Bangor University

DOCTOR OF PHILOSOPHY

Studies to provide new intermediates for industrial chemistry

Mustafa, Hussein Habeeb

Award date:
2013

Awarding institution:
Bangor University

[Link to publication](#)

Studies to provide new intermediates for industrial chemistry

A thesis submitted to Bangor University

for the degree of Doctor of Philosophy

By

Hussein Habeeb Mustafa

PRIFYSGOL
BANGOR
UNIVERSITY

1884
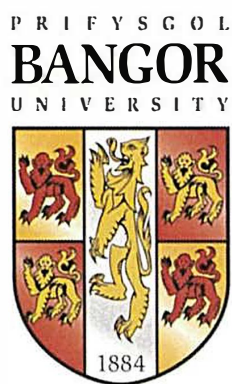
Supervisor Professor Mark S. Baird

2013

Acknowledgements

My Family

My Government

Professor M.S. Baird

Dr. Juma'a, Al-Dulayymi

Dr. David Justice

Dr. David Rowles

Iraqi Embassy

Table of Contents

Abbreviation and acronyms

aq.	*Aqueous*
B	*Broad*
BTHF	*Borane-tetrahydrofuran*
BMS	*Borane-dimethyl sulfide*
°C	*Degrees Celsius*
DMF	*Dimethylformamide*
DHP	*Dihydropyran*
DDT	*Dichlorodiphenyltrichloroethane*
Dd	*Double doublet*
D	*Doublet*
ECF	*Ethyl chloroformate*
ESR	*Electron spin resonance*
GC	*Gas chromatography*
Hz	*Hertz*
HPLC	*High performance liquid chromatography*
HMPA	*Hexamethylphosphoric triamide*
IBX	*1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide*
IPM	*Integrated pest management*
IMS	*Industrial methylated spirit*
IR	*Infra-Red*
J	*Coupling constant*

LAH	*Lithium aluminium hydride*
M	*Multiplet*
MS	*Mass Spectroscopy*
m.p.	*Melting Point*
mol eq.	*Molar equivalents*
MHz	*Megahertz*
mmol	*Millimols*
NMR	*Nuclear magnetic resonance*
PCC	*Pyridinium chlorochromate*
Ppm	*Parts per million*
PPTS	*Pyridinium p-toluenesulfonate*
PUFA	*Polyunsaturated fatty acid*
PTC	*Phase transfer catalysis*
PTSA	*p-Toluenesulfonic acid monohydrate*
p-TsCl	*p-Toluene sulfonyl chloride*
Q	*Quartet*
R.T.	*Room temperature*
S	*Singlet*
Sat.	*Saturated*
T	*Triplet*
THF	*Tetrahydrofuran*
TLC	*Thin-layer chromatography*
WHO	*World Health Organization*

Abstract

This project examines a number of aspects of the development of products for application in industry. This project consists of three parts.

The first part investigated optimising an industrial process leading to (S)-4-benzyl-oxazolidin-2-one (**1**). This study has secured a protocol which allows its preparation in high yield and at lower cost.
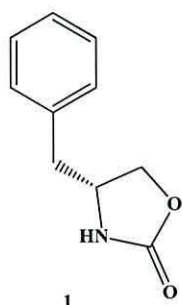
The second part is concerned with the development of a cheap method to access pheromones containing diene, triene and tetraene groups, using acetal (**58**) derived from the ozonolysis of cyclonona-1,4,7-triene.
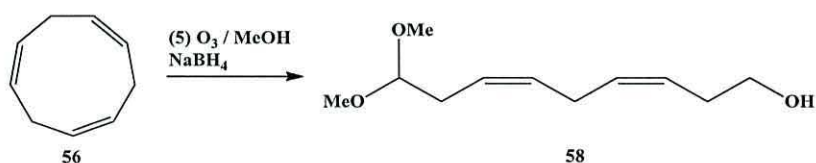
The third part of the study entails the use of the same Z,Z,Z-cylonona-1,4,7-triene to synthesize novel *bis* and *tris*-cyclic allenes with eleven and twelve membered rings.
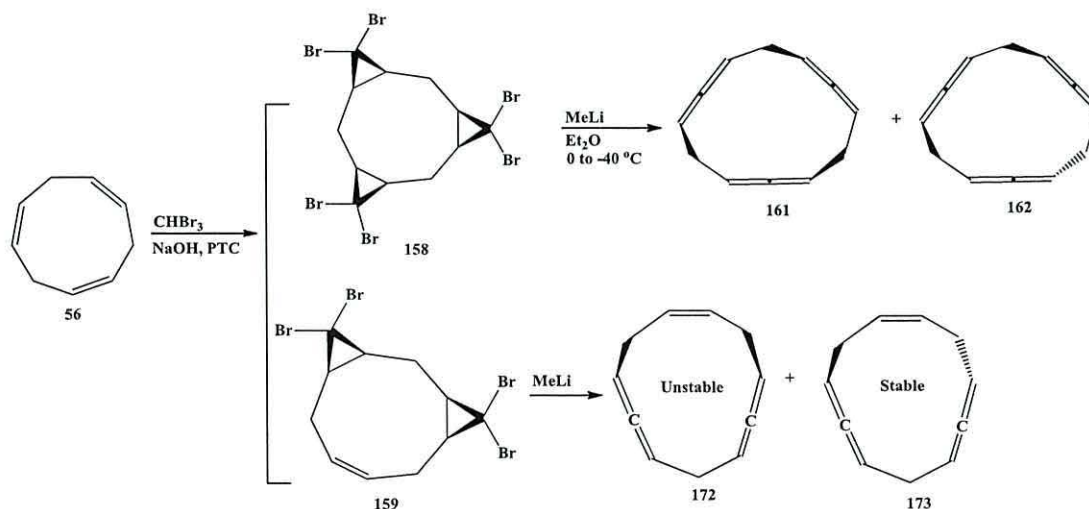
The structure of the thesis

This thesis reports three separate studies all linked to providing intermediates or product for use in the chemical industry. It is therefore written as three separate main sections, each part with introduction and results and discussion sections, while the experimental chapter includes the experiments for all the three parts. The first chapter relates to the preparation of *(S)*-4-benzyl-oxazolidin-2-one, while the second involves the preparation of insect pheromones and polyunsaturated intermediates. The final chapter concentrates on the synthesis of a novel cyclic allenes (*tris* and *bis* allenes).

Chapter 1.   Optimisation of an industrial process to produce *(S)*-4-benzyl-oxazolidin-2-one

1.1 Overview

(S)-4-Benzyl-oxazolidin-2-one **(1)** is one of a family of oxazolidin-2-ones which have been widely applied as auxiliaries in Evans's asymmetric strategy.[1] This strategy allows the preparation of chiral naturally occurring organic molecules.[2a] *(S)*-4-Benzyl-oxazolidin-2-one may be easily obtained from L-amino carboxylic acids, which occur naturally.

1.1.1 Aim of the project

The aim of the project was to increase the efficiency and reduce the cost of an existing industrial method for the preparation of *(S)*-4-benzyl-2-oxazolidinone.

1.1.2 Why was there commercial interest in the preparation of this compound?

Since their introduction in the early 1980's, the application of the Evans oxazolidinone class of chiral auxiliary has become firmly established in asymmetric synthetic methodology. Their principal use is in the formation of the chiral enolates of carboxylic acid derivatives, which can then either be alkylated or acylated in processes which are frequently found to be highly stereoselective. The Evans *syn*-aldol protocol has enjoyed particular success in this regard, and remains the most popular means of accessing single diastereoisomers of β-hydroxycarboxy derivatives.

The principal Evans oxazolidinone auxiliaries in use are 4-benzyl-2-oxazolidinone **(1)**, and 4-isopropyl-2-oxazolidinone **(2)**, derived from the amino acids phenylalanine and valine respectively (the more readily available *(S)*-(-) enantiomers are given in Figure 1). However, the former variant is often preferred, due to the fact that most of its derivatives are found to be crystalline solids, which facilitates the purification of diastereoisomeric

products later in the synthetic sequence. In addition, high levels of asymmetric induction are obtained with this species.
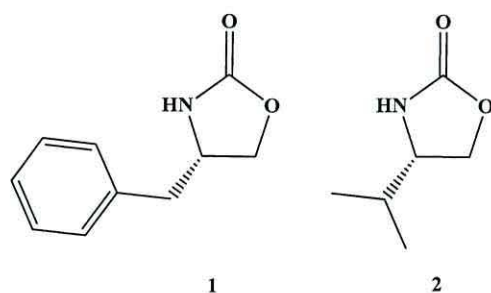
Figure 1: 4-Benzyl-2-oxazolidinone (1) and 4-isopropyl-2-oxazolidinone (2)

Examples of the employment of the 4-benzyl substituted oxazolidinone chiral template in synthesis are very common in the literature,[2b] and only selected ones will be discussed.

In the arena of total synthesis, extensive use of the *syn*-aldol reaction is made in the construction of macrolide natural products of polyketide biosynthetic origin, with their distinctive 1,3-oxygenation profile. Examples include the synthesis of the A-ring portion **(3)**, of bryostatin 2,[3] the synthesis of the C1-C19 subunit **(4)**, of phorboxazole B;[4] and the synthesis of the 5-hydroxy acid fragment **(5)**, of the cryptophycin nucleus (Scheme 1).[5]
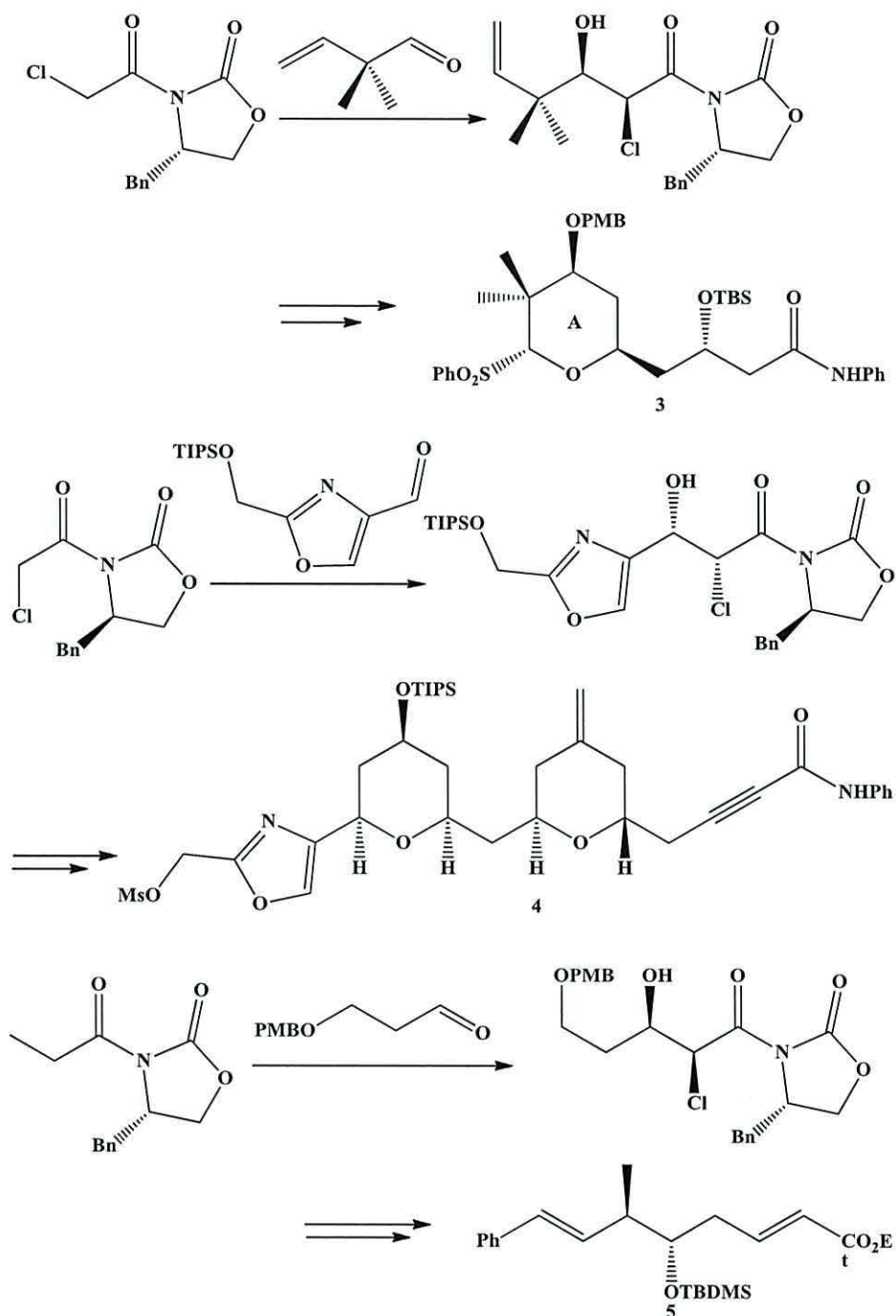
Scheme 1: Oxazolidinone chiral in construction of natural products

In addition, this chiral template finds utility in drug design and target synthesis. For example, the multi-kilogram synthesis of the LTB$_4$-receptor antagonist **(6)**,[6] and, in an instance of an Evans asymmetric alkylation, the synthesis of the renin inhibitor, CGP60536B (Novartis' Aliskirenhemifumarate) **(7)** (Scheme 2).[7]
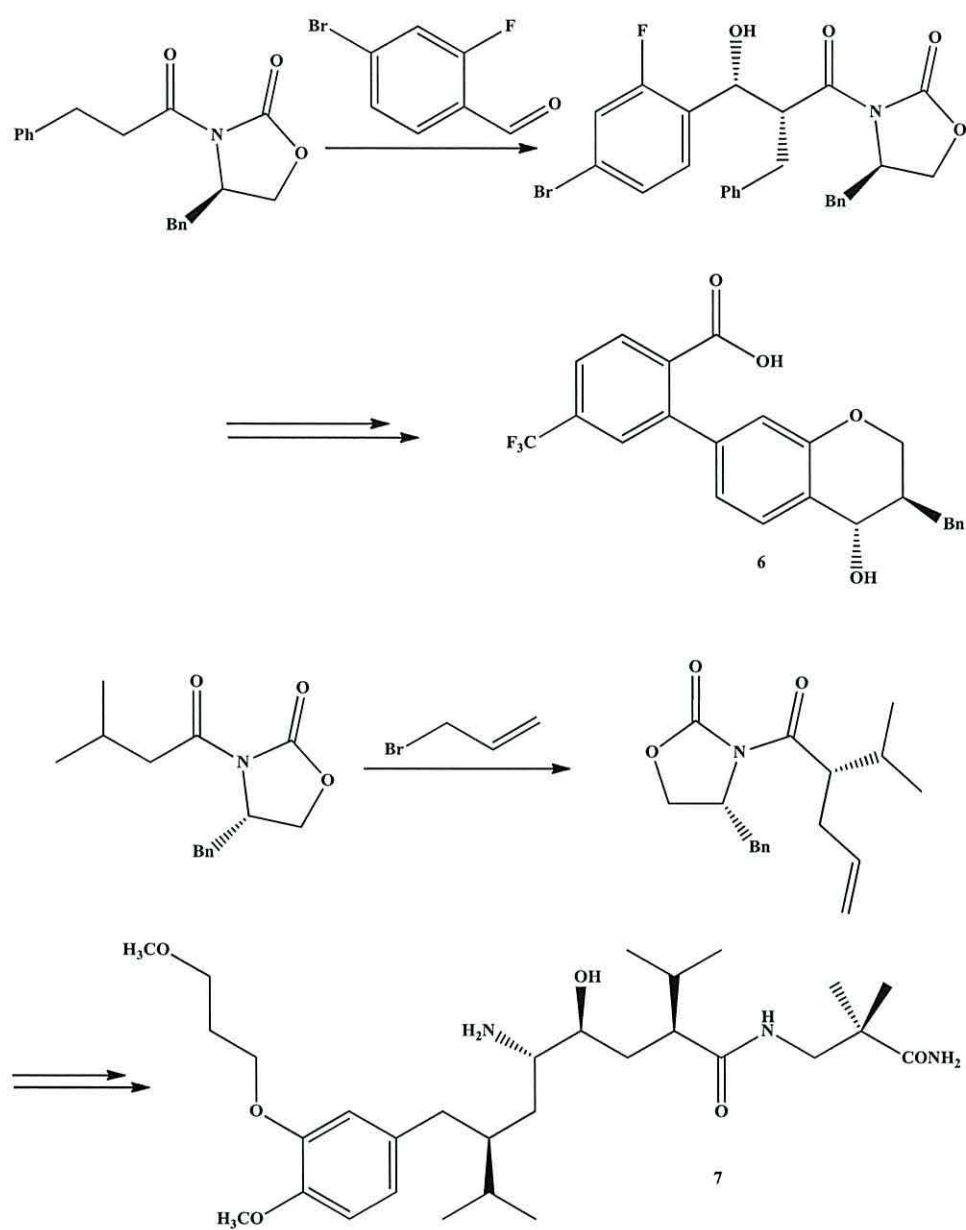
Scheme 2: Chiral oxazolidinone in the synthesis of a renin inhibitor

1.1.3 A current industrial process

One current industrial process for the production of (*S*)-4-benzyl-2-oxazolidinone involves reducing the amino acid (**8**) with sodium borohydride in the presence of sulphuric acid, iodine or boron trifluoride to generate the borohydride ion, which is used for the reduction. This is followed by cyclisation to give the final chiral auxiliary (Scheme 3).
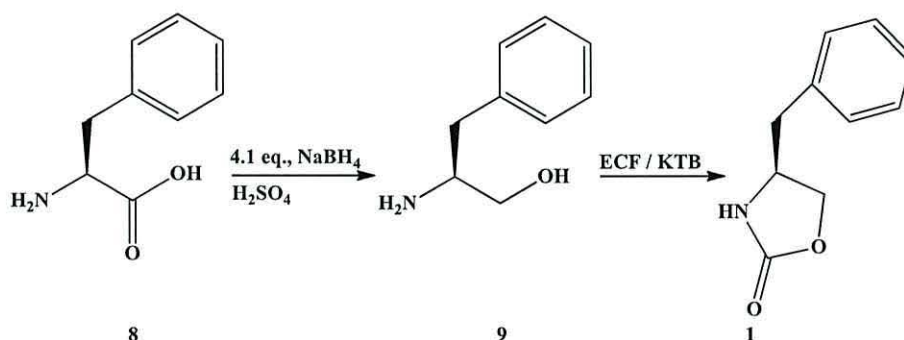
Scheme 3: (S)-4-benzyl-2-oxazolidinone using NaBH₄ / H₂SO₄

Using this method, problems arise during both reaction steps, as discussed below.

The first step in this process is the formal production of BH_3, and this can currently be produced using three different methods:

1) $NaBH_4 + 1/2\ H_2SO_4 \rightarrow BH_3 + H_2 + 1/2\ Na_2SO_4$

2) $NaBH_4 + 1/2\ I_2 \rightarrow BH_3 + NaI + 1/2\ H_2$

3) $NaBH_4 + 4/3\ BF_3 \rightarrow 4/3\ BH_3 + NaBF_4$

Both methods 1 and 2 prove inefficient, in that one mole of H_2 gas is produced for every one mole of BH_3 synthesised. Method 1 is also reported to be problematic when scaling up, while method 2 produces iodide waste, which is very expensive. In contrast, method 3 is more efficient, producing 1.33 moles of 'BH_3' per mole of $NaBH_4$ used, while also not generating any H_2 gas or iodide waste products. It was estimated by the company partner in this work that method 2 was the most expensive method of producing BH_3, with an estimated production cost of $250 per Kg produced, while the costs for methods 1 and 3 are approximately $130 and $140 per Kg respectively. Although method 3 is marginally more expensive than method 1, it is believed to be more efficient for acid reduction.

The second step of the synthesis involves reduction of the acid group to the corresponding alcohol. It was thought that 2.66 equivalents of BH_3 were required to reduce the amino acid to the amino alcohol, due to the BH_3 coordinating to the amine group. It has also been reported that pre-forming a BF_3 adduct with the amino acid can reduce the amount of borane required to 1:1 equivalents. Some work had been undertaken on pre-forming this BF_3 adduct, before reducing the amino acid with borane; however at the start of this project, these experiments had only been performed on a small scale. Analysis of the reduction product had only been performed by LC, therefore no isolated yields or data had been reported.

There was, therefore, a great commercial need to investigate these reactions on larger scales, and to develop new, more cost effective, pathways for the synthesis of the chiral auxiliary.

1.1.4 Proposed synthetic pathway

In order to improve the synthesis of the chiral auxiliary, it was proposed to reverse the order of the synthesis, and firstly prepare an ethyl carbamate intermediate (with a target yield of 95 %) to block the amine group and reduce the amount of borane required for the reduction of the acid group (theoretically to 1.33 equivalents). Borane could then be produced either by method 1 or method 3 (as discussed previously) to reduce the acid group to the corresponding primary alcohol. This alcohol could then be cyclised using basic conditions or thermally (Scheme 4).
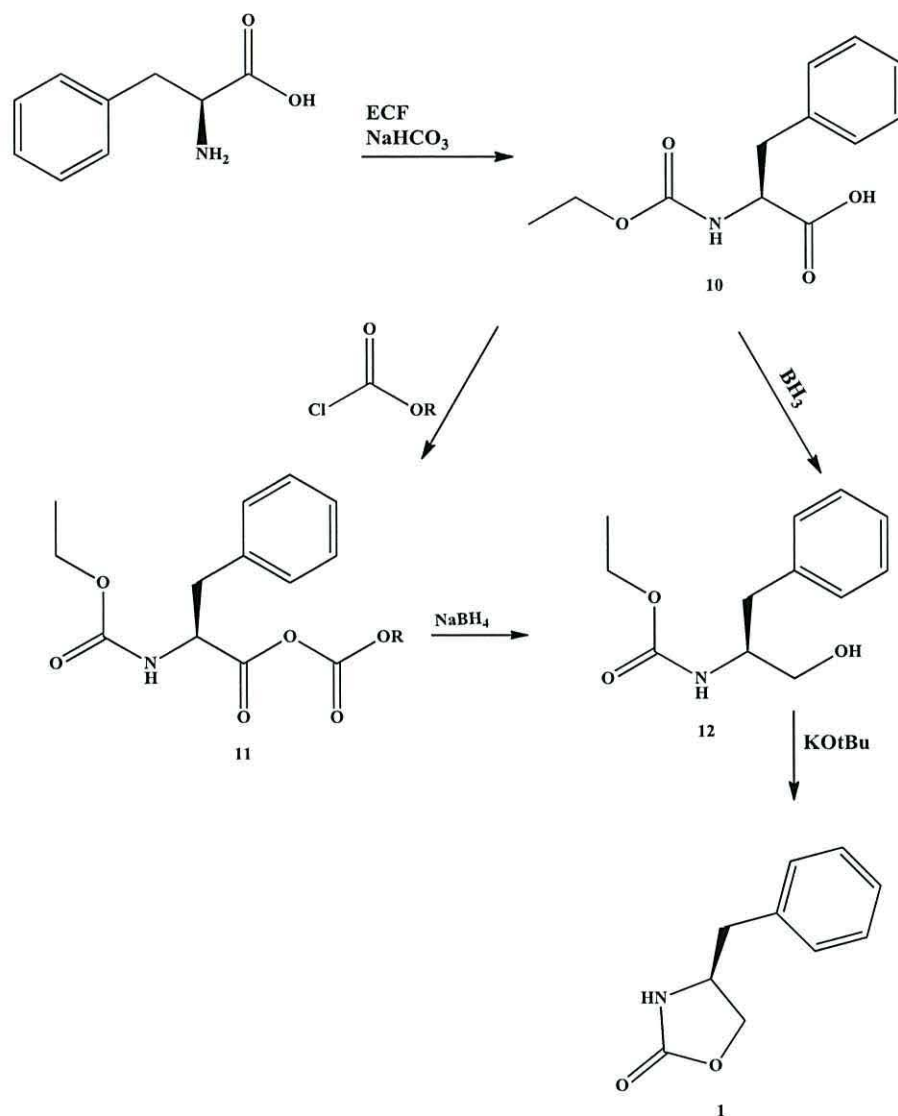
Scheme 4: Routes to prepare (S)-4-benzyl-2-oxazolidinone

It was firstly proposed that the carbamate intermediate would be generated in large quantities having ensured that a good yield for its formation could be achieved. The next step would involve evaluating the methods for producing borane (method 1 or method 3) and analysing which was most cost effective for the reduction of the acid group of the carbamate. This step would then be further investigated in order to optimise the minimum equivalence of BH_3 required for complete reduction of the acid to occur. The final synthetic step would involve confirming that the alcohol derived from this route could be cyclised to give the desired chiral auxiliary product, of acceptable quality and in a good yield, and it was proposed that this could be achieved by thermal cyclisation with elimination of ethanol.

Finally, the data obtained would be used in a cost modelling exercise to compare the cost of this method, with the method currently being used for the synthesis of the desired chiral auxiliary.

1.2   Chiral oxazolidin-2-ones

Generally, oxazolidinones are prepared from amino alcohols, which in turn are prepared from amino acids by reduction, for example using a metal hydride.[8,9]

Evans,[1] was the first person to define the oxazolidin-2-one system as a chiral auxiliary. The common structure of oxazolidin-2-one is shown in Figure 2.
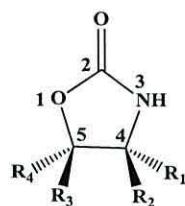
R1, R2, R3 and R4 can be H or alkyl or aryl

Figure 2: Substituted oxazolidin-2-one

1.3   Synthesis of various oxazolidin-2-ones

The auxiliaries can be obtained from several different sources, for instance amino sugars, amino alcohols, amino acids, terpenes and sugars. Usually, in the laboratory, amino acids are used to prepare oxazolidin-2-ones, the synthesis involving firstly reduction of R-or S-amino acid to an amino alcohol[1] and then through two steps to produce the oxazolidinone. The literature describes numerous methods, one of which was pioneered by Evans and co-workers during the early 1980s.[1] Evans's syntheses includes cyclization of alkyl or aryl carbamates (in the presence of acidic or other catalysts) and triphenylphosphonium salts or N-nitroso compounds. They also include carbonylation of 2-aminoethinols, using a range of chemicals.[1]
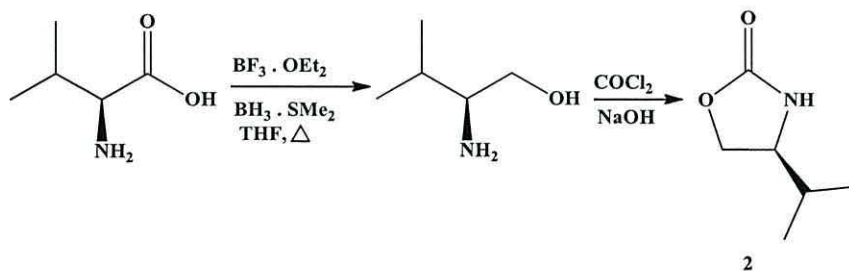
Scheme 5: Oxazolidinones using phosgene

There are three problems with these methods: (a) they tend to involve hazardous chemicals (e.g., cyanates, phosgene); (b) they tend to require extremes of temperature (very high and very low); and (c) they produce large quantities of toxic wastes - production of oxazolidin-2-ones can cause serious pollution or necessitate expensive protocols to prevent it.

As a result, current research centres on finding an alternative, environmentally innocuous means of producing oxazolidin-2-ones, with the use of less problematic and less wasting of chemicals and catalysts. Such catalysts have many potential advantages; these include versatility, the need for only mild preparation conditions, re-usability, high yields, and the absence of polluting by-products. As a result, 1,2-amino alcohols and amino acids are commonly used as substrates in the preparation of oxazolidin-2-ones.[10]

Oxazolidinones were prepared by the reaction of individual amino alcohols of phenylalanine, valine, and phenylglycine with either phosgene or diethyl carbonate (Figure 3):
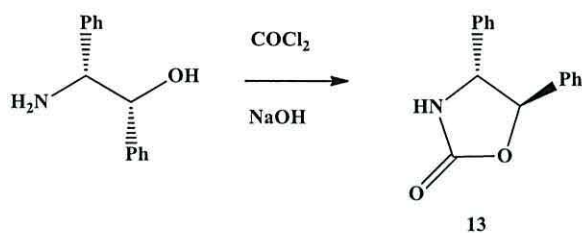
Figure 3: Preparation of oxazolidinones using phosgene

The oxazolidinone can be obtained by reaction of β-amino alcohols and isocyanates; this is followed by the cyclization of the substituted urea, using heat or acid.[11] However, the toxicity of the isocyanate and phosgene makes such methods undesirable. There is some

flexibility in the use of amino alcohols as starting materials; they may be N-substituted, for instance.[12]

Isobutyl chloroformate may be used as an alternative to phenyl chloroformate; however, using it requires heat to complete the cyclization.[13]

In another method, oxazolidin-2-one derivatives was prepared using urea and ethanolamine reagents, which on microwave irradiation in a chemical paste medium in presence of a catalytic amount of nitromethane to absorb the microwaves and generated hot spots undergo cyclisation (Figure 4).[14]
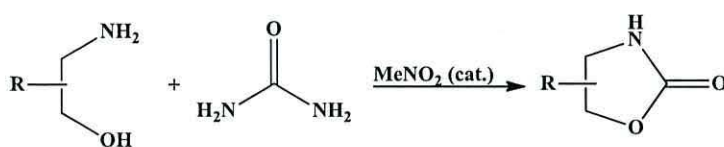
Figure 4: Preparation of oxazolidinones using urea and ethanolamine

The oxazolidinone can also be prepared by the reduction of N-(ethoxycarbonyl) amino esters with sodium borohydride-calcium chloride. The mixture is then cyclized with potassium carbonate in toluene under reflux.[15,16]

1.4 Oxazolidin-2-ones applications

Oxazolidin-2-ones are compounds that have numerous applications in organic chemistry. They are used as chiral auxiliaries for asymmetric synthesis.[17] In this regard, oxazolidines may be used to prepare enantiomerically pure alcohols, aldehydes, carboxylic acids, and aromatic aldehydes.[18]

Moreover, derivatives of 1,3-oxazolidin-2-ones are used in medicine as antibacterial agents against most significant kinds of gram-positive pathogens. Examples include vancomycin, macrolide, penicillin, methicillin and macrolides.
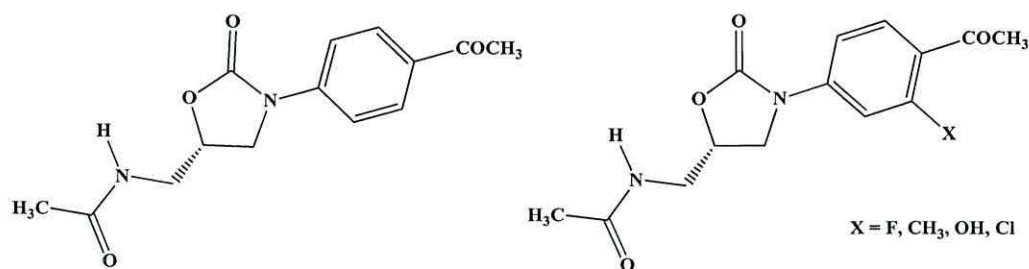
Figure 5: Oxazolidin-2-ones as drugs

Oxazolidin-2-one derivatives are also represented in drugs for certain conditions like Alzheimer's disease and pain, and they are present in sleep medications as analgesic agents.[19]
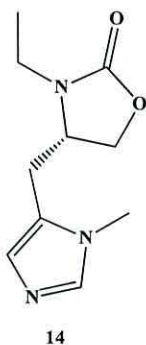
Figure 6: Oxazolidin-2-one for Alzheimer's disease

However, the importance of oxazolidin-2-ones to biochemistry extends beyond this. Oxazolidin-2-ones are relevant to preparation of, for example, antibiotics, immunosuppressant chemicals, antihistaminic agents, ant allergic agents, and antifungal agents. They are also involved in numerous antibacterial agents.[20a,b]

1.5   Results and discussion

The present chapter describes experiments conducted for the purpose of determining a low cost and high yielding method of accessing 4-benzyl-oxazolidin-2-one. Each step of the process was optimised.

In the first step, the amino acid was reduced using different equivalents of several reagents ($NaBH_4$ / H_2SO_4, $NaBH_4$ / $BF_3.OEt_2$, and BH_3 / THF), in order to determine the most effective reductant system for accessing the chiral amino alcohol. In the second step the chiral amino alcohol was then reacted with EtO_2CCl to give the carbamate. Finally, the carbamate was cyclised using K_2CO_3 at 125–130 °C under vacuum to obtain the chiral 4-benzyl-oxazolidin-2-one in high yields. These results suggest that it is possible to prepare 4-benzyl-oxazolidin-2-one in high yield and at low cost.

A comparison of the experimental data obtained allowed an assessment of the relative cost effectiveness of the various reagent systems studied. For consistency over all the routes, Aldrich catalogue prices are used for all chemicals in this calculation.

1.5.1   Reduction of amides
1.5.1.1   Reduction using BH_3.THF

Firstly, borane was investigated as the reducing agent to reduce the carboxylic acids to the corresponding alcohol (Figure 7).
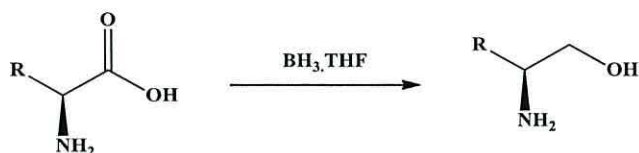
Figure 7: Reduction of carboxylic acid to alcohol.

Borane reagents have become an important part of today's fine chemical industry. Borane (BH_3) is a strong Lewis acid (electron-pair acceptor) with an empty *p*-orbital on the boron atom available for interaction with electron pairs. This allows for its reduction of carboxylic acid.

Borane, is a useful reagent with many applications, however, its simplest available form, diborane (B_2H_6), is pyrophoric, gaseous and not convenient to handle. There are a wide range of boranes: decaborane for example is not as reactive as diborane and is used as reducing agent too. Borane-tetrahydrofuran (BTHF) and borane-dimethyl sulfide (BMS, DMSB) are often used as a borane source. Both reagents are available in solution (e.g. 1 M in THF), and are therefore easier to handle than diborane. Volatility and flammability are always a drawback. BMS is more stable than BTHF but has an unpleasant odor.

A set of experiments was carried out in order to determine the amount of borane required for the complete conversion of the carboxylic acid into the corresponding alcohol, and a summary of the conversion percentage and yields of these reactions is shown below:

Equivalents of amino acid	Equivalents of BH_3.THF	Conversion to alcohol (%)	Yield %
1	2	100	82
1	1.75	100	81
1	1.5	2.5:1 (product:starting material)	61
1	1	1:4 (product:starting material)	27

Table 1: Variation of the number of equivalents of BH₃.THF and respective yields of amino alcohol.

The results above show that improvements can be made on the method that is currently being used in industry. When performing the reduction using the current industry method (Table 1, row 1), full conversion of the carboxylic acid was achieved in an 82 % yield. However, reducing the number of equivalents of borane used to 1.75 also gave full conversion of the carboxylic acid to the alcohol with no significant change in the yield. This suggests that using 1.75 equivalents of borane is sufficient in this step, a reduction of 0.25 equivalents of an expensive reagent, therefore proving more cost effective.

The number of equivalents could not be further reduced due to incomplete conversion occurring under those conditions, and with the starting material and the product being extremely difficult to separate.

1.5.1.2 Using NaBH$_4$/BF$_3$.Et$_2$O

When NaBH$_4$/BF$_3$.Et$_2$O is employed for the reduction of amino carboxylic acids to alcohols, the boron trifluoride diethyl etherate increases the rate of reduction of the carboxylic acid group and thus promotes a good yield because of its increasing the electrophilicity of the carbonyl group. However, borontrifloride diethyl etherate is more expensive than BH$_3$.THF.
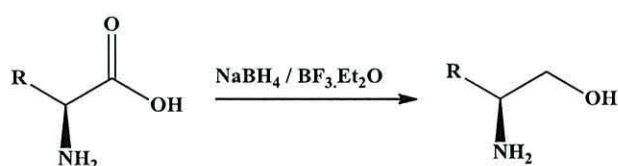
Figure 8: Reduction of amino carboxylic acid using NaBH$_4$/BF$_3$.Et$_2$O.

A set of experiments were therefore carried out in order to determine the amount of NaBH$_4$ and BF$_3$.Et$_2$O required for the complete reduction of the carboxylic acid to the corresponding alcohol, and a summary of the conversion percentage and yields of these reactions is shown below:

Equivalents of amino acid	Equivalents of NaBH$_4$	Equivalents of BF$_3$.O(Et)$_2$	Conversion to alcohol (%)	Yield %
1	2	4	100 (no starting material)	78
1	2	3.5	100 (no starting material)	87
1	1.7	3.5	100 (no starting material)	90
1	1.5	3.5	Mix (product:starting material)	80
1	2	2.5	Mix (product:starting material	73

Table 2: Variation of equivalents of NaBH$_4$ and BF$_3$.Et$_2$O and respective yields of amino alcohol.

Again, the results obtained suggest that significant improvements can be made to the method that is currently being used in industry. When using the current industrial method (Table 2, row 1), full conversion of the alcohol was achieved; however, this could also be achieved using fewer equivalents of the reagents. When the amount of $NaBH_4$ was reduced to 1.7 equivalents, and the amount of $BF_3.OEt_2$ reduced to 3.5 equivalents, full conversion of the alcohol was again achieved, and an increase in the yield from 78 % for the current industrial method to 90 % was achieved. This suggests that using these amounts both reduces the cost of this step, as well as increasing the amount of product obtained.

Again, the number of equivalents cannot be further reduced due to incomplete conversion occurring under those conditions, with the starting material and the product, again, extremely difficult to separate. This suggests that the use of 1.7 equivalents of $NaBH_4$ and 3.5 equivalents of $BF_3.Et_2O$ constitutes the optimum conditions for this process.

1.5.1.3   Using $NaBH_4/H_2SO_4$

The figure below shows reduction of amino-3-phenyl-propionic acid by $NaBH_4/H_2SO_4$ to amino alcohol (*(S)*-2-amino-3-phenyl-propan-1-ol). Sodium borohydride was used to reduce the phenylalanine starting material to obtain phenyl alaninol, and methanol was used to destroy the excess of BH_3.
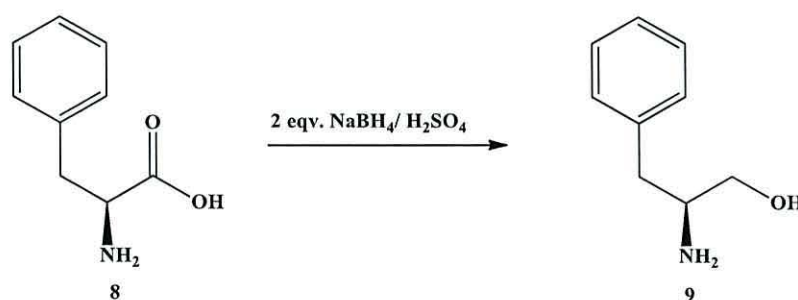
Figure 9: Reduction of amino carboxylic acid using $NaBH_4/H_2SO_4$.

The only variable manipulated in this study was the loading of $NaBH_4$. Table 3 shows a summary of conversion percentage and yields for these different experimental conditions.

Equivalents of amino acid	Equivalents of NaBH₄	Conversion to alcohol (%)	Yield (%)
1	2.8	100 (no starting material)	83
1	2	100	83
1	1.7	100	70
1	1.5	100	61

Table 3: Yields of alcohol with different equivalents of NaBH₄.

The literature[15] suggests that the use of 2.8 equivalents of sodium borohydride is effective. However, the results of the present study suggest that 2 equivalents are optimal. It was found that the use of both 2.8 equivalent and 2.0 equivalents of NaBH₄, respectively provided a yield of around 83%. The same yield could therefore be achieved at great reduction of cost.

Further decreasing the number of equivalents used did not decrease the conversion percentage of acid to alcohol; however, it did cause a decrease in the yield of the reaction.

The proton NMR of (9) showed peaks at δ 3.61 and δ 3.42 as double of doublets corresponding to the two protons adjacent to the hydroxyl group, and a broad multiplet signal at δ 3.16 (1H, m) corresponding to the hydrogen on the chiral α-carbon. Two doublets of doublets at δ 2.8 and δ 2.58 corresponded to the two hydrogen protons of the benzylic methylene group. The ^{13}C NMR showed a signal at δ 76.7 which corresponds to the carbon bearing the hydroxyl group. A signal at δ 54.2 corresponds to the chiral carbon centre. The signal at δ 40.9 corresponds to the benzylic carbon atom. There were no signals associated with the carboxylic acid group in either the ^{1}H NMR or ^{13}C NMR spectra. The IR spectrum also showed an O–H stretch at 3357 cm^{-1}. Moreover, the melting point corresponded to that given in the literature for this compound.[20]

1.5.2 Preparation of (S)-2-ethoxycarbonyl amino-3-phenyl-propionic acid

The next step in improving the efficiency of the synthesis was protecting the amino group, as mentioned above, in order to prevent coordination of the boron species, and to further reduce that amount of reducing agent required, again further reducing the cost. The first

step towards achieving this was to protect the amino group of L-phenylalanine as a carbamate by using ethyl chloroformate, in the presence of NaOH or sodium carbonate as the base (Figure 10).

In this step, the number of equivalents of ethyl chloroformate was varied under controlled conditions. The yields of the product were found to vary according to the experimental conditions employed. Table 4 shows the yields obtained from using the NaOH method.

Equivalents of ECF:amino acid	Volume of 1N NaOH/mL	Time (hrs)	Yield (%)
1	80	3	17
1	50	3	37
1.5	80	3	52
1.5	50	3	84

Table 4: Yields of (S)-2-ethoxycarbonyl amino-3-phenyl-propionic acid using NaOH .

From this table, it can be seen that using 1 equivalent of ethyl chloroformate generally produces low yields (17 and 37 %). Increasing the number of equivalents of the chloroformate increased the yield obtained, with the best yield (84 %) being obtained by using 1.5 equivalents of ethyl chloroformate with 50 mL of 1N NaOH solution. That means that just the two factors (dilution and equivalents of ethyl chloroformate) had an effect on the yield of the product.

While when the ethyl chloroformate was used in the presence of just sodium hydrogen carbonate, the yield increasing to 92%.
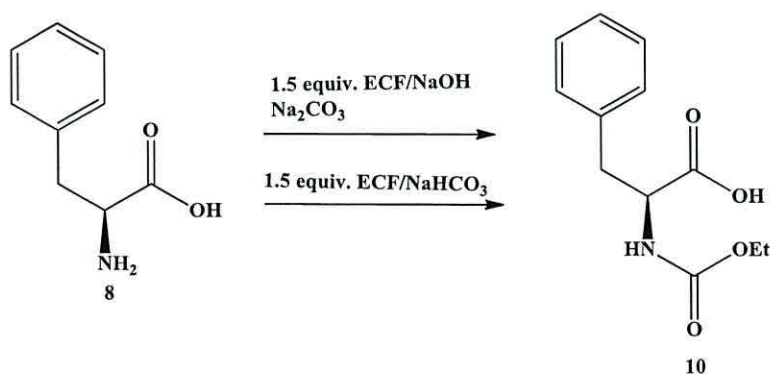
Figure 10: Protection of amino group of L-phenylalanine.

The ^{1}H NMR spectrum of the product showed a peak at δ 4.72 corresponding to the chiral α proton. The new ethyl group signals appeared as a quartet at δ 4.10 for the methylene environment and at δ 1.24 for the methyl. Signals at δ 3.23 and δ 3.15 correspond to the two hydrogens situated next to the aryl ring. The ^{13}C NMR showed a signal at δ 176.1 corresponding to the carbonyl carbon of the carboxylic group. A second signal at δ 156.2 corresponds to the carbonyl carbon of the carbamate. A signal at δ 61.4 corresponded to the α-carbon. A signal at δ 54.5 corresponds to the CH_2 carbon of the carbamate ethyl group, and a signal at δ 14.5 corresponds to the CH_3 group. A signal at δ 37.7 corresponded to the benzylic carbon.

1.5.3 Reduction of *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid with NaBH$_4$/H$_2$SO$_4$

The next step was to selectively reduce the acid group to the corresponding alcohol, without the reduction of the amide, because the protecting group is later required for the cyclisation. This was performed using various reagents as discussed below.

Firstly, NaBH$_4$/H$_2$SO$_4$ was used. The protected acid (**10**) was treated with NaBH$_4$/H$_2$SO$_4$ to form (*(S)*-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester according to the scheme below:
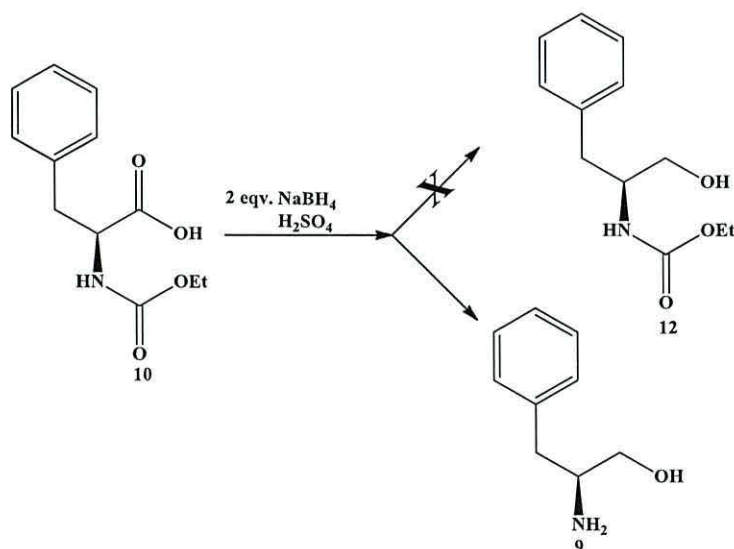
Scheme 6: Reduction of (S)-2-ethoxycarbonyl amino-3-phenyl-propionic acid using

NaBH$_4$/H$_2$SO$_4$

However, the ^{1}H NMR spectrum of the product showed that the reductive deprotection of the amine had occurred under the conditions employed. This produced *(S)*-2-amino-3-phenyl-propan-1-ol **(9)**, instead of *((S)*-1-hydroxy-methyl-2-phenyl-ethyl)-carbamic acid ethyl ester **(12)**. This was a disadvantage due to the loss of the protecting group on the amine, which is needed for the cyclisation. Using this method would therefore require the re-protection of the amine, increasing the number of reaction steps, and in turn, increasing the cost.

As a result, the aim of this study was to optimise the process so as to not only improve the efficiency of cost effectiveness, but also the chemo-selectivity. Three different approaches were taken.

The first approach was to convert the acid group into an anhydride, followed by reduction with NaBH$_4$/MeOH. This can be seen in the Scheme 7:
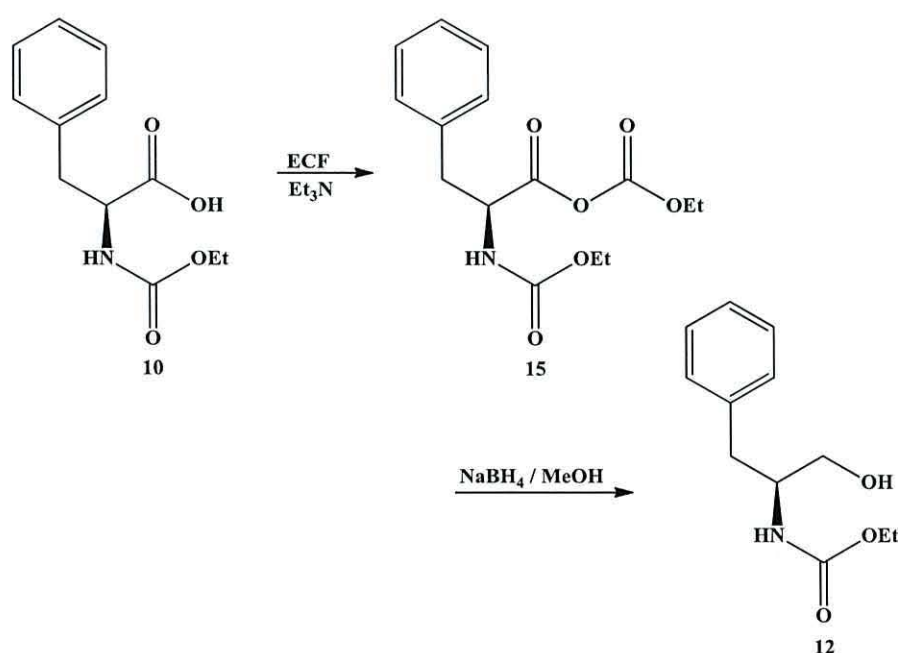
Scheme 7: Reduction of (S)-2-amino-3-phenyl-propionic acid

The *(S)*-2-((ethoxycarbonyl)amino)-3-phenylpropanoic acid **(10)**, when treated with ethyl chloroformate, led to the desired anhydride *(S)*-2-((ethoxycarbonyl)amino)-3-phenyl-propanoic (ethyl carbonic) anhydride, which was then reduced to *(S)*-ethyl (1-hydroxy-3-phenylpropan-2-yl)carbamate by using sodium borohydride. However, the product was impure, with some of the amino acid starting material being present in the product mixture.

Column chromatography was used to separate the two. The ^{1}H NMR spectrum showed peaks at δ 4.0 (2H, t) corresponding to the methylene environment of the carbamate ethyl group, together with a singlet at δ 3.93 which integrated for one proton corresponding to the hydrogen on the chiral carbon; there were also peaks at δ 3.66 (1H, t) and δ 3.56 (1H, dd) corresponding to the protons situated next to the oxygen of the alcohol, at δ 2.86 (2H, d) corresponding to the two hydrogen protons of the benzylic methylene group and a triplet signal at δ 1.20 (3H), corresponding to the methyl environment of the carbamate. The ^{13}C NMR spectrum showed a signal at δ 156.8, which corresponds to the carbamate carbonyl group. Signals at δ 135.7- 126.8 correspond to the aromatic carbon environments. A signal at δ 63.9 corresponds to the carbon atom bearing the hydroxyl group. A signal at δ 53.9 corresponds to the chiral carbon atom bearing the amine group, and the benzylic carbon atom resonates at δ 37.4. A signal at δ 14.5 corresponds to the methyl carbon of the carbamate ethyl group.

This method thus provides ambiguous results. On the one hand, it is arguably the simplest and cheapest method of preparing the amino alcohol. This makes it highly attractive. On the other hand, in order to utilize it fully, a simple and cost-effective means of removing the residual amino acid from the amino alcohol has to be found. This is a subject for future research.

The second approach was reducing the acid using $NaBH_4/BF_3.Et_2O$ as seen in Figure 11:
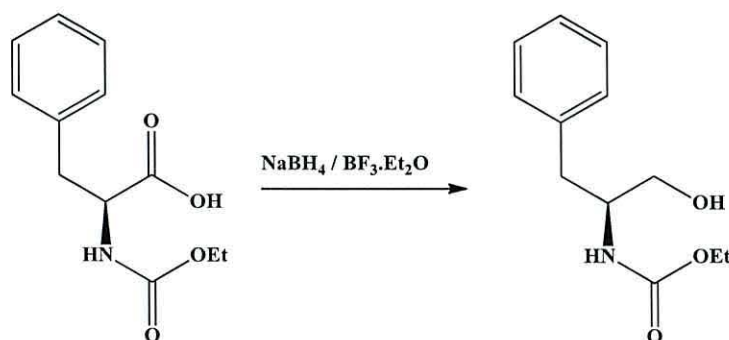
Figure 11: Reduction of amino carboxylic acid using NaBH₄/BF₃.Et₂O.

The product was analysed using both NMR and IR spectroscopy, which showed that the target molecule had been successfully synthesised. The ^{1}H NMR showed peaks at δ 4.0 (2H, t) corresponding to the methylene environment of the carbamate ethyl group, together with a singlet at δ 3.93 integrated for one proton corresponding to the hydrogen on the

chiral carbon, at δ 3.66 (1H, t) and δ 3.56 (1H, dd) corresponding to the protons situated to the oxygen of the alcohol, at δ 2.86 (2H, d) corresponding to the two hydrogen protons of the benzylic methylene group and a triplet signal at δ 1.20 (3H), corresponding to the methyl environment of the carbamate. The ^{13}C NMR showed a signal at δ 156.8, which corresponds to the carbamate carbonyl group. Signals at δ 135.7- 126.8 correspond to the aromatic carbon environments. A signal at δ 63.9 corresponds to the carbon atom bearing the hydroxyl group. A signal at δ 53.9 corresponds to the chiral carbon atom bearing the amine group, and the benzylic carbon atom resonated at δ 37.4. A signal at δ 14.5 corresponds to the methyl carbon of the carbamate ethyl group.

The final approach was to reduce the acid with BH_3.THF, as seen in Figure 12:
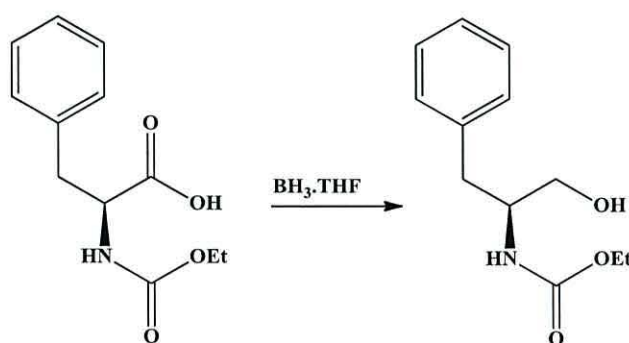
Figure 12: Reduction of amino carboxylic acid using BH_3.THF

NMR and IR analysis of the product gave identical spectra to those obtained when performing the reduction with $NaBH_4/BF_3.Et_2O$, again confirming that the target molecule had been successfully synthesised, without de-protection of the amine group. The yield in this method was better (82%), but it is unattractive because the BH_3.THF is an expensive reagent.

1.5.4 Cyclization of ((S)-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester

The final stage of this process was cyclisation of the protected amino alcohol.

The carbamate was successfully cyclised using potassium carbonate to give ((S)-4-benzyl-oxazolidin-2-one) in 83 % yield. The product was confirmed by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, and mass spectrometry. The proton NMR spectrum showed peaks at δ

4.35 (1H, t) and 4.08 (1H, dd) corresponding to the CH$_2$ group next to the oxygen, at δ 4.06 (1H, m) corresponding to the hydrogen on the chiral carbon and two peaks at δ 2.91 (1H, dd) and δ 2.86 (1H, dd) corresponding to the benzylic methylene group. The ^{13}C NMR showed signals at δ 135.7, 128.8, 128.6 and 126.8, which correspond to the aromatic carbons. A signal at δ 77.3 corresponded to the CH$_2$ situated next to the oxygen. A signal at δ 53.4 corresponds to the ring carbon atom situated next to the nitrogen. A signal at δ 40.9 corresponds to the benzylic carbon atom.

1.6   An economic analysis of the process

L-Phenylalanine was reduced to L-phenylalaninol with sodium borohydride and H$_2$SO$_4$. The resultant amino alcohol was protected with ethyl chloroformate to afford the carbamate, which was cyclized by K$_2$CO$_3$. These reactions were investigated using a number of reagents and with different numbers of equivalents. An Excel based spreadsheet used in the company to analyse the efficiency of new processes was applied to understand the commercial opportunities provided by the modified process (p24). Through the use of the Excel programme the cost of each step was accounted for on the basis of the prices of the chemicals used, and the final cost all the steps that have been followed in each route were calculated and then compared. This confirmed that the most economically crucial step (i.e. that step which required the use of the most expensive chemicals) was the reduction. The results of this analysis are summarised below.

The results show that the best and cheapest way for achieving the reduction required the use of 2 equivalents of NaBH$_4$ / H$_2$SO$_4$ at a cost of £912 per kilo. By reducing the number of equivalents of NaBH$_4$ from 2.8 (the current commercial practice) to 2 equivalents, it was found that a cost reduction of £ 47 per kilo could be achieved. This outcome resulted from a number of trials where various numbers of equivalents of sodium borohydride were investigated. It was determined that a yield of 83% could be accessed with this loading of reductant, which compares very favourably with the current commercial process (83 %).

In investigating the NaBH$_4$: BF$_3$.OEt$_2$ reductant system, it was found that by reducing the reactant ratio from 2 : 4 (the current commercial practise) to 1.7 : 3.5, a substantial improvement in yield was afforded (78 % → 90 %) with a concomitant cost reduction of £ 179 per kilo. This method, however, even after this process of optimisation, still proves to be the most expensive (£ 968 per kilo) (Table 5).

When the use of BH$_3$.THF was examined by the same approach, it was found that by reducing the reactant ratio from 2 mole equivalent to 1.75 the percentage yield was not affected, which will reduce the cost of the reduction.

The steps to this point involved no protection of the amino group; however, due to coordination of the boron species to the amino group, it was decided to first protect it, as a carbamate, as mentioned in the discussion. Direct reduction of *(S)*-2-ethoxycarbonylamino-3-phenylpropionic acid with NaBH$_4$/H$_2$SO$_4$ was successful; however, both functional groups were reduced, which was undesirable. This could be overcome by first converting the acid group to an anhydride before performing the reduction. This led to the desired product being formed; however, additional steps in the synthesis were required, reducing the benefit of this method. When performing the reduction of the *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid with BH$_3$.THF, the number of equivalents of reagent could be reduced from 2 to 1.75, therefore reducing the cost per Kg of product from £2034 to £1898. Using NaBH$_4$/BF$_3$.Et$_2$O also successfully led to the formation of the desired product, however this reagent is expensive, therefore, this method of reduction is not as desirable as those previously discussed.

The Excel chart below shows that the cost of the first step, the reduction of the acid group to an alcohol using NaBH$_4$ / H$_2$SO$_4$, was £348 with a yield of 83%. This was applied in the second step, which involved protecting the amino group with ethyl chloroformate; this time the cost was £246 with a yield of 92%. Finally both steps above were followed by the cyclization step to give 4-benzyloxazolidin-2-one; this step cost £33 and a yield of 84%. Combining the cost of all these three steps gives the final price of this method £627 (per 0.68 kilo) or £912 per kilo. This was cheaper compared to the cost of the previous commercial method (£ 959 per kilo). Based on these results it was found that using 2 equivalents of NaBH$_4$ / H$_2$SO$_4$ was best to give a good yield and a low cost (Table 5). The corresponding Excel spreadsheets for the other methods are presented in the Appendix.

Reducing agent	Reduction step yilde	Cost per kilo	previous cost per kilo
NaBH$_4$ / H$_2$SO$_4$	83 %	£ 912	£ 959
NaBH$_4$: BF$_3$.OEt$_2$	90 %	£ 968	£ 1147
BH$_3$.THF	92 %	£ 1898	£ 2034

Table 5: Comparing yields and cost for preparation 4-benzyloxazolidin-2-one

Version	1/D.Justice
Costing	Based on Aldrich catalogue prices/assumed solvent prices
	Yields Based on results provided by Hussien, 26/Mar2010
Date	٢٣ نيسان، ٢٠١٠
Route 4	(1) NaBH4/Sulphuric acid (2) ECF carbamate protectiom (3) potassium carbonate cyclisation

PRODUCT:	Stage 1 Product	Stage 1	
STEP	1	of	3
WEIGHT OF PRODUCT (A):	0.760	Kg	
STAGE YIELD:	83%		
CUMULATIVE YIELD	83%		

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE Kg	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CARBAMATE PROTECTION									
Phenyl alanine	1.00	165	6.05	1.32	£243.00	£243.00	Aldrich 1Kg lots	63-91-2	38.7%
Sodium Borohydride	0.46	38	12.15	0.61	£174.50	£80.24	Aldrich/Venpure 2Kg lots	16940-66-2	12.8%
Sulphuric Acid	0.59	98	6.06	0.78	£8.56	£5.08	Alddrich 2.5L lots	7664-93-3	0.8%
THF	10.00			13.16	£2.00	£20.00	Assumed		3.2%

| STAGE 1 RAW MATERIALS | | | | | | £348.32 |
| TOTAL STAGE 1 COST | | | | | | £348.32 |

	QTY	M/WT	MOLES	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 1	0.7597	151	5.02	83.0%	83.0%	£348.32

PRODUCT:	Stage 2 Product	Stage 2	
STEP	2	of	3
WEIGHT OF PRODUCT (A):	0.97	Kg	
STAGE YIELD:	92%		
CUMULATIVE YIELD	76%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
BORANE REDUCTION									
Stage 1	0.760	151	5.02	0.78	0.00	£0.00			0.0%
NaHCO3 solution	25.00			25.68	£1.00	£25.00	Assumed		4.0%
Ethyl chloroformate	0.76	109	7.04	0.78	£86.50	£66.09	Aldrich 500ml lots	541-41-3	10.5%
Ethyl acetate	75.00			77.05	£2.00	£150.00	Assumed		23.9%
Hydrochloric acid	1.00			1.03	£5.00	£5.00	Assumed		0.8%
Water	6.61			6.79	£0.00	£0.00	Assumed		#REF!
									0.0%

| STAGE 2 RAW MATERIALS | | | | | | £246.09 |
| TOTAL STAGE 2 COST | | | | | | £246.09 |

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 2	0.973	211	4.62	92%	76.4%	£594.41

PRODUCT:	Stage 3 Product	Stage 3	
STEP	3	of	3
WEIGHT OF PRODUCT (A):	0.69	Kg	
STAGE YIELD:	84%		
CUMULATIVE YIELD	64%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CYCLISATION									
Stage 2	0.973	211	4.62	1.00	0.00	£0.00			0.0%
Potassium carbonate	1.760	138	12.73	1.81	13.40	£23.58	Aldrich 1Kg lots	584-08-7	3.8%
Solvent	4.975			5.11	2.00	£9.95	Assumed		1.6%

| STAGE 3 RAW MATERIALS | | | | | | £33.53 |
| TOTAL STAGE 3 COST | | | | | | £33.53 |

Output of stage 3	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
	0.688	177	3.88	84%	64.1%	£627.94

Cost of Goods manufacture/Kg =   £912.68

Excel sheet 1: Cost of preparation (S)-4-benzyl-oxazolidin-2-one using 2 equivalents

NaBH₄/H₂SO₄ for the reduction step

1.7 Conclusions

A number of routes for the synthesis of the chiral oxaziladine were investigated to obtain the most cost effective industrial method. Initial work looked at the reduction of L-phenylalanine using various numbers of equivalents of reducing agents, $NaBH_4$ / H_2SO_4, $NaBH_4$: $BF_3.OEt_2$ and $BH_3.THF$. It was found that the most cost effective reducing agent was $NaBH_4$ / H_2SO_4, and 2 equivalents of $NaBH_4$ led to the lowest cost.

The next investigation looked at protecting the amino group, hoping to prevent coordination of the boron species, therefore reducing the amount of reducing agent required. Unfortunately, with the $NaBH_4$ / H_2SO_4 this was not successful as both the protected amino group and the acid group were both reduced, but this could be avoided by firstly converting the acid into an anhydride. This, however, is undesirable because it increases the number of reaction steps. With the other reagents, the reaction proved successful; however, there was no advantage in this route because the same numbers of equivalents were needed. This analysis concentrated only on the first step, because the remaining two steps are identical, regardless of which reagent is used. By using $NaBH_4$ / H_2SO_4 for the reduction in the first step, the overall cost of producing 1 Kg of the desired chiral oxazolidine was £912 which is a reduction in cost from £959 which is the current commercial cost.
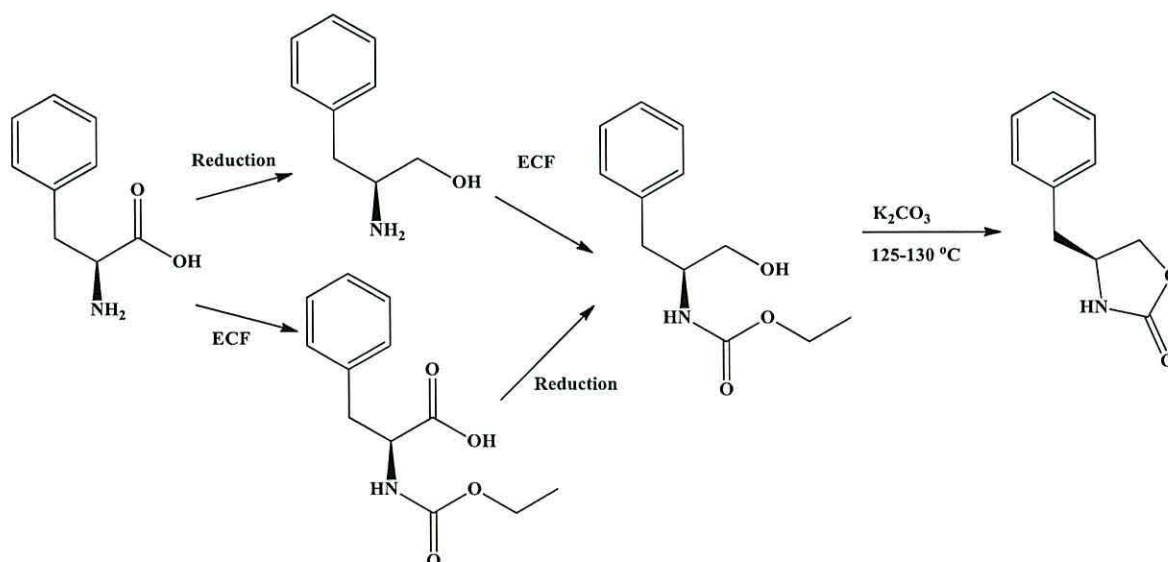
Scheme 8: Routes to prepare (S)-4-benzyl-oxazolidin-2-one

Chapter 2.   A flexible route to pheromones containing *Z,Z*-1,4-dienes

2.1 Introduction

The problem of pest control has preoccupied farmers for a long time. Pests are defined as living organisms that cause damage or illness to man or his possessions, and these could be insects, molluscs, fungi, mites, weeds or birds.[21]

Agricultural pests in the form of insects, diseases and weeds have been estimated to account for the loss of about one-half of the world's food supply, while many other pests spread disease among mankind. In the fight against them, humans have increasingly relied upon the use of chemical pesticides, an approach which has had serious environmental consequences. Therefore, a more environmentally friendly method of controlling pest populations is being sought. Organic chemists have, therefore, been making extensive efforts to produce alternatives to pesticides, and among these are pheromones. These can be used to deter pests (by luring insects into traps and killing them, or by repelling other insects or animals from coming into a certain area) at very low concentrations, therefore causing less damage to both humans and the environment than alternative pest control methods, while also being more selective and cost effective than other alternatives.

This chapter describes a new and flexible method for preparing pheromones containing a *Z,Z*-1,4-diene group. It involves a different approach from the standard method of alkyne coupling followed by selective hydrogenation, and instead the method involves selective ozonolysis of cyclonona-1,4,7-triene to yield a new unsaturated product containing the 1,4-*Z,Z*-diene fragment. This is then converted into a number of pheromones containing this fragment.

2.2   Pheromones

'Pheromone' derives from *Greek* words *pherein*, to transfer and *hormon*, to excite.[22] Pheromones are thus chemical signals used by animals and plants to transmit information to other organisms. A simplistic but incorrect view of pheromones is that they act as "exo-hormones", which are analogous to hormones. Although there are similarities between pheromones and hormones, there are also important differences. Pheromones, unlike hormones, tend to be species-specific. Also, they tend to be mixtures of different chemicals. In view of this fact, at least in part, a given pheromone may produce an array of different behaviours, according to context. Thus an alarm pheromone (see below) of a social insect may induce, for example, the action of searching, attack, or retreat. To such complications one may add that simplistic views of instinct, as popularized by, for example, Konrad Lorenz,[23] that imagine instinctive behaviour as innate, non-modifiable, and rigid, have long been discredited in vertebrates and appear equally suspect in insects.[24] Honey bees, for instance, are known to respond to classical conditioning.[24]

In addition; the waggle dance of honey bees is in part learned, for bees reared in isolation fail to dance correctly.[25] Because of this, animal, including insect, responses to pheromones may vary according to the organism's past experience.

Complications lie in the fact that many chemicals may elicit behaviour in organisms, yet the chemicals need not be pheromones. Thus, for example, the synthetic compound trimedlure attracts the male Mediterranean fruit flies (*Ceratitis capitata*). Trimedlure is unknown in nature, so cannot have evolved as a pheromone.[24] Chemicals such as trimedlure are termed *para-pheromones*. Related to this, the borderline between a pheromone and chemical detection is vague. Thus, for instance, human hair has long been known to be a genetic marker: the quality or lack of hair may be taken as a signal of disease or genetic defect.[26] Hair odour would also appear to carry important signals.[26]

It is unclear, however, whether hair odour should be viewed as a pheromone: in one sense it is, because it is clearly conveying a message; but in another it isn't, because it is not so much emitted by the emitter as received by the receiver. Hair odour in humans appears to be an accidental signal. Another complication is that a pheromone may act, not only as pheromone for the same species, but also as an *allomone* or a *kairomone* for another species; this is discussed in detail later.

Pheromones are thought to be widely used by higher organisms, and have been extensively studied in insects. They may trigger a number of conditions, including sexual readiness and alarm. As such there are advantages and disadvantages of chemical signalling in insects. Advantages include the ability to sense at long distances, in the dark, and around obstacles, and relative invisibility to predators. A disadvantage of pheromones is that, when emitted by prey species, they may alert predators to its presence. Moreover, pheromones cannot be "switched off" once emitted. Therefore there will be selective pressure for pheromones to be detectable only by the same species. Each species tends to have a pheromone "waveband",[24] analogous to the limited wavebands of TV and radio stations. The situation is similar to that of bird alarm calls. These appear "designed" so that they are especially difficult for predators both to detect and to locate,[27] and the same holds true of pheromones. However, as discussed below, this "waveband specificity" is imperfect, because predator species in many cases do detect prey species' pheromones.

