INVESTIGATION OF DIASTEREOMERIC INDUCTION IN THE DIELS-ALDER REACTIONS OF ACYLNITROSO DIENOPHILES.

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Thesis submitted for the degree of Doctor of Philosophy.

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Oxidation of hydroxamic acids, and also related N-hydroxyureas and N-hydroxycarbamates, gives acylnitroso dienophiles. These are highly reactive species and cannot be isolated, however they can be trapped with dienes, undergoing hetero Diels-Alder reactions to give cycloadducts. The aim of this project was to investigate diastereomeric induction in the hetero-Diels-Alder reactions of acylnitroso dienophiles by attaching them to chiral auxiliaries. The chiral auxiliaries used were mainly based on 1,2-trans-cyclohexylamines or 1,2-trans-cyclohexanols and used a large equatorial 2-substituent to shield one face of the dienophile. It was hoped that intramolecular hydrogen bonding in nitrosoformamide dienophile 234 would restrict the rotation of the dienophile and hence increase the diastereoselectivity of the cycloaddition, in comparison with nitrosoformate dienophiles 238 and 292 which cannot have this intramolecular hydrogen bonding.

These hetero Diels-Alder reactions were carried out at both 0°C and -78°C using either tetraethylammonium periodate or Swern oxidation conditions to generate the acylnitroso dienophile which was trapped in situ with either cyclopentadiene or cyclohexadiene. The ratio of diastereomers was measured by NMR spectroscopy. It was found that:-

1. Cycloadditions of both the nitrosoformamide and nitrosoformate dienophiles proceeded in good yield, giving the expected cycloadducts with both cyclopentadiene and cyclohexadiene.
2. A phenyl or C(CH₃)₂Ph group gave modest diastereomeric ratios (d.r.) 3:1 to 7:1, with best d.r. 7:1 with 8-phenylmenthol as a chiral auxiliary. Changing the large group to a phthaloyl group resulted in no diastereomeric induction.
3. Highest diastereomeric induction was obtained at low temperature using the Swern oxidation conditions.
4. Intramolecular hydrogen bonding in nitrosoformamide dienophiles had little effect since there was little difference in diastereoselectivity between nitrosoformamide dienophiles and the corresponding nitrosoformate dienophiles.
5. The camphor based dienophiles did not show any diastereoselection.

The initially formed mixtures of diastereomers were separated by a combination of chromatography and recrystallisation. The stereochemistry of the major diastereomers was determined by X-ray crystallography. Assuming that the diene attacks the nitroso group in an endo manner from the face opposite to the large group, then the X-ray structures suggest that nitrosoformate 238 reacts via a trans conformation of the acylnitroso group whilst nitrosoformamide 234 and nitrosoformate 292 react via a cis conformation of the acylnitroso group.
I would like to thank Prof. Kirby for all his help and support throughout this work. I would also like to thank my wife, Sandra and my mum and dad for their encouragement. Thanks to Dr Gary Tustin for helpful comments and advice, Dr Robert Atkinson for encouragement and Dr David Morris and Dr Karl Ryder for many stimulating conversations.
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Section 1.1 Introduction to acylnitroso cycloadditions.

Scheme 1.

Scheme 2.

Scheme 3.
Section 1.1 Introduction to acylnitroso cycloadditions.

Section 1.1.1 Introduction.

Acylnitroso compounds 1 can undergo a Diels-Alder reaction with dienes to form cycloadducts 2 (Scheme 1). In this introduction, I will attempt to review several main divisions of these Diels-Alder reactions.

i. The different types of nitroso dienophiles. I will mainly concentrate on acylnitroso dienophiles, but I will briefly consider $\alpha$-chloronitroso dienophiles, with special attention on the use of chiral induction in these reactions.

ii. The different types of dienes that can be used and the chemistry of the cycloadducts formed.

iii. Attempts to control the stereochemistry of the reaction using chiral auxiliaries to make chiral dienophiles i.e. attempts to produce only one diastereomer in the reaction.

iv. The use of the regiochemical and stereochemical control to create synthetically useful adducts and the further manipulation of these adducts to make the desired targets.

Section 1.1.2 Nitroso compounds and their use in Diels-Alder reactions.

The nitroso compounds can be subdivided into 3 classes, with increasing electron withdrawing substituents, leading to greater reactivities:-

i. arene nitroso compounds e.g. nitrosobenzene,

ii. $\alpha$-chloronitroso compounds e.g. $\alpha$-chloronitrosocyclohexyl

iii. acylnitroso compounds, on which I will concentrate.

In the nitrosobenzenes, the presence of electron withdrawing groups greatly increases the rate of the reaction e.g. $p$-nitro nitrosobenzene reacts 3500 times faster than $p$-methoxy nitrosobenzene with cyclohexadiene.¹

With the $\alpha$-chloronitroso compounds 6 (Scheme 2) the cycloaddition reaction is slow. However, since the initially formed cycloadduct 7 is solvolysed in alcoholic solvents, to give oxazine salt 8 and acetal 9, the reaction is irreversible. The acetal can easily be converted back into the parent ketone, a transformation that is especially useful for chiral ketones which can then be recovered.
Section 1.1.3 C-nitrosocarbonyl compounds. What are acylnitroso compounds?

