starting material was completely consumed, the product was isolated in a poor yield (40%). Diol 26 was obtained in a similar way by reacting 2 with the Grignard reagent prepared from 4-bromo-biphenyl and Mg metal in THF at 0° C. Different diols 34 and 35 were prepared by reacting 2 with different Grignard reagents prepared from 2-bromo-anisole and 4-bromo-toluene respectively. 34 and 35 were also obtained in 40% yield. 26 was utilized to produce the other enantiomer of the glycerol 12 as shown in the figure 21.

Figure 21



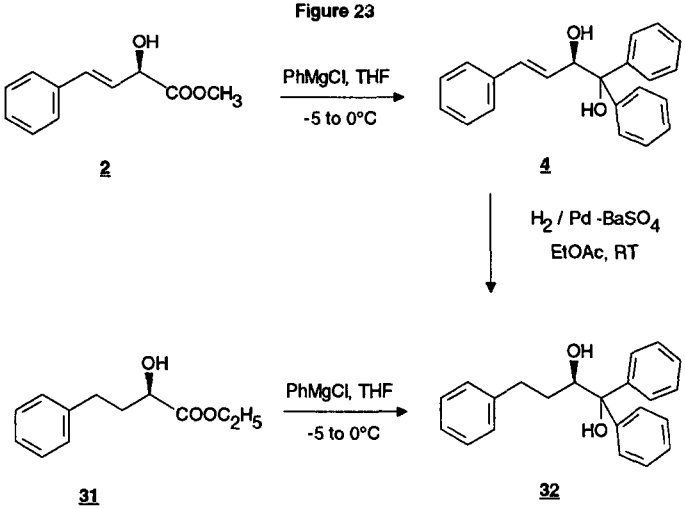
To improve the yield, the free hydroxy group was protected as a silyl ether e.g. as trimethyl silyl (TMS) [39] 3 or tert. butyl dimethyl silyl (TBDMS) [40] 22 ether. On reacting these ethers with PhMgCl, the yield of the Grignard reaction could be improved to some extent (50%). The TMS protecting group has an advantage over the TBDMS, as TMS is very acid sensitive and therefore can be removed easily during the reaction work up, whereas the TBDMS group requires the use of tetra butyl ammonium fluoride for deprotection. The acidic work up conditions of the Grignard reaction (pH 1-2) removes the TMS protecting group to give the diol 4 as shown in figure 22.

Figure 22



The yield of the Grignard reaction was somewhat lower than expected. In order to obtain the analog of **4** as ligand the diol **32** was prepared. The aliphatic chain in **32** should give more rotational freedom than the double bond of compound **4**. Compound **31**, the saturated analog of **2** was readily available as ethyl ester in 99% optical purity [41]. It was reacted with the Grignard reagent PhMgCl at -5 to 0° C in THF to obtain the diol **32** in more than 90% yield. **32** could also be prepared by reduction of **4** over 5% Pd on $BaSO_4$ at room temperature in ethyl acetate. The yield of the reaction using the saturated analog **31** was quantitative. In the case of the Grignard reaction of **2** leading to **4**, the yields are much lower. We were unable to isolate the side products. We hoped to improve the yield using a large excess of Grignard reagent. Some inseparable apolar side products were observed on the TLC, one of them might be the unsaturated hydroxy "ketone intermediate" (see the fig. 22 above). There are examples known in the literature where after the first Grignard addition the reaction stops in the intermediate keto stage, probably because of stearic hindrance [42a]. Even by using four equivalents of Grignard reagent the yield could not be improved. This was not observed in the case of it's saturated analog. **32** was isolated in about 90% yield. Therefore other reasons than the stearic hindrance must be responsible for the lower yields in the unsaturated case of **2**. Figure 23 shows the reaction sequence.

Figure 23



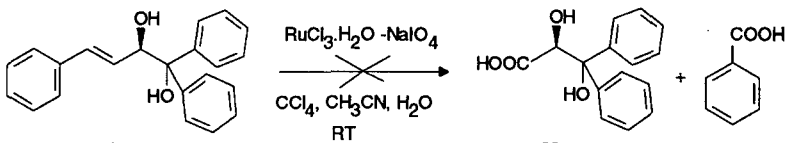
4 and 32 have similarity with the HYTRA ligands developed by M. Braun [42b].

3.3 Synthesis of the diol acid 33

3.3.1 Protecting group requirement of the diol 4.

In our synthetic strategy the next chemical conversion was the oxidative cleavage of the double bond to the carboxylic acid 33. Various methods are used for this purpose e.g. the combination of $RuCl_3 \cdot H_2O$-$NaIO_4$ [43], ozonolysis [44], and $KMnO_4$ [45] to mention a few. We first tried the $RuCl_3 \cdot H_2O$ - $NaIO_4$ system. Using the modification of A. Greene, diol 4 was dissolved in a biphasic solvent system consisting of $RuCl_3$ / $NaIO_4$ and $NaHCO_3$ [46]. The solvent system was a mixture of CCl_4, CH_3CN and H_2O in the ratio of 1:1:1.5. The reaction was stirred for 3 hr at room temperature. The TLC showed a mixture of different products. The ozonolysis of 4 in CH_2Cl_2 at -78° C also showed similar results. Therefore it seemed necessary to protect both hydroxy groups. Figure 24 shows the reaction.

Figure 24

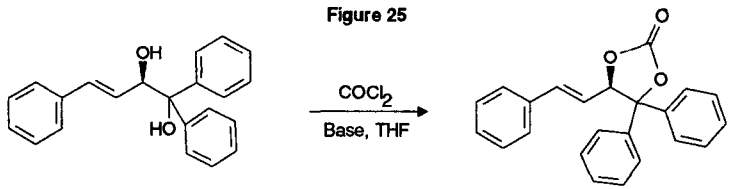


4 33

3.3.2 Cyclic carbonate :

The carbonate group was the first choice [47] as it is easy to prepare and both the OH groups are protected by one protecting group. The diol **4** was dissolved in THF and reacted with an equimolar amount of phosgene (20% solution in toluene) at room temperature in the presence of 2.5 equivalents of triethyl amine as the base [48]. Reaction is shown in figure 25.

Figure 25



4 5

It was not a clean reaction though a small amount (20%) of the desired product **5** was isolated after chromatography. Other bases such as N-methyl morpholine and pyridine were also used in order to improve the yield, but without any success.

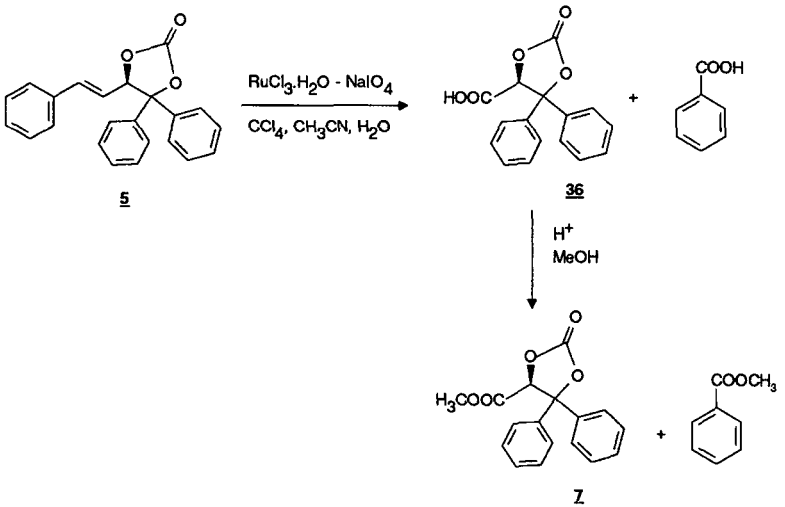
The reagent N,N'- carbonyldiimidazole was found to be the most efficient reagent to introduce the cyclic carbonate group [49]. The diol **4** and N,N'- carbonyldiimidazole were dissolved in THF and stirred overnight at room temperature. After complete consumption of **4** the reaction was worked up. The crude product was passed over a short silica gel column and the solid obtained after removing the solvent was recrystallized. The product **5** was obtained in more than 90% yield.

In view of these phosgene experiments we come to the conclusion that the formation ot the cyclic carbonate group was not trivial. So instead of persuing the same protecting group with different reagents like N,N'- carbonyldiimidazole, different protecting groups which could be easily prepared were tried out. (See chapters 3.3.4 and 3.3.5).

3.3.3 Oxidative fission of styryl carbonate 5

Carbonate 5, obtained by using N,N'-carbonyldiimidazole, was subjected to double bond cleavage using the reagent $RuCl_3$ (3.5 mol%) - $NaIO_4$ (4.1 equivalent) in a solvent system consisting of CCl_4, CH_3CN and H_2O in 1:1:1.5 ratio. The reaction was carried out at room temperature for 6 hours. The protecting group survived the oxidation conditions very well to get 36 (not isolated in pure form) and benzoic acid in equal amounts. Figure 26 shows the reaction sequence.

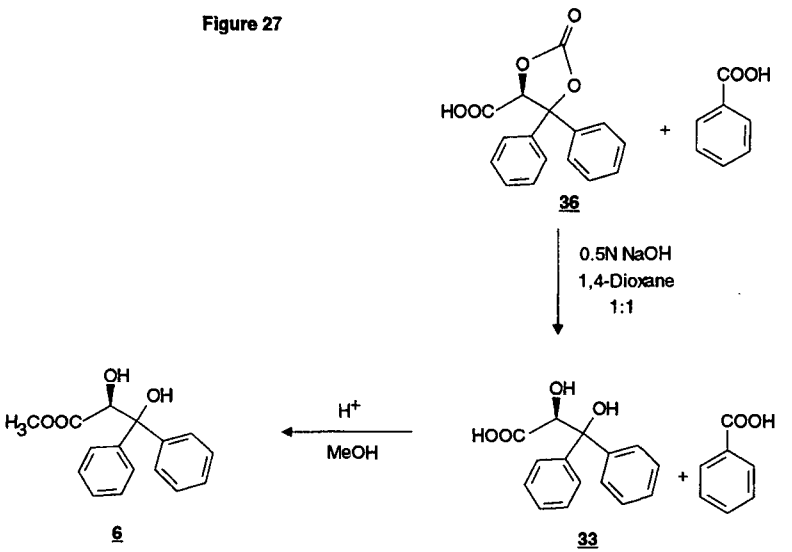
Figure 26



5 36 7

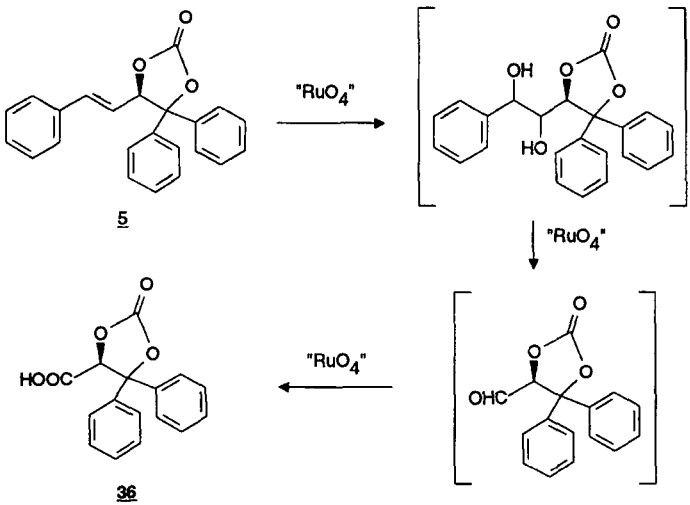
All attempts to separate the mixture of the two acids by chromatography failed. Therefore this mixture was treated with methanol containing 1M HCl gas and stirred overnight at room temperature. Both acids were converted to their corresponding methyl esters. The boiling point of methyl benzoate is relatively low. Hence this mixture of esters was subjected to high vacuum distillation with stirring (0.02 mbar, up to 50° C bath temperature) for three hours. By this procedure most of the methyl benzoate was removed and the remaining carbonate ester 7 could be purified by chromatography. Figure 27 shows the reaction scheme.

Figure 27



The carbonate group could also be cleaved at the stage of **36** . The crude reaction product was dissolved in 1:1 mixture of 1,4-dioxane and water containing 0.5N NaOH and stirred for one hour at room temperature [50]. Then the reaction is acidified with 1N HCl and after normal work up the acid mixture was esterified to methyl esters **6** and methyl benzoate. Methyl benzoate was removed on high vacuum as described above. The crude diol ester **6** was recrystallized from acetone : water. **6** was obtained in 46% overall yield based on carbonate **5**.

Figure 28



5

36

Reaction mechanism for the oxidation of the double bond to an acid

Recently T. K. M. Shing *et al* published two articles [51] about ruthenium catalyzed oxidation of alkenes. Using the same system as developed by Sharpless with a small change concerning the ratio of the solvents, temperature and reaction time they could isolate cis diols with very high chemical yield. A 2:2:3 mixture of carbon tetrachloride, acetonitrile, and water was proposed by Sharpless whereas Shing and coworkers used a 3:3:1 ratio of the same solvents. Ethyl acetate was also found to be good substitute for carbon tetrachloride. $RuCl_3.(H_2O)_3$ was used in 0.07 mol equivalent and $NaIO_4$ 1.5 mol equivalent. The reaction was run at 0° C for three minutes. Under this conditions they were able to isolate cis-dihydroxylated products in high chemical yield and good diastereoselectivities [51]. First the diol is produced, which is then cleaved oxidatively to an aldehyde which further gets oxidized to an acid as shown in figure 28 above. It is also known that this system also oxidizes the phenyl ring to an acid [43], which probably justifies the low overall yield of the reaction sequence **5** to **6**.

3.3.4 Acetonide :

As the carbonate group could not be introduced in good yield during our first attempts with phosgene, several other protecting groups were tried out. The next protecting group of choice was the acetonide group. Acetonide is also one of the most commonly used protecting group for 1,2 - diols. It has many advantages:

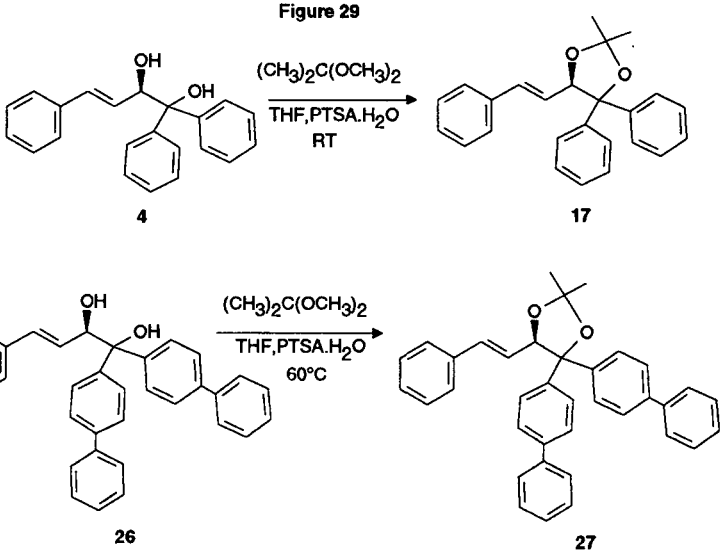
A) This group is easy to introduce and many different methods are available for it's formation.

B) It is quite stable to a broad range of conditions including oxidation and basic pH.

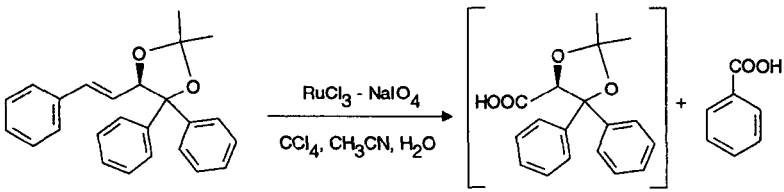
C) As it is very widely used, many different methods have been developed for the deprotection.

The diol **4** was dissolved in THF and reacted with 2,2-dimethoxy propane in the presence of a catalytic amount of p-toluene sulfonic acid·H_2O (PTSA·H_2O) [52]. The reaction mixture was stirred overnight at room temperature. After the workup, it gave the desired crude product **17** which was recrystallized from n-hexane to give fine colorless crystals in more than 90% yield. In a similar way **26** was reacted with 2,2-dimethoxy propane. The reaction was carried out for 10 hr. at 60° C in THF and **27** was obtained. The crude product was passed over a short silica gel column and the solid obtained was recrystallized to get **27** in 88% yield. The reaction to produce **27** from **26** required 10 hours at 60° C where as **17** could be produced from **4** at room temperature. This suggests that probably **26** has more stearic hindrance as compared to **4**. See figure 29.

Figure 29



17 was then subjected to an oxidative cleavage of the carbon-carbon double bond to the carboxylic acids. For this, $RuCl_3 \cdot H_2O$ and $NaIO_4$ was used as the oxidant utilizing a CCl_4, CH_3CN, H_2O (1:1:1.5) mixture as the solvent system [43]. The reaction proceeds quite smoothly at room temperature. The desired acid 37 was produced in equimolar amounts together with benzoic acid. The reaction is stirred for fifteen minutes with an excess of solid $NaHCO_3$ which is added in one portion to the reaction. By this modification the acid mixture can be easily isolated as a it's sodium salt [46].

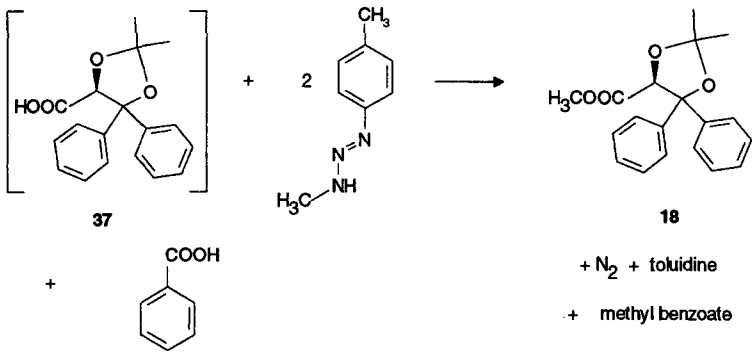


17 37

This mixture of acids was very difficult to separate. Therefore advantage was taken of the fact that the esters of benzoic acid are easily distillable under high vacuum whereas the esters of the desired acid have much higher boiling points. The crude reaction product which was a mixture of the above acids was directly converted to their corresponding methyl ester 18 and methyl benzoate respectively by reacting with 3-Methyl-1-(p-tolyl)-triazen in methylene chloride. The reaction was complete after stirring overnight at room temperature. As we later learned, the acetonides of this class are quite stable to acid. Therefore, the reaction mixture was extracted with 10% aqueous citric acid solution until the organic phase was free from toluidine, which was the byproduct of this reaction. The acetonide group survived the workup conditions. After the usual workup the raw product was subjected to high vacuum distillation (0.02 mbar) and the flask was gently heated in an oil bath at 50° C. After about four hours, most of the methyl benzoate was removed from the mixture and then the crude product was purified by flash chromatography on a silica gel column using toluene as eluent. The yield of 18 after the two steps (oxidation and esterification) was moderate at around 40%. It is known that under this oxidation reaction conditions ($RuCl_3$ - $NaIO_4$) the phenyl ring can also undergo degradation [43]. This could explain the low overall yield obtained in this transformation. A white

crystalline product was obtained after recrystallization. The following Figure 30 shows the reaction sequence.

Figure 30



3.3.5 Other protecting groups used :

Benzylidene acetal :

The advantage of this protecting group is the easy preparation and more importantly, it can be cleaved hydrogenetically under mild conditions [53]. This protecting group, which is similar to the acetonide group can be attached by refluxing the diol **4** with benzaldehyde in toluene as a solvent and in the presence of an acid catalyst for example p-toluene sulfonic acid·H_2O (PTSA·H_2O) [54]. The reaction was refluxed until no more water separated in the Dean-Stark apparatus. Since the yield of the reaction was not good and a mixture of diastereomers was obtained, this reaction was not investigated any further. It has also to be taken into consideration that during cleavage of the benzylidene acetal by hydrogenation, the benzylic tertiary carbon oxygen bond might be cleaved along with the protecting group.

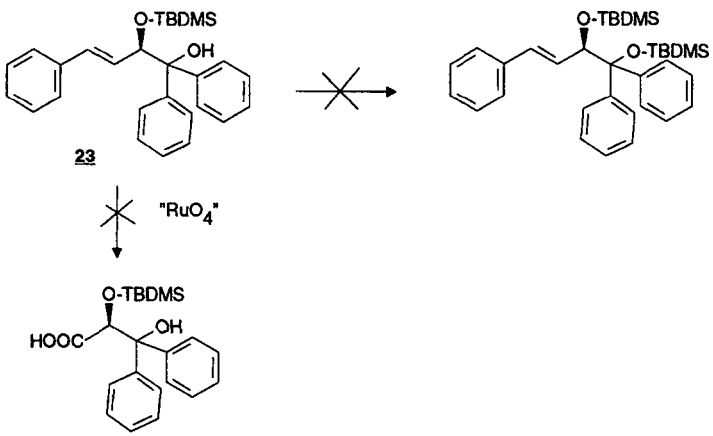
Silyl ethers :

An attempt was made to prepare the silyl analog of the acetonide group by reacting the diol **4** with dichloro dimethyl silane in different solvents such as acetonitrile, CH_2Cl_2, DMF, toluene : CH_2Cl_2 (1:1 mixture) and in the presence of different bases such as imidazole, N-methyl morpholine, or pyridine [55]. The reaction failed to give the expected product. It always gave some "polymeric product" of unknown structure.

Bis-TBDMS :

The mono TBDMS protected diol **23** was refluxed with 1.2 equivalent of TBDMS-Cl and 1.5 equivalent of imidazole in acetonitrile, but still it did not react. All attempts to protect the tertiary OH failed. Hence **23** was reacted with $RuCl_3 \cdot H_2O$-$NaIO_4$ system which also failed to give the desired acid **33**. The reaction produced a mixture of many products. One of the products could be identified as benzophenone, which is formed by oxidative cleavage of **23**. The reaction scheme is shown in the figure 31.

Figure 31



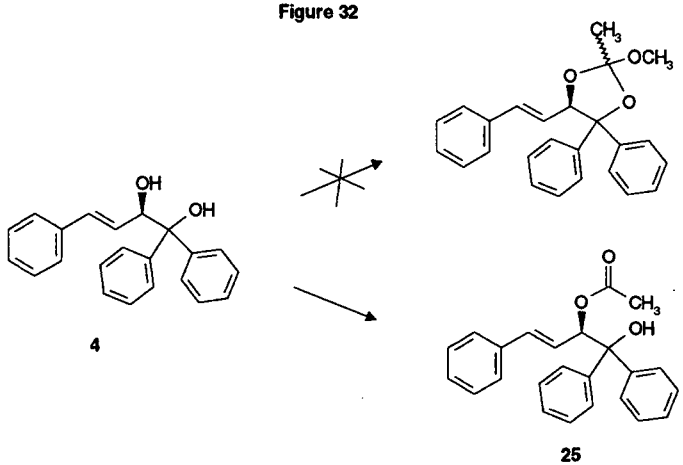
Phenyl boronate :

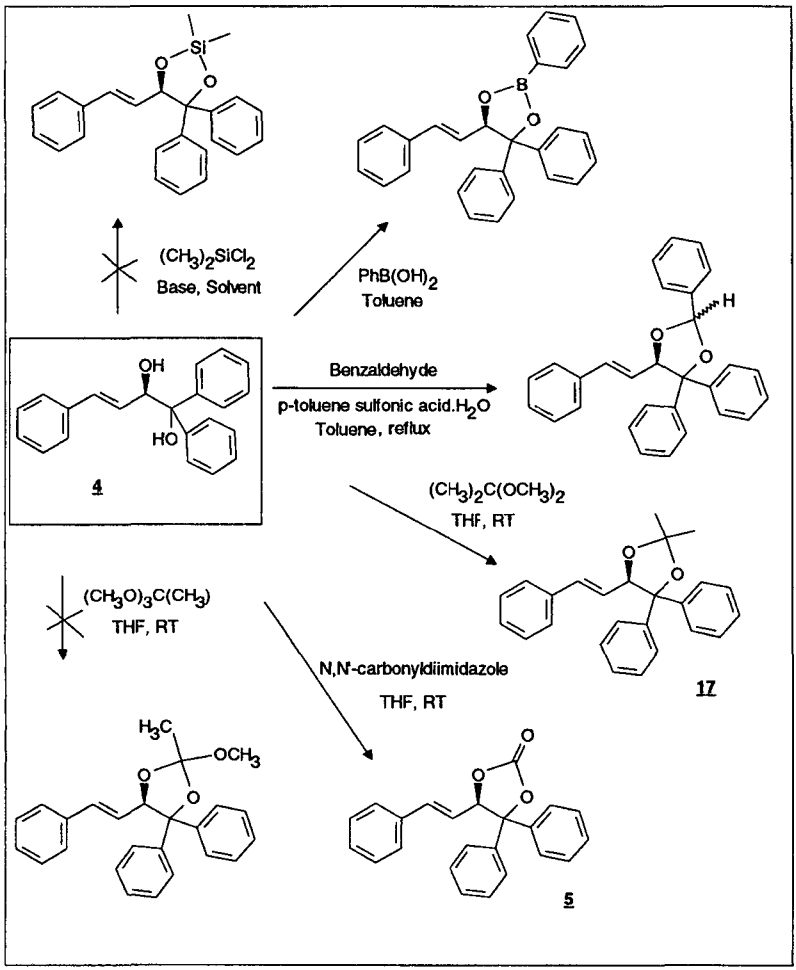
An attempt was made to protect the diol **4** as a cyclic phenyl boronate. Diol **4**, phenyl boronic acid $PhB(OH)_2$ and cat. amount of $PTSA \cdot H_2O$ were refluxed in toluene for six hours [56]. The product was isolated and subjected to $RuCl_3 \cdot H_2O$-$NaIO_4$ oxidation, which gave a mixture of many products. Therefore the use of this protecting group was not persuaded further.

Cyclic ortho ester :

Diol **4**, trimethyl orthoacetate and catalytic amount of $PTSA \cdot H_2O$ were dissolved in THF and stirred at room temperature for 8 hr [57]. The reaction failed to give the cyclic ortho ester, but instead gave the mono acetylated product **25** as shown in figure 32. The scheme in figure 33 shows different protecting groups used to protect the diol **4**.

