THE USE OF EPHEDRINE AND CAMPHOR IN ASYMMETRIC DIELS-ALDER REACTIONS

By

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Pietermaritzburg

January 1997

DECLARATION

I hereby certify that this research is the result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed: .....

K.N.Kriel

I hereby certify that this statement is correct.

Signed: .....

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Supervisor

Department of Chemistry

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January 1997

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LIST OF ABBREVIATIONS AND SYMBOLS

Ac	acetyl
aq.	aqueous
atms	atmospheres
ATP	Adenosine triphosphate
bisTMSA	N,O-bis(trimethylsilyl)acetamide
b.p.	boiling point
Bn	benzyl
br s	broad singlet
Bu	butyl
c	complex
d	doublet, days
dil.	dilute
DABCO	1,4-diazabicyclo[2,2,2]octane
DMA	dimethylanaline
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
de	diastereomeric excess
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
EWG	Electron Withdrawing Group
FMO	frontier molecular orbital
GC/MS	Gas Chromatography/Mass Spectromatry
h	hour/s
HIV	Human Immunodeficiency Virus
hplc	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
i	iso

LICA	lithium isopropylcyclohexylamide
L_n	ligand
m	multiplet
M	metal atom
M^+	molecular ion
min	minute/s
ML_n	metal ligand
m.p.	melting point
Me	methyl
MCPBA	*meta*-chloroperbenzoic acid
MO	molecular orbital
NADP/H	Nicotinamide adenine dinucleotide/hydride
NaHMDS	Sodium hexamethyl disilazane
NMR	Nuclear Magnetic Resonance
OAc	acetate
Ph	phenyl
q	quartet
rt	room temperature
s	singlet
sat.	saturated
s-BuLi	*secondary*-Butyllithium
t	triplet
TBDMSCl	tertiary butyldimethylsilyl chloride
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride

SUMMARY

Due to the ever increasing demand for the production of enantiopure drugs and biologically active compounds, the study of asymmetric synthesis and the production of more efficient and cost effective methods of obtaining chiral compounds suggests that there are expanding opportunities for Organic Chemists in this field. Of the broad range of chiral technologies available today for the synthesis of even the most complex multi-centre chiral molecules, the use of chiral auxiliaries continues to remain an important means of obtaining single enantiomer chiral compounds.

In this investigation, the imidazolidinone chiral auxiliary (i) was synthesised in order to determine its efficiency and ability to transfer chiral information in Diels-Alder cycloaddition reactions. The products of such reactions are extensively used in the synthesis of natural compounds and pharmaceutical drugs.

The synthesis of the imidazolidinone auxiliary is described and mention is made of the fact that the starting materials are cheap and readily available in both enantiomeric forms. The pathway involves only a single reaction that is easily carried out in moderate yields of 60-65%. An adaptation of this auxiliary is the cyclohexyl derivative (ii) which was obtained in a single hydrogenation step of (i) in very high yields (98%).

This was compared to the synthesis of the bornane-10,2-sultam auxiliary (iii). Although the starting materials are also cheap and readily available, there are more reaction steps involved. The synthesis of the imidazolidinone auxiliary proved to be much more simple as well as more time and cost effective. The huge advantage of these auxiliaries is the fact that they are both crystalline which facilitates their purification and that of their derivatives.

A possible deficiency of the imidazolidinone auxiliary and the bornane-10,2-sultam auxiliary was the fact that substitution reaction yields with various α,β-unsaturated acyl chlorides were consistently low ($< 50\%$). A major by-product of the acylation

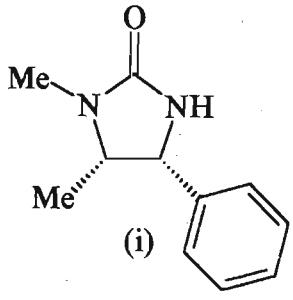
reaction was a 'double-adduct' compound that severely affected the reaction yields. This was overcome by employing a new method of acylation developed during the course of this research. It involves the use of DABCO as base with reaction yields between 60 and 98%. In addition to this, reaction conditions were mild and work up procedures simple.

The *N*-acylimidazolidinone auxiliary proved to be extremely successful in Diels-Alder reactions with cyclopentadiene with results equalling those obtained with the well known and highly publicised bornane-10,2-sultam auxiliary. The scope of the *N*-acylimidazolidinone auxiliary in these reactions included the use of α- and β-substituted dienophiles. Although reactions with β-methyl and α-methyl substituted dienophiles were successful, the auxiliary proved to be unreactive with β-phenyl and β,β-dimethyl substituted dienophiles. The scope of dienes used was extended to include the relatively less reactive isoprene and 2,3-dimethyl-1,3-butadiene. Only the former reacted successfully in Diels-Alder reactions with the *N*-acylimidazolidinone auxiliary. Crystallinity was imparted to all the products except for the cyclohexyl derivative whose cycloaddition adducts only solidified on standing.

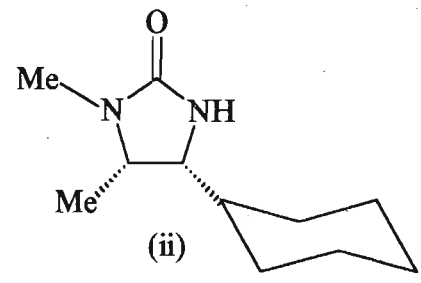
The Diels-Alder adducts were successfully cleaved under standard reaction conditions to give products with ee's ranging from 95:5 to 99:1.

This investigation also includes the use of the tertiary amine, DABCO, as a catalyst in the Diels-Alder reaction with, specifically, the *N*-acryloylimidazolidinone chiral auxiliary. Most examples of Diels-Alder reactions involve the use of Lewis acids as a means of improving the rate and selectivity of Diels-Alder reactions. DABCO not only increased the reactivity of the *N*-acryloylimidazolidinone auxiliary towards cyclopentadiene, but selectivity was also observed. An explanation was put forward as to the mechanism of the reaction as well as to the source of selectivity. Selectivity was much more pronounced in Diels-Alder reactions with the *N*-acryloylimidazolidinone auxiliary than with the *N*-acryloylbornane-10,2-sultam auxiliary. It was predicted that DABCO catalysed reactions are amenable to large scale procedures. Due to the fact that the diastereomeric cycloadducts are easily purified by recrystallization or

chromatography, and together with the practical advantages and mild reaction conditions this could render the DABCO methodology with the *N*-acryloylimidazolidinone auxiliary industrially viable.



(i)



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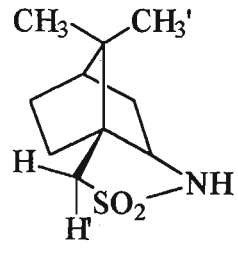

(iii)

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1) Jensen, K.N., Roos, G.H.P. *Tetrahedron: Asymm.* **1992**, *3*, 1553.

2) Kriel, K.N., Emslie, N.D., Roos, G.H.P. *Tetrahedron Lett.* **1997**, *38*, 109.

1. INTRODUCTION

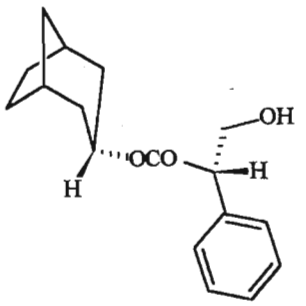
PART A:

1.1 ASYMMETRIC SYNTHESIS

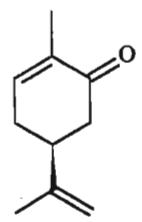
The quest for obtaining optically pure materials has become an important aspect of organic chemistry.[1] Ever since the discovery by chemists such as Pasteur, Le Bel and van't Hoff[2] that a vast majority of organic molecules exist as either one of two possible structures *i.e.* enantiomers that are related as non-superimposable mirror images but have similar physical and chemical properties except in their interactions with polarised light and with other enantiomers, major inroads into the study of stereochemistry and asymmetric synthesis have been made.

Although solid state materials and inorganic compounds can also be chiral and frequently have unique and exploitable properties in optically pure form, it is the chirality of the biological world that has received the most attention.[3]

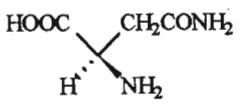
That biologically active molecules often show effective activity as one enantiomer has been recognised for a long time. For example, in the early 1900s, Cushney demonstrated that (-)-hyoscyamine (**1**) was approximately twice as potent as the racemate (atropine) in its effect on pupil nerve endings.[4] Numerous examples exist of the differing biological effects of enantiomers.[5,6] One of the enantiomers of carvone (**2**) smells of caraway, the other of spearmint. The (*R*) enantiomer of asparagine (**3**) tastes sweet whereas the (*S*) enantiomer tastes bitter. Both enantiomers of sucrose (**4**) are equally sweet, but only the naturally occurring D-enantiomer is metabolised, making the synthetic L-enantiomer a potential dietary sweetener. In the protection of crops from insects, one enantiomer of deltamethrin (**5**) is a potent insecticide while the other is inactive and the mixture is ineffective.



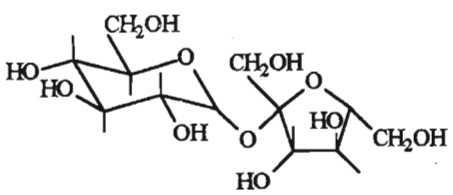
(-)-Hyoscyamine (1)



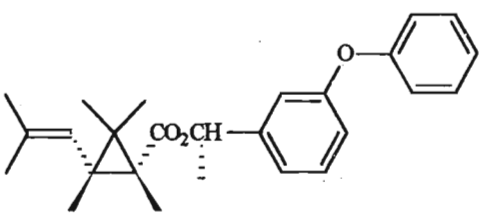
(*S*)-Carvone (2)
caraway flavour



(*R*)-Asparagine (3)
sweet taste



D-Sucrose (4)

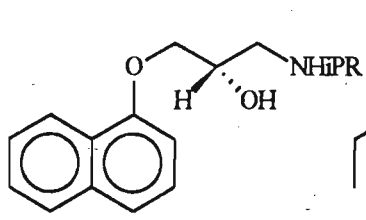


(*R,R,S*)-Deltamethrin (5)

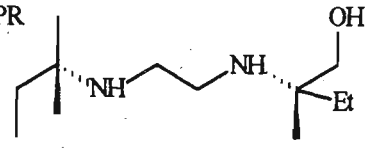
Enantioselective synthesis strongly impacts on the perfume, flavour and agricultural industries as well as the pharmaceutical industry.[7] The manufacture of chemical products, for the effective growth and maintenance of plants and animals and for the combat of pests as well as for the promotion of health, is now increasingly concerned with enantiomeric purity since a large proportion of these products contain at least one, if not several, chiral centres. The most appropriate methodology for the synthesis of organic molecules that contain one or more stereogenic centres has become one which takes into account stereochemical control. This often has an overriding effect on strategic considerations, including the choice of a particular route.

Examples from the pharmaceutical industry alone demonstrates the enormous importance of chiral chemistry. In the past, complex structures were constructed with reasonable efficiency and it was usually unimportant whether the substrate and intermediates were enantiomerically pure or racemic. To date, although more than 50% of commercial drugs are chiral, less than half of these are marketed in an enantiomerically pure form.[8] This is despite the fact that dramatic examples of the

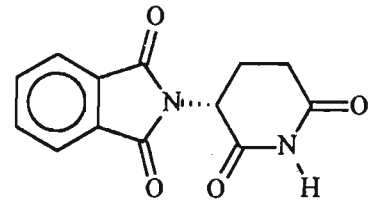
differences in pharmacological responses of enantiomers are known.[6] (*S*)-Propanolol (**6**) is a β-blocking agent which acts as an antihypertensive and antiarythmic used in the treatment of heart disease, whereas the *R* enantiomer acts as a contraceptive. The (*S,S*) enantiomer of ethambutol (**7**) is a tuberculostatic and the (*R,R*) enantiomer causes blindness. Thalidomide (**8**) had beneficial effects against morning sickness. In the 1960s, thalidomide, commercially known as Softenon, was originally used as a racemate. Only the (*R*) enantiomer is responsible for the desired sedative effect whereas the (*S*) enantiomer was only confirmed to cause teratogenic defects in 1979.[9] The thalidomide tragedy might have been avoided if the 1963 drug regulations had insisted on the separate pharmacological testing of enantiomers[10], although recent evidence suggests that homochiral thalidomide racemises under physiological conditions.[5]



(*S*)-Propanolol (**6**)



(*S,S*)-Ethambutol (**7**)



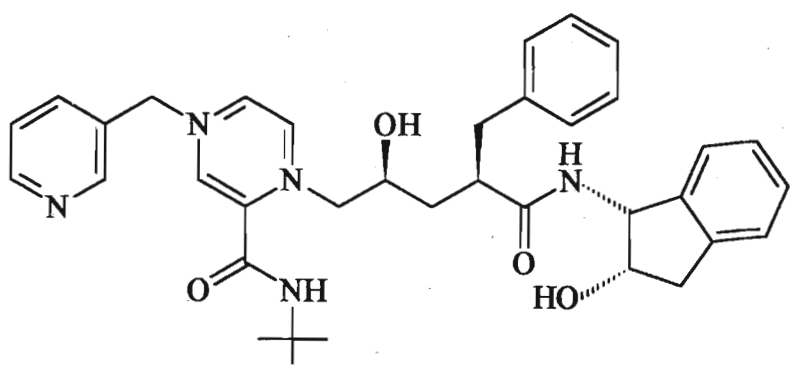
(*R*)-Thalidomide (**8**)

It was not until 1988 that submission of information about the enantiomer composition of chiral substances in new drugs was required by law, specifically by the Food and Drug Administration of the United States.[11] Such examples are a strong incentive for the pharmaceutical industry to market chiral compounds as single enantiomers. Davies and Reider[12] have recently reported that during the past ten years there has been an increasing realisation in the pharmaceutical industry of the need to prepare drugs in enantiomerically pure form. In fact, the policy of most major pharmaceutical companies is that they will be developing only single enantiomer drugs.

The challenge rests with process chemists to design new multi-centre chiral drugs and to prepare them economically. For productions to be of practical large scale use,

enantiomeric excesses (ee's) should be at least 70%, if not 80%.[6] The quest for acceptable levels of selectivity has accordingly had a major impact on the development of modern synthetic methodology, especially over the last decade.

In a recent report, Cannarsa[13] states that of the existing single-enantiomer drugs, antibiotics account for 30% of chiral pharmaceutical sales and cardiovascular drugs make up another 30% of these. Protease inhibitors have recently attracted attention as they are an important new class of drugs for treating HIV infected patients.[12,13] Protease inhibitors entered clinical trials in the early 1990s and, recognising that there might be a need for large quantities of the product in a short time, the originators and several fine chemical companies began work to develop synthetic methods. One of these was developed by Merck and the final product is called *Crixvan*-Indinavir (9)



Crixivan-Indinavir (9)

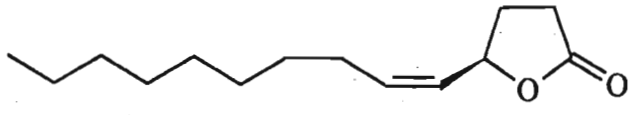
These compounds are complex molecules containing multiple chiral centres and provide an interesting challenge to synthetic chemists as they are totally synthetic-their total synthesis requiring as many as 15 steps, several of which involve complex chiral transformations. Protease inhibitor dosage is large, greater than 2g/day per patient and patients will probably require the medication for life. Its importance will thus equal those of many common antibiotics and cardiovascular drugs and a major effort will be needed to ensure that the high demand will be met.

This illustrates the increasing importance of research efforts, not only towards the discovery of syntheses of enantiomerically pure products, but also towards being able to prepare them efficiently, in a cost-effective way and on large commercial scales.[6,12]

1.2 SYNTHESISING ENANTIOMERICALLY PURE COMPOUNDS

According to Crosby[6], who has written an extensive review article on the subject, the desirable reasons for producing optically pure materials include:

1. Biological activity is associated with only one enantiomer;
2. Enantiomers may exhibit very different types of activity. Both enantiomers may be beneficial or one may be beneficial and the other undesirable. Production of only one enantiomer allows separation of the effects;
3. The optically pure compound may be more than twice as active as the racemate because of antagonism. For example, the pheromone of the Japanese beetle (**10**), as little as 1% of the (*S,Z*)-isomer inhibits the activity of the (*R,Z*)-isomer;[14]
4. Registration constraints[11] - production of materials as the required enantiomer is now a question of law in certain countries in Europe and in the United States, the unwanted enantiomer being considered an impurity;
5. Where the switch from racemate to enantiomer is feasible, there is the opportunity to effectively double the capacity of an industrial process and allows for more specific drug action and a reduction in the amount of drug administered;
6. Improved cost efficacy.



(*R,Z*)-isomer isolated from the Japanese beetle (**10**)

1.3 METHODS OF OBTAINING ENANTIOMERICALLY PURE COMPOUNDS

Asymmetric synthesis remains the leading strategy available for the synthesis of homochiral compounds. Mosher and Morrison[15] define an asymmetric synthesis as "a reaction in which an achiral unit in an ensemble of substrate molecules (with either enantiotopic or diastereotopic groups) is converted by a reactant into a chiral unit in such a way that the stereoisomeric products (enantiomeric or diastereomeric) are produced in unequal amounts. This is to say an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result". Ideally, the aim is for the major isomer to be produced in substantially greater proportions than the minor one(s).[16]

In general, synthetic stereoselective processes fall into two broad categories:[17]

1. Reactions that lead to the selective formation of enantiomers.
2. Reactions that lead to the selective formation of diastereoisomers.

In broad terms, most enantioselective reactions involve substrates that are achiral and are characterised by chirality in the reagent, chiral auxiliary, catalyst or reaction medium. Selectivity is achieved either by a direct enantioselective reaction on an achiral starting material or a sequence that achieves the selective formation of an enantiomer through the temporary incorporation of a chiral auxiliary, followed by one or more diastereoselective reactions and then cleavage of the auxiliary. Diastereoselective reactions are primarily concerned with the introduction of new stereogenic centres into chiral substrates. The configurations of the new stereocentres are established in a relative relationship to the pre-existing stereocentre(s) in response to differential interactions arising from the reactant approaching along alternative trajectories, for example, avoidance of steric interactions, minimisation of tortional strain and optimisation of orbital interactions. For a racemic substrate the individual enantiomers can be expected to react with achiral reagents in a stereochemical sense to establish the same relative relationship between the new and pre-existing stereocentres

in each of the enantiomers. In this way, the homogeneity of the diastereomeric relationships for the individual enantiomers in the racemic product is maintained.

Only the first category involving procedures that are overall enantioselective will be discussed in this report. For this reason, the temporary incorporation of a chiral auxiliary, even though it involves a diastereoselective stage resembling that of the second category, will also be included in this section.

1.3.1 Enantioselective Synthesis

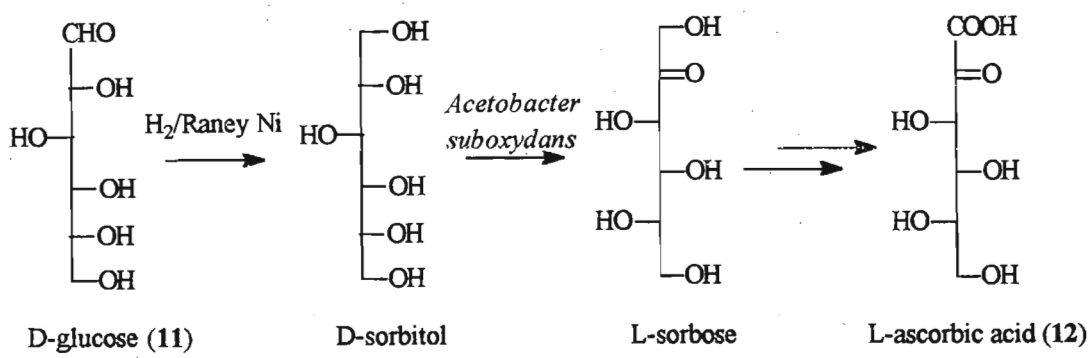
Enantioselective syntheses depend on the availability of enantiomerically pure compounds from natural or industrial sources at a reasonable cost to serve as chiral inducers with achiral substrates.[18,19] Chemists traditionally recognise five methods of single enantiomer production. These are:

1. The use of homochiral reactants or substrates.
2. Resolution of racemic mixtures.
3. Enzyme transformations or biotransformations.
4. The use of homochiral catalysts.
5. The use of chiral auxiliaries attached to achiral substrates.

1.3.1.1 Homochiral Reactants or Substrates

The first is the 'chiral pool' or chiral substrates of natural origin. The enantiomeric substrates or reactants with their inherent asymmetric centres are used as building blocks and are incorporated into the target molecules with any necessary modification in order to achieve the desired chiral features. Examples include natural amino acids (such as cysteine), hydroxy acids (such as tartaric acid or malic acid), terpenes (such as carvone or camphor), alkaloids (such as the cinchona bases) and carbohydrates and their derivatives as well as the 'new pool' of industrially produced chiral products.

The most extensive studies have been concerned with the use of sugars which possess multiple sites of chirality in well defined relative configurations.[20] For example, the most abundant sugar, and therefore an important source of naturally and readily available chiral compounds, is D-glucose (**11**) which provides one of the earliest industrial examples of a chiral pool substance being used in synthesis in the multistep Reichstein-Grussner preparation of L-ascorbic acid (**12**)[6] (Scheme 1).

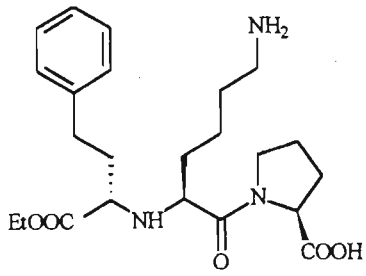


Scheme 1

L-Ascorbic acid may be converted to the useful C_3 synthon (*R*)-solketal which is employed in the synthesis of (*S*)-β-blockers. An efficient use of D-sorbitol is its conversion to the coronary vasodilator isosorbide dinitrate.[6]

A disadvantage of the use of carbohydrates as chiral substrates is that they are generally only available in one enantiomeric form and elaborate modifications requiring multistep conversions are often required.[18] This disadvantage is offset, though, by the fact that they are extremely abundant and therefore cheap and readily available.

Another important group of chiral substrates are the amino acids and hydroxy acids. Both antipodes are readily available, usually with high ee's, although one will often be a lot cheaper than the other, e.g. D-alanine 25g, $59.85; L-alanine 100g, $37.00. An example of industrially important amino acids are, for example, the peptides which are included in some important drugs. The angiotensin-converting enzyme (ACE) inhibitors, lisinopril (**13**), enalapril (**14**), and captopril (**15**) all incorporate L-proline.[6]



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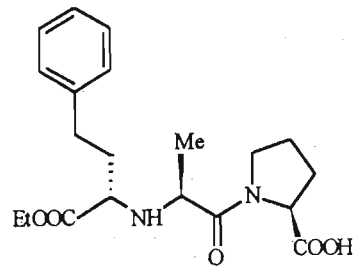

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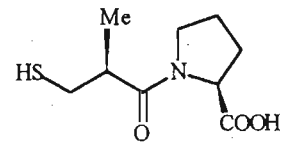
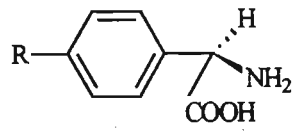


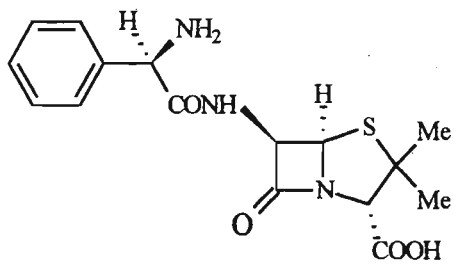
(15)

D (-)-phenylglycine (**16**) and D (-)-4-hydroxyphenylglycine (**17**) are made in large quantities as building blocks for the production of semisynthetic β-lactam antibiotics such as ampicillin (**18**) and amoxicillin (**19**) respectively.

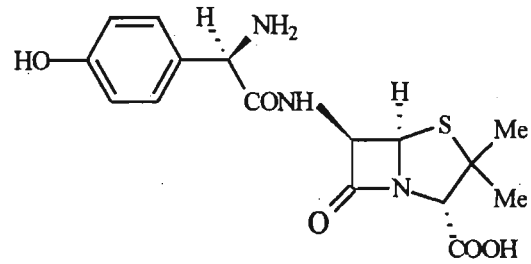


R=H (**16**)

R=OH (**17**)



Ampicillin (**18**)



Amoxicillin (**19**)

1.3.1.2 Resolution of Racemic Mixtures

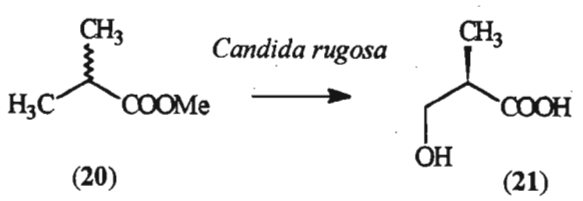
The second method of obtaining pure enantiomers is resolution, which involves the separation of mixtures of enantiomers using a variety of techniques including crystallization and chromatography. This may also involve classical resolution *via* diastereoisomer crystallization. A racemic mixture is converted into a mixture of diastereoisomers with different physical and/or chemical properties which may then be more readily separated. Classical resolution is widely used industrially despite its 'low technology' image and remains an important means of obtaining optically active drugs not derived from natural products.[21] A potential disadvantage of the resolution

approach is that half the material will consist of the undesired enantiomer unless both enantiomers are required or if classical resolution is combined with deracemisation[22] in which an *in situ* conversion to the required enantiomer takes place. Precipitation of one diastereomer drives the equilibrium in favour of that isomer.

Increasingly more effective chromatography columns with chiral stationary phases are being developed which may therefore reduce the need for chiral resolving agents.[23]

1.3.1.3 Enzyme Transformations or Biotransformations

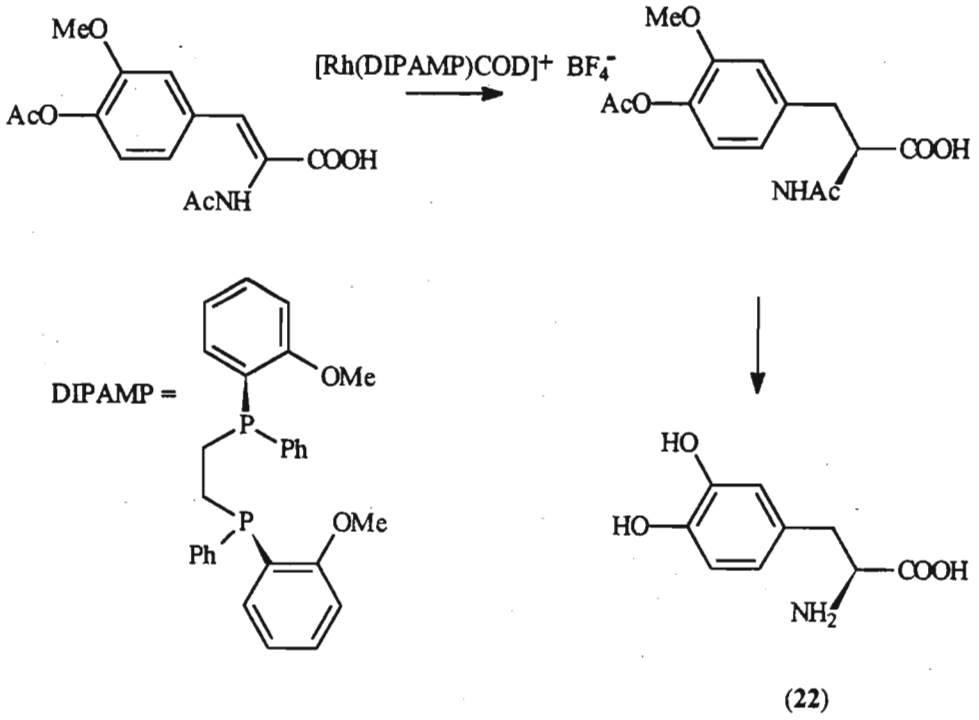
Enzyme transformations provide an enantiomerically pure product through the action of enzymes on a substrate. Enzymes catalyse a broad spectrum of standard organic reactions[24] under mild conditions and usually require coenzymes, such as NAD(P)/H or ATP in water as the solvent and tend to be relatively expensive. Enzymes are highly stereoselective as well as chemoselective in their action which tends to limit the range of reactants which can be used, but the advantage is that protecting groups are seldom necessary. Despite their advantages, their applications tend to occur in areas where standard chemical methodology has been most deficient.[17] Thus, their use is mainly restricted to simple enantioselective processes and in the kinetic resolution of racemates. An example of such simple transformations involves an oxidoreductase enzyme from the yeast, *Candida rugosa*, for the production of (*R*)-(-)-3-hydroxyisobutyric acid (**20**) from methyl 2-methylpropanoate (**21**) which is required for the synthesis of a great variety of pharmacologically active compounds, such as the Squibb cardiovascular drug, captopril (**15**).[6] The β-hydroxy acid (**20**) is also an important precursor to chiral polymers.[2,5] Polymers derived from enantiomerically pure monomers exhibit interesting properties and they find wide application, for example, as high strength lightweight materials and for liquid crystal applications.



(**20**) (**21**)

1.3.1.4 The use of Homochiral Catalysts

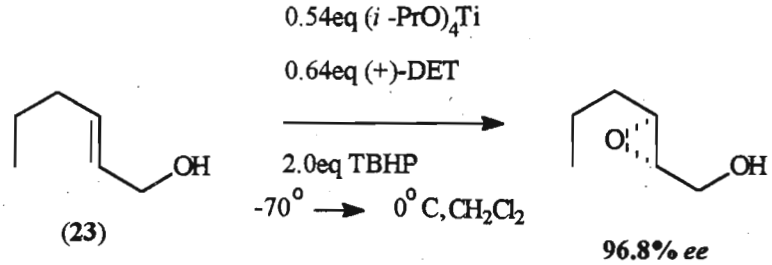
The use of asymmetric catalysts in enantioselective syntheses has gradually gathered momentum over the past two decades.[26] The advantages of asymmetric catalysts are that they promote a reaction so that only a single isomer is produced, a small quantity of catalyst can provide a large amount of single enantiomer product and the antipodes are also easily available since catalysts may be obtained in both configurations. Homochiral catalysts include reagents complexed with chiral ligands, chiral transition metal complexes, chiral bases and chiral Lewis acids.[17] The greatest variety of commonly used reagents in asymmetric synthesis are for the reduction of C=O or C=C double bonds.[5] Asymmetric catalytic hydrogenation of C=C bonds can be done with high enantioselectivity by using rhodium or ruthenium complexes as catalysts.[17] Asymmetric hydrogenation has its origins in the Wilkinson catalyst[27] modified with chiral phosphine ligands which led to the industrial asymmetric Monsanto process for levodopa (**22**) (Scheme 2). Levodopa, commercialised in the early 1970s, is used for the management of parkinsonism.



(22)

Scheme 2

One of the most valuable developments in asymmetric oxidation reactions is the utilization of various mixtures of dialkyl tartrates, titanium tetra-alkoxides and *tert*-butyl hydroperoxide (TBHP) to effect the enantioselective formation of epoxides from primary allylic carbinols (**23**).[28] A 90% enantiomeric excess is usually achieved. One of the features of the reaction is that the configuration of the major epoxide is entirely dependant on the absolute configuration of the tartrate ester regardless of the substituents attached to the olefinic bond. A representative reaction is depicted in Scheme 3.[29]



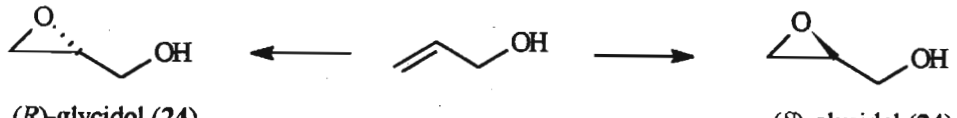
(**23**)

96.8% *ee*

(*E*)-2-hexen-1-ol DET = diethyl tartrate (*E*)-2-hexen-1-ol

Scheme 3

The catalytic version of the process has been used by ARCO for the production of both enantiomers of glycidol (**24**).[30]



(*R*)-glycidol (**24**) (*S*)-glycidol (**24**)

More recent advances by Sharpless and co-workers[31] have led to the discovery of the phthalazine class of ligands, which are now commercially available, and the acceleration of osmate ester hydrolysis in the presence of organic sulfonamides. Taken together, these advances have led to one general procedure which is applicable to a wide range of olefinic substrates whereas originally, osmium-catalysed asymmetric dihydroxylations were restricted to primary allylic alcohols.

1.3.1.5 The use of Chiral Auxiliaries attached to Achiral Substrates

One of the most reliable strategies for achieving an enantioselective synthesis is the temporary incorporation of a chiral auxiliary into the substrate.[32] The chiral auxiliary is attached to, or near to, the reactive centre of an achiral molecule by way of a covalent bond in order to carry out the relevant transformation. This takes place *via* a diastereomeric transition state which, when the chiral auxiliary is cleaved after the reaction(s), gives rise to homochiral compounds. The chiral auxiliary may be isolated and recycled.[17]

It was not before 1955 that Prelog[33] rationalised asymmetric inductions on the basis of preferred conformations and steric repulsions in the transition state. The products formed *via* a diastereomeric transition state have different energies of activation for their formation and hence will be formed at different rates and in unequal amounts. The stereochemical outcome is thus determined by the differences in free energy associated with the diastereomeric transition state or product. Factors which further maximise the difference between the diastereomeric reaction pathways include rigidity which prevents conformational or vibrational changes in geometry, steric hindrance by bulky functional groups, minimization of tortional strain and optimization of orbital interactions. These factors cause a preferential shielding of one of the stereoheterotopic faces of a molecule which produces a reaction of very high overall stereoselectivity. In addition to this, further kinetic resolution is possible by recrystallization and chromatography.

1.3.2 Chiral Auxiliaries

The chiral pool is still an attractive source for enantiomerically pure chiral auxiliaries.[34] Reasons for this can be attributed to the fact that the vast majority of them are obtained from natural compounds that already possess the essential elements of chirality. In addition to this, natural products are usually readily available and a more economically viable source of these agents. The synthesis of chiral catalysts or chiral auxiliaries obtained from non-natural starting materials, on the other hand, can

require extensive designing and the use of expensive compounds. Natural compounds can either be used 'as is' or the carbon backbone with the essential elements of chirality remains unchanged, but appropriate modifications to functional groups and/or additional substituents are introduced in order to get the desired properties.

Blaser[6] has extensively reviewed effective chiral auxiliaries and by studying only the really highly efficient ones , he was able to find structural elements that were common to many of the best chiral auxiliaries. According to Blaser, then, a chiral auxiliary should possess the following properties:

1. It needs to be reactive enough to be able to partake in reactions in high chemical as well as optical yields but at the same time it must be readily cleaved after the stereoselection reaction has taken place;
2. It needs to have the asymmetric centre as close as possible to the reacting centre for efficient stereotransfer;
3. It needs to have physical properties such as crystallinity to facilitate purification and to allow for further kinetic resolution as well as solubility for easier reaction procedures;
4. It needs to possess structural features such as bulky or aromatic substituents that will enhance selectivity without being too bulky to decrease accessibility of the reactants to the reactive centre;
5. It also needs to possess other structural features such as a rigid ring structure as mentioned above. Rigidity can be further enhanced in bidentate ligands by co-ordination with a central metal atom.

Blaser concludes by saying that, even if one succeeded in designing an auxiliary with all these structural elements, there would still be no guarantee for success. Each and every chemical reaction requires its own unique type of chiral agent that will be sufficiently reactive and will have the ability to control the stereochemistry with high stereospecificity as well as being able to be removed without altering the structure. This requires a unique combination of donor atoms in a properly defined chiral environment. Each new auxiliary represents a new set of these features that needs to

be researched for its efficiency and stereotransfer ability in as wide a range of organic asymmetric reactions as possible. The quest for the discovery of new naturally available chiral auxiliaries when so many have already been designed has, therefore, not yet ended.

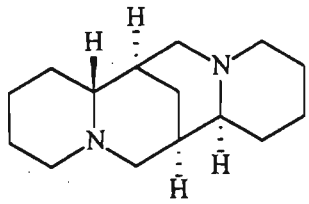
The first reports of chiral auxiliary-induced stereoselective reactions began in the early 20th century and McKenzie[35] in 1906 found face differentiations on reductions and Grignard reactions of terpenes. Most of the early work was based on menthol and oxazolines but after about 1980, the field of asymmetric induction started to expand with the development of new chiral templates obtained mainly from 'natural' sources. Since then, many chiral auxiliaries have been developed and successfully applied in asymmetric synthesis. The range of examples is enormous and have been the subject of numerous publications and reviews.[36] A collection of chiral auxiliaries is presented in groups according to their source which highlight the properties and structural features required for effective chiral auxiliaries as well as relevant aspects of asymmetric synthesis such as the effect of Lewis acids and π-π interactions.

The most common classes of natural compounds used as starting materials in asymmetric syntheses include:[6,18]

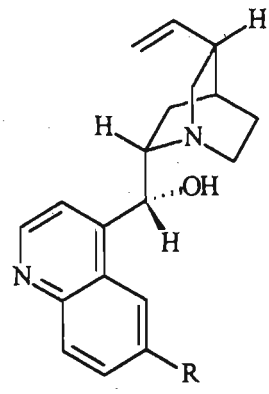
1. Alkaloids.
2. Amino acid derivatives.
3. Hydroxy acids.
4. Carbohydrates.
5. Terpenes.

1.3.2.1 Alkaloids

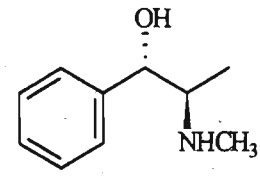
The first of these groups of compounds are derived from the alkaloids. Of the many types of alkaloids known today, only a very few have been found to be effective chiral ligands.



sparteine (**25**)



R = H cinchonidine (**26**)
R = OMe quinine (**27**)



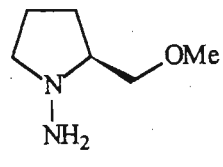
ephedrine (**28**)

Alkaloids have been found to be more effective when unmodified and have been used for a variety of transformations. For example sparteine[37] (**25**) has been used for the polymerisation of acrylic acid derivatives showing ee's of 100%. The cinchona alkaloids[38] (**26**) and (**27**) possess unique multifunctionality and have been used successfully in Michael addition reactions, additions of Me_3SiCN to aldehydes and in the dihydroxylation of olefins. They are successfully used as chiral auxiliaries and chiral catalysts and have been quite prominantly used as resolving agents ever since Pasteur first used quinine to effect the resolution of racemic acids. Ephedrine (**28**) is most often used as a ligand for organometallic chiral reagents or catalysts. As a chiral reagent, it has been used for the hydride reduction of ketones to yield 2° alcohols with ee's of up to 98%, it effects the addition of methyl groups to aldehydes with ee's of about 90% and the 1,4 addition of RCuM to enones proceeds with an ee of up to 95%.[39, 40]

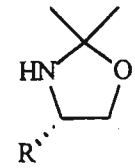
1.3.2.2 Amino Acids

Amino acids are an important source of chiral auxiliaries, not only because they are cheap and commercially available in high optical purity, but also because a large variety is available with readily elaborated functionalities which provides the opportunity of designing auxiliaries for special purposes. Another important aspect of chiral auxiliaries derived from amino acids is the ready availability of both antipodes. Some important amino acids which are frequently used as building blocks for the

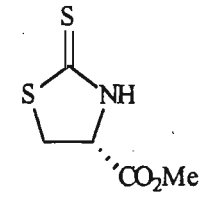
preparation of auxiliaries are alanine, cysteine, valine, leucine, phenylalanine and proline. A small selected group of these is presented below.



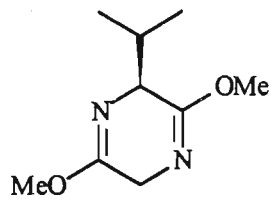
SAMP (**29**)



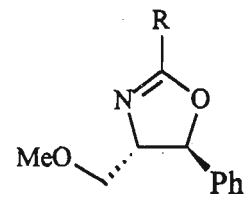
R = iPr, t-Bu, Ph (**30**)



(**31**)

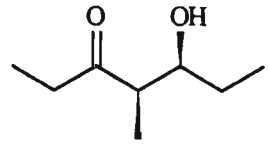


(**32**)

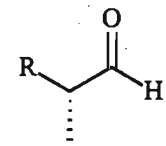


(**33**)

Enders *et al.*[41] introduced the (*S*)-1-amino-2-methoxymethylpyrrolidine or SAMP (**29**) chiral auxiliary. Both enantiomers of this auxiliary are commercially available. Diastereoselective alkylations with these auxiliaries provides α-alkylated aldehydes, ketones or amines in high optical purities. Many examples of the use of chiral hydrazone methodology in total synthesis have appeared in the literature. Kocienski has used this methodology in the synthesis of the C(1)-C(15) segment of Fujimycin, the immunosuppressant FK 506.[42] Enders has synthesised the aggregation pheromone sitophilure (**34**) and the artificial fragrances lilial (**35**) and methyl undecanal (**36**).[43,44]



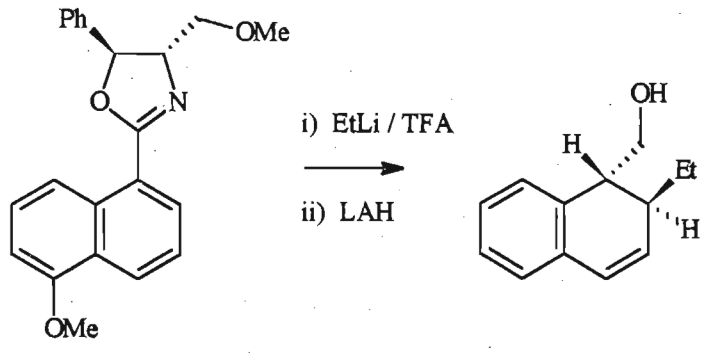
(**34**)



(**35**) R = 4-^{t}BuC$_6$H$_4$CH$_2$
(**36**) R = n-C$_9$H$_{19}$

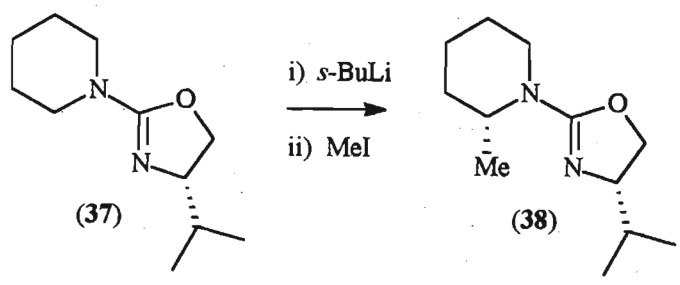
The auxiliaries (**30**) and (**31**) are modified versions of the Evans auxiliary (**33**) and have been successfully used to improve results obtained in many kinds of reactions including aldol reactions in which high anti-selectivities were obtained with (**30**)[45] and high syn-selectivities were obtained with (**31**).[46] The chiral glycine derivative

(32) has been developed by Schöllkopf *et al.*[47] for the production of unnatural amino acids which is becoming an important development in biological and medicinal chemistry. During the 70s, the Meyers' group[48] investigated the use of chiral oxazolines (33) derived from the readily available (1*S*, 2*S*)-1-phenyl-2-amino-1,3-propanediol in two steps. Oxazolines have been used in many reactions such as the synthesis of dialkyl acids and lactones *via* asymmetric alkylations and, more recently, in the stereoselective protonation of azaenolates with trifluoroacetic acid (TFA). Reduction of the intermediate product afforded 1,2-disubstituted-1,2-dihydronaphthalenes in up to 94% ee (Scheme 4).[49]



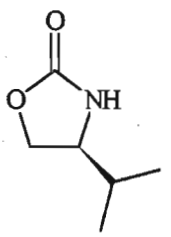
Scheme 4

Despite the high levels of stereochemical control obtained with chiral oxazolines, a major limitation is the inaccessibility of the antipode of (33). A publication by Gawley *et al.*[50] describes the diastereospecific alkylation of the chiral oxazoline (37) derived from L-valinol (Scheme 5). Due to the availability of both antipodes of valinol, oxazoline (38) and those derived from them are readily accessible.



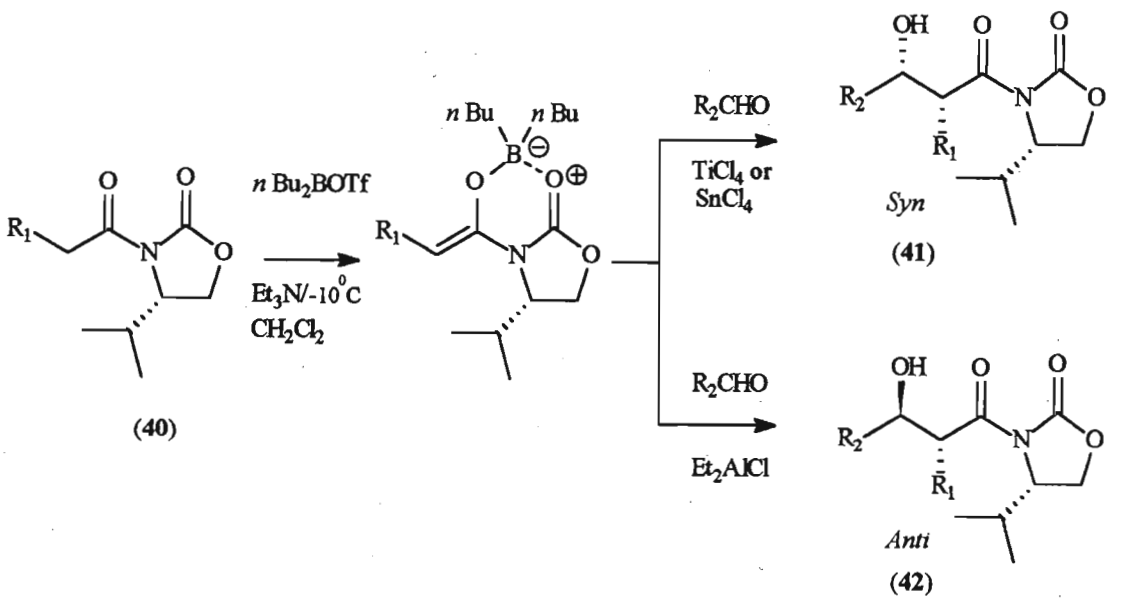
Scheme 5

One of the most important group of chiral auxiliaries are the oxazolidinones e.g. (**39**) introduced by Evans *et al.* in 1981.[51] This has been made evident by the vast amount of literature available on this auxiliary.[52]



(**39**)

An amino acid, usually valine, *tert*-leucine, phenylalanine or phenylglycine is reduced to the corresponding amino alcohol which is then cyclised with phosgene or diethyl carbonate to the chiral oxazolidinone. The oxazolidinones are normally attached to the substrate *via* imide-bond formation.[53]



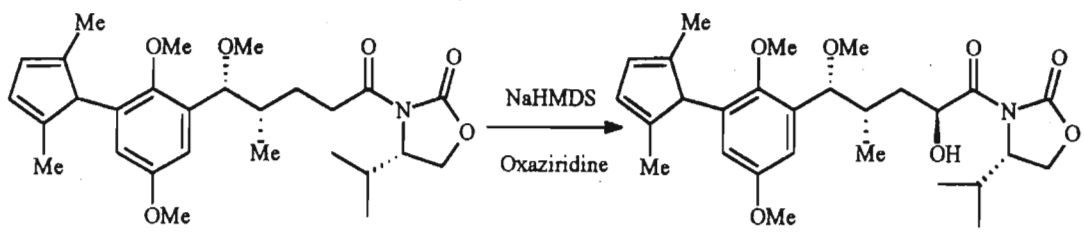
(**40**) (**41**) (**42**)

Scheme 6

For aldol reactions of the *N*-acylated oxazolidinone[54] (**40**) with dibutylboron triflate, *syn*-aldol products (**41**) and (**42**) have been obtained with high selectivity (Scheme 6). In the presence of an additional Lewis acid, "small" Lewis acids like $SnCl_4$ or $TiCl_4$ lead to *syn*-aldol products whereas "bulky" Lewis acids like Et_2AlCl afford the

corresponding *anti*-aldols due to interaction of the Lewis acid with the R substituent of the enolate.

The auxiliary has also been successfully applied in a wide range of reactions including alkylations of enolates[55], acylation reactions[56] and the Diels-Alder reaction.[57] The significance of Evans' auxiliary has been made obvious by its numerous applications in natural product synthesis. For example, it has been used in the total synthesis of fujimycin,[58] an immunosuppresive agent containing a 1,2,3-tricarbonyl unit. It has also been used in the synthesis of the α-hydroxylated product (**43**) (Scheme 7) as a single isomer in 83% yield.[59] The product is an intermediate in the synthesis of the antitumor antibiotics macbecin I and II.



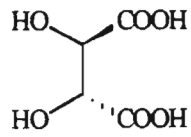
(43)

Scheme 7

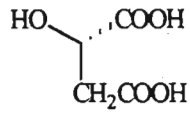
1.3.2.3 Hydroxy Acids

The hydroxy acids offer a similar potential as chiral auxiliaries as amino acids.[6] In many cases, only the backbone is left unchanged while the OH and/or the COOH groups are protected or transformed to give efficient ligands.

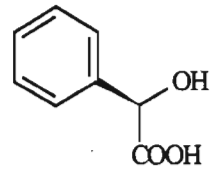
Tartaric acid (**44**), malic acid (**45**), mandelic acid (**46**) and lactic acid (**47**) are the most commonly used starting materials for a variety of highly selective chiral agents. However, they are more often used as chiral resolving agents and chiral catalysts, for example in the Sharpless epoxidation reactions of allylic alcohols (See Scheme 3).



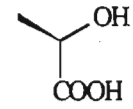
(44)



(45)



(46)



(47)

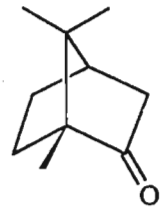
1.3.2.4 Carbohydrates

Carbohydrates are a group of compounds that contain the most asymmetric centres and functional groups and their use as chiral auxiliaries[6] is therefore very tempting. In many cases, though, the hydroxyl groups have to be protected or removed in order to obtain the desired ligand. They do, however, possess a rigid ring structure and ligands attached to the ring are easily accessible. Because of this they are more often used as chiral catalysts and complexed, for example with rhodium for the hydrogenation of enamides. Sugars occur naturally as oligomers eg. cyclodextrins and polymers eg. cellulose and these materials have been applied with success as inclusion catalysts and as polymeric ligands.

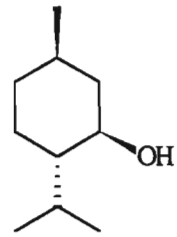
Their use as chiral auxiliaries has been reviewed[20] and it is evident that pre-orientation of the reactive and shielding groups through the formation of complexes has to take place before they can be used successfully in reactions such as aldol reactions, alkylations, Diels-Alder reactions and Michael additions.

1.3.2.5 Terpenes

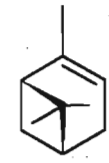
The terpenes offer several groups of extensively studied chiral auxiliaries. Terpenes include camphor (**48**), menthol (**49**), α-pinene (**50**) and 2-carene (**51**).[18]



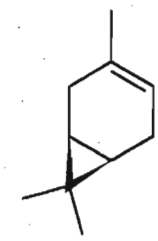
camphor (**48**)



menthol (**49**)



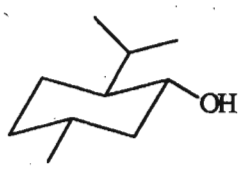
α-pinene (**50**)



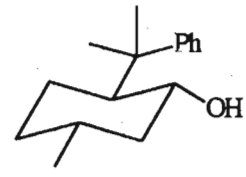
2-carene (**51**)

These compounds all have rigid ring structures but require the addition of appropriate functional groups. This can be advantageous if specific functional groups are required for a particular type of reaction. As a result of the 'designing' or 'tuning' of auxiliaries in this way, a large number of chiral auxiliaries have arisen from this group of compounds. Only a selected few are presented.

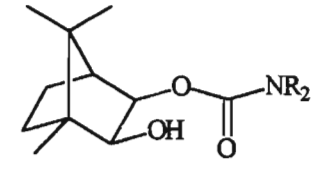
The 2 - carene (**51**) and especially the α-pinene (**50**), have mainly been used as chiral reagents to form organoboranes for the reduction of ketones and the hydroboration of olefins in which the ligand is attached directly to the boron atom *via* a carbon atom.[60]



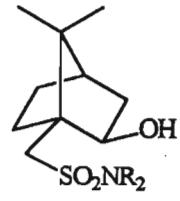
Menthol (**49**)



8-Phenylmenthol (**53**)

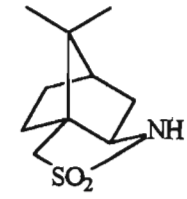


C(2)/C(3)-functionalised (**54**) bornane

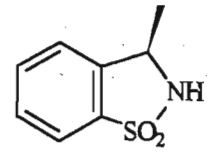


R = iPr, cyclohexyl

C(2)/C(10)-functionalised (**55**) bornane

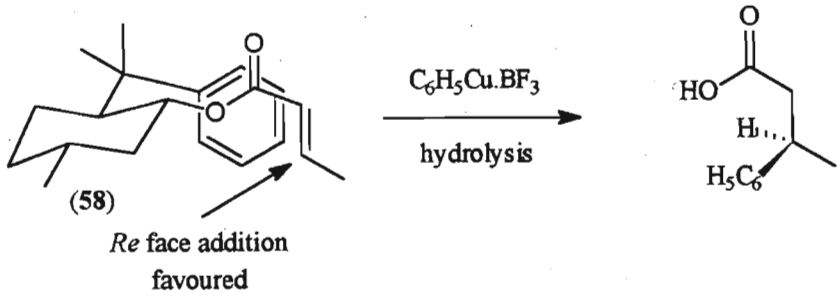


Camphor sultam (**57**)



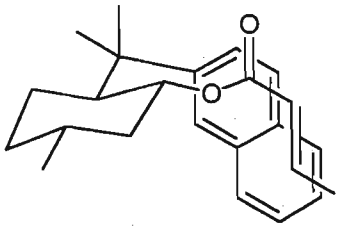
N-{N'-[bis(methylthio)methylidene]glycyl}bornane-10,2-sultam (**56**)

Menthol (**52**), as already mentioned, has been widely used in asymmetric syntheses. Many structurally related auxiliaries have been synthesised in order to 'suit' particular reactions.[61a] A variation of this ligand is the 8-phenylmenthol auxiliary (**53**) derived from (*R*)-pulegone which possesses a bulkier directing group.[61] These auxiliaries have been used in a wide variety of reactions but one example clearly demonstrates the effect of chiral auxiliary design on the stereoselectivity of a reaction. The conjugate addition of phenylmagnesium bromide to menthyl crotonate gave very discouraging levels of diastereoselectivity[62] but substitution of 8-phenylmenthol as the chiral auxiliary (**58**) gave more encouraging results (Scheme 8).[63]



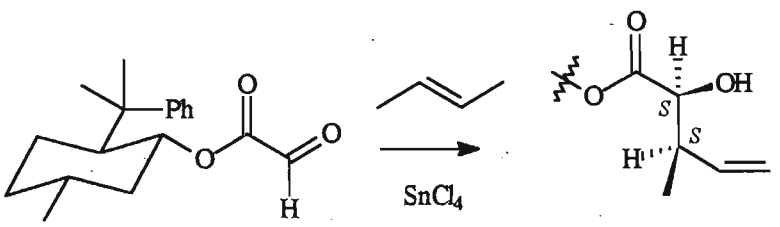
Scheme 8

The configuration of the products can be rationalised by assuming that the α,β-unsaturated esters of secondary alcohols take up a preferred conformation in which the carbonyl group is *s-trans* to the olefinic bond and synperiplanar with the alkoxy methine CH bond (Scheme 8). According to Eliel *et al.*[17], *s-cis* and *s-trans* are descriptors that refer to the conformation about a single bond that links two conjugated double bonds. The synperiplanar conformation is called *s-cis* and the antiperiplanar one is called *s-trans*. The *si*-face of the β-carbon atom of the crotonate moiety is thereby hindered and approach takes place almost exclusively from the *re*-face. Although conjugate addition of ammonia and amines to (**53**) gave poor levels of stereoselection, utilization of the 2-naphthyl analogue (**59**) gave excellent results, for example of benzylamine under high pressure (15 kbar) afforded the *re* addition product almost exclusively (99% de). The authors concluded that π-π interactions contributed significantly to the greater level of stereoselectivity since the crotonate methyl group was discovered to lie above the plane of the naphthyl ring.[64]



(59)

The 8-phenylmenthol auxiliary (**53**) has also afforded good induction in several reactions including the ene-type addition of *trans*-2-butene to its glyoxylate derivative (**60**) (Scheme 9).[60] These ene reactions of glyoxylates have been used for the synthesis of a number of natural products and have provided the key steps in the routes to specionin and xylomollin.[65]



(**60**) *S,S*:*S,R* = 15:1 (**61**)

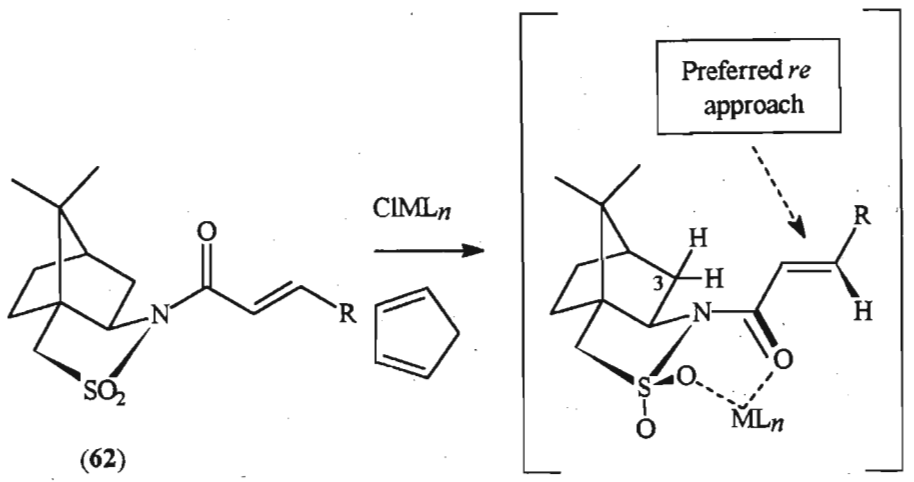
Scheme 9

Major limitations of 8-phenylmenthol as an auxiliary include the difficulty of purification since it and its products are oils, the fact that its (+)-enantiomer is not readily available and removal of the chiral auxiliary is not always very successful.

The abundance, crystallinity and the numerous transformations possible with (+)-camphor (**48**) have made this natural product an extremely popular choice of building block for an enormous number of chiral auxiliaries.[66] Another advantage is the availability of both antipodal forms. The inherent topological bias of the camphor skeleton made it easy to design conformationally rigid systems where one diastereotopic face of a reactive π-bond is sterically shielded. Camphor derivatives as chiral auxiliaries have been extensively studied by Oppolzer[67,68,69] who has written numerous literature and review articles on this topic. From these reviews, it is evident

that the scope of both the types of auxiliaries available and the reactions to which they can be applied to is enormous.

Of the many reactions possible with these camphor auxiliaries, the most important have been the π-face topological differentiation reactions to their enoyl as well as enolate derivatives.[67] They have been employed in many reactions including conjugate addition,[70,71] hydrogenation,[72,73] alkylation,[74,75] aldolisation[76,77] and α-acetoxylation reactions.[78] Chiral products obtained with the ester enolates of auxiliaries (**54**) and (**55**) were frequently obtained in greater than 90 % diastereomeric excesses, many of which could be purified to almost 100% by recrystallization. The Oppolzer group[68,79,80] have employed these auxiliaries extensively in Diels-Alder reactions. They found, though, that the reaction of cyclopentadiene with the crotonate derivatives of these auxiliaries in the presence of a Lewis acid proceeded so slowly that they failed to give cycloadducts in synthetically useful yields. This lead to their development of one of the most important and fascinating chiral auxiliaries, the bornane-10,2-sultam (**57**).[81,82,69] They found that by stronger chelation with Lewis acids this chiral control element increased dienophilicity as well as simultaneously controlling π-facial selectivity. In this way, they were able to extend the scope of the Diels-Alder reaction to include the less reactive crotonate dienophile and the less reactive dienes, butadiene and isoprene in high yields and with excellent *endo*- and face selectivities (de > 99%). The observed reactivity and topological control of the $EtAlCl_2$- or $TiCl_4$-promoted Diels-Alder reactions with (**62**) are consistent with a chelation of the SO_2 and C=O groups by the metal which directs the diene to the less hindered C_α *re*-face of the rigid conformation (Scheme 10).

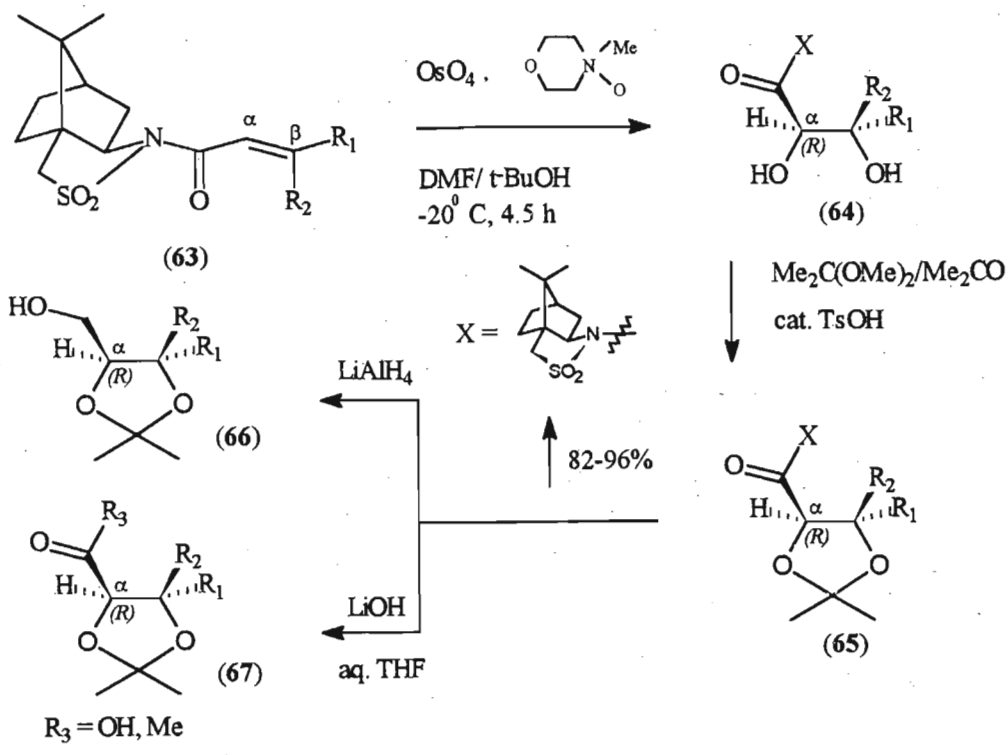


(62)

Scheme 10

Bornane-10,2-sultam auxiliaries (**57**) are accessable by four simple steps from the inexpensive (+)- and (-)-camphor-10-sulfonic acids in both enantiomeric forms. They rank as one of the most practical auxiliaries and this is confirmed by the fact that both antipodes are commercially available in kilogram quantities. Most of all their *N*-acyl derivatives are stable and can be readily purified by recrystallization, directly analysed by ^{1}H NMR spectroscopy and/or GC to determine their stereochemical purity and are easily cleaved with $LiAlH_4$, LiOH, LiOOH, MeOMgI, *etc.* under mild conditions without loss of the induced chirality and with excellent recovery of the auxiliary.

Apart from the Diels-Alder reaction, the chiral sultam auxiliaries have exhibited excellent chirality transfer in chemical transformations such as alkylations, acylations, aldol reactions, catalytic hydrogenations, conjugate hydride and Grignard reagent additions and the formation of β-Silylcarboxyl derivatives by 1,4-additions of organocopper reagents. These have been excellently reviewed in Oppolzer's review article where he includes natural product applications.[67] A valuable transformation reported by Oppolzer involves the diastereoselective OsO_4-catalysed bis-hydroxylations of β-substituted α,β-enoyl sultams (**63**) (Scheme 11).[83]



Scheme 11

The products of the reaction are enantiomerically pure alcohols (**66**) or carboxylic acids (**67**). These are important intermediates for the synthesis of enantiomerically pure deoxy- and amino-sugars, of (-)-viridofloric acid, (-)-dihydromahubanolide B, biopterin, *Scolytus multistriatus* pheromone, fungal metabolite LLP-880β and α,β-dihydroxymethylvaleric acid.

Another commercially available and versatile chiral auxiliary is the sultam (**56**) which also achieves high π-facial discriminations in many reactions of its 'enolate' derivatives.[97]

The above discussion has stressed the growing importance of asymmetric synthesis to modern organic chemistry. This has undoubtedly been the cause of the huge surge of literature available on this topic as chemists rise to meet the challenge of obtaining near-perfect selectivity in synthetic reactions.

One of the methods used to achieve near-perfect selectivity in synthetic reactions is the use of natural products as chiral auxiliaries which induce chirality in a substrate. These are chosen on the basis of their ability to control the selectivity of a reaction and their ease of use as well as their availability and cost.

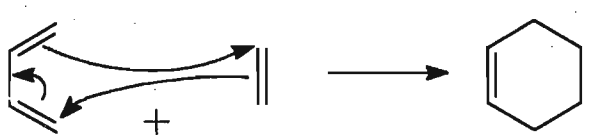
In order to achieve greater efficiency in asymmetric reactions, many natural chiral auxiliaries have been modified by changing the size or function of functional groups. To this end, research still continues as a clearer understanding of the effect certain compound structures and functionalities have on selectivity is gained.

It should be clear from the above discussions that a move was made towards chiral auxiliaries possessing sites for chelation with metal atoms. The most effective auxiliaries have tended to be those that display bidentate chelation such as the popular Evans' oxazolidinones and Oppolzer's camphor sultam auxiliaries. These auxiliaries have also found major application in natural product synthesis as the examples included in this report show.

PART B:

1.4 DIELS-ALDER CYCLOADDITION REACTIONS

In 1928, Otto Diels and Kurt Alder[84] showed that many conjugated dienes undergo addition reactions with certain alkenes or alkynes to form substituted cyclohexenes without the elimination of any other species.



Diene Dienophile

Figure 1. A simplified version of the Diels-Alder Reaction.

Since then, the Diels-Alder reaction has become one of the most important reactions in organic synthesis as it is able to induce asymmetry in carbon-carbon bond forming reactions.[85] Substantial work on the methodology and application of this reaction has been carried out as is evident by the vast amount of literature available on this subject.

Mechanistically, the Diels-Alder reaction is both a pericyclic reaction - a reaction that occurs in one step by a cyclic flow of electrons and a cycloaddition reaction - an addition reaction that forms a ring.

More specifically, the Diels-Alder reaction is one between a conjugated diene (a 4π electron system) and a double bond (a 2π electron system) of a dienophile. In the reaction, two new σ bonds are formed at the expense of two π bonds of the diene and dienophile which usually provides a significant driving force (ΔG^0) for the reaction. Cycloaddition reactions are classified according to the number of participating π electrons in each reacting molecule, thus the Diels-Alder reaction is described as a [4+2] cycloaddition reaction.

