DOCTOR OF PHILOSOPHY

Approaches to methylcyclopropanes and a new route to methylenecyclopropanes

Mohammed, H. M.

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Approaches To α-Methylcyclopropanes And A New Route To Methylenecyclopropanes.

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By

H. M. Mohammed

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Contents.

Chapter 3: Methylenecyclopropanes.

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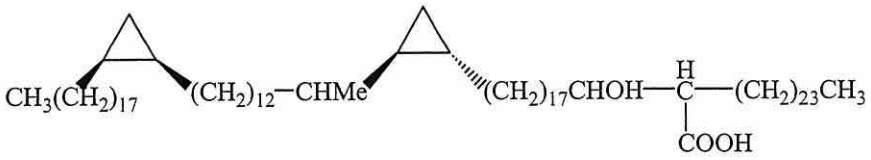
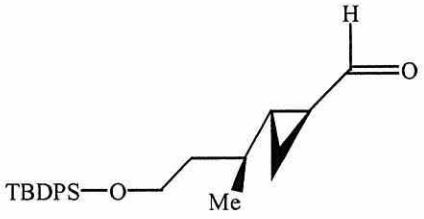
2.1.1 Abstract.

Mycolic acids show an unusual variety of structural features including the α-methyl-*trans*-cyclopropane (**61**), which is thought to be a key factor in stopping drugs getting into the cells of *Mycobacterium tuberculosis*.



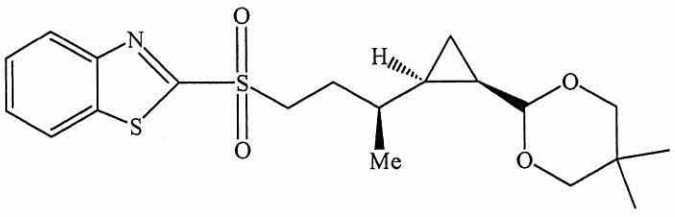
(61)

The synthesis of an optically pure cyclopropane as an intermediate for the synthesis of the *trans*-α-methyl mycolic acid was achieved as part of this work by preparation of (**88**).



(88)

The required α-methylcyclopropane was also prepared by a different route by preparation of (**119**).



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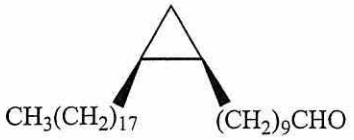
Additionally, the synthesis of the intermediate long chain *cis*-cyclopropanes as single enantiomers was completed by preparation of (**125**) and its enantiomer (**143**).



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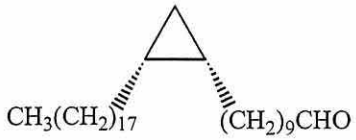
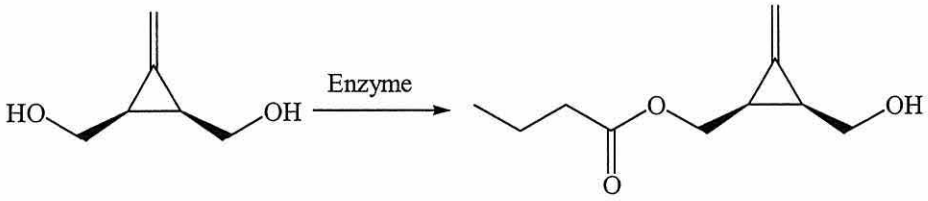


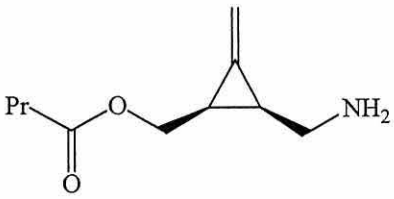
(143)

A new route to prepare methylenecyclopropanes as single enantiomers was achieved by an enzymatic desymetrization of (**172**) to obtain (**174**).



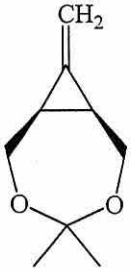
(172) (174)

A set of methylenecyclopropanes such as (**184**) were prepared, which might be useful in organic synthesis.



(184)

A new and cheap method to provide methylenecyclopropanes was achieved by preparation of (**207**).



(207)

Abbreviations

ACE	angiotensin-converting enzyme.
ACC	Aminocyclopropanecarboxylic acid
CPFAs	Cyclopropene fatty acids
aq	aqueous.
br	broad.
b. p.	boiling point.
Bz	benzyl.
cat.	Catalyst.
Cetrimide	hexadecyl trimethyl ammonium bromide.
cm^{-1}	per centimetre.
CoA	Co Enzyme A.
Conc	concentration.
d	doublet.
dd	doublet of doublets.
DIBAl-H	di-isobutylaluminium hydride.
DMF	dimethylformamide.
DMSO	dimethylsulfoxide.
eq.	Equivalent.
Ether	diethyl ether.
Fig	figure.
g	gram(s).
g. l. c	gas-liquid chromatography.
^1H	proton (^1H isotope).
HMPA	hexamethyl phosphoramide.
Hz	Hertz.
HPLC	high performance liquid chromatography.
h	hour.
IR	infra-red.

J	coupling constant.
L	litre.
m	multiplet.
Me	methyl.
MeOH	methanol.
ml	millilitre.
min	minutes.
mg	milligrams(s).
mmHg	millimetres of mercury.
mmol	millimole(s).
mp	melting point.
M	molar.
MS	mass spectrometry.
NMR	nuclear magnetic resonance.
Nu^-	nucleophile.
PCC	pyridinium-chlorochromate.
Ph	phenyl.
ppm	parts per million.
PTSA	para-Toluenesulfonic acid
q	quartet.
R	alkyl.
s	singlet.
sat.	saturated.
sec	second.
t	triplet.
TBDPS	*tert*-butyldiphenyl silyl.
TBAF	tetrabutylammonium fluoride.
TEBA	triethylbenzylammonium chloride
THF	tetrahydrofuran.
t. l. c	thin layer chromatography.

Chapter One

Introduction

1.1 Introduction.

Human cultures have for centuries been fascinated by natural products. They extracted them from plants, animals, and organisms, and then used them for the treatment of disease, as poisons, as euphorics, and as stimulants. Three-membered carbocyclic-rings (cyclopropanes, cyclopropenes) and their derivatives are of great interest to organic and bioorganic chemists because of their biological activity, due to their unusual bonding, inherent ring strain and related biochemistry.[1]

The cyclopropyl functionality is found as a structural element in a wide range of naturally occurring compounds and in synthetic drugs. A growing number of cyclopropane derivatives are known to constitute the basic framework of active compounds in animals, plants and micro-organisms, or to be generated transiently in primary and secondary metabolism.[2] Naturally occurring or non-natural cyclopropane containing compounds are widely used to probe the mechanisms of biological processes. The biological properties affected by a cyclopropane ring have become clear only very recently, and range from antibiotic, insecticidal, anti-fungal, control of plant growth, fruit ripening, phytotoxic, herbicidal activities, anti-microbial and antiviral (HSV, HIV) activities and inhibition of enzyme activity.

1.2 The biological importance of the cyclopropyl group.

The most important points of the cyclopropyl group as a structural element are that it: -

- Plays a key role in biological pathways and transformations of bioorganic molecules.
- It can exist as a stable structural entity in secondary metabolites.
- During bioorganic transformation, a transient cyclopropanoid intermediate is often observed in both primary and secondary metabolites.

1.3 Biological and biochemical effects of Cyclopropane and Cyclopropene Fatty Acids (CPFAs)

The cyclopropane ring is a common unit in a large number of natural products; fatty acids are one such group. They are biologically important molecules, which consist of a hydrocarbon chain generally having 16 – 24 carbons and a terminal carboxylic acid group. Fatty acids are the characteristic building blocks of most lipids and do not normally occur in free or uncombined form in cells and tissue. They are present in covalently bound form in a variety of classes of lipids from which they can be released by enzymatic or chemical hydrolysis.[3]

Many different kinds of fatty acids have been isolated from the lipids of different species and are different from each other in many ways: -

- The length of the chain.
- The presence of double bonds
- The presence of methyl-group branching.
- The number of double bonds in the chain.
- The position of the double bond in the chain.
- The presence of a cyclopropane or cyclopropene.

The long hydrocarbon chain may be unsaturated or fully saturated with any number of double bonds present, which are usually in the *cis*-geometry and arranged in a skip-conjugated or divinyl methane array. It is generally observed that there are twice as many unsaturated fatty acids in nature as saturated ones.

The majority of fatty acids, which occur naturally, have an even number of carbon atoms, of which C_{16} and C_{18} are the most common.

Fatty acid synthesis is the process by which organisms ranging from bacteria to humans produce their own fatty acids. Fatty acids are the building blocks of fatty molecules used for energy storage (adipose tissue), cell membranes, and cell signalling.

There are two key enzymes, ACC and FAS (fatty acid synthase) that are responsible for manufacturing fatty acids from carbohydrates or protein in the diet.

Fatty acids are also present in the environment, and in large amounts in the western diet. Some fatty acids contain in the chain either a cyclopropane ring (present in bacterial lipids) or a cyclopropene ring (some seed oils).

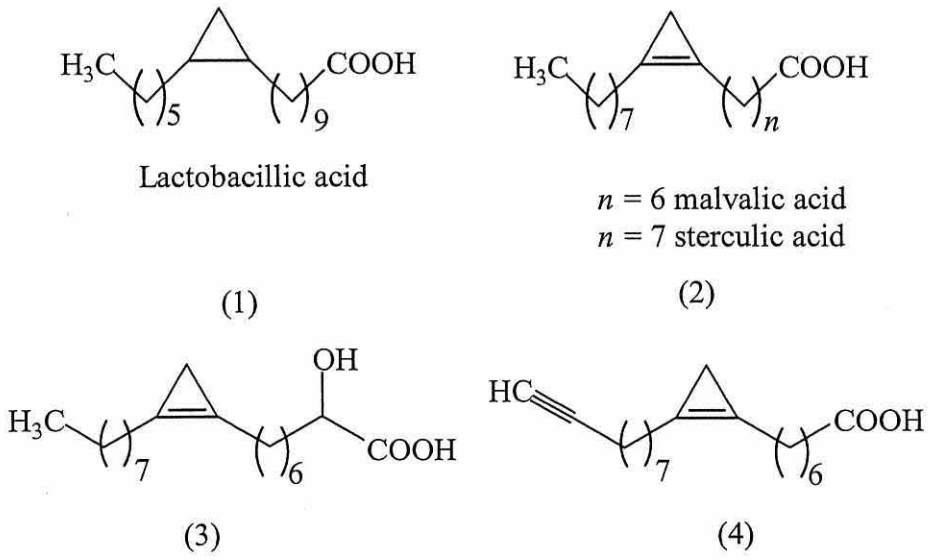
Among cyclopropane acids, lactobacillic acid (11,12-methyleneoctadecanoic acid) (**1**) (Figure 1) is found mainly in gram-negative bacteria, *Lactobacillus arabinosus*, where it was discovered in 1951[4] but also in protozoa, some seed oils and in all milk products and in the gut.

Many microorganisms produce cyclopropane and cyclopropene fatty acids.[5][6][7] Another cyclopropane fatty acid (9,10-methylenehexadecanoic acid) was recently shown to be present in phospholipids of heart and liver mitochondria.[8] Its amount in bovine heart (about 4 % of all fatty acids) is much greater than in other tissues (less than 0.3 %). The origin and the physiological role of these compounds remain unclear.

Cyclopropene fatty acids cause biological and biochemical effects ranging from slowed development or genital system malfunctions in chickens, rats and mice, to liver cancer in synergy with aflatoxins in rainbow trout. CPFAs also modify lipid protein and carbohydrate metabolisms and affect mixed hepatic oxidase systems.[12] It has been known for over a century that when pigs were fed a diet containing cotton seed oil they produced fat with a higher than normal melting point. [13] Similar effects were reported for cows, while hens fed in a similar way produced eggs with a pasty yolk and pink white, apparently due to an increase in the permeability of the vitellin membrane surrounding the yolk.[14] These effects have been linked to the presence of CPFAs in the seed oil. Later research linked these effects to the inhibition by the CPFAs of enzymes causing the desaturation of saturated fatty acids.[15]

Since these early studies, there have been a large number of reports of the detection of CPFAs in natural oils, and of their physiological and biochemical effects. The origin of these effects has been linked to the fact that sterculic acid (**2**, n = 7) (Figure 1) is very similar in structure to oleic acid, the product of Δ^9-desaturation. Because of the strained three-membered ring it is much more reactive towards addition of thiols across the double bond; an irreversible binding of the CPFAs to an enzyme site has therefore been suggested.[16] In support of this sterculic acid also inhibits yeast alcohol dehydrogenase, an enzyme known to contain a thiol group.[17] However, studies using tritium labelled sterculate indicate that it is not retained by the protein from rat liver mitochondria containing the Δ^9-desaturase enzyme, suggesting a non-covalent binding.[18]

The effects are all caused by the natural cyclopropene fatty acids, and principally by sterculic acid or its esters, because sterculic acid controls the production of unsaturated fatty acids and is of great importance in relation to diet. Furthermore this and linked compounds have been shown to be of possible therapeutic value in the treatment of advanced cancer in humans.



Lactobacillic acid

(1)

n = 6 malvalic acid
n = 7 sterculic acid

(2)

(3)

(4)

Figure (1)

Cyclopropene acids including malvalic acid (**2,** n = 6) (Figure 1), are found also in Malvales seed oils (*Sterculiaceae, Tiliaceae*, *Malvalaceae)* and Baobab, Kapok and mowrah seed oils, which are used as human food in Madagascar. They can reduce the commercial value of cotton seed oil (Malvales, Gossypium) in interfering with animal fatty acid metabolism (desaturation of stearic acid).

Sterculic acid is obtained from the kernel oil of *Sterculia foetida* and its biosynthesis is believed to occur by addition of a one-carbon fragment. Malvalic acid is obtained from malva seed oil and its biosynthesis is believed to be from sterculic acid, with an α-oxidation step to remove a one-carbon fragment; synthetic analogues have become increasingly important.[9]

The related compound sterculynic acid (**4**), found in *Sterculia alata,* also has a terminal acetylene group. Another CPFA, hydroxysterculic acid (**3**) has also been isolated and identified.[19][10] The hydrogenation of sterculic acid (**5**) (Figure 2) over palladium in ethanol produced dihydrosterculic acid (**6**); as catalytic hydrogenation would lead to *cis*-addition of hydrogen, dihydrosterculic acid is regarded as having the *cis*-geometry.[11]

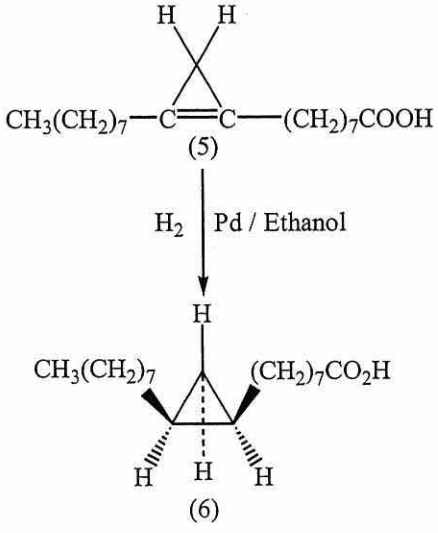


Figure (2)

1.4 *Mycobacterium tuberculosis.*

1.4.1 What is TB?

Tuberculosis is an infectious disease caused by several species of mycobacterium, collectively known as tubercle bacillus. The form of tuberculosis in humans is usually caused by *mycobacterium tuberculosis*. Tuberculosis was reported as a fatal disease more than 2000 years ago in ancient Greece. Hippocrates described a common illness that he called "phthisis"; subsequently Aristotle described it as a contagious infection caused by "pernicious air".[20] This is believed to be the same disease that we today call tuberculosis. It can affect many parts of the body, but is found most commonly (80 % of the time) in the lungs, where it is called "pulmonary tuberculosis".

Tuberculosis became a public problem during the industrial revolution, when cities were overcrowded and the civil facilities were inadequate for the number of residents. Today, tuberculosis remains the leading cause of death due to infection worldwide.

In the 1930's and 40's it was very prevalent in Britain, particularly among the poorer population. The poor public health care facilities and the increase in the number of people living in crowded settings promoted the spread of tuberculosis.[21] Treatment of patients suffering from it consisted of long periods of rest in isolated sanatoriums; in the 18^{th} and 19^{th} centuries it was the cause of 25 % of all adult deaths in European cities. Subsequently, several public health measures followed by the introduction of anti-tuberculosis agents reduced appreciably the occurrence of the infection. In the early 1950's drugs such as isoniazide, ethambutol and in particular antibiotics were developed that were very effective in treating tuberculosis. When the appropriate antibiotic therapy is given, people infected with TB quickly become non-infectious. The wide availability of these drugs in the 1950's led to the belief that the disease would eventually be eliminated; however, despite all these improvements the complete disappearance of this disease was only an illusion.

It always remained active in developing countries; furthermore, during the 1980's, in developed countries such the United States, the annual rate of tuberculosis began to rise again.

In the early 1980's there was a vast increase in the incidence of tuberculosis, and the number of deaths arising from it escalated rapidly. This was partly due to the increase in the number of people infected with HIV (the virus that causes AIDS), which severely damages the immune system.

The symptoms of TB are, a cough, which is persistent and not responsive to antibiotics, fever and weight loss (leading to death). TB can occur outside the lungs in lymph nodes, bones, kidneys, and the central nervous system. TB at these sites often causes serious illness, but patients are not likely to transmit the disease unless they also have pulmonary TB.

The germ that causes tuberculosis (TB) is called *Mycobacterium tuberculosis* and is passed from person to person on droplets in the air by coughing, sneezing, sharing the same breathing space or by the exchange of bodily fluids. Only one in ten infected by the germ actually develops active TB. The remainder have a healthy immune system that contains the infection in a dormant state. However, many years or decades later, dormant infections may reactivate and cause disease when the immune system fails.

This disease destroys the tissues in the lungs when the immune system fails to stop the infection and the bacterium is spread around the body, which often leads to permanent damage or death if no immediate treatment is given. It is estimated that as much as one third of the world's 6 billion population (1.9 billion) has been infected.[22] Most of the new cases of active tuberculosis develop from this pool of infected persons. The chance that anyone will become ill with TB after infection is low (one in ten), but in the HIV infected person the chance is accelerated by the failing immune system, and may be as high as 50 % lifetime risk or 10 % per year.

Tuberculosis is now considered to be the world's number one killer among infectious diseases, and it is estimated that every 10 seconds a person dies somewhere in the world from it. In 1997, new cases of TB totalled an approximate 8 million, 3 million resulting in death.

1.4.2 The course of infection.

Mycobacterium tuberculosis infection is acquired through inhalation of infective bacilli. Though tuberculosis is transmitted by airborne spread (like the common cold) it is not nearly as infectious. Transmission usually takes place after long-standing close organization such as usually occurs within households.

Once in the lung, the bacteria are internalised by alveolar macrophages and set up infection foci in the tissue of the alveolar wall. These expand through bacterial growth and recruitment of macrophages and lymphocytes that build the granuloma that defines this infection.

The granuloma seems to support limited bacterial growth and prevents metastasis of the infection. It also protects the bacterium from the immune response and is probably responsible for the persistent or latent nature of the infection.

The way tuberculosis affects children is different from adults. The former get "primary" disease, which is not usually infectious. Adults develop "post-primary" disease, which is infectious in about half of the cases and sometime very infectious.

National guidelines for screening contacts of cases to determine whether infection or disease is present have recently been published.[23] However infection is more likely to occur if the person who has the disease, has so called cavities in their lungs, which will be full of bacteria, which can be passed into water droplets in the air and inhaled by other people. The more time an uninfected person spends with the index case, the more likely that person will be to become infected.

1.4.3 Treatment of TB.

TB treatments not only make patients well and save lives, but also stop the extent of infection and development of drug-resistant TB. In fact, no treatment is better than poor treatment because poor treatment may cause drug resistance.

The treatment of TB by the end of the 1930's was changed by surgeons, who tried to eliminate the space that formed in the lung, which was seriously infected. This method remained the best treatment for the next thirty years until it was realised that drug treatment alone provided an effective cure, and a new treatment began in 1944 when the antibiotic 'streptomycin' was first used. By the end of the 1950's, drug treatments which could be given at home, and might eliminate the need for hospitalisation were introduced.

Mycobacterium tuberculosis and other members of the *M.Tuberculosis* complex use several strategies to resist the action of anti-microbial agents. The mycobacterial cell is surrounded by a specialized, highly hydrophobic cell wall that results in decreased permeability to many compounds.[25][26]

When the right antibiotic treatment is given, people infected with TB quickly become non-infectious and this prevents further spreading of the disease. Catching TB depends on two factors, infection and then the development of the infection to the disease, although certain groups of society are more prone to become infected than others. The clinician must therefore be aware of risk factors, which may raise the possibility of drug resistant tuberculosis. Drug resistant *M. tuberculosis* damage has begun to appear. Thus there is a clear need for new drugs to prevent the spread TB.[24]

1.4.4 The important risk factors.

- Previous treatment for tuberculosis, especially if prolonged.
- Contact with another patient known to have drug resistant disease.
- Immigration from an area with a high incidence of drug resistance.
- Substance abuse.
- Homelessness.

1.4.5 Multi-drug resistant tuberculosis.

Before the discovery of specific antibiotics for the treatment of tuberculosis, there was no cure. Later, treatment had to be continued with good quality drugs for as long as six months to ensure cure. The difficulties in ensuring this occurs, especially in poor countries, have resulted in an increasing incidence of tubercle bacteria resistant to the most effective drugs, so called multi-drug resistant tuberculosis. Unfortunately the success of the drug treatment of tuberculosis has been the catalyst for the emergence of a new wave of drug resistance.

Genetic studies have shown that resistance of *M Tuberculosis* to anti-mycobacterial drugs is the consequence of spontaneous mutations in genes that encode either the target of the drug, or enzymes that are involved in drug activation. Resistance-associated point mutations, deletions or insertions have been described for all first-line drugs isoniazid, (**7**) (Figure 3), pyrazinamide (**11**), ethambutol (**8**), and streptomycin (**9**) and for several second-line and newer drugs (ethionamide, fluoroquinolones, macrolides, nitroimidazopyrans).[27][28]

However the treatment of pulmonary disease caused by environmental mycobacteria is much more difficult than the treatment of *M.tuberculosis*. In vitro sensitivity testing is thought to be a poor guide to success; environmental mycobacteria are usually resistant to all first line anti-tuberculosis drugs with the exception of ethambutol (**8**) (Figure 3).

In the late 1960s a new and perhaps the most important drug in the treatment of tuberculosis was discovered: Rifampicin. It was able to kill the very slowly dividing bacteria, the so-called "persistors" in a way that the other drugs could not. It was found that by combining it with at least two others, the length of treatment could be reduced to as little as six months. So the new standard of treatment of tuberculosis became isoniazid (H) (7) (Figure 3), rifampicin (R) and pyrazinamide (Z) for two months followed by isoniazid and rifampicin for four months. This is generally shortened to 2HRZ/4HR.

Finally multi-drug resistant tuberculosis is defined as resistance to isoniazid (7) and rifampicin whether there is resistance to other drugs or not. It is therefore incorrect, by this definition, to classify a patient as having multi-drug resistant tuberculosis (MDRTB).[23]

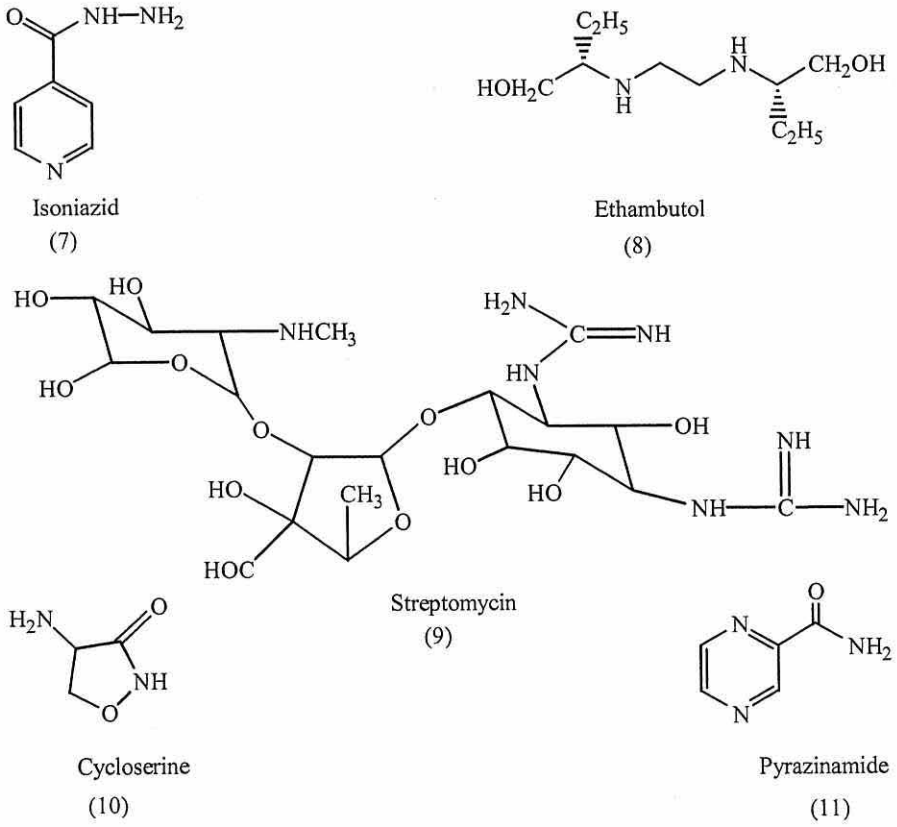


Figure (3)

1.5 Why Research?

The question is, why research into TB if there is already treatment available? First, people suffering from HIV and AIDS are more prone to TB and it is responsible for the quick weakening or death of the long-suffering.
Second, a lot of drugs that were effective in the treatment of TB have now become ineffective due to their misuse, which has led to a strain of the bacteria which is hard to treat. Third, there are now a great number of people living in poor conditions both in the UK and overseas, which has led to a greater number of infections, both in adults and in children in recent years. Due to the reasons above, there is a need for the better understanding and the inhibition of the biosynthetic pathways in *mycobacteria*.

1.6 Conclusions.

The action and mechanism of resistance to the three most important anti-tuberculosis drugs are still not fully understood. However current molecular evidence indicates that routine application of rapid molecular tests in the clinical management of drug-resistant tuberculosis is essential.
Tuberculosis is out of control in many developing countries of the world. There is even a "knock on" effect, so that through migration many developed countries are also experiencing an increase in cases. Though the reasons for this increase involve many factors, it is within the ability of the world to re-exert control providing that the political will is present.

1.7 Cell walls.

The cure for tuberculosis is extremely difficult because *Mycobacterium tuberculosis*, which is the effective cause of this sickness, has cell walls that show unusually low permeability, a factor which contributes to their resistance to most common antibiotics and chemo-therapeutic agents.[22] The reason for this is partly due to the composition of the bacterial cell wall that is the first defence against possible toxins for the mycobacteria.

Minnikin was the first to suggest a model of the mycobacterial cell wall (Figure 4).[42] The major feature of this model is the judgment that mycolic acids are orientated at right angles with respect to the plasma covering.

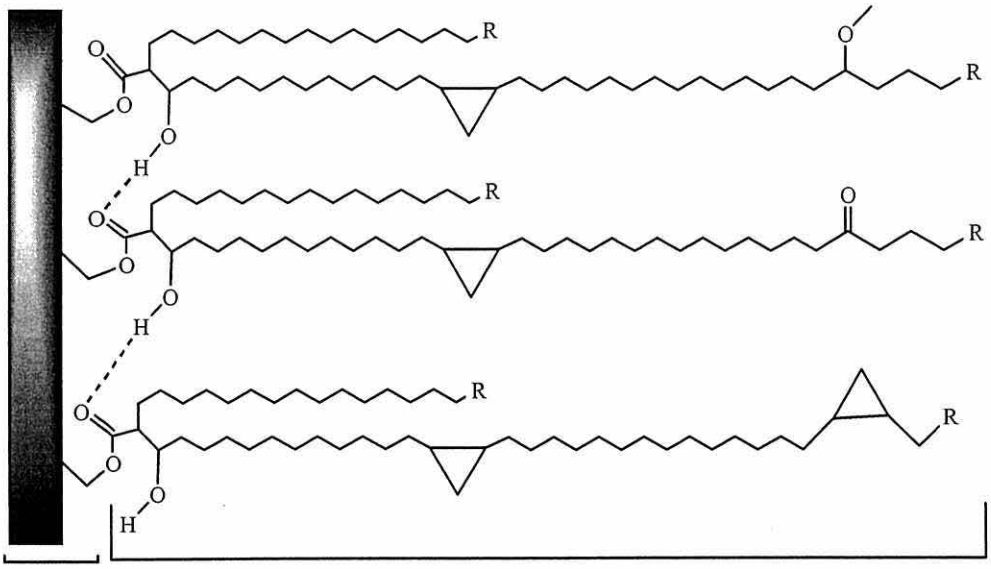
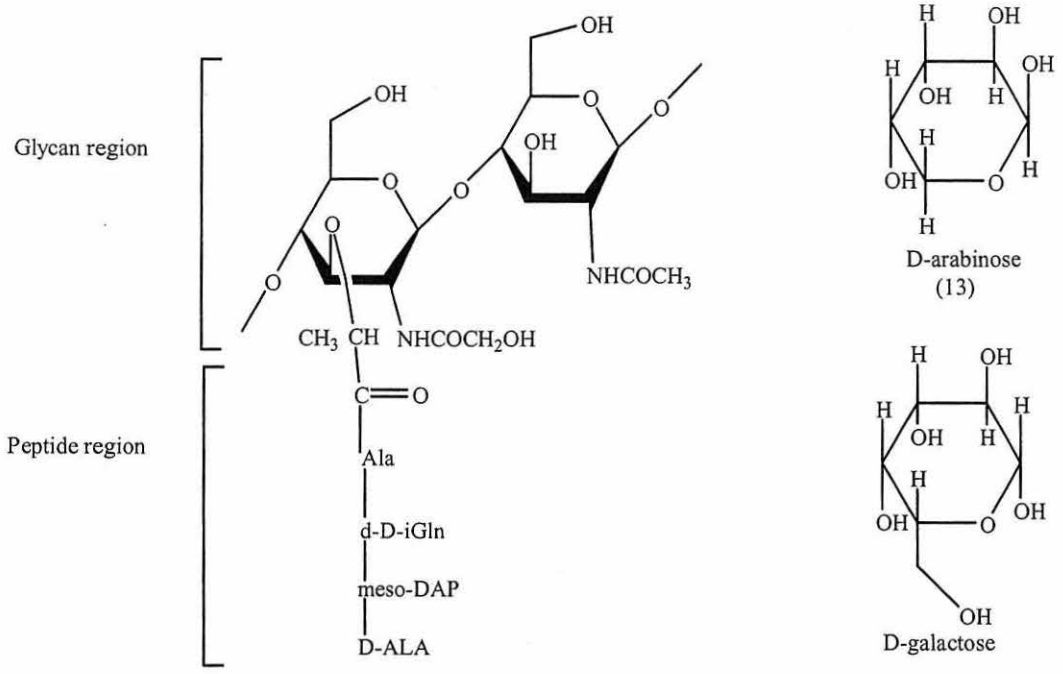


Figure (4)

The cell walls of mycobacteria have complex lipid-rich structures. There is a large amount of lipid cell envelope, more than 40-60 % of the dry weight of the organism and the quantities of materials present make the cell wall very impermeable. They are highly complex but include esters of very long chain (R, R)-α-hydroxy-acids (R`CH(OH))CH(COOH)R``), typically containing C_{70} - C_{90} and represent the major components of mycrobacterial cell walls.[22]

In the case of *Mycobacterium tuberculosis*, the cell envelope consists of three covalently linked substructures called peptidoglycan, arabinogalactan and mycolic acids.[31][32] The envelope is based on a plasma membrane and external peptidoglycan. The peptidoglycan is linked to an arabinogalactan polysaccharide, whose termini are esterified to long-chain mycolic acids.[32]

Peptidoglycan is the outer substructure and consists of alternating units of N-acetylglucosamine and muramic acid with tetra-peptide side chains (**12**) (Figure 5).[32] It serves as scaffolding for the arabinogalactan.



(12) (13) (14)

Figure (5)[41]

The arabinogalactan substructure consists of D-arabinose (**13**) and D-galactose (**14**) units (Figure 5) and is joined to the peptidoglycan sub-unit through a phosphodiester bond.

Branching of some residues in the arabinan structure serves as possible points of attachment for mycolic acids.[32] The synthesis of mycolic acids could be useful in preparing a model of the multi-layer structure present in *M. tuberculosis*, and targeting the biosynthesis of mycolic acid is an aim of chemotherapeutics as well as the first line drugs which could effectively treat *M. tuberculosis*.

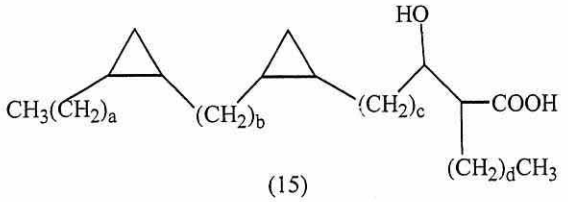
1.7.1 Mycolic Acids.

Mycolic acids are high molecular weight α-alkyl-β-hydroxy fatty acids.[36] They are the most abundant molecules in the mycobacterial cell wall, and the types produced by different mycobacterial species vary widely in structure. The acids contain between 60 and 90 carbon atoms.

Mycolic acids form key components of the cell walls of bacteria such as *Mycobacterium tuberculosis* and *M. leprae*. Three main types of mycolic acids have been isolated from the cell walls of *M. Tuberculosis*. These "mycolic acids" show an unusual variety of structural features including two *cis*-cyclopropanes (**15**) with different chain lengths, called α-mycolic acids. Less abundant are the ketomycolic acids (**16**) and the methoxymycolic acids (**17**), which contain one *cis*-cyclopropane ring. Also present in minor quantities are keto-*trans* (**18**) and methoxy-*trans*- (**19**) acids containing a *trans*-cyclopropane ring (Figure 6).[35][34]

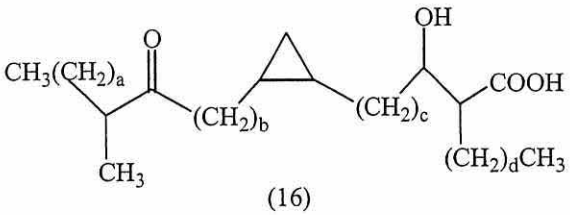
In each case there is a common α-hydroxy-β-alkyl acid functionality,[35] while the acids are generally present as mixtures of homologues with variable chain lengths.

α-Mycolic acid.



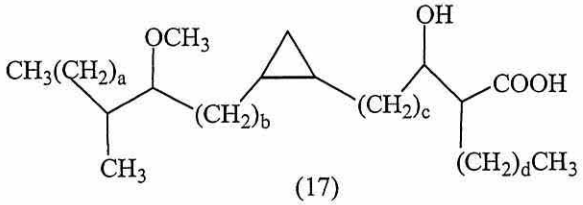
(15)

Keto.



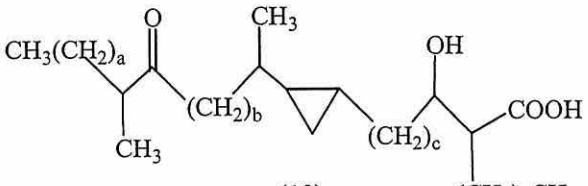
(16)

Methoxy.



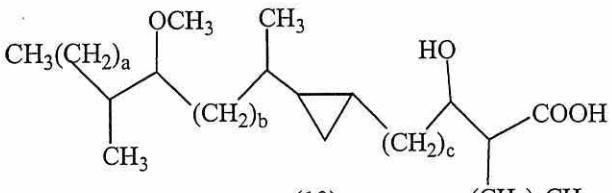
(17)

Keto *trans*.



(18)

Methoxy *trans*.



(19)

a = 15, 17, 18, 19.
b = 10, 14, 16.
c = 15, 17, 19, 21.
d = 21, 23.

Figure (6)

The balance of these structures, which is dependent on the mycobacterium, changes membrane permeability and fluidity and hence resistance to a therapeutic agent. However, mycolic acids containing a *trans*-cyclopropane substituent at the position in the chain closest to the hydroxy-acid have a particular effect on the cell wall and therefore on the sensitivity of mycobacterial species to hydrophobic antibiotics.[35]

Determining the structure of the mycolic acids has been a very difficult problem, mainly because they are isolated as complex mixtures of closely related homologues that are very difficult to separate. It was quickly apparent that mycolic acids were high molecular weight β-hydroxy acids. Pyrolysis of the methyl esters of the mycolic acids gave the corresponding meromycoaldehyde plus the methyl ester of a long chain saturated fatty acid (Figure 7).

The meromycoaldehyde was easily oxidised by chromic acid to the corresponding acid, which was then treated with diazomethane to give the methyl meromycolate.

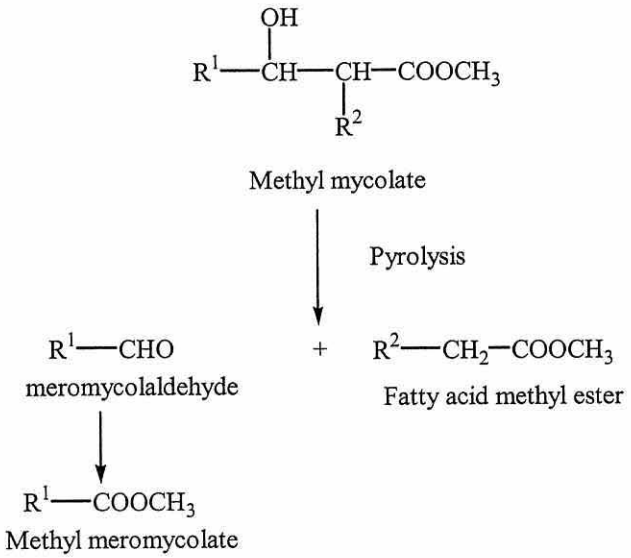


Figure (7)

The nuclear magnetic resonance and infrared spectra of the methyl meromycolate ester as well as the parent mycolate, and in particular their mass spectral fragmentation patterns have provided the data from which the structures have been arrived at. The mass spectral studies were invariably complicated by the fact that they were not those of a single pure compound, but rather of groups of functionally and structurally related compounds. Another serious handicap was that there was lack of availability of any appropriate model compounds.

This latter factor was corrected in 1997 when W. J. Gensler synthesised a representative methyl meromycolate containing two *cis*-disubstituted cyclopropane rings see (Figure 8).[37]

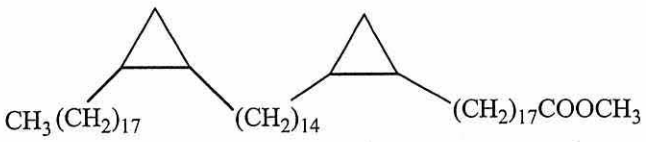


Figure (8)

The compound was not optically active; the authors reported that work was continuing to try and prepare optically active compounds, but to date no publication has been forthcoming. The first report of the synthesis of a chiral methyl meromycolate was in 2000.[38]

Gensler in an accompanying paper reported on the mass spectroscopy of his synthetic methyl meromycolate and on one of the intermediates containing only one *cis*-cyclopropane ring (Figure 9).[39]

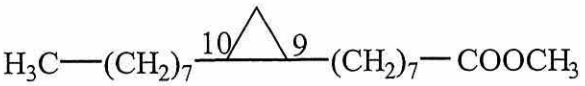


Figure (9)

They then investigated modifying the cyclopropanes to make the mass spectra more informative. Oxidation with chromic acid of cyclopropanes fused with a straight chain converts the methylene group adjacent to the three-membered ring into a ketone. Thus oxidation of the above methyl ester with a single cyclopropane in ring produces two keto derivatives (Figure 10).

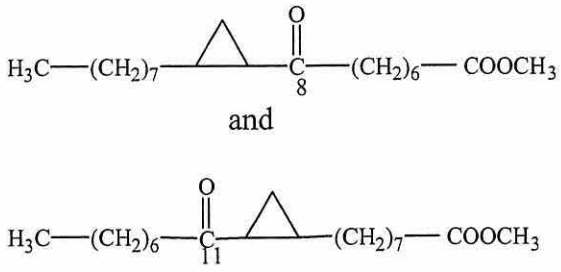


Figure (10)

These two ketones were separated by preparative thin layer chromatography and subjected to mass spectral analysis. It was known there was a tendency for cleavage to occur on either side of the carbonyl group. The fragmentation patterns of the two ketones showed that the cyclopropane ring was in the 9, 10 position in the alkyl chain. Gensler in the same paper examined the spectra of the mono-ketones obtained by the chromic acid oxidation of the synthetic methyl meromycolate that he had prepared. Here four mono-ketones could theoretically be produced (Figure 11)

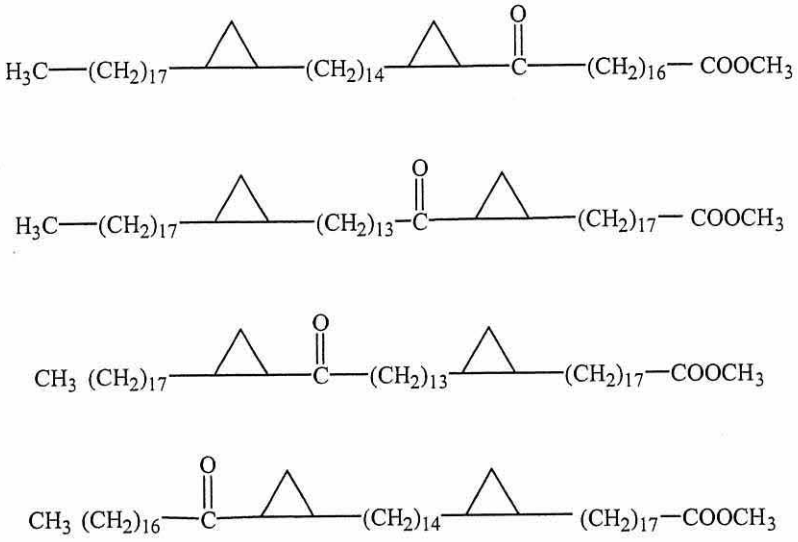


Figure (11)

The mixture of mono ketones was subjected to mass spectral analysis, and even though the spectra were very complex, peaks of higher relative intensities could be identified that fixed the position of the cyclopropane rings. Improvements in high performance liquid chromatography (HPLC) in the 1970's allowed the separation of homologous series of mycolic acids. After isolating the mycolic acids from *Mycobacterium tuberculosis*, they were converted into their β-bromo-phenacyl esters. These esters were then separated by reverse phase HPLC and the purified esters subjected to mass spectral analysis.[22] The authors also prepared the keto derivatives of the meromycolic acids by oxidation of the methyl-α-mycolates with chromic acid, the meromycolic acids being formed by the oxidative cleavage of the α and β carbon linkage. The keto meromycolic acids were esterified with diazomethane to produce the methyl esters, which again were subjected to mass spectral analysis. Both strains of *Mycobacterium tuberculosis* yielded as the main constituents two identical esters, in a molar ratio of 100 : 90, with slight variations in the minor constituents, which were present in a molar ratio 10 : 25.

Over the last 35 years numerous investigators have reported the structure of mycolic acids that they have isolated from *Mycobacterium tuberculosis* but as the reports reveal difficulties in isolating pure compounds and the complexity of the mass spectra, it is not surprising that there are fairly wide variations.

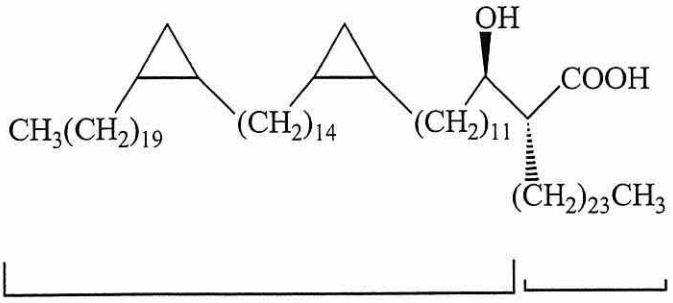
The lengths of the chains have greater variation, due not only to the fact that there are different homologous sequences in the mycobacterium but also because it is enormously hard to resolve the correct structure of such complex compounds and so different structures have often been put forward.

The synthesis of mycolic acids could prove very useful in finding the real structure of natural mycolic acids and identifying the stereochemistry and providing a better understanding of the reasons for the low permeability of the cell wall of *M. tuberculosis*.

Methyl hominomycolate (Figure 12) has been found to be a major component of the mycobacterial cell envelope of *Mycobacterium tuberculosis*; up till now, the stereochemistry of the cyclopropane functionally in the molecule is unidentified. Furthermore both the stereo centres at the α- and β-positions with respect to the carboxylic group, are in the R-arrangement.

Research in this field has only led to a partial synthesis of a mixture of stereoisomers. A single enantiomer of hominomycolic acid is necessary to decide the stereochemistry; this will enable investigation into their effects, and may yield a great deal of knowledge about the nature of diseases such as tuberculosis.

In the first synthesis of an α-mycolic acid (Figure 12), the structure of this was selected according to data obtained by Minnikin.[42] However the ideal synthetic method should also be simply modified for the preparation of other similar structures.



α-Mycolic acid

Figure (12)

1.7.2 Biosynthesis of Mycolic Acids.

Research on the biosynthesis of the mycolic acids will certainly be accelerated with the publication of the complete genome sequence of *M. Tuberculosis*.[40][33] Already it has become apparent from this work that there are about 250 distinct enzymes involved in the fatty acid metabolism of *M. Tuberculosis*.[21]

Yuan and Barry established the main route for the biosynthesis of the cyclopropane ring, which is connected to the biogenesis of the methoxy and the cyclopropyl-mycolic acids.[43]

By determining the structure of the mycolic acids produced following expression of each of the genes individually and in combination, the group were able to elucidate the possible biosynthetic path for the production of the *cis* and *trans*-methoxymycolates (Figure 18).

A common cationic intermediate, (Figure 18) has been suggested by the C. E. Barry group[44][45] to account for the various types of mycolic acids. They proposed a new route for the biosynthesis of the methoxy, α-methyl and cyclopropyl mycolic acids, by identifying a family of six homologous enzymes by heterologous expression in the saprophytic species *Mycobacterium smegmatis*.

These are involved in generating structural diversity among these molecules by the apparent addition of a methyl group from *S*-adenosyl–L-methionine (SAM). SAM has been shown to be an alkylating agent in many enzymatic reactions. It is formed by the reaction of adenosine triphosphate and methionine (Figure 13).

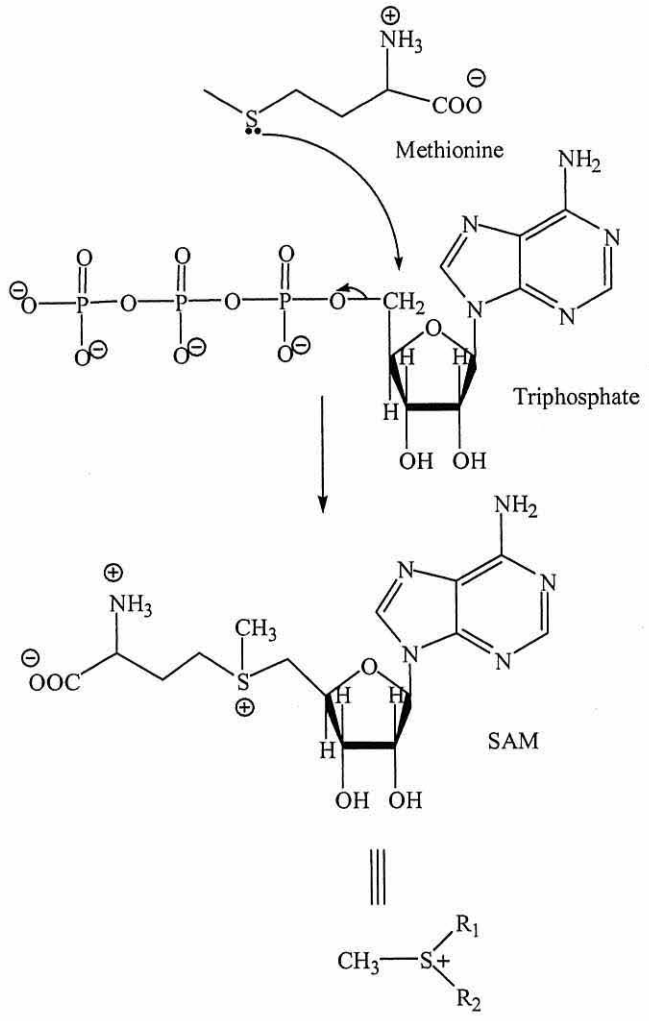
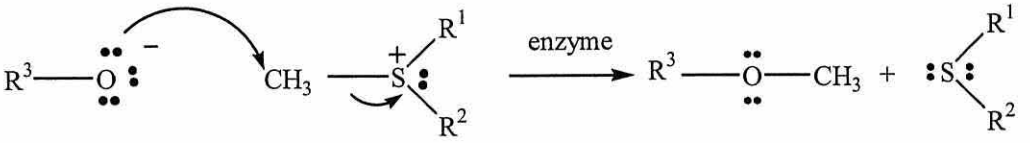


Figure (13)

The cyclopropane fatty acids which occur in bacteria and protozoa are known to be formed from the addition of a C_1 unit from (SAM) across the double bond of the olefinic fatty acid, as proved by Hofmann and Liu.[46]

The cyclopropanation is thought to be possible due to the versatility of sulphur (II) which allows SAM to be introduced into a molecule as an electrophile, nucleophile, or radical as well as a sulphur-stabilised carbanion, carbocation, carbene or carbon radical.[47][48][49]

The sulfonium ion *S*-adenosylmethionine (SAM) is used to transport methyl groups to biological nucleophiles. Although the structure of SAM is complex, we can understand its chemistry by focusing only on its sulfonium ion functional group. Similar to other sulfonium ions, SAM reacts with nucleophiles at the methyl carbon, liberating a sulfide-leaving group, (figure 14).



A biological nucleophile SAM

Figure (14)

SAM is stable enough to survive in aqueous solution, but is reactive enough to undergo enzyme-catalysed S_N2 reactions. Proof of an S_N2 mechanism in methylation reactions involving SAM has been obtained by a very elegant experiment. The methyl carbon of SAM was made asymmetric only by isotopic substitution. It was found that displacements on this methyl group occur with inversion of configuration, exactly as expected for the S_N2 mechanism (Figure 15).

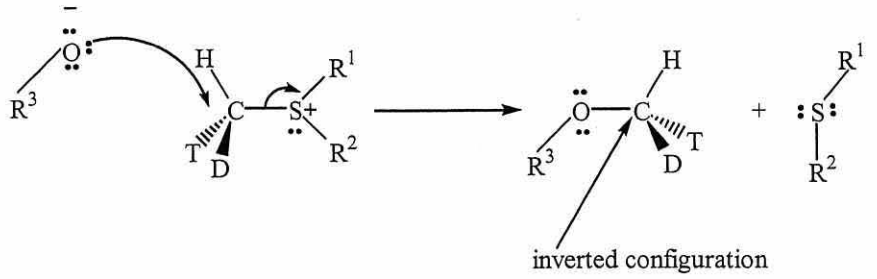


Figure (15)

However it is not known whether a proton is removed to form a methylene group in cyclopropanation before or after the carbon-carbon bond is formed.[50] A range of chemical mechanisms have been proposed. For example, a sulphur ylid could provide its methylene unit to a metal such as copper. The metal-carbenoid species could then methylenate the double bond, giving a cyclopropane (Figure 16).[51]

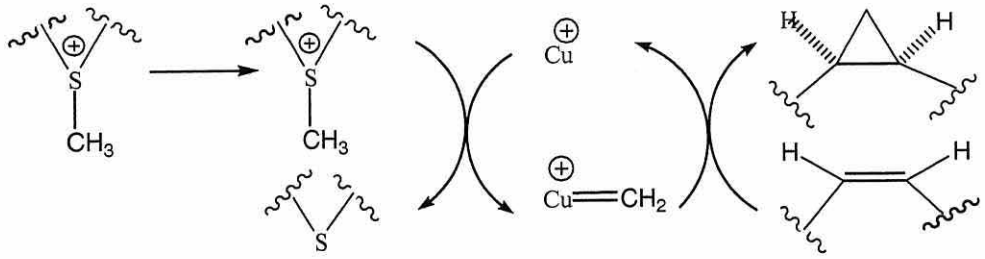


Figure (16)

The proposal has been made that the methylide of SAM is involved via an analogous copper induced methylene transfer from the ylide of SAM to the alkene, although it is known that ylides are usually unreactive to unactivated double bonds. This would involve a complex (Figure 17) between the copper and the ylide in which two of the heteroatoms of the SAM structure are involved, helping the delivery of the methylene group by electron donation of the metal.

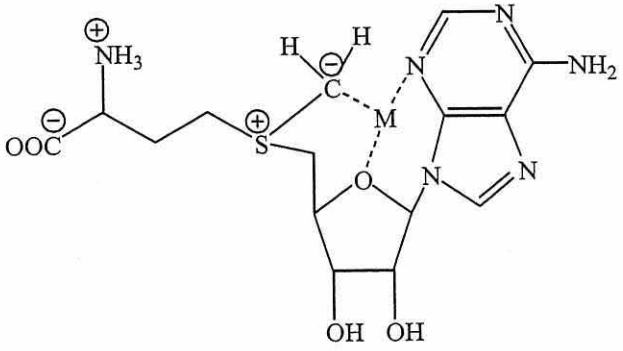


Figure (17)

Thus the genes contains a typical SAM binding site, and this allows the methylation of the *cis*-unsaturated mycolic acids by SAM to give a cationic intermediate as shown below. The mechanism of methylation by these enzymes has been proposed to involve the formation of an intermediate carbocation (Figure 18), which can then be deprotonated to give either a cyclopropyl group (**20**) or a double bond (**21**) (Figure 18), which could be the precursor of the *trans*-cyclopropyl series of mycolic acids. Moreover, the cation could react with water to give a hydroxy group, (**22**), which is then alkylated to give a methoxy mycolic acid (Figure 18).

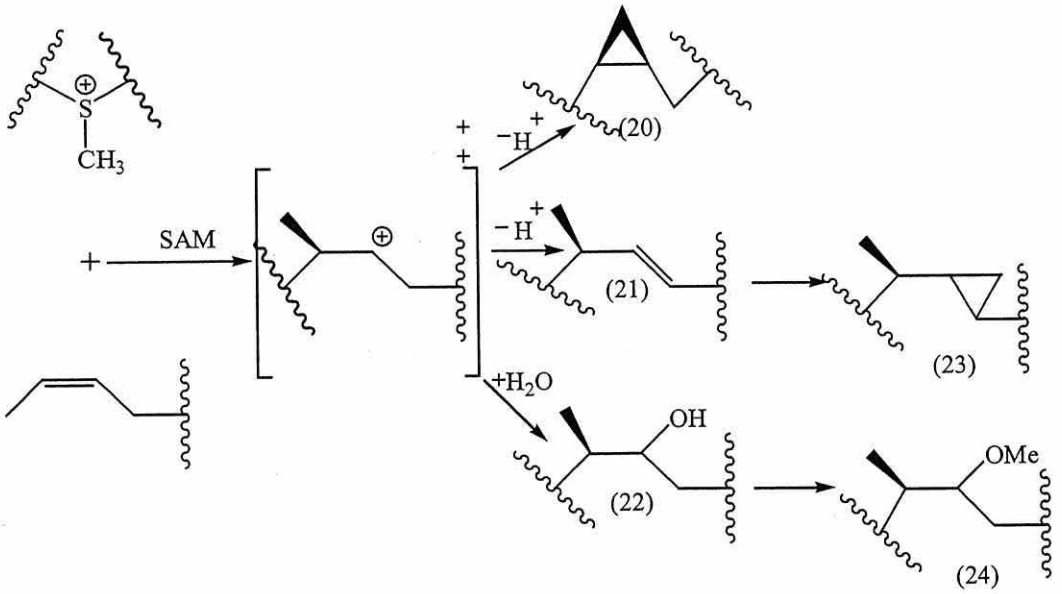


Figure (18)

Moreover other mycolic acids are present in many mycobacterial cell envelopes like *M. leprae*, which contains keto-mycolic acids, *M. avium* complex and *M. kansaii*, which contain both keto and methoxy-mycolic acids. Therefore resolution of their structures and biosynthesis could be useful in the dealing with the other diseases caused by these mycobacteria.

