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ABSTRACT

The objectives of this thesis were to conduct model work on two systems in anticipation of using them on the pathway chosen to synthesize the side-chain of paclitaxel. The model systems chosen were benzoyl-1,3-dithiane, [1-phenyl-2-(1,3-dithiacyclohexyl)ethanone] and hydrocinnamoyl-1,3-dithiane, [4-phenyl-1-(1,3-dithiacyclohexyl)butan-2-one]. This work consisted of screening several acyl equivalents to determine which one could best be used for a one carbon homologation. Enantioselective reduction of the carbonyl group, using three different chiral reducing agents, was also studied. Studies were also conducted to determine the most efficient manner in which to unmask the carbonyl group and convert it to the more stable methyl ester.

Several acyl equivalents, tris(methylthio)methane, tris(phenylthio)methane and 1,3-dithiane, were tested and 1,3-dithiane was determined to be the most advantageous as determined by the efficiency of creating the anion and the stability of the final products **91** and **98**.

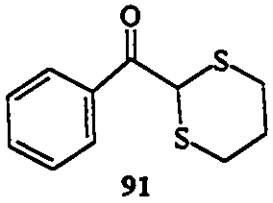
Enantioselective reduction of benzoyl-1,3-dithiane **91** and hydrocinnamoyl-1,3-dithiane **98** using Corey's (s)-oxazaborolidine reagent **105** produced different results for each compound. This reducing agent **105** produced the highest enantiomeric excess (87%) of those studied on benzoyl-1,3-dithiane **91**. Reduction of hydrocinnamoyl derivative **98** resulted only 45% enantiomeric excess however the yield was much higher at 85%.

Results from asymmetric reduction of the benzoyl-1,3-dithiane **91** and the hydrocinnamoyl-1,3-dithiane **98** using the modified Corey's (s)-oxazaborolidine reagent **108** indicated lower selectivity for this reagent. The benzoyl-1,3-dithiane **91** had an enantiomeric excess of only 44% while the higher homologue **98** had a much lower enantiomeric excess (3%).

The use of (-)-diisopinocampheylchloroborane (Dip-Cl) as the enantioselective reducing

agent produced much improved selectivity for both systems. Reduction of the benzoyl derivative **91** afforded alcohol **92** with an enantiomeric excess of 55% while the reduction of the hydrocinnamoyl derivative **98** afforded the alcohol **99** with an enantiomeric excess of 87% and in 90% yield.

The final target methyl ester **103** in the hydrocinnamoyl model system was prepared by two separate routes. Dithiane **93** and **100** were oxidatively hydrolyzed to afford the aldehydes **94** and **101** on treatment with mercuric(II) chloride and cadmium carbonate. The methyl ester **103** was then prepared by oxidation and concomitant esterification of the aldehyde **101** on treatment with bromine/sodium bicarbonate/methanol. The second route consisted of oxidation of the unmasked aldehyde **101** to the corresponding carboxylic acid **102** on treatment with silver (I) oxide and then esterification on treatment with diazomethane to afford the methyl ester **103**. Authentic sanples of both methyl esters **96** and **103** were also synthesized.



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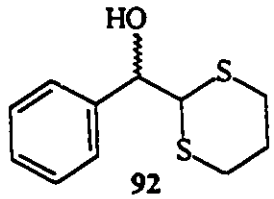

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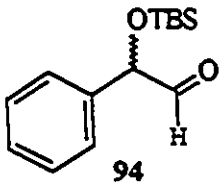

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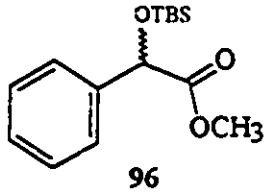

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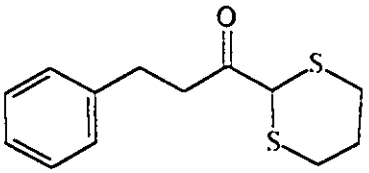

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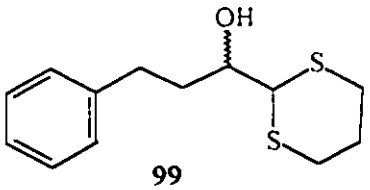

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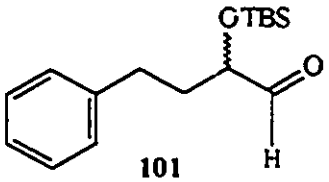

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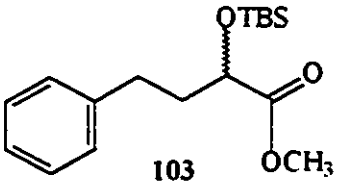

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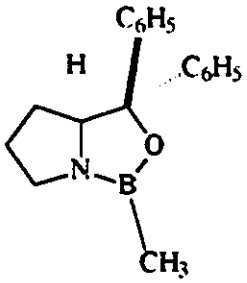
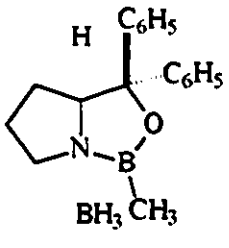
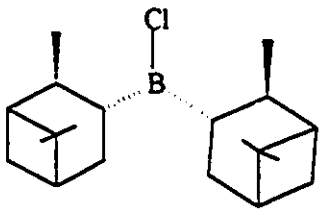


(S)-oxazaborolidine



Modified (S)-oxazaborolidine



(-)-Dip Cl

To my wife, Mary and children, Grace, Claire and Mark for their patience and everlasting love.

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Ac	acetyl
BMS	borane-dimethyl sulfide complex
Boc	*t*-butyl carbamate
n-BuLi	*n*-Butyllithium
c	concentration ($gmol^{-1}$)
cat.	catalytic
CAN	ammonium cerium (IV) nitrate
m-CPBA	*m*-chloroperoxybenzoic acid
DCC	*N,N*-dicyclohexylcarbodiimide
DDQ	dichlorodicyanobenzoquinone
DEAD	diethyl azodicarboxylate
L-(+)-DET	diethyl L-tartrate
DIBAH	diisobutylaluminium hydride
Dip-Cl	diisopinocampheylchloroborane
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DQCB	dihydroquinidine 4-chlorobenzoate
ee	enantiomeric excess
eq.	equivalent(s)
ether	diethyl ether
Et_3N	triethylamine
EtOAC	ethyl acetate

g	gram(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Im	imidazole
IR	infra red
J	coupling constant (given in Hertz)
M	molar
M^+	molecular ion
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megaHertz
mmol	millimole(s)
mp	melting point
MTPA	Mosher's acid
MS (CI)	mass spectrum by chemical ionization
MS (EI)	mass spectrum by electron impact
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMMO	*N*-methyl-morpholine *N*-oxide
NMR	nuclear magnetic resonance
obs.	observed
PDC	pyridinium dichromate

Ph	phenyl
PPh_3	triphenylphosphine
4-PPNO	4-phenyl-pyridine N-oxide
PPTS	pyridinium *p*-toluenesulfonate
ppm	parts per million
py	pyridine
rt	room temperature
TBAF	*t*-butyl ammonium fluoride
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	*t*-butyldiphenylsilyl
TsOH	toluenesulfonic acid

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Firstly, I would like to thank Dr. Hallis for all his support, guidance and encouragement over the course of obtaining my Masters degree. His patience and understanding were greatly appreciated.

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I would like to say thanks to all the people I have crossed paths with over the course of my post-graduate studies at the University of Ottawa. Many thanks to Dr. Peter Wilson for his help in proof-reading this manuscript and the help he has given me. I would also like to thank Martin Dimitroff and Dr. Mike Tjepkema for their help over the course of my studies. Many thanks to Dr. Claudio Sturino for his friendship over the years. I would also like to thank Claudio and Kristian Gravelle for providing the working music in the lab. Thanks to Dr. Timothy Wong for his help analyzing NMR spectra and simplifying them for me. Thanks to Tham Pham, Irina Brinza, Bogdan Comanita, Curt Harwig and Jody Laver for their friendship and interesting discussions over the years. Thanks to Poonam Tauh for help and collaboration on my thesis. Thanks to Terry Connolly for letting me use some of his NMR time down the stretch and for bailing me out when the NMR would act up at 1:00am. Thanks

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I would like to thank all the other group members, both past and present, for helping to make my experience at University of Ottawa an enjoyable one.

1 INTRODUCTION

1.1 Overview

This thesis studied two models systems to test conditions and reagents in preparation for use in the synthesis of a taxoid side-chain. Three enantioselective reducing agents, containing boron, were used to determine their efficiency in asymmetric reduction of the carbonyl group. Several acyl equivalents were also tested for use in one carbon homologation of optically pure phenylglycine.

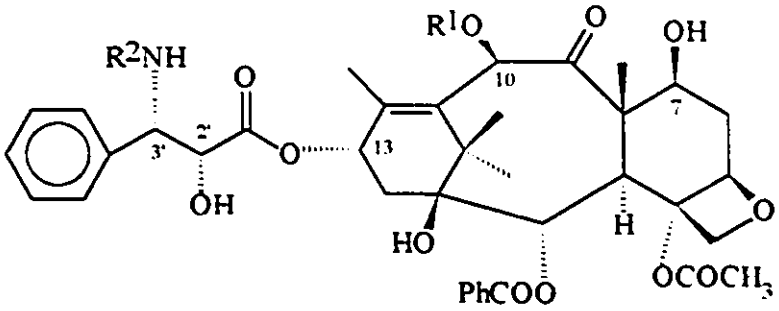
Research in the area of enantioselective reduction of prochiral ketones using boron as the hydride source has received a great deal attention as a result of the Food and Drug Administration requirements for enantiomerically pure compounds for drug submissions. The number of enantioselective boron derivatives containing chiral auxiliaries has increased over the last decade as indicated by the large number of publications recently.[1,2] These boron hydrides use chiral auxiliaries to control the facial selectivity and thereby enhance the enantioselectivity.

Enantiopure materials are useful building blocks for synthesis. Consequently, several groups have utilized phenylglycine as a starting material for the paclitaxel side-chain. An early approach in our laboratories was stopped with Greene's publication[3] as the routes were nearly identical. However, it was realized that the group required access to the side-chain in addition to the need for improved methods that could be readily scaled-up starting with a natural source.

1.2 Background

The taxanes (Figure 1.2.1), specifically paclitaxel **1** (Taxol®) and docetaxel **2** (Taxotere®) have been touted as "the most promising anticancer agents developed in the last decade".[4] The mode of action for these agents is unique as they promote tubuler polymerization then bind to the

microtubules which prevents disassembly and further cell division. Paclitaxel **1** was the first taxane to be approved for human use and has shown promising results in treatment of ovarian cancer, breast cancer and non-small-cell lung cancer. Docetaxel **2** has recently been approved (September 1995) for use in treatment of similar tumors.



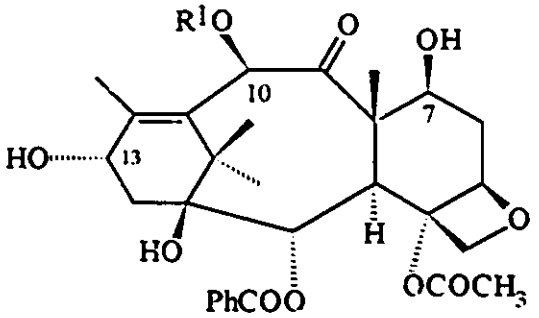
1. Paclitaxel $R^1 = Ac$ $R^2 = PhCO$

2. Docetaxel $R^1 = H$ $R^2 = t\text{-BuOCO}$

Figure 1.2.1. Structures of paclitaxel 1 and docetaxel 2

Paclitaxel **1** was first detected, in its crude form, in 1856 by Lucas[5] but it was not until 1971 that Wani and Wall[6] determined the structure of the compound. This material was isolated from the bark of the American yew, *Taxus brevifolia*. Initially in short supply, the supply problem has been over come due to the partial synthesis using baccatin III **3** (Figure 1.2.2) which is isolated from the needles. As the needles can be harvested annually this represents a renewable resource. Several groups around the world are attempting the total synthesis of paclitaxel **1** motivated by curiosity and the desire to synthesis more active and potent analogues. To date, three groups

(Holton[7a,b], Nicolaou[8] and Danishefsky[9]) have successfully completed total synthesis of paclitaxel **1**. However their synthetic routes, while elegant, are not economically viable due to low overall yields and the large number of synthetic steps required. Docetaxel **2** is more effective, less toxic and more water soluble than paclitaxel **1** . It can be readily prepared by a semi-synthetic route. This involves the conversion of 10-desacetylbaccatin III **4** (Figure 1.2.2), obtained from the needles of the European yew, *Taxus baccata*, to docetaxel **2**.



3.	Baccatin III	R^1 = Ac
4.	10-desacetylbaccatin III	R^1 = H

Figure 1.2.2. Structures of baccatin III 3 and 10-desacetylbaccatin III 4

Structure activity studies of **1** and **2** have shown that several of the functional groups are essential for biological activity. The oxetane ring plays an important role in binding to the tubulin and helping to maintain the conformation of the taxane skeleton which was demonstrated by Kingston.[10a] The side chain is essential for activity particularly the hydroxyl group attached to the 2′ position.[10b] To date, studies have shown that substituents attached to the hydroxyl groups at C7 and C10 can vary without drastic changes in activity. Biological testing of the C7 dehydroxy

derivative, prepared by Kingston *et al.*,[10c] established that this compound was 40 times more cytotoxic than paclitaxel **1**.

1.3 Previous synthesis of the Taxane Side-Chain

In view of the importance of the semi-synthetic routes to these drugs, several groups have developed routes to the taxane side-chains as outlined below.

1.3.1 Greene's Epoxidation Routes

The first synthesis of the paclitaxel side-chain was accomplished by Greene *et al.*[11a] using *cis*-cinnamyl alcohol as the starting material (Scheme 1.3.1.1). Sharpless asymmetric epoxidation produced (2*S*,3*R*)-epoxy-alcohol **5** in 61-65% yield and with 76-80% enantiomeric excess. The epoxide **5** was opened regioselectively when treated with azidotrimethylsilane and a catalytic amount of zinc chloride. The resultant alcohol **6** was then protected as the benzoyl derivative **7**. Hydrogenation of azide **7** was accompanied with an O → N benzoyl transfer which afforded the methyl ester form **8** of paclitaxel side-chain. One crystallization from chloroform produced optically pure amino alcohol **8** (≥ 95%) in 23% yield. The alcohol of amino alcohol **8** was then converted to the MOM derivative **9** which was suitable for attachment to paclitaxel. This strategy was later refined, by the same group,[11b] by employment of Sharpless dihydroxylation to prepare the diol **10** from methyl cinnamate (Scheme 1.3.1.2). The C2 alcohol of the diol **10** was selectively protected as the corresponding tosylate and the epoxide **5** was prepared on treatment with wet potassium carbonate. The resultant epoxide **5** was opened regioselectively on treatment with sodium azide in excellent yield (95%). Finally, treatment of alcohol **6** with benzoyl chloride and

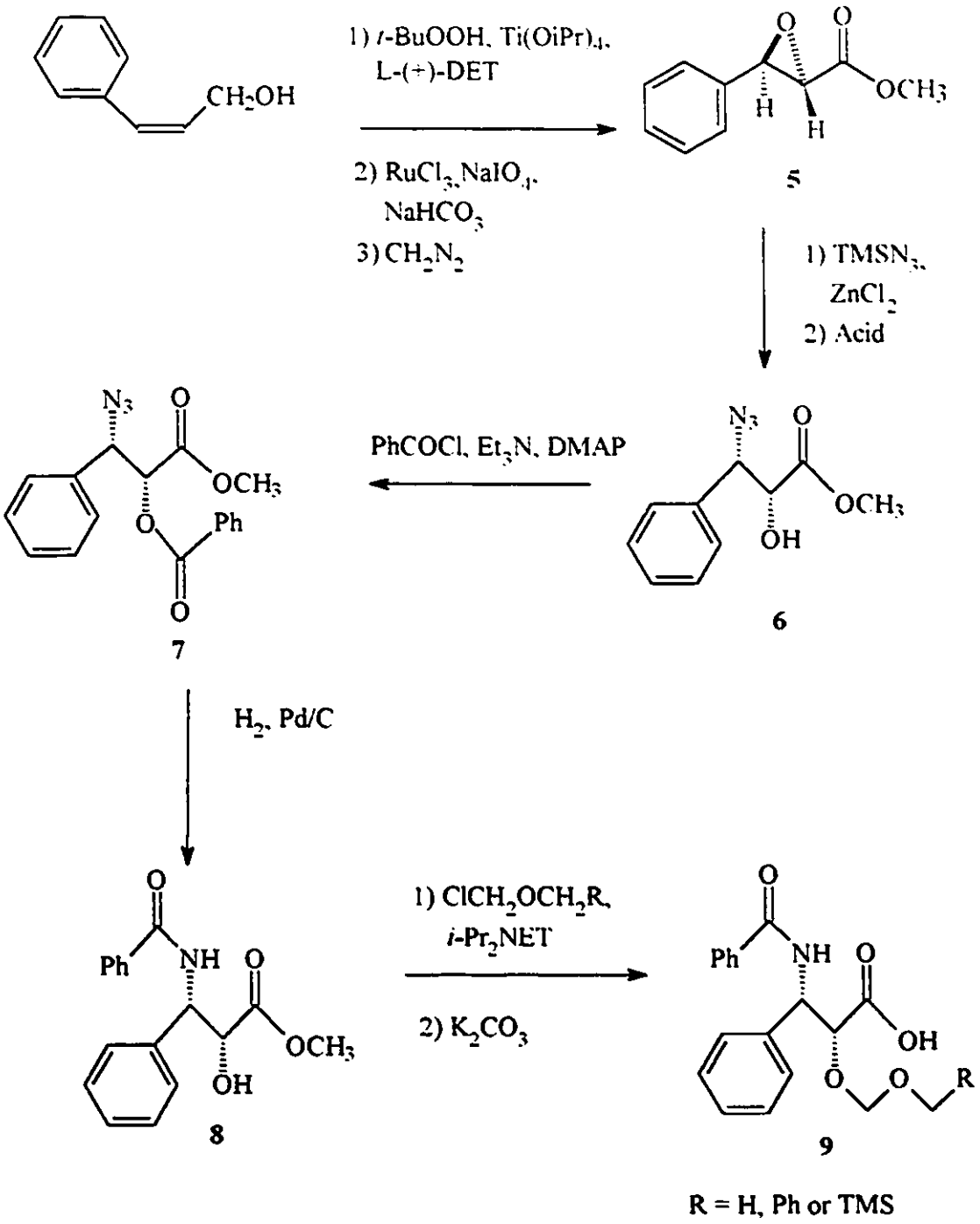
hydrogenation yielded the paclitaxel side-chain as the methyl ester **8**. This route has also been used to prepare the side-chain for docetaxel **2**.

1.3.2. Sharpless's Dihydroxylation Route

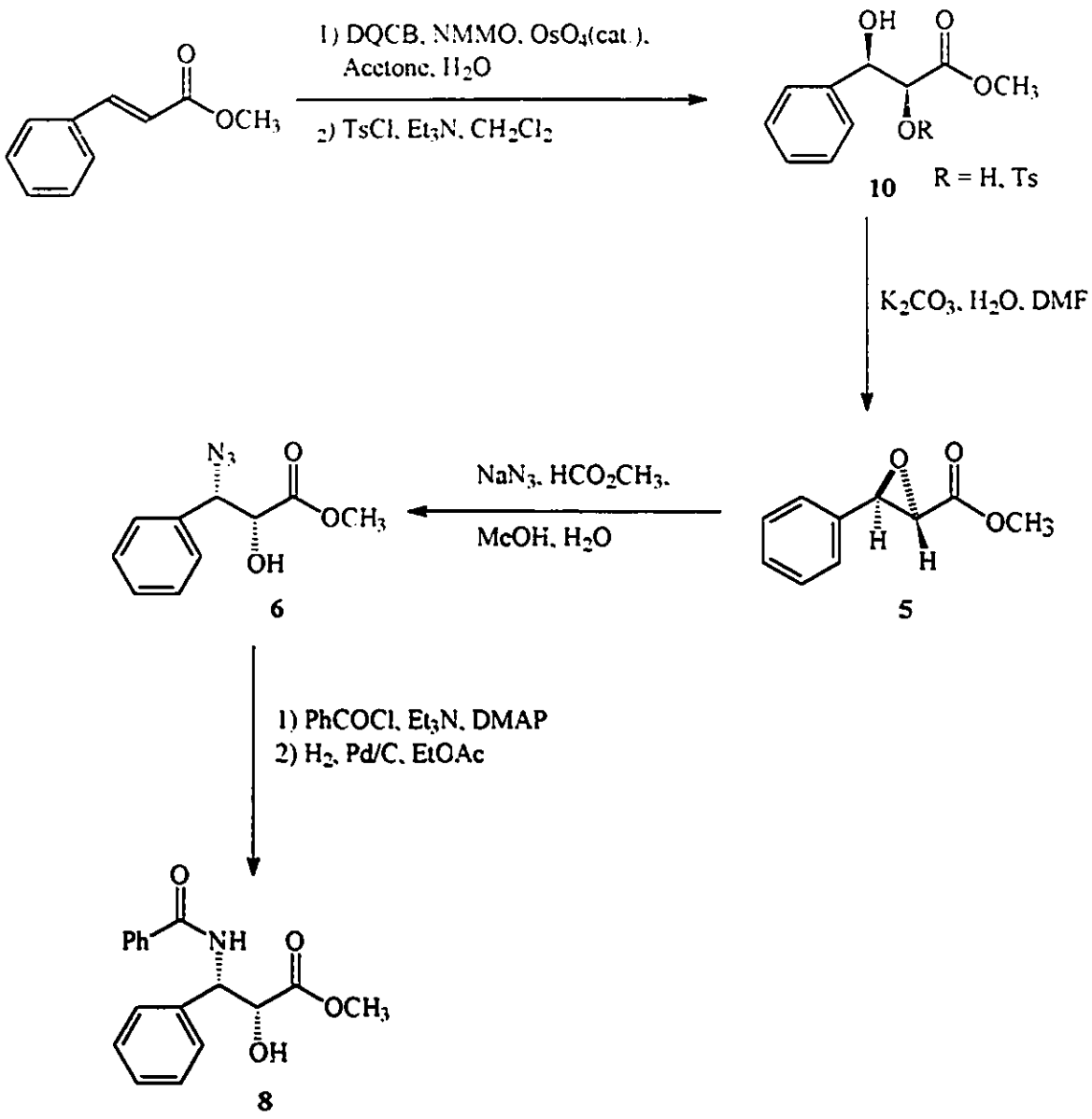
Sharpless and Kolbe[12] used the chiral catalyst $(DHQ)_2$-PHAL to perform the asymmetric dihydroxylation of methyl cinnamate to give diol **10** in 69-76% yield and with excellent enantiomeric excess (99%)(Scheme 1.3.2). The diol **10** was then converted to the side-chain methyl ester **8** in 4 additional steps via the azide route.

1.3.3. Deng and Jacobson's Epoxidation Route

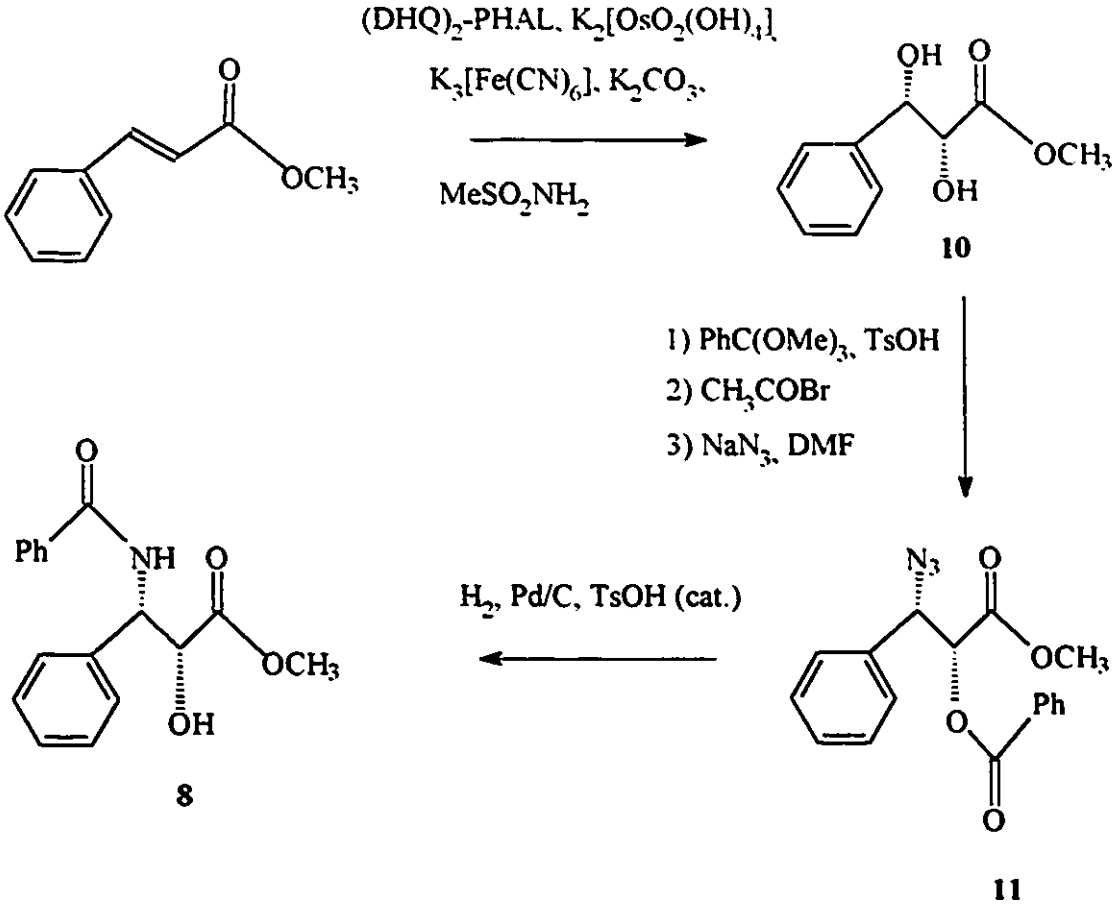
Deng and Jacobsen[13] used their manganese(III) chiral catalyst in a short route to the free acid form of the side-chain **14** (Scheme 1.3.3). Ethyl phenylpropiolate was hydrogenated with the aid of Lindlar catalyst. The(*R,R*)-epoxide **5** was synthesized, in excellent optical purity (97%), when the alkene was treated with commercial bleach and 4-PPNO(cat). The amide **12** was afforded on treatment of the epoxide **5** with ammonia in ethanol. Hydrolysis of the amide **12**, on treatment with barium hydroxide, produced the amino alcohol **13**. Protection of the amino alcohol **13**, on treatment with benzoyl chloride and base, afforded the acid-form of **14** which was isolated in excellent enantiomeric excess (> 97%). This strategy is similar to Greene's but is one step shorter due to the direct formation of amine **12**, which avoided the azide reduction step.