Figure 32





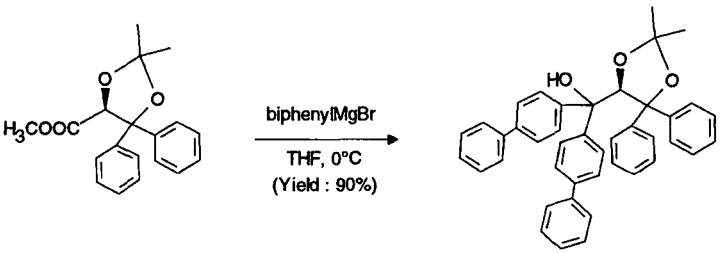
Different protecting groups tried for diol 4

Figure 33

3.4 Deprotection of the acetonide protecting groups.

To proceed towards the target molecule **12**, the next step in the synthesis was the Grignard reaction of a protected ester with biphenylMgBr. **18** was used as starting material. The reaction was carried out at 0°C in dry THF and after a mild acidic workup with aqueous 10% citric acid solution, the crude product obtained was purified by flash chromatography on a silica gel column using hexane : toluene mixture (2:3) as eluent. The product **19** was obtained in 90% yield. The reaction sequence is shown in figure 34.

Figure 34



18 **19**

3.4.1 Deprotection of 19.

Now the target molecule, the tetra aryl glycerol **12**, was just one step away : deprotection of the acetonide protecting group. In order to cleave the acetonide, **19** was dissolved in THF and stirred with a few drops of aqueous 1N HCl at room temperature for several hours [58]. No reaction was observed. Hence the mixture was refluxed for five hours [59], still **19** was unaffected. Hence a few drops of conc. HCl were added and the mixture was refluxed overnight. The reaction was worked up and purified. Instead of **12**, **20** had formed in quantitative yield by elimination of water. Figure 35 shows the reaction sequence.

Since this method did not work, other methods reported in the literature were tried for the deprotection of acetonides and the results are summarized in Table 1.

Figure 35

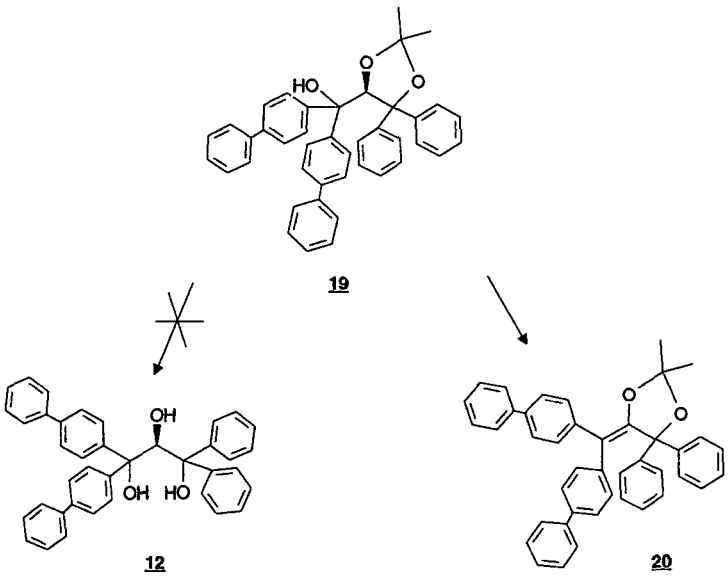


Table 1

Conditions used to deprotect the acetonide 19

N0.	Reagent	Conditions	Product (Yield%)
1	aq. 1N HCl [58]	Rt to reflux in THF	20 (90%)
2	conc. HCl [59]	Rt to reflux in THF	20 (90%)
3	trifluoro acetic acid [60]	Rt to reflux in MeOH	20 (90%)
4	$FeCl_3$ - SiO_2 [61]	Rt in $CHCl_3$	mixture
5	$FeCl_3$ - SiO_2 [61]	Rt in acetone	mixture
6	anhyd. $FeCl_3$ [62]	Rt in CH_2Cl_2	mixture
7	$SnCl_2$ + Naphthalene (1:1) [63]	0°C to Rt in CH_2Cl_2	mixture
8	trifluoro acetic acid + H_2O (1:1)	Rt	mixture
9	BCl_3, BBr_3, BF_3·etherate [64]	different solvents of different polarity	mixture
10	Dowex 50W x 8 [65]	Rt, EtOH : H_2O (8:2)	no reaction

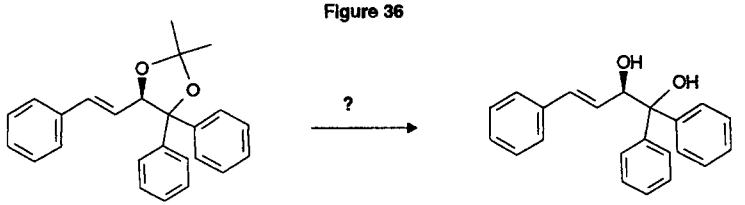
The acidic reaction conditions (Entry # 1 to 3) gave just water elimination product **20**. But a mixture of many products was obtained when Lewis acids were used to cleave the acetonide group e.g. $FeCl_3$ on SiO_2 or anhydrous $FeCl_3$ or $SnCl_2$ gave mixtures of several products. Entry # 9 shows results of the reactions with boron Lewis acids BCl_3, BBr_3 and BF_3·etherate. These Lewis acids were utilized in solvents of different polarity without any success. Entry # 10 shows an attempt with Dowex. No reaction was observed and unreacted starting was isolated.

To keep the protecting group until the last step i.e. until **19** , is ideal only if it can be removed at the end. All the conditions tried to deprotect **19** in order to obtain the triol **12** failed.

3.4.2 Deprotection of 17.

Since there were so many difficulties in finding a method to deprotect **19**, it was decided to deprotect the acetonide group at an earlier stage. Hence **17** was selected as the first substrate. The results are summarized below in Table 2 and figure 36 shows the reaction.

Figure 36



17 **4**

Table 2

Conditions used to deprotect the acetonide 17

N0.	Reagent	Conditions	Product (Yield%)
1	ethylene glycol, conc.HCl	reflux, MeOH	mixture
2	cat. p-toluene sulfonic acid·H_2O [66]	reflux, MeOH	no reaction
3	cat. trifluoro acetic acid [60]	Rt, MeOH	no reaction
4	$SnCl_2 \cdot 2H_2O$ [63]	reflux, CH_2Cl_2	no reaction
5	molecular sieve 5A	reflux, CH_2Cl_2	no reaction
6	pyridinium p-toluene-4-sulfonate [67]	reflux, MeOH	no reaction

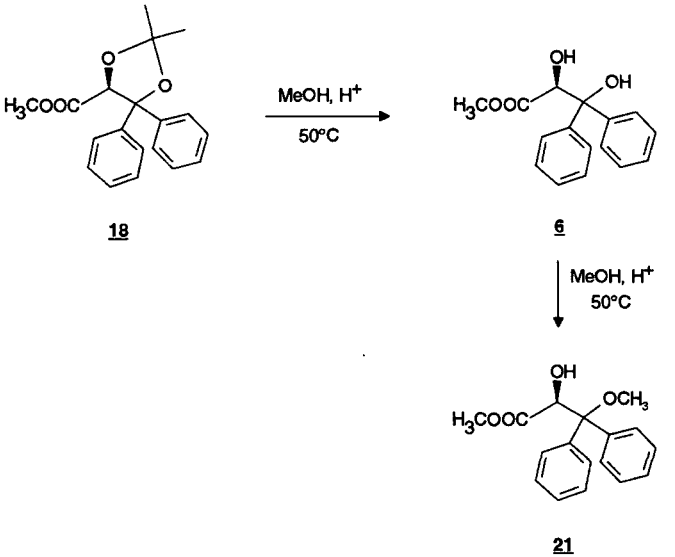
17 was refluxed in methanol with ethylene glycol and few drops of conc. HCl. The idea was that the ethylene glycol would form a ketal, from acetone set free by cleavage of 17, and this would shift the equilibrium towards the diol 4. But the reaction gave a complex mixture.

Refluxing in methanol with p-toluene sulfonic acid·H_2O or reacting with trifluoro acetic acid did not give the diol 4. Refluxing with the Lewis acid $SnCl_2 \cdot 2H_2O$ or with a zeolite 5°A molecular sieve did not change the results. Finally pyridinium toluene-4-sulfonate in refluxing methanol also did not give any reaction product. Under all conditions reported in the table 2, the acetonide group of 17 could not be removed. These experiments showed that it is extremely difficult to remove the isopropylidine from our molecule under acidic conditions.

3.4.3 Deprotection of 18 to 6.

The next substrate was the methyl ester 18. The conditions tried are summarized in Table 3 and figure 37 shows the reaction sequence.

Figure 37



18 6 21

Table 3

Conditions used to deprotect the acetonide 18

No.	Reagent	Conditions	Product (Yield%)
1	trifluoro acetic acid, MeOH [60]	reflux, CH_2Cl_2	no reaction
2	acetic acid :THF :H_2O(3:1:1) [60]	70°C	no reaction
3	$PdCl_2$ $(CH_3CN)_2$ 1mole% [68]	rt, acetone	no reaction
4	DDQ [69]	rt, acetonitrile : H_2O (6.3 + 0.7 ml)	no reaction
5	BCl_3, BBr_3, BF_3·etherate [64]	in different solvents & from -78°C to rt	6, only once with BCl_3
6	1M HCl [58]	50°C, MeOH 4 hr	6 (~50, recycle thrice)
7	1M HCl in Isopropanol [58]	75°C, 30 hr	mixture
8	1M HCl in THF [58]	75°C, 30 hr	no reaction
9	1 drop con. H_2SO_4	Reflux, MeOH	6 (~40, recycle thrice)
10	conc. trifluoro acetic acid [60]	reflux, dichloroethane	no reaction

18 was dissolved in CH_2Cl_2 and an excess of MeOH (8 equivalents) and trifluoro acetic acid (equimolar) were added and the mixture was refluxed for several hours without any product formation.

Similarly refluxing at 70° C in the mixture of acetic acid, THF, H_2O (3:1:1) gave no product.

The use of $PdCl_2$·acetonitrile complex (1 mol%) in acetone at room temperature was also ineffective.

In the literature it is reported that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is used to cleave the acetonide group in acetonitrile : H_2O mixture very effectively. The same conditions were applied but lead to no product formation.

Boron Lewis acids are also known to cleave the acetonide group efficiently. Hence BCl_3 as a 1M solution in CH_2Cl_2 was reacted with **18**. 10 mg of **18** was used as a solution in 1 ml CH_2Cl_2. The reaction was carried out at room temperature. TLC control of the reaction after 3 hr showed complete conversion (by comparing with the reference sample of **6**) to a much more polar substance identified to be the highly desired diol ester **6**. When the reaction was repeated on a larger scale (50 mg), it only produced undesired side products. Quenching the reaction after just one minute and still afforded the undesired products. Even reaction at -78° C was unsuccessful to produce the diol ester **6**. The above result could not be reproduced.

The acetonide ester **18** was dissolved in methanol containing 1M HCl gas and stirred overnight at room temperature. A very small amount of polar product **6** was observed on a TLC control. Hence the reaction flask was heated at 50° C for another 8 hr. TLC showed that the concentration of **6** had increased, but the starting material **18** was still the major product. A third less prominent product with an R_f inbetween these two products, was also observed. When the reaction was continued, the spot of this third product became more prominent. Therefore the experiment was stopped at this stage. The solvent was completely removed on the rotary evaporator and the solid obtained was chromatographed over silica gel using a toluene : ethyl acetate mixture (9:1) as eluent. All the three components were separated. The first eluted product was the unreacted **18**, the most polar fraction was the desired product, the diol ester **6** and the middle fraction was the product of the reaction between the diol ester **6** and methanol in presence of the acid (methyl ether formation). The byproduct was characterized to be methyl-3,3-diphenyl-3-methoxy-2-hydroxy-propionate **21**.

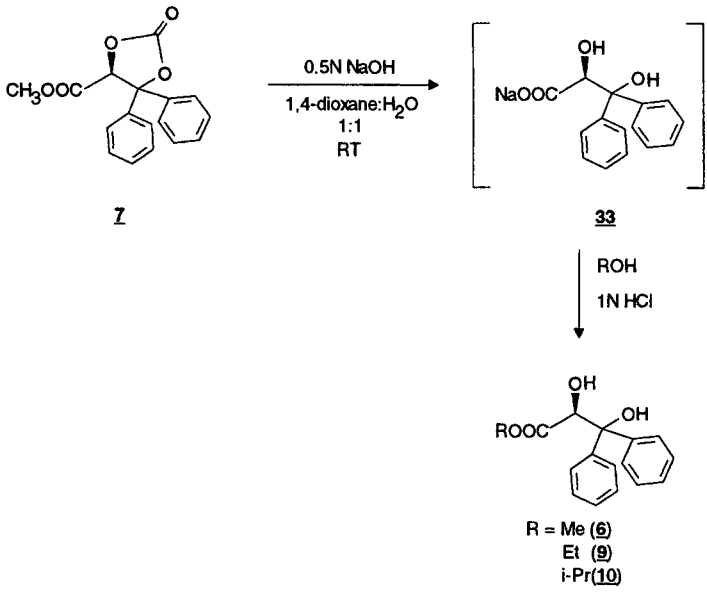
In order to minimize the loss of the product **6**, the reaction was always stopped when the beginning of formation of **21** was observed. The starting material **18** and the product **6** were separated by chromatography and **18** was reused in the next run. After three recycles, the yield of the product **6** was around 50% after chromatography. So in principle the acetonide protecting group could be

cleaved with HCl but since this method was very tedious and difficult, therefore the search for other protecting groups was continued (See below). Finally we found N,N'-carbonyldiimidazole to be the most convenient reagent to introduce the carbonate protecting group, which was stable to the oxidative degradation of the double bond to give carboxylic acid. This protecting group could also be easily removed. (see section 3.3.3)

3.5 Synthesis of the diol esters (6), (9) and (10) via the carbonate route.

As mentioned earlier (Chap. 3.3.2), the introduction of the carbonate group to protect the 1,2-diol 4 had been tried using phosgene solution in toluene. The yield had been very low. N,N'-carbonyldiimidazole, however was found to be very successful in affording a high yield of the desired product under very mild conditions. Also the cyclic carbonate protecting group survived the oxidation of the double bond to give 36 (see chapter 3.3.3). Without cleaving the carbonate the product could be directly converted to methyl ester 7 and isopropyl ester 8. Before reacting with the second Grignard reagent biphenyl MgBr the protecting group was cleaved as follows:
0.5 N NaOH solution was prepared in a 1:1 solvent mixture of 1,4-dioxane and H_2O, then the carbonate ester 7 was dissolved in this solution and stirred at room temperature for 30 minutes. The reaction was complete and the free acid diol 33 was converted directly to the esters, methyl 6, ethyl 9 and isopropyl 10 by treating the acid diol with 1M HCl in methanol, ethanol and isopropanol respectively. The yield after the two step cleavage for all the three esters was around 50%. The different diol esters were prepared because these esters were later used as ligands in the Sharpless epoxidation. It was planned to study the effect of the ester size on the selectivity in the epoxidation reaction. Figure 38 shows the reaction.

Figure 38



7

33

R = Me (6)
Et (9)
i-Pr(10)

3.6 Synthesis of tetra aryl glycerols 12 and 30 .

In addition to the earlier mentioned reasons for synthesizing the tetra aryl glycerols one more point is worth mentioning. In the case of Seebach's TADDOL or Wandrey's bicyclic version of the TADDOL, the two hydroxy groups are relatively fixed because of the rigidly fixed backbone structure where as in the case of these tetra aryl glycerols, one can imagine that the two tertiary hydroxy groups are not fixed. If we selectively protect the secondary hydroxy, it could be analog to TADDOLS but with more flexibility. Figure 39 shows the probable structure of the glycerol-metal complex.

Probable structure of the tetra aryl glycerol - Metal complex

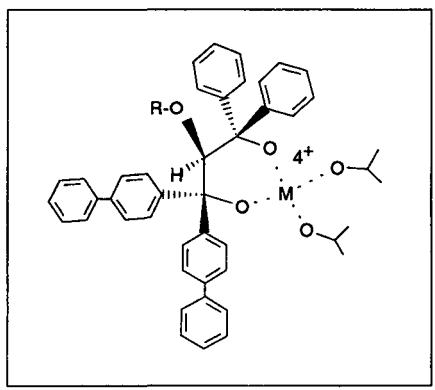
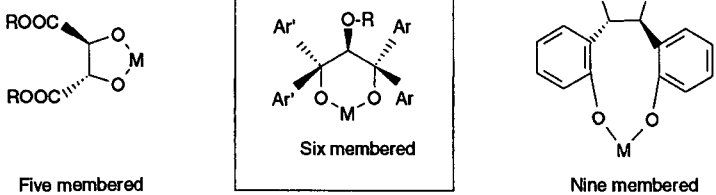


Figure 39

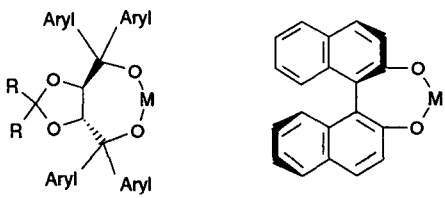
If the secondary OH is protected, then the two free OH groups of the glycerol can build a complex with a metal. The complex will be a six membered ring. It will be interesting to compare this six membered ring with the other ligands known in the literature forming five, seven and nine membered rings [70a]. These different ring sizes are shown below in figure 40.

Diol - Metal complexes forming rings of different sizes



Five membered

Nine membered



TADDOLate

BINOLate

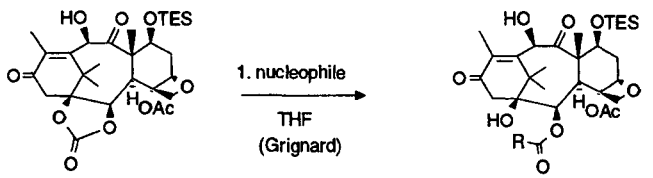
Seven membered

Figure 40

It will be interesting to see whether the catalyst formed by glycerol - metal complex induces high enantioselectivity. The complex formed from this type of ligand does not possess any symmetry. From the previous Grignard experiments it was known that the OH groups should be protected during the Grignard reaction. When the OH groups are not protected, some side products are produced during the reaction and the yield is lower. The diol ester **6** was therefore treated with TMS-Cl and Imidazole in THF and reacted for six hours at 40° C affording TMS protected di silyl ether **11** in 90% yield. **11** was reacted with the Grignard reagent biphenyl MgBr at 0° C in THF expecting that the triol **12** would be formed. But contrary to the assumption, the reaction did not take place at all. The unreacted starting material **11** was recovered.

In the total synthesis of *Taxol*, Nicolaou *et al* [70b] also used a cyclic carbonate as 1,2-diol protection.

Figure 41



Taxol precursor

TES = Triethylsilyl

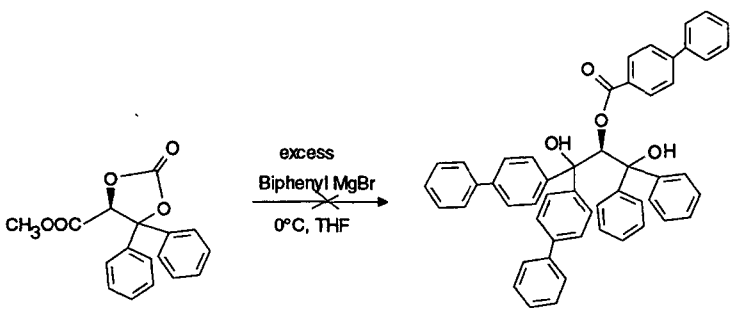
In one step they successfully introduced the Grignard reagent and at the same step could cleave the protecting group as shown in figure 41.

Using this analogy, we thought it should be possible in one step :

1) To react the ester group with Grignard reagent introducing two biphenyl groups and consequently the second tertiary -OH.

2) To cleave the cyclic carbonate and protect the secondary -OH to obtain the protected triol **34** as shown in the reaction scheme in figure 42.

Figure 42



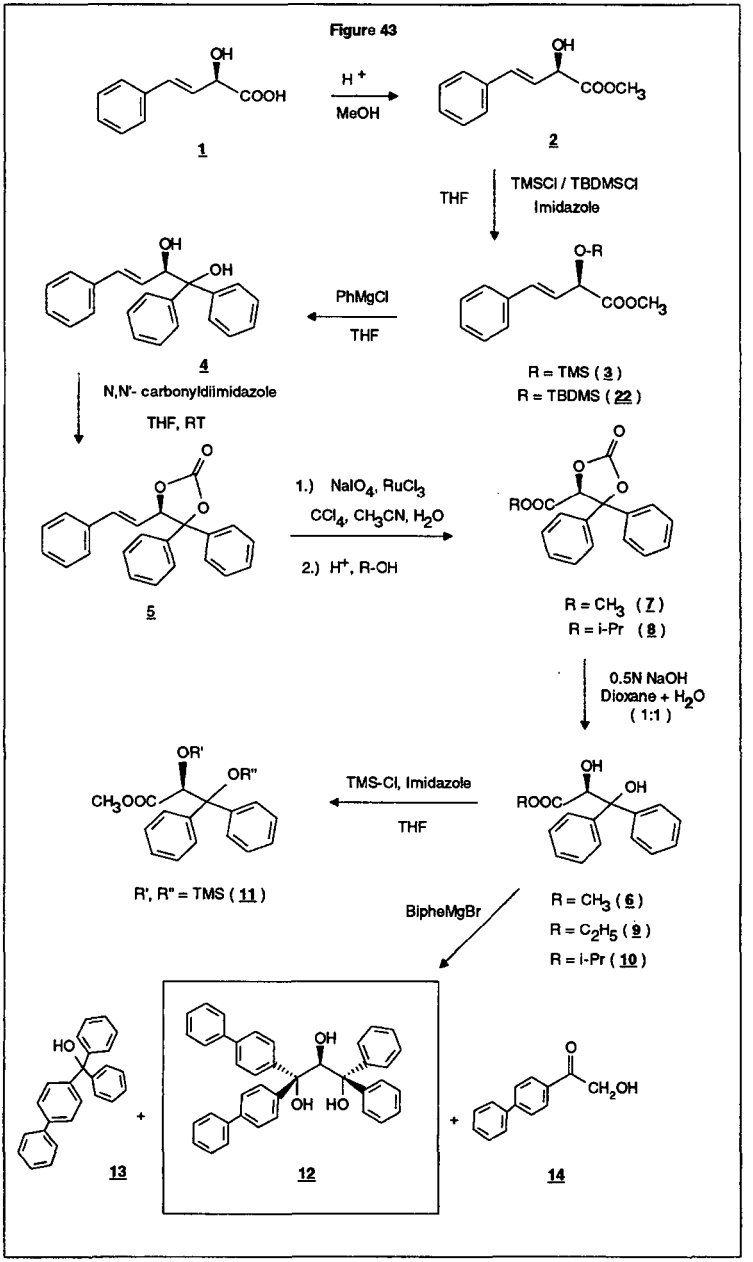
7 **34**

Unfortunately with our substrate **7**, the reaction mixture showed many different products on the TLC. Therefore diol ester **6** was reacted with Grignard reagent biphenyl MgBr in THF at 0° C. Finally the longawaited product, 1,1-bis-(biphenyl)-3,3-bis-(phenyl)-1,2*(S)*,3-propane triol (**12**) was obtained, but with a poor yield of around 15%. The reason for the low yield was the fragmentation of **12** under the reaction conditions. Along with the glycerol **12**, the two other products 1,1-bis-(phenyl)-1-biphenyl-

methane-1-ol **13** (12%) and 2-biphenyl-2-one-ethane-1-ol **14** (15%) were isolated. This degradation was independent of the reaction temperature (-20° C, 0° C or at room temperature).

Thus, the *(S)* enantiomer of the tetra aryl glycerol was synthesized by acetonide route as well as carbonate route. The product obtained by both the routes had the same optical purity. Figure 43 shows the reaction sequence by the carbonate route.