As the name suggests, these compounds have a nitroso group next to a carbonyl group and due to the electron withdrawing effect of the carbonyl group are very good dienophiles in hetero Diels-Alder reactions. They can react with a wide variety of dienes to form cycloadducts. Indeed, they are so reactive that they cannot be isolated and have to be generated in situ. One method of generation of acylnitroso derivatives is by oxidation of the corresponding hydroxamic acid 3 or hydroxamic acid derivative hydroxyurea 4 or hydroxycarbamate 5 (Scheme 1). Acylnitroso compounds can also be generated by heating a cycloadduct (e.g. the cycloadduct of dimethylanthracene (DMA) 16 or 17) whereupon a retro Diels-Alder reaction occurs releasing the acylnitroso compound which can then be trapped with another diene (Scheme 3). Both of these methods have been used in the literature although it is more common to use the oxidation method. Other derivatives of hydroxamic acids can be used to generate acylnitroso derivatives, e.g. hydroxyureas 4 and N-hydroxycarbamates 5.

Section 1.1.4 Generation of acylnitroso dienophiles.

Hydroxamic acids can be oxidised in a variety of ways, the most common way is to use a periodate salt. The periodate can be present as either the sodium salt or since most of these reactions are carried out in non aqueous solvents, as an ammonium salt, which can be used as a phase transfer reagent. Ammonium periodate salts can be easily made by neutralising the appropriate ammonium hydroxide with periodic acid.

An advantage of using periodate salts is that they are very easy to use. However there are several disadvantages in using periodate salts:

i. Most importantly, as the temperature of the reaction drops, so does the rate of the oxidation reaction and although it is very fast between 0°C and room temperature, at lower temperatures, incomplete oxidation and very slow reactions can be a problem.

ii. It can also be too fierce for some more sensitive dienes and hydroxamic acids leading to degradation, although this is not a problem with the simpler dienes e.g. cyclopentadiene and cyclohexadiene.
Section 1.1 Introduction to acyl nitroso cycloadditions.

\[ \text{HOHN} \xrightarrow{\text{Et}_4\text{NIO}_4, \text{CH}_2\text{Cl}_2} \text{O} \]

\[ \begin{align*}
\text{benzene, heat} & \quad \xrightarrow{\Phi_3\Phi} \\
\end{align*} \]

18a R = H, b R = Cl, c R = MeO, d R = NO₂

\[ \text{Scheme 4.} \]

\[ \begin{align*}
\text{20} \xrightarrow{\text{PhCON}=\text{O}} & \quad \xrightarrow{\text{PhCON}=\text{O}} \\
\end{align*} \]

\[ \text{21} \]

\[ \text{Scheme 5.} \]
Section 1.1 Introduction to acylnitroso cycloadditions.

\[
\begin{align*}
R-N=O & \quad \xrightarrow{\text{cyclopentane}} \quad R-N \\
R & = \begin{array}{c}
\text{NO}_2 + \text{CH}_3 + \text{NO}_2 \\
\text{S} & \text{O} & \text{Ph-CO}
\end{array} \\
\text{F}_3\text{CO} & \quad \text{O}_2\text{N} + \begin{array}{c}
\text{NO}_2 \\
\text{H}_2\text{N} & \text{H}_2\text{N} & \text{CO}
\end{array} \\
\text{CF}_3\text{CO-N} & \quad \xrightarrow{\text{H}_2, \text{cat}} \quad \text{CF}_3\text{CO-N} \\
\text{CF}_3\text{CO-} & \quad \xrightarrow{\text{NaBH}_4} \quad \text{HN}
\end{align*}
\]

\[
\begin{align*}
\text{NO}_2 & \quad \text{NO}_2 \quad \text{NO}_2 \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{22} & \quad \xrightarrow{1. \text{diborane} \quad 2. \text{AcOH}} \quad \text{NO}_2 & \quad \text{NO}_2 \\
\text{23} & \quad \xrightarrow{\text{NH}_3, \text{MeOH} \quad \text{or KOH, MeOH}} \quad \text{HN} & \quad \text{HN}
\end{align*}
\]

Scheme 6.
Section 1.1 Introduction to acylnitroso cycloadditions.

Scheme 7.
Section 1.1 Introduction to acylnitroso cycloadditions.

Section 1.1.5 Reactions of acylnitroso dienophiles in hetero Diels-Alder reactions.

C-nitrosocarbonyl compounds 2 have been trapped in Diels-Alder reactions. Kirby and Sweeny found that when aceto or benzo hydroxamic acids were oxidised with periodate, the acylnitroso derivatives 10&11 formed were trapped with thebaine 12 to give the corresponding adducts 13 and 14 in high yield (Scheme 3). The corresponding adducts with cyclopentadiene, cyclohexadiene and DMA could also be formed. When dimethylantracene adducts 16 & 17 were heated in benzene in the presence of thebaine 12 they could be converted to the thebaine cycloadducts 13 & 14. This intramolecular diene transfer has been used in synthesis.

Further evidence for the presence of the acylnitroso compounds as intermediates came when Kirby et al heated the dimethylantracene cycloadducts 18a-d in the presence of triphenylphosphine resulting in the formation of the isocyanates 19a-d. (Scheme 4).3

Acylnitroso compounds can also react with dienes in an ene type reaction. However since the Diels-Alder reaction is faster than the ene reaction, the Diels-Alder reaction is usually observed. An interesting exception to this is the trapping of acylnitroso dienophiles with dimethylbutadiene 20 (Scheme 5). This diene cannot adopt a cis, cis conformation due to steric repulsion of the two methyl groups and is forced to adopt a trans, trans conformation. This means that it cannot undergo a Diels-Alder reaction and instead undergoes an ene type reaction with nitrosobenzene to give 21.