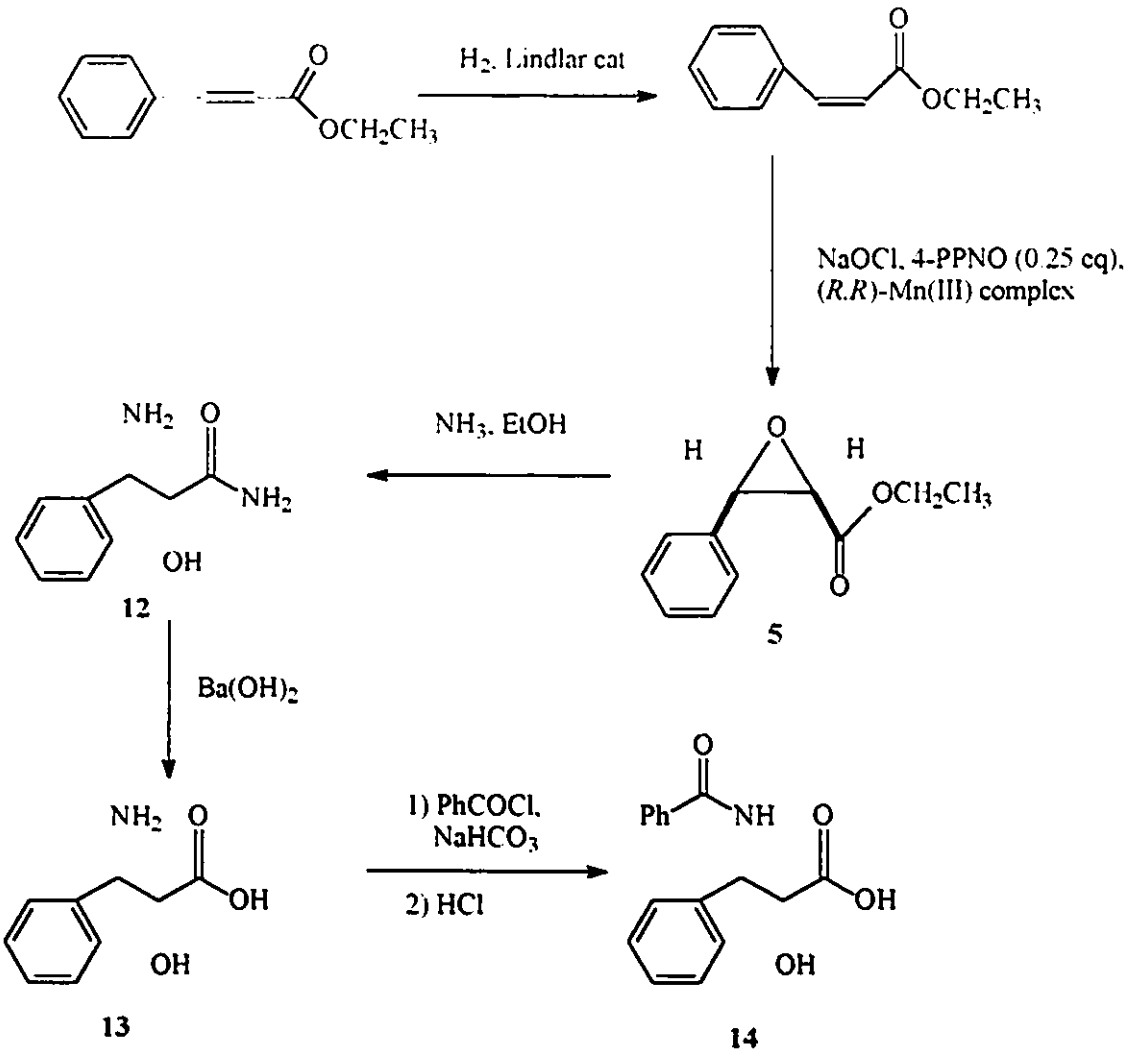
Scheme 1.3.1.1. Greene's epoxidation route



Scheme 1.3.1.2. Greene's asymmetric dihydroxylation route



Scheme 1.3.2. Sharpless's asymmetric dihydroxylation route



Scheme 1.3.3. Deng and Jacobsen's epoxidation route

1.3.4 Commercon's Oxazolidine Route

Greene *et al.*[14,15] discovered up to 15% epimerization at the C2 center when the open form of the side-chain and forcing conditions were used to attach the side-chain to a taxane. In an attempt to disfavor the potential hydrogen abstraction and resultant epimerizaion, the use of cyclic protection groups to lock in the steric configuration was investigated. Commercon *et al.*[16] synthesized the N,O-protected *β*-phenylisoserine **19** to test this theory (Scheme 1.3.4). The

bromoalcohol **16** was synthesized on condensation of the boron enolate of (4*S*,5*R*)-3-bromoacetyl-4-methyl-5-phenyl-2-oxazolidinone **15** with benzaldehyde. The bromoalcohol **16** was converted to the epoxide **5** on treatment with base. The epoxide **5** was opened regioselectively on treatment with sodium azide to afford the amino alcohol **17**. The amine group of the amino alcohol **17** was protected as the Boc derivative **18**. Protection of compound **18** with methoxypropene and PPTS and subsequent saponification afforded oxazolidine **19**. After esterification with the desired taxane, deprotection of the side-chain also removed the Boc group from the amine. N-acylation and O-deprotection afforded paclitaxel **1** and docetaxel **2** in good yields (59-62%) and high optical purity.

To eliminate the deprotection of the amine that occurred during the deprotection of the side-chain, Commercon *et al.*[17] substituted 4-methoxy-phenyl or 3,4-dimethoxy-phenyl substituents at the 2 position of the oxazolidine which are less stable oxazolidines. Oxazolidine **19** could then be opened on treatment with methanesulfonic acid or *p*-toluenesulfonic acid at room temperature with retention of the Boc group on the nitrogen.

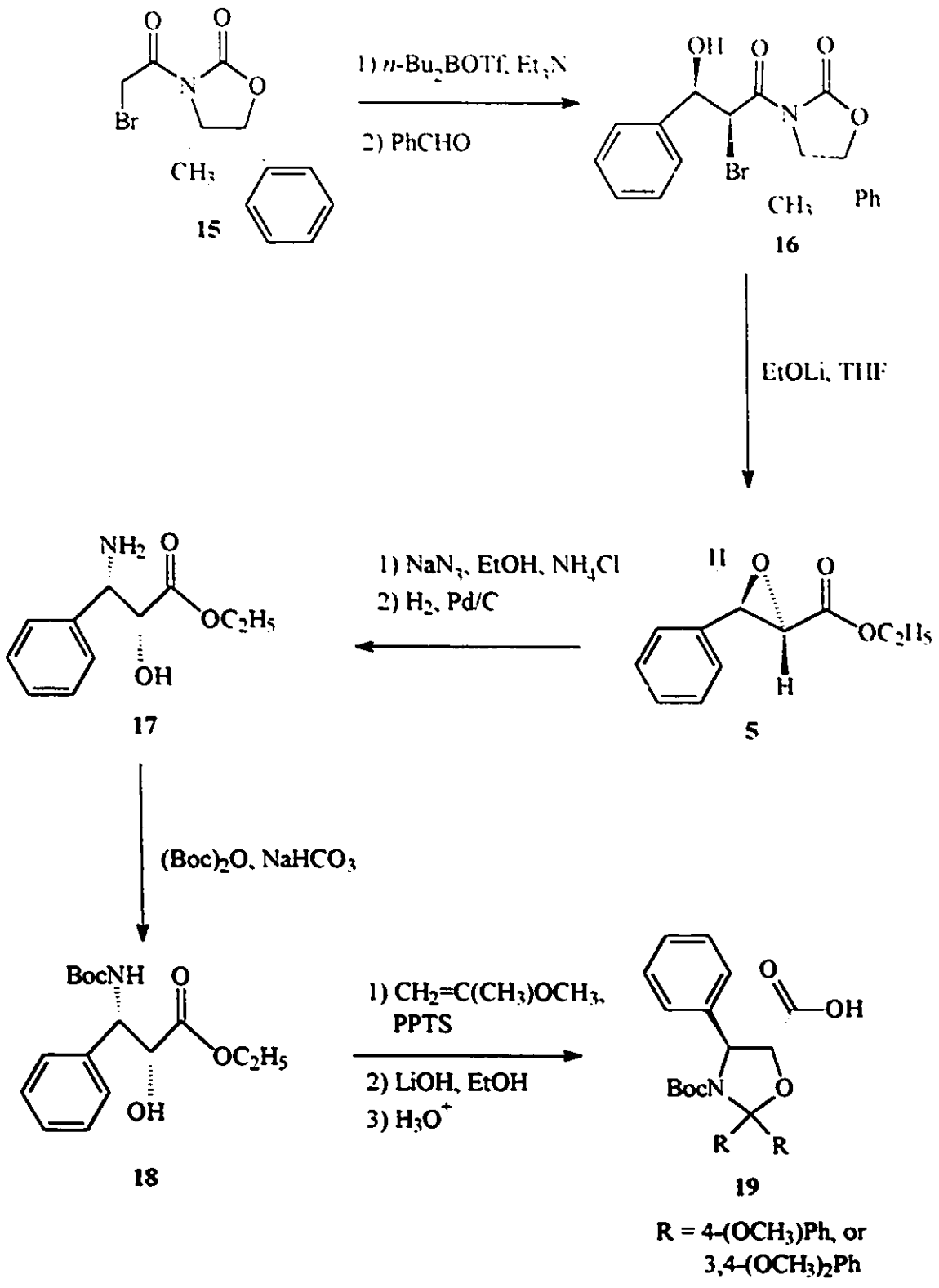
1.3.5 Greene's Route Using Camphorsultam as a Chiral Auxiliary

Greene *et al.*[14,15] used Oppolzer's L-(+)-camphorsultam as a chiral auxiliary to further expand the strategy of using 1,3-oxazolidines as intermediates for the side-chain (Scheme 1.3.5). Oppolzer's camphorsultam was coupled to enolate **20** through the acid chloride to produce camphorsultam **21**. With the chiral auxiliary attached, the π face attack was controlled sterically and the addition of the imine afforded diasteriomer **22** in 68% yield with excellent optical purity (≥ 99.5%). Protection of amide **22**, using DDQ, afforded 1,3-oxazolidine **23** in excellent optical purity (> 99%) and in 94% yield. The sultam amide **23** was oxidatively hydrolyzed, on treatment

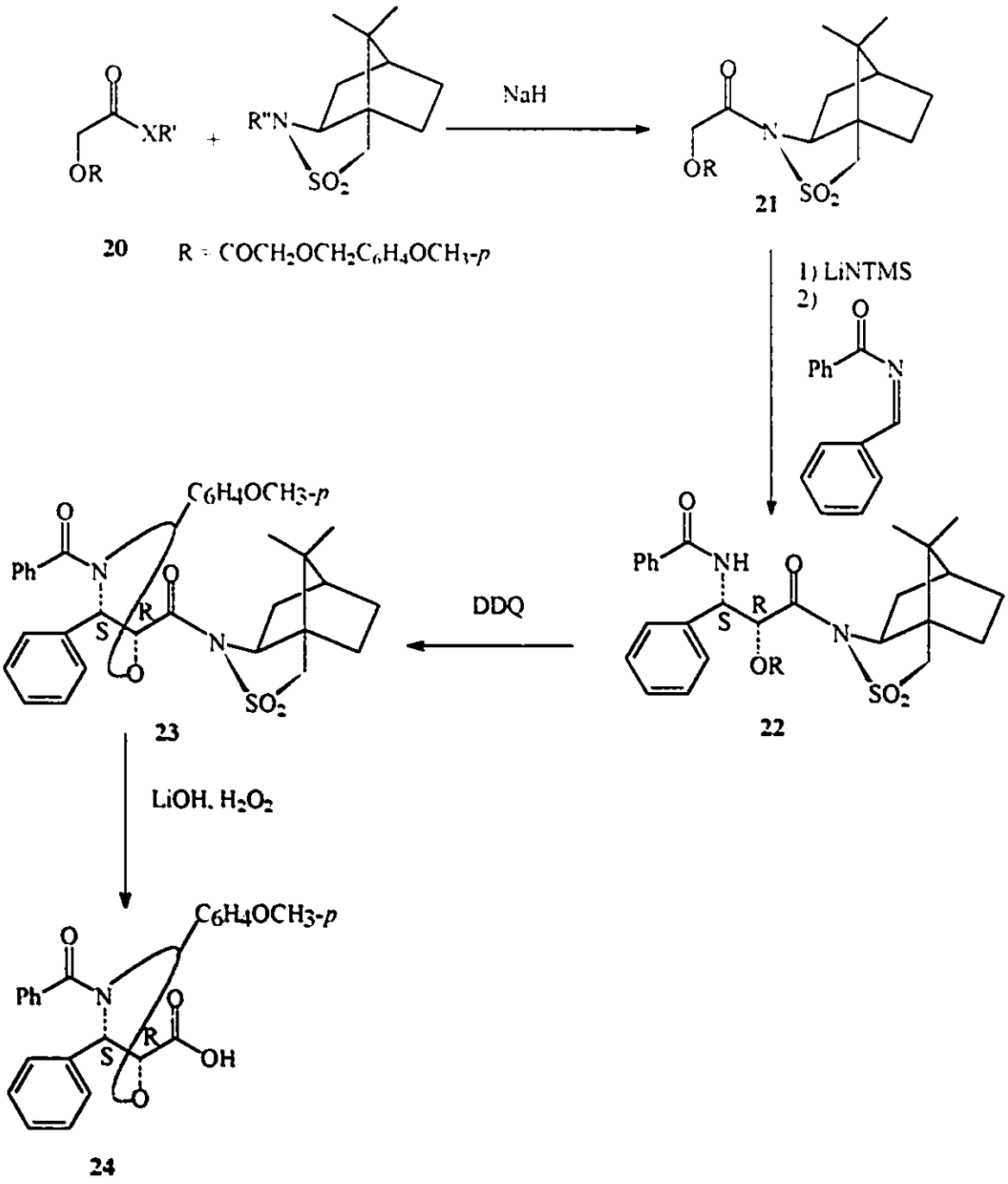
with hydrogen peroxide, to afford the *p*-methoxy benzylidine protected paclitaxel side-chain **24** in nearly quantitative yield

1.3.6 Greene's Phenylglycine Route

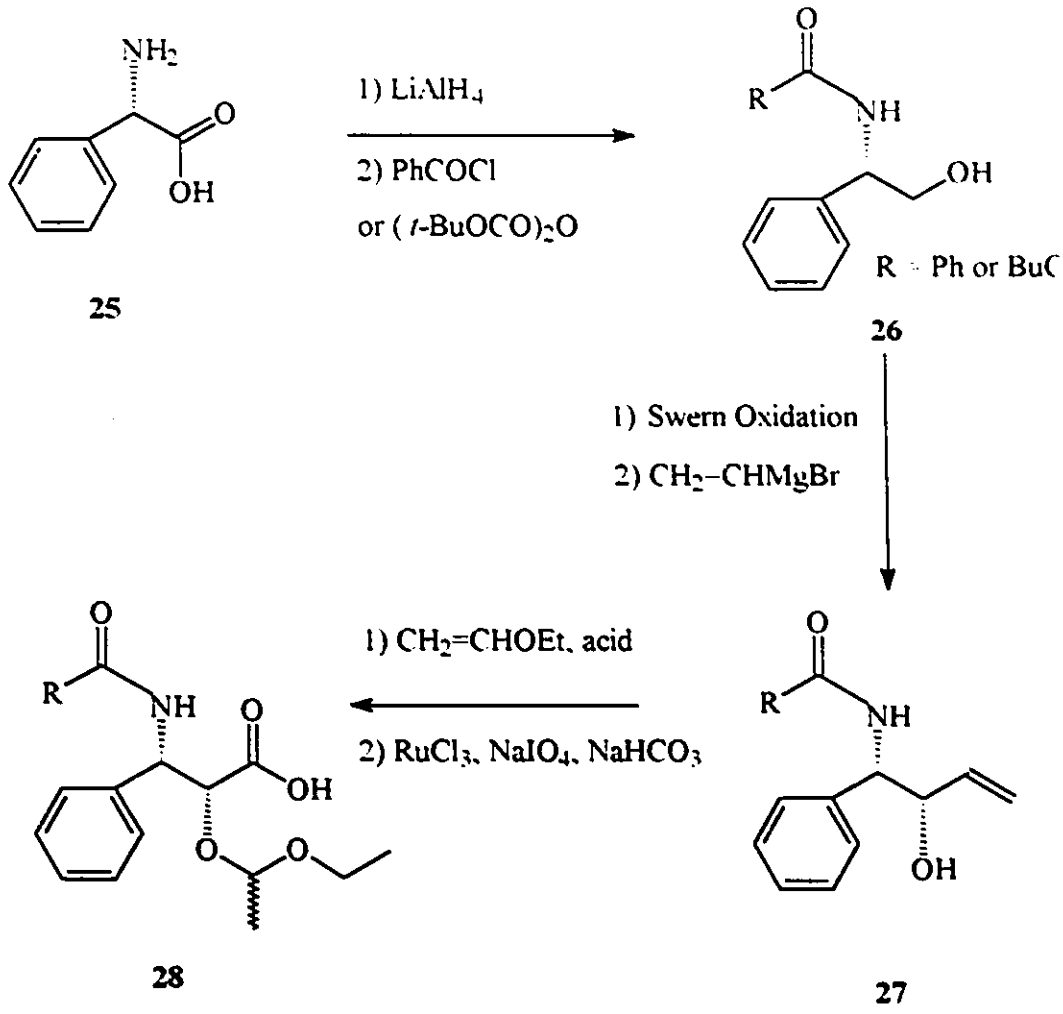
The strategy of using phenylglycine as the starting material for the synthesis of the side chain of paclitaxel was first reported by Greene *et al* [3] (Scheme 1.3.6). (*S*)-(+)-Phenylglycine **25** was reduced on treatment with lithium aluminum hydride and the resultant amine was protected as the benzoyl or Boc derivative **26**. The alcohol of amide **26** was oxidized to the corresponding aldehyde then treated with vinylmagnesium bromide to afforded alkene **27** with good *syn* diastereoselection (9:1) and without loss of enantiomeric purity. The alcohol of alkene **27**, on protection with ethyl vinyl ether, was oxidatively cleaved to afford the corresponding carboxylic acid **28**. This protected form of the taxol side-chain was prepared in 30% yield with excellent optical purity (≥ 99%).



Scheme 1.3.4. Commercon's epoxidation route



Scheme 1.3.5. Greene's route using camphorsultam as chiral auxiliary



Scheme 1.3.6. Greene's phenylglycine route

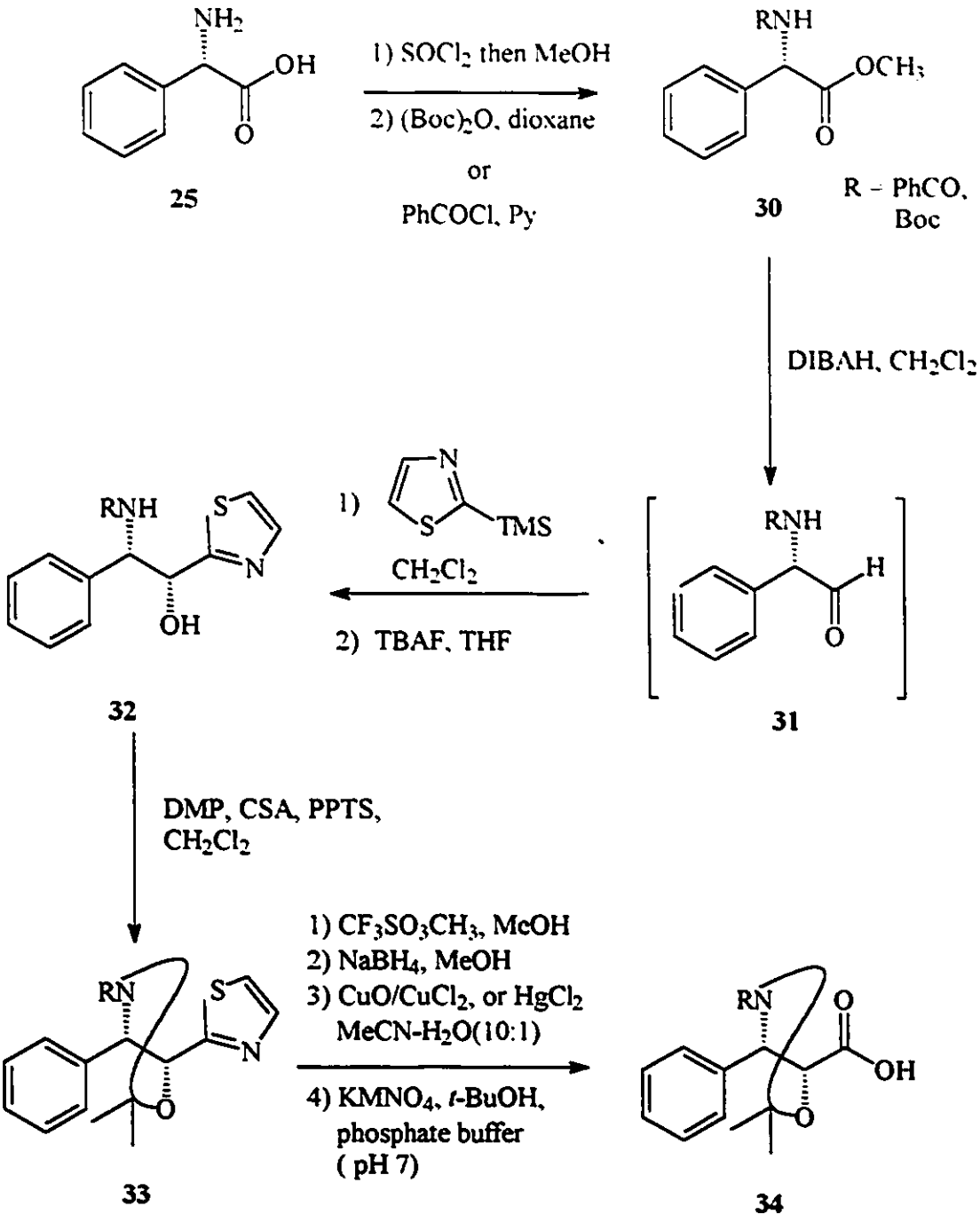
1.3.7 Dondoni's Thiazole Route

Another route using (*S*)-(+)-phenylglycine **25** as the starting material was reported by Dondoni *et al.*[18] (Scheme 1.3.7). The amino acid **25** was first converted to the acid chloride and then transformed into the methyl ester. The amine group of the methyl ester was protected as the Boc or benzoyl derivative **30**. The methyl ester **30** was reduced on treatment with DIBAH to

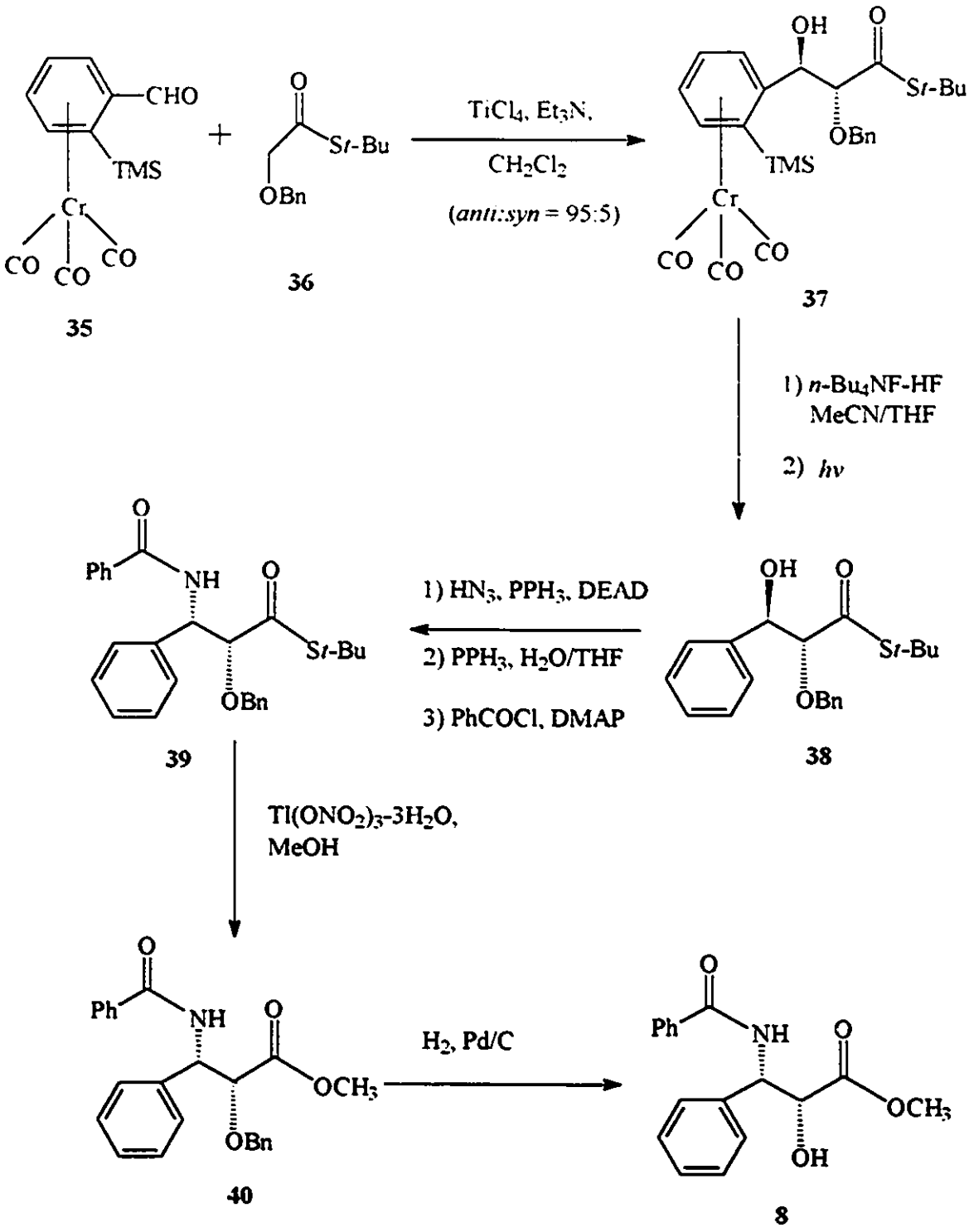
afforded the corresponding aldehyde **31**. The thiazole anion was prepared *in situ* by desilylation and then a 1,2 addition to the crude aldehyde **31** afforded the *syn* amino alcohol **32** with excellent diastereomeric selectivity (95%) and in 75% yield. Oxazolidine **33** was formed on treatment of thiazole **32** with DMP, CSA and PPTS. The carbonyl group was unmasked on treatment of thiazole **33** with methyl triflate, reduction with sodium borohydride and finally mercury(II) or copper (II) assisted hydrolysis. The resultant aldehyde was oxidized using potassium permanganate in *t*-butyl alcohol to afford the acid form of the side-chain **34** in 47% overall yield.

