ASYMMETRIC DIELS-ALDER REACTIONS OF ACYLNITROSO COMPOUNDS

A thesis presented in part fulfilment of the requirements for the degree of M.Sc.

By

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This thesis was written on an *IBM* Computer (Personal System/2, Model 30 286) with the word processing software package, *Microsoft Word* (Version 5.0). The font style employed was *Helvetica*, except in the case of data tables which were done in *Courier*. Laser printouts were obtained on an *IBM* Personal Pageprinter.

Chemical reaction schemes and figures were designed and drawn using a *LINEX* 1166S (7 mm) template and a 0.5 mm HB microshaft pencil.

DEDICATION

On April 4th, 1937, in the Sala Rossa of the Palazzo Tursi in Genoa, Italy, a certain Guarnerius violin was carefully removed from its protective glass show-case, where it had rested for over one hundred years, and was presented to a very honoured Giulio Bignami, at that time Professor of Violin at the Florence Conservatory. On the violin nicknamed *Il Cannone*, Signor Bignami along with his accompanist, Sandro Fuga, proceeded to give a specially arranged radio broadcast recital, and so, for the first time, the world heard the voice of the violin that had once been the prized possession of one of the most extraordinary and quite exceptional violinists that has ever lived.

That violinist was Nicolò Paganini and, through his development and extension of violin technique, he progressed violin playing to the point where, even today, it has advanced little further.

This thesis is dedicated to the memory of Nicolò Paganini. We shall never see and hear of his likes again.

ACKNOWLEDGEMENTS

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PETER SNEDDEN

CONTENTS

SUMMARY

The Diels-Alder cycloaddition reactions of a small selection of transient *C*-nitroso compounds (two achiral and one chiral) were carried out with the unsymmetrically substituted, conjugated diene (*E*)-penta-1,3-diene **111** (piperylene). The aim of these experiments was to study the regiochemistry and any associated asymmetric induction of the cycloadducts.

Acetohydroxamic acid **182d** was oxidized, with periodate, in the presence of (*E*)-penta-1,3-diene **111** at 0 ^{o}C, and the transient nitrosocarbonylmethane **183d** thus formed was trapped, *in situ*, to afford a mixture of the racemic, cycloadducts **184d** and **185d**. The ratio of the regioisomers was determined by ^{1}H NMR spectroscopy to be *ca.* 1:1, therefore indicating no degree of regiospecificity in the reaction.

In the same way, benzohydroxamic acid **182a** was oxidized in the presence of (*E*)-penta-1,3-diene **111**, to afford a mixture of the racemic, cycloadducts **184a** and **185a**. The ratio of **184a**:**185a** was determined to be *ca.* 2.8:1.0, thus indicating the preferential formation of the 6-methyldihydro-oxazine regioisomer.

A chiral dienophile was used next, the chiral unit being derived from mandelic acid **179b**. In the usual way, (±)-mandelohydroxamic acid **182b** was oxidized in the presence of (*E*)-penta-1,3-diene **111** at 0 ^{o}C, to yield a mixture containing the racemic cycloadducts **186**, **187**, **188** and **189**. The structures of the 6-methyldihydro-oxazine **186** and 3-methyldihydro-oxazine **188** were determined by X-ray crystallography. The ratio of the four isomers was determined, by integration of the ^{1}H NMR spectrum, to be, respectively, 3.0:1.0:1.2:1.2. The experiment was repeated at -70 ^{o}C, in the hope of achieving better levels of asymmetric induction; the ratio, this time, was determined to be **186**:**187**:**188**:**189** = 2.2:1.0:1.3:1.2. At both temperatures the ratio of the 3-methyldihydro-oxazines **188**:**189** was found to remain more or less the same, with

virtually no asymmetric induction being observed. In the case of the 6-methyl isomers, a marked level of induction was found, being slightly greater at higher temperature when the ratio of **186**:**187** was *ca.* 3.0:1.0 (corresponding to a fair d.e. value of 50%). Formation of the main component **186** of this **186**-**187** mixture is consistent with *endo* addition, to the diene **111**, of the intramolecularly hydrogen-bonded (involving a six-membered ring) dienophile **183b** from the face *anti* to the phenyl group. This result lends support to the conclusions of previous work, in which asymmetric induction in Diels-Alder cycloaddition reactions was thought to be enhanced with *C*-nitrosocarbonyl compounds containing an α-OH group.

In order to investigate further the idea of intramolecular H-bonding, IR and NMR studies were carried out on the cycloadducts **186**-**189**. It was shown from the results of these studies that intramolecular hydrogen-bonding was taking place in each of the cycloadducts. In order to assess the mode of H-bonding (*i.e.* involving a five- or six-membered ring), a 'model' compound, the mandelic-piperidine amide **194**, was prepared and studied. This also was found to exhibit intramolecular hydrogen-bonding. Nevertheless, hydrogen-bonding in the cycloadducts involving the oxazine oxygen in a six-membered ring is the more likely.

CHAPTER 1

INTRODUCTION

SECTION I

1.1 Asymmetric Diels-Alder reactions.

The principle subject of this thesis is asymmetric Diels-Alder reactions of acylnitroso compounds. Before proceeding with this subject, however, it is necessary to review the basic principles and ideas of asymmetric induction in Diels-Alder reactions.

In the following discussion, an analysis will be made of the Diels-Alder reactions of achiral and chiral acrylate esters with the conjugated dienes buta-1,3-diene **1** and pentadiene **5**. The former is chosen as an example of a diene that does not contain pro-chiral atoms on C(1) and C(4).

Firstly, consider the reaction with an achiral dienophile. Figure 1 shows the cyclo-adducts to be expected from the reaction of the achiral acrylate **2** with the dienes **1** and **5**. With butadiene **1**, both the *exo* and *endo* modes of addition of the dienophile to each, identical face of the diene will result in the formation of a racemate of the enantiomeric adducts **3** and **4**. With pentadiene **5**, *endo* addition of the dienophile from each face to the diene will produce a racemic mixture of the enantiomeric adducts **6** and **7**. Similarly, *exo* addition will produce a racemic mixture of the adducts **8** and **9**. The *endo* and *exo* racemates will, however, be formed at different rates and, as a result, one racemate, usually the *endo*, will be formed in an excess.

Now consider the reaction with a chiral acrylate dienophile **10** (Figure 2). Attack of the dienophile from one face on butadiene **1** will proceed more easily than attack from the other face. This result holds true for both *exo* and *endo* modes of addition, and so the outcome of the reaction is the formation of an unequal mixture of the diastereoisomeric adducts **11** and **12**. With pentadiene **5**, *endo* addition of the dienophile from both faces on the diene leads to an unequal mixture of the diastereoisomeric adducts **13** and **14**. Similarly, *exo* addition leads to an unequal

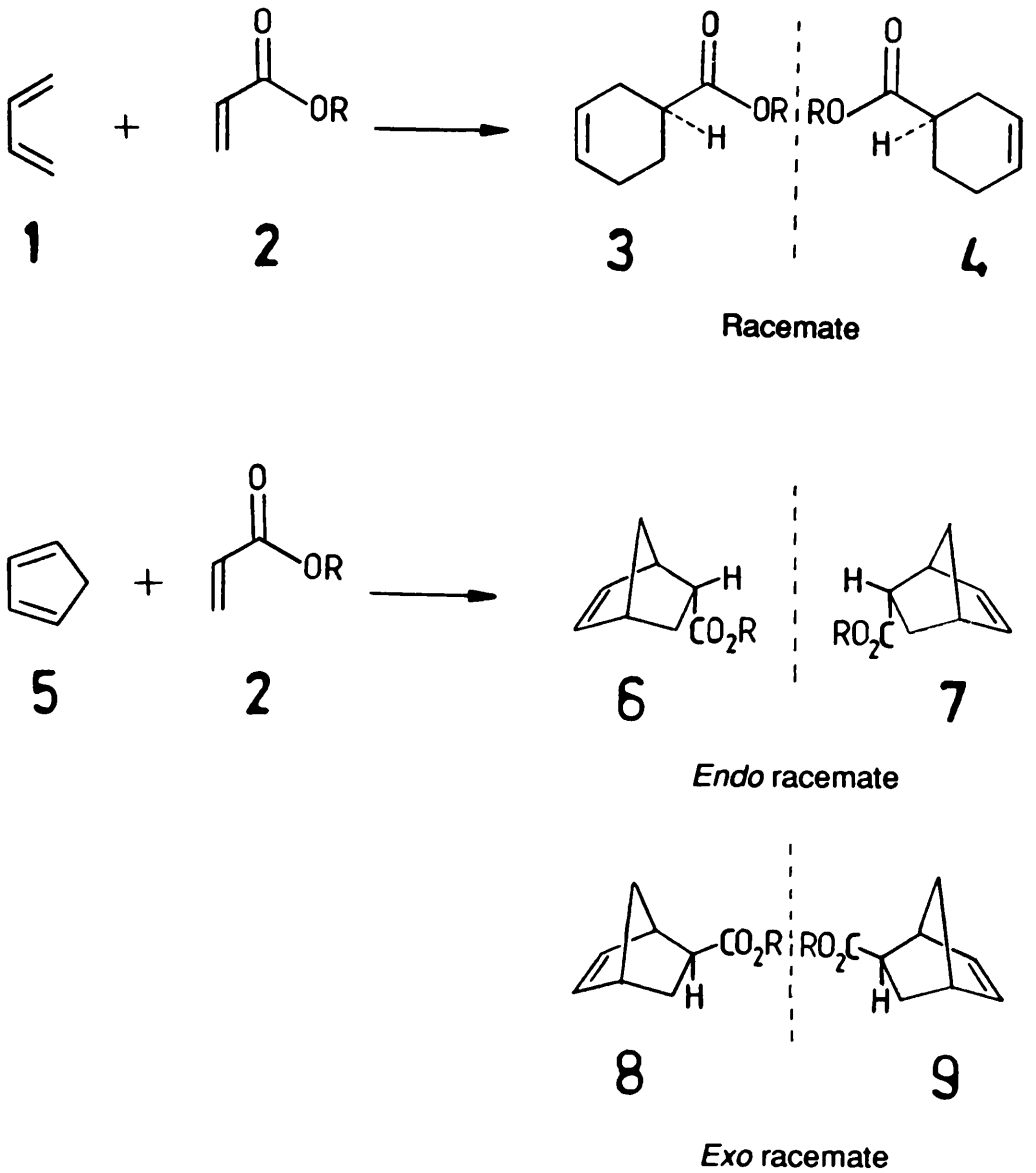
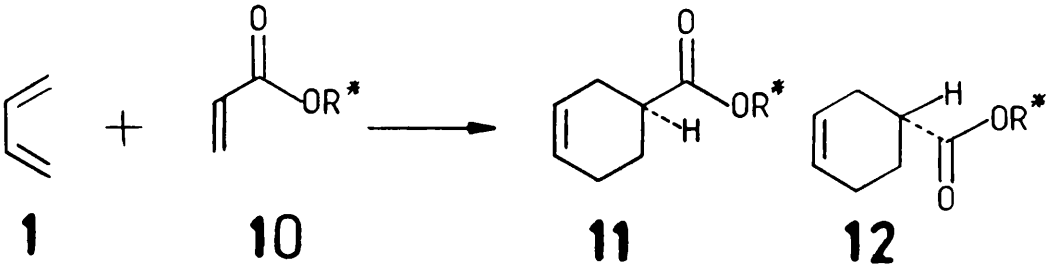
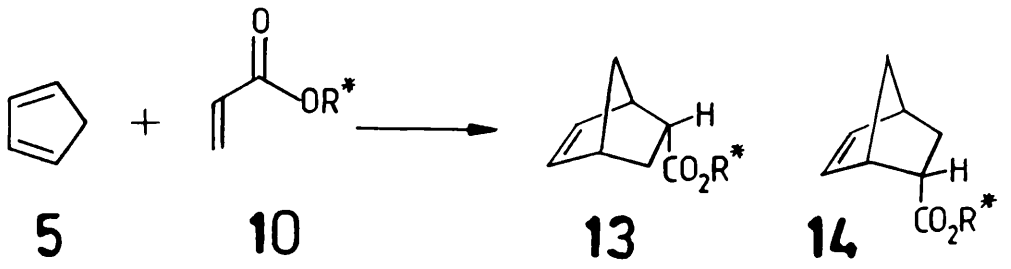


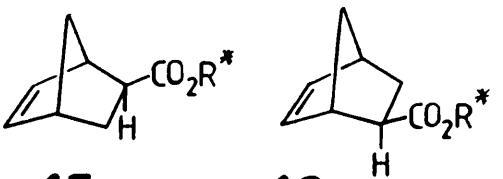
Fig. 1 Cycloadducts from achiral acrylate



Diastereoisomers



Endo diastereoisomers



Exo diastereoisomers

Fig. 2 Cycloadducts from chiral acrylate

mixture of the diastereoisomers **15** and **16**. The reaction should therefore produce four compounds - *exo* and *endo* diastereoisomeric pairs.

Although both *exo* and *endo* modes of addition of the dienophile have been discussed, usually one mode will predominate. With acrylate esters, for example, the *endo* adduct will usually predominate; this comes about as the result of a secondary FMO effect. In the *endo* transition state, there is a stabilising interaction between the p orbital of the acrylate carbonyl group and the p orbital of C-2 of the diene.

The above analysis has, so far, only taken into account symmetrical dienes. If the diene is unsymmetrically substituted, then there are also two possible orientational approaches for the diene and the dienophile in the Diels-Alder reaction. This leads to the formation of a pair of regioisomers. Figure 3 shows the cycloaddition reaction of the 1-substituted diene **17** and the achiral dienophile **2** to produce a mixture of the regioisomeric adducts **18** and **19**. Each regioisomer will, as explained before, exist as a mixture of stereoisomers.

Another point to consider is the lack of *endo* and *exo* stereoisomers for the cycloadducts of certain heterodienophiles, like R-N=O. There cannot be distinct *endo* and *exo* adducts because N cannot form a stereogenic centre. *Endo* and *exo* modes of addition will lead, therefore, to the formation of identical products.

The approach geometry adopted by a diene and chiral dienophile, in either the *endo* or *exo* mode, will be such as to minimise the steric repulsion of neighbouring groups and atoms, resulting in the preferential formation of one particular compound having a specific stereochemistry. This is the basis of asymmetric induction. For example, cyclopentadiene **5** (Figure 2) might attack one face of the chiral dienophile **10** faster than the other, leading to an unequal mixture of the *endo* adducts **13** and **14**. If a chemical reaction produces a pair of enantiomers in unequal mixture, then it is

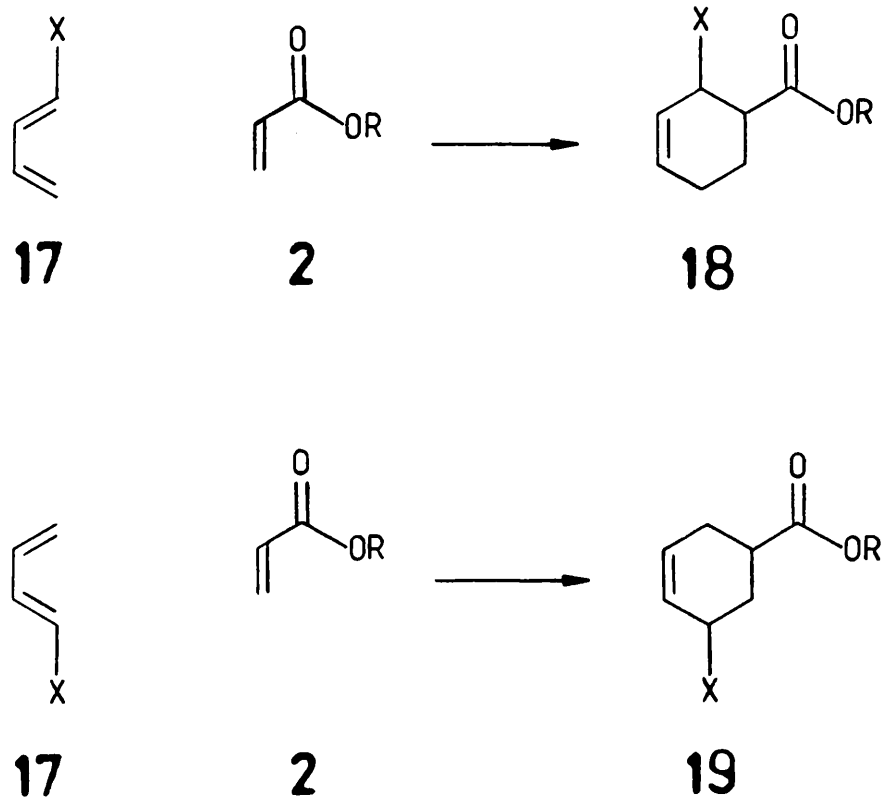


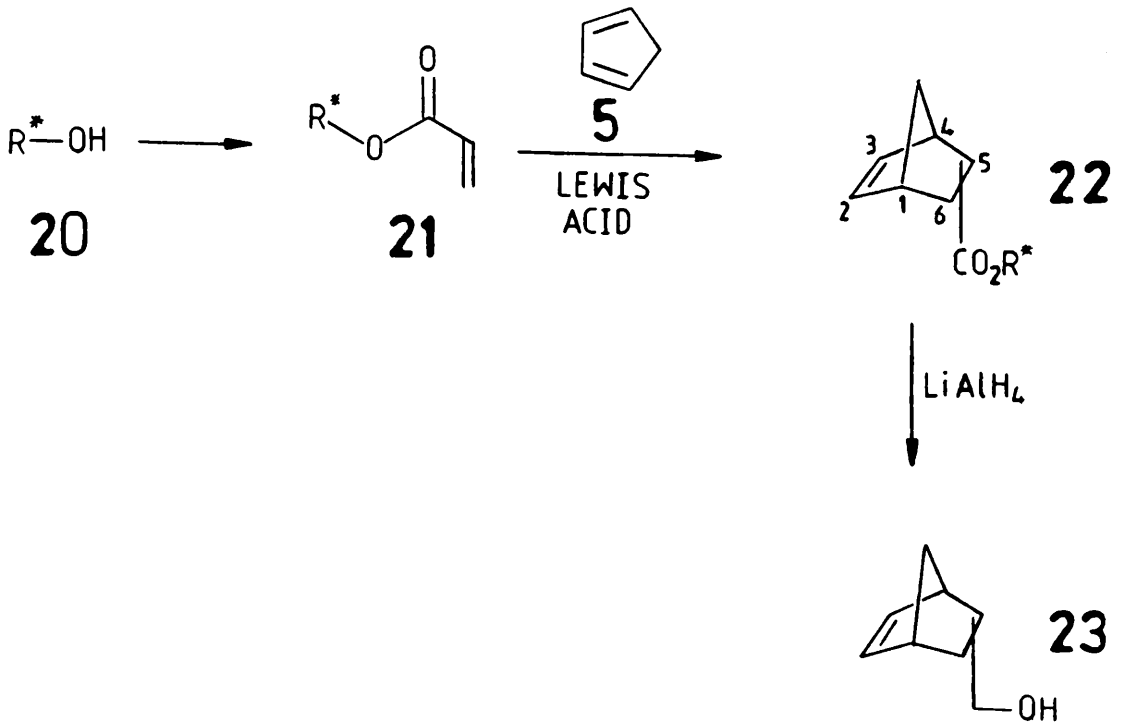
Fig. 3 Regioselectivity in the Diels-Alder reaction of the acrylate ester **2** and the asymmetric diene **17**

customary to define a quantity known as the *enantiomeric excess* (e.e.). Let the ratio of the major and the minor enantiomers, respectively, be A:B. Then, the enantiomeric excess is defined as: ([A-B]/[A+B]) X 100%. This value gives an indication of the extent of asymmetric induction achieved in a reaction. A similar expression can be used to define the *diastereomeric excess* (d.e.) from the ratios of the major and minor diastereoisomers.

The majority of studies into asymmetric Diels-Alder reactions involve the addition of chiral acrylate esters to conjugated dienes. In most cases, the acrylates are prepared from elaborate chiral units derived from natural products (*e.g.* terpenes). A comprehensive literature review of these and other asymmetric Diels-Alder reactions has been given by Oppolzer[1]. Some examples from this review, illustrating the use of chiral acrylates in asymmetric synthesis, are given below.

Scheme 1 shows the Diels-Alder cycloaddition reactions of the acrylate esters **21** with cyclopentadiene **5**, which give the 2-norbornene esters **22**. The acrylate esters **21** are derived from the corresponding alcohols **20** (the different chiral units, R^*, are represented by the structures **a**-**e**). The adducts **22** can easily be converted by reduction with lithium aluminium hydride into the norbornene alcohols **23**. In all the examples below, the acrylate esters **21** showed very high *endo* selectivities (typically, in excess of 90%) with the diene. No reference, therefore, is made to the *exo* adducts.

With the acrylates **21** derived from (-)-menthol **20a** and (-)-8-phenylmenthol **20b**, high yields of the *endo* adducts **22** were obtained, with d.e. values of, respectively, 62% and 90% in favour of the (5*R*)-adducts. Note that the diastereoselectivity was greater with the phenylmenthol chiral unit **b**. The acrylate **21c**, derived from the neopentyl *cis*-3-hydroxyisonorbornyl ether **20c**, was observed to give the (5*R*)-adduct **22c**, with a d.e. of *ca.* 99%. Similarly, with the other enantiomer **20d** of the ether, the (5*S*)-adduct **22d** was obtained in *ca.* 99% d.e. As a final example, the *N,N*-dicyclohexyl- and *N,N*-diisopropyl-


R*—OH
20
R*
O
O
21
5
LEWIS
ACID
3
4
5
2
1
6
CO2R*
22
LiAlH4
23
OH
R* =
Me
R
Me
Me
Me
Me
OR
Me
Me
Me
RO
Me
Me
Me
SO2NR2
a; R = H
b; R = Ph
c; R = CH2CMe3
d; R = CH2CMe3
e; R =
f; R = CHMe2

Scheme 1

sulphonamides **20e** and **20f** have shown high diastereoselectivities with cyclopentadiene, with d.e. values in the range 88-93% in favour of the (5*R*)-adducts **22**. The sulphonamides **20** (**e** and **f**) were prepared, *via* the acid chlorides, from camphor-10-sulphonic acid.

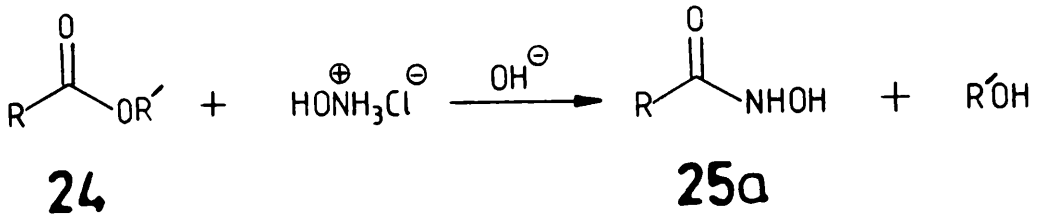
1.2 Acylnitroso compounds - Introduction.

A relatively new class of transient dienophile that has been studied in recent years is the acylnitroso compound, XCONO. The structural types, preparation and reactions of these compounds are described in the following text.

As their name implies, acylnitroso compounds have a nitroso group (N=O) directly attached to a carbonyl carbon atom. The other group attached to the carbonyl carbon can be either an alkyl or aryl group, or a group involving a heteroatom like oxygen or nitrogen. There are three principle classes of acylnitroso compounds: *C*-nitroso-carbonyl compounds, RCONO **33a**; *C*-nitrosoformate esters, ROCONO **33b**; and the *C*-nitrosoformamides, RR'NCONO **33c** (Scheme 6). The preparation of these, and the compounds that they are derived from, is discussed below.

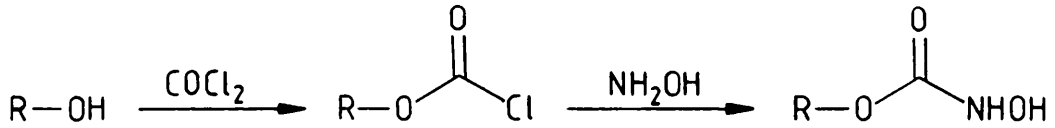
A paper detailing the preparation and reactions of *C*-nitrosocarbonyl compounds, RCONO, published in 1981, described work done by Kirby and Sweeny[2a]. Nitroso-carbonyl-alkanes and -arenes had been proposed as far back as 1964 as short-lived intermediates formed by the oxidation of hydroxamic acids, RCONHOH[3-5]. There was no direct evidence at the time, however. Kirby[6] proposed that, in principle, it would be possible to trap the nitrosocarbonyl species as stable Diels-Alder cycloadducts by performing the oxidation of the hydroxamic acids in the presence of a conjugated diene. This hypothesis was proven by the preparation and characterization of a range of these cycloadducts. In a series of papers[2c,2d,7a,7b,8], the ground work was laid for the chemistry of *C*-nitrosocarbonyl compounds.

Scheme 6 summarises the preparation of *C*-nitrosocarbonyl compounds. The hydroxamic acid **25a** is oxidized to the transient species **33a**, which is trapped *in situ* with a conjugated diene of the general type **34** to give the cycloadduct(s) **35a**. An experimental procedure for the preparation of hydroxamic acids has been described in



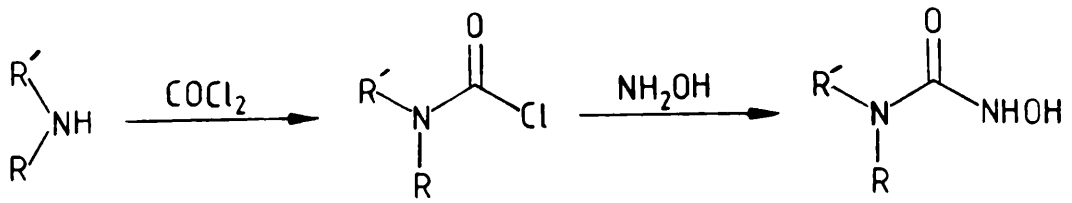
24 25a

Scheme 2



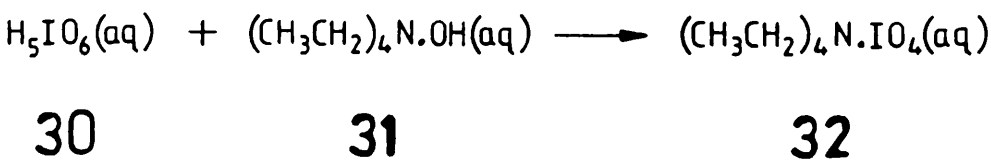
26 27 25b

Scheme 3



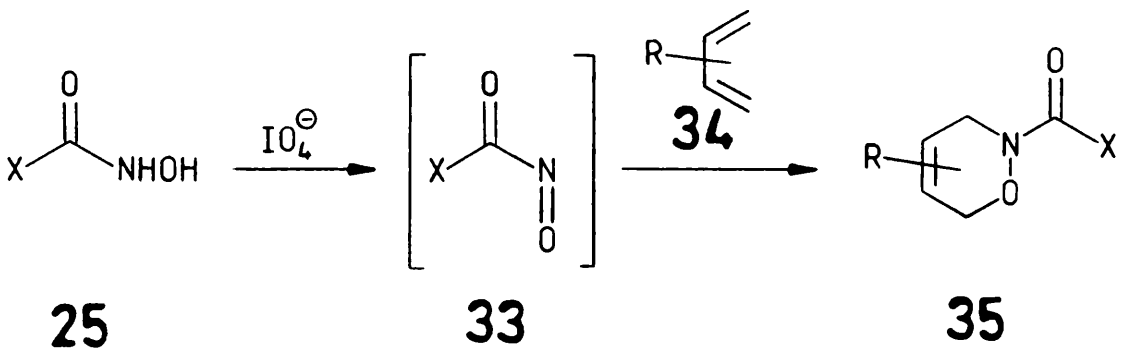
28 29 25c

Scheme 4



30 31 32

Scheme 5



25 33 35

a ; X = R

b ; X = OR

c ; X = NRR´

Scheme 6

the literature by Sandler and Karo[9]. This method involves the treatment of the ester **24** with hydroxylamine (prepared *in situ* by the action of alkali on its hydrochloride salt) to produce the derived hydroxamic acid **25a** (Scheme 2).

For the oxidation of the hydroxamic acid, heterogeneous (two phase) and homogeneous (single phase) systems can be employed. The former method involves an aqueous solution of sodium periodate (with sodium acetate acting as a pH buffer), and a solution of an organic solvent containing the conjugated diene. The hydroxamic acid is then added in small portions (typically, over several minutes) and the solution allowed to stir for *ca.* 30-60 mins. A simpler and cleaner oxidizing system, however, is the homogeneous method. Here, typically, a solution, in an organic solvent, of the diene and an organic-soluble oxidizing agent like, for example, tetraethylammonium periodate (the tetra-*n*-butyl variant can be used also) is stirred while the hydroxamic acid is added as described for the heterogeneous phase technique. Tetraethylammonium periodate **32** can easily be prepared[10] by the reaction of cold, aqueous solutions of periodic acid **30** and tetraethylammonium hydroxide **31** (Scheme 5).

Organic solvents used in the above methods commonly include ethyl acetate, chloroform, dichloromethane or methanol. Reaction temperatures can vary. For the heterogeneous system, 0 ^{o}C is used, but with the single, organic phase system lower temperatures, in some cases down to -70 ^{o}C, can be used.

Figure 4 shows a variety of cycloadducts formed by the Diels-Alder reactions of *C*-nitrosocarbonyl compounds with different types of conjugated dienes. Similar cycloadducts have been prepared with *C*-nitroso -formates, ROCONO[7a], and -formamides, RR'NCONO[8]. A brief review of some of the more interesting Diels-Alder reactions of these dienophiles (R, achiral) is presented in Chapter 1.3.

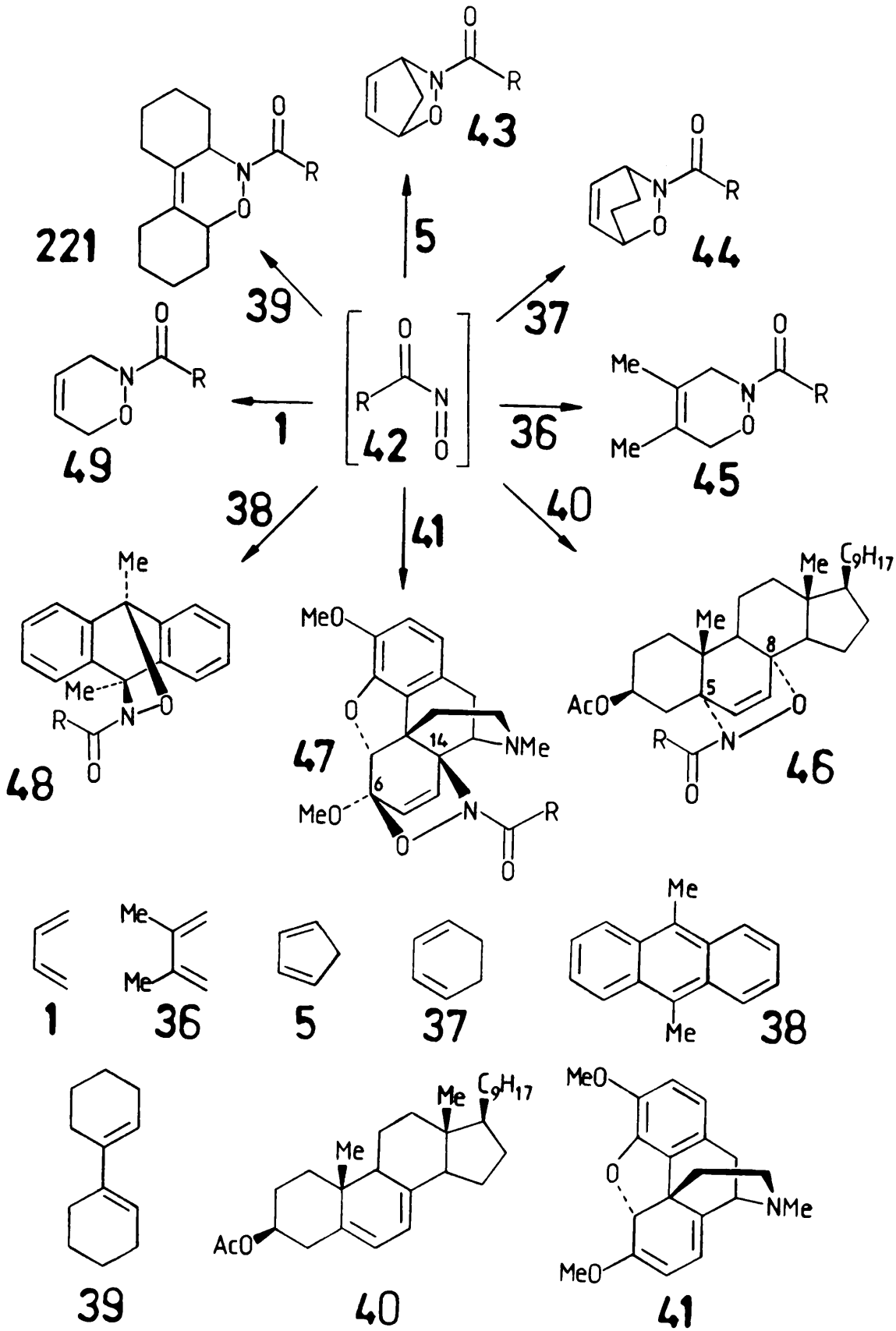


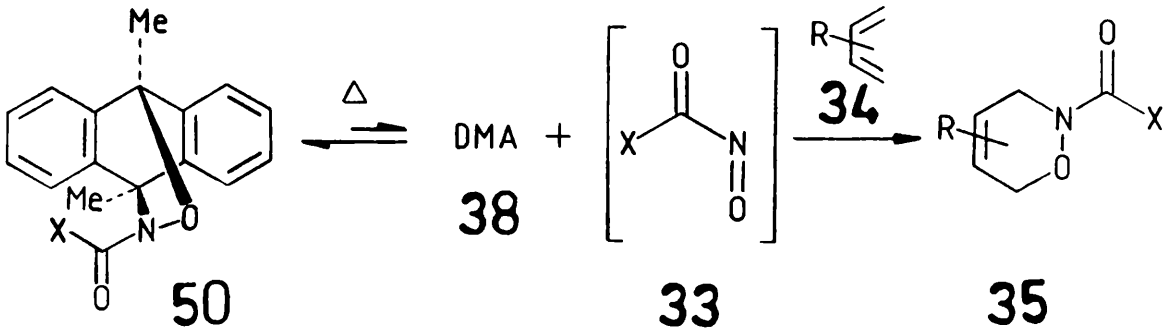
Fig. 4 Cycloadducts from *C*-nitrosocarbonyl compounds

If the diene is particularly sensitive to oxidative conditions or is not sufficiently reactive to trap the nitroso compound rapidly, then an alternative method is used to form the transient nitrosocarbonyl species. This is commonly achieved by refluxing a solution, in an inert solvent (*e.g.* benzene), of the diene **34** and the 9,10-dimethylanthracene (DMA) adduct **50** of the nitrosocarbonyl compound **33** (Scheme 7). Heating causes a retro Diels-Alder reaction and releases into solution DMA **38** and the dienophile **33**, which is then free to react with the diene. This method was used by Corrie *et al.*[2b] in the preparation of isocyanates **52** (Scheme 8), since the phosphine **51** would have been oxidized by periodate in the 'direct' method for generating the dienophile **57b**.

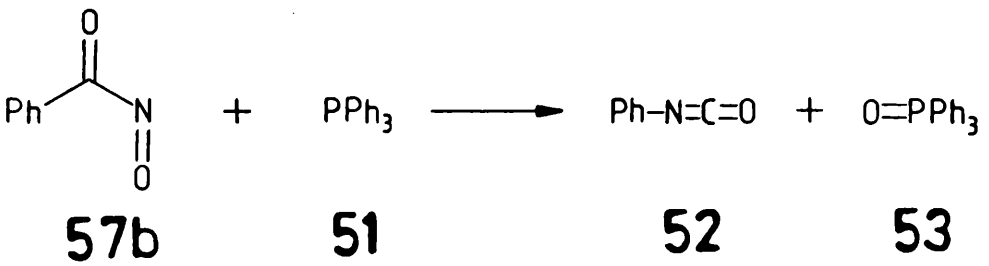
Other oxidizing agents have been used apart from the sodium and tetra-alkylammonium periodates described above. Miller *et al.*[28a] have carried out reactions in dichloromethane at -78 ^{o}C with the so-called *Swern* oxidant - oxayl chloride [$(COCl)_2$] and dimethyl sulphoxide/triethylamine.

The second class of acylnitroso compounds are the *C*-nitrosoformate esters **33b**. The preparation and reactions of these compounds were first reported by Kirby *et al.*[7a] in 1985. Thus (Scheme 6), the oxidation of *N*-hydroxycarbamic esters **25b** gives *C*-nitrosoformate esters **33b** which are also a transient species. These compounds, too, can be trapped as stable Diels-Alder cycloadducts **35b**. The *N*-hydroxycarbamic esters **25b** can be prepared according to Scheme 3. The alcohol **26** can be converted, with phosgene, into the chloroformate ester **27**. Reaction of **27** with hydroxylamine affords the product **25b**.