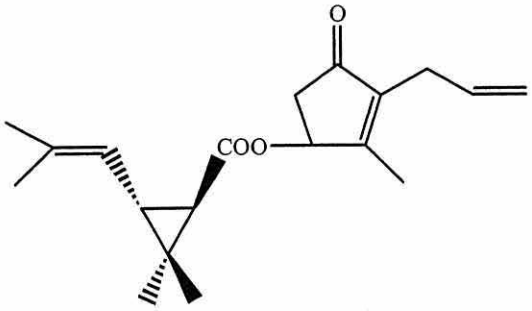
Thus it is confirmed that *M. avium* complex, *M. kansasii*, *M. fortuitum*, and *M. chelonae* cause opportunistic infection in immunologically compromised patients such as AIDS patients.[52]

1.8 Examples Of Other Types Of Natural Cyclopropane.

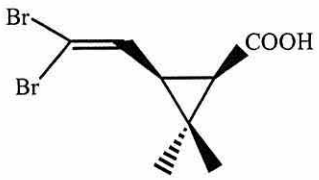
There are many other important cyclopropane-containing compounds found in nature. This is why there is great interest in the study of their chemistry and biochemistry. Among these compounds are:-

1.8.1 Pyrethrin.

The natural pyrethrin (**25**) is present in the flower of *chrysanthemum Cinerariaefolium* and has a defense function in this plant.[53] It is an antifeedant for herbivores and an insect repellent; synthetic derivatives have been developed as insecticides, and dibromovinyl-chrysanthemic acid (**26**) was for many years the most powerful synthetic insecticide sold worldwide.[54][55]



(25)

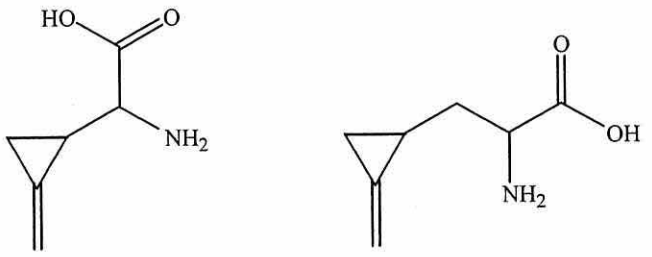


(26)

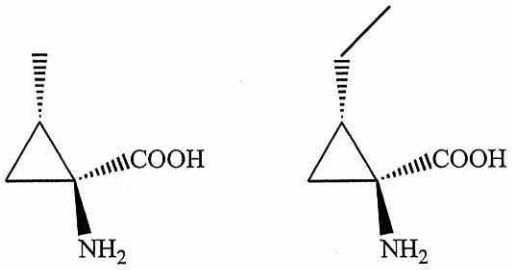
Figure (19)

1.8.2 Aminocyclopropanecarboxylic acid (ACC) and related amino acids.

There is a wide range of natural cyclopropanes containing a carboxylic acid and an amino group, such as Hypoglycine (A) (**27**) (Figure 20), a methylenecyclopropanoid amino acid (MCPA), and 2-methylenecyclo-propylglycine (**28**), two related compounds which are present in the ackee nut.[56][57] Eating this fruit causes hypoglycaemia (lowering the blood sugar level); due to this property, it is believed that 5000 people have been killed in Jamaica between 1886-1950.[58]



(27) (28)

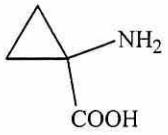


(29) (30)

Figure (20)

Another three-membered ring amino acid (norcoronamic acid) (**29**) and its derivatives, coronamic acid (**30**) are currently attracting attention because of their outstanding biological activity and potential use in conformationally restricted peptides, providing biosynthetic and mechanistic probes.[61]

Another naturally occurring cyclopropane ACC (**31**), which was isolated in 1957, is present in most citrus fruit. It is converted into ethene, which sets off the ripening process and coprine (**32**), present in the inky-cap mushroom. Taken with alcohol this causes convulsions. It is used as 'antabuse', a drug for alcoholism.[59][60]



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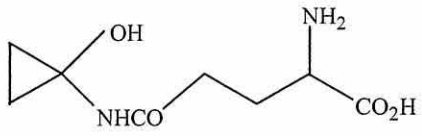


(32)

Figure (21)

1.8.3 Cylcopropyl steroids.

The marine cyclopropyl steroid Aragusterol A (Figure 22) possesses potent antitumoral activity. It was isolated from a sponge of the genus Xestospongia on the coral of the reef of Aragusuku Island in Japan.[62]

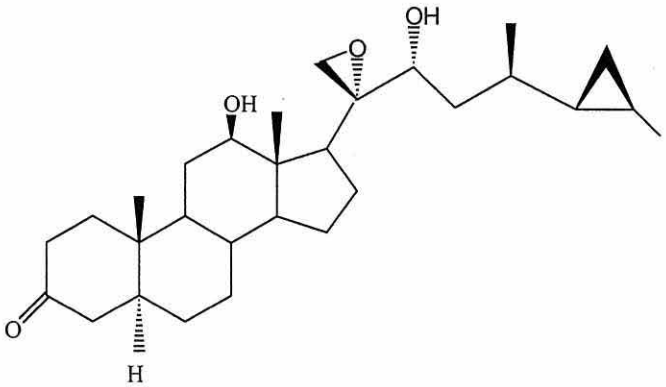
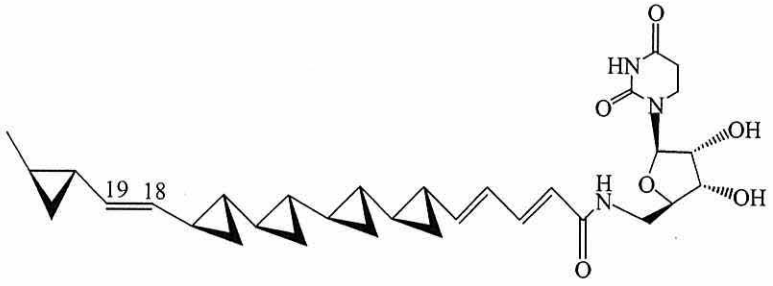


Figure (22)

1.8.4 Polycyclopropanes.

FR-900848 (Figure 23) is a natural product isolated recently from the fermentation broth of *Streptoverticillium Fervens.*[63] It shows remarkably selective activity against filamentous fungi such as *Aspergillus niger* but is essentially inactive against non-filamentous fungi such as *Candida albicans* and gram-positive and negative bacteria. FR-900848 is a fatty acid nucleoside, which possesses an unprecedented five cyclopropanes on a single fatty acid backbone, four of which are located on consecutive two carbon fragments.



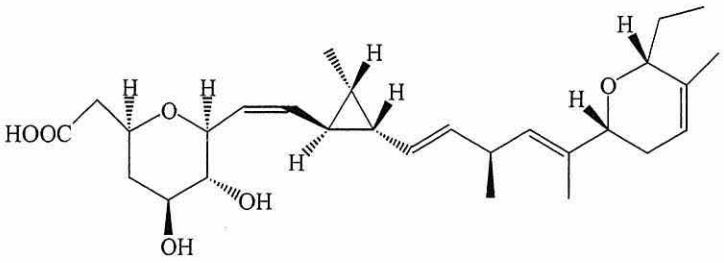
FR-900848

Figure (23)

The geometry of Δ^{18}, the stereochemistry of the isolated cyclopropane and the stereochemistry of the tetracyclopropane unit were established in a recent report.[84] The combination of the unusual structure and the selective biological activity makes FR-900848 and its analogues attractive synthetic targets.

1.8.5 Polyether Antibiotics.

Ambruticin (Figure 24) is an anti-fungal antibiotic found in the fermentation medium *polyangium Celluosum Var fulvum.*[64][65] It is highly active against systemic pathogenic fungi.

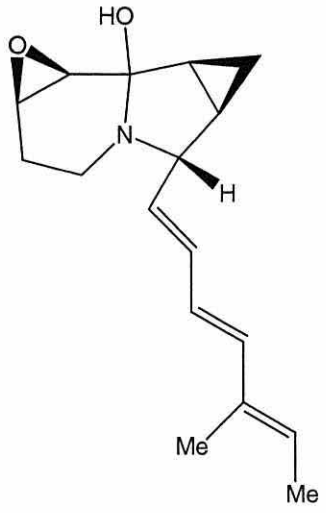


Ambruticin

Figure (24)

1.8.9. Indolizomycin.

In Japan, the interesting discovery was made that the union by protoplast synthesis of two inactive S*treptomyces* strains, S*treptomyces tenjimariensis* NM16, and S*treptomyces grisline* NP1-1, afforded a mostly active copy (termed SK2-52) that produces the antibiotic indolizomycin.[66]



Indolizomycin

Figure (25)

1.9 Cyclopropanes In Medicine.

There are various kinds of drug that contain a cyclopropane ring, such as Ciprofibrate (Figure 26). This is a potent, long-acting hypolipidemic agent. It is effective in type IIa, IIb, III and IV hyperlipoproteinemias and produces a useful rise of anti-atherogenic high-density lipoprotein.[67]

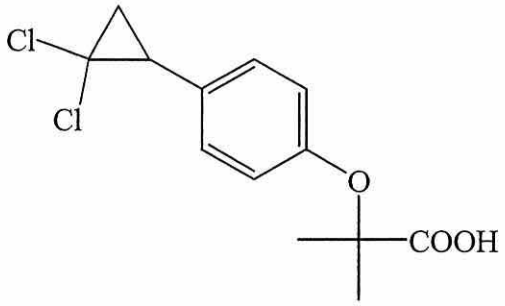


Figure (26)

It is effective for the control of different neoplastic diseases, as well as controlling and correcting various endocrine confusions. Its mode of action is known to include an aggressive inhibition at the estrogen receptor (ER), as well as an estrogen permanent cytotoxic action linked to antagonism activated cellular processes.[68] Inhibition of estrogen is a potentially useful strategy for the treatment of hormone-dependent breast tumours in postmenopausal females and possible tumour avoidance in pre-menopausal women. It has been reported that the introduction of a cyclopropyl or dichlorocyclopropyl moiety in place of the olefin link in estrogen reduces or stops the estrogenic activity.[69]

1.10 Ring Strain in Cyclopropanes.

The carbon chain in alkanes may connect to form a ring. These hydrocarbons are the cycloalkanes. The simplest cycloalkane with three carbon atoms joined in a ring is cyclopropane.

Cyclopropane has a high energy relative to propane because the three carbon atoms are distorted from their normal 109.5° bond angles and the angles between the carbons atoms are 60° (Figure 27).

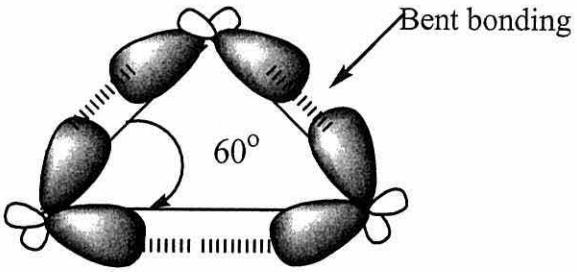
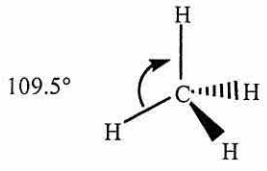


Figure (27)

1.10.1 Cyclopropane Bonds.

The bonds of the cyclopropane ring are thought to be some way between σ- and π-bonds (Figure 27).[70] This is because the deformation of their electron density, which lies outside the lines connecting the carbon atoms, produces bent or "banana" like bonds. However, note that σ-bonding involves "end-on overlap" and π-bonding involves "sidelong overlap". σ-Bonding is stronger than π-bonding. Bent bonding is midway between σ- and π-bonding, the overlap being neither end-on nor sidelong; this makes it less efficient than σ-overlap, and the cyclopropane C-C (**34**) bonds are weaker than simple C-C σ-bonds (Figure 28). This is described as angle strain.



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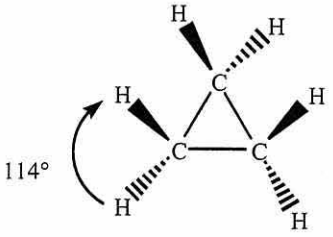


(34)

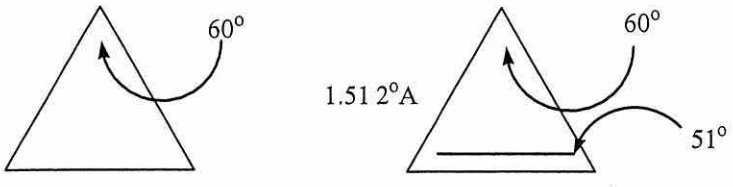
Figure (28)

The C-C bond length for cyclopropane is 1.512 Å and the C-H bond length is 1.083 Å. It is observed that the C-H bonds in cyclopropane are shorter and stronger than the average alkyl C-H bond and those in other cyclic systems, because of a larger than normal s-character. The C-C bonds are shorter due to their bent nature. They have slightly more p-character,[71] and are slightly weaker than normal alkanes. Consequently, the H-C-H bond angle also changes, becoming slightly greater than tetrahedral at 114 Å; this is seen in Figure 40 which shows a diagrammatic representation of bonding thought to be in operation in cyclopropane.[72]

This gives rise to the observed ring strain energy of 117.6 KJ mol^{-1}. For this reason cyclopropane is much more reactive than other cyclic alkanes such as cyclohexane and cyclopentane. Another factor that contributes to ring strain in cyclopropane is the eclipsing of the C-H bonds so the molecule has torsional strain as well as angle strain.

However two models for the bonding in cyclopropane have been proposed. The first was described by Walsh in 1947.[73] The carbon-hydrogen bonds have sp^2 hybrid orbitals and the carbon-carbon bonds have p orbitals along with sp^2 orbitals pointing towards the centre of the cyclopropane ring. Coulson and Moffitt[74] later in 1947 described the carbons in cyclopropane as sp^5 hybridised. The bonds were also described as "bent" in this model that has poor orbital overlap and weak carbon-carbon bonds.

1.10.2 Cyclopropene Rings.



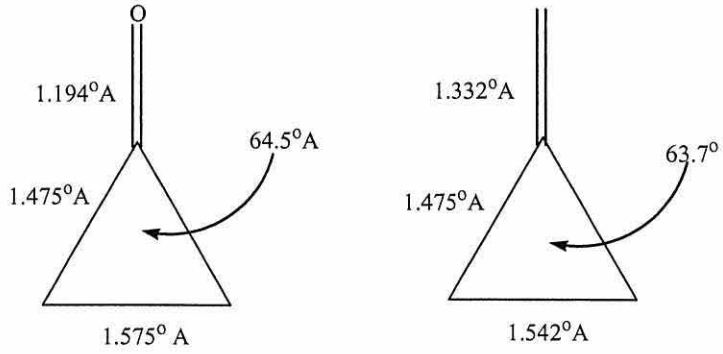
(35) (36)

Figure (29)

Cyclopropene (**36**) is even more highly strained than cyclopropane.[75] The ring strain of cyclopropene is ca. 228 KJ mol^{-1} as opposed to ca. 117.6 KJ mol^{-1} for cyclopropane. This is because the carbon-carbon single bond is shorter and the ring angle at the methylene position is smaller. The angles between the carbon atoms in cyclopropene is 51° for the $C_1C_2C_3$ angle and 64.5° for the $C_2C_1C_3$ angle, and the carbon-carbon single bond is weaker in cyclopropene than in cyclopropane. The carbon-carbon double bond length is 1.30 Å compared to that of ethylene which is 1.34 Å. The carbon-carbon single bond length is 1.512 Å compared to ethane and propane in which it is 1.54 Å.

1.10.3 Cyclopropanone and methylenecyclopropane.

The structure of cyclopropanone (**37**)[76][77] has been described with the assistance of microwave and Raman spectroscopy. The oxygen substituent shortens the bond next to it so that it is shorter than the C-C bond in cyclopropane, but lengthens the opposite bond more, i.e. C_1-C_2 is shorter and C_2-C_3 is longer than in cyclopropane.



(37) (38)

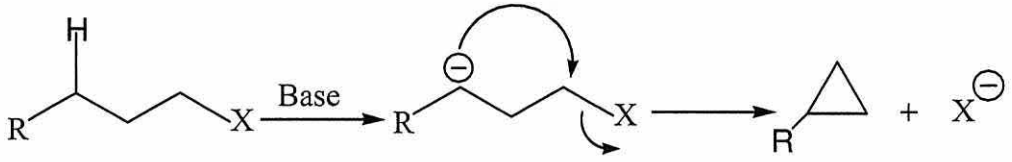
Figure (30)

A similar system to the oxygen substituent of cyclopropanone (**37**), the methylene of the methylenecyclopropane (**38**) shortens the bond next to it and lengthens the bond opposite in comparison to the length of the C-C bond in cyclopropane.[78]

1.11 Some methods for the preparation of cyclopropanes.

1.11.1 1,3-Elimination of HX.

One of the best and simplest methods for the synthesis of cyclopropanes is via intramolecular S_N2 displacement of a suitable leaving group from the γ-carbon of a substrate bearing a carbanion at the α-carbon atom (Figure 31).
The leaving group (X) is usually a tosyl group or a halogen and the R-group could be an ester, ketone, or nitrile, which stabilizes the carbanion. [79][80]

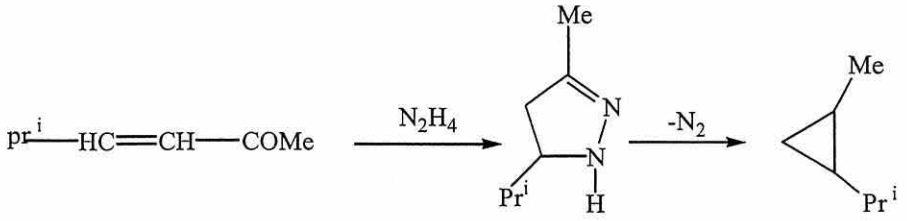


(39) (40)

Figure (31)

1.11.2 Ring Contraction.

Addition of hydrazine to α-β–unsaturated ketones can lead to the elimination of nitrogen from the intermediate **(42)** to give a cyclopropane; by involving photochemical decomposition.[81]

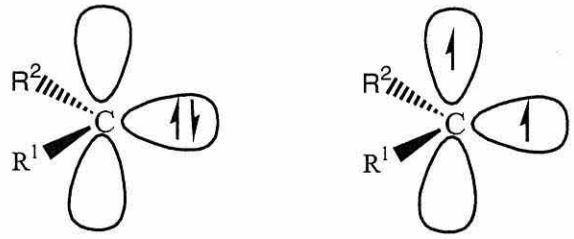


(41) (42) (43)

Figure (32)

1.11.3 Addition of carbenes to alkenes.[82]

Carbenes are divalent carbon species that have two additional electrons that can be either in singlet or triplet states. If the two-nonbonded electrons are spin paired then the carbene is a singlet (A) (Figure 33), and if the spins of the electrons are parallel, then the carbene is a triplet (B).



(A) (B)

Figure (33)

Carbenes are normally electrophilic and will react with olefins to form cyclopropanes. As was suggested by Skell, the stereochemistry of the addition of carbenes to alkenes depends on the spin state of the carbene.

He proposed that the spin-paired singlet carbene would undergo a stereospecific, concerted addition to a double bond thus preserving the stereochemistry of alkene. For a triplet carbene, the cycloaddition must go through a triplet diradical intermediate (Figure 34). Before this can close to give a cyclopropane, there has to be an inversion of spin of one of the electrons, a slow process. If the free rotation about the C-C bonds of the diradical is faster than the spin inversion, then the stereochemistry of the original olefin will not be retained in the cyclopropane.

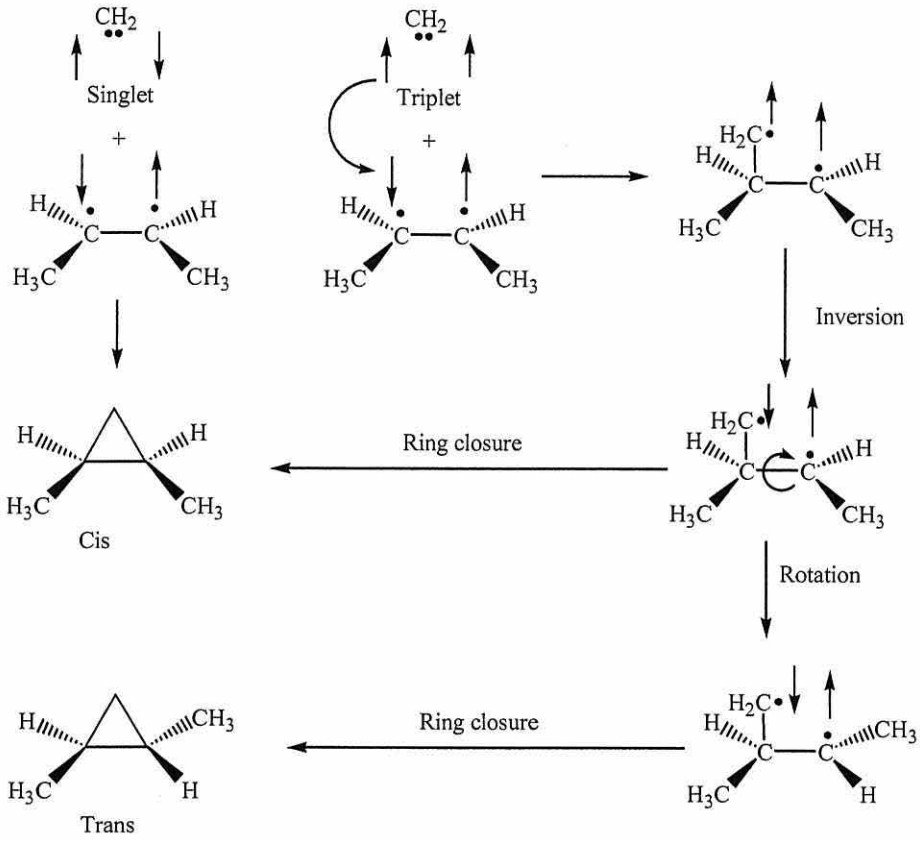


Figure (34)

1.11.4 Phase transfer catalysed carbene addition.

Dihalocarbenes are usually made by the reaction of a haloform ($CHCl_3$, $CHBr_3$) with aqueous sodium hydroxide in the presence of a quaternary salt. Using various alkenes, dichloro or dibromo-cyclopropanes were isolated in good yield (Figure 35).[83][85]

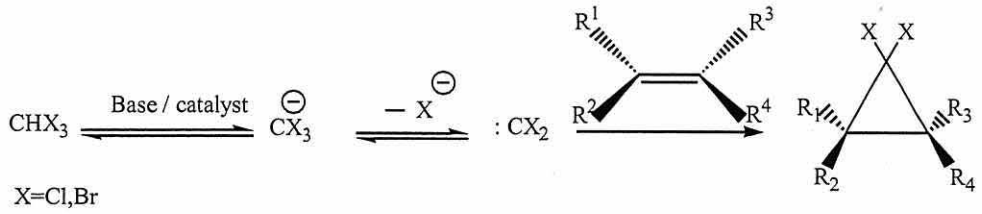


Figure (35)

The phase transfer reaction was used first by Starks and Makosza.[86][87] The generation of dihalocarbene from haloform uses a strong base like sodium hydroxide. This is not soluble in the organic phase but reacts with the phase transfer catalyst (TEBA) to produce a quaternary ammonium hydroxide which is a strong base, soluble in organic solvent and the active species in the phase transfer process. The hydroxide ion is now able to deprotonate the haloform in the organic phase or at the interface to form a trihalomethyl anion from which the dihalocarbene is generated by loss of the halide ion. The by-products of the reaction (H_2O and QX) pass back into the aqueous phase where the catalyst is available to react with further sodium hydroxide. The dihalocarbene generated in the organic phase reacts mainly with the alkene to form a cyclopropane and only to a minor extent with water (Figure 36). The phase transfer process gives a simple procedure, inexpensive reagents, and constitutes possibly the most valuable supply of dihalocarbenes.

The suggested mechanism is:

$$NaOH_{(aq)} + Q^+X^- \rightleftharpoons QOH_{(aq)} + NaX_{(aq)}$$

$$QOH_{(aq)} \rightleftharpoons QOH_{(org)}$$

$$QOH_{(org)} + CHX_3 \rightleftharpoons X_3C^-Q^+_{(org)} + H_2O$$

$$X_3C^-Q^+_{(org)} \rightleftharpoons Q^+X^-_{(org)} + :CX_2{}_{(org)}$$

$$Q^+X^-_{(org)} \rightleftharpoons Q^+X^-(aq)$$

X = halogen.

Q^+ = quaternary ammonium ion.

Figure (36)

1.11.5 The Simmons-Smith reaction.

Simple alkenes can undergo cyclopropanation in the presence of diiodomethane and zinc-copper couple [Simmons-Smith reaction] (Figure 37).[88]

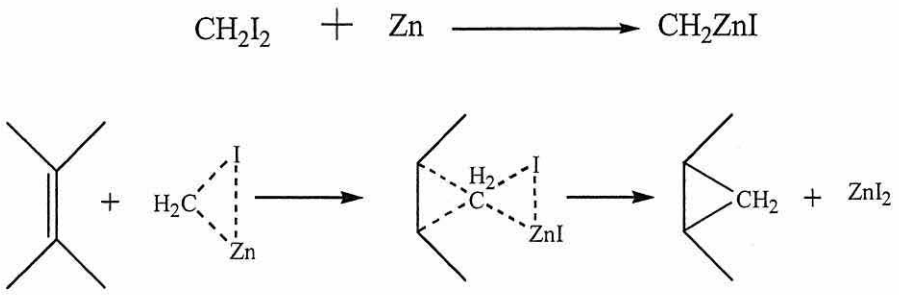


Figure (37)

The reagent was modified by Furakawa who used diethylzinc instead of the zinc copper couple.[89][90] This is in many ways very similar to the old method, but has advantages:

- Reagent preparation is fast under mild conditions.
- It is useful for the cyclopropanation of vinyl ethers, which was not possible by the old method, and similar substrates that are liable to polymerization under Simmons-Smith conditions.[91]
- The reaction in Furakawa's method is more homogeneous.
- Furakawa's conditions can be used with alkyl and phenyl carbenoids.[92]

1.12 Some methods to prepare methylenecyclopropanes.

The addition of dihalocarbenes to 1,2-and 1,3-substituted allenes takes place at the more substituted double bond (Figure 38).[93]

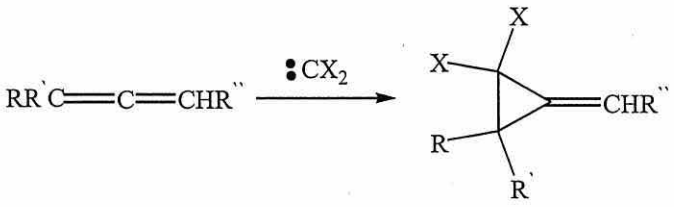


Figure (38)

Substituted methylenecyclopropanes can also be prepared by treatment of 1-halo-2-alkylcyclopropanes with potassium t-butoxide.[94] Following dehydrohalogenation, the more strained cyclopropenes are changed to less strained methylenecyclopropanes by base induced proton shifts (Figure 39).

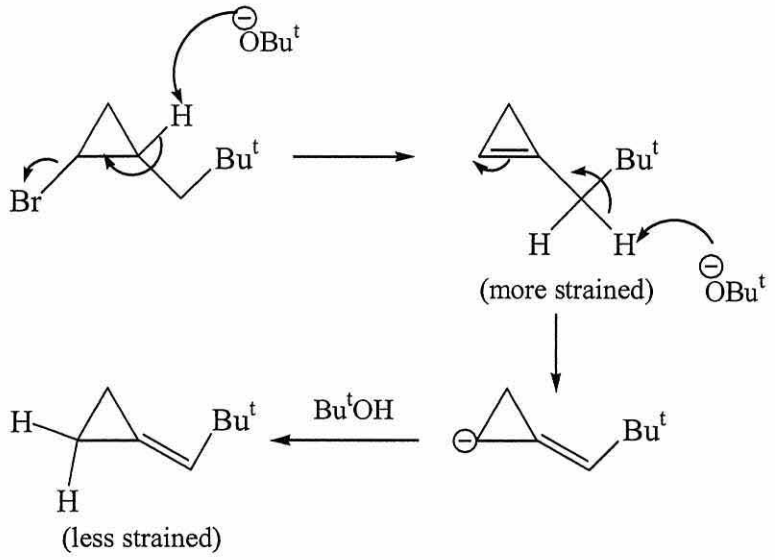
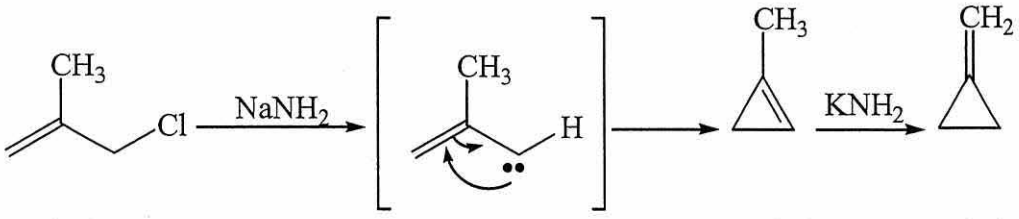


Figure (39)

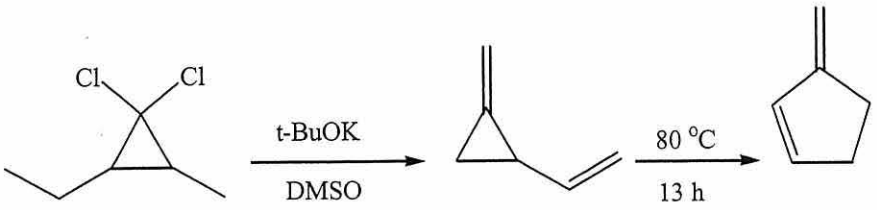
An alkyl-substituted allylic chloride can react with strong base to give an alkylcyclopropene which may react further to form a methylenecyclopropane. Thus the reaction of 3-chloro-2-methylprop-1-ene (**44**) with sodium amide in THF at 65 °C can give large quantities of 1-methylcyclopropene (**45**), but with potassium amide as base this reacts further to form methylenecyclopropane (**46**) (Figure 40).[95]



(44) (45) (46)

Figure (40)

Certain vinyl methylenecyclopropanes (**48**) were converted into methylenecyclopentene (**49**) by refluxing in toluene (Figure 41).[96][97]



(47) (48) (49)

Figure (41)

This may occur via a free radical rearrangement or through a sigmatropic shift.

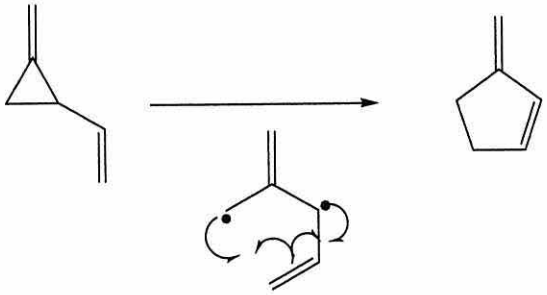


Figure (42)

1.13 Ring opening of cyclopropanes.

The strain of cyclopropane is released when the ring is opened; for example cyclopropane reacts with hydrogen bromide to give bromopropane (**50**) or with hydrogen in the presence of nickel as a catalyst to give propane (**51**).

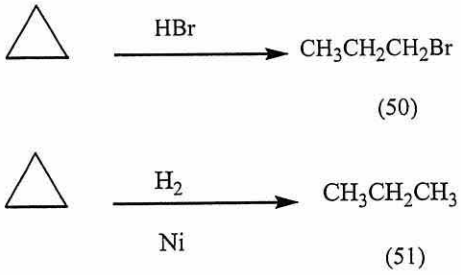


Figure (43)

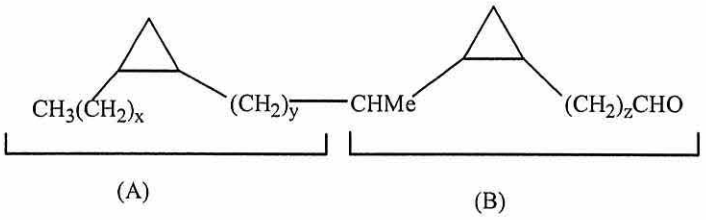
Chapter Two

α-Methylcyclopropanes

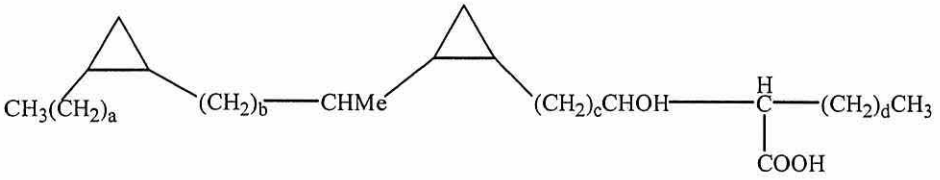
Results and discussion

2.1. Introduction.

Minnikin and Polgar reported the isolation of a meromycolaldehyde (**52**, x = z = 17, y = 12) from the thermolysis of the mycolic acid from *mycobacterium avium*,[34] and proposed that the parent mycolic acid was (**53 a**).[34] In this early paper both cyclopropanes were assigned *cis*-configuration, though it has subsequently become clear in other examples (**53 b**) that the one closer to the aldehyde is *trans*.[30a] In no case has the absolute stereochemistry of the cyclopropanes or the methyl branch been determined.



(52)



a, a = 17, b = 12, c = 17, d = 23.

b, a = 17, b = 14, c = 18, d = 21.

(53)

Figure (44)

Therefore, the aim in the project was to synthesise a single enantiomer of (**52**, x = z =17, y = 12) using a method that could be varied easily to produce homologues. First it was necessary to prepare the α-methyl cyclopropane fragment (B).

2.1.1 Carbon-Carbon bond formation.

Asymmetric synthesis is a widely used method for stereo-controlled creation of C-C bonds in organic molecules, which has contributed greatly to progress in the directed introduction of various functionalities, and in highly controlled formation of new centres of chirality.

Preparation of the latter in optically pure form by using a chiral starting material is very advantageous, enabling precise planning and efficient realization of synthetic pathways. Many mono-saccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules. In this work, (R)-2,3-O-isopropylideneglyceraldehyde (**56**) was the chosen chiral starting material. The first effective preparation of (**56**) was reported by Baer and Fisher in 1949.[98]

D-Mannitol (**54**), a naturally occurring inexpensive poly-hydroxy compound, was used as starting material (Figure 45).

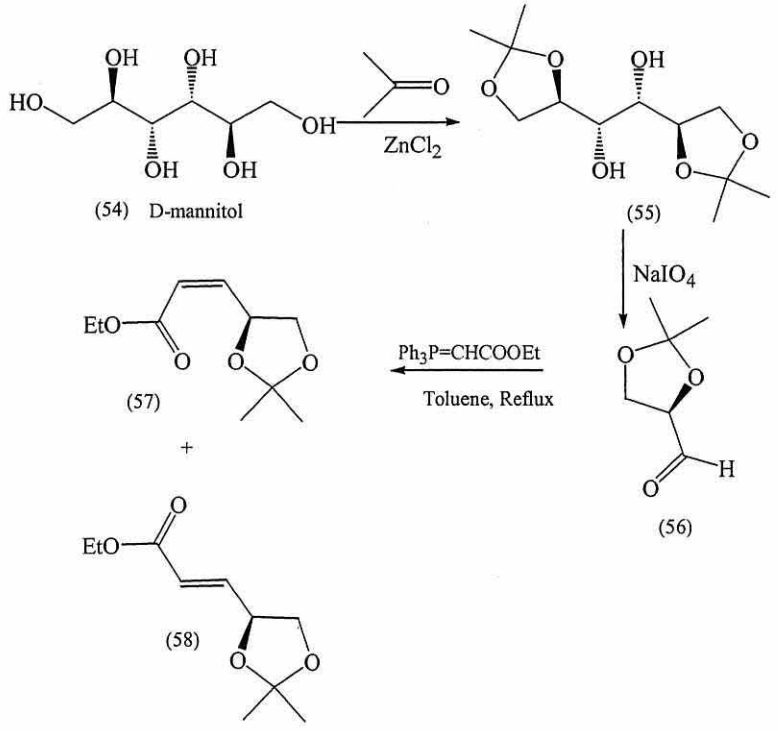


Figure (45)

Using the literature method [99][100] to diprotect D-mannitol (**54**) by using dry acetone and zinc chloride gave (**55**) in 83 % yield. The ^{1}H n.m.r spectrum showed two multiplets at δ 4.15 ppm and 4.0 corresponding to the protons attached to the isopropylidene groups. The two protons attached to the hydroxyl groups were seen as a triplet at 3.7 with coupling constant 6.4 H_Z, and two singlets at 1.45 and 1.35 corresponding to the four-methyl groups. Isopropylidene acetal formation is a thermodynamically controlled process; thus, in the case of reaction 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, hence their formation is favoured over the formation of six membered acetals.

The next step was the oxidative cleavage of (**55**) to give 2,3-O-isopropylidene-D-glyceraldehyde (**56**),[100] the chiral aldehyde used as starting material in the synthetic routes for α-methyl-*trans*-cyclopropanes. The aldehyde (**56**) was prepared by the addition of sodium (meta) periodate to the diprotected D-mannitol (**55**) in dichloromethane, and then water was added. The mixture was stirred at room temperature for 3 h, and then magnesium sulphate was added. The precipitate was filtered off, and the solvent was evaporated at 14 mm Hg and 15 °C to give (**56**) in 95 % yield. This proved to be a difficult stage as the aldehyde polymerises at room temperature. However, the polymerisation process was slowed for long periods when the aldehyde was dissolved in toluene or in ether and stored at low temperature.

The ^{1}H n.m.r spectrum showed the change of the diprotected D-mannitol (**55**) to the aldehyde (**56**), which could be seen by the appearance of a sharp doublet for aldehydic proton at δ 9.7 with coupling constant 1.85 H_Z, the ^{13}C n.m.r spectrum showed the presence of the carbonyl group at 202 ppm.

A Wittig reaction of the aldehyde (**56**) with carbethoxymethylenetriphenyl phosphorane gave a mixture of Z- and E-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester (**57**) and (**58**). Following a literature procedure,[102] refluxing for 3 h in toluene gave a 74 % yield; g.l.c showed the ratio of E to Z isomers was 5:2.

Repeating the same procedure and stirring the reaction mixture for 16 h gave the same ratio. Moreover, when using methanol as solvent the ratio of Z to E isomers was 4:5. The ^{1}H n.m.r spectrum of the mixture showed the different coupling constant between the olefinic protons for E and Z isomers. The two isomers were separated by column chromatography on silica eluting with petrol ether / ether (5 : 2).

The ^{1}H n.m.r spectrum for the *trans*-isomer showed two double doublets in the alkene region integrating for two protons at δ 6.9 ppm and 6.1 with coupling constant 15.6, 5.6 H_Z, and 15.6, 1.4 H_Z ($[\alpha_D]^{23}CHCl_3$ +38, *lit* $[\alpha_D]$ +41).[101] The *cis*-isomer showed a double doublet integrating for one proton at δ 6.38 with coupling constants 11.5, 6.5 H_Z, and another broad doublet at 5.85 with coupling constant 11.5 H_Z, ($[\alpha_D]^{23}CHCl_3$ +118, *lit* $[\alpha_D]$ +123).[101] Using the literature method,[102] the two separated isomers were treated with diisobutyl aluminium hydride in dichloromethane to give the alcohols (**59**) and (**60**) respectively.

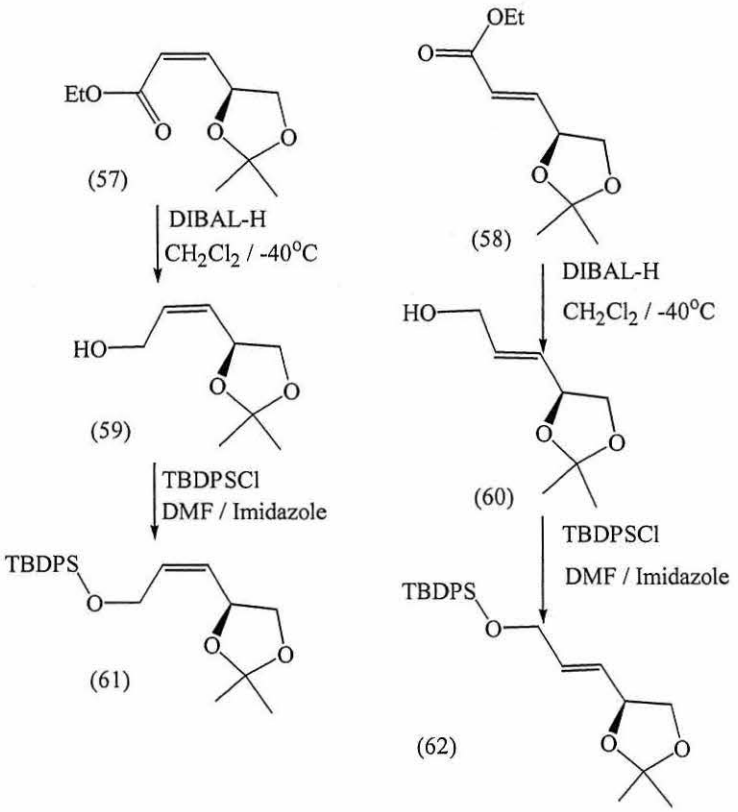


Figure (46)

The reduction of the esters (**57**) and (**58**) to the alcohols could be seen clearly in the infrared spectrum, the disappearance of C=O group stretching band and the appearance of the O-H group stretching at 3410 cm^{-1} confirming that the reaction had occurred. The ^{13}C n.m.r spectrum, which showed the disappearance of the carbonyl group, confirmed the observation.

Both the alcohols (**59**) and (**60**) were protected with TBDPSCl in DMF in the presence of imidazole, and the I.R spectra for (**61**) and (**62**) showed that the protection of the alcohol has been successful with loss of the hydroxyl group broad band. The ^{1}H n.m.r spectrum of the protected alcohol (**62**) showed the appearance of a singlet at δ 1.07 ppm integrating for 9 H for the tertiary butyl protecting group. The ^{13}C n.m.r spectrum showed clearly the two olefinic carbons at δ 131 ppm and 130, and the specific rotation for (**61**) [(α) = +3.7, c = 1.25, $CHHCl_3$), *lit* (α) = +3.9, c = 1.12].[103]

A Simmons-Smith reaction of protected alcohols (**61**) and (**62**) gave (**63**) and (**64**). This is the most widely used method for the stereoselective cyclopropanation of olefins.[104] The cyclopropanation occurred from the bottom face of the E or Z-double bond configuration (A) (Figure 47) because of the chiral centre of the dioxolane ring.[105]

The stereoselectivity of the cyclopropanation is controlled by the directing effect of the allylic oxygen of the dioxolan ring, which coordinates to the reagent, and the diastereoselectivity for the protecting groups increased in order TBDPS > MOM > Bn.[106]

Demonstrated that by drawing Newman projection for the free rotation around the bond connecting the *trans*-alkene to the allylic stereo-centre the preferred arrangement shown below:

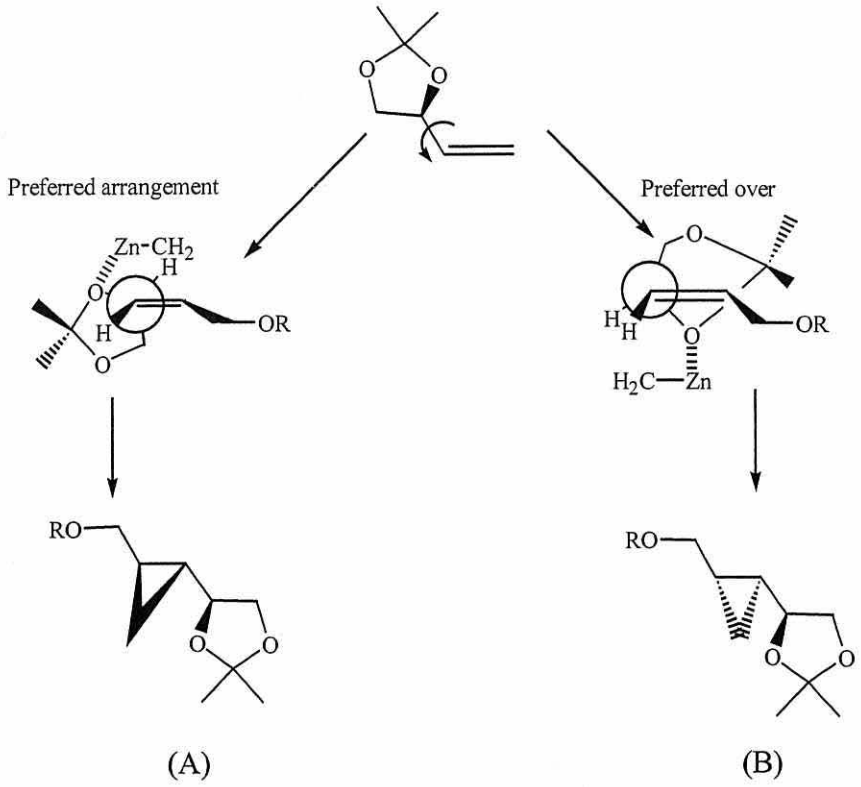


Figure 47

The cyclopropanation process by coordination of the zinc with the allylic oxygen of the dioxolane ring allows the methylene transfer to the bottom face of the double bond, which gives the major cyclopropane (A).

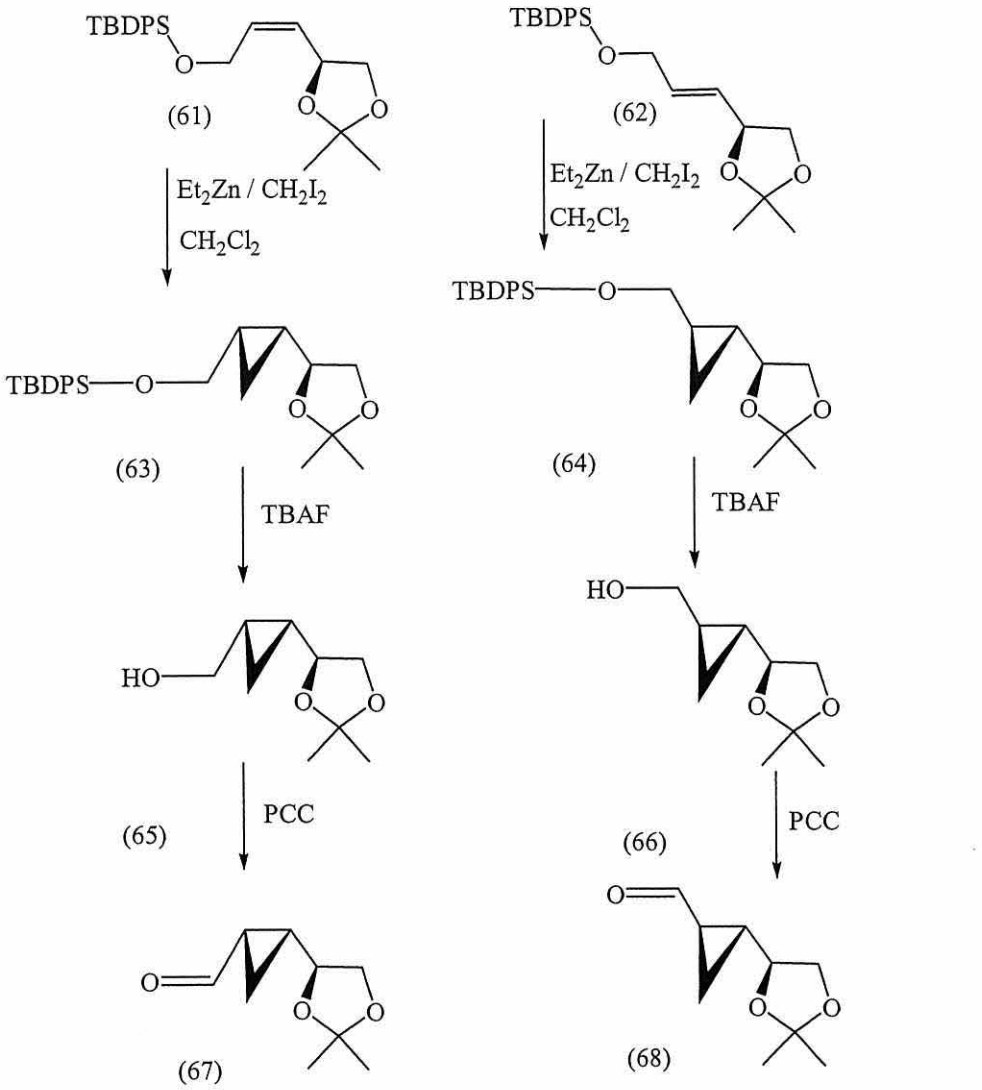


Figure (48)

In the literature[106][107] using Et_2Zn (5 eq) and CH_2I_2 (10 eq), the claimed yield was 84 - 97 %; using the same amount of diethylzinc and diiodomethane the yield in this work was 81 – 86 %. The ^1H n.m.r and the ^{13}C n.m.r spectrum for (**63**) and (**64**) showed the successful cyclopropanation by the disappearance of the olefinic protons and olefinic carbons. The infrared spectra indicated the loss of the olefinic C-H stretching band.

Removal of the protecting group with tetrabutylammonium fluoride produced the alcohols (**65**) in 78 % yield, and (**66**) in the same yield. The IR spectrum indicated the deprotection had been successful by showing the broad signal for the hydroxyl group at 3428 cm^{-1}, while the ^1H n.m.r showed the loss of the TBDPS group and the appearance of a broad singlet at 1.65 integrating for one hydroxyl proton. Two singlets for the two methyl groups of the dioxolane ring were still present as before, which showed the selectivity of the deprotection. The selective oxidations of (**65**) and (**66**) were successfully carried out in CH_2Cl_2 solution using PCC as oxidizing agent at room temperature and led to (**67**) and (**68**) in very good yields. The I.R specta showed strong C=O stretches at 1709 cm^{-1} consistent with the desired aldehyde functionality. The ^1H n.m.r spectrum of (**68**) showed a sharp doublet at δ 9.1 corresponding to the aldehyde proton with coupling constant 5.0 H_Z. Slightly different, the ^1H n.m.r spectrum of (**67**) showed a sharp doublet for the aldehydic proton at δ 9.41 with coupling constant 5.1 H_Z due to the deshielding by the isopropylidene group. For (**67**), the ^{13}C n.m.r spectrum indicated the carbonyl signal at δ 200.7, while for (**68**) it was at 199.0.

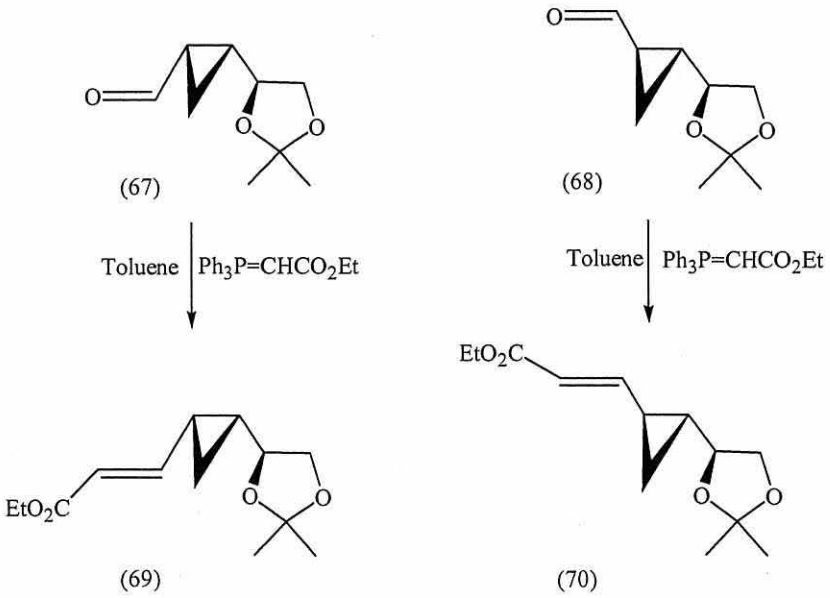


Figure (49)

A second Wittig reaction using carboethoxymethylene triphenylphosphorane and aldehydes (**68**) and (**67**) gave a major E-isomer (**70**) in 76 %, and (**69**) in 71 % yield together with a small amount of the corresponding Z-alkene isomer (less than 5 %). The ^{1}H n.m.r for compound (**70**) showed the *trans*-coupling, with a double doublet integrating to one proton in the alkene region at δ 6.7 with coupling constant 15.5 and 5.5 H_Z, and a doublet at 5.8 for the other one with a coupling constant 15.5 H_Z.

The ^{1}H n.m.r spectrum of (**69**) showed a double doublet at 6.6 with coupling constant 15.2, 10.3, and a doublet at 5.9 with coupling constant 15.2 H_Z. The ^{13}C n.m.r spectrum included signals at δ 167 for the carbon of the carbonyl group, and at 150 and 122 for the olefinic carbons.

The next step was to introduce the α-methyl group next to the cyclopropane ring. When the *trans*-cyclopropane (**70**), was allowed to react with methylmagnesium bromide in the presence of cuprous bromide at - 40 – 0 °C, a mixture of two isomers was obtained in 1:1 ratio (Figure 50); these were difficult to separate by column chromatography.

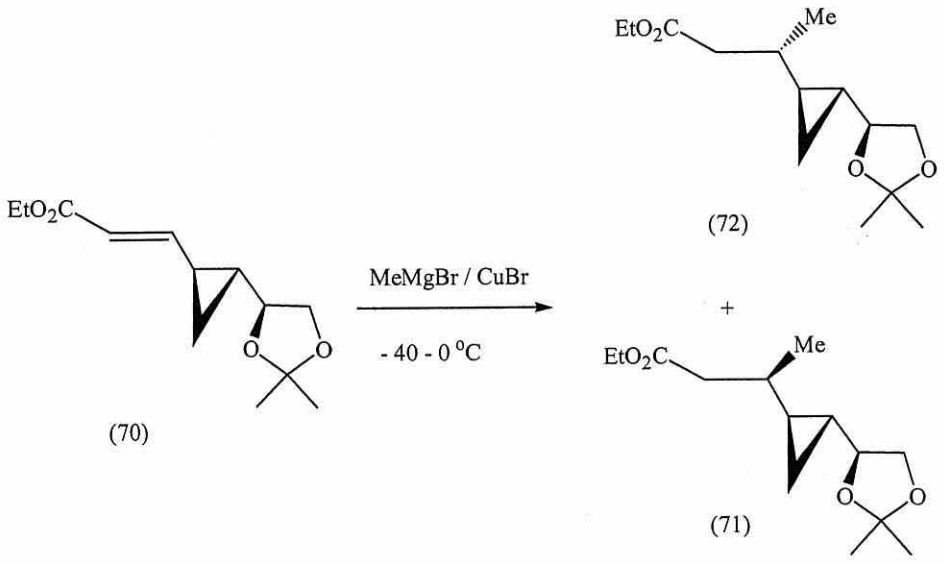


Figure (50)

Organocopper reagents of different composition are highly useful tools in organic synthesis for the formation of a new carbon-carbon bond.[108] Great efforts have been made to reach high stereoselectivity in the bond formation. Enantioselectivity via chiral auxiliaries in the copper reagents or ligands shows some striking examples of success.[110] Karolina and Christina[109] have focused on a better understanding of the mechanism for the carbon-carbon bond formation between the organocopper reagent, mostly R_2CuLi, and enones or enoates.