1.3.8 Hanaoka's Aldol Condensation Route

Hanaoka *et al.*[19] synthesized an optically pure form of the side-chain through an asymmetric aldol condensation using a (+)-chromium(0)-complexed benzaldehyde (Scheme 1.3.8). The alcohol **37** was synthesized when (+)-Tricarbonyl(η^6-o-trimethylsilylbenzaldehyde) chromium(0) complex **35** was treated with the titanium enolate **36**, which had been prepared *in situ*. The *anti*-aldol product **37** was then desilylated and irradiated with ≥ 300 nm light, to remove the chromium carbonyl moiety, to afford thioester **38**. The Mitsunubo reaction of thioester **38** with HN_3, PPH_3 and DEAD gave a *syn* amide. Reduction of the azide on the *syn* amide with PPH_3 and water and subsequent protection of the amine, on treatment with benzoyl chloride and base, afforded the amide **39** in excellent optical purity (98%) and in 63% yield. The thioester **39** was then converted to the methyl ester **40**, in quantitative yield, on treatment with thallium trinitrate in methanol. Deprotection of the alcohol **40**, by hydrogenation, afforded the methyl ester of the taxol side-chain **8**.



Scheme 1.3.7. Dondoni's thiazole route

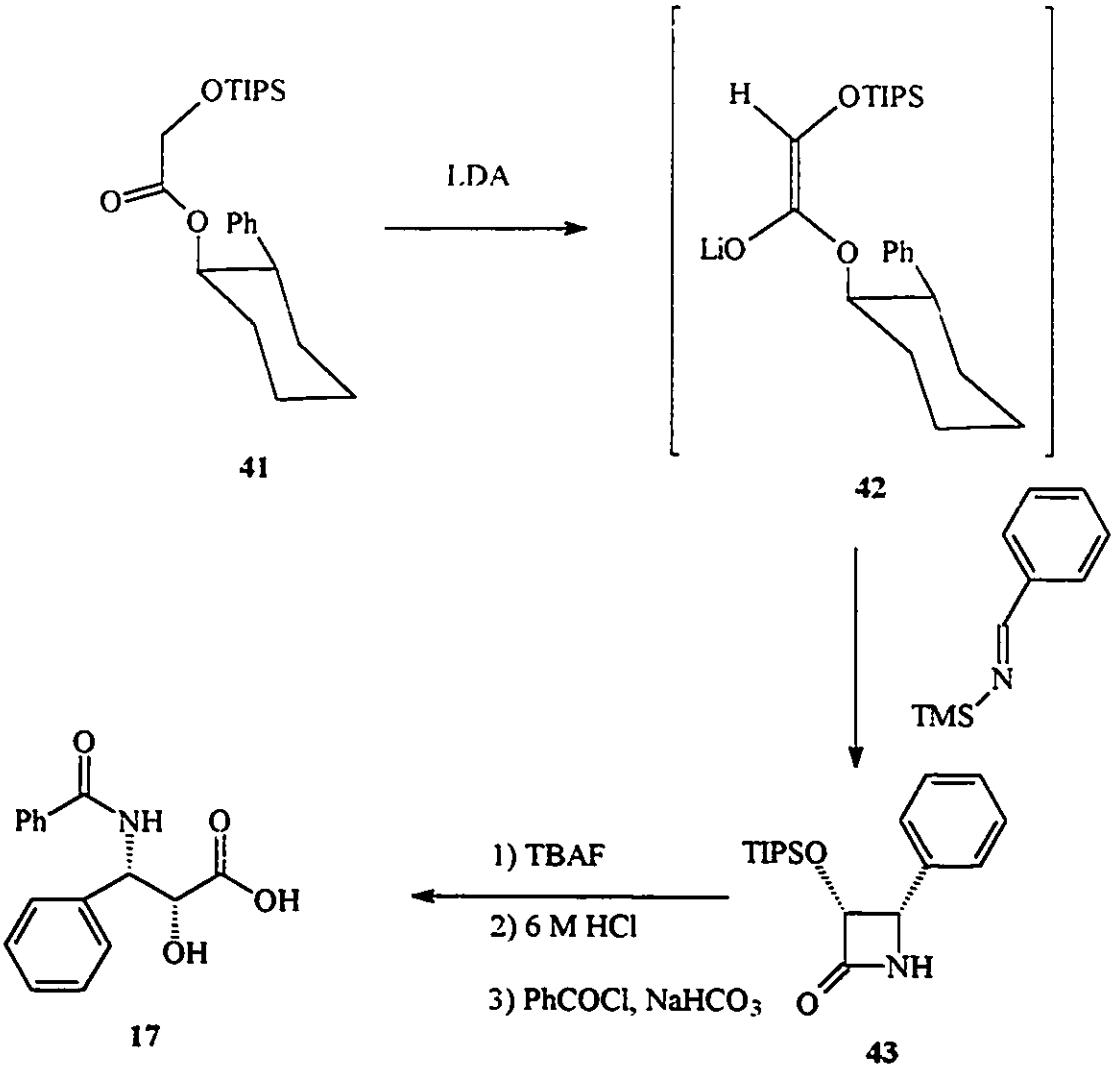


Scheme 1.3.8 Hanaoka's aldol condensation route

1.3.9 *β*-Lactam Pathways using *trans*-2-Phenyl-1-cyclohexyl as a Chiral Auxiliary

The use of *β*-lactams as precursors for the synthesis of the side-chain has been studied by several groups. Ojima *et al*[20] prepared the side-chain by a chiral lithium ester enolate-imine cyclocondensation method (Scheme 1.3.9). Treatment of (silyloxy)acetate **41** with LDA afforded the (E)-lithium enolate **42**. Addition of *N*-(trimethylsilyl)imine gave a *N*-lithiated *β*-aminoester which cyclized to afford the *β*-lactam **43**. The*β*-lactam **43** was deprotected on treatment with *t*-butylammonium fluoride and then hydrolyzed to afford the phenylisoserine. The amine group was protected as the benzoyl derivative, on treatment with benzoyl chloride and base, to afford the free acid form of the side-chain **17.** The enantiomeric purity and yield were directly affected by the O-protecting group and the chiral auxiliary. Derivatives bearing triisopropylsilyl as the O-protecting group and (-) or (+)-*trans*-2-phenyl-1-cyclohexyl as the chiral auxiliary afforded the *cis*-*β*-lactams with excellent enantiomeric purity (96-98%) and in yields of 80-85%.

Similar work has been completed by Swindell and Tao[21] using chiral auxiliaries to control the steric environment during the cycloaddition reaction. With their imine and ketene acetal system, (1*R*,2*S*)-(-)-*trans*-2-phenyl-1-cyclohexyl produced respectable endo-exo discrimination (70:18) and good π-face discrimination (88:12). Other chiral auxiliaries, (1*R*,2*R*,3*R*,5*S*)-(-)-iospinocampheyl, (1*R*,2*S*,5*R*)-(-)-menthyl and (1*R*,2*S*,5*R*)-(-)-8-phenylmenthyl, produced better endo-exo and π-face discrimination but the unnatural 2′*S*,3′*R* enantiomer was isolated. The ligand that gave the best results was (1*S*,2*R*)-(+)-*trans*-2-(1-methyl-1-phenylethyl)-1-cyclohexyl which produced excellent endo-exo discrimination (93:0) and good π-face discrimination (93:7).

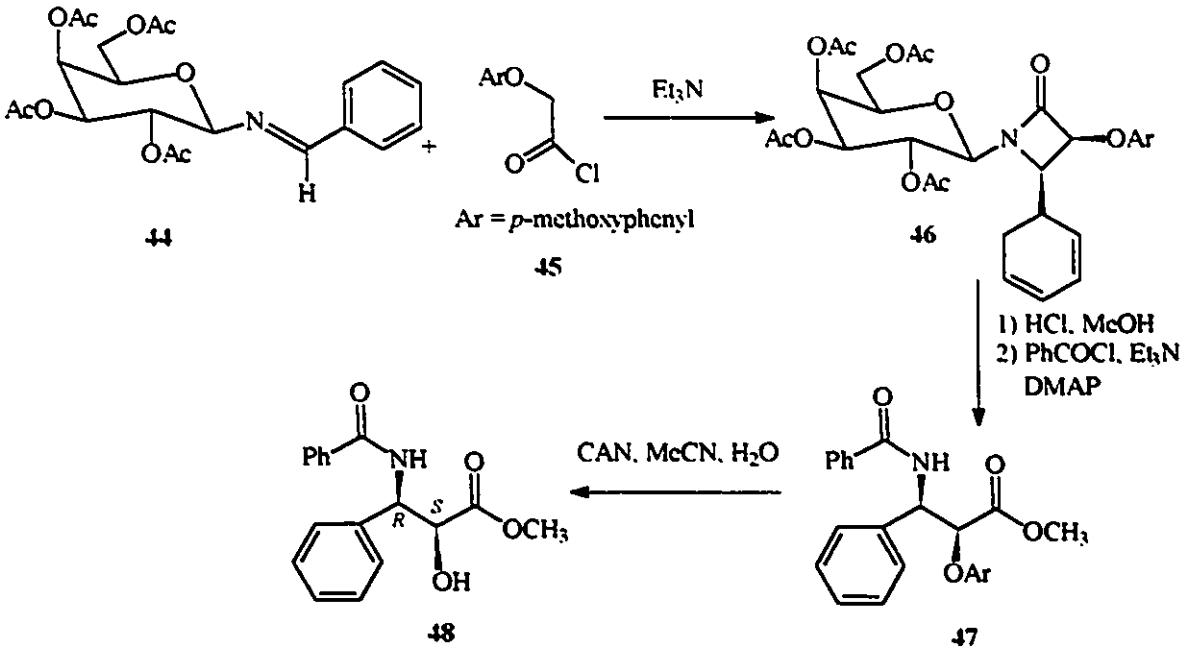


Scheme 13.9. Ojima's β-lactam route

1.3.10 Georg's β-Lactam Route

Georg *et al.*[22] have synthesized β-lactam and phenylisoserines asymmetrically *via* the Staudinger reaction (Scheme 13.10). Treatment of the galactose imine **44** with the aryl acid chloride **45** yielded one diastereoisomer **46** in *cis* stereochemistry. Hydrolysis of the β-lactam **46** and subsequent treatment with benzoyl chloride and base afforded the *N*-benzoyl-3-phenylisoserine derivative **47**. The phenylisoserine methyl ester **48** was synthesized by

oxidative dearylation of methyl ester **47** on treatment with ammonium cerium (IV) nitrate to cleave the aryl group. Unfortunately, optical rotation of this compound revealed that the 2*S*,3*R* isomer had been synthesized.



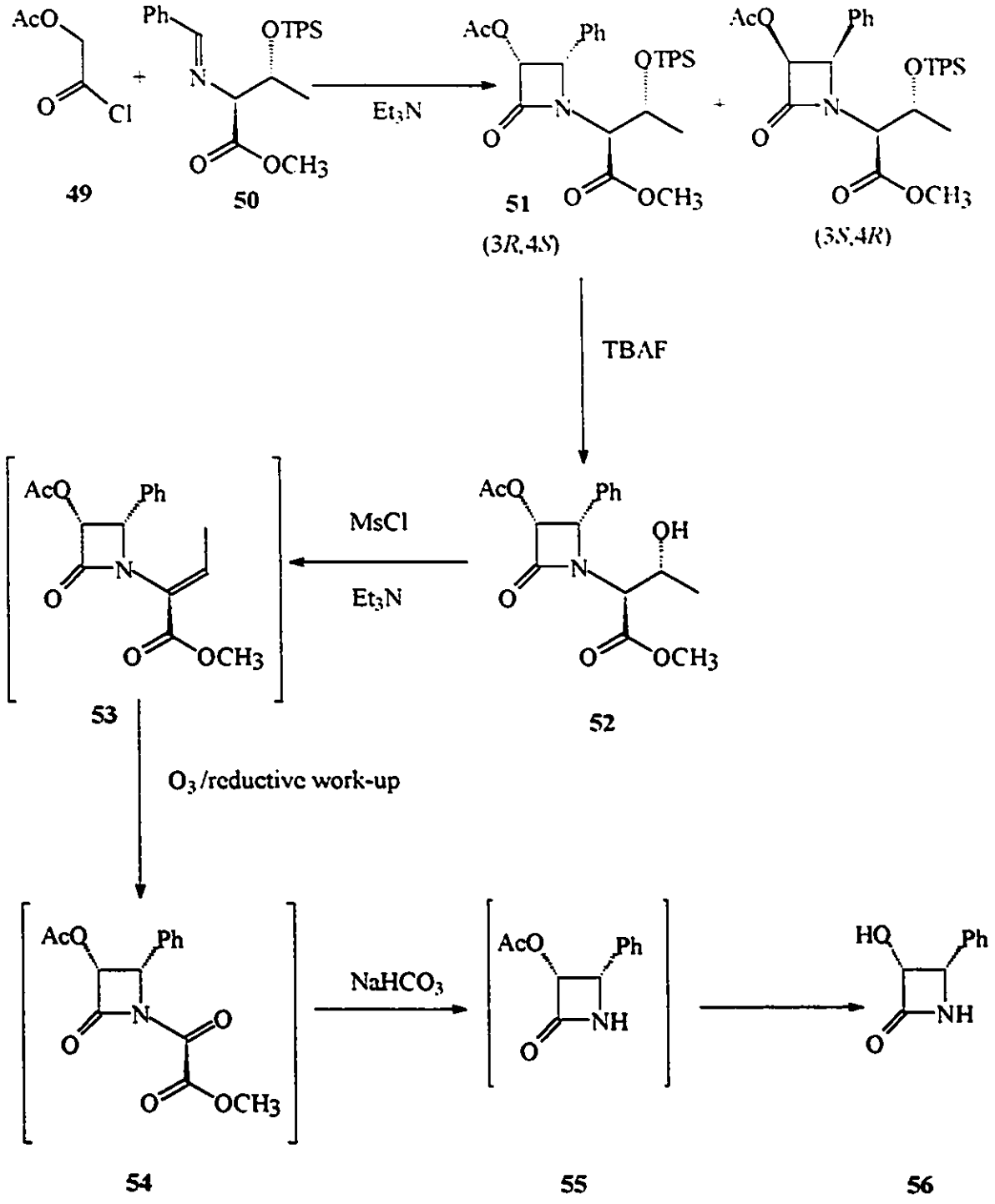
Scheme 1.3.10 Georg's *β*-lactam route

1.3.11 Farina's β-lactam Route

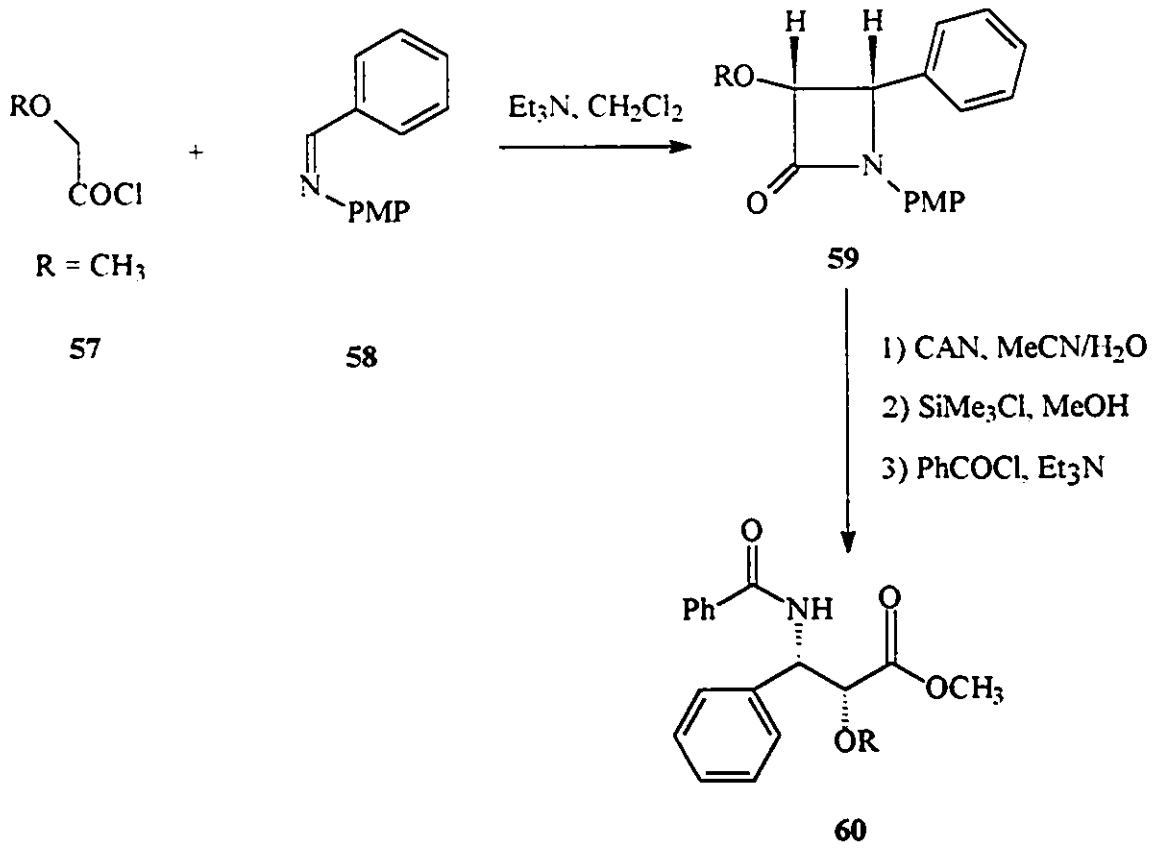
Farina *et al.*[23] used silylated L-threonine ester **50** as a chiral auxiliary to prepare the β-lactam **56** (Scheme 1.3.11). The L-threonine ester **50** was condensed with the acetoxyacetyl chloride **49** in the presence of base to afford the β-lactam **51** in 74% yield and a diastereomeric ratio of 11.5:1. *t*-Butyl ammonium fluoride was used to deprotect the secondary alcohol **51** and then mesylation/elimination afforded the alkene **53.** The ozalimide **54** was prepared, cleanly, by ozonolysis and then without purification was treated with sodium bicarbonate, to afford the β-lactam **56**.

1.3.12 Palomo's β-Lactam Route

The usefulness of the Staudinger reaction to synthesize β-lactams was also demonstrated by Palomo *et al.*[24] (Scheme 1.3.12). A single *cis* isomer **59** was obtained from the condensation of the acid chloride **57** with the imine **58.** The *cis* β-lactam **59** was oxidatively dearylated, on treatment with ammonium cerium (IV) nitrate. The ring system was opened on treatment with chlorotrimethylsilane in methanol to afford the corresponding β-amino ester which was isolated as the benzoyl derivative **60.**



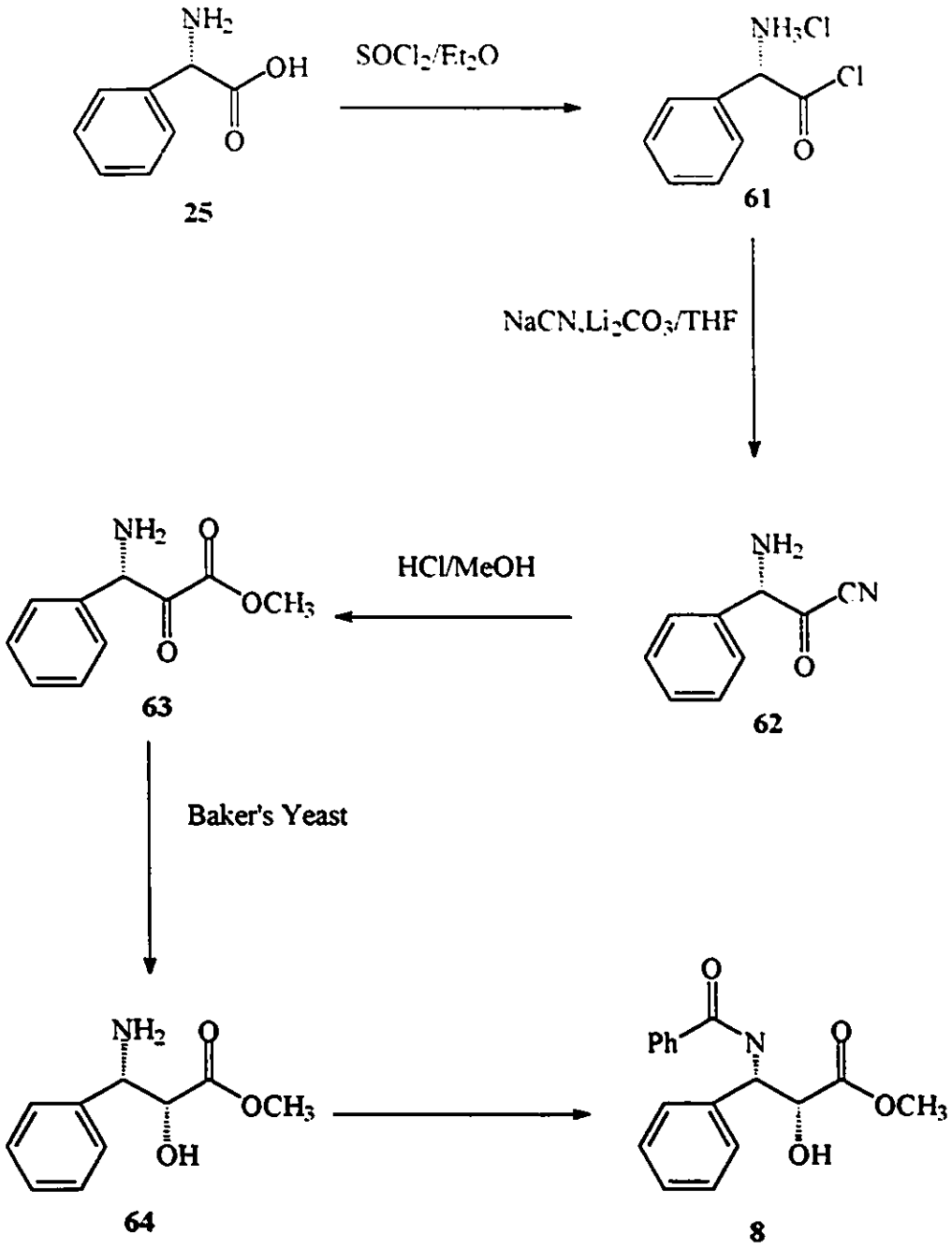
Scheme 1.3.11. Farina's β-lactam route



Scheme 1.3.12. Palomo's β-lactam route

1.3.13 Kayser's Route using Baker's Yeast

Kayser and Kearns[25] used Baker's yeast to catalyze the enantioselective reduction of dione **63** on route to the paclitaxel side-chain (Scheme 1.3.13). Inexpensive phenylglycine **25** was converted to the acid chloride **61** , when heated at reflux with thionyl chloride, and then transformed into a nitrile group **62** on treatment with sodium cyanide. Alcoholysis of the resultant nitrile group **62** afforded the methyl ester **63**. It was found that Baker's yeast reduced the carbonyl group at the C3 position enantioselectively to afford the R alcohol **64**. The amine of alcohol **64** was protected as the amide using Georg's[26] methodology to yield (2*R*, 3*S*)-N-benzoyl-3-phenylisoserine **8** in 91% yield.



