The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

L’auteur a accordé une licence irrévocable et non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de sa thèse de quelque manière et sous quelque forme que ce soit pour mettre des exemplaires de cette thèse à la disposition des personnes intéressées.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

L’auteur conserve la propriété du droit d’auteur qui protège sa thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

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, [l-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 samples of both methyl esters 96 and 103 were also synthesized.
(S)-oxazaborolidine  
Modified (S)-oxazaborolidine  
(-)-Dip Cl
To my wife, Mary and children, Grace, Claire and Mark for their patience and everlasting love.
# TABLE OF CONTENTS

ABSTRACT ........................................................................................................... ii

TABLE OF CONTENTS ......................................................................................... vi

LIST OF SCHEMES ............................................................................................... viii

LIST OF FIGURES ................................................................................................. ix

LIST OF TABLES .................................................................................................... x

LIST OF ABBREVIATIONS ....................................................................................... xi

ACKNOWLEDGMENTS ............................................................................................ xiv

1 INTRODUCTION

1.1 Overview ...................................................................................................... 1

1.2 Background .................................................................................................. 1

1.3 Previous synthesis of the Taxane Side-Chain .............................................. 4

1.3.1 Greene’s Epoxidation Routes ................................................................. 4

1.3.2 Sharpless’s Dihydroxylation Route ........................................................ 5

1.3.3 Deng and Jacobson’s Epoxidation Route ............................................... 5

1.3.4 Commercon’s Oxazolidine Route ............................................................ 9

1.3.5 Greene’s Route Using Camphorsultam as a Chiral Auxiliary ................ 10

1.3.6 Greene’s Phenylglycine Route ............................................................... 11

1.3.7 Dondoni’s Thiazole Route ..................................................................... 14

1.3.8 Hanaoka’s Aldol Condensation Route .................................................. 15

1.3.9 β-Lactam Pathways using *trans*-2-phenyl-1-cyclohexyl

    as chiral auxiliary ........................................................................................................... 18

1.3.10 Georg’s β-Lactam Route ....................................................................... 19
1.3.11 Farina’s β-lactam Route .......................... 21
1.3.12 Palomo’s β-Lactam Route ......................... 21
1.3.13 Kayser’s Route using Baker’s Yeast .......... 23
1.3.14 Chen’s Enzymatic Route ................................ 25
1.3.15 Sih’s Enzyme Studies .................................. 25
1.4 Synthesis of Prodrugs ........................................ 27
1.5 Preparation of Water Soluble Derivatives .......... 28
1.6 Preparation of p-Substituted 3’-Phenyl Analogues .. 31
1.7 Preparation of 2’-Methyl Analogue ..................... 33
1.8 Proposed Route to Taxoid Side-chain .................. 35
2 RESULTS AND DISCUSSION .................................. 37
3 CONCLUSIONS .................................................. 50
4 EXPERIMENTAL
  4.1 General .................................................... 52
5 REFERENCES .................................................... 82
6 CLAIMS TO ORIGINAL RESEARCH ....................... 87
7 APPENDIX
  7.1 Spectra ....................................................... 88
LIST OF SCHEMES

Scheme 1.3.1.1.  Greene's epoxidation route ............................................ 6
Scheme 1.3.1.2.  Greene's asymmetric dihydroxylation route ...................... 7
Scheme 1.3.2.  Sharpless's asymmetric dihydroxylation route .................... 8
Scheme 1.3.3.  Deng and Jacobsen's epoxidation route ................................ 9
Scheme 1.3.4.  Commercon's epoxidation route ........................................ 12
Scheme 1.3.5.  Greene's route using camphorsultam as chiral auxiliary ......... 13
Scheme 1.3.6.  Greene's phenylglycine route .......................................... 14
Scheme 1.3.7.  Dondoni's thiazole route ................................................ 16
Scheme 1.3.8.  Hanaoka's aldol condensation route ................................... 17
Scheme 1.3.9.  Ojima's β-lactam route ................................................. 19
Scheme 1.3.10.  Georg's β-lactam route ................................................ 20
Scheme 1.3.11.  Farina's β-lactam route .............................................. 22
Scheme 1.3.12.  Palomo's β-lactam route ............................................... 23
Scheme 1.3.13.  Kayser's route using Baker's yeast .................................. 24
Scheme 1.3.14.  Chen's enzymatic route ............................................... 26
Scheme 1.7.  Greene's route to prepare 2' methyl derivative of docetaxel .... 34
Scheme 1.8.  Proposed route to the paclitaxel side-chain ............................ 36
Scheme 2.1.  Proposed route for the benzoyl model system ........................ 38
Scheme 2.2.  Proposed route for the hydrocinnamoyl model system ............. 41
LIST OF FIGURES