1.4.1 Reactivity in the Diels-Alder Reaction

To react with the majority of dienes, the dienophilic double or triple bond needs to be electron deficient. The vast majority of reactions involve electron withdrawing groups such as carbonyls (-CO), esters ($-CO_2R$), cyano (-CN), nitro ($-NO_2$) and sulfonyl ($-SO_2R$) groups on the dienophile and electron donating groups, such as alkyl and alkoxy, NR_2, and SR groups, on the diene. Theoretical rationalisations of the Diels-Alder reaction are well established in the Conservation of Orbital Symmetry and Frontier Orbital Theories of Woodward-Hoffman and Fukui.[86,87]

Molecular orbital considerations provide the following rationalization.[88] In a 'normal' Diels-Alder reaction of an electron-poor dienophile with an electron-rich diene, the main interaction is between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The smaller the energy separation between these orbitals, the more readily the reaction proceeds. Electron withdrawing substituents on the dienophile facilitate the reaction by lowering the energy of the LUMO and this results in a decrease in the energy separation between the LUMO and the HOMO molecular orbitals and, consequently, the activation enthalpy (ΔH^0) of the reaction.

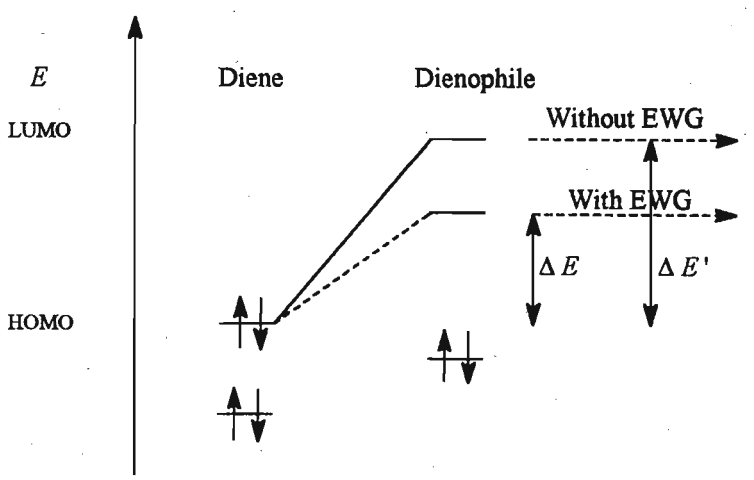


Figure 2 HOMO-LUMO Arrangements in Diels-Alder Reactions showing the effect of Electron Withdrawing Groups on the Dienophile.

The electron donating substituents on the diene accelerate the reaction by raising the energy level of the HOMO. In line with the above statements, maleic anhydride is a potent dienophile due to the presence of two carbonyl carbons on either side of the double bond and 2,3-dimethyl-1,3-butadiene is a potent diene due to the positive inductive effect of the two methyl groups.

In Diels-Alder reactions with inverse electron demand involving electron-rich dienophiles (*e.g.* enamines, vinyl ethers and vinyl sulfides) and electron deficient dienes, it is the HOMO (dienophile)-LUMO (diene) overlap which controls the reaction. Alkenes and alkynes, such as ethene and ethyne, that are notoriously poor dienophiles can be activated by introducing an activating moiety, such as NO_2 and SO_2R, which can be readily removed after the cycloaddition reaction.

Other types of rate enhancements which increase the reactivity and therefore the scope of Diels-Alder reactions rely on rendering the activation entropy ($\Delta S^{\ddagger}$) less negative. This can be done by using a catalyst, high pressure, ultrasound, microwaves, aggregation effects in water, adsorption on dry SiO_2, or clays and zeolites.[89] Discussion of these topics, although important, are beyond the scope of this report. Due to its major influence on Diels-Alder reactions, the use of catalysts will be discussed.

Another requirement of the Diels-Alder reaction is that the diene component must be in the *s-cis* conformation. Dienes that are actually 'locked' into *s-cis* conformations, such as cyclopentadiene are unusually reactive. In fact, cyclopentadiene will undergo a Diels-Alder reaction on itself even at room temperature to form dicyclopentadiene. A diene in this *s-cis* conformation and a dienophile approach in parallel planes and the π-electron clouds of both molecules are able to overlap to form bonds. Experimental evidence also shows that dienes 'locked' into *s-trans* conformations are unreactive in the Diels-Alder reaction.[90]

The applications of the Diels-Alder cycloaddition reaction are extremely diverse, making it one of the most valuable synthetic methodologies. It is a powerful means of

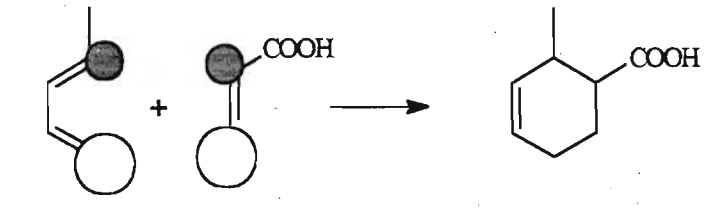
forming C-C bonds and is used in the construction of carbon rings, including bicyclic systems and a large variety of dienes and dienophiles bearing a variety of functional groups are tolerated. Not all of the atoms involved in the ring closure need be carbon atoms so that heterocyclic rings can also be synthesised using this reaction. It is, however, mainly due to its high degree of regio- and stereoselectivity which is often possible in both inter- and intra-molecular reactions that it has found widespread application in the total synthesis of complex natural products. Oppolzer[85], in his excellent review on the achievement of absolute stereocontrol in Diels-Alder reactions, underscores the various principles of chiral control groups to this end and outlines their synthetic potential in their application to the syntheses of physiologically interesting chiral natural products such as some prostaglandins, antibiotics, terpenoids, shikimic acids, alkaloids and kainoids.

In view of the extensive scope of the Diels-Alder reaction, this report will be limited to the formation of 'all-carbon' six-membered rings by intermolecular reactions. In addition to this, the absolute control of stereochemistry will be discussed focussing specifically on chiral induction by the addition of a prochiral diene to a dienophile bearing a removable chiral auxiliary. Other methods of stereocontrol include the use of chiral auxiliaries that are not removed after the reaction, chiral dienes and chiral catalysts. An adequate report on all of these would vastly exceed the limits of this thesis.

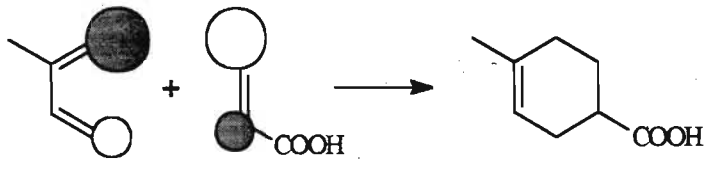
1.4.2 Regiochemistry

The reaction of an unsymmetrical diene with an unsymmetrical dienophile could give rise to two regioisomeric products, but in practice one product generally predominates.[88] Their relative proportions depend on the nature of and the interplay between substituent effects. In Frontier Orbital terms, these orientation effects have been shown to be governed largely by the atomic orbital coefficients at the termini of the conjugated systems concerned and these are altered depending on the substituents. The atoms with the larger terminal coefficients on each addend bond preferentially in the transition state. For example, the reaction of acrylic acid derivatives (69) with

substituted butadienes leads to two possible types of regio-adduct. The terminal coefficients of acrylic acid and the 1- and 2-substituted butadienes (Scheme 12) are represented by the relative sizes of the circles. The predominant large-large/small-small interactions of the frontier orbitals lead mainly to the 'ortho' (1,2-) adduct (**70**) with 1-substituted butadienes (**68**) and to the 'para' (1,4-) adduct (**72**) with 2-substituted butadienes (**71**).[91]



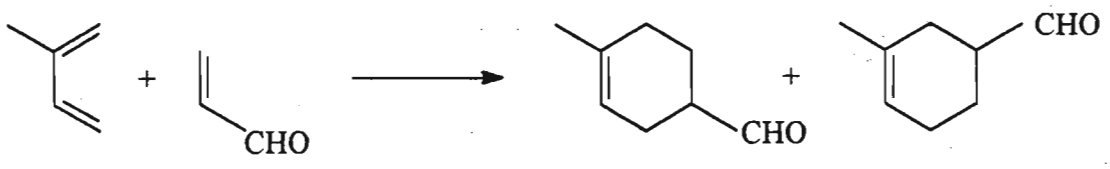
HOMO (**68**) LUMO (**69**) (**70**)



HOMO (**71**) LUMO (**69**) (**72**)

Scheme 12

In the presence of Lewis acids, not only is the rate of reaction dramatically increased, but the proportion of the expected isomer formed is also frequently increased and under these conditions, very high yields of a single isomer can often be obtained.[92] This effect is also shown (Scheme 13) by the addition of an $SnCl_4.5H_2O$ catalyst to the addition reaction of acetaldehyde to isoprene.

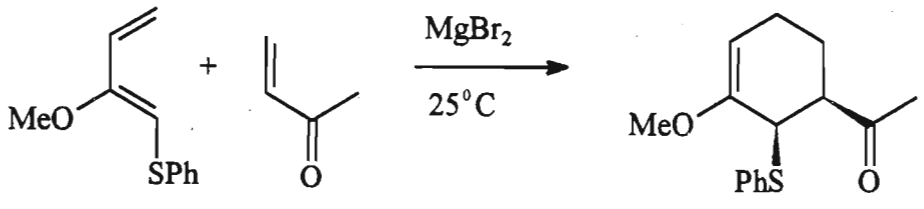


(71) (69)

	% para	% meta
toluene, 120° C, no catalyst, 70d	59	41
benzene, 25° C, $SnCl_4.5H_2O$, 3h	96	4

Scheme 13

Substituents do not all have the same directing power. The presence of a substituent causes the atomic orbital coefficient at the terminus of the conjugated system to change in a characteristic way. Substituents, then, with more directing power control the orientation of addition. For example, the addition reaction of 2-methoxy-1-phenylthiobutadiene (**73**) and methyl vinyl ketone (**74**) gives predominantly the adduct (**75**) in which the methoxy group is 'meta' to the carbonyl group of the dienophile and in this example, the regioselectivity is controlled by the phenylthio group (Scheme 14). The reaction of 2-methoxybutadiene with methyl vinyl ketone, however, gives the 'para' isomer.[93]



(73) (74) (75)

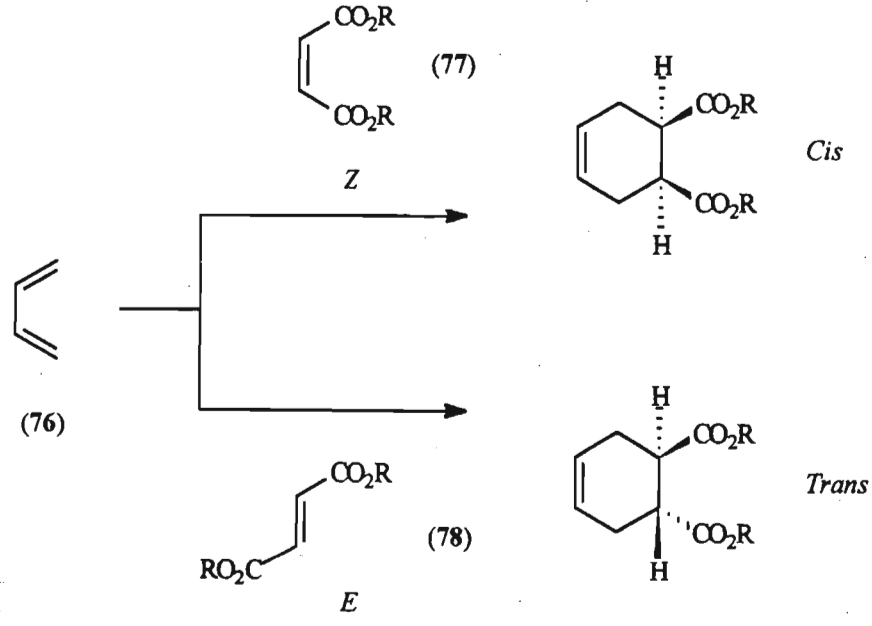
Scheme 14

1.4.3 Stereochemistry

Another invaluable feature of the Diels-Alder cycloaddition reaction is its high degree of stereoselectivity. It is probably this factor more than any other which has lead to its wide application in the synthesis of complex natural products.[88,94] Up to four new

chiral centres may be set up simultaneously in the reaction between a diene and a dienophile, but it is frequently found that one of the several possible isomers is formed in proponderant amount or even exclusively.

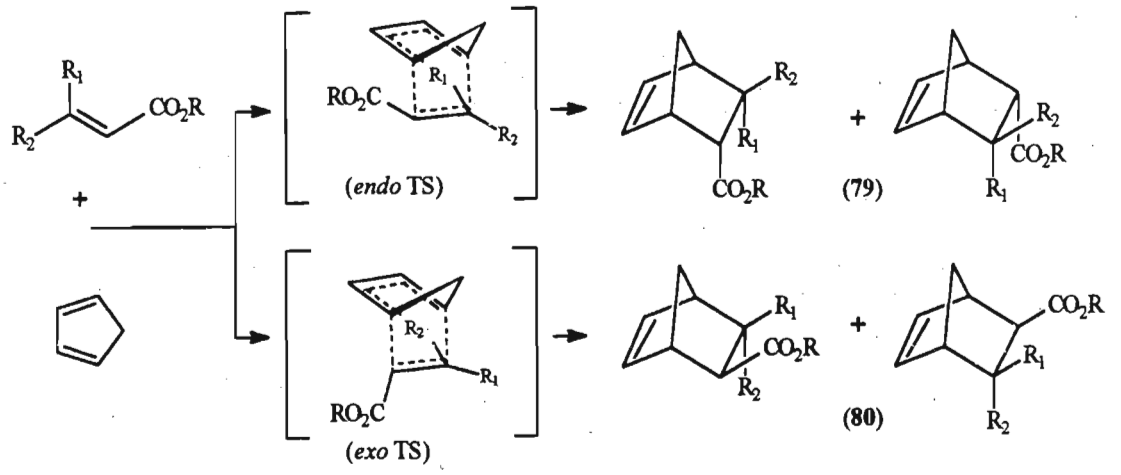
The stereochemistry [17,88] can generally be predicted on the basis of two rules, the *cis* rule and the Alder *endo* rule. Again, the presence of a Lewis acid significantly increases the proportion of the expected isomer formed. The *cis* rule states that the *cis-trans* relationships between substituents in the reactants should be preserved in the products. The diene, as stated earlier, is in the *s-cis* conformation (**76**) and, consistent with a supra/supra/facial mode of addition in the transition state, the reactions of butadiene with maleic (**77**) and fumaric (**78**) esters thus afford *cis* and *trans* adducts respectively (Scheme 15).[89]



Scheme 15 Retention of *cis* and *trans* Geometry in [4+2] Cycloadditions.

The Alder *endo* rule states that the diene and dienophile arrange themselves in parallel planes and the most stable transition state is that in which there is maximum possibility of π-orbital overlap. It is therefore possible for there to be two relative orientations of the reactants in the transition state (Scheme 16).[17,89] The *endo* adduct (**79**) is assumed to be kinetically favoured for electronic reasons (secondary orbital interactions)[95] and the *exo* isomer (**80**) is thermodynamically preferred because of

steric factors. Alder's *endo* rule specifies a preference for *endo* over *exo* addition especially in the case of additions of cyclic dienophiles to cyclic dienes (Scheme 16). The *endo* preference of substituents does, however, vary.



Scheme 16 *Endo* and *exo* Pathways for [4+2] Cycloadditions.

Each of the (*Z*)- or (*E*)-dienophiles yields a set of two diastereoisomers due to the *endo* and *exo* orientations of the dienophile substituents in the transition states. From a (*Z*)-dienophile (R_1 = substituent, R_2 = H), both substituents will be *endo* or *exo* orientated, whereas from an (*E*)-dienophile (R_1 = H, R_2 = substituent), one substituent will be in an *endo* orientation and the other will be in the *exo* orientation. In the case of the latter example, even dienophiles with competing geminal substituents can still react in a highly *endo/exo* selective manner depending on the substituents and the type of Lewis acid used. This has resulted in extensive research into the understanding and application of the addition of a variety of Lewis acids to Diels-Alder reactions.

Another stereochemical issue that arises is that of π-facial selectivity.[17,89] In the absence of π-facial control, cycloaddition of a dienophile occurs at the same rate to the top and bottom faces of a diene to give a 50:50 mixture of enantiomers. Much progress has been made in directing Diels-Alder additions with up to 99.5% selectivity to either face, thereby controlling the absolute configuration of the newly generated stereogenic centres.[96,97] Procedures have included the temporary attachment of a chiral control group to either the dienophile or the diene, or the use of chiral

catalysts. So far, the stoichiometric use of covalently bound chiral control groups has proved to be the more efficient and predictable means of obtaining this selectivity. (Scheme 20).

1.4.4 Catalysis by Lewis Acids

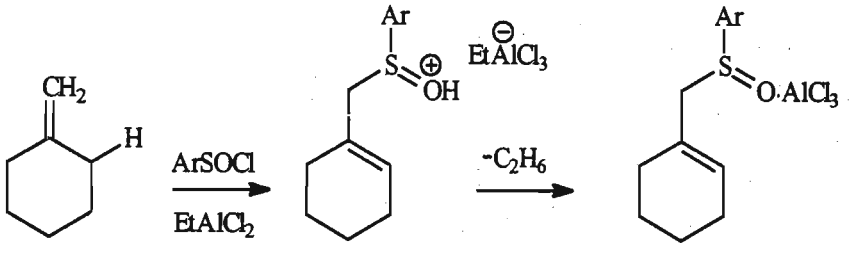
Since the discovery in 1960 by Yates and Eaton[98] that $AlCl_3$ dramatically accelerated cycloaddition reactions, the scope of the Diels-Alder reaction has been vastly increased and numerous other Lewis acids have been explored, including $EtAlCl_2$, Et_2AlCl, $BF_3{\cdot}OEt_2$, $TiCl_4$, $TiCl_2(OR)_2$, $SnCl_4$, $ZnCl_2$ and $MgBr_2$.[89] The literature on the acceleration of Diels-Alder reactions by common Lewis acids is extensive.[94] Only a few special applications of catalysts will, therefore, be discussed.

Lewis acid catalysed cycloaddition reactions, as already mentioned, do not only proceed more rapidly than their thermal counterparts, but are also generally more regio-, *endo* and π-face selective. This is done *via* coordination of the Lewis acid with the dienophile partner in a defined conformation to ensure π-facial discrimination in a predictable manner.[99]

The FMO theory can once again be successfully applied to explain how the Lewis acid catalyst increases reaction rates.[89,91] Donor-acceptor interactions between the dienophile and the catalyst lower the energy of the HOMO and the LUMO of the dienophile. In the case of a [4πs+2πs] cycloaddition reaction with normal electron demand, this means that the separation between the MOs will decrease and the stabilization of the transition state will increase. Increased selectivity can also be attributed to the fact that reactions with Lewis acids can take place at much lower temperatures. In this way, the kinetically favoured stereoisomer is greatly preferred over the thermodynamically more stable adduct.

Snider *et al.*[100] have reported on the use of alkylaluminium halides as Lewis acid catalysts as valuable reagents in Diels-Alder reactions. They provide the following reasons for promoting their use. Lewis acids act as strong Brønsted acids in the

presence of co-catalysts such as water. This, however, may increase the possibility of unwanted side reactions and would therefore require the use of strictly anhydrous reactants and reaction conditions. Unfortunately, it is very difficult to prepare anhydrous, proton-free $AlCl_3$, BF_3, *etc.* Alkylaluminium halides, though, are anhydrous and furthermore scavange any adventitious water, liberating an alkane and generating a new Lewis acid in the process. This can be of value when side reactions are caused by the presence of adventitious protons and it is especially useful when acidic protons are produced by the reaction. In these cases, use of the appropriate alkylaluminium halide in stoichiometric amount gives high yields of products not formed at all with other Lewis acids. An example of this type of reaction is the Friedel-Crafts addition of arylsulfinyl halides to alkenes to give allylic sulfoxides (**82**) and HCl which reacts with $EtAlCl_2$ to give $AlCl_3$ and ethane (Scheme 17).[101] Use of $ZnCl_2$ or $AlCl_3$ leads to proton induced side reactions.



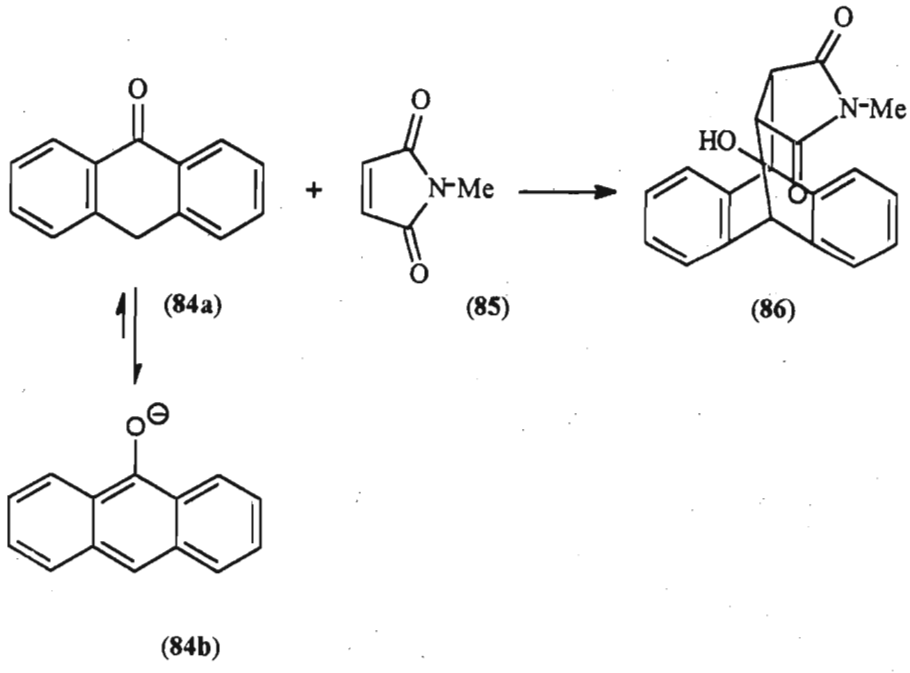
(**81**) (**82**) (**83**)

Scheme 17

A possible disadvantage of alkylaluminium compounds as Lewis acids is the nucleophilicity of the alkyl group. Addition of the alkyl group to the reagent-Lewis acid complex would be undesirable. The ease of alkyl donation is $R_3Al>R_2AlCl>R_3Al_2Cl_3>RAlCl_2$. In addition, ethylaluminium compounds are more nucleophilic than methylaluminium compounds and can donate a hydride as well as an ethyl group. Therefore, use of Me_2AlCl may be preferable to the use of Et_2AlCl, although the latter reagent is much cheaper.

The alkylaluminium halides cover a wide range of Lewis acidity. Replacing chlorines with alkyl groups decreases Lewis acidity so that $EtAlCl_2$ is only slightly less acidic than $AlCl_3$ and on the other end of the scale, Me_3Al is a very mild Lewis acid. These reagents are also easier to use than standard Lewis acids and are soluble in all organic solvents. For these reasons, the alkylaluminium halides have become a very popular choice of Lewis acid and have been used in some of the most well-known Diels-Alder reactions. For example, Oppolzer used them in his work with the *N*-acylbornane-10,2-sultam auxiliaries[68,81] and Evans used them in his work with the *N*-acyloxazolidinone auxiliaries.[57] Comparative studies of Lewis acids should be carried out in order to determine the particular Lewis acid of choice for any given reaction.

The use of Lewis bases as catalysts in Diels-Alder reactions has attracted far less attention. In 1989, Rickborn and co-workers[102,103] reported the first evidence for a base-catalysed Diels-Alder reaction. In the presence of triethylamine, anthrone (**84a**) functions as a masked diene with various dienophiles, *e.g.* with *N*-methylmaleimide (NMM) (**85**) to form the cycloadduct (**86**) exclusively (Scheme 18). This was ascribed to an oxyanion (**84b**) acceleration, presumably *via* the enolate of (**84a**).

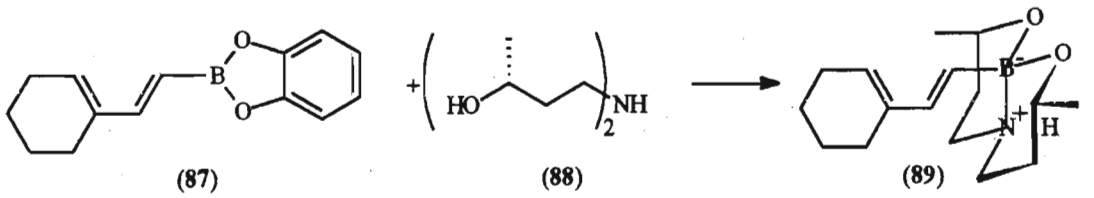


(84a) (85) (86)

(84b)

Scheme 18

Since then, other reports have appeared in the literature. Kagan and co-workers[104] furthered the work of Rickborn *et al.* using chiral amines, such as alkaloids, to catalyse the reaction between anthrone (**84a**) and *N*-methylmaleimide (**85**) and they were able to obtain optically active cycloadducts in high yield. Wang[105] describes the use of a chiral aminodiol (**88**) which acts as a Lewis base and reacts with 1,3-dienylboronates (**87**) *in situ* to generate a chiral diene (**89**) for asymmetric Diels-Alder reactions with *N*-phenylmaleimide to form the *endo* product exclusively.



(87) (88) (89)

Scheme 19

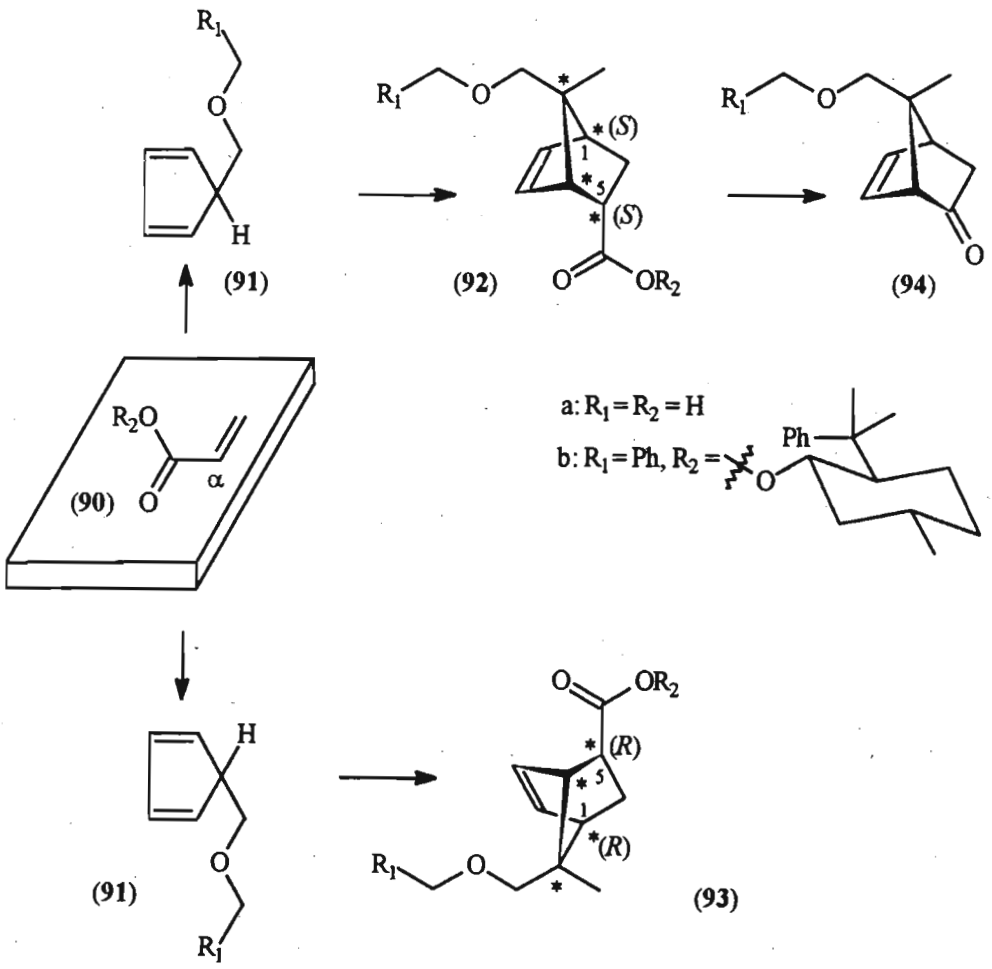
A recent example using DABCO as a base in Diels-Alder reactions will be discussed in Chapter 2.

1.4.5 Chiral Dienophiles

The use of stereoface-selective Diels-Alder reactions are the ultimate means of obtaining enantiomerically pure compounds in these types of reactions as all aspects of stereoselectivity, *endo/exo* ratio and π-face diastereoselectivity, are taken into account.[17,85] Up until the present moment, the majority of reported investigations deal with the stoichiometric use of covalently bound chiral control groups to dienophiles together with the use of Lewis acids as a means of effectively shielding one of the diastereotopic faces in the transition state complex. Applications of this kind have been the subject of numerous reviews.[85,89,96]

Studies on the control of the absolute topicity of the Diels-Alder reaction started in 1961,[106] but it was not until the 1980s that substantial progress was achieved. One of the first uses of an asymmetric Diels-Alder reaction in enantioselective synthesis was by Corey and Ensley.[107] In this reaction, the addition of

5-(methoxymethyl)cyclopentadiene (**91a**) to acrylic acid (**90a**) proceeded *endo* selectively and *anti* with respect to the diene substituent. Consequently, the relative configuration of the four new chiral centres in the adduct was determined and, of four possible diastereoisomers, one was formed selectively. But, as expected, the diene added at the same rate to the two enantiotopic dienophile π- faces, affording a 1:1 mixture of enantiomers.

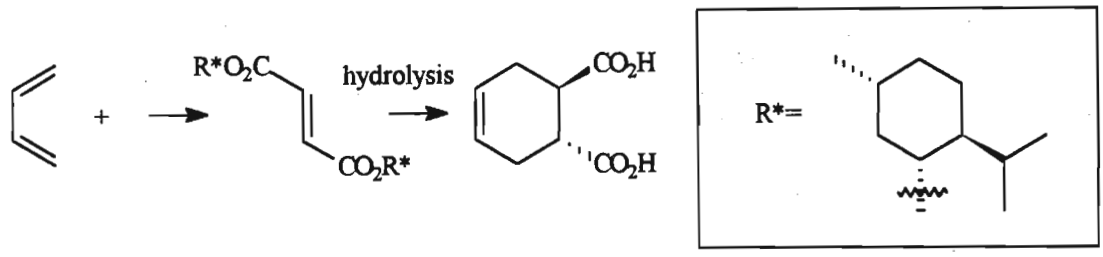


Scheme 20

Since only the (1*S*)-enantiomer is suitable for the synthesis of prostaglandins, exclusive diene addition from the C_α *re*-face was required. Attachment of an appropriate ester group R^2 to the dienophile (**90b**) caused steric shielding of the now diastereotopic C_α *si*-face thereby directing the $AlCl_3$-promoted addition of 5-(methoxymethyl)cyclopentadiene (**91b**) to the C_α *re*-face. As a result of the π-face

differentiation, the desired (1*S*)-enantiomer (**92**) was obtained in significant excess over the undesired (1*R*)-isomer (**93**). This compound was then converted to the ketone and the chiral control element, R^2, was removed to yield enantiomerically pure (**94**). The above example clearly demonstrates the importance of π-facial control and how this can be achieved by the use of a chiral controlling group.

Some of the earlier attempts at obtaining enantioselectivity in uncatalysed thermal Diels-Alder reactions based on the use of chiral auxiliaries showed poor results. The reaction by Walborsky *et al.*[108] of (-)-dimenthyl fumarate (**96**) with butadiene (**95**) followed by hydrolysis afforded the (*R,R*)-(-)-diacid (**97**) in only a 5.4% ee (Scheme 21a)



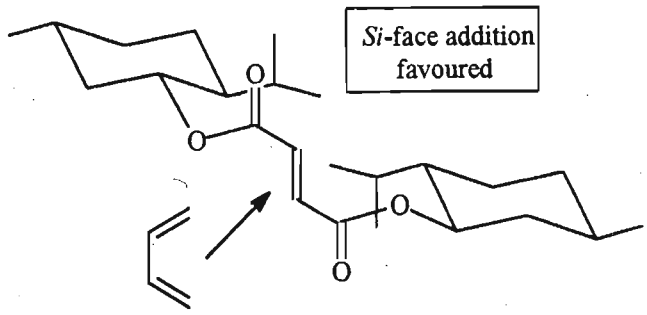
(**95**) (**96**) (**97**)

Scheme 21a

A dramatic increase in diastereoselectivity with the predominant formation of the alternative *S,S* diastereomer was observed with the use of a Lewis acid catalyst. The best result of 78% ee in this early study was obtained with titanium tetrachloride ($TiCl_4$) in toluene, but has subsequently been improved by Yamamoto *et al.*[109] to 90% ee with the use of diisobutylaluminium chloride (Bu^i_2AlCl).

These outcomes have been rationalised in terms of a transition state based on the *s-trans* conformer (Scheme 21b) in which the diene approaches the upper face of the dienophile away from the isopropyl groups in the menthol auxiliaries. The enhanced diastereoselectivity, then, is attributed to the greater conformational rigidity of the

complexed dienophile and to the lower reaction temperatures that are possible with Lewis acid catalysts.



Scheme 21b The [4+2] Cycloaddition between Butadiene and Dimenthyl fumarate.

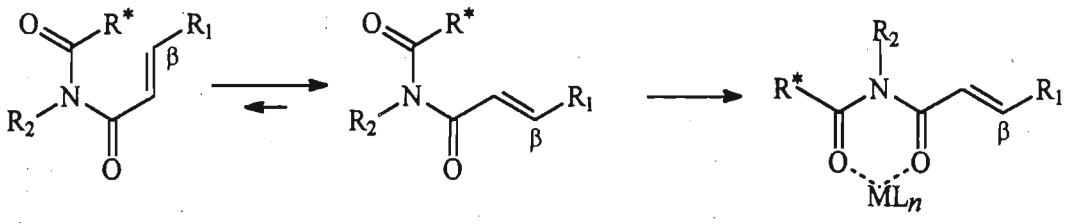
The above example demonstrates that, since the chiral controlling element is located externally to the ring being formed, it is necessary to select reaction conditions with a view to limiting conformational freedom in the transition states and that this can be effectively achieved with the use of Lewis acid catalysts. Metal chelation thus plays a crucial role in fixing the stereogenic centres and reaction sites in a well defined manner. It is also necessary, therefore, that the auxiliary possesses sites such as a conjugated C=O or C=N moiety, for coordination with a metal in order to achieve this control.

In line with these facts, the vast majority of work on asymmetric Diels-Alder reactions has been done on the addition of 1,3-dienes to α,β-alkenic carbonyl derivatives. Applications of this kind have been numerous and for this reason, the following examples will focus specifically on *N*-acyl-*N*-enoyl derivatives which have included work on two of the most important chiral auxiliaries in the Diels-Alder reaction.

1.4.5.1 Chelated *N*-Acyl-*N*-Enoyl Derivatives

The use of *N*-acyl-*N*-enoyl derivatives as chiral auxiliaries in Diels-Alder reactions has provided some of the most interesting and efficient as well as synthetically important examples of chiral induction reactions.

Chelated α,β-alkenic amide derivatives prefer a C=O/C_α=C_β *s-cis* arrangement (**99**) over (**98**) to avoid repulsions between C_β /COR* or C_β /R^2 (Scheme 22). This also holds for the chelated dienophiles (**100**) where rotation around the (C=O)-N of the dienophile and the (C=O)-N of the enoate bonds is further inhibited by the metal (ML_n).[89]

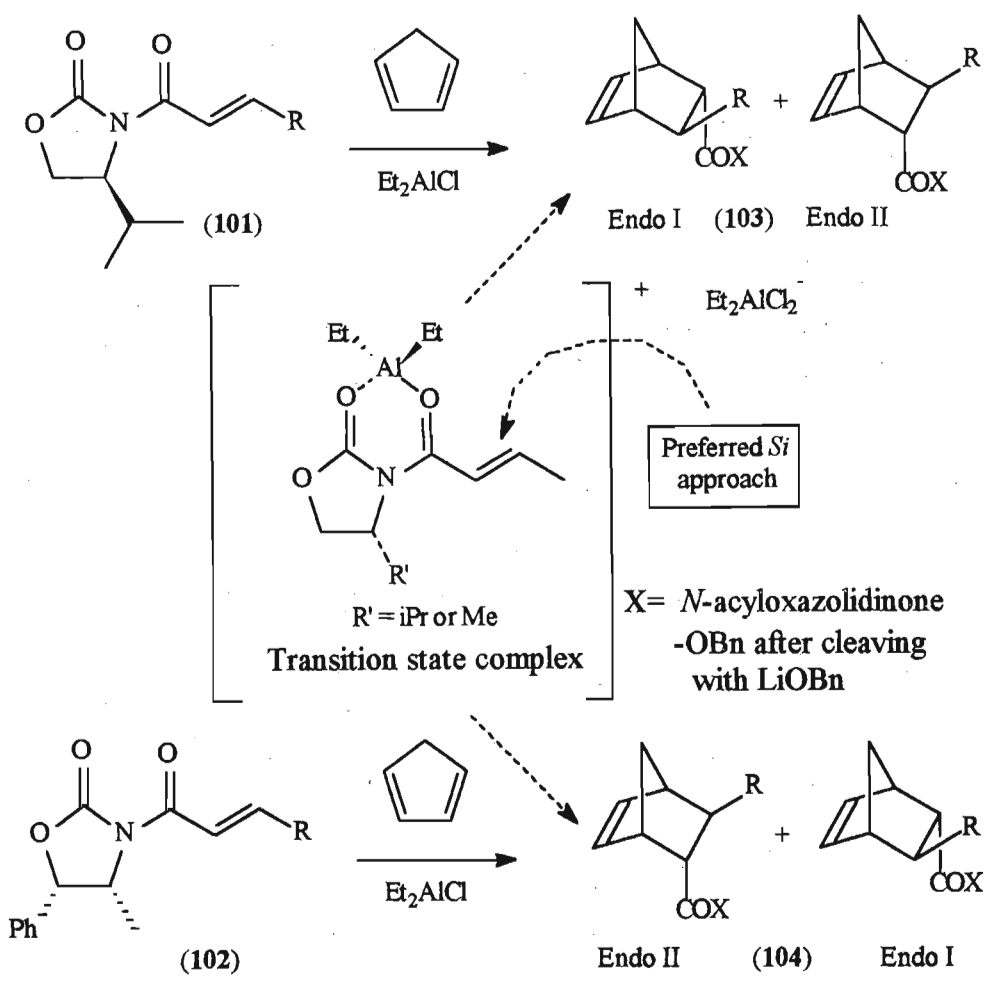


(**98**) *s-trans* (**99**) *s-cis* (**100**) *s-cis*

Scheme 22 Chelation in α,β-Alkenic Amides

1.4.5.2 *N*-Acyloxazolidinones

The use of chiral *N*-acyloxazolidinones in Diels-Alder cycloaddition reactions have been studied extensively by Evans *et al.* since 1984.[57,110,111] The scheme below outlines [4+2] cycloaddition reactions of oxazolidinones (**101**) and (**102**) with cyclopentadiene (Scheme 23).



Scheme 23

Table 1 Asymmetric Diels-Alder Additions of Cyclopentadiene to α,β-Unsaturated *N*-Acyloxazolidinones.

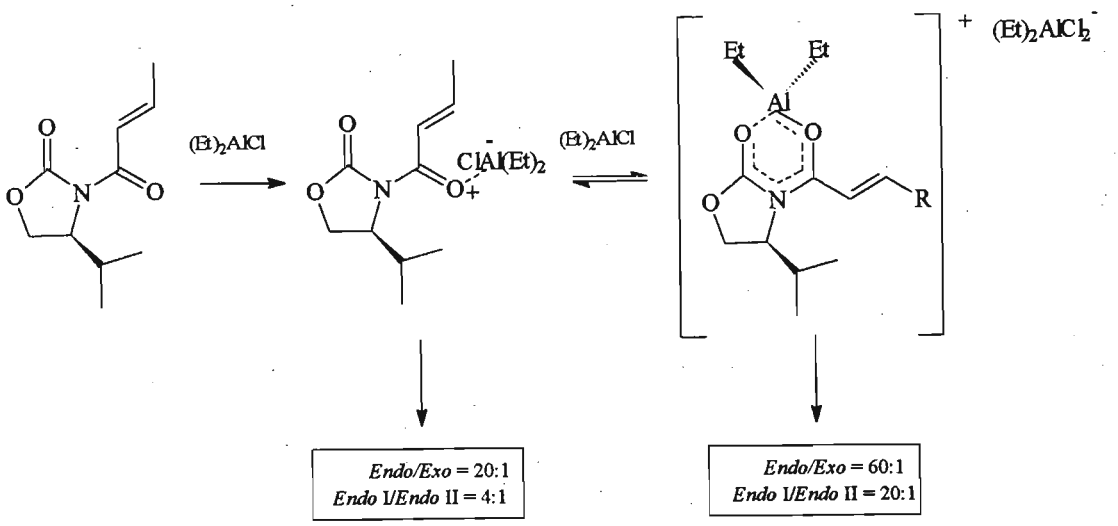
Entry	Dienophile	R	*Endo/Exo*	*Endo* I/*Endo* II	Yield (%)
1	**(101a)**	H	>100:1	93:7	81
2	**(102a)**	H	>100:1	5:95	82
3	**(101b)**	Me	48:1	95:5	82
4	**(102b)**	Me	60:1	2:98	88
5	**(101c)**	Ph	>50:1	93:7	83

Comparative studies by Evans and co-workers of several Lewis acids revealed the advantages of using Et_2AlCl, whereas $TiCl_4$ and $SnCl_4$ gave poor inductions. Thus the Et_2AlCl-induced (1.4 equivalent) additions of the oxazolidinone dienophile (**101**) and

(**102**) to cyclopentadiene was complete within 2 min at -100°C to yield norbornenes (*Endo* I and *Endo* II) (**103**) and (**104**) with 98-99% *endo*-selection in ratios of >93:<7 (entries 1,2). In this case the (*S*)- benzyl derivatives (**102**) displayed much higher diastereoselectivity than the isopropyl derivatives (**101**). Good stereoface selectivities were achieved on additions to (*E*)-C_β-substituted *N*-enoyloxazolidinones (**101b**) and (**102b**) at temperatures between -100 and 0°C (Table 1, entries 3,4). Additions to (*Z*)-*N*-crotonoyl or β-cinnamoyl (**101c**, entry 5) dienophiles were less useful due to (*Z/E*) equilibration or insufficient reactivity.

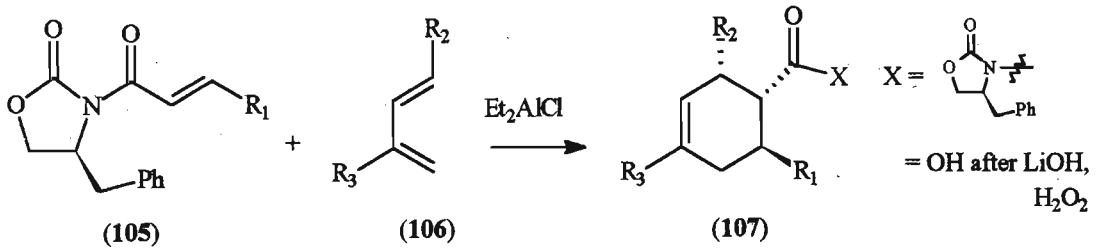
Inverse π-face topicity was displayed with similar efficacy by the norephedrine-derived dienophiles. After recrystallization (the dienophiles are highly crystalline) or chromatography the resulting major cycloadduct was obtained in 81-88% yield and >98% diastereomeric purity. Nondestructive cleavage of the oxazolidinone auxiliary from the adduct by transesterification, hydrolysis or reduction to afford esters, carboxylic acids or alcohols with concomitant non-destructive removal of the auxiliary. Sterically hindered addition products, *e.g.* (**101c**), were preferably saponified with LiOH/30% H_2O_2 in THF.

The influence exerted by Et_2AlCl on the Diels-Alder additions was attributed to bidentate chelation with the dienophile (Scheme 24) which then exhibits C=C/C=O *syn* planarity. The electron deficiency and the rigid structure of the transition state now accounts for the high reactivity and good π-face differentiation. From a systematic study on the stoichiometry of the reaction, it was deduced that the molar ratio of the Lewis acid had to exceed unity. These outcomes were rationalized in terms of the equilibria outlined in Scheme 24.



Scheme 24 Influence of Lewis Acid Stoichiometry on Stereoselectivity in a [4+2] Cycloaddition.

The exceptional reactivity of these dienophile-Lewis acid complexes allows reaction with even less reactive acyclic dienes (**106**) (Scheme 25).



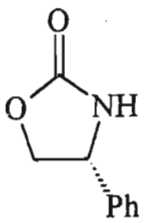
(105) **(106)** **(107)**

R_1 , R_2 = H , R_3 = Me
R_1 , R_3 = Me , R_2 = H
R_1 , R_3 = H , R_2 = Me

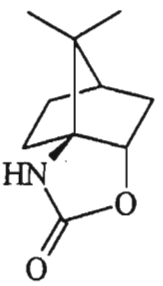
Scheme 25

Due to their excellent diastereocontrol and ease of purification of the products, chiral *N*-acyloxazolidinones have been used in many elegant total syntheses. These include the synthesis of the essential oil (+)-α-cuparenone,[112] a fragment of the streptogramin antibiotic madumycin II,[113] the antifungal lipopeptide Eschinocandin D[75] [114] and (+)-ionomycin.[115] The chiral oxazolidinone auxiliary is also useful in intramolecular reactions of 2,7,9-decatrienoyl- and 2,8,10-undecatrienoyl derivatives.[110]

Other useful oxazolidinones that have shown good diastereocontrol in Diels-Alder reactions include (**108**) and (**109**), derived from (S)-phenylalaninol[57] and ketopinic acid[116] respectively.



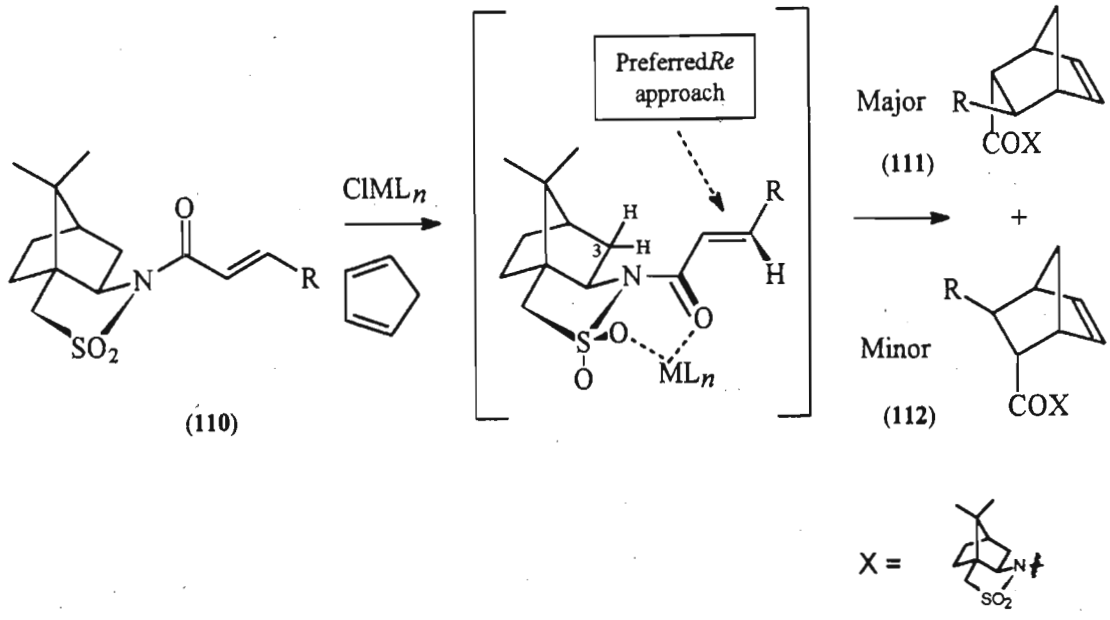
(**108**)



(**109**)

1.4.5.3 *N*-Acylbornane-10,2-sultams

Both bornane-10,2-sultam (**57**) and its antipode have been widely researched by Oppolzer *et al.* since 1984.[67-72,79,81-83,85,97] and are ranked among the most practical auxiliaries.[67,69,75,145] As already mentioned, the sultam auxiliary was initially developed in order to increase the dienophilicity of their *N*-enoyl derivatives to extend the scope of asymmetric Diels-Alder reactions.[81] The strongly dienophilic *N*-enoylbornane-10,2-sultams (**110**) are readily prepared by direct *N*-acylation with NaH and RCOCl or with Me_3Al and RCO_2Me or *via* phosphonates by means of a modified Wittig-Horner reaction. The observed reactivity and topological control by the Lewis acid are depicted below (Scheme 26).



Scheme 26

Table 2 Asymmetric Diels-Alder Additions of Cyclopentadiene to *N*-Enoylbornane-10,2-sultams.

Entry	R	Lewis acid (mol equiv.)	Temp (°C) (time, h)	*endo/exo* (C=O)	Ratio *endo* I/*endo* II	Yield (%)
1(**110a**)	H	$EtAlCl_2$(1.5)	-130 (6)	200:1	97.5 : 2.5	83
2(**110a**)	H	$TiCl_4$(0.5)	-130 (6)	25:1	97 : 3	-
3(**110b**)	Me	$TiCl_4$(0.5)	-78 (1)	100:1	96.5 : 3.5	83
4(**110b**)	Me	$EtAlCl_2$(1.5)	-78(18)	24:1	99 : 1	-

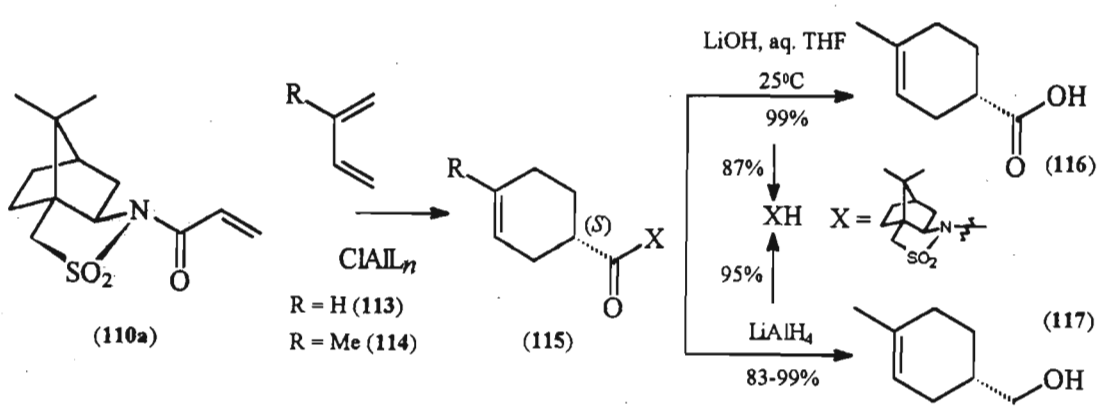
Most of all their *N*-acyl derivatives are stable and can be readily purified by recrystallization, directly analysed by ^{1}H NMR and/or GC to determine their stereochemical purity and are easily cleaved with $LiAlH_4$, LiOH, LiOOH, MeOMgI, *etc.* under mild conditions without loss of the induced chirality and with excellent recovery of the auxiliary.

In the presence of $TiCl_4$, $EtAlCl_2$, Et_2AlCl or Me_2AlCl, cyclopentadiene added smoothly to the acryloyl sultam (**110a**) at -130°C (Table 2, entries 1 and 2) and to the less reactive crotonyl sultam (**110b**) at -78°C (Table 2, entries 3 and 4). The adducts

(**111**) and (**112**) were formed with excellent *endo* as well as π-face selectivities and obtained pure and in good yields after recrystallization.

The remarkable $TiCl_4$- and $EtAlCl_2$-enhanced rate and π-face differentiation of [4+2] cycloadditions to *N*-enoylsultams was rationalized in terms of the transition state chelated complex (Scheme 26) involving the di-coordination of the Lewis acid to the carbonyl O-atom and the upper sulfonyl O-atom. Attack by dienes occurs from the C_α *si* π-face opposite to the C-3 methylene group. X-ray crystal structure analyses of non-coordinated and $TiCl_4$-chelated *N*-crotonylsultam show in both cases *s-cis* disposed C=O/C_α=C_β bonds, but an NSO_2/C=O *s-trans* arrangement in the absence of $TiCl_4$. In the $TiCl_4$ chelated transition state complex, the NSO_2 and C=O groups are locked into a rigid *s-cis* conformation (Scheme 26) where, compared with H_{exo} of C_3, the Cl atoms play only a minor role in blocking the C_α *si*-face.

$EtAlCl_2$- or Me_2AlCl-promoted Diels-Alder addition of butadiene (**113**) or isoprene (**114**) to *N*-enoylbornane-10,2-sultams (**110a**) also proceeded readily at -78 or -94°C to give, after recrystallization, ~100% pure (*S*)-cyclohexenes (**115**) (Scheme 27), (Table 3, entries 1,2 and 3).

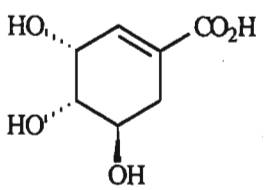


Scheme 27

Table 3 Asymmetric Diels-Alder Additions of Butadiene and Isoprene to *N*-Enoylbornane- 10,2-sultams.

Entry	Diene R	Lewis acid (mol equiv.)	Temp.(°C) (time, h)	Ratio *endo* I/*endo* II	Yield (%)
1	H	$EtAlCl_2$(1.5)	-78 (6)	98.5 : 1.5	81
2	Me	$EtAlCl_2$(1.5)	-94 (6)	97.2 : 2.8	64
3	H	Me_2AlCl(1.5)	-78 (44)	95 : 5	53-60

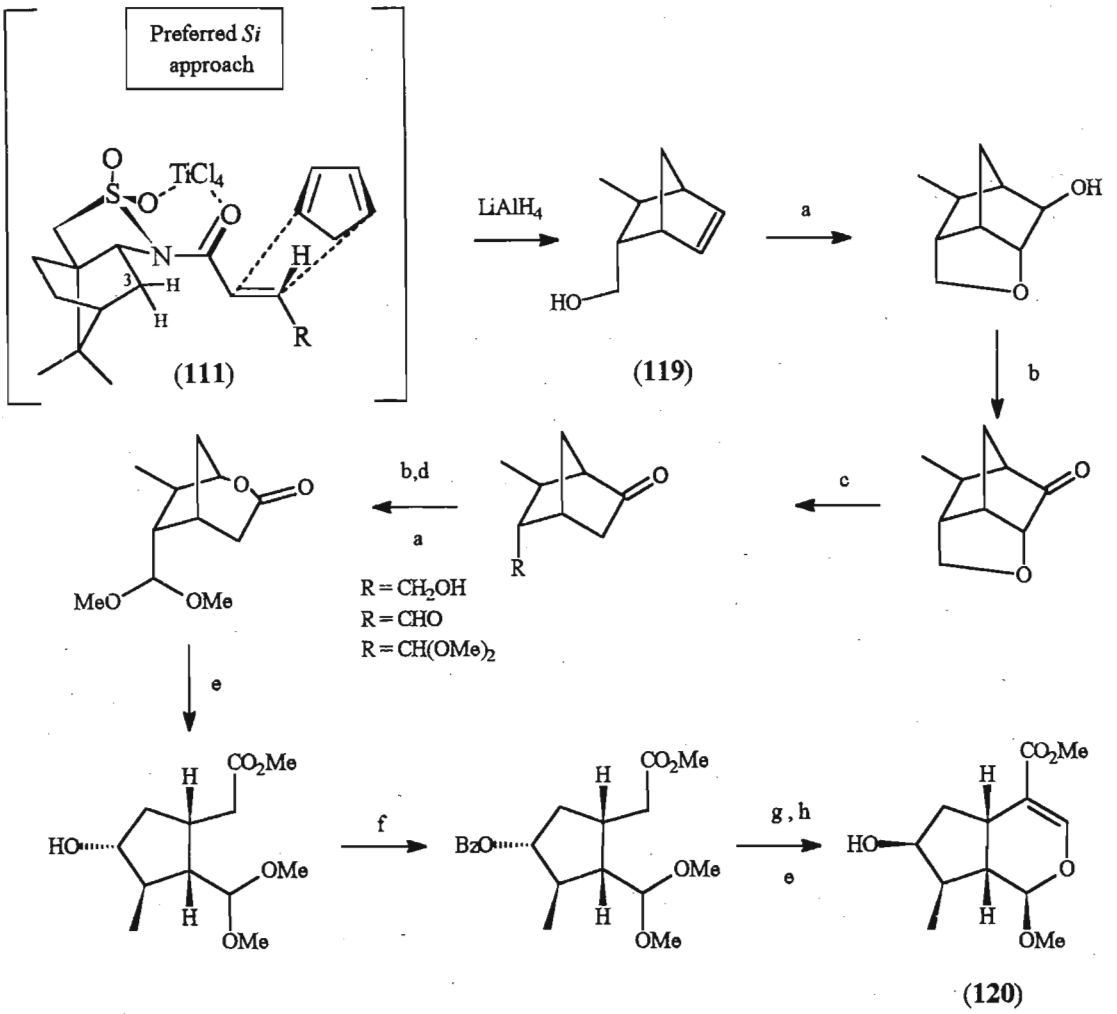
Reductive cleavage of the cycloadducts with $LiAlH_4$ gave the pure alcohols (**116**) by simple bulb-to-bulb distillation and the auxiliary was recovered with 89-95% yield after recrystallization. Alternatively, saponification of the adduct with LiOH afforded the acid (**117**) which is a potential precursor for a synthesis of (-)-shikimic acid (**118a**) without epimerization. Previous attempts at this precursor using conjugated α-hydroxy ketones was cumbersome due to the fact that the preparation of these chiral auxiliaries is laborious and, on oxidative removal, the auxiliary is destroyed.[117]



(118a)

The sense of asymmetric induction could easily be reversed by using the readily available antipodes of *N*-enoylbornane-10,2-sultam dienophiles. Of industrial importance, several of these sultam-controlled [4+2] cycloaddition reactions were smoothly carried out with 10g, 15g and 112g batches of dienophile.

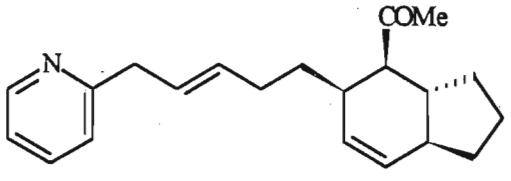
A natural synthesis application of this work involves the cyclopentadiene adduct (**111**) (Scheme 26).[69] Reduction of adduct (**111**) with $LiAlH_4$ yields the alcohol (**119**) which can be transformed into enantomerically pure (-)-1-*O*-methyl loganin aglucone (**120**) (Scheme 28).



a) mCPBA, CH_2Cl_2, -10°C to rt.; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C; c) Al-Hg, THF, EtOH, rt.; d) $MeOSiMe_3$, Me_3SiOTf, CH_2Cl_2, -78°C; e) NaOMe, MeOH, rt.;
f) DEAD, PhCOOH, Ph_3P, CH_2Cl_2,rt.; g) Kot.Bu, LICA, THF, -78°C; HCOOMe, -78°C to -40°C; h) $BF_3.OEt_2$, CH_2Cl_2, 0°C.

Scheme 28

The bornane-10,2-sultam auxiliaries were also successfully used in intramolecular Diels-Alder reactions[81] and in this way, the enantioselective total synthesis of the marine natural product (-)-pulo'upone (**188b**)[118] was carried out.



(-)-Pulo'upone (**188b**)

Apart from the Evans oxazolidinone[57] and the camphor sultam[82] asymmetric syntheses, few examples of highly enantioselective intramolecular Diels-Alder reactions exist.

The above examples of chiral auxiliaries in Diels-Alder reactions rank today as two of the most practical auxiliaries. They both provide a wide range of Diels-Alder adducts in high chemical yields with high *endo/exo* as well as π-facial selectivity, both antipodes are readily available, they are capable of efficient attachment to the dienophile with nondestructive removal from the adduct with complete retention of configuration, they allow for reliable analysis of the reaction mixture by NMR spectroscopy, GC or HPLC and they enable facile purification of the major cycloadduct due to the crystallinity they impose on intermediates and cycloaddition products.

The aim of this introduction was to provide an overview of stereoselective synthesis and to include relevant aspects of the stoichiometric use of chiral auxiliaries obtained from natural sources as pertaining to this thesis.

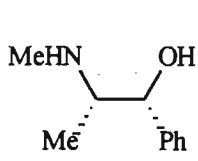
2. DISCUSSION

2.1 INTRODUCTION

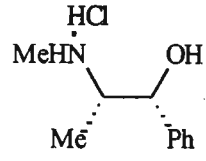
Research groups around the world are actively involved in developing methods of obtaining optically pure chiral compounds. A measure of the organic chemist's commitment to this end is the growing number of reviews and specialist conferences and new journals dedicated to this topic.

One of the most reliable strategies for achieving an enantioselective synthesis is the temporary incorporation of a chiral auxiliary into the substrate. The chiral auxiliary is attached to the reactive centre of an achiral molecule by way of a covalent bond in order to carry out the relevant transformation. The chiral pool is still an attractive source of enantiomerically pure chiral auxiliaries as natural products are usually readily available and a more economical source of these agents.

An often overlooked source of chirality for asymmetric synthesis is the alkaloid ephedrine (**121**) which is readily available as its hydrochloride salt (**122**).

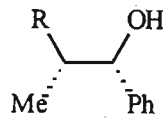


(**121**)



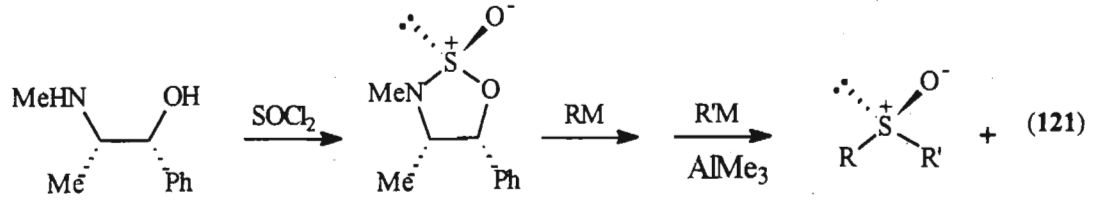
(**122**)

Acyclic ephedrine derivatives (**123**)-(**125**), as mentioned in Chapter 1, are used mostly as ligands for organometallic chiral reagents or catalysts.



$R = NHSO_2R$ (**123**)
$R = NMe_2$ (**124**)
$R = MeN(CH_2)NMe_2$ (**125**)

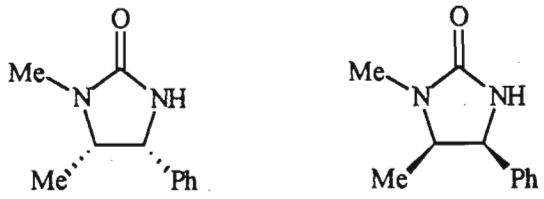
In recent years, discoveries have been made of cyclic ephedrine derivatives, the auxiliaries of greatest interest being those which are covalently bound to the starting material. A report by Benson *et al.*[119] demonstrated the chirality transfer ability of the ephedrine moiety (**121**). They were able to synthesise chiral sulfoxides with ee's exceeding 99% (Scheme 29).



(**121**) (**126**) (**127**)

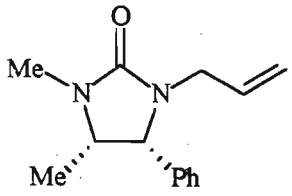
Scheme 29

Additional examples that have recently found use in asymmetric synthesis are the imidazolidin-2-ones (**128**) and (**129**). They are synthesised from (-) and (+)-ephedrine hydrochloride (**122**), respectively.[120]

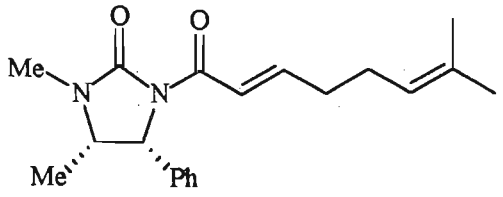


(**128**) (**129**)

Helmchen and co-workers[121] found application for (**128**) in diastereoselective homoaldol additions of the carbanion of the *N*-allyl derivative (**130**) to aldehydes and ketones to afford homochiral γ-lactones. In recent years, diastereoselective alkylations[122,123,124] of *N*-acylimidazolidin-2-ones have also been achieved. The facile and efficient synthesis of (+)-citronellic acid described by Stephan *et al.*[125,126] has, as its crucial step, the diastereoselective conjugate addition of a methyl cuprate to the *N*-enoyl derivative (**131**).



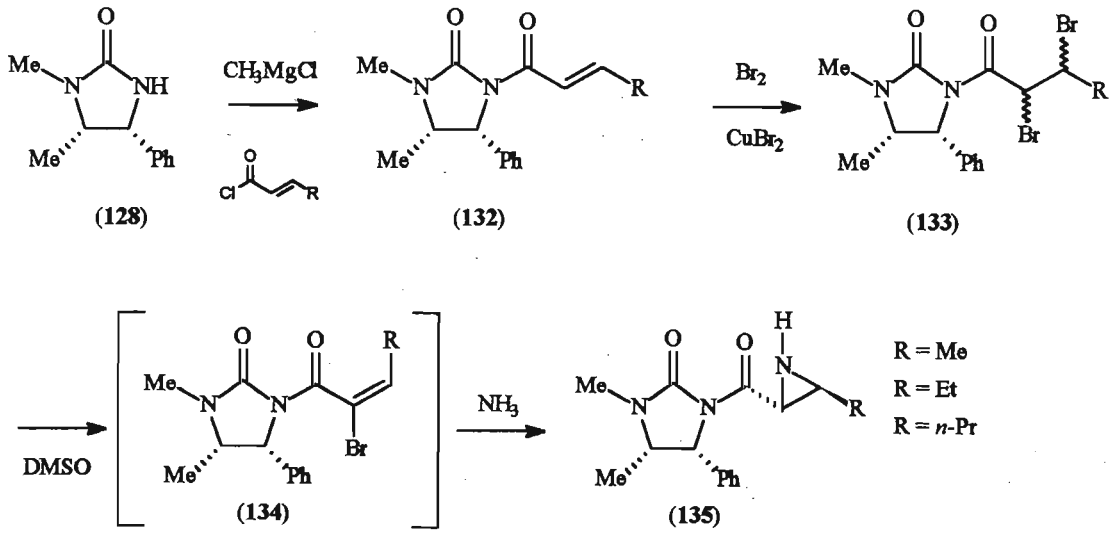
(130)



(131)

In each of the above examples, the imidazolidin-2-one auxiliaries (**128**) and (**129**) exhibited excellent levels of asymmetric induction.

Very recent examples include work done by Cardillo and co-workers[127] who report on the asymmetric 1,4-addition of nucleophiles to chiral α,β-unsaturated carbonyl compounds controlled by means of the *N*-acylimidazolidinone chiral auxiliary (**128**). On the basis of this work, they attempted the Gabriel-Cromwell addition of ammonia to chiral α,β-unsaturated derivatives (**132**) to synthesise chiral aziridine-2-carboxylate derivatives (**135**) (Scheme 30).