The final class of acylnitroso compounds to be discussed are the *C*-nitrosoform-amides **33c**, first reported by Christie *et al.*[8] in 1985. These transient species are prepared by the oxidation of the corresponding *N*-hydroxyurea **25c**, and can be trapped



Scheme 7

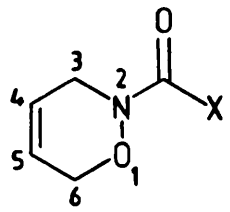


Scheme 8

as the cycloadducts **35c** (Scheme 6). The *N*-hydroxyureas **25c** are prepared from the amines **28** *via* the chlorocarbamates **29** (Scheme 4).

As described above, an acylnitroso compound of the general type **33** can be trapped *in situ* with a conjugated diene **34** to afford the cycloadduct(s) **35** (Scheme 6). The nomenclature systems used to name the adducts depend on whether an acyclic or cyclic diene has been used. If the diene was acyclic, the resulting cycloadduct is referred to as a 2-acyl-3,6-dihydro-2*H*-1,2-oxazine; the numbering of the oxazine ring is shown in Figure 5. With a cyclic diene, a bridged oxazine structure is formed and the nomenclature is slightly different. In this case, the adduct is referred to as a 3-acyl-2-oxa-3-aza-bicyclo[a.b.c]alk-5-ene; the integers a,b and c indicate the number of atoms between the bridgehead atoms. The numbering of the bicyclic system begins at the bridgehead carbon C(1) in the usual way (Figure 5). If the diene is of a more complex structural type, *e.g.* thebaine **41** (Figure 4), then the resulting adduct is named according to the positions of attachment (and stereochemistry) of the N and O atoms of the nitroso group.

The number of cycloadducts formed in the reaction of a diene with an acylnitroso compound will depend on the starting compounds. If the diene is unsymmetrically substituted, then regioisomers may be formed. However, when a chiral acylnitroso dienophile is used, unequal mixtures of diastereoisomers may be produced. It is therefore of interest to examine the asymmetric induction achieved with different types of chiral acylnitroso compounds. A comprehensive review of asymmetric Diels-Alder reactions of chiral *C*-nitroso compounds in general is presented in Chapter 1.5.



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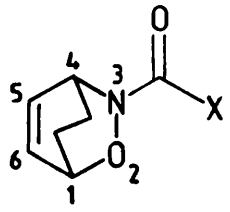

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Fig. 5 Ring numbering systems for the cycloadducts derived from acyclic (**54**) and cyclic (**55**) dienes

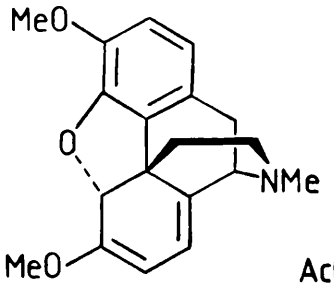
1.3 Diels-Alder reactions of achiral acylnitroso compounds.

The previous chapter gave a brief introduction on the types and general chemistry of acylnitroso compounds. Before proceeding with the subject of asymmetric Diels-Alder reactions with chiral acylnitroso compounds (Chapter 1.5), a brief review will be given on some of the more interesting Diels-Alder reactions involving the achiral types.

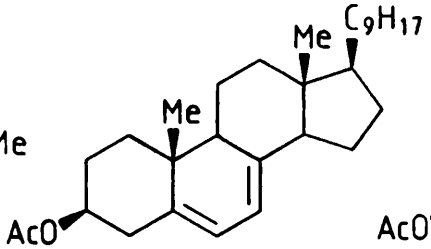
Kirby and Sweeny[2a] have reported the reactions of *C*-nitrosocarbonyl compounds with the asymmetric, conjugated diene thebaine **41** (Scheme 9). Nitrosocarbonylmethane **57a**, prepared by the oxidation of the corresponding hydroxamic acid **56a**, reacted with thebaine **41**, to afford the single cycloadduct **58a**, in which the nitrogen atom of the dienophile was attached β at C(14). Similarly, nitrosocarbonylbenzene **57b** gave the adduct **58b**, adopting the same stereochemistry as in **58a**.

In a later paper, Kirby and Mackinnon[2d] investigated the cycloaddition reactions of *C*-nitrosocarbonyl compounds with another asymmetric diene, ergosteryl acetate **40** (Scheme 9). Nitrosocarbonylmethane **57a** gave the single adduct **59a**, in which the nitrogen atom of the dienophile was attached α at C(5). However, with nitrosocarbonylbenzene **57b**, two regioisomeric adducts were formed, **59b** and **60b** (ratio unspecified), the latter compound having nitrogen attached α, this time, at C(8).

Kirby *et al.* have also reported the cycloaddition reactions of *C*-nitroso-formate esters and -formamides with both thebaine **41** and ergosteryl acetate **40** (Scheme 9). The *C*-nitrosoformate esters (Kirby *et al.*[7a]), prepared by the oxidation of the corresponding *N*-hydroxycarbamic ester, reacted with thebaine **41** to give, in each case, a single adduct **58** (**c**, **e** and **f**), with the 14β stereochemistry. In a similar manner, with **56c** and **56d**, ergosteryl acetate **40** yielded the single adducts **59c** and **59d**, both of which adopted the 5α,8α stereochemistry.



41



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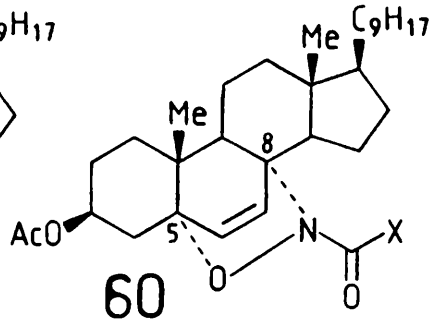
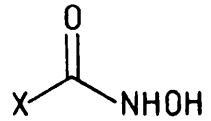


60



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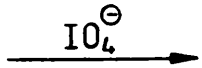
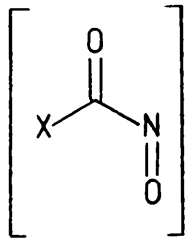
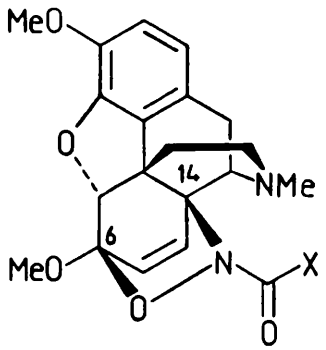




57

41 40



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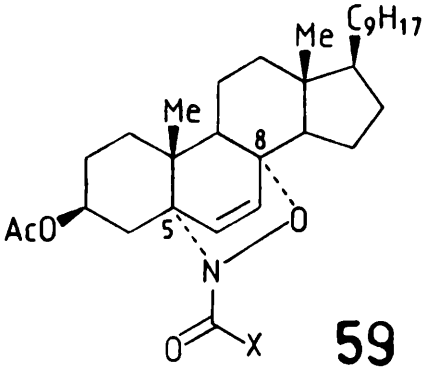


59

a; X = Me
b; X = Ph

c; X = OCH_2Ph
d; X = OCH_2CCl_3
e; X = OBu^t
f; X = $OCH_2CH_2SO_2C_6H_4Me$

g; X = NH_2
h; X = NHPh

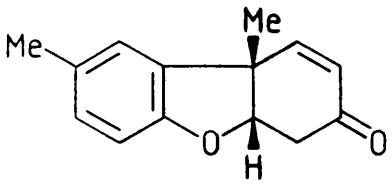
i; COX = CN

Scheme 9

Similarly (Christie *et al.*[8]), the *C*-nitrosoformamides were prepared by the oxidation of the corresponding *N*-hydroxyureas (Scheme 9). With thebaine **41**, both *C*-nitrosoformamide **57g** and *N*-phenyl-*C*-nitrosoformamide **57h** gave the single adducts **58g** and **58h**, again with the nitrogen attached β at C(14). Only *N*-hydroxy-*N* '-phenylurea **56h** was chosen for study with ergosteryl acetate **40**; the single adduct **59h** was formed, with the usual 5α,8α stereochemistry.

Before the above studies were carried out, it was reported by Horsewood *et al.*[12] that nitrosyl cyanide **57i** (Scheme 9) gave the single adduct **58i** with thebaine **41**, but a mixture of the regioisomers **59i** and **60i** (ratio unspecified) with ergosteryl acetate **40**. In each of these cases the dienophile was prepared by the thermal dissociation of its DMA adduct.

One of the most structurally exotic, conjugated dienes used in cycloaddition reactions with *C*-nitroso and *C*-nitrosocarbonyl compounds is the pyrrolidine dienamine **62** of Pummerer's ketone **61**[13] (Scheme 10). Freer *et al.*[14] have examined the reactions of this 2-aminocyclohexa-1,3-diene **62** with nitrosocarbonylmethane **57a** and nitrosobenzene **66**. The diene **62** gave a complex mixture of products with both dienophiles, in varying proportions depending on the initial reaction conditions. Nitrosocarbonylmethane **57a** gave at least three compounds (Scheme 10); the bridged 1,2-oxazine **63** incorporating 2 mol equivalents of the dienophile (interestingly, with the reductive loss of 1 nitroso oxygen), the acetamido enone **64**, and the pyrrolidino enone **65**. The reaction pathways to the former two compounds are unknown, but a mechanism has been proposed for the formation of **65**. Nitrosobenzene **66** also gives a complex mixture of products with the dienamine **62** (Scheme 11); the compounds identified were the bridged oxazine **67** (incorporating 1 mol equiv. of the dienophile), the phenylamino enone **68**, and the bridged amino ketone **69**, the latter containing 2 mol equivs. of the dienophile. Again, the compounds **68** and **69** showed reductive loss of nitroso oxygen. Reaction pathways to these compounds remain uncertain. Interestingly, however, the



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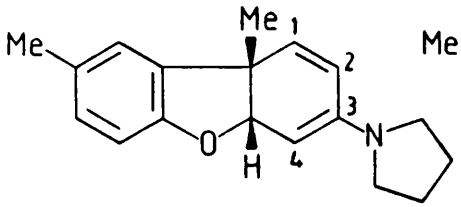
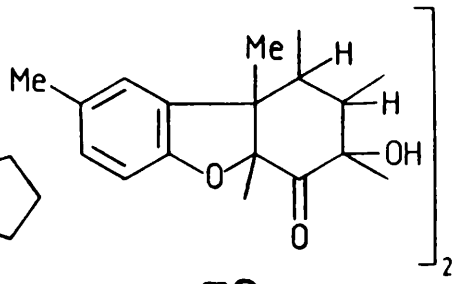
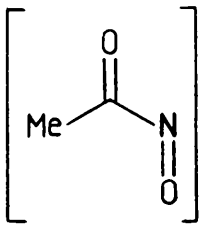


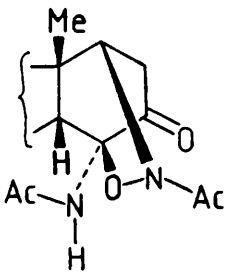
62



70



57a



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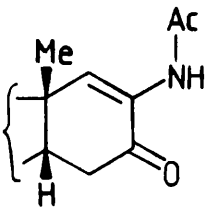
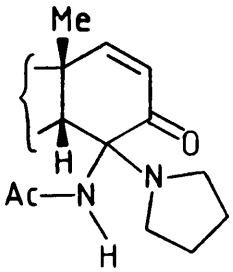
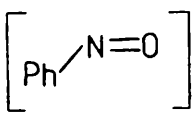


64



65

Scheme 10



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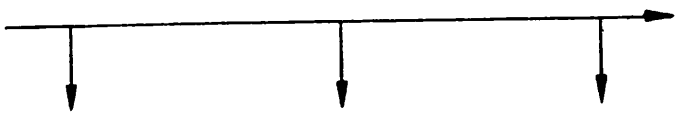

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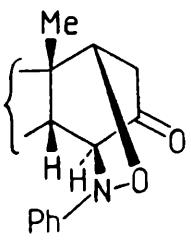

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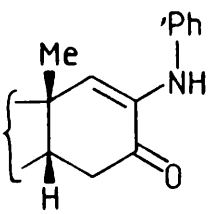
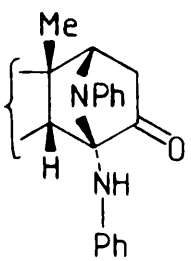


68



69

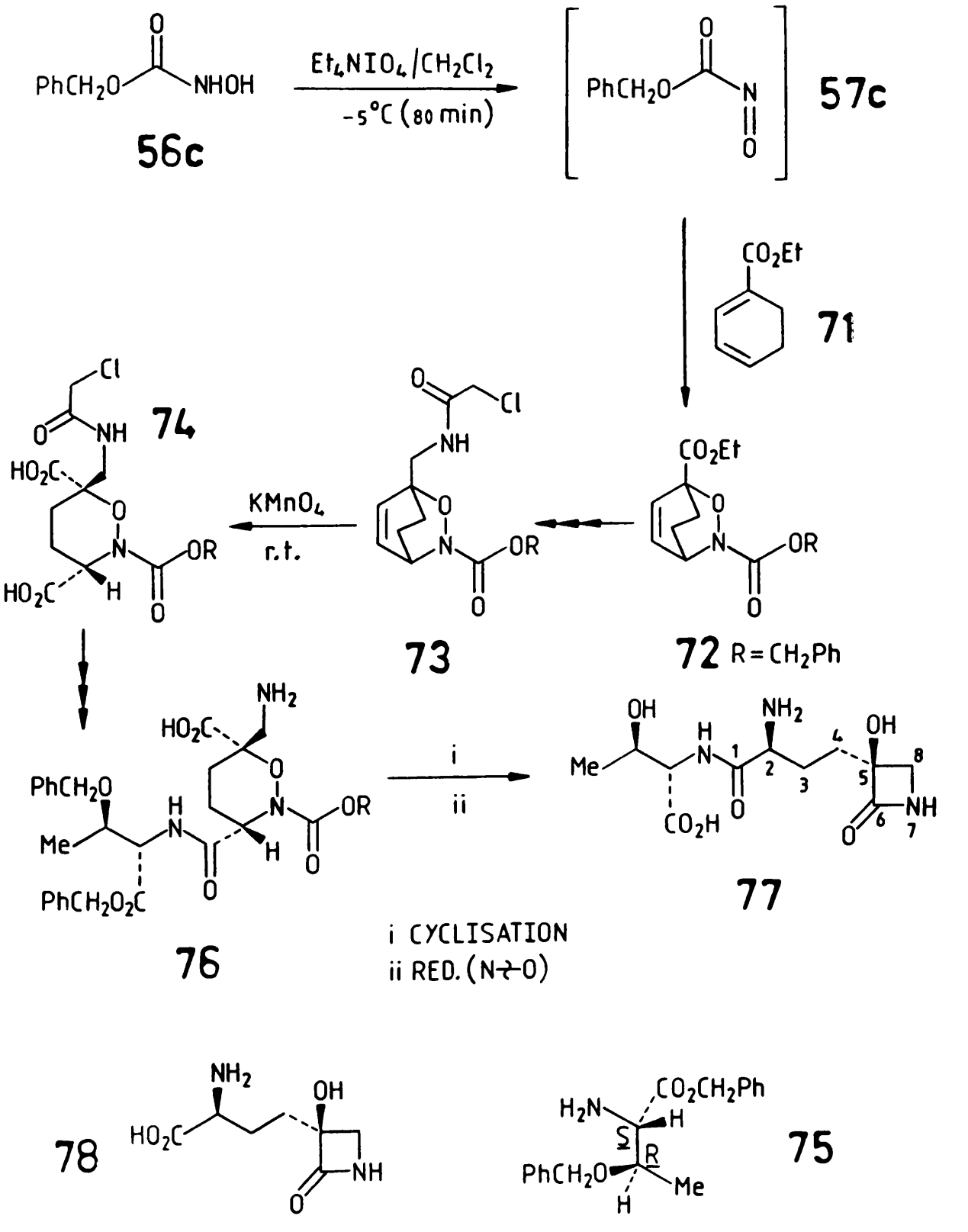
Scheme 11

major product of the reaction was a nitrogen-free, caged dimer **70** of the 4-oxo derivative of Pummerer's ketone.

One of the most interesting applications of acylnitroso compounds is to the synthesis of natural products. In some cases, an early or principle step in a synthetic pathway involves the Diels-Alder cycloaddition reaction of a diene with an XCONO compound. To conclude this chapter, some illustrative examples are given below.

In 1984, Baldwin *et al.*[15a] reported the first total synthesis of tabtoxin (from *Pseudomas Tabaci*) **77** (Scheme 12), the toxin responsible for the Wildfire disease of tobacco plants[16]. The first step involved the oxidation of benzyl *N*-hydroxycarbamate **56c** to benzyl nitrosoformate **57c**, which was trapped *in situ* with ethyl cyclohexa-1,3-dienecarboxylate **71** to give a single regioisomer of the racemic, bicyclic ester **72** (the regiochemistry was confirmed by X-ray crystallography). This Diels-Alder reaction immediately set up the correct stereochemical relationship between the C(2)-amino and C(5)-hydroxy groups in the eventual product, **77**. Conversion of the ester group in **72** to an aminomethyl group was followed by protection of the latter as the *N*-chloroacetamide **73**. Permanganate oxidative cleavage of the olefin **73** gave the diacid **74**, which was then condensed with *O*-benzyl-*L*-threonine benzyl ester **75** to give the β-amino acid **76**, after deprotection of the aminomethyl group, and separation of the diastereoisomers. The formation of the threonine amide occurred selectively at only one carboxylate group in **74**. The remaining steps in the synthesis involved cyclisation of the β-amino acid **76** to produce the spiro β-lactam moiety in **77**, followed, finally, by reductive cleavage of the perhydro-1,2-oxazine ring and removal of the benzyl protecting groups, by catalytic hydrogenolysis, to leave the final product, tabtoxin **77**.

Baldwin *et al.*[15b] have also reported the synthesis of tabtoxinine-β-lactam **78** (Scheme 12), a known glutamine sythetase inhibitor[17]. This compound was prepared using the same methodology as outlined (see above) for the synthesis of tabtoxin **77**


PhCH2O
NHOH
56c
Et4NIO4/CH2Cl2
-5°C (80 min)
57c
CO2Et
71
Cl
NH
74
HO2C
KMnO4
r.t.
OR
73
72 R = CH2Ph
NH2
PhCH2O
Me
PhCH2O2C
76
i
ii
OH
77
i CYCLISATION
ii RED. (N→O)
78
CO2CH2Ph
H2N
S
R
75

Scheme 12

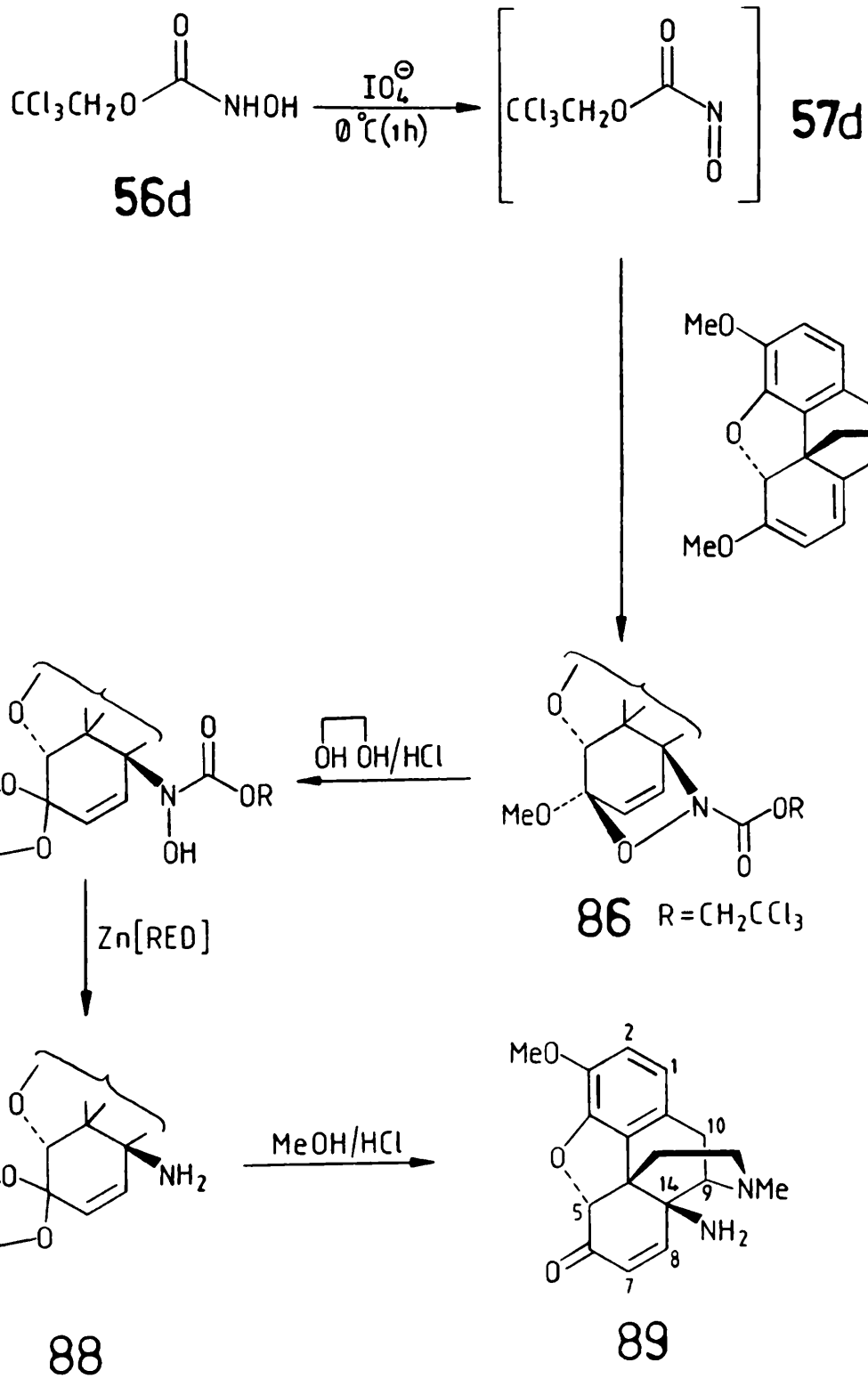
(Scheme 12), with the exception that the step involving the formation of the amide **76** from the *L*-threonine derivative **75** was omitted.

In 1989, Baldwin *et al.*[18] reported the total synthesis of (±)-isonitrin B (deoxytrichoviridine) **85** (Scheme 13), derived from the fungal family *Trichoderma*; **85** is a rare example of a natural product containing an isonitrile group[19]. Benzyl *N*-hydroxycarbamate **56c** was oxidized to benzyl nitrosoformate **57c**, which was trapped *in situ* with 1-acetylcyclopentadiene **80** (prepared *in situ* by the addition of *p*-toluenesulphonic acid to the fulvene **79**), to produce a single regioisomer of the racemic, bicyclic ketone **81**. This initial step established the positions of the isonitrile nitrogen and hydroxyl oxygen in the final product **85**. Diastereoselective reduction of the ketone **81** with K-Selectride, followed by protection of the resultant secondary alcohol as a *tert*-butyldimethylsilyl ether, gave **82**. Treatment of the silyl ether **82** with sodium amalgam in methanol reductively cleaved the N-O bond. This was followed by epoxidation of the double bond with 3-chloroperbenzoic acid to produce the epoxide **83**. The benzyl ester group of **83** was removed to give the corresponding amine, which was converted into the vinyl formamide **84**. The remaining steps in the synthesis involved treatment of **84** with diisopropylamine and triflic anhydride to give the desired vinyl isonitrile group and, lastly, deprotection of the secondary alcohol with tetrabutyl-ammonium fluoride to give the final product, (±)-isonitrine B **85**.

Kirby and McLean[20] reported a new synthesis of 14β-aminocodeinone **89** from thebaine **41** (Scheme 14). The former compound has proved a useful starting molecule for the synthesis of the series of analgesic 14β-acyl- and 14β-alkyl-amino-codeinones and -morphines. 2,2,2-Trichloroethyl *N*-hydroxycarbamate **56d** was oxidized with periodate in the presence of thebaine **41** to yield the single, epoxyimino derivative **86**; the dienophile **57d** added, as usual, to the β face of the diene portion of the thebaine molecule. The adduct **86** was then transformed into the ethylene acetal **87** by treatment with glycolic hydrogen chloride. Cleavage of the *N*-hydroxy bond and removal of the

PhCH2O
NHOH
Et4NIO4
CH2Cl2
56c
57c
80
81
R = CH2Ph
i K-selectride
ii t-BuMe2SiCl
(CH2Cl2)
i Na/Hg (MeOH)
ii MCPBA(CH2Cl2)
X = SiMe2But
83
82
84
i (iPr)2NH / (CF3SO2)2O
ii Bu4NF (THF)
85
79
OSiMe3
Me

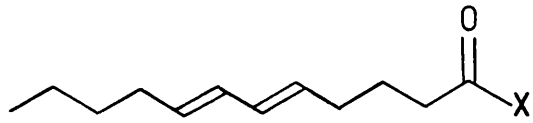
Scheme 13


CCl3CH2O
NHOH
IO4⊖
0 °C(1h)
56d
57d
MeO
NMe
41
87
OH OH/HCl
OR
OH
86 R=CH2CCl3
Zn[RED]
MeOH/HCl
NH2
88
89
2
1
10
9
14
5
8
7

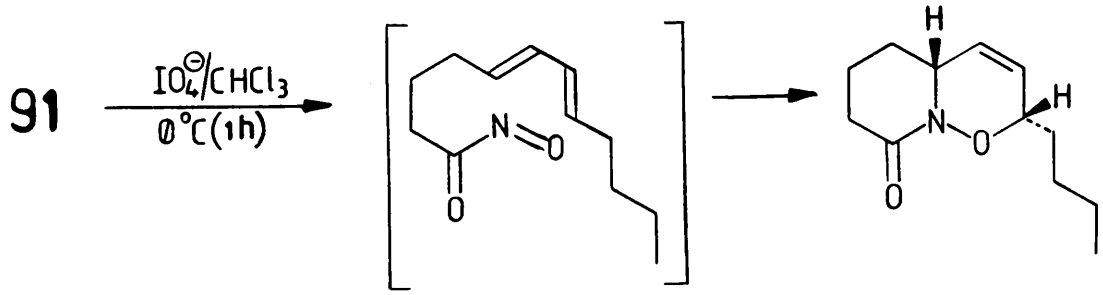
Scheme 14

trichloroethoxycarbonyl group was achieved by reduction with zinc to leave the amino acetal **88** which was converted into 14β-aminocodeinone **89** by hydrolysis with methanolic hydrogen chloride. The overall, *ca.* 70%, yield of the sequence made it an efficient method for the preparation of **89**.

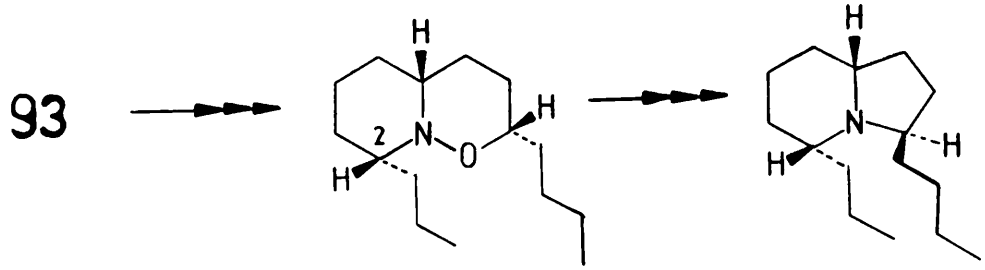
The neurotoxin alkaloid gephyrotoxin (GTX) **95** (Scheme 15), isolated from the skin of the poison-dart frog[21], has attracted synthetic interest in the past few years. A new synthesis of (±)-GTX involving, as an early step, an intramolecular Diels-Alder reaction of an acylnitroso compound, has been reported by Iida *et al.*[22]. The (5*E*,7*E*)-ester **90** was converted into the hydroxamic acid **91**, which was then oxidized with periodate to give the transient acylnitroso species **92**. This then underwent an intramolecular Diels-Alder reaction, with complete stereochemical control, to yield the dihydro-1,2-oxazine **93**. Catalytic hydrogenation of **93** followed by attachment of an *n*-propyl side-chain at the 2-position gave the 1,2-oxazine **94**. The remaining stages of the synthesis involved the reductive cleavage of the N-O bond to give a monocyclic amino alcohol which was then cyclised to afford the pyrrolidine moiety of the final product, **95**.



90 X = OMe
91 X = NHOH



92 **93**



94 **95**

Scheme 15

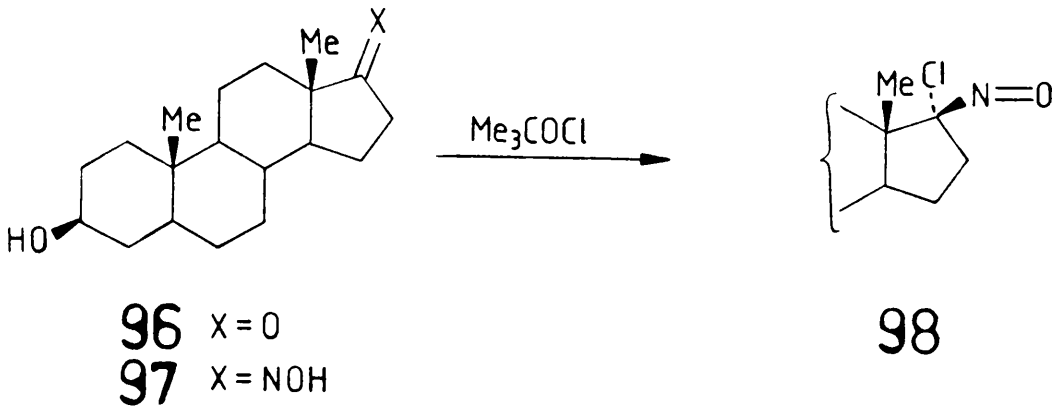
SECTION II

1.4 Diels-Alder reactions of chiral α-chloronitroso compounds.

The two remaining chapters of this section (1.4 and 1.5) are concerned with the asymmetric Diels-Alder reactions of *chiral C*-nitroso compounds. Before moving on to the principle subject of this thesis - induction with chiral acylnitroso compounds - a brief look will be taken at the reactions of α-chloronitroso dienophiles, RR'C(Cl)NO. Unlike the former class of dienophiles, α-chloronitroso compounds have the chiral unit directly attached to the nitroso function. In addition, they are also relatively stable species (*c.f.* transient XCONO compounds) and do not have to be prepared and trapped *in situ*. Some examples of asymmetric cycloaddition reactions with α-chloronitroso compounds are discussed below.

As part of studies on the synthesis of streptamine analogues[23], Sabuni *et al.*[24a] investigated the asymmetric Diels-Alder reactions of chiral α-chloronitroso compounds. The authors mention the merits of utilizing a nitroso compound that possesses a rigid molecular framework with sterically, bulky groups near the C(Cl)NO portion of the molecule, thereby inhibiting free rotation of the nitroso group around the C-NO bond. This means that in the cycloaddition reaction, preferential attack of the conjugated diene will occur on the less hindered side of the nitroso group and high stereo-selectivities may be obtained.

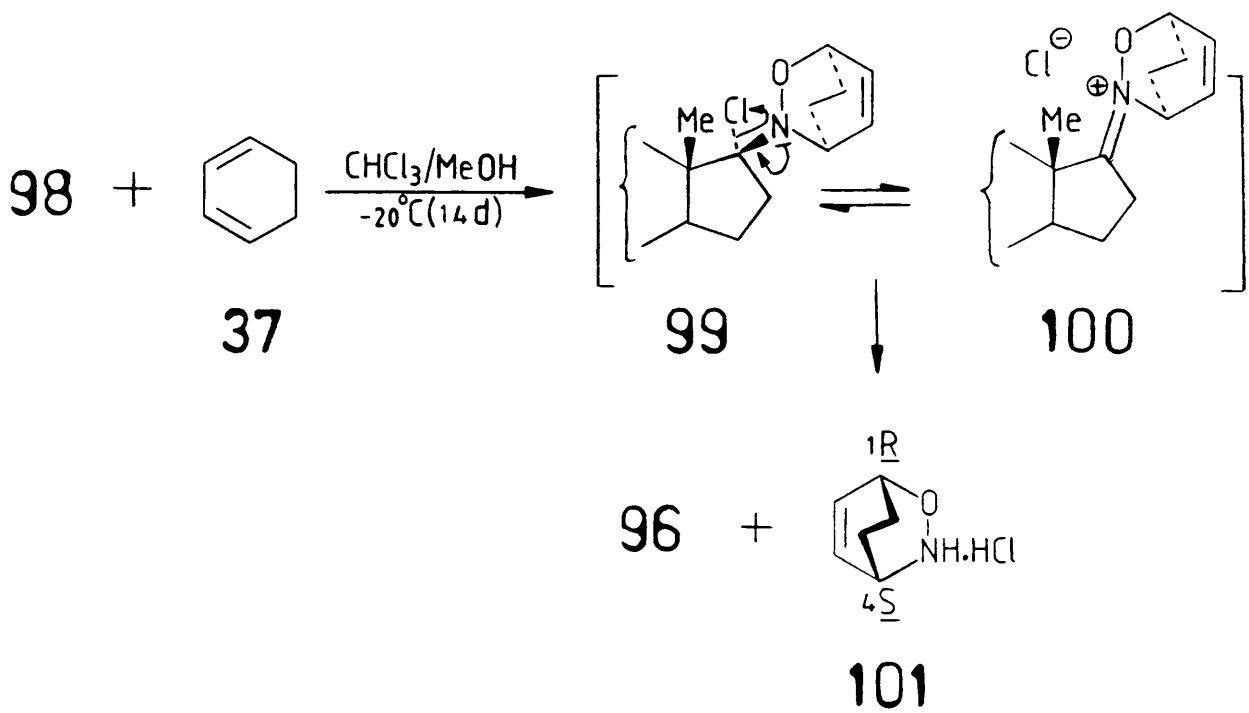
The α-chloronitroso compound chosen for the above study was 17α-chloro-17β-nitroso-3β-hydroxy-5α-androstane **98**, prepared from the oxime **97** of the steroid, epiandrostane **96** (Scheme 16). The nitroso compound **98** reacted with cyclohexa-1,3-diene **37** (Scheme 17) to afford (after solvolysis of the immonium salt **100** of the adduct **99**) the optically active oxazine salt **101** in *ca.* 95% enantiomeric excess. The product **101** was shown to have a 1-(*R*),4-(*S*) configuration by degradation to a known reference compound. An approach geometry of diene and dienophile consistent with this preferred stereochemistry is shown in Figure 6.



96 X = O
97 X = NOH

98

Scheme 16



Scheme 17

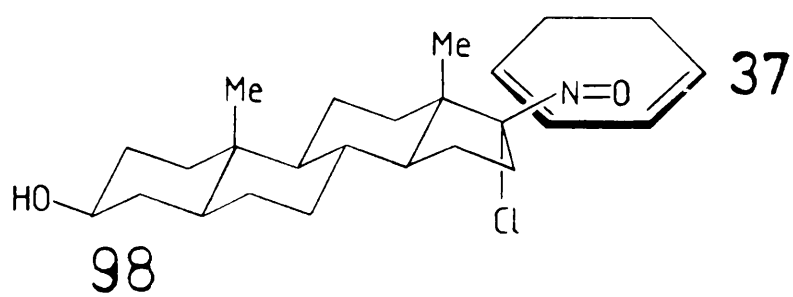
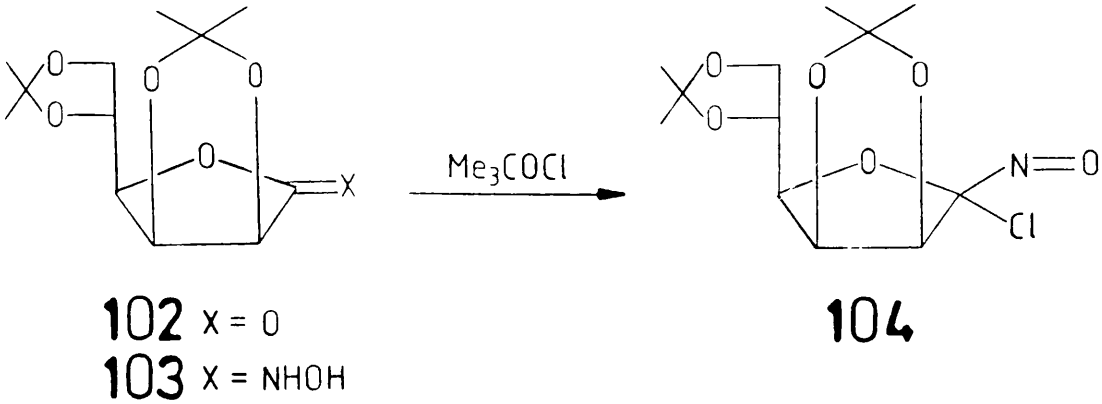


Fig. 6

The same research group (Felber *et al.*[24b]) converted the carbohydrate 2,3:5,6-di-*O*-isopropylidine-*D*-mannofuranose **102** into the α-chloro-α-nitroso ether **104** *via* the known[25] lactone oxime **103** (Scheme 18). Reaction of **104** with cyclohexa-1,3-diene **37** (Scheme 19) gave the adduct **105** which, after solvolysis of the immonium salt **106**, yielded the optically active oxazine salt **107** in *ca.* 95% enantiomeric excess. The configuration of the oxazine salt **107** was found to be 1-(*S*),4-(*R*), being opposite to that of the product **101** from the reaction of cyclohexa-1,3-diene **37** with 17α-chloro-17β-nitroso-3β-hydroxy-5α-androstane **98** (Scheme 17). An approach geometry of diene and dienophile consistent with the stereochemistry of **107** is shown in Figure 7.