Just and Gutrone have reported that a variety of dienophiles can react with cyclopentadiene to give the corresponding cycloadducts (Scheme 6). Hydrogenation of cycloadduct 22 gave oxazobicycloheptane 23 which was then hydrolysed under basic conditions to give the free amine 24.

Kirby et al formed cyclopentadiene adduct 25, cyclohexadiene adduct 26 and DMA adduct 17 from acylnitroso dienophile 11 derived from benzohydroxamic acid (Scheme 7). The attempted trapping of dienophile 11 with cyclooctatetraene proved unsuccessful although this cycloadduct 27 could be made by intramolecular diene transfer with dimethylanthracene adduct 17 or by reaction of 11 with diene 28 and dehalogenation of the diastereomeric cycloadducts 29a&b with zinc (Scheme 7).
Section 1.1 Introduction to acylnitroso cycloadditions.

Scheme 8.
Section 1.1 Introduction to acylnitroso cycloadditions.

35 a) R= PhCH$_2$
b) R= CCl$_3$CH$_2$
c) R= Bu$^t$
d) R= 4-MeC$_6$H$_4$SO$_2$CH$_2$CH$_2$

\[ R\text{-O} - \text{N} \]

36

\[ \text{a, b and c} \]

\[ \text{a} \]

37

\[ \text{b} \]

38

\[ \text{b} \]

39

\[ \text{a} \]

40

\[ \text{a, c and d} \]

41

\[ \text{a} \text{ and } \text{b} \]

42

Scheme 9.
Section 1.1 Introduction to acylnitroso cycloadditions.

\[
\text{R}^*\text{X}_\text{NHOH} \xrightarrow{\text{oxidant}} \text{Acylnitroso} \xrightarrow{\text{mixture of diastereomers}} \text{R}^*\text{X}_\text{N} \text{O} \text{C} \text{O}
\]

\[\text{R}^*\text{X} = \text{R}^*\text{NH}, \text{Hydroxyurea} \]
\[\text{R}^*\text{X} = \text{R}^*\text{O}, \text{Hydroxycarbamate} \]
\[\text{R}^*\text{X} = \text{R}^*, \text{Hydroxamic acid} \]

Scheme 10.
Kirby et al\(^6\) have also reported the reaction of C-nitrosoformamides (derived from hydroxyureas 30a-e, by oxidation with periodate) with 2,3-dimethylbutadiene, cyclopentadiene and cyclohexadiene to give the expected adducts 31, 32 and 33 (Scheme 8). Attempted diene exchange between the cyclopentadiene adduct 32 and 2,3-dimethylbutadiene gave the expected cycloadduct 31 and ene product 34 as a 20\% by-product (Scheme 8) indicating that for the C-nitrosoformamides, the ene reaction is only four times slower than the Diels-Alder reaction. Kirby et al\(^6\) have also investigated the reactions of C-nitrosoformates 35a-d and found that they form the expected adducts 36-42 with cyclopentadiene, butadiene, 2,3-dimethylbutadiene, bicyclohexenyl, dimethylanthracene, thebaine and ergosteryl acetate respectively, (Scheme 9).

**Section 1.1.6 Diastereomeric Induction.**

If the hydroxamic acid is attached to a chiral auxiliary then it will no longer be achiral and most importantly, the acylnitroso derivative generated from this chiral hydroxamic acid will also be chiral. When such a chiral dienophile is reacted with either a prochiral or a chiral diene then the resulting cycloadducts will be formed as a mixture of diastereomers (Scheme 10). Since the cycloadducts are diastereomers, they will be formed \textit{via} diastereomeric transition states which will not be of equal energies and so a disparate ratio of diastereomers will be formed. Hence, stereoselection can be introduced to the reaction. The degree of diastereoselection depends on the chiral auxiliary used, the diene, the method of oxidation, the temperature and the solvent used. Diastereoselection is increased at lower temperatures, since although the energy difference between the two possible transition states is temperature independent, as the temperature of the reaction drops, so the overall energy of the molecules is reduced and it becomes a proportionately larger barrier. This means that as the temperature falls \textbf{more} of the reaction proceeds \textit{via} the lower energy transition state and \textbf{less} by the higher energy transition state. As has already been stated, the periodate reaction is more effective at higher temperatures and so other methods of oxidation may have to be used if the reaction is to be carried out efficiently at lower temperatures.

The Corey oxidation conditions can be used, \textit{i.e.} \textit{N}-chlorosuccinimide (NCS) and dimethyl sulfoxide or the Swern oxidation conditions \textit{i.e.} dimethyl sulfoxide (DMSO) and oxalyl chloride (Scheme 11). In both of these methods, the triethylamine, which is added to
Section 1.1 Introduction to acylnitroso cycloadditions.

Swern Oxidation.

Corey Oxidation

Scheme 11.
decompose the initially formed hydroxamic acid-sulfur compound, can be added very slowly using a syringe pump in an attempt to increase the diastereomeric induction.
Section 1.2 Use of acynitroso derivatives in racemic synthesis.

Scheme 12.