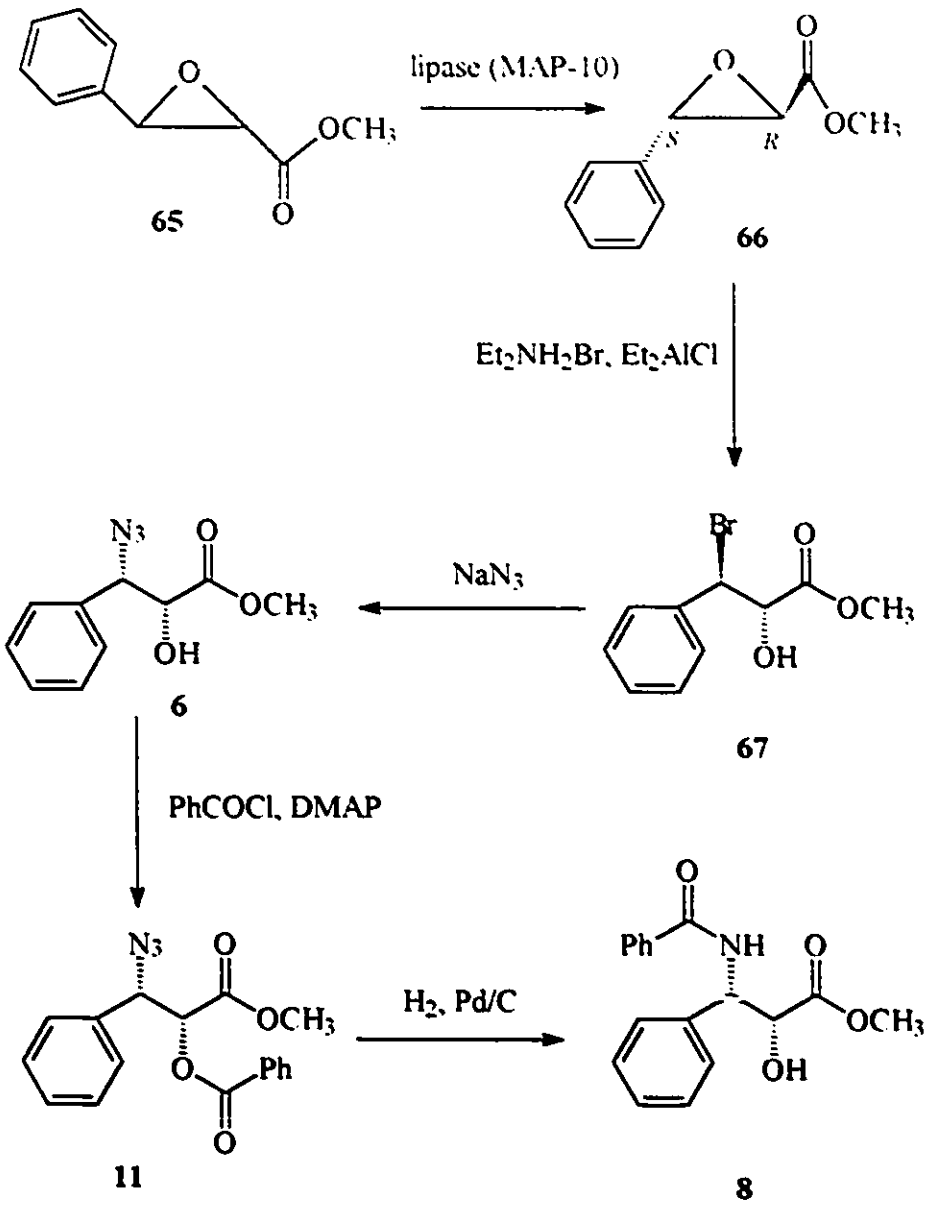
Scheme 1.3.13. Kayser's route using Baker's yeast

1.3.14 Chen's Enzymatic Route

Chen *et al.*[27] used *Mucor miehei* lipase MAP-10 and isobutyl alcohol to resolve (±)-methyl *trans*-β-phenylglycidate **65** in high optical purity and chemical yields (Scheme 1.3.14). The epoxide **66** was opened regioselectively to yield *2R,3S*-hydroxybromine **67** in 90% yield. Displacement of the bromine at C3 on treatment with sodium azide afforded the inverted product **6**. The hydroxy group of azide **6** was converted to the benzoyl derivative **11.** On hydrogenation of the azide and the accompanying O→N benzoyl transfer afforded the side-chain methyl ester **8** in 40% overall yield.

1.3.15 Sih's Enzyme Studies

A variety of lipases were screened by Sih *et al.*[28] for their ability to selectively cleave the ester at C3 or open the β-lactam ring. In an attempt to increase the reaction rate and not compromise the enantiomeric purity, several conditions were studied. The effect of cosolvents, temperature, and water concentration on the reaction was studied. The addition of a cosolvent (10% acetonitrile) and elevated incubation temperatures increased the reaction rates. To improve the medium for the biocatalytic transformation, several organic solvents were tested. *t*-Butyl methyl ether and isopropyl ether afforded the most results. The effect of water concentration in the *t*-butyl methyl ether on the cleavage of the C3 acetyl group was investigated. It was found that 10 molar equivalents was the optimum level. It was noted that when methanol (5 eq.) was substituted for the water, the C3 acetyl group was removed but in addition the β-lactam ring was opened to give the required *2R,3S* configuration of the side-chain.



Scheme 1.3.14. Chen's enzymatic route

1.4 Synthesis of Prodrugs

In order to overcome the formulation problems associated with paclitaxel **1**, which include low water solubility and lack of functional groups to allow salt formation, several routes have been devised to synthesize prodrugs of paclitaxel **1**. The C2′ and C7 site would seem to have the most potential for derivatization without substantial lost of biological activity.

Kingston *et al.*[29] completed a structure-activity study where 2′, 2′,7 and 7 acetates were prepared, characterized and tested for biological activity. The results indicated that paclitaxel **1** and the 7-acetylpaclitaxel had similar biological activity while the 2′-acetylpaclitaxel was approximately half as active. The 2′,7-diacetylpaclitaxel was approximately 10-fold less active than paclitaxel **1**.

Nicolaou *et al.*[30] systematically prepared and tested the biological activity of several propaclitaxel compounds and determined that high temperature and pH controlled the rate at which paclitaxel **1** was released. The compounds studied were of two basic types (Figure 1.4). The rate of release of paclitaxel **1** from Type I compounds increases when the electron-withdrawing ability of the aryl substituent on the sulfone moiety was increased. Similarly, the rate of release from Type II compounds also increased with the electron-withdrawing ability of the hetroatom linkage. Using this trend, its was proposed that simple chemical principles could be used to fine-tune future derivatives to maximize their biological and pharmacological properties.

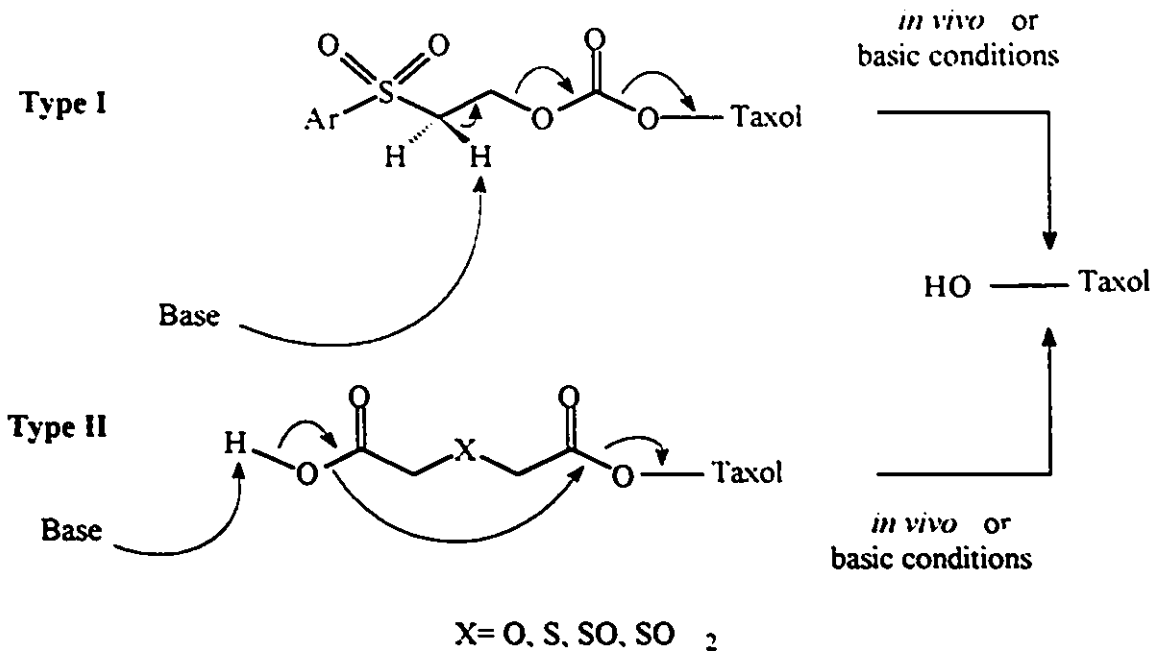


Figure 1.4. Mechanistic rationale for the design of propaclitaxels

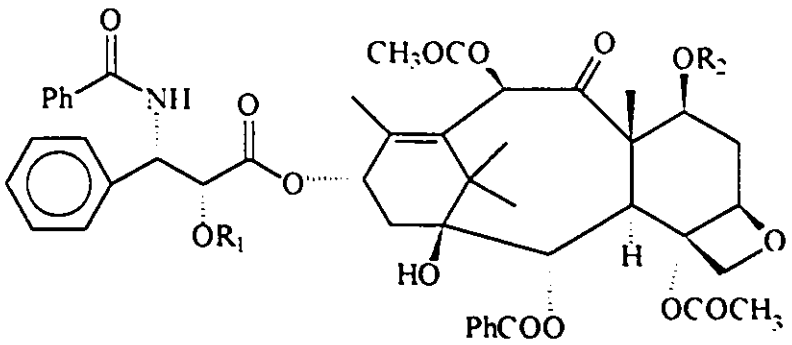
1.5 Preparation of Water Soluble Derivatives

In an attempt to increase water solubility as well as enhance the activity of the prodrug, Kingston *et al.*[31] studied two routes for the preparation of the sulfonate derivatives of the 2'-succinylpaclitaxel **75** and the two 2'-acylpaclitaxel derivatives (Figure 1.5.1). The first approach to the sulfonate derivative consisted of coupling of the 2'-succinylpaclitaxel **75** with the t-butylammonium salt of taurine or 3-amino-1-sulfopropionic acid *via* the mixed anhydride reaction. The amino acid derivatives **68** and **69** were then converted to the water soluble sodium salts. The 2'-acryloylpaclitaxel **70** was prepared by the mixed anhydride method and then Michael addition of sodium metasulfite to the α,β-unsaturated ester afforded the sulfonate derivative **71**. The sulfonate derivatives were between 100-200 times more water soluble than paclitaxel **1** however their

biological activity was only slightly diminished as compared to paclitaxel **1**. Both 2′-glycyclpaclitaxel **72** and the 2′-(γ-aminobutryl)paclitaxel **73** were prepared but were too unstable to conduct further testing.

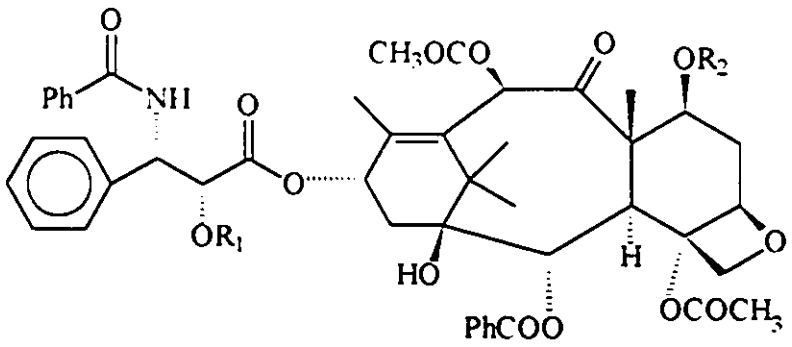
Stella *et al.*[32] synthesized and evaluated several compounds by introducing an amino acid to the C2′ or C7 positions. Coupling of 3-(*N,N*-diethylamino)propionic acid methanesulfonate with paclitaxel **1** using DCC and DMAP in dichloromethane produced the C2′ derivative **74** with the greatest water solubility (> 10mg/mL) and equal or better biological availability compared to paclitaxel **1**. The C7 derivatives had a much lower activity for inhibiting tumor growth and melanoma cell proliferation. The similarity in activities between the C2′ analogues and paclitaxel **1** was thought to be due to the *in vivo* conversion of the analogues to paclitaxel **1** or an active metabolite.

Deutsch *et al.*[33] prepared several water-soluble 2′-monoderivatives of paclitaxel **1** on treatment with succinic anhydride or glutaric anhydride (Figure 1.5.2). These derivatives were then converted to the sodium, triethanolamine and *N*-methylglucamine salts and screened for biological activity. In this series, the sodium and triethanolamine salts of the 2′-monoglutarate **76** were the most potent and active of those tested. All attempts to prepare a basic prodrug were unsuccessful except for the coupling of an acidic prodrug with a dibasic amine. The amino amide **77** was synthesized when the 2′-glutarylpaclitaxel was coupled with the 3-(dimethylamino)-1-propylamine. The hydrochloride salt of this compound had good solubility and was the most potent and active of all agents reported.



68.	Sulfonate derivatives of taurine analogues of 2'-succinyl paclitaxel	$R=COCH_2CH_2CONHCH_2CH_2SO_3^-X^+$ $X=N^+Bu_4,Na^+$
69.	Sulfonate Derivatives of 3-Amino-1-sulfopropionic acid analogues of 2'-succinyl paclitaxel	$R=COCH_2CH_2CONHCH_2CH_2CH_2SO_3^-X^+$ $X=N^+Bu_4,Na^+$
70.	2'-Acryloyl paclitaxel	$R=COCH=CH_2$
71.	Sulfonate derivative of 2'-acryloyl paclitaxel	$R=COCH_2CH_2SO_3^-Na^+$
72.	2'-Glycyl paclitaxel	$R=COCH_2CH_2CH_2NHCOOCH_2C_6H_5$
73.	2'-(γ-aminobutyryl)paclitaxel	$R=COCH_2CH_2CH_2NH_3^+HCOO^-$
74.	Sulfonate derivative of 2'-[3-(*N,N*-diethylamino)propionyl paclitaxel	$R=COCH_2CH_2CH_2N(C_2H_5)CH_2SO_3H$

Figure 1.5.1. Structures of water soluble derivatives of paclitaxel



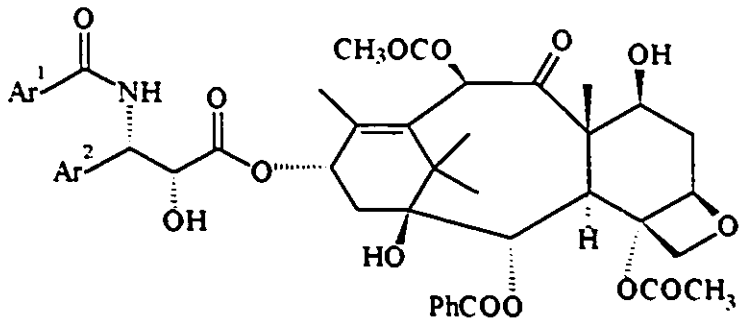
75.	2'-succinylpaclitaxel	R^1=$CO(CH_2)_2CO_2X$ R^2=H X=H, Na, $(HCOCH_2CH_2)NH$
76.	2'-glutarylpaclitaxel	R^1=$CO(CH_2)_3CO_2X$ R^2=H X=H, Na, $(HCOCH_2CH_2)NH$
77.	Amino amide adduct	R^1=$CO(CH_2)_3CONH(CH_2)_3N(CH_2)_2$ R^2=H

Figure 1.5.2. Structures of succinyl, glutaryl and amino amide paclitaxel derivatives

1.6 Preparation of *p*-Substituted 3'-Phenyl Analogues

A series of analogues synthesized by Swindell *et al.*[34] and Potier *et al.*[35] revealed several important points about the structure-activity of the side-chain. These two groups found that the C3' acyl group was essential for activity however the amide's aryl group may be substituted with another aryl or alkyl group. The C3' aryl group is required as demonstrated by a 19-fold decrease in activity with replacement by a methyl group. One of the polar functional groups on the C2' or C3' can be removed with little effect on biological activity. However the removal or interchange of both groups caused a drastic reduction in activity. It was also noted that the natural (2'*R*, 3'*S*) isomer was much more active than the (2'*S*, 3'*R*) enantiomer and that the (2'*S*, 3'*S*) and (2'*R*, 3'*R*) diasteriomers of the side-chain maintained similar activity to the natural isomer.

The first derivatives of paclitaxel **1** possessing substituents on the two phenyl rings of the side-chain were reported by Georg *et al.*[36] (Figure 1.6). An ester enolate cyclocondensation reaction afforded a β-lactam with a chlorine substituent at the C4 position of the ring. *N*-acylation of the β-lactam led to phenylisoserine **78** with a chlorine substituent at the C3′ amine position. Both paclitaxel analogues were prepared in good yield and had similar activity to the parent compound.



78.	*p*-Chlorophenyl paclitaxel	$Ar^1 = p\text{-}ClC_6H_4$ $Ar^1 = C_6H_5$	$Ar^2 = C_6H_5$ $Ar^2 = p\text{-}ClC_6H_4$
79.	*p*-Fluorophenyl paclitaxel	$Ar^1 = p\text{-}FC_6H_4$	$Ar^2 = C_6H_5$
80.	*p*-Dimethylamino paclitaxel	$Ar^1 = p\text{-}(CH_3)_2NCH_6H_4$	$Ar^2 = C_6H_5$

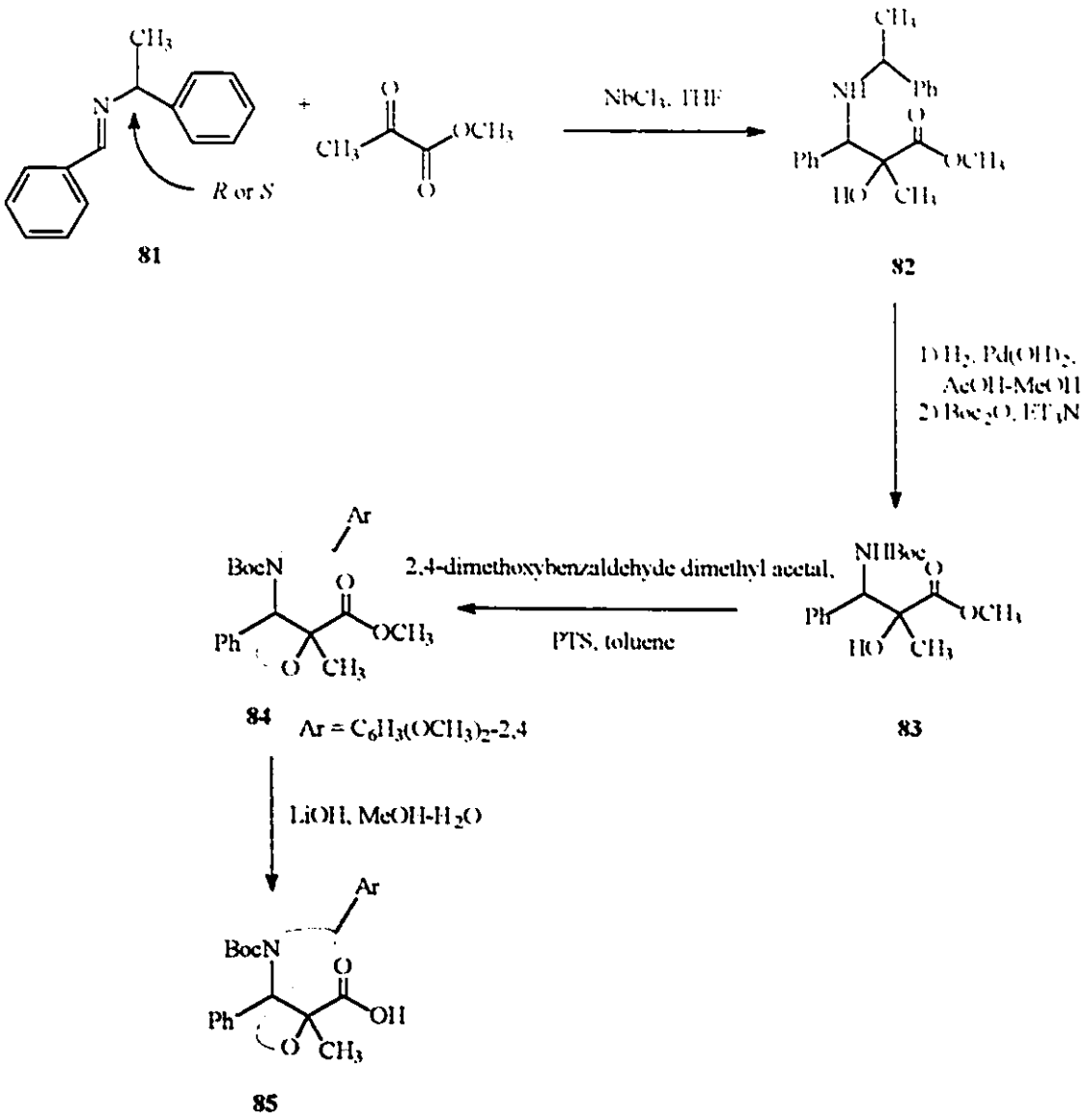
Figure 1.6. Structures of *p*-substituted 3′aromatic paclitaxel derivatives

Subsequently, Commercon *et al.*[37] have prepared two additional 3′-phenyl ring derivatives using the Staudinger reaction. These side-chain analogues contained fluorine **79** or dimethylamino **80** groups at the para position (Figure 1.6) and were coupled to O-diprotected baccatin III. Double deprotection of the two compounds afforded two new taxoid analogues with substituents at the para position of the 3′ phenyl group. The overall yield was reported as 23% for the fluorine derivative

and 42% for the dimethylamino analogue. The fluorine derivative was reported to have an IC50 of 0 03 μg/mL as compared to docetaxel **2** (IC50 = 0.04 μg/mL).

1 7 Preparation of 2′-Methyl Analogue

The first preparation of a 2′ alkylated analogue of the 2*S*,3*R* and 2*R*,3*S* side-chain was reported by Greene *et al.*[38] (Scheme 1.7). The *N*-benzylidene-1-phenylethylamine **81** was afforded on condensation of 1-phenylethylamine with benzaldehyde. Addition of methyl pyruvate to a stirred suspension of the imine **81** and niobium (III) chloride in THF at -20°C afforded the *syn*-diastereoisomerically favored product **82** (9:1). Hydrogenation and protection of the amine with a Boc group transformed methyl ester **82** into the C2′ methyl docetaxel side-chain **83**. Attempts to open the *p*-methoxybenzylidene side-chain under acidic conditions were unsuccessful. Preparation of the more acid labile 2,4-dimethoxybenzylidene **85** resolved the problem however the coupling procedure failed to afford the desired product. Substitution of a di-2-pyridyl variant, for DCC, afforded the docetaxel **2** in 72% (2*S*,3*R)* and 40% (2*R*,3*S*) yields respectively. Unfortunately, opening of the dimethoxybenyzlidene ring also removed the Boc group and the amine had to be reprotected as the Boc derivative before the final deprotection of the C7 and C10 hydroxy groups to afford the 2′ methylated analogue. The 2′*S*,3′*R* derivative showed no biological activity however the 2′*R*,3′*S*-2′methyl docetaxel showed significantly greater activity than that of docetaxel **2**.