Pheromones are of interest in agriculture because they can be used as an effective means of pest control. This may use what is known as a *pheromone trap*, which may contain a reserve of a given pheromone. This may attract insects to it. The "trap" includes some mechanism that then kills or collects the insects. Other uses of pheromones in pest control include "coating" males with female sex pheromones, with the result that other males attempt to mate with the coated males in preference to females; this, it is hoped, will reduce the insect population. The use of pheromones for pest control is discussed in detail below.

There are two major advantages attributed to the use of pheromones in pest control. First, because they tend to be species-specific, they can be used to target a particular species without harm to friendly insects. This is in contrast to traditional pesticides. Use of parathion in the USA, during the 1970s for instance, to protect crops against weevils had the unfortunate side effect of killing bees, with consequent severe losses to US fruit and flower growers.[28] Second, insects tend not to develop resistance to pheromones as they are "natural". Again this is in contrast to traditional pesticides: weevils in the USA soon developed resistance to parathion.[28]

Thus, the rationale of the present study is to develop a cheap, effective route to a range of pheromones that may be used in agriculture to protect crops from insect pests.

2.3 Insect damage to crops

Images for *Insect damage to cotton* *https://www.google.co.uk/search?q=Insect+damage*

Insect damage to crops is extensive. There are thought to be at least 1 million species of insect, some 10,000 of which are thought to attack crops. Of these, some 700 species cause the majority of damage worldwide. Thus, for example, bollworms and budworms are thought to cause US$500 million damage to cotton crops each year, and a further half billion dollars worth of damage to other crops.[29] In 1998, the cotton bollworm infested over 9 million acres of US cotton and caused a 2.7 % yield reduction for the total US crop.[30] In the same year, boll weevils caused a 2.3 % yield reduction on 5.9 million infested acres. Similarly, in the USA the diamondback moth (*Plutella xylostella*) causes an estimated US$1 billion of damage each year.[31] Diamondback moth caterpillars feed on the leaves of vegetables, sometimes killing the plant. Other insect pests include plant bugs, aphids, and thrips.[32]

In order to fight such pests, the world spends US$ 20 billion on pesticides each year. Despite this, it loses some 15 % of its crops to insect pests.

As indicated, use of conventional insecticides is often far from ideal. These may cause environmental damage (parathion, for instance, is highly toxic to birds and other wildlife),[28] may be poisonous to humans (over 100 Americans died from parathion poisoning during the 1970s),[28] and may, in any event, lead to resistance in the target species. Pheromones offer an attractive alternative. Many pheromones, especially sex pheromones, have been investigated, with most attention being given to those pertaining to the control of agricultural insect pests. Despite their promise in pest control, the use of

pheromones represents less than 5% of the world insecticide market. This is partly because pheromones, being species-specific, may not protect crops plagued by a wide variety of insects. Cost is also an important factor, as pheromones can be expensive to manufacture. This is because many are long chain Z-alkenes, with an alcohol, aldehyde or acetate at C-1. Conventional synthesis often requires the preparation of long chain alkynes and the use of a strong base. It may also require liquid ammonia to introduce the correct functional group. In addition, controlled hydrogenation of the alkynes will provide the desire Z-alkenes; however, such procedures may also result in the formation of the E-isomer as an unwelcome and potentially damaging by-product.

2.4 Semiochemicals

Pheromones are a class of semiochemical. Semiochemicals are chemicals that transmit signals to plants and animals.[33,34] Often, they affect organisms, either by encouraging movement towards a particular phenomenon or by encouraging movement away from it.

There are two main types of semiochemical : *pheromones* and *alleochemicals*.

2.5 Types of pheromone

Pheromones may be classified into four main types depending on their particular function:[24] aggregation, alarm, trail, and sex. They may act in different ways under different conditions and there is a thin line between different types of pheromone. An alarm pheromone, for example, that causes an insect to change location (move away from potential danger) may also serve to bring the insect closer to a potential mate, so may also act as a sex pheromone.[24] This is an example of *pheromone parsimony*. Although many species use several pheromones, they all tend to use as few as possible, and, in doing so, may use a given pheromone to direct several distinct activities.[24]

2.5.1 Aggregation pheromones

Aggregation pheromones are those that induce conspecifics, of one or both sexes, to congregate within a limited area.[35] As such, they may function in defence or as a means of attracting mates. For this reason, sex pheromones emitted by females can be viewed as aggregation pheromones in that they may result in a large number of males congregating around the emitting female. Aggregation pheromones are used in pest control, for example, control of the boll weevil (*Anthonomus grandis*) and the pea and bean weevil (*Sitona lineatus*),[36] because they can be used to lure large numbers of pests to a chosen site, then the pests may be killed. They have the advantages of being effective in small quantities and are non-toxic to friendly species.

2.5.2 Alarm pheromones

Alarm pheromones are used to signal the presence of danger, often in the form of attack by a rival species,[37] and may provide a signal to escape from the attack. For example, when an aphid is attacked by a predator, the attack stimulates the release of the sesquiterpene (*E*)-β-farnesene from cornicles on the surface of the aphid's abdomen. This induces nearby aphids to disperse. Alarm pheromones could also induce effective defence. Bees and termites, for example, use alarm pheromones to launch an attack on an intruder.[38] Among honey bees (*Apis mellifera*) such alarm pheromones can be relatively specific. When a bee stings, the barb sting stays in the attacked organism's skin - the sting and the poison gland are ripped from the attacking bee's body. The sting sheath gland then releases a pheromone to induce other bees to sting the target organism.[24] Honey bees use a different alarm pheromone when guarding the hive, which appears to deter robber bees from raiding it. The latter example, in contrast to bees' stings, provides a good illustration of pheromone parsimony. The bees apparently use the same pheromone to mark as "depleted" those flowers they have drained of nectar.[24]

16
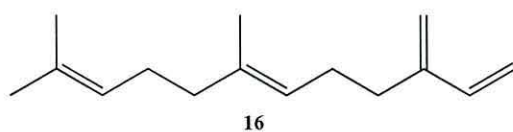
Figure 13: (E)-β-Farnesene

2.5.3   Trail pheromones

Trail pheromones are used to sense the presence of food.[39] They are common in the social insects, especially ants. Ants lay down pheromone trails that are followed by other ants and the trails lead to food. Examples include the pyrrole-based pheromones used by the leaf cutter ant *Atta texana*.

2.5.4   Sex pheromones

Sex pheromones may perform two functions which are often overlapping. First, they may act as aphrodisiacs and secondly they may signal the presence of a prospective mate. In the latter instance, they may act over long distances. Sex pheromones are produced by males as well as females; however, in insects they are produced predominantly by females to attract males.[24,39] In principle, sex pheromones may comprise only one chemical. However, in practice, they tend to be mixtures of two or more chemicals, often in specific ratios. Typically, a female insect releases a sex pheromone from a gland in her abdomen. The pheromone may have a molecular mass in the range 200–300, and the amount released tends to be small, measured in nanograms. The pheromone is not highly volatile, or else it would evaporate and lose its effectiveness. Males are highly sensitive to such pheromones, being able to detect, via their antennae, as little as one molecule of it.[24]

Having detected the pheromone; a male follows the scent (the "plume") to the female. Upon approaching the female, the male may emit a male pheromone. This appears to act as an aphrodisiac for the female.

Pheromonal activity is dependent on the length of the alkene chain and the degree of unsaturation of functional groups. Also, in cases in which the pheromone comprises a mixture of chemicals, the chemicals have to be in the correct ratio. Generally, mixtures are a blend of two or three alcohols, plus aldehyde and acetate, and these may be of different chain length. As indicated, pheromones are species-specific, so each species has its own distinct pheromone, which often consists of a distinct mixture in distinct ratios. Insect pheromones have been intensively studied since 1959, when the pheromone of the female silkworm moth (*Bombyxmori*) was isolated and identified.[39] This substance has been synthesized and proved to be *E,Z*-10,12-hexadecadien-1-ol.

2.5.5   Other uses

Aggression, alarm, trail, and sex are not the only behaviours found to be regulated by pheromones. Honey bees (*A. mellifera*), for example, use a large array of pheromones. Worker honey bees use pheromones to stimulate capping of worker brood cells, to stimulate incubation of pupae, and to recognise hive mates.[24] Honey bee queens also emit specific pheromones, these include, among virgin queens, a pheromone that deters worker bees from attacking the virgin.[24]

2.6   Alleochemicals

Alleochemicals are similar to pheromones in that they are chemical signals; however, they differ from pheromones in that they affect the behaviour of species different from the organism that emits the chemical. Therefore a chemical can act as a pheromone for one species but as an alleochemical for another species. Alleochemicals are of three main types: those that benefit the emitter, those that benefit the receiver, and those that benefit both the emitter and the receiver. The first type is called *allomones*. An example is the allomone found in the wild potato, *Solanum berthaultii*, which produces the aphid alarm pheromone, (*E*)-β-farnesene (Figure 13). As such, aphids avoid the potato and it is protected.[40]

Some alleochemicals operate in such a way as to appear to benefit the receiver and these substances are called *kairomones*.[41] Strictly speaking, "pure" kairomones does not exist, because the existence of any signal that benefits only the recipient would be contrary to the principles of Darwinian evolution. However, in practice, *kairomones* benefit the emitter, but in a different context from that of receiver; for example, bark beetles use a pheromone between themselves, to their advantage, but the pheromone acts as a *kairomone* for those beetles that prey on bark beetles.[42] Similarly, wasps of the species *Vespula germanica* are attracted to the sex pheromone of male Mediterranean fruit flies (*Ceratitis capitata*), which they produce when lekking.[43] (a lek is a particular gathering behaviour exhibited by the males, of a certain animal species, for the purposes of mating). Thus *kairomones* have some advantage to the emitting species, only when acting as pheromones.

Alleochemicals that benefit both the receiver and the emitter are termed synomones. Synomones are often linked to symbiotic relationships. In the fruit fly orchid,

Bulbophyllum cheiri, for example, the flower emits methyl eugenol, which attracts male fruit flies. The orchid benefits from this because, in being attracted to the scent, the fruit flies help pollinate the orchid. In return, the flies benefit by being allowed to feed on the floral attractant.[44]

17
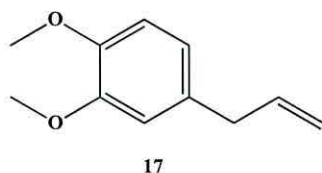
Figure 14: Methyl eugenol

2.7 Identification of semiochemicals

There are a variety of techniques for isolating and identifying semiochemicals. The choice often depends upon the source, and the techniques used for plant materials are different from those used for animal materials. Solvents are used to extract semiochemicals from plants, and the solvent employed varies according to the precise nature of the semiochemical under investigation.

The situation is more complicated with insects. Typically, the pheromone gland is removed from the insect; for example in female moths, the gland lies at the tip of the insect's abdomen. This gland is abstracted and placed in solvent. In the past, this procedure was highly inefficient. The pioneering work that identified the silk worm pheromone required half a million glands.[45] However, modern techniques allow for identification of the pheromone using only a few glands.[46]

2.8 Techniques used for insect pheromone identification

Modern methods for identifying pheromones include gas chromatography (GC), high performance liquid chromatography (HPLC), and mass spectrometry (MS).[47]

A more recent method involves taking an electroantennogram (EAG).[48] This involves amputating the insect's antennae and passing an electric current through the antenna tip. When a pheromone is passed over the tip, the pheromone molecule binds with the

olfactory receptors in the tip, and this disrupts the electric current, causing a pulse. EAG can be integrated with GC and MS, allowing for the efficient and fast isolation and identification of pheromones. Modern techniques also include *single cell recordings*. These works on the basis that specialised structures exist within aphid antennae, termed *secondary rhinaria*,[49] that may be used to test individual compounds. Secondary rhinaria are visible when using an electron microscope. They appear as dark circular patches when using an optical microscope.[50]

2.9 Pheromone structure and chemistry

Pheromones are relatively small molecules, typically containing 8–30 carbon molecules. They often contain a hydrocarbon chain. This chain may include, in addition to hydrogen and carbon, atoms of oxygen, nitrogen, or other elements. The simplest pheromones are mono-unsaturated acetates, alcohols, or aldehydes. Compounds **18–20** are examples of female sex pheromones. [24]
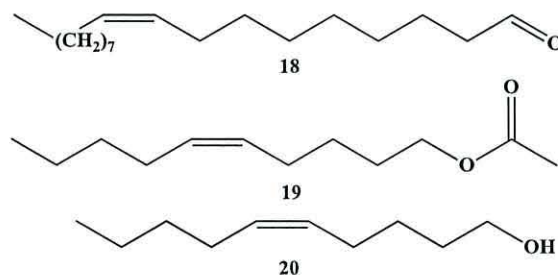
Figure 15: Common components of female sex pheromones

Pheromones may also can be di or tri-unsaturated as shown in Figure 16.[24]
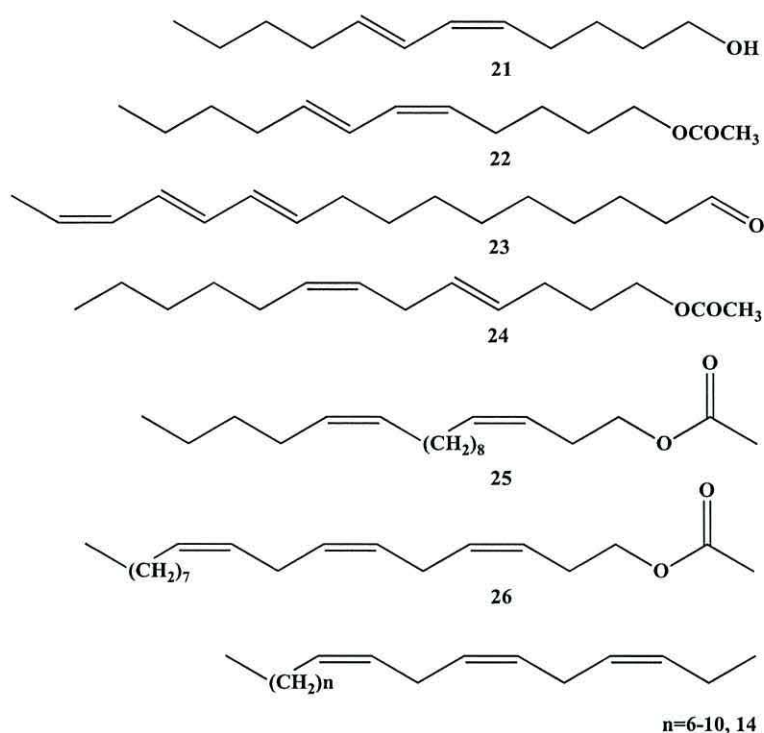
Figure 16: Unsaturated sex pheromones

The character of a pheromone is determined by the length of the carbon chain, the presence and position of any double bonds within the chain, and the nature and position of any additional elements or groups. It follows that the number of distinct pheromones is potentially vast. It also follows that they may comprise esters or other acids, ketones, epoxides, or hydrocarbons (Figures 17);[24] these are all examples of female sex pheromones.
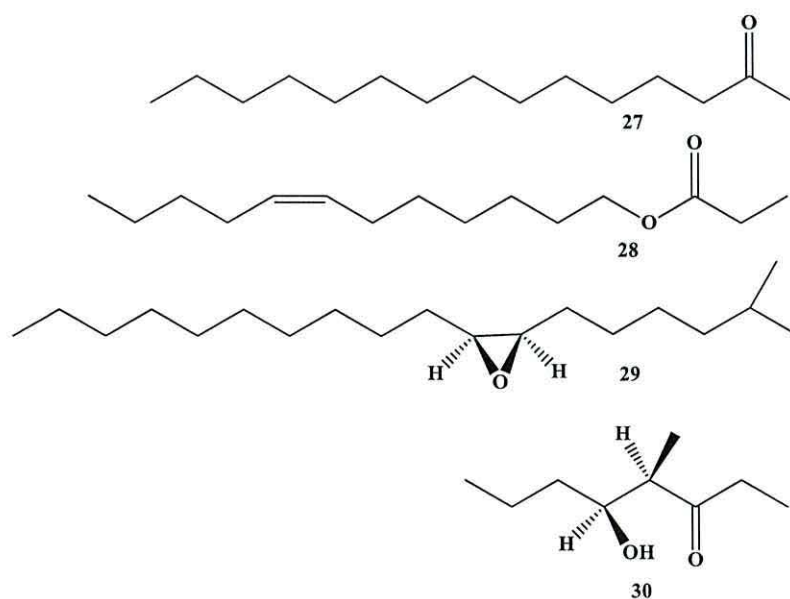
Figure 17: Sex pheromone containing different functional groups

Pheromones may also include terpenoids which can be biosynthesized using mevalonic acid, a six-carbon compound. The synthesis, however, involves the loss of one carbon atom. Thus terpenoid pheromones are built from "head to tail" linking of five-carbon isoprene. Figure 18 shows a monoterpenoid (**31**) and a sesquiterpenoid (**32**).[24]
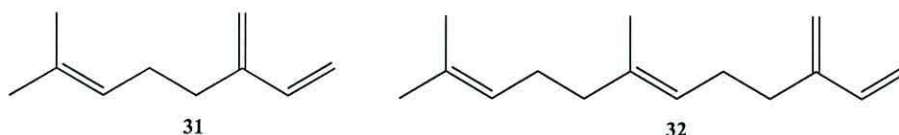
Figure 18: Terpenoid pheromones

The above examples illustrate the fact that some pheromones are composite and comprise more than one distinct molecular structure. This, coupled with the vast number of permutations made possible by inclusion and positioning of double bonds, inclusion of atoms other than carbon and hydrogen, and carbon rings, adds to their richness and variety. (3Z,6Z,8E)-3,6,8-dodecatrien-1-ol, is a trail following pheromone of a Southern subterranean termite, and it is an example of pheromones with a triene system. This type of pheromone is very efficient, and therefore the amount which required to stimulate the worker termites is very low.[51]
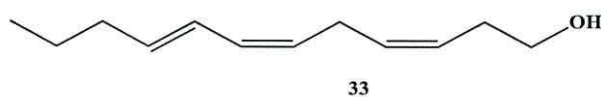
Figure 19: (3Z,6Z,8E)-3,6,8-Dodecatrien-1-ol

(4E,7Z,10Z)-Trideca-4,7,10-trien-1-yl acetate (**34**) is a component of the pheromone of the potato tuberworm moth (*Phthorimaea operculella*) and was synthesized by an acetylenic route through five steps including a Grignard reaction.[52]
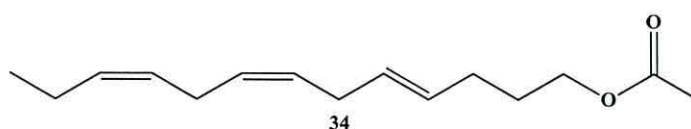
Figure 20: (4E,7Z,10Z)-Trideca-4,7,10-trien-1-yl acetate

Other structures of pheromones, known as a polyene and epoxide types are shown in Figure 21.
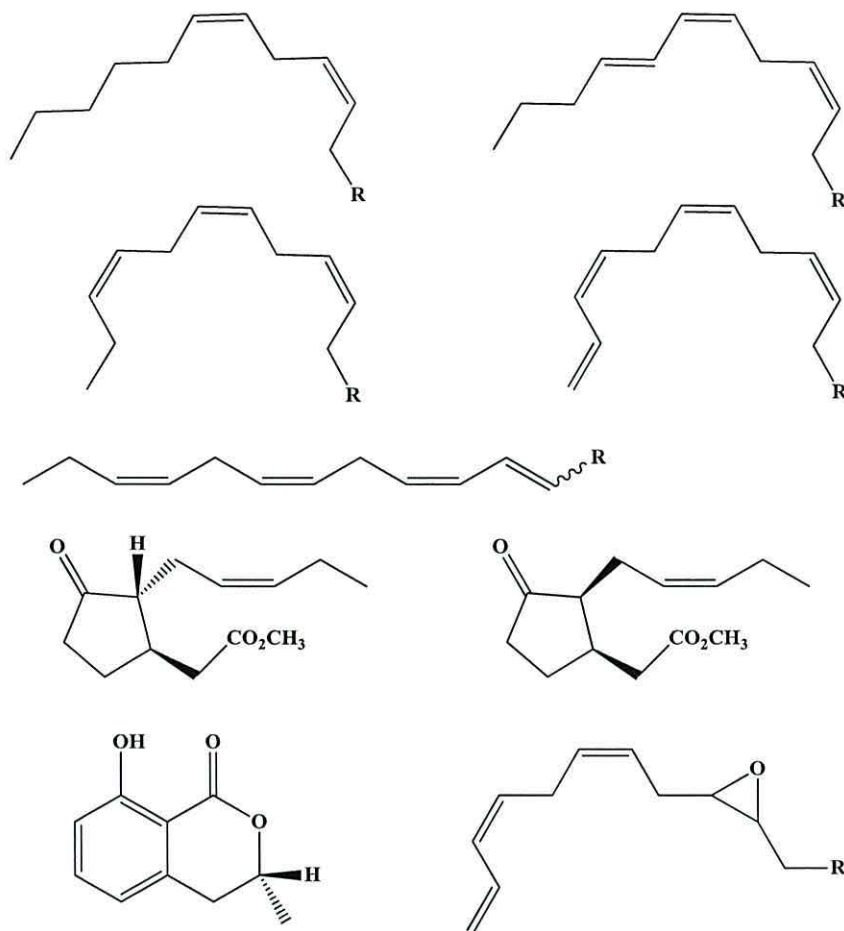
Figure 21: Structures for polyene, epoxide and heterocyclic pheromone components

2.10 The conventional methods for the preparation of pheromones

The chemical structures of many insect pheromones contain double bonds, a long carbon chain and different functional groups. In this section, several methods are discussed as examples to prepare these.

2.10.1 Reduction of alkynes

Reduction of alkynes can lead to alkenes. This can be done by using several reducing agents; for example, Warthen and Jacobson used sodium with liquid ammonia to give an (*E*)-alkene.[53]
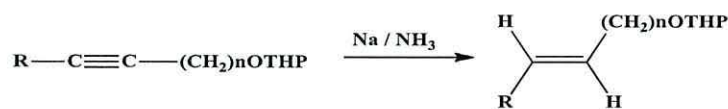
Figure 22: Sodium/liquid ammonia reduction to prepare (E)-alkene pheromones

Lithium aluminium hydride also has been used to reduce an alkyn-1-ol to the corresponding *E*-alkenol in excellent yield.[54]
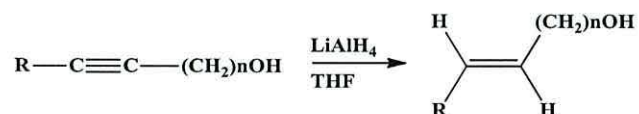
Figure 23: Reduction by lithium aluminium hydride to prepare (E)-alkene pheromones

In addition, the hydrogenation of alkynes can be employed to preparation of (*Z*)-alkenes, but the product often contains small amounts of (*E*)-isomer. The catalyst that is widely used for this purpose is Lindlar's palladium catalyst,[55] which in general consists of palladium on $CaCO_3$ which has been treated or "poisoned" with lead, usually $Pb(OAc)_2$.
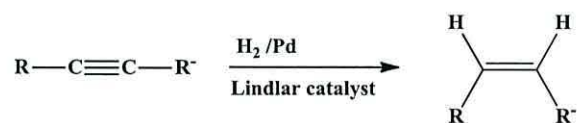
Figure 24: (Z)-Alkenes via hydrogenation of alkynes

Acetylenes were used to produce intermediates in many syntheses of pheromones (Figure 25):[56]
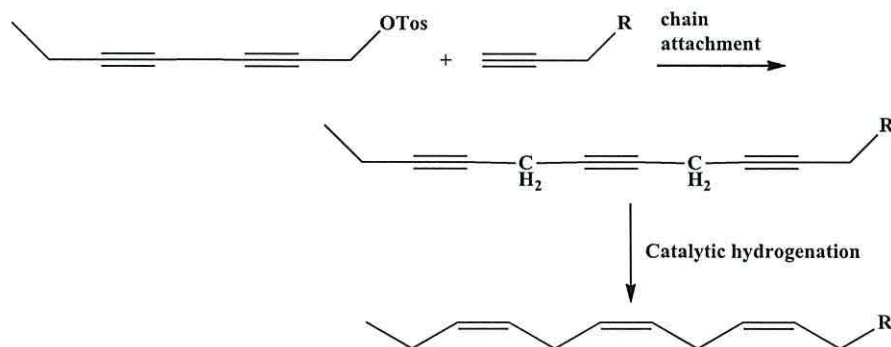
Figure 25: Using acetylenes to synthesise pheromones

2.10.2 The Wittig reaction

In general, the Wittig reaction is a reaction between an aldehyde or ketone with a triphenylphosphonium ylid, to form an alkene which can achieve in a high selectivity the *cis* or *trans* configuration, depending on the conditions used in the reaction. There are many conditions that can affect the stereochemistry of the product.

The ylid can be prepared using $NaN(SiMe_3)_2$ as a base.
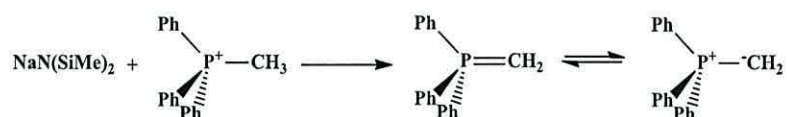
Scheme 9: Preparation of ylid

The mechanism of the coupling between the salt and aldehyde to give an alkene has been thoroughly studied. The initial step in the Wittig reactions involves treating the phosphonium salt (which is normally prepared by treatment of the bromo-compound with triphenylphosphine in dry acetonitrile or toluene) with a base to form an ylid. The Wittig reaction in the current works gave all products in the Z-configuration, using sodium *bis*(trimethylsilyl)amide as a base under control of the reaction conditions (high dilution and low temperature) to ensure access to high yield of the alkenes in the Z-configuration.

This reaction was used in the second approach to obtain pheromones containing (Z)-double bonds. For example, a Wittig reaction was used to prepare muscalure, (Z)-9-tricosene; in this method different bases can be used to improve the yield of (Z)-alkenes. The Wittig reaction carried out in DMSO with n-butyl lithium gave an 85 : 15 Z : E ratio. The reaction was modified by using potassium in HMPA as the base to give 94% of (Z)-alkene plus 6% of its (E)-isomer.[57]
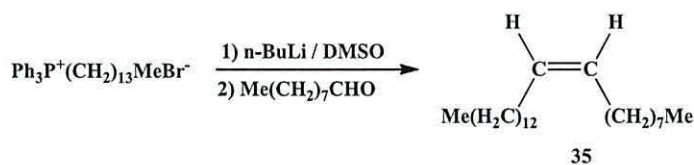
Figure 26: Wittig reactions to prepare (Z)-alkene pheromones

Bestmann reported that using sodium *bis*(trimethylsilyl)amide as a base improved the stereoselectivity of the Wittig reaction product to give 98% of (*Z*)-alkene which was then used to eventually prepare 2-decyl-3-(5-methylhexyl)oxirane as a pheromone with an epoxide functional group.[58]

Figure 27: Bestmann route to (Z)-alkenes and derived epoxide containing pheromones

In addition, a Wittig reaction was also successfully used to synthesise pheromones with a non-conjugated diene system:[59]

Figure 28: Wittig reaction based synthesis of isolated diene system pheromones

Yamakawa, *et. al.*, synthesized (6*Z*,9*Z*,12*Z*)-6,9,12-octadecatriene by a double Wittig reaction between hexanal and an ylide derived from (*Z*)-1,6-di-iodo-3-hexene.[60]

Figure 29: Preparation of (6Z,9Z,12Z)-6,9,12-octadecatriene

2.10.3 Linoleic and linolenic acids

In other attempts, fatty acids were broadly used to produce several unsaturated pheromones. For instance, 6Z,9Z-dienes and 3Z,6Z,9Z-trienes of 18 or more carbons usually are synthesized easily by reduction of linoleic or linolenic acid esters to the corresponding alcohols, which undergo a tosylation process, followed by reduction or chain extension. This method is generally not practical because the carboxylic acids are expensive.[61]
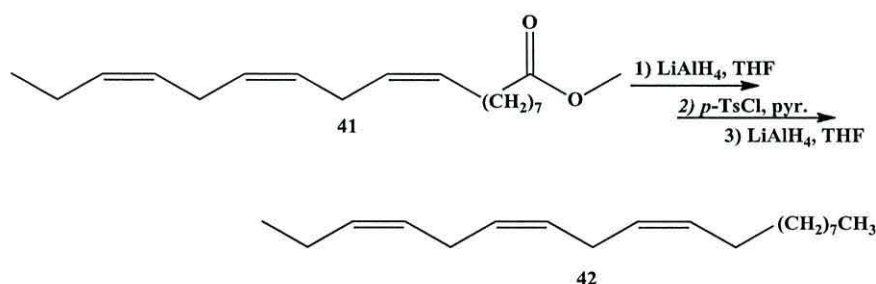
Figure 30: Unsaturated pheromones from fatty acids

2.10.4 The use of a Grignard reaction in pheromone synthesis

1,5-Cyclooctadiene (**43**) has been used to prepare *cis*-1,8-oct-4-ene-diol (**44**) which was used as a starting material of 100% (*Z*)-configuration to synthesise several sex pheromone (Scheme 10). The Grignard reaction is the main reaction used to increase the chain length

by coupling products, then through many known steps like (mono-protection with dihydropyran (DHP), tosylation, and Grignard reaction of the tosylate with methyl magnesium chloride or n-propyl-magnesium chloride, etc.) the goal had been achieved. [62]
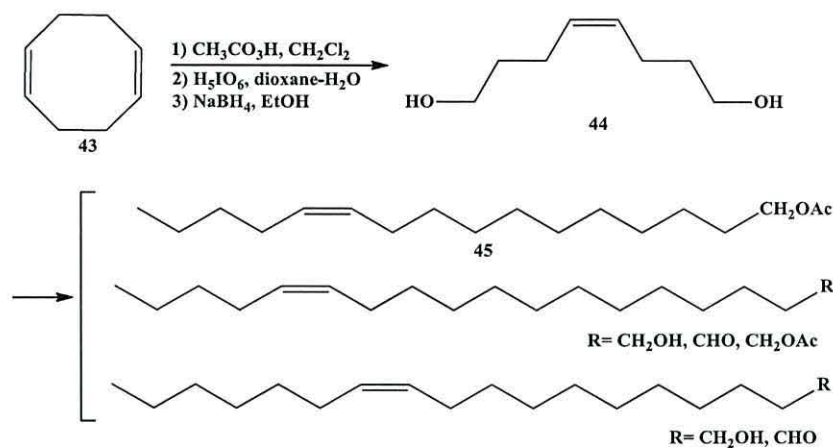
Scheme 10: Six components of the rice leaf-folder moth sex pheromone

This kind of sex pheromone is widely employed to control a serious pest, the rice leaffolder moth, an important leaf feeding pest of rice. It is known that one leaf folder consumes 6 to 7 leaves during the larval stage.

2.10.5 Ozonolysis

Tolstikov *et al*, developed a route to Lepidopteran sex pheromones via ozonolysis of (1Z,5Z)-1-methylcycloocta-1,5-diene to produce (Z)-8-oxonon-4-enal, then through several transformations to give 1-acetoxy-7Z-dodecene and 1-acetoxy-9Z-tetradecene.[63]
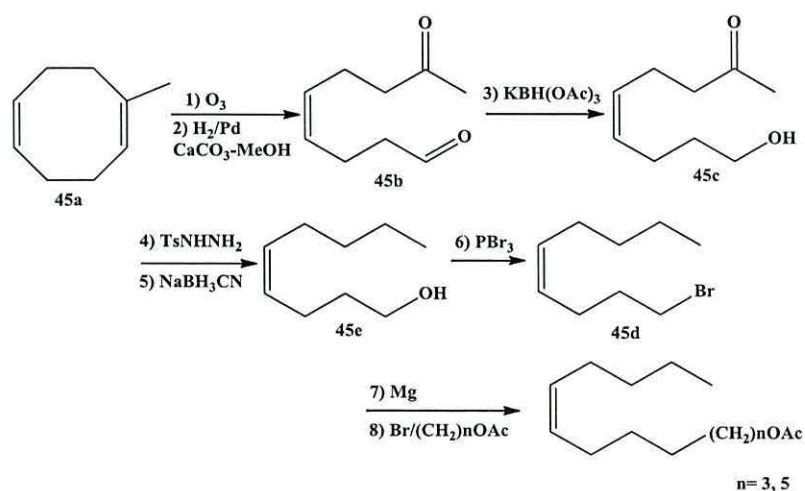
Scheme 11: Pheromones from ozonolysis of (1Z,5Z)-1-methylcycloocta-1,5-diene

2.11 Insects

2.11.1 Types of insect

There are three types of common insect:[64] *apterygotes*, *exopterygotes*, and *endopterygotes*.

2.11.1.1 Apterygotes

The apterygotes are small, wingless insects. They live on and within decaying vegetation. It is unclear whether the ancestors of apterygotes had wings.

2.11.1.2 Exopterygotes

The exopterygotes are insects that have, or had at some stage in their evolutionary history, two pairs of wings. However, exopterygotes are relatively "primitive". The wings develop from external buds on the thorax. These grow proportionately larger as the young insect passes through its nymph stage. The same external growth applies to the insects' genitalia.

2.11.1.3 Endopterygotes

Endopterygotes may have, or may not have, wings. They have complex life cycles, involving an egg stage, a larval stage, and an imago stage (the stage at which the insect is sexually mature, often referred to as the adult stage). The insect undergoes complete metamorphosis between the larval and imago stages. Wings (if present) and genitalia develop internally within the larva. Because of the complexity of their life cycle, the endopterygotes are termed *higher insects*. They include beetles, true flies, butterflies and moths, and the social insects (e.g. bees, ants, and wasps).

2.12 Examples of insect pests

Because of the vast number of insect pests, and the vast number of different agricultural products they affect, this section is limited to discussion of pests on only four example agricultural products: cotton, rice, forests, and fruits and vegetables.

2.12.1 Cotton pests

Cotton is possibly the crop most plagued by insect pests. This is all the more so in that cotton pests have, in general, evolved resistance to pesticides while widespread use of these in the past killed the pests' predators. The following are just some of the pests that plague cotton.

2.12.1.1 Pink bollworm (Pectinophoragossypiella)

Pink bollworm is the most widely distributed cotton pest.[24,65] It plagues cotton in the USA and Asia, and functions in tropical and temperate climates. It is, in practice, immune to insecticides. This is because the larvae, on hatching from eggs laid on cotton plants, bore immediately into the cotton plant bolls. The larvae live in these bolls where they feed and develop. Inside the bolls, they are impervious to contact insecticides. Because of this, almost all control of pink bollworm today uses pheromones.

The sex pheromone of the moth is a mixture of (7Z,11Z)–hexadecadienyl acetate (**46**) and (7Z,11E)–hexadecadienyl acetate (**47**). It is named *Gossyplure*, and is used as an insect lure in pheromone traps.
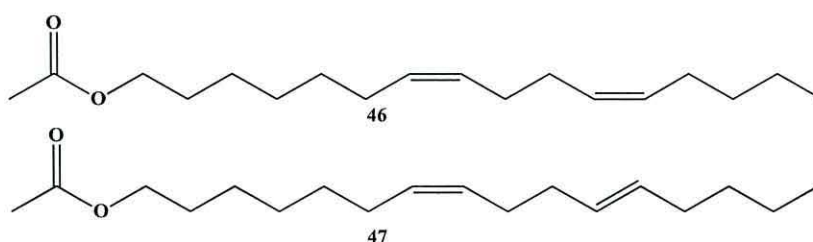
Figure 31: (7Z,11Z- and 7Z,11E-)-hexadeca-7,11-dien-1-yl acetate

2.12.1.2 Cotton leafworm (*Spodoptera littoralis*)

Cotton leafworm is found in tropical Australia, Asia, and Polynesia. It is a pest, not only of cotton, but of other crops. In the Asia and Polynesia, the major means of control is manual: teams of children pick eggs off plants.[24]

2.12.1.3 Cotton whitefly (*Bemisia tabaci*)

Cotton whitefly is native to Asia. In Pakistan, it has evolved resistance to organophosphates and synthetic pyrethroids. At present, management of the pest relies on rotation of alternative pesticides (acephate, fenpropathrin, lambda-cyhalothrin, and bifenthrin), for which the whitefly has limited resistance.[66]

2.12.1.4 Cotton bollworm (*Helicoverpa armigera*)

The cotton bollworm is native to the USA. It is a pest of a wide variety of crops, and has now entered the UK. It has evolved resistance to a range of insecticides.[24]

2.12.2 Rice pests

Rice appears second only to cotton in the degree of infestation by insect pests.[24] Rice stem borers of *Chilo* spp. and *Scirpophaga* spp. present similar problems to pink bollworm. For example, newly hatched larvae bore into rice stems, and live within the stem throughout larval development and pupation. As with pink bollworms, this renders them relatively impervious to contact insecticides. The yellow stem borer (*Scirpophaga incertulas*) is the most serious rice pest in India. At present, systemic pesticides provide some control of *Chilo* spp. and *Scirpophaga* spp. However, such insecticides are ineffective in wet weather because of rapid leaching into the soil.

2.12.3 Forest pests

In the early 1970s tussock moths (*Lymantria* spp.) presented serious problems to US forests. The gypsy moth (*Lymantria dispar*) caused defoliation of 13 million acres of forest, at a loss of US$350 million in one year alone.[24,28]

Other forest pests include pine weevils and spruce budworms. Although, as indicated, such pests can be and have been controlled by DDT, use of the pesticide is at best only an interim measure. First, there is the problem of the pests evolving resistance; second, there is the problem of collateral damage to other insect life, with knock-on effects on higher organisms.

Trees are also plagued by a variety of beetles. Of these, the four species of bark beetle (*Dendroctonus*) are especially savage.[24]

2.12.4 Fruit and vegetable pests

A famous fruit pest is phylloxera which attacks vine roots. In the mid 19th century, phylloxera insects (*Daktulosphaira vitifoliae*), organisms related to aphids, devastated Europe's wine industry. Phylloxera is native to the USA, where the vines have some resistance. When the insects were inadvertently imported to Europe, the European vines had no resistance. The 19th century philloxera infestation destroyed between two-thirds and nine-tenths of Europe's vineyards. Phylloxera is countered not by pesticides, but by grafting. As indicated, US vines are at least partly resistant to phylloxera. Thus US vine roots are grafted onto European vine roots. It is this grafting that saved Europe's wine industry.[67]

Other fruit and vegetable pests include the codling moth (*Cydia pomonella*), which afflicts apples and pears worldwide, the oriental fruit moth (*Grapholita molesta*), which afflicts peaches and nectarines in Australia, North America, and South Africa, the Mediterranean fruit fly (*Ceratitis capitata*), which afflicts a wide variety of fruits in Europe, and the tomato pinworm (*Keiferia lycopersicella*), which afflicts tomatoes in North, Central, and South America. Tomato pinworm is a major problem in Mexico.[24]

2.13 Integrated pest management

The term *integrated pest management* (IPM) pertains to systems of agriculture that seek to minimise use of pesticides while maintaining high yields. A variety of techniques may be used in IPM to realise these aims.[28,67]

Techniques of IPM include development of pest resistant strains, introducing natural predators of pests, fallowing, and destroying crop wastes. IPM may also seek to maximise the efficiency of pesticide use, by, for example, spraying only plant stems with pesticides in cases in which the pests typically climb the plant stems.[67] IPM should not be confused with organic farming. Although organic farms may use aspects of IPM, the aim of IPM, as indicated, is to use a variety of methods of pest control in combination. Thus IPM does not

preclude such modern approaches to agriculture as use of pesticides, use of artificial fertilizers, and use of genetically modified (GM) crops.[67]

Indeed, modern methods of agriculture not only appear to give rise to higher yields; they also tend to lead to less soil erosion.[67]

Because IPM uses a variety of coordinated approaches, it is logical that it should include, where possible, pheromone control of pests.

2.14 Use of semiophones to control insect pests

Semiophones, including pheromones, may be used in four main ways to control insect pests: to *monitor* pests, to *mass trap* pests, to *lure and kill* pests, and to *disrupt mating* of pests. At present, the semiochemical industry worldwide has a sales income in excess of US$30 million.[68]

2.14.1 Monitoring

Monitoring of pests may serve three broad functions. First, it may *detect* pests. This may provide early warning of infestation. It may also allow for quarantine. Thus, for example, the Mediterranean fruit fly (*C. capitata*) has been kept out of North America, despite repeated invasions, by monitoring using Trimedlure (the Trimedlure is a protein hydrolysate, and is a powerful attractant for males) in conjunction with 'food lures'. The food lures are much less efficient than the trimedlure. Females, which cause direct damage to the fruit, are the main target for control. Research concerned with the development of new insect detection and control techniques has been focused on mating behaviour, because traps based on sexual communication signals tend to be efficient and highly selective. Monitoring of the fly has also been successful in Japan. As soon as the fly is detected, it is eliminated by extensive spraying with pesticides.[24] Monitoring may also be used to determine pest thresholds. In addition, it may be found to be useful in timing treatments (e.g., use of pesticides) and to assess risks. Thus, for example, sampling of the olive fly (*Bactrocera oleae*) enables agriculturalists to determine the maturity of eggs within the female. If they are mature, spraying with insecticide can commence immediately. If they are immature, spraying can be delayed. The effect of such monitoring,

therefore, is to ensure that the minimum amount of pesticide is used, but to maximum effect.[24]

A third use of monitoring is to assess population trends. This has been found possible in the case of the spruce budworm (*Choristoneura fumiferana*), which plagues pine forests. Monitoring has shown that the budworm has a cyclical population density, with each cycle lasting 35–40 years, and with maximum population density lasting 5–10 years.[24] Monitoring to determine population trends, can however be problematic. For instance, male Lepidoptera tend to be promiscuous, and female Lepidoptera may be highly fecund, and consequently, the population is determined largely by the number of females. In addition, male Lepidoptera tend to be more sensitive to pheromones than their female counterparts. The males of the species *Atheraea polyphemus* have antennae of surface area 85mm^2, whereas the females have antennae with a surface area of only 18 mm^2. Also, males of the species have an estimated 110,000 specialist receptors in their antennae, along with 20,000 generalist receptors. The females, however, have no specialist receptors, but have an estimated 24,000 generalist receptors. The existence of such differences may lead pheromone monitoring to detect disproportionate numbers of males.[24] There are practical considerations when using pheromones for monitoring. In principle, one should use more than one pheromone trap to catch the insects. However, this leads to the problem of trap placement. If pheromone traps are placed too close to each other, one trap may "poach" insects from another trap. This may lead to underestimates of insect numbers. However, some farms may be too small to place a sufficient number of traps at the optimal separation. Another practical consideration is height. It may, for some species, be best to place traps at considerable height (e.g., 10 metres). However, this may make inspection of the traps problematic, especially for busy farmers. Another consideration is expense. The best traps release the pheromone at a constant, steady rate; however, such traps are expensive. Cheaper traps release the most pheromone in the early days of use, with the amount of released pheromone gradually diminishing.

There is also the problem of saturation. Pheromone traps that use adhesive, for instance, may catch so many insects that they become overcrowded. In this regard, the nature of the pheromone used in the trap can be important. The pea moth *Cydia nigricana*, for example, uses a natural pheromone with (*E,E*)-8,10-dodecadien-1-yl acetate(*E,E*-8,10–12:Ac) (**48**) as a major component. This pheromone, however, is too "strong" and its use in traps often leads to saturation. Use of the related compound, (*E*)-10-dodecen-l-yl acetate (*E*-10–

12:Ac), produces better results, and is "weaker" than the natural pheromone, an as such leads to less saturation.
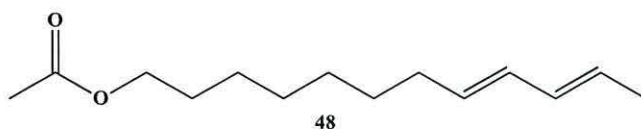
Figure 32: (8E,10E)-dodeca-8,10-dien-1-yl acetate

Despite such practical problems, pest monitoring is becoming widespread. It is estimated that around 50% of apple growers use some form of pest monitoring.

2.14.2 Mass trapping

The idea behind mass trapping is simple. A large number of traps, baited with pheromones, are placed around a crop. These will capture a sufficient number of insect pests to greatly reduce the damage the pests cause to the crop. In practice, however, mass trapping is found to be problematic for several reasons.[24]

The first pertains to the lack of female responses to pheromones as found in the Lepidoptera. It is estimated that, to achieve a 95% reduction in certain moths, one would need to place five traps for every fertile female. Much, however, depends on the species.

Another problem is trap design. Although pheromones may attract up to 95% of insect pests in a given area to traps, the traps themselves tend to be very inefficient. Measured trap efficiencies have been as low as 0.4% and 8.7%.

Nonetheless, there have been successes. For instance, the boll weevil *A. grandis*, responds to the male-produced pheromone Grandlure. This acts as a sex pheromone for females and as an aggregation pheromone for both sexes. Use of Grandlure for mass trapping and monitoring, coupled with intensive use of insecticides, greatly reduced boll weevil numbers in the south eastern and south western USA.[24]
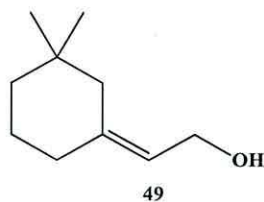
Figure 33: Grandlure: (Z)-2-(3,3-dimethylcyclohexylidene)ethanol

Mass trapping has also been used successfully to control tree infestation by beetles. In this approach, the tree may first be "laced" with an insect attractor. Upon infection, the beetles emit their own pheromone that attracts still more beetles. When suitably infected, the tree may then be felled and burned, thus destroying the beetles. Such a policy can be effective with Douglas fir beetles (*D. pseudosugae*), mountain pine beetles (*D. ponderosae*), spruce beetles (*D. rufipennis*), and western balsam bark beetles (*D. confusus*).

Mass trapping, coupled with targeted use of insecticides, has also proved effective in control of the Mediterranean flour moth (*Ephestia kühniella*). In one study, funnel traps, using the major component of the moth pheromone (*Z,E*-9,12-tetradecadienyl acetate), **(50)**, used in conjunction with occasional fumigation, succeeded in reducing the moth population by 95–97% for one year. The trap density was relatively low, at one per 260–280 m^3.[24]
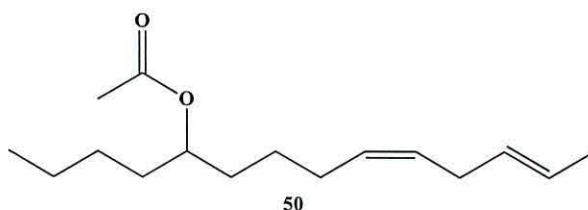
Figure 34: (9Z,12E)-Tetradeca-9,12-dien-5-yl acetate

As indicated, the use of pheromone lures has the advantage that pheromones tend to be species-specific. Thus use of pheromone lures reduces the risk of friendly insects being destroyed. However, the pheromone lure may be complemented by other insect attractors. These include odours of foodstuffs favoured by the insect in question. Various fruit flies, for instance, respond to proteinaceous food baits. This is important in temperate zone fruit flies (e.g., *Rhagoletis* spp.) for which to date no Para-pheromones have been developed that attracts them. Such food baits may be used in combination with signs of food decay

(e.g., ammonium salts, urea). Flies may also respond to colour. The sticky traps used in one study of *R. cerasi* in a cherry orchard were most effective when coloured yellow. In order to achieve effectiveness, there had to be a high density of the traps, at over one per tree. A 1971 study used 1680 traps to protect 1200 trees; this proved 100% effective. However, an earlier study conducted achieved only 75% effectiveness, yet used 992 traps to protect a mere 397 trees.[24]

2.14.3 Lure and kill

Lure and kill is similar to mass trapping, save that mass trapping does not kill the insect. Lure and kill, by contrast, does. Lure and kill strategies have two components: a lure (e.g., a pheromone, a *kairomone*) and an affecter (e.g., insecticide, electric grid). This is sometimes referred to as *attracticide* or *attraction-annihilation*.

The technique has been used with great success to eliminate populations of fruit flies. A 1965 study used the para-pheromone methyl eugenol to attract male *B. dorsalis* (oriental fruit flies).[24] The para-pheromone was mixed with an insecticide. The procedure eliminated the fly from the island within 6 months. A similar operation eliminated the fly from all of Japan's Ogasawara Island but took 10 years. These operations worked because, in selectively attracting only male flies, they deprived females of mates.

Lure and kill is also used to destroy tsetse flies (*Glossina* spp.). This approach uses a visual lure: a dark insecticide-drenched rectangular cloth which mimics the flies' vertebrate hosts.[24] Tsetse flies have an unusual life cycle. Young larvae develop within the mother's body. When the lava is mature, the mother gives birth to it. It then bores into the earth and pupates. After 30 days, a new adult emerges from the ground. This life cycle makes conventional control of tsetse flies problematic, as the larvae are protected for almost all of their development. However, the life cycle means that tsetse flies are much less fecund than other flies. Thus small reductions in the populations can have large long-term impacts.

2.14.4 Mating disruption

The elimination of male *B. dorsalis* illustrates that pests may be controlled by denying them the opportunity to mate. In this, pheromones may play an especially important role

because many insects rely on pheromones to find mates. There are three ways of using pheromones to disrupt insect mating.[24]

The first involves bombarding the insects with sex pheromones. The method is termed *confusion* because the prevalence of pheromone confuses the males of the species such that, when confronted with a genuine pheromone from a genuine female, the males do not recognize it. The second method involves *trail-making*. This involves obliterating the natural pheromone with a synthetic pheromone. Because all natural pheromones are overwhelmed by this method, males of the target species cannot find mates, so the females fail to lay eggs. The third method involves *false-trails*. It requires that large numbers of false pheromone trails are laid, and these dwarf the number of genuine pheromone trails, with the result, again, that males fail to find mates. Mating disruption by means of pheromones requires detailed knowledge of the target organism's life cycle because it will only work if applied when the organism's mate. It also requires detailed knowledge of the target organism's pheromones, both in terms of chemistry and in terms of how they function. For these reasons, effective use of mating disruption developed relatively slowly. However it has several advantages. For instance, the Pink bollworm (*P. gossypiella*) is a major pest on cotton, and is largely immune to insecticides because the larvae bore into cotton plants and develop within in them. Thus contact pesticides cannot reach them. However, today pink bollworm infestations are controlled by the synthetic pheromone Gossypure. There are a variety of ways of using Gossypure. These include hollow fibre and laminate flakes glued to foliage, micro-capsules and polymer beads, mixed in water and sprayed on crops, and hand-applied solid polymer dispensers. Ideally, all methods should dispense the Gossypure at a constant rate. Gossypure has been shown to be effective in controlling pink bollworm, so much so that today governments from the USA through Pakistan and Egypt encourage its use.[24] Similar developments are taking place as regards rice stem borers; studies suggest that pheromone control, through mating disruption, of *S. incertulas* in India is at least as effective as control using insecticides, but without the collateral damage. Research also suggests that, when mating disruption using pheromones is carried out, the ratio of predator organisms that prey on pest species increases.

2.15 Aims of the project

The present chapter involves finding a cheap new route to prepare pheromones and polyunsaturated fatty acid derivatives with different functional groups by using an intermediate derived by ozonolysis of cyclonona-1,4,7-triene.

2.16 Results and Discussion

The key feature of the present work was the ozonolytic cleavage of cyclonona-1,4,7-triene, where all alkenes are present in the *cis*-form, which itself can be prepared from a cheap and available starting material, 1,5-cyclooctadiene. This approach could be used to synthesise many pheromones and polyunsaturated fatty acid derivatives.
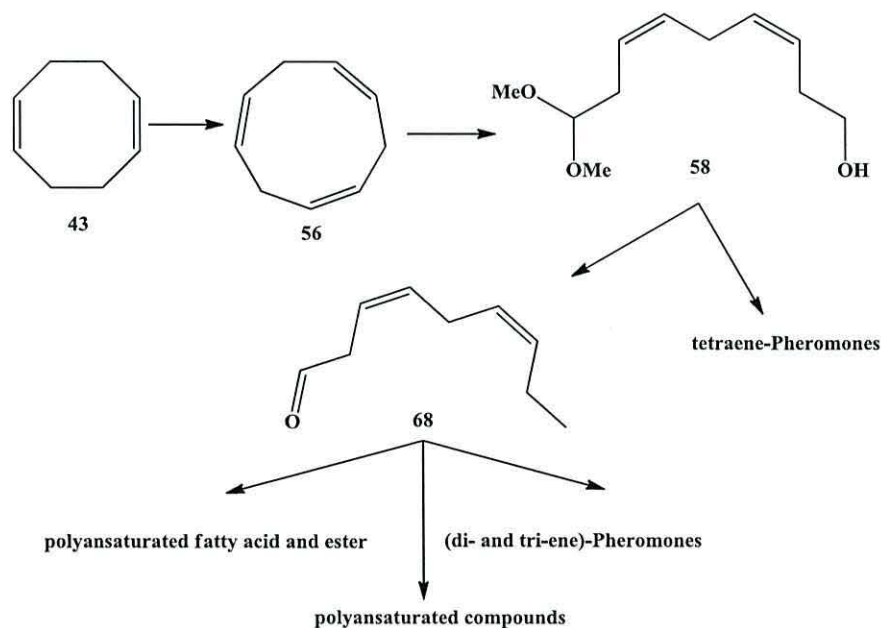
Scheme 12: Using (3Z,6Z)-nona-3,6-dienal (68) in different routes

2.16.1 Preparation of 1,4,7-cyclononatriene (56)

1,5-Cyclooctadiene (**43**) was transformed into 1,4,7-cyclononatriene (**56**) in four steps.[91,147]
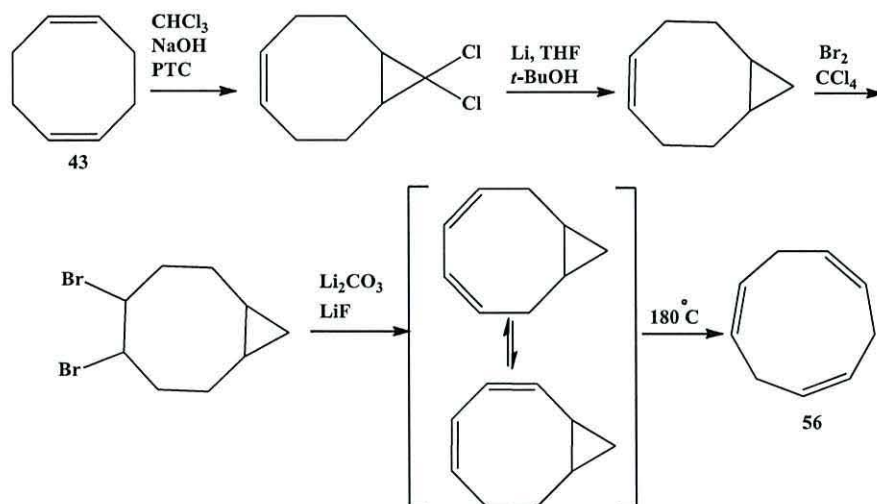
Scheme 13: Preparation of 1,4,7-cyclononatriene (56)

The key to this work is a carbene addition to the alkene double bonds. Carbenes are electrically neutral molecules characterised by their containing a divalent carbon atom with two unshared electrons. Carbenes are important in synthetic chemistry, because they undergo insertion, rearrangement, and facile addition reactions.[117] One of the most common and widespread carbene reactions is their addition to carbon-carbon double bonds to obtain cyclopropane derivatives and or the corresponding rearranged products.

Dihalocarbenes can be prepared by various different methods.[69] For example, one of the common methods is the reaction of organic polyhalides with strong bases. Also, carbenes can be formed by β-elimination reactions.[70] Doering and Hoffmann, in 1954, obtained the best yields of dihalo-cyclopropanes by treating haloforms with potassium *tert*-butoxide in the presence of an alkene (Figure 35);[71] the strong base deprotonates the haloform to give the trihalomethyl anion which then readily loses halide ion to generate a dihalocarbene through α-elimination.
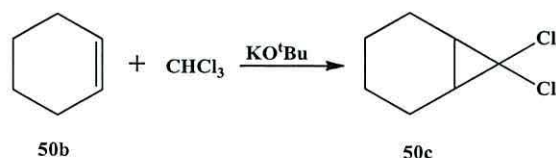
Figure 35: Doering and Hoffmann approach

Dichlorocarbenes may also be prepared from the thermal decarboxylation of sodium trihaloacetates, where again a trihalomethyl anion is produced which can lose halide ion to give a carbene. This method is particulary useful when the alkene is sensitive to strongly basic conditions.[71,72]

The advent of phase transfer catalysis (PTC) in 1969 by Makosza,[73] provided an elegant method for the preparation of dichlorocarbene which does not require rigorously anhydrous reaction condition.[73] Starks,[74] and co-workers were among the first to use chloroform and aqueous sodium hydroxide with a phase transfer catalyst for the generation of dichlorocarbene. The advantage of using a phase transfer catalyst is that it reacts with sodium hydroxide, which is not soluble in the organic layer and forms a quaternary ammonium hydroxide, which is soluble in the organic phase. Baird and co-workers[74] have shown that the nature of the reacting species is highly dependent on the catalyst employed with cetyl trimethylammoniumbromide (cetrimide), the dichlorocarbene is favoured, hence this is the catalyst of choice for electron rich alkenes; conversely, electron deficient alkenes will react more efficiently with trihalomethyl anion and this is produced in a phase transfer reaction using benzyltriethylammonium bromide (TEBA) as a catalyst.

Reaction of 1,5-Cyclooctadiene (43) with aqueous sodium hydroxide and chloroform under phase transfer conditions in the presence of cetrimide led to (Z)-9,9-dichloro-bicyclo[6.1.0]non-4-ene (51) in 60 % yield (Figure 36).
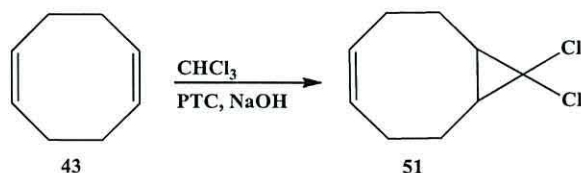
Figure 36: Preparation of (Z)-9,9-dichlorobicyclo[6.1.0]non-4-ene

The reaction was carried out several times to optimise the yield of the product (51).

The proton NMR spectrum showed a new multiplet at δ 1.66, which corresponded to the cyclopropane hydrogens, while the ^{13}C NMR spectrum showed a peak at δ 66 corresponding to the carbon next to chlorine. The yield was only 60 %, but the advantage of this route was that the starting materials could be recovered and reused. Furthermore, it was easy to separate the major product, (Z)-9,9-dichlorobicyclo[6.1.0]non-4-ene (51), from the bis-adduct (5,5,10,10-tetrachlorotricyclo[7.1.0.0^{4,6}]decane), because the first fraction could be removed through distillation, while the bis-adduct fraction was a solid which remained in the distillation flask.

The second step involved de-chlorination of (Z)-9,9-dichlorobicyclo[6.1.0]non-4-ene (51) using lithium in dry tetrahydrofuran, in the presence of t-butyl alcohol to give (Z)-bicyclo[6.1.0]non-4-ene (52) (74 %) (Figure 37). Monitoring the reaction by G.C. indicated complete consumption of starting material after 18 hrs reflux at 100 °C. The product showed only one peak corresponding to (Z)-bicyclo[6.1.0]non-4-ene (52). Furthermore, the ^{1}H-NMR spectrum showed two signals at δ 0.67 and δ -0.15 corresponding to the two protons of the cyclopropane methylene group.
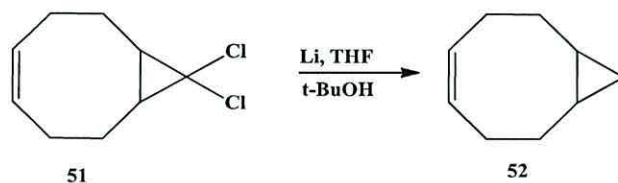
Figure 37; Preparation of (Z)-bicyclo[6.1.0]non-4-ene (52)

Bromination of (Z)-bicyclo[6.1.0]non-4-ene (52), with a solution of bromine in carbon tetrachloride led to the formation of 4,5-dibromobicyclo[6.1.0]nonane (53) in 94 % yield. This was characterized by the ^{1}H NMR spectrum, which showed the disappearance of the alkene signal and the appearance of a new signal at δ 4.3 (2H), corresponding to the protons next to bromine.
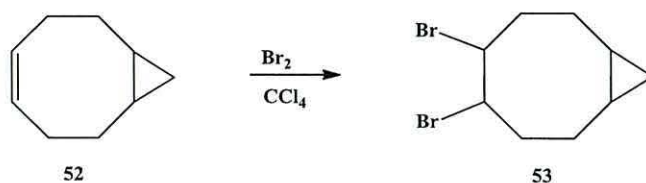
Figure 38: Bromination of (Z)-bicyclo[6.1.0]non-4-ene (52)

The next step involved the elimination of hydrogen bromide by reacting (53) with anhydrous lithium carbonate and anhydrous lithium fluoride to give bicyclo[6.1.0]nona-diene as a mixture of the (2Z,4Z)-bicyclo[6.1.0]nona-2,4-diene (54) and (3Z,5Z)-bicyclo[6.1.0]nona-3,5-diene (55). The crude ^{1}H NMR spectrum showed both compounds because of two quartets in the high-field region centered at δ -0.038 and δ -0.135, each one belonging to one of the cyclopropane hydrogen methylene group of the two respective compounds.
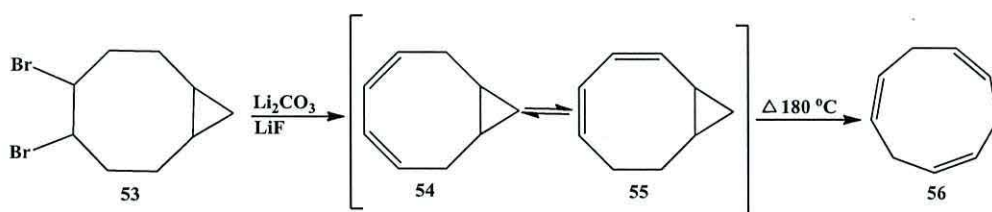
Scheme 14: Preparation of (1Z,4Z,7Z)-cyclonona-1,4,7-triene (56)

Sigmatropic rearrangements represent the migration, in an uncatalyzed, concerted molecular process, of a σ-bond, adjacent to one or more π system to a new position in a molecule, with the π systems become reorganised in the process.[74]
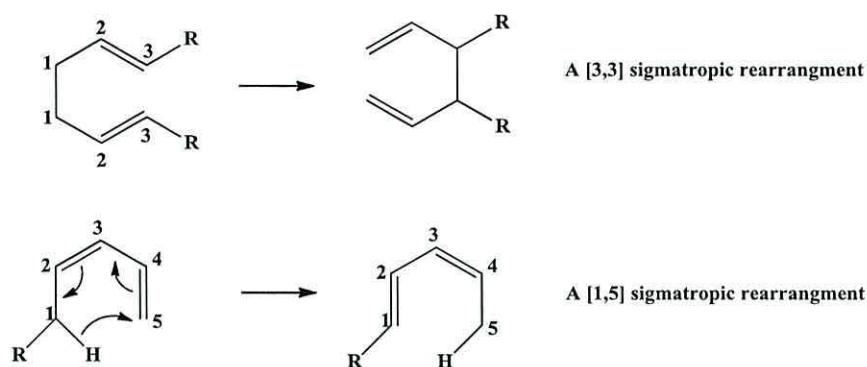
Figure 39: Sigmatropic rearrangements

On the basis of our findings, we believe that the two isomers within the crude elimination product interconvert via a thermal [1,5]-hydride shift. The final step in the sequence involves the thermal, sigmatropic ring expansion of bicyclononadiene (55),[75] in a process

which requires relatively high temperatures to achieve. Therefore, the mixture was heated in a closed system at 185 °C for one hour, to give crystalline (1Z,4Z,7Z)-cyclonona-1,4,7-triene (**56**) in 60 % yield. It has been claimed that the compound (**53**) gives (2Z,4Z)-bicyclo[6.1.0]nona-2,4-diene (**55**), which then undergoes ring opening and rearrangement to give (**56**),[74] while other research has suggested an alternative process, where the compound (3Z,5Z)- (**54**) is the one which converts into (**56**).[75] However, in our work, we suggest that, when crude elimination product mixture is heated, it is isomer (**55**) which undergo a homo-[1,5]-hydrogen shift entailing the opening of the cyclopropane ring and resulting in the ring expanded product (**56**).
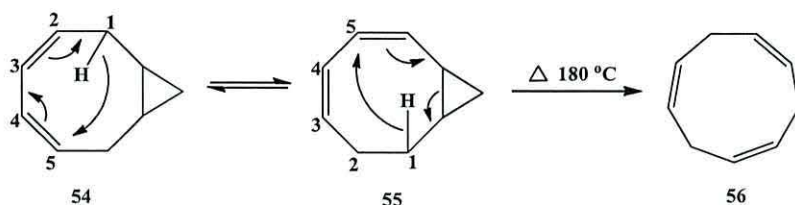
Scheme 15: The mechanism of 1,5-hydrogen shift of (54) and (55)

The mass spectrum of compound (**56**) showed the correct molecular ion for C_9H_{12} [$(M)^+$: 120.0949]. The ^1H NMR spectrum showed a multiplet at δ 5.49 (6H) for the alkene hydrogens, while the signals at δ 3.7 (3H) and δ 2.3 (3H) each appeared as a broad singlets corresponding to the methylene group hydrogens; these two hydrogens on each methylene group undergo exchange between the inner and outer positions on the NMR timescale, which accounts for the broad appearance of their respective signals. [75]
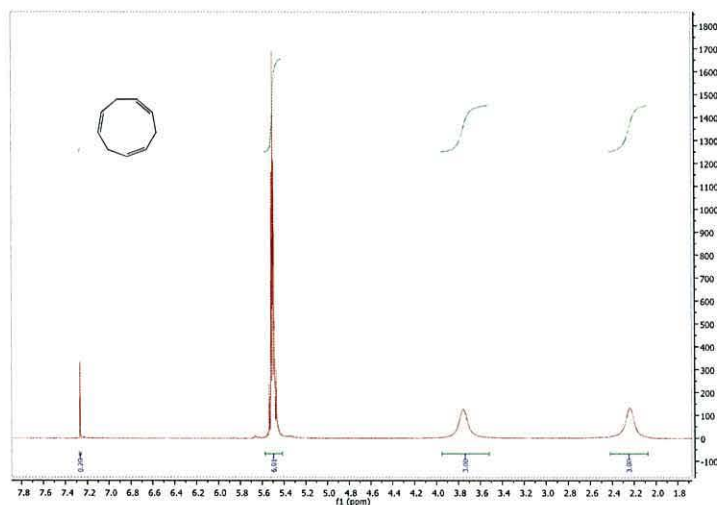
Figure 40: ^1H NMR spectrum of (1Z,4Z,7Z)-cyclonona-1,4,7-triene (56)

2.17 Preparation of pheromones

2.17.1 Synthesis of (3Z,6Z)-9,9-dimethoxynona-3,9-dien-1-ol (58)

As shown above, cyclonona-1,4,7-triene (56) is readily obtained from cyclo-octa-1,5-diene in four simple steps.[76,77,78,79] The selective ozonolysis of (1Z,5Z)-1,5-cyclooctadiene (43) can lead to formation of acetal (57) with an exclusively *cis*-olefin, which has already been used in the synthesis of pheromones which contain Z-alkenes.[80,81] This sequence has been successfully carried out on a large laboratory scale. The aim of the present work was to apply this general method to the ozonolysis of triene (56) to make the diene (58) with retention of two alkenes both entirely in the *cis*-form.
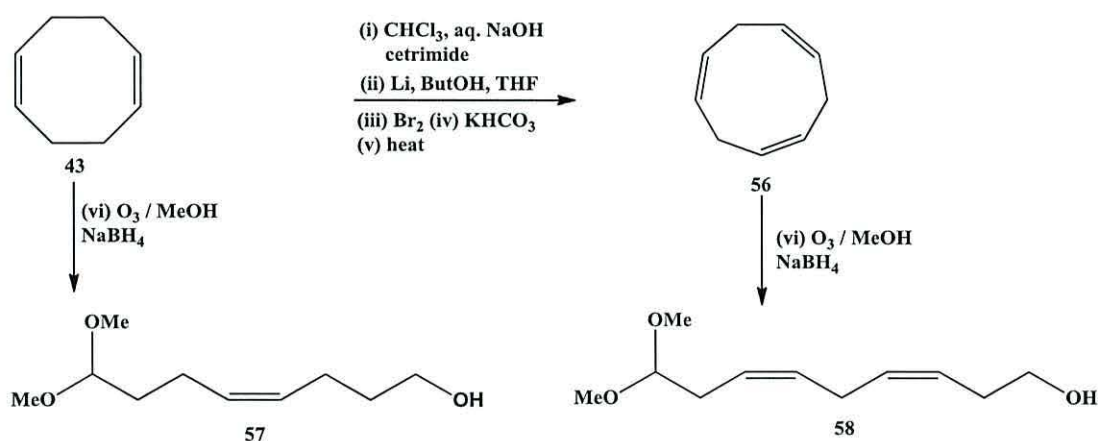
Scheme 16: Ozonolysis of (43) and (56)

There are many pheromones that can be formed from the compound (58), resulting from the ozonolysis process. The ozonolysis involved reacting 0.04 mol of triene (56), dissolved in MeOH, with 0.6 equivalent of ozone at low temperature. The ozone was passed through the mixture for 6.5 min; after completion of the reaction, nitrogen gas was passed through the mixture to eliminate excess ozone and oxygen. *p*-Toluenesulfonic acid monohydrate was added to the ozonide, followed by the addition of sodium borohydride in small portions. This process was strongly exothermic; therefore the temperature had to be maintained at -30 to -5 °C. This gave a 43 % yield of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-ol (58).
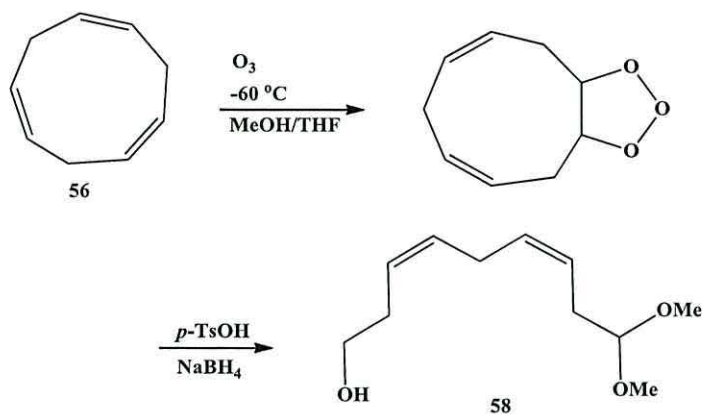
Figure 41: Preparation of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-ol (58)

The best conditions found for this reaction required a temperature of -60 °C, but because of precipitate formation from the starting material, a system of 20 % THF:MeOH was used as a solvent instead of methanol. Also, it was found that a decrease in the ozone concentration increased the yield of product.