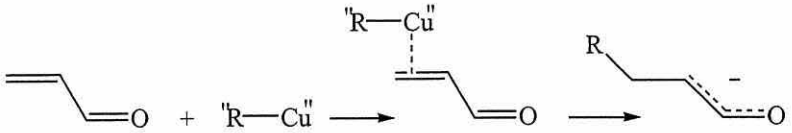
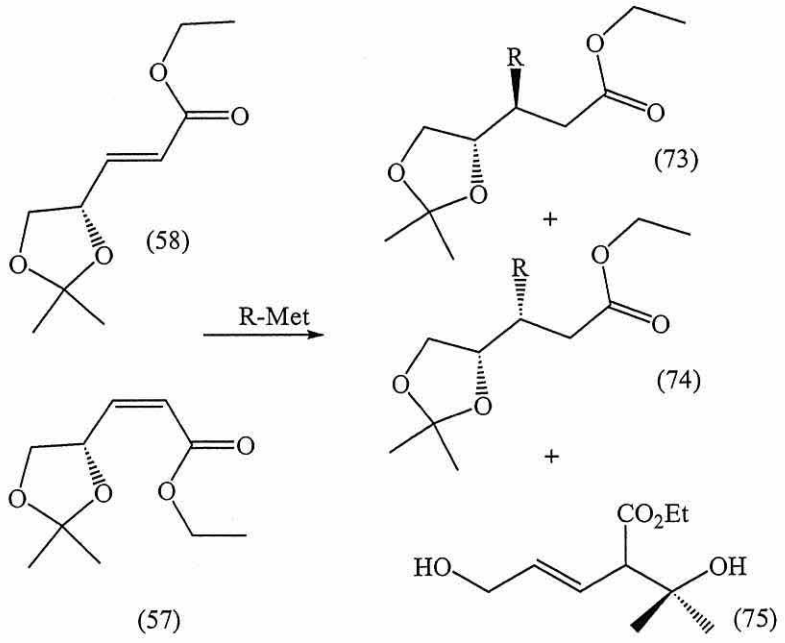


Figure (51)

A study of the addition of a range of organometallic reagents to the E and Z isomers of ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate, (**57**) and (**58**) respectively (Figure 52) proved di*alkyl* cuprates are not useful reagents for the formation of a new carbon-carbon bond.[109]

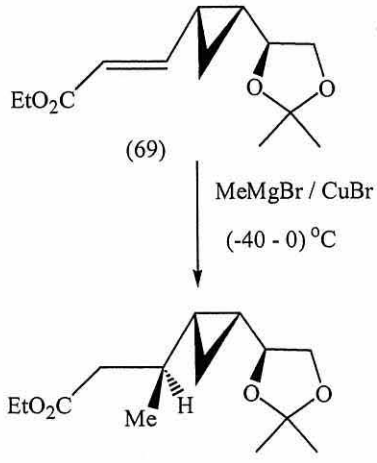


R = methyl, butyl or phenyl.

Figure (52)

The stereoselectivity of the carbon-carbon bond formation of α-methyl cyclopropane, by using methylmagnesium bromide and cuprous bromide in THF could be explained by unselective Michael addition to the α,β-unsaturated ester next to the *trans*-cyclopropane (**70**) giving a 1 : 1 ratio of distereoisomers (**71**) and (**72**), which were hard to separate. The ^{1}H n.m.r spectrum for the mixture showed clearly that there were no signals for olefinic protons, and there were two doublets for the α-methyl groups next to the *trans*-cyclopropane. The ^{1}H n.m.r spectrum in C_6D_6 showed the methylene group next to the carbonyl of the ester of one isomer as two double doublets at 2.32 (J= 3.15, 7.4 H_Z) and 2.26 (J= 3.15, 7.4 H_Z). Another double triplet 2.16 (J= 3.9, 7.4 H_Z), confirmed the presence of the second isomer (ratio 1:1). The ^{13}C n.m.r spectrum of the product again confirmed the formation of two isomers due to the appearance of two carbonyl carbons at δ 172.8 and 172.6.

However when the *cis*-cyclopropane (**69**) was allowed to react with methyl magnesium bromide in the presence of cuprous bromide under the same conditions it gave two isomers in ratio 15.5 : 1, which gave one peak by g.l.c and one spot by t.l.c for the major isomer (**76**) and the stereochemistry of the addition of the methyl group was proved by X-ray crystallography.[30a]



(76)

Figure (53)

The *cis*-cyclopropane geometry indeed allows the possibility that the dioxolane oxygen may deliver the cuprate (via co-ordination to Mg) or my shield one top-face attach from underneath (see below):

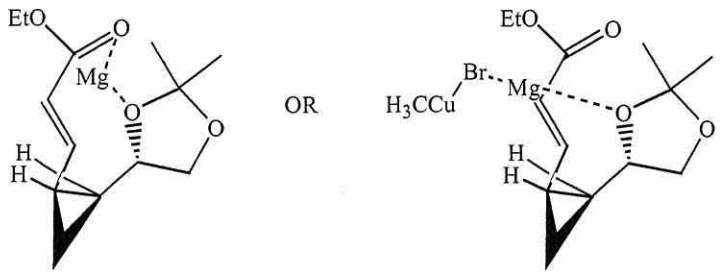
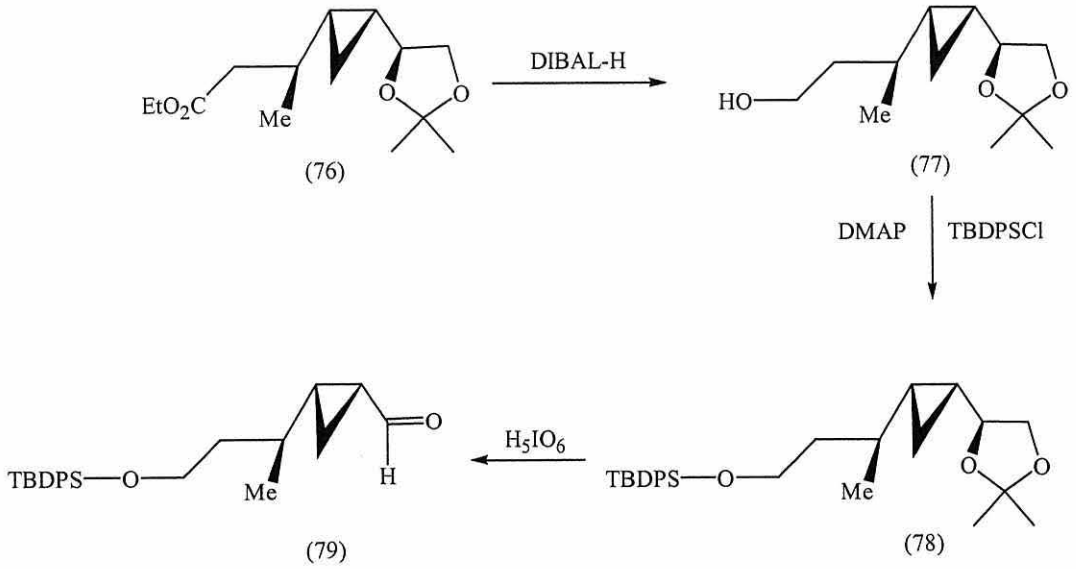


Figure (54)

The ^{1}H n.m.r spectrum obtained from the product of Michael addition to the α,β-unsaturated ester (**69**) showed just one major isomer (**76**). The product gave the correct measured mass for $C_{13}H_{22}O_4$. The I.R spectrum displayed a broad band at 1735 cm^{-1} for the C=O stretch. In the ^{1}H n.m.r spectrum, the methylene group next to the ester group showed two double doublets at δ 2.27 ppm and 2.13 (J = 3.9, 14.6 H_Z and 9.45, 14.6 H_Z respectively), together with a doublet at 1.03 integrating to three protons with coupling constant 6.7 H_Z. The ^{13}C n.m.r spectrum showed the signal of the carbonyl carbon at δ 173, and three signals for the carbons next to oxygen at 79.1, 71.3 and 61.6. Moreover the DEPT ^{13}C n.m.r spectrum showed four signals for CH_2 groups and eight for CH and CH_3 groups.

The next step was the reduction of the ester group of (**76**) with DIBAL-H (diisobutyl aluminium hydride), conducted following the method described by Miniami.[110] The crude product, alcohol (**77**) (Figure 55) was purified by column chromatography. The successful reduction of the ester group was observed by the appearance of a broad O-H stretch at 3418 cm^{-1} and the disappearance of the C=O stretch (present in the starting material). The ^{1}H n.m.r spectrum showed the disappearance of the signals corresponding to the ethoxy group of the ester, and the appearance of a sharp triplet for two protons corresponding to the methylene group next to the hydroxyl group.

Using the literature method,[111] compound (**77**) was protected using tert-butyldiphenylchlorosilane in the presence of triethylamine and a catalytic amount of dimethylaminopyridine in CH_2Cl_2 at room temperature and purified by column chromatography to give (**78**) in 70 % yield.



(Figure 55)

The ^1H n.m.r spectrum of (**78**) showed two multiblet at δ 7.66 and 7.12 integrating for ten protons (aromatic rings). I.R spectrum also indicated the successful protection of the alcohol with the disappearance of the hydroxyl stretching frequency. The isopropylidene group in (**78**) was removed using PTSA-aqueous methanol and the resultant diol cleaved to provide the aldehyde (**79**) with sodium periodate. Unfortunately the acid catalysed step was only effective when carried out under conditions of high-dilution. A more concentrated reaction mixture led to concomitant removal of the TBDPS group.

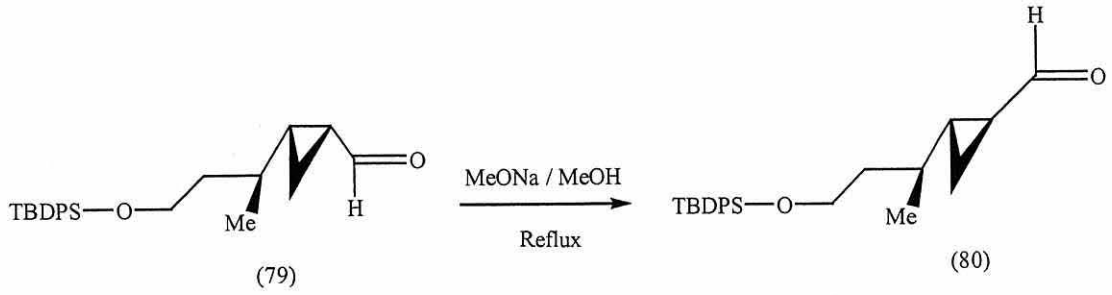
To avoid this problem, periodic acid in anhydrous ether was used to effect removal of the isopropylidene group and oxidative cleavage of the resultant diol to provide the aldehyde (**79**) in 79 % yield.[112][111]

The proton n.m.r spectrum showed that the deprotection had been successful with the loss of the two singlets for the methyl groups of isopropylidene ring and also the successful oxidation of the resulting diol to give the aldehyde group by the appearance of a sharp doublet of the aldehyde group at 9.3 ppm with coupling constant 5.8 H_Z.

It was apparent that epimerisation had not occurred. This was because a second doublet further up field was not observed which would be expected if the *trans*-cyclopropane diastereomer was present. Additionally the spectrum indicated that the cyclopropane signals had shifted downfield due to the deshielding by the carbonyl group. The ^{13}C n.m.r spectrum confirmed the formation of compound (**79**), showing only one aldehyde carbon atom at δ 200.4. The I.R spectrum was also consistent, with the presence of a carbonyl group stretch at 1704 cm^{-1}.

As mentioned before, the natural product contains the α-methyl *trans*-cyclopropane unit; therefore the α-methyl *cis*-cyclopropane (**79**) must be epimerized to the *trans*-cyclopropane isomer. Therefore (**79**) was treated with sodium methoxide in methanol, refluxing for 48 h and monitoring the reaction by ^1H n.m.r.[113] The mixture was quenched by the addition of saturated aqueous ammonium chloride to give (**80**) and (**79**) (Figure 56) in ratio 19 : 1 with a 64 % yield.

The ^1H n.m.r spectrum showed the aldehydic proton shifted to high field at δ 8.9 as a doublet with coupling constant 5.5 H_Z. The optical rotation was found to be $[\alpha]_D$ = +9.4 (c= 1.23, $CHCl_3$).



(79) (80)

Figure (56)

Although the above method was successful in producing the required α-methyl-*trans*-cyclopropane unit, it was quite long and limited by the cost of the cyclopropanation step. A second method was therefore studied in which the cyclopropane was introduced as a very simple a chiral unit and then desymmetrised.

2.2 Enzymatic Resolution.

Enantiopure compounds have undoubtedly gained a central role in the development of modern chemical technology. This is evident from the changes in the drug market, where single-enantiomer drugs currently occupy a share of some 35 billion US dollars. Two-thirds of the world market of the top 25 selling drugs is covered by enantiomeric compounds, and the sales are steadily growing at an average annual rate of nearly 7 %.[114] At the same time, the sales of racemic drugs are diminishing by nearly 30 % per year, currently covering only some 1.4 billion dollars.[114]

The kinetic resolution of a racemic substrate in the presence of an enzyme is by far the most commonly applied method in the resolution of optical centres. Historically, Louis Pasteur carried out the first enzymatic kinetic resolution in 1858.[115] 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 transformation to the developing science of chemical synthesis.

2.3 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 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,[124] and may be described with the aid of a simple schematic mechanism (equations 1 and 2), where R and S represent the fast and slow reacting substrates respectively. Enz-R and Enz-S represent enzyme-substrate complexes; further reaction of such complexes leads to the formation of the desired products P and Q.

$$Enz + R \rightleftharpoons Enz - R \longrightarrow Enz + P \quad \text{----------(1)}$$

$$Enz + S \rightleftharpoons Enz - S \longrightarrow Enz + Q \quad \text{----------(2)}$$

The rates of formation of the products (P & Q) are $\upsilon = (Vmax / Km)R$ and $\upsilon = (V`max / K`m)S$ respectively, and the reaction is pseudo-first order with respect to the enantiomers R and S where Enz is the biocatalyst; Vmax is the maximal velocity and Km is the Michaelis constant.

The enantiomer ratio, E, is simply the ratio of the pseudo-first order rate constant, $E = (Vmax / Km) / (V`max / K`m)$. Implicit in this derivation is the assumption that R is the fast reacting enantiomer and the system is irreversible 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, one enantiomer (typically the unreacted) may still 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 Aqueous versus organic media.

Pasteur achieved enzymatic resolutions at 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 enzyme's "natural habitat", hence maintaining enzyme activity throughout reactions where a number of variables such as the temperature and pH of the solution may fluctuate and otherwise denature 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 buffered aqueous solution via the enantioselective enzymatic hydrolysis of derivatised starting materials including esters, amides and carbamates.[116]

More recently, pioneering studies conducted by the group of Klibanov have shown that many enzymes remain catalytically active in organic solvents containing little or no added water.[117] The deployment of enzymes in monophasic organic solvents at low water activity has several advantages: enzymes may be more stable in organic solvents than in water and enzyme enantioselectivity may be enhanced in organic media; water-insoluble organic substrates are sometime transformed at a faster rate in organic solvents than in an aqueous medium; undesired side reactions involving water are repressed. However, the most important advantage is the possibility of shifting the thermodynamic equilibrium to favour synthesis over hydrolysis. Thus, hydrolytic enzymes such as lipases and proteases have been extensively used for preparative enantioselective synthesis via transacylation processes in organic media.

The general aim of this present work is the successful development of efficient routes that will enable the large scale preparation of optically pure cyclopropane building blocks Hence, the successful development of an enzymatic route would enable the efficient preparation of such compounds, which could then be used as starting materials in the total synthesis of α-methyl mycolic acids.

2.5 The application of enzymes in organic solution.

One of the main growth areas in the application of enzyme technology in organic solution 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,[118] acids,[119] esters[120] and amines.[121]

The aim of the present study was to successfully apply such techniques to the desymmetrisation of a simple, readily available meso-cyclopropane containing substrate, 1,2-dihydroxymethylcyclopropane, the synthesis of which will be discussed in detail later.

2.6 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 of a single enantiomer of a racemic substrate.

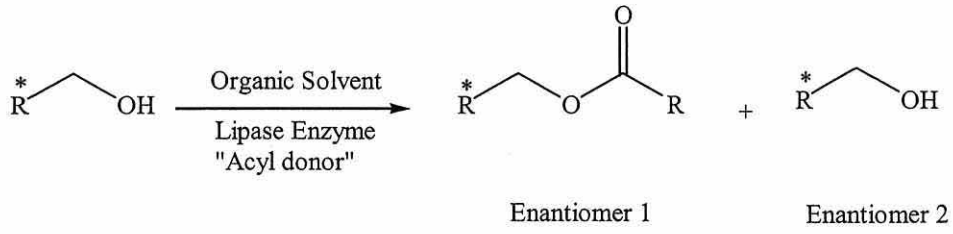


Figure (57)

One inherent problem that is often encountered with kinetic resolutions of this type is the effect of the competing reverse reaction of the chiral alcohol component of the acyl transfer with the desired optically active ester produced (as seen in Figure 76). This reverse process consequently leads to a decrease in the optical purity of the desired product, and is therefore undesirable.

To avoid this problem, irreversible acyl transfer agents or "acyl donors" have been developed. The application of these effectively eliminates the reverse reaction. Examples of suitable acyl donor reagents include the enol acetates, vinyl acetate, vinyl butyrate and isopropenyl acetate, which have since become the reagents of choice when carrying out lipase-mediated acetylation of alcohols in organic solution.[122]

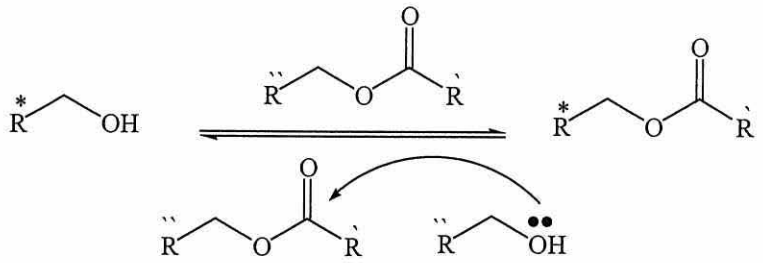


Figure (58)

The desired kinetic resolution is generally catalysed by the presence of a range of hydrolytic enzymes collectively known as hydrolase 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, regio-selectivity and stereo-selectivity.

2.7 Chiral cyclopropanes.

The cyclopropane ring is a common unit in a large number of natural products and compounds of pharmaceutical interest.[123] As most of them are optically active, an easy access to optically pure versatile cyclopropane intermediates would be valuable. Dimethyl *cis*-1,2-cyclopropanecarboxylate (**82**) was prepared following a literature procedure by McCoy.[124,125]

Condensing methyl acrylate and methyl chloroacetate using sodium methoxide as a base gave two compounds, dimethyl *cis*-1,2-cyclopropane ester (**82**) and dimethyl *trans*-1,2-cyclopropane ester (**81**), which were easily separated by column chromatography. The ester (**82**) was reduced to *cis*-1,2-dihydroxymethylcyclopropane (**83**) using lithium aluminium hydride in 90 % yield (Figure 59).

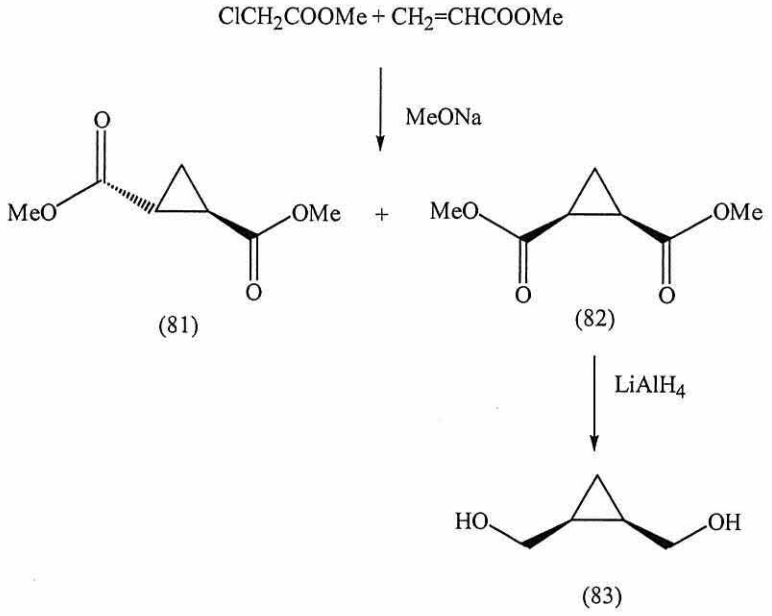


Figure (59)

It is known that Grandjean and co-workers[126] successfully obtained an optically pure cyclopropane synthon *cis*-(*1R, 2S*)-butyryloxymethyl-2-hydroxymethylcyclopropane (**85**) (Figure 60) via an enzyme resolution. Using a crude lipase extracted from pig pancreas (PPL) they were able to catalyse the cleavage of the meso-diester *cis*-1,2-bis(butyryloxymethylcyclopropane) (**84**) at pH 6.5 and ~ 3° C in water-ethylene glycol. The optically pure monoester (**85**) was isolated in excellent yield with ee > 99% [$(\alpha)_D$ = 18.2, c = 2.8 $CHCl_3$].[126]

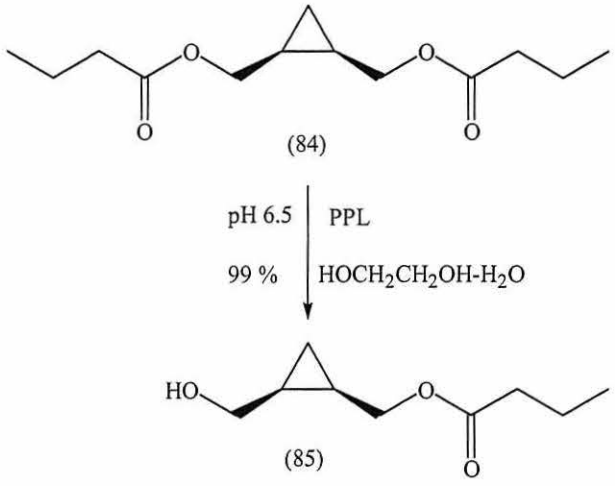


Figure (60)[126]

The enantiomer (**86**) was obtained in this work by the enzymatic transesterification of *cis*-1,2–bis(hydroxymethyl)cyclopropane (**83**) with 2,2,2–trifluoroethyl butyrate or vinyl butyrate in THF in the presence of lipase. 2,2,2–Trifluoroethanol was readily esterified with butyric anhydride in diisopropyl ether in the presence of a catalytic amount of trimethylsilyl trifluoromethane sulphonate. The butyric acid formed and any slight excess of butyric anhydride were easily washed out and the resulting solution, which was assumed to contain 90 % of the theoretical quantity of 2,2,2-trifluoroethyl butyrate was successfully used in transesterification reactions.

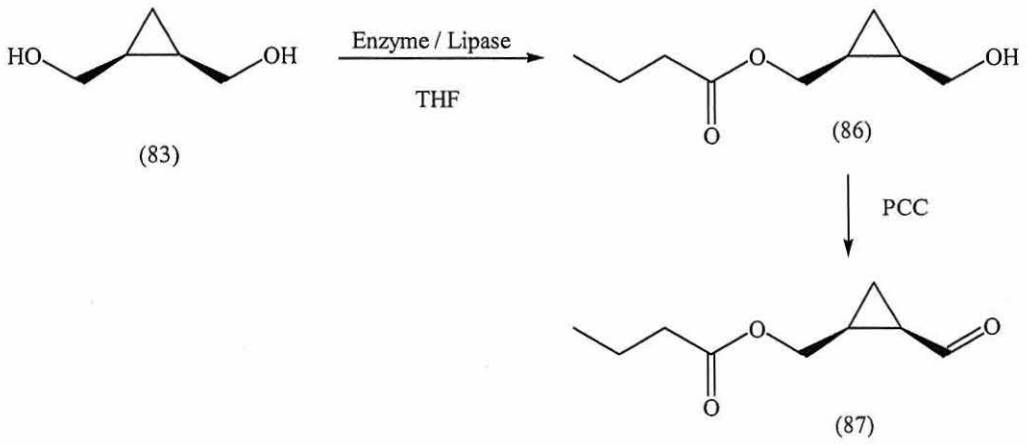


Figure (61)

The enzyme reaction was followed by g.l.c analysis, which showed different retention times for the diol, mono butyrate, and dibutyrate, and by t.l.c analysis which showed different R_f values. When g.l.c showed no starting material was left, the lipase and any solid was filtered off, and the filtrate was evaporated. The residue was purified by column chromatography to give (**86**) in 74 % yield which gave [$(\alpha)_D$ = - 18.7, c = 1.2, $CHCl_3$] while the $(\alpha)_D$ = 18.2 for the (**85**).[126][127]

The ^1H n.m.r spectrum (**86**) showed two double doublets at δ 4.5 ppm and 3.8 with coupling constants 5.6, 11.8 H_Z and 8.8, 11.9 H_Z respectively each integrating for one proton. The ^{13}C n.m.r showed the expected signals including one in the carbonyl region at δ 173, while I.R spectroscopy showed stretches at 3428 and 1731 cm^{-1} for the hydroxyl and carbonyl groups respectively.

The oxidation of (**86**) with P.C.C in dichloromethane gave (**87**) in 87 % yield. The oxidation was seen by the IR spectrum, the disappearance of the hydroxyl group confirming the formation of the product, while the ^1H n.m.r spectrum showed a sharp doublet at 9.47 with coupling constant 4.4 H_Z for the aldehydic proton. The ^{13}C n.m.r spectrum showed 9 signals including two in the carbonyl region resonating at δ 200 and 173.

The next step was to protect the aldehyde as an acetal. The aldehyde (**87**) and ethylene glycol were dissolved in toluene in the presence of PTSA and refluxed for 2 h and the water produced was separated by Dean Stark apparatus, which gave (**88**) (Figure 62) in 87 % yield.

The ^1H n.m.r spectrum for compound (**88**) showed the disappearance of the aldehydic proton and a new a doublet at δ 4.49 for the acetal proton. The ^{13}C n.m.r spectrum confirmed the formation of the product due to the disappearance of the carbon at δ 200 and showed only one signal in the carbonyl region, while the infrared spectrum showed a carbonyl group stretch at 1728 cm^{-1}.

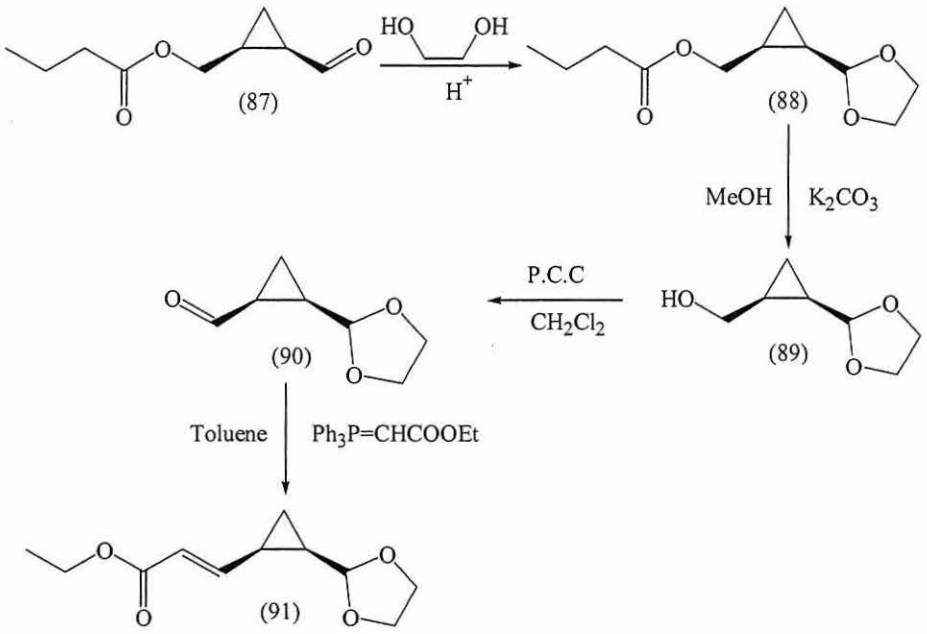


Figure (62)

Moreover, hydrolysis of (**88**) with potassium carbonate in methanol gave the alcohol (**89**) in 75 % yield. The successful hydrolysis of the ester was observed by the appearance in the I.R spectrum of a band at 3426 cm^{-1} which confirmed the presence of the desired alcohol functionality; the disappearance of the C=O stretching band also confirmed this observation.

Oxidation of the alcohol (**89**) with P.C.C gave the aldehyde (**90**) in very low yield, which was used without purification for the next step. The aldehyde (**90**) was allowed to react with carboethoxymethylene triphenylphosphorane in toluene at room temperature, producing the α,β-unsaturated ester (**91**) in 80 % yield, which was almost exclusively the *trans*-isomer. The I.R spectrum confirmed the formation of the α,β-unsaturated ester due to the presence of intense bands corresponding to C=C and C=O at 1648 and 1732 cm^{-1} respectively. The ^1H n.m.r spectrum showed a double doublet at δ 6.73 ppm with coupling constants 10.4 and 15.5 H_Z corresponding to the alkene proton in the β-position with respect to the carbonyl group.

As mentioned before, the required natural product contains an α-methyl cyclopropane; therefore the α,β-unsaturated cyclopropane (**91**) was subjected to Michael addition to introduce the α-methyl group (Figure 63).

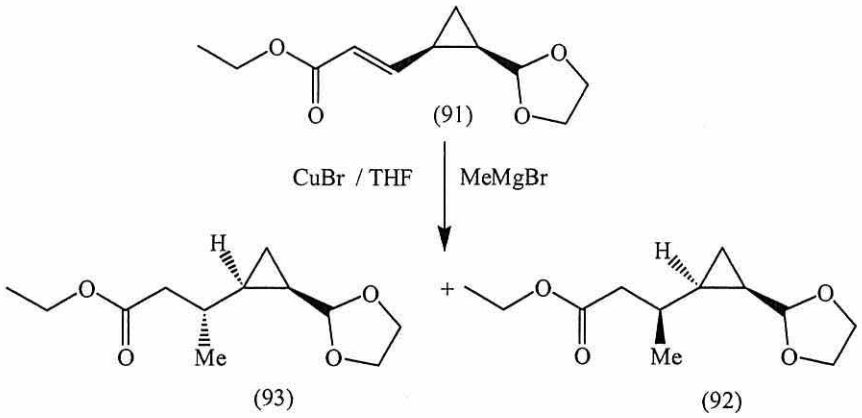


Figure (63)

When the cyclopropane (**91**) was allowed to react with methyl magnesium bromide in the presence of copper bromide a mixture of two isomers (**92**) and (**93**) was obtained in ratio 3:1. The two isomers were difficult to separate; however the separation processes was repeated many times and it was possible to get samples for ^{1}H n.m.r analysis which showed the two isomers having the same coupling constant for the doublet of the α-methyl cyclopropane which was 6.4 H_Z at δ 1.07 ppm for the first isomer and at 1.15 for the second isomer. The ^{13}C n.m.r showed the expected 12 signals for one of the isomers, including one for the carbonyl at δ 173 and another one for the carbon next to the two oxygen atoms at 116 and three signals at 76, 69 and 59 for the carbons next to the oxygen atoms. The IR spectrum confirmed the formation of the product, with the disappearance of the double bond stretch at 1648 cm^{-1}. The poor yield that was obtained and the complicated separation process led to a search for another route with a better yield and less difficult separation.

The proposal was to find a new protecting group using 2,2-dimethyl-1,3-propandiol which was more bulky but similar to the isopropylidene in not introducing further chiralty, which played a vital role in the Michael addition as mentioned before.

The aldehyde (**87**) was treated with 2,2-dimethyl-1,3-propandiol in toluene in the presence a catalytic amount of pyridinium para-toluene-sulfonate and refluxed for 16 h, using a Dean-Stark apparatus to separate the water. After work up the product (**94**) (Figure 64) was obtained in 90 % yield.

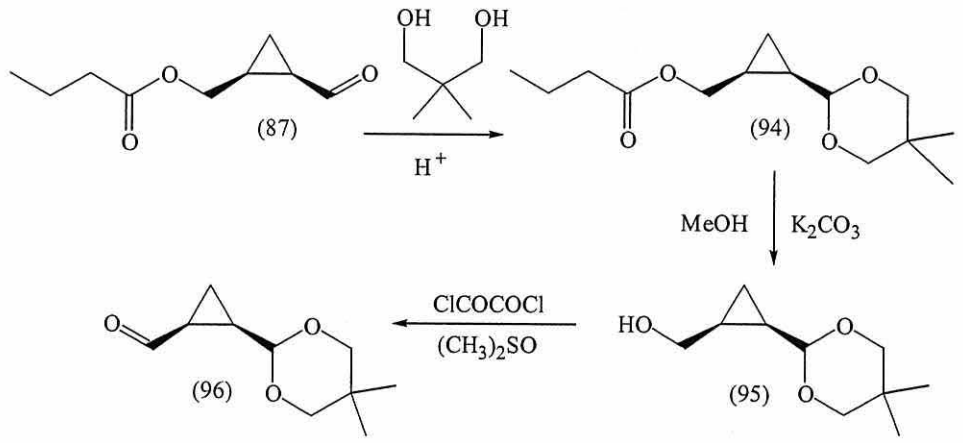


Figure (64)

The successful protection of the aldehyde (**95**) was seen in the ^1H n.m.r spectrum which showed three multiplets at δ 4.02, 3.47 and 3.28 integrating for 7 protons next to the oxygen atoms. The carbon N.M.R spectrum of (**94**) included the expected 14 signals including one carbonyl carbon at δ 173.2, and four signals at 103.3, 76.6, 76.0 and 69.2 for the carbons next to the oxygen atoms, and the IR spectrum showed the stretching of carbonyl group at 1700 cm^{-1}.

The hydrolysis of (**94**) with potassium carbonate in methanol or reduction of the ester group using lithium aluminium hydride in THF gave the alcohol (**95**). The successful reduction was observed in the I.R spectrum by the appearance of a broad O-H stretch band at 3490 cm^{-1}.

The next step was the oxidation of the alcohol (**95**) to aldehyde (**96**). Due to the low yield of (**90**) which was obtained and the difficulty of the purification from the addition of pyridinium chlorochromate to the alcohol (**89**), a better oxidation method was sought using oxalyl chloride and dimethyl sulphoxide. This is one of the most common transformations in organic synthesis, the oxidation of the hydroxyl group by Swern oxidation.[118] When the alcohol (**95**) was treated with 1.1 molar equivalents of oxalyl chloride, 2.2 molar equivalents of dimethyl sulphoxide, and 5 molar equivalents of triethylamine in dry dichloromethane at –78 °C, it gave the aldehyde (**96**) in 47 % yield. The proton N.M.R of this showed a doublet at δ 9.2 with coupling constant 5.2 H_Z for the proton of the aldehyde group. The ^{13}C n.m.r spectrum indicated the carbonyl carbon group at δ 202.7, while the stretching of the carbonyl group appeared in the infrared spectrum at 1722 cm^{-1}.

Again the aldehyde (**96**) reacted with carboethoxymethylenetriphenylphosphorane in toluene to produce the α,β-unsaturated ester (**97**) in 75 % yield, which was mainly the E-isomer.

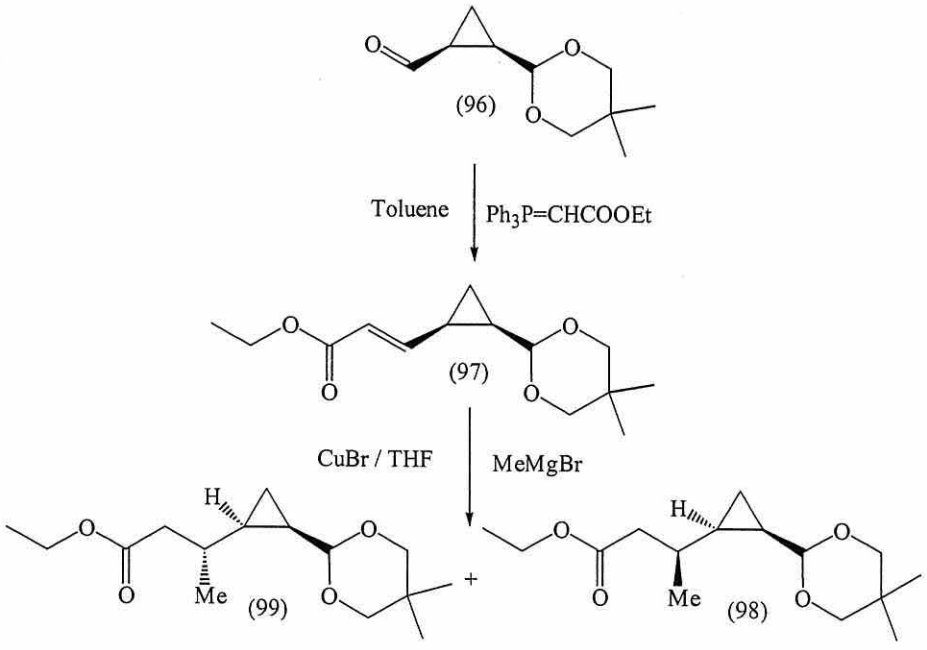


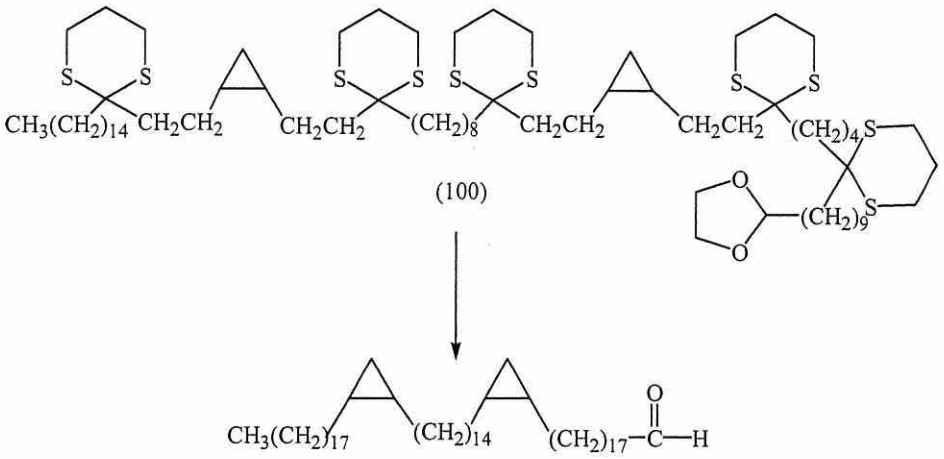
Figure (65)

Formation of the α,β-unsaturated ester (**97**) was confirmed the appearance of the intense bands corresponding to C=C and C=O stretches at 1650 and 1722 cm^{-1} respectively. Analysis by ^{1}H n.m.r and g.l.c revealed that the desired olefinic bond was formed with > 97 % selectivity. Indeed none of the alternative Z-isomer was observed. This could be clearly seen in the olefinic region of the ^{1}H n.m.r spectrum of (**97**) which showed a double doublet at δ 6.78 (J = 10 and 15.25 H_Z) corresponding to the β-olefinic proton, while the second olefinic proton in the α-position showed a broad doublet at 5.95 with (J = 15.25 H_Z). The ^{13}C n.m.r spectrum showed the expected signals including the carbonyl of ester at δ 167.8 and the two olefinic carbons appearing at 148 and 120.0.

The next step was to introduce the α-methyl group next to the cyclopropane ring. When the E α,β-unsaturated ester *cis*-cyclopropane (**97**) was reacted with methyl magnesium bromide in the presence of cuprous bromide at – 40 °C under the same conditions as before, two isomers (**98**) and (**99**) were obtained which showed two peaks by g.l.c in ratio 3:1, and also showed two close spots by t.l.c.

The two isomers were separated by column chromatography eluting with petroleum ether / ether 4:3 to give the major isomer in 38 % yield and the minor isomer (12 %). The analysis of isolated products by I.R spectroscopy revealed the presence of a sharp peak at 1729 cm^{-1} for the carbonyl group for the major isomer, and the disappearance of the corresponding C=C stretch of the starting material indicated that the reaction had reached completion. The major isomer showed the α-methyl group appeared as a doublet with coupling constant 6.4 H_Z at δ 1.03 ppm, which is identical to α-methyl compound (**76**). In comparison, the ^{1}H n.m.r spectrum of the minor isomer showed the doublet for the α-methyl group resonated at 1.1.

In 1977, Gensler[128] described for the first time a synthesis of a mixture of four stereoisomers of a meromycolic acid (**101**) containing two *cis*-cyclopropanes by coupling of different portions, which gave a structure with the same carbon numbers of meromycolic acid. Finally, this compound was transformed to the desired product (Figure 66).

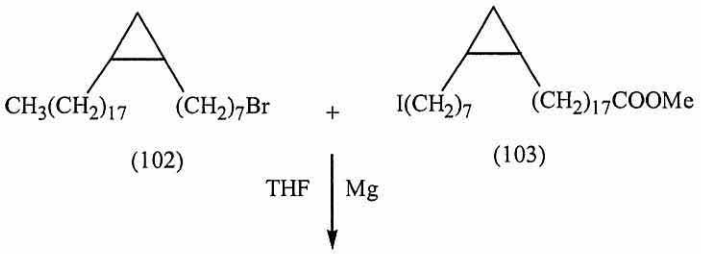


(100)

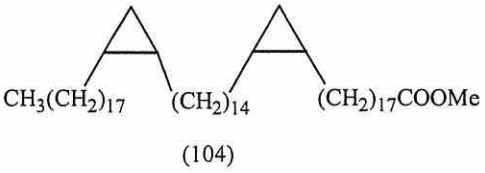
(101)

(Figure 66)

Later, Gensler suggested another approach, which was believed to be shorter and could be easily expanded by using a Grignard reagent obtained from the alkyl bromide (**102**) (Figure 67) in THF which was coupled with alkyl iodide (**103**) to give the mero-mycolate (**104**) directly.[128]



(102) (103)



(104)

(Figure 67)

However, this method gave a very low yield due to the limited solubility of the reagents, and it was also difficult to control the absolute stereochemistry of the second cyclopropane in relation to the first one.

Recently, Baird and co-workers[129] succeeded in the synthesis of a single enantiomer of an analogue of meromycolic acid (**108**) by coupling two units which were previously prepared by using Julia and Wittig reactions.

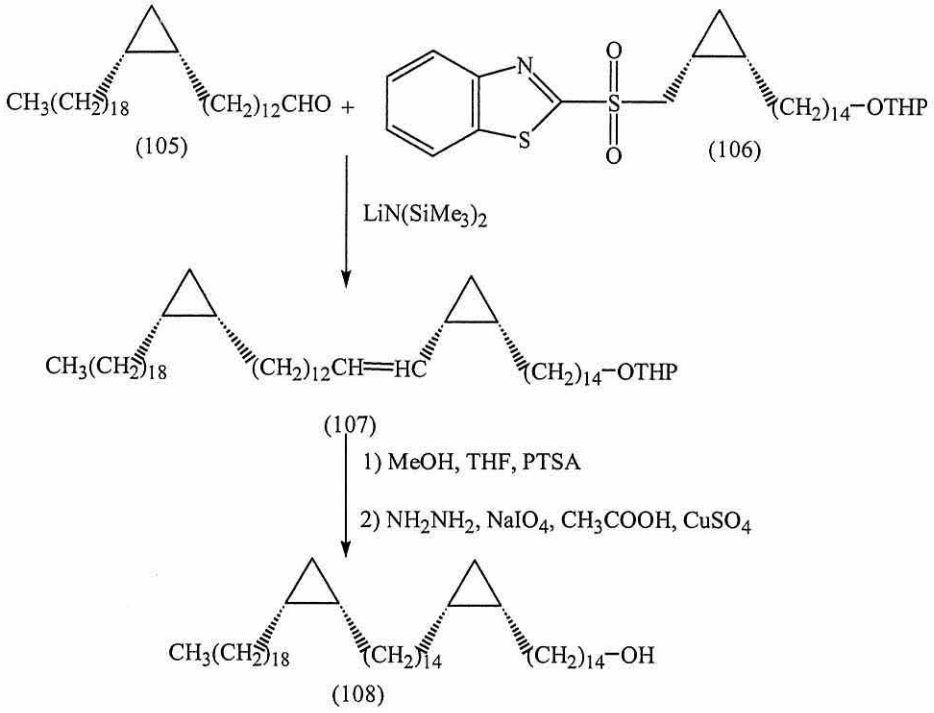


Figure (68)

In this approach, the key step is the Julia reaction between two cyclopropanes (**105**) and (**106**) using lithium bis-trimethylsilylamide to give the compound (**107**) as a mixture E and Z-isomers, followed by deprotection of the hydroxyl group and hydrogenation of the double bond to give (**108**).

Therefore the next step of the present synthesis was to reduce the ester group in (**98**) to produce the alcohol (**109**) followed by the activation of the hydroxyl functionality. Activation of this group was necessary to enable the efficient coupling of two intermediates that would be required in the synthesis of the target molecule (**112**) (Figure 69).

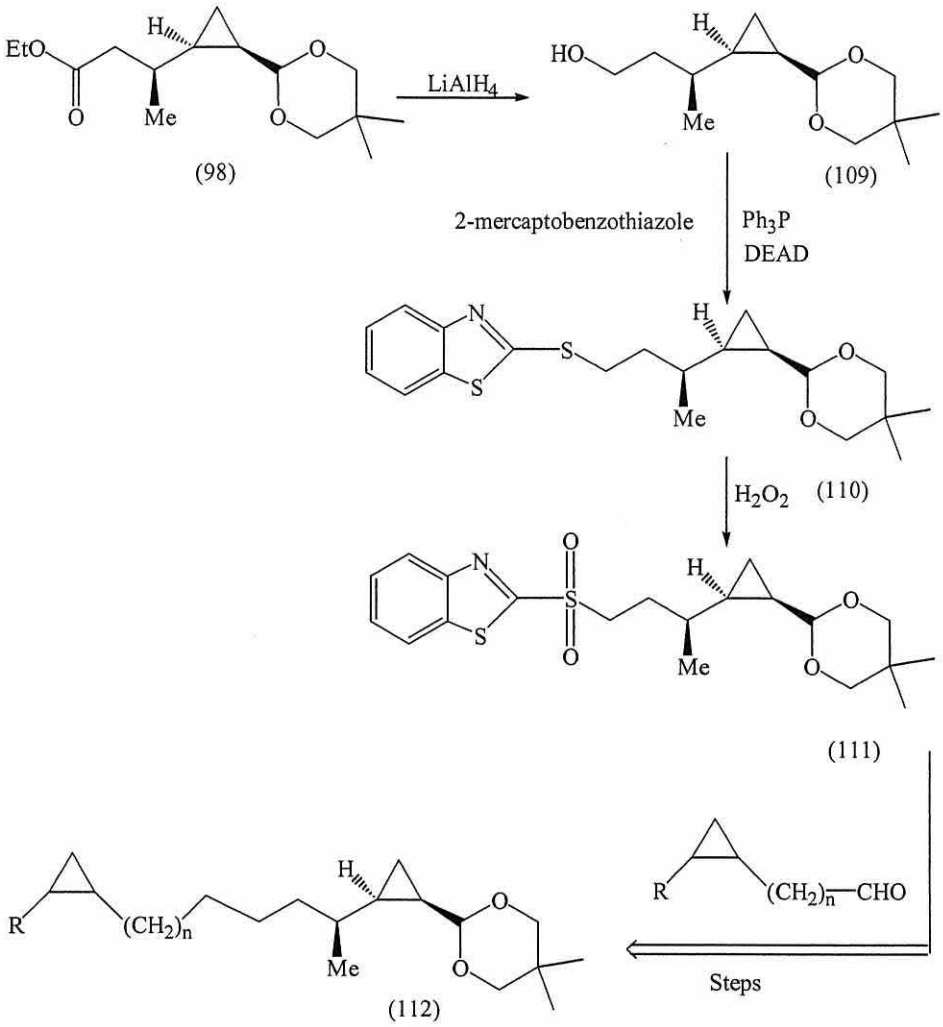


Figure (69)

Reduction of the cyclopropane ester (**98**) to the alcohol (**109**) in 80 % yield was carried out using lithium aluminium hydride in tetrahydrofuran at 0 °C, then refluxing for 2 h. The successful reduction of the ester was observed in the IR spectrum, which showed the stretching of the hydroxyl group at 3421 cm^{-1}. The α-methyl group appeared as a doublet at 1.02 with coupling constant 6.4 H_Z. The ^{13}C n.m.r showed the expected 13 signals including four in the region for carbons next to the oxygen at δ 103.2, 77.4, 77.03, and 60.4.

The alcohol (**109**) was converted into the sulphide (**110**) by reaction with 2-mercaptobenzothiazole in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran at room temperature. to gave a pale yellow oil (**110**) in 62 % yield. The formation of the sulphide (**110**) was confirmed by the disappearance of the O-H stretch in the I.R spectrum of the starting material. The ^{1}H n.m.r spectrum of (**110**) showed in the aromatic region two broad doublets at 7.85 and 7.75 each integrating one proton with coupling constant 8 H_Z together with a broad triplet at 7.41 with coupling constant 7.3 H_Z and a multiplet at 7.3.

Oxidation of (**110**) with hydrogen peroxide solution (35 %) in the presence of ammonium heptamolybdate (VI) tetrahydrate in ethanol gave (**111**) as a colourless oil in 72 % yield. The proton n.m.r spectrum showed the four aromatic protons as two broad doublets at 8.21 and 8.02 with the same coupling constant 8.0 H_Z integrating for two protons, and a multiplet at 7.26 integrating to another two protons.

Compound (**111**) now available, the coupling to a *cis*-cyclopropane as in opened the way to the synthesis of the complete required meromycolate. However, one further approach to the α-methyl-*trans*-cyclopropane unit was first examined. As mentioned before, the addition of methyl magnesium bromide to the α,β-unsaturated vinyl cyclopropane (**97**) gave two isomers in ratio 3:1 which were difficult to separate.

Therefore, methyl magnesium bromide was added to a stirred solution of the aldehyde (**96**) to give after work up a mixture of alcohols (**113**) in 66 % yield (Figure 70). This mixture gave one spot by t.l.c which was purified using column chromatography eluting with petroleum ether / ethyl acetate (5:3). This mixture was oxidized to the ketone (**114**) in 51 % yield using Swern oxidation.

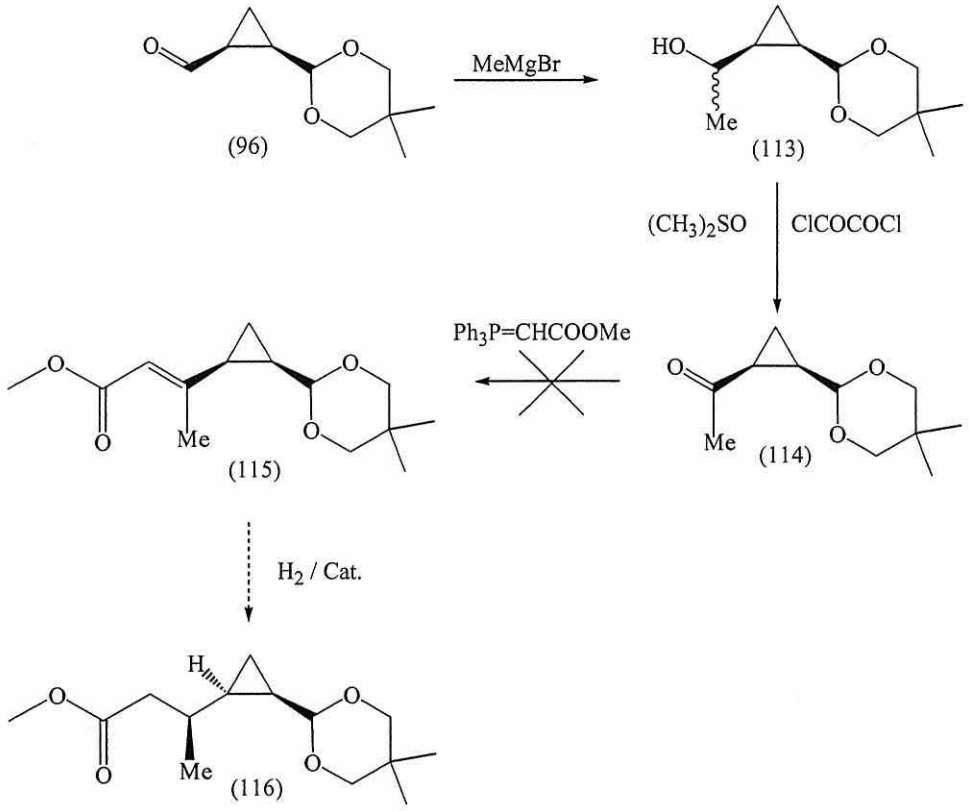


Figure (70)

I.R spectroscopy of the alcohols (**113**) showed that the strong band corresponding to the C=O stretch in the starting material had in fact disappeared and the appearance of a broad O-H stretching band at 3446 cm^{-1} confirmed the formation of the product. The formation of the methyl ketone (**114**) was also confirmed by the I.R spectroscopy due to the appearance of a very strong C=O stretch at 1714 cm^{-1}, consistent with the desired ketone functionality. The fact that no O-H stretching was observed in this spectrum indicated that the reaction had reached completion.

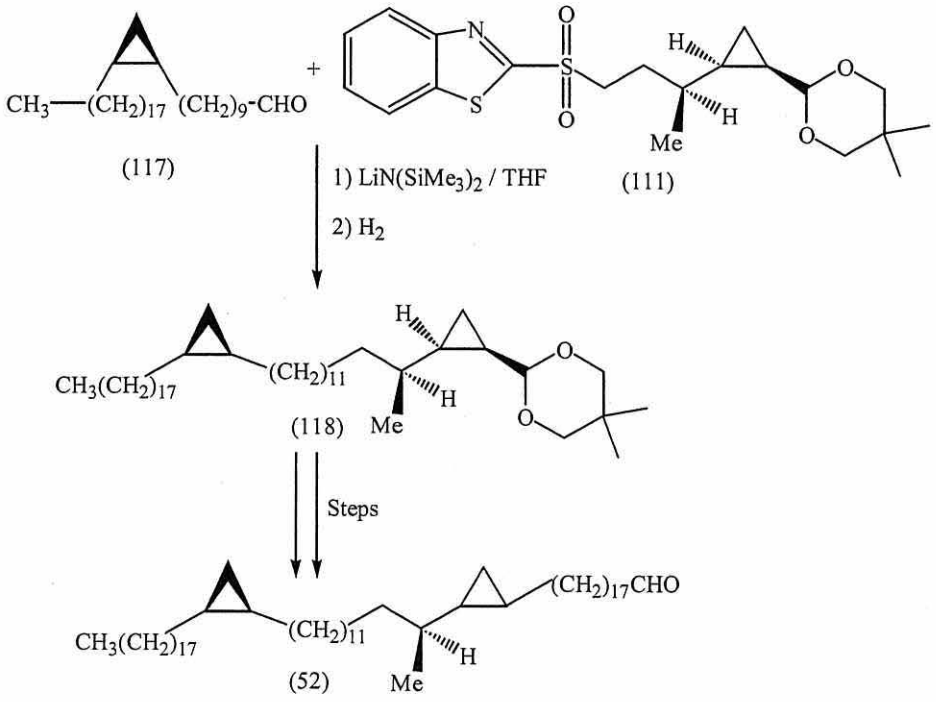
The successful isolation of the ketone (**114**) in moderate yield facilitated the application of traditional Wittig type chemistry in the construction of an α,β-unsaturated ester that could then be subjected to asymmetric hydrogenation, hoping to get one isomer.

However, treatment of the ketone (**114**) with a two-fold excess of a suitable stabilised carbomethoxymethylene or carboethoxymethylene triphenylphosphorane failed to introduce the required olefinic double bond under several different conditions (i.e at room temperature or refluxing for 72 h). The ^{1}H n.m.r spectrum for the crude mixture showed a singlet at 2.3 for the methyl ketone starting material and no signals for olefinic protons.

3.1 *Cis*-Cyclopropanes with long chain substituents.

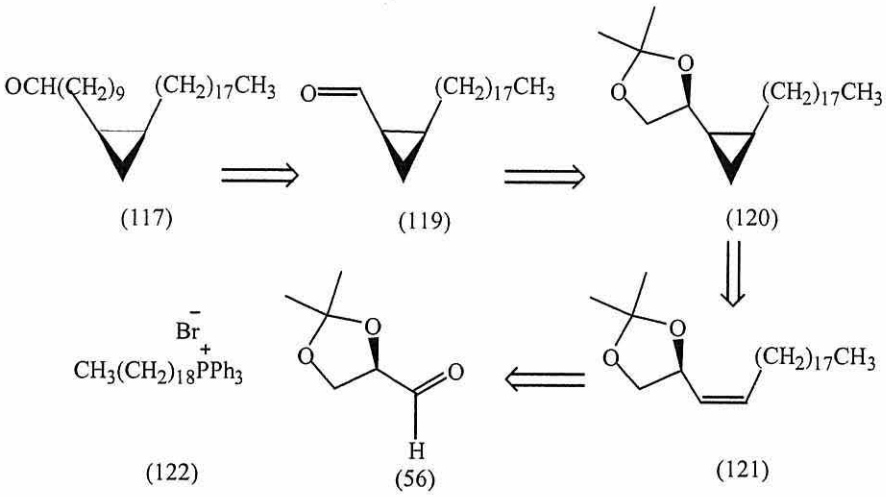
3.1 1 Preparation of fragment (A) of compound (52).

As mentioned before, the aim of the project was to prepare a single enantiomer of (**52**) by the coupling of the two cyclopropane intermediates (**117**) and (**111**). The synthesis of α-methyl cyclopropane (**111**) was discussed in the previous section; therefore the next section will involve the synthesis of the intermediate cyclopropane (**117**).