Figure 1.2.1. Structures of paclitaxel and docetaxel ...................... 2
Figure 1.2.2. Structures of baccatin III and 10-desacetyl baccatin III. .......... 3
Figure 1.4. Mechanistic rationale for the design of propaclitaxels. .............. 28
Figure 1.5.1. Structures of water soluble derivatives of paclitaxel. .................. 30
Figure 1.5.2 Structures of succinyl, glutaryl and amino amide paclitaxel derivatives. 31
Figure 1.6. Structures of $p$-substituted 3’aromatic paclitaxel derivatives. ....... 32
Figure 2.1 (s)-Oxazaborolidine chair transition state .................................. 45
Figure 2.2 (-)-Dip Cl boat transition state ................................................. 47
List of Tables

Table 2.1 Summary of enantioselective reduction ................................. 48
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>BMS</td>
<td>borane-dimethyl sulfide complex</td>
</tr>
<tr>
<td>Boc</td>
<td>t-butyl carbamate</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>c</td>
<td>concentration (g mol(^{-1}))</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CAN</td>
<td>ammonium cerium (IV) nitrate</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>(m)-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>DCC</td>
<td>(N,N)-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>dichlorodicyanobenzocquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>L-(+)-DET</td>
<td>diethyl L-tartrate</td>
</tr>
<tr>
<td>DIBAH</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>Dip-Cl</td>
<td>diisopinocampheylchloroborane</td>
</tr>
<tr>
<td>DMAP</td>
<td>(N,N)-dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
</tr>
<tr>
<td>DQCB</td>
<td>dihydroquinidine 4-chlorobenzoate</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>ether</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et(_3)N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>EtOAC</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>Im</td>
<td>imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>infra red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (given in Hertz)</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>M⁺</td>
<td>molecular ion</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>MHz</td>
<td>megaHertz</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MTPA</td>
<td>Mosher's acid</td>
</tr>
<tr>
<td>MS (Cl)</td>
<td>mass spectrum by chemical ionization</td>
</tr>
<tr>
<td>MS (EI)</td>
<td>mass spectrum by electron impact</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMNO</td>
<td>N-methyl-morpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>obs.</td>
<td>observed</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPh</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>4-PPNO</td>
<td>4-phenyl-pyridine N-oxide</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>TBAF</td>
<td>t-buty lammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPS</td>
<td>t-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>toluenesulfonic acid</td>
</tr>
</tbody>
</table>
ACKNOWLEDGMENTS

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

I would like to thank my wife, Mary and children Grace, Claire and Mark for allowing me the opportunity to complete my Masters degree. Their understanding during all the long hours away from them is greatly appreciated. I would like to thank my mother and sister for all their support throughout the years as well.

I would like to thank Mr. R. Capoor and Dr. G. Facey for their efforts in conducting the high field NMR especially the $^{19}$F NMR. I would also like to thank Lise Maisoneuve for her help in dealing with all the paperwork and red tape that goes along with graduate studies.

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
also to our two French post-docs, Sandrine Py and Helene Audrain, for their friendship and helpful suggestions during their stay with us.

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.\textsuperscript{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\textsuperscript{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\textsuperscript{®}) and docetaxel 2 (Taxotere\textsuperscript{®}) have been touted as “the most promising anticancer agents developed in the last decade”.\textsuperscript{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.