The proton NMR spectrum of (58) displayed broad multiplets at δ 5.47 (2H) and δ 5.39 (2H) characteristic of the two double bonds, while a triplet at δ 4.38 was characteristic of the single hydrogen of the acetal. In addition, it showed two protons as a triplet at δ 3.64 for the methylene group next to the primary alcohol. The six protons of the methoxy groups appeared as a singlet at δ 3.33, and peaks at δ 2.8 and 2.4 corresponded to the methylene groups between and next to the two double bonds respectively. The ^{13}C NMR spectrum confirmed that the compound had been formed as it showed signals at δ 130.4, 130.1, 125.8 and 123.8 for the olefinic carbons. Signals were also seen at δ 104 for the carbon of the acetal group, δ 62 for the methyl group next to OH, δ 52.9 for the two carbons next to the two oxygen groups, and δ 32, 30 and 25 for the methylene groups. The infrared spectrum of compound (58) had a broad absorbance at 3400 cm^{-1} for the alcohol functionality, and at 723 cm^{-1} for the *cis*-alkenes. Additionally, the mass spectrum gave a correct molecular ion at 200.

2.17.2 Preparation of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl 4-methyl-benzenesulfonate (59)

In order to make the hydroxyl group of (58) into a good leaving group, the (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl 4-methylbenzenesulfonate (59) was prepared by dissolving compound (58) in pyridine which acted both as a solvent and as a base, and treating with *p*-toluenesulfonyl chloride. The reaction proceeded over a period of 16 hrs at 0 °C. A yield of 89 % was obtained. The transformation into the tosylate was confirmed by the mass spectrum which showed the correct molecular ion (M+Na)$^+$ at 377. Furthermore, the proton NMR spectrum showed the appearance of aromatic signals at δ 7.77 and δ 7.33, while the methylene group which was next to the primary alcohol shifted downfield from δ 3.64 to δ 4.00. In addition, the IR spectrum showed the disappearance of the peak at 3400 cm^{-1} for the OH stretch which had been present in the starting material.
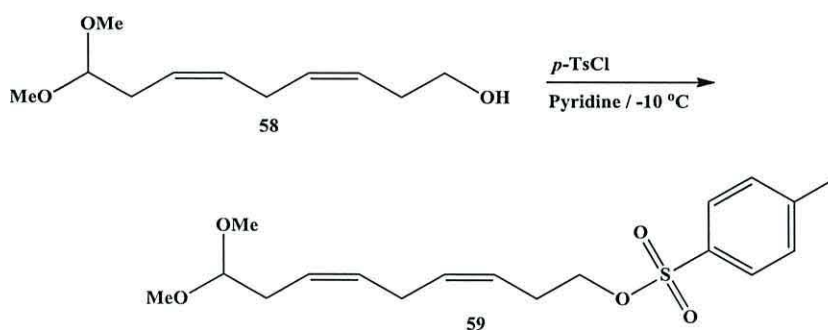
Figure 42: Preparation of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl 4-methyl-benzenesulfonate (59)

2.17.3 Preparation of (3Z,6Z)-1,1-dimethoxyheptadeca-3,6-diene (62)

In order to prepare (3Z,6Z)-1,1-dimethoxyheptadeca-3,6-diene (62), different reactions were attempted, changing the starting materials or the conditions. All attempts were unsuccessful. The first reaction was between (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl 4-methylbenzenesulfonate (59) and Grignard reagent (61) which was prepared under a dry inert atmosphere from bromoheptane (60) and activated Mg turnings in dry THF. Unfortunately, the NMR spectrum for the reaction residue showed that no coupling had occurred, and only starting material signals were seen.
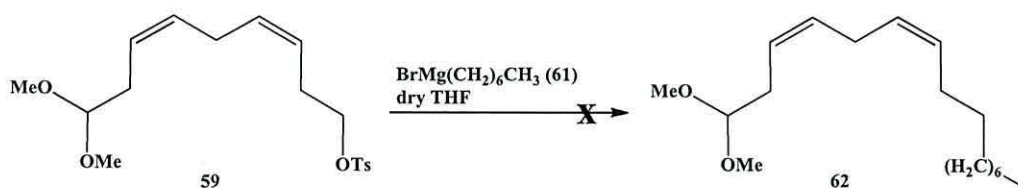
Figure 43: Grignard reaction to prepare (3Z,6Z)-1,1-dimethoxyheptadeca-3,6-diene (62)

The reaction was repeated in the presence of lithium dimethylcuprate. However, the same result was obtained. In another approach, the tosylate group in (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl-4-methylbenzenesulfonate (59) was converted into a better leaving group. The substitution with the iodide ion was done by treating the tosylate (59) with sodium iodide in acetone at 50 °C in the presence of sodium hydrogen carbonate. This provided a good yield of (3Z,6Z)-9-iododimethoxynona-3,6-dien (63) (87 %) as shown in Figure 44. The NMR spectra for (59) and (63) were essentially alike, except that the signals for the tosyl group had disappeared, and the triplet signal of the methylene next to the tosylate had shifted up field from δ 4.00 to 3.15. Infra-red spectroscopy provided further evidence for the structure of compound (63), with a band at v_{max} 824 cm^{-1} for the carbon iodine bond. Moreover, a signal at δ 5.1 in the ^{13}C NMR spectrum, corresponding to the carbon next to iodine confirmed that the compound (63) had been formed.
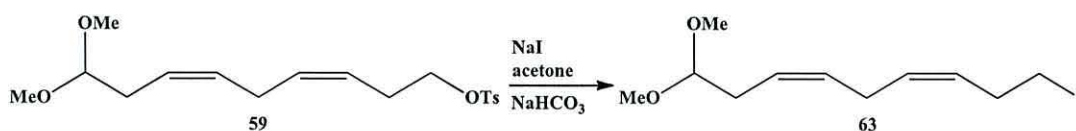
Figure 44: Preparation of (3Z,6Z)-9-iododimethoxynona-3,6-diene (63)

In a further attempt to introduce a long chain, the Grignard reagent (61) was added to the (3Z,6Z)-9-iododimethoxynona-3,6-diene (63) as shown in Figure (45), but the NMR spectrum for the reaction residue still showed only the signals for the starting material.
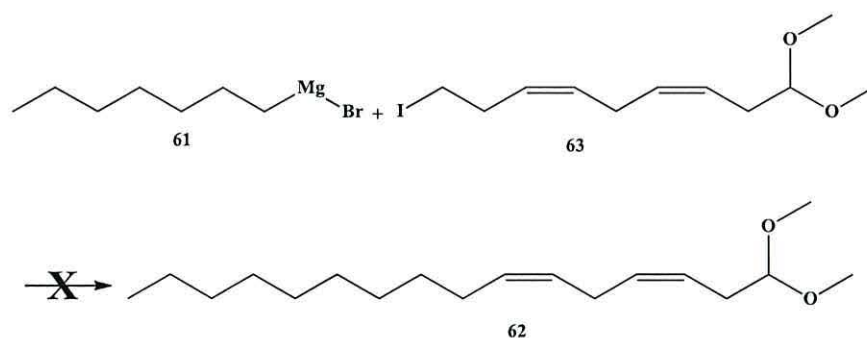
Figure 45: Attempted preparation of (3Z,6Z)-1,1-dimethoxyheptadeca-3,6-diene (62)

The conversion of compound (63) itself into the Grignard reagent (64), then coupling with different alkyl halides was attempted by treating iodide (63) with magnesium turnings in THF (Figure 46); unfortunately only the stating material was recovered.
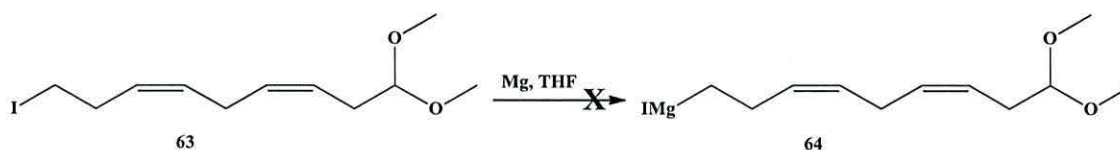
Figure 46: ((3Z,6Z)-9,9-Dimethoxynona-3,6-dien-1-yl)magnesium iodide (64)

This reaction was repeated using different solvents; for example, instead of THF, ether was used, then a mixture of THF and ether, but all attempts failed.

In conclusion, the use of the Grignard reaction for chain extension to form a key diene intermediate, for example (62), for the preparation of pheromones was unsuccessful.

2.17.4 Preparation of (3Z,6Z)-9-iodonona-3,6-dienal (65)

The aldehyde (3Z,6Z)-9-iodonona-3,6-dienal (65) was expected to arise from (3Z,6Z)-9-iododimethoxynona-3,6-diene (63) upon its being treated with *p*-toluensulfonic acid monohydrate, under standard conditions. However, in this instance; the dimethoxy acetal was deprotected to give the aldehyde group, which was followed by a rearrangement which transferred the double bond to give (2E,6Z)-9-iodonona-2,6-dienal (64), with a conjugated double bond, which is more thermodynamically stable. The product's NMR spectrum included a doublet at δ 9.52 characteristic of the aldehyde hydrogen, and a triplet at δ 3.17 for the methylene protons next to the iodine. In addition, the I.R. spectrum of the

product showed a signal for an aldehyde at 1688 cm^{-1} and at 720 cm^{-1} for the carbon-iodine bond.
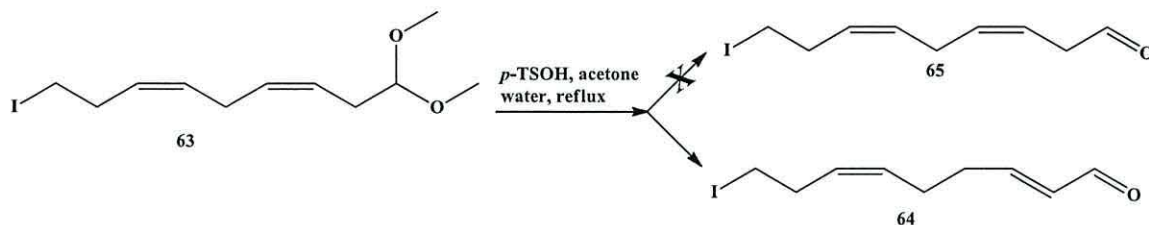
Scheme 17: Preparation of (2E,6Z)-9-iodonona-2,6-dienal (64)

The conjugated compound (**64**) is potentially useful, however, in applications such as the preparation of unsaturated (*Z,E,Z* and *E,E,Z*) trienes, e.g. by Wittig couplings.

2.17.5 Preparation of (3Z,6Z)-1,1-dimethoxynona-3,6-diene (66)

Sandri described the first synthesis of (3Z,6Z)-1,1-dimethoxynona-3,6-diene (**66**),[82] using a Wittig reaction between triphenyl(propyl)phosphonium bromide and (*Z*)-6,6-dimethoxyhex-3-enal:
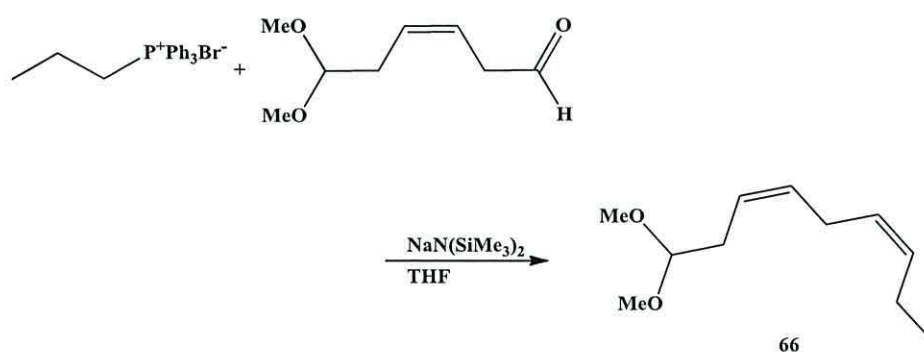
Figure 47: Sandri preparation of (66)

In our work, it was decided to investigate the possibility of avoiding the Wittig reaction for homologation, by accessing the key intermediate (**66**) via the reductive removal of either iodide or tosylate from (**63**) or (**59**) with lithium aluminium hydride. When (3Z,6Z)-9-

iododimethoxynona-3,6-diene (**63**) was treated with lithium aluminium hydride in dry THF at °C, (3Z,6Z)-1,1-dimethoxynona-3,6-diene (**66**) was obtained in 86 % yield. The NMR spectrum provided conclusive evidence for the product by the appearance of the methyl group as a triplet at δ 0.97. The signal for the methylene hydrogen adjacent to the iodine at δ 3.17 had disappeared. The product structure was confirmed by the infra-red spectrum which showed the disappearance of the peak at 720 cm^{-1} for the C-I bond. In addition, the ^{13}C NMR provide conclusive evidence for formation of the product, showing signals at δ 14.2 for the terminal methyl group together with signals at δ 132, 130, 126 and 123 for the alkene carbons.

Using the same method, lithium aluminium hydride in THF was used for the reduction of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl-4-methylbenzenesulfonate (**59**) to (3Z,6Z)-1,1-dimethoxynona-3,6-diene (**66**) in 90 % yield. The NMR and infra-red spectra of this were the same as those above.
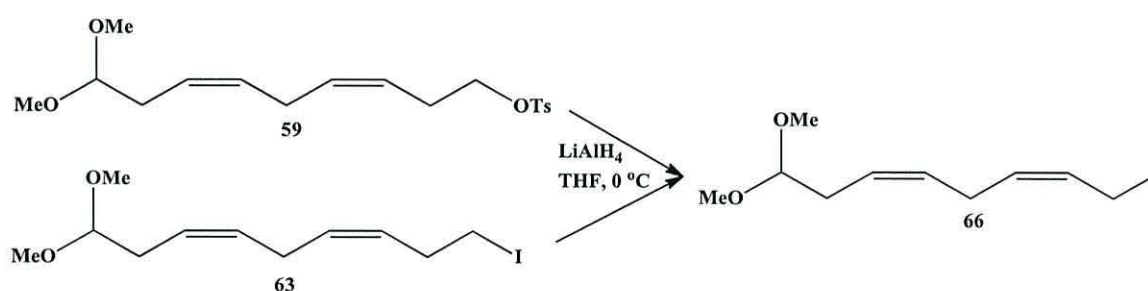
Scheme 18: (3Z,6Z)-1,1-dimethoxynona-3,6-diene (66)

2.17.6 Preparation of (3*E*,6*Z*)-nona-2,6-dienal (67)

(3*E*,6*Z*)-Nona-2,6-dienal (**67**) had been prepared before in the work of Sandri as a side product in 30 % yield, when he attempted to prepare (3Z,6Z)-nona-3,6-dienal (**68**), via the hydrolysis of dimethyl acetal (3Z,6Z)-1,1-dimethoxynona-3,6-diene (**66**), using 0.15 equivalent of acid in a mixture of acetone and water.
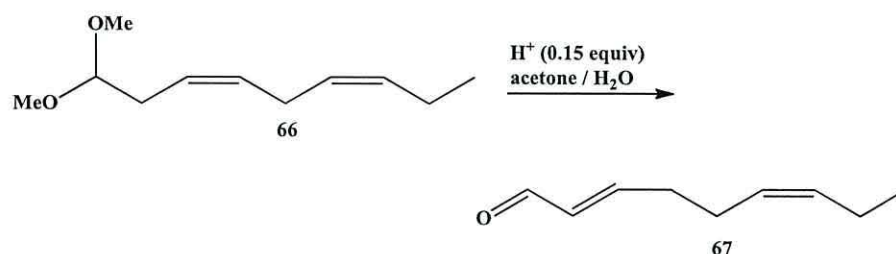
Figure 48: Sandri preparation of (3E,6Z)-nona-2,6-dienal (67)

In the present work, the hydrolysis of (3Z,6Z)-1,1-dimethoxynona-3,6-diene (**66**) was attempted by several alternative procedures, to prepare (3Z,6Z)-nona-3,6-dienal (**68**),[82,83] but most attempts were unsuccessful.

In the first method, (3Z,6Z)-1,1-dimethoxynona-3,6-diene (**66**) was deprotected using HCl in aqueous acetone.[88] The reaction was carried out by stirring the mixture for 3 hrs at room temperature, but it gave (3E,6Z)-nona-2,6-dienal (**67**) in 80 % yield instead of (3Z,6Z)-nona-3,6-dienal (**68**). The proton NMR spectrum of the product displayed the aldehyde proton as a doublet at δ 9.52. Infra-red spectroscopy confirmed that the aldehyde had been formed as it showed a strong absorbance at v_{max} 1688 cm^{-1} for the conjugated carbonyl group.
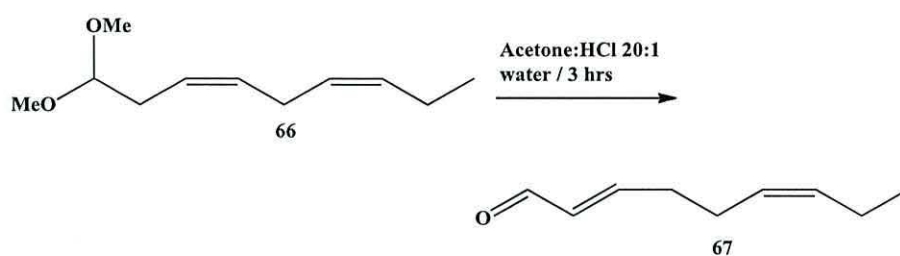
Figure 49: Preparation of (3E,6Z)-nona-2,6-dienal (67)

The reaction was repeated using THF and water as a solvent system, in the presence of *p*-TsOH. In this case, the NMR spectrum and infra-red for the product showed a mixture of aldehydes (**67**) and (**68**) as shown below, in ratio 1:1 which could not be separated by column chromatography.
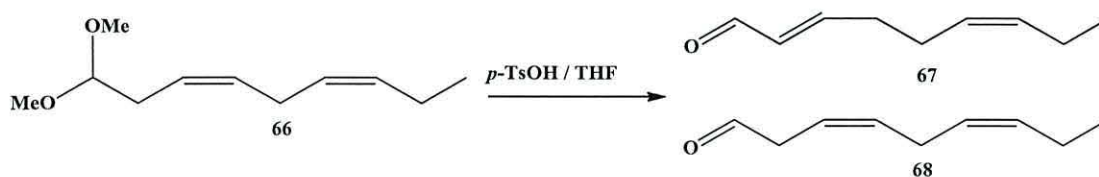
Scheme 19: Mixture of Z and E aldehydes (68) and (67)
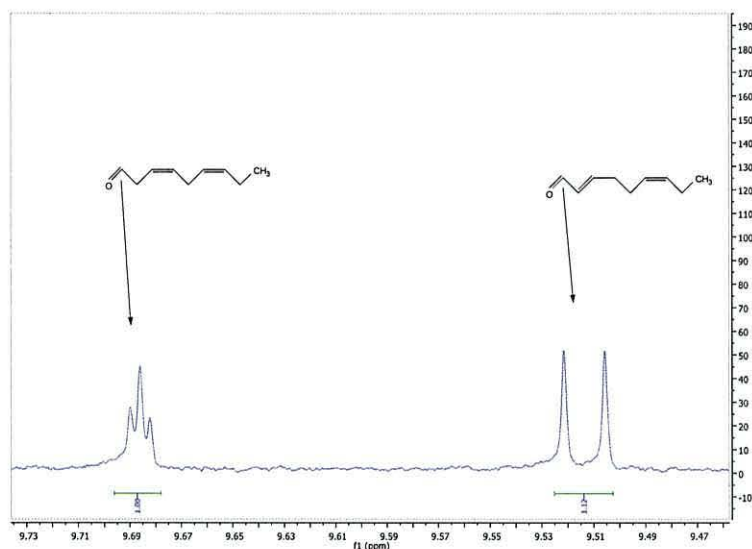
Figure 50: ^{1}H NMR spectrum of mixture of Z and E aldehydes (68) and (67)

In another attempt, oxalic acid was used for the deprotection of the acetal group of (66). Here, the required aldehyde (68) was obtained in 60 % yield and with 40 % recovery of the starting material. In attempting to improve the yield by increasing the reaction time, the undesired, conjugated aldehyde (67) was observed to begin to form.

Finally deprotection of the acetal group was successfully achieved through the use of 80% formic acid in water.[84,85] When the dimethoxy acetal (66) was dissolved in dioxane then treated with formic acid 80% at room temperature, the desired aldehyde (68) was obtained in 96% as the sole product.
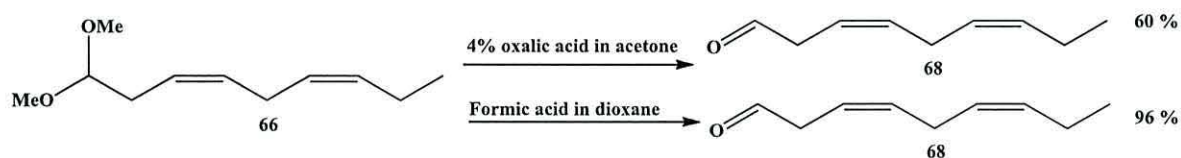
Scheme 20: Preparation of aldehyde (68)

The proton NMR spectrum of (68) displayed the aldehyde proton as a triplet at δ 9.68; the signals for the four alkene protons appeared as four multiplets in the region δ 5.7-5.27. A doublet at δ 3.24 was observed for the two protons of the methylene next to the aldehyde group, a triplet at δ 2.79 for the two protons between the two double bonds, and finally there were two signals, one occurring as a pentet at δ 2.07 corresponding to the methylene between the alkene and methyl groups, and one occurring as a triplet at δ 0.96 for the terminal methyl protons.
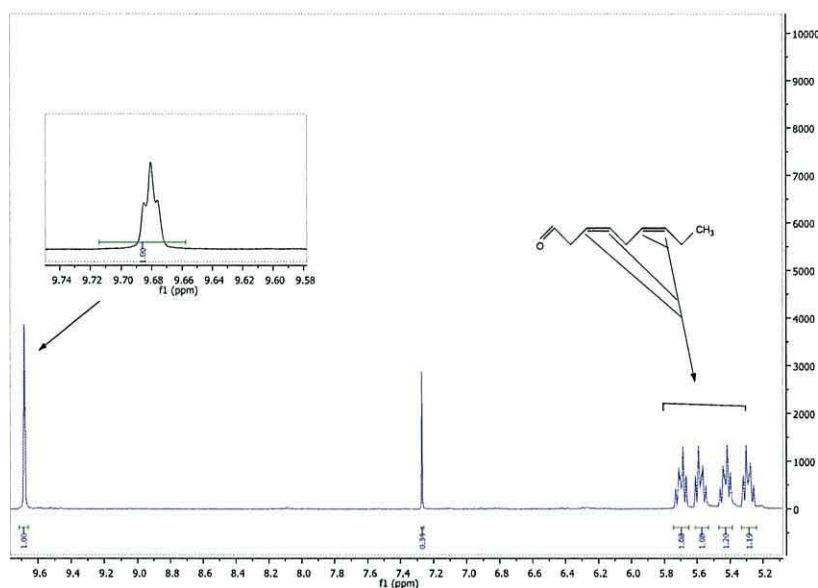
Figure 51: ^{1}H NMR spectrum of (3Z,6Z)-nona-3,6-dienal (68)

Comparing this with the literature, [82] the aldehyde proton has been described as occuring as a broad singlet, however it appears clearly in this spectrum as a triplet.

Additionally, the carbon NMR spectrum of the product displayed a resonance at δ 199.4 for the carbonyl carbon of the aldehyde. The presence of the aldehyde group was confirmed in the infrared spectrum, which showed a strong absorbance at 1727 cm^{-1} for the aldehyde carbonyl compared with the conjugated carbonyl group which appears at 1688 cm^{-1} in (67).

(3Z,6Z)-Nona-3,6-dienal (68) had been prepared previously by Kajiwara in 1975, by using propargyl alcohol as starting material, which underwent coupling and hydrogenation to give nona-3,6-diyn-1-ol, followed by oxidation.[86] The disadvantages of this method relate to the use of acetylene couplings and the difficulty of controlling the hydrogenation.
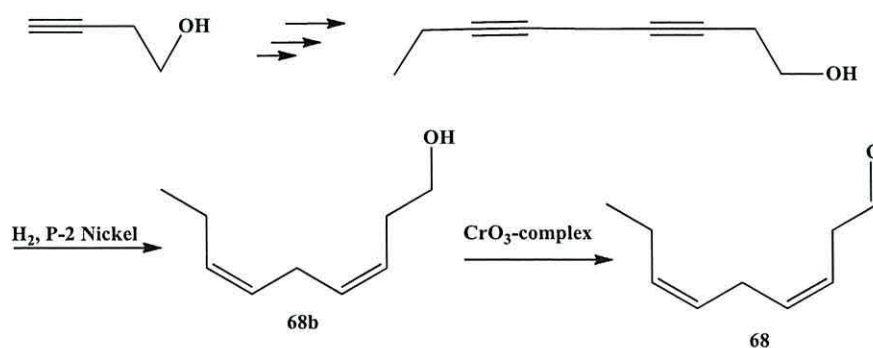
Figure 52: Kajiwara preparation of (68)

2.18 Pheromones containing a triene unit

There are a large number of pheromones containing a skip-conjugated all-*cis* triene unit. Sex pheromones containing a (3Z,6Z,9Z)-3,6,9-triene are components of many of the lepidopterous insect pests distributed worldwide. These compounds have a high ability to attract males; therefore they can be used in integrated pest management to protect many important agricultural crops. The table below shows the products prepared in this work, with example of their uses.

No. of compound	Name of pheromones	Use for
69	(*3Z,6Z,9Z*)-heptadeca-3,6,9-triene	*Lomographa Semiclarata* *Abraxas grossulariata* *Itame occiduaria*
70	(*3Z,6Z,9Z*)-octadeca-3,6,9-triene	*Neachrostia bipuncta* *Eufidonia convergaria*
71	(*3Z,6Z,9Z*)-nonadeca-3,6,9-triene	*Alsophila japonensis* *Alsophila pometaria* *Crocalis tusciaria*
72	(*3Z,6Z,9Z*)-icosa-3,6,9-triene	*Pareuchates pseudoinsulata* *Anticarsia gemmatalis* *Sicya macularia*
73	(*3Z,6Z,9Z*)-henicosa-3,6,9-triene	*Amata phegea* *Empyrenma affinis* *Creatonotos gangis*
74	(*3Z,6Z,9Z*)-pentacosa-3,6,9-triene	*Halysidota leda*

Table 6: Z,Z,Z-Triene pheromones and their uses

For the syntheses of the (3Z,6Z,9Z)-triene pheromones, a number of different synthetic methodologies have been developed, including the use of Wittig-type olefination (Bestmann *et al*),[87] desilylation / Wittig reaction (Bestmann *et al.*),[88] and a sila-cope elimination reported by Langlois *et al.*[89] The alkenes (Z,Z,Z)-3,6,9-hepta-decatriene (69),[90,91] (Z,Z,Z)-3,6,9-octadecatriene (70), (3Z,6Z,9Z)-nonadeca-3,6,9-triene (71),[92,93,94] (Z,Z,Z)-3,6,9-eicosatriene (72), and (Z,Z,Z)-3,6,9-heneicosatriene (73),[95,96] are all pheromones that have been synthesised before. In general, every method involved at some stage the partial hydrogenation of an alkyne. The Wittig reaction was employed to extend the chain via the reaction between different bromo alkanes with triphenylphosphine in toluene or acetonitrile to obtain the corresponding Wittig salts (C8, C9, C10, C11, and C12).

Becker *et al.*, have prepared (3Z,6Z,9Z)-3,6,9-nonadecatriene (71) by using 1-undecyne as a starting material.[94] In addition Wang,[92] has prepared most of these pheromones from linolenic acid, which was converted into the corresponding alcohol by reduction with lithium aluminium hydride, followed by reaction with tri-fluromethanesulfonic anhydride and pyridine. The resulting product was treated with methyl magnesium bromide in the presence of Li$_2$CuCl$_4$ as a catalyst (Scheme 21).
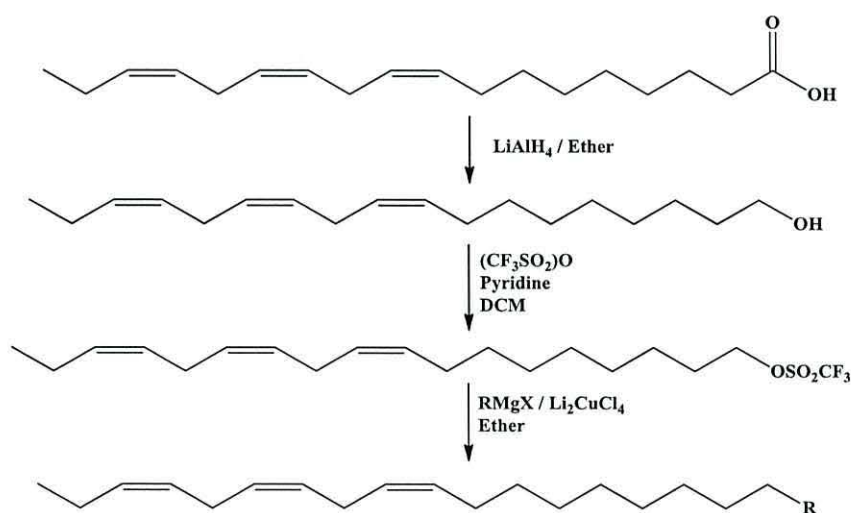
Scheme 21: Wang preparation of pheromones (71)

These types of pheromones comprising polyunsaturated hydrocarbons are a characteristic feature of macro-lepidopteran families such as, *Arctiidae, Geometridae, Noctuidae,* and

Lymantriidae. For example, (3Z,6Z,9Z)-3,6,9-octadecatriene (**70**) and (3Z,6Z,9Z)-3,6,9-nonadecatriene (**71**) are pheromone components of *Erannis bajaria.* [96]

In the current study, the Wittig reaction was used to prepare six pheromones by extending the diene motif of (**68**) by 8, 9, 10, 11, 12 and 16 carbon atoms respectively, employing Wittig salts of different chain lengths in dry THF at low temperature, in the presence of sodium *bis*(trimethylsilyl)amide as a base, to give five pheromones (**69-73**) (Scheme 22), the structures of which were confirmed by their mass spectra and the NMR spectra, all of which were identical to those given in the literature.[93]

The ^{1}H NMR spectra of (**69**) – (**73**) each showed a highly complex, overlapping vinylic signal between δ 5.4 and δ 5.2 which corresponded to two sets of overlapping multiplets, integrating to four and two protons respectively. The two sets of methylene protons situated between the double bonds appeared as a multiplet at δ 2.8. The methylene protons next to the double bond appear as a signal at δ 2.0, while the chain methylene groups appear as a signal at δ 1.2, and the signals at δ 0.9 and 0.8 respectively were for the two terminal methyl groups. The ^{13}C NMR spectra showed the required number of resonances, including six alkene protons signals between δ 131 and δ 127 ppm. The terminal methyl carbon signals were observed at δ 14.2 and δ 14.1 ppm. No trace of *trans* or conjugated compounds could be found by ^{13}C NMR and ^{1}H NMR analysis.
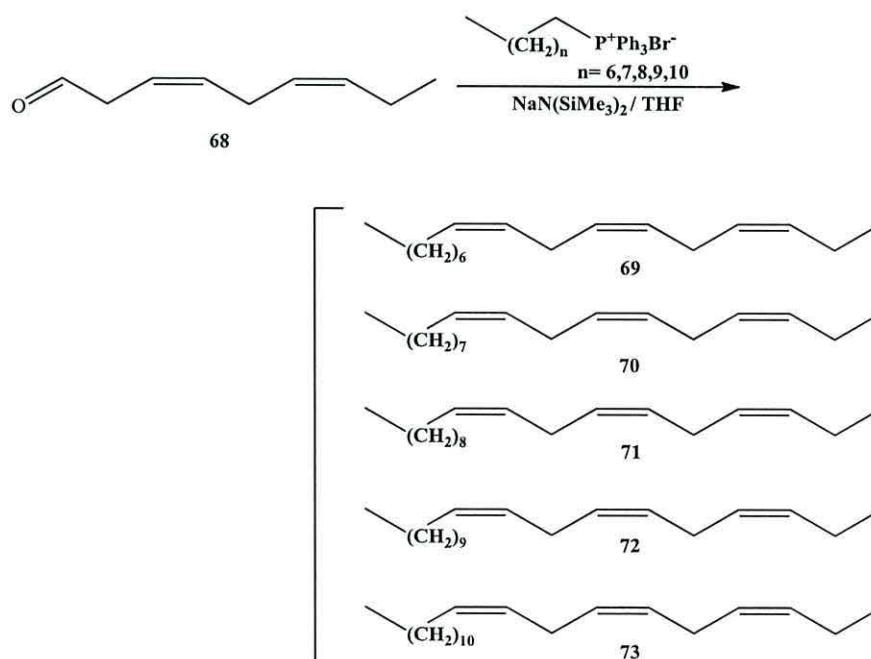
Scheme 22: Sex pheromone structure with trienes

The same route and conditions were used to synthesise (3Z,6Z,9Z)-pentacosa-3,6,9-triene (74), a pheromone of the neo-tropical tiger moth, *Halysidota leda*,[97] which does not appear to have been prepared before. It was prepared using a Wittig reaction between the (3Z,6Z)-nona-3,6-dienal and hexadecyltriphenylphosphonium bromide in dry THF at low temperature in the presence of sodium *bis*(trimethylsilyl) amide (Figure 53). The ^{1}H NMR spectrum of (74) displayed a multiplet between δ 5.44- 5.29 for the six vinylic protons. The methylene protons between the two double bonds appeared as a four proton triplet at δ 2.82 with a coupling constant of *J* 6.16 Hz, and the other methylene protons next to the double bonds appeared as a four proton multiplet at δ 2.07. The remaining methylene protons of the alkyl chain (26 protons) appeared as a multiplet at δ 1.27. The two terminal methyl groups were observed as triplets at δ 0.99 and 0.89, with coupling constants of *J* 7.52 Hz and *J* 6.64 Hz respectively. The ^{13}C NMR spectrum confirmed the presence of six alkene carbon signals between δ 131 and δ 127 ppm. The methylene carbon between the two double bonds occurred with the carbons of the chain methylene groups between δ 31.9 and δ 20.5. The terminal methyl carbon signals were observed at δ 14.2 and δ 14.1 ppm. Furthermore, the product showed the correct molecular ion (*m/z* 346) for $C_{25}H_{46}$.
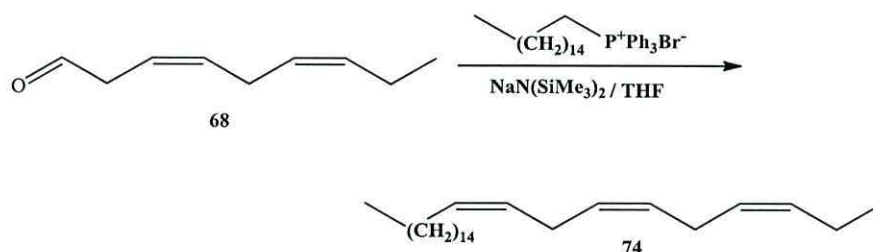
Figure 53: Preparation of (3Z,6Z,9Z)-pentacosa-3,6,9-triene (74)

2.19 Preparation of pheromones with a functional group:
2.19.1 Synthesis of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl acetate (75)

The second objective was to prepare pheromones with a functional group in addition to the double bonds. Alcohol (58) was acetylated to produce (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl acetate (75) in 79 % yield, by reaction with acetyl chloride in the presence of triethylamine. The ^{1}H NMR spectrum of (75) showed the vinylic protons as a four proton multiplet at δ 5.52. The single acetal proton appeared as a triplet at δ 4.39 with a coupling

constant of *J* 5.76 Hz, and the methylene group next to the oxygen as a triplet at δ 4.08 with a coupling constant of *J* 6.8 Hz. The six protons of the methoxy groups appeared as a singlet at δ 3.34, the methylene protons between the two double bonds as a two proton triplet at δ 2.82 with a coupling constant of *J* 6.84 Hz, and the four protons corresponding to the two methylene groups adjacent to the alkene appeared as a multiplet at δ 2.42. The acetyl methyl appeared as a singlet at δ 2.05. The ^{13}C NMR spectrum showed signals at δ 171.1 ppm corresponding to the carbonyl carbon, while the four olefinic carbons appeared between δ 130 and δ 124 ppm. The acetal carbon appeared as a signal at δ 104 ppm, the carbon of the methylene next to the oxygen at δ 63 ppm, and the dimethoxy carbons at δ 52 ppm. The remaining methylene groups and the terminal acetate carbon appeared at δ 31.03, 26.81, 25.87 and 20.94 ppm respectively. The infrared spectrum confirmed that the acetate had been prepared, in that the hydroxyl absorbance had disappeared at 3400 cm^{-1}.

The acetate (**75**) was treated with formic acid 80 % in dioxane to deprotect the acetal group, and produce the unstable aldehyde (**76**), in 84 % yield. The proton NMR spectrum of this displayed the aldehyde proton as a broad singlet at δ 9.68, and the four alkene protons as a multiplet between δ 5.65 and δ 5.3. The methylene hydrogens next to the acetate group appeared as a triplet (*J* 6.92 Hz). In addition, the methylene group protons adjacent to the aldehyde functionality appeared as a broad doublet at δ 3.24 and the acetal signal had disappeared completely from δ 4.39. The carbon NMR spectrum of the synthetic material displayed a resonance at δ 199.2 for the aldehyde carbon and the acetyl carbonyl carbon occurred at the same chemical shift as before of δ 171.1. The infrared spectrum confirmed that the aldehyde group was present, as there were strong absorbances at 1738 and 1698 cm^{-1} for the carbonyl groups of both the acetate and the aldehyde.
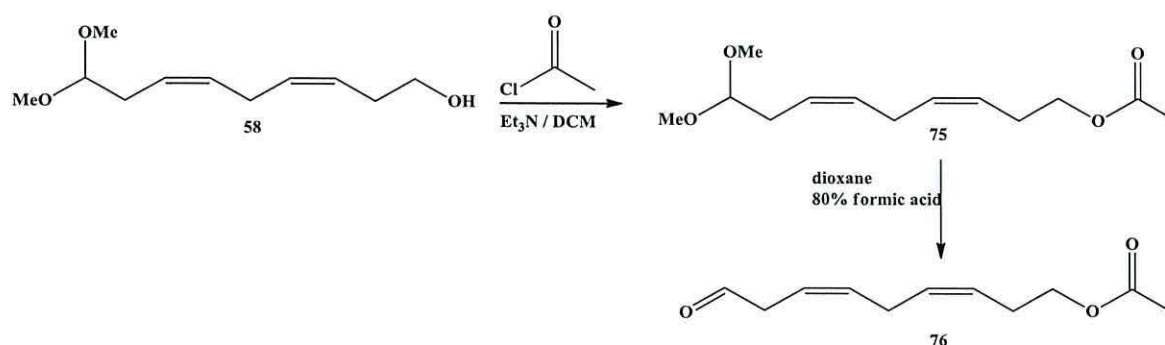
Scheme 23: (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl acetate and its derivatives

2.19.2 Synthesis of (3Z,7E)-9-oxonona-3,7-dien-1-yl acetate (77)

The conjugated aldehyde (3Z,7E)-9-oxonona-3,7-dien-1-yl acetate (77) had also not been synthesized before; we succeeded in synthesising it by treatment of (3Z,6Z)-9-oxonona-3,6-dien-1-yl acetate (76) with sodium *bis*(trimethylsilyl)amide, in dry THF at -78 °C, then employing the same workup as before.

The ^{1}H NMR spectrum of this product showed a doublet at δ 9.51 (*J* 7.84 Hz) for the aldehyde proton. The alkene proton adjacent to the aldehyde group showed a double doublet at δ 6.16 (*J* 7.84, 15.6 Hz), and the other proton appeared as a doublet of triplets at δ 6.85. The methylene protons between the two double bonds had shifted up-field from 2.82 to 2.29, which occurred as a consequence of changing the location of the double bond.
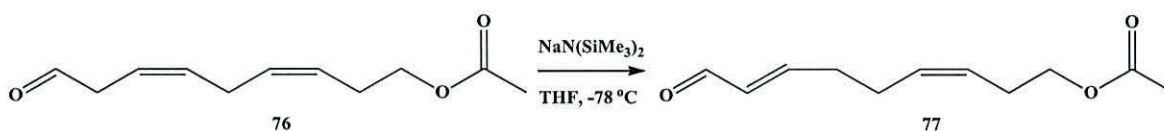
Scheme 24: (3Z,7E)-9-oxonona-3,7-dien-1-yl acetate (77)

2.19.3 Preparation of (3Z,6Z,9Z)-octadeca-3,6,9-trien-1-yl acetate (78).

The next step involved the conversion of the aldehyde group into a carbon-carbon double bond. This was achieved by using the Wittig reaction between (3Z,6Z)-9-oxonona-3,6-dien-1-yl acetate (76), and nonyltriphenylphosphonium bromide, with sodium *bis*(trimethylsilyl)amide in dry THF at -78 °C, which gave (3Z,6Z,9Z)-octadeca-3,6,9-trien-1-yl acetate (78).
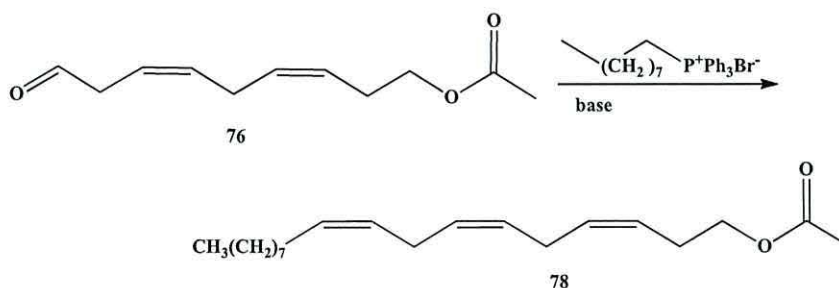
Figure 54: Preparation of (3Z,6Z,9Z)-octadeca-3,6,9-trien-1-yl acetate (78)

The formation of product (**78**) was confirmed from the proton NMR spectrum, which showed the alkene protons as a six proton multiplet at δ 5.38, and the methylene protons between the three double bonds as a four proton quartet at δ 2.83 (*J* 7.04 Hz). The methylene groups next to the oxygen, and the two next to the terminal double bond, occurred at the same chemical shifts of δ 4.08, 2.42 and 2.05 respectively, while new signals appeared as a 12 proton multiplet at δ 1.3 corresponding to the alkyl chain, and the three protons of the terminal methyl group as a triplet at δ 0.88. The carbon NMR spectrum confirmed that the carbon of the aldehyde group had disappeared and showed six signals for olefinic carbons between δ 130 – 124, as well as a signal at δ 14.1 ppm corresponding to the terminal methyl carbon. Furthermore, the identity of the product was confirmed by its mass spectrum, which showed a molecular ion at 306 ($C_{20}H_{34}O_2$).

This compound has been reported to be present in the pheromone blend of *Ectropis oblique Prout* (*Lepidoptera: Geometridae*).[98] This is an important tea bush pest in Southeast China. Population outbreaks can completely defoliate leaves on the bushes.[99]

The main components of the sex pheromone of the female *E.oblique* were identified as (*Z,Z,Z*)-3,6,9-octadecatriene and 6,7-epoxy-(*Z,Z*)-3,9-octadecadiene.[100]

2.20 Preparation of (9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienal

2.20.1 Preparation of (9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienoic acid (83)

α-Linolenic acid (**83**) is an important compound found in many common vegetable oils. This acid is essential for humans and they can get it through diets comprising flax seed, walnut, soy, canola and fish oil (cold water fish such as salmon, cod and mackerel). These types of fatty acids show many benefits against inflammatory conditions, such as asthma, allergies, nausea, sunstroke, heart diseases, as well as being used as anticancer agents and as an antispasmodic.[101]

83
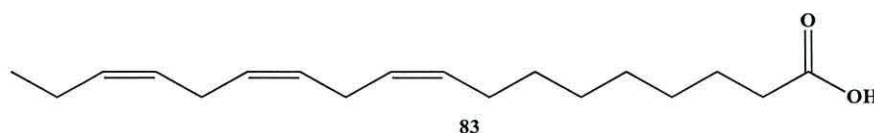
Figure 55: α-Linolenic acid (83)

In this work, during the preparation of the pheromone (9Z,12Z,15Z)-octadeca-9,12,15-trienal (**85**), α-linolenic acid was prepared as an intermediate by Wittig coupling of dienal (**68**) with (8-carboxyoctyl)triphenylphosphonium bromide (**82**) in the presence of base.
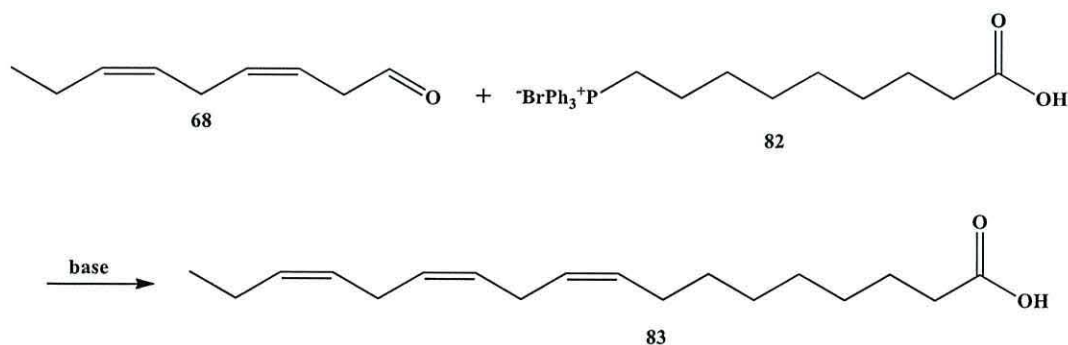
Figure 56: preparation of α-Linolenic acid (83)

The Wittig salt which was used in this reaction was prepared from 1,9-nonadiol, which was firstly reacted with HBr to convert it into 9-bromononan-1-ol, and then into the 9-bromononanoic acid by oxidation with potassium permanganate. Finally, the bromo acid was converted into (8-carboxyoctyl)-triphenylphosphonium bromide (**82**) through reaction with triphenylphosphine. The structure of (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid (**83**) was confirmed by the IR and NMR spectra which were identical to those reported.[101]

2.20.2 Preparation of (9Z,12Z,15Z)-octadeca-9,12,15-trien-1-ol (84)

Cabrera *et al.* in 2001 prepared this alcohol by reducing methyl linolenate with lithium aluminium hydride.[102] In 1998 Natasha *et al.*, employing an alkyne coupling strategy, synthesized the deuterated linolenyl alcohol, and used it for biosynthetic studies.

In this work, Linolenyl alcohol (**84**) was prepared as an intermediate in the preparation of (9Z,12Z,15Z)-octadeca-9,12,15-trienal (**85**).
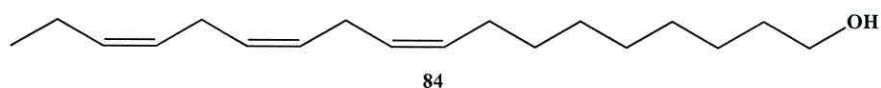
Figure 57: (9Z,12Z,15Z)-octadeca-9,12,15-trien-1-ol (84)

The α-linolenic acid (83) prepared above was reduced with lithium aluminium hydride in THF, to give the trienol (84) in a yield of 88%. In the ^{1}H NMR spectrum, the methylene group of the alcohol appeared as a triplet at δ 3.65 and the ^{13}C NMR spectrum showed the carbon of the carbonyl group to have disappeared. The IR spectrum showed a broad band at v_{max} 3437 cm^{-1} for the OH stretch.

2.20.3 Preparation of (9Z,12Z,15Z)-octadeca-9,12,15-trienal (85)

85
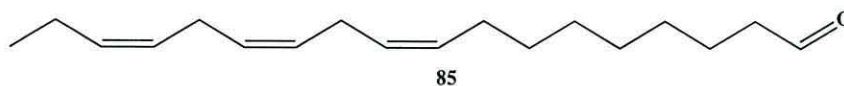
Figure 58; (9Z,12Z,15Z)-Octadeca-9,12,15-trienal (85)

(9Z,12Z,15Z)-Octadeca-9,12,15-trienal (85) is present in the sex pheromone glands in two types of females of the fall webworm, *Hyphantria cunea (Drury) (Lepidoptera: Arctiidae)*. Moreover, the linolenic aldehyde (85) has been identified in the sex pheromone gland of many Arctiid species, including the Red hairy caterpillar, *Amsacta albistriga (Walker)*, the Bihar hairy moth, *Diacrisia obliqua* (Walker) and the Saltmarsh caterpillar, *Estigmene acrea (Drury)*.[103] The Bihar hairy moth causes considerable damage, where caterpillars feed on the leaves voraciously and defoliate the plants, leaving only the mid-ribs and veins in severe cases and this pheromone is an important to control these kinds of insects.

The alcohol (84) was oxidised to this aldehyde. The reaction was carried out by addition of pyridinium chlorochromate (PCC) to a rapidly stirred solution of the alcohol (84) in dichloromethane, which gave aldehyde (85) in good yield. The infrared spectrum confirmed that the aldehyde had been prepared as no hydroxyl absorbance was present but had been replaced by a strong absorbance at 1728 cm^{-1} for the aldehyde carbonyl group. The ^{1}H NMR spectrum showed a triplet at δ 9.77 (*J* 1.84 Hz) for the aldehyde proton. In addition, the carbonyl carbon displayed a resonance at δ 202.8 in the carbon NMR spectrum. This was prepared easily through our route, and showed the same GC-MS data as those reported.[104]

2.21 Pheromones containing dienes

2.21.1 Preparation of Z,Z-nona-3,6-dien-1-ol

The next pheromone to be prepared was (3Z,6Z)-nona-3,6-dien-1-ol (86).[48,91] This substance has been used to control the Mexican fruit fly, *Anastrepha ludens* (Loew), which is a harmful pest of various fruit crops in Mexico and Central America. This damage appears as a significant effect in mango and citrus fruits in particular.

The alcohol was prepared from (3Z,6Z)-nona-3,6-dienal (68). The aldehyde was reduced in the presence of lithium aluminium hydride in 88 % yield. The ^{1}H NMR spectrum of (86) showed a broad triplet at δ 3.66 for the two protons adjacent to the hydroxyl group. The ^{13}C NMR spectrum confirmed the result in so far as the carbon of the aldehyde had disappeared. The IR included a broad peak at 3400 cm^{-1} for the OH. These data were identical to those in the literature.[105]
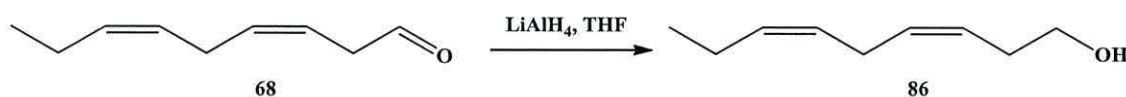
Figure 59: Preparation of (3Z,6Z)-nona-3,6-dien-1-ol

2.22 Pheromones containing tetraene units

2.22.1 Synthesis of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (88):

(3Z,6Z)-9-Iodo-1,1-dimethoxynona-3,6-diene (63) was transformed into a phosphonium salt, ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenyl-phosphonium iodide (88) in 71% yield by reaction with triphenylphosphine and calcium carbonate as a drying agent in dry acetonitrile and heating for 3 days at 50 °C.
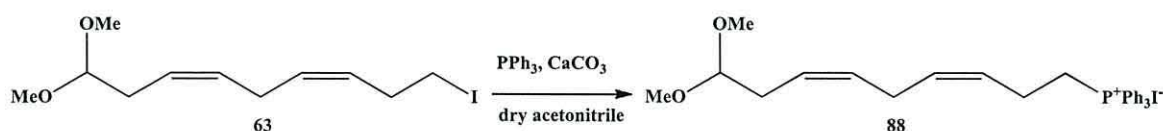
Figure 60: Preparation of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenyl-phosphonium iodide (88)

The ^{1}H NMR spectrum of (88) included multiplets at δ 7.80 for the 15 aromatic protons of the three phenyl groups, multiplets between δ 5.6-5.3 for the four alkene protons, and a triplet at δ 4.29 for the acetal proton, while the CH$_2$ adjacent to phosphorus gave a broad doublet of triplets at δ 3.81 (–CH$_2$P$^+$Ph$_3$Br$^-$). The methoxy protons appeared as a six proton singlet at δ 3.28. Other signals appeared at δ 2.57, 2.40 and 2.23 for the methylene protons between and next to the two double bonds. The ^{13}C NMR showed signals between δ 135.1 and 117.5 for the aromatic and alkenes carbons, and a signal at δ 104.2 for the acetal carbons, The other signals were as expected.

The salt (88) with two double bond prepared above, was employed to generate new acetal containing products with three double bonds by Wittig reactions.

2.22.2 Preparation of (3Z,6Z,9Z)-1,1-dimethoxy-pentadeca-3,6,9-triene (89) and (3Z,6Z,9Z)-1,1-dimethoxy-heptadeca-3,6,9-triene (90).

The phosphonium iodide (88) was treated with sodium *bis*(trimethylsilyl)amide, and to the resulting phosphonium ylid reacted with saturated aldehydes of different chain lengths (C6 and C8) at -78 °C, to give (3Z,6Z,9Z)-1,1-dimethoxy-pentadeca-3,6,9-triene (89) and (3Z,6Z,9Z)-1,1-dimethoxy-heptadeca-3,6,9-triene (90) respectively.
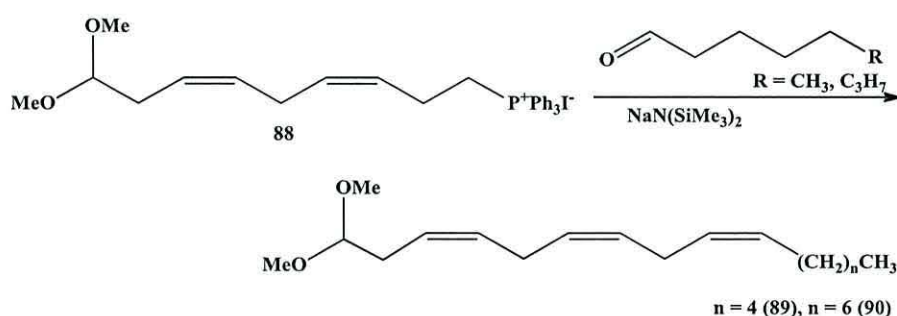
Figure 61: Preparation of (3Z,6Z,9Z)-1,1-dimethoxy-pentadeca-3,6,9-triene and (3Z,6Z,9Z)-1,1-dimethoxyheptadeca-3,6,9-triene

The ^{1}H NMR and ^{13}C NMR spectra were used to confirm the structure of the products. The ^{1}H NMR spectrum of compounds (89) and (90) showed the expected signals between δ 1.3 and 1.28 ppm for the long chain, while the terminal methyl group showed a triplet at δ 0.89

ppm. The other signals appeared almost the same, for example the alkene hydrogens appeared at δ 5.3, the acetal single proton at δ 4.39, six methoxy protons at δ 3.34 and finally the methylene protons next and between the double bonds appeared at δ 2.4 and δ 2.82 respectively. Moreover, the ^{13}C NMR spectrum confirmed the result, because the carbon of the aldehyde carbonyl group had disappeared.

2.22.3 Preparation of (3Z,6Z,9Z,12Z)-octadeca-3,6,9,12-tetraene and (3Z,6Z,9Z,12Z)-eicosa-3,6,9,12-tetraene pheromones

The tetraene (3Z,6Z,9Z,12Z)-eicosa-3,6,9,12-tetraene (**92**) had previously been prepared by a coupling between (Z)-3-undecenal (**90d**) and the (3Z,6Z)-nona-3,6-dien-1-ylidenetriphenyl-phosphorane in dry THF.[60] The synthesis was started from 3-butyn-1-ol (**90a**), which was protected as a THP ether, followed by coupling with 1-bromoheptane to give (**90b**). Partial hydrogenation and deprotection of (**90b**) gave (**90c**). This alcohol was then converted into the corresponding aldehyde (**90d**) by oxidation with 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (IBX).
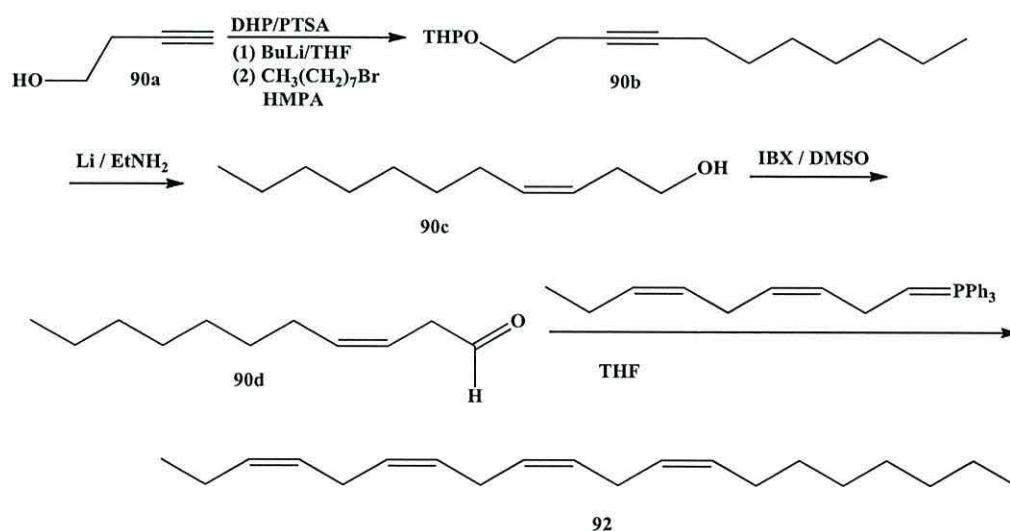
Scheme 25: Preparation of (3Z,6Z,9Z,12Z)-3,6,9,12-eicosatetraene

In the present work, acetals (**89**) and (**90**) were deprotected by using formic acid to give unstable aldehydes, which were the coupled without purification in a second Wittig reaction to obtain the emerald moth sex pheromones (3Z,6Z,9Z,12Z)-octadeca-3,6,9,12-

tetraene (**91**) and (3Z,6Z,9Z,12Z)-eicosa-3,6,9,12-tetraene (**92**), which contain tetraene units.

Figure 62: Preparation of (3Z,6Z,9Z,12Z) octadeca-3,6,9,12-tetraene and (3Z,6Z,9Z,12Z)-eicosa-3,6,9,12-tetraene

The structures of the final compounds were confirmed by NMR spectroscopy. In the ^{1}H NMR spectra of (**91**) and (**92**), the olefinic signals appeared as eight proton multiplets at δ 5.36, and the methylene protons between the four double bonds as a six proton broad pentet centered at δ 2.83. The two methylene groups next to the double bonds were observed as a four proton broad sextet at δ 2.08, while the remaining methylene protons of the alkyl chain appeared as a multiplet at δ 1.31. The two terminal methyl groups gave a triplet at δ 0.99 and 0.90. The carbon NMR spectrum showed the required number of resonances, including the eight olefinic carbons, and the signals corresponding to the carbon atoms of the methylene groups appeared between δ 31.8 – 20.5. In addition, it showed signals at δ 14.2 and 14.1 ppm respectively, for the two terminal methyl carbons.

2.23 Synthesis of new intermediates and fatty acids

By coupling the phosphonium salt (**88**) and aldehyde (**68**) in a Wittig reaction using sodium *bis*(trimethylsilyl)amide, it was possible to obtain two fractions; the first was mono-acetal (**93**) which was obtained in a 63% yield,[98,106] while the second fraction was di-acetal (**94**) obtained in 25% yield. Both were quite stable but they were converted easily to the corresponding aldehydes. The deprotection of the acetal group of (**93**) with 80% formic acid in dioxane led to the corresponding aldehyde (3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaenal (**95**) in 75% yield. The reaction of (**94**) with 80% formic acid in

dioxane led to (3Z,6Z,9Z,12Z,15Z)-18,18-dimethoxyoctadeca-3,6,9,12,15-pentaenal (**96**) in 64% yield.[98]

The ^{1}H NMR spectrum of aldehyde (**95**) showed a triplet at δ 9.69 (1H, J 1.72 Hz) for the aldehyde proton. The olefinic protons were observed as a ten proton multiplet between δ 5.69 and 5.39, and the methylene protons next to the aldehyde as a doublet at δ 3.24 (2H, J 7.12 Hz). The methylene protons between and next to the five double bonds appeared as a broad pentet at δ 2.83 (8H, J 5.08 Hz), and at 2.08 (2H, J 7.48 Hz) respectively; finally, the terminal alkyl protons appeared as a triplet at δ 0.98 (3H, J 7.56 Hz). The ^{13}C NMR showed signals at δ 199.2 for the carbonyl carbon of the aldehyde, at δ 42.4 for the carbon next to the aldehyde carbon, and showed the required ten alkene carbons between δ 133.1-118.6. The terminal methyl carbon appeared at δ 14.2 and a signal occurred at δ 20.5 for the methylene groups adjacent to this alkyl group. The infrared spectrum confirmed the success of the deprotection, showing an absorbance at 1731 cm^{-1} corresponding to the aldehyde carbonyl group.

Using the same method as discussed before, the aldehyde (3Z,6Z,9Z,12Z,15Z)-18,18-dimethoxyoctadeca-3,6,9,12,15-pentaenal (**96**) was prepared using partial deprotection of the (3Z,6Z,9Z,12Z,15Z)-1,1,18,18-tetramethoxyoctadeca-3,6,9,12,15-pentaene (**94**) with 80 % formic acid in dioxane. The final product structure was confirmed by ^{1}H NMR, ^{13}C NMR and IR. The ^{1}H NMR spectrum showed the expected olefinic and methylene signals. In addition, a new signal appeared as a triplet at δ 9.68 (J 1.6 Hz) for the aldehyde proton and in the ^{13}C NMR spectrum, a signal appeared at δ 199.3 for the aldehyde carbonyl carbon.
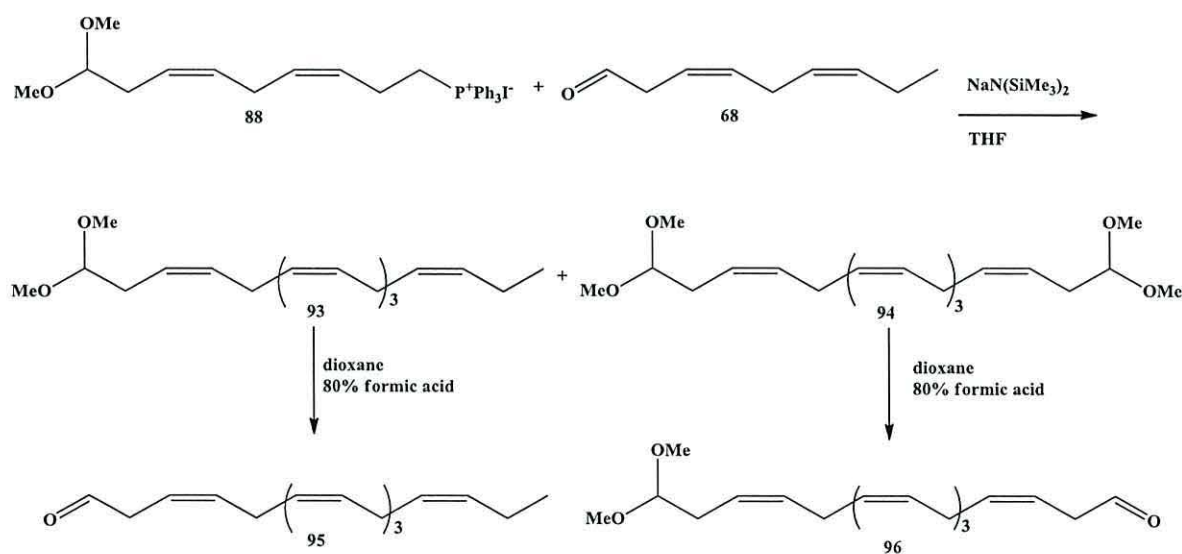
Scheme 26: Preparation of polyunsaturated aldehydes

2.23.1 Preparation of (6Z,9Z,12Z,15Z,18Z,21Z)-tetracosa-6,9,12,15,18,21-hexaenoic acid (98)

Several studies have shown that this type of (Z) fatty acid is very important in human nutrition, in that it has been demonstrated that they are necessary for normal growth and cell function.[98]

Tetracosahexaenoic acid (98) has been prepared before according to the Scheme 27, via a two-carbon elongation of docosahexaenoic acid (DHA) ethyl ester. DHA ethyl ester (96a) was converted into an iodide (96b), after reduction with LiAlH₄, and subsequent conversion of the alcohol to the tosylate. The iodination was achieved with LiI. Diethyl malonate was then introduced to the iodide and, after hydrolysis of the diester with LiOH, decarboxylation was conducted in a mixture of distilled THF and CH$_3$COOH with concentrated HCl at 90 °C for 48 h.[106]
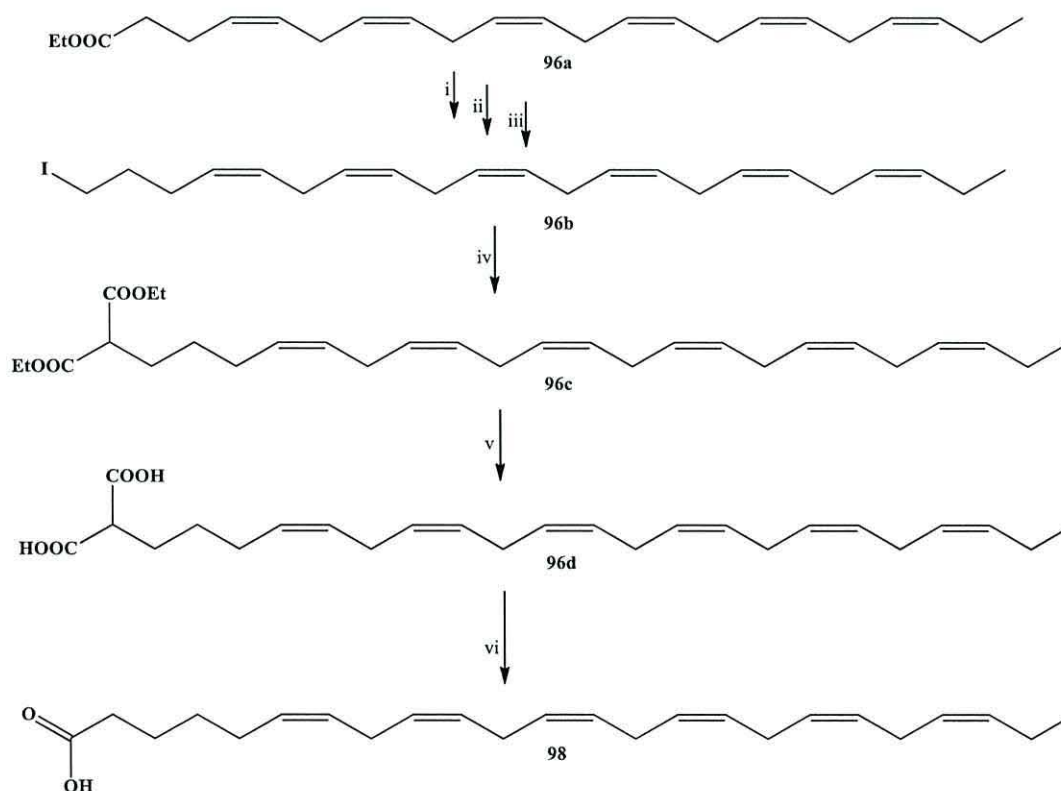
Reagents: i. LiAlH₄; ii. toluene-*p*-sulfonyl chloride; iii. LiI; iv. diethyl malonate, NaH in DMF–THF (1:1); v. LiOH (aq.); vi. 0.0001% HCl in AcOH, 90°C, 74 h

Scheme 27: Previous method to prepare tetracosahexaenoic acid (98)

In this study, reaction of the aldehyde (95) with the phosphonium salt (5-carboxypentyl)-triphenylphosphonium bromide (97) in the presence of sodium *bis*(trimethylsilyl)amide led to (6Z,9Z,12Z,15Z,18Z,21Z)-tetracosa-6,9,12,15,18,21-hexaenoic acid (98) in 78% yield.
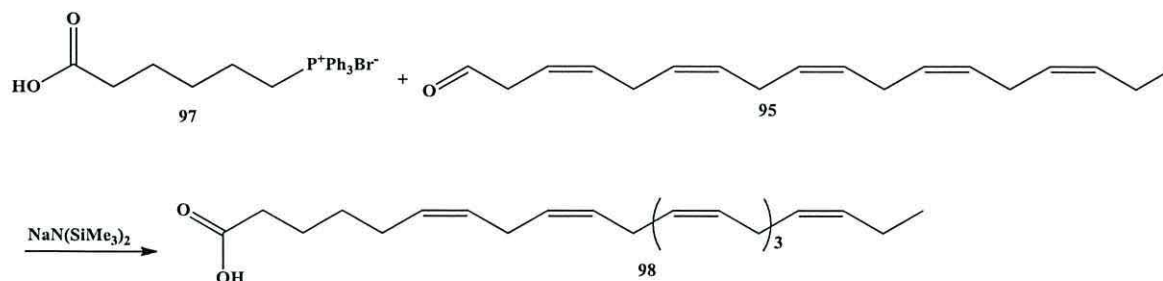
Figure 63: Preparation of (98)

The ^{1}H NMR spectrum of the product (98) showed a multiplet at δ 5.39 for the twelve alkene protons, reflecting the presence of six double bonds within the molecule. A multiplet occurred at δ 2.86 for the methylene protons between the six double bonds. The methylene protons next to the terminal alkyl group appeared at δ 2.08 while the terminal methyl group appeared as a triplet at δ 0.98. However, the aldehyde signal had disappeared while a new signal appeared at δ 2.38, corresponding to the methylene protons next to the carboxylic acid group. The alkyl chain signals appeared at δ 2.08, 1.66 and 1.43 respectively. The ^{13}C NMR spectrum showed the required number of resonances, including the carbonyl carbon signal at δ 179.5, with the twelve alkene carbons resonating between δ 132 and 127 ppm, and with signals occurring at δ 33.8, 28.9, 26.8, 25.6, 25.5, 24.2, 20.5 and 14.2, respectively, for the carbons of the chain and the terminal methyl groups. The IR spectrum included a broad peak at 3444 cm^{-1} for the OH stretch and a peak at 1709 cm^{-1} for the C=O stretch.