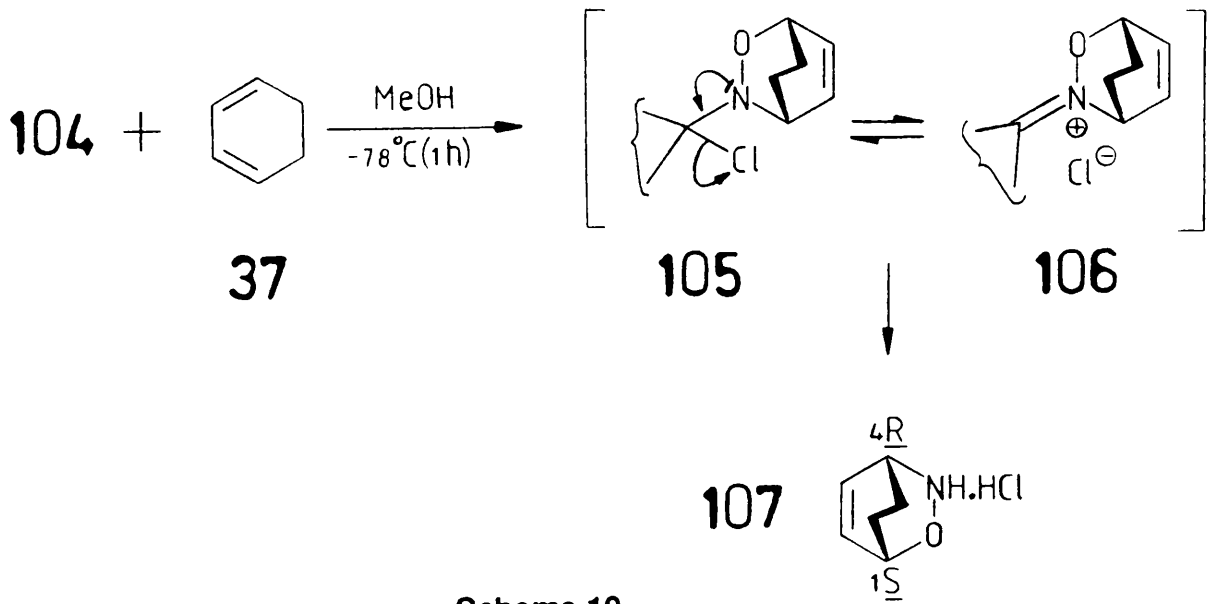
The success achieved with the α-chloronitroso ether **104** (Scheme 19) in obtaining high asymmetric induction with cyclohexa-1,3-diene prompted further studies to be undertaken. In a later paper, Felber *et al.*[24c] published the diastereoselectivities obtained with **104** and the conjugated dienes (Scheme 20) *trans*-1,2-dimethoxy-cyclohexa-1,3-diene **108**, (*E*,*E*)-hexa-2,4-diene **109**, ethyl sorbate **110**, and *trans*-piperylene **111** [(*E*)-penta-1,3-diene]. The α-chloronitroso compound **104** reacted with each of the dienes **108**-**110** to give (after solvolysis of the intermediate immonium salts), respectively, the diastereoisomeric dihydro-oxazine derivatives **113**, **114** and **115**. In every case, diastereoselectivities in excess of *ca.* 96% were achieved. Similarly, with *trans*-piperylene **111**, a mixture of the regioisomers **116** and **117** (each as a mixture of diastereoisomers) was obtained in a ratio of, respectively, *ca.* 2:1; separation of the regioisomers (and hence d.e. values) could not be obtained. In all cases, the absolute configurations of the adducts **113**-**117** were not determined. The diastereo-selectivities were measured by acylation of the dihydro-oxazines (except for **116** and **117**) with either (+)-camphor-10-sulphonyl chloride or (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride to give, respectively, the amides **118** and **119**; the ratios of the diastereoisomers were then obtained by proton NMR spectroscopy. In addition to the above results, the reactive conformation of the dienophile **104** in the Diels-Alder



102 X = O
103 X = NHOH

104

Scheme 18



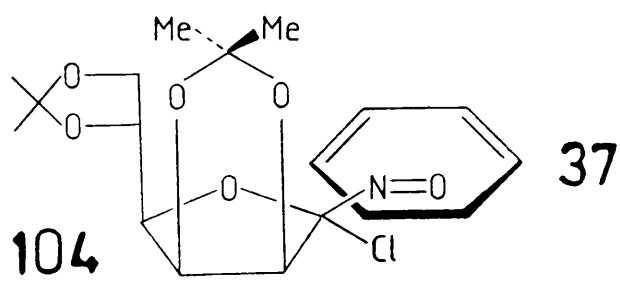
37

105

106

107

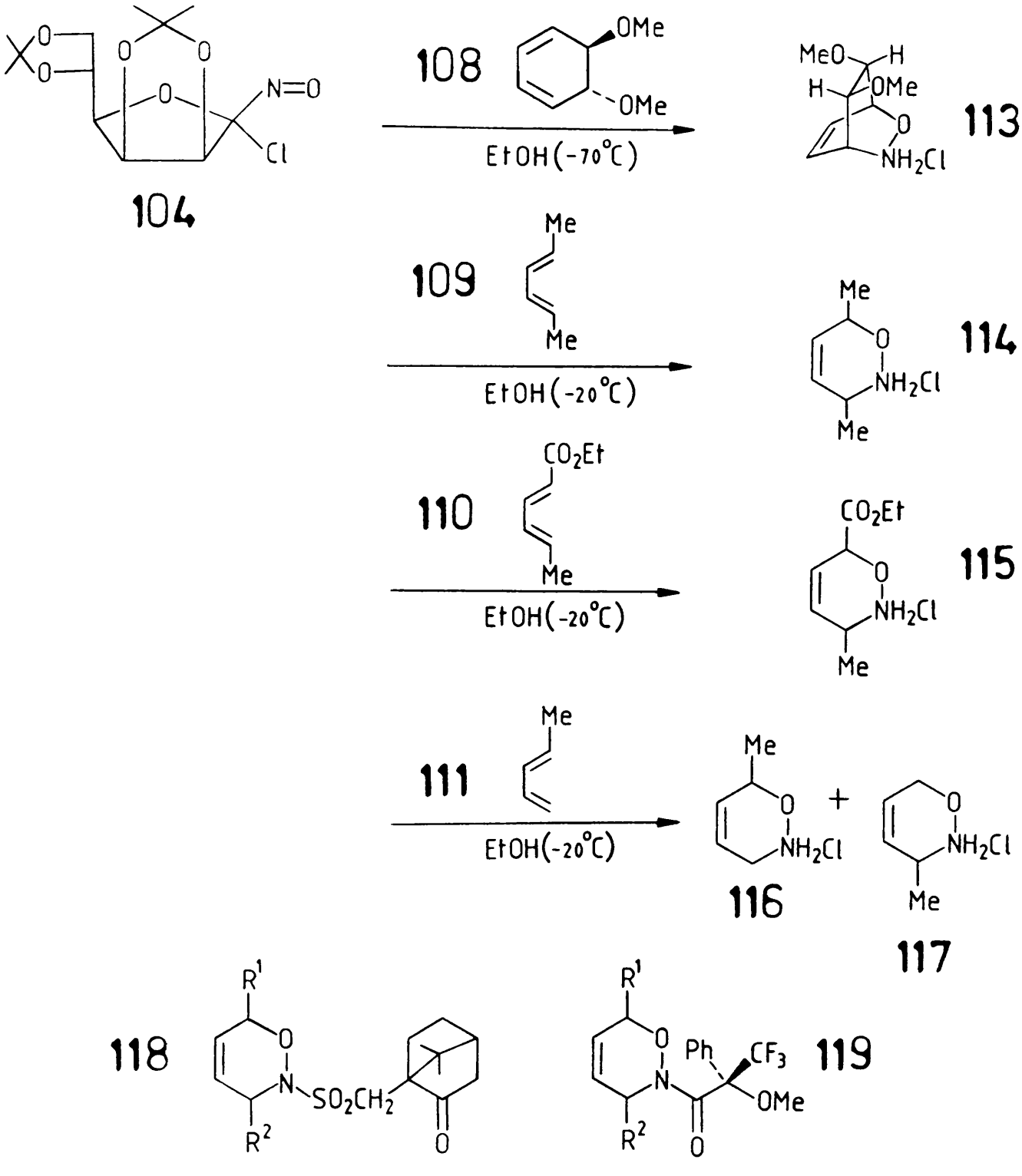
Scheme 19



104

37

Fig. 7



Scheme 20

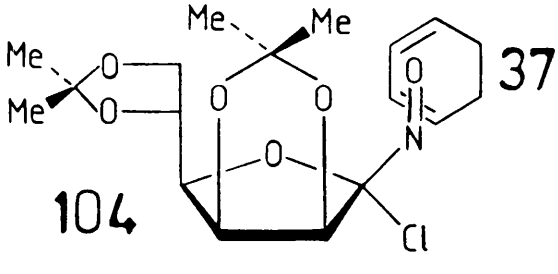
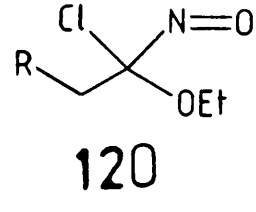


Fig. 8



a ; R = H
b ; R = Cl
c ; R = Me

Fig. 9

reaction was deduced from X-ray studies. This conformation, if it is the same as that in the crystal, is shown in Figure 8, and has the nitroso group on the same side of the molecule as the C(1)-O bond. Attack of the diene occurs on the less sterically hindered side of the nitroso group, as indicated in the Figure. *Endo* addition of cyclohexa-1,3-diene, in this fashion, leads to the experimentally observed stereochemistry (see paragraph above; Scheme 19).

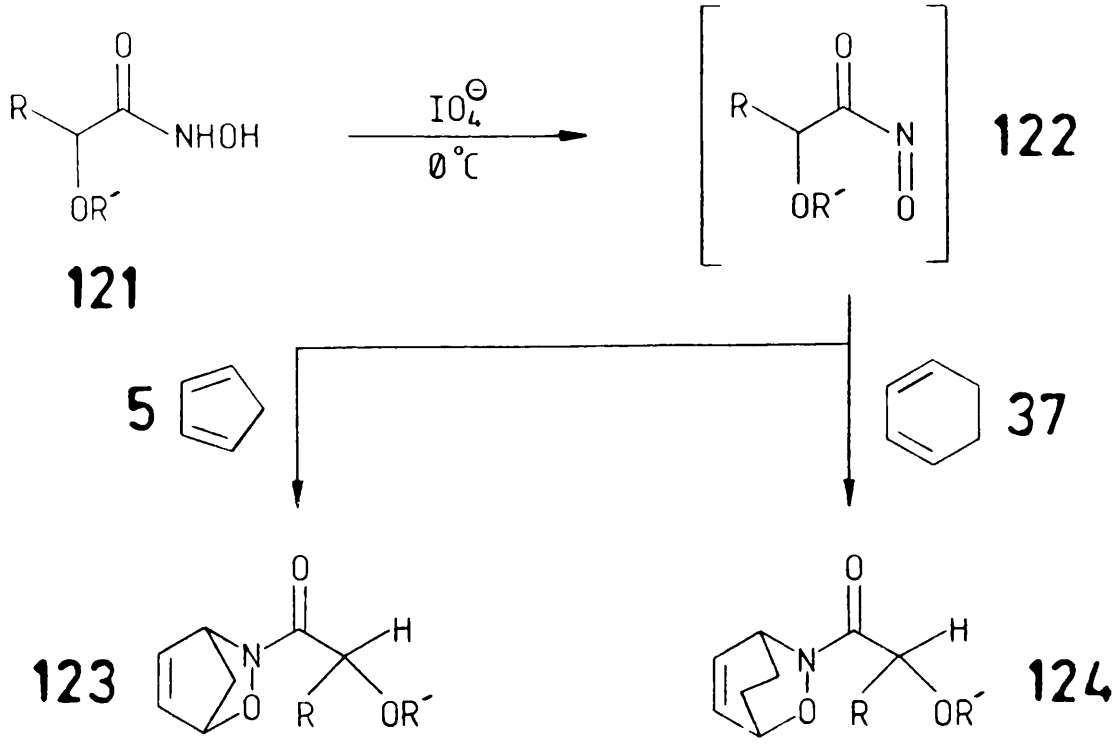
It appears that the relatively high, for a tertiary *C*-nitroso compound, reactivity of **104** can be attributed to the two electronegative substituents (-Cl and -OR) attached at C(1). In order to examine the influence of the C(1) alkoxy group, the racemic α-chloronitroso ethers **120** (Figure 9) were prepared and treated with a selection of dienes; similar reactivities to **104** were observed. Thus, the compounds **120** provide another source of potentially useful chiral α-chloronitroso dienophiles.

1.5 Diels-Alder reactions of chiral acylnitroso compounds.

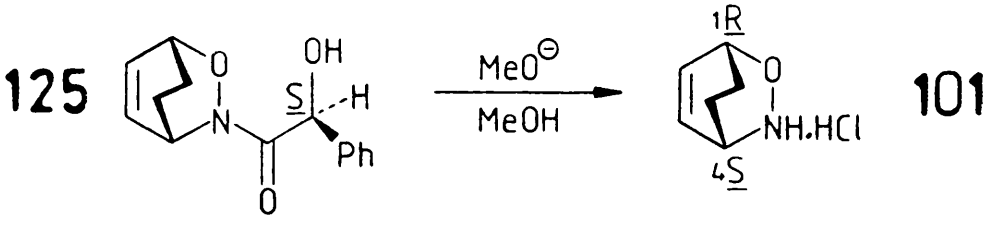
Attention is finally turned to the asymmetric Diels-Alder reactions of chiral acylnitroso compounds, R^*CONO. Unlike the α-chloronitroso compounds, RR'C(Cl)NO (see previous chapter), the chiral unit in R^*CONO is one atom displaced from the nitroso group. It is to be generally expected, therefore, that the asymmetric induction will be less, since owing to the more 'remote' proximity the chiral group is further from that involved in bonding (N=O). Nevertheless, it is of interest to examine the reactions of dienes with chiral acylnitroso compounds, so as to assess their worth as dienophiles in asymmetric Diels-Alder reactions. Already, a significant amount of work has been done on this subject, as summarised below.

It was suggested by Christie *et al.*[8] that intramolecular hydrogen-bonding in chiral α-amino and α-hydroxy acylnitroso compounds (*e.g.* **126**, Figure 10) might enhance asymmetric induction in the Diels-Alder reactions with conjugated dienes. In order to investigate this idea, Kirby and Nazeer[26] prepared a variety of racemic, α-hydroxy derivatives **121** and measured the ratios of the diastereoisomeric cycloadducts obtained from the nitroso compounds **122** and the achiral, cyclic, dienes cyclopentadiene **5** and cyclohexa-1,3-diene **37**. Scheme 21 summarises the reactions carried out. The following nitrosocarbonyl dienophiles were employed; the mandelic **122a**, *O*-methylmandelic **122b**, hexahydromandelic **122c**, and *tert*-butylglycolic **122d** derivatives.

The ratios of the diastereoisomeric adducts obtained are summarised in Table 1. The highest ratios of diastereoisomers were obtained with the mandelic derivatives of cyclopentadiene **123a** (*ca.* 5.1:1; 0 ^{o}C), and the *tert*-butylglycolic derivatives of cyclohexadiene **124d** (*ca.* 10:1; -70 ^{o}C). the ratios obtained with the *O*-methylmandelic derivatives **123b** and **124b** were smaller than those with the α-OH derivatives, thereby supporting the idea that a hydrogen-bonded dienophile is important for enhancing asymmetric induction. It was shown that the major isomer of the cycloadducts **124a** had



Scheme 21



Scheme 22

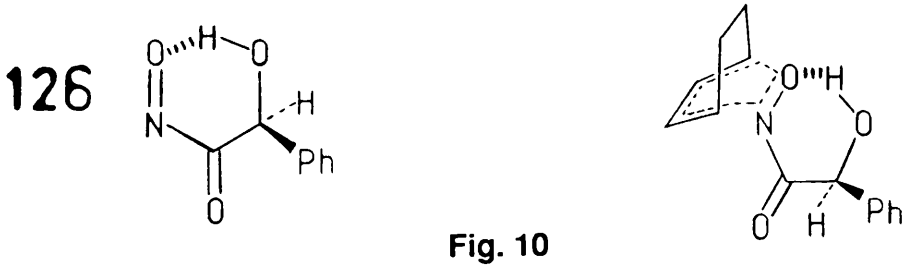


Fig. 10

	a	b	c	d
R	Ph	Ph	cyc-C_6H_{11}	Bu^t
R´	H	Me	H	H

the structure **125** (Scheme 22). This was done by hydrolysis of this isomer, derived from (*S*)-mandelic acid, to give the oxazine **101** of known[24a] absolute configuration. Preferential formation of **125** was consistent with *endo* addition of the hydrogen-bonded dienophile **126** from the face *anti* to the phenyl group, as shown in Figure 10.

Table 1 Ratios of the diastereoisomeric adducts **123** and **124** (Scheme 21).

	R / R' groups			
Adducts	**a**	**b**	**c**	**d**
123	5.1:1	2.6:1	3.6:1	3.4:1
124	3.5:1	2.1:1	2.5:1	4.6:1

N.b. **a**; R = Ph, R' = H

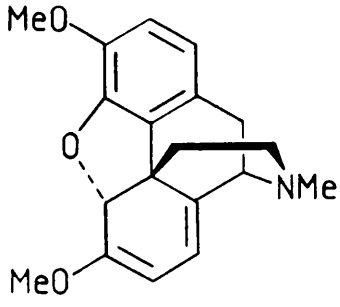
b; R = Ph, R' = Me

c; R = *cyc*-C_6H_{11}, R' = H

d; R = Bu^t, R' = H

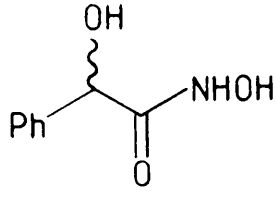
Apart from the work described above with the α-hydroxy mandelic derivatives and cyclopentadiene and cyclohexadiene, Nazeer[27] has investigated the asymmetric Diels-Alder reactions of other acylnitroso compounds. The results of this work are summarised in the paragraphs below.

As mentioned previously, the diene thebaine **41** is known to form a range of cycloadducts with various types of acylnitroso compounds[2a,7a,8] (Scheme 9); the observed regiochemistry of the adducts involved attachment of the N and O atoms at, respectively, C-14 and C-6. As usual, attack occurred from the β-face with the production of a 6-α methoxy group. Nazeer investigated the reaction of thebaine with a chiral, racemic nitrosocarbonyl dienophile (Scheme 23) to see if enantioselectivity could be achieved. Thus, (±)-mandelohydroxamic acid **121a** was oxidized at 0 °C in the presence of thebaine **41**. The diastereoisomers **127** and **128** were produced, with the



41

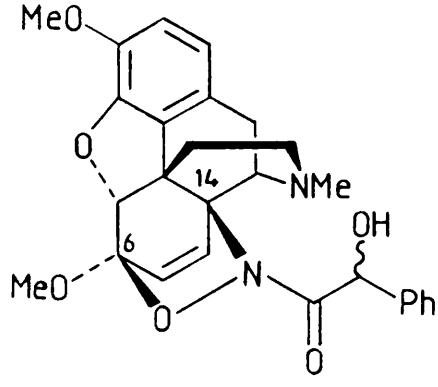
+



121a

EtOAc

$NaIO_4/H_2O$ (0°C)



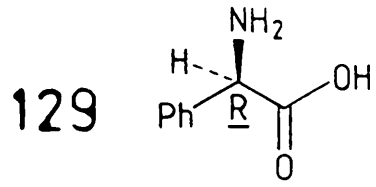
127 and 128

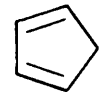
Scheme 23

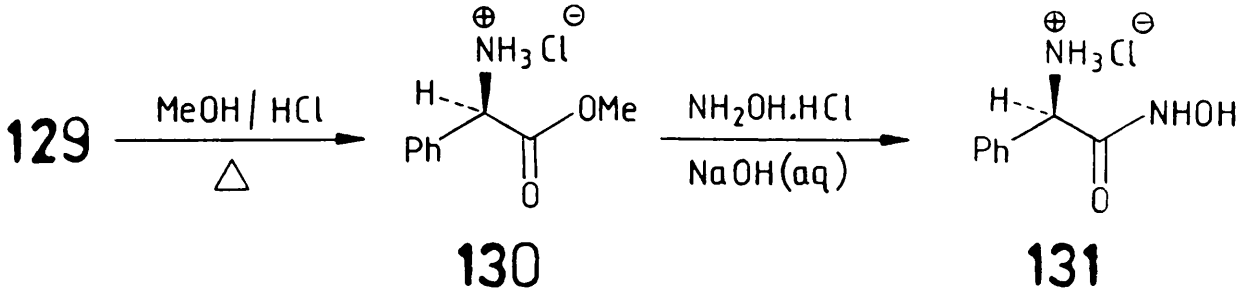
same regio- and stereo-chemistry. Their ratio, measured by proton NMR spectroscopy, was found to be *ca.* 1:1, therefore indicating no significant degree of enantioselectivity in the reaction. The critical experiment involved adding, to the periodate solution, a 1:2 mixture of thebaine **41** and (±)-mandelohydroxamic acid **121a** in the hope that the (+)- and (-)-nitroso enantiomers would react competitively with the diene. However, a 1:1 mixture of the adducts **127** and **128** was still produced. Since it seems unlikely that both nitroso enantiomers would react with thebaine at exactly the same rate, it was concluded that the rate of the Diels-Alder reaction was faster than the rate of the oxidation of the hydroxamic acids.

The cycloaddition reactions of the nitrosocarbonyl compounds derived from (*R*)-(+)-phenylglycine **129** were next investigated (Scheme 24). The first to be examined was the hydroxamic acid hydrochloride of (*R*)-phenylglycine **131**. This was prepared from (*R*)-phenylglycine **129** *via* the methyl ester hydrochloride **130**. Oxidation (Scheme 26) of **131** in the presence of cyclohexa-1,3-diene **37** at 0 ^{o}C, however, gave a complex mixture of products with no sign of the expected diastereoisomers **135a** and **136a**. This reaction was carried out using both the single- and two-phase periodate oxidizing systems, with the same results. Cyclopentadiene **5**, too, gave no sign of any cycloadducts with **131**. Next, the hydroxamic acid **134** derived from *N*-acetyl-(*R*)-phenylglycine **132** was prepared from (*R*)-phenylglycine **129** as shown in Scheme 25. This time, oxidation (Scheme 26) with tetraethylammonium periodate (EtOAc) at 0 ^{o}C in the presence of cyclohexa-1,3-diene **37** gave a mixture of the diastereoisomers **135b** and **136b**, in a ratio of *ca.* 1:1, *i.e.* without significant diastereoselectivity.

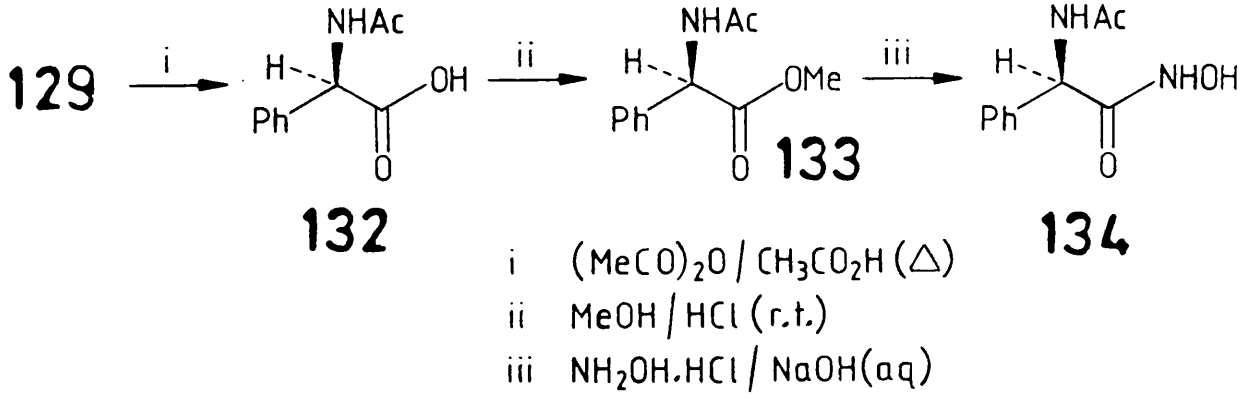
Finally, the *N*-hydroxycarbamic ester **140** (Scheme 27), with a *trans*-2-phenylcyclohexyl group serving as the chiral unit, was prepared from *trans*-2-phenyl-cyclohexanol **138** *via* the chloroformate ester **139**. The alcohol **138** was prepared, in turn, by a Grignard reaction on cyclohexene oxide **137**. Oxidation of the *N*-hydroxy-carbamic ester **140** (Scheme 27) in the presence of cyclohexa-1,3-diene **37** was carried



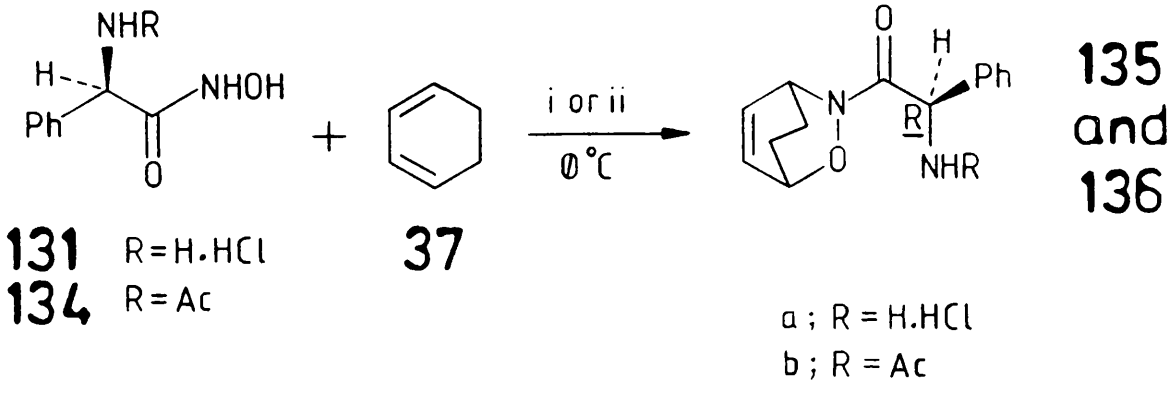




Scheme 24

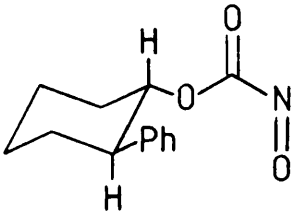


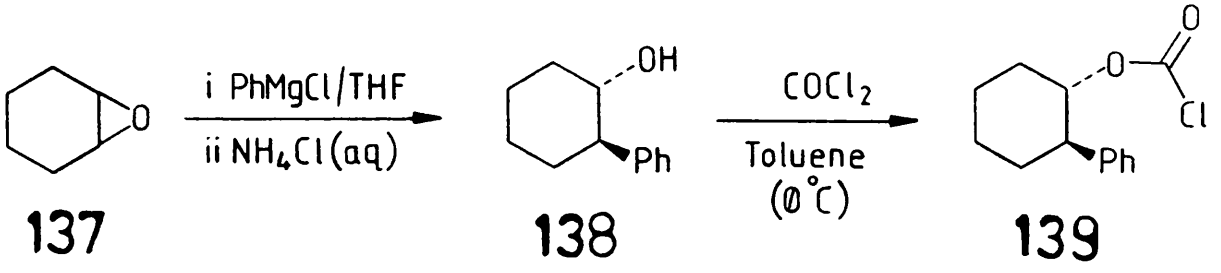
Scheme 25



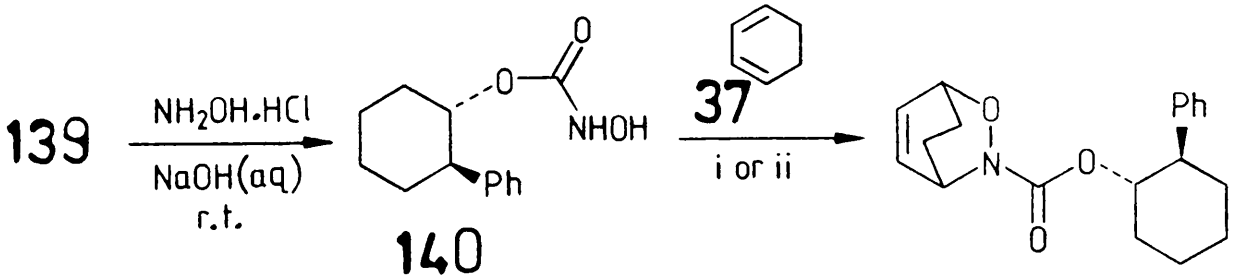
Scheme 26 i EtOAc / $NaIO_4$ / H_2O (pH 6)
ii Et_4NIO_4 / EtOAc

141





137 138 139

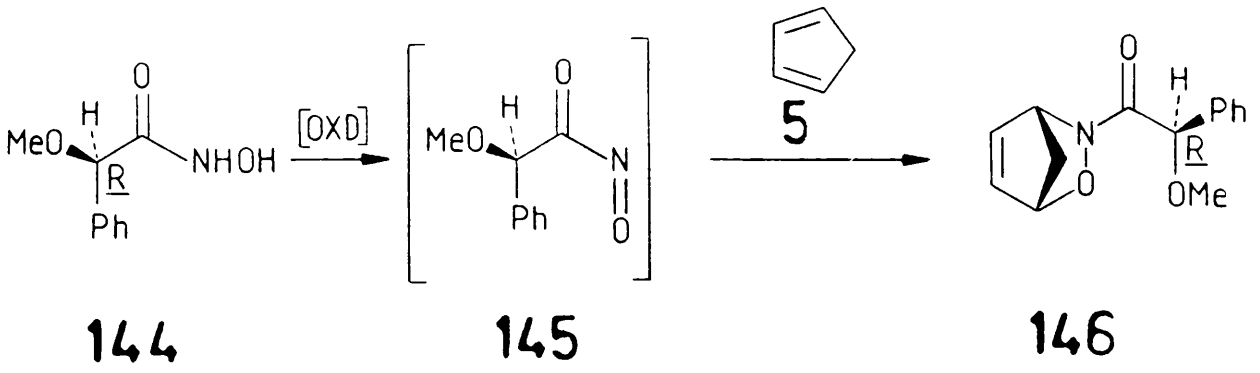


139 140 142 and 143

Scheme 27 i EtOAc/$NaIO_4$/H_2O (0°C)
ii Et_4NIO_4/CH_2Cl_2 (0 and -78°C)

out at 0 ^{o}C with both the single- and two-phase oxidizing systems. Proton NMR spectroscopy revealed signs of the diastereoisomeric cycloadducts **142** and **143**, and, in addition, significant amounts of impurities. The reaction was repeated at -78 ^{o}C (Et_4NIO_4/CH_2Cl_2), then giving a cleaner mixture of the adducts **142** and **143** in a ratio of *ca.* 3.56:1, corresponding to a modest d.e. value of 56%.

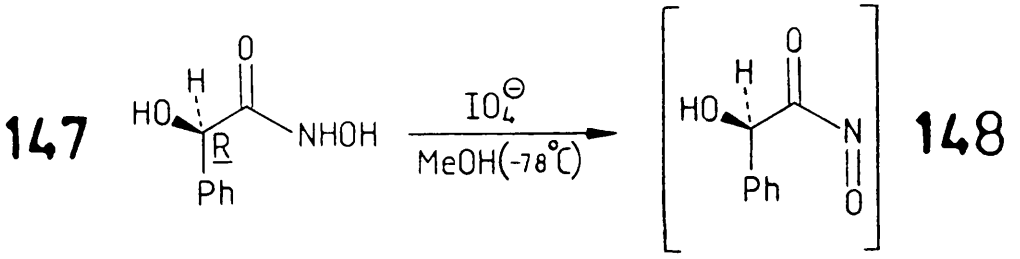
A similar study to Kirby and Nazeer's work with the mandelic nitrosocarbonyl derivatives[26] has been carried out by Miller *et al.*[28a]. The (*R*)-*O*-methylmandelic derivative **144** was oxidized to the nitrosocarbonyl dienophile **145** (Scheme 28) using a variety of different oxidizing agents, at various reaction temperatures, to yield a pair of the diastereoisomeric cycloadducts, the major isomer of which was shown, by X-ray crystallography, to have the structure **146**. The highest ratio of diastereoisomers obtained was *ca.* 5.4:1, with tetraethylammonium periodate and methanol at -50 ^{o}C, in favour of the isomer **146**. The (*R*)-mandelic acid derivative **147** was then oxidized in the presence of both cyclopentadiene **5** and cyclohexa-1,3-diene **37** at -78 ^{o}C (Scheme 29). The major isomers of the derived cycloadducts were, respectively, **149** and **150**. The relative configuration of **149** was determined by methylation of the crude reaction mixture, thus allowing stereochemical correlation with the cycloadduct **146** (Scheme 28); the absolute configuration of **150** was determined by methanolysis (Scheme 29) of the reaction mixture containing **150** to provide a sample of the optically active oxazine **107**, of known[24b] absolute configuration. The ratio of the diastereoisomers was *ca.* 7:1 in both cases; thus the diastereoselectivity was greater than that obtained for the *O*-methylmandelic derivative. These results are similar to those obtained by Kirby and Nazeer[26], with the difference that, in the former study, reactions carried out at lower temperatures produced bigger diastereoisomeric ratios and hence improved levels of asymmetric induction. In addition, the observed stereochemistry of the major diastereoisomers (**146**, **149** and **150**) is consistent with the approach geometry of the intramolecularly hydrogen-bonded dienophile **126** (Figure 10).

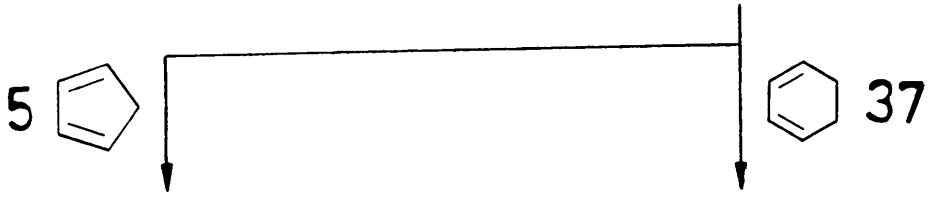


144 145 146

Scheme 28

(major isomer)

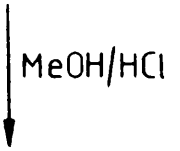


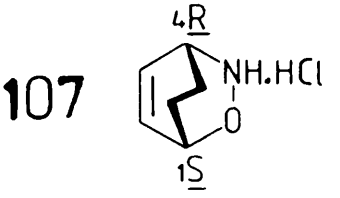


149 150

(major isomer)

(major isomer)





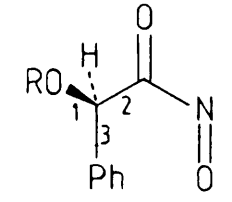
107

Scheme 29

In a following paper, Miller and Procter[28b] published a series of theoretical molecular mechanics calculations carried out to try and explain the diastereoselectivities observed in their own experimental work[28a] and that of others[26]. The dienophiles studied were the mandelic **148** and *O*-methylmandelic **145** nitrosocarbonyl derivatives shown in Figure 11.

In each case, some 150 different conformational geometries were examined, and the minimum energies determined for each. The conformations were generated by performing incremented rotations about each of the bonds 1,2 and 3, all the time keeping the carbonyl and nitroso groups in an *anti* arrangement, which was shown to be more stable than the corresponding *syn* arrangement. With the mandelic derivative **148**, the two lowest energy states had conformations involving an intramolecular hydrogen-bond between the nitroso oxygen and the hydroxyl hydrogen. The most stable conformation **148a** (Figure 11) had the carbonyl group in a near eclipsed arrangement with the methine proton. Assuming an *endo* approach of dienophile and diene, these results support the observed stereochemistries of the derived cycloadducts **151** with the dienes **5** and **37**. Similarly, in the case of the *O*-methylmandelic derivative **145**, the lowest energy conformation corresponded to that of **145a** (Figure 11), in which the phenyl and carbonyl groups are in a near eclipsed arrangement. Again, *endo* attack of the diene on the dienophile in this conformation leads to the experimentally observed stereochemistries of the adducts **151**.