![Chemical Structures](image)

1. Paclitaxel  \( R^1 = \text{Ac} \quad R^2 = \text{PhCO} \)

2. Docetaxel  \( R^1 = \text{H} \quad R^2 = \text{t-BuOCO} \)

**Figure 1.2.1. Structures of paclitaxel 1 and docetaxel 2**

Paclitaxel 1 was first detected, in its crude form, in 1856 by Lucas but it was not until 1971 that Wani and Wall 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 overcome 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\textsuperscript{7,a,b}, Nicolaou\textsuperscript{5} and Danishefsky\textsuperscript{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-desacetylbaaccatin III 4 (Figure 1.2.2), obtained from the needles of the European yew, Taxus baccata, to docetaxel 2.

![Chemical structure of baccatin III and 10-desacetylbaaccatin III](image)

3. Baccatin III \( R^1 = \text{Ac} \)

4. 10-desacetylbaaccatin III \( R^1 = \text{H} \)

**Figure 1.2.2. Structures of baccatin III 3 and 10-desacetylbaaccatin 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\textsuperscript{10a}. The side chain is essential for activity particularly the hydroxyl group attached to the 2' position.\textsuperscript{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.,\textsuperscript{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.\textsuperscript{11a} using
\textit{cis}-cinnamyl alcohol as the starting material (Scheme 1 3.1.1). Sharpless asymmetric epoxidation
produced (2S,3R)-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 $\rightarrow$ N benzoyl transfer which afforded the
methyl ester form 8 of paclitaxel side-chain. One crystallization from chloroform produced
optically pure amino alcohol 8 (\geq 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,\textsuperscript{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\textsuperscript{12} used the chiral catalyst (DHQ)\textsubscript{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\textsuperscript{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 phenylpropionate 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
1.3.4 Commercon's Oxazolidine Route

Greene et al.\textsuperscript{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 epimerization, the use of cyclic protection groups to lock in the steric configuration was investigated. Commercon \textit{et al.}\textsuperscript{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 \((4S,5R)-3\text{-bromoacetyl-4-methyl-5-phenyl-2-oxazolidinone}\) 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.\(^\text{17}\) 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.\(^\text{14,15}\) 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 \(\pi\) face attack was controlled sterically and the addition of the imine afforded diasteromer 22 in 68\% yield with excellent optical purity \((\geq 99.5\%)\). 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). (\( \Delta \))-(\( \Delta \))-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 \( \text{syn} \) 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 (\( \geq 99\% \)).
Scheme 1.3.4. Commercon's epoxidation route
Scheme 1.3.5. Greene's route using camphorsultam as chiral auxiliary
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

Scheme 1.3.6. Greene's phenylglycine route
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. 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(η⁶-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 HN₃, PPH₃ and DEAD gave a syn amide. Reduction of the azide on the syn amide with PPH₃ 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
13.9 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.\textsuperscript{20} prepared the side-chain by a chiral lithium ester enolate-imine cyclocondensation method (Scheme 13.9). 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 trisopropylsilyl 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\textsuperscript{31} using chiral auxiliaries to control the steric environment during the cycloaddition reaction. With their imine and ketene acetal system, (1R,2S)-(-)-trans-2-phenyl-1-cyclohexyl produced respectable endo-exo discrimination (70:18) and good π-face discrimination (88:12). Other chiral auxiliaries, (1R,2R,3R,5S)-(-)-iospinocampheyl, (1R,2S,5R)-(-)-menthyl and (1R,2S,5R)-(-)-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 (1S,2R)-(+) -trans-2-(1-methyl-1-phenylethyl)-1-cyclohexyl which produced excellent endo-exo discrimination (93:0) and good π-face discrimination (93:7).
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$\alpha$,3R isomer had been synthesized.

Scheme 1.3.10 Georg's $\beta$-lactam route
1.3.11 Farina's β-lactam Route

Farina et al. 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. (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 Kearns25 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’s25 methodology to yield (2R, 3S)-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.\textsuperscript{27} used \textit{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.\textsuperscript{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. \textit{t}-Butyl methyl ether and isopropyl ether afforded the most results. The effect of water concentration in the \textit{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 I.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 loss of biological activity.

Kingston et al.\textsuperscript{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.\textsuperscript{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 heteroatom linkage. Using this trend, it was proposed that simple chemical principles could be used to fine-tune future derivatives to maximize their biological and pharmacological properties.
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.\textsuperscript{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'-acyloxypaclitaxel 70 was prepared by the mixed anhydride method and then Michael addition of sodium metasulfite to the $\alpha\beta$-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'-glycylpaclitaxel 72 and the 2'-(γ-aminobutyryl)paclitaxel 73 were prepared but were too unstable to conduct further testing.