2.23.2 Preparation of the methyl ester (99)

Methyl (6Z,9Z,12Z,15Z,18Z,21Z)-tetracosa-6,9,12,15,18,21-hexaenoate (**99**) was prepared through reaction of the acid (**98**) with an excess of diazomethane in ether at room temperature to afford the methylester in 97 % yield.
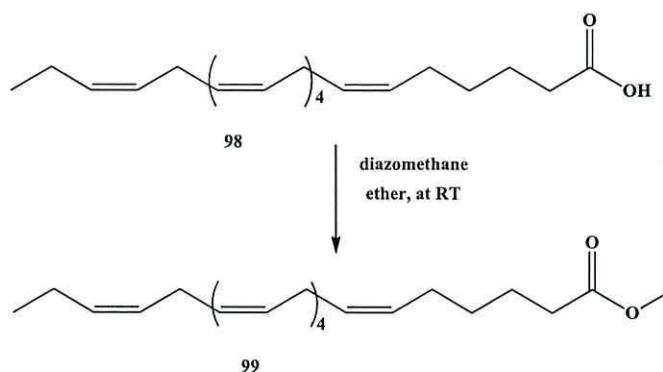
Figure 64: Preparation of methyl ester (99)

The NMR spectra of compound (**99**) were found to be similar to those of the free acid, however a characteristic peak appeared as a singlet at δ 3.67 in the ^{1}H NMR spectrum, which confirmed the presence of the ester functional group. The ^{13}C NMR spectrum showed a signal at δ 174.1 for the carbonyl carbon, and a signal at δ 51.4 for the ester methyl. Similar NMR spectra were also reported in the literature. Mass spectrometry gave a molecular ion with the expected mass.

2.23.3 Synthesis of (3Z,6Z,9Z,12Z,15Z,18Z,21Z,24Z)-1,1-dimethoxyheptacosa-3,6,9,12,15,18,21,24-octaene (100)

Using the same method as discussed before, the (3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaenal (95) was coupled with the ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenyl-phosphonium iodide (88) using sodium *bis*(trimethylsilyl)amide as a base to give (3Z,6Z,9Z,12Z,15Z,18Z,21Z,24Z)-1,1-dimethoxyheptacosa-3,6,9,12,15,18,21,24-octaene (100) in 68 % yield.
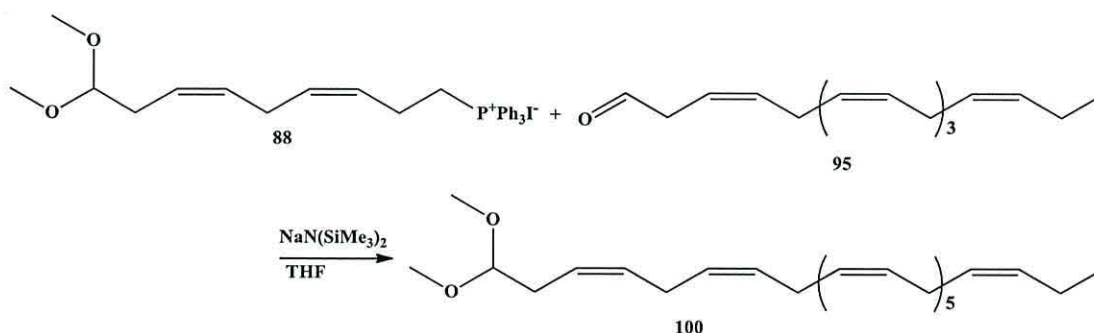
Figure 65: Preparation of (3Z,6Z,9Z,12Z,15Z,18Z,21Z,24Z)-1,1-dimethoxyheptacosa-3,6,9,12,15,18,21,24-octaene (100)

The ^{1}H NMR spectrum of the acetal (100) included a multiplet at 5.53- 5.29 for the 16 alkene protons. Moreover, the ^{13}C NMR spectrum showed as 16 carbons for alkene region between δ 132.0 and 124.0 ppm, In addition to the disappearance of the aldehyde carbonyl carbons from 199.2 ppm.

2.24 Conclusion:

There is a wide range of tactics or methods of pest management and pheromones are among the most ecologically selective pest suppression agents. Unlike the conventional insecticides, they are non toxic and they are effective at very low concentrations.

Here, the development of a cheap method to access pheromones containing the *triene* and *tetraene* groups was investicated, originating with the ozonolysis of cyclonona-1,4,7-triene. Ozonolysis of the triene leads to a 1,9-difunctionalised *Z,Z*-3,6-nonadiene which is readily converted into a range of polyunsaturated pheromones and fatty acids. There are many pheromones (examples are shown below) that could in principle, be prepared at a low cost by using 1,4,7-cyclononatriene through several steps starting with ozonolysis, to prepare the dimethoxy-diene-alcohol that retains two of the *Z*-alkenes, followed by removal of the terminal hydroxyl group through its transformation into good leaving groups then reducing with LiAlH$_4$. The main intermediate in this work is the aldehyde (3*Z*,6*Z*)-nona-3,6-dienal, which is formed by deprotection of the acetal group after the reduction step, and which can then be coupled with various phosphonium ylid reagents through the use of the Wittig olefination reaction.
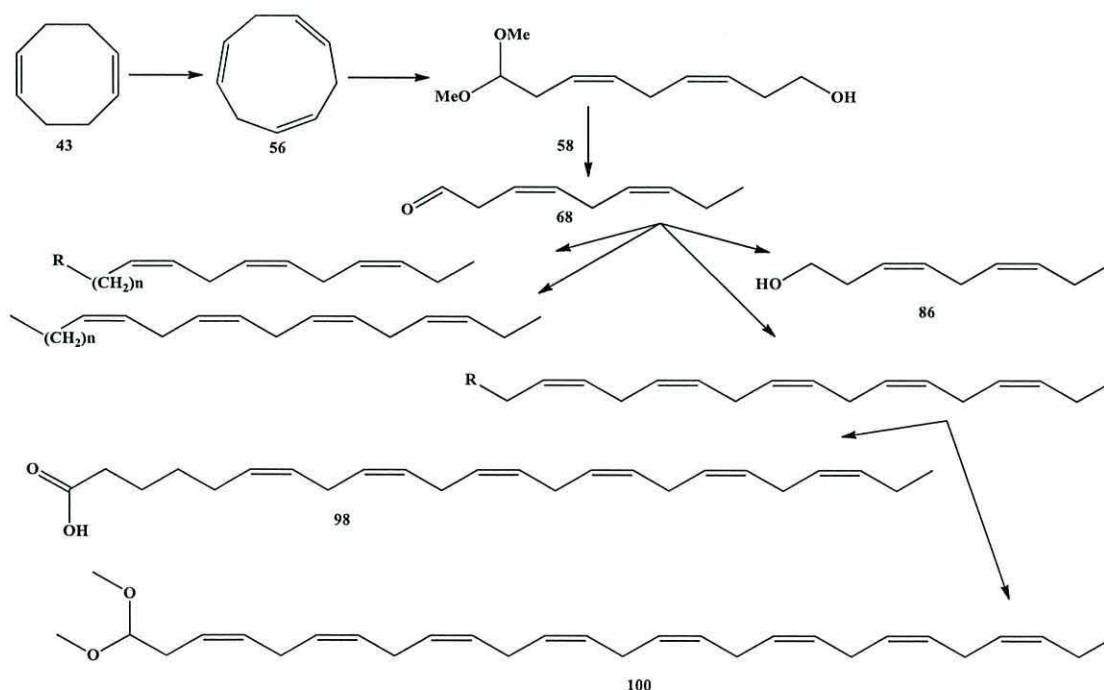
Scheme 28: Generic strategy for the synthesis of polyunsaturated fatty acid compounds starting from (1Z,5Z)-cycloocta-1, 5-diene

Chapter 3. Cyclic *bis*- and *tris*-allenes derived from cyclonona-1,4,7-triene

3.1 Introduction

Allenes have rich coordination and organometallic chemistry. It is well established that they can form transition metal complexes with one of their double bonds. Upon coordination, allenes are activated and can participate in various organometallic reactions. In addition, the transition-metal-catalysed cyclisation reactions of allenes constitute useful methods for the construction of heterocycles, and are useful for academic and industrial researchers Heterocyclic compounds are worth our attention for many reasons; chief among them being their biological activities; Therefore, their production by new and efficient synthetic transformations, would be of great interest. A transition-metal-catalysed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions, again making these syntheses more cost effective in industry. Transition-metal-catalysed intramolecular reactions of carbon-carbon unsaturated compounds have been extensively studied and have become a powerful tool for the synthesis of heterocycles.[107]

3.2 Allene structure

Usually, dienes are classified into three broad groups: conjugated, isolated, and cumulated (Figure 66).
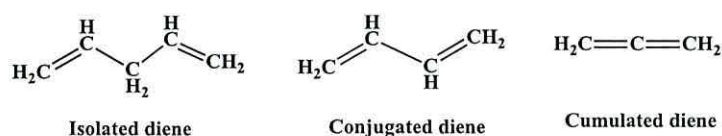
Figure 66: Diene classes

A cumulated diene (allene) is a compound in which three carbons atom are linked to each other in a linear arrangement by two contiguous π bonds. The central carbon atom, C_2, in

this arrangement is *sp*-hybridized and the two outer carbon atoms, C_1 and C_3, are sp^2-hybridized. The two *p* orbitals of the central carbon atom are mutually perpendicular and each overlaps with the *p* orbitals of one of the adjacent, external carbon atoms, causing the resulting π bonds, and hence the terminal substituents, [R_1, R_2] and [R_3, R_4], to exist in orthogonal planes.
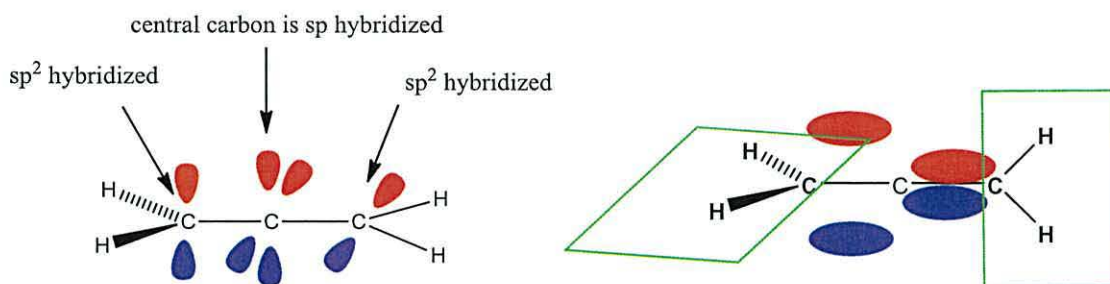
Figure 67: The bonding orbitals in allenes

As a consequence of this spatial arrangement, if C_1 and C_3 should have different substituents (e.g. $R_1=R_3$; $R_2 \neq R_4$) then chirality is introduced, and the resulting stereoisomers exist as a pair of enantiomers (e.g. non-superimposable mirror-image forms). This property gives allene importance in a number of applications across industry and research, such as their use as drugs, anti-oxidants, and dyes.[107]
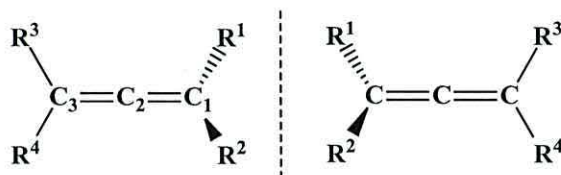
Figure 68: Chiral allene structure

Allene π-bond lengths are shorter than those of other olefins and they are thermodynamically less stable than isolated and conjugated dienes, and therefore react much more readily than ordinary alkenes.[107] Some of these properties are shown clearly in IR and ^{13}C-NMR spectra; for example, π-bonds shift from 1650 cm^{-1} in alkene to around 1900-2000 cm^{-1} in allenes.[108,109] Furthermore, in ^{13}C-NMR spectroscopy, olefinic carbons give signals in the region 120-140 ppm, but the central carbon atom, C_2, of an allene, resonates in the region 201-220 ppm.[110]

3.3 Allenes in nature

Allenes are biologically active and participate in a number of biochemical processes. At present, about 150 allenes are known to occur naturally. These include insect pheromone (107) and grasshopper ketone (108).[111,112,113]
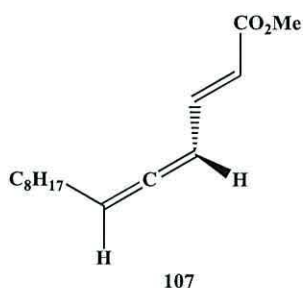
Figure 69: Insect pheromone
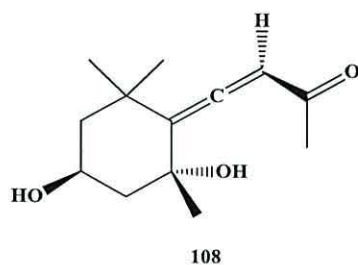
Figure 70: Grasshopper ketone

Most such naturally occurring allenes are chiral; however, they are not necessarily enantiomerically pure. Allenes are also important as pharmaceutical agents. Examples include vitamin B6-dependent decarboxylase inhibitor (109)[114] and the antibiotic mycomycin (110)[115] (Figures 71, 72).
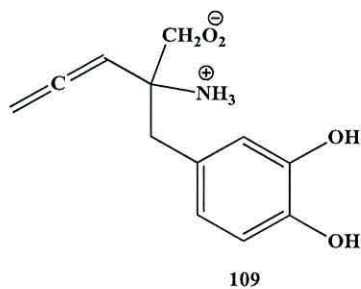
Figure 71: Vitamin B6-dependent decarboxylase inhibitor

110
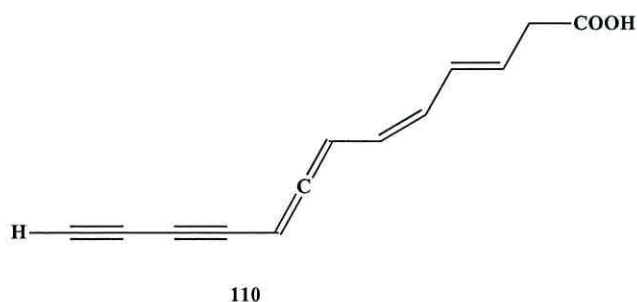
Figure 72: Mycomycin

3.4   Preparation of allenes

3.4.1   Reaction of 1,1-dibromocyclopropanes with alkyl lithium

The reaction of 1,1-dibromocyclopropanes with alkyl lithium reagents provides one of the most efficient routes to allenes.[124] This process proceeds by initial lithium-bromine exchange, to form a lithium-bromide intermediate, (a), from which the cyclopropylidene, (b), or a related carbenoid which may eliminate the lithium-bromide. The major reaction of cyclopropylidenes is the formation of allenes, which in many cases occur rapidly and efficiently even at -90 °C (Figure 73).
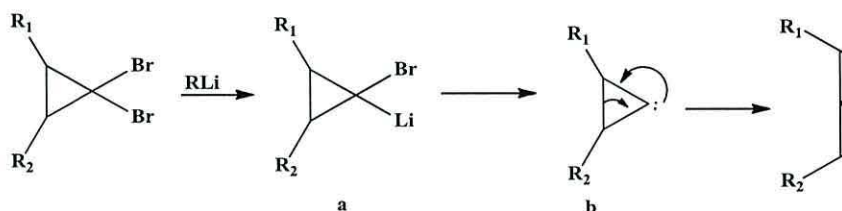
Figure 73: Preparation of allene from 1,1-dibromocyclopropanes

3.4.2 Preparation from alkynes

3.4.2.1 Allenes from propargyl electrophiles via LiAlH₄

A wide area in allene synthesis involves the use of aluminium reagents. The use of aluminium based Lewis acids for C–C bond formation represents the smaller part in this field; much more developed is the formation of C–H bonds with aluminium hydrides. Various propargylic electrophiles such as alcohols, ethers, halides and oxiranes can give rise to the corresponding allenes with the aid of lithium aluminum hydride, diisobutylaluminum hydride (DIBAL-H) and other aluminum hydrides.[115]
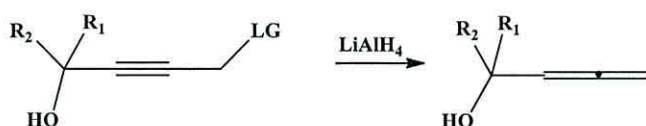
Moreover, several methods had been used for preparing allenes using single enantiomers of propargyl esters.[116]

R₁ = Ph, *t*-Bu, octyl, Me
LG = OS(O)Me or OSO₂Me
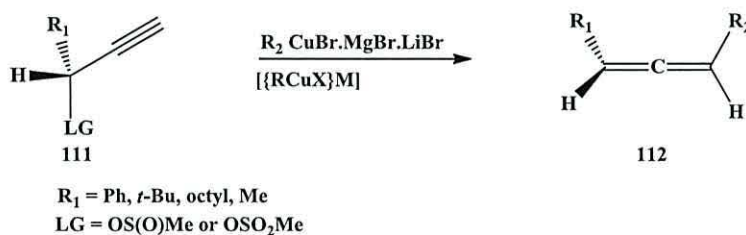
a
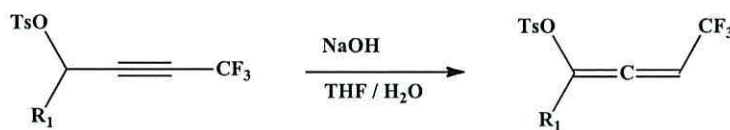
b

Figure 74: a- & b- Preparation of allenes from alkyne

3.4.3 Preparation from alkenes

Simple and mild indium- and zinc-mediated dehalogenation reactions of vicinal dihalides in an aqueous solvent enable the synthesis of various allenylmethyl aryl ethers and mono substituted allenes in very good yields. [116]
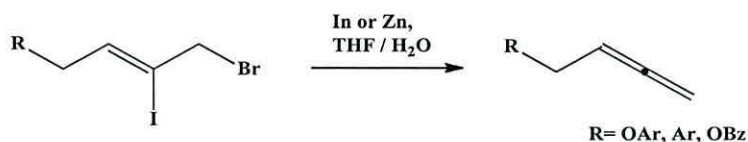
Figure 75: Preparation of allenes from alkene

3.5 Strained cyclic allenes

The equilibrium geometry for allenes is linear and they are not inherently "strained". Strain implies some deviation from an ideal bonding geometry; this is not true for compounds which contain ordinary *sp-* and *sp^2*-hybridized carbons. However, the electronic structure of allenes and their ability to form stabilized intermediates do make them reactive and many allenes dimerize easily. As with cycloalkenes and cycloalkynes, ring constraints in cyclic allenes cause increasing angle strain as the ring size diminishes particularly in allenes present in rings of eight carbons or less.
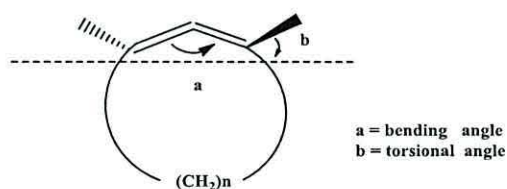
Figure 76: Bending and torsional angles in cyclic allenes

Bending and torsional angles in cyclic allenes make them non-isolable and highly reactive intermediates as n is reduced (Figure 76). Due to that, the synthesis, isolation and trapping of cyclic-strained allenes have been attracting more and more interest in the past few decades.[117] Besides the synthesis, these compounds have been the subject of several theoretical investigations.[118,119,120]

3.6   Allenes with different sized rings

3.6.1   Five-membered ring allenes

Several researchers such as Balci *et al.* have attempted to synthesise monocyclic allenes with different molecular size (C5 to C9).[121] The first attempt was made by Favorskii[122] in 1935 to synthesise a five-member ring allene, followed by the studies of Ceylan *et al.*[123] in the same area, but unfortunately both attempts were unsuccessful.

Only the method of Doering-Moore-Skattebøl[126,136] was successfully applied in generating **(116b)**. Backes *et al.* reported that the treatment of 3-bromo-3-fluorotricyclo[3.3.0.0^{2,4}]octane **(116a)** with methyl lithium in the presence of furan, gave rise to the tetracyclic product **116c**, which is obviously a [4+2]-cyclo-adduct of furan to the 1,2-cyclopentadiene derivative **(116b)**.[124]
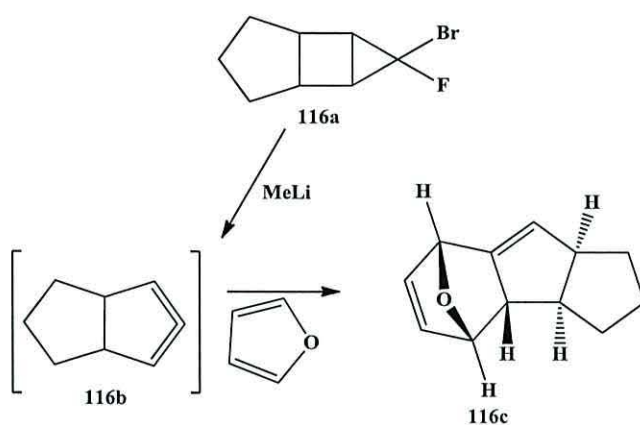
Figure 77: Five-member ring allenes

3.6.2   Six-membered ring allenes

Several attempts have been made to synthesise six-membered cyclic allenes such as the parent **(117c)**, including those of Favorskii *et al.*,[122] Wittig[125], Moore and Moser,[126,127] and Johnson.[117] The allene was an intermediate in the reactions, but the main products were a non-volatile oligomer,[128] or a dimerisation product; in other cases trapping was used to prove allene formation.

Favorskii *et al.*, tried to synthesize unsubstituted cyclohexa-1,2-diene **(117c)** in 1935.[122] They claimed that dehalogenation of 1-chlorocyclohexene **(117a)** and dichloro derivative **(117b)**

forms a non-volatile oligomer [128] and the intermediate in these two reactions is cyclohexa-1,2-diene (**117c**) (Scheme below).
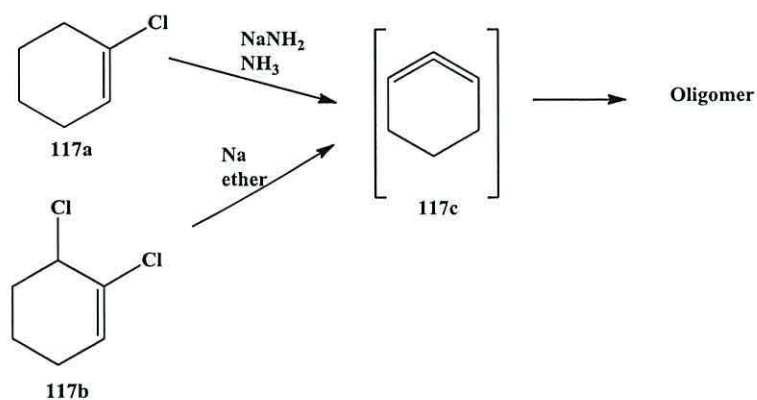
Scheme 29: Cyclohexa-1,2-diene (117c)

Christl *et al.*[129] were successful in preparing an enantiomerically pure precursor of a six-membered cyclic allene. The reaction involved dissolving the starting material (**123**) in 2,5-dimethyl-2-*tert*-butyl-5-methyl- or 2,5-*bis*(*tert*-butyl)furan, then treating the mixture with methyllithium, which gave rise to the chiral [4+2]-cycloadducts of (**124**) and (**125**) (Scheme 30).
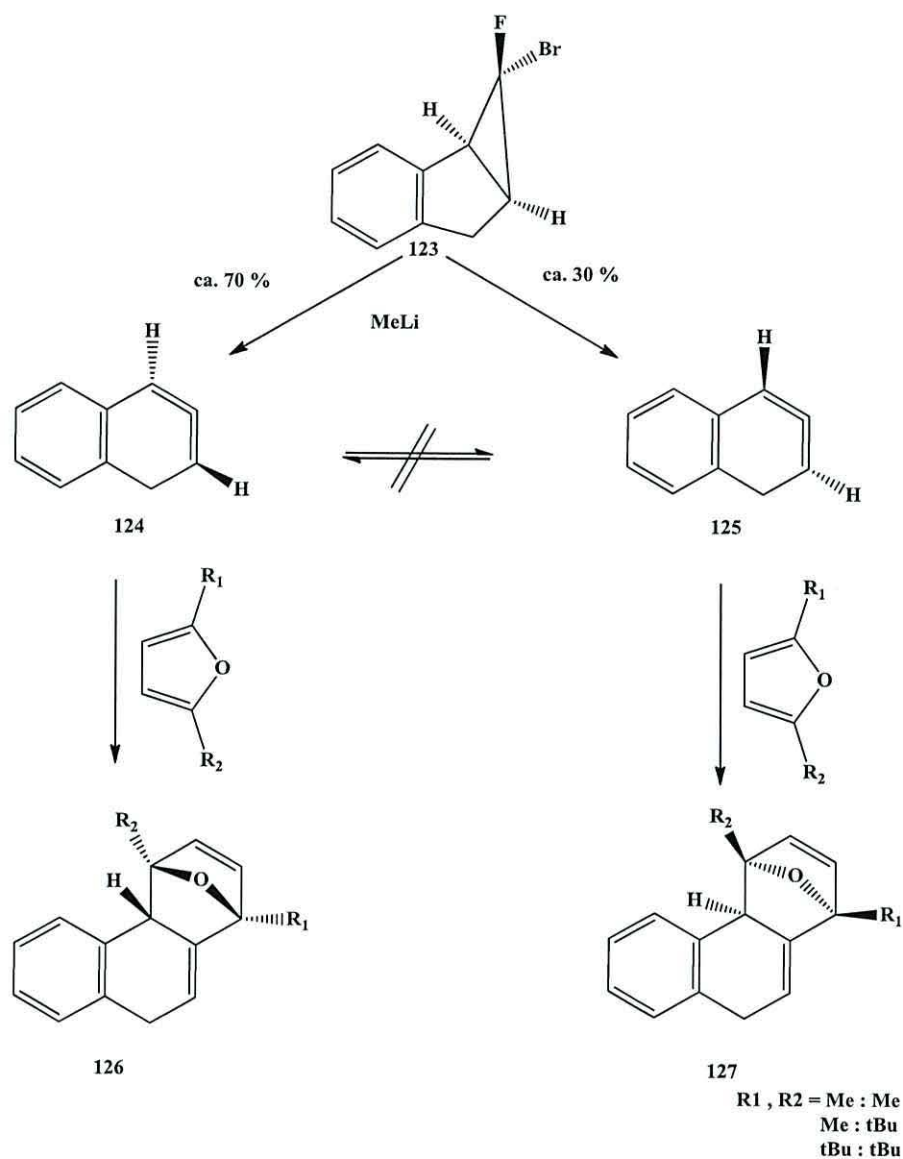
Scheme 30: A chiral molecule six membered cyclic allene

3.6.3 Seven membered ring allenes

An enormous amount of work has been dedicated to seven-membered cyclic allenes, but this still presents some problems, because the final step generally gives several other compounds; for example, Favorskii in 1936 tried to synthesise cyclohepta-1,2-diene (130) by treating 1-bromo-2-chlorocycloheptene (129) with Na in ether.[122] He suggested that the reaction yielded a dimer (131), and this result remained unchallenged until the work of Ball and Landorin 1961,[130] who isolated the same dimer by the dehydrohalogenation of 1-

chlorocycloheptene (**128**). They confirmed that cyclohepta-1,2-diene is too reactive to be isolated.[125, 130]
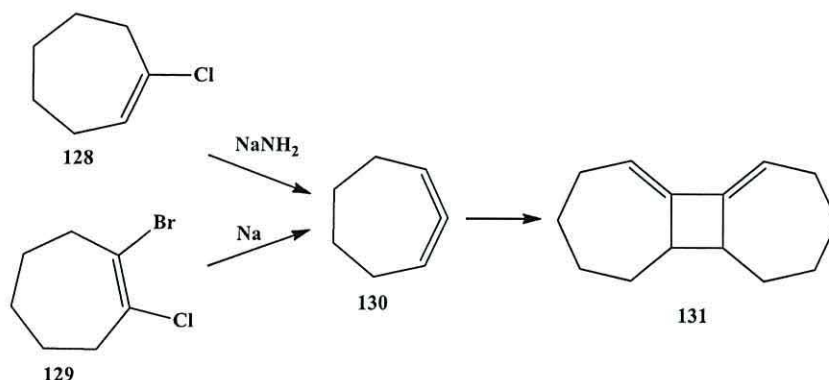
Scheme 31: Dimerisation of (130)

Another method was used by Köbrich and Goyert[131] and Schleyer *et al.*[132] The reaction of dibromonorcarane with MeLi led to insertion products of the intermediate cyclopropylidene, (**132**) and (**133**), instead of the required allene (**134**).
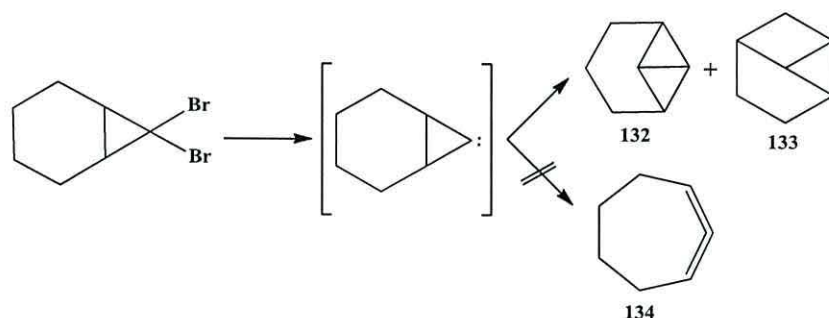
Scheme 32: Examples of intermolecular C-H-insertions

3.6.4 Eight membered ring allenes

An attempt to synthesise cycloocta-1,2-diene (**139**) was undertaken in 1961 by Ball and Landor.[130] They reported that the allene dimer (**140**) was could be separated from the dehydrohalogenation of 1-chlorocyclooctene (**136**). A carbenoid method was applied by Marquis and Gardner[133] for the formation of the same allene (**139**), which involved treating 8,8-dibromobicyclo[5.1.0]octane (**138**) with MeLi. Moreover, Kropp *et al.*

described the formation of cycloocta-1,2-diene[134] as an intermediate in the photolysis of vinyl iodide (137) in methanol.
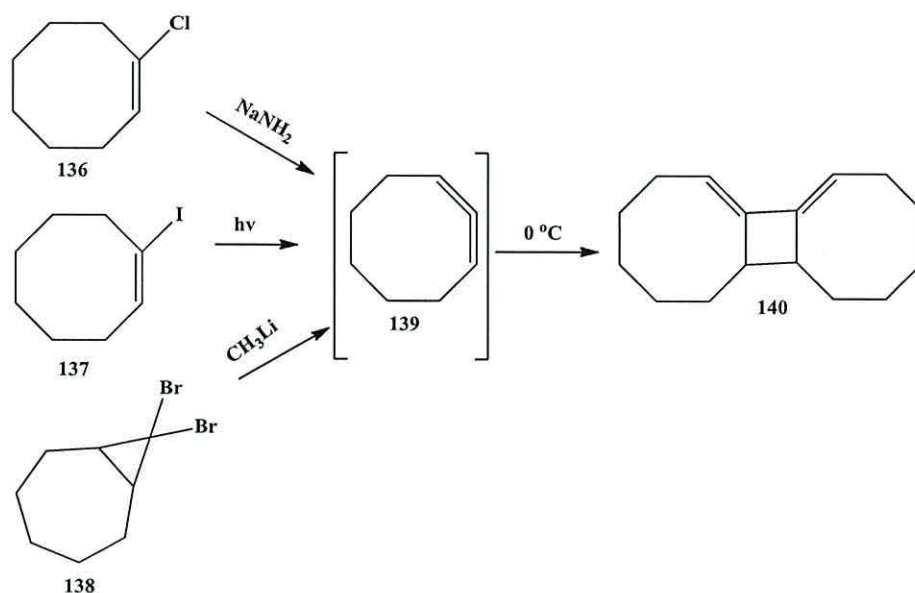
Scheme 33: Dimerisation of (139)

3.6.5 Nine membered ring allenes

The first study of the synthesis of cyclonona-1,2-diene was done by Blomquist *et al.*[135] in 1951. They suggested that this cyclic allene is a distillable liquid at room temperature. After that, Skattebøl succeeded in preparing this allene in a high yield by the ring expansion of cyclooctene (143).[136] The cyclonona-1,2-diene allene dimerises easily upon heating to 150 °C.
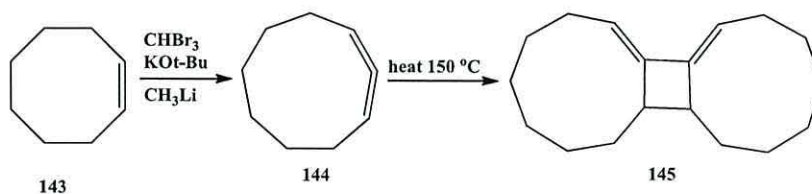
Figure 78: Dimerisation of cyclonona-1,2-diene

3.7   Cyclic *bis*-allenes:

Bis-cyclic allenes in general contain two sets of cumulated double bonds. Skattebøl[136] succeeded in preparing cyclodeca-1,2,6,7-tetraene (**148**) as an example of this type of allene by treating 5,5,10,10-tetrabromotricyclo[7.1.0.0^{4,6}]decane (**147**) with methyllithium.[137] Skattebøl's method also succeeded for the synthesis of sixteen-member ring allenes; thus treating 8,8,16,16-tetrabromotricyclo[13.1.0.0^{7,9}]hexadecane (**149**) with methyllithium at -40 °C gives cyclohexadeca-1,2,9,10-tetraene (**150**).
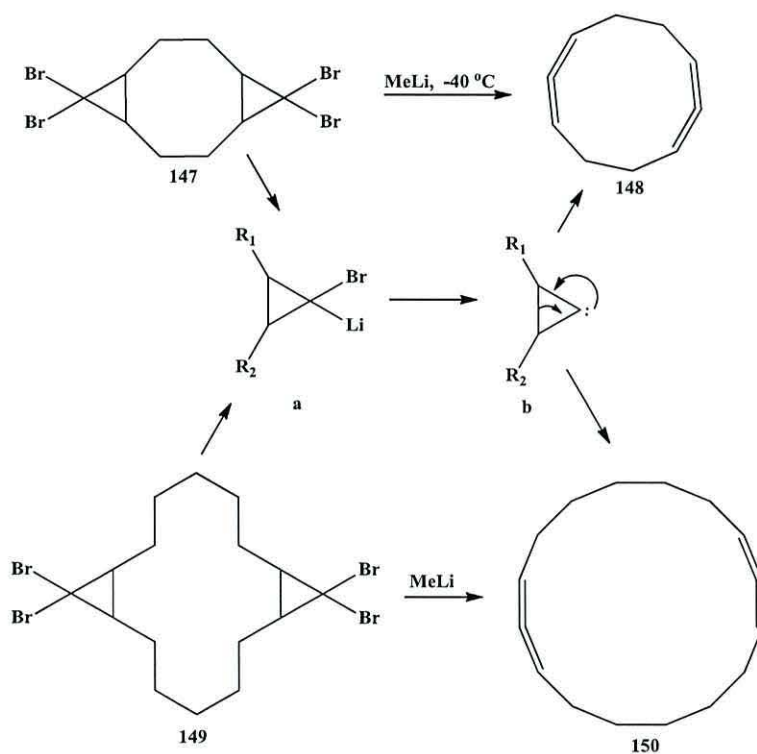
Scheme 34: Preparation of bis-cyclic allenes

A synthesis of cyclodeca-1,2,5,6-tetraene was reported by Baird and Reese. The *bis*-allene was generated by the same process, treating 4,4,10,10-tetrabromotricyclo[7.1.0.0^{3,5}]-decane (**154**) with methyl lithium in ether at 25-30 °C.[138]
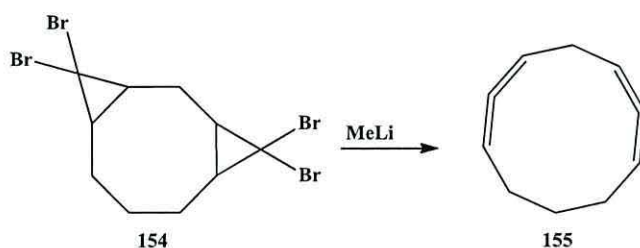
Figure 79: Synthesis of cyclodeca-1,2,5,6-tetraene (155)

Also, Baird and Reese[138] reported that the treatment of (3Z,5Z)-9,9-dibromobicyclo-6.1.0-nona-3,5-diene (**156**) with methyl lithium in ether at 25-30 °C led to the allene dimer (**157**) in 80% yield, though none of the monomeric allene (**146**) being detected. However, when the reaction temperature was kept below -40 °C, and the products worked-up also at low temperature, allene (**146**) was obtained as the major product.
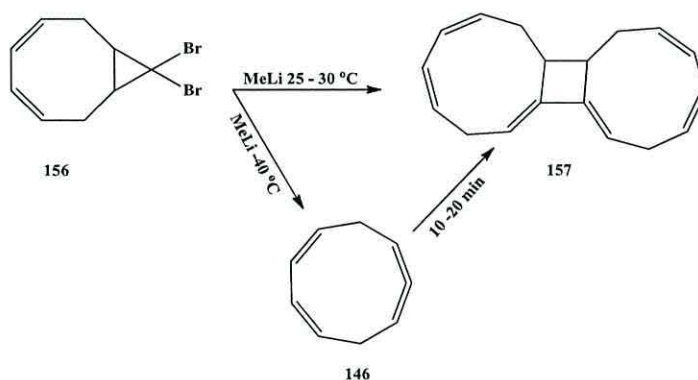
Figure 80: Synthesis of allene dimers

3.8   The aim of the present study

The synthesis of cyclic allenes is of considerable interest in organic chemistry because of the high strain and reactivity of these species. However, studies on cyclic *bis-* and *tris-*allenes are limited when compared with the cyclic mono-allenes. In this part of the study we were successful in obtaining novel cyclic allenes where the allene bonds are located in an eleven and twelve-membered ring, starting with cyclononatriene followed by ring expansion of the resulting *bis-* and *tris-*dibromocarbene adducts. Firstly, by using a triple cyclopropylidene–allene rearrangement, two diastereomers of the *tris-*allene, cyclododeca-1,2,5,6,9,10-hexaene, were obtained. Secondly, a mixture of meso and racemic cycloundeca-1,2,5,6,9-pentaenes and their derivatives was obtained.

3.9   Results and discussion

3.9.1   Preparation of *tris-* and *bis-*dibromocarbene adducts of cyclonona-1,3,5-triene

This part of the study focuses on the application of (1*Z*,4*Z*,7*Z*)-cyclonona-1,4,7-triene (**56**) as a starting material to prepare 4,4,8,8,12,12-hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]-dodecane (**158**). This *tris-*adduct (**158**) has been prepared before using bromoform and potassium *t*-butoxide, with benzene as a solvent.[138] In order to avoid the use of benzene, which is known to be carcinogenic, an alternative method was sought. The method employed entailed a biphasic system under P.T.C. The reaction used in this preparation is an important and common reaction, which involves dihalocarbene addition to alkenes. Dihalocarbenes are electrophilic, and they react preferentially with the most nucleophilic double bond in a given molecule. 4,4,8,8,12,12-Hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]-dodecane (**158**) (and its enantiomer) was first synthesised in 73% yield, via dibromocarbene addition to the alkene bonds, using bromoform in the presence of sodium hydroxide as a base under phase transfer conditions. The mixture was stirred for 24 hrs, and the isolated reaction residue consisted of two products; *tris-*adduct (**158**), and *bis-*adduct 4,4,11,11-tetrabromo-tricyclo[8.1.0.0^{3,5}]undec-7-ene (**159**). The reaction was repeated several times, and it was found that both the reaction time and the quantity of bromoform affected the ratio of products. For example, a prolonged reaction time led to a

higher yield of *tris*-adduct, while decreasing the reaction time led to the appearance of the *bis*-adduct.
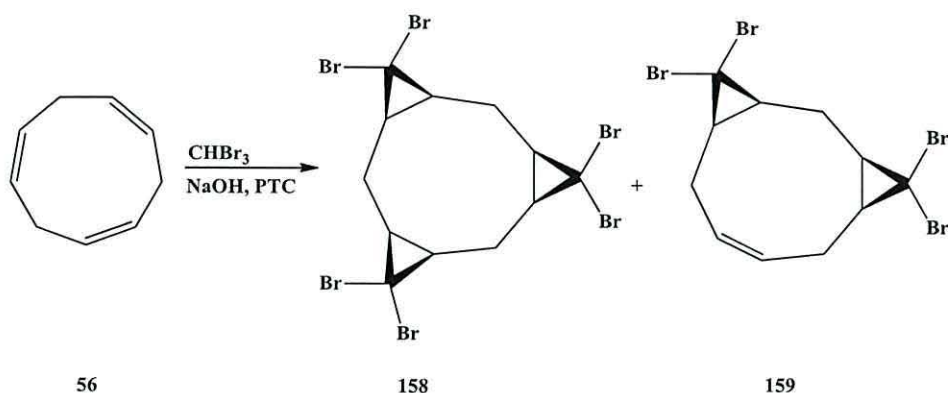
Scheme 35: Preparation of tris- and bis-adducts

The stereochemistry of the *tris*-adduct (**158**) had confrmed by the NMR spectropy. The ¹H NMR showed only one three-hydrogen doublet (see below) corresponding to the *trans*-protons of the methylene group between the cyclopropanes, while, the dept-NMR spectrum (DEPT with quaternary carbons using gradients (deptqgpsp.2)) of (**158**) showed just three lines at δ 32.4, 31.7, and 24.6 (Figure 81), which confirmed the stereochemistry as being all *cis* and there being just three carbons in different environments.
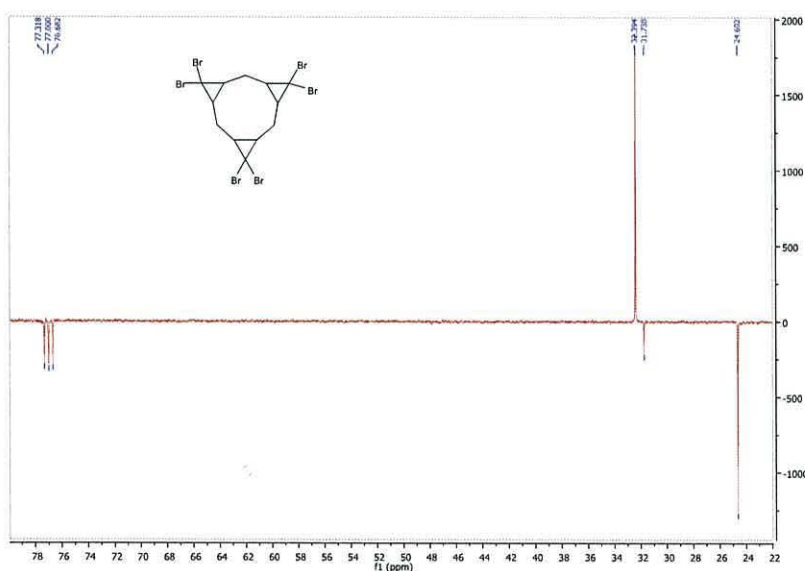
Figure 81: dept-NMR spectrum of (158)

There was no difference in the shapes and line separations of the signals when the solvent was changed from CDCl$_3$ (Figure 82a) to C$_6$D$_6$ (Figure 82b), other than a small high-field shift.

<center>a</center>

<center>b</center>
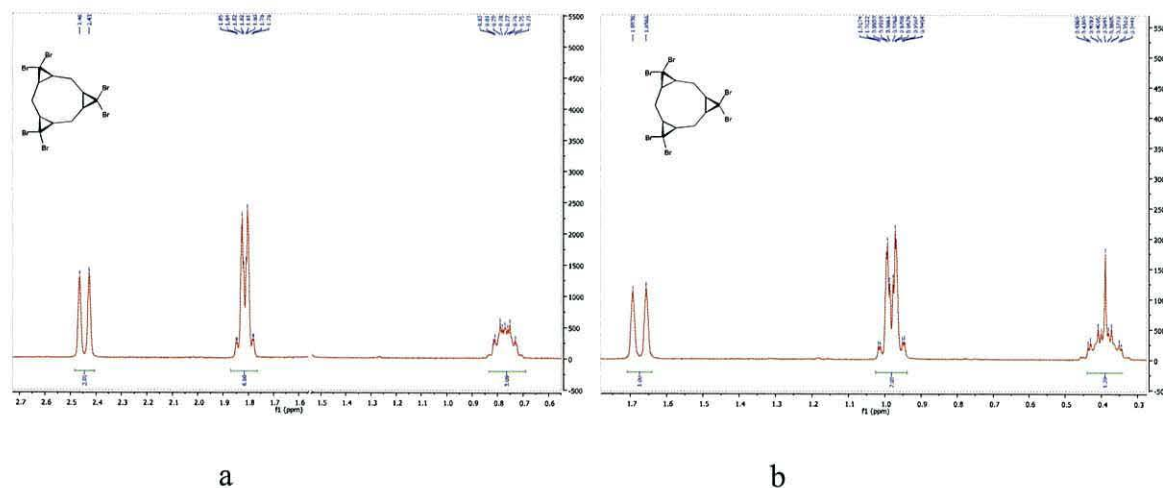
<center>***Figure 82: The ^{1}H NMR spectrum of (158), a- in CDCl$_3$ and b- in C$_6$D$_6$***</center>

The ^{1}H NMR spectrum of the *tris*-adduct in C$_6$D$_6$ showed a doublet at δ 1.68 ppm for one hydrogen of the methylene group between the cyclopropanes, coupled only to the geminal proton, while the latter proton appeared at δ 0.39 as a complex single-hydrogen multiplet, in this case coupled to the adjacent cyclopropane hydrogens. The coupling constant between the *trans*-methylene hydrogen and the adjacent cyclopropane proton for these compounds is essentially zero, due to the angle between them, which is around 90 °. This was confirmed by selective decoupling of the signal at δ 0.39 which caused the doublet at δ 1.68 to become a singlet (Figure 83).

<center>a</center>

<center>b</center>
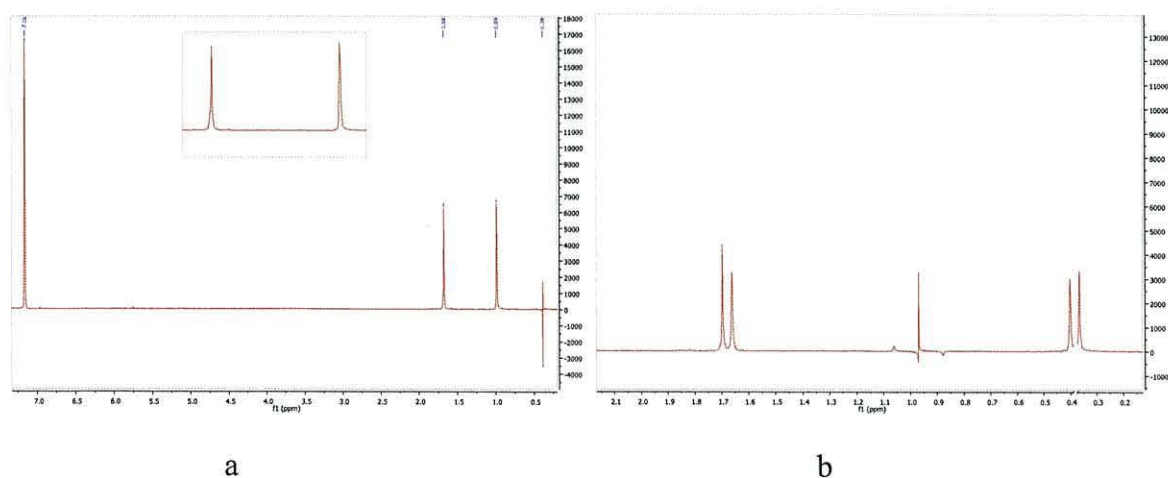
<center>***Figure 83: Selective decoupling of tris adduct (158): a- at δ 0.39, b- at δ 0.97 ppm***</center>

In addition, the COSY NMR spectrum (Figure 84) showed that one hydrogen of the methylene group between the cyclopropanes at δ 1.68 coupled only to the geminal proton, while the second proton appeared at δ 0.39 as a complex multiplet, because in addition to the geminal coupling, it coupled to the adjacent cyclopropane hydrogens

Figure 84: COSY NMR of tris adduct (158)

Another product of this reaction was (*Z*)-4,4,11,11-tetrabromotricyclo[8.1.0.0^{3,5}]undec-7-ene (**159**) (*bis*-adduct), which not been reported before. This is a likely intermediate in the formation of the *tris*-adduct. The latter appears as a white precipitate in dichloromethane, while the *bis*-adduct was soluble. The two products were separated by filtration, and evaporation of the filtrate gave *cis*-adduct (**159**).

Figure 85: The high field ^1H NMR of (159)

Figure 86: 4,4,11,11-tetrabromotricyclo[8.1.0.0³,⁵]undec-7-ene (159)

The proton NMR spectrum (CDCl₃) showed a broad signal as a pentet at δ 5.66, corresponding to the alkene protons. The stereochemistry of the *bis* adduct (**159**) was confirmed by the ¹H NMR spectrum, which showed a sharp doublet for the one hydrogen (H$_d$) of the methylene group between the cyclopropanes at δ 2.54, coupled only to the geminal proton, while the latter proton (H$_c$) appeared at δ 1.05 as a multiplet, in this case coupled to the cyclopropane protons. Two of the allylic hydrogens (H$_a$,H$_{a'}$) appeared as a double doublet at δ 2.4 with coupling constant (*J* 4.0, 13.5 Hz) which are coupled to the geminal and vinylic protons, but not to the adjacent cyclopropane protons. The other protons (H$_b$,H$_{b'}$) appear as a multiplet at δ 1.8. Finally, the cyclopropane protons appeared as a multiplet at δ 1.68 ppm. This was confirmed by the COSY experiment.

The spectrum clearly shows a sharp doublet for the one hydrogen of the methylene group between the cyclopropanes at δ 2.54, coupled only to the geminal proton, while the latter proton appeared at δ 1.05 as a complex single-hydrogen multiplet, in this case coupled to the adjacent cyclopropane hydrogens. The fact that the two hydrogens are not equivalent to each other confirms the *cis*-stereochemistry of the meso-compound (**159**) as the trans-isomer would have an axis of symmetry, and equivalent hydrogens at this position.
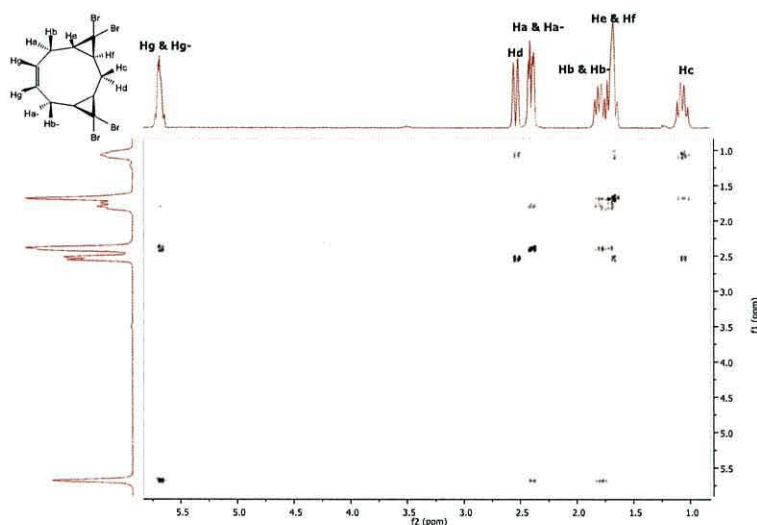
Figure 87: COSY NMR of bis adduct (159)

Selective decoupling in CDCl₃ of the signal at δ 5.6 caused the signal at δ 2.40 to appear as a doublet and the signal at δ 1.8 to be simplified. This confirmed that there is coupling between both hydrogens of the methylene with the alkene proton, in addition to the geminal coupling.

Moreover, when the spectrum was run in C_6D_6, the high field signals were shifted upfield from δ 2.54 to δ 1.85 and the peak between 1.8-1.6 in CDCl₃ was split into three two-hydrogen signals (multiplets, triplet and triplet at δ 1.40, 1.19, and 0.98 respectively). Additionally, the *cis*-hydrogen of the methylene group between the cyclopropanes appeared as doublet of triplets at δ 0.75.
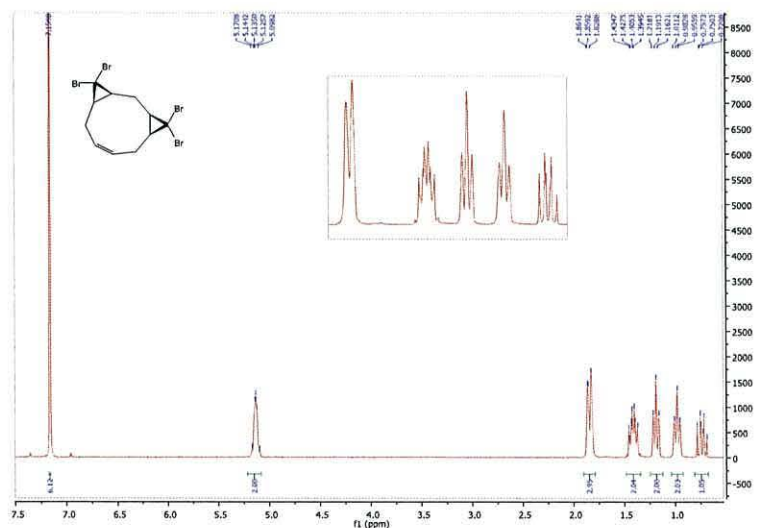
Figure 88: The ¹H NMR spectrum of (159) in C_6D_6

Selective decoupling in C_6D_6 showed the effects upon the signals more clearly. Irradiation at δ 5.13 caused the signals at δ 1.85 to appear as a double triplet (*J ca.* 3.72, 14.76 Hz), the signal at δ 1.40 to appear as a broad triplet (*J ca.* 12.2 Hz), and the signal at δ 1.2 and 0.9 to appear as a triplet of doublets (*J ca.* 2.6, 10.7, 22.44 and 2.44, 11.64, 22.32 Hz) (Figure 89).
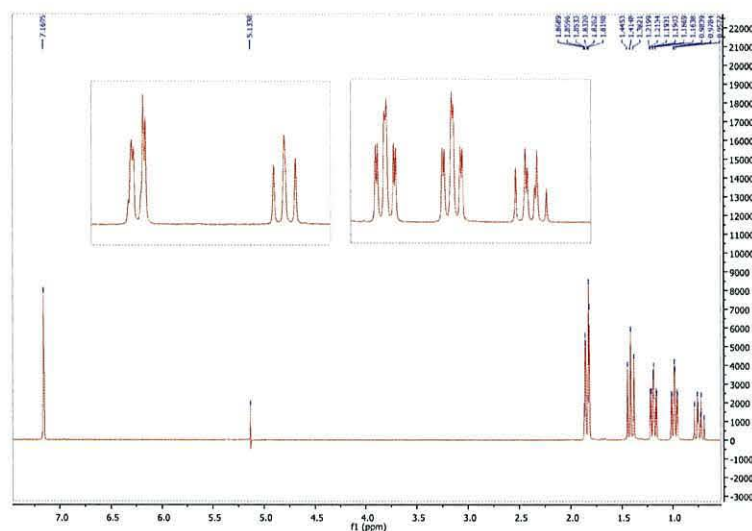
Figure 89: Selective decoupling NMR spectrum of (159) at δ 5.1 in C₆D₆

3.9.2 Attempted synthesis of cyclic *tris*-allenes

The 4,4,8,8,12,12-hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]dodecane **(158)** prepared as described above was then used to synthesise the corresponding allene, cyclododeca-1,2,5,6,9,10-hexaene.

The synthesis of some cyclic allenes has been discussed above (Section 3.6). For example, the reactions of *bis*-dibromocarbene adducts of *cis,cis*-cycloocta-1,5-diene or cyclotetradeca-1,9-diene with methyl lithium are known to give the corresponding *bis*-allene exclusively as one diastereoisomer, the meso-form in the case of the smaller ring. Dehmlow showed that either *syn*- or *anti-bis*-dibromocarbene adducts of cyclo-1,5-octadiene give the same stereoisomer of allene and proposed that, when the initial alkene contains a relatively small ring, the reaction will be controlled by strain and be highly stereoselective. [137] Moreover, it is known that either *syn*- or *anti*-isomers of the tetrabromo-dicyclopropanes derived by the addition of two molecules of dibromocarbene to 1,1,6,6-

tetramethoxy-*cis,cis*-cyclodeca-3,8-diene react with methyllithium to yield a 1:2 mixture of the racemic and meso- forms of the diallene, 1,1,7,7-tetramethoxycyclododeca-3,4,9,10-tetraene.

The ring opening of cyclo-propylidenes formed by the reaction of dibromocyclopropanes with methyllithium is an extremely fast process. In this case, reaction of, 4,4,8,8,12,12-hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]dodecane (**158**) with methyllithium, in ether at -40 – 0 °C led to a mixture of (**161**) and (**162**) in a ratio of ca 1:3.
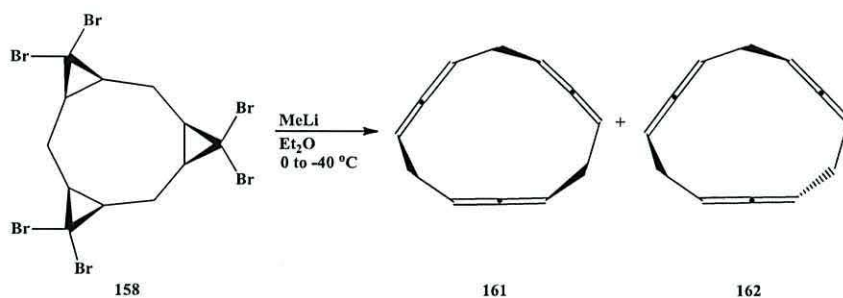
Figure 90: Synthesis of R,R,R-(161) and R,R,S (162) (each as racemate)

The ^{1}H NMR spectrum of the crude product showed two multiplets at δ 5.25 and δ 2.60 and showed no signals corresponding to the starting material (Figure 91); indeed there was no evidence for products other than the allenes. The ^{13}C NMR spectrum included a signal at δ 206 which confirmed the formation of the allene. Further confirmation was provided by the I.R. spectrum, which showed a peak at 1996 cm^{-1} characteristic of the C=C=C stretch of an allene.
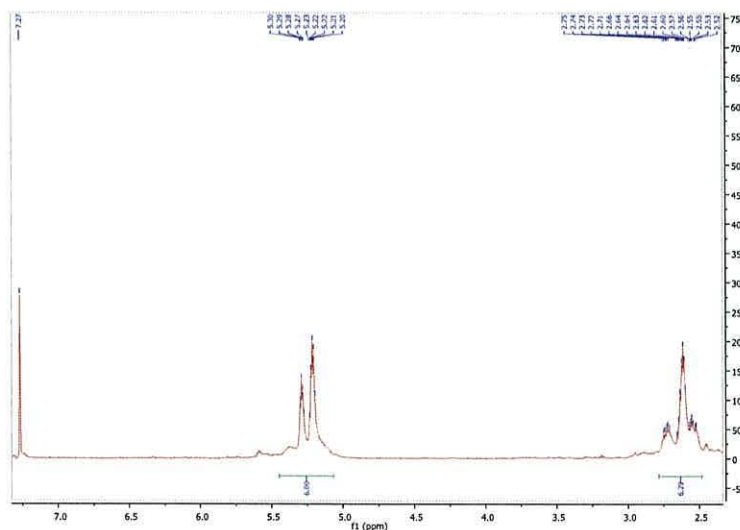
Figure 91: The ^{1}H NMR spectrum of the crude tris-allene

Hydrogenation of the mixture using 5% Pd/C as catalyst yielded a single product, cyclododecane (90%), which showed only one signal at δ 1.4 ppm in its ^{1}H NMR spectrum, while the ^{13}C NMR spectrum showed just a singlet at δ 23.6 ppm.

Little is known about these allenes, except for some calculations of the shape and energy, that predict a C_3 symmetry for the former (**161**) and C_2 or, more probably, C_1 symmetry for the latter (**162**). Computer modelling has been used in these studies.[138]

The formation of (**161**) and (**162**) would appear most likely to occur by three sequential lithium-bromine exchanges and cycloproylidene-allene rearrangements. The first of these would produce a 1:1 mixture of *R*- and *S*- mono allenes; if there is no control by the stereochemistry of the second process, this would statistically produce 1:1 mixture of *RR* (*SS*)- and *RS* (*SR*)- *bis*-allene, and the third a 1:3 mixture of *RRR* (*SSS*)- and *RRS* (*SSR*)- allen. This is close to the observed ratio.

The isomeric allenes could be partially separated by selective crystallisation from methanol, with the minor isomer being isolated as a white crystallise solid. They were not separated by chromatography on silica gel but were separated by chromatography on silica gel impregnated with 5% silver nitrate (coordinated to the double bond). Silver nitrate complexes of a number of cyclic allenes, including cyclodeca-1,2,6,7-tetraene, have been reported.[139] Both methods gave a white solid of *R,R,R-tris* allene (**161**) (8%), m.p.: 53-55 °C, and the mass spectrum showed an accurate mass ion in agreement with $[C_{12}H_{12}+ H]^+$. The dept-NMR spectrum (CDCl$_3$) showed just three peaks at δ 27.8 (CH$_2$), 89.8 (CH), while the central allenic carbon peak was shifted downfield as expected and appeared at δ 206.5 (Figure 92). The I.R. spectrum showed the characteristic C=C=C stretching absorption at 1964 cm^{-1}.
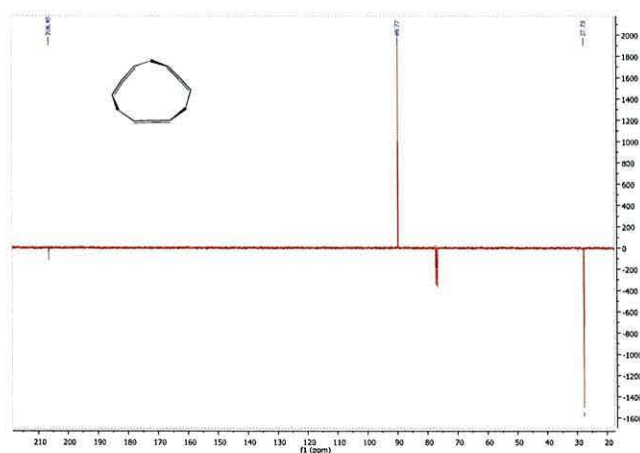
Figure 92: dept-NMR spectrum of (161)

The proton NMR spectrum in (CDCl$_3$) for (**161**), showed just two six-hydrogen multiplets for the allenic hydrogens centred at δ 5.29 and the methylene groups centred at δ 2.59, (Figure 93).
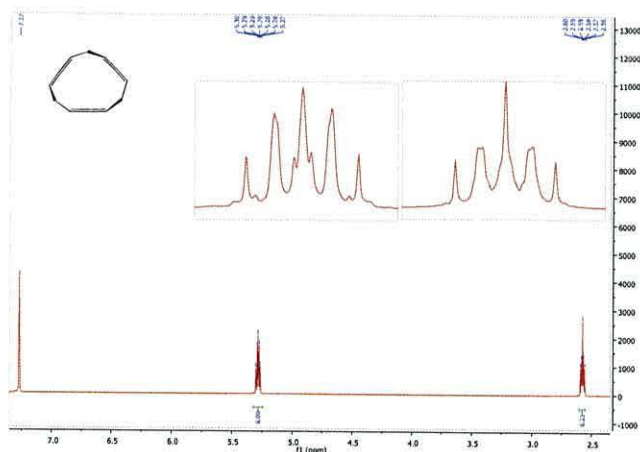
Figure 93: Proton NMR spectrum of (161)

The multiplets at first sight appeared to be complex pentuplets or triplets of triplets (*J ca.* 3.8, 4.0 Hz), though additional lines were also present, corresponding to non-first-order multiplets. There was no difference in the shapes and line separations of the multiplets when the solvent was changed from CDCl$_3$ to C$_6$D$_6$ or if the spectrum was run at 500 MHz rather than 400 MHz. Each multiplet had a width of 14.8 Hz between the major outer lines, and irradiation of the multiplet at δ 5.22 caused the signal at δ 2.62 to become a single line, and decoupling the peak at δ 2.6 also led to one singlet signal at δ 5.22.

There was no change when the spectrum was run at -45 °C in CDCl$_3$.

a   b
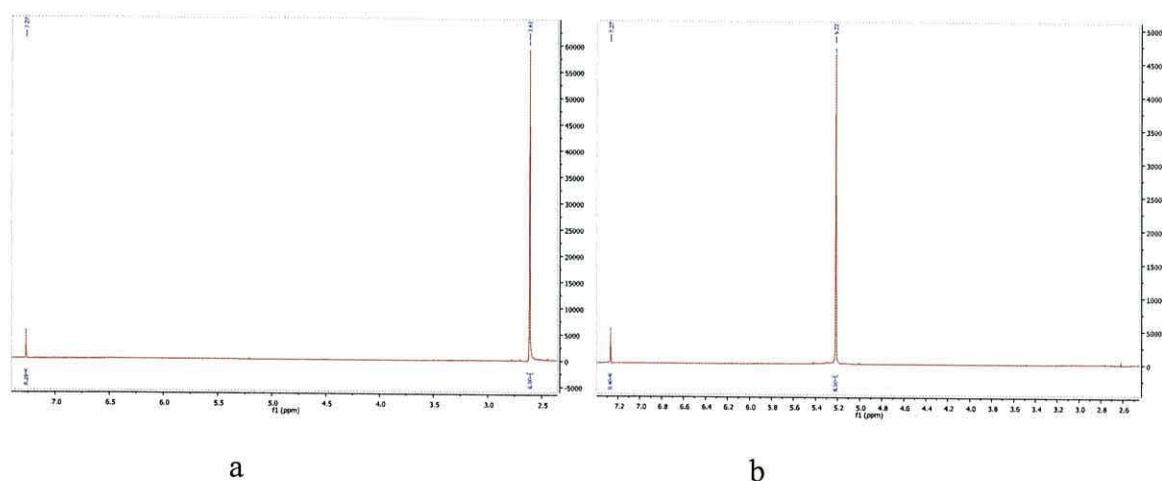
Figure 94: Selective decoupling NMR spectrum of (161): (a) at δ 5.2, (b) at δ 2.6

The spectra were consistent with those expected for a molecule (**161**) with D_3 symmetry (at least on the NMR timescale – even at at -45 °C) in which there are three allenes of the same absolute stereochemistry (Figure 95), showing six chemically equivalent but magnetically inequivalent hydrogens and in which the six hydrogens of the methylene groups are also chemically equivalent but magnetically inequivalent, each one having the opposite combination of a pair of dihedral angles to the two adjacent allenic hydrogens. The molecule appears in solution to have a three-fold axis of symmetry as seen in Figure 95a, and three C_2 axes, one of which is shown in Figure 95b.