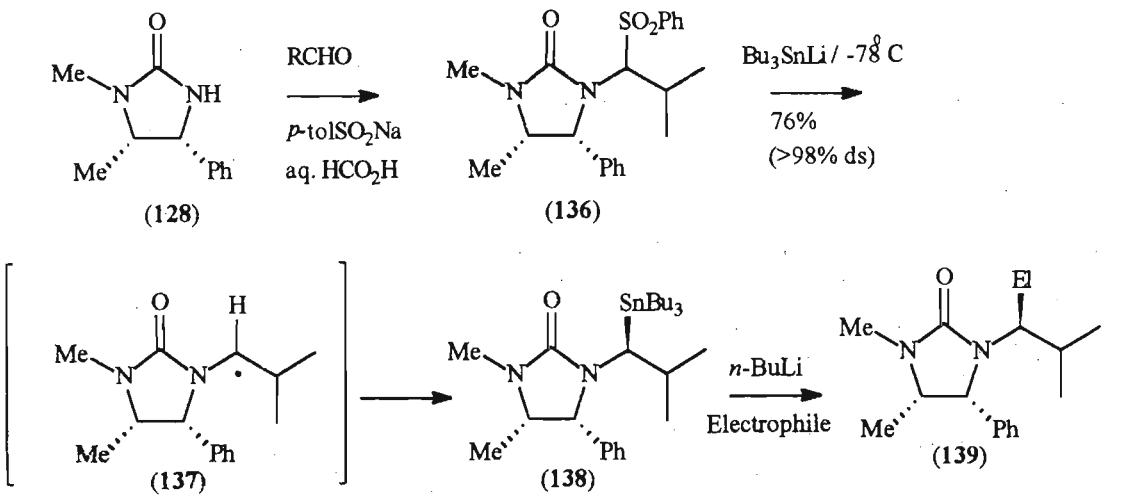
Scheme 30

Previous attempts at synthesising chiral aziridine-2-carboxylate derivatives were only successful with C-3 unsubstituted α,β-unsaturated derivatives (**132**), where R = H, using as chiral auxiliary Oppolzer's camphor-derived sultam. Unfortunately, the

reaction resulted in a 1:1 diastereomeric mixture when applied to the preparation of 3-methyl aziridines (**135**), where R = Me. Cardillo and co-workers found that the reaction proceeded at room temperature in aprotic DMSO affording the optically active 3-substituted *trans* aziridines (**135**) in high yield and good diastereoselectivity. The origin of the diastereoselectivity was attributed to the favourable conformation of the chelate enolate in the transition state with the imidazolidinone auxiliary. Treatment of the α,β-unsaturated derivatives (**132**) with bromine in the presence of $CuBr_2$ yields a mixture of two diastereomeric dibromo compounds (**133**), both of which are transformed into the (*E*)-α,β-unsaturated α-bromo intermediate (**134**) (Scheme 30).

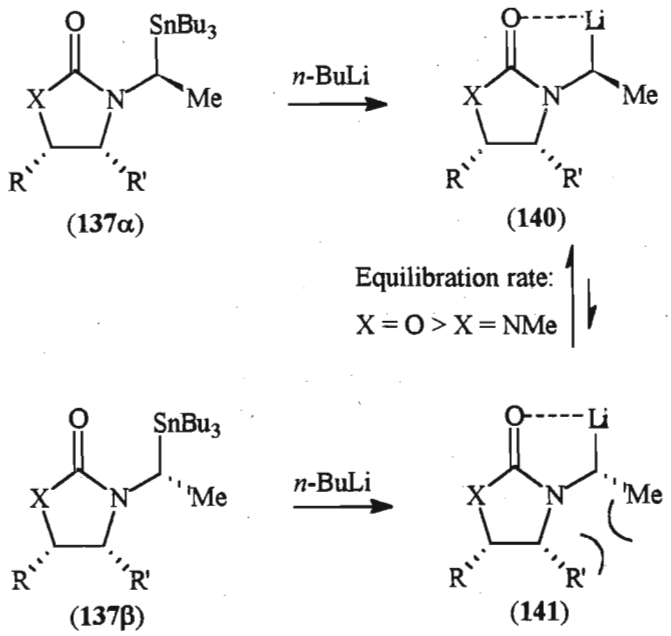
The non-destructive removal of the chiral auxiliary with lithium benzyloxide yields enantiomerically pure benzyl aziridine-2-carboxylates and, *via* a few simple transformations, leads to the stereocontrolled synthesis of β-hydroxy α-amino acids.

N-acylimidazolidinones have also been used to achieve high levels of absolute stereocontrol in radical reactions. Pearson *et al.*[128] worked on the synthesis of non-racemic, nitrogen-substituted organolithium compounds. They achieved excellent results in transmetallation reactions using the chiral imidazolidinone auxiliary (**128**) (Scheme 31). The condensation of the chiral imidazolidinone (**128**) with sodium *p*-toluenesulfinate, an aldehyde and formic acid produces a single diastereomeric sulfone (**136**). Displacement of the sulfone with tributylstannyllithium gives the *N*-[(1-tri-*n*-butylstannyl)alkyl]-imidazolidinone (**138**) as a single isomer *via* the radical intermediate (**137**). The preferred conformation of the radical intermediate is the one in which steric interactions between the isopropyl and the carbonyl group are minimised.



Scheme 31

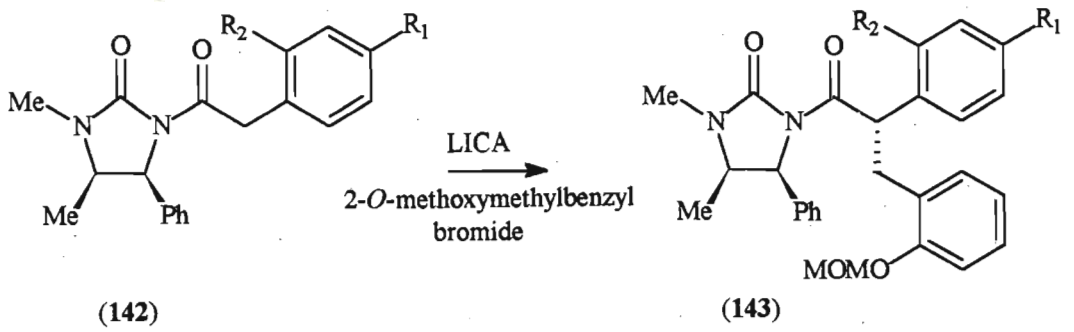
Transmetallation of branched chiral stannanes such as (**138**) with *n*-butyllithium at -78°C in THF and quenching with a variety of electrophiles occurs with complete retention of configuration (**139**) to produce optically pure derivatives of β-amino alcohols and α-amino acids as shown in Scheme 31. An interesting feature of this reaction is that, if the opposite isomer (**137**β) to that of the radical reaction (**137**α) is obtained, the oxazolidinone and the imidazolidinone auxiliaries produce products in the *n*-BuLi and electrophile reaction resulting from opposite organolithium diastereomers (**140**) and (**141**), respectively (Scheme 32). This was predicted to be due to the varying degrees of epimerisation that take place with the organolithium species.



Scheme 32

Due to the poorer lithium-ligating ability of the carbamate carbonyl oxygen of the oxazolidinone versus the urea carbonyl oxygen of the imidazolidinone, the 'looser' chelate of the oxazolidinone would be expected to allow for easy conversion to the more stable organolithium diastereomer whereas slow epimerisation of the imidazolidinone results in reactions taking place with the more sterically hindered diastereomer.

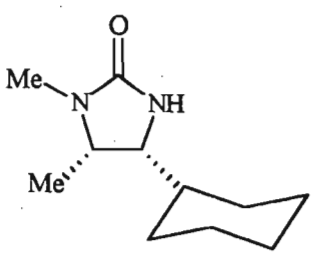
Ferreira and co-workers,[129] in their attempt at introducing chirality into the synthesis of isoflavanoids for the first time, opted for a protocol of stereoselective α-benzylation of phenylacetic acid derivatives using Evans' oxazolidinone as the chiral auxiliary followed by cyclization to establish the isoflavan framework. Low yields were attributed to considerable ketene formation in the deprotonation step, and the auxiliary was thus changed to the imidazolidin-2-one with poorer nucleofugic properties relative to the oxazolidinones. The *N*-acyl imidazolidin-2-ones (**142**) could accordingly be alkylated in excellent yields with only one diastereoisomer (**143**) detectable by NMR spectroscopy (Scheme 33).



(142) (143)

Scheme 33

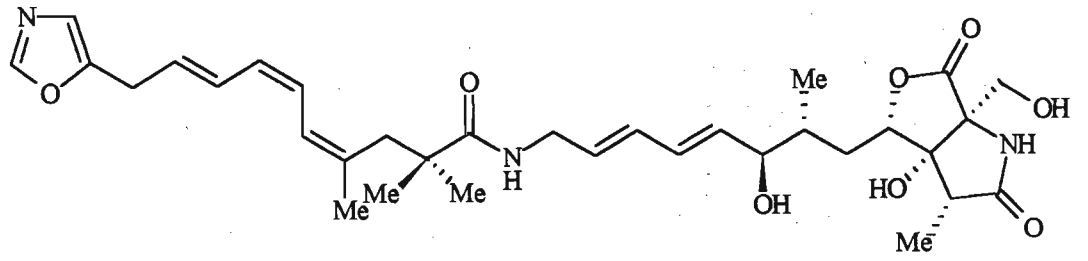
Drewes *et al.*[130,131] have reported on the use of *N*-acylimidazolidinones in aldol reactions of boron enolates of the *N*-propionyl derivative of **(128)** with various aldehydes. Aromatic aldehydes reacted in a diastereoselective *syn* manner, while aliphatic aldehydes exhibited poor diastereoselectivity. This was mainly ascribed to the shortcomings of the phenyl substituent as a steric control element. Work carried out by Masamune *et al.*[132] revealed a precedent for chiral enolates containing a cyclohexyl substituent to show a vast improvement in diastereoselection over analogous chiral enolates containing a phenyl ring. For this reason, the *N*-acylimidazolidinone phenyl ring was successfully hydrogenated to the cyclohexyl derivative **(144)** to improve the the auxiliary's ability to transfer chirality and thereby extending the generality of the auxiliary.



(144)

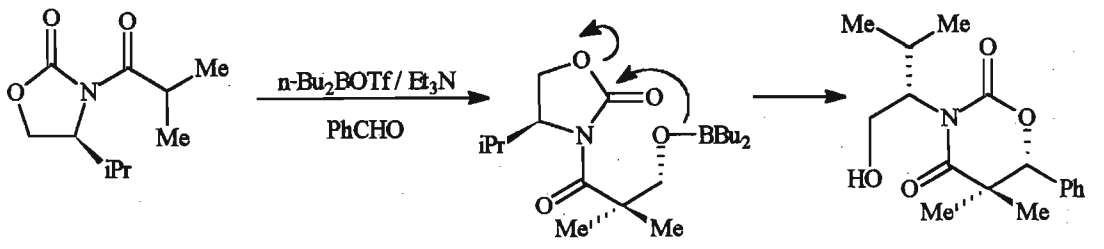
The boron enolates of *N*-propionyl and *N*-butyryl derivatives underwent diastereoselective aldol reactions showing enhanced diastereoselectivity with both aromatic and aliphatic aldehydes. Both derivatives of **(128)** and **(144)** were also successfully diastereoselectively alkylated and acylated.

An additional feature of their findings was related to the work of Kende *et al.*[133] who attempted a synthesis of the novel polyene lactam-lactone antibiotic neooxazolomycin (**145**) using the Evans oxazolidinone methodology.



(**145**)

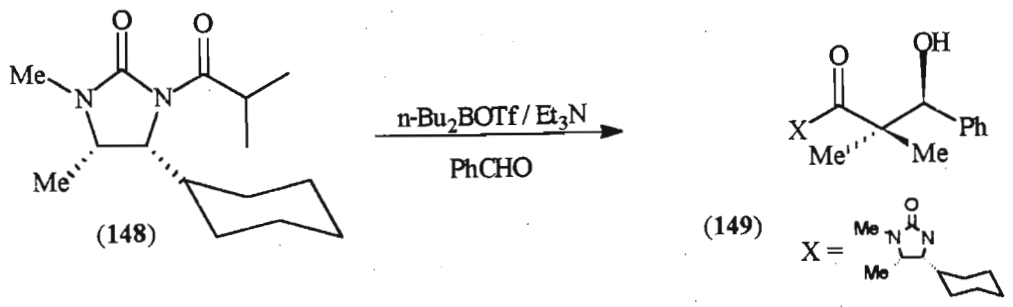
The asymmetric synthesis required a method of incorporating the α,α-disubstituted β-hydroxycarbonyl moiety *via* a diastereoselective aldol reaction. The oxazolidinone (**146**) was found to be subject to nucleophilic ring opening and afforded the corresponding oxazinedione (**147**) (Scheme 34).



(**146**) (**147**)

Scheme 34

Due to decreased activation of the imidazolidinone carbonyl by back donation of the *N*-Me lone pair, this auxiliary (**148**) resisted similar nucleophilic attack and the normal aldol reaction ensued to yield product (**149**) with high diastereoselectivities exceeding 99% and yields of approximately 80% (Scheme 35).



Scheme 35

With the above information available from the literature on the structure and reactivity of the *N*-acylimidazolidin-2-one auxiliary, together with the fact that it displayed numerous features favourable of efficient chiral auxiliaries, it was decided to extend the scope of this auxiliary and its cyclohexyl derivative to include the Diels-Alder cycloaddition reaction. A literature search revealed that there had been no prior attempts in this field of work.

It was recognised that considerable structural homology exists between the enolate auxiliaries in aldol and alkylation reactions and potential chiral dienophiles. Due to structural features of *N*-acylimidazolidin-2-ones, the presence of an enolate carbonyl and the urea carbonyl would allow for bidentate chelation with Lewis acid catalysts.

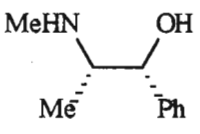
2.1.1 Aim of this Investigation

The aim of this thesis is to report on the efficiency of *N*- acylimidazolidin-2-ones as chiral dienophiles in the Diels-Alder reaction with cyclopentadiene. The sense of stereoselection in the major products was confirmed and thus the mechanism of face selectivity in the transition state was determined. A range of dienophiles was prepared and less reactive dienophiles were employed to determine the scope of these reactions. The use of a base as a catalyst in the Diels-Alder reactions was also attempted. The ratios of products of the Diels-Alder reactions were determined by H^1 NMR spectroscopy and GC/MS after having obtained spectra of the four isomers by other chemical transformation methods. Products were also converted to the known benzyl esters in order to be able to compare stereoselectivities with literature results. In order

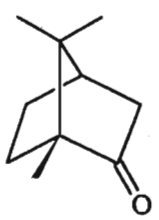
to be able to make practical comparisons and to gain practical experience, Oppolzer's camphor-derived bornane-10,2-sultam auxiliary was synthesised, and methodology and reactivity were compared with those obtained with the imidazolidinone auxiliary where applicable.

2.1.2 Chiral Natural Products used in this Investigation

The natural products, ephedrine (**121**) and camphor (**48**), which possess innate chirality, were used in this investigation. Ephedrine, existing naturally as the (-)-ephedrine enantiomer, is an alkaloid which constitutes 1% of the stems and leaves of *Ephedra equisetina* Bunge,[134] a plant indigenous to China and India. Camphor occurs naturally as the (+)-camphor form. It is a terpene ketone which is extracted from the prolific camphor tree, *Cinnamomum camphora* by steam distillation.[135] Both ephedrine and camphor, being naturally sourced compounds, are thus a cheap and renewable resource. Both their enantiomers, norephedrine and (-)-camphor are also cheaply and readily available commercially.



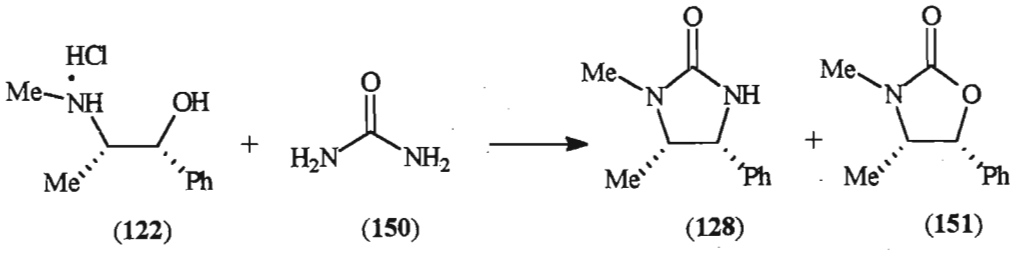
(**121**)



(**48**)

2.2 The Synthesis of (4R,5S)-1,5-Dimethyl-4-phenylimidazolidin-2-one

The chiral imidazolidin-2-one (**128**) was synthesised according to the method published by Close[120] in which (-)-ephedrine hydrochloride (**122**) is fused with urea (**150**) (Scheme 36). Both starting materials are inexpensive and readily available.



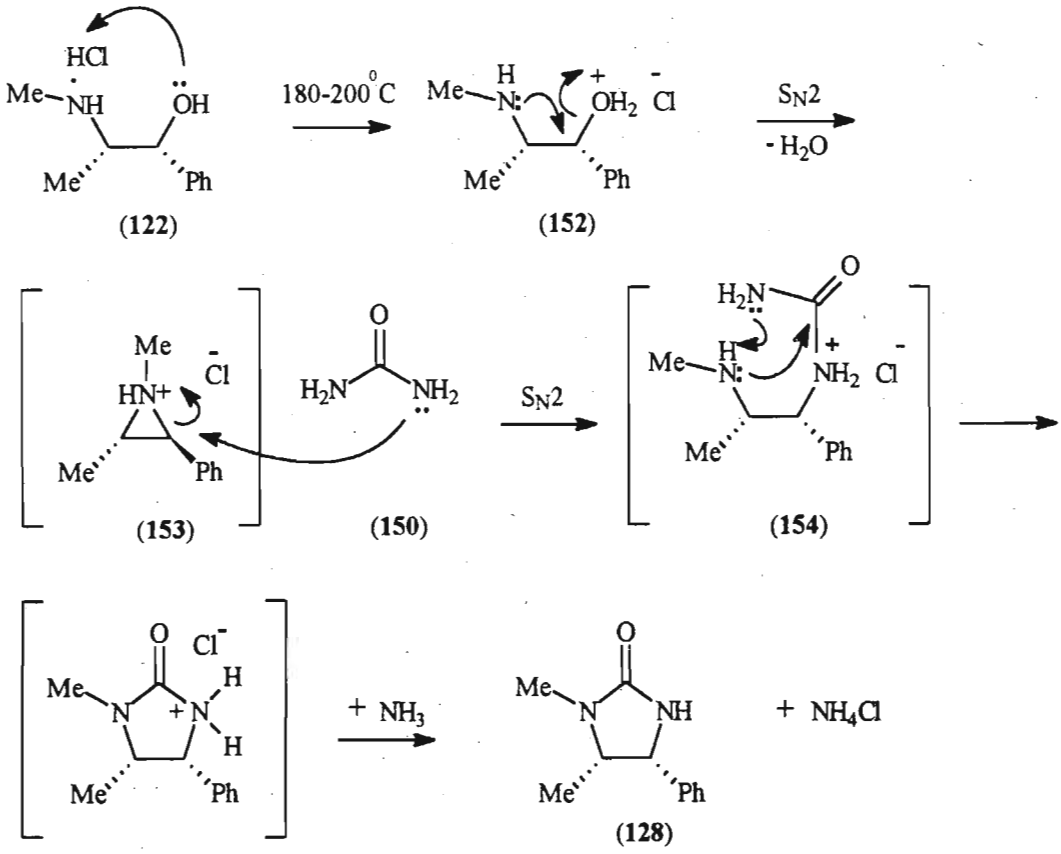
(122) (150) (128) (151)

Scheme 36

The yield of **(128)** reported by Close is relatively low, mainly due to the competing condensation process which affords the oxazolidin-2-one **(151)**. An attempt was made to improve the yield of **(128)** by using an overhead mechanical stirrer to increase the efficiency of stirring. In this way, moderate yields of approximately 60% were obtained.

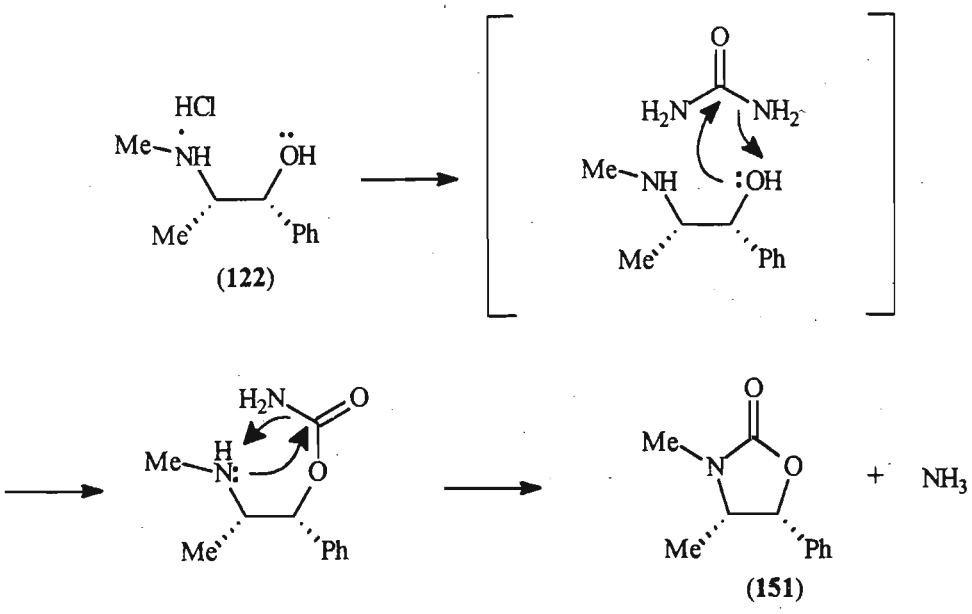
Close concluded that the product of the fusion reaction is the 4,5-*trans* configuration. Helmchen and co-workers[121] established, though, that the product was the 4,5-*cis* configuration from an X-ray crystal structure of the homoaldol product. Since they did not offer an explanatory mechanism, Drewes *et al.*[137] reported that the likely mechanism proceeds *via* a double inversion pathway, commonly referred to as the neighbouring group mechanism which involves two S_N2 steps.

The first step of the proposed mechanism (Scheme 37) involves protonation of the hydroxyl group of **(122)**. The first S_N2 step involves the attack of the nitrogen lone pair (neighbouring group) at the benzylic carbon **(152)** to form an intermediate aziridine salt **(153)**. This is followed by regioselective attack of the urea **(150)** nitrogen lone pair at the more reactive benzylic carbon. Subsequent ring closure **(154)** and the loss of ammonia yields the desired *N*-acylimidazolidin-2-one **(128)**. The product readily crystallises from the oxazolidin-2-one **(151)** impurity.



Scheme 37

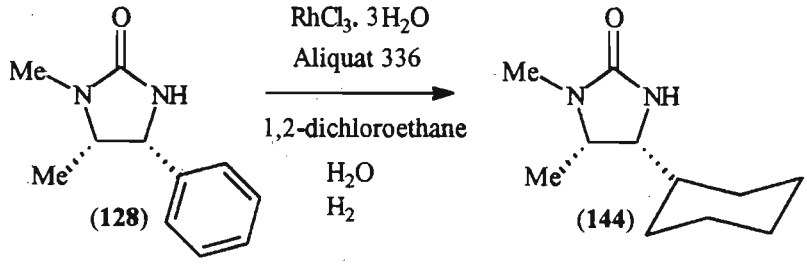
An explanation for the competing oxazolidinon-2-one formation is illustrated in Scheme 38. In this mechanism, nucleophilic attack by the ephedrine hydroxyl (**122**) and amine lone pairs at the urea carbonyl lead to the undesired oxazolidin-2-one (**151**) (Scheme 38).



Scheme 38

2.3 The Synthesis of (4R,5S)-4-Cyclohexyl-1,5-dimethylimidazolidin-2-one

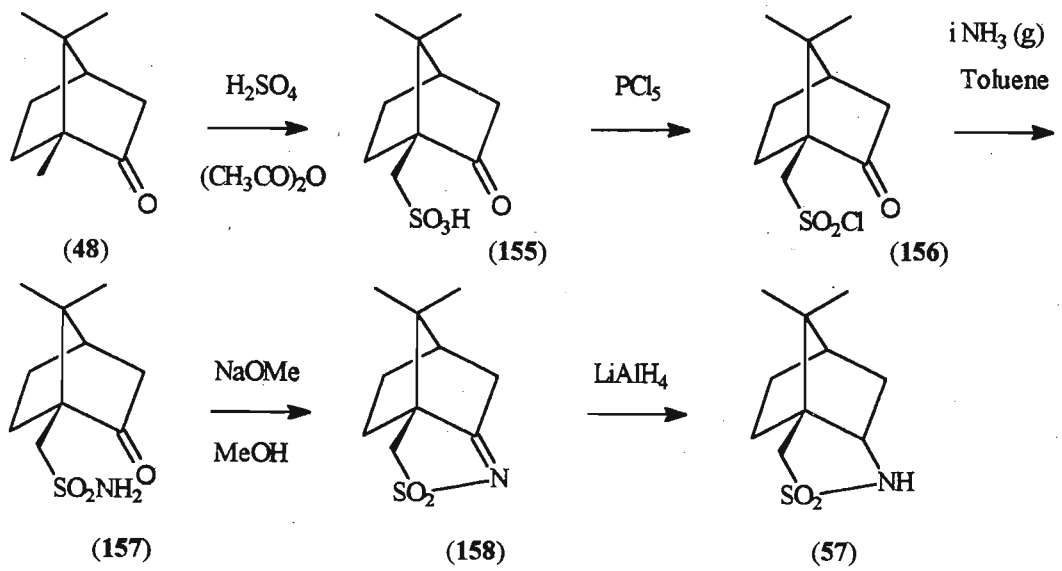
The hydrogenation reaction to convert the phenyl imidazolidin-2-one auxiliary to the cyclohexyl derivative was carried out according to the method of Blum *et al.*[138] and proved to be efficient and reproducible with yields exceeding 95%. The method is carried out under 5atms of hydrogen pressure (Scheme 39).



Scheme 39

2.4 The Synthesis of Bornane-10,2-sultam

The synthesis of the Oppolzer camphor derived auxiliary, bornane-10,2-sultam (**57**), is well documented in the literature.[69] The (+)-camphor sulfonic acid (**155**) was commercially available and four steps were required to obtain the desired product. The route followed is outlined in the scheme below (Scheme 40). The scheme also includes the step that would be required if the starting material available is the naturally occurring R-(+)-camphor (**48**). The reaction procedures were fairly straight forward. The extent of reaction for the ring closure to form the imine (**158**) was monitored by IR spectroscopy and the disappearance of the carbonyl peak indicated the completion of the reaction. The two methyl substituents of the borneol were also used to monitor the extent of the reaction since these groups of (**157**) and (**158**) were easily discernible by NMR spectroscopy.



(**48**) (**155**) (**156**)

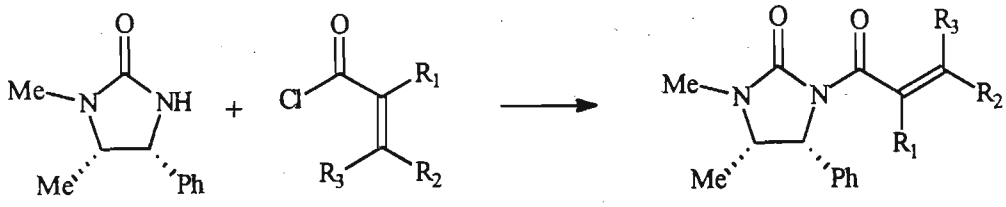
(**157**) (**158**) (**57**)

Scheme 40

From Schemes 37 and 40 outlining the synthesis of the two auxiliaries, it is clearly evident that the imidazolidin-2-one auxiliary (**128**) is more readily derived from its starting materials.

2.5 *N*-Acylation of (4R,5S)-1,5-Dimethyl-4-phenylimidazolidin-2-one

Difficulties were encountered during the *N*-functionalisation of the imidazolidin-2-one auxiliaries with various α,β-unsaturated acyl chlorides according to published procedures resulting in low yields of consistently less than 50% in all cases. (Scheme 41).



(128) **(159)** **(160)- (164)**

Scheme 41

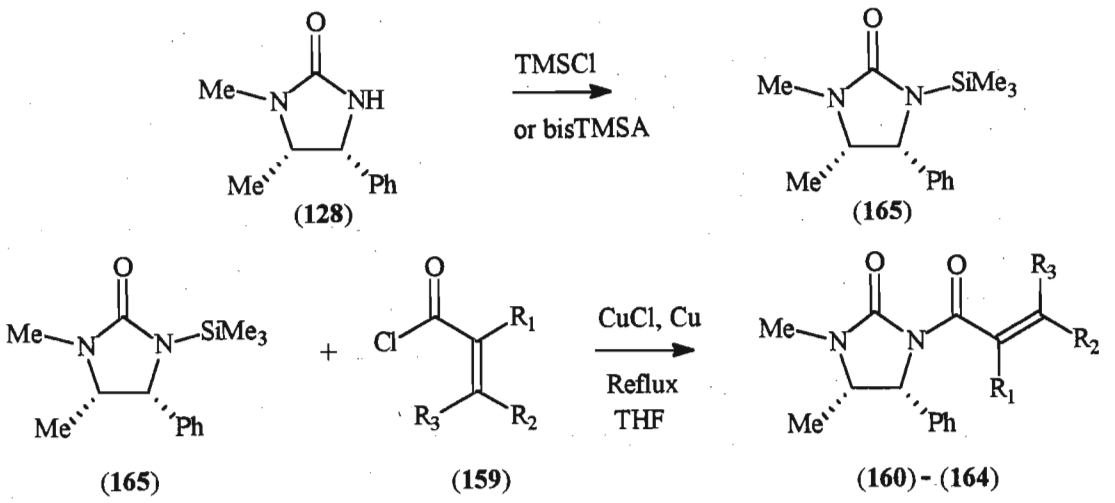
These included the use of BuLi,[111] NaH,[69,81] dimethylaminopyridine (DMAP) with Et_3N and CuCl,[139] as well as dimethylaniline (DMA)[125] as base catalysts. Problems encountered included long reaction times, polymerisation of the acyl chlorides themselves and difficulty experienced during work-up procedures.

Table 4. Reaction Conditions and Yields of attempted *N*-Acylation Reactions with Acryloyl Chloride (**159**) where R_1, R_2, R_3 = H..

Entry	Reaction conditions	Yield [%]
1	BuLi (1equiv.), THF, 0°C, 3 h.	68
2	NaH, toluene, r.t., 24 h	43
3	Et_3N (2 equiv.), toluene, rfx, 2.5 h	36
4	DMAP, Et_3N, Cu and CuCl, CH_2Cl_2, r.t., 3 h.	20
5	DMA, CH_2Cl_2, rfx, 7 h.	54

In an attempt to find an alternative route, the basicity of the imidazolidin-2-one was decreased by transforming the amine to the trimethylsilyl derivative (**165**) *via* two different methods. The first was with the use of trimethylsilyl chloride (TMSCl)[140] and the second with the use of *N,O*-bis(trimethylsilyl)acetamide (bisTMSA)[129] to effect the transformation. These TMS-derivatives were acylated in greatly improved

yields (Scheme 42), (Table 5) compared to those obtained by previous methods for *N*-acylation of the auxiliary (Table 4).



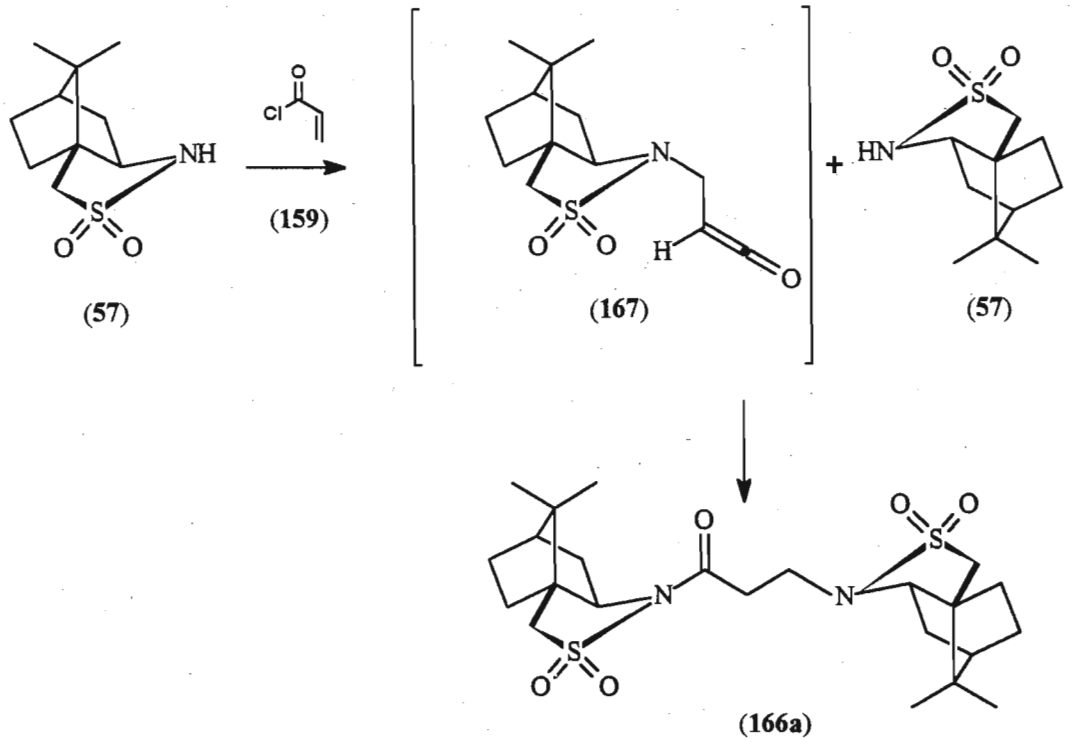
Scheme 42

Table 5. Yields of Dienophiles obtained on *N*-Acylation of Imidazolidin-2-one *via* the TMS Intermediate derived from TMSCl or bisTMSA.

Acid chloride(159)	TMSCl Yield[%]	bisTMSA Yield[%]
R_1,R_2,R_3 = H	70	40
R_1,R_3 = H, R_2=Me	80	60

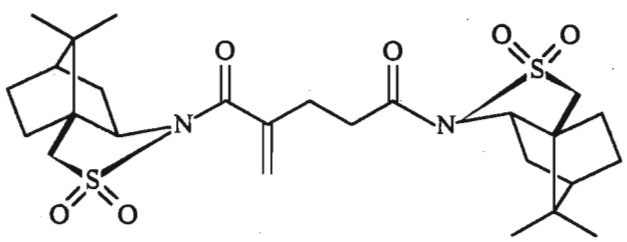
A more efficient method was still required to improve on the yields of the acylation reactions obtained thus far. In addition to the problems mentioned above, it has been reported that in the *N*-acryloylation of the bornane-10,2-sultam (**57**), a major by-product of the reaction was a crystalline 'double' adduct incorporating two molecules of the auxiliary. The product of this reaction (**166**) was isolated and identified to be the result of a conjugate addition reaction. Kocieński *et al.*[140] showed that this was not the result of conjugate addition of the desired product with another molecule of auxiliary by deliberately attempting to prepare the 'double' adduct. They found that no reaction took place when reacting the *N*-acryloylated product with the starting sultam auxiliary. Instead, they proposed that the first step that takes place is the conjugate addition-elimination reaction of (**57**) with acryloyl chloride (**159**) resulting in the formation of

the ketene (**167**) which then rapidly reacts with a second molecule of the auxiliary to produce the observed product (**166**) as outlined in Scheme 43.



Scheme 43

A 'double' adduct was also encountered in this work during the *N*-acryloylation of the bornane-10,2-sultam (**57**). The compound was isolated, characterised and a crystal structure was solved by crystallographic means[141] (Figure 3). The results confirmed the formation of the unusual product (**166b**) and provides another explanation for the consistently low yields obtained in the acylation reactions.



(**166b**)

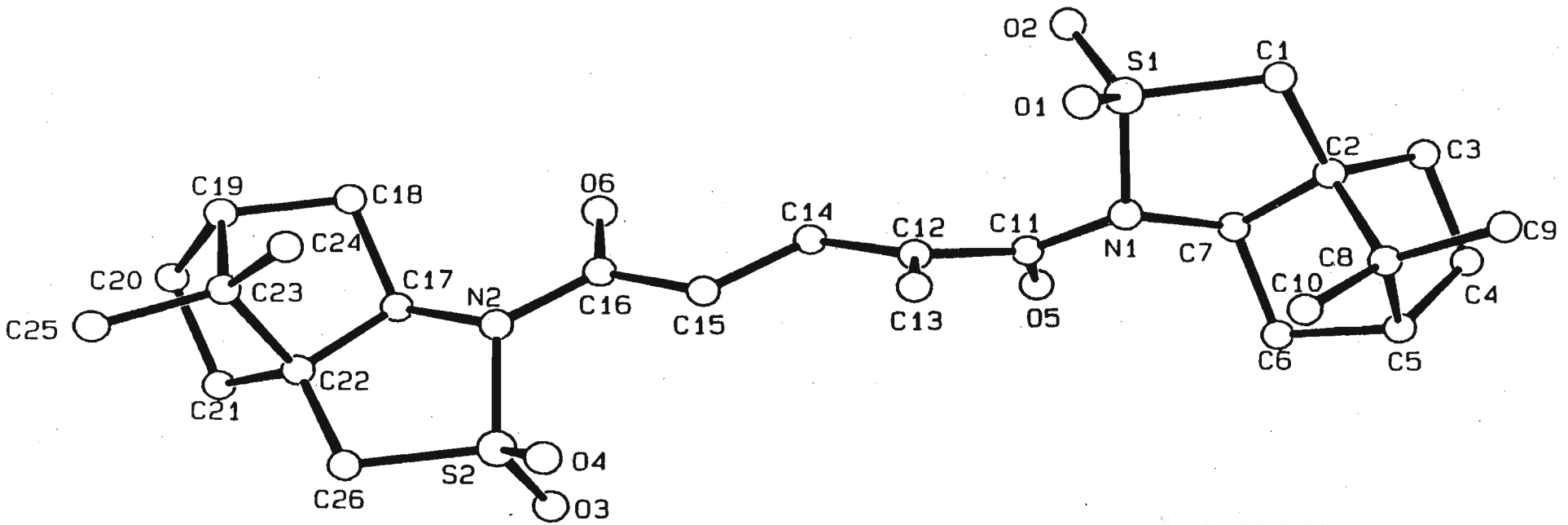
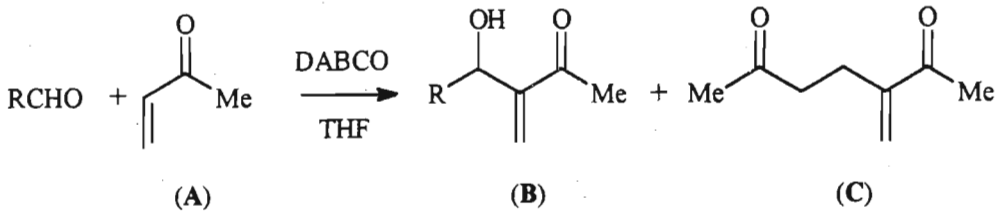

O2
S1
C1
O1
C2
C3
C19
C18
O6
C14
C12
C11
N1
C7
C9
C24
C8
C20
C17
N2
C16
C15
C13
O5
C10
C4
C25
C23
C6
C5
C22
C21
O4
S2
C26
O3

Figure 3

This type of compound has also been encountered by Basavaiah *et al.*[141a] They report the formation of the 'double' adduct (**C**) as a by-product in Baylis-Hillman coupling reactions of methyl vinyl ketone (**A**) with a variety of aldehydes in the presence of the tertiary amine, DABCO, to produce α-methylidene-β-hydroxy ketones (**B**). They concluded that the 2-methylidene-1,5-diketone by-products (**C**) were the result of DABCO catalysed dimerisation of the vinylic ketones (**A**) (Scheme 43a).

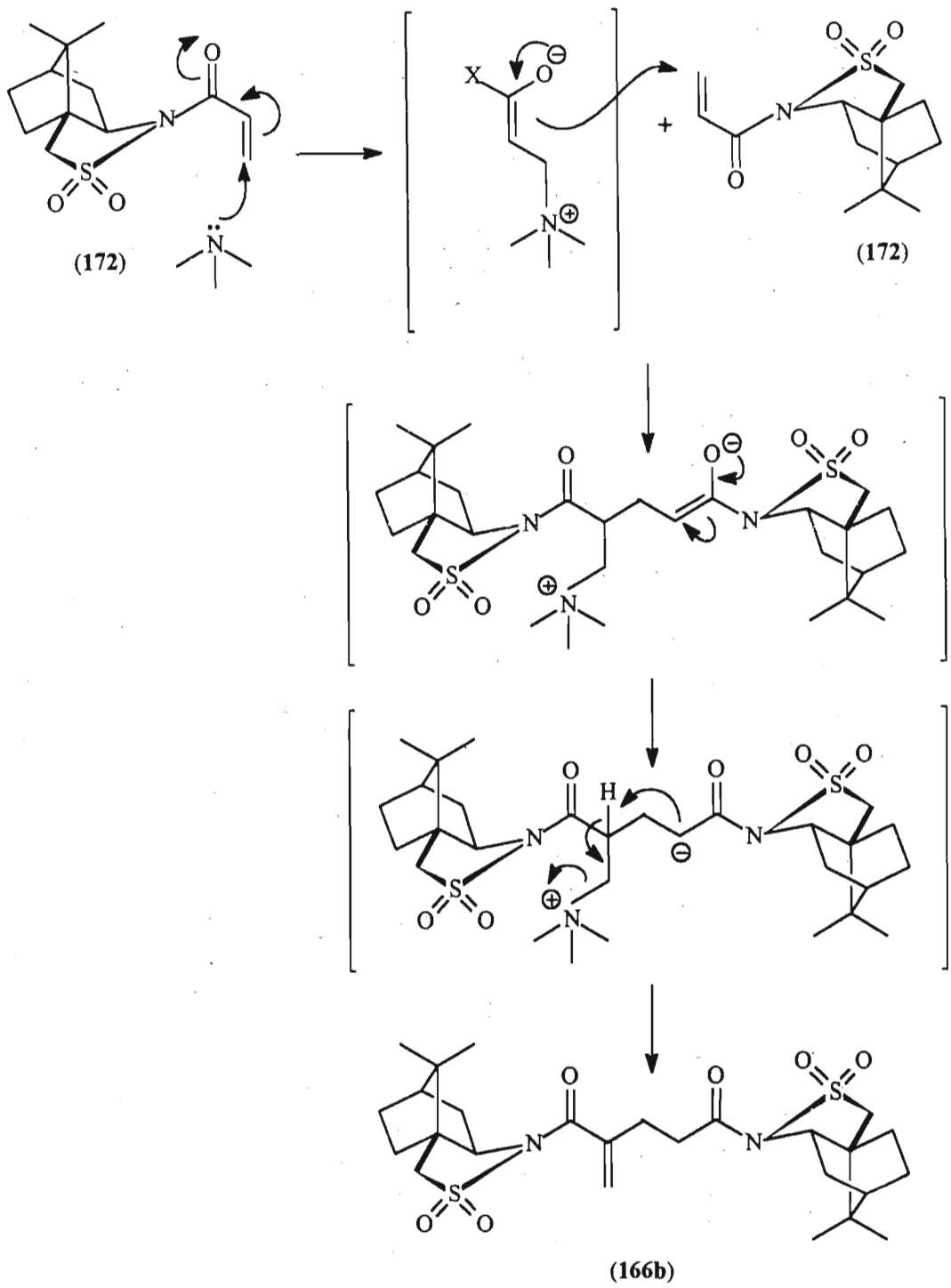


(**A**) (**B**) (**C**)

Scheme 43a

No mechanism was proposed for the formation of (**C**) and, therefore, two possible mechanisms have been suggested below.

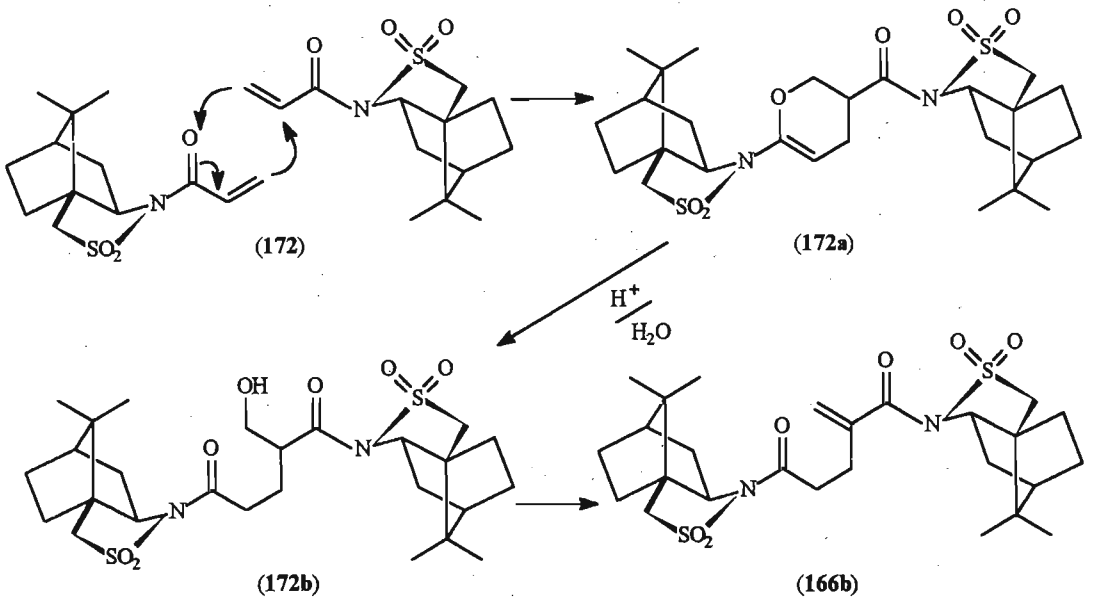
The first mechanism involves the Michael type addition of a tertiary base, such as Et_3N, to the α,β-unsaturated *N*-acylimidazolidinone (**172**). The zwitterion that forms undergoes spontaneous Michael addition to another molecule of the α,β-unsaturated *N*-acylimidazolidinone (**172**). The resulting anion abstracts the α-proton, intermolecularly, which is rendered acidic by the neighbouring carbonyl and amine moieties. Subsequent elimination of the tertiary amine yields the 'double' adduct (**166b**).



Scheme 43b

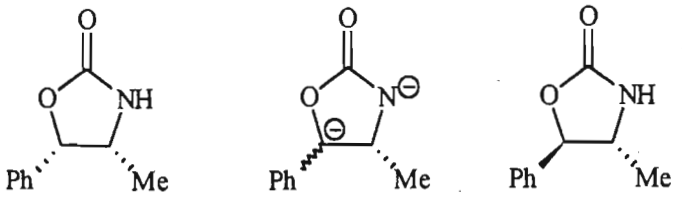
The second mechanism that has been proposed involves two acylated product molecules (**172**) undergoing a heteroatom Diels-Alder reaction to form the cyclic product (**172a**). The cyclic vinyl ether is then cleaved during work-up which involves

washing with dil. HCl solution to remove excess tertiary amine. Subsequent dehydration of the β-alcohol gives rise to the 'double' adduct (**166b**).



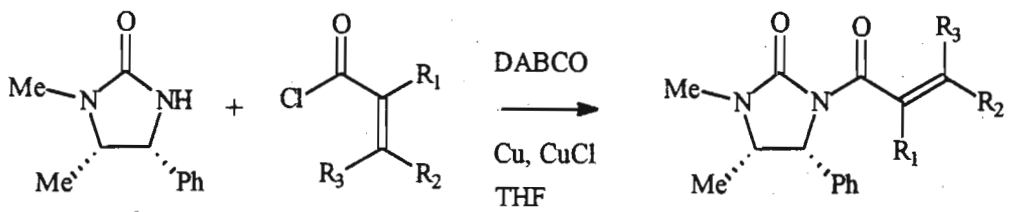
Scheme 43c

Previous reports on work that has been carried out with imidazolidinone auxiliaries have indicated that the reactivity of these auxiliaries is lower than that of the Evans' oxazolidinone auxiliary due to decreased activation of the imidazolidinone carbonyl by back donation of the *N*-Me lone pair.[129] A successful method of *N*-acylation would thus require the proper choice of base in order to carry out the substitution reaction but at the same time, base epimerisation of the auxiliary's innate chiral centres has to be avoided. Davies *et al.*[142] have reported on the base induced C-5 epimerisation that takes place with 4-methyl-5-phenyloxazolidinones when treated with more than one equivalent of butyllithium. In this case, the *cis*-4-methyl-5-phenyloxazolidinone (**167**) becomes contaminated by a product resulting from epimerisation which takes place *via* an *N*, C-5-dianion (**168**). This generates, after protonation, a 1:4 mixture of epimers with the 'unwanted' epimer (**169**) forming in excess.



(167) (168) (169)

A new route to this end was discovered during the course of this work and the choice of base was 1,4-diazabicyclo[2,2,2]octane (DABCO) with the addition of CuCl and copper powder. The tertiary amine proved to be a sufficiently strong base to abstract the amide proton of the auxiliary (**128**), but it is not able to cause epimerisation of the auxiliary's innate chiral centres. The role of the copper is to prevent polymerisation of the α,β-unsaturated chlorides (**159**) during the reaction and during work-up.[140] This novel method of acylation takes place at room temperature, with relatively short reaction times and the α,β-unsaturated imides (**160**) to (**164**) are produced in almost quantitative yields (Scheme 44).



(128) (159) (160)-(164)

Scheme 44

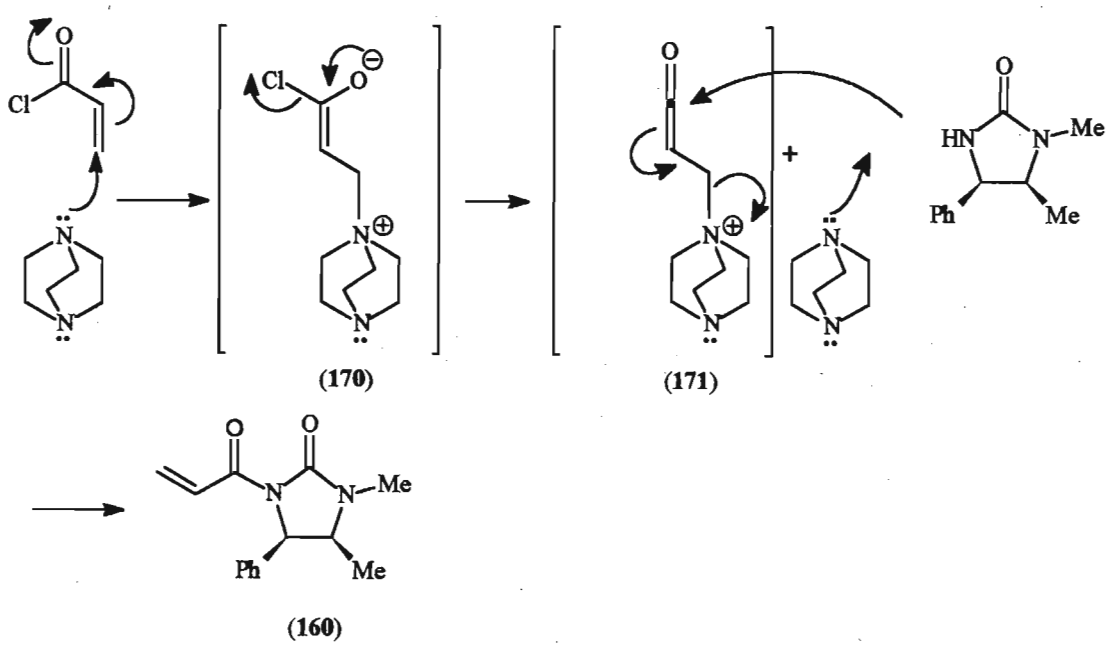
Table 6 Yields of Dienophiles obtained on *N*-Acylation of Imidazolidin-2-one.

Entry		Dienophile	Yield
1	(160)	R_1, R_2, R_3 = H	98
2	(161)	R_1, R_3 = H, R_2 = Me	96
3	(162)	R_1 = Me, R_2, R_3 = H	57
4	(163)	R_1 = H, R_2, R_3 = Me	95
5	(164)	R_1, R_3 = H, R_2 = Ph	98

Low yields obtained using methacryloyl chloride (**162**) were attributed to the fact that the presence of the α-methyl group significantly destabilises the *s-cis* unsaturated

carbonyl moiety rendering this acyl chloride less reactive. Due to much slower reaction times, polymerisation could not be prevented.

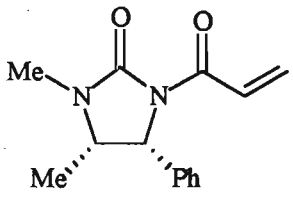
The success of the use of DABCO for the *N*-acryloylation of the imidazolidin-2-one auxiliary can be attributed to the novel way in which it reacts with the reagent. Hoffman and Rabe[143] have outlined the mechanism of the Baylis-Hillman reaction which involves the addition of α,β-unsaturated carbonyls to aldehydes with the use of DABCO as catalyst. Mason[144] has reported on the use of DABCO as the tertiary amine used to catalyse the rearrangements of allylic alcohols and esters *via* an S_N2' mechanism. In both instances, there is a Michael addition of DABCO to an α,β-unsaturated carbonyl compound to form the reactive intermediate. For this reason, it is proposed that the mechanism of acryloyl chloride addition to imidazolidin-2-ones takes place *via* a similar route. DABCO adds to acryloyl chloride by conjugate addition to form the zwitterion **(170)** followed by elimination to yield a ketene intermediate **(171)** which then rapidly reacts with a molecule of the auxiliary **(128)** to produce the desired *N*-acylated product **(160)**. This is the only mechanism available so far to explain the exceptionally high yield of *N*-acryloylation (Scheme 45).



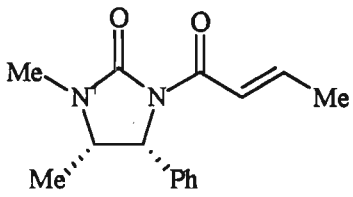
Scheme 45

The mechanism resembles that of the formation of the 'double' adduct (**166a**) (Scheme 43).[140] In this case it is the DABCO and not the amine of the auxiliary that reacts with the acryloyl chloride to form the ketene. DABCO (a tertiary amine) is eliminated at the final step of the reaction whereas, the auxiliary (a secondary amine) remains intact and hence, the 'double' adduct (**166a**) is formed.

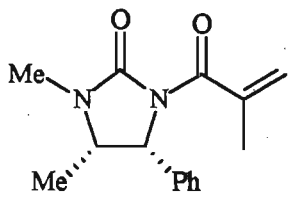
Acylation reactions with DABCO was the method used for the acylations required to produce the dienophiles (**160**)-(**164**) for subsequent Diels-Alder reactions. The mechanism of these reactions is a substitution reaction since β-substituted acyl chlorides are too sterically hindered to allow the approach by DABCO to the β-position. The success of DABCO as a base in these reactions is confirmed by the reaction yields (Scheme 44) (Table 6, entries 2,4 and 5).



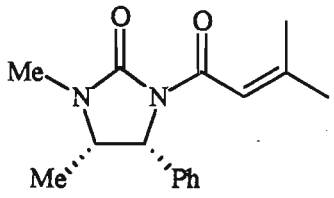
(**160**)



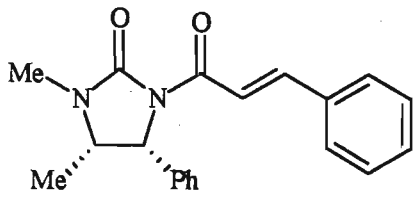
(**161**)



(**162**)



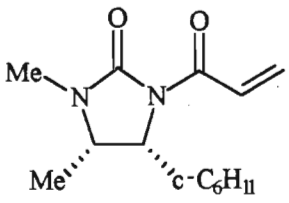
(**163**)



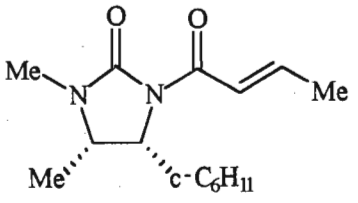
(**164**)

The above dienophiles include the reactive *N*-acryloylimidazolidinone (**160**), the less reactive *N*-crotonyl (**161**) and *N*-methacryloylimidazolidinones (**162**) as well as the sterically bulky β,β-dimethacryloyl (**163**) and cinnamoylimidazolidinones (**164**).

The *N*-acylation of the cyclohexyl derivative (**144**) proceeded just as smoothly and yielded the *N*-acryloyl (**173**) and (**174**) *N*-crotonyl substituted derivatives in yields of 95-98%.

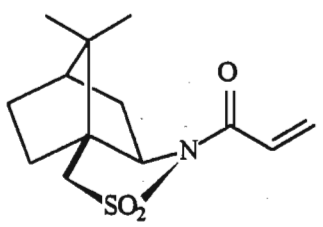


(173)



(174)

The acylation of bornane-10,2-sultam (**57**) and acryloyl chloride with DABCO and CuCl was carried out in order to test for the generality of this reaction. Again, quantitative yields were obtained. The *N*-acylbornane-10,2-sultam (**172**) is a highly reactive auxiliary that has been widely reported in the literature.[145]



(172)

All of the above dienophiles, the *N*-acylimidazolidin-2-ones and the cyclohexyl derived *N*-acylimidazolidin-2-ones (**160**)-(**164**) and (**173**)-(**174**) and the bornane-10,2-sultam (**172**) are crystalline and have excellent shelf lives once they have been obtained in the pure state.

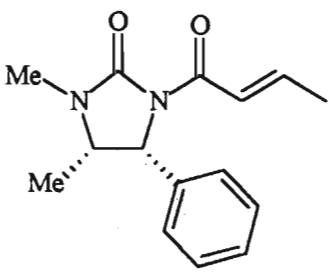
This simple, mild and efficient procedure for the *N*-acylation of imidazolidin-2-ones should increase the use of these auxiliaries in further diastereoselective processes such as the use of chiral auxiliaries in the synthesis of optically pure carbamates, in ene and radical reactions.

A recently published report by Ager *et al.*[136] describes the *N*-acylations of chiral oxazolidinone auxiliaries using a catalytic DMAP-Et_3N method with 1.0-2.0 equivalents of the anydride or acid chloride in anhydrous THF at room temperature. This method also proved to be simple, mild and efficient.

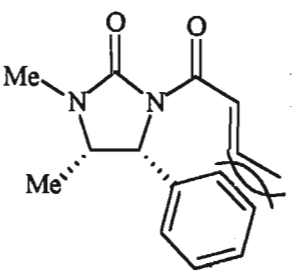
2.6 Diels-Alder Cycloaddition Reactions

The structural design of an effective chiral dienophile should exhibit a well-defined diastereofacial bias. The efficiency of dienophiles thus depends on the extent of their control of the various rotational degrees of freedom interconnecting chiral and prochiral centres, as well as possessing a spacial geometry that allows for effective shielding of one face of the dienophile system.

N-acylimidazolidin-2-one dienophiles possess structural features that have great potential for controlling these two stereochemical elements. The uncomplexed α,β-unsaturated carbonyl moiety exists exclusively in the *s-cis* **(175)** conformation in order to avoid severe non-bonding interactions present between the olefin and the chiral auxiliary in its *s-trans* **(176)** conformation.

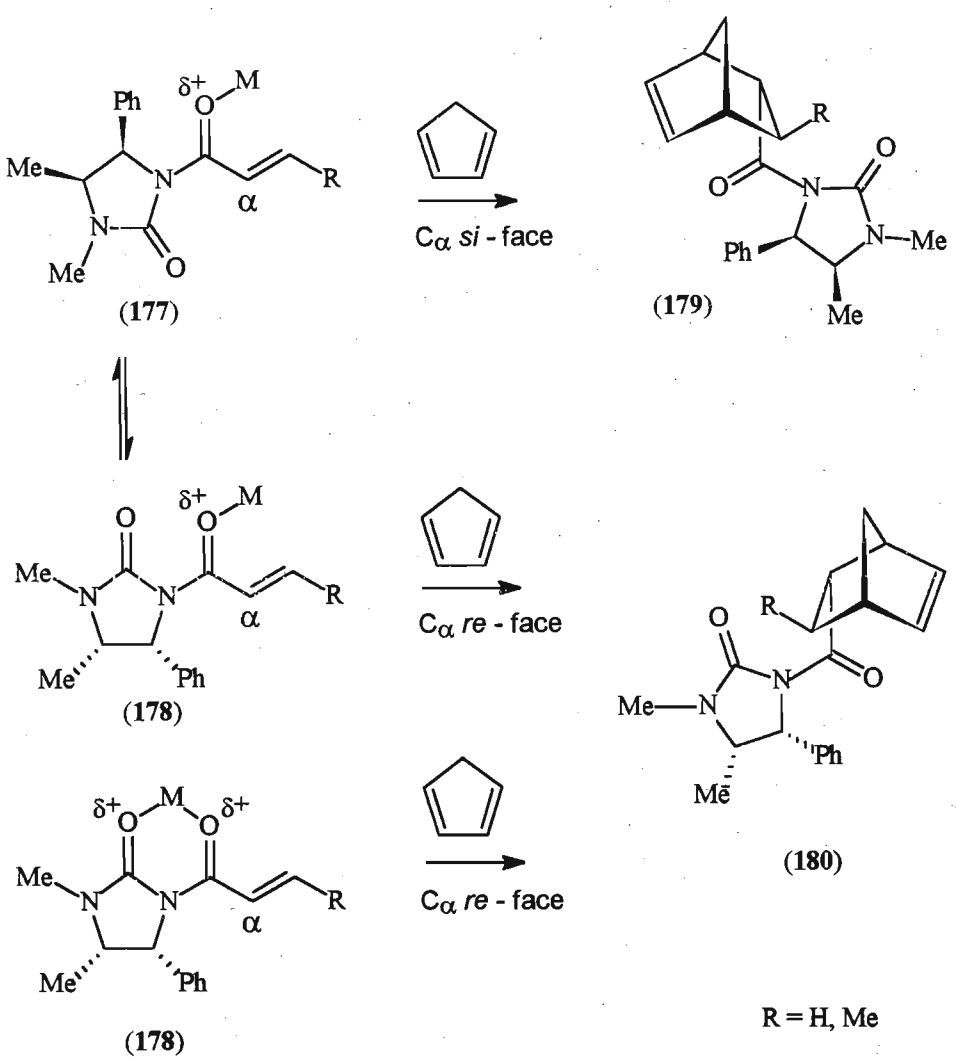


s-cis **(175)**



s-trans **(176)**

The topographical relationship between the chiral centre of the imidazolidin-2-one and the prochiral *s-cis* dienophile also needs to be established. Poor diastereofacial differentiation would result unless bidentate chelation could be achieved between the Lewis acid promoter and the two carbonyl groups of the substrate (Scheme 46).

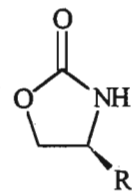


Scheme 46

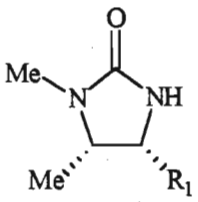
Coordination to only one carbonyl moiety would give rise to two possible conformations **(177)** and **(178)** of the Lewis acid-dienophile complex due to free rotation possible about the N-CO bond. Approach of a reacting diene would therefore be equally possible from either face of the prochiral *s-cis* dienophile and this would result in a 1:1 mixture of *endo* isomers **(179)** and **(180)**. Bidentate chelation prevents rotation about the N-CO bond restricting the conformation to **(178)**. With one face of the dienophile shielded by the bulky phenyl or cyclohexyl functionality, the other face is preferred for the approach of a reacting diene such as cyclopentadiene. In this way, diastereofacial bias is introduced to the chiral imidazolidin-2-one and the prochiral *s-cis* dienophile system resulting in only the one *endo* isomer **(180)** being formed. This type of structure and coordination results in an exceptionally reactive and highly organised dienophile. The reactivity is greatly enhanced by the strongly electron

withdrawing effects of the Lewis acid. This thesis reports on the *N*-acylimidazolidin-2-ones fulfilling all of the above design criteria.

The choice of reaction conditions was based largely on work done by Evans and co-workers. Considerable structural homology exists between the Evans chiral α,β-unsaturated oxazolidinones (**39a**) and (**39b**) and imidazolidinones (**128**) and (**144**).



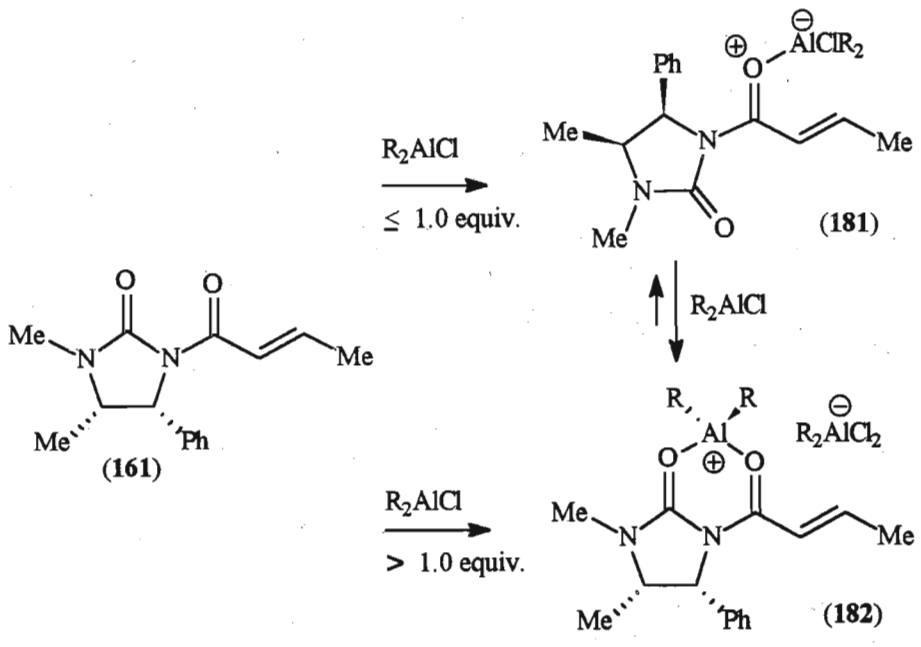
R=$CHMe_2$ (**39a**)
R=CH_2Ph (**39b**)



R_1=Ph (**128**)
R_1=c-C_6H_{11} (**144**)

For this reason, it was decided to employ similar reaction conditions based on work they had carried out. A report published by Evans *et al.*[111] in 1988 included an extensive survey of Lewis acid catalysts and their ability to maintain bidentate chelation with oxazolidinones in Diels-Alder reactions. They discovered that many catalysts, such as $SnCl_4$, $TiCl_4$ and $AlCl_3$, resulted in unacceptable levels of reaction stereoselectivity. Diethylaluminium chloride (Et_2AlCl) promoted by far the most diastereoselective Diels-Alder reactions. Et_2AlCl afforded both high levels of *endo* diastereoselection as well as the highest combined *endo/exo* ratios of all the Lewis acids screened. Dimethylaluminium chloride (Me_2AlCl) afforded similar levels of reaction stereoselectivity as well as fewer byproducts. Me_2AlCl is appreciably more expensive than Et_2AlCl and it was therefore decided to use Et_2AlCl for this research. Evans and co-workers also undertook a study of the reaction stereoselectivity as a function of Me_2AlCl stoichiometry (Chapter 1, Scheme 24). They concluded that when less than 1 equivalent of Me_2AlCl was added, the Lewis acid complexed with the α,β-unsaturated carbonyl oxygen only to produce a 1:1 mixture of diastereomeric products (**181**) and (**182**). (Scheme 47). In the presence of excess Me_2AlCl, both dienophile reactivity and reaction diastereoselectivity dramatically increased since the Lewis acid complexed to both carbonyls of the dienophile (**182**). The scheme involves the

N-acylimidazolidinone auxiliary (**161**) instead of Evans' auxiliary (**40**) to demonstrate the degree of structural similarity between the two auxiliaries. The same principles would therefore also apply to our system.