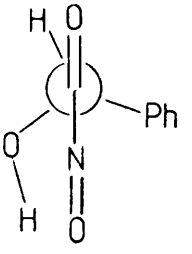
In two other papers[29a,29b], Procter and co-workers described the potential synthetic uses for the adducts obtained from stereoselective Diels-Alder reactions of chiral acylnitroso compounds. Miller and Procter[29a] outlined some potentially useful synthetic transformations of the cycloadduct **149** (Scheme 30) into a monocyclic system suitable for development into naturally occurring 'carbacyclic nucleosides'[30]. A stereoselective cycloaddition reaction of the *C*-nitrosocarbonyl dienophile **148** [derived from (*R*)-mandelic acid] with cyclopentadiene **5** could be used to obtain the desired isomer **149**.



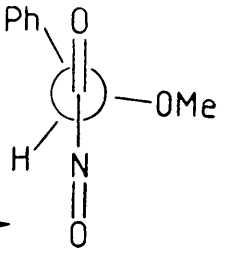
145 R = Me

148 R = H

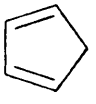
DIENE ATTACK →



148a →



145a



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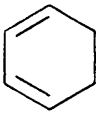
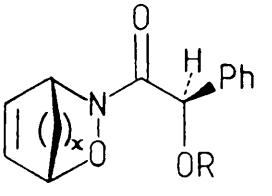


37

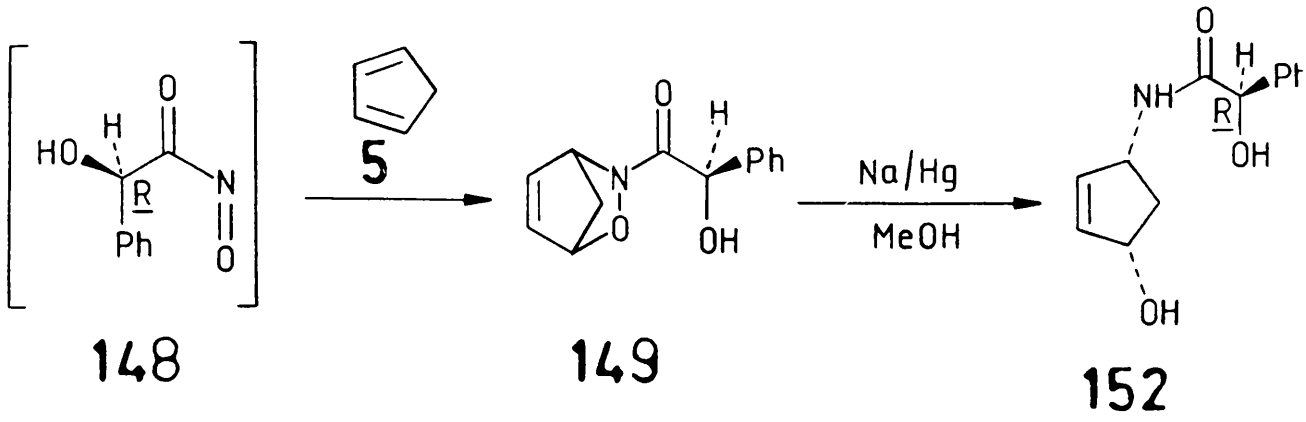


151

Major diastereoisomer

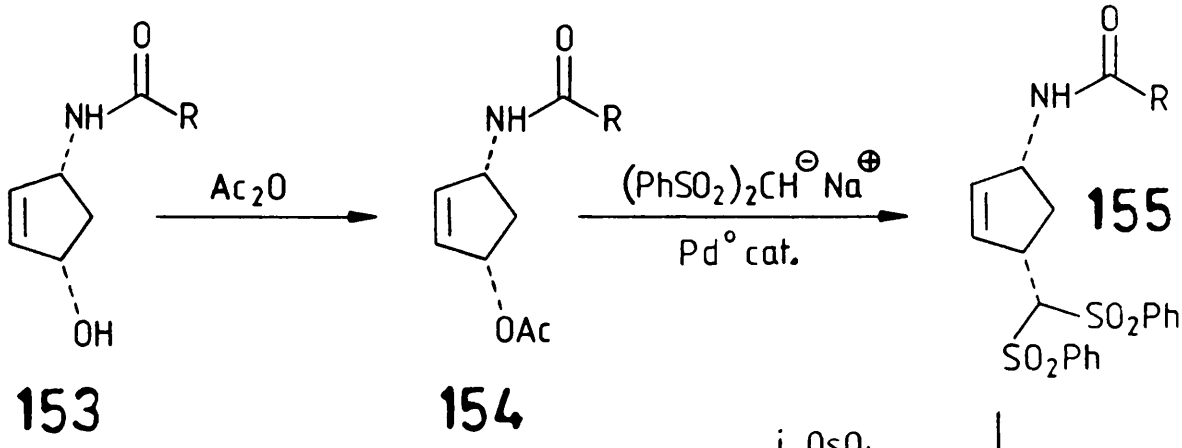
(x = 1,2)

Fig. 11

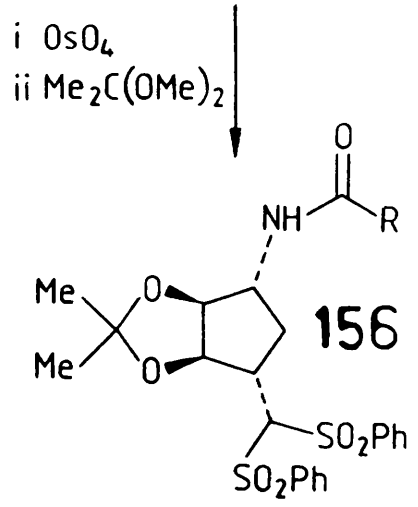


148 149 152

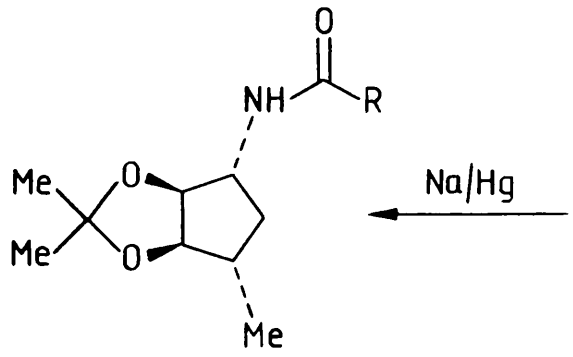
Scheme 30



153 154 155

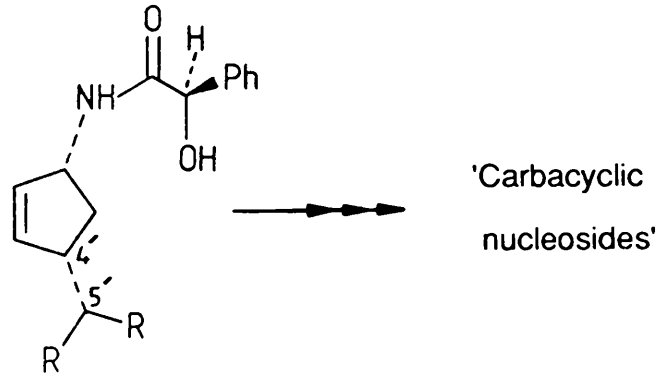


156



157

Scheme 31



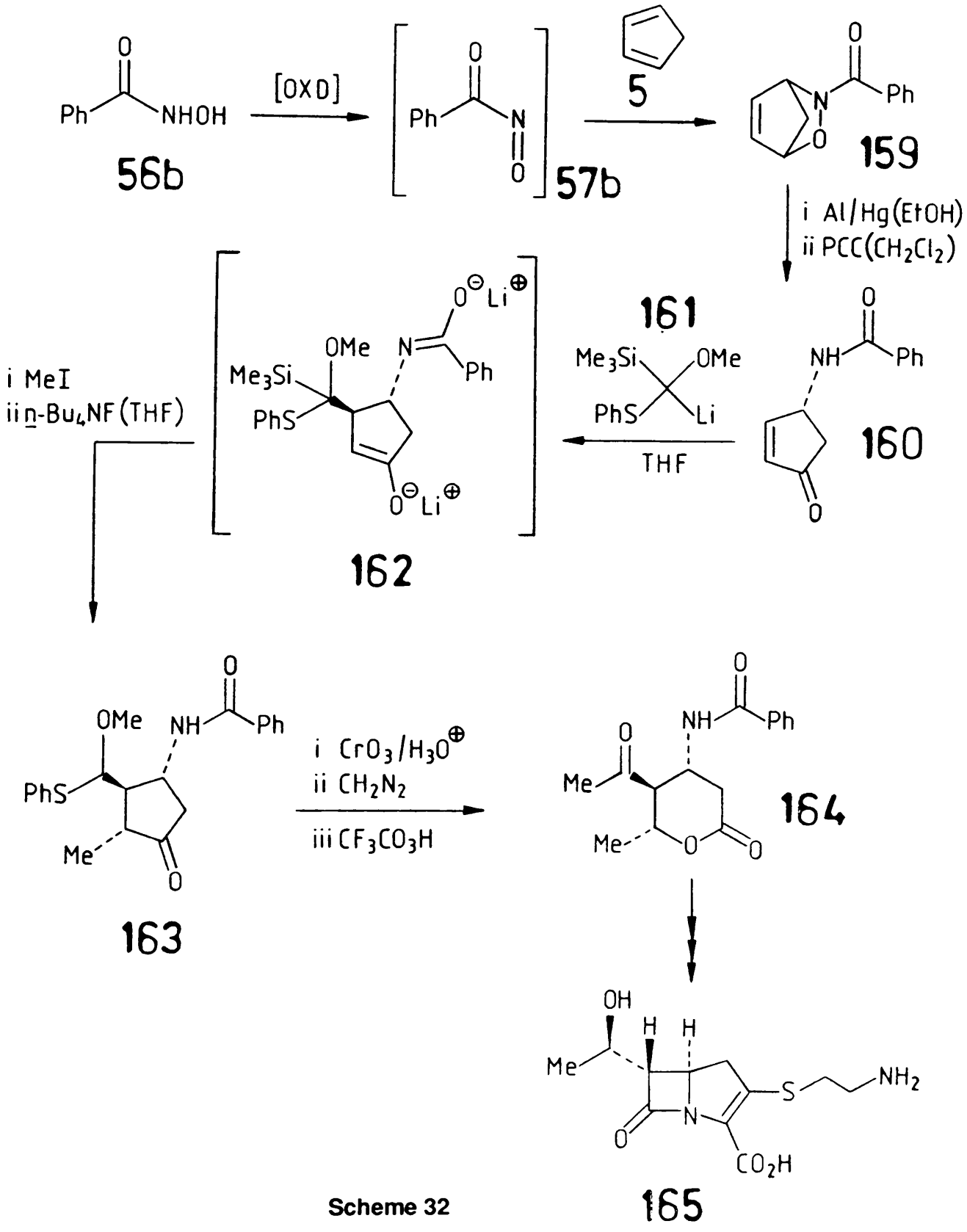
158

'Carbacyclic nucleosides'

Fig. 12

Reductive cleavage of the N-O bond would then give the monocyclic amido-alcohol **152** (with the amino group already protected as the mandelic amide). In order to convert **152** into a carbacylic nucleoside, a C(4')-C(5') bond would have to be generated (Figure 12). The authors outlined a method of achieving this; these studies were carried out on the racemic compounds **153** (Scheme 31), obtained from achiral, nitrosocarbonyl dienophiles *e.g.* nitrosocarbonylbenzene. The alcohol **153** was acetylated with acetic anhydride to give the allylic acetate **154**, which was converted into the sulphone **155** by a Pd(0) catalyzed displacement reaction [the latter step was carried out with both diethylmalonate and *bis*(phenylsulphonyl)methane anions]. *cis*-Hydroxylation of **155** with osmium tetroxide produced a diol which was protected as its acetonide **156**. The remaining step involved the reduction of the sulphone **156** into the acetal **157**, which possessed a suitable framework for further elaboration into nucleoside derivatives[31].

In the second paper, Morley *et al.*[29b] reported a new, alternative route to the synthesis of carbapenems. Initial studies employed achiral *C*-nitrosocarbonyl dienophiles to gauge the suitability of the reaction sequence. In this way, use was made of the cycloaddition reaction (Scheme 32) of nitrosocarbonylbenzene **57b** with cyclopentadiene **5** as an initial step in the synthesis of the *N*-benzoyl lactone **164**, the latter being an important intermediate in the *Merck* synthesis of the carbapenem, thienamycin **165**[32]. The nitrosocarbonyl species **57b** was generated by the oxidation of benzohydroxamic acid **56b**, in the presence of cyclopentadiene **5**, to afford the racemic, bicyclic adduct **159**. Reductive cleavage of the N-O bond to the amido-alcohol, followed by oxidation with pyridinium chlorochromate, gave the enone **160**. The conjugate addition to the double bond was achieved by treating the enone **160** with an excess of the anion **161** to give the intermediate dienolate **162**, which was methylated with methyl iodide. Quenching of the reaction mixture with tetrabutylammonium fluoride produced the cyclopentanone **163**, with the desired relative stereochemistry (only a small amount, *ca.* 11%, of the *cis*-methylated stereoisomer was obtained). Oxidation of the CH(SPh)(OMe) side-chain of **163** with chromic acid, followed by esterification with

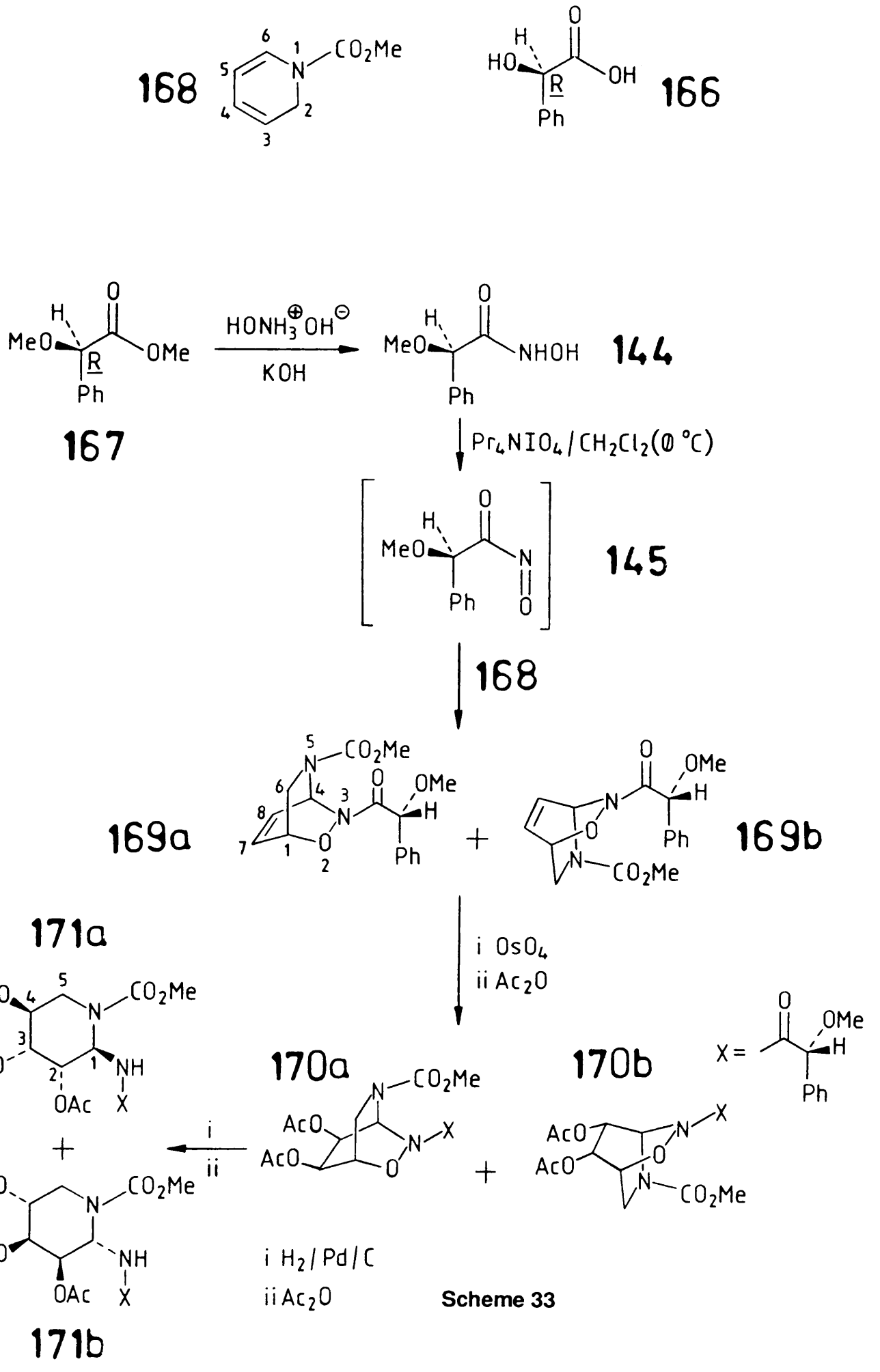

Ph
NHOH
[OXD]
Ph
N
O
57b
5
N
O
Ph
159
i Al/Hg(EtOH)
ii PCC(CH_2Cl_2)
NH
Ph
O
160
Me_3Si
OMe
PhS
Li
THF
161
i MeI
ii n-Bu_4NF(THF)
OMe
N
Ph
Me_3Si
PhS
$O^{\ominus}Li^{\oplus}$
162
OMe
NH
Ph
PhS
Me
O
163
i $CrO_3/H_3O^{\oplus}$
ii CH_2N_2
iii CF_3CO_3H
NH
Ph
Me
Me
O
164
OH
H
H
Me
S
NH_2
N
O
CO_2H
165

Scheme 32

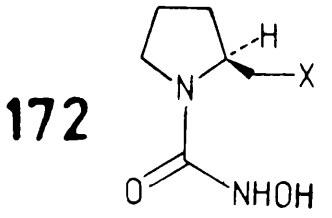
diazomethane, gave a cyclopentanone ester which was ring-expanded with trifluoroperacetic acid to give the desired product, the lactone derivative **164**.

As part of studies concentrating on the synthesis of diamino-dideoxylyxose derivatives[33], Defoin *et al.*[34] investigated the Diels-Alder reactions of a range of acylnitroso dienophiles with the conjugated diene, *N*-methoxycarbonyl-1,2-dihydro-pyridine **168** (Scheme 33). As an initial step to obtaining optically active amino sugars, asymmetric induction with a chiral dienophile was examined, namely that derived from the *O*-methyl ether of (*R*)-(-)-mandelic acid **166**. (*R*)-(-)-*O*-Methoxymethyl mandelate **167** was converted (Scheme 33) into the hydroxamic acid **144** by treatment with hydroxylamine. The hydroxamic acid **144** was then oxidized with tetrapropylammonium periodate to give the transient nitrosocarbonyl species **145**, which was trapped *in situ* with *N*-methoxycarbonyl-1,2-dihydro-pyridine **168** to afford a mixture of the diastereoisomeric adducts **169a** and **169b** (the cycloaddition reaction proceeded regioselectively to give the so-called 'inverse' adducts). The ratio of the cycloadducts was found to be *ca.* 3:2, but the diastereoisomers could not be distinguished. The asymmetric induction in this reaction was consequently poor, d.e. 20%. The adducts **169a** and **169b** were then converted into the bicyclic, acylated *cis*-diols **170a** and **170b** with osmium tetroxide (cat.) and then acetic anhydride (*cis*-hydroxylation proved to be stereospecific, leading to the exclusive formation of the '*anti*'-diols). Finally, conversion to the diastereoisomeric, optically active aminolyxose derivatives **171a** and **171b** was achieved by hydrogenolysis (Pd/C) of the diacetates **170a** and **170b**, followed by the reaction of the resultant alcohols with acetic anhydride to produce the final products. It was not possible to determine the absolute configurations of **171a** and **171b**.

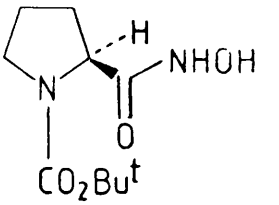
The same research group, Brouillard-Poichet *et al.*[35], have investigated the cycloaddition reactions of a series of optically active *N*- and *C*-nitrosocarbonyl dienophiles obtained from *L*-proline (Scheme 34). The hydroxamic acids prepared included the *N*-hydroxyurea series **172a-d**, each compound of which having a different


168
166
167
144
145
169a
169b
171a
171b
170a
170b
HONH3 OH
KOH
Pr4NIO4 / CH2Cl2 (0 °C)
i OsO4
ii Ac2O
i
ii
i H2 / Pd / C
ii Ac2O
X =

Scheme 33

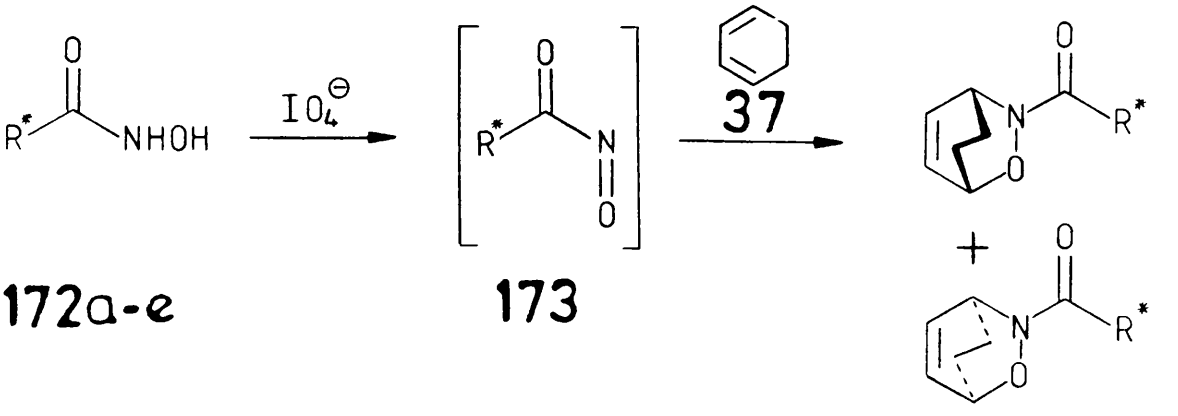


172



172e

a ; X = OH
b ; X = OMe
c ; X = NHPh
d ; X = CO_2Me



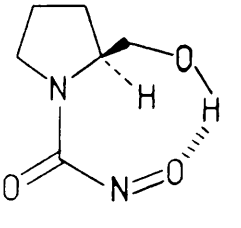
172a-e

173

174/175 †

† which isomer is which is unknown

Scheme 34



173a

Fig. 13

CH_2X side-chain attached to the 2-position of a proline ring, and the structural variant **172e** in which the hydroxamic acid portion was attached to the 2-position of a *N-tert*-butoxycarbonylproline ring. Each of the compounds **172a-e** was oxidized to the corresponding nitrosocarbonyl dienophile **173** and trapped with cyclohexa-1,3-diene **37** to give, in every case, a pair of diastereoisomers, **174** and **175**, formed in unequal amounts. The ratios of the **174/175** cycloadducts were estimated by ^{13}C NMR spectroscopy, and the d.e. values calculated to be 52, 68, 64, 54 and 20% for, respectively, the adducts **172a-e**. Thus, the highest d.e. value was obtained with the nitrosoformamide **173b** (68%) and the lowest with the *C*-nitrosocarbonyl derivative **173e** (20%). In the nitrosoformamides **173a-d**, there is hindered rotation about the N(1)-CO bond, whereas in **173e** there is free rotation about the C(2)-CO bond. The authors believe that the structural rigidity found in the former series of dienophiles is the likely explanation for the observed asymmetric induction. The authors have also noted the relatively low d.e. value obtained with the dienophile **173a**, and have referred to the intramolecular hydrogen-bonding idea put forward by Kirby[26]. If H-bonding were to take place in **173a**, however, it would involve an unfavourable 8-membered ring (Figure 13). Hydrogen-bonding aside though, steric factors may be solely responsible for the lesser induction obtained with **173a**, as the X groups in **173b-d** are larger and bulkier than the hydroxyl group in **173a**.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Introduction

Past work involving the Diels-Alder reactions of acylnitroso compounds has utilized a wide variety of dienes of differing chemical reactivity and structure. Examples of dienes used in previous synthetic work have already been reviewed, and the corresponding cycloadducts are displayed in Figure 4.

So far, no example of a simple, 1-substituted butadiene has been studied. The simple possible example is penta-1,3-diene ('piperylene'). This molecule can exist as two geometrical isomers, one with the methyl group in the *trans* position [the (*E*)-isomer, **111**] and the other with the methyl group *cis* [the (*Z*)-isomer, **112**]. Pure samples of both isomers are readily available, commercially, as is also a mixture of the two isomers. At room temperature, both isomers exist as clear, colourless, volatile liquids; boiling points differ by only *ca.* 2 ^{o}C, that of the (*E*)-isomer being 42 ^{o}C, and of the (*Z*)-isomer, 44 ^{o}C.

It was decided to investigate asymmetric induction with chiral acylnitroso compounds using piperylene as the simplest alkylbutadiene able to give a chiral oxazine ring. A mixture of regioisomers was expected, and it was of interest to compare the extent of asymmetric induction when the methyl group was close to or distant from the chiral acyl group. It is important to point out that, unlike typical dienophiles containing C=C, *endo* and *exo* modes of attack by acylnitroso compounds will lead to identical products, because the nitrogen of the oxazine rings is not a chiral centre. However, as discussed later, any asymmetric induction arising from *endo* attack may differ in both magnitude and configurational sense from that arising from *exo* attack. Preliminary experiments with nitrosocarbonyl-methane and -benzene were carried out to develop suitable reaction conditions and to gauge the regioselectivity to be expected with chiral acylnitroso dienophiles.

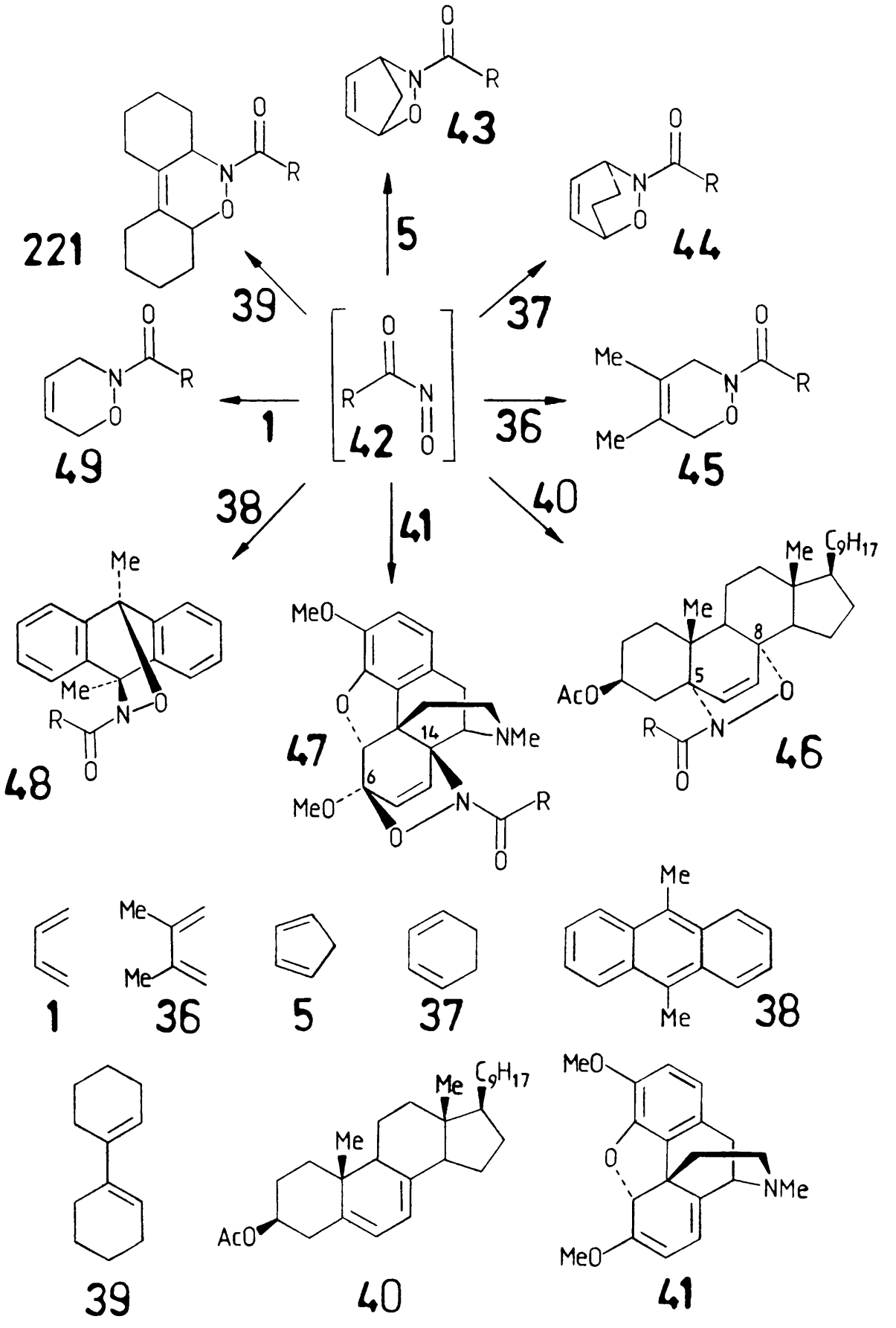
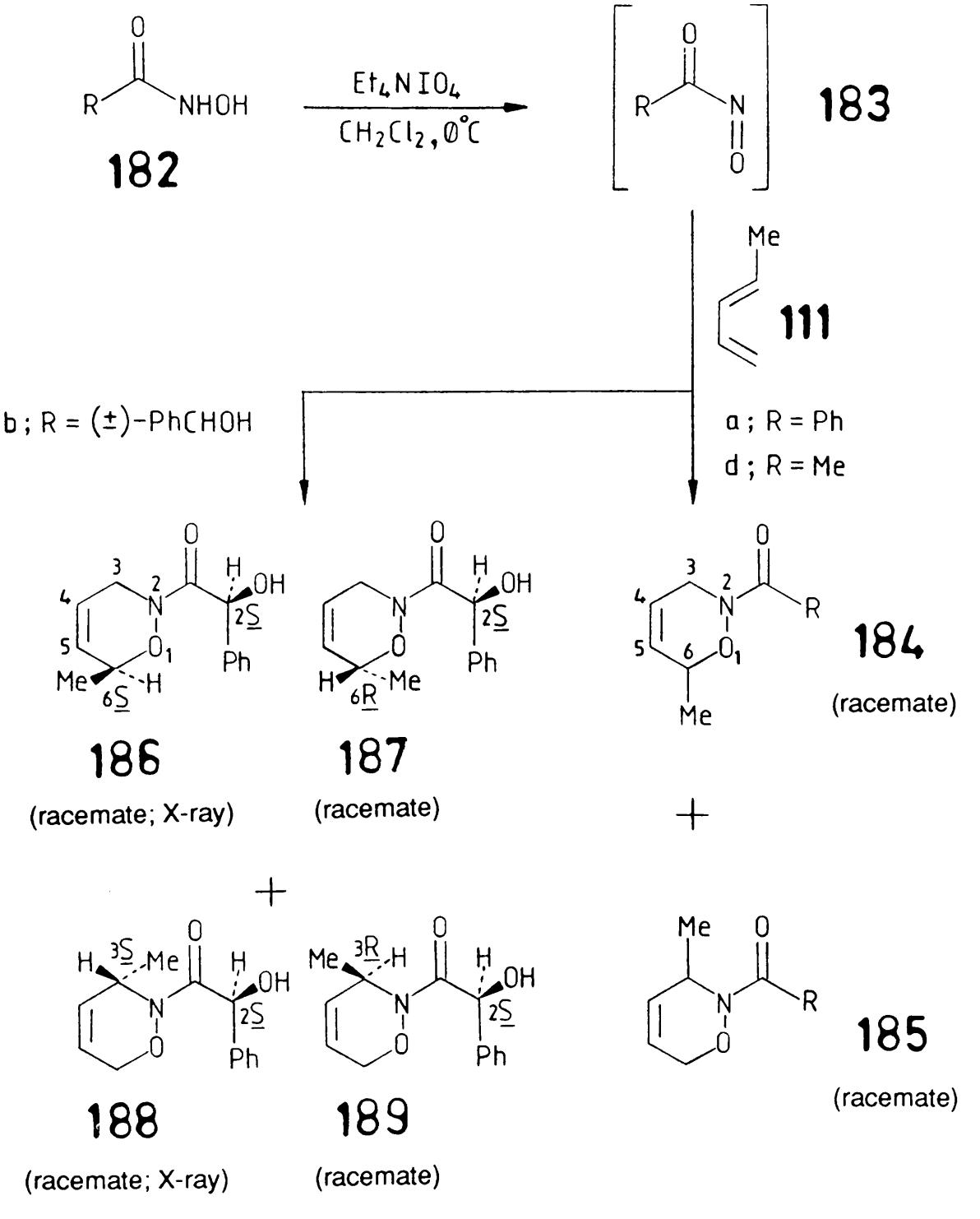


Fig. 4 Cycloadducts from *C*-nitrosocarbonyl compounds

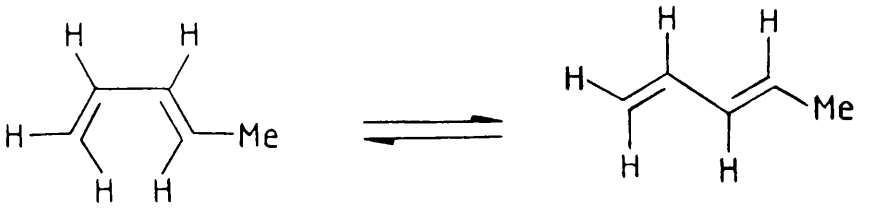
We were provided with a generous supply of piperylene by Mr. J. H. Young (*Synthetic Chemicals Ltd.*). This was a mixture of (*Z*)- and (*E*)-isomers, but it was expected that the major (*E*)-isomer would be much the more reactive of the pair. Therefore, no attempt was made to separate the isomers or use the more expensive, pure (*E*)-isomer. This piperylene mixture was determined from proton and carbon NMR studies to be an approximate 1:2.36 (30:70) ratio of the geometrical isomers, with the (*E*)-isomer **111** as the principle component of the mixture. The major isomer of the mixture was identified by examination of the two 4-H signals in the proton NMR spectrum. The 4-H signal of the (*E*)-isomer showed the *trans* coupling constant, *J* 14.9 Hz, whereas the (*Z*)-isomer showed the smaller *cis* coupling constant, *J* 10.7 Hz. See Tables 2 and 4 for a summary of, respectively, proton and carbon NMR chemical shifts for both isomers. See, also, Table 3 for a list of proton coupling constants. A selection of the dienes' physical properties is presented in Table 5.

The achiral acylnitroso dienophile, nitrosocarbonylmethane (MeCONO) **183d**, can react with the unsymmetrically substituted butadiene, piperylene **111**, to give, in principle, a pair of regioisomers, *viz.* the 3-methyl **184d** and 6-methyldihydro-oxazine **185d** isomers (Scheme 38). Of course, with this *achiral* dienophile attack on the two faces of the diene will proceed at equal rates and lead to racemic mixtures. Because of stereoelectronic and steric effects of the piperylene methyl group the regioisomers will be produced in unequal amounts.

As mentioned before, we shall assume that the (*E*)-isomer of piperylene, the major isomer of the mixture, reacts so much faster than the (*Z*)-isomer that the latter has little, if any, effect on the stereochemical composition of the reaction mixture, when the mixture of dienes is used in a large excess. The *s-cis* conformation of the (*Z*)-isomer, required for a concerted cycloaddition, is sterically much more hindered than that of the (*E*)-isomer (Figure 14). The assumption is fully justified by literature reports on the relative reactivity of the geometrical isomers. Thus, Diels-Alder cycloaddition reactions


R
NHOH
182
Et_4NIO_4
CH_2Cl_2, 0°C
R
N
O
183
Me
111
b ; R = (±)-PhCHOH
a ; R = Ph
d ; R = Me
186
(racemate; X-ray)
187
(racemate)
184
(racemate)
188
(racemate; X-ray)
189
(racemate)
185
(racemate)

Scheme 38



(*E*)-isomer **111**

(*Z*)-isomer **112**

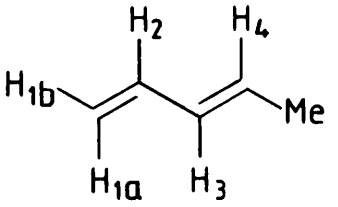
Fig. 14 *Cisoid* (*s-cis*) (left) and *transoid* (*s-trans*) (right) forms of (*E*)- and (*Z*)-penta-1,3-diene

Table 2 ^{1}H NMR Spectra δ (200 MHz; $CDCl_3$) of (*E*)-penta-1,3-diene **111**, and (*Z*)-penta-1,3-diene **112**.