(a)   (b)

(c)
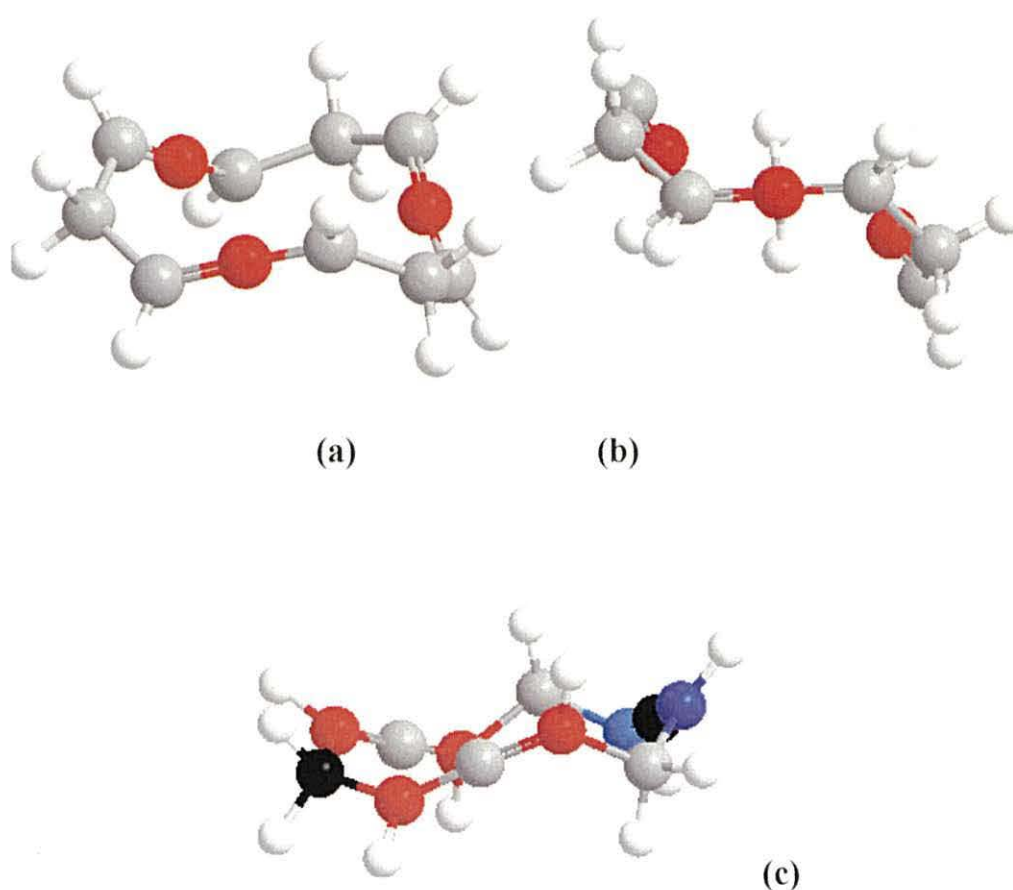
Figure 95: (a) A model of R,R,R-161 with D3 symmetry; the C3 axis is vertical through the centre of the molecule. The central allene carbons are shown in red; (b) showing one of three C₂ axes through the front central allenic carbon and the (back) opposite methylene group. The symmetry axes are shown on the structure in the ESI. (c) R,R,S-162 with the R-allene segments in red and the S-allene segment in blue and showing the C2 axis between the methylene group and the centre carbon of the S-allene (black).

In addition, preliminary calculations at a semi-empirical level representing a D_3 structure of (**161**) revealed a molecule having a central cavity with a HOMO providing a triple co-ordination site on each face[138] (Figure 96 a and b). In each fragment $=CH_x–CH_aH_{a'}–CH_{x'}=$, the H_a has a dihedral angle of approximately 23° to H_x and 92° to $H_{x'}$, and $H_{a'}$ has a dihedral angle of approximately 23° to $H_{x'}$ and 92° to H_x.

(a)   (b)
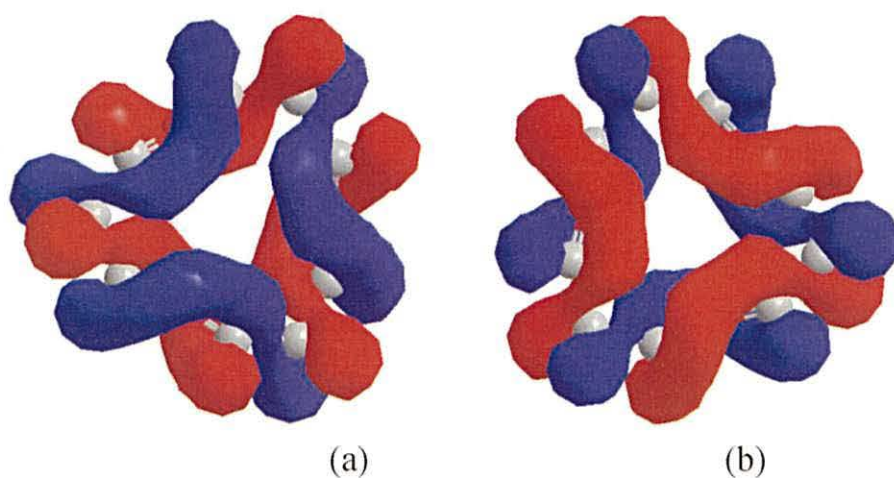
Figure 96: (a) and (b) The calculated HOMO orbital of a D₃ model of 161 seen from opposite faces.

Finally, X-Ray crystal structure analysis of *tris*-allene was carried out to determine its exact conformation in the solid state (Figure 97).
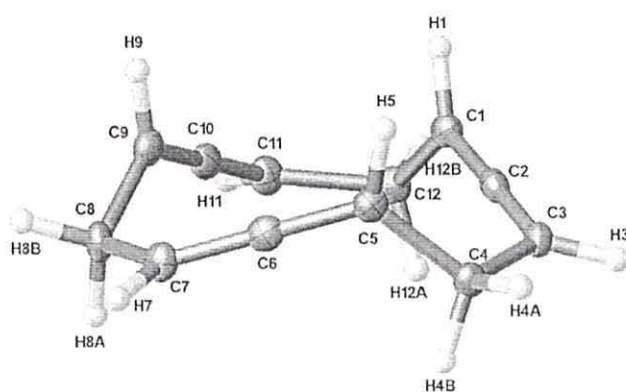
Figure 97: Single crystal X-Ray structure of (161)

As can be seen from the X-ray structure, the stereochemistry of the allene remains very similar as that observed in solution (see Figure 95). An analysis of the crystal structure shows that the bond angles are consistent with a somewhat distorted C_3-structure rather than D_3 (see Table 7).

Thus the H-C-C-H angles around the structure are slightly different for each methylene group. The distortion may simply reflect the fact that the crystal was not of the highest quality. Nonetheless, the solid state structure appears to be different to that in solution. It would be interesting to determine the gas structure by electron diffraction.

Atom No.	H-C-C-H Angle
H_{4A}-H_3	28
H_{4B}-H_3	84
H_{4A}-H_5	54
H_{4B}-H_5	167
H_{8A}-H_7	88
H_{8B}-H_7	75
H_{8A}-H_9	50
H_{8B}-H_9	165
H_{12A}-H_{11}	37
H_{12B}-H_{11}	81
H_{12A}-H_1	52
H_{12B}-H_1	171

Table 7: Bond angles of the crystal of (161)

The second component which was separated from (**158**) on silica gel/AgNO₃ was *R,R,S-*cyclododeca-1,2,5,6,9,10-hexaene (**162**) (and its enantiomer) which was obtained in 37% yield. This showed NMR spectra which were consistent with a molecule (**162**) having C_2 symmetry on the NMR timescale (Figure 95c).

The carbon NMR spectrum in CDCl₃ showed two signals for two methylene groups together at δ 27.7, δ 28.2 in ratio (2:1) respectively (Figure 98), with three signals at δ 91.7, δ 90.2 and δ 89.8 (all CH), and δ 206.7 and 205.8 for the central carbons of the allenes. This means all the methylene groups, centeral carbons and terminal CH groups are different. The proton NMR spectrum in CDCl₃ showed three two hydrogen multiplets in the range δ 2.5 – 2.8, a two hydrogen multiplet at δ 5.2 and a four hydrogen multiplet at δ 5.3 ppm (Figure 98). When the proton NMR was run in C₆D₆ solution, the signals in the allenic region were split into three complex two-hydrogen multiplets, corresponding to the three types of allenic hydrogen (Figure 99), which confirms that mentioned above, that all the allenic CH are not the same.
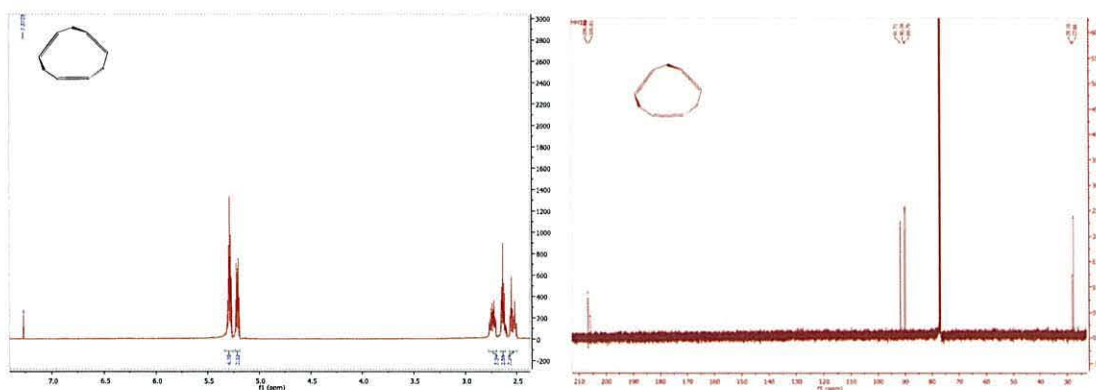
Figure 98: Proton & carbon NMR spectra of (162) in CDCl₃
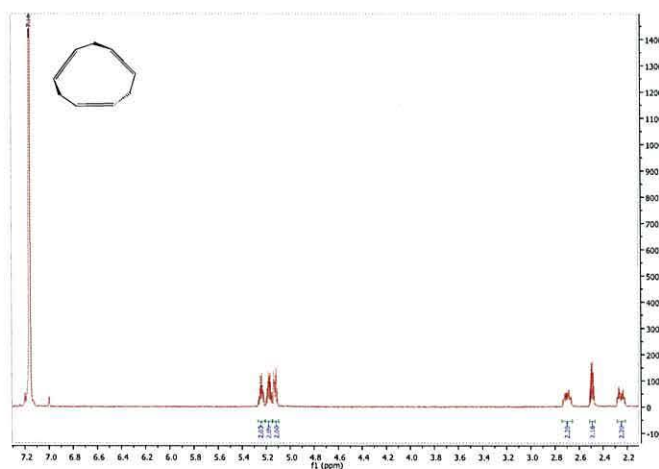
Figure 99: The proton NMR spectrum of (162) in C₆D₆

3.9.3 Synthesis and trapping of *bis*-cyclic allene:

As discussed above, 4,4,11,11-tetrabromotricyclo[8.1.0.0^{3,5}]undec-7-ene (**159**) was obtained, by adding bromoform to *cis,cis,cis*-cyclonona-1,4,7-triene (**56**) under phase transfer conditions.

The same efficient reaction used before was applied to synthesise *bis*-allenes. It was attempted to synthesise (Z)-cycloundeca-1,2,5,6,9-pentaene by treating *bis*-adduct (**159**) with methyllithium in dry ether at room temperature. The reaction proceeded via lithium-bromine exchange, followed by the formation of a cyclopropylidene and, finally, rearrangement and ring-opening to allenes. The product was obtained as a mixture of two allenes (**172**) and (**173**), in a ratio of 2.0:2.5 by proton NMR.
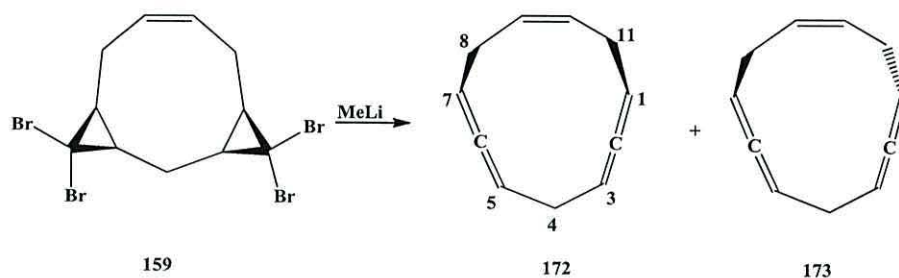
Scheme 36: Synthesis of (R,R and R,S-Z)-Cycloundeca-1,2,5,6,9-pentaene

This result was confirmed by observing the NMR spectrum, which showed two sets of signals in the proton NMR spectrum, each integrating overall to six hydrogens one in the region of alkene hydrogens the other in the region of bis-allylic hydrogens. No cyclopropane signals were observed at high field.
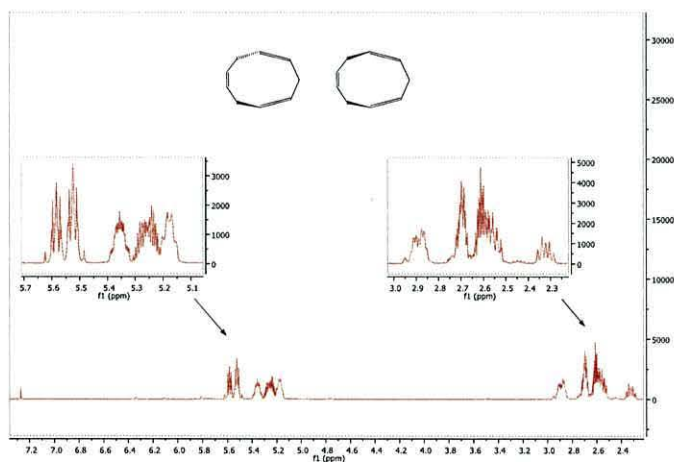
Figure 100: The 400 MHz ^{1}H NMR spectrum for the crude mixture of bis-allenes at room temperature

The reaction was repeated several times to prove that the first allene (**172**) was unstable at 20 °C compared to the minor isomer allene (**173**), which could be isolated pure after the complete rearrangement of (**172**) in the mixture by column chromatography.

Compound (**173**) could be characterised by the presence of six signals in the ^{13}C NMR spectrum, three for the allenes at δ 207.0, 91.2, and 90.6, one for the alkene at δ 127.9, and two for the methylene groups at δ 26.4 and 26. The proton NMR spectrum (Figure 101) is discussed in detail later.
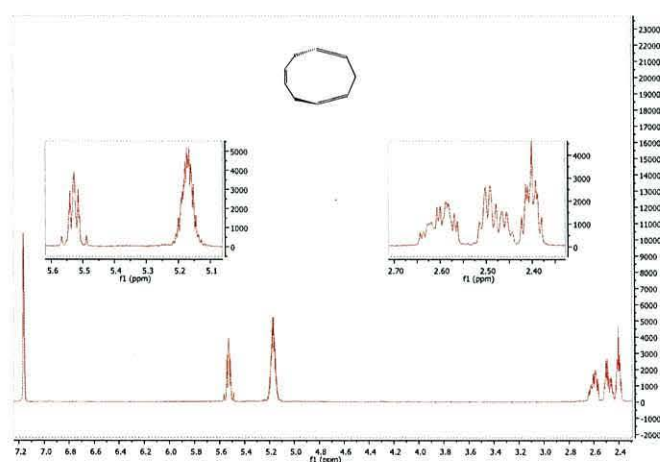
Figure 101: The ^{1}H NMR spectrum of stable bis-allene (173)

The other expected *bis*-allene (**172**) could be distinguished if the signals for (**173**) were subtracted from those of the crude mixture of allenes. In this way, three two hydrogen

multiplets were seen at δ 5.65, 5.45 and 5.25 in CDCl₃, together with a two hydrogen mutiplet at δ 2.95, a three hydrogen multiplet at δ 2.6. Importantly, there was a one hydrogen double triplet at δ 2.4 (*J* 14.7, 7.5 Hz); this can be assigned to one of the protons of the methylene group in the (*R,S*)-isomer, allene (**172**), which has a plane of symmetry on the NMR timescale (the second proton is presumably under the signal at δ 2.6).

a   *b*
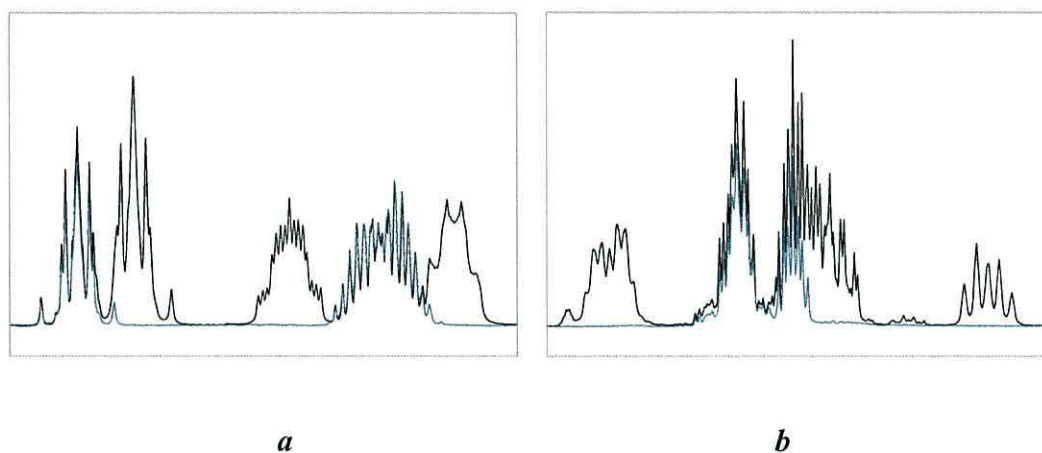
Figure 102: ¹H NMR spectrum (400 MHz, CDCl₃) for mixture of two allenes (172 and 173): a- low-field region, b- high-field region

The NMR spectra showed that the allene (**172**) signals began to change within 5 min at 20 °C until they disappeared completely, while new signals appeared. Therefore, in later experiments, the reaction was quenched with water at -40 °C. It was also demonstrated that the best condition which can be used for the storage of the product is -80 °C, since, at this temperature, the mixture remained stable for more than 90 days.

The mixture of allenes was allowed to stand in the NMR spectrometer in CDCl₃ and the spectrum taken at regular intervals. The new signals that appeared suggested that two compounds (**174**) and (**175**) formed over several hours; at the same time, the signals corresponding to allene (**172**) became smaller. Over the next 18 hours, the signals for allene (**172**) disappeared completely, while those for the first product reached a maximum and then also decreased; by the end of this time, the signals for the first product (**174**) had been completely replaced by a further product, (**176**) as shown below.
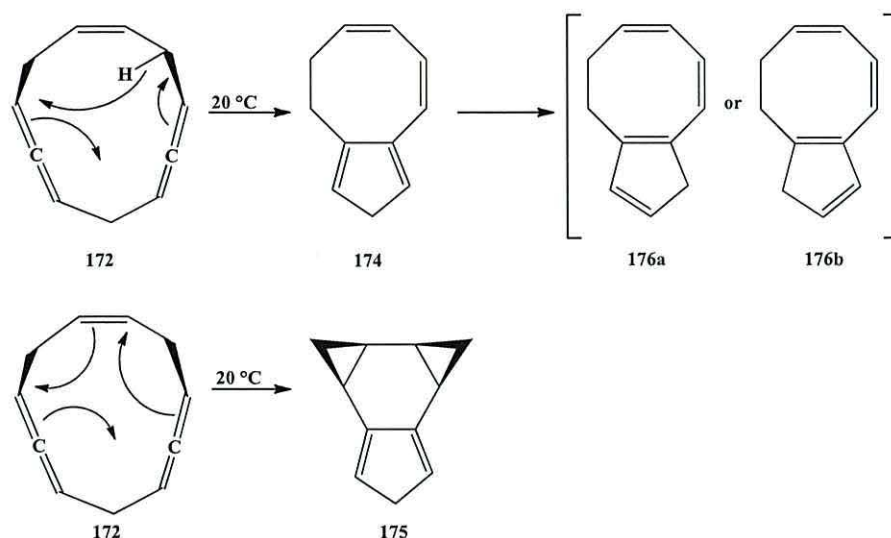
Scheme 37: Re-arrangement of (R,R-Z)-cycloundeca-1,2,5,6,9-pentaene (172).

After 24 hrs, compound (174) had disappeared completely and the signals for cyclopentadiene (176a) had begun to grow via a second [1,5]-sigmatropic shift. This was confirmed by NMR analysis, which showed six single hydrogen signals in the alkene region. Two double triplets were seen at δ 6.49 (*J* = 5.2, 1.6 Hz) and 6.38 (*J* = 5.2, 1.5 Hz) for H-9 and H-10 of the cyclo-pentadiene. The remaining four signals were a doublet at 6.19 (*J* = 12.2 Hz) for H5, coupled to a doublet doublet at 5.82 (*J* = 12.2, 3.8 Hz,), in turn coupled to a double doublet at 6.12 (*J* = 10.6, 3.8 Hz), in turn coupled to a double doublet at 6.06 (*J* = 10.6, 7.3 Hz). The alkene signals included a multiplet at 3.17 (m, 2H) for H-11 and H-11' as well as multiplets at 2.85 – 2.80 (m, 2H) and 2.66 – 2.59 (m, 2H), which were identical to those reported in the literature.[139]
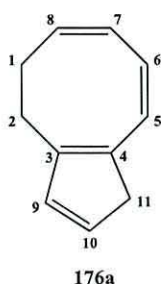
Figure 103: Cyclopentadiene (176a)
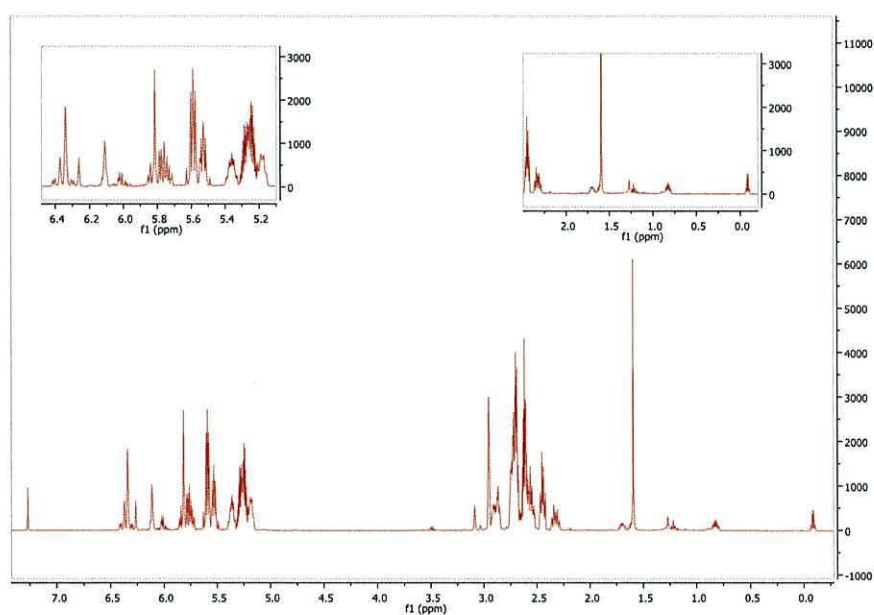
a
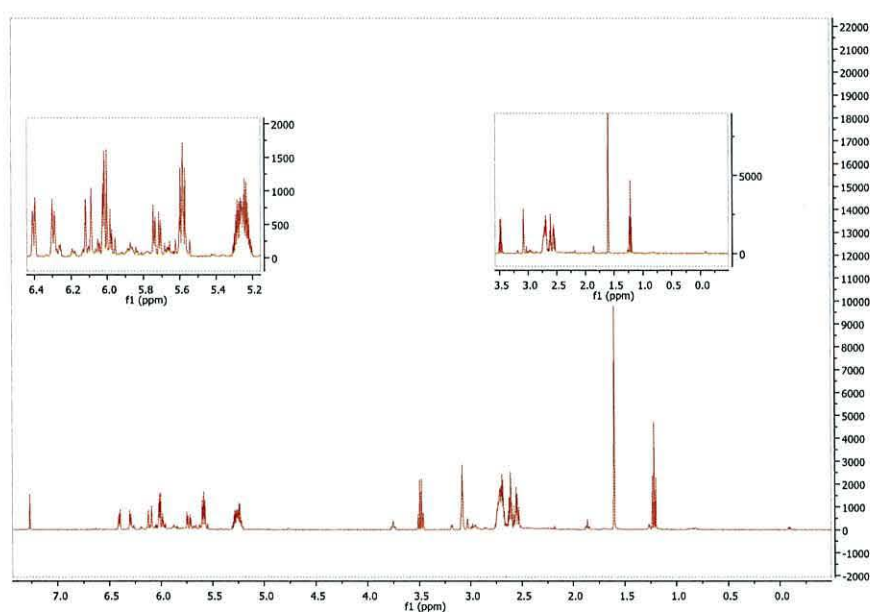
b

Figure 104: The ^{1}H NMR spectra show the rearrangement of (R,R,Z)-cycloundeca-1,2,5,6,9-pentaene (172): a- after 2 hours, b- after 18 hours

Finally, from the expected allene (**172**), a second intermediate, cyclopropane (**175**) was also obtained, which showed peaks at δ 6.26, 3.03, 1.69, 1.6, 0.82 and at δ -0.09. This product could not be isolated. In order to provide evidence for this analysis, a number of trapping experiments were carried out.

3.9.3.1 Trapping the *bis*-allene rearrangement products with maleic anhydride

To confirm the structures proposed for products of allene rearrangement, maleic anhydride was added immediately to the mixture of allenes and this was allowed to stand at room temperature for 24 hrs, followed by evaporation of the solvent to yield a residue, which was purified by column chromatography. This gave four components, the allene (**173**), two maleic anhydride adducts (**177**) and (**178a**), and an unexpected product characterised as **179**.
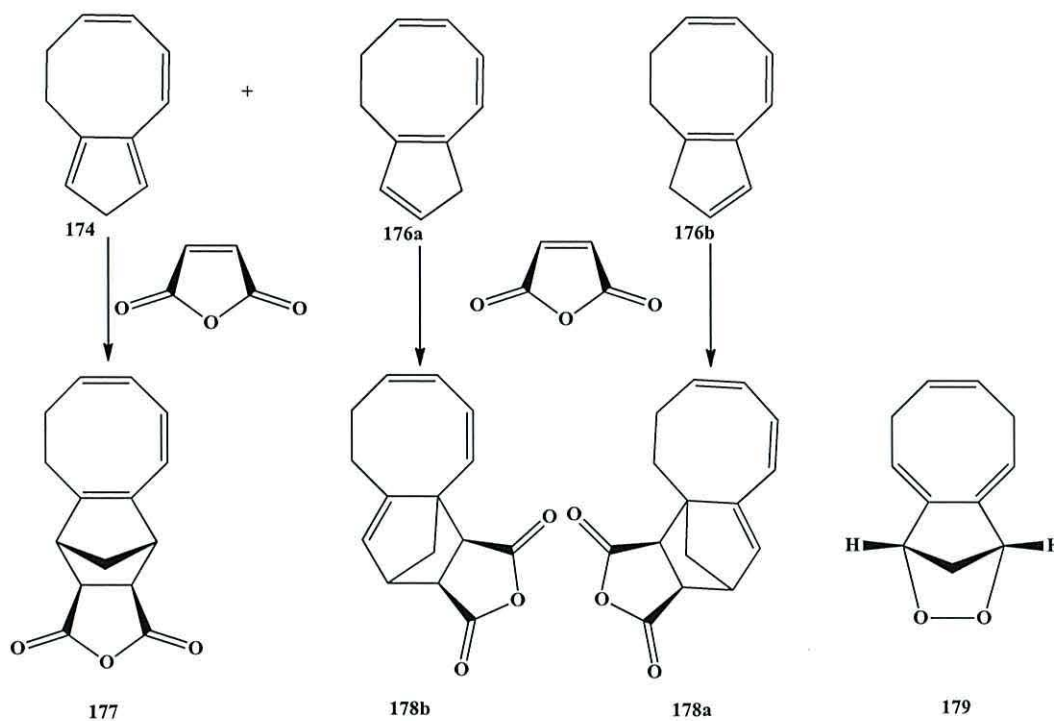
Scheme 38: Trapping of intermediates with maleic anhydride

The non-rearranged allene (**173**) was isolated in a 13% yield based on the ^{1}H- and ^{13}C-NMR spectroscopies data. The ^{1}H NMR spectrum (CDCl$_3$) showed 2H and 4H multiplets in the alkene region at δ 5.76 and δ 5.37, as well as 4H multiplets at δ 2.8 two hydrogen multiplets at δ 2.73-2.6. In C$_6$D$_6$, the high-field region was split into three two hydrogen multiplets at δ 2.60, δ 2.48 and δ 2.40. While double bond peaks were observed at δ 5.52 and δ 5.16 ppm (Figure 106a).
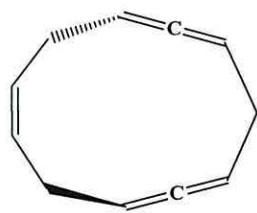
173

Figure 105: Stable bis-allene (173)

Selective decoupling of the signal at δ 5.17 for the four allenic hydrogens caused the multiplets signals at δ 2.60 and 2.48 to be reduced to broad double doublets (*J* ca. 14.5, 5.3 Hz and 14,5, 5.6 Hz) (Figure 106b). Moreover, the selective decoupling of the signal for the alkene hydrogen at δ 5.53, caused minor changes to the signal at δ 2.40, but simplified each of those at δ 2.60 and 2.48 causing them to appear as double double doublets (1H, ddd, *J* 14.3, 5.0, 3.5 Hz), (1H, ddd, *J* 14.3, 6.8, 2.9 Hz) (Figure 106c). More importantly, the multiplet at δ 2.4 was reduced to a singlet as expected for the isomer (**173**), possessing, as it does, an axis of symmetry and two chemically equivalent hydrogens between the allene groups.

a

b   c
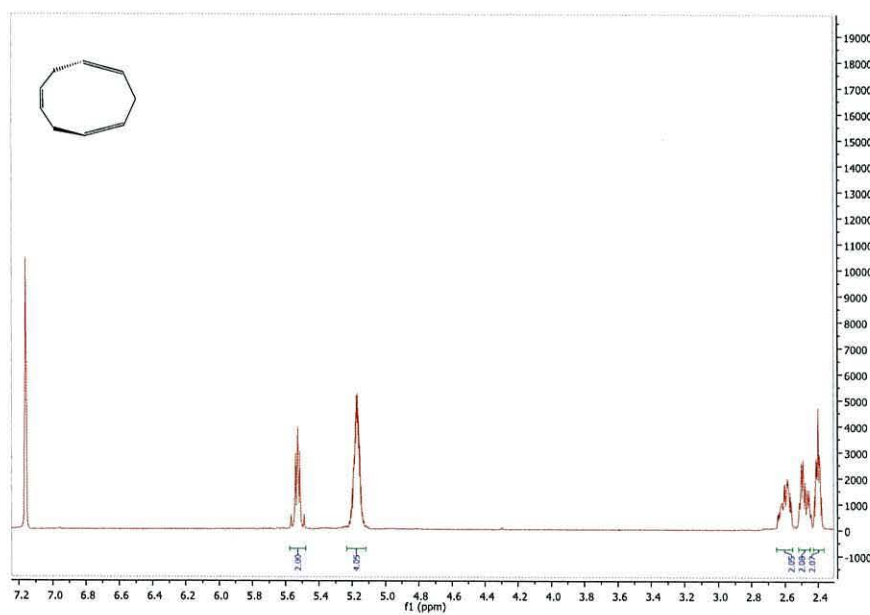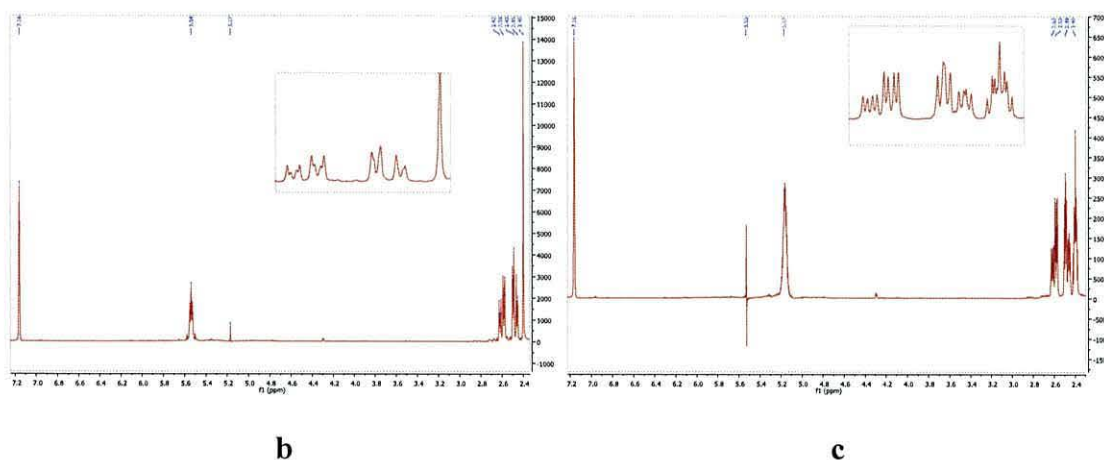
Figure 106: a-¹H NMR spectrum of (173) in C₆D₆, b- selective decoupling at δ 5.17 and c- at δ 5.53 ppm

The first trapping product was (3aS,4R,7Z,9Z,11S,11aR)-3a,4,5,6,11,11a-hexahydro-4,11-methanocyclo-octafisobenzo-furan-1,3-dione (**177**), obtained in a 10% yield.

174   177
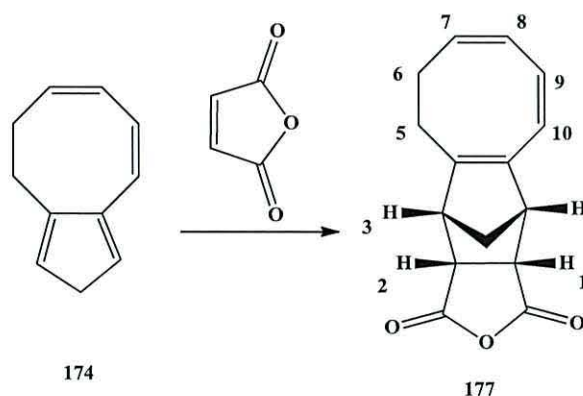
Figure 107: Trapping of (174)with maleic anhydride

Compound (**177**), the Diels-Alder adduct of (**174**), showed fifteen signals in its proton decoupled ^{13}C NMR spectrum, including two carbonyl carbons at δ 171.2 and 170.9, two quaternary alkene carbons, four tertiary alkene carbons and seven signals between δ 25-55, three of these secondary and four tertiary. The six protons of the bicyclo[2.1.1]heptene fragment appeared as a pair of doublets, each with a small additional triplet coupling at δ 1.45 (dt, J = 9.0, 145 Hz, 1H) and 1.83 (dt, J = 9.0, 1.7 Hz, 1H), as a narrow two hydrogen

multiplet at δ 3.65, and two broad 1H singlets at δ 3.25 and 3.35 (CDCl₃). The cyclo-octatriene fragment was best resolved in C_6D_6 solution. The alkene region showed four single hydrogen signals, a doublet (H10, J = 12.1 Hz), coupled to a double doublet (H9, J = 12.1, 4.2 Hz), coupled to a double doublet (H8, J = 11.0, 4.2 Hz), finally coupled to a double triplet (H7, J = 1.7, 8.0 Hz). The protons of the two methylene groups in the cyclo-octatriene appeared as complex one proton and three proton mulitplets at δ 2.3 − 2.5 in both solvents.

The reaction of **176a** with maleic anhydride gave a second fraction of adduct, characterised as compound **178a**. The reaction leading to the formation of the isomer (**176a**), constitutes an intramolecular 1,5-hydrogen shift process on the intermediate compound (**174**).
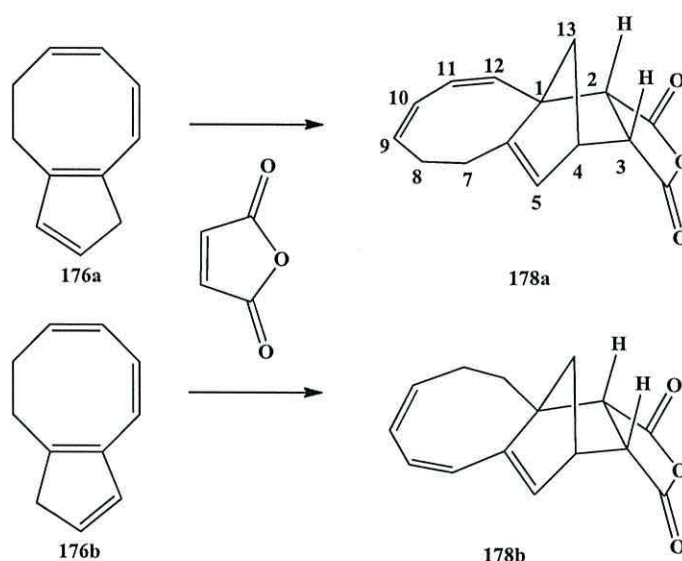
Figure 108: Trapping of (176a&b)with maleic anhydride

The ¹H NMR spectrum of **178a** in CDCl₃ was complicated, but when a C_6D_6 solution was used, the spectrum was clearer and included a doublet at δ 5.85 (J 0.6 Hz) for H-12 and a double double doublet for H-9 at δ 5.69 (J 11.0, 7.8, 6.8 Hz). In addition, a signal for H-5 appeared as a broad triplet at δ 5.43 (J 13.3 Hz), a double doublet for H-11 at δ 5.39 (J 6.1, 4.9 Hz), and a double doublet with a small additional coupling for H-10 at δ 5.36 (J 8.9, 5.7 Hz). Additionally, the spectrum showed signals for five other protons: a double doublet for H-3 at δ 3.66 (J 8.1, 4.6 Hz), a doublet at δ 3.50 (J 8.1 Hz) corresponding to H-2, and a multiplet for H-4 between δ 3.36 and 3.27. The signals for the hydrogens of the methylene group of the cyclo-octadiene ring were each complex multiplets occuring between δ 2.72

and 2.15. Finally, three signals, a double doublet at δ 1.88 (*J* 8.9, 1.5 Hz) and a broad doublet δ 1.57 (*J* 12.3 Hz), corresponded to the H-13 and H-13'.
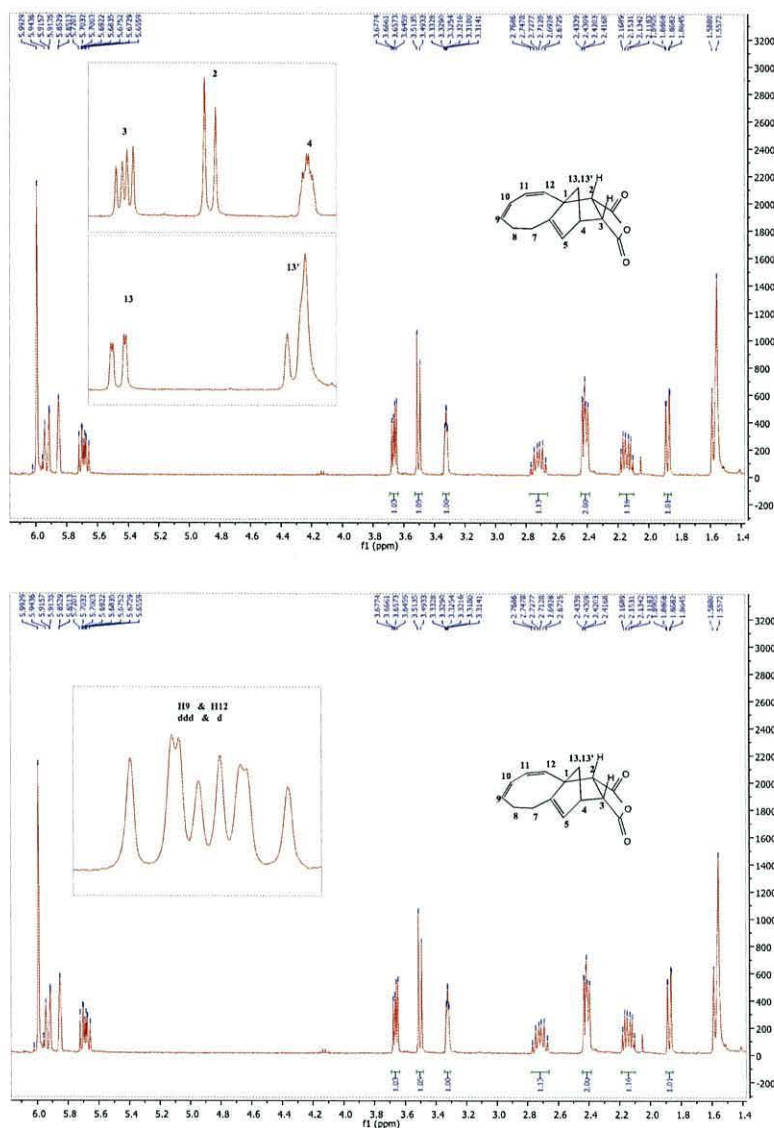
Figure 109: ^{1}H NMR spectrum of 178a in CDCl$_3$

In addition to isolating the expected trapping products (**177**) and (**178**), the reaction generated an unexpected product, compound (**179**), which was apparently formed from (**175**) by oxidation with air in a pericyclic reaction. As mentioned above, the cyclopropane product (**175**) could not be isolated from the reaction mixture when no maleic anhydride was added.
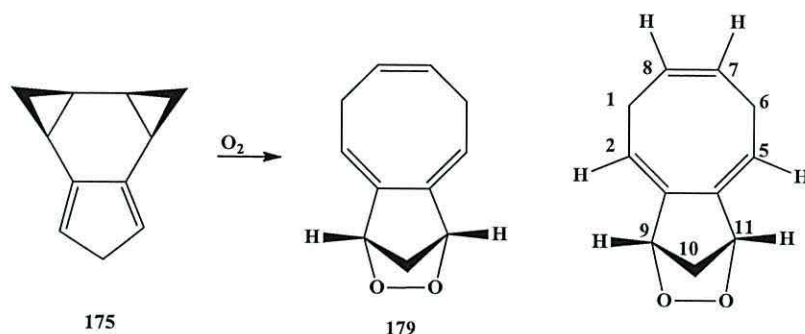
Figure 110: Proposed reaction of cyclopropane product (175)

This product was identified by proton NMR, which showed the expected four alkene hydrogens, a two hydrogen triplet at δ 5.86 (*J* 6.6 Hz) and a multiplet at δ 5.66 (2H), a narrow multiplet at δ 4.77 (2H) for the bridgehead hydrogens, two multiplets at δ 3.01 (2H, br.td, *J* 6.8, 15.5 Hz) and 2.79 (2H, br.td, *J* 7.0, 15.5 Hz) for the cyclo-octatriene methylene hydrogens, and a triplet of doublets at δ 2.23 (*J* 2.1, 10.0 Hz), and doublet at δ 2.18 (*J* 10.0 Hz) for the bridge methylene group. The ^{13}C NMR spectrum showed one quaternary and two tertiary alkene carbons, one signal at δ 85.8 for the bridgehead carbons adjacent to oxygen, and two high field methylene groups at 45.0 and 24.9.

When the crude mixture of allenes was left for 16 hours at room temperature in chloroform solution and then maleic anhydride was added, three compounds were obtained. Two of them were (**173**) and (**178a**), as above, while the third, minor, compound was (**178b**). The proton NMR spectrum showed five signals between δ 6.1 and 5.57 ppm, corresponding to the alkene protons and nine protons between δ 3.52 and 1.42 ppm for the methylene groups, which confirmed this structure. Compounds **178a** and **178b** could be distinguished from their ^{1}H NMR spectra. For compound **178a**, the proton on carbon 5 in principle should appear as a double triplet due to allylic coupling with the protons on carbon 7, and coupling to the proton on carbon number 4. This is in contrast to **178b**. Here, the proton on carbon 5 should appear as a double doublet, due to coupling to the proton on carbon 4, and the allylic proton coupling on carbon 7. Selective decoupling of this signal led to the signal for H4 being simplified to a narrow doublet of triplets, but also to the signals for H7 and H7' being simplified by the removal of a small coupling constant in each case. On this basis, H5 shows allylic coupling to the two hydrogens on H7, eastablishing the structure of this product as **178a** rather than **178b**, the product from isomeric cyclopentadiene **176b**.

Compound (**177**) was not obtained when the mixture of allenes was allowed to stand at room temperature in this way, and then reacted with maleic anhydride, because compound (**174**) had by then rearranged completely to cyclopentadienes (**176a**) and (**176b**), This was confirmed by ^{1}H NMR which showed that the signals for the primary product **174** had completely disappeared.

The kinetics of the rearrangement

The decomposition of the major allene was followed over 24 hrs. Increase in reaction time showed a decrease in the signals for allene (**172**), and increases in the integrals for the signals of other products as shown in the chart. For example the changes in the integrals for the signals of allene (**172**) are collected in Table 8 and plotted in Fig. 114.

Time min	5.52	5.36	5.18	2.32	2.88	2.56 ppm
104	0.51	0.65	0.63	0.62	0.73	0.58
136	0.7	0.62	0.53	0.59	0.72	0.57
153	0.71	0.63	0.47	0.61	0.7	0.47
185	0.67	0.63	0.39	0.61	0.61	0.39
202	0.62	0.51	0.36	0.56	0.65	0.35
220	0.56	0.45	0.31	0.51	0.51	0.34
269	0.47	0.36	0.23	0.42	0.41	0.34
318	0.42	0.33	0.16	0.41	0.34	0.28
368	0.38	0.29	0.13	0.34	0.23	0.26
418	0.27	0.21	0.09	0.24	0.16	0.24
484	0.17	0.15	0.06	0.15	0.15	0.24
533	0.13	0.12	0.02	0.12	0.13	0.24

Table 8: Changes in the ^{1}H NMR integrals of peaks for allene (172) with time
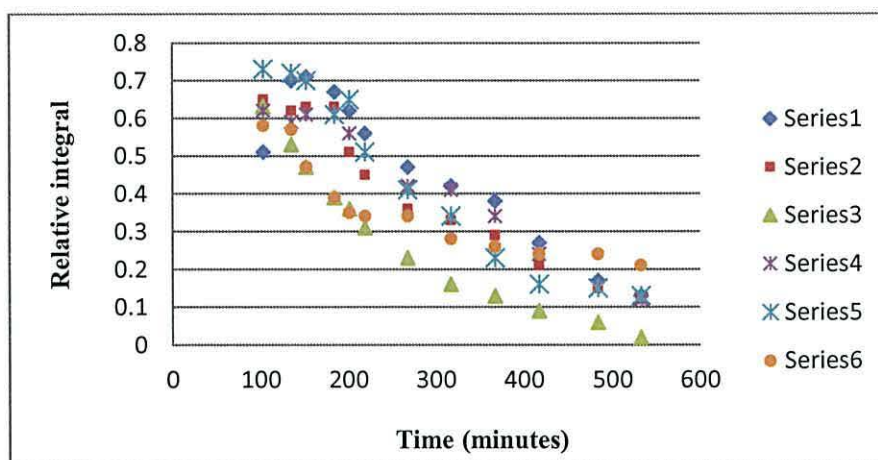
Figure 111: The change with time in the integrals for the signals for (172) at δ 5.52 (series 1), 5.36 (series 2), 5.18 (series 3), 2.32 (series 4), 2.88 (series 5) and 2.56 (series 6) (time in mint, integrals relative to the signal for 173 as standard

Using the information in Table 8 (the values taken were from the signal at 5.18 ppm), the rate constant of the re-arrangement of compound 172 can be estimated. By plotting the negative of the natural log of the concentration against time, a straight line is obtained as expected for a first order reaction and the rate constant can be determined. This is depicted in Figure 112:
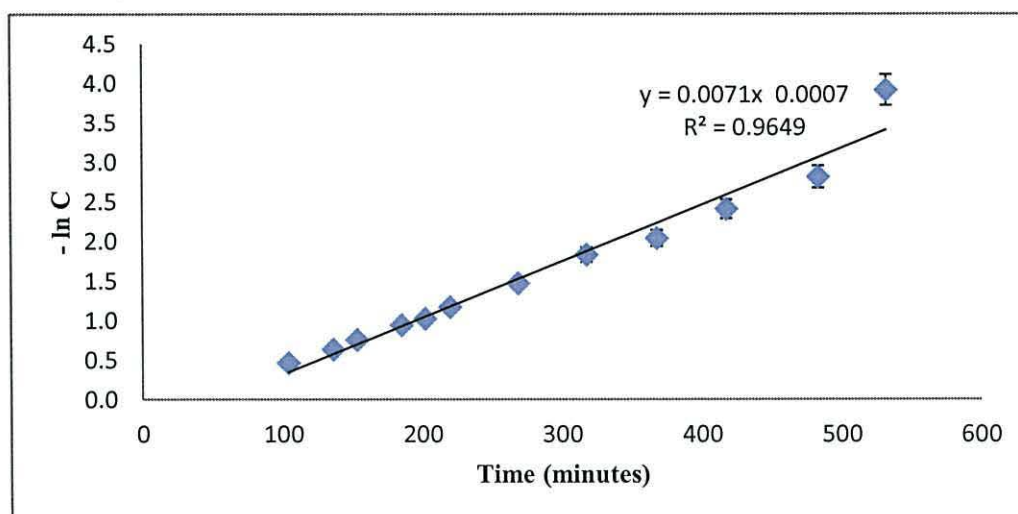
Figure 112: Kinetics study of the rearrangement of compound (172)

$$-\ln C = kt - lnC_0$$

$$y = mx + c$$

The gradient of the graph was determined as 0.0071 ± 0.0007, therefore, the rate constant for the re-arrangement of the allene **172** was 0.0071 min^{-1}.[168]

In addition, the cyclopropane (**175**) peaks increased in the beginning, but then began to decrease slowly with time as shown in Table 9; these changes are plotted in Figure 113.

Time	6.26	3.03	1.69	1.6	0.82	-0.09
min			ppm			
136	0.03	0.02	0.05	0.04	0.04	0.03
153	0.03	0.02	0.06	0.06	0.05	0.05
185	0.05	0.03	0.08	0.08	0.07	0.06
202	0.05	0.04	0.09	0.08	0.07	0.07
220	0.06	0.05	0.1	0.1	0.08	0.07
269	0.07	0.06	0.11	0.1	0.09	0.09
318	0.08	0.06	0.11	0.11	0.1	0.09
368	0.08	0.07	0.12	0.12	0.1	0.1
418	0.08	0.08	0.12	0.1	0.1	0.09
484	0.08	0.08	0.12	0.12	0.1	0.1
533	0.08	0.08	0.1	0.1	0.09	0.08

Table 9: Changes in the ^1H NMR integrals of peaks for cyclopropane (175) with time
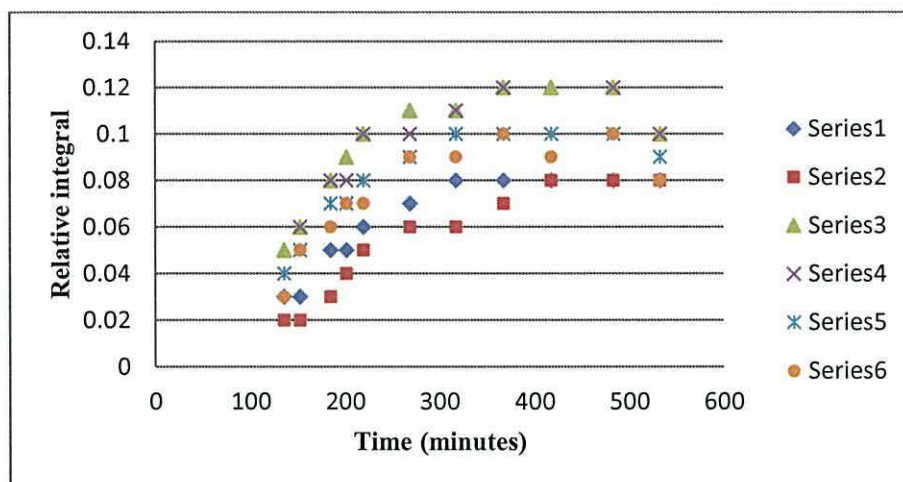
Figure 113: The change with time in the integrals for the signals for (175) at δ 6.26 (series 1), 3.03 (series 2), 1.69 (series 3), 1.6 (series 4), 0.82 (series 5) and -0.09 (series 6) (time in mint, integrals relative to the signal for 173 as standard

The above data is consistent with that expected for compound **175**. As the maximum amount of this compound is produced, the signals reach a maximum, before finally going down somewhat after a period of approximately 6 hours. The compound may be being trapped by oxygen, as apparently happened in the maleic anhydride trapping experiment, changing the peaks slightly, and accounting for this reduction in peak size after this time. The ^{1}H NMR signals of (**174**) increased over a period of about 5 hours, and then decreased, which indicates the formation of the product, followed by decomposition. It was possible to follow some of the peaks of the compound as shown in Table 10.

Time min.	6.34	2.95	2.44 ppm
87	0.07	0.07	0.08
104	0.11	0.09	0.08
136	0.27	0.25	0.26
153	0.34	0.31	0.31
185	0.44	0.39	0.4
202	0.46	0.43	0.42
220	0.48	0.46	0.46
269	0.52	0.49	0.5
318	0.52	0.49	0.49
368	0.51	0.47	0.48
418	0.46	0.41	0.43
484	0.41	0.39	0.4
533	0.37	0.35	0.36
600	0.33	0.3	0.32
682	0.26	0.27	0.28
826	0.18	0.19	0.21
930	0.14	0.16	0.16

Table 10: Changes in the ^1H NMR integrals of peaks for (174) over time
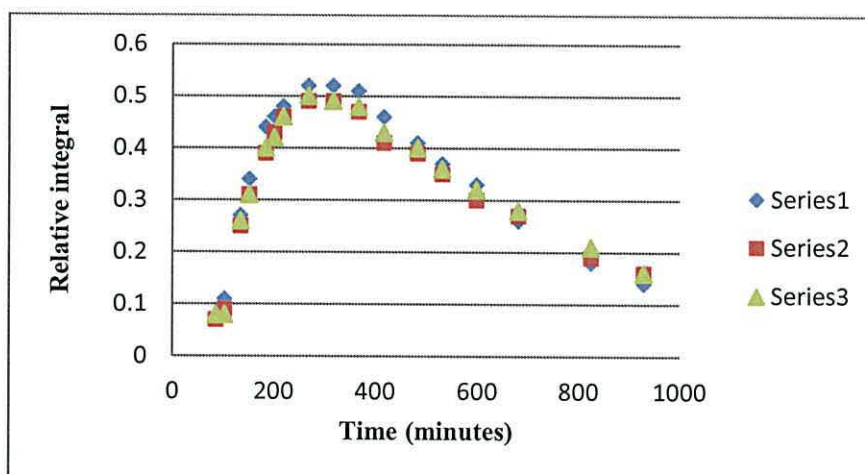
Figure 114: The change with time in the integrals for the signals for (174) at δ 6.34 (series 1), 2.95 (series 2) and 2.44 (series 3) (time in mint, integrals relative to the signal for 173 as standard

This pattern is consistent with that expected for compound **174** which is initially formed, leading to an increase in its concentration, followed by a reduction in its concentration as the compound undergoes re-arrangement to **(176a)** and **(176b)**.

In contrast, the allene **(173)** was stable and the NMR signals remained constant, as shown in the following results.

Time min	5.61	5.29	2.69	2.62
0	0.86	0.88	1.04	1.27
18	1.02	1.13	1.11	1.02
46	1.12	1.14	1.13	1.14
62	1.12	1.14	1.24	1.2
87	1.12	1.13	1.27	1.14
104	1.02	1.12	1.23	1.15
136	1.14	1.13	1.1	1.21
153	1.18	1.18	1.08	1.18
185	1.2	1.2	1.16	1.2
202	1.16	1.16	1.1	1.21
220	1.18	1.17	1.15	1.12
269	1.16	1.16	1.16	1.2
318	1.22	1.22	1.14	1.23
368	1.22	1.22	1.13	1.18
418	1.22	1.22	1.13	1.14
484	1.26	1.26	1.13	1.15
533	1.28	1.28	1.15	1.14
600	1.3	1.28	1.13	1.12
682	1.3	1.29	1.15	1.14
826	1.3	1.28	1.13	1.12
930	1.3	1.28	1.19	1.14

Table 11: Changes in ^1H NMR signals of allene (173) with time
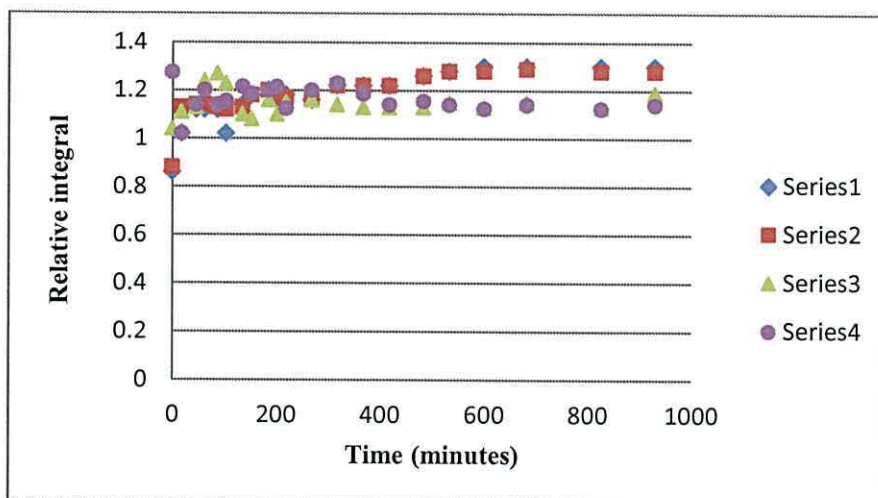
Figure 115: The change with time in the integrals for the signals for (173) at δ 5.61 (series 1), 5.29 (series 2), 2.69 (series 3) and 2.62 (series 4)

Finally, the change with time in one of the signals for compounds **172**, **174**, **175** and **176a** respectively is shown in Figure 116.
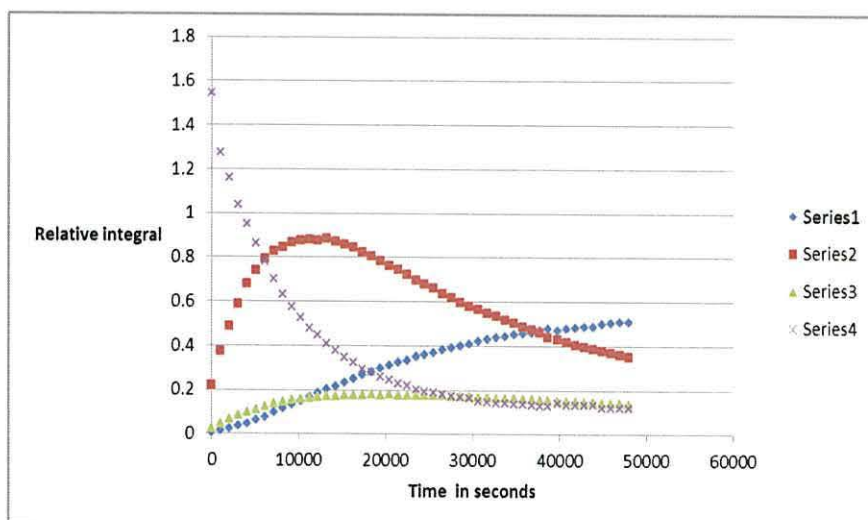
Figure 116: The change in the integrals with time for the signals at δ 5.53 for allene 172 (series 4), the signal at δ 0.003 for compound 175 (series 3), the signal at δ 3.05 for compound 174 (series 2) and the signal at δ 6.4 for compound 176a (series 1) (time in seconds, integrals relative to signal for 173 at δ 5.57 for two hydrogens)

3.10 Conclusion:

Cyclonona-1,4,7-triene could be converted into either the *bis-* or *tris*-dibromo-cyclopropanes. Reacting these adducts with methyllithium resulted in the formation of novel *bis-* and *tris*-cyclic allene respectively.

The *tris*-allene was formed as both the symmetric and asymmetric diastereoisomers which were separated through complexation with AgNO$_3$ and silica column chromatography. Both isomers were found to be stable.

The *bis*-allene was also produced as both the symmetric and asymmetric diastereoisomers; however, in this case, the symmetric isomer was found to be unstable with respect to rearrangement and gave different transient species which could be trapped via Diels-Alder reaction with maleic anhydride.
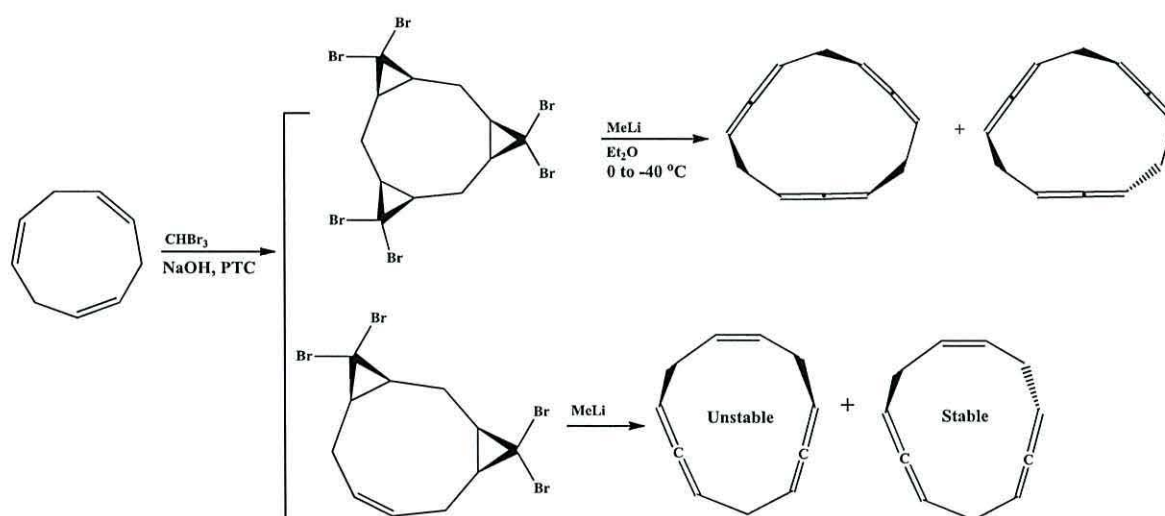
Scheme 39: bis- and tris-cyclic allene and their derivatives

3.11 Overall conclusion and future work:

This thesis involved three projects linked to potential applications in industry:

i)- The first part, which related directly to a problem in industry, examined several routes to produce (S)-4-benzyl-oxazolidin-2-one (1). This is a chemical with enormous potential in organic synthesis, not least because it enables the synthesis of enantiomerically pure products. Moreover, it is used as a chiral auxiliary for asymmetric synthesis. It has featured in the synthesis of several biological products, in addition to its use in generating new chiral molecules in a highly enantiomrically enriched form. It is an expensive reagent; this study has secured a protocol which allows its preparation in high yield and at lower cost. Different methods were investigated, and then the most cost effective one was defined *via* the use of an Excel programme used in industry to compare project costs.

The amino acid was reduced using different equivalents of several reagents ($NaBH_4/H_2SO_4$, $NaBH_4/BF_3.OEt_2$, and BH_3/THF) to choose the best to give the corresponding chiral amino alcohol. The chiral amino alcohol was then reacted with EtO_2CCl to give the carbamate. The carbamate was cyclised using K_2CO_3 at 125–130˚C under vacuum to obtain the chiral 4-benzyl-oxazolidin-2-one in high yields.

ii)- The second part was not directly connected to an industrial problem, but is still of significant commercial potential because it led to a series of pheromones and related compounds; pheromones are of increasing commercial importance in crop pest control. Here, a short protocol has been developed, which allows the synthesis of the de-symmetrised (3*Z*,6*Z*)-nona-3,6-diene motif, (**58**), originating from the inexpensive, commercially available (1*Z*,5*Z*)-cycloocta-1,5-diene. Compound (**58**), bearing the *cis, cis*-1,4-diene ('skipped' diene) functionality, possesses obvious potential utility as an intermediate in the synthesis of various long chain, polyunsaturated fatty acid natural products of polyketide origin. To demonstrate the versatility of the intermediate, a number of triene insect pheromones were synthesised. Two tetraene insect pheromones, one diene insect pheromone, as well as the important dietary substance, the omega-3 fatty acid, α-linolenic acid, and a polyunsaturated fatty acid with six double bonds were also synthesised. A summary of the strategy developed in this part of the project, is shown in Scheme 28.
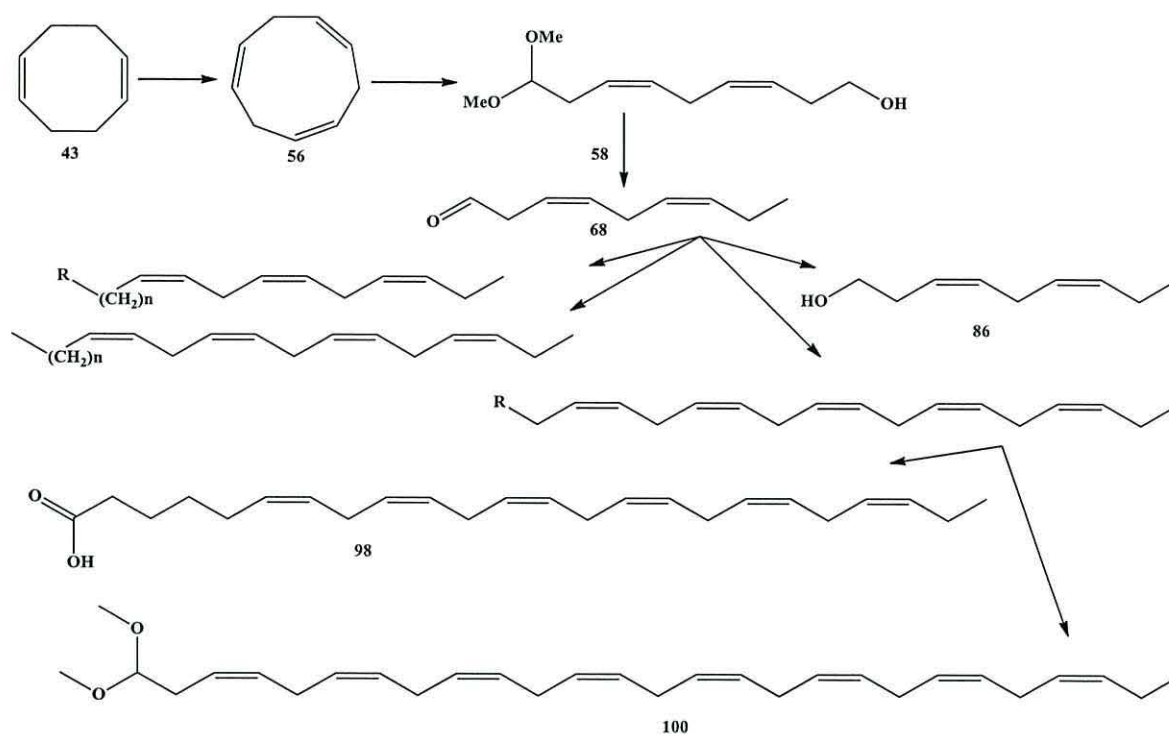
Scheme 28

Beginning with (1*Z*, 5*Z*)-cycloocta-1, 5-diene, and employing standard conditions for the *in situ* generation of dichlorocarbene, the *mono*-dichlorocyclopropane adduct, (**51**), was formed, which was then reduced with lithium/*tert*-butyl alcohol to give cyclopropane, (**52**). Bromination of this compound, followed by base-mediated elimination, afforded an equilibrium mixture of diene isomers, (**54**) and (**55**), which was then heated in order to induce thermal sigmatropic rearrangement (*1,5*-hydride shift), resulting in the formation of the ring-expanded product, (1*Z*,4*Z*,7*Z*)-cyclonona-1,4,7-triene, (**56**), in good yield. This compound was then cleaved by ozonolysis, in the presence of *p*-TsOH and NaBH₄, to give the key dimethyl acetal intermediate, (**58**).

Homologation of this species is, in principle, possible at both termini; however, for the model syntheses explored, the hydroxyl group was either removed to give a methyl terminus (conversion of primary alcohol into the corresponding iodide or tosylate, followed by hydride displacement), or acylated to form a terminal acetate ester.

The aldehyde was then revealed through hydrolytic cleavage of the diacetal, employing a method which avoids the formation of the undesired conjugated enal rearrangement product, and this was then coupled stereoselectively with a variety of phosphonium salts, via the Wittig olefination reaction, to access the desired chain extended products bearing

the necessary *cis*-olefin linkage. As mentioned before, this approach hass advantages compared to other methods, being based on using cheap and available starting material with mild reaction conditions.

