DOCTOR OF PHILOSOPHY

Synthetic studies in cyclopropane chemistry

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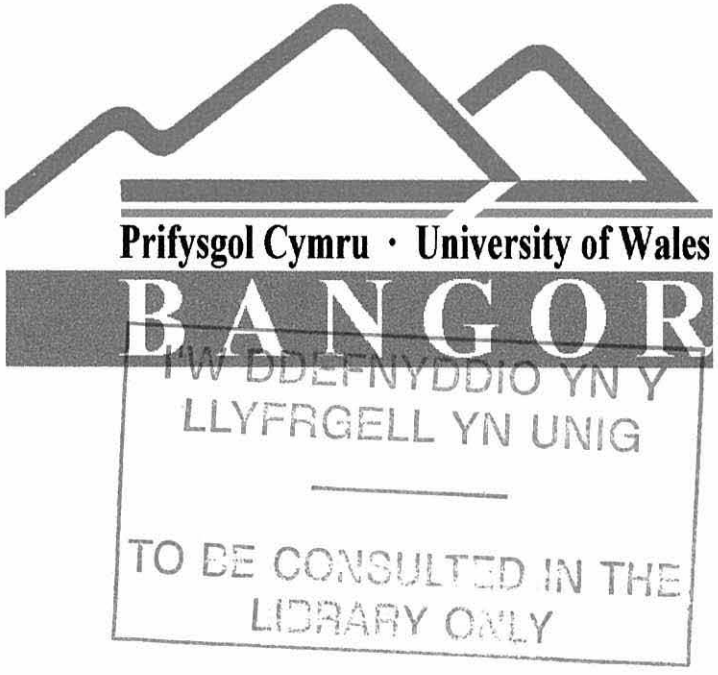
Synthetic Studies in Cyclopropane Chemistry



A thesis submitted to the University of Wales, Bangor
in candidature for the degree of
Doctor of Philosophy

by

Peter Licence BSc (Wales) 1996

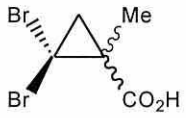
2000

This PhD thesis is dedicated to my family, in particular to my Mum and Dad without whose love and support this work would not of been possible.

Abstract

This PhD thesis describes the laboratory scale preparation of a number of optically active, cyclopropane containing building blocks that are derived from simple, readily available starting materials. The methodologies employed during the completion of these studies may be readily divided into two discrete groups: Firstly, the chemical resolution of racemic starting materials via both reagent and enzymatically mediated routes. And secondly, the induced stereoselective cyclopropanation of optically active starting materials drawn directly from the "chiral pool".

The racemic cyclopropane containing carboxylic acids 2,2-dibromo-1-methylcyclopropanecarboxylic acid (***i***), and 2,2-dibromocyclopropanecarboxylic acid (***ii***) were readily resolved in moderate yields using the commercially available optically active amines, (+)-dehydroabietylamine and (+) or (-)-(α)-methyl benzylamine respectively.



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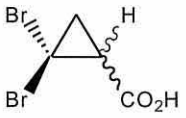
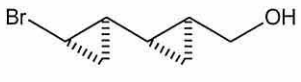


ii

Furthermore, the resolved carboxylic acids (+) and (-)-(***ii***) have successfully been employed in the development of a versatile synthetic route that enables the stereocontrolled stepwise construction of polycyclopropane containing arrays such as those found in the natural products FR-900848 and U-106305, examples prepared include (***iii*** – ***vi***).

iii



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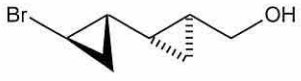

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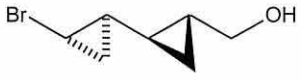


vi

The stereocontrolled cyclopropanation of the unsaturated sugar methyl-4,6-*O*-benzylidene-α-D-erythro-hex-2-enopyranoside has allowed the moderately large-scale preparation of the polyfunctionalised chiral building block, ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-propane-1,2,3-triol, a molecule that shows considerable potential for application in synthesis.

Acknowledgements

First and foremost, I would like to express sincere thanks to my supervisor, Professor Mark S. Baird for the constant support and encouragement that he has provided throughout the highs and lows that were experienced during the preparation of this thesis. I fear, if it wasn't for his optimism and determination, this thesis would still be a pile of loose papers hiding somewhere in the bottom of a cupboard. For this, I am deeply indebted.

Considerable thanks are also due to a couple of very special friends, firstly, Dr Juma'a Al-Dulayymi, whose friendship and wisdom I have grown to cherish during my time in Bangor, and secondly, Professor Ivan G. Bolesov whose inspiration and advice has been greatly appreciated over the past four years. Furthermore, I would like to extend my thanks to all of my colleagues and friends from both group 101 and the Department of Chemistry in general, especially to Mr Evan Roberts, Dr Florian Huber, Dr T. Huw Roberts and Dr Slava Tverezovsky.

Special thanks also go to the technical and administrative staff in the Department of Chemistry without whose enduring support; this work could not be completed. Last but not least, it remains for me to thank my generous sponsors the EPSRC for the financial support that has allowed me to carry out this work.

Abbreviations and Acronyms

ACC	1-amino-1-cyclopropanecarboxylic acid
AM1	Austin Model 1
bp	boiling point
CI	chemical ionisation
de	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EAA	excitatory amino acid
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
gem-	geminal
GCMS	gas chromatographic mass spectroscopy
GLC	gas liquid chromatography
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HSV	herpes simplex virus
Hz	hertz
IPA	*iso*-propyl alcohol (propan-2-ol)
LD_{50}	lethal dose fifty: the amount of a toxic agent (as a poison, virus or radiation) that is sufficient to kill 50 % of a given population or organisms within a given time
M	molar
Me	methyl
mGluRs	metabotropic glutamate receptors
MHz	megahertz
mp	melting point

Ms	mesyl
NMO	4-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
petrol	petroleum ether
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTC	phase transfer catalyst
PTSA	*p*-toluenesulfonic acid
SCF	Self Consistent Field approximation
TBAF	tetrabutylammonium fluoride
TBDPS-Cl	*t*-butyldiphenylsilyl chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl; *p*-toluenesulfonyl (*p*-Me-C_6H_4-SO_2-)
vic-	vicinal

Table of Contents

Introduction

1 Introduction

1.1 Structure and Bonding in Three Membered Carbocycles

1.1.1 Cyclopropanes

Cyclopropanes are unique among carbocycles in their bonding and consequently their associated reactivity and chemical properties.[1] Such reactivity, not shown in larger carbocycles such as cyclopentane and cyclohexane, has led to the application of cyclopropanes as mechanistic probes in the study of numerous reaction mechanisms and similarly in the study of reactive intermediates.[2] Cyclopropanes are highly strained molecules, the strain energy of cyclopropane itself being 115 $kJmol^{-1}$.[3] This is due to the acute bond angles and the fact that the carbon - hydrogen bonds are all eclipsed to one another. The inter-carbon (C-C-C) "pseudo bond angles" and inter atomic distances associated with cyclopropane may be seen in **Figure 1.1** compared with those of cyclohexane.

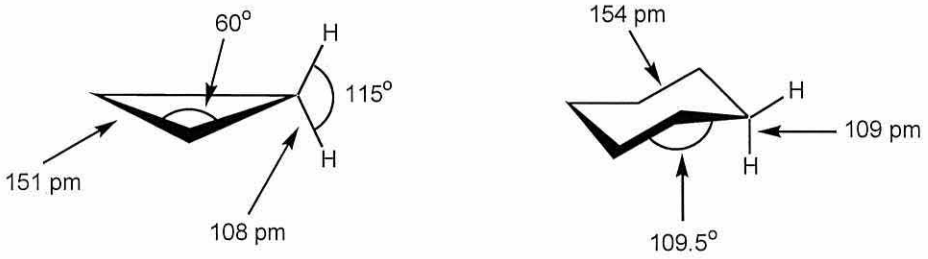


Figure 1.1

As can be seen in **Figure 1.1**, the internal C-C-C angle in cyclopropane is noted at 60°, which is considerably less than the natural bond angle of 109.5° for sp^3 hybridised carbon. To account for this we must consider the hybridisation of the atomic orbitals involved in the bonding of the cyclopropane ring.[4] Unlike normal sp^3 hybridised carbon where each of the four hybrid orbitals is approximately equal, the hybrid orbitals formed about a cyclopropyl carbon are far from equal. To satisfy the geometrical requirements of the structure, the internal orbitals, those involved in carbon - carbon bond formation, must be rich in *p* character, leaving the remaining external orbitals consequently rich in *s* character. The carbon - carbon bonds in cyclopropane are hence formed from the overlapping of two sp^5 hybrid orbitals. Molecular calculations[4] show that such bonds are not truly σ in character and that the bulk of the electron density associated with the bond does not lie about the line that

directly joins the two atoms together (bond path). As a result, the combination of these orbitals leads to the formation of a bent, or so called "*banana*" bond.[5] Consequently, the carbon - carbon bonds of cyclopropane are slightly shorter (the true length lies along the curved path that is significantly longer than the inter atomic distance) and hence weaker than those of normal alkanes. To compensate for the fact that extra *p* character is used in the carbon - carbon bonds, the carbon - hydrogen bonds exhibit more *s* character. Consequently, the bond becomes shorter and stronger than the average alkyl carbon - hydrogen bond; the bond angle is also changed, becoming slightly greater than the tetrahedral angle at 115°. **Figure 1.2** shows a diagrammatic representation of the Förster-Coulson-Moffitt[4,5] bonding model for cyclopropane.

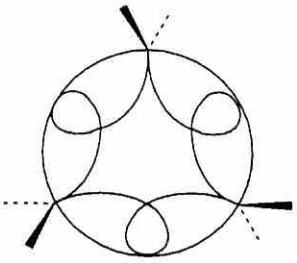


Figure 1.2

X-ray crystallographic studies of cyclopropane derivatives have proved this theoretical model to be correct. It has been shown that the deformation density of the carbon - carbon bonds indeed lies outside the triangle formed by the three carbon atoms. A plot of this type, based upon the theoretically calculated electron density is shown in **Figure 1.3**.[6]

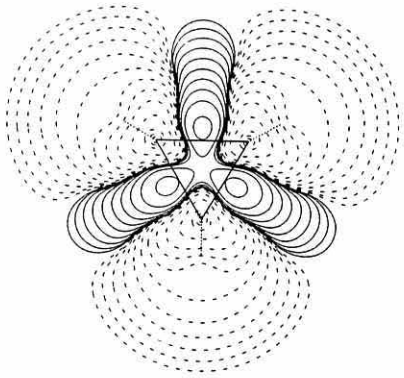


Figure 1.3

1.1.2 Cyclopropenes

As the chemically educated mind may well imagine, cyclopropenes are a group of very highly strained molecules, in fact, it has been calculated that cyclopropene itself has a ring strain equal to *ca* 219 $kJmol^{-1}$.[7] This additional strain is due to a deviation in the hybridisation of the alkene carbons away from the ideal sp^2 arrangement observed in open chain and large ring alkenes. Analysis of structural data from a range of cyclopropene derivatives has led to the conclusion that the alkene carbon atoms employ $sp^{1.19}$ hybrid orbitals in bonding to substituent groups and $sp^{2.68}$ hybrids to the σ framework.[8] The unusual hybridisation involved in cyclopropenes is manifested in the unusual bond angles encountered with C(1)–C(2)–C(3) being 64.5° and C(1)-C(3)-C(2) being 51°.[9] The bond lengths associated with cyclopropene may be seen in **Figure 1.4.**

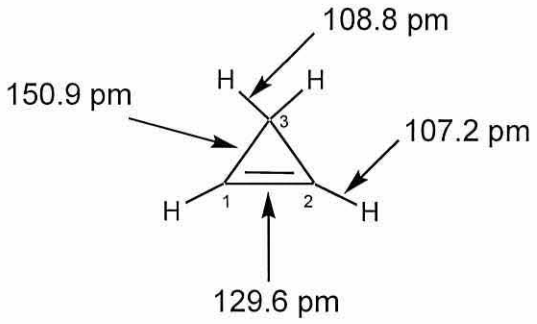


Figure 1.4

1.2 Strain in Small Ring Structures

1.2.1 The concept of Strain[6]

As a result of the rapid development of scientific technique in the latter half of the nineteenth century, it was noticed that many organic compounds contained five and six membered rings; smaller rings were very rarely observed. These observations led Adolf von Baeyer to present his theory of molecular strain in 1885.[10] In his paper, Baeyer deduced that small, three and four membered rings would be less stable due to the deviation in bond angles away from the normal tetrahedral values as described by van't Hoff and LeBel in 1874.

The concept of molecular strain has since been developed from von Baeyer's original theories[10] and it is now accepted that bond angle distortion is not the only

contributing factor towards the overall strain of a molecule. The total strain within a given molecule may be described as a function with terms corresponding to: bond length distortion, bond angle distortion, torsional strain, non-bonded interactions and a final term that describes any energy change resulting from a change in hybridisation.

1.2.2 Calculation of Strain Energies[6]

The strain energy of a molecule is derived from its observed heat of formation from the elements (ΔH_f) by comparison with a hypothetical "strain less" model system. For example, cyclohexane is very often employed as an arbitrary standard, its heat of formation is –123.4 kJmol^{-1}, equivalent to –20.6 kJmol^{-1} per methylene group. Using this value we can calculate the expected heat of formation for "strain less" cyclopropane as –61.7 kJmol^{-1}. This figure must be compared with the experimentally derived heat of formation for cyclopropane; +53.3 kJmol^{-1}. The difference between these figures is equal to the strain energy; in this case the value is 115 kJmol^{-1}. The heats of formation and strain energies of some selected examples are shown in **Table 1**.

							
ΔH_f /kJmol^{-1}	+53.3	+28.4	-77.2	-123.4	+62.6	+47.9	+84.0
SE /kJmol^{-1}	115.0	110.9	25.9	0.0	218.8	117.1	406.7

Table 1. Experimentally determined heats of formation (ΔH_f) and calculated strain energies (SE)[11]

Strain energies have proved to be very valuable "yardstick" with which to examine organic compounds with unusual geometries. The heats of formation of molecules composed of different numbers of atoms are difficult to compare directly, whereas the strain energy only considers the number of bonds and atoms present, therefore giving a value that is more easily compared among compounds of differing composition.

1.2.3 Chemical Consequences of Strain

One might consider that the release of increased molecular strain by strained molecules such as those seen in **Table 1** would lead to a substantial increase in their reactivity, and hence, rate of reaction; this is however, not always the case. Major factors that must be considered when answering the question of reactivity are the

location of the transition state or activated species along the reaction co-ordinate and the strain energies associated with the products or reactive intermediates formed during the reaction. If the structure of the transition state or activated species closely resembled that of the reactants, then very little of the strain energy would be released in the rate-determining step, hence, there would be little rate acceleration. This point is illustrated by the action of electrophiles on cyclopropanes and cyclobutanes.[6] It can be seen in **Figure 1.5** that the release of strain energy is essentially the same, but whereas cyclopropanes are quite reactive, cyclobutanes are essentially inert.

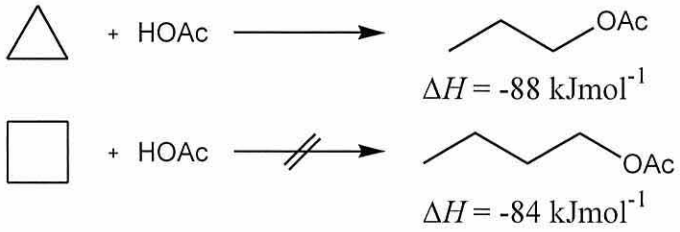


Figure 1.5

1.3 Cyclopropanes in Nature

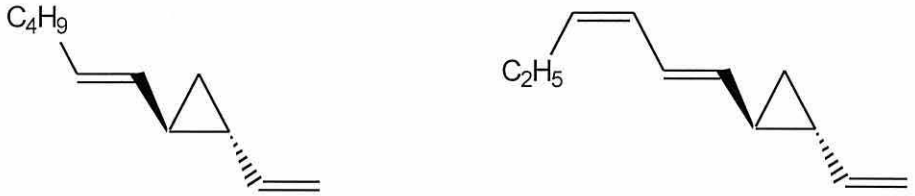
1.3.1 Introduction

Cyclopropane containing compounds, due to their unusual bonding and inherent ring strain, are of great interest to medicinal chemists and bioorganic chemists alike,[12] and have been found to show activity in a wide range of biological functions; properties include: enzyme inhibition, plant growth and fruit ripening control, insecticidal and herbicidal activity, antibiotic and antimicrobial activity, antiviral (HIV, HSV) activity, carcinogenic or antitumoral activity, gluconeogenesis inhibition (hypoglycaemia) and neurochemical activity.[13] The three membered carbocycle is found as a structural element in a wide variety of naturally occurring compounds found in plants and in microorganisms, both fungal and bacterial. The examples outlined in the following survey are classified according to their structural framework and substitution of the cyclopropyl moiety.

1.3.2 Polyacetates

The dictyopterenes A (**1**) and B (**2**) are both examples of polyacetate derived 1,2-disubstituted cyclopropane containing natural products. Both were isolated by the

groups of Moore[14] and Kajiwara[15] from the brown seaweeds *Dictyopteris plagiogramma* and *D. australis* found in the waters around Hawaii. The dictyopterenes all exhibit remarkable physiological activities[16] with the tri-olefinic cyclopropane, dictyopterene B (**2**), being a sex pheromone released by the female plants to attract male gametes. Interestingly, the unusual C_{11} hydrocarbons have a characteristic odour that is associated with ocean beaches.



1 2

Figure 1.6

1.3.3 Fatty Acids

Cyclopropane containing fatty acids are a well known group of compounds that are often found in bacterial membranes. Lactobacillic acid (**3**) has been isolated from *Lactobacillus arabinosus*,[17] *Brucella abortus* and *B. melitensis*[18] and is commonly found in everyday dairy products such as milk and yoghurt.

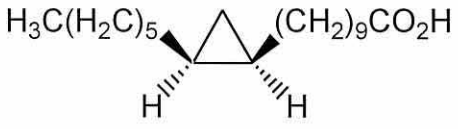


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Figure 1.7

A much larger compound, mycolic acid (**4**) has been isolated from the cell walls of *M. tuberculosis var. hominis*;[19] the bacterium responsible for causing tuberculosis in humans. Until the discovery of streptomycin in 1944 by the American microbiologist Selman Waksman, tuberculosis was the cause of many millions of deaths worldwide.

Unfortunately, tuberculosis is still found to be a major cause of premature death throughout third world countries, in fact the World Health Organisation estimates that up to eight million people contract tuberculosis every year (of which 95 % live in developing countries). Furthermore, it is estimated that approximately 3 million of

these sufferers will die prematurely each year as a direct result of tuberculosis infection.

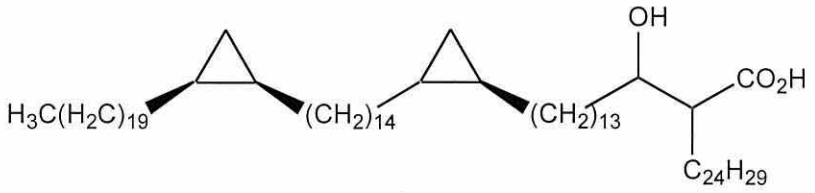

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Figure 1.8

The blue-green mat-forming marine cyanobacterium *Lyngbya majuscala* is noted for its production of biologically active metabolites. Compounds isolated include the cyclopropane fatty acid derivative grenadiene (**5**) which was isolated from *L. majuscala* collected around Grenada in the Southern Caribbean. Grenadiene (**5**) shows an interesting profile of cytotoxicity towards cancer cells and has been selected for *in-vivo* evaluation.[20]

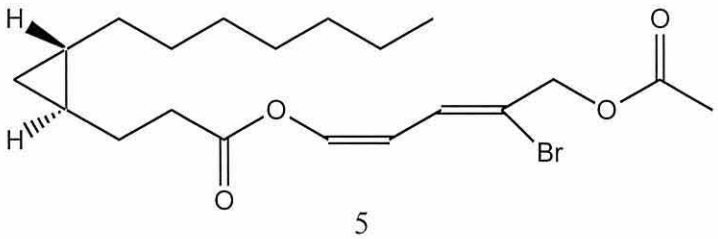

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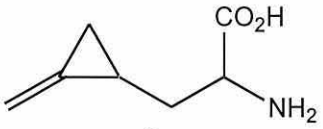
Figure 1.9

1.3.4 Amino Acids

There are very many interesting cyclopropane amino acids. In the following section we shall examine just a few. For a more comprehensive review on cyclopropane amino acids please see the excellent review by Salaün and Baird.[13]

Hypoglycine A (**6**) is an unusual example of a methylenecyclopropane containing amino acid, it is found in the unripe fruit of the *Blighia sapida*[21] (akee tree) and has been found to be the principal causative agent in hypoglycaemia. This toxic condition, also known as Jamaican vomiting sickness has a high incidence in the Caribbean where the syndrome is often termed "ackee ackee" by the locals. The ingestion of hypoglycine A (**6**) (20–200 mg/kg bodyweight) causes the onset of severe hypoglycaemia, within hours of ingestion gluconeogenesis is inhibited and the

animal/human simply runs out of glucose when their glycogen reserves are exhausted.[22]



6

Figure 1.10

The second example, (2*S*, 3*S*, 4*R*)-α-(carboxycyclopropyl) glycine (**7**) is a member of a group of amino acids knows as excitatory amino acids (EAA).[23] EAAs are known to mediate synaptic excitation, and therefore nerve signal transmission within the mammalian central nervous system by binding to EAA receptors.[24] (2*S*, 3*S*, 4*R*)-α-(Carboxycyclopropyl) glycine (**7**) has been identified as a highly selective agonist for Group II metabotropic glutamate receptors (mGluRs).[25] Such receptors have been associated with long lasting changes to nerve cells, and have been implicated in learning and memory functions.

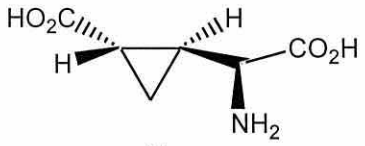


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Figure 1.11

The final example in this group of compounds is the parent, 1-amino-1-cyclopropanecarboxylic acid (ACC) (**8**) and its derivatives which are currently attracting special attention due to their outstanding bioactivity and potential use in conformationaly - constrained peptides, providing both biosynthetic and mechanistic probes.[13] ACC (**8**) is a common constituent in the flesh of apples, pears, grapefruit and many other plant tissues, it is biosynthesised from (*S*)-adenosylmethionine and is the immediate biosynthetic precursor to ethylene, the phytohormone that initiates and controls many aspects of plant growth including germination and fruit ripening.[26]

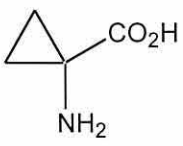

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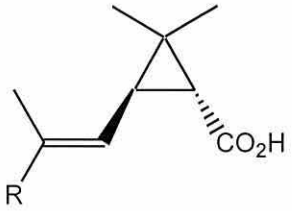
Figure 1.12

1.3.5 Terpenes

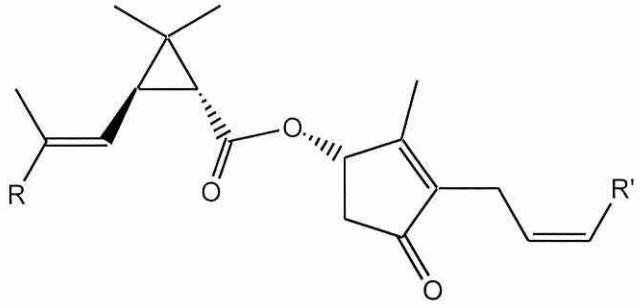
Pyrethroids are a group of cyclopropane containing terpenoids derived from two naturally occurring cyclopropanecarboxylic acids, chrysanthemic (**9**) and pyrethric (**10**) acids.



9, R = Me
10, R = CO_2Me

Figure 1.13

Pyrethrum, a powder prepared from the dried flowers of the common *Chrysanthenum cinarariaefolium*, first found application as an insecticide in the early nineteenth century. The active ingredients are esters of (**9**) and (**10**); the cinerins (**9a**, **10a**), jasmolins (**9b**, **10b**) and pyrethrins (**9c**, **10c**).[27] The latter are not only the most abundant components, but are also the most potent as antifeedants for herbivores. The mechanism of insecticidal action has been attributed to blocking of the sodium channel in target cell membranes and consequent blocking of ion transport pathways.[28]



9a, R = Me, R' = Me, Cinerin I
9b, R = Me, R' = C_2H_5, Jasmolin I
9b, R = Me, R' = $CH=CH_2$, Pyrethrin I
10a, R = CO_2Me, R' = Me, Cinerin II
10b, R = CO_2Me, R' = C_2H_5, Jasmolin II
10b, R = CO_2Me, R' = $CH=CH_2$, Pyrethrin II

Figure 1.14

An enormous effort has gone into the successful development of pyrethroids as commercial insecticides and many thousands of synthetic analogues have been prepared. Many of the synthetic pyrethroids have been found to exhibit increased insecticidal activity and photo stability. The most potent insecticidal activity was achieved with the introduction of a benzylic cyano group and a *gem*-dibromovinyl

substituent with the two main substituents on the cyclopropane ring of deltamethrin (**11**)[29] being orientated *cis*- to one another. Further detail of the pharmacological mechanism of pyrethroids is unknown.

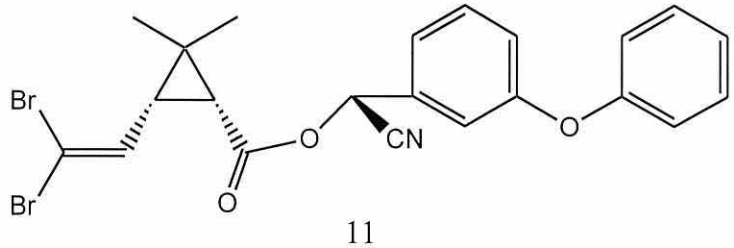


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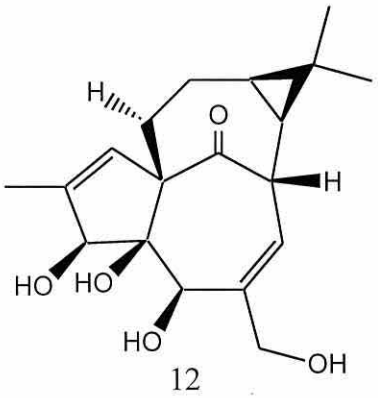
Figure 1.15

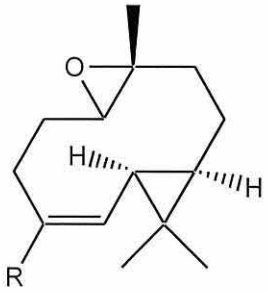
Ingenol (**12**) is a highly oxygenated tetracyclic diterpenoid that was isolated from the *Euphorbia ingens* species of the *Euphorbiaceae* plant family.[30] Ingenol (**12**) mimics the function of diacylglycerol which functions as the endogenous activator of protein kinase C, the phosphorylating enzyme that mediates cellular signal transduction, thereby exhibiting antitumoral activity. Much work has been carried out on the synthesis of ingenol (**12**) and its structural analogues. For a comprehensive review on the differing strategies employed please see the excellent review by Kim and Winkler.[31]



12

Figure 1.16

The final examples of cyclopropane containing terpenes that will be examined are the madolins (**13a-c**), a series of sesquiterpenes isolated from the stem and roots of *Aritolochia cucurbitafolia.*[32]

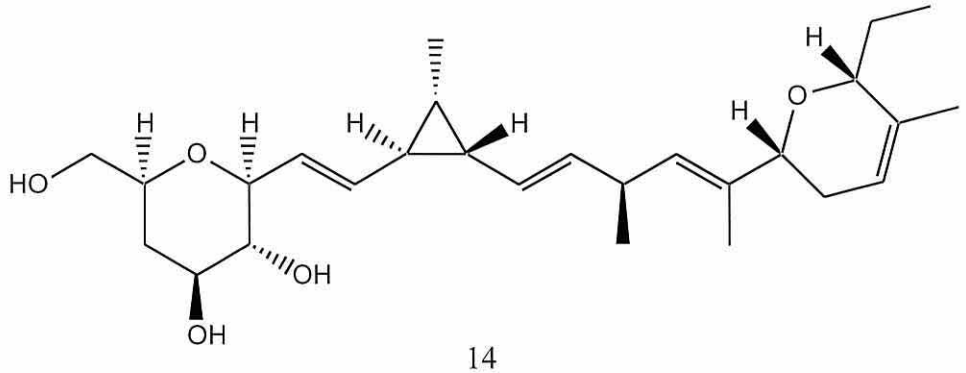


13a, R = CHO, Madolin A
13b, R = CO_2H, Madolin B
13c, R = H, Madolin C

Figure 1.17

1.3.6 Polyether Antibiotics

Ambruticin (**14**) is an antifungal antibiotic agent isolated from the fermentation broth of *Polyangium cellulosum var. fulvum*. It is highly active against systematic pathogenic fungi such as *Histoplasma capsulatum* and *Coccidioides immitis.*



14

Figure 1.18

1.3.7 Steroids

Marine organisms such as the sea sponges of the genus *Xestospongia*, found on the coral reef of Aragusuku island (Okinawa, Japan) have been the source of many steroids whose biogenetic origins have not yet been resolved. The example shown in **Figure 1.19**, aragusterol A (**15**) exhibits potent *in-vivo* antitumoral activity in mice.[33]

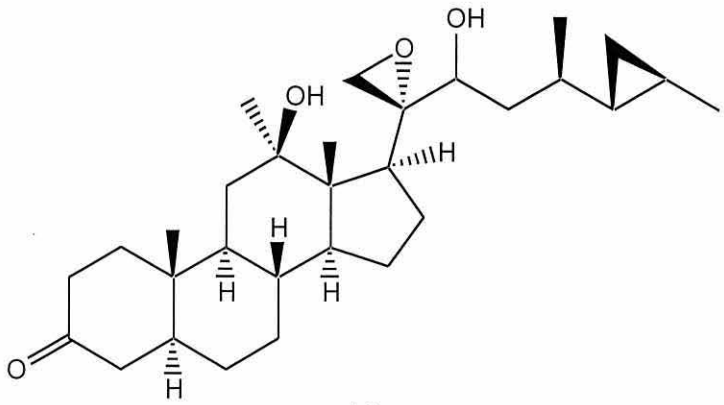


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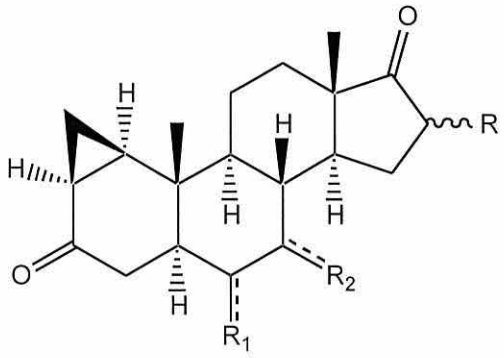
Figure 1.19

Synthesis of steroid analogues has led to the preparation cyclopropylandrostenediones (**16a-b**). These compounds have been found to possess potent anti-cancer properties.[34]

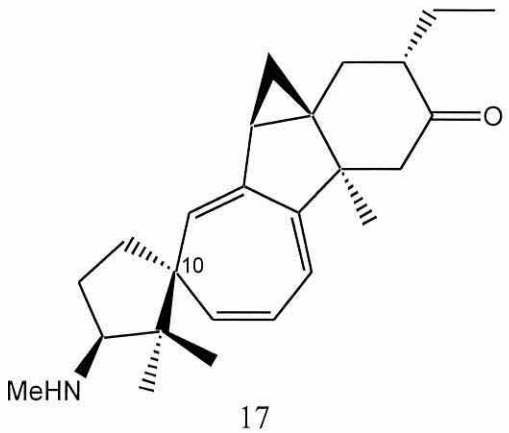


16a, R = H, R_1 or R_2 = CH_2
16b, R = F, R_1 or R_2 = CH_2

Figure 1.20

1.3.8 Alkaloids

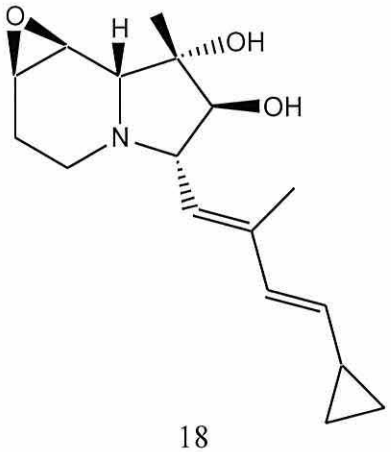
Found widely distributed across the northern landmasses of Europe and Asia, the shrub *Buxus sempervirens* (L.) has been the provider of a great number of bioactive extracts. These extracts known collectively as the Buxus alkaloids have been shown to exhibit a promising activity in the treatment of human immunodeficiency virus (HIV) infection.[35] Spirofornabuxine (**17**) is the first of a new structural family of Buxus alkaloids with a spiro-linked cyclopentane at C10 of the structurally unique cycloheptatriene ring.



17

Figure 1.21

Another interesting alkaloid is the unusual indolizidinediol, cyclizidine (**18**). It was isolated from the *Streptomyces* species NCIB 11649[36] and exhibits non-selective immunostimulatory properties. Furthermore, the acetate of (**18**) exhibits properties associated with β-blocking drugs, i.e. it causes a reduction in the frequency of beats in cultured heart cells.



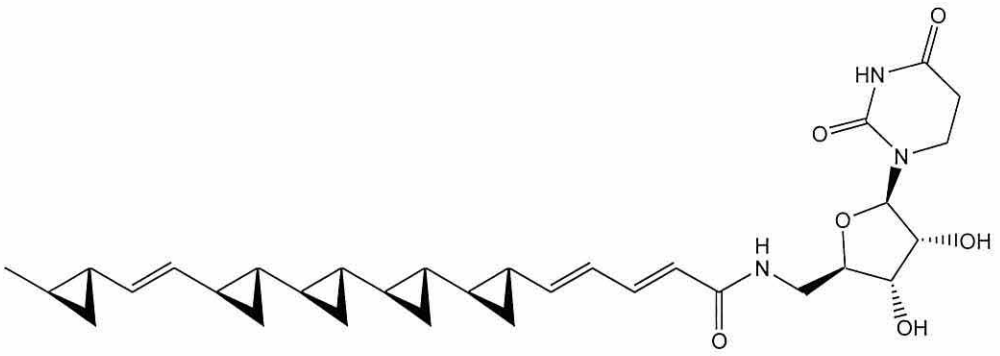
18

Figure 1.22

1.3.9 Polycyclopropanes

In 1990 Yoshida *et al* reported the isolation and partial structure elucidation of a remarkable natural product from the fermentation broth of *Streptoverticillium fervens*.[37] Full structure elucidation[38] and consequently total synthesis of FR-900848 (**19**) was to follow, with the groups of Barrett[39] and Falck[40] publishing independently in 1996. FR-900848 (**19**) displays potent, highly specific inhibitory activity against filamentous fungi and a number of pathogens directly responsible for significant human morbidity/mortality. Its low toxicity towards mammalian forms (LD_{50} > 1

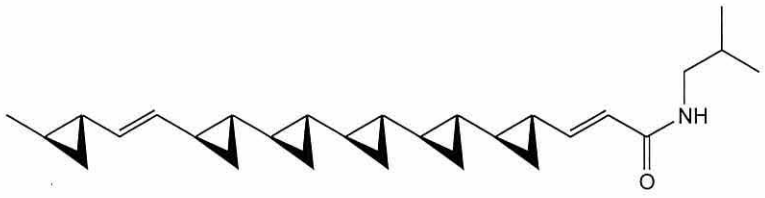
g/kg) renders FR-900848 (**19**) an important development in the effective treatment of drug resistant strains that have evolved due to the over use of existing traditional antibiotic agents.



19

Figure 1.23

A second member of this new class of compounds isolated in 1995 by Kuo *et al*, U-106305 (**20**) was isolated from the fermentation broth of *Streptomyces sp.* UC 11136.[41] Like FR-900848 (**19**), U-106305 (**20**) also exhibits quite striking biological activity. U-106305 (**20**) has been shown to inhibit cholesteryl ester transfer protein (CETP), one of the enzymes responsible for the redistribution of cholesteryl esters. It is commonly felt that this compound may be of interest in the treatment of coronary heart disease. The groups of Barrett[42] and Charette[43] have both completed total syntheses of U-106305 (**20**) with both groups publishing simultaneously in 1996.



20

Figure 1.24

1.4 The Synthesis of Cyclopropanes[44]

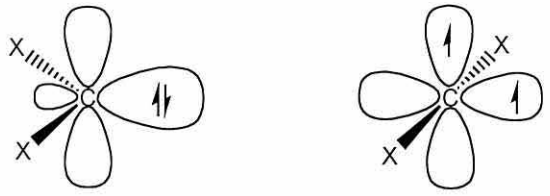
There are many synthetic routes reported in the literature for the efficient introduction of a cyclopropane into the existing carbon framework of a substrate. A brief survey of a number of these synthetic routes is highlighted below.

1.4.1 Combination of a C_2 and a C_1 Unit

1.4.1.1 Carbenes[45]

The trapping of a carbene or carbenoid within electron rich olefinic double bonds has been the favoured route for the introduction of three membered rings since its first reported application by Doering and Hoffmann in 1954.[46]

The term carbene may be defined as "neutrally charged, divalent, reactive intermediate", hence, a carbene would possess two non-bonded electrons. If both of the non-bonded electrons are spin paired, the carbene would exist as a singlet species and would adopt a bent sp^2 hybridised structure. The spin paired non-bonding electrons would occupy a single hybrid orbital leaving a vacant p orbital. Alternatively if the non-bonded electrons have parallel spins, the carbene would be a triplet species; the carbene would have a linear sp hybridised structure with an electron singly occupying each residual p orbital. Representative structures of singlet and triplet carbenes are shown diagrammatically in **Figure 1.25**.

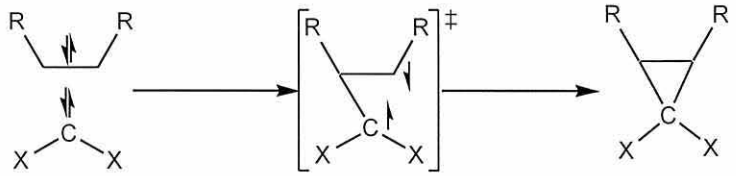


Singlet Triplet

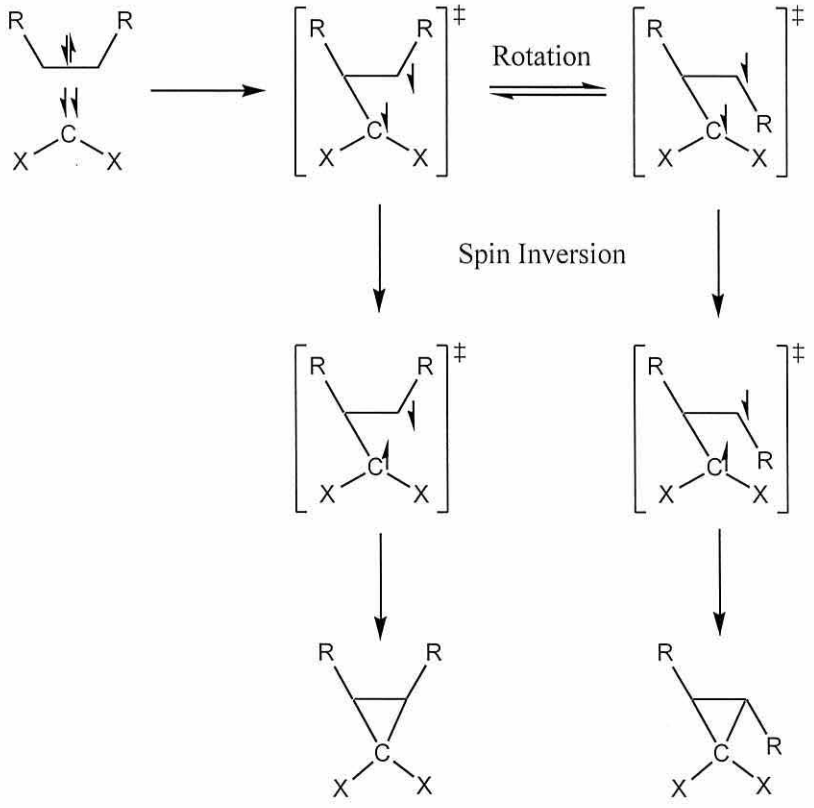
Figure 1.25

The nature of the ground state of the carbene depends upon the relative energies of the two non-bonding orbitals; if the orbitals are degenerate, then Hund's rule decrees that each electron shall occupy a separate orbital and their spins shall be parallel. Alternatively, if the orbitals are non-degenerate, both electrons will occupy the orbital with the lower energy and shall be spin paired.

The stereochemistry of the carbene addition is defined by the spin state of the carbene present during the reaction. This observation was first reported in 1956 by Skell and Woodworth,[47] who showed that singlet carbenes always undergo addition to double bonds in a stereospecific manner; this observation is often considered as evidence of a concerted process. The addition of triplet carbenes on the other hand is non-stereospecific. This is due to an internal rotation within the intermediate as one of the single electrons undergoes a slow spin inversion necessary to enable successful ring closure of the intermediate triplet state 1,3-diradical. The mechanistic processes involved are best described in the form of a diagram and may be seen in **Figure 1.26**.



Stereospecific Singlet Addition



Nonstereospecific Triplet Addition

Figure 1.26

The full stereochemical definitions for the addition of carbenes to double bonds have recently been summarised[48] and are detailed in **Figure 1.27**.

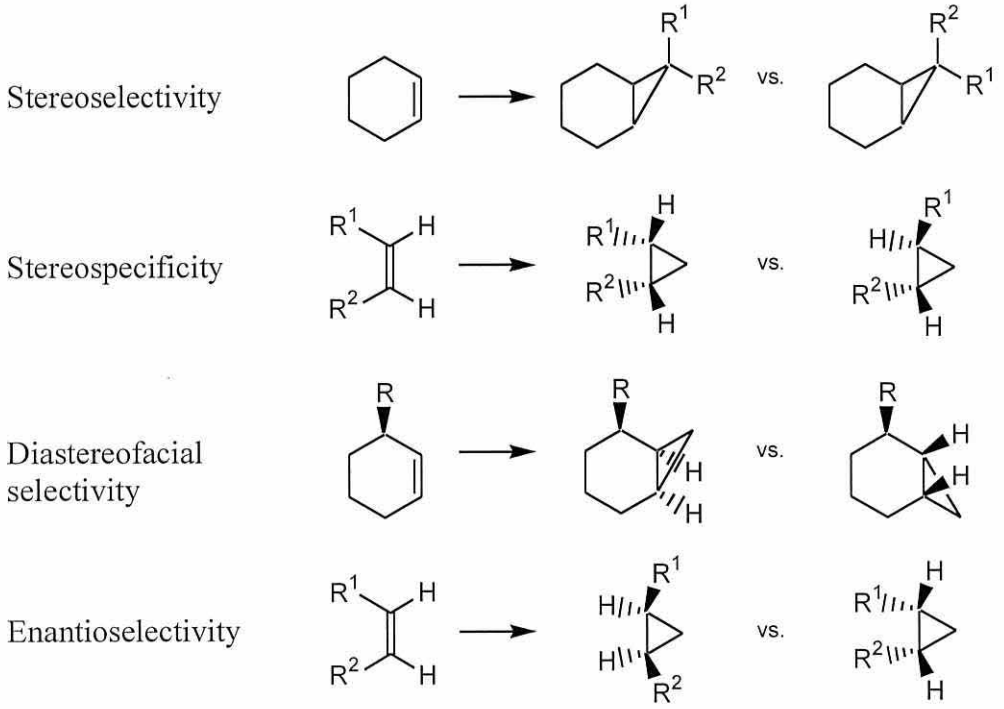


Figure 1.27

1.4.1.2 Dihalocarbenes[49]

The addition of dihalocarbenes to the electron rich olefinic double bond[50] is often the reaction of choice in the preparation of *gem*-dihalocyclopropanes. The singlet ground state of dihalocarbenes ensures that the reaction proceeds in a stereospecific manner, hence preserving the stereochemistry within the alkene component. The reactivity of halocarbenes is dependent upon temperature; **Figure 1.28** illustrates a comparative representation of the reactivities and hence the selectivity of a range of common dihalocarbenes at a given temperature (20 °C).[51]

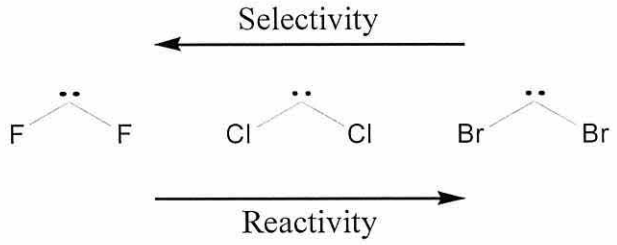


Figure 1.28

Dihalocarbenes may be prepared by a wide variety of reactions. In general they are most conveniently generated from haloforms by one of two commonly applied routes.

The first method of generation, seen in **Figure 1.29**, is the reaction of a haloform with a strong base, generally potassium *t*-butoxide. The reaction was originally reported in 1954 by Doering and Hoffmann[46] and may be explained by the following steps. The strong base deprotonates the haloform so generating a trihalomethyl anion, then elimination of halide ion yields the neutrally charged carbene in moderate yield. The major disadvantage of this procedure is the formation of *t*-butanol as a by-product. The carbene generated may undergo side reactions with *t*-butanol thus lowering the efficiency of the reaction.

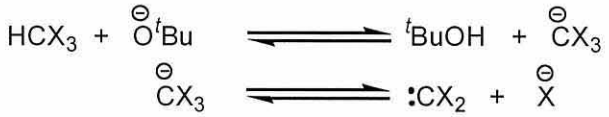


Figure 1.29

The second, more versatile method for generating dihalocarbenes is carried out under phase transfer catalysis. Developed in 1969 by Makosza and Wawrzniewicz,[52] this method is carried out in a biphasic system in which a haloform is treated with a concentrated aqueous sodium hydroxide solution in the presence of a phase transfer catalyst (PTC).[53] Common phase transfer catalysts include crown ethers and more commonly quaternary ammonium salts (QX) such as *n*-hexadecyltrimethylammonium bromide. The postulated mechanism for the generation of dihalocarbenes under phase transfer conditions may be seen diagrammatically in **Figure 1.30**.

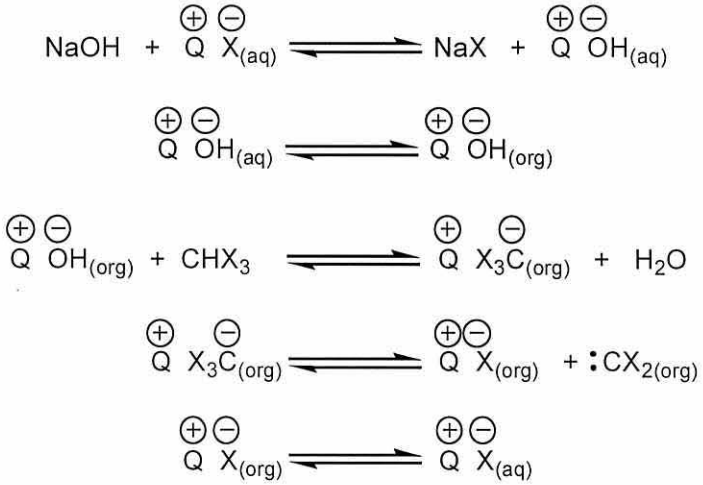


Figure 1.30

Dihalocarbenes can also be generated by a number of other procedures including the thermal decomposition of sodium trihaloacetates,[54] the treatment of

poyhalomethanes with an alkyl lithium reagent,[55] thermolysis of trihalomethyl phenylmercury,[56] or by the treatment of ethyl trihaloacetate with sodium ethoxide.[57]

1.4.1.3 Methylene

The stereospecific trapping of a methylene equivalent by the double bond of an alkene was first reported in 1958 by Simmons and Smith.[58] Since that date, the Simmons Smith reaction has been applied exhaustively in the preparation of cyclopropanes. The original procedure for this reaction involved the generation of a methylene equivalent by the reaction of diiodomethane with zinc - copper couple. It was postulated that the active "reagent" was the product of the initial reaction between the zinc – copper couple and diiodomethane.[59] (Iodomethyl)zinc iodide, or the "zinc reagent" is thought to undergo a concerted cheletropic addition to the olefinic double bond. The formation of a three-membered transition state, **Figure 1.31**, is often used to account for the conservation of alkene configuration within the product.[59]

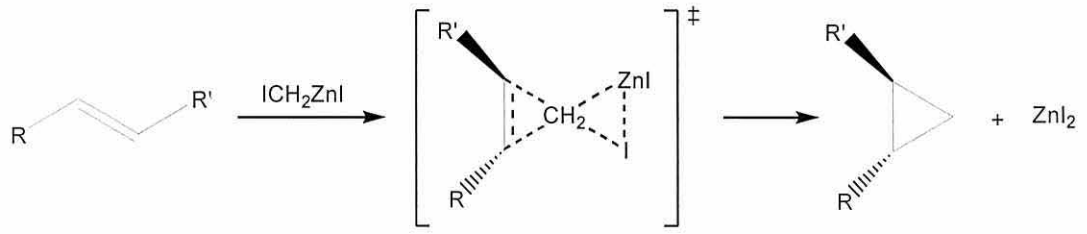


Figure 1.31

One of the initial problems associated with the Simmons Smith reaction was the efficient preparation of the zinc – copper couple.[59] Extensive studies have been carried out on the structure of the active species (halomethyl zinc reagents) and it is believed that (iodomethyl)zinc iodide exists in a Schlenk type equilibrium with bis(iodomethyl) zinc and zinc iodide.[60] The X-ray crystal structure of bis(iodomethyl)zinc was reported by Denmark in 1992;[61] it was demonstrated that this highly reactive species was stabilized by co-ordination to molecules of solvent.

Further development of the Simmons Smith reaction has led to the introduction of more efficient procedures that may be used in the preparation of the carbene equivalent. The application of alkylzinc reagents in the generation of carbenes was introduced in 1968 by Furukawa;[62] the carbenoid generated in the Furukawa modified Simmons Smith reaction is often found to be more reactive than the conventional "zinc reagent". It has been suggested that the increased reactivity is due to the formation of a less sterically congested cyclopropanation reagent.[63]

Another common source of methylene is the photolysis (200–260 nm) of diazomethane. Direct photolysis of diazomethane leads to the preparation of highly reactive singlet carbenes; such species may easily insert into carbon – hydrogen bonds as well as undergoing addition to olefinic double bonds. The competing reactions may, however, be controlled by carrying out the photolytic decomposition in the presence of metal salts. Palladium (II) acetate, for example, has been reported to be a very efficient catalyst for the promotion of the cyclopropanation of alkenes using diazomethane, **Figure 1.32**.[64]

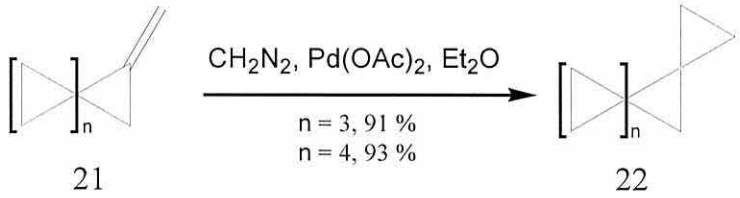


Figure 1.32

1.4.1.4 Cyclopropanation of Michael Acceptors

Many unsaturated systems that are susceptible to Michael additions may also undergo cyclopropanation reactions in the presence of sulfur ylides.[65] An example of such an ylide is dimethyloxosulfonium methanide (**23**); **Figure 1.33** shows the application of (**23**) in the synthesis of a range of novel cyclopropanated barbiturates (**25**).

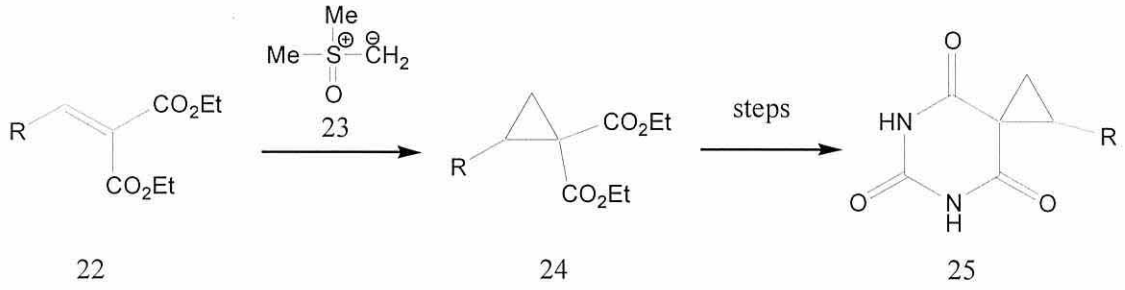


Figure 1.33

1.4.2 From a C_3 Building Block

1.4.2.1 1,3-Elimination of Two Heteroatoms

The reductive elimination of 1,3-dihalides has proved to be an efficient route in the synthesis of a number of highly strained cyclopropanes, most notably being the propellanes.[66] An example of the application of this reaction is shown in the synthesis of [1,1,1]-propellane (**28**), **Figure 1.34**.[67]

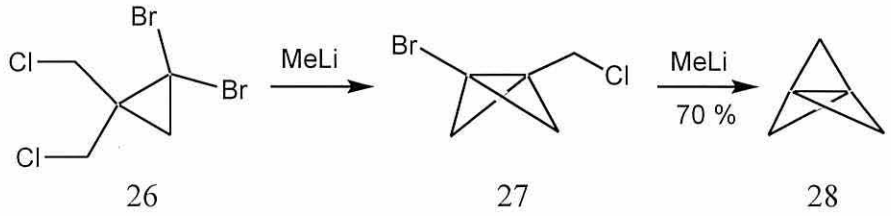


Figure 1.34

1.4.2.2 1,3-Elimination of HX

A very common and convenient general synthesis of cyclopropanes is the intramolecular S_N2 displacement of a suitable leaving group from the γ carbon of a substrate bearing an anion at the α carbon. A generalised form for this type of reaction may be seen in **Figure 1.35** where X is a good leaving group such as a halogen or mesylate/tosylate and ASG is an anion stabilising group such as an ester,[68] ketone[69] or nitrile.[70]

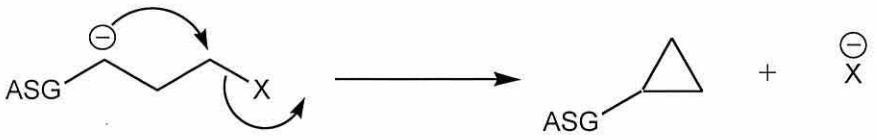


Figure 1.35

1.4.2.3 From Cyclopropenes[71]

The generation of cyclopropanes from cyclopropenes may be realised by the application of a wide variety of reactions. Substituted cyclopropenes readily undergo the addition of organometallic reagents,[72] catalytic hydrogenation and metal hydride reductions with respectable yields.[71] A further example of the reactivity of cyclopropenes is the electrophilic addition of iodine across the double bond.[73] This reaction has found application as an efficient protecting group for cyclopropenes as the

diiodocyclopropane readily undergoes deiodination by reaction with alkyl lithium reagents, **Figure 1.36**.[74]

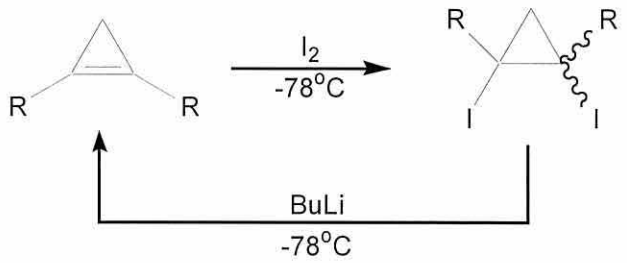
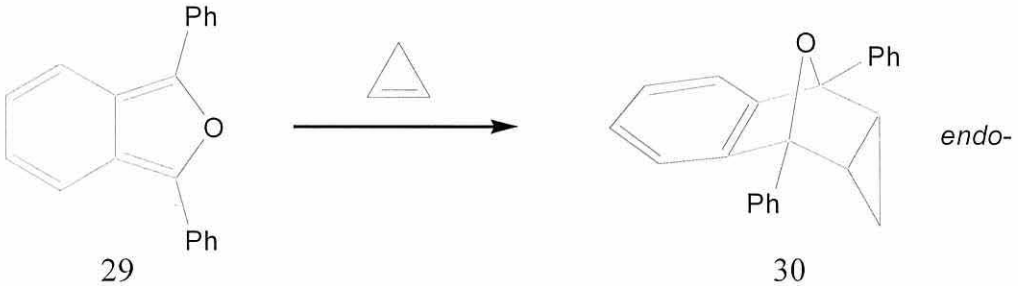


Figure 1.36

As with many activated double bond species, cyclopropenes may undergo a wide range of pericyclic reactions including both [2+2] and [4+2] cycloadditions. Thermally allowed [4+2] (Diels – Alder) cycloadditions in particular, have often been employed as a "chemical trap" enabling the efficient identification of cyclopropenes as intermediate species in a number of reactions.[75]

The stereochemistry of the reaction has been shown to be dependent upon the substitution of both the cyclopropene and the diene component. Cyclopropene along with 1,2-disubstituted analogues yields predominantly *endo*- adducts with most dienes. 3,3-Disubstituted cyclopropenes yield predominantly *exo*- adducts upon reaction with open chain dienes or unhindered cyclic dienes; the use of sterically hindered cyclic dienes for example, substituted cyclopentadienes, on the other hand leads to the formation of primarily *endo*- adducts.[75]

A common reagent that is often employed in the trapping of reactive cyclopropenes is 1,3-diphenylisobenzofuran (**29**). As expected, the stereochemistry of the Diels – Alder adduct (**30**) recovered shows predominantly *endo*- addition, **Figure 1.37**.[76]



29 30

Figure 1.37

1.5 The Enantioselective Synthesis of Chiral Cyclopropanes

Enantioselective syntheses involve the selective generation of new stereogenic centres (stereocentres) by the chemical transformation of prochiral groups into chiral ones. Such transformation may be achieved in one of two ways:

i) As a consequence of asymmetric induction caused by existing stereocentres within the substrate (substrate control of enantioselectivity),

ii) The application of reagents (or catalysts) that are chiral, either intrinsically or as a consequence of becoming transiently "associated" with the substrate throughout the reaction via temporary mechanisms such as chelation or solvation (reagent/catalyst control of enantioselectivity).

The recent application and subsequent modification of materials drawn from the chiral pool has led to a renaissance in the development of new chiral reagents and catalysts for application in synthesis. Such developments combined with the fashionable image associated with "*cleaner, elegant chemistry*" have enabled reagent/catalyst controlled stereoselective syntheses to become a more attractive alternative than the more mundane traditional methodologies.

The former, more traditional approach, originated with Emil Fischer's classical conversion of arabinose into glucose and mannose in 1894;[77] this technique has been applied exhaustively in chiral synthesis since that date. The master of substrate controlled diastereoselective synthesis, R. B. Woodward, demonstrated the power of this technique on many occasions; Woodward's synthesis of vitamin B_{12} stands as a testament to this methodology with the efficient generation of numerous chiral centres within an extensive carbon framework.[78] As these techniques have such a wide range of applications, a short review of their use in the cyclopropanation of alkenes will follow.

1.5.1 Substrate Controlled Enantioselectivity

The formation of new chiral centres may be achieved as a consequence of asymmetric induction from existing stereocentres within the starting material. Such stereocentres may be present directly within the substrate, or may be introduced temporarily in the form of a chiral auxiliary. The presence of existing stereocentre(s) renders the

reaction diastereoselective as opposed to enantioselective; hence, the products of the reaction are diastereomers. It so follows that any transition states involved *en-route* to the products will also be diastereomeric; this means that the energies associated with each transition state, and hence any thermodynamic barriers are not necessarily equal. Assuming that the reaction is effectively irreversible, the ratio of the products recovered is directly related to the difference in transition state energies. Hence, one diastereomeric product may be formed in preference to the other. An example of a diastereoselective reaction including an approximation of the accompanying reaction profile curve may be seen in **Figure 1.38**.

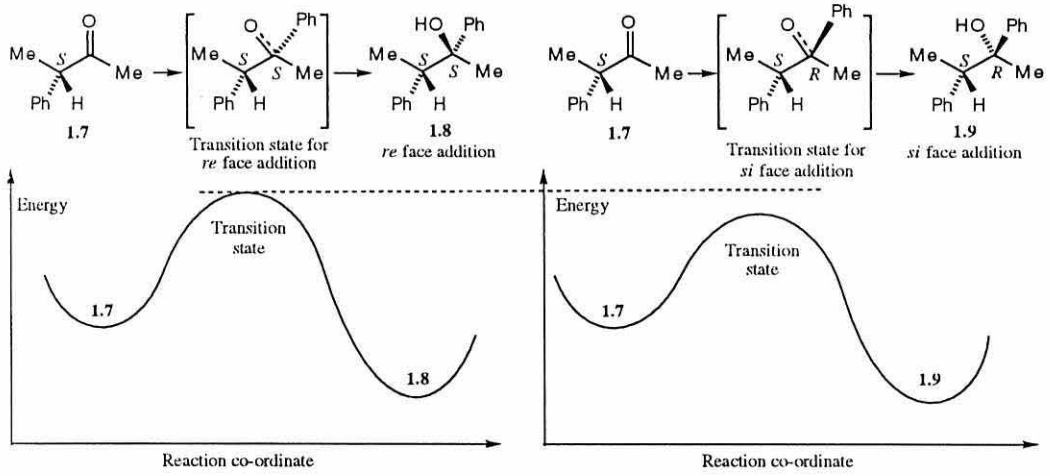


Figure 1.38[79]

1.5.1.1 Induction from Existing Stereocentres

As mentioned in Section **1.5.1**, the presence of existing stereocentres within a substrate renders ensuing reactions upon neighbouring prochiral centres diastereomeric. Hence, the activation energies associated with such diastereomeric transition states are not necessarily equal. Differences in the energies or thermodynamic barriers associated with such transition states give rise to differentiation between diastereotopic reaction sites and hence introduces selectivity. Such differentiation may be accredited to two main principles that are associated with the nature of the controlling stereocentre; these principles are outlined below, but can also be seen diagrammatically in **Figure 1.39**.[80]

i) The proximity of a larger group at the controlling stereocentre may cause extra steric strain within one of the transition states, notably by providing steric hindrance about one diastereotopic reaction site (face). The

influence of such proximal groups has been described as an "inert volume" effect.

ii) The presence of co-ordinating groups such as hydroxyl groups about the controlling stereocentre may lead to the directed addition of the reagent to one diastereotopic reaction site (face); this alternative effect has been described as an "active volume" effect.

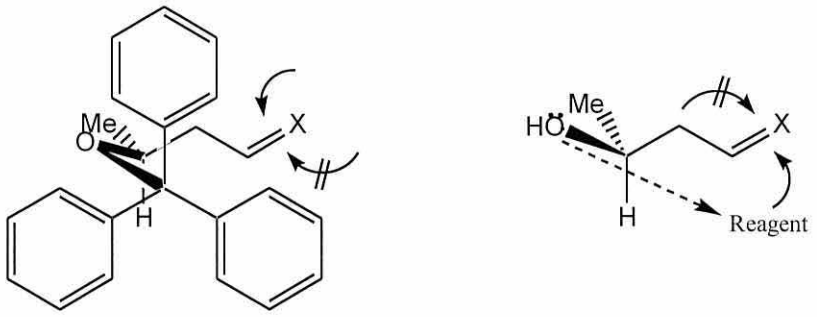


Figure 1.39

The natural carbohydrate D-mannitol (**31**) has often been utilised as a readily available source of the chiral "building block" isopropylidene-D-glyceraldehyde (**32**).[81] This building block and a number of related derivatives have been employed in the synthesis of a wide variety of target molecules including biologically active pyrethtroids[82] and a number of marine metabolites including the constanolactones (**35a, b**).[83]

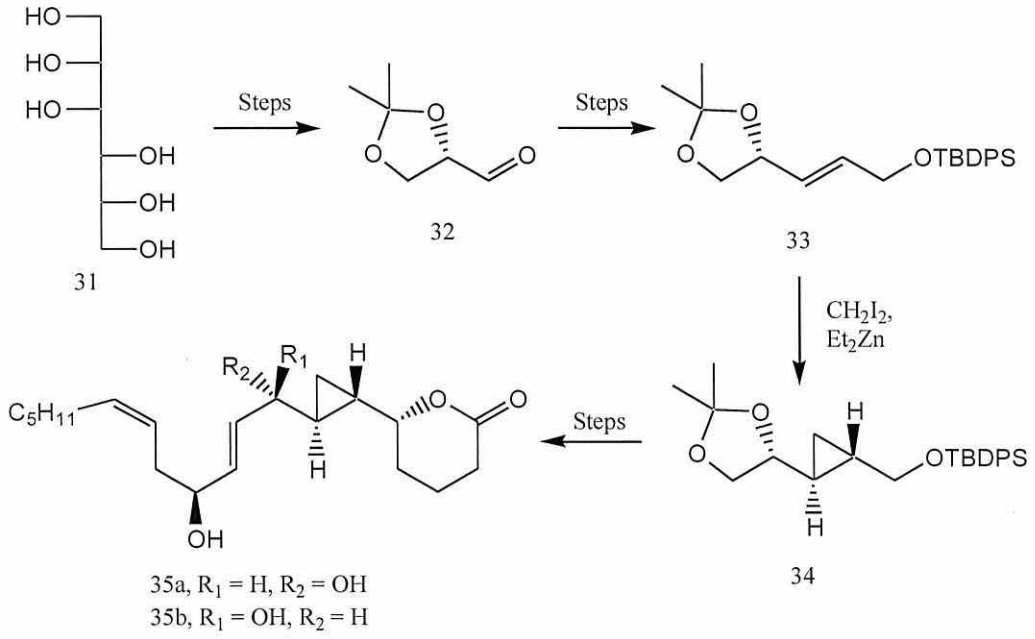
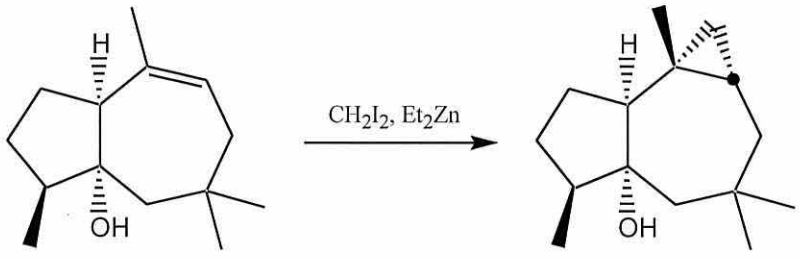


Figure 1.40

The starting material, isopropylidene-D-glyceraldehyde (**32**) was converted into the *trans*-(*E*)-allylic alcohol under standard conditions (Wittig olefination followed by DIBAL-H reduction). Protection of the primary alcohol as its TBDPS ether (**33**) followed by chelation controlled cyclopropanation[84] under Furukawa modified Simmons Smith conditions yielded the optically active constanolactone precursor (**34**) in 97 % yield with "high optical purity". The example cited above, is an example of "active volume" controlled selectivity; chelation of the zinc reagent with the oxygen functionality of the acetal leads to the directed delivery of the methylene group to a single diastereotopic face of the starting material.