Stella et al.\textsuperscript{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 \textit{in vivo} conversion of the analogues to paclitaxel 1 or an active metabolite.

Deutsch et al.\textsuperscript{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
   \[ R = COCH_2CH_2CONHCH_2CH_2SO_3^-; X' = N'-Bu, Na' \]

69. Sulfonate Derivatives of 3-Amino-1-sulfopropionic acid analogues of 2'-succinyl paclitaxel
   \[ R = COCH_2CH_2CONHCH_2CH_2CH_2SO_3^-; X' = N'-Bu, Na' \]

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
   \[ R = COCH_2CH_2NHCOOCH_2C_6H_5 \]

73. 2'-\((\gamma\text{-aminobutyryl)})paclitaxel
   \[ R = COCH_2CH_2CH_2NH, HCOO \]

74. Sulfonate derivative of 2'-[3-(\(N,N\)-dichydroxypropionyl)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**  
   \[ R^1 = \text{CO}(\text{CH}_2)_2\text{CO}_2X \quad R^2 = \text{H} \]  
   \[ X = \text{H}, \text{Na}, (\text{HCOCH}_2\text{CH}_2)\text{NH} \]

76. **2'-glutarylpaclitaxel**  
   \[ R^1 = \text{CO}(\text{CH}_2)_3\text{CO}_2X \quad R^2 = \text{H} \]  
   \[ X = \text{H}, \text{Na}, (\text{HCOCH}_2\text{CH}_2)\text{NH} \]

77. **Amino amide adduct**  
   \[ R^1 = \text{CO}(\text{CH}_2)_3\text{CONH}(\text{CH}_2)_3\text{N}(\text{CH}_2)_2 \]  
   \[ R^2 = \text{H} \]

**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) diastereomers 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.\textsuperscript{16} (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.

![Diagram of paclitaxel derivatives](image)

78. \( p \)-Chlorophenyl paclitaxel  
\[ \text{Ar}^1 = p-\text{ClC}_6\text{H}_4 \]  
\[ \text{Ar}^2 = \text{C}_6\text{H}_5 \]

79. \( p \)-Fluorophenyl paclitaxel  
\[ \text{Ar}^1 = p-\text{FC}_6\text{H}_4 \]  
\[ \text{Ar}^2 = \text{C}_6\text{H}_5 \]

80. \( p \)-Dimethylamino paclitaxel  
\[ \text{Ar}^1 = p-(\text{CH}_3)_2\text{NCH}_2\text{H}_4 \]  
\[ \text{Ar}^2 = \text{C}_6\text{H}_5 \]

**Figure 1.6. Structures of \( p \)-substituted 3'aromatic paclitaxel derivatives**

Subsequently, Commercon et al.\textsuperscript{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 2S,3R and 2R,3S side-chain was reported by Greene et al.18 (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% (2S,3R) and 40% (2R,3S) yields respectively. Unfortunately, opening of the dimethoxybenzylidene 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's route to prepare 2'-methyl derivative
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 tert-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 homologation 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 homologation 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 \(^1\)H 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 -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$_3$, CuCl$_2$/CuO,$^{46}$ NCS/AgNO$_3$, 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 -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 = OCH₂CH₃) 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 (CHOS₂) 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.\textsuperscript{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.\textsuperscript{39} Unfortunately the $^{11}$B NMR and $^1$H NMR spectrum were different from those reported. An alternative method has also been
reported\textsuperscript{41} for the preparation of the reagent 105 and this was attempted. (S)-(\textndash)-
(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\textsuperscript{60} and the enantiomeric
excess for the respective compounds (92 and 99) was 87\% and 45\% as determined by
\textsuperscript{19}F NMR.

A further improvement in the chiral reducing agent was made by Mathre \textit{et al.}\textsuperscript{49,43}
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 \textit{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)-(\textndash)-
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 19F 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 19F NMR for alcohol 99.
Figure 2.1 (S)-Oxazaborolidine Chair Transition State
d\textsuperscript{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.\textsuperscript{40} 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 $\alpha$-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.\textsuperscript{41} However when both aliphatic and cyclic hindered ketones were used high enantioselectivities were obtained.