Scheme 13.
Section 1.2.1 Racemic synthesis involving acylnitroso derivatives

The hetero Diels-Alder reaction between acylnitroso dienophiles and dienes is a useful method for the synthesis of cis-1,4-aminoalcohols. These compounds can be used as synthetic intermediates in the synthesis of many natural products, pharmaceuticals and other interesting molecules. One obvious advantage of these intermediates is the presence of the double bond which can be further functionalised e.g. to give diols or dicarboxylic acids. The wide range of dienes which can react with acylnitroso dienophiles leads to many synthetically useful intermediates. This section will deal with some synthetic uses of the racemic cycloaddition reaction that have been reported in the literature.

Section 1.2.2 Investigation of the synthesis of lycoricidine 87

The first investigations into the synthetic utility of cycloadducts was carried out by Keck and Fleming\(^1\) in which they investigated the synthesis of 1,4-aminoalcohol 45 (Scheme 12) which is an intermediate in the synthesis of lycoricidine 87 and other narcissus alkaloids. These alkaloids show potent anti-tumour activity against larynx and cervix carcinoma.

The desired cis-aminoalcohol 46 was obtained by reacting phenyl nitrosocarbonyl with cyclohexadiene to give cycloadduct 44. The oxazine N-O bond was then cleaved with aluminium amalgam to give cis-1,4-aminoalcohol derivative 45. This was then oxidised with osmium tetroxide and N-methylmorpholine-N-oxide (NMO) giving anti-dihydroxylate 46 as the sole product.

Section 1.2.3 Synthesis of 14-β-aminocodeine 50.

Kirby and McLean have prepared 14-β-aminocodeine 50\(^9\) from thebaine 12 using acylnitroso derivatives (Scheme 13). Trichloroethoxy acylnitroso dienophile reacted with thebaine to give the desired cycloadduct 47 as the only regioisomer in good yield. This was converted to the ethylene acetal 48 using ethylene glycol and dry HCl. After reduction to the amino acetal 49 with zinc and ammonium chloride, the acetal group was hydrolysed with methanolic HCl to give the product 50. All of the reactions proceeded with good yields.
Section 1.2 Use of acyl nitroso derivatives in racemic synthesis.

\[
\begin{align*}
\text{51} & \quad \text{52} \\
\text{Cl}_2\text{C}_2\text{C}_2 + \text{CCl}_2 & \xrightarrow{\text{HEAT}} \text{ClCN} \xrightarrow{\text{pyridine/reflux}} \text{53} \\
\text{54} & \quad \text{55} \\
\text{Et}_4\text{NO}_4, \text{PhCH}_2\text{OCONHOH} & \xrightarrow{} \text{54} \xrightarrow{1. \text{NaBH}_3(\text{OCOCF}_3)} \xrightarrow{2. \text{iBuOCOCl}} \text{55} \\
\text{56} & \quad \text{57} \\
& \xrightarrow{\text{KMnO}_4} \text{PhCH}_2\text{O}_2\text{CCl}, \text{pyridine} \xrightarrow{} \text{56} \xrightarrow{} \text{57} \\
\text{57} & \quad \text{58} \\
& \xrightarrow{\text{HCO}_2\text{H}} \xrightarrow{\text{Ph}_3\text{P, (PyS)}_2} \xrightarrow{\text{CH}_3\text{CN}} \text{58} \\
\text{52} & \xrightarrow{\text{H}_2/\text{Pd/C}}
\end{align*}
\]

Scheme 14.
Section 1.2 Use of acyl nitroso derivatives in racemic synthesis.

Scheme 15.
Table 1, Yields of cycloadducts 62 from acyl nitroso dienophiles 61a-d.

<table>
<thead>
<tr>
<th>R'</th>
<th>Total yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a OMe</td>
<td>75</td>
</tr>
<tr>
<td>b OCH₃Ph</td>
<td>85</td>
</tr>
<tr>
<td>c CH₂Ph</td>
<td>40</td>
</tr>
<tr>
<td>d Ph</td>
<td>23</td>
</tr>
<tr>
<td>e NMe₂</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

![Diagram of chemical reactions involving acylnitroso derivatives and their products.](image)

**Scheme 16.**

Table 2, Regioselectivity and yields of acylnitroso dienophiles 65a-f.

<table>
<thead>
<tr>
<th>R</th>
<th>Ratio 67:68</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Ph</td>
<td>0:100</td>
<td>99</td>
</tr>
<tr>
<td>b PhCH₂</td>
<td>0:100</td>
<td>92</td>
</tr>
<tr>
<td>c CH₃</td>
<td>0:100</td>
<td>67</td>
</tr>
<tr>
<td>d CH₃O</td>
<td>1:1</td>
<td>78</td>
</tr>
<tr>
<td>e PhCH₂O</td>
<td>1:1</td>
<td>100</td>
</tr>
<tr>
<td>f Me₂N</td>
<td>3:1</td>
<td>75</td>
</tr>
<tr>
<td>g Ph-N=O</td>
<td>100:0</td>
<td>80</td>
</tr>
</tbody>
</table>
Section 1.2.4 Synthesis of tabtoxin 51.

Baldwin et al. have used the adduct of 1-cyanocyclohexadiene 53 and benzyl-C-nitrosoformate in their synthesis of tabtoxin\(^{10}\) 51 and analogue 52 (Scheme 14). Tabtoxin 51 is a dipeptide exotoxin which inhibits glutamine synthetase and is produced by *Pseudomonas tabaci*, the organism responsible for wildfire disease of tobacco plants.

The adduct 54 was hydrogenated giving the free amine which was then protected with a BOC group giving 55. The double bond was then cleaved with permanganate to give diacid 56. After selective protection, amine 57 was deprotected and \(\beta\)-lactam 58 was formed. Deprotection and the oxazine bond cleavage were carried out simultaneously using catalytic hydrogenation to give the desired product 52.