Scheme 47

The Diels-Alder reactions were initially carried out using cyclopentadiene as it is highly reactive and results using cyclopentadiene in Diels-Alder reactions are well documented in the literature. This enabled us to determine the sense of selectivity obtained with *N*-acylimidazolidinones in Diels-Alder reactions by transforming their Diels-Alder adducts into their respective benzyl ester derivatives. A comparison was then made of their optical rotations with those obtained by researchers such as Oppolzer[69] and Evans[111] who have carried out similar studies using the bornane-10,2-sultam and the *N*-acyloxazolidinone auxiliary, respectively. The results are in agreement with those anticipated: an equal, but opposite sense of induction was achieved compared to results obtained with the *N*-acyloxazolidinone auxiliary and the same sense of induction as the bornane-10,2-sultam auxiliary. In order to obtain the opposite sense of induction, the *N*-acylimidazolidinone auxiliary would have to be synthesised using the inexpensive and readily available enantiomer of ephedrine,

norephedrine. The choice of auxiliary, however, would depend on the induction required for a particular synthetic reaction.

Lehmkuhl and Kobs[146] have derived a model of Lewis acids involved in bidentate chelation. Using this model, the sense of asymmetric induction in the Diels-Alder reaction between the dienophile (**161**) and cyclopentadiene was established by the stereochemical correlation illustrated in Figure 4.

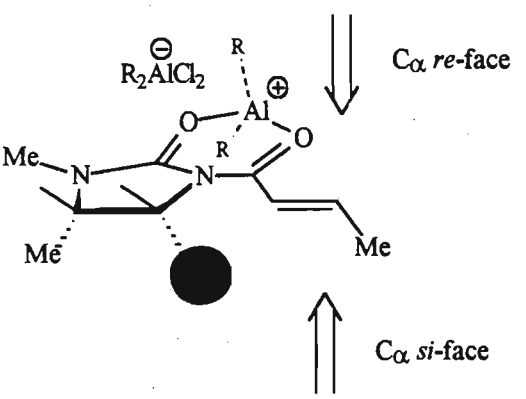


Figure 4

In accordance with this model, cycloaddition should occur selectively from the C_α *re*-face of the crotonyl imide. This is the same sense of induction that occurs in the case of the bornane-10,2-sultam auxiliary. The *N*-acyloxazolidinone auxiliary cycloaddition reaction was likewise determined to take place selectively from the C_α *si*-face, resulting in an equal but opposite rotation of the respective benzyl esters.

As an added confirmation of the above results, an X-ray crystal structure of the major product (**183**) of the Diels-Alder reaction between the *N*-acryloylimidazolidinone dienophile and cyclopentadiene was obtained.[147] (Figure 5). The sense of induction and thus the absolute configuration was determined to be in agreement with those obtained from the Lehmkuhl and Kobs model and the comparison of benzyl ester optical rotations.

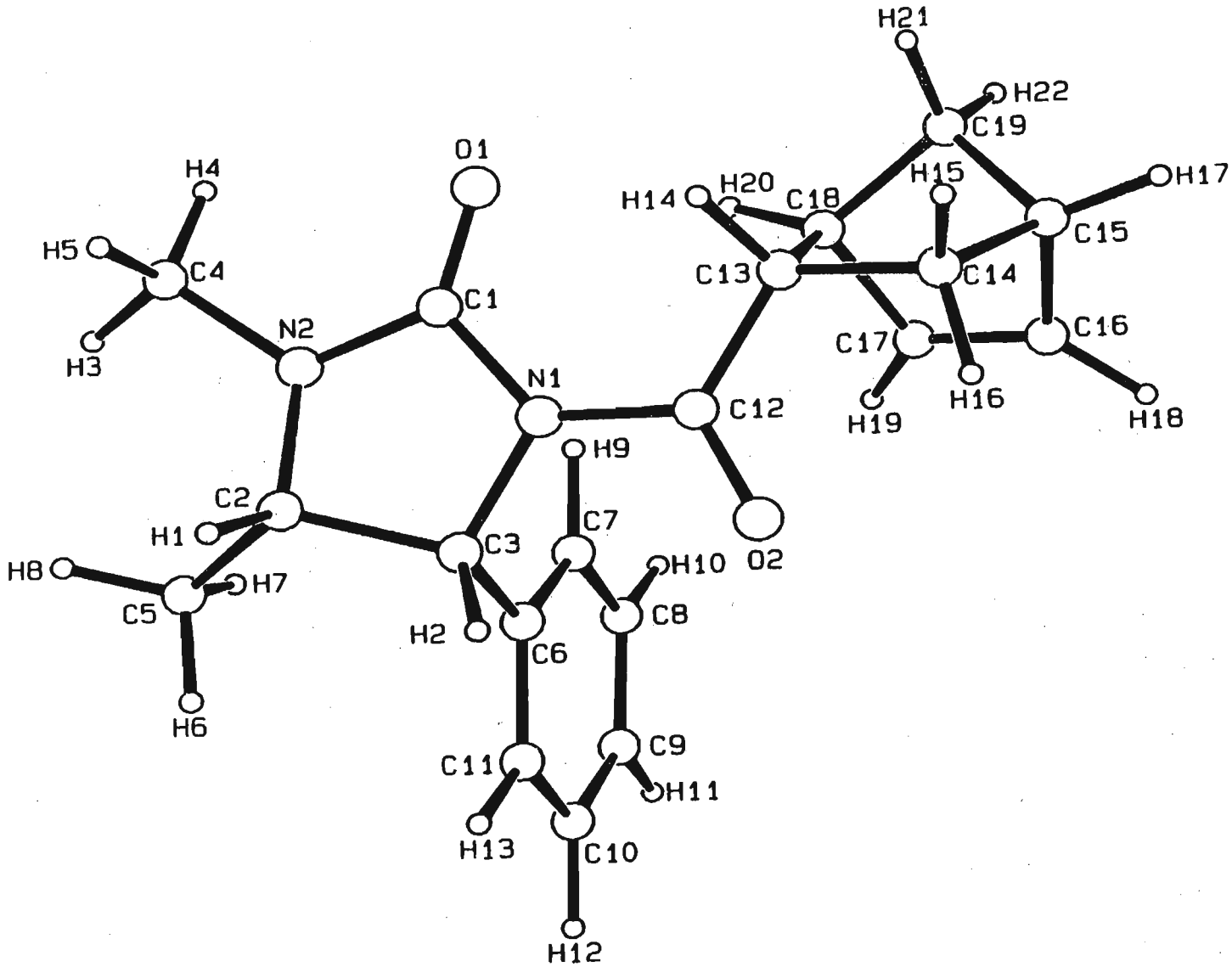
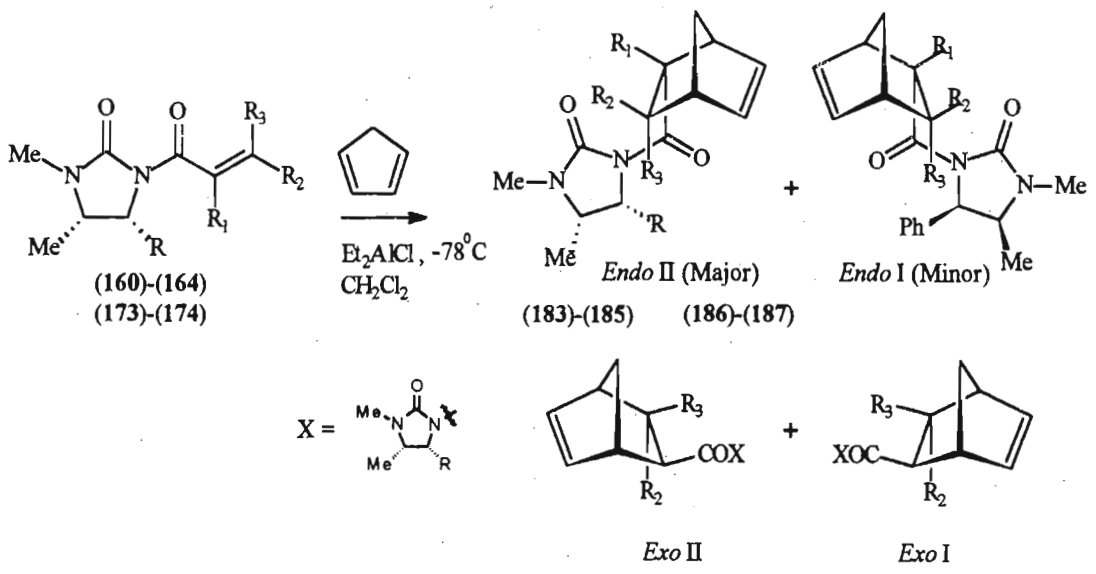

H21
H22
C19
O1
H4
H20
C18
H15
H17
H14
C15
H5
C4
C13
C14
C1
N2
C17
C16
H3
N1
H16
C12
H19
H18
H9
C2
C7
H1
C3
H10
O2
H8
H7
C8
C5
H2
C6
H6
C9
C11
H11
H13
C10
H12

Figure 5

2.6.1 Diels-Alder Reactions Involving the *N*-Acylimidazolidin-2-one Auxiliary

The initial study of the stereodifferentiation efficiency of *N*-acylimidazolidin-2-ones involved the Lewis acid (Et_2AlCl, 2 eq.) catalysed reaction at low temperatures (-78°C) of the dienophiles with cyclopentadiene. Dicyclopentadiene was heated to reflux for several hours to crack the dimer into its monomer units, cyclopentadiene.The cyclopentadiene was then distilled and used immediately (Scheme 48), (Table 7).



Scheme 48

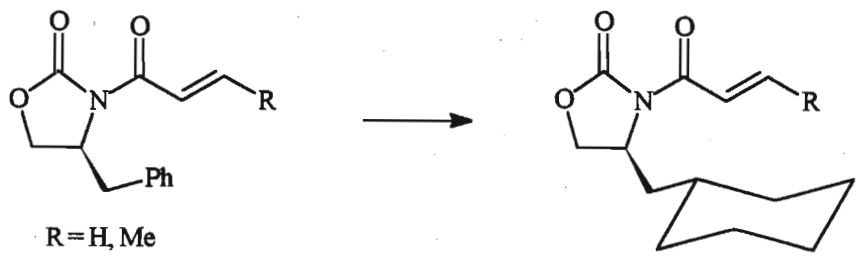
Table 7. Reaction of Dienophiles (**160**)-(**164**) and (**173**)-(**174**) with Cyclopentadiene.

Entry	Auxiliary	Dienophile	∑*endo*:∑*exo*	*Endo* de[a]	Yield[%] [b]
1(**160**)	R= Ph	R_1,R_2,R_3= H	>99:1	86(98)	80
2(**161**)	R= Ph	R_1,R_3=H, R_2= Me	94:6	70(99)	78
3(**162**)	R= Ph	R_1=Me, R_2,R_3= H	82:18	50	52
4(**163**)	R= Ph	R_1=H, R_2,R_3= Me	no reaction	—	—
5(**164**)	R= Ph	R_1,R_3=H, R_2= Ph	no reaction	—	—
6(**173**)	R= c-C_6H_{11}	R_1,R_2,R_3= H	>99:1	98	70
7(**174**)	R= c-C_6H_{11}	R_1,R_3=H, R_2= Me	>99:1	98	62

[a] Values in parentheses reflect material after double recrystallization.
[b] Yields obtained for isolated major isomer.

The diastereomeric ratios were determined by H^1 NMR spectroscopy as well as GC/MS. There was a good correlation between NMR spectroscopy and GC/MS values in all cases. All new compounds gave satisfactory analytical and spectral data consistent with the structures shown.

The results (Table 7) prove that both the *N*-acylimidazolidin-2-one **(160)-(164)** and its cyclohexyl derivative **(173)-(174)** showed excellent *endo/exo* and π-facial selectivity, the most reactive acryloyl system **(160)** yielding the best results of the corresponding dienophiles. The cyclohexyl derivatives **(173)** and **(174)** proved to be superior diastereofacial directors presumably due to the increased steric shielding compared to that of the phenyl ring. This also indicates that stereoselection is controlled primarily *via* steric rather than electronic factors. This is in stark contrast to the observation of Evans and co-workers[111] who report a drop in stereoselectivity when the related 4-benzyl-oxazolidin-2-one auxiliary **(105)** is converted to its methylcyclohexyl analogue, **(105a)**.



(105) **(105a)**

Whilst this was rationalised in terms of electronic charge-transfer interactions (π-stacking), it is clearly not paralleled in this system which lacks the additional mobility conferred by the extra methylene present in the Evans system.

The cycloaddition reactions with the phenyl derivatives **(160)-(164)**, though, readily afforded highly diastereomerically enriched products by means of double recrystallization or separation by chromatography. (Table 7, entries 1 and 2). The crystallinity of the cyclohexyl derivatives **(173)** and **(174)** was not readily imparted to the cycloaddition adducts as they only solidified on standing. This detracts appreciably from their success as chiral auxiliaries in Diels-Alder reactions as further purification and isolation of the products is rendered much more difficult. This is clearly seen by

the yields obtained for these reactions (Table 7, entries 6 and 7). In addition to this, the cyclohexyl derived imidazolidinone auxiliaries had longer reaction times of three hours as opposed to one hour for their phenyl analogues. This was attributed to the positive inductive effect created by the cyclohexyl functionality which would render the dienophile less reactive and cause a reduction in cycloaddition reaction rates.

A comparative study by Evans[111] highlights the degree of reactivity of bidentate chelated dienophiles. Methyl crotonate, when treated under similar conditions and even at elevated temperatures, is recovered unchanged. This is in stark contrast to our results (Table 7, entry 2). As a consequence of the high level of reactivity of the dienophile-Lewis acid complex, *β*-substitution within the dienophile is tolerated.

The β-phenyl substituted phenyl compound **(164)** (Table 7, entry 5) was synthesised in order to determine whether the dienophile could tolerate aryl substitution. Diels-Alder reactions with these dienophiles under standard conditions proved to be unsuccessful suggesting that the overall reactivity of the dienophiles was not sufficient for cycloaddition to take place. These dienophiles thus showed lowered reactivity when compared to the related oxazolidinone auxiliaries of Evans.[111] It is proposed that this is a result of the increased overall positive inductive effect attributable to the ring *N*-Me instead of O. This reduces electron withdrawal from the dienophile enoyl system thereby lowering its reactivity. Evans[111] does report, though, that the oxazolidinone auxiliary and Oppolzer's camphor sultam auxiliary are the only ones known to be able to tolerate β-phenyl substitution in the dienophile.

The β,β-dimethyl substituted compound **(163)** (Table 7, entry 4) was synthesised to further test the scope of substituents tolerated by the dienophile. Reactions with this dienophile were also unsuccessful even under thermal conditions after several days. It is proposed that this is probably a result of a combination of the above inductive effect, worsened by the additional inductive effect of the dimethyl substitution, along with increased steric demand. Evans' β,β-dimethylacryloyl oxazolidinone auxiliary also failed to react with cyclopentadiene at low temperatures.[111]

The α-methyl dienophile (**162**) (Table 7, entry 3) was synthesised to yield a quaternary carbon centre in the subsequent Diels-Alder adduct. It is well documented in the literature that methacrylate dienophiles have a propensity to undergo *exo* cycloaddition and it was therefore no surprise to discover a poor *endo/exo* selectivity. In addition to this, it is proposed that the presence of the α-methyl group significantly destabilises the *s-cis* unsaturated carbonyl moiety and the result is poor π-facial selectivity.

The dienophiles were easily separated by chromatography to yield isolated *endo* diastereoisomers (**185a**) and (**185b**). The major *endo* isomer (**185a**) is a colourless oil whereas the minor *endo* isomer (**185b**) is a white solid. The *exo* isomers (**185c**) and (**185d**), were not separated from each other. An attempt was made to cleave the auxiliary according to standard literature procedures[111] (Scheme 50). Although the reaction was successful and the desired product was detected and confirmed by GC/MS, the yield was low and the isolated product was not characterised. These types of compounds are difficult to cleave due to the electron donating properties of the α-methyl group. However, since *N*-acylimidazolidinone auxiliaries show lowered reactivity because of the ring *N*-Me instead of O such that the electron withdrawing effect is reduced, the auxiliary removal was proposed to be facilitated to yield a cycloaddition product with a quaternary carbon centre. The more effective method of lithium hydroxide and hydrogen peroxide in aqueous THF for the nondestructive removal of the auxiliary would have to be employed. (See Section 2.7). This will more than likely increase the yield of the reaction as this method has been shown to be very effective in removal of camphor lactam auxiliaries from adducts with quaternary carbon centres.[148]

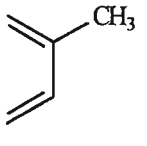
Fuji[149], in his review article on the growing interest in the asymmetric creation of quaternary carbon centres due to the fact that they occur in a number of biologically active natural products, reports the results obtained by Evans and Meyer on this subject. The results they achieved are comparable with those obtained in this study. Evans did not determine the structure of the major isomer obtained with his methacrylate derived oxazolidinone auxiliary and Meyer confirms that the analogous

reaction using his chiral bicyclic lactams yielded the major product arising from an *endo* addition to the less hindered *si*-face. Since the configuration of the quaternary carbon adduct was the same as the analogous examples that do not possess a quaternary carbon centre, the sense of addition of the diene to the α-methyl-substituted dienophile was the same. It was therefore assumed that the major product achieved with the analogous imidazolidinone auxiliary was the result of an *endo* addition to the C_α *re*-face of the dienophile-Lewis acid complex. NOE experiments were unsuccessful in confirming this prediction A crystal structure of the crystalline *endo* adduct awaits to be elucidated in order to be sure of the configuration of the major adduct.

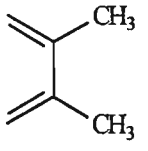
An elegant study of successful sultam auxiliaries in the synthesis of quaternary carbon centres was reported by Boeckman *et al.*[148] Extremely high selectivities, *eg.* 82:9:5:4, were obtained which once again highlights the fact that chiral auxiliaries often need to be modified in order to accommodate for certain reaction types.

2.6.2 Diels-Alder Reactions with Less Reactive Dienes

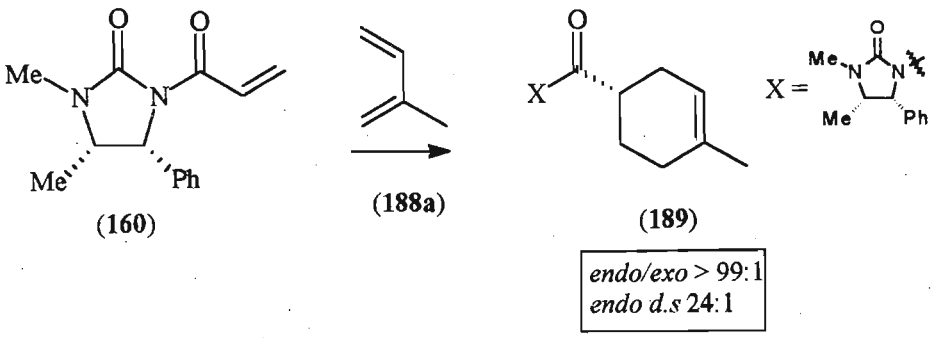
An extension of this work involved the reaction of the acrylate derivative of *N*-acylimidazolidinone (**160**) with less reactive acyclic dienes. The cycloaddition reaction with 2,3-dimethyl-1,3-butadiene (**188b**) proved to be unsuccessful. The same dienophile reacted well with isoprene (**188a**) (Scheme 49) to yield the adduct (**189**) in excellent *endo*/*exo* as well as π-facial selectivity. Reaction conditions were altered slightly to accommodate for the less reactive diene by elevating reaction temperatures from -78°C to -60°C.



(188a)

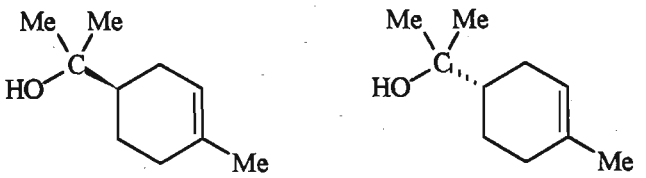


(188b)



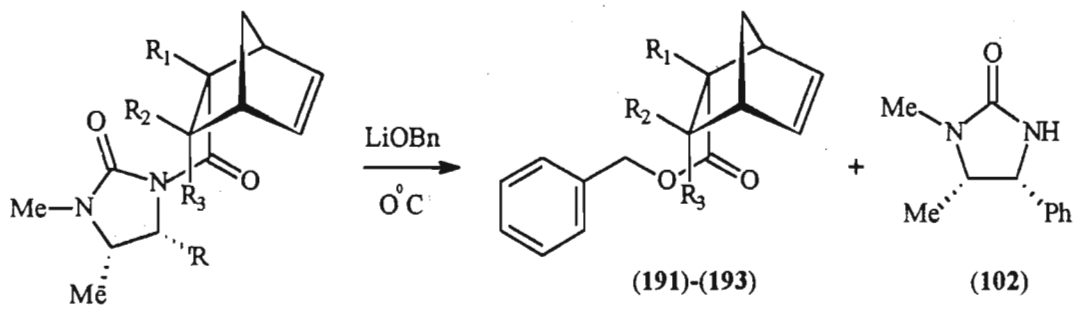
Scheme 49

The isoprene cycloadduct may be converted to (-)-α-terpineol (**190b**)[111] by cleaving off the auxiliary with lithium benzyloxide, followed by the addition of excess methylmagnesium bromide. This affords the equivalent but opposite isomer of the natural product, (+)-α-terpineol (**190a**).[111] The same sense of induction could also be obtained with the *N*-acylimidazolidinone auxiliary by employing the enantiomer of ephedrine, norephedrine, in the synthesis of the auxiliary.



2.7 Removal of the Chiral Auxiliary

The removal of the imidazolidinone auxiliaries was accomplished using lithium benzyloxide in THF (0°C, 3 h) to afford the corresponding benzyl esters in yields of 75-95% from the purified Diels-Alder acrylate and crotonate cycloadducts. No epimerisation occurs during the course of these transesterifications and the auxiliary is recovered, unaltered in yields of 90-98% (Scheme 50), (Table 8). In the cases where crystallinity was not successfully imparted to the cycloaddition adducts, purification of the major *endo* diastereoisomers was not as successful and therefore the ee's of the benzylation products are lowered (Table 8, entries 4 and 5).



Endo (II) Major

(183)-(185) **(186)-(187)** **(191)-(193)** **(102)**

Scheme 50

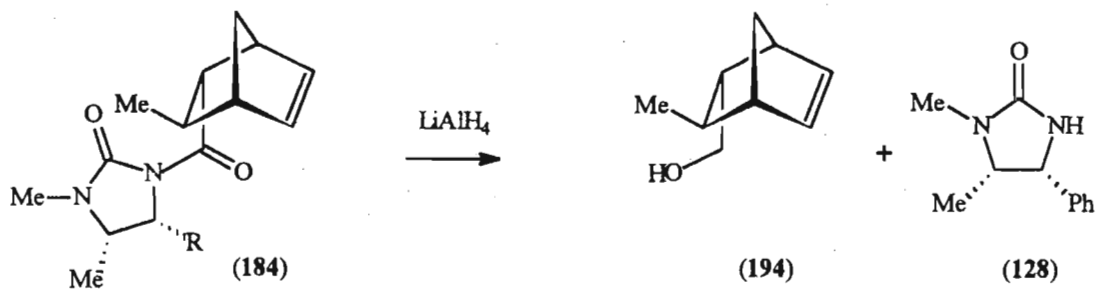
Table 8. Removal of the Chiral Auxiliary to yield the corresponding Benzyl Esters.

Entry	Auxiliary	Dienophile	Diene	Ester	Yield [%]	ee.[a]
1	R= Ph	**(183)**	cyclopentadiene	**(191)**	98	98
2	R= Ph	**(184)**	cyclopentadiene	**(192)**	95	98
3	R= Ph	**(185a)**	cyclopentadiene	**(193)**	–[b]	–
4	R= c-C_6H_{11}	**(186)**	cyclopentadiene	**(191)**	96	94
5	R= c-C_6H_{11}	**(187)**	cyclopentadiene	**(192)**	90	90
6	R= Ph	**(189)**	isoprene	**(190)**	98	98

[a] The ee's were determined using $Eu(HFC)_3$ as chiral shift reagent.

[b] The product was analysed by GC/MS. The isloated yield was too low for further characterisations.

The removal of the *N*-acylimidazolidin-2-one auxiliary from the Diels-Alder adduct (**184**) was also attempted using $LiAlH_4$ to yield the alcohol (**194**) (Scheme 51).



(**184**) (**194**) (**128**)

Endo (II) Major

Scheme 51

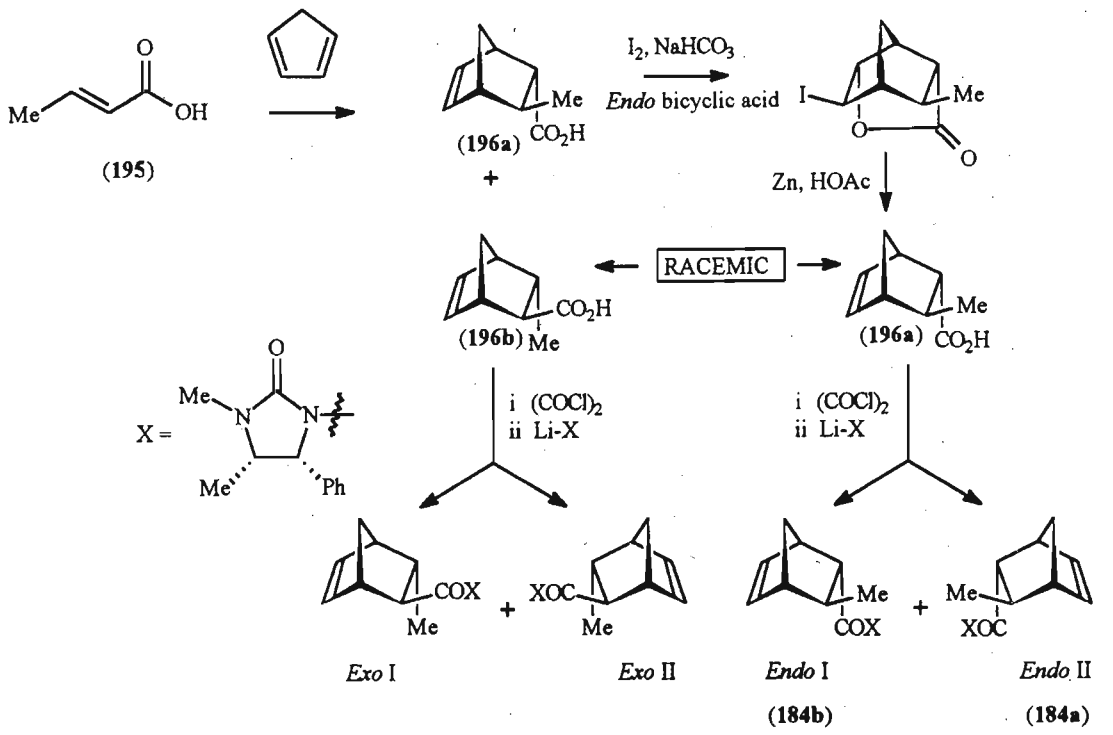
The norbornene (**111**) is an important intermediate in the synthesis of 1-O-methyl-loganin aglucone, a member of the naturally occurring iridoid compounds.[69] The diastereoselective transformation of the norbornene (**111**) to 1-O-methyl-loganin aglucone (**120**) (Scheme 28) with the bornane-10,2-sultam as the chiral auxiliary has already been described in Chapter 1. The synthesis of the norbornene (**184**) using the *N*-acylimidazolidin-2-one auxiliary also proved to be successful and the product was detected and determined by GC/MS. It was not isolated and the completion of this task would confirm another application of the *N*-acylimidazolidin-2-one auxiliary. In addition to this, the *N*-acylimidazoidin-2-one auxiliary is synthesised in two simple steps whereas the bornane-10,2-sultam auxiliary requires four steps to synthesise the equivalent dienophile.

2.8 Summary of Results

The *N*-acylimidazolidin-2-one auxiliary has proved to be a highly efficient chiral auxiliary in the Diels-Alder reaction and has added important and unique features to this field of work. Although it may not display the same level of reactivity and stereoselectivity as some of the auxiliaries reported in the literature, these factors may not necessarily be a disadvantage. Every synthetic reaction requires its own unique set of reaction conditions and for this reason, the *N*-acylimidazolidin-2-one auxiliary may, for example, be preferred for reactions that require less reactive systems and which will not interfere with key step reactions.

2.9 The Synthesis of Diels-Alder Authentic Mixtures

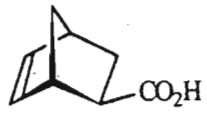
In order to be able to identify and make correct assignments of the four possible diastereoisomers by H^1 NMR spectroscopy and GC/MS, it was necessary to obtain authentic samples of the diastereoisomers according to the route indicated in Scheme 52. The analysis and characterisation of Diels-Alder reaction mixtures were then based on these spectral data.



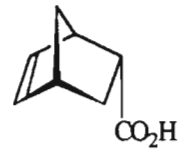
Scheme 52

Crotonic acid (**195**) was condensed thermally with cyclopentadiene[150,151] and the resultant *endo* and *exo* bicyclic acids (**196a**) and (**196b**) were separated by iodolactonisation.[152] The *endo* bicyclic acid was retrieved by reaction of the iodolactone with powdered zinc in acetic acid.[153] The diastereomerically pure *endo* acid (**196a**) was then treated successively with oxalyl chloride[154] and 3-lithio-imidazolidin-2-one,[111] to afford the two authentic *endo* diastereomeric Diels-Alder adducts. It was not possible to isolate the *exo* acid from the reaction mixture and for this reason, the process was repeated but this time, the two acids were not separated and treated in the same way. The assignment of spectral peaks to the *exo* diastereoisomers was then done by comparing the spectra of the two sets of *endo* and *exo* diastereoisomers with the spectra of the *endo* diastereoisomers.

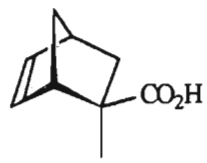
The same procedure was repeated with acrylic acid to produce the *endo* and *exo* bicyclic acids (**196c**) and (**196d**) and with methacrylic acid to produce the *endo* and *exo* bicyclic acids (**196e**) and (**196f**).



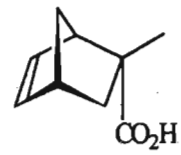
(196d)



(196c)



(196f)

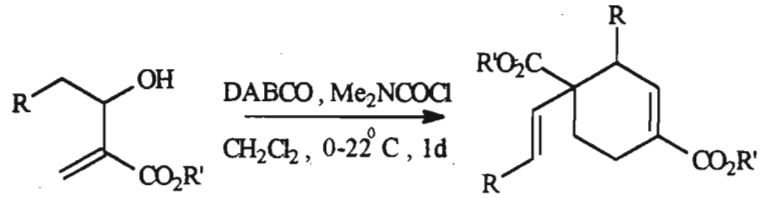


(196e)

This process proved to be invaluable for the correct assignment of spectral peaks and analysis of results for these types of reactions where four possible diastereomeric products are formed. It was very tempting to make intuitive guesses for the expected spectra without obtaining authentic samples of the diastereoisomers. The results proved that intuition would not always have given the correct answer.

2.10 DABCO Catalysed Diels-Alder Reactions

Janse van Rensberg[155] reported an efficient synthesis of substituted cyclohexenes (**198**) using allylic alcohols (**197**) derived from the Baylis-Hillman reaction (Scheme 53).



R = H, CH_3, CH_2CH_3

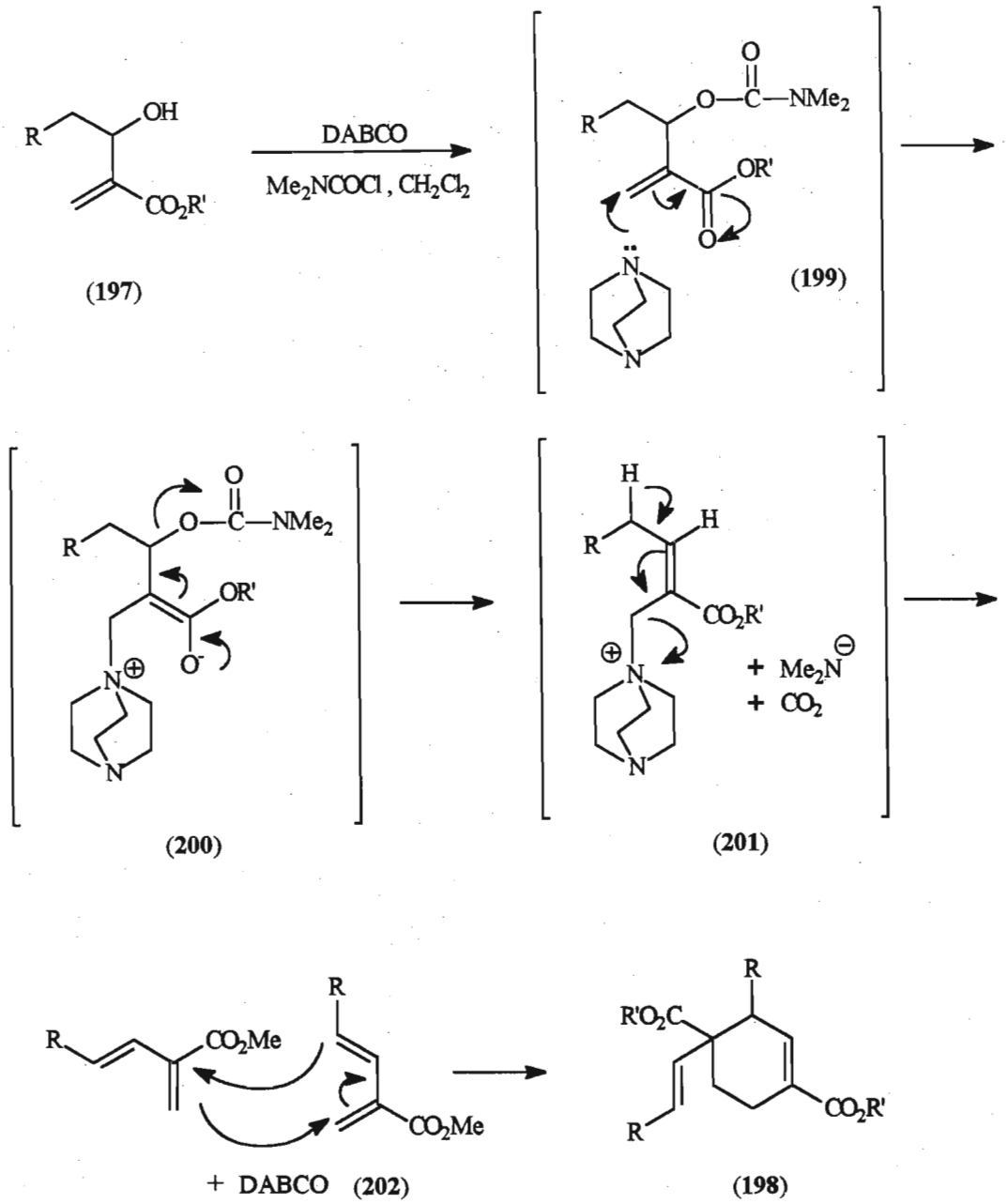
R' = CH_3, CH_2CH_3, $CH_2CH_2CH_3$

(197)

(198)

Scheme 53

The proposed mechanism for the formation of the substituted cyclohexene (198) is shown in Scheme 54.



Scheme 54

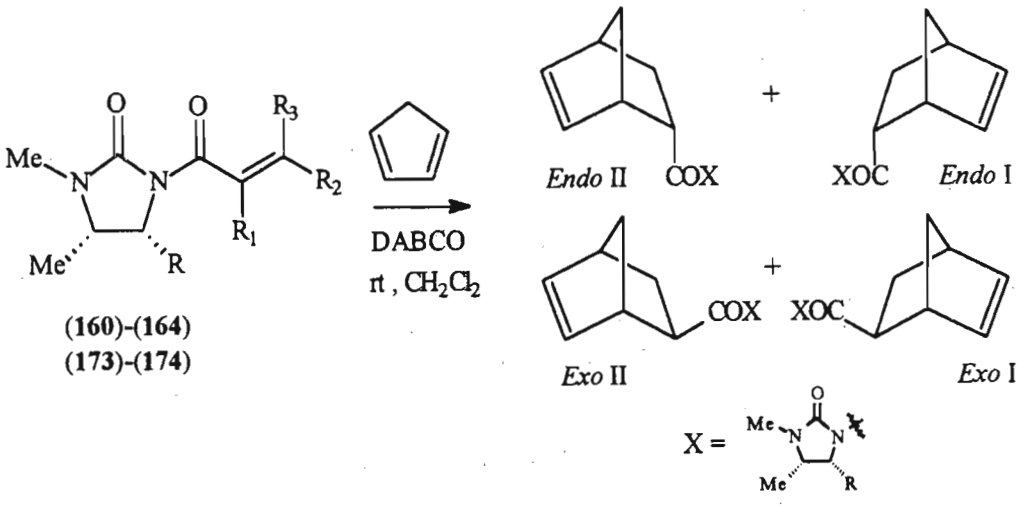
The mechanism involves the formation of an allylic carbamate intermediate (199) from the allylic alcohol (197). The allylic carbamate (199) then reacts rapidly with DABCO in an S_N2' reaction affording the ammonium salt (200). The formation of the dimethyl amine anion and carbon dioxide and (201) is a result of the spontaneous decomposition of the carbamate leaving group. The dimethyl amine anion may be involved in the

abstraction of the allylic proton of (201) and subsequent formation of the diene ester (202) results from the concerted elimination of DABCO to yield a highly reactive 1,3-butadiene which spontaneously dimerises. Dimerisation proceeds *via* a Diels-Alder type cycloaddition reaction affording the substituted cyclohexene (198). Since the formation of the substituted cyclohexenes (198) took place under unexpectedly mild reaction conditions (Scheme 54), Janse van Rensberg speculated that the intermolecular Diels-Alder cycloaddition reaction may have been DABCO-assisted.

This prompted an investigation as to whether DABCO could be used as a catalyst in Diels-Alder cycloaddition reactions using *N*-acylimidazolidin-2-ones as the chiral auxiliary.

The investigation was initiated by comparing the reaction of uncatalysed Diels-Alder cycloadditions with those containing a catalytic amount of DABCO (0.1 equiv.) using the most reactive dienophile, the *N*-acryloylimidazolidinone and the most reactive diene, cyclopentadiene in dichloromethane. Even at elevated temperatures and after several days, no reaction had taken place in the uncatalysed reaction and the starting material was recovered. The reaction conducted in the presence of DABCO showed complete conversion after 2 days to the cycloadduct under similar conditions but at room temperature only. The investigation thus established that the Diels-Alder cycloaddition reaction was indeed DABCO-catalysed.

The following results were obtained for DABCO-catalysed Diels-Alder cycloaddition reactions. (Scheme 55), (Table 9).



Scheme 55

Table 9. DABCO-Catalysed Diels-Alder reactions of *N*-Acylimidazolidin-2-one Dienophiles **(160)**-**(162)** and **(173)**-**(174)** with Cyclopentadiene.

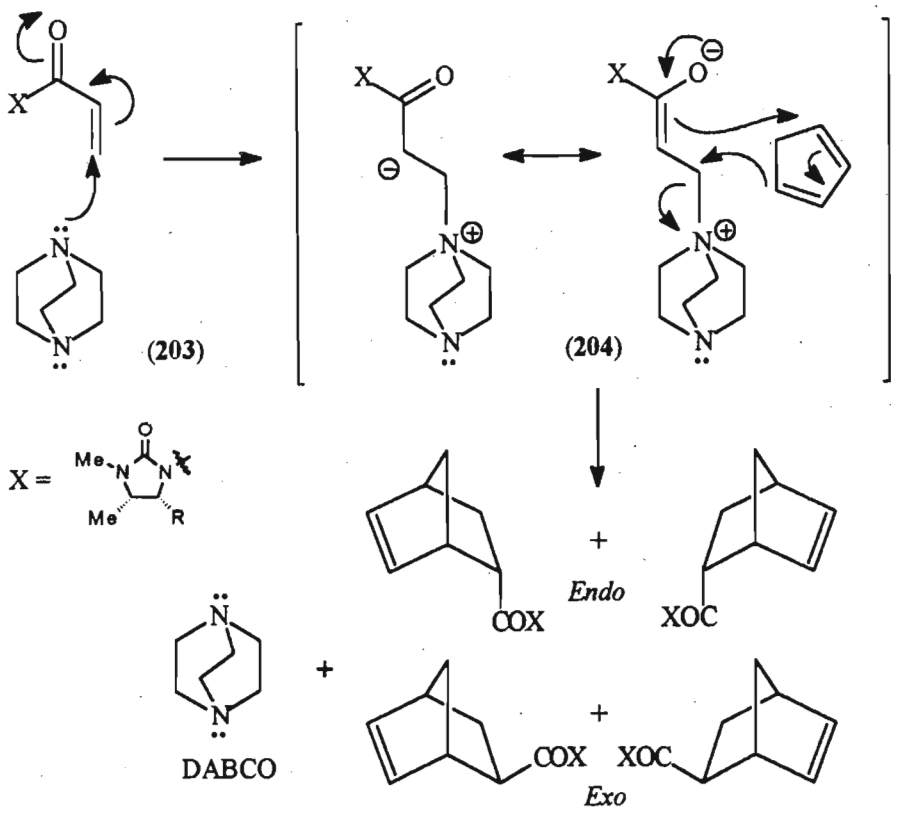
Entry	Auxiliary	Dienophile	∑*endo*:∑*exo*	*Endo* de[a]	Yield[%] [b]
1(**160**)	R= Ph	R_1,R_2,R_3= H	90:10	62(98)	75
2(**161**)	R= Ph	R_1,R_3=H, R_2= Me	NR	—	—
3(**162**)	R= Ph	R_1=Me, R_2,R_3= H	NR	—	—
4(**173**)	R= c-C_6H_{11}	R_1,R_2,R_3= H	82:18	2	60
5(**174**)	R= c-C_6H_{11}	R_1,R_3=H, R_2= Me	NR	—	—

[a] Values in parentheses reflect material after a single recrystallization or chromatography.
[b] Yields obtained for isolated major isomer.
NR = no result. Dienophile unreactive in DABCO catalysed Diels-Alder reaction.

The results of the Diels-Alder reactions catalysed by DABCO indicate that a certain amount of selectivity is also exhibited. The sense of selectivity is the same as that obtained in Lewis acid-catalysed reactions. Reactions of this nature, though, are restricted to α- and β-unsubstituted dienophiles (Table 9, entries 1 and 4). These results are in agreement with the proposed mechanism derived for DABCO-catalysed Diels-Alder reactions.

The proposed mechanism was once again based on results obtained by Hoffman and Rabe[143] and Mason[144] who have outlined mechanisms for reactions which involve the

Michael addition of DABCO to α,β-unsaturated and β-unsubstituted carbonyls. The proposed mechanism is outlined below (Scheme 56).



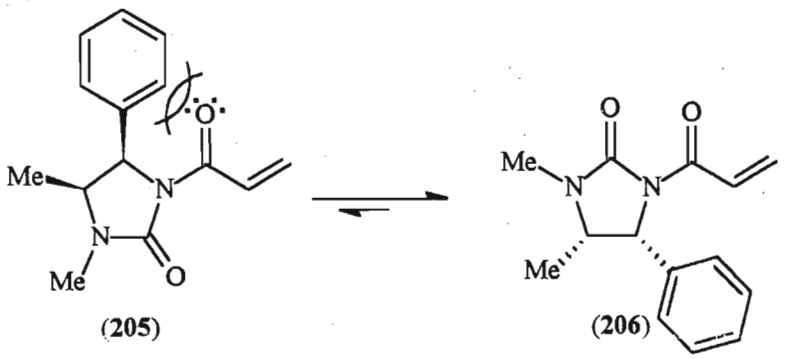
Scheme 56

The mechanism involves the Michael addition of DABCO to the α,β-unsaturated and β-unsubstituted carbonyl (**203**). The zwitterion intermediate that forms (**204**) then reacts spontaneously with the diene in a non-concerted Diels-Alder reaction followed by the concerted elimination of DABCO to afford the four respective cycloadducts.

Reactions with β-substituted dienophiles were unsuccessful due to the fact that they are sterically hindered and attack by DABCO at this position can therefore not take place.

The phenyl *N*-acylimidazolidinone auxiliary surprisingly showed impressive π-facial results (Table 9, entry 1) despite the fact that no bidentate chelation is possible between the auxiliary carbonyl and the α,β-unsaturated carbonyl moieties. The only explanation for this diastereofacial bias is that the orientation of the dienophile system

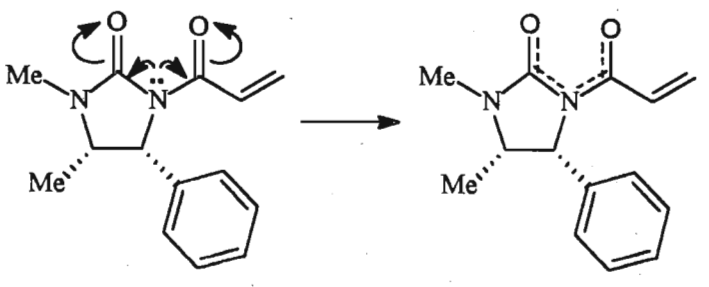
is restricted to the orientation in which electronic repulsion between the α,β-unsaturated carbonyl oxygen and the phenyl ring is avoided as shown in Figure 6 (205) and (206).



(205) (206)

Figure 6

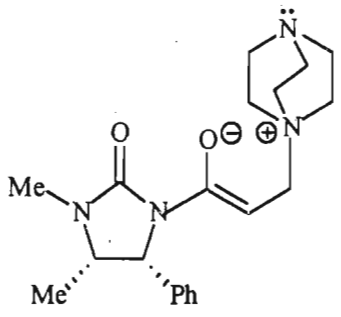
In addition to this, back-donation of the nitrogen nonbonded electron pair to the carbonyls on either side gives rise to an energetically favourable conformation due to the more even distribution of charges (207) (Figure 7). However, in order for this to occur, the carbonyl π-orbitals must be orientated in such a way as to enable maximum overlap between them and the lone pair orbital of the nitrogen. Maximum overlap occurs when both carbonyls are parallel to one another. In this way, the two π-orbitals which are perpendicular to the carbonyl double bonds are in the same plane as the nitrogen lone pair orbital (208). The orientation that is thus taken up is the same as the one observed in Lewis acid-catalysed reactions. Therefore, the reacting cyclopentadiene molecule will selectively approach the C_α *re*-face of the dienophile which is in accordance with the stereoselectivity expected from the results obtained.



(207) (208)

Figure 7

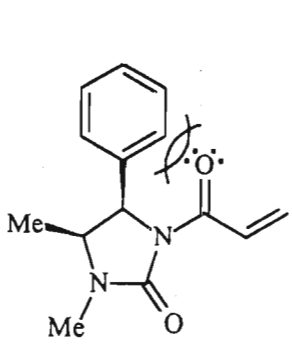
The formation of the dienophile-DABCO complex provides another possible explanation for the π-facial selectivity observed. On formation of the zwitterion, the intermediate takes up a position such that the negative charge of the enolate oxygen and the positive charge of the DABCO-nitrogen are aligned (**209**) (Figure 8). The intermediate, therefore, remains in the correct orientation for the C_α *re*-face approach of cyclopentadiene.



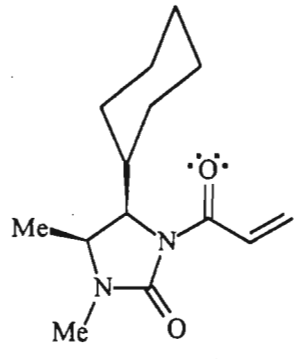
(**209**)

Figure 8

Of the two reacting dienophiles, the phenyl-substituted imidazolidinone auxiliary (Table 9, entry 1) proved to be more successful than its cyclohexyl analogue (Table 9, entry 4). This is in sharp contrast to the Et_2AlCl catalysed reactions (Table 7, entries1 and 6). Reasons for this were attributed to the fact that electronic repulsions between the α,β-unsaturated carbonyl oxygen lone pairs of electrons and the π-electrons of the phenyl ring (**210**) are greater than those experienced by the same oxygen and the cyclohexyl functionality of the cyclohexyl analogue (**211**) (Figure 9).



(**210**)



(**211**)

Figure 9

Therefore, diastereofacial bias is not experienced by the cyclohexyl analogue since two possible conformations of the cyclohexyl analogue, (**212**) and (**213**) (Figure 10), can exist. Approach of a reacting diene would, therefore, be possible from either face of the dienophile.

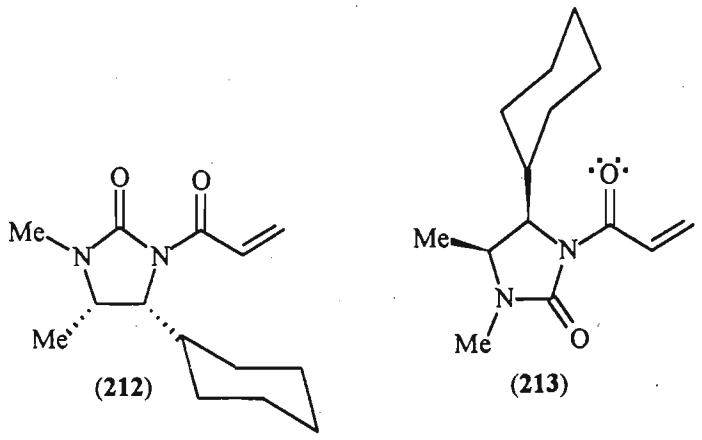
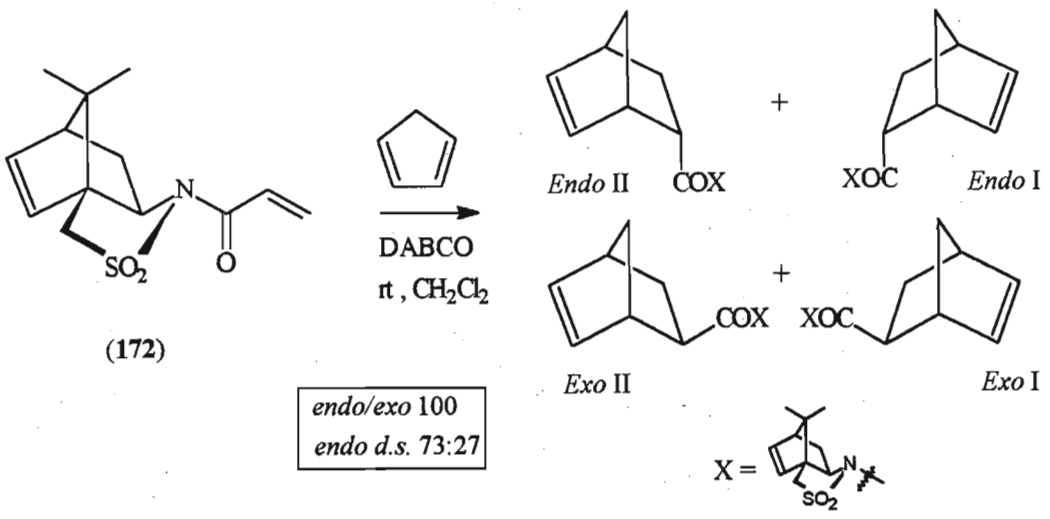


Figure 10

Although the above results were clearly not as successful as the analogous reactions catalysed by Et_2AlCl (Scheme 48, Table 7), it is predicted that DABCO catalysed reactions are amenable to large scale procedures. Due to the fact that the diastereomeric cycloadducts are easily purified by recrystallization or chromatography, and together with the practical advantages and mild reaction conditions, this could render the DABCO methodology with the *N*-acylimidazolidinone auxiliary industrially viable.

In order to determine the scope of DABCO-catalysed Diels-Alder reactions, the reactions were carried out with the less reactive dienes, isoprene and 2,3-dimethyl-1,3-butadiene. Even at elevated temperatures and after several days, no reaction occurred with either of the acyclic dienes and the dienophile was recovered, unaltered. To determine whether more reactive dienophiles would improve the efficiency of DABCO-catalysed reactions, the *N*-acryloyl-substituted bornane-10,2-sultam (**172**) was employed as the dienophile (Scheme 57).



Scheme 57

The result shows that the increased reactivity may have increased the *endo/exo* selectivity, but the dienophile does not exhibit diastereofacial bias to the extent that the *N*-acryloyl-substituted imidazolidinone auxiliary does (Table 9, entry 1).

2.11 Conclusions

The *N*-acylimidazolidin-2-one auxiliary and its cyclohexyl derivative have shown near-perfect diastereo- and π-facial selectivity in Diels-Alder cycloaddition reactions. Their facile preparation from low-cost, natural product starting materials ensures that the use of these auxiliaries is practically and economically advantageous. The enantiomer, norephedrine, is also commercially available so that both antipodes may be synthesised. The novel method of acylation to produce the dienophiles has further increased the advantages of employing these auxiliaries in Diels-Alder reactions.

The cycloaddition products were produced with predictable π-face stereodifferentiation and directly analysed by H^1 NMR spectroscopy and GC/MS to determine their stereochemical purity.

The sense of induction was determined to be the approach of dienes taking place from the C_α *re*-face of the *N*-acylimidazolidinone dienophile intermediate. This was

confirmed by comparisons with literature optical rotation values for the respective benzyl ester derivatives as well as an X-ray crystal structure of the major product of the reaction between the acrylate derived imidazolidinone and cyclopentadiene.

Crystallinity was imparted to most of the cycloaddition products which greatly facilitates purification and enables further stereochemical homogeneity from diastereomer mixtures. The imidazolidin-2-ones were also sufficiently soluble in the solvents required for the various reactions, even those that took place at low temperatures of -78°C.

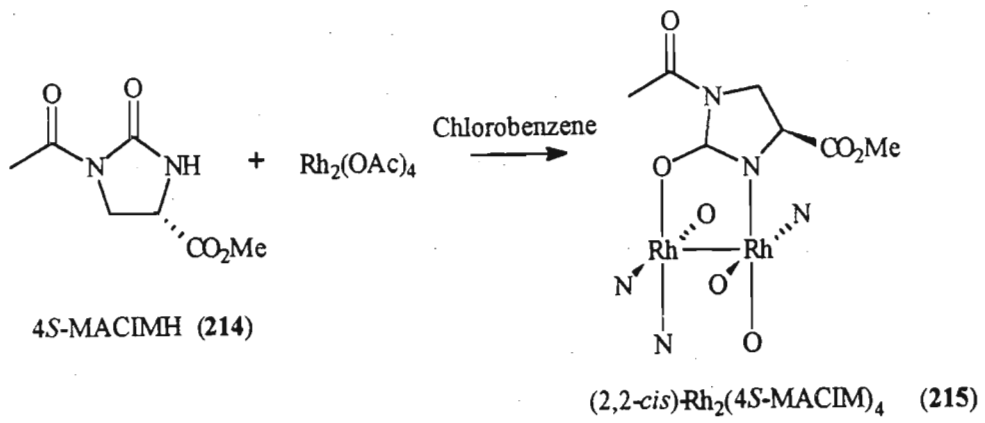
The removal of the auxiliary was possible under standard conditions which did not alter the chirality of the cycloaddition products nor the recoverable auxiliary.

Finally, Diels-Alder cycloaddition reactions with certain *N*-acryloylimidazolidin-2-ones catalysed by a tertiary amine base, DABCO, were found to take place smoothly under mild reaction conditions and, in some cases, with unexpectedly high levels of stereodifferentiation.

2.12 Future Work

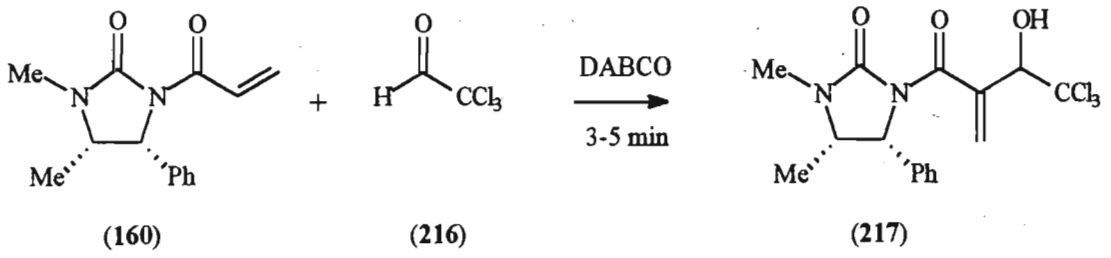
The synthesis of an alternative imidazolidinone auxiliary which possesses a *N*-acyl rather than an *N*-alkyl substituent would be an interesting study that could be undertaken, although beyond the scope of this work. In this way, results of the reversal of inductive effect leading to increased reactivity of the system could be studied. The added transformations required would detract from the advantage that these auxiliaries have of being readily synthesised at low cost. This phenomenon has been observed in studies by Raab[156] which involved imidazolidinones as bridging ligands in dirhodium (II) catalyst species. Here, the *N*-alkyl inductive effect interferes with ligand exchange , presumably by stabilising the intermediate. In this case, the problem was overcome by the use of alternative imidazolidinones which possess an *N*-acyl rather than an *N*-alkyl substituent. The reversal of inductive effect then

allowed for smooth exchange to occur. (Scheme 58). The auxiliary (**214**), however, is obtained in an 8 step synthesis.



Scheme 58

In order to extend the scope of reactions possible with *N*-acylimidazolidinones, several Baylis-Hillman reactions were carried out with the acryloyl derivative and various aldehydes, such as acetaldehyde, propionaldehyde, benzaldehyde and trichloroacetaldehyde with DABCO as the catalyst. (Scheme 59).

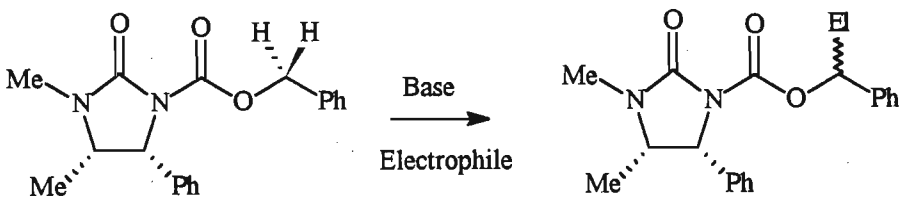


Scheme 59

Results proved disappointing with only the trichloroacetaldehyde (**216**) reactive enough to undergo reaction to form the alcohol (**217**). It would be interesting to determine the effect of adding a complexing agent to these reactions since the Lewis acid, by complexing simultaneously to the two carbonyls of the system, would not only increase the reactivity of the system towards the aldehyde but it would also improve the stereoselectivity of the reaction by restricting rotation about the bond

connecting the chiral auxiliary and the prochiral moiety and thereby increasing the diastereofacial bias of the system. $ZnCl_2$ was used in a Baylis-Hillman reaction with the Camphor sultam auxiliary (**172**) and acetaldehyde but preliminary results proved unsuccessful.

Work leading to yet another application of the *N*-acylimidazolidinone was begun and although it remains to be completed, looked much more promising. It started out as an extension of the work being carried out on carbamates in our laboratory.[157] It was our aim to introduce stereoselectivity to these reactions by the use of *N*-acylimidazolidinones (**128**) as the chiral inducer.



(**218**) (**219**)

Scheme 60

The first step of the study involved the formation of the carbamate (**218**) by *N*-acylation with benzyl chloroformate in the same way as the dienophiles were prepared. The following step involves the removal of a benzylic proton to form an anion which could then be quenched with a variety of electrophiles such as *tert*-butyldimethylsilyl chloride (TBDMSCl) (**219**). The use of *n*-BuLi, *tert*-BuLi and LDA to remove the proton caused the auxiliary to cleave rather than the formation of the anion to take place. This reaction remains to be successfully attempted with the proper choice of base that does not cause the auxiliary to cleave.

The H^1 NMR spectrum of the chiral carbamate revealed the fact that it has potential to undergo stereoselective reactions with electrophiles. Normally the benzylic protons of the carbamate appear as a singlet at about 5ppm. The benzylic protons of the chiral carbamate (**218**) appeared as a doublet of doublets in the same region, probably due to the difference in chemical environment caused by the diastereofacial bias of the

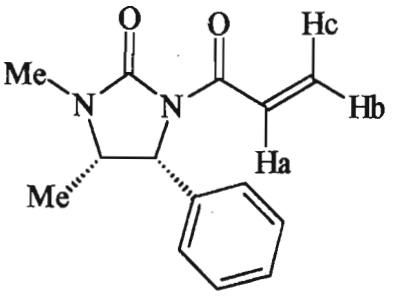
chiral auxiliary. Removal of the proton with a suitable base and quenching with an electrophile should take place selectively from the most exposed face of the chiral carbamate system. This would require the addition of at least 2 equivalents of base in order to abstract the proton and to ensure bidentate chelation with the two carbonyl oxygens to enforce π-facial selectivity.

The success of this reaction would result in another important application of work possible with the *N*-acylimidazolidin-2-one auxiliary.

3. EXPERIMENTAL

3.1 INDEX OF COMPOUNDS PREPARED

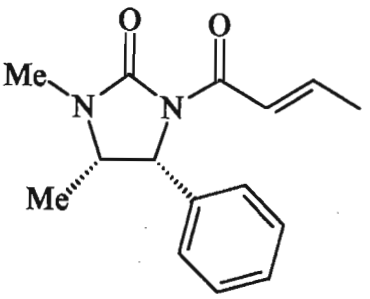
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-prop-2'-enoylimidazolidin-2-one



124
178
179

(160)

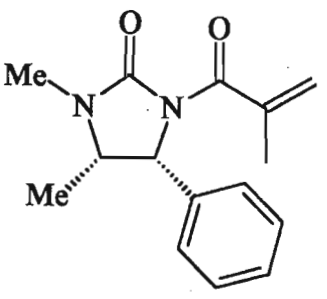
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-but-2'-enoyl-imidazolidin-2-one



125
180
181

(161)

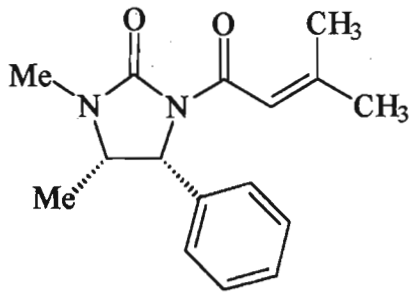
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-(2'-methylprop-2'-enoyl)-imidazolidin-2-one



126
182
183

(162)

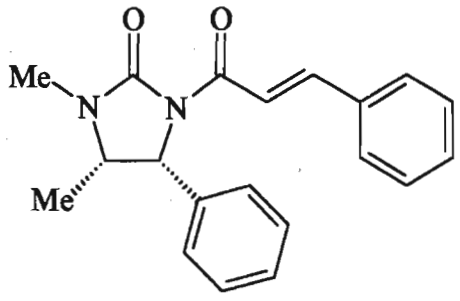
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-(3'-methylbut-2'-enoyl)-imidazolidin-2-one



(163)

127
184
185

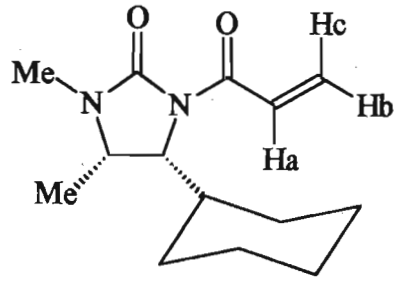
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-(3'-phenylprop-2'-enoyl)-imidazolidin-2-one



(164)

128
186
187

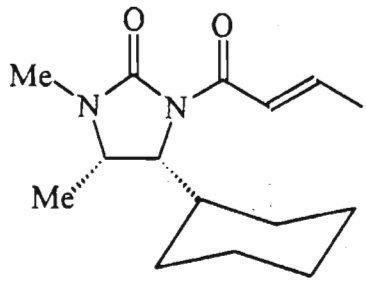
(4R, 5S)-4-Cyclohexyl-1,5-dimethyl-3-prop-2'-enoyl-imidazolidin-2-one



(173)

129
188
189

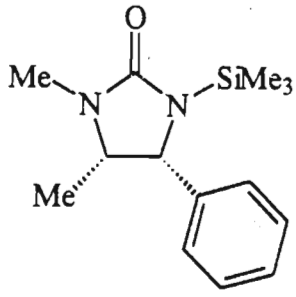
(4R, 5S)-4-Cyclohexyl-1,5-dimethyl-3-but-2'-enoylimidazolidin-2-one



(174)

130
190
191

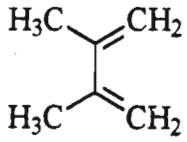
(4R,5S)-1,5-Dimethyl-4-phenyl-3-trimethylsilylimidazolidin-2-one



(165)

131
192
193

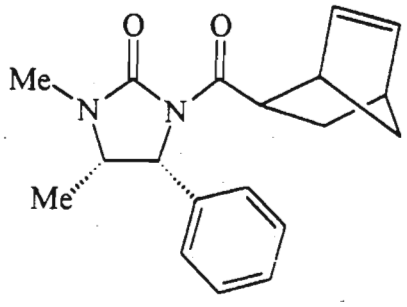
2,3-Dimethyl-1,3-butadiene



(188b)

133
194
195

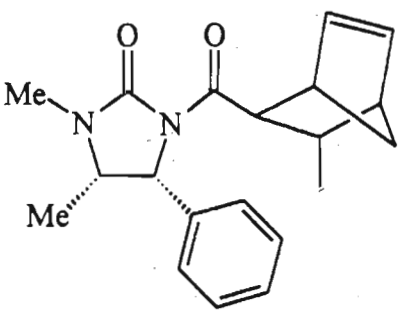
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-bicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one



(183)

135
196
197

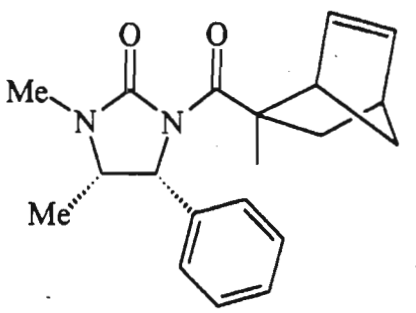
(4R,5S)-1,5-Dimethyl-4-phenyl-3-((3'S,4'S,5'R, 6'R)-5'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one



136
198
199

(184)

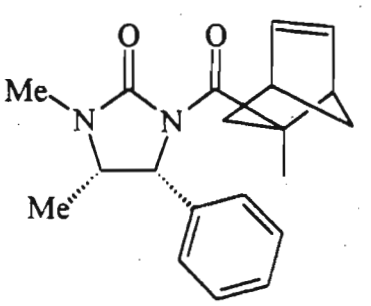
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one



137
200
201

(185a)

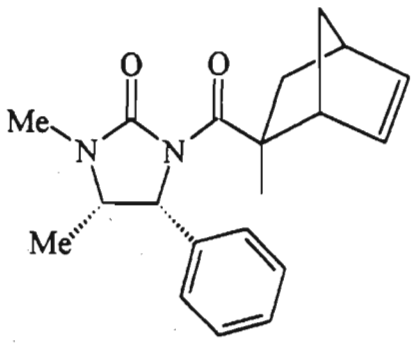
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'R, 6'R)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one



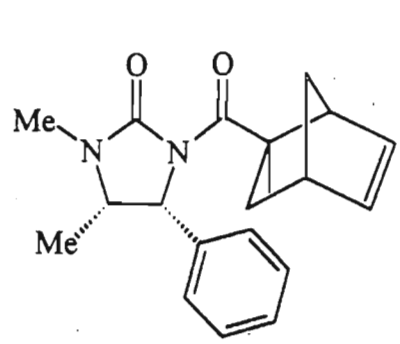
138
202
203

(185b)

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'S, 6'R)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one and *(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'R, 6'S)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one*



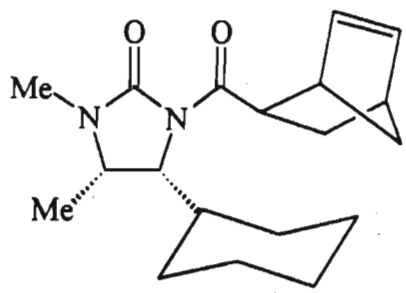
(185c)



(185d)

138
204
205

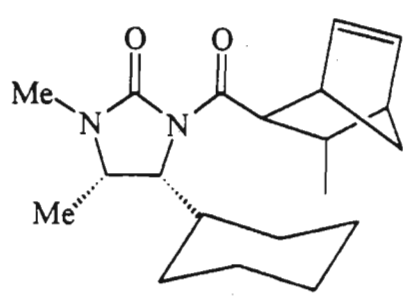
(4R, 5S)-4-Cyclohexyl-1,5-dimethyl-3-((3'S, 4'S, 6'S)-bicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one



(186)

139
206
207

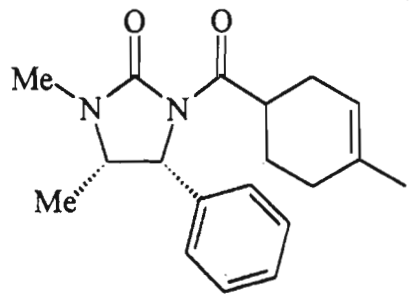
(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-((3'S,4'S,5'R,6'R)-5'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one.