A second example of asymmetric cyclopropanation by chiral induction, taken from the total synthesis of africanol (**36**) may be seen in **Figure 1.41**.[85] In the final step of this synthesis, the optically pure bicycle (**35**) is cyclopropanated under Furukawa modified Simmons-Smith conditions to yield the product (**36**) in 81 % yield with a diastereomeric excess of greater than 92 %.



35 36

Figure 1.41

The addition of the methylene group occurs from the less hindered convex face of the starting material bearing the hydroxyl group. Consequently, this example exhibits elements of control due to both steric contributions ("inert volume") and direction due to the co-ordination of the "zinc reagent" with the proximal hydroxyl group ("active volume").

1.5.1.2 The Application of Chiral Auxiliaries

One of the most reliable and hence often employed strategies for achieving enantioselective synthesis has been the application of chiral auxiliaries. A chiral auxiliary may be defined as "a compound that is attached to a prochiral starting material, thereby causing groups or faces within the starting material that were enantiotopic to become diastereotopic". It should be noted that the auxiliary is

chemically bonded to the substrate so forming a discrete, isolable compound, not just an intermediate. The auxiliary may then be cleaved from the product molecule when the desired asymmetric synthetic step has been carried out. This sequence may be outlined schematically in **Figure 1.42**.

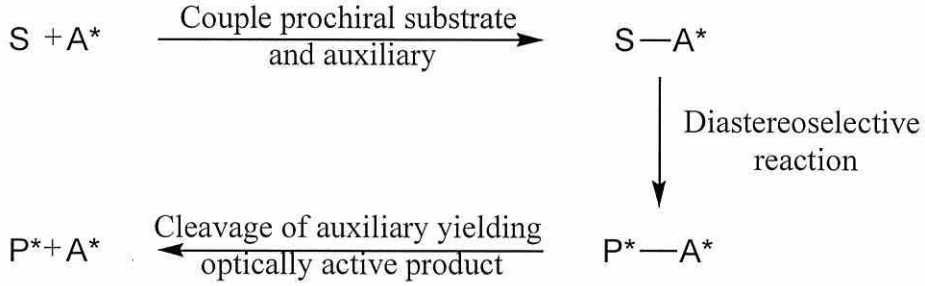


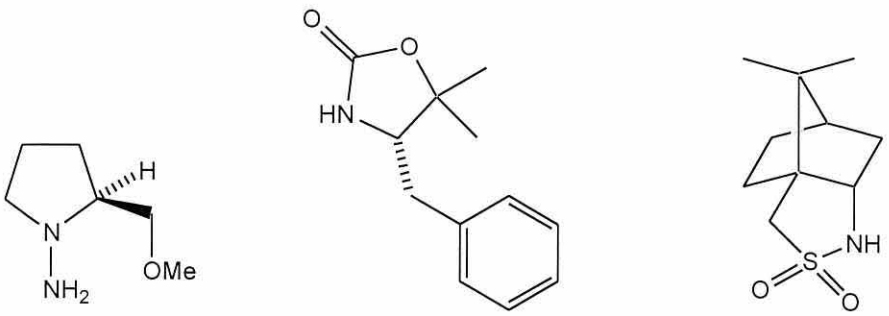
Figure 1.42

Considering the requirements highlighted above, the *ideal* auxiliary may be characterised as possessing both of the following features.

i) A suitable functionality that allows the ready incorporation and removal of the auxiliary to the substrate, both before and after the desired reaction. Important consideration must also be paid to the stability of the auxiliary towards the conditions employed during the reaction.

ii) A sterically demanding structure: Attention must be paid to this property, as it will provide any element of stereocontrol that is required for the successful generation of new chiral centres.

The extensive application of chiral auxiliaries by both industry and academia has subsequently led to the development of a wide range of auxiliaries available for application in many fundamental areas of synthesis including alkylation reactions,[86] Aldol condensations[87] and Diels-Alder cycloadditions.[88] The most commonly applied auxiliaries are generally derived from abundant materials drawn directly from the chiral pool or synthetically modified equivalents of such molecules. Examples include derivatives of carbohydrates, amino acids, terpenes (including camphor, menthol and pinene) and optically active diols. The structures of three commonly used chiral auxiliaries including the amino acid derivative 1(*S*)-amino-2-methoxymethylpyrrolidine (SAMP) (**37**) and an example of Oxford Asymmetry' commercial range of "Superquots" (**38**) are shown in **Figure 1.43**.

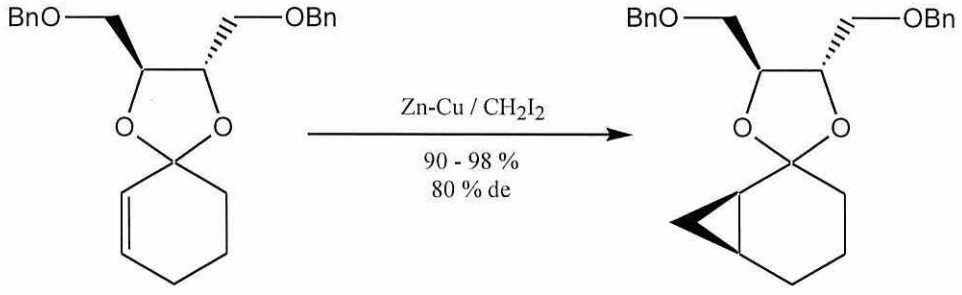


37 38 39

Figure 1.43

The Simmons Smith cyclopropanation in particular, lends itself quite nicely to the application of chiral auxiliaries. Indeed, the cyclopropanations of many substrates modified by the addition of chiral auxiliaries have afforded optically active cyclopropanes with both respectable yields and enantiomeric excesses. In 1968, the group of Sawada and Inouye reported that when (-)-menthol esters of α,β-unsaturated carboxylic acids were subjected to standard Simmons Smith conditions diastereoselectivity was observed. [89] The selectivity observed was small (only 9 % de), but this served as a foundation stone upon which further development could be based.

The systematic variation of the structure of the auxiliary and indeed the substrate-auxiliary connectivity by a number of groups enabled the further development of such reactions. Subsequently, in 1985, Mash reported that, when subjected to classical Simmons Smith conditions, chiral tartrate derived ketals afforded optically active cyclopropanes in excellent yields of 90 – 98 % with reasonably high levels of diastereoselectivity (80 % de),[90] **Figure 1.44**.



40 41

Figure 1.44

In a very similar system, also appearing in 1985, Yamamoto reported the application of dialkyl tartrate derived acetals of cyclic and acyclic α,β-unsaturated aldehydes.[91] Subsequent treatment of the acetal with diethyl zinc and diiodomethane

yielded optically active cyclopropanes in respectable yield (90 %) with correspondingly high diastereomeric excesses of 85 – 94 %. The application of such homochiral protecting groups as chiral auxiliaries has been very popular in synthesis; an example of its successful application in the total synthesis of 5,6-methanoleukotriene A_4 (**44**),[92] a stable and selective inhibitor of leukotriene biosynthesis may be seen in **Figure 1.45**.

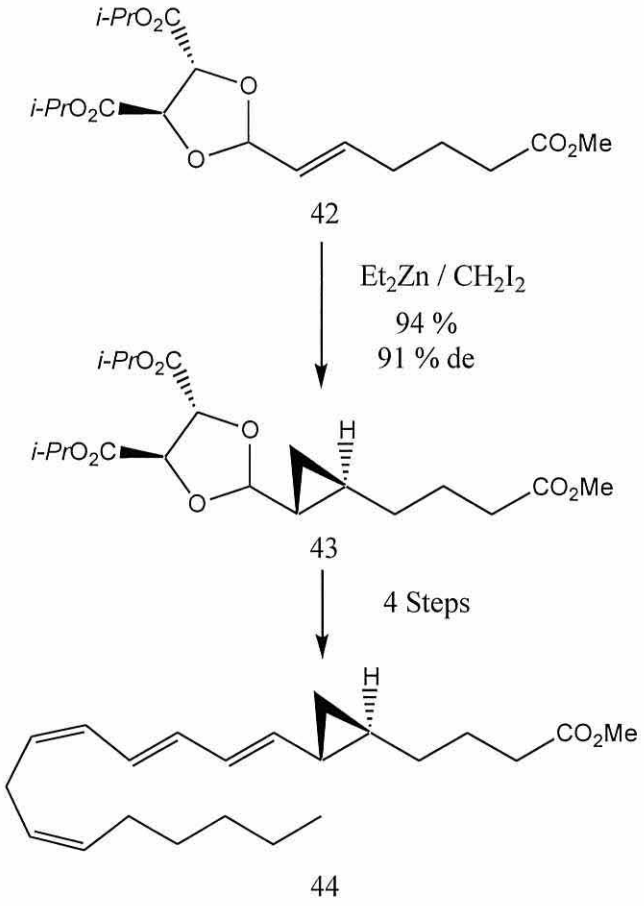
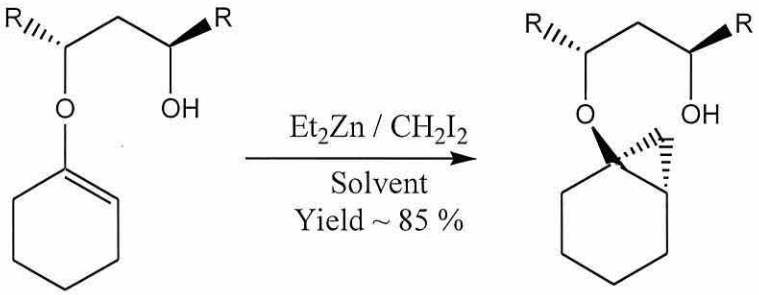


Figure 1.45

An alternative strategy, also employing chiral diols as auxiliaries appeared in the literature just a few years later. In 1988, Tai and co-workers reported that the cyclopropanation of chiral enol ethers derived from optically active diols such as (2*R*, 4*R*)-pentane-2,4-diol (**45a**) proceeded with an element of stereocontrol (with diastereomeric excesses ranging from 8 – 95 %).[93] Furthermore, they noted that the selectivity of the reaction was heavily dependent upon the nature of the solvent employed. It was hence postulated that the formation of an intermediate [substrate – reagent – solvent] complex lead to reagent modification and hence, a substantial reduction in the selectivity of the reaction. This solvent effect was apparently minimised by the introduction of sterically hindered diols, for example (3*S*,5*S*)-2,6-

dimethylheptane-3,5-diol (**45b**). It is thought that the presence of the larger substituent groups suppresses the formation of the intermediate complex, hence preserving the desired selectivity.



45a, R = Me

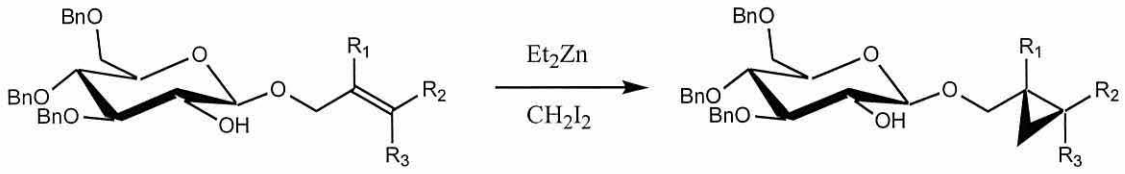
46a, R = Me, de = 8 % in ether
de = 95 % in DME

45b, R = *i*Pr

46b, R = *i*Pr, de = 99.5 % in ether

Figure 1.46

Carbohydrates, being one of the principal sources of naturally occurring chiral compounds are one of the largest contributors to the chiral pool. It is not surprising then that simple carbohydrates have found varied application in the field of enantioselective and diastereoselective synthesis. In particular, the group of Charette has excelled in the application of carbohydrates as chiral auxiliaries in the diastereoselective cyclopropanation of allylic alcohols.[94] 2-Hydroxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose in particular has been shown to be a cheap, efficient and practical auxiliary. Excellent results have been obtained in the asymmetric cyclopropanation of a wide range of substrates with diastereomeric excess of greater than 96 % being reported in near quantitative yield, **Figure 1.47**.



47 48

Figure 1.47

Charette subsequently proved the versatility of this methodology by completing the total synthesis of all four stereoisomers of coronamic acid (**49a-d**),[95] **Figure 1.48**. In this work, Charette was successful in identifying a general synthetic route enabling the efficient synthesis of a wide range of biologically important 3-methanoamino acids.

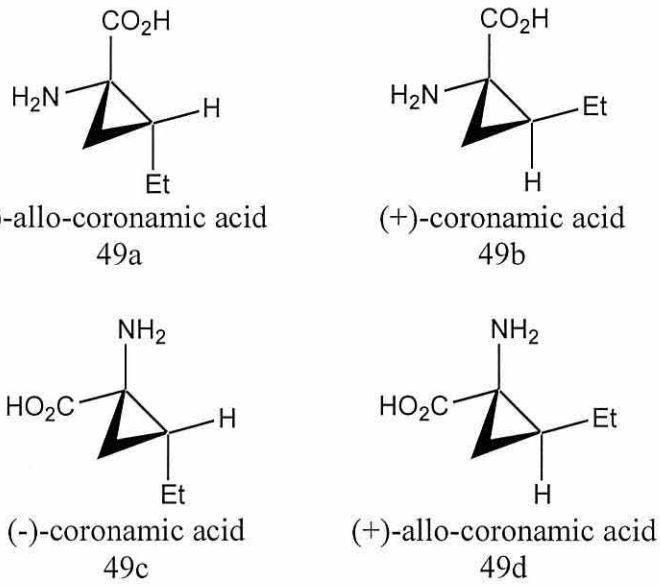


Figure 1.48

The examples highlighted above in Section **1.5.1** form a brief review of substrate controlled asymmetric cyclopropanation reactions; this short review is by no means comprehensive and further examples of related reactions may be found in the literature cited throughout this section and references cited therein.

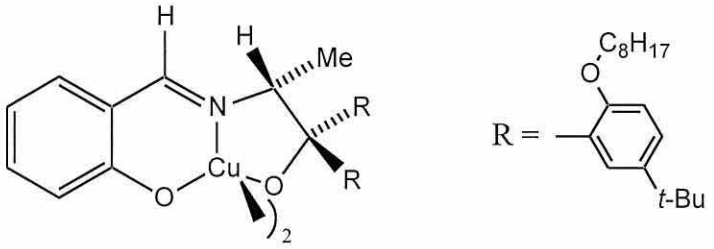
1.5.2 Reagent/Catalyst Controlled Enantioselectivity

The development of catalytic, enantioselective reactions is at present one of the most important and challenging branches of organic chemistry. Indeed the enantioselective cyclopropanation reaction has attracted continued attention since the first reported examples appeared in 1966.[96] The synthesis of optically enriched cyclopropanes may generally be carried out by the application of two distinct classes of reagent, transition metal-based carbenoids or zinc-based carbenoids;[97] each shall be considered separately.

1.5.2.1 Transition Metal-based Carbenoids

Historically the application of transition metal-based carbenoids in the synthesis of chiral cyclopropanes has by far been the most successful. Indeed, the first example of such a reaction was reported by the group of Nozaki in 1966.[96] The application of a copper (II), chiral Schiff base complex enabled the cyclopropanation of styrene (by decomposition of ethyl diazoacetate) to proceed with an enantiomeric excess of less than 10 %. The selectivity of this reaction may well have been low, but the stage was set for further development of this system.

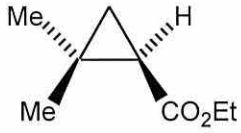
After extensive screening of a range of Schiff base ligands, Aratani and co-workers reported the development of a dimeric copper Shiff base catalyst (**50**).[98]



50

Figure 1.49

Aratani's catalyst has since found commercial application in the synthesis of chrysanthemic acid esters (examples **9a, 9b**) used in pyrethroid synthesis[99] and in the preparation of enantiomerically pure ethyl 2,2-dimethylcyclopropanecarboxylate (**51**) which is used in the synthesis of cilastatin (**52**), an *in-vivo* stabilizer of the antibiotic imipenum (*N*-formidoylthienamycin).[100]



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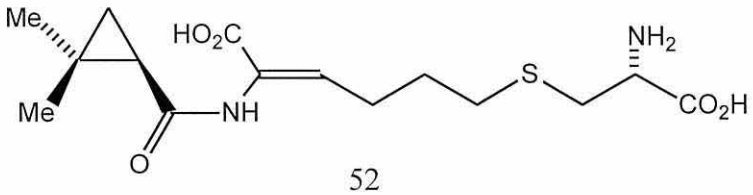


52

Figure 1.50

The development of other transition metal catalysts including the dirhodium (II) complexes employed by the groups of Doyle[101] and Davies,[102] has greatly improved the enantioselectivities and yields obtained from reactions of this type. An example of the synthetic application of this technology is seen in **Figure 1.51**. The intramolecular cyclopropanation of 2-propen-1-yl diazoacetate (**53**) proceeds in respectable yields (greater than 70 %) with a corresponding enantiomeric excess of 95 %.[103] Further examples of the use of transition metal stabilised carbenoids in the synthesis of three membered rings may be found in the recent reviews by Doyle[104] and Davies.

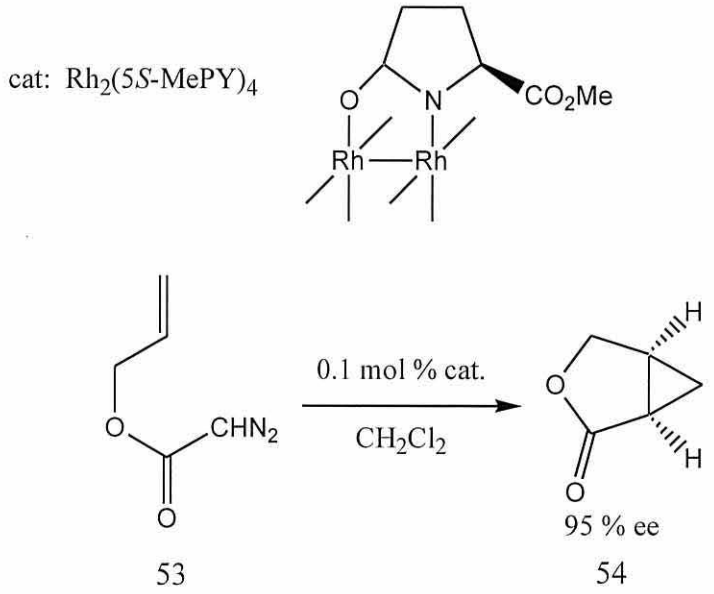


Figure 1.51

1.5.2.2 Zinc-Based Carbenoids

The Simmons Smith reaction, by virtue of its relative simplicity and cheapness has been the focus of much attention and modification, enabling its successful application in the asymmetric synthesis of cyclopropanes. Variants of the Simmons Smith reaction may be easily classified into three clearly defined groups, each dependent upon the nature of the modification applied:

i) Methods based upon the application of chiral auxiliaries (discussed previously in Section **1.5.1.2**).[90 - 96]

ii) Procedures involving stoichiometric equivalents of an external chiral modifier.

iii) The application of sub-stoichiometric amounts of chiral promoters (catalytic).

As highlighted in Section **1.5.1.2**, the application of chiral auxiliaries is indeed very effective in the synthesis of optically active cyclopropanes. Unfortunately, this approach involves the addition of two more synthetic steps, the incorporation of the auxiliary within the starting material, and its subsequent removal upon completion of the desired asymmetric step, (see **Figure 1.42**). This renders the approach rather inefficient; hence the development of alternative routes that avoided the application of covalently bonded auxiliaries has become a very attractive target.

1.5.2.2.1 The Application of Stoichiometric Chiral Modifiers

As expected, many early reports of the application of chiral modifiers in conjunction with the Simmons Smith reagents yielded variable results, typically with moderate yield but showing very little enantioselectivity. For example, in an attempt to further modify his new "zinc reagent" Furukawa reported the attempted asymmetric cyclopropanation of a range of vinyl ethers in the presence of two equivalents of L-leucine.[105] Although no enantiomeric excesses were published in the paper, the very low specific rotations observed in the products laid doubt to the efficiency of L-leucine as a chiral modifier.

In 1992, the group of Fujisawa reported increased levels of enantioselectivity of up to 79 % ee in the cyclopropanation of simple allylic alcohols such as cinnamyl alcohol.[106] The increased levels of enantioselectivity were realised by adding a stoichiometric equivalent of a chiral modifier, a chiral diol, to the reaction mixture. Interestingly Fujisawa *et al* termed this modifier a "chiral auxiliary"; as the intermediate complex formed is non-isolable, this terminology is in fact incorrect (see **1.5.1.2.**).

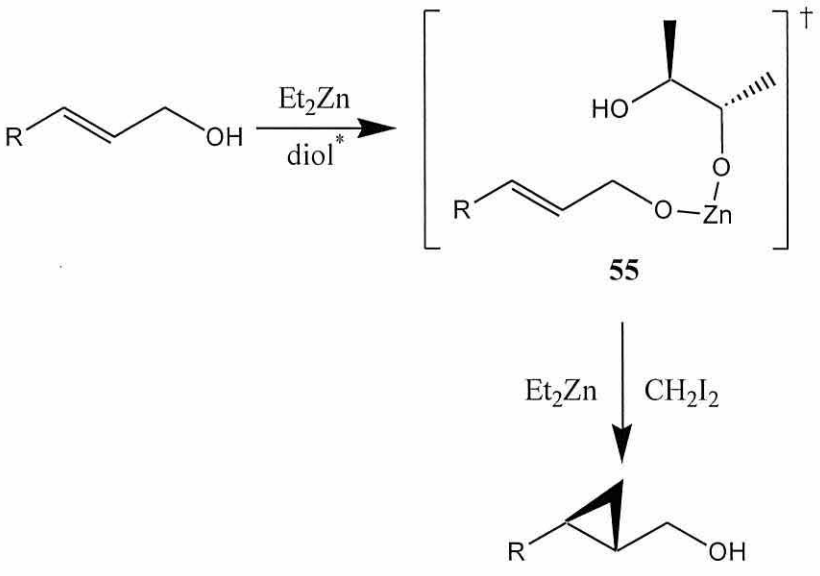
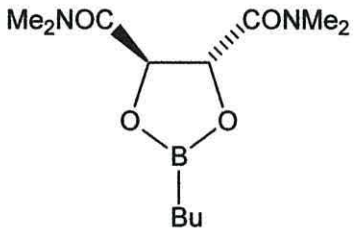


Figure 1.52

The authors postulated that any selectivity was due to a chiral, zinc-bridged intermediate "complex" (**55**) that was formed upon the reaction of the allylic alcohol with diethyl zinc and the chiral diol. Subsequent treatment of the chiral "complex" with a suitable methylene equivalent (diethylzinc and diiodomethane) would lead to selective addition directed by the remaining uncoordinated hydroxyl group of the chiral diol. Hydrolysis of the chiral zincate complex upon work up enables the

recovery of the desired product and the chiral diol; a diagrammatic representation of this process may be seen in **Figure 1.52**. Further development of chiral modifiers, most notably by the group of Charette,[107] has led to the application of optically active dioxaborolane complexes derived from functionalised tartrate ligands such as (*R,R*)-(+)-N,N,N',N'-tetramethyltartaric acid diamide.



56-*R,R*

Figure 1.53

The clever design of the dioxaborolane complex (**56**), incorporating both an acidic (boron) and a basic (amide) functionality enables the efficient complexation of the acidic Simmons Smith reagent (halomethylzinc) and the basic allylic alcohol. Hence the formation of two chelate rings within the transition state leads to the highly stereospecific pseudo intramolecular delivery of the Simmons Smith reagent to a single face of the double bond. A Chem 3D[108] representation of the proposed transition state is shown diagrammatically in **Figure 1.54**.

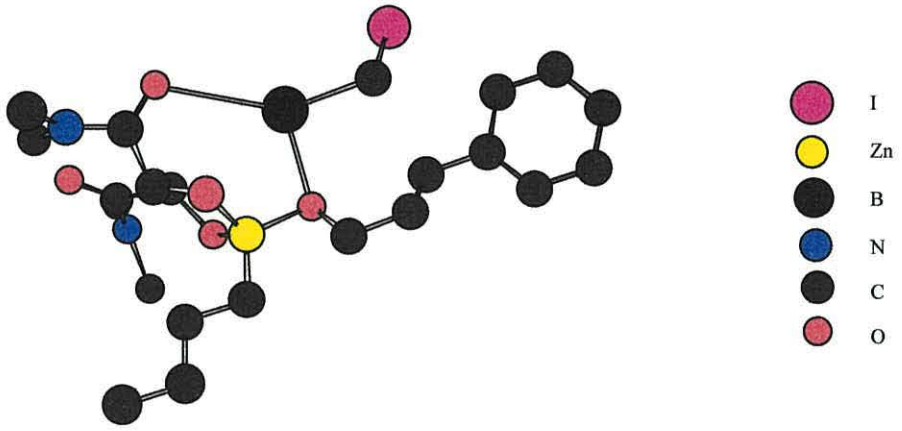
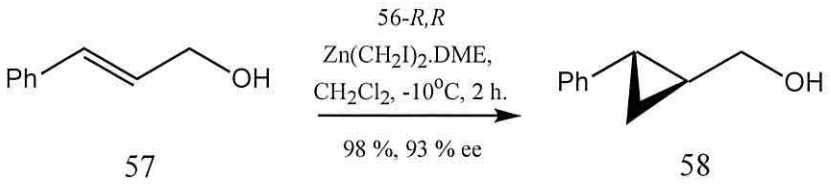


Figure 1.54

The dioxaborolane complex (**56**) has been shown to be extremely versatile and efficient, affording a wide range of optically active products typically in excess of 95 % yield with associated ee's of greater than 90 %.[109] The simple preparation of (**56**) from commercially available precursors, coupled with its efficient recovery from the reaction mixture upon work up has rendered the Charette protocol one of the most

commonly applied routes in the synthesis of optically active cyclopropanes; an example of this reaction showing typical reaction conditions may be seen in **Figure 1.55**.



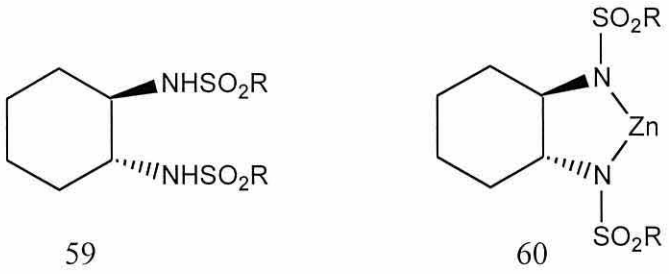
57 58

Figure 1.55

1.5.2.2.2 The Application of Catalytic Promoters

As mentioned previously in Section **1.5.2**, the development of catalytic asymmetric processes is a major growth area in chemistry. The development of catalytic asymmetric Simmons Smith reactions has benefited from this highly topical drive towards cleaner, more efficient, chemistry.

The first catalytic enantioselective Simmons Smith type reaction to appear in the literature was reported in 1992 by the group of Kobayashi.[110] They detailed the cyclopropanation of simple allylic alcohols using Furukawa's zinc reagent in the presence of catalytic amounts of chiral C_2-symmetric disulfonamide ligands (**59**). It was postulated that the ligand (**59**) formed an active Lewis acidic species (**60**) *in-situ* upon reaction with diethylzinc, hence facilitating the subsequent cyclopropanation of the substrate.

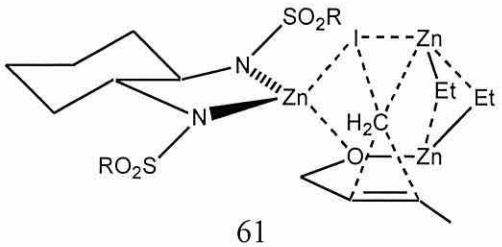


59 60

Figure 1.56

The enantioselectivity of the reaction, typically around 70 % ee, was explained by the formation of a tri-nuclear zinc species (**61**). It is thought that the zinc alkoxide species (derived from the allylic alcohol starting material) and the iodine molecule of iodomethyl zinc become coordinated to the chiral Lewis acidic zinc complex (**60**). This would generate a chiral environment in which the selective delivery of methylene

may take place. A diagrammatic representation of the tri-nuclear zinc species is seen in **Figure 1.57**.

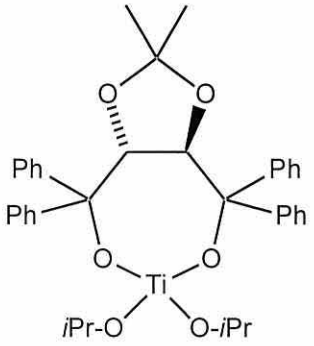


61

Figure 1.57

This methodology has been successfully applied to many allylic alcohols bearing a variety of substituents including the first catalytic enantioselective synthesis of a number of silyl- and stannyl- substituted cyclopropyl methanols;[111] these materials have found application as chiral building blocks in the synthesis of a number of target molecules including the polycyclopropane antibiotic FR-900848 (**19**).[40]

An alternative strategy, reported by the group of Charette in 1995[112] employed the addition of a sub-stoichiometric amount of a chiral Ti-TADDOL[113] based Lewis acid complex (**62**) to reactions under otherwise normal Furukawa conditions.[62]



62

Figure 1.58

The cyclopropanation of simple substrates (such as cinnamyl alcohol) in the presence of 25 mol % quantities of catalyst was shown to proceed in moderate yields (80 %) with respectable enantioselectivities of up to 90 % ee. Unfortunately, the reported substrate generality of this method was limited to use with aryl-substituted allylic alcohols. The cyclopropanation of alkyl-substituted substrates on the other hand, furnished products with a lower selectivity yielding enantiomeric excesses of around 60 %.

Synthesis of Chiral Cyclopropyl Building Blocks

2 Synthesis of Chiral Cyclopropyl Building Blocks

2.1 Aim

The primary aim of the work discussed in this chapter was the successful development of simple laboratory procedures that would enable the medium to large-scale preparation of enantiomerically pure cyclopropane containing building blocks. Such materials are of great interest as they may form the basis of subunits that may be required in the synthesis of many larger target molecules; examples of such molecules include methanoproline[114] and the polycyclopropane containing natural products FR-900848[37-40] and U-106305.[41-43]

For simplicity, this chapter is broken down into three discrete sections each of which highlights an alternative strategy, all of which share the same general aim, as stated above. Whilst there are many documented procedures enabling the synthesis of optically active cyclopropanes, as discussed in Section **1.5**, such techniques are seldom viable on a larger scale. Hence techniques involving the resolution of readily available racemic starting materials were chosen as a means of preparing optically active material on a reasonably large scale.

2.2 Classical Resolution Techniques

2.2.1 Introduction

The most commonly employed method for the large-scale resolution of a racemate involves the separation of diastereomeric compounds derived from a racemic starting material. This process involves the direct combination of the racemate with a single enantiomer of a chiral reagent (or resolving agent). The diastereomeric products are subsequently separated via simple techniques such as fractional crystallisation, distillation or simple chromatography.

The classical technique of resolution in its simplest form was pioneered in 1853 by Louis Pasteur.[115] His resolution of tartaric acid (**63**) was achieved by the selective recrystallisation of diastereomeric salts of the racemate with the optically active, natural alkaloids (+)-cinchotoxine (**64**) and (+)-quinotoxine (**65**). Upon recovery, the optically active salts could be further enantiomerically enriched by sequential recrystallisation before decomposition of the salt to yield the optically pure acid and

the recycled resolution agent. A simple diagrammatic representation of Pasteur's original resolution may be seen in **Figure 2.1**.

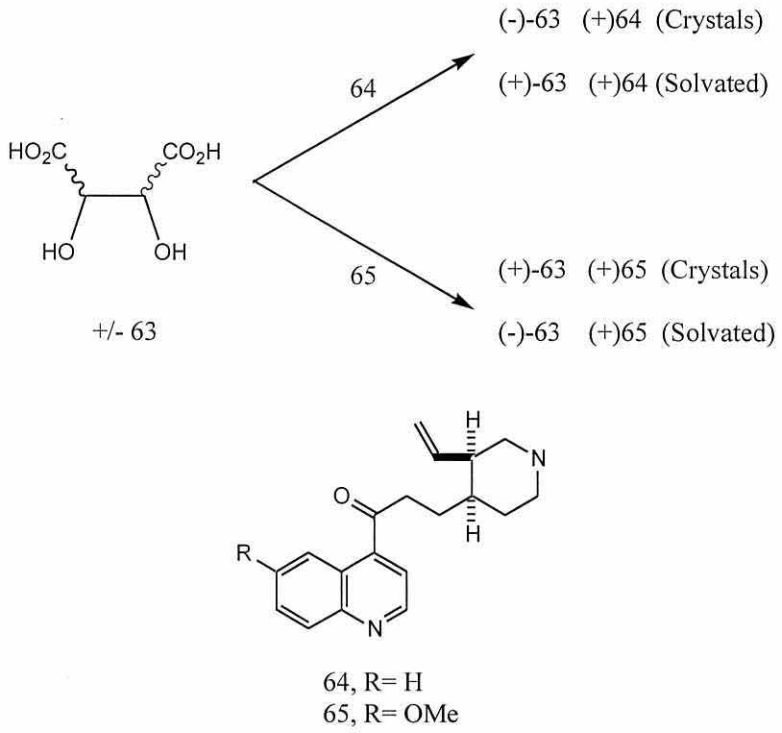


Figure 2.1

The efficient resolution of a racemic starting material is dependent upon many variables including (among others) the solvent composition, differences in the relative solubility of each diastereomeric product and above all, the suitability of the chosen resolution agent. Unfortunately there are no hard and fast rules that apply to the choice of a resolution agent for a particular substrate. It is generally considered that a potential resolution agent must satisfy the following characteristics before being considered as a possible candidate for large-scale application:

i) The material should be readily available and have a stable, non-seasonal line of supply.

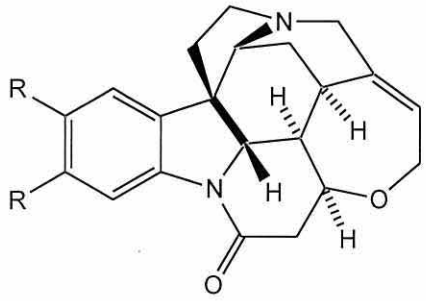
ii) The material should be relatively cheap to buy and it should also be easy to recover and re-use.

iii) Ideally both enantiomers of the material should be available in high optical purity.

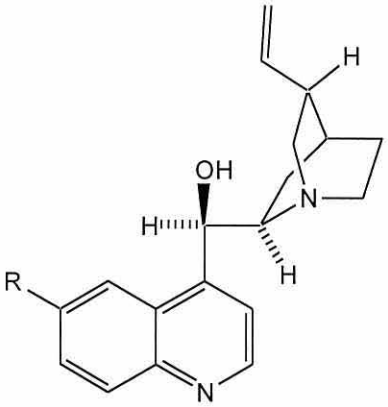
iv) The resolution agent must be safe to use, i.e. it must have a low toxicity and must not be environmentally damaging.

Unfortunately, it is not always possible to satisfy all of these conditions and trade offs have to be made. Examples of some materials often employed in the resolution of

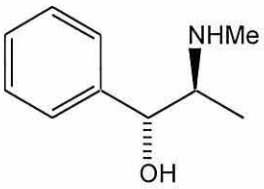
racemic carboxylic acids, including the highly toxic alkaloids strychnine (**66**) and brucine (**67**), may be seen in **Figure 2.2**.



R = H, Strychnine, 66
R = OMe, Brucine, 67



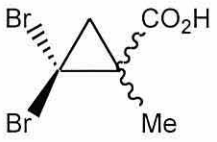
R = H, Cinchonidine, 68
R = OMe, Quinine, 69



(1*R*, 2*S*)-(-)-Ephedrine, 70

Figure 2.2

It was our primary aim to successfully apply this classical methodology in the resolution of the readily available racemic dibromocyclopropylcarboxylic acids (**71**) and (**72**), hence enabling the large-scale preparation of a number of simple functionalised chiral building blocks.



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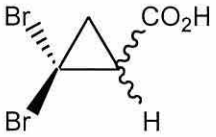


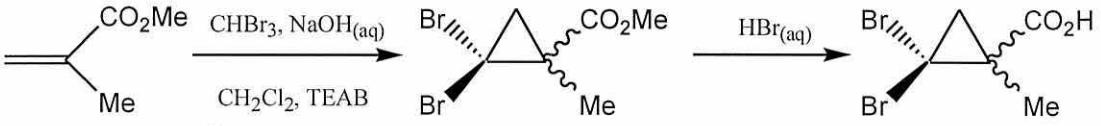
72

Figure 2.3

2.2.2 The Resolution of 2,2-Dibromo-1-methylcyclopropanecarboxylic acid (71)[116]

2.2.2.1 The Preparation of Racemic 2,2-Dibromo-1-methylcyclopropane carboxylic acid (71)[117]

Racemic 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**71**) was readily prepared on a moderate scale (up to 100 g per batch) in two synthetic steps from the commercially available starting materials, methyl methacrylate (**73**) and bromoform. The synthetic pathway is outlined below in **Figure 2.4**.



73 74 71

Figure 2.4

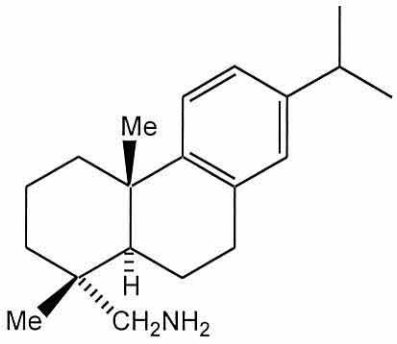
Interestingly, the formation of the intermediate ester, methyl 2,2-dibromo-1-methylcyclopropanecarboxylate (**74**) does not involve the addition of dibromocarbene to the olefin as one might expect. The reaction proceeds via a 1,4- Michael addition of Br_3C^- to the α,β-unsaturated starting material, followed by a three membered ring closure with the elimination of bromide. The crude ester was recovered as a sweet smelling liquid, excess bromoform being removed from the product at room temperature by flash distillation under reduced pressure into a cooled vessel (-78 °C). The pure product was subsequently recovered after careful distillation under reduced pressure (92 °C at 14 mmHg). Hydrolysis of the ester (**74**) yielded the desired acid (**71**) in high yield, 84 % over two steps. The acid was recovered as a cream coloured, pleasantly fragrant, semi-crystalline solid. All physical and spectroscopic data was consistent with that quoted in the literature and the acid was used after recrystallisation from hexane and ethanol (5:1).

2.2.2.2 Choice of Resolution Agent

As mentioned previously in Section **2.2.1**, the resolution of carboxylic acids may be facilitated by the separation of diastereomeric salts formed upon reaction of the racemate with a suitable resolution agent. Indeed, the resolution of many cyclopropane containing carboxylic acids has been carried out using a wide range of chiral bases often resulting in successful patent applications. It is common that a high

proportion of the chiral bases that find application in the resolution of carboxylic acids are highly toxic. It was therefore decided to choose a less-toxic base for use in the resolution of acid (**71**).

In 1965, Gottstein and Cheney of the Bristol-Myers Chemical Company reported the isolation of (+)-dehydroabietylamine (**75**),[118] from the commercially available amine mixture known as amine D™.[119] Its relatively low toxicity, coupled with its low cost and remarkable ability to form highly crystalline salts with many organic acids, renders (+)-dehydroabietylamine (**75**) a suitable base for application in large-scale resolutions. With these properties in mind, it was decided to use this amine in the attempted resolution of acid (**71**).



75

Figure 2.5

(+)-Dehydroabietylamine (**75**) was commercially available in its crude form as a mixture of high molecular weight primary amines (presumably similar to those found in the previously mentioned amine D™), from the Aldrich Chemical Co. at a cost of £183.20 /Kg.[120] Separation of the desired resolution agent (**75**) from the remaining components of the mixture was achieved by recrystallisation of its acetate from hot toluene.[118] This simple process afforded substantial amounts of optically pure amine in yield ranging from 50 – 70 % depending upon the batch of starting material.

2.2.2.3 Studies on the Resolution of 2,2-Dibromo-1-methylcyclopropane carboxylic acid (71)

Preliminary studies of the resolution of 2,2-dibromo-1-methylcyclopropane carboxylic acid (**71**) with freshly purified (+)-dehydroabietylamine (**75**) from hot aqueous methanol showed that the efficiency of the initial separative crystallisation step was highly dependent upon a number of factors including:

i) The ratio of amine to acid employed.

ii) The composition of the solvent used.

iii) The rate of cooling of the solution.

With these factors in mind, a series of small-scale resolutions were carried out enabling the identification of optimised resolution conditions to be employed on a larger scale. Throughout these experiments, the enantiomeric excess of the acid (**71**) regenerated from the diastereomeric salt-pair was measured by chiral GLC analysis of the corresponding methyl ester. Chiral GLC was carried out on a DP-TFA-γ-cyclodextrin column[121] using helium as the carrier gas; base line separation of both enantiomers was achieved thus enabling the accurate determination of enantiomeric excess. The results of these studies are discussed below.

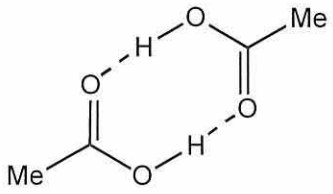
2.2.2.3.1 The effect of changing the acid: amine ratio during salt formation

The first series of experiments was designed to determine the effect of a change in the initial salt component ratio on the efficiency of the desired resolution. The experiments were all carried out on the same scale (5.0 g of acid), using a common solvent (100 % methanol, 50 ml) and allowing each solution to cool slowly by standing at room temperature overnight. A summary of the results obtained from these experiments may be seen in **Table 2**.

Ratio (Acid:Amine)	% Recovery (-)-(**71**)	Enantiomeric Excess
1:1	98 (of both enantiomers)	-
2:1	48	71
4:1	60	74

Table 2. The resolution of (71); dependence on acid: amine ratio

It was initially expected that the salt formed during the reaction of acid (**71**) with amine (**75**) would be a simple binary salt of composition 1:1 (acid:amine). Hence, it was decided that the first experiment would be carried out with a 1:1 ratio of starting materials. Unfortunately, total salt precipitation was experienced and the crystalline solid recovered after acid regeneration showed no sign of optical enrichment. Evaporation of solvent from the mother liquor yielded a thick oily residue that was identified as unreacted amine (**75**). Further analysis of the salt by proton NMR and CHN microanalysis revealed that it had the unexpected composition of 2:1 (acid:amine). On reflection, this observation is not that unusual; many simple carboxylic acids such as acetic acid are known to exist as dimeric pairs (**76**) and (**77**), it is therefore quite feasible that they may retain such dimeric structures during salt formation.



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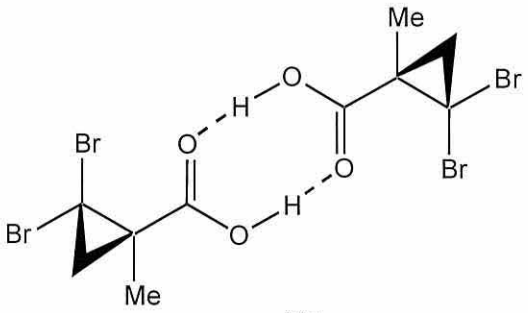

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Figure 2.6

With this new information at hand, it was possible to modify the ratio of the two starting materials employed; the obvious modification was to reduce the amount of amine present by a half. As expected, the selective crystallisation of one diastereomeric salt was indeed noted when the acid to amine ratio was adjusted to 2:1. Although the enantiomeric excess of the salt recovered was reasonably high (71 % ee), the absolute recovery was low, with only 48 % of one enantiomer of the acid being recovered in the first crystallisation step. Fortunately, when the acid to amine ratio was further adjusted to 4:1, an increase in the recovery of the enriched acid (**71**) was observed; this increase to 60 % recovery occurred without any apparent decrease in optical activity.

As a result of this series of simple experiments, it was concluded that the optimal ratio of acid to amine required to yield the greatest amount of enantiomerically enriched material (in a single crystallisation) was 4:1. Using these conditions it was routinely possible to recover material with an enantiomeric excess of greater that 70

%. Treatment of the salt-pair with 10 % aqueous sodium hydroxide solution followed by extraction into dichloromethane enabled the regeneration of the optically active acid (**71**). Analysis of the regenerated acid by polarimetry revealed that the acid rotated the plane of polarised light in a negative (-) direction. Consequently, this information revealed that the diastereomeric salt-pair (precipitated in this case) was composed of acid and amine components with opposing optical rotations; (+)-amine (**75**), (-)-acid (**71**), such diastereomeric salt-pairs have been designated *n*. Conversely, diastereomeric salt-pairs that contain components with the same sign of rotation are known as *p* (p_+ if both are + and p_- if both are -). Such notation will be used throughout the following sections of this thesis.

2.2.2.3.2 The effect of changing solvent composition

As mentioned in Section **2.2.2.3.1** above, it was concluded by experimentation that the optimal ratio of components for the efficient resolution of acid (**71**) was 4:1 (acid to amine). The aim of the following series of experiments was to further assess the effect of varying solvent composition upon small-scale resolutions employing this predetermined optimal ratio. As with the previous set of experiments, these experiments were all carried out on the same scale (5.0 g of acid) with the same amount of amine (1.36 g, 0.25 equiv). Each resolution was carried out with a particular solvent composition (total volume 50 ml), allowing each solution to cool slowly by standing at room temperature overnight. The results obtained from these experiments comparing the absolute recovery and corresponding enantiomeric excesses obtained are summarised in **Table 3**.

Solvent Composition MeOH:H_2O	% Recovery (-)-(71)	Enantiomeric Excess
100:0	60	74
90:10	81	84
80:20	81	53
70:30	84	48
60:40	87	32

Table 3. The resolution of (71); the effect of changing solvent composition

It can be seen from the experimental data presented in **Table 3** that the addition of water to the resolution solvent (methanol) has quite a marked effect on the absolute recovery and the enantiomeric excesses observed. As the amount of water added to the solution increases, the solubility of the salt-pair appears to decrease and the absolute recovery increases. Unfortunately, the speed at which crystallisation occurs is also quite dramatically increased, from a period of hours in the case of 100 % and 90 % methanol solution, to a period of just minutes as the concentration of water increases. As a result, the optical activity of the diastereomeric salts recovered from resolutions carried out with increasing amounts of water decreases as the relative concentration of water increases. Indeed, when the resolution is carried out in aqueous methanol solutions of greater than 50 % water, bulk precipitation is observed as the components crash out of solution in a matter of seconds. As expected, the products of such mass crystallisation often showed no optical rotation.

As a result of the experiments carried out in Sections **2.2.2.3.1** and **2.2.2.3.2**, it can be concluded that the initial crystallisation step of the resolution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**71**) is best carried out by reaction of the acid starting material with 0.25 equivalents of (+)-dehydroabietylamine (**75**) in hot 10 % aqueous methanol solution. The highest recovery of optically active material was achieved by allowing the hot solution to cool slowly over a period of hours at room temperature; typically, yields in excess of 80 - 85 % (of one enantiomer) were recovered with corresponding enantiomeric excesses in excess of 80 %. Further enrichment of the optically active diastereomeric *n* salt-pair was carried out by recrystallisation from hot 10 % aqueous methanol solution. The highly crystalline salt recovered, typically afforded enantiomerically pure (ee > 99 %) (-)-2,2-dibromo-1-methylcyclopropanecarboxylic acid (**71**) in approximately 50 – 55 % yield after regeneration of the acid by treatment with aqueous sodium hydroxide solution followed by solvent extraction.

2.2.2.3.3 Recovery of the second enantiomer

The procedures in Sections **2.2.2.3.1** and **2.2.2.3.2** have highlighted the efficient recovery of one enantiomer of the racemate in the form of the precipitated *n* salt-pair. Unfortunately, for the resolution to be synthetically useful, it must be the source of both optically pure enantiomers in moderate yields. Consequently it is important that

the residual second enantiomer is efficiently recovered from the mother liquor. In practice, this process proved to be quite straightforward and the second enantiomer was recovered in three simple manipulative steps, highlighted below.

The mother liquor was initially concentrated to approximately half of its initial volume under reduced pressure; this enabled a second crop of *n* salt-pair crystals to be collected. The second crop of crystals was also enriched with the first enantiomer as expected, but exhibited a lower enantiomeric excess (typically in the order of 40 – 50 % ee); these crystals were put aside to be combined in future resolutions. As a consequence, the remaining mother liquor became suitably enriched with the second enantiomer (+)-(**71**). Treatment of the residual mother liquor with 10 % aqueous sodium hydroxide solution enabled the regeneration of the optically active acid (+)-(**71**). The acid was recovered as a moist, white semi-crystalline solid; analysis of the acid by chiral GLC revealed that it exhibited a moderate enantiomeric excess in the order of 45 – 50 % ee. Further enantiomeric enrichment of the acid was carried out by slow recrystallisation from a minimum amount of refluxing *n*-hexane. After 15 hours at 5 °C, crystal growth was observed; these crystals were carefully removed from the solution and analysed by chiral GLC. Surprisingly, the crystals had an enantiomeric excess of just 7 %, being only slightly enriched with the second enantiomer (+)-(**71**). Subsequent analysis of the mother liquor, also by chiral GLC, revealed that the acid remaining in solution exhibited an enantiomeric excess of greater than 99 %. Evaporation of the residual solvent enabled the easy recovery of enantiomerically pure (+)-(**71**) as a colourless oil that crystallised overnight to form a white crystalline solid.

In conclusion, this simple three-step procedure has enabled the quick, efficient recovery of approximately 50 – 55 % of the second enantiomer (+)-(**71**) with an enantiomeric excess of greater than 99 %. Furthermore, the absolute stereochemistry of the second enantiomer of the resolved material was subsequently determined unambiguously by X-ray crystallography on a single crystal of the amide, (+)-2,2-dibromo-1(*R*)-methylcycopropanecarboxamide (**78**) formed by reaction of 2,2-dibromo-1(*R*)-methylcyclopropanecarbonyl chloride with 35 % aqueous ammonia solution; a representation of the crystal structure may be seen in **Figure 2.7**.

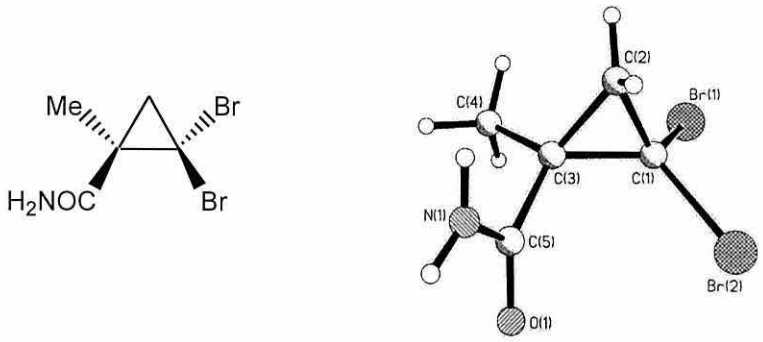

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Figure 2.7

Figure 2.7 shows the structure of one of the two hydrogen bonded molecules of (+)-2,2-dibromo-1(*R*)-methylcycopropanecarboxamide contained within the unit cell. This representation confirms the absolute stereochemistry of the substituents on C[3] as having an *R* configuration.

2.2.2.3.4 Summary

In summary, Sections **2.2.2.3.1**, **2.2.2.3.2** and **2.2.2.3.3** above, have discussed the development of a procedure that has enabled the efficient resolution of 1-methyl-2,2-dibromocyclopropanecarboxylic acid (**71**). The resolution is successful as it provides a moderately large supply of both enantiomers, each exhibiting an enantiomeric excess of greater than of 99 %. A schematic diagram of the final resolution procedure may be seen in **Figure 2.8**.

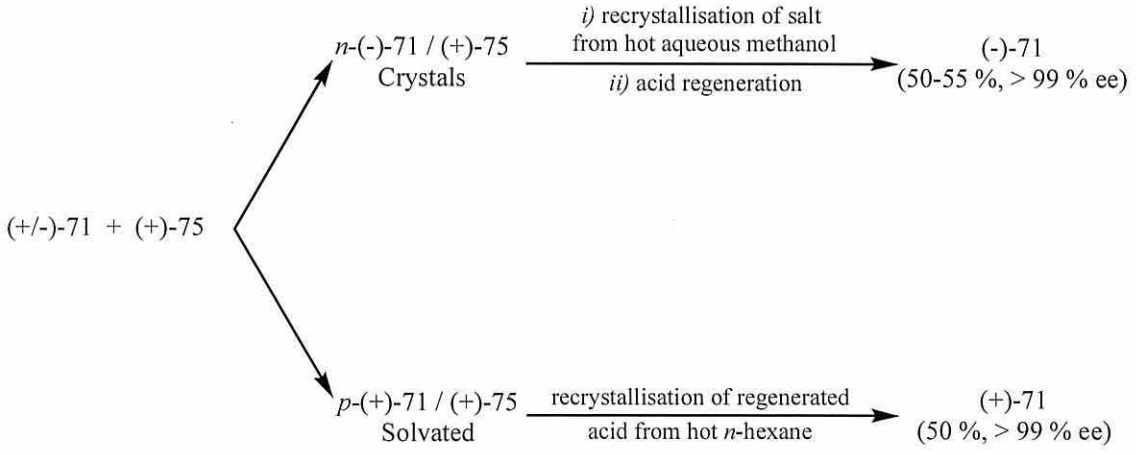


Figure 2.8

2.2.3 The Resolution of 2,2-Dibromocyclopropanecarboxylic acid (72)

2.2.3.1 The Preparation of Racemic 2,2-Dibromocyclopropanecarboxylic acid (72)

Unfortunately, the structurally analogous second substrate, 2,2-dibromocyclopropane carboxylic acid (**72**) was not readily available by the direct dihalocyclopropanation of methyl acrylate. This reaction has previously been shown to be somewhat inefficient, presumably due to additional side reactions that may be initiated by removal of the proton adjacent to the acid functionality in the desired product. However, a number of alternative synthetic routes have been explored, thus enabling the efficient preparation of the desired racemic starting material (**72**) from commercially available starting materials in a minimal number of synthetic steps.

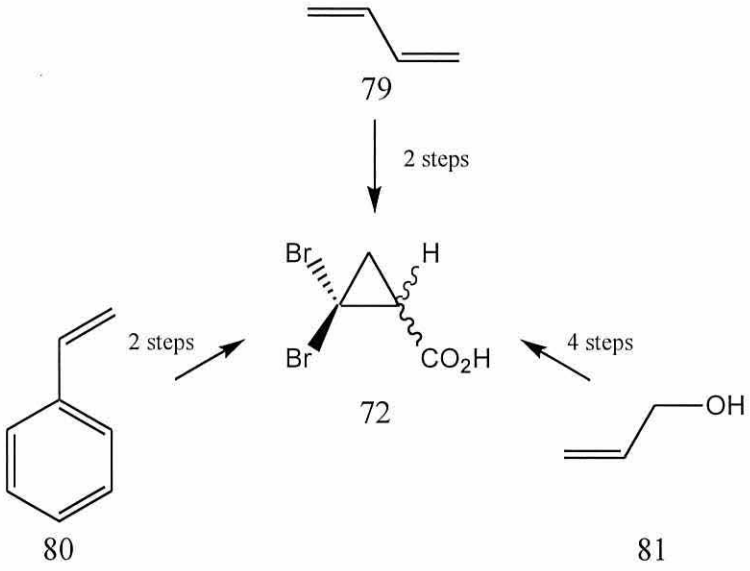
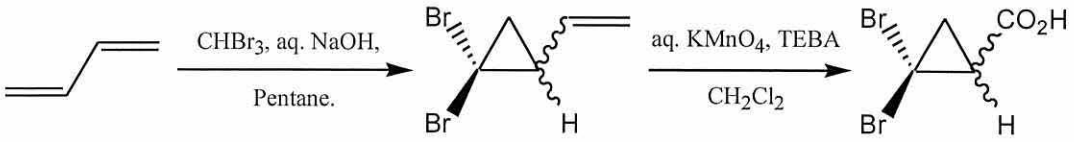


Figure 2.9

2.2.3.1.1 Method 1: The Oxidation of 2,2-dibromo-1-vinylcyclopropane (82)

The first synthetic route that was studied in the search of an efficient preparation of racemic 2,2-dibromocyclopropanecarboxylic acid (**72**) was the two-step procedure highlighted in **Figure 2.10**. The second stage of this route required the efficient oxidation of the vinyl substituent of the intermediate compound (**82**). This process was indeed carried out successfully, but great care had to be exercised when isolating the product from the crude reaction mixture.



79 82 72

Figure 2.10

The synthesis of the intermediate compound, 2,2-dibromo-1-vinylcyclopropane (**82**) was carried out by the controlled low temperature addition of dibromocarbene (generated *in-situ* by the reaction of bromoform with a strong base) to pre-condensed 1,3-butadiene (**79**). The addition of bromoform was carried out at –30 °C in a suitably insulated vessel equipped with a dry-ice condenser, hence minimising any loss of the volatile starting material (**79**). The low temperature of the reaction was maintained for approximately 3 hours before allowing the reaction solution to warm to room temperature. The crude product was isolated by solvent extraction as a light brown coloured viscous liquid. Excess bromoform was removed at room temperature by flash distillation under reduced pressure into a cooled receiver (-78 °C) and the product, 2,2-dibromo-1-vinylcyclopropane (**82**) was the recovered from the residue by careful distillation at reduced pressure (49 °C at 7 mmHg). The distilled product was recovered as a colourless viscous liquid in 73 % yield and was stored in a freezer at –5 °C. This precaution was taken to avoid thermal decomposition via a vinylcyclopropane – cyclopentene[122] rearrangement that occurred when (**82**) was stored for prolonged periods at room temperature.

Oxidation of the intermediate 2,2-dibromo-1-vinylcyclopropane (**82**) was carried out by treatment of the starting material with 3 equivalents of acidified potassium permanganate solution in the presence of a phase transfer catalyst. The temperature of the reaction was carefully controlled during the addition of the permanganate solution such that the internal temperature did not rise above 5 °C. The solution was then stirred for 24 hours at room temperature before reductive work-up and subsequent isolation of the product.

Initially, work-up was carried out by the dropwise addition of a 5 % aqueous hydrazine hydrate solution to the cooled reaction mixture over a prolonged period of time.[123] The resulting solution was then acidified and the product isolated by extraction into the organic phase. This work-up procedure was shown to be suitable for small-scale reactions only (up to 50 g of starting material), but application on

larger reactions was shown to be too dangerous as the exotherm observed during work-up in this manner was found to be nearly impossible to control. An alternative procedure employing the careful addition of sodium metabisulfite to the acidified solution was therefore used in larger scale reactions.[124] An exotherm was also observed throughout this alternative work-up procedure, but it was not as severe and was easily held under control by the periodic addition of ice to the reaction mixture. The crude product was recovered as a cream coloured waxy solid; recrystallisation from hexane – benzene solution (5: 2) afforded 2,2-dibromocyclopropanecarboxylic acid (**72**) in 74 % yield as a white crystalline solid. All physical and spectroscopic data was consistent with that quoted in the literature.

2.2.3.1.2 Method 2: The Oxidation of 2,2-dibromo-1-phenylcyclopropane (83)

The second synthetic route that was investigated in the synthesis of the racemic precursor, 2,2-dibromocyclopropanecarboxylic acid (**72**), was the two-step procedure that may be seen in **Figure 2.11**.

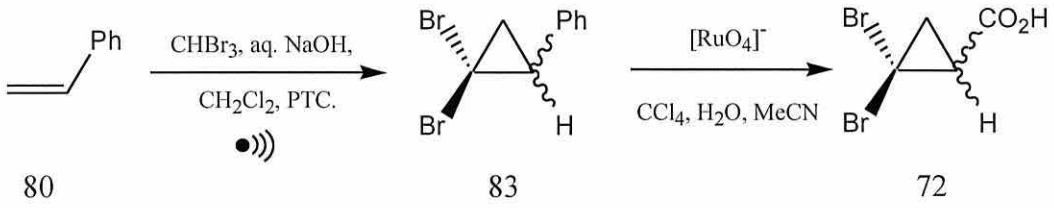


Figure 2.11

The synthesis of 2,2-dibromo-1-phenylcyclopropane (**83**) in 47 % yield was achieved by the addition of dibromocarbene (generated by the reaction of bromoform with a strong base) to the olefinic bond of vinyl benzene (**80**). The flask containing the reaction mixture was fitted with an air condenser and subsequently immersed in an ultrasonic cleaning bath (up to the depth of the meniscus of the reaction solution, as seen in **Figure 2.12**). The solution was then irradiated with ultrasonic radiation (47 kHz, 160 W) for 2 hours; such exposure has been shown to promote the formation of the reactive carbene and hence the desired product. Residual phase transfer catalyst and excess base were removed by filtration before 2,2-dibromo-1-phenylcyclopropane (**83**) was isolated in 47 % yield as a colourless oil after distillation under reduced pressure (82 °C at 0.1 mmHg).

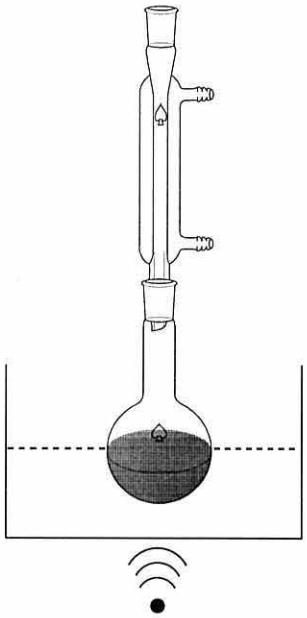


Figure 2.12

The second step of the synthesis, the complete oxidation of the aromatic substituent of 2,2-dibromo-1-phenylcyclopropane (**83**) was successfully carried out in a tri-phasic solution composed of carbon tetrachloride (2 ml), acetonitrile (2 ml) and water (3 ml). The active oxidation catalyst, ruthenium tetroxide was generated *in-situ* from the initial reaction of ruthenium (III) chloride hexahydrate with periodic acid. Periodic acid also acted as a re-oxidant for the reduced catalytic material. The resulting reaction mixture was heated at reflux overnight, before cooling and diluting with diethyl ether and water. Solvent extraction followed by evaporation under reduced pressure yielded the product (**72**) in high purity (used without further recrystallisation) as a white semi-crystalline solid in 80 % yield.

2.2.3.1.3 Method 3: The Oxidation of 2,2,-dibromo-1-hydroxymethylcyclopropane (86)

The third and final route studied in the laboratory scale preparation of 2,2-dibromocyclopropanecarboxylic acid (**72**) was the formal addition of dibromocarbene to the commercially available starting material allyl alcohol (**81**). Unfortunately, the cyclopropanation of allyl alcohol (**81**) could not be carried out efficiently in a single step, consequently the starting material was protected as its 1-methoxy-1-methylethyl ether (**84**). The protection of (**81**) was successfully carried out in 90 % yield by reaction with 2-methoxypropene in the presence of an acid catalyst, pyridinium *p*-toluenesulfonate (PPTS). The subsequent cyclopropanation step was carried out under

phase transfer conditions whilst paying particular attention to the pH of the bromoform added during the reaction. Commercially available bromoform is commonly supplied with trace amounts of ethanol in solution; the ethanol acts as an efficient stabiliser during the storage and shipment of bromoform but consequently renders the solution slightly acidic. Subsequent neutralisation of such acidic bromoform by the dropwise addition of triethylamine prevented the undesired hydrolysis of the acid labile protecting group, hence maximising the absolute yield of product.