Recent publications\textsuperscript{12-44} 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 $\alpha$-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.

![Chemical Diagram]

**Figure 2.2 (-)-Dip Cl Boat Transition State**

The above figure illustrates the boat transition 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.

<table>
<thead>
<tr>
<th>Chiral Reducing Agent</th>
<th>Benzoyl-1,3-Dithiane (91)</th>
<th>Hydrocinnamoyl-1,3-Dithiane (98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-oxazaborolidine</td>
<td>87.2</td>
<td>45.2</td>
</tr>
<tr>
<td>Modified (S)-oxazaborolidine</td>
<td>43.5</td>
<td>2.5</td>
</tr>
<tr>
<td>(-)-Dip Cl</td>
<td>55.1</td>
<td>86.5</td>
</tr>
</tbody>
</table>

To prepare a silyl ether with a more stable O-protecting group for the direct oxidation of the aldehyde to the methyl ester, i-butylidiphenylsilyl was substituted for the i-butylidimethylsilyl group however it was not possible to hydrolysis the dithiane with the i-butylidiphenylsilyl 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 i-butylidimethylsilyl 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, 0.15 and -0.04 ppm in the $^1$H NMR spectra characteristic of the i-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 i-butylidimethylsilyl 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 from the carbonyl group and singlets at 0.78, -0.13 and -0.24 ppm in the $^1$H NMR spectra representative of the tert-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 oxidation 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\(_3\), \(\delta 7.24\) ppm; \(^{13}\)C: \(\delta 77.0\) ppm). Fluorine magnetic resonance spectra (\(^{19}\)F NMR) were measured at 282 MHz with a Varian XL-300 spectrometer using an external reference of trifluoroacetic acid, \(\delta 0.00\). All chemical shifts are reported downfield from tetramethylsilane (\(\delta\) 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 \(\mu\)L 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°F. 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)

\[
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{S} \\
\text{S}
\end{array}
\]

1,3-dithaine (1.0 g, 8.3 mmol) was dissolve in dry tetrahydrofuran (100 mL), cooled to -78°C, and \( \mu \)-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 \textit{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 (CHCl₃, cm⁻¹) 2922, 1679, 1448, 731; \(^1\)H NMR (200 MHz, CDCl₃) 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); \(^1^C\) NMR (50 MHz, CDCl₃) δ 192.6, 134.6, 133.4, 128.7 42.7, 29.9, 26.6, 25.2; HRMS calcd for C₁₁H₁₂O₂S (M⁺): 224.0330. found 224.0328; Anal. Calcd for C₁₁H₁₂O₂S: C, 58.89; H, 5.39. Found: C, 58.98; H, 5.42.
The major by-product, alcohol 104, was also isolated and characterized as follows: 
mp 162-163°C; IR (CHCl₃, cm⁻¹) 3498, 3092, 2916, 1274, 1066, 727; ^1H NMR (200 MHz, CDCl₃) 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; ^13C NMR (50 MHz, CDCl₃) δ 139.7, 128.3, 127.8, 126.6, 81.9, 55.2, 30.2, 29.5, 25.3 ppm.

Preparation of (±)-1-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, 1.66 mmol). The resultant solution was stirred at 21°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. (19 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, 1'H NMR (200 MHz, CDCl₃) 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. 13C NMR (50 MHz, CDCl₃) δ 140.7, 129.1, 128.9, 127.4, 127.3, 75.3, 53.4, 28.8, 28.2, 26.0 ppm. HRMS calcld for C₁₁H₁₃S₂ (M+OH): 209.0459. found: 209.0417. MS (Cl) calcld for C₁₁H₁₃S₂ (M+OH): 209.0. found: 208.9 (100%); Anal. Calcld. for C₁₁H₁₄OS₂: C, 58.39; H, 6.24. Found: C, 58.57; H, 6.14.