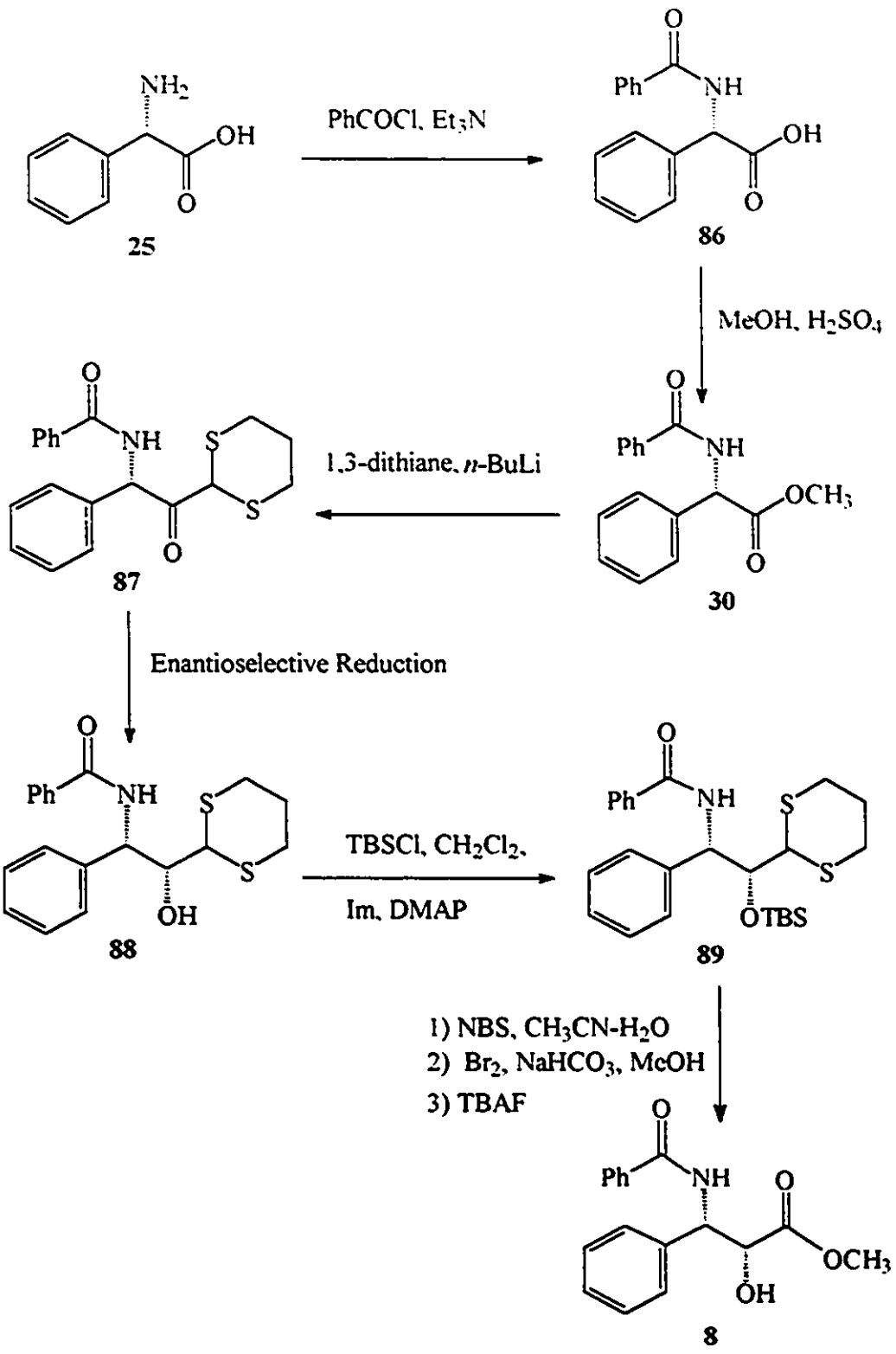


Scheme 1.7. Greene' route to prepare 2'methyl derivative

1 8 Proposed Route to Taxoid Side-chain

Our planned route for the synthesis of the methyl ester of the paclitaxel side-chain **8** is outlined in Scheme 1 8

Optically pure phenylglycine **25**, would be converted to the amide **86** on treatment with benzoyl chloride and triethylamine. The carboxylic acid **86** would be treated with methanol and a catalytic amount of sulfuric acid to afforded the methyl ester **30.** A one carbon homolagation would be completed with the addition of the cyclic S,S acetal to the terminal carbonyl group. The next step would be to distereoselectively reduce the carbonyl group to generate the correct geometry. Enantioselective reduction of the ketone **87** would afford the alcohol **88** in high optical purity. The alcohol **88** would then be protected as the silyl ether to afford the *t*-butyl dimethyl silane derivative **89.** The aldehyde would then be unmasked and directly oxidized to the methyl ester first by oxidation with *N*-bromosuccinimide and then esterification with bromine/sodium bicarbonate/methanol. Deprotection of the hydroxy group would afford the methyl ester of paclitaxel side-chain **8.**



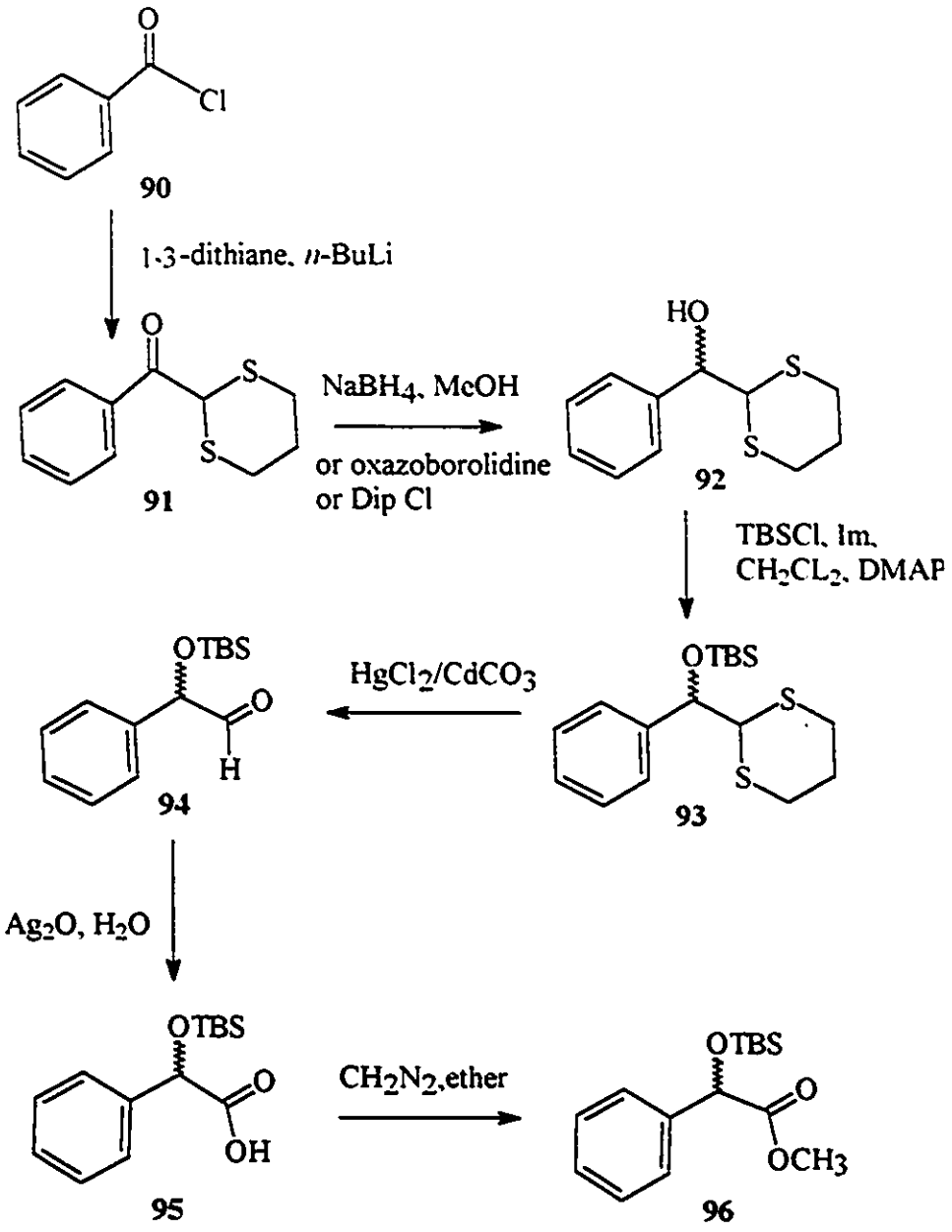
Scheme 1.8. Proposed route to paclitaxel side-chain

2 RESULTS AND DISCUSSION

In order to establish the feasibility of the approach outlined in Scheme 1.8, model systems were examined and these studies form the basis of this thesis. Benzoyl and hydrocinnamoyl compounds were chosen for the model work to determine the effect of steric crowding and the adjacent dithiane group on the stereocontrolled reduction. The initial model work consisted of a one carbon homolagation afforded by the addition of an acyl equivalent and then enantiomeric reduction of the carbonyl group with the adjacent sulfur groups in place.

The pathway using the first model system, benzoyl chloride, is outlined in Scheme 2.1.

The first step involved a one carbon homolagation on addition of an acyl equivalent. Tris(methylthio)methane was the initial acyl equivalent chosen to add to the carbonyl group. The instability of the resulting product led us to try tris(phenylthio)methane as a logical alternative. Unfortunately similar results were obtained with this reagent. In an attempt to increase the stability of the product of the first step, 1,3-dithiane was studied as the acyl equivalent. The 1,3-dithiane was treated with *n*-BuLi at -78°C for 20 minutes then added *via* a cannula to the benzoyl chloride **90** in THF. After work-up, the ketone **91** was isolated in 61% yield. The IR spectrum indicated a strong signal at 1679 cm^{-1} characteristic of a conjugated ketone. The major by-product was isolated and identified as an alcohol containing two dithiane units. This side reaction has been reported previously.[42] Treatment of the ketone **91** with sodium borohydride afforded a racemic mixture of the alcohol **92** characterized by a broad signal at 3425 cm^{-1} in the IR spectrum and doublets at 4.90 ppm(PhCH) and 4.06 ppm (HCS_2)and a broad singlet at 2.95 ppm (OH) in the ^1H NMR spectrum.



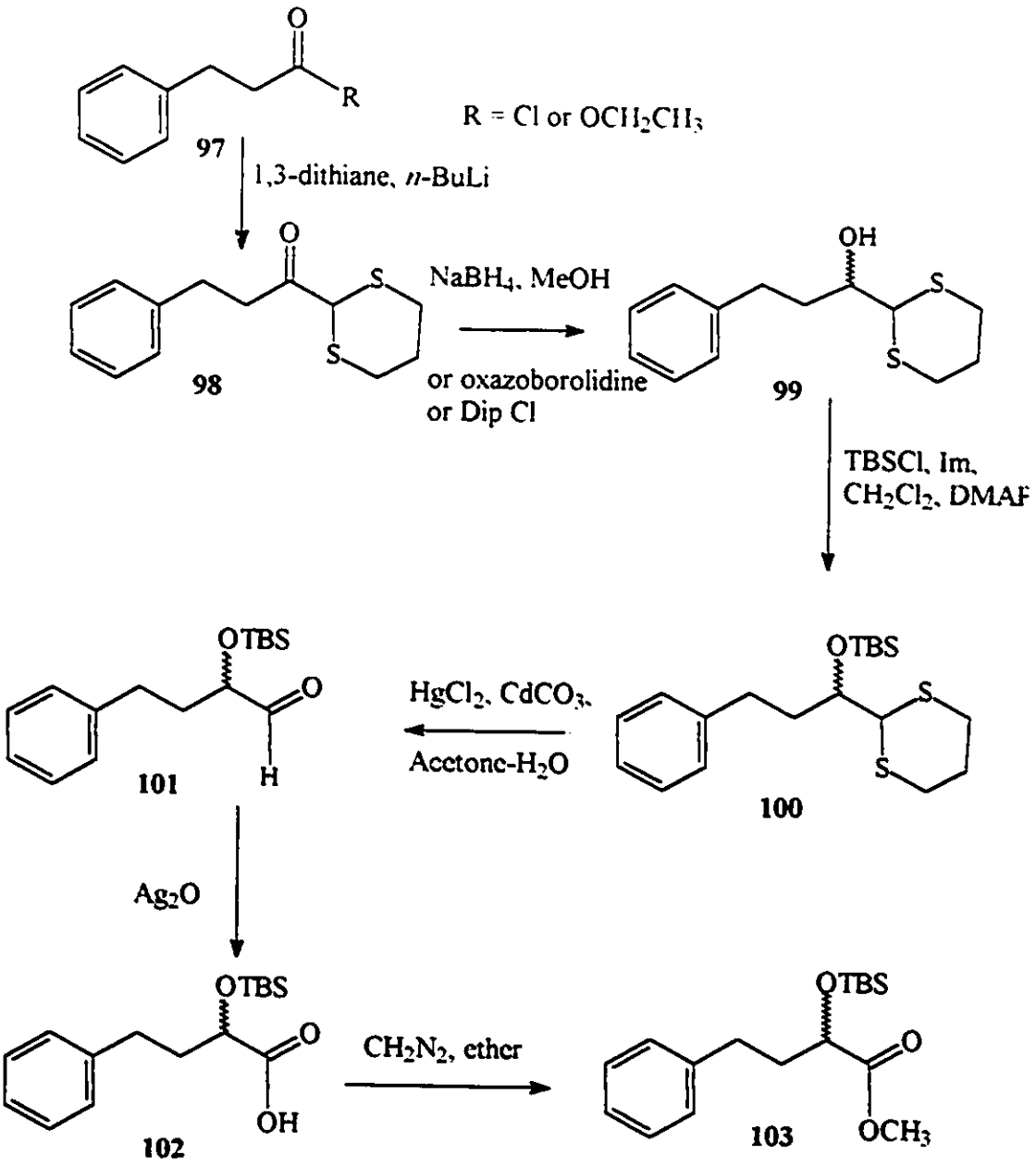
Scheme 2.1. Proposed route for benzoyl model system

The purified alcohol **92** was protected as a silyl ether on treatment with *t*-butyldimethyl silyl chloride. Characteristic signals were noted in the ^{1}H NMR spectrum at 0.86 and 0.07

ppm for the *t*-butyl and methyl of the protecting group. The broad singlet for the hydrogen of the alcohol at 2.95 ppm in the ^{1}H NMR spectrum also disappeared. The final step of the synthesis was to unmask the aldehyde **94** and converted it to the more stable methyl ester **96.** The benzoyl derivative **93** was dissolved in acetonitrile and water (80:20) and treated with *N*-bromosuccinimide (6 eq) and collidine (12 eq) at 0°C. Under these conditions all the starting material disappeared and a new very polar spot was detected by TLC. However only a small peak was detected at 9.36 ppm in the ^{1}H NMR and the IR spectrum indicated a major peak at 1715 cm^{-1} which is low for an aldehyde.[57,58] Several other methods were tried to hydrolysis the dithiane with little or no success. These included NBS/$AgNO_3$,[45] $CuCl_2$/CuO,[46] NCS/$AgNO_3$,[45] Choramine-T,[47] m-CPBA,[48] methyl iodide,[49] and CAN.[50] 1,3-Dithianes are reported to be stable to hydrolysis using mercuric salts at room temperature.[51] However heating the mixture to 50°C in aqueous acetone (1:6) and using cadmium carbonate to control the pH near neutrality was reported to unmask the aldehyde. The dithiane **93** was dissolved in acetone-water (80:20) and treated with mercuric(II) chloride and cadmium carbonate for 24 hours at 50°C to afford the aldehyde **94**. The aldehyde **94** was only partially characterized, by a singlet at 9.50 ppm in the ^{1}H NMR spectrum, a peak at 199.5 ppm in the ^{13}C NMR and a band at 1746 cm^{-1} in the IR spectrum, due to the unstable nature of the compound Several methods were tried to directly oxidize the aldehyde **94** to the methyl ester **96**. These included *t*-butyl hypochlorite,[52] PDC/methanol,[53] I_2/NaOH/methanol,[54] and Br_2/$NaHCO_3$/methanol.[55] Unfortunately none of these methods worked satisfactory on the benzoyl system.

The higher homologue was prepared *via* the same route as shown in Scheme 2.2. Treatment of hydrocinnamic acid with oxalyl chloride afforded the acid chloride **97** (R=Cl). Treatment of 1,3-dithiane with *n*-BuLi at -78°C for 20 minutes afforded the anion. The

solution containing the anion was added *via* a cannula to the acid chloride **97** to afford the dithiane **98** in 52% yield. This method was later modified to use the more stable ethyl ester **97** (R = OCH_2CH_3) instead of the acid chloride. This modification allowed a stable and easier to handle starting material to be used and produced a modest improvement in yield (54%). A strong signal at 1732 cm^{-1} was detected in the IR spectrum which was characteristic of a ketone. Treatment of the ketone **98** with sodium borohydride afforded the alcohol **99** in 82% yield. The alcohol **99** was characterized by a broad signal at 3436 cm^{-1} in the IR spectrum and a doublet at 3.87 ppm ($CHOS_2$) a broad singlet at 2.57 ppm (OH) in the ^1H NMR spectrum. The alcohol **99** was then protected as a silyl ether on treatment with *t*-butyldimethylsilyl chloride. This was confirmed by the disappearance of the alcohol signal in the IR spectrum and the emergence of a singlet at 0.98 ppm and two singlets at 0.18 and 0.13 ppm in the ^1H NMR spectrum which are characteristic of the *t*-butyl and methyl groups on the silyl ether. The dithiane **100** was dissolved in acetone-water and treated with mercuric(II) chloride and cadmium carbonate for 24 hours at 50°C to afford the aldehyde **101.** The aldehyde **101** was only partially characterized, by a singlet at 9.58 ppm in the ^1H NMR spectrum and a band at 1735 cm^{-1} in the IR spectrum, due to the unstable nature of the compound. The aldehyde **101** was treated with all the reagents tried on the benzoyl model system with similar results except that the bromine/sodium bicarbonate/methanol method worked. Unfortunately the alcohol on methyl ester **8** was deprotected in the process and had to be reprotected to maintain its chemical stability. The methyl ester **103** was characterized by a singlet at 3.69 ppm in the ^1H NMR representing the 3 hydrogens on the methoxy group.



Scheme 2.2. Proposed route for hydrocinnamoyl model system

Due to the addition of the step to reprotect the alcohol, a simpler route was investigated to try to increase the overall yield of the oxidation final steps. Silver (I) oxide was chosen as

the oxidizing agent to convert the aldehyde to the corresponding acid and diazomethane would be used to esterify the compound. The aldehyde **101** was dissolved in water and treated with silver(I) oxide (2 eq.) to afford the corresponding carboxylic acid **102** in a small amount. Treatment of the carboxylic acid **102** with freshly prepared diazomethane in ether afforded methyl ester **103.**. The ^{1}H NMR spectra from the methyl ester **103** concurred with the spectra from the methyl ester **103** prepared by the other route.

With these materials in hand, the enantioselective reduction of the carbonyl group was studied using three chiral reagents. The chiral reducing agents chosen were Corey's (s)-oxazaborolidine reagent, modified Corey's (s)-oxazaborolidine reagent and (-)-Dip Cl.

Corey *et al.*[39] first reported, in 1987, a highly enantioselective reduction of ketones using borane and a catalytic amount of chiral oxazaborolidine reagent. Synthesis of the catalyst was carried out by heating at reflux (*S*)-(-)-2-diphenylhydroxymethylpyrrolidine with 3 equivalents of BH_3-THF under an atmosphere of Ar-BH_3. Removal of the solvent and sublimation resulted in the pure compound. Subsequently, Boron-methyl and Boron-*n*-butyl derivatives were prepared, by substitution of methylboronic acid and *n*-butylboronic acid for borane in the synthetic pathway, so as to make the compounds less sensitive to air and moisture. These catalysts do not reduce double bonds and amide functionalities, as occurs with borane. The catalysts are more reactive and so can be used at lower temperatures which was found to improve the stereoselectivity in reduction reactions. This increased the scope of these reagents for synthesis to α-hydroxy acids and α-amino acids.

The preparation of the N-methyl derivative of chiral oxazaborolidine **105** (Corey's reagent) was attempted as outlined in the literature.[39] Unfortunately the ^{11}B NMR and ^{1}H NMR spectrum were different from those reported. An alternative method has also been

reported[43] for the preparation of the reagent **105** and this was attempted. (*S*)-(-)-(Diphenylhydroxymethyl)pyrrolidine was treated with trimethylboroxine in toluene. Excess methylboronic acid was removed by distillation of toluene as an azeotropic mixture. The ketones **91** and **98** were dried by distillation of benzene and then treated independently with borane in THF and a catalytic amount of Corey's reagent. The benzoyl alcohol **92** was isolated in 52% yield while the hydrocinnamoyl alcohol **99** was isolated in 85% yield.

A small portion of each alcohol was converted to Mosher's ester[60] and the enantiomeric excess for the respective compounds (**92** and **99**) was 87% and 45% as determined by ^{19}F NMR

A further improvement in the chiral reducing agent was made by Mathre *et al.*[40,43] when a stable, free-flowing crystalline form of a borane complex was prepared. In Corey's initial papers, this reagent was only identified as an important intermediate responsible for the enantioselective reduction of ketones. However, Mathre *et al.* were able to isolate the intermediate, obtain a single-crystal X-ray structure and prepare it on a large-scale. The reagent is reported to be stable for over 3 years at room temperature when stored under nitrogen. It was found that two of the three hydrides were effectively transferred during the reaction and that the enantioselectivity was highest for the transfer of the first hydride.

The literature procedure involved treatment of (S)-(-)-diphenylhydroxymethyl)pyrrolidine in dry toluene with trimethylboroxine at 21°C. Excess methylboronic acid was removed by repeated washing with toluene as an azeotropic mixture by distillation. BMS complex was added to the mixture at 20°C and stirred for 0.5 hours. On addition of dry hexane a white precipitate formed. The suspension was cooled to -10°C and stirred for 2 hours. Removal of the solvent left a white fluffy material. The ketone **91** and the

modified Corey's reagent **108** were dried by distillation of toluene as an azeotropic mixture. A stoichiometric amount of the reducing agent **108** was dissolved in dry dichloromethane and cooled to -20°C. The ketone **91** was dissolved in dry dichloromethane and added by syringe pump, over 1 hour, maintaining the temperature at -20°C. After 4 hours the reaction was quenched with chilled methanol (-20°C) and purified. The spectral data was in agreement with the data obtained for the racemic alcohol **92** however the enantiomeric excess was only 43.5% by ^{19}F NMR. The ketone **98** was treated in the same manner except 2 eq. of the chiral reagent **108** was used. Unfortunately the enantiomeric excess was a disappointing 2.5% by ^{19}F NMR for alcohol **99**.

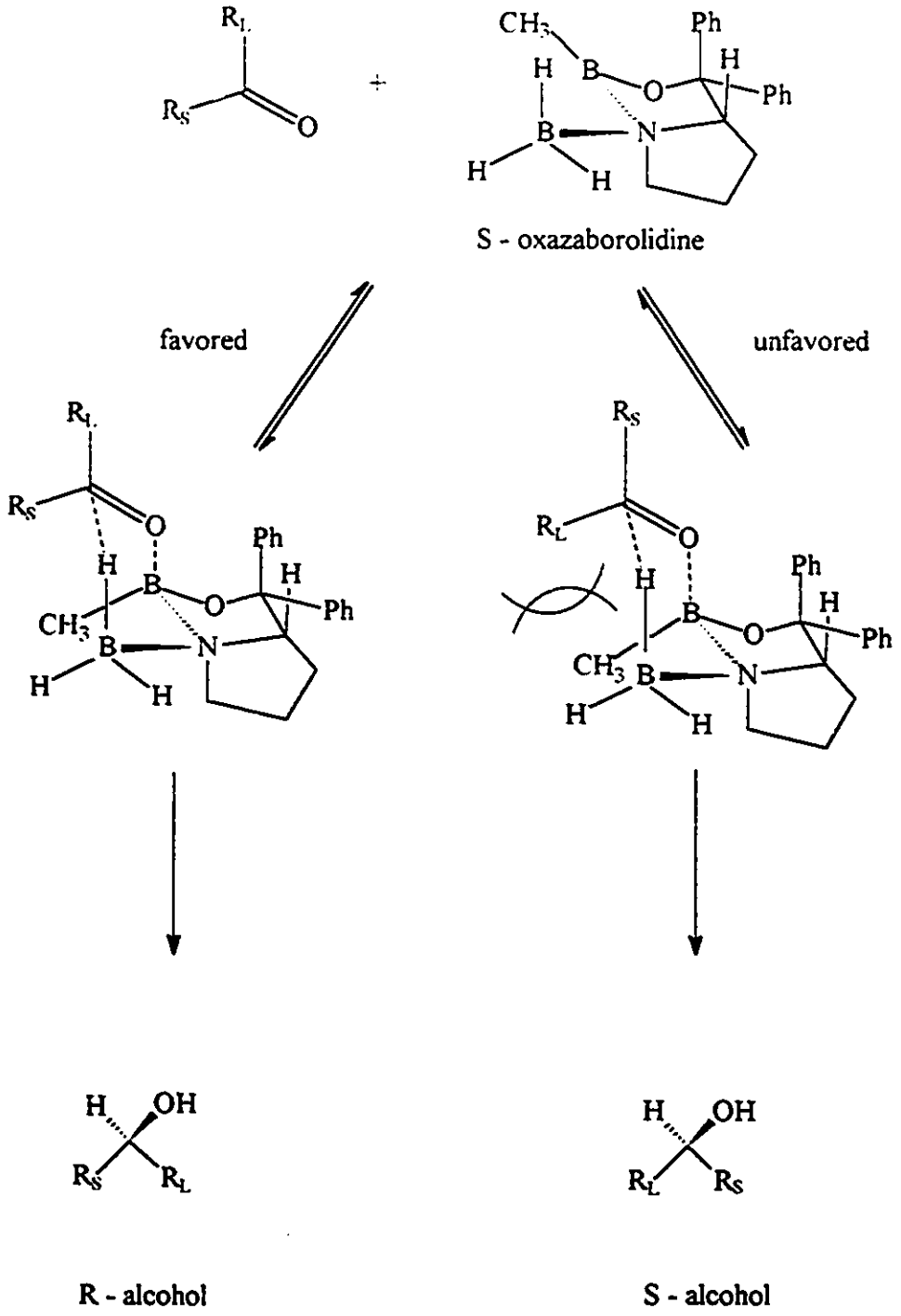


Figure 2.1 (S)-Oxazaborolidine Chair Transition State[40]

From the above model, it would be expected that the S-isomer of both of the oxazaborolidine chiral reducing agents would produce the R-alcohol for both model systems. These results concure with those reported by DeNinno *et al.*[59] using Corey's reagent and similar dithiane systems. The differences seen in the enantioselective reduction between the two model systems was also reported by DeNinno's group when an ethyl group was substituted for a methyl group.