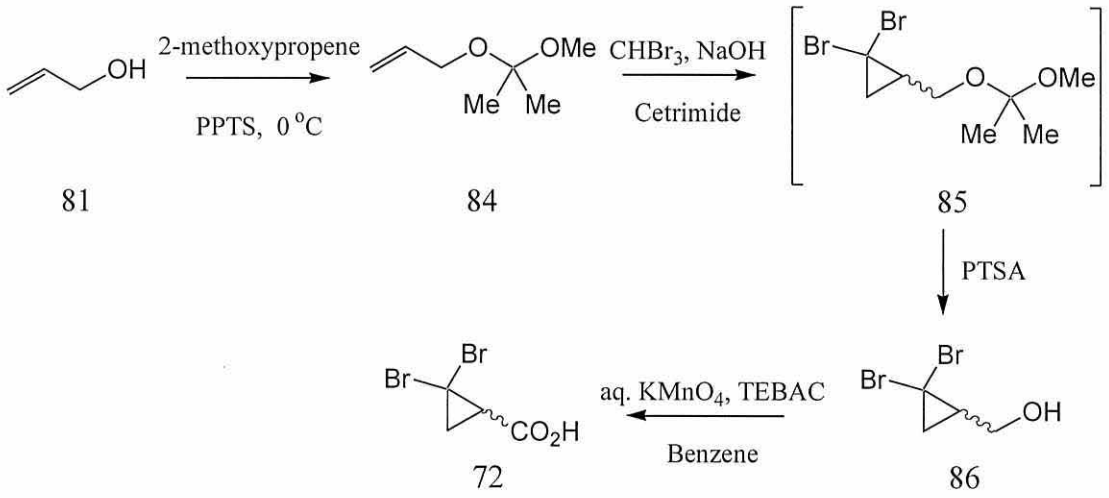


Figure 2.13

Acid catalysed hydrolysis of the cyclopropanated intermediate (**85**) followed by distillation under reduced pressure (82 - 85 °C at 0.3 mmHg) afforded the desired cyclopropylmethanol (**86**) as a colourless oil in a respectable 70 % yield (over two steps). Subsequent oxidation of the alcohol (**86**), was carried out via routine procedures i.e. employing a "purple benzene" solution containing 5 equivalents of potassium permanganate. The reaction was carried out in the presence of a simple quaternary ammonium salt (benzyl triethylammonium chloride) and was stirred vigorously at room temperature overnight. Upon completion, the reaction mixture was subjected to a reductive work-up similar to that employed in the previously discussed oxidation of 2,2-dibromo-1-vinylcyclopropane (**82**), (see Section **2.2.3.1.1**). The product was recovered as a creamy white solid; recrystallisation from boiling hexane – benzene solution (5: 2) afforded pure 2,2-dibromocyclopropanecarboxylic acid (**72**) in 93 % yield as a white crystalline solid.

2.2.3.1.4 Summary

The three methods discussed above in Sections **2.2.2.3.1**, **2.2.3.1.2** and **2.2.3.1.3** all proved successful in the synthesis of the desired product, 2,2-dibromocyclopropanecarboxyllic acid (**72**). For simplicity, experimental data including the overall yields returned from the synthetic routes employed may be seen tabulated in **Table 4**. By careful consideration of these figures along with additional factors such as experimental considerations and supply costs, it is possible to choose a preferred method for the large-scale preparation of the second racemic acid (**72**).

Method	Number of steps	Overall % yield
1 (**2.2.3.1.1**)	2	54
2 (**2.2.3.1.2**)	2	37
3 (**2.2.3.1.3**)	4	59

Table 4. Comparison of the synthetic routes employed in the preparation of 2,2-dibromocyclopropanecarboxyllic acid (72)

By simple comparison of the overall recovered yields obtained from each method, it is clear that methods 1 and 3 stand out as the most efficient in the synthesis of 2,2-dibromocyclopropanecarboxyllic acid (**72**). Apart from the obvious disadvantage of a lower yield, method 2 may only be considered for application on small-scales due to increased environmental awareness and the restricted availability of one of the solvents employed during the reaction (carbon tetrachloride). *Article 2D* of the *1987 Montreal Protocol on Substances that Deplete the Ozone Layer* identifies carbon tetrachloride as a group II ozone-damaging compound, consequently it was agreed that the application of carbon tetrachloride would be unilaterally phased out by the year 2010. As a result, carbon tetrachloride is now only available in small "reagent quantities" and no longer as a bulk solvent. Such restrictions in the supply of carbon tetrachloride unfortunately render this otherwise attractive route unsuitable for application on scales of greater than a few grams.

In comparison, the starting materials and reagents that are required in methods 1 and 3 are all commercially available and are subject to minimal restrictions in supply and shipping. The yields recovered from each of the two routes are comparable, but the number of steps involved and indeed the difficulty of each step differs between

each of the synthetic routes. In the first method, one of the starting materials 1,3-butadiene (**79**) is supplied in a steel canister (or lecture bottle) as a low boiling gas; consequently the reaction mixture requires cooling to enable efficient product formation without excessive loss of the volatile starting material. Hence the requirement of carefully controlled low temperature reaction conditions coupled with the cost of 1,3-butadiene (**79**) (approximately £100 /Kg)[120] renders this method the less attractive of the two remaining viable routes.

With four steps, the third and final route is the longest method studied. Initially this may appear as unattractive but when commercial and environmental pressures are considered, this factor is negated. The preparative steps involved in this synthetic route do not require any special reaction conditions and all the starting materials are readily available (in bulk) from commercial suppliers. Using this method it was possible to routinely prepare batches of 2,2-dibromocyclopropanecarboxylic acid (**72**) in excess of 100 g in 2 – 3 days.

2.2.3.2 The Attempted Resolution of 2,2-Dibromocyclopropanecarboxylic Acid (72) Using (+)-Dehydroabietylamine (75)

As the previous resolution of the structurally similar 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**71**) had proceeded with a moderate level of success, it was initially thought that the methodology employed during the previous resolution would serve as a good starting point for the investigation of the resolution of 2,2-dibromocyclopropanecarboxylic acid (**72**). As in the previous resolution, discussed in Section **2.2.2.3**, the efficiency of the resolution was found to be dependent upon the solvent composition and to a lesser extent, the ratio of acid and amine combined in the initial salt formation step.

The optimal ratio of acid:amine employed in salt formation was determined by a short series of small scale experiments similar to those discussed in Section **2.2.2.3.1**. The yield of salt recovered was extremely low in all cases (when compared with Section **2.2.2.3.1**), but the optimal ratio was shown to be 8:1 (acid:amine) with a maximum recovery of 25 % of one enantiomer. A second series of experiments similar to those discussed in Section **2.2.3.1.2** was carried out to investigate the effect that varying the solvent composition has upon the efficiency of the resolution. The results of these experiments may be seen in **Table 5**.

Solvent Composition $MeOH:H_2O$	% Recovery (-)-(72)	Enantiomeric Excess
100:0	13	69
90:10	17	86
80:20	21	82
70:30	22	81
60:40	26	70
50:50	29	64

Table 5. The resolution of (72); the effect of changing the solvent composition

It can be seen from the experimental data presented above in **Table 5**, that the enantiomeric excesses exhibited by salt-pairs recovered during each of the experiments was indeed quite high, ranging from approximately 70 to 80 % ee. Unfortunately, the yields associated with these experiments were not as commendable, typically in the range of 20 – 25 % of one enantiomer recovered. The poor efficiency of the resolution of (**72**) may be explained by the apparent increased solubility of the salt-pair in the resolution solvent; the salt appears to be very soluble in aqueous methanol (even with high concentrations of water) and the recovery of salt remains low until the solution is cooled below 0 °C. When crystallisation was carried out at low temperature, complete crystallisation was observed and consequently the material recovered was essentially racemic. Further analysis of the precipitated salt-pair by proton NMR and CHN microanalysis revealed that the salt had a 2:1 composition (acid:amine); this observation had also been made about the analogous salt-pair isolated during the previous resolution of (**71**).

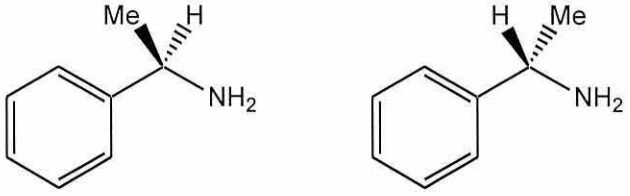
As a result of these simple experiments, it was concluded that the initial recrystallisation of the salt-pair formed by the reaction of racemic acid (**71**) and chiral amine (**75**) in the ratio 8:1 was best carried out from refluxing 50 % aqueous methanol. By employing these new experimentally defined optimal conditions, it was possible to recover approximately 20 % of each enantiomer with an associated enantiomeric excess of greater than 98 % typically upon completion of five consecutive recrystallisation steps of the acid:amine salt-pair from aqueous methanol

followed by a further recrystallisation of the regenerated acid from *n*-hexane. In contrast, the resolution of (**71**) yielded approximately 60 % of each enantiomer each with an enantiomeric excess greater than 99 %, in typically just two recrystallisation steps (for comparison see **Table 3**).

Unfortunately such low levels of recovery render the resolution inefficient and therefore unsuitable for application on a large scale. It was therefore decided after considerable experimentation that an alternative resolution agent should be considered.

2.2.3.3 The Resolution of 2,2-Dibromocyclopropanecarboxylic Acid (72) Using (α)-Methylbenzylamine (87)

As mentioned earlier in Section **2.2.3.2**, the resolution of 2,2-dibromocyclopropanecarboxylic acid (**72**) using the relatively non-toxic chiral amine, (+)-dehydroabietylamine (**75**) did not proceed with the desired level of efficiency and was therefore not suitable for use on a larger preparative scale. As a result, it was decided that a more traditional resolution agent such as those highlighted in Section **2.2.1** would be employed in a second, hopefully more efficient resolution. The optically active amine chosen as a replacement for (+)-dehydroabietylamine (**75**) was (α)-methylbenzylamine (**87**). Unlike dehydroabietylamine (**75**), both enantiomers of pure (α)-methylbenzylamine (**87-*R*** and **87-*S***) are commercially available in high optical purity from regular suppliers, and as a result they were suitable for use without further purification.



87-*R* 87-*S*

Figure 2.14

Ironically, the second resolution of racemic (**72**) employing both enantiomers of (α)-methylbenzylamine (**87-*R*** *or* **87-*S***) was successful on the first attempt, hence no further studies were carried out to examine the effect of solvent composition or acid: amine ratio upon the resolution efficiency were carried out. A general outline of the resolution process is highlighted below.

Diastereomeric salt formation was carried out by the simple treatment of the racemic acid (**72**) with one equivalent of *either* enantiomer of (α)-methylbenzylamine (**87-*R*** *or* **87-*S***) in refluxing ethanol. Subsequent cooing to room temperature followed by storage at 10 °C overnight, led to the precipitation of the *n* salt-pair (in each case) as a white crystalline solid. The solid was removed from the mother liquor (which was retained to enable the recovery of the second enantiomer) by filtration and washed with ice-cold ethanol before drying *in-vacuo*. Recrystallisation of the dry solid from refluxing ethanol afforded the purified salt-pair as a fine white crystalline solid; analysis of the purified salt-pair by proton NMR and CHN microanalysis revealed that the salt had an unexpected 1: 1 composition (acid: amine). The salt-pair composition differs from those observed in the two previous resolutions employing (+)-dehydroabietylamine (**75**); this variation is more than likely a result of employing a different resolution agent, hence they should not be directly compared to one another.

Optically active 2,2-dibromocyclopropanecarboxylic acid (**72-*R* *or* 72-*S***) may be recovered from the salt-pair by simple treatment with 10 % aqueous sodium hydroxide solution followed by solvent extraction. Typically optically active acid (**72-*R* *or* 72-*S***) prepared in this way exhibited an enantiomeric excess of greater than 98 %. Recovery of the second enantiomer (**72-*R* *or* 72-*S***) from the mother liquor was carried out by firstly regenerating the acid again by treatment with 10 % aqueous sodium hydroxide solution followed by solvent extraction and secondly by carrying out a repeat resolution process, this time employing the *other* enantiomer of the resolution agent (α)-methylbenzylamine (**87-*R*** *or* **87-*S***).

In conclusion the application of this modified "*two stage*" resolution process proved to be very efficient in the preparation of enantiomerically pure 2,2-dibromocyclopropanecarboxylic acids (**72**). Indeed, the successful recovery of approximately 60 % of each optically pure enantiomer (ee > 98 %) was routinely obtained from resolutions ranging in size from 1 g up to 50 g. It should also be noted, that any residual racemic (or near racemic) acid (the remaining 40 %) was simply added to the next batch to be resolved.

Further work carried out within our research group by Viacheslav (Slava) Tverezovsky, a visiting researcher from Moscow State University has subsequently led to the determination of the absolute stereochemistry of C[1] within the cyclopropane ring. This information was obtained through the application of (**72-*R***) in the synthesis of (2*S*, 3*R*, 4*S*)-3,4-methanoproline,[125] a natural product obtained from

Aesculus parviflora. The absolute stereochemistry of this had been determined again by X-ray crystallography.

2.2.4 Conclusion

In summary, the application of classical resolution techniques has been successfully employed in the preparation of the enantiomerically pure cyclopropane containing carboxylic acids on a moderately large laboratory scale. A summary of the efficiency of each of the resolutions carried out may be seen below in **Table 6**.

Acid	Typical yield (one enantiomer)	$[\alpha]_D^{20}$ / °	% ee
71-*S* [i]	50 - 55	-55.1	>99
71-*R* [i]	50 –55	+54.8	>98
72-*S* [i]	20 – 25	-138.2	>98
72-*R* [i]	15 - 20	+132.9	>94
72-*S* [ii]	70 - 80	-138.2	>98
72-*R* [ii]	60 - 65	+137.9	>96

Table 6. The resolution efficiency of the carboxylic acids (71) and (72); employing either [i] (+)-dehydroabeitylamine (75), or [ii] (α)-methylbenzylamine (87) as the resolution agent

The studies that were carried out on the resolution of the two analogous acids, 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**71**) and 2,2-dibromocyclopropane carboxylic acid (**72**), have shown that it is indeed not possible to prepare a generalised "recipe-type" method enabling the efficient resolution of a particular class of substrates. Indeed these studies have exemplified the fact that each individual resolution has its own unique set of conditions that must be identified and hence applied if an efficient separation of enantiomers is to be achieved.

2.3 Preparation of Diastereomeric Amides

2.3.1 Introduction

The second strategy employed in the attempted synthesis of optically active cyclopropane containing building blocks was the preparation and subsequent separation of diastereomeric amides derived from the racemic starting material, again 2,2-dibromocyclopropanecarboxylic acid (**72**).

This alternative method may be considered as a variation or modification to classical resolution techniques such as those examined in Section **2.2**. Unlike these classical resolutions, this alternative approach involves the efficient separation of covalently bonded diastereomeric intermediate compounds as opposed to diastereomeric salt-pairs (as in Section **2.2**). Separations of this type are commonly carried out on a moderately large scale, often employing preparative techniques such as column chromatography and preparative HPLC, hence overcoming the inefficiencies that are often associated with other fractional techniques such as crystallisation.

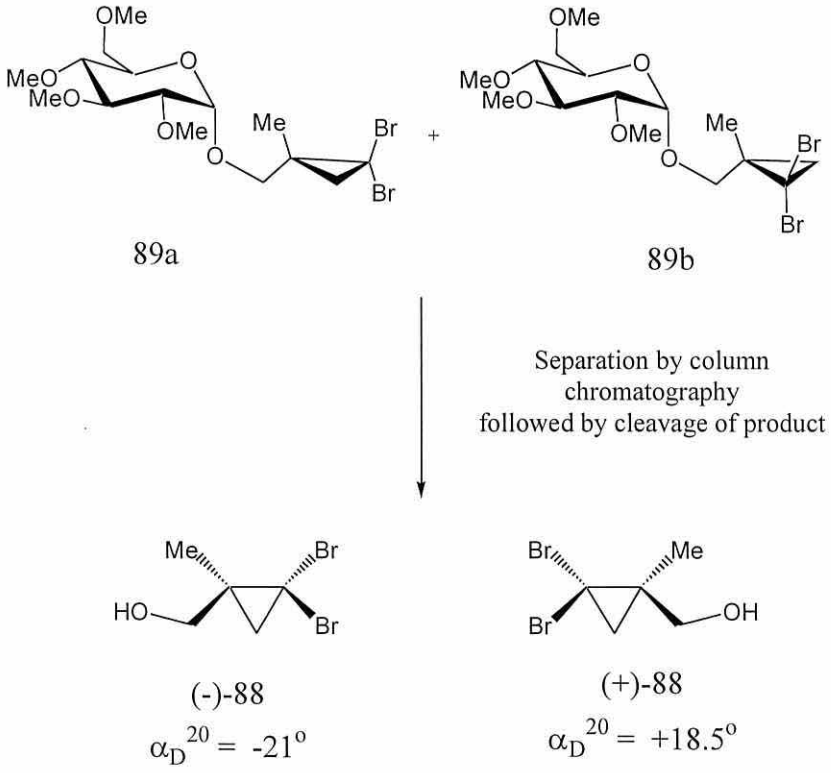


Figure 2.15

An example of the successful application of this method also carried out within the research group may be seen in **Figure 2.15**. The successful resolution of 2,2-dibromo-

1-methylcyclopropyl)-methanol (**88**) was carried out on a preparative scale (up to 40 g) by the efficient separation of the diastereomeric glucosides (**89a**) and (**89b**) by simple flash chromatography on silica gel.[126] Subsequent cleavage of the glucose moiety afforded the desired optically active cyclopropylmethanols (+)-(**88**) and (-)-(**88**) in moderate yield. There are many other examples in the literature that detail the successful resolution of chiral centres via this method, indeed diastereomeric derivatives of many functional groups including aldehydes, ketones and amines (to name just a few) are readily prepared by reaction with a wide range of suitable resolution agents many of which also find common application as chiral auxiliaries (see Section **1.5.1.2)**.

The aim of the work discussed in this Section was the application of this strategy to the resolution of 2,2-dibromocyclopropanecarboxylic acid (**72**), hence developing an alternative method that would enable the isolation of optically active cyclopropyl fragments bearing no methyl substituent on C[1], unlike (**88**). It was thought that the derivatisation of the racemic starting material as diastereomeric amides would facilitate the chromatographic separation and hence affect a resolution; the proposed reaction scheme is highlighted in **Figure 2.16**.

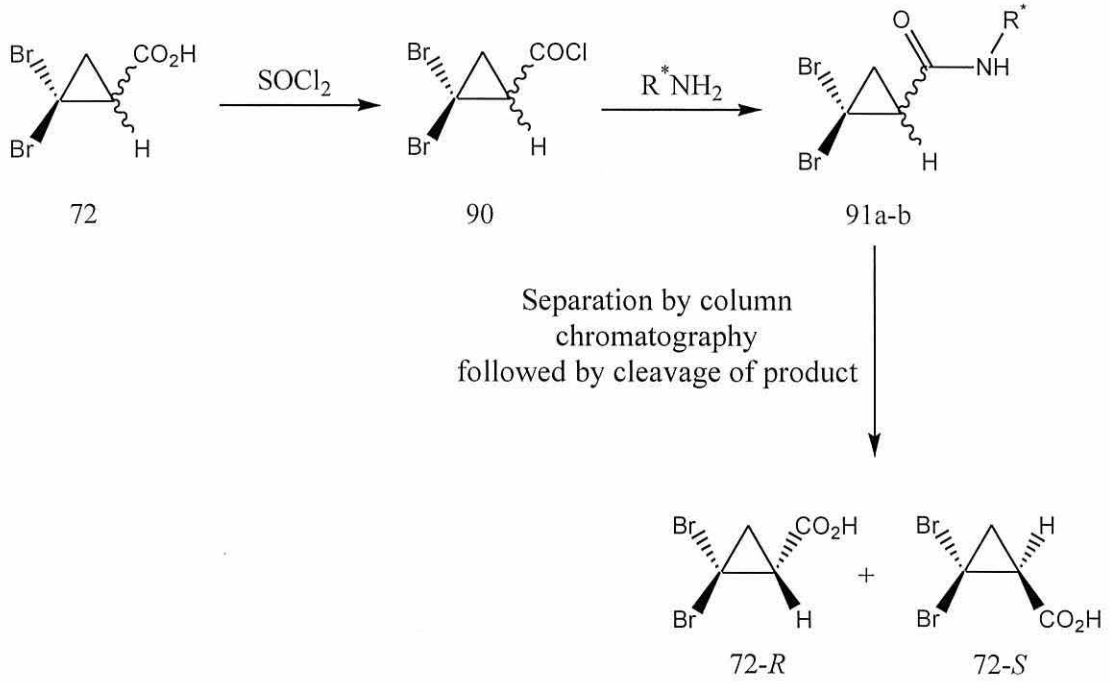


Figure 2.16

2.3.2 The Preparation and Separation of Diastereomeric Amides

2.3.2.1 The Preparation of 2,2-Dibromocyclopropanecarbonyl Chloride (90)

As highlighted in **Figure 2.16**, it was proposed that the diastereomeric amide mixture would be readily prepared in two simple synthetic steps. The first synthetic step, the activation of the acid functionality as its acid chloride (**90**), was carried out by treatment of the starting material (**72**) with excess thionyl chloride. The resulting solution was stirred at room temperature whilst monitoring the reaction by IR spectroscopy. After 6 hours, the presence of only one (C=O) stretch band (shifted from 1722 to 1779 cm^{-1}), coupled with the decrease in the intensity of the broad acidic, (O-H) stretch band at 3093 cm^{-1} gave firm indication that the reaction had reached completion. Excess unreacted thionyl chloride was subsequently removed by distillation at ambient pressure enabling the isolation of 2,2-dibromocyclopropane carbonyl chloride (**90**) as a tan coloured, pungent smelling oil in 92 % yield by careful distillation of the residue under reduced pressure, (bp 47 – 49 °C at 0.9 mmHg). The highly reactive product was stored in the freezer at –5 °C under an inert atmosphere of argon to prevent decomposition (or unwanted reaction) prior to use.

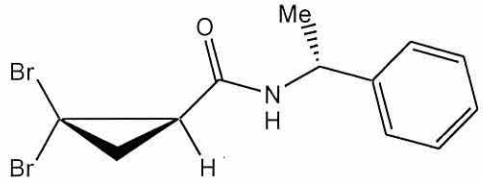
2.3.2.2 Choice of Amine

The second step of the synthesis, amide formation, was carried out by reaction of the previously prepared racemic acid chloride (**90**) with a suitable chiral amine. The choice of this amine, as with the choice of any resolution agent must be made with care, hence the guidelines that characterise suitable resolution agents (discussed in Section **2.2.1**) must be taken into consideration. As mentioned previously in Section **2.2.3.3**, both enantiomers of the chiral amine, (α)-methylbenzylamine (**87-*R*** and **87-*S***) are commercially available in high optical purity from regular suppliers. It was therefore decided, since this amine had been used earlier in diastereomeric salt formation, it would be a good candidate for use in diastereomeric amide formation.

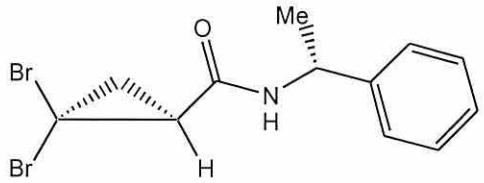
2.3.2.3 Formation and Separation of Diastereomeric Amides

The preparation of the desired mixture of diastereomeric amides (**92-*R,R*** and **92-*S,R***) was carried out by the careful, low temperature (0 °C) addition of 2.2 equivalents of (+)-(α)-methylbenzylamine (**87-*R***) to a 10 % solution of the previously prepared racemic acid chloride (**90**) in HPLC grade chloroform, the resulting solution was then

allowed to warm to room temperature and stirred for a further 3 hours. TLC analysis (1:1, petrol:ether) of the crude reaction mixture showed the formation of two new spots with similar R_f (0.39 and 0.52), which were later identified as the desired diastereomeric amides. Aqueous work-up followed by solvent extraction afforded the crude diastereomeric mixture as an off-white powder (mp 114 – 116 °C) in 94 % yield.



92-*R,R*



92-*S,R*

Figure 2.17

The IR spectrum of the crude diastereomeric mixture was measured as a KBr pellet, and clearly showed only one strong band at 3286 cm^{-1}, corresponding to the single (N-H) stretch observed in secondary amides. A second characteristic band, the amide type I (C=O) stretch was also observed at 1654 cm^{-1}. Further analysis of the sparingly soluble diastereomeric mixture by proton NMR clearly showed the product as a mixture of two compounds in a 1:1 ratio. In fact, each of the three cyclopropyl signals appearing in the region 1.8 – 2.6 ppm is "doubled up" with an identically profiled signal appearing adjacent to it (with a variation in chemical shift of between 0.01 – 0.03 ppm); this region of the NMR spectrum may be seen in **Figure 2.18**.

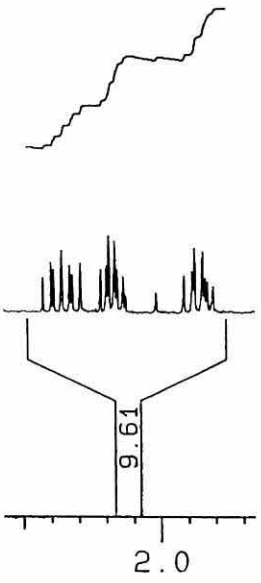
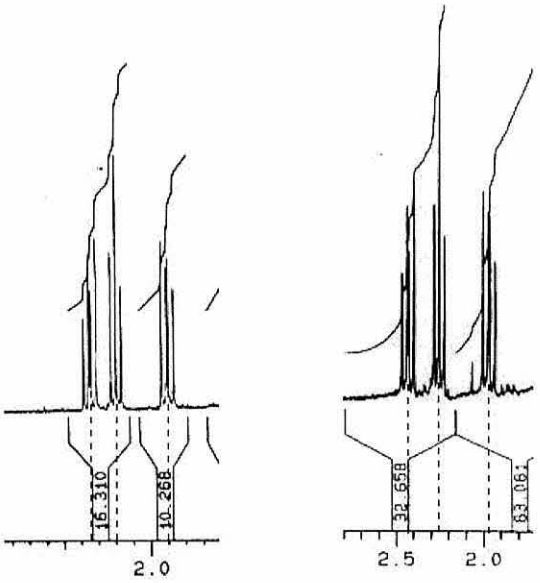


Figure 2.18

Separation of the two diastereomers (**92-*R,R*** and **92-*S,R***) was routinely carried out by simple flash chromatography on silica gel. The diastereomeric mixture was preloaded onto a small amount of silica gel and then "dry loaded" onto the top of a wide silica column. Elution of the column with 1:1 petrol:ether solution under medium pressure (maintained with a hand bellows) enabled the quantitative separation of the two diastereomeric components of the mixture. The separated diastereomeric amides were then recovered simply by removing the excess solvent under reduced pressure; both of the individual components were subsequently recovered as finely crystalline white powders. Analysis of the separate components by proton NMR revealed that each of the previously "doubled-up" signals was indeed simplified; the cyclopropyl regions of the proton NMR spectra for each component are shown in **Figure 2.19**.



High Running Compound Low Running Compound

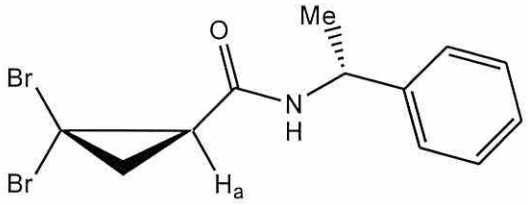
Figure 2.19

Although the preparation and subsequent chromatographic separation of the diastereomeric amides (**92-*R,R*** and **92-*S,R***) was shown to proceed in a clean and efficient manner, this procedure would only find application as a viable source of enantiomerically pure 2,2-dibromocyclopropanecarboxylic acid (**72**) if the substrate could be easily recovered by cleavage of the amide bond.

2.3.3 The Attempted Cleavage of Secondary Amides

2.3.3.1 Amide Hydrolysis

The conversion of amides into carboxylic acids is often considered as a routine procedure, however in practise this is not always straightforward. The inherent stability of the amide bond coupled with the presence of a poor leaving group (compared to -OR in ester hydrolysis) often leads to the requirement for extreme, forcing conditions. Many simple amides are reported to readily undergo hydrolysis under both acidic and basic conditions; typical hydrolysis conditions involve the prolonged treatment of the starting material in either refluxing concentrated acids (such as 6M HCl), or hot base solutions (such as 40 % aqueous NaOH). In general, the yields of such reactions are moderately good, but occasionally the severe reaction conditions employed cause considerable decomposition of the desired product, often due to decarboxylation of the desired acid product. In the case of the particular substrates (**92-*R,R*** and **92-*S,R***), considerable questions were raised about the acidic nature of the cyclopropyl proton (H_a) and hence its lability when exposed to basic solutions. It was thought that prolonged treatment of the substrate with strong base solutions could lead to de-protonation and consequently racemisation of the associated chiral centre, or even ring opening of the cyclopropane itself. Hence it was decided that base catalysed hydrolysis routes should not be employed, thereby hopefully eliminating any possibility of degrading the valuable starting material.



92-*R,R*

Figure 2.20

Exhaustive treatment of the amides (**92-*R,R*** and **92-*S,R***) in refluxing concentrated acids (both HCl and H_2SO_4) was subsequently shown to be unsuccessful, indeed only starting material was recovered in each case. It was subsequently proposed that this apparent lack of reactivity might possibly be due to the lack of solubility (of the substrate) in the reaction media. Unfortunately, the subsequent addition of miscible co-solvents such as methanol and THF (in an attempt to increase the substrate

solubility) had no effect on the desired reaction; similarly only unreacted starting material was recovered upon work-up.

A slightly modified procedure involving the treatment of the refluxing acidic (H_2SO_4) solution with an excess of solid sodium nitrite[127] was shown to be successful on a small scale (up to 200 mg). The product (**72**) was recovered as a dirty brown oil in 65 – 70 % yield and was obviously in need of further purification. Analysis of the crude product by chiral GLC (of the corresponding methyl ester) revealed that the enantiomeric excess of the acid regenerated appeared to be unaffected. This initial result raised hopes that this method could indeed be applied on a larger scale hence enabling the efficient regeneration of enantiomerically pure acids.

Unfortunately upon scale-up, the efficiency of the reaction and consequently the yields obtained dropped quite dramatically. As the reaction was carried out as a direct scale up of the previous small-scale preparation, it was decided that the only variable that could not be accurately reproduced on a larger scale was the stirring efficiency. It was also noted that upon addition of the solid sodium nitrite, a finely dispersed "living" foam was being formed which readily filled the reaction vessel. Consequently, the efficient stirring of the reaction mixture became considerably inhibited and as a result, the yield decreased (< 20 %). In an effort to improve the stirring efficiency and hopefully raise the yields, alternative methods of stirring including the use of larger fleas and eventually mechanical stirring were examined. Unfortunately these changes appeared to have no effect on the efficiency of the reaction and low yields were again observed. With this apparent scale-up problem at hand, it was decided that an alternative method should be sought.

In 1975, a short paper was published in which the authors spoke of a "rapid procedure for the hydrolysis of amides to acids".[128] The paper detailed the mild action of sodium peroxide[129] in the successful hydrolysis of a wide variety of substrates including a range of primary, secondary and indeed tertiary amides. The products of the reaction (either the carboxylic acid or alternatively the amine component) were readily recovered in high yield (70 - 95 %) with very little (if any) decarboxylation being observed. The apparent efficiency and remarkably mild reaction conditions employed throughout this method therefore rendered it an extremely attractive alternative route that would hopefully enable the efficient hydrolysis of the chiral amides (**92-*R,R*** and **92-*S,R***), thereby providing a ready supply of the desired optically active acids (**72-*R*** and **72-*S***). Unfortunately, when attempted, this alternative

procedure was also shown to be unsuccessful; in fact, no hydrolysis products were observed at all. This apparent lack of reactivity was explained by the low solubility of the starting materials (**92-*R,R*** and **92-*S,R***) in the reaction solvent, water, preventing the nucleophilic action of the solvated peroxide anion. Substitution of the solvent with lower alcohols including methanol, ethanol and *i*-propanol (as noted by the authors) had little effect on the solubility of the substrate and as expected no effect on the reactivity observed.

A summary of the key results obtained from each of the experiments carried out examining the hydrolysis of (**92-*R,R*** and **92-*S,R***) may be seen in **Table 7**. It was obvious at this point that chemical hydrolysis was not an efficient way of regenerating the desired optically active acids (**72-*R*** and **72-*S***) and as a result an alternative method should be examined.

Starting material	Reagent mixture	Observation
92-*R,R*	cHCl	no reaction
92-*R,R*	cHCl / THF	no reaction
92-*R,R*	cHCl / MeOH	no reaction
92-*R,R*	cH_2SO_4	no reaction
92-*R,R*	cH_2SO_4 / $NaNO_2$	80 %†, (7%‡) reaction
92-*R,R*	H_2O / Na_2O_2	no reaction
92-*R,R*	MeOH / Na_2O_2	no reaction
92-*R,R*	EtOH / Na_2O_2	no reaction
92-*R,R*	*i*-PrOH / Na_2O_2	no reaction

Table 7. Summarised results from the experiments examining the hydrolysis of amide 92-*R,R*, († < 200 mg scale, ‡ > 200 mg scale).

2.3.3.2 Amide Reduction

An alternative approach that was examined with the general aim of cleaving the amide bond within the starting material (**92-*R,R*** and **92-*S,R***), involved the attempted reduction of the amide functionality inherent within the substrate with a suitable hydride containing reagent. The selective, hydride mediated reduction of N-alkylated amides was first reported in 1963 by the group of H. C. Brown.[130] In this paper Brown showed that the introduction of alkoxy substituents into lithium aluminium hydride

provided a simple method of modifying the reducing power of the reagent. The application of these milder reducing agents such as triethoxyaluminohydride enabled the selective reduction of a range of simple tertiary amides and was subsequently used in the preparation of aldehydes and related alcohols.

Unfortunately, the resolved chiral amide substrates (**92-*R,R*** and **92-*S,R***) of interest were both secondary amides and consequently unsuitable for direct reduction. As a result, further alkylation of the substrates had to be carried out before any reduction could be attempted. N-Alkylation of primary and secondary amides is readily carried out by treatment of the starting material (secondary amide) with a suitable base hence facilitating deprotonation and the generation of the corresponding anion; subsequent quenching of the anion with a suitable alkyl halide provides the desired alkylation and hence the tertiary amide required for the ensuing reduction step. The idealised synthetic scheme associated with this alternative approach may be seen in **Figure 2.21**.

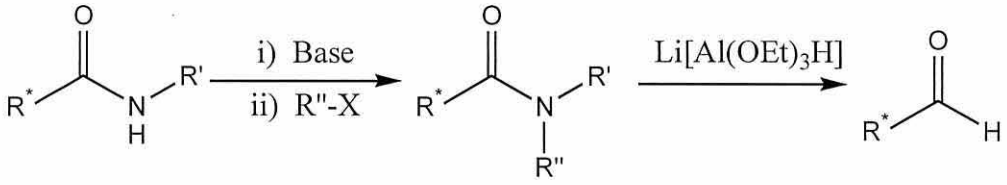
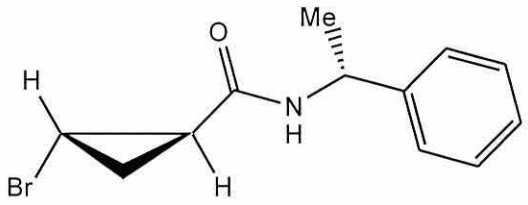


Figure 2.21

Unfortunately, alkylation of the secondary amides (**92-*R,R* and 92-*S,R***) was found to be more complicated than first imagined. Indeed the attempted alkylation of (**92-*R,R***) employing a freshly prepared suspension of sodium hydride in dry DMF (as base) followed by benzyl bromide (as the chosen alkylation agent) proceeded with no reaction at all. In fact, only unreacted starting material was recovered upon work-up. It was therefore decided that the experiment should be repeated, this time employing an alternative base.

The second attempted alkylation of (**92-*R,R***) was duly carried out using an alternative organometallic base, methyl lithium. Deprotonation was carried out at low temperature (-60 °C) by reaction of 1.2 equivalents of methyl lithium with the starting material in ethereal solution, as in the previous experiment benzyl bromide was subsequently employed as the desired alkylation agent. Upon work-up, a new product was indeed observed; unfortunately though it was found not to be the desired tertiary amide. Preliminary analysis of the unknown product, a red –brown crystalline solid (mp. 141 °C) by TLC indicated that it was homogeneous and not a mixture. IR

spectroscopy confirmed the retained presence of the secondary amide group with the observation of a strong absorbance band at 3286 cm^{-1}, corresponding to the single (N-H) stretch observed in secondary amides and a second characteristic band, the amide type I (C=O) stretch band was observed at 1640 cm^{-1}. Subsequent identification of the molecular ion and hence any isotopic ratio by mass spectrometry indicated that the molecule contained only one bromine atom. This observation was confirmed upon further examination of the product by proton NMR. The observation of a characteristic relatively low field signal appearing at 3.15 ppm confirmed that a reduction of the *gem*-dibromo- substituent of the cyclopropane had indeed taken place. Furthermore, the appearance of only one such signal indicated that only one of the two possible geometrical isomers had been produced. Careful examination of the coupling constants associated with each of the cyclopropyl signals enabled the elucidation the relative stereochemistry of the cyclopropyl substituents. Indeed, the appearance of one *cis*- and two *trans*- coupling constants within the low field signal indicated that the bromide group was in fact *trans*- to the amide substituent. As a result of considerable analysis, the unknown compound was identified as the reduced monobromo-cyclopropane (**93**).



93

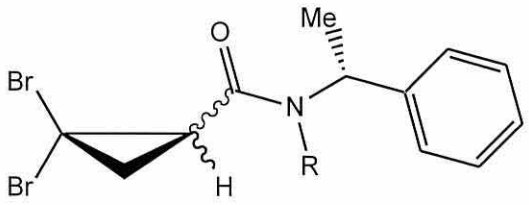
Figure 2.22

This result was indeed interesting, but unfortunately the reaction was unsuccessful in achieving the desired goal, the reduction of the amide functionality enabling the regeneration of the chiral building block. The apparent inertness of the secondary amide towards alkylation is obviously due to the presence of the more reactive gem-dibromo-substituents reacting in preference to the desired reaction site (the amide functionality). With this observation at hand, it was decided that further alkylation of the resolved amides could not be easily achieved and consequently should be abandoned.

2.3.4 Conclusion

As mentioned in Section **2.3.3**, the conversion of amides into carboxylic acids is often considered as a routine procedure, however in practise this is not always straightforward. Unfortunately to our misfortune and frustration, this statement was indeed found to be true.

Although the preparation and separation of the diastereomeric amides (**92-*R,R*** and **92-*S,R***) was found to be efficient (Section **2.3.2**), the subsequent regeneration of the chiral building blocks by cleavage of the amide bond was found to be unsuccessful. The secondary amides examined were shown to be extremely inert towards hydrolysis and furthermore the presence of an incompatible functional group (*gem*-dibromide) rendered alkylation and subsequent reduction of the resulting tertiary amide unsuitable. As a result, it was decided that the alternative direct preparation of tertiary amides (prior to separation) should be examined. This was readily carried out by direct reaction of the racemic acid chloride precursor (**90**) with suitably substituted, chiral secondary amines. The tertiary amides (**94a**) and (**94b**) were subsequently both prepared in moderate yield (> 75 %), but unfortunately the efficient separation of the two diastereomers produced was not possible. Consequently the further study of this system was put aside and work on the general application of chiral amides in the resolution of cyclopropane containing building blocks was not continued.



94a, R = *i*Pr
94b, R = Bn

Figure 2.23

2.4 Enzymatic Resolution

2.4.1 Introduction

The kinetic resolution of a racemic substrate in the presence of an enzyme is by far the most commonly applied method employed in the resolution of optical centres. Historically, the first enzymatic kinetic resolution was carried out in 1858 by the forefather of resolution, Louis Pasteur.[131] This was in fact Pasteur's third reported resolution, namely, the resolution of tartaric acid by fermenting yeast; his discovery consequently revolutionised the new field of biochemistry and introduced the application of enzymes and biomimetic transformations to the developing science of chemical synthesis.

2.4.1.1 Kinetic Principles and Resolution Efficiency

The efficiency of an enzymatic resolution (carried out in either aqueous or organic media) is wholly dependent upon the kinetics (or the comparative rates of reaction) of the two competing reactions under consideration. Enzymatically-catalysed reactions, such as the resolution of a chiral ester (by selective hydrolysis) obey Michaelis-Menten kinetics[132] and may be described with the aid of a simple schematic mechanism such as that seen in **Figure 2.24**, where *R* and *S* represent the fast and slow reacting substrates respectively. *Enzyme-R* and *Enzyme-S* represent enzyme-substrate complexes; further reaction of such complexes leads to the formation of the desired products *P* and *Q*.

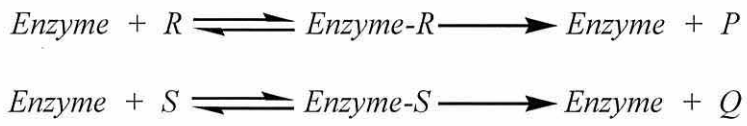


Figure 2.24

The rates of formation of the products (*P* and *Q*) are $v = (V_{max}/K_m)R$ and $v = (V'_{max}/K'_m)S$ respectively and the overall reaction is pseudo-first order with respect to the enantiomers (*R* and *S*) where V_{max} is the maximal velocity and K_m is the Michaelis constant. The enantiomer ratio (**E**) is often employed as a measure of the enantioselectivity of a given system (hence also serving as a measure of the efficiency of a resolution). **E** is simply derived by comparing (as a ratio) the two pseudo-first order rate constants of each of the competing reactions, $\mathbf{E} = (V_{max}/K_m)/(V'_{max}/K'_m)$.

Implicit in this treatment is the assumption that *R* is the faster reacting enantiomer and that the system is non-reversible and devoid of product inhibition. For a particular enzymatic reaction or resolution to be considered efficient, i.e. both enantiomers are obtained in high optical purity in a single kinetic resolution, the value of **E** must be in excess of 100. On the other hand, when reactions display lower values of **E**, only one enantiomer (typically the unreacted one) may be recovered with high enantiomeric enrichment. This is normally achieved as the reaction nears completion, and consequently yields of optically enriched material are normally quite low.

2.4.1.2 Aqueous *versus* Organic Media?

Traditionally, enzymatic resolutions of the type employed by Pasteur have been carried out at an ambient temperature in aqueous media containing a suitable ionic buffer solution. Such constraints have enabled chemists to maintain reaction conditions somewhat akin to those of the enzymes "*natural habitat*", hence maintaining enzyme activity throughout reactions where a number of variables such as the pH and temperature of the solution may fluctuate and otherwise denature the active catalyst. As a result, the resolutions of a wide variety of substrates including carboxylic acids, alcohols and amines have been successfully carried out in traditionally buffered aqueous solutions via the enantioselective enzymatic hydrolysis of derivatised starting materials including esters, amides and carbamates.[133]

More recently, pioneering studies conducted by the group of Klibanov[134] have shown that many enzymes remain catalytically active in organic solvents containing little or no added water. The obvious advantage of organic substrate solubility (compared with solubility in traditional aqueous media), coupled with increased thermal enzyme stabilities (in organic solution) and the ease of product recovery have promoted the development and application of such enzymatic processes in the last fifteen years. Developments of this nature have subsequently served as a turning point in the traditional organic chemist's perception of enzymatic transformations. Subsequently modern chemists, both academic and industrial, no longer subscribe to the rigid "*one enzyme - one reaction - one substrate*" paradigm, and as a consequence accept the application of enzymes as an important alternative source of a wide variety of extremely versatile enantioselective catalysts.

As mentioned in Section **2.1**, the general aim of the work discussed previously in this chapter (and indeed in the following sections) is the successful development of

efficient routes that will enable the large-scale preparation of optically active cyclopropyl containing materials. Hence, the successful development of an enzymatic route that would enable the efficient preparation of such compounds is therefore a very interesting and worthwhile avenue of research. The application of resolution techniques in both organic and aqueous media will be discussed in greater detail in Sections **2.4.2** and **2.4.3**.

2.4.2 The Application of Enzymes in Organic Solution

2.4.2.1 Introduction

One of the main growth areas in the application of enzyme technology in organic solutions has been the area of enzymatic resolutions; indeed the application of lipase enzymes in particular has led to the successful resolution of a wide variety of substrates including alcohols,[135] acids,[136] esters[137] and amines.[138] It was our aim to successfully apply such techniques to the resolution of a simple, readily available racemic cyclopropane containing substrate, 2,2,-dibromo-1-hydroxymethyl cyclopropane (**86**), the synthesis of which was discussed in Section **2.2.3.1.3**.

2.4.2.2 The Enzymatic Resolution of Alcohols

The kinetic resolution of a range of racemic alcohols is commonly carried out in a wide variety of organic solvents by the lipase catalysed enantioselective esterification (ester formation) of a single enantiomer of a racemic substrate. A general reaction scheme for this type of reaction may be seen in **Figure 2.25**.

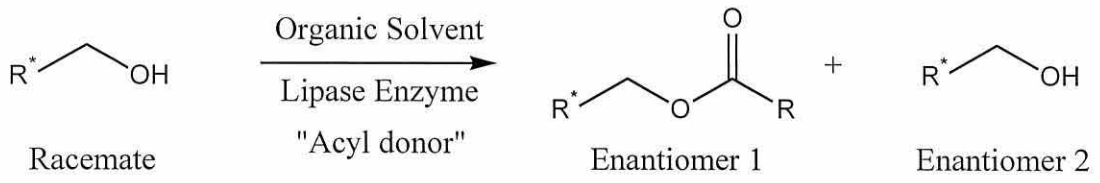


Figure 2.25

One inherent problem that is often encountered with kinetic resolutions of this type is the effect of the competing reverse reaction of the achiral alcohol component of the acyl transfer reagent with the desired optically active ester produced (as seen in **Figure 2.26**). This reverse process consequently leads to a decrease in the optical purity of the desired product and is therefore undesirable. To circumvent this problem, irreversible acyl transfer agents or "acyl donors" have been developed. The

application of these effectively eliminates the competing reverse reaction and thereby renders the reaction essentially irreversible. Examples of suitable acyl donor reagents include the enol acetates, vinyl acetate and isopropenyl acetate, which have since become the reagents of choice when carrying out lipase-mediated acetylation of alcohols in organic solution.[135]

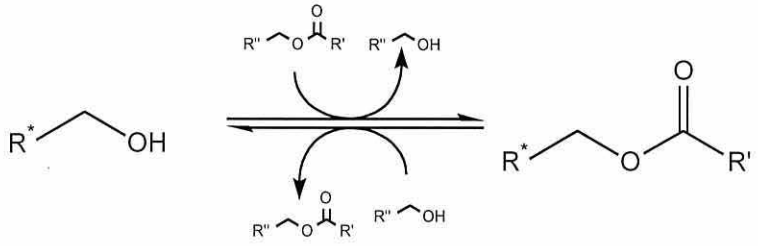


Figure 2.26

The desired kinetic resolution is generally catalysed by the presence of a range of hydrolytic enzymes collectively known as hyrolase enzymes; this classification includes the subcategorised lipase and esterase type enzymes. In general, such enzymes have been shown to be very versatile, highly efficient and selective in their activity, that is, selective with respect to functionality, regioselectivity, and stereoselectivities observed. However there is little information available on the substrate selectivity of lipase enzymes in organic solution and as a result, there is no straightforward protocol that enables the easy selection of the most suitable enzyme for a particular process. Unfortunately, this task is complicated further when one considers that the range of suitable enzymes available in nature is very large (approximately 640 hydrolase enzymes have been characterised to date). Fortunately the high costs associated with the isolation and subsequent supply of many of the more exotic enzymes makes the task of enzyme selection somewhat easier on economic grounds (as only 125 are commercially available). Indeed, many of the larger commercial suppliers such as Fluka and Sigma, in an effort to service the growing demand for enzymatic preparations, market a moderately sized range of general use enzymes that find varied application in a wide range of reactions.

As highlighted above, one of the prime variables that must be considered in the design of any particular enzymatic resolution is indeed the choice of enzyme employed. However, unlike resolutions that are carried out in aqueous media, the nature of the organic solvent employed is not fixed, thereby introducing another variable that enables the further tuning of the desired process. Indeed, the solution employed may be selected from a wide range of commonly available solvents

including aromatics such as toluene and benzene, simple alicyclics or aliphatics such as cyclohexane or C5 - C8 hydrocarbons, chlorinated lipophilic solvents such as chloroform and dichloromethane or ethers such as diethyl, di-isopropyl and preferably *tert*-butyl methyl ether.

With this in mind, it was decided that a comprehensive series of experiments should be carried out, hence enabling the examination of each of the variables in turn; further details of the experiments carried out are discussed in the following Section.

2.4.2.3 Attempted Resolutions in Organic Solution

An extensive series of small-scale experiments was conducted to examine the suitability of enzymatically-mediated resolutions towards the large-scale preparation of cyclopropyl containing building blocks. As highlighted in the previous Section, there are a number of variables present in such systems including, the nature of the acyl donor, the organic solvent used and indeed the type of enzyme employed as catalyst. Each variable was duly examined in an attempt to identify the optimal conditions for the proposed resolution. Each individual experiment was carried out using a common procedure in a standard 5-dram glass sample vial, each reaction was subjected to the same external conditions and was incubated at an ambient temperature of between 24 – 26 °C for a pre-determined period of time.

In general, 500 mg (2.2 mmol) of the racemic substrate (**86**) was dissolved in 5 ml of the chosen organic solvent. An acyl donor (0.55 equiv) was then added to the stirred solution before treatment with the chosen enzyme preparation (50 mg). The resulting solution was stirred at room temperature whilst monitoring the reaction by TLC and GLC; after 48 hours it was filtered to remove any enzyme and hence stop the reaction. The product recovered was then subjected to analysis by GLC (and chiral GLC when necessary) enabling the comparison of individual retention times against those of chemically prepared reference samples (of both the starting material and the desired product). The results obtained from this series of experiments may be seen in **Table 8** and **Table 9**.

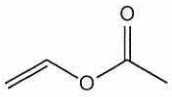
Acyl Donor	Enzyme	Solvent	Observation
Vinyl Acetate  0.55 equiv.	Sigma-*PPL* (*Porcine Pancreas*)	THF	unknown product observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed
	Lipase-*Ps* (Amano) (*Pseudamonas cepacia*)	THF	unknown product observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed
	Lipase-G (Amano) (*Penicillium camemberti*)	THF	unknown product observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed
	Lipase-*R* (Amano) (*Penicillium roqueforti*)	THF	no products observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed

Table 8. Results obtained from the attempted enzymatic resolution of (86) in a variety of organic solvents employing 0.55 equivalents of the acyl donor, vinyl acetate

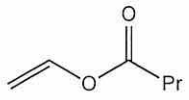
Acyl Donor	Enzyme	Solvent	Observation
Vinyl Butyrate  0.55 equiv.	Sigma-*PPL* (*Porcine Pancreas*)	THF	unknown product observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed
	Lipase-*Ps* (Amano) (*Pseudamonas cepacia*)	THF	unknown product observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed
	Lipase-G (Amano) (*Penicillium Camemberti*	THF	unknown product observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed
	Lipase-*R* (Amano) (*Penicillium Roqueforti*)	THF	no products observed
		Et_2O	no products observed
		iPr_2O	no products observed
		tBuOMe	no products observed
		$CHCl_3$	no products observed
		CH_2Cl_2	no products observed

Table 9. Results obtained from the attempted enzymatic resolution of (86) in a variety of organic solvents employing 0.55 equivalents of the acyl donor, vinyl butyrate

It can be seen from the data presented in **Table 8** and **Table 9** that the enzymatic resolution of the racemic substrate in a range of organic solutions was not successful. In all the trial resolutions except those carried out in THF, no reaction was observed at all, indeed between 95 and 100 % of the racemic starting material was recovered from each individual reaction. Hence it was concluded after considerable experimentation that this method was not able to fulfil the desired aim and afford an efficient resolution of racemate (**86**). Perhaps this apparent lack of resolution activity is simply due the lack of a suitable lipase enzyme; increasing the number of enzymes available for trial may therefore lead to the identification of a particular enzyme that is better suited to this task.

Interestingly though, three of the attempted resolutions carried out using THF as the reaction solvent gave rise to an unexpected product (**95**) and not the expected acylated product. The unknown product was routinely prepared in the presence of three of the four enzymes employed in the enzymatic trials. The maximum yields obtained were as high as 35 % from reactions using either Sigma-*PPL* or Lipase-*Ps* (Amano) as the active catalyst, a yield of around 15 % was experienced from reactions using Lipase-*G* (Amano) and the remaining enzyme Lipase-*R* (Amano) appeared inactive. Further study of this unusual reaction showed that it was indeed an enzymatic process; no reaction was evident when a control experiment was carried out in the absence of any enzyme. Interestingly though, the reaction was also found to occur in the absence of acyl donors, although their presence appeared to accelerate the rate of product formation.

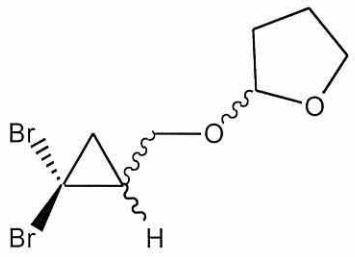
The product (**95**) was characterised by a mid - high running spot with an $R_f = 0.54$ on TLC (5:1, petrol: ether) and was subsequently separated from the residual starting material ($R_f = 0.11$) by flash chromatography on silica gel. Analysis of the residual alcohol by chiral GLC (of the corresponding acetate) in each case subsequently showed the unreacted starting material to be racemic. The absence of any enantiomeric enrichment at all (in the unreacted starting material) was a fair indicator that the unknown product was also likely to be racemic; this was indeed confirmed when the product was found to exhibit no optical rotation.

The IR spectrum of the isolated product (**95**) provided very little information in the form of characteristic bands that are associated with many functional groups. Consequently, the absence of such bands enabled the quick elimination of many functional groups from consideration. Interestingly, the absence of a strong (O–H)

stretching band in the product also indicated that the hydroxyl group of the starting material was no longer evident. The presence of strong characteristic bands in the region between 1050–1200 cm^{-1} was consistent with the (C–O–C) stretching vibrations commonly observed in the spectra of acetals and ethers, (perhaps formed by reaction of the alcohol).

The ^{1}H NMR spectrum of (**95**) (measured as a solution in $CDCl_3$) proved to be very complex; this unexpected observation indicated that although homogenous by TLC and GLC, the product was perhaps a mixture of co-eluting components, perhaps diastereomeric in nature. Many of the signals that were present within the spectrum of the (**95**) were in fact directly comparable to those of the racemic starting material (**86**); such correlations are often interpreted as signs of structural analogy, thereby indicating that the structures of the product and starting material are very similar indeed. Additional signals that were also observed in the product spectrum included a low field multiplet (5.1 ppm, 1H) characteristic of an acetal, a moderately high field multiplet (3.9 ppm, 2H) consistent with an ethereal CH_2 and a very complicated four proton multiplet appearing at approximately 1.9 ppm. Interestingly, a similar correlation between the ^{13}C NMR - DEPT spectra of the starting material and the product was also noted, additional signals corresponding to three CH_2 groups and a CH signal characteristic of an acetal (104 ppm) were also noted.

Considerable analysis of the information provided by IR spectroscopy, NMR and mass spectrometry led to the tentative identification of the unknown material (**95**) as a mixture of diastereomers of the adduct formed upon reaction of the starting material with the solvent (THF), the structure of which may be seen in **Figure 2.27**.



95

Figure 2.27

2.4.2.4 Summary

Unfortunately, as the experimental data presented in **Table 8** and **Table 9** shows, the attempted enzymatic resolution of 2,2,-dibromo-1-hydroxymethylcyclopropane (**86**) via the contemporary approach employing the application of lipase enzymes in a range of organic solutions was unsuccessful. The attempted irreversible enantioselective acylation of the starting material (**86**) was studied in a comprehensive series of experiments where the effect of a number of variables (including the enzyme and solvent employed) was examined. Unfortunately, in all but six of the forty-eight experiments carried out, there was no sign of reaction at all; consequently racemic starting material was recovered in each case. In the remaining six experiments, an unexpected compound (**95**), the product of an enzyme catalysed reaction between the starting material and the solvent (THF) was observed; unfortunately there was no sign of the desired reaction product.

The disappointing results obtained throughout this series of experiments may be explained quite simply as a result of the unsuitability of the chosen enzymes towards the desired substrate. Although comprehensive, the study was limited by the number of lipase enzymes available for assessment, indeed it only examined the application of four commonly available variants. Increasing the number of variants available for trial would perhaps enable the identification of a more suitable enzyme and hence enable the efficient resolution of the substrate. As increasing the range of enzymes available for application was not economically viable, it was decided that the resolution of a similar substrate would be attempted using the traditional method of enzymatic ester hydrolysis in buffered aqueous media.

2.4.3 The Application of Enzymes in Aqueous Media

2.4.3.1 Introduction

As mentioned briefly in Section **2.4.1.2**, the enzymatic resolution of racemic alcohols may also be carried out by means of a more traditional approach, the enantioselective hydrolysis of corresponding esters. Such processes are routinely carried out in aqueous media containing a suitable ionic buffer solution; a schematic diagram of this process may be seen in **Figure 2.28**.

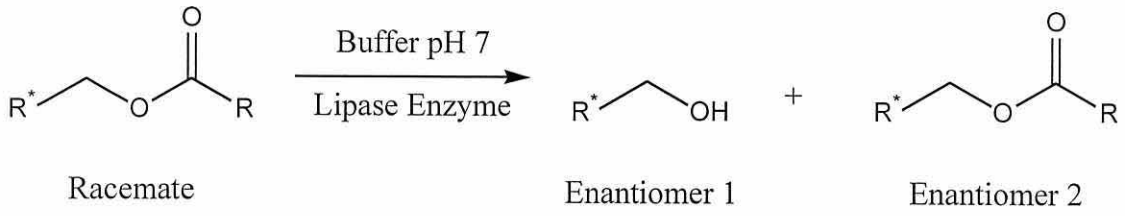


Figure 2.28

2.4.3.2 Substrate Preparation

The racemic substrate that was chosen for application in the proposed enzymatic resolution was the ester, 2,2-dibromo-1-hydroxymethylcyclopropyl butyrate (**96**).

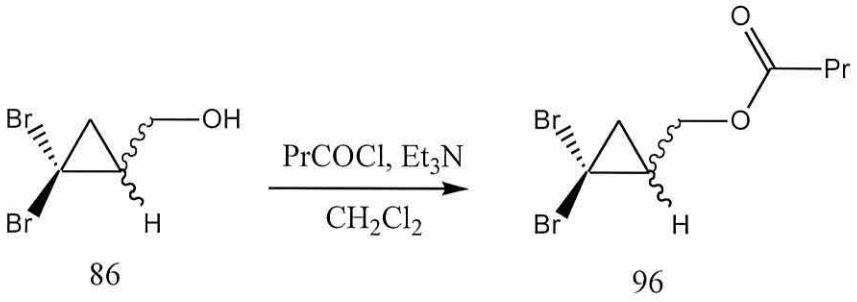


Figure 2.29

The racemic butyrate starting material (**96**) was readily prepared in a single step by the reaction of (**86**) with 1.2 equivalents of butryl chloride in the presence of an excess of triethylamine. The resulting solution was stirred at room temperature whilst the reaction was monitored by TLC (5:1, petrol: ether); the formation of the desired product was observed with the appearance of a new high running spot with $R_f = 0.75$. The reaction appeared to reach completion after 3 hours and the resulting crude product was subjected to purification by flash chromatography on silica. The purified product was recovered as a colourless, fragrant oil in 83 % yield. Spectroscopic data (IR and proton NMR) confirmed that the synthesis was successful, and the product was used without further purification.

2.4.3.3 Preparation of Aqueous Buffer Solution

As mentioned previously in Section **2.4.1**, enzymatically mediated hydrolyses are typically carried out carried out at ambient temperature in aqueous media in the presence of a suitable buffer solution. Such reaction conditions are necessary to enable the efficient reproduction of conditions similar to those found in the enzyme's natural environment; within the cells of living organisms such as bacteria and higher

life forms. The buffer solution chosen for application in the enzymatic hydrolysis of our substrate (**96**) was the commonly employed phosphate buffer, composed of individual aqueous solutions of a salt (*S*) and an acid (*A'*), K_2HPO_4 and KH_2PO_4 respectively.

The mathematical basis of buffer action is the logarithmic dependence given by the *Henderson-Hasselbalch* equation, which is quite flat when pK_a = pH. This principle may be shown diagrammatically in the form of a plot of pH against the volume of titrant added (i.e. added H_3O^+) and may be seen in **Figure 2.30**.

$$pH = pK_a - \log\frac{[A']}{[S]}$$

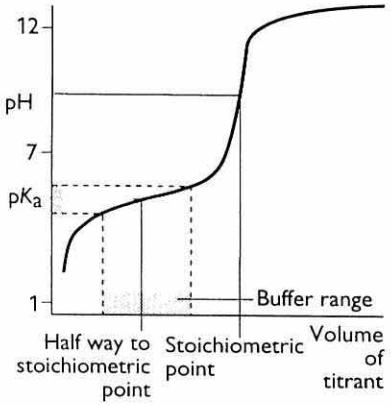


Figure 2.30

The physical basis of buffer action may be explained as the existence of an abundant supply of A^- ions (due to the presence of a salt) that can neutralise any H_3O^+ ions formed during the *in-situ* reaction. Similarly, the existence of an equally abundant supply of HA molecules can supply H_3O^+ ions to react with any base that may also be formed during the reaction. This establishment and subsequent stabilisation of a dynamic equilibrium acting against any by-products formed during the reaction may be regarded as an example of Le Chatelier's principle.

As mentioned in the previous paragraph, the buffer that was chosen for use during this series of experiments was a simple phosphate buffer solution; the equilibrium reaction between the two components may be seen below. The solution was prepared using standard procedures from equimolar solutions of the two components, K_2HPO_4 and KH_2PO_4 in varying ratios dependent upon the final pH required, such ratios are noted in **Table 10**.

$$H_2PO_4^-{}_{(aq)} + H_2O_{(l)} \rightleftharpoons H_3O^+{}_{(aq)} + HPO_4^{2-}{}_{(aq)}$$

Desired pH	Vol of 1M K_2HPO_4 ml*	Vol of 1M KH_2PO_4 ml*
6.8	49.7	50.3
7.0	61.3	38.7
7.2	71.7	28.3
7.4	80.2	19.8
7.6	86.6	13.4

Table 10. Composition of solutions required for the preparation of 0.1M aqueous phosphate buffer solution, * solutions are combined and then diluted to make a total volume of 1 l

2.4.3.4 Attempted Resolutions in Aqueous Solution

A short series of experiments was conducted to examine the suitability of this method for application in the large-scale preparation of cyclopropyl containing building blocks. Each experiment was carried out in standard laboratory glassware at an ambient temperature of between 24 – 26 °C. The common procedure employed during these reactions is described in the following paragraph.

In general, 1.0 g (3.3 mmol) of the racemic substrate (**96**) was suspended in 10 ml of freshly prepared phosphate buffer solution (0.1M, pH 7). The solution was then treated with the chosen crude enzyme preparation (typically 100 mg) and slowly stirred at room temperature whilst monitoring the solutions pH using a suitable pH meter. The pH of the reaction solution was then maintained at pH 7 by the controlled addition of molar sodium hydroxide solution. Upon completion (typically after the consumption of 0.5 equivalent of base), the solution was extracted with ethyl acetate, the enzyme removed by filtration and the products separated by flash column chromatography on silica gel. The enantiomeric excesses of the individual components, both residual butyrate (**96**), and alcohol (**86**) produced (as its acetate) were measured by chiral GLC. The results from these experiments may be seen in **Table 11**.

Enzyme	Equiv. of base	% Conversion†	ee. [residual ester]‡	ee. [alcohol]‡
Sigma *PPL*	0.25	21	-	18
	0.50	46	-	12
	1.00	96	-	<5
Lipase-*Ps* (Amano)	0.25	11	9	93
	0.50	29	45	85
	0.75	41	51	77
	1.00	53	62	69
	1.50	87	83	48

Table 11. Results obtained from the attempted enzymatic resolution of 94 in aqueous 0.1M phosphate buffer solution, † measured by GLC, ‡ determined by chiral GLC

The information presented in **Table 11** clearly shows that the enzymatic resolution of our chosen substrate was found to be moderately successful. Small-scale resolution experiments were carried out in the presence of two commercially available lipase enzymes (Sigma-*PPL* and Lipase-*Ps* (Amano)), both of which catalysed the partial kinetic resolution of the racemic substrate. Unfortunately, the efficiency of each of the observed resolutions was shown to be quite poor, particularly in the case of the Sigma-*PPL* mediated resolutions, where the enantiomeric excesses exhibited by the recovered materials were indeed very low (typically between 5 – 20 % ee).

The low efficiency of the attempted resolutions may be explained in terms of the kinetics of the two competing hydrolysis reactions. As mentioned previously in Section **2.4.1.1**, the efficiency of enzymatic resolutions is wholly dependent upon the comparative pseudo-first order rate constants of the two competing reactions (the hydrolysis of each enantiomer) and hence the enantiomer ratio (**E**). For a particular enzymatic resolution to be considered efficient, the value of **E** must be in excess of 100, or simply, the rate of hydrolysis of enantiomer 1 must be 100 times greater than that of enantiomer 2. With this point in mind, it may be inferred that the difference between the comparative rates of the two competing reactions (in each resolution) was indeed less than 100; as a consequence the enantiomeric excess of the isolated products was correspondingly low.