(187)

140
208
209

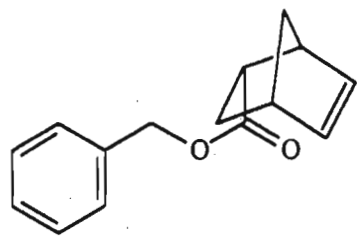
(4R,5S)-1,5-Dimethyl-4-phenyl-3-((4'S)-1'-methylcyclohexene-4'-carbonyl)-imidazolidin-2-one



142
210
211

(189)

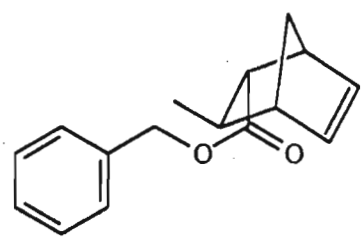
Phenylmethyl (3S, 4S, 6S)-bicyclo[2.2.1]heptene-4-carboxylate



144
212
213

(191)

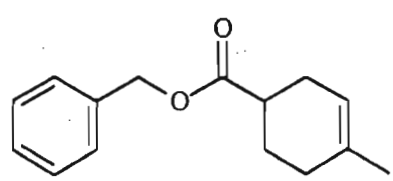
Phenylmethyl (3S, 4S, 5R, 6R)-5-methylbicyclo[2.2.1]heptene-4-carboxylate



145
214
215

(192)

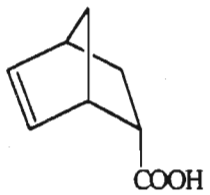
Phenylmethyl (4S)-1-methylcyclohexene-4-carboxylate



146
216
217

(190)

5-Bicyclo[2.2.1.]heptene-4-carboxylic acid (*endo* enantiomers)



Endo

(196c)

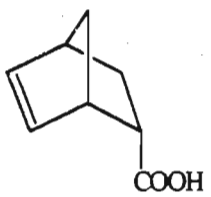
149

218

219

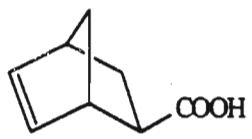
5-Bicyclo[2.2.1.]heptene-4-carboxylic acid (*endo* enantiomers) and

5-Bicyclo[2.2.1.]heptene-4-carboxylic acid (*exo* enantiomers).



Endo

(196c)



Exo

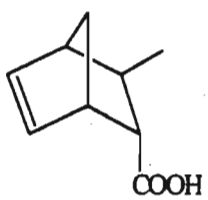
(196d)

149

220

221

5-Methylbicyclo[2.2.1]heptene-4-carboxylic acid (*endo* enantiomers)



Endo

(196a)

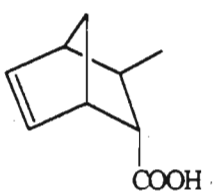
150

222

223

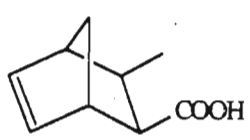
5-Methylbicyclo[2.2.1]heptene-4-carboxylic acid (*endo* enantiomers) and

5-Methylbicyclo[2.2.1.]heptene-4-carboxylic acid (*exo* enantiomers).



Endo

(196a)



Exo

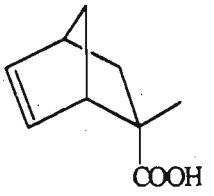
(196b)

150

224

225

4-Methylbicyclo[2.2.1]heptene-4-carboxylic acid (*endo* enantiomers)



Endo

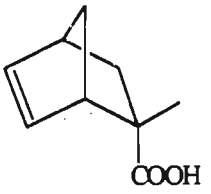
(196e)

151

226

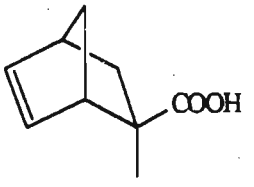
227

4-Methylbicyclo[2.2.1]heptene-4-carboxylic acid (*endo* enantiomers) and *4-Methylbicyclo[2.2.1.]heptene-4-carboxylic acid* (*exo* enantiomers).



Endo

(196e)



Exo

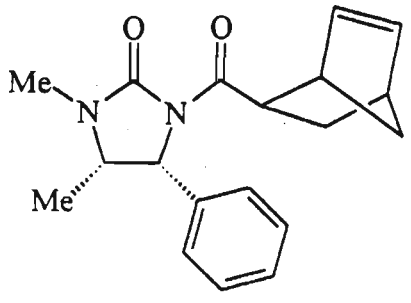
(196f)

151

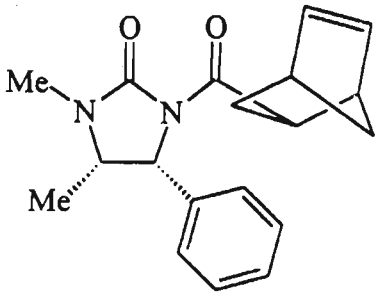
228

229

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-bicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (major *endo* isomer) and *(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'R, 6'R)-bicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one* (minor *endo* isomer).



(183a)



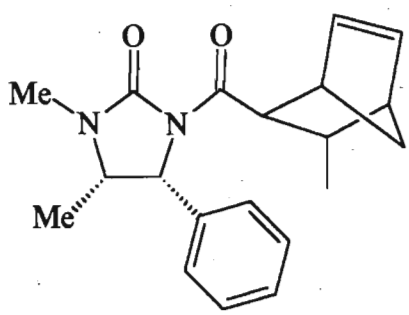
(183b)

153

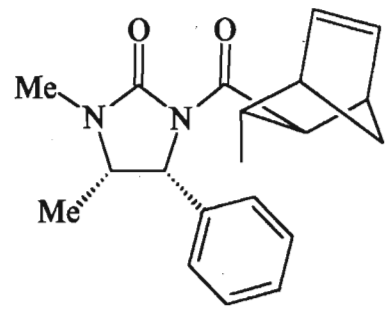
230

231

[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (major *endo* isomer) and *(4R,5S)-1,5-Dimethyl-4-phenyl-3-((3'R,4'R,5'S, 6'S)-5'-methylbicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one* (minor *endo* isomer).



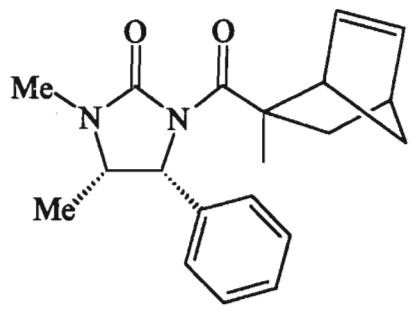
(184a)



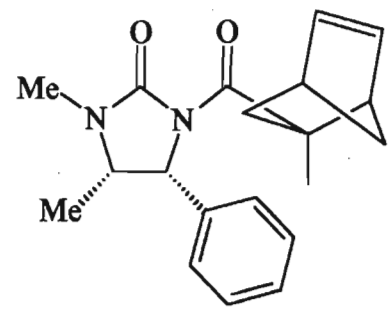
(184b)

155
232
233

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-4'-methylbicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (major *endo* isomer) and *(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'R, 6'R)-4'-methylbicyclo [2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one* (minor *endo* isomer).



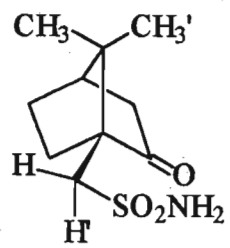
(185a)



(185b)

157
234
235

(1S,4R)-7,7-Dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-methanesulfonamide

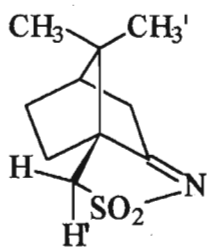


(157)

159
236
237

(1S,7R)-10,10-Dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]

dec-3-ene-5,5-dioxide



(158)

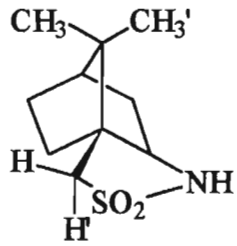
160

238

239

(1S,7R)-10,10-Dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-

5,5-dioxide



(57)

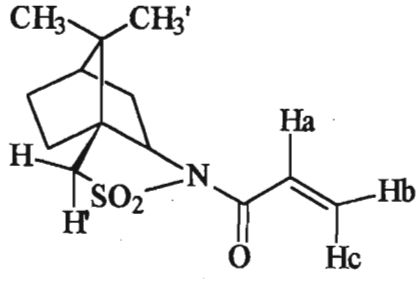
161

240

241

4-Prop-2'enoyl-(1S,7R)-10,10-dimethyl-5-thia-4-azatricyclo

[5.2.1.$0^{3,7}$]decane-5,5-dioxide



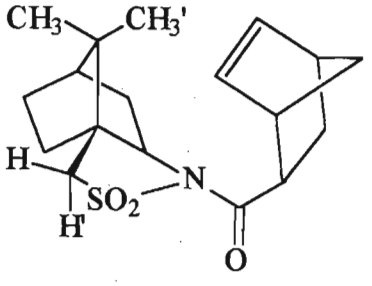
(172)

162

242

243

4-((5R,6S)-6-Methylbicyclo{2.2.1]hept-2-en-5-carbonyl)-(1S,7R)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide



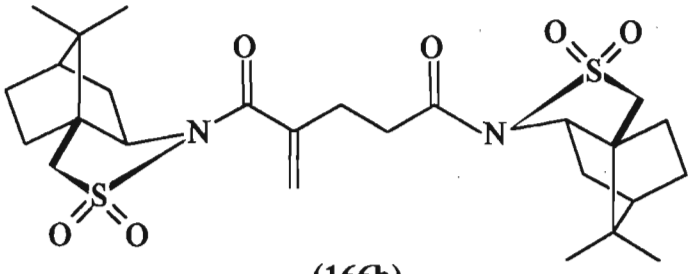
163

244

245

(172a)

Major By-product of Acylation Reaction.



164

246

247

(166b)

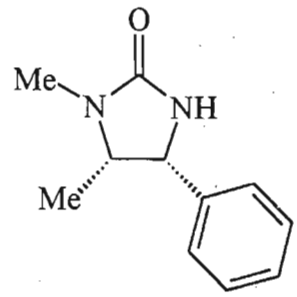
3.2 CHEMICALS AND INSTRUMENTATION

Solvents and liquid reagents were dried using standard techniques and distilled prior to use. Preparative column chromatography was performed using the technique of Still and co-workers[158] on Merck silica gel 60 (230-400 mesh). Pre-coated Kieselgel 60 F_{254} Merck plastic sheets were used for thin-layer chromatography. Cobalt (II) thiocyanate was used as the dip reagent for TLC plate development.[159a] Centrifugal chromatography was carried out using a Harrison Research Chromatotron (7924T) on 4 mm Merck silica gel (200-400 mesh) coated glass plates. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. NMR spectra (^{1}H 200 MHz and ^{13}C 50 MHz) were recorded on Varian Gemini 200 and Varian T60 (^{1}H 60 MHz) instruments. All chemical shifts are reported in parts per million (ppm, δ) downfield from Me_4Si (TMS) as internal standard, using $CDCl_3$ as the solvent. Mass spectra were recorded on a Hewlett-Packard mass spectrometer (HP5988A), linked to a gas chromatograph (Column type: HP-1). Diastereomeric ratios (*i.e .endo:exo* ratios) were determined by gas chromatographic-mass spectrometry and NMR spectroscopy. Optical rotations were determined on a Perkin-Elmer 241 digital polarimeter. Infra-red spectra were recorded as a thin film on NaCl or KBr plates using a Perkin-Elmer 1420 or a Shimadzu FTIR-4300 spectrometer. Elemental analysis was carried out on a Perkin-Elmer 2400 CHN elemental analyser. Low temperatures were maintained using dry-ice solvent baths according to the procedure of Phipps and Hume.[159b]

3.3 PREPARATIONS

3.3.1 Preparation of *N*-Acylimidazolidinone Auxiliaries

(4R,5S)-1,5-Dimethyl-4-phenylimidazolidin-2-one

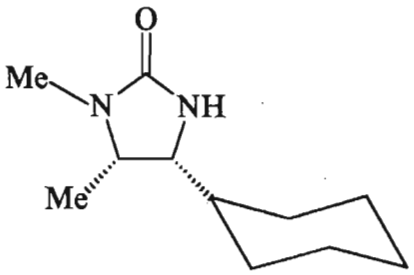


(128)

Ephedrine hydrochloride (50 g, 0.248 mol) and urea (45 g, 0.749 mol) were mixed using a mechanical stirrer and heated for 30 min at 170-175°C followed by 1 h at 200-210°C. The mixture was cooled to 100°C and then treated with water. The slightly oily solid which precipitated was washed with 5% HCl and water and then filtered. Recrystallization from ethanol gave pure white crystals (**128**) (28.8 g, 60%).

m.p. 177°C (lit.[137] 177-179°C); (Found: C, 69.46; H, 7.83; N, 14.57. $C_{11}H_{14}N_2O$ requires C, 69.45; H, 7.42; N, 14.72%); $[\alpha]_D$ -44.3° (*c* 0.9, MeOH) (lit.[137], $[\alpha]_D$ -44.5° (*c* 3.0, MeOH)); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3460 (NH) and 1704 (CO); δ_H (200 MHz) 0.74 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 2.73 (3H, s, NC*H*$_3$), 3.87 (1H, dq, *J* = 6.6 and 8.4 Hz, C*H*CH$_3$), 4.77 (1H, d, *J* = 8.6 Hz, C*H*Ph), 5.62 (1H, br s, N*H*), 7.23-7.38 (5H, m, Ph); δ_C (50 MHz) 14.28 (q, CHC*H*$_3$), 28.15 (q, NC*H*$_3$), 57.58 (d, *C*HCH$_3$), 58.10 (d, *C*HPh), 127.16, 127.91 and 128.41 (d, Ph), 138.30 (s, Ph), 162.64 (s, *C*O); *m/z* 190 (M^+, 27%), 175 (55), 58 (100).

(4R, 5S)-4-Cyclohexyl-1,5-dimethylimidazolidin-2-one



(144)

A teflon reaction vessel was charged with a mixture of $RhCl_3.3H_2O$ (263 mg, 1.26 mmol) in water (30 ml), Aliquat 336 (588 mg, 1.44 mmol) and **(128)** (6.00 g, 26.32 mmol) in 1,2-dichloroethane (30 ml). The reaction mixture was stirred at 30°C for 48 h under H_2 pressure (5 atms) in an autoclave. The phases were separated and the organic phase was filtered through basic alumina, treated with activated charcoal, filtered and concentrated. Recrystallization of the residue from EtOAc afforded **(144)** as white crystals (4.90 g, 95%).

m.p.159°C, (Lit.[137] 162°C); (Found: C, 67.54; H, 10.55; N, 14.51. $C_{11}H_{20}N_2O$ requires C, 67.31; H, 10.27; N, 14.27%); $[\alpha]_D$ -1.2° (*c* 1.195, $CHCl_3$), (Lit.[137] $[\alpha]_D$ -1.0° (*c* 0.60, $CHCl_3$)); υ_{max}(KBr)/cm^{-1} 3354 (NH), 2968 (CH_3) and 1679 (CO); δ_H (200MHz) 0.90-1.79 (11H, m, cyclo-C_6H_{11}), 1.10 (3H, d, J = 6.4 Hz, $CHCH_3$), 2.75 (3H, s, NCH_3), 3.29 (1H, m, CHcyclo-C_6H_{11}), 3.59 (1H, dq, J = 6.5 and 6.6 Hz, $CHCH_3$), 5.33 (1H, br s, N*H*); δ_C (50MHz) 10.65 (q, $CHCH_3$), 25.57, 25.60 and 26.24 (t, 3 x CH_2 of cyclo-C_6H_{11}), 27.90 (q, NCH_3), 29.63 and 29.94 (t, 2 x CH_2 of cyclo-C_6H_{11}), 37.17 (d, *C*H of cyclo-C_6H_{11}), 56.01 (d, CHcyclo-C_6H_{11}), 59.79 (d, $CHCH_3$), 162.59 (s, NCON); *m/z* 196 (M^+, 4%), 181(3), 113(100).

3.3.2 Preparation of Dienophiles

3.3.2.1 Preparation of Acid Chlorides

Acryloyl chloride

Acrylic acid (20.0 g, 0.28 mol) and PCl_3 (11.0 g, 0.08 mol) were placed in a flask fitted with a reflux condenser and a $CaCl_2$ drying tube. The flask was gently warmed until boiling began and then maintained at 60-70^{0}C for 15 min, then allowed to stand at rt for 2 h. The mixture separated into two layers; the upper layer was removed and hydroquinone (0.20 g) was added. This was then distilled to afford acryloyl chloride (20.9 g, 83%). b.p. 73-75°C. (Lit.[160] 72-76°C).

CH_2=CHCOCl

Crotonyl chloride

Crotonic acid (20.0 g, 0.23 mol) and PCl_3 (11.0 g, 0.08 mol) were treated following the procedure described for the preparation of acryloyl chloride, affording crotonyl chloride (19.0 g, 75%). b.p. 120-123^{0}C. (Lit.[160] 120-123°C).

CH_3CH=CHCOCl

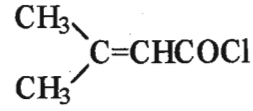
Methacryloyl chloride

Methacrylic acid (20.0 g, 0.23 mol) and PCl_3 (11.0 g, 0.08 mol) were treated following the procedure described for the preparation of acryloyl chloride, affording methacryloyl chloride (20.6 g, 85%). b.p. 94-96^{0}C. (Lit.[160] 95-96°C).

CH_2=CCH_3COCl

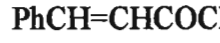
3,3-Dimethyl acryloyl chloride

Dimethyl acrylic acid (20.0 g, 0.20 mol) and PCl_3 (11.0 g, 0.08 mol) were treated following the procedure described for the preparation of acryloyl chloride, affording dimethyl acryloyl chloride (18.5 g, 78%). b.p. 145-147^{0}C. (Lit.[160] 145-147°C).



Cinnamoyl chloride

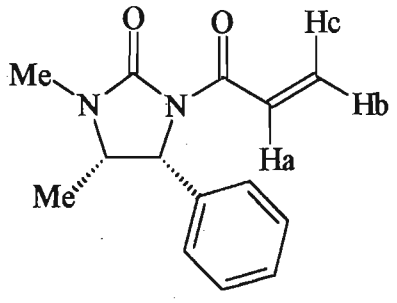
Cinnamic acid (10.0 g, 0.07 mol) and $SOCl_2$ (24.6 g, 0.21 mol) were placed in a flask fitted with a reflux condenser and a $CaCl_2$ drying tube. The flask was gently warmed until all the solid had dissolved and then left to stir at rt for 2h. The mixture was distilled and after cooling, the solid which formed was washed with cold hexane to afford the product as a white crystalline product (9.0 g, 80%). m.p. 35^{0}C, (Lit.[160] 37° C).



3.3.2.2 General Procedure for the Preparation of *N*-Acylimidazolidinones using DABCO

A solution of imidazolidinone (**128**) (0.30 g, 1.58 mmol) and DABCO (0.35 g, 3.16 mmol) in dry THF (20 ml) was left to stir under N_2 at rt for 30 min. Fine copper powder (0.10 g, 1.58 mmol) and CuCl (0.17 g, 1.74 mmol) were then added and the mixture was again left to stir for a further 15 min. The appropriate acyl chloride (2eq, 3.16 mmol) was then added slowly allowing HCl gas to escape. The mixture was left to stir overnight. The THF was removed under reduced pressure and a 2 cm column plug of neutral alumina was run eluting with EtOAc. The residue was recrystallized from CH_2Cl_2.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-prop-2'-enoylimidazolidin-2-one

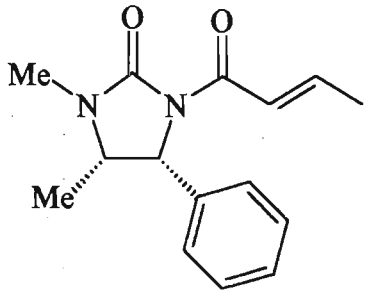


(160)

Dienophile **(160)** was synthesised according to the general procedure and isolated as white crystals (0.378 g, 98%).

m.p. 138°C; (Found: C, 68.78; H, 6.44; N, 11.30. $C_{14}H_{16}N_2O_2$ requires C, 68.83; H, 6.60; N, 11.47%); $[\alpha]_D$ -121.60° (*c* 1.028, $CHCl_3$); υ_{max} (KBr, cm^{-1}) 2960 (CH_3), 1712 (CO), 1676 (CO) and 1620 (C=C); δ_H (200MHz) 0.81 (3H, d, J = 6.6 Hz, $CHCH_3$), 2.84 (1H, s, NCH_3), 3.92 (1H, dq, J = 6.6 and 8.5 Hz, $CHCH_3$), 5.36 (1H, d, J = 8.5 Hz, CHPh), 5.75 (1H, dd, J = 2.0 and 10.4 Hz, H_b), 6.39 (1H, dd, J = 2.0 and 17.0 Hz, H_c), 7.14-7.37 (5H, m, Ph), 7.72 (1H, dd, J = 10.4 and 17.0 Hz, H_a);
δ_C (50 MHz) 14.93 (q, $CHCH_3$), 28.15 (q, NCH_3), 53.91 (d, $CHCH_3$), 59.39 (d, CHPh), 126.92, 128.04 and 128.47 (d, Ph), 128.74 (d, $CH=CH_2$), 129.67 (t, $CH=CH_2$), 136.50 (s, Ph), 155.62 (s, NCON), 164.50 (s, NCOCH); *m/z* 244 (M^+, 14%), 189 (30), 132 (100).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-but-2'-enoylimidazolidin-2-one

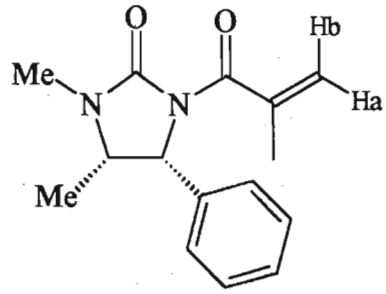


(161)

Dienophile **(161)** was synthesized according to the general procedure and isolated as white crystals (0.387 g, 95%).

m.p. 167°C; (Found C, 69.52; H, 7.18; N, 10.93. $C_{15}H_{18}N_2O_2$ requires C, 69.75; H, 7.02; N, 10.84%); $[\alpha]_D$ -104.30° (*c* 0.67, $CHCl_3$); υ_{max} (KBr, cm^{-1}) 2960 (CH_3), 1720 (CO), 1652 (CO) and 1634 (C=C); δ_H (200 MHz) 0.81 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.90 (3H, dd, *J* = 1.7 and 6.9 Hz, CH=CHC*H*$_3$) 2.84 (3H, s, NC*H*$_3$), 3.91 (1H, dq, *J* = 6.6 and 8.5 Hz, C*H*CH_3) 5.35 (1H, d, *J* = 8.5 Hz, C*H*Ph), 7.01 (1H, dq, *J* = 6.9 and 15.3 Hz, CH=C*H*CH_3), 7.13-7.33 (5H, m, Ph), 7.48 (1H, dq, *J* = 1.7 and 15.3 Hz, C*H*=$CHCH_3$); δ_C (50 MHz) 14.98 (q, $CHCH_3$), 18.40 (q, CH=$CHCH_3$), 28.19 (q, NCH_3), 53.93 (d, $CHCH_3$), 59.39 (d, *C*HPh), 123.16 (d, *C*H=$CHCH_3$), 126.93, 127.99 and 128.48 (d, Ph), 136.69 (s, Ph), 144.46 (d, CH=*C*HCH_3), 156.20 (s, NCON), 164.78 s, NCOCH); *m/z* 258 (M^+, 18%), 189 (40), 132 (100).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-prop-2',2'-enoylmethylimidazolidin-2-one

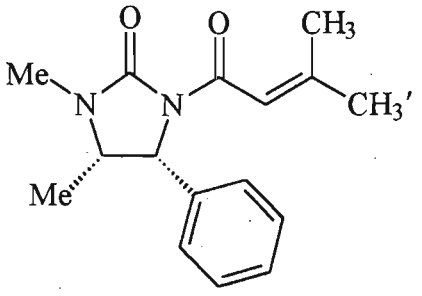


(162)

Dienophile **(162)** was synthesized according to the general procedure and isolated as white crystals (0.236 g, 58%).

m.p. 124°C; (Found: C, 69.57; H, 6.86; N, 10.74. $C_{15}H_{18}N_2O_2$ requires C, 69.75; H, 7.02; N, 10.84%); $[\alpha]_D$ -90.77° (*c* 0.542, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2993 (CH_3), 1728 (CO) and 1641 (CO); δ_H (200 MHz) 0.80 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 2.04 (3H, dd, *J* = 0.6 and 1.1 Hz, C*H*$_3$C=CH$_2$), 2.82 (3H, s, NCH_3), 3.93 (1H, dq, *J* = 6.6 and 8.4 Hz, C*H*CH_3), 5.25 (1H, dd, *J* = 0.4 and 0.9 Hz, CH_3C=C*H*$_a$H$_b$), 5.29 (1H, dd, J = 0.5 and 1.4 Hz, CH_3C=CH$_a$*H*$_b$), 5.35 (1H, d, *J* = 8.7 Hz, C*H*Ph), 7.15-7.39 (5H, m, Ph); δ_C (50 MHz) 15.15 (q, CH*C*H_3), 19.63 (q, *C*H_3C=CH_2), 28.21 (q, N*C*H_3), 54.16 (d, *C*HCH$_3$), 59.10 (d, *C*HPh), 117.57 (s, CH_3*C*=CH_2), 126.77, 128.09 and 128.54 (d, Ph), 136.38 (s, Ph), 141.50 (t, CH_3C=*C*H$_2$), 154.81 (s, N*C*ON), 170.49 (s, N*C*OCCH$_3$); *m/z* 258 (M^+, 13%), 189 (22), 132 (100).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-(3'-methylbut-2'-enoyl)imidazolidin-2-one

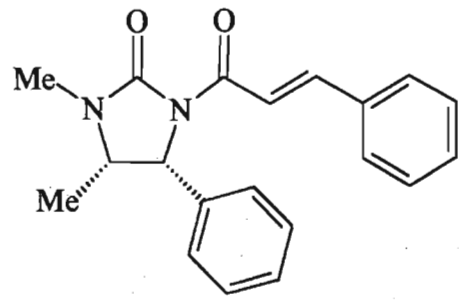


(163)

Dienophile (**163**) was synthesized according to the general procedure and isolated as white crystals (0.408 g, 95%).

m.p.148°C; (Found: C, 70.18; H, 7.26; N, 10.42; $C_{16}H_{20}N_2O_2$ requires C, 70.56; H, 7.40; N, 10.28%); $[\alpha]_D$ -94.23° (*c* 0.745, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2993 (CH_3), 1729 (CO), 1668 (CO) and 1632 (C=C); δ_H (200 MHz) 0.79 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.93 (3H, s, CH=CC*H*$_3$'), 2.05 (3H, s, CH=CC*H*$_3$), 2.82 (3H, s, NC*H*$_3$), 3.88 (1H, dq, *J* = 6.6 and 8.5 Hz, C*H*CH$_3$), 5.35 (1H, d, *J* = 8.6 Hz, C*H*Ph), 7.14-7.37 (5H, m, Ph), 7.29 (1H, s, COC*H*=C(CH$_3$)$_2$); δ_C (50MHz) 15.01 (q, CH*C*H$_3$), 21.13 (q, CH=C*C*H$_3$'), 27.92 (q, CH=C*C*H$_3$), 28.21 (q, N*C*H$_3$), 53.88 (d, *C*HCH$_3$), 59.22 (d, *C*HPh), 117.21 (d, COCH), 126.91, 127.88 and 128.47 (d, Ph), 128.48 (s, CH=*C*CH$_3$), 136.96 (s, Ph), 155.98 (s, N*C*ON), 164.99 (s, N*C*OCH); *m/z* 272 (M^+, 15%), 189 (73), 132 (83), 83 (100).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-(3'-phenylprop-2'-enoyl)imidazolidin-2-one

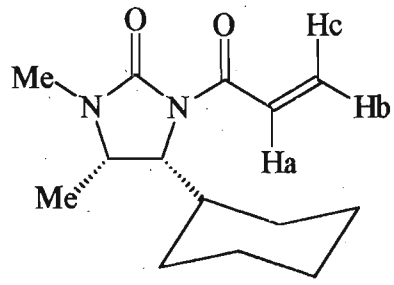


(164)

Dienophile **(164)** was synthesized according to the general procedure and isolated as white crystals (0.495 g, 98%).

m.p. 153°C; (Found: C, 74.76; H, 6.12; N, 8.91; $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%); $[\alpha]_D$ -25.22° (*c* 0.575, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2935 (CH_3), 1712 (CO), 1666 (CO), 1635 (C=C); δ_H (200MHz) 0.83 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 2.86 (3H, s, NCH_3), 3.95 (1H, dq, *J* = 6.6 and 8.5 Hz, $CHCH_3$), 5.42 (1H, d, *J* = 8.5 Hz, CHPh), 7.17-7.61 (10H, m, 2xPh), 7.70 (1H, d, *J* = 15.8 Hz, CH=CHPh), 8.19 (1H, d, *J* = 15.8 Hz, CH=CHPh); δ_C (50MHz) 15.68 (q, $CHCH_3$), 28.88 (q, NCH_3), 54.64 (d, $CHCH_3$), 60.23 (d, CHPh), 119.45 (d, CH=CHPh), 127.65-130.69 (d, 2xPh), 135.76 (s, CH=CHPh), 137.27 (s, CHPh), 145.01 (d, CH=CHPh), 156.64 (s, NCON), 165.59 (s, NCOCH); *m/z* 320 (M^+, 12%), 189(47), 132(100).

(4R, 5S)-4-Cyclohexyl-1,5-dimethyl-3-prop-2'-enoylimidazolidin-2-one

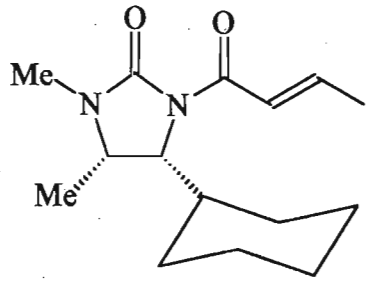


(173)

Dienophile **(173)** was synthesized according to the general procedure and isolated as white crystals (0.316 g, 80%).

m.p. 105°C; (HRMS Found:250.1808; $C_{14}H_{22}N_2O_2$ requires 250.1813); $[\alpha]_D$ -43.64° (*c* 0.967, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2981 (CH_3), 1720 (CO), 1674 (CO) and 1618 (C=C); δ_H (200MHz) 1.12-1.74 (11H, m, cyclo-C_6H_{11}), 1.34 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 2.78 (3H, s, NC*H*$_3$), 3.71 (1H, dq, *J* = 6.9 and 7.0 Hz, C*H*CH_3), 4.42 (1H, dd, *J* = 2.8 and 7.2 Hz, C*H*cyclo-C_6H_{11}) 5.78 (1H, dd, *J* = 2.1 and 10.4 Hz, H_b), 6.45 (1H, dd, *J* = 2.1 and 17.1 Hz, H_c), 7.67 (1H, dd, *J* = 10.4 and 17.0 Hz, H_a); δ_C (50MHz) 12.96 (q, CH*C*H_3), 26.08, 26.86 and 27.63 (t, 4xCH_2, cyclo-C_6H_{11}), 27.70 (q, N*C*H_3), 32.43 (t, *C*H_2, cyclo-C_6H_{11}), 39.20 (d, cyclo-*C*H), 54.56 (d, *C*HCH_3), 59.07 (*C*Hcyclo-C_6H_{11}), 129.02 (d, *C*H=CH_2), 129.24 (t, CH=*C*H_2), 156.27 (s, N*C*ON), 165.30 (s, N*C*OCH); *m/z* 250 (M^+, 7%), 167(45), 125(18), 113(100) 55(53).

(4R, 5S)-4-Cyclohexyl-1,5-dimethyl-3-but-2'-enoylimidazolidin-2-one



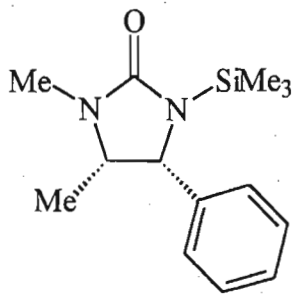
(174)

Dienophile (**174**) was synthesized according to the general procedure and isolated as white crystals (0.355 g, 85%).

m.p. 117°C; (Found: C, 67.98; H, 9.21; N, 10.45. $C_{15}H_{24}N_2O_2$ requires C, 68.15; H, 9.15; N, 10.59%); $[\alpha]_D$ -52.89° (*c* 1.677, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2977 (CH_3), 1720 (CO), 1672 (CO) and 1633 (C=C); δ_H (200MHz) 0.97-1.87 (11H, m, cyclo-C_6H_{11}), 1.33 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.93 (3H, dd, *J* = 1.6 and 6.9 Hz, CH=CHC*H*$_3$), 2.77 (3H, s, NC*H*$_3$), 3.76 (1H, dq, *J* = 6.9 and 7.0 Hz, C*H*CH_3), 4.44 (1H, dd, *J* = 2.8 and 7.3 Hz, C*H*cyclo-C_6H_{11}), 7.05 (1H, dq, *J* = 6.8 and 15.3 Hz, CH=C*H*CH_3), 7.43 (1H, dq, *J* = 1.6 and 15.3 Hz, C*H*=$CHCH_3$); δ_C (50MHz) 13.02 (q, $CHCH_3$), 18.39 (q, CH=$CHCH_3$), 26.11, 26.89 and 27.66 (t, 4xCH_2, cyclo-C_6H_{11}), 27.71 (q, NCH_3), 32.42 (t, CH_2, cyclo-C_6H_{11}), 39.22 (d, cyclo-C*H*), 54.59 (d, *C*HCH_3), 58.94 (d, *C*Hcyclo-C_6H_{11}), 123.43 (d, *C*H=$CHCH_3$), 143.86 (d, CH=*C*HCH_3), 156.56 (s, N*C*ON), 165.54 (s, N*C*OCH); *m/z* 264 (M^+, 8%), 181(21), 113(100).

3.3.2.3 Preparation of the Trimethylsilyl Intermediate

(4R,5S)-1,5-Dimethyl-4-phenyl-3-trimethylsilylimidazolidin-2-one



(165)

To a stirred solution of (**128**) (0.5 g, 2.63 mmol) and Ph_3CH (catalytic) in THF (40ml) at 0°C under N_2 was added dropwise BuLi (1.66 mls of a 1.74M solution in hexanes, 2.89 mmol) until the end point and the mixture stirred for 15 min. The temperature was taken down to -78°C and Me_3SiCl (0.65 mls, 5.27 mmol) was added slowly. The mixture was allowed to warm up to r.t. and left to stir for 1 h. Volatiles were removed *in vacuo* and the remaining solution was triturated with toluene to give a white powdery solid which was filtered to remove the LiCl. The toluene was then removed *in vacuo* to give a pure white solid (0.57g, 83%).

m.p. 127°C; (HRMS Found: 262.1505. $C_{14}H_{22}N_2OSi$ requires 262.1501); $[\alpha]_D$ +15.76° (*c* 0.184, $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2958 (CH_3) and 1662 (CO); δ_H (200 MHz) 0.12 (9H, s, $Si(CH_3)_3$) 0.73 (3H, d, J = 6.5 Hz, $CHCH_3$), 2.70 (3H, s, NCH_3), 3.81 (1H, dq, J = 6.5 and 8.5 Hz, $CHCH_3$), 4.55 (1H, d, J =8.5 Hz, CHPh), 7.15-7.34 (5H, m, Ph); δ_C (50 MHz) -0.48 (s, $Si(CH_3)_3$, 15.24 (q, $CHCH_3$), 28.47 (q, NCH_3), 57.97 (d, $CHCH_3$), 61.30 (d, CHPh), 127.77 and 128.18 (d, Ph), 139.58 (s, Ph), 164.97 (s, CO); *m/z* 262 (M^+, 11%), 247 (40), 162 (63), 73 (100).

3.3.2.4 General procedure for the Acylation of the Trimethylsilyl Intermediate

To a stirred solution of (**165**) (0.5 g, 1.91 mmol) in benzene (10 ml) under N_2 was added CuCl (0.28 g, 2.83 mmol) and Cu (0.01 g, 0.16 mmol) and finally freshly distilled acid chloride (4 eq., 11.39 mmol). The solution was left to reflux overnight. The mixture was filtered and the filtrate was concentrated down *in vacuo*. A chromatotron was used to purify the compound with 10% EtOAc:hexane as the eluent. The desired product was isolated and recrystallized from ether.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-prop-2'-enoylimidazolidin-2-one

Dienophile (**160**) was synthesized according to the general procedure and isolated as white crystals (0.33 g, 1.35 mmol, 70%). m.p. 138°C.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-but-2'-enoylimidazolidin-2-one

Dienophile (**161**) was synthesized according to the general procedure and isolated as white crystals (0.39 g, 1.51 mmol, 80%). m.p. 167°C

3.3.2.5 Preparation of *N*-Acylimidazolidinones using bisTMSA

To a stirred solution of (**128**) (2.0 g, 10.53 mmol) in THF (20 ml) under N_2 was added N,O-bis(trimethylsilyl)acetamide (3.12 mls, 18.33 mmols). The cloudy solution turned colourless after 1h. on formation of the trimethylsilyl intermediate. To this was added freshly distilled acid chloride (2.5 eq., 27.34 mmol) at 0°C and the solution was left to stir overnight. The mixture was then washed with sat. $NaHCO_3$ and then with water, dried and concentrated down *in vacuo*. The solid was recrystallized from EtOAc.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-prop-2'-enoylimidazolidin-2-one

Dienophile **(160)** was synthesized according to the general procedure and isolated as white crystals (1.02 g, 40%). m.p. 138°C.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-but-2'-enoylimidazolidin-2-one

Dienophile **(161)** was synthesized according to the general procedure and isolated as white crystals (1.63 g, 60%). m.p. 167°C.

3.3.3 Preparation of the Diels-Alder Adducts

3.3.3.1 Preparation of the Dienes

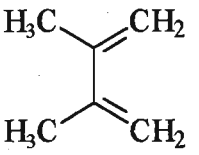
Cyclopentadiene

Dicyclopentadiene (50 ml) was refluxed for several hours to crack the dimer. A Vigreux distillation column and a short path condenser were then fitted and cyclopentadiene was distilled at 41-42°C. (Lit.[162] 42°C). Cyclopentadiene was used within 1 h of distillation.[162]

2,3-Dimethyl-1,3-butadiene

To 2,3-dimethylbutane-2,3-diol (11.80 g, 0.10 mol) in a 50ml round-bottomed flask was added *conc.*HBr (1.5 ml) and the mixture was stirred for 1h. The flask was then equipped for distillation and the mixture was slowly distilled until the temperature reached 95^{0}C. The two phase distillate was transferred to a separating funnel and the aqueous phase was removed. The organic phase was washed with water (5 ml) and

dried over anhydrous magnesium sulphate. The mixture was then filtered through a small filter funnel plugged lightly with glass wool. Slow distillation of the mixture afforded 2,3-dimethyl-1,3-butadiene (**188b**) (4.26 g, 52%). b.p.68°C. (Lit.[161] 69-70°C); δ_H (200MHz) 1.92 (6H, s, 2 x CC*H*$_3$), 5.06 (4H, s, 2 x C=C*H*$_2$);
δ_C (50MHz) 20.54 (q, C*C*H$_3$) 112.99 (t, C=*C*H$_2$) 143.35 (s, *C*=CH$_2$); *m/z* 82 (M^+, 59%), 79(11), 67(100), 54(27), 41(41), 39(54).

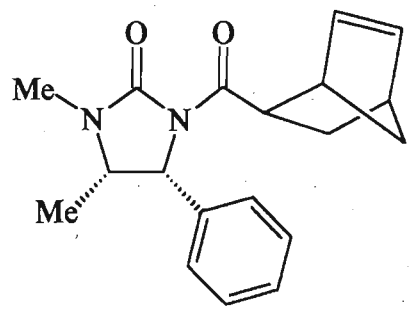


(188b)

3.3.3.2 General Procedure for the Diels-Alder Cycloaddition Reactions using Cyclopentadiene

To a stirred solution of the appropriate dienophile (**160**)-(**164**) and (**173**)-(**174**), (1 eq., 2.05 mmol)) with excess, freshly distilled cyclopentadiene (2 mls) in dry CH_2Cl_2 (2 ml) under N_2 at -78°C was added diethylaluminium chloride (1.5eq. of a 1,0M solution in hexanes). The reaction was kept at -78°C for a minimum of 1h before the solution was poured onto hydrochloric acid (50 ml, 1M). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulphate and filtered. The solvent was removed under reduced pressure and the product was purified by using a chromatotron with 10% EtOAc:hexane as the eluent. The major isomer was isolated by double recrystallization from EtOAc:hexane.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-bicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one

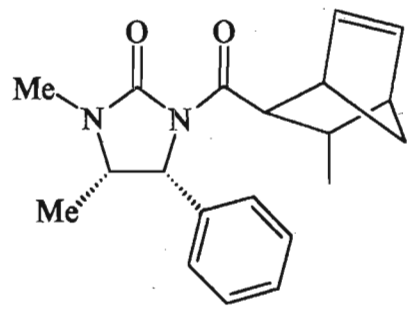


(183)

The Diels-Alder adduct (**183**) was synthesised from dienophile (**160**) according to the general procedure to yield pure white crystals (0.508 g, 80%).

m.p.167°C; (Found C, 73.29; H, 7.10; N, 8.93. $C_{19}H_{22}N_2O_2$ requires C, 73.52; H, 7.14; N, 9.02%); $[\alpha]_D$ -198° (*c* 0.392, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2968 (CH_3), 1728 (CO), 1679 (CO) and 1637 (C=C); δ_H (200MHz) 0.80 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.39 (2H, br s, H-7′), 1.47 (1H, ddd, *J* = 1.9, 4.5 and 11.5 Hz, H-5′), 1.82 (1H, ddd, *J* = 3.6, 9.0 and 11.5 Hz, H-5′), 2.83 (3H, s, NC*H*$_3$), 2.86 (1H, br s, H-6′), 3.39 (1H, br s, H-3′), 3.88 (1H, dq, *J* = 6.6 and 8.7 Hz, C*H*CH_3), 4.20 (1H, m, H-4′), 5.28 (1H, d, *J* = 8.7 Hz, C*H*Ph), 5.37 (1H, dd, *J* = 3.3 and 5.7 Hz, H-2′), 6.04 (1H, dd, *J* = 3.1 and 5.7 Hz, H-1′), 7.13-7.38 (5H, m, Ph); δ_C (50MHz) 15.06 (q, $CHCH_3$), 28.24 (q, NCH_3), 28.71 (t, C-5′), 43.01 (d, C-6′), 43.33 (d, C-4′), 46.87 (d, C-3′), 50.04 (t, C-7′), 53.89 (d, *C*HCH_3), 59.26 (d, *C*HPh), 126.88, 127.91 and 128.39 (d, Ph), 131.19 (d, H-2′), 136.88 (s, Ph), 137.58 (d, H-1′), 155.89 (s, N*C*ON), 173.76 (s, N*C*OCH); *m/z* 310 (M^+, 33%), 245(94), 191(43), 189(54), 132(100).

(4R,5S)-1,5-Dimethyl-4-phenyl-3-((3'S,4'S,5'R, 6'R)-5'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one

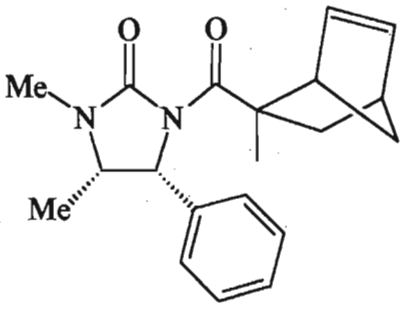


(184)

The Diels-Alder adduct **(184)** was synthesised from dienophile **(161)** according to the general procedure to yield pure white crystals (0.518 g, 78%).

m.p. 196°C; (Found: C, 74.30; H, 7.09; N, 8.57. $C_{20}H_{24}N_2O_2$ requires C, 74.07; H, 7.46; N, 8.63%); $[\alpha]_D$ -264.30° (*c* 0.465, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2966 (CH_3), 1724 (CO), 1679 (CO) and 1636 (C=C); δ_H (200MHz) 0.81 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.10 (3H, d, *J* = 7.1 Hz, H-8'), 1.41 (1H, dd, *J* = 1.6 and 8.5 Hz, H-7'), 1.71 (1H, dd, *J* = 0.6 and 8.5 Hz, H-7'), 2.02 (1H, m, H-5'), 2.44 (1H, br s, H-6'), 2.84 (3H, s, NC*H*$_3$), 3.37 (1H, br s, H-3'), 3.73 (1H, dd, *J* = 3.4 and 4.4 Hz, H-4'), 3.87 (1H, dq, *J* = 6.6 and 8.6 Hz, C*H*CH$_3$), 5.28 (1H, dd, *J* = 3 and 6 Hz, H-2'), 5.30 (1H, d, *J* = 8.8 Hz, C*H*Ph), 6.14 (1H, dd, *J* = 3.2 and 5.7 Hz, H-1'), 7.12-7.37 (5H, m, Ph); δ_C (50MHz) 15.10 (q, CHCH$_3$), 20.45 (q, C-8'), 28.25 (q, NCH$_3$), 35.38 (d, C-5'), 46.81 (t, C-7'), 47.81 (d, C-6'), 49.58 (d, C-4'), 51.95 (d, C-3'), 53.85 (d, *C*HCH$_3$), 59.19 (d, *C*HPh), 126.99, 127.98 and 128.37 (d, Ph), 130.93 (d, C-2'), 136.89 (s, Ph), 139.02 (d, C-1'), 155.95 (s, N*C*ON), 173.44 (s, N*C*OCH); *m/z* 324 (M^+, 18%), 259(100), 191(41), 189(63), 132(58), 105(15).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one

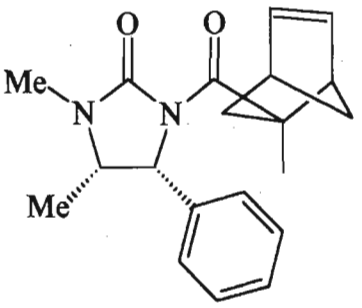


(185a)

The Diels-Alder adduct **(185a)** was synthesised from dienophile **(162)** according to the general procedure. The major *endo* isomer was isolated as a colourless oil (0.345 g, 52%) by using a chromatotron with 5% ether:hexane as the eluent.

(HRMS Found: 324.1833. $C_{20}H_{24}N_2O_2$ requires 324.1838); $[\alpha]_D$ -11.22° (*c* 1.292, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2875 (CH_3), 1730 (CO) and 1670 (CO); δ_H (200MHz) 0.75 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.24-1.61 (2H, m, H-7′), 1.62 (3H, s, H-8′), 1.90 (2H, m, H-5′), 2.74 (1H, br s, H-6′), 2.80 (3H, s, NC*H*$_3$), 3.04 (1H, br s, H-3′), 3.84 (1H, dq, *J* = 6.6 and 9.1 Hz, C*H*CH$_3$), 5.33 (1H, d, *J* = 9.2 Hz, C*H*Ph), 5.66 (1H, dd, *J* = 2.8 and 5.5 Hz, H-2′), 5.92 (1H, dd, *J* = 3.0 and 5.6 Hz, H-1′), 7.05-7.31 (5H, m, Ph); δ_C (50MHz) 15.53 (q, CH*C*H$_3$), 25.20 (q, C-8′), 28.50 (q, N*C*H$_3$), 40.65 (t, C-5′), 42.05 (d, C-6′), 45.58 (t, C-7′), 51.81 (d, C-3′), 53.31 (d, C-4′), 53.83 (d, *C*HCH$_3$), 59.96 (d, *C*HPh), 127.01, 127.71 and 128.06 (d, Ph), 136.75 (d, C-2′), 136.90 (d, C-1′), 137.26 (s, Ph), 154.84 (s, N*C*ON), 177.58 (s, N*C*OCH); *m/z* 324 (M^+, 29%), 259(100), 189(18), 132(75), 105(35).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'R, 6'R)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one



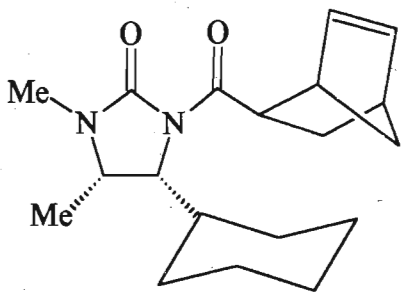
(185b)

The Diels-Alder adduct (**185b**) was synthesised from the dienophile (**162**) according to the general procedure. The minor *endo* isomer was isolated as pure white crystals (0.186 g, 28%).

m.p. 120°C; (HRMS Found: 324.1833. $C_{20}H_{24}N_2O_2$ requires 324.1838); $[\alpha]_D$ -98.72° (*c* 0.934, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2875 (CH_3), 1730 (CO) and 1670 (CO); δ_H (200MHz) 0.76 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.31 -1.60 (2H, m, H-7′), 1.61 (3H, s, H-8′), 1.74 (1H, dd, *J* = 3.1 and 12.7 Hz, H-5′), 1.97 (1H, dd, *J* = 3.6 and 12.8 Hz, H-5′), 2.76 (1H, br s, H-6′), 2.78 (3H, s, NC*H*$_3$), 2.85 (1H, br s, H-3′), 3.86 (1H, dq, *J* = 6.6 and 8.1 Hz, C*H*CH$_3$), 5.15 (1H, d, *J* = 8.2 Hz, C*H*Ph), 6.04 (1H, dd, *J* = 3.0 and 5.6 Hz, H-2′), 6.16 (1H, dd, *J* = 2.9 and 5.6 Hz, H-1′), 7.09-7.36 (5H, m, Ph); δ_C (50MHz) 14.81 (q, CH*C*H$_3$), 25.24 (q, C-8′), 27.99 (q, N*C*H$_3$), 40.97 (t, C-5′), 42.09 (d, C-6′), 45.59 (t, C-7′), 52.07 (d, C-3′), 53.07 (d, C-4′), 53.64 (d, *C*HCH$_3$), 60.81 (d, *C*HPh), 126.57, 127.80 and 128.44 (d, Ph), 136.43 (d, C-2′), 137.12 (d, C-1′), 138.46 (s, Ph), 154.90 (s, N*C*ON), 176.38 (s, N*C*OCH); *m/z* 324 (M$^+$, 29%), 259(100), 189(18), 132(75), 105(35).

Spectral data for the *exo* isomers (**185c**) and (**185d**) are included but they were not characterised.

(4R, 5S)-4-Cyclohexyl-1,5-dimethyl-3-((3'S, 4'S, 6'S)-bicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one

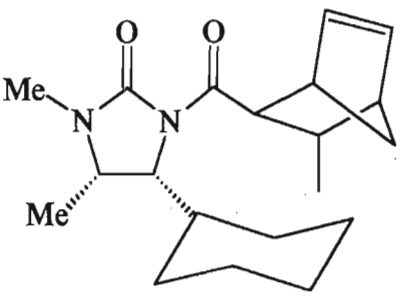


(186)

The Diels-Alder adduct **(186)** was synthesised from dienophile **(173)** according to the general procedure to yield a colourless oil which solidified on standing (0.441 g, 68%).

m.p.137°C; (HRMS Found: 316.2141. $C_{19}H_{28}N_2O_2$ requires 316.2151); $[\alpha]_D$ -77.84° (*c* 1.065, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2976 (CH_3), 1722 (CO), 1672 (CO) and 1620 (C=C); δ_H (200MHz) 1.01-1.75 (14H, m, cyclo-C_6H_{11}, H-7′ and H-5′), 1.31 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 2.07 (1H, ddd, *J* = 3.7, 9.3 and 11.4 Hz, H-5′), 2.78 (3H, s, NC*H*$_3$), 2.89 (1H, br s, H-6′), 3.12 (1H, br s, H-3′), 3.67 (1H, dq, *J* = 7.0 and 7.0 Hz, C*H*CH_3), 4.11 (1H, m, H-4′), 4.26 (1H, dd, *J* = 2.8 and 7.2 Hz, C*H*-cyclo-C_6H_{11}), 5.93 (1H, dd, *J* = 2.7 and 5.6 Hz, H-2′), 6.21 (1H, dd, *J* = 3.0 and 5.6 Hz, H-1′); δ_C (50MHz) 13.06 (q, $CHCH_3$), 26.13, 26.14, 26.17 and 26.90 (t, 4x CH_2, cyclo-C_6H_{11}) 27.67 (q, NCH_3), 30.84 (t, CH_2, cyclo-C_6H_{11}), 32.35 (t, C-5′), 39.05 (d, CH, cyclo-C_6H_{11}), 42.79 (d, C-6′), 43.60 (d, C-4′), 46.07 (d, C-3′), 49.95 (t, C-7′), 54.63 (d, $CHCH_3$), 59.26 (d, CH-cyclo-C_6H_{11}), 132.54 (d, C-2′), 137.23 (d, CH_2CHCH=CH), 156.81 (s, NCON), 174.71 (s, NCOCH); *m/z* 316 (M^+, 13%), 251(42), 197(17), 167(20), 120 (14), 113 (100).

(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-((3'S,4'S,5'R,6'R)-5'-methylbicyclo[2.2.1] heptene-4'-carbonyl)-imidazolidin-2-one.



(187)

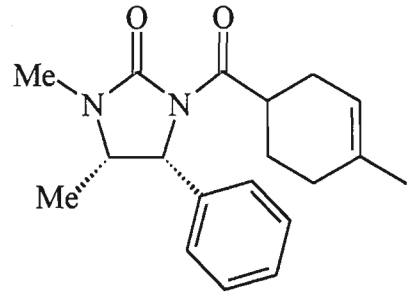
The Diels-Alder adduct (**187**) was synthesised from dienophile (**174**) according to the general procedure to yield a colourless oil (0.420 g, 62%).

(HRMS Found: 330.2300. $C_{20}H_{30}N_2O_2$ requires 330.2307); $[\alpha]_D$ -113.30° (*c* 1.26, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 3035 (CH_3), 2866 (CH_3), 1722 (CO) and 1676 (CO); δ_H (200MHz) 0.80-1.76 (13H, m, cyclo-$C_6H_{11}$and H-7'), 1.10 (3H, d, *J* = 7.1 Hz, COCHCHC*H*$_3$) 1.32 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 2.13 (1H, m, H-5'), 2.51 (1H, br s, H-6'), 2.77 (3H, s, NC*H*$_3$), 3.44 (1H, br s, H-3'), 3.53 (1H, dd, *J* = 3.4 and 4.6 Hz, H-4'), 3.67 (1H, dq, *J* = 6.8 and 7.0 Hz, C*H*CH_3), 4.35 (1H, dd, *J* = 2.6 and 7.4 Hz, C*H*-cyclo-C_6H_{11}), 5.85 (1H, dd, *J* = 2.8 and 5.7 Hz, H-2'), 6.40 (1H, dd, *J* = 3.1 and 5.7 Hz, H-1'); δ_C (50MHz) 13.15 (q, CH*C*H_3), 20.55 (q, COCHCH*C*H_3) 26.08, 26.36, 26.92 and 27.67 (t, 4x *C*H_2, cyclo-C_6H_{11}) 27.78 (q, N*C*H_3), 32.48 (t, *C*H_2, cyclo-C_6H_{11}), 35.29 (t, C-5'), 39.16 (d, *C*H, cyclo-C_6H_{11}), 47.26 (d, C-6'), 48.56 (d, C-4'), 49.47 (d, C-3'), 52.15 (t, C-7'), 54.59 (d, *C*HCH_3), 58.67 (d, *C*H-cyclo-C_6H_{11}), 131.37 (d, C-2'), 139.46 (d, CH_2CH*C*H=CH), 156.50 (s, N*C*ON), 174.18 (s, N*C*OCH); *m/z* 330 (M^+, 18%), 265 (59), 196(25), 180 (25), 112 (100).

3.3.3.3 Diels-Alder Cycloaddition Reaction using Isoprene

To a stirred solution of the appropriate dienophile (160) (0.50 g, 2.05 mmol) with excess isoprene (2 mls) in dry CH_2Cl_2 (2 ml) under N_2 at -78°C was added diethylaluminium chloride (1.5eq. of a 1,0M solution in hexanes). The reaction was kept at -35°C for a minimum of 5h before the solution was poured onto hydrochloric acid (50 ml, 1M). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulphate and filtered. The solvent was removed under reduced pressure and the product was purified by using a chromatotron with 10% EtOAc:hexane as the eluent. The major isomer was isolated by double recrystallization from EtOAc:hexane.

(4R,5S)-1,5-Dimethyl-4-phenyl-3-((4'S)-1'-methylcyclohexene-4'-carbonyl)-imidazolidin-2-one



(189)

The Diels-Alder adduct (**189**) was synthesised from dienophile (**160**) according to the general procedure to yield white crystals (0.480 g, 75%).

m.p. 58°C; (HRMS Found: 312.1831. $C_{19}H_{24}N_2O_2$ requires 312.1838); $[\alpha]_D$ -72.78° (*c* 0.452, $CHCl_3$); υ_{max} (KBr/cm^{-1}) 2929 (CH_3), 1733 (CO) and 1681 (CO); δ_H (200MHz) 0.79 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.63 (3H, s, CH=CC*H*$_3$), 1.86-2.26 (6H, m, C*H*$_2$CHC*H*$_2$C*H*$_2$), 2.82 (3H, s, NC*H*$_3$), 3.87 (2H, m, CH$_2$C*H*CH$_2$CH$_2$ and C*H*CH$_3$), 5.31 (1H, d, *J* = 8.7 Hz, C*H*Ph), 5.33 (1H, m, C*H*=CCH$_3$), 7.10-7.37 (5H, m, Ph); δ_C (50MHz) 15.02 (q, CH*C*H$_3$), 23.48 (q, CH=C*C*H$_3$), 25.52 (t, CH*C*H$_2$CH$_2$), 28.09 (q, N*C*H$_3$), 28.19 (t, CHCH$_2$*C*H$_2$), 29.67 (t, CH*C*H$_2$CH) 38.80 (d, *C*HCH$_2$CH$_2$) 53.80 (d, *C*HCH$_3$), 59.30 (d, *C*HPh), 119.48 (d, *C*H=CCH$_3$), 126.80, 127.98 and 128.49 (d, Ph), 133.57 (s, Ph), 136.86 (s, CH=*C*CH$_3$), 155.66 (s, N*C*ON), 176.04 (s, N*C*OCH); *m/z* 312 (M$^+$, 38%), 191(55), 189(100), 132(33).

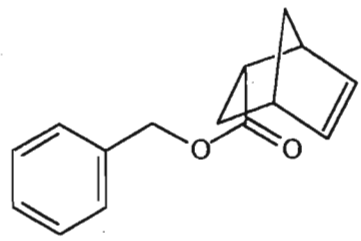
3.3.3.4 Diels-Alder Cycloaddition Reaction using 2,3-Dimethyl-1,3-butadiene

The Diels-Alder reaction with (160) and 2,3-Dimethyl-1,3-butadiene (**188b**) was carried out using the same procedure as the reaction with isoprene (**188a**). However, in this instance, the reaction mixture was allowed to warm to rt and left to stir for two days. No reaction took place and only starting material was recovered.

3.3.4 Preparation of the Benzyl Esters

To a stirred solution of freshly distilled benzyl alcohol (0.07 ml, 0.645 mmol) in anhydrous THF (2 ml, ~0.2M) under N_2 at -78°C was added *n*-butyllithium (0.30 ml, of a 1.64M solution in hexanes, 0.484 mmol)). A solution of the appropriate Diels-Alder adduct (1eq., 0.323 mmol) in anhydrous THF (1 ml, ~1M) was added *via* cannula and the reaction mixture was left to warm to rt. The mixture was left to stir at that temperature for 4 h and then quenched with excess saturated ammonium chloride. The mixture was concentrated *in vacuo*, diluted with water and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The resultant oily product was purified by using a chromatotron eluted with 50% dichloromethane: hexane to yield a colourless oil.

Phenylmethyl (3S, 4S, 6S)-bicyclo[2.2.1]heptene-4-carboxylate

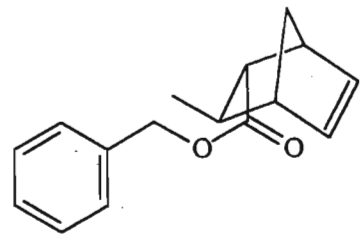


(191)

The known benzyl ester **(191)** was prepared from cycloadducts **(183)** and **(186)** according to the general procedure to yield a colourless oil (72 mg, 98%).

$[\alpha]_D$ -124.22° (*c* 0.30, $CHCl_3$), (lit.[111] -129° (*c* 1.39, $CHCl_3$)); δ_H (200MHz) 1.23-1.45 (2H, m, H-7′), 1.48 (1H, ddd, *J* = 2.5, 4.2 and 11.9 Hz, H-5′), 1.91 (1H, ddd, *J* = 3.7, 9.3 and 11.9 Hz, H-5′), 2.90 (1H, br s, H-6′), 3.00 (1H, m, H-4′), 3.22 (1H, br s, H-3′), 5.07 (2H, dd, *J* = 12.5 and 14.7 Hz, C*H*$_2$Ph), 5.87 (1H, dd, *J* = 2.8 and 5.7 Hz, H-2′), 6.18 (1H, dd, *J* = 3.0 and 5.7 Hz, H-1′), 7.24-7.37 (5H, m, Ph); δ_C (50MHz) 29.23 (t, C-5′), 42.56 (d, C-6′), 43.36 (d, C-4′), 45.79 (d, C-3′), 49.62 (t, C-7′), 66.00 (t, *C*H$_2$Ph), 128.04 and 128.48 (d, Ph), 132.27 (d, C-2′), 136.31 (s, Ph), 137.80 (d, C-1′), 174.58 (s, *C*OOCH$_2$Ph); *m/z* 228 (M^+, 2%), 156 (10), 137 (7), 91 (100), 77 (16), 66 (58).

Phenylmethyl (3S, 4S, 5R, 6R)-5-methylbicyclo[2.2.1]heptene-4-carboxylate

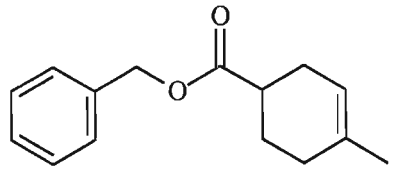


(192)

The known benzyl ester **(192)** was prepared from cycloadducts **(184)** and **(187)** according to the general procedure to yield a colourless oil (74 mg, 95%).

$[\alpha]_D$ -124.22° (*c* 0.32, $CHCl_3$) (lit.[111] $[\alpha]_D$ -130 (*c* 2.14, $CHCl_3$)); δ_H (200MHz) 1.19 (3H, d, J = 7.0 Hz, COCHCHC*H*$_3$) 1.40-1.58 (2H, m, H-7′), 1.86 (1H, m, H-5′), 2.44 (2H, m, H-6′ and H-4′), 3.13 (1H, br s, H-3′), 5.07 (2H, dd, *J* = 12.5 and 14.8 Hz, C*H*$_2$Ph), 5.95 (1H, dd, *J* = 2.8 and 5.6 Hz, H-2′), 6.26 (1H, dd, *J* = 3.0 and 5.6 Hz, H-1′), 7.26-7.38 (5H, m, Ph); δ_C (50MHz) 20.97 (q, COCHCH*C*H$_3$), 37.85 (d, C-5′), 45.99 (d, C-6′), 45.99 (t, C-7′), 48.83 (d, C-4′), 52.52 (d, C-3′), 65.89 (t, *C*H$_2$Ph), 128.48, 128.00 and 128.89 (d, Ph), 133.19 (d, C-2′), 136.36 (s, Ph), 138.74 (d, C-1′), 174.53 (s, *C*OOCH$_2$Ph); *m/z* 242 (M^+, 1%), 177 (21), 91 (100), 79 (14), 69 (20).

Phenylmethyl (4S)-1-methylcyclohexene-4-carboxylate



(190)

The known benzyl ester (**190**) was prepared from cycloadduct (**189**) according to the general procedure to yield a colourless oil (73 mg, 98%).

$[\alpha]_D$ -31.42° (*c* 0.134, $CHCl_3$); δ_H (200MHz) 1.59-1.76 (1H, m, H-5′), 1.64 (3H, s, H-7′), 2.00 (3H, m, H-6′ and H-5′), 2.25 (2H, m, H-3′), 2.55 (1H, m, H-4′), 5.13 (2H, br s, CH_2Ph), 5.37 (1H, m, H-2′). 7.30-7.38 (5H, m, Ph); δ_C (50MHz) 23.48 (q, C-7′), 25.47 (t, C-5′), 27.66 (t, C-6′), 29.25 (t, C-3′), 39.28 (d, C-4′), 66.04 (t, CH_2Ph), 119.17 (d, C-2′), 127.96, 128.09 and 128.53 (d, Ph), 133.76 (s, Ph), 136.25 (s, C-1′), 175.84 (s, $COOCH_2$); *m/z* 230 (M^+, 1%), 139 (44), 111(9), 93(100), 91(80).