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

![Image](image)

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. (19 ethyl
acetate/petroleum ether) afforded 540 mg (90%) of compound 93 as a white crystalline
solid, mp 54-59°C; IR (ethyl acetate, cm⁻¹) 3063, 3030, 2940, 1253, 1093, 774; ¹H NMR
(200 MHz, CDCl₃) 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;
¹³C NMR (50 MHz, CDCl₃) 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(Cl) calcd for C₁₁H₁₃S₂: (M⁺-C₄H₈) 209.1. found:
208.9(100%). Anal. Calcd for C₁₇H₂₈OS₂Si: 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)

![Chemical structure](image)

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°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°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 °C; IR (CHCl₃, cm⁻¹) 3064, 3028, 2944, 1732, 1242; ¹H NMR (200 MHz, CDCl₃) 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; ¹³C NMR (50 MHz, CDCl₃) 201.8, 140.6, 128.5, 128.3, 126.2, 47.0, 41.6, 30.2, 26.2, 25.2 ppm; HRMS caled for C₁₃H₁₆O₃S (M⁺): 252.0643, found 252.0638; Anal. Calcd for C₁₃H₁₆O₃S: C, 61.86; H, 6.39. Found C, 62.02; H, 6.55.

**Preparation of Ethyl 4-phenyl-butanoate (97)**

![Chemical Structure](attachment:image.png)

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, CDCl₃) δ 7.32-7.18 (m, 5H), 4.11 (q, J = 15.8 Hz, J₂ = 7.2 Hz, 3H), 2.95 (t, J = 15.4 Hz, J₂ = 7.4 Hz, 2H), 2.61 (t, J₁ = 15.8 Hz, J₂ = 7.8 Hz, 2H), 1.23 (t, J₁ = 14.2 Hz, J₂ = 7.2 Hz, 3H) ppm. \(^{13}\)C NMR (75 MHz, CDCl₃) δ 171.8, 140.1, 127.8, 127.7, 125.6, 59.5, 35.2, 30.3, 13.5 ppm; HRMS calcd for C₁₁H₁₄O₂(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 hydrocinnamate as the starting material.

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

![Chemical Structure](attachment:image)

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%o) of alcohol 99, mp 39-40°C. IR (CDCl₃, cm⁻¹) 3436, 3026, 2919, 1422, 1276. ¹H NMR (500 MHz, CDCl₃) 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), ¹³C NMR (125 MHz, CDCl₃) 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 (Cl) calcd for C₁₃H₁₈OS₂: 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 C₁₃H₁₈OS₂: C, 61.40; H 7.14; Found: C, 61.78; H, 6.83.

Preparation of (±)-2-tert-Butyldimethylsilyloxy-4-phenyl-1-(1,3-dithiacyclophe-xyl)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 tert-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 (19 ethyl acetate/petroleum ether) gave 0.678 g (94%) of the desired product. mp 59-62°C, IR (CDCl3, cm⁻¹) 3028, 2944, 2857, 1468, 1065, 734 cm⁻¹; ¹H NMR (200 MHz, CDCl3) δ 7.35-7.18 (m, 5H), 4.25 (d, J = 5.2 Hz, 1H), 3.98-3.90 (q, J1 = 16.0 Hz, J2 = 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; ¹³C NMR (50MHz, CDCl3): 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 calc'd for C₁₀H₂₁OS₂ (M⁺ -C₄H₉): 311.0960. found 311.0932; MS (Cl) calc'd for C₁₅H₂₆OS₂ (M⁺ - C₄H₉): 311.1. found: 310.9 (33.0%), 249.0 (48%) 131.0 (100.0%). Anal. Calc'd for C₁₀H₁₄OS₂Si: C, 61.90; H, 8.75. Found: C, 61.76; H, 8.84.