Section 1.2.5 Synthesis of aminosugar derivatives.

Defoin et al. have investigated the synthesis of various aminosugar derivatives using acylnitroso derivatives *e.g.* ribose, allose and lyxose derivatives as well as erythritol and erythrose derivatives.

Section 1.2.5a Synthesis of aminodeoxyribose 59 and aminodideoxyallose 60 derivatives

In the synthesis of aminodideoxyallose derivatives 60\(^{11}\) (Scheme 15) they used the cycloaddition of acylnitroso dienophiles 61a-d with a dimethylacetal diene to obtain the cycloadducts 62a-d, which were only obtained with the meta regiochemistry (Table 1). This regiochemistry was attributed to steric interactions between the acetal group and the dienophile disfavoring the ortho adducts. Dihydroxylation of the cycloadducts with catalytic osmium tetroxide and NMO gave *cis*-glycols 63a-d as the only products *i.e.* with the glycol *anti* to the acetal group. After protection with acetic anhydride and reductive cleavage of the oxazine bond, the resulting open chain aminosugar derivative 64, spontaneously cyclised on acetal deprotection to giving the products 60. A similar reaction sequence was used to make aminodeoxyribose derivative 59.

Section 1.2.5b Synthesis of lyxose derivatives 69.

In their synthesis of lyxose derivatives\(^{11}\) 69 (Scheme 16) the cycloadducts between the nitrosocarbonyls 65a-f and dihydropyridine 66 were formed in the usual manner. It was
Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

Scheme 17.
Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

Table 3, Yields of $\text{70} \& \text{71}$ from different acylnitroso dienophiles.

<table>
<thead>
<tr>
<th>R'</th>
<th>Ratio 70:71</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a CONMe$_2$</td>
<td>100:0</td>
<td>85</td>
</tr>
<tr>
<td>b COPh</td>
<td>2.3:1</td>
<td>66</td>
</tr>
<tr>
<td>c CO$_2$(CH$_2$)$_2$SiMe$_3$</td>
<td>3:1</td>
<td>97</td>
</tr>
<tr>
<td>d CO$_2$CH$_2$Ph</td>
<td>1.5:1</td>
<td>93</td>
</tr>
<tr>
<td>e CO$_2$Me</td>
<td>1:1</td>
<td>68</td>
</tr>
<tr>
<td>f COCH$_2$Ph</td>
<td>1:1</td>
<td>56</td>
</tr>
<tr>
<td>g COMe</td>
<td>1:1</td>
<td>79</td>
</tr>
<tr>
<td>h SO$_2$Ph</td>
<td>100:0</td>
<td>50</td>
</tr>
<tr>
<td>i Ph</td>
<td>4:1</td>
<td>100</td>
</tr>
</tbody>
</table>
Section 1.2 Use of acyl nitroso derivatives in racemic synthesis.

Scheme 18.
found that the ratio of regioisomers varied according to the R substituent on the dienophile 65, for example 65a-c (R = Me, Ph or PhCH2) gave only meta adducts 68a-c whilst 65d&e (R = OMe or OCH2Ph) gave 1:1 mixtures of the ortho and meta cycloadducts (Table 2). Dihydroxylation as above gave cis-diols with the diol being anti to the oxazine bridge. The oxazine was then catalytically hydrogenated to give the lyxose derivatives 69. Using the (S)-mandeloylnitroso dienophile (Scheme 9) a 60/40 mixture of diastereomers was obtained and these were converted as above to lyxose derivative 69 in good yield.

Section 1.2.5c Synthesis of erythritol and erythrose derivatives

For the erythritol and erythrose series13 (Scheme 17) the cycloadducts 70& 71 from the reaction of various dienophiles and 1-siloxy diene 72 were formed in the usual way. It was found that the ratio of regioisomers formed varied according to the R substituent on the dienophile, for example R = CONMe2 and SO2Ph gave only the meta adducts 70a&h whilst the other dienophiles gave mixtures of meta 70 and ortho 71 cycloadducts (Table 3).

Dihydroxylation with osmium tetroxide and NMO to give as the only product 73&74 with the cis-diol anti to the siloxy group. The method used to reduce the oxazine bond depended on the nature of the R¹ group of the hydroxamic acid. When the dimethylformate diol 74a was treated with Raney nickel, it reduced both the oxazine bond and the ensuing aldehyde to a primary alcohol giving the erythritol 75. Cycloadducts 74c&d underwent catalytic hydrogenation giving meso amino erythritol 76, i.e. both the oxazine and the formate bonds were reductively cleaved. Diol 74a was also protected as dimethylacetal and desilylated to give 77. Treatment with titanium(III) chloride, gave erythrose 78.

Section 1.2.6 Synthesis of neplanocin A 79.

Retey et al, have investigated the synthesis, of neplanocin A14 79, a carbacyclic analogue of adenosine which has antitumour activity (Scheme 18). They used as a starting material, the cycloadduct of 3,5-dinitrophenyl nitrosocarbonyl and cyclopentadiene, 80. Dihydroxylation gave 81 as the only isomer and this was protected as acetal 82. Hydrolysis of the amide group with base followed by reductive cleavage of the oxazine bond gave aminoalcohol 83. Protection with benzyl chloroformate followed by oxidation of the alcohol with pyridiniumchlorochromate gave the cyclic ketone 84. This was transformed to epoxide
Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

Scheme 19.
Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

Scheme 20.
85 with dimethylsulphoxomethylene ylid. After opening epoxide 85 with acetic acid, the resulting amine was deprotected by catalytic hydrogenation giving 86. The purine nucleus was then constructed and final deprotection gave neplanocin A 79.