3.3.5 Preparation of Diels-Alder Authentic Adducts

3.3.5.1 Thermal Diels-Alder Reactions

Thermal Diels-Alder cycloaddition reactions were carried out with the appropriate carboxylic acid and cyclopentadiene at elevated temperatures and extended reaction times in order to enable the formation of the thermodynamically more stable *exo* isomer to take place at the expense of the kinetically favoured *endo* isomer. The carboxylic acids used were acrylic acid, crotonic acid and methacrylic acid.

The appropriate carboxylic acid (1 eq., 0.624 mol) and freshly distilled cyclopentadiene (50 g, 1.1 eq., 0.686 mol) were refluxed for 4 h. The resulting mixture was purified by using a chromatotron and first eluting with 500 ml hexane followed by 20% EtOAc:hexane. The appropriate fraction was collected and the solvents removed *in vacuo* to yield the desired product.

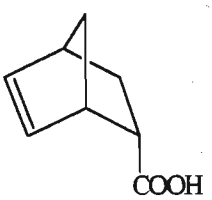
3.3.5.2 Iodolactonisation Reactions

A mixture of bicyclic carboxylic acid (1 eq., 14.50 mmol) and $NaHCO_3$ (3eq. 43.50 mmol) dissolved in 100 ml water was added to a mixture of iodine (2 eq. 29.00 mmol) and KI (6eq. 87.00 mmol) dissolved in water (200 ml). The reaction flask was wrapped in tin foil and kept in the dark for 24 h. The dark red solution was then transferred to a separating funnel to which dichloromethane and aqueous sodium thiosulphate was added and this was shaken until two colourless phases were obtained. The aqueous layer was extracted with dichloromethane (3 x 20 ml) and the combined extracts were washed successively with aqueous sodium bicarbonate and water, dried over magnesium sulphate and concentrated *in vacuo* to yield a colourless oil (*ca.* 1.53 g, 40%). Anaysis by GC/MS revealed that the iodolactone was formed with all three bicyclic carboxylic acids (*m/z*: M^+ 264, 278 and 278).

The respective bicyclic carboxylic acids were retrieved by reacting the iodolactone (1.5 g, 5.68 mmol) with zinc powder (2 g, 30.60 mmol) and excess acetic acid (15 ml) in ethanol (15ml). The reaction mixture was left to stir at rt overnight. The mixture was then filtered and the solvent concentrated down *in vacuo*. EtOAc and water were then added and the solution was transferred to a separating funnel. The aqueous phase was extracted with EtOAc (3 x 20 ml), the organic fractions were combined, dried over magnesium sulphate, filtered and the solvent concentrated down *in vacuo*. The product was purified by using a chromatotron with 20% EtOAc:hexane as the eluent. Analysis by GC/MS and NMR spectroscopy revealed that the bicyclic carboxylic acids were retrieved and that the *endo* isomer (0.110 g, 80%) had been isolated from the *exo* isomer.

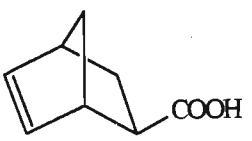
5-Bicyclo[2.2.1.]heptene-4-carboxylic acid (*endo* enantiomers) and

5-Bicyclo[2.2.1.]heptene-4-carboxylic acid (*exo* enantiomers)



Endo

(196c)



Exo

(196d)

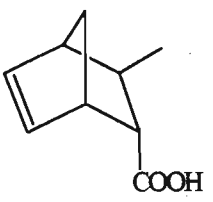
The known bicyclic carboxylic acids were prepared from acrylic acid (45 g, 0.624 mol) according to the general procedure to yield an oily solid. (51.67 g, 60%).
m.p. 40-42°C), (Lit.[151] 45.7-46.2°C).

Endo isomer: m.p 63-66°C, (Lit.[151] 67.5-68.5°C). δ_H (200 MHz) 1.26-1.56 (3H, m, H-5 and H-7), 1.92 (1H, m, H-5), 2.92 (1H, br s, H-6), 2.99 (1H, m, H-4), 3.24 (1H, br s, H-3), 5.99 (1H, dd, J = 3 and 6 Hz, H-2), 6.10 (1H, dd, J = 3 and 6 Hz, H-1), 10.70 (1H, br s, OH); δ_C (50MHz) 29.10 (t, C-4), 42.54 (d, C-6), 43.31 (d, C-5), 45.69 (d, C-3), 49.72 (t, C-7), 132.43 (d, C-2), 137.89 (d, C-1), 181.46 (s, COOH); *m/z* 138 (M^+, 9%), 93 (4), 91 (10), 77 (7), 73 (3), 66 (100).

Exo isomer: δ_H (200MHz) 1.26-1.56 (2H, m, H-7), 1.92 (1H, m, H-5), 2.25 (1H, m, H-5), 2.92 (1H, br s, H-6), 2.99 (1H, m, H-4), 3.10 (1H, br s, H-3), 6.13 (2H, m, H-2 and H-1), 9.50-10.70 (1H, br s, OH); δ_C (50MHz) 30.31 (t, C-5), 41.65 (d, C-6), 43.17 (d, C-4), 46.37 (d, C-3), 46.68 (t, C-7), 135.71 (d, C-2), 138.12 (d, C-1), 182.97 (s, COOH); *m/z* 138 (M^+, 9%), 93 (4), 91 (10), 77 (7), 73 (3), 66 (100).

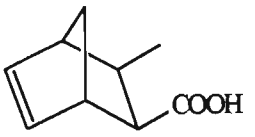
5-Methylbicyclo[2.2.1]heptene-4-carboxylic acid (*endo* enantiomers) and

5-Methylbicyclo[2.2.1.]heptene-4-carboxylic acid (*exo* enantiomers)



Endo

(196a)



Exo

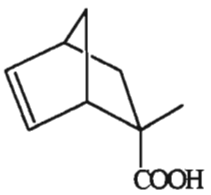
(196b)

The known bicyclic carboxylic acids (**196a**) and (**196b**) were prepared from crotonic acid (2 g, 23.23 mmol) according to the general procedure to yield a white solid (2.05 g, 58%). m.p. 84-85°C (Lit.[150] 88-89°C);

Endo isomer: m.p. 93°C, (Lit.[150] 95-96°); δ_H (200MHz) 1.17 (3H, d, J = 7 Hz, CHCH_3), 1.49 (2H, m, H-7), 1.82 (1H, m, H-5), 2.41 (1H, dd, J = 3 and 5 Hz, H-4), 2.47 (1H, br s, H-6), 3.13 (1H, br s, H-3), 6.06 (1H, dd, J = 3 and 6 Hz, H-2), 6.27 (1H, dd, J = 3 and 6 Hz, H-1), 8.70-11.50 (1H, br s, OH); δ_C (50MHz) 20.89 (q, CHCH_3), 37.92 (d, C-5), 45.84 (d, C-6), 46.06 (d, C-4), 48.81 (d, C-3), 52.41 (t, C-7), 133.31 (d, C-2), 138.80 (d, C-1), 181.21 (s, COOH); *m/z* 152 (M^+, 0.4%), 107 (2), 91 (4), 87 (5), 66 (100).

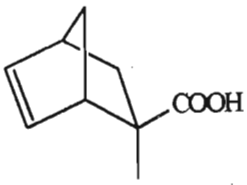
Exo isomer: δ_H (200MHz) 0.92 (3H, d, J = 7 Hz, CHCH_3), 1.42-1.69 (3H, m, H-7 and H-5), 2.41 (1H, dd, J = 3 and 5 Hz, H-4), 2.72 (1H, br s, H-6), 2.99 (1H, br s, H-3), 6.17 (1H, dd, J = 3 and 6 Hz, H-2), 6.23 (1H, dd, J = 3 and 6 Hz, H-1), 8.70-11.50 (1H, br s, OH); δ_C (50MHz) 19.02 (q, CHCH_3), 39.34 (d, C-5), 45.77 (d, C-6), 47.25 (d, C-4), 48.11 (d, C-3), 51.21 (t, C-7), 135.38 (d, C-2), 136.54 (d, C-1), 182.81 (s, COOH); *m/z* 152 (M^+, 0.4%), 107 (2), 91 (4), 87 (5), 66 (100).

4-Methylbicyclo[2.2.1]heptene-4-carboxylic acid (*endo* enantiomers) and *4-Methylbicyclo[2.2.1.]heptene-4-carboxylic acid* (*exo* enantiomers).



Endo

(196e)



Exo

(196f)

The known bicyclic carboxylic acids were prepared from methacrylic acid (2 g, 23.23 mmol) according to the general procedure to yield a white solid (2.30 g, 65%). m.p. 36-41°C, (Lit.[163] 41-57°C);

Endo isomer: m.p. 92°C, (Lit.[162] 94-95°C); δ_H (200MHz) 1.48 (3H, s, CCH_3), 1.41-1.60 (3H, m, H-7 and H-5), 1.82 (1H, dd, J = 3 and 12 Hz, H-5), 2.79 (1H, br s, H-6), 2.83 (1H, br s, H-3), 6.11 (1H, dd, J = 3 and 3 Hz, H-2), 6.17 (1H, dd, J = 3 and 6 Hz, H-1), 10.00-11.50 (1H, br s, OH); δ_C (50MHz) 26.49 (q, CHCH_3), 37.64 (t, C-5), 42.58 (d, C-6), 46.89 (s, C-4), 49.99 (d, C-3), 50.75 (t, C-7), 135.46 (d, C-2), 137.92 (d, C-1), 184.29 (s, COOH); *m/z* 152 (M^+, 6%), 107 (2), 91 (8), 77 (7), 66 (100).

Exo isomer: δ_H (200MHz) 0.87 (2H, m, H-7), 1.16 (3H, s, CCH_3), 2.44 (1H, dd, J = 3 and 12 Hz, H-5), 3.05 (2H, m, H-6 and H-3), 6.23 (2H, m, H-2 and H-1), 10.00-11.50 (1H, br s, OH); δ_C (50MHz) 24.21 (q, CHCH_3), 37.35 (t, C-5), 42.85 (d, C-6), 49.04 (s, C-4), 49.51 (d, C-3), 50.43 (t, C-7), 133.54 (d, C-2), 138.73 (d, C-1), 185.91 (s, COOH); *m/z* 152 (M^+, 6%), 107 (2), 91 (8), 77 (7), 66 (100).

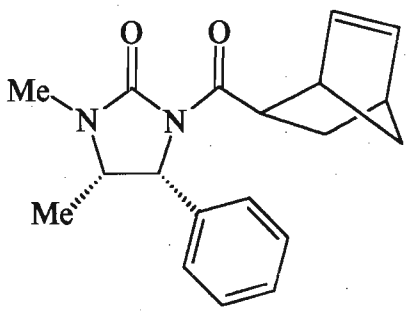
3.3.5.3 Conversion of the Bicyclic Carboxylic Acids to the Acid Chlorides.

To the bicyclic carboxylic acid (0.725 mmol) was added oxalyl chloride (2.5 eq., 1.813 mmol) and the reaction mixture was left to stir at rt overnight. The excess oxalyl chloride was removed *in vacuo* to yield the acid chloride (~0.11 g, 95%) which was analysed by GC/MS (*m/z*: M^+ 156, 170 and 170).

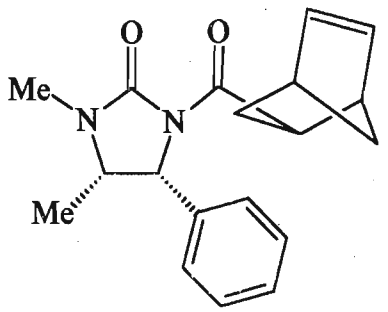
3.3.5.4 Addition of the Imidazolidin-2-one Auxiliary to the Carboxylic Acid Chlorides.

To a solution of imidazolidin-2-one (0.10 g, 0.526 mmol) in anhydrous THF (2 ml) under N_2 at -78°C was added *n*-butyllithium (0.40 ml, 1.1equiv of a 1.50M solution in hexanes, 0.580 mmol). The mixture was stirred for 5 min and the appropriate acid chloride (1eq., 0.526 mmol) in anhydrous THF (1 ml) was then added *via* cannula. The reaction mixture was allowed to warm up to rt and then left to stir for a further 4 h. The reaction was quenched with saturated aqueous sodium bicarbonate and the THF was removed *in vacuo.* Dichloromethane and water were then added and the mixture was transferred to a separating funnel where the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over magnesium sulphate and the solvent removed *in vacuo.* The product was purified by using a chromatotron with 20% EtOAc:hexane as the eluent. The products were analysed by GC/MS, NMR spectroscopy and HPLC. NMR spectral data are given for the two *endo* isomers only. They were obtained by comparing the NMR spectra of the two *endo* isomers with that of the isolated major *endo* isomer. The NMR spectra of the *endo* and *exo* isomers reveal the presence of four isomers. The two minor *exo* isomers are discernable from the two *endo* isomers providing an indication of position and proportion of *exo* isomers to *endo* isomers.

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-bicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (major *endo* isomer) and
(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'R, 6'R)-bicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (minor *endo* isomer).



(183a)



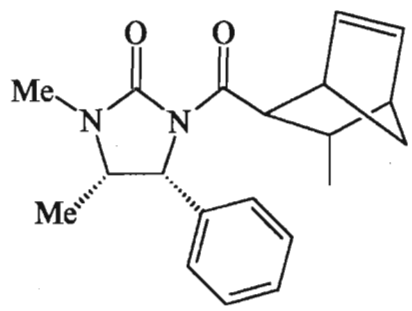
(183b)

The Diels-Alder adduct was synthesised from auxiliary **(128)** and bicyclic acid **(196c)** according to the general procedure to yield pure white crystals (0.147 g, 90%). m.p.167°C.

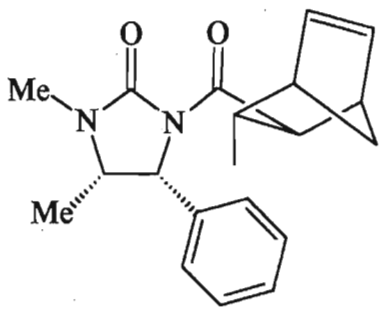
Major *endo* isomer: δ_H (200MHz) 0.79 (3H, d, J = 7.0 Hz, CHC*H*$_3$), 1.39 (2H, br s, H-7′), 1.40 (1H, m, H-5′), 1.80 (1H, m, H-5′), 2.84 (3H, s, NC*H*$_3$), 2.86 (1H, br s, H-6′), 3.39 (1H, br s, H-3′), 3.89 (1H, m, C*H*CH$_3$), 4.17 (1H, m, H-4′), 5.28 (1H, d, J = 9.0 Hz, C*H*Ph), 5.38 (1H, dd, J = 3.3 and 5.5 Hz, H-2′), 6.05 (1H, dd, J = 3.0 and 5.5 Hz, H-1′), 7.08-7.36 (5H, m, Ph); δ_C (50MHz) 15.03 (q, CH*C*H$_3$), 28.22 (q, N*C*H$_3$), 28.70 (t, C-5′), 43.00 (d, C-6′), 43.30 (d, C-4′), 46.85 (d, C-3′), 50.03 (t, C-7′), 53.87 (d, *C*HCH$_3$), 59.24 (d, *C*HPh), 127.01, 127.97 and 128.37 (d, Ph), 131.18 (d, H-2′), 136.89 (s, Ph), 137.54 (d, H-1′), 155.87 (s, N*C*ON), 173.70 (s, N*C*OCH); *m/z* 310 (M^+, 33%), 245(94), 191(43), 189(54), 132(100).

Minor *endo* isomer: δ_H (200MHz) 0.81 (3H, d, J = 7 Hz, CHC*H*$_3$), 1.39 (2H, br s, H-7′), 1.40 (1H, m, H-5′), 1.80 (1H, m, H-5′), 2.85 (3H, s, NC*H*$_3$), 2.86 (1H, br s, H-6′), 3.26 (1H, br s, H-3′), 3.89 (1H, m, C*H*CH$_3$), 4.17 (1H, m, H-4′), 5.20 (1H, d, J = 9 Hz, C*H*Ph), 5.86 (1H, dd, J = 3.3 and 5.5 Hz, H-2′), 6.16 (1H, dd, J = 3 and 5.5 Hz, H-1′), 7.08-7.36 (5H, m, Ph); δ_C (50MHz) 14.84 (q, CH*C*H$_3$), 28.12 (q, N*C*H$_3$), 29.48 (t, C-5′), 42.85 (d, C-6′), 43.35 (d, C-4′), 46.61 (d, C-3′), 50.12 (t, C-7′), 53.87 (d, *C*HCH$_3$), 59.76 (d, *C*HPh), 126.84, 127.88 and 128.46 (d, Ph), 131.67 (d, H-2′), 136.24 (s, Ph), 137.59 (d, H-1′), 155.93 (s, N*C*ON), 173.86 (s, N*C*OCH); *m/z* 310 (M^+, 33%), 245(94), 191(43), 189(54), 132(100).

(4R,5S)-1,5-Dimethyl-4-phenyl-3-((3'S,4'S,5'R, 6'R)-5'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (major *endo* isomer) and *(4R,5S)-1,5-Dimethyl-4-phenyl-3-((3'R,4'R,5'S, 6'S)-5'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one* (minor *endo* isomer).



(184a)



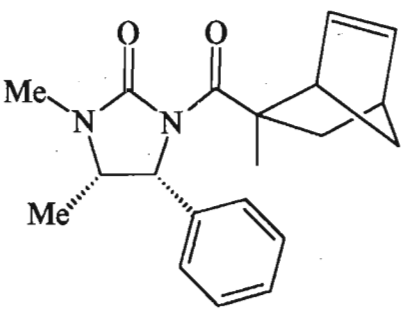
(184b)

The Diels-Alder adduct was synthesised from auxiliary **(128)** and bicyclic acid **(196a)** according to the general procedure to yield pure white crystals (0.145 g, 85%). m.p. 196°C.

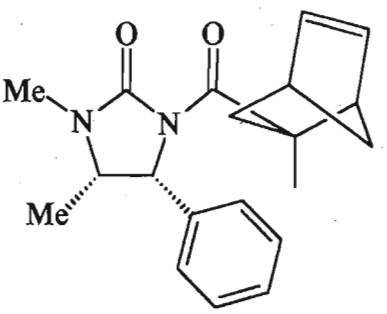
Major *endo* isomer: δ_H (200MHz) 0.81 (3H, d, J = 7 Hz, CHCH_3), 1.10 (3H, d, J = 7 Hz, H-8'), 1.40 (1H, m, H-7'), 1.71 (1H, m, H-7'), 1.96 (1H, m, H-5'), 2.44 (1H, br s, H-6'), 2.84 (3H, s, NCH_3), 3.37 (1H, br s, H-3'), 3.75 (1H, m, H-4'), 3.89 (1H, m, C*H*CH$_3$), 5.28 (1H, m, H-2'), 5.29 (1H, d, J = 9 Hz, C*H*Ph), 6.14 (1H, m, H-1'), 7.09-7.36 (5H, m, Ph); δ_C (50MHz) 15.11 (q, CH*C*H$_3$), 20.46 (q, C-8'), 28.26 (q, N*C*H$_3$), 35.42 (d, C-5'), 46.83 (t, C-7'), 47.84 (d, C-6'), 49.59 (d, C-4'), 51.98 (d, C-3'), 53.88 (d, *C*HCH$_3$), 59.23 (d, *C*HPh), 126.81, 127.94 and 128.40 (d, Ph), 130.94 (d, C-2'), 136.88 (s, Ph), 139.07 (d, C-1'), 155.95 (s, N*C*ON), 173.51 (s, N*C*OCH); *m/z* 324 (M^+, 18%), 259(100), 191(41), 189(63), 132(58), 105(15).

Minor *endo* isomer: δ_H (200MHz) 0.79 (3H, d, J = 7 Hz, CHC*H*$_3$), 1.07 (3H, d, J = 7 Hz, H-8′), 1.40 (1H, m, H-7′), 1.71 (1H, m, H-7′), 1.96 (1H, m, H-5′), 2.44 (1H, br s, H-6′), 2.85 (3H, s, NC*H*$_3$), 3.24 (1H, br s, H-3′), 3.75 (1H, m, H-4′), 3.89 (1H, m, C*H*CH$_3$), 5.20 (1H, d, J = 8.5 Hz, C*H*Ph), 5.83 (1H, dd, J = 3 and 5.5 Hz, H-2′), 6.29 (1H, dd, J = 3 and 5.5 Hz, H-1′), 7.09-7.36 (5H, m, Ph); δ_C (50MHz) 14.88 (q, CH*C*H$_3$), 20.54 (q, C-8′), 28.14 (q, N*C*H$_3$), 36.66 (d, C-5′), 47.10 (t, C-7′), 47.72 (d, C-6′), 49.55 (d, C-4′), 51.55 (d, C-3′), 53.78 (d, *C*HCH$_3$), 59.98 (d, *C*HPh), 127.00, 128.01and 128.46 (d, Ph), 131.24 (d, C-2′), 136.97 (s, Ph), 139.15 (d, C-1′), 155.95 (s, N*C*ON), 173.97 (s, N*C*OCH); *m/z* 324 (M^+, 18%), 259(100), 191(41), 189(63), 132(58), 105(15).

(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'S, 4'S, 6'S)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one (major *endo* isomer) and *(4R, 5S)-1,5-Dimethyl-4-phenyl-3-((3'R, 4'R, 6'R)-4'-methylbicyclo[2.2.1]heptene-4'-carbonyl)-imidazolidin-2-one* (minor *endo* isomer).



(185a)



(185b)

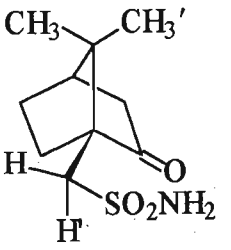
The Diels-Alder adduct was synthesised from auxiliary **(128)** and bicyclic acid **(196e)** according to the general procedure. The major *endo* isomer was isolated as a white solid (85 mg, 50%).

Major *endo* isomer: δ_H (200MHz) 0.75 (3H, d, J = 7 Hz, CHCH_3), 1.24-1.61 (2H, m, H-7'), 1.62 (3H, s, H-8'), 1.94 (2H, m, H-5'), 2.76 (1H, br s, H-6'), 2.81 (3H, s, NCH_3), 3.04 (1H, br s, H-3'), 3.84 (1H, m, CHCH$_3$), 5.33 (1H, d, J = 8 Hz, CHPh), 5.66 (1H, dd, J = 3 and 5.5 Hz, H-2'), 5.92 (1H, dd, J = 3 and 5.5 Hz, H-1'), 7.06-7.36 (5H, m, Ph); δ_C (50MHz) 15.53 (q, CHCH$_3$), 25.20 (q, C-8'), 28.50 (q, NCH$_3$), 40.65 (t, C-5'), 42.05 (d, C-6'), 45.58 (t, C-7'), 51.81 (d, C-3'), 53.31 (d, C-4'), 53.83 (d, CHCH$_3$), 59.96 (d, CHPh), 127.01, 127.71 and 128.06 (d, Ph), 136.75 (d, C-2'), 136.90 (d, C-1'), 137.26 (s, Ph), 154.84 (s, NCON), 177.58 (s, NCOCH); *m/z* 324 (M^+, 29%), 259(100), 189(18), 132(75), 105(35).

Minor *endo* isomer: δ_H (200MHz) 0.76 (3H, d, J = 7 Hz, CHC*H*$_3$), 1.24-1.61 (2H, m, H-7′), 1.61 (3H, s, H-8′), 1.94 (2H, m, H-5′), 2.76 (1H, br s, H-6′), 2.79 (3H, s, NC*H*$_3$), 2.89 (1H, br s, H-3′), 3.84 (1H, m, C*H*CH$_3$), 5.15 (1H, d, J = 8 Hz, C*H*Ph), 6.04 (1H, dd, J = 3 and 5.5 Hz, H-2′), 6.15 (1H, dd, J = 3 and 5.5 Hz, H-1′), 7.06-7.36 (5H, m, Ph); δ_C (50MHz) 14.81 (q, CH*C*H$_3$), 25.24 (q, C-8′), 27.99 (q, N*C*H$_3$), 40.98 (t, C-5′), 42.09 (d, C-6′), 45.59 (t, C-7′), 52.07 (d, C-3′), 53.07 (d, C-4′), 53.64 (d, *C*HCH$_3$), 60.81 (d, *C*HPh), 126.57, 127.80 and 128.44 (d, Ph), 136.43 (d, C-2′), 137.12 (d, C-1′), 138.46 (s, Ph), 154.90 (s, N*C*ON), 176.83 (s, N*C*OCH); *m/z* 324 (M^+, 29%), 259(100), 189(18), 132(75), 105(35).

3.3.6 Preparation of N-Acylbornane-10,2-sultam Diels-Alder Adduct

(1S,4R)-7,7-Dimethyl-2-oxo-bicyclo[2.2.1]heptyl-1-methanesulfonamide

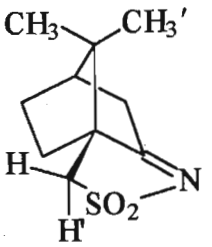


(157)

A mechanically stirred solution of sulfonyl chloride (**156**) (20,0 g, 80.0 mmol) in toluene (200 ml) was saturated with gaseous NH_3 under cooling with ice. Filtration, washing of the insoluble residue with toluene (15 ml), recrystallization from water (200 ml), filtration again and drying by means of a freeze dryer gave camphor sulfonamide (**157**) (13.64 g, 59.04 mmol, 73%).

m.p. 132-133°C, (lit.[69] 133-134°C); (Found: C, 51.96; H, 7.46; N, 6.27. $C_{10}H_{17}NO_3S$ requires C, 51.93; H, 7.41; N, 6.06%); δ_H (200 MHz) 0.93 (3H, s, CH_3), 1.01 (3H, s, CH_3'), 1.49 (1H, m, $CCHHCH_2$), 1.71 (1H, m, CCH_2CHH), 1.96 (1H, d, J = 18.7 Hz, $COCHH$), 1.98-2.21 (4H, m, $CCHHCH_2$, CCH_2CHH , CH_2CHCH_2), 2.43 (1H, m, $COCHH$), 3.13 (1H, d, J = 15.0 Hz, $CHH'SO_2$), 3.51 (1H, d, J = 15.0 Hz, $CHH'SO_2$), 5.31-5.48 (2H, br s, NH_2); δ_C (50MHz) 19.37 (q, CH_3), 19.95 (q, CH_3'), 26.72 (t, CCH_2CH_2), 27.04 (t, CCH_2CH_2), 42.76 (d, CH_2CHCH_2), 43.05 (t, $COCH_2CH$), 49.10 (s, $C(CH_3)_2$), 53.91 (t, CH_2SO_2), 59.33 (s, CCH_2SO_2), 217.67 (s, C=O).

(1S, 7R)-10,10-Dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]dec-3-ene-5,5-dioxide

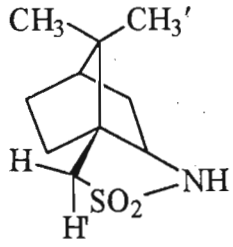


(158)

A 1% solution of NaOMe in dry MeOH (8 ml) was added to a solution of **(157)** (10.0 g, 43.29 mmol) in dry MeOH (300 ml) under N_2. The mixture was stirred at rt for 4 h, another portion of 1% NaOMe was added and the mixture was once again left to stir for 60 h. The solvent was removed *in vacuo*, dichloromethane and water were added, the two layers were separated in a separating funnel and the aqueous phase was extracted with dichloromethane (3 x 20 ml). The organic fractions were combined, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to yield a white solid **(158)** (9.04 g, 98%).

m.p. 224°C, (lit.[69] 225°C); (Found: C, 56.06; H, 6.81; N, 6.62. $C_{10}H_{15}NO_2S$ requires C, 56.06; H, 7.09; N, 6.57%); δ_H (200 MHz) 0.87 (3H, s, CH_3), 1.09 (3H, s, CH_3'), 1.48 (1H, m, CC*H*HCH$_2$), 1.78 (1H, m, CCH$_2$C*H*H), 2.00-2.11 (2H, c, CCH*H*CH$_2$, CCH$_2$CH*H*), 2.26 (1H, m, CH$_2$C*H*CH$_2$), 2.38 (1H, d, CNCH*H*), 2.77 (1H, m, CNC*H*H), 2.98 (1H, d, *J* = 13.3 Hz, C*H*H'SO$_2$), 3.19 (1H, d, J = 13.3 Hz, CH*H*'SO$_2$); δ_C (50MHz) 18.96 (q, CH_3), 19.42 (q, CH_3'), 26.59 (t, CCH$_2$CH$_2$), 28.36 (t, CCH$_2$CH$_2$), 35.88 (t, CNCH$_2$CH), 44.57 (d, CH$_2$C*H*CH$_2$), 47.96 (s, *C*(CH$_3$)$_2$), 49.39 (t, CH$_2$SO$_2$), 64.49 (s, *C*CH$_2$SO$_2$), 195.71 (s, *C*=N); *m/z* 213 (M^+, 1%), 149(6), 134(33), 108(100), 93(49).

(1S, 7R)-10,10-Dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide

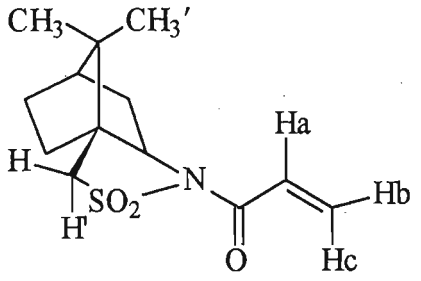


(57)

$LiAlH_4$ (1.45 g, 37.60 mmol) was added at 0°C to a stirred solution of (**158**) (8,0 g, 37.56 mmol) in dry THF (150 ml) under N_2. The mixture was stirred at rt for 4 h, quenched by the slow addition of aq. HCl (1N) (10 ml) at 0°C,filtered and washed with dichloromethane. The solution was transferred to a separating funnel and the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The solid was recrystallized from EtOH to give the pure white camphor sultam (**57**) (7.40 g, 34.42 mmol, 92%).

m.p. 184°C, (lit.[69] 182-183°C); (Found: C, 55.72; H, 7.81; N, 6.42. $C_{10}H_{17}NO_2S$ requires C, 55.78; H, 7.96; N, 6.51%); δ_H (200 MHz) 0.93 (3H, s, CH_3), 1.13 (3H, s, CH_3'), 1.32 (1H, m, $CCHHCH_2$), 1.46 (1H, m, CCH_2CHH), 1.80-1.98 (5H, c, $CCHHCH_2$, CCH_2CHH, $CNCH_2$, CH_2CHCH_2), 3.12 (2H, dd, J = 14.3 and 14.3 Hz, CH_2SO_2), 3.43 (1H, m, $CHNH$), 4.20-4.35 (1H, br s, NH); δ_C (50MHz) 20.44 (q, CH_3), 20.48 (q, CH_3'), 26.80 (t, CCH_2CH_2), 31.85 (t, CCH_2CH_2), 36.05 (t, $CNCH_2CH$), 44.68 (d, CH_2CHCH_2), 47.46 (s, $C(CH_3)_2$), 50.35 (t, CH_2SO_2), 54.97 (s, CCH_2SO_2), 62.83 (d, CHNH); *m/z* 215 (M^+, 1%), 136(98), 134(54), 119(100), 108(96).

4-Prop-2'enoyl-(1S, 7R)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide

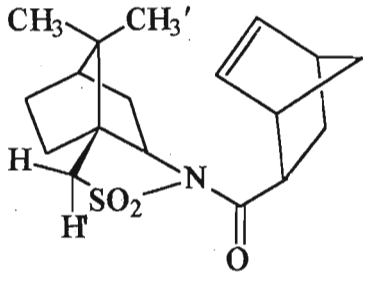


(172)

A solution of camphor sultam (**57**) (1.0 g, 4.65 mmol) and DABCO (1.04 g, 9.30 mmol) in dry THF (15 ml) was left to stir under N_2 at rt for 30 min. Fine copper powder (0.30 g, 4.65 mmol) and CuCl (0.25 g, 2.56 mmol) were then added and the mixture was again left to stir for a further 15 min. Acryloyl chloride (0.78 mls, 9.30 mmol) was then added slowly allowing HCl gas to escape. The mixture was left to stir overnight. The THF was removed under reduced pressure and a 2 cm column plug of neutral alumina was run eluting with EtOAc. The residue was recrystallized from CH_2Cl_2 to yield a pure white solid (1.23 g, 98%).

m.p. 198-200°C, (lit.[81] 196-197°C); (Found: C, 58.25; H, 7.10; N, 4.98. $C_{13}H_{19}NO_3S$ requires C, 57.97; H, 7.11; N, 5.20%); δ_H (200 MHz) 0.98 (3H, s, CH_3), 1.18 (3H, s, CH_3'), 1.41 (2H, m, CC*H*HCH$_2$, CCH$_2$C*H*H), 1.91 (3H, m, CCH*H*CH$_2$,CCH$_2$CH*H*, CNC*H*H), 2.13 (2H, m, CNCH*H*, CH$_2$C*H*CH$_2$), 3.50 (2H, dd, J = 13.8 and 18.5 Hz, C*H*$_2$SO$_2$), 3.95 (1H, dd, J = 5.6 and 7.2 Hz, C*H*N), 5.86 (1H, dd, J = 1.7 and 10.3 Hz, Hb), 6.50 (1H, dd, J = 1.7 and 16.7 Hz, Hc), 6.88 (1H, dd, J = 10.3 and 16.7 Hz, Ha); δ_C (50MHz) 19.89 (q, CH_3), 20.84 (q, CH_3'), 26.46 (t, CCH$_2$CH$_2$), 32.84 (t, CCH$_2$CH$_2$), 38.40 (t, CNCH$_2$CH), 44.66 (d, CH$_2$CHCH$_2$), 47.79 (s, C(CH$_3$)$_2$), 48.55 (t, CH$_2$SO$_2$), 53.09 (s, CCH$_2$SO$_2$), 65.10 (d, CHN), 127.73 (d, CH=CH$_2$), 131.36 (t, CH=CH$_2$), 163.79 (s, C=O); *m/z* 269 (M^+, 0.6%), 190(3), 162(5), 93(7), 79(8), 55(100).

4-((5R,6S)-6-Methylbicyclo{2.2.1]hept-2-en-5-carbonyl)-(1S, 7R)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide

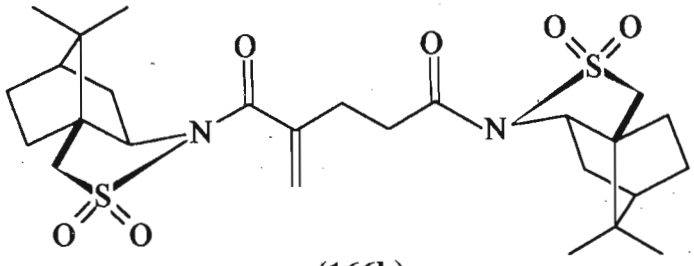


(172a)

To a stirred solution of (**172**), (0.50 g, 1.86 mmol) with excess, freshly distilled cyclopentadiene (2ml) in dry CH_2Cl_2 under N_2 at -78°C was added diethylaluminium chloride (1.86 ml of a 1,0M solution in hexanes). The reaction was kept at -78°C for 1 h before the solution was poured onto hydrochloric acid (50 ml, 1 M). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulphate and filtered. The solvent was removed under reduced pressure and the product was purified by using a chromatotron with 10% EtOAc:hexane as the eluent. The major isomer was isolated by double recrystallization from EtOAc:hexane (0.57g, 92%).

m.p. 183°C, (lit.[81] 179-183°C); δ_H (200 MHz) 0.98 (3H, s, CH_3), 1.21 (3H, s, CH_3'), 1.15-2.06 (11H, m, CCH_2CH_2, CCH_2CH_2, $CNCH_2$, CH_2CHCH_2, H-5′ and H-7′), 2.95 (1H, br s, H-6′), 3.49 (4H, m, CH_2SO_2, CHN, H-4′), 3.84 (1H, br s, H-3′), 5.75 (1H, dd, J = 2.6 and 5.6 Hz, H-2′), 6.26 (1H, dd, J = 3.1 and 5.5 Hz, H-1′); δ_C (50MHz) 19.86 (q, CH_3), 20.67 (q, CH_3'), 26.47 (t, CCH_2CH_2), 28.55 (t, C-5′), 32.59 (t, CCH_2CH_2), 38.49 (t, $CNCH_2CH$), 43.15 (d, C-6′), 44.49 (d, CH_2CHCH_2), 44.49 (d, C-4′), 47.71 (s, $C(CH_3)_2$), 48.00 (d, C-3′), 48.21 (s, CCH_2SO_2), 50.34 (t, C-7′), 53.12 (t, CH_2SO_2), 65.22 (d, CHN), 130.13 (d, C-2′), 138.55 (d, C-1′), 173.33 (s, C=O); *m/z* 335 (M^+, 6%), 93(32), 66(88), 55(100).

3.3.6.1 Major By-product of Acylation Reaction.



(166b)

m.p. 183°C; (Found: C,57.97; H,7.09; N,5.20. $C_{26}H_{38}N_2O_6S_2$ requires C,57.99; H,7.06; N, 5.21%); υ_{max} (KBr/cm^{-1}) 1699 (CO) and 1682 (CO), 1626 (C=C); δ_H (200 MHz) 0.97 and 0.99 (6H, s, CH_3), 1.16 and 1.23 (6H, s, CH_3), 1.08-1.48 (4H, m, CC*H*HCH2, CCH_2CHH), 1.81-2.13 (10H, m, CCH*H*CH_2, CCH_2CHH, $CNCH_2$, CH_2CHCH_2), 2.72 (2H, m, C=CCH_2CH_2CO), 2.97 (2H, m, C=CCH_2CH_2CO), 3.49 (4H, d, J = 4.7 Hz, CH_2SO_2), 3.86 (1H, dd, J = 5.3 and 7.5 Hz, C*H*N), 4.05 (1H, m, C*H*N), 5.76 (2H, d, J = 16.9 Hz, C=CH_2); δ_C (50MHz) 19.88 and 19.88 (q, CH_3), 20.83 and 21.32 (q, CH_3), 26.43 and 26.90 (t, CCH_2CH_2), 29.67 (t, C=CCH_2CH_2CO), 32.79 and 33.16 (t, CCH_2CH_2), 33.60 (t, C=CCH_2CH_2CO), 38.30 and 38.40 (t, $CNCH_2CH$), 44.63 and 45.19 (d, CH_2CHCH_2), 47.67 and 47.74 (s, $C(CH_3)_2$), 47.93 and 48.49 (t, CH_2SO_2), 52.82 and 53.50 (s, CCH_2SO_2), 65.13 and 65.47 (d, CHN), 124.62 (t, C=CH_2), 141.31 (s, C=CH_2), 170.49 and 170.58 (s, C=O); *m/z* 538 (M^+, 0.6%), 324(100), 296(8), 135(58), 93(61).

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$C_{26}H_{38}S_2O_6N_2$

a: 7.2239 (10) Å, α: 69.978 (15)°, b: 9.1521 (17) Å, β: 85.707 (12)°,

c: 10.6089 (18) Å, γ: 84.710 (13)°, vol: 655.49 (19) $Å^3$;

Cell type: TRICLINIC; Space group: *P1*; Z = 1; R factor: 0.0429.

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$C_{19}H_{22}O_2N_2$

a: 8.3381 (19) Å, b: 9.9542 (19) Å, c: 20.1692 (32) Å, vol: 1674.02 (55) $Å^3$;

Cell type: ORTHORHOMBIC; Space group: $P2_12_12_1$; Z = 4; R factor: 0.0544.

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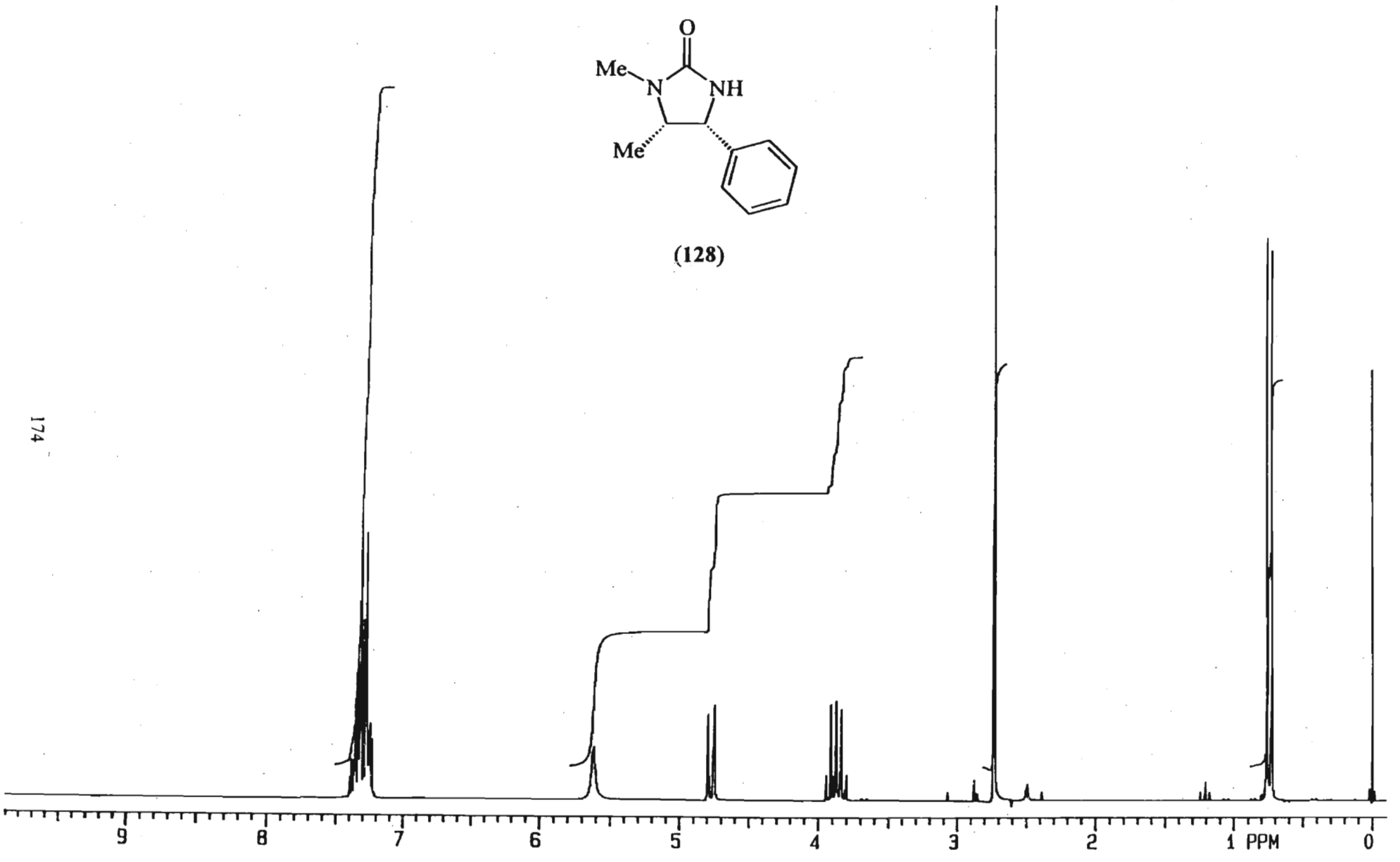
5. APPENDIX: ^{1}H AND ^{13}C NMR SPECTRA



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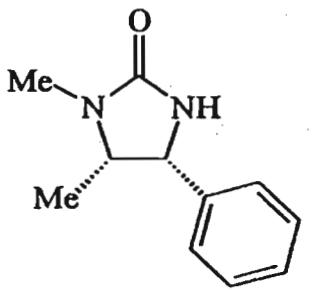

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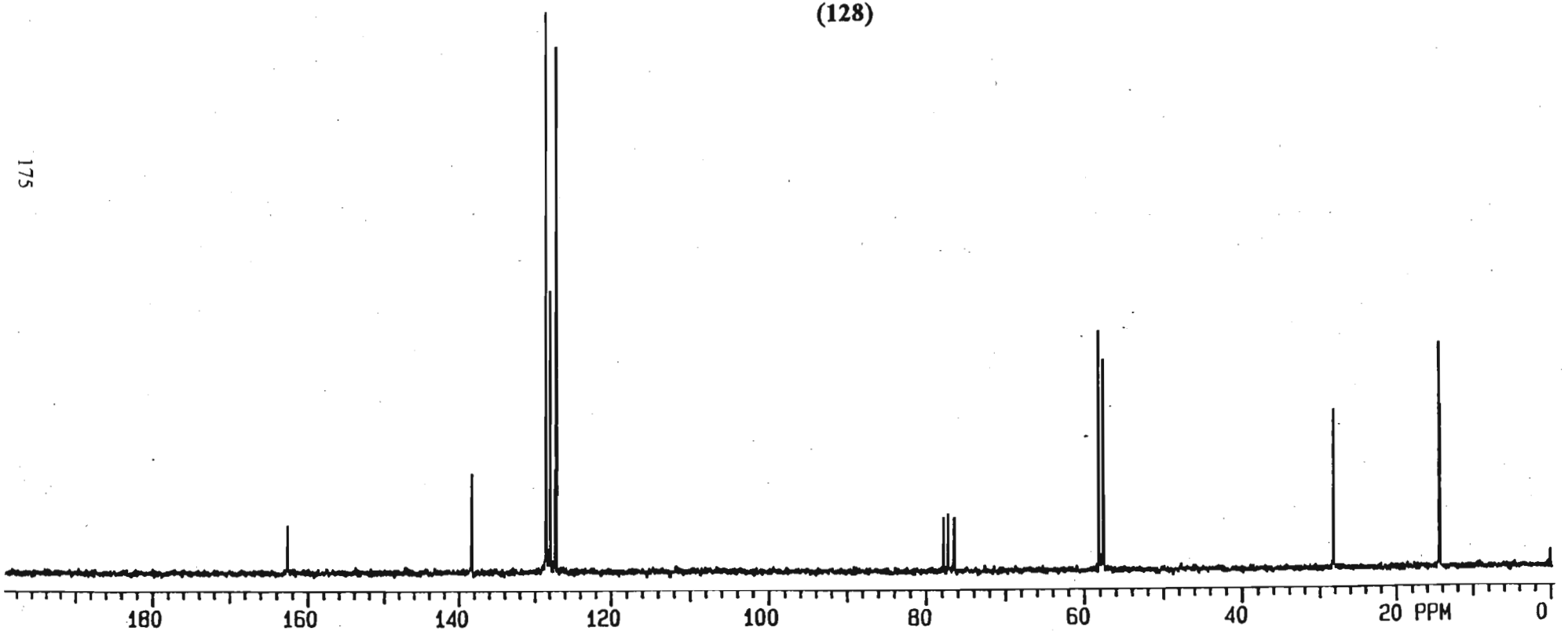

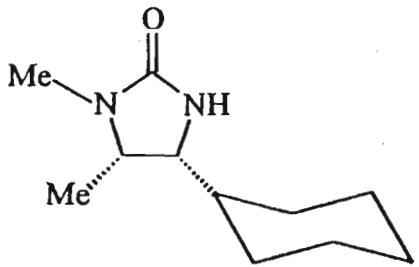

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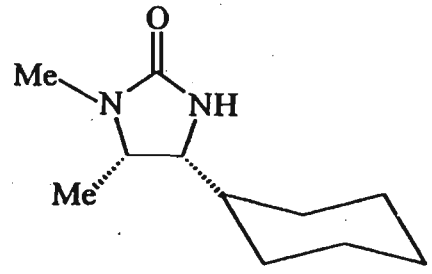

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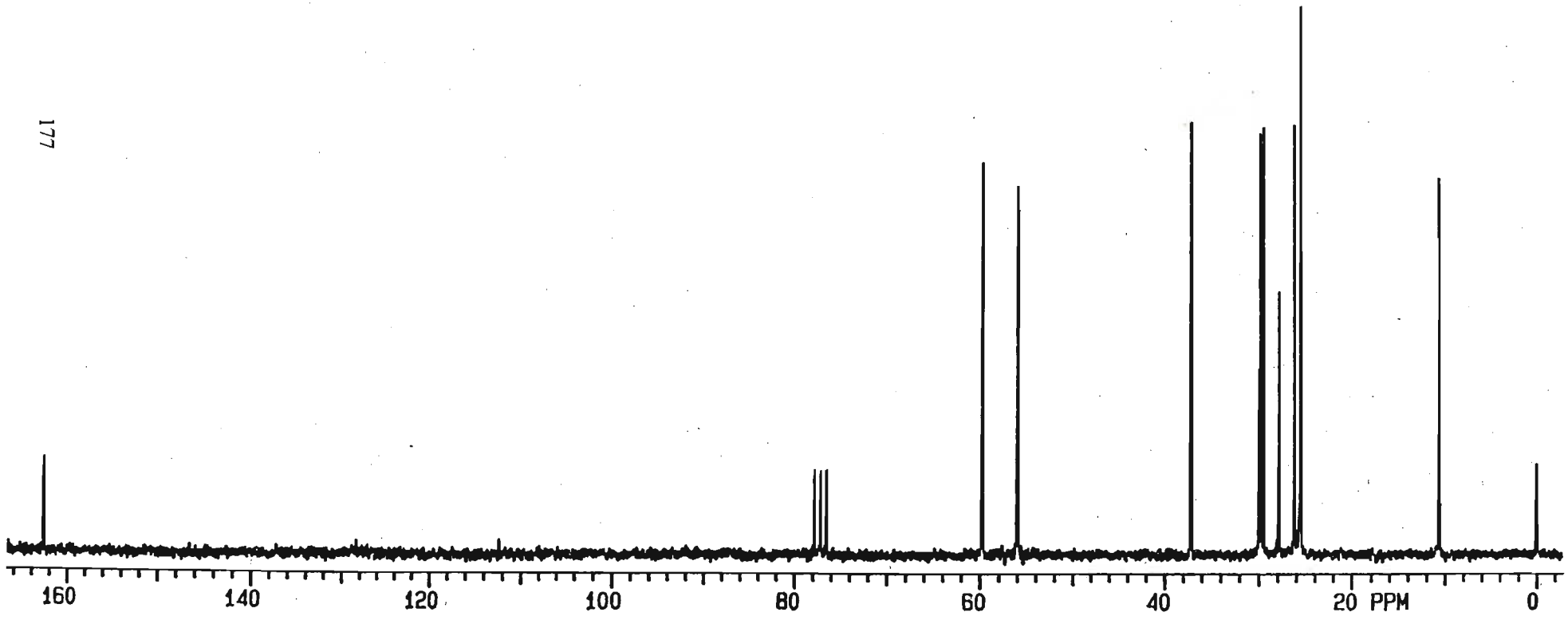

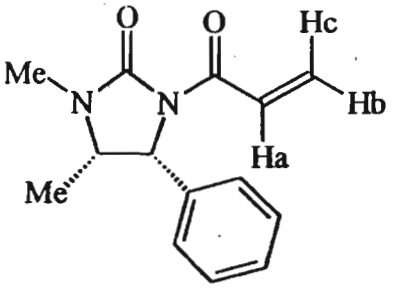

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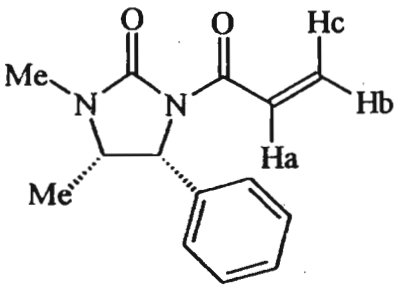

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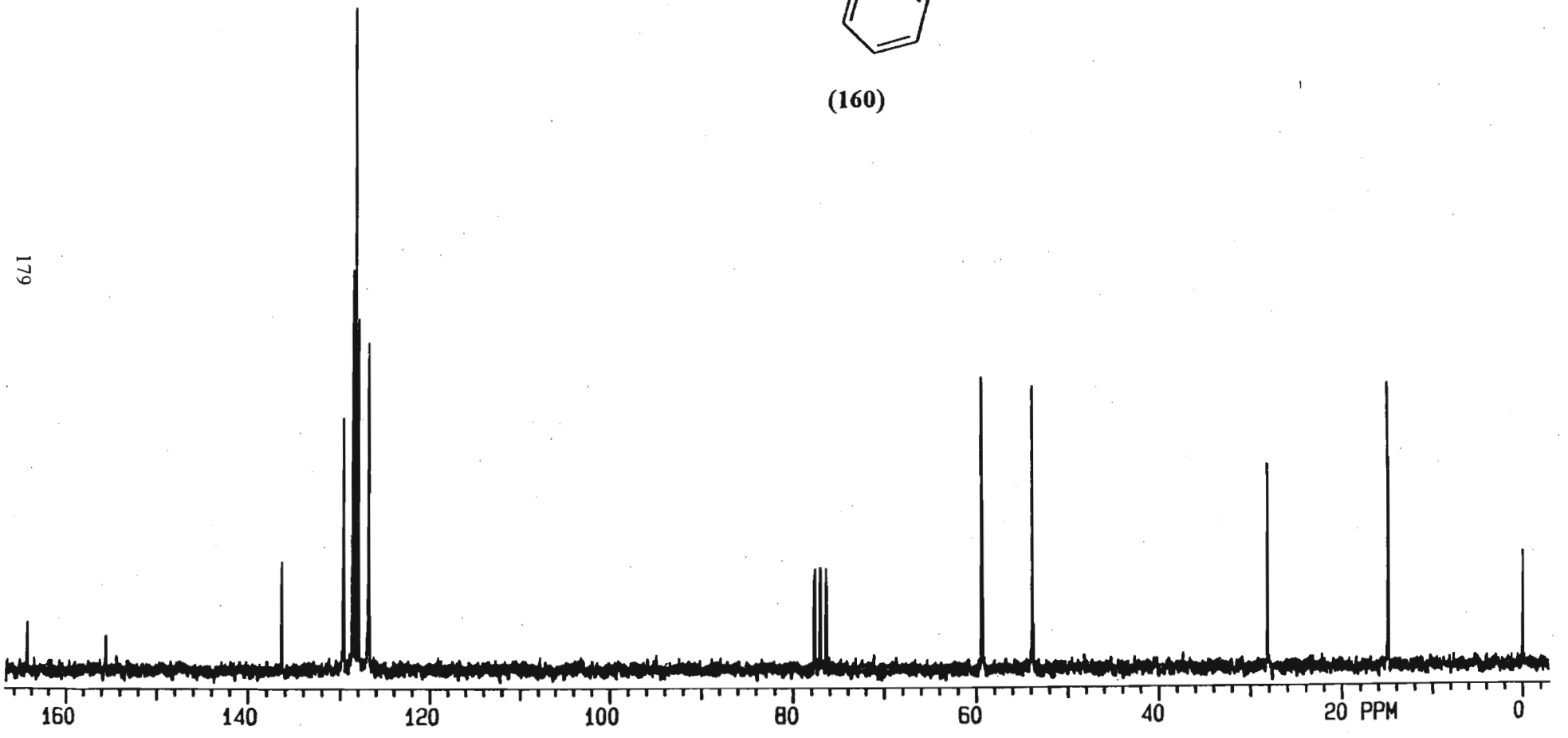

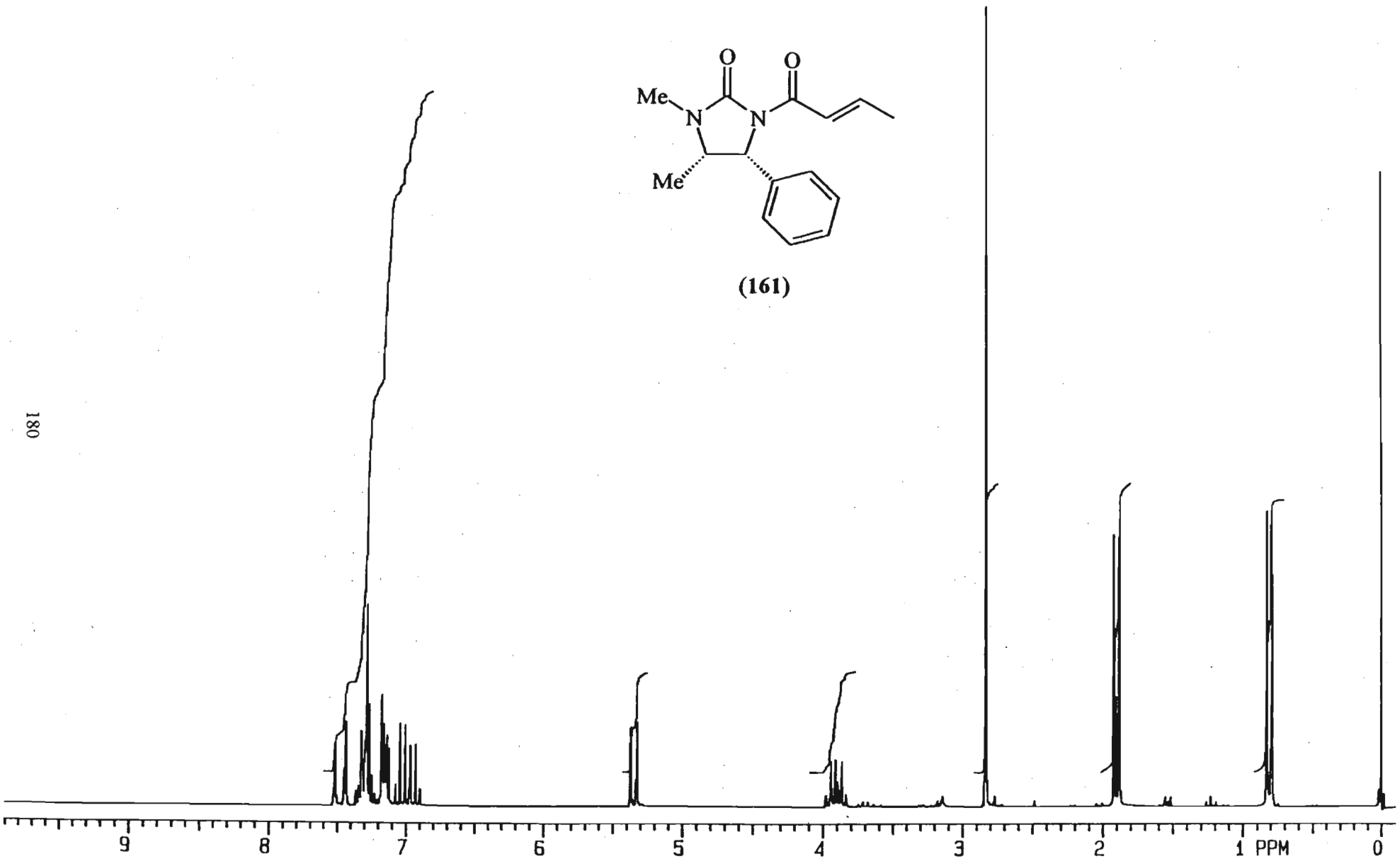

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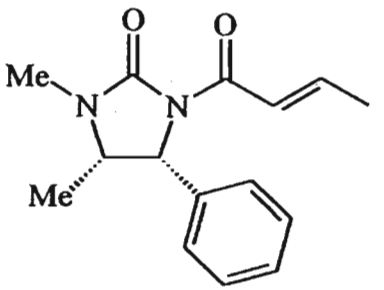

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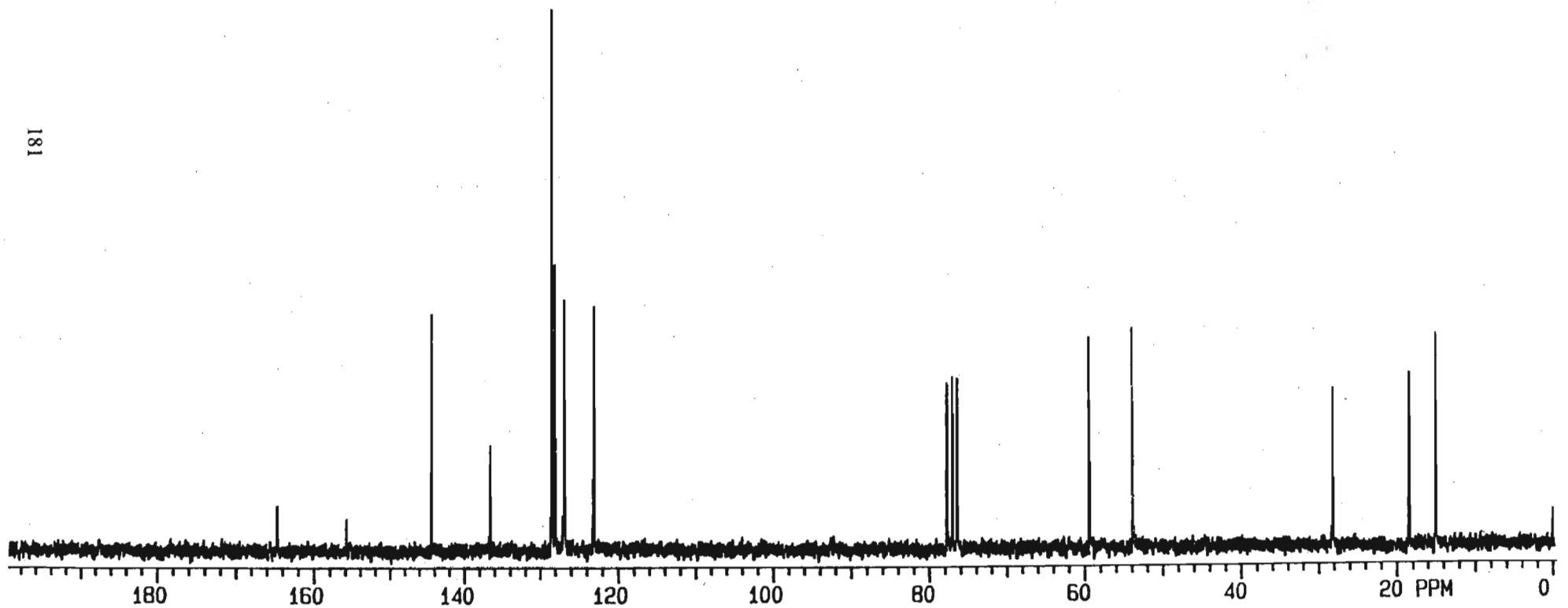

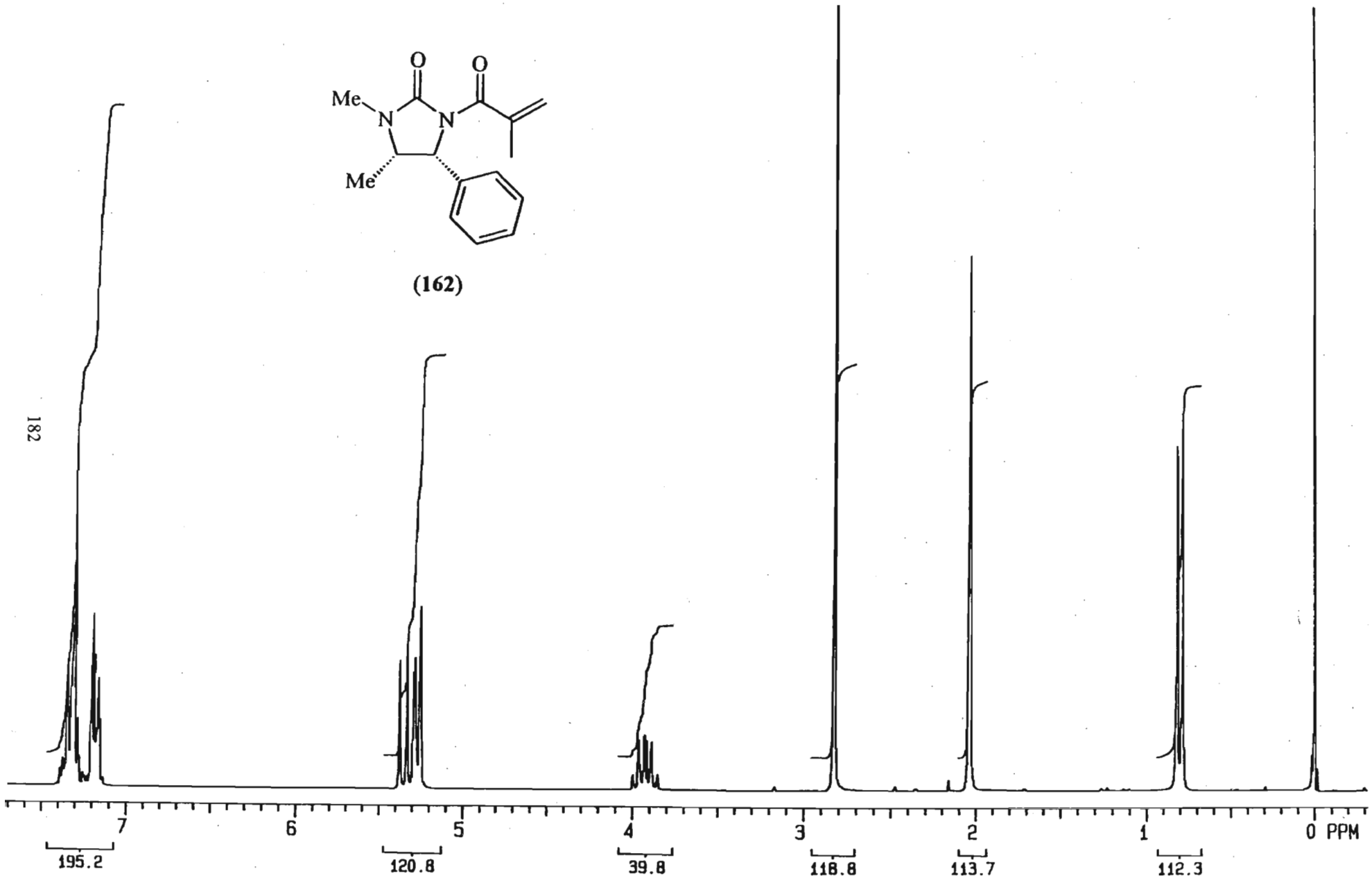

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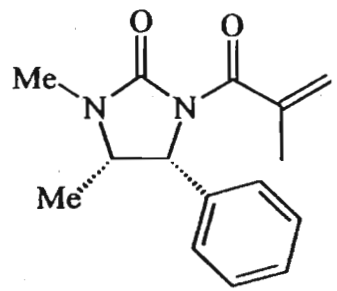