(Figure 71)

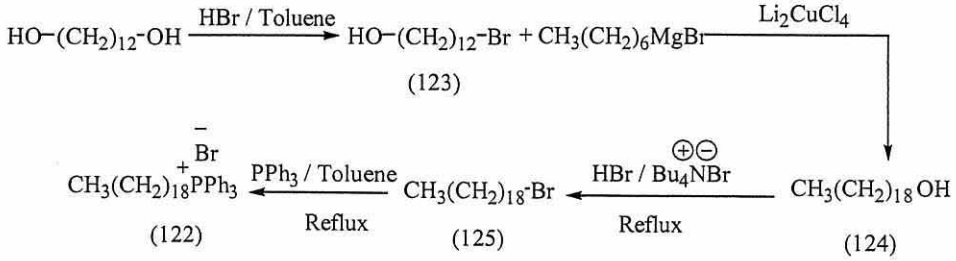
A retrosynthesis of optically pure (*1R, 2S*)-cyclopropane (**117**) gave 2,3-O-isopropylideneglyceraldehyde (**56**) and n-nonadecyl triphenylphosphonium bromide (**122**) as the starting materials.



(Figure 72)

The Wittig reaction of (**56**) with n-nonadecyl triphenylphosphonium bromide (**122**) synthesised from 1-bromononadecane would generate the alkene intermediate (**121**) with the desired 18 carbon chain length. Asymmetric cyclopropanation and standard transformations would give the optically pure cyclopropane (**119**), which with another Wittig reaction would give after reduction, hydrogenation, and oxidation the aldehyde (**117**).

3.1.2 Preparation of nonadecyl triphenylphosphonium bromide (122).



(Figure 73)

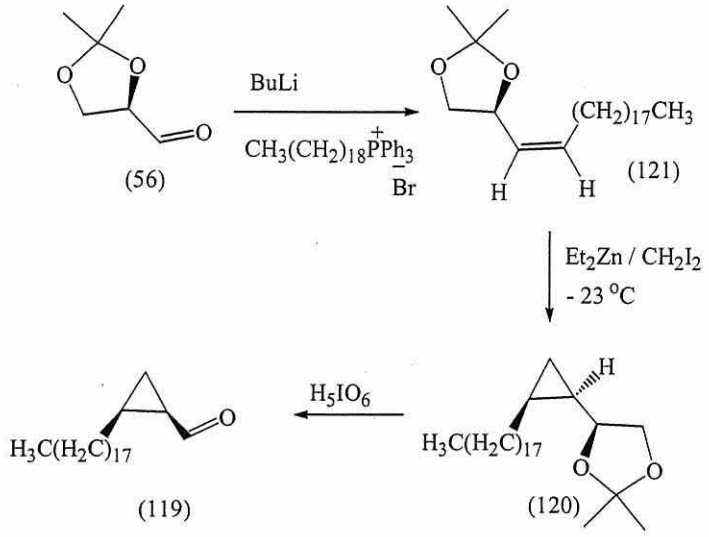
The first step was the substitution of an alcohol with bromine by treatment with hydrobromic acid. Compound (**123**) was characterized using N.M.R, M.S, I.R, and showed the same physical and chemical properties as those described in literature.[130] An excess of heptyl magnesium bromide was then added to a stirred solution of 12-bromododecanol (**123**) in THF at 0 °C followed by cooling to – 40 °C when 0.1 molar equivalents of lithium tetrachlorocuprate was added. The mixture was stirred at this temperature for two hours then at room temperature for 16 h to give nonadecanol (**124**) in 83 % yield. The alcohol (**124**) was characterised and its data compared with the ones reported in literature.[130]

1-Bromononadecane (**125**) was prepared by the addition of (**124**) to a stirred solution of hydrobromic acid (48 %) and tetrabutyl ammonium bromide. The reaction was refluxed for 3 h to yield the bromoalkane (**125**). Compound (**125**) showed the same physical and chemical properties as described in the literature.[44]

n-Nonadecyl triphenylphosphonium bromide (**122**) was then prepared by the addition of bromoalkane (**125**) to a stirred solution of triphenyphosphine in toluene and refluxing for 66 h. The ^{1}H n.m.r spectrum indicated that the reaction had been successful with the phenyl protons appearing at 7.9 – 7.45 (15 H) as a complex multiplet. The long aliphatic chain appeared as a broad singlet at 1.2 integrating for 32 H, while the methylene group next to phosphorus appeared as a multiplet at 3.75.

The well documented 2,3-O-iso-propylidene-D-glyceraldehyde (**56**) was prepared as discussed previously, from D-mannitol via oxidative cleavage of the diacetonide using sodium metaperiodate.

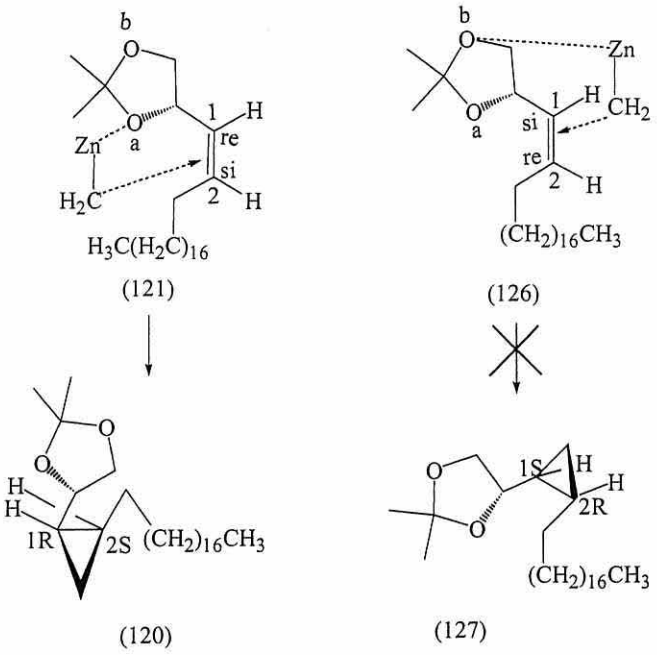
The desired Z-geometry of the alkene (**121**) was achieved via Wittig chemistry using n-nonadecyltriphenylphosphonium bromide (**122**), generating the ylid using n-butyl lithium in THF at – 78 °C followed by the addition of the aldehyde (**56**) at – 78 °C, and stirring for 2 h at – 10 to 0 °C followed by allowing the reaction to reach room temperature. This led mainly to the Z- isomer in 71 % yield.



(Figure 74)

The ^1H n.m.r spectrum of (**121**) indicated that the reaction had been successful with alkene signals appearing at δ 5.68 and 5.4 as a double triplet (J = 10.5, 7.6 H_Z) and a double doublet (J = 7.6, 10.5 H_Z), confirming the Z- configuration. The ^{13}C n.m.r spectrum indicated the alkene carbon atoms at δ 133.1 and 127.

Diastereoselective cyclopropanation of (**121**) gave the cyclopropane (**120**) in 86 % yield by the addition of diethyl zinc and CH_2I_2 in dichloromethane at – 23 °C. The absolute configuration was assigned as (*1R, 2S*) on the grounds of the stereoselective cyclopropanation previously reported by Taguchi et. Al.[109] Stereoselectivity occurs as the zinc carbenoid coordinates with the axial oxygen atom O-a on the isopropylidene ring of the alkene (**121**). This directs the methylene transfer to the 1re – 2si face (i.e., attack from the bottom face) giving the cyclopropane with (*1R, 2S*) absolute configuration (**120**). Attack the opposite 1si – 2re face (**126**) via coordination with the equatorial oxygen O-b (ie attack from the top face) does not occur and so the other enantiomer (**127**) is not formed.



(Figure 75)

The ^1H n.m.r spectrum of (**120**) indicated that the cyclopropanation had been successful with the disappearance of the alkene protons signals and appearance of a multiplet at δ 0.22 (1 H), which was characteristic of a cyclopropane proton. The carbon n.m.r spectrum indicated the secondary cyclopropane carbon atom at δ 10.55 ppm.

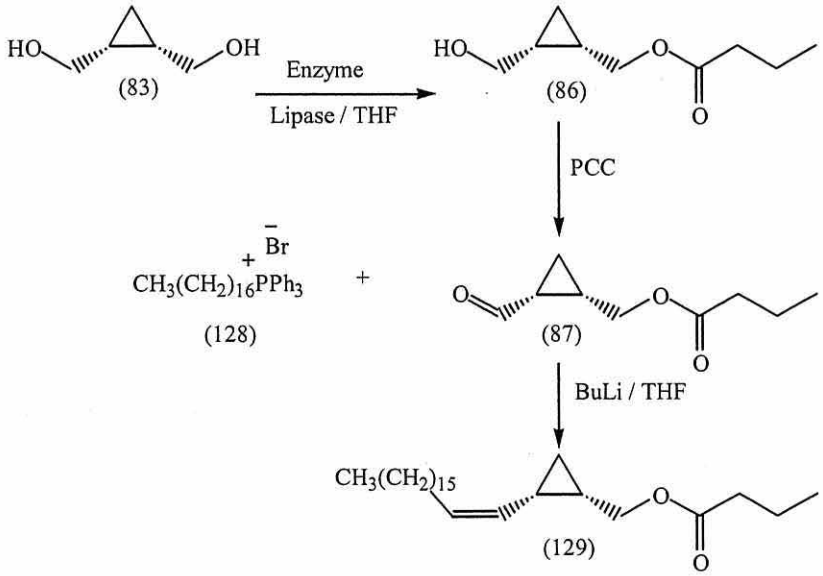
Moreover, when the cyclopropane (**120**) was treated with periodic acid under anhydrous conditions in dry ether for 3 hours, g.l.c showed no starting material was left and after work-up gave (**119**) in 72 % yield.

The ^1H n.m.r spectrum of this indicated that the deprotection and oxidation processes had been successful with the aldehyde proton appearing as a sharp doublet at δ 9.3 with coupling constant 5.5 H_Z. It was apparent that epimerisation had not occurred, because a second signal further up field was not observed which could be expected if the *trans*-diastereomer was present. The spectrum also indicated that the cyclopropane signals had shifted downfield due the deshielding by the carbonyl group.

The ^{13}C n.m.r spectrum showed the aldehyde carbon as a signal at δ 201.9 and confirmed the deprotection and oxidation of the resulting diol by the disappearance of the isopropylidene group signals. The cyclopropane carbons shifted downfield due the overlapping of the p-orbital on the carbonyl group. The I.R spectrum was also consistent with the presence of a carbonyl group stretch at 1694 cm^{-1}.

The alternative (*1S,2R*)-enantiomer (**132**) was prepared by a different approach with better yield. This was achieved as discussed previously, by the enzymatic transesterification of *cis*-1, 2-bis(hydroxymethylcyclopropane) (**83**) in THF which was mixed with 2,2,2-trifluoroethyl butyrate in isopropyl ether in the presence of pig liver esterase, then stirring for 48 hours to produce the half ester (**86**).

This was oxidised with PCC to the aldehyde (**87**), which was then treated with n-heptadecyl triphenylphosphonium bromide (**128**) and strong base to give the unsaturated ester (**129**), which was mainly the Z-isomer.

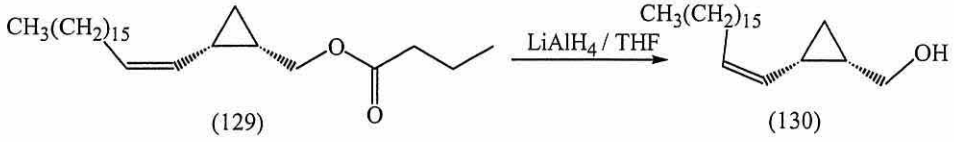


(Figure 76)

I.R spectroscopy confirmed the formation of (**129**) by the appearance of a C=C stretch at 1465 cm^{-1}. The ^1H n.m.r spectrum showed a broad double triplet in the olefinic region integrating for one proton at δ 5.46 with coupling constants 7 and 10.3 H_Z.

Similarly the signal corresponding to the second olefinic proton was observed as a broad triplet with coupling constant 10.3 H_Z at δ 5.03.

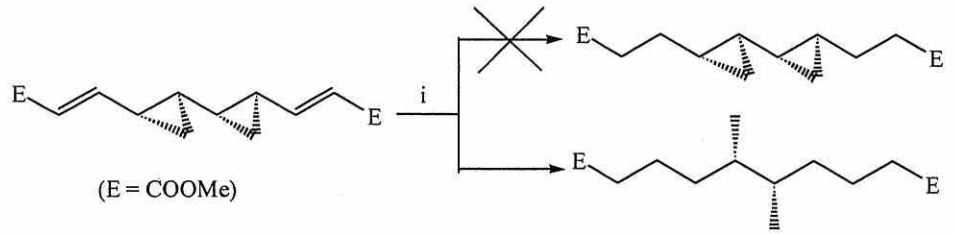
Reduction of (**129**) with lithium aluminium hydride led to the alcohol (**130**) in 70 % yield. Again the I.R spectrum confirmed the reduction due to the appearance of a broad O-H stretching band at 3367 cm^{-1} for the desired alcohol functionality, and the disappearance of the C=O stretching band (present in the starting material).



(129) (130)

Figure (77)

It is known that selective hydrogenation of a double bond in the presence of a cyclopropane with (5 – 10 %) palladium on charcoal under an atmosphere of hydrogen can lead to ring opening.[131][132]

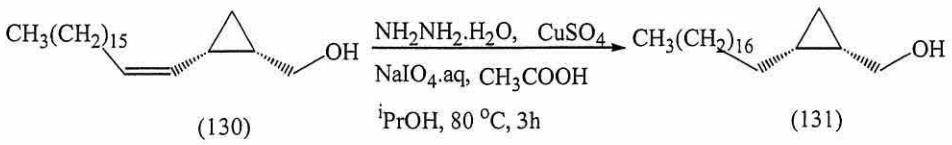


(E = COOMe)

I = 10 % Pd / C, H_2, EtOH, 25 °C, 48 h, 78 %.

Figure (78)

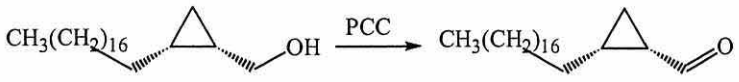
Therefore, a less harsh approach was required using reagent reported by Nishida (*et al*) reagents for reduction of the double bond (**130**).[133] The generation of the diimide which was necessary to reduce the double bond, was achieved by dissolving sodium (meta) periodate in water and adding it to a mixture of the cyclopropane (**130**), hydrazine hydrate, copper (II) sulphate, and acetic acid in isopropyl alcohol at 80 °C, and stirring for 3 h to yield the cyclopropane (**131**) in 71 % yield.



(130) (131)

Figure (79)

The ^{1}H n.m.r spectrum of this showed the disappearance of the alkene signals and the appearance of a broad quartet at δ – 0.03 (J = 4.6 H_Z) indicating one of the cyclopropane protons. It was apparent that no ring opening had occurred and the cyclopropane protons indicated that the reduction had been selective. The ^{13}C n.m.r spectrum also confirmed the reduction due to the disappearance of the olefinic carbons signals. The alcohol (**131**) was oxidised with PCC in dichloromethane at room temperature to give the aldehyde (**132**) in 73 % yield.

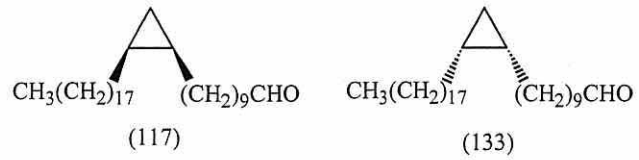


(131) (132)

Figure (80)

The I.R spectrum of compound (**132**) showed a very strong C=O stretch at 1644 cm^{-1}, consistent with the desired aldehyde functionality, and the disappearance of a broad O-H stretch. The ^{1}H n.m.r spectrum showed a sharp doublet at δ 9.35 for the aldehyde proton with coupling constant 5.6 H_Z. It was apparent that epimerisation had not occurred because a second doublet was not observed which would be expected if the *trans*-diastereomer was present. Additionally, the α-cyclopropane proton appeared as a multiplet shifted downfield due to the deshielding by the carbonyl group. The ^{13}C n.m.r confirmed the formation of the compound (**132**) and showed only one carbon signal at δ 203 corresponding to the aldehydic carbon. The optical rotation exhibited by (**119**) and its enantiomer (**132**) were found to be of comparable magnitudes, but in opposing directions, the observed specific rotations being + 13.0 and – 8.06 respectively.

3.1.3 Preparation of (1R, 2S)–13-(2-eicosylcyclopropyl)tridecanal (125) and its enantiomer (1S, 2R)–13-(2-eicosylcyclopropyl)tridecanal (143).



(117) (133)

The proposed synthesis of (**117**) is shown below:

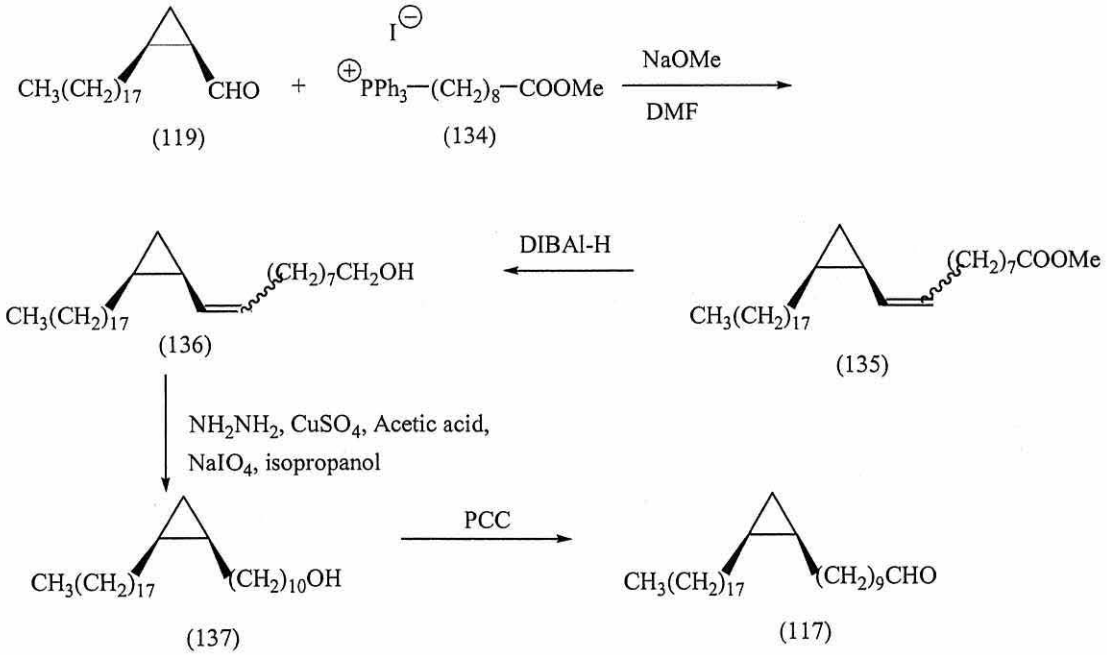
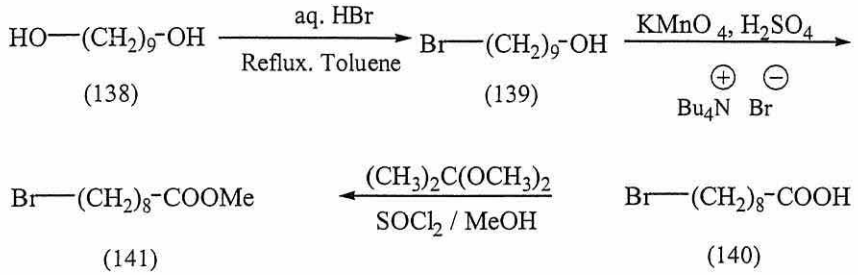


Figure (81)

Reaction of (**119**) with the Wittig reagent prepared from 1-carbomethoxy-9-triphenylphosphoniumnonaneiodide (**134**) was expected to give (**135**). Reduction with DIBAl-H would lead to the alcohol (**136**), which would be reduced to the saturated alcohol (**137**) by treatment with di-imide and then oxidised to the corresponding aldehyde (**117**).

3.1.4 Preparation of 1-carbomethoxyoctan-8-yltriphenylphosphonium iodide (134).



(138) (139) (141) (140)

Figure (82)

In this approach the first step was the synthesis of 9-bromononan-1-ol (**139**) by refluxing diol (**138**) with 48 % HBr in toluene to give (**139**) in 83 % yield. The ^{1}H n.m.r spectrum of the (**139**) indicated the methylene group adjacent to the hydroxy group at δ 3.6 ppm as a triplet with coupling constant 6.9 H_Z, while the methylene group adjacent to the bromine appeared as a triplet (J = 7 H_Z) at 3.4. The next step was to oxidise (**139**) with potassium permanganate in the presence of sulphuric acid and tetra-butyl ammonium bromide, which gave 9-bromononanoic acid (**140**) in 96 % yield. The ^{1}H n.m.r confirmed the formation of the product due to the appearance of a triplet at 2.32 integrating for two protons adjacent to the COOH group. The ^{13}C n.m.r spectrum also showed the appearance of one signal in the carbonyl region.

Esterification of (**140**) by treatment with 2,2-dimethoxypropane in the presence of thionyl chloride in methanol gave (**141**) in 84 % yield. The ^{1}H n.m.r spectrum showed a singlet at δ 3.7 integrating for three protons corresponding to the methoxy group.

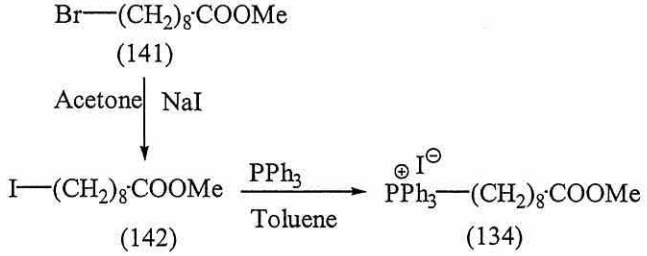


Figure (83)

The bromo-compound (**141**) was converted into the iodo-compound (**142**) by refluxing with sodium iodide in acetone for 3 h. The crude product was purified by column chromatography on silica to give 9-iodononanoic acid methyl ester in 92 % yield. The ^{1}H n.m.r spectrum showed the methylene group adjacent to the bromine atom that appeared in the starting material at δ 3.42 was shifted to higher field in the product.

The phosphonium salt (**134**) was prepared by addition of triphenylphosphine to a stirred solution of (**142**) in toluene and refluxing for 42 h to give a viscous yellow oil in 93 % yield.

To achieve the coupling between aldehyde (**119**) and the phosphonium salt (**134**), sodium methoxide was added to a stirred solution of (**134**) in dry dimethylformamide at ~ 0 °C, and stirred for 16 h at room temperature with (**119**) to give a mixture of Z and E-**135** in ratio 9:1.

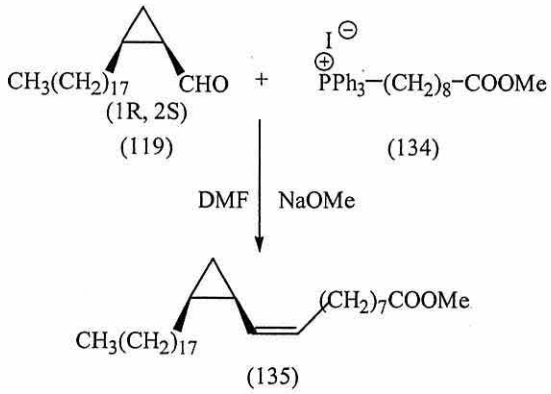
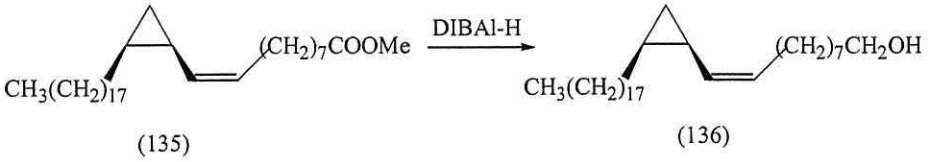


Figure (84)

The mixture was purified by column chromatography to give the major Z-isomer in 75 % yield. The ^{1}H n.m.r spectrum showed a double triplet at δ 5.4 with coupling constants 7.9 and 10.0 H_Z corresponding to the alkene proton together with a broad triplet at 5.04 with coupling constant 10.0 H_Z corresponding to the alkene proton, while the I.R spectrum showed two characteristic peaks at 1730 and 1650 cm^{-1} respectively resulting from the C=O and C=C stretches.

The next step was the reaction of the ester group with DIBAl-H or $LiAlH_4$. The addition of the reducing agent, DIBAl-H had to be conducted at – 60 °C because the reaction was exothermic, then the mixture was allowed to reach room temperature and stirred overnight, followed by quenched with methanol at – 30 °C; work up gave (**136**) in 86 % yield.

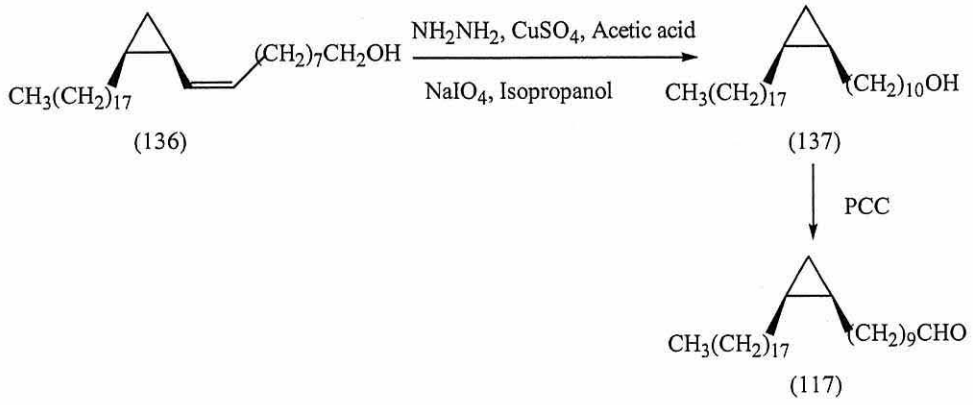


(135) (136)

Figure (85)

The successful reduction of the ester group was observed by I.R spectroscopy due to the disappearance of the C=O stretch at 3324 cm^{-1}. The ^1H n.m.r spectrum confirmed the reduction by the disappearance of the singlet corresponding to the methoxy group, and the appearance of a sharp triplet (2 H) corresponding to the methylene adjacent to the hydroxyl group at δ 3.63.

The selective reduction of the double bond of the compound (**136**) with diimide, as mentioned previously produced the saturated compound (**137**) in 64 % yield.



(136) (137) (117)

Figure (86)

The ^{1}H n.m.r spectrum indicated the selective reduction of the double bond had been successful with the disappearance of the alkene protons. The ^{13}C n.m.r also indicated the loss of the alkene and showed the cyclopropane carbon atoms at δ 10.2, 14.0 and 15.8.

Moreover, oxidation of (**137**) was achieved using two molar equivalents of pyridinium chlorochromate PCC in dichloromethane. The mixture was stirred for 3 h, and then t.l.c showed no starting material was left. The crude product was purified by column chromatography to give (**117**) in 71 % yield. In the ^{1}H n.m.r spectrum, the proton of the aldehyde appeared as broad singlet at δ 9.77. The ^{13}C n.m.r spectrum showed one signal in the carbonyl region at δ 202.8.

3.1.5 Synthesis of (1S, 2R)-13-(2-eicosyl cyclopropyl)tridecanal (133).

(133)

Figure (87)

The alternative (1S, 2R) enantiomer (**133**) was also synthesised from the aldehyde (**132**) using the same methodology employed to generate the (*1R*, *2S*)-13-(2-eicosylcyclopropyl)tridecanal.

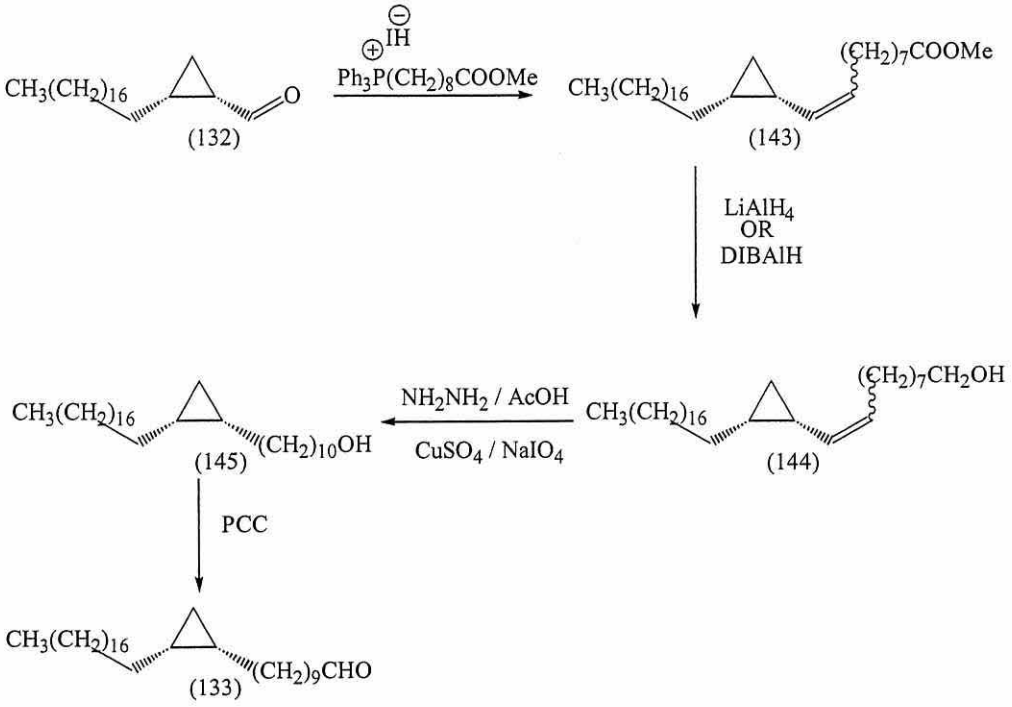
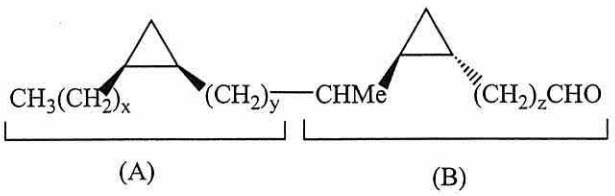


Figure (88)

The Wittig reagent, prepared from 1-carbomethoxyoctan-8-yltriphenylphosphonium iodide and sodium methoxide in dimethylformamide was reacted with (*1S*, *2R*)-2-eicosylcyclopropane carbaldehyde (**132**). Reduction with diisobutyl aluminium hydride gave alcohol (**144**) as a mixture Z and E-isomers. Saturation of the alkene using diimide, generated by the oxidation of hydrazine and oxidation of the derived alcohol (**145**) with P.C.C led to the (*1S*, *2R*)-13-(2-eicosylcyclopropyl)tridecanal (**133**) $[\alpha]_D$ = - 1.24, which showed identical spectra to the its enantiomer (**117**) ($[\alpha]_D$ = +0.12).

3.2 Conclusion.

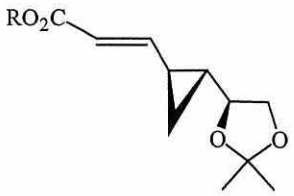
The ultimate target of this work was the synthesis of (**52,** x = z = 17, y = 12).



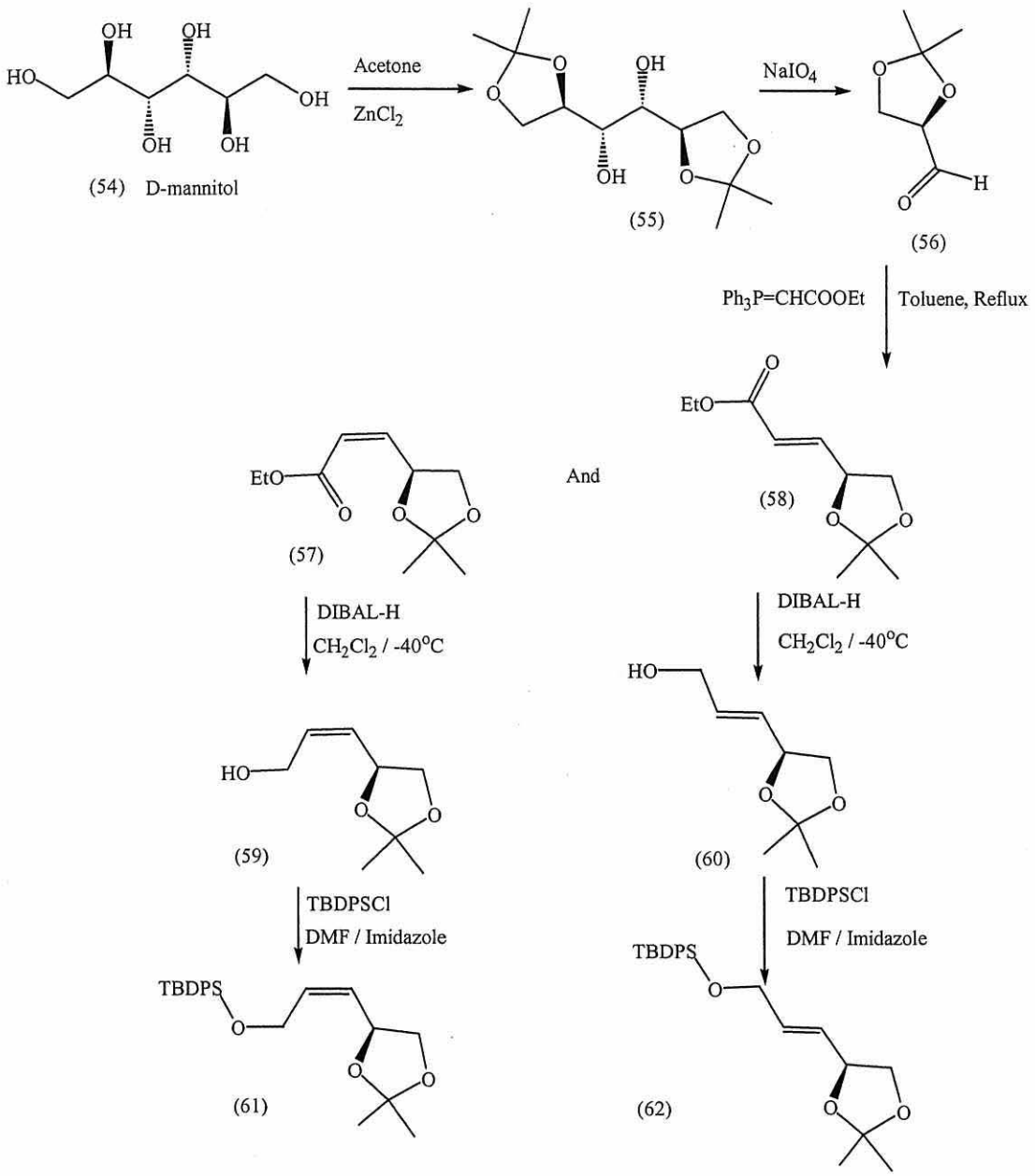
(52)

The work was divided into two parts, the synthesis of an α-methyl *trans*-cyclopropane and the synthesis of the long chain *cis*-cyclopropane.

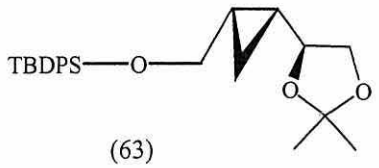
The main problem was to find a route to chiral intermediates that could be used to synthesise α-methylcyclopropanes that would in turn be used to synthesise mycolic acids. It was thought that the α-methyl group next to cyclopropane could be introduced by the Michael addition of methyl magnesium bromide to structures of the type shown below.



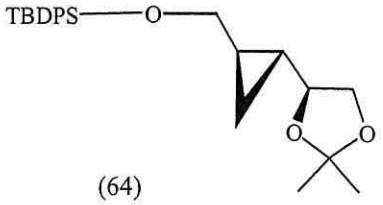
Two routes were identified, the first from D-mannitol (**54**) and the second from enzymatic desymmetrization of *cis*-1,2-bis(hydroxymethyl)cyclopropane (**83**). In the first route, the initial step was to prepare a mixture of (**57**) and (**58**). The mixture was separated into two isomers quite easily by chromatography. Both the Z and E isomers were readily reduced to allylic alcohols by DIBAL-H and protected as the TBDPS derivative (**61**) and (**62**) in high yields.



Difficulties were initially encountered in the cyclopropanation of (**61**) and (**62**) and the yield was low. Alteration in the conditions and the ratio of Et_2Zn and CH_2I_2 resulted in much higher yields. In the both cases only one isomer was formed, the *cis*-isomer (**63**) from (**61**) and the *trans*-isomer (**64**) from (**62**).

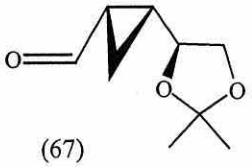


(63)

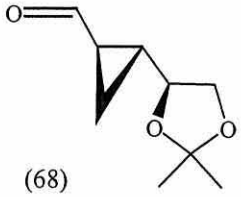


(64)

No problems were encountered in the deprotection and oxidation of the resulting cyclopropanes to give aldehydes (**67**) and (**68**).

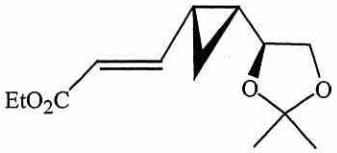


(67)

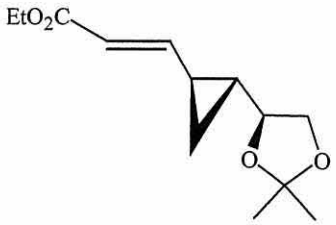


(68)

Wittig reaction on the aldehydes produced the required structures for the Michael addition, i.e. (**69**) and (**70**) respectively. In both cases the E-isomer was the major product.

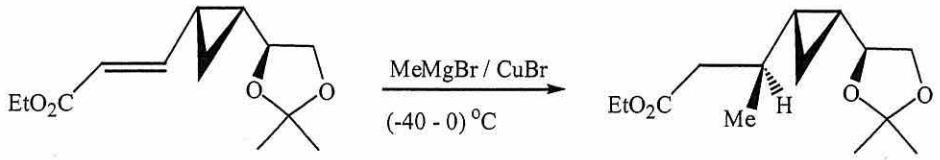


(69)



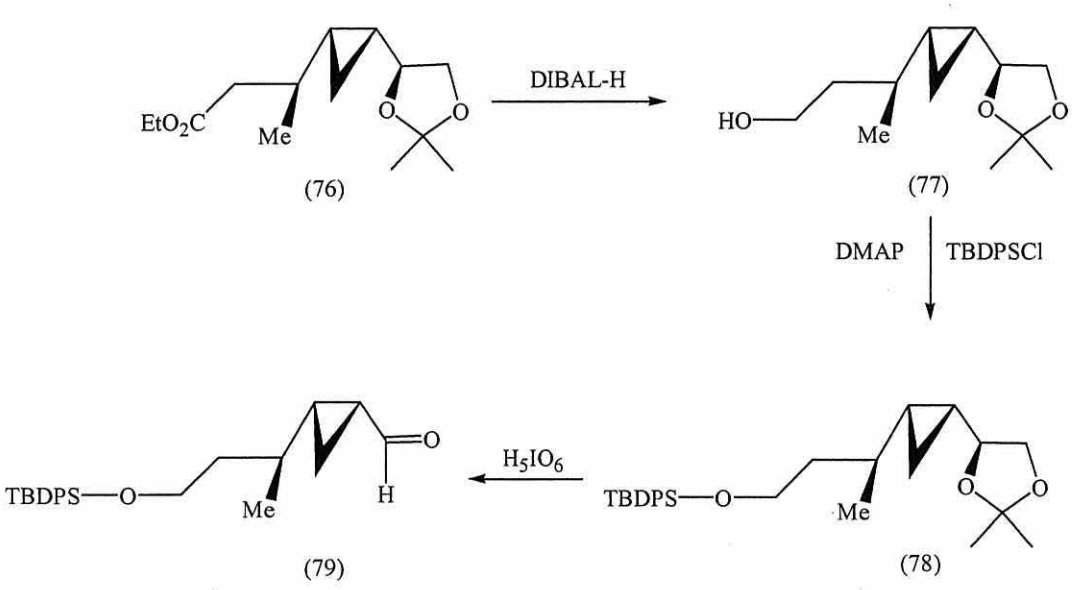
(70)

Major difficulties arose when the Michael addition to these α, β-unsaturated esters was carried out; the yields were low and in the case of the E-isomer, cyclopropane (**70**), two isomers of α-methyl product were formed in approximately equal amount and could not be separated by chromatography. In the case of Z-isomer cyclopropane (**69**) again the yield was low but one isomer was formed in a ratio 15:1 to the other; the predominant isomer was (**76**).



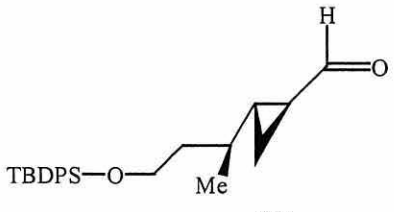
(69) (76)

The structure was confirmed by X-ray crystallography.[30a] The compound was readily converted into the corresponding alcohol by DIBAL-H, protected with TBDPS and oxidised to the aldehyde (**79**).



(76) (77) (78) (79)

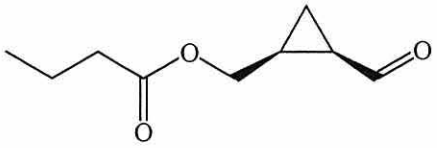
This was epimerised by refluxing with sodium methoxide in methanol for 48 h and produced (1:19) a mixture of the *cis* and *trans*-isomers, which was purified by column chromatography to gave *trans*-isomer (**80**) in good yield.



(80)

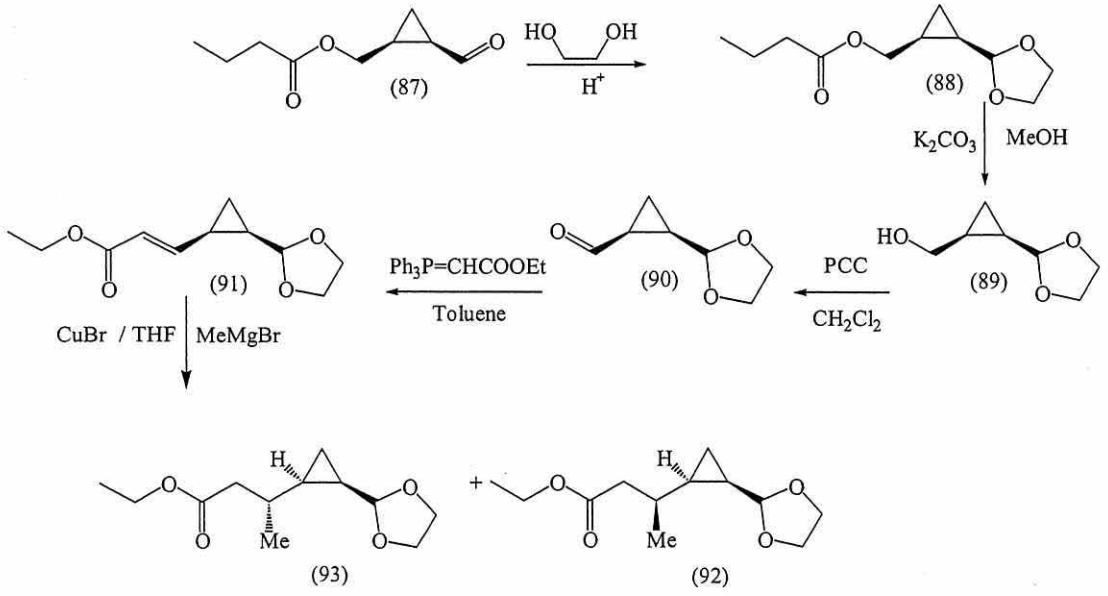
Thus the key intermediate for the synthesis of the α-methyl *trans*-mycolic acids had been prepared. One of the major difficulties in the above route was the cyclopropanation reaction. The initiation of the reaction of diethyl zinc was very variable and difficult to observe. In some cases too rapid an addition of diethyl zinc resulted in a violent reaction. This and the high cost of diethyl zinc was a major factor in looking at an alternative method of forming the required intermediate.

In the second route the starting aldehyde (**95**) was prepared without difficulty following the literature route.

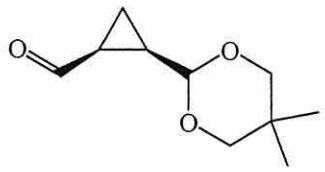


(87)

The aldehyde was protected with ethylene glycol as the acetal, followed by hydrolysis of the ester group and oxidation to the aldehyde (**90**). Difficulties were encountered in the P.C.C-oxidation, low yield and difficulty in purification. The aldehyde (**90**) was converted as before via Wittig reaction into compound (**91**), and the Michael addition of the methyl magnesium bromide was carried out.

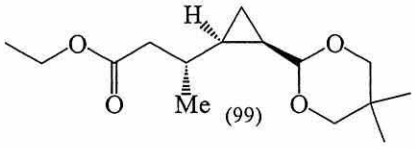


This resulted into two isomers in a ratio 3:1 in low yield that could not separated. Because of the previous difficulties, the use of an alternate protecting group for the aldehyde was attempted. Thus using 2,2-dimethyl-1,3-propandiol and following the same sequences, (**96**) was prepared, the final oxidation to the aldehyde being achieved under Swern conditions.

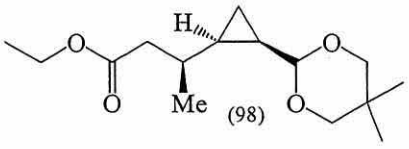


(96)

This resulted in a higher yield and a more easily purified product. Following the Wittig reaction as before and Michael addition, the two isomers (**98**) and (**99**) were isolated in a yield of 47 %. Repeated chromatography on silica yielded pure samples of both isomers. In view of these difficulties in the separation, the route described earlier from D-mannitol to α-methyl-*trans*-cyclopropanes was preferred.

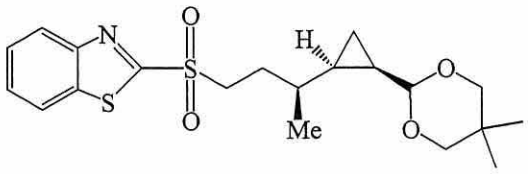


(99)



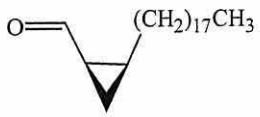
(98)

However, since the ultimate intention was to synthesise a mycolic acid with two cyclopropanes rings, an intermediate that could be used to introduce the second cyclopropane was prepared from (**98**). Thus (**98**) was reduced to the alcohol and converted by the usual procedures into the Julia reagent (**111**).



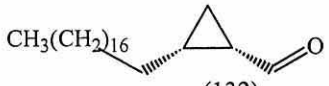
(111)

The synthesis of the long chain substituted chiral *cis*-cyclopropane (**119**) followed a previous described procedures but with an alkyl chain length of 18 carbons instead of the original 20 carbons.



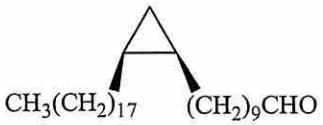
(119)

The enantiomer of (**119**), (**132**), was prepared through enzymatic resolution of *cis*-1,2-bis(hydroxymethylcyclopropane) (**83**).

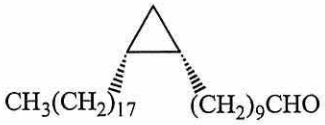


(132)

Both of the aldehyde isomers were converted by Wittig reaction and di-imide reduction to saturated alcohols which were oxidized by PCC to the aldehydes (**117**) and (**133**).



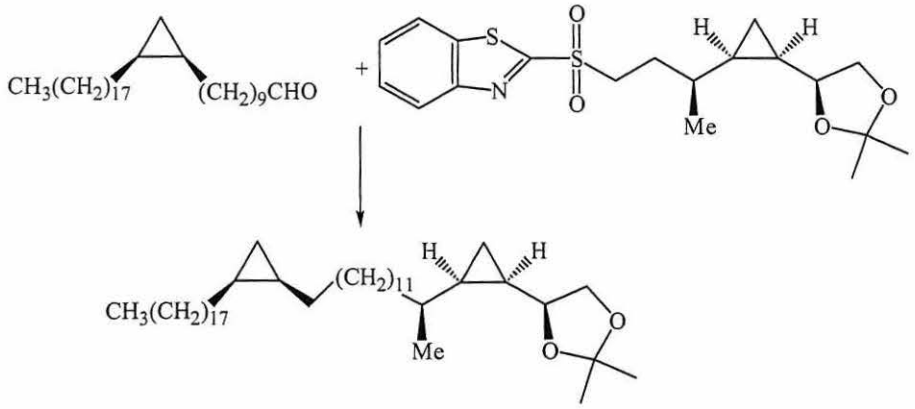
(117)



(133)

Thus the work was successful in producing necessary synthons to produce the target molecule. Only small amounts of the products were available for the attempted final coupling. However this coupling has subsequently been done by the group,[30a] and the final product (**52**) was isolated. The n.m.r spectrum showed an identical pattern to that reported in the literature for such compounds;[30b] however, the product was clearly not that described originally by Minnikin (as the *cis*-isomer).[34] Further analysis is currently under way to compare it to later described α-methyl-*trans*-cyclopropane containing mycolates. From the nature of the method, it can be seen

that any required chain lengths could be introduced into the final meromycolate and therefore any reported examples can in principle be prepared.



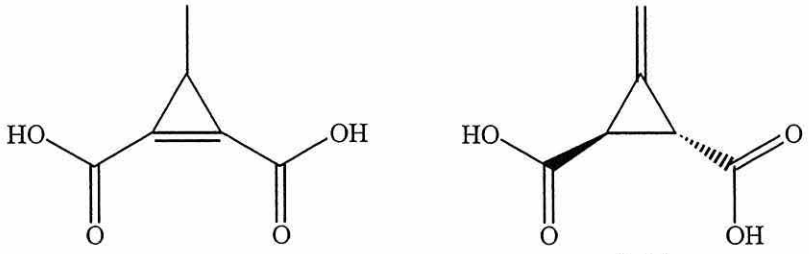
Chapter Three

Methylenecyclopropane

Results and discussion

4.1 Introduction.

In 1893, Feist[140] reported the synthesis of an important compound; the structure was originally thought to be 3-methyl-1,2-cyclopropene-dicarboxylic acid (**146**) (Figure 111). The structure remained in dispute until the 1950's when several authors showed that it had the methylenecyclopropane structure (**147**).[146]



(146) (147)

3-Methylcycloprop-1-ene-1,2-dicarboxylic acid

3-Methylenecyclopropane-1,2-dicarboxylic acid

Figure (89)

The methylenecyclopropane unit is an element in a number of natural products and an intermediate in the synthesis some medicines; the thermal unimolecular rearrangement of optically pure derivatives of methylenecyclopropanes remains an attractive subject for research because the classical tools of stereochemistry and kinetics can be used to great advantage to obtain an insight into the details of bond-breaking and bond-forming processes.[144][145]

There is increasing importance in synthetic applications of Feist's acid leading to oxetanocin (**152** a),[134][139] and related antibacterial and antiviral agents.[135] Among them, cyclobut-G (**152** b) displays broad-spectrum activity against herpes-viruses and HIV, and related compounds are considered as promising agents for the treatment of AIDS.[136]

Using the protected *trans*-2,3-bis(hydroxymethyl) cyclobutanones (**151** b-e) as key intermediates, several successful syntheses of (**152** a-b) have appeared.[137][142] Chi-Nung and Steven[138] recognized that Feist's acid[140] (**147**) could be used as an ideal starting material to prepare (**151** c), and the resolution of this starting diacid had already been reported by Doering and Roth.[141]

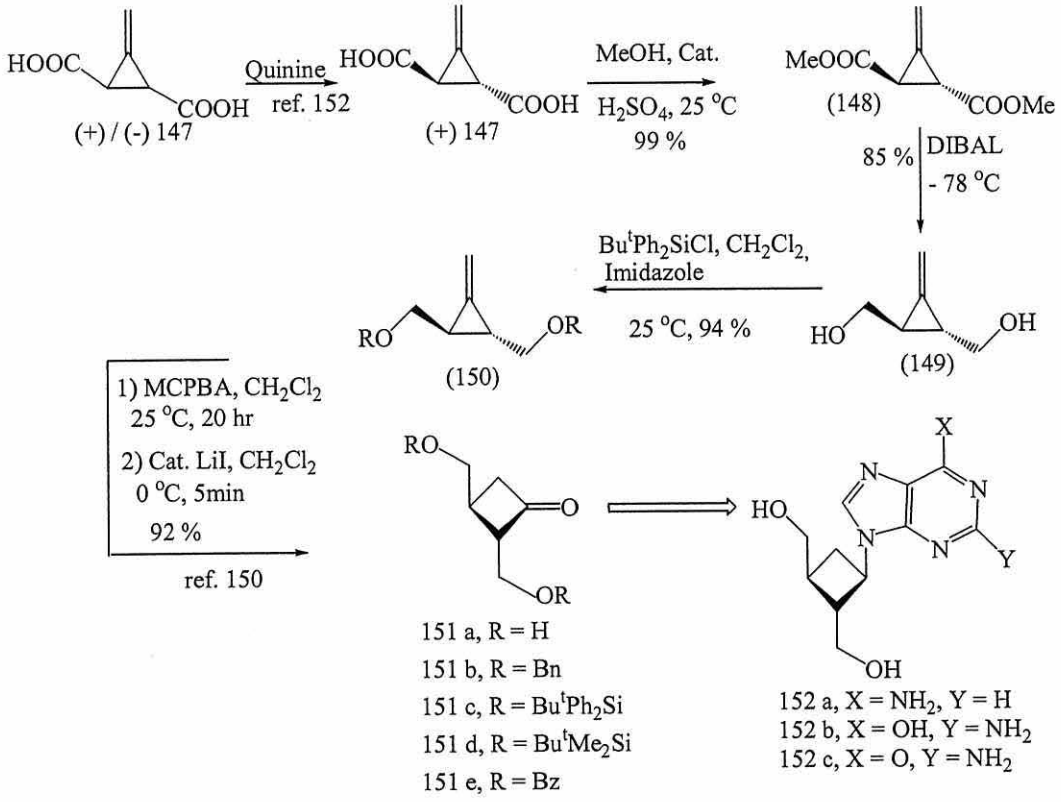
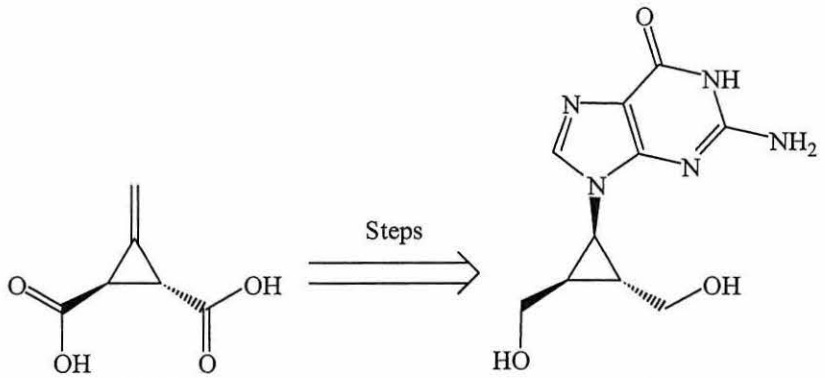


Figure (90)

The racemic Feist's acid was resolved as its quinine salt by recrystallization from ethanol yielding optically pure (+) **147** in good yield.[141] Treatment of (+) **147** with methanol and catalytic sulfuric acid gave diester (**148**), which could be reduced to diol (**149**) with diisobutylaluminum hydride, then again (**149**) could be protected as the bis (tert-butyldiphenyl) silyl ether (**150**).

This, after epoxidation and rearrangement provided (**151** c) in excellent yield, which has been used as a key intermediate for the preparation of carbocyclic analogues of oxetanocin (**152** a).

In order to explore the structure-activity relationship of the ring size to the antiviral activity, Daniel and Hing[143] have successfully synthesized ($\bar{+}$) cyclopropane–G (**153**) by using Feist's acid (**147**) as starting material. This was tested for activities against HSV-1, HSV-2, against HIV-1 in MT-2 and ATH-8.



(147) (153)

Feist's acid

Figure (91)

The aim of this present project was to develop a new route to optically pure chiral methylenecyclopropanes by using enzyme reactions, to prepare differently functionalised methylenecyclopropanes, and to investigate the thermal rearrangements of optically pure derivatives of Feist's acid.