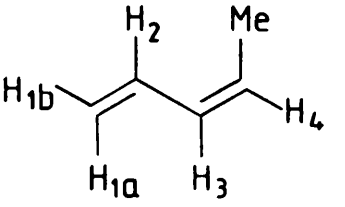
	Protons					
Isomer	Me	1b-H	1a-H	4-H	3-H	2-H
(*E*)	1.78 (d)	4.96 (dm)	5.09 (dm)	5.73 (dqm)	6.09 (ddm)	6.33 (ddd)
(*Z*)	1.78 (d)	5.12 (dm)	5.20 (dm)	5.54 (dqm)	6.04 (ddm)	6.69 (dddd)

Table 3 Selection of coupling constants for (*E*)- and (*Z*)-penta-1,3-diene.

	J / Hz					
Isomer	*J* (Me,4)	*J* (3,4)	*J* (2,4)	*J* (2,3)	*J* (1a,2)	*J* (1b,2)
(*E*)	6.7	14.9	*ca.*0	10.2	16.9	10.1
(*Z*)	7.1	10.7	1.1	10.0	17.5	12.4

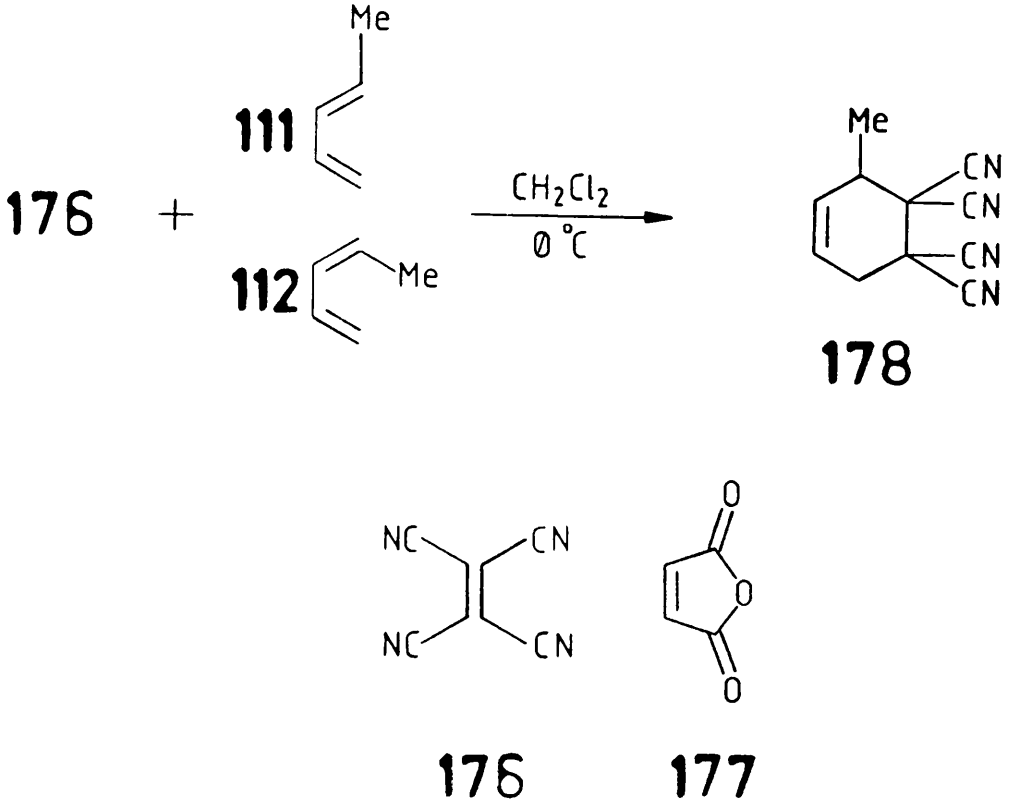


(*E*)-isomer **111**



(*Z*)-isomer **112**

of the (*E*)- and (*Z*)-isomers of piperylene have been reported by several groups[37,38]. Among them, Rucker *et al.*[37] have made a kinetic study of the cycloaddition reactions of a series of isomeric, substituted buta-1,3-dienes (including piperylene) with the dienophiles, tetracyanoethylene **176** and maleic anhydride **177**. It was found that the (*E*)-isomer of piperylene **111** reacted *ca.* 46,000 times faster than that of the (*Z*)-isomer with tetracyanoethylene **176** (Scheme 35). Maleic anhydride **177** did not react cleanly with the (*Z*)-isomer **112**; at high temperatures (*ca.*100 ^{o}C) only a low yield of the corr-



176 + 111/112 : k(**111**) = 0.175 l mol^{-1} s^{-1}

k(**112**) = 3.83 X 10^{-6} l mol^{-1} s$^{-1'}$

k(**111**)/k(**112**) = *ca.* 46,000

Scheme 35 Rates of the Diels-Alder reactions of TCNE with *cis*- and *trans*-piperylene

Table 4 ^{13}C NMR Spectra δ (50 MHz; $CDCl_3$) of (*E*)-penta-1,3-diene **111**, and (*Z*)-penta-1,3-diene **112**.

	Carbons				
Isomer	C-5	C-1	C-4	C-3	C-2
(*E*)	17.9	114.3	129.7	132.3	137.2
(*Z*)	13.2	116.5	126.7	130.1	132.0

Table 5 A selection of physical data[36a] on (*E*)-penta-1,3-diene **111**, and (*Z*)-penta-1,3-diene **112**.

Isomer	m.p./°C	b.p./°C[a]	ρ/gcm^{-3}	η_D[b]	Flash pt./°C
(*E*)	-87	42	0.683	1.4300	-28
(*Z*)	-141	44	0.691	1.4371	-28

[a]b.p. at 760 mm [b]refractive index (20 °C)

esponding cycloadduct was obtained[39]. Therefore, the assumption that the (*Z*)-isomer of piperylene should play little (if any) part in the reactions of nitrosocarbonyl compounds with a mixture of the piperylene isomers, is a reasonably valid one to make. The Diels-Alder reactions of the isomers of piperylene have been reviewed by Fringuelli and Taticchi[40]. The general chemical and physical properties of piperylene are described in the relevant sections of "Diene Synthesis" by Onishchenko[41].

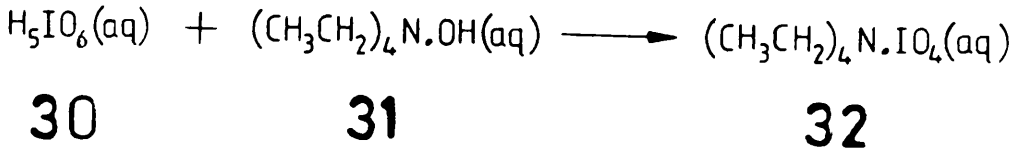
In all the Diels-Alder reactions carried out with nitrosocarbonyl compounds, a large excess of the piperylene was used (typically, 10 mol equivs.) to ensure there was a plentiful supply of the (*E*)-isomer available to participate in the cycloadditon reaction.

2.2 Cycloadducts from acetohydroxamic acid and piperylene.

Acetohydroxamic acid **182d** was prepared in the standard way by the reaction of ethyl acetate **181d** with hydroxylamine hydrochloride (1 mol equiv.) in the presence of 10 M aqueous sodium hydroxide, to yield, after work up, the product as a white solid in 19% yield (Scheme 37). IR analysis (Nujol mull) revealed a band at ν_{max} 1620 cm^{-1}, attributed to the carbonyl stretching frequency.

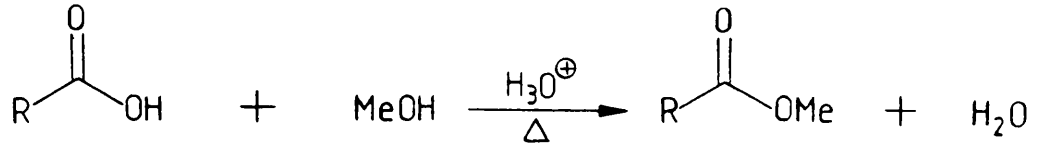
The acetohydroxamic acid **182d** was then added to a solution, in dichloromethane, of piperylene **111/112** (5 mol equivs.) and the oxidizing agent tetraethylammonium periodate, at 0 ^{o}C. Work up of the reaction mixture afforded a yellow, oily residue consisting of a mixture of the isomeric, racemic cycloadducts **184d** and **185d** in 44% total yield (Scheme 38). Two bands were observed in the IR spectrum (liquid film), one at ν_{max} 1650 cm^{-1}, and the other at ν_{max} 1670 cm^{-1}; both bands were of approximately the same intensity, and were assigned, separately, to the carbonyl group of each isomer. Low resolution mass spectrometry revealed a peak at *m/z* 141 (6.3%) consistent with the parent ion with molecular formula $C_7H_{11}NO_2$; the base peak at *m/z* 43 was indicative of the fragment [MeCO], formed by fission of the *N*-acetyl bond.

Preliminary proton NMR (90 MHz; $CDCl_3$) spectroscopy revealed what appeared to be a pair of very closely separated (< *ca.*2 Hz) upfield *Me*CH doublets and two closely separated (< *ca.*2 Hz) MeCO singlets, so it appeared that both regioisomers had been formed. In order to try and achieve a better separation of the signals, the spectrum was rerun in hexadeuteriobenzene, again at 90 MHz, this time to reveal a pair of relatively well separated (*ca.* 12 Hz) *Me*CH doublets and two slightly separated (*ca.* 3 Hz) MeCO singlets. A 200 MHz spectrum was also run in hexadeuteriobenzene, and although most of the individual peaks for each isomer overlapped to some extent, all the expected signals were located and identified, including the *Me*CH doublets at δ 0.90 and δ 1.14, and the MeCO singlets at δ 1.91 and δ 1.95. The MeCO singlets were not



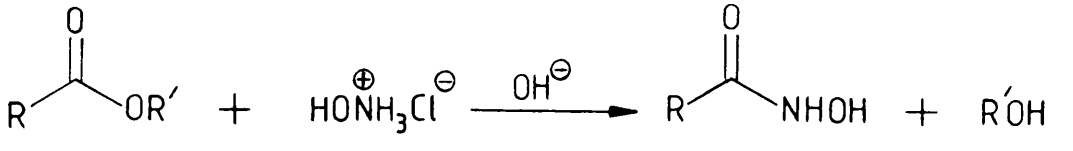
30 31 32

Scheme 5



179 180

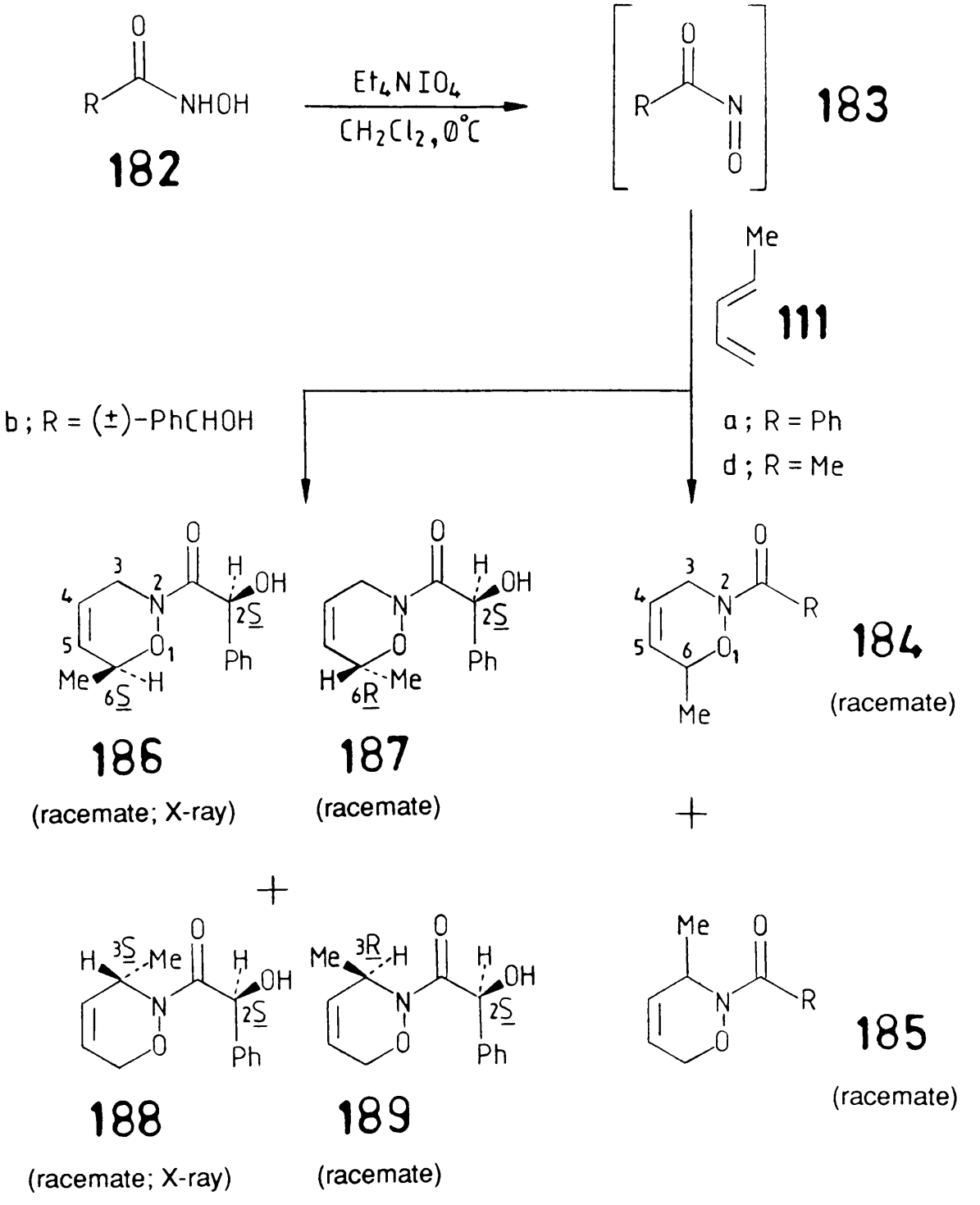
Scheme 36



181 182

Scheme 37 For **181a-c**, R' = Me; **181d**, R' = Et

a ; R = Ph
b ; R = (±)-PhCHOH
c ; R = (R)-(-)-PhCHOH
d ; R = Me


R
NHOH
182
Et4NIO4
CH2Cl2, 0°C
183
Me
111
b ; R = (±)-PhCHOH
a ; R = Ph
d ; R = Me
186
(racemate; X-ray)
187
(racemate)
184
(racemate)
188
(racemate; X-ray)
189
(racemate)
185
(racemate)

Scheme 38

sufficiently far apart enough for reliable integrals to be taken, but the *Me*CH signals were, and the ratio of the isomers was determined to be approximately 1:1. Details of proton chemical shifts (200 MHz; C_6D_6) and coupling constants for the isomers are given in Table 6.

Table 6 ^{1}H NMR Spectra δ (200 MHz; C_6D_6) of the cycloadducts **184d** and **185d** from acetohydroxamic acid **182d** and piperylene **111/112**. *J* values are in Hz.

*Me*CH	COMe	C*H*H	CH*H*	MeC*H*	4- and 5-H
0.90 (d) *J* 6.7	1.91 (s)	3.69 (dm) *J* 18.0	4.29 (dm) *J* 18.0	4.12 (m)	5.20-5.45 (2 X dm)
1.14 (d) *J* 6.7	1.95 (s)	3.71 (dm) *J* 14.9	3.96 (dm) *J* 14.9	4.78 (m)	5.20-5.45 (2 X dm)

N.b. Since the ratio of the cycloadducts **184d**:**185d** was *ca.* 1:1, the major and minor components of the mixture could not be sorted out. Each of the above quoted chemical shifts could belong to either **184d** or **185d**. The values in each column, therefore, are not listed in any particular order relating to which isomer they belong to.

Carbon NMR spectroscopy was used in an attempt to try and identify each regio-isomer. This was done by identifying the C-3 and C-6 carbon atom signals in the DEPT spectrum in order to establish whether the methyl group was on the 3- or 6-position of the oxazine ring. Assuming oxygen to cause a much greater downfield shift than nitrogen, then, with the methyl group on C-3, one would expect to see an upfield methine (CH) signal for C-3 and a downfield methylene (CH_2) signal for C-6. However, with the methyl group on C-6, then the reverse of the above pattern is expected, *i.e.* an upfield methylene signal for C-3 and a downfield methine signal for C-6. As was already shown by proton NMR spectroscopy, however, the isomers were formed in approximately equal amounts, and so, although the two sets of C-3 and C-6 signals

could easily be identified, the other signals (with the exception of those for the ring methyl carbons) could not be assigned to a specific, individual isomer. Table 7 lists the ^{13}C chemical shifts (50 MHz; C_6D_6) for both isomers.

Table 7 ^{13}C NMR Spectra δ (50 MHz; C_6D_6) of the cycloadducts **184d** and **185d** from acetohydroxamic acid **182d** and piperylene **111/112**.

3-Me	6-Me	COMe	C-3	C-6	C-4	C-5	COMe
17.5 **185d**	18.6 **184d**	19.9 20.2	41.5 **184d** 47.5 **185d**	69.4 **185d** 75.2 **184d**	122.3 123.0	128.3 128.9	168.5 169.4

N.b. In columns 3 & 6-8, the chemical shifts could not be assigned to a specific isomer.

No separation of the isomers was achieved on t.l.c. [one spot, R_f 0.53, ethyl acetate-light petroleum (1:1)]; no attempts were made to isolate and purify the individual isomers.

The conclusion to be drawn from this experiment is that piperylene appears to be a reasonably good trapping diene for nitrosocarbonylmethane. However, the dienophile showed little or no regioselectivity towards the diene. Discussion of the above results will be extrapolated on following analysis of the results of the next experiment with nitrosocarbonylbenzene, described in the following section.

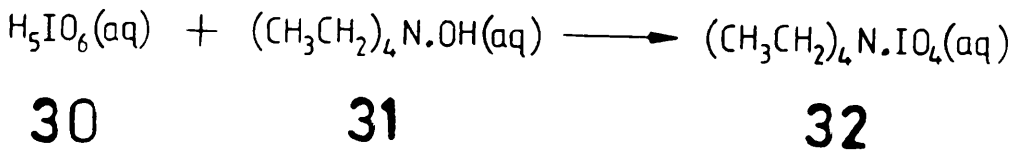
2.3 Cycloadducts from benzohydroxamic acid and piperylene.

In the previous section, details were given on the use of nitrosocarbonylmethane as a dienophile in a trial experiment with the diene, piperylene. From the analysis of the results, the conclusion was drawn that the dienophile did not exhibit any significant degree of regioselectivity towards the diene. It was therefore decided next to use nitrosocarbonylbenzene, PhCONO, an achiral dienophile possessing a larger and sterically bulkier group.

Methyl benzoate **181a** was prepared using a common esterification procedure, by refluxing benzoic acid **179a** in methanol (Scheme 36). The ester product was then used to prepare benzohydroxamic acid **182a** (Scheme 37) using the standard procedure for the preparation of hydroxamic acids, as briefly outlined in the previous chapter. The product was isolated as a pinkish solid in 27% yield (from the original ester). The IR spectrum (Nujol mull) showed a strong carbonyl absorption at ν_{max} 1625 cm^{-1}.

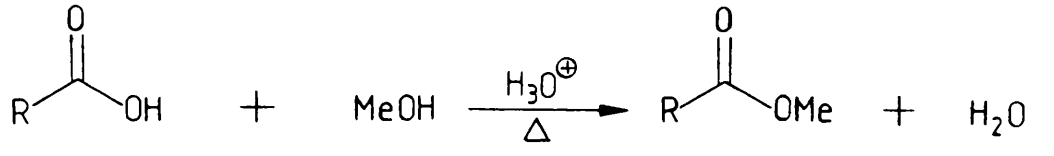
Benzohydroxamic acid **182a** was then added to a solution, in dichloromethane, of piperylene **111/112** and tetraethylammonium periodate (Scheme 38), to yield a yellow oil consisting of a mixture of the isomeric, racemic cycloadducts **184a** and **185a** (total yield, 58%). The IR spectrum showed two bands at ν_{max} 1645 cm^{-1} and ν_{max} 1665 cm^{-1} (the former band being the more intense), each due to the carbonyl absorption for, presumably, the individual isomers. Low resolution mass spectrometry gave a peak at *m/z* 203 (8.2%) due to the parent ion, consistent with the molecular formula $C_{12}H_{13}NO_2$. The base peak was found at *m/z* 105, and can be attributed to the fragment [PhCO], formed by fission of the *N*-benzoyl bond.

As before, the ratio of the isomers **184a** and **185a** was determined by ^1H NMR spectroscopy (200 MHz; $CDCl_3$). The spectrum showed the expected two sets of signals, one for each isomer. In particular, there were two, upfield, *Me*CH doublets at δ



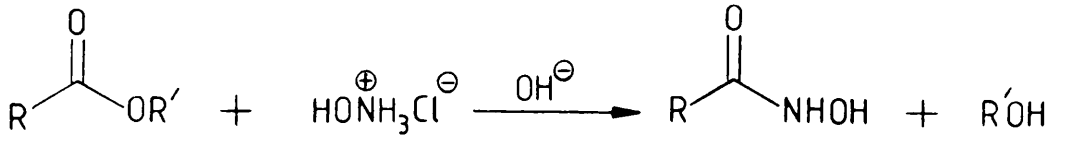
30 31 32

Scheme 5



179 180

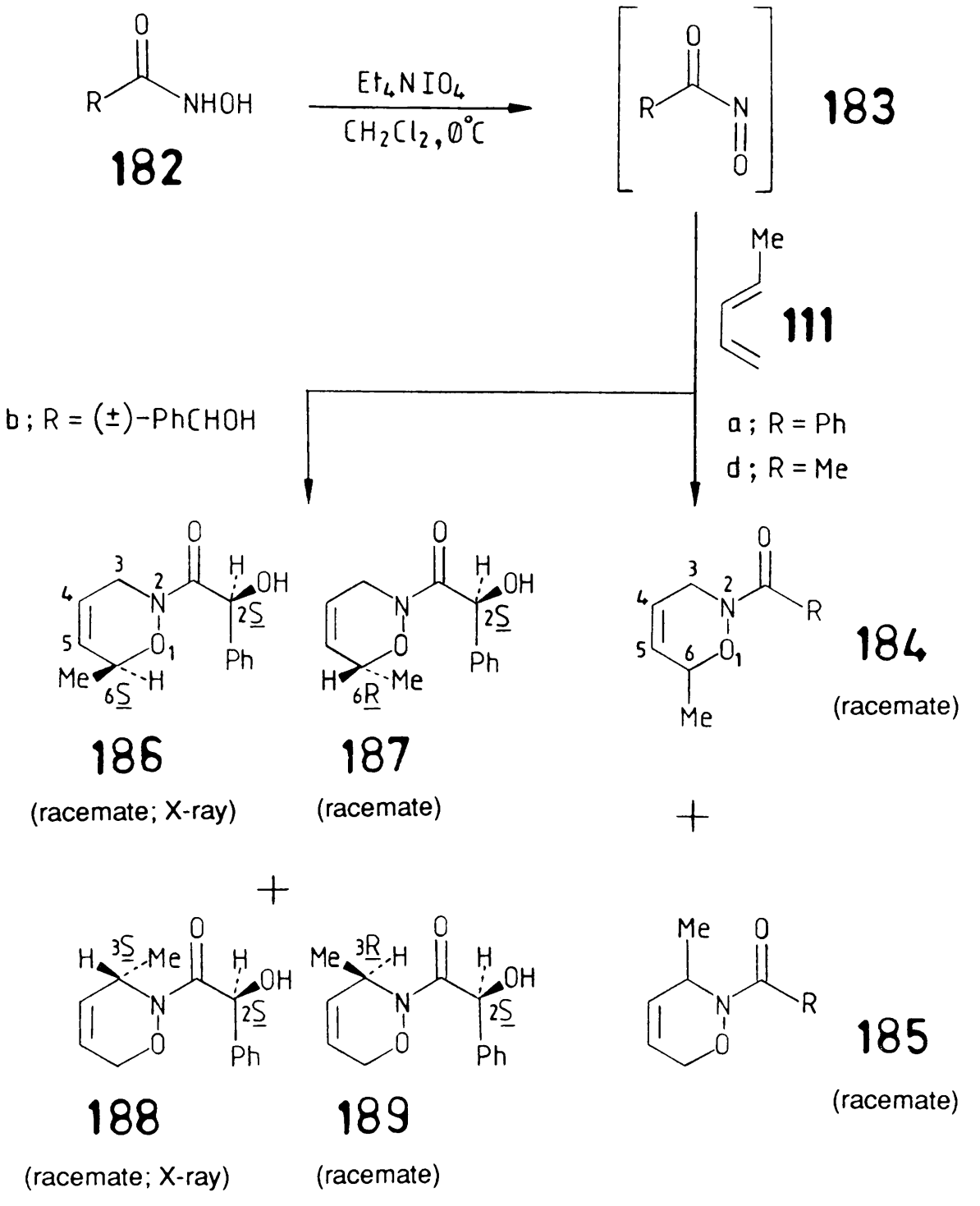
Scheme 36



181 182

Scheme 37 For **181a-c**, R' = Me; **181d**, R' = Et

a ; R = Ph
b ; R = (±)-PhCHOH
c ; R = (R)-(-)-PhCHOH
d ; R = Me


R
NHOH
182
Et_4NIO_4
CH_2Cl_2, 0°C
183
Me
111
b ; R = (±)-PhCHOH
a ; R = Ph
d ; R = Me
186
(racemate; X-ray)
187
(racemate)
184
(racemate)
188
(racemate; X-ray)
189
(racemate)
185
(racemate)

Scheme 38

1.11 and δ 1.39 which integrated, respectively, as approximately 2.8:1.0. ^{13}C NMR Spectroscopy (see paragraph below), showed that the major isomer of the mixture was the 6-methyldihydro-oxazine **184a**. Details of proton chemical shifts and coupling constants, for the two isomers, are given in Table 8.

Table 8 ^{1}H NMR Spectra δ (200 MHz; $CDCl_3$) of the cycloadducts **184a** and **185a** from benzohydroxamic acid **182a** and piperylene **111/112**. *J* values are in Hz.

	Protons					
Isomer	*Me*CH	C*H*H	CH*H*	MeC*H*	4- and 5-H	Ph-H
184a	1.11 (d) *J* 6.7	4.04 (dm) *J* 16.6	4.54 (dm) *J* 16.6	4.50 (m)	5.60-5.90 (2 X dm)	7.2-7.8 (5 X m)
185a	1.39 (d) *J* 6.7	4.14 (dm) *J* 15.3	4.45 (dm) *J* 15.3	4.87 (m)	5.60-5.90 (2 X dm)	7.2-7.8 (5 X m)

Using the arguments set out in the previous chapter, the major isomer of the mixture was identified by analysing the DEPT portion of the ^{13}C NMR spectrum (50 MHz; $CDCl_3$), by taking note of the positions, substitution (*i.e.* CH or CH_2) and relative intensities of the C-3 and C-6 signals. In this way, it was found that the 6-methyl isomer **184a**, was the major component of the mixture. ^{13}C Chemical shifts, for both cycloadducts, are summarised in Table 9. Note that the C-5 and phenyl signals have been omitted since these signals could not be fully assigned.

No separation of the isomers **184a** and **185a** could be achieved on t.l.c. Analytical t.l.c. [ether-light petroleum (1:1); double elution] gave two spots of R_f 0.45 (intense) and R_f 0.71 (very faint), but the latter spot was shown to be an impurity. No attempts were made to isolate and purify the cycloadducts.

Table 9 ^{13}C NMR Spectra δ (50 MHz; $CDCl_3$) of the cycloadducts **184a** and **185a** from benzohydroxamic acid **182a** and piperylene **111/112**.

	Carbons				
Isomer	*Me*CH	C-3	C-6	C-4	*C*OMe
184a	18.6	42.9	75.4	121.6	169.4
185a	17.8	48.9	69.7	122.6	168.8

N.b. The C-5 and phenyl-C & -CH signals are not listed since assignments are uncertain.

It is concluded that nitrosocarbonylbenzene shows a marked degree of regioselectivity towards the diene, piperylene, favouring the formation of the 6-methyl isomer **184a** over that of the 3-methyl isomer **185a**, by a factor of *ca.* 2.8:1.

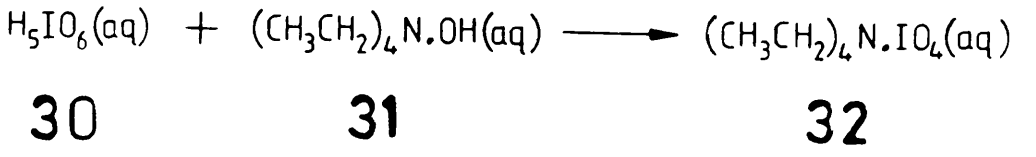
In the previous experiment, it was shown that nitrosocarbonylmethane showed no significant degree of regioselectivity towards piperylene. In contrast, nitrosocarbonylbenzene, having a bulkier phenyl group, gave a 2.8:1.0 mixture in favour of the 6-methyl isomer. This is consistent with steric repulsion between the phenyl group and the methyl group of piperylene leading to a reduction in the amount of the 3-methyl isomer **184b**. Although phenyl and methyl groups also have different electronic effects in the nitroso dienophiles, these would have to be relayed to the nitroso groups through the intervening carbonyl groups. It is likely therefore that these electronic differences would have little influence on the ratio of regioisomers.

2.4 Cycloadducts from (±)-mandelohydroxamic acid and piperylene.

When a chiral dienophile, such as the mandelic derivative **183b** (Scheme 38), is used attack on the enantiotopic faces of piperylene will, in general, occur at different rates. So each regioisomer will be formed as an unequal mixture of diastereoisomers. If a racemic dienophile is used, each diastereoisomeric product will be formed as a racemate.

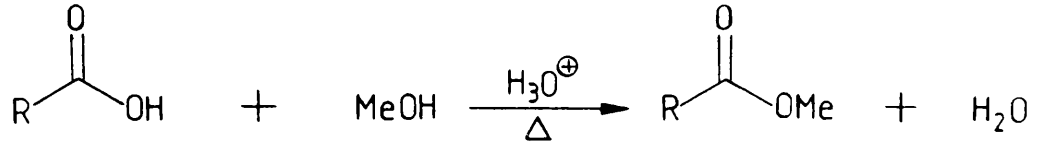
The previous two experiments have examined the reactions of piperylene with simple, achiral nitrosocarbonyl compounds. The reaction of piperylene with a chiral dienophile was then studied. Kirby and Nazeer[26] have recently investigated the asymmetric cycloaddition reactions of nitrosocarbonyl dienophiles derived from mandelic acid and other α-hydroxy acids, with the symmetric dienes cyclopentadiene and cyclohexa-1,3-diene. It was suggested that intramolecular hydrogen-bonding in the dienophile derived from mandelic acid may enhance asymmetric induction. Similar work has also been carried out, more recently, by Miller *et al.*[28a]. In the work done with cyclopentadiene and cyclohexadiene, a pair of diastereoisomers was obtained. With piperylene, however, regioisomers may also be formed. Racemic mandelic acid was chosen for the following experiment.

(±)-Mandelohydroxamic acid **182b** was prepared in the usual manner, by the reaction of methyl (±)-mandelate **181b** [prepared, in turn, from (±)-mandelic acid **179b** (Scheme 36)] with hydroxylamine hydrochloride and sodium hydroxide (Scheme 37). The product **182b** was obtained as a pinkish solid in 17% yield, m.p. 146-147 ^{o}C (from ethyl acetate-light petroleum; lit.[42] 146-147 ^{o}C). The IR spectrum showed a strong carbonyl absorption at ν_{max} 1640 cm^{-1}. ^{1}H NMR (90 MHz; CD_3SOCD_3) Spectroscopy revealed the expected signals of 3 OHs, 1 CH and 5 Ph protons.



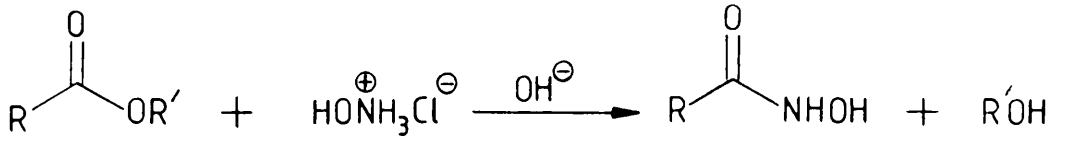
30 31 32

Scheme 5



179 180

Scheme 36



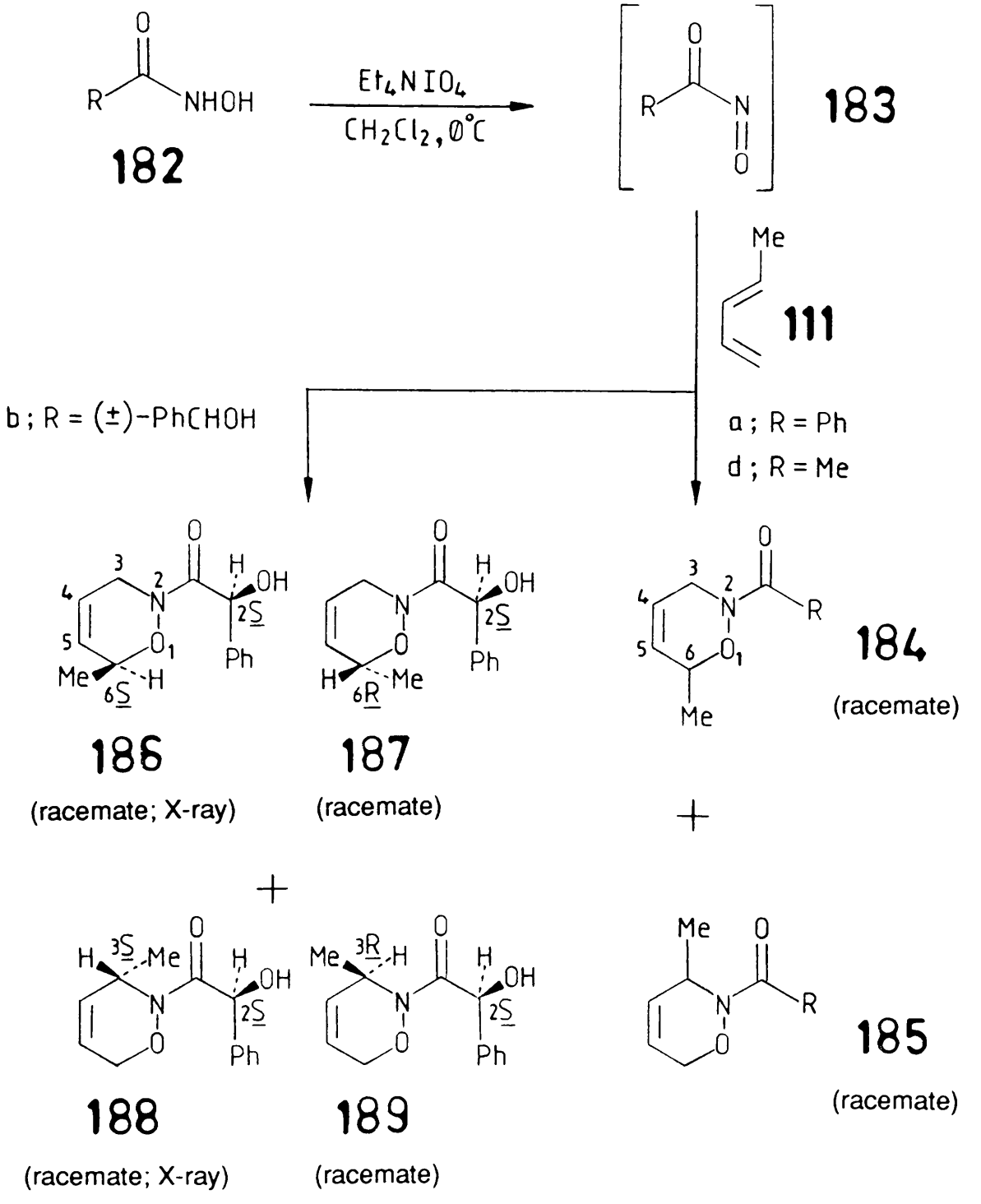
181 182

Scheme 37 For **181a-c**, R' = Me; **181d**, R' = Et

a; R = Ph
b; R = (±)-PhCHOH
c; R = (R)-(-)-PhCHOH
d; R = Me

(±)-Mandelohydroxamic acid **182b** was then added to a solution, in dichloromethane, of tetraethylammonium periodate and piperylene **111/112** (10 mol equivs.) at 0 °C. The usual work up afforded a crude reaction mixture, in the form of an orange-brown, sticky solid, consisting of the four isomeric, racemic cycloadducts **186**, **187**, **188** and **189**, in 42% total yield (Scheme 38). Preliminary proton NMR spectroscopy (200 MHz; $CDCl_3$) of a sample of the crude mixture, revealed 4, upfield, methyl doublets at δ 1.01, 1.16, 1.20 and 1.32, indicating the formation of the 4 diastereoisomers expected theoretically, *i.e.* 2 pairs of racemic, diastereoisomeric regioisomers. Analytical t.l.c. [ether-light petroleum (1:1); triple elution] of the crude mixture revealed three spots (hence a pair of the isomers appeared to be running together) of R_f 0.26, 0.44 and 0.55.