In the case of the Sigma-*PPL* mediated resolution, the rates of the competing reactions were almost equal; as a result, the enantiomer ratio (**E**) was small and only

material that was essentially racemic was recovered. Similarly, in the case of the Lipase-*Ps* (Amano) mediated resolution, the enantiomer ratio (**E**) was also less than 100; fortunately though the resolution efficiency appeared to be considerably greater than that observed in the Sigma-*PPL* mediated resolution. This observation inferred that the enantiomer ratio (**E**) of this resolution was greater than that observed in the previous example. As a result, higher enantiomeric excesses were obtained, but in much lower yields than desired; indeed, it was only possible to obtain a small amount (typically less than 20 %) of only one enantiomer during each resolution. Such optically active material was recovered either as the hydrolysed alcohol (early in the reaction), or alternatively as the unreacted starting material as the hydrolysis reaction neared completion. Although the enantiomeric excess of the material recovered was quite respectable (ranging from 50 – 90 % ee), the efficiency of the resolution could only be considered as poor.

2.4.3.5 Summary

In summary, the small-scale enzymatic hydrolysis of (**96**) proceeded with a marginal degree of success but unfortunately the absolute efficiency of the observed resolution was quite poor. Consequently it was concluded that unless a more suitable enzyme could be found, this process was not efficient enough to enable the easy separation of both enantiomers of our chosen racemate.

2.4.4 Conclusion

In conclusion, the application of enzymatically mediated resolution techniques was on the whole unsuccessful. A small range of commercially available lipase enzymes was exhaustively employed in a comprehensive study of the resolution of the chosen substrates (**86** and **96**). Such resolution experiments were carried out in both organic and aqueous media but unfortunately very little success was noted in each case.

The lack of enzymatic activity observed throughout these studies may be explained simply in terms of enzyme - substrate selectivity. As mentioned previously in Section **2.4.2.2**, the range of suitable hydrolase type enzymes available in nature is very large (approximately 640 have been characterised to date). Consequently the brief survey of enzyme activity outlined above (employing just 4 commercially available enzymes), can only be considered as a starting point in the process of identifying a suitable enzyme that is catalytically active towards the substrate. As a result, it is not possible

to state whether this process will (or will not) eventually be of use in the larger scale preparation of the enantiomerically pure cyclopropane containing building blocks as conceptually desired.

The Diastereoselective Synthesis of Polycyclopropanes

3 Diastereoselective Synthesis of Polycyclopropanes

3.1 Aim

The general aim of the work discussed throughout this chapter is the application of simple, enantiomerically pure cyclopropane containing building blocks (the preparation of which was discussed in Chapter 2) in the diastereoselective synthesis of polycyclopropane subunits such as those found in the fatty acid side chains of the natural products FR-900848 (**19**)[37-40] and U-106305 (**20**).[41-43]

For convenience, this chapter is broken into two separate sections, each of which describes an alternative strategy employed in the synthesis of the desired target molecules.

3.2 Introduction

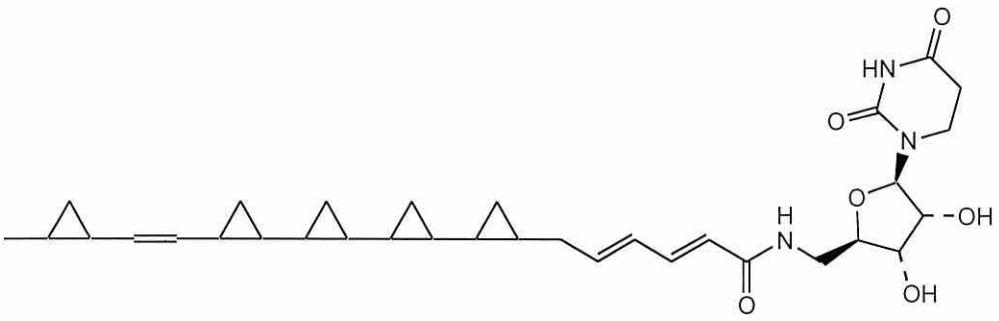
3.2.1 Polycyclopropanes

Prior to late 1990, the directed synthesis and subsequent study of polycyclopropane moieties (in general) was perceived, by many, to be yet another esoteric pursuit that was carried out by a small portion of the academic research community. Luckily this opinion was to change in the mid 1990's with the identification of two remarkable metabolites, both of which were isolated from the fermentation broths of selected microbes. A brief introduction into these materials is given in the following sections.

3.2.1.1 FR-900848 (19)

In 1990, a group of industrial research chemists led by Yoshida (of the Fujisawa Pharmaceutical Co. based in Tsukuba, Japan), reported the isolation and partial structural elucidation of the then, structurally unique, natural product (FR-900848) (**19**) from the fermentation broth of *Streptoverticillium fervens*.[37] Fractionation of the broth followed by extensive chromatography led to the isolation of the remarkable nucleoside, the structure of which was established by extensive application of NMR spectroscopy and partial degradation studies. The proposed structure of FR-900848 (**19**) (seen in **Figure 3.1**) as reported by Yoshida *et al.*,[37] though constitutionally correct, still possessed eleven elements of ambiguity with regards the stereochemical nature of the unusual pentacyclopropane containing fatty acid side chain. These

ambiguities were later resolved, after an extensive series of papers detailing further degradation studies[139] and the stereocontrolled synthesis of model polycyclopropane arrays.[140] Subsequently, the full stereochemical elucidation[38] and indeed the first total synthesis of FR-900848 (**19**) were reported by the group of Barrett in 1996.[39]



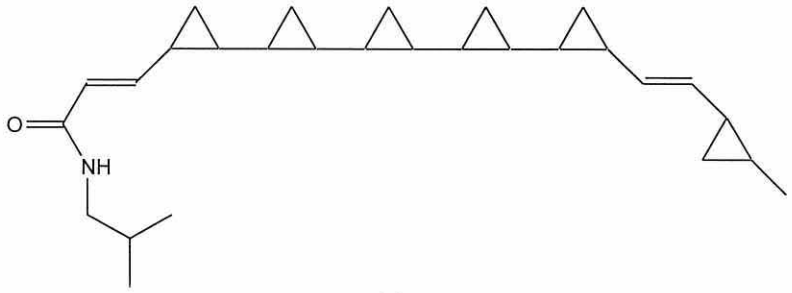
19

Figure 3.1

The fully stereochemicaly assigned structure of FR-900848 (**19**), as reported by Barrett may be seen diagrammatically in Figure 1.23.

3.2.1.2 U-106305 (20)

The subsequent isolation in late 1995 of a second polycyclopropane containing natural product, U-106305 (**20**), from the fermentation broth of *Streptomyces sp.* (UC 11136),[41] stimulated further interest in the already expanding field of polycyclopropane chemistry. The general structure of the isolate was again elucidated via the extensive application of NMR spectroscopy and mass spectrometry. However, a notable omission from the original paper was the determination of the absolute stereochemistry associated with the polycyclopropane array; the structure of U-106305 (**20**) as reported by Kuo *et al* may be seen in **Figure 3.2**.



20

Figure 3.2

The total synthesis and subsequent full stereochemical assignment of U-106305 (**20**), as seen in Figure 1.24, was completed (via an analogous method to that

employed in the total synthesis of FR-900848 (**19**)) by the group of Barrett working at Imperial College (London).[42]

3.2.1.3 Biological Activity

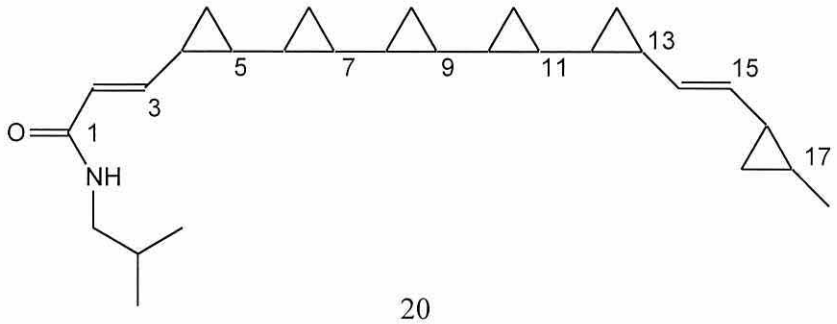
The heightened interest in polycyclopropane containing materials such as FR-900848 (**19**) and U-106305 (**20**), may well be attributed to the remarkable biological activity that is exhibited by both of these materials. Indeed, FR-900848 (**19**) displays a potent, highly specific inhibitory activity against filamentous fungi and a number of pathogens directly responsible for significant human morbidity / mortality. Its low toxicity towards mammalian forms (LD_{50} > 1 g / kg) renders FR-900848 (**19**) an important development in the effective treatment of drug resistant strains that have evolved due to the over use of existing traditional antibiotic agents. U-106305 (**20**), on the other hand, is known to be an efficient inhibitor of the *in-vitro* cholesteryl ester transfer protein (CETP) enzyme. As a result of this apparent activity, it is thought that U-106305 (**20**) and other structural analogues may well find widespread application in the treatment of arteriosclerosis and associated coronary heart disease.

It is certain, that the fatty acid side chains of FR-900848 (**19**) and U-106305 (**20**) are indeed subjected to a considerable degree of conformational restriction; the influence of this restriction upon their remarkable biological activity and anti-fungal properties is, as yet, not fully understood. It is thought, that further probing of these remarkable systems via the synthesis of structural analogues will eventually shed light upon the modes of action operating within these unusual materials.

3.2.1.4 Biosynthesis of Polycyclopropanes

A comprehensive study carried out by the group of Kuo (published with the original isolation of U-106305 (**20**)),[41] showed that the biosynthesis of the polycyclopropane backbones such as those found in U-106305 (**20**) and FR-900848 (**19**) is (as expected) related to the recognised fatty acid biosynthesis pathway. A number of "feeding" experiments were conducted employing ^{13}C-enriched acetate as the microbial feedstock. The products isolated from such "enriched" fermentation broths (after work-up and extensive chromatographic separation), indeed showed regular, positive enhancements in the magnitude of predicted signals in the ^{13}C NMR. For example, in the feeding experiment where [1-^{13}C]-acetate was used, positive enhancements were measured in the signals assigned to carbons 1, 3, 5, 7, 9, 11, 13, 15 and 17; no other

signal enhancements were observed. Such results, confirmed that the backbone was indeed derived from acetate subunits. Furthermore, acetate subunits were more than likely linked together via the commonly accepted head – tail, polyketide biosynthesis mechanism.



20

Figure 3.3

Unfortunately, although this biosynthetic route adequately explained the origin of the backbone carbons, it did not explain the corresponding origin of the methylene carbons associated with each of the cyclopropane rings. Generally speaking, it is commonly accepted that a vast majority of C_1 sub units (or branching methyl groups) present in many similar metabolites, originate from the methyl group of L-methionine. Subsequent "feeding" experiments carried out employing a suitably labelled L-methionine substrate confirmed the operation of this pathway in the synthesis of polycyclopropanes. The proposed biosynthetic pathway (illustrating one such methyl addition) may be seen diagrammatically in **Figure 3.4**.

Unfortunately, this study was carried out only for the second natural product, U-106305 (**20**), but it is commonly thought that this biosynthetic pathway may well be common to both materials.[42] Structural similarities between the two natural products (**19**) and (**20**), such as the comparable stereochemistries present throughout the two polycyclopropane chains, coupled with the fact that both of the products are isolated from a common source (related microbial fermentation broths), makes this theory quite feasible.

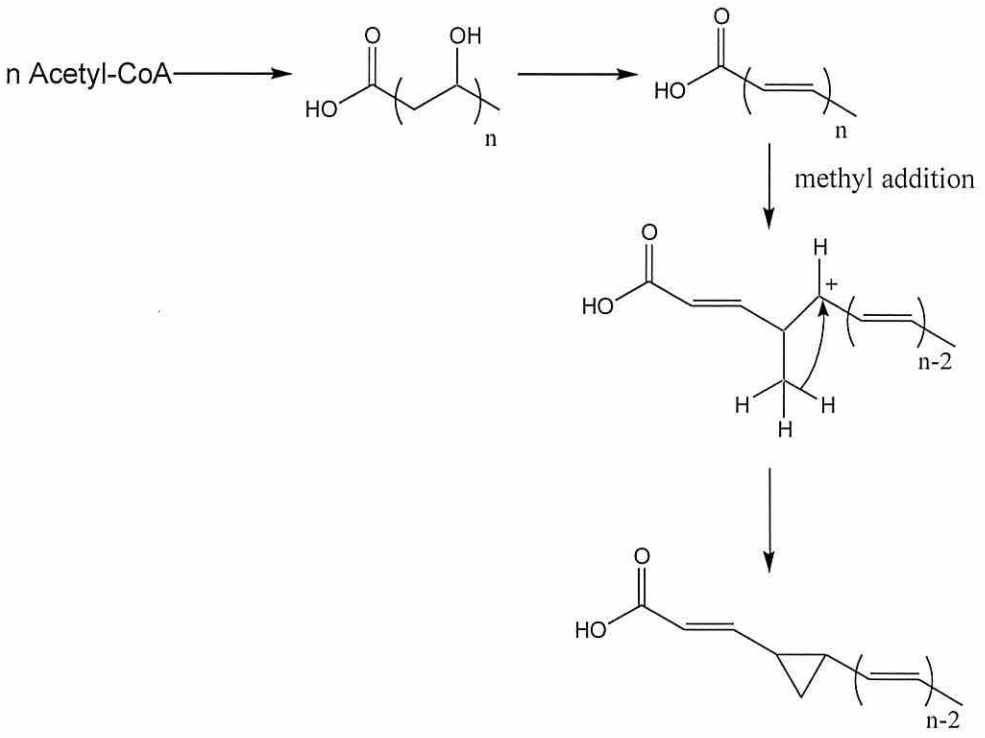
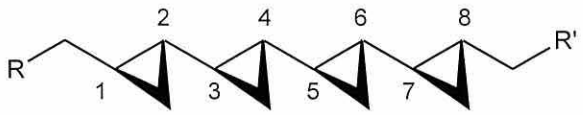


Figure 3.4

3.2.1.5 Stereochemical Nomenclature of Polycyclopropanes

If one considers the fatty acid side chains of the natural products, FR-900848 (**19**) and U-106305 (**20**), it is quite evident that there are a substantial number of chiral centres present throughout the backbone of these relatively simple structures. Indeed, in the quatercyclopropane array of FR-900848, there are eight such chiral centres. Consequently the number of possible diastereomeric structures available for this simple tetracyclopropane array is also correspondingly high. Bearing in mind that for a particular compound containing n stereocentres, there are 2^n possible optical isomers, in the case of the example illustrated in **Figure 3.5**, there would be a total of 256 possible diastereomeric structures.



97

Figure 3.5

Evidently, an efficient nomenclature system is required to enable the description of the stereochemical relationship of each of these possible structures. This is provided quite adequately by the systematic nomenclature system recommended by IUPAC,

where each individual chiral centre is assigned a stereochemical descriptor (either *R* of *S*) in accordance with the Cahn-Ingold-Prelog sequence law. Unfortunately (as in carbohydrate chemistry) this system often gives rise to complicated names. In an effort to avoid this complication, the application of simple stereochemical descriptors is commonly employed when describing the relative stereochemistries of polycyclopropanes. The descriptors employed (*cis*-, *trans*-, *syn*- and *anti*-) are best described with the aid of a simple diagram, which may be seen in **Figure 3.6**, a brief description also follows below.

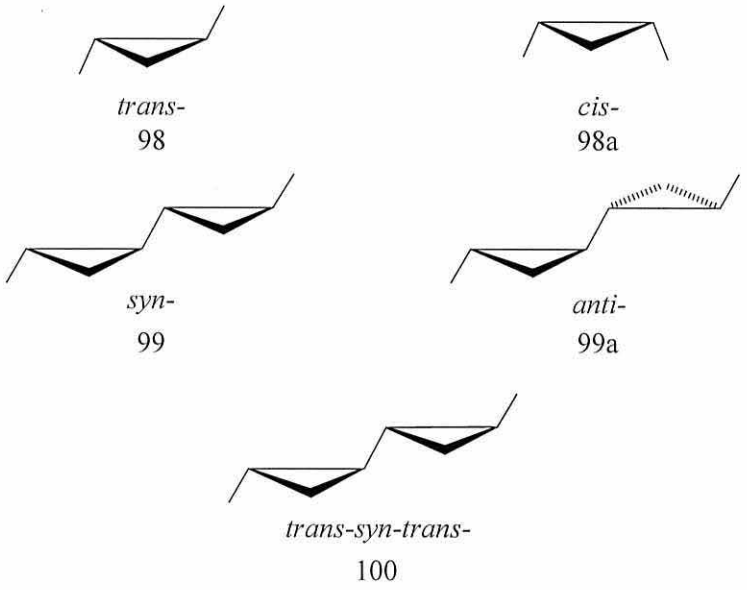


Figure 3.6

The descriptors *cis*- and *trans*- are effectively used to describe the stereochemical relationship of the backbone of the polycyclopropane framework with respect to the plane of the particular cyclopropane ring being described (analogous to two substituents on the ring). The application of these terms is illustrated in **Figure 3.6**, by structures (**98**) and (**98a**). The second pair of descriptive labels on the other hand, describes the relative stereochemistries of adjacent cyclopropanes with respect to the common carbon backbone of the polycyclopropane unit, which is considered in a fully extended form, as seen in **Figure 3.5**. The first descriptor, *syn*- refers to fragments on the same face of the skeletal framework, whereas the second, *anti*- refers to those on opposite faces. The application of this second pair of descriptors is also illustrated in **Figure 3.6**, by structures (**99**) and (**99a**). An example of the application of this simple nomenclature system in the efficient naming of a simple biscyclopropane is also shown in **Figure 3.6**, by structure (**100**).

3.2.2 Synthesis of Polycylopropanes

There is an extensive literature on the synthesis and subsequent reactions of biscyclopropane arrays, for example Buchert and Reissig[141] have reported the synthesis of highly substituted biscyclopropanes. In addition, Nijveldt and Vos[142] have carried out extensive X-ray studies upon the nature of biscyclopropane itself. Unfortunately, prior to the discovery of FR-900848 (**19**) in 1990, little attention was paid to the issues of stereochemistry in the synthesis of biscyclopropane arrays. Consequently this previous work will not be discussed in the following introduction.

As mentioned previously in Sections **3.2.1.1** and **3.2.1.2**, a number of successful total syntheses of the polycyclopropane containing natural products, FR-900848[39, 40] (**19**) and U-106305[42, 43] (**20**) have appeared in the literature over the past decade. As well as these very obvious reports, an increasing number of papers detailing the stereoselective synthesis of polycyclopropane units in general have also increased over the past five years in particular. By far the most active research group in this field at the moment is that of Barrett at Imperial College (London); in fact, of the thirty-seven citations returned during a recent current literature search,[143] nineteen, were from the group of Barrett.

A brief review of the current literature detailing the stereoselective preparation of polycyclopropanes may be found in the following sections. The review is conveniently categorised by the names of the three principle authors who carried out the work discussed; however, it is intended that this will only serve as a brief introduction to the strategies currently employed in the synthesis of enantiomerically pure polycyclopropanes. Consequently, it is not meant to be comprehensive in any way, and it should be stated, that the authors mentioned within the review are not the sole contributors to the scientific literature on the topic of polycyclopropane synthesis. Collectively, they have provided a major contribution to the literature in this field of study, and consequently they are often seen as frontier breakers within this area.

3.2.2.1 A. G. M. Barrett (Imperial College London)

Over the four-year period between 1994 and 1998, Barrett published a total of nineteen research papers detailing the successful development of a flexible, synthetic methodology that enabled the efficient construction of polycyclopropane units with tremendous control over the stereochemistry of each individual cyclopropane in turn.

His strategy employed the efficient application of a number of individual methods that enabled the controlled generation of new optical centres, particularly the Charette mediated asymmetric Simmons-Smith cyclopropanation of allylic alcohols,[107] and the application of homo-chiral acetal protecting groups.[91, 92] These methods have both been previously discussed in some detail in Sections **1.5.2.2.1** and **1.5.1.2** respectively. The subsequent application of these techniques in conjunction with his simple, alcohol oxidation – Wittig chain extension – Dibal® reduction – cyclopropanation, reaction cycle (as seen in **Figure 3.7**), has enabled Barrett to successfully complete the total syntheses of both of the aforementioned natural products, FR-900848[39] (**19**) and U-106305[42] (**20**).

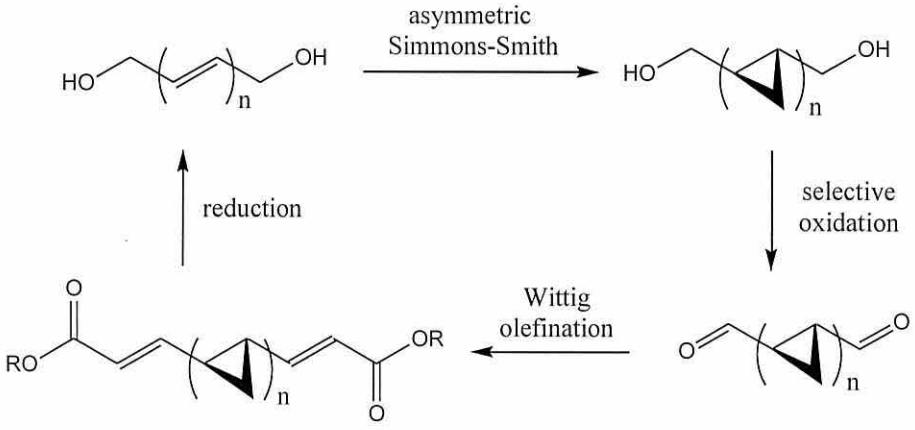


Figure 3.7

Barrett's stepwise methodology has also enabled the synthesis of similar polycyclopropane containing subunits containing up to seven contiguous cyclopropanes, each with defined stereochemistry. The synthesis of such compounds has enabled the further study of the possible conformations that similar chains may adopt in their bioactive forms; X-ray crystallography has indeed shown that large polycyclopropane arrays of this type generally adopt a helical "cork screw" type structure, an example of which, a precursor to the pentacyclopropane array of U-106305 (**20**), may be seen in **Figure 3.8**.[144]

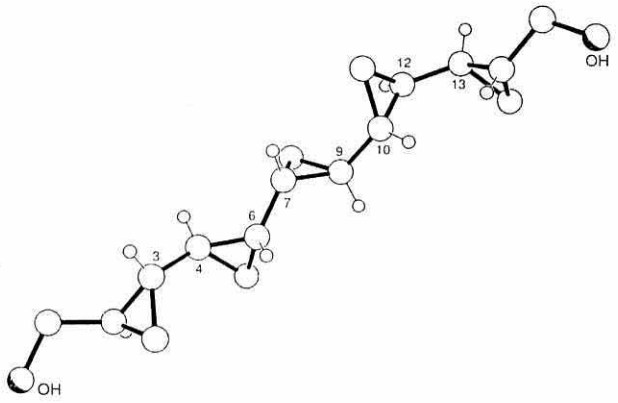
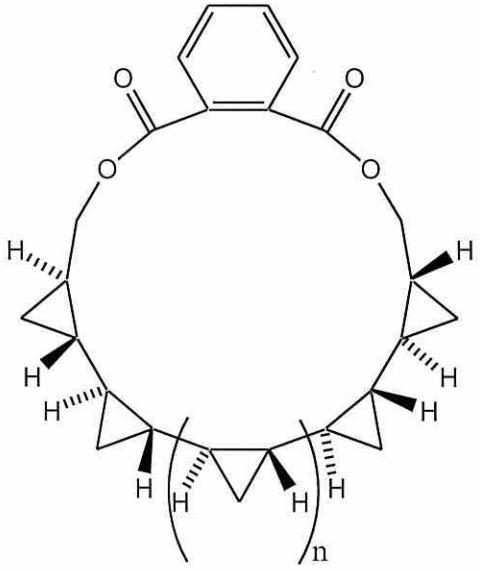


Figure 3.8

Furthermore, application of this synthetic methodology has led to a novel series of macrocyclic coronanes based upon *anti-trans-* related polycyclopropanes. Such compounds have been prepared by the intramolecular coupling of *anti-trans-* polycylopropane diols under high dilution conditions, hence avoiding competing intramolecular reactions. An example of the prototype materials already prepared by Barrett may be seen in **Figure 3.9**.



101 n = 1
102 n = 3

Figure 3.9

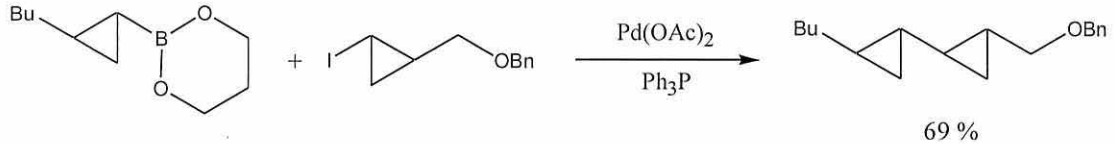
3.2.2.2 A. B. Charette (Univ. de Montréal)

The work of Charette, via his excellent boroxolane mediated asymmetric cyclopropanation (discussed in Section **1.5.2.2.1**), though not obvious when one considers a list of relevant publications, is probably one of most commonly applied

methodologies used in the asymmetric synthesis of cyclopropanes in general. This observation is also true in the synthesis of polycyclopropanes; indeed cyclopropanation techniques developed by Charette[107] were successfully employed by Barrett in his stepwise polycyclopropane synthesis (Section **3.2.2.1**).

In 1996, Charette reported the enantioselective total synthesis of U-106305 (**20**).[43] The methodology employed was quite similar to that of Barrett in his parallel, total synthesis of the same product. Charette employed a novel methodology in the synthesis of the terminal fragments of U-106305 (**20**), but the synthesis of the polycyclopropane unit was very similar to that employed by Barrett. Charette employed a slightly different olefination step, via a Wadsworth-Emmons reaction, but the remaining steps were essentially the same.

Early reports of an alterative synthetic methodology examined the application of unsymmetrical, Suzuki-type cross coupling reactions in the synthesis of biscyclopropanes.[145] The reaction was shown to proceed in moderate yield, typically between 20 and 60 %, but initial studies were carried out using racemic starting materials, and consequently no reference was made to the diastereoselectivity of the reaction. An example of the palladium catalysed Suzuki reaction proposed by Charette may be seen in **Figure 3.10**.



103 104 105

Figure 3.10

3.2.2.3 J. R. Falck (Univ. of Texas)

In 1996, soon after Barretts total synthesis of FR-900848 (**19**) (via the stepwise methodology highlighted in Section **3.2.2.1**) appeared in the primary literature, Falck reported an alternative, convergent synthesis of the polycyclopropane containing natural product.[40] The strategy employed, one of a reiterative dimerisation process, was considered to be a subtle variant of the previously described Horeau principle.[146] However, the starting point for the synthesis was again the application of an asymmetric cyclopropanation via the protocols established by Charette.[107] Unfortunately, the generation and subsequent purification of the initial, optically

active cyclopropane containing starting material was found to be somewhat inefficient, with the eventual requirement of a number of chromatographic (HPLC) steps to ensure the desired starting material purity. This obvious limitation, coupled with the need for product desymmetrisation after each dimerisation reaction consequently rendered this process less attractive than the alternative procedure developed by Barrett. The synthetic methodology employed by Falck in the synthesis of the polycyclopropane fragment of FR-900848 may be seen diagrammatically in **Figure 3.11**.

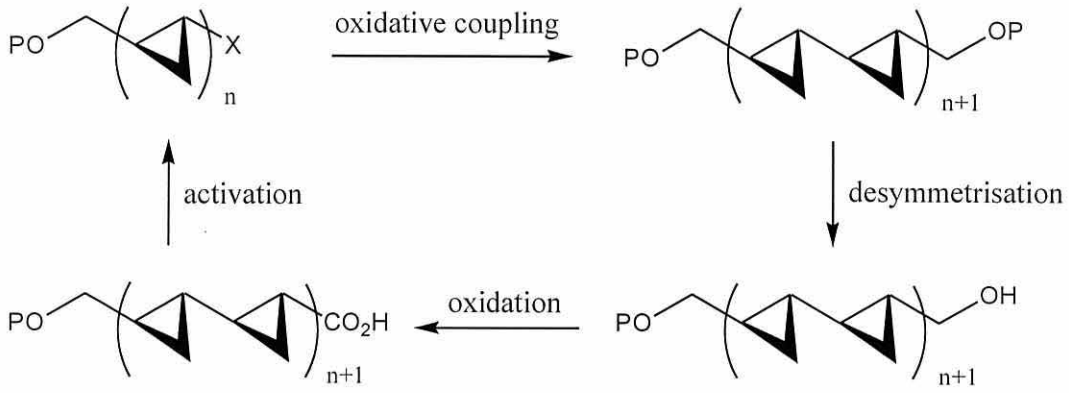


Figure 3.11

3.2.2.4 Summary

As mentioned previously in Sections **3.2.2.1**, **3.2.2.2** and **3.2.2.3** a considerable amount of work has been carried out recently on the asymmetric synthesis of polycyclopropanes. The efficient preparation of such subunits is commonly carried out by one of two general routes:

i) Via a sequential process involving a Wittig type chain homologation followed by reduction and finally asymmetric cyclopropanation (as by Barrett and Charette).

ii) Via a reiterative strategy involving the sequential dimerisation of smaller monomer units, thus creating a C_2 symmetric dimmer (as by Falck).

Although these developments are highly effective, these routes are often flawed by the presence of one or sometimes two difficult or inefficient steps. Indeed all of the strategies highlighted above in Sections **3.2.2.1**, **3.2.2.2** and **3.2.2.3**, required the desymmetrisation of a symmetrical polycyclopropane containing diol before being incorporated into the eventual product. This step was typically carried out via the selective protection of the symmetrical diol that was typically formed as the direct product from each of the highlighted polycyclopropane syntheses. Desymmetrisation

reactions of this type are inherently inefficient simply because, during such reactions, there is typically more than one product recovered (mono- and di-protected), as well as unreacted starting material. The distribution of the products recovered is very variable, and yields of the desired mono-protected (desymmetrised) product are typically not in excess of 55 %. The requirement of such a desymmetrisation step is generally seen as undesirable, as the poor recoveries typically returned from such reactions obviously lower the total efficiency of the overall process, hence lowering the absolute yields of the desired product.

3.3 The Diastereoselective Synthesis of 1,1′-Biscyclopropanes

As mentioned previously in Section **3.1**, the general aim of the work discussed in this Chapter was the application of simple, enantiomerically pure cyclopropane containing building blocks (the preparation of which was discussed in Chapter 2) in the diastereoselective synthesis of polycyclopropane subunits such as those highlighted throughout Section **3.2.2**. 1,1′-Biscyclopropanes have been identified as important intermediates in the preparation of larger polycyclopropane containing arrays such as those found in the natural products FR-900848 (**19**) and U-106305 (**20**).[147, 148] As highlighted in Section **3.2.2.4**, the synthesis of such compounds, is currently carried out by one of two general synthetic routes, via a stepwise reaction cycle as illustrated by Barrett (Section **3.2.2.1**), or via an alternative, more convergent, reiterative dimerisation strategy such as that employed by Falck (Section **3.2.2.3**). It was consequently decided that the viability of each of these synthetic routes should be examined, with the general aim of developing a reliable and flexible route that would enable the efficient stereocontrolled synthesis of 1,1′-biscyclopropanes (and indeed larger polycyclopropane containing arrays) that may be used in the synthesis of FR-900848 (**19**), U-106305 (**20**) and other analogous materials. A detailed discussion of the studies conducted during the development of these synthetic routes is outlined in the following two sections.

3.3.1 Strategy 1: The Application of a Reiterative Dimerisation Strategy

3.3.1.1 Introduction

As mentioned above in Section **3.2.2.3**, soon after Barrett's first total synthesis of FR-900848 in 1994, Falck published an alternative, more convergent synthesis of the same target molecule. His strategy employed the novel principle of enantiomeric amplification commonly known as the Horeau Gambit; this methodology employed the reiterative dimerisation of smaller, enantiomerically enriched cyclopropane containing chirons (with ee's typically around 88 – 90 %), thus facilitating enantiomeric enrichment via the simple chromatographic separation of unwanted diastereomeric by-products. A generalised scheme of the strategy employed by Falck in the construction of the quatercyclopropane array of FR-900848 (**95**, when R =

OTBDPS), may be seen diagrammatically in **Figure 3.11**. It can be seen from this diagram, that the starting material employed by Falck in the synthesis of (**95**) was a derivatised, optically active *trans*-substituted cyclopropanemethanol (**106**), the second substituent on the cyclopropane ring being a reactive organometallic (tri-*n*-butyltin) group.

106

Figure 3.12

Unfortunately, a complicated, chromatographic separation employing preparative HPLC was required during the synthesis of this relatively trivial starting material. As a result, this step decreased the convenience of this precursor (also increasing the cost) for application on a larger scale. With this point in mind, it was suggested that the chiral building block 2,2-dibromocyclopropanecarboxylic acid (**72**) could possibly be used as an alternative, large scale precursor to the structurally analogous protected *trans*-bromocyclopropanemethanol (**107**); it was perceived that this material could be employed as a direct synthetic alternative to the stannyl compound (**106**) as used by Falck.

107

Figure 3.13

Furthermore, the successful dimerisation of (**107**) would lead to the preparation of an identical C_2 symmetric biscyclopropane as that employed by Falck in the total synthesis of FR-900848, the successful preparation of which would constitute an alternative, formal synthesis of the aforementioned natural product. A diagrammatic representation of the proposed synthesis of (**107**) and indeed the C_2 symmetric biscyclopropane (**110**) may be seen overleaf in **Figure 3.14**.

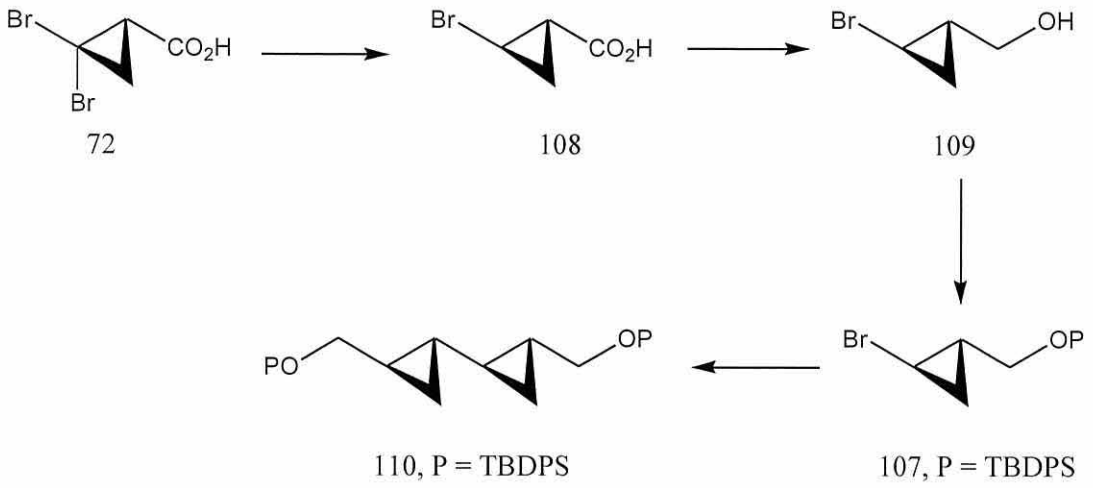


Figure 3.14

A detailed discussion of the individual steps carried out during the attempted synthesis of the C_2 symmetric biscyclopropane (**110**) is outlined in the following sections.

3.3.1.2 The Selective Reduction of 2,2-Dibromocyclopropanecarboxylic acid (72)[116]

If one considers the schematic diagram seen in **Figure 3.14** above, it is quite obvious that a key problem with the initial step of the proposed synthesis is the diastereoselective reduction of the *gem*-dibromocyclopropane starting material (**72**), thus leading to the generation of the desired *trans*-monobromoacid (**108**). In theory, there is an equal probability that the formation of both the desired *trans*- disubstituted product (**108**), and the competing, undesired *cis*- disubstituted product (**108a**) could occur (**Figure 3.15**). Thus the formation of the undesirable alternative product (**108a**) could effectively reduce the recovered yield of the required product (**108**) and hence lower the efficiency of the desired reaction.

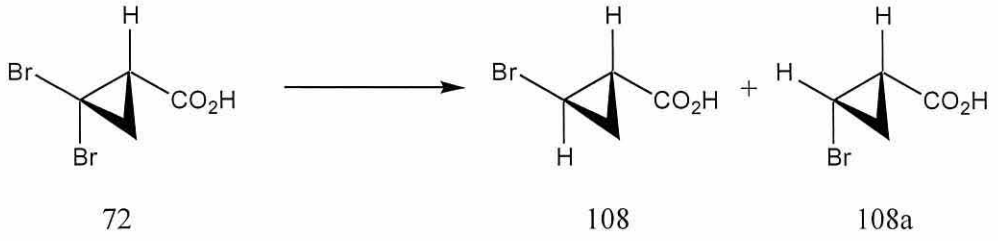
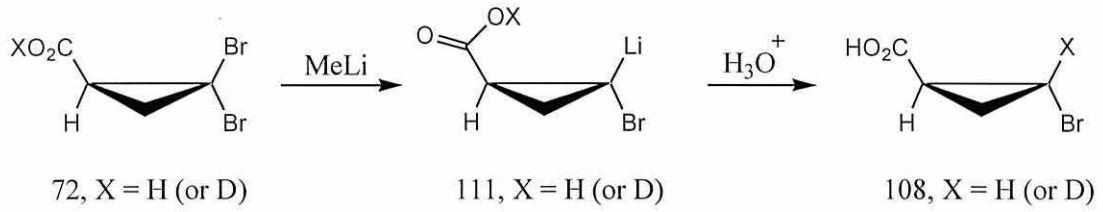


Figure 3.15

The partial (and indeed complete) reduction of gem-dihalocyclopropanes is a very popular field in the area of small ring chemistry, and consequently, reactions of this type often find major application throughout the area of organic synthesis. As a result

of the apparent popularity of this reaction, the selection of synthetic reagents available to successfully carry out reductions of this type is very diverse indeed. Suitable reagent systems include Bu_3SnH, $NaBH_4$, Mg, Zn/AcOH, $LiAlH_4$, RedAl® and a variety of alkyl lithium reagents;[149] notable attention has also been paid to this reaction in the field of synthetic electroorganic chemistry.[150]

Fortunately, the desired diastereoselective reduction of racemic *gem*-dibromocyclopropanecarboxylic acids, including the chosen substrate (**72**) (in its racemic form), are known to proceed in near quantitative yield by the low temperature reaction of the substrate with a slight excess (between 1.2 and 1.5 mol. equiv) of methyl lithium solution.[151] The reaction proceeds cleanly with only one product observed, the desired *trans*-monobromoacid. It is thought that reactions of this type generally proceed via an initial lithium-bromine exchange resulting in the formation of simple lithio-bromocyclopropane derivatives such as (**111**),[152] which may be seen in **Figure 3.16**.



72, X = H (or D) 111, X = H (or D) 108, X = H (or D)

Figure 3.16

It is postulated that intramolecular stabilisation of the lithio-bromocyclopropane (**111**) by the carboxylic acid functionality prevents the expected elimination of lithium bromide and consequently eliminates the formation of allene products.[153] Subsequent quenching of the lithio-bromocyclopropane via the intramolecular transfer of the acidic proton (or deuteron) prior to acid hydrolysis leads to the stereoselective formation of the desired *trans*-monobromoacid (**108**) in high yield.[154]

A brief discussion of the mono-reduction of the classically resolved, optically active substrates (**72-*R***) and (**72-*S***) using methyllithium at 0 °C is outlined in the following paragraphs. This reaction was carried out employing both enantiomers of the starting material, (**72-*R***) and (**72-*S***), but for simplicity, the discussion focuses upon the reaction of only one of these, (**72-*S***).

The desired reaction was carried out using standard pre-dried, laboratory scale glassware under a blanket of a suitable inert gas, i.e. dry nitrogen or argon. The flask was carefully charged with the substrate, (**72-*S***) as a 10 % solution in freshly distilled

dry diethyl ether, the solution was then cooled to 0 °C in an ice bath, whilst being magnetically stirred using a suitable, oval shaped (heavy) flea. When the internal temperature of the reaction vessel had equilibrated at the desired temperature (0 °C), a 1.5 M ethereal solution of methyllithium was carefully added whilst maintaining the low internal reaction temperature. Upon addition, the colourless solution turned golden brown; in general this colour change could often be observed as an "end point" as the colour was only long lived when the required amount of reagent had been delivered. The reaction mixture was subsequently allowed to warm to room temperature slowly, by allowing the ice bath temperature to rise naturally.

Efficient monitoring of the reaction was carried out by GLC, by withdrawing small samples from the vessel at given times and subjecting the sample to a small-scale quench followed by analysis. In general, the reaction was found to have reached completion after a period of between 60 and 90 minutes after the addition of 1.5 mol. equiv of methyllithium solution. When complete, the reaction mixture was subjected to a mild acidic work-up followed by extraction into ethyl acetate. The crude product, was duly recovered as a fragrant golden brown oil which yielded pure (1*S*,2*R*)-2-bromocyclopropanecarboxylic acid (**108-*S,R***) as a colourless oil in around 90 % yield after treatment with decolourising charcoal.

Analysis of the ^{1}H NMR spectrum of the product indeed confirmed that only one product had been formed during the reaction. This was evident in the appearance of only a single multiplet (ddd) signal corresponding to the proton geminal to the remaining bromine atom (H_1), appearing at 3.29 ppm; an image of this signal (generated using experimentally measured data) may be seen in **Figure 3.17**.

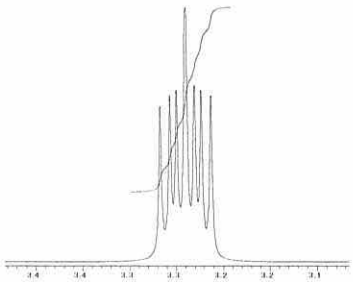
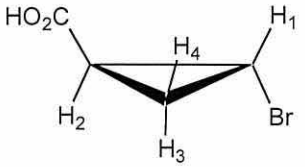


Figure 3.17

Further consideration of the coupling constants obtained from this signal in the ^{1}H NMR spectrum of the product confirmed the relative stereochemistry of the two remaining substituents (bromine and carboxylic acid) of the cyclopropane ring.

Indeed, the presence of one large *cis*- coupling constant (7.9 Hz) and two smaller *trans*- coupling constants (5.3 and 3.1 Hz) confirmed that the product in fact exhibited the desired *trans*- geometry.



$J(H_1 - H_2)$ 3.1 Hz
$J(H_1 - H_3)$ 5.3 Hz
$J(H_1 - H_4)$ 7.9 Hz

108-*S,R*

Figure 3.18

The remaining three cyclopropyl protons (H_2, H_3 and H_4) each gave rise to very similar signals, each of which being a discrete multiplet (ddd), with the signal corresponding to H_2 appearing at 2.06 ppm and the geminal protons, H_3 and H_4, appearing at 1.50 and 1.69 ppm respectively. The position of the broad signal that corresponded to the acidic proton was found to be concentration dependent, but typically appeared at around 10.4 ppm.

The ^{13}C NMR spectrum of the product again confirmed the selectivity of the reaction, when, as expected, only four signals were observed.

Identification of the expected molecular ion (by electron impact mass spectrometry) exhibiting the predicted isotopic pattern commonly observed when only one bromine atom is present, hence confirming that the desired reduction had indeed been successful. Examination of the product (**108-*S,R***) by polarimetry (as a solution in chloroform, c = 1.03) revealed that it indeed rotated the plane of polarised light in a counter clockwise manner, the observed specific rotation (α_D^{26}) being -154.1 °. By comparison, examination of the product (**108-*R,S***) obtained from the same reaction using the enantiomeric starting material (**72-*R***) (as a solution in chloroform, c = 1.15) revealed that the observed specific rotation (α_D^{24}) in this case was +153.9 °.

3.3.1.3 Preparation of the Protected *trans*-2-bromo-1-hydroxymethyl cyclopropane (107)

Unfortunately, the direct reduction of carboxylic acids (with simple metal hydride reagents) thus enabling the generation of alcohols and aldehydes is often found to be inefficient and therefore typically not appropriate for application in multi-step syntheses. As a result, activation of the carboxyl functionality is often required to enable maximisation of the yield and consequently the efficiency of this reaction.

Activation is typically carried out by one of two commonly employed methods, either by esterification of the acidic functionality, or by conversion of the acid into the related acid halide derivative. After careful consideration of each of these options, it was decided that esterification would be the initial line of study, primarily because the techniques employed were simpler and the intermediate product was considerably more stable to hydrolysis.

108 112, X = OMe 109

Figure 3.19

Esterification of the *trans*-monobromoacid (**108-*S,R***) was routinely carried out via one of two procedures, depending upon the scale of the reaction. On smaller scales (less than 500 mg) the reaction was carried out very quickly and efficiently in quantitative yields by the direct reaction of the acid substrate (**108-*S,R***) with a freshly prepared ethereal solution of diazomethane.[155] Larger scale reactions on the other hand were carried out by simply refluxing the acid substrate (**108-*S,R***) with a suitable alcohol (methanol) in the presence of an acid catalyst. Reactions of this type were generally carried out overnight, and the desired product was typically recovered in yields of around 90 – 95 %.

The products recovered from each of these reactions were both fully characterised by ^{1}H NMR, ^{13}C NMR, IR, mass spectrometry and polarimetry, as expected they were both found to be identical. IR spectroscopy of the product showed that the strong band corresponding to the (O-H) stretch in the starting material had in fact disappeared; furthermore a shift was noted in the (C=O) stretch band from 1707 cm^{-1} in the starting material to 1731 cm^{-1} in the product. Both of these observations are consistent with the derivatisation of a carboxylic acid as an ester.

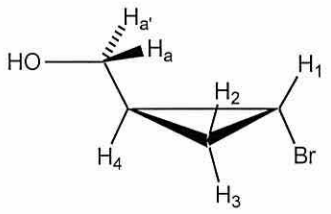
In general, the pattern of the signals observed in the ^{1}H NMR spectrum of the *trans*-monobromoester product (**112-*S,R***) was very similar to that observed in the corresponding spectrum of the starting material (**108-*S,R***). The presence of a new, low field signal; a singlet integrating to three protons appearing at 3.70 ppm subsequently confirmed the presence of the desired methyl ester. This observation was duly confirmed by the presence of a similar new signal in the ^{13}C NMR at 52.2 ppm. Furthermore, the signal appeared as a positive resonance in the corresponding

DEPT spectrum, therefore it could be assigned as either a CH or a CH_3 group, the relative size of the signal indicated that it was in fact a methyl group.

Polarimetry studies revealed that the product (**112-*S,R***) rotated the plane of polarised light in a counter clockwise direction, indeed the observed specific rotation (α_D^{22}) was measured at –107.5 ° (as a solution in chloroform, c = 1.15). Similarly its enantiomer (**112-*R,S***) exhibited an observed specific rotation (α_D^{23}) of +108.2 °.

Subsequent treatment of the activated ester (**112-*S,R***) with two molar equivalents of DIBAL-H solution under standard low temperature conditions (-78 °C) afforded the desired *trans*-2-bromo-1-hydroxymethylcyclopropane (**109-*S,R***) in approximately 85 % yield (over two steps). IR spectroscopy confirmed that the complete reduction of the starting material had indeed been successful. The appearance of a broad (O-H) stretching band at 3384 cm^{-1} confirmed the presence of the desired alcohol functionality; the disappearance of the (C=O) stretching band (present within the starting material) also confirmed this observation.

The ^1H NMR spectrum of the product was subsequently found to be remarkably complex for a relatively simple molecule; the following discussion of this spectrum is made with reference to the assignations made in **Figure 3.20**.



109

Figure 3.20

As expected, the absolute position of the broad singlet that corresponded to the alcohol proton was found to be extremely concentration dependent, although it was commonly observed between 1.6 - 2.0 ppm. The assignation of this signal was confirmed when the sample was shaken with a few drops of D_2O, after which the signal disappeared completely. The protons of the methylene group of the hydroxymethyl substituent (H_a and $H_{a'}$) were observed as a pair of heavily "tented" double doublets, thus forming an excellent example of the classical ABX pattern (centred about 3.55 ppm). Unfortunately, it was not possible to distinguish between H_a and $H_{a'}$. In general, the pattern of the signals observed in the ^1H NMR spectrum of the product (**109-*S,R***) was very similar to that observed in the corresponding

precursors (**108-*S,R***) and (**112-*S,R***). Indeed the signals corresponding to the single proton geminal to the bromine substituent (H_1) and the geminal protons (H_2 and H_3) were very similar to those seen in the immediate precursors and consequently will not be discussed any further. The remaining cyclopropyl signal on the other hand, corresponding to the single proton adjacent to the hydroxymethyl substituent (H_4) appears as a very complicated ddddd, coupling to each of the other protons (H_a, $H_{a'}$, H_1, H_2 and H_3) in turn. A reproduction of this signal (generated using experimentally measured data) may be seen in **Figure 3.21**.

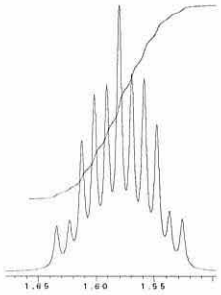


Figure 3.21

The observed optical rotations exhibited by the product (**109-*S,R***) and its enantiomer (**109-*R,S***) were measured and indeed found to be of equal magnitude, but in opposing directions, the specific rotations being -42.4 ° and +41.7 ° respectively.

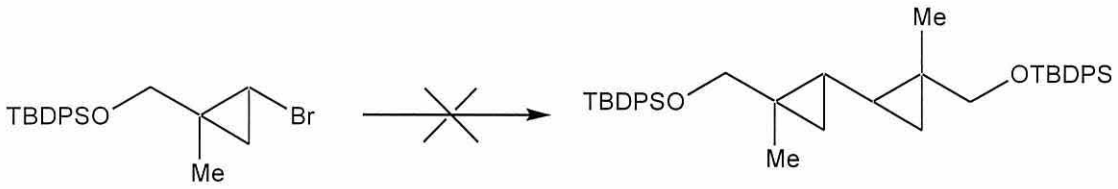
Reaction of the chiral alcohol (**109-*S,R***) with TBDPS-Cl and imidazole in dry distilled DMF afforded the target synthon, protected alcohol (**107-*S,R***) in approximately 80 % yield. Formation of the desired protected alcohol was confirmed by IR and NMR spectroscopy; as expected, the ^{1}H NMR spectrum of the product was very similar to that of its immediate precursor (**109-*S,R***). The only difference was the appearance of new signals corresponding to the silyl protecting group, i.e. the aromatic signals, appearing between 7.3 and 7.8 ppm, and the large singlet of the *tert*-butyl group, appearing at 1.02 ppm.

In brief summary, the desired target molecule (**107-*S,R***) was readily prepared in four simple synthetic steps from the readily available pre-resolved precursor (**72-*S***), the overall yield of the process being 67 %. Similarly the enantiomeric product, (**107-*R,S***) was prepared via an identical route from (**72-*R***) in 56 % yield. The successful dimerisation of the first product (**107-*S,R***), would result in the generation of Falck's intermediate biscyclopropane (**110**) and hence complete a formal synthesis of the

natural product FR-900848 (**19**). The attempted dimerisation of this substrate is discussed in the following section.

3.3.1.4 Model Dimerisation Reactions

Preliminary studies carried out on the oxidative dimerisation of racemic substrates similar to (**107-*S,R***) (not discussed in this thesis) showed that the dimerisation process was inherently inefficient. Indeed, the attempted dimerisation of the structural analogue (**113**) resulted in none of the desired dimmer (**114**) being recovered at all; in fact, only the fully reduced hydrocarbon was isolated.

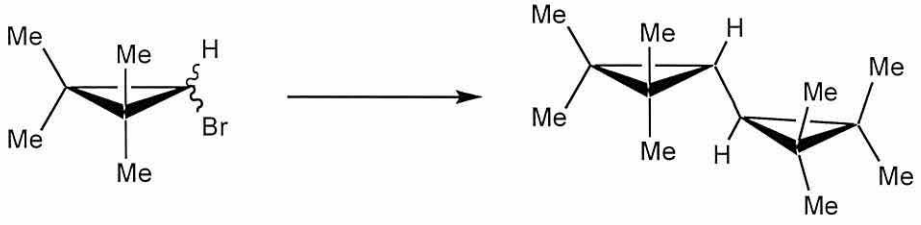


113 114

Figure 3.22

In the drive to successfully carry out the dimerisation of the chiral protected alcohol (**107-*S,R***), it was decided that this important oxidative dimerisation step should first be optimised using a simple (easily prepared) model compound.

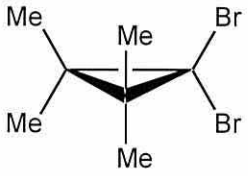
Unfortunately, the choice of a suitable model compound was not as simple as initially thought; this was because the generation of a new carbon – carbon bond could possibly lead to the production of a number of diastereomeric products, hence complicating any quantitative analysis by NMR. This problem was alleviated by the careful choice of the symmetric monobromide starting material, 3-bromo-1,1,2,2-tetramethylcyclopropane (**115**), the dimerisation of which would lead to the formation of the highly symmetric biscyclopropane, 2,2,3,3,2',2',3',3'-octamethylbiscyclo propane (**116**), as the only product.



115 116

Figure 3.23

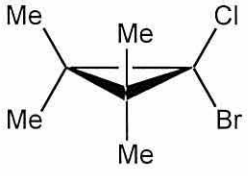
The dibromide precursor to (**115**), 1,1-dibromo-2,2,3,3-tetramethylcyclopropane (**117**) was readily prepared in 63 % yield by reaction of 2,3-dimethylbutene with dibromocarbene (generated by the reaction of potassium *t*-butoxide with bromoform in pentane solution). Compound (**117**) was isolated as a pleasantly fragrant, white highly crystalline solid, the ^{1}H NMR of which was very simple indeed and was composed of just one singlet appearing at 1.29 ppm. This signal corresponded to the four equivalent methyl groups.



117

Figure 3.24

The application of ultrasonic radiation during an attempted alternative preparation of (**117**) gave rise to an alternative, unexpected product, 1-bromo-1-chloro-2,2,3,3-tetramethylcyclopropane (**118**). Indeed, the ultrasonic irradiation of a mixture of 2,3-dimethylbutene, bromoform and dichloromethane in the presence of finely powdered sodium hydroxide, gave rise to the isolation of (**118**) as a white crystalline solid in approximately 40 % yield. The mechanism of the process is not known, but it has been postulated that a halogen exchange reaction occurs between the substrate (bromoform) and the solvent (dichloromethane) prior to the cyclopropanation step.[156] This reaction is very interesting indeed from a synthetic point of view, as the efficient preparation of *gem*-bromochlorocyclopropanes is not easy using traditional methods such as the addition of carbenes derived from simple polyhalomethanes. The equivalent reaction employing dibromochloromethane is particularly inefficient as the product obtained is typically contaminated with both *gem*-dibromo- and *gem*-dichlorocyclopropanes.[157]



118

Figure 3.25

Reduction of (**117**) with ethylmagnesium bromide and titanium (IV) isopropoxide[158] at low temperature (-78 °C) furnished the required monobromide (**115**) in 83 % yield. Reduction of the *gem*-dibromide group in this way consequently reduced the level of symmetry present within the product (**115**). As a direct result, two discrete methyl singlets appearing at 1.14 and 1.10 ppm were observed in the ^{1}H NMR spectrum of the product in addition to the lower field (2.74 ppm) singlet associated with the single cyclopropyl proton situated geminal to the residual bromide substituent.

The desired oxidative dimerisation reaction, although formally a "one-pot" process, may be conveniently considered as a three-stage reaction composed of an initial lithiation step, followed by a transmetallation reaction (cupration) and finally the oxidative dimerisation of the generated organocuprate species. A schematic representation of this type of reaction may be seen in **Figure 3.26**.

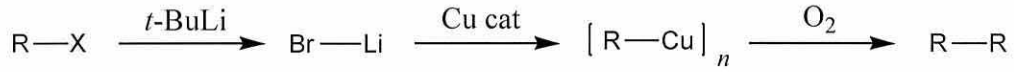


Figure 3.26

Unfortunately, early attempts at the oxidative dimerisation of (**115**) via Falcks original method[40] employing his recommended homogeneous copper catalyst, tetrakis[iodo(tri-n-butylphosphine)copper(I)][159] were shown to be unsuccessful, with only the fully reduced hydrocarbon being recovered after each attempt. This observation, though not desired, at least indicated that the first step, the lithiation of the substrate was being successfully achieved. This implied that any problem with the reaction could possibly stem from either an inefficient transmetallation of the lithiated substrate, or indeed, the oxidative coupling reaction itself.

Cuprate mediated coupling reactions of this type are very common in the field of organic synthesis,[160] indeed a number of very similar reactions have been carried out independently by the groups of Walborsky[161] and Michl.[162] Both of these groups have reported considerable success whilst employing copper (I) iodide in the preparation of intermediate organocuprate derivatives. Unfortunately, unlike tetrakis[iodo(tri-n-butylphosphine)copper(I)], copper (I) iodide is not soluble in typical organic reaction solvents, consequently the transmetallation step occurs more slowly and at a slightly higher temperature (-30 °C as opposed to –78 °C). Interestingly when anhydrous copper (I) iodide was employed in the attempted dimerisation of (**115**), an immediate improvement was observed. Careful control of the reaction temperature throughout

the reaction enabled the optimisation of this reaction and eventually led to the preparation of the desired dimer (**116**) in approximately 70 % yield.

Analysis of the product (**116**) by both ^{1}H and ^{13}C NMR gave rise to some rather unexpected observations. Prior to the acquisition of these spectra, it was assumed that the high degree of symmetry present within the target molecule would somewhat simplify the spectra. It was initially assumed that the product of the dimerisation would contain a C_2 axis of symmetry; therefore each of the cyclopropane moieties would be identical thus limiting the number of signals. Furthermore, it was thought that additional symmetry within each cyclopropane would further reduce the number of signals observed. Consequently, it was initially expected that a total of three signals would be observed in the ^{1}H NMR spectrum, a singlet integrating to 1H and two singlets each integrating to 6H. When measured, the ^{1}H NMR spectrum of (**116**) was found to contain a total of five signals, a singlet integrating to 1H, and four larger singlets each integrating to 3H. This inferred that the level of symmetry present within the product was not as high as first expected. This observation was echoed in the ^{13}C NMR spectrum, when a total of seven signals were observed (initially expected four signals).

With these observations in mind, a simple geometry optimisation calculation was conducted using the molecular modelling package Hyperchem 5.[163] The aim of this exercise was to establish the relative symmetries of the individual methyl substituents of each cyclopropane ring and consequently re-evaluate the number of signals that would be expected in the observed NMR spectra. The semi-empirical SCF calculation carried out using the AM1 method was executed on a standard personal computer and gave rise to the optimised geometry that may be seen in **Figure 3.27**.

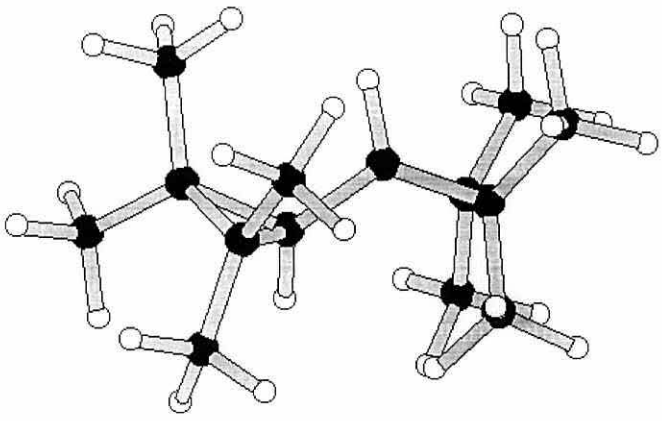


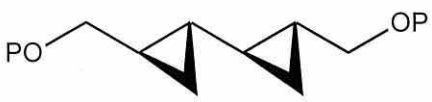
Figure 3.27

It can be clearly seen from the image shown in **Figure 3.27** that the product does indeed possess C_2 symmetry however, the individual cyclopropane rings of the biscyclopropane product (**116**) are slightly twisted away from each other, i.e. they are not parallel. The slight inclination between the planes of each individual cyclopropane reduces the level of symmetry within each individual ring and consequently renders each individual methyl substituent discrete. In conclusion it is evident that each individual methyl group is in a chemically (and magnetically) unique environment and will therefore give rise to a discrete signals in both the ^{1}H and ^{13}C NMR spectra.

In brief summary, the study of this model compound enabled the development and optimisation of the desired oxidative coupling reaction. This reaction could now be used in confidence in the preparation of the desired biscyclopropane (**110**) by the dimerisation of the chiral protected alcohol substrate (**107-*S,R***); this reaction is discussed in the following section.

3.3.1.5 The Preparation of Biscyclopropane (110)

As a result of the studies carried out on the dimerisation of a number of model compounds[164] (including (**115**), as previously discussed in Section **3.3.1.4)**, the dimerisation of the optically active protected alcohol (**107-*S,R***) proceeded quite smoothly and afforded the desired dimeric product in a respectable 41 % yield. Analysis of the product, by NMR (^{1}H and ^{13}C) coupled with the identification of the molecular ion by mass spectrometry confirmed the structure of the product to be identical to that of Falck's key intermediate (**110**) in the synthesis of FR-900848. The observed optical rotation exhibited by the product ($\alpha_D^{21.5}$ = - 39.8 °, c 1.39, EtOH) was also comparable to that reported by Falck (α_D^{23} = - 41.4 °, c 0.23, EtOH), and consequently serves as additional confirming evidence supporting the formation of the intermediate biscyclopropane (**110**).



110, P = TBDPS

Figure 3.28

3.3.1.6 Conclusion

In conclusion, the studies carried out above in Section **3.3.1** have detailed the successful application of the simple, enantiomerically pure cyclopropane containing building block (**72**) (the preparation of which was discussed in Chapter 2) in the diastereoselective synthesis of the biscyclopropane (**110**). In completing the synthesis of this intermediate compound, we have been successful in completing an alternative formal synthesis of the natural product FR-900848 (**19**).

It is our general opinion, that the application of readily available chiral building blocks materials such as (**72**) is quite favourable indeed, as it avoids the application of costly purification process such as preparative HPLC as used by Falck in the preparation of his alternative starting material (**106**).

Although the formal synthesis was successful in the application of an alternative, more readily available starting material, it should be stressed that this process is still somewhat inefficient. Indeed the oxidative dimerisation step in particular has been shown to be problematic and in the case of this synthesis, proceeds with a maximum yield of only 41 % (although yields of up to 70 % have been obtained with non-oxygenated model compounds). Furthermore, the next step of the synthesis (if it was indeed carried on to the final product, FR-900848) involves the desymmetrisation of the C_2 symmetric protected diol (**110**). As mentioned previously in Section **3.2.2.4**, reactions of this type are inherently inefficient and are typically carried out under conditions of high dilution. Ideally, the avoidance of such problematic reactions would render any alternative synthetic routes much more favourable. The application of a stepwise reaction cycle, such as that advocated by Barrett *et al.* would subsequently avoid the application of each of these problematic reactions; indeed a variation of this reaction system employing the readily available optically active starting materials (**109-*S,R***) and (**109-*R,S***) is discussed in the following section.

3.3.2 Strategy 2: The Application of a Stepwise Reaction Cycle

3.3.2.1 Introduction

The highly successful, stepwise Wittig - reduction - Simmons Smith type reaction cycle, pioneered by the group of Barrett,[42] is commonly employed in the stereocontrolled synthesis of 1,1′-biscyclopropanes and many larger polycyclopropane containing arrays. This alternative strategy has received much attention and has indeed benefited from a wide range of modifications, an example being, the application of classical phosphorane ylides or Wadsworth – Emmons type phosphonate esters during the chain homologation step; consequently, a variety of improved variants of this stepwise reaction cycle have been published.[165, 166]

As mentioned briefly in Section **3.2.1.5**, polycyclopropane arrays are generally constructed about an ordered carbon backbone composed of a contiguous array of optically active centres. Indeed, simple unsymmetrical 1,1′-biscyclopropanes contain four such contiguous chiral centres; as a result, there are 2^4 (16) possible diastereomeric products available. Fortunately, the relative stereochemistries observed within the fatty acid side chains of the natural products FR-900848 (**19**) and U-106305 (**20**) are common in that all the cyclopropane rings present are substituted with both individual substituents orientated *trans*- to one another. Previous studies have shown that similar polycyclopropane arrays bearing *cis*- substituted cyclopropanes do not share the same levels of bioactivity as those with *trans*- substitution.[148] As a result, it was decided that only 1,1′-biscyclopropanes exhibiting a *trans*, *trans*- type geometry would be prepared; the resulting four target molecules, two pairs of enantiomers, may be seen in **Figure 3.29**.