In the literature,[146][147] Feist's acid was prepared from the α-pyrone (**154**), which was prepared by passing dry hydrogen chloride through ethyl acetoacetate, and the claimed yield was 54 %. In a slight modification of the literature procedure, Feist's acid was prepared in three steps starting from ethyl acetoacetate by catalytic condensation with dry hydrogen bromide; this gave a 77 % yield of (**154**), providing a convenient large-scale route to the α-pyrone.

The α-pyrone (**154**) was readily converted into the corresponding α-bromopyrone (**155**) by reaction with bromine in dichloromethane. Hydrolysis of the α-bromopyrone with potassium hydroxide then acidification with sulfuric acid led to the formation of Feist's acid (**147**) in 55 % yield. This synthesis caused some difficulties in the procedure including the purification and the moderate yield.

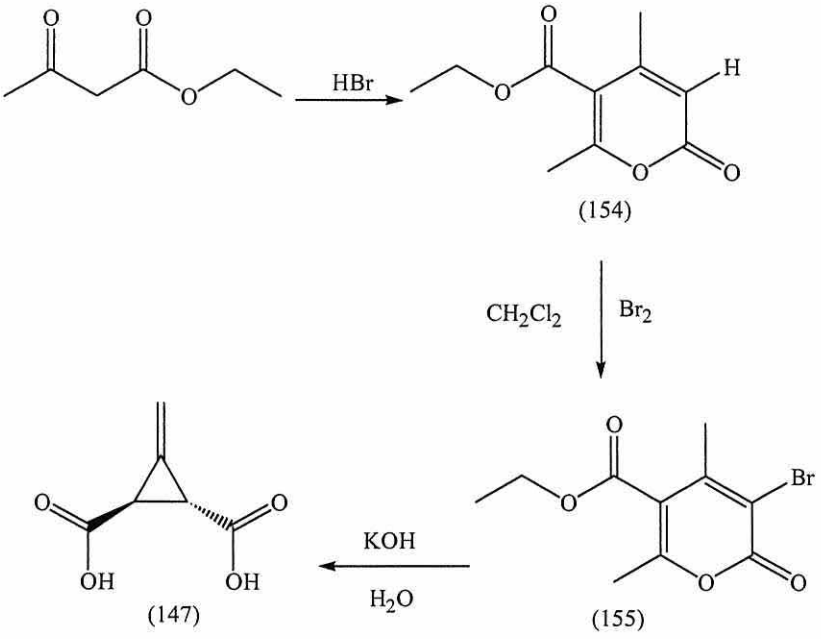


Figure (92)

The ^1H n.m.r spectrum of (**147**) in deuteriomethanol showed two broad singlets for the methylene group at δ 5.87 and 5.31, together with a triplet for the cyclopropane ring protons at 2.98 with coupling constant 2.3 Hz. The ^{13}C spectrum showed four signals, including one in the carbonyl region and two in the olefinic region, together with a signal at δ 27.5 for the cyclopropane ring. A reasonable explanation for the formation of Feist's acid (**147**) may involve attack of the hydroxide ion at the carbonyl group of the pyrone (**155**) followed by ring opening to give anion (**156**).

Reprotonation and deprotonation by reaction with hydroxide ion at the methyl group can lead to an alternative anion (**158**). Elimination of bromide ion would give the cyclopropane, which reacts further with the hydroxide ion at the carbonyl group with loss of acetic acid to give the final product (**147**).

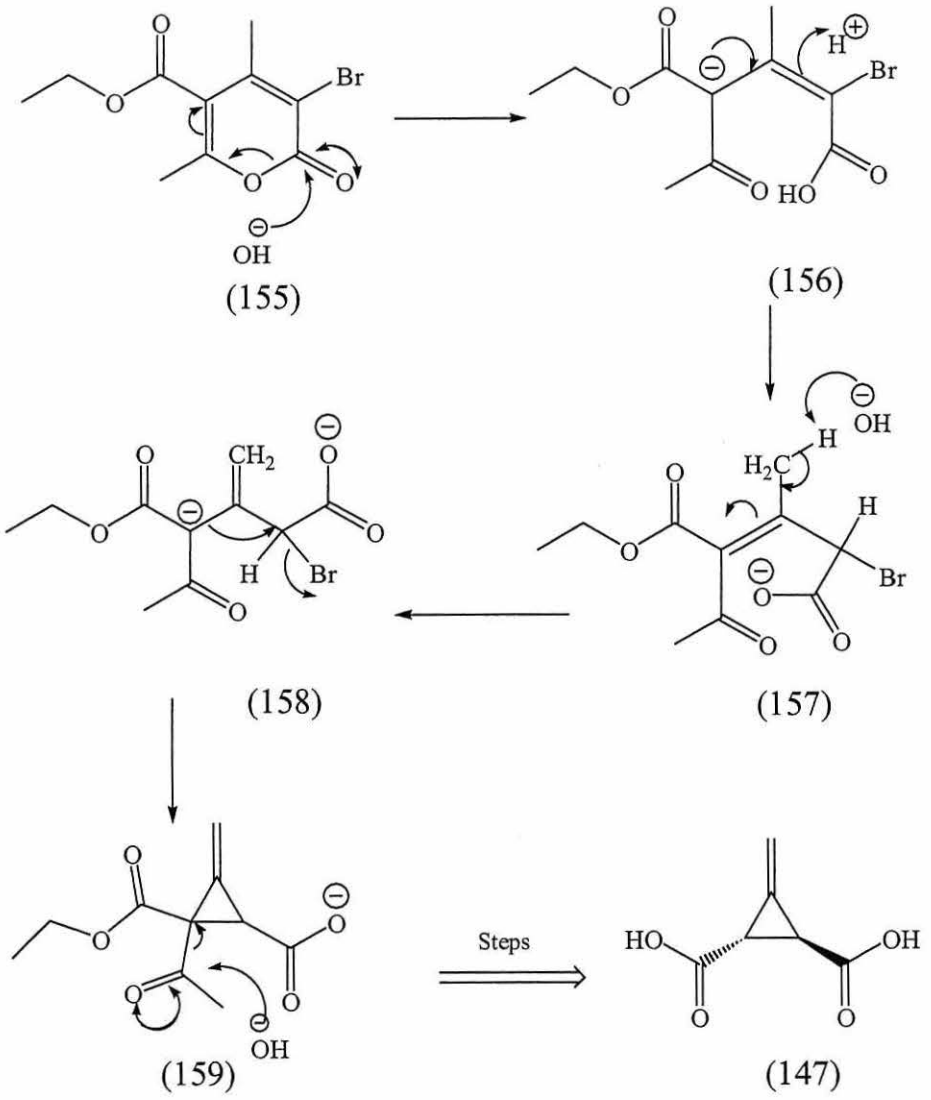


Figure (93)

However, Ullman [148] has proposed the following mechanism:

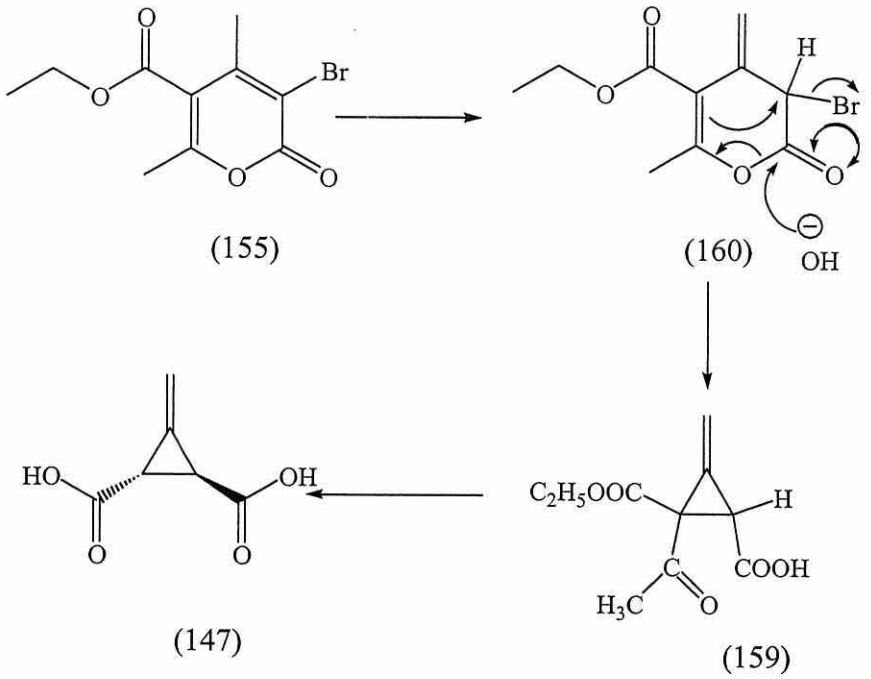


Figure (94)

Feist's acid was converted successfully into the 6-methylene-3-oxa-bicyclo[3.1.0]hexane-2,4-dione (**161**) by refluxing with acetic anhydride in the presence of potassium acetate.[149] The anhydride was reduced to the diol (**162**) by lithium aluminum hydride in 77 % yield. Moreover, Feist's acid was converted into the diester (**148**) by refluxing in methanol catalyzed by few drops of sulfuric acid. The *trans*-diester was converted to the *trans*-diol (**149**) using lithium aluminum hydride.

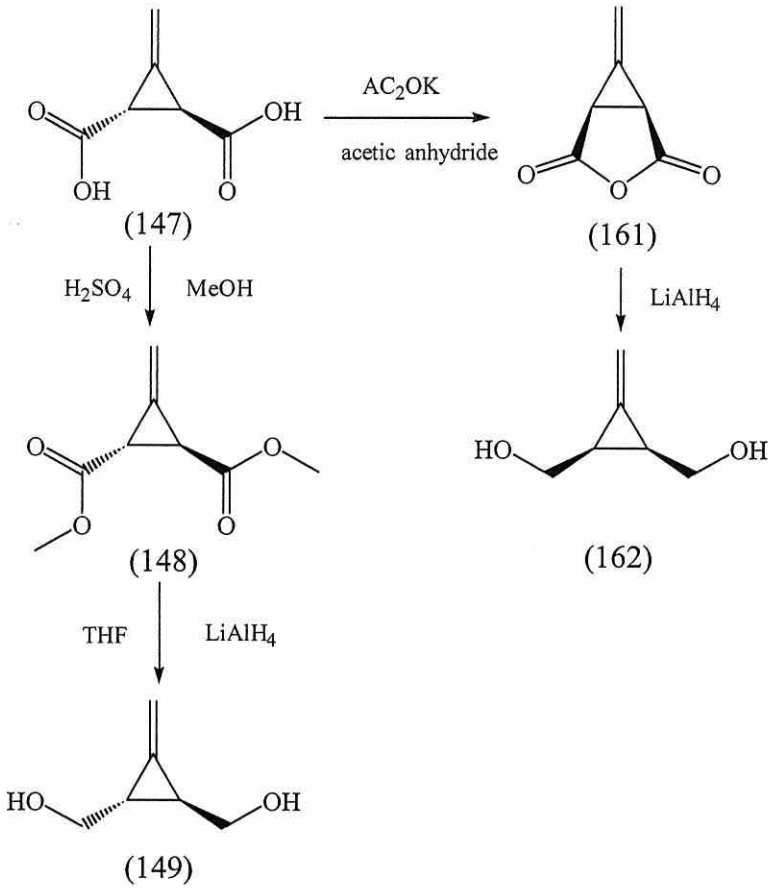


Figure (95)

4.2 Enzymatic Resolution.

The cyclopropane ring is a common unit in a large number of natural products and compounds of pharmaceutical interest.[150] As most of them are optically active, an easy access to optically pure versatile cyclopropane intermediates would be valuable. Synthesis of chiral cyclopropanes has been recently reviewed.[151] It usually requires either chemical or enzymatic resolution, or diastereoselective or enantioselective cyclopropanation.

The chiral cyclopropanes are not only useful for restricting the conformation of biologically active compounds to improve activity but are also important as key fragments in many natural products.[152]

Enzymatic resolution was employed to resolve *cis*–1,2-dihydroxymethyl-3-methylenecyclopropane (**162**), which was stirred in THF in the presence of pig liver esterase and vinyl butyrate (**163**) at room temperature. This gave monoester (**164**) in 54 % yield and the $[\alpha]^{22}_{D}$ was -10.71 in $CHCl_3$. The racemic mono butyrate of the *cis*-diol (**162**) was prepared and purified by column chromatography. Chiral g.l.c analysis gave 2 peaks of equal height. One of the peaks had the same retention time as the mono-ester (**164**) prepared by enzymatic desymmetrization.

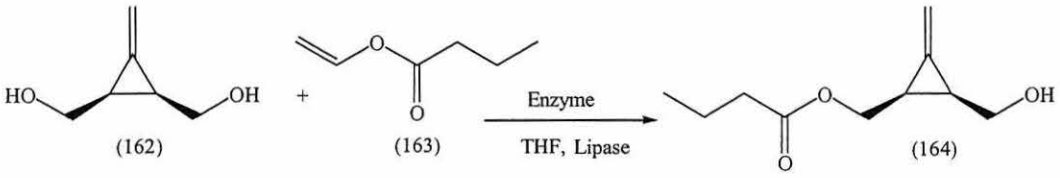


Figure (96)

The selective mono-esterification using pig liver esterase as catalyst was also carried out with 2,2,2-trifluroethyl butyrate (**167**) to give the same yield as before. The trifluoroester was readily prepared by esterification of trifluoroethanol (**166**) with butyric anhydride (**165**) in di-isopropyl ether in the presence of catalytic trimethylsilyl trifluoromethane sulphonate.

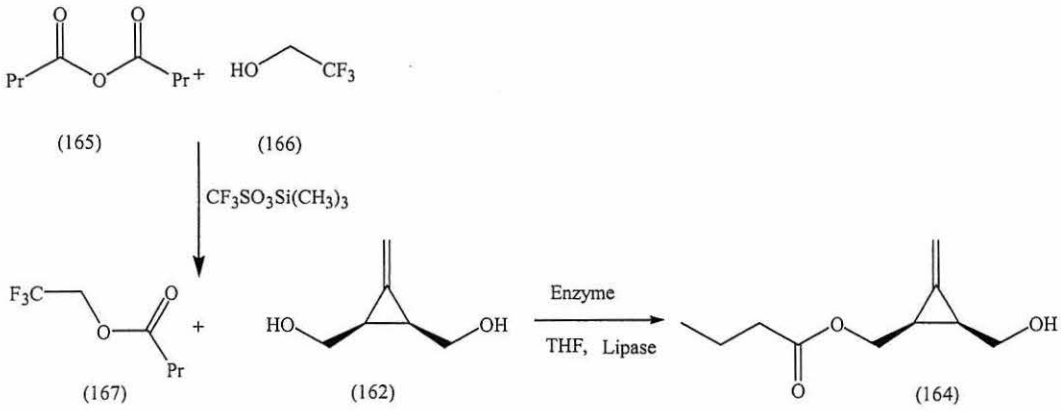


Figure (97)

The infrared spectrum indicated the carbonyl group at 1735 cm^{-1} and a hydroxyl group at 3438 cm^{-1}. The absolute configuration of butyric acid (*1R*, *2S*)-2-hydroxymethyl-3-methylene-cyclopropylmethyl ester (**164**) was assigned relative to the literature,[137] which used the same enzymatic resolution to prepare (**86**).

Oxidation of (**164**) was successfully carried out in dichloromethane solution by 2 mol.quiv. of pyridinium chlorochromate (PCC). The crude product was purified by column chromatography to give (**168**) in 92 % yield. The I.R spectrum of the product (**168**), exhibited a very strong C=O stretch at 1731 cm^{-1}, consistent with the desired aldehyde functionality and no O-H stretch was observed. The ^1H n.m.r spectrum of (**168**) showed as expected, a doublet at δ 9.1 with coupling constant 5.5 Hz for the aldehyde group.

One of the aims of this work was introducing different functional groups into the methylenecyclopropane, therefore the aldehyde (**168**) was treated with 1.2 mol.equiv. of a suitable, stabilised phosphorane, carboethoxymethylene triphenylphosphorane enabling the efficient introduction of the olefinic double bond.

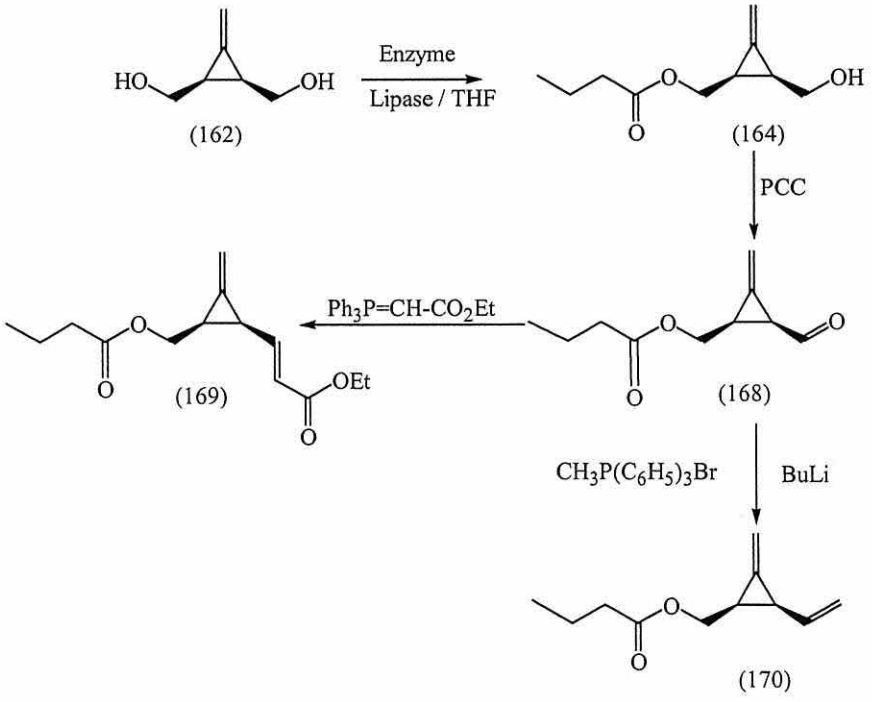


Figure (98)

Wittig reactions of this type are typically carried out overnight at room temperature in toluene solution. Unfortunately the crude product was generally recovered as a thick paste that contained not only the desired ester (**169**) 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 enabled the efficient bulk separation of the two components; further purification was carried out by flash column chromatography and (**169**) was subsequently recovered as an oil in 83 % yield.

The I.R spectrum confirmed the formation of the α,β-unsaturated ester by the appearance of the bands corresponding to C=O and C=C stretches at 1736 and 1632 cm^{-1} respectively. Analysis of the purified product by ^1H n.m.r revealed that the E-alkene had been formed selectively. One of the olefinic signals was observed at δ 6.6 as a double doublet with coupling constants 15.4 and 8.8 H_Z. Similarly the signal corresponding to the second olefinic proton, was observed as a doublet with coupling constant 15.4 H_Z.

Moreover, reaction of (**168**) with methyl triphenylphosphonium bromide (**171**) in tetrahydrofuran using butyl lithium as a base at –78 °C led to the formation of (**170**) in 77 % yield.

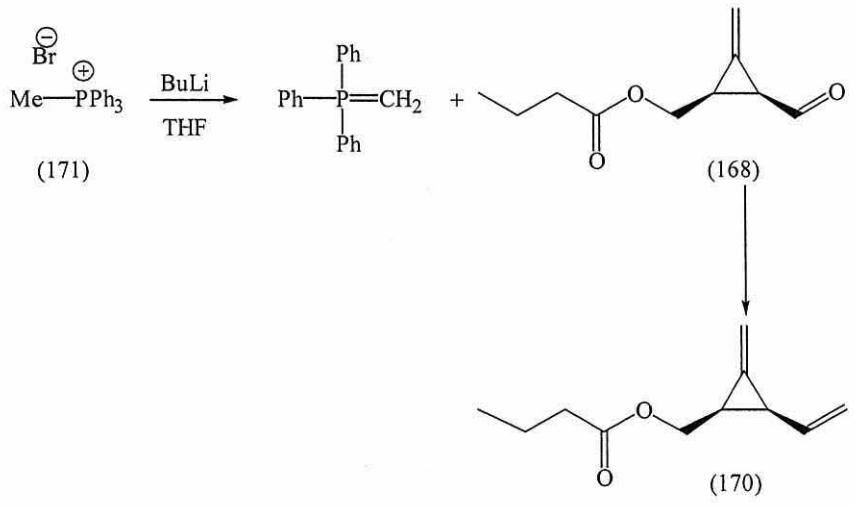


Figure (99)

The ^{1}H n.m.r spectrum of (**170**) showed a double double doublet for proton H_a at δ 5.63 with coupling constants 7, 10 and 17 H_Z, two broad doublets at 5.13 and 5.05 for protons H_b and H_c with coupling constants 10 and 17 H_Z respectively, and a broad singlet at 5.48 integrating for two protons (H_e and $H_{e'}$).

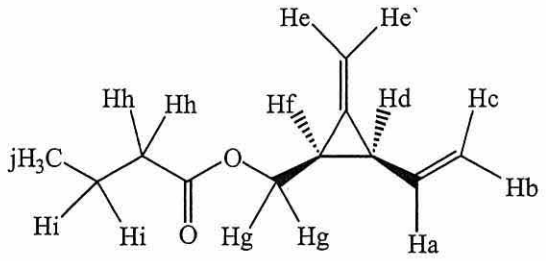


Figure (100)

The methylene group adjacent to the oxygen atom (H_g) appeared as two double doublets with coupling constants 6.1, 11.6 H_Z and 9.1, 11.6 H_Z respectively. A broad multiplet was seen at δ 2.33 (H_d) together with a triplet at 2.24 (J = 7.3 H_Z) for the methylene group next the carbonyl group, which was, coupled to the neighbouring methylene groups. This appeared as a sextet at 1.6 (J = 7.4 H_Z). A multiplet appeared at 2.06 integrating for one proton, together with a three hydrogen triplet resonated at 0.91 with coupling constant 7.3 H_Z. The ^{13}C n.m.r spectrum showed the expected signals including peaks at δ 135.3, 133.1, 117 and 105.8 for the vinyl and methylene groups, and at 173 for the carbonyl carbon.

One of the aims in this project was to introduce different functional groups, which might prove to be useful in organic synthesis. Therefore, the mono-ester (**164**) was successfully converted into the amide (**172**) by reaction with triphenylphosphine, phthalimide and diethyl azodicarboxylate in dry THF at room temperature in 61% yield.

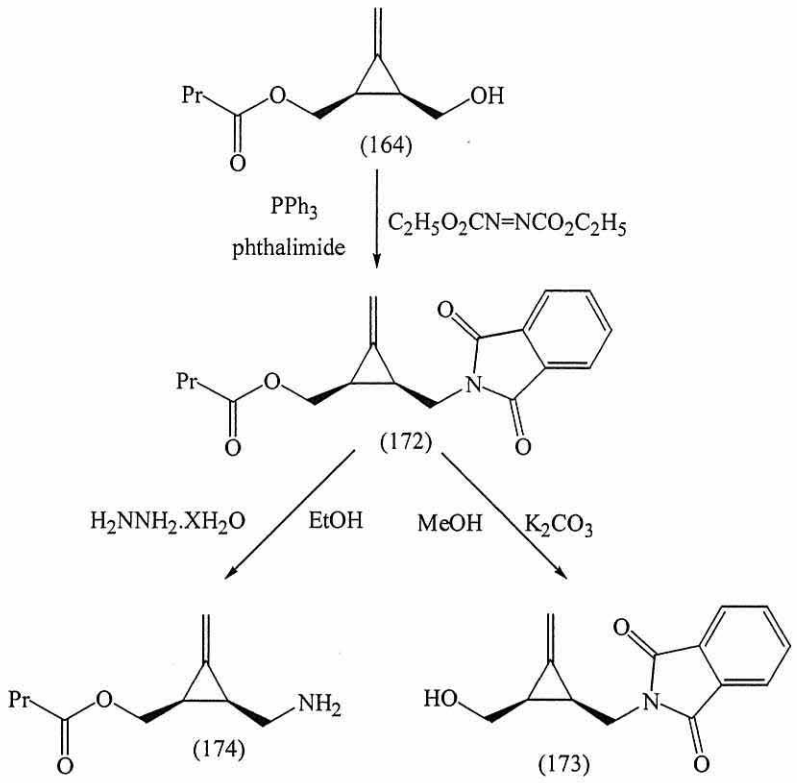


Figure (101)

When alcohols are allowed to react with phthalimide in THF in the presence of diethyl azodicarboxylate, triphenylphosphine and butyric acid at room temperature, the corresponding *N*-alkylphthalimides are obtained. Mitsunobu and Yamada described how the reaction of alcohols or nucleosides with either carboxylic acids or hydrogen phosphate ester in presence of equimolar amounts of diethyl azodicarboxylate and triphenylphosphine affords carboxylic or phosphoric esters.[153]

The ^{1}H n.m.r spectrum for (**172**) showed two multiplets in the aromatic region integrating for four protons at δ 7.8 and 7.7, a broad singlet at 5.4 integrating for two protons for the alkene methylene group. The infrared spectrum showed the stretching of the carbonyl group at 1713 cm^{-1}.

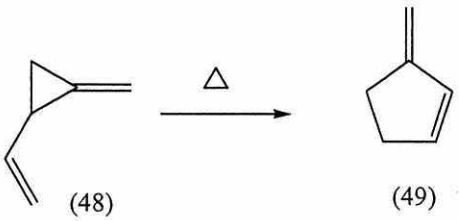
Treatment of (**172**) with potassium carbonate in methanol at room temperature afforded the desired alcohol (**173**) in 78 % yield.

I.R spectroscopy confirmed that the hydrolysis of the starting material had indeed been successful. The appearance of a broad O-H stretch band at 3448 cm^{-1} confirmed the presence of the desired alcohol functionality. The ^1H n.m.r (**173**) in D_2O showed two broad multiplets in the aromatic region at δ 7.57 and 7.45.

Moreover, the treatment of (**172**) with hydrazine hydrate in ethanol gave amine (**174**) in 81 % yield. The ^1H n.m.r spectrum of (**174**) showed the successful conversion from imide to the amine by the disappearance of the signals of phthalimide and the appearance of a broad singlet at δ 6.72. The I.R spectrum showed the stretch for the carbonyl group at 1649 cm^{-1}.

4.3 Cyclisation and thermal rearrangement of methylenecyclopropanes.

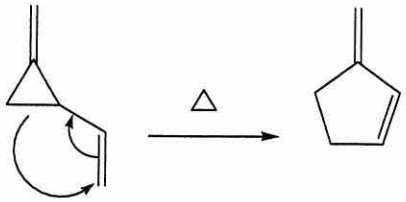
The syntheses of various vinyl-substituted methylenecyclopropanes have been reported in recent years.[154][155] By analogy to the formation of methylenecyclopentenes from methylenecyclopropanes at high temperature shown below, it was of interest to study the rearrangement of such species.[157][156]



(48) (49)

Figure (102)

The formation of (**49**) may occur either through a sigmatropic shift or a free radical rearrangement (Introduction chapter).[158]



(48) (49)

Figure (103)

When the vinyl methylenecyclopropane (**169**) was refluxed in toluene in the presence of 0.5 mol equivalent of morpholine, the methylenecyclopentene (**175**) was isolated in 28 % yield.

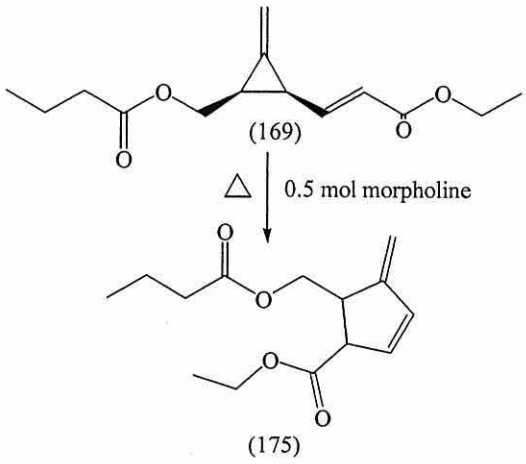


Figure (104)

The ^{1}H n.m.r spectrum of the (**175**) showed coupling constants which demonstrated the product structure.

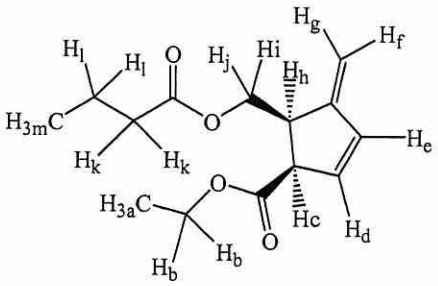
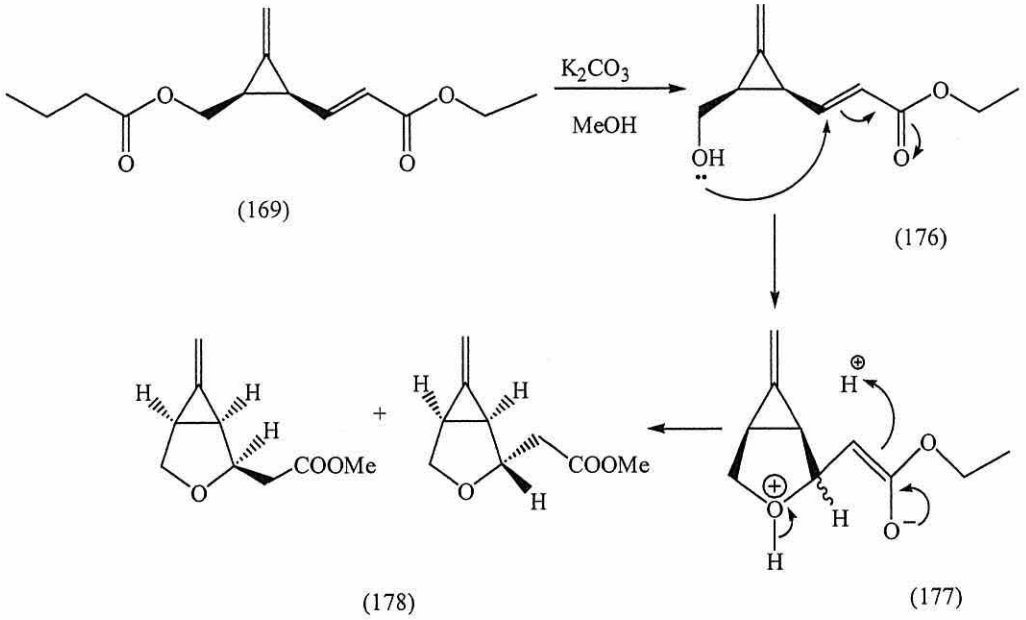


Figure (105)

A double doublet was seen for proton H_e at δ 6.2 (J = 2.2, 5.5 H_Z), the result of coupling with H_d and H_c, proton H_d appeared as a broad multiplet at 6.04, while the methylene group protons H_f and H_g appeared as a two broad singlets at 5.04 and 4.9. Two double doublets appeared at 4.25 and 4.1 for H_i, H_j with a geminal coupling constant of 11 H_Z, and two protons H_b appeared as a quartet at 4.15 with coupling constant 7.1 H_Z. Proton H_c appeared as a broad quartet at 3.5 with coupling constant 3.0 H_Z, a broad multiplet for the H_h at 3.45. ^{13}C n.m.r spectrum showed the expected signals including four in the olefinic region at δ 152, 135, 134 and 106. There were also two signals in the carbonyl region at 174 and 173 and two signals for the carbons next to oxygen atoms at 66.05 and 60.95. In addition the ^{13}C n.m.r DEPT spectrum showed five positive signals at 106, 66, 60, 36 and 18 for CH_2 groups, and six negative signals at 135, 134, 54, 43, 14 and 13 for CH_3 and CH groups. The infrared showed the carbonyl stretching at 1739 cm^{-1}. The coupling between H_h and H_c was observed to be 2.7 Hz on average. In a similar system, which has been defined as *trans* the corresponding coupling constant is 5.7 Hz.[175] These values of coupling are sufficiently different to suggest that the compound (**175**) must be of *cis* geometry between H_h and H_c.

The Lewis acid mediated cyclisation of various methylenecyclopropyl ketones, ketals and aldehydes has been investigated as a new route to five, six and seven-membered rings.[159] The cycloaddition of methylenecyclopropanes across carbon-carbon double bonds has also appeared in the literature.[160] In this work alternative cyclisation was studied.

Treatment of (**169**) with potassium carbonate in methanol at room temperature for one hour led to the bicycle (**178**) as a mixture of two isomers in ratio 1 : 1 which were hard to separate. The reaction may initially involve the hydrolysis of the ester (**169**) followed by intramolecular Michael addition reaction.



(169) (176) (178) (177)

Figure (106)

The ^1H n.m.r spectrum for the two isomers (**178**) showed the two methylene groups protons as a three broad singlets at δ 5.52, 5.49 and 5.46. A singlet for the methoxy groups, integrating to six protons was seen at 3.7. The ^{13}C n.m.r spectrum confirmed there were two isomers present and showed two carbons for the carbonyl group at δ 171.7 and 171.1. The I.R spectrum was also consistent the presence of a carbonyl group with a C=O stretch at 1736 cm^{-1}.

In this work, we investigated the addition of mercuric acetate to *trans* –1,2-dihydroxymethyl-3-methylenecyclopropane (**149**), followed by reaction with NaOH–$NaBH_4$, which led to the formation of (3-oxa-bicyclo[3.1.0]hex–6-yl)-methanol (**179**). In contrast, acetoxy-mercuration of the *cis*-1,2-dihydroxymethyl-3-methylenecyclopropane (**162**) led to the formation of 3-methylene-pent-4-ene-1,2-diol (**180**).

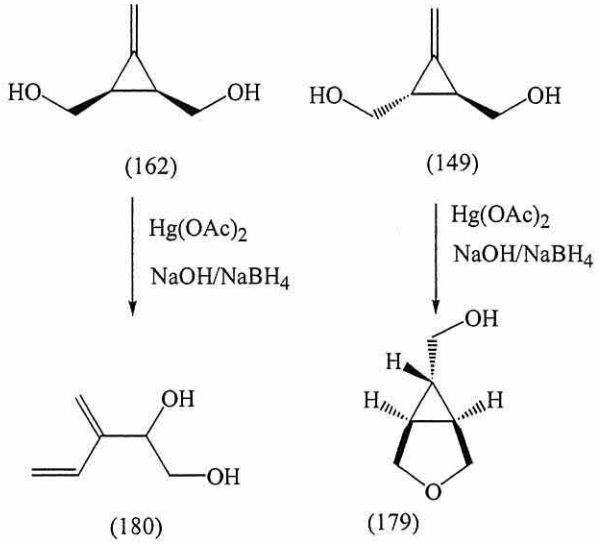


Figure (107)

The origin of the diol (**180**) is not certain. However, The reaction may involve initial attack of $^{+}$Hg(OAc) at the hydroxyl group followed by the ring opening to give the epoxide (**182**) which leads to the diol after reaction with the hydroxide ion.

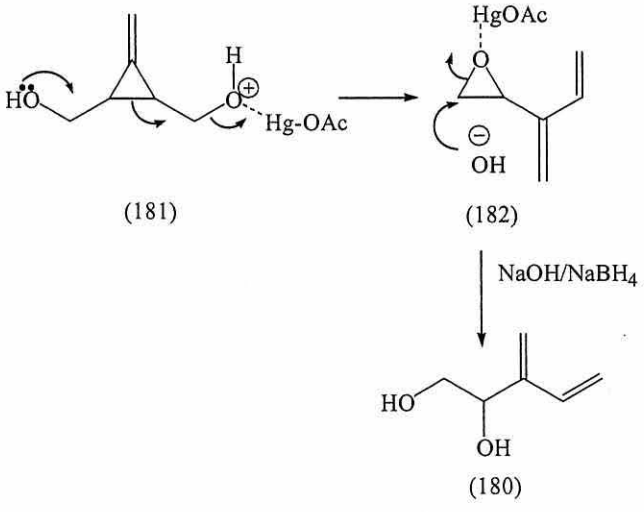


Figure (108)

The diol (**180**) showed a hydroxyl band in the IR spectrum, while the ^{1}H.n.m.r spectrum showed two broad singlets for the methylene group at δ 5.32 and 5.22, together with one double doublet at 6.3 (J = 11 and 17.7 H_Z) and two broad doublets for the vinyl group at 5.29 and 5.09 (J = 17.7 and 11.1 H_Z).

However, with *trans*-diol (**149**), the isolated product was the bicycle (**179**), which may involve an initial attack of $^{+}$Hg(OAc) at the double bond as in (**183**) followed by intramolecular cyclization (**184**).

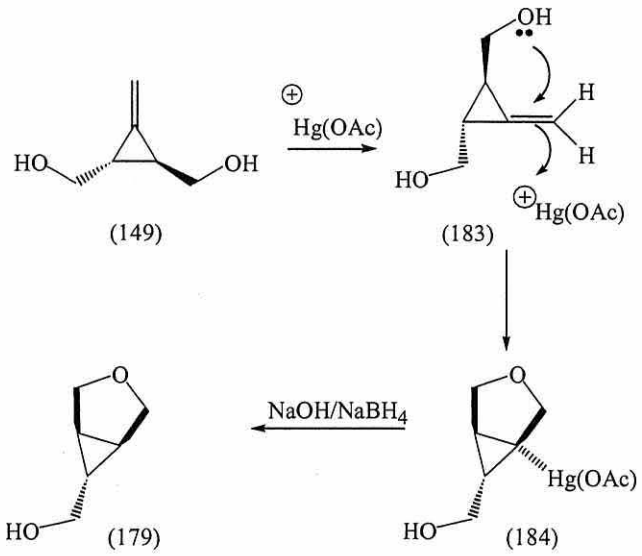


Figure (109)

Moreover, addition of bromine in dichloromethane to the *trans*-diol (**149**) led only to addition at the double bond without any cyclization .

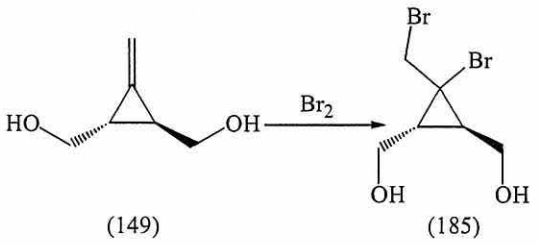


Figure (110)

5.1 An alternative route to methylenecyclopropanes.

The synthesis of Feist's acid from ethyl acetoacetate showed some difficulties in the procedure including the purification and the low yield, therefore a new route to *cis*-diol (**162**), with low cost and high yield was required. Hence the *cis*-diol (**187**) was used as the starting material in the preparation as shown below.

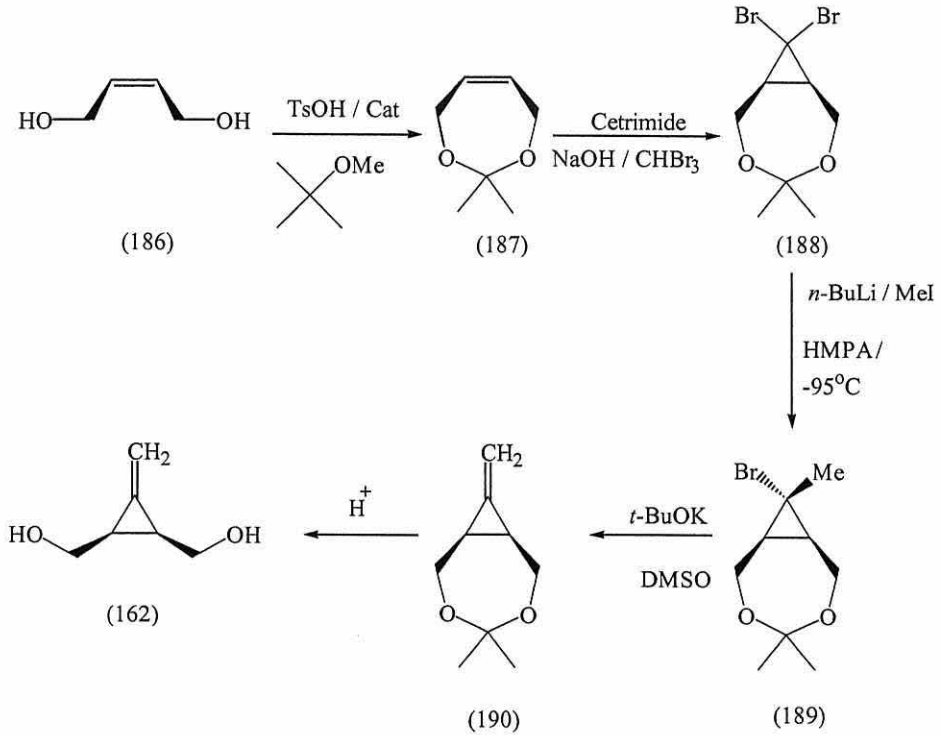
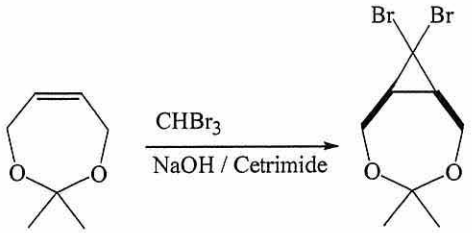


Figure (111)

The initial step was the protection of *cis*-2-butene-1,4-diol (**186**) using 2,2-dimethoxypropane by the method of Bannock and Lappin,[32] using a catalytic amount of p-toluene sulphonic acid to give 2,2-dimethyl-4,7-dihydro-1,3-dioxepine (**187**) in 85 % yield.[161]

The crystalline *gem*-dibromocyclopropane (**188**) was prepared in good yield by dihalocarbene addition to the double bond to give 8,8-dibromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (**188**).[162] The cyclopropanation was carried out by a phase transfer reaction using cetrimide as the catalyst, bromoform, and sodium hydroxide as strong base, as explained in the Introduction.

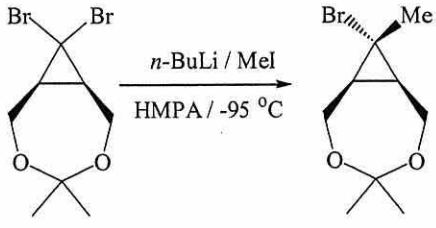


(187) (188)

Figure (112)

This reaction smoothly gave the product in quite high yield 84 %. The ^{1}H n.m.r spectrum was proof of cyclopropanation due to the presence of a multiplet integrating to 2 H at δ 2.07, corresponding to the two protons of the cyclopropane ring and to the disappearance of the protons of the double bond.

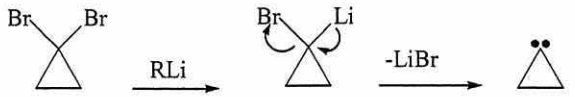
The next step was to introduce a methyl group at C-8 by low temperature alkylation.



(188) (189)

Figure (113)

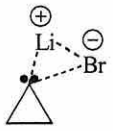
It is known that the reaction of *gem*-dibromocyclopropanes with alkyl lithium is a route to cyclopropylidenes (**193**).[163] This may occur by an initial lithium halogen exchange, to the product (**192**) which then loses lithium halide to produce (**193**).



(191) (192) (193)

Figure (114)

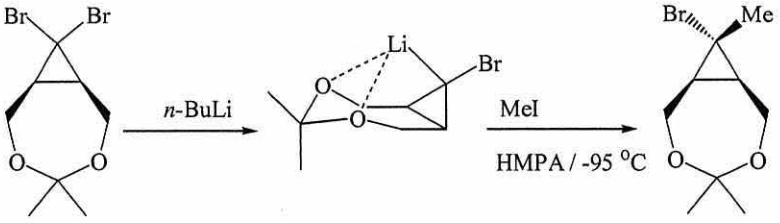
The existence of the free carbene in the present case is difficult to prove and co-ordination to the lithium halide to give a carbenoid (**194**) is likely.



(194)

Figure (115)

Also co-ordination occurs between the lithium and oxygen and the methyl group in endo-position as shown below.[164]



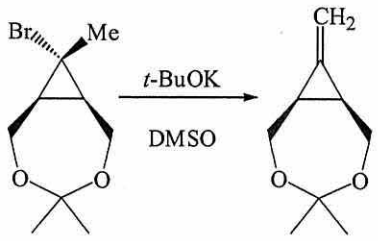
(188) (195) (189)

(Figure 116)

When the resulting carbenoid (**195**) is treated with methyl iodide, the selectivity in the alkylation is dependent on the solvent plus the reaction time. At the same time the addition of hexamethylphosphoric triamide (HMPA) increases the nuclophilic coupling of the carbenoid with alkyl halides.

However, the carbenoid (**195**) failed to react with methyl iodide at –78 °C and –15 °C when the reaction solvent was ether.

The addition of tetrahydrofuran to the reaction, dissolved (**195**) and allowed methylation to carry on. The low solubility of (**195**) was judged not to be the key factor in the lack of reaction with methyl iodide. The effect of THF is most probably to loosen the Li atom of (**195**) from coordination with the ring oxygen atoms, in order for methylation to occur to give (**189**).[165] After g.l.c showed no starting material was left, the reaction was quenched with water, extracted with dichloromethane and purified by column chromatography to give a 71 % yield of (**189**). The ^{1}H n.m.r spectrum showed a new singlet at 2.05 for the 8-methyl and the ^{13}C n.m.r spectrum showed one extra peak from the starting material spectrum. The next step was to eliminate HBr from (**189**) to get the methylenecyclopropane (**190**). This is could be achieved by using strong base (such as potassium *t*-butoxide) and DMSO as solvent to give (**190**) in 76 % yield.

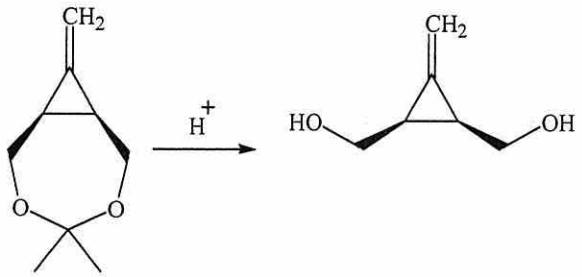


(189) (190)

Figure (117)

The ^{1}H n.m.r spectrum of (**190**) showed a broad singlet methylene and cyclopropane protons at δ 5.4, and two double doublets at 4.07 and 3.81 (J = 2.1, 12.8 H_Z and 1.1, 12.8 H_Z respectively) for the protons next to oxygen. A broad singlet for the two-cyclopropane protons was seen at 1.81, and two singlets appeared at 1.34 and 1.22 for the methyl groups. The ^{13}C n.m.r spectrum showed the quaternary carbons at δ 137 and 102.3.

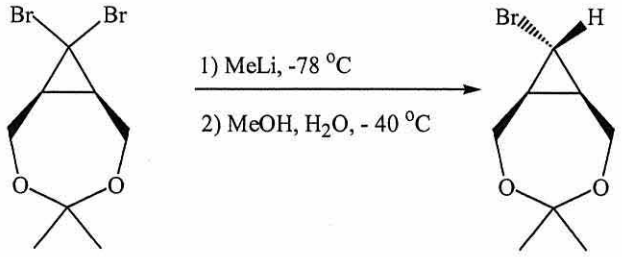
The hydrolysis of (**190**) with dilute acid gave compound (**162**), which was identical by n.m.r to that obtained earlier.



(190) (162)

Figure (118)

Following the literature procedure,[165] exo-8-bromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (**196**) was prepared in 79 % yield, by elimination of one bromine by adding 1.5 mol.equiv of methyllithium at –78 °C to (**188**), then quenching with water and methanol at –40 °C.



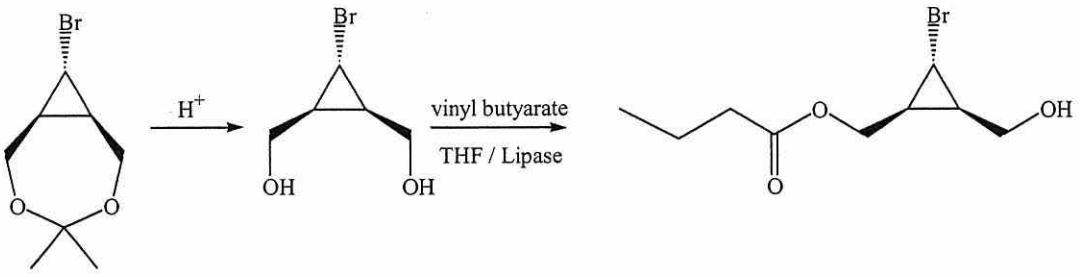
(188) (196)

Figure (119)

Again, the coordination between the oxygen and Li as shown the short lived intermediate (**195**) which was trapped by quenching with water and methanol to give the product (**196**). The g.l.c showed that all the starting material had reacted in 5 – 10 minutes to form the product.

The ^{1}H n.m.r spectrum for the mono-bromocyclopropane (**196**) showed that one of the cyclopropane protons (CHBr) at 2.69 as a triplet (J = 3.9 H_Z) confirming the exo-stereochemistry. The ^{13}C n.m.r showed the shift of the cyclopropane carbon carrying two bromine for the starting material to a carbon carrying one bromine for the product.

As mentioned before, synthetic approaches to single enantiomers of cyclopropanes remain an attractive target for much research, therefore we successfully prepared the mono-bromocyclopropane (**198**) as a single enantiomer by enzymatic reaction of (**197**).



(196) (197) (198)

Figure (120)

The hydrolysis of the protecting group of (**196**) under acidic conditions using para-toluene sulphonic acid monohydrate gave diol (**197**). This reaction was monitored by g.l.c, occurring with quite high yield (80 %). The IR spectrum (**197**) indicated a broad band at 3335 cm^{-1} corresponding to the OH groups. The ^{1}H n.m.r spectrum showed the successful deprotection by the disappearance of the two-methyl groups. Since compound (**197**) was symmetrical, the ^{13}C NMR spectrum showed just three peaks, including one at δ 60.6 for the carbons of the CH_2OH groups.

Enzymatic reaction of (**197**) was carried out using vinyl butyrate. It was found that the esterification could also be carried out with 2,2,2-trifluoroethyl butyrate. 2,2,2-Trifluoroethanol was readily esterified with butyric anhydride in di-isopropyl ether in the presence of catalytic amounts of trimethylsilyl trifluoromethane sulphonate. The diol (**197**) was treated with different types of lipase such as R, G, and PS in presence of vinyl butyrate and tetrahydrofuran as solvent. These reactions were followed by chiral g.l.c, which showed after 72 h mainly one peak for the product in the reaction with lipase PS in 96 % ee.

The product was purified by column chromatography. The infrared spectrum of (**198**) showed a broad band at 3438 cm^{-1} for an OH group, and at 1735 cm^{-1} corresponding to carbonyl group. The ^{13}C n.m.r spectrum gave a peak at δ 173 corresponding to the carbonyl group, and peaks at 62 and 60 for the two carbons to the next oxygen atoms. The discussion of the ^{1}H n.m.r spectrum for product (**198**) shown below:

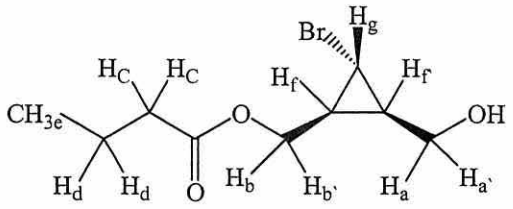


Figure (121)

As expected, the position of the broad singlet that corresponded to the alcohol was found to be extremely concentration dependent, although it was commonly observed between 1.6 – 2.0. The assignment of this signal was confirmed when the sample was shaken with drop of D_2O, when the signal disappeared completely. The protons for the methylene group of hydroxy-methyl substituent H_a and $H_{a`}$ were observed as a multiplet. A triplet integrating for one proton at δ 2.6 corresponded to the proton geminal to the bromine atom H_g, and the methylene group next to the oxygen of the ester group appeared as two double doublets (J = 5.0, 12.3 and 9.3, 12.3 H_Z respectively), at 4.42 and 3.43 for H_b and $H_{b`}$. The remaining cyclopropane protons H_f, H_f gave a multiplet at 2.01, while the aliphatic chain H_c, H_d, H_e appeared at 2.2, 1.6 and 0.9.

Compound (**197**) was also treated with butyric anhydride and catalytic amounts of trimethylsilyl trifluoromethane sulfonate in THF without using an enzyme to give the racemic compound (**199**).

The reaction was monitored using the same chiral g.l.c column as before. After work up, the product (**199**) was purified column chromatography in 48 % yield. The chiral g.l.c showed two peaks at 18.5 and 19.7 min in 1 : 1 ratio showing that the product was racemic and confirming that the product from the enzyme reaction before was a single enantiomer.

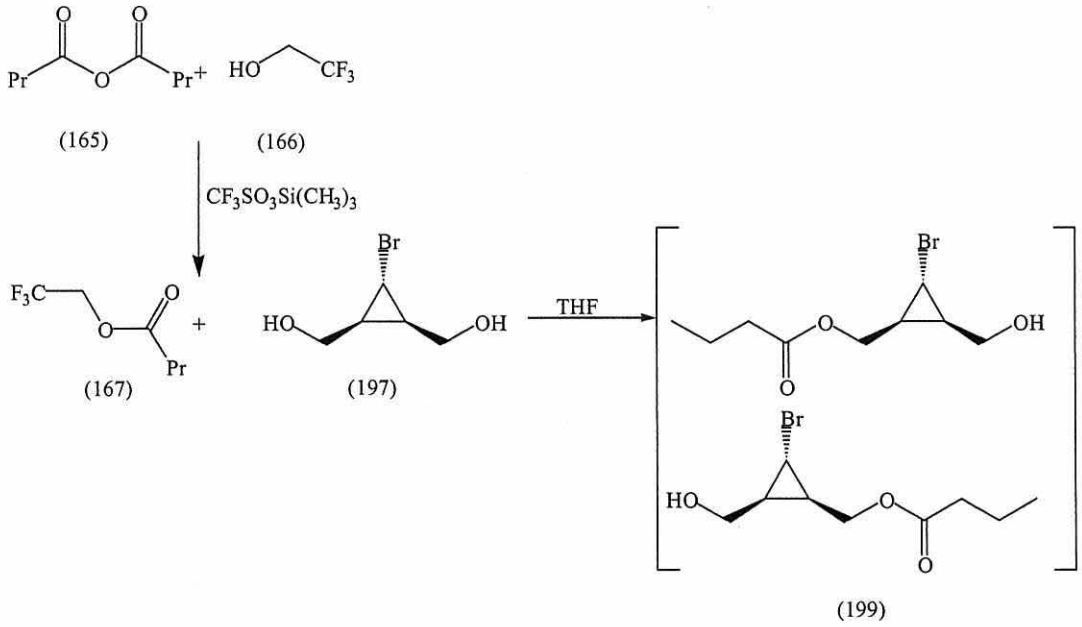
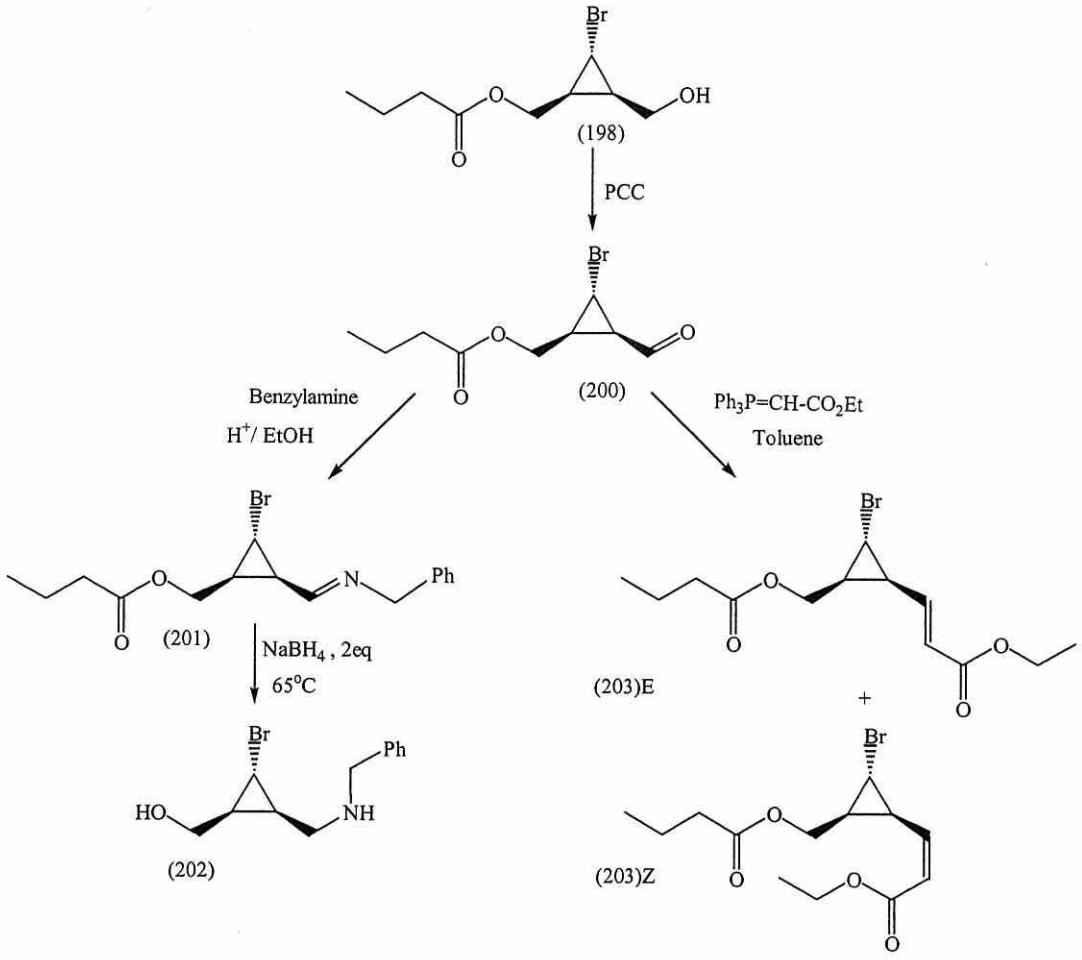


Figure (122)

One of the aims of this project was to create different functional cyclopropanes as single enantiomers like the mono-bromocyclopropane (**198**), which could be useful in organic synthesis. Therefore the monoester (**198**) was treated with pyridinium chlorochromate to give aldehyde (**200**) in 90 % yield.