In an attempt to separate the individual isomers, the crude reaction mixture (*ca.* 490 mg) was chromatographed by conventional 'flash-column' techniques. A mixed solvent system of ethyl acetate-light petroleum was used in the hope of achieving a more efficient product separation. Pure light petroleum was used to give the first fraction collected (25 ml), each subsequent fraction (25 ml) being obtained with progressively more ethyl acetate. When the ratio of the solvents reached 1:1, this composition was used for the remainder of the experiment. T.l.c. [ether-light petroleum (1:1); triple elution] of each of the fractions 7-10 revealed, in each case, two spots of R_f 0.44 and 0.55. NMR studies revealed the spot of R_f 0.44 to be due to a diastereoisomer of the 6-methyldihydro-oxazine (*i.e.* **186** or **187**), while the spot of R_f 0.55 was shown to be due to a diastereoisomer of the 3-methyl cycloadduct (*i.e.* **188** or **189**). T.l.c. of each of the remaining fractions of interest, 11-13, revealed, in each case, only one spot of R_f 0.26. NMR studies confirmed the expected conclusion that this spot was due to two compounds, the diastereoisomeric partners to the two regioisomers found in the previous fractions (7-10). The total weight of material isolated from the column was *ca.* 400 mg, corresponding to a recovery of 82%.


R
NHOH
182
Et_4NIO_4
CH_2Cl_2, 0°C
183
Me
111
b ; R = (±)-PhCHOH
a ; R = Ph
d ; R = Me
186
(racemate; X-ray)
187
(racemate)
184
(racemate)
188
(racemate; X-ray)
189
(racemate)
185
(racemate)

Scheme 38

A colourless solid, m.p 113-117 ^{o}C, crystallised out of a deuteriochloroform solution (left in an NMR tube) of the combined contents of fractions 11-13. A sample was submitted for X-ray analysis in order to determine the relative configuration. This revealed the compound to be the cycloadduct **186** (for the X-ray crystal structure, see Figure 15). This fixed, by default, the configuration of the diastereoisomeric partner **187** (R_f 0.44) found in fractions 7-10. An elemental analysis of the crystalline cycloadduct **186** confirmed the molecular formula of $C_{13}H_{15}NO_3$. High resolution mass spectrometry gave a molecular mass measurement of *m/z* 233.1053 (3.7%) ($C_{13}H_{15}NO_3$ requires *M*, 233.2694); the base peak, *m/z* 99.0685, corresponded to C_5H_9NO. IR Spectroscopy revealed two bands in the carbonyl region, at ν_{max} 1650 cm^{-1} and ν_{max} 1670 cm^{-1} (the former being the more intense), and a hydroxyl absorption at ν_{max} 3470 cm^{-1}. Proton and carbon NMR spectra ($CDCl_3$) revealed the expected signals.

Fractions 7-10 were combined and dissolved in a small volume of dichloromethane. Light petroleum was gradually added, and, after a time, colourless crystals, m.p. 100-103 ^{o}C, formed. T.l.c. (R_f 0.55) and NMR work revealed the crystals to be one of the 3-methyl cycloadducts (*i.e.* **188** or **189**). A sample was submitted for X-ray analysis to determine the relative configuration, and it was found that the compound was the cycloadduct **188** (for the X-ray crystal structure, see Figure 16). This meant that the diastereoisomeric partner, found in fractions 11-13, was the cycloadduct **189** (R_f 0.26). As with **186**, an elemental analysis of the cycloadduct **188** was consistent with the molecular formula of $C_{13}H_{15}NO_3$. High resolution mass spectrometry gave a molecular mass measurement of *m/z* 233.1075 (4.1%); the base peak, *m/z* 84.0464, corresponded to C_4H_6NO. IR Spectroscopy revealed bands in the carbonyl region, at ν_{max} 1645 cm^{-1} and ν_{max} 1665 cm^{-1} (the former being the more intense), and a hydroxyl peak at ν_{max} 3450 cm^{-1}. Proton and carbon NMR spectra ($CDCl_3$) were as expected.

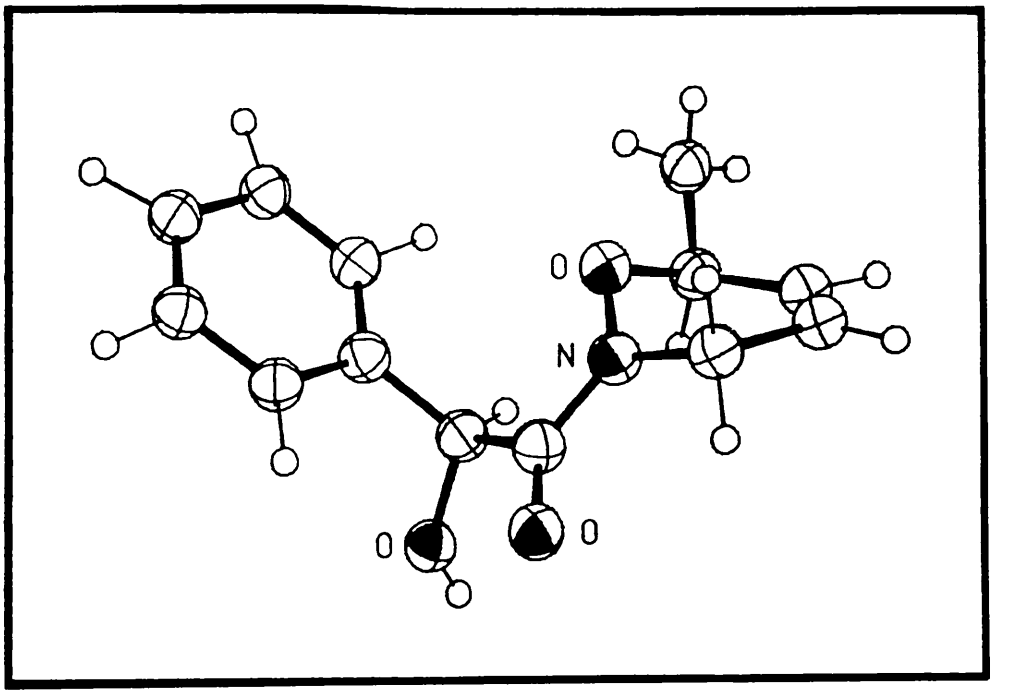


Fig. 15 X-Ray crystal structure of the cycloadduct **186**. Note on the oxazine ring that the methyl group appears to be axial.

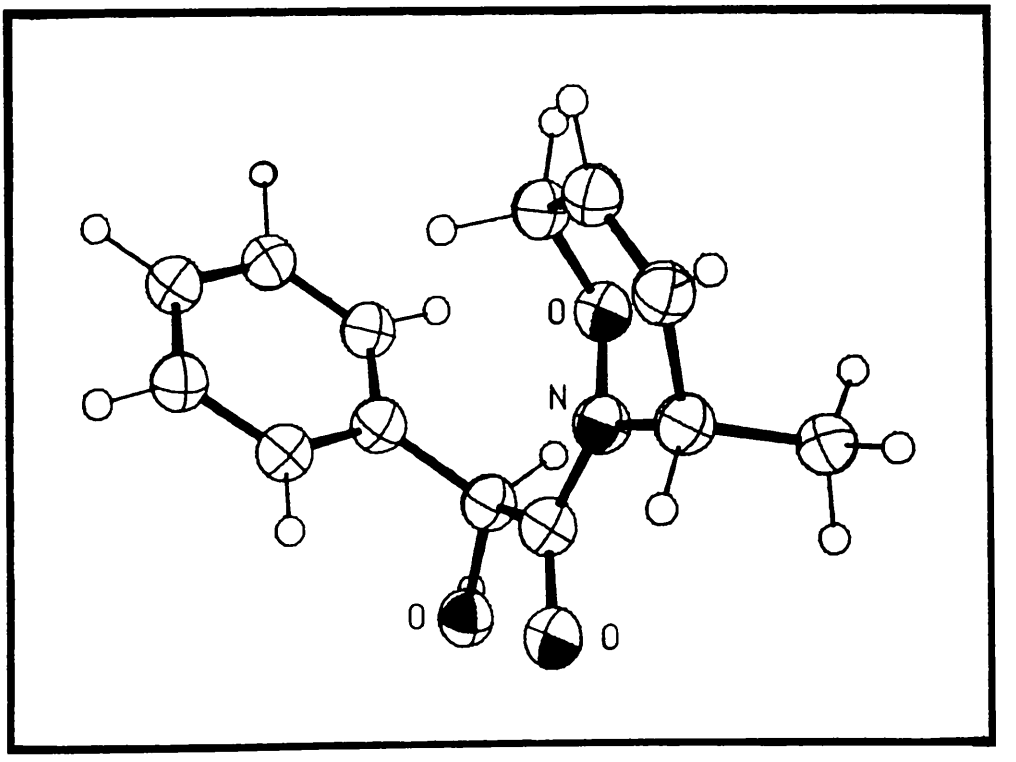


Fig. 16 X-Ray crystal structure of the cycloadduct **188**. Note that the oxazine ring appears boat-like in conformation, with an axial methyl group.

No attempts were made to isolate and purify the cycloadducts **187** and **189**. Proton and carbon NMR data ($CDCl_3$) were extracted from the spectra of the two mixtures of the cycloadducts (**187/188**, and **186/189**), obtained from the column chromatography experiment. Spectra of **187** and **189** were similar to those obtained for **186** and **188**, the only anomalous point being in the case of the proton spectrum of **187**, where an unusually low chemical shift (δ 3.21) was obtained for the ring methine proton (MeC*H*). This value is, on average, some 1.5 p.p.m. lower than those values obtained for the other isomers (*cf.* δ 4.68, **186**; 4.70, **188**; and 4.81, **189**).

As described in the previous two chapters, 3- and 6-methyl regioisomers were distinguished by an analysis of the DEPT portion of the ^{13}C NMR spectra (50 MHz; $CDCl_3$). Tables 10 and 11 summarise, respectively, the ^{1}H and ^{13}C NMR spectra of the cycloadducts **186-189**. Note in Table 11 that the C-5 and Ph-CH signals had similar chemical shifts and so, as a result, it was difficult to assign a specific shift value to C-5 for each isomer [the relative intensities of the *o*- and *m*-Ph-CH signals should be greater than that for the C-5 signal (two carbons to one carbon, in each case), but the *p*-Ph-CH signal should have a similar intensity to that of C-5].

The ratio of the four cycloadducts **186-189** was determined using proton NMR spectroscopy (200 MHz) as follows. A sample of the crude reaction mixture was dissolved in deuteriochloroform, and the proton spectrum taken. From an initial look at the spectrum, it was clear that the only effective way to determine the ratio of the cycloadducts was to integrate the 4, upfield, methyl doublets; all other signals in the spectrum overlapped to various extents. The 4 methyl signals were fairly evenly spaced, except for the inner two doublets which slightly overlapped. The *Me*CH chemical shifts were as follows: δ 1.01, **187**; 1.16, **189**; 1.20, **186**; and 1.32, **188**. In an attempt to achieve a better, overall, doublet separation, the spectrum was rerun in hexadeuteriobenzene. The chemical shifts in this solvent were: δ 0.64, **187**; 0.69, **186**; 0.87, **189**; and 1.08, **188**. The δ 0.87 and 1.08 signals were well spaced and so reliable

Table 10 ^{1}H NMR Spectra δ (200 MHz; $CDCl_3$) of the cycloadducts **186**, **187**, **188** and **189** from (±)-mandelohydroxamic acid **182b** and piperylene **111/112**. *J* values are in Hz.

	Protons						
Isomer	*Me*CH	CHH	OH	MeC*H*	C*H*OH	4- & 5-H	Ph-H
186	1.20 (d) *J* 6.7	3.80 (dm) *J* 17.6 4.55 (dm) *J* 17.6	4.25 (br s)	4.68 (m)	5.33 (s)	5.73 (dm) 5.73 (dm)	7.2-7.5 (5 X m)
187	1.01 (d) *J* 6.7	3.90 (dm) *J* 17.6 4.43 (dm) *J* 17.6	4.43 (br s)	3.21 (m)	5.38 (s)	5.49 (dm) 5.71 (dm)	7.2-7.5 (5 X m)
188	1.32 (d) *J* 6.7	3.02 (dm) *J* 15.5 3.77 (dm) *J* 15.5	4.45 (br s)	4.70 (m)	5.32 (s)	5.55 (dm) 5.70 (dm)	7.2-7.5 (5 X m)
189	1.16 (d) *J* 6.8	4.24 (dm) *J* 16.2 4.54 (dm) *J* 16.2	4.33 (br s)	4.81 (m)	5.33 (s)	5.77 (dm) 5.77 (dm)	7.2-7.5 (5 X m)

integrals could be taken. With the δ 0.64 (**187**) and 0.69 (**186**) signals, however, there was a slight overlap (not as much as for the $CDCl_3$ solution, though) near the base of each peak. A simple arithmetical averaging procedure was used to obtain approximate integrals for these two doublets, and is described as follows. The integral for the furthest upfield, singlet portion of the δ 0.64 doublet was doubled to give an approximate integral value for **187**. The integral for **186** was then obtained by subtract-

Table 11 ^{13}C NMR Spectra δ (50 MHz; $CDCl_3$) of the cycloadducts **186**, **187**, **188** and **189** from (±)-mandelohydroxamic acid **182b** and piperylene **111/112**.

	Carbons							
Isomer	Me	C-3	CHOH	C-6	C-4	C-5	Ph-C/CH	C=O
186	18.5	41.9	71.3	75.9	121.3	128.17*	127.10 128.47 128.58* 139.5	171.0
187	18.2	42.3	71.7	74.8	120.5	128.30*	127.06 128.56 128.83* 139.7	171.2
188	17.5	48.9	68.8	71.8	122.7	126.60*	127.79 128.23* 128.62 139.9	170.6
189	17.3	48.3	69.9	71.3	122.3	127.18*	126.75 127.57* 127.91* 139.3	170.2

N.b. (a) C-5 and phenyl-CH shifts are stated to two decimal places because they are placed so close together.

(b) Pairs of C-5 and phenyl-CH chemical shifts marked with an asterisk* may need to be interchanged because assignments are uncertain. For compound **189**, where three signals are asterisked, C-5 could have any one of these indicated shifts.

ion of the new integral for **187** from the combined **186/187** integrals. A similar procedure was carried out on the δ 0.69 doublet, this time working with the furthest downfield, singlet portion to obtain an approximate integral value for **186**, and hence, an integral value for **187** as well. This analysis gave two sets of integrals for **186** and **187**. Averages were then obtained, to serve as final integral values, and, taken with the integrals for **188** and **189**, the ratio of the cycloadducts was determined to be, **186**:**187**:**188**:**189** = 2.94:1.00:1.16:1.19 (corresponding to, respectively, 47, 16, 18 and

19%). In an attempt to achieve better asymmetric induction at lower temperatures, the reaction was repeated at -70 ^{o}C (acetone-dry ice bath) and the integrals were calculated in the same manner as that described above. This time, the ratio of the cycloadducts was found to be, **186**:**187**:**188**:**189** = 2.19:1.00:1.32:1.19 (corresponding to, respectively, 38, 18, 23 and 21%).

In summary, the ratio of the cycloadducts are: at 0 ^{o}C, **186**:**187**:**188**:**189** = 3.0:1.0:1.2:1.2; and at -70 ^{o}C, **186**:**187**:**188**:**189** = 2.2:1.0:1.3:1.2. In the following discussions of these ratios, reference will be made to Figure 17, which shows a set of possible addition modes of dienophile to diene to account for the observed stereochemistries of the cycloadducts **186**-**189**.

First of all, consider regiochemistry. At 0 ^{o}C, some 63% of the total mixture of the cycloadducts was composed of the 6-methyl isomers **186** and **187**. At -70 ^{o}C, this bias towards the 6-methyl decreased by *ca.* 7%, with only 56% of the 6-methyl isomers being formed. At both temperatures, however, the 6-methyl isomers were favoured. The preferred formation of 6-methyl cycloadducts can be explained using arguments similar to those discussed in the previous chapter for nitrosocarbonylbenzene but the apparent drop in regiospecificity at the lower temperature is difficult to account for.

Now consider the asymmetric induction. At both temperatures, the ratio of the 3-methyl diastereoisomers was very close to 1:1, with **188**:**189** ratios of 1.0:1.0 at high temperature, and 1.3:1.2 at low temperature. It appears, then, that there is no apparent degree of induction in the formation of the 3-methyl isomers, which is interesting, since their transition states involve a closer approach of the chiral unit with the piperylene methyl group than for the 6-methyl isomers. In contrast, the ratios of the 6-methyl diastereoisomers were substantial. Thus, the **186**:**187** ratio was 3.0:1.0 at high temperature and 2.2:1.10 at low temperature, corresponding to modest diastereomeric excesses of, respectively, 49% and 37%. At both temperatures, by far the main

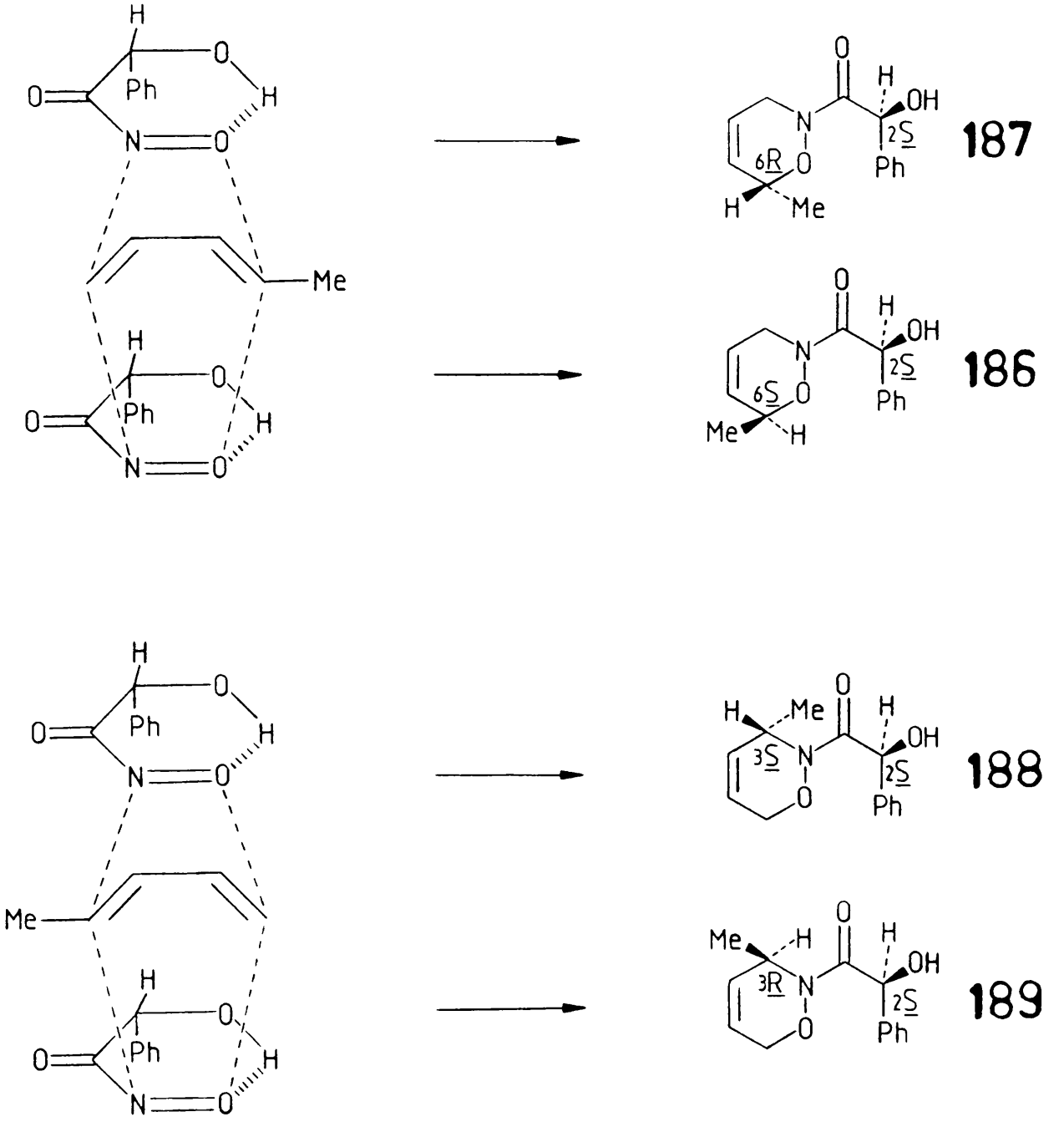


Fig. 17 Cycloadducts from (±)-mandelohydroxamic acid **182b** and (*E*)-piperylene **111**. Approach geometries are shown for *endo* addition of the dienophile [(*S*)-isomer arbitrarily shown] to the diene.

component of the mixture of cycloadducts was the isomer **186**. An approach geometry consistent with the observed relative configuration of **186** is *endo* addition of the intramolecularly hydrogen-bonded dienophile from the face *anti* to the phenyl group (Figure 17). Kirby and Nazeer[26] have investigated the cycloaddition reaction of the same nitrosocarbonyl compound with cyclohexa-1,3-diene, and obtained a mixture of diastereoisomers of *ca.* 3.5:1.0 at 0 ^{o}C. The formation of the main isomer, in this case, was also explained in terms of the addition geometry described above (see also, Miller *et al.*[28a]). Considering again the ratios of the 6-methyl isomers **186** and **187**, one might have expected less induction here compared to that for the 3-methyl isomers, because, in the former case, the chiral unit and piperylene methyl group are further apart in space. There is no simple, convincing explanation for this result.

The results of the aforementioned chromatographic separation of the cycloadducts **186-189**, along with details of R_f values and the calculated ratios, are summarised in Table 12. Also, Table 13 gives a summary of the yields and ratios for all the cycloadducts featured in this and the previous experiments.

It was originally planned to repeat the above experiment using an enantiomer of mandelohydroxamic acid. (*R*)-(-)-Methyl mandelate **180c** [prepared from (*R*)-(-)-mandelic acid **179c** (Scheme 36)] was used to prepare a sample of (*R*)-(-)-mandelohydroxamic acid **182c** (Scheme 37). The latter was then oxidized , in the presence of piperylene **111/112**, in the usual way. A dark, brown viscous oily product was isolated that showed identical proton and carbon NMR spectra to the cycloadducts obtained from the racemic mandelohydroxamic acid. However, after similar chromatographic separation none of the cycloadducts could be isolated in the crystalline state, even after repeated attempts. Separation of the isomers was therefore not achieved. However, during the experimental work, it was discovered that the previously reported value for the optical rotation of (*R*)-(-)-mandelohydroxamic acid was in error: Nazeer[27] reported a value of $[\alpha]_D$ -162^{o}, when, in fact, the correct value was

Table 12 Chromatographic separation of the cycloadducts **186**-**189**.

Fraction[a] number	Weight of product/mg	Composition[b] (R_f values)	δ (Me doublet)[c] /ppm
1-6	Negligible		
7	15	**187** (0.44),	0.64 (**187**),
8		**188** (0.55)	1.08 (**188**)
9	375		
10			
11		**186** (0.26),	0.69 (**186**),
12		**189** (0.26)	0.87 (**189**)
13	12		
14-15	Negligible		

[a]Successive elution with light petroleum (b.p. 60-80 °C), fraction 1, then increasing amounts of EtOAc up to 50% at fraction 10.

[b]Ratio of products at 0 °C, **186**:**187**:**188**:**189** = 2.94:1.00:1.16:1.19; ratio at -70 °C, **186**:**187**:**188**:**189** = 2.19:1.00:1.32:1.19.

[c]Chemical shifts in C_6D_6.

found to be $[\alpha]_D$ -63.0° (*c.* 1.6 in H_2O). Mr. S. B. King (Cornell Univ., USA) is to be thanked for originally drawing our attention to this discrepancy.

Table 13 Summary of yields and ratios of the cycloadducts of various *C*-nitroso-carbonyl compounds with piperylene (Scheme 38). Low temperature ratios were obtained only for **183b**.

Dienophile	Adducts	Yield/%	Ratio (0 °C)	Ratio (-70 °C)
183d	**184d:185d**	22-44	1.0:1.0	---
183a	**184a:185a**	38-58	2.8:1.0	---
183b	**186:187:188:189**	23-63	3.0:1.0:1.2:1.2	2.2:1.0:1.3:1.2

N.b. **183** = [RCONO] **a**; R = Ph

b; R = (±)-PhCHOH

d; R = Me

2.5 A study of hydrogen-bonding in the cycloadducts derived from piperylene and (±)-mandelohydroxamic acid.

It was suggested from the results of earlier work[26] that in the nitrosocarbonyl dienophile derived from mandelohydroxamic acid, and similar compounds with an α-OH group, intramolecular hydrogen-bonding may lead to enhancement of asymmetric induction in the Diels-Alder reactions with conjugated dienes. Figure 18 shows the hydrogen-bonded dienophile, in which the hydroxyl proton hydrogen-bonds to the oxygen atom of the nitroso group, thus forming a rigid, six-membered ring, with no free rotation about the ON-CO and PhCH(OH)-CO bonds. Such 'conformational locking' of the dienophile is the determining factor that is thought to enhance asymmetric induction. Indirect evidence of the above postulate was available, as it was possible to predict the stereochemical outcome of the Diels-Alder reaction by considering specific approach geometries of the hydrogen-bonded dienophile and diene (see the discussion and conclusions section of the previous chapter). Also, the dienophile derived from *O*-methylmandelic acid showed less asymmetric induction in its reactions with cyclopentadiene and cyclohexadiene.

If hydrogen-bonding does, indeed, occur in the dienophile in the way described above, then there is also a good chance that the same mode of hydrogen-bonding could occur in the derived cycloadduct, since the dienophile atoms need not change their relative positions and orientations appreciably in the transformation from reactant to product(s). It was decided to examine whether hydrogen-bonding was occurring in the cycloadducts derived from mandelohydroxamic acid and piperylene. Structure **187a** in Figure 19 shows the adduct **187** forming a six-membered ring, intramolecular hydrogen-bond.

There are various experimental techniques that can be used to study hydrogen-bonding. One of the easiest and simplest methods involves the use of solution IR

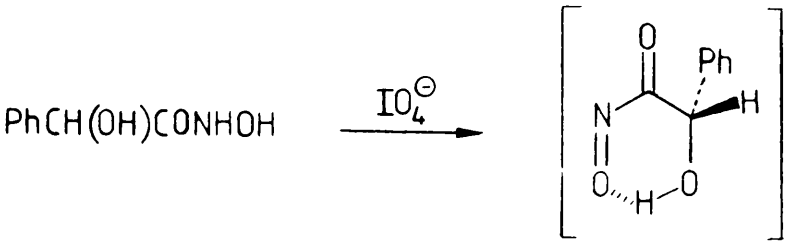


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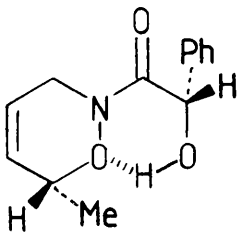
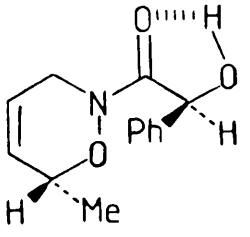
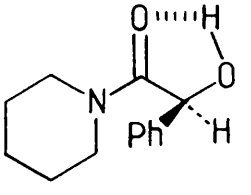
Fig. 18 The intramolecularly H-bonded *C*-nitrosocarbonyl dienophile derived from (*S*)-mandelic acid



187a



187b



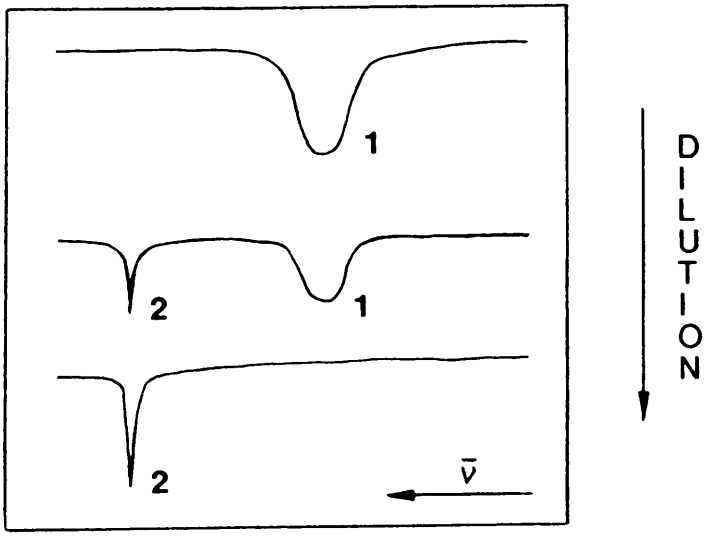
194

Fig. 19 Possible modes of intramolecular hydrogen-bonding in the cycloadduct **187** and the structurally similar amide **194**

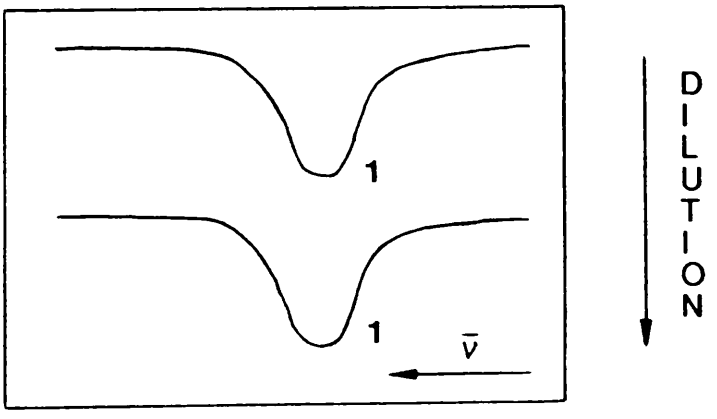
spectroscopy; proton NMR spectroscopy can be used similarly. These techniques were chosen for the investigation at hand. The theory and results for the IR, followed by the NMR, method are described below.

Generally, for IR studies of hydrogen-bonding a dry, aprotic solvent, commonly chloroform or carbon tetrachloride, is used and a series of spectra are run at differing concentrations. Particular attention is paid to the shape and frequency of the OH stretching band(s). If only *inter*molecular hydrogen-bonding is taking place, then the broad, low frequency OH band observed at high concentrations should gradually disappear with a decrease in concentration, to be replaced by a sharp band at a higher frequency, the latter, 'free' OH stretching band predominating once the molecules are too far apart to hydrogen-bond (Figure 20A). On the other hand, *intra*molecular hydrogen-bonding will persist regardless of dilution, and only a broad OH band should be observed at all concentrations (Figure 20B). A H-bonded OH group is usually characterized by a broad peak in the range ν_{max} 3200-3600 cm^{-1}; the lower the wavenumber, the stronger the H-bond. A 'free' OH group, on the other hand, is characterized by a sharp peak in the range ν_{max} 3590-5650 cm^{-1}.

Since all the cycloadducts **186-189** (Figure 17) should be able to show either inter- or intra-molecular hydrogen-bonding, all four were examined at once in the form of the total reaction mixture. A sample of the crude reaction mixture (5 mmol) containing the cycloadducts **186-189** was dissolved in dry chloroform (10 ml), to make a 0.50 M solution. The IR (difference) spectrum was then run in a 0.1 mm cell. The solution was then diluted with chloroform to *ca.* 0.05 M and the spectrum was rerun (0.1 mm cell). The spectrum of the 0.05 M solution showed strong bands in the carbonyl region at ν_{max} 1645 cm^{-1} and ν_{max} 1665 cm^{-1}, and a broad OH absorption at ν_{max} 3450 cm^{-1}; there was no sign of any free OH stretching band at higher frequency. The spectrum of the 0.05 M solution was identical, again showing a broad OH band but no free OH band. A weak band could be seen at ν_{max} 3680 cm^{-1}, but this was later discovered to



A Intermolecular



B Intramolecular

1 Hydrogen-bonded OH (broad)

2 Free OH (sharp)

Fig. 20 Variations in the IR, O-H stretching frequency with increasing dilution, for **A** inter- and **B** intra-molecular hydrogen-bonding. Case **A** shows a concentration dependence whereas case **B** does not.

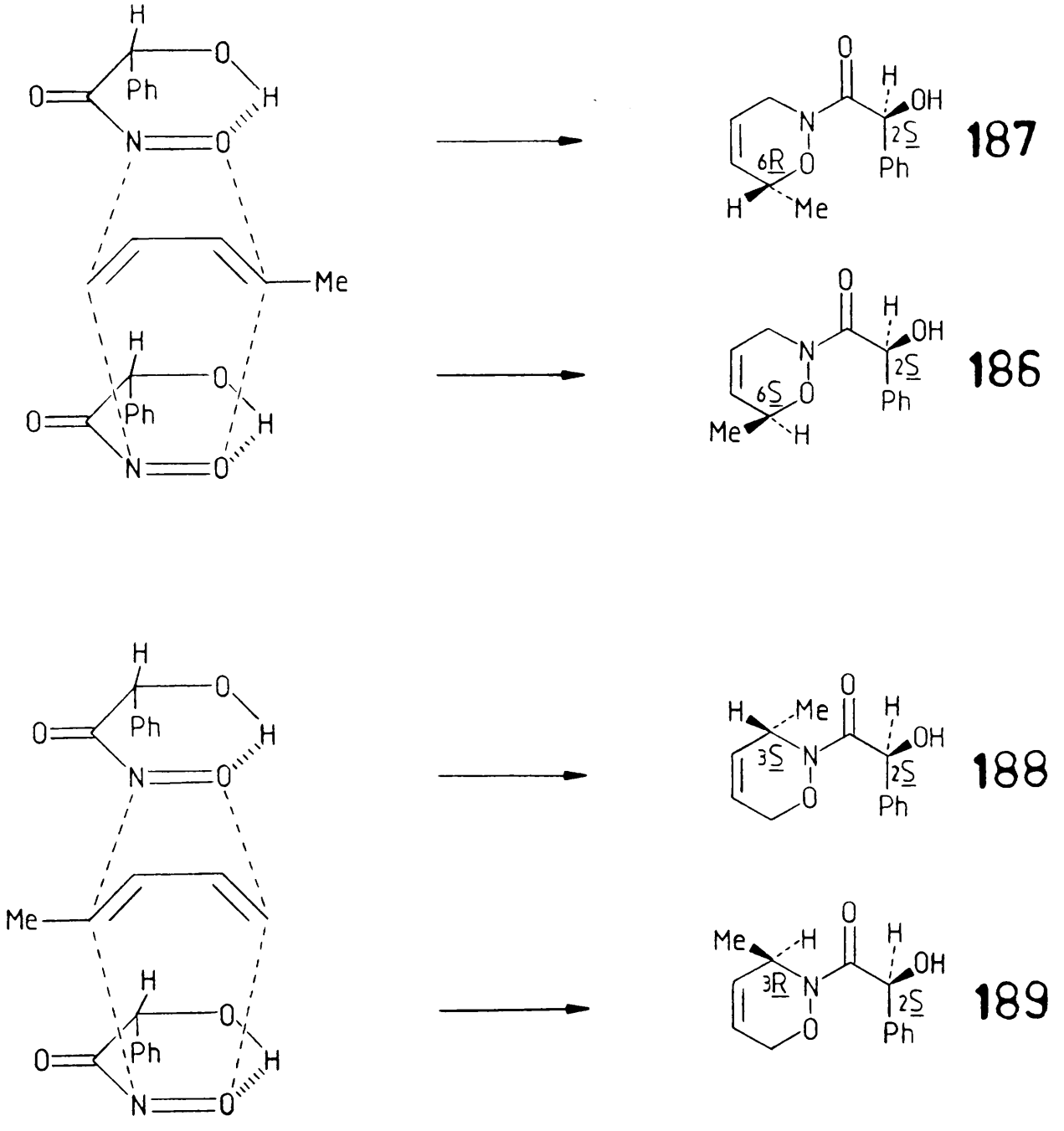


Fig. 17 Cycloadducts from (±)-mandelohydroxamic acid **182b** and (*E*)-piperylene **111**. Approach geometries are shown for *endo* addition of the dienophile [(*S*)-isomer arbitrarily shown] to the diene.

be due to the chloroform. Since the IR spectrum did not change from the result of a ten-fold dilution, each of the cycloadducts **186-189** was intramolecularly hydrogen-bonded.

^{1}H NMR Spectroscopy can also be used to study hydrogen-bonding. Again, the spectrum is run at different concentrations, and the position of the hydroxyl resonance noted. If intermolecular hydrogen-bonding is taking place, the OH signal should move upfield with dilution. With intramolecular hydrogen-bonding, the OH signal should not shift significantly.