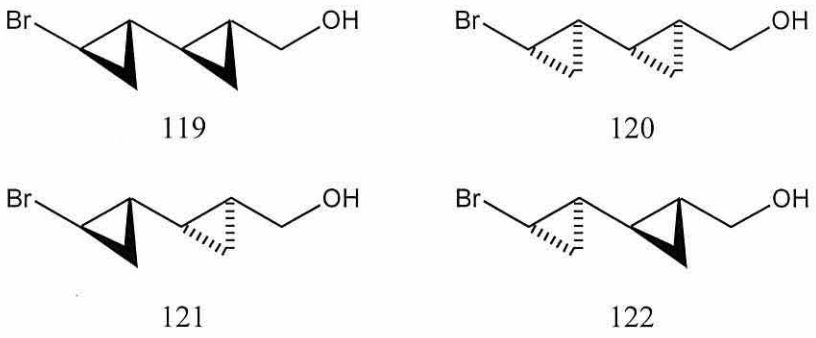


Figure 3.29

The readily available *trans*-2-bromo-1-hydroxymethylcyclopropanes (**109-*S,R***) and (**109-*R,S***) (the preparation of which was discussed in Section **3.3.1.3**) may be considered as perfect starting materials for application in such reaction cycles as the fixed stereochemistry inherent within these building blocks is an ideal starting point in the synthesis of *trans*, *trans*- type polycyclopropanes including the four target molecules highlighted in **Figure 3.29**. A schematic representation of the proposed reaction scheme may be seen in **Figure 3.30**.

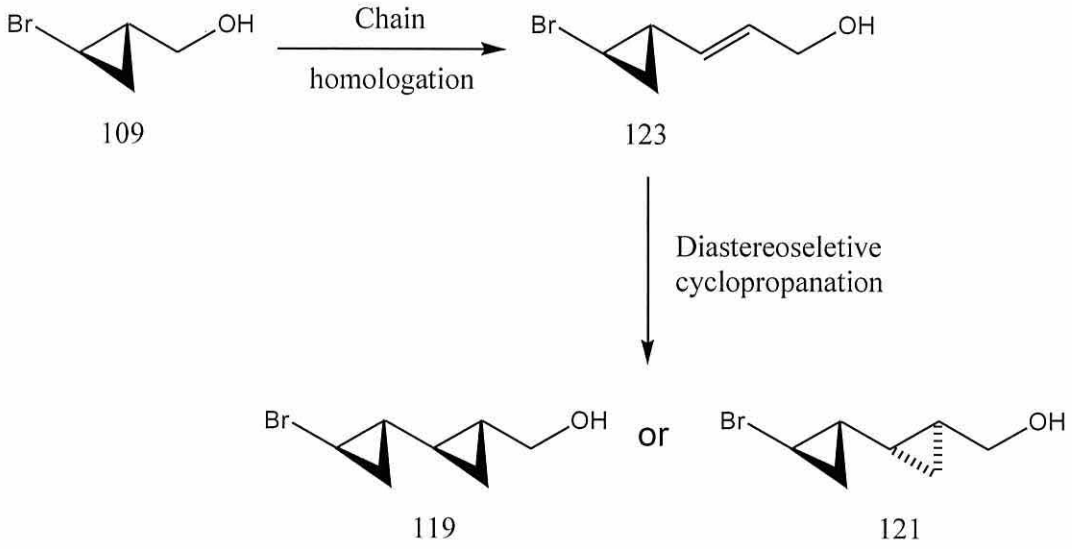


Figure 3.30

As highlighted above in **Figure 3.30**, this proposed synthetic route may be conveniently broken down into two specific areas of study: firstly, the preparation of suitable allylic alcohols, and secondly, the asymmetric cyclopropanation of these substrates leading to the generation of the desired target molecules. Each of these specific areas is discussed in greater detail in the following Sections.

3.3.2.2 Generation of a Suitable Allylic Alcohol Via a Wittig Type Chain Homologation

As mentioned in Section **3.3.2.1**, the readily available *trans*-2-bromo-1-hydroxymethylcyclopropanes (**109-*S,R***) and (**109-*R,S***) may be considered as a perfect starting materials for application in the synthesis of a variety of simple *trans, trans*-substituted biscyclopropanes. Elaboration of these simple starting materials via selective oxidation and Wittig type chemistry followed by hydride mediated reduction of the intermediate olefinic ester gave rise to suitable allylic alcohol substrates that are ideal candidates for asymmetric cyclopropanation under boroxolane mediated

conditions. The general strategy employed may be seen diagrammatically in **Figure 3.31**.

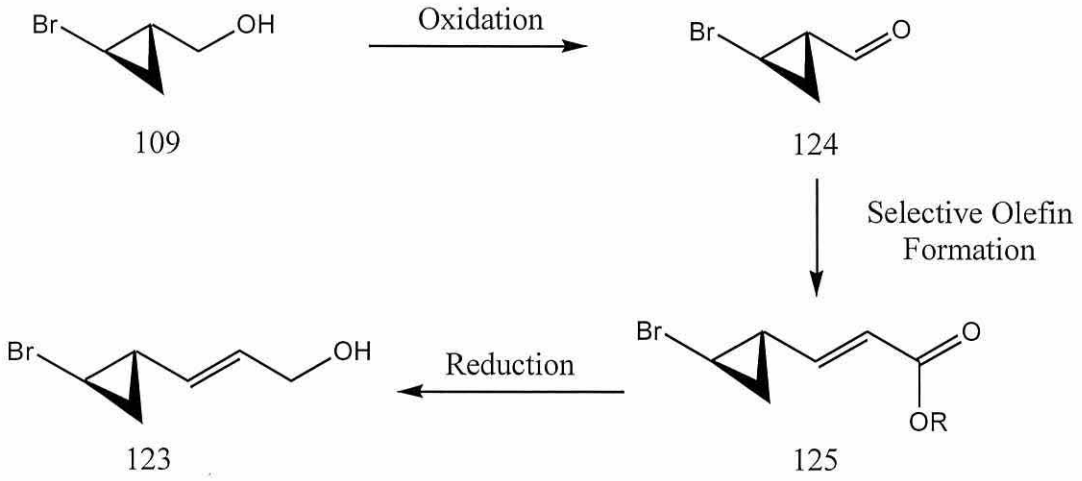


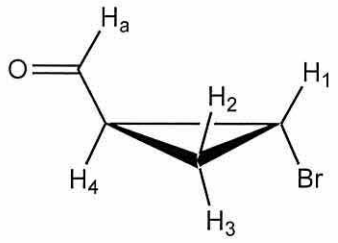
Figure 3.31

It should be noted, that the synthetic transformations highlighted above in **Figure 3.31** were indeed carried out employing both enantiomers of the optically active starting material, (**109-*S,R***) and (**109-*R,S***). These parallel reaction series enabled the successful preparation of a pair of enantiomeric *trans*-allylic alcohols (**123-*S,R***) and (**123-*R,S***), consequently enabling the generation of all four target molecules (**119 – 122**). For simplicity, this discussion focuses upon only one of these parallel reaction series, the preparation of (**123-*S,R***).

3.3.2.2.1 The Selective Oxidation of (109)

One of the most commonly employed and indeed challenging reactions in organic synthesis is the selective oxidation of primary alcohols enabling the facile preparation of aldehydes. Unfortunately, it is quite common for the desired product to become over-oxidised, consequently leading to the generation of unwanted carboxylic acids. The selective (room temperature) oxidation of (**109-*S,R***) was successfully carried out in dichloromethane solution by the action of 2 mol. equiv. of pyridinium chlorochromate (PCC) supported on an excess of diatomaceous earth (celite). The resulting solution was stirred vigorously for 90 minutes before being filtered through a sintered glass funnel, thus facilitating the efficient separation of the product (**124-*S,R***) from the heavy tarry by-products formed during the reaction. Careful removal of the reaction solvent using a suitably trapped rotary evaporator enabled the efficient isolation of the volatile product in approximately 75 % yield as a fragrant, tan coloured oil. The aldehyde product was used immediately without further

purification, as it was suggested that the stability of (**124-*S,R***) towards epimerisation of the carbon adjacent to the aldehyde functionality (H_4) would be quite low.



124

Figure 3.32

The IR spectrum of the isolated product (**124-*S,R***), exhibited a very strong (C=O) stretch at 1713 cm^{-1}, consistent with that of the desired aldehyde functionality. The fact that no (O-H) stretch was observed in this spectrum was quite satisfying indeed, as this inferred two things: firstly that the reaction had reached completion and consequently no alcohol remained, and secondly that the product had not been over-oxidised and that there was no carboxylic acid present. These observations were later confirmed by the application of ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of (**124-*S,R***) as expected, consisted of five signals each of which integrated to a single proton. The aldehydic proton (H_a) was clearly observed as a sharp doublet (J = 3.1 Hz) appearing at 9.5 ppm. The remaining four cyclopropyl signals shared the common pattern that had previously been observed in a range of similarly *trans*-substituted cyclopropanes including the starting material (**109-*S,R***).

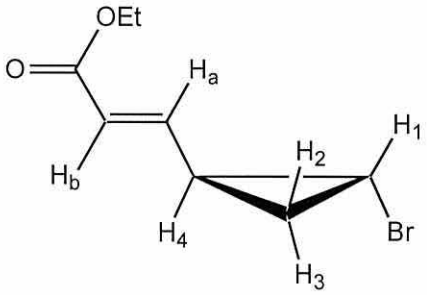
The optical rotations exhibited by the product (**124-*S,R***) and its enantiomer (**124-*R,S***) were measured and found to be approximately equal in magnitude, but in opposing directions, the observed specific rotations being –36.4 ° and +35.9 ° respectively.

3.3.2.2.2 Introduction of the Desired *Trans*- Orientated Double Bond

The successful isolation of the monobromoaldehydes (**124-*S,R***) and (**124-*R,S***) in high yield facilitated the application of traditional Wittig type chemistry in the construction of the desired *trans*- orientated olefinic double bond. Subsequent treatment of the monobromoaldehydes (**124-*S,R***) and (**124-*R,S***) with a two-fold excess of a suitable, stabilised phosphorane, carboethoxymethylene triphenylphosphorane (or carbomethoxymethylene triphenylphosphorane) enabled the efficient introduction of

the required olefinic double bond. Wittig reactions of this type were typically carried out overnight at room temperature in toluene solution.

Unfortunately the crude product was generally recovered (after removal of the reaction solvent under reduced pressure) as a thick paste that contained not only the desired product (**125-*S,R***), but also the by-product of the reaction, triphenylphosphine oxide; consequently further purification steps were required. Treatment of the paste with refluxing petrol followed by filtration (whilst hot) enabled the efficient bulk separation of the two components, and further purification (if required) was carried out by flash column chromatography on silica gel. The desired product (**125-*S,R***) was readily eluted from the column with petrol – ether (10:1), leaving any residual triphenylphosphine oxide on the top of the silica column. The purified product (**125-*S,R***) was subsequently recovered as a pleasantly fragrant oil in 79 % yield.



125

Figure 3.33

IR spectroscopy confirmed the formation of the α,β-unsatutated ester (**125-*S,R***) by the appearance of intense bands corresponding to (C=C) and (C=O) stretches at 1648 and 1715 cm^{-1} respectively, similarly the appearance of an unsaturated (C–H) stretch at 3005 cm^{-1} confirmed this observation.

Subsequent analysis of the purified product by ^1H NMR and GLC revealed that the desired olefinic bond was formed with > 99 % selectivity; indeed none of the alternative *cis*- isomer was observed. This observation can be clearly seen in the olefinic region of the ^1H NMR spectrum of (**125-*S,R***) which may be seen in **Figure 3.34**. The olefinic signal corresponding to H_a was observed as a dd (J = 15.4, 9.7 Hz) resonant at 6.42 ppm, similarly the signal corresponding to the second olefinic proton, H_b was observed as a doublet (J = 15.4 Hz) resonating at 5.89 ppm. Furthermore, only one set of signals, a low field quartet (2H) appearing at 4.18 ppm, and a high field

triplet (3H) resonant at 1.28 ppm, was observed for the ethoxy substituent of the ester functionality.

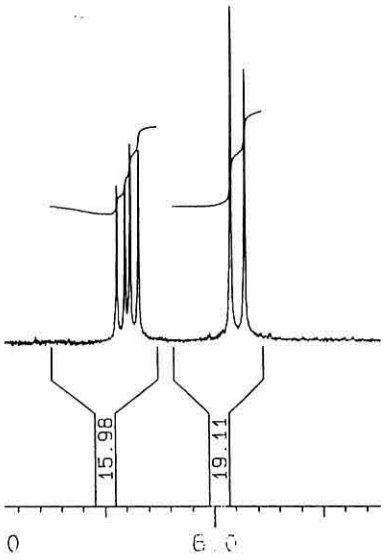


Figure 3.34

As expected, the signals resulting from the cyclopropyl protons, H_1, H_2 and H_3 were again very similar to those observed in precursor materials, each signal was observed as a ddd occurring at 2.96, 1.46 and 1.28 ppm respectively. The final signal, corresponding to H_4 was observed as a complicated dddd, coupling to the three other cyclopropyl protons (H_1, H_2 and H_3) and the olefinic proton (H_a), an expansion of this signal may be seen in **Figure 3.35**.

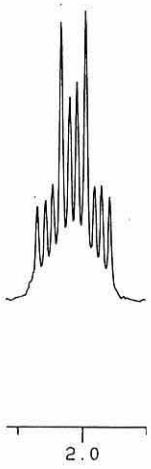


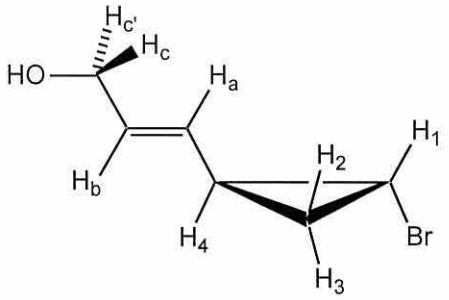
Figure 3.35

^{13}C NMR identified eight discrete carbon environments including the carbonyl of the ester at 166 ppm, and the two olefinic carbons appearing at 147 and 121 ppm. Furthermore, the physical characterisation of this product was completed with the

successful identification of the molecular ion (as the ammonium adduct) by high resolution mass spectrometry. The optical rotations exhibited by the product (**125-*S,R***) and its enantiomer (**125-*R,S***) were measured and indeed found to be of comparable magnitudes, but in opposing directions, the specific rotations being –157.1 ° and +155.6 ° respectively.

3.3.2.2.3 Generation of the Allylic alcohol (123)

Subsequent treatment of the α,β-unsaturated ester (**125-*S,R***) with two molar equivalents of DIBAL-H solution under standard low temperature conditions (-78 °C) afforded the desired allylic alcohol (**123-*S,R***) in approximately 81 % yield. IR spectroscopy confirmed that the complete reduction of the starting material had indeed been successful. The appearance of a broad (O-H) stretching band at 3332 cm^{-1} confirmed the presence of the desired alcohol functionality, whereas the disappearance of the (C=O) stretching band (present within the starting material) confirmed that the reaction had reached completion.



123

Figure 3.36

In general, the ^1H NMR spectrum of the allylic alcohol (**123-*S,R***) was very similar to that of the α,β-unsaturated ester (**125-*S,R***). The reduction of the ester group had a number of impacts on the appearance of the spectrum in general, the most noticeable effect being the disappearance of the signals corresponding to the ethoxy group of the ester, and the appearance of a sharp dd (2H) corresponding to the methylene group adjacent to the olefinic double bond (H_c and $H_{c'}$). In addition to this, the removal of the deshielded region caused by the presence of the associated carbonyl group induced a shift in the position of the signals corresponding to the olefinic proton H_a and H_b; this was most pronounced in the case of H_a where the signal shifted to a higher field (5.27 ppm). The general profile of both of the olefinic signals also changed quite

considerably, as each of the protons was now coupled to the two methylene protons (H_c and $H_{c'}$), an expanded image of the olefinic region may be seen in **Figure 3.37**.

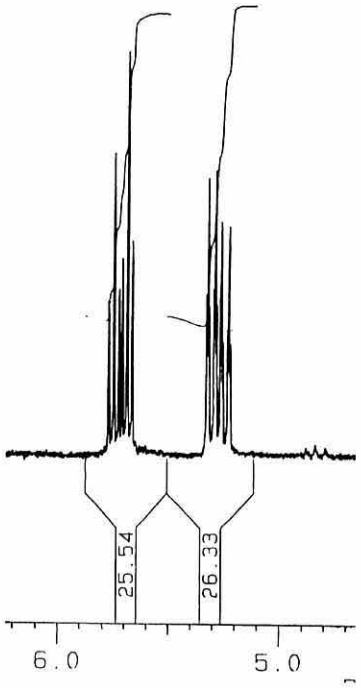


Figure 3.37

^{13}C NMR identified six discrete carbon environments including the two olefinic carbons appearing at 131 and 129 ppm. The optical rotations exhibited by the product (**123-*S,R***) and its enantiomer (**123-*R,S***) were measured and found to be of comparable magnitudes, but in opposing directions, the observed specific rotations being –108.1 ° and +109.6 ° respectively.

3.3.2.2.4 Summary

In brief summary, Sections **3.3.2.2.1**, **3.3.2.2.2** and **3.3.2.2.3** have highlighted the successful preparation of the enantiomeric allylic alcohols (**123-*S,R***) and (**123-*R,S***) in three synthetic steps from the readily available chiral building blocks (**109-*S,R***) and (**109-*R,S***). The optically active intermediate compounds formed during each of these steps were fully characterised. The two optically active allylic alcohols (**123-*S,R***) and (**123-*R,S***) were prepared as suitable substrates for use in the boroxolane mediated asymmetric cyclopropanation reaction; further application of these substrates is discussed in the following section.

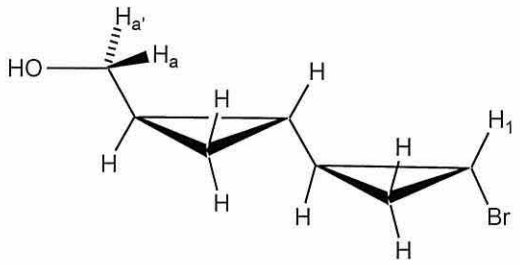
3.3.2.3 Preparation of the Desired Biscylopropane Target Molecules, (119-122)

As mentioned briefly in Section **1.5.2.2.1**, the application of a wide variety of optically active, stoichiometric chiral modifiers such as the chiral dioxaborolane complexes (**56-*R,R***) and (**56-*S,S***) has revolutionised the synthetic preparation of enantiomerically pure cyclopropanes from a wide variety of olefinic starting materials. Furthermore, the successful application of these particular modifiers, most notably by the groups of Barrett[38, 42] and Charette,[43] has also enabled the stereocontrolled synthesis of a number of polycyclopropane containing arrays including those found in the natural products FR-900848 (**19**) and U-106305 (**20**). The general aim of the work discussed in this section was the successful application of these tartrate derived dioxaborolane complexes in the asymmetric cyclopropanation of the enantiomeric allylic alcohols (**123-*S,R***) and (**123-*R,S***), thereby facilitating the efficient synthesis of the four target molecules, the biscyclopropanes (**119 – 122**), from readily available optically active precursors. A brief discussion detailing the synthesis of one of these products (**120**), is outline in the following paragraphs; similarly, details of the results obtained from the synthesis of all four products are presented at the end of this section in **Table 12**.

3.3.2.3.1 The Preparation of (120)

The asymmetric cyclopropanation of (**123-*R,S***) in the presence of the dioxaborolane complex (**56-*R,R***) enabled the preparation of the biscyclopropane (**120**). This product was of high interest, as it exhibited the same relative stereochemistry as that exhibited by the polycyclopropane arrays found in the natural products FR-900848 (**19**) and U-106305 (**20**). The reaction was carried out employing the modified Charette-Juteau protocol[167] which involved the low temperature (-15 °C) addition of a pre-prepared solution of the methylene equivalent, bis(iodomethyl)zinc.DME, to an equimolar solution of the allylic alcohol (**123-*R,S***) and the optically active dioxaborolane complex (**56-*R,R***). The resulting solution was stirred for a further 2 hours at –15 °C before aqueous work-up and product isolation was carried out. Subsequent treatment of the crude product with an aqueous base facilitated the easy removal of the chiral modifier hence enabling the efficient recovery of the product as a yellow coloured oil. Further purification by flash column chromatography on silica gel afforded the pure product as a colourless oil

Analysis of the isolated product by IR spectroscopy revealed the presence of a broad (O-H) stretch appearing at 3325 cm^{-1} and the disappearance of the corresponding (C=C) stretch of the starting material indicated that the reaction had reached completion.



120

Figure 3.38

As expected, the ^{1}H NMR spectrum of the product (**120**) was extremely complicated, with only three sets of signals being completely resolved. The methylene group of the hydroxymethyl substituent (H_a and $H_{a'}$) was clearly observed as a pair of sharp dd appearing at 3.41 and 3.35 ppm. The only other signal that could be assigned in the spectrum was a ddd appearing at 2.57 ppm. This signal was quite characteristic as that of the single proton situated geminally to bromine in monobromocyclopropanes (H_1). The coupling constants observed within this signal (*J* 7.5, 3.5 and 3.4 Hz) were consistent with those observed in other similar *trans*- disubstituted cyclopropanes. The remaining signals, corresponding to a total of seven cyclopropyl protons and a hydroxyl group give rise to a very complicated series of multiplets appearing between 0.2 and 1.5 ppm an extract of this region may be seen in **Figure 3.39**.

The ^{13}C NMR spectrum of the product (**120**) was, as expected, considerably less complicated, with the observation of seven signals, three corresponding to CH_2's and the remaining four corresponding to CH's. The only distinct signal was the methylene of the hydroxymethyl group, appearing at 66 ppm.

The observed specific rotation exhibited by the product was measured as a solution in absolute ethanol (c = 0.91) and was determined to be +80.5 °; for comparison, the specific rotation exhibited by the enantiomeric product (**119**) was measured to be – 82.0 °. The characterisation of this important biscyclopropane containing product was subsequently completed with the successful identification of the molecular ion (as its ammonium adduct) by high resolution mass spectrometry.

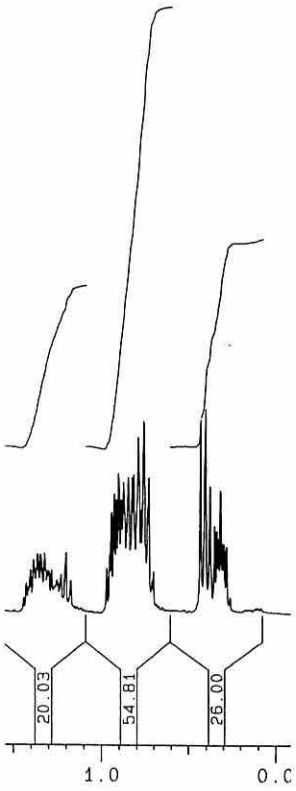


Figure 3.39

3.3.2.3.2 Summary

The successful synthesis of the desired target molecules (**119 – 122**) was subsequently carried out in moderate yields, by the reaction of a single enantiomer of the allylic alcohol (**123-*S,R***) or (**123-*R,S***) with a suitable methylene equivalent generated under modified Charette-Juteau conditions[107, 167] in the presence of the desired optically active dioxaborolane complex. The individual reagent combinations employed in the synthesis of each of the four target molecules may be seen in **Table 12**.

Allylic alcohol	Dioxaborolane	Product	Yield %	α_D
123-*S,R*	**56-*R,R***	**121**	60	-62.1°
	56-*S,S*	**119**	64	-82.0°
123-*R,S*	**56-*R,R***	**120**	59	+80.5°
	56-*S,S*	**122**	64	+65.0°

Table 12. Reagent mixtures employed in the preparation of the target molecules (119 – 122)

3.4 Conclusion

In conclusion, the work discussed throughout this chapter has been successful in illustrating the application of the enantiomerically pure cyclopropane containing building block, 2,2-dibromocyclopropanecarboxylic acid (**72**), in the synthesis of polycyclopropane arrays such as those found in the natural products FR-900848 (**19**) and U-106305 (**20**).

Two alternative synthetic strategies have been examined, both of which shared a common aim; the efficient construction of a range of diastereomeric polycyclopropane arrays. The first approach examined, involved a convergent, reiterative dimerisation strategy, this methodology was moderately successful and consequently led to the completion of an alternative formal synthesis of the natural product FR-900848 (**19**). Simple structural elaboration of (**72**) enabled the efficient preparation of a common synthetic intermediate (**110**), previously identified by Falck in his synthesis of the natural product FR-900848 (**19**).

The second approach that was examined was one of a stepwise, chain homologation – asymmetric cyclopropanation type strategy. This type of reaction scheme was shown to be very versatile, and consequently led to the successful preparation of four diastereomeric *trans*, *trans*- orientated biscyclopropanes. Unlike the former, convergent strategy, the stepwise approach could be employed in a cyclic reaction scheme that could, in theory, enable the preparation of much larger polycyclopropane arrays. Furthermore, it is perfectly feasible that arrays containing any combination of *trans*- stereochemistries could indeed be generated by careful manipulation of this reaction cycle.

Chiral Cyclopropyl Building Blocks Derived From Simple Carbohydrates

4 Chiral Cyclopropyl Building Blocks Derived From Simple Carbohydrates

4.1 Aim

The general aim of the work discussed in this chapter is the development of a synthetic route that would enable the large-scale generation of highly functionalised optically pure cyclopropanes by exploitation of the inherent chirality observed in carbohydrates. Carbohydrates form a major component of the highly fashionable "chiral pool" and consequently they may be considered as a natural and, more importantly, renewable source of optically pure materials that may find application in synthesis.

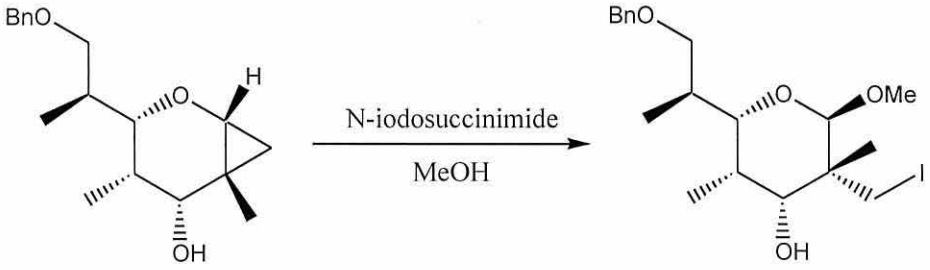
4.2 Introduction

As mentioned previously in Section **2.1**, the development of optically active "building blocks" for application in synthesis is an on going line of research throughout the scientific community. Chapter 2 of this thesis described the efficient generation of a number of functionalised cyclopropane containing building blocks via the efficient resolution of readily available racemic starting materials. As mentioned earlier in Section **4.1**, the aim of the work discussed in this chapter, was the successful development of a similar, highly functionalised, optically active cyclopropane containing building block, this time based on a readily available naturally occurring component drawn directly from the chiral pool, α-D-glucose.

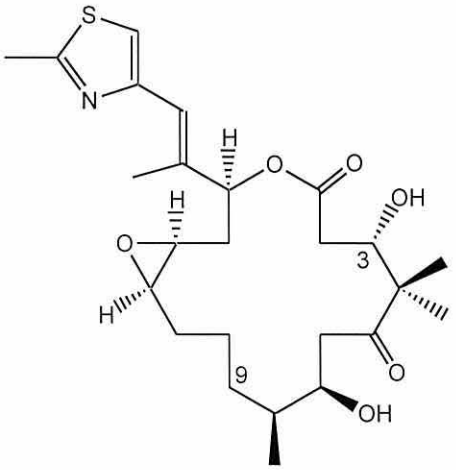
The synthesis of highly functionalised alicyclic compounds containing more than one asymmetric centre poses a considerable problem to the synthetic organic chemist. As mentioned previously in Section **1.5**, the selective generation of new stereogenic centres (stereocentres) by the chemical transformation of prochiral groups or reaction centres may be achieved as a consequence of asymmetric induction caused by the presence of existing stereocentres within the substrate, or by the application of chiral reagents (or catalysts). Consequently the direct exploitation of naturally abundant optically active materials drawn directly from the chiral pool seemed a logical starting point in the synthesis of optically active, highly functionalised building blocks.

Traditionally, carbohydrate compounds such as α-D-glucose have been considered hard to work with, one possible reason being the obvious requirement of selective

protection and deprotection of the chemically distinct hydroxyl groups. However the synthesis of many cyclopropanated carbohydrates typically begins with the removal of two such hydroxyl groups thus enabling the formation of an olefinic double bond that may then undergo cyclopropanation. Although the need for protection is still evident in such systems, the number of orthogonal protecting groups required is somewhat reduced. The development of new methods and reagents, coupled with the commercial availability of many partially protected unsaturated carbohydrates (glycals) has led to an increase in the application of cyclopropanated carbohydrate derivatives in synthesis; an example being the oxidative ring opening of the cyclopropanated carbohydrate (**126**) in Danishefsky's total synthesis of the epothilones A (**128**) and B.[168] Further elaboration and eventual cleavage of the glycoside provided the acyclic aldehyde that was incorporated as the C-3 to C-9 portion of epothilone A.



126 127



128

Figure 4.1

4.2.1 Nomenclature

Carbohydrates may be described as a class of naturally abundant optically active materials bearing multiple hydroxyl functionality. Consequently, the precise structure and stereochemistry of each individual carbohydrate must be recorded accurately with the aid of a suitable nomenclature system. The structural stereochemistry inherent in all carbohydrates (or sugars) is often described with the aid of two discrete forms of nomenclature, each of which is discussed briefly in the following sections.

4.2.1.1 Systematic Nomenclature

Carbohydrates and sugars may be collectively seen as a series of simple molecules that contain multiple chiral centres. Consequently, modern systematic nomenclature systems (such as that recommended by IUPAC) may be similarly employed in the accurate naming of carbohydrate compounds (just as with any other chiral compound). During this procedure, the absolute stereochemistry of each individual stereocentre is defined and individual stereochemical labels (*R* or *S*) are assigned in accordance with the Cahn-Ingold-Prelog sequence law. These stereochemical labels are then used in the generation of a suitable systematic name. Although systematic, this system often gives rise to very long, complicated names. A notable example being; (2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanal, which is the IUPAC recommended, systematic name for the common sugar (traditionally known as) α-D-glucose.

4.2.1.2 Traditional Nomenclature

The alternative, more traditional nomenclature system on the other hand, may be broken down into a number of simple descriptors that may (when used in conjunction with each other) efficiently characterise all simple carbohydrates and sugars. This alternative system is often used preferentially in the area of carbohydrate chemistry, simply because a majority of the names derived are considerably shorter and more convenient than their modern systematic equivalents; this comparison is highlighted by the simple example (cited previously in Section **4.2.1.1**), α-D-glucose. A more detailed description of this descriptive nomenclature system is highlighted in the following paragraphs.

Glyceraldehyde, the simplest carbohydrate compound known, contains only one chiral centre and as a consequence exists as a pair of enantiomers. Each of its

enantiomers was originally assigned with one of the stereochemical descriptors (D or L) (as seen in **Figure 4.2**).

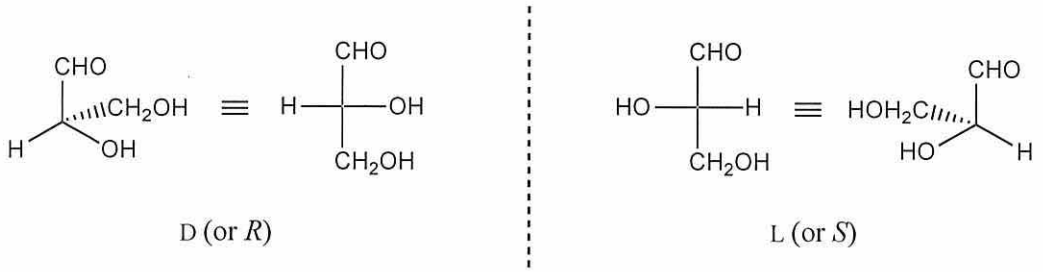


Figure 4.2

It must be stressed that the descriptors D and L originally had no bearing upon the direction of rotation of plane-polarised light observed in each sample. Incidentally, the term dextrorotatory is often represented by descriptor *d* and laevorotatory as *l*, but importantly not as capital letters. At the time of assignation, the absolute configuration of glyceraldehyde and hence any link between the absolute stereochemistry and any optical rotations observed was unknown. Luckily the proponents of this nomenclature system chose the assignation of the descriptors correctly, and consequently labelled dextrorotatory (+)-glyceraldehyde as D, and laevorotatory (-)-glyceraldehyde as L.

Using this traditional convention, all carbohydrates that share the same configuration as D-glyceraldehyde at the stereocentre most distant from the carbonyl group are characterised with the stereochemical descriptor D (regardless of the direction of the observed optical rotation). Similarly, carbohydrates that share the opposite configuration are characterised with the alternative descriptor L.

Application of the D and L descriptors efficiently describes the stereochemistry of a single chiral centre; unfortunately many simple carbohydrates contain multiple chiral centres. Hence the relative stereochemistry of each optical centre must be described in turn thus enabling the accurate naming of any carbohydrate system under consideration. Bearing in mind that for a particular compound containing n stereocentres, there are 2^n possible optical isomers (diastereomers). For example, there are 16 possible aldohexose structures, half of which may be described using the previously discussed stereochemical descriptor D (with the remainder bearing the alternative descriptor L). To avoid the use of longer, more cumbersome names, each of the eight isomeric structures (either D or L) has been further assigned a trivial name. Consequently, the stereochemistry of each of the sixteen possible diastereomeric

structures may be efficiently described with the aid of just two descriptive terms, for example D-glucose. The names assigned to each of the eight D-aldohexose structures may be seen in **Figure 4.4**.

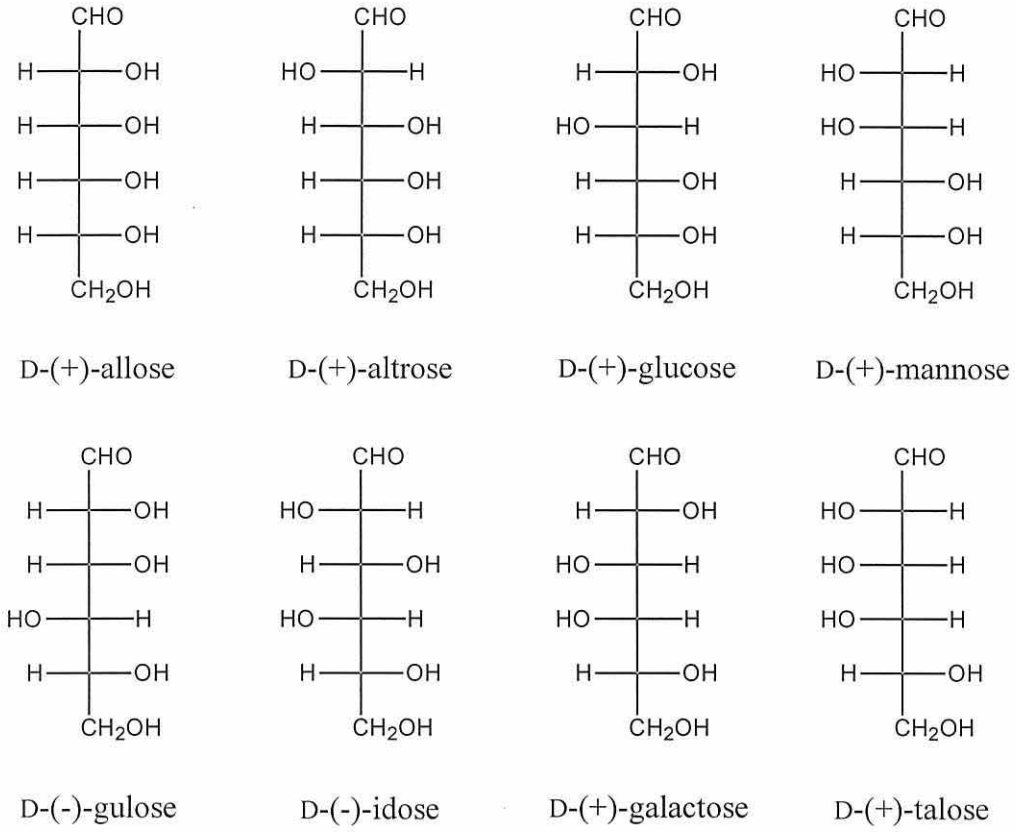


Figure 4.3

Rather unsurprisingly, longer chain carbohydrates such as D-glucose do not exist solely in the open chain form (as seen in **Figure 4.3**). In fact, they commonly exist as a thermally dependent equilibrium mixture that lies between the open and cyclic hemiacetal forms. Although either the five-membered (furanose) or six-membered (pyranose) hemiacetal structure is possible, almost all simple sugars exist in the six-membered (pyranose) form. Upon formation of such cyclic hemiacetal structures, the former aldehyde carbon (C-1) naturally becomes a new stereocentre. As a result, the cyclic sugar may commonly exist in either one of two possible geometrically isomeric forms, as seen in **Figure 4.4**. Such structural isomers differ only in the configuration of the hydroxyl substituent at C-1, the hemiacetal carbon. Structural isomers of this type are known as *anomers*; consequently the hemiacetal carbon is commonly described as the *anomeric* carbon. Anomeric sugars of this type are commonly differentiated by the assignment of a second stereochemical descriptor (α or β) as seen in **Figure 4.4**, which illustrates the two anomeric structures associated with D-glucose.

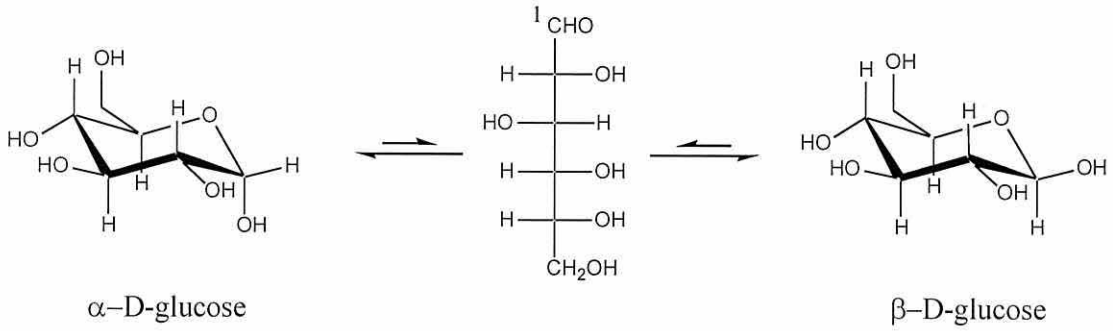


Figure 4.4

The application of this final descriptor facilitates the full characterisation of a particular carbohydrate (or sugar), consequently the full descriptive name of our previously cited example may be written α-D-glucopyranoside.

4.2.2 The Preparation of Cyclopropyl Containing Carbohydrates

As expected, the efficient introduction of a cyclopropyl ring into the carbon skeleton of a wide range of simple carbohydrate substrates may be simply carried out by employing any of the general techniques discussed previously in Section **1.4**. Furthermore, the commercial availability of a range of unsaturated carbohydrates (or glycals) renders cyclopropanation by carbene addition by far the most attractive synthetic route available. The three most popular methods employed in the cyclopropanation of glycals are the Simmons-Smith reaction,[169] transition metal mediated decomposition of diazo compounds[170] and the addition of dihalocarbenes under phase transfer catalysis.[171] Each of these principle reactions was discussed in greater detail in Sections **1.4** and **1.5**.

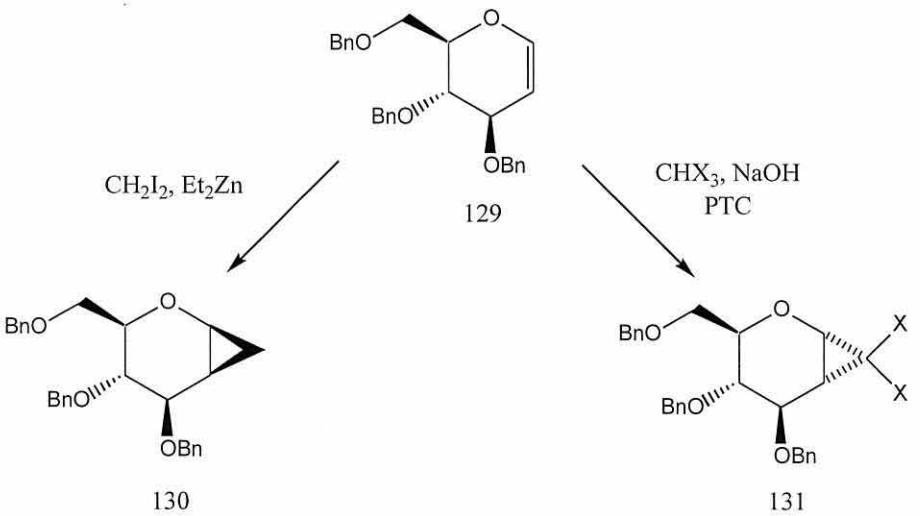


Figure 4.5

The stereoselectivity observed during the cyclopropanation of many simple carbohydrates may be explained quite simply in terms of steric direction. The conformational bias that is often associated with simple carbohydrates (in the cyclic hemiacetal form) coupled with the high degree of inherent chirality is often sufficient to produce a substantial degree of chiral induction, hence stereoselectivity is observed. By "loading" the starting material with sterically demanding, bulky substituents, it is therefore possible to obtain stereoselectivities in the order of 250:1.[169a]

A second, much larger contribution that is observed in the case of the Simmons-Smith cyclopropanation is the directing effect of oxygen functionalities within the substrate by complexation of the intermediate "zinc reagent". It is commonly accepted that the asymmetric Simmons-Smith cyclopropanation proceeds via a chiral intermediate complex formed between the generated "zinc reagent" and any proximal oxygen functionalities within the substrate (such as allylic alcohols). The formation of such intermediate complexes leads to the selective addition of the carbene equivalent to a single face of the olefinic bond present within the starting material. It is therefore quite feasible that similar interactions may also be present during Simmons-Smith mediated cyclopropanations of carbohydrate materials that are also rich in oxygen functionality.

An alternative route, successfully employed in the total synthesis of both enantiomers of chrysanthemic acid (**9**), involved the controlled addition of a suitable phosphonate ester to the sugar epoxide (**132**). Subsequent hemiacetal cleavage of the annulated sugar (**133**), followed by further structural elaboration yielded both the (+) and (-) enantiomers of the desired product (**9**) with overall yields of 27 and 24 % respectively (10 steps).[172]

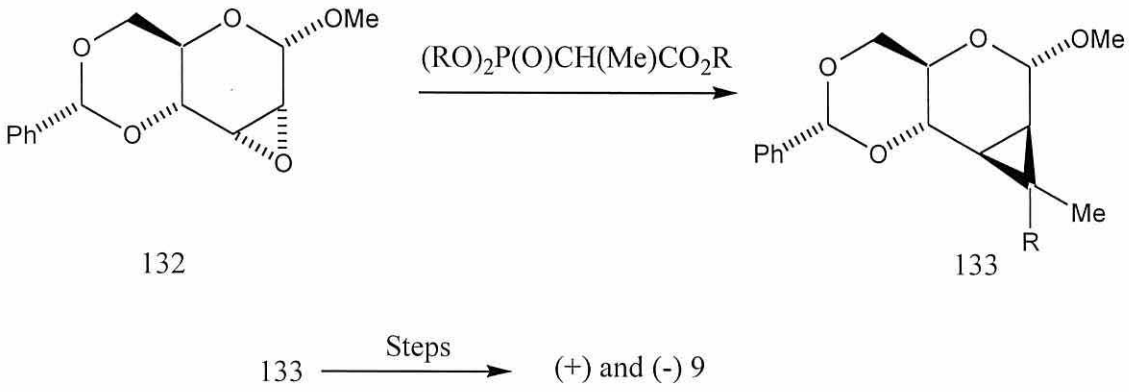


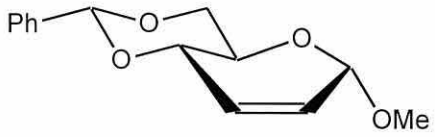
Figure 4.6

4.3 The Synthesis of Cyclopropanated Carbohydrates

4.3.1 Selection and Preparation of a Suitable Starting Material

As mentioned briefly in Section **4.1**, the aim of the work discussed in this section was the preparation of highly functionalised cyclopropane containing building blocks derived from raw materials drawn directly from the chiral pool. Carbohydrates were consequently seen as a sustainable source of the optically active precursors that were required for the development of this work.

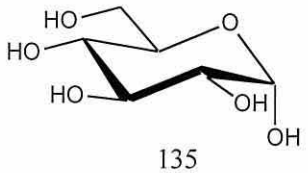
Previous work carried out on the preparation of annulated sugars within the research group generally centred upon the study of furanose systems and commercially available glycals such as 3,4,6-tri-*O*-benzyloxy-D-glucal (**130**).[173] Annulated sugars based upon such compounds appear quite widely in the primary literature and are readily used in the synthesis of more elaborate target molecules such as the epothilones (mentioned previously in Section **4.2**) and calimycin.[174] Initial studies carried out on the cyclopropanation of the 2,3-unsaturated sugar, methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**134**)[175] were shown to be very interesting indeed. Consequently it was decided that further studies should be carried out, with the aim of preparing an optically active building block that would find application in the synthesis of a number of synthetic targets including lactobacillic acid (**3**) and a range of cyclopropyl amino acids such as α-(carboxycyclopropyl) glycines (**7**).



134

Figure 4.7

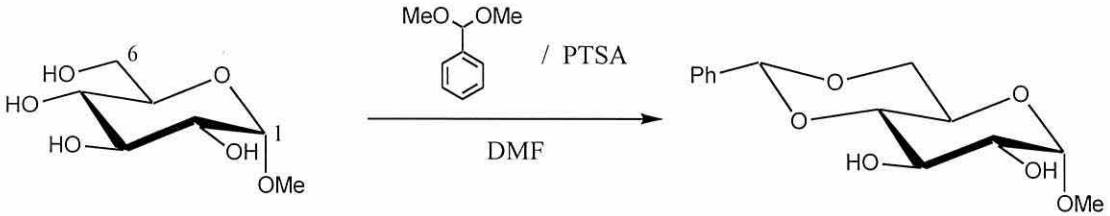
Unfortunately, methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**134**) was not commercially available at a reasonable cost; consequently a suitable precursor to this material was required. The carbohydrate that was eventually chosen as the starting material was the naturally occurring sugar, α-D-glucopyranoside (**135**).



135

Figure 4.8

Although readily available in bulk, it was evident that partial protection of selected hydroxyl functionalities within the crude starting material was required before useful, directed synthetic transformations could be efficiently carried out. Fortunately, a suitably protected sugar, methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**137**), was also found to be commercially available. Unfortunately, the protected sugar had an inflated cost of approximately £ 1,500.00 / Kg[120] and it was decided that a cheaper precursor should be sought. The immediate precursor to (**137**), methyl-α-D-glucopyranoside (**136**), was also found to be commercially available, and to our surprise the cost of this partially protected sugar was considerably less at £ 85.00 / Kg.[120] Subsequent protection of the 4,6-diol functionality present within the partially protected sugar (**136**), as its benzylidene acetal (**137**) was carried out using the excellent procedure first reported in 1972 by Evans;[176] this method may be seen schematically in **Figure 4.9**.



136 137

Figure 4.9

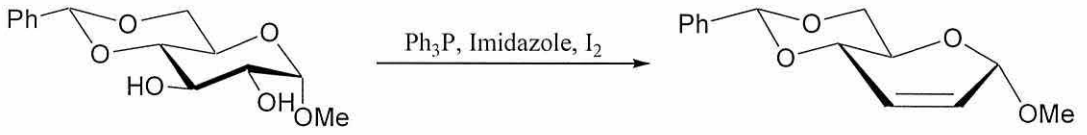
Methyl-α-D-glucopyranoside (**136**) was thoroughly dried overnight in a vacuum oven at 100 °C prior to reaction with α,α-dimethoxytoluene (benzaldehyde dimethyl acetal) in dried DMF containing a trace of acid.[177] The reaction was conveniently carried out on a moderately large scale (up to 100 g) using a standard, laboratory scale rotary evaporator with the reactants being rotated at approximately 45 °C for a period of 1 hour under a moderate vacuum (14 mmHg). At this point, a short path distillation adapter was fitted between the flask and the vapour duct, and the excess of DMF was removed. The crude product, methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**137**) was recovered as a waxy, cream coloured paste. Subsequent recrystallisation of the crude product from refluxing IPA afforded pure (**137**) in 80 % yield as a white

crystalline solid. All analytical data was subsequently shown to be identical to that exhibited by standard samples obtained from commercial suppliers.[178]

4.3.2 Introduction of the Olefinic Bond

4.3.2.1 Introduction

As mentioned in Section **4.2.2**, the introduction of a cyclopropyl ring into the skeletal framework of carbohydrates is readily carried out by the stereospecific addition of a carbene to a suitable olefin. Consequently, the immediate task at hand, was the efficient introduction of a suitable double bond into the starting material, thereby generating the desired cyclopropanation substrate, methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**134**).



137 134

Figure 4.10

The conversion of *vic*-diols to olefins, thereby enabling the generation of unsaturated sugars, has been a major area of research in the field of carbohydrate chemistry. Such modification opens a great number of routes that enable the efficient structural modification (including cyclopropanation) of many biologically important molecules such as glycosidic antibiotics[179] and nucleosides.[180] The wide variety of synthetic methods that are typically employed in the preparation of unsaturated sugars depends primarily upon the stereochemical relationship of the starting *vic*-diol. For example, in *cis*- orientated systems, simple derivatives including cyclic acetals,[181] cyclic thiocarbonate *O*-esters[182] and bisdithiocarbonates[183] are readily decomposed to form the required olefinic bond. On the other hand, reductive elimination of activated *trans*- 1,2-diols systems[184] (such as sulfonates[185] and phosphonates[186]) similarly yields the desired olefinic functionality.

The stereochemistry of the remaining diol functionality present within the "commercially" available precursor (**137**) was in fact *trans*-, hence it was assumed that a suitable reductive elimination pathway would be followed. However earlier work carried out by a previous PhD student[174] showed that routes of this type were not

always efficient, and often entailed multiple steps; indeed yields were typically shown to be in the order of 50 – 55 %. It was consequently decided that an alternative (possibly single step) route should be sought. A second, more thorough examination of the primary literature eventually revealed that an alternative procedure had indeed been reported in 1979 by the group of Garegg and Samuelsson.[187] In their original paper, the authors reported the application of a "new" reagent system that enabled the conversion of *vic*-diols (both *cis*- and *trans*-) into olefinic bonds, thus enabling the efficient preparation of a range of unsaturated carbohydrates including the target glycal, methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**134**).

Garegg and Samuelsonn's original procedure involved the reaction of the starting diol with a ternary reagent system composed of triphenylphosphine, imidazole and iodine in the ratio of 4:4:3 (respectively) to 1 equivalent of diol in refluxing toluene. It is thought that the reaction proceeds via an intermediate $[O{=}P^{+}(Ph)_3\ I^{-}]$; subsequent elimination of triphenylphosphine oxide and iodine affords the olefinic product in reportedly moderate yield. A diagrammatic representation of this process may be seen in **Figure 4.11**.

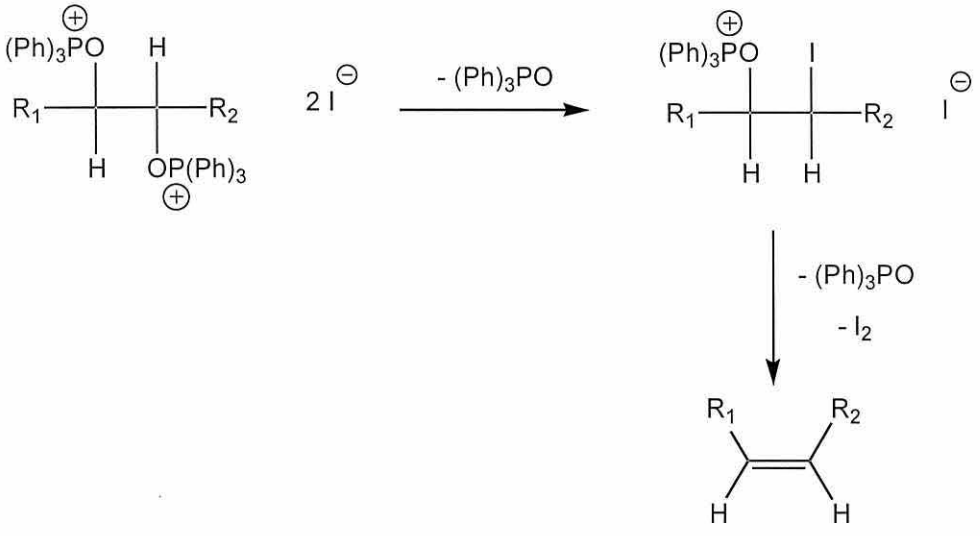


Figure 4.11

A second paper (by the same authors),[188] appearing only 4 months later detailed a slight modification in the reagent system employed. Although there was no increase in the yields obtained from this modified procedure, the subsequent introduction of 2,4,5-triiodoimidazole reduced the number of equivalents of imidazole required (from 4 mol. equiv to 2 mol. equiv) and eliminated the requirement of iodine completely. Unfortunately, though more efficient in terms of atom efficiency,[189] the cumbersome

preparation of 2,4,5-triiodoimidazole renders this alternative procedure unfavourable. Consequently it was decided that the original procedure should be followed.

4.3.2.2 The Preparation of Methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-eno pyranoside (134).

Unfortunately, the efficient introduction of a suitable olefinic bond within the pyranose ring of the starting material proved to be quite a problematic process. This step, although sounding trivial, was not as straightforward as was first imagined. As mentioned above in Section **4.3.2.1**, it was decided that Garegg and Samuelsson's original process would be followed, thus avoiding the notoriously cumbersome preparation of 2,4,5-triiodoimidazole. This involved the careful addition of iodine to a refluxing solution of the diol (**137**), imidazole and triphenylphosphine in toluene. Unfortunately, this reportedly simple procedure was also found to have its negative points and it was discovered that the efficiency of the reaction was highly dependant upon a number of factors. These included, both the molar ratios (of the reagents employed) and the bulk reaction conditions (including reaction temperature and stirring efficiency). If these optimised conditions were not carefully maintained, the efficiency of the reaction was routinely reduced from around 80 % to less than 30 % recovery.

A major factor that was identified very quickly, involved the physical nature of the reagents used throughout the reaction. Indeed, when reagents were used "as supplied" (typically in a course granular form), yields obtained from the reaction were usually between 50 and 60 %. By finely grinding the reagents (and starting material) using a pestle and mortar immediately prior to use, it was possible to increase the average yield by approximately 20 %. This effect was most pronounced in the case of iodine; it was assumed that pre-grinding of the iodine enabled a more controlled addition of the reagent to the reaction mixture. Indeed, when un-ground iodine was employed, the reaction mixture became very dark and tarry after addition of approximately 10 % of the required iodine, and consequently isolated yields were low. By comparison, when ground iodine was employed, a white "snow-storm" type suspension was observed and the solution only became slightly coloured when approximately 75 % of the required iodine had been added. This slight adjustment minimised tar formation and thereby maximised product formation and isolation.

Accurate control of the internal temperature of the reaction mixture was also shown to be very important during the optimisation of this step. Optimal yields were recovered, when the internal temperature of the reaction vessel was carefully maintained between 115 and 120 °C. If the internal reaction temperature dropped below the minimum level, an apparent decrease in the solubility of the reactant / reagents was observed, again resulting in the premature formation of a thick black tar on the bottom of the reaction vessel, hence inhibiting the reaction's progress. Similarly, if the reaction temperature was too high, i.e. greater that 120 °C, considerable product decomposition was observed and again the yield was suppressed. As a result of these observations, the reaction was routinely carried out using standard laboratory glassware (a mechanically stirred 1 litre, 3-necked flask equipped for reflux and solid addition), which was heated by means of an internally monitored, thermostatically controlled oil bath (employing a K-type thermocouple on a feed back loop).

Unfortunately though, the constraints outlined above limited the scale upon which this reaction could be efficiently carried out. As a result, larger-scale preparations of the olefinic product were routinely carried out via a batch type method, with each batch being duly processed on a limited scale of up to 10 g. Larger scale reactions were shown to be somewhat inefficient and as a result were not employed in favour of the batch type process.

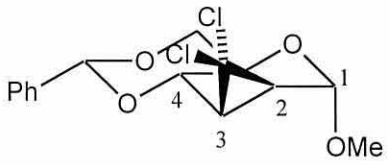
By paying particular attention to the factors outlined in the previous paragraphs, it was routinely possible to obtain the desired unsaturated carbohydrate in moderate yield, greater than 80 %. Purification of the crude product was routinely carried out by column chromatography on silica gel; the product, methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**134**), was then recovered (upon removal of solvent) as a very fine, white solid. All physical and spectroscopic data observed from the product was identical to that quoted in the literature and the product was routinely used for further study without further purification.[187]

4.3.3 Preparation and Deprotection of the Annulated Sugar

Unfortunately, the unsaturated sugar (**134**), has previously been shown to be remarkably unreactive towards carbenoid type reagents,[190] and was in fact recovered unchanged after reaction with dichlorocarbene (generated by reaction of ethyl

trichloroacetate with a strong base).[191] Such apparent unreactivity of this system with dichlorocarbene is in complete contrast to the behaviour of glycals of the vinyl ether type (such as **129**, seen in **Figure 4.5**). Simmons-Smith type reactions on the other hand, have had a small amount of success, with one example being reported in the presence of a Zn / Cu couple;[192] the reaction indeed proceeded with a moderate yield of 20 %, but this example again illustrates the lack of reactivity of this particular system.

The unreactive nature of this particular olefin was also manifested in the desired cyclopropanation with dichlorocarbene. In this case, the reactive singlet dichlorocarbene was generated by the reaction of concentrated sodium hydroxide and chloroform in the presence of a suitable phase-transfer catalyst (*n*-hexadecyltrimethylammonium bromide). However, as with the previous example, the Simmons-Smith reaction, the desired cyclopropanation reaction proceeded very slowly indeed. After 2 days, the resulting solution was quenched and worked-up to remove the active reagents and catalyst. Initial analysis of the crude product mixture by proton NMR showed that the reaction had only reached a 20 % conversion. Consequently, the crude product mixture was again subjected to fresh reagents and catalyst. After a further 2 days, the reaction was again quenched and worked up as before. Subsequent analysis indicated a higher conversion of the starting material with approximately 60 % product formation. The components of the mixture were subsequently separated by fractional recrystallisation from boiling IPA and the desired annulated sugar (**138**) was recovered in 56 % yield (after a second crop) as a white crystalline solid. Considering the apparent lack of reactivity manifested by this precursor, this moderate yield was considered to be quite remarkable. The remaining unreacted starting material (**134**) recovered was retained and subsequently added to the next batch for eventual conversion at a later date.



138

Figure 4.12

Subsequent analysis of the product by IR spectroscopy and NMR (both ^{1}H and ^{13}C) revealed that the double bond had indeed reacted with the carbene to generate the

desired cyclopropyl ring. The apparent simplicity of both the ^{1}H and ^{13}C NMR indicated that the selectivity of the carbene addition was extremely high, with only one set of signals apparent in each case (indicating that a single product had indeed been formed). The stereochemistry assigned to the product (D-mannose), also indicated in **Figure 4.12**, was confirmed by correlation of the coupling constants observed around the cyclopropyl functionality with those of similar compounds from the literature.[193] The relevant coupling constant data extracted from the ^{1}H NMR spectrum of the product is tabulated in **Table 13**, with reference to **Figure 4.3** and **Figure 4.12**.

Coupling Constant	Magnitude /Hz†	D-Mannose‡	D-Allose‡
$^{3}J_{1,2}$	0	0	2.5 - 4.5
$^{3}J_{2,3}$	11.1	-	-
$^{3}J_{3,4}$	2.4	-	-

Table 13. Selected coupling constants comparing the stereochemistries of cyclopropane ring in the annulated sugar (n),† with those of structurally similar reference compounds‡[193]

It can be seen quite clearly, from the data seen in **Table 13**, that the observed $^{3}J_{1,2}$ coupling constant is consistent with that exhibited by analogous D-mannose type structures,[193] and is quite distinct to those exhibited by the alternative geometry (D-allose). The magnitude of such ^{3}J coupling constants is greatly dependent upon the dihedral angle between the two incident C-H bonds (ϕ), This dependence is governed by the Karplus equation ($^{3}J = A + B \cos \phi + C \cos^{2} \phi$) which may be simply represented in the form of a graph plotting $^{3}J_{observed}$ against the dihedral angle (ϕ). An example of a simple Karplus curve may be seen in **Figure 4.13**

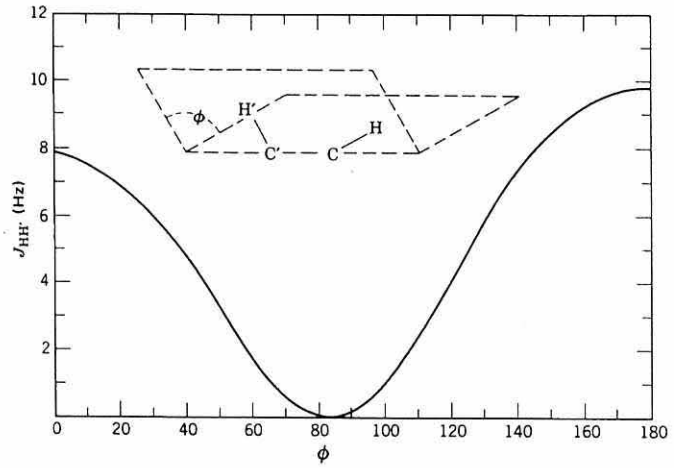


Figure 4.13

If one considers this curve, it may be seen that for a ^{3}J coupling constant to have a magnitude approaching zero, the dihedral angle must tend towards a minimum; this is evident when ϕ approaches approximately 86°. This observation may be easily confirmed (or predicted) by the careful application of computational chemistry. It is possible, by the execution of a number of simple low theory (MM2) energy minimisation calculations (using carefully constructed models) to get a crude indication of the magnitude of individual bond lengths and angles present within a particular molecule. Therefore it is also reasonable to assume that it is possible (by employing the Karplus equation) to predict the magnitude of a particular coupling constant, hence establishing a generalised idea about the possible conformation or stereochemistry present within the molecule under consideration. For example, simple MM2 calculations[108] were carried out examining each of the possible products from the previously discussed cyclopropanation reaction, i.e. the D-mannose and D-allose annulated sugars. The results of the calculations are presented in **Table 14**.

	$\phi_{Calculated}$ / ° †	$^{3}J_{Calculated}$ / Hz‡	$^{3}J_{Observed}$ / Hz
D-Mannose	88.1	0 – 1	0
D-Allose	12.2	7 – 8	2.5 – 4.5

Table 14. A comparison of observed ^{3}J coupling constants with those calculated using a simple molecular mechanics MM2 force field†, [108] in conjunction with the Karplus curve (as seen in Figure 4.13)‡

Careful consideration of these calculated figures (and subsequent comparison with "real data" obtained from a range of analogous compounds), leads to the conclusion that the MM2 energy minimisation calculations were indeed successful in predicting the relevant magnitudes of the ^{3}J coupling constants observed and hence the correct stereochemistries of each of the possible products (D-mannose or D-allose).

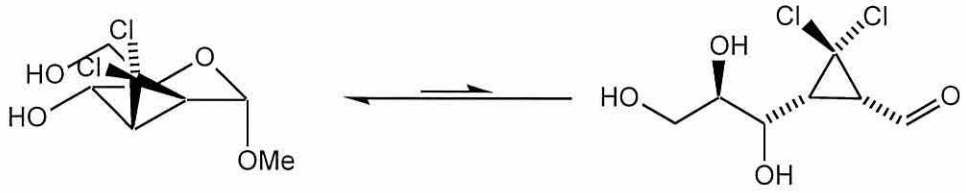
Subsequent removal of the benzylidene protecting group from (**138**) was carried out in near quantitative yields (> 98 %) by simple hydrogenolysis in the presence of a palladium catalyst (5 % Pd on carbon). The product, 7,7-dichloro-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol (**139**) was subsequently isolated as a white needle like, crystalline solid that readily absorbed water. As a result, the product (**139**) was stored at room temperature in a vacuum desicator over pre-dried silica gel until required. Simple ^{1}H NMR spectroscopy was again used to confirm the stereochemistry of the deprotected sugar, and as expected, a very similar set of

coupling constants was observed for the protons in the vicinity of the cyclopropane ring.

4.3.4 Generation of the Open Chain Cyclopropanated Sugar

4.3.4.1 Introduction

The efficient synthesis of the cyclopropanated sugar (**139**) was immediately identified as a viable route enabling the large-scale preparation of synthetically useful, optically active "building blocks" from sustainable precursors. Although the annulated sugar was an interesting molecule in its own right, it was thought that cleavage of the sugar acetal would enable a wider scope for further synthetic development. As mentioned previously in Section **4.2.1.2**, it is commonly accepted that carbohydrate systems exist in a finely balanced state of equilibrium between the desired open chain and the cyclic acetal (or hemiacetal) forms. Unfortunately (in this case), the equilibrium lies heavily on the side of the cyclic acetal form; consequently any ring-opened sugar quickly reverts to the more stable cyclic form.



139 140

Figure 4.14

The efficient trapping of the open chain sugar thus renders the reaction irreversible, thereby eliminating any regeneration of the starting material or its associated β-anomer, may be carried out by the selective protection of either one of the two discrete functional groups formed during ring opening step:

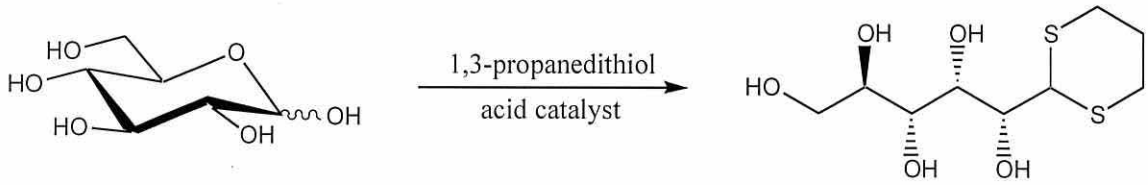
i) The hydroxyl group.

ii) The aldehyde functionality.