Section 1.2.7 Synthetic studies on lycoricidine 87 and pancratistatin 88.

Martin and Tso¹⁵ have carried out synthetic studies into the synthesis of lycoricidine 87 and pancratistatin 88, members of the narcicilane family of alkaloids. Their synthesis (Scheme 19) used the cis-1,4-aminoalcohol 89 made from the addition of benzynitrosoformate to cis-1,2-dihydrocatechol 90. Reduction of the oxazine bond and hydrolysis of the benzylcarbamate gave 91, which was coupled with acid chloride 92 to give after protection 93. The attempted ring closure under radical conditions did not work and so they used instead a modified Heck reaction using as a base thallium(I) acetate to give 94 which completed the skeleton of the alkaloid. Deprotection gave racemic lycoricidine 87.

Section 1.2.8 Synthesis of tropane and derivatives

Kibayashi et al.⁶ have developed a synthesis for tropane alkaloids based on the hetero Diels-Alder reaction of acylnitroso derivatives (Scheme 20).

Their initial work investigated the formation of the tropane skeleton (Scheme 20) and involved the reaction of phenacylnitroso dienophile and cycloheptadiene to give the adduct 97 in good yield. Reductive cleavage of the oxazine bond and hydrogenolysis of the olefin gave amino alcohol 98. The amino alcohol 98 was converted to chloride 99 with inversion of configuration at the chloride. In the key step, chloride 99 cyclised under basic conditions giving the tropane derivative 100 in excellent yield.

Section 1.2.8b Synthesis of Pseudotropine 95 and tropacocaine 96.

This method was slightly altered to synthesise pseudotropine 95 and tropacocaine 96, since the phenacylnitroso dienophile did not form the expected cycloadduct with the cycloheptadiene 101. Instead, the cycloaddition between 1-chloro-1-nitrosocyclohexane 6 and cycloheptadiene 101 gave a 4:1 mixture of the exo& endo cycloadducts. After separation, catalytic reduction of the major exo-adduct 102 resulted in cleavage of the oxazine bond. Protection of the resulting amine with ethyl chloroformate and chlorination of the alcohol followed by ring closure as above gave 103. Reduction with lithium aluminiumhydride gave pseudotropane 95.
Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

Scheme 21.
Section 1.2 Use of acyl nitroso derivatives in racemic synthesis.

Scheme 22.
Protection of the aminoalcohol with benzyl chloroformate instead of ethyl chloroformate and ring closure as before gave 104. Deprotection by catalytic hydrogenation followed by an Eschweiler-Clarke reaction with formic acid and formaldehyde gave tropacocaine 96.

**Section 1.2.9 Synthetic studies on carbacyclic nucleosides.**

Procter and Miller have investigated the use of the protected amino alcohol 105 in the synthesis of carbacyclic nucleosides17 (Scheme 21). They investigated the reactions of acetate 105 with sodium diethyl malonate and sodium bis(phenylsulphone)methane with a variety of Pt° and Pd° catalysts (Table 4).

<table>
<thead>
<tr>
<th>R₂CH⁻</th>
<th>Catalyst</th>
<th>Yield of 106 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PhSO₂)₂CH⁻</td>
<td>Pd(Ph₃P)₄</td>
<td>62</td>
</tr>
<tr>
<td>(PhSO₂)₂CH⁻</td>
<td>Pd(OAc)₂/Ph₃P</td>
<td>88</td>
</tr>
<tr>
<td>(PhSO₂)₂CH⁻</td>
<td>Pd(Ph₃P)₂Cl₂</td>
<td>81</td>
</tr>
<tr>
<td>(EtO₂C)₂CH⁻</td>
<td>Pd(Ph₃P)₄</td>
<td>80</td>
</tr>
<tr>
<td>(EtO₂C)₂CH⁻</td>
<td>Pd(dbp)/dppe</td>
<td>68</td>
</tr>
<tr>
<td>(EtO₂C)₂CH⁻</td>
<td>Pt(cod)/dppe</td>
<td>48</td>
</tr>
</tbody>
</table>

These reactions proceeded in 70-80\% yields giving only one diastereomer 106. Sulfone 106a was dihydroxylated to give acetal 107. The sulfone group was reductively removed with sodium amalgam to give 108.

**Section 1.2.10 Synthetic studies on thienamycin synthesis.**

Procter et al14 have also investigated the conversion of cycloadduct 109 to the lactone 110 which is an important intermediate in the Merck synthesis of thienamycin 111 (Scheme 22). Oxazine 109 was reductively cleaved and the resulting amino alcohol oxidised to give 112. Two equivalents of 113 were added to give the conjugate addition product which was trapped with methyl iodide giving 114, formed as an 8:1 ratio of diastereomers. 114 was then desilylated and oxidised to 115 which underwent a Baeyer-Villiger oxidation to give the desired lactone 110.
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 23.
Section 1.3.1 Stereocontrol using chiral auxiliaries, diastereomeric induction.

Various different chiral auxiliaries have been attached to the hydroxamic acid group (CONHOH) with the aim of achieving greater stereocontrol in the hetero Diels-Alder reactions of acynitroso derivatives. The range of success has been varied, with some of the chiral auxiliaries used giving very little diastereomeric control and others giving only one detectable diastereomer. This section will review the progress made in this area.