Brown and his group have synthesized many boron reagents over the years using α-pinene as the chiral auxiliary. Dip-Cl has gained popularity in the asymmetric reduction of ketones. It is commercially available in both enantiometric forms and even though sensitive to oxygen and moisture, it has a shelf-life of several years when stored under an inert atmosphere below 25°C. The reagent was originally tested on unhindered aliphatic ketones with disappointing results.[41] However when both aliphatic and cyclic hindered ketones were used high enantioselectivities were obtained.

Recent publications[1,2,44] described the use of Dip-Cl as a chiral reducing agent in a sterically crowded environment. Thus, it was decided to study this reagent. The ketone **91** was dissolved in dry THF and treated with 2.2 eq. of Dip-Cl in THF under an atmosphere of dry nitrogen at 21°C for 14 days. The yield from the reaction was only 25%. The experiment was repeated however this time the solid reagents were combined neat . After several hours the mixture began to liquefy and the reaction was allowed to proceed for 14 days at 21°C. The mixture was then placed on a high vacuum to remove the α-pinene. The oily material was diluted with ether, 2.2 eq. of diethanolamine was added and stirred for 1 hour at 21°C. The precipitate was removed by filtration and washed with *n*-pentane. The benzyl alcohol **92** was isolated in 41% yield with an enantiomeric excess of 55.1%. The ketone **98** was treated under

the same neat conditions. After work-up and purification, the alcohol 99 was isolated in 90% yield with an enantiomeric excess of 86.5% by ^{19}F NMR.

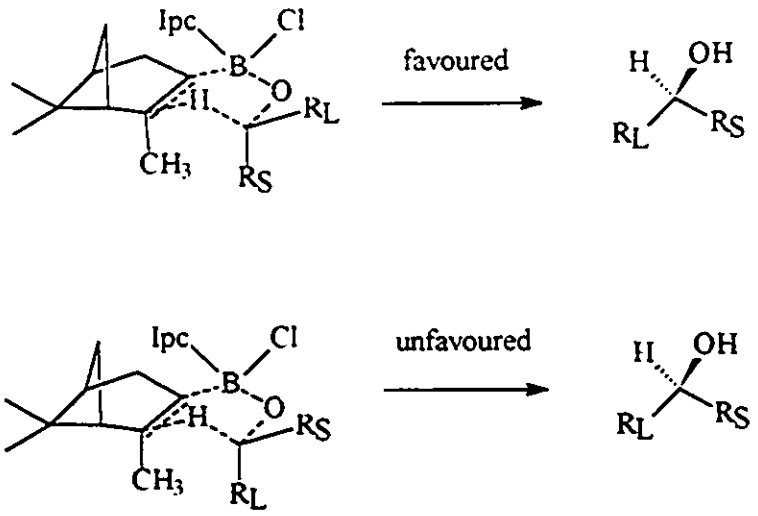


Figure 2.2 (-)-Dip Cl Boat Transition State[44]

The above figure illustrates the boat transistion state for the enantioselective reduction of the carbonyl groups using Dip Cl. The (R)-(-)-isomer of Dip Cl would be expected to produce the S-alcohol using the above model.

The results from the enantioselective reduction of the two model systems using the three different chiral reducing agents is summarized in Table 2.1.

Table 2.1 Summary of Enantioselective Reduction.

	% Enantiomeric Excess	
Chiral Reducing Agent	**Benzoyl-1,3-Dithiane (91)**	**Hydrocinnamoyl-1,3- Dithiane (98)**
(S)-oxazaborolidine	87.2	45.2
Modified (S)-oxazaborolidine	43.5	2.5
(-)-Dip Cl	55.1	86.5

To prepare a silyl ether with a more stable O-protecting group for the direct oxidation of the aldehyde to the methyl ester, *t*-butyldiphenylsilyl was substituted for the *t*-butyldimethylsilyl group however it was not possible to hydrolysis the dithiane with the *t*-butyldiphenylsilyl group in place.

Authentic material of both methyl esters was synthesized by different routes. (±)-Mandelic acid was protected as the silyl ether on treatment with *t*-butyldimethylsilyl chloride. The carboxylic acid **96** was dissolved in ether and treated with freshly prepared diazomethane to afford the authentic methyl ester **96.** The methyl ester **96** displayed a singlet at 3.57 ppm in the ^{1}H NMR spectrum characteristic of the methoxy group, a signal at 173.2 ppm in the ^{13}C NMR and 1749 cm^{-1} in the IR spectra for the carbonyl group and singlets at 0.94, 0.13 and - 0.04 ppm in the ^{1}H NMR spectra characteristic of the *t*-butyl and methyl groups on the O-protecting group.

The authentic material for the methyl ester **103** was also prepared. 3-L-Phenyllactic acid was dissolved in dichloromethane and treated with *t*-butyldimethylsilyl chloride at 21°C to afford carboxylic acid **102.** The resultant carboxylic acid was dissolved in ether and treated

with freshly prepared diazomethane to afford the corresponding methyl ester **103.**. Methyl ester **103** displayed a characteristic singlet at 3.66 ppm in the ^{1}H NMR for the methoxy group, a signal at 173.2 ppm in the ^{13}C NMR and 1747 cm^{-1} in the IR spectra for the carbonyl group and singlets at 0.78, - 0.13 and - 0.24 ppm in the ^{1}H NMR spectra representative of the *t*-butyl and two methyl groups on the O-protecting group. Spectra from this authentic compound concurred with the spectra from the methyl esters **103** prepared by the two studied methods.

Development of a HPLC system using several chiral columns to measure the enantiomeric purity of several compounds was attempted However none of the columns tested or solvent systems tried resulted in baseline resolution. The alcohols **92** and **99** were tested on all three types of chiral columns using solvent systems varying in composition from 50:50 to 0:100 for methanol/hexane and isopropyl alcohol/hexane mixtures. Mosher esters of the alcohols **92** and **99** were tested on the (R)-naphthyl urea using the above combinations of mobile phase and these showed the best results using a mobile phase of 2.98 methanol/hexane at 1 mL/minute. 3,5-Dinitrobenzoyl and camphor sulfonate derivatives were synthesized for the hydrocinnamoyl compound. These derivatives were tested on the (R)-naphthyl urea and 3,5-dinitrobenzoyl glycine propylsilyl column using the above combinations of mobile phase however baseline resolution was not achieved.

3 Conclusion

Of the acyl equivalents studied, 1,3-dithiane was the most advantageous. Both tris(methylthio)methane and tris(phenylthio)methane proved difficult to create the anion and the resulting products were not stable enough for further testing. 1,3-Dithiane afforded a stable anion using a literature procedure and the resulting products **91** and **98** were crystalline and proved to be very stable.

As a result of our investigations into the enantioselective reduction of the carbonyl group in the benzoyl-1,3-dithiane and hydrocinnamoyl-1,3-dithiane models, several points were determined. Corey's reagent **105** reduced the benzoyl derivative **91** more selectively than the hydrocinnamoyl derivative **98** (87% vs 45%) however the isolated yield was better for the hydrocinnamoyl derivative than the benzoyl derivative (85% vs 52%). Studies using the modified Corey's reagent **108** as the reducing agent indicated that the benzoyl derivative **91** was again reduced in the more selective manner. Comparison of the enantiomeric excess for the two models systems indicated benzoyl compound **91** to be more selectively reduced than hydrocinnamoyl derivative **98** (45% vs 2.5%). When Dip-Cl was used as the reducing agent for the asymmetric reduction of both of the ketones **91** and **98**, hydrocinnamoyl derivative **98** was reduced more selectively (86.5% vs 55.1%) and with a better isolated yield (90% vs 41%) than benzoyl derivative **91**.

The unmasking of the aldehyde **101** and conversion to the stable methyl ester **103** was completed, for hydrocinnamoyl-1,3-dithiane **100**, by two different routes. Hydrolysis of the dithiane was finally accomplished using a mercuric (II) chloride and cadmium carbonate system. Aldehyde **101** was directly oxidized on treatment with bromine/sodium

bicarbonate/methanol to afford the methyl ester **103** in very low yield. The longer route of oxidization of the aldehyde **101** to the corresponding acid **102** with silver oxide and then esterification to the methyl ester **103** using diazomethane was also followed. However the yield from this pathway was also low.

4 Experimental

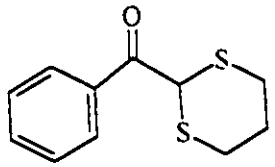
4.1 General

Melting points were obtained in capillary tubes using a Thomas-Hoover Unit melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained using a Bomem MB 100 FTIR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured at either 200 MHz with a Varian Gemini spectrometer or at 500 MHz with a Bruker AMX500 spectrometer in the stated solvent. Carbon magnetic resonance spectra (^{13}C NMR) were measured at either 50 MHz on a Varian Gemini spectrometer or at 125 MHz with a Bruker AMX500 spectrometer, with an internal reference ($CDCl_3$, δ 7.24 ppm; ^{13}C: δ 77.0 ppm). Fluorine magnetic resonance spectra (F^{19} NMR) were measured at 282 MHz with a Varian XL-300 spectrometer using an external reference of trifluoroacetic acid, δ 0.00. All chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. The signal multiplicity are indicated by (s=singlet, d=doublet, t=triplet, q=quartet, br=broad) and coupling constants and number of protons are indicated in parentheses. A V.G. micromass 7070 HS instrument at an ionization energy of 70 eV or chemical ionization (CI) was used to determine mass spectra (MS). Elemental analyses were conducted by either M-H-W Laboratories, Phoenix, Az, USA or in-house using a Perkin-Elmer 2400 Series II Analyzer. The HPLC system consisted of a Varian (Model 9012) pump, a Varian (Model 9050) UV detector set at 254 nm and 20 μL sample loop. The guard and analytical columns used were a 250 x 4.6 mm Chiralcel OB, 250 x 4.6 mm, a 5 micron Supelcosil LC-(R)-naphthyl urea and a 250 x 4.6 mm, 5 micron (R)-3,5-dinitrobenzoyl phenyl glycine propylsilyl. Composition of the mobile

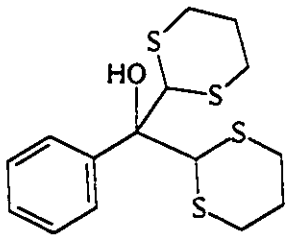
phase used with each column is outlined in the discussion. Commercial aluminum sheets coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck) were used for analytical thin layer chromatography (TLC). Silica gel (E. Merck, 70-230 or 230-400 mesh) was used for all column chromatography.

Petroleum ether was a hydrocarbon fraction with a boiling range 30-60^{0}C. Anhydrous tetrahydrofuran was distilled from potassium/benzophenone while anhydrous dichloromethane was dried over calcium hydride. Anhydrous magnesium sulfate was used to dry solutions in organic solvents. A Buchi rotatory evaporator connected to a water aspirator was used to remove solvents. Unless otherwise stated, all starting materials were purchased from Aldrich Chemical Company.

Preparation of 1-Phenyl-2-(1,3-dithiacyclohexyl)ethanone (91)



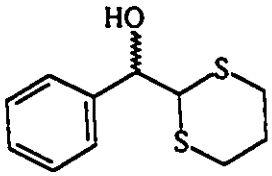
1,3-dithaine (1.0 g, 8.3 mmol) was dissolve in dry tetrahydrofuran (100 mL), cooled to -78°C, and *n*-BuLi (3.3 mL of a 2.5 M in hexanes, 8.3 mmol) was added. After 20 minutes, the solution containing the anion was added *via* a cannula, using a stream of dry nitrogen over 15 minutes, into a solution of the benzoyl chloride **90** (0.6 g, 4.3 mmol) in dry tetrahydrofuran (50 mL). After 2 hours, work-up consisted of the addition of saturated aqueous solution of ammonium chloride, and dilution with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography, (1:9 ethyl acetate/petroleum ether) yielded 0.79 g (61%) of ketone **91** as a white crystalline solid; mp 98-99°C; IR ($CHCl_3$, cm^{-1}) 2922, 1679, 1448, 731; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.59-7.40 (m, 3H), 5.1 (s, 1H), 3.4-3.3 (m, 2H), 2.7-2.6 (m, 2H), 2.2-2.0 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.6, 134.6, 133.4, 128.7 42.7, 29.9, 26.6, 25.2; HRMS calcd for $C_{11}H_{12}OS_2$ (M^+): 224.0330. found 224.0328; Anal. Calcd for $C_{11}H_{12}OS_2$: C, 58.89; H, 5.39. Found: C, 58.98; H, 5.42.



By-Product (104)

The major by-product ,alcohol **104**, was also isolated and characterized as follows; mp 162-163^{0}C; IR ($CHCl_3$, cm^{-1}) 3498, 3092, 2916, 1274, 1066, 727; ^1H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, J = 5.6 Hz, 2H), 7.42-7.34 (m, 3H), 4.86 (s, 2H), 3.50 (s, 1H), 2.88-2.68 (m, 8H), 2.03-1.75 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.7, 128.3, 127.8, 126.6, 81.9, 55.2, 30.2, 29.5, 25.3 ppm.

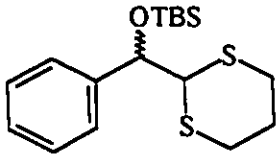
Preparation of (±)-l-Phenyl-2-(1,3-dithiacyclohexyl)ethanol (92)



To a solution of the ketone **91** (752.1 mg, 3.33 mmol) in ethanol (10 mL) was added sodium borohydride (63 mg, 6.66 mmol). The resultant solution was stirred at 21^{0}C for 3 hours. The mixture was then acidified to pH ≈ 6.0 with 10% HCl, quenched with water and extracted with ethyl acetate. On concentration of the dried organic

extract, purification by column chromatography, (1:9 ethyl acetate/petroleum ether) yielded 639.7 mg (85%) of the alcohol **92** as a white crystalline solid, m.p. 74-78°C (Lit.71.3-72.1°C); IR (ethyl acetate, cm^{-1}) 3425, 3029, 2915, 1452, 1421, 1253; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44-7.30 (m, 5H), 4.90 (d, J = 7.4 Hz, 1H), 4.06 (d, J = 7.6 Hz, 1H), 2.99-2.86 (m, 2H), 2.95 (s, 1H), 2.76-2.64 (m, 2H), 2.08-1.94 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7, 129.1, 128.9, 127.4, 75.3, 53.4, 28.8, 28.2, 26.0 ppm; HRMS calcd for $C_{11}H_{13}S_2$ (M^+-OH):209.0459, found 209.0417; MS (CI) calcd for $C_{11}H_{13}S_2$ (M^+ - OH) 209.0, found: 208.9 (100%); Anal. Calcd. for $C_{11}H_{14}OS_2$: C, 58.39; H, 6.24. Found: C, 58.57; H, 6.14.

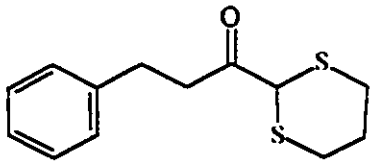
Preparation of (±)-1-*t*-Butyldimethylsilyloxy-1-Phenyl-2-(1,3-dithiacyclohexyl)ethane (93)



The alcohol **92** (400 mg, 1.77 mmol) was dissolved in dry dichloromethane (20 mL) and flushed with dry nitrogen. 2,4,6-Collidine (1.1 mL, 5 eq) and *t*-butyldimethylsilyl trifluoromethanesulfonate (2.3 mL, 5 eq) were added sequentially and the solution was stirred at 21°C for 4 days . The reaction was quenched with water followed by saturated aqueous solution of sodium bicarbonate. The aqueous phase was

extracted with dichloromethane (3 x 50 mL),washed with brine, dried over magnesium sulphate and concentrated. Purification by column chromatography, (1:9 ethyl acetate/petroleum ether) afforded 540 mg (90%) of compound **93** as a white crystalline solid, mp 54-59^{0}C; IR (ethyl acetate, cm^{-1}) 3063, 3030, 2940, 1253, 1093, 774; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 4.72 (d, J = 7.2 Hz, 1H), 4.26 (d, J = 7.0 Hz, 1H), 2.84-2.69 (m, 4H) 2.10-1.99 (m, 2H), 0.86 (s, 9H), 0.08 (s, 3H), -0.17 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.5, 128.0, 127.9, 126.8, 76.4, 55.1, 30.1, 29.7, 25.8, 25.7, 18.2, -4.7, -5.1 ppm; MS(CI) calcd for $C_{11}H_{13}S_2$: (M^+-C_4H_9) 209.1. found: 208.9(100%); Anal. Calcd for $C_{17}H_{28}OS_2Si$: C, 59.95; H, 8.29; Found: C, 59.95; H, 8.30.

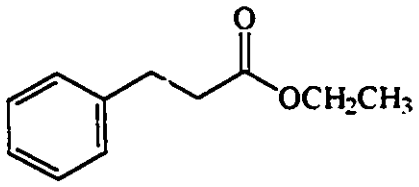
Preparation of 4-Phenyl-1-(1,3-dithiacyclohexyl)butan-2-one (98)



Hydrocinnamic acid (3 g, 20 mmol) was dissolved in dry tetrahydrofuran (20 mL) and purged with dry nitrogen. Oxalyl chloride (1.9 mL, 22 mmol) was added slowly and the resultant solution was heated at reflux for 3 hours under a nitrogen atmosphere to afford acid **97**. The acid chloride solution was then cooled to -78^{0}C. In another dry round bottom flask, (100 mL), 1,3-dithiane (2.4 g, 0.02 mol) was dissolved in dry tetrahydrofuran (20 mL) flushed with dry nitrogen and cooled to -78^{0}C. *n*-BuLi (8.8 mL,

20 mmol) was added slowly over 5 minutes. After 15 minutes, the resultant solution was added *via* a cannula to the freshly prepared acid chloride **97** using a stream of dry nitrogen. After 3 hours, the reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate, partitioned between ethyl acetate (3 x 100 mL) and dried over magnesium sulphate. Following concentration and purification by column chromatography, (1:9 ethyl acetate/petroleum ether), 2.75 g (54%) of the title compound was isolated as a white crystalline solid: mp 80-82^{0}C; IR ($CHCl_3$, cm^{-1}) 3064, 3028, 2944, 1732, 1242; ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.31-7.16 (m, 5H), 4.13 (s, 1H), 3.24-3.11 (m, 2H), 2.97-2.93 (m, 4H), 2.59-2.48 (m, 2H), 2.07-1.93 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 201.8, 140.6, 128.5, 128.3, 126.2, 47.0, 41.6, 30.2, 26.2, 25.2 ppm; HRMS calcd for $C_{13}H_{16}OS_2$ (M^+): 252.0643, found 252.0638; Anal. Calcd for $C_{13}H_{16}OS_2$: C, 61.86; H, 6.39. Found C, 62.02; H, 6.55.

Preparation of Ethyl 4-phenyl-butanoate (97)



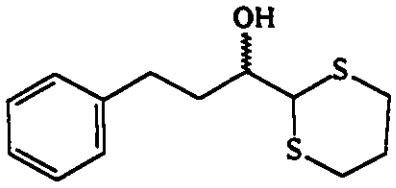
Hydrocinnamic acid (5g, 33 mmol) was dissolved in ethanol 99% (20 mL). Concentrated sulphuric acid (3 drops) was added and the mixture was heated to reflux for 3 hours. The reaction mixture was washed with saturated aqueous solution of sodium

bicarbonate and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine, dried over magnesium sulphate and concentrated to yield a colorless oil. Purification by column chromatography, (1:9 ethyl acetate/petroleum ether) afforded 5.4 g (92%) of the title compound as a clear colorless oil; IR (neat, cm^{-1}) 3065, 3029, 2982, 2935, 1735, 1242; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 4.11 (q, J_1 = 15.8 Hz, J_2 = 7.2 Hz, 3H), 2.95 (t, J = 15.4 Hz, J_2 = 7.4 Hz, 2H), 2.61 (t, J_1 = 15.8 Hz, J_2 =7.8 Hz 2H), 1.23 (t, J_1 = 14.2 Hz, J_2 = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 140.1, 127.8, 127.7, 125.6, 59.5, 35.2, 30.3, 13.5 ppm; HRMS calcd for $C_{11}H_{14}O_2$(M^+); 178.09938, found 178.09869.

The structure was confirmed by comparison with an authentic sample from Aldrich Chemical Company.

Compound **98** was prepared as above using ethyl hydrocinnamoate as the starting material.

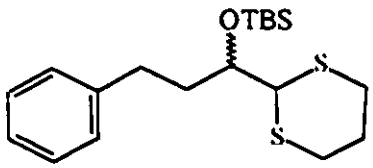
Preparation of (±)-4-Phenyl-1-(1,3-dithiacyclohexyl)butan-2-ol (99)



The ketone **98** (5 g, 19.8 mmol) was dissolved in ethanol (40 mL). To the cooled solution (0°) an excess of sodium borohydride was added and stirred for 3 hours. Work-

up consisted of adjustment the pH ≈ 6 with 10% hydrochloric acid and extraction with chloroform (3 x 100 mL). The organic layer was washed with brine and dried over magnesium sulfate. Concentration and purification by column chromatography, (1:4 acetone/petroleum ether) yielded 4.1 g (82%) of alcohol **99**, mp 39-40°C, IR ($CDCl_3$, cm^{-1}) 3436, 3026, 2919, 1422, 1276, ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 3.87 (s,1H), 2.89-2.81 (m, 2H), 2.73-2.68 (m, 4H), 2.57 (s,1H), 2.19-2.15 (m, 2H), 2.07-2.00 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 128.5, 128.4, 125.9, 71.3, 52.3, 35.7, 32.0, 28.2, 27.8, 25.7 ppm. MS (CI) calcd for $C_{13}H_{18}OS_2$: 254.1; found: 254.0 (39.8%), 237.0 (21.1%), 149.0 (52.4%) 118.9 (100.0%), 107.0 (100.0%). Anal. Calcd. for $C_{13}H_{18}OS_2$: C, 61.40; H 7.14; Found: C, 61.78; H, 6.83.

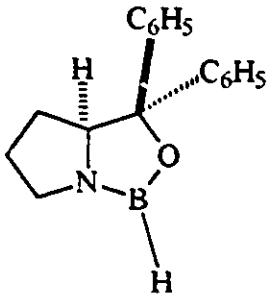
Preparation of (±)-2-*t*-Butyldimethylsilyloxy-4-phenyl-1-(1,3-dithiacyclohexyl)butane (100)



The alcohol **99** (0.5 g, 1.96 mmol) was dissolved in dry dichloromethane (30 mL) and treated with imidazole (0.160 g, 2.35 mmol), DMAP(catalytic) and *t*-butyldimethylsilyl chloride (0.353 g, 2.35 mmol). for 7 days at 21°C. The reaction was then quenched with water and diluted with ethyl acetate, (3 x 50 mL). The organic layer

was washed with brine and dried over magnesium sulphate Concentration and purification by column chromatography, (1 9 ethyl acetate/petroleum ether) gave 0.678 g (94%) of the desired product, mp 59-62^{0}C, IR($CDCl_3$, cm^{-1}) 3028, 2944, 2857, 1468, 1065, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.18 (m,5H), 4.25 (d, J = 5.2 Hz, 1H), 3.98-3 90 (q, J_1 = 16.0 Hz, J_2 = 5.4 Hz, 1H), 2.91-2.86 (m, 4H), 2.80-2.63 (m, 2H), 2.14-1 87 (m, 4H) 0.98 (s, 9H), 0.18-0.13 (d, J = 9.4 Hz, 6H) ppm; ^{13}C NMR (50MHz, $CDCl_3$); 142.0, 128.4, 128.3, 125.8, 74.4, 54.2, 36.3, 31.2, 30.5 30.4, 26.3, 25.9, 25.7, 18 2, -4.4. HRMS calcd for $C_{19}H_{23}OS_2$ (M^{+} -C_4H_9): 311.0960. found 311.0932; MS(CI) calcd for $C_{15}H_{23}OS_2$(M^{+}- C_4H_9) 311.1, found: 310.9 (33.0%), 249.0 (48%) 131.0 (100.0%). Anal. Calcd for $C_{19}H_{32}OS_2Si$: C, 61.90; H, 8.75. Found: C, 61.76; H, 8.84.