Unfortunately, the presence of existing hydroxyl functionality (diol) within the substrate rendered the first option (hydroxyl protection) unsuitable. This was due to the fact that a three-fold excess of the trapping reagent (protecting group) would be required to enable the complete protection of the eventual product (a triol). With this in mind, it was decided that the second option was probably the most advantageous, as

it avoided the additional synthetic steps associated with protection and subsequent deprotection of the hydroxyl groups.

The ring opening of simple carbohydrates via an acid catalysed transacetalisation in the presence of a suitable dithiol (of diol) is typically carried out under catalysis of simple mineral acids (such as HCl) or alternatively, common Lewis acids such as boron trifluoride diethyletherate ($BF_3.OEt_2$). The yields of open chained products obtained from reactions of this type seem to be quite variable, but are typically in the order of 50 –75 %; an example of this type of reaction may be seen in **Figure 4.15**.[194]



141 142

Figure 4.15

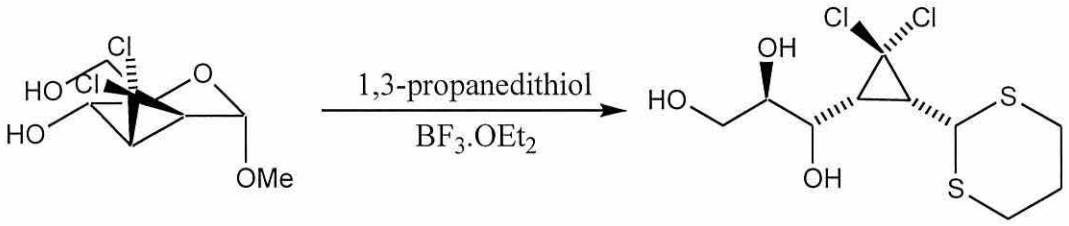
Dithioacetal protected aldehydes of this type have generally found continued application in the field of organic synthesis, particularly by the group of K. C. Nicolaou[195] and others working in the area of natural products synthesis.[196] The inherent ability to stabilise a negative charge on the central thioacetal carbon (thereby effectively reversing the polarity of the "masked aldehyde" functionality), renders intermediates of this type extremely useful in the synthesis of larger target molecules. This property, generally described as "*umpolung*"[197] is commonly exploited in the formation of new carbon – carbon bonds via alkylation employing electrophilic alkylation agents such as alkyl halides or other carbonyl containing compounds.

4.3.4.2 The preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclo propyl)-propane-1,2,3-triol (143)

The attempted ring opening (acetal cleavage) of the cyclopropanated sugar derivative (**139**) was carried out using the methodology described above in Section **4.3.4.1**, namely the acid catalysed transacetalisation of the substrate in the presence of a suitable dithiol. Such reaction conditions have been shown to be quite versatile in the isolation of a large variety of open chain dithioacetals, derived from substrates ranging from simple sugars such as α/β-D-glucose (as seen in **Figure 4.15**), to more complicated acetal containing steroidal structures.[198]

Unfortunately, initial studies concluded that the transacetalisation reaction did not proceed in the presence of simple mineral acid catalysts. Consequently, the focus of attention centred upon the improvement of the Lewis-acid catalysed reaction. Furthermore, the transacetalisation reaction was found to be very sensitive to any variation in the reaction conditions employed. Indeed, at the first attempt, the Lewis-acid catalysed reaction yielded a disappointing 9% recovery of the desired sugar dithioacetal (**143**) (unreacted starting material (**139**) was subsequently recovered for use in later reactions). After a small amount of reaction modification, the yields obtained from this process were considerably improved; yields typically in excess of 70 % were routinely recovered from reactions carried out on a scale of up to 1 g.

As a result of the experiments carried out on process optimisation, it was concluded that the major factor involved in increasing the yields obtained, was the concentration of the catalyst solution employed. Initial reactions were carried out by simply adding a neat solution of $BF_3.OEt_2$ dropwise, to the cooled (-60 °C), stirred solution. As mentioned previously, the yields obtained from these early reactions were disappointingly low, typically around 10 %. Subsequent dilution of the catalyst solution with still dried CH_2Cl_2 afforded an immediate improvement in the yields. Indeed, when a 20 % (v/v) catalyst solution was employed, yields were raised to a respectable 70 % after removal of excess 1,3-propanedithiol by flash column chromatography; the product was subsequently eluted from the column using ethyl acetate and petrol (ratio 4:1).



139 143

Figure 4.16

The product, ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-propane-1,2,3-triol (**143**), was recovered as a fine white powder (after removal of chromatographic solvent) and was typically used in this form. Recrystallisation of the solid from refluxing IPA afforded the product as a highly crystalline, opaque white solid (mp 142 - 143 °C).

Analysis of (**143**) by IR spectroscopy revealed an intense, broad band appearing at 3380 cm^{-1} corresponding to an intermolecularly hydrogen bonded (O-H) stretch; the appearance of this band confirmed that the alcohol functionality remained unaffected during the reaction. The absence of a strong band corresponding to a carbonyl at approximately 1720 cm^{-1}, and the appearance of band at 1420 cm^{-1} confirmed that the aldehyde functionality had indeed been converted into the desired dithioacetal derivative.

Further analysis of the product by ^{1}H NMR and ^{13}C NMR, followed by correlation of the signals observed, with those of standard reference compounds[199] confirmed the presence of the desired 1,3-dithioacetal protecting group. Analysis of the solid by high resolution mass spectrometry employing chemical ionisation techniques (NH_3), duly identified the expected molecular ion ($M+NH_4$ = 336.0260) and consequently revealed the molecular formula as $C_{10}H_{16}S_2Cl_2O_3+NH_4$ confirming the structure as predicted.

4.3.5 Application of the Carbohydrate Building Block

4.3.5.1 Introduction

In summary, the procedures discussed above in Sections **4.3.1**, **4.3.2**, **4.3.3** and **4.3.4** have outlined the synthesis of the highly functionalised cyclopropanated carbohydrate building block (**143**) in six steps from the commercially available sugar, methyl-α-D-glucopyranoside (**136**). The high degree of functionality present within the molecule renders it an ideal staring material for application in the synthesis of a wide variety of target molecules, an example being the *cis*-α-(carboxycyclopropyl)glycine analogue (**148**). The proposed synthetic scheme enabling the synthesis of (**148**) is highlighted below in **Figure 4.17**; a brief outline of the proposed synthesis is outlined in the following paragraph.

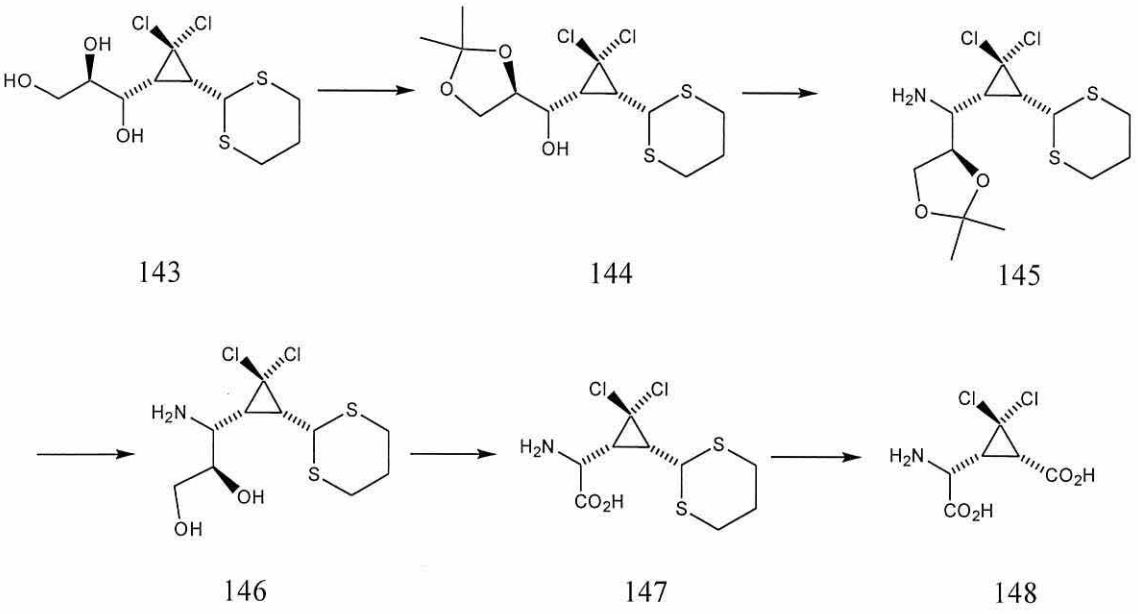


Figure 4.17

As can be seen in **Figure 4.17**, the initial step of the proposed synthesis of the cyclopropane containing amino acid (**148**) involved the selective protection of the terminal diol fragment of a 1,2,3-triol unit, hence enabling the selective activation of the hydroxyl group adjacent to the cyclopropane ring. Subsequent displacement of the activated hydroxyl group with a suitably nucleophilic source of nitrogen would enable the introduction of the required amine functionality. Deprotection and subsequent oxidative cleavage of the diol fragment would then complete the construction of the desired α-amino acid functionality. Cleavage of the dithioacetal protecting group followed by mild oxidation of the regenerated aldehyde would subsequently lead to the formation of the desired product in a minimal number of simple functional group transformations.

4.3.5.2 Selective Protection of the Terminal 1,2-Diol

Isopropylidene acetal formation is a thermodynamically controlled process; thus, in the case of reactions where the generation of more than one product is possible, the thermodynamically more stable product will prevail. In general, five membered acetals (dioxolanes) are thermodynamically more stable and hence their formation is favoured over the formation of six membered acetals (dioxanes). The selective protection of diols as isopropylidene acetals is typically carried out by one of two general methods (each of which is discussed below); suitable examples which exhibit both the alternative strategies employed and indeed the regiochemistry observed in such processes may be seen in **Figure 4.18**.

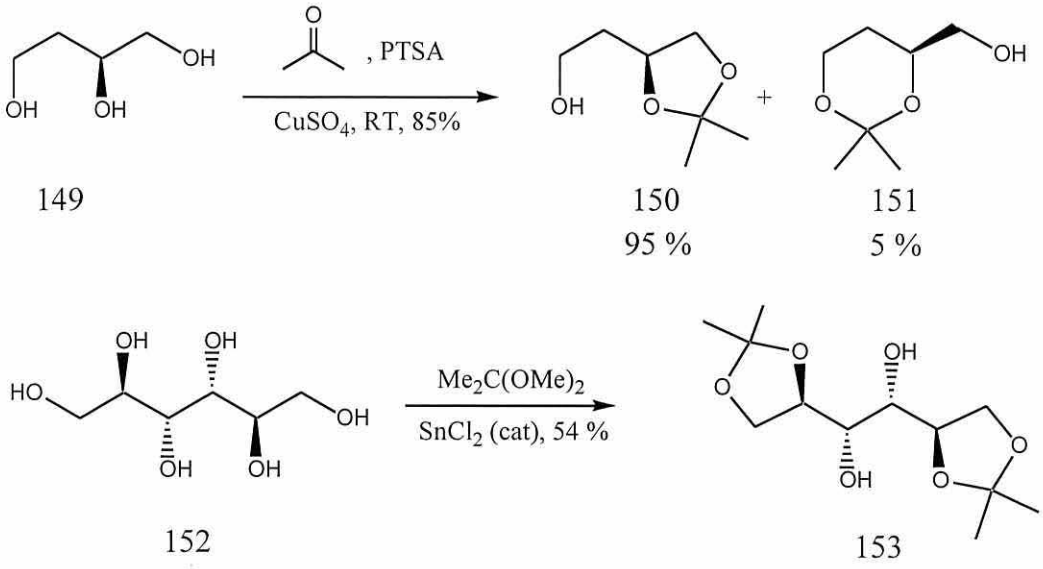


Figure 4.18

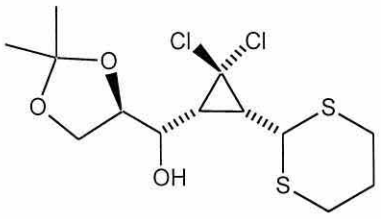
The first and indeed oldest method employed in the preparation of isopropylidene acetals (acetonides) involves the direct reaction of the chosen diol substrate with dry propanone in the presence of a suitable acid catalyst, typically PTSA or CSA. [200] Since a molecule of water is generated during the reaction, an efficient means of dehydration is typically required to drive the equilibrium reaction to completion. As the boiling point of the reaction solution (typically propanone) is low (56 °C), simple removal of water by azeotropic distillation is not possible; hence an alternative dehydration agent must be employed. Suitable reagents range from pre-dried molecular sieves (commonly employed in small scale reactions), to anhydrous inorganic materials such as copper (II) sulfate.

Alternatively, the desired isopropylidene acetal may be efficiently prepared via a transacetalisation reaction between the chosen diol substrate and a cheap, commercially available acetal such as 2,2-dimethoxypropane. A similar variant of this type of reaction was employed in the preparation of the benzylidene acetal precursor, methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**137**) (see Section **4.3.1**). The application of this alternative procedure avoids the need for additional dehydrating agents as the reaction liberates two molecules of methanol as opposed to water. Providing that the equilibrium established during the reaction is favourable (as it is in most cases), the transacetalisation reaction will readily reach completion; in less favourable cases, 2-methoxypropene or 2-trimethylsilyloxy-propene may be used as an alternative.[201] In the case of the latter modification, the formation of the thermodynamically stable bis-trimethylsilyl ether drives the desired reaction to

completion. Transacetalisation reactions of this type, have now become established as the method of choice in the synthesis of isopropylidene acetals; such reactions are now commercially employed (on a hundred kilogram scale) in the synthesis of many synthetic intermediates including 1,2:5,6-di-*O*-isoproylidene-D-mannitol (**153**), a key intermediate in the synthesis of the chiral "building block" isopropylidene-D-glyceraldehyde (**32**).[81]

4.3.5.3 The preparation of ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclo-propyl)-1,3-isopropylidene-propan-2-ol (144), (method 1)

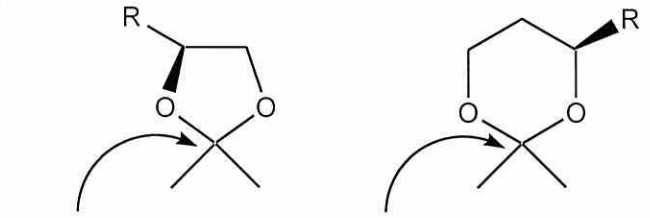
Protection of the terminal 1,2-diol functionality present within the starting material (**143**) was readily carried out by the acid catalysed reaction of the starting material and anhydrous propanone. The reaction was carried out in pre-dried glassware at 0 °C, employing PTSA as catalyst and anhydrous copper (II) sulfate, as a dehydrating agent. The resulting solution was allowed to warm to room temperature and was stirred for 1 hour before monitoring by TLC (4:1, ethyl acetate: petrol). The appearance of a new, higher running spot (R_f = 0.85) indicated the formation of a new (less polar) compound, the protected diol. The reaction was stirred overnight, but there was no apparent change in the comparative intensities of the spots observed for the product and the starting material. Further studies later showed that the reaction reached its maximum conversion after approximately 1 hour. Filtration of the reaction mixture to facilitate removal of the inorganic dehydration agent (now blue) and subsequent neutralisation of the acid catalyst (with saturated sodium bicarbonate solution) enabled the recovery of the product by extraction into ethyl acetate. Evaporation of the dried solvent afforded the crude product as a viscous, yellow oil that was subjected to purification by flash column chromatography (elution solvent, 4:1, ethyl acetate: petrol). The product (**144**) was subsequently recovered (after solvent removal) in 53 % yield, as a cream coloured paste.



144

Figure 4.19

Subsequent analysis of **(144)** by ^{1}H NMR spectroscopy (as a solution in d^{6}-benzene), clearly showed the presence of the isopropylidene group by the observation of two large singlets at 1.30 and 1.38 ppm, each corresponding to one of the two diastereotopic methyl groups present within the isopropylidene protecting group. Furthermore, the absence of any additional signals in this region indicated that the acetal formed was indeed the sole (acetal containing) product, it was therefore concluded that none of the alternative acetal products were formed during the reaction. Greater weight was added to this conclusion when only one set of signals corresponding to a single product was observed in the corresponding ^{13}C NMR spectrum. ^{13}C NMR also provides a sensitive analytical method that enables the quick and easy assaying of the ring size of isopropylidene acetal formed. The chemical shifts of the acetal carbons of both five and six membered acetal rings have been shown to have quite characteristic chemical shifts (as seen in **Figure 4.20**).[200] The observation of a quaternary acetal signal at 109.3 ppm in the ^{13}C NMR spectrum of the product, characteristic as that of a five membered acetal gave positive confirmation that the acetal formed was indeed the desired product, (**144**).



δ = 109 ppm δ = 98 ppm

Figure 4.20

4.3.5.4 The preparation of ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclo-propyl)-1,3-isopropylidene-propan-2-ol (144), (method 2)

The efficient protection of the terminal 1,2-diol functionality present within the carbohydrate starting material (**143**) was also carried out via the alternative transacetalisation method outlined above in Section **4.3.5.2**. The two components (the diol starting material (**143**) and the commercially available acetal, 2,2-dimethoxypropane) were simply stirred together (as a solution in dichloromethane) at room temperature in the presence of a mild acid catalyst (PPTS). The resulting solution was stirred for one hour (whilst monitoring by TLC), at which point the reaction appeared to have reached completion. The solution was treated with aqueous

sodium bicarbonate solution (to neutralise the catalyst), and the product was then extracted with dichloromethane. The solution was dried over magnesium sulfate and solvent removed to yield the crude product (**144**) as a thick creamy oil in 96 % yield. Analysis of the crude product by ^{1}H NMR and ^{13}C NMR, showed that the product was identical to that formed by the previously described procedure (Section **4.3.5.3**). Furthermore, the purity of the product obtained via this alternative procedure was superior to that of the previous method. In fact, the material was clean enough to be used in subsequent reactions without the requirement of additional purification steps such as chromatography.

4.3.5.5 The Attempted Introduction of Amine Functionality

The next step of the synthesis of the desired target molecule (**148**), was the efficient activation of the residual hydroxyl functionality, adjacent to the cyclopropane ring. Activation of this group, hence rendering it a "leaving group" was necessary to enable the efficient introduction of the amine functionality that would be required in the eventual generation of the desired α-amino acid derivative. The proposed synthetic scheme for the introduction of this functionality may be seen schematically in **Figure 4.21**.

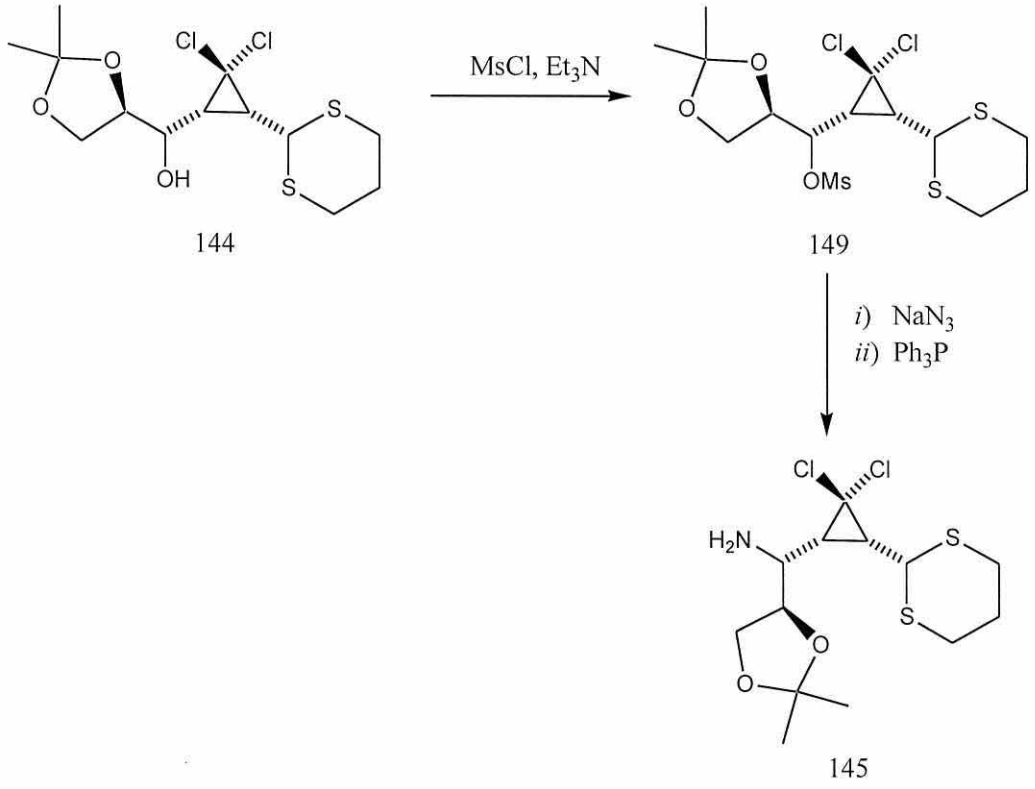
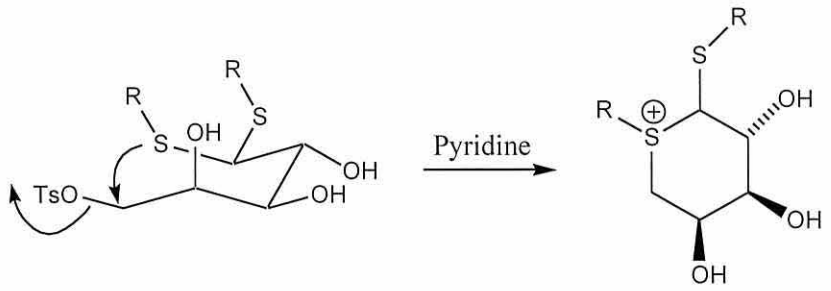


Figure 4.21

The activation of the hydroxyl group by the formation of its mesylate (**149**) was attempted on numerous occasions, but unfortunately was unsuccessful on each attempt. Systematic variation of the reaction conditions employed and even the commercial source of the activating agent (mesyl chloride), all had no effect on the efficiency of the reaction, with near quantitative recovery of the starting material every time. This apparent "unreactivity" was also observed when similar experiments were carried out in an attempt to prepare the analogous tosylate derivative of the same starting material. At this time, in an effort to understand what could be happening, a detailed search of the primary literature was again conducted.

One relevant paper was indeed found,[202] which detailed the facile displacement of activated alcohols (mesylates and tosylates) via an intramolecular nucleophilic attack by the sulfur component of proximal dithioacetals. An example of this interaction, detailed within the paper, including the author's postulated mechanism, may be seen in **Figure 4.22**.



150 151

Figure 4.22

The reaction conditions employed by the authors whilst carrying out reactions of this type were very similar to those employed in the attempted activation of the alcohol functionality within the protected carbohydrate (**150**), i.e. excess mesyl (or tosyl) chloride and a similar excess of a suitable organic base (Et_3N or pyridine). With these points in mind, it may well be postulated that a similar reaction mechanism may be involved during the attempted activation of the present substrate (**144**), consequently eliminating the activated group as it forms. Hydrolysis of the intermediate formed during this reaction (upon aqueous work up) could well give rise to a quantitative regeneration of the original starting material. A possible reaction mechanism (derived from the example seen in **Figure 4.22**) may be seen in **Figure 4.23**. It must be emphasised though, that this mechanism is just a postulate, as evidence either confirming or disproving it has yet to be obtained.

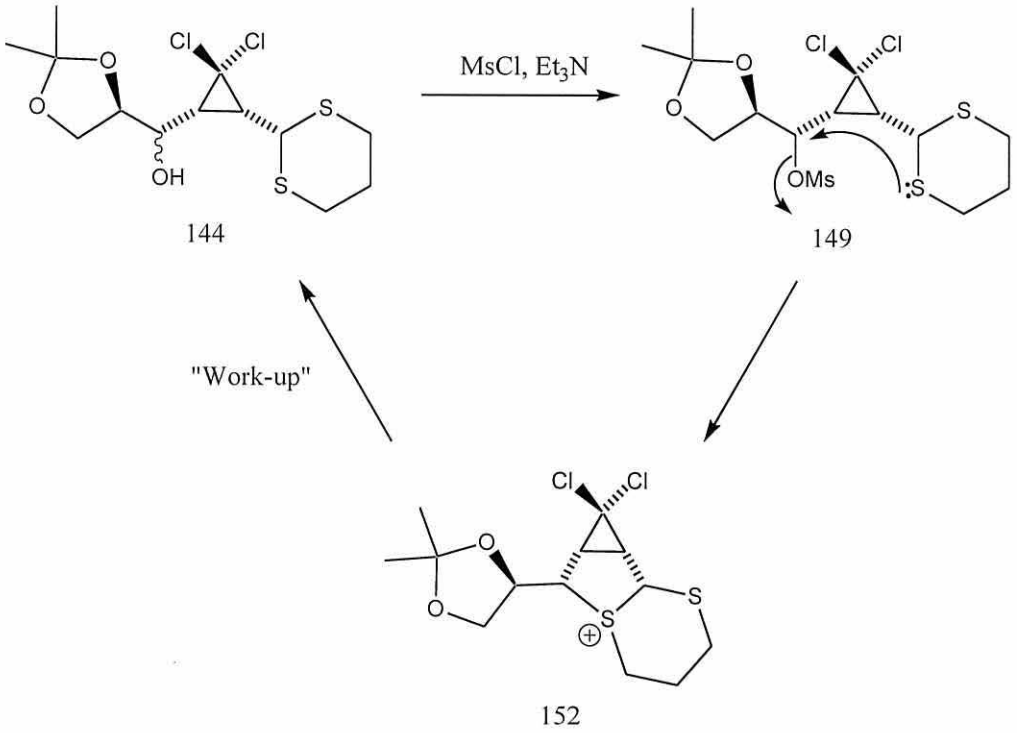


Figure 4.23

4.4 Conclusion

In conclusion, the work discussed throughout this chapter has been moderately successful, as it has enabled the further development of a synthetically useful protocol for the efficient large scale preparation of the commonly employed unsaturated sugar methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**134**). Furthermore, the successful cyclopropanation of (**134**) has enabled the development of useful synthetic routes to the highly functionalised cyclopropane containing building blocks (**143**) and (**144**). It is hoped that the variety of different functionalities that are available as potential reaction sites within these building blocks, will eventually render them extremely versatile in the field of synthetic organic chemistry. Possible avenues of research may include not only the most obvious functionalities of the triol side chain and the halogenated cyclopropane, but more interestingly the subtle chemistries associated with the dithiane functionality and indeed the de-protected aldehyde itself. Indeed, alkylation of either the dithiane or indeed the de-protected aldehyde is an obvious source or attraction, synthetic elaboration of this type could possibly render these building blocks as potential starting materials for larger cyclopropane containing natural products including the fatty acid, lactobacillic acid (**3**), the simple polyacetate

dictyopterenes (**1** and **2**) and a whole range of pyrethroids (**9** – **11**) to mention just a few.

Unfortunately, considerable problems were experienced in the attempted synthesis of the *cis*-α-(carboxycyclopropyl)glycine analogue (**148**), via the synthetic scheme outlined in **Figure 4.17**. Obviously, further work within this area of study could possibly re-examine this synthetic route. A simple revision of the synthetic strategy employed is quite obviously required to enable the desired synthetic elaboration of the individual cyclopropane substituents. Such moves could possibly eliminate intramolecular interactions such as those experienced in the attempted activation of the alcohol functionality in (**144**) and consequently open a simple route to the large scale synthesis of a wide variety of cyclopropane containing amino acids.

Experimental Section

5 Experimental Section

5.1 List of Experiments

5.2 General Considerations

5.2.1 Materials

All chemicals were purchased from Lancaster Synthesis Ltd., Aldrich Chemical Co. Ltd., or Avocado Chemical Co. Ltd., and were used either as received, or after purification as suggested by Perrin and Armarego.[203] Diethyl ether, THF and DME were distilled from sodium and benzophenone, whilst dichloromethane and 1,2-dichloroethane were distilled from calcium hydride. Petrol refers to the fraction of light petroleum collected between 40 and 60 °C and was used without further purification.

5.2.2 Techniques

Unless otherwise stated, all reactions were conducted in oven-dried glassware under a static atmosphere of either dry argon or nitrogen. Organic solutions were dried over anhydrous magnesium sulfate and bulk solvents were removed at 14 mmHg; residual traces of solvent were subsequently removed at 0.1 mmHg. Column chromatography was conducted under medium pressure using silica gel (Kieselgel 230 – 400 mesh); thin layer chromatography (TLC) was carried out on pre-coated Kieselgel 60 F254 (Art. 5554; Merck) plates.

5.2.3 Instrumentation

Routine gas liquid chromatography (GLC) was performed using a temperature programmable Carlo Erba HRGC 5300 Mega Series instrument equipped with a 30 m, 0.25 mm internal diameter DB5 liquid phase capillary column. The column was fitted with a Carlo Erba FID - 40 flame ionisation detector and operated using nitrogen as the carrier gas. Chiral GLC was carried out using an isothermal Perkin Elmer Sigma 4 instrument fitted with a 25 m, 0.25 mm internal diameter heptakis-(3-*O*-acetyl-2-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin capillary column. The column had a splitless injector employing helium as the carrier gas; the column was fitted with a Perkin Elmer flame ionisation detector. Infra red spectra were recorded as KBr discs (solids) and as thin films (liquids) on NaCl windows using a Perkin Elmer 1600 series FT-IR spectrometer. Melting points were measured using a Gallenkamp melting point

apparatus and are uncorrected. Optical rotations were measured as solutions of known concentration (as stated) using a Polaar 2001 automatic polarimeter. Routine NMR [^{1}H NMR (250.133 MHz), ^{13}C{^{1}H} NMR (62.896 MHz)] spectra were recorded at room temperature on a Bruker AC 250 spectrometer as solutions in deuterated chloroform ($CDCl_3$). All chemical shifts are quoted in δ relative to the trace resonance of protonated chloroform (δ 7.25 ppm), and $CDCl_3$ (δ 77.0 ppm), all coupling constants (*J*) are quoted in Hz. Low resolution mass spectra using both electron impact (EI) and chemical ionisation (CI) (using NH_3 as the reagent gas) were measured at 70 eV on a Finnigan MAT 8430 spectrometer; accurate mass determinations were carried out at the EPSRC National Mass Spectrometry Service, University of Wales, Swansea. Elemental analysis was carried out by Mr G. Connolly (U.W.B) using a Carlo Erba EA1108 elemental analyser (using helium as the carrier gas).

5.3 Experimental

5.3.1 The preparation of (+)-dehydroabietylamine acetate

A solution of glacial acetic acid (17 ml) in toluene (150 ml) was added dropwise over a period of 40 minutes to a cooled (0 °C) solution of 60 % (+)-dehydroabietylamine (70.00 g, 0.245 mol) in toluene (400 ml). The resulting solution was stirred at 10 °C for 2 hours and the precipitate formed was collected under reduced pressure, washed with ice cold toluene (150 ml) and air dried. The waxy white solid was recrystallised from refluxing toluene (300 ml) to yield *(+)-dehydroabietylamine acetate* (55.25 g, 0.16 mol, 52 %) as fine white needle-shaped crystals, mp 141 - 3 °C, $[\alpha]_D^{22}$ +50.0 ° (c 5.0, pyridine); all other analytical data was concordant with the literature.[118]

5.3.2 The regeneration of (+)-dehydroabietylamine (75)

Dehydroabietylamine acetate (50.00 g, 0.145 mol) was dissolved in warm deionised water (150 ml) and the solution was cooled to room temperature before adding a 10 % aqueous solution of sodium hydroxide (120 ml). The resulting solution was stirred for 1 hour before extracting the free amine into diethyl ether (2 × 250 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and reduced in volume under reduced pressure. Residual solvent was removed *in-vacuo* (0.1 mmHg) to yield

(+)-dehydroabietylamine (39.65 g, 0.138 mol, 96 %) as a highly viscous yellow oil that crystallised slowly over an extended period (3 weeks), $[\alpha]_D^{22}$ +40.1 ° (c 1.0, ethanol); all other analytical data was concordant with the literature.[118]

5.3.3 The preparation of diazomethane[204]

Caution: Diazomethane is highly toxic and has been known to explode,[205] known detonation initiators include, rough glass surfaces, alkali metals and strong light. This preparation should be carried out within an efficient fume hood with all apparatus shielded behind a suitable blast shield. The apparatus used in the following preparation, a one piece distillation unit (with no ground glass joints) equipped with a Teflon™ tapped dropping funnel (introduced into the reaction vessel through a bored rubber stopper) was carefully checked for chips, cracks or uneven edges prior to use.

Potassium hydroxide (5.0 g, 90 mmol) was dissolved in deionised water (8 ml) and diluted with absolute ethanol (25 ml). The resulting solution was carefully transferred to the reaction flask of the apparatus and warmed to 60 ± 5 °C whilst being stirred magnetically. A solution of Diazald™[206] (21.5 g, 0.1 mol) in diethyl ether (250 ml) was then added to the reaction flask in small portions. The product was co-distilled as a yellow - green ethereal solution into an ice cooled receiver. When addition was complete, the dropping funnel was rinsed with diethyl ether (10 ml) and the washings added to the reaction vessel. Distillation was continued until any yellow coloration had disappeared. Upon completion, the product, a yellow green solution that contains approximately 80 mmol of diazomethane was stored in a corked glass bottle within a freezer.

The glassware used in this preparation was rinsed with a solution of acetic acid before normal washing.

5.3.4 The preparation of methyl 2,2-dibromo-1-methylcyclopropanecarboxylate (74)

A 1 litre three-necked flask equipped for mechanical stirring, reflux and addition was charged with methyl methacrylate (50 g, 0.5 mol), dichloromethane (100 ml), bromoform (190 g, 0.75 mol) and benzyl triethylammonium chloride (5.0g, 20 mmol, PTC). To the rapidly stirred solution, 50 % aqueous sodium hydroxide solution was added taking care not to allow the internal temperature to rise above 25 °C. The

resulting solution was then stirred at room temperature whilst monitoring by GLC. After 6 hours the reaction mixture was poured onto iced water (1 litre) and the resulting solution was stirred for a further 20 minutes. The two-phase solution was separated and the aqueous layer extracted with dichloromethane (2 × 500 ml), the combined organic fractions were washed with saturated brine solution (2 × 200 ml) and water (200 ml). The organic phase was reduced in volume under reduced pressure and the residue dissolved in petrol (250 ml). The solution was dried over anhydrous magnesium sulfate, filtered through a pad of celite and the filtrate reduced in volume to yield the crude product as a straw coloured oil. The crude product was purified by flash distillation at reduced pressure and the title compound was recovered as a colourless oil (114.4 g, 0.44 mol, 89 %), bp 92 °C at 14 mmHg, (lit.,[151] bp 42 °C at 0.2 mmHg).

δ_H	3.8 (3H, s, OMe), 2.40 (1H, d, *J* 7.8 Hz), 1.59 (3H, s, Me), 1.57 (1H, d, *J* 7.8 Hz)
δ_C	159.8, 52.7, 34.8, 32.7, 29.8, 20.7
ν_{max}/cm^{-1}	2998, 2950, 1736, 1453, 1434, 1316, 1277, 1161, 1031, 689, 657
m/z	270 $(M)^+$, 239 (M - OMe)

5.3.5 The preparation of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (71)

A 500 ml round bottomed flask equipped for magnetic stirring and reflux was charged with methyl 2,2-dibromo-1-methylcyclopropanecarboxylate (50.0 g, 0.18 mol) and 48% aqueous hydrobromic acid (150 ml); the resulting solution was stirred at reflux for 4 hours before cooling and stirring overnight at room temperature. The product, a cream coloured solid, was recovered by filtration and dissolved in diethyl ether (200 ml). The resulting solution was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product was recrystallised from propanone to yield *2,2-dibromo-1-methylcyclopropanecarboxylic acid* as a white crystalline solid (44.83 g, 0.17 mol, 94 %), mp 110 - 112 °C, (lit.,[207] mp 109 °C).

δ_H	2.43 (1H, d, *J* 7.9 Hz), 1.64 (3H, s, Me), 1.61 (1H, d, *J* 7.9 Hz)
δ_C	175.5, 34.6, 33.13, 29.46, 20.72
ν_{max}/cm^{-1}	3100 - 2400 (broad O-H), 2936, 1706, 1455, 1414, 1317, 1032, 941;
m/z	256 $(M)^+$

Found: C, 23.27; H, 2.33 %. Calc. for $C_5H_6O_2Br_2$: C, 23.30; H, 2.30 %

5.3.6 The resolution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (71) using (+)-dehydroabietylamine (75)

A hot solution of freshly purified dehydroabietylamine (5.73 g, 20 mmol) in methanol (100 ml) was added to a stirred hot solution of racemic, 2,2-dibromo-1-methylcyclopropanecarboxylic acid (20.50 g, 80 mmol) in aqueous methanol (water 20 ml, methanol 80 ml). The solution was stirred for approximately one minute until the first signs of crystallisation were observed. Stirring was then stopped and the solution cooled to room temperature over a period of 3 hours, allowing complete crystallisation. The crystals were collected by suction filtration, washed with ice-cold methanol (10 ml) and allowed to dry in the air. The product, a salt of compositional ratio 2:1 (acid - amine) was recovered as finely divided white crystalline needles (13.06 g, 16.2 mmol). The corresponding methyl ester of the free acid, (generated on small scale, by treatment with aqueous NaOH) exhibited an enantiomeric excess of 93 % (-). Recrystallisation of the salt from refluxing aqueous methanol (10 % H_2O, 90 % MeOH) (150 ml) afforded the enantiomerically enriched salt as a fine white crystalline solid (9.11 g, 11.3 mmol); mp 209 - 210 °C; $[\alpha]_D^{20}$ -9.4° (c 0.472, MeOH); Found: C 45.1; H 5.5; N 1.6 %. Calculated for $C_{30}H_{43}Br_4NO_4$: C 44.97; H 5.41; N 1.75 %.

The enriched amine salt (9.11 g, 11.3 mmol) was treated with 10 % aqueous sodium hydroxide solution (100 ml) and dichloromethane (100 ml); the resulting biphasic solution was stirred until all solids had dissolved. The solution was then separated and the organic solution was extracted with 10 % aqueous sodium hydroxide solution (50 ml), the combined aqueous fractions were washed with dichloromethane (50 ml) and then acidified with 20 % sulfuric acid. The acidified solution was extracted with ethyl acetate (2 × 150 ml), dried over anhydrous magnesium sulfate, filtered and solvent removed to yield enantiomerically pure *(1S)-2,2-dibromo-1-methylcyclopropane carboxylic acid* as a white crystalline solid (5.59 g, 21.7 mmol, 28 %), mp 62 - 62.5 °C, $[\alpha]_D^{20}$ -55.1 ° (c 1.015, $CHCl_3$). All other spectroscopic data was identical to that quoted previously [***5.3.5***]. Chiral GLC analysis of the corresponding methyl ester (prepared on small scale by the addition of ethereal diazomethane) showed an enantiomeric excess greater than 99 %.

The combined mother liquors (from the initial crystallisation) were condensed to approximately half volume (175 ml) under reduced pressure and allowed to cool slowly to room temperature. After 12 hours, a second crop of crystals (2.21 g, 2.8 mmol) was collected, acid regenerated from this crop showed an enantiomeric excess of 60 % (-). Solvent was removed from the remaining mother liquor under reduced pressure and the remaining salt was treated with 10 % aqueous sodium hydroxide solution (200 ml) and dichloromethane (200 ml). The biphasic solution was stirred at room temperature until all solid had dissolved, the resulting solution was separated and the organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml). The combined aqueous fractions were washed with dichloromethane (50 ml) and acidified with 20 % sulfuric acid, the acidified solution was extracted with ethyl acetate (2 × 150 ml) and the organic phase dried over anhydrous magnesium sulfate, filtered and solvent removed to yield enantiomerically enriched *(1R)-2,2-dibromo-1-methylcyclopropanecarboxylic acid* as a cream - white crystalline solid which showed an enantiomeric excess of 48 % (+).

Further enantiomeric enrichment of the acid was carried out by slow recrystallisation from refluxing *n*-hexane (10 ml). The solution was allowed to cool and after 15 hours at 5 °C the mother liquor was decanted from the crystallised racemic acid (6.51 g, 25.3 mmol). The remaining mother liquor was evaporated to yield a colourless oil that crystallised overnight to yield *(1R)-2,2-dibromo-1-methylcyclopropanecarboxylic acid* (5.88 g, 22.8 mmol, 29 %) as a white crystalline solid, mp 62 - 62.5 °C, $[\alpha]_D^{20}$ +54.7 ° (c 1.089, $CHCl_3$). All other spectroscopic data was identical to that quoted previously [***5.3.5***]. Chiral GLC analysis of the corresponding methyl ester (prepared on small scale by the addition of ethereal diazomethane) showed an enantiomeric excess of 99 %.

5.3.7 The preparation of 2,2-dibromo-1-vinylcyclopropane (82)

A 2 litre three-necked flask equipped for addition and mechanical stirring at low temperature (dry ice condenser) was charged with a suspension of ground potassium *t*-butoxide (61.6 g, 0.50 mol) in dry pentane (400 ml). The flask was cooled to -30 °C before adding condensed 1,3-butadiene (27.0 g, 0.50 mol) by syringe. The resulting solution was stirred vigorously while a solution of bromoform (131.0 g, 0.50 mol) in dry pentane (200 ml) was added dropwise over 90 minutes. The reaction mixture was

stirred for a further 90 minutes at -30 °C, before being allowed to warm slowly to room temperature whilst stirring overnight. The reaction mixture was then cooled (0 °C) before adding water (500 ml) to the reaction vessel. The resulting solution was separated and the aqueous layer extracted with pentane (3 × 100 ml). The combined organic fractions were washed with brine solution, dried over anhydrous magnesium sulfate, filtered and excess pentane removed *in-vacuo*. The residue was distilled to yield the product, *2,2-dibromo-1-vinylcyclopropane* (82.08 g, 0.36 mol, 73 %) as a colourless liquid; bp 48 - 50 °C at 7 mmHg, (lit., [208] bp 69.5 °C at 26 mmHg).

δ_H	5.57 (1H, ddd, *J* 17.0, 9.9, 8.0 Hz), 5.34 (1H, dd, *J* 17.0, 1.5 Hz), 5.29 (1H, dd, *J* 9.9, 1.5 Hz), 2.30 (1H, ddd, *J* 10.2, 8.0, 7.7 Hz), 1.97 (1H, dd, *J* 10.2, 7.4 Hz), 1.58 (1H, dd, *J* 7.7, 7.4 Hz)
δ_C (dept)	135.8(+), 118.8(-), 34.26(+), 29.4(-), 25.2(.)
ν_{max}/cm^{-1}	3086, 1636, 1431, 1418, 1214, 1188, 1105, 1046, 1010, 983, 917, 717.

5.3.8 The preparation of 2,2-dibromocyclopropanecarboxylic acid (72); Method I, the oxidation of 2,2-dibromo-1-vinylcyclopropane

A 5 litre flange flask equipped for mechanical stirring was charged with a solution of 2,2-dibromo-1-vinylcyclopropane (74.0 g, 0.33 mol) and n-hexadecyl trimethylammonium chloride (3.2 g, 10 mmol, PTC) in dichloromethane (1 litre) and water (1 litre). The solution was then cooled to 0 °C whilst 9 M sulfuric acid (120 ml) was added in small portions over 30 minutes. Solid potassium permanganate (156.5 g, 0.99 mol) was then added to the stirred solution in small portions ensuring that the reaction temperature did not rise above 5 °C. The reaction was then allowed to warm to room temperature and was stirred for a further 24 hours.

The reaction vessel was cooled to 0 °C before 50 % aqueous sulfuric acid (400 ml) was carefully added; sodium sulfate (as required to reduce manganese by products) was then added in small portions. The resulting straw coloured solution was stirred for 10 minutes before being separated and the aqueous phase extracted with dichloromethane (2 × 400 ml). The combined organic fractions were washed with saturated brine solution and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in-vacuo* to yield the crude product as a creamy paste which was recrystallised from hexane-benzene (5:2) to yield *2,2-*

dibromocyclopropanecarboxylic acid, (59.5 g, 0.24 mol, 74 %) as a white crystalline solid, mp 94 - 95 °C, (lit.,[208] mp 95 °C)..

δ_H	10.65 (1H, bs), 2.64 (1H, dd, *J* 9.6, 7.7 Hz), 2.19 (1H, dd, *J* 7.7, 7.6 Hz), 2.09 (1H, dd, *J* 9.6, 7.6 Hz)
δ_C	173.2(.), 33.1(+), 28.7(-), 19.7(.)
ν_{max}/cm^{-1}	3092, 2924, 2667, 2584, 1722, 1459, 1410, 1377, 1353, 1252, 1201, 1102, 1074, 922, 722, 668
m/z	260 $(M + NH_4)^+$, 199 $(M - CO_2)$

5.3.9 The preparation of 2,2-dibromo-1-phenylcyclopropane (83)

A 50 ml round bottomed flask fitted with a reflux condenser was charged with finely powdered sodium hydroxide (2.4 g, 60 mmol), a solution of styrene (1.04 g, 10 mmol) in dichloromethane (10 ml) was added and the flask immersed into the water bath of an ultrasonic cleaning bath (47 kHz, 160 W). The flask was positioned approximately 1 cm above the centre of the ultrasonic horn; the bath was filled with water so that the level was equal to that of the solvent within the flask. *n*-Hexadecyltrimethylammonium bromide (100 mg, 0.1 mmol, PTC) and bromoform (3.8 g, 15 mmol) were added to the flask and the resulting solution was subjected to ultrasonic irradiation at room temperature for 2 hours. The reaction mixture was filtered through a pad of celite that was washed with dichloromethane (25 ml) after the filtration. All volatiles were removed *in-vacuo* and *2,2-dibromo-1-phenylcyclopropane* was isolated by distillation under reduced pressure as a colourless oil (1.29 g, 4.7 mmol, 47 %); bp 82 °C at 0.1 mmHg, (lit.,[50a] bp 94 °C at 2 mmHg).

δ_H.	7.5 - 7.3 (5H, m, Ar H), 3.98 (1H, t, *J* 9.1 Hz), 2.15 (1H, t, *J* 9.1 Hz), 2.03 (1H, t, *J* 9.1 Hz)
δ_C (dept)	137.1(.), 128.9(+), 128.3(+), 127.6(+), 35.9(+), 28.5(.), 27.2(-)
ν_{max}/cm^{-1}	3084, 3060, 3030, 1947, 1873, 1800, 1740, 1603, 1496, 1450, 1423, 1224, 1107, 1039, 940, 760, 735, 697

5.3.10 The preparation of 2,2-dibromocyclopropanecarboxylic acid (72); Method II, the oxidation of 2,2-dibromo-1-phenylcyclopropane

A 10 ml round bottomed flask was charged with 2,2-dibromo-1-phenylcyclopropane (200 mg, 0.73 mmol), carbon tetrachloride (2 ml), acetonitrile (2 ml) and water (3 ml). The resulting solution was stirred at room temperature as ruthenium (III) chloride hydrate (3.5 mg, 0.01 mmol) and periodic acid (865 mg, 3.8 mmol) were added. The solution was stirred at room temperature for 30 minutes before bringing to reflux and stirring overnight. The solution was cooled to room temperature and diluted with diethyl ether (10 ml) and water (10 ml), the two phases were separated and the aqueous layer extracted with diethyl ether (5 ml). The combined organic solutions were washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered and solvent removed under reduced pressure. *2,2-Dibromocyclopropanecarboxylic acid* was recovered as a cream solid (145 mg, 0.59 mmol, 81 %); all spectroscopic data was identical to that quoted previously [***5.3.8***].

5.3.11 The preparation of 3-(1-methoxy-1-methylethoxy)-propene (84)

A 1 litre round bottomed flask equipped for magnetic stirring was charged with allyl alcohol (80 g, 1.38 mol) in diethyl ether (250 ml) and the resulting solution was cooled to 0 °C before adding pyridinium *p*-toluenesulfonate (6.7 g, 26 mmol). 2-Methoxypropene (149.3 g, 196 ml, 2.07 mol) was then carefully added to the stirred solution maintaining an internal temperature less than 5 °C. The reaction mixture was stirred at room temperature whilst monitoring by TLC; after 30 minutes no starting material remained. The reaction was quenched by adding saturated sodium bicarbonate solution (25 ml) and water (50 ml); the biphasic solution was separated and the organic phase washed with saturated sodium bicarbonate solution (10 ml) and water (50 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed under reduced pressure (water aspirator). *3-(1-Methoxy-1-methylethoxy)-propene* was recovered as a colourless solution (164.2 g, 1.26 mol, 91 %); analytical data showed good agreement with that quoted in the literature.[208b]

δ_H 5.86 (1H, ddt, *J* 17.1, 10.3, 5.5 Hz), 5.21 (1H, ddt, *J* 17.1, 1.7, 1.5 Hz), 5.09 (1H, ddt, *J* 10.3, 1.5, 1.5 Hz), 3.89 (2H, ddt, *J* 5.5,1.7, 1.5 Hz), 3.14 (3H, s, OMe), 1.31 (6H, s, 2Me)

δ_C (dept) 135.2(+), 115.9(-), 100.1(.), 61.9(-), 48.4(+), 24.4(+)

ν_{max}/cm^{-1} 2991, 2942, 2869, 1647, 1463, 1379, 1214, 1075, 1044, 919, 859

5.3.12 The preparation of 2,2-dibromo-1-hydroxymethylcyclopropane (86)

A 2 litre three-necked round bottomed flask equipped for mechanical stirring, reflux and addition was charged with bromoform (253 g, 89.5 ml, 1.0 mol), *n*-hexadecyltrimethylammonium bromide (10 g, 30 mmol, PTC) and dichloromethane (200 ml). Triethylamine (4 drops) was added to neutralise the slightly acidic solution that changed from pale yellow when acidic to colourless when neutral. The resulting solution was then cooled to 0 °C before freshly prepared 3-(1-methoxy-1-methylethoxy)-propene (85 g, 0.65 mol) was added. Aqueous sodium hydroxide (265 g, 6.6 mol in 265 ml) was added to the rapidly stirred solution over a period of 2 hours maintaining an internal temperature less than 15 °C. The resulting solution was stirred for 48 hours taking great care not to allow the internal temperature of the reaction to rise above 15 °C.

The reaction was quenched by diluting the reaction mixture with dichloromethane (500 ml) and saturated brine solution (500 ml). The resulting biphasic solution was stirred vigorously for 90 minutes before separating and extracting the aqueous layer with dichloromethane (2 × 100 ml). The combined organic solutions were washed with brine solution (250 ml) and water (500 ml) and reduced in volume under reduced pressure. The residue was re-dissolved in petrol/diethyl ether (500 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered through a pad of celite; subsequent removal of solvent *in-vacuo* yielded the protected product, *1,1-dibromo-2-(1-methoxy-1-methylethoxymethyl)-cyclopropane* as a yellow brown viscous oil (163.3 g, 0.54 mol, 83 %).

The protected alcohol (163.3 g, 0.54 mol) was dissolved in methanol (500 ml) and water (50 ml) and treated with *p*-toluenesufonic acid (15.0 g, 79 mmol). The resulting solution was stirred at room temperature for 3 hours before saturated sodium bicarbonate solution (250 ml) and diethyl ether (500 ml) was added. The biphasic solution was stirred vigorously for 30 minutes before separation, the aqueous solution was extracted with diethyl ether (2 × 100 ml) and the combined organic solutions were washed with water (250 ml) before drying over anhydrous magnesium sulfate. The dry solution was concentrated *in-vacuo* and the product isolated by distillation under

reduced pressure. *2,2-Dibromo-1-hydroxymethylcyclopropane* was recovered (111.2 g, 0.48 mol, 90 %) as a colourless liquid, bp 51 °C at 0.3 mmHg, (lit.,[208b] bp 58 °C at 0.5 mmHg).

δ_H	3.87 (1H, dd, *J* 12.2, 5.1 Hz), 3.57 (1H, dd, *J* 12.2, 8.5 Hz), 1.97 (1H, dddd, *J* 10.4, 8.5, 7.3, 5.1 Hz), 1.76 (1H, dd, *J* 10.4, 7.3 Hz), 1.39 (1H, t, *J* 7.3 Hz)
δ_C	64.9, 32.4, 26.5, 25.9
ν_{max}/cm^{-1}	3345, 3000, 2932, 2877, 1432, 1388
m/z	245 $(M + NH_4)^+$

5.3.13 The preparation of 2,2-dibromocyclopropanecarboxylic acid (72); Method III, the oxidation of 2,2-dibromo-1-hydroxymethylcyclopropane

A 5 litre flange flask equipped for mechanical stirring was charged with a solution of 2,2-dibromo-1-hydroxymethylcyclopropane (80.0 g, 0.35 mol) and benzyl triethylammonium chloride (16.0 g, 70 mmol, PTC) in benzene (800 ml). Aqueous potassium permanganate solution (276.6 g, 1.75 mol in 2 litres of water) was then added to the vigorously stirred solution in small portions ensuring that the reaction temperature did not rise above 15 °C. The reaction was then stirred at room temperature overnight.

The reaction vessel was cooled to 0 °C before 50 % aqueous sulfuric acid (800 ml) was carefully added; sodium sulfate (as required to reduce manganese by products) was then added in small portions. The resulting straw coloured solution was stirred for 1 hour before being separated and the aqueous phase extracted with ethyl acetate (2 × 500 ml). The combined organic fractions were washed with saturated brine solution and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in-vacuo* to yield the crude product as a creamy white solid. The crude product was recrystallised from hexane - benzene (5:2) to yield *2,2-dibromocyclopropanecarboxylic acid* (79.8 g, 0.32 mol, 94 %) as white crystals, mp 94 - 95 °C, all spectroscopic data was identical to that quoted previously [***5.3.8***].

5.3.14 The resolution of 2,2-dibromocyclopropanecarboxylic acid (72) using (+)-dehydroabietylamine (75)

A hot solution of freshly purified (+)-dehydroabietylamine (11.2 g, 0.039 mol) in methanol (30 ml) was added quickly to a hot solution of racemic 2,2-dibromocyclopropanecarboxylic acid (76.5 g, 0.314 mol) in methanol (185 ml) and water (400 ml). After 15 hours at room temperature, the solid formed was filtered from the mother liquor, washed with cold (0 °C) methanol - water (1:1, 50 ml) and dried *in-vacuo* to yield a white crystalline salt (42.4 g). The salt was treated with 10 % aqueous sodium hydroxide solution (50 ml) and chloroform (200 ml) to enable the regeneration of the optically enriched acid. The resulting biphasic solution was stirred until all solids had dissolved. The solution was then separated and the organic layer extracted with 10 % aqueous sodium hydroxide solution (50 ml). The combined aqueous fractions were washed with chloroform (50 ml) and acidified with 20 % sulfuric acid (45 ml, 0.100 mol). The acidified solution was extracted with chloroform (3 × 150 ml) and the organic phase was dried over anhydrous magnesium sulfate. The dried solution was filtered and solvent removed to yield enantiomerically enriched *(1S)-2,2-dibromocyclopropanecarboxylic acid* as a viscous colourless liquid (18.5 g, 76 mmol, 24 %). Chiral GLC analysis of the corresponding methyl ester (prepared on small scale by the addition of ethereal diazomethane) showed an enantiomeric excess of 75 %.

Enantiomeric enrichment of the acid was carried out by slow recrystallisation from refluxing *n*-hexane (60 ml). After 15 hours at 5 °C, the mother liquor was decanted from any solids and solvent removed *in-vacuo* to yield *(1S)-2,2-dibromocyclopropanecarboxylic acid* as a viscous colourless liquid (12.6 g, 51.7 mmol, 17 %). Chiral GLC analysis of the corresponding methyl ester showed an enantiomeric excess of 96 %.

Further enrichment of *(1S)-2,2-dibromocyclopropanecarboxylic acid*, to greater than 99 % ee was carried out by recrystallisation of the acid (5.00 g, 20.5 mmol) with (+)-dehydroabietylamine (0.74 g, 2.56 mmol) from aqueous methanol as highlighted in the first paragraph of this procedure. The product, a salt of the ratio 2:1 (acid - amine) was recovered as finely divided white crystalline needles (1.92 g, mmol); mp 180 - 182 °C; Found: C 43.30, H 5.19, N 1.68 %. Calculated for $C_{28}H_{39}Br_4NO_4$: C 43.49, H 5.08, N 1.81 %.

Subsequent acid regeneration as highlighted above yielded *(1S)-2,2-dibromocyclopropanecarboxylic acid* (1.18 g, 4.8 mmol) as a white crystalline solid, mp 62 - 64 °C, $[\alpha]_D^{20}$ -138.2 ° (c 0.982, $CHCl_3$). Chiral GLC analysis of the corresponding methyl ester showed an enantiomeric excess of greater than 99 %, all spectroscopic data was identical to that quoted previously for the racemate [***5.3.8***].

The combined mother liquors (from the original recrystallisation) were evaporated at reduced pressure and the resulting solid was treated with chloroform (200 ml) and 10 % aqueous sodium hydroxide solution (150 ml). The resulting biphasic solution was shaken until all solid had dissolved; the aqueous layer was washed with chloroform (100 ml) and then acidified with 20 % aqueous sulfuric acid (100 ml). The acidified solution was extracted with chloroform (3 x 200 ml) and the combined organic fractions were dried over anhydrous magnesium sulfate, filtered and solvent was removed to yield *(1R)-2,2-dibromocyclopropanecarboxylic acid* (55.4 g) as a cream coloured solid. Analysis of the corresponding methyl ester by chiral GLC showed that the acid had an enantiomeric excess of 25 %.

Enantiomeric enrichment of this acid was carried out by dissolving the acid in boiling hexane (150 ml), the resulting solution was cooled and stored overnight at 5 °C. The supernatant solution was decanted from the crystals formed and solvent removed to yield *(1R)-2,2-dibromocyclopropanecarboxylic acid* (10.1 g, 41.4 mmol) as a viscous colourless liquid that crystallised over a number of weeks. The product was recovered as a white crystalline solid, mp 61 - 63 °C, $[\alpha]_D^{20}$ +132.9° (c 1.104, $CHCl_3$). Analysis of the corresponding methyl ester by GLC showed that the acid had an enantiomeric excess of 96 %. All other analytical data was identical to that quoted for the racemate [***5.3.8***].

5.3.15 The resolution of 2,2-dibromocyclopropanecarboxylic acid (72) using (+)-α-methylbenzylamine (87)

A hot solution of (+)-α-methylbenzylamine (12.1 g, 100 mmol) in absolute ethanol (50 ml) was added quickly to a hot solution of racemic 2,2-dibromocyclopropanecarboxylic acid (24.4 g, 100 mmol) in absolute ethanol (75 ml). The resulting solution was swirled briefly before being allowed to cool to room temperature. After 6 hours at room temperature crystallisation was apparent and the solution was stored overnight at 10 °C. The crystals formed were removed from the

supernatant by filtration, washed with cold (0 °C) absolute ethanol (50 ml) and dried *in-vacuo* to yield a white crystalline salt (16.1 g), recrystallisation from hot ethanol afforded a highly crystalline white solid (14.6 g), mp 141 – 143 °C, Found: C 39.15, H 4.16, N 3.91 %. Calculated for $C_{12}H_{15}Br_2NO_2$: C 39.48, H 4.14, N 3.84 %.

The salt was treated with 10 % aqueous sodium hydroxide solution (40 ml) and chloroform (50 ml) enabling the regeneration of the optically enriched acid. The resulting biphasic solution was shaken until all solid had dissolved, the solution was separated and the organic layer extracted with 10 % aqueous sodium hydroxide solution (2 × 10 ml). The combined aqueous fractions were washed with chloroform (2 × 10 ml) and acidified with 20 % sulfuric acid (30 ml). The acidified solution was extracted with chloroform (3 × 50 ml) and the organic phase was dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield enantiomerically enriched (1*S*)-2,2-dibromocyclopropanecarboxylic acid as a viscous colourless liquid (9.15 g, 38 mmol, 38 %). Chiral GLC analysis of the corresponding methyl ester (prepared on small scale by the addition of ethereal diazomethane) showed an enantiomeric excess of 98 %.

The original mother liquor was reduced in volume and treated with 10 % aqueous sodium hydroxide solution and chloroform to enable the regeneration of optically enriched starting material (13.14 g, 54 mmol). Subsequent treatment with (-)-α-methylbenzylamine (6.50 g, 54 mmol) in hot absolute ethanol (as above) furnished *(1R)-2,2-dibromocyclopropanecarboxylic acid* (7.29 g, 30 mmol, 30 %). Chiral GLC analysis of the corresponding methyl ester (prepared on small scale by the addition of ethereal diazomethane) showed an enantiomeric excess of 96 %.

5.3.16 The preparation of 2,2-dibromocyclopropanecarbonyl chloride (90)

A 50 ml round bottomed flask was charged with to 2,2-dibromocyclopropanecarboxylic acid (24.4 g, 0.1 mol); thionyl chloride (25 ml, 0.34 mol) was added and the resulting solution was stirred at room temperature for 4 hours. Excess thionyl chloride was removed by simple distillation, *2,2-dibromocyclopropanecarbonyl chloride* was recovered by distillation under reduced pressure as a pungent, tan coloured oil (24.2g, 0.92mmol, 92 %), bp 47 – 49 °C at 0.9 mmHg, (lit.,[208b] bp 48 -50 °C at 1.0 mmHg).

δ_H	3.12 (1H, dd, *J* 9.2, 7.6 Hz), 2.27 (1H, dd, *J* 7.9, 7.6 Hz), 2.18 (1H, dd, *J* 9.2, 7.9 Hz)
δ_C (dept)	170.8(.), 42.6(+), 31.2(-), 19.5(.)
ν_{max}/cm^{-1}	3010, 1779, 1416, 1346, 1104, 1001, 837, 689

5.3.17 The preparation and chromatographic resolution of 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (92)

A 25 ml round bottomed flask was charged with a 10 % solution of racemic 2,2-dibromocyclopropanecarbonyl chloride (1.0 g, 3.8 mmol) in HPLC grade chloroform (10 ml). The solution was cooled to 0 °C, before optically pure (+)-α-methylbenzylamine (1.01 g, 8.4 mmol) was added dropwise to the stirred solution. The reaction mixture was warmed to room temperature and stirred while monitoring by TLC, after 3 hours no starting material remained and the reaction was quenched by cooling the solution to 0 °C and carefully adding water (5 ml) dropwise. The resulting solution was stirred vigorously for 5 minutes before separation of the biphasic solution. The aqueous phase was subsequently extracted with dichloromethane (2 × 5 ml) and the combined organic fractions washed with 5 % hydrochloric acid solution (10 ml), saturated sodium bicarbonate solution (5.0 ml) and water (5.0 ml). The resulting organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the crude product as a thick colourless oil that solidified overnight yielding an off white powdery solid (1.24 g, 3.6 mmol, 94 %), mp 114 - 116 °C. Chromatographic separation of the two diastereomeric components was readily achieved by flash column chromatography with each diastereomer eluting separately (R_f = 0.39 and 0.52) with a solution of petrol:ether (1:1).

$\delta_{H\ (Rf=0.52)}$	7.35 (5H, m), 6.1 (1H, bs), 5.14 (1H, pentet, *J* 7.6 Hz), 2.35 (1H, dd, *J* 9.7, 7.5 Hz), 2.20 (1H, t, *J* 7.5 Hz), 1.92 (1H, dd, *J* 9.7, 7.5 Hz), 1.60 (3H, d, *J* 7.6 Hz)
$\delta_{C\ (Rf=0.52)}$	164.4, 142.6, 128.7, 127.6, 126.4, 49.9, 34.9, 26.6, 21.7, 21.2
$\delta_{H\ (Rf=0.39)}$	7.35 (5H, m), 6.1 (1H, bs), 5.14 (1H, pentet, *J* 7.6 Hz), 2.42 (1H, dd, *J* 9.7, 7.5 Hz), 2.26 (1H, t, *J* 7.5 Hz), 1.95 (1H, dd, *J* 9.7, 7.5 Hz), 1.59 (3H, d, *J* 7.6 Hz)
$\delta_{C\ (Rf=0.39)}$	164.5, 142.4, 128.7, 127.6, 126.4, 49.6, 35.0, 26.6, 21.4, 20.9

ν_{max}/cm^{-1} 3286, 3086, 3063, 3030, 2974, 2929, 1654, 1544, 1449, 1378, 1206, 1106, 1001

m/z 346 $(M + H)^+$

Measured mass: 345.9441, Calc. for $C_{12}H_{14}Br_2NO$: 345.9442.

5.3.18 The attempted hydrolysis of 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (92), method 1

A 10 ml round bottomed flask equipped for reflux was charged with a suspension of racemic 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (100 mg, 0.3 mmol) and concentrated HCl (2.0 ml). The resulting suspension was heated under strong reflux for 24 hours whilst monitoring the reaction by TLC; no reaction was observed by this time and only starting material was noted. The solution was heated under reflux for a further 24 hours, but similarly no reaction was observed. The starting material was recovered in excess of 95 % yield with no significant sign of decomposition.