The diastereomeric excess of the major product is a measure of the degree of stereocontrol in a cycloaddition. This is true whether the acynitroso dienophile is racemic or a single enantiomer. If a reaction produces two diastereomers A and B as the products, then a stereocontrolled reaction will produce more of one diastereomer, say product A; ideally this will be produced as the sole product. On the other hand, a reaction with no stereocontrol at all will produce equal amounts of A and B. Most reactions using chiral auxiliaries will produce a major diastereomer and a minor diastereomer. To define this mixture quantitatively, the term diastereomeric excess, d.e., is used. Thus the diastereomeric excess of the major product A over the minor product B is defined as :-

\[ \text{d.e.} = \frac{(a-b)}{(a+b)} \]

where a and b are the relative amounts of A and B in the mixture.

The diastereomeric excess is usually expressed as a percentage. The closer this ratio is to 100% then the more stereoselective the reaction is. If d.e. = 100% then only product A is formed whereas if d.e. = 0% then A and B are formed in equal amounts, i.e. with no stereocontrol whatsoever.

The relative amounts of the diastereomers can be measured by NMR spectroscopy, both \(^{13}\text{C}\) and \(^{1}\text{H}\), by analytical HPLC and also by separation and weighing of the cycloadducts. If possible the relative configuration of the products should be determined. This can be done by X-ray crystallography or by transformation of the products into compounds with known absolute stereochemistry and known optical rotations.

Section 1.3.2 \(\alpha\)-chloronitroso dienophiles.

Kresze et al (Scheme 23), investigated the cycloadditions with cyclohexadiene of the chiral \(\alpha\)-chloronitroso dienophile 117 derived from ribose\(^{19}\) which gave cycloadduct 119 and steroid derivative 116\(^{20}\) which gave cycloadduct 118. These oxazines are enantiomeric cycloadducts i.e. they are mirror images of one another. These cycloadducts were formed
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 24.

Table 5. Cycloadditions of acylnitroso dienophiles 123a-d (Kirby and Nazeer).  

<table>
<thead>
<tr>
<th>R</th>
<th>OR'</th>
<th>T/°C</th>
<th>cyclopentadiene</th>
<th>cyclohexadiene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>d.r.  Yield %</td>
<td>d.r. Yield %</td>
</tr>
<tr>
<td>123a</td>
<td>Ph</td>
<td>OH</td>
<td>5.1  68</td>
<td>3.5  55</td>
</tr>
<tr>
<td>123b</td>
<td>Ph</td>
<td>OMe</td>
<td>2.6  65</td>
<td>2.1  59</td>
</tr>
<tr>
<td>123c</td>
<td>Bu'</td>
<td>OH</td>
<td>3.4  75</td>
<td>4.6  58</td>
</tr>
<tr>
<td>123d</td>
<td>c-C₆H₁₁</td>
<td>OH</td>
<td>3.6  80</td>
<td>2.5  55</td>
</tr>
<tr>
<td>123a</td>
<td>Ph</td>
<td>OH</td>
<td>-78  71</td>
<td>6.1  53</td>
</tr>
<tr>
<td>123b</td>
<td>Ph</td>
<td>OMe</td>
<td>-78  63</td>
<td>3.3  54</td>
</tr>
<tr>
<td>123c</td>
<td>Bu'</td>
<td>OH</td>
<td>-78  70</td>
<td>11   60</td>
</tr>
<tr>
<td>123d</td>
<td>c-C₆H₁₁</td>
<td>OH</td>
<td>-78  83</td>
<td>5.1  56</td>
</tr>
</tbody>
</table>
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 25.
essentially as single diastereomers and were solvolysed *in situ* to give single enantiomers 118 and 119. Optical rotation measurements on the oxazine hydrochlorides showed that the e.e. of both reactions was >98%. The absolute stereochemistry of oxazine 118 was determined by conversion into a chiral amide and determining the relative stereochemistry by X-ray crystallography.\(^\text{20}\) However the initially reported absolute configuration proved to be incorrect and the correct configuration, \(IR, 4S\), was established when the enantiomer 119 was converted into amide 120 which was compared with a sample prepared from L-glutamic acid.\(^\text{21}\) Hence oxazine 118, \([\alpha_\text{D}] = -24.0^\circ\), from dienophile 116 was shown to have the opposite, *i.e.* \(1S,4R\) configuration.

Therefore in theory the absolute stereochemistry of a single diastereomer of a cyclohexadiene adduct of an acylnitroso derivative can be determined by hydrolysis of the amide bond to give one or other of the enantiomeric oxazines 118 or 119. The sign of its optical rotation will give the absolute stereochemistry of the oxazine and hence of the original cycloadduct. If the absolute stereochemistry of the chiral auxiliary is also known, the nature of the transition state of the cycloaddition can often be inferred. Unfortunately, when the corresponding cyclopentadiene cycloadducts are hydrolysed the resulting oxazine is too unstable to be isolated in useful yield.