Most of the compounds prepared in this work were characterized by double bonds separated by a single methylene group; because of the existence of other types of pheromones with double bonds separated by two methylene groups, future work will focus on the ozonalysis of larger ring systems with three isolated double bonds of defined stereochemistry separated by two methylene groups like (1*Z*,5*E*,9*E*)-cyclododeca-1,5,9-triene. This would lead to ring-opened intermediates of defined stereochemistry for use in preparing such pheromones.

iii)- The third part of the study entails the use of the same *Z*,*Z*,*Z*-cylonona-1,4,7-triene to synthesize novel *bis* and *tris*-cyclic allenes and their derivatives. Many chemists have been fascinated by the cumulated diene system of allenes with its extraordinary properties, such as the axial chirality of the elongated tetrahedron and a higher reactivity than non-cumulated C-C double bonds. The synthesis of cyclic allenes is of considerable interest in chemistry because of their high strain and reactivity.

Treatment of cylonona-1,4,7-triene with bromoform and base under PTC leads to 4,4,8,8,12,12-hexa-bromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]dodecane (*tris*-adduct) and (*Z*)-4,4,11,11-tetrabromotricyclo-[8.1.0.0^{3,5}]undec-7-ene (*bis*-adduct). The reaction of methyllithium with the hexabromide gave both diastereomers of the stable *tris*-allene *RRR* (*SSS*) and *RRS* (*SSR*)-cyclododeca-1,2,5,6,9,10-hexaene (**161** and **162** respectively). On the NMR timescale, compound (**161**) has D3 symmetry, which confirmed there are three allenes of the same absolute stereochemistry. The second tris-allene (**162**) has C2 symmetry and the ^{1}H NMR spectrum in C$_6$D$_6$ showed three complex two hydrogen multiplets corresponding to the three types of allenic hydrogen with $^{3}J_{H,H}$ coupling between each different allenic hydrogen and both the adjacent hydrogens of the methylene groups, and $^{5}J_{H,H}$ to the two protons of each methylene group at the other end of the allene. The multiplets show non-first order effects due to the constrained geometry of the molecule and the presence of chemically equivalent, but magnetically inequivalent, protons.
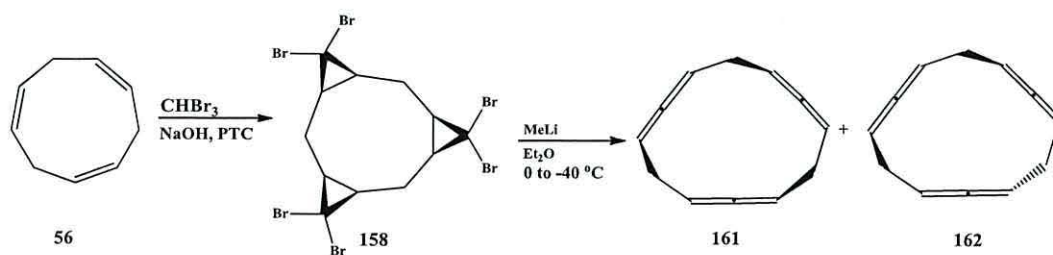
On the other hand, the addition of methyllithium to the 4,4,11,11-tetrabromotricyclo-[8.1.0.0^{3,5}]undec-7-ene leads to a mixture of (*R,R*)- and (*R,S*)-*Z*-cycloundeca-1,2,5,6,9-pentaenes. The latter is unstable at 20 °C, and undergoes rearrangement to give unstable intermediates. These were trapped with maleic anhydride to produce stable compounds, the exact structures of these having been elucidated on the basis of mass spectrometric and NMR spectroscopic data.
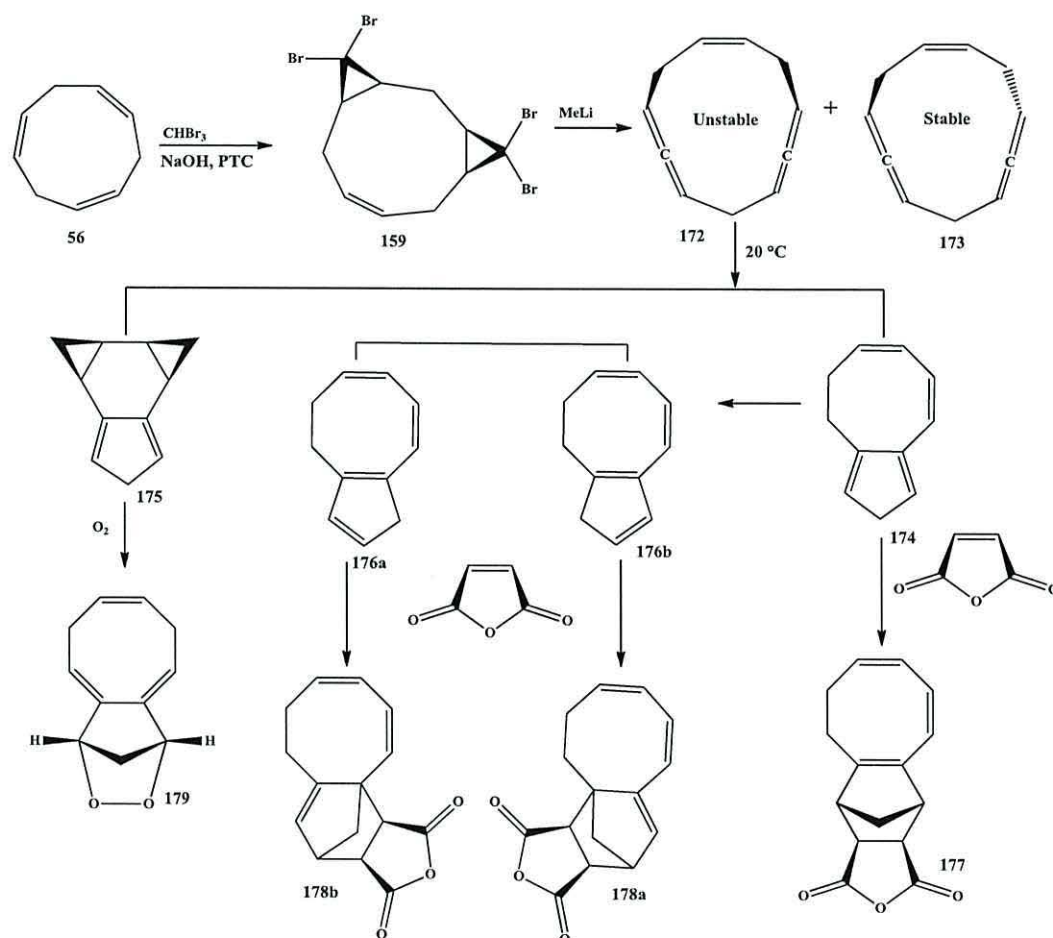
The stable bis-allene (**173**) was characterized by the presence of six signals in the ^{13}C NMR spectrum, three for the allene carbons, one for the alkene, and two for the methylene groups. The ^{1}H NMR spectrum in C$_6$D$_6$, showed two and four hydrogen multiplets in the alkene region and three two-hydrogen multiplets for the methylene groups. Selective

decoupling of the signal for the four allenic hydrogens, caused the multiplet assigned to the methylene group between the two allenic groups to be simplified to a sharp singlet. On this basis, this compound can be assigned as a racemic mixture of the allene (173), with formal C2 symmetry and chemically equivalent of methylene protons, with its enantiomer.

Through our study we were able to determine the properties of the allenes prepared using NMR in solution; in one case X-Ray data were obtained which provided information about the solid state. Future plans will focus on study of rotational measurement using microwave spectroscopy to determine the structures of the molecules in the gas phase. Also, more interesting would be to use the Electron diffraction which used in solid state physics and chemistry to study the crystal structure of allenes. In these instruments, electrons are accelerated by an electrostatic potential in order to gain the desired energy and determine their wavelength before they interact with the sample to be studied.

In addition, these types of allenes could also be used in coordination with metals. One interesting potential application could be in the area of organic electronic conductors, where the cyclic allene, with its disk-like molecular structure and its central cavity, could be envisaged stacking in an alternate sequence with metal ions, via some π-interaction, allowing the transfer of electrons from one ion to the next through the hole in the centre of the allenes. Another potential application could be as catalysts or chiral reagents due to the chirality of the cyclic allene compounds.
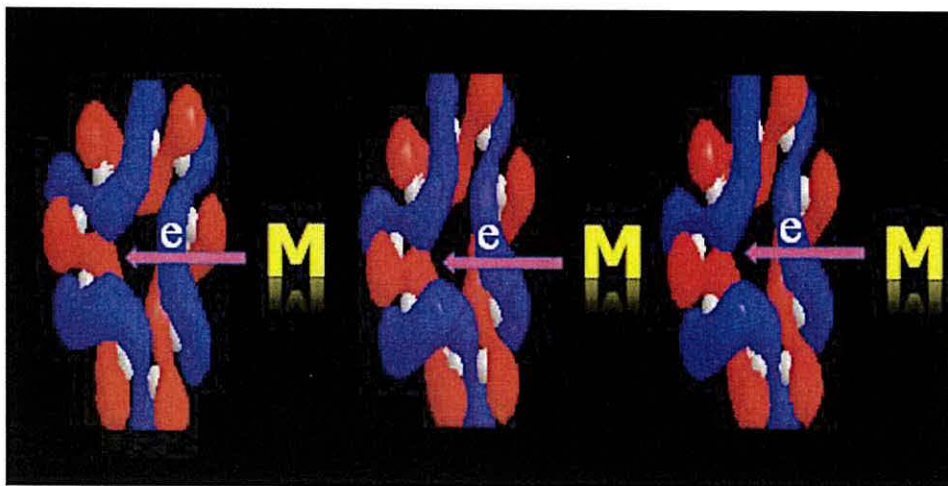
Figure 117: Possible binding of metals to the allene (161) in alinear array: the two faces of the allene are linked to the metals and the central hole allows the movement of electrons from one metal to another.

Chapter 4. Experimental

General considerations

All chemicals used were purchased from commercial suppliers. Unless otherwise stated, all reagents and solvents were of reagent grade. However, solvents such as THF and diethyl ether were distilled over sodium wire and benzophenone under nitrogen, whereas dichloromethane was distilled over calcium hydride powder. Petroleum spirit was of boiling point 40–60 °C and is referred to as petrol. All organic solutions were dried over anhydrous magnesium sulfate. Solvents were removed by Buchi rotavapor at 14 mmHg and the residual traces were finally removed using the high vacuum evaporator at 0.1 mmHg. Reactions carried out under inert conditions were subjected to a slow stream of nitrogen using a nitrogen balloon. A cooling bath of methylated spirit and liquid nitrogen was used for reactions carried out at low temperatures. Pre-coated silica plates and silica gel obtained from Aldrich were used for TLC and column chromatography.

Optical rotations $[\alpha]_D^T$ were measured using a POLAR 2001 optical activity polarimeter and the solvent used was $CHCl_3$. Values were calculated using the following equation:

$$[\alpha]_D^T = \frac{10^4 \, x \, \alpha}{l \, x \, c}$$

α = observed angle of rotation

l = light path length in mm

c = concentration in g/100cm^3

T = temperature

Melting points were measured using a Gallenkamp melting point apparatus.

Infrared [IR] measurements were carried out on Perkin Elmer 1600 series FT-IR or Bruker Tensor 27 spectrometer as KBr discs (solids) or thin films on NaCl windows.

The ^1H spectra were run at 400 and 500 MHz and dept- and ^{13}C spectra were run at 101 or 126 MHz. Deuterated chloroform ($CDCl_3$) was used as the reference solvent if not otherwise stated. Chemical shifts for ^1H and $\delta 7.27$ ppm and $\delta 77.0$ ppm respectively. Data were reported as follows: chemical shift, integration, multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; sext, sextet; hept, heptet, m, multiple), coupling constant.

Mass spectra were obtained using a Bruker MicroTOF time of flight mass spectrometer and Matrix-assisted laser desorption ionisation (MALDI) were measured by using a Bruker Daltonics *Reflex IV*.

An assessment form for the control of substances hazardous to health (COSHH) was completed for each experiment according to health and safety regulations.

Preparation of *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid (10)
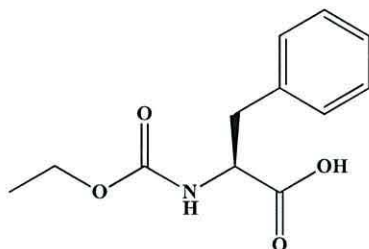
Method A1

Solid sodium carbonate (0.29 g, 28.3 mmol) and ethyl chloroformate (4.91 g, 45.3 mmol) were added respectively to an ice-cooled solution of *(S)*-2-amino-3-phenyl-propionic acid (4.90 g, 29.9mmol) in 1N NaOH (100 mL). The reaction mixture was stirred for 30 min with cooling and a further 3 hrs at room temperature, then carefully acidified with concentrated HCl to (pH 1). After that, the resulting solution was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to give a solid which was recrystallized from ethyl acetate and petrol to give *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid (**10**) (5.93 g, 84 %).[140] The product showed the same NMR spectra to the ones reported in the literature.[141,142]

mp :   79 - 82 °C, (lit.[140-142] mp: 81 °C)

$[\alpha]_D^{22}$:   +43.6 (c = 1.14, CHCl₃), [lit.[142] $[\alpha]_D^{24}$ = +43.3° (c = 5.9, CHCl₃)]

δ_H(500 MHz):   10.43 (1H, br s), 7.3-7.24 (5H, m), 5.15 (1H, br d, *J* 7.85 Hz), 4.72 (1H, br q, *J* 6.35 Hz), 4.10 (2H, q, *J* 7 Hz), 3.23 (1H, br dd, *J* 5.35, 14.2 Hz), 3.15 (1H, br dd, *J* 6.3, 14.2 Hz), 1.24 (3H, t, *J* 6.95 Hz).

δ_C (126 MHz):   176.1, 156.1, 135.5, 129.3, 128.6, 127.1, 61.4, 54.4, 37.7, 14.4

$v_{max}/$ cm⁻¹ :   3339, 1720, 1686, 1261, 1100, 970.

Method B1

Ethyl chloroformate (3.89 g, 35.9 mmol) was slowly added to a stirred solution of *(S)*-2-amino-3-phenyl-propionic acid (3.9 g, 24 mmol) in 1M NaHCO₃ (100 mL) at room temperature. After stirring for an additional 2 hrs, the mixture was extracted with ethyl

acetate (2 x 150). Concentrated hydrochloric acid (20 mL) was added to the aqueous layer at 0 °C until pH 1. The solution was extracted with ethyl acetate (3 x 200 mL) and the combined organic layers were dried over MgSO$_4$, then the solvent was evaporated under reduced pressure to give *(S)*-2-ethoxycarbonylamino-3-phenyl–propionic acid (**10**) as an oil which solidified under reduced pressure at 60 °C, (5.32 g, 92 %); this showed identical spectra to those above.

Reduction of *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid (10)
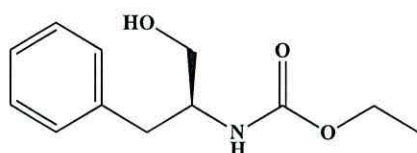
(i) Using BH$_3$.THF

(S)-2-Ethoxycarbonylamino-3-phenylpropionic acid (2.3 g, 10 mmol) in THF (10 mL) was added dropwise to a stirred solution of borane tetrahydrofuran (20 mL, 20 mmol) at 0°C under nitrogen atmosphere for 30 min. The reaction mixture was stirred for 3 hrs at 0°C, then quenched with 10 % HOAC in MeOH (10 mL). The solvent was evaporated to give an oil which dissolved in ethyl acetate followed by extraction with 1M HCl. The combined organic layers were dried over MgSO$_4$ to give (*(S)*-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester (**12**)[143] (1.8 g, 82 %).

mp :   72–75 °C(lit.[146] mp: 64.5–66.0°C)

$[\alpha]_D^{22}$:   -23.8 (c 1.5, CHCl$_3$).; lit. [146] $[\alpha]_D^{24}$ 23.1 (c 1.0, CHCl$_3$);

δ_H(500 MHz):   7.3 - 7.2 (5H, m), 5.3 (1H, br s), 4.0 (2H, br t, *J* 6.95 Hz), 3.93 (1H, s),

                3.66 (1H, dd, *J* 3.8, 11.05 Hz), 3.56 (1H, dd, *J* 4.5, 10.75 Hz), 2.86 (2H,

                br d, *J* 6 Hz), 2.0 (1H, s), 1.20 (3H, br t, *J* 6.95 Hz)

δ_c(126 MHz):   156.7, 137.6, 129.2, 128.5, 126.5, 63.9, 60.9, 53.9, 37.3, 14.4

v_{max}/ cm^{-1} :   3331, 3032, 2978, 1693, 1686, 1263,1032.

(ii) Using NaBH₄/BF₃.Et₂O

Boron trifluoride diethyl etherate (1.98 g, 13.9 mmol) was added to a stirred suspension of NaBH₄ (0.27 g, 7.13 mmol) in THF (10 mL) at 0 °C under nitrogen. After that, *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid (0.99 g, 4.21 mmol) was added to the slurry at 0 °C. The mixture was stirred at room temperature for 16 hrs, followed by addition of MeOH (10 mL) to quench the excess of NaBH₄. The reaction mixture was concentrated under reduced pressure to give white slurry which was stirred at 25 °C for 10 hrs with aqueous NaOH (26.5 mL, 20 %). The product was extracted with CHCl₃ (4 x 100), and the combined organic layers were washed with brine, dried and the solvent was evaporated under reduced pressure to give (*(S)*-1-hydroxymethyl-2-phenylethyl)carbamic acid ethyl ester[144] (**12**) (0.75 g, 83 %); this showed the same data to those provided by method above.

Preparation of *(S)*-2-amino-3-phenyl-propan-1-ol (9)
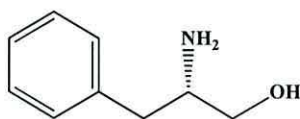
Method A3: Using NaBH₄ / H₂SO₄

(S)-2-Amino-3-phenyl-propionic acid (1.50 g, 9.10 mmol) was added to a stirred suspension of NaBH₄ (0.68 g, 18.1 mmol) in THF (10 mL). The flask was immersed in an ice-water bath, and a solution of conc. H₂SO₄ (0.66 mL, 12.3 mmol) in ether (1.4 mL) was slowly added maintaining the temperature at 0 - 20 °C. The mixture was then stirred at room temperature for 16 hrs. Methanol (5 mL) was then added carefully to destroy the excess of borane. The reaction mixture was concentrated and 5N NaOH (10 mL) was then added. After removing the solvent under vacuum at 60 °C, the mixture was heated at a reflux for 3 hrs. The turbid aqueous mixture was cooled and filtered through a thin pad of celite, which was washed with water. The filtrate and the washings were combined and diluted with additional water (10 mL). The product was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried to give a white solid, *(S)*-2-amino-3-phenyl-propan-1-ol (**9**) (1.16 g, 82 %).[145]

mp :   90 – 91 °C, lit[145] m.p. 91–92 °C

$[\alpha]_D^{24}$:   -23.1 (c 1.17, CHCl₃). lit.[145] $[\alpha]_D^{22}$ = –22.5.0 (c = 1.0, CHCl₃)

δ_H(500 MHz):	7.3 (5H, m), 3.6 (1H, dd, J 4.1, 10.75 Hz), 3.42 (1H, dd, J 7.25, 10.7
	Hz), 3.16 (1H, br m), 2.8 (1H, dd, J 5.35, 13.55 Hz), 2.58 (1H, dd, J 8.5,
	13.25 Hz), 1.9 (3H, br s)
δ_C(126 MHz):	138.6, 129.2, 128.5, 128.4, 66.3, 54.2, 40.9.
v_{max}/ cm^{-1} :	3357, 3299, 3081, 3022, 2940, 1578.

Method B3: Using NaBH$_4$/BF$_3$.Et$_2$O

Boron trifluoride diethyl etherate (5.2 mL, 42 mmol) was slowly added to a stirred suspension of NaBH$_4$ (0.77 g, 20.40 mmol) in THF (10 mL) at 0 °C under nitrogen; then *(S)*-2-amino-3-phenyl-propionic acid (1.9 g, 12 mmol) was added in portions to the white slurry. The reaction mixture was stirred at room temperature for 16 hrs; MeOH was then added to destroy the excess of NaBH$_4$. The solution was concentrated under reduced pressure to remove the THF. The resulting white slurry was stirred at room temperature for 10 hr with 20 % NaOH (53.3 mL). The aqueous solution was extracted with CHCl$_3$ (4 x 75 mL), and the combined organic layers were washed with brine, dried and the solvent was evaporated under reduced pressure to give *(S)*-2-amino-3-phenyl-propan-1-ol (9) (1.7 g, 90 %) as a white solid; which showed the same data to those provided by the method above.

Preparation of (*(S)*-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester (12).

Ethyl chloroformate (0.98 g, 9.03 mmol) was slowly added to a stirred solution of *(S)*-2-amino-3-phenyl-propan-1-ol (1 g, 6 mmol) in 1N NaHCO$_3$ solution (25 mL). The mixture was stirred for an additional 3 hrs at room temperature. The product was extracted with ethyl acetate (100 x 3). The combined organic layers were dried over MgSO$_4$, and the solvent was removed to give an oil, which solidified under reduced pressure at 60 °C to give (*(S)*-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester (12) (5.32 g, 92 %), which showed the same data as formethod above.

Reduction of *(S)*-2-ethoxycarbonylamino-3-phenyl-propionic acid with NaBH$_4$-H$_2$SO$_4$

(S)-2-Ethoxycarbonylamino-3-phenyl-propionic acid (14.9 g, 63.2 mmol) was added to a stirred suspension of NaBH$_4$ (4.78 g, 126 mmol) in THF (100 mL). The flask was immersed in an ice-water bath and a solution of concentrated H$_2$SO$_4$ (6.6 mL, 63.2 mmol) in ether (20 mL) was added dropwise at such a rate to maintain the reaction mixture below 20 °C. The reaction mixture was then stirred for 16 hrs at room temperature, then MeOH (10 mL) was added carefully to destroy the excess borane. The mixture was concentrated to ca. 50 mL and 5N NaOH (100 mL) was added. The solvent that distilled below 100 °C was removed by rotary evaporator and the residue of the reaction mixture was then heated at a reflux for 3hrs. The turbid aqueous mixture was cooled, filtered through a thin pad of celite and then washed with water. The filtrate and the washings were combined and diluted with additional water to ca. 100 mL. The product was extracted with CH$_2$Cl$_2$ (3 x 150 mL). The combined organic layers were dried and evaporated to give a solid, *(S)*-2-amino-3-phenyl-propan-1-ol (**9**); this was re-crystallized from 1:1 ethyl acetate and petroleum (11.3 g, 80 %). This showed identical spectrum to those above.

Preparation of (*(S)*-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester (12).

Triethylamine (11.5 g, 113 mmol) was slowly added to a stirred solution of *(S)*-2-amino-3-phenyl-propionic acid (26.99 g, 163.4 mmol) in tetrahydrofuran (420 mL) at −10 °C. Ethyl chloroformate (12.4 g, 113.8 mmol) was then added at −10 °C. The reaction mixture was then stirred for 15 min, then NaBH$_4$ (6.502 g, 171.9 mmol) was added in one portion to the resulting white slurry. The mixture was allowed to reach 0 °C, then MeOH (350 mL) was added dropwise. The reaction mixture was stirred for 15 min, then neutralized with 1N H$_2$SO$_4$. The organic solvent was evaporated under reduced pressure and the resulting product was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with H$_2$SO$_4$ (1N, 35 mL), H$_2$O (100 mL), aq. NaHCO$_3$ (50 mL, 5 %), then H$_2$O (150 mL). The organic layer was dried and evaporated to give (*(S)*-1-hydroxymethyl-2-phenyl-ethyl)carbamic acid ethyl ester (**12**) (12.3 g, 55 %). This showed identical spectra to those above.

Preparation of (S)-4-Benzyl-oxazolidin-2-one (1)
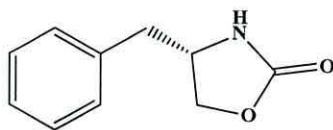
Powdered potassium carbonate (0.99 g, 7.21 mmol) was added to ((S)-1-hydroxymethyl-2-phenyl-ethyl)-carbamic acid ethyl ester (1.70 g, 7.62 mmol). The mixture was then heated under reduced pressure at 125–130 °C (oil bath), until gas evolution stopped. The reaction mixture was then cooled to room temperature to give a white solid, (S)-4-Benzyl-oxazolidin-2-one (1) (0.68 g, 83 %),[146] which was recrystallized from ethylacetate / hexane (1:1).

mp : 88-89 °C, (lit.[146] mp 87-88 °C)

$[\alpha]_D^{26}$: - 66 (c = 1.05, CHCl$_3$), lit.[146] $[\alpha]_D^{22}$ = -62 (c = 1, CHCl$_3$).

δ_H(500 MHz): 7.3 -7.2 (5H, m), 6.2 (1H, br s), 4.35 (1H, br t, J 8.2 Hz), 4.08 (2H, m),

2.91 (1H, dd, J 6.5, 13.5 Hz), 2.86 (1H, dd, J 6.5, 13.2 Hz).

δ_C(126 MHz): 159.7, 135.8, 128.9, 128.6, 126.8, 69.2, 53.4, 40.9.

v_{max}/ cm^{-1} : 3284, 2925, 1709,1610, 1021.

Preparation of (1Z,4Z,7Z)-cyclonona-1,4,7-triene

Preparation of (Z)-9,9-dichlorobicyclo[6.1.0]non-4-ene (51)
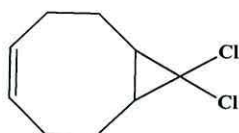
Sodium hydroxide (222.0 g, 5.55 mol, 50 % in water) was added as portions every 10 minutes to a stirred solution of 1,5-cyclooctadiene (100 g, 920 mmol), chloroform (500 mL) and cetrimide (4.5 g, 10 mmol). The reaction mixture was stirred vigorously over night at room temperature. The product was extracted with dichloromethane (3 x 400 mL) and the combined organic layers washed with water and brine (500 mL), and evaporated. Afterthat, Petrol (100 ml) was added to the residue, dried over magnesium sulphate then filtered and evaporated to give yellow oil. Vacuum distillation of the residue at 70 °C and

14 mm Hg afforded unreacted 1,5-cyclooctadiene (10 g, 16 %). The residue was distilled under high vacuum (0.5 mm/Hg) to give (Z)-9,9-dichlorobicyclo[6.1.0]non-4-ene (51) (110 g, 60 %), as an oil; and a solid residue of bis-adduct, 5,5,10,10-tetrachlorotricyclo[7.1.0.0^{4,6}]decane (60 g, 21%).[147]

b.p.   85 °C

δ_H(500 MHz):   5.58 (2H, br. pent, J 11 Hz), 2.37 (2H, m), 2.11 (4H, m), 1.86 (2H, m), 1.66 (2H, m).

δ_C(126 MHz):   129.1, 66.3, 32.1, 25.9, 24.5.

ν_{max}/ cm^{-1} :   3012, 2840, 1662, 1482,1442, 777, 550.

Preparation of (Z)-bicyclo[6.1.0]non-4-ene (52).
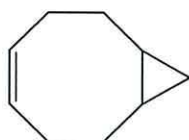
A solution of 9,9-dichlorobicyclo[6.1.0]non-4-ene (85.0 g, 445 mmol) and *tert*-butanol (195 g, 2.64 mol, 252 mL) in dry tetrahydrofuran (400 mL) was added slowly to a stirred suspension of lithium wire (24.0 g, 3.45 mol) in dry THF (400 mL) maintaining the temperature below 5 °C. The mixture was heated at 100 °C for 18 hrs, when G.C analysis showed no starting material was left. The reaction mixture was cooled to R.T. and poured into ice-water (1L). The product was extracted with petrol (3 x 500 mL), and the combined organic layers were washed with water and brine (500 mL), dried over MgSO$_4$ and filtered. The solvent was removed by simple distillation to give a residue which was purified by flash distillation under reduced pressure to afford (Z)-bicyclo[6.1.0]non-4-ene (52) (54.0 g, 91 %).[148]

b.p.:   75 – 80 °C at 14 mm/Hg

δ_H(500 MHz):   5.65 (2H, t, J 4.4 Hz), 2.28 (2H, m), 2.12 (4H, m), 1.28 (2H, m), 0.86 (2H, m), 0.67 (1H, dt, J 4.1, 8.2 Hz), -0.15 (1H, br. q, J 5.35 Hz).

δ_C(126 MHz):   130.3, 56.6, 53.5, 35.1, 35.0, 25.1, 24.3, 16.7, 14.0.

ν_{max}/ cm^{-1} :   3059, 2991, 1655, 1462, 1020.

Preparation of (1*Z*,4*Z*,7*Z*)-cyclonona-1,4,7-triene (56)

A solution of bromine (42 mL) in CCl$_4$ (65 mL) was added slowly to a stirred solution of bicyclo[6.1.0]non-4-ene (100 g, 818 mmol) in carbon tetrachloride (500 mL) at 0 °C, until the red colour persisted. When the G.C. analysis showed no starting material was left, the mixture was concentrated on a rotary evaporator to give a yellow oil, 4,5-dibromobicyclo[6.1.0]nonane (53) (215 g, 94 %),[149] which was used for the next step without purification. Anhydrous lithium carbonate (260 g, 3.51 mol) was added to a mechanically stirred solution of 4,5-dibromobicyclo[6.1.0]nonane (100 g, 354 mmol) in anhydrous DMF (700 mL), followed by the addition of anhydrous lithium fluoride (91.8 g, 3.54 mol). The reaction mixture was heated at 100 °C with stirring for 36 hrs, when G.C analysis showed no starting material was left, then cooled to R.T. and poured into ice - water (1L). The product was extracted with hexane (3 x 400 mL) the combined organic layers were washed with water and brine (400 mL) then dried over MgSO$_4$.

The solvent was removed by simple distillation and the residue was distilled under high vacuum (0.5 mm/Hg). The distillate was heated in a closed system at 185 °C for one hour, then allowed to cool to give a white solid which was filtered to give crystals of (1*Z*,4*Z*,7*Z*)-cyclonona-1,4,7-triene (56) (21.8 g, 69 %).[77,91]

mp: 49 - 50 °C (lit.[77] mp: 50-51 °C)

Mass Found M$^+$::   120.0949   (C$_9$H$_{12}$) required   120.0939

δ_H(500 MHz):   5.49 (6H, m), 3.76 (3H, br s), 2.23 (3H, br.s).[91]

δ_c(126 MHz):   127.3, 24.6

v_{max}/ cm^{-1} :   3014, 2964, 1680, 719.

Preparation of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-ol (58)
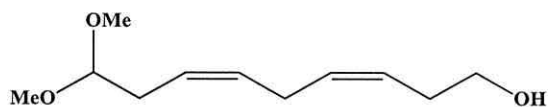
A stirred solution of (1Z,4Z,7Z)-cyclonona-1,4,7-triene (4.99 g, 41.5 mmol) in 150 mL of a mixture of (20 THF:80 methanol) in a three-neck round bottom flask which was fitted to admit ozone, with a digital thermometer and a condenser. The flask was cooled to -60 — - 55 °C, then ozone was passed through a stirred solution for 6.5 min (4L/min O_2, 6.36 mmol/min O_3). After that, nitrogen was passed through the reaction mixture over 5 min then the cooling bath was removed. *p*-Toluensulfonic acid monohydrate (0.35 g, 1.84 mmol) was added at -35 — -20 °C, then the solution was allowed to reach room temperature and stirred for 3 hrs. The reaction mixture was cooled to -10 °C and sodium borohydride (2.5 g, 66 mmol) was added in small portions. The mixture was allowed to reach room temperature over 30 min, then quenched with ice water (250 mL) and the product was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography on silica eluting with petrol: ethyl acetate (5:2) to give (Z)-6,6-dimethoxyhex-3-en-1-ol[150] (1.5 g, 18%) and (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-ol (**58**) (2.5 g, 43 %).

Mass Found m/z: 200.03   ($C_{11}H_{20}O_3$)

δ_H(500 MHz):   5.47 (2H, m), 5.39 (2H, m), 4.38 (1H, t, *J* 5.05 Hz), 3.64 (2H, t, *J* 4.75 Hz), 3.33 (6H, s), 2.86 (2H, br t, *J* 7.25 Hz), 2.42 (2H, br t, *J* 6.2 Hz), 2.38 (2H, br q, *J* 6.76 Hz).

δ_C(126 MHz):   130.4, 130.1, 125.8, 123.8, 104.0, 61.9, 52.9, 31.0, 30.9, 25.8.

v_{max}/ cm^{-1} :   3400, 2938, 2831, 1690, 1444, 1363, 1191, 1056.

Preparation of (3*Z*,6*Z*)-9,9-dimethoxynona-3,6-dien-1-yl 4-methylbenzenesulfonate (59)
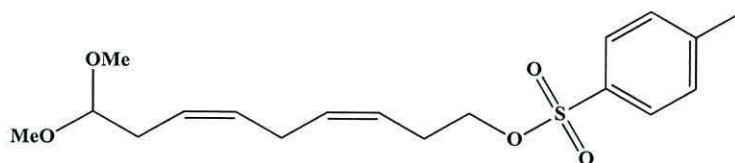
p-Toluenesulfonyl chloride (0.85 g, 4.22 mmol) was added to a stirred solution of 9,9-dimethoxynona-3,6-dien-1-ol (0.52 g, 2.50 mmol) in pyridine (2 mL) at 0 °C. The reaction mixture was stirred for 2 hrs at 0 °C, then left overnight in the fridge. After that, water (10 mL) was slowly added to the mixture at 0 °C, followed by pouring it into a separating funnel which contained water (20 mL); the product was extracted with dichloromethane (3 x 30 mL). The combined organic layers were cooled to -5°C and a solution of 2M hydrochloric acid (40 mL) was added dropwise maintaining the temperature below 5°C (until the water layer became acidic). The organic layer was separated and the water layer was re-extracted with dichloromethane (30 mL). The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give a crude product. The crude product was purified by column chromatography on silica eluting with petrol:ethyl acetate (10:1) to give (3*Z*,6*Z*)-9,9-dimethoxynona-3,6-dien-1-yl 4-methyl-benzenesulfonate (59) (0.78 g, 89 %).

Found (M+Na)$^+$: 377.1019 C$_{18}$H$_{26}$O$_5$S requires: 377.1399

δ_H(500 MHz): 7.77 (2H, dd, *J* 1.95, 8.3 Hz), 7.33 (2H, br d, *J* 7.9 Hz), 5.38 (4H, m)

4.35 (1H, br ddd, *J* 1.9, 5.7, 11.45 Hz), 4.00 (2H, ddd, *J* 1.5,

5.48, 18.96 Hz), 3.31 (6H, s), 2.73 (2H, br t, *J* 5.4 Hz), 2.42 (3H, br, s)

2.39 (4H, br m).

δ_C(126 MHz): 131.4, 129.8, 129.6, 127.8, 124.2, 123.4, 104.0, 69.5, 52.6, 31.0, 27.0,

25.8, 21.6

ν_{max}/ cm^{-1}: 2931, 2831, 1598, 1495, 1448, 1361, 1189, 1177, 964, 816.

Preparation of (3Z,6Z)-9-iodo-dimethoxynona-3,6-diene (63)
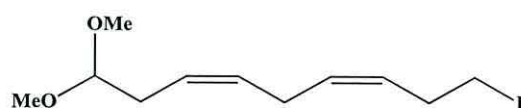
(3Z,6Z)-9,9-Dimethoxynona-3,6-dien-1-yl 4-methylbenzenesulfonate (0.17 g, 0.50 mmol) was added to a stirred solution of sodium iodide (0.5 g, 3.3 mmol) in acetone (5 mL), followed by the addition of sodium hydrogen carbonate (0.2 g, 2.4 mmol). The reaction mixture was refluxed for 2 hrs, then cooled to room temperature. The acetone was evaporated and the residue was diluted with dichloromethane (10 mL), washed with water (10 mL), then the organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried, evaporated to give a residue which was purified by column chromatography on silica eluting with petrol : ethyl acetate (10:1) to give (3Z,6Z)-9-iododimethoxynona-3,6-diene (63) (0.13 g, 87 %).

δ_H(500 MHz):   5.52 (4H, m), 4.39 (1H, t, J 5.7 Hz), 3.35 (6H, s), 3.15 (2H, br t,

J 7.2Hz), 2.81 (2H, br t, J 6.9 Hz), 2.67 (2H, br q, J 6.6 Hz), 2.41 (2H,

br t, J 6.0 Hz).

δ_C(126 MHz):   130.2, 129.8, 128.4, 124.2, 104.1, 53.0, 31.4, 31.1, 26.0, 5.0.

v_{max}/ cm^{-1} :   2932, 2828, 1444, 1240, 1169, 1123, 1059, 824.

Attempted preparation of (3Z,6Z)-1,1-dimethoxyheptadeca-3,6-diene
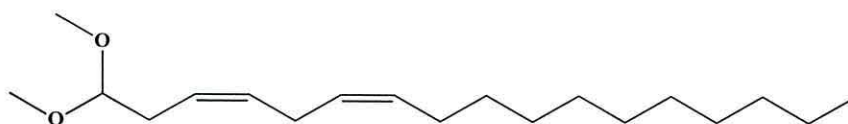
Method 1

A round bottom flask fitted with a reflux condenser and magnetic stirring bar, was charged with magnesium turnings (0.15 g, 6.17 mmol) and tetrahydrofuran (2 mL). 1-Bromoheptane (0.50 g, 2.79 mmol) in tetrahydrofuran (2 mL), was added gradually so as to maintain the mixture just at reflux. After that the reaction mixture was refluxed for 1 hour to give heptylmagnesium bromide. Heptylmagnesium bromide was added to a stirred solution of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl-4-methylbenzenesulfonate (0.20 g,

0.52 mmol) in dry THF (3 mL) at -30 °C under nitrogen atmosphere. The reaction mixture was stirred for 10 min at -30 °C, allowed to reach room temperature and stirred for 16 hrs,then quenched with sat. aq. ammonium chloride (4 mL) at -10 °C. The product was extracted with ethyl acetate (3 x 20 mL), the combined organic layers were dried over magnesium sulphate and evaporated to give residue. The NMR spectrum showed starting material peaks.

Method 2

Heptylmagnesium bromide prepared as before was added to a stirred solution of lithium tetrachlorocuprate in THF at -30 °C. The mixture was stirred for 1 hr before addition of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl 4-methylbenzenesulfonate (0.2 g, 0.5 mmol) in THF at -30 °C. The mixture was stirred at -30 °C for 2hrs then allowed to reach room temperature and stirred for 16 hrs, work up as above to give a residue.The ^{1}H NMR spectrum again showed starting material peaks.

Method 3

Heptylmagnesium bromide was prepared by using magnesium turnings (0.15 g, 6.17 mmol), tetrahydrofuran (2 mL) and 1-bromoheptane (0.3 g, 1.6 mmol). It was reacted with a solution of (3Z,6Z)-9-iododimethoxynona-3,6-diene (0.1 g, 0.3 mmol) in THF (4 mL) at -30 °C. The mixture was stirred at this temperature for 30 min, then worked up as above. The NMR spectrum showed no coupling and just starting material peaks were present.

Preparation of (2E,6Z)-9-iodonona-2,6-dienal (64)
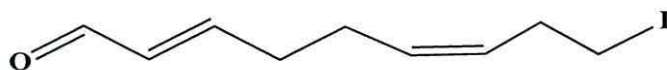
p-Toluenesulfonic acid monohydrate (0.07 g, 0.36 mmol) was added to a stirred solution of (3Z,6Z)-9-iodo-1,1-dimethoxynona-3,6-diene (0.32 g, 0.91 mmol) in acetone (10 mL) and water (5 mL). The mixture was refluxed for 2 hrs, quenched by pouring it into ice-water (20 mL), then the product was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over MgSO$_4$, filtered and evaporated to give a crude

product which was purified by column chromatography on silica eluting with petrol : ethylacetate (10:1) to give (2*E*,6*Z*)-9-iodonona-2,6-dienal (**64**) (0.18 g, 71 %).

δ_H(500 MHz): 9.52 (1H, d, *J* 7.85 Hz), 6.87 (1H, dt, *J* 6.6, 15.8 Hz), 6.61 (1H, m), 5.54 (1H, m), 5.41 (1H, m), 3.17 (2H, t, *J* 6.95 Hz), 2.66 (2H, q, *J* 6.6 Hz), 2.44 (2H, q, *J* 6.9 Hz), 2.28 (2H, q, *J* 7.25 Hz).

δ_C(126 MHz): 193.9, 157.3, 133.3, 130.1, 129.5, 32.4, 31.3, 25.7, 5.0.

v_{max}/ cm^{-1} : 2935, 2816, 2737, 1722, 1688, 1635, 1423, 1242, 1169, 1120, 973, 720.

Preparation of (3*Z*,6*Z*)-1,1-dimethoxynona-3,6-diene (66)
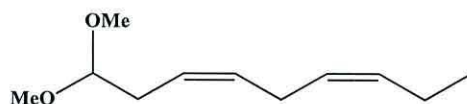
Method (1):

A solution of (3*Z*,6*Z*)-9-iodo-1,1-dimethoxynona-3,6-diene (0.4 g, 1.3 mmol) in tetrahydrofuran (3 mL) was added dropwise to a suspension of lithium aluminium hydride (0.3 g, 9.2 mmol) in tetrahydrofuran (13 mL) at 0 °C. The mixture was stirred overnight, then diluted with THF (5 mL) and quenched with sat.aq. sodium sulfate (3 mL) at -10 °C. The mixture was stirred until a white precipitate had formed, then THF (5 mL) and MgSO$_4$ were added. The mixture was filtered through silica and MgSO$_4$. The filtrate was evaporated and the crude product was purified by column chromatography on silica eluting with petrol:ethyl acetate (20:1) to give (3*Z*,6*Z*)-1,1-dimethoxynona-3,6-diene (**66**) (0.2 g, 86 %).[95]

δ_H(400 MHz): 5.51-5.39 (4H, m), 4.39 (1H, t, *J* 5.76 Hz), 3.34 (6H, s), 2.80 (2H, t, *J* 7.12 Hz), 2.41 (2H, t, *J* 6.08 Hz), 2.07 (2H, pent, *J* 7.48 Hz), 0.97(3H, t, *J* 7.52 Hz).

δ_C(126 MHz): 132.1, 130.6, 126.7, 123.6, 104.1, 52.9, 30.9, 25.7, 20.5, 14.2.

v_{max}/ cm^{-1} : 2961, 2831, 1657, 1462, 1362, 1124, 1061, 756.

Method (2):

A solution of (3*Z*,6*Z*)-9,9-dimethoxynona-3,6-dien-1-yl 4-methylbenzenesulfonate (2.0 g, 5.6 mmol) in tetrahydrofuran (20 mL) was added dropwise to a suspension of lithium aluminium hydride (2.0 g, 52 mmol) in tetrahydrofuran (100 mL) 0 °C. The reaction mixture was stirred 16 hrs and worked up as above to give (3*Z*,6*Z*)-1,1-dimethoxynona-3,6-diene (**66**) (0.9 g, 90 %), which showed identical spectra to those above.

Preparation of (3*E*,6*Z*)-nona-2,6-dienal (67)

A solution of (3*Z*,6*Z*)-1,1-dimethoxynona-3,6-diene (0.20 g, 1.02 mmol) in acetone, conc. HCl (20:1) (20 mL) and water (0.3 mL) was stirred for 3 hrs, then quenched with sat.aq. sodium hydrogen carbonate (4 mL) at 0 °C. The mixture was extracted with dichloromethane (3 x 25 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated at reduced pressure to give a crude product which was purified by column chromatography on silica eluting with petrol: ethyl acetate (10:1) to give (3*E*,6*Z*)-nona-2,6-dienal (**67**) (0.12 g, 80 %).[82]

δ_H(500 MHz) :   9.52 (1H, d, *J* 7.9 Hz), 6.88 (1H, dt, *J* 6.6, 15.75 Hz), 6.17 (1H, m),5.48

(1H, m), 5.34 (1H, m), 2.43 (2H, br q, *J* 6.6 Hz), 2.29 (2H, br q, *J* 7.25

Hz), 2.08 (2H, m), 0.99 (3H, t, *J* 7.55 Hz).

δ_C(126 MHz):   194.0, 158.0, 133.3, 133.2, 126.7, 32.7, 25.4, 20.6, 14.2.

v_{max}/ cm^{-1} :   2935, 2737, 1722, 1688, 1635, 1423, 1212, 1169, 1120, 973, 720.

Preparation of (3Z,6Z)-nona-3,6-dienal (68)

Several methods were attempted to prepare (3Z,6Z)-nona-3,6-dienal:[82,151]

Method 1

p-Toluenesulfonic acid monohydrate (0.01 g, 0.05 mmol) was added to a stirred solution of (3Z,6Z)-1,1-dimethoxynona-3,6-diene (0.03 g, 0.16 mmol) in tetrahydrofuran (2 mL) and water (0.2 mL) at room temperature. After that the mixture was stirred for 30 min, then sat. aq. sodium hydrogen carbonate (1 mL) was added at 0 °C. The product was extracted with ether (2 x 15 mL) and the combined organic layers were dried over MgSO₄, filtered and evaporated to give a crude product (0.17 g, 75 %), which was a mixture of (2E,6Z)-nona-2,6-dienal (**67**) and (3Z,6Z)-nona-3,6-dienal (**68**) in ratio 1:1.

Method 2

(3Z,6Z)-1,1-Dimethoxynona-3,6-diene (0.2 g, 1.0 mmol) was added to a stirred solution of oxalic acid in acetone (4 %) (10 mL) and water (0.3 mL), at room temperature for 3.5 hours then quenched with sat.aq.sodium chloride (5 mL). The product was extracted with ether (3 x 15 mL), and then the combined organic layers were washed with water, sat.aq. sodium hydrogen carbonate and brine, dried over MgSO₄ and evaporated to give a crude product which was purified by column chromatography on silica eluting with petrol : ethylacetate (10:1) to give a mixture of (2E,6Z)-nona-2,6-dienal (**67**) and (3Z,6Z)-nona-3,6-dienal (**68**) in ratio 1:2 .

Method 3

A solution of formic acid 80 % in water (5.2 mL) was added dropwise to a stirred solution of (3Z,6Z)-1,1-dimethoxynona-3,6-diene (0.42 g, 2.12 mmol) in dioxane (6 mL) at room temperature. The reaction mixture was stirred for 1.5 hrs at room temperature then water (10 mL) was added. The product was extracted with dichloromethane (3 x 10 mL) and the combined organic layer was washed with NaHCO₃ (10 mL), brine (5 mL) then dried over MgSO₄ and evaporated to give (3Z,6Z)-nona-3,6-dienal (**68**) (0.29 g, 96 %),[96,152] which was used for the next step without purification.

δ_H(400 MHz): 9.68 (1H, t, J 1.84), 5.7-5.27 (4H, m), 3.24 (2H, d, J 7.16 Hz), 2.79 (2H, t, J 7.24 Hz), 2.07 (2H, pent, J 7.4 Hz), 0.96 (3H, t, J 7.52 Hz).

δ_C(126 MHz): 199.4, 133.5, 132.6, 125.9, 118.3, 67.0, 42.4, 25.8, 20.5, 14.1

v_{max}/ cm^{-1} : 2859, 1727, 1646, 1609, 1494, 1452, 1122, 874, 717.

Preparation of diene pheromones

Preparation of (3Z,6Z)-nona-3,6-dien-1-ol (86)
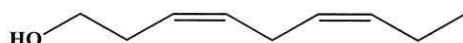
(3Z,6Z)-Nona-3,6-dienal (0.22 g, 1.43 mmol) in dry tetrahydrofuran (5 mL) was added to a stirred suspension of lithium aluminium hydride (0.16 g, 4.21 mmol) in tetrahydrofuran (20 mL) at 0 °C under nitrogen. The mixture was stirred for 16 hrs at room temperature then diluted with THF (20 mL), followed by quenching with sat.aq. sodium sulfate (10 mL) at 0 °C until a white precipitate was formed. The mixture was filtered through a bed of silica and MgSO$_4$. The filtrate was evaporated and the crude product was purified by column chromatography on silica eluting with petrol: ethyl acetate (5:2) to give (3Z,6Z)-nona-3,6-dien-1-ol (86) (0.16 g, 88 %).[82,105] This was identical to the literature by H NMR.[105]

δ_H(400 MHz): 5.58-5.52(4H, m), 3.66 (2H, br t, J 6.4 Hz), 2.82 (2H, t, J 7.2 Hz), 2.35 (2H, br q, J 6.6 Hz), 2.08 (2H, br pent., J 7.1 Hz), 0.97 (3H, t, J 7.6 Hz).

δ_C(126 MHz): 132.1, 131.5, 126.8, 125.3, 62.2, 30.7, 25.6, 20.5, 14.2.

v_{max}/ cm^{-1} : 3400, 2963, 2932, 2862, 1609, 1493, 1050.

Preparation of triene pheromones

Preparation of (3Z,6Z,9Z)-heptadeca-3,6,9-triene (69)
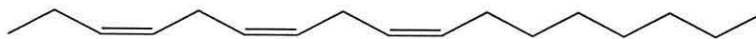
Sodium bis(trimethylsilyl)amide (2.8 mL, 2.8 mmol) was added dropwise to a stirred slurry of octyltriphenylphosphonium bromide (0.8 g, 1.7 mmol) in dry THF (25 mL) -78 °C, under nitrogen. The reaction mixture was allowed to reach room temperature and stirred for 30 min, then cooled again to -78 °C, and (3Z,6Z)-nona-3,6-dienal (0.2 g, 1.4 mmol) in dry THF (3 mL) was added. The mixture was stirred and allowed slowly to reach room temperature, then cooled to 0 °C and quenched with sat.aq. NH$_4$Cl (15 mL). The product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over MgSO$_4$ and evaporated. The residue was purified by column chromatography on silica eluting with petrol to give (3Z,6Z,9Z)-heptadeca-3,6,9-triene (69) (0.2 g, 75 %),[91]

Found m/z: 234 (C$_{17}$H$_{30}$ requires: 234)

δ_H(400 MHz):   5.44 - 5.30 (6H, m), 2.82 (4H, t, J 6.08 Hz), 2.07 (4H, m), 1.28 (10H, m),

0.98 (3H, t, J 7.56 Hz), 0.89 (3H, t, J 6.64 Hz).

δ_c(126 MHz):   131.9, 130.4 , 128.3, 128.2, 127.6, 127.1, 31.8, 30.9, 29.6, 29.3,

29.2, 27.2, 25.6, 25.5, 22.6, 20.5, 14.2, 14.1.

v_{max}/ cm^{-1} :   3015, 2926, 2859, 1751, 1607, 1493, 824, 721.

Preparation of (3Z,6Z,9Z)-octadeca-3,6,9-triene (70)

(3Z,6Z,9Z)-Octadeca-3,6,9-triene (70) (0.25 g, 71 %) was prepared as above from (3Z,6Z)-nona-3,6-dienal (0.20 g, 1.45 mmol), triphenyl(nonyl)phosphonium bromide (0.81 g, 1.72 mmol) and sodium bis(trimethylsilyl)amide (2.6 mL, 2.6 mmol) in dry THF (25 mL).The product showed the same ^{1}H NMR spectrum to the one reported in the literature.[91]

Found m/z: 248 (C$_{18}$H$_{32}$ requires   248)

δ_H(400 MHz):	5.44 (6H, m), 2.82 (4H, t, J 6.08 Hz), 2.07 (4H, m), 1.28 (12H, m),
	0.98 (3H, t, J 7.52 Hz), 0.89 (3H, t, J 6.6 Hz).
δ_C(126 MHz):	131.9, 130.4, 128.3, 128.2, 127.6, 127.1, 31.8, 29.6, 29.5, 29.3, 29.2,
	27.2, 25.6, 25.5, 22.6, 20.5, 14.2, 14.1.
v_{max}/ cm^{-1} :	3011, 2925, 2854, 1607, 1493, 875, 720.

Preparation of (3Z,6Z,9Z)-nonadeca-3,6,9-triene (71)

(3Z,6Z,9Z)-Nonadeca-3,6,9-triene (71)[87,94] (0.21 g, 71 %), was prepared as above from (3Z,6Z)-nona-3,6-dienal (0.15 g, 1.08 mmol), triphenyl(decyl)phosphonium bromide (0.63 g, 1.30 mmol) and sodium bis(trimethylsilyl)amide (1.95 mL, 1.95 mmol) in dry THF (25 mL). The product showed the same NMR spectrum to the one reported in the literature.

Found m/z:	262 (C$_{19}$H$_{34}$ requires 262)
δ_H(400 MHz):	5.44 (6 H, m), 2.82 (4H, t, J 6.08 Hz), 2.07 (4H, m), 1.28 (14H, m), 0.98
	(3H, t, J 7.56 Hz), 0.89 (3H, t, J 6.64 Hz).
δ_C(126 MHz) :	131.9, 130.4, 128.3, 128.2, 127.6, 127.1, 31.8, 29.7, 29.6, 29.5, 29.32,
	29.31, 27.2, 25.6, 25.5, 22.6, 20.5, 14.3, 14.1.
v_{max}/ cm^{-1} :	3013, 2925, 2855, 1646, 1493, 875, 721.

Preparation of (3Z,6Z,9Z)-eicosa-3,6,9-triene (72)

(3Z,6Z,9Z)-Eicosa-3,6,9-triene (72)[87,92] (0.25g, 62 %) was prepared as above from triphenyl(undecyl)phosphonium bromide (0.43 g, 0.86 mmol),[153,154] (3Z,6Z)-nona-3,6-dienal (0.11 g, 0.72 mmol) and sodium bis(trimethylsilyl)amide (1.3 mL, 1.3 mmol) in dry THF (20 mL).

Found M$^+$, m/z: 276 (C$_{20}$H$_{36}$ requires: 276)

δ_H(400 MHz):   5.43- 5.29 (6H, m), 2.82 (4H, t, J 6 Hz), 2.07 (4H, m), 1.27 (16H, m),

0.98 (3H, t, J 7.52 Hz), 0.88 (3H, t, J 6.52 Hz).

δ_C(126 MHz):   131.9, 130.4 , 128.3, 128.2, 127.6, 127.1, 31.9, 29.7, 29.6, 29.5, 29.3,

29.2, 27.2, 25.6, 25.5, 22.6, 20.5, 14.2, 14.1.

v_{max}/ cm^{-1} :   3012, 2925, 2854, 1647, 1493, 1399, 875, 724.

Preparation of (3Z,6Z,9Z)-henicosa-3,6,9-triene (73)

Sodium bis(trimethylsilyl)amide (2.6 mL, 2.6 mmol) was added dropwise to a stirred slurry of triphenyl(dodecyl)phosphonium bromide (0.8 g, 1.7 mmol) in dry THF (25 mL), under nitrogen. The reaction mixture was allowed to reach room temperature and stirred for 30 min, then cooled again to -78 °C and (3Z,6Z)-nona-3,6-dienal (0.2 g, 1.4 mmol) in dry THF (3 mL) was added. The reaction mixture was stirred and allowed slowly to reach room temperature, then cooled down to 0 °C and worked up as above to give (3Z,6Z,9Z)-henicosa-3,6,9-triene (73) (0.3 g, 71 %),[92,95,87] whose NMR spectra were identical to the ones reported.

Found M$^+$, m/z: 290   (C$_{21}$H$_{38}$ requires: 290)

δ_H(400 MHz):   5.44 (6H, m), 2.82 (4H, t, J 6.04 Hz), 2.07 (4H, m), 1.27 (18H, m),

0.98 (3H, t, J 7.52 Hz), 0.89 (3H, t, J 6.56 Hz).

δ_C(126 MHz):   131.9, 130.4, 128.2, 128.2, 127.6, 127.1, 31.9, 29.68, 29.65, 29.56,

29.35, 29.33, 27.2, 25.6, 25.5, 22.6, 20.5, 14.2, 14.1.

v_{max}/ cm^{-1} :   2925, 2854, 1647, 1493, 1050, 875, 721.

Preparation of (3Z,6Z,9Z)-pentacosa-3,6,9-triene (74) [98]

Sodium bis(trimethylsilyl)amide (2.40 mL, 2.40 mmol) was added dropwise to a stirred slurry of triphenyl(dodecyl)phosphonium bromide[161] (0.9 g, 1.6 mmol) in dry THF (25 mL) at -78 °C under nitrogen. The mixture was allowed to reach room temperature and

stirred for 30 min, then cooled again to -78 °C and (3Z,6Z)-nona-3,6-dienal (0.15 g, 1 mmol) in dry THF (3 mL) was added. The mixture was stirred and allowed slowly to reach room temperature, then cooled to 0 °C and quenched with sat.aq. NH$_4$Cl (15 mL). The product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over MgSO$_4$ and evaporated. The residue was purified by column chromatography on silica eluting with petrol to give (3Z,6Z,9Z)-pentacosa-3,6,9-triene (**74**) (0.28 g, 75 %).

Found M$^+$:	346 (C$_{25}$H$_{46}$ requires: 346)
δ_H(400 MHz) :	5.44- 5.29 (6H, m), 2.82 (4H, t, J 6.16 Hz), 2.07 (4H, m), 1.27 (26H, m), 0.99 (3H, t, J 7.52 Hz), 0.89 (3H, t, J 6.64 Hz).
δ_C(126 MHz):	131.9, 130.4, 128.3, 128.2, 127.6, 127.1, 31.9, 29.7, 29.6, 29.5, 29.36, 29.33, 27.2, 25.6, 25.5, 22.6, 20.5, 14.2, 14.1.
v_{max}/ cm^{-1} :	3012, 2854, 1647, 1493, 1399, 1266, 874, 720.

Preparation of (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid (83)
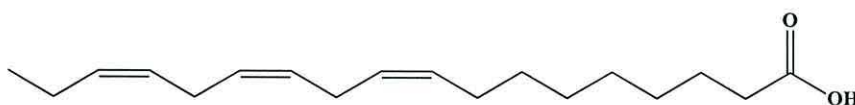
Sodium bis(trimethylsilyl)amide (4.30 mL, 4.30 mmol) was added dropwise to a stirred solution of (8-carboxyoctyl)triphenylphosphonium bromide (0.86 g, 1.72 mmol) in dry THF (25 mL) under nitrogen at -78 °C. The reaction mixture was gradually warmed to room temperature over 30 min. The mixture was cooled again to -78 °C and (3Z,6Z)-nona-3,6-dienal (0.20 g, 1.45 mmol) in dry THF (3 mL) was added and the mixture was allowed to reach room temperature. After 30 min the reaction was quenched with sat.aq. NH$_4$Cl (15 mL) at 0 °C. The product was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over MgSO$_4$ and evaporated. The residue was purified by column chromatography eluting with petrol : ethyl acetate (5:2) to give (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid (**83**) (0.30 g, 75 %). The NMR spectra were identical to the leterature.[101]

δ_H(400 MHz):	10.79 (1H, br s), 5.43-5.29 (6H, m), 2.81(4H, t, J 6.24 Hz), 2.35 (2H, t, J 7.48 Hz), 2.13-2.03 (4H, m), 1.64 (2H, br pent, J 7.4 Hz), 1.43-1.23 (8H, m), 0.99 (3H, t, J 7.52 Hz).
δ_C(126 MHz):	179.5, 131.9, 130.2, 128.3, 128.2, 127.7, 127.1, 33.9, 29.5, 29.2, 29.1, 29.0, 27.1, 25.6, 25.5, 24.6, 20.5, 14.2, 10.9.
v_{max}/ cm^{-1} :	3467, 3014, 2928, 1710, 1609, 1494, 824, 721.

Preparation of (9Z,12Z,15Z)-octadeca-9,12,15-trien-1-ol (84)

(9Z,12Z,15Z)-Octadeca-9,12,15-trienoic acid (0.40 g, 1.42 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.16 g, 4.21mmol) in dry tetrahydrofuran (20 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 16 hrs at room temperature then diluted with THF (5 mL) and quenched with sat.aq.sodiumsulfate (10 mL) at 0 °C until a white precipitate was formed. The precipitate was filtered through a bed of silica. The filtrate was evaporated and the crude product was purified by column chromatography, eluting with petrol: ethyl acetate (5:2) to give (9Z,12Z,15Z)-octadeca-9,12,15-trien-1-ol (84) (0.32 g, 88 %).[92,102]

δ_H(400 MHz):	5.44 (6H, m), 3.65 (2H, t, J 6.6 Hz), 2.82 (4H, br t, J 6.16 Hz), 2.05 (6H, m), 1.58 (2H, m), 1.32 (8H, m), 0.97 (3H, br t, J 7.52 Hz).
δ_C(126 MHz):	131.9, 130.3, 128.2, 127.6, 127.1, 63.0, 32.8, 29.6, 29.4, 29.3, 29.2, 27.2, 25.7, 25.6, 25.5, 20.5, 14.2.
v_{max}/ cm^{-1} :	3437, 3014, 2927, 2857, 1609, 1493, 824, 723.

Preparation of (9Z,12Z,15Z)-octadeca-9,12,15-trienal (85)

(9Z,12Z,15Z)-Octadeca-9,12,15-trien-1-ol (0.19 g, 0.75 mmol) in dichloromethane (7 mL) was added dropwise to a stirred suspension of pyridinium chlorochromate (0.49 g, 2.27 mmol) in dichloromethane (10 mL). The mixture was stirred for 1 hr at room temperature, when the TLC showed no starting material was left; petrol / ethyl acetate (5:1) (15 mL) was added. The precipitate was filtered through a bed of silica and the filtrate was evaporated to give a crude product, which purified by column chromatography, eluting with petrol : ethylacetate (5:1) to give as a colourless oil, (9Z,12Z,15Z)-octadeca-9,12,15-trienal (85)[102] (0.14 g, 73 %).

Found m/z: 262   ($C_{18}H_{30}O$ requires: 262)

δ_H(400 MHz) :   9.77 (1H, t, J 1.84 Hz), 5.43-5.29 (6H, m), 2.81 (4H, t, J 6.16 Hz),

                        2.43 (2H, ddd, J 1.76, 7.32, 14.68 Hz), 2.15-1.99 (4H, m), 1.63 (2H, br

                        pent., J 7.24 Hz), 1.43-1.22 (8H, m), 0.98 (3H, t, J 7.52 Hz).

δ_C(126 MHz):   202.8, 131.9, 130.2, 128.3, 128.2, 127.8, 127.1, 43.9, 29.5, 29.2, 29.1,

                        29.0, 27.1, 25.6, 25.5, 22.1, 20.5, 14.2.

v_{max}/ cm^{-1} :   2858, 1728, 1608, 1494, 824, 725.

Preparation of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl acetate (75)
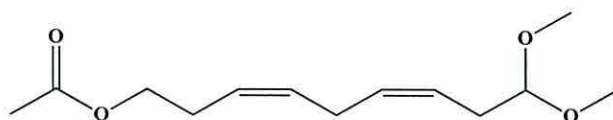
Acetyl chloride (0.85 mL, 12 mmol) was added at 0 °C to a stirred solution of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-ol (0.39 g, 1.99 mmol) and triethylamine (0.8 g, 7.9 mmol, 1.1 mL) in dichloromethane (10 mL). The reaction mixture was stirred for 2 hrs at room temperature. When TLC showed no starting material was left, the reaction mixture was quenched with sat.aq.NH$_4$Cl (10 mL). The product was extracted with dichloromethane (3 x 30 mL).The combined organic layers were dried over MgSO$_4$ and evaporated. The

residue was purified by column chromatography, eluting with petrol:ethyl acetate (5:1) to give (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl acetate (**75**) (0.38 g, 79 %).

Found m/z:	242	($C_{13}H_{22}O_4$ requires:	242)

δ_H(400 MHz): 5.52 - 5.36 (4H, m), 4.39 (1H, br t, J 5.76 Hz), 4.08 (2H, t, J 6.8 Hz), 3.34 (6H, s), 2.82 (2H, br t, J 6.84 Hz), 2.42 (4H, m), 2.05 (3H, s).

δ_C(126 MHz): 171.1, 130.5, 130.1, 124.9, 124.1, 104.0, 63.7, 52.9, 31.0, 26.8, 25.8, 20.9.

v_{max}/ cm^{-1} : 2933, 2861, 1741, 1609, 1493, 1239, 1125, 1051, 824, 723.

Preparation of (3Z,6Z)-9-oxonona-3,6-dien-1-yl acetate (76)
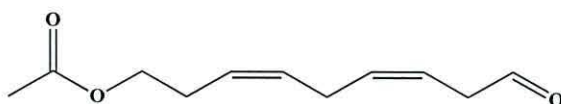
A solution of formic acid 80 % (5.2 mL) was added dropwise to a stirred solution of (3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl acetate (0.4 g, 1.65 mmol) in dioxane (6 mL) at room temperature. The reaction mixture was stirred for 1.5 hrs and worked up as before to give (3Z,6Z)-9-oxonona-3,6-dien-1-yl acetate (**76**) (0.27 g, 84 %).

δ_H(400 MHz): 9.68 (1H, br s), 5.65 (2H, m), 5.38 (2H, m), 4.07 (2H, t, J 6.92 Hz), 3.24 (2H, br d, J 6.88 Hz), 2.82 (2H, t, J 6.48 Hz), 2.41 (2H, br q, J 6.4 Hz), 2.05 (3H, br s).

δ_C(126 MHz): 199.2, 171.1, 132.8, 129.6, 125.5, 118.8, 63.6, 52.9, 42.4, 26.8, 26.0, 20.9.

v_{max}/ cm^{-1} : 2957, 1738, 1698, 1493, 1365, 1239, 1037, 824, 721.

Preparation of (3Z,6Z,9Z)-octadeca-3,6,9-trien-1-yl acetate (78)
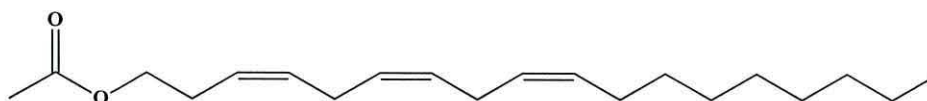
Sodium *bis*(trimethylsilyl)amide (2 mL, 2 mmol) was added to a stirred solution of nonyltriphenylphosphonium bromide (0.62 g, 1.32 mmol) at -78 °C in dry THF (20 mL).

The reaction mixture was gradually warmed to room temperature then cooled down again to -78 °C and (3Z,6Z)-9-oxonona-3,6-dien-1-yl acetate (0.2 g, 1.0 mmol) was added.The reaction was stirred for 1 hr, then quenched as above to give (3Z,6Z,9Z)-octadeca-3,6,9-trien-1-yl acetate (**78**) (0.22 g, 70 %).

Found M$^+$:   306   (C$_{20}$H$_{34}$O$_2$ requires: 306)

δ_H(400 MHz):   5.38 (6H, br m), 4.08 (2H, t, J 6.96 Hz), 2.83 (4H, br q, J 7.04 Hz), 2.42
                (2H, br q, J 6.96 Hz), 2.05 (5H, m), 1.30 (12 H, m), 0.88 (3H, t, J 6.16, Hz)

δ_c(126 MHz):   171.1, 130.7, 130.5, 128.7, 127.6, 127.4, 124.8, 63.8, 31.8, 29.6, 29.5,
                29.3, 29.29, 27.2, 26.8, 25.67, 25.63, 22.6, 20.9, 14.1.

v_{max}/ cm^{-1} :   2926, 1744, 1655, 1493, 1456, 1363, 1237, 1036, 824, 720.

Preparation of (3Z,7E)-9-oxonona-3,7-dien-1-yl acetate (77)
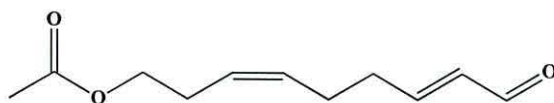
Sodium bis(trimethylsilyl)amide (2 mL, 2 mmol) was added to a stirred solution of (3Z,6Z)-9-oxonona-3,6-dien-1-yl acetate (0.2 g, 1.0 mmol) at -78 °C in dry THF (10 mL). After 3 hrs, the reaction was quenched with sat.aq. NH$_4$Cl (10 mL) at 0 °C. The product was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over MgSO$_4$ and evaporated. The residue was purified by column chromatography eluting with petrol: ethyl acetate (5:2) to give (3Z,7E)-9-oxonona-3,7-dien-1-yl acetate (**77**) (0.19 g, 95 %).

δ_H(400 MHz):   9.51 (1H, d, J 7.84 Hz), 6.85 (1H, dt, J 6.64, 15.44 Hz), 6.16 (1H, dd,
                J 7.84, 15.6 Hz), 5.52-5.40 (2H, m), 4.06 (2H, t, J 6.88 Hz), 2.39 (4H,
                sexet, J 7.04 Hz), 2.29 (2H, q, J 6.96 Hz), 2.04 (3H, s).

δ_c(101 MHz):   193.9, 171.0, 157.5, 133.3, 130.4, 126.2, 63.6, 32.5, 26.8, 25.5, 20.9.

v_{max}/ cm^{-1} :   2926, 1736, 1690, 1494, 1364, 1239, 1037, 824.

Preparation of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (88)
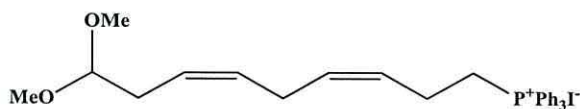
Triphenylphosphine (1.4 g, 5.3 mmol) was added to a stirred solution of (3Z,6Z)-9-iodo-1,1-dimethoxynona-3,6-diene (0.99 g, 3.20 mmol) in dry acetonitrile (7 mL) at room temperature. The mixture was heated for 3 days at 50 °C in the presence of calcium carbonate (0.1 g). After filtration, the filtrate was evaporated and the residue was purified by column chromatography on silica eluting with CH_2Cl_2 / MeOH (95:5) to give ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (**88**) (1.4 g, 71 %).