Attempted Preparation of (S)-Corey’s Reagent⁹⁰(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 Å molecular sieves were added.
Alternative Synthesis of (S)-Corey's Reagent \textsuperscript{43} (105)

\[
\text{C}_6\text{H}_5
\]

\[
\text{H}
\]

\[
\text{C}_6\text{H}_5
\]

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 \(-20^\circ\text{C}\).
Preparation of (R*)-1-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°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, CDCl₃) 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, CDCl₃) 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 (CDCl₃, cm⁻¹) 3436, 3026, 2919, 1422, 1276. ¹H NMR (500 MHz, CDCl₃) 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). ¹³C NMR (125 MHz, CDCl₃) 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\textsuperscript{60} (106)

(R)-(+)-\(\alpha\)-methoxy-\(\alpha\)-(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 (\(\equiv 100^\circ\text{C} \) 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)

\[
\text{H}_3\text{C} - \text{C} - \text{O} - \text{R}
\]

\[
\text{F}_3\text{C}
\]

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$^\circ$C or until complete. The reaction was quenched with distilled 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 on page 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*)-1-Phenyl-2-(1,3-dithiacyclohexyl)ethanol (92)

using (S)-Oxazaborolidine-Borane Complex

\[
\begin{align*}
&\text{HO} \\
&\text{S} \\
&\text{S} \\
&\text{C}_6\text{H}_5
\end{align*}
\]

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° 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° 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°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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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)

![Chemical structure](image)

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°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°C. The resultant mixture was stirred for 48 hours after which the reaction was quenched by addition of chilled methanol (-20°C). The solution was warmed to 21°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 (CDCl₃, cm⁻¹) 3436, 3026, 2919, 1422, 1276, ¹H NMR (500 MHz, CDCl₃) 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)

![Chemical Structure](image)

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°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°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)

\[
\text{OH}
\begin{array}{c}
\text{phe} \\
\text{thi} \\
\text{cyc} \\
\text{hex}
\end{array}
\]

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°C 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%; \([\alpha]_D^{21} = -27.9^\circ\) (c 0.033, CHCl₃); mp 35-38°C; IR (CDCl₃, cm⁻¹) 3436, 3026, 2919, 1422, 1276, \(^1\)H NMR (500 MHz, CDCl₃) 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, CDCl₃) 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 \((\pm)-2-(t\text{-Butyldiphenylsilyloxy})-1\text{-phenyl-}2\text{-(1,3-dithiacyclohexyl)ethane (109)}\)

The alcohol 92 (1.34 g, 0.59 mol) was dissolved in dry DMF (5 mL). Imidazole (2.2 eq) and \(t\text{-butyldiphenylsilane chloride (1.1 eq)}\) 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; \(^1\text{H NMR (200 MHz, CDCl}_3)\) \(\delta\) 7.81-7.77 (m, 2H), 7.52-7.21 (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; \(^{13}\text{C NMR (200 MHz, CDCl}_3)\) \(\delta\) 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 \(\text{C}_{23}\text{H}_{32}\text{OS}_2\text{Si (M}^+\text{-C}_6\text{H}_6)\): 407.0960. found 407.0933; MS (CI) calcd for \(\text{C}_{11}\text{H}_{13}\text{S}_2 (M}^+\text{-C}_{16}\text{H}_{10}\text{OSi) 208.9. found 208.9 (100%): Anal. Calcd for \(\text{C}_{27}\text{H}_{32}\text{OS}_2\text{Si: C, 69.78; H, 6.94. Found: C, 69.93; H, 6.83.}\)
Preparation of $\pm$-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, $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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_{11}H_{18}OSi (M -C_{4}H_{10})
435 1274, found 435 1256, MS (Cl) calcd for C_{2}H_{2}OSi 435.1, found 434.8 (62\%).

Attempted Preparation of (±)-2-(t-Butyldimethylsilyloxy)-2-phenylethan-1-one (94)

\[
\begin{align*}
\text{OTBS} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

The dithiane 93 (224 mg, 0.7 mmol) was dissolved in a 6:1 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, CDCl₃) 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, CDCl₃) δ 199.5, 136.5, 128.7, 128.3, 126.4, 79.9, 25.7, 18.3, -4.9.
Preparation of (+)-2-(t-Butyldimethylsilyloxy)-1-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 (CH₂Cl₂ cm⁻¹) 3054, 2986, 2957, 1735, 1440, 1269, 1100; ¹H NMR (200 MHz, CDCl₃) 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 (CH₂Cl₂, cm⁻¹) 3466, 3057, 2946, 1736, 1447, 1266, 1102, 738; ¹H NMR (500 MHz, CDCl₃) δ 7.27-7.15 (m, 5H), 4.24 (m, J₁ = 11.8 Hz, J₂ = 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) ¹³C NMR (500 MHz, CDCl₃) 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 procedure⁶⁶ 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.
NMR (200 MHz, CDCl₃) δ 7.30-7.12 (m, 5H), 4.24 (t, J₁ = 11.8 Hz, J₂ = 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 procedure⁵⁶, 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$_3$ $\delta$ 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$_3$) $\delta$ 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$_2$Si (M$^+$ -C$_4$H$_9$) 223.0791. found 223.0783.