Figure 43


OH
COOH
1
H+
MeOH
OH
COOCH3
2
THF
TMSCl / TBDMSCl
Imidazole
O-R
COOCH3
R = TMS (3)
R = TBDMS (22)
PhMgCl
THF
OH
OH
4
N,N'- carbonyldiimidazole
THF, RT
O
O
O
5
1.) NaIO4, RuCl3
CCl4, CH3CN, H2O
2.) H+, R-OH
O
O
O
ROOC
R = CH3 (7)
R = i-Pr (8)
0.5N NaOH
Dioxane + H2O
(1:1)
OH
OH
ROOC
TMS-Cl, Imidazole
THF
OR'
OR"
CH3OOC
R', R" = TMS (11)
BiphеMgBr
R = CH3 (6)
R = C2H5 (9)
R = i-Pr (10)
HO
13
+
OH
OH
HO
12
+
O
CH2OH
14

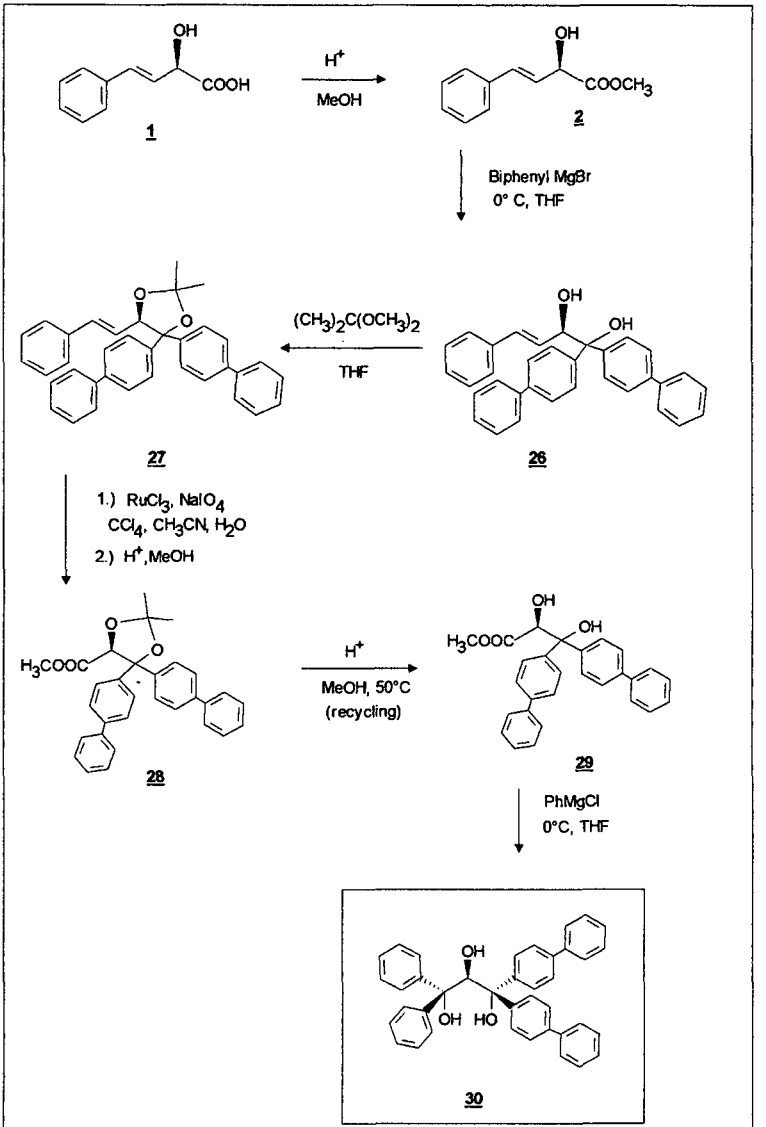
The *(R)* enantiomer **30** was obtained by reacting **29** with biphenyl MgBr at 0° C in 15% yield. The yield of this reaction was also low like in the synthesis of the *(S)* enantiomer. The *(R)* enantiomer was synthesized by the acetonide route, as the synthesis had already been accomplished with this tidious route before the carbonate route was realized. The following scheme in figure 44 shows the acetonide route of the synthesis of the *(R)* enantiomer **30**.

The purification was time consuming because the yield was low and the side products formed had R_f values close to the R_f of the glycerol. After two successive chromatographies on a silica gel column the glycerol was obtained as a colorless thick viscous oil. Even after standing at 0° C for an extended period of time it did not solidify.

The ^{1}H-NMR showed aromatic signals between 7.7- 6.7 ppm for 28 aromatic protons. At 5.8 ppm a doublet for one proton is observed which becomes a singlet with D_2O exchange experiments. This suggests that it is the proton on the chiral centre which couples with the H of the hydroxy group on the same chiral centre. In the starting ester diol this signal appears at 5.0 ppm. This down field shift can be attributed to the anisotropic effect of the aromatic rings. The two tertiary hydroxy protons are observed as one singlet at 5.0 ppm. This singlet disappears completely when exchanged with D_2O. The secondary hydroxy appears at 2.9 ppm as a doublet, also completely exchangeable with D_2O. These spectral data are in accordance with the proposed structure. The ^{13}C spectrum also supports the structure. The IR shows a broad band between 3600-3300 cm^{-1} typical for H bonded OH. This also supports the structure. MS and high resolution MS, showed the exact molecular weight. The structure of the tetra aryl glycerol was confirmed by MS and high resolution MS.

The two enantiomers could be very well separated by HPLC, using the *Chiralpak AD* column and hexane : isopropanol (8:2) mixture. The *(S)* enantiomer eluted at 12.6 minutes while the *(R)* enantiomer eluted at 23.2 minutes. The *(R)* enantiomer had 98% ee while the *(S)* enantiomer had 99% ee.

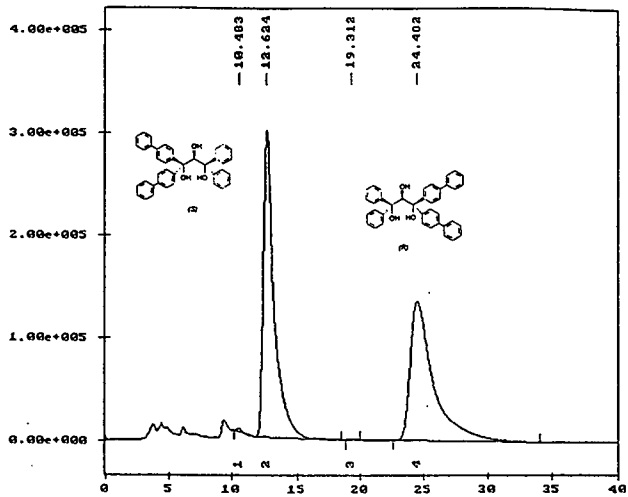
The Optical Rotatory Dispersion (ORD) spectrum of both the enantiomers was recorded in methanol. The two spectra were almost mirror images of each other. The HPLC separation chromatogram and the ORD spectrum of the two enantiomers **12** and **30** are shown in figure 45.



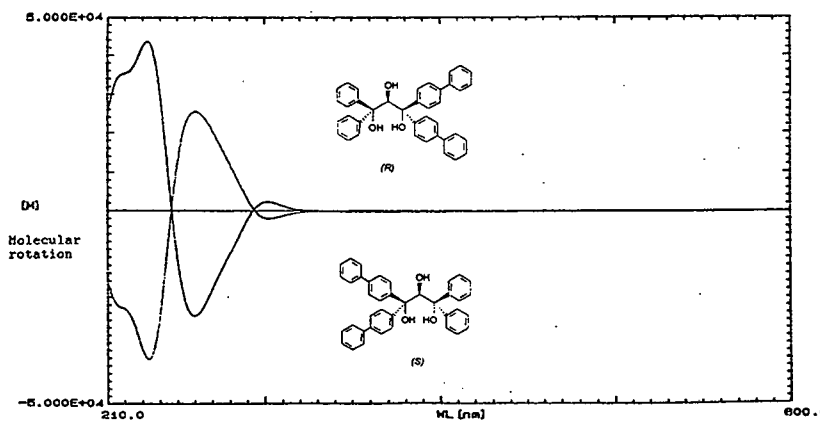
Synthesis of (R) enantiomer via acetonide route

Figure 44

HPLC separation chromatogram of 12 and 30



ORD spectrum of 12 and 30



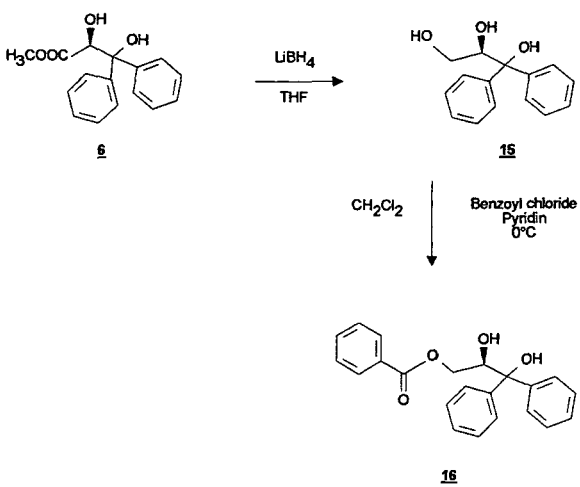
3.7 Synthesis of 1,1-bis(phenyl)-1,2,3-propane triol 15 and it's mono benzoyl derivative 16.

As shown above, the tetra aryl glycerols were difficult to synthesize in reasonable yield. Therefore they were not available in sufficient quantities to test their behavior as ligands for enantioselective catalytic reactions. However, triol **16** should be easily accessible from **6**, and could serve as a model for **30** and **12**.

The diol ester **6** was reduced to the triol **15** by using excess of $LiBH_4$ [71]. The reaction was carried out in THF at room temperature and the triol was isolated in 77% yield. This triol was of use as a chiral ligand.

The primary OH of the triol could be selectively benzoylated to give 3-O-benzoyl-1,1-bis(phenyl)-propane-1,2-diol **16** . It was prepared selectively by the following method : **15** was dissolved in dry CH_2Cl_2 along with an excess of the base pyridine. The reaction was then cooled to 0° C and exactly 1.0 equivalent of benzoyl chloride was added dropwise. The reaction was slowly brought to room temperature and stirred for an hour and then worked up. A small amount of di and tri benzoyl derivatives were also formed but after chromatography the desired product **16** was obtained in 72% yield. The ligand **16** should be used in the Sharpless epoxidation (see chapter 4.2). The reaction sequence is shown in figure 46.

Figure 46



6 **15** **16**

4.0 Enantioselective catalytic reactions

4.1 Introduction

Until 50 years ago the access to the chiral substances with high enantiomeric excess (e.e.) was considered to be possible only by biological or enzymatic methods. In the last 10-15 years the use of chiral substances in pharmaceutical and agro industry increased very rapidly and hence new methods to synthesize substances with high e.e.'s were in high demand [72]. The use of "metal complexes" using enantiomerically pure chiral ligands as a tool to synthesize chiral substances from a prochiral starting material has become the method of choice. Now this method has so much developed that sometimes it is even superior to biological methods and has been used in industry (see chapter 1.2.2).

Useful enantioselective catalytic reactions have to fulfill the two following conditions:

a) The chiral metal complex should function as a good catalyst for the reaction studied. The rate of the catalyzed reaction has to be considerably higher than the uncatalyzed reaction.

b) The catalytic reaction should produce mainly the desired enantiomer.

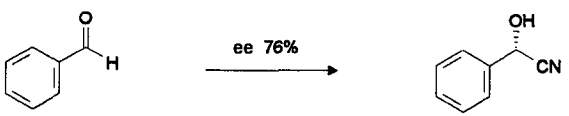
In the beginning most of the reactions which were enantioselective required stoichiometric amount of the chiral reagent but in the recent years a number of different catalytic systems have been developed which show a good catalytic activity giving high stareoselective induction.

Here are few examples.

Carbon-Carbon bond forming reactions :

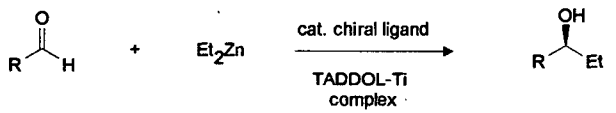
A chiral triol ligand-Ti ion complex selectively adds CN group to an aromatic aldehyde with 76% ee [23]. But the reaction is not catalytic (See chapter 3.1). Figure 47 shows the reaction.

Figure 47



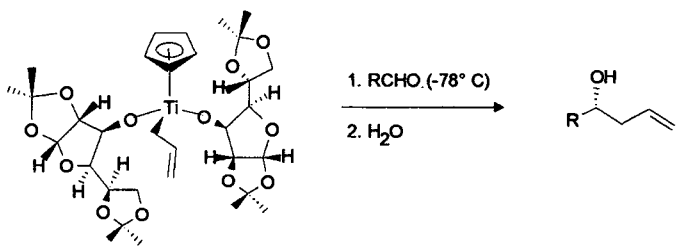
Addition of an alkyl or allyl group via their corresponding Zn reagent to an aldehyde gives chiral hydroxy compounds. A number of different ligands with diverse structures are developed for this reaction. Most important among them are the TADDOLate ligands developed by D.Seebach [73] (see chapter 3.1). Figure 48 shows it's application.

Figure 48



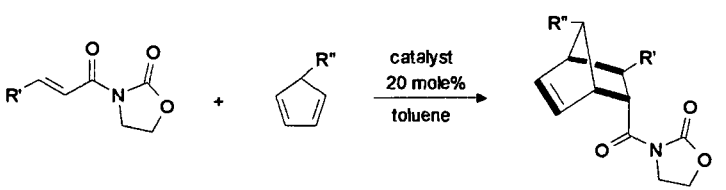
A reagent developed by R.O.Duthaler, A. Hafner and M. Riediker [74] of CIBA also gives very high chiral induction. This is a chiral carbohydrate-Ti complex (figure 49) giving very high chemical yield and ee upto 95-97%.

Figure 49



Another very important reaction is the Diels-Alder reaction. For this reaction also many different chiral ligands [75] have been developed and used as catalysts. Some chiral Lewis acids [78] have also been used to give very good selectivity as shown in figure 50.

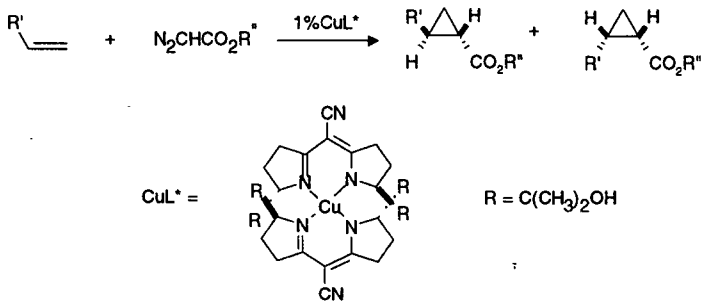
Figure 50



endo : exo ratio vary from 81:19 upto > 99 : 1 and ee from 91% to 95%.

For olefin cyclopropanation reactions, chiral semicorin-Cu complexes are very good catalysts giving high trans/cis (84:16) selectivity. For the trans product the ee was 93% while for cis 92% [77] as shown in figure 51.

Figure 51

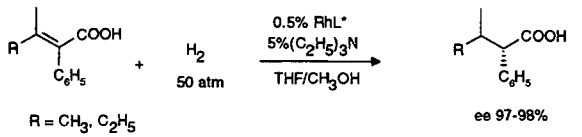


Hydrogenation :

Another very important and widely used reaction is hydrogenation. To introduce chiral centers in a molecule with a hydrogenation step is very attractive. Hence a prochiral compound containing either a double bond, a carbonyl group or imines can be converted to a chiral compound by enantioselective reductions. In the last few years a number of chiral reagents have been developed. Most of the successful ligands are phosphorus ligands and in many cases with Rh as the central metal ion give very high enantioselectivity, sometimes near to 100%. Figure 52 shows few examples a few examples [78-80].

Figure 52

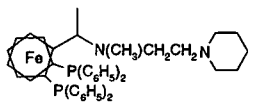
Olefin reduction



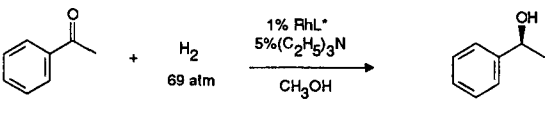
R = CH_3, C_2H_5

ee 97-98%

RhL* = 1/2[RhCl(nbd)]$_2$ + $AgBF_4$ +

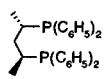


Ketone reduction

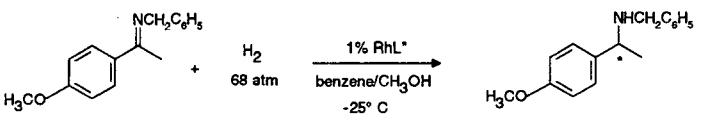


ee 82%

RhL* = 1/2[Rh(nbd)Cl]$_2$ +

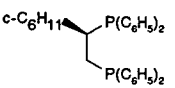


Imines reduction

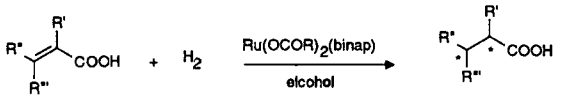


ee 91%

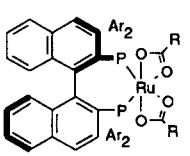
RhL* = 1/2[Rh(nbd)Cl]$_2$ +



Ru/BINAP reagent



ee 80-100%



BINAP

The last example shows the Ru/BINAP complex reduction. BINAP is the recent landmark development in the reduction reactions [81]. BINAP, discovered by R. Noyori and co-workers, is available in both enantiomeric forms and it's complex with Ru has proved to be a highly efficient catalyst. As both the BINAP enantiomers are available both product enantiomers can be synthesized. The utility of BINAP has been demonstrated in various areas from natural product synthesis to the synthesis of biologically active products [82].

Oxidation :

Another important class of reactions are oxidation processes. The group of K.B.Sharpless has been working in this area for many years and has made a great number of contributions in this area. In the recent years two major breakthroughs namely asymmetric epoxidation (AE) [83] and asymmetric dihydroxylation (AD) [84] have been developed in his laboratory. Originally both reactions were using stoichiometric amounts of the chiral reagent. In 1987 because of continued efforts in AE it was found that maintaining the same reaction conditions but by just adding 4 Å molecular sieve to the reaction, the reaction can be performed using catalytic amounts (5-10 mol%) of chiral reagents without loosing the activity as well as the selectivity (figure 53) [85]. The AD reaction is now also a truly catalytic process [86].

Using poly-L-leucine, α,β-unsaturated ketones can be epoxidized with high enantiomeric excess [86a]. Figure 54 shows the Sharpless AD system.

Asymmetric Epoxidation (AE)

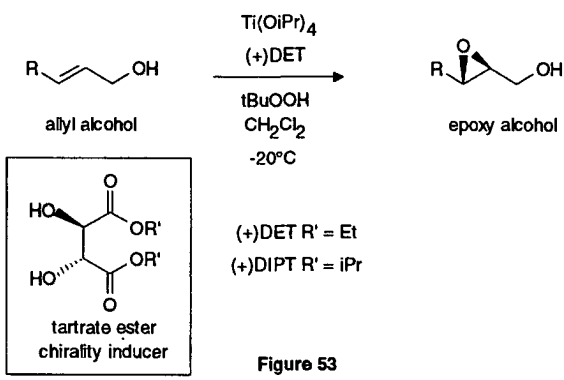


Figure 53

Asymmetric Dihydroxylation (AD)

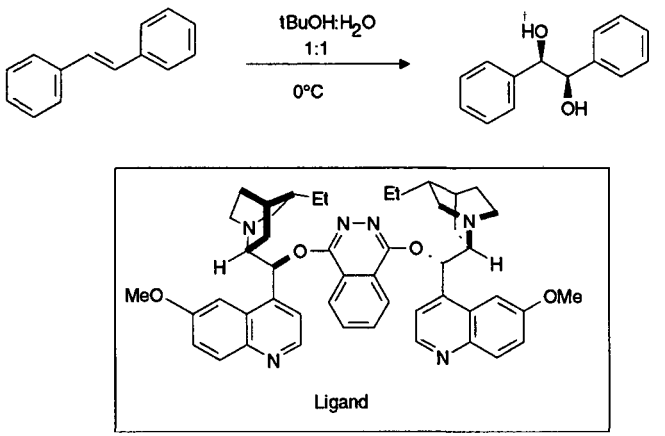
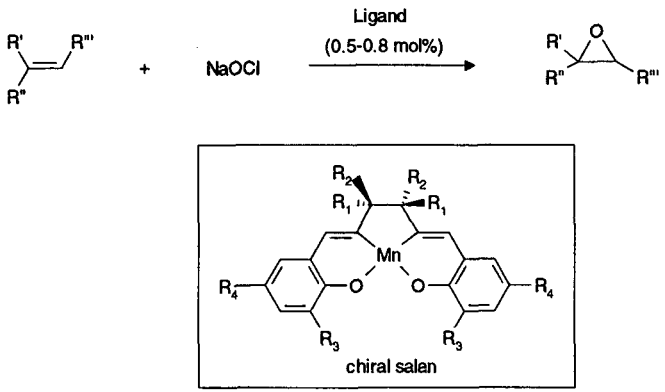


Figure 54

Even though the Sharpless epoxidation procedure was developed as a catalytic process, it still has one major drawback. Though it was successful in epoxidizing many types of molecules bearing different functionality, it could only epoxidize molecules bearing an alcohol group in the allylic position of the double bond i.e. only allyl alcohols as the substrate. A double bond which does not have a hydroxy group at it's allylic position could not be epoxidized. But recently this drawback was also overcome by E. N. Jackobson. He developed a system which uses chiral salenes as the ligand and manganese as the central metal ion [87]. These complexes epoxidize many types of double bonds in very high enantioselectivity using catalytic amounts of the reagent. Figure 55 shows Jackobson system.

Figure 55



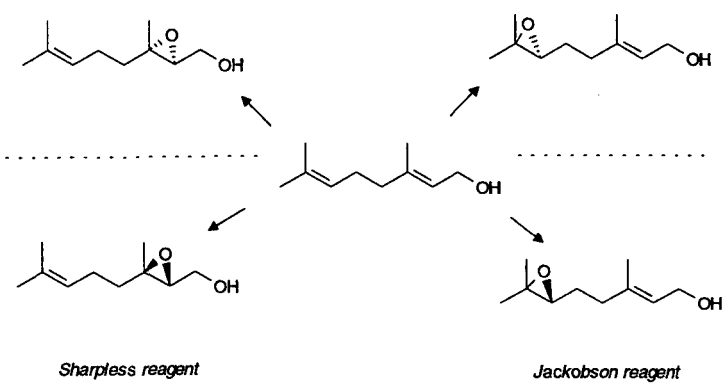
Starting from the 2-*(R)*-hydroxy-4-phenyl-3-butenoic acid 1 going to tetraaryl glycerols 2(*S*) 12 and 2*(R)* 30 , all the intermediates are chiral and enantiomerically enriched. In principle all of these compounds could be tested as ligands for the preparation of chiral catalyst system and different reactions can be tested. Considering the functional groups in the chiral ligands and comparing them with the literature from the known reactions, Katsuki - Sharpless epoxidation and Mikami glyoxylate ene reaction were the two reactions selected for the study.

4.2 Katsuki - Sharpless epoxidation

4.2.1 General importance of chiral epoxides :

Epoxides are very important organic intermediates since they can be easily synthesized from alkenes using various available methods. During the epoxidation reaction of the alkene, chirality can be introduced into the molecule and depending on the substrate two chiral centers can be created in one step as shown below. Starting from the epoxides, various functionalities can be introduced in a molecule e.g. by selectively opening the epoxide ring of the correct enantiomer using different nucleophiles. Here is an example in which two different double bonds exist in the molecule of geraniol. Using either the Sharpless or Jackobson reagents, geraniol can be selectively epoxidized [88]. Figure 56 shows the epoxidation reaction.

Regio- and Enantioselective Monoepoxidations of Geraniol



Sharpless reagent *Jackobson reagent*

Figure 56

An epoxidation reaction in which an asymmetric induction was achieved for the first time was reported in 1965 by Henbest. He reported the asymmetric induction using percamphoric acid. The enantioselectivity was very low (8%) [89]. It took another fifteen years till Katsuki and Sharpless discovered the system which allowed the enantioselective introduction of epoxides with a good selectivity which worked for a wide variety of substrates. With this system enantioselectivity was higher than 90% in most of the cases and in some cases > 98%.

4.2.2 Different methods of epoxidation

Epoxidation is an important process, and can be achieved utilizing a variety of reagents. The most commonly used reagent is m-chloroperbenzoic acid (MCPBA). This is a very diverse epoxidizing reagent which can epoxidize acyclic, and cyclic alkenes even bearing electron withdrawing groups. Other peroxy acids can also be used. e.g. peracetic acid, trifluoro peracetic acid, performic acid, 4-nitroperbenzoic acid to mention a few.

Other important epoxidizing reagents are the alkyl hydroperoxides, like t-butyl hydroperoxide. Trityl hydroperoxide and cumyl hydroperoxide are also used.

Hydrogen peroxide is also used for epoxidation reactions. Several acidic oxides such as MoO_3, WO_3 and compounds of selenium, arsenic and boron are effective catalysts. They generate inorganic peroxo acids in the presence of H_2O_2 which epoxidizes the alkene [90].

First row transition metals catalyze the epoxidation process. e.g. it was seen that iron porphyrins can catalyze epoxidation under mild conditions, using iodosylbenzene as oxidant. This has led to many studies based on a metalloporphyrin/ O_2 /reducing agent to bring about epoxidation of alkenes [90]. Even air or oxygen is used as epoxidizing reagent in the presence of an adequate catalyst [91].

4.2.3 Asymmetric epoxidation mediated by Ti-tartrate

In 1980 Katsuki and Sharpless developed an epoxidation method which gave very high chemical and optical yield [83]. The system consisted of L(+)-diisopropyl tartrate as the chiral ligand, titanium tetra isopropoxide (Ti [IV] alkoxide, in general) as the source of titanium metal ion, and alkyl hydroperoxide (t-butyl hydroperoxide, in general) as the oxidizing reagent. The substrate was an allyl alcohol e.g. cinnamyl alcohol. With this combination, the reaction was generally complete in 3-4 hours at -18 to -15° C. The most important factor was that the reaction had to be carried out under absolute dry conditions using freshly dried reagents and solvents. The tartrate ester was necessary in stoichiometric amounts. Though high chemical and optical yields could be obtained, it was an expensive procedure and the isolation of the product was difficult. In 1987 another breakthrough in this reaction came from the same group [85]. Instead of using stoichiometric amounts of chiral ligand only 5-10 mole% was sufficient. This improvement was achieved by the introduction of the 4 Å molecular sieves in the reaction. The role of molecular sieve is to trap the small amount of water

present in the reaction to prevent deactivation of the catalyst complex. Because of this the reaction became much more economical and the product isolation became easier without compromising the activity as well as the selectivity. In an another improvement, sensitive low molecular weight epoxides which are difficult to isolate can be in situ derivatized and then isolated [85]. A number of other ligands bearing similar structural features to the tartrates as well as ligands without any similarity to tartrates were tested as the catalyst [92,93].

As there are many parameters involved, many variations are possible [94]. The major factors are the following :

Stoichiometry :

Two stoichiometries are important factors. One factor is the ratio of titanium : tartrate used to produce the catalyst and the second is the ratio of catalyst : substrate. To obtain the best results it is necessary to have at least 10% excess of tartrate ester to titanium (IV) alkoxide. This holds good for stoichiometric as well as catalytic reactions. The reaction rate is slowed down if an excess of more than 20% of the ligand is used. The observed ideal ratio of substrate : catalyst is (100 : 10), as the chemical and the optical yields obtained are highest.

Concentration :

If the substrate concentration is high, some side products are produced along with the product. The reactions can be performed up to substrate concentration of 1M with the catalytic process. Before the catalytic process was introduced the maximum substrate concentration possible was 0.1M as some side reactions were observed when the concentration exceeded this limit.