The simple procedure highlighted above was repeated exhaustively employing concentrated H_2SO_4 and similarly co-solvents including THF and methanol as alternative solvent systems. In each case, only the starting material was recovered, again with no sign of decomposition.

5.3.19 The attempted hydrolysis of 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (92), method 2

A 50 ml round bottomed flask equipped for reflux was charged with a suspension of racemic 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (200 mg, 0.6 mmol) and concentrated H_2SO_4 (10 ml). The resulting suspension was heated to 80 °C before slowly adding an excess of solid sodium nitrite (0.3 g, 4.3 mmol) in small portions. Upon addition, the colour of the suspension deepened (dark brown) and the evolution of a gas was noted, the resulting slurry was stirred for a further 5 minutes before cooling to 0 °C. The contents of the flask were then transferred into a 200 ml, high-sided glass beaker before water (20 ml) was carefully added. The aqueous solution was extracted with dichloromethane (2 × 20 ml) and the combined organic solutions washed with saturated brine solution (15 ml) and water (15 ml). The organic was dried over anhydrous magnesium sulfate, filtered and solvent removed to

yield the crude product as a thick brown oil (103 mg, 0.4 mmol, 67 %). Direct reaction of the product with an ethereal solution of diazomethane followed by analysis by GLC, confirmed the products identity as that of the desired carboxylic acid, of *2,2-dibromocyclopropanecarboxylic acid*; all spectroscopic data was identical to that quoted previously [***5.3.8***].

5.3.20 The attempted hydrolysis of 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (92), method 3

A 10 ml round bottomed flask equipped for reflux was charged with a suspension of racemic 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (50 mg, 0.15 mmol), water (2 ml) and methanol (0.5 ml). The resulting solution was stirred at 50 °C for 30 minutes before solid sodium peroxide (11.0 mg, 0.15 mmol) was added. The resulting solution was stirred for a further 90 minutes before cooling to room temperature and acidifying with 1M H_2SO_4 (5 drops). The acidified solution was extracted with chloroform (2 × 10 ml) and the resulting organic solution washed with water (5 ml) and 1M H_2SO_4 (5 ml). The organic was then dried over anhydrous magnesium sulfate, filtered and solvent removed to yield a white powdery residue (41 mg). Unfortunately, further analysis of the residue revealed that it was unreacted starting material.

5.3.21 The preparation of trans-2-bromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (93)

A 10 ml round bottomed flask equipped for magnetic stirring was charged with 2,2-dibromo-cyclopropanecarboxylic acid (1-phenyl-ethyl)-amide (150 mg, 0.04 mmol) in still dried diethyl ether (5 ml). The resulting solution was cooled to - 60 °C as a 1.5 M ethereal solution of methyllithium (0.62 ml, 0.09 mmol) was added dropwise. The resulting solution was then stirred to room temperature before heating to a gentle reflux. After 1 hour (at reflux), no starting material remained (TLC) and the reaction was subsequently quenched by cooling the solution to 0 °C and carefully adding water (1.0 ml). The solution was acidified with dilute (10 %) sulfuric acid and the resulting solution was stirred vigorously before separation of the two layers. The aqueous phase was extracted with diethyl ether (2 × 5 ml) and the combined organic fractions washed with saturated sodium bicarbonate solution (5 ml) and water (5 ml). The organic

solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the title compound as a brown crystalline solid (99 mg, 0.03 mmol, 84 %), mp 149 °C.

δ_H	7.35 (5H, m), 5.9 (1H, bs), 5.14 (1H, pentet, *J* 7.6 Hz), 3.21 (1H, ddd, *J* 7.8, 5.3, 3.1 Hz), 1.79 (1H, ddd, *J* 7.8, 5.9, 3.1 Hz), 1.59 (1H, ddd, *J* 12.1, 5.9, 5.3 Hz), 1.46 (3H, d, *J* 7.6 Hz), 1.26 (1H, ddd, *J* 12.1, 5.9, 3.1 Hz)
δ_C	169.0, 142.8, 129.0, 127.5, 126.2, 49.3, 25.8, 21.7, 18.9, 17.7
ν_{max}/cm^{-1}	3286, 3063, 3030, 2977, 2933, 1640, 1629, 1547, 1447, 1383, 1214, 1111, 1045
m/z	268 $(M + H)^+$

Measured mass: 268.0332, Calc. for $C_{12}H_{15}BrNO$: 268.0337.

5.3.22 A general procedure for the attempted enzymatic resolution of 2,2-dibromo-1-hydroxymethylcyclopropane (86) in organic solvents

A standard 5-dram, glass sample vial equipped with a small magnetic flea was charged with a solution of racemic 2,2-dibromo-1-hydroxymethylcyclopropane (500 mg, 2.2 mmol) in the desired organic solution (5 ml). The resulting suspension was subsequently stirred at an ambient temperature of 24 – 26 °C (using a water bath if necessary) for 1 hour to allow complete thermal equilibration. A predetermined amount of a chosen acyl donor compound (vinyl acetate or vinyl butyrate) was then added to the stirred solution, which was subsequently treated with the chosen crude enzyme preparation. The reaction mixture was then gently stirred continuously whilst monitoring the reaction by TLC and GLC. After a 48 hour period, the reaction mixture was filtered to remove the enzyme and the solvent was removed under reduced pressure. The crude product mixture was analysed by GLC, and if necessary, the components separated by flash column chromatography on silica gel (petrol: ether, 3:1). Analytical data obtained by examination of the separated components from each reaction (except those carried out in THF) was consistent with that of the unreacted starting material (2,2-dibromo-1-hydroxymethylcyclopropane).

A summary of the results obtained from the comprehensive series of experiments carried out employing a range of enzyme preparations in several organic solvents, may be seen in Table 8 and Table 9. The analytical data obtained from the product of the

reactions carried out employing THF (as reaction solvent); an inseparable mixture of diastereomeric acetals (**95**) is presented below.

δ_H	5.19 (1H, m), 3.91 (2H, m), 3.73 (1H, m), 3.52 (1H, m), 2.09 – 1.8 (4H, m), 1.80 (2H, m), 1.37 (1H, m)
δ_C	104.0, 103.5, 68.8, 68.3, 67.1, 66.9, 32.6, 32.4, 30.6, 29.9, 26.9, 26.8, 25.9, 25.7, 23.5, 23.4
ν_{max}/cm^{-1}	2964, 2875, 1460, 1363, 1280, 1174, 1107
m/z	298 $(M)^+$

Measured mass: 297.9207, Calc. for $C_8H_{12}Br_2O_2$: 297.9204

5.3.23 The small scale preparation of 2,2-dibromo-1-hydroxymethylcyclopropyl butyrate (96)

A 10 ml round bottomed flask was charged with 2,2-dibromo-1-hydroxymethylcyclopropane (230 mg, 1 mmol), dichloromethane (5.0 ml) and butyric anhydride (174 mg, 0.18 ml, 1.1 mmol). The resulting solution was cooled to 0 °C, before a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (2 mol %) was added to the stirred solution. The resulting solution was then stirred to room temperature while the reaction was monitored by GLC. After 10 minutes, no starting material remained and the reaction was subsequently quenched by cooling the solution to 0 °C and carefully adding a saturated sodium bicarbonate solution (1.0 ml). The resulting solution was stirred vigorously before separation of the biphasic solution. The aqueous phase was subsequently extracted with dichloromethane (2 × 1.0 ml) and the combined organic fractions washed with saturated sodium bicarbonate solution (5.0 ml) and water (5.0 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the crude product as a fragrant colourless oil; purification by flash chromatography on silica gel afforded pure *2,2-dibromo-1-hydroxymethylcyclopropyl butyrate* as a colourless oil, (271 mg, 91 mmol, 91 %). Selected spectroscopic data identical to that found in the literature[209] is detailed below.

δ_H	4.26 (1H, dd, *J* 11.9, 5.9 Hz), 4.03 (1H, dd, *J* 11.9, 8.1 Hz), 2.31 (2H, t, *J* 7.4 Hz), 1.96 (1H, dddd, *J* 10.4, 8.1, 7.3, 5.9 Hz), 1.80 (1H, dd, *J*

	10.4, 7.3 Hz), 1.62 (2H, m), 1.41 (1H, dd, *J* 7.4, 7.4Hz), 0.94 (3H, t, *J* 7.4 Hz)
δ_C	173.4, 65.6, 36.1, 29.1, 26.8, 24.8, 18.4, 13.6
ν_{max}/cm^{-1}	3085, 2964, 2875, 1739, 1460, 1363, 1174

5.3.24 The large scale preparation of 2,2-dibromo-1-hydroxymethylcyclopropyl butyrate (96)

A 100 ml round bottomed flask was charged with 2,2-dibromo-1-hydroxymethylcyclopropane (23.0 g, 0.11 mol), dichloromethane (50 ml) and butryl chloride (12.8 g, 12.4 ml, 0.12 mol). The resulting solution was cooled to 0 °C, before triethylamine solution (15.2 g, 21.5 ml, 0.15 mol) was added to the stirred solution. The resulting solution was then stirred to room temperature while the reaction was monitored by TLC and GLC. After 3 hours, no starting material remained and the reaction was subsequently quenched by cooling the solution to 0 °C and carefully adding water (25 ml) and dilute hydrochloric acid (5 %) to neutralise any excess triethylamine. The resulting solution was stirred vigorously before separation of the biphasic mixture. The aqueous phase was subsequently extracted with dichloromethane (2 × 25 ml) and the combined organic fractions washed with saturated sodium bicarbonate solution (10 ml) and water (50 ml). The combined organic solutions were dried over anhydrous magnesium sulfate, filtered and excess solvent removed to yield the crude product as a fragrant yellow coloured oil, purification by flash chromatography on silica gel afforded pure *2,2-dibromo-1-hydroxymethylcyclopropyl butyrate* as a colourless oil, (29.7 g, 100 mmol, 83 %). All analytical data observed was identical to that reported in the previous procedure [***5.3.23***].

5.3.25 A general procedure for the attempted enzymatic resolution of 2,2-dibromo-1-hydroxymethylcyclopropyl butyrate (96) in aqueous solution

A 10 ml round bottomed flask equipped for magnetic stirring was charged with racemic 2,2-dibromo-1-hydroxymethylcyclopropyl butyrate (1.0 g, 3.3 mmol) and freshly prepared 0.1 M (pH 7) aqueous phosphate buffer solution (10 ml). The resulting suspension was stirred at an ambient temperature of 24 – 26 °C (using a water bath if necessary) for 1 hour to allow complete thermal equilibration. The

reaction mixture was then treated with the desired crude enzyme preparation (100 mg) and the pH of the resulting solution constantly monitored using a suitable pH meter; the reaction solution was subsequently maintained at pH 7 by the controlled addition of molar sodium hydroxide solution.

When the desired amount of base had been added, the reaction was terminated by extraction of the solution with ethyl acetate (50 ml). The organic solution was subsequently washed with saturated sodium bicarbonate solution (25 ml) and water (25 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and excess solvent removed under reduced pressure. The crude product mixture was analysed by GLC, and the components separated by flash column chromatography on silica gel (petrol: ether, 3:1). Analytical data obtained by examination of the individual components was consistent with that of residual starting material [***5.3.23***] and the desired hydrolysis product, *2,2-dibromo-1-hydroxymethylcyclopropane* [***5.3.12***]. The separated components were then analysed by chiral GLC. A summary of the results obtained from a series of experiments carried out employing Sigma-*PPL* and Lipase-*Ps* (Amano) enzymes may be seen in Table 11.

5.3.26 The preparation of trans-2-bromo-1-methylcyclopropanecarboxylic acid

A 100 ml round bottomed flask equipped for magnetic stirring was charged with 2,2-dibromo-1-methylcyclopropanecarboxylic acid (5.14 g, 20 mmol) in still dried diethyl ether (55 ml). The resulting solution was cooled to 0 °C as a 1.5 M ethereal solution of methyllithium (20.0 ml, 30 mmol) was added dropwise. The colourless solution turned a golden brown colour with an obvious end point when the correct amount of reagent had been delivered. The resulting solution was then stirred to room temperature while the reaction was monitored by GLC. After 1 hour, no starting material remained and the reaction was subsequently quenched by cooling the solution to 0 °C and carefully adding water (10 ml). The solution was acidified with dilute (10 %) sulfuric acid (20 ml) and the resulting solution was stirred vigorously before separation of the two layers. The aqueous phase was extracted with diethyl ether (25 ml) and the combined organic fractions washed with saturated sodium bicarbonate solution (50 ml) and water (50 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield *trans-2-bromo-1-*

methylcyclopropanecarboxylic acid as a golden semi-solid (3.29 g, 18.3 mmol, 92 %), bp 113 °C at 11mmHg, (lit.,[210] bp 110 °C at 10 mmHg).

δ_H	10.10 (1H, bs, Acid H), 3.56 (1H, dd, *J* 8.2, 5.5 Hz), 1.90 (1H, dd, *J* 8 .2, 5.8 Hz), 1.48 (3H, s, Me), 1.09 (1H, dd, *J* 5.8, 5.5 Hz)
δ_C (dept)	179.9(.), 32.5(.), 28.9(+), 25.7(+), 16.4(-)
ν_{max}/cm^{-1}	3055, 2979, 2706, 2606, 1962, 1414, 1320, 1185
m/z	196 $(M + NH_4)^+$

5.3.27 The preparation of methyl trans-2-bromo-1-methylcyclopropanecarboxylate, small scale

An excess of ethereal diazomethane solution as prepared in [***5.3.3***] was added to a solution of *trans*-2-bromo-1-methylcyclopropanecarboxylic acid (51.0 mg, 0.284 mmol) in diethyl ether (1 ml). The resulting solution was stirred at room temperature for 10 minutes before all volatiles were removed *in vacuo* to yield *methyl trans-2-bromo-1-methylcyclopropanecarboxylate* (53.2 mg, 0.276 mmol, 97 %), as a viscous colourless oil, bp 59 °C at 1.1mmHg, (lit.,[211] bp 63.5 °C at 6.5 mmHg).

δ_H	3.67 (3H, s, OMe), 3.50 (1H, dd, *J* 8.2, 5.4 Hz), 1.84 (1H, dd, *J* 8.2, 5.9 Hz), 1.46 (3H, s, Me), 1.01 (1H, dd, *J* 5.5, 5.4 Hz)
δ_C (dept)	173.6(.), 52.4(+), 32.7(.), 28.7(+), 25.1(+), 16.8(-)
ν_{max}/cm^{-1}	2952, 1731, 1439, 1358, 1153; 980
m/z	192 $(M)^+$

5.3.28 The preparation of methyl trans-2-bromo-1-methylcyclopropanecarboxylate, large scale

A solution of *trans*-2-bromo-1-methylcyclopropanecarboxylic acid (5.0 g, 28 mmol) in methanol (50 ml) was stirred at room temperature as concentrated sulfuric acid (0.5 ml) was added dropwise; the resulting solution was stirred at reflux overnight. The solution was then cooled to room temperature, diluted with dichloromethane (100 ml) and the resulting solution washed with saturated sodium bicarbonate solution (2 × 50 ml) and water (2 × 100 ml). The resulting organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the product, *methyl trans-2-*

bromo-1-methylcyclopropanecarboxylate as a viscous colourless oil (4.69 g, 24.3 mmol, 87 %); all analytical data was identical to that quoted previously [***5.3.27***].

5.3.29 The preparation of (trans-2-bromo-1-methylcyclopropyl)-methanol

An oven dried 10 ml round bottomed flask was charged with a slurry of lithium aluminium hydride (99 mg, 2.6 mmol) in still dried diethyl ether (2.0 ml). The suspension was stirred at -60 °C as a solution of methyl *trans*-2-bromo-1-methylcyclopropanecarboxylate (500 mg, 2.6 mmol) in still dried diethyl ether (2 ml) was added dropwise. The resulting solution was stirred at -60 °C for 20 minutes before warming to room temperature and stirring for a further 40 minutes when TLC showed complete conversion of the starting material. The reaction was quenched by cooling to -60 °C and carefully adding ethyl acetate (0.2 ml) followed by water (5 ml); the resulting solution was extracted with diethyl ether (2 × 10 ml). The organic solution was washed with dilute sulfuric acid (10 ml) and water (10 ml) and then dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as a yellow brown oil; purification by column chromatography on silica yielded pure *(trans-2-bromo-1-methylcyclopropyl)-methanol* as a colourless oil (333 mg, 2.0 mmol, 78 %). All spectroscopic data showed good agreement with that quoted in the literature.[151]

δ_H	4.32 (1H, bs, OH), 3.51 (1H, d, *J* 11.25 Hz, AB pattern), 3.39 (1H, d, *J* 11.25 Hz, AB pattern), 2.97 (1H, dd, *J* 7.9, 4.4 Hz), 1.26 (3H, s, Me), 1.10 (1H, dd, *J* 7.9, 6.2 Hz), 0.63 (1H, dd, *J* 6.2, 4.4 Hz)
δ_C (dept)	68.4(-), 29.7(+), 23.1(.), 19.9(-), 18.2(+)
ν_{max}/cm^{-1}	3344, 2927, 1437, 1300, 1207, 1044, 1026
m/z	182 $(M + NH_4)^+$

5.3.30 The preparation of (trans-2-bromo-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane (113), method 1

An oven dried 50 ml round bottomed flask was charged with a solution of (*trans*-2-bromo-1-methylcyclopropyl)-methanol (1.50 g, 9.0 mmol) in still dried dichloromethane (20 ml). The solution was cooled to 0 °C as DMAP (150 mg, 1.2 mmol) and triethylamine (1.9 ml, 13.6 mmol) were added; the resulting deep red

solution was stirred vigorously as TBDPS-Cl (3.46 ml, 13.6 mmol) was added dropwise using a syringe. The solution was warmed to room temperature and stirred overnight. TLC showed that the starting material had been consumed; the reaction was diluted with dichloromethane (10 ml) and washed with saturated brine solution (20 ml) and water (20 ml). The combined aqueous fractions were extracted with dichloromethane (2 × 10 ml) and the combined organic solution dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as an orange oil; purification by column chromatography on silica yielded *(trans-2-bromo-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane* as a colourless oil (1.36 g, 3.34 mmol, 37 %).

δ_H	7.65 - 7.62 (4H, m, Ar H), 7.45 - 7.37 (6H, m, Ar H), 3.62 (1H, d, *J* 10.3 Hz, AB pattern), 3.45 (1H, d, *J* 10.3 Hz, AB pattern), 3.02 (1H, dd, *J* 7.9, 4.3 Hz), 1.29 (3H, s, Me), 1.20 (1H, dd, *J* 7.9, 6.0 Hz), 1.05 (9H, s, *t*-Bu), 0.66 (1H, dd, *J* 6.0, 4.3 Hz)
δ_C (dept)	135.6(+), 133.4(.), 129.7(+), 127.7(+), 67.6(-), 36.5(+), 26.8(+), 23.0(.), 19.5(-), 19.0(.), 18.4(+)
ν_{max}/cm^{-1}	3070, 2958, 2930, 2857, 1959, 1888, 1823, 1589, 1471, 1427, 1111, 823, 702
m/z	402 $(M)^+$

Measured mass: 402.1015, Calc. for $C_{21}H_{27}BrOSi$: 402.1015.

5.3.31 The preparation of (trans-2-bromo-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane (113), method 2

An oven dried 50 ml round bottomed flask was charged with a solution of (*trans*-2-bromo-1-methylcyclopropyl)-methanol (1.5 g, 9.0 mmol) and TBDPS-Cl (2.56 ml, 10.0 mol) in dried, distilled DMF (25 ml). The solution was stirred at 0 °C as freshly ground imidazole (740 mg, 10.9 mmol) was added to solution. The resulting solution was warmed to room temperature and stirred overnight. TLC analysis showed that the starting material had been consumed and the reaction was quenched by adding saturated brine solution (10 ml). The solution was transferred to a separating funnel and extracted with ethyl acetate (2 × 50 ml), the combined organic fractions were washed with 10 % hydrochloric acid (2 × 50 ml) and water (2 × 100 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to

yield the crude product as a heavy orange oil, column chromatography on silica afforded pure *(trans-2-bromo-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane* as a colourless oil (2.83 g, 7.0 mmol, 78 %). All analytical data was identical to that quoted previously [***5.3.30***].

5.3.32 The preparation of (1-methylcyclopropylmethoxy)-t-butyldiphenylsilane

An oven dried 5 ml round bottomed flask equipped for magnetic stirring was charged with a solution of (*trans*-2-bromo-1-methylcyclopropylmethoxy)-*t*-butyldiphenylsilane (100 mg, 0.25 mmol) in still dried THF (2 ml). The stirred solution was cooled to –80 °C before a 1.45 M solution of *t*-butyllithium in pentane (0.20 ml, 0.30 mmol) was added dropwise. The resulting solution was stirred at –80 °C for 15 minutes before a saturated solution of ammonium chloride (5 drops) was added, the resulting solution was warmed to room temperature and diluted with diethyl ether (2 ml). The solution was dried over anhydrous magnesium sulfate and filtered through a plug of cotton wool. Solvent was removed *in-vacuo* to yield *(1-methylcyclopropylmethoxy)-t-butyldiphenylsilane* as a colourless oil (61 mg, 0.195 mmol, 78 %).

δ_H	7.80 - 7.60 (4H, m, Ar H), 7.51 - 7.35 (6H, m, Ar H), 3.51 (2H, s, CH_2O), 1.26 (3H, s, Me), 1.10 (9H, s, *t*-Bu), 0.39 (2H, m, cyclopropane), 0.28 (2H, m, cyclopropane)
δ_C (dept)	135.7(+), 134.1(.), 129.5(+), 127.6(+), 70.5(-), 26.8(+), 23.0(.), 20.9(+), 17.6(.), 10.5(-)
ν_{max}/cm^{-1}	3070, 2954, 2894, 2857, 1956, 1889, 1824, 1589, 1472, 1427, 1111, 1081, 938
m/z	310 $(M)^+$

5.3.33 The preparation of (trans-2-trimethylsilyl-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane

An oven dried 5 ml round bottomed flask equipped for magnetic stirring was charged with a solution of (*trans*-2-bromo-1-methylcyclopropylmethoxy)-*t*-butyldiphenylsilane (100 mg, 0.25 mmol) in still dried THF (2 ml). The stirred solution was cooled to –80 °C before a 1.45 M solution of *t*-butyllithium in pentane (0.20 ml, 0.30 mmol) was added dropwise. The resulting solution was stirred at –80 °C for 15 minutes before

trimethylsilyl chloride (5 drops, excess) was added, the resulting solution was warmed to room temperature and diluted with diethyl ether (2 ml). The solution was quenched with saturated ammonium chloride solution (5 drops), dried over anhydrous magnesium sulfate and filtered through a plug of cotton wool. Solvent was removed *in-vacuo* to yield *(trans-2-trimethylsilyl-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane* as a colourless oil (85 mg, 0.21 mmol, 86 %).

δ_H	7.76 - 7.60 (4H, m, Ar H), 7.43 - 7.35 (6H, m, Ar H), 3.45 (1H, d, *J* 9.9 Hz, AB pattern), 3.36 (1H, d, *J* 9.9 Hz, AB pattern), 1.19 (3H, s, Me), 1.07 (9H, s, *t*-Bu), 0.57 (1H, dd, *J* 10.4, 3.4 Hz), 0.26 (1H, dd, *J* 7.2, 3.4 Hz), 0.04 (9H, s, TMS), -0.44 (1H, dd, *J* 10.4, 7.2 Hz)
δ_C (dept)	135.7(+), 134.7(.), 129.5(+), 127.5(+), 73.2(-), 26.9(+), 23.0(.), 19.3(.), 18.7(+), 14.9(-), 8.9(+), -0.3(+)
ν_{max}/cm^{-1}	3070, 3050, 2954, 2894, 2857, 1956, 1889, 1824, 1716, 1653, 1635, 1589, 1558, 1472, 1427, 1389, 1361, 1111, 1081, 938
m/z	396 $(M)^+$, 323 (M - TMS)

Measured mass: 396.2305, Calc. $C_{24}H_{36}OSi_2$: 396.2305.

5.3.34 The preparation of tetrakis-[iodo(tri-n-butylphosphine)copper(I)][159]

In a 250 ml conical flask, copper(I) iodide (20.0 g, 0.10 mol) was dissolved in saturated potassium iodide solution (150 ml). To the stirred suspension, a solution of tri-*n*-butylphosphine (20.0 g, 0.10 mol) in diethyl ether (100 ml) was added. The resulting solution was stirred at room temperature for 1 hour before being transferred to a separating funnel. The aqueous phase was discarded and the organic solution washed with saturated potassium iodide solution (150 ml) and water (200 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the crude product as a white waxy solid (31.9 g). The crude product was dissolved in propanone - methanol (90:10; 25 ml), and cooled to –10 °C, *tetrakis-[iodo(tri-n-butylphosphine)copper(I)]* was subsequently recovered as a white crystalline solid (30.55 g, 19 mmol, 77 %); mp 75 °C, (lit.,[159] mp 75 °C). **Note:** The product was stored at –5 °C under an atmosphere of argon; without refrigeration the product decomposed to a green solid or viscous oil after a few days.

5.3.35 The attempted dimerisation of (trans-2-bromo-1-methylcyclopropylmethoxy)-t-butyldiphenylsilane (113)

An oven dried 10 ml two-necked flask equipped for magnetic stirring was charged with a solution of (*trans*-2-bromo-1-methylcyclopropylmethoxy)-*t*-butyldiphenylsilane (500 mg, 1.24 mmol) in still dried THF (5 ml). The stirred solution was cooled to –80 °C before a 1.45 M solution of *t*-butyl lithium in pentane (1.03 ml, 1.5 mmol) was added dropwise. The resulting solution was stirred at –80 °C for 1 hour before tetrakis-[iodo(tri-*n*-butylphosphine)copper(I)] (243 mg, 0.15 mmol) was added, the resulting suspension was stirred for a further hour at –80 °C.

The flask was fitted with a dry guard tube (filled with $CaCl_2$) and a fritted gas inlet tube submerged within the reaction mixture. The orange solution was vigorously oxygenated by passing a stream of dry oxygen through the reaction mixture. Oxygenation was continued for 40 minutes by which time the solution had turned a deep blue colour. The solution was diluted with diethyl ether (5 ml) and washed with saturated ammonium chloride solution (5 ml). The organic phase was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield a colourless oil (300 mg). Initial analysis of the product by ^{1}H NMR and GCMS showed no sign of the desired product; the product was identified as *(1-methyl-cyclopropylmethoxy)-t-butyldiphenylsilane* and showed analytical data identical to that quoted previously [***5.3.32***].

5.3.36 The preparation of 1,1-dibromo-2,2,3,3-tetramethylcyclopropane (117)

A 250 ml round bottomed flask equipped for mechanical stirring and reflux was charged with a suspension of potassium *t*-butoxide (4.03 g, 36 mmol) in pentane (200 ml). The solution was cooled to 0 °C and 2,3-dimethylbutene (3.53 ml, 30 mmol) was added, a solution of bromoform (3.14 ml, 35 mmol) in pentane (10 ml) was then added dropwise to the vigorously stirred solution. The reaction mixture was warmed to room temperature and stirred overnight. Upon return, the reaction was poured onto iced water (250 ml) and diluted with diethyl ether (100 ml), the biphasic solution was separated and the aqueous phase extracted with diethyl ether (2 × 100 ml) and ethyl acetate (2 × 50 ml). The combined organic fractions were washed with saturated brine solution (250 ml), water (250 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as a grey

coloured solid. Recrystallisation from dichloromethane (15 ml) afforded pure *1,1-dibromo-2,2,3,3-tetramethylcyclopropane* as a white crystalline solid, (4.84 g, 18.9 mmol, 63 %), mp 75 – 77 °C, (lit.,[50b] mp 77 – 78 °C).

δ_H	1.29 (12H, s)
δ_C (dept)	58.9(.), 29.7(.), 21.7(+)
ν_{max}/cm^{-1}	2954, 2949, 1460, 1448, 1372, 1102, 1031, 937, 855
m/z	256 $(M)^+$, 175 (M – Br)

5.3.37 The preparation of 1-bromo-1-chloro-2,2,3,3-tetramethylcyclopropane (118)

A 50 ml round bottomed flask fitted with a reflux condenser was charged with finely powdered sodium hydroxide (7.2 g, 180 mmol), a solution of 2,3-dimethylbutene (3.53 ml, 30 mmol) in dichloromethane (25 ml) was added and the flask immersed into the water bath of an ultrasonic cleaning bath (47 kHz, 160 W). The flask was positioned approximately 1 cm above the centre of the ultrasonic horn, the bath was filled with water so that the level was equal to that of the solvent within the flask. Benzyltriethylammonium chloride (140 mg, 0.6 mmol, PTC) and bromoform (3.14 ml, 36 mmol) were added to the flask and the resulting solution was subjected to ultrasonic irradiation at room temperature for 2 hours. The reaction mixture was filtered through a pad of celite that was washed with dichloromethane (25 ml) after the filtration. All volatiles were removed *in-vacuo*. The residue was dissolved in petrol (50 ml) and the resulting solution dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as a grey solid. Recrystallisation from dichloromethane (15 ml) afforded *1-bromo-1-chloro-2,2,3,3-tetramethylcyclopropane*as a white crystalline solid, (2.61 g, 12.3 mmol, 41 %), mp 64 °C, (lit.,[212] mp 63 – 65 °C).

δ_H	1.26 (6H, s), 1.21 (6H, s)
δ_C (dept)	58.9(.), 29.7(.), 21.7(+), 19.2(+)
ν_{max}/cm^{-1}	2955, 2951, 1472, 1454, 1372, 1108, 1032, 990, 943, 884, 861
m/z	212 $(M)^+$, 131 (M – Br)

5.3.38 The preparation of 3-bromo-1,1,2,2-tetramethylcyclopropane (115)

A oven dried 50 ml two necked round bottomed flask equipped for reflux and magnetic stirring was charged with a solution of 1,1-dibromo-2,2,3,3-tetramethylcyclopropane (2.0 g, 7.8 mmol) in still dried diethyl ether (20 ml). Titanium isopropoxide (0.11 ml, 0.4 mmol) was added to the stirred solution which was then cooled to 0 °C before a 1 M solution of ethyl magnesium bromide (10.15 ml, 10.1 mmol) was added dropwise over a period of 20 minutes. The resulting solution was stirred at room temperature whilst monitoring by GLC. When all starting material had been consumed, the black solution was quenched by carefully adding water (10 ml) dropwise at first. The solution was then separated and the aqueous phase extracted with diethyl ether (2 × 25 ml), the combined organic phases were filtered through a pad of silica and solvent removed to yield *3-bromo-1,1,2,2-tetramethylcyclopropane* as a fragrant colourless oil, (1.14 g, 6.4 mmol, 83 %), bp 35 °C at 11 mmHg, (lit.,[213] bp 51 °C at 22 mmHg).

δ_H	2.74 (1H, s), 1.14 (6H, s), 1.10 (6H, s)
δ_C (dept)	44.6(+), 22.9(.), 21.8(+), 19.5(+)
ν_{max}/cm^{-1}	2954, 2949, 1460, 1457, 1377, 1102, 1033, 937, 855
m/z	176 $(M)^+$

5.3.39 The preparation of 2,2,3,3,2',2',3',3'-octamethylbiscyclopropane *(116)*

An oven dried 25 ml two-necked flask equipped for magnetic stirring was charged with a solution of 3-bromo-1,1,2,2-tetramethylcyclopropane (500 mg, 2.84 mmol) in still dried THF (7.5 ml). The stirred solution was cooled to –78 °C before a 1.70 M solution of *t*-butyllithium in pentane (2.00 ml, 3.4 mmol) was added dropwise. The resulting yellow solution was stirred at –78 °C for 90 minutes before warming to –30 °C; anhydrous copper(I) iodide (541 mg, 2.84 mmol) was then added and the resulting suspension was stirred for a further 60 minutes. The flask was then fitted with a pre-dried guard tube (filled with $CaCl_2$) and a fritted gas inlet tube was submerged within the reaction mixture. The grey solution was then vigorously oxygenated by passing a stream of dry oxygen through the reaction mixture, oxygenation was continued for 30 minutes by which time the solution had turned a deep green colour. The solution was diluted with diethyl ether (5 ml) and washed with saturated ammonium chloride

solution (5 ml). The biphasic solution was extracted with diethyl ether (2 × 5 ml) and the combined organic phases washed with water (10 ml) and dried over anhydrous magnesium sulfate. The dried solution was filtered and solvent removed to yield a thick yellow coloured oil; purification by chromatography on silica afforded the product; *2,2,3,3,2',2',3',3'-octamethylbiscyclopropane*[214] as a colourless oil, (186 mg, 1.00 mmol, 69 %).

δ_H	1.23 (3H, s), 1.17 (3H, s), 1.10 (3H, s), 1.04 (3H, s), 1.01 (1H, s)
δ_C	32.3, 31.7, 29.8, 25.3, 23.7, 22.0, 17.9
ν_{max}/cm^{-1}	2975, 2964, 1734, 1465, 1377, 1173, 908, 735
m/z	194 $(M)^+$, 179 (M – Me)

Measured mass: 194.2035, Calc. $C_{14}H_{26}$: 194.2035.

5.3.40 The preparation of (1S,2R)-2-bromo-1-methylcyclopropanecarboxylic acid

Following the procedure detailed previously [***5.3.26***], the title compound was prepared from (1*S*)-2,2-dibromo-1-methylcyclopropanecarboxylic acid in 92 % yield; *(1S,2R)-2-bromo-1-methylcyclopropanecarboxylic acid* was isolated as a light golden coloured semi-solid, all spectroscopic data was identical to that detailed previously [***5.3.26***].

$[\alpha]_D^{25}$ -81.5 ° (*c* 1.02, $CHCl_3$)

5.3.41 The preparation of (1R,2S)-2-bromo-1-methylcyclopropanecarboxylic acid

Following the procedure detailed previously [***5.3.26***], (2*S,1R)*-2-bromo-1-methylcyclopropanecarboxylic acid was prepared from (1*R*)-2,2-dibromo-1-methylcyclopropanecarboxylic acid in 89 % yield; *(1R,2S)-2-bromo-1-methylcyclopropanecarboxylic acid* was isolated as a light golden coloured semi-solid, all spectroscopic data was identical to that detailed previously [***5.3.26***].

$[\alpha]_D^{25}$ +80.9 ° (*c* 1.00, $CHCl_3$)

5.3.42 The preparation of (1S,2R)-2-bromocyclopropanecarboxylic acid (72-S,R)

A 100 ml oven dried round bottomed flask was charged with (1*S*)-2,2-dibromocyclopropanecarboxylic acid (4.86 g, 20 mmol) in still dried diethyl ether (50 ml). The resulting solution was cooled to 0 °C and a 1.5 M solution of methyllithium

in diethyl ether (20.0 ml, 30 mmol) was added dropwise over a period of 5 minutes. The golden brown solution was warmed to room temperature and stirred for 1 hour. The reaction was monitored by GLC and when the starting material was no longer evident, the solution was cooled to 0 °C and water (20ml) was added (dropwise at first). The resulting solution was stirred for 10 minutes before being separated, the organic phase was extracted with water (20 ml) and the combined aqueous fractions acidified with 15 % aqueous sulfuric acid. The acidified aqueous phase was then extracted with ethyl acetate (2 × 75 ml) and the combined organic extracts dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in-vacuo* to yield the crude product as a golden brown oil. The crude product was dissolved in propanone (20 ml) and heated to reflux over activated charcoal (0.2 g) for 10 minutes, the solution was then cooled, filtered and solvent removed *in-vacuo* to yield *(1S,2R)-2-bromocyclopropanecarboxylic acid* as a colourless oil (2.95 g, 17.8 mmol, 85 %), bp 113 °C at 3.1 mmHg, (lit.,[210] bp 105 °C at 1.5 mmHg).

δ_H	10.37 (1H, bs), 3.29 (1H, ddd, *J* 7.9, 5.3, 3.1 Hz), 2.06 (1H, ddd, *J* 9.2, 5.8, 3.1 Hz), 1.69 (1H, ddd, *J* 7.9, 5.9, 5.8 Hz), 1.50 (1H, ddd, *J* 9.2, 5.9, 5.3 Hz)
δ_C (dept)	177.6(.), 23.6(+), 19.4(-), 19.1(+)
ν_{max}/cm^{-1}	3072, 2680, 1707, 1455, 1443, 1316, 1263, 1214, 1197, 1030
m/z	165 $(M)^+$, 121 (M - CO_2)
$[\alpha]_D^{26}$	-154.1 ° (*c* 1.03, $CHCl_3$)

5.3.43 The preparation of (1R,2S)-2-bromocyclopropanecarboxylic acid (72-R,S)

The title product was prepared in 91 % yield from (1*R*)-2,2-dibromocyclopropanecarboxylic acid by the same method outlined previously [***5.3.42***]. All spectroscopic data was identical to that quoted above.

$[\alpha]_D^{23}$	+153.9 ° (*c* 1.15, $CHCl_3$)

5.3.44 The preparation of methyl (1S,2R)-2-bromocyclopropanecarboxylate (112-S,R)

A solution of (1*S*,2*R*)-2-bromocyclopropanecarboxylic acid (2.0 g, 12 mmol) in methanol (30 ml) was stirred at room temperature as concentrated sulfuric acid (0.10

ml) was added dropwise; the resulting solution was stirred at reflux overnight. The solution was then cooled to room temperature, diluted with dichloromethane (50 ml) and the resulting solution washed with saturated sodium bicarbonate solution (2 × 25 ml) and water (2 × 50 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield methyl *(1S,2R)-2-bromocyclopropanecarboxylate* as a viscous, colourless fragrant oil (2.11 g, 11.8 mmol, 98 %), bp 99 °C at 22 mmHg, (lit.,[215] bp 108 °C at 25 mmHg). .

δ_H	3.70 (3H, s, OMe), 3.23 (1H, ddd, *J* 7.9, 5.0, 3.1 Hz), 2.05 (1H, ddd, *J* 9.3, 5.9, 3.1 Hz), 1.60 (1H, ddd, *J* 7.9, 5.9, 5.9 Hz), 1.42 (1H, ddd, *J* 9.3, 5.9, 5.0 Hz)
δ_C (dept)	172.0(.), 52.2(+), 23.6(+), 18.9(-), 18.6(+)
ν_{max}/cm^{-1}	3069, 3002, 2952, 2848, 1731, 1439, 1378, 1250, 1205, 1174, 1038, 925
m/z	165 (M - Me)
$[\alpha]_D^{22}$	–107.5 ° (*c* 1.15, $CHCl_3$)

5.3.45 The preparation of methyl (1R,2S)-2-bromocyclopropanecarboxylate (112-R,S)

The title product was prepared in 89 % yield from (1*R*,2*S*)-bromocyclopropanecarboxylic acid by the method outlined previously [***5.3.44***]. All spectroscopic data was identical to that quoted above.

$[\alpha]_D^{23}$	+108.2 ° (*c* 1.05, $CHCl_3$)

5.3.46 The preparation of (1S,2R)-2-bromo-1-hydroxymethylcyclopropane (109-S,R)

A 250 ml round bottomed flask equipped for magnetic stirring was charged with a solution of methyl (1*S*,2*R*)-2-bromocyclopropanecarboxylate (3.70 g, 20.0 mmol) in still dried dichloromethane (50 ml). The solution was cooled to –80 °C before a 1 M solution of DIBAL-H in hexanes (40.0 ml, 40 mmol) was added dropwise to the vigorously stirred solution. During the addition, care was taken not to allow the internal temperature to rise above –70 °C. The resulting solution was stirred for 30 minutes at – 70 °C before warming to room temperature. The reaction was monitored

by TLC and when the starting material had been consumed (after approximately 2 hours) was cooled to 0 °C and quenched by adding saturated ammonium chloride solution (5 ml) dropwise. The solution was warmed to room temperature at which point a thick suspension formed; 2 M hydrochloric acid (20 ml) and water (50 ml) was added to dissolve the paste, the resulting solution was stirred vigorously for 1 hour before being transferred to a separating funnel. The two layers were separated and the aqueous phase extracted with dichloromethane (2 × 50 ml). The combined organic fractions were washed with 2 M hydrochloric acid (25 ml), water (2 × 50 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in-vacuo* to yield the crude product as a yellow oil. The crude product was purified by column chromatography on silica to yield *(1S,2R)-2-bromo-1-hydroxymethylcyclopropane* as a colourless oil (2.79 g, 18.4 mmol, 92 %). All spectroscopic data was consistent with that appearing in the literature.[216]

δ_H	3.61 (1H, dd, *J* 11.5, 6.3 Hz, AB pattern), 3.51 (1H, dd, *J* 11.5, 6.7 Hz, AB pattern), 2.75 (1H, ddd, *J* 7.5, 3.9, 3.3 Hz), 1.85 (1H, bs, OH), 1.58 (1H, ddddd, *J* 9.6, 6.7, 6.5, 6.3, 3.3 Hz), 1.09 (1H, ddd, *J* 9.6, 6.5, 3.9 Hz), 0.98 (1H, ddd, *J* 7.5, 6.5, 6.5 Hz)
δ_C (dept)	64.1(-), 24.6(+), 17.2(+), 13.7(-)
ν_{max}/cm^{-1}	3384, 2974, 2928, 1440, 1396, 1257, 1224, 1026, 900
m/z	168 $(M + NH_4)^+$
$[\alpha]_D^{22}$	–42.2 ° (*c* 1.03, $CHCl_3$)

5.3.47 The preparation of (1R,2S)-2-bromo-1-hydroxymethylcyclopropane (109-R,S)

The title product was prepared in 89 % yield from methyl (1*R*,2*S*)-2-bromocyclopropanecarboxylate by the same method outlined previously [***5.3.46***]. All spectroscopic data was identical to that quoted above.

$[\alpha]_D^{23}$	+41.7 ° (*c* 1.08, $CHCl_3$)

5.3.48 The preparation of ((1S,2R)-2-bromo-1-hydroxymethylcyclopropyl)-t-butyldiphenylsilane (107-S,R)

An oven dried 50 ml round bottomed flask was charged with a solution of (1*S*,2*R*)-2-bromo-1-hydroxymethylcyclopropane (1.51 g, 10.0 mmol) and TBDPS-Cl (3.07 ml, 12.0 mol) in dried, distilled DMF (25 ml). The solution was stirred at 0 °C as freshly ground imidazole (825 mg, 12.0 mmol) was added to solution. The resulting solution was warmed to room temperature and stirred overnight. TLC analysis showed that the starting material had been consumed and the reaction was quenched by adding saturated brine solution (10 ml). The solution was transferred to a separating funnel and extracted with ethyl acetate (2 × 40 ml), the combined organic fractions were washed with 10 % hydrochloric acid (2 × 25 ml) and water (2 × 50 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the crude product as a thin yellow oil, column chromatography on silica afforded *((1S,2R)-2-bromo-1-hydroxymethylcyclopropyl)-t-butyldiphenylsilane* as a colourless oil (3.15 g, 8.1 mmol, 81 %).

δ_H	7.71 (4H, m Ar H), 7.36 (6H, m, Ar H), 3.73 (1H, dd, *J* 10.9, 4.8 Hz, AB pattern), 3.50 (1H, dd, *J* 10.9, 5.6 Hz, AB pattern), 2.73 (1H, ddd, *J* 6.4, 3.9, 3.3 Hz), 1.47 (1H, m), 1.02 (9H, s, *t*-Bu), 1.01 - 0.94 (2H, m)
δ_C (dept)	135.5(+), 133.4(.), 129.7(+), 127.7(+), 63.7(-), 29.8(+), 24.2(+), 19.2(.), 17.6(+), 13.1(-)
ν_{max}/cm^{-1}	3073, 2954, 2889, 2857, 1959, 1889, 1824, 1589, 1472, 1440, 1115, 941
m/z	390 (M + 1)
$[\alpha]_D^{22}$	–52.4 ° (*c* 1.18, $CHCl_3$)

5.3.49 The preparation of ((1R,2S)-2-bromo-1-hydroxymethylcyclopropyl)-t-butyldiphenylsilane (107-R,S)

The title product was prepared in 78 % yield from (1*R*,2*S*)-2-bromo-1-hydroxymethylcyclopropane by the same method outlined previously [***5.3.48***]. All spectroscopic data was identical to that quoted above.

$[\alpha]_D^{23}$	+51.6 ° (*c* 1.20, $CHCl_3$)

5.3.50 The preparation of 2,2'-bis-(t-butyl-diphenylsilyl-hydroxymethyl)-bicyclopropane (110)

An oven dried 50 ml two-necked flask equipped for magnetic stirring was charged with a solution of ((1*S*,2*R*)-2-bromo-1-hydroxymethylcyclopropyl)-*t*-butyldiphenylsilane (1.00 g, 2.60 mmol) in still dried THF (10 ml). The stirred solution was cooled to –78 °C before a 1.20 M solution of *t*-butyllithium in pentane (2.58 ml, 3.1 mmol) was added dropwise. The resulting yellow solution was stirred at –78 °C for 90 minutes before warming to –30 °C. Anhydrous copper(I) iodide (500 mg, 2.90 mmol) was then added; the resulting suspension was stirred for a further 75 minutes at –30 °C. The flask was then fitted with a pre-dried guard tube (filled with $CaCl_2$) and a fritted gas inlet tube was submerged within the reaction mixture. The solution was then vigorously oxygenated by passing a stream of dry oxygen through the reaction mixture, oxygenation was continued for 30 minutes by which time the solution had turned a deep green colour. The solution was diluted with diethyl ether (5 ml) and washed with saturated ammonium chloride solution (5 ml). The biphasic solution was extracted with diethyl ether (2 × 5 ml) and the combined organic phases washed with water (10 ml) and dried over anhydrous magnesium sulfate. The dried solution was filtered and solvent removed to yield a cloudy oil; purification by chromatography on silica afforded the desired product, *2,2'-bis-(t-butyl-diphenylsilyl-hydroxymethyl)-bicyclopropane* as a colourless oil, (321 mg, 0.50 mmol, 41 %). All spectroscopic data was consistent with that appearing in the literature.[40]

δ_H	7.72 (8H, m, Ar H), 7.35 (12H, m, Ar H), 3.60 (2H, dd, *J* 10.6, 5.9 Hz, AB pattern), 3.44 (2H, dd, *J* 10.6, 6.2 Hz, AB pattern), 1.05 (18H, s), 0.76 (4H, m), 0.25 (4H, m)
δ_C	135.6, 134.1, 129.5, 127.5, 67.2, 26.9, 19.3, 19.1, 17.7, 8.1
ν_{max}/cm^{-1}	3061, 2975, 2953, 2852, 1782, 1729, 1439, 1378, 1268, 1204, 1174, 969, 737
m/z	379 (M - TBDPS)
$[\alpha]_D^{21.5}$	–39.8 ° (*c* 1.39, EtOH)

5.3.51 The preparation of (1S,2R)-2-bromocyclopropanecarboxaldehyde (124-S,R)

A 100 ml round bottomed flask was charged with (1*S*,2*R*)-2-bromo-1-hydroxymethylcyclopropane (2.00 g, 13.3 mmol) and dichloromethane (50 ml); the resulting solution was stirred vigorously at room temperature as a homogeneous mixture of PCC (5.71 g, 26.6 mmol) and celite (5.5 g) was added in small portions. The solution was stirred at room temperature and the reaction monitored by TLC and GLC. Over a period of 90 minutes, when TLC showed that all the starting material had been consumed, the reaction mixture changed colour from colourless to a very dark brown; a granular solid was also noted within the solution. The reaction was filtered through a pad of celite, which was washed with dichloromethane (25 ml) and the filtrate reduced in volume under reduced pressure; this was carried out using a water aspirator as the product was volatile. Any residual solvent was removed by passing a steady stream of nitrogen over the solution at room temperature. *(1S,2R)-2-Bromocyclopropane carboxaldehyde* was isolated as a tan coloured oil, (1.46 g, 9.7 mmol, 73 %) which was used immediately without further purification.

δ_H	9.5 (1H, d, *J* 3.1 Hz, CHO), 3.31 (1H, ddd, *J* 7.7, 5.3, 3.1 Hz), 2.41 (1H, dddd, *J* 12.2, 5.9, 3.1, 3.1 Hz), 1.78 (1H, ddd, *J* 7.7, 5.9, 5.9 Hz), 1.57 (1H, ddd, *J* 12.2, 5.9, 5.3 Hz)
δ_C (dept)	199.4(+), 32.0(+), 19.5(-), 19.4(+)
ν_{max}/cm^{-1}	3060, 2975, 2953, 2852, 1713, 1424, 1354, 1233, 1162, 1058, 969, 737
m/z	390 (M + 1)
$[\alpha]_D^{22}$	–36.4 ° (*c* 0.99, $CHCl_3$)

Measured mass: Due to the high volatility of this sample, no measured mass was observed.

5.3.52 The preparation of (1R,2S)-2-bromocyclopropanecarboxaldehyde (124-R,S)

The title product was prepared in 78 % yield from (1*R*,2S)-2-bromo-1-hydroxymethylcyclopropane by the same method outlined previously [***5.3.51***]. All spectroscopic data was identical to that quoted above.

$[\alpha]_D^{22}$	+35.9 ° (*c* 1.00, $CHCl_3$)

5.3.53 The preparation of ethyl (E)-3-((1S,2R)-2-bromocyclopropyl)-prop-2-enoate (125-S,R)

A 100 ml round bottomed flask was charged with a solution of carboethoxymethylene triphenylphosphorane (9.60 g, 27.5 mmol) in toluene (50 ml); the solution was cooled to 0 °C before adding a solution of (1*S*,2*R*)-2-bromocyclopropanecarboxaldehyde (2.10 g, 14.0 mmol) in toluene (5 ml) dropwise. The resulting solution was warmed to room temperature and stirred overnight. Analysis by GLC and TLC showed that the reaction had reached completion and the solvent was removed *in*-vacuo. The residue, a pink solid was treated with petrol - ether (10:1, 50 ml) and the resulting solution was heated to reflux for 30 minutes. The hot solution was filtered through a pad of cotton wool and the residue (triphenylphosphine oxide) washed with a further aliquot of hot solvent (25 ml). Solvent was removed from the filtrate under reduced pressure to yield the crude product as a cream coloured oil. Over a period of 1 hour, further crystallisation of triphenylphosphine oxide was noted and purification by column chromatography on silica furnished ethyl *(E)-3-((1S,2R)-2-bromocyclopropyl)-prop-2-enoate* as a colourless oil, (2.43 g, 11.0 mmol, 79%).

δ_H	6.42 (1H, dd, *J* 15.4, 9.7 Hz), 5.89 (1H, d, *J* 15.4 Hz), 4.18 (2H, q, *J* 7.1 Hz), 2.96 (1H, ddd, *J* 7.7, 4.7, 3.2 Hz), 2.00 (1H, dddd, *J* 9.7, 9.4, 6.0, 3.2 Hz), 1.46 (1H, ddd, *J* 9.4, 6.5, 4.7 Hz), 1.29 (1H, ddd, *J* 7.7, 6.5, 6.0 Hz), 1.28 (3H, t, *J* 7.1 Hz)
δ_C (dept)	166.1(.), 147.8(+), 121.1(+), 60.3(-), 25.0(+), 20.5(+), 19.0(-), 14.2(+)
ν_{max}/cm^{-1}	3005, 2980, 2976, 1715, 1648, 1444, 1375, 1273, 1198, 1145, 1039, 976, 889
m/z	236 $(M + NH_4)^+$, 218 $(M)^+$

Measured mass: 236.0286, Calc. for $C_8H_{15}BrNO_2$: 236.0286.

$[\alpha]_D^{23}$	-157.1 ° (*c* 1.13, $CHCl_3$)

5.3.54 The preparation of ethyl (E)-3-((1R,2S)-2-bromocyclopropyl)-prop-2-enoate (125-R,S)

The title compound was prepared in 74 % yield from (1*R*,2*S*)-2-bromocyclopropanecarboxaldehyde using the procedure detailed above [***5.3.53***], all spectroscopic data was identical to that quoted previously.

$[\alpha]_D^{23}$ +155.6 ° (*c* 1.10, $CHCl_3$)

5.3.55 The preparation of (E)-3-((1S,2R)-2-bromocyclopropyl)-prop-2-en-1-ol (123-S,R)

An oven dried 100 ml round bottomed flask was charged with a solution of ethyl (*E*)-3-((1*S*,2*R*)-2-bromocyclopropyl)-prop-2-enoate (1.92 g, 8.8 mmol) in still dried dichloromethane (25 ml). The solution was cooled to –78 °C before a 1 M solution of DIBAL-H in hexanes (17.5 ml, 17.5 mmol) was added dropwise to the vigorously stirred solution. During the addition, care was taken not to allow the internal temperature to rise above –70 °C. The resulting solution was stirred for 30 minutes at –70 °C before warming to room temperature. The reaction was monitored by TLC and when the starting material had been consumed (after approximately 2 hours) was cooled to 0 °C and quenched by adding saturated ammonium chloride solution (1 ml) dropwise. The solution was warmed to room temperature, at which point a thick suspension formed and 2 M hydrochloric acid (20 ml) and water (50 ml) was added to dissolve the paste. The resulting solution was stirred vigorously for 1 hour before being transferred to a separating funnel, the two layers were separated and the aqueous phase extracted with dichloromethane (2 × 50 ml). The combined organic fractions were washed with 2 M hydrochloric acid (25 ml), water (2 × 50 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in-vacuo* to yield the crude product as a yellow oil. The crude product was purified by flash column chromatography on silica and pure *(E)-3-((1S,2R)-2-bromocyclopropyl)-prop-2-en-1-ol* was recovered as a colourless oil, (1.26 g, 7.1 mmol, 81 %).

δ_H 5.70 (1H, dt, *J* 15.3, 5.7 Hz), 5.27 (1H, ddt, *J* 15.3, 8.3, 1.2 Hz), 4.03 (2H, dd, *J* 5.7, 1.2 Hz), 2.76 (1H, ddd, *J* 7.7, 4.5, 3.3 Hz), 2.38 (1H, bs, OH), 1.79 (1H, dddd, *J* 9.4, 8.3, 6.4, 3.3 Hz), 1.21 (1H, ddd, *J* 7.7, 6.4, 4.4 Hz), 1.06 (1H, ddd, *J* 9.4, 4.5, 4.4 Hz)

δ_C (dept) 131.2(+), 129.6(+), 62.9(-), 24.5(+), 20.4(-), 17.4(+)

ν_{max}/cm^{-1} 3332, 3051, 2999, 2925, 1666, 1438, 1375, 1265, 1231, 1087, 1005, 963, 738

m/z 194 $(M + NH_4)^+$, 176 $(M + NH_4 - H_2O)$

Measured mass: 176.0075, Calc. for $C_6H_{11}BrN$: 176.0078.

$[\alpha]_D^{23}$ -108.1 ° (*c* 1.10, $CHCl_3$)

5.3.56 The preparation of (E)-3-((1R,2S)-2-bromocyclopropyl)-prop-2-en-1-ol (123-R,S)

The title compound was prepared in 74 % yield from ethyl (*E*)-3-((1*R*,2*S*)-2-bromocyclopropyl)-prop-2-enoate using the procedure detailed above [***5.3.55***], all spectroscopic data was identical to that quoted previously.

$[\alpha]_D^{24}$ $+109.6$ ° (*c* 1.50, $CHCl_3$)

5.3.57 The preparation of n-butylboronic acid

An oven dried 1 litre round bottomed flask was charged with a solution of freshly distilled trimethyl borate (20.6 ml, 0.18 mol) in still dried diethyl ether (500 ml). The contents of the flask were cooled to 0 °C as sodium hydride as a dispersion in mineral oil (8.0 g, 0.20 mol) was added to the vigorously stirred solution. The reaction mixture was then cooled to –78 °C before adding a 2 M solution of *n*-butylmagnesium bromide in diethyl ether (100 ml, 0.20 mol) being careful to maintain an internal temperature less than –70 °C. The resulting reaction mixture was stirred for 2 hours at –78 °C before warming to room temperature and stirring for a further 30 minutes; the solution was then cooled to 0 °C before water (100 ml) and concentrated hydrochloric acid (to pH 1) was added with caution. The biphasic solution was stirred for 15 minutes before being separated and the aqueous layer extracted with diethyl ether (3 × 100 ml). The combined organic fractions were washed with 10 % hydrochloric acid (150 ml) and water (150 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as white paste. Recrystallisation from dichloromethane (50 ml) afforded *n-butylboronic acid* as a white flaky solid, (11.6 g, 0.11 mol, 63 %), mp 92 - 93 °C. All spectroscopic data was identical to that of commercially available material.[217]

5.3.58 The preparation of anhydrous dimethylamine

A 500ml round bottomed flask equipped for stirring was charged with potassium hydroxide pellets (10.0 g, 0.18 mol) and a 40 % aqueous solution of dimethylamine (300 ml). The flask was fitted for distillation with a Claisen still head and condenser

and the solution heated to 60 °C, the distillate was passed through a 50 cm drying tube (packed with potassium hydroxide) and collected in a cooled quick-fit measuring cylinder. The product, *anhydrous dimethylamine* (110 ml) was collected as a colourless liquid, the volatile solution was then used immediately.

5.3.59 The preparation of (R,R)-(+)-N,N,N',N'-tetramethyltartaric acid diamide

A dry 250 ml quick fit conical flask fitted with a calcium chloride drying tube was charged with diethyl-L-tartrate (88.0 g, 0.43 mol) in freshly distilled methanol (80 ml). To the solution, freshly distilled dimethylamine (approx 120 ml, excess) was added in one aliquot; the resulting solution was swirled briefly for 5 minutes and left to stand at room temperature in the back of the fume hood for 5 days.

Upon return, large "brick" shaped crystals had formed, the solution was decanted away and the crystals washed with cold methanol (50 ml), after drying *in-vacuo* for 5 hours, *(R,R)-(+)-N,N,N',N'-tetramethyltartaric acid diamide* was subsequently recovered as a white crystalline solid (54.9 g, 0.27 mol, 63 %), mp 187 °C, (lit.,[107c] mp 187 - 189 °C).

δ_H	4.62 (2H, d, *J* 7.3 Hz), 4.21 (2H, bd, *J* 7.3 Hz), 3.10 (6H, s), 2.98 (6H, s), the signal at 4.62 ppm collapsed to a singlet and the signal at 4.21 ppm disappeared when the sample was shaken with D_2O.
ν_{max}/cm^{-1}	3299, 2921, 2853, 1618, 1512, 1463, 1430, 1404, 1377, 1257, 1153, 1054, 1045, 862, 758
$[\alpha]_D^{23}$	+45.6 ° (*c* 1.50, EtOH)

A second crop of crystals (9.4 g, 0.05 mol) was recovered after a further 10 days at room temperature.

5.3.60 The preparation of (4R,5R)-2-butyl-N,N,N',N'-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide (56-R,R)

A 50 ml round bottomed flask equipped for magnetic stirring and azeotropic removal of water using a Dean-Stark trap was charged with (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartaric acid diamide (3.85 g, 18.9 mmol), *n*-butylboronic acid (2.3 g, 22.5 mmol) and toluene (40 ml). The mixture was heated under strong reflux for 24 hours to enable the azeotropic removal of water produced in the reaction. The solution was

then cooled to room temperature and the solvent removed under reduced pressure. The residue was treated with a minimal amount of still dried dichloromethane (10 ml), and filtered to remove excess *n*-butylboronic acid. The filtrate was concentrated under reduced pressure to yield *(4R,5R)-2-butyl-N,N,N',N'-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide* as a grey coloured viscous oil, (4.64 g, 17.2 mmol, 91 %). All spectroscopic data was identical to that of commercially available material.[107c]

δ_H	5.5 (2H, s), 3.20 (6H, s), 2.98 (6H, s), 1.30 (4H, m), 0.85 (5H, m)
δ_C	168.4, 75.7, 37.1, 35.9, 25.8, 25.2, 13.8, 10.0
ν_{max}/cm^{-1}	2989, 2929, 2871, 1649, 1502, 1502, 1465, 1402, 1256, 1156, 1061

5.3.61 The preparation of (4S,5S)-2-butyl-N,N,N',N'-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide (56-S,S)

The title compound was prepared in 95 % yield from commercial (*S,S*)-(-)-*N,N,N',N'*-tetramethyltartaric acid diamide using the procedure detailed above [***5.3.60***], all spectroscopic data was identical to that quoted above.

5.3.62 A general procedure for the preparation of bis(iodomethyl)zinc.DME complex

A suitably sized, oven dried round bottomed flask was charged with a 1 M solution of diethylzinc in hexanes (1.0 equiv); the diethylzinc solution was diluted with an equal volume of still dried dichloromethane and the temperature reduced to –15 °C. Anhydrous 1,2-dimethoxyethane (1.0 equiv) was added to the stirred solution followed by the slow addition of freshly distilled diiodomethane (2.0 equiv). Care was taken not to allow the internal temperature to rise above –10 °C throughout the addition; the resulting milky solution was stirred for 5 minutes at –15 °C before use. When required, the solution was transferred to the reaction vessel either using a cannula or suitable syringe.

5.3.63 The preparation of (1S,2S)-2-phenyl-1-hydroxymethylcyclopropane

An oven dried 250 ml round bottomed flask equipped with an egg shaped magnetic follower was charged with a solution of cinnamyl alcohol (1.0 g, 7.5 mmol) in still dried dichloromethane (35 ml), powdered oven dried 4 Å molecular sieves (300 mg)

and a solution of (4*R*,5*R*)-2-butyl-*N,N,N',N'*-tetramethyl-1,3,2-dioxaborolane-4,5-dicarbox amide (2.20g, 8.2 mmol) in still dried dichloromethane (2 ml). The vigorously stirred solution was cooled to –15 °C and a freshly prepared [***5.3.62***] solution of bis(iodomethyl)zinc.DME (37 mmol in 37 ml of dry dichloromethane) was added dropwise maintaining the internal temperature below –10 °C. The reaction mixture was stirred at –15 °C for 2 hours after which time TLC showed the complete consumption of starting material. The reaction was quenched by the careful addition of saturated aqueous ammonium chloride (5 ml) and water (50 ml). The biphasic solution was stirred vigorously for 10 minutes before separation of the layers and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic fractions were stirred vigorously for 12 hours with 5 M potassium hydroxide solution (50 ml). The solution was again separated and the organic layer washed with 10 % aqueous hydrochloric acid (50 ml), saturated sodium bicarbonate solution (25 ml) and water (50 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the crude product as a yellow oil, column chromatography on silica afforded *(1S,2S)-2-phenyl-1-hydroxymethylcyclopropane* as a colourless oil, (1.02 g, 6.9 mmol, 84 %). All spectroscopic data was consistent with that appearing in the literature.[107]

δ_H	7.31 (2H, m, Ar H), 7.23 (1H, m, Ar H), 7.09 (2H, m, Ar H), 3.61 (1H, dd, *J* 11.3, 6.7 Hz, AB pattern), 3.55 (1H, dd, *J* 11.3, 6.8 Hz, AB pattern), 1.79 (1H, ddd, *J* 9.3, 4.4, 4.3 Hz), 1.55 (1H, bs, OH), 1.42 (1H, m), 0.91 (2H, m)
δ_C (dept)	142.2( ), 128.4(+), 125.8(+), 125.6(+), 66.5(-), 25.3(+), 21.3(+), 13.9(-)
ν_{max}/cm^{-1}	3420, 3058, 3025, 2953, 2927, 2869, 1604, 1496, 1463, 1324, 1193, 1110, 1092, 1031, 965, 744, 696
$[\alpha]_D^{22}$	+65.4 ° (c 1.39, EtOH)

5.3.64 The preparation of 2-((1S,2R)-2-bromocyclopropyl)-(1S,2S)-1-hydroxymethylcyclopropane (121)

An oven dried 50 ml round bottomed flask was charged with a solution of (*E*)-3-((1*S*,2*R*)-2-bromocyclopropyl)-prop-2-en-1-ol (250 mg, 1.4 mmol) and (4*R*,5*R*)-2-butyl-*N,N,N',N'*-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide (405 mg, 1.5 mmol) in still dried dichloromethane (10 ml); powdered 4 Å molecular sieves (250

mg) were added to the stirred solution which was then cooled to –30 °C. A freshly prepared [***5.3.62***] solution of bis(iodomethyl)zinc.DME (7.0 mmol in 7 ml of dry dichloromethane) was added to the solution dropwise, maintaining an internal temperature below –20 °C. The resulting solution was stirred at –30 °C for 1 hour and at 0 °C for a further 2 hours, the solution was then warmed to room temperature and stirred overnight.

The reaction was quenched by cooling to 0 °C followed by the careful addition of saturated aqueous ammonium chloride (1 ml) and water (5 ml). The biphasic solution was stirred vigorously for 10 minute before separation of the layers and the aqueous phase extracted with diethyl ether (2 × 5 ml). The combined organic fractions were stirred vigorously for 6 hours with 5 M potassium hydroxide solution (10 ml). The solution was again separated and the organic layer washed with 10 % aqueous hydrochloric acid (5 ml), saturated sodium bicarbonate solution (2 ml) and water (5 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield the crude product as a cream coloured paste. Column chromatography on silica afforded pure *2-((1S,2R)-2-bromocyclopropyl)-(1S,2S)-1-hydroxymethyl cyclopropane* as a colourless oil, (160 mg, 0.8 mmol, 60 %).