The oxidation was followed by t.l.c, which showed a different R_f for the starting material and product.



(Figure 123)

The ^{1}H n.m.r spectrum of compound (**200**) showed a doublet at δ 9.72 for the aldehyde proton group with coupling constant 2.5 H_Z. The ^{13}C n.m.r spectrum showed a peak at δ 196.8 corresponding to the aldehyde carbon. The IR spectrum showed no hydroxyl group and instead showed two peaks close together between 1745 and 1734cm^{-1} for the carbonyl groups.

When the aldehyde (**200**) was treated with 1.2 equivalent of carboethoxymethylene triphenylphosphorane in toluene it produced the α,β-unsaturated ester (**203**-E) as a major, and (**203**-Z) as a minor product in ratio 9 : 1 in 66 % yield. The two isomers were purified by column chromatography.

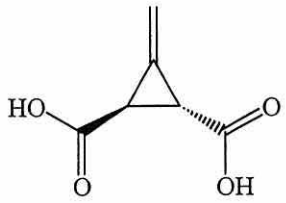
The ^{1}H n.m.r spectrum of the (**203**-E) showed *trans*-coupling for the alkene protons by the appearance of a double doublet at δ 6.5 with coupling constant 9.8 and 15.4 H_Z, and a doublet at 6.0 with a coupling constant of 15.4 H_Z. The formation of (**203**-E) was also confirmed by the ^{13}C n.m.r spectrum, which showed two signals at δ 196 and 165 corresponding to two carbons of the carbonyl groups, and another two signals at 143 and 124 for the carbons of the double bond. The I.R spectrum showed the stretching of the C=O at 1714 cm^{-1}, and for the C=C stretching at 1644 cm^{-1}.

The syntheses of amines under mild conditions has received much attention and many methods have been devised.[165] Generally, the hydroxyl group of an alcohol must first be converted into another functional group such as halogen or carbonyl before an amine can be synthesized from an alcohol.[166] Treatment of the aldehyde (**200**) with benzylamine in ethanol in the presence of acid at 0 °C then room temperature gave (**201**) in 78 % yield. The IR spectrum confirmed the formation of the product (**201**) by the appearance of a band corresponding to the C=N stretches at 1492 cm^{-1} and the disappearance of the carbonyl group at 1734 cm^{-1}. The ^{1}H n.m.r spectrum showed the disappearance of the aldehydic proton for the starting material and the appearance of a multiplet at δ 7.65 integrating to one proton due to the proton of the imino group; a multiplet for the aromatic protons appeared at δ 7.27. The ^{13}C n.m.r identified all the expected carbons including the carbonyl of the ester at δ 172 and the imine carbon appearing at 164.

It is known that the reduction of the imino-group to secondary amines using sodium borohydride is highly selective.[167] Therefore (**201**) was treated with sodium borohydride in methanol and refluxed for 15 min, when t.l.c showed no starting material was left. The product was extracted after quenching with sodium hydroxide solution and purified by column chromatography to give (**202**) in 70 % yield. The ^{1}H n.m.r spectrum of the product confirmed again that the reduction had occurred from the disappearance of the olefinic proton of the imino group. I.R spectroscopy confirmed that the reduction of the imine and also the ester of the starting material had indeed been successful.

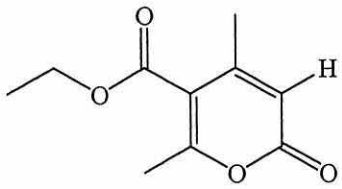
5.2 Conclusion.

As stated in the introduction, methylenecyclopropane derivatives are widely distributed in nature and have been used in the syntheses of important pharmaceuticals, in particular Oxetanocin and cyclopropane-G. This section of the work sought to examine the use of Feist's acid (**147**) in the synthesis of such compounds and to investigate whether enzymatic methods could be used to desymmetrise Feist's acid derivatives.



(147)

The literature method for the synthesis of Feist's acid involved the reaction of dry hydrogen chloride and ethyl acetoacetate to give (**154**). The disadvantage of this process is that it requires 14 days for the reaction to reach completion, and then only gives a moderate yield.

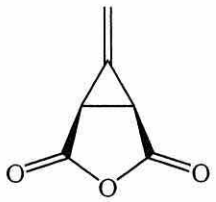


(154)

When the hydrogen chloride was replaced with dry hydrogen bromide, the reaction reached completion in 24 h and gave (**154**) in a 77 % yield. The literature sequence to produce Feist's acid was then followed, except that the final stage resulted in difficulties in the crystallisation and up to four crops had to isolated.

Changing the solvent for crystallisation to a mixture of ethyl acetate and isopropyl ether allowed isolation as two crops. From crystallisation residues, further quantities of Feist's acid could be recovered as its di-methyl ester by treatment with methanol and concentrated sulphuric acid. All these modifications, resulted in a considerable improvement in time, cost and yield of Feist's acid.

The next problem was conversion of Feist's acid, which is a 1,2-*trans*-dicarboxylic acid, into the anhydride (**161**) of *cis*-dicarboxylic acid.



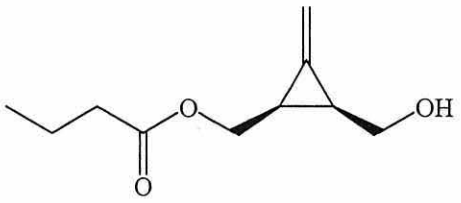
(161)

This had been prepared in 1957 by refluxing Feist's acid in acetic anhydride in the presence of potassium acetate and isolating it by vacuum distillation. A later publication reported a warning of caution, that sometimes there was possibility of ignition of the tarry residues from distillation. Initial experiments illustrated the difficulty in isolation by vacuum distillation. A method was developed in which the anhydride was co-distilled with a high boiling petroleum ether fraction at 220 °C. The anhydride was almost insoluble in the petroleum ether at room temperature and any residue of the high boiling petroleum ether was easily removed by washing with petroleum ether b.p. 40 – 60 °C.

The anhydride was readily reduced to the *cis*-1,2-dihydroxymethyl compound (**162**).

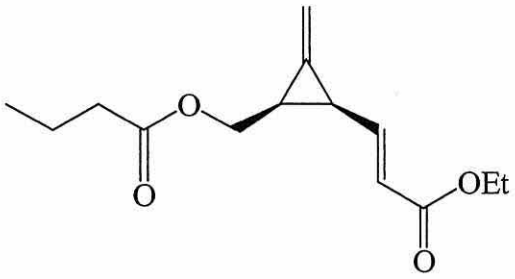
(162)

The successful desymmetrization to a single optically pure mono-butyrate (**164**) by lipase transesterification with either vinyl butyrate or 2,2,2-trifluoroethyl butyrate was confirmed by chiral g.l.c.

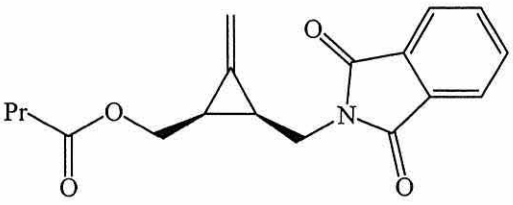


(164)

The optically pure mono-butyrate (**164**) was converted, by standard reactions, into a number of derivatives, e.g. by oxidation to the aldehyde followed by various Wittig reactions, eg. to give (**169**) and Mitsunobu reaction with phthalimide to give an amide (**172**). The resulting compounds may eventually be useful in natural product synthesis.



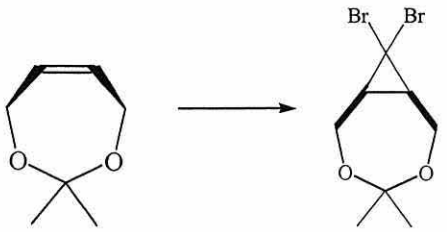
(169)



(172)

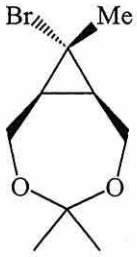
Because of the lengthy process of preparing the *cis*-anhydride (**161**), which is the key intermediate in preparing optically pure mono-butyrate (**164**), an alternative synthesis was investigated based on Z-2-butene-1,4-diol.

The *gem*-dibromocyclopropane intermediate (**188**) was successfully prepared in high yield by careful control of the conditions for the addition of dibromocarbene to the double bond (**187**) derived by protection of the diol as the acetonide.

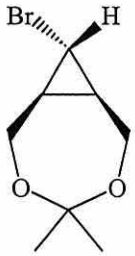


(187) (188)

The replacement of one bromine in (**188**) using either methyl or butyl lithium, allowed the preparation of both (**196**) and (**189**), the first by treatment with methyl lithium and aqueous methanol, the second treatment with butyl lithium and methyl iodide.

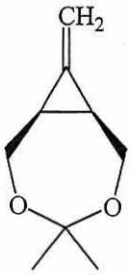


(189)



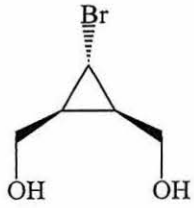
(196)

Many experiments were carried out to obtain the right conditions to prepare (**189**) but unfortunately the conditions were extreme, involving the use of HMPA and a temperature of – 90 °C. Elimination of HBr from (**189**) with potassium *t*-butoxide gave the desired methylenecyclopropane (**190**). This reaction still needs to be scaled up, but the hydrolysis of the acetonide did produce the corresponding diol (**162**).

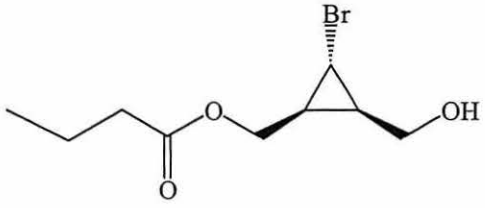


(190)

A larger scale preparation of (**196**) was carried out, and it was hydrolysed to the bis-hydroxy methyl compound (**197**).



(197)



(198)

This compound was subjected to lipase catalysed esterification and yielded a mono-butyrate (**198**) that appeared to be mainly one enantiomer by chiral g.l.c. This again was reacted further to prepare various compounds, such as vinyl substituted and amino derivatives. Thus in this work we have successfully developed routes to a range of tri-substituted cyclopropanes as single enantiomers.

Chapter Four

Experiments

General Experimental Details

6.1 Instrumentation

All ^{1}H-NMR data were obtained from Bruker AC 250 MH_Z CP/MAS NMR or Bruker AVANCE 500 MH_Z spectrometers. The ^{13}C-NMR spectra were recorded using Bruker AC 250. The mass spectra were obtained using either an AEI MS9, a Kratos MS 80 RF or Finnigan Mat 1020 spectrometer. Microanalyses were performed with a Carlo-Erba Model 1106 CHN. The infrared spectra were obtained as KBr discs (solids) or as liquid films using NaCl plates on a Perkin Elmer 1600 FTIR as liquid films.

6.3 Reagents.

All reagents were obtained commercially from *Aldrich Chemical Company* or *Lancaster Synthesis Limited* and used without further purification unless otherwise stated.

6.2 Solvents.

Solvents were purified when necessary using the method suggested in "The purification of Laboratory Chemicals" by D. D. Perrin, W. L. F. Armarego and D. R. Perrin. In particular: Dry dichloromethane was distilled from calcium hydride. Dry diethyl ether was distilled from sodium benzophenone. Tetrahydrofuran was distilled over sodium wire. Dry dimethylformamide and dimethylsulphoxide were obtained from *Aldrich Chemical Company* and stored under argon.

6.4 Chromatography.

G. L. C was conducted using a Perkin-Elmer Model (F17) F.I.D. on a capillary column (30 × 0.32 mm id Phase, DB5 split ratio of 50:1); the carrier gas was hydrogen (30 ml min^{-1}) and the quantity injected was 5 μl of a 5% solution. Alternatively a Carlo Elba machine was used with a capillary column, length 15 metre and width 0.53 mm (80 °C, 1 minute, 20 °C per minute to 200 °C, 2 minutes, 30 °C per minute to 230 °C). 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 gas; the instrument was fitted with a Perkin Elmer flame ionisation detector. T. L. C. plates: Glass-precoated, Silica Gel 60 (F 254), layer thickness 0.25 mm.

6.5 Miscellaneous.

All NMR spectra were obtained from solution in $CDCl_3$ unless stated otherwise. Reactions requiring anhydrous conditions were performed using oven dried glassware (250 °C) that was cooled under nitrogen, and were carried out under a positive stream of nitrogen or argon. All reactions were carried out under dry nitrogen, unless stated. All yields are for the purified compounds unless otherwise stated. Solids were purified by recrystallisation or chromatography while oils were purified by chromatography or distillation. All new compounds were homogeneous by thin layer chromatography or by gas liquid chromatography.

Reaction mixtures were stirred by Teflon-coated magnetic stirring bars. Organic solutions were dried using magnesium sulphate and products were isolated from solution by evaporation under water-aspirator vacuum using a Buchi rotary evaporator. The solvents were removed using high vacuum (ca 0.5 mmHg). Crystalline compounds were dried in a dessicator under vacuum (ca 0.5 mmHg). Reactions were carried out at room temperature unless otherwise stated.

If a similar reaction was repeated using a different starting material than described in the method, the data is listed below the standard experimental procedure.

EXPERIMENT: 1

Preparation of 1,2,5,6-di-O-isopropylidene-D-mannitol (55).

Anhydrous zinc chloride (98.7 g, 0.72 mol) was dissolved in dry acetone (600 ml) at room temperature. D-Mannitol (60 g, 0.32 mol) was added and stirred with a mechanical stirrer for 18 h. Aqueous potassium carbonate (100 g) in water (100 ml) was then added and a white precipitate was observed. The precipitate was filtered on a sinter and washed with dichloromethane (300 ml); the filtrate was concentrated under vacuum to yield a white solid, which was extracted into dichloromethane (200 ml). The organic layer was then washed with water (150 ml), brine (130 ml) and dried over anhydrous magnesium sulphate (25 g). The solvent was evaporated under reduced pressure to give a crude product as a solid, which was then re-crystallised, from ethyl acetate and petrol (40-60) to give (1S,2S)-1,2-bis-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)ethane-1,2-diol (mp 122-123 °C) (*lit* 122-123°C),[92] (71.6 g 83 %), δ_H: 4.15 (4 H, m), 4.0 (2 H, m), 3.7 (2 H, t, J 6.4 Hz), 2.55 (2 H, br s), 1.45 (6H, s), 1.35 (6H, s); ν_{MAX}: 3300, 2920, 1455, 1372, 1215 cm^{-1}.

EXPERIMENT: 2

Preparation of 2,3-O-isopropylidene-D-glyceraldehyde (56)

Sodium (meta) periodate (32.6 g, 0.15 mol) was added to a stirred solution of (1S,2S)-1,2-bis-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)ethane-1,2-diol (20 g, 0.076 mol) in dichloromethane (200 ml) at 25 °C, followed by the addition of distilled water (3 ml). The mixture was stirred for 2 h at room temperature and anhydrous magnesium sulphate (20 g) was added; and stirring was continued for a further 15 min. The precipitate was filtered and washed with dichloromethane (2 × 30 ml). The filtrate was evaporated at 14 mm Hg to give (R)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (29.8 g, 98 %)[100] which showed δ_H: 9.7 (1 H, d, J 1.85 Hz), 4.45 (1 H, dt, 1.85, 7.2 Hz), 4.05-4.15 (2 H, m), 1.45 (3 H, s), 1.4 (3 H, s); δ_C: 202.0, 111.35, 79.9, 65.6, 30.9, 26.3, 25.2; ν_{MAX}: 3438, 2987, 2936, 1734, 1457, 1374 cm^{-1}.

EXPERIMENT: 3

Preparation of (Z)-3-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)acrylic acid ethyl ester (57) and (E)-3-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)acrylic acid ethyl ester (58).

Method A

Carboethoxymethylenetriphenylphosphorane (25 g, 0.071 mol) was added to a stirred solution of 2,3-O-isopropylidene-D-glyceraldehyde (10 g, 0.076 mol) in toluene (25 ml) at room temperature. The mixture was refluxed for 3 h, when T.L.C showed no starting material was left. The organic solvent was evaporated and the residue was columned on silica eluting with petroleum ether / ether (5: 2) to give (E)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)acrylic acid ethyl ester (11.5 g, 75 % yield)[108][107] as the major isomer, which showed δ_H: 6.9 (1 H, dd, J 15.6, 5.6 Hz), 6.1 (1 H, dd, J 15.6, 1.4 Hz), 4.7 (1 H, brq, J 7.0 Hz), 4.2 (3 H, m, including a quartet with coupling constant 7.1 H_Z), 3.7 (1 H, dd, J 7.1, 8.2 Hz); 1.42 (3 H, s), 1.40 (3 H, s), 1.32 (3 H, t, J 7.1 H_Z); δ_C: 167.5, 133.7, 128, 109.2, 76.4, 69.3, 62.3, 30.9, 26.3, 25.8, 23.9; ν_{max}: 2981, 1735, 1373, 1266 cm^{-1}; $(\alpha)_D$ +38° in $CHCl_3$ (*lit* $(\alpha)_D$ +41°).[101] The second isomer was (Z)-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester (4.5 g, 29 %) as a minor isomer, which showed: δ_H: 6.38 (1 H, dd, J 11.5, 6.5 H_Z), 5.85 (1 H, d, J 11.5 H_Z), 5.51 (1 H, m), 4.38 (1 H, dd, J 8.2, 7.1 H_Z), 4.18 (2 H, br q, J 7.1 H_Z), 3.7 (1 H, dd, J 8.2, 6.9 H_Z), 1.44 (3 H, s), 1.37 (3 H, s), 1.28 (3 H, t, J 7.1 H_Z); δ_C: 166.2, 134.5, 123.9, 109.7, 76.4, 64.4, 62.5, 31.8, 25.8, 14.6; ν_{MAX}: 2931, 1720, 1440, 1373, 1266 cm^{-1}, $(\alpha)_D$ +118° in $CHCl_3$ (*lit* $(\alpha)_D$ +123°).[107]

Method B

(R)-2,2-Dimethyl[1,3]dioxolane-4-carbaldehyde (20 g, 0.15 mol) in toluene (25 ml) was added to a stirred solution of carboethoxymethylenetriphenylphosphorane (58.8 g, 0.16 mol) in toluene (250 ml) at room temperature. The reaction mixture was stirred for 16 h, at room temperature, when t.l.c. showed no starting material was left. The organic solvent was evaporated, to a give a thick oil, which was treated with petroleum ether (b.p 40 – 60 ° C) (100 ml) / ether (40 ml). The precipitate was filtered off; evaporation of the solvent gave a brown oil (26.3 g, 87 %) which was a mixture of *trans* and *cis* alkenes in the same ratio (5 : 2) as above (method A).

Method C

Carboethoxymethylenetriphenylphosphorane (96 g, 0.28 mol), was added to a stirred solution of (R)-2,2-dimethyl[1,3]dioxolane-4-carbaldehyde (35.5 g, 0.27 mol) in methanol (250 ml), at 0 °C over 1 h. The mixture was stirred in 0 °C for 1 h, then the solvent was evaporated and the residue was refluxed for 30 min with a mixture of petroleum (b.p 40 – 60 ° C) / ether (3 : 7). The process was repeated 3 times and the combined solution concentrated to yield a colourless oil which was separated into two isomers by column chromatography on silica gel eluting with petroleum (b.p 40 – 60 ° C) / ether (5 : 2), giving *trans* and *cis* alkenes (5 : 4) (39 g, 76 %).

EXPERIMENT: 4

Preparation of (Z)-3-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)prop-2-en-1-ol (59)

Di-isobutyl aluminium hydride (25 ml, 1M solution in hexane) was added to a stirred solution of (Z)-4-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)but-3-enoic acid ethyl ester (2 g, 10 mmol) in dry dichloromethane (25 ml) at – 40 °C under nitrogen. The mixture was allowed to reach room temperature and stirred for 30 min, when T.L.C showed no starting material was left. The mixture was quenched with sat. aq. ammonium chloride (4 ml) at –40 °C and allowed to reach room temperature, followed by the addition of dilute hydrochloric acid (10 ml, 2 M) until a clear solution was obtained. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 15ml). The combined organic layers were dried, and evaporated to give a pale yellow oil, which was purified by column chromatography on silica eluting with petroleum ether (b.p 40 – 60° C) / ethyl acetate (5 : 2) to give (Z)-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)prop-2-en-1-ol (1.37 g, 86 %)[102] which showed: δ_H: 5.91-5.70 (1 H, m), 5.64-5.51(1 H, m), 4.91 (1 H, br q, J 7.9 H_Z), 4.31-4.16 (1 H, m), 4.13 (2 H, dd, J 4.8, 1.6 H_Z), 3.65 (1 H, m), 3.14 (1 H, br s), 1.45 (3 H, s), 1.41 (3 H, s); δ_C: 133.4, 129.5, 109.6, 71.8, 69.4, 58.7, 26.6, 25.9; ν_{MAX}: 3408, 2987, 1374, 1223 cm^{-1}.

EXPERIMENT: 5

Preparation of (E)-3-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)prop-2-en-1-ol (60).

Di-isobutyl aluminium hydride (41.2 ml, 2 eq, 1M solution in hexane) was added to a stirred solution of (E)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)acrylic acid ethyl ester (4.12 g, 0.02 mol), in dry dichloromethane (25 ml) at –40 °C under nitrogen. The mixture was allowed to reach room temperature and stirred for 30 min, when T.L.C showed no starting material was left, and then quenched with sat. aq. ammonium chloride (6 ml) at – 40 °C, followed by hydrochloric acid (4 %, 10 ml). The cooling was removed, and the organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 100 ml). The combined organic layers were dried and evaporated to give (E)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)prop-2-en-1-ol (2 g, 64 %),[102] which showed δ_H: 5.96 (1 H, dt, J 15.5, 5.0 H_Z), 5.7 (1 H, ddt, J 15.5, 7.4, 1.4 H_Z), 4.57 (1 H, br q, J 7.2 H_Z), 4.18 (2 H, dd, J 5.0, 1.4 H_Z), 4.1 (1 H, dd, J 6.2, 8.0 H_Z), 3.6 (1 H, t, J 8.0 H_Z), 2.1 (1 H, br, s), 1.4 (3 H, s), 1.38 (3 H, s); δ_C: 144.6, 122.4, 110.1, 74.9, 68.7, 60.5, 26.4, 25.7; ν_{MAX}: 3410, 3015 cm^{-1}.

EXPERIMENT: 6

Preparation of *tert*-Butyl[(Z)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)-allyloxy]diphenylsilane (61)

tert-Butyldiphenylsilylchloride (9.15 g, 33.2 mmol) was added to a stirred solution of (Z)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)prop-2-en-1-ol (9.14 g, 57.8 mmol) in dichloromethane (140 ml) and triethylamine (11.4 ml) at 0 °C under nitrogen followed by the addition of 4-dimethylaminopyridine (≈ 10 mg). The mixture was stirred for 2 h, when t.l.c. showed no starting material was left. The reaction was quenched with (10 ml) water and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic layers were dried and evaporated to give a brown oil, which was purified by column chromatography on silica eluting with petroleum (b.p 40 – 60° C) / ether (5 : 1) to give *tert*-butyl[(Z)-3-((S)-2,2-dimethyl-

[1,3]dioxolan-4-yl)allyloxy]diphenylsilane (13.7 g, 86 %),[(α) = +3.7, c = 1.25, $CHHCl_3$), *lit* (α) = +3.9, c = 1.12], [103] which showed δ_H: 7.69 (2 H, m), 7.66 (2 H, m), 7.42 (6 H, br m), 5.92 (1 H, m), 5.5 (1 H, m), 4.64 (1 H, br q, J 7.0 H_Z), 4.35 (1 H, ddd, J 13.4, 6.1, 1.5 H_Z), 4.25 (1 H, ddd, 1.5, 2.4, 6.1 H_Z), 3.9 (1 H, dd, J 8.0, 6.1 H_Z), 3.54 (1 H, t, J 8.0 H_Z), 1.39 (3 H, s), 1.32 (3 H, s), 1.05 (9 H, s); δ_C: 135.7, 135.2, 133.5, 131.4, 128.3,127.8, 109.2, 72.2, 69.5, 59.6, 54.1, 26.8, 25.7, 25.5, 20.3; ν_{MAX}: 3021, 2924, 1477, 1365, 1261 cm^{-1}.

EXPERIMENT: 7

Preparation of *tert*-Butyl-[(E)-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-allyloxy]diphenylsilane (62).

tert-Butyldiphenylsilyl chloride (2.28 g, 8.3 mmol) in dry dimethylformamide (18 ml) was added to a stirred solution of (E)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)prop-2-en-1-ol (1.7 g, 0.01 mol) and imidazole (2.1 g, 0.03 mol) in dry dimethylformamide (20 ml) under nitrogen at 0 °C. When t.l.c showed no starting material was left, the reaction was quenched with water (40 ml) and the product extracted with diethyl ether (3 × 75 ml). The combined organic layers were evaporated to give a crude product which was purified on silica eluting with petroleum (b.p 40 – 60 °C) / ether (1 : 1) to give *tert*-butyl[(E)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)allyloxy]diphenylsilane (2.9 g, 85 %)[103] which showed δ_H: 7.69 (2 H, m), 7.66 (2 H, m), 7.41 (6 H, m), 5.95 (1 H, dt, J 3.97, 15.5 H_Z), 5.72 (1 H, br dd, J 5.8, 15.5 H_Z), 4.57 (1 H, br q, J 7.0 H_Z), 4.23 (2 H, br d, J 3.9 H_Z), 4.10 (1 H, dd, J 8.2, 6.1 H_Z), 3.6 (1 H, br t, J 7.9 H_Z), 1.44 (3 H, s), 1.41 (3 H, s), 1.07 (9 H, s); δ_C: 135.6, 133.6, 131.0, 130.0, 128.4, 127.4, 109.3, 69.4, 62.6, 60.5, 31.4, 25.9, 25.6, 20.1; ν_{MAX}: 3015, 2953, 1471, 1370, 1254 cm^{-1}.

EXPERIMENT: 8

Preparation of *tert*-Butyl[(1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropylmethoxy]diphenylsilane (63)

Diethyl zinc (220 ml, 1M solution in hexane) and diiodomethane (118 g, 0.44 mol) were added dropwise to a stirred solution of *tert*-butyl[(Z)-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)allyloxy]diphenylsilane (12 g, 0.03 mol) in dry dichloromethane (150 ml) at – 23 °C under nitrogen. The mixture was stirred for 10 h maintaining the temperature at –23 to – 10 °C followed by quenching with ammonium chloride solution (24 ml) and the organic layer was separated, then the aqueous layer was extracted with dichloromethane (2 × 75 ml). The combined organic layers were washed with brine solution, dried, and evaporated to give a brown oil which was columned on silica eluting with petroleum (b.p 40 – 60° C) / ether (5 : 1) to give *tert*-butyl[(1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropylmethoxy]diphenylsilane (11.1 g, 88 %),[104] which showed δ_H: 7.6 (4 H, br m), 7.4 (6 H, br m), 4.23 (1 H, m), 3.94 (1 H, dd, J 11.3, 5.5 H_Z), 3.8-3.67 (2 H, m), 3.42 (1 H, br dd, J 11.3, 9.1 H_Z), 1.47 (3 H, s), 1.37 (3 H, s), 1.07 (11 H, br s, including t-butyl group and cyclopropane protons), 0.89 (1 H, m), 0.39 (1 H, q, J 5.5 H_Z); δ_C: 137, 136.9, 135.11, 131.18, 129.19, 129.16, 110.07, 79.02, 71.65, 65.66, 60.4, 56.04, 27.2, 24.1, 20.66, 19.84, 19.02, 15.81, 9.66; ν_{MAX}: 2987, 2867, 2734, 1462, 1371 cm^{-1}.

EXPERIMENT: 9

Preparation of *tert*-Butyl-[(1R,2R)-2-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-cyclopropylmethoxy]diphenylsilane (64)

Diethyl zinc (86 ml, 1M) was added dropwise to a stirred solution of *tert*-butyl[(E)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)allyloxy]diphenylsilane (4.73 g, 2.52 mmol) in dry dichloromethane (50 ml) under nitrogen at –30 °C, followed by the addition of diiodomethane (45.56 g, 0.17 mol) and then the solution was stirred for 10 h at –23 to 10 °C. Then the reaction was quenched with ammonium chloride solution (30 ml); the organic layer was separated then the aqueous layer was extracted with dichloromethane (2 × 30 ml). The combined organic layers were washed with water (30 ml), dried, and evaporated to give a brown oil which was columned on silica eluting with petroleum ether / ether (5 : 1) to give *tert*-butyl[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropylmethoxy]diphenylsilane (4 g, 81 %)[104] which showed δ_H: 7.67 (2 H, m),

7.64 (2 H, m), 7.41 (6 H, m), 4.06 (1 H, dd, J 8.2, 6.1 H_Z), 3.73 (1 H, dd, J 5.2, 7.3 H_Z), 3.68 (1 H, d, 7.3 H_Z), 3.5 (1 H, dd, J 6.1, 14.0 H_Z), 3.38 (1 H, dd, J 7.3, 10.6 H_Z), 1.44 (3 H, s), 1.35, (3 H, s), 8-1.1 (11 H, br s, including t-butyl group and cyclopropane protons), 0.8 (1 H, m), 0.54 (1 H, m); δ_C: 135.4, 133.7, 129.62, 127.6, 108.88, 79.94, 69.33, 27.26, 26.8, 25.7, 19.1, 18.84, 17.6, 7.9; ν_{MAX}: 837 cm^{-1}.

EXPERIMENT: 10

Preparation of [(1S,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]-methanol (65)

Tetrabutylammonium fluoride (TBAF) (19.7 ml, 1M solution in THF) was added to a stirred solution of *tert*-butyl[(1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropylmethoxy]dimethylsilane (4.71 g, 16.4 mmol) in dry tetrahydrofuran (75 ml) at room temperature under nitrogen. The mixture was stirred for 12 h, when t.l.c showed no starting material was left. The reaction was quenched with ammonium chloride solution (10 ml) and diluted with ethyl acetate (15 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 30 ml). The combined organic layers were dried and evaporated, to give a residue which was purified by column chromatography on silica eluting with petroleum (b.p 40 – 60° C) / ethyl acetate (5 : 2) to give [(1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]methanol (1.95 g, 78 %)[167] (Found (M - H^+): 171.1023; $C_9H_{15}O_3$ requires: 171.1021) as a light yellow oil, which showed, δ_H: 4.1 (1 H, dd, J 7.8, 5.9 H_Z), 3.95 (2 H, m), 3.72 (1 H, t, J 7.8 H_Z), 3.42 (1 H, dd, J 8.5, 11.3 H_Z), 1.65 (1 H, br s), 1.46 (3 H, s), 1.34 (3 H, s), 1.23 (1 H, m), 1.05 (1 H, dq, 5.5, 8.2 H_Z), 0.9 (1 H, m), 0.53 (1 H, q, J 5.2 H_Z); δ_C: 109.5, 79.03, 71.38, 64.24, 28.26, 19.49, 19.1,15.53, 9.8; ν_{MAX}: 3428, 2994, 2928, 1226, 913 cm^{-1}; $[\alpha]^{22}_D$ = - 19.20 (c = 1.24, $CHCl_3$).

EXPERIMENT: 11

[(1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol (66)

Tetrabutylammonium fluoride (TBAF) (19.7 ml, 1M) was added to a solution of *tert*-butyl-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropylmethoxy]diphenyl-silane (4.5 g, 0.011 mol) in dry tetrahydrofuran under nitrogen and stirred at room temperature for 12 h, when T.L.C showed no starting material was left. The reaction was quenched with ammonium chloride solution (20 ml) and diluted with ethyl acetate (20 ml). The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (2 × 30 ml). The combined organic layers were dried, and evaporated, to give [(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol (2.2 g, 78 %) (Found ($M + NH_4^+$): 190.1449; $C_9H_{20}NO_3$ requires: 190.1443) as a light yellow oil, which showed δ_H: 4.0 (1 H, dd, J 5.5, 7.3 H_Z), 3.6 (1 H, br, t, J 7.3 H_Z), 3.5 (1 H, J 5.5, 7.3 H_Z), 3.4 (1 H, 6.7, 11.1 H_Z), 3.3 (1 H, 6.7, 11.1 H_Z), 2.8 (1 H, br, s), 1.34 (3 H, s), 1.24 (3 H, s), 0.92 (1 H, m), 0.78 (1 H, m), 0.57 (1 H, dt, J 5.0, 8.5 H_Z), 0.47 (1 H, dt, J 5.0, 8.3 H_Z); δ_C: 108.95, 79.1, 69.2, 65.9, 26.8, 25.7, 19.7, 17.8, 8.0; ν_{MAX}: 3377, 2985 cm^{-1}; $(\alpha)^{22}_D$ = - 16.2 (c = 0.995, $CHCl_3$).

EXPERIMENT: 12

Preparation of (1S,2R)-2-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-cyclopropanecarbaldehyde (67)

[(1S,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol (1.5 g, 8.7 mmol) in dichloromethane (5 ml) was added to a suspension of pyridinium chlorochromate (3.75 g, 17.4 mmol) in dichloromethane (20 ml) at room temperature. The reaction was stirred for 3 h, when t.l.c. showed no starting material was left, then diluted with ether (10 ml) and filtered through a pad of silica gel and celite. The filtrate was then evaporated to give (1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl) cyclopropanecarbaldehyde (1.4 g, 93 %)[168] (Found ($M - H^+$): 169.0854; $C_9H_{13}O_3$ requires: 169.0865), which showed, δ_H: 9.41 (1 H, d, J 5.1 H_Z), 4.12 (1 H, dt, J 6.1, 7.1 H_Z), 3.98 (1 H, dd, J 7.9, 6.1 H_Z), 3.66 (1 H, dd, J 7.9, 7.1 H_Z), 1.97 (2 H, m), 1.56 (1 H, br m), 1.48 (1 H, br m), 1.42 (3 H, s), 1.36 (3 H, s); δ_C: 200.0, 102.3, 69.9, 63.2, 19.4, 18.5, 16.6, 9.5, 6.5; ν_{MAX}: 2988, 2932, 1695, 1218, 907 cm^{-1}; $[\alpha]^{22}_D$ = + 36.05 (c = 1.19, $CHCl_3$).

EXPERIMENT: 13

Preparation of (1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropanecarbaldehyde (68)

[(1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol (2 g, 0.024 mol) in dichloromethane (5 ml) was added to a suspension of pyridium chlorochromate (5 g, 0.023 mmol) in dichloromethane (45 ml) at room temperature The reaction was stirred for 3 h, when T.L.C showed no starting material was left, then diluted with ether and filtered through silica gel on a sintered funnel. The organic solvent was evaporated at 14 mmHg to give *(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropane carbaldehyde* (1.6 g, 84 %) (Found (M + NH_4^+): 188.1287; $C_9H_{18}NO_3$ require: 188.1287), which showed δ_H: 9.1 (1 H, d, J 5.0 H_Z), 4.1 (1 H, dd, J 5.8, 7.7 Hz), 3.8 (1 H, br q, J 6.7 H_Z), 3.65 (1 H, dd, J 6.7, 7.7 H_Z), 1.85 (1 H, m), 1.66 (1 H, m), 1.41 (3 H, s), 1.32 (3 H, s), 1.2 (2 H, m); δ_C: 199.0, 102.3, 69.8, 66.1, 18.4, 17.7, 9.5, 7.5; ν_{MAX}: 1709 cm^{-1}; $(\alpha)^{24}_D$ = - 66 (c = 1.33, $CHCl_3$).

EXPERIMENT: 14

Preparation of (E)-3-[(1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid ethyl ester (69)

(1S,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropanecarbaldehyde (3.2 g, 18.8 mmol) was added to a stirred solution of carboethoxymethylene triphenyl phosphorane (7.8 g, 22 mmol) in toluene (50 ml) at room temperature. The reaction mixture was stirred for 16 h at room temperature, when t.l.c showed no starting material was left. The solvent was evaporated to give a thick oil. This was treated with petroleum (b.p 40 – 60 °C) (50 ml) and ether (20 ml). The precipitate was filtered off; evaporation of the solvent gave a brown oil which was purified by column chromatography eluting with petroleum / ether (5 : 2) to give a major isomer *(E)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid ethyl ester* (2.1 g, 71 %) as an

oil (Found: C: 64.9, H: 8.4 Calculated for $C_{13}H_{20}O_4$ C: 64.98, H: 8.39) $[\alpha]^{22}_D$ = -22.76; (c = 1.05, $CHCl_3$), which showed δ_H: 6.6 (1 H, dd, J 10.3, 15.2 H_Z), 5.9 (1 H, d, J 15.2 H_Z), 4.1 (2 H, q, J 6.7 H_Z), 4.0 (1 H, br t, J 7.9 H_Z), 3.7 (1 H, br q, J 7.6 H_Z), 3.6 (1 H, br t, J 7.6 H_Z), 1.7 (2 H, br, m), 1.3 (3 H, s), 1.28 (3 H, s), 1.1 (4 H,br t, including one cyclopropane proton, J 6.7 H_Z), 0.93 (1H, br m); δ_C: 167.55, 150.0, 122.8, 110.5, 78.0, 70.4, 61.1, 30.4, 27.1, 25.8, 20.0, 15.6, 15.0; ν_{MAX}: 2984, 2936, 2871, 1715, 1644 cm^{-1}.

EXPERIMENT: 15

Preparation of (E)-3-[(1S,2R)-2-((R)-2,2-Dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]acrylic acid ethyl ester (70)

(1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropanecarbaldehyde (1.5 g, 8.82 mmol) was added to a stirred solution of carboethoxymethylene triphenyl phosphorane (3.6 g, 10.33 mmol) in toluene (25 ml) at room temperature. The reaction mixture was stirred for 16 h at room temperature. When TLC showed no starting material was left, the solvent was evaporated to give a thick oil. This was treated with petroleum (bp 40 – 60 °C) (50 ml) and ether (20 ml). The precipitate was filtered off; evaporation of the solvent gave a brown oil which was purified by column chromatography eluting with petroleum / ether (5 : 2) to give as the major isomer *(E)-3-[(1S,2R)-2-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid ethyl ester* (1.6 g, 76 %) (Found: C 64.8, H 8.4. Calculated for $C_{13}H_{20}O_4$: C 64.98, H 8.39) as an oil which showed δ_H: 6.7 (1 H, dd, J 15.5, 5.5 H_Z), 5.8 (1 H, d, J 15.5 H_Z), 4.16 (2 H, q, J 7.3 H_Z), 3.85 (1 H, t, J 7.3 H_Z), 3.7 (1 H, q, J 8.2 H_Z), 3.5 (1 H, t, J 7.3 H_Z), 1.78 (2 H, br m), 1.5 (3 H, s), 1.48 (3 H, s), 1.18 (4 H, br t, including one cyclopropane proton, J 7.3 H_Z), 0.8 (2 H, br m); δ_C: 167.86, 152.82, 121.38, 110.54, 79.1, 70.47, 61.5, 28.06, 27.03, 26.06, 19.7, 15.02, 14.28; ν_{MAX}: 2983, 2935, 2873, 1715, 1645 cm^{-1}.

EXPERIMENT: 16

Preparation of 3-[(1S,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]-butyric acid ethyl ester (71) (72)

Methyl magnesium bromide (6 ml 3.0 M in diethyl ether) was added dropwise to a suspension of cuprous bromide (1.29 g, 8.99 mmol) in dry tetrahydrofuran (15 ml) at –40 °C under nitrogen. The resulting yellow green mixture was stirred for 10 min, then a solution of (E)-3-[(1S,2R)-2-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid ethyl ester (1.44 g, 6.0 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. At the end of the addition the mixture was warmed to –15 °C over 15 min, when G.L.C, showed all the starting material had reacted. The mixture was cooled to –40 °C and quenched with sat.aq. ammonium chloride (7 ml). The organic solvent was evaporated and the residue was treated with water (10 ml) and ethyl acetate (30 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic layers were washed with 10 % aqueous ammonium hydroxide (2 × 30 ml) and brine (50 ml), dried and evaporated to give a crude product. This was purified by column chromatography eluting with petroleum / ether (7: 3) to yield two isomers (1 : 1) which were hard to separate of *3-[(1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyric acid ethyl ester* (0.55 g, 35 %) which showed δ_H: 4.09 (3 H, m), 3.68 (1 H, br q, J 7.6 H_Z), 3.46 (1 H, br q, J 7.3 H_Z), 2.37 (1 H, m), 2.11 (1 H, dd, J 6.7, 14.6 H_Z), 1.42 (3 H, s), 1.33 (4 H, br s, including one cyclopropane proton), 1.25 (3 H, br t, J 7.0 H_Z), the signals for other isomer overlapped these except for the methyl doublet, which occurred at δ 1.25 in state at δ 1.01, 1.01 (3 H, m), 0.78 (1 H, br m), 0.54 (2 H, br m); δ_C: for two isomers 172.7, 172.6, 108.91, 108.76, 79.95, 79.8, 69.26, 69.15, 60.21, 41.76, 41.71, 34.87, 34.78, 26.77, 25.71, 25.68, 22.2, 22.1, 20.25, 19.91, 19.77, 19.57, 14.2, 9.78, 9.17; ν_{MAX}: 2984, 2873, 1715, 1456, 1369, 1062 cm^{-1}.

EXPERIMENT: 17

Preparation of 3-[(1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyric acid ethyl ester (76)

Methyl magnesium bromide (3.6 ml 3.0 M in diethylether) was added dropwise to a suspension of cuprous bromide (0.78 g, 5.4 mmol) in dry tetrahydrofuran (10 ml) at – 40 °C under nitrogen. The resulting yellow green mixture was stirred for 10 min, then a solution of (E)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid ethyl ester (0.88 g, 3.6 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. At the end of the addition the mixture was warmed to –15 °C over 15 min, when g.l.c. showed all the starting material had reacted. The mixture was cooled to –40 °C and quenched with sat. aq. ammonium chloride (5 ml). The organic solvent was evaporated and the residue was treated with water (10 ml) and ethyl acetate (30 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic layers were washed with 10 % aq. ammonium hydroxide (2 × 25 ml) and brine (30 ml), dried and evaporated to give a crude product. This was purified by column chromatography eluting with petroleum / ether (7 : 3) to yield *3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyric acid ethyl ester* (0.3 g, 33 %) (Found M^+ : 256.168. Calculated for $C_{14}H_{24}O_4$: 256.170) which showed δ_H: 4.11 (2 H, m, including quartet, J 7.3 H_Z), 3.74 (1H, dt, J 6.1, 7.6 H_Z), 3.65 (1 H, br t, J 7.6 H_Z), 2.27 (1 H, dd, J 3.9, 14.6 H_Z), 2.13 (1H, dd, J 9.45, 14.6 H_Z), 1.55 (1 H, br, m), 1.39 (3 H, s), 1.31 (3 H, s), 1.21 (3 H, t, J 7.3 H_Z), 1.03 (3 H, d, J 6.7 H_Z), 0.94 (1 H, m), 0.8 (1 H, m), 0.74 (1 H, m), 0.32 (1 H, q, J 4.8 H_Z); δ_C: 173.79, 109.8, 79.08, 71.33, 61.61, 43.36, 32.56, 24.43, 22.36, 20.67, 20.14, 17.58, 15.62, 10.64; $\nu_{max.}$ 2934, 1735, 1456, 1369, 1033 cm^{-1}; $[\alpha]^{22}_D = +8.5$ (c = 1.52, $CHCl_3$).

EXPERIMENT: 18

Preparation of 3-[(1R,2R)-2-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]-butan-1-ol (77)

Di-isobutyl aluminium hydride (2.5 ml, 1M solution in hexane) was added to a stirred solution of 3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyric acid ethyl ester (0.25 g, 0.9 mmol) in dry dichloromethane (15 ml) at – 78 °C under

nitrogen. The mixture was allowed to reach room temperature for 2 h, when t.l.c showed no starting material was left, then quenched with methanol (1 ml) at – 40 °C. The cooling was removed and the mixture was allowed to reach room temperature followed by the addition of hydrochloric acid (0.5 ml, 2 M). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 10 ml). The organic layers were washed with brine solution, dried and evaporated. The residue was purified by column chromatography eluting with petroleum / ethyl acetate (5 : 3) to give a yellow oil, *3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol* (0.17 g, 85 %) (Found (M^+ - CH_3): 199.1344; $C_{11}H_{19}O_3$ requires: 199.1334); $[\alpha]^{23}_D$ = -10.98 (c= 1.02, $CHCl_3$) which showed δ_H: 4.12 (1 H, dd, 7.6, 5.7 H_Z), 3.82 (1 H, dt, J 6.0, 7.9 H_Z), 3.74 (1 H, m), 3.71 (1 H, t, J 7.9 H_Z), 3.64 (1 H, br m), 2.0 (1 H, br s), 1.65 (1 H, br m), 1.54 (1 H, br, m), 1.4 (3 H, s), 1.32 (3 H, s), 1.25 (1 H, br, m), 1.0 (3 H, d, J 6.4 H_Z), 0.9-0.6 (3 H, m), 0.23 (1 H, q, J 5.1 H_Z); δ_C: 108.38, 77.57, 71.88, 60.04, 40.15, 30.84, 26.71, 25.67, 24.29, 20.95, 14.1, 7.17; ν_{MAX}: 3418, 2986, 1456, 1371, 1214 cm^{-1}.

EXPERIMENT: 19

Preparation of *tert*-Butyl{3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (78)

To a solution of 3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol (0.13 g, 0.6 mmol) in dry dichloromethane (10 ml), under argon at 0 °C, was added triethylamine (0.12 ml, 0.08 mol). After stirring for 10 min. tert-butyl diphenylsilylchloride (0.17 g, 0.61 mmol) was added, followed by the addition of 4-dimethylaminopyridine (≈10 mg). The mixture was stirred for 7 h at room temperature, when t.l.c showed no starting material was left, quenched by addition of water (3 ml) followed by extraction into ether (25 ml). The organic phase was washed with water (7 ml), sodium bicarbonate (5 ml) and brine (10 ml) then dried over magnesium sulphate, and evaporated to give a crude product. This was purified by column chromatography eluting with petroleum (b.p 40 – 60 °C) / ethyl acetate (4 : 1) to yield *tert-butyl-{3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenyl-silane*, $(\alpha]^{22}_D$ = -4.69, c = 1.215, $CHCl_3$) (0.19g, 70 %) (Found M^+: 452.2747; $C_{28}H_{40}O_3Si$

requires: 452.2747) which showed δ_H: 7.66 (4 H, m), 7.12 (6 H, m), 4.18 (1 H, dd, J 6.0, 9.0 H_Z), 3.74 – 3.59 (4 H, m), 1.72 (1 H, br m), 1.52 (1 H, br m), 1.47 (3 H, s), 1.34 (3 H, s), 1.09 (1 H, br, s), 1.06 (9 H, s), 0.95 (3 H, d, J 6.1 H_Z), 0.88 (2 H, m), 0.68 (1 H, br, m), 0.28 (1 H, q, J 5.1 H_Z); δ_C: 129.05, 128.29, 127.23, 123.10, 121.15, 101.75, 71.25, 43.56, 35.90, 33.48, 23.14, 20.32, 19.16, 17.43, 13.1, 12.75, 2.8.

EXPERIMENT: 20

Preparation of (1R,2R)-2-[3-(*tert*-Butyldiphenyl-silanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (79)

tert-Butyl{3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4- yl)cyclopropyl]butoxy} diphenyl silane (0.15 g, 0.33 mmol) in dry ether (10 ml) was added to a stirred suspension of periodic acid (0.19 g, 0.82 mmol) in ether (15 ml) at room temperature under nitrogen. The mixture was stirred for 16 h at room temperature, when g.l.c showed no starting material was left, then filtered prior to evaporation of the ether. The crude product was dissolved in chloroform (15 ml), insoluble salts were removed by filtration and the filtrate was evaporated to yield a thick oil, which was purified by column chromatography eluting with petroleum / ether (4 : 1) to give *(1R,2R)-2-[3-(tert-butyldiphenylsilanyloxy)-1-methyl-propyl]cyclopropane carbaldehyde* $[\alpha]^{22}_D$ = +3.51, c = 1.08, $CHCl_3$) (0.1 g, 79 %) (Found: C 75.5, H 8.6; calculated for $C_{24}H_{32}O_2Si$: C: 75.74, H: 8.47), which showed δ_H: 9.3 (1 H, d, J 5.8 H_Z), 7.67 (4 H, br, s), 7.42 (6 H, br, s), 3.67 (2 H, br, m), 1.87 (1 H, br, m), 1.67 (1 H, br, m), 1.53 (1 H, br, m), 1.26 (2 H, br, m), 1.16 (1 H, br, s), 1.0 (9 H, s), 0.97 (1 H, br, s), 0.89 (3 H, m); δ_C: 200.4, 133.51, 132.77, 131.82, 131.67, 127.46, 125.48, 58.29, 36.3, 28.12, 25.7, 25.09, 23.24, 16.17, 14.4, 9.95; ν_{MAX}: 3070, 2929, 1704, 1471, 1427, 1111.4 cm^{-1}.

EXPERIMENT: 21

Preparation of (1S,2R)-2-[3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (80)

(1R,2R)-2-[3-(tert-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropane carbaldehyde (0.08 g, 0.21 mmol) in methanol (5 ml) was added to a stirred solution of sodium methoxide (0.022 g, 0.42 mmol) in methanol (10 ml) at room temperature. The mixture was refluxed for 48 h, then cooled to room temperature and quenched with water (2 ml). The product was extracted with dichloromethane (2 × 10 ml). The combined organic layers were washed with brine (5 ml), dried and evaporated to give a thick oil, which was purified by column chromatography eluting with petroleum (b.p 40 - 60 °C)/ ether (4 : 1) to give *(1S,2R)-2-[3-(tert-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde*, $[\alpha]^{22}_{D}$ = +9.4; (c = 1.23, $CHCl_3$) (0.015 g, 64 %), (Found: C 75.6, H 8.3. Calculated for $C_{24}H_{32}O_2Si$: C 75.74, H 8.47) which showed δ_H: 8.9 (1 H, d, J 5.5 H_Z), 7.73 (4 H, m), 7.44 (6 H, m), 3.76 (2 H, br, m), 1.71 (1 H, br, m), 1.55 (1 H, br, m), 1.31 (1 H, br, m), 1.24 (2 H, br, m), 1.11 (1 H, br, s), 1.09 (9 H, br, s), 0.98 (1 H, br, m), 0.91 (3 H, d, J 6.7 H_Z); δ_C: 200.65, 138.33, 136.6, 135.8, 135.3, 134.6, 133.0, 129.1, 128.96, 127.47, 61.31, 39.25, 33.25, 29.19, 26.73, 22.58, 20.42, 19.31, 14.31, 13.53; ν_{MAX}: 3070, 2957, 1706, 1471, 1427, 1112 cm^{-1}.

EXPERIMENT: 22

Preparation of (1R*,2R*)-Cyclopropane-1,2-dicarboxylic acid dimethyl ester (81) and (1S,2R)-Cyclopropane-1,2- dicarboxylic acid dimethyl ester (82)

Sodium methoxide (355 g, 6.57 mol) was added in portions (12-15 g) to a stirred mixture of methyl acrylate (1385 ml, 15.38 mol) and methyl chloroacetate (575 ml, 6.56 mol) in a 3-neck round bottom flask fitted with a mechanical stirrer, maintaining the temperature in the range of 20-32 °C using an ice-bath. When the addition of sodium methoxide was complete the ice bath was removed and the mixture was stirred at room temperature for a further 1 h. After that, the mixture was quenched with water (1500 ml) and stirred for 10 min. Then the organic layer was separated and washed with sat. aq. sodium chloride (2 × 250 ml). The organic layer was dried and filtered. The combined aqueous phases were re-extracted with dichloromethane (2 × 200 ml), dried and

evaporated to yield a yellow liquid, which was combined with the main organic phase. The combined organic phases were vacuum distilled at 4 mm / Hg and ~ 40 °C to remove most of the methyl acrylate; after that the temperature was raised 70 °C to distil most of the *trans*-isomer which was mixed with the small amount of the *cis*-isomer, then to 80 °C to distil the *cis*-isomer which was mixed with a small amount of the *trans*-isomer. For further purification the isomers were separated by column chromatography on silica eluting with petroleum (b.p 40-60 °C) and ether (10:1) to give in the first fraction *cis*-cyclopropane-1,2-dicarboxylic acid dimethyl ester[124][125] (598 g) which showed δ_H: 3.65 (6 H, s), 1.66 (2 H, br s), 0.93 (2 H, m). The second fraction was *trans*-cyclopropane-1,2-dicarboxylic acid dimethyl ester (907 g).

EXPERIMENT: 23

Preparation of ((1S,2R)-2-Hydroxymethylcyclopropyl)methanol (83)

cis-Cyclopropane-1,2-dicarboxylic acid dimethyl ester (23.79 g, 226 mmol) in tetrahydrofuran (200 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (8.69 g, 226 mmol) in tetrahydrofuran (430 ml) at 5 °C under nitrogen. After that the mixture was refluxed for 2 h, when g.l.c showed no starting material was left, then cooled to room temperature and quenched carefully with sat. aq. sodium sulphate dihydrate (400 ml). The precipitate was filtered through a pad of magnesium sulphate and washed with tetrahydrofuran (2 × 100 ml). The filtrate was evaporated under reduced pressure then high vacuum to give ((1S,2R)-2-hydroxymethylcyclopropyl)methanol[137] (13.56 g, 90 %), which showed δ_H: 4.0 (2 H, br d, J 8.3 H_Z), 3.6 (2 H, br t, J 10.6 H_Z), 3.2 (2 H, br s), 1.3 (2 H, br m), 0.74 (1 H, dt, J 5.1, 8.2 H_Z), 0.15 (1 H, br q, J 5.2 H_Z); δ_C: 62.8, 17.45, 8.5; ν_{MAX}: 3324 cm^{-1}.

EXPERIMENT: 24

Preparation of Butyric acid (1S,2R)-2-hydroxymethylcyclopropylmethyl ester (86)

Method A:-

Vinyl butyrate (2.1 ml, 16.6 mmol) was added to a stirred solution of ((1S,2R)-2-hydroxymethylcyclopropyl)methanol (1 g, 9.8 mmol) in tetrahydrofuran (10 ml) and lipase (PG)(1 g) at room temperature. The mixture was stirred for 48 h, when g.l.c showed no starting material. The precipitate was filtered through celite and the filter cake was washed with ether, then the solvent was evaporated to give a crude product. The residue was diluted with sat. aq. sodium bicarbonate (30 ml) and the product was extracted with dichloromethane (50 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined organic layers were washed with water, dried, and evaporated to give a pale yellow oil, which was purified by column chromatography on silica eluting with petroleum (b.p 40 - 60 °C) / ether (5 : 2) to give butyric acid (1S,2R)-2-hydroxymethyl-cyclopropylmethyl ester[127] (1.2 g, 75 %), which showed: δ_H: 4.5 (1 H, dd, J 5.6, 11.8 H_Z), 3.8 (2 H, m), 3.4 (1 H, dd, J 8.8, 11.9 H_Z), 2.3 (2 H, t, J 7.1 H_Z), 1.65 (2 H, sextet, J 7.0 H_Z), 1.3 (2 H, m), 0.93 (3 H, t, J 7.3 H_Z), 0.83 (1 H, dt, J 5.1, 8.4 H_Z), 0.21 (1 H, q, J 5.4 H_Z); δ_C: 173.6, 62.34, 56.3, 36.1, 18.45, 14.3, 13.5, 7.64, ν_{MAX}: 3428, 1731 cm^{-1}.