Aging of the catalyst :

For the best results the catalyst is freshly prepared at -20° C by mixing Ti (IV) alkoxide and the tartrate in the solvent, and then adding either TBHP or the allyl alcohol and aging the system at this temperature for 20-30 minutes. This is essential for good results. For the bulky hydroperoxides this period is increased to 1 hour. After this the reaction is brought to the temperature at which the reaction is performed and the last reagent, the allyl alcohol or the hydroperoxide, is added.

Oxidant :

t-Butylhydroperoxide (TBHP) is the preferred oxidizing reagent. However, in some cases cumylhydroperoxide [85] and trityl hydroperoxide are also used [93] and better results are obtained. 5.5 M TBHP in isooctane is preferred over 3.0 M TBHP in isooctane.

Tartrate esters :

For asymmetric epoxidation tartrate esters e.g. the dimethyl, diethyl and diisopropyl tartrates are used. It has been found that they are all equally good with minor variations.

Titanium alkoxide :

Though 26 metals from the periodic table catalyze the epoxidation reaction, Titanium is the best central metal ion [88]. Titanium (IV) isopropoxide is normally used as the source of titanium but in reactions in which the epoxy alcohol product is sensitive to ring opening, titanium tert. butoxide is preferred.

Molecular sieves :

Molecular sieves are used to protect the catalyst from the slight amount of water that may be present in the reactions. Powdered 4 Å sieves are generally preferred but 3 Å, 4 Å, 5 Å in pellets are also equally effective.

4.2.4 Mechanism

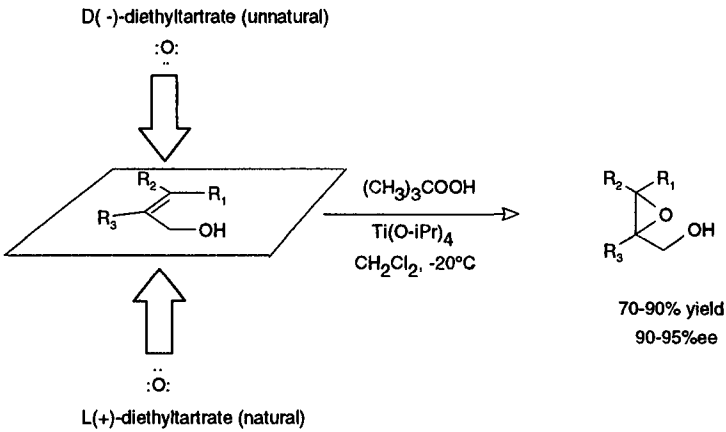
This reaction became a routine tool for the synthetic chemists because of it's simplicity, high selectivity, reproducibility and wide applicability. In spite of great efforts by Sharpless and co-workers and many other groups, the reason for it's high selectivity is still not well understood. The exact mechanism is not established because the catalytically active complex could not be isolated in crystalline form which would allow the X-ray structure to be determined. The vanadium complex of the tartrate ester could be isolated and it's X-ray structure was determined. Therefore the structure is a topic of debate.

Origin of selectivity :

The accepted mechanism is that proposed by Sharpless. As shown in the scheme in figure 57 below, depending on the configuration of the tartrate ester, the delivery of the oxygen atom from the peroxide to the double bond comes from above or below the plane of the double bond. Thus if L(+)-diethyl tartrate, the naturally occurring enantiomer, is used as the chiral ligand, then the chiral transition complex (the hydroperoxide part of the complex) sits below the plane. Hence the oxygen is

delivered from below the plane resulting in only one enantiomer. On the other hand, if D(-)-diethyl tartrate is utilized as the chiral ligand, then the oxygen is introduced only from the top of the plane. Hence only the other enantiomer is produced. The enantioselectivity is determined in the transition state and depends on the configuration of the chiral ligand. Figure 58 shows both the possibilities.

Figure 57



Enantiofacial selectivity in the epoxidation of prochiral allylic alcohols with Ti/tartrate/TBHP

Catalyst structure :

When titanium alkoxide and dialkyl tartrate are mixed in equimolar quantities in solution, there is a rapid exchange of titanium ligands. The equilibrium shown below is quickly reached.

$$Ti(OR)_4 + \text{tartrate} \rightleftharpoons Ti(\text{tartrate})(OR)_2 + 2ROH$$

The equilibrium is shifted far to the right as the chelating diol (i.e. the tartrate) has a much higher binding constant for titanium than the monodentate alcohols. The rapid exchange continues even after the addition of hydroperoxide and the allylic alcohol to the reaction. The kinetic study by the Sharpless group showed a first-order rate dependence on the Ti - tartrate complex, hydroperoxide, and the allylic alcohol and inverse secondorder dependence on the non olefinic alcohol ligands, isopropyl alcohol. The rate law equation is as shown below in Figure 58.

Figure 58

$$\text{Rate} = k \frac{[\text{Ti(tartrate)(OR)}_2]\,[\text{TBHP}]\,[\text{allylic alcohol}]}{[\text{ligand alcohol}]^2}$$

After formation of the Ti(tartrate)$(OR)_2$ complex, the remaining two alkoxide ligands are replaced in a reversible exchange reaction by the hydroperoxide TBHP and the allyl alcohol to give the "loaded complex" Ti(tartrate)(TBHP)(allyl alcohol). In the rate determining step, oxygen is transferred from the coordinated hydroperoxide to the allylic alcohol giving the complex :Ti (tartrate)(t-OBu)(epoxy alcohol). The product alkoxides are replaced by more allyl alcohol and TBHP to regenerate the loaded complex and complete the catalytic cycle as shown in the figure 59 below.

Ligand exchange on Ti during epoxidation reaction

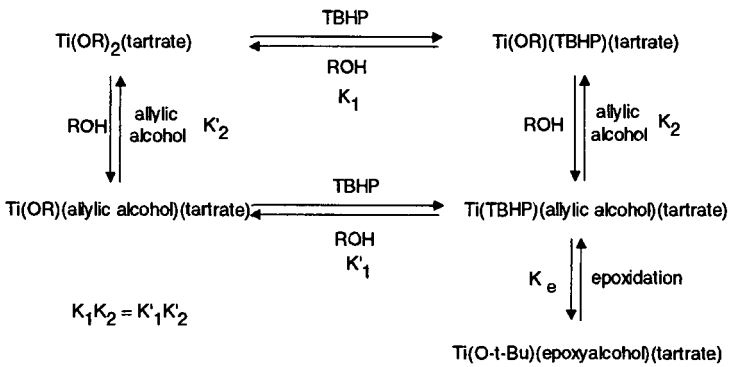


Figure 59

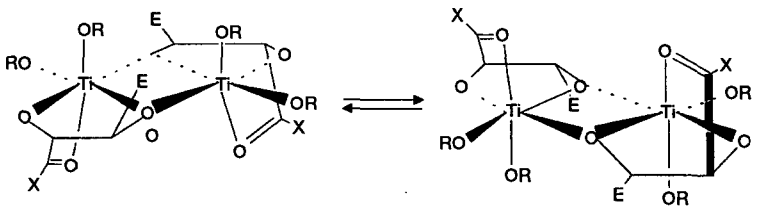
In the epoxidation reaction the olefinic double bond acts as a nucleophile towards the activated peroxide oxygen. Hence electron withdrawing nitro group substituted at para position on cinnamyl alcohol decreases the rate of the epoxidation while electron releasing p-methoxy group increases the epoxidation rate [95].

The rapid ligand exchange makes the characterization of the catalyst difficult. Sharpless proposes a dimeric species formed in the solution, $Ti_2(tartrate)_2(OR)_4$. It was impossible to isolate this dimeric complex in the crystalline form, which would allow determination of the X-ray crystal structure.

Information provided by Ti_2(dibenzyl tartramide)$_2$(OR)$_4$, which is a closely related complex and gives similar enantiofacial selectivity, supports the proposal of the dimeric structure [96].

From this analogy the following structure for the dimer was proposed. Catalysis of the epoxidation process is proposed to involve only one titanium atom, but the possibility that two are required has not yet been ruled out. Figure 60 shows the equilibrium structure.

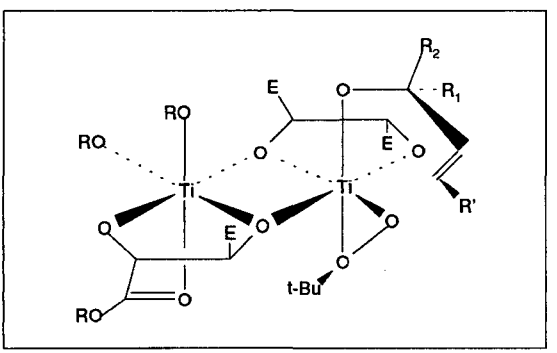
Figure 60



Titanium - tartrate complex equilibrium structure proposed by Sharpless

When hydroperoxide and substrate are added i.e. 'loading' of the catalyst as proposed by Sharpless, two axial and one equatorial site become available by exchange of two isopropoxide units and dissociation of the coordinated ester carbonyl group. The coordination of the hydroperoxide is assumed to be bidentate and must occupy one axial and one equatorial coordination sites and the allylic alcohol in the remaining axial site. Figure 61 shows the 'loaded complex'.

Figure 61



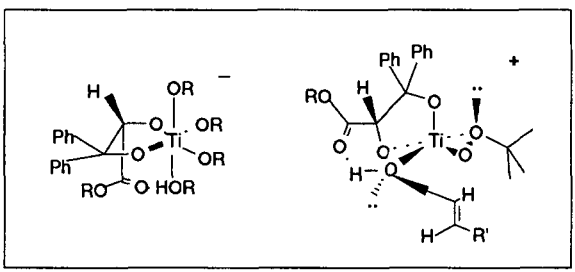
Loaded Complex

In order to transfer the oxygen from peroxide to the alkene double bond smoothly, it is necessary that both are close to each other. The distal peroxide oxygen is assumed to be transferred to the olefin and hence it is placed in the equatorial site and the proximal oxygen in the axial sight. The lower axial sight is chosen for the peroxide because then the larger t-Bu group can be accommodated in the larger space. The other axial sight is used for the coordination of the allylic alcohol.

A transition state model for the asymmetric epoxidation complex has been calculated by a frontier orbital approach by Jorgenson and co-workers and is consistent with the postulated structure [97].

E. J. Corey proposed a mechanism in which an ion-pair is involved in the transition state [98]. This proposal requires two more alcohol species in the transition state complex. Kinetic studies disagree with this proposal. The structure of the complex of ligand **6** according to his postulate would look as shown below in figure 62.

Figure 62



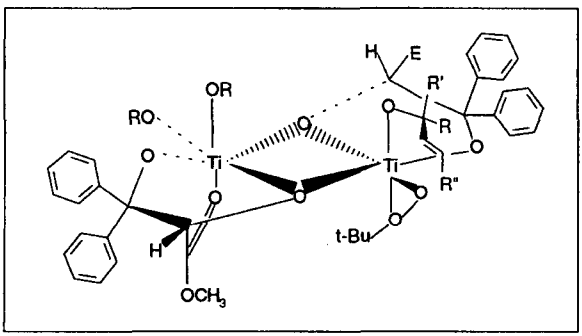
Corey proposal

According to this model, the chiral complex exists as an ion pair. One molecule of the ligand is chelated to the central Ti of the cationic moiety as shown above. The hydroxy group of the allylic alcohol is coordinated to the Ti so as to allow hydrogen bonding to the carbonyl of the ligand ester. The *tert*-butylperoxy (t-BuOO) group is chelated to the Ti with the terminal oxygen cis to the coordinated allylic OH and the t-BuO subunit trans to the allylic OH. Five donor atoms are coordinated to the central Ti of the cationic moiety, and any further coordination is strongly disfavored by the bulk of the *tert*-alkoxy subunit. The specific arrangement of ligand about Ti in the cationic moiety makes that Ti a chiral center with the absolute configuration determined by the ligand.

Recently Wu and Lai published the results of their calculations to model titanium catalyzed epoxidation of alkenes [99]. They used nonlocal density functional methods for their calculations. Their calculations also support the Sharpless proposal and disagree with Corey's proposal.

If the Sharpless model is applied to our ligand **6** containing two hydroxy groups and one ester group, two phenyl rings replace the second ester group. The loaded complex structure is shown below in the figure 63.

Figure 63



Probable loaded complex structure of the ligand 6

This model predicts that similar enantioselectivity should be obtained and that the epoxidation may be taking place by a similar mechanism as the one proposed by Sharpless.

4.2.5 Results of the epoxidation experiments

Unless mentioned otherwise all the epoxidation experiments were carried out using the following quantities of the reagents, at -18° C.

Ligand (**6**,**9**,**10**,**15**,**16**)	:	0.558 mmole (1.2 eq. of Ti reagent, 0.151 g, ligand **6**)
Dry CH_2Cl_2	:	46.5 ml (in order to make the substrate conc. 0.1M)
3Å MS	:	0.55 g
$Ti(O\text{-}iPr)_4$	:	0.465 mmole (0.136 ml, 1.0 eq.)
t-BuOOH	:	9.3 mmole (20 eq., ~3M solution in isooctane)
Cinnamyl alcohol	:	4.65 mmole (10 eq., 0.625 g)

Table 4

L	substrate	Ti reagent	Solvent	Oxi. reagent	S / C	conversion[a]	ee%
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	100 : 10	~40%	68 94[b]
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2[c]	~3M t-BuOOH	100 : 10	~50%	63
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	EtOAc	~3M t-BuOOH	100 : 10	no rea.	0
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	toluene[d]	~3M t-BuOOH	100 : 10	~60%*	33
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	toluene[e]	~3M t-BuOOH	100 : 10	~30%*	34
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~5.5M t-BuOOH	100 : 10	~50%	62
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	1 : 1 stoichio.	~50%	64
9	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	100 : 10	~40%	69
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	cumyl hydroperoxide (70% in cumol)	100 : 10	~10%	7
6	cinnamyl alcohol	$Ti(O\text{-}tBu)_4$	CH_2Cl_2	~5.0-6.0M t-BuOOH	100 : 10	~50%	65
6	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~5.0-6.0M t-BuOOH	1 : 1 stoichio.	~40%	60
10	cinnamyl alcohol	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	100 : 10	~20%	60
6	m-TFM cinnamyl alcohol[f]	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	100 : 10	~60%*	37
6	m-TFM cinnamyl alcohol[f]	$Ti(O\text{-}iPr)_4$	toluene	56% t-BuOOH	100 : 50	~90%	60[h]
15	m-TFM cinnamyl alcohol[f]	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	100 : 30	~40%	13
16	m-TFM cinnamyl alcohol[f]	$Ti(O\text{-}iPr)_4$	CH_2Cl_2	~3M t-BuOOH	100 : 15	~50%	17

L = ligand
S = substrate
C = catalyst
a = unless mentioned otherwise all yields are after chromatography without recrystallization
b = after chromatography followed by recrystallization
c = reaction at -5° C
d = reaction at 20° C (RT), ~60% product formation by ^{1}H-NMR
e = reaction at -20° C, ~30% product formation by ^{1}H-NMR
f = m-trifluoro methyl cinnamyl alcohol as a 27% solution in toluene
g = conversion to the epoxide determined by ^{1}H-NMR (denoted by *) or by TLC
h = experiment performed by Mr. M. Rinderspacher. Reaction at -20° C for fourteen days.

The **Table 4** shows the results of the epoxidation experiments. It shows that the ee of the products are not as high as those obtained by tartrate esters. Since the discovery of Sharpless and Katsuki no other ligand has been reported which gives better ee than the tartrates.

As shown in the table 4, the diol esters **6**, **9** and **10**, the triol **15** and it's mono benzoyl derivative **16** were used as the ligands. Cinnamly alcohol and substituted m-trifluoromethyl cinnamyl alcohol were used as substrates. The epoxidizing agent tert-butyl hydroperoxide used was in two different concentrations. ~3.0M in isooctane (Fluka) and ~5.5-6.0M in decane (Aldrich) and cumyl hydroperoxide (70% solution in cumol). The titanium source was $Ti(O\text{-}iPr)_4$ and the more bulky $Ti(O\text{-}t\text{-}Bu)_4$. Freshly dried solvents were used. CH_2Cl_2, toluene and ethyl acetate were used for the investigation.

The effects of different parameters used can be analyzed as follows :

Ligand :

Among the ligands used only the diol esters **6**, **9** and **10** showed good selectivities. This can be explained by the fact that these diol esters have certain similarities with the successful tartrate esters. Like tartrates, they also possess two hydroxyl groups but instead of two ester groups they contain only one ester group. As discussed earlier the titanium metal ion builds a chiral complex in which the ligand, the substrate allyl alcohol and the epoxidation reagent are involved. Thus the two hydroxy groups and one of the two ester groups of the tartrate ester are coordinated to the central Ti metal ion. The second ester group is not involved in the complex formation. So allowing a similar Ti complex the ligands **6**, **9** and **10** can form a similar structure as the one proposed for the loaded complex of the tartrate ester. It is obvious that the titanium ion is coordinated to the two hydroxy units and the ester as before and the second ester does not take part in the coordination. The replacement of the second ester by other groups, for example by two phenyl rings, does not hinder the complex formation. The hydroxy group of the substrate allyl alcohol and the oxygen from the epoxidation reagent are also coordinated to Ti as explained above. The reaction proceeds with the same mechanism to give the chiral epoxides as shown in the figure 63.

In the procedure reported by Sharpless using the L-(+)-diisopropyl tartrate ligand, all the epoxidations were complete in 3.5 - 4.0 hours at -20 to -15° C. Our reaction conditions were the same as the one reported by Sharpless. But contrary to the Sharpless observations, where the allyl alcohol was

completely converted under his conditions to the epoxide, in our case only 40% of the allyl alcohol was converted to the epoxide and the rest remained as unreacted starting material. Longer reaction times did not improve the conversion.

The activity of the catalyst prepared from the ligands **6**, **9** and **10** was not as high as the reactivity of tartrate esters. May be the two phenyl rings in the active loaded complex are now bulky and therefore the catalyst is less reactive than tartrate esters.

Enantiofacial selectivity

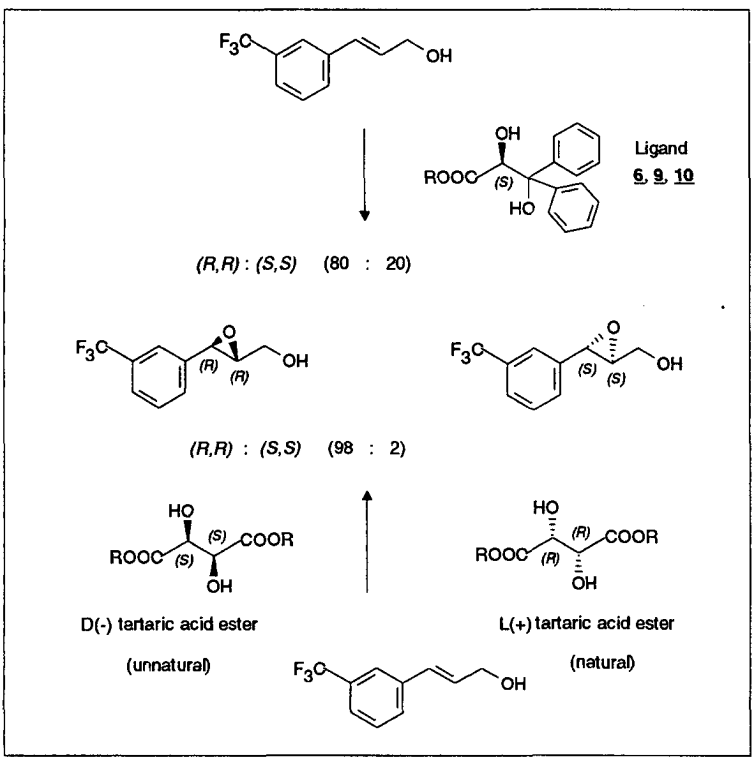


Figure 64

The absolute configuration at the chiral center of all the ligands used is ***S***. The epoxidation of cinnamyl alcohol with L-(+)-diisopropyl tartrate, which has ***R*** configuration at chiral centers 2 and 3, gives epoxy alcohol (2***S***-trans)-3-(m-trifluoro-methyl)-phenyloxiranemethanol. That means that a

ligand with the ***R*** configuration gives the epoxy alcohol with the ***S*** configuration. The epoxy alcohol, (2***R***-trans)-3-(m-trifluoro-methyl)-phenyloxiranemethanol, was obtained by epoxidation of cinnamyl alcohol using the ligands **6**, **9** and **10** which possess the ***S*** configuration at the chiral center. This shows that the same enantiofacial selectivity is observed, which suggests that the reaction proceeds by a similar mechanism as that proposed by Sharpless. Figure 64 shows the observed enantiofacial selectivity.

The comparison of the ee's of the product epoxy alcohol obtained in reactions using methyl, ethyl and isopropyl esters **6**, **9** and **10** respectively did not show any remarkable influence of the bulk at the ester group. All the ee's obtained were almost in the same range.

Ti reagent :

An experiment with a different titanium source, $Ti(O\text{-}tBu)_4$ instead of $Ti(O\text{-}iPr)_4$, was carried out. It showed that the increased bulk of the t-butyl over i-propyl had no dramatic effect on the ee of the product.

Temperature and the solvent :

Reaction in CH_2Cl_2 at -5° C, instead of at -18° C, did not change dramatically neither the yield of the epoxy alcohol nor the ee. The ee was 63% and yield of epoxy alcohol 45%.

The reaction in toluene at room temperature, maintaining the other conditions, increased the chemical yield. In this case the yield of the product was 60% (determined by ^{1}H-NMR), but the ee was reduced to 33%. Reducing the reaction temperature to -20° C reduced the chemical yield as well. The conversion of the cinnamyl alcohol to the epoxy alcohol was only up to 30% (determined by ^{1}H-NMR) and the ee was practically unchanged (34%).

No reaction took place in ethyl acetate as the titanium forms a complex with the solvent itself. Hence methylene chloride was found to be the best solvent.

Epoxidizing agent :

Changing the concentration of the epoxidation reagent from the usual ~3M t-Bu hydroperoxide solution in isooctane to ~ 5 - 6M did not change the selectivity. Cumyl hydroperoxide in 70% cumol dramatically reduced the ee to 7%.

Substrate :

Using the ligand **6** for epoxidizing m-trifluoro methyl cinnamyl alcohol under standard conditions produced the epoxide with an ee of 37%. In the experiment RG 1712, using the same substrate and an increased ratio of substrate to catalyst (2 : 1 instead of 10 : 1), the reaction was nearly complete after fourteen days. This is In accordance with Sharpless observation that cinnamyl alcohol with electron withdrawing substituent undergoes epoxidation at a substantially decreased reaction rate [95]. Fresh t-BuOOH was introduced from time to time. The increased amount of ligand increased the selectivity. The ee was 60% of the *(R,R)* stereomer in this experiment.

The experiments using the triol **15** as ligand, reduced the ee dramatically to a mere 13%. This reduced ee may be because there are many combinations in which the Ti ion can build complexes with the three OH. Hence the selectivity is dramatically reduced. When the primary OH is protected as benzoyl ester **16**, the additional C=O provides structure with similarities to the diol esters used earlier. We hoped that ligand **16** may also give good ee. But with this ligand the enantioselectivity was disappointing (ee 17%).

4.3 Ene reaction :

4.3.1 INTRODUCTION :

The Ene reaction was discovered in 1943 by Kurt Alder [100] and classified in his Noble lecture as '*ene synthesis*' in 1950 [101]. It is a C-H bond activation and C-C bond formation reaction, which is very important from the synthetic point of view. It is defined as a six-electron pericyclic process between an alkene bearing an allylic hydrogen (an 'ene') and an electron deficient multiple bond (an enophile) to form two σ-bonds with migration of the π-bond. Figure 65 shows the ene reaction scheme.

Ene reaction

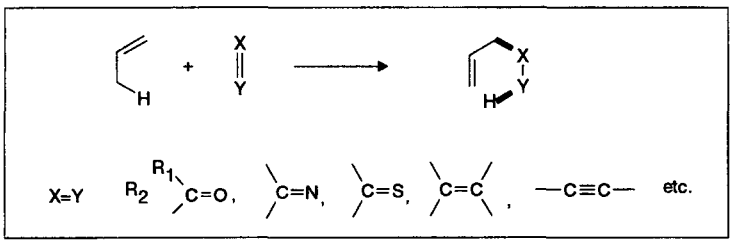


Figure 65

It is mechanistically related to the Diels-Alder reaction. Compared to the Diels-Alder reaction the Ene reaction requires higher activation energies and hence higher reaction temperatures are required. In terms of enophiles (X=Y), it can have a vast number of variations, e.g. C=O, C=N, C=S, C=C. Olefins are relatively unreactive as enophiles compared to acetylenes. Under high pressure, acetylene reacts with a variety of simple alkenes to form 1,4-dienes [102]. When carbonyl compounds are used as enophiles, alcohols are produced exclusively [103]. The intramolecular ene reactions with Schiff bases, the nitrogen analog of aldehydes, provide homoallylic amines [107]. Thiocarbonyl compounds on the other hand react to give mainly allylic sulfides rather than homoallylic thiols as thiocarbonyl compounds in the ene reaction form C-S rather than C-C bonds.

From the synthetic point of view, the carbonyl ene reaction is an efficient alternative to the nowadays popular carbonyl addition reaction of allyl-metals for carbon skeleton construction with stereocontrol. Figure 66 shows both the strategies.

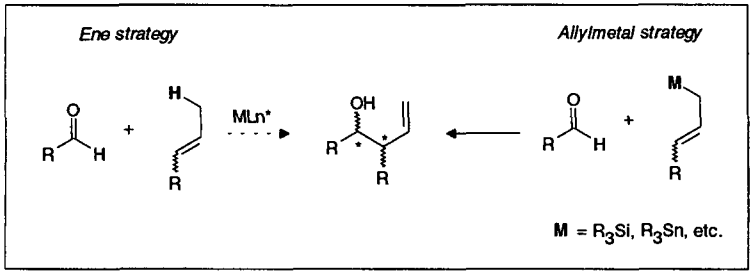


Figure 66

As mentioned earlier, the ene reaction was not popular as it required higher temperatures to activate the C-H σ and X=Y π bonds. In the last couple of years, however, different Lewis acids have been shown to as catalysts in this reaction e.g. $AlCl_3$, $SnCl_4$, $TiCl_4$ act as a catalyst. The other advantage of Lewis acid over Broensted acids is that undesired proton catalyzed side reactions e.g. cyclizatlon of the product alcohol, are prevented. Here are a few examples with different enophiles and different Lewis acid promoters (figures 67-69) :

$SnCl_4$ promotes the reaction between formaldehyde and a symmetrical diene to give lavanduol in 55% yield [104].