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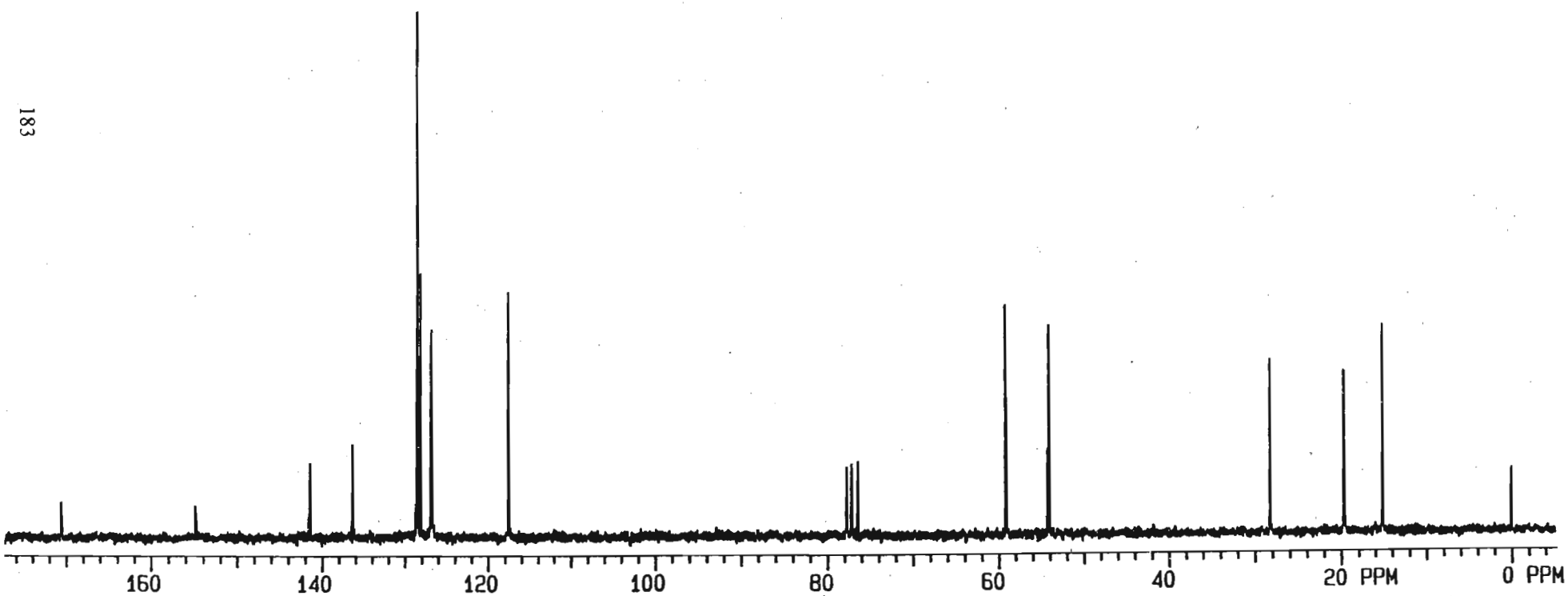

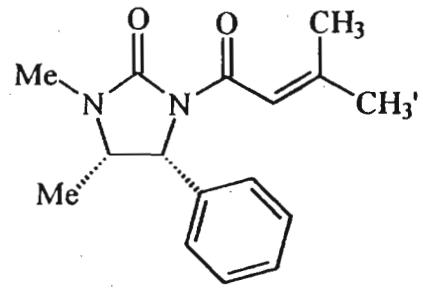

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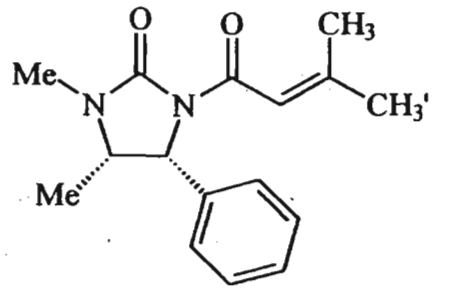

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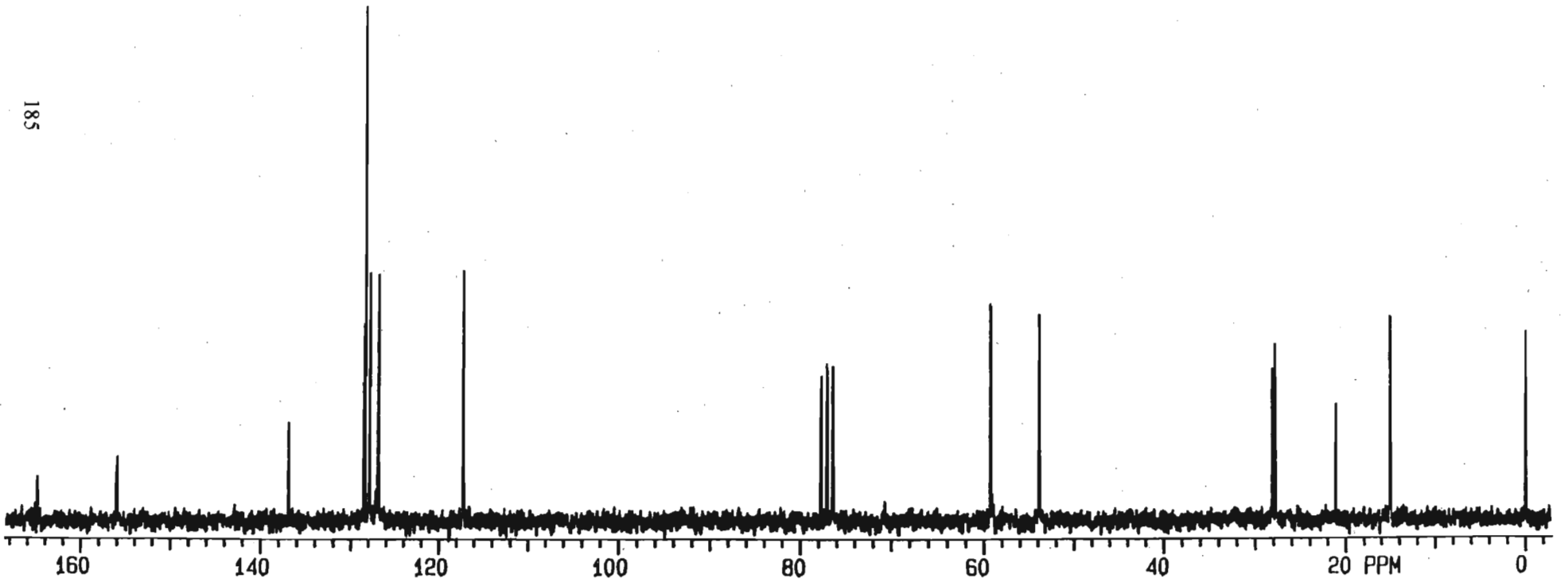

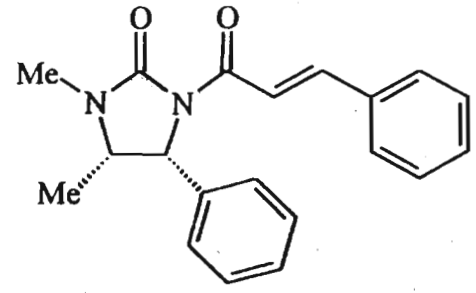

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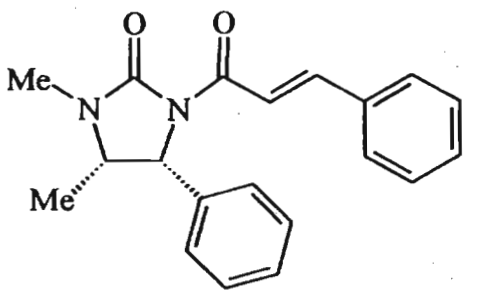

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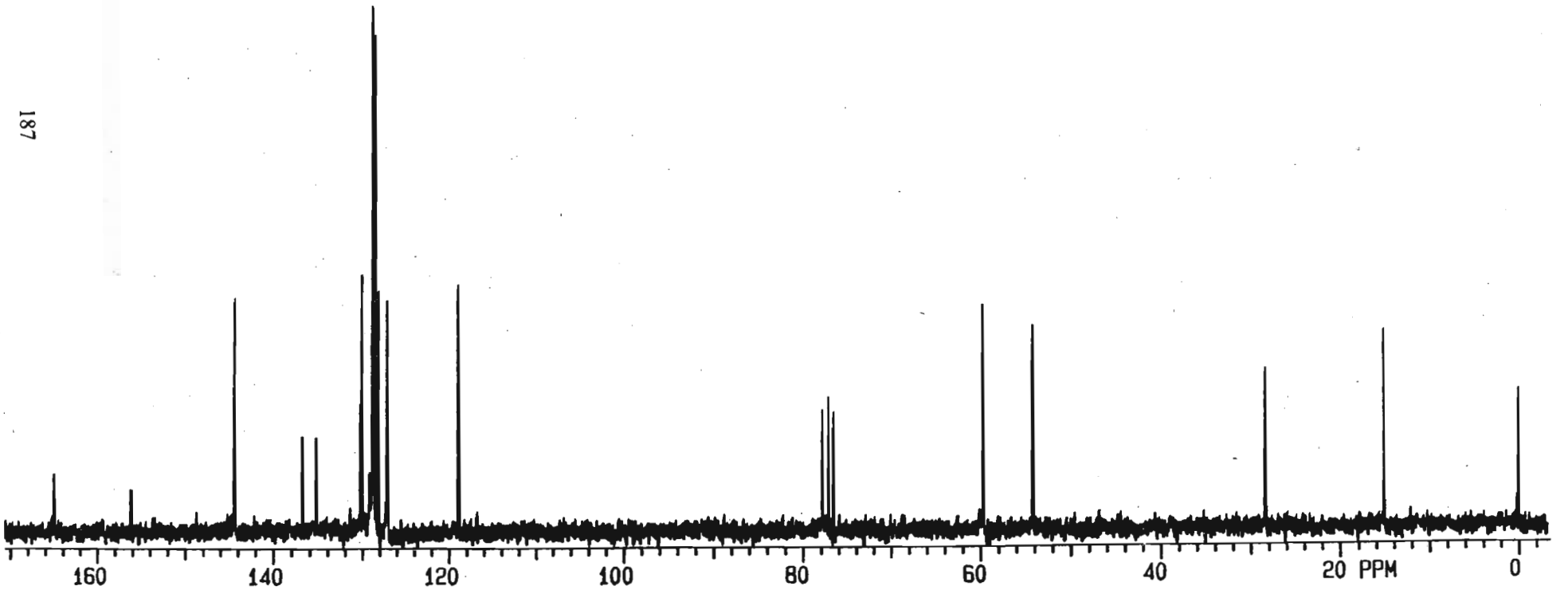

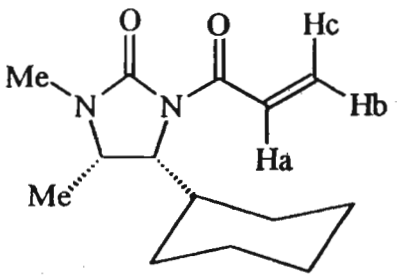

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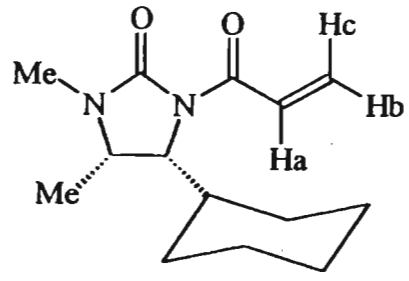

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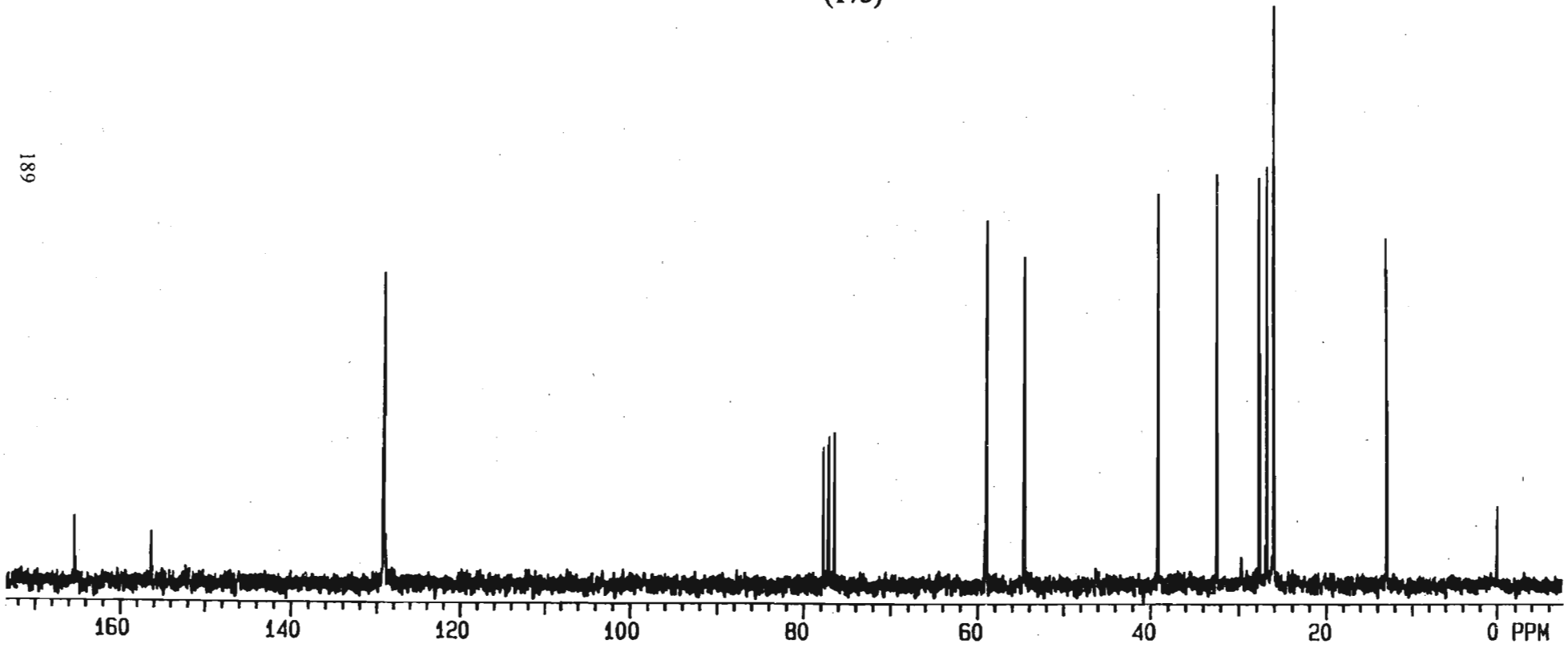

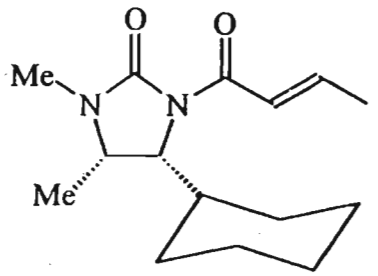

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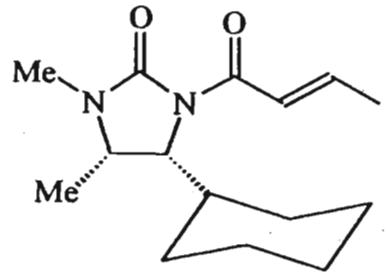

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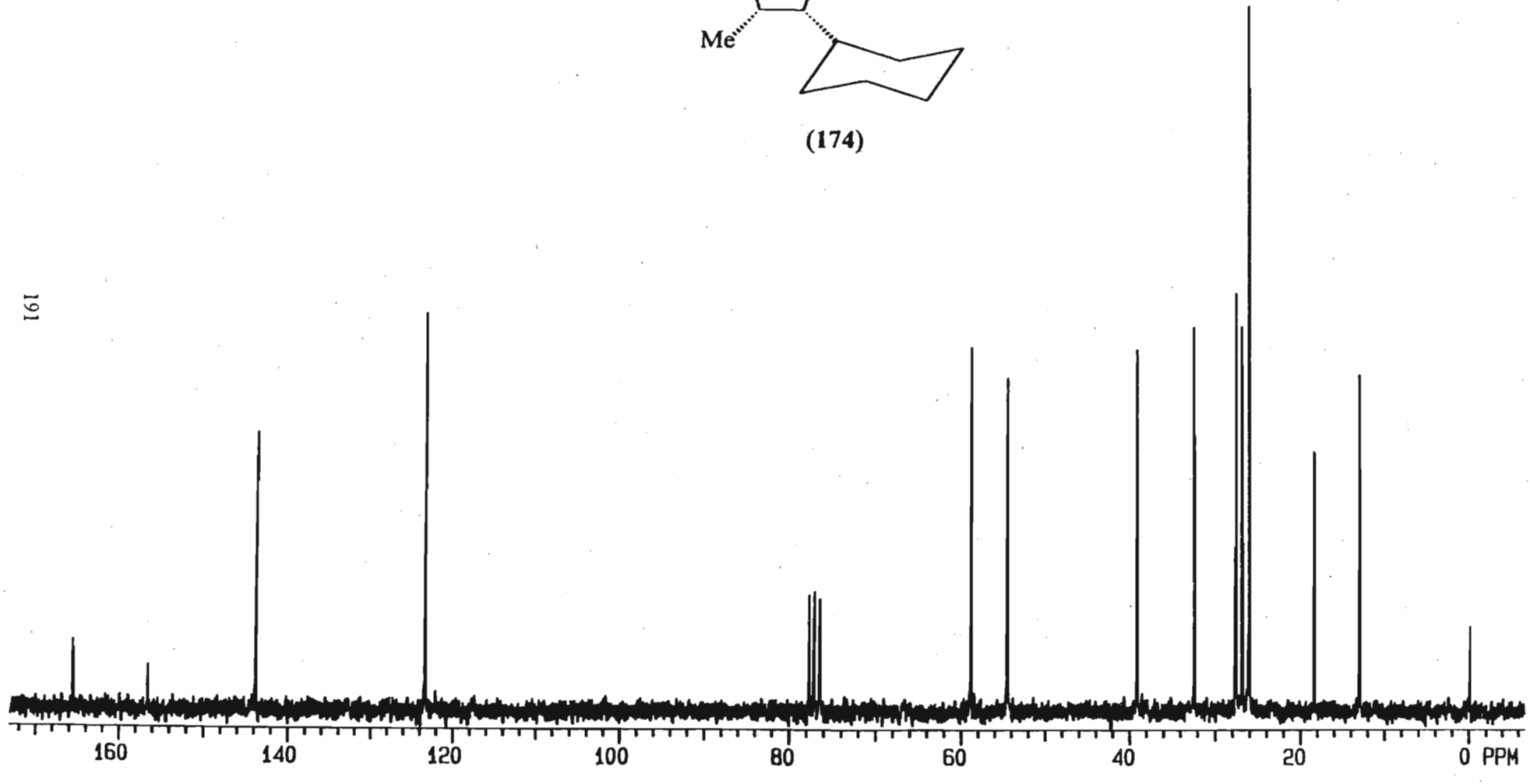

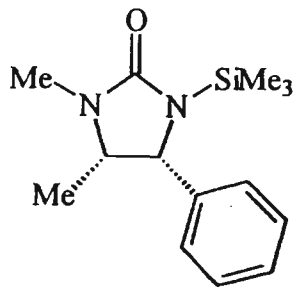

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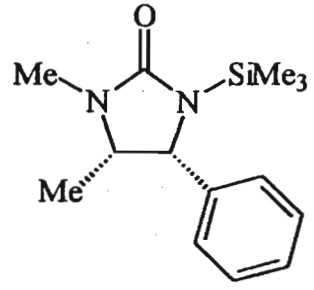

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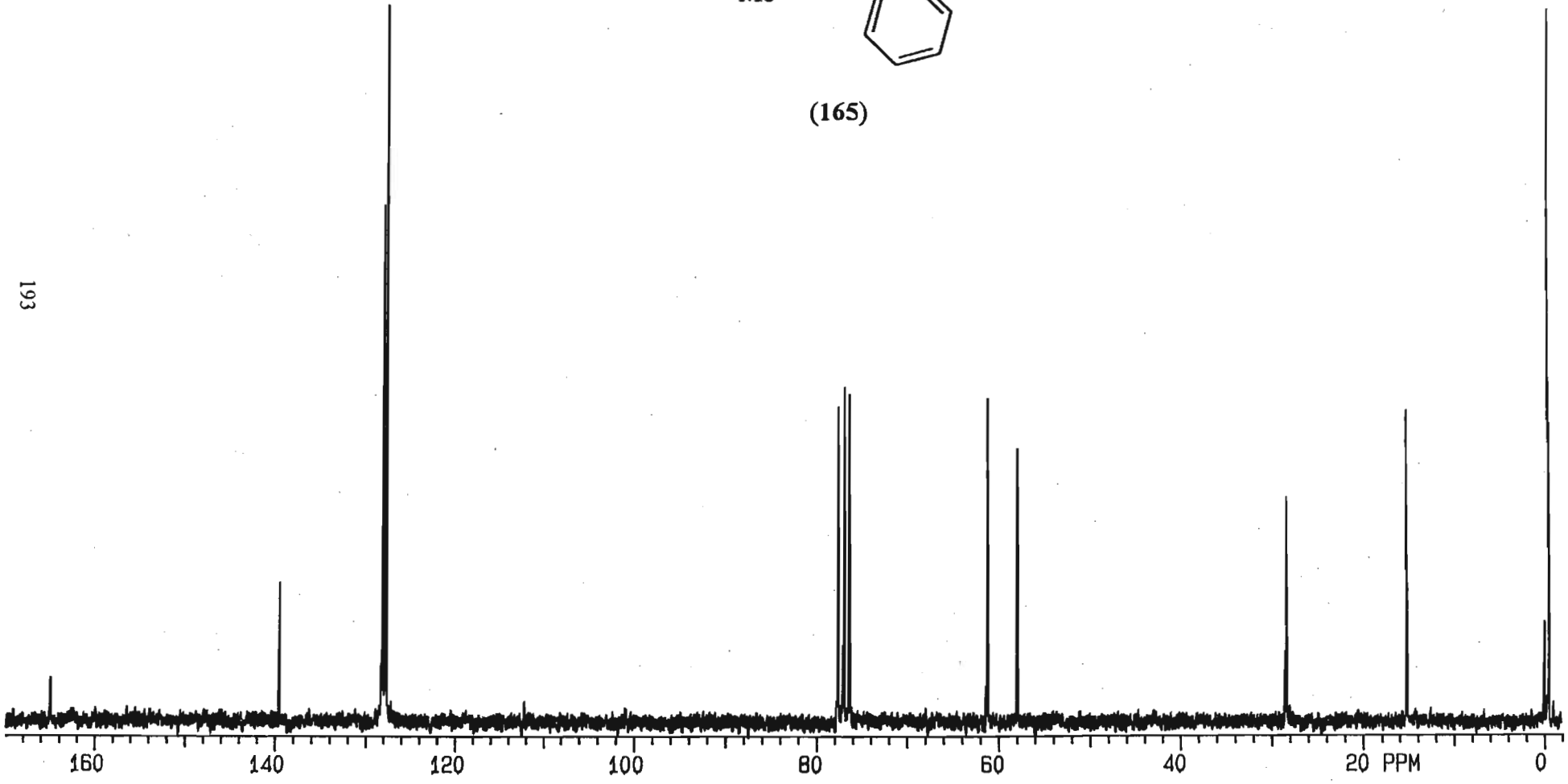

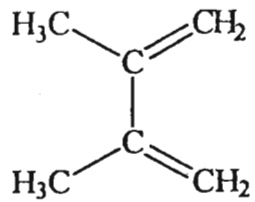

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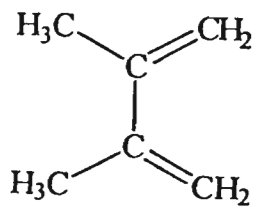

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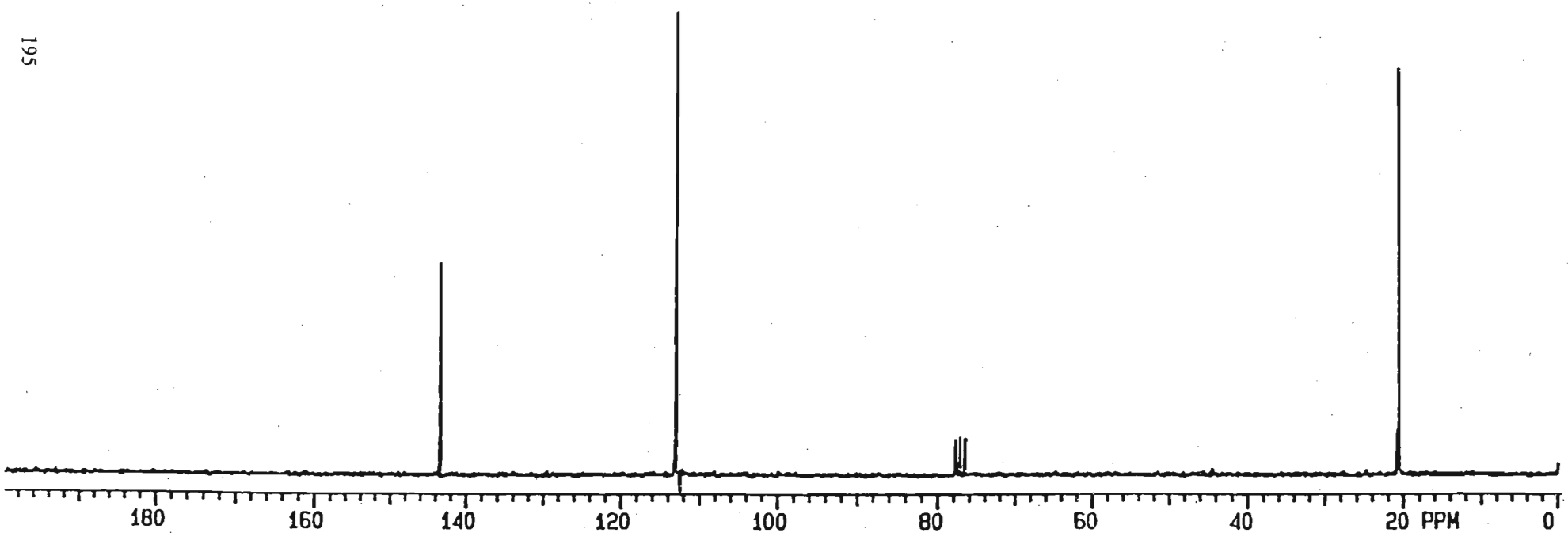

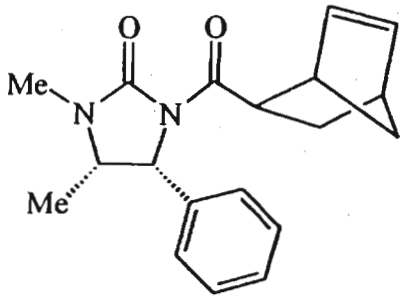

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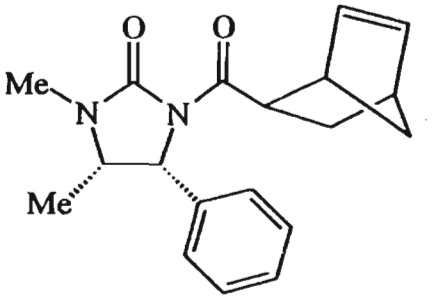

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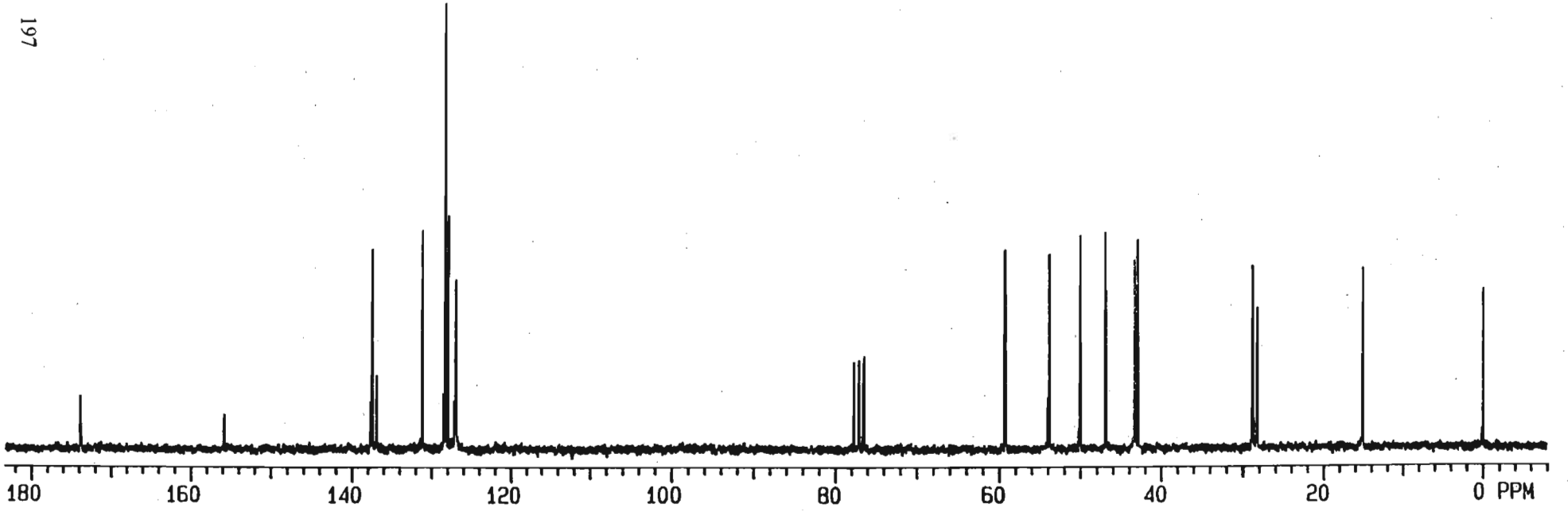

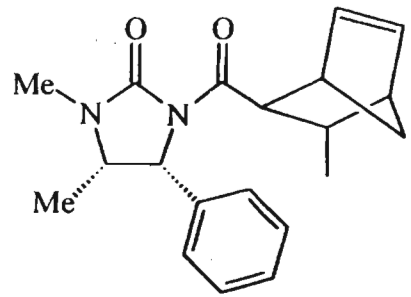

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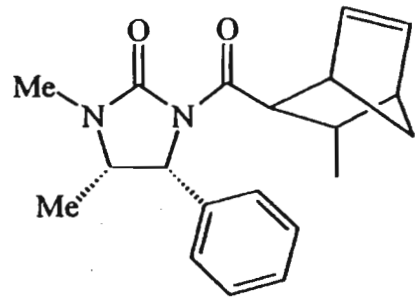

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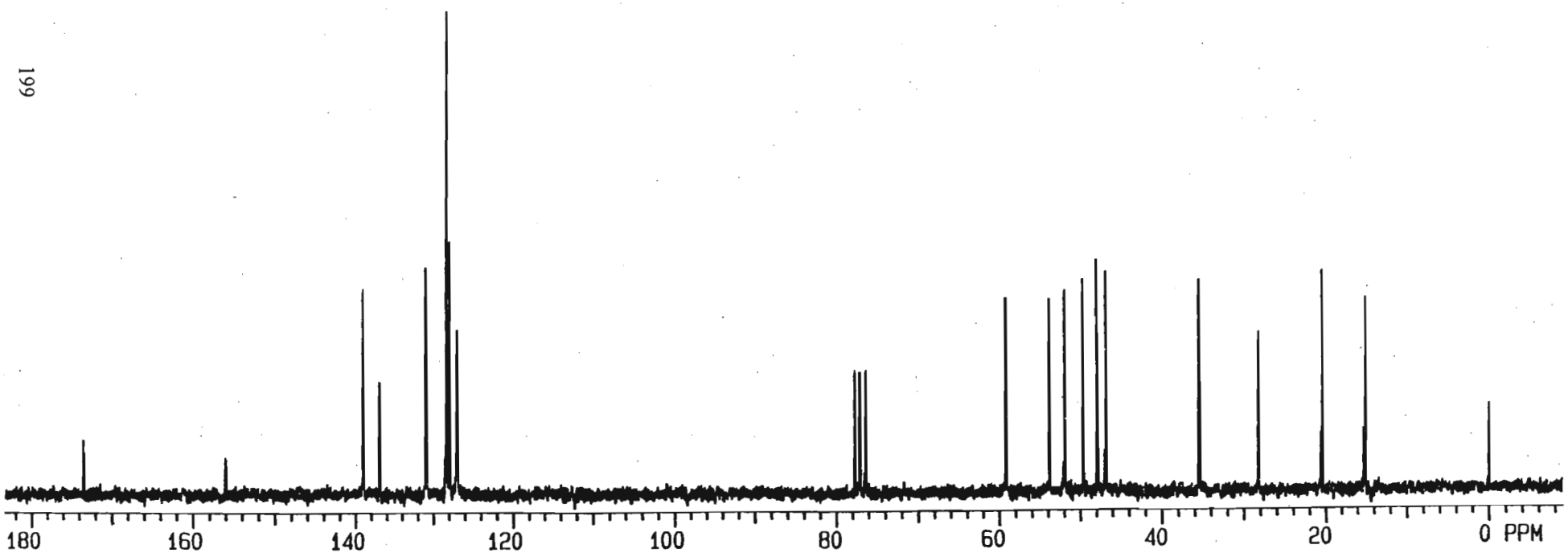

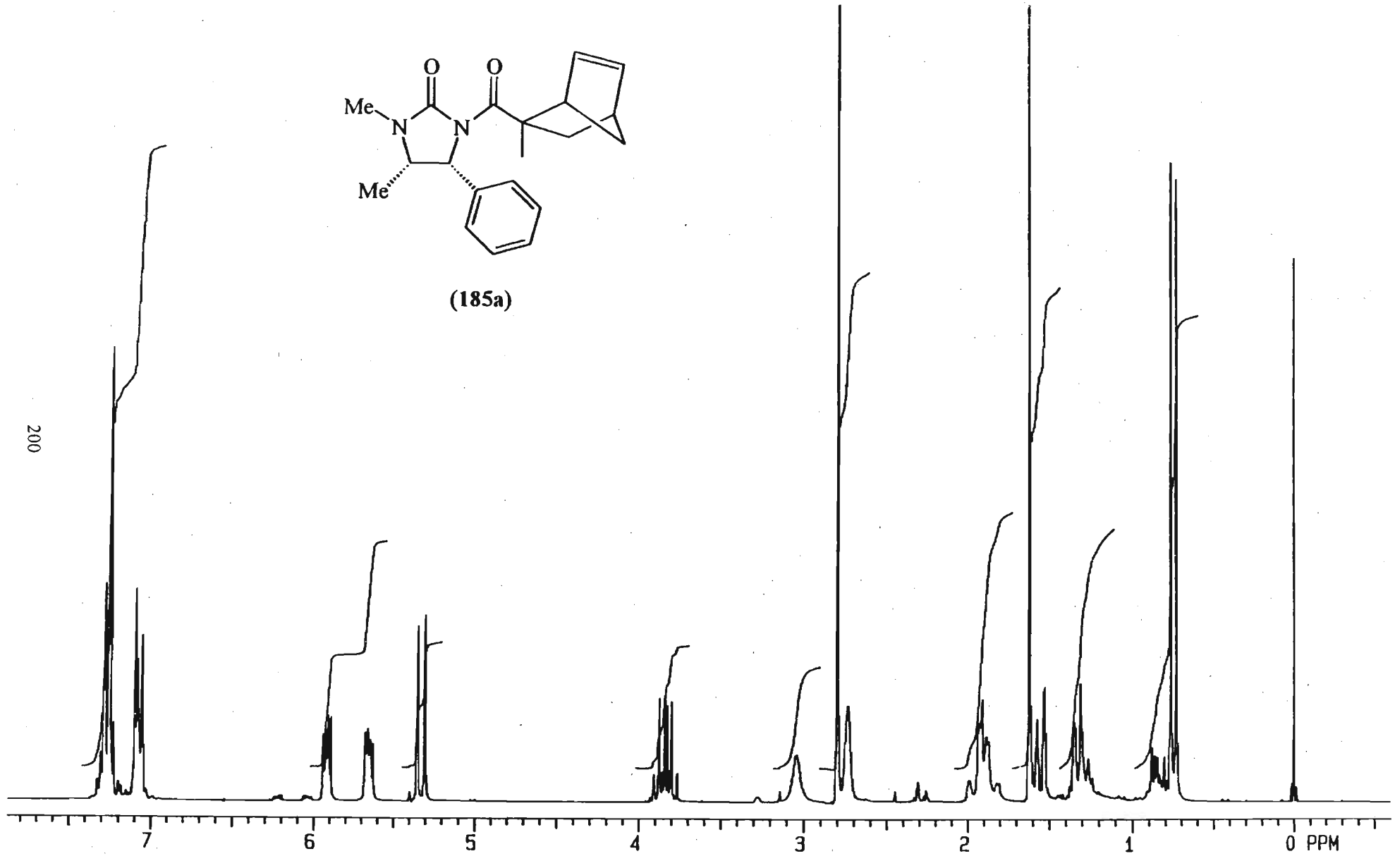

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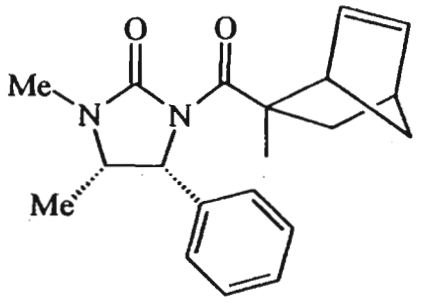

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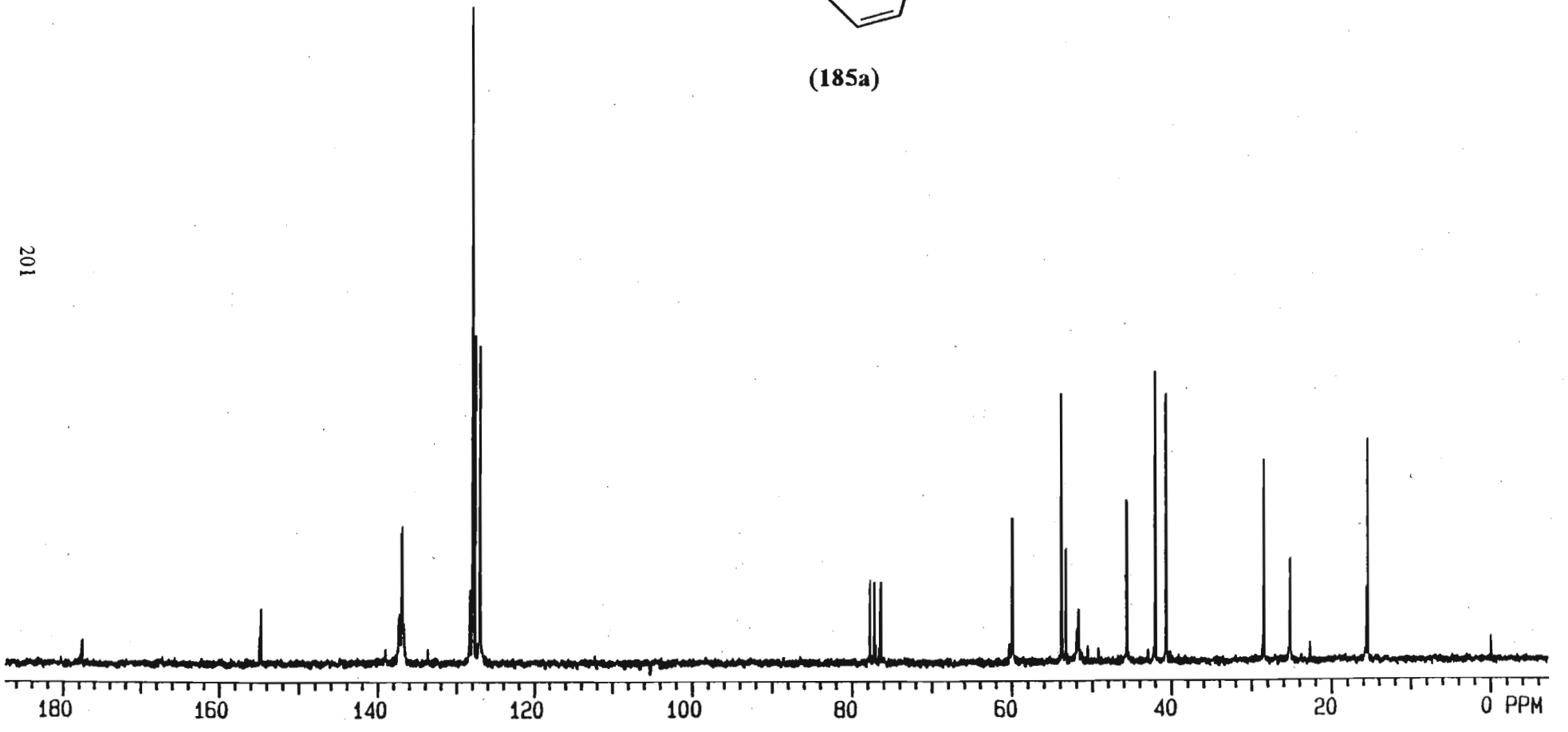
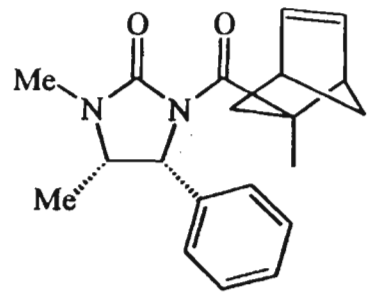
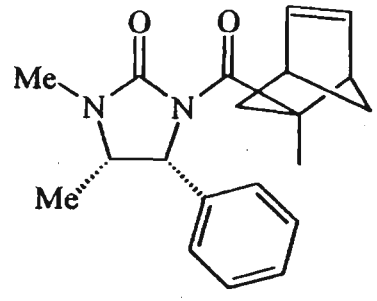


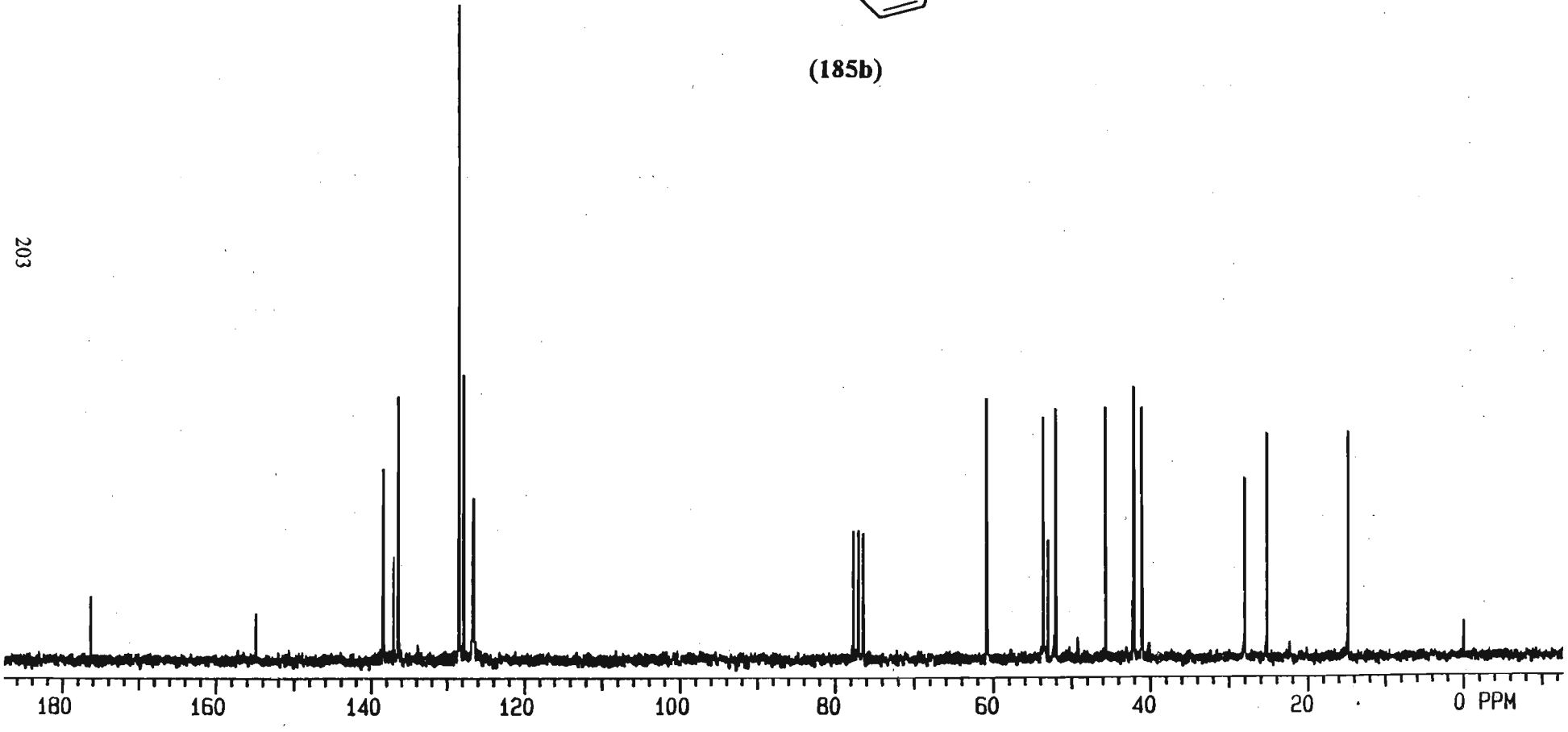


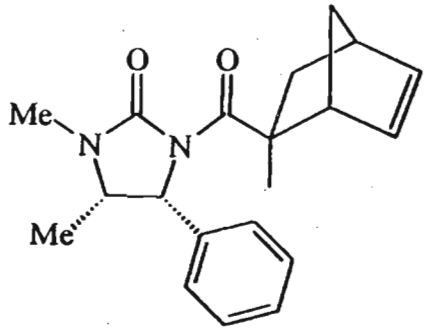
(185b)

8 7 6 5 4 3 2 1 0 PPM

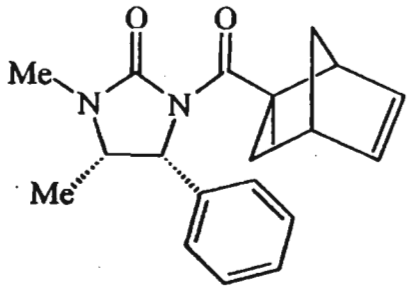


(185b)

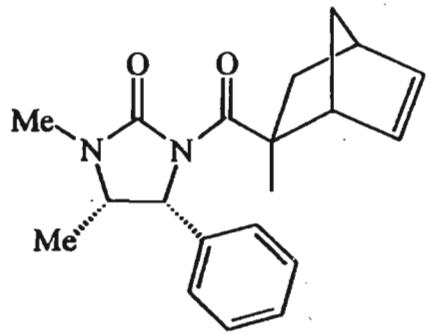




(185c)



(185d)



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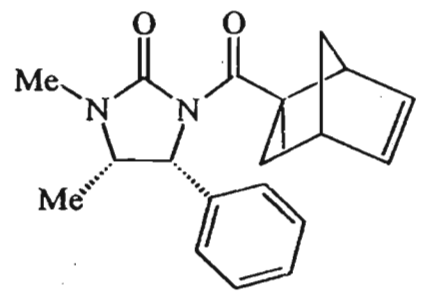
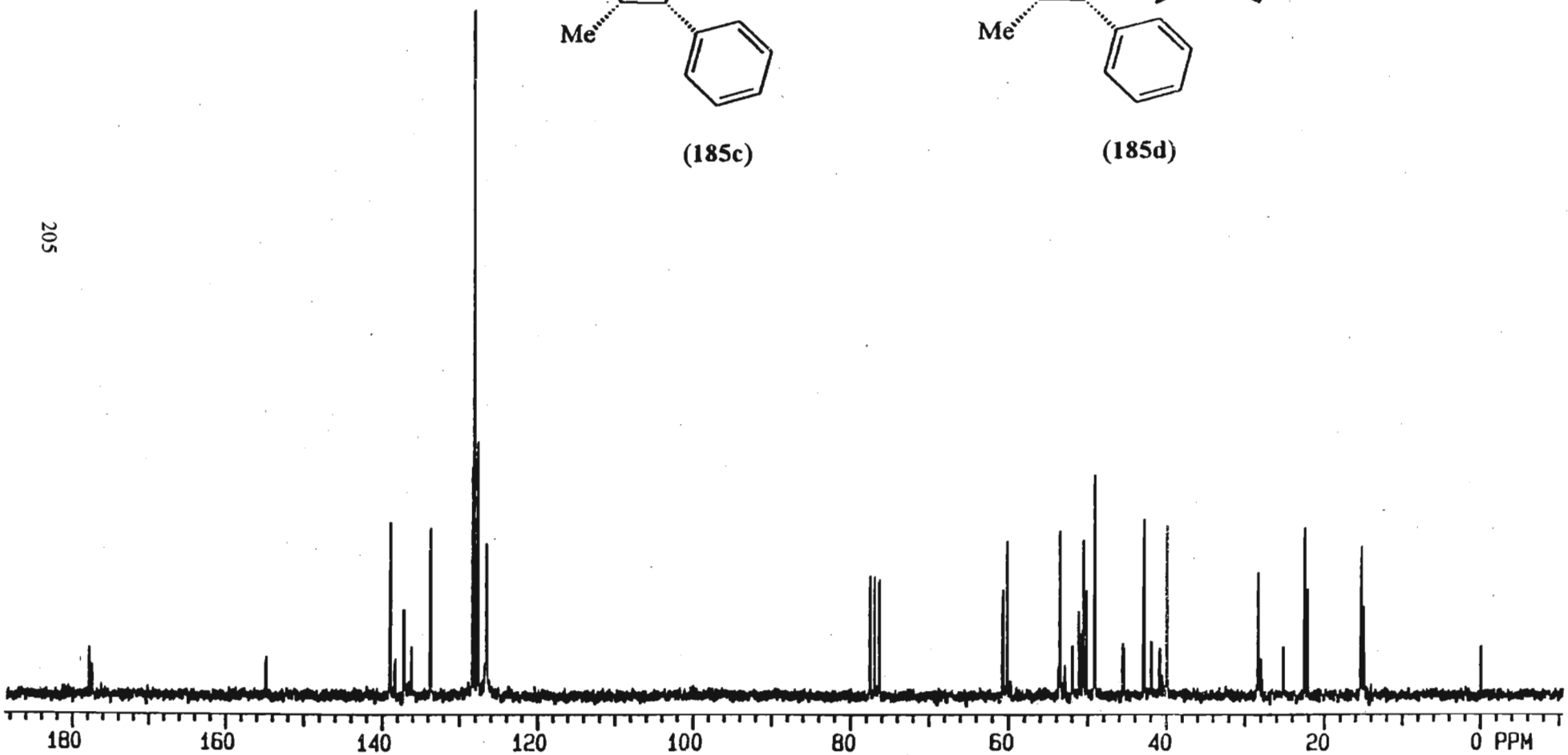
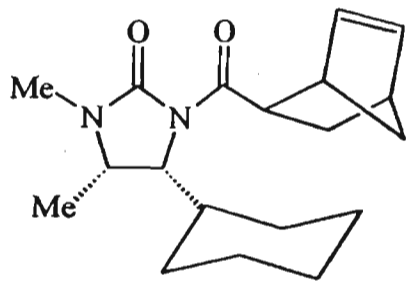
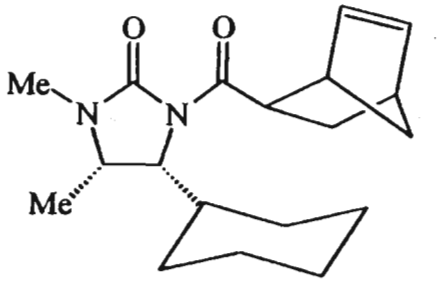


(185d)

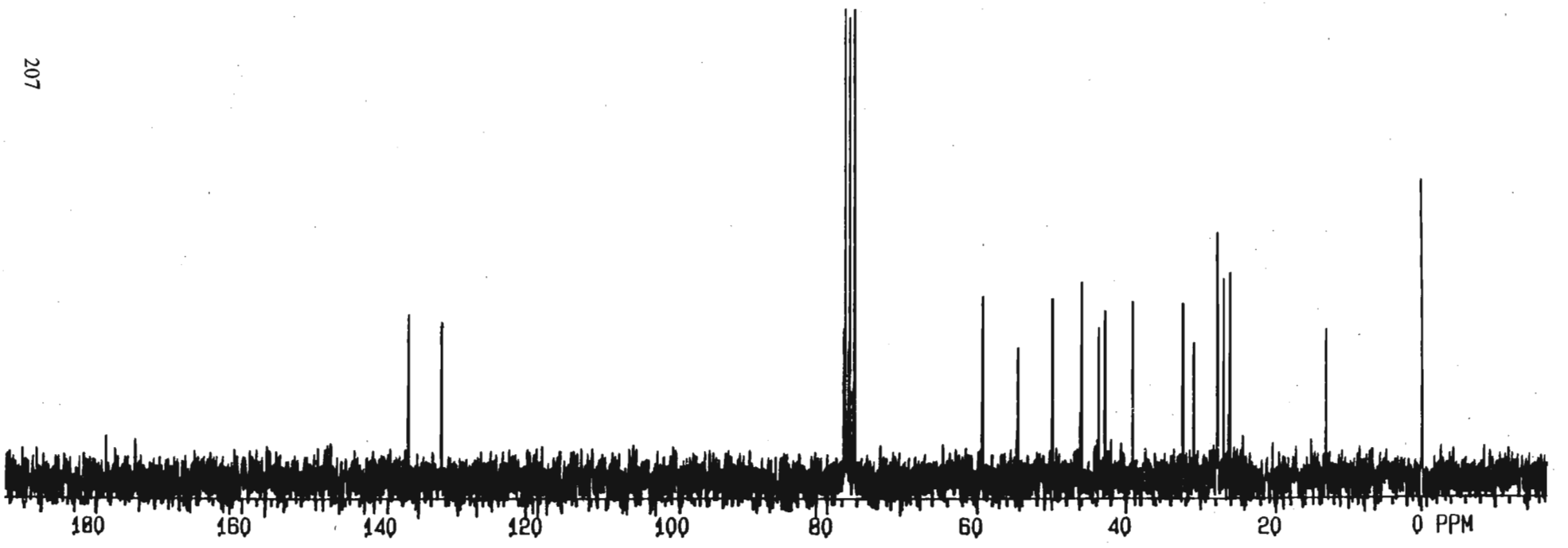


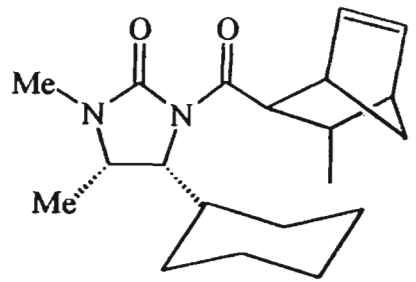


(186)

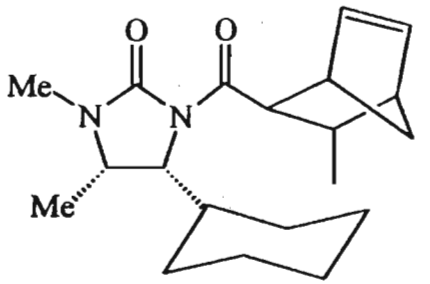


(186)

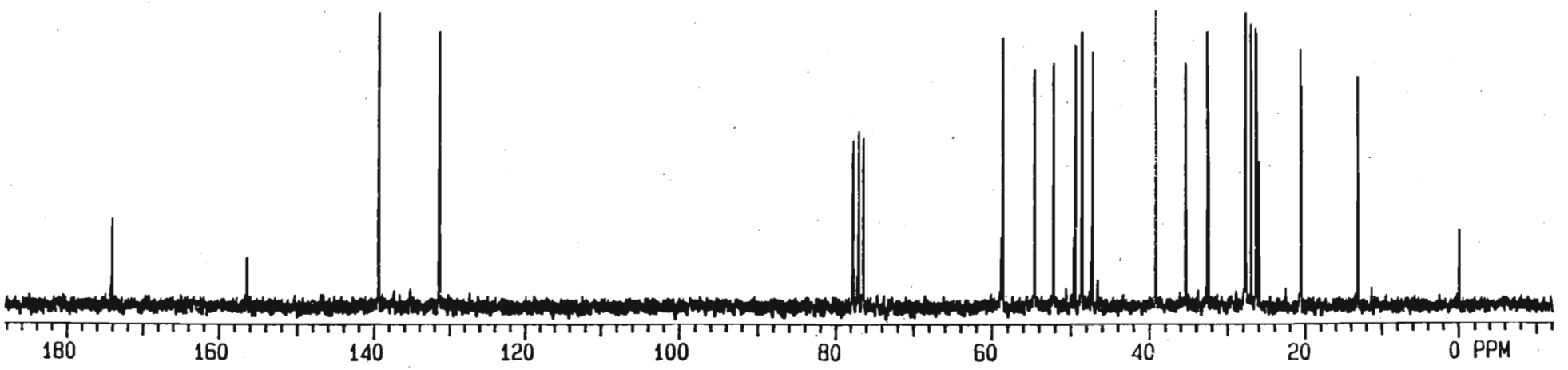


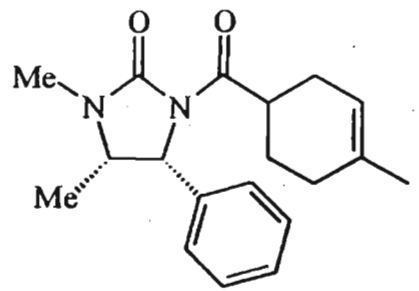


(187)

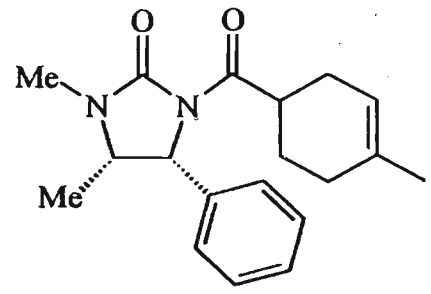


(187)

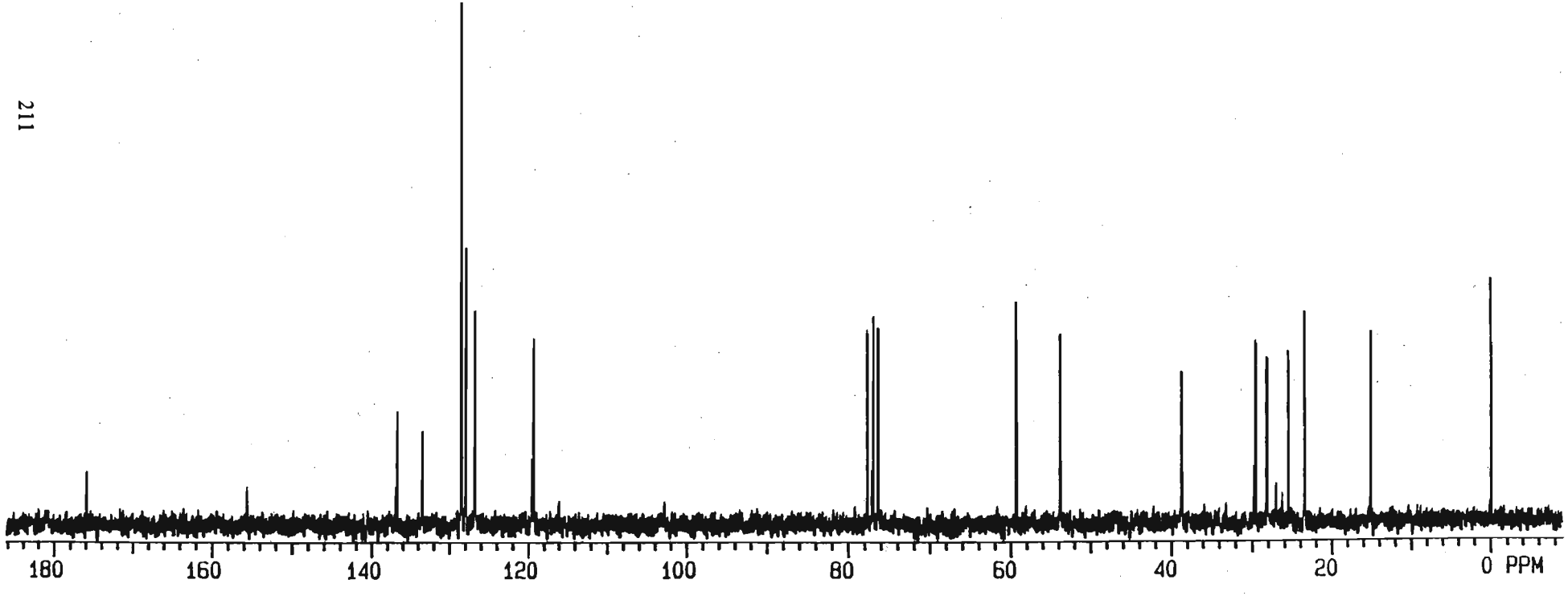


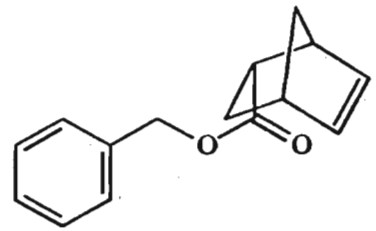


(189)

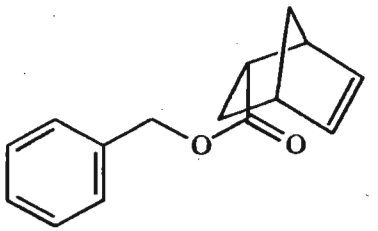


(189)





(191)



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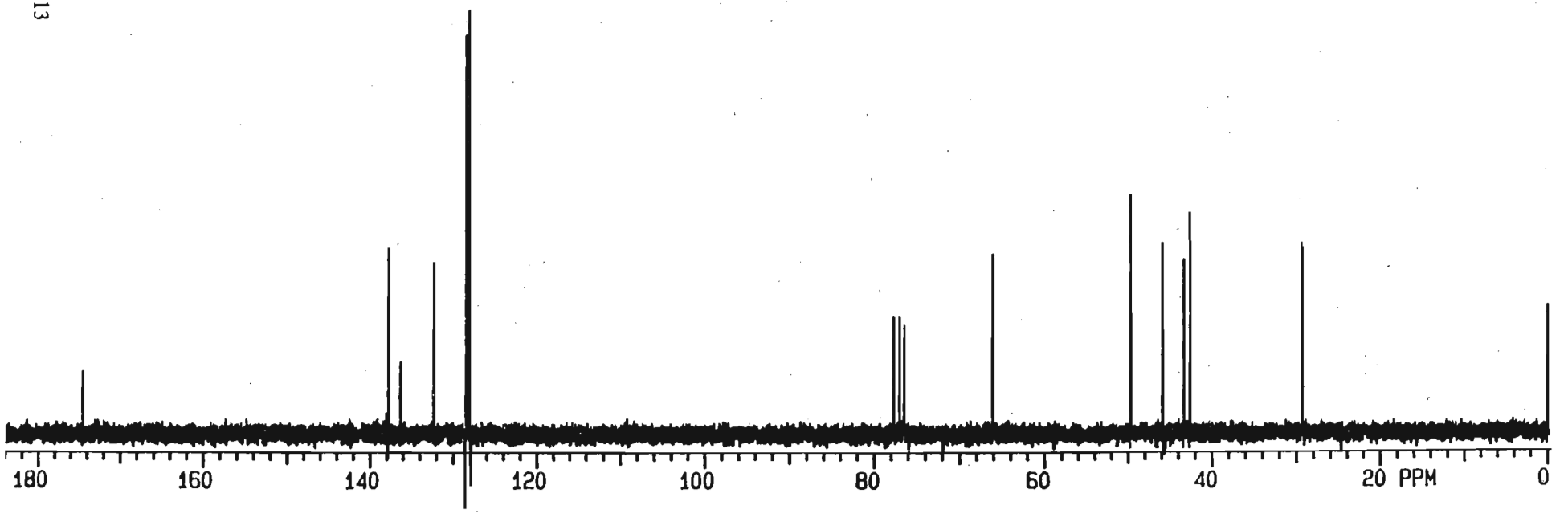
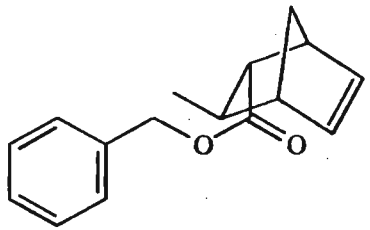
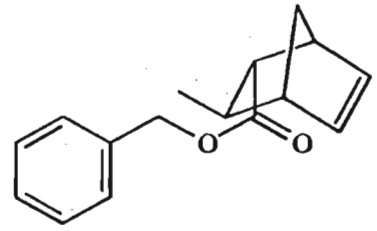
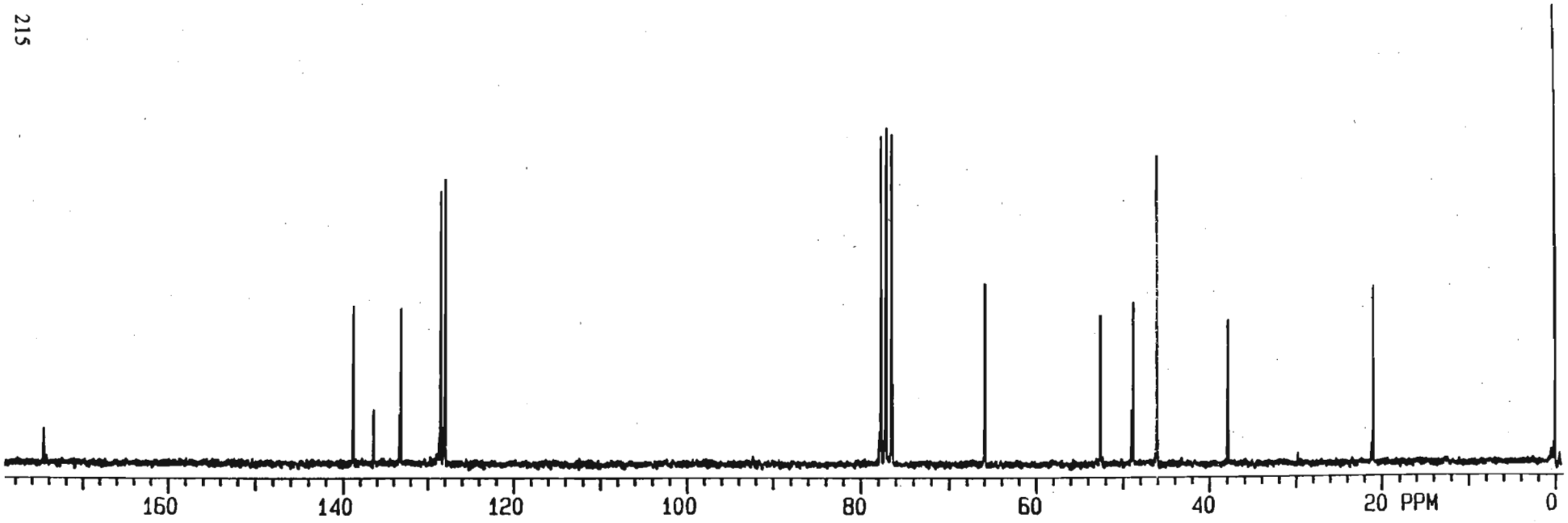


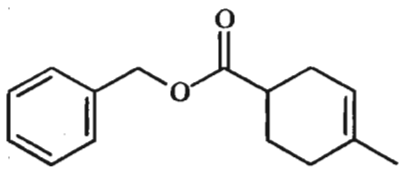


(192)



(192)