Method B:-

Butyric anhydride (46 ml, 0.29 mol) was added to a stirred solution of 2,2,2,-trifluoroethanol (25 g, 0.25 mol) in isopropyl ether (260 ml). The mixture was stirred and cooled to 4 °C, then trimethylsilyltrifluoromethane sulphonate (1.0 ml) was added. An exothermic reaction occurred and the temperature rose to 23 °C. The cooling bath was removed and the mixture was stirred at room temperature for 90 min. After that a solution of sodium hydroxide (10.0 g, 0.25 mol) in water (200 ml) was added followed by sodium carbonate (10 g). The reaction mixture was stirred

for 10 min, then the organic layer was separated and the aqueous layer was extracted with isopropyl ether (35 ml). The combined organic layers were washed with sat. aq. sodium chloride (200 ml), dried and filtered. The filtrate was added to a stirred solution of *cis*-1,2-dihydroxymethylcyclopropane (13.0 g, 0.127 mol) in tetrahydrofuran (60 ml) followed by the addition of lipase (12 g). The mixture was stirred at ambient temperature and monitored by g.l.c. After 48 h, this showed a very small amount of starting material was left. The reaction mixture was worked up as above to give after purification, butyric acid (1S,2R)-2-hydroxymethylcyclopropylmethyl ester (17.85 g, 81.2 %), which showed an identical spectrum to that above.

EXPERIMENT: 25

Preparation of Butyric acid (1S,2R)-2-formyl-cyclopropylmethyl ester (87)

A solution of butyric acid (1S,2R)-2-hydroxymethylcyclopropylmethyl ester (4.8 g, 27.9mmol) in dichloromethane (25 ml) was added to a stirred suspension of pyridinium chlorochromate (12 g, 27.9 mmol) in dichloromethane (50 ml) at room temperature under nitrogen. The mixture was stirred for 4 h, when t.l.c showed no starting material was left. Diethyl ether (150 ml) was added together with Celite (10 g). The mixture was filtered through a pad of silica and washed with ether (3 × 30 ml). The filtrate was evaporated to give a pale yellow oil, butyric acid (1S,2R)-2-formyl-cyclopropylmethyl ester[127] (4.17 g, 87 %), which showed δ_H: 9.47 (1 H, d, J 4.4 H_Z), 4.47 (1 H, dd, J 6.1, 12.0 H_Z) 3.8 (1 H, dd, J 9.15, 12.0 H_Z), 2.2 (2 H, t, J 7.3 H_Z), 2.05 (1 H, m), 1.8 (1 H, m), 1.6 (2 H, sextet, J 7.0 H_Z) 1.3 (2 H, m), 0.87 (3 H, t, J 7.3 H_Z); δ_C: 200.0, 173.2, 62.2, 36.8, 26.6, 22.4, 18.4, 13.6, 12.7; ν_{MAX}: 1700 cm^{-1}.

EXPERIMENT: 26

Preparation of Butyric acid (1S,2R)-2-[1,3]dioxolan-2-ylcyclopropylmethyl ester (88)

Butyric acid (1S,2R)-2-formylcyclopropylmethyl ester (4.5 g, 0.026 mol) was added to a stirred solution of 1,2-ethanediol (4.92 g, 0.079 mol) and pyridinium p-toluenesulfonate (0.33 g, 1.3 mmol) in toluene (100 ml). The mixture was refluxed for 16 h to separate the water using a Dean-Stark apparatus, and then cooled to room temperature, and the toluene was evaporated. The residue was washed with sodium bicarbonate solution (5 %) (10 ml), and the product was extracted with dichloromethane (2 × 50 ml). The combined organic layers were washed with water, dried and evaporated to give a residue which was purified by column chromatography eluting with petroleum / ether (bp 40 – 06 °C) (1 : 1) to yield *butyric acid (1S,2R)-2-[1,3]dioxolan-2-ylcyclopropylmethyl ester* (4.9 g, 87 %) $[\alpha]^{22}_{D}$ = -10.9 (c = 1.44, $CHCl_3$; Found M^+: 213.1125; $C_{11}H_7O_4$ requires 213.1127) which showed δ_H: 4.49 (1 H, d, J 6.4 H_Z), 4.0 (2 H, br, d, J 7.6 H_Z), 3.84 (2 H, m), 3.7 (2 H, m), 2.15 (2 H, t, J 7.6 H_Z), 1.5 (2 H, sextet, J 7.0 H_Z), 1.2 (1 H, m), 1.07 (1 H, m), 0.8 (3 H, t, J 7.6 H_Z), 0.75 (1 H, m), 0.43 (1 H, br, q, J 5.5 H_Z); δ_C: 173.6, 115.9, 104.5, 73.4, 64.8, 64.0, 36.1, 18.4, 18.2, 13.9, 13.6, 7.2, 4.3; ν_{MAX}: 2964, 2875, 1728, 1461, 1367, 1251, 1180, 1044, 986 cm^{-1}.

EXPERIMENT: 27

((1S,2R)-2-[1,3]Dioxolan-2-yl-cyclopropyl)methanol (89)

Butyric acid (1S,2R)-2-[1,3]dioxolan-2-yl-cyclopropylmethyl ester (4.2 g, 0.096 mol) in methanol (15 ml) was added to a stirred solution of potassium carbonate (8.1 g, 0.058 mol) in methanol (80 ml) at room temperature. The reaction was

stirred at room temperature for 1 h, when t.l.c showed no starting material was left. The precipitate was filtered off through a pad of celite and the filter was washed with methanol (30 ml), then the solvent was evaporated; the residue was diluted with water (30 ml) and dichloromethane (100 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic layers were dried and evaporated to give a residue which was purified by column chromatography on silica eluting with petroleum (bp 40 – 60 °C) / ether (1 : 1) to give *((1S,2R)-2-[1,3]dioxolan-2-yl-cyclopropyl)methanol* (2.1 g, 75 %); $[\alpha]^{22}_{D}$ = -81.26 (c = 1.19, $CHCl_3$) Found: C 58.4, H 8.3. Calculated for $C_7H_{12}O_3$: C 58.32, H 8.39 %; which showed δ_H: 4.3 (1 H, br, d, J 6.9 H_Z), 3.67 (1 H, br, t, J 7.3 H_Z), 3.6 (4 H, m), 3.1 (1 H, br, dd, J 9.15, 11.57 H_Z), 1.3 (1 H, br, s), 0.97 (1 H, m), 0.8 (1 H, m), 0.54 (1 H, m), 0.19 (1 H, m); δ_C: 116.5, 75.62, 74.32,67.45, 17.64, 9.5, 7.64; ν_{MAX}: 3426, 2878, 1351, 1081cm^{-1}; *m/z*: 143 (M^+-H), 113 (M^+-H, -CH_2O), 83 (M^+-H, -$C_2H_4O_2$), 83/55 (M^+-H, -C_2H_4).

EXPERIMENT: 28

(1S,2R)-2-[1,3]Dioxolan-2-ylcyclopropanecarbaldehyde (90)

((1S,2R)-2-[1,3]Dioxolan-2-yl-cyclopropyl)methanol (5.2 g, 36 mmol) in dichloromethane (15 ml) was added to a stirred suspension of pyridinium chlorochromate (15.7 g, 72 mmol) in dichloromethane (115 ml) at room temperature. The mixture was stirred for 6 h, and then refluxed for 2 h. The reaction was cooled, diluted with ether (100 ml) and filtered through a pad of silica. The solvent was evaporated to give a brown oil, which was purified by column chromatography eluting with petroleum (bp 40 –60 °C) / ether (5 : 1) to give *(1S,2R)-2-[1,3]dioxolan-2-ylcyclopropanecarbaldehyde* which showed several spots on t.l.c and a complicated ^1H n.m.r spectrum; ν_{MAX}: 2973, 2907, 1764, 1373 cm^{-1}.This impure material was used without further purification.

EXPERIMENT: 29

(E)-3-((1R,2R)-2-[1,3]Dioxolan-2-ylcyclopropyl)acrylic acid ethyl ester (91)

(1S,2R)-2-[1,3]Dioxolan-2-yl-cyclopropanecarbaldehyde (4.5 g, 0.03mol) in toluene (15 ml) was added to a stirred solution of carboethoxy methylenetriphenylphosphorane (22 g, 0.063 mol) in toluene (150 ml) at room temperature. The mixture was stirred for 16 h, then the solvent was evaporated and the residue was dissolved in petroleum (bp 40 –60 °C) / ether (5 : 2) (70 ml) and filtered; the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica eluting with petroleum (b.p 40 –60 °C) / ether (5 : 2) to give as the major product *(E)-3-((1R,2R)-2-[1,3]dioxolan-2-ylcyclopropyl)acrylic acid ethyl ester* (5.4 g, 80 %), which showed δ_H: 6.73 (1 H, dd, J 10.4, 15.5 H_Z), 5.97 (1 H, d, J 15.5 H_Z), 4.72 (1 H, d, J 6.4 H_Z) , 4.15 (2 H, q, J 7.3 H_Z), 3.97 (2 H, m), 3.86 (2 H, m), 1.8 (1 H, m), 1.64 (1 H, m), 1.48 (1 H, m), 1.26 (3 H, t, J 7.3 H_Z), 0.9 (1 H, br, q, J 5.8 H_Z); δ_C: 167.8, 148.6, 119.7, 116.5, 74.3, 69.4, 59.6, 21.6, 13.7, 9.4, 7.2; ν_{MAX}: 2988, 1732, 1422, 1856 cm^{-1}.

EXPERIMENT: 30

3-((1R,2R)-2-[1,3]Dioxolan-2-ylcyclopropyl)-butyric acid ethyl ester (92) and (93)

Methyl magnesium bromide (3.0 M in diethyl ether, 0.7 ml) was added to a suspension of cuprous bromide (0.12 g, 0.83 mmol) in dry tetrahydrofuran (12 ml) at – 40 °C under nitrogen. The resulting yellow-green mixture was stirred for 10 min, then a solution of (E)-3-((1R,2R)-2-[1,3]dioxolan-2-ylcyclopropyl)acrylic

acid ethyl ester (0.12 g, 0.56 mmol) in dry tetrahydrofuran (10 ml) was added dropwise, maintaining the temperature below – 30 °C. After that, the reaction mixture was allowed to reach –15 °C when g.l.c showed all starting material had reacted. The mixture was cooled again to – 40 °C, then quenched with sat.aq. ammonium chloride (5 ml); the solvent was evaporated, and water (10 ml), and ethyl acetate (30 ml) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic layers were dried and evaporated to give a crude product which was purified by column chromatography eluting with petroleum (bp 40 –60 °C) / ether (4 : 3) to give two isomers in ratio (3 : 1), which were hard to separate, of *3-((1R,2R)-2-[1,3]dioxolan-2-ylcyclopropyl)-butyric acid ethyl ester* (0.04 g, 31 %). The major isomer showed δ_H: 4.56 (1 H, d, J 7.6 H_Z), 4.13 (2 H, q, J 7.0 H_Z), 4.02 (2 H, m), 3.83 (2 H, m), 2.84 (1 H, dd, J 3.1, 14.95 H_Z), 2.2 (1 H, dd, J 10.4, 14.95 H_Z), 1.62 (1 H, m), 1.26 (3 H, t, J 7.0 H_Z), 1.07 (3 H, d, J 6.4 H_Z), 1.06 (1 H, m), 0.8 (2 H, m), 0.35 (1 H, m); the minor isomer showed δ_H: 4.54 (1 H, d, J 7.6 H_Z), 4.13 (2 H, q, J 7.0 H_Z), 4.02 (2 H, m), 3.38 (2 H, m), 2.43 (1 H, dd, J 6.4, 14.9 H_Z), 2.29 (1 H, br, t, J 6.4 H_Z), 1.62 (1 H, m), 1.27 (3 H, t, J 7.0 H_Z), 1.15 (3 H, d, J 6.4 H_Z), 1.06 (1 H, m), 0.6 (2 H, m), 0.2 (1 H, m); δ_C: 173.2, 116.85, 76.1, 69.5, 59.1, 41.1, 32.8, 22.1, 20.0, 14.3, 9.25, 4.1; ν_{MAX}: 2967, 1721, 1459, 1119 cm^{-1}.

EXPERIMENT: 31

Butyric acid (1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropylmethyl ester (94)

Butyric acid (1S,2R)-2-formylcyclopropylmethyl ester (6.36 g, 37 mmol) was added to a stirred solution of 2,2-dimethyl-1,3-propandiol (11.68 g, 0.11 mol) and

pyridinium p-toluenesulfonate (0.47 g, 2.1 mmol) in toluene (130 ml). The reaction was refluxed for 16 h to separate water by a Dean-Stark apparatus. When g.l.c showed no starting material was left the mixture was worked up as before and purified by column chromatography eluting with petroleum (bp 40 –60 °C) / ether (1 : 1) to give *butyric acid (1S,2R)-2-(5,5-dimethyl-[1,3]dioxan-2-yl)-cyclopropylmethyl ester* (8.6 g, 90%) $[\alpha]^{22}_{D}$ = +2.08 (c = 1.01, $CHCl_3$; Found: C 65.4, H 9.5. Calculated for $C_{14}H_{24}O_4$: C 65.60, H 9.44) which showed δ_H: 4.02 (3 H, m), 3.47 (2 H, m), 3.28 (2 H, m), 2.2 (2 H, t, J 7.5 H_Z), 1.54 (2 H, sextet, J 7.5 H_Z), 1.19 (2 H, br, m), 1.08 (3 H, s), 0.83 (3 H, t, J 7.5 H_Z), 0.67 (1 H, br, m), 0.58 (3 H, s), 0.43 (1 H, q, J 5.7 H_Z); δ_C: 173.2, 103.3, 76.6, 76.0, 69.2, 39.8, 31.3, 22.4, 21.1, 19.5, 18.8, 13.4, 9.5, 7.5; ν_{MAX}: 1700 cm^{-1}.

EXPERIMENT: 32

[(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]methanol (95)

Butyric acid (1S,2R)-2-(5,5-dimethyl-[1,3]dioxan-2-yl)-cyclopropylmethyl ester (8.5 g, 0.033 mol) in methanol (20 ml) was added to a stirred solution potassium carbonate (13.7 g, 0.099 mol) in methanol (110 ml) at room temperature. The reaction was stirred at room temperature for 3 h, when t.l.c showed no starting material was left then worked up as before and purified by column chromatography eluting with petroleum (bp 40 –60 °C) / ether (5 : 2) to yield *[(1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]methanol* (4.9 g, 79 %), $[\alpha]^{22}_{D}$ = -78.76, (c=1.32, CHCl3; Found: C 64.3, H 9.8. Calculated for $C_{10}H_{18}O_3$: C 64.49, H 9.74) which showed δ_H: 4.7 (1 H, d, J 5.7 H_Z), 3.63 (2 H, m), 3.32 (1 H, m), 3.13 (1 H, m), 1.9 (1 H, br s), 1.54 (2 H, br m), 0.83 (3 H, s), 0.81 (3 H, s), 0.5 (1 H, br m), 0.13 (1 H, m); δ_C: 106.8, 76.3, 69.1, 61.1, 32.5, 22.8, 21.3, 19.1, 9.6, 4.1;

ν_{MAX}: 3490, 2951, 2869, 1471 cm^{-1}; *m/z*: 187 (M^+), 155 (M^+-CH_3OH), 99 (M^+-$C_5H_{12}O$), 155/83 (M^+-C_4H_8O).

EXPERIMENT: 33

(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropanecarbaldehyde (96)

(A) [(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]methanol (4.4 g, 23 mmol) in dichloromethane (15 ml) was added to a stirred suspension of pyridinium chlorochromate (10.2 g, 47.3 mmol) in dichloromethane (130 ml) at room temperature. The mixture was stirred for 2 h, when t.l.c. showed no starting material was left, then worked up as before and purified by column chromatography eluting with petroleum (b.p 40 –60 °C) / ether (1 : 1) to give *(1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropanecarbaldehyde* (0.85g, 19 %) ($[\alpha]^{22}_D$ = -20.55, c = 1.08, $CHCl_3$) (Found M^+: 183.1028; $C_{10}H_{15}O_3$ requires: 183.1021) which showed δ_H: 9.2 (1 H, d, J 5.2 H_Z), 4.3 (1 H, d, J 5.5 H_Z), 3.46 (2 H, m), 1.82 (1 H, br, m), 1.65 (1 H, br, m), 1.35 (1 H, br, m), 1.0 (3 H, s), 0.71 (1 H, br, m), 0.56 (3 H, s); δ_C: 202.7, 108.9, 75.2, 70.1, 33.0, 24.5, 22.3, 21.8, 20.2, 13.3; ν_{MAX}: 2967, 2871, 1722, 1471cm^{-1}.

(B) To a stirred solution of oxalyl chloride (0.75 g, 5.9 mmol) in dry dichloromethane (15 ml) at –78 °C, dry dimethyl sulphoxide (0.92 g, 0.83 ml, 11.8 mmol) was added and stirring was continued for another 5 min then [(1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]methanol (1 g, 5.3 mmol) in dry dichloromethane (10 ml) was added. The mixture was stirred for 15 min at –78 °C, then triethylamine (3.7 ml, 0.026 mol) was added. The mixture was stirred for 5

min before being allowed to reach room temperature over a period of 1 h. After that, it was poured into brine (100 ml) containing sat. sodium hydrogen carbonate (10 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 × 25 ml). The combined organic layers were washed with water (50 ml), dried, and evaporated to give a residue which was purified by column chromatography on silica eluting with petroleum (bp 40 – 60 °C) / ether (1:1) to give a colourless oil (0.47 g, 47 %) which was identical by n.m.r. to that in (A.).

EXPERIMENT: 34

(E)-3-[(1R,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]acrylic acid ethyl ester (97)

(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropanecarbaldehyde (2.1 g, 0.011mmol) in toluene (10 ml) was added to a stirred solution of carboethoxy methylenetriphenylphosphorane (5.9 g, 0.016 mol) in toluene (60 ml) at room temperature. The mixture was stirred for 16 h, then the organic solvent was evaporated and the residue was dissolved in petroleum (bp 40 –60 °C) / ether (5 : 2) (50 ml), the precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica eluting with petroleum (b.p 40 –60 °C) / ether (5 : 2) to give *(E)-3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]acrylic acid ethyl ester* (2.17 g, 75%), $[\alpha]^{22}_{D}$ = -33.87, c = 1.11, $CHCl_3$; (Found: C, 65.8; H, 8.7. Calculated for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72) which showed: δ_H: 6.78 (1 H, dd, J 10.0, 15.25 Hz), 5.95 (1 H, d, J 15.25 Hz), 4.36 (1 H, d, J 6.1 Hz), 4.17 (2 H, q, J 7.3 Hz), 3.62 (2 H, br, m), 3.42 (2 H, br, m), 1.78 (1 H, br, m), 1.59 (1 H, br, m), 1.26 (3 H, t, J 7.3 Hz), 1.19 (4 H, br, s), 0.94 (1 H, q, J 5.4 Hz), 0.71 (3 H, s); δ_C: 167.8, 148.0, 120.0,

103.1, 76.25, 62.9, 48.0, 33.1, 23.1, 22.8, 21.75, 19.5, 13.2, 6.9; ν_{MAX}: 2967, 2876, 1726, 1655, 14.61cm^{-1}.

EXPERIMENT: 35

3-[(1R,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]butyric acid ethyl ester (98) and (99)

Methyl magnesium bromide (3.0 M in diethyl ether, 7.8 ml) was added to a suspension of cuprous bromide (1.6 g, 11.15 mmol) in dry tetrahydrofuran (15 ml) at – 40 °C under nitrogen. The resulting yellow-green mixture was stirred for 10 min, then a solution of (E)-3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)-cyclopropyl]acrylic acid ethyl ester (2 g, 7.8 mmol) in dry tetrahydrofuran (10 ml) was added dropwise, maintaining the temperature below – 30 °C. The mixture was allowed to reach -15° C when g.l.c showed no starting material was left. The mixture was cooled again to – 40 °C, then quenched with sat. aq. ammonium chloride (5 ml); the solvent was evaporated, and water (10 ml), and ethyl acetate (30 ml) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried and evaporated to give a crude product which was purified by column chromatography eluting with petroleum (bp 40 –60 °C) / ether (4 : 3) to give two isomers in ratio (3 : 1) of *3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)-cyclopropyl]butyric acid ethyl ester* (0.81 g, 38 %) which were separated by column chromatography eluting with petroleum ether (bp 40 –60 °C) / ether (1 : 1). The major isomer showed δ_H: 4.1 (3 H, m), 3.57 (2 H, dd, J 2.41, 11.6 H_Z), 3.39 (2 H, dd, J 3.9, 11.0 H_Z), 2.79 (1 H, dd, J 3.05, 14.9 H_Z), 2.1 (1 H, dd, J 10.37, 14.9 H_Z), 1.52 (1 H, br, m), 1.23 (3 H, t, J 7.3 H_Z), 1.19 (3H, br, s), 1.03 (3 H, d, J 6.4

H_Z), 0.76 (3 H, br, m), 0.68 (3 H, s), 0.25 (1 H, m); δ_C: 173.3, 103.0, 76.5, 59.9, 56.3, 31.4, 29.9, 22.9, 22.4, 21.8, 20.3, 20.2, 14.2, 7.8; ν_{MAX}: 2957, 2869, 1729, 1470, 1108 cm^{-1}; m/z: 269 (M^+-H), 241 (M^+- H, -C_2H_2), 185 (M^+- H, -$C_4H_4O_2$), 169 (M^+-H, -$C_5H_8O_2$), 169/128 (M^+- H, -C_3H_5). The minor isomer showed: δ_H:- 4.12 (3 H, m), 3.63 (2 H, br d, J 11.0 H_Z), 3.42 (2 H, br d, J 10.97 H_Z), 2.42 (1 H, br dd, J 6.4, 14.3 H_Z), 2.25 (1 H, br dd, J 7.9, 14.3 H_Z), 1.60 (2 H, m), 1.26 (3 H, t, J 7.0 H_Z), 1.21 (3 H, s), 1.1 (3 H, d, J 6.4 H_Z), 0.79 (2 H, br m), 0.75 (3 H, s), 0.26 (1 H, m); δ_C: 173.1, 102.7, 76.3, 60.15, 56.65, 31.7, 29.9, 22.9, 22.35, 21.8, 20.0, 19.9, 14.2, 7.5.

EXPERIMENT: 36

3-[(1R,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]butan-1-ol (109)

3-[(1R,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]butyric acid ethyl ester (0.8 g, 2.9mmol) was added dropwise to a stirred suspension of lithium aluminium hydride (0.22 g, 5.7 mmol) in tetrahydrofuran (50 ml). After the addition the reaction mixture was refluxed for 1 h, when t.l.c showed no starting material was left, cooled to room temperature and quenched by slow addition of sat. aq. sodium sulphate (3 ml). The product was extracted with dichloromethane (2 × 35 ml), dried, and evaporated to give *3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)-cyclopropyl]butan-1-ol* an oil (0.54 g, 80 %) $[\alpha]^{24}_D$ = 14.6, c = 1.43, $CHCl_3$; (Found: M^+ 228.1718, $C_{13}H_{24}O_3$ requires: 228.1725); which showed δ_H: 4.05 (1 H, br d, J 7.6 H_Z), 3.75 (1 H, m), 3.6 (3 H, br d, including J 10.5 H_Z), 3.4 (2 H, d, J 10.5 H_Z), 2.77 (1 H, br s), 1.6 (2 H, br m, including J 5.2 H_Z), 1.2-1.18 (5 H, brs), 1.02 (3 H, d, J 6.4 H_Z), 0.9-0.6 (5 H, m) 0.16 (1 H, br m); δ_C: 103.2, 77.4, 77.03, 60.4, 40.7, 29.9, 29.2, 22.8, 22.6, 21.7, 21.3, 20.8, 6.9; ν_{MAX}: 3421, 1104cm^{-1}; *m/z*: 229 (M^+), 141 (M^+-$C_5H_{12}O$), 141/115 (M^+-C_2H_2), 141/85 (M^+-C_3H_4O), 85/69 (M^+-CH_4), 85/55 (M^+-CH_2O).

EXPERIMENT: 37

2-{3-[(1R,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]butylsulfanyl}-benzothiazole (110)

Diethyl azodicarboxylate (0.4 g, 2.26 mmol) in dry tetrahydrofuran (5 ml) was added to a stirred solution of 3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]butan-1-ol (0.45 g, 1.97 mmol), triphenylphosphine (0.595 g, 2.26 mmol) and 2-mercaptobenzthiazole (0.35 g, 2.06 mmol) in dry tetrahydrofuran (10 ml) at 0 °C . The mixture was allowed to reach room temperature and stirred for 18 h, then the solvent was evaporated and the residue was treated with petrol/ether (5:2) and the precipitate was filtered off on a sinter. The filter cake was washed with petroleum / ether. The combined organic layers were evaporated to give *2-{3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]butylsulfanyl}benzothiazole* as a pale yellow oil, which was purified by column chromatography on silica eluting with petrol / ether (5 : 2) to give a thick oil (0.46 g, 62 %) ($[\alpha]^{23}_D$ = -33.18, c = 1.13, $CHCl_3$) (Found: C 63.6, H 7.2, N 3.5. Calculated for $C_{20}H_{27}NO_2S_2$: C 63.62, H 7.21, N 3.71) which showed δ_H: 7.85 (1 H, br d, J 8.0 H_Z), 7.75 (1 H, br d, J 8.0 H_z), 7.41 (1 H, br t, J 7.3 H_Z), 7.3 (1 H, m), 4.05 (1 H, d, J 7.3 H_Z), 3.6 (1 H, dd, J 11.0, 2.75 H_Z), 3.74 (1 H, m), 3.37-3.28 (3 H, m, including a doublet with J 11.0 H_Z), 3.15 (1 H, br d, J 11.0 H_Z), 2.23 (1 H, m), 1.8-1.6 (2 H, m), 1.2 (1 H, m), 1.15 (3 H, s), 1.04 (3 H, d, J 6.5 H_Z), 0.85 (1 H, m), 0.75 (1 H, m), 0.6 (3 H, s), 0.22 (1 H, m, including J 5.5 H_Z); δ_C: 167.43, 153.4, 135.0, 126, 124, 121.4, 120.8, 102.7, 77.4, 76.5, 65.7, 32.3, 31.5, 29.7, 22.85, 21.6, 20.6, 19.7, 7.1; ν_{MAX}: 2955, 1460, 1427, 1106 cm^{-1}; *m/z*: 377 (M^+), 378 (M+1), 379 (M+2), 263 (M^+-$C_6H_{10}O_2$), 263/229 (M^+-H_2S), 263/177 (M^+-C_6H_{14}), 263/167 (M^+-$C_6H_{10}N$), 177/149 (M^+-C_2H_2).

EXPERIMENT: 37

2-{3-[(1R,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]butane-1-sulfonyl}benzothiazole (111)

Hydrogen peroxide solution in water (0.9 ml, 8.8 mmol) was added dropwise to a stirred solution of 2-{3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]butylsulfanyl}benzothiazole (0.35 g, 1 mmol) and ammonium molybdate (VI) (0.39 g, 0.33 mmol) in ethanol (10 ml) at 0 °C. The mixture was stirred for 16 h at room temperature, then water (10 ml) was added and the product was extracted with dichloromethane (2 × 15 ml), the combined organic layers were washed with brine (10 ml), dried and evaporated to give a residue which was purified by using column chromatography eluting with petroleum / ether (5:3) to give *2-{3-[(1R,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]butane-1-sulfonyl}benzothiazole* (0.27 g, 72 %) ($[\alpha]^{23}_{D}$ = 28.9, c = 1.04, $CHCl_3$) which showed δ_H: 8.21 (1 H, br d, J 8.0 H_Z), 8.02 (1 H, br d, J 8.0 H_Z), 7.26 (2 H, m), 4.02 (1 H, d, J 7.3 H_Z), 3.75-3.4 (3 H, m), 3.33 (1 H, br d, J 11.3 H_Z), 3.24 (2 H, br m), 2.2 (1 H, m), 1.8 (1 H, m), 1.15 (2 H, m), 1.11 (3 H, s), 1.04 (3 H, d, J 6.6 H_Z), 0.86 (2H, m), 0.62 (3 H, s), 0.21(1 H, m, including J ca.5.5 H_Z); δ_C: 166.1, 153.6, 136.4, 126.1, 124.3, 123.1, 122.25, 106.5, 78.4, 77.4, 48.3, 34.2, 32.2, 28.0, 22.9, 21.65, 20.7, 18.5, 9.7, 3.2; ν_{MAX}: 2953, 1471, 1323, 1145 and 1104 cm^{-1}.

EXPERMINT: 38

1-[(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]ethanol (113)

Methylmagnesium bromide (5.4 ml, 3M), was added dropwise to a stirred solution

of (1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropanecarbaldehyde (2 g, 10.8 mmol), in tetrahydrofuran (15 ml) at – 78 °C, then the mixture was stirred at room temperature for 15 min, cooled to 0 °C and sat. aq. ammonium chloride (1 ml) was added and stirred for 10 min, when the crude product was extracted with diethyl ether (2 × 10 ml). After evaporation of the solvent the residue was purified using column chromatography eluting with petroleum (bp 40 – 60 °C) and ethyl acetate (5 : 3) to give a mixture of two isomers in a 1 : 1 ratio *1-[(1S,2R)-2-(5,5-dimethyl-[1,3]dioxan-2-yl)cyclopropyl]ethanol* (1.45 g, 66 %), (as mixture of isomers ca.) which showed δ_H: 4.73 (2 H, br m), 4.26 (1 H, q, J 7.0 H_Z), 3.9 (1 H, pent, J 6.4 H_Z), 3.38 (6 H, br m), 3.1 (2 H, m), 1.62 (1 H, br m), 1.52 (1 H, br m), 1.42 (1 H, br m), 1.33 (1 H, br m), 1.23 (3 H, d, J 6.4 H_Z), 1.12 (3 H, d, J 6.4 H_Z), 0.91 (6 H, s), 0.85 (6 H, s), 0.49 (1 H, br m), 0.38 (1 H, br m), 0.22 (1 H, br m, including J ca.5.5 H_Z), 0.09 (1 H, br m); δ_C: 104.9, 104.7, 73.5, 73.3, 73.2, 72.8, 71.0, 69.3, 35.9, 35.6, 23.9, 23.0, 22.2, 22.0, 21.8, 21.6, 21.3, 21.2, 20.1, 19.4, 17.3, 14.1; ν_{MAX}: 3446, 2879 cm^{-1}.

EXPREMENT: 39

1-[(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]ethanone (114)

To a stirred solution of oxalyl chloride (0.69 g, 5.5 mmol) in dry dichloromethane (10 ml) at – 78 °C, dry dimethyl sulphoxide (0.85 g, 11.0 mmol) was added and stirring was continued for another 5 min, then 1-[(1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]ethanol (1 g, 5.0 mmol) in dry dichloromethane (10 ml) was added. The mixture was stirred for 15 min at – 78 °C, and then triethylamine (2.5 g, 24.7 mmol) was added. The mixture was stirred for 5 min before being allowed to reach room temperature over a period of 1 h. After that, it was poured into brine (100 ml) containing sodium hydrogen carbonate.

The organic compounds were extracted with ether (50 ml) and the aqueous layer was extracted with ether (2 × 25 ml). The combined organic layers were washed with water (50 ml), dried and evaporated to give a residue which was purified by column chromatography on silica eluting with eluting petroleum / ether (5 : 1) to give *1-[(1S,2R)-2-(5,5-dimethyl[1,3]dioxan-2-yl)cyclopropyl]ethanone* (0.51 g, 51 %) as a colourless oil (Found: C 66.3, H 8.9. Calculated for $C_{11}H_{18}O_3$: C 66.64, H 9.15) which showed δ_H: 4.19 (1 H, d, J 7.9 H_Z), 3.61 (1 H, dd, J 2.6, 11.1 H_Z), 3.51 (1 H, dd, J 2.6, 11.1 H_Z), 3.45 (1 H, d, J 11.1 H_Z), 3.3 (1 H, d, J 11.1 H_Z), 2.3 (3 H, s), 2.15 (1 H, m), 1.7 (1 H, m), 1.38 (1 H, br m), 1.19 (3 H, s), 1.07 (1 H, m), 0.68 (3 H, s); δ_C: 210.34, 105.25, 74.36, 74.14, 36.1, 24.32, 22.67, 21.53, 21.12, 20.67, 13.94; ν_{MAX}: 2876, 1714 cm^{-1}.

EXPREMENT: 40

3-[(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]but-2-enoic acid methyl ester (115)

1-[(1S,2R)-2-(5,5-Dimethyl[1,3]dioxan-2-yl)cyclopropyl]ethanone (0.4 g, 0.2 mmol) in toluene (5 ml) was added to a stirred solution of carboethoxymethylene triphenylphosphorane (1 g, 3.0 mmol) in toluene (15 ml) at room temperature. The reaction mixture was refluxed for 16 h and stirred for 72 h, and monitored by ^1H n.m.r, which showed no reaction had taken place.

EXPERIMENT: 41

Preparation of 10-(1R, 2S)-2-Octadecylcyclopropyl)decanal (117).

10-((1R,2S)-2-Octadecyl-cyclopropyl)-decan-1-ol (1.0 g) in dichloromethane (5 ml) was added to a suspension of pyridiumchlorochromate (0.07 gm, 0.35 mmol) in dichloromethane (5 ml) at room temperature. The reaction was stirred for 4 h, when t.l.c showed no starting material was left. The reaction was diluted with ether (5 ml) and filtered through silica gel on a sintered funnel. The organic compound was purified by using column chromatography eluting with petroleum (bp 40 - 60 °C) / ether (10 : 1) to give *10-((1R,2S)-2-octadecyl-cyclopropyl)-decanal* ($[\alpha]^{20}_D$ = + 0.12°, c = 1.1, $CHCl_3$) (0.07 g, 70%) (Found M^+: 448.4647. $C_{31}H_{60}O$ requires: 448.4644) which showed δ_H: 9.77 (1 H, br s), 2.43 (2 H, t, J 7.0 H_Z), 1.42-1.1 (52 H, br s, including two protons cyclopropane ring), 0.86 (3 H, t, J 6.1 H_Z), 0.64 (1 H, br s), -0.33 (1 H, br s); δ_C: 202.8, 43.9, 43.85, 41.3, 32.0, 30.2, 30.15, 29.8, 29.6, 29.4, 29.35, 29.3, 29.25, 29.2, 28.8, 22.7, 22.6, 22.0, 15.7, 14.0, 10.9; ν_{MAX}: 2916, 2848, 1694, 1466 cm^{-1}.

EXPERIMENT: 42

Preparation of (1R,2S)-2-octadecylcyclopropanecarbaldehyde (119).

(S)-2,2-Dimethyl-4-((S)-2-octadecylcyclopropyl)[1,3]dioxolane (1 g, 2.5 mmol) was added to a stirred suspension of periodic acid (1.4 g, 6.3 mmol) in dry ether (15 ml) at room temperature under nitrogen. The mixture was monitored by g.l.c. and when this showed no starting material, it was filtered prior to evaporation of the ether. The crude product was dissolved in chloroform (10 ml), insoluble salts were removed by filtration and the filtrate was evaporated to yield a white solid, *(1R,2S)-2-octadecyl-cyclopropanecarbaldehyde* (0.72 g, 72 %) which was used without further purification. An analytical sample was obtained by column chromatography on silica eluting with petroleum (bp 40 - 60 °C) / ether (9 : 1) as a white solid (m.p: 40 - 41 °C) $[\alpha]^{20}_D$ = +13.0, c = 1.025, $CHCl_3$;

[Found: C 81.6, H 13.2. $C_{22}H_{42}O$ requires: C 81.92, H 13.12] which showed δ_H: 9.3 (1 H, d, J 5.5 H_Z), 1.78 (1 H, m), 1.45 (2 H, m), 1.56-1.62 (35 H ,br s), 0.88 (3 H, t, J 6.1 H_Z); δ_C: 201.9, 31.9, 29.9, 29.7, 29.5, 29.35, 29.25, 28.2, 27.8, 24.8, 22.7, 14.75, 14.1; ν_{MAX}: 1694 cm^{-1}.

EXPERIMENT: 43

Preparation of (S)-2,2-Dimethyl-4-((1R,2S)-2-octadecylcyclopropyl)[1,3]dioxolane (120).

Diethyl zinc (22.7 ml, 1M, solution in hexane) was added to a stirred solution of (S)-4-((Z)-eicos-1-enyl)-2,2-dimethyl[1,3]dioxolane (1.73 g, 4.5 mmol) and diiodomethane (12.2 g, 45.5 mmol) in dichloromethane (25 ml) under argon at – 23 °C. The mixture was stirred vigorously for 10 h at -23 – 0 °C, when t.l.c. showed no starting material was left. It was quenched with aqueous ammonium chloride (10 ml) and the product was extracted with dichloromethane (3 × 50 ml). The organic phases were washed with sat. aq. sodium thiosulphate (20 ml) followed by brine (50 ml), dried, filtered then evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica eluting with petroleum / ether (9 : 1) to give *(S)-2,2-dimethyl-4-(2-(1R, 2S)-octadecylcyclopropyl)[1,3]dioxolane* (1.55 g, 86 %) ($[\alpha]^{22}_D$ = 7.4, c = 1.55, $CHCl_3$) [Found: C 79.4, H 12.8. Calculated for $C_{26}H_{50}O_2$: C, 79.12, H, 12.77], which showed δ_H: 4.09 (1 H, br q, J 5.7 H_Z), 3.6 (2 H, m), 1.4 (3 H, s), 1.35 (3 H, s), 1.25 (35 H, br s including 1 H cyclopropane), 0.87 (5 H, br t, J 6.1 H_Z including 2 H cyclopropane), 0.22 (1 H, br, m); δ_C: 108.32, 78.04, 69.67, 31.0, 30.0, 29.7, 29.6, 29.5, 29.3, 29.3, 26.9, 25.8, 22.65, 18.0, 15.4, 14.1, 10.55; ν_{MAX}: 2924, 2853, 1466, 1368, 1064 cm^{-1}.

EXPERIMENT: 44

Preparation of (S)-4-((Z)-Icos-1-enyl)-2,2-dimethyl[1,3]dioxolane (121).

n-Butyl lithium (1.6 M, 30.7 ml) was added dropwise to a stirred solution of 1-nonadecyltriphenylphosphonium bromide (20.6 g, 0.033 mol) in dry tetrahydrofuran (100 ml) at –40 °C under argon. The mixture was allowed to reach room temperature and stirred for 1 h, then cooled to –80 °C and 2,2-dimethyl[1,3]dioxolane-4-carbaldehyde (4 g, 0.03 mol) in tetrahydrofuran (10 ml) was added. The mixture was stirred at room temperature overnight. Sat. aq. ammonium chloride (5 ml) was added dropwise followed by petroleum / ether (1 : 1) (100 ml). The organic layer was separated and the aqueous layer was extracted with petroleum / ether (1 : 1) (2 × 50 ml). The combined organic phases were washed with water (2 × 75 ml), dried, filtered and evaporated to give the crude product. This was purified by column chromatography eluting with petroleum / ether (9 : 1) to give *(S)-4-((Z)-icos-1-enyl)-2,2-dimethyl-[1,3]dioxolane* (8.4 g, 71 %) ($[\alpha]^{22}_D$ = 1.8; c = 1.77, $CHCl_3$) [Found M^+: 380.3641; $C_{25}H_{48}O_2$ requires: 380.3654] which showed δ_H: 5.68 (1 H, dt, J 7.6, 10.5 H_Z), 5.4 (1 H, dd, J 7.6, 10.5 H_Z), 4.8 (1 H, br q, J 6.4 H_Z), 4.06 (1 H, br t, J 7.6 H_Z), 3.5 (1 H, br t, J 7.6 H_Z), 2.1 (2 H, br m), 1.6 (3 H, s), 1.5 (3 H, s), 1.26 (32 H, s), 0.88 (3 H, t, J 5.1 H_Z); δ_C: 133.1, 127.0, 108.9, 71.9, 69.4, 31.9, 29.7, 29.3, 27.7, 26.7, 25.9, 22.6, 14.07; ν_{MAX}: 2922, 2852, 1465, 1377, 1368 cm^{-1}.m/z = 380 (M^+), 365 (M^+- CH_3), 350 (M^+- C_2H_2), 322 (M^+- C_3H_6O), 322/305 (M^+- OH).

EXPERIMENT: 45

Preparation of nonadecyltriphenylphosphonium bromide (122).

1-Bromononadecane (29 g, 83.5 mmol) was added to a stirred solution of

triphenylphosphine (33.00 g, 125 mmol) in toluene (250 ml). The mixture was refluxed for 72 h. The solvent was evaporated and petroleum (bp 40-60 °C) (100 ml) was added and again evaporated. The residue was treated with diethyl ether (150 ml) and petroleum (bp 40-60 °C) (150 ml) then stirred for 1 h; by this time a slurry of fine crystals had formed. These were filtered off and washed well with diethyl ether and then dried to give 1-nonadecyltriphosphonium bromide (43.5 g, 85.4 %)[169] which showed δ_H: 7.9-7.45 (15 H, m), 1.6 (4 H, m), 1.2 (32 H, br s), 0.8 (3 H, t, J 7.0 Hz); δ_C:135, 133.7, 133.6, 130.6, 130.4, 119.1, 117.75, 31.9, 30.5, 30.3, 29.67, 29.3, 29.2, 23.2, 22.7, 14.1.

EXPERIMENT: 46

Preparation of 1-nonadecanol (124).

A) Nonadecanoic acid (30 g, 100 mmol) in tetrahydrofuran (500 ml) was added dropwise over a period of 15 min to a suspension of lithium aluminium hydride (6 g, 157.9 mmol) in tetrahydrofuran (200 ml) at room temperature. The mixture was refluxed for 1 h then quenched carefully with freshly prepared sat. aq. sodium sulphate (40 ml) followed by the addition of magnesium sulphate (10 g). The mixture was stirred vigorously for 10 min, then filtered through a pad of celite and washed well with tetrahydrofuran (2 × 50 ml). The filtrate was evaporated and the residue was recrystallized from aqueous methanol (methanol 500 ml and water 30 ml). The mixture was kept at –10 °C for 12 h; the solid was filtered off, and washed with cold methanol (50 ml) to give 1-nonadecanol (23.75 g, 83 %)[130] (m.p 61 - 62 °C; *Lit.* 61.7 °C) which showed δ_H: 3.65 (2 H, t, J 7.1 Hz), 1.6 (2 H, pent, J 6.8 Hz), 1.3 (33 H, br, s), 0.9 (3 H, t, J 7.1 Hz); δ_C: 63.1, 32.8, 31.9, 29.7, 29.4, 29.35, 25.7, 22.7, 14.1; ν_{MAX}: 3430 cm^{-1}.

B) 1-Bromoheptane (13.6 g, 76 mmol) was added dropwise to a mixture of magnesium turnings (1.97 g, 81 mmol) in dry tetrahydrofuran (80 ml) at a rate

sufficient to maintain a steady reflux. Once the exothermic reaction had subsided the mixture was heated under reflux for 1 h then cooled to room temperature. The reagent was cooled to -10 °C, then 12-bromododecanol (5.3 g, 20 mmol) in tetrahydrofuran (50 ml) was added. The mixture was cooled to - 40 °C followed by the addition of dilithium tetrachlorocuprate (5 ml). The mixture was stirred for 2 h at this temperature then for 12 h at room temperature. Sat.aq. ammonium chloride (100 ml) was added, the organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with water, dried and evaporated to give a residue, which was treated with petroleum (b.p 40 – 60 °C) (50 ml). The solution was cooled to –10 °C for 12 h, and the solid was filtered off to give 1-nonadecanol (5.2 g, 91 %), which showed identical spectra to those above.

EXPERIMENT: 47

Preparation of 1-bromononadecane (125).

1-Nonadecanol (23.75 g, 83.62 mmol) was added to a stirred solution of hydrobromic acid 48 % (100 ml) and tetrabutylammonium bromide (1 g). The mixture was refluxed for 3 h then cooled to room temperature and diluted with dichloromethane (120 ml) and water (300 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2 × 40 ml); the combined organic layers were washed with sat. aq. sodium bicarbonate (200 ml), sodium chloride solution (200 ml), and dried over magnesium sulphate. The solvent was evaporated to give a solid which was crystallised from petroleum (bp 40 – 60 °C) to give a white solid, 1-bromononadecane (28.7 g, 99%) (m.p 38.5, *Lit.*[44] 38-39) which showed δ_H: 3.4 (2 H, t, J 7.0 H_Z), 1.86 (2 H, pent, J 7.3 H_Z), 1.27 (32 H, br, s), 0.89 (3 H, t, J 6.7 H_Z); δ_C: 33.9, 32.8, 31.9, 29.7, 29.6, 29.5, 29.4, 29.35, 28.8, 28.2, 25.7, 22.7, 14.1.

EXPERIMENT: 48

Preparation of 1-heptadecyltriphosphonium bromide (128).

The procedure used to prepare nonadecyltriphenylphosphonium bromide (**122**) using 1-bromoheptadecane (20 g), to give 1-heptadecyltriphenylphosphonium bromide,[170] (20.2 g, 55 %) which showed δ_H: 7.74-7.59 (15 H, m), 1.4 (4H, m), 1.12 (28 H, br s), 0.72 (3 H, t, 6.7 H_Z); δ_C: 134.99, 134.95, 133.6, 133.4, 130.53, 130.3, 118.8, 117.45, 53.5, 31.7, 31.7, 30.4, 30.2, 29.5, 29.4, 29.35, 29.2, 29.0, 23.1, 22.5, 22.4, 22.35, 15.1, 13.95; ν_{MAX}: 2923, 2852, 1473, 1113 cm^{-1}.

EXPERIMENT: 49

Preparation of Butyric acid (1S,2S)-((Z)-2-octadec-1-enyl)-cyclopropylmethyl ester (129).

n-Butyl lithium (1.6 M, 28 ml) was added dropwise to a stirred solution of 1-heptadecyltriphenylphosphonium bromide (19.6 g, 0.033 mol) in dry tetrahydrofuran (110 ml) at –40 °C under argon. The mixture was allowed to reach room temperature and stirred for 1 h, then cooled to –78 °C and butyric acid (1S,2R)-2-formylcyclopropylmethyl ester (4.8g, 0.028 mol) in tetrahydrofuran (10 ml) was added. The mixture was stirred at room temperature overnight. Sat. aq. ammonium chloride solution (7 ml) was added dropwise followed by the addition of petroleum / ether (1 : 1) (100 ml). The organic layer was separated and the aqueous layer was extracted with petroleum / ether (1 : 1) (3 × 50 ml). The combined organic phases were washed with water (2 × 100 ml), dried, filtered and evaporated to give the crude product. This was purified by column chromatography eluting with petroleum / ether (9 : 1) to give *butyric acid (1S,2S)-((Z)-2-octadec-1-enyl)cyclopropylmethyl ester* (8.7 g, 65 %)

$[\alpha]^{22}_D$ = +37.98, c = 0.895, $CHCl_3$; (Found: C, 79.8, H, 12.4; requires: C, 79.53, H, 12.32) which showed δ_H: 5.46 (1 H, dt, J 7.0, 10.3 H_Z), 5.03 (1 H, br t, J 10.3 H_Z), 4.15 (1 H, dd, J 7.3, 11.5 H_Z), 3.98 (1 H, dd, J 8.2, 11.5 H_Z), 2.29 (2 H, t, J 7.3 H_Z), 2.13 (2 H, br q, J 7.0 H_Z), 1.65 (2 H, m), 1.26 (30 H, br s), 1.12 (1 H, m), 0.97 (3 H, t, 7.3 H_Z), 0.89 (3 H, t, J 6.7 H_Z), 0.40 (1 H, m); δ_C: 173.8, 132.2, 127.3, 65.0, 36.2, 31.9, 29.7, 17.6, 22,6, 18.45, 16.6, 14.02, 13.6, 12.2, 10.3; ν_{MAX}: 2927, 2853, 1737, 1465, 1180, cm^{-1}.

EXPERIMENT: 50

Preparation of [(1S,2S)-((Z)-2-Octadec-1-enyl)cyclopropyl]methanol (130).

Butyric acid (1S,2S)-((Z)-2-octadec-1-enyl)cyclopropylmethyl ester (6.7g, 0.017 mol), in dry THF (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.3 g, 0.034 mol) in dry THF (100 ml) at room temperature, maintaining the temperature under 65 °C. After the end of the addition the mixture was refluxed for 90 min, then allowed to reach room temperature. Sat.aq. magnesium sulphate (50 ml) was added carefully, filtered and the filtrate was washed with dichloromethane (100 ml) and evaporated to give the major isomer *[(1S,2S)-((Z)-2-octadec-1-enyl)cyclopropyl]methanol* (3.9 g, 70 %) which showed, δ_H: 5.45 (1 H, dt, J 7.3, 10.0 H_Z), 5.09 (1 H, br t, 10.0 H_Z), 3.75 (1 H, dd, J 6.4, 11.5 H_Z), 3.46 (1 H, dd, J 8.8, 11.5 H_Z), 2.17 (2 H, brq, J 7.0 H_Z), 1.7 (2 H, m), 1.25 (28 H, br s), 1.02 (1 H, dt, 5.2, 13.1 H_Z), 0.9 (3 H, t, 7.0 H_Z), 0.38 (1 H, br q, J 5.2 H_Z); δ_C: 132.2, 127.8, 63.7, 31.9, 29.5, 27.6, 22.65, 20.7, 14.1, 13.8, 12.3; ν_{MAX}: 3367, 2923, 2851, 1466, 1368, 1234, 1038, 722 cm^{-1}.

EXPERIMENT: 51

Preparation of ((1S,2R)-2-Octadecylcyclopropyl)methanol (131).

Sodium metaperiodate (9.9 g, 0.046 mol) was dissolved in water (75 ml) and added dropwise over 2 h to a stirred solution of [(1S,2S)-((Z)-2-octadec-1-enyl)-cyclopropyl]methanol (2 g, 6.2 mmol), sat. aq. copper sulphate (1 ml), acetic acid (1 ml), and hydrazine hydrate (9.3 ml, 0.18 mol) in isopropanol (50 ml) at 55-60 °C. The temperature was maintained below 60 °C; after the end of the addition, the mixture was cooled to room temperature and diluted with ether (50 ml) and water (50 ml). The organic layer was separated and the aqueous layer was re-extracted with ether (50 ml). The combined organic layers were washed with water (50 ml), dried and evaporated to give crude product which was purified by column chromatography eluting with petroleum / ether (9 : 1) to give *((1S,2R)-2-octadecylcyclopropyl) methanol* (1.42 g, 71%) ($[\alpha]^{22}_D$ = -7.75, c = 1.16, $CHCl_3$), (Found: C, 81.65, H, 13.4. $C_{22}H_{44}O$ requires: C, 81.41, H, 13.66) (m p 45-46 °C), which showed δ_H: 3.62 (2 H, br m, including J 8.2 H_Z), 1.38 (2 H, br m), 1.4-1.26 (34 H, br s), 1.06 (1 H, m), 0.88 (3 H, t, J 7.3 H_Z), 0.69 (1 H, dt J 4.5, 11.9 H_Z), -0.03 (1 H, br q, J 4.6 H_Z); δ_C: 63.3, 34.3, 31.9, 30.1, 29.7, 29.61, 29.5, 29.3, 28.5, 22.65, 21.0, 18.15, 16.1, 14.1, 14.05, 9.4; ν_{MAX}: 3308, 2930, 2851, 1462 cm^{-1}.

EXPERIMENT: 52

Preparation of (1S,2R)-2-Octadecylcyclopropanecarbaldehyde (132).

((1S,2R)-2-Octadecylcyclopropyl)methanol (1.3 g, 4.0 mmol) in dichloromethane (5 ml) was added to a suspension of pyridium chlorochromate (1.7 gm, 8.0 mmol) in dichloromethane (10 ml) at room temperature. The reaction was stirred for 3.5 h, when t.l.c showed no starting material was left. The reaction was diluted with ether and filtered through silica gel. The organic compound was purified by using column chromatography eluting with

petroleum / ether (10 : 1) to give *(1S,2R)-2-octadecylcyclopropane carbaldehyde* (0.95 g, 73 %) $[\alpha]^{22}_{D}$ = -8.06, c = 1.24, $CHCl_3$; [Found: M^+, 322.3249. Calculated for $C_{22}H_{42}O$: 322.3236] which showed; δ_H: 9.35 (1 H, d, J 5.6 H_Z), 1.84 (1 H, m), 1.49 (2 H, m), 1.32 (34 H, br s), 1.28 (1 H, m), 0.89 (3 H, t, J 5.9 H_Z); δ_C: 203.0, 34.9, 32.2, 29.85, 29.7, 29.5, 29.3, 26.5, 22.81, 23.3, 23.1, 22.7, 17.8, 14.7, 14.35, 14.2; ν_{MAX}: 3065, 2987, 1644, 1234 cm^{-1}.

EXPERIMENT: 53

Preparation of 10-((1S,2R)-2-Octadecylcyclopropyl)decanal (133).

10-((1S,2R)-2-Octadecylcyclopropyl)decan-1-ol (0.08 g, 0.17 mmol) in dichloromethane (5 ml) was added to a suspension of pyridium chlorochromate (0.07 gm, 0.35 mmol) in dichloromethane (5 ml) at room temperature. The reaction was stirred for 4 h, when t.l.c showed no starting material was left. The reaction was diluted with ether (5 ml) and filtered through silica gel on a sintered funnel. The organic compound was purified by using column chromatography eluting with petroleum (bp 40 - 60 °C) / ether (10 : 1) to give *10-((1S,2R)-2-octadecyl-cyclopropyl)decanal* ($[\alpha]^{20}_{D}$ = - 1.24°, c = 1.3, $CHCl_3$) (0.05 g, 71%) (Found M^+: 448.4647. $C_{31}H_{60}O$ requires: 448.4644) which showed δ_H: 9.77 (1 H, br s), 2.43 (2 H, t, J 7.0 H_Z), 1.42-1.1 (52 H, br s, including two protons cyclopropane ring), 0.86 (3 H, t, J 6.1 H_Z), 0.64 (1 H, br s), -0.33 (1 H, br s); δ_C: 202.8, 43.9, 43.85, 41.3, 32.0, 30.2, 30.15, 29.8, 29.6, 29.4, 29.35, 29.3, 29.25, 29.2, 28.8, 22.7, 22.6, 22.0, 15.7, 14.0, 10.9; ν_{MAX}: 2916, 2848, 1694, 1466 cm^{-1}.

EXPERIMENT: 54

Preparation of 1-carbomethoxyoctan-8-yltriphenylphosphonium iodide (134)

9-Iodononanoic acid methyl ester (23 g, 0.077 mol) was added to a stirred solution of triphenylphosphine (35 g, 0.13 mmol) in toluene (110 ml). The mixture was refluxed for 42 h. The solvent was evaporated and dry diethyl ether (100 ml) was added. A very viscous lower layer separated and this was agitated with the ether upper layer as well as possible. The ether layer was decanted off and the procedure repeated with diethyl ether (2 × 200 ml). The bottom layer was then dried under vacuum to leave a viscous yellow oil, 1-carbomethoxyoctan-8-yltriphenylphosphonium iodide (39.4 g, 93 %)[171] which showed δ_H: 7.75 – 7.6 (15 H, m), 3.55 (3 H, s), 3.5 (2 H, br m), 2.19 (2 H, t, J 7.4 H_Z), 1.5 (12 H, m).

EXPERIMENT: 55

Preparation of (Z)-10-((1S,2R)-2-Octadecyl-cyclopropyl)-dec-9-enoic acid methyl ester (135).

The down procedure was repeated using (1S,2R)-2-octadecyl-cyclopropanecarbaldehyde (0.75 g) to give *(Z)-10-((1S,2R)-2-Octadecyl-cyclopropyl)-dec-9-enoic acid methyl ester* (0.71 g, 64 %) which showed identical spectra to its enantiomer down.

EXPERIMENT: 56

Preparation of (Z)-10-((1R,2S)-2-Octadecyl-cyclopropyl)-dec-9-enoic acid methyl ester (143).