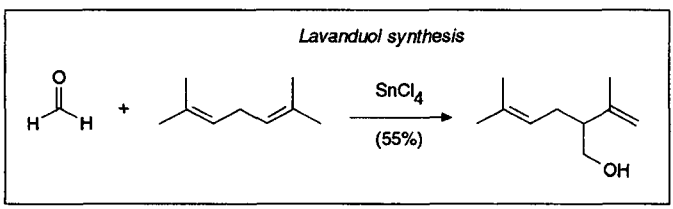
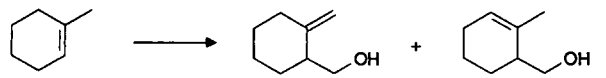


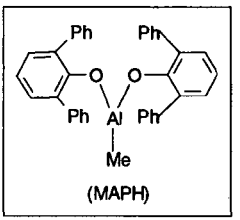
Figure 67

Snider used the complex of paraformaldehyde with Me_2AlCl or $EtAlCl_2$ for the formaldehyde-ene reaction [105]. Recently Yamamoto used the bulky aluminium reagent MAPH for the same reaction with superb regioselectivity.

Figure 68

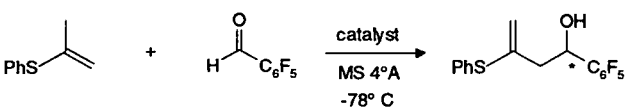


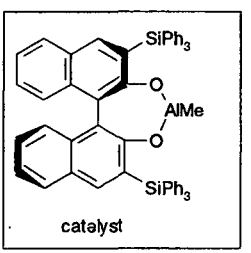
CH_2O:$AlMe_2Cl$ (0°C)	92%	41	:	59
CH_2O:MAPH (-78°C)	80%	100	:	0



Again Yamamoto *et al.* developed a modified BINOL-derived aluminium reagent as a catalyst. The example shows the reaction of penta fluoro benzaldehyde using 20 mole% of the catalyst at -78° C in the presence of 4Å MS (88% ee) [108].

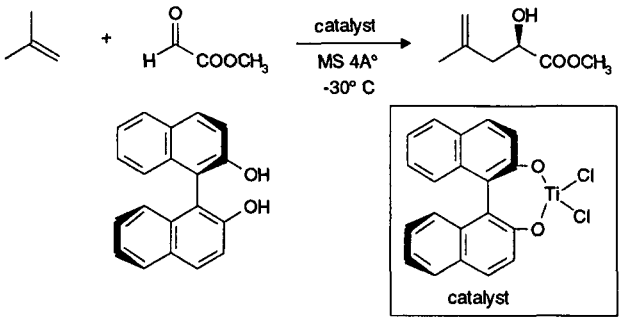
Figure 69





Recently Mikami *et al.* discovered another BINOL- Lewis acid derived catalyst which gives ee higher than 90%. Figure 70 shows the reaction system.

Figure 70

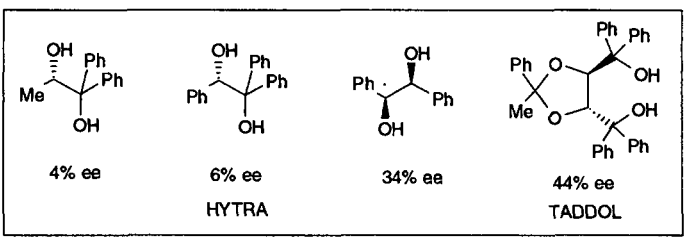


The catalyst is the chiral Ti complex as shown in the figure above. It is prepared in situ from diisopropoxytitanium dihalide and optically pure BINOL in the presence of 4Å molecular sieves. The use of 10 mole% of the catalyst gave a 72% yield and 95% ee of the product alcohol [109].

Very recently, a moisture tolerable catalyst for the same reaction which afforded very high (98% ee) optical purity as well as high chemical yields (93%), was reported by Nakai *et al.* It is prepared in situ by mixing $Ti(O\text{-}iPr)_4$ and optically pure BINOL. The i-PrOH formed is removed by azeotropic distillation [103].

All the above examples showed high selectivity using a chiral diol-Ti complex as the catalyst. We thought that we could use the various diols already prepared as chiral ligands, to prepare the Ti complex, and then use the chiral complex as catalysts in the ene reaction. In the literature some aliphatic diols have been reported to be used as a ligand in the ene reaction [111]. Figure 71 shows some of the ligands.

Figure 71



4.3.2 Results and Discussion

The Glyoxylate-ene reaction is a very efficient way for synthesizing α-hydroxy esters. If a high degree of chirality can be introduced during this C-C bond formation reaction, one can very easily obtain chiral α-hydroxy esters, which are important chiral building blocks. We choose α-methyl styrene and methyl glyoxylate as the two ene starting reactants as both are very cheap starting materials and lead to the product which could be a starting material for ACE inhibitors. In the literature this procedure is very well documented using (*R*)-BINOL [110]. Figure 72 shows the ene reaction.

ENE REACTION

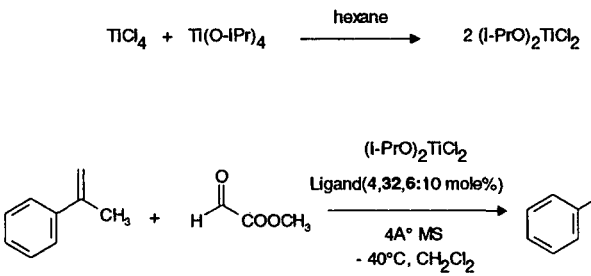


Figure 72

As shown in the above scheme, the titanium reagent was prepared by stirring the mixture of $TiCl_4$ and $Ti(O\text{-}iPr)_4$ in hexane at room temperature. An exothermic reaction occurred and a white precipitate of the product $(i\text{-}PrO)_2TiCl_2$ separated after a few minutes. Stirring was stopped after 10 minutes and the reaction mixture was allowed to stand for 6 hours at room temperature. The solvent was removed by syringe, washed once with hexane and recrystallized from hexane to get a colorless crystalline product. It was directly used for the reaction.

From the literature it is known that (*R*)-BINOL, an aromatic diol, is a very efficient ligand. Instead of BINOL we decided to use the different diols which we had prepared during the tetra aryl glycerol synthesis. As a chirality inducer, the diols **4**, **6**, and **32** were used. Diisopropoxytitanium (IV) dichloride was prepared as described in the literature procedure and for the ene reaction the literature procedure was followed as well. One experiment was performed with (*S*)-BINOL following the literature procedure [110]. The result of the reactions are given in the following table 5.

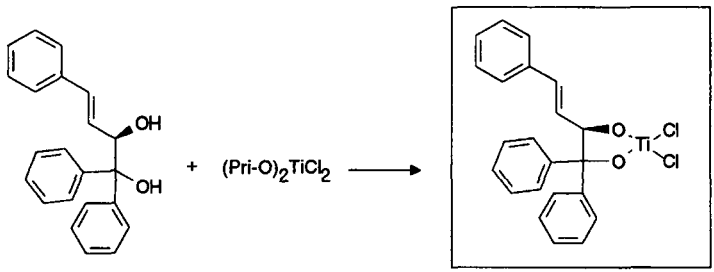
Table 5

No.	Ligand	mol %	Temp. °C	Time hr.	Yield % *	ee %
1	*(S)*-BINOL	0.5	- 35	6.0	33	80
2	without ligand, with Ti rea.	-	- 35	6.0	4	0
3	4	10.0	- 40	6.0	20	5
4	4 + triethyl amine (1:2)	10.0	- 40	8.0	no rea.	-
5	32	10.0	- 40	8.0	20	3
6	32 + triethyl amine (1:2)	10.0	- 40	8.0	no rea.	-
7	6	10.0	- 40	8.0	20	2

* = isolated yield by chromatography. The rest remained as unreacted starting material.

The initial experiment with *(S)*-BINOL gave the product with 80% ee. The literature results shows optical yield (ee%) and chemical yield of more than 90%. Our reactions were not optimized. Therefore our chemical yield was low but the ee was comparable with the literature results. Then we repeated the same experiment using the $(i\ PrO)_2TiCl_2$ as catalyst but without any ligand which induces chirality in the product. The yield obtained was very low (4%) giving a racemic product. In the following experiments ligands 4 and 32 were used as ligands instead of BINOL. The yield was much lower than with BINOL (20%) but still much higher than the reaction without ligand. However, the ee were negligible. This suggests that the ligand - Ti complex enhances the rate of the reaction. In BINOL, the OH protons are acidic hence it reacts with the titanium precursor rapidly to get complete exchange of the BINOL OH protons with the Ti reagent (by eliminating 2 iPrOH) and forms the chiral complex as shown in the earlier examples, which produces producing enantiomerically enriched product. The OH in the ligands 4, 32 and 6 are aliphatic and much less acidic compared to BINOL OH protons. Another reason could be that the five membered ring which a 1,2 diol would build with the titanium reagent may be thermodynamically disfavored. Because of this the 1,2 diol would react with the titanium precursor to a smaller extent and not all the ligand molecules would be complexed to titanium. This may be the reason for the lower chemical and optical yields. Figure 73 shows probable complex structure.

Probable complex structure of diol - titanium reagent



4

Figure 73

To activate the alcohol, it was worthwhile to try to deprotonate the alcohol using some base. The experiments were again repeated by adding two equivalents of triethyl amine per one equivalent of the ligand. After addition of base the reaction mixture became slightly warm and white fumes were observed. The reaction mixture was stirred for ten hours at room temperature before cooling and adding the reagents. Unfortunately the ligand - titanium reagent exchange reaction did not take place at all. It may be that the amine reacted with the titanium and prevented the complex from being formed.

In conclusion it can be said that this type of diol is not suitable as a ligand in the ene reaction. In the literature there are some examples known where aliphatic diols were used as ligands for ene reaction [111]. In those cases, the ene product had ees between 4% and 44%.

5.0 EXPERIMENTAL PART

5.1 General remarks :

The characteristic physical data of the substances synthesized in this work are presented in the following order : Yield, Thin layer chromatography, melting point, Optical rotation, IR, ^{1}H-NMR, ^{13}C-NMR, MS, Elemental analysis, HPLC.

5.1.1 Melting point

The melting points were measured in an open glass capillary on a *Büchi 520* melting point apparatus and are uncorrected. The recrystallization solvent is mentioned in the experimental part.

5.1.2 Chromatography

Thin layer chromatography (TLC)

Analytical thin layer chromatography was performed on (0.2 mm) precoated silica gel plates of the type Kieselgel 60 F_{254} with fluorescent indicator supplied by *Merck*, Darmstadt and the TLC was run in a glass chamber containing the solvent system. To develop the TLC, the spray reagent CPS was used. It was prepared by the following procedure :

10.0 g of Ce (IV) sulfate tetrahydrate and 25.0 g of phosphorus molybdinic acid hydrate were added to 70 ml of conc. H_2SO_4 and stirred until completely dissolved. Then this liquid was diluted 1.0 liter by adding deionised water, affording the lemonyellow colored CPS (Cerium Phosphor molybdnium Saüre) reagent. It was sprayed as it is on the TLC plates.

Flash Chromatography :

Flash Chromatography was performed on silica gel of the type Kieselgel 60, partical size 0.040-0.063 mm, 230-400 mesh size supplied by *Merck*, Darmstadt.

5.1.3 IR-Spectroscopy

The IR spectra were recorded on *Brucker FTIR* spectrometer IFS48 instrument. The samples were in the form of a KBr pellet (1% sample) or in CH_2Cl_2 as 3% solution in a NaCl cuvette. The bands are in cm^{-1}. The band absorption intencities are w = weak, m = medium, s = strong and br = broad.

5.1.4 NMR-Spectroscopy

The ^{1}H-NMR and ^{13}C-NMR were recorded on *Brucker 250* (250 MHz) and *Varian U500R* (500 MHz) instruments. Deuteriated Chloroform (99.5 Atom% D) supplied by *Dr.Glaser AG*, Basel was used as the solvent. The chemical shifts δ are indicated in ppm with respect to TMS. The coupling constants J

are in Hz. The signal multiplicities are as follows : s = Singlet, d = Doublet, t = Triplet, q = quartret, sep = septetet and br = broad.

5.1.5 Massspectroscopy

Electron Impact (EI) : *Finningen MAT (MAT 212)*

Fast Atom Bombardment (FAB) : *Finningen MAT (MAT 90)*

Field Dissorption (FD) : *Finningen MAT 8430*

High resolution : *VG 70-SE (Fisons Instruments, Manchester)*

5.1.6 Polarimetry

The optical rotations were measured on *Perkin-Elmer 241*and at wavelength 589 nm (Na_D).

5.1.7 Elemental analysis

Elemental analysis were performed at *CIBA-GEIGY AG*, Basel.

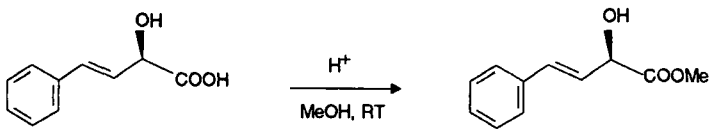
5.1.8 Chemicals and solvents

The chemicals used were from *Fluka AG* (Buchs, Switzerland), *Merck* (Darmstadt-D) and *Aldrich Chemical Company, Inc.* (U.S.A.).

Chemicals:	
2,2-Dimethoxy propane	Fluka purum
Toluene-4- sulfonic acid.H_2O	Merck zur Analyse
Trimethyl silyl chloride	Fluka, puriss
t-Butyldimethylsilyl chloride	Fluka, purum
Sodium (meta) periodate	Fluka, purum
Ruthenium(III) chloride Hydrate	Fluka, purum
Mg turnings for Grignard reaction	Fluka, purum
2-Bromoanisole	Fluka, purum
4-Bromobiphenyl	Fluka, purum
Phenyl Mg chloride (~25% in THF)	Fluka
Imidazole	Fluka, puriss
1,1'-Carbonyldiimidazole	Fluka, purum
5% Pd/ $BaSO_4$	Degussa
3-Methyl-1-(p-tolyl) triazene	Ciba-Geigy, Pharma
Pyridine	Fluka, puriss
Benzoylchloride	Fluka, puriss
Triethylamine	Fluka, puriss
4-Dimethylaminopyridine	Fluka, purum
Cinnamyl alcohol	Fluka, purum
Tetraisopropyl-orthotitanate	Fluka, pract.
tert-Butyl hydroperoxide anhydrous (~3M in isooctane)	Fluka, purum
Molecular sieve 3Å, 4Å	Merck
Diethyl L-(+)-tartrate	Aldrich
α-methyl styrene	Fluka, purum
Methyl glyoxylate	Hoechst, France
Solvents :	
Acetonitrile	Fluka, puriss
Carbontetrachloride	Fluka, puriss
Diethylether	Fluka, puriss

Ethylacetate	Techanical
Ethanol	Fluka, puriss
Hexane	Merck, puriss
Methanol	Fluks, puriss
Tetrahydrofuran	Fluka, puriss
Toluene	Fluka, puriss
Toluene	Techanical

2(*R*)-Hydroxy-4-phenyl-but-3-enoic acid methyl ester (2)



1 2

In a 2.0 liter round bottom flask, α-hydroxy acid 1 (400 g, 2.24 mole) was dissolved in 1.0 liter MeOH containing 1.0 M of HCl gas. The yelloworange colored solution was stirred overnight at room temperature. The solvent was completely removed at reduced pressure and the residue was redissolved in 1.5 liter ethyl acetate and washed with 10% $NaHCO_3$ (200 ml) solution until free from acid. The organic phase was separated and first washed with water (2x100 ml) followed by brine solution (100 ml) and then dried over anhydrous Na_2SO_4. It was concentrated at reduced pressure to obtain 425 g of a red-orange oil.

This crude product was then vacuum distilled. The pure methyl ester distilled at 110°C (0.18 mbar, bath temp. 140° C) as a lemonyellow colored liquid.

Yield : 310 g (72%)

R_f. : 0.37 (toluene : EtOAc [4:1], blue to CPS)

M.p. : 27-28° C

$[a]_D^{20}$: - 98° (c = 4.5, $CHCl_3$)

IR (KBr) :

3458s (-OH), 1742s (ester C=O), 1261s, 1211s, 1132s, 970s, 739s, 694s.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.40 -7.20 (m, 5H, Ar); 6.80 (d, J = 15.0 Hz, 1H, H-C(4)), 6.25 (dxd, J = 6.8,15.0 Hz, 1H, H-C(3)); 4.85 (t, J = 6.7 Hz, 1H, H-C(2)); 3.80 (s, 3H, esters); 3.10 (d, J = 6.8 Hz, 1H, H-O, exchange with D_2O).

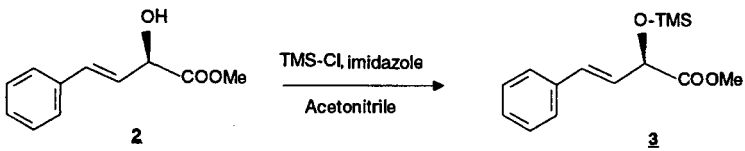
^{13}C-NMR (62 MHz, $CDCl_3$) :

173.8 (C(1)), 136.0 (C(1')), 132.3 (C(3)), 128.6 (C(3') + C(5')), 128.0 (C(4')), 126.7 (C(2') + C(6')), 125.2 (C(4)), 71.3(C(2)), 53.0 (ester -OCH3)

MS :

192 (M^+, 58), 133 (100), 115 (60), 103 (42), 77 (56), 55 (80), 51 (52).

2*(R)*-Trimethylsiloxy-4-phenyl-but-3-enoic acid methyl ester (3)



2 3

In a 750 ml round bottom flask hydroxy ester 2 (38.4 g, 200 mmole) and imidazole (20.42 g, 300 mmole) were dissolved in dry acetonitrile (400 ml) under argon atmosphere. A catalytic amount of N,N-dimethyl amino pyridine (DMAP) was added. A clear homogeneous solution was formed. Through a dropping tunnel trimethyl chlorosilane (30.55 ml, 240 mmole) was dropwise added. At the end of the addition, a white precipitate of imidazole·HCl precipitated from the reaction mixture. The reaction mixture was stirred at 40° C overnight.

The solid was filtered off and the solvent was removed at reduced pressure. The residue obtained was dissolved in 300 ml toluene washed once with 100 ml water tollowed by 50 ml brine solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to obtain a yellow colored liquid. It was used as it is for the next reaction.

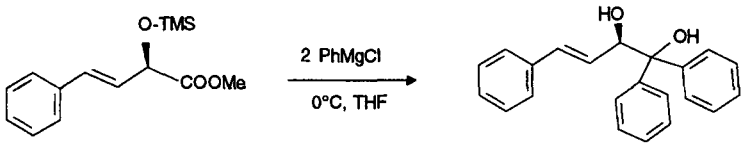
Yield : 53 g (90%)

R_f : 0.72 (toluene : EtOAc [6:1], blue to CPS)

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.25 - 7.00 (m, 5H, Ar); 6.55 (d, J = 17.2 Hz, 1H, H-C(4)); 6.10 (dxd, J = 6.9, 17.2 Hz, 1H, H-C(3)); 4.70 (d, J = 6.9 Hz, 1H, H-C(2)); 3.50 (s, 3H, ester); 0.0 (s, 9H, TMS).

1,1,4-Triphenyl-but-3-ene-1,2(*R*)-diol (4)



3 4

A 2.5 liter four necked reactor equipped with a thermometer, dropping funnel, magnetic stirrer, gas Inlet/outlet was dried at 300° C by hot air blower and dry nitrogen was passed through it for five minutes.

425 ml of THF solution containing 25% PhMgCl (108.48 g, 800 mmole, 25% solution in THF from Fluka) was transferred to the reactor. Methyl ester 3 (53 g, 200 mmole) was dissolved in 50 ml dry THF and transferred to the dropping funnel. The reactor was cooled to -10° C with an ice-salt mixture. The methyl ester was added dropwise at such a rate that the temperature was constant between - 5° C to 0° C. The addition was complete in 1 hr. Then the reaction was warmed slowly to room temperature and stirred overnight.

The reaction mixture was again cooled to 0° C and 50 ml of water was added dropwise. A white yellow slurry separated. 500 ml of ethyl acetate was added to the mixture followed by 1N HCl solution until pH 2. The whole slurry dissolved and two phases separated. The organic phase was separated and first washed with water (2x100 ml) until free from acid followed by brine (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure to get a solid crude product. It was crystallized from hot ethanol - water mixture to afford white crystals.

Yield : 30 g (47%)

R_f : 0.57 (toluene : EtOAc [4:1], blue to CPS)

M.p. : 138 - 139° C

$[a]_D^{20}$: + 152.7° (c = 1.5, CH_2Cl_2)

IR (CH_2Cl_2) :

3560 - 3580s, 3030m, 1600m, 1493s, 1450s, 1140s, 970s

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.65 - 7.15 (m, 15 arom. H); 6.65 (d, J = 17.2 Hz, 1H, H-C(4)); 6.20 (dxd, J = 6.9, 17.2 Hz,1H, H-C(3)); 5.25 (d, J = 6.9 Hz, 1H, H-C(2)); 3.10 (s, exchange with D_2O, OH-C(1)); 2.20 (bs, exchange with D_2O, OH-C(2))*.

* attribution based on line broadening of the signal at 2.20 ppm.

^{13}C-NMR (62 MHz, $CDCl_3$) :

144.6, 143.6 (C(1'), C(1")); 136.5 (C(1'")); 133.4 (C(3)); 128.5* (C(3'),C(5'),C(3"),C(5")); 128.2 (C(3'"), C(5'")); 127.8, 127.3, 127.1, 126.8 (C(4'),C(4"),C(4'"),C(4)); 126.5 (C(2'),C(6'),C(2"),C(6")); 126.0 (C(2'"),C(6'")); 80.0 (C(1); 76.6 (C(2).

* attribution based on relative intensity.

FD - MS :

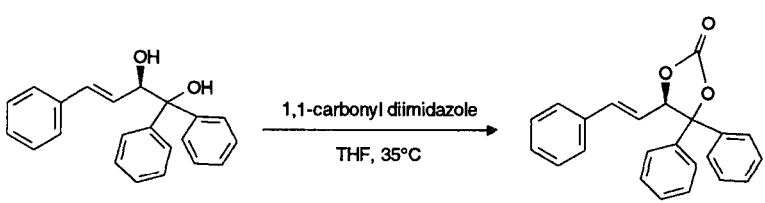
316 (M^+,4), 298 (10), 282 (2), 184 (10), 183 (100), 182 (4)

Elemental analysis :

$C_{22}H_{20}O_2$ *Calculated* C : 83.53, H : 6.37, O : 10.11

Found C : 83.45, H : 6.35, O : 10.41

2-Oxo-4,4-diphenyl-5*(R)*-styryl-[1,3]dioxolane (**5**)



4 **5**

In a 1.0 liter round bottom flask, **4** (22.0 g, 69.62) and N,N-carbonyl-diimidazole (45.15 g, 278.48 mmole) were mixed and dissolved in 750 ml of dry THF to get a yellow clear solution. The reaction was stirred at 35° C overnight.

The solvent was completely removed and the solid obtained was dissolved in 900 ml of ethyl acetate. It was washed with 10% aqueous citric acid solution (2x200 ml) until free from base, then washed with water (2x100 ml) followed by brine (100 ml). The organic phase was dried

over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. A dark yellow viscous oil was obtained. It was purified over a short silica gel column using toluene as eluent. Toluene was removed at reduced pressure and a yellowwhite crystalline solid was obtained. It was recrystallized from a ether-hexane mixture.

Yield : 21.0 g (90%)

R_f. : 0.37 (toluene, blue to CPS)

M.p. : 100 - 101° C

$[a]_D^{20}$: + 216.7° (c = 1.14, $CHCl_3$)

IR (KBr) :

3439w*, 1786s, 1448m, 1325w, 1219m, 1198w, 1040s, 1015m, 991m, 773w, 756s, 694s, 669w, 642w.

* the presence of the hand at 3439 cm^{-1} could not be explained (H_2O in KBr?)

^{1}H-NMR (250 MHz , $CDCl_3$) :

7.55 - 7.15 (m, 15 arom.H); 6.85 (d, J = 18.0 Hz, 1H, H-C(4)); 5.80 (d, J = 6.9 Hz, 1H, HC(2)); 5.60 (dxd, J = 6.9,18.0 Hz, 1H, H-C(3)).

^{13}C-NMR (62 MHz, $CDCl_3$) :

153.5 (C(5)carbonate); 139.9, 137.4, 134.7 (C(1'),C(1"),C(1'")); 136.8 (C(3)); 128.7, 128.6, 128.5, 128.4, 128.3, 128.2 (C(3'),C(5'),C(3"),C(5"), C(4'),C(4"),C(4'")); 126.6, 125.9, 125.5 (C(2'),C(6'),C(2"),C(6"),C(2'"),C(6'")); 121.3 (C(4)); 88.9 (C(1)); 86.0 (C(2)).

An additional signal at 93.2 ppm could not be interpreted.

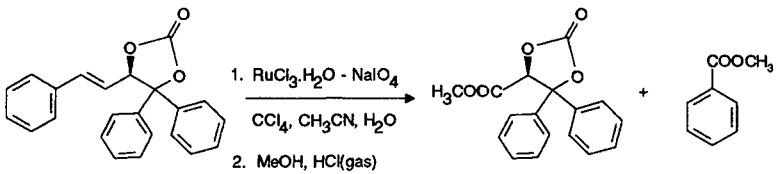
MS :

342 (M^+, 62); 269 (46); 183 (48); 167 (40); 166 (96); 165 (90); 116 (96); 115 (100); 105 (85); 77 (66); 51 (35).