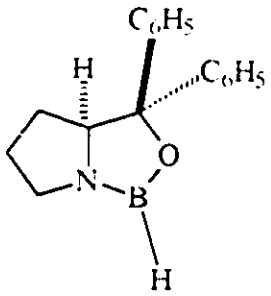
Attempted Preparation of (S)-Corey's Reagent [39](105)



(*S*)-(-)-2-(Diphenylhydroxymethyl)pyrrolidine (100 mg, 0.4 mmol) was dissolved in dry toluene (20 mL) and methylboronic acid (45 mg, 0.75 mmol) was added and the

resultant solution was heated to reflux for 5 hours in Dean-Stark apparatus The volume was reduced to 5 mL and 4 A molecular sieves were added

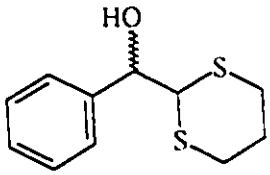
Alternative Synthesis of (S)-Corey's Reagent [43] (105)



Dry toluene (10 mL) was added to (*S*)-(-)-2-(diphenylhydroxymethyl)pyrrolidine (100 mg, 0.4 mmol) and purged with dry nitrogen. Trimethylboroxine (37 µL, 0.67 Eq) was added slowly over 2 minutes and the mixture was stirred at 21°C for 30 minutes. Toluene and methylboronic acid (as trimethylboroxine) were removed by distillation as an azeotropic mixture. Toluene washes (3 x 10 mL) were added and distillation was continued to completely remove the water and any excess methylboronic acid. Solvent was removed and unpurified reagent **105** was stored for future use under nitrogen at -20°C.

Preparation of (R*)-l-Phenyl-2-(1,3-dithiacyclohexyl)ethanol (92)

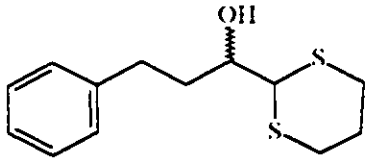
Using (S)-Corey's Reagent



The ketone **91** (600 mg, 2.68 mmol) was dried by preparing azeotropic mixtures with benzene (3 x 20 mL). Dry tetrahydrofuran (20 mL) and Corey's Reagent (0.05 Eq) was added and stirred for 0.5 hours under an atmosphere of nitrogen. Borane in tetrahydrofuran (1.2 Eq) was added and the mixture was stirred for 3 hours at 21^{0}C. Work-up included addition of methanol (20 mL), solvent removal, addition twice more with methanol and extraction with ether. The organic layer was washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography (3:7 ether/ petroleum ether) resulted in 313 mg (52%) of alcohol **92** as a white crystalline solid. ee = 87.2% ,mp = 68-70°C; IR (ethyl acetate, cm^{-1}) 3425, 3029, 2915, 1452, 1421, 1253; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.30 (m, 5H), 4.90 (d, J = 7.4 Hz, 1H), 4.06 (d, J = 7.6 Hz, 1H), 2.99-2.86 (m, 2H), 2.95 (s, 1H), 2.76-2.64 (m, 2H), 2.08-1.94 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7, 129.1, 128.9, 127.4, 75.3, 53.4, 28.8, 28.2, 26.0 ppm.

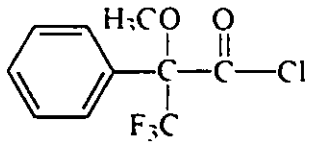
Preparation of (R*)-4-Phenyl-1-(1,3-dithiacyclohexyl)butan-2-ol (99)

Using (S)-Corey's Reagent



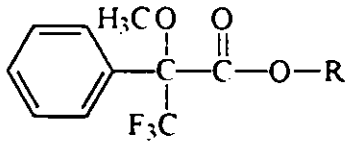
The ketone **98** (510 mg, 2.01 mmol) was dried by distillation as an azeotropic mixture with toluene (3 x 20 mL). Corey's Reagent **105** (0.05 eq) was dissolved in dry tetrahydrofuran (20 mL) and transferred by syringe to a round bottom flask (50 mL) containing the ketone **98** and stirred at 21°C for 0.5 hours. Borane in tetrahydrofuran (1.2 eq) was then added and the reaction was followed by TLC for 3 hours to completion. Work up consisted of addition of methanol (10 mL), solvent removal, addition twice more of methanol, solvent removal and extraction with ether. The organic layer was washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography (3:7 ether/ petroleum ether) yielded 439 mg (85.3%) of alcohol **99** as a white crystalline material. ee = 45.2%; mp = 37-39°C; IR ($CDCl_3$, cm^{-1}) 3436, 3026, 2919, 1422, 1276, ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 3.87 (s,1H), 2.89-2.81 (m, 2H), 2.73-2.68 (m, 4H), 2.57 (s,1H), 2.19-2.15 (m, 2H), 2.07-2.00 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 128.5, 128.4, 125.9, 71.3, 52.3, 35.7, 32.0, 28.2, 27.8, 25.7 ppm.

Preparation of R-(+)-Mosher's Acid Chloride[69] (106)



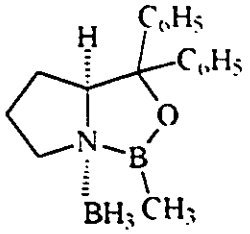
(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid was converted to the acid chloride on addition of thionyl chloride (3 mL per 250 mg of acid) and a trace of sodium chloride. The mixture was heated to reflux for 50 hours. The excess thionyl chloride was removed under low vacuum and the solution was purified by distillation using a Kuhelrohr distillation apparatus (≅ 100°C at 2 mm Hg) to give the title compound. IR (neat, cm $^{-1}$) 3069, 2990, 2953, 2852, 1786.

General Procedure for Preparation of R-(+)-Mosher's Ester[60] (107)



The alcohol was dissolved in dry dichloromethane (2 mL), DMAP (1 eq) was added and the flask was purged with dry nitrogen. Triethylamine (1 eq) and MTPA **106** were then added. The mixture was stirred for 1.5 hours at 21°C or until complete. The reaction was quenched with distiiled water, saturated aqueous solution of ammonium chloride and diluted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography (1:9 ethyl acetate/ petroleum ether) yielded the desired esters. ^{19}F NMR was then used to determine enantiomeric excess of the alcohols.

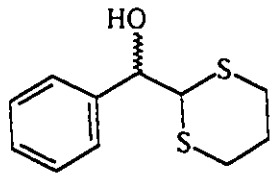
Preparation of (S)-Oxazaborolidine-Borane Complex [40] (108)



(*S*)-(-)-2-(Diphenylhydroxymethyl)pyrrolidine (885.4 mg, 3.5 mmol) was dissolved in dry toluene (30 mL) and flushed with dry nitrogen. Trimethylboroxine (0.8 eq) was added and the mixture stirred at 21°C for 0.5 hours. The flask was then fitted with a distillation apparatus and the volume was reduced to approximately 5 mL. Toluene flushes (3 x 30 mL) were then added and the distillation repeated. The solution was cooled to 21°C, borane-dimethyl sulfide (1.2 Eq) was added and the mixture was stirred for 0.5 hours. A white precipitate formed on addition of dry hexane (20 mL). The suspension was cooled to -10°C and stirred for 2 hours at which point TLC (3:7 acetone/ petroleum ether) showed one spot. Solvent was removed under high vacuum (0.2 mm) to leave a fluffy white solid which gave satisfactory spectral data.

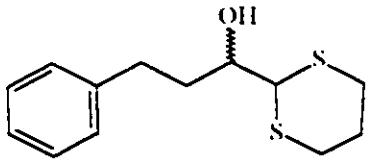
Preparation of (R*)-l-Phenyl-2-(1.3-dithiacyclohexyl)ethanol (92)

using (S)-Oxazaborolidine-Borane Complex



The ketone **91** (224 mg, 1 mmol) and the oxazaborolidine-borane complex **108** (160 mg, 0.89 mmol) were dried separately by distillation with dry toluene (3 x 20 mL). The oxazaborolidine-borane complex **108** was dissolved in dry dichloromethane (10 mL), flushed with dry nitrogen and cooled to -20^0 C in a saturated aqueous calcium chloride/dry ice bath. The ketone **91** was then dissolved in dry dichloromethane (10 mL) and added by syringe pump over 1 hour maintaining the temperature at -20^0 C. The reaction was followed by TLC for 4 hours then quenched by addition of chilled (-20°C) methanol. The solution was warmed to 21^{0}C, the solvent was removed and then washed twice more with methanol (2 x 10 mL) and concentrated. The oil was diluted in ether, washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography afforded alcohol **92** as a white crystalline solid. ee = 43.5%; IR (ethyl acetate, cm^{-1}) 3425, 3029, 2915, 1452, 1421, 1253; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.30 (m, 5H), 4.90 (d, J = 7.4 Hz, 1H), 4.06 (d, J = 7.6 Hz, 1H), 2.99-2.86 (m, 2H), 2.95 (s, 1H), 2.76-2.64 (m, 2H), 2.08-1.94 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7, 129.1, 128.9, 127.4, 75.3, 53.4, 28.8, 28.2, 26.0 ppm.

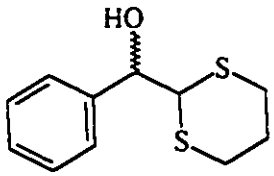
Preparation of (R*)-4-Phenyl-1-(1,3-dithiacyclohexyl)butan-2-ol (99) using (S)-Oxazaborolidine-Borane Complex (99)



The ketone **98** (325 mg, 1.28 mmol) and the oxazaborolidine-borane complex **108** (480 mg, 2.7 mmol) were dried separately by distillation as an azeotropic mixtures with dry benzene (3 x 20 mL). Oxazaborolidine-borane complex **108** was dissolved in dry dichloromethane (10 mL), flushed with dry nitrogen and cooled to -20^{0}C in a calcium chloride/dry ice bath. The ketone **98** was then dissolved in dry dichloromethane (10 mL) and added by syringe pump over 1 hour maintaining the temperature at -20^{0}C. The resultant mixture was stirred for 48 hours after which the reaction was quenched by addition of chilled methanol (-20^0 C). The solution was warmed to 21^{0}C, the methanol was removed and washed twice more with methanol (2 x 10 mL) and concentrated. The oil was diluted in ether (30 mL), washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography (3:7 ether/petroleum ether) resulted in 196 mg (59.8%) of alcohol **99** as a white crystalline solid. ee = 2.5%; mp = 36-39°C; IR ($CDCl_3$, cm^{-1}) 3436, 3026, 2919, 1422, 1276, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 3.87 (s,1H), 2.89-2.81 (m, 2H), 2.73-2.68 (m, 4H), 2.57 (s,1H), 2.19-

2.15 (m, 2H), 2.07-2.00 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 128.5, 128.4, 125.9, 71.3, 52.3, 35 7, 32 0, 28.2, 27.8, 25.7 ppm.

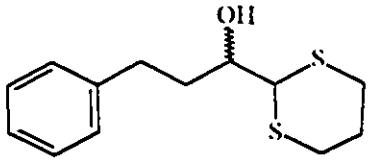
Preparation of of (S*)-l-Phenyl-2-(1,3-dithiacyclohexyl)ethanol (92) using (-)-Dissopinocampheylchloroborane (DIP-Chloride)



The ketone **91** (848 mg, 3.79 mmol) was treated with (-)-Dip-Cl (2.7 g, 2.2 eq) under an inert atmosphere. The mixture was stirred (neat) at 21^{0}C for 14 days. The oil was placed under a high vacuum (0.2 mm of Hg) for 2 hours, and then diluted with ether (50 mL). Diethanolamine (2.2 eq) was added and the solution was stirred for 1 hour at 21^{0}C. The resultant precipitate was removed by filtration, washed with *n*-pentane and the filtrate was concentrated. Purification by column chromatography (3:7 ether/petroleum ether) yielded 346 mg (40.5%) of alcohol **92** as a white crystalline solid; ee = 55.1%, $[\alpha]_D^{21}$= -18.2^0, (c 0.0178, $CHCl_3$); IR (ethyl acetate, cm^{-1}) 3425, 3029, 2915, 1452, 1421, 1253; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.30 (m, 5H), 4.90 (d, J = 7.4 Hz, 1H), 4.06 (d, J = 7.6 Hz, 1H), 2.99-2.86 (m, 2H), 2.95 (s, 1H), 2.76-2.64 (m, 2H), 2.08-1.94 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7, 129.1, 128.9, 127.4, 75.3, 53.4, 28.8, 28.2, 26.0 ppm.

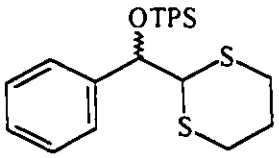
Preparation of (S*)-4-Phenyl-1-(1,3-dithiacyclohexyl)butan-2-ol (99)

using (-)-Dissopinocampheylchloroborane (DIP-Chloride)



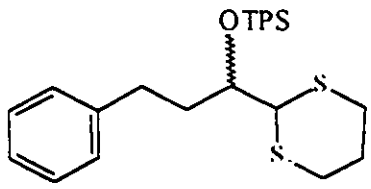
In an inert atmosphere of dry nitrogen, (-) Dip-Cl (2.29 g, 7.13 mmol, 2 eq) was added to the ketone **98** (901 mg, 3.55 mmol). The resultant mixture was stirred, neat, at 21^0C for 14 days then placed under a high vacuum (0.2 mm of Hg) for 2 hours.. Work-up consisted of dilution with ether and addition of diethanolamine (2 eq) and the solution was stirred for 2 hours. The resultant precipitate was filtered off, washed with ether and the solvent was removed. Purification by column chromatography (3:7 ether/ petroleum ether) yielded 818 mg (90%) of alcohol **99**; ee = 86.5%; $[\alpha]_D^{21}$= -27.9^0 (c 0.033, $CHCl_3$); mp 35-38°C; IR ($CDCl_3$, cm^{-1}) 3436, 3026, 2919, 1422, 1276, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 3.87 (s,1H), 2.89-2.81 (m, 2H), 2.73-2.68 (m, 4H), 2.57 (s,1H), 2.19-2.15 (m, 2H), 2.07-2.00 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 128.5, 128.4, 125.9, 71.3, 52.3, 35.7, 32.0, 28.2, 27.8, 25.7 ppm.

Preparation of (±)-2-(*t*-Butyldiphenylsilyloxy)-1-phenyl-2-(1,3-dithiacyclohexyl)ethane (109)



The alcohol **92** (1.34 g, 0.59 mol) was dissolved in dry DMF (5 mL). Imidazole (2.2 eq) and *t*-butyldiphenylsilane chloride (1.1 eq) were added and the solution was stirred for 2 days at 20°C under an atmosphere of dry nitrogen. Work-up consisted of the addition of saturated aqueous solution of ammonium chloride and dilution with dichloromethane (3 x 50 mL). The dried organic layer was concentrated and purified by column chromatography (1:9 ether/ petroleum ether) to yield 1.23g (92%) of the desired compound **109**. Crystallization from ether/ petroleum ether afforded an analytically pure sample. mp 105-106°C; ^{1}N NMR (200 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.52-721 (m, 13H), 4.89 (d, J = 5.8 Hz, 1H), 4.22 (d, J = 6.0 Hz, 1H), 2.70-2.56 (m, 4H), 1.99-1.92 (m, 1H), 1.90-1.70 (m, 1H), 1.10 (s, 9H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 140.4, 136.1, 135.9, 129.6, 128.0, 127.7, 127.4, 127.3, 127.2, 77.6, 55.1, 29.8, 27.0, 25.8, 19.5 ppm; HRMS calcd for $C_{23}H_{23}OS_2Si$ (M^{+}-C_4H_9): 407.0960. found 407.0933; MS (CI) calcd for $C_{11}H_{13}S_2$ (M^{+} -$C_{16}H_{19}OSi$) 208.9. found 208.9 (100%); Anal. Calcd for $C_{27}H_{32}OS_2Si$: C, 69.78; H, 6.94. Found: C, 69.93; H, 6.83.

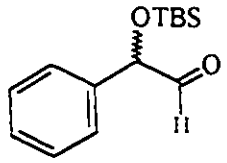
Preparation of (±)-2-(*t*-Butyldiphenylsilyloxy)-4-phenyl-1-(1,3-dithiacyclohexyl)butane (110)



The alcohol **99** (2.00g, 7.88 mmol) was dissolved in dry DMF (5 mL). Imidazole (2.2 eq) and *t*-butyldiphenylsilane chloride (1.1 eq) were added and the solution was stirred for 2 days at 20°C under an atmosphere of dry nitrogen. Work-up consisted of addition of aqueous solution of ammonium chloride and extraction with dichloromethane (3 x 50 mL). The dried organic layer was concentrated and purified by column chromatography (1:9 ether/ petroleum ether) to yield 2.0g (82%) of the desired compound **110**. Crystallization from ether/ petroleum ether afforded an analytically pure sample. mp 72-74°C; IR ($CDCl_3$, cm^{-1}) 3069, 3027, 2941, 2895, 2858, 1427, ^1H NMR (200 MHz, $CDCl_3$) δ 7.94-7.83 (m, 4H), 7.54-7.43 (m, 6H), 7.32-7.21 (m, 3H), 7.12-7.08 (m, 2H), 4.20-4.11 (m, 2H), 2.84-2.81 (m, 2H), 2.75 (s, 1H), 2.70 (d, J = 2.2 Hz, 2H), 2.61 (m, 2H), 2.14-2.04 (m, 2H), 1.96-1.84 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.5, 136.0, 135.9, 133.8, 133.6, 129.6, 128.2, 128.1, 127.5, 127.4, 125.6, 75.0, 55.1,

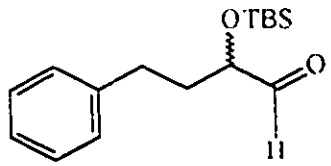
35.8, 31.8, 30.8, 30.4, 27.0, 26.3, 19.5 ppm. HRMS calcd for $C_{24}H_{27}OS_2Si$ ($M^+ - C_4H_9$) 435.1274. found 435.1256, MS (CI) calcd for $C_{25}H_{27}OS_2Si$ 435.1. found 434.8 (62%)

Attempted Preparation of (±)-2-(*t*-Butyldimethylsilyloxy)-2-phenylethanal (94)



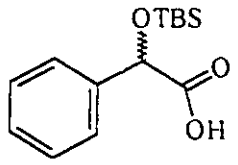
The dithiane **93** (224 mg, 0.7 mmol) was dissolved in a 6:1 of mixture of acetone-water (10 mL) and treated with mercuric(II) chloride (985 mg) and cadmium carbonate (1478 mg) at 21°C. The resultant suspension was heated at 50°C for 24 hours. The suspension was cooled, potassium iodide (851 mg) was added and the suspension was stirred for 15 minutes as the color changed from yellow to grey. The precipitate was filtered off and washed with acetone. The compound was extracted with ether (3 x 25 mL) and washed with saturated aqueous solution of potassium iodide and the organic phase was dried over magnesium sulphate. Due to the unstable nature of the aldehyde **94**, the crude product was only partially characterized. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.40-7.32 (m, 5H), 5.00 (s, 1H), 0.94 (s, 9H), 0.11 (s, 3H), 0.03 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199..5, 136.5, 128.7, 128.3, 126.4, 79.9, 25.7, 18.3, - 4.9.

Preparation of (±) -2-(*t*-Butyldimethylsilyloxy)-4-phenylbutanal (101)



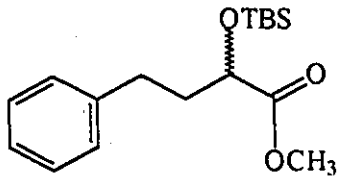
The dithiane **100** (536 mg, 1.6 mmol) was dissolved in a mixture of acetone-water (6:1, 25 mL) and treated with mercuric(II) chloride (4.4 g) and cadmium carbonate (3.6 g) at 21°C. The resultant suspension was heated to 50°C for 24 hours. The suspension was cooled, potassium iodide (2.0 g) was added and the suspension was stirred for 15 minutes as the color changed from yellow to grey. The precipitate was filtered off and washed with acetone. The compound was extracted with ether (3 x 50 mL), washed with a saturated aqueous solution of potassium iodide and the organic phase was dried over magnesium sulphate. Due to the unstable nature of the aldehyde **101**, the crude product was only partially characterized. IR (CH_2Cl_2, cm^{-1}) 3054, 2986, 2957, 1735, 1440, 1269, 1100; ^1H NMR (200 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.33-7.17 (m, 5H), 4.09 (s, 1H), 2.63 (m, 2H), 1.90 (m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H).

Attempted Preparation of (±)-2-(*t*-Butyldimethylsilyloxy)-4-phenylethanoic acid (95)



The aldehyde **94** (crude) was suspended in water (10 mL) and freshly prepared silver(I) oxide (2.2 eq) was added. The mixture was stirred at 21°C for 1 hour or until no starting material was left. The reaction was quenched with saturated aqueous solution of ammonium chloride and the resulting precipitate was filtered off and washed with dichloromethane. The solution was further diluted with dichloromethane washed with brine and dried over magnesium sulphate. No product was detected in the IR spectra.

Preparation of (±) Methyl 2-(*t*-butyldimethylsilyloxy)-4-phenylbutanoate (103)



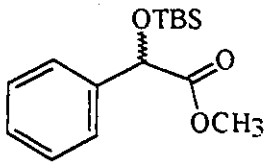
The aldehyde **101** (crude) was suspended in a 1.5:7 mixture of water-methanol (10 mL) at 21°C. Sodium bicarbonate (20 eq.) and bromine (5 eq.) was added sequentially

and the solution was stirred overnight. Sodium thiosulfate (1M) was added dropwise until the brown color disappeared. Work-up consisted of the addition of saturated aqueous solution of ammonium chloride and extraction with dichloromethane (3 x 50 mL). The organic phase was washed with brine and dried over magnesium sulphate. Concentration and purification by column chromatography (1.5:8.5 acetone/petroleum ether) afforded methyl ester **103** as a white crystalline solid. IR (CH_2Cl_2, cm^{-1}) 3466, 3057, 2946, 1736, 1447, 1266, 1102, 738; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.15 (m, 5H), 4.24 (m, J_1 = 11.8 Hz, J_2 = 5.8 Hz, 1H), 3.69 (s, 1H), 2.73-2.65 (m, 2H), 2.05-1.99 (m, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.0, 141.4, 128.4, 128.3, 125.9, 71.7, 51.7, 36.8, 31.4, 25.7, 18.3, - 4.9, - 5.3.

Methyl ester **103** was also prepared by the following method. The aldehyde **101** (crude) was suspended in water (10 mL) and freshly prepared silver(I) oxide (2.2 eq) was added. The mixture was stirred at 21°C for 1 hour or until no starting material was left. The reaction was quenched with saturated aqueous solution of ammonium chloride and the resulting precipitate was filtered off and washed with dichloromethane (3 x 50 mL). The solution was further diluted with dichloromethane washed with brine and dried over magnesium sulphate. The solution was concentrated *in vacuo*, redissolved in ether and cooled to 0°C. Diazomethane was prepared by a literature procedure[56] and added dropwise until a yellow color remained whilst stirring in an ice bath. A solution of glacial acetic acid (2 mL) in ether (50 mL) was added dropwise until the yellow color just disappeared. The solvent was then removed *in vacuo* and the methyl ester **103** purified by column chromatography (1:9 ether/petroleum ether) to yield a white crystalline solid.. ^1H

NMR (200 MHz, $CDCl_3$) δ 7.30-7.12 (m, 5H), 4.24 (t, J_1 = 11.8 Hz, J_2 = 5.8 Hz, 1H), 3.69 (s, 1H), 2.72-2.64 (m, 2H), 2.07-1.99 (m, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

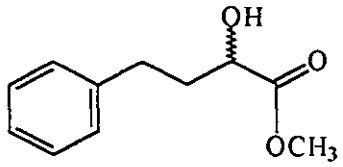
Preparation of Authentic (±) Methyl 2-(*t*-butyldimethylsilyloxy)-2-phenylethanoate (96)



(±)-Mandelic acid (1 g, 4.1 mmol) was dissolved in ether and cooled to 0°C. Diazomethane, prepared by a literature procedure[56], was added dropwise until a yellow color remained whilst the solution was stirred at 0°C. A solution of glacial acetic acid (2 mL) in ether (50 mL) was added dropwise until the yellow color just disappeared. The solvent was removed *in vacuo* and redissolved in dry dichloromethane (25 mL). To the stirred solution, *t*-butyldimethylsilyl chloride (1.2 eq.), imidazole (1.2 eq.) and DMAP (cat.) was added. The mixture was stirred at 21°C for 48 hours. Work-up included addition of saturated aqueous solution of ammonium chloride and extraction the dichloromethane (3 x 25 mL). The organic layer was washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography (1:9 ether/petroleum ether) resulted in 961 mg (80.3%) of the methyl ester **103** as an oil. IR (neat, cm^{-1}) 3066, 3032, 2945, 2858, 1749, 1260, 1156, 855; ^1H NMR (200 MHz,

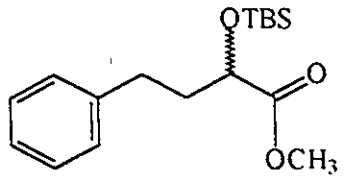
$CDCl_3$) δ 7.46 (m, 2H), 7.26 (m, 3H), 5.26 (s, 1H), 3.57 (s, 3H), 0.94 (s, 9H), 0.13 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.0, 138.9, 128.0, 127.8, 126.0, 74.1, 51.5, 25.4, 18.0, - 5.42, - 5.53; HRMS calcd for $C_{11}H_{15}O_3Si$ (M^+ -C_4H_9) 223.0791. found 223.0783.