Sodium methoxide (0.33 g, 6.1 mmol) was added to a stirred solution of 1-carbomethoxyoctan-8-yltriphenylphosphonium iodide (3.4 g, 6.2 mmol) in dry

dimethylformamide (10 ml) at –2 to 0 °C, under argon. The mixture was stirred for 1 h then (1R,3S)-2-methyl-3-octadecylcyclopropanecarbaldehyde (0.5 g, 1.5 mmol) in a mixture of dimethylformamide (10 ml) and tetrahydrofuran (3 ml) was added. The mixture was stirred for 16 h, then sat. aq. ammonium chloride (5 ml) was added and the mixture was diluted with water (3 ml) and dichloromethane (15 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2 × 30 ml). The combined organic phases were washed with brine (3 × 20 ml), dried and evaporated, to yield a brownish residue. This was dissolved in dichloromethane and mixed with silica then the solvent was evaporated to give a solid which was purified by column chromatography eluting with petroleum / ether (97 : 3) to give mainly *(Z)-10-((1R,2S)-2-octadecylcyclopropyl)dec-9-enoic acid methyl ester* (0.53 g, 75 %) ($[\alpha]^{23}_D$ = 41.84, c = 1.14, $CHCl_3$) (Found: C, 80.4, H, 12.7. $C_{32}H_{60}O_2$ requires: C, 80.61, H, 12.68) which showed δ_H: 5.4 (1 H, dt, J 7.9, 10.0 Hz), 5.04 (1 H, br t, J 10.0 Hz), 3.5 (3 H, s), 2.36 (2 H, t, 7.0 Hz), 2.21 (2 H, br, q, J 6.4 Hz), 1.58 (2 H, br, m), 1.38 (7 H, m), 1.26 (40 H, s), 1.08 (3H, t, J 7.0 Hz), 0.09 (1 H, br, m); δ_C: 171.1, 130.0, 129.55, 51.4, 34.1, 31.9, 29.7, 29.1, 27.5, 24.9, 22.7, 18.45, 14.2, 14.1; ν_{MAX}: 1730, 1650 cm^{-1}. (The E-isomer could not be detected by NMR).

EXPERIMENT: 57

Preparation of (Z)-10-((1R,2S)-2-Octadecyl-cyclopropyl)-dec-9-en-1-ol (144).

Di-isobutylaluminum hydride (5 ml, 1M solution in hexane) was added to a stirred solution of (Z)-10-((1R,2S)-2-octadecyl-cyclopropyl)-dec-9-enoic acid methyl ester (1 g, 2.1 mmol) in dichloromethane (30 ml) at –78 °C. The mixture was allowed to reach room temperature and stirred for 1 h, when t.l.c. showed

no starting material. The reaction was quenched by the addition of methanol (3 ml) at - 40 °C, and allowed to reach room temperature followed by the addition of dilute hydrochloric acid (8 ml, 2M). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 20 ml). The combined organic layers were washed with brine, dried and evaporated to give a residue which was purified by column chromatography eluting with petroleum / ethyl acetate (5 : 2), to give *(Z)-10-((1R,2S)-2-octadecyl-cyclopropyl)-dec-9-en-1-ol* as an oil (0.85 g, 86 %) ($[\alpha]^{22}_D$ = +44.9, C = 1.32, $CHCl_3$) (Found: C, 82.9; H, 13.5. $C_{31}H_{60}O$ requires: C 82.96, H 13.47) which showed δ_H: 5.38 (1 H, dt, J 7.3, 10.3 H_Z), 5.03 (1 H, t, J 10.9 H_Z), 3.65 (2 H, t, J 6.4 H_Z), 2.14 (2 H, br q, J 5.1 H_Z), 1.57 (5 H, br, m), 1.26 (44 H, br, s), 0.88 (5 H, br, t, 6.3 H_Z), 0.1 (1 H, br, m); δ_C: 130.1, 129.5, 63.1, 32.8, 31.9, 29.7, 29.5, 29.5, 29.3, 29.2, 27.5, 25.7, 22.67, 18.45, 14.2, 14.1, 13.9; ν_{MAX}: 3314, 2918, 1652, 1467, 1076, 1056 cm^{-1}.

EXPERIMENT: 58

Preparation of (Z)-10-((1S,2R)-2-Octadecylcyclopropyl)dec-9-en-1-ol (136).

The above procedure was repeated using (Z)-10-((1S,2R)-2-octadecyl-cyclopropyl)dec-9-enoic acid methyl ester (0.5 g) to give *(Z)-10-((1S,2R)-2-octadecyl-cyclopropyl)-dec-9-en-1-ol* (0.29 g, 61 %) which showed δ_H: 5.39 (1 H, dt, J 7.3, 10.6 H_Z), 5.02 (1 H, br t, J 10.6 H_Z), 3.63 (2 H, t, J 7.0 H_Z), 2.11 (2 H, br q, J 7.0 H_Z), 1.55 (5 H, br m), 1.27 (44 H, br s), 0.89 (5 H, br t, J 7.0 H_Z), 0.09 (1 H, br m); δ_C: 130.1, 129.7, 63.1, 32.8, 32.1, 29.7, 29.5, 29.5, 29.3, 29.22, 27.5, 25.7, 22. 8, 18.45, 14.2, 14.1, 13.9; ν_{MAX}: 3324, 2917, 1467 cm^{-1}.

EXPERIMENT: 59

Preparation of 10-((1S,2R)-2-Octadecylcyclopropyl)decan-1-ol (137).

(Z)-10-((1S,2R)-2-Octadecylcyclopropyl)dec-9-en-1-ol (0.2g, 0.44 mmol), in dry THF (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.3g, 0.89 mmol) in dry THF (5 ml) at room temperature, maintaining the temperature under 65 °C. After the addition, the mixture was refluxed for 90 min, then allowed to reach room temperature, sat. aq. magnesium sulphate (3 ml) was added carefully, and filtered. The filtrate was washed with dichloromethane (10 ml), evaporated, and the crude product was purified by column chromatography using (10 : 1) petroleum / ether to give *10-((1S,2R)-2-octadecylcyclopropyl)decan-1-ol* (0.13 g, 64 %) (Found M^+: 450.4795; $C_{31}H_{62}O$ requires: 450.4801), ($[\alpha]^{20}_D$ = + 0.5, c = 1.4, $CHCl_3$) which showed, δ_H: 3.65 (2 H, t, J 6.7 H_Z), 1.55 (2 H, m) 1.4-1.2 (51 H, br s, including one cyclopropane ring proton), 0.88 (3 H, t, J 7.0 H_Z), 0.64 (2 H, br m), -0.32 (1 H, m); δ_C: 63.0, 32.7, 31.8, 30.1, 29.6, 29.3, 29.3, 28.6, 25.6, 22.6, 15.8, 14.0, 10.2; ν_{MAX}: 3418 cm^{-1}.

EXPERIMENT: 60

Preparation of 10-((1R,2S)-2-Octadecyl-cyclopropyl)-decan-1-ol (145).

The above procedure was repeated using (Z)-10-((1R,2S)-2-octadecyl-cyclopropyl)dec-9-en-1-ol (0.6 g) to give 10-((1R,2S)-2-octadecyl-cyclopropyl)decan-1-ol (0.39 g, 62 %) which showed an identical ^1H n. m. r spectrum to that above.

EXPERIMENT: 61

Preparation of 9-bromonon-1-ol (139)

Hydrobromic acid 48 % (25 ml, 0.22 mol) was added to a stirred solution of 1,9-nonanediol (25 g, 0.15 mmol) in toluene (400 ml) at room temperature. The reaction mixture was refluxed for 24 h, then cooled to room temperature and the organic layer was separated. The aqueous layer was extracted with toluene (2 × 30 ml). The combined organic layers were evaporated to give a brown oil, which was dissolved in dichloromethane (250 ml) and washed with sat. aq. sodium bicarbonate (50 ml), water (100 ml), dried over magnesium sulphate, and evaporated to give an oily residue. This was purified by column chromatography on silica eluting with petroleum (b.p. 40 –60 °C) / ether (5 : 2) to give 9-bromononan-1-ol (29 g, 83 %)[172] which showed δ_H: 3.6 (2 H, t, J 6.9 H_Z), 3.4 (2 H, t, J 7 H_Z), 1.85 (3 H, m, including the hydroxyl group), 1.5 (2 H, m), 1.4 – 1.25 (1 OH, br, s); δ_C: 62.4, 32.8, 32.7, 32.6, 29.3, 29.3, 28.6, 28.1, 25.7; ν_{MAX}: 3220 cm^1.

EXPERIMENT: 62

Preparation of 9-bromononanoic acid (140).

Potassium permanganate (40 g,0.25 mol) was added in portions over a period of 1 h to a mechanically stirred solution of 9-bromononan-1-ol (28 g, 0.125 mol), water (627 ml), dichloromethane (627 ml), acetic acid (2 ml), tetrabutylammonium bromide (1 g) and a solution of concentrated sulphuric acid (15 ml) in water (30 ml) at 5 °C. The mixture was allowed to reach room temperature and stirred for 18 h, then sodium bisulphate was added to destroy the excess of potassium permanganate and to give a clear solution. The organic layer was separated, and the aqueous layer extracted with dichloromethane (2 × 50 ml). The combined organic layers were washed with brine (200 ml), dried and evaporated to give a white solid, 9-bromononanaoic acid (29 g), which was dissolved in methanol (100 ml) together with concentrated sulphuric acid (2 ml).

The reaction mixture was refluxed for 3h, when t.l.c showed no starting material, the solvent was evaporated and the residue was treated with sat. aq; sodium bicarbonate (15 ml) and dichloromethane (150 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic layer were washed with water (100 ml), dried and evaporated to give 9-bromononanoic acid (29 g, 96 %)[173] which showed an identical spectrum to an authentic sample (δ_H: 10.3 (1H, br s), 3.35 (2 H, t, J 7.3 H_Z), 2.32 (2 H, t, J 7.4 H_Z), 1.75 (2 H, pent, J 7.0 H_Z), 1.6 (2 H, br pent, J 7.6 H_Z), 1.4-1.1 (10 H, br s)).

EXPERIMENT: 63

9-Bromononanoic acid methyl ester (141).

Thionyl chloride (2.2 ml) was added dropwise to a stirred mixture solution of 9-bromononanoic acid (29 g, 0.122 mol) and 2,2-dimethoxypropane (6.7 ml), in methanol (226 ml) at room temperature. The mixture was stirred for 16 h, when t.l.c showed no starting material was left. Water (50 ml) and dichloromethane (200 ml) were added, the organic layer was separated washed with brine (50 ml), dried, and evaporated to give 9-bromononanoic acid methyl ester (26 g, 84 %), which showed an identical n.m.r. spectrum to an authentic sample[163] (δ_H: 3.7 (3 H, s), 3.42 (2 H, t, J 7.0 H_Z), 2.38 (2 H, t, J 7.3 H_Z), 1.86 (2 H, pent, J 7.0 H_Z), 1.63 (2 H, br pent, J 7.1 H_Z), 1.3 (10 H, br s).

EXPERIMENT: 64

9-Iodononanoic acid methyl ester (142).

9-Bromononanoic acid methyl ester (25 g, 0.1 mol) was added to a stirred solution of sodium iodide (50 g, 0.33mol) in acetone (350 ml) at room temperature, followed by the addition of sodium bicarbonate (9.5 g, 0.2 mol). The mixture was refluxed for 3 h, when g.l.c showed no starting material. The solvent was evaporated and the residue was diluted with water (300 ml), and dichloromethane (300 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2 × 50 ml). The combined organic layers were washed with sat. aq. sodium thiosulphate (50 ml), dried and evaporated to give a pale yellow oil, which was purified by column chromatography on silica eluting with petroleum (b.p 40 – 60 °C) / ether (5 : 1) to give 9-iodononanoic acid methyl ester (27 g, 90 %)[163] which showed δ_H: 3.6 (3 H, s), 3.1 (2 H, t, J 7 H_Z), 2.24 (2 H, t, J 7.4 H_Z), 1.75 (2 H, br,pent, J 7H_Z), 1.4-1.2 (10 H, m).

EXPERIMENT: 65

Preparation of 2,4-Dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid ethyl ester (154).

Dry hydrogen bromide was bubbled into an ice-cold stirred solution of ethyl acetoacetate (188 g, 1.44 mol) until one equivalent had been absorbed by weight. The resulting solution was warmed to room temperature for 16 h, when g.l.c showed no starting material, then the mixture was poured into water (500 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 ml). The combined organic layers were washed with sat. aq. sodium bicarbonate (200 ml), dried over magnesium sulphate, filtered, then the solvent was evaporated at 14 mm Hg. The residual oil was distilled to give 2,4-dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid ethyl ester[147] (225 g, 77

%) as a colorless oil (b.p 130 – 132 °C at 1.5 – 2 mmHg) which showed δ_H: 5.83 (1 H, br, s), 4.17 (2 H, q, J 7.12 H_Z), 2.2 (3 H, s), 2.04 (3 H, s), 1.2 (3 H, t, J 7.1 H_Z); δ_C: 165.2, 164.5, 160.4, 154.3, 113.0, 61.5, 21.0, 19.4, 14.0; ν_{MAX}: 2985, 1750, 1551, 1398, 1305, 1082 cm^{-1}.

EXPERIMENT: 66

5-Bromo-2,4-dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid ethyl ester (155).

Bromine (39 ml, 0.76mmol) was added slowly to a rapidly stirred solution of 2,4-dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid ethyl ester (112 g, 0.5 mol) in dichloromethane (250 ml) at 0 °C. The mixture was stirred for 16 h, at ambient temperature. When g.l.c showed no starting material was left, ice water (500 ml) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 ml), the combined organic layers were washed with sodium thiosulphate solution (200 ml), and sodium bicarbonate (100 ml). The organic layer was dried over magnesium sulphate, filtered, then the solvent was evaporated to give a brown solid, which was recrystallized from methylated spirit to give white crystals of 5-bromo-2,4-dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid ethyl ester (135.5 g, 85 %) which showed δ_H: 4.3 (2 H, q, J 7.12 H_Z), 2.28 (6 H, s), 1.31 (3 H, t, J 7.1 H_Z); δ_C: 165.00, 161.04, 157.36, 152.00, 114.14, 110.08, 62.12, 21.82, 18.87, 14.08; ν_{MAX}: 3018, 1725, 1215 cm^{-1}, (m. p 82–84 °C; *lit.* 83–84 °C). The n.m.r spectrum was identical to that reported.[147]

EXPERIMENT 67

3-Methylenecyclopropane-*trans*-1,2-dicarboxylic acid (147).

5-Bromo-2,4-dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid ethyl ester (40 g,

144.9 mmol) was added slowly to a stirred solution of potassium hydroxide (78.4 g) in water (200 ml, 7M) at 102 – 104 °C. The reaction was exothermic and the temperature was kept below 105 °C throughout the addition. After that the reaction was stirred for 30 min before cooling to 0 °C; it was then acidified carefully with dilute sulphuric acid (5 %), maintaining the temperature below 27 °C. Ethyl acetate (100 ml) was added and the precipitate was filtered off. The filter cake was washed with ethyl acetate and the organic layer was separated, treated with charcoal, dried over magnesium sulphate, then evaporated to approximately 50 ml, then di-isopropyl ether (50 ml) and ethyl acetate (10 ml) were added. The mixture was left to settle overnight to give a brown precipitate, 3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid, which was filtered and washed with cooled ether (11.1 g, 53 %), (mp 202-204, *lit* [141] 203-205 °C) which showed in (CD_3OD) δ_H: 5.87 (1H, br s), 5.31 (1 H, br s), 2.98 (2 H, t, J 2.3 Hz); δ_C: 173.3, 132.0, 106.7, 27.5.

EXPERIEMENT: 68

3-Methylenecyclopropane-*trans*-1,2-dicarboxylic acid dimethyl ester (148).

Sulphuric acid (1.5 ml) was added to a stirred solution of 3-methylene-cyclopropane-*trans*-1,2-dicarboxylic acid (5 g, 35.2 mmol) in methanol (50 ml) followed by the addition of 2,2-dimethoxypropane (6 ml) at room temperature. When g.l.c showed no starting material was left, the reaction was diluted with dichloromethane (50 ml), and brine (10 ml). The organic layer was extracted with dichloromethane (2 × 20 ml). The combined organic layers were washed with sat. aq. sodium bicarbonate, dried and evaporated to give a pale yellow oil, dimethyl 3-methylenecyclopropane-*trans*-1,2-dicarboxylate[141] (4.3 g, 72 %), which showed δ_H: 5.61 (2 H, narrow t, J 2.3 Hz), 3.65 (6 H, s), 2.82 (2 H, narrow t, J 2.35 Hz); δ_C: 169.6 (s), 128.8 (s), 106.6 (t), 52.4 (d), 25.6 (q); ν_{max}: 1732.4 cm^{-1}.

EXPERIEMENT: 69

2-*Trans*-Hydroxymethyl-3-methylenecyclopropylmethanol (149).

3-Methylenecyclopropane-*trans*-1,2-dicarboxylic acid dimethyl ester (3.93 g, 23.1 mmol) in tetrahydrofuran (20 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.3 g) in tetrahydrofuran (30 ml) at room temperature. The mixture was refluxed for 2 h, when t.l.c showed no starting material, then the cooled mixture was quenched with sat. aq. sodium sulphate (7 ml) and the precipitated salt was filtered off through magnesium sulphate. The filtrate was evaporated to give 2-*trans*-hydroxymethyl-3-methylenecyclopropylmethanol[141] (2.0 g, 76 %), which showed: δ_H: 5.45 (2 H, t, J 1.9 H_Z), 3.92 (2 H, dd, J 4.2, 11.5 H_Z), 3.2 (2 H, dd, J 9.0, 11.4 H_Z) 1.67 (2 H, m); δ_C: 133.94 (s), 105 (t), 64 (t), 24.65 (d); ν_{MAX}: 3374 cm^{-1}.

EXPERIEMENT: 70

6-Methylene-3-oxabicyclo[3.1.0]hexane-2,4-dione (161).

Potassium acetate (0.05 g) was added to a stirred solution of 2-*trans*-hydroxymethyl-3-methylenecyclopropylmethanol (2 g, 14 mmol) in acetic anhydride (10 ml). The reaction was refluxed for 2 h, when an ^1H n.m.r spectrum showed no starting material. The mixture was cooled and the acetic acid and acetic anhydride were evaporated at 14 mmHg and 40 – 45 °C. The residue was treated with diethyl ether, filtered, then evaporated at 14 mmHg to give an oil, which was purified by bulb-to-bulb distillation to give 6-methylene-3-oxa-bicyclo[3.1.0]hexane-2,4-dione[149] (1.1 g, 63 %) which showed δ_H: 5.87 (2 H, s), 3.29 (2 H, s); δ_C: 165.1, 124.1, 107.9, 26.3.

EXPERIMENT: 71

Cis-2-hydroxymethyl-3-methylenecyclopropylmethanol (162).

6-Methylene-3-oxabicyclo[3.1.0]hexane-2,4-dione (0.4 g) was dissolved in dry tetrahydrofuran (10 ml) and added to a suspension of lithium aluminum hydride (0.24 g) in tetrahydrofuran (20 ml) under nitrogen at room temperature. The reaction was refluxed for 2 h, when t.l.c showed no starting material. The mixture was cooled and quenched with sat. aq. ammonium chloride (3 ml). The precipitate was filtered through celite and the filter cake washed with ethyl acetate (3 × 10 ml), then the solvent was evaporated to give a crude oil. Column chromatography on silica eluting with ethyl acetate / petroleum (b.p 40 - 60 °C) (3 : 1) gave *cis*-2-hydroxymethyl-3-methylenecyclopropylmethanol[174] (0.27 g, 77 %) which showed δ_H: 5.45 (2 H, t, J 1.9 H_Z), 3.92 (2 H, dd, J 4.2, 11.5 H_Z), 3.2 (2 H, dd, J 9.0, 11.4 H_Z), 1.67 (2 H, m); δ_C: 133.9 (s), 105.0 (t), 64.0 (t), 24.65 (d); ν_{MAX}: 3374 cm^{-1}.

EXPERIMENT: 72

Butyric acid (1R,2S) 2-hydroxymethyl-3-methylenecyclopropylmethyl ester (164).

Vinyl butyrate (1 ml, 7.8 mmol) was added to a stirred solution of *cis*-2-hydroxymethyl-3-methylenecyclopropylmethanol (0.53 g, 4.6 mmol) in tetrahydrofuran (20 ml) and lipase (PG) (0.5 g) at room temperature. The reaction was stirred for 48 h, when g.l.c showed no starting material was left. The precipitate was filtered through celite and the filter cake washed with ether then the solvent was evaporated to give a crude oil which was washed with sat. aq. sodium bicarbonate. The product was extracted with dichloromethane, dried and evaporated to give a pale yellow oil, which was subjected to column chromatography on silica gel eluting with petroleum (bp 40 - 60 °C) / ether (5:2).

This gave gave butyric acid 2-hydroxymethyl-3-methylenecyclopropylmethyl ester (0.45 g, 54 %) (Found $[C_{10}H_{16}NaO_3]^+$: 207.0991; requires 207.0992), $([\alpha]^{22}_D$ = -10.7l, c = 0.85, $CHCl_3$), which showed δ_H: 5.4 (2 H, br, s), 4.43 (1 H, m), 3.85 (2 H, br dd, J 9.2, 12.3 H_Z), 3.41(1 H, dd, J 9.2, 12.3 H_Z), 2.27 (2 H, t, J 7.3 H_Z), 2.00 (2 H, br, m), 1.62 (2 H, sextet, J 7.4 H_Z), 0.91 (3 H, t, J 7.3 H_Z); δ_C: 173.66 (s), 133.46 (s), 105.36 (t), 62.16 (t), 60.45 (t), 36.21 (t), 23.01 (d), 18.78 (d), 18.37 (t), 13.58 (q); ν_{MAX}: 3438, 1735 cm^{-1}.

EXPERIMENT: 73

Butyric acid (1R,2S) 2-formyl-3-methylenecyclopropylmethyl ester (168).

Butyric acid 2-hydroxymethyl-3-methylenecyclopropylmethyl ester (2 g, 10.8 mmol) was added at room temperature to a stirred suspension of pyridinum chlorochromate (4.6 g, 21.3 mmol) in dichloromethane (60 ml). A black precipitate appeared after 10 min. The reaction was stirred for 3 h, when t.l.c showed no starting material was left. The reaction was diluted with ether (150 ml), and filtered through a pad of silica. The solvent was evaporated to give a colorless oil, butyric acid 2-formyl-3-methylenecyclopropylmethyl ester (1.75 g, 92 %) which showed; δ_H: 9.1 (1 H, d, J 5.5 H_Z), 5.68 (1 H, t, J 2.1 H_Z), 5.62 (1 H, t, J 2.1 H_Z), 4.54 (1 H, dd, J 5.5, 12.1 H_Z), 4.06 (1 H, dd, J 8.7, 12.1 H_Z), 2.56 (2 H, br m), 2.24 (2 H, t, J 7.3 H_Z), 1.60 (2 H, sextet, J 7.3 H_Z), 0.9 (3 H, br, t, J 7.3 H_Z); δ_C: 197.0 (d), 173.3 (s), 130.6 (s), 108.2 (t), 60.8 (t), 35.96 (t), 31.81 (d), 24.48 (d), 18.34 (t), 13.57 (q); ν_{MAX}: 1731.4 cm^{-1}.

EXPERIMENT: 74

Butyric acid (1R,2S) 2-((E)-2-ethoxycarbonyl-vinyl)-3-methylene-cyclopropylmethyl ester (169).

To a stirred solution of butyric acid 2-formyl-3-methylenecyclopropylmethyl ester

(2 g, 10.9 mmol) in toluene (25 ml), carboethoxymethylentriphenylphosphorane (4.2 g, 12 mmol) was added at room temperature. The mixture was stirred for 18 h, then the solvent was evaporated to give a thick oil which was treated with petroleum (bp 40 - 60° C) / ether (5 : 2). The precipitate was filtered off; evaporation of the solvent gave a pale yellow oil which was purified by column chromatography eluting with petroleum (bp 40 - 60° C) / ether (5 : 2) to give *butyric acid 2-((E)-2-ethoxycarbonylvinyl)-3-methylenecyclopropylmethyl ester* (2.25 g, 83 %) which showed δ_H: 6.6 (1 H, dd, J 8.8, 15.4), 5.8 (1 H, d, J 15.4 H_Z), 5.55 (1 H, t, J 2.1 H_Z), 5.5 (1 H, t, J 2.1), 4.2 (1 H, dd, J 5.96, 11.9 H_Z), 4.1 (2 H, q, J 7.1 H_Z), 3.8 (1 H, dd, J 8.9, 11.9 H_Z), 2.4 (1 H, m), 2.3 (1 H, m), 2.2 (2 H, t, J 7.2 H_Z), 1.5 (2 H, sextet, J 7.1 H_Z), 1.2 (3 H, t, J 7.1 H_Z), 0.8 (3 H, t, J 7.3 H_Z); δ_C: 173.50 (s), 166.04 (s), 144.62 (t), 134.48 (s), 122.51(t), 106.9 (s), 61.85 (d), 60.23(d), 36.1 (d), 30.9 (s), 23.0 (t), 18.4(d), 14.24 (q), 13.6 (q); ν_{MAX}: 2967, 1736, 1632 cm^{-1}.

EXPERIMENT: 75

Butyric acid (1R,2S) 2-methylene-3-vinylcyclopropylmethyl ester (170).

Butyl lithium (3.4 ml, 1.5 M) was added to a stirred solution of methyl triphenyl-phosphonium bromide (1.5 g, 4.2 mmol) in dry tetrahydrofuran (25 ml) at –78 °C. The reaction was allowed to reach room temperature for 15 min then cooled again to – 60 °C, and butyric acid 2-formyl-3-methylenecyclopropylmethyl ester (0.7 g, 3.8 mmol) in tetrahydrofuran (5 ml) was added. The reaction was allowed to reach room temperature for 3 h, then quenched with sat. aq. ammonium chloride (4 ml); the product was extracted with diethyl ether (3 × 30 ml), dried and evaporated to give a thick oil which was purified by column chromatography on silica eluting with petroleum (b.p 40 - 60 °C) / ether (5 : 2) to give *butyric acid 2-methylene-3-vinylcyclopropylmethyl ester* (0.58 g, 77 %) which showed δ_H: 5.63 (1 H, ddd, J, 7, 10, 17 H_Z), 5.48 (2 H, br s), 5.13 (1 H, d, J 17 H_Z), 5.05 (1 H, d, J 10 H_Z), 4.17 (1 H, dd, J 6.1, 11.6 H_Z), 3.9 (1 H, dd, J 9.1, 11.6 H_Z), 2.33 (1 H, m), 2.24

(2 H, t, J 7.3 H_Z), 2.06 (1 H, m), 1.6 (2 H, sextet, J 7.4 H_Z), 0.91 (3 H, t, J 7.3 H_Z); δ_C: 173.6 (s), 135.3 (s), 133.1 (d), 117 (t), 105.8 (t), 62.1 (t), 36.2 (t), 23.5 (d), 20.9 (d), 18.4 (t), 13.6 (q); ν_{max}: 1736, 1632 cm^{-1}; *m/z*: 180 (M^+), 166 (M^+-CH_2), 126 (M^+-C_4H_6), 109 (M^+-C_4H_7O), 126 / 70 (M^+-C_3H_4O).

EXPERIMENT: 76

Butyric acid (1R,2S) 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-3-methylene-cyclopropylmethyl ester (172).

Diethyl azodicarboxylate (2.27 g, 12 mmol) was added to a stirred solution of butyric acid (1R,2S)-2-hydroxymethyl-3-methylenecyclopropylmethyl ester (2 g, 10 mmol), triphenyl phosphine (3.1 g, 11.8 mmol) and phthalimide (1.75 g, 11.9 mmol) in tetrahydrofuran (50 ml) at 0 °C. The resulting yellow solution was stirred at room temperature for 20 h, then the solvent was evaporated and the residue was treated with hexane / ether (2 : 1) and the precipitate was filtered off to give a yellow solution, which was purified by flash chromatography on silica eluting with petroleum (b.p 40 - 60° C) / ether to give *butyric acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-3-methylenecyclopropylmethyl ester* (2.1 g, 61 %), (Found $[C_{18}H_{19}NNaO_4]^+$: 336.1220; requires 336.1206), $[\alpha]^{23}_D$ = +15.33 (c = 1.03, $CHCl_3$), which showed δ_H: 7.8 (2 H, m), 7.7 (2 H, m), 5.4 (2 H, br s), 4.5 (1 H, dd, J 5.7, 11.8 H_Z), 3.9 (1 H, dd, J 9.7, 11.8 H_Z), 3.7 (2 H, m), 2.25 (1 H, m), 2.08 (2 H, t, J 7.3 H_Z), 2.02 (1 H, m), 1.4 (2 H, sextet, J 7.6 H_Z), 0.9 (3 H, t, J 7.3 H_Z); δ_C: 173.28 (s), 167.94 (s), 133.9 (d), 132.1 (s), 123.1 (d), 123.0 (s), 105.4 (t), 62.1 (t), 36.1 (t), 35.8 (t), 18.9 (d), 18.7 (d), 18.2 (t), 13.5 (q); ν_{MAX}: 2964, 1713.0 cm^{-1}; m/z: 313 (M^+), 225 (M^+-$C_4H_8O_2$), 160 (M^+-$C_8H_{11}NO_2$), 160/104 (M^+-C_4H_8), 104/76 (M^+-C_2H_4).

EXPERIMENT: 77

(1R,2S) 2-(2-Hydroxymethyl-3-methylenecyclopropylmethyl)isoindole-1,3-dione (173)

Butyric acid 2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-3-methylene-cyclopropylmethyl ester (0.5 g, 1.6 mmol) was added to a suspension of anhydrous potassium carbonate (0.4 g) in methanol (10 ml) at room temperature. The reaction was stirred for 3 h, when t.l.c showed no starting material was left then the precipitate was filtered off, the residue washed with methanol, then the filtrate was evaporated to give a solid residue, *2-(2-hydroxymethyl-3-methylene-cyclopropylmethyl)isoindole-1,3-dione* (0.3 g, 78 %) which (dissolved in D_2O) showed δ_H: 7.57 (2 H, br m), 7.45 (2 H, br m), 5.53 (1 H, s), 5.49 (1 H, s), 3.73 (1 H, dd, J 6.2, 11.5 Hz), 3.61 (1 H, dd, J 7.8, 11.5 Hz), 3.42 (1 H, dd, J 6.4, 14.2 Hz), 3.35 (1 H, dd, J 14.2, 7.3 Hz), 2.0 (2 H, m); δ_C: 166.54, 165.92, 156.86, 132.35, 131.74, 128.11, 127.69, 104.82, 75.87, 44.6, 43.71, 36.55; ν_{MAX}: 3448, 1725, 784 cm^{-1}.

EXPERIMENT: 78

Butyric acid (1R,2S) 2-aminomethyl-3-methylene-cyclopropylmethyl ester (174).

Hydrazine hydrate (0.36 g, 7.1 mmol) was added dropwise to a stirred solution of butyric acid (1R,2S)-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-3-methylene-cyclopropylmethyl ester (1.9 g, 6 mmol) in ethanol (30 ml) at room temperature. The mixture was refluxed for 3 h, then cooled to room temperature and concentrated. Hydrochloric acid (6 ml) was added then the precipitate was removed by filtration and the product was extracted with dichloromethane (3 × 50 ml). The combined organic layers were dried and evaporated to give a residue which was purified by column chromatography on silica gel eluting with petroleum (bp 40 - 60° C) / ethyl acetate (1 : 1) to give *butyric acid 2-aminomethyl-3-methylene-cyclopropylmethyl ester* (0.9 g, 81 %) (Found $[C_{10}H_{17}NNaO_2]^+$: 206.1158; requires 206.1151) as an oil which showed $[\alpha]^{24}_D$ = +17.0 (c = 1.8, $CHCl_3$), δ_H: 6.72 (1 H, br, s), 5.39 (1 H, br s), 5.37 (1 H, br s), 4.17 (1 H, br s), 4.0 (1 H, dd, J 4.7, 11.8 Hz), 3.65 (1 H, m), 3.35 (1 H, br, t, J 11.8 Hz) 3.0 (1 H, ddd, J 4.7, 10.1, 14.7 Hz), 2.1 (2 H, t, J 7.4 Hz), 1.9 (1 H, m), 1.7 (1 H,

m), 1.62 (2 H, sextet, J 7.4 H_Z), 0.93 (3 H, t, J 7.4 H_Z); δ_C: 173.8 (s), 134.5 (s), 104.5 (t), 59.8 (t), 38.7 (t), 36 (t), 22.5 (d), 20.2 (d), 19.1 (t), 13.7 (q); ν_{MAX}: 3290.4, 1649.1 cm^{-1}

EXPERIMENT: 79

5-Butyryloxymethyl-4-methylenecyclopent-2-enecarboxylic acid ethyl ester (175).

Butyric acid 2-((E)-2-ethoxycarbonylvinyl)-3-methylenecyclopropyl methyl ester (0.7 g, 2 mmol) was dissolved in toluene (7 ml) then morpholine (0.12 g, 1.3 mmol) was added, and the mixture was refluxed. After 2 h, when ^1H n.m.r spectra showed no starting material; the solution was evaporated and the residue was purified by column chromatography on silica eluting with petroleum (bp 40 - 60° C) / ether (5 : 1) to give *5-butyryloxymethyl-4-methylenecyclopent-2-ene carboxylic acid ethyl ester* (0.2 g, 28 %), $[\alpha]^{26}_D$ = +19.1 (c = 0.4, $CHCl_3$), which showed δ_H: 6.2 (1 H, dd, J 2.2, 5.5 H_Z), 6.04 (1 H, br m), 5.04 (1 H, br s), 4.9 (1 H, d, J 2.2 H_Z), 4.25 (1 H, dd, J 5.2, 11 H_Z), 4.15 (2 H, q, J 7.1 H_Z), 4.1 (1 H, dd, J 7.6, 11 H_Z), 3.5 (1 H, br q, J ca. 3.0 H_Z), 3.45 (1 H, br m), 2.27 (2 H, t, J 7.3 H_Z), 1.62 (2 H, sextet, J 7.3 H_Z), 1.26 (3 H, t, J 7.0 H_Z), 0.92 (3 H, t, J 7.3 H_Z); δ_C: 173.56 (s), 172.62 (s), 152.03 (s), 135.44 (d), 134.37 (d), 106.3 (t), 66.05 (t), 60.95 (t), 54.1 (d), 43.72 (d), 36.11(t), 18.32 (t), 14.13 (q), 13.58 (q); ν_{MAX}: 2966.3, 1739.5 cm^{-1}.

EXPERIMENT: 80

6-Methylene-3-oxabicyclo[3.1.0]hex-2-yl-acetic acid methyl ester (178).

Potassium carbonate (0.35 g, 2.08 mmol) was added to a stirred solution of butyric acid 2-((E)-2-ethoxycarbonyl-vinyl)-3-methylene-cyclopropylmethyl ester (0.5gm, 2.1 mmol) in methanol (5 ml) at room temperature. The reaction was stirred for 2 h, then t.l.c showed no starting material was left. The reaction was

filtered, the filtrate was washed with water and the product was extracted with dichloromethane, dried, and evaporated, to give an oil, which was purified by column chromatography on silica eluting with petroleum / ether (5 : 1) to give two isomers in ratio 1:1 of *6-methylene-3-oxa-bicyclo[3.1.0]hex-2-yl-acetic acid methyl ester* which showed: δ_H: 5.52 (1 H, br m), 5.49 (2 H, br s), 5.46 (1H, br s), 4.55 (1 H, br t, J 6.9 H_Z), 4.46 (1 H, br m), 4.06 (1 H, d, J 8.2 H_Z), 4.01 (1 H, d, J 8.2 H_Z), 3.90 (1 H, m), 3.7 (6 H, s), 2.7-2.4 (4 H, m), 2.2-2.0 (4 H, br s); δ_C (for the two isomers): 171.7, 171.1, 134.3, 132.75, 106.57, 105.36, 78.21, 77.77, 71.37, 69.52, 51.7, 38.2, 25.62, 24.43, 22.12, 21.3, 19.39, 14.27; ν_{MAX}: 2951, 2868, 1736 cm^{-1}.

EXPERIMENT: 81

(1R*,5S*,6s*) 1-(3-Oxabicyclo[3.1.0]hex-6-yl)methanol (179).

Mercuric acetate (0.9 g) was stirred for 15 min in tetrahydrofuran (10 ml) then 2-*trans*-hydroxymethyl-3-methylene-cyclopropylmethanol (0.3 g) was added. The mixture was stirred for 3 h, then sodium hydroxide (6 ml, 3 M) and sodium borohydride (6 ml, 0.5 M in 3M sodium hydroxide) were added. After 5 min, brine (10 ml) was added, the organic layer was separated then the aqueous layer was extracted with ethyl acetate; the combined organic layers were dried and evaporated to give an oil which was columned on silica eluting with petroleum (b.p 40 - 60° C) / ether (1 : 1) to give *1-(3-oxa-bicyclo[3.1.0]hex-6-yl)methanol* (0.25 g, 27 %) which showed δ_H: 3.86 (2 H, brd, J 8.3 H_Z), 3.68 (2 H, brd, J 8.1 H_Z), 3.51 (2 H, brd, J 7.0 H_Z), 1.53 (2 H, narrow t, J 1.7 H_Z), 1.07 (1 H, m); δ_C: 70.87 (t), 69.35 (t), 22.49 (d), 22.1 (d); ν_{MAX}: 3340.2 cm^{-1}.

EXPERIMENT: 82

3-Methylenepent-4-ene-1,2-diol (180).

Mercuric acetate (0.9 g) was stirred for 15 min in tetrahydrofuran (10 ml) then *cis*-

2-hydroxymethyl-3-methylenecyclopropylmethanol (0.32 g) was added and the mixture was stirred for 3 h. Sodium hydroxide (6 ml, 3 M) and sodium borohydride (6 ml, 0.5 M in 3M sodium hydroxide) were then added. After 5 min, brine was added and the organic layer was separated then the aqueous layer was extracted with ethyl acetate; the combined organic layers were dried and evaporated to give an oil which was columned on silica eluting with petroleum (bp 40 - 60 °C) / ether (1 : 1) to give *3-methylenepent-4-en-1,2-diol* (0.1 g, 31 %) which showed δ_H: 6.3 (1 H, dd, J 11, 17.7, H_Z), 5.32 (1 H, br, s), 5.29 (1 H, d, J 17.7 H_Z), 5.22 (1 H, br, s), 5.09 (1 H, d, J 11.1 H_Z), 4.5 (1 H, narrow, m), 3.7 (1 H, dd, J 3.1, 11.1 H_Z), 3.55 (1 H, dd, J 7.2, 11.1 H_Z); δ_C: 145, 136.2, 115.9, 114.2, 71.45, 66.2; ν_{MAX}: 3300, 1623cm^{-1}.

EXPERIMENT 83

2-Bromo-2-bromomethyl-3-hydroxymethylcyclopropylmethanol (185).

Bromine (0.24 ml, 4.5 mmol) was added dropwise to a stirred solution of 2-*trans*-hydroxymethyl-3-methylenecyclopropyl)methanol (0.5 g, 4.3 mmol) in dichloromethane (10 ml). The reaction was stirred for 10 min when g.l.c showed no starting material, then quenched with sat. aq. sodium metabisulphite (3 ml). The product was extracted with dichloromethane (3 × 25 ml), dried and evaporated to give a solid which was purified by column chromatography on silica eluting with petroleum (bp 40 - 60 °C) / ether (5 : 2) to give *2-bromo-2-bromomethyl-3-hydroxymethylcyclopropylmethanol* (0.9 g, 75 %) which showed δ_H: 4.02 (2 H, dt, J 11.8, 2.4 H_Z), 3.9-3.6 (4 H, m, including a doublet at 3.83 with coupling constant 11.8 H_Z), 1.85 (1 H, m), 1.3 (1 H, m); δ_C: 64.8 (t), 60.1 (t), 42.5 (s), 41.4 (t), 36.3 (d), 32.7 (d); ν_{MAX}: 3344 cm^{-1}.

EXPERIMENT: 84

2,2-Dimethyl-4,7-dihydro[1,3]dioxepine (187).

p-Toluene sulfonic acid monohydrate (0.27 g, 1.4 mmol) was added to a stirred solution of 2-butene –1,4-diol (25 g, 0.283 mol) and 2,2-dimethoxypropane (60 g, 0.57 mol) in dichloromethane (150 ml) at room temperature. The reaction was stirred and monitored by g.l.c; when no starting material was left, the mixture was quenched by the addition of sodium bicarbonate solution (60 ml), the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 30 ml). The combined organic layers were washed with water (75 ml), dried, and the solvent was evaporated under atmospheric pressure to give 2,2-dimethyl-[1,3]dioxole[161][162] as a pale yellow liquid (34.1 g, 93 %) which showed δ_H 5.65 (2 H, d, J 2.5 H_Z) 4.2 (4 H, d, J 2.5 H_Z) 1.45 (6 H, s); δ_C 130.88, 129.36, 101.87, 61.29, 58.22, 24.36, 23.85; ν_{MAX}: 1640 cm^{-1}.

EXPERIMENT: 85

8,8-Dibromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (188).

Sodium hydroxide (20 g, 0.5mol) in water (20 ml) was added dropwise to a stirred solution mixture of 2,2-dimethyl-4,7-dihydro[1,3]dioxepine (19.5 g, 0.152mol), n-hexadecyltrimethylammonium bromide (3 g) and bromoform (77 g, 40.7ml) in dichloromethane (50 ml) at room temperature. The reaction was stirred for 48 h, when the g.l.c showed no starting material was left. Dichloromethane (120 ml) was added followed by brine (150 ml), and the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined organic layers were washed with water (100 ml), dried and evaporated, to give crude product which was purified by column chromatography eluting with petroleum ether (b.p 40 – 60 °C) / ether (5 : 1) to give 8,8-dibromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane[163] (40.2 g, 87 %) which showed δ_H: 4.2 (2 H, br, d, J 2.6 H_Z), 3.9 (2 H, br, d, J 2.5 H_Z), 2.07 (2 H, m), 1.36 (3 H, s), 1.28 (3 H, s); δ_C: 103.5, 60.86, 34.66, 24.47; ν_{MAX} : 1645, 1453, 1374 cm^{-1}; (mp: 75-77°C, *Lit*[41] 73 – 75 °C).

EXPERIMENT: 86

8-Bromo-4,4,8-trimethyl-3,5-dioxabicyclo[5.1.0]octane (189).

Butyl lithium (3.1 ml, 4.9 mmol) was added dropwise to a stirred solution of 8,8-dibromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (1 g, 3.3 mmol), hexamethylphosphoramide (1.15 ml, 6.5 mmol) and methyl iodide (1 ml, 16 mmol) in dry tetrahydrofuran (20 ml) at –95 °C under nitrogen. When the g.l.c showed all the starting material had reacted, the reaction was quenched with water (4 ml) and allowed to reach room temperature, then extracted with dichloromethane (15 ml). The aqueous layer was re-extracted with dichloromethane (2 × 5 ml). The combined organic layers were washed with water (25 ml) dried and evaporated; the crude product was purified by column chromatography on silica eluting with petroleum ether (b.p 40 –60 °C) / ether (5 : 2) to give exo-8-bromo-4,4,8-trimethyl-3,5-dioxabicyclo[5.1.0]octane (0.56 g, 71%)[165] which showed δ_H: 4.13 (2 H, br d, J 13.1 H_Z), 3.85 (2 H, br d, J 13.1 H_Z), 2.05 (3 H, s), 1.82 (2 H, br s), 1.31 (3 H, s), 1.25 (3 H, s), δ_C: 95.37, 53.45, 52.84, 23.7, 20.8, 17.7, 16.36, 15.28, 13.53; ν_{MAX}: 2988, 2947, 1447, 1372; *m/z*: 236 (M+2), 205 (M^+-C_2H_6), 205/148 (M^+-C_2O_2), 148/97 (M^+-C_4H_4), 148/67 (M^+-HBr), 67/52 (M^+-CH_3).

EXPERIMENT: 87

4,4-Dimethyl-8-methylene-3,5-dioxabicyclo[5.1.0]octane (190).

8-Bromo-4,4,8-trimethyl-3,5-dioxabicyclo[5.1.0]octane (0.2 g, 0.84 mmol), was added to a stirred solution of potassium butoxide (0.2 g) in dimethylsulphoxide (10 ml), at room temperature under nitrogen. When g.l.c showed no starting material was left, the reaction was quenched by the addition of water (20 ml), and extracted with dichloromethane (25 ml), the organic layer was washed with sodium bicarbonate (15 ml), then brine (13 ml), separated, dried and evaporated to

give a crude product which was purified by column chromatography on silica eluting with petroleum ether (b.p 40 –60 °C) / ether (5 : 1) to give *4,4-dimethyl-8-methylene-3,5-dioxabicyclo[5.1.0]octane* (0.1 g, 76 %) which showed δ_H: 5.4 (2 H, br s), 4.07 (2 H, dd, J 1.1, 12.8 Hz), 3.81 (2 H, d, J 12.8 Hz), 1.81(2 H, br s), 1.34 (3 H, s), 1.22 (3 H, s); δ_C: 137.2, 102.3, 102.32, 61.9, 61.1, 24.32, 20.33, 14.2, 13.6; ν_{MAX}: 3009, 2941, 1381, 1215, 1031cm^{-1}; *m/z*: 139 (M^+-Me), 129 (M^+-C_2H_6O), 109/95 (M^+-CH_2), 95/67 (M^+-CO), 95/53 (M^+-C_3H_6).

EXPERIMENT: 88

8-Bromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (196)

Methyl lithium (22 ml, 1.5M) was added dropwise to a stirred solution of 8,8-dibromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (5 g, 0.016 mol) in dry ether (25 ml) under nitrogen at –78 °C. The mixture was stirred for 5 min, when g.l.c showed no starting material was left. The mixture was quenched with methanol (3 ml), and allowed to reach room temperature, then water (10 ml) was added. The organic layer was separated and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried, evaporated and the crude product was purified by column chromatography on silica eluting with ethyl acetate / ether (2 : 1) to give *exo-8-bromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane*[165] (2.9 g, 80 %) which showed δ_H: 4.1 (2 H, dd, J 2.9, 13.1 Hz), 3.83 (2 H, dd, J, 1.17, 13.1 Hz), 2.69 (1 H, t, J 3.9 Hz), 1.77 (2 H, br s), 1.62 (3 H, s), 1.6 (3 H, s); δ_C: 138.2, 63.1, 62.3, 52.2, 17.2, 15.8, 14.7, 13.04; ν_{MAX} 2941, 453, 1290 cm^{-1}; *m/z*: 223 (M+2), 223/208 (M^+-CH_3), 167 (M^+-C_3H_4O), 167/149 (M^+-H_2O), 149/91 (M^+-C_3H_{10}), 134/55 (M^+-Br).

EXPERIMENT: 89

2-Bromo-3-hydroxymethylcyclopropylmethanol (197).

para-Toluene sulphonic acid monohydrate (≈10 mg) was added to a stirred solution of 8-bromo-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (2.46 g, 0.011 mol) in methanol (25 ml) and water (1.0 ml) at room temperature. The mixture was stirred for 2 h when the g.l.c showed no starting material was left; the solution was evaporated, the residue was dissolved in dichloromethane (10 ml) and washed with sat. aq. of sodium bicarbonate (7 ml). The organic layers was separated and the aqueous layer was extracted with dichloromethane (2 × 6ml). The combined organic layers were dried, evaporated, and the crude product was purified by column chromatography on silica eluting with petroleum (b.p 40 – 60 °C) / ethyl acetate (1 : 1) to *2-bromo-3-hydroxymethylcyclopropylmethanol* (1.6 g, 80 %) which showed δ_H: 4.1 (2 H, dd, J 5.7, 11.8 H_Z), 3.3-2.9 (4 H, br dd, J 10.15, 11.8 H_Z), 2.64 (1 H, t, J 3.8 H_Z), 2.16 (2 H, m); δ_C: 60.6, 28.56, 20.7; ν_{MAX}: 3335 cm^{-1}. The above method used to prepare (**172**).

EXPERIMENT: 90

Butyric acid 2-bromo-3-hydroxymethylcyclopropylmethyl ester (198)

Vinyl butyrate (0.125 g, 0.13 ml, 1.09 mmol) was added dropwise to a stirred solution of 2-bromo-3-hydroxymethycyclopropylmethanol (0.153 g, 0.8 mmol), and enzyme (PS lipase) (0.022 g) in tetrahydrofuran (10 ml) at room temperature. The mixture was stirred for 18 h, when g.l.c showed no starting material was left. The precipitate was filtered off through a pad of celite and this was washed with methanol (3 ml). The filtrate was evaporated and the residue was dissolved in dichloromethane (10 ml) and washed with sat. aq. of sodium bicarbonate (5 ml). The organic layer was separated, dried, and evaporated to give a crude product, which was purified by column chromatography on silica eluting with petroleum ether (b.p 40 – 60 °C) / ether (5 : 2) to give *butyric acid 2-bromo-3-hydroxymethylcyclopropylmethyl ester* (0.15 g, 70 %) which showed one peak by chiral g.l.c while the racemic showed two peaks, which showed δ_H: 4.42 (1 H, dd, J 5.0, 12.3 H_Z), 3.85 (2 H, m), 3.43 (1 H, dd, J 9.3, 12.3 H_Z), 2.63(1 H, t, J 4.1 H_Z) 2.27 (2 H, t, J 7.3 H_Z), 2.01 (2 H, br, m), 1.63 (2 H, sextet, J 7.3 H_Z), 0.92 (3 H, t, J 7.3 H_z); δ_C: 173.66, 62.16, 60.45, 36.2, 24.2, 23.01, 18.78, 18.37, 13.58; ν_{MAX}:

3438, 2965, 1735cm^{-1}; *m/z*: 253 (M+2), 251 (M), 233 (M^+-H_2O), 171 (M^+-C_5H_6O), 162/134 (M^+-C_2H_2), 171/90 (M^+-HBr), 90/71 (M^+-H_3O).

EXPERIMENT: 91

2-Bromo-3-propoxymethylcyclopropanecarbaldehyde (200)

Butyric acid 2-bromo-3-hydroxymethyl-cyclopropylmethyl ester (0.5 g, 1.99 mmol) in dichloromethane (3 ml) was added to a stirred suspension of pyridiniumchlorochromate (0.85 g, 3.9 mmol) in dichloromethane (15 ml) at room temperature. The mixture was stirred for 2 h at room temperature, when t. l. c showed no starting material was left, diluted with ether (20 ml), and filtered through a pad of celite. The solvent was evaporated to give a yellow oil, *2-bromo-3-propoxymethylcyclopropanecarbaldehyde* (0.45 g, 90 %) which showed δ_H: 9.72 (1 H, d, J 2.5 Hz), 4.43 (1 H, dd, J 6.3, 12.0 Hz), 3.92 (1 H, dd, J 8.6, 12.0 Hz), 3.47 (1 H, t, J 5.0 Hz), 2.54 (1 H, m), 2.35 (1 H, m), 2.23 (2 H, t, J 7.4 Hz), 1.64 (2 H, sextet, J 7.4 Hz), 0.90 (3 H, t, J 7.4 Hz); δ_C: 196.78, 59.58, 35.92, 35.76, 33.45, 21.56, 18.36, 13.58; ν_{MAX}: 1745, 1734 cm^{-1}; *m/z*: 251 (M+2), 249 (M), 221 (M^+-CO), 221/161 (M^+-C_3H_8O), 161/100 (M^+-C_3H_9O), 161/82 (M^+-Br), 100/71 (M^+-$[C_2H_2]^+$).

EXPERIMENT: 92

Butyric acid 2-[benzyliminomethyl]-3-bromo-cyclopropylmethyl ester (201)

2-Bromo-3-propoxymethylcyclopropanecarbaldehyde (0.4 g, 1.6 mmol) in ethanol (7 ml) was added dropwise to a stirred solution of benzylamine (0.18 g, 1.7 mmol), concentrated sulphuric acid (0.1 ml) in ethanol (12 ml) at 0 °C. The mixture was allowed to reach room temperature, when t.l.c. showed no starting material was left, then quenched by the addition of sodium bicarbonate (10 ml) and extracted with dichloromethane (15 ml). The organic phase was washed with water (7 ml), separated, and dried, evaporated, to give crude product which was

purified by column chromatography on silica eluting with petroleum (b.p 40 –60 °C) / ethyl acetate (5 : 1), to give *butyric acid 2-[benzyliminomethyl]-3-bromo-cyclopropylmethyl ester* (0.48 g, 78 %) which showed δ_H: 7.65 (1 H, m), 7.27 (5 H, m), 4.54 (2 H, br s), 4.33 (1 H, dd, J 6.7, 11.0 Hz), 3.95 (1 H, dd, J 8.5, 11.9 Hz), 3.35 (1 H, t, J 4.4 Hz), 2.3 (1 H, m), 2.23 (2 H, t, J 7.6 Hz), 2.06 (1 H, m), 1.56 (2 H, sextet, J 7.4 Hz), 0.92 (3 H, t, 7.4 Hz); δ_C: 172.3, 164.6, 137.71, 129.23, 128.45, 125.6, 69.6, 59.7, 35.52, 21.6, 20.43, 19.13, 18.16, 13.2; ν_{MAX}: 2982, 1728, 1492, 674 cm^{-1}.

EXPERIMENT: 93

[(2-(Benzylaminomethyl)-3-bromocyclopropyl]methanol (202)

Sodium borohydride (0.055 g, 1.4 mmol) in methanol (5 ml) was added to a stirred solution of butyric acid 2-[benzyliminomethyl]-3-bromo-cyclopropylmethyl ester (0.25 g, 0.7 mmol) in methanol (7 ml). The mixture was refluxed 15 min, then cooled to room temperature, water (10 ml) and sodium hydroxide (1 M, 10 ml) were added, then extracted with dichloromethane (10 ml). The aqueous layer was extracted with dichloromethane (2 × 5 ml). The combined organic layers were washed with brine solution (10 ml), separated, dried and evaporated, to give *2-(benzylaminomethyl)-3-bromocyclopropyl]methanol* (0.14 g, 70 %) which showed δ_H: 7.71 (1 H, br s), 7.3 (5 H, m), 4.06 (1 H, dd, J 5.5, 12.3 Hz), 3.8 (1 H, d, J 12.7 Hz), 3.6 (1 H, d, J 12.7 Hz), 3.31 (1 H, br dd, J 5.5, 12.4 Hz), 3.11 (1 H, dd, J 11.0, 12.1 Hz), 2.61 (1 H, t, J 3.6 Hz), 2.22 (1 H, dd, J 5.5, 12.1 Hz), 1.87 (1 H, br m), 1.65 (1 H, br m); δ_C: 128.65, 128.28, 127.49, 60.92, 53.53, 48.72, 29.28, 26.17, 22.41; ν_{MAX}: 3296, 2848, 764 cm^{-1}.

EXPERIMENT: 94

(E)-1-(2-Bromo-3-propoxymethylcyclopropylpent)-1-en-3-one (203)

2-Bromo-3-propoxymethyl-cyclopropanecarbaldehyde (0.3 g, 1.2 mmol), was added to a stirred solution of carboethoxymethylenetriphenylphosphorane (0.46 g, 1.3 mmol) in toluene (10 ml) at room temperature the reaction mixture was stirred for 16 h at room temperature, when the t.l.c showed no starting material was left. The solvent was evaporated to give a thick oil, which was treated with petroleum (b p 40 –60 °C) (10 ml) and ether (4 ml). The precipitate was filtered off; evaporation of the solvent gave a brown oil which was purified by column chromatography eluting with petroleum (b.p 40 –60 °C) / ether (5 : 2) to give *(E)-1-(2-bromo-3-propoxymethyl-cyclopropylpent)-1-en-3-one* (0.34 g, 89 %) which showed : δ_H: 6.5 (1 H, dd, J 9.8, 15.4 H_Z), 6.0 (1 H, d, J 15.4 H_Z), 4.34 (3 H, m, including q, J 7.3 H_Z), 3.9 (1 H, dd, J 7.3, 12.1 H_Z), 3.02 (1 H, t, J 4.25 H_z), 2.35 (2 H, t, J 7.3 H_z), 2.2 (1 H, m), 2.1 (1 H, br m), 1.7 (2 H, sextet, J 7.3 H_Z), 1.3 (3 H, t, J 7.3 H_Z), 0.9 (3 H, t, J 7.3 H_Z); δ_C: 196.7,165.4, 143.0, 124.0, 61.6, 60.4, 36.0, 35.7, 29.7, 23.2, 18.3, 14.2, 13.5; ν_{MAX}: 2966, 1714, 1644cm^{-1}; *m/z*: 321(M+2), 319 (M), 250 (M^+-C_4H_7O), 239 (M^+-C_5H_6O), 239/152 (M^+-$C_4H_7O_2$), 152/71 (M^+-HBr).

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