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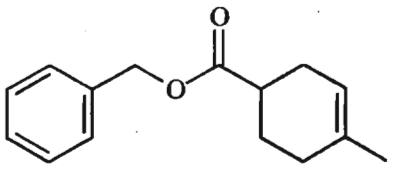
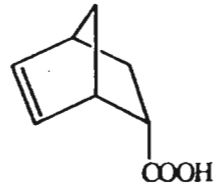
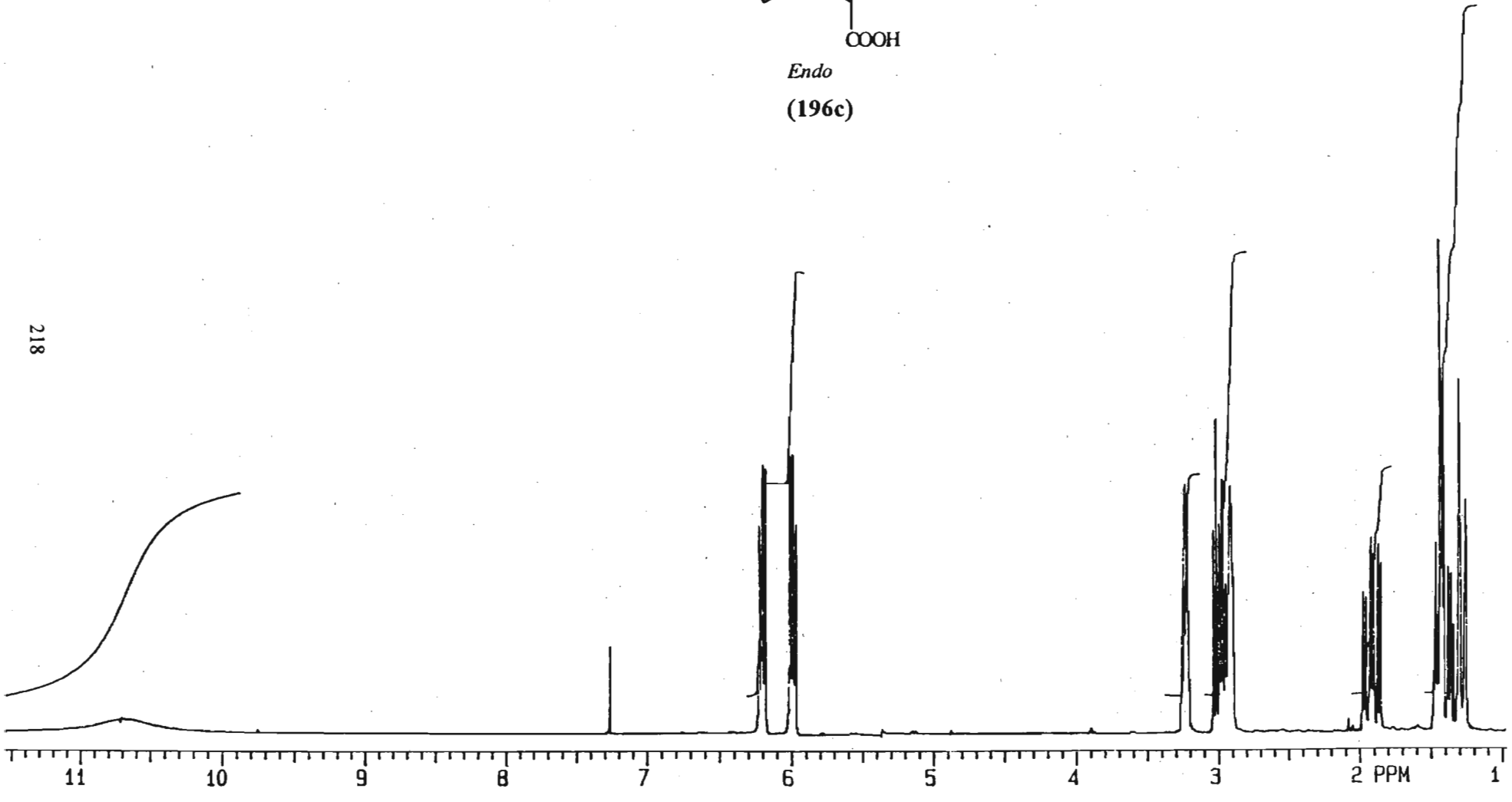


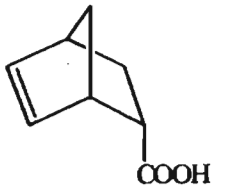
(190)



Endo

(196c)





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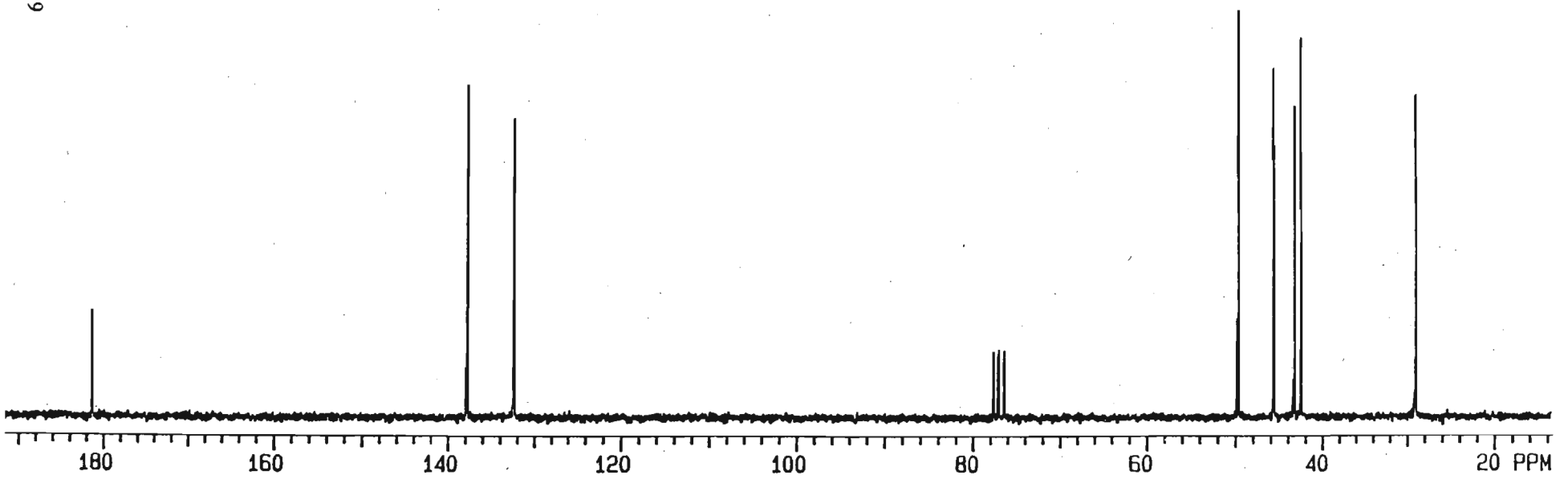
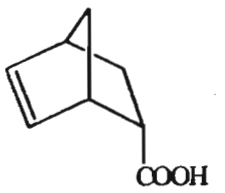
(196c)





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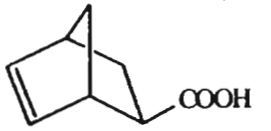
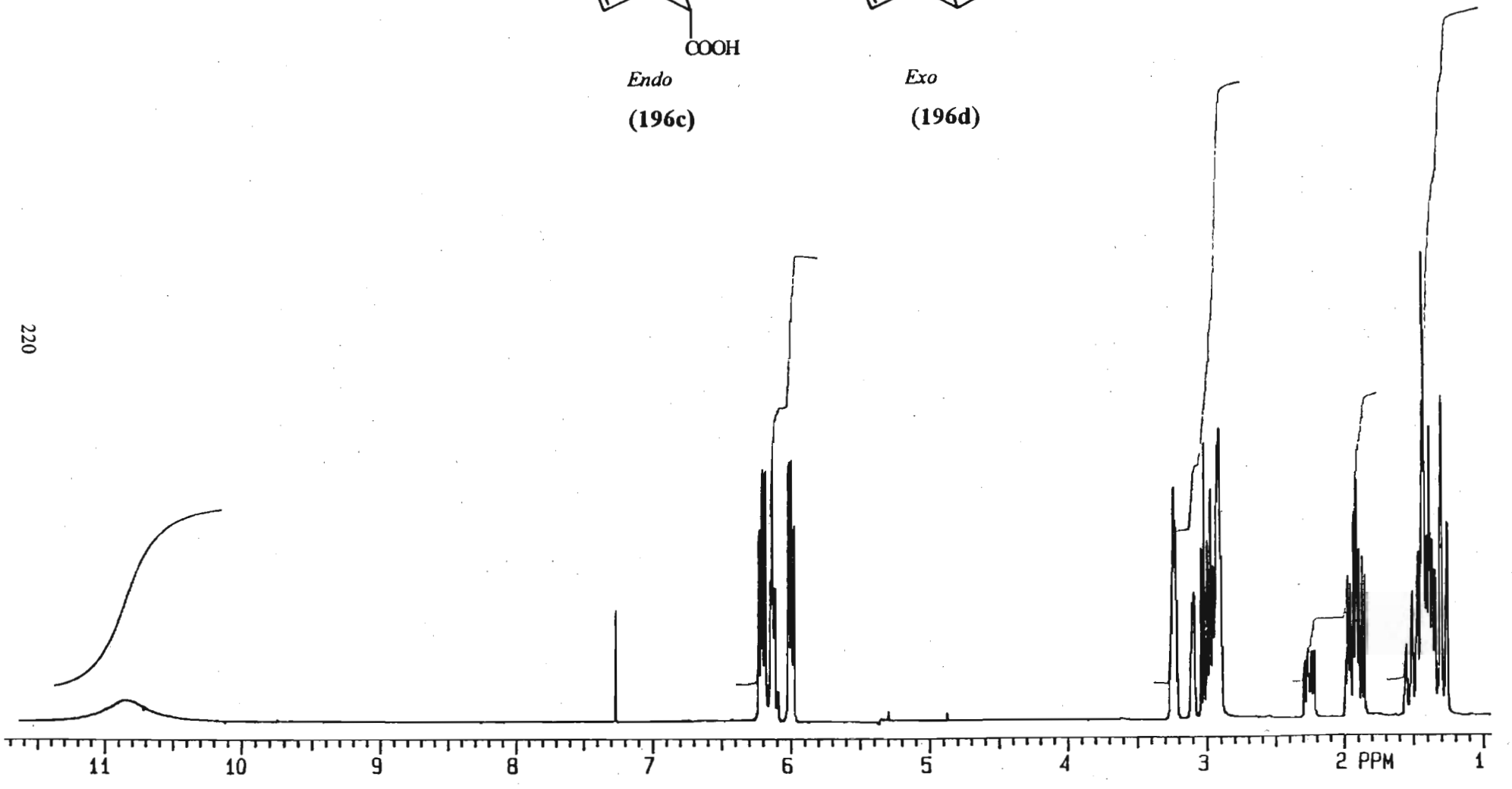
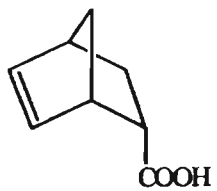
(196c)



Exo

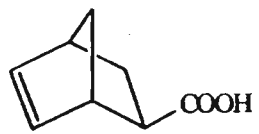
(196d)





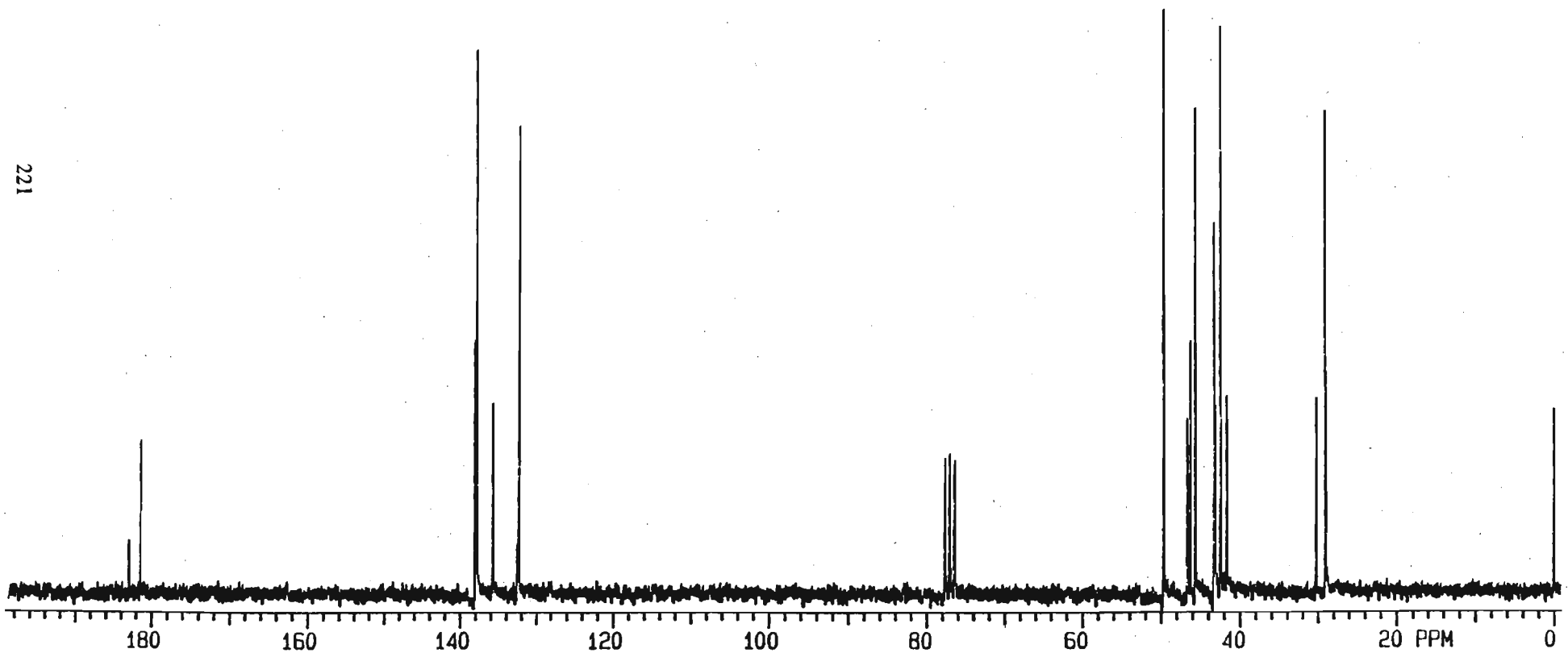
Endo

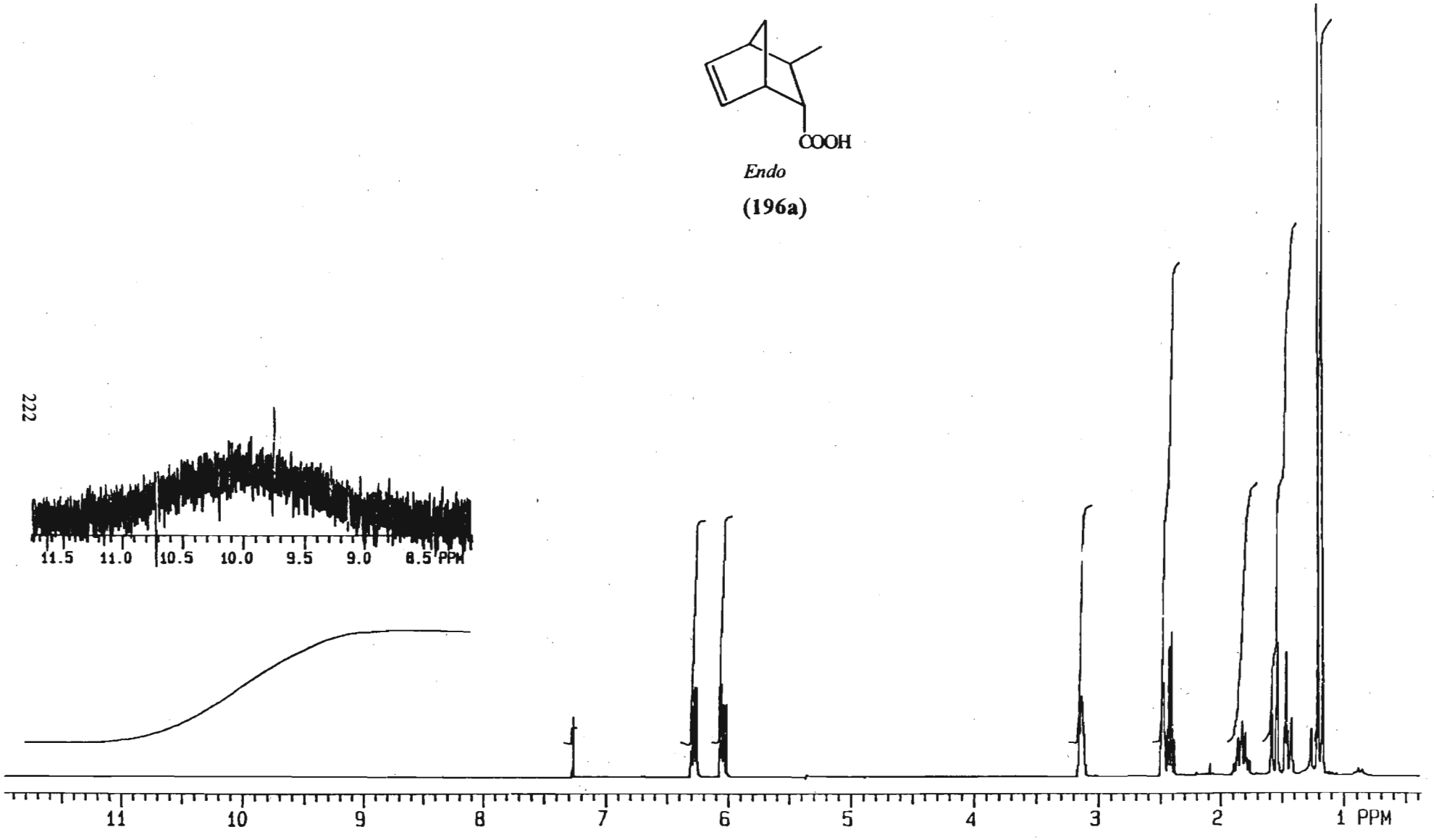
(196c)



Exo

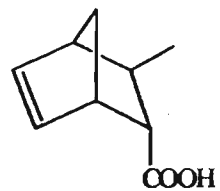
(196d)





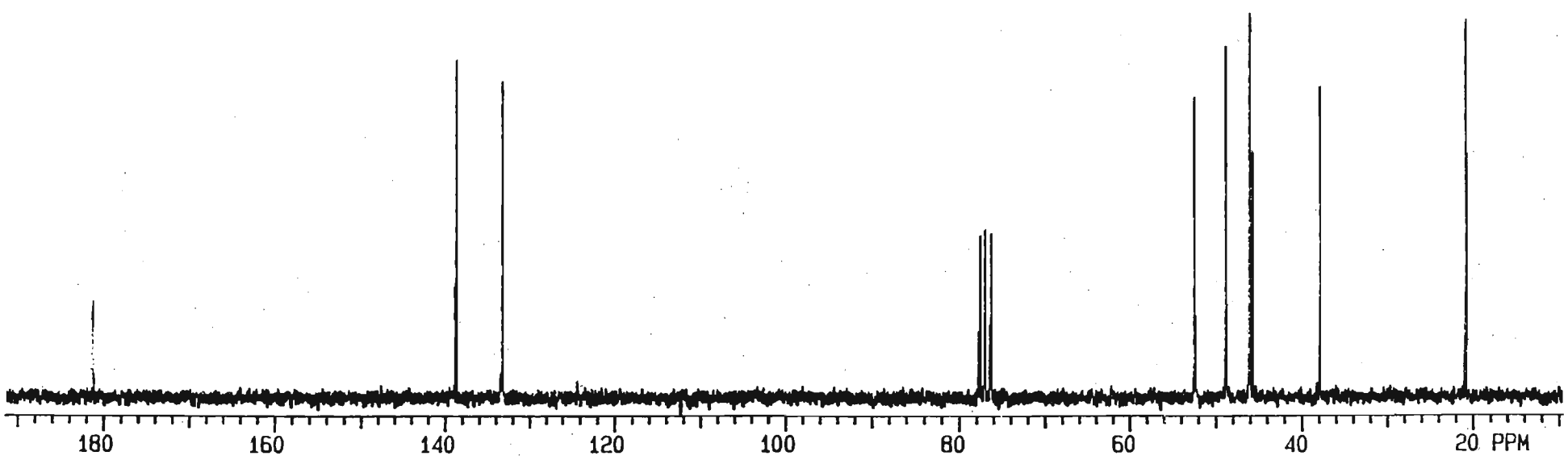
Endo

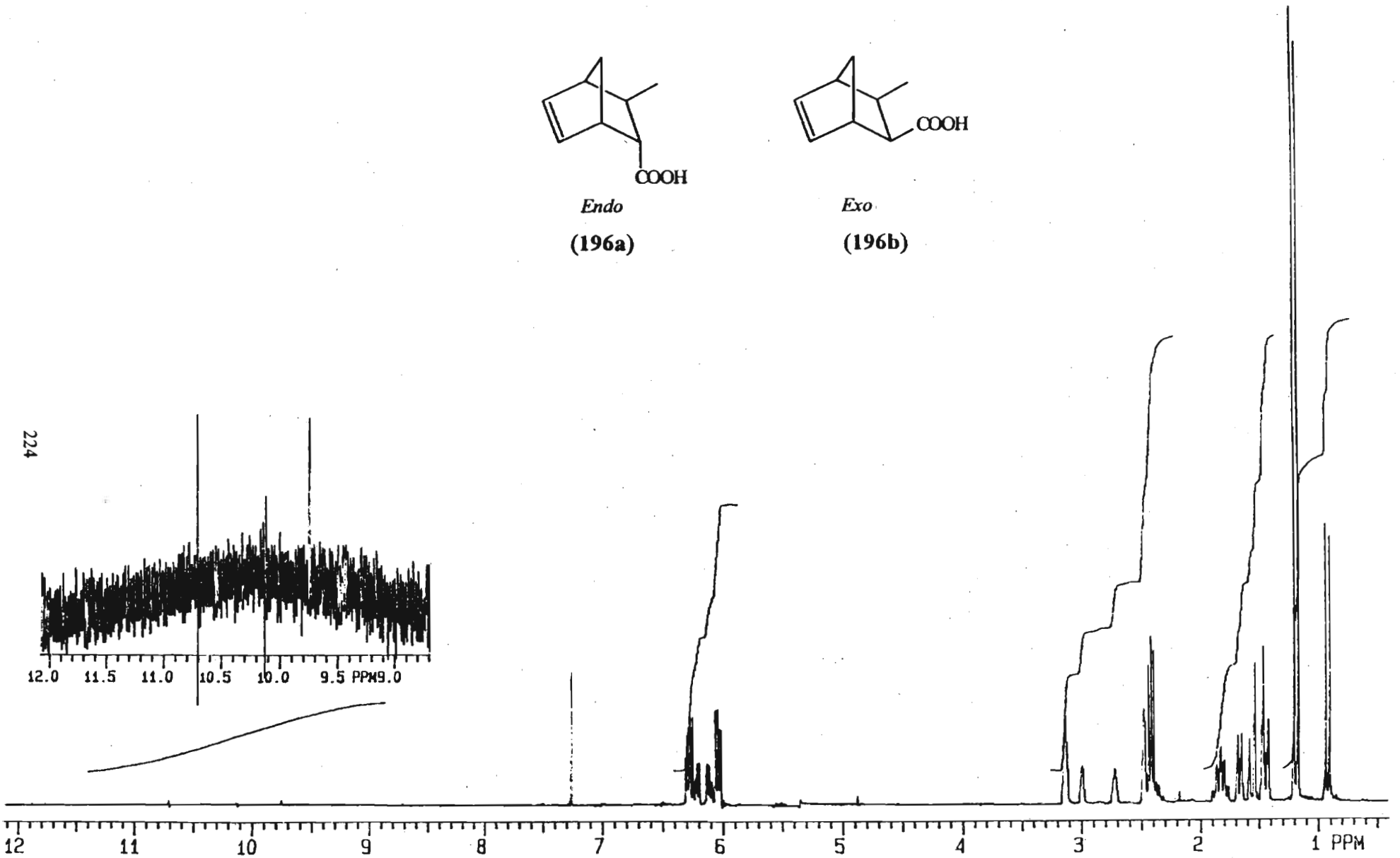
(196a)



Endo

(196a)



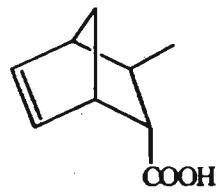


Endo

(196a)

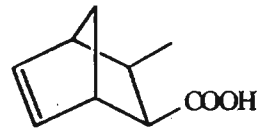
Exo

(196b)



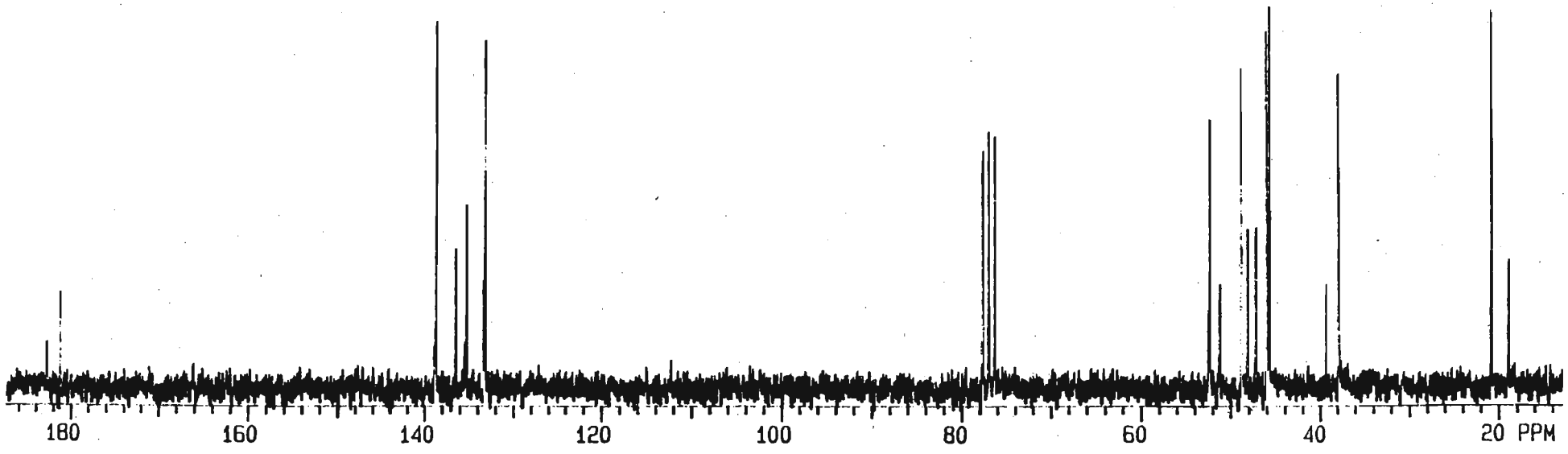
Endo

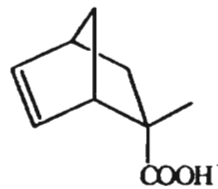
(196a)



Exo

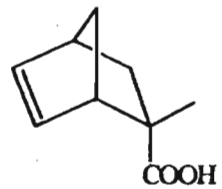
(196b)





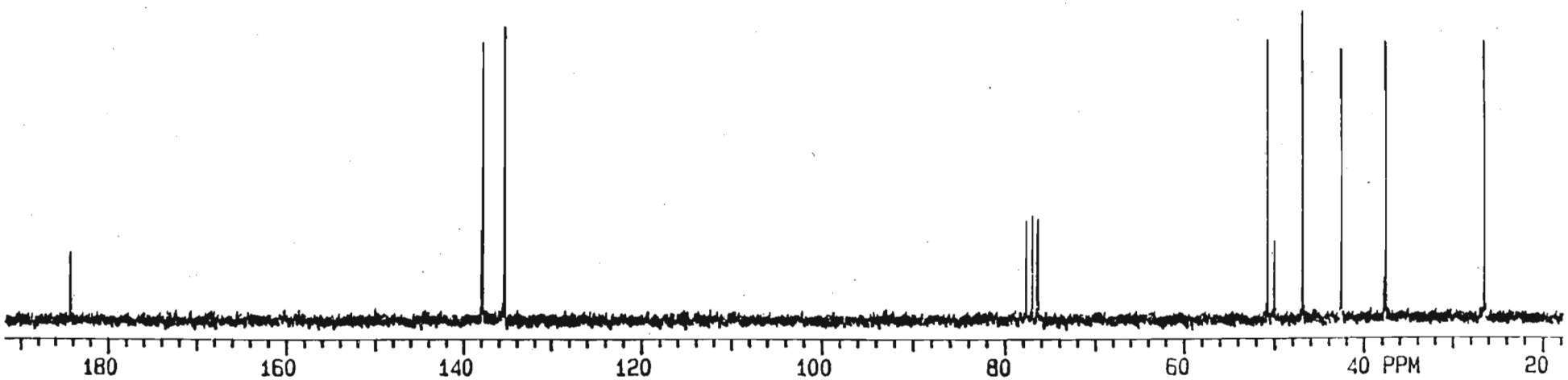
Endo

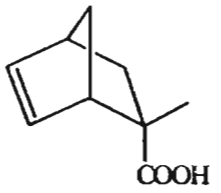
(196e)



Endo

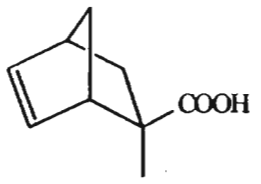
(196e)





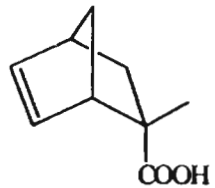
Endo

(196e)



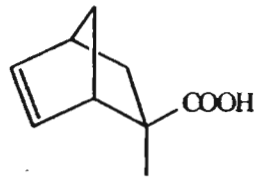
Exo

(196f)



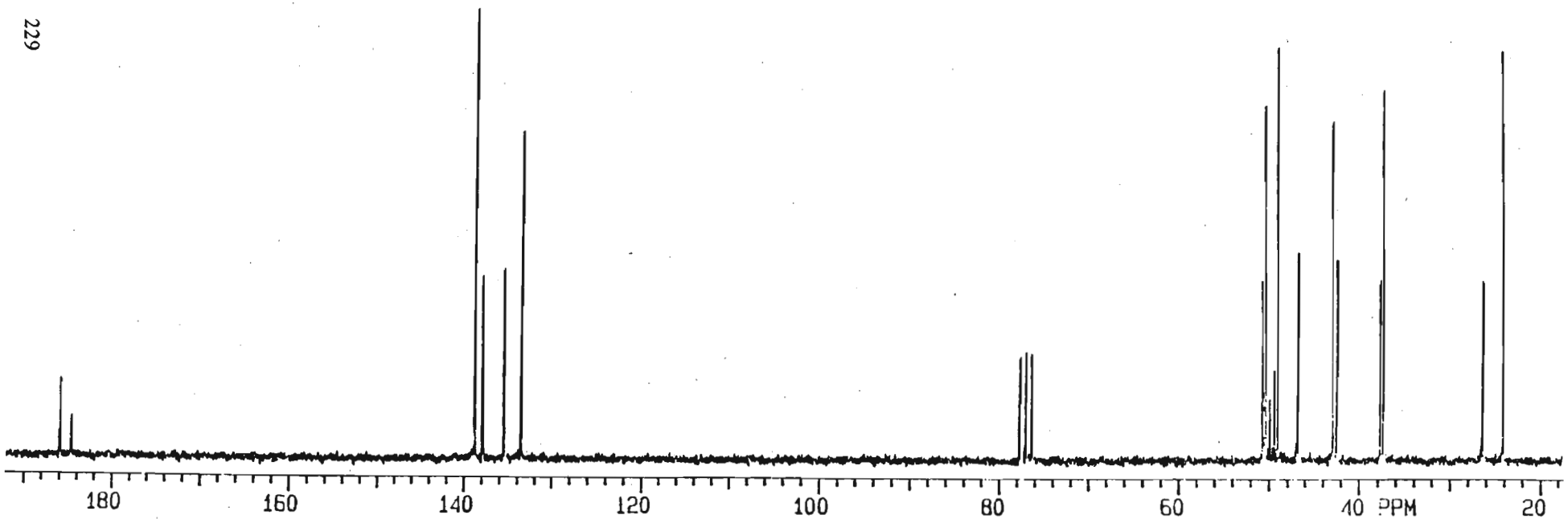
Endo

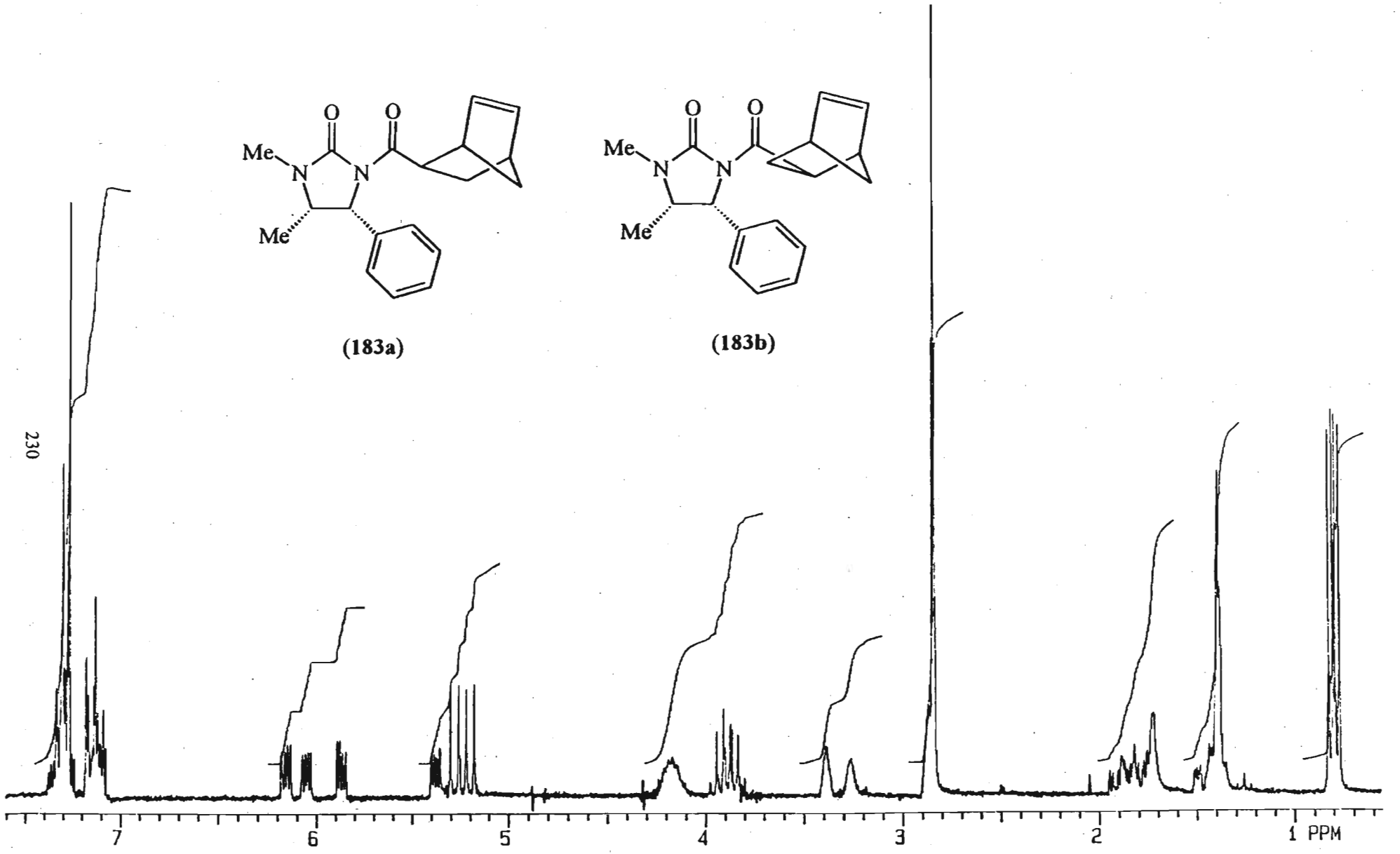
(196e)



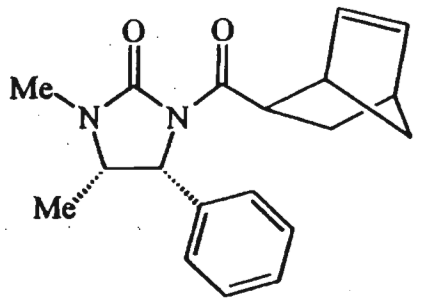
Exo

(196f)

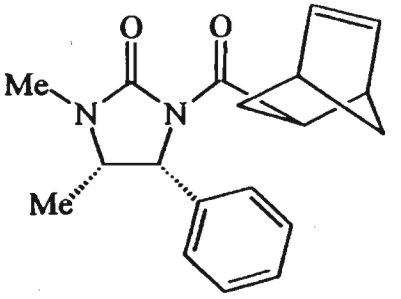




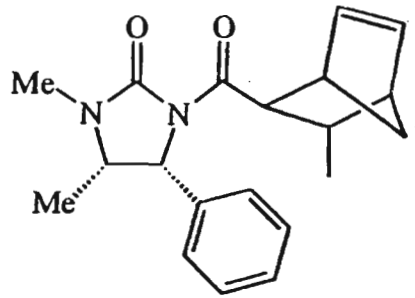
(183a) **(183b)**



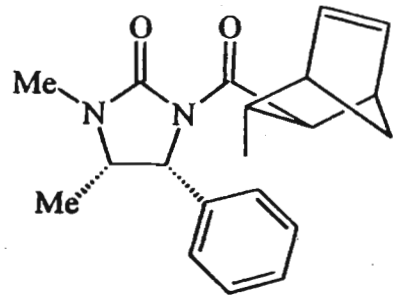
(183a)



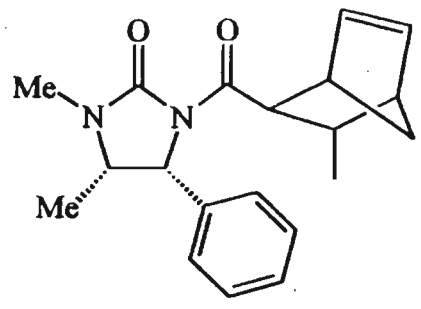
(183b)



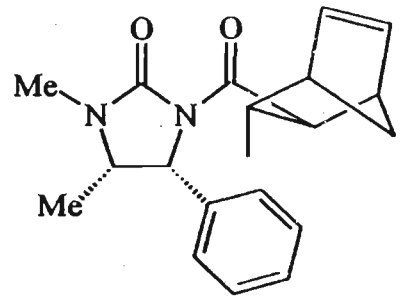
(184a)



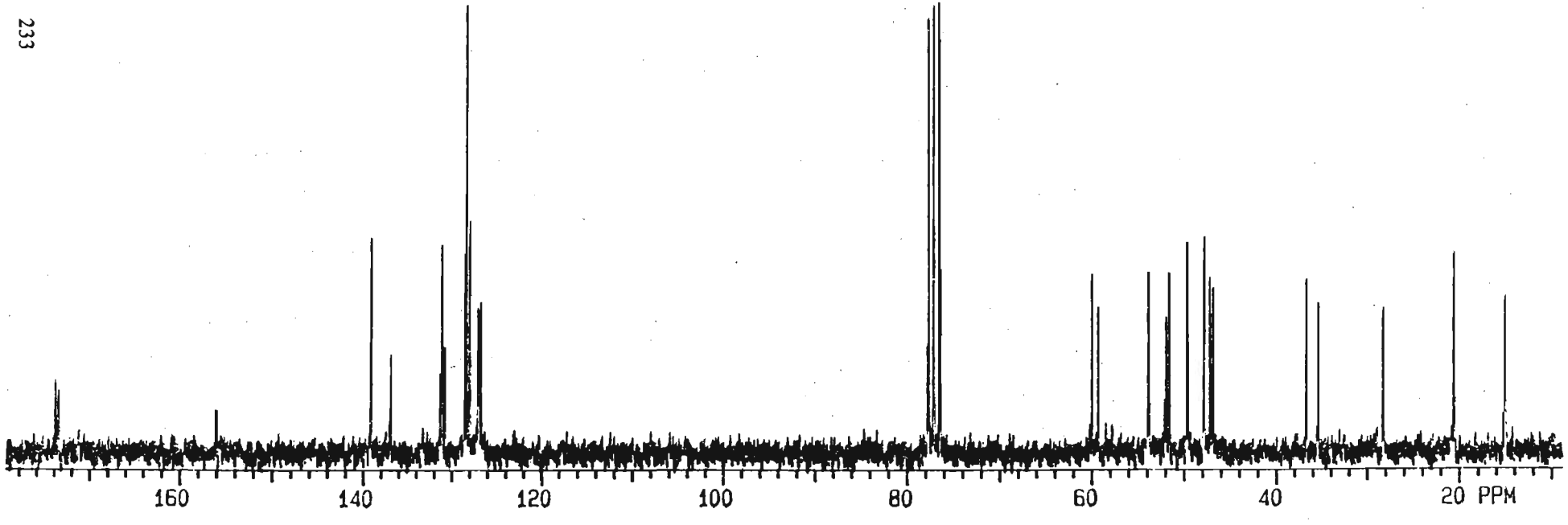
(184b)

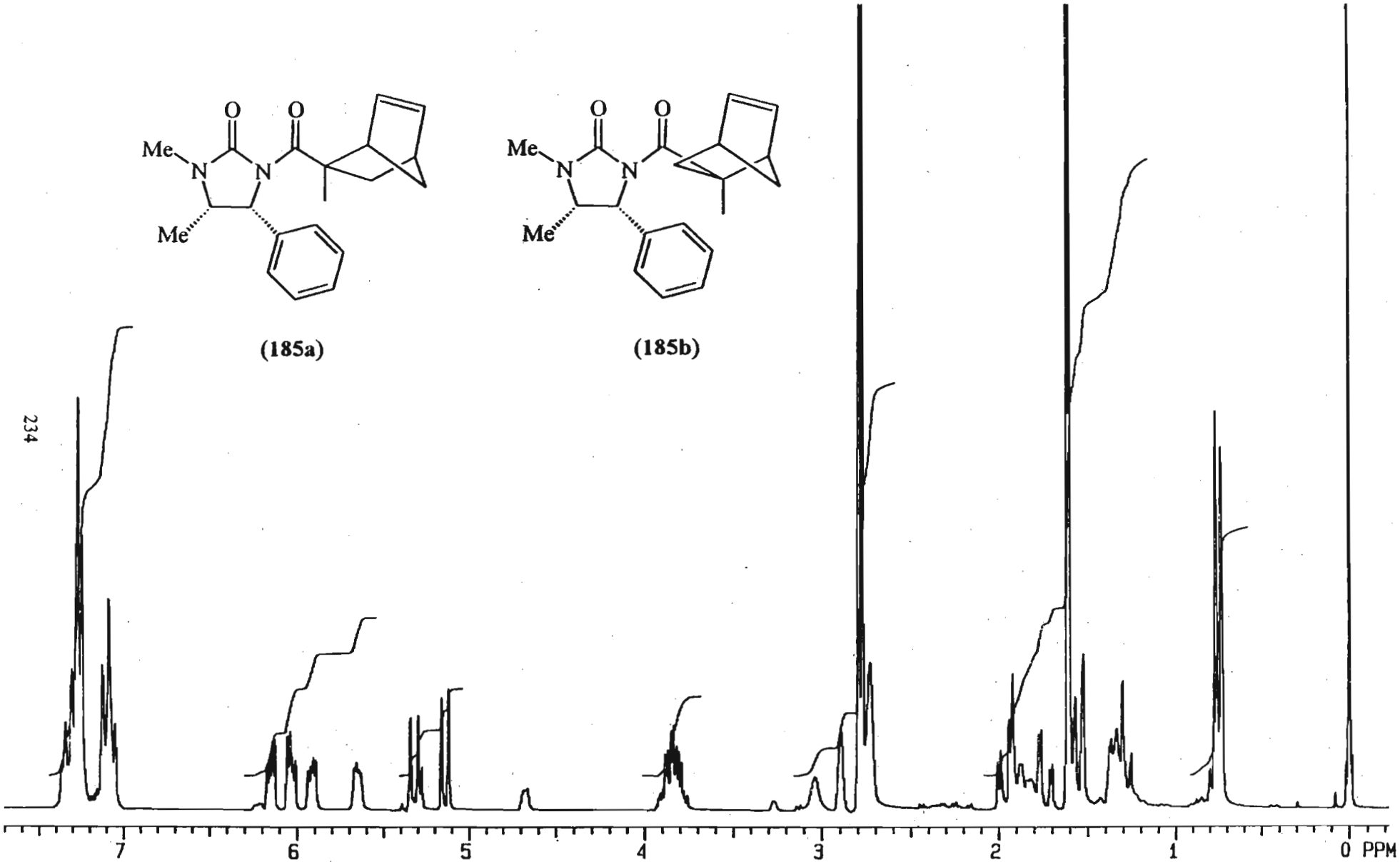


(184a)



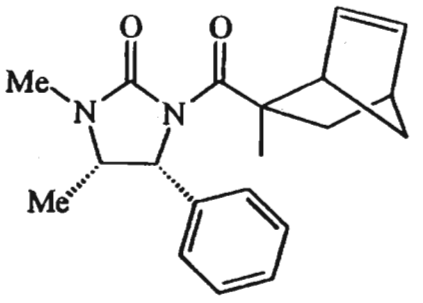
(184b)



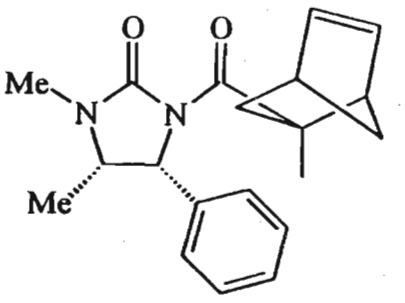


(185a)

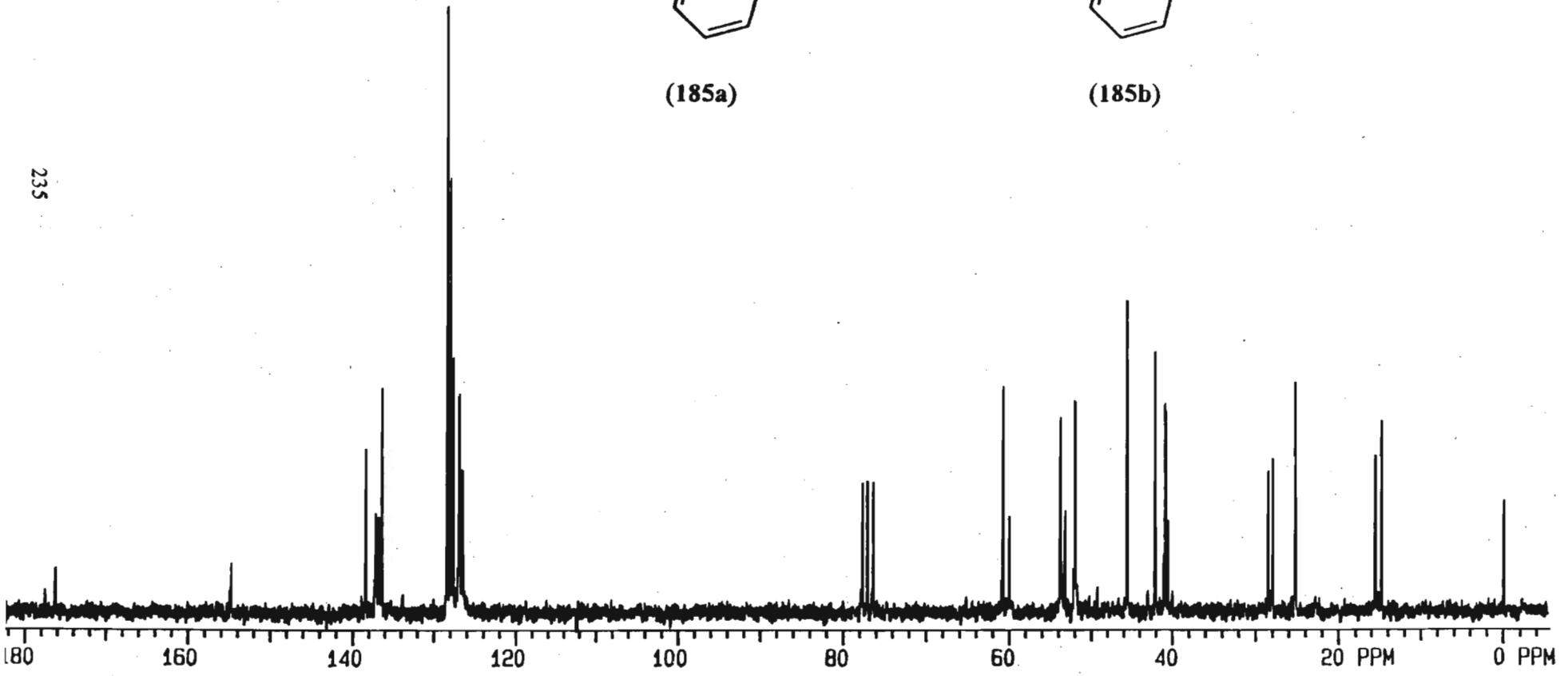
(185b)

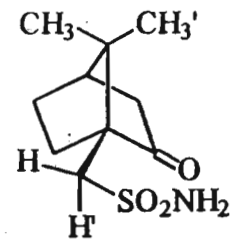


(185a)

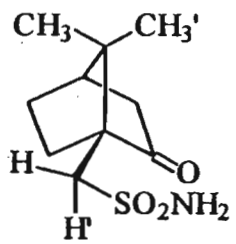


(185b)

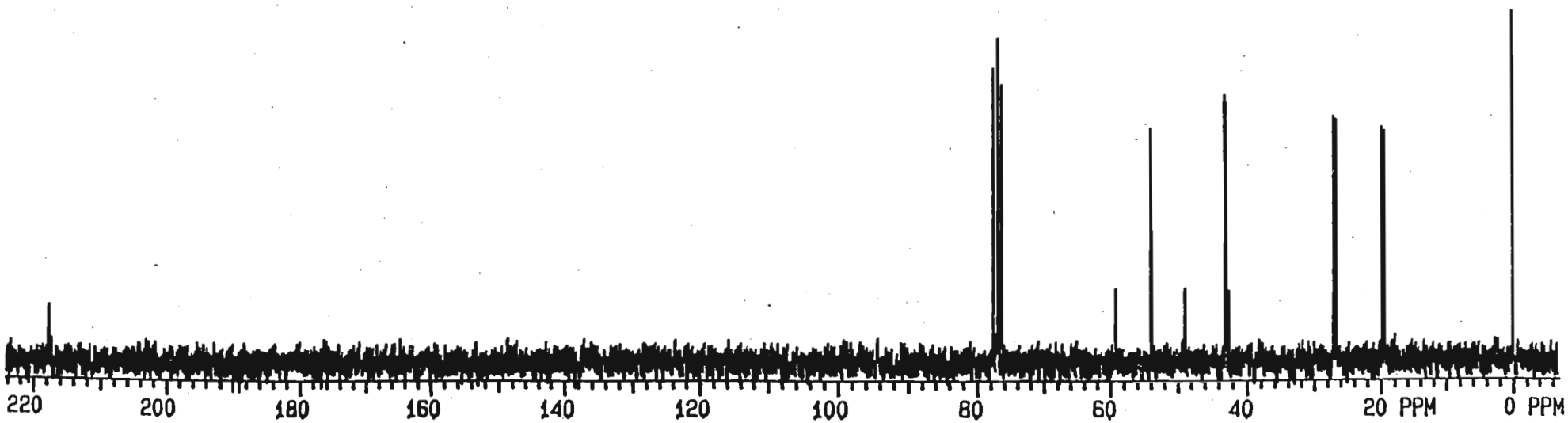


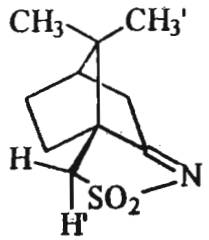


(157)

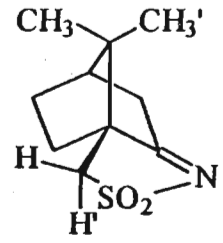

CH3
CH3'
H
O
SO2NH2
H'

(157)


220
200
180
160
140
120
100
80
60
40
20 PPM
0 PPM



(158)



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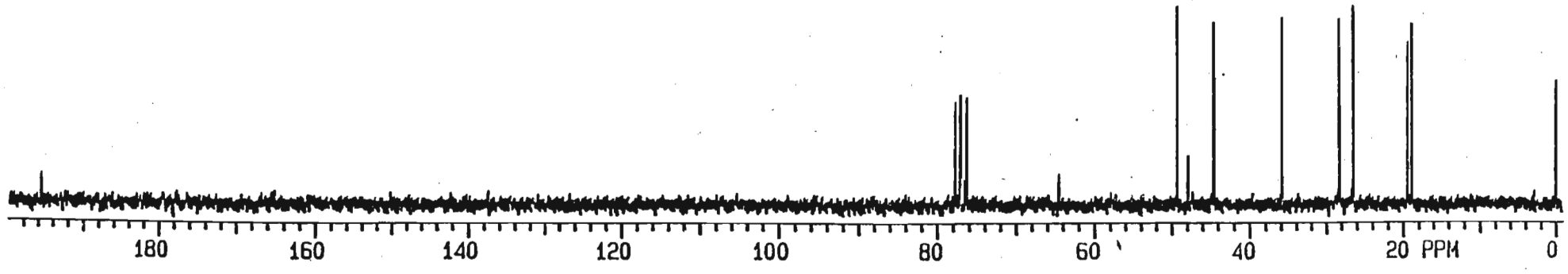
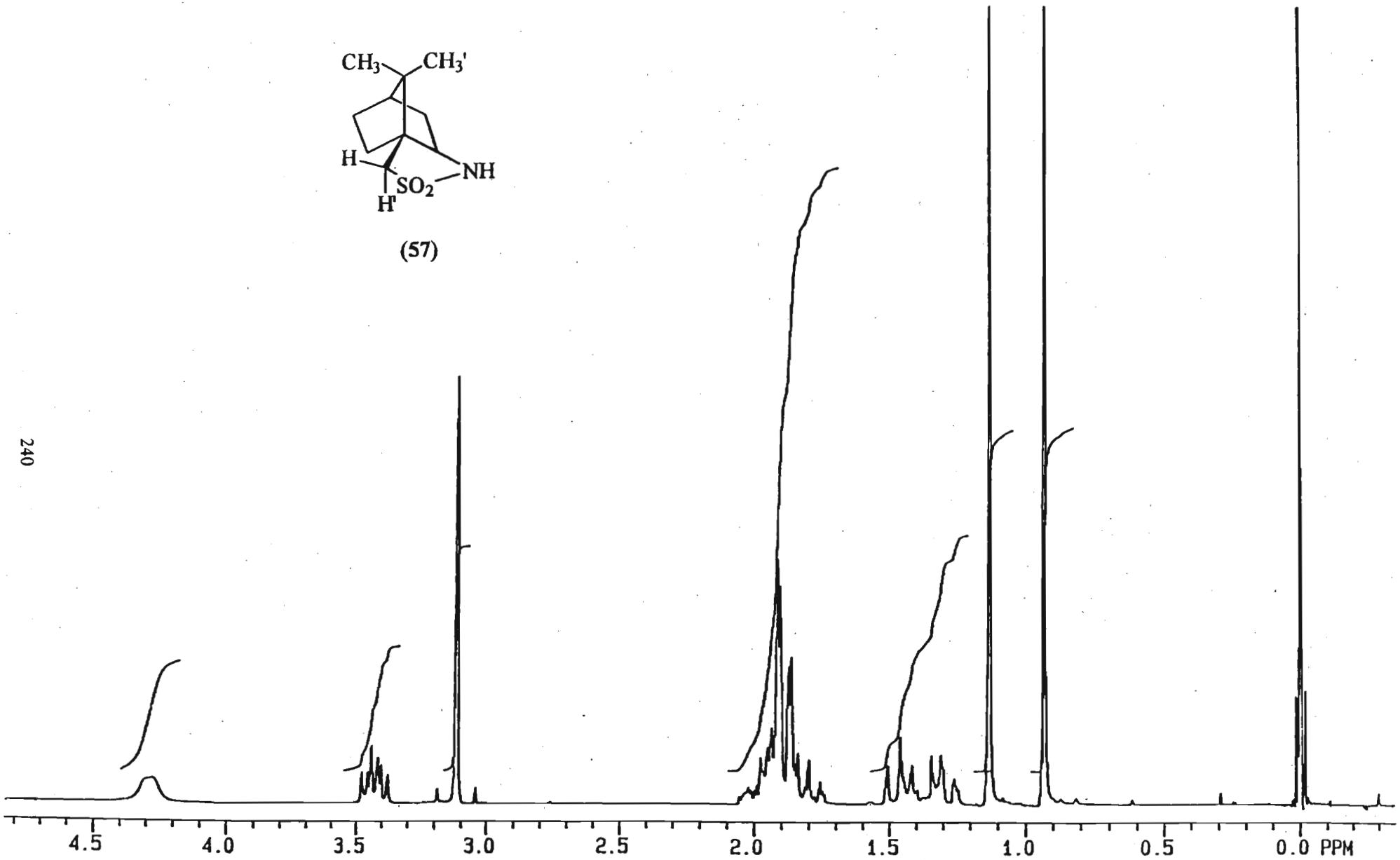
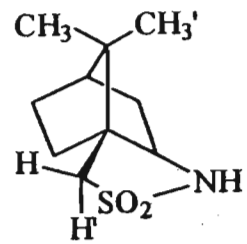
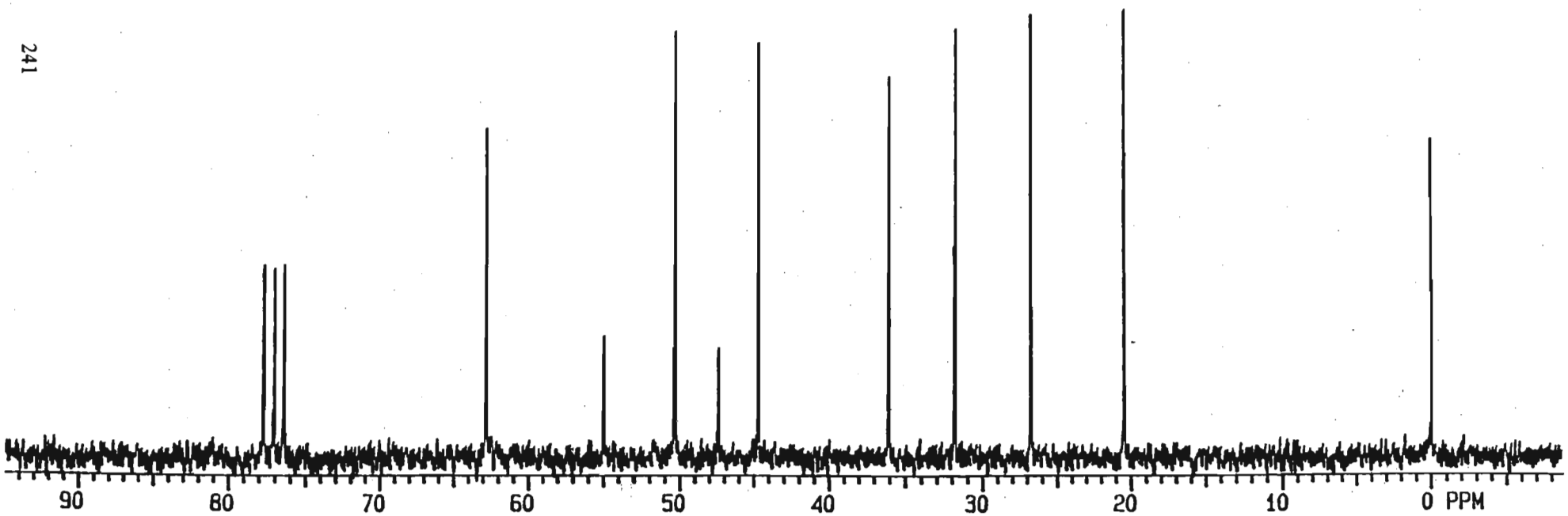


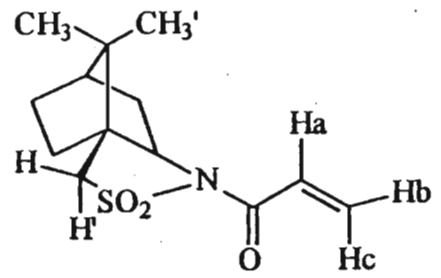


(57)

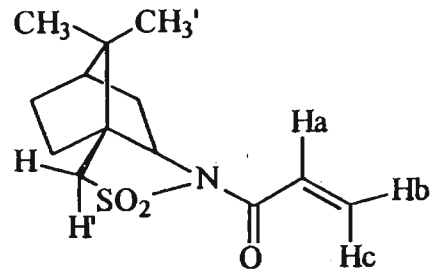


(57)

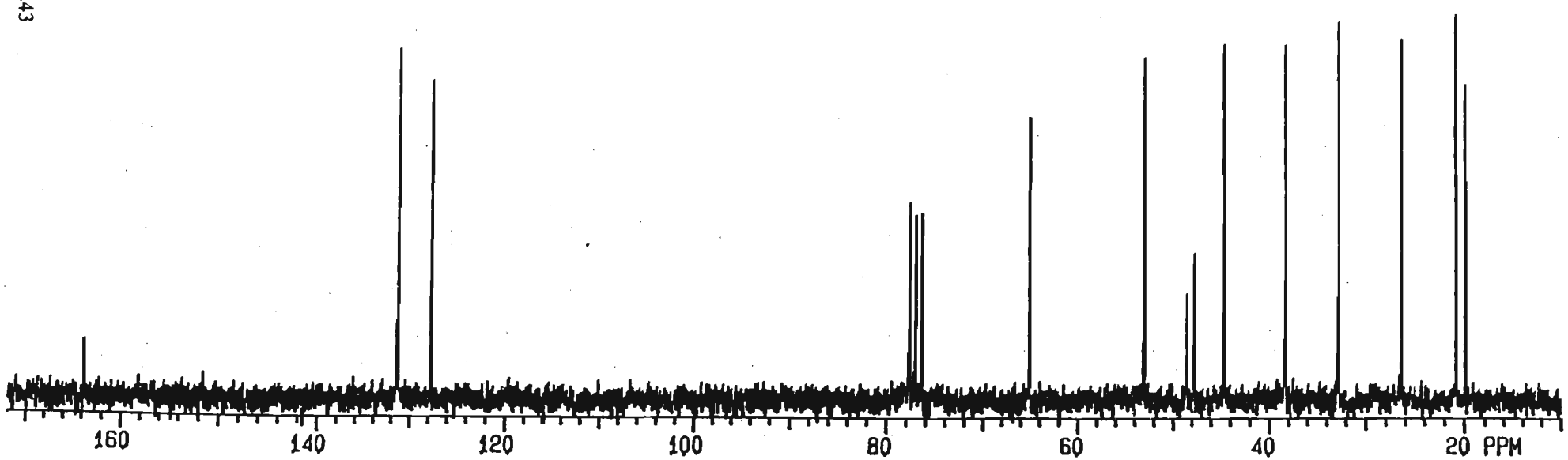


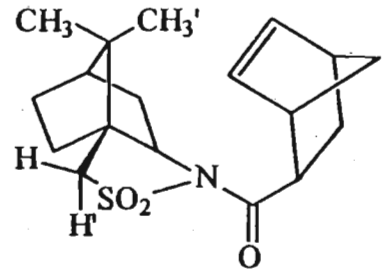


(172)

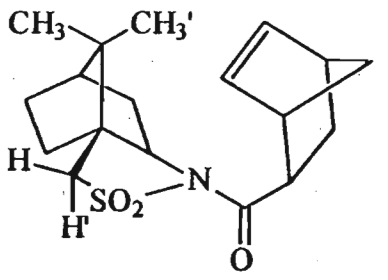


(172)





(172a)



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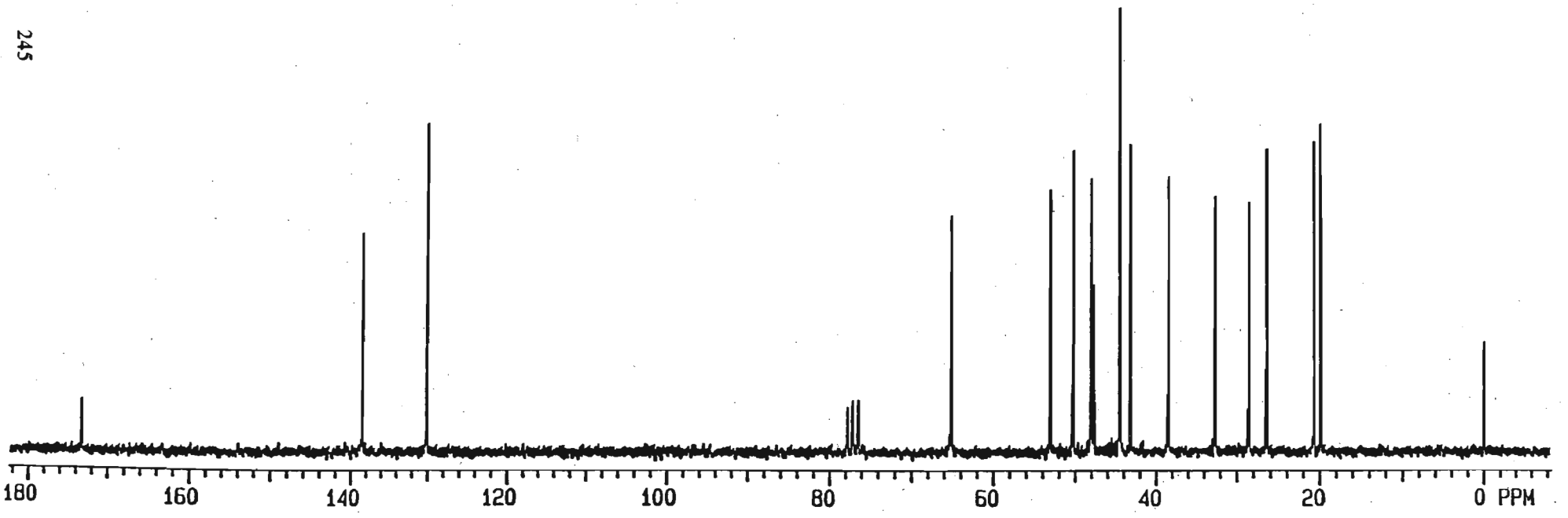
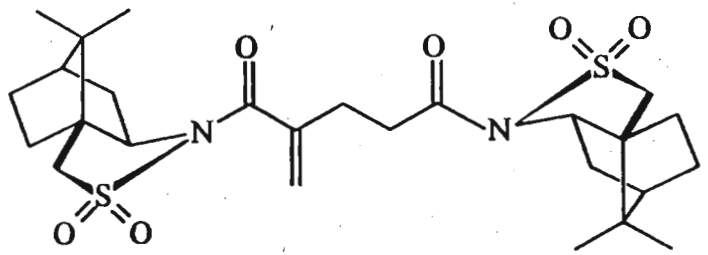
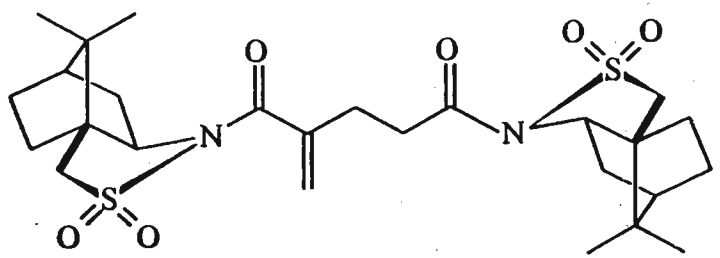




(166b)



(166b)