Accordingly, hydrogen-bonding in the cycloadducts **187** and **188** was then studied by NMR spectroscopy. The sample of **188** used was pure, but the cycloadduct **187** contained a very small amount (< *ca.* 5%) of **188**. The ^{1}H NMR spectrum (90 MHz) of **187** in deuteriochloroform was taken. The solution was diluted and the spectrum rerun. The solution was diluted once more, and again the spectrum was run. This procedure was repeated with the cycloadduct **188**. The results of these experiments are summarised in Table 14. The position of the C*H*OH signal should not, of course,

Table 14 Proton NMR spectra δ (90 MHz; $CDCl_3$) of the cycloadducts **187** and **188**, (Scheme 38), showing the variation of chemical shift of the OH and C*H*OH protons with concentration (solutions in $CDCl_3$).

	Cycloadducts					
	187			**188**		
Conc./mol.l^{-1}	0.27	0.13	0.038	0.63	0.077	*ca.*0.0077
δ OH/ppm	4.33	4.33	4.33	4.40	4.35	4.33
δ C*H*OH/ppm	5.33	5.33	5.33	5.27	5.25	5.27

N.b. The hydroxyl resonance of **187** was found to partially overlap one half of one of the C*H*H double multiplets. As a result, the OH chemical shifts quoted are only approximate.

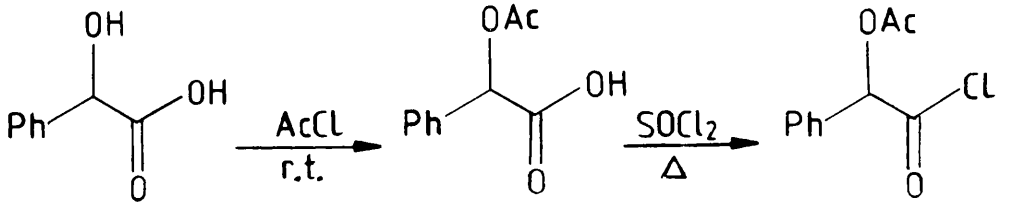
depend significantly upon concentration, and so is shown in the Table as a reference for the OH chemical shift. The OH signal for both cycloadducts did not shift appreciably with changes in the solution concentration. The OH signal for **187** partially overlapped one half of one of the C*H*H double multiplets at δ 4.45 (this was also found to be the case at 200 MHz). The overlapping signals integrated for two protons, and showed a pronounced shoulder which disappeared after a D_2O exchange experiment (the signal then integrated for one proton). From an examination of the profile of the C*H*H peak, the OH signal did not appear to shift appreciably on dilution. These results (Table 14), therefore, support the conclusions of the IR study - that intramolecular hydrogen-bonding occurred in the cycloadducts **186**-**189**.

The results of the above experiments lend some support to the idea of the hydrogen-bonded dienophile outlined at the beginning of the chapter. However, as can be seen from Figure 19, there is an additional mode of intramolecular hydrogen-bonding possible in the cycloadduct **187**, namely one involving hydrogen-bonding of the hydroxyl proton to the carbonyl oxygen atom, to give the structure **187b** with a five-membered ring. The results of the foregoing IR and NMR experiments do not discriminate between the two H-bonding modes. It may be possible, however, to make a discrimination by considering the relative values of both hydroxyl and carbonyl group frequencies of the cycloadducts and related, model compounds. When a carbonyl group acts as an acceptor for hydrogen-bonding, its stretching frequency is affected as well. In general, the stronger the hydrogen-bond, the lower the carbonyl stretching frequency will be. This phenomenon is quite common in compounds like α-amino and α-hydroxy-aryl ketones, where ν_{max} (C=O) lies (typically) in the range 1635-1655 cm^{-1}. Other factors like, for example, steric hindrance and substitution patterns also affect the position of the C=O band. The following study was designed to shed more light on the mode of hydrogen-bonding adopted by the cycloadducts **186**-**189**.

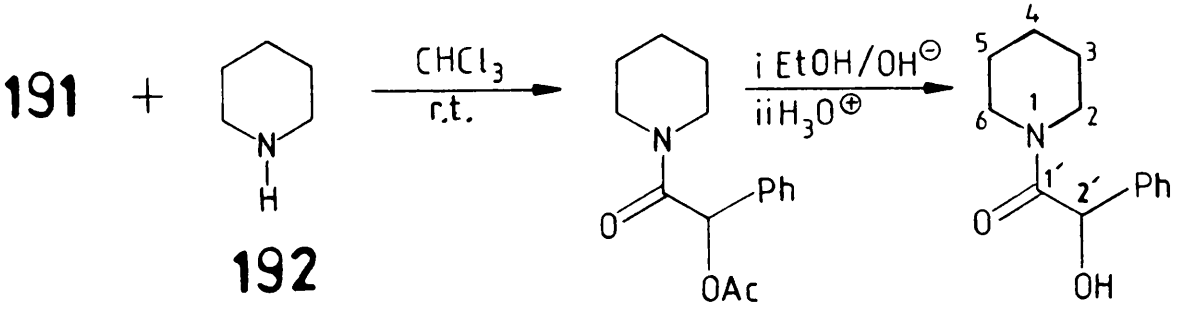
The known, model compound **194** (Figure 19), *N*-mandeloylpiperidine, which can show only one type of intramolecular hydrogen-bonding, was prepared as summarised in Scheme 39. The route was adapted from a more general synthesis of mandelic amides published by Cocolas *et al.*[43]. (±)-Mandelic acid **179b** and acetyl chloride were stirred at room temperature to give the acetate **190**. The latter was heated with thionyl chloride, under reflux, to yield the acid chloride **191**, which was then added in chloroform to a solution, also in chloroform, of piperidine **192**. The acetyl protecting group of the resulting amide-acetate **193** was removed in ethanolic sodium hydroxide at room temperature. The amide **194**, was obtained in 65% overall yield from the original acid. The crude solid was recrystallised from ether, yielding needles, m.p. 75-77 ^{o}C (lit.[44] 77 ^{o}C). The IR and NMR spectra were as expected.

The IR (difference) spectrum of a 0.051 M solution of the amide **194** in chloroform was obtained with a 0.1 mm cell. This solution was then diluted to *ca.* 0.010 M and the IR spectrum was taken also. Finally, the solution was diluted to 0.0051 M and the spectrum was obtained with a 0.5 mm cell. The spectra obtained with the 0.5 mm cell were of better quality than those with the 0.1 mm cell, and so these were used for the H-bonding analysis. The spectrum of the 0.051 M solution showed a band in the carbonyl region at ν_{max} 1640 cm^{-1}, and a broad OH absorption at ν_{max} 3390 cm^{-1}, with no sign of any free OH stretching band. As in the IR study of the cycloadducts, a sharp peak was found at ν_{max} 3680 cm^{-1}, but was due to the chloroform. The spectrum of the 0.0051 M solution likewise showed a broad OH absorption, and no indications of any free OH.

Since the spectrum of the amide **194** was concentration independent, it was clear that the intramolecular hydrogen-bond shown in Figure 19 was present. Thus, in the cycloadducts **186-189**, H-bonding to the carbonyl oxygen (see **187b**) cannot be ruled out. However, six-membered hydrogen-bonded rings are normally considered to be



179b 190 191



192 193 194

Scheme 39

more stable than five-membered rings. The carbonyl group frequencies were also compared to help discriminate between the five- and six-membered ring modes.

Table 15 Characteristic IR stretching frequencies of cycloadducts of piperylene and *C*-nitrosocarbonyl compounds (Scheme 38) and of the mandeloylpiperidide **194**.

	Compound			
IR Band	**184d/185d**[a]	**184a/185a**[a]	**186-189**[b]	**194**[b]
ν_{max} (C=O) /cm^{-1}	1650 & 1670	1645 & 1665	1650 & 1670	1640
ν_{max} (O-H) /cm^{-1}	---	---	3450	3390

[a]liquid film [b]$CHCl_3$ soln.

Table 15 summarises the carbonyl and hydroxyl group IR stretching frequencies of the amide **194** and various cycloadducts discussed in the previous chapters. For the *N*-acetyl (**184d/185d**) and *N*-benzoyl (**184a/185a**) cycloadducts, which do not contain hydroxyl groups, the C=O stretching frequencies have rather similar values, falling in the range ν_{max} 1645-1670 cm^{-1}. The IR spectrum of the crude mixture of the hydroxyl-containing cycloadducts **186-189** showed two bands in the carbonyl region at ν_{max} 1650 cm^{-1} and ν_{max} 1670 cm^{-1}. For the amide **194**, where only one mode of H-bonding is present (Figure 19), the recorded carbonyl frequency of ν_{max} 1640 cm^{-1} is slightly lower than those values quoted above. These results suggest that in the cycloadducts **186-189** the six-membered intramolecular hydrogen-bonded ring (Figure 19, **187a**) is the more likely to occur, since for a five-membered ring (Figure 19, **187b**) a lower carbonyl frequency is to be expected since the C=O group is hydrogen-bonded. For the amide **194**, the hydroxyl frequency is ν_{max} 3390 cm^{-1}, compared to the higher value of ν_{max} 3450 cm^{-1} obtained for the cycloadducts **186-189**. This lower hydroxyl frequency for the amide suggests a relatively stronger hydrogen-bond compared to the one in the cycloadducts. In these discussions, it must be remembered that the

cycloadducts are hydroxylamides rather than simple amides, and so comparisons between the carbonyl stretching frequencies have to be made carefully.

Figures 15 and 16 show the X-ray crystal structures of the cycloadducts **186** and **188**. In each compound, the O-C-C-O-(H) atoms of the mandelic portion lie more or less in the same plane, thereby suggesting intramolecular H-bonding in the crystal state. In the X-ray analyses of both **186** and **188**, the OH proton co-ordinates could not be determined, and so the hydrogen atom positions indicated in the Figure have been arbitrarily set, and do not reflect the true positions of the atoms. However, it is clear that there are no intramolecular H-bonds involving the oxazine oxygens. The forces between molecules, however, are usually quite different in the solution and crystalline states, so this observation does not prove that H-bonding in solution involves the carbonyl groups.

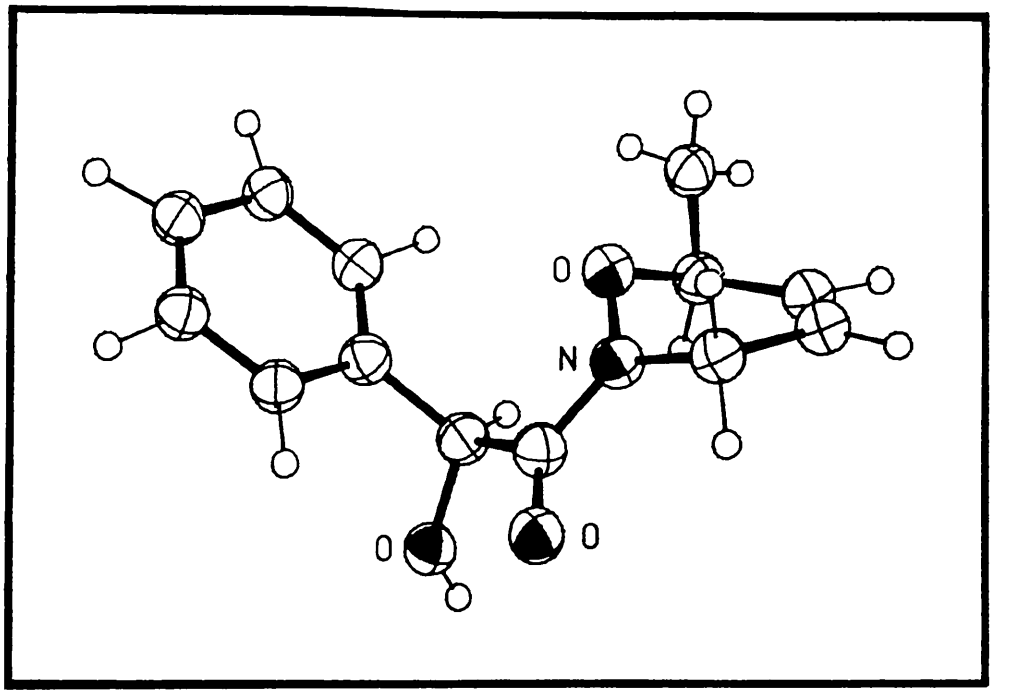


Fig. 15 X-Ray crystal structure of the cycloadduct **186**. Note on the oxazine ring that the methyl group appears to be axial.

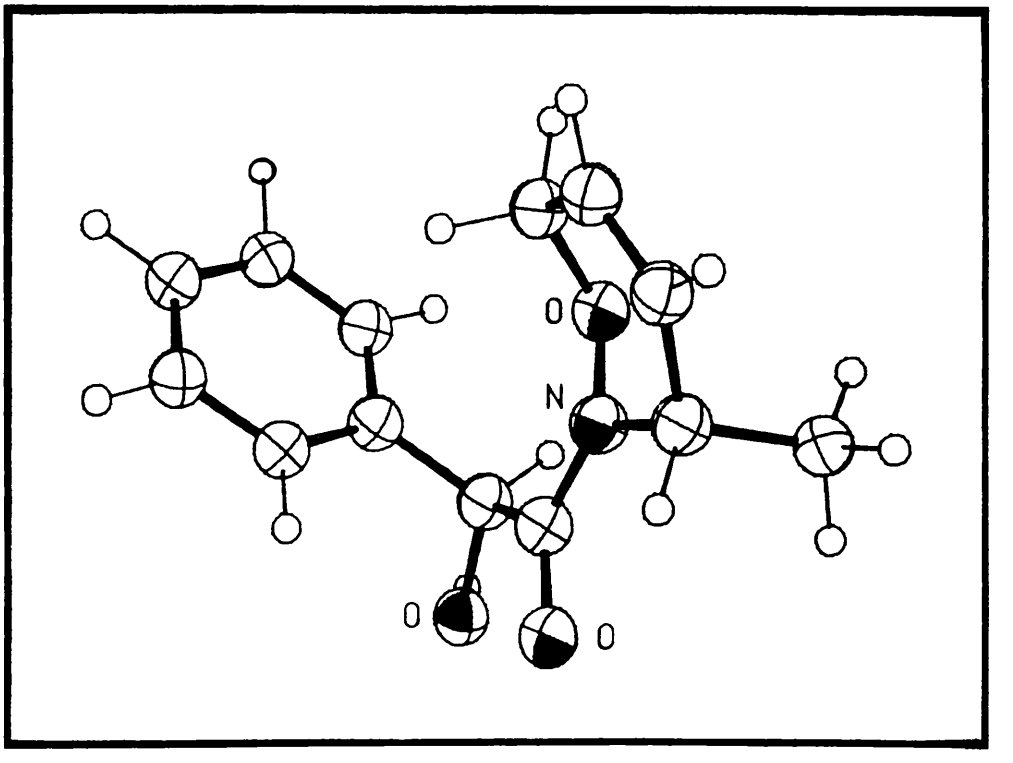


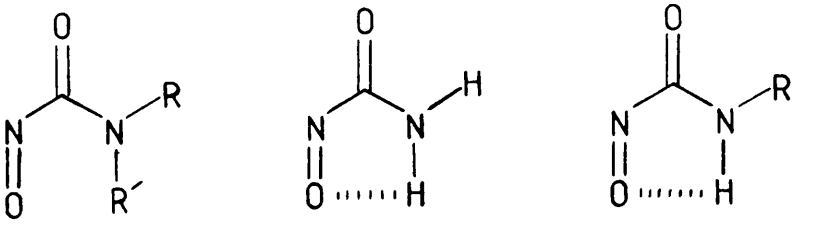
Fig. 16 X-Ray crystal structure of the cycloadduct **188**. Note that the oxazine ring appears boat-like in conformation, with an axial methyl group.

2.6 Ideas for future study.

There are other types of transient *C*-nitrosocarbonyl compounds that are capable of acting as dienophiles. The group attached to the carbonyl group need not be alkyl or aryl. Heteroatom groups involving oxygen and nitrogen can be used as well. Kirby *et al.*[7a] have investigated the formation and reactions of *C*-nitrosoformate esters, ROCONO. These can be prepared by the oxidation of the corresponding *N*-hydroxycarbamic esters, ROCONHOH. Another class of transient dienophile, described by Christie *et al.*[8], are the *C*-nitrosoformamides, R^1R^2NCONO, derived by the oxidation of *N*-hydroxyureas, $R^1R^2NCONHOH$.

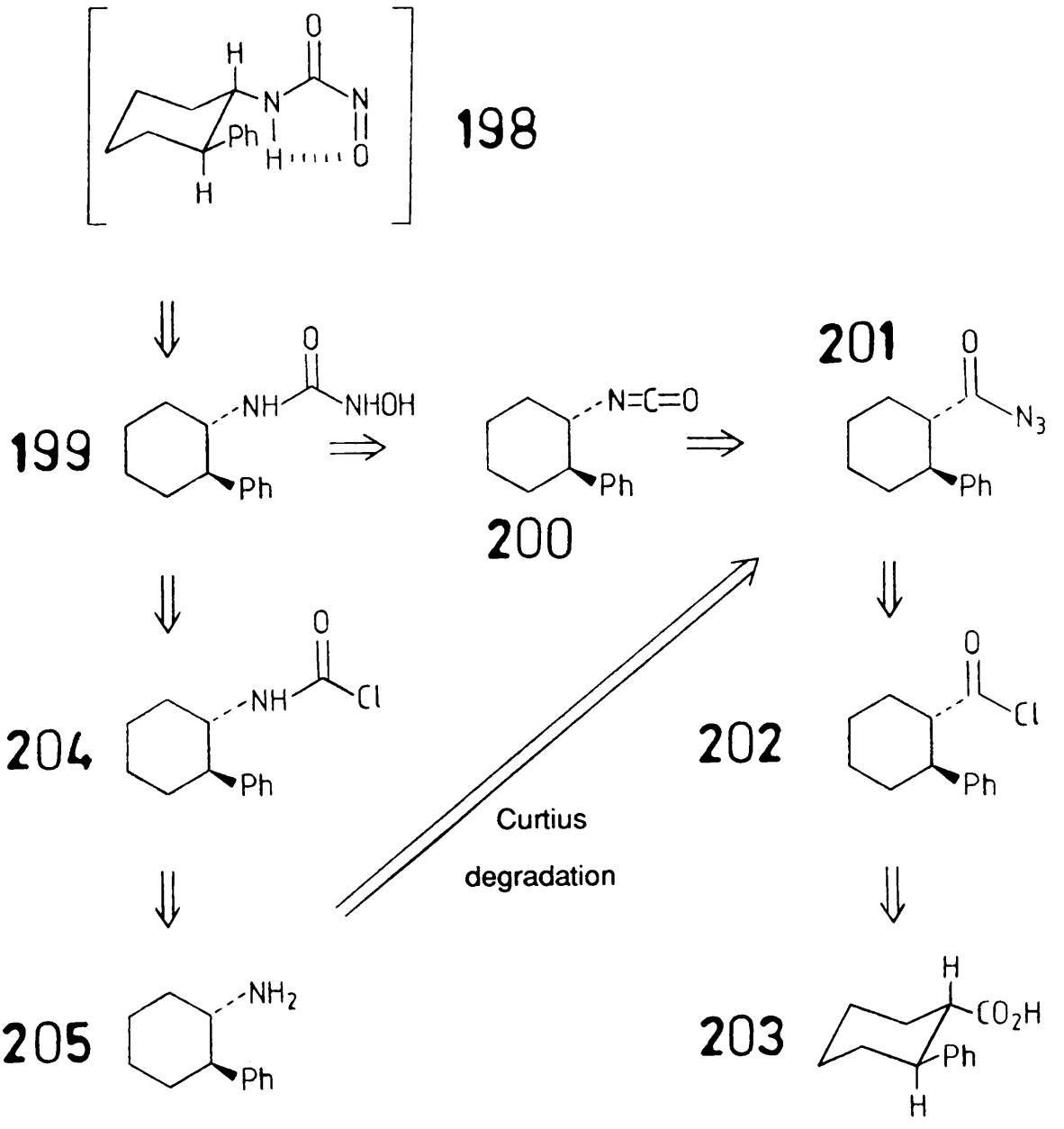
It was found from a study of reaction rates[8] that *N,N*-dialkyl- and *N,N*-diaryl-nitrosoformamides **195** (Figure 21) were less stable than the nitrosoformamides **196** and **197** containing either one or two hydrogen atoms on N. This extra stability of **196** and **197** might arise from intramolecular hydrogen-bonding between the NH proton and the NO oxygen atom, in the form of a five-membered ring. Such H-bonding might also increase the electrophilic nature of the dienophile towards the conjugated diene in the Diels-Alder reaction.

It has been mentioned previously that intramolecular hydrogen-bonding in nitrosocarbonyl compounds containing an α-hydroxy group may lead to enhancement of levels of asymmetric induction in cycloaddition reactions[26]. In much the same way, possibly, this might also be true for chiral nitrosoformamides of the type **197**, where R is chiral. An example of a molecule of this type is the nitrosoformamide **198** (Scheme 40), with a *trans*-2-phenylcyclohexyl group acting as the chiral unit. This molecule has structural design features which merit it as a potentially interesting dienophile for use in asymmetric Diels-Alder cycloaddition reactions with conjugated dienes. Firstly, rotation about the N-CO bond should be slow (unlike C-CO), thereby assisting 'conformational locking' of the dienophile by the intramolecular hydrogen-bond to the carbonyl oxygen.



195 196 197

Fig. 21 Nitrosoformamides with different substitutions on N



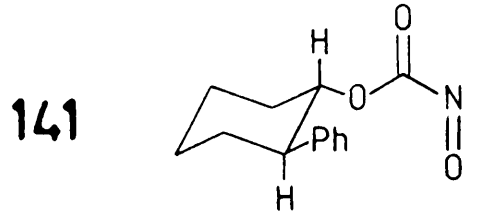
Scheme 40 Retrosyntheses of the *C*-nitrosoformamide **198** from *trans*-2-phenylcyclohexanecarboxylic acid **203** and *trans*-2-phenylcyclohexylamine **205**

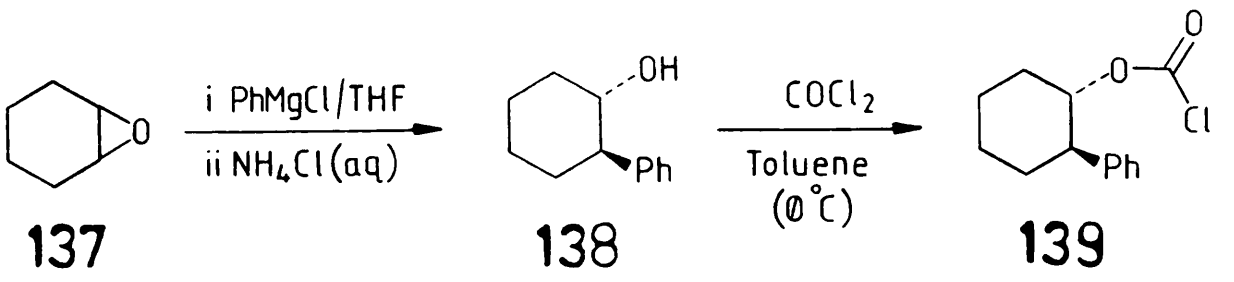
Secondly, in the conformation **198**, one side of the nitroso group would be shielded by the phenyl group, therefore making attack on the dienophile more facially discriminate.

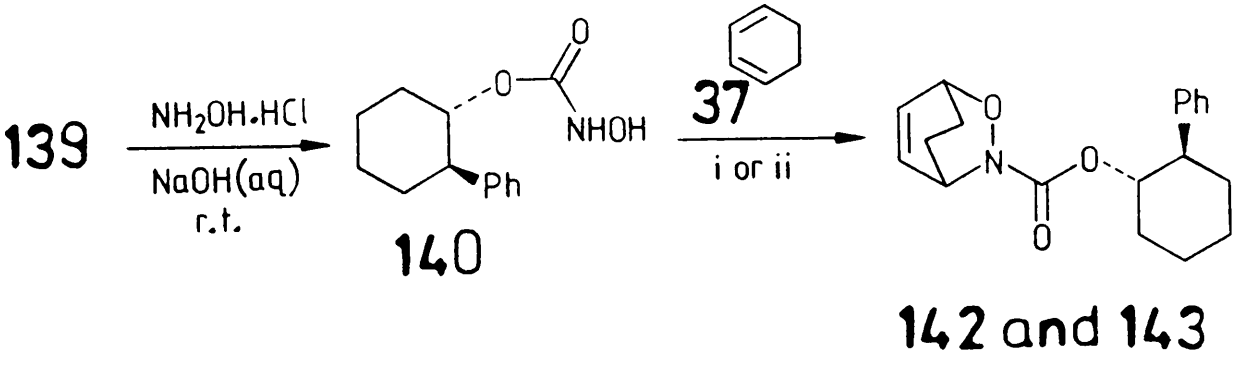
trans-2-Phenylcyclohexanol **138** has already been used as a chiral unit for purposes similar to those above. Starting with cyclohexene oxide **137** (Scheme 27), Nazeer[27] synthesized **138**, and in turn, the derived *N*-hydroxycarbamic ester **140**. The latter was oxidized, at -78 ^{o}C, to give the corresponding nitrosoformate ester **141**, which was trapped *in situ* with cyclohexa-1,3-diene, to afford a mixture of the diastereoisomeric, racemic cycloadducts **142** and **143**. Proton NMR spectroscopy revealed the ratio of the diastereoisomers to be *ca.* 3.6:1 (corresponding to a d.e. value of 57%). Whitesell *et al.*[45] have also investigated asymmetric induction reactions using *trans*-2-phenyl-cyclohexanol as a chiral unit. The dienophiles, however, were not nitrosocarbonyl compounds.

As an idea for future study, it may prove fruitful to synthesize the nitrosoformamide **198** and investigate its cycloaddition reactions with conjugated dienes to determine the levels of asymmetric induction achievable. Some ideas for the synthesis of **198** are given below.

Two retrosyntheses of the *C*-nitrosoformamide **198** are shown in Scheme 40. The transient compound itself would be prepared by the oxidation of the corresponding *N*-hydroxyurea **199**, so the main problem would lie in the synthesis of the latter. The urea **199** could be made from hydroxylamine and the isocyanate **200**, which in turn, could be prepared by a Curtius rearrangement of the acyl azide **201**. The acid chloride **202** could be used to make the acyl azide, by treating it with sodium azide (details of a homogeneous phase technique for the preparation of acyl azides has been reported in the literature by Allen and Bell[46]). The acid chloride **202** would be made from the known *trans*-2-phenylcyclohexanecarboxylic acid **203**. Alternatively, the *N*-hydroxyurea **199** could be prepared from *trans*-2-phenylcyclohexylamine **205**. Treatment of the





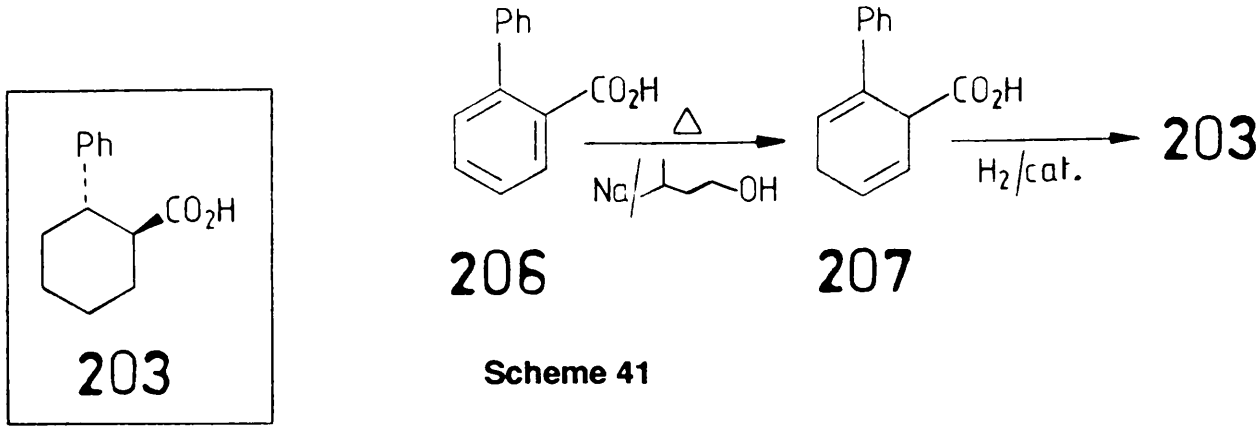


Scheme 27 i $EtOAc/NaIO_4/H_2O$ (0°C)
ii Et_4NIO_4/CH_2Cl_2 (0 and -78°C)

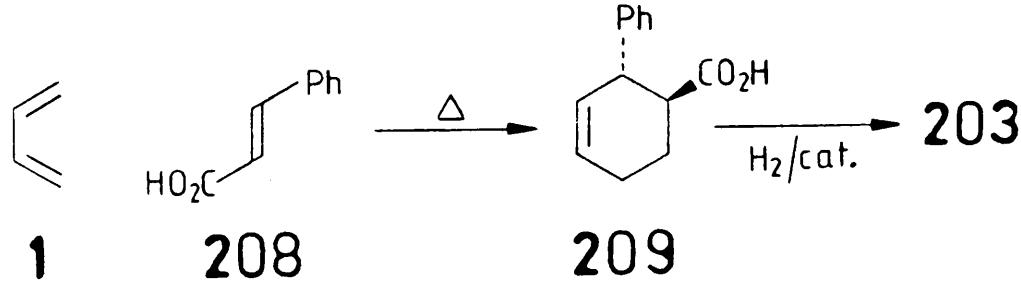
amine **205** with phosgene would give the carbamoyl chloride **204**, which could be condensed with hydroxylamine to give the desired product, **199**.

Unfortunately, neither the acid **203** nor the amine **205** are commercially available compounds. Syntheses, however, of both molecules are given in the literature. In fact, one of the published syntheses of the amine **205** (Arnold and Richardson[47]) involves the acid **203** as a starting material. The amine is prepared from **203** *via* the route **203**-**202**-**201**-**205**, as shown in Scheme 40. The latter transformation, **201**-**205**, involves a Curtius rearrangement of the acyl azide **201**. A short summary of a selection of routes to the acid **203**, m.p. 105-107 ^{o}C, are given below.

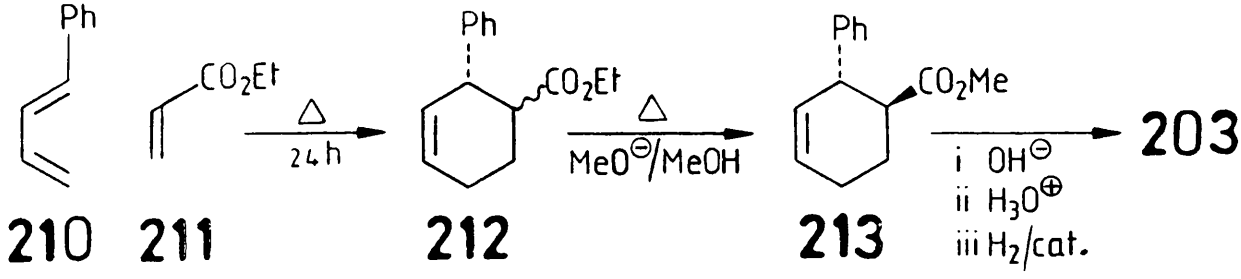
A Birch reduction of *o*-phenylbenzoic acid **206** to the acid **203** could not be found in the literature, but there is a synthesis by Ranedo and Leon[48] (Scheme 41) involving the treatment of **206** with metallic sodium in amyl alcohol, to give the cyclohexadiene **207**. Catalytic hydrogenation of **207** then yielded the desired product, **203**. One of the simplest alternative routes to the acid might involve the Diels-Alder reaction of *trans*-cinnamic acid **208** with buta-1,3-diene **1** (Scheme 42), to give the cyclohexene **209** which could be hydrogenated to form **203**. Another synthesis involving a Diels-Alder reaction as its primary step has been published by Ropp and Coyner[49] (Scheme 43). Here, *trans*-1-phenylbuta-1,3-diene **210** undergoes a cycloadditon reaction with ethyl acrylate **211** (acrylic acid can also be used) to yield the cyclohexene ester **212**. Base-catalyzed equilibration of **212** with sodium methoxide in methanol gave the desired *trans*-isomer **213**. Alkaline hydrolysis of the latter, followed by acidification and catalytic hydrogenation of the acid, gave **203**. As mentioned previously, a synthesis of the amine **205** from the acid **203** has been reported[47]. The acid **203** was prepared (Scheme 44) from the isomeric, *cis* acid **215** by the base-catalyzed equilibration of the methyl ester **216**. The *cis* acid **215** was prepared, in turn, by the method of Alder *et al.*[50], from *trans*-1-phenylbuta-1,3-diene **210** and acrylic acid **214**.



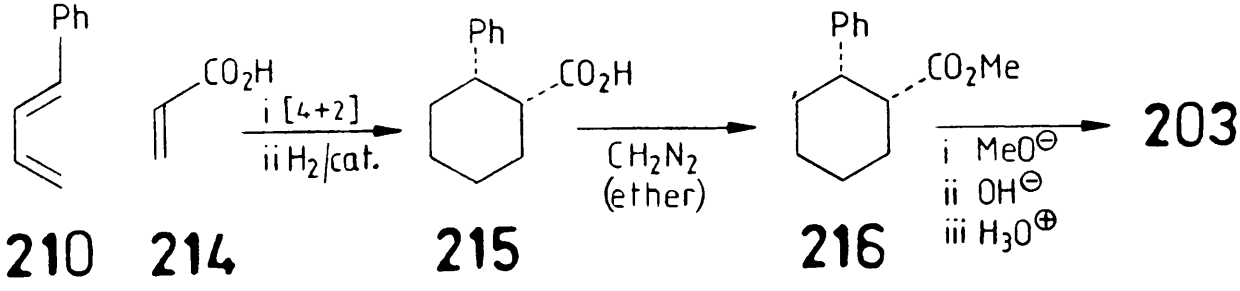
Scheme 41



Scheme 42



Scheme 43

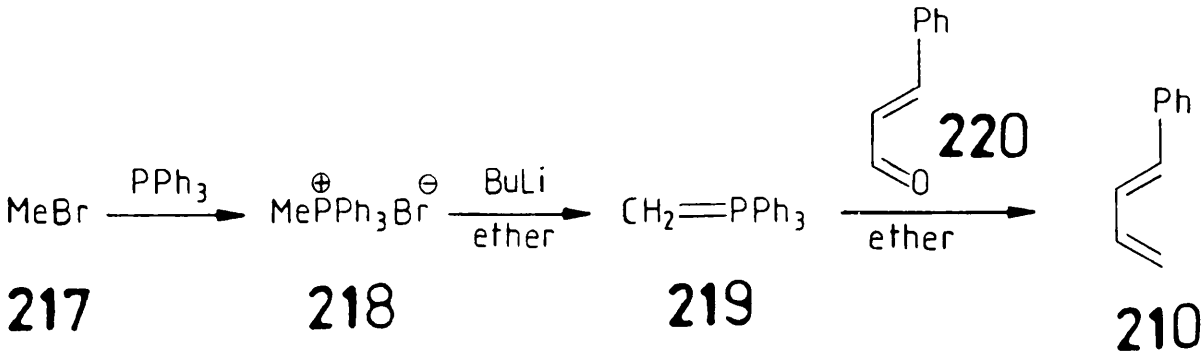


Scheme 44

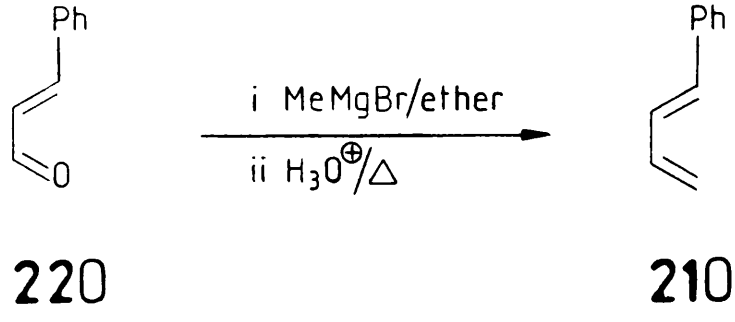
Schemes 41-44 Syntheses of *trans*-2-phenylcyclohexanecarboxylic acid **203**

The two latter synthetic routes to the acid **203** both involve the use of *trans*-1-phenylbuta-1,3-diene **210**. This compound is not commercially available and so would have to be synthesized. Two literature methods of preparing **210** are shown in Schemes 45 and 46.

A synthesis of the phenylbutadiene **210**, reported by Wittig and Schollkopf[51], involved a Wittig reaction (Scheme 45), between *trans*-cinnamaldehyde **220** with the methylene ylid **219** (derived from methyl bromide **217**) in ether. A Grignard route to **210** by Grummit and Becker[52] is shown in Scheme 46. Cinnamaldehyde **220** was treated with methylmagnesium bromide. Acidification of the Grignard salt, followed by heating, gave the product **210**. However, the latter two steps in the synthesis have to be controlled very carefully since the authors reported the formation of a polymeric by-product of **210** if the experimental method is not followed correctly.



Scheme 45



Scheme 46

Schemes 45-46 Syntheses of *trans*-1-phenylbuta-1,3-diene **210**

CHAPTER 3

EXPERIMENTAL

Instrumentation

Melting points were determined with a Kofler hot-stage apparatus. Temperatures are stated accurate to the nearest degree centigrade.