Preparation of Authentic (±) Methyl 2-(Hydroxy)-4-phenylbutanoate (111)



3-L-phenyllactic acid (500 mg, 2.6 mmol) was dissolved in ether (25 mL) and cooled to 0°C. Diazomethane, prepared by a literature procedure,[56] was added dropwise until a yellow color remained whilst the solution was stirred at 0°C. A solution of glacial acetic acid (2 mL) in ether (50 mL) was added dropwise until the yellow color just disappeared. Removal of the solvent *in vacuo* provided an analytically pure sample. IR (neat, cm^{-1}) 3460, 3065, 3031, 2954, 1737, 1098, 911, 735; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 4.42 (m, 1H), 3.70 (s, 3H), 3.33 (s, 1H), 3.06 (m, 2H), 2.97 (m, 2H), ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.3, 136.3, 129.2, 128.1, 126.6, 71.1, 52.1, 40.3.

Preparation of Authentic (±) Methyl 2-(*t*-butyldimethylsilyloxy)-4-phenylbutanoate (103)



To a stirred solution of the alcohol **111** dissolved in dichloromethane, *t*-butyldimethylsilyl chloride (1.2 eq.), imidazole (1.2 eq.) and DMAP (cat.) were added. The mixture was stirred at 21°C for 48 hours. Work-up included the addition of saturated aqueous solution of ammonium chloride, and extraction with dichloromethane (3 x 25 mL). The organic layer was washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography (1:9 ether/petroleum ether) resulted in 733 mg (88.1 %) of the methyl ester **103** as an oil. IR (neat, cm^{-1}) 3065, 3030, 2944, 2857, 1747, 1605, 1263, 1153; ^1H NMR (200 MHz, $CDCl_3$) δ 7.24-7.12 (m, 5H), 4.36-4.30 (m, 2H), 3.66 (s, 3H), 3.06 (m, 2H), 2.96 (m, 2H), 0.78 (s, 9H), - 0.13 (s, 3H), - 0.24 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 173.2, 137.2,129.6, 128.0, 126.4, 73.6, 51.5, 41.4, 25.4, 18.0, - 5.7, - 5.9.333

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6 Claims to Original Research

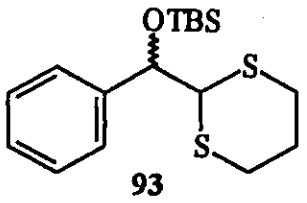
1. The extension of an aliphatic hydrocarbon chain by one unit using various acyl equivalents was studied. The use of 1,3-dithiane for this purpose was determined to be the most appropriate.

2. The asymmetric reduction of a carbonyl group in two model systems using three different chiral reducing agents was investigated. Corey's reagent, modified Corey's reagent and Dip-Cl were all studied for their selectivity in reducing the carbon group in 1-phenyl-2-(1,3-dithiacyclohexane)ethanone and 4-phenyl-1-(1,3-dithiacyclohexane)butan-2-one model systems.

3. Routes to unmask the aldehyde and convert it to a more stable methyl ester were investigated. Mercuric (II) chloride and cadmium carbonate was determined to be the most appropriate system to unmask the aldehyde in the two model systems studied. Direct esterification was used to convert the 2-*t*-butyldimethylsiloxy-4-phenyl-1-(1,3-dithiacyclohexane)butan-2-one to the methyl ester. Alternatively, the aldehyde was oxidized to the acid and then esterified.

SPECTRAL LINES FOR TH= 14.88
RFL= 1881.2 RFP= 1447.8

INDEX	FREQ	PPM	INTENSITY
01	1471.21	7.357	35.246
02	1468.36	7.333	83.481
03	1463.52	7.318	81.688
04	1461.42	7.308	38.642
05	1460.51	7.305	37.976
06	1458.18	7.292	38.225
07	1455.64	7.279	22.640
08	947.40	4.736	32.834
09	940.22	4.702	38.475
10	854.37	4.272	38.705
11	847.23	4.237	33.284
12	584.20	2.922	23.405
13	561.68	2.809	38.763
14	557.18	2.786	20.462
15	554.43	2.773	25.463
16	551.65	2.759	46.315
17	547.80	2.739	38.718
18	541.98	2.710	32.582
19	538.15	2.690	20.867
20	400.38	2.002	15.318
21	171.46	0.857	556.026
22	12.50	0.062	172.460
23	-34.57	-0.173	168.061



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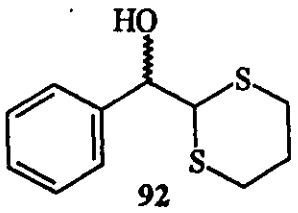

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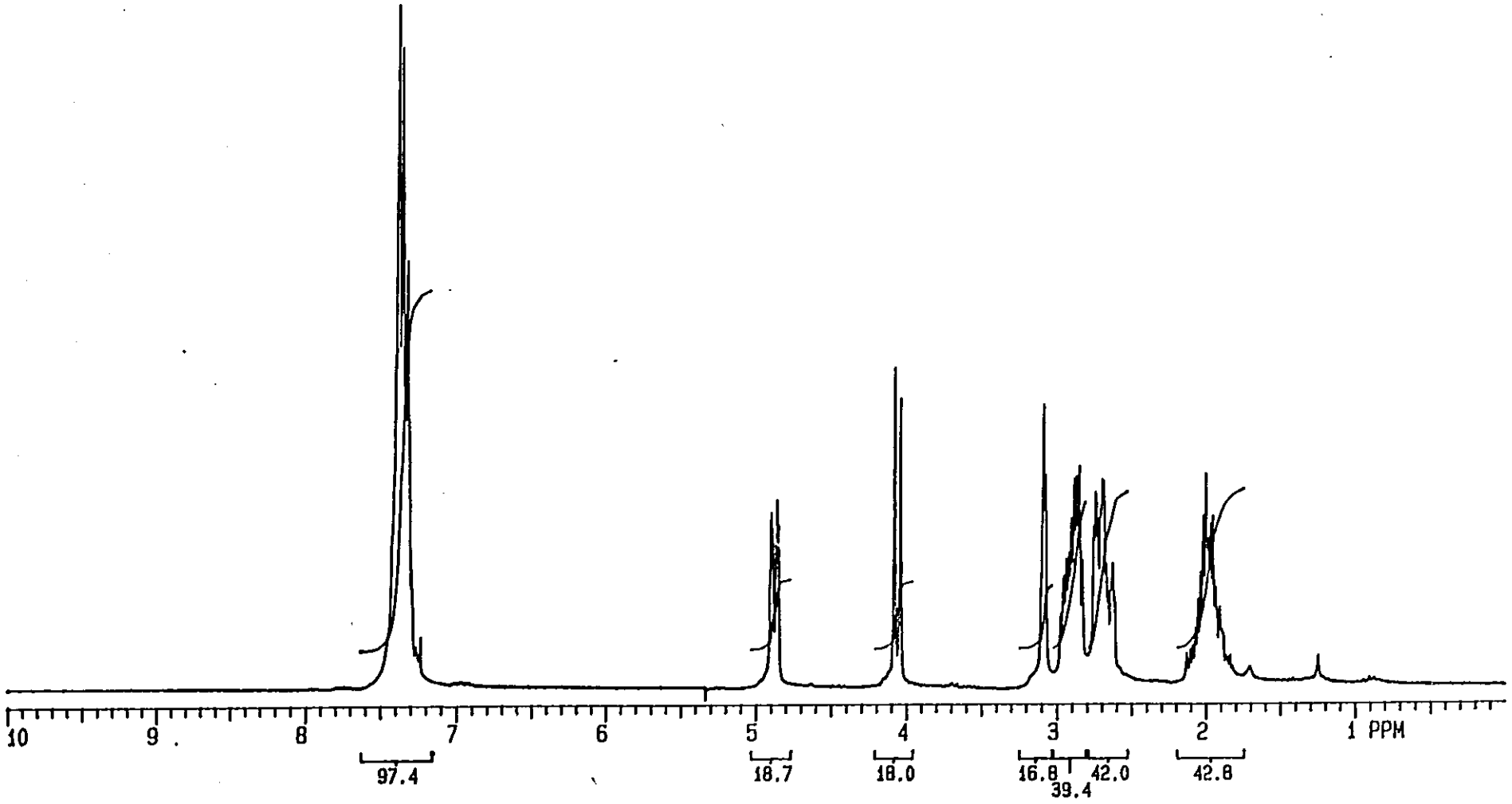

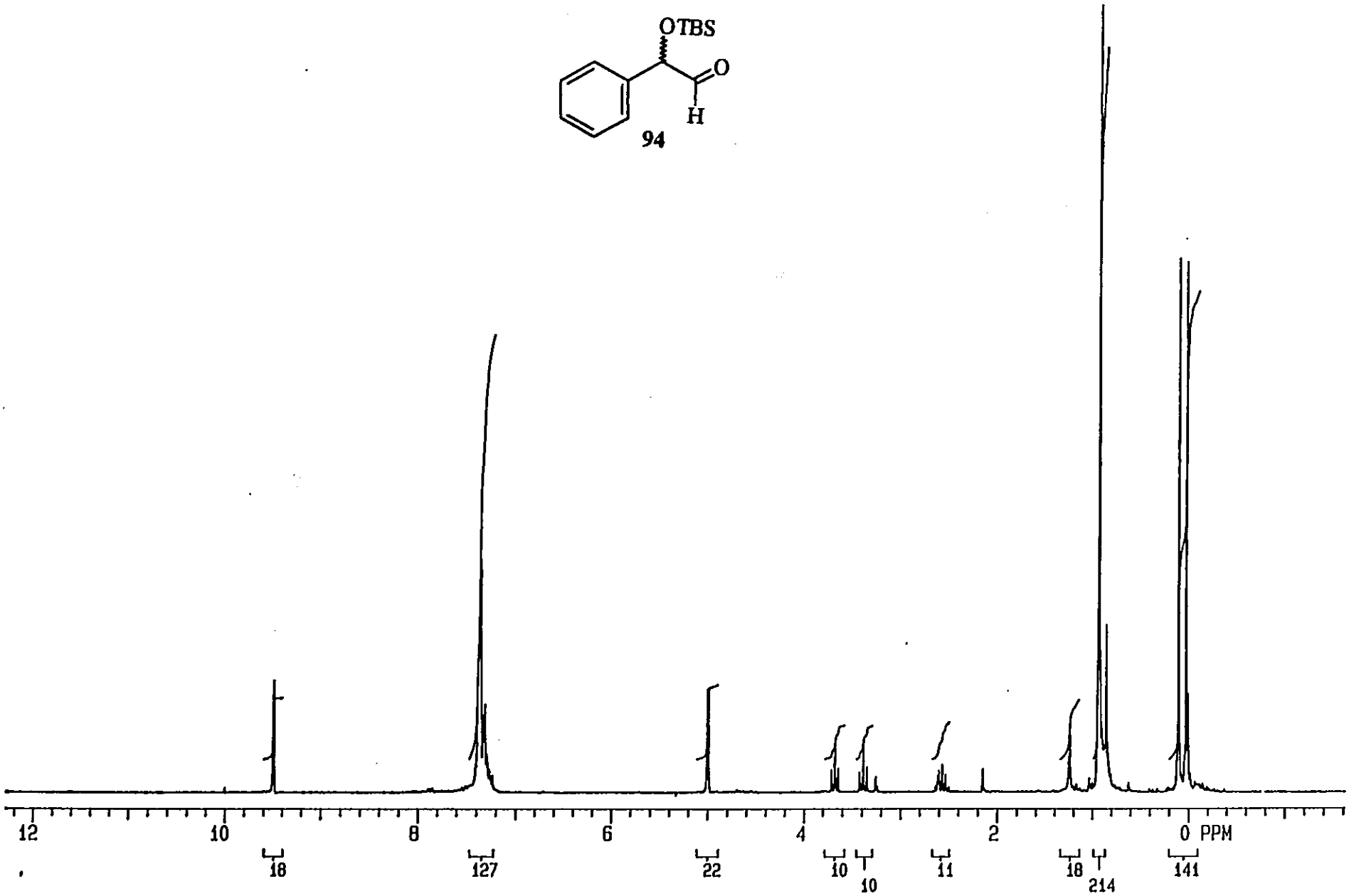
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O
H
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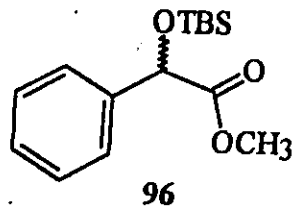
8
6
4
2
0 PPM
18
127
22
10
10
11
18
214
141

SPECTRAL LINES FOR TH= 14.17
RFL= 1881.2 RFP= 1447.8

INDEX	FREQ	PPM	INTENSITY
01	1498.45	7.493	17.824
02	1491.82	7.460	24.479
03	1490.94	7.456	25.303
04	1457.25	7.287	24.909
05	1455.46	7.278	16.575
06	1449.56	7.249	36.007
07	1447.36	7.238	20.570
08	1052.15	5.261	34.361
09	714.53	3.573	135.383
10	712.44	3.563	45.799
11	188.81	0.944	298.262
12	186.66	0.933	114.978
13	181.85	0.909	20.525
14	26.45	0.132	101.166
15	24.26	0.121	34.098
16	8.79	0.044	100.722
17	6.59	0.033	34.224



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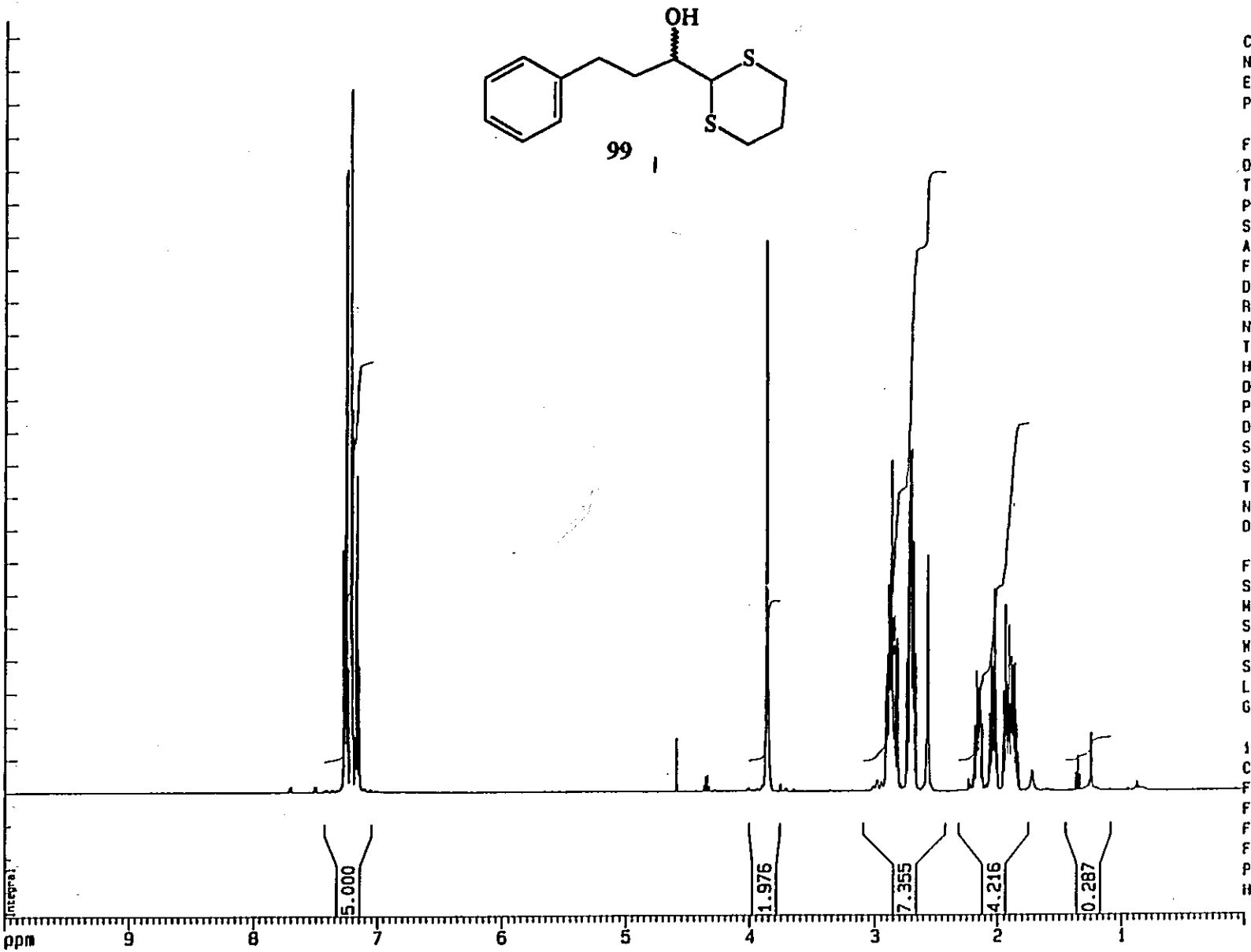

Current Data Parameters
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EXPNO 1
PROCNO 1

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FIORES 0.107456 Hz
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RG 256
NUCLEUS 1H
TE 300.0 K
HL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
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DS 0

F1 - Processing parameters
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WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
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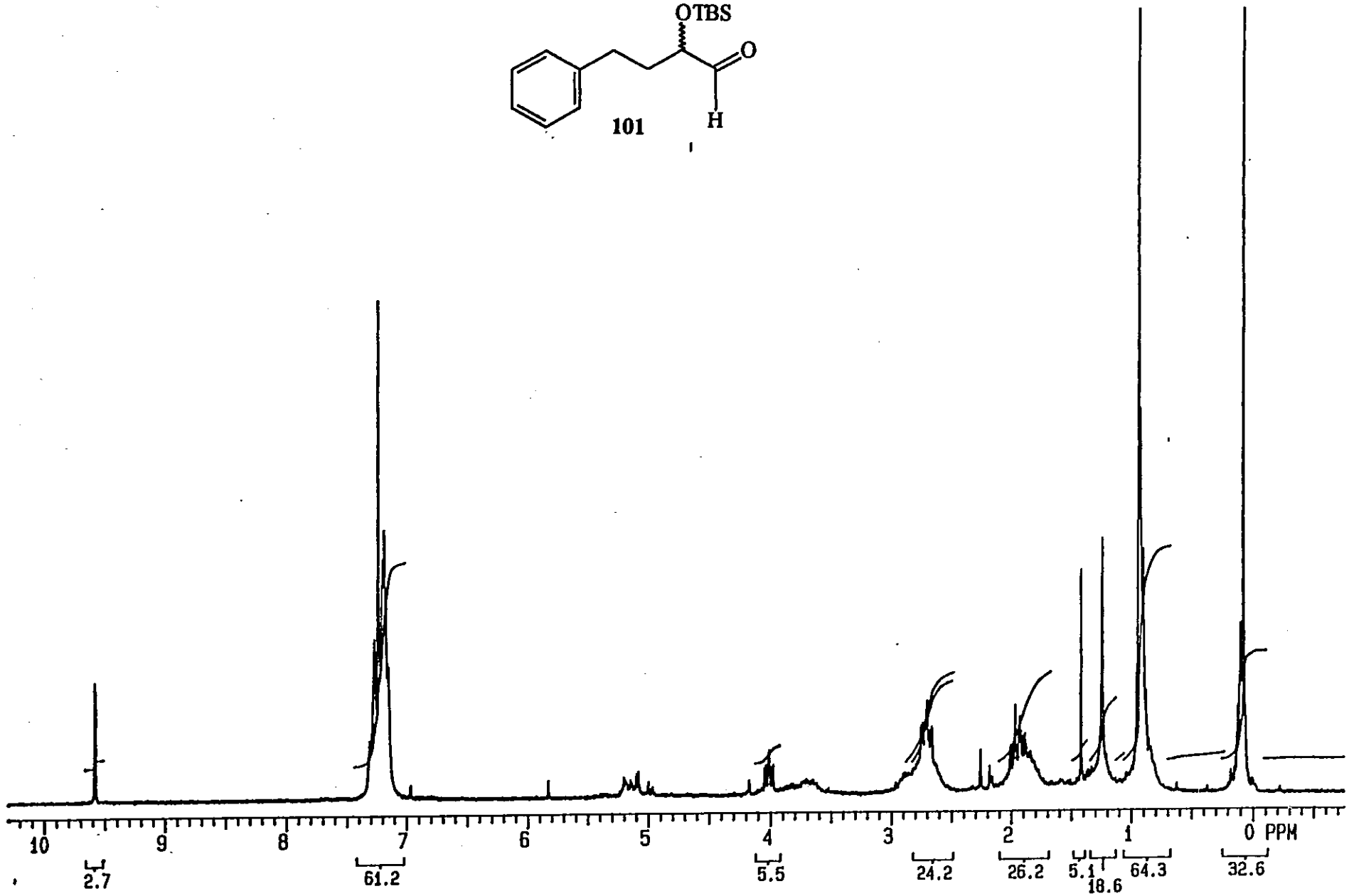
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.47619 ppm/cm
HZCM 238.15973 Hz/cm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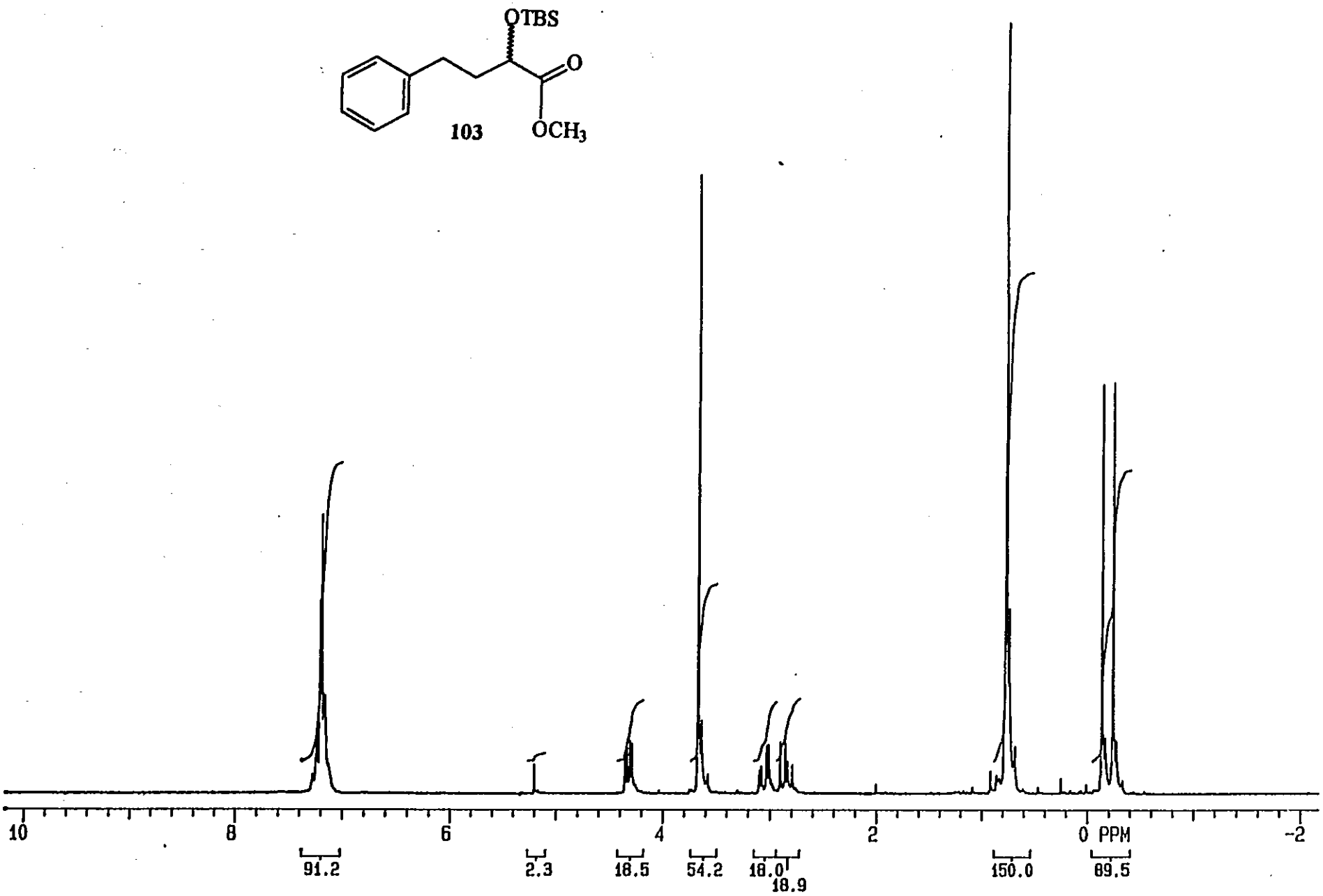
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