δ_H	3.41 (1H, dd, *J* 11.5, 6.4 Hz, AB pattern), 3.35 (1H, dd, *J* 11.5, 6.2 Hz, AB pattern), 2.57 (1H, ddd, *J* 7.5, 3.5, 3.4 Hz), 1.49 (1H, bs, OH), 1.30 (1H, m), 0.85 (2H, m), 0.75 (2H, m), 0.32 (2H, m)
δ_C (dept)	66.2(-), 23.6(+), 19.6(+), 18.4(+), 17.1(+), 14.4(-), 8.4(-)
ν_{max}/cm^{-1}	3328, 3068, 3000, 2921, 2870, 1463, 1437, 1416, 1235, 1070, 1037, 856, 734
m/z	208 $(M + NH_4)^+$, 190 $(M)^+$

Measured mass: 208.0338, Calc. for $C_7H_{15}BrNO$: 208.0337.

$[\alpha]_D^{23}$	–62.1 ° (*c* 1.09, $CHCl_3$)

5.3.65 The preparation of 2-((1S,2R)-2-bromocyclopropyl)-(1R,2R)-1-hydroxymethylcyclopropane (119)

The title compound was prepared in 64 % yield from (*E*)-3-((1*S*,2*R*)-2-bromocyclopropyl)-prop-2-en-1-ol. The procedure outlined above [***5.3.64***] was followed, employing the alternative boroxolane catalyst, (4*S*,5*S*)-2-butyl-*N,N,N',N'*-

tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide instead. Analytical data was identical to that quoted previously [***5.3.64***].

δ_C (dept) 66.2(-), 23.7(+), 18.9(+), 18.5(+), 16.9(+), 13.9(-), 7.5(-)

$[\alpha]_D^{22}$ –82.0 ° (*c* 1.01, $CHCl_3$)

5.3.66 The preparation of 2-((1R,2S)-2-bromocyclopropyl)-(1S,2S)-1-hydroxymethylcyclopropane (120)

The title compound was prepared in 59 % yield from (*E*)-3-((1*R*,2*S*)-2-bromocyclopropyl)-prop-2-en-1-ol using the procedure detailed above [***5.3.64***]. Analytical data was identical to that quoted previously [***5.3.65***].

$[\alpha]_D^{24}$ +80.5 ° (*c* 0.91, $CHCl_3$)

5.3.67 The preparation of 2-((1R,2S)-2-bromocyclopropyl)-(1R,2R)-1-hydroxymethylcyclopropane (122)

The title compound was prepared in 64 % yield from (*E*)-3-((1*R*,2*S*)-2-bromocyclopropyl)-prop-2-en-1-ol. The procedure outlined above [***5.3.64***] was followed, employing the alternative boroxolane catalyst, (4*S*,5*S*)-2-butyl-*N,N,N',N'*-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide instead. Analytical data was identical to that quoted previously [***5.3.64***].

$[\alpha]_D^{24}$ +65.0 ° (*c* 1.03, $CHCl_3$)

5.3.68 The preparation of α,α-dimethoxytoluene

A 250 ml round bottomed flask equipped for magnetic stirring and reflux was charged with freshly distilled benzaldehyde (21.2 g, 0.2 mol), trimethyl orthoformate (24.0 g, 0.225 mol), methanol (100 ml) and Amberlite® IR-120 [H^+] (1.0 g). The resulting solution was stirred at reflux and the reaction monitored by TLC and GLC. When all the starting material had been consumed, after 4 hours, the solution was cooled to room temperature and the Amberlite® removed by filtration. The filtrate was concentrated *in-vacuo* and the product isolated by simple distillation. *α,α-Dimethoxytoluene* was recovered (25.3 g, 0.166 mol, 83 %) as a colourless liquid, bp

87 - 89 °C at 14 mmHg. All observed spectroscopic data was identical to that of commercially available material.[218]

5.3.69 The preparation of methyl-4,6-O-benzylidene-α-D-glucopyranoside (137)

A dry 250 ml round bottomed flask was charged with oven dried (100 °C overnight) methyl-α-D-glucopyranoside (9.7 g, 50 mmol), α,α-dimethoxytoluene (7.6 g, 50 mmol), dry DMF (40 ml), *p*-toluenesulfonic acid (200 mg, 0.1 mmol) and rotated on an evacuated rotary evaporator at room temperature until all solids had been dissolved. The water bath temperature was then raised to 55 °C (± 5 °C) to enable a gentle reflux within the solvent vent; this was carried out for 40 minutes before raising the bath temperature to 100 °C and removing all solvent. The crude product was recovered as a white powder that yielded pure *methyl-4,6-O-benzylidene-α-D-glucopyranoside* as a white crystalline solid (11.3 g, 39.9 1 mmol, 80 %) upon recrystallisation from propan-2-ol (100 ml), mp 164 °C, (lit.,[178] mp 164 - 165 °C).

δ_H	7.50 (2H, m, Ar H), 7.40 (3H, m, Ar H), 5.58 (1H, s), 4.82 (1H, d, *J* 5.0 Hz), 4.31 (1H, dd, *J* 12.5, 5.0 Hz), 3.97 (1H, bm), 3.78 - 3.85 (2H, m), 3.68 (1H, ddd, *J* 12.5, 12.5, 5.0 Hz), 3.54 (1H, d, *J* 12.5 Hz), 3.46 (3H, s, OMe), 2.68 (1H, s), 2.20 (1H, d, *J* 12.5 Hz)
δ_C (dept)	136.0(.), 128.0(+), 127.9(+), 126.0(+), 101.6(+), 99.9(+), 81.0(+), 72.4(+), 70.5(+), 68.9(-), 62.2(+), 55.1(+)
ν_{max}/cm^{-1}	3461, 3352, 3018, 2913, 1670, 1450, 1372, 1192, 1060, 997, 757, 668
m/z	283 (M + 1), 251 (M - OMe)
$[\alpha]_D^{20}$	+113.1 ° (c 1.018, $CHCl_3$)

5.3.70 The preparation of methyl-2,3-bis-O-diphenylphosphino-4,6-O-benzylidene-α-D-glucopyranoside

An oven dried 100 ml two-necked flask equipped for magnetic stirring and reflux was charged with methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (540 mg, 1.9 mmol), imidazole (650 mg, 9.6 mmol) and dry toluene (30 ml). The resulting solution was stirred at room temperature as chlorodiphenylphosphine (780 mg, 3.5 mmol) was added dropwise by syringe. The resulting thick suspension was stirred for 15 minutes at 80 °C before iodine (810 mg, 3.2 mmol) was added over a period of 10 minutes, the

solution was then stirred at 80 °C overnight. The mixture was cooled to room temperature and washed with aqueous sodium thiosulfate solution (25 ml), 1M sodium hydroxide (25 ml) and water (25 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed to yield a thick creamy oil which was purified by flash column chromatography on silica. *Methyl-2,3-bis-O-diphenylphosphino-4,6-O-benzylidene-α-D-glucopyranoside* was recovered, after solvent removal, as a yellow powder (568 mg, 0.87 mmol, 46 %), mp 130 - 131 °C, (lit.,[187] mp 131 °C).

δ_H	7.90 - 7.73 (8H, m, Ar H), 7.60 - 7.39 (14H, m, Ar H), 7.38 (3H, m, Ar H), 5.48 (1H, s), 4.78 (1H, d, *J* 3.7 Hz), 4.23 (2H, dd, *J* 9.3, 6.3 Hz), 4.12 (1H, m), 3.82 (1H, m), 3.64 (1H, t, *J* 10.2 Hz), 3.44 (1H, t, *J* 9.3 Hz), 3.38 (3H, s, OMe)
δ_C	136.6, 132.6, 132.0, 131.8, 131.6, 131.4, 129.1, 128.8, 128.7, 128.5, 128.2, 126.3, 101.9, 98.8, 81.1, 76.8, 69.2, 68.9, 61.9, 55.6
ν_{max}/cm^{-1}	3015, 2984, 2918, 1947, 1875, 1740, 1670, 1496, 1450, 1334, 1116, 1060, 997, 668
m/z	484 ($M + NH_4 - PPh_2$)
$[\alpha]_D^{20}$	-8.1 ° (c 2.5, $CHCl_3$)

5.3.71 The attempted preparation of methyl-4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside (134) (Imidazole/I_2)

To a stirred solution of methyl-2,3-bis-*O*-diphenylphosphino-4,6-*O*-benzylidene-α-D-glucopyranoside (300 mg, 0.4 mmol) and imidazole (56 mg, 0.82 mmol) in toluene (10 ml), was added iodine (210 mg, 0.82 mmol) at 80 °C. The resulting solution was then stirred at reflux for 4 hours, when TLC showed no reaction. The solution was stirred at reflux overnight. TLC again showed no reaction and only starting material was observed; aqueous work up enabled near quantitative recovery of the starting material only.

5.3.72 The attempted preparation of methyl-4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside (134) (Zn/Acetic acid)

To a stirred solution of methyl-2,3-bis-*O*-diphenylphosphino-4,6-*O*-benzylidene-α-D-glucopyranoside (208 mg, 0.32 mmol) in absolute ethanol (20 ml), was added zinc powder (200 mg, 3.22 mmol) and glacial acetic acid (40 mg, 0.65 mmol) at room temperature. The resulting solution was then stirred for 1 hour before being filtered through a pad of celite. The filtrate was extracted with ethyl acetate (2 × 25 ml) and washed with 1M sodium hydroxide solution (2 × 10 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and solvent removed under reduced pressure to yield a cream coloured residue (184 mg). Analysis of the residue showed that only starting material remained.

5.3.73 The preparation of methyl-4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside (134) (method 1)

An oven dried 500 ml three-necked flask fitted for mechanical stirring and reflux at a controlled temperature was charged with dry toluene (200 ml), finely ground triphenylphosphine (18.6 g, 70.8 mmol) and finely ground imidazole (4.84 g, 70.8 mmol). The solution was heated to near reflux (100 °C) before adding methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (5.0 g, 17.7 mmol). After heating the solution at reflux (110 °C) for 30 minutes, ground iodine (13.48 g, 53.2 mmol) was added in small portions over a period of 70 minutes whilst stirring the solution vigorously (if the iodine was added too quickly, a red tar was formed around the reaction vessel and consequently the yield was considerably reduced). After each addition, the sides of the reaction vessel were washed with dry toluene making up the total volume to approximately 450 ml. The resulting solution was then heated under strong reflux for 5 hours before being cooled to room temperature and stirred for a further 90 minutes.

Iodine (4.5 g, 18 mmol) and 10 % sodium hydroxide solution (50 ml) was then added to the reaction vessel which was stirred until any residue was dissolved. The solution was then decanted into a large separating funnel and washed with saturated sodium thiosulfate solution (2 × 200 ml), saturated sodium bicarbonate solution (2 × 200 ml) and water (2 × 200 ml). The aqueous washings were extracted with dichloromethane (2 × 50 ml) and the combined organic fractions dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was

loaded on silica and purified by column chromatography to yield *methyl-4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside* as a white flake like, crystalline solid (3.56 g, 14.3 mmol, 81 %), mp 117 °C, (lit.,[188] mp 116 - 118 °C).

δ_H	7.42 (5H, m, Ar H), 6.16 (1H, d, *J* 10.4 Hz), 5.75 (1H, dt, *J* 10.4, 2.4 Hz), 5.60 (1H, s), 4.93 (1H, bs), 4.35 (1H, dd, *J* 8.5, 3.0 Hz), 4.17 (1H, dd, *J* 8.5, 2.4 Hz), 3.74 - 3.95 (2H, m), 3.49 (3H, s, OMe)
δ_C (dept)	137.4(.), 130.8(+), 129.0(+), 128.4(+), 126.7(+), 126.3(+), 102.2(+), 96.1(+), 75.3(+), 69.5(-), 63.9(+), 55.9(.)
ν_{max}/cm^{-1}	3016, 2983, 2829, 1652, 1465, 1450, 1384, 1314, 1217, 1105, 1070, 963, 696
m/z	266 $(M + NH_4)^+$, 249 (M + 1)

Found: C, 68.1; H, 6.8 %. Calc. for $C_{14}H_{16}O_4$: C, 67.9; H, 6.75 %.

$[\alpha]_D^{20}$	+126.1 ° (c 1.1, $CHCl_3$)

5.3.74 The preparation of methyl-4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside (134) (method 2)

An oven dried 100 ml two-necked flask equipped for magnetic stirring and reflux was charged with methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (540 mg, 1.9 mmol) and dry toluene (50 ml). Triphenylphosphine (2.00 g, 7.6 mmol), iodoform (1.49 g, 3.8 mmol) and imidazole (260 mg, 3.8 mmol) were added to the vigorously stirred solution at room temperature before bringing the reaction mixture to reflux. The reaction was followed by TLC and when all starting material had been consumed the solution was cooled to room temperature before being washed with saturated sodium bicarbonate solution. The biphasic solution was separated and the aqueous phase extracted with toluene (2 × 10 ml). The combined organic solutions were washed with sodium thiosulfate solution (15 ml), and water (20 ml) before being dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in-vacuo* to yield a brown residue that was extracted with hot hexane (50 ml). Evaporation of the hexane extract furnished *methyl-4,6-O-benzylidene-α-D-erythro-hex-2-enopyranoside* as a white crystalline solid (165 mg, 0.6 mmol, 34 %). mp 116 - 118 °C, all other analytical data was identical to that quoted previously [***5.3.73***]

5.3.75 The preparation of 7,7-dichloro-4,5-O-benzylidene-4-hydroxymethyl-2-methoxy-3-oxa-bicyclo[4.1.0]heptan-5-ol (138)

A 250 ml three-necked flask fitted for mechanical stirring, reflux and addition was charged with methyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (4.5 g, 18.0 mmol), chloroform (100 ml) and *n*-hexadecyltrimethylammonium bromide (3.0 g, 0.84 mmol, PTC) the resulting solution was stirred vigorously whilst 50 % aqueous sodium hydroxide solution (60 ml) was added dropwise over 90 minutes. The resulting solution was stirred at room temperature for 2 days after which time; TLC analysis showed that starting material was still present. The solution was poured onto brine solution (300 ml) and extracted into dichloromethane (2 × 100 ml), dried over anhydrous magnesium sulfate, filtered and reduced in volume to yield a brown solid. The solid was dissolved in diethyl ether and filtered to remove the undissolved phase transfer catalyst. The resulting solution was the evaporated to dryness and the crude product was treated with fresh reagents (as above). After a further 2 days the reaction was worked up in the same manner. The crude product was recrystallised from hot propan-2-ol (125 ml) to yield *7,7-dichloro-4,5-O-benzylidene-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0 heptan -5-ol* as a white crystalline solid (2.67 g, 8.06 mmol, 45 %).

The concentrated mother liquor was loaded on silica and purified by column chromatography to yield additional product as a fine white powder (0.62 g, 1.9 mmol, 12 %). Combined yield (3.38 g, 10.2 mmol, 57 %) mp 141 - 143 °C.

δ_H	7.42 (5H, m, Ar H), 5.65 (1H, s), 4.83 (1H, s), 4.30 (1H, dd, *J* 8.0, 3.4 Hz), 3.70 (3H, m), 3.45 (3H, s, OMe), 2.30 (1H, dd, *J* 11.1, 2.4 Hz), 2.00 (1H, d, *J* 11.1Hz)
δ_C	137.1, 129.3, 128.4, 126.2, 102.3, 95.4, 73.0, 69.3, 61.6, 60.3, 55.2, 31.2, 29.3
ν_{max}/cm^{-1}	3054, 3024, 3016, 2983, 2893, 1467, 1366, 1216, 1066, 1004, 967, 700
m/z	348 $(M + NH_4)^+$, 331 (M + 1)

Measured mass: 348.0772, Calc. for $C_{15}H_{20}Cl_2NO_4$: 348.0769

Found: C, 54.2; H, 4.5 %. Calc. for $C_{15}H_{16}Cl_2O_4$: C, 54.4; H, 4.9 %.

$[\alpha]_D^{19}$	+153.0 ° (c 0.52, MeOH)

5.3.76 The preparation of 7,7-dichloro-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol (139)

A solution of 7,7-dichloro-4,5-*O*-benzylidene-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol (100 mg, 3.0 mmol) in methanol (10 ml) was hydrogenolysed in the presence of 5 % palladium on charcoal (500 mg) under hydrogen gas (atmospheric pressure). Analysis by TLC showed no starting material remained after 4 hours and the catalyst was consequently removed by filtration through a celite pad and washed well with methanol. The combined filtrate and washings were evaporated *in vacuo.* The residue was absorbed on silica and purified by column chromatography yielding *7,7-dichloro-4-hydroxymethyl-2-methoxy-3-oxabicyclo [4.1.0]heptan-5-ol* as a white crystalline solid (720 mg, 2.9 mmol, 98 %), mp 141 - 142 °C.

δ_H	4.82 (1H, s), 3.94 (1H, ddd, *J* 9.6, 5.3, 1.6 Hz), 3.81 (2H, overlapping dd, *J* 4.2, 4.1 Hz), 3.44-3.49 (1H, m), 3.41 (3H, s, OMe), 2.45 (1H, d, *J* 5.3 Hz, OH), 2.11 (1H, dd, *J* 11.0, 1.6 Hz), 1.93 (1H, d, *J* 11.0 Hz), 1.81 (1H, t, *J* 4.1 Hz, OH)
δ_H [D_2O]	4.82 (1H, s), 3.94 (1H, dd, *J* 9.6, 1.6 Hz), 3.81 (2H, d, *J* 4.2 Hz), 3.44-3.49 (1H, simplified m), 3.41 (3H, s, OMe), 2.11 (1H, dd, *J* 11.0, 1.6 Hz), 1.93 (1H, d, *J* 11.0 Hz)
δ_C	94.7, 68.2, 62.8, 62.4, 55.0, 33.8, 29.0, 20.3
ν_{max}/cm^{-1}	3251, 3020, 2983, 2955, 1474, 1438, 1379, 1130, 1058, 932
m/z	260 $(M + NH_4)^+$

Measured mass: 260.0459, Calc. for $C_8H_{16}Cl_2NO_4$: 260.0456

Found: C, 39.5; H, 4.85 %. Calc. for $C_8H_{12}Cl_2O_2$: C, 39.5; H, 5.0 %.

$[\alpha]_D^{19.5}$	+74.3 ° (c 0.24, MeOH)

5.3.77 The preparation of 7,7-dichloro-4,5-O-diacetyl-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol

Finely ground 7,7-dichloro-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol (200 mg, 0.82 mmol) was carefully added to a stirred solution of acetic anhydride (5 ml) and pyridine (1 ml). The resulting solution was then warmed to 60 °C and the reaction monitored by TLC. After 90 minutes no starting material remained and all

volatiles were removed *in-vacuo*. The residue was dissolved in dichloromethane (10 ml) and the resulting solution washed with saturated ammonium chloride solution (2 × 5 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and reduced in volume under reduced pressure. The title compound, *7,7-dichloro-4,5-O-diacetyl-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol*, was recovered as a pale yellow thick oil (270 mg, 0.8 mmol, 98 %).

δ_H	4.88 (1H, s), 4.83 (1H, dd, *J* 10.1, 1.7 Hz), 4.01 - 4.21 (2H, m), 3.79 (1H, ddd, *J* 10.1, 5.6, 2.8 Hz), 3.43 (3H, s, OMe), 2.13 (3H, s), 2.07 (3H, s), 2.02 (1H, dd, *J* 10.9, 1.7 Hz), 1.91 (1H, d, *J* 10.9 Hz)
δ_C	170.6, 169.5, 94.8, 64.3, 62.6, 62.5, 58.9, 55.0, 31.7, 28.6, 20.8, 20.7
ν_{max}/cm^{-1}	2956, 2835, 1745, 1336, 1221, 1128, 1044, 973, 800
m/z	344 $(M + NH_4)^+$, 327 $(M)^+$

Measured mass: 344.0676, Calc. for $C_{12}H_{20}Cl_2NO_6$: 344.0668

$[\alpha]_D^{19.5}$	+84.9 ° (c 1.01, MeOH)

5.3.78 The preparation of 7,7-dichloro-4,5-O-di(t-butyldimethylsilyl)-4-hydroxymethyl-2-methoxy-3-oxabicyclo [4.1.0] heptan-5-ol

An oven dried 25 ml round bottomed flask equipped for magnetic stirring was charged with 7,7-dichloro-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol (200 mg, 0.82 mmol) and imidazole (560 mg, 8.2 mmol) in dry DMF (5 ml). The resulting solution was stirred at 0 °C as a solution of TBDMS-Cl (610 mg, 4.1 mmol) in dry DMF (3 ml) was added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with water and extracted with dichloromethane (2 × 10 ml). The combined organic fractions were washed with water (2 × 10 ml), dried over anhydrous magnesium sulfate, filtered and solvent removed to yield a creamy paste. The crude product was purified by flash column chromatography on silica and pure *7,7-dichloro-4,5-O-di(t-butyldimethylsilyl)-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol* was subsequently recovered as a thick colourless oil, after solvent removal (370 mg, 0.78 mmol, 96 %).

δ_H	4.78 (1H, s), 3.82 (1H, dd, *J* 11.1, 1.7 Hz), 3.71 (1H, dd, *J* 9.6, 1.7 Hz), 3.63 (1H, dd, *J* 11.1, 6.0 Hz), 3.40 - 3.43 (1H, m), 3.40 (3H, s, OMe),

1.96 (1H, dd, *J* 11.2, 1.7 Hz), 1.85 (1H, d, *J* 11.2 Hz), 0.93 (9H, s), 0.88 (9H, s), 0.18 (3H, s), 0.13 (3H, s), 0.05 (3H, s), 0.04 (3H, s)

δ_C 94.5, 70.2, 62.3, 62.2, 60.0, 54.4, 35.0, 29.4, 25.8, 25.6, 18.3, 17.9

ν_{max}/cm^{-1} 2954, 2929, 2856, 1471, 1362, 1254, 1130, 1090, 1069

m/z 489 $(M + NH_4)^+$, 471 $(M)^+$

Measured mass: 488.2180, Calc. for $C_{20}H_{44}Cl_2NO_4Si_2$: 488.2186

$[\alpha]_D^{19.5}$ +72.4 ° (c 1.10, MeOH)

5.3.79 The preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-propane-1,2,3-triol (143)

An oven dried 25 ml two-necked flask equipped for magnetic stirring and reflux was charged with 7,7-dichloro-4-hydroxymethyl-2-methoxy-3-oxabicyclo[4.1.0]heptan-5-ol (1.0 g, 4.1 mmol) and dry THF (25 ml); the resulting solution was stirred at room temperature while 1,3-propanedithiol (0.96 ml, 9.2 mmol) was added dropwise. The solution was then cooled to -60 °C before adding a solution of freshly distilled borontrifluoride diethyletherate in still dried dichloromethane (0.4 ml, 3.3 mmol in 2.0 ml of dichloromethane) dropwise over a period of 10 minutes. The resulting solution was then allowed to warm to room temperature before heating to reflux whilst monitoring the reaction by TLC. The reaction was judged to have reached completion after 48 hours and quenched by adding 10 % sodium hydroxide solution (5 ml) and water (5 ml). The product was extracted into ethyl acetate (3 × 10 ml) and then washed with saturated sodium bicarbonate solution (2 × 10 ml) and water (2 × 10 ml). The combined organic fractions were then dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was loaded on silica and purified by column chromatography to yield the title compound, *((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-propane-1,2,3-triol* as a white powder (940 mg, 2.9 mmol, 70.7 %), mp 142 - 143 °C.

δ_H 3.69 - 3.95 (5H, m, overlapping signals), 3.05 (1H, bd, *J* 5.3 Hz), 2.91 (4H, m, overlapping signals), 2.75 (1H, bd, *J* 3.6 Hz), 2.02 - 2.20 (4H, m, overlapping signals), 1.97 (1H, dd, *J* 6.9, 14.1 Hz)

δ_H [MeOD] 4.00 (1H, m), 3.94 (1H, m), 3.77 (1H, m), 3.68 (2H, m), 2.90 (4H, m), 2.08 (3H, m), 1.89 (1H, m)

δ_C [d^4-MeOH] 73.1(+), 70.5(+), 62.3(-), 60.45(.), 42.6(+), 36.6(+), 36.5(+), 29.0(-), 28.9(-), 24.8(-)

ν_{max}/cm^{-1} 3383, 2988, 2893, 2828, 1421, 1277, 1215, 1050, 933, 825

m/z 336 $(M + NH_4)^+$

Measured mass: 336.0260, Calc. for $C_{10}H_{20}Cl_2NO_3S_2$: 336.0262.

$[\alpha]_D^{19.5}$ –6.6 ° (c 0.23, MeOH)

5.3.80 The preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol (144), (method 1)

A 50 ml single necked flask equipped for magnetic stirring was charged with ((1R,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-propane-1,2,3-triol (1.0 g, 3.1 mmol), reagent grade propanone (30 ml), anhydrous copper (II) sulfate (2.0 g) and a catalytic amount of *p*-toluenesulfonic acid. The resulting solution was stirred at room temperature whilst monitoring the reaction by TLC. The solution was stirred for 3 hours before quenching with saturated sodium bicarbonate solution (10 ml) and water (10 ml). The solution was filtered to remove the inorganic salt which was washed with propanone (2 × 5 ml); the organic fractions were then washed with saturated sodium bicarbonate solution (3 × 10 ml) and water (3 × 10 ml), dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was loaded on silica and purified by column chromatography, *((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol* was recovered as a creamy coloured heavy oil (920 mg, 2.56 mmol, 82 %).

δ_H [d^6benzene]4.6 (1H, ddd, *J* 6.9, 6.9, 2.8 Hz), 3.99 (1H, dd, *J* 8.9, 6.9 Hz), 3.89 (1H, bdd, *J* 10.6, 2.8 Hz), 3.77 (1H, dd, *J* 8.9, 6.8 Hz), 3.68 (1H, d, *J* 11.8 Hz), 2.55 (1H, bs, OH), 2.13 - 2.30 (4H, m, dithiane), 1.91 (1H, dd, *J* 11.8, 10.8 Hz), 1.42 (1H, dd, *J* 10.8,10.6 Hz), 1.38 (3H, s, Me), 1.30 - 1.38 (2H, m, dithiane), 1.30 (3H, s, Me)

δ_C (dept) 109.3(.), 77.6(+), 67.8(+), 63.6(-), 62.0(.), 42.8(+), 36.6(+), 35.8(+), 29.6(-), 29.4(-), 26.9(+), 25.2(-), 25.0(+)

ν_{max}/cm^{-1} 3220, 2984, 2927, 1708, 1455, 1422, 1370, 1220, 1173, 1061, 966, 749

m/z 376 $(M + NH_4)^+$, 359 $(M)^+$

Measured mass: 376.0573, Calc. for $C_{13}H_{24}Cl_2NO_3S_2$: 376.0575.

$[\alpha]_D^{20}$ –7.8 ° (c 0.51, MeOH)

5.3.81 The preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol (144), (method 2)

A 10 ml single necked flask equipped for magnetic stirring was charged with ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-propane-1,2,3-triol (50 mg, 0.15 mmol), 2,2-dimethoxypropane (20 mg, 0.19 mmol) and dichloromethane (2 ml). The resulting suspension was stirred at 0 °C before adding a catalytic amount of pyridinium *p*-toluenesulfonate. The resulting solution was stirred at room temperature whilst monitoring the reaction by TLC. The solution was stirred for 1 hour before quenching with saturated sodium bicarbonate solution (1 ml) and water (2 ml); the solution was separated and the aqueous phase extracted with dichloromethane (2 ml). The combined organic fractions were washed with saturated sodium bicarbonate solution (3 ml) and water (3 ml) before drying over anhydrous magnesium sulfate. The dry solution was filtered and evaporated under reduced pressure to yield *((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol* as a thick creamy oil (54 mg, 0.15 mmol, 96 %) that did not require further purification. All analytical data was identical to that mentioned before [***5.3.80***].

5.3.82 The attempted preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-prop-2-yl mesylate (149), (method 1)

A 5 ml round bottomed flask was charged with a stirred solution of ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol (40 mg, 0.1 mmol) in dry dichloromethane (2 ml). The solution was cooled to 0 °C as triethylamine (0.03 ml, 0.16 mmol) was added dropwise. The resulting solution was stirred for 10 minutes before adding methanesulfonyl chloride (0.013 ml, 0.16 mmol). The solution was warmed to room temperature and stirred for 1 hour. The reaction was quenched by the addition of water (1 ml), the resulting biphasic solution separated and the aqueous fraction extracted with dichloromethane (2 × 1 ml). The combined organic fractions were washed with water (3 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as a yellow coloured gum. Purification by column chromatography on silica yielded a cream coloured thick oil (38 mg) which was identified as the starting material and was

recovered in 95 % yield; all spectroscopic data was identical to that detailed above [***5.3.80***].

5.3.83 The attempted preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-prop-2-yl mesylate (149), (method 2)

An oven dried 5 ml round bottomed flask was charged with a stirred solution of methanesulfonyl chloride (0.013 ml, 0.16 mmol) in still dried dichloromethane (1 ml). The solution was cooled to 0 °C before triethylamine (0.03 ml, 0.16 mmol) was added dropwise, the resulting solution was warmed to room temperature and stirred for 5 minutes before again cooling to 0 °C. A solution of ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol (40 mg, 0.1 mmol) in dry dichloromethane (2 ml) was added to the reaction mixture which was warmed to room temperature and stirred for 1 hour. The reaction was quenched by the addition of water (1 ml); the resulting biphasic solution was separated and the aqueous fraction extracted with dichloromethane (2 × 1 ml). The combined organic fractions were washed with water (3 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield a cream coloured gum (35 mg). The product was again identified as the starting material and was recovered in 88 % yield; all spectroscopic data was identical to that detailed above [***5.3.80***].

5.3.84 The attempted preparation of ((1R,3S)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-prop-2-yl tosylate

A 5 ml round bottomed flask was charged with a stirred solution of ((1*R*,3*S*)-2,2-dichloro-3-[1,3]dithian-2-yl-cyclopropyl)-1,3-isopropylidene-propan-2-ol (40 mg, 0.1 mmol) in dry dichloromethane (2 ml). The solution was cooled to 0 °C as triethylamine (0.03 ml, 0.16 mmol) was added dropwise. The resulting solution was stirred for a further10 minutes before adding *p*-toluenesulfonyl chloride (30 mg, 0.16 mmol) dropwise, to the cooled, stirred solution. The solution was warmed to room temperature and stirred for 1 hour. The reaction was quenched by the addition of water (1 ml), the resulting biphasic solution was separated and the aqueous fraction extracted with dichloromethane (2 × 1 ml). The combined organic fractions were washed with water (3 ml) and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed to yield the crude product as a yellow

coloured gum. Purification by column chromatography on silica yielded a cream coloured thick oil (38 mg) which was identified as the starting material and was recovered in 95 % yield; all spectroscopic data was identical to that detailed above [***5.3.80***].

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Appendix 1

Pergamon

Tetrahedron 55 (1999) 2773–2784

TETRAHEDRON

Enantiomerically Pure 2,2-Dibromocyclopropanecarboxylic Acids, Simple Chiral Building Blocks

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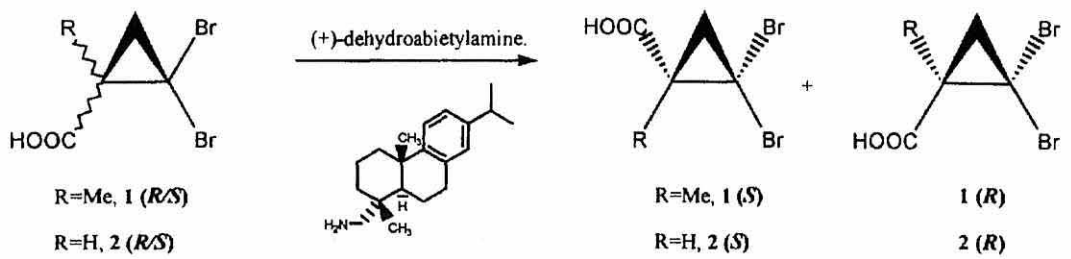
Abstract: Simple chiral building blocks 1-(*R*)- and 1-(*S*)-2,2-dibromocyclopropanecarboxylic acids and 2-(*R*)-bromo-1-(*S*)-cyclopropanecarboxylic acids and their 1-methyl analogues, have been obtained on a preparatively useful laboratory scale.

There are now many examples of the synthesis of single enantiomers of cyclopropanes, particularly in routes to important natural products and synthetic drugs,[1] either by introduction of the cyclopropane ring into starting materials taken from the chiral pool,[2] or, *e.g.* by processes such as cyclopropanation using a diazo-compound in the presence of a chiral catalyst.[3] Although many of these are very effective, there are relatively few reports of the preparation of single enantiomers of simple 1,1-dihalocyclopropanes and the applications of the many synthetically important reactions of such dihalides in asymmetric synthesis. We now report the resolution of two simple 2,2-dibromocyclopropanecarboxylic acids in procedures that may be readily applied on a large scale. In addition, we describe the application of a known reaction to convert optically pure acids **1** and **2**, into single enantiomers of the corresponding trans-2-bromocyclopropanecarboxylic acids **6** and **7**.



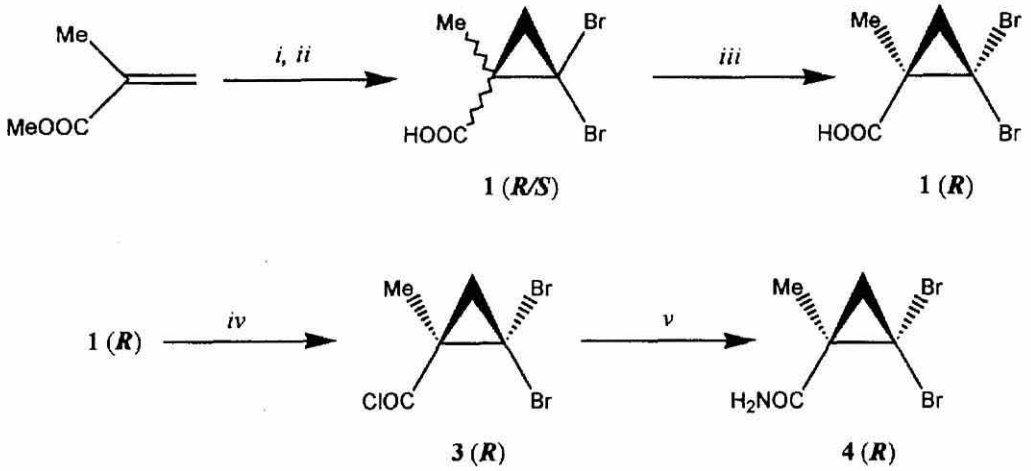
R=Me, **1** (*R/S*)
R=H, **2** (*R/S*)

R=Me, **1** (*S*)
R=H, **2** (*S*)

1 (*R*)
2 (*R*)

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00048-4

2,2-Dibromo-1-methylcyclopropanecarboxylic acid **1 (*R/S*)**, is readily prepared by the reaction of methyl methacrylate with bromoform and aqueous sodium hydroxide in the presence of a phase transfer catalyst;[4] subsequent acid hydrolysis leads to the formation of the desired product **(Scheme 1)**:



Scheme 1: *i*) $CHBr_3$, NaOH(aq), TEAB, 15 °C, 6 hrs, 89 %; *ii*) HBr(aq), reflux, 4 hrs, 95 %; *iii*) (+)-dehydroabietylamine resolution; *iv*) $SOCl_2$, reflux, 2 hrs, 96 %; *v*) NH_3(aq), 1 hr, 86 %.

The acid **1 (*R/S*)** was readily resolved by treatment with dehydroabietylamine in aqueous methanol,[5] the details of this procedure being presented below. The optical purity of the acid obtained in this way could be determined by gas liquid chromatography using a chiral column, which gave baseline resolution on both enantiomers of the corresponding methyl esters. The absolute stereochemistry of one enantiomer was determined unambiguously by X-ray crystallography on a single crystal of the amide **4 (*R*)** ($[\alpha]_D^{20}$ + 41.6) derived from **1 (*R*)**, the structure of which is shown in *Fig. 1*.

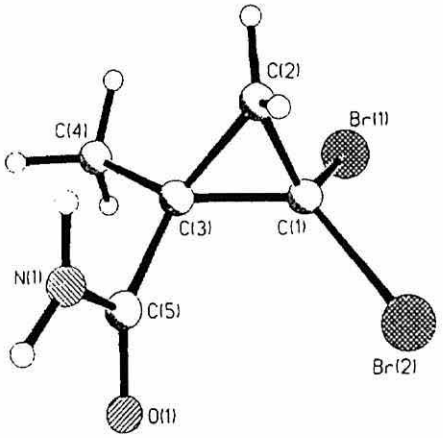
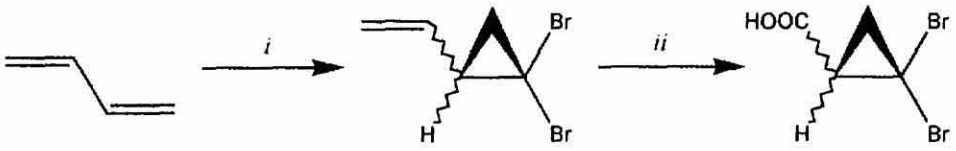


Fig. 1: Structure of one of the two independent molecules of 2,2-dibromo-1(*R*)-methylcyclopropanecarboxamide, showing the confirmed absolute stereochemistry. Molecules are linked together by N--H--O hydrogen bonds.

The analogous acid **2 (*R/S*)** cannot be obtained efficiently by the dihalocyclopropanation of methyl acrylate under phase transfer conditions because of further reaction, presumably initiated by removal of the proton adjacent to the acid-group.[6] However, addition of dibromocarbene to 1,3-butadiene leads readily to the vinylcyclopropane **5 (*R/S*)**,[7] which upon oxidation with aqueous potassium permanganate yielded the acid **2 (*R/S*)** in moderate yield **(Scheme 2)**. This oxidation has previously been carried out on small scale using sodium periodate and ruthenium trichloride in 89 % yield.[8] Although this yield is slightly higher than that obtained with potassium permanganate, it is not the oxidant of choice due to its higher cost when carrying out reactions on a larger scale.



5 (*R/S*) **2 (*R/S*)**

Scheme 2: *i*) $CHBr_3$, NaOH(aq), Pentane, -30 °C, 3 hrs, 76 %; *ii*) $KMnO_4$(aq), CH_2Cl_2, *n*-hexadecyltrimethyl-ammonium chloride, 20 °C, 48 hrs, 81 %.

Resolution of the acid **2 (*R/S*)** in a similar manner to that above, led again to both enantiomers of the optically pure acid. Unfortunately the resolution of **2 (*R/S*)** did not proceed with a similarly high recovery rate to that experienced for acid **1 (*R/S*)**. The recovery rate of each enantiomer (e.e. > 99 %) was around 20 % compared to a recovery rate of approximately 55 % of each enantiomer in the resolution of **1**. The absolute stereochemistry of **2 (*R*)** was established through its use in the synthesis of (2*S*, 3*R*, 4*S*)-3,4-methanoproline,[9] a natural product obtained from *Aesculus parviflora*. The absolute stereochemistry of this was determined again by X-ray crystallography.[10]

The racemic dibromocyclopropane carboxylic acids **1 (*R/S*)** and **2 (*R/S*)** upon reaction with methyllithium are known to lead to the corresponding trans-2-bromocyclopropane carboxylic acids. The reaction is thought to proceed by an intramolecular transfer of the acid proton within the intermediate 2-bromo-2-lithiocyclopropane.[11]

R=Me, **1 (*S*)** **6 (1*S*, 2*R*)**

R=H, **2 (*S*)** **7 (1*S*, 2*R*)**

Scheme 3: *i*) 1.2 equiv. MeLi, diethyl ether, 0 °C, 90 mins, 98 %.

The application of this known reaction to the optically active acids **1** (***S***) and **2** (***S***) led to the controlled formation of a second chiral centre and hence the optically active trans-monobromoacids **6** (**2*R*, 1*S***) and **7** (**2*R*, 1*S***) ($[\alpha]_D^{25}$ –81.5 and -154.1° respectively) in high yield **(Scheme 3).**

The acids **1**, **2**, **6**,and **7** provide valuable precursors to a wide range of simple chiral cyclopropanes, for example the synthesis of (2*S*, 3*R*, 4*S*)-3,4-methanoproline.[9] Other applications are currently under examination.

EXPERIMENTAL SECTION

Reagents were obtained from commercial suppliers and were used without further purification unless stated. Dichloromethane was distilled over calcium hydride. Diethyl ether and tetrahydrofuran were distilled over sodium wire. Petroleum was either of boiling point 40 - 60 or 60 - 80 °C and was distilled. Reactions requiring anhydrous conditions were performed using oven dried glassware (250 °C) that was cooled under either dry nitrogen or argon; experiments were conducted under a positive atmosphere of one of these gases. Organic solutions were dried over anhydrous magnesium sulphate, and, unless stated, were evaporated at 14 mmHg. Yields quoted are for the purified compounds unless otherwise stated.

All new compounds were homogeneous by t.l.c. or by g.l.c. which was conducted using a Perkin-Elmer Model F17 F.I.D. on a capillary column (30 m x 0.32 mm id Phase, DB5 split ratio of 50:1) using nitrogen as carrier gas. Chiral g.l.c. was conducted using a 2,6-diamyl-3-trifluoroacetyl-γ-cyclodextrin fused silica column (40 m x 0.23 mm ID, film 0.12 mm), using helium as a carrier gas at 2 bar pressure (see acknowledgement). T.l.c. was performed using Aldrich silica gel 60 plates (F254). Compounds were visualised either by examination under an ultraviolet source or by exposure to iodine vapour. Column chromatography was conducted with Merck 7736 silica gel under medium pressure.

Melting points are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer as liquid films unless otherwise stated. Low resolution mass spectra were measured using a Finigan MAT 1020 spectrometer. Accurate mass measurements refer to ^{79}Br and ^{35}Cl isotopes unless stated and were carried out by the EPSRC Mass Spectroscopy Service (Swansea). Microanalysis was carried out on a Carlo Erba model 1106 CHN analyser. NMR spectra were recorded in $CDCl_3$ unless otherwise stated using a Bruker AC250 spectrometer at 250MHz (^1H) and 62.9MHz (^{13}C). ^{13}C spectra were broad band decoupled and in most cases corresponding DEPT spectra were also recorded. The results of DEPT spectra are quoted in the form of the signs + (corresponding to CH and CH_3 groups) and – (corresponding to CH_2 groups), signals which appear with no sign correspond to quaternary carbons.

Purification of (+)-dehydroabietylamine.

(+)-Dehydroabietylamine was obtained from Aldrich Chemical Co. as a mixture of high molecular weight primary amines. The purity was determined as 60 % by g.l.c. and the reagent was purified by crystallisation of its acetate[5] as outlined below.

A solution of glacial acetic acid (17 ml) in toluene (150 ml) was added dropwise over a period of 40 minutes to a cooled (0 °C) solution of (+)-dehydroabietylamine (70.00 g, 0.245 mol) in toluene (400 ml). The solution was stirred at 10 °C for 2 hours and the resulting precipitate collected under reduced pressure, washed with ice cold toluene (150 ml) and air dried. The white waxy solid was recrystallised from refluxing toluene (300 ml) to yield dehydroabietylamine acetate (55.25 g, 52 %) as fine white needle-shaped crystals, m.p. 141-3 °C, $[\alpha]_D^{21}$ + 31 (c 2.5, MeOH) (lit.,[5] m.p. 141 – 143.5 °C, $[\alpha]_D^{25}$ + 30.2).

Dehydroabietylamine acetate (50.00 g, 0.145 mol) was dissolved in warm deionised water (150 ml) and cooled to room temperature before adding 10 % aqueous sodium hydroxide (120 ml). The resulting solution was stirred for 1 hour before extracting the free amine into diethyl ether (250 ml). The organic solution was dried, filtered and reduced in volume under reduced pressure. Residual solvent was removed *in-vacuo* (0.1 mmHg) to yield (+)-dehydroabietylamine (39.65 g, 96 %) as a highly viscous yellow oil which crystallised slowly over an extended period (3 weeks), , m.p. 41.3 °C, $[\alpha]_D^{19}$ + 56.5 (c 2.55, pyridine) (lit.,[5] m.p. 41 °C, $[\alpha]_D^{22}$ + 55.6).

Resolution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid, 1 (*R/S*).

A hot solution of purified dehydroabietylamine (5.73 g, 20 mmol) in methanol (100 ml) was added to a stirred hot solution of **1** (***R/S***) (20.50 g, 80 mmol) in aqueous methanol (water 20 ml, methanol 80 ml). The solution was stirred for approximately one minute until the first signs of crystallisation were observed. Stirring was then stopped and the solution allowed to cool to room temperature over a period of 3 hours to allow complete crystallisation. The crystals were collected *in vacuo*, washed with ice cold methanol (10 ml) and allowed to dry in the air. The product, an ammonium salt with the ratio 2:1 (acid:amine) was recovered as finely divided white crystalline needles (13.06 g, 16.2 mmol, 81 %). Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of 93 %. Further enantiomeric enrichment of the salt (up to 99 % e.e.) was carried out by recrystallisation of the salt from refluxing aqueous methanol (10 % H_2O, 90 % MeOH) (150 ml), and afforded fine white crystals (9.11 g, 11.3 mmol, 57 %), m.p. 209-210 °C (Found: C 45.1; H 5.5; N 1.6 %. Calculated for $C_{30}H_{43}Br_4NO_4$: C 44.97; H 5.41; N 1.75 %) which showed $[\alpha]_D^{20}$ -9.4 (c 0.472, MeOH) which showed δ_H: 0.87 (1 H, m), 0.99 (1 H, m), 1.08 (3 H, s), 1.19 (3 H, s), 1.23 (6 H, d, *J* 6.8), 1.40 (2 H, d, *J* 7.5), 1.5 (6 H, s), 1.6 – 1.8 (4 H, m), 2.30 (1 H, d broad, *J* 12.4), 2.46 (2 H, dd, *J* 9.6, 7.8), 2.75 –2.96 (5 H, m), 6.09 (6 H, s broad), 6.89 (1 H, s), 6.98 (1 H, d, *J* 8.2), 7.15 (1 H, d, *J* 8.2).

Treating the ammonium salt (9.11 g, 11.3 mmol), obtained as described above with 10 % aqueous sodium hydroxide solution (100 ml) and dichloromethane (100 ml) enabled the bulk regeneration of the optically active acid. The biphasic solution was stirred until all solids had dissolved and the resulting solution was then separated. The organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml) and the combined aqueous fractions washed with dichloromethane (50 ml) [The combined organic layers were dried and evaporated enabling the efficient re-cycling of (+)-dehydroabietylamine]. The combined aqueous fractions were acidified with 20 % sulfuric acid and extracted with ethyl acetate (150 ml). The organic phase was dried, filtered and solvent removed to yield enantiomerically pure **1 (*S*)** (5.59 g, 21.7 mmol, 97 %) as a white crystalline solid, m.p. 62-62.5 °C (Found: C 23.5; H 2.5 %. Calculated for $C_5H_6Br_2O_2$: C 23.29; H 2.34 %) which showed $[\alpha]_D^{20}$ -55.1 (c 1.015, $CHCl_3$), all other analytical data was identical to that of racemic material.[4] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of greater than 99 %.

The combined mother liquors were condensed to approximately half volume (175 ml) under reduced pressure and allowed to cool slowly to room temperature. After 12 hours, a further crop of crystals was collected *in vacuo*, washed with ice cold methanol (10 ml) and allowed to dry in the air. The crystals (2.21 g, 2.8 mmol, 14 %) were isolated as large white nodules and showed an enantiomeric excess of 60.2 %.

Enantiomerically enriched acid was regenerated from the mother liquor [which showed an enantiomeric excess of 47.8 % (+)] after evaporation of solvent under reduced pressure. Acid regeneration was carried out by treating the residual salt with 10 % aqueous sodium hydroxide solution (200 ml) and dichloromethane (200 ml). The biphasic solution was stirred until all solids had dissolved and the resulting solution was then separated. The organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml) and the combined aqueous fractions washed with dichloromethane (50 ml). The combined aqueous fractions were acidified with 20 % sulfuric acid and extracted with ethyl acetate (250 ml). The organic phase was dried, filtered and solvent removed to yield enantiomerically enriched **1** (12.43 g, 48.3 mmol, 60 %) as a cream/white crystalline solid which showed an enantiomeric excess of 47.8 % (+) [The combined organic layers were dried and evaporated enabling the efficient recycling of (+)-dehydroabietylamine].

Further enantiomeric enrichment (up to 99 % e.e.) was carried out by slow recrystallisation of the acid (12.4 g, 48.2 mmol) from refluxing *n*-hexane (10 ml). After 15 hours at 5 °C, the crystals (6.51 g, 25.3 mmol, 53 %), which had an enantiomeric excess of 7 % (+) were removed. The mother liquor was evaporated to yield a colourless oil, which crystallised over night yielding **1 (*R*)** (5.88 g, 22.8 mmol, 47 %) as a white crystalline solid, m.p. 62-62.5 °C (Found: C 23.5; H 2.5 %. Calculated for $C_5H_6Br_2O_2$: C 23.29; H 2.34 %), which showed $[\alpha]_D^{20}$ +54.7 (c 1.089, $CHCl_3$) (all other analytical data was identical to that of

racemic material).[4] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of 99 %.

Methyl 2,2-dibromo-1(*S*)-methylcyclopropanecarboxylate.

An excess of ethereal diazomethane solution was added to acid **1 (*S*)** (51.0 mg, 0.198 mmol) and the resulting solution was stirred at room temperature for 10 min. All volatiles were removed *in vacuo* to yield methyl 2,2-dibromo-1(*S*)-methylcyclopropanecarboxylate (53.2 mg, 99 %), as a viscous colourless oil, $[\alpha]_D^{20}$ -62.7 (c 1.060, $CHCl_3$) which showed a ^1H NMR spectrum identical to the racemate.[4]

Analysis by chiral g.l.c. showed an enantiomeric excess of > 99 % within the detection limits at baseline resolution. On the same chiral column the (*R*) enantiomer (prepared in the same way) gave a 99 % e.e., with a retention time of 19.4 min (compared to the (*S*) enantiomer with a retention time of 19.2 min).

2(*R*)-Bromo-1(*S*)-methylcyclopropane carboxylic acid, 6.

A 100 ml oven dried round bottomed flask was charged with **1 (*S*)** (5.14 g, 20 mmol) in still dried diethyl ether (55 ml). The resulting solution was then cooled to 0 °C and a 1.5 M solution of MeLi in diethyl ether (20.0 ml, 30 mmol) was added dropwise over a period of 5 minutes. The golden yellow solution was then allowed to warm to room temperature and stirred for 1 hour.

Water (20 ml) was added to the reaction (dropwise at first) and the resulting solution was stirred for 10 minutes before being separated. The organic phase was extracted with water (20 ml) and the combined aqueous fractions acidified with 15 % aqueous sulfuric acid. The acidified aqueous phase was then extracted with ethyl acetate (100 ml), the organic extracts were dried, filtered and solvent removed *in vacuo* to yield **6 (2*R*, 1*S*)** (3.29 g, 92 %) as a light golden semi-solid; $[\alpha]_D^{25}$ -81.5 (*c* 1.02 in $CHCl_3$) which showed ^1H NMR and IR spectra identical to those of the racemate,[12] δ_C: 16.39, 23.65, 25.72, 28.86, 179.90.

2,2-Dibromo-1(*R*)-methylcyclopropanecarbonyl chloride, 3 (*R*).[9]

Thionyl chloride (25 ml, 0.34 mol) was added to **(1, *R*)** (26.4 g, 0.1 mol) and the resulting solution was heated under reflux for 2 hrs. Excess thionyl chloride was removed by distillation and the residue was distilled at 39 – 40 °C at 0.8 mmHg to yield **3 (*R*)** (27.2 g, 96%) as a pungent oil; $[\alpha]_D^{20}$ - 0.3 (c 1.104, $CHCl_3$) that showed δ_H: 1.77 (3H, s), 1.78 (1H, d, *J* 8.0), 2.52 (1H, d, *J* 8.0); δ_C: 21.76+, 34.37-, 42.97, 156.35.

2,2-Dibromo-1(*R*)-methylcyclopropanecarboxamide, 4 (*R*).

2,2-Dibromo-1(*R*)-methylcyclopropanecarbonyl chloride **3 (*R*)** (0.80 g, 2.89 mmol) was added slowly to a stirred 35 % solution of ammonia in water (5 ml). The reaction was stirred for 1 hr before adding water (20 ml) and extracting the product into chloroform (3 x 25 ml). The organic fractions were combined, dried and solvent was removed *in vacuo*. Recrystallisation of the residue from chloroform yielded **4(*R*)** (0.64 g, 86 %), as a white crystalline solid m.p. 157-158 °C, $[\alpha]_D^{20}$ +41.6 (c 1.014, $CHCl_3$), (Found: C 23.6, H 2.7, N 5.5. Calculated for $C_5H_7Br_2NO$: C 23.37, H 2.75, N 5.45) which showed δ_H: 1.57 (1H, d, *J* 7.8), 1.64 (3H, s), 2.39 (1H, d, *J* 7.8), 5.81 (2H, s); δ_C: (CD_3OD): 21.90, 31.72, 32.44, 36.56, 170.41; ν_{max}/cm^{-1}: 3376, 3211, 3080, 2992, 2976, 2931, 2783, 1658, 1453, 1432, 1401.

X-ray Crystallography of 2,2-dibromo-1(*R*)-methylcyclopropanecarboxamide, 4 (*R*).

Crystal data for $C_5H_7Br_2NO$, M_r = 256.94, monoclinic, space group $P2_1$, a = 9.812(3), b = 6.4409(16), c = 12.304(3) Å, β = 98.941(6)°, V = 768.1(4)Å^3, Z = 4, D_c = 2.222 g cm^{-3}, Mo Kα radiation, λ = 0.71073 Å, μ = 10.47 mm^{-1}, T = 160 K. From a crystal of size 0.65 x 0.55 x 0.03 mm on a Bruker AXS SMART CCD diffractometer, 8795 reflections were measured, giving 3441 unique data (θ < 28.2°, R_{int} = 0.160, corrected for absorption by face-indexed methods). The structure was solved by direct methods and refined on F^2 for all data with weighting $w^{-1} = \sigma^2(F_o^2) + (0.0452P)^2 + 9.9808P$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were assigned anisotropic displacement parameters, and hydrogen atoms were included with riding model constraints. Final $R_w = \{\Sigma [w(F_o^2 - F_c^2)^2]/\Sigma [w(F_o^2)^2]\}^{1/2} = 0.1714$, conventional $R = 0.0652$ on F values of 3281 reflections having $F_o^2 > 2\sigma(F_o^2)$, $S = 1.101$ on all F^2 values and 164 refined parameters. Residual difference map extremes (+1.95, -1.46 eÅ^3) are close to Br atoms. The enantiopole parameter[13] refined to 0.02(3), unambiguously identifying the absolute stereochemistry, which is the same for both independent molecules in the asymmetric unit. Programs were standard Bruker AXS control and integration software,[14] SHELXTL,[15] and local programs. Atomic co-ordinates, displacement parameters, and molecular geometry have been deposited at the Cambridge Crystallographic Data Centre.

2,2-Dibromo-1-vinylcyclopropane, 5 (*R/S*).

A 2 litre three necked flask equipped for addition and mechanical stirring at low temperature (dry ice condenser) was charged with a suspension of ground potassium *tert*-butoxide (61.6 g, 0.50 mol) in dry pentane (400 ml). The flask was cooled to -30 °C before adding condensed 1,3-butadiene (27.0 g, 0.50 mol) by syringe. The resulting solution was stirred vigorously while a solution of bromoform (131.0 g, 0.50 mol) in dry pentane (200 ml) was added dropwise over 90 minutes. The reaction mixture was stirred for a further 90 minutes at -30 °C, before being allowed to warm slowly to room temperature whilst stirring overnight. The reaction mixture was then cooled (0 °C) before adding water (500 ml) to the reaction vessel. The

resulting solution was separated and the aqueous layer extracted with pentane (100 ml). The combined organic fractions were washed with brine, dried, filtered and pentane was removed *in vacuo*. The residue was distilled to yield the product, **5 (*R/S*)** (82.1 g, 73 %) as a colourless liquid, b.p. 48-50 °C at 7 mmHg (lit.,[7] b.p. 69.5 °C at 26 mmHg) which showed δ_H: 1.58 (1 H, dd, *J* 7.7, 7.4), 1.97 (1 H, dd, *J* 10.2, 7.4), 2.30 (1 H, ddd, *J* 10.2, 8.0, 7.7), 5.29 (1 H, dd, *J* 9.9, 1.5), 5.34 (1 H, dd, *J* 17.0, 1.5), 5.57 (1 H, ddd, *J* 17.0, 9.9, 8.0); δ_C: 25.23, 29.39-, 34.16+, 118.77-, 135.81+.

2,2-Dibromocyclopropanecarboxylic acid, 2 (*R/S*).

A 5 litre flange flask equipped for mechanical stirring was charged with a solution of **5 (*R/S*)** (74 g, 0.330 mol) and *n*-hexadecyltrimethylammonium chloride (3.2 g, 10 mmol) in dichloromethane (1 l) and water (1 l). The solution was then cooled to 0 °C whilst 9 M sulfuric acid solution (120 ml) was added in small portions over 30 minutes. Potassium permanganate (156.5 g, 990 mmol) was then added to the stirred solution in small portions ensuring that the reaction temperature did not rise above 5 °C. The reaction was then allowed to warm to room temperature and stirred for a further 24 hours.

The reaction vessel was cooled to 0 °C before adding 50 % aqueous sulfuric acid (400 ml). Sodium sulfate (100 g or as required to reduce manganese by-products) was then added in small portions. The resulting straw coloured solution was stirred for 10 minutes before being separated and the aqueous phase extracted with dichloromethane (800 ml). The combined organic fractions were washed with saturated brine solution and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in vacuo* to yield the crude product as a creamy residue. The residue was recrystallised from hexane-benzene (5:2) to yield **2 (*R/S*)** (59.5 g, 74 %) as white crystals, m.p. 94-95 °C (lit.,[7,8] m.p. 95 °C) which showed δ_H: 2.09 (1 H, dd, *J* 9.6, 7.6), 2.19 (1 H, dd, *J* 7.7, 7.6), 2.64 (1 H, dd, *J* 9.6, 7.7), 10.65 (1 H, s); δ_C: 19.73, 28.66, 33.10, 173.20.

Resolution of 2,2-dibromocyclopropanecarboxylic acid, 2 (*R/S*).

A hot solution of (+)-dehydroabietylamine (11.2 g , 39 mmol) in methanol (30 ml) was added quickly to a hot solution of racemic **2 (*R/S*)**-(76.5 g, 314 mmol) in methanol (185 ml) and water (400 ml). After 15 hrs at room temperature, the crystals formed were filtered from the mother liquor and washed with cold (0 °C) methanol - water (1:1, 50 ml). The crystals were dried *in vacuo* to yield a white crystalline solid (42.4 g). The crystals, an ammonium salt of the ratio 2:1 (acid:amine) was treated with aqueous sodium hydroxide solution (5 g, 125 mmol in 20 ml of deionised water) and chloroform (200 ml) to enable the regeneration of the optically enriched acid. The biphasic solution was stirred until all solids had dissolved and the resulting solution was then separated. The organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml) and the combined aqueous fractions washed with chloroform (50 ml) [The

combined organic layers were dried and evaporated enabling the efficient re-cycling of (+)-dehydroabietylamine]. The combined aqueous fractions were acidified with 20 % sulfuric acid (45 ml, 100 mmol) and extracted with chloroform (3 × 150 ml). The organic phase was dried, filtered and solvent removed to yield enantiomerically enriched **2 (*S*)** (18.5 g, 76 mmol, 24 %) as a viscous colourless liquid, the corresponding methyl ester (prepared by reaction with excess ethereal diazomethane solution) showed an e.e. of 74.7 % e.e. by chiral g.l.c.

Enantiomeric enrichment of the acid was carried out by slow recrystallisation from refluxing *n*-hexane (60 ml). After 15 hours at 5 °C, the mother liquor was decanted from the crystals and evaporated to yield **2 (*S*)** (12.6g, 52 mmol, 17 %) as a viscous colourless liquid. Slow crystallisation over a number of weeks yielded a white crystalline solid, m.p. 61–63 °C. Analysis of the corresponding methyl ester showed the solid to be 95.9 % e.e. by chiral g.l.c.

Further enrichment of **2 (*S*)** to >99 % e.e. was carried out by recrystallisation of **2 (*S*)** (5.00 g, 20.5 mmol) with (+)-dehydroabietylamine (0.74 g, 2.56 mmol) from aqueous methanol as highlighted in the first paragraph of this procedure. The product, an ammonium salt of the ratio 2:1 (acid:amine) was recovered as finely divided white crystalline needles (1.92 g), m.p. 180-182 °C, (Found: C 43.30, H 5.19, N 1.68. Calculated for $C_{28}H_{39}Br_4NO_4$: C 43.49, H 5.08, N 1.81) which showed δ_H: 0.89 (1 H, m), 0.96 (1 H, m), 1.06 (3 H, s), 1.22 (3 H, s), 1.22 (2 H, d, *J* 6.9), 1.25 – 1.77 (6 H, m), 1.84 (2 H, dd, *J* 9.6, 7.4), 1.98 (2 H, dd, *J* 7.8, 7.4), 2.30 (1 H, d broad, *J* 12.4), 2.46 (2 H, dd, *J* 9.6, 7.8), 2.75 –2.96 (5 H, m), 6.09 (6 H, s broad), 6.89 (1 H, s), 6.98 (1 H, d, *J* 8.2), 7.15 (1 H, d, *J* 8.2).

Subsequent acid regeneration as highlighted above yielded **2 (*S*)** (1.18 g, 5 mmol) as white crystals, m.p. 62–64 °C, $[\alpha]_D^{20}$ –138.2 (c 0.982, $CHCl_3$), (Found: C 19.7, H 1.7. Calculated for $C_4H_4O_2Br_2$: C 19.70, H 1.65), all other analytical data was identical to that of racemic material.[7,8] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of greater than 99 %.

The original mother liquor was evaporated before adding chloroform (200 ml) and sodium hydroxide (12 g, 0.30 mol) in water (200 ml). The resulting two phase system was shaken until all the salt had dissolved. The aqueous layer was washed with chloroform (100 ml) and then acidified with 20 % aqueous sulfuric acid. The product was extracted into chloroform (3 x 200 ml) and the combined organic fractions were dried, filtered and solvent was removed to yield **2 (*R*)**, (55.4 g, 229 mmol) as a cream coloured solid with a 25.2 % e.e. (by chiral g.l.c. analysis of the corresponding methyl ester). This acid was dissolved in boiling hexane (150 ml) and the solution was left overnight at 5 °C. The supernatant solution was decanted from the crystals and evaporation of solvent afforded **2 (*R*)** (10.1 g, 42 mmol, 14 %) as a viscous colourless liquid that crystallised over a number of weeks to yield a white crystalline solid, m.p. 61 - 63 °C, $[\alpha]_D^{20}$

+132.9 (c 1.104, $CHCl_3$), (Found: C 19.6, H 1.7. Calculated for $C_4H_4O_2Br_2$: C 19.70, H 1.65), all other analytical data was identical to that of racemic material.[7,8] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of 96 %.

Methyl 2,2-dibromo-1(*R*)-cyclopropanecarboxylate.

An excess of ethereal diazomethane solution was added to acid **2 (*R*)** (54.3 mg, 0.223 mmol) and the resulting solution was stirred at room temperature for 10 min. All volatiles were removed *in vacuo* to yield methyl 2,2-dibromo-1(*R*)-cyclopropanecarboxylate (56.1 mg, 98 %), as a viscous colourless oil, $[\alpha]_D^{20}$ +112.6 (c 1.018, $CHCl_3$) which showed a ^1H NMR spectrum identical to that of racemic material.[5]

Analysis by chiral g.l.c. showed a 92.5 % e.e. within the detection limits at baseline resolution. On the same chiral column the (*S*) enantiomer (prepared in the same way) gave a 98 % e.e., with a retention time of 14.92 min (compared to the (*R*)-enantiomer with a retention time of 14.14 min).

2(*R*)-Bromo-1(*S*)-cyclopropanecarboxylic acid, 7.

A 100 ml oven dried round bottomed flask was charged with **2 (*S*)** (4.86 g, 20 mmol) in still dried diethyl ether (50 ml). The resulting solution was then cooled to 0 °C and a 1.5 M solution of MeLi in diethyl ether (20.0 ml, 30 mmol) was added dropwise over a period of 5 minutes. The golden brown solution was then allowed to warm to room temperature and stirred for 1 hour.

Water (20ml) was added to the reaction (dropwise at first) and the resulting solution was stirred for 10 minutes before being separated. The organic phase was extracted with water (20 ml) and the combined aqueous fractions acidified with 15 % aqueous sulfuric acid. The acidified aqueous phase was then extracted with ethyl acetate (100 ml) and the organic extracts were dried, filtered and solvent removed *in vacuo* to yield the crude product as a golden brown oil.

The crude product (3.15g) was decolourised by heating under reflux in acetone (20 ml) over activated charcoal (0.2 g) for 10 minutes, the solution was then cooled, filtered and solvent removed *in vacuo* to yield **7 (2*R*, 1*S*)**, 2(*R*)-bromo-1(*S*)-cyclopropanecarboxylic acid (2.95 g, 89 %) as a colourless oil, $[\alpha]_D^{25}$ -154.1 (*c* 1.03 in $CHCl_3$) which showed) which showed ^1H NMR and IR spectra identical to those of the racemate,[11] δ_C: 19.08-, 19.44+, 23.67-, 177.96.

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