**Preparation of Authentic (±) Methyl 2-(Hydroxy)-4-phenylbutanoate (I11)**

![Methyl 2-(Hydroxy)-4-phenylbutanoate](image)

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; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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, CDCl₃) 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); ¹³C NMR (200 MHz, CDCl₃) 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
5 REFERENCES


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-tert-butyl(dimethyl)siloxy-4-phenyl-1-(1,3-dithiacyclohexane)butan-2-one to the methyl ester. Alternatively, the aldehyde was oxidized to the acid and then esterified.
<table>
<thead>
<tr>
<th>INDEX</th>
<th>FREQ</th>
<th>PPM</th>
<th>INTENSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>1471.21</td>
<td>7.357</td>
<td>35.245</td>
</tr>
<tr>
<td>02</td>
<td>1466.36</td>
<td>7.333</td>
<td>33.461</td>
</tr>
<tr>
<td>03</td>
<td>1463.52</td>
<td>7.318</td>
<td>81.688</td>
</tr>
<tr>
<td>04</td>
<td>1481.42</td>
<td>7.306</td>
<td>30.642</td>
</tr>
<tr>
<td>05</td>
<td>1469.51</td>
<td>7.305</td>
<td>37.876</td>
</tr>
<tr>
<td>06</td>
<td>1450.16</td>
<td>7.292</td>
<td>38.225</td>
</tr>
<tr>
<td>07</td>
<td>1455.64</td>
<td>7.279</td>
<td>22.640</td>
</tr>
<tr>
<td>08</td>
<td>947.46</td>
<td>4.736</td>
<td>32.034</td>
</tr>
<tr>
<td>09</td>
<td>940.22</td>
<td>4.702</td>
<td>36.475</td>
</tr>
<tr>
<td>10</td>
<td>954.37</td>
<td>4.272</td>
<td>33.785</td>
</tr>
<tr>
<td>11</td>
<td>947.23</td>
<td>4.237</td>
<td>33.294</td>
</tr>
<tr>
<td>12</td>
<td>584.20</td>
<td>2.822</td>
<td>23.495</td>
</tr>
<tr>
<td>13</td>
<td>561.89</td>
<td>2.669</td>
<td>30.763</td>
</tr>
<tr>
<td>14</td>
<td>557.10</td>
<td>2.786</td>
<td>26.462</td>
</tr>
<tr>
<td>15</td>
<td>554.43</td>
<td>2.773</td>
<td>25.453</td>
</tr>
<tr>
<td>16</td>
<td>551.85</td>
<td>2.753</td>
<td>46.315</td>
</tr>
<tr>
<td>17</td>
<td>547.86</td>
<td>2.733</td>
<td>39.710</td>
</tr>
<tr>
<td>18</td>
<td>541.90</td>
<td>2.710</td>
<td>32.902</td>
</tr>
<tr>
<td>19</td>
<td>539.10</td>
<td>2.696</td>
<td>20.907</td>
</tr>
<tr>
<td>20</td>
<td>480.30</td>
<td>2.882</td>
<td>15.310</td>
</tr>
<tr>
<td>21</td>
<td>171.46</td>
<td>0.857</td>
<td>556.025</td>
</tr>
<tr>
<td>22</td>
<td>12.59</td>
<td>0.962</td>
<td>472.463</td>
</tr>
<tr>
<td>23</td>
<td>-34.57</td>
<td>-0.173</td>
<td>106.061</td>
</tr>
</tbody>
</table>
SPECTRAL LINES FOR TH = 14.17
RFL = 1681.2 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 7.267 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
11 166.81 0.944 298.262
12 166.66 0.933 114.978
13 161.85 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