Elemental analysis :

$C_{23}H_{18}O_3$	*Calculated*	C : 80.68, H : 5.30, O : 14.02
	Found	C : 80.65, H : 5.37, O : 14.00

2-Oxo-5,5-diphenyl-[1,3]-dioxolane-4*(R)*-carboxylic acid methyl ester (7)



5 7

The cyclic carbonate 5 (18.66 g, 54.66 mmole) was dissolved in a solvent mixture (40 ml CCl_4, 40 ml CH_3CN, 60 ml H_2O) in a 500 ml three necked flask fitted with thermometer and magnetic stirrer. To this heterogenous system $NaIO_4$ (47.84 g, 223.7 mmole, 4.1equivalent) was added in portions over a period of 1hr. The flask was then immersed in a water bath and $RuCl_3$. H_2O (0.429 g, 1.9 mmole, 3.5 mole%) was added portion-wise. The addition was completed in 15 min. After a few minutes, an exothermic reaction was observed with gas evolution and the temperature rose up to 45° C. After about 15 min. the temperature decreased and stirring was continued for one more hour.

Then another portion of $NaIO_4$ (11.66 g, 1.0 equivalent) was added in 10 min. followed by $RuCl_3$. H_2O (0.1 g) in one portion. The reaction was stirred for 6 hr. at room temperature. Then a 10% $NaHCO_3$ (130 ml) solution was added to the reaction mixture. A grey reaction mixture was formed with evolution of gas. After stirring for 30 minutes the reaction was filtered and the filtrate was extracted with ethyl acetate (2x400 ml). The aqueous layer was separated and acidified with 1N HCl until pH 2 and extracted with ethyl acetate (3x500 ml). The organic layer was separated, washed with water (2x100 ml) until free from acid followed by brine (100ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. A white solid consisting of a mixture of the desired acid 36 and benzoic acid was obtained (14.0 g).

The inseparable mixture of 36 and benzoic acid was treated with 1N HCl in MeOH, and both the corresponding methyl esters were obtained. Treatment with 1N HCl in isopropanol gave the corresponding i-Pr esters. Methyl benzoate was removed on high vacuum. The physical data for the methyl and isopropyl ester are as follows:

Yield : 8.0 g (50%)

R_f : 0.7 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 136 - 137° C

$[a]_D^{20}$: + 258.7° (c = 0.987, $CHCl_3$)

IR (KBr) :

1807s, 1757s, 1232m, 1211m, 1084s, 696m.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.20 (m, 10 arom H); 5.70 (s,1H); 3.35 (s,3H, ester).

^{13}C-NMR (62 MHz, $CDCl_3$) :

166.4 (COOR); 149.5 (OCOOR); 139.4,136.6 (C(1'),C(1")); 129.5, 129.1 (C(4'),C(4")); 129.0, 128.3 (C(3'),C(5'),C(3"),C(5"));, 126.3, 126.2 (C(2'),C(6'),C(2"),C(6"); 89.4 (C(3)); 81.7 (C(2)); 52.5 (OCH_3).

MS :

298(M^+ ,20), 221(100), 121(93), 116(60), 105(68), 77(62), 44(44).

2-Oxo-5,5-diphenyl-[1,3]-dioxolane-4*(R)*-carboxylic acid isopropyl ester (8)

Yield : 8.8 g (50%)

R_f : 0.78 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 175 - 176° C

$[a]_D^{20}$: + 242.9° (c = 0.177, $CHCl_3$)

IR (KBr) :

1809s, 1737m, 1240w, 1213w, 1037m.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.20 (m, 10 arom H); 5.65 (s,1H); 4.65 (sep., J = 6.8 Hz, 1H, iPr H); 0.98 (d, J = 6.8 Hz, 3H, CH_3); 0.87 (d, J = 6.8 Hz, 3H, CH_3).

^{13}C-NMR (62 MHz, $CDCl_3$) :

165.0 (COOR); 154.5 (OCOOR); 129.3, 129.0 (C(4'),C(4")); 128.9,128.3(C(3'), C(5'),C(3"), C(5")); 126.5, 126.1 (C(2'),C(6'),C(2"),C(6")); 82.2 (C(3); 81.7 (C(2); 70.8 ($\underline{C}H(CH_3)_2$); 21.2, 20.9 ($CH(\underline{C}H_3)_2$).

MS :

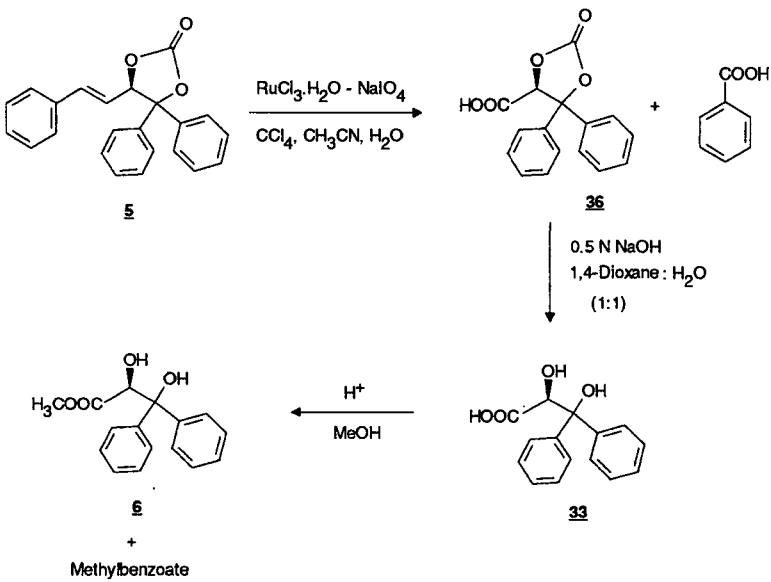
326 (M^+, 6), 183 (74), 165 (36), 105 (62), 77 (40), 43 (100)

Elemental analysis :

$C_{19}H_{18}O_5$ *Calculated* C : 69.93, H : 5.56, O : 24.51

Found C : 69.67, H : 5.52, O : 24.72

3,3-Diphenyl-1,2(*S*)-dihydroxy-propionic acid methyl ester (**6**)



5 **36** **6** + Methylbenzoate **33**

To avoid the preparation of the carbonate ester **7**, the acid carbonate **36** was converted directly to the ester diol by carbonate group cleavage via **33**. The carbonate protecting group was cleaved as follows :

In a solvent mixture of 1,4-dioxane (150 ml) and H_2O (150 ml) containing sodium hydroxide (6.0 g, 150 mmole), the mixture of acids was dissolved and stirred for 1 hr. at room temperature. After acidifying with 1N HCl to pH 2 and extraction with ethyl acetate (2x500 ml), the organic layer was washed with water (2x100 ml) until free from acid followed by brine (100 ml) and finally dried over anhydrous Na_2SO_4. On concentration at reduced pressure, the diol acid **33** was obtained together with benzoic acid.

Diol acid 33 and benzoic acid mixture was dissolved in 100 ml methanol containing 1M HCl (gas) and warmed to 35° C overnight to obtain the corresponding methyl esters. After complete conversion, methanol was removed at reduced pressure. The methyl benzoate was removed from the mixture by heating at 40° C under high vacuum (0.02 mbar) overnight.

The diol ester 6 was recrystallised from acetone : H_2O mixture to get fine colorless needles.

Yield : 7.0 g, (46% from 5)

R_f : 0.59 (toluene : EtOAc : Methanol [5:3:2] , blue to CPS)

M.p. : 145 - 146° C

$[a]_D^{20}$: + 146.2° (c = 0.50, $CHCl_3$)

IR (KBr) :

3522s, 3433s, 1713s, 1240w, 1109w, 698m.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.50 - 7.10 (m, 10 arom. H); 4.95 (d, J = 6.9 Hz, 1H, H-C(2)); 3.75 (s, exchange with D_2O, OH-C(3)); 3.45 (s, 3H, ester); 3.25 (d, J = 6.9 Hz, exchange with D_2O, OH-C(3)).

^{13}C-NMR (62 MHz, $CDCl_3$) :

172.4 (C(1)); 142.2, 142.0 (C(1'),C(1")); 127.3, 127.1 (C(3'),C(5'),C(3"),C(5")); 126.5, 126.4 (C(4'),C(4")); 125.5, 124.9 (C(2'),C(6'),C(2"),C(6")); 78.6 (C(3)); 74.6 (C(2));

51.4 (ester -OCH3).

FD-MS :

272 (M^+, 70); 255 (12); 184 (26); 183 (100); 182 (20).

Elemental analysis :

$C_{16}H_{16}O_4$	*Calculated*	C : 70.57, H : 5.92, O : 23.50
	Found	C : 70.82, H : 5.93, O : 23.42

The ethyl ester 9 and isopropyl 10 esters were similarly prepared by treating the acid mixture with 1N HCl in ethanol or isopropanol, respectively. Their physical data are as follows :

3,3-Diphenyl-1,2*(S)*-dihydroxy-propionic acid ethyl ester (**9**)

Yield : 6.94 g (45% from **5**)

R_f : 0.53 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 152 - 153° C

$[a]_D^{20}$: + 127° (c = 1.026, $CHCl_3$)

IR (KBr) :

3539m, 3416m, 1714s, 1449w, 1227m, 1169w, 1107w, 768w, 700m.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.20 (m,10 arom H); 5.05 (d, J = 6.8 Hz, 1H, H-C(2)); 3.95 (A× B × q, J = 7.0,12.5 Hz, 2H,-CH_2-); 3.80 (s, exchange with D_2O, t-OH); 3.35 (d, J = 6.8 Hz, exchange with D_2O, sec-OH); 0.90 (t, J = 7.0 Hz, 3H, -CH_3)

^{13}C-NMR (62 MHz, $CDCl_3$) :

172.5 (COOR); 142.9, 142.4 (C(1'),C(1")); 127.7, 127.5 (C(3'),C(5'),C(3"),C(5")); 127.0, 126.8 (C(4'),C(4")); 125.9, 125.5 (C(2'),C(6'),C(2"),C(6")); 79.0 (C(3)); 74.9 (C(2)); 61.2 (-$\underline{C}H_2CH_3$)); 13.0 (-$CH_2\underline{C}H_3$).

FD MS :

286 (M^+,61), 183 (62), 182 (100)

Elemental analysis :

$C_{17}H_{18}O_4$	*Calculated*	C : 71.31, H : 6.34, O : 22.35
	Found	C : 71.38, H : 6.29, O : 22.31

3,3-Diphenyl-1,2*(S)*-dihydroxy-propionic acid isopropyl ester (**10**)

Yield : 7.8 g (48% from **5**)

R_f : 0.57 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 177 -178° C

$[a]_D^{20}$: + 125° (c = 0.951, $CHCl_3$)

IR (KBr) :

3536m, 3400m, 1706s, 1240m, 1106m, 749w, 698m

^{1}H-NMR (250 MHZ, $CDCl_3$) :

7.60 - 7.20 (m,10 arom H); 5.00 (brs,1H,H-C(2)); 4.85 (sep., J = 6.8 Hz, 1H,i-Pr.); 3.80 (s,exchange with D_2O,t-OH); 3.35 (s,exchange with D_2O, sec-OH); 1.10 (d, J = 6.8 Hz, 3H, i-Pr.); 0.80 (d, J = 6.8 Hz, 3H, i-Pr.)

^{13}C-NMR (62 MHz, $CDCl_3$) :

172.3 (COO-iPr.); 143.1, 142.3 (C(1'),C(1")); 127.6, 127.4 (C(3'),C(5'),C3"),C(5")); 126.8, 126.7 (C(4'),C(4")); 125.7, 125.4 (C(2'),C(6'),C(2"),C(6")); 81.0 (C(3)); 74.7 (C(2)); 69.3 ($\underline{C}H(CH_3)_2$); 20.8, 20.3 ($CH(\underline{C}H_3)_2$)).

FD-MS :

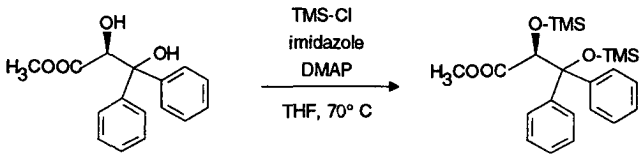
300 (M^+,100), 184(38), 183(10)

Elemental analysis :

$C_{18}H_{20}O_4$ *Calculated* C : 71.98, H : 6.71, O : 21.31

Found C : 72.00, H : 6.59, O : 21.35

2*(S)*,3-Bis-(trimethylsiloxy)-3,3-diphenyl-propionic acid methyl ester (**11**)



6 **11**

In a 50 ml round bottom flask, the diol methyl ester 6 (200 mg, 0.735 mmole) was dissolved in 20 ml of THF. To this solution imidazole (0.23 g, 3.38 mmole) and a catalytic amount of N,N-dimethyl amino pyridine (DMAP) were added. Then TMS-Cl (0.3 ml, 2.2 mmole) was added dropwise with stirring. The reaction was heated and stirred overnight at 70° C. The solvent was completely evaporated, and the residue was dissolved in 50 ml of ethyl acetate. The solution was washed with water (50 ml) followed by brine (25 ml) and dried over anhydrous Na_2SO_4. On evaporating the solvent, the product was obtained as solid.

Yield : 0.275 mg (90%)

R_f : 0.74 (toluene : EtOAc, [6:1]; blue to CPS)

$[a]_D^{20}$: + 86.3° (c = 0.78, $CHCl_3$)

IR (KBr) :

1766m,1252w, 1202w, 1148s, 1128w, 880m, 841s, 752w, 701w

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.45 - 7.25 (m,10 arom H); 5.15 (s,1H); 3.40 (s,3H, ester); 0.20 (s,9H,TMS);

0.00 (s,9H,TMS)

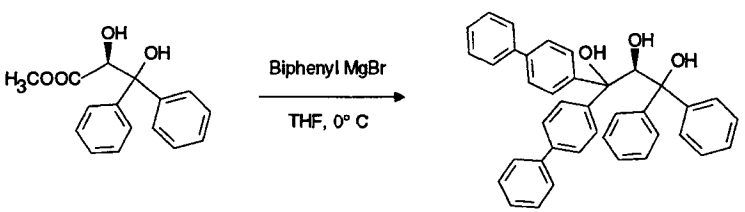
^{13}C-NMR (62 MHz, $CDCl_3$) :

171.4 (COOR); 145.5,144.9 (C(1'),C(1")); 128.1 (C(4'),C(4")); 127.5, 127.2 (C(2'),C(6') , C2"),C(6")); 127.0, 126.9 (C(3'),C(5'),C(3"),C(5")); 82.5 (C(3)); 51.2 (C(2)); 2.1, 0.0 ($Si(CH_3)_3$).

MS :

439.2 (MNa^+)

1,1-bis(biphenyl)-3,3-bis(phenyl)-1,2*(S)*,3-propane triol (12)



6 12

In a previously dried three necked 250 ml flask fitted with thermometer, dropping funnel, argon inlet / outlet and a magnetic stirrer, the Grignard reagent biphenyl MgBr (0.64M in THF, 34.46 ml, 22.0 mmole) was added with 100 ml of dry THF. The diol methyl ester 6 (1.0 g, 3.67 mmole) was dissolved in 50 ml of THF and transferred to the dropping funnel.

The flask was cooled to - 5 to 0° C and 6 was added to the Grignard solution over 30 min. A dark pink-violet colored reaction mixture was obtained. The reaction mixture was allowed to warm to room temperature. and stirring was continued for another 30 min. Then 20 ml of water was added to the reaction slowly. A white precipitate was formed. 60 ml of ethyl acetate was added and stirring was continued for a while. The precipitate was filtered off and washed with

ethyl acetate (2× 100 ml). The combined organic layers were washed with water (1× 50 ml) until neutral, followed by brine (1× 25 ml) and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure to get the crude product (4.7 g).

The mixture was chromatographed on silica gel column using toluene as eluent. The polarity of the eluent was increased gradually up to toluene : ethyl acetate 4:1. The pure triol **12** was obtained as a colorless oil.

Yield : 0.2 g. (10%)

R_f : 0.52 (toluene : EtOAc [6:1], blue to CPS)

$[a]_D^{20}$: - 10.7 ° (c = 0.244, $CHCl_3$)

IR (KBr) :

3400s, 3040w, 3020w, 1485s, 1450w, 835w, 760s, 740m, 695s.

^{1}H- NMR (250 MHz, $CDCl_3$) :

7.70 - 6.70 (m, 28 arom. H); 5.80 (s,1H, H-C(2)); 5.00 (s, exchange with D_2O, two -OH); 2.95 (brs, exchange with D_2O, one -OH).

^{13}C-NMR (62 MHz, $CDCl_3$) :

146.3, 145.2, 143.4, 142.2, 141.0, 140.4, 139.7, 138.4, 128.7, 128.5, 128.4, 128.2, 127.4, 127.3, 127.1, 127.0, 126.9, 126.8, 126.3, 126.2, 126.1, 125.8, 125.7, 125.4 (C(arom)); 82.3 (C(1)); 82.1 (C(3)); 75.5 (C(2)).

MS :

(PD MS) $(M+Na)^+$ 572 (M^+ = 548.7)

High resolution MS :

$M+Li^+$ = 555

Molecular formula found by High resolution MS is $C_{39}H_{32}O_3$

Method : FABPKMTCH

Instrument : VG 70-SE (Fisons Instruments, Manchester)

Optical purity :

99.5 % ee by HPLC analysis

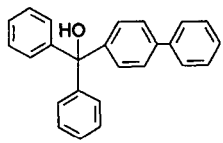
HPLC analysis parametars :

R_t	12.58 min.
HPLC column	Chiralpak AD (25 × 0.46 cm)

Mobile phase	Hexane : Isopropanol 8:2
Flow rate	1 ml / min.
Detection	UV 220 nm

Along with the triol two by products (**13** and **14**) were isolated and identified as the triol fragmentation products.

1,1-bis(phenyl)-1-biphenyl-methane-1-ol (**13**)



13

Yield : 0.46 g (38%)

R_f : 0.65 (toluene : EtOAc [6:1] , pink-orange to CPS)

$[a]_D^{20}$: no rotation

IR (KBr) :

3660s, 3439br, 1487m, 1447w, 1157w, 1009m, 770s, 727s, 689w, 635w.

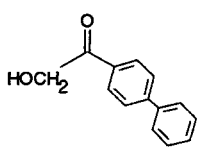
^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60- 7.30 (m, 19 arom H); 2.85 (s, exchange with D_2O).

MS :

336 (M+, 86), 259(96), 231(45), 181(45), 105(100), 77(67).

1-biphenyl-2-hydroxy-1-ethanone (**14**)



14

Yield : 0.23 g (30%)

R_f : 0.30 (toluene : EtOAc [6:1] , blue to CPS)

$[a]_D^{20}$: no rotation

IR (KBr) :

3423s, 3387s, 1686s, 1603m, 1234w, 1209w, 1109m, 976m, 764s.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.85 (q, J = 10.3 Hz, 4H, p-sub. arom); 7.65 - 7.40 (m, 5 arom H); 4.90 (d, J = 5.5 Hz, 2H); 3.60 (t, J = 5.5 Hz, exchange with D_2O, 1-OH).

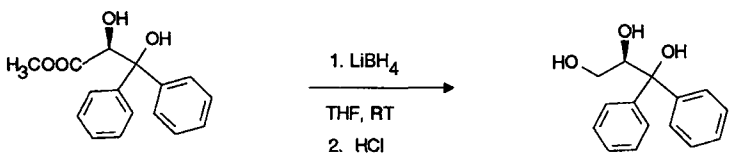
^{13}C-NMR (62 MHz, $CDCl_3$) :

197.2 (C=O); 146.2 (C(1')); 138.8 (C(1")); 131.3 (C(4')); 128.3 (C(4")); 127.8, 127.5 126.8, 126.5(C(2'),C(2"),C(3'),C(3")C(5'),C(5"), C(6'),C(6");, 64.7 (CH_2OH).

MS :

212 (M^+, 28), 181 (100), 153 (58), 152 (70)

1,1-bis(phenyl)-propane-1,2*(R)*,3-triol (**15**)



6 **15**

To a 100 ml two necked dry flask equipped with dropping funnel, magnetic stirring bob and argon inlet / outlet, $LiBH_4$ (0.186 g, 8.53 mmol) was added followed by 20 ml dry THF to get a suspension. **6** (1.0 g, 3.67 mmol) was dissolved in 27 ml dry THF and transferred to the dropping funnel, and then added dropwise at room temperature with vigorous stirring over 20 minutes. Stirring was continued for 6 hr.

An aqueous solution of 2N HCl was dropwise added to obtain pH 1. Then the reaction mixture was extracted with ethyl acetate (2x150 ml). The organic layer was washed with water (2x50 ml) until acid free followed by brine solution (50 ml), dried over Na_2SO_4 and evaporated at reduced pressure to get the crude product.

The crude product was chromatographed over 100 g silica gel using toluene, ethyl acetate 2:1 mixture as eluent. The polarity of the eluent was slowly increased up to (1:1) toluene : ethyl acetate. A white crystalline solid was obtained and recrystallised from toluene.

Yield : 0.67 g (77%)

R_f : 0.1 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 114 - 115° C

$[a]_D^{20}$: + 141° (c = 0.988, $CHCl_3$)

IR (KBr) :

3326br, 1449s, 1104m, 1046m, 754s, 698s, 667m, 639m.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.15 (m,10 arom H), 4.55 (m, 1H, HC(2)), 4.05 (s,exchange with D_2O, t-OH), 3.60 - 3.40 (m, 2H, H_2C(3)), 3.35 (d, J = 4.0 Hz,exchange with D_2O, sec-OH), 2.80 (bs, exchange with D_2O, pri.-OH).

^{13}C-NMR (62 MHz, $CDCl_3$) :

144.5, 143.1 (C(1'),C(1")); 127.8, 127.7 (C(3'),C(5'),C(3"),C(5")); 126.6, 126.3 (C(4'),C(4")); 125.7, 124.6 (C(2'),C(6'),C(2"),C(6")); 79.4(C(1)); 73.4 (C(2)); 62.40 (C(3)).

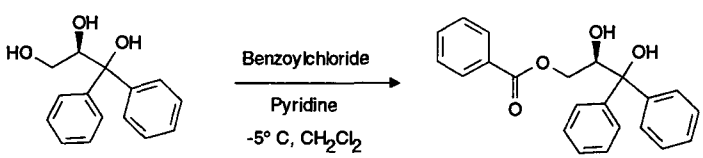
FD-MS :

244 (M+,54), 185(100), 182(30)

Elemental analysis :

$C_{15}H_{16}O_3$	*Calculated*	C : 73.75, H : 6.60, O : 19.65
	Found	C : 74.02, H : 6.62, O : 19.51

3-(O-benzoyl)-1,1-diphenyl-propane-1,2*(R)*-diol (**16**)



15 **16**

In a 100 ml three necked dry flask under argon atmosphere, 15 (0.976 g, 4.0 mmole) was dissolved in 80 ml of dry CH_2Cl_2. To the clear solution pyridine (0.484 ml, 6.0 mmole) was added by a syringe. The system was cooled with an salt-ice bath to - 5° C and benzoyl chloride (0.464 ml, 4.0 mmole) was added dropwise by a syringe. This addition was completed in 10 minutes. The reaction was slowly warmed to room temperature and stirred for 2 hr.

The solvent was removed at reduced pressure and the solid obtained was dissolved in 150 ml of ethyl acetate. This solution was washed with aqueous 2N HCl solution until the pH of the aqueous phase was about 1. The organic phase was separated and washed with water (2× 50 ml) followed by 50 ml brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to afford a white solid. The white solid was purified by flash chromatography over silica gel using toluene as a eluent. The polarity of the eluent was slowly increased up to toluene : ethyl acetate (2:1).

Yield : 1.0 g (72%)

R_f : 0.5 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 90-91° C

$[a]_D^{20}$: + 80.2° (c = 0.978, $CHCl_3$)

IR (KBr) :

3540m, 3486br, 1716s, 1698s, 1449s, 1332m, 1283s, 1178w, 1165w, 1120m, 1071m, 1026w, 984w, 893w, 751s, 697s, 661w, 639w.

^{1}H-NMR (250 MHz, $CDCl_3$) :

8.00 - 7.15 (m, 15 arom H), 5.00 (d x d, J = 2.7,8.9 Hz,1H, H-C(2)), 4.43 (d x d, J = 8.9,11.7 Hz,1H, H_A-C(3)), 4.27 (d x d, J = 2.7,11.7 Hz, 1H, H_B-C(3)), 3.30 (s, exchange with D2O, HO-C(2)), 2.95 (brs, exchange with D_2O, HO-C(1))

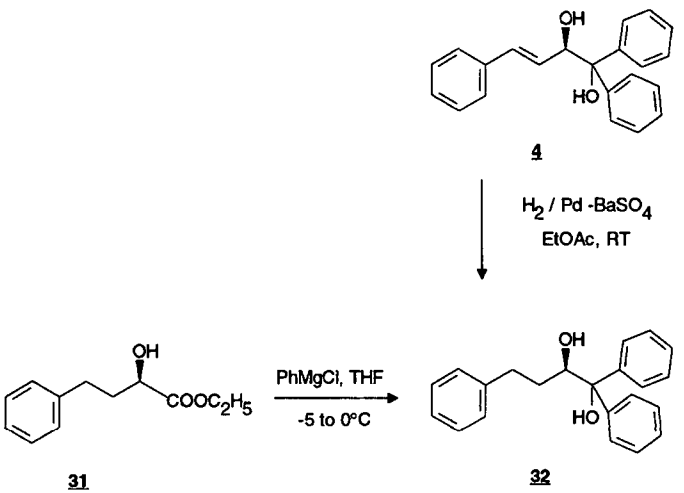
^{13}C-NMR (62 MHz, $CDCl_3$) :

164.5 (benzoyl); 145.1,142.8 (C(1'),C(1")); 133.2 (C(4'"));129.7, 128.6 (C(1'"),C(2"),C(6'")); 128.5, 128.48,128.4 (C(3'),C(5'),C(3"),C(5"),C(3'"),C(5'")); 127.3, 127.2 (C(4')C(4")); 126.2, 125.4 (C(2'),C(6'),C(2"),C(6")); 79.0 (C(3)); 73.8 (C(2)); 66.6 (C(1)).