Mass spectra were obtained using two machines. Low resolution spectra were obtained by electron impact at 70 eV on an A.E.I. M.S.12 instrument, and high resolution spectra similarly on an A.E.I. M.S.9 instrument driven by an on-line GEC-905 computer system with software for data collection and manipulation.

Microanalyses were carried out by Mrs. Kimberly Wilson and her staff.

Proton NMR spectra were recorded on three different machines. At 90 MHz, two continuous wave instruments were used, a *Perkin-Elmer* R-32 and a *Perkin-Elmer* EM 390. For work at higher field and also for running carbon spectra, a 200 MHz *Bruker* WP 200 SY pulsed Fourier transform instrument was used; spectra were run and manipulated by Dr. David S. Rycroft and Mr. James Gall and their staff. Proton spectra were run at 200.13 MHz, and carbon spectra at 50.32 MHz. The NMR solvent commonly employed was deuteriochloroform, using $CHCl_3$ at 7.25 p.p.m. as a reference for the proton spectra (tetramethylsilane at 0 p.p.m. was used as a reference when the chloroform peak was obscured), and $CDCl_3$ at 77.0 p.p.m. as a reference for the carbon spectra. Proton chemical shifts are stated in p.p.m. using the chemical shift parameter, δ. *J* values are in Hz.

Infra-red spectra were run on either a *Perkin-Elmer* 257 or 580 machine, operated by Mr. George McCulloch and staff. Spectra were commonly obtained for chloroform solutions with cell sizes of 0.1 mm and 0.5 mm.

The optical rotation of (*R*)-(-)-mandelohydroxamic acid was measured using a

Lippich-type polarimeter (*Bellingham & Stanley Ltd.*). The wavelength of light used was the **D** line of sodium at 5893 Angstroms.

The two X-ray crystal structure analyses in this thesis were carried out by Dr. Andrew A. Freer and Sean Tierney.

General methods

'Bulk grade' solvents were purified using standard purification procedures and techniques[53a]. Typically, the bulk grade solvent was first washed and dried, then either fractionated or distilled, and finally stored in a dark glass bottle. Water used in experiments (commonly for washing procedures) was distilled and deionized before use.

'Ether' refers to diethyl ether and, unless otherwise stated, light petroleum refers to the fraction with boiling point range 60-80 ^{o}C.

Aqueous-washed organic solvents were dried with conventional drying agents, commonly anhydrous magnesium sulphate, and the solvent was evaporated under reduced pressure (water pump) on a *Buchii* rotary evaporator.

Glassware used in experiments was of the *Qwik-Fit* type. All filtration procedures were carried out using sintered-glass filtration funnels (suction provided by water pump). Reaction mixtures were stirred with a magnetic stirrer plate and stirrer bar.

Flash-column chromatography was carried out using *Merck* Kieselgel HF_{254} silica in a glass-sintered filtration funnel (suction at water pump). For preparative thin-layer chromatography, 20 cm X 20 cm glass plates were coated with *Merck* GF_{254} silica (surface thickness, 0.5 mm). Analytical thin-layer chromatography was carried out on

plastic sheets pre-coated with *Merck* GF_{254} silica (surface thickness, 0.25 mm). Both preparative and analytical grade silicas had fluorescent indicators which allowed them to be examined under uv light (254 nm). The analytical plates were developed with iodine vapour.

Abbreviations

Common abbreviations and symbols used throughout this thesis are listed below.

s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br	broad
p.p.m.	parts per million
J	coupling constant/Hz
Hz	hertz
MHz	megahertz
IR	infra-red
NMR	nuclear magnetic resonance
b.p.	boiling point/^{o}C
m.p.	melting point/^{o}C
r.t.	room temperature
h	hour
min	minute
t.l.c.	thin-layer chromatography
Ar	aryl group
R	alkyl group

In NMR spectra, multiple combinations of symbols are commonly employed to describe peak multiplicities. For example, 'dd' means a doublet of doublets; 'dqm' means a doublet of quartet multiplets, *etc.*

3.1 Preparation of tetraethylammonium periodate 32 (Scheme 5).

The following method is essentially the same as that described by Sklarz and Qureshi[10].

Periodic acid **30** (7.72 g, 34 mmol) was dissolved in distilled water (20 ml) and added, in portions, to cold 25% (by wt.) aqueous tetraethylammonium hydroxide **31** (20 ml, 34 mmol). Evaporation of the mixture on a rotary evaporator left a crude white solid which was extracted with one portion of hot *tert*-butyl alcohol (100 ml). The product, tetraethylammonium periodate **32**, was precipitated with *di*-isopropyl ether and recrystallised from *tert*-butyl alcohol, to give the pure salt **32** (8.49 g, 78%). (**CAUTION:** Evaporation of the aqueous solution and extraction of the crude salt should be carried out behind a protective screen. Excessive heating of the salt could lead to an explosion[11].) The salt **32** gave δ_H (90 MHz; D_2O, ref. DOH at δ 4.74) 1.27 [tt, J_{vic} 7 and $J(HCC^{14}N)$ *ca.* 2, CH_3] and 3.27 (q, J_{vic} 7, CH_2).

3.2 Preparation[53b] of methyl benzoate 180a (Scheme 36).

Benzoic acid **179a** (15.02 g, 0.123 mol), dry methanol (50 ml, 39.55 g, 1.24 mol) and concentrated sulphuric acid (1.3 ml, 2.4 g) were added to a 250 ml round-bottomed flask and the mixture was gently refluxed for 2.25 h. The excess of methanol was removed on a rotary evaporator and the remaining mixture allowed to cool before being poured into a 250 ml separatory funnel containing distilled water (125 ml). The liquid ester was extracted with ether (2 X 25 ml), and the resulting ethereal solution washed

with a portion of saturated aqueous sodium hydrogen carbonate. Washing was repeated until effervescence ceased. Finally, the ethereal solution was washed with a portion of water, dried over anhydrous magnesium sulphate, and evaporated. Methyl benzoate **180a** (11.68 g, 70%) was obtained by distillation (1 atm), b.p. 198-200 ^{o}C; δ_H [90 MHz; $CDCl_3$, ref. ether (t, CH_3) at δ 1.15] 3.85 (s, CH_3), 7.1-7.7 (m, *m*- and *p*-Ph-H) and 7.7-8.3 (m, *o*-Ph-H).

3.3 Preparation of methyl (±)-mandelate 180b (Scheme 36).

Following a standard method for preparing methyl esters[53c], (±)-mandelic acid **179b** (15.37 g, 0.101 mol) was dissolved in methanol (100 ml) in a 250 ml round-bottomed flask and cooled in ice. Acetyl chloride (7 ml, 7.73 g, 0.098 mol) was added cautiously. When addition was complete, the ice-water bath was removed and the mixture was heated under reflux for 24 h. The mixture was evaporated, and the brownish, oily residue was distilled under reduced pressure (water pump) to give methyl (±)-mandelate **180b** (12.03 g, 72%), b.p. 188 ^{o}C, m.p. 52-54 ^{o}C (from ether) (lit.[36b] 51-54 ^{o}C); ν_{max} (Nujol mull)/cm^{-1} 1740 and 3420; δ_H (90 MHz; $CDCl_3$, ref. TMS at δ 0) 3.40 (br s, OH, exch. with D_2O), 3.74 (s, CH_3), 5.17 (s, C*H*OH) and 7.35 (s, 5 X Ph-H).

3.4 Preparation of (R)-(-)-methyl mandelate 180c (Scheme 36).

(*R*)-(-)-Mandelic acid **179c** (10.00 g, 66 mmol), in a solution of methanolic hydrogen chloride, prepared from methanol (70 ml) and acetyl chloride (4.6 ml, 5.08 g, 65 mmol), was heated under reflux in the manner previously described for the preparation of methyl (±)-mandelate. The usual work up afforded crude (*R*)-(-)-methyl mandelate **180c** (10.50 g, 98%). Distillation at reduced pressure (water pump) followed by recrystallisation yielded the pure ester, m.p. 56-58 ^{o}C (from ether) (lit.[36b] 57-58 ^{o}C).

3.5 Preparation of acetohydroxamic acid 182d (Scheme 37).

The following procedure was based upon the general procedure for preparing hydroxamic acids described by Sandler and Karo[9].

Ethanol (12 ml) and distilled water (15 ml) were added to a 250 ml round-bottomed flask along with a magnetic stirrer bar. With the stirrer running, hydroxylamine hydrochloride (6.99 g, 0.10 mol) was added in small spatula-fulls to assure complete dissolution. An ice-water bath was then inserted under the flask and the flask contents allowed to cool. While maintaining an internal temperature of below 20 ^{o}C, 10 M aqueous sodium hydroxide (20 ml, 0.2 mol) was slowly added. When the addition was complete, the ice-water bath was removed and, with continued stirring, freshly distilled ethyl acetate **181d** (10 ml, 9.01 g, 0.10 mol) was added from a Pasteur pipette, and stirring was continued for 1 h. The contents of the flask were then cooled as before and, with continued stirring, concentrated hydrochloric acid (*ca.* 7.5 ml, 0.09 mol) was added dropwise until the end point, as detected with pH paper, of pH 6 was reached. The reaction mixture was then evaporated to near dryness, after which ethanol (33 ml) was added and evaporation was continued to completion. The crystalline residue was extracted with two portions (33 ml each) of boiling ethyl acetate as follows: boiling ethyl acetate (33 ml) was added to the flask and the contents were stirred vigorously. Filtration separated off the insoluble sodium chloride. Another portion (33 ml) of ethyl acetate was added and the above procedure repeated. The combined, filtered extracts were then concentrated on a rotary evaporator until a faint cloudiness appeared. The solution was allowed to cool, and light petroleum was added to precipitate the product, acetohydroxamic acid **182d** (1.46 g, 19%) as a white solid; ν_{max} (Nujol mull)/cm^{-1} 1620.

3.6 **Preparation of benzohydroxamic acid** 182a **(Scheme 37).**

Methyl benzoate **181a** (4.55 g, 33 mmol) and hydroxylamine hydrochloride (2.31 g, 33 mmol) were allowed to react in the presence of 10 M sodium hydroxide solution in the manner previously described for acetohydroxamic acid. The usual work up afforded benzohydroxamic acid **182a** (1.22 g, 27%) as a pinkish solid; ν_{max} (Nujol mull)/cm^{-1} 1625; δ_H [90 MHz; CD_3SCD_3, ref. CHD_2SCD_3 (s) at δ 2.48] 7.1-7.9 (m, 5 X Ph-H), 8.93 (s, NH or OH) and 11.13 (s, NH or OH).

3.7 **Preparation of (±)-mandelohydroxamic acid** 182b **(Scheme 37).**

Methyl (±)-mandelate **181b** (5.07 g, 31 mmol) and hydroxylamine hydrochloride (2.14 g, 31 mmol) were allowed to react in the manner previously described for aceto-hydroxamic acid. The usual work up afforded (±)-mandelohydroxamic acid **182b** (880 mg, 17%) as a pinkish solid, m.p. 146-147 ^oC (from ethyl acetate-light petroleum) (lit.[42] 146-147 ^oC); ν_{max} (Nujol mull)/cm^{-1} 1640, 3170, 3280 and 3440; δ_H (90 MHz; CD_3SOCD_3, ref. CHD_2SOCD_3 at δ 2.49) 4.90 (s, C*H*OH), 5.90 (s, CHO*H*), 7.45 (m, 5 X Ph-H), 8.70 (s, NH or NHO*H*) and 10.65 (s, NH or NHO*H*).

3.8 **Preparation of** (R)-(-)-**mandelohydroxamic acid** 182c **(Scheme 37).**

(*R*)-(-)-Methyl mandelate **181c** (10.31 g, 62 mmol) and hydroxylamine hydrochloride (4.34 g, 62 mmol) were allowed to react in the presence of 10 M aqueous sodium hydroxide in the manner previously described for acetohydroxamic acid. The usual work up afforded (*R*)-(-)-mandelohydroxamic acid **182c** (4.32 g, 42%) as a pinkish solid, m.p. 137-139 ^oC (from ethyl acetate-light petroleum) (lit.[27] 138-139 ^oC); $[\alpha]_D$ -63.0^o (*c.* 1.6 in H_2O). The rotation value of $[\alpha]_D$ -162^o for (*R*)-(-)-mandelohydroxamic acid, as reported earlier by Nazeer[27], is in error. I am grateful to Mr. S. B. King of Cornell University, USA, who originally pointed this mistake out; Mr. King's own measurement

of the rotation was found to be in agreement with the new value reported above.

3.9 (E)-Penta-1,3-diene 111 and (Z)-penta-1,3-diene 112 (piperylene).

A sample of the diene piperylene (penta-1,3-diene, containing the (*E*)-isomer **111**) was presented as a gift, courtesy of Mr. J. H. Young (*Synthetic Chemicals Ltd.*). The label on the sample, however, did not give any indication of the diene's purity, particularly as to whether it was a single isomer or a mixture of (*Z*)- and (*E*)-isomers.

The ^{1}H NMR spectrum (200 MHz; $CDCl_3$) revealed only one *Me*CH doublet, but there were, by far, too many olefinic resonances in the spectrum to account for the presence of only one isomer alone. The sample thus appeared to consist of a mixture of (*Z*)- and (*E*)-isomers. This was confirmed by the ^{13}C NMR spectrum (50 MHz), which clearly showed two sets of signals, one set for each geometrical isomer. The NMR data were as follows, for the (*E*)-isomer **111** and the (*Z*)-isomer **112** respectively. δ_H (200.1 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) (*E*): 1.78 (d, with fine splitting, *J* 6.7, *Me*CH), 4.96 (dm, *J* 10.1, 1b-H), 5.09 (dm, *J* 16.9, 1a-H), 5.73 (dqm, *J* 14.9 and 6.7, 4-H), 6.09 (ddm, *J* 14.9 and 10.2, 3-H) and 6.33 (ddd, *J* 16.9, 10.2 and 10.1, 2-H); (*Z*): 1.78 (d, with fine splitting, *J* 7.1, *Me*CH), 5.12 (dm, *J* 12.4, 1b-H), 5.20 (dm, *J* 17.5, 1a-H), 5.54 (dqm, *J* 10.7 and 7.1, 4-H), 6.04 (ddm, *J* 10.7 and 10.0, 3-H) and 6.69 (dddd, *J* 17.5, 12.4, 10.0 and 1.1, 2-H); δ_C (50.3 MHz; $CDCl_3$, ref. $CDCl_3$ at δ 77.0) (*E*): 17.9 (Me), 114.3 (C-1), 129.7 (C-4), 132.3 (C-3) and 137.2 (C-2); (*Z*): 13.2 (Me), 116.5 (C-1), 126.7 (C-4), 130.1 (C-3) and 132.0 (C-2).

Proton and carbon NMR data for both of the piperylene isomers are summarised in, respectively, Tables 2 and 4. See, also, Table 3 for a selection of proton coupling constants.

The major isomer of the mixture was identified by examination of the two 4-H signals

in the ^{1}H NMR spectrum. Both signals were doublets of quartets (the quartets showing additional fine coupling), but the signal with the larger integral showed the greater doublet separation of the quartet components, due to the *trans* coupling constant, *J* 14.9 Hz; hence, the (*E*)-isomer was the major component. The signal 4-H for the (*Z*)-isomer showed the smaller *cis* coupling constant, *J* 10.7 Hz. Although the 4-H signals for each isomer could just be integrated separately, the 2-H protons gave the cleanest signals in the spectrum and so were used to obtain an approximate ratio of the two geometrical isomers. This ratio was found to be 1:2.36 (30:70) in favour of the (*E*)-isomer.

In the following experimental sections, the term 'piperylene **111/112**' specifically refers to the *mixture* of (*E*)- and (*Z*)-isomers.

3.10 **Preparation of the cycloadducts** 184d **and** 185d **from piperylene** 111/112 **and acetohydroxamic acid** 182d **(Scheme 38).**

The general procedure for the oxidation of hydroxamic acids in the presence of a conjugated diene is given by Kirby and Sweeny[2a].

Acetohydroxamic acid **182d** (0.75 g, 10 mmol) was added in small portions over 5-10 min, with stirring, to a solution of freshly distilled piperylene **111/112** (b.p. *ca.* 42 ^{o}C) (5 ml, 3.42 g, 50 mmol) and tetraethylammonium periodate (3.21 g, 10 mmol) in dichloromethane (80 ml) in a 100 ml round-bottomed flask at 0 ^{o}C (ice-water bath). Stirring was continued for a period of 45 min, after which the reaction solution was washed successively with equal volumes of 5% aqueous sodium thiosulphate, 10% aqueous sodium hydroxide, brine and distilled water. The organic solution was dried over anhydrous magnesium sulphate and evaporated to leave a yellow, oily residue consisting of a mixture of the isomeric, racemic cycloadducts 2-acetyl-3,6-dihydro-6-methyl-2*H*-1,2-oxazine **184d**, and 2-acetyl-3,6-dihydro-3-methyl-2*H*-1,2-oxazine **185d**

(621 mg in total, yield 44%); ν_{max} (liquid film)/cm^{-1} 1650 and 1670 (the bands were approx. of the same intensity); δ_H (200.1 MHz; C_6D_6, ref. C_6D_5H at δ 7.15) 0.90 (d, *J* 6.7. *Me*CH, **184d** or **185d**), 1.14 (d, *J* 6.7, *Me*CH, **184d** or **185d**), 1.91 (s, COMe, **184d** or **185d**), 1.95 (s, COMe, **184d** or **185d**), 3.69 (dm, J_{gem} 18.0, C*H*H, **184d** or **185d**, overlapped by the signal at δ 3.71), 3.71 (dm, J_{gem} 14.9, C*H*H, **184d** or **185d**, overlapped by the signal at δ 3.69), 3.96 (dm, J_{gem} 14.9, C*H*H, **184d** or **185d**), 4.12 (m, MeC*H*, **184d** or **185d**), 4.29 (dm, J_{gem} 18.0, C*H*H, **184d** or **185d**), 4.78 (m, MeC*H*, **184d** or **185d**) and 5.20-5.45 (4 X dm, 4- and 5-H, **184d** and **185d**); δ_C (50.3 MHz; C_6D_6, ref. C_6D_6 at δ 128.0) 17.5 (3-Me, **185d**), 18.6 (6-Me, **184d**), 19.9 (CO*Me*, **184d** or **185d**), 20.2 (CO*Me*, **184d** or **185d**), 41.5 (C-3, **184d**), 47.5 (C-3, **185d**), 69.4 (C-6, **185d**), 75.2 (C-6, **184d**), 122.3 (C-4, **184d** or **185d**), 123.0 (C-4, **184d** or **185d**), 128.3 (C-5, **184d** or **185d**), 128.9 (C-5, **184d** or **185d**), 168.5 (*C*OMe, **184d** or **185d**) and 169.4 (*C*OMe, **184d** or **185d**); *m/z* 141 ($M^{+\cdot}$). No separation of the isomers **184d** and **185d** was achieved on t.l.c. [R_f 0.53, ethyl acetate-light petroleum (1:1)]. The ratio of the isomers (*ca.* 1:1) was obtained by integration of the *Me*CH doublets in the 200 MHz NMR spectrum. Because the isomers were present in approximately equal amounts, proton chemical shifts could not be assigned to a specific isomer. Certain carbon chemical shifts, however, were assigned to isomers on the basis of simple electronegativity arguments (*i.e.* oxygen causing a larger downfield shift than nitrogen).

See Tables 6 and 7 for a summary of, respectively, proton and carbon NMR data on both the cycloadducts.

3.11 **Preparation of the cycloadducts** 184a **and** 185a **from piperylene** 111/112 **and benzohydroxamic acid** 182a **(Scheme 38).**

The cycloadducts were prepared as in the preceding experiment by the addition of benzohydroxamic acid **182a** (1.36 g, 9.9 mmol) to a solution in dichloromethane (50 ml) of piperylene **111/112** (5 ml, 3.42 g, 50 mmol) and tetraethylammonium periodate (3.18

g, 9.9 mmol) at 0 °C. The usual work up afforded a yellow oil consisting of a mixture of the isomeric, racemic cycloadducts 2-benzoyl-3,6-dihydro-6-methyl-2*H*-1,2-oxazine **184a**, and 2-benzoyl-3,6-dihydro-3-methyl-2*H*-1,2-oxazine **185a** (1.17 g in total, yield 58%); ν_{max} (liquid film)/cm^{-1} 1645 and 1665 (the former band was the more intense); δ_H (200.1 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) 1.11 (d, *J* 6.7, *Me*CH, **184a**), 1.39 (d, *J* 6.7, *Me*CH, **185a**), 4.04 (dm, J_{gem} *ca.* 16.6, C*H*H, **184a**, partially overlapped by the signal at δ 4.14), 4.14 (dm, J_{gem} *ca.* 15.3, C*H*H, **185a**, partially overlapped by the signal at δ 4.04), 4.45 (dm, J_{gem} *ca.* 15.3, C*H*H, **185a**, partially overlapped by the signal at δ 4.54), *ca.* 4.50 (m, MeC*H*, **184a**, hidden underneath two partially overlapping signals at δ 4.45 and 4.54), 4.54 (dm, J_{gem} *ca.* 16.6, C*H*H, **184a**, partially overlapped by the signal at δ 4.45), 4.87 (m, MeC*H*, **185a**), 5.6-5.9 (4 X dm, 4- and 5-H, **184a** and **185a**) and 7.2-7.8 (m, 10 X Ph-H, **184a** and **185a**); δ_C (50.3 MHz; $CDCl_3$, ref. $CDCl_3$ at δ 77.0) 17.8 (3-Me, **185a**), 18.6 (6-Me, **184a**), 42.9 (C-3, **184a**), 48.9 (C-3, **185a**), 69.7 (C-6, **185a**), 75.4 (C-6, **184a**), 121.6 (C-4, **184a**), 122.6 (C-4, **185a**), 127.7 (phenyl-CH, **184a**), 127.8 (phenyl-CH or C-5, **185a**), 128.0 (phenyl-CH or C-5, **185a**), 128.4 (phenyl-CH, **184a**), 128.6 (phenyl-C, **184a** or **185a**. Other phenyl-C could not be found - it was assumed to overlap another signal), 128.7 (phenyl-CH or C-5, **184a** or **185a**), 128.8 (phenyl-CH or C-5, **184a** or **185a**), 130.4 (phenyl-CH or C-5, **184a** or **185a**), 130.6 (phenyl-CH or C-5, **184a** or **185a**), 168.8 (*C*OPh, **185a**) and 169.4 (*C*OPh, **184a**); *m/z* 203 ($M^{+\cdot}$). No separation of the isomers **184a** and **185a** could be achieved on t.l.c. in ether-light petroleum (1:1). Two spots, R_f 0.45 (intense) and R_f 0.71 (very faint) were observed (double elution). However, the spot with R_f 0.71 was due to an impurity. The ratio of the isomers was determined from the proton NMR spectrum. Integration of the *Me*CH doublets gave an approximate ratio of 1:2.8, **184a** being the major isomer. Identification of the isomers was made on the basis of the simple electronegativity argument that oxygen shifts the methylene signal for C-6 (δ 69.7) in **185a** further downfield than nitrogen shifts that for the methylene signal for C-3 (δ 42.9) in **184a**.

Summaries of proton and carbon NMR data on both the cycloadducts are given,

respectively, in Tables 8 and 9.

3.12 Preparation of the cycloadducts 186-189 from piperylene 111/112 and (±)-mandelohydroxamic acid 182b (Scheme 38).

(±)-Mandelohydroxamic acid **182b** (839 mg, 5.0 mmol) was added in portions to a solution in dichloromethane (50 ml) of piperylene **111/112** (5 ml, 3.41 g, 50.1 mmol) and tetraethylammonium periodate (1.766 g, 5.5 mmol) at 0 ^{o}C in the manner previously described for acetohydroxamic acid. The usual work up produced a crude mixture containing the four isomeric, racemic cycloadducts **186**, **187**, **188** and **189** in the form of an orange-brown sticky solid (490 mg in total, yield 42%). A preliminary, proton NMR (200 MHz; $CDCl_3$) spectrum of the crude reaction mixture showed four, upfield, methyl doublets at δ 1.01, 1.16, 1.20 and 1.32, indicating the formation of all four possible, racemic stereoisomers. Analytical t.l.c. [ether-light petroleum (1:1); triple elution], revealed three spots of R_f 0.26, 0.44 and 0.55, indicating that two of the isomers were running together.

The crude reaction mixture was chromatographed on a silica column by conventional 'flash-column' techniques. The method employed and subsequent results are explained in detail in the following section.

3.13 Chromatographic separation and purification of the mixture of cyclo-adducts 186-189.

A sample of the crude reaction mixture (490 mg), containing the four cycloadducts **186**, **187**, **188** and **189** was chromatographed on a column (sintered glass funnel, 75 mm long X 42 mm wide) containing *Merck* Kieselgel HF_{254} silica (*ca.* 20 g). A mixture of ethyl acetate and light petroleum was used for elution. Pure light petroleum was used to elute the first fraction (*ca.* 25 ml) collected, each subsequent fraction being eluted

with progressively less light petroleum and more ethyl acetate; an increase in the mole fraction of ethyl acetate was made of *ca.* 0.04-0.08 (mole fraction units) per fraction until about the 10th or 11th fraction after which a constant mixture (1:1) of the two solvents was used. About 15 fractions (25 ml each) were collected in all. The first 6 fractions did not show any signs of product and so were rejected. Products first started to appear in fraction 7 and 8 (total weight *ca.* 15 mg), with the bulk of material being collected in fractions 9-12 (total weight *ca.* 375 mg). Fraction 13 contained little (*ca.* 12 mg) material, and all subsequent fractions contained nothing observable. Total weight of material isolated was *ca.* 400 mg (recovery, 82%).

Analytical t.l.c. [ether-light petroleum (1:1); triple elution] of fractions 7-10 showed two spots (R_f 0.44 and 0.55), and subsequent NMR and X-ray studies revealed that the topmost spot (R_f 0.55) was due to the diastereoisomer **188** having a 3-methyl group. The lower spot (R_f 0.44) was similarly shown to be due to the diastereoisomer **187** with a 6-methyl group. T.l.c. (as before) of fractions 11-13 revealed only one spot (R_f 0.26). However, they were later found to contain the diastereoisomeric partners **186** and **189** of the cycloadducts found in previous fractions, 7-10.

Fractions 11-13 were combined and evaporated and the residue was dissolved in deuteriochloroform for NMR analysis. After a few days in the NMR tube at room temperature, some of the solvent had evaporated to leave a solution containing some clear crystals (m.p. 113-117 ^{o}C). The proton and carbon spectra showed the crystals to be of a single, 6-methyl diastereoisomer, *i.e.* **186** or **187**. A crystal was submitted for X-ray structure analysis, and the relative configuration of this racemate determined to be *(6S,6R)-2-[(2S,2R)-2-hydroxy-2-phenyl] acetyl -3,6- dihydro -6- methyl -2H-1,2- oxazine* **186**. This automatically fixed the configuration of the diastereoisomeric partner **187** (R_f 0.44), found in fractions 7-10. An attempt was made to crystallise the isomer **186** from ordinary chloroform instead of the deuteriochloroform, but this failed; it seems that the compound is less soluble in $CDCl_3$ than in $CHCl_3$.

The combined contents of fractions 7-10 were dissolved in a small volume of warm dichloromethane. Light petroleum was gradually added, and the solution left overnight. By the next day clear crystals (m.p. 100-103 ^{o}C) had formed. The proton and carbon NMR spectra showed the crystals to be of a single, 3-methyl diastereoisomer, *i.e.* **188** or **189** (t.l.c. gave one spot, R_f 0.55). A sample was submitted for X-ray structure analysis, and the relative configuration of this racemate was determined to be *(3S,3R)-2-[(2S,2R)-2-hydroxy-2-phenyl]acetyl-3,6-dihydro-3-methyl-2H-1,2-oxazine* **188**. As before, this automatically fixed the configuration of the other diastereoisomeric partner **189** (R_f 0.26), found in fractions 11-13. No attempts were made to isolate and purify compounds **187** and **189**.

The relative amounts of the four cycloadducts were determined by proton NMR spectroscopy (200 MHz). In deuteriochloroform, two of the methyl doublets (δ 1.16, **189** and 1.20, **186**) partially overlapped thus preventing reliable integrals from being taken. In hexadeuteriobenzene, however, a slightly better separation of the doublets was achieved (δ 0.64, **187**; 0.69, **186**; 0.87, **189**; and 1.08, **188**), and the ratio of the cycloadducts was determined to be, **186**:**187**:**188**:**189** = 2.94:1.00:1.16:1.19, corresponding to 47, 16, 18 and 19%, respectively. These represent the results for a reaction temperature of 0 ^{o}C. The experiment was repeated under the same conditions except that the reaction temperature was -70 ^{o}C [achieved with an acetone-CO_2(s) bath]. The ratios were measured in the same way, and found to be **186**:**187**:**188**:**189** = 2.19:1.00:1.32:1.19, corresponding to 38, 18, 23 and 21%, respectively.

Details of the foregoing chromatographic separation are summarised in Table 12.

Experimental data on the four cycloadducts are given below. Since the mandelohydroxamic acid used in the synthesis was a racemic mixture, all of the products were racemates. The NMR spectra of the isomers **187** and **189**, which were not isolated in a

pure state, were obtained from mixtures with the crystalline isomers **188** and **186**, respectively.

(6S,6R)-2-[(2S,2R)-2-hydroxy-2-phenyl] acetyl -3,6- dihydro -6- methyl -2H-1,2- oxazine **186**; m.p. 113-117 ^{o}C (from deuteriochloroform) (Found: C, 67.2; H, 6.6; N, 6.0. $C_{13}H_{15}NO_3$ requires C, 66.95; H, 6.4; N, 6.0%); ν_{max} ($CHCl_3$)/cm^{-1} 1650, 1670 (former band the more intense) and 3470; δ_H (200.1 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) 1.20 (d, *J* 6.7, *Me*CH), 3.80 (dm, J_{gem} 17.6, C*H*H), 4.25 (br s, OH, exch. with D_2O), 4.55 (dm, J_{gem} 17.6, C*H*H), 4.68 (m, MeC*H*), 5.33 (s, C*H*OH), 5.73 (2 X dm, 4- and 5-H) and 7.2-7.5 (m, 5 X Ph-H); δ_C (50.3 MHz; $CDCl_3$, ref. $CDCl_3$ at δ 77.0) 18.5 (Me), 41.9 (C-3), 71.3 (CHOH), 75.9 (C-6), 121.3 (C-4), 127.10 (phenyl-CH), 128.17 (phenyl-CH or C-5), 128.47 (phenyl-CH), 128.58 (phenyl-CH or C-5), 139.5 (phenyl-C) and 171.0 (C=O); *m/z* 233.1053. $C_{13}H_{15}NO_3$ requires *M*, 233.2694.

(6*R*,6*S*)-2-[(2*S*,2*R*)-2-hydroxy-2-phenyl] acetyl -3,6- dihydro -6- methyl -2*H*-1,2- oxazine **187**; δ_H (200.1 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) 1.01 (d, *J* 6.7, *Me*CH), 3.21 (m, MeC*H*), 3.90 (dm, J_{gem} 17.6, C*H*H), 4.43 (dm, J_{gem} 17.6, C*H*H), *ca.* 4.43 (br s, OH, exch. with D_2O, superimposed on the signal at δ 4.43), 5.38 (s, C*H*OH), 5.49 (dm, 4- or 5-H), 5.71 (dm, 4- or 5-H) and 7.2-7.5 (m, 5 X Ph-H); δ_C (50.3 MHz; $CDCl_3$, ref. $CDCl_3$ at δ 77.0) 18.2 (Me), 42.3 (C-3), 71.7 (CHOH), 74.8 (C-6), 120.5 (C-4), 127.06 (phenyl-CH), 128.30 (phenyl-CH or C-5), 128.56 (phenyl-CH), 128.83 (phenyl-CH or C-5), 139.7 (phenyl-C) and 171.2 (C=O).

(3S,3R)-2-[(2S,2R)-2-hydroxy-2-phenyl] acetyl -3,6- dihydro -3- methyl -2H-1,2- oxazine **188**; m.p. 100-103 ^{o}C (from dichloromethane-light petroleum) (Found: C, 66.7; H, 6.5; N, 5.95. $C_{13}H_{15}NO_3$ requires C, 66.95; H, 6.4; N, 6.0%); ν_{max} ($CHCl_3$)/cm^{-1} 1645, 1665 (former band the more intense) and 3450; δ_H (200.1 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) 1.32 (d, *J* 6.7, *Me*CH), 3.02 (dm, J_{gem} 15.5, C*H*H), 3.77 (dm, J_{gem} 15.5, C*H*H), 4.45 (br s, OH, exch. with D_2O), 4.70 (m, MeC*H*), 5.32 (s, C*H*OH), 5.55 (dm, 4- or 5-H),

5.70 (dm, 4- or 5-H) and 7.2-7.5 (m, 5 X Ph-H); δ_C (50.3 MHz; $CDCl_3$, ref. $CDCl_3$ at δ 77.0) 17.5 (Me), 48.9 (C-3), 68.8 (C-6), 71.8 (CHOH), 122.7 (C-4), 126.60 (phenyl-CH or C-5), 127.79 (phenyl-CH), 128.23 (phenyl-CH or C-5), 128.62 (phenyl-CH), 139.9 (phenyl-C) and 170.6 (C=O); *m/z* 233.1075. $C_{13}H_{15}NO_3$ requires *M*, 233.2694.

(3*R*,3*S*)-2-[(2*S*,2*R*)-2-hydroxy-2-phenyl] acetyl -3,6- dihydro -3- methyl -2*H*-1,2- oxazine **189**; δ_H (200.1 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) 1.16 (d, *J* 6.8, *Me*CH), 4.24 (dm, J_{gem} 16.2, C*H*H), 4.33 (br s, OH, exch. with D_2O, partially overlapping with the signal at δ 4.24), 4.54 (dm, J_{gem} 16.2, C*H*H), 4.81 (m, MeC*H*), 5.33 (s, C*H*OH), 5.77 (2 X dm, 4- and 5-H) and 7.2-7.5 (m, 5 X Ph-H); δ_C (50.3 MHz; $CDCl_3$, ref. $CDCl_3$ at δ 77.0) 17.3 (Me), 48.3 (C-3), 69.9 (C-6), 71.3 (CHOH), 122.3 (C-4), 126.75 (phenyl-CH), 127.18 (phenyl-CH or C-5), 127.57 (phenyl-CH or C-5), 127.91 (phenyl-CH or C-5), 139.3 (phenyl-C) and 170.2 (C=O).

Proton and carbon NMR data on the cycloadducts **186-189** are summarised, respectively, in Tables 10 and 11. The X-ray crystal structure of **186** is shown in Figure 15, and that of **188** in Figure 16.

3.14 Preparation of (±)-1-(2'-hydroxyphenylacetyl)piperidine 194 (Scheme 39).

This synthesis is adapted from that published by Cocolas *et al.*[43].

Acetyl chloride (7.3 ml, 8.03 g, 102 mmol) was added to (±)-mandelic acid **179b** (1.50 g, 9.9 mmol) and the resulting solution was stirred at room temperature for 30 min. The excess of acetyl chloride was evaporated to leave the acetate **190** of mandelic acid. This crude acetate was then heated under reflux for 35 min with thionyl chloride (2.9 ml, 4.73 g, 40 mmol). The excess of thionyl chloride was then evaporated to leave, as a solid residue, the acid chloride **191**. This was dissolved in chloroform (20 ml) and added, with stirring, to a solution of piperidine **192** (1.7 ml, 1.46 g, 17 mmol) in

chloroform (20 ml). Stirring was continued for a period of 2 h. The chloroform solution was then washed with dilute hydrochloric acid (20 ml), followed by distilled water (20 ml). The organic solution was dried with anhydrous magnesium sulphate, and the chloroform was evaporated, leaving an oil that solidified on cooling to a brown solid residue, the amide-acetate **193**. Removal of the acetyl group was achieved by stirring overnight at room temperature in ethanolic sodium hydroxide [ethanol (25 ml) and 2 M sodium hydroxide (25 ml)]. After hydrolysis, the ethanol was evaporated and the remaining, aqueous solution diluted with distilled water (20 ml). The solution was acidified with dilute hydrochloric acid (20 ml), and was then extracted with dichloromethane (20 ml). The organic extract was dried with anhydrous magnesium sulphate and evaporated to dryness, leaving a brown oil that solidified on cooling to give (±)-1-(2'-hydroxyphenylacetyl)piperidine **194** (1.40 g, 65% from the original acid **179b**). The crude solid was recrystallised from ether, yielding pale brown needles, m.p. 75-77 ^{o}C (lit.[44] 77 ^{o}C); ν_{max} ($CHCl_3$)/cm^{-1} 1640 and 3390; δ_H (90 MHz; $CDCl_3$, ref. $CHCl_3$ at δ 7.25) 0.7-1.9 (m, 3-, 4- and 5-H_2), 3.0-4.0 (m, 2- and 6-H_2), 4.85 (d, *J ca.* 6, CHO*H*, exch. with D_2O), 5.20 (d, *J ca.* 6, C*H*OH, collapsed to s after D_2O exch.) and 7.35 (s, 5 X Ph-H).

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