δ_H(400 MHz):   7.80 (15H, br m), 5.65 (1H, br q, J 7.1 Hz), 5.43-5.31 (3H, m), 4.29 (1H, t, J 5.7 Hz), 3.81 (2H, br dt, J 7.8, 12.1 Hz), 3.28 (6H, s), 2.57 (2H, br t, J 5.88 Hz), 2.40 (2H, m), 2.23 (2H, t, J 5.72 Hz).

δ_c(126 MHz):   135.1, 135.1, 133.7, 133.6, 130.6, 130.4, 130.2, 129.3, 126.4, 126.2, 124.3, 118.3, 117.5, 104.2, 53.4, 31.3, 25.7, 23.5, 23.0, 20.3.

v_{max}/ cm^{-1} :   2930, 2863, 1733, 1610, 1485, 1438, 1188, 824, 721.

Preparation of (*3Z,6Z,9Z*)-1,1-dimethoxypentadeca-3,6,9-triene (89)
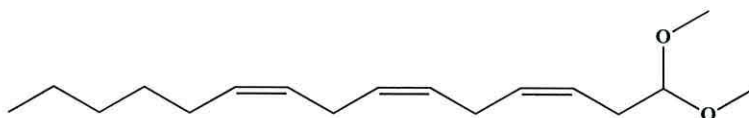
Sodium *bis*(trimethylsilyl)amide (3 mL, 3 mmol) was added to a stirred suspension of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (1.28 g, 2.21 mmol) in THF (25 mL) at -85 °C under nitrogen. The mixture was allowed to reach room temperature for 15 min, before cooling to -85 °C followed by the addition of hexanal (0.14 g, 1.4 mmol). The reaction was stirred for 30 min. at room temperature before quenching with sat.aq. NH₄Cl (15 mL) at 0 °C. The product was extracted with ethyl acetate (3 x 30 mL). The organic layers were dried over MgSO₄ and evaporated. The residue was purified

by column chromatography on silica eluting with petrol:ethyl acetate (10:1) to give (3Z,6Z,9Z)-1,1-dimethoxypentadeca-3,6,9-triene (**89**) (0.28 g, 75 %).

δ_H(400 MHz):   5.38 (6H, m), 4.39 (1H, br t, J 5.8 Hz), 3.34 (6H, s), 2.82 (4H, br pent,

J 5.88 Hz), 2.42 (2H, br t, J 6.2 Hz), 2.06 (2H, br q, J 6.84 Hz), 1.3

(6H, br m), 0.89 (3H, br t, J 6.4 Hz).

δ_C(126 MHz):   130.5, 130.3, 128.6, 127.6, 127.4, 123.8, 104.1, 52.9, 31.5, 31.0, 29.3,

27.2, 25.8, 25.6, 22.5, 14.0.

v_{max}/ cm^{-1} :   2928, 2859, 1493, 1360, 1125, 824, 724.

Preparation of (*3Z,6Z,9Z,12Z*)-octadeca-3,6,9,12-tetraene (91)

3Z,6Z,9Z,12Z-Octadeca-3,6,9,12-tetraene (**91**)[155] (0.18 g, 81 %) was prepared using the same method as above from triphenyl(propyl)phosphonium bromide (0.50 g, 0.99 mmol), sodium bis(tri-methylsilyl)amide (1.70 mL, 1.70 mmol) and (3Z,6Z,9Z)-pentadeca-3,6,9-trienal (0.20 g, 0.94 mmol) in THF (25 mL) under nitrogen.

δ_H(400 MHz):   5.37 (8H, m), 2.83 (6H, br pent, J 5.32Hz), 2.08 (4H, br sext, J 7.44 Hz),

1.31 (6H, m), 0.99 (3H, t, J 7.56 Hz), 0.90 (3H, t, J 6.64 Hz).

δ_C(126 MHz):   132.0, 130.4, 128.5, 128.4, 127.9, 127.8, 127.5, 127.0, 31.5, 29.3,

27.2, 25.7, 25.6, 25.5, 22.5, 20.5, 14.2, 14.0.

v_{max}/ cm^{-1} :   2928, 2859, 1647, 1609, 1493, 824, 727.

Preparation of (*3Z,6Z,9Z*)-1,1-dimethoxyheptadeca-3,6,9-triene (90)
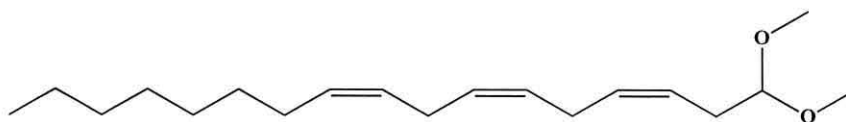
Sodium bis(trimethylsilyl)amide (3.40 mL, 3.40 mmol) was added to a stirred suspension of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (0.97 g, 1.69 mmol) in THF (25mL) at -85 °C under nitrogen. The mixture was allowed to reach room

temperature for 15 min. before cooling to -85 °C followed by the addition of octanal (0.20 g, 1.56 mmol). The reaction was stirred for 30 min. at room temperature, then quenched and worked up as above to give (3Z,6Z,9Z)-1,1-dimethoxyheptadeca-3,6,9-triene (**90**) (0.32 g, 80 %).

δ_H(400 MHz):   5.39 (6H, m), 4.39 (1H, br t, J 5.8 Hz), 3.34 (6H, s), 2.82 (4H, brpent,

                    J 5.84 Hz), 2.41 (2H, br t, J 6.2 Hz), 2.06 (2H, br q, J 6.72 Hz), 1.28 (8H,

                    br m), 0.89 (3H, br t, J 4.72 Hz).

δ_c(126 MHz):   130.5, 130.3, 128.6, 127.6, 127.4, 123.8, 104.0, 52.9, 31.8, 31.0, 29.6,

                    29.3, 29.2, 27.2, 25.8, 25.6, 22.6, 14.1.

v_{max}/ cm^{-1} :   2926, 2856, 1646, 1493, 824, 721.

Preparation of (*3Z,6Z,9Z,12Z*)-eicosa-3,6,9,12-tetraene (92)

(3Z,6Z,9Z,12Z)-Eicosa-3,6,9,12-tetraene (**92**) (0.1 g, 76 %),[60] was prepared as above from triphenyl(propyl)phosphonium bromide (0.2 g, 0.4 mmol), sodium bis(trimethylsilyl)amide (1.7 mL) and (3Z,6Z,9Z)-heptadeca-3,6,9-trienal (0.1 g, 0.5 mmol) in THF (25 mL) under nitrogen atmosphere.

Found M$^+$:   274   ($C_{20}H_{34}$ requires: 274)

δ_H(400 MHz):   5.36 (8 H, m), 2.82 (6H, br pent., J 5.28), 2.08 (4H, br sexset, J 7.48 Hz),

                    1.31 (10H, m), 0.99 (3H, t, J 7.56 Hz), 0.90 (3H, t, J 6.56 Hz).

δ_c(126 MHz):   132.0, 130.4, 128.5, 128.4, 127.98, 127.9, 127.5, 127.0, 31.8, 29.6, 29.3,

                    29.2, 27.2, 25.7, 25.6, 25.5, 22.6, 20.5, 14.2, 14.1.

v_{max}/ cm^{-1} :   2926, 2859, 1750, 1609, 1493, 724.

Preparation of (3Z,6Z,9Z,12Z,15Z)-1,1-dimethoxyoctadeca-3,6,9,12,15–pentaene (93)
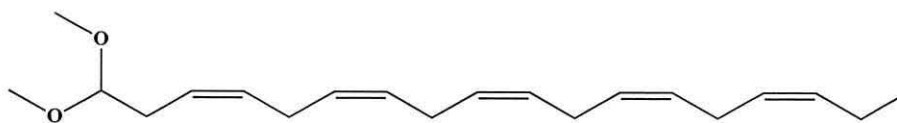
Sodium bis(trimethylsilyl)amide (2.60 mL, 2.60 mmol) was added to a stirred solution of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (0.99 g, 1.72 mmol) in dry THF (25 mL) at -85 °C under nitrogen atmosphere. The reaction mixture was allowed to reach 0 °C and stirred for 2 hrs before being cooled down to -85 °C, followed by the dropwise addition of (3Z,6Z)-nona-3,6-dienal (0.15 g, 0.99 mmol) and HMPA (2 mL) in dry THF (5 mL). The reaction mixture was stirred for 2 hrs at -50 to -30 °C before quenching with sat.aq. NH$_4$Cl at -10 °C. The product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried and evaporated to give a residue which was purified by column chromatography on silica eluting with petrol:ethyl acetate (10 :1) to give two fraction; the first fraction was (3Z,6Z,9Z,12Z,15Z)-1,1-dimethoxyoctadeca-3,6,9,12,15-pentaene (**93**),[85](0.21 g, 63 %).

Found M$^+$:   304   (C$_{20}$H$_{32}$O$_2$ requires: 304)

δ_H(400 MHz):   5.54- 5.29 (10H, m), 4.40 (1H, br t, J 5.8 Hz), 3.35 (6H, s), 2.84

(8H, m), 2.42 (2H, br t, J 6.04 Hz), 2.08 (2H, br pent, J 7.56 Hz),

0.98 (3H, t, J 7.52 Hz).

δ_C(126 MHz):   132.0, 130.2, 128.5, 128.2, 128.0, 127.9, 127.8, 127.0, 123.9, 104.0,

52.9, 31.0, 25.8, 25.63, 25.61, 25.5, 20.5, 14.2.

v_{max}/ cm^{-1} :   2962, 2931, 2830, 1647, 1558, 1493, 1451, 1399, 1360, 722.

The second fraction was (3Z,6Z,9Z,12Z,15Z)-1,1,18,18-tetramethoxyoctadeca-3,6,9,12,15-pentaene (**94**) (0.11 g, 25 %).
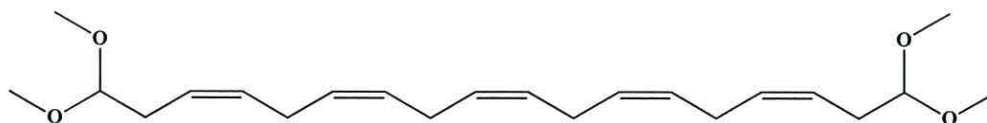
δ$_H$(400 MHz):   5.53-5.35 (10H, m), 4.39 (2H, br t, *J* 6.56 Hz), 3.34 (12H, s), 2.85 (8H, br s), 2.41(4H, br t, *J* 6.04 Hz).

δ$_c$(126 MHz):   130.0, 128.0, 127.9, 127.7, 123.7, 103.8, 52.7, 30.8, 25.6, 25.4.

v_{max}/ cm^{-1} :   2927, 2861, 1609, 1558, 1493, 1451, 1402, 727.

Preparation   of   (3Z,6Z,9Z,12Z,15Z)-1,1,18,18-tetramethoxyoctadeca-3,6,9,12,15-pentaene (94)

Sodium bis(trimethylsilyl)amide (2.60 mL, 2.61 mmol) was added to a stirred solution of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (0.99 g, 1.72 mmol) in dry THF (25 mL) at -85 °C under nitrogen, followed by the addition of HMPA (2 mL). The mixture was stirred for 2 hrs at room temperature, before quenched with sat.aq. NH$_4$Cl at -10 °C. The product was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried and evaporated to give a residue which was purified by column chromatography on silica eluting with petrol:ethyl acetate (10:1) to give (3Z,6Z,9Z,12Z,15Z)-1,1,18,18-tetramethoxyoctadeca-3,6,9,12,15-pentaene (**94**) (0.22 g, 31 %). The ^{1}H NMR spectrum showed an identical spectrum to the second fraction in the Experiment above.

Preparation of (*3Z,6Z,9Z,12Z,15Z*)-octadeca-3,6,9,12,15-pentaenal (95)
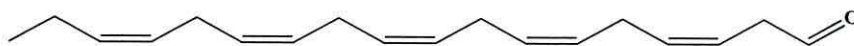
Formic acid 80 % (3 mL) was added dropwise to a stirred solution of (3Z,6Z,9Z,12Z,15Z)-1,1-dimethoxyoctadeca-3,6,9,12,15-pentaene (0.19 g, 0.65 mmol) in dioxane (3 mL) at room temperature. The mixture was stirred at room temperature for 1.5 hrs, followed by the addition of water (5 mL). The product was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were washed with sat.aq. NaHCO$_3$ (10 mL), brine (10 mL) and dried over MgSO$_4$then evaporated to give a crude product which was purified by column chromatography on silica eluting with petrol:ethyl acetate (5:1) to give (3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaenal (**95**) (0.12 g, 75 %).[85,106]

δ_H(400 MHz): 9.69 (1H, t, *J* 1.72), 5.69 (2H, m), 5.39 (8H, m), 3.24 (2H, br d, *J* 7.12 Hz), 2.83 (8H, br pent., *J* 5.08 Hz), 2.08 (2H, br pent., *J* 7.48 Hz), 0.98 (3H, t, *J* 7.56 Hz).

δ_C(126 MHz): 199.2, 133.1, 132.0, 128.8, 128.6, 128.4, 127.8, 127.7, 127.1, 126.9, 118.6, 42.4, 25.9, 25.64, 25.63, 25.5, 20.5, 14.2.

v_{max}/ cm^{-1} : 2926, 2861, 1731, 1609, 1558, 1494, 1050, 724.

Preparation of (*3Z,6Z,9Z,12Z,15Z*)-18,18-dimethoxyoctadeca-3,6,9,12,15-pentaenal (96)
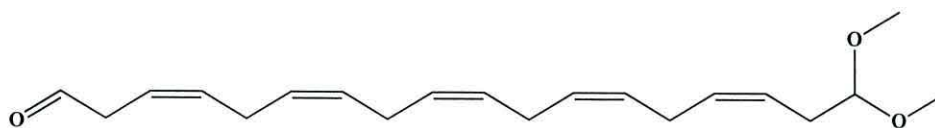
(3Z,6Z,9Z,12Z,15Z)-18,18-Dimethoxyoctadeca-3,6,9,12,15-pentaenal (**96**) (0.11 g, 64 %) was prepared as above by addition of formic acid 80 % (3 mL) to stirred (3Z,6Z,9Z,12Z,15Z)-1,1,18,18-tetramethoxyoctadeca-3,6,9,12,15-pentaene (0.20 g, 0.55 mmol) in dioxan (3 mL).

δ_H(400 MHz): 9.68 (1H, t, *J* 1.6 Hz), 5.69 (2H, m), 5.39 (8H, m), 4.40 (1H, t, *J* 5.72 Hz), 3.34 (6H, s), 3.24 (2H, br d, *J* 7.0 Hz), 2.84 (8H, br q, *J* 5.04 Hz), 2.41 (2H, br t, *J* 6.12 Hz).

δc(126 MHz):   199.3, 130.2, 128.2, 128.1, 128.0, 127.9, 124.0, 123.9, 118.7, 104.1, 52.9,

42.5, 31.0, 29.7, 25.9, 25.8, 25.6.

v_{max}/ cm^{-1} :   2927, 2861, 1730, 1609, 1493, 1451, 1402, 727.

Preparation of (*6Z,9Z,12Z,15Z,18Z,21Z*)-tetracosa-6,9,12,15,18,21-hexaenoic acid (98)
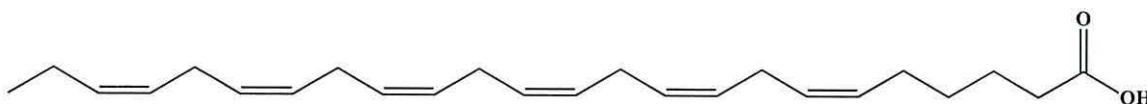
Using the same procedure as above, (6Z,9Z,12Z,15Z,18Z,21Z)-tetracosa-6,9,12,15,18,21-hexaenoic acid (**98**)[155] (0.21 g, 74 %) was prepared by using (5-carboxypentyl)triphenylphosphonium bromide (0.46 g, 1.10 mmol), sodium bis(trimethylsilyl)amide (1.7 mL) and (3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9,12,15-pentaenal (0.19 g, 0.77 mmol) in THF (15 mL) under nitrogen. The reaction was worked up as before and the product was purified by column chromatography eluting with petrol : ethylacetate (5:2) to give (**98**).

Found M$^+$:   356   ($C_{24}H_{36}O_2$ requires: 356)

δH(400 MHz):   5.39 (12H, br m), 2.86 (10H, br d, J 14.64 Hz), 2.38 (2H, br t, J 7.36 Hz),

2.08 (4H, br pent, J 7.8 Hz), 1.66 (2H, pent, J 7.44 Hz), 1.43 (2H, pent, J

7.6 Hz), 0.98 (3H, t, J 7.48 Hz).

δc(126 MHz):   179.5, 132.0, 129.5, 128.5, 128.3, 128.24, 128.21, 128.1, 128.0, 128.0,

127.8, 127.0, 33.8, 28.9, 26.8, 25.6, 25.5, 24.2, 20.5, 14.2.

v_{max}/ cm^{-1} :   3444, 3013, 2962, 2930, 2860, 1709, 1658, 1609, 1493, 724.

Preparation of methyl (*6Z,9Z,12Z,15Z,18Z,21Z*)- tetracosa-6,9,12,15,18,21-hexaenoate (99)
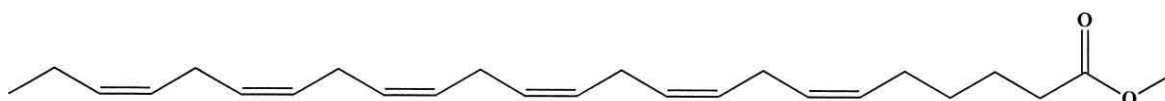
Excess diazomethane in ether was added to (6Z,9Z,12Z,15Z,18Z,21Z)-tetracosa-6,9,12,15,18,21-hexaenoic acid (0.19 g, 0.56 mmol) at room temperature. The reaction

mixture was stirred for 15 min. then the solvent was evaporated under reduced pressure to give methyl (6Z,9Z,12Z,15Z,18Z,21Z)-tetracosa-6,9,12,15,18,21-hexaenoate (**99**) (0.19 g, 97 %).[155]

Found $(M+K)^+$: 370.2881 ($C_{25}H_{38}O_2$ requires: 370.2872)

δ_H(400 MHz): 5.40-5.35 (12H, br m), 3.67 (3H, s), 2.85-2.80 (10H, br m), 2.32 (2H, br t, J 7.4 Hz), 2.08 (4H, br pent, J 6.6 Hz), 1.65 (2H, pent., J 7.48 Hz), 1.40 (2H, pent., J 7.68 Hz), 0.98 (3H, t, J 7.52 Hz).

δ_C(126 MHz): 174.1, 132.0, 129.6, 128.5, 128.4, 128.3, 128.2, 128.16, 128.11, 128.10, 128.0, 127.8, 127.0, 51.5, 33.9, 29.1, 26.8, 25.6, 25.5, 24.6, 20.5, 14.3.

v_{max}/ cm^{-1} : 2962, 2930, 2859, 1703, 1658, 1610, 1493, 824, 722.

Preparation of (3Z,6Z,9Z,12Z,15Z,18Z,21Z,24Z)-1,1-Dimethoxyhepta-cosa-3,6,9,12,15,18,21,24-octaene (100)
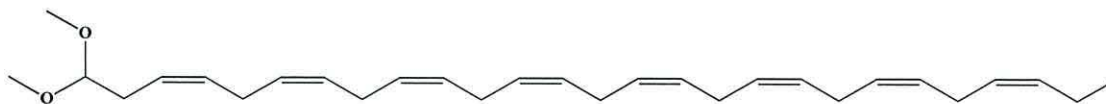
Sodium *bis*(trimethylsilyl)amide (1.7 mL) was added to a stirred solution of ((3Z,6Z)-9,9-dimethoxynona-3,6-dien-1-yl)triphenylphosphonium iodide (**88**) (0.66 g, 1.16 mmol) in dry THF (20 mL) at -85 °C under nitrogen. The reaction mixture was allowed to reach 0 °C and stirred for 30 min., then cooled to -85 °C (3Z,6Z,9Z,12Z,15Z)-octadeca-3,6,9, 12,15-pentaenal (**95**) (0.2 g, 0.77 mmol) was added as dropwise followed by additional HMPA (2 mL) in dry THF (5 mL). The mixture was stirred for 16 hrs at room temperature before quenched with sat. aq. NH₄Cl at -10 °C. The product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried and evaporated to give a residue which was purified by column chromatography on silica eluting with petrol : ethyl acetate (20:1) to give (3Z,6Z,9Z,12Z,15Z,18Z,21Z,24Z)-1,1-dimethoxy-heptacosa-3,6,9,12,15,18,21,24-octaene (**100**) (0.22 g, 68 %).

$\delta_{H(400\ MHz)}$: 5.53- 5.29 (16H, m), 4.39 (1H, br, J 5.8 Hz), 3.34 (6H, s), 2.84 (14H, m), 2.41 (2H, br t, J 5.88 Hz), 2.08 (2H, br pent, J 7.36 Hz), 0.98 (3H, t, J 7.52 Hz).

δ_C (126 MHz):	132.0, 130.3, 128.6, 128.3, 128.2, 128.1, 128.09, 128.0, 127.9, 127.0, 123.9, 104.1, 52.9, 31.0, 25.8, 25.6, 25.5, 20.5, 14.3.
ν_{max} / cm^{-1}:	2962, 2931, 2830, 1647, 1558, 1493, 1451, 1399, 1360, 721.

Preparation of 4,4,8,8,12,12-hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]dodecane (158)
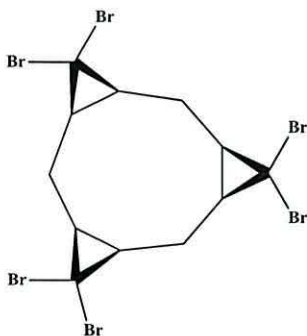
Aqueous sodium hydroxide (17.0 g, 425 mmol, 50 %) was added slowly to a stirred solution of (1Z,4Z,7Z)-cyclonona-1,4,7-triene (1.99 g, 16.6 mmol), bromoform (41.99 g, 166.2 mmol, 14.5 mL) and cetrimide (0.50 g, 1.35 mmol) in dichloromethane (20 mL). The mixture was stirred rapidly for 72 hrs at room temperature. The product was extracted with dichloromethane (3 x 100 mL) and the combined organic layers were washed with water and brine (150 mL), dried over MgSO$_4$ and the solvent was evaporated. The residue was distilled to remove all the bromoform, then the oil residue was treated with dichloromethane to give a white precipitate which was filtered to give 4,4,8,8,12,12-hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]dodecane (**158**)[138] (6.50 g, 61 %), as a white solid.

mp :	247-250 °C [lit[138] m.p 240-246 °C].
Mass Found M$^+$:	635.6230 (C$_{12}$H$_{12}$^{79}Br$_6$ requires: 635.6476)
δ_H(400 MHz):	2.45 (3H, d, J 14.8 Hz), 1.82 (6H, br q, J 9.32 Hz), 0.78 (3H, m).
δ_H (400 MHz, C$_6$D$_6$)	1.68 (3H, d, J 14.8 Hz), 0.98 (6H, m), 0.39 (3H, m).
δ_C(126 MHz):	32.4, 31.7, 24.6.
ν_{max}/ cm^{-1} :	1465, 895, 777, 698, 515, 494.

The filtrate was evaporated under reduced pressure to give 4,4,11,11-tetrabromotricyclo-[8.1.0.0^{3,5}]undec-7-ene (**159**) (1.5 g, 20 %).

mp :	155-157 °C.
Mass Found M$^+$:	459.7529 (C$_{11}$H$_{12}$^{79}Br$_4$ requires: 459.7672)
δ_H(400 MHz, CDCl$_3$) :	5.66 (2H, br pentet., J 10.48 Hz), 2.54 (1H, d, J 14.8 Hz), 2.40 (2H, dd, J 4.0, 13.56 Hz), 1.8 (2H, m), 1.68 (4H, m), 1.0 (1H, m).
δ_H (400 MHz, C$_6$D$_6$):	5.25 – 5.04 (2H, m), 1.84 (3H, d, J 14.1 Hz), 1.46–1.35 (2H, m), 1.18 (2H, t, J 11.2 Hz), 0.97 (2H, t, J 11.1 Hz), 0.73 (1H, dt, J 14.5, 11.7 Hz)
δ_c(126 MHz):	128.0, 34.5, 33.8, 31.6, 24.9, 25.5.
v_{max}/ cm^{-1} :	3017, 1662, 1465, 783, 485.

Preparation of cyclododeca-1,2,5,6,9,10-hexaene (162) and (161)

Methyl lithium (10.4 mL, 15.7 mmol) was added to a stirred suspension of 4,4,8,8,12,12-hexabromotetracyclo[9.1.0.0^{3,5}.0^{7,9}]dodecane (0.99 g, 1.57 mmol) in dry ether (20 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 min, cooled to -20 °C and quenched with water (5 mL), then allowed to reach room temperature. The mixture was extracted with ether (3 x 15 mL), and the combined organic layers were dried and the solvent evaporated. The residue was purified by column chromatography eluting with petrol:ethyl acetate (10:1). The product was obtained as a mixture (0.2 g, 81 %) of two diastereoisomers (**161**) and (**162**) in a ratio of ca. 1 : 3.

The mixture was separated by column chromatography on silica treated with silver nitrate. Silica (25 g) was added to a stirred silver nitrate (10 g) in acetonitrile (90 mL) in a round bottom flask, which was covered with aluminium foil for 10 min. After that the solvent was evaporated to give the silica powder which was used for the column. Column chromatography eluting with petrol:ethyl acetate (10:1) gave two fraction. The first fraction was a racemic mixture of *SSR*- and *RRS*-cyclododeca-1,2,5,6,9,10-hexaenes (**162**) (0.09 g, 50 %), as an oil.
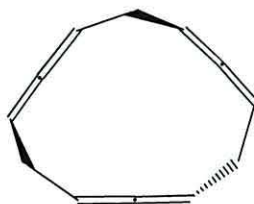
Found (M+H)$^+$::   157.1010 ((C$_{12}$H$_{12}$+H)$^+$ requires: 157.1012)

δ_H(400 MHz, CDCl$_3$): 5.3 (4H, m), 5.2 (2H, m), 2.74 (2H, m), 2.63 (2H, m), 2.53 (2H, m).

δ_H(400 MHz, C$_6$D$_6$):   5.24 (2H, m), 5.18 (2H, m), 5.13 (2H, m), 2.70 (2H, m), 2.49 (2H, m),

          2.25 (2H, m)

δ_C(126 MHz):   206.7, 205.8, 91.7, 90.2, 89.8, 28.2, 27.7.

v_{max}/ cm^{-1} :   2910, 1996, 1434, 790, 720.

The second fraction was a racemic mixture of *SSS*- and *RRR*-cyclododeca-1,2,5,6,9,10-hexaene (**161**) (0.02 g, 11 %), as a colourless solid.
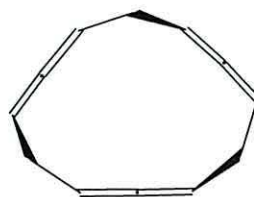
m.p: 53-55 °C

Mass Found (M + H)$^+$:   157.1010   (C$_{12}$H$_{12}$ + H)$^+$ requires: 157.1012

δ_H(400 MHz):   5.22 (6H, br pent., *J* 5.1 Hz), 2.62 (6H, br pent., *J* 5.0 Hz).

δ_C(126 MHz):   206.5, 89.8, 27.8.

v_{max}/ cm^{-1} :   2919, 2852, 1994, 1715, 1438, 871, 720.

Hydrogenation of cyclododeca-1,2,5,6,9,10-hexaenes.
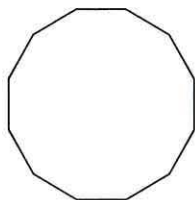
Palladium (10 %) on carbon (0.50 g, 4.69 mmol) was added to a stirred solution of the mixture of cyclododeca-1,2,5,6,9,10-hexaenes (0.2 g, 1.28 mmol). The reaction mixture was stirred at room temperature for 16 hrs under hydrogen. It was then filtered and the filtrate was evaporated under reduced pressure to give cyclododecane (**162a**) (0.18 g, 85 %).[156]

δ_H(400 MHz):   1.34 (24H, s).

δ_c(126 MHz):   23.7.

Preparation of (*Z*)-cycloundeca-1,2,5,6,9-pentaene (173) and its derivatives

Methyl lithium (2.0 mL, 3.16 mmol) was added to a stirred suspension of 4,4,11,11-tetrabromo-tricyclo[8.1.0.0^{3,5}]undec-7-ene (0.42 g, 0.90 mmol) in dry ether (15 mL) at room temperature under a nitrogen atmosphere. The temperature of the reaction reached 24 °C throughout the addition. The reaction mixture was stirred for 5 min then quenched with water (5 mL) at -20 °C. The ether layer was decanted and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic layers were dried with MgSO$_4$ and evaporated to give a crude product (0.12 g, 92 %) as mixture of the allenes **172** and **173** ca 2.15:2.65.

δ_H(400 MHz):   5.59 (2H, m), 5.52 (2H, m), 5.36 (2H, m), 5.27 (4H, m), 5.18 (2H, m), 2.89 (2H, m), 2.70 (3H, m), 2.57 (3H, m), 2.54 (3H, m), 2.32 (1H, dt, *J* 13.7, 7.5 Hz).

Maleic anhydride (0.07 g, 0.74 mmol) was added to a stirred solution of the crude product (0.06 g, 0.4 mmol) in CDCl$_3$ (4mL) at room temperature and stirred for 16 hrs. The solvent was evaporated and the residue was purified by column chromatography eluting with petrol:ethyl acetate (5:1) to give four fractions.

The first fraction was (Z)-cycloundeca-1,2,5,6,9-pentaene (173) (0.02 g, 13 %)

Found M$^+$:	144.0946 (C$_{11}$H$_{12}$ requires 144.0939)
δ_H(400 MHz, CDCl$_3$) :	5.76 (2H, m), 5.37 (4H, m), 2.80 (4H, m), 2.73-2.6 (2H, m).
δ_H(400 MHz, C$_6$D$_6$):	5.59 – 5.48 (2H, m), 5.22 – 5.12 (4H, m), 2.60 (2H, m),
	2.48 (2H, m), 2.40 (2H, m)
δ_C(126 MHz):	207.0, 127.9, 91.2, 90.6, 26.4, 26.1
v_{max}/ cm^{-1} :	2920, 2861, 1987, 1609, 1493, 1450, 1050.

The second fraction was (1R,4S,4aE,7Z,10E)-1,4,6,9-tetrahydro-1,4-methanocyclo-octa-1,2-dioxine (179) (0.004 g, 4 %).
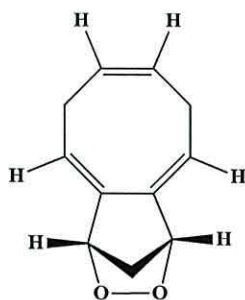
Found M$^+$:	176.0905 (C$_{11}$H$_{12}$O$_2$ requires: 176.0837)
δ_H(400 MHz, CDCl$_3$):	5.86 (2H, br, t, J 6.6 Hz), 5.72–5.63 (2H, m), 4.77 (2H, br, d, J 1.0
	Hz), 3.01 (2H, td, J 6.76, 15.56 Hz), 2.79 (2H, td, J 7.04, 15.36
	Hz), 2.23 (1H, dt, J 2.1, 10.0 Hz), 2.20 – 2.16 (1H, m).
δ_C(126 MHz) :	138.8, 127.3, 125.7, 85.8, 44.9, 30.9, 24.9.
v_{max}/ cm^{-1} :	2926, 2860, 1609, 1493, 1452, 1403, 1050, 823.

The third fraction was (3a*S*,4*R*,7*Z*,9*Z*,11*S*,11a*R*)-3a,4,5,6,11,11a-hexahydro-4,11-methanocycloocta[f]isobenzofuran-1,3-dione (**177**) (0.01 g, 10 %).
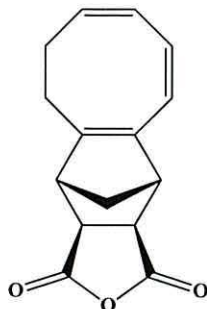
Found M$^+$:   242.0949   (C$_{15}$H$_{14}$O$_3$ requires: 242.0943)

δ_H(400 MHz, CDCl$_3$): 5.96 (2H, dd, *J* 3.8, 10.9), 5.77 (2H, br dd, *J* 12.52, 14.88 Hz), 3.65 (2H, m), 3.33 (1H, br, s), 3.26 (1H, br s), 2.56 (1H, m), 2.41 (3H, m), 1.81 (1H, dt, *J* 9.0, 1.7 Hz), 1.44 (1H, dt, *J* 9.0, 1.3 Hz).

δ_H(400 MHz, C$_6$D$_6$): 5.87 (1H, dd, *J* 4.2, 11.0 Hz), 5.73 (2H, m), 5.60 (1H, dd, *J* 4.2, 12.1 Hz), 2.65 (2H, s), 2.55 (2H, m), 2.35 (1H, m), 2.23–2.05 (3H, m), 1.12 (1H, dt, *J* 1.7, 8.8 Hz), 0.46 (1H, dt, *J* 1.3, 8.8 Hz)

δ_c(126 MHz) :   171.2, 170.9, 144.9, 137.7, 135.2, 128.5, 127.3, 124.3, 52.82, 52.2, 49.9, 48.3, 47.7, 31.6, 25.5.

v_{max}/ cm^{-1} :   2927, 2862, 1853, 1777, 1607, 1494, 1452, 1224, 824.

The fourth fraction was (8*Z*,10*Z*)-3a,4,6,7-tetrahydro-1H-4,11a-methanocyclo-octa[e]isobenzofuran-1,3(11bH)-dione (**178a**) (0.009 g, 9 %).
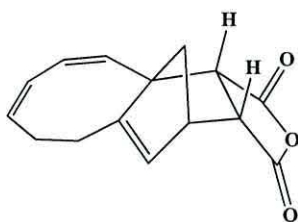
Found M$^+$:   242.0962   (C$_{15}$H$_{14}$O$_3$ requires: 242.0943)

δ_H(400 MHz, CDCl$_3$): 5.99 (2H, br, s), 5.93 (1H, d, *J* 11.2 Hz), 5.85 (1H, br, s), 5.69 (1H, ddd, *J* 6.8, 7.8, 11.0 Hz), 3.66 (1H, dd, *J* 4.6, 8.1 Hz), 3.50

(1H, d, *J* 8.1 Hz), 3.36 – 3.29 (1H, br m), 2.72 (1H, td, *J* 8.2, 16.2 Hz), 2.45 – 2.39 (2H, m), 2.14 (1H, dt, *J* 5.5, 11.9 Hz), 1.88 (1H, dd , *J* 1.5, 8.9 Hz), 1.28 (1H, m), 0.87 (1H, ddd, *J* 6.7, 10.1, 14.4 Hz).

δH(400 MHz, C$_6$D$_6$): 5.85 (1H, d, *J* 0.6 Hz), 5.69 (1H, ddd, *J* 11.0, 7.8, 6.8 Hz), 5.43 (1H, br t, *J* 13.3 Hz), 5.39 (1H, dd, *J* 6.1, 4.9 Hz), δ 5.36 (1H, dd, *J* 8.9, 5.7 Hz), 3.66 (1H, dd, *J* 8.1, 4.6 Hz), δ 3.50 (1H, d, *J* 8.1 Hz), 3.36-3.27 (1H, m), 2.7-2.1 (2H, m), 1.88 (1H, dd, *J* 8.9, 1.5 Hz), 1.57 (1H, br d, *J* 12.3 Hz), 0.77 (1H, d, *J* 8.7 Hz).

δc(126 MHz): 171.5, 170.4, 151.3, 136.4, 131.5, 130.48, 130.44, 128.5, 127.1, 59.3 , 53.3, 49.2, 44.8, 30.9, 27.8, 26.4

v_{max}/ cm^{-1} : 2926, 2860, 1777, 1606, 1493, 1451, 1050, 824.

Preparation of (6*Z*,8*Z*)-3a,4,10,11-tetrahydro-1H-4,11a-methanocyclo-octa[e]-isobenzofuran-1,3(11bH)-dione
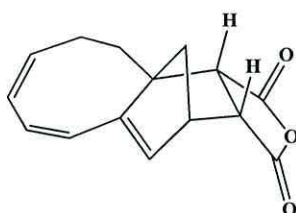
Methyl lithium (2.00 mL, 3.16 mmol) was added to a stirred suspension of (*E*)-4,4,11,11-tetrabromotricyclo[8.1.0.0^{3,5}]undec-7-ene (0.68 g, 1.41 mmol) in dry ether (25 mL) at room temperature under nitrogen atmosphere. The temperature of the reaction was reached 24 °C throughout the addition. The reaction mixture was stirred for 5 min then quenched with water (6 mL) at -20 °C. The ether layer was decanted and the aqueous layer was extracted with ether (2 x 8 mL). The combined organic layers were dried with MgSO$_4$ and evaporated to give a crude product (0.2 g, 93 %). The crude product (0.11 g, 0.69 mmol) in CDCl$_3$ (2 mL) was left in the NMR machine for 16 hrs. Proton NMR was recorded every 30 min approximately started from -40 °C to room temperature. Then maleic anhydride (0.12 g, 1.20 mmol) in CDCl$_3$ (2 mL) was added. The solvent was evaporated and the

residue was purified by column chromatography eluting with petrol : ethyl acetate (5:1) to give three fractions. The first two fraction were (**173**) and (**178a**) as above. The third fraction was (6Z,8Z)-3a,4,10,11-tetrahydro-1H-4,11a-methanocyclo-octa[e]-isobenzofuran-1,3(11bH)-dione (**178b**) (0.02 g, 12.5 %).

δ_H(400 MHz, CDCl$_3$);   6.17 (1H, dd, J 4.5, 11.9 Hz), 5.95 (1H, d, J 2.5 Hz), 5.92 (1H, m), 5.80 (1H, d, J 12.0 Hz), 5.60 (1H, m), 3.52 (1H, dd, J 1.4, 7.5 Hz), 3.32 (1H, d, J 1.5 Hz), 3.11 (1H, d, J 7.5 Hz), 2.52 (2H, m), 1.78 (1H, dd, J 1.5, 10.0 Hz), 1.57 (2H, d, J 10.1 Hz), 1.42 (1H, d, J 8.0 Hz).

δ_C(101 MHz, CDCl$_3$):   171.3, 171.2, 131.2, 130.9, 130.8, 126.6, 125.6, 51.8, 49.6, 47.8, 45.7, 30.8, 26.0.

Single crystal X-ray data for *tris* allene (161)

Formula	$C_{12}H_{12}$
M.W.	156.22
Temperature/K	100.15
a/$\mathring{A}$	8.1641 (3)
b/$\mathring{A}$	14.5904 (5)
c/$\mathring{A}$	7.7555 (3)
α/°	90.00
β/°	103.703 (4)
γ/°	90.00
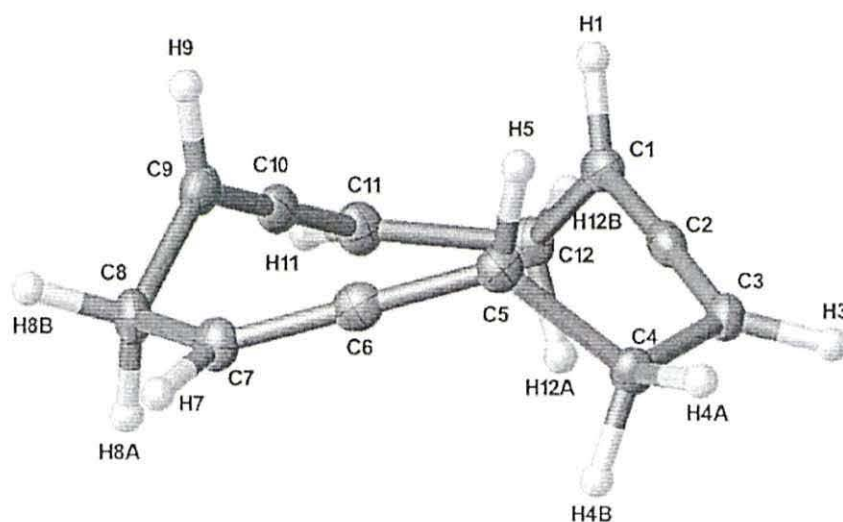
Single crystal X-Ray structure of (161)

Table 12: Fraction atomic coordinates (x10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for tris-allene (161). Ueq is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor

ATOM	X	Y	Z	U(eq)
C1	4201.8 (15)	1264.2 (8)	5175.7 (17)	17.8 (2)
C7	-1628.9 (16)	250.7 (9)	3275.9 (17)	20.8 (3)
C4	2373.6 (15)	-1008.7 (8)	4097.8 (17)	18.4 (2)
C8	-1679.2 (15)	1275.2 (9)	2920.0 (18)	20.6 (3)
C2	4156.2 (15)	383.3 (9)	4863.6 (15)	17.8 (2)
C12	4024.3 (16)	2000.4 (9)	3775.5 (18)	19.7 (2)
C9	-340.9 (15)	1803.5 (8)	4212.7 (18)	20.7 (3)
C3	4039.6 (15)	-493.6 (8)	4541.5 (16)	18.3 (2)
C11	2357.0 (16)	2507.0 (9)	3487.2 (18)	21.0 (3)
C5	1075.5 (16)	-608.8 (8)	4976.6 (17)	18.4 (2)
C6	-294.5 (16)	-187.9 (8)	4129.2 (18)	18.9 (2)
C10	995.7 (16)	2165.9 (8)	3845.4 (18)	19.8 (2)

Table 13: Anisotropic Displacement Parameters ($\dot{A}^2$ x 10^3) for tris allene (161). The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hkaxbxU_{12}]$

ATOM	U11	U22	U33	U23	U13	U12
C1	14.6 (5)	19.6 (5)	18.9 (5)	-2.1 (4)	3.2 (4)	-1.8 (4)
C7	16.4 (5)	21.0 (6)	25.5 (6)	0.5 (5)	6.0 (5)	-1.9 (5)
C4	17.9 (5)	15.0 (5)	21.7 (6)	-1.5 (4)	3.4 (4)	0.3 (4)
C8	13.9 (5)	21.0 (6)	26.0 (6)	2.4 (5)	3.0 (4)	3.7 (4)
C2	12.7 (5)	23.6 (6)	16.5 (5)	2.9 (4)	2.3 (4)	0.7 (4)
C12	16.3 (5)	18.6 (5)	24.1 (6)	0.5 (4)	4.6 (4)	-3.1 (4)
C9	19.7 (6)	19.2 (5)	23.6 (6)	1.0 (5)	5.9 (5)	5.6 (5)
C3	14.8 (5)	19.7 (5)	20.1 (6)	0.0 (4)	3.9 (4)	2.6 (5)
C11	21.3 (6)	15.3 (5)	25.4 (6)	0.4 (4)	3.3 (5)	0.4 (5)
C5	19.4 (5)	16.4 (5)	19.7 (6)	0.6 (4)	5.4 (4)	-1.3 (4)
C6	19.1 (5)	16.9 (5)	22.2 (6)	-0.7 (4)	7.7 (4)	-5.0 (4)
C10	20.5 (6)	15.3 (5)	22.1 (6)	-1.4 (4)	1.9 (4)	4.1 (4)

186

Table 14: Bond Lengths for tris allene (161)

ATOM	ATOM	LENGTH/Å	ATOM	ATOM	LENGTH/Å
C1	C2	1.3068 (18)	C8	C9	1.5080 (18)
C1	C12	1.5098 (18)	C2	C3	1.3028 (17)
C7	C8	1.5188 (18)	C12	C11	1.5182 (18)
C7	C6	1.3011 (18)	C9	C10	1.3034 (18)
C4	C3	1.5203 (17)	C11	C10	1.3026 (18)
C4	C5	1.5067 (18)	C5	C6	1.3084 (18)

Table 15: Bond Angles for tris allene (161)

ATOM	ATOM	ATOM	ANGLE/°	ATOM	ATOM	ATOM	ANGLE/°
C2	C1	C12	124.95 (12)	C10	C9	C8	125.05 (13)
C6	C7	C8	124.05 (11)	C2	C3	C4	123.34 (11)
C5	C4	C3	113.18 (10)	C10	C11	C12	124.16 (12)
C9	C8	C7	113.46 (10)	C6	C5	C4	124.31 (12)
C3	C2	C1	177.51 (13)	C7	C6	C5	178.27 (13)
C1	C12	C11	112.47 (11)	C9	C10	C11	178.39 (12)

Table 16: Hydrogen Atom Coordinates ($\dot{A}^2$ x 10^4) and Isotropic Displacement parameters ($\dot{A}^2$ x 10^3) for tris allene (161)

ATOM	X	Y	Z	U(eq)
H3	5060 (20)	-829 (11)	4530 (20)	22 (4)
H1	4270 (20)	1492 (12)	6380 (20)	28 (4)
H12A	4150 (20)	1726 (12)	2590 (20)	27 (4)
H12B	4910 (20)	2441 (12)	4170 (30)	26 (4)
H9	-470 (20)	1871 (11)	5420 (20)	23 (4)
H8A	-1660 (20)	1359 (11)	1670 (20)	27 (5)
H8B	-2740 (20)	1537 (12)	3010 (20)	23 (4)
H5	1250 (30)	-649 (12)	6250 (30)	28 (5)
H7	-2690 (20)	-78 (11)	2810 (20)	23 (4)
H11	2300 (20)	3131 (11)	3000 (20)	21 (4)
H4A	2590 (20)	-1670 (11)	4440 (20)	20 (4)
H4B	1900 (20)	-1044 (12)	2760 (30)	30 (5)

Quantum mechanical calculations

Preliminary semi-empirical calculations out on the allene (**161**) using the AM1 method showed that the C3 form was an energy minimum, with the D3 form a third order transition state some 6.7 kcal/mol higher in energy. The symmetry axes for the D3 form are shown below:
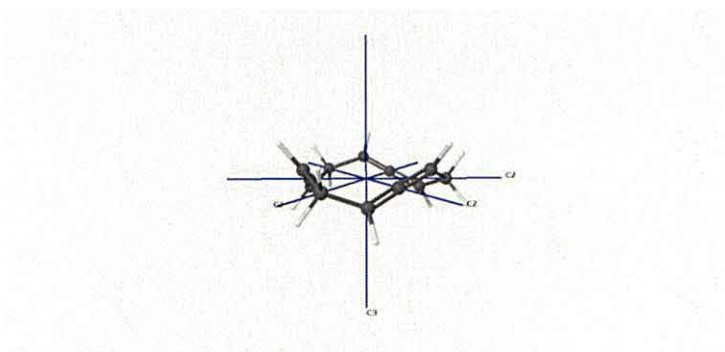
The atomic coordinates for the D3 form are as below:

C	0.00000000	0.00000000	0.00000000
C	1.23615418	0.64926705	0.49199445
C	2.43815418	0.56726705	-0.00000555
C	3.64015418	0.64926705	-0.49200555
C	4.87630836	-0.00000000	-0.00001109
C	4.82051471	-1.39517348	0.49198630
C	4.14849895	-2.39513698	-0.00000944
C	3.61851135	-3.47710049	-0.49200550
C	2.43815418	-4.22300692	-0.00000555
C	1.25779701	-3.47710049	0.49199440
C	0.72780942	-2.39513698	-0.00000166
C	0.05579365	-1.39517348	-0.49199739
H	-0.63284582	-1.59873295	-1.33700555
H	0.73719248	-3.97169836	1.33700531
H	2.07315418	-4.89873295	-0.82800555
H	2.80315418	-4.89873295	0.82799445
H	4.13911588	-3.97169836	-1.33701640
H	5.50915418	-1.59873295	1.33699445
H	5.64400145	0.02176538	-0.82801367
H	5.27900710	0.65396066	0.82798882
H	3.80818336	1.34742440	-1.33701565
H	1.06812500	1.34742440	1.33700456
H	-0.76769309	0.02176538	0.82800258
H	-0.40269874	0.65396066	-0.82799991

Preliminary calculations *ab initio* were also carried out on the allene **(161)** (personal communication, R. A. Davies and J. Morris), using Gaussian 03 with a HF/6-31G(d) basis set; this gave similar results.

References

1. Evans, D. A., Bartroli, J. and Shih, T. L., *J. Am. Chem. Soc.*, **1981**, 103, 2127.

2. a- Evans, D. A., *Aldrichimica Acta*, **1982**, 23, 15.

    b- Pandit, N., Singla, R., Shrivastava, B., *Int. J. Med. Chem.*, **2012**, 2012, 24.

3. Evans, D. A., Carter, P. H., Carreira, E. M. and Charette, A. B., *J. Am. Chem. Soc.*, **1999**, 121, 7540-7552.

4. Evans, D. A., Fitch, D. M., Smith, T. E. and Cee, V. J., *J. Am. Chem. Soc.*, **2000**, 122, 10033-10046.

5. Phukan, P., Sasmal, S. and Maier, M. E., *Eur., J. Chem.*, **2003**, 1733-1740.

6. Hawkins, M. and Watson, T., *Angew. Chem. Int. Ed.*, **2004**, 43, 3224 –3228.

7. Rüeger, H., Stutz, S., Göschke, R., Spindler, F. and Maibaum, J., *Tetrahedron Lett.*, **2000**, 41, 10085-10089.

8. Alsubari, A., Bouhfid, R. and Essassi, E., *ARKIVOC*, **2009** (xii), 337-346.

9. Park, C. H., Brittelli, D. R., Wang, C. L., Marsh, F. D., *J. Med. Chem.*,**1992**, 35, 1156-1165.

10. a- Zappia, G., Gacs-Baitz, E., Delle-Monache, G.; Misiti, D.; Nevola, L.; Botta, B., *Curr. Org. Syn.*, **2007**, 4, 81.

    b- Adrián, O. and Ignacio, A. R., *ARKIVOC*, **2008** (xiv), 330-343.

11. a- Mizuno, T., Takahashi, J. and Ogawa, A., *Tetrahedron*, **2002**, 58, 7805–7808.

    b- Katsumura, S., Yamamoto, N, Morita, M, Han Q, *Tetrahedron Asymmetry*, **1994**, 5, 161-164.

12. a- Lynn, J. W., *Chem. Abstr.*, **1961**, 55, 16568.

    b- Feroci, M., Gennaro, A., Inesi, A., Orsini, M., Palombi, L., *Tetrahedron Lett.*, **2002**, 43, 5863–5865.

13. a- Wuts, P. G. M. and Pruitt, L. E., *Synthesis*, **1989**, 8, 622.

    b- Eric, J. S., Arthur, J. C., *Org. Proc. Res. Dev.*, **2000**, *4*, 264–269.

14. Pandit, N., Singla, R., Shrivastava, B., *Int. J. Med. Chem.*, **2012**, 414, 21-24.

15. a- Atsushi, A. and Satoru, M., *Tetrahedron Lett.*,, **1992**, 33, 5517-5518.

    b- Lei, Y., Tie, S., *Chinese Chemical Lett.*, **2010**, 21, 155 – 158.

16. Danielmeyer, K. and Streckhan, E., *Tetrahedron Asymmetry*, **1995**, 6, 1181.

17. Kim, S. M., Jin, H. and Jun, J. G., *Bull. Korean Chem. Soc.,* **2002**, 23, 749.

18. Bergmeier, S. C., *Tetrahedron*, **2000**, 56, 2561-2576.

19. a- Mavrova, A. T., Denkovab, P. and Tsenov, J. A., *Eur. J. Chem.*, **2011**, 2, 18, 24.

    b- Sheila, H., Johnson, A., *United States patent*, **1990**, 977, 172.

20. a- Romero, C. G., Bernal, P., Benavides, A., *Pure Appl. Chem.*, **2007**, 79, 181–191.

    b- Marc J. M. and Meyers, A. I., *J. Org. Chem.* **1993**, 58, 3568-3571.

21. Matthews, G. A., *Pest management, Longman Publishing Group*, **1984**.

22. Fred, E. R. and John H. L., *J. Lip. Res.*, **1968**, 9, 541-551.

23. Lorenz, K., *on aggression*, New York: *Mariner Books*, **1974**.

24. Howse, P., Stevens. I. and Jones, O., *Insect pheromones and their use in pest Management*, London: Chapman & Hall. **1998**.

25. Gould, J. and Gould, C., *The honey bee*, New York: Scientific American Library, **1995**.

26. Porter, P. S. and Lobitz, W. C., Jr., *Human hair: a genetic marker. Brit. J. Dermatology*, **1970**, 83, 225.

27. Dawkins, R., *The selfish gene*, Oxford, Oxford University Press, **1976**.

28. Wildavsky, A., *But is it true?* Cambridge, MA: Harvard University Press. **1996**.

29. Aspelin, A. L., Grube, A. *Pesticide Industry Sales and Usage U.S. Environmental Protection Agency*, **1996**.

30. Williams, M. R., *Beltware Cotton Conferences*, **1997**, 2, 834.

31. Talekar, N. S., Shelton, A. M., *Annu. Rev. Entomol.*, **1993**, 38: 275.

32. Parajulee, M., *National Cotton Council, Proceeding Beltwide Cotton Conferences*, **1999**.

33. Atkins M. D. Introduction to insect behaviour. New York: Macmillan. **1980**.

34. Kelly, D.R., *Chem. Brit.*, **1990**, 26, 124.

35. Gibson, R. W. and Pickett, J. A., *Nature*, **1983**, 302 (5909), 608.

36. Landolt, J. P., *American Entomologist*, **1997**, 43, 12–22.

37. Butenandt, A., Hecker, E., Hopp, M. and Koch, W., *Justus Liebigs Annalen der Chemie*, **1962**, 658, 39.

38. Šobotník, J., Hanus, R., Kalinová, B., Piskorski, R., Bourguignon, T. and Roisin, Y., *J. Chem. Ecol.*, **2008**, 34, 478.

39. Kennedy, C. E. J., Payne, T. L. and Birch, M. C., *Mechanisms in insect olfaction*, New York: Clarendon Press., **1986**.

40. Pickett, J. A. and Griffiths, D. C., *J. Chem. Ecol.*, **1980**, 6, 349.

41. Agosta, W., *Chemical Communication: The language of pheromones*, New York: Scientific American Library, **1992**.

42. Wyatt, T. D., Pheromones and animal behaviour, Cambridge U.K.: Cambridge University Press, **2003**.

43. Grasswitz, T.R. and G.R. Jones (**2002**). "*Chemical Ecology*". *Encyclopedia of Life Sciences*. John Wiley & Sons, Ltd. doi:10.1038/npg.els.0001716.

44. Tan K. H., Nishida R. and Toong, Y. C., *J. Chem. Ecol.,* **2002**, 28, 1161.

45. a- Hummel, H. E. and Millar, T. A., *Techniques in pheromone research*, New York: Springer Verlag, **1984**.

    b- Jacobson, M., *Insect sex attractants*, New York: Academic Press. **1972**.

46. Finlay, J. A. and Macdonald, D. R., *Chem. Can.*, **1966**.

47. Schneider, D., Hecker, E., *Z. Naturforsch*, **1956**, 11b, 121.

48. Prestwich, G.D., Wei, C. S, Mayer, M. S. and Dickens, J. C., *J. Chem. Ecol.*, **1990**, 16, 1761.

49. Boeckh, J., Z.*Vergleich, Physiol.*, **1962**, 46, 212.

50. Pickett, J. A., *J. Biol. Education*, **1989**, 23, 180.

51. a- Matsumura, F., Tai, A. and Coppel, H. C, *Nature*, **1968**, 219, 963.

    b- Tai, A., Matsumura, F. and Coppel, H. C, *J. Org. Chem.*, **1969**, 34, 2180.

52. Voerman, S. and Rothchild, G. H. L., *J. Org. Ecol.*, **1978**, 4, 531.

53. Schwarz, M. and Waters, R. M., *Synthesis*, **1972**, 567.

54. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems and T. Walker, *J. Chem. Soc*, **1952**, 1094 - 1111.

55. Lindlar, H. and Dubuis, R., *Org. Synth. Col.*, **1973**, 5, 880.

56. Attenburrow, J. and Cameron, A. E. B., *J. Chem. Soc*, **1952**, 1094.

57. Bestmann, H. J., Vostrowsky, O. and Platz, H., Chem. Zeit., **1974**, 98, 161.

58. Bestmann, H. J., Vostrowsky, O. and Stransky, W., *Chem. Ber.*, **1976**, 109, 3375.

59. Bestmann, H. J., Vostrowsky, O. and Stransky, W., *Tetrahedron lett.*, **1974**, 779.

60. Yamakawa, R., Do, D. N., Adachi, Y., Kinjo, M., Ando, T., *Tetrahedron Lett.*, **2009**, 50, 4738–4740.

61. Mori, K., *Tetrahedron*, **1975**, 31, 1381.

62. Kim, S.; Hong, Y., *Bull. Korean Chem. Soc.*, **2011**, 32, 8, 3120.

63. Tolstikov, G.A., Odinokov, V.N., Galeeva, R.I., Bakeeva, R.S., Akhunova, V.R., *Tetrahedron lett.*, **1979**, 20, 4851- 4854.

64. a- Jervis, M. and Kidd, N., *Insect natural enemies*, New York: Chapman & Hall. **1996**.

   b- Jutsum, A. R. and Gordon, R. F. S., *Insect pheromones in plant protection*, New York: Wiley, 1988.

65. a- University of California, UC IPM : Pestmanagement guidelines., **1994**.

   b- Bohmfalk, G. T., Frisbie, R. E., Sterling, W. L. and Metzer, R. B., *Texas Agricultural Extension Service*, **1982**, B-933.

   c- Plains, H., Plains, R., Texas Agricultural Extension Service, *Managing cotton insects in the high plains, rolling plains and trans pecos areas of Texas* 1999-2000, **2001**, E-6.

66. Ahmad, M., Ahmad, Z. and Denholm, I., *Pest Management Science,* **2001**, 58: 203.

67. a- Ordish, G., *The great wine blight*, London: Pan Macmillan, **1987**.

   b- Avery, D. T., *Saving the planet with pesticides and plastic, Indianapolis*, IN: Hudson Institute. **1995.**

68. Mafra-Neto, A. and Baker, T. C., *J. Agr. Entomol.*, **1996**, 13: 149.

69. Regitz, M. (Ed.), *Methoden der Organischen Chemie (Houben Weyl)*, Fourth Edition, Thieme Verlag, Stuttgart, **1989**, E 19a.

70. Nair, V., *Comprehensive Organic Chemistry*, Trost, B.M. (Ed.), Pergamon Press, New York, **1991**, 4, 999-1006.

71. Doering , W. V. and Hoffmann, A.K., *J. Am. Chem. Soc.*, **1954**, 76, 6162.

72. Bell, J. A., *Progr. Phys. Org. Chem.*, **1964**, 2, 1.

73. Makosza, M. and Wawrznicwicz, M., *Tetrahedron Lett.*, **1969**, 10, 4659.

74. a- Stark, C. M., *J. Am. Chem. Soc.*, **1971**, 93, 195.

   b- Baird, M. S., Baxter, A. G. W.; Devling, B. R. J.; Searle, R. J .G., *J. Chem. Soc., Chem. Comm, 1979, 210.*

   c- Woodward, R. B.; Hoffmann, R., *"Conservation of Orbital Symmetry", p. 114, Acadimic press, New York, 1970.*

   d- Roth, W.R., *Justus Liebigs Annalen der Chemie*, **1964** , vol. 671, p. 10 – 25.

75. a- Detty M. R., Paquette L. A., *Tetrahedron Lett.*, **1977**, 18, 347.

   b- David, S., Robert S. Boikess, S. Winstein, *Tetrahedron Lett.*, **1966**, 7, 999-1008.

   c- Untch, K. G. and Martin, D. J., *J. Org. Chem.,* **1964**, 29, 1903–1904.

76. a- Untch, K.G., *J. Am. Chem. Soc.*, **1963**, 85, 345 – 346.

   b- Takakis, I.M., Agosta, W.C., *J. Org. Chem.*, **1979**, 44, 1294–1301.

   c- Roth, W.R., *Justus Liebigs, Ann. Chem.*, **1964**, 671, 10 – 25.

d- Frank A. L., Anet, M. G., *J. Am.Chem.Soc*, **1980**, 102, 2528 – 2533.

e- Paquette, L. A. Crouse, G. D., *Tetrahedron*, **1981**, 37, 1, 281-287.

77. Thies, R.W., Hong, P. K., Buswell, R., Boop, J., *J. Org. Chem.*, **1975**, 40, 585-590.

78. Detty M. R., Paquette L. A., *Tetrahedron Lett.*, **1977**, 18, 347.

79. Untch, K. G., Kurland, R.J., *J. Amer.Chem.Soc.*, **1963**, 85, 343–344.

80. Odinokov, V.N., Tolstikov, G., Galeyeva, R., *Tetrahedron Lett.*, **1982**, 23, 1371-1372.

81. Mena, P. L., Pilet, O., Djerassi, C., *J. Org. Chem.*, **1984**, 49, 3260–3264.

82. Sandri, J., Viala, J., Synthesis, **1995**, 3, 271 – 275.

83. Saha, G., Basu, M., K., Adiyaman, M., *Tetrahedron Lett.*, **1999**, 40, 7179–7184.

84. Michaud, S., Viala, J., *Tetrahedron*, **1999**, 55, 3019-3024.

85. Flock, S., Lundquist, M., Skattebol, L., *Acta Chem. Scand.*, **1999**, 53, 436-445.

86. Kajiwara, T., Odake, Y., *Agricultural and Biological Chemistry*, **1975**, 39, 1617-1621.

87. Bestmann, H. J., Roth, K., Michaelis, K., Vostrowsky, O., Schaefer, H., Michaelis, R., *Liebigs Ann. Chem.*, **1987**, 417-422.

88. Bestmann, H. J., Dotzer, R., Manero-Alvarez, J., *Tetrahedron Lett.*, **1985**, 26, 2769- 2772.

89. Langlois, Y., Konopski, L., Riche, C., *Tetrahedron Lett.*, **1990**, 31, 1865-1868.

90. Toth, M., Buser, H.R., Guerin, P., Francke, W., *J. Chem. Ecol.*, **1992**, 18, 13-25.

91. Sabharwal, A., Sharma, S., J., *J. Ind. Chem. Soc.*, **1990**, 67, 173 – 174.

92. Wang, S, Zhang, A., *J. Agric. Food Chem.*, **2007**, 55, 6929 – 6932.

93. Becker, D., Cyjon, R., Cosse, A., Moore, I., Kimmel, T., *Tetrahedron Lett.*, **1990**, 31, 4923 – 4926.

94. a- Becker, D., Kimmel, T., Moore, I., *Tetrahedron Lett.*, **1983**, 24, 5505–5508.

    b- Davies, N.W., Meredith, G, Smith, J.A., *Aust. J. Chem.*, **2007**, 60, 848–849.

95. Badioli, M., Ballini, R., Torregiani, E., *J. Org. Chem.*, **2002**, 67, 8938–8942.

96. a- Szöcs, G., Toth, M., Francke, W., Franke, S., Plass, E., *Book of Abstracts: 13th Annual Meeting, Int. Soc. Chem. Ecol. Prague*, **1996**, 178.

    b- Goller,S., *J Chem Ecol*, **2007**, 33,1505–1509.

97. Descoins, C., Lalanne-Cassou, B., Frérot, B., Malosse, C. and Renou, M., *Acad. Sci. Ser.*, **1989**, 3, 309, 577-581.

98. Li, **1988**, *Seminar Insect Semiochemicals (Pherobase)*, 29.

99. a- Hu, C., Zhu, J., Ye, G., Hong, J.,**1994**, *Ectropis oblique* Prout, a serious geometrid pest of tea bush in East China. Scientific and Technical Publishers, Shanghai, 226-228.

   b- Yang, Y., *Gao, H., Wan, X.,* **2011**. *Mating Strategy of Ectropis oblique, Florida Entomologist,* 94 (1).

100. Yao, E.Y., Li, Z.M., Lou, Z.Q., Shang, Z.Z., **1991**, *Prog. Nat. Sci.,* 1, 566-569.

101. a- Asif, M., Health effects of omega-3,6,9 fatty acids, *Orient Pharm Exp Med,* **2011**, 11, 51–59, DOI 10.1007/s13596-011-0002-x, Research Article.

   b- Loreau, O., Maret, A., Poullain, D., Chardigny, J., *Chemistry and Physics of Lipids,* **2000**, 106, 65–78.

   c- Crombie, L., David, O., *J. Chem. Soc. Perkin Trans. 1,* **1991**, 581-587

102. Cabrera, A., Eiras, A., Gries, G., Gries, R., Urdaneta, N., Miras, B., Badji, C. and Jaffe, *J. Chem. Ecol.,* **2001**, 27, 2097-2107.

103. El-Sayed, A. M., *The Pherobase: Database of Insect Pheromones and Semiochemicals,* http://www.pherobase.com., 2004.

104. EL-Sayed, A.M., Gibb, A.R., Suckling, D.M., *New Zealand Plant Protection,* **2005**, 58, 31-36.

105. Jacques, V. and Jacqueline, S., *Tetrahedron Lett.,* **1992**, 33, 34, 4897-4900.

106. a. Itoh, T., Murota, I., Yoshikai, K., Yamamoto, K., *Bioorg. Med. Chem.,* **2006**, 14, 98 – 108.

   b- Holmeide, A.K., Li, **1988**, *Seminar Insect Semiochemicals (Pherobase),* 29– 2276.

   c- Flock, S., Holmeide, A. K., Skattebøl, L., *Synth. Commun.,* **2007**, 37, 4005– 4015.

   d- Naomichi B., Md. Khorshed A., Yoshihiro M., Syed S. H., *J. Chem. Soc., Perkin Trans. 1,* **2001**, 221–223.

107. a- Bai, T., Shengming M., Guochen J., *Coordination Chemistry Reviews,* **2009**, 253, 423–448.

   b- Ogasawara, M., *Tetrahedron Asymmetry,* **2009**, 20, 259.

   c- Blanchard, J. S., Marcinkeviciene, J. A., *Biochemistry,* **1995**, 34, 6621.

   d- Fischer, H., '*The Chemistry of Allenes*', Patai, S. (Ed.), Interscience Publishers Inc. London, **1964.**

108. Wotiz, J.H., Mancuso, D.E., *J. Org. Chem.,* **1957**, 22, 207-211.

109. Simmons, H. E., Blanchard, E., Hartzler, H., *J. Org. Chem.*, **1966**, 31, 295-301.

110. Friedel, R.A., Retcofsky, H.L., *J. Am. Chem. Soc.,* **1963**, 85, 1300-1306.

111. Luche, J., Damiano, J., Cohen-Addad, C., *J. Am. Chem. Soc.*, **1980**, 102, 5370–5374.

112. López, C. S., Faza, O., York, D., de Lera, A., *J. Org. Chem.*, **2004**, 69, 3635 – 3644.

113. Dollat, J., Luche, J., Crabbé, P., *J. Chem. Soc., Chem. Comm.,* **1977**, 761–762.

114. Krause, N, Hoffmann, A., *Allenic Natural Products and Pharmaceuticals, In Modern Allene Chemistry*, Krause, N, Hashmi, A., Eds., Wiley-VCH: Weinheim, **2004**, 997–1039.

115. a- Celmer, W. D., Solomons, I. A., *J. Am. Chem. Soc.*, **1952**, 74, 1870 –1871.
    b- A. Claesson, L.-L. Olsson, *J. Am. Chem. Soc.*, **1979**, 101, 7302

116. a- Elsevier, C.J., Vermeer, P., *J. Org. Chem.*, **1989**, 54, 3726 –3730.
    b- Lin, M., Tsai, W., Hung, S., *J. Org. Chem.*, **2011**, 76, 8518-8523.

117. a- Sydnes, L.K., *Chem. Rev.*, **2003**, 103, 1133-1150.
    b- Johnson, R. P., *Chem. Rev.*, **1989**, 89, 1111.

118. Schmidt, M. W., Angus, R. O., Johnson, R. P., *J. Am. Chem. Soc.*, **1982**, 104, 6838–6839.

119. Kistiakowski, G. B., Ruhoff, J. R., Smith, H. A., Vaughan, W., *J. Am. Chem. Soc.*, **1936**, 58, 146–153.

120. Christl, M., *in Modern Allene Chemistry*, Krause, N., Hashmi, A. S. K. Eds., Wiley-VCH Verlag, Weinheim, **2004**, 1, 243-358.

121. a- Balci, M., Taskesenligil, Y., *Advanced Strained Organic Molecules*, **2000**, 8, 43-75.
    b- Johnson, P. R., Daoust, K. J., Hernandez, S. M., Konrad, K. M., Mackie, I. D., Winstanley, J., *J. Org. Chem.*, **2006**, 71, 5708-5714.

122. a- Favorskii, A. E., *J. Gen. Chem. USSR* (Engl. Transl.), 6, 720, **1936**
    b- Ceylan, M., Balcl, M., *Turk. J. Chem.*, **2003**, 27, 287-294.

123. a- Ceylan, M., Secen, H., Sütbeyaz, Y., *J. Chem. Res.*, **1997**, 70-71.
    b- Ceylan, M., Secen, H., Sütbeyaz, Y., *J. Chem. Res.*, **1993**, 293-294.

124. a- Backes, J., Brinker, U. H., *in Methoden der Organischen Chemie, 4th ed.*, **1989**, E. 19b, 391-510.