FD-MS :

348 (M^+, 6); 305 (42); 183 (100); 165 (38).

1,1,4-triphenyl-1,2*(R)*-dihydroxy butane (**32**)



In a 50 ml round bottom flask fitted with a H_2 inlet / outlet and equipped with a magnetic stirrer, **4** (1.0g, 3.16 mmole) was dissolved in 25 ml of ethyl acetate. To this clear solution 5% Pd on $BaSO_4$ (0.2 g) was added. This suspension was stirred at room temperature and hydrogen was continusly bubbled into the reaction. After about 90 minutes the reaction had consumed 71.31 ml of hydrogen (theory 70.89 ml), and no further consumption was observed. The suspension was filtered and the filtrate was evaporated at reduced pressure. A white solid was obtained. It was recrystallized from ethanol.

Yield : 0.96 g (96%)

R_f : 0.57 (toluene : EtOAc [4:1], blue to CPS)

M.p. : 122 - 123° C

$[a]_D^{20}$: + 95.3° (c = 0.937, $CHCl_3$)

IR (KBr) :

3569m, 3485m, 1494w, 1448w, 749s, 699s

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.10 (m, 15 arom. H); 4.55 (d x d, J = 10.0, 3.5 Hz, 1H, HC(2)); 3.00 (brs, exchange with D_2O, -OH); 2.70 - 2.55 (m,2H,H_2C(4)); 1.90 - 1.60 (m, H_2C(3), -OH).

^{13}C-NMR (62 MHz, $CDCl_3$) :

145.6, 143.5, 141.8 (C(1'),C(1"),C(1'")); 128.7,128.5, 128.3, 128.2, 127.2, 126.8, 126.0, 125.9, 125.5 (9 arom); 80.0 (C(1)); 74.8 (C2)); 32.4 (C(3)); 31.7(C(4)).

FD-MS :

318 (M^+, 100), 183 (37), 166 (20)

Elemental analysis :

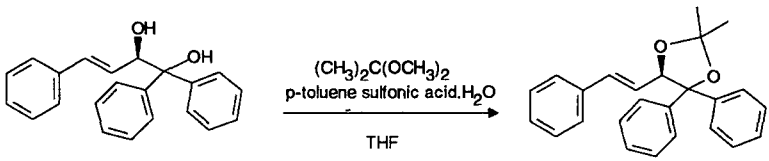
$C_{22}H_{22}O_2$	*Calculated*	C : 82.99, H : 6.96, O : 10.05
	Found	C : 82.91, H : 6.84, O : 10.07

The same product **32** was also obtained by the reaction of PhMgCl with **31** as follows : (**31** was available trom Kuraray Co., Japan in 99% ee)

A dry 250 ml three necked round bottom flask under argon atmosphere was fitted with a thermometer, a dropping funnel and magnetic stirring bob. **31** (10.4 g, 50 mmole) was added to the flask and dissolved in 100 ml dry THF. PhMgCl (23.95 g as a 25% solu. in THF, 175 mmole) was transferred to the dropping funnel. With the help of a salt-ice bath the reaction flask was cooled to -10° C. The Grignard reagent was added to the vigorously stirred reaction mixture over 40 minutes. After the addition was complete, the reaction temperature was allowed to increase slowly to room temperature and stirring was continued for eight hours. The reaction was again cooled to 0° C and 70 ml of 10% NH_4Cl was dropwise added. A precipitate separated. The pH of the reaction was adjusted to pH 2 by adding 2N HCl, then the reaction mixture was extracted with ethyl acetate (2x 250 ml). The organic layer was separated and washed with H_2O (2x 50 ml) followed by 50 ml of brine solution. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed at reduced pressure to afford 14 g of crude product. The crude product was recrystallized from ethanol. All the physical data were exactly the same as for the product **32** .

Yield : 94%

2,2-Dimethyl-4,4-diphenyl-5*(R)*-styryl-[1,3]dioxolone (17) :



4 17

In a 250 ml round bottom flask, diol 4 (18.96 g, 60 mmole) and 2,2-dimethoxy propane (50 ml, excess) were dissolved in 110 ml of THF. A catalytic amount of p-toluene sulfonic acid. H_2O (200 mg) was added to it and the reaction was stirred overnight at room temperature.

The reaction mixture was added to 250 ml of ethyl acetate. The organic phase was washed once with 40 ml of 10% $NaHCO_3$ solution. The organic layer was separated, washed with water followed by brine solution and finally dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain 20 g of crude yellow product. The crude product was purified by flash chromatography over silica gel using toluene as eluant and recrystallised from n-hexane to get colorless needles.

Yield : 18 g (84.2 %)

R_f : 0.65 (toluene, blue to CPS)

M.p. : 85 - 86° C

$[a]_D^{20} = +185.0°$ (c = 0.9, $CHCl_3$)

IR (KBr) :

3084w, 3049w, 2990m, 2889w, 1489m, 1447m, 1369m, 1265m, 1211s,1180m, 1167m, 1086w, 1047s, 1022s, 970s, 891s, 750s, 700s.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.10 (m, 15 arom. H); 6.80 (d, J = 13.8 Hz, 1H, PhC<u>H</u>=CH) 5.70 (dxd, J = 6.9,13.8 Hz, 1H, PhCH=C<u>H</u>); 5.30 (d, J = 6.9 Hz, 1H, HC(2)); 1.80 (s, 3H); 1.40 (s, 3H).

^{13}C-NMR (62 MHz, $CDCl_3$) :

145.5 ; 142.7, 136.3 (C(1'),C(1"),C(1"')); 134.3 (C(1)); 128.5, 128.1, 128.0, 127.7, 127.4 (C(3'),C(5'),C(3"),C(5"),C(3"'),C(5"'));127.2,127.1,126.7,126.2(C(4'),C(4"),C(4"'),C(2'),C(2"),C(2"');109.1 (C(4)); 93.5 (<u>C</u>$(CH_3)_2$); 87.6(C(3)); 85.9 (C(2)); 27.0 (-CH_3); 25.7 (-CH_3).

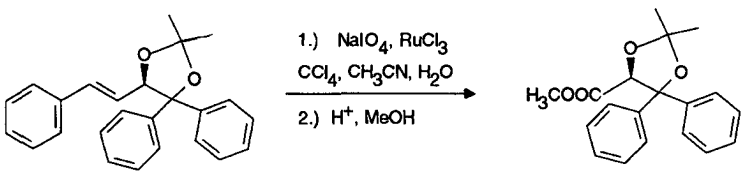
MS :

356 (M^+), 224 (30), 175 (40), 165 (62), 159 (48), 156 (18), 131 (22), 116 (68), 115 (80), 105 (46), 91 (16), 77 (48), 55 (16), 43(40).

Elemental analysis:

$C_{25}H_{24}O_2$	*Calculated*	C : 84.24	H : 6.79	O : 8.98
	Found	C : 84.07	H : 6.62	O : 9.00

2,2-Dimethyl-5,5-diphenyl-[1,3]dioxolane-4*(S)*-carboxylic acid methyl ester (**18**)



17 **18**

"Styryl acetonide" **17** (9.0 g, 25.28 mmole) was transferred to a 500 ml four necked reactor and dissolved in the solvent system (CCl_4, 75 ml + CH_3CN, 75 ml + H_2O, 110 ml [1.0:1.0:1.5]). This biphasic system was vigorously stirred at room temperature. Solid $NaHCO_3$ (21.0 g, 250.0 mmole) was added to it in one portion. Then $NaIO_4$ (48.65 g, 227.5 mmole) was added in small portions over one hour. After fifteen minutes, $RuCl_3$. H_2O (1.71 g, 8.24 mmole, 0.3 eq.) was added to the reaction in one portion. Stirring was continued for twelve hours, over which time the reaction color slowly changed to gray yellow. 100 ml of H_2O was added and the reaction mixture was stirred for another fifteen minutes. The mixture was filtered over celite and the filtrate was extracted with 250 ml of ethyl acetate. The aqueous layer was separated and acidified with 2 N aqueous HCl to pH 2. The aqueous layer was again extracted with ethyl acetate (3 x 250 ml). The organic layer was separated, washed with H_2O (2 x 75 ml) until free of acid followed by brine solution (50 ml) and finally was dried over anhydrous Na_2SO_4. On evaporation at reduced pressure a white crystalline mixture of the desired acid and benzoic acid was obtained (6.1 g).

The mixture of benzoic acid and the desired product was dissolved in 100 ml of methanol containing 1.0 M (3.55 g) of HCl and stirred at room temperature overnight to convert both acids to their corresponding methyl esters. Then methanol was completely removed at reduced pressure. The residue was heated at 40° C under high vacuum (0.01 mbar) for four hours until most of the methyl benzoate had been removed. The remaining solid was flash chromatographed on a silica gel column with toluene. The polarity of the eluent was slowly increased to 10% ethyl acetate and the pure methyl ester was obtained as a white crystalline solid. Recrystallisation from n- hexane gave white colorless crystals.

Yield : 3.0 g (38%)

R_f : 0.76 (toluene / EtOAc / MeOH [5:3:1], blue to CPS)

M.p. : 74 - 75° C

$[\alpha]_D^{20}$ = + 218.2° (c = 1.14 , $CHCl_3$)

IR (KBr) :

2986w, 1734s, 1445m, 1383m, 1269s, 1246w, 1221s, 1184w, 1094m, 1043m, 1024m, 864w, 756m, 698s, 609w.

^{1}H-NMR (250 MHz , $CDCl_3$) :

7.70 (d, J = 6.8 Hz, 2 arom. H), 7.45 - 7.20 (m, 8 arom. H), 5.40 (s, 1H), 3.25 (s, 3 H, methyl ester H), 1.85 (s, 3 H, methyl H), 1.20 (s, 3H, methyl H).

^{13}C-NMR (62 MHz, $CDCl_3$) : 169.4 (ester C=O), 144.4 (C(1')); 141.7 (C(1")), 128.2, 127.7 (C(4'),C(4")); 127.6, 127.5 (C(3'),C(5'),C(3"),C(5")); 127.2, 127.0 (C(2'),C(6'),C(2"),C(6"); 111.3 (-$\underline{C}(CH_3)_2$), 88.9 (C(3)); 84.0 (C(2)); 51.7 (ester-$\underline{C}H_3$), 26.9 (-CH_3), 25.9 (CH_3).

MS :

312 (M^+), 236(22), 235(100), 217(21), 177(58), 165(24), 149(30), 130(88), 121(58), 105(56), 77(50), 73(100), 59(28), 51(20), 43(70).

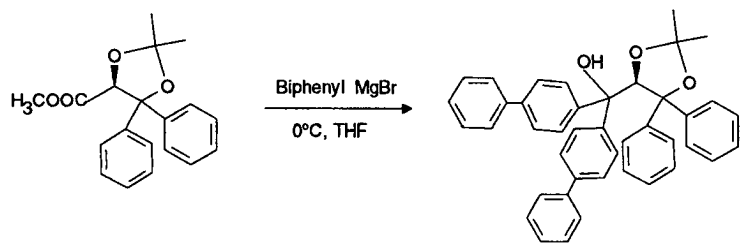
Elemental analysis : $C_{19}H_{20}O_4$

Calculated	C : 73.06	H : 6.45	O : 20.49
Found	C : 72.76	H : 6.34	O : 20.69

Method II :

The methyl esters **18** was also prepared using 3-methyl-1-(p-Tolyl) triazene [H_3C-Ph-N=N-NHCH]. The 6.0 g acid mixture was dissolved in 100 ml of CH_2Cl_2. Triazene (5.7 g, 3 equivalents) was dissolved in 35 ml of CH_2Cl_2 and added dropwise to the above solution over 15 minutes. Nitrogen evolution was observed. The reaction was stirred at room temperature overnight, then it was added to 200 ml ethyl acetate. The organic phase was washed with 2N HCl until the mixture was free from the byproduct toluidine . The organic layer was washed with H_2O until free of acid (2x100 ml) followed by brine solution (50 ml). 4.0 g of crude substance was obtained on removing the solvent. It was dried at reduced pressure and silica gel chromatography in toluene/ ethyl acetate (9:1) gave 3.2 g acetonide methyl ester **18** (51.28 %). All the analytical data tallied exactly with the data of the product obtained by the first method.

Bis-biphenyl-4-yl-(2,2-dimethyl-5,5-diphenyl-[1,3]dioxolan-4(-yl)-methanol (**19**)



18 **19**

A 350 ml four necked reactor fitted with a dropping funnel, thermometer and a magnetic stirring bob was dried under nitrogen atmosphere. Grignard reagent was prepared in dry THF solution using 4-bromo-biphenyl (6.52 g, 28 mmole) and Mg turnings (0.72 g, 30 mmole). The acetonide methyl ester **18** (1.84 g, 5.89 mmole) was dissolved in 25 ml dry THF and transferred to the dropping funnel. The reactor was cooled to -10° C. The dropwise addition was completed in fifteen minutes at 0° C. The reaction was slowly warmed to room temperature and stirring was continued for another hour. 10 ml of water was added dropwise while controlling the temperature below 30° C. The reaction mixture was stirred for ten minutes, then 10% aqueous citric acid solution was added till pH 5.5. The reaction mixture was extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with water (2 x 75 ml) till neutral, followed by brine solution (50 ml). Reaction mixture was dried over

anhydrous Na_2SO_4 and evaporated at reduced pressure to provide yellow crystalline product. The product was purified by flashchromatography utilizing first hexane as eluent, then the polarity of the eluent was increased by adding toluene until a ratio of hexane : toluene (2:3) was achieved.

Yield : 3.1 g (89.8 %)

R_f : 0.37 (toluene : n-Hexane [2:3], blue to CPS)

M.p. : 106 - 107° C

$[\alpha]_D^{20}$ = + 60.7° (c = 1.0, CH_2Cl_2)

IR (3% in CH_2Cl_2) :

3550m , 3020m, 1600w, 1490s, 1390s, 1215s, 1175s, 1100w, 1050s, 1020m, 1010m, 970w, 900w, 870w, 830m

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 6.75 (m, 28 arom H), 6.00 (s, 1H, H-C(2)), 2.95 (s, exchange with D_2O, -OH), 1.75 (s, 3H, $-CH_3$), 1.15 (s, 3H, $-CH_3$)

^{13}C-NMR (62 MHz, $CDCl_3$) :

147.6, 144.6, 144.2, 141.3, 140.9, 140.7, 139.3, 138.9 128.7, 128.6, 128.3, 128.0, 127.2, 127.1, 127.0, 126.9, 126.8, 126.6, 126.5, 126.4, 126.2 (aromatic); 108.6 ($\underline{C}H(CH_3)_2$)); 88.6 (C(1)); 86.9 (C(3)); 78.1 (C(2)); 27.0 ($\underline{C}H_3$); 26.3 ($\underline{C}H_3$).

ESI-MS :

611 (100, MNa^+), 321 (28), 301 (35), 289 (65)

High resolution MS :

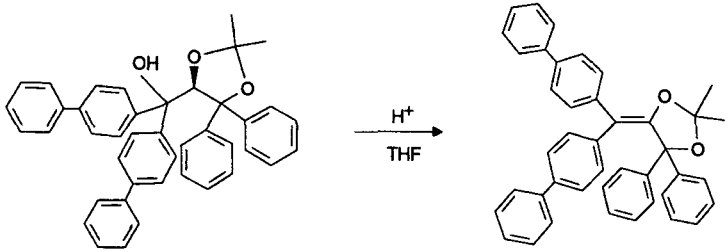
$M+Na^+ = 611$

Molecular formula found by High resolution MS is $C_{42}H_{36}O_3$

Method : FABPKMTCH

Instrument : VG 70-SE (Fisons Instruments, Manchester)

2,2-Dimethyl-4,4-diphenyl-5-(2,2,biphenyl-vinyl)-[1,3]dioxolone (20)



19 20

The above alcohol 19 (0.587 g, 1.0 mmol) was dissolved in 15 ml of THF to get a colorless clear solution. To this 1.5 ml of 1N aqueous HCl was added and the mixture was stirred at room temperature for 10 hours. No reaction was observed, therefore the reaction mixture was refluxed for 8 hours, which afforded the product in very good yield.

Yield : 0.5 g (90%)

M.p. : 174 - 175° C

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 6.70 (m, 28 arom H), 1.50 (s, 6H, $-CH_3$)

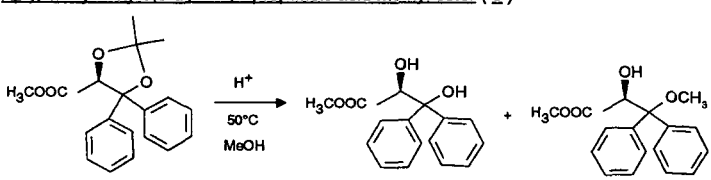
^{13}C-NMR (62 MHz, $CDCl_3$) :

151.4, 142.3, 141.0, 140.9, 139.0, 138.7, 138.4, 136.9, 131.4, 129.4, 129.1, 128.7, 128.6, 127.4, 127.0, 126.9, 126.8, 126.5, 126.2 (aromatic); 113.4 (C(1)); 111.1 ($\underline{C}(CH_3)_2$)); 92.4 (C(3)); 90.3 (C(2)); 27.6 ($\underline{C}H_3)_2$.

MS :

570 (M^+, 72); 512 (40); 485 (38); 484 (100); 331 (32); 330 (80); 43 (38).

2(*S*),3-dihydroxy-3,3-diphenyl- propanoic acid methyl ester (6)



18 6 21

The acetonide methyl ester **18** (1.2 g, 3.84 mmole) was dissolved in methanol containing 1M HCl gas and heated at 50°C overnight. Along with the desired product **6** the methyl ether **21** was formed. To avoid more sideproduct formation, the solvent was completely evaporated at this stage and the crude product was chromatographed on silica gel in toluene and polarity of the eluent was slowly increased until it reached upto toluene / ethyl acetate (6:1).

Yield : 0.26 g (26%)

The recovered starting material is reacted again with fresh methanol containing 1M HCl gas. This time

0. 227 g (22.7%) of product and 0.09 g (8.2%) of byproduct was isolated.

The product was recrystallised from acetone / H_2O mixture.

R_f : 0.2 (toluene : EtOAc [9:1]. blue to CPS)

M.p. : 145 - 146° C

$[\alpha]_D^{20}$ = + 146.2° (c = 0.5, $CHCl_3$)

The product analytical data (M.p., ^{1}H-NMR, ^{13}C-NMR, MS, elemental analysis) tallied exactly with the analytical data of the product **6** obtained by the carbonate route.

The byproduct was isolated and characterized to be 3,3-diphenyl-3-methoxy-2(*S*)-hydroxy-propionic acid methyl ester **21** , the mono methoxy derivative of the diol ester **6**.

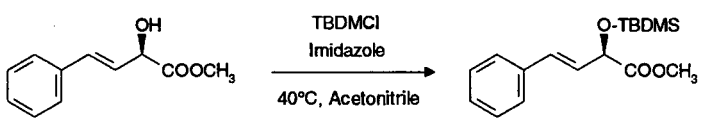
^{1}H-NMR (250 MHz, $CDCl_3$) :

7.40 - 7.20 (m, 10 arom H), 5.15 (d, J = 6.8 Hz, 1H, H-C(2)), 3.60 (s, 3H, ester), 3.10 (s, 3H, -OCH_3), 2.95 (d, J = 6.8 Hz, exchange with D_2O, -OH),

^{13}C-NMR (62 MHz, $CDCl_3$) :

171.8 (ester C=O), 139.5,138.8 (C(1'),C(1")), 127.9, 127.5, 127.2, 126.8, 126.7, 126.5 (aromatic), 83.9 (C(3)), 72.8 (C(2)), 51.4, 51.3 (OCH_3)

2*(R)*-Tert.butyldimethylsiloxy-4-phenyl-but-3-enoic acid methyl ester (**22**)



2 **22**

The starting α-hydroxy methyl ester **2** (10.0 g, 52 mmole), 1.2 equivalent of t-butyl dimethyl chlorosilane (9.42 g, 62.5 mmole), and 1.5 equivalent imidazole (5.31 g, 78 mmole) were dissolved in 220 ml acetonitrile in a 500 ml flask. It gave a clear solution. It was stirred at 40° C for 15 hours.

After the reaction was complete, acetonitrile was completely removed at reduced pressure. The solid was again dissolved in 250 ml of toluene and washed with 100 ml of water followed by 50 ml brine solution. It was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to get the crude product. It was flash chromatographed over silica gel in toluene to get pure yellow liquid product **22**.

Yield : 13.6 g (85 %)

R_f : 0.58 (toluene, blue to CPS)

$[\alpha]_D^{20}$: - 32° (c = 0.99, $CHCl_3$)

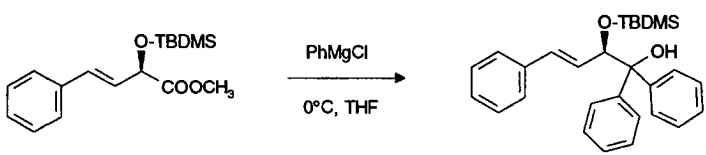
IR (KBr) :

2953w, 2930w, 1760s, 1225s, 1153s, 837s, 780m

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.35 - 7.05 (m, 5 arom.H), 6.70 (d, J = 17.0 Hz, H-C(4)), 6.25 (dxd, J = 6.8,17.0 Hz, H-C(3)), 4.80 (d, J = 6.8 Hz, H-C(2)), 3.70 (s, 3H, ester), 0.90 (s, 9H,t-butyl), 0.10 (2 s, 6H, Si-$(CH_3)_2$).

2*(R)*-Tert.butyldimethylsiloxy-1,1,4-triphenyl-but-3-ene-1-ol (**23**)



22 **23**

A 150 ml four necked reactor was fitted with a dropping funnel, a magnetic stirring bob, a thermometer and flame dried under nitrogen atmosphere. PhMgCl (10.94 g, 80.0 mmole, 2.0 M solution in THF) was transferred to the reactor. The TBDMS protected methyl ester **22** (8.1g, 26.47 mmole) was dissolved in 40 ml dry THF and transferred to the dropping funnel. The reactor was cooled with an ice-salt mixture to -10° C and methyl ester **22** added dropwise over 30 minutes. The temperature of the reaction mixture was slowly increased to room temperature and the mixture was stirred for 6 hours. 10% citric acid solution (80 ml) was added dropwise to the reaction mixture with

cooling. The pH was 4. The mixture was stirred for 15 minutes and extracted with ethyl acetate (2× 150 ml). The organic layer was washed with water (2×50 ml) followed by brine solution (50ml) and finally dried over anhydrous Na_2SO_4. On concentration solid crude product was obtained which was purified by silica gel chromatography utilizing a petrol ether : toluene (3:2) mixture as eluent.

Yield : 6.2 g (54.5 %)

R_f : 0.7 (toluene, blue to CPS)

$[\alpha]_D^{20}$: + 81° (c = 0.80, $CHCl_3$)

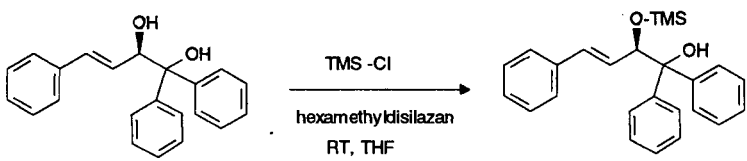
IR (KBr) :

3535m, 2954w, 2929m, 2857w, 1448m, 1250w, 1054s, 973s, 867w, 838s, 826s, 777m, 750s, 699s

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.80 -7.20 (m, 15 arom. H), 6.55 (d, J = 13.0 Hz,1H, HC(4)), 6.30 (dxd, J = 6.8,13.0 Hz,1H, H-C(3)), 5.20 (d, J = 6.8 Hz, 1H, H-C(2)), 3.50 (s, exchange with D_2O, OH), 0.85 (s, 9H, Si-t-butyl), 0.10 (s, 3H, Si-CH_3), 0.00 (s, 3H, Si-CH_3).

2*(R)*-Trimethylsiloxy-1,1,4-triphenyl-but-3-ene-1-ol (**24**)



4 **24**

The diol **4** (1.14 g, 3.6 mmole) was dissolved in 80 ml of dry THF under nitrogen atmosphere. Once it had completely dissolved , TMS-Cl (0.455 ml, 3.6 mmole) was added dropwise followed by hexamethyldisilazane (0.75 ml, 3.6 mmole). The reaction was stirred for fifteen hours at room temperature. The solvent was removed, the liquid obtained redissolved in 100 ml ethyl acetate, then the organic mixture was washed with saturated NH_4Cl solution (25 ml) followed by brine (25 ml). The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated at reduced vacuum to get a white crystalline product which was purified on a silica gel column utilizing toluene as eluent. Only mono siliated product was obtained.

Yield : 1.25 g (90%)

R_f : 0.64 (toluene)

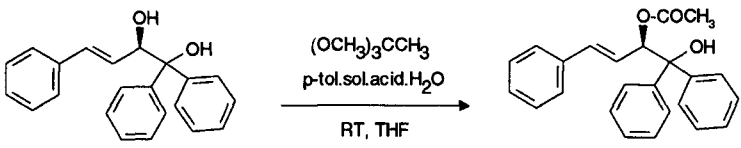
^{1}H-NMR (250 MHz, $CDCl_3$) :

7.70 - 7.10 (m, 15 arom. H), 6.50 (d, J = 17.0 Hz, 1H, H-C(4)), 6.20 (dxd, J = 6.8,17.0 Hz, 1H, H-C(3)), 5.15 (d, J = 6.8 Hz, 1H, H-C(2)), 3.45 (s, exchange with D_2O, OH), 0.10 (s, 9H,TMS).

^{13}C-NMR (62 MHz, $CDCl_3$) :

145.6,143.3,136.4 (C(1'),C(1"),C(1'")), 132.5 (C(4)), 128.1, 127.6, 127.5, 127.2, 126.4, 126.3, 126.1, 126.0 (aromatic), 92.1 (C(3)), 79.8 (C(1)), 78.7 (C(2)), 30.0, 0.5

2*(R)*-acetyloxy-1,1,4-triphenyl-but-3-ene-1-ol (**25**)



4 **25**

The diol **4** (2.0 g, 6.32 mmole), orthoacetic acid trimethylester (5.0 ml, 6.0 equivalent) and a catalytic amount of p-toluene sulfonic acid.H_2O were dissolved in THF in a 50 ml flask and stirred at room temperature overnight.