125. Wittig, G., Fritze, P., *Justus Liebigs Ann. Chem.*, **1968**, 82, 711-712.

126. Moore, W. R., Moser, W. R., *J. Am. Chem. Soc.*, **1970**, 92, 5469-5474.

127. Bottini, A. T., Corson, F., Fitzgerald, R., Frost, K., *Tetrahedron*, **1972**, 28, 4883-4904.

128. Wittig, G., Fritze, P., *Angew. Chem. Int. Ed. Engl.*, **1966**, 5, 846.

129. Christl, M., Braun, M., Fischer, H., Groetsch, S., Leusser, D., Deurlein, S., Stalke, D., Arnone, M., Engels, B., Eur., *J. Org. Chem.*, **2006**, 22, 5045-5058.

130. a- Ball, W. J., Landor, S. R., *Proc. Chem. Soc.*, **1961**, 143-144.

   b- Ball, W. J., Landor, S. R., *J. Chem. Soc.*, **1962**, 2298-2304.

   c- Balci, M., Jones, W. M., *J. Am. Chem. Soc.*, **1980**, 102, 7607-7608

131. Köbrich, G., Goyert, W., *Tetrahedron*, **1968**, 24, 4327-4342.

132. Bettinger, H. F., Schleyer, P. V.R., Schreiner, P. R. Schaefer, H. F., *J. Org. Chem.*, **1997**, 62, 9267-9275.

133. Marquis, E. T., Gardner, P. O., *Tetrahedron Lett.*, **1966**, 2793-2795.

134. Kropp, P.J., Davis, R.D., *J. Am. Chem. Soc.*, **1983**, 105, 6907- 6915.

135. Blomquist, A., Bohrer, J., Sucsy, A., *J. Am. Chem. Soc.*, **1951**, 73, 5510-5511.

136. a- Skattebøl, L., *Tetrahedron Lett.*, 1961, 2, 167-172.

   b- Skattebøl, L., Solomon, S., *Organic Synthesis*, **1969**, 49, 35-38.

   c- Skattebøl, L., *Acta Chem. Scand.*, **1963**, 17, 1683-1693.

137. a- Irngartinger, M. and Jager, H.U., *Tetrahedron Lett.*, **1970**, 4047–4050.

   b- DehmLow, E. V. and Stiehm, T., *Tetrahedron Lett.*, **1990**, 31, 1841–1844.

   c- Xu, L., Tao, F., Yu, T., *Tetrahedron Lett.*, **1985**, 26, 4231 – 4234.

138. a- Baird, M.S., Reese, C.B., *Tetrahedron*, **1976**, 32, 2153-2156

   b- Poulter, C., Boikes, R., Brauman, J., *J. Am. Chem. Soc.*, **1972**, 94, 2291-2296.

   c- Yavari, I, Jabbari A., Samadizadeh M., *J. Chem. Research (S)*, **1999**, 154–155.

   d- Initial semi-empirical and ab initio calculations predict that the D_3 form is not an energy minimum, but a transition state between two minima (R. A. Davies, unpublished results).

   e- Visualised using Chem3D Pro 12.0.

139. a- Nagendrappa, G., Joshi, G. C., D., *J. Organomet. Chem.*, **1971**, 27, 421–426.

   b- Schönleber, D., *Chem. Ber.*, **1969**, 102, 1789-1801.

140. Xu, Q., Yang, H. Pan, X. and Chan, A. S. C., *Tetrahedron Asymmetry*, **2002**, 13, 945.

141. Langer, K. and Mattay, J., *J. Org. Chem.*, **1995**, 60, 22, 7256-7266.

142. Thomas L. C., Raymond H. B. and Henry R., *J. Org. Chem.*, **1985**, 50, 21, 3972-3979.

143. Stanfied, C. F., Parker, J. E. and Kanellis, P., *J. Org. Chem.*, **1981**, 46, 4797.

144. Miller, M. and Hegedus, L. S., *J. Org. Chem.*, **1993**, 58, 6779.

145. a- Marc J. M. and Meyers, A. I., *J. Org. Chem.*, **1993**, 68, 13, 3670.

    b- Akamanchi, K. G.; Shah B. L., *Indian J. Chem.*, **1996**, 35B, 293–302.

    c- Umbreen S., Brockhaus M., Ehrenberg H., Schmidt B., *Eur. J. Org. Chem.*, **2006**, 4585–4595.

146. a- Wu, Y. and Shen, X., *Tetrahedron Asymmetry*, **2000**, 11, 4359–4363.

    b- Bartolo Gabriele, *J. Org. Chem.*, **2003**, 68, 601-604

147. Deyrup, J. A. and Betkouski, M. F., *J. Org. Chem.*, **1975**, 40, 3, 284.

148. Albelo, G. and Rettig, M. F., *J. Org., Chem.*, **1972**, 42, 183-198.

149. Carl, R., *Tetrahedron Lett.*, **1994**, 35, 42, 7735-7738.

150. Irie, O., Samizu, J. Henry, *J. Org. Chem.*, **1999**, 64, 587-595.

151. Laurence, W., Jacques, V., *Synthesis*, **2002**, 3, 326 – 330.

152. Frerot, E., Bagnoud, A., *J. Agr. Chem.*, **2011**, 59, 4057 – 4061.

153. Ahad, A. M., Zhou, L. L., Mash, E. A., Zuohe, S., *Bioorganic and Medicinal Chemistry*, **2011**, 19, 6, 2046-2054.

154. Takao, K. and Nigawara, Y., *Tetrahedron*, **1994**, 50, 19, 5681–5704.

155. a- Yamakawa, R., Kinjo, M., Terashima, Y., *J. Chem. Ecol*, **2011**, 37, 105-113.

    b- Itoh, T., Tomiyasu, A., *Lipids*, **2011**, 46, 455–461.

156. Christian W., *Chem. Eur. J.*, **2007**, 13, 9462–9477.

157. a- Buss, A. D., Warren, Stuart, *J. Chem. Soc., Perkin Trans.*1: **1985**, 2307 – 2326.

    b- Bergelson L.D,,Barsukov L.1., Shemyakin M.M., *Tetrahedron*, **1967**, 23, 2709.

158. Pelter, A., Smith, K., Elgendy, S., Rowlands, M., *Tetrahedron*, **1993**, 49, 32, 7104 – 7118.

159. a- Odinokov, V., Akhmetova, V., *J. Org. Chem.*, **1985**, 21, 3, 443 – 447.

    b- Kenji, M., Wu, J., *Liebigs Annalen der Chemie*, **1991**, 1991, 213–217.

160. Kodato, S., Nakagawa, M., *Tetrahedron*, **1989**, 45, 23, 7247–7262.

161. Zhu, Y., Soroka, D. N., Sang, S., *J. Agric. Chem.*, **2012**, 60, 35, 8624-8631.

162. Deroose, F. D., De Clercq, P. J., *J. Org. Chem.*,**1995**, 60, 2, 321–330.

163. a- Moman, E., Nicoletti, D., Mourino, A., *J. Org. Chem.*, **2004**, 69, 14, 4615–4625.

b- Narasimhan, S.; Prasad, K. Ganeshwar; Madhavan, *Indian Journal of Chemistry*, Section B: *Organic Chemistry Including Medicinal Chemistry*, **1996**, 35, 99 - 101

164. Perlman, N., Livneh, M., Albeck, A., *Tetrahedron*, **2000**, 56, 11, 1505–1516.

165. a- Abad, J., Fabrias, G., Camps, F., *J. Org. Chem.*, **2000**, 65, 25, 8582 – 8588.

b- Pahl, A., Oetting, J., Holzkamp, *Tetrahedron*, **1997**, 53, 21, 7255 – 7266.

166. a- Nakatani, M., Fukunaga Y., Haraguchi H., Taniguchi M., *Bulletin of the Chemical Society of Japan*, **1986**, 59, 3535 -3540.

b- Poulain, S., Noiret, N., Fauconnot, L., *Tetrahedron*, **1999**, 55, 12, 3595–3604.

167. a- Saskia, T., Walter, V., *Tetrahedron*, **2007**, 63, 5, 1140 – 1145.

b- Duffy, P. E., Quinn, S., Evans, P., *Tetrahedron*, **2006**, 62, 20, 4838–4843.

168. Mert H., Yalçın Y., Kılıç M., San N. and Çınar Z., E., *J. Adv. Oxid. Technol.*, **2008**, 11, 2, 199-207.

Appendix

Preparation of triphenyl(propyl)phosphonium bromide.

1-Bromopropane (25 g, 200 mmol) was added to a stirred solution of triphenylphosphine (65 g, 248 mmol) in toluene (250 mL). The mixture was refluxed for 48 hours, then the solvent was evaporated. After that petrol (200 mL) was added and evaporated. The residue was treated with diethylether (200 mL) then stirred for one hour; by this time slurry of crystals had formed. These were filtered, washed with ether and dried to give a white solid of tri-phenyl(propyl)phosphonium bromide[157] (58 g, 93 %).

δ_H(400 MHz) : 7.85 (9H, br m), 7.70 (6H, br, m), 3.77 (2H, br m), 1.69 (2H, br hept., J 7.2 Hz), 1.23 (3H, br t, J 7.2 Hz).

δ_c(126 MHz) : 135.0, 134.9, 133.7, 133.6, 130.5, 130,4, 118.7, 1180, 24.3, 16.6, 15.4.

v_{max}/ cm^{-1} : 3050, 2959, 2883, 2856, 1437, 1112, 720, 690, 530.

Preparation of octyltriphenylphosphonium bromide

As above, octyltriphenylphosphonium bromide[158] (20 g, 85 %), was prepared by using 1-bromooctane (10 g, 50 mmol), PPh$_3$ (17.6 g, 67 mmol), toluene (120 mL).

δ_H(400 MHz) : 7.88-7.78 (9H, br m), 7.73-7.68 (6H, m), 3.84-3.79 (2H, br m),1.63 (4H, br s), 1.34-1.11 (8H, m), 0.88 (3H, br t, J 6.76 Hz).

δ_c(126 MHz) : 134.9, 134.9, 133.7, 133.6, 130.5, 130.3, 118.8, 117.9, 31.6, 30.4, 30.2, 29.1, 22.6, 22.5, 22.5, 14.0.

Preparation of nonyltriphenylphosphonium bromide

As above, 1-bromononane (10.0 g, 48 mmol) and PPh$_3$ (16.4 g, 60 mmol) in toluene (120 mL) were reacted to obtain nonyltriphenylphosphonium bromide[159] (19.3 g, 84 %).

δ_H(400 MHz) : 7.80-7.09 (15H, m), 3.75-3.68 (2H, m), 1.54 (4H, br d, J 3.68 Hz), 1.14 (10H, m), 0.76 (3H, t, J 6.72 Hz)

δ_c(126 MHz) : 134.9, 134.9, 133.7, 133.6, 130.4, 130.3, 118.8, 117.9, 31.7, 30.2, 29.1, 29.1, 29.0, 23.0, 22.6, 22.5, 14.0.

v_{max}/ cm^{-1} : 3050, 2959, 2883, 2856, 1437, 1112, 720, 690, 530.

Preparation of decyltriphenylphosphonium bromide

As above, decyltriphenylphosphonium bromide[160] (15.0 g, 71 %), was prepared by using 1-bromodecane (10.0 g, 45 mmol), PPh3 (15.4 g, 58 mmol), toluene (120 mL).

δ_H(400 MHz) : 7.84-7.69 (15H, m), 3.71 (2H, br m), 1.60 (4H, br s), 1.16 (12H, br s), 0.82 (3H, br t, J 6.2 Hz)

δ_c(126 MHz) : 134.9, 134.9, 133.6, 133.5, 130.4, 130.3, 118.6, 117.8, 31.6, 30.4, 30.2, 29.3, 29.1, 29.0, 22.9, 22.5, 22.4, 14.0.

Preparation of triphenyl(undecyl)phosphonium bromide

As above for the preparation of triphenyl(undecyl)phosphonium bromide[154]
(17 g, 80 %), 1-bromoundecane (10 g, 42 mmol) was reacted with PPh3 (15 g, 55 mmol) in toluene (120 mL).

δ_H(400 MHz) : 7.86-7.68 (15H, m), 3.77 (2H, br t, J 7.24), 1.61 (4H, br s), 1.22 (14H, m), 0.85 (3H, t, J 5.56)

δ_c(126 MHz) : 134.9, 134.9, 133.6, 133.6, 130.4, 130.3, 118.7, 118.0, 31.7, 30.4, 30.2, 29.4, 29.1, 29.1, 29.1, 22.9, 22.6, 22.5, 14.0.

Preparation of dodecyltriphenylphosphonium bromide

As above 1-bromododecane (10 g, 40 mmol), PPh3 (13g, 52 mmol), toluene (120 mL); were used to obtain dodecyltriphenylphosphonium bromide[161] (16 g, 80 %).

δ_H(400 MHz) : 7.89-7.68 (15H, m), 3.83 (2H, br p, J 9.72 Hz), 1.63 (4H, br s), 1.28 (16H, m), 0.87 (3H, t, J 6.64 Hz).

δ_c(126 MHz) : 134.9, 134.9, 133.7, 133.6, 130.4, 130.3, 118.8, 117.9, 31.8, 30.4, 30.2, 29.5, 29.4, 29.2, 29.2, 29.1, 22.9, 22.6, 22.5, 14.0.

Preparation of hexadecyltriphenylphosphonium bromide

As above, for the preparation of hexadecyltriphenylphosphonium bromide[161] (17 g, 88 %), 1-bromohexadecane (10 g, 32 mmol) was react with PPh$_3$ (11g, 42 mol) in toluene (120 mL).

δ_H(400 MHz) :   7.80 (15H, m), 3.83 (2H, br m), 1.62 (4H, br s), 1.24 (24H, br m),

0.87 (3H, t, J 6.64 Hz).

δ_C(126 MHz) :   134.9, 133.7, 133.6, 130.4, 130.3, 31.8, 30.4, 30.2, 29.6, 29.5, 29.4,

29.2, 29.2, 29.1, 23.0, 22.6, 22.5, 14.0.

Preparation of (5-carboxypentyl)-triphenylphosphonium bromide

As above 6-bromohexanoic acid (5 g, 25 mmol), PPh$_3$ (9 g, 33 mmol), toluene (100 mL) gave (5-carboxypentyl)-triphenylphosphonium bromide[162,163] (10 g, 81 %).

δ_H(400 MHz) :   7.79 (15H, m), 3.63 (2H, br m), 2.39 (2H, br s), 1.67 (6H, br m).

δ_C(126 MHz) :   175.7, 135.1, 135.1, 133.6, 133.5, 130.6, 130.5, 118.5, 117.7, 34.2, 29.5,

29.4, 23.9, 22.7, 22.2, 21.8, 21.8.

Preparation of pentyltriphenylphosphonium bromide

As above 1-bromopentane (10 g, 66.2 mmol), PPh$_3$ (22 g, 86 mmol), toluene (120 mL) gave pentyltriphenylphosphonium bromide[157,163] (24 g, 88 %).

δ_H(400 MHz) :   7.75 (15H, m), 3.7 (2H, br m), 1.58 (4H, br s), 1.25 (2H, m),

0.87 (3H, t, J 7.28 Hz).

δ_C(126 MHz) :   134.9, 134.9, 133.6, 133.5, 130.5, 130.4, 118.6, 117.8, 32.3, 32.2, 22.9,

22.4, 22.2, 22.2, 22.1, 13.5.

Preparation of (3-hydroxypropyl)-triphenylphosphonium bromide

As above (3-hydroxypropyl)triphenylphosphonium bromide[164] (13 g, 88 %) was prepared by using 3-bromopropan-1-ol (5 g, 35 mmol) and triphenylphosphine (12g, 46 mmol) in), toluene (120 mL).

δ_H(400 MHz) :   7.81 (15H, m), 3.86 (4H, br m), 1.85 (2H, br s).

δ_C(126 MHz) :   135.04, 135.01, 133.56, 133.46, 130.59, 130.46, 60.39, 60.22, 25.86,

20.55, 20.03.

Preparation of 9-bromononan-1-ol

Hydrobromic acid 48 % (25 mL) was added to a stirred solution of 1,9-nonadiol (25 g, 156 mmol) in toluene (300 mL) at room temperature. The mixture was refluxed for 24 hrs, when TLC showed no starting material was left then the toluene was decanted and evaporated. The residue was treated with sodium hydrogen carbonate (25 mL) then extracted with dichloromethane (3 x 25 mL), dried and evaporated. The crude product was purified by column chromatography on silica eluting with petrol : ethyl acetate (5:1) to give 9-bromononan-1-ol[165] (26 g, 76 %).

δ_H(400 MHz) :   3.64 (2H, t, J 6.6 Hz), 3.40 (2H, t, J 6.84 Hz), 1.85 (2H, pent, J 6.92 Hz),

1.56 (2H, pent, J 6.8 Hz), 1.31 (10H, br s).

δ_C(126 MHz) :   62.9, 33.9, 32.77, 32.75, 29.3, 29.2, 28.6, 28.1, 25.6.

v_{max}/ cm^{-1} :   3419 (br), 2930, 2853, 1734.

Preparation of 9-bromononanoic acid

Potassium permanganate (4 g, 25 mmol) was added in small portions to a stirred solution of 9-bromononan-1-ol (2 g, 9 mmol), dichloromethane (15 mL), water (11 mL), acetic acid (1 mL), hexadecyltrimethylammonium bromide (cetrimide) (0.5 g) and sulphuric acid (1.35 mL, 1M) at 0 °C. The reaction mixture was stirred for 16 hrs at room temperature. After that, TLC showed no starting material was left then reaction mixture was quenched carefully with sat.aq. sodium metabisulphite until a clear solution was obtained. The product was extracted with dichloromethane (3 x 50 mL), dried and evaporated. The

residue was purified by column chromatography on silica eluting withpetroleum :ethyl acetate (5:2) to give 9-bromononanoic acid[166] (1.7 g, 80 %).

δ_H(400 MHz) :   11.22 (1H, br s, OH), 3.41 (2H, t, J 6.88 Hz), 2.36 (2H, t, J 7.4 Hz),

1.86 (2H, pent, J 7.32 Hz), 1.64 (2H, pent, J 7.28 Hz), 1.33 (8H, br m).

δ_C(126 MHz) :   179.6, 33.97, 33.95, 32.7, 29.0, 28.8, 28.5, 28.0, 24.5.

v_{max}/ cm^{-1} :   3000 (br), 2925, 2854, 1707.

Preparation of (8-carboxyoctyl)triphenylphosphonium bromide

9-Bromononanoic acid (1.6 g, 6.7 mmol) and triphenylphosphine (1.9 g, 7 mmol), were dissolved in dry acetonitrile (25 mL). The mixture was refluxed for 72 hours then allowed to cool to room temperature then the solvent was removed under vacuum, affording a crude white solid. The solid residue was treated with ether (100 mL) and the suspension was refluxed for 1 hour. The white precipitate was filtered off under vacuum and the white solid was washed with dry ether to give (8-carboxyoctyl)triphenylphosphonium bromide[167] (2.9 g, 87 %).

δ_H(500 MHz) :   7.78 (9H, br, m), 7.69 (6H, br, m), 3.62 (2H, br m), 2.31 (2 H, t, J 7.36

Hz), 1.57 (6H, br m), 1.27 (6H, br m).

δ_C(126 MHz) :   177.1, 135.0, 133.7, 130.5, 118.5, 34.3, 30.0, 29.8, 28.38, 28.35, 24.4,

22.8, 22.3.

v_{max}/ cm^{-1} :   3437 (br), 3030, 2927, 2860, 1741, 1608, 1555.

Supplementary

Version	1/D.Justice
Costing	Based on Aldrich catalogue prices/assumed solvent prices
	Yields Based on results provided by Hussien, 26/Mar2010
Date	23 April 2010
Route 4	(1) *NaBH4/Sulphuric acid* (2) *ECF carbamate protectiom* (3) potassium carbonate cyclisation

PRODUCT:	Stage 1 Product	Stage 1	
STEP	1	of	3
WEIGHT OF PRODUCT (A):	0.760	Kg	
STAGE YIELD:	83%		
CUMULATIVE YIELD	83%		

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE Kg	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CARBAMATE PROTECTION									
Phenyl alanine	1.00	165	6.05	1.32	£243.00	£243.00	Aldrich 1Kg lots	63-91-2	36.8%
Sodium Borohydride	0.64	38	17.00	0.85	£174.50	£112.20	Aldrich/Venpure 2Kg lots	16940-66-2	17.0%
Sulphuric Acid	0.59	98	6.06	0.78	£8.56	£5.08	Alddrich 2.5L lots	7664-93-3	0.8%
THF	10.00			13.16	£2.00	£20.00	Assumed		3.0%

| STAGE 1 RAW MATERIALS | | | | | | £380.29 | | | |
| TOTAL STAGE 1 COST | | | | | | £380.29 | | | |

	QTY	M/WT	MOLES	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 1	0.7597	151	5.02	83.0%	83.0%	£380.29

PRODUCT:	Stage 2 Product	Stage 2	
STEP	2	of	3
WEIGHT OF PRODUCT (A):	0.97	Kg	
STAGE YIELD:	92%		
CUMULATIVE YIELD	76%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
BORANE REDUCTION									
Stage 1	0.760	151	5.02	0.78	0.00	£0.00			0.0%
NaHCO3 solution	25.00			25.68	£1.00	£25.00	Assumed		3.8%
Ethyl chloroformate	0.76	109	7.04	0.78	£86.50	£66.09	Aldrich 500ml lots	541-41-3	10.0%
Ethyl acetate	75.00			77.05	£2.00	£150.00	Assumed		22.7%
Hydrochloric acid	1.00			1.03	£5.00	£5.00	Assumed		0.8%
Water	6.61			6.79	£0.00	£0.00	Assumed		#REF!
									0.0%

| STAGE 2 RAW MATERIALS | | | | | | £246.09 | | | |
| TOTAL STAGE 2 COST | | | | | | £246.09 | | | |

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 2	0.973	211	4.62	92%	76.4%	£626.37

PRODUCT:	Stage 3 Product	Stage 3	
STEP	3	of	3
WEIGHT OF PRODUCT (A):	0.69	Kg	
STAGE YIELD:	84%		
CUMULATIVE YIELD	64%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CYCLISATION									
Stage 2	0.973	211	4.62	1.00	0.00	£0.00			0.0%
Potassium carbonate	1.760	138	12.73	1.81	13.40	£23.58	Aldrich 1Kg lots	584-08-7	3.6%
Solvent	4.975			5.11	2.00	£9.95	Assumed		1.5%

| STAGE 3 RAW MATERIALS | | | | | | £33.53 | | | |
| TOTAL STAGE 3 COST | | | | | | £33.53 | | | |

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of stage 3	0.688	177	3.88	84%	64.1%	£659.91

Cost of Goods manufacture/Kg = £959.15

Excel sheet 2: Cost of preparation (S)-4-benzyl-oxazolidin-2-one using 2.8 equivalent NaBH₄/H₂SO₄ for the reducion step

Version	1/D.Justice
Costing	Based on Aldrich catalogue prices/assumed solvent prices
	Yields Based on results provided by Hussien, 26/Mar2010
Date	٢٣ نيسان ، ٢٠١٠
Route 4	(1) NaBH4/BF3 etherate reduce (2) ECF carbamate protectiom (3) potassium carbonate cyclisation
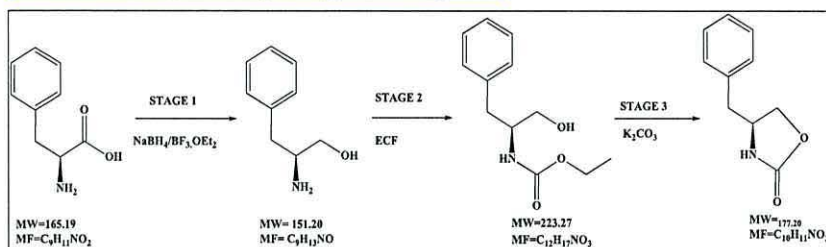
PRODUCT:	Stage 1 Product	Stage 1	
STEP	1	of	3
WEIGHT OF PRODUCT (A):	0.714	Kg	
STAGE YIELD:	78%		
CUMULATIVE YIELD	78%		

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE Kg	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CARBAMATE PROTECTION									
Phenyl alanine	1.00	165	6.05	1.40	£243.00	£243.00	Aldrich 1Kg lots	63-91-2	32.8%
Sodium Borohydride	0.46	38	12.15	0.64	£174.50	£80.24	Aldrich/Venpure 2Kg lots	16940-66-2	10.8%
Boron trifluoride diethyl etherate	3.43	142	24.17	4.80	£34.69	£118.99	Aldrich 1Kg lots	109.63.7	16.0%
THF	10.00			14.01	£2.00	£20.00	Assumed		2.7%
STAGE 1 RAW MATERIALS						£462.22			
TOTAL STAGE 1 COST						£462.22			

	QTY	M/WT	MOLES	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 1	0.7139	151	4.72	78.0%	78.0%	£462.22

PRODUCT:	Stage 2 Product	Stage 2	
STEP	2	of	3
WEIGHT OF PRODUCT (A):	0.91	Kg	
STAGE YIELD:	92%		
CUMULATIVE YIELD	72%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
BORANE REDUCTION									
Stage 1	0.714	151	4.72	0.78	0.00	£0.00			0.0%
NaHCO3 solution	25.00			27.33	£1.00	£25.00	Assumed		3.4%
Ethyl chloroformate	0.76	109	7.04	0.84	£86.50	£66.09	Aldrich 500ml lots	541-41-3	8.9%
Ethyl acetate	75.00			81.98	£2.00	£150.00	Assumed		20.2%
Hydrochloric acid	1.00			1.09	£5.00	£5.00	Assumed		0.7%
Water	6.61			7.23	£0.00	£0.00	Assumed		#REF!
									0.0%
STAGE 2 RAW MATERIALS						£246.09			
TOTAL STAGE 2 COST						£246.09			

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 2	0.915	211	4.34	92%	71.8%	£708.31

PRODUCT:	Stage 3 Product	Stage 3	
STEP	3	of	3
WEIGHT OF PRODUCT (A):	0.65	Kg	
STAGE YIELD:	84%		
CUMULATIVE YIELD	60%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CYCLISATION									
Stage 2	0.915	211	4.34	1.00	0.00	£0.00			0.0%
Potassium carbonate	1.760	138	12.73	1.92	13.40	£23.58	Aldrich 1Kg lots	584-08-7	3.2%
Solvent	4.975			5.44	2.00	£9.95	Assumed		1.3%
STAGE 3 RAW MATERIALS						£33.53			
TOTAL STAGE 3 COST						£33.53			

Output of stage 3	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
	0.647	177	3.65	84%	60.3%	£741.84

Cost of Goods manufacture/Kg = | £1,147.35 |

Excel sheet 3: Cost of preparation (S)-4-benzyl-oxazolidin-2-one using NaBH₄:

BF₃.OEt₂ (2 : 4 equivalents) for reducion step

Version	1/D.Justice
Costing	Based on Aldrich catalogue prices/assumed solvent prices
	Yields Based on results provided by Hussien, 26/Mar2010
Date	۲۳ نيسان ۲۰۱۰
Route 4	(1) NaBH4/BF3 etherate reduce (2) ECF carbamate protection (3) potassium carbonate cyclisation

MW=165.19 MF=C$_9$H$_{11}$NO$_2$ — STAGE 1 NaBH$_4$/BF$_3$OEt$_2$ — MW=151.20 MF=C$_9$H$_{13}$NO — STAGE 2 ECF — MW=223.27 MF=C$_{12}$H$_{17}$NO$_3$ — STAGE 3 K$_2$CO$_3$ — MW=177.20 MF=C$_{10}$H$_{11}$NO$_2$
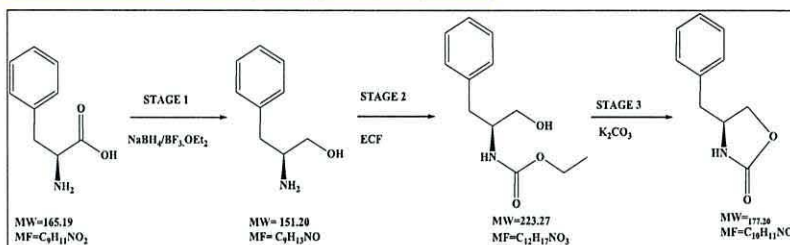
PRODUCT:	Stage 1 Product	Stage 1	
STEP	1	of	3
WEIGHT OF PRODUCT (A):	0.824	Kg	
STAGE YIELD:	90%		
CUMULATIVE YIELD	90%		

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE Kg	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CARBAMATE PROTECTION									
Phenyl alanine	1.00	165	6.05	1.21	£243.00	£243.00	Aldrich 1Kg lots	63-91-2	33.6%
Sodium Borohdride	0.39	38	10.31	0.47	£174.50	£68.06	Aldrich/Venpure 2Kg lots	16940-66-2	9.4%
Boron trifluoride diethyl etherate	3.22	142	22.69	3.91	£34.69	£111.70	Aldrich 1Kg lots	109.63.7	15.5%
THF	10.00			12.14	£2.00	£20.00	Assumed		2.8%
STAGE 1 RAW MATERIALS						£442.76			
TOTAL STAGE 1 COST						£442.76			

	QTY	M/WT	MOLES	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 1	0.8238	151	5.45	90.0%	90.0%	£442.76

PRODUCT:	Stage 2 Product	Stage 2	
STEP	2	of	3
WEIGHT OF PRODUCT (A):	1.06	Kg	
STAGE YIELD:	92%		
CUMULATIVE YIELD	83%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
BORANE REDUCTION									
Stage 1	0.824	151	5.45	0.78	0.00	£0.00			0.0%
NaHCO3 solution	25.00			23.68	£1.00	£25.00	Assumed		3.5%
Ethyl chloroformate	0.76	109	7.04	0.72	£86.50	£66.09	Aldrich 500ml lots	541-41-3	9.1%
Ethyl acetate	75.00			71.05	£2.00	£150.00	Assumed		20.8%
Hydrochloric acid	1.00			0.95	£5.00	£5.00	Assumed		0.7%
Water	6.61			6.26	£0.00	£0.00	Assumed		#REF!
									0.0%
STAGE 2 RAW MATERIALS						£246.09			
TOTAL STAGE 2 COST						£246.09			

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 2	1.056	211	5.01	92%	82.8%	£688.84

PRODUCT:	Stage 3 Product	Stage 3	
STEP	3	of	3
WEIGHT OF PRODUCT (A):	0.75	Kg	
STAGE YIELD:	84%		
CUMULATIVE YIELD	70%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CYCLISATION									
Stage 2	1.056	211	5.01	1.00	0.00	£0.00			0.0%
Potassium carbonate	1.760	138	12.73	1.67	13.40	£23.58	Aldrich 1Kg lots	584-08-7	3.3%
Solvent	4.975			4.71	2.00	£9.95	Assumed		1.4%
STAGE 3 RAW MATERIALS						£33.53			
TOTAL STAGE 3 COST						£33.53			

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of stage 3	0.746	177	4.21	84%	69.6%	£722.38

Cost of Goods manufacture/Kg =   £968.28

Excel sheet 4: Cost of preparation (S)-4-benzyl-oxazolidin-2-one using NaBH$_4$:

BF$_3$.OEt$_2$ (1.7 : 3.5 equivalents) for reducion step

Route	Based on Method provided by Husein Mustafa 28/JAN2010
Version	2/D.Justice
Costing	Based on Aldrich catalogue prices/assumed solvent prices
Date	٢٣ نيسان، ٢٠١٠
Route 1	(1) Carbamate protect; (2) Borane/THF Reduce (3) potassium carbonate cyclisation

PRODUCT:	Stage 1 Product	Stage 1	
STEP	1	of	3
WEIGHT OF PRODUCT (A):	1.321	Kg	
STAGE YIELD:	92%		
CUMULATIVE YIELD	92%		

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE Kg	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CARBAMATE PROTECTION									
Phenyl alanine	1.00	165	6.05	0.76	£243.00	£243.00	Aldrich 1Kg lots	63-91-2	17.6%
NaHCO3 solution	25.00			18.92	£1.00	£25.00	Assumed		1.8%
Ethyl chloroformate	0.98	109	8.99	0.74	£86.50	£84.34	Aldrich 500ml lots	541-41-3	6.1%
Ethyl acetate	75.00			56.76	£2.00	£150.00	Assumed		10.8%
Hydrochloric acid	1.00			0.76	£5.00	£5.00	Assumed		0.4%

STAGE 1 RAW MATERIALS						£507.34			
TOTAL STAGE 1 COST						£507.34			

	QTY	M/WT	MOLES	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 1	1.3213	237	5.57	92.0%	92.0%	£507.34

PRODUCT:	Stage 2 Product	Stage 2	
STEP	2	of	3
WEIGHT OF PRODUCT (A):	1.02	Kg	
STAGE YIELD:	82%		
CUMULATIVE YIELD	75%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
BORANE REDUCTION									
Stage 1	1.321	237	5.57	1.30	0.00	£0.00			0.0%
Borane THF solution (1M)	9.81	133	11.15	9.62	82.40	£808.26	Aldrich 20L lots	14044-65-6	58.4%
Acetic acid/methanol	0.50			0.38	£2.00	£1.00	Assumed		0.1%
Ethyl acetate	13.21			10.00	£2.00	£26.42	Assumed		1.9%
HCL (1M)	6.61			5.00	£0.50	£3.30	Assumed		0.2%
Ammonium chloride solution	6.61			5.00	£0.50	£3.31	Assumed		0.2%
Water	6.61			5.00	£0.00	£0.00	Assumed		0.0%

STAGE 2 RAW MATERIALS						£842.29			
TOTAL STAGE 2 COST						£842.29			

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 2	1.020	223	4.57	82%	75.4%	£1,349.63

PRODUCT:	Stage 3 Product	Stage 3	
STEP	3	of	3
WEIGHT OF PRODUCT (A):	0.68	Kg	
STAGE YIELD:	84%		
CUMULATIVE YIELD	63%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CYCLISATION									
Stage 2	1.020	223	4.57	1.00	0.00	£0.00			0.0%
Potassium carbonate	1.760	138	12.73	1.73	13.40	£23.58	Aldrich 1Kg lots	584-08-7	1.7%
Solvent	4.975			4.88	2.00	£9.95	Assumed		0.7%

STAGE 3 RAW MATERIALS						£33.53			
TOTAL STAGE 3 COST						£33.53			

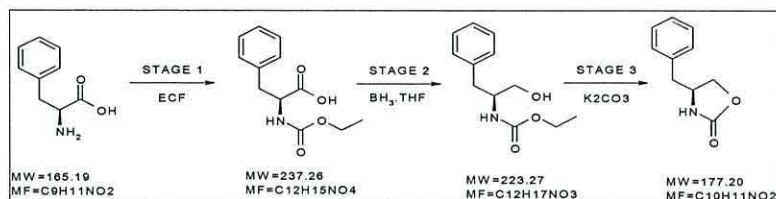| Output of stage 3	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
	0.680	177	3.84	84%	63.4%	£1,383.16

Cost of Goods manufacture/Kg =	£2,034.88

Excel sheet 5: Cost of preparation (S)-4-benzyl-oxazolidin-2-one using 2 equivalents of BH$_3$.THF for reducion step

Route	Based on Method provided by Husein Mustafa 28/JAN2010
Version	2/D.Justice
Costing	Based on Aldrich catalogue prices/assumed solvent prices
Date	٢٣ نيسان ٢٠١٠
Route I	(1) Carbamate protect; (2) Borane/THF Reduce (3) potassium carbonate cyclisation

PRODUCT:	Stage 1 Product	Stage 1	
STEP	1	of	3
WEIGHT OF PRODUCT (A):	1.321	Kg	
STAGE YIELD:	92%		
CUMULATIVE YIELD	92%		

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE Kg	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CARBAMATE PROTECTION									
Phenyl alanine	1.00	165	6.05	0.76	£243.00	£243.00	Aldrich 1Kg lots	63-91-2	19.0%
NaHCO3 solution	25.00			18.92	£1.00	£25.00	Assumed		2.0%
Ethyl chloroformate	0.98	109	8.99	0.74	£86.50	£84.34	Aldrich 500ml lots	541-41-3	6.6%
Ethyl acetate	75.00			56.76	£2.00	£150.00	Assumed		11.7%
Hydrochloric acid	1.00			0.76	£5.00	£5.00	Assumed		0.4%
STAGE 1 RAW MATERIALS						£507.34			
TOTAL STAGE 1 COST						£507.34			

	QTY	M/WT	MOLES	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 1	1.3213	237	5.57	92.0%	92.0%	£507.34

PRODUCT:	Stage 2 Product	Stage 2	
STEP	2	of	3
WEIGHT OF PRODUCT (A):	1.01	Kg	
STAGE YIELD:	81%		
CUMULATIVE YIELD	75%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
BORANE REDUCTION									
Stage 1	1.321	237	5.57	1.31	0.00	£0.00			0.0%
Borane THF solution (1M)	8.57	133	9.74	8.47	82.40	£706.17	Aldrich 20L lots	14044-65-6	55.1%
Acetic acid/methanol	0.50			0.38	2.00	£1.00	Assumed		0.1%
Ethyl acetate	13.21			10.00	2.00	£26.42	Assumed		2.1%
HCL (1M)	6.61			5.00	0.50	£3.30	Assumed		0.3%
Ammonium chloride solution	6.61			5.00	0.50	£3.31	Assumed		0.3%
Water	6.61			5.00	0.00	£0.00	Assumed		0.0%
STAGE 2 RAW MATERIALS						£740.20			
TOTAL STAGE 2 COST						£740.20			

	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of step 2	1.012	223	4.53	81%	74.9%	£1,247.53

PRODUCT:	Stage 3 Product	Stage 3	
STEP	3	of	3
WEIGHT OF PRODUCT (A):	0.67	Kg	
STAGE YIELD:	84%		
CUMULATIVE YIELD	63%		
COMMENTS			

RAW MATERIAL	QTY (B) Kg	M/WT	Moles	USAGE (B/A)	PRICE (C)	COST (B*C)	SOURCE	CAS	CONTRIBUTION
	Kg			kg/kg	£/Kg				
CYCLISATION									
Stage 2	1.012	223	4.53	1.00	0.00	£0.00			0.0%
Potassium carbonate	1.760	138	12.73	1.74	13.40	£23.58	Aldrich 1Kg lots	584-08-7	1.8%
Solvent	4.975			4.92	2.00	£9.95	Assumed		0.8%
STAGE 3 RAW MATERIALS						£33.53			
TOTAL STAGE 3 COST						£33.53			

|	QTY	M/WT	Moles	STAGE YIELD	CUM YIELD	CUM. COST
Output of stage 3	0.675	177	3.81	84%	62.9%	£1,281.07

| Cost of Goods manufacture/Kg =	£1,898.57

Excel sheet 6: Cost of preparation (S)-4-benzyl-oxazolidin-2-one using 1.7 equivalents of BH₃.THF for reducion step

^{1}H & ^{13}C- NMR spectrum of (**1**)
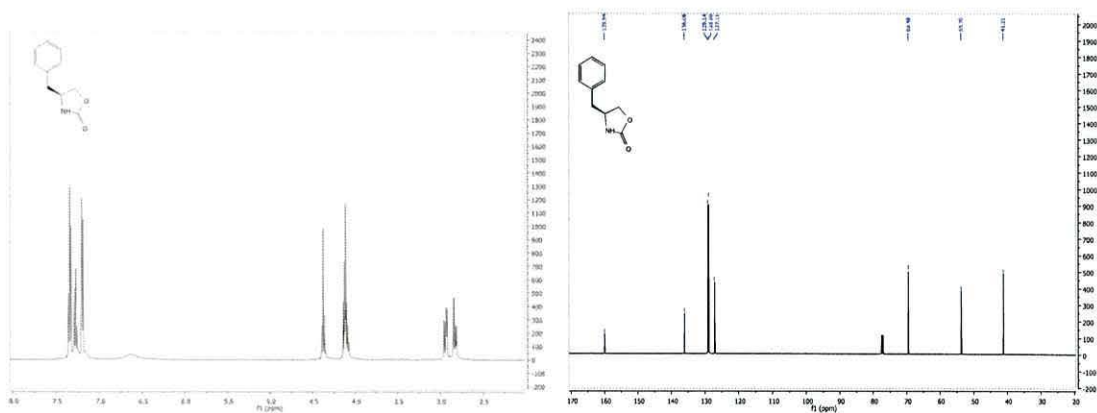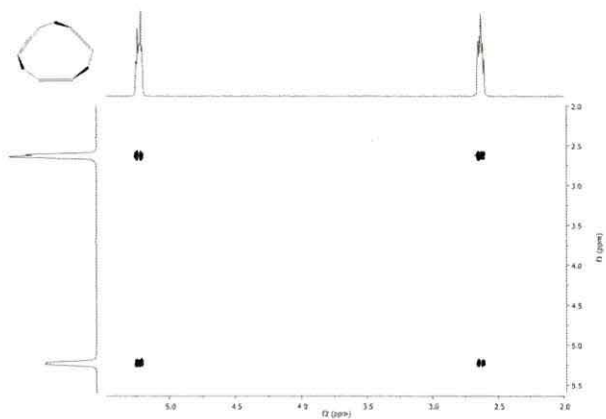

^{1}H, ^{13}C- NMR & Mass spectrum of (**56**)
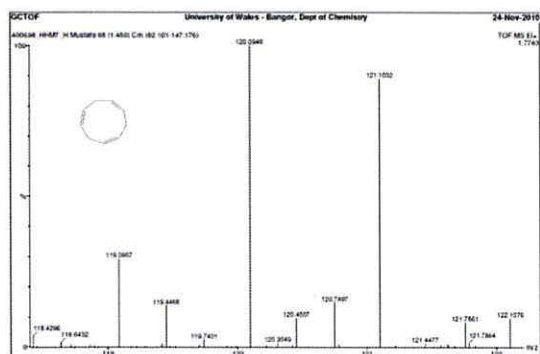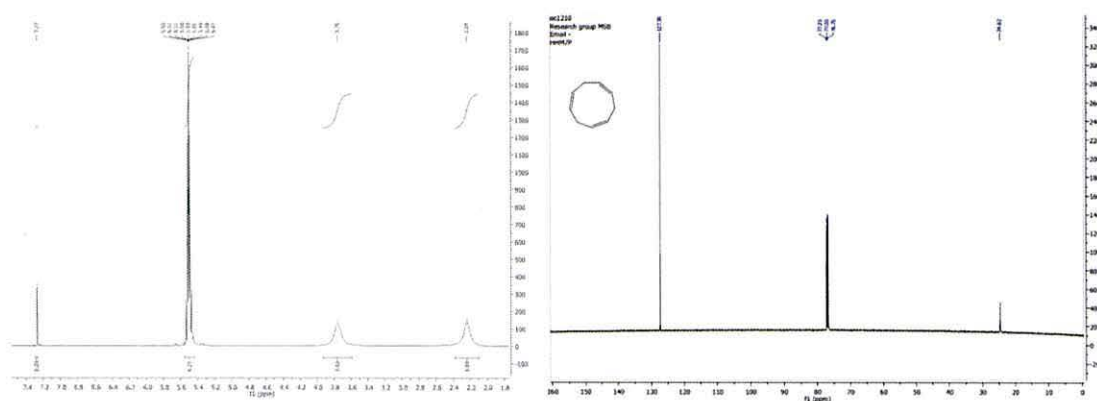
^{1}H & ^{13}C- NMR spectrum of (**58**)
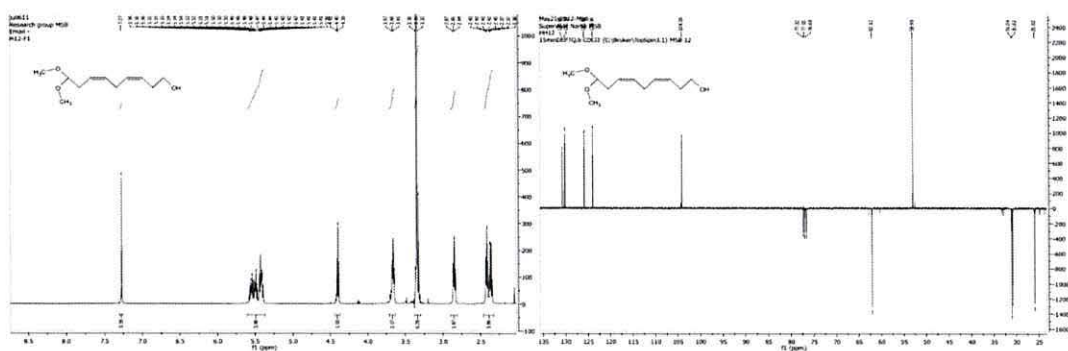
^{1}H & ^{13}C- NMR spectrum of (**59**)
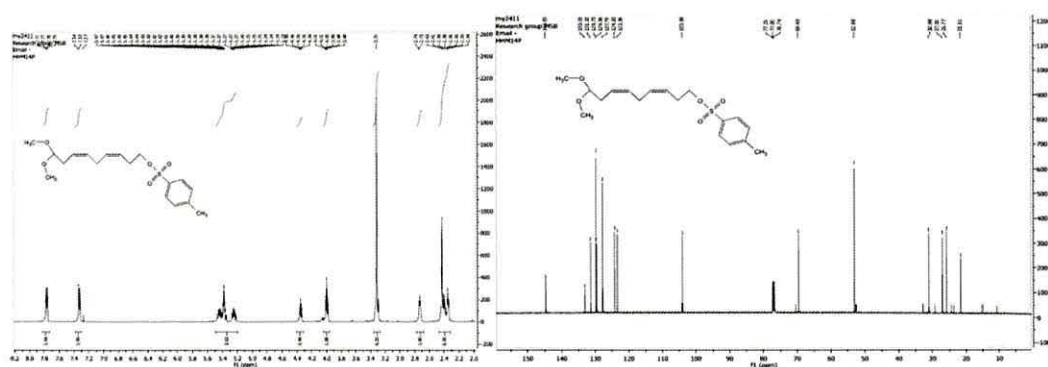
^{1}H & ^{13}C- NMR spectrum of (**66**)
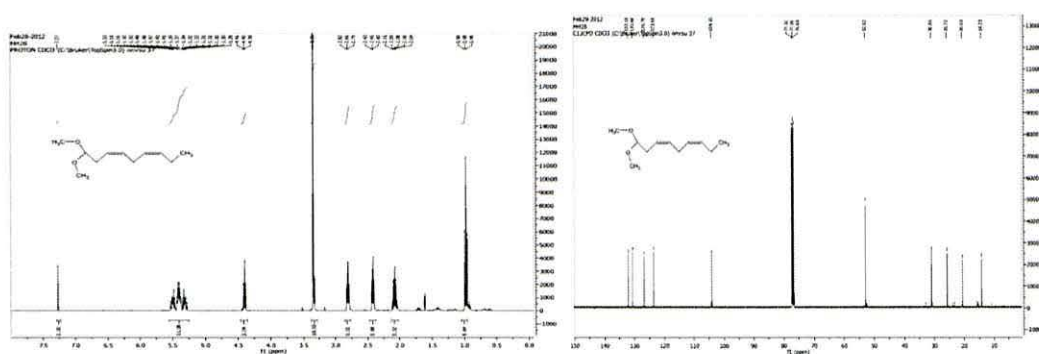
^{1}H & ^{13}C- NMR spectrum of (**68**)
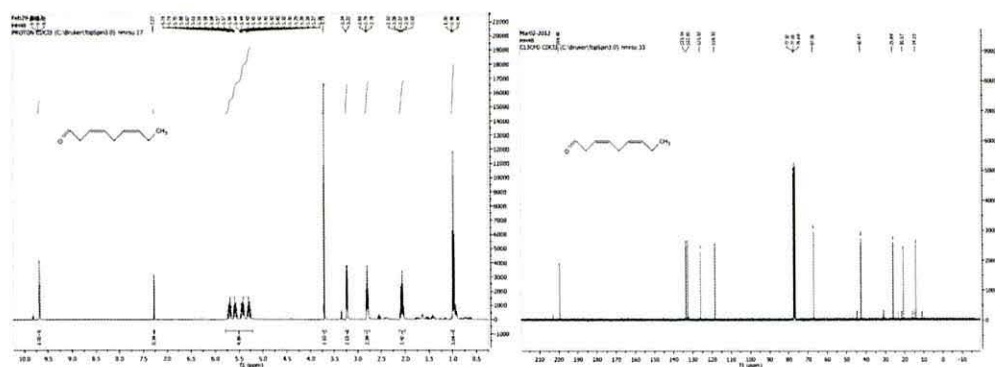
^{1}H, ^{13}C- NMR & Mass spectrum of (**74**)

^{1}H, ^{13}C- NMR & Mass spectrum of (**73**)

^{1}H & ^{13}C- NMR spectrum of (**78**)

^{1}H & ^{13}C- NMR spectrum of (**83**)

^{1}H & ^{13}C- NMR spectrum of (**85**)

^{1}H & ^{13}C- NMR spectrum of (**86**)
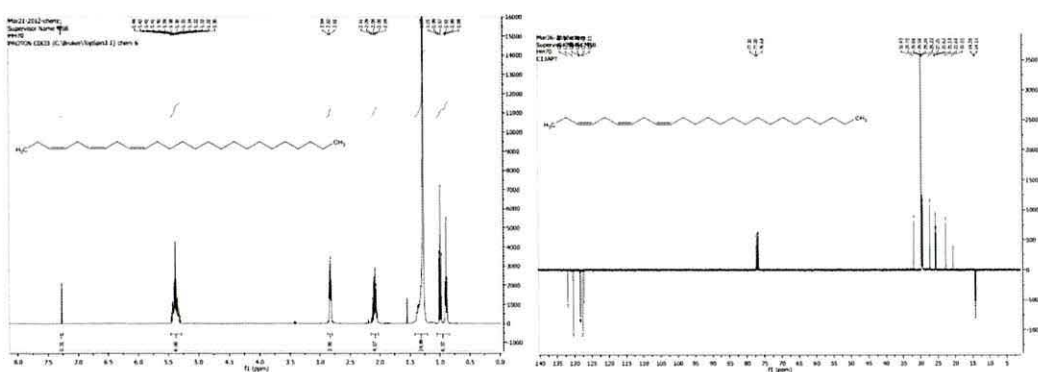
^{1}H & ^{13}C- NMR spectrum of (**89**)
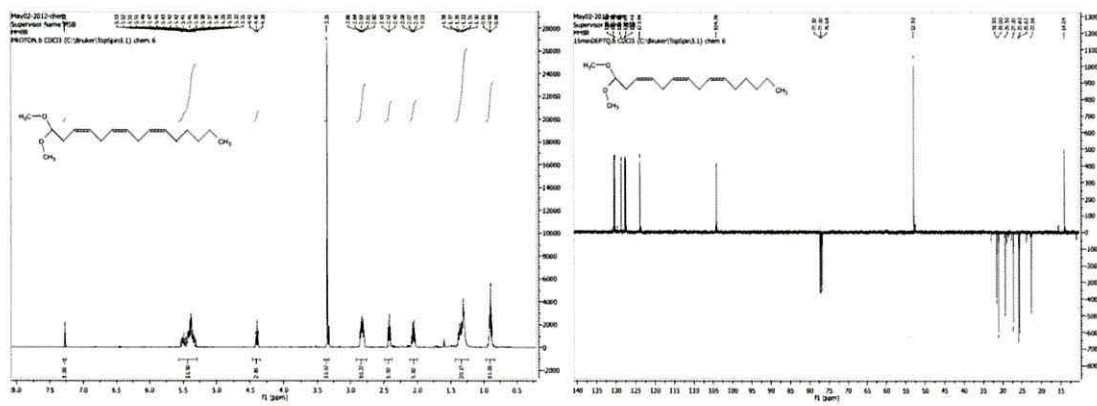
^{1}H & ^{13}C- NMR spectrum of (**91**)
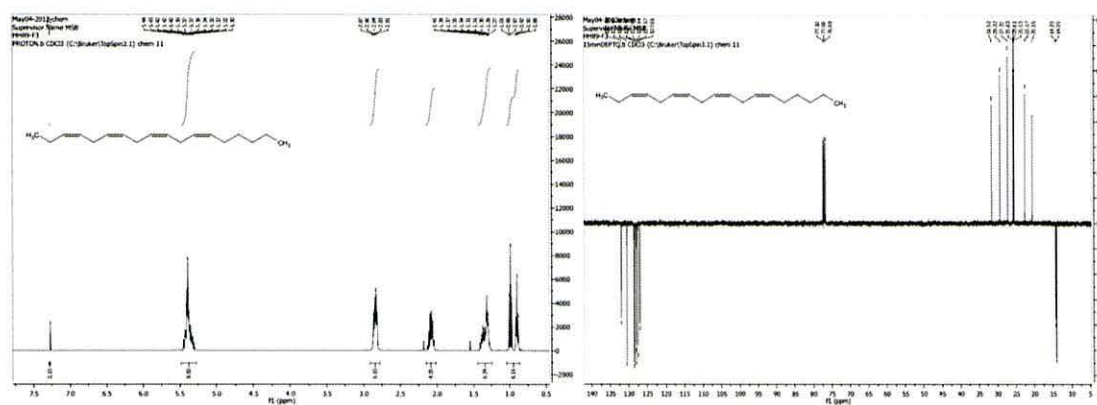
^{1}H & ^{13}C- NMR spectrum of (**90**)

^{1}H & ^{13}C- NMR spectrum of (92)

^{1}H & ^{13}C- NMR spectrum of (93)

^{1}H & ^{13}C- NMR spectrum of (94)
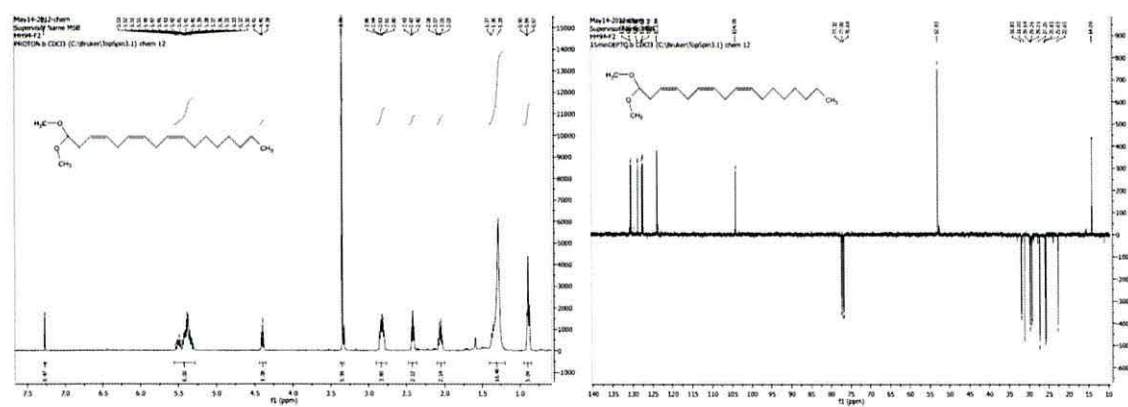
^{1}H & ^{13}C- NMR spectrum of (95)
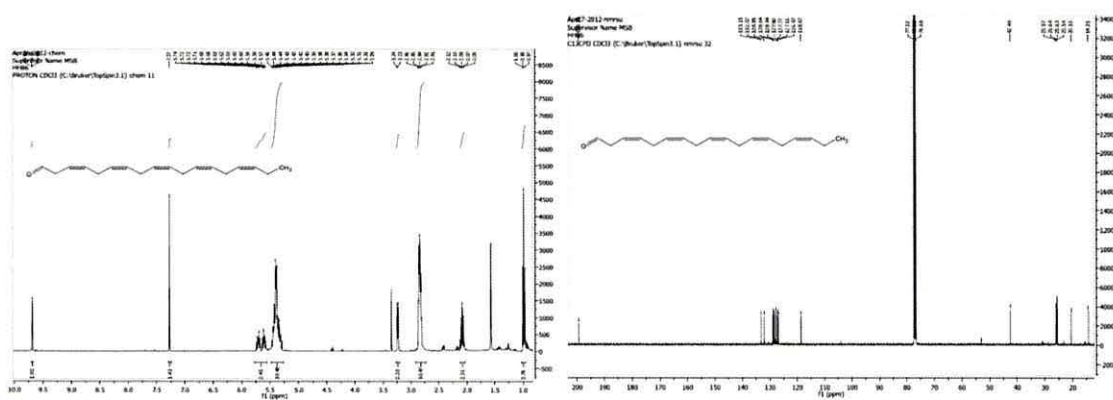
^{1}H & ^{13}C- NMR spectrum of (98)
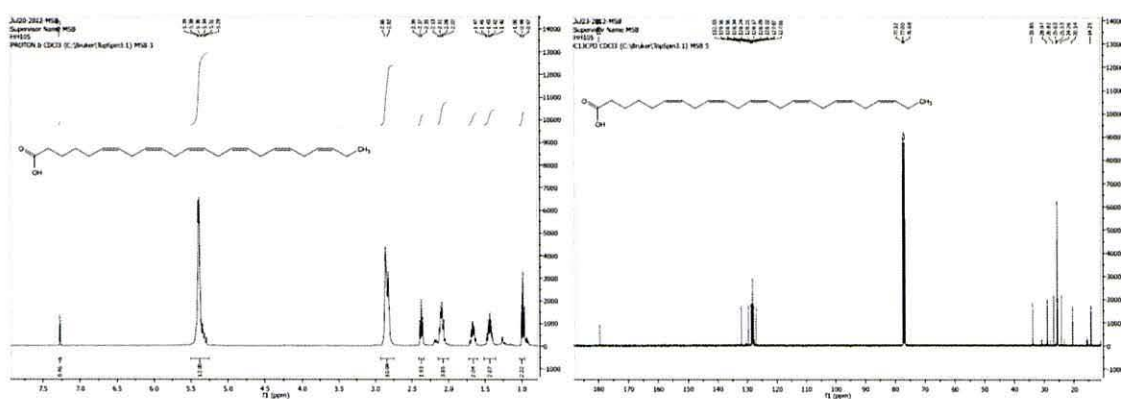
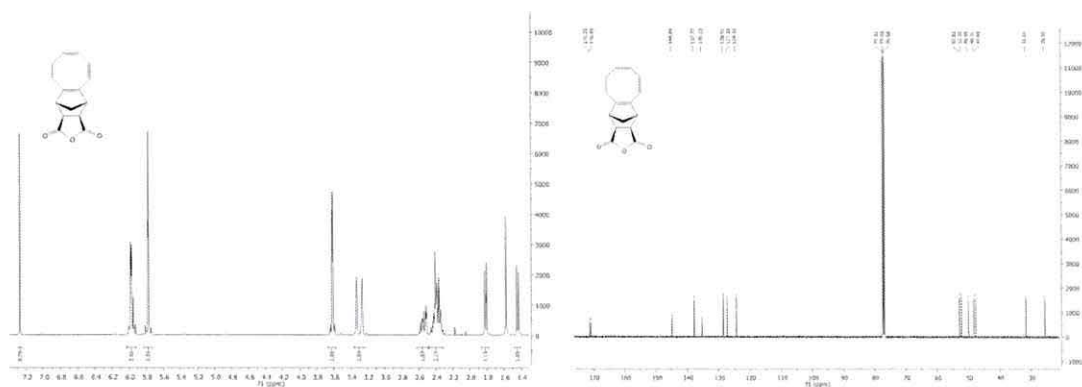## ^{1}H & ^{13}C- NMR spectrum of (100)
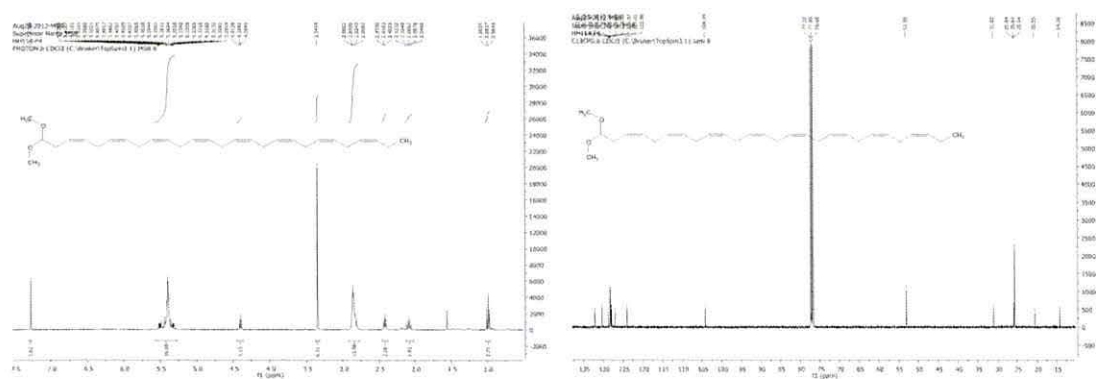
¹H, dept- NMR, Mass, Cosy & HSQC spectrums of (**159**)
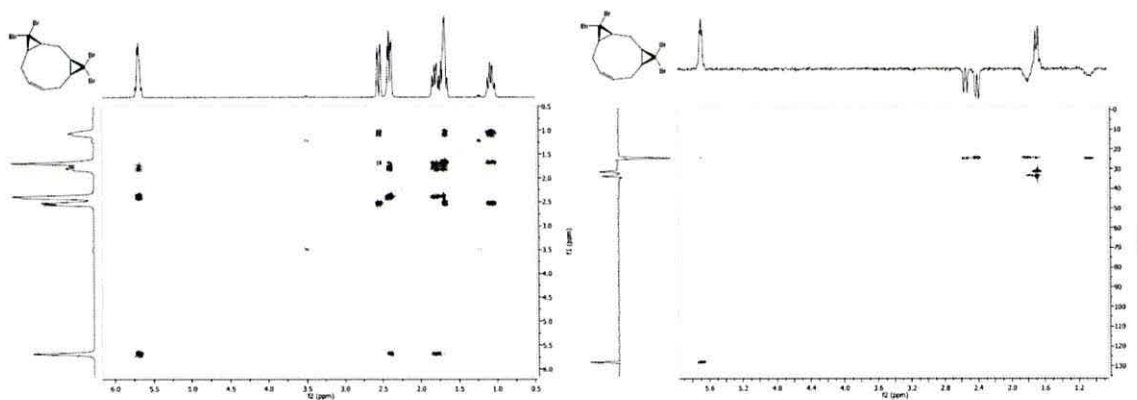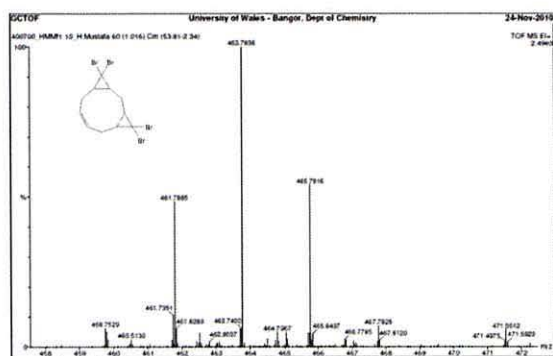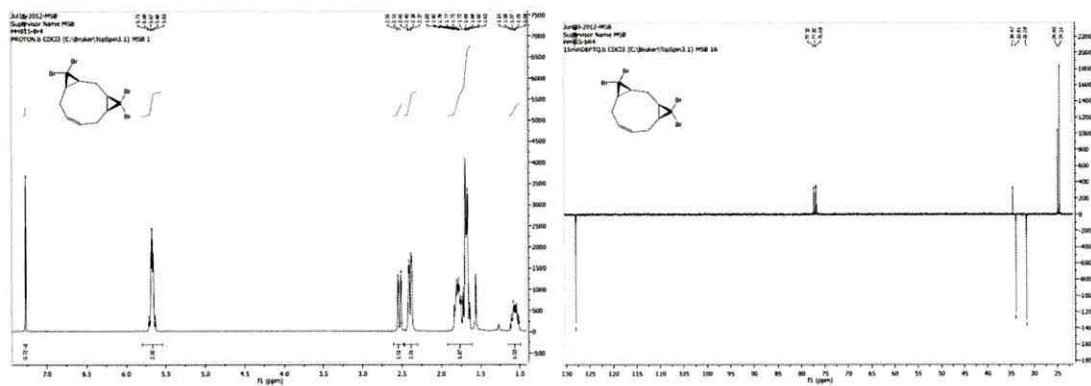
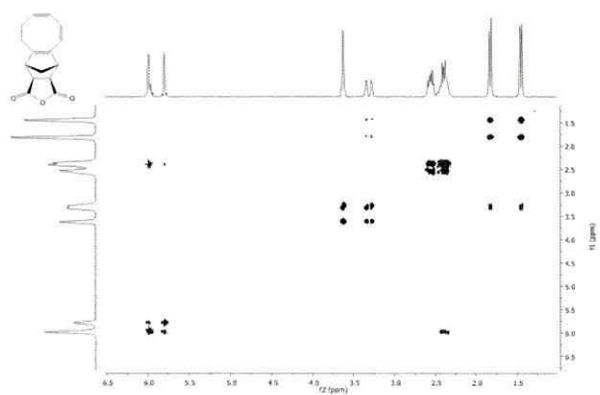¹H, dept- NMR, Mass & Cosy spectrums of (**158**)

^{1}H, ^{13}C- NMR & Cosy spectrums of (162)

^{1}H, dept- NMR & Cosy spectrums of (161)
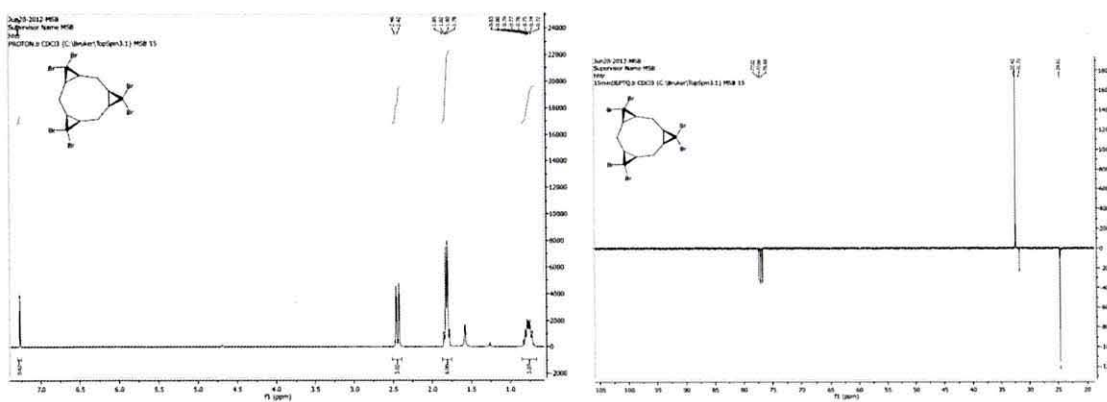
^{1}H, ^{13}C- NMR & Cosy spectrums of (**173**)
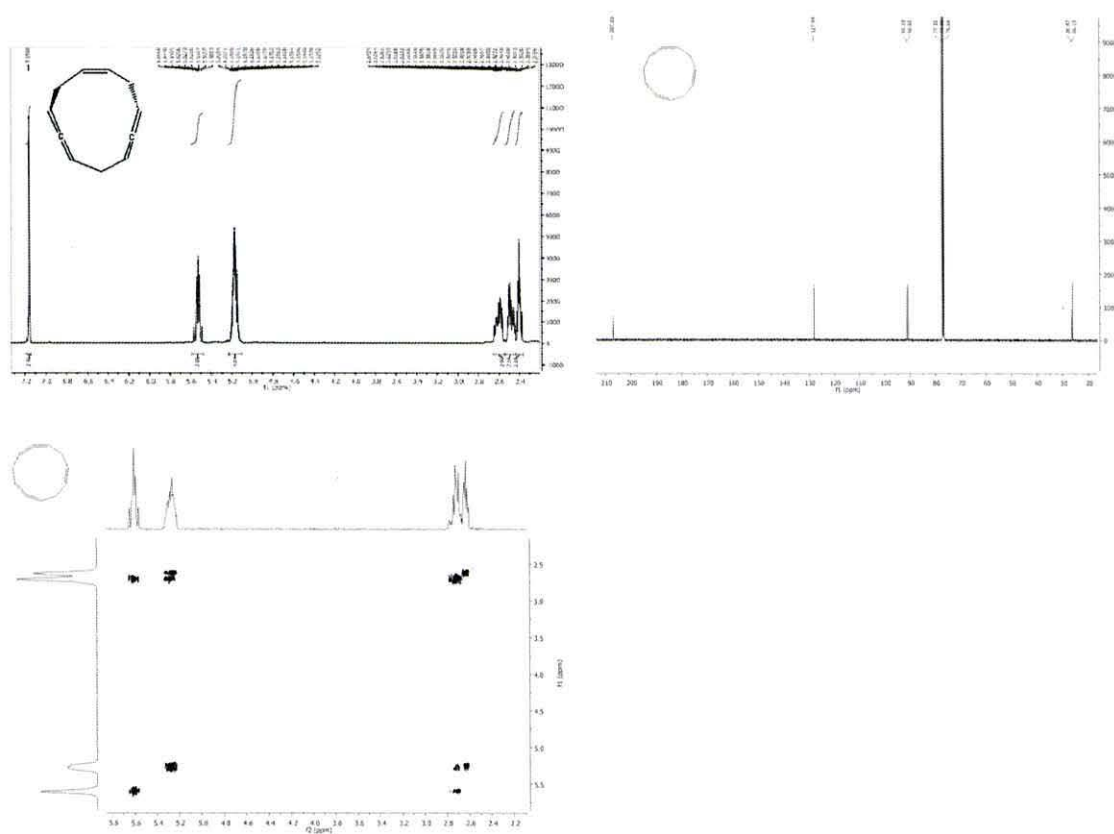
^{1}H, ^{13}C- NMR & Cosy spectrums of (**177**)

^{1}H & ^{13}C- NMR spectrum of (179)