The solvent was removed and the product obtained was dissolved in 100 ml of ethyl acetate. The organic phase was washed with water (50 ml) followed by brine (25 ml) and dried over anhydrous Na_2SO_4. A yellowish white solid was obtained on concentration. The product was washed with hot *n*-hexane to efford a white crystalline powder.

Yield : 1.35 g (60%)

R_f : 0.22 (toluene, blue to CPS)

M.p. : 181 - 182° C

$[\alpha]_D^{20}$: + 137° (c = 0.649, $CHCl_3$)

IR (KBr) :

3533m, 1715s, 1449w, 1246s, 1155m, 972s, 753m, 694s.

^{1}H-NMR (250 MHz , $CDCl_3$) :

7.45 - 7.00 (m, 15 arom. H), 6.45 (d, J = 17.0 Hz, 1H, H-C(4)), 6.30 (d, J = 6.8 Hz, 1H, H-C(2)), 6.05 (dxd, J = 6.8,17.0 Hz, 1H,H-C(3)), 2.75 (s, exchange with D_2O, OH);

1.85 (s, 3H,CH_3)

^{13}C-NMR (62 MHz, $CDCl_3$) :

169.8 (acetyl C=O), 144.6, 142.9, 136.2 (C(1'),C(1"),C(1'")), 135.4 (C(4)), 128.4, 128.3, 128.2, 128.0, 127.3, 127.2, 126.6, 126.0, 125.9 (aromatic), 123.1 (C(3)), 79.8 (C(1), 62.7n (C(2)), 21.0 ($CO(\underline{C}H_3)$).

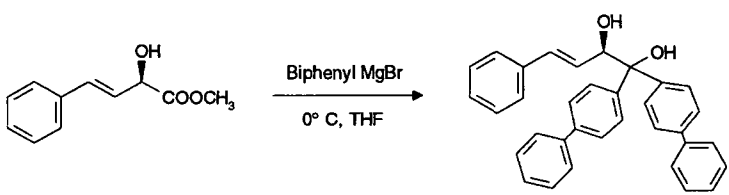
FD MS :

358 (M^+, 32), 299 (16), 298 (38), 184 (8), 183 (100), 175 (8), 168 (5)

When the diol was refluxed for three hours with an excess of acetyl chloride in dichloroethane in the presence of cat. dimethyl amino pyridine the same mono acetylated alcohol as above was obtained.

Biphenyl route :

1,1-bis-biphenyl-4-phenyl-but-3-ene-1,2*(R)*-diol (**26**)



2 **26**

A 500 ml four necked reactor fitted with a dropping funnel, a thermometer, magnetic stirrer and nitrogen inlet/outlet was flame dried under nitrogen atmosphere. The Grignard reagent biphenyl MgBr was prepared in this reactor (Mg turnings 2.25 g, 93.0 mmole and 4-bromobiphenyl 19.0 g, 81.5 mmole in 140 ml dry THF). The α-hydroxy methyl ester **2** was dissolved in 100 ml of dry THF and transferred to the dropping funnel. The reactor was cooled to -10° C, then the ester was added to the vigorously stirred reaction mixture dropwise over 30 minutes. After the addition was complete, the

temperature was slowly increased to room temperature and the mixture was stirred for another three hours.

The reaction mixture was then acidified with 2N HCl till pH 2 and extracted with ethyl acetate (3x400 ml). The organic layer was separated, washed with water until free from acid followed by 50 ml brine solution and finally dried over anhydrous Na_2SO_4. On evaporating the solvent crude product was obtained which was then recrystallized from an ethanol-H_2O mixture.

Yield : 3.4 g (32.0 %)

R_f : 0.5 (toluene : EtOAc [5:1], blue to CPS)

M.p. : 209 - 210° C

$[\alpha]_D^{20}$: + 129° (c = 1.0, $CHCl_3$)

IR (KBr) :

3420bs, 3055w, 1487m, 831m, 762m, 746s, 694s

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.70 - 7.15 (m, 23 arom. H), 6.65 (d, J = 17.2 Hz, 1H), 6.20 (dxd, J = 6.8,17.2 Hz, 1H), 5.25 (d, J = 7.0 Hz, 1H), 3.10 (s, exchange with D_2O, -OH), 2.10 (s, exchange with D_2O, -OH)

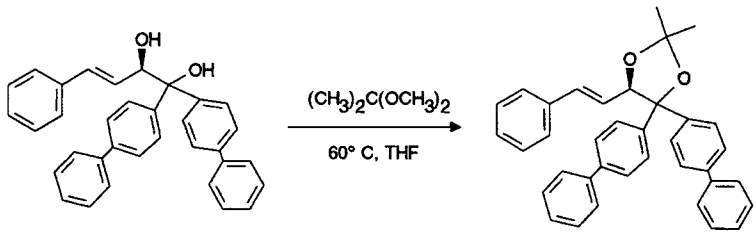
^{13}C-NMR (62 MHz, $CDCl_3$) :

143.6,142.6,140.5,140.2,139.9(C(1'),C(1"),C(1'"),C(11'),C(12'),C(11"),C(12"));136.4(C(4)); 133.7 (C(3)); 128.8, 128.7, 128.5, 127.8, 127.4, 127.3, 127.1, 127.0, 126.9, 126.7., 126.6, 126.4 (aromatic); 79.9 (C(1)); 76.7(C(2)).

MS :

491.2 (MNa^+, 100)

2,2-Dimethyl-4,4-dibiphenyl-5*(R)*-styryl-[1,3]dioxolane (**27**)



26 **27**

The diol **26** (2.1 g, 4.68 mmole) and 2,2-dimethoxy propane (8 ml, in excess) were mixed in a 100 ml round bottom flask and dissolved in 50 ml of dry THF. A catalytic amount of p-toluene sulfonic acid. H_2O was added to it and the mixture was heated with stirring at 60° C for 8 hr. The solvent was completely evaporated at reduced pressure. The solid obtained was again dissolved in 150 ml ethyl acetate and washed once with 30 ml water followed by 30 ml brine solution. It was separated and dried over anhydrous Na_2SO_4. On concentration at reduced pressure a thick yellow viscous substance was obtained. It was purified by flash chromatography on silica gel using toluene as eluent to get a colorless solid.

Yield : 2.0 g (88%)

R_f : 0.65 (toluene, blue to CPS)

M.p. : 64 - 65° C

$[\alpha]_D^{20}$: + 143° (c = 1.0, $CHCl_3$)

IR (KBr) :

3028w, 2986w, 1486m, 1380w, 1210m, 1168m, 1039m, 1007m, 967w, 835w, 766w, 750s, 695s

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.70 - 7.15 (m, 23 arom. H), 6.85 (d, J = 14.0 Hz, 1H), 5.85 (dxd, J = 10.0,14.0 Hz, 1H), 5.35 (d, J = 10.0Hz, 1H), 1.85 (s, 3H), 1.45 (s, 3H)

^{13}C-NMR (62 MHz, $CDCl_3$) :

144.5,141.8,140.7,140.6,140.0,139.8(C(1'),C(1"),C(1"'),C(11'),C(12'),C(11"),C(12"));136.3(C(4)); 134.7(C(3)); 129.0, 128.8, 128.7, 128.5, 128.1, 127.9, 127.3, 127.2, 127.0, 126.9, 126.8, 126.6, 126.4, 126.0 (aromatic); 109.3 (C(5)); 87.5 (C(1)); 86.1(C(2)); 27.1, 25.8 (2 x -CH_3).

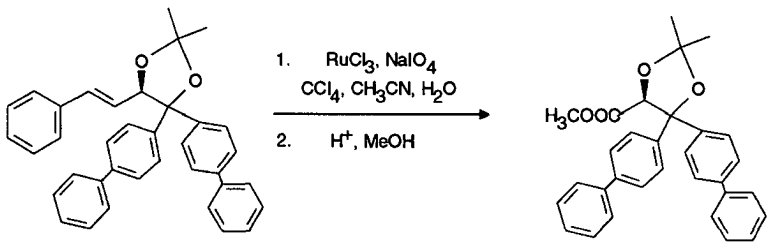
FD-MS :

508 (M^+,100), 335 (19), 334 (22),

Elemental analysis : $C_{37}H_{32}O_2$

Calculated	C: 87.37	H: 6.34	O: 6.29
Found	C: 87.55	H: 6.38	O: 6.44

2,2-Dimethyl-5,5-dibiphenyl-[1,3]-dioxolane-4*(S)*-carboxylic acid methyl ester (**28**)



27 **28**

The acetonide **27** (2.0 g, 3.93 mmole) was dissolved in a solvent mixture (CCl_4 [30 ml] + CH_3CN [30 ml] + H_2O [44 ml]) in a 500 ml three necked flask fitted with a thermometer and magnetic stirrer. To this heterogeneous system $NaHCO_3$ (3.3 g, 39.3 mmole) was added in one portion followed by the portionwise addition of $NaIO_4$ (7.56 g, 35.37 mmole) over 60 minutes. Then $RuCl_3.H_2O$ (0.26 g, 1.29 mmole) was added in one portion with vigorous stirring. The reaction was stirred at 45° C for 8 hr. over which time the black color changed to gray. The mixture was cooled to room temperature, stirring for another 15 minutes, then the suspension was filtered. The filtrate was extracted with ethyl acetate (3 x 50 ml). The aqueous layer was separated and acidified with 1N HCl until pH 2 and extracted with ethyl acetate (3 x 200 ml). The organic layer was separated, washed with water until acid free (2 x 50 ml) and then once with 50 ml brine solution. It was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. A white solid consisting of a mixture of the desired product and benzoic acid was obtained (1.5 g).

When this mixture was reacted with 1N HCl in MeOH, the methyl ester of both acids were obtained. Methyl benzoate was removed at a reduced pressure. The residue was further purified by flash chromatography on silica gel using toluene as eluent, providing the pure product as a colorless oil.

Yield : 0.5 g (30%)

R_f : 0.61 (toluene : EtOAc [6:1], blue to CPS)

$[\alpha]_D^{20}$: + 150.9° (c = 1.0, $CHCl_3$)

IR (KBr) :

3029w, 2989w, 2947w, 1762s, 1733m, 1435w, 1381m, 1299m, 1263m, 1210s, 1173s, 1104s, 1036m, 1007m, 836m, 767s, 750m, 731m, 696s.

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.80 - 7.25 (m, 18 arom. H), 5.40 (s, 1H), 3.30 (s, ester 3H), 1.85 (s, acetonid 3H), 1.25 (s, acetonid 3H).

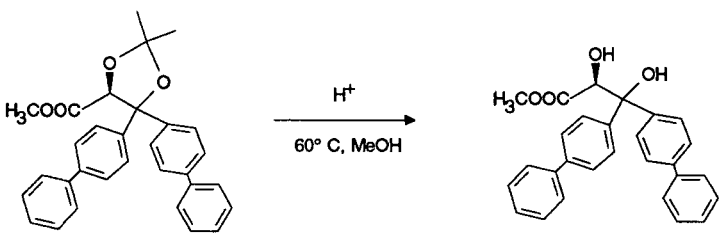
^{13}C-NMR (62 MHz, $CDCl_3$) :

169.0(esterC=O);149.3,146.7,142.7,140.7,140.6,140.3,(C(1'),C(1"), C(11'),C(11"), C(12'),C(12"));
129.7,129.6,129.4,128.8,128.7,127.5,127.4,127.3,127.2,127.1, 127.0, 126.9, 126.3 (aromatic); 111.8 (C(4)); 88.5 (C(3)); 83.9 (C(2)); 51.9 (ester OCH_3); 26.8, 25.8 (2 x CH_3).

FD MS :

464 (M^+, 100).

3,3-dibiphenyl-2*(S)*,3-dihydroxy-propionic acid methyl ester (**29**) :



28 **29**

The acetonide ester **28** (3.7 g, 8.0 mmole) was dissolved in 70 ml MeOH contalning 1N HCl and heated at 60° C with stirring for 1 hr. The solvent was removed and the solid obtained was chromatographed on silica gel using toluene : ethyl acetate (6:1) mixture as eluent. The desired diol ester **29** was obtained as a white solid. The recovered starting material was treated again with MeOH containing 1N HCl. This recycling and chromatography sequence was carried out for five times in succession to obtain diol ester **29**.

Yield : 0.8 g (23% after five cycles)

R_f : 0.27 (toluene : EtOAc [6:1], blue to CPS)

M.p. : 161 - 162° C

$[\alpha]_D^{20}$: + 92.5° (c = 0.18, $CHCl_3$)

IR (KBr) :

3526m, 3420m, 1720s, 1486m, 1105w, 768m, 738m, 696m

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.60 - 7.25 (m,18 arom.H), 5.05 (d, J = 6.9 Hz; 1H), 3.85 (s, exchange with D_2O, ter.-OH), 3.45 (s, ester 3H), 3.45 (d, J = 6.9 Hz, exchange with D_2O, sec.-OH)

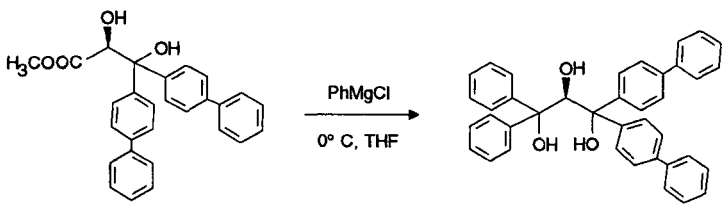
^{13}C-NMR (62 MHz, $CDCl_3$) :

173.4(esterC=O);142.2,141.9,140.5,140.4,140.3 (C(1'),C(1"),C(11'), C(11"),C(12'),C(12")); 129.4, 128.8, 127.4, 127.1, 127.0, 126.9, 126.8, 126.4 (aromatic); 79.5 (C(3)); 75.5 (C(2); 52.6 (ester -OCH_3).

FAB - MS :

447 (MNa^+, 20), 407(95), 347(45), 335(88), 319(30), 181(100),

1,1-Dibiphenyl-3,3-diphenyl-1,2*(R)*,3-propane triol (**30**) :



29 **30**

In a 250 ml previously dried three necked flask fitted with thermometer, dropping funnel, argon inlet / outlet and a magnetic stirring bar, methyl ester diol **29** (0.424 g, 1.0 mmole) was added and dissolved in 20 ml of dry THF. The Grignard reagent PhMgCl (2.5 ml, 4.5 mmole as a 2.0 M solution in THF) was transferred to the dropping funnel.

The assembly was cooled to - 5 to 0° C with a cooling system and the Grignard reagent added dropwise with stirring. The addition was completed in 10 min. After maintaining the temperature at 0° C for another 10 min., the cooling bath was removed and the reaction mixture stirred at room temperature for 3 hr.

Then 5 ml of H_2O was added without observing a rise in temperature. The reaction was extracted with ethyl acetate (2× 100 ml). The organic layer was washed with 50 ml water followed by 50 ml brine solution end was dried over anhydrous Na_2SO_4 and the solvent was removed et reduced pressure. The solid obtained was purified over a silica gel column eluting with a mixture of toluene : ethyl acetate (6:1).

Yield : 0.07 g (15%)

R_f : 0.54 (toluene : EtOAc [6:1], blue to CPS)

$[\alpha]_D^{20}$: + 9.5° (c = 0.084, $CHCl_3$)

IR (KBr) :

3422s, 1486w, 763w, 746w, 697s

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.65 - 6.65 (m, 28 arom. H), 5.75 (d, J = 2.0 Hz, 1H, H-C(2)), 4.85 (s, exchange with D_2O, two -OH), 2.75 (d, J = 2.0 Hz, exchange with D_2O, sec-OH)

FAB - MS :

583 (M+Cl^-) (M^+ = 548.7)

High resolution MS :

M+Li^+ = 555

Molecular formula found by High resolution MS is $C_{39}H_{32}O_3$

Method : FABPKMTCH

Instrument : VG 70-SE (Fisons Instruments, Manchester)

Optical purity :

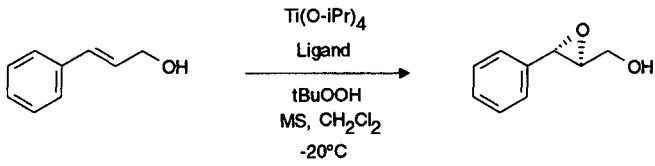
98% ee by HPLC analysis

HPLC analysis parameters :

R_t	24.33 min.
HPLC column	Chiralpak AD (25× 0.46 cm)

Mobile phase	Hexane : Isopropanol 8:2
Flow rate	1 ml / min.
Detection	UV 220 nm

Sharpless Epoxidation : Typical procedure.



To a flame dried 250 ml three-necked flask equipped with magnetic stirrer, thermometer and dropping funnel, flushed with nitrogen and charged with the ligand diol ester [6, 9, 10] (0.558 mmole) and 50 ml of freshly dried CH_2Cl_2 was added. After the ligand had dissolved the mixture was cooled to -20°C. Then 0.55 g of activated, powdered 3Å molecular sieves, 0.136 ml (0.131 g, 0.465 mmole) of Ti(O-i-Pr)$_4$, and 3.11 ml of a 3M solution of TBHP in isooctane (9.33 mmole) were added sequentially through a syringe. The mixture was stirred at - 20°C for 1 hr and then treated with a solution of 0.625 g (4.65 mmole) of freshly distilled (E)-3-phenyl-2-propenol in 1.7 ml CH_2Cl_2, added dropwise over 25 minutes. After 3 hr at - 20°C the reaction was quenched as follows : 0.4 ml of 10% NaOH solution saturated with NaCl was added followed by 10 ml ether. Then the cooling bath was removed. After warming slowly to 10°C, 0.55 g of $MgSO_4$ and 0.250 g of celite were added. The reaction was stirred at this temperature for 15 min., the solid was allowed to settle down and then filtered over celite. Azeotropic removal of the TBHP with toluene at reduced pressure gave the crude product. Flash chromatography on a silica gel column utilizing toluene : ethyl acetate mixture (2:1) as eluent gave the white crystalline epoxide in 40% yield. About 50% of the starting material was recovered.

Yield : 0.28 g (40%)

R_f : 0.32 (toluene : EtOAc [2:1], blue to CPS)

M.p. : 50 - 51° C

$[a]_D^{20}$: + 32.5° (c = 0.6, EtOH)

^{1}H-NMR (500 MHz, $CDCl_3$) :

7.40 - 7.20 (m, 5 arom H); 4.05 (dxdxd , J = 2.0,5.0,13.0 Hz, 1H); 3.93 (d, J = 4.0 Hz,1H, $H_AC(1)$); 3.81 (dxdxd, J =4.0,7.6,13.0 Hz, 1H, $H_BC(1)$); 3.23 (txd, J = 2.0,4.0, 1H, HC(2)); 1.85 (dxd, exchange with D_2O, 1-OH)

Optical purity :

(Enantiomeric excess in %ee) was determined by two independent methods.

a) HPLC

b) Using NMR shift reagent TAE.

HPLC anelysis parameters :

Rt	24.23 min.(2R,3R), (21.52 min. (2S,3R))
HPLC Column	Chiralpak AD (25 x 0.46 cm)
Mobile phase	Hexane : Ethanol (95:5)
Flow rate	1.0 ml / min
Detection	UV 210 nm
Pressure	30 bar

NMR shift experiments :

NMR shift experiments were carried out on a Varian 500 MHz instrument in $CDCl_3$ as the solvent. The signals were shifted by adding 30 mg of TAE [1-(9-anthryl)-2,2,2-trifluoro-ethanol] to the original sample.

The ee% was determined by comparing the signals of the proton HC(1) on the epoxide ring. First spectrum was obtained by running the spectrum without shift reagent and for the second spectrum the shift reagent was added. Under the influence of the shift reagent the protons HC(1) and HC(2) were separated for the two enantiomers. For HC(1) the signals for the (2*R*,3*R*) enantiomer was shifted to lower field whereas for HC(2) the signals of the (2*R*,3*R*) enantiomer were shifted to higher field.

Glyoxylate - ene reaction :

2*(S)*-hydroxy-4-phenyl-4-pentenoic acid methyl ester :

$$Ti\,(O\text{-}iPr)_4 + Ti\,Cl_4 \xrightarrow[RT]{Hexane} 2\ Cl_2\,Ti\,(O\text{-}iPr)_2$$

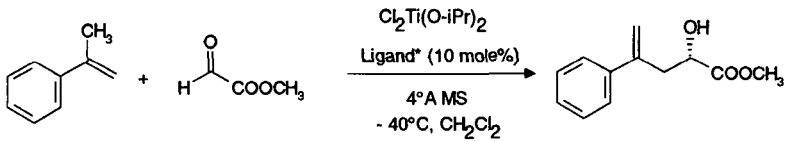
A. Preparation of dilsopropoxytitanium (IV) dichloride :

A 50 ml two-necked, round-bottomed flask predried under argon atmosphere equipped with a magnetic stirring bar and a rubber septum was charged with 5 ml of dry hexane and titanium (IV) isopropoxide (2.98 ml, 10 mmole) at ambient temperature and stirred for 5 minutes. To this

suspension titanium (IV) chloride (1.1 ml, 10 mmole) was slowly added. An exothermic reaction was observed and the reaction mixture warmed to 37° C. After stirring for about 10-15 minutes, a white precipitate precipitated. The stirring was stopped and the precipitate was allowed to settle and then the solvent was removed with a syringe. The precipitate was washed with 5 ml dry hexane and recrystallized in 3 ml of hexane in the same flask by heating at 40° C. The flask was left at room temperature overnight. Again the supernatant liquid was removed by syringe and the crystalline white residue was dried at reduced pressure to give a highly moisture sensitive product.

Yield : 1.1 g (46%)

Typical procedure.



(Ligand* : see chapter 4.3.2)

A 50 ml three-necked flask was dried with a hot air blower under argon atmosphere. This flask was equipped with a magnetic stirring bar, dropping funnel, a thermometer, and an argon inlet. The flask was charged with 10 ml of freshly dried CH_2Cl_2. An appropriate amount of ligand (10 mole%) was added to the CH_2Cl_2 and the resulting mixture was stirred at room temperature till completely dissolved (about 10 min). Freshly dried powdered molecular sieves 4Å (1.1 g) were added. $(i\text{-}PrO)_2TiCl_2$ (0.206 g, 0.87 mmole) crystals were added to the suspension. A bloodred colored solution was obtained. The suspension was stirred at room temperature for one hour and then cooled to -40° C. To the reaction mixture was added dropwise a mixture of α-methyl styrene (1.59 g, 13.5 mmole) and 2 ml CH_2Cl_2 followed by a solution of freshly distilled methyl glyoxylate (0.77 g, 8.75 mmole) in 2 ml CH_2Cl_2. The glyoxylate addition was completed in 20 minutes. The reaction was stirred at this temperature for 8 hours and left overnight. Then 10 ml of saturated $NaHCO_3$ solution was added to the reaction and the mixture was stirred for 10 minutes. The molecular sieves were filtered over celite and the solution was extracted with 200 ml of ethyl acetate washed with water dried over anhydrous Na_2SO_4. The organic mixture was concentrated at reduced pressure to afford the crude product.

The crude product was flash chromatographed over silica gel using a toluene : ethyl acetate mixture (2:1) as eluent.

Yield : 0.33 g (19 %)

R_f : 0.48 (toluene : EtOAc [2:1])

^{1}H-NMR (250 MHz, $CDCl_3$) :

7.45 - 7.25 (m, 5 arom H), 5.40 (d, J = 4.0 Hz,1 alkene H), 5.20 (d, J = 4.0 Hz, 1 alkene H), 4.30 (m, 1H), 3.60 (s, 3H, -$COOCH_3$), 3.10 (dxd, J = 4.0, 6.0 Hz, 1H); 2.85 (dxd, J = 6.0, 8.0 Hz, 1H); 2.65 (bs, exchange with D_2O, -OH).

HPLC analysis perameters :

Rt	8.7 mln. (2R), 9.7 min. (2S)
HPLC column	Chiralcel AD (P.H.Stehelin & Cie AG Basel, 25 × 0.4 cm)
Mobile phase	Hexane : Isopropanol 85:15 and 0.1 ml trifluoro acetic acid
Flow rate	0.8 ml / min.
Detection	UV 210 nm
Pressure	22 bar

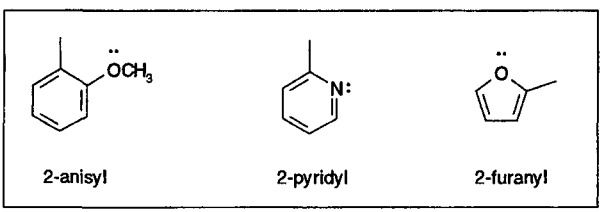
6.0 FUTURE WORK

Our first goal to synthesize tetra aryl gylcerol in both enantiomers was achieved successfully. The application of these glycerols as a ligand in catalytic enantioselective reactions was not achieved because till now it has not been possible to obtain the tetra aryl gylcerols in larger amounts.

We observed that with protected diol ester, the yield of second Grignard reaction is more than 90%. If we can find a suitable protecting group which is stable during the Grignard reaction and can be easily removed after that, then it may be possible to obtain glycerols in larger amounts which will make it possible to test them as a catalyst e.g. try some protecting groups at the diol ester stage.

The idea behind is we can use the glycerols as a ligand e.g.

- In enantioselective addition of CN to aldehydes with trimethyl silyl cyanide as cyanide reagent.
- Prepare different tetra aryl glycerols contalning hetero atoms in the aromatic ring e.g. 2-anisyl, 2-pyridinyl, 2-furanyl which can further stabilize the central metal ion because of the additional electron pair.



2-anisyl 2-pyridyl 2-furanyl

Otherwise one can selectively protect the secondary OH with a suitable protecting group and use this protected glycerol as

- An analog of TADDOL and can try the reactions which are carried out successfully using the TADDOL as a ligand. e.g. enantioselective alkyl addition to aldehydes with the help of diethyl zinc or enantioselective Diels-Alder reaction.

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