**Section 1.3.1.a The use of mandelic acid derivatives as chiral auxiliaries.**

Kirby and Nazeer\(^\text{22}\) (Scheme 24), Defoin *et al*\(^\text{23}\) (Scheme 26) and Procter *et al*\(^\text{24}\) (Scheme 26) have investigated the cycloadditions of acylnitroso derivatives derived from mandelic acid 121. Mandelic acid is an interesting chiral auxiliary to study since both enantiomers are readily and cheaply available, as is the racemate. Also since it has an hydroxyl group \(\alpha\) to the carbonyl group, Kirby suggested that there is the possibility of H-bonding in the acylnitroso compound. This hydrogen bonding could increase the diastereoselection of the cycloaddition due to the predominance of a single conformation. (Scheme 25).

Kirby and Nazeer also investigated the stereoselection of differently substituted \(\alpha\)-hydroxy dienophiles 123b,c,d, and compared them with mandeloyl derivative 123a (Scheme 24). These experiments were carried out using a series of racemic hydroxamic acids 122a-d which on oxidation with periodate in the presence of either cyclopentadiene or cyclohexadiene reacted to give a mixture of racemic diastereomers 124&125a-d and 126&127a-d respectively. Since \(O\)-methylmandeloylnitroso 123b would have no
Section 1.3 Chiral auxiliaries and diastereomeric induction.

![Chemical structure and reactions](image)

**Scheme 26.**

**Table 6.** Cycloadditions of (R)-mandeloylnitroso dienophiles 123a&b with cyclohexadiene and cyclopentadiene. (Procter et al\(^{24}\))

<table>
<thead>
<tr>
<th>R</th>
<th>OR'</th>
<th>diene</th>
<th>Oxid(^a)</th>
<th>Solvent</th>
<th>T/°C</th>
<th>d.r.</th>
<th>d.e. %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>OH</td>
<td>C(_6)H(_5)</td>
<td>Et(_4)NIO(_4)</td>
<td>MeOH</td>
<td>-78</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>a</td>
<td>Ph</td>
<td>OH</td>
<td>C(_6)H(_5)</td>
<td>Et(_4)NIO(_4)</td>
<td>MeOH</td>
<td>-78</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>OMe</td>
<td>C(_6)H(_5)</td>
<td>NaIO(_4)</td>
<td>EtOAc, H(_2)O</td>
<td>25</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>OMe</td>
<td>C(_6)H(_5)</td>
<td>Et(_4)NIO(_4)</td>
<td>MeOH</td>
<td>-50</td>
<td>5.4</td>
<td>69</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>OMe</td>
<td>C(_6)H(_5)</td>
<td>(COCl(_2))/DMSO</td>
<td>CH(_2)Cl(_2)</td>
<td>-78</td>
<td>5.4</td>
<td>69</td>
</tr>
</tbody>
</table>

**Table 7.** Cycloadditions of (R)-mandeloylnitroso dienophiles 123a&b with cyclohexadiene. (Defoin et al\(^{25}\)).

<table>
<thead>
<tr>
<th>R</th>
<th>OR'</th>
<th>Diene</th>
<th>T/°C</th>
<th>d.r.</th>
<th>de %</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>OH</td>
<td>20</td>
<td>2.2</td>
<td>42</td>
<td>67</td>
</tr>
<tr>
<td>a</td>
<td>Ph</td>
<td>OH</td>
<td>0</td>
<td>3.2</td>
<td>52</td>
<td>-</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>OMe</td>
<td>20</td>
<td>1.4</td>
<td>16</td>
<td>67</td>
</tr>
</tbody>
</table>
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 27.
Section 1.3 Chiral auxiliaries and diastereomeric induction.

H-bonding, it was compared with O-hydroxymandeloylnitroso 123a to see if H-bonding resulted in increased stereoselectivity. The results of these experiments are summarised in Table 5.

As expected, in all cases higher stereoselectivity was observed when the reaction was carried out at -78°C than at 0°C and the α-methoxy dienophile 123b gave consistently lower ratios (approx. 3:1) than the α-hydroxy dienophile 123a with both dienes (approx. 5:1 or greater). This supported the idea that hydrogen bonding may be important in the cycloaddition although the larger size of the methoxy group may also have a similar effect.

To determine the absolute stereochemistry of the cycloaddition, Kirby and Nazeer repeated the cycloaddition of the mandeloylnitroso dienophile 123a and cyclohexadiene using a dienophile made from (S)-mandelic acid rather than (±)-mandelic acid (Scheme 24). The two diastereomers 124&125a formed in the cycloaddition were acetylated and separated by chromatography to give the major diastereomer 124 (R= Ac) as a single diastereomer. Cleavage of the chiral auxiliary with methoxide gave the chiral oxazine 119 showing that the major diastereomer 124a had absolute configuration 1R, 4S (and by analogy that the major diastereomer 126a had the same absolute configuration).

Section 1.3.3.b

Procter et al have carried out independent studies24 (Scheme 26) using mandeloylnitroso dienophiles 123a&b derived from (R)-mandelic acid. They have trapped the acyl nitroso derivatives 123a&b with cyclohexadiene and cyclopentadiene to give the cycloadducts 129&130a&b and 131&132a&b respectively (Table 6).

These experiments confirm that there is an increase in stereoselection at lower temperatures and that hydrogen bonding probably increases the stereoselection since dienophile 123a gives consistently higher stereoselection than dienophile 123b. It is interesting to note that the use of the Swern oxidation conditions did not result in an increase in the stereoselection. They confirmed the absolute stereochemistry of the major cyclohexadiene adduct 129a (Scheme 26) by hydrolysing it with hydrochloric acid to give the chiral oxazine 118 which has absolute stereochemistry 1S,4R. Further they showed by X-ray crystallography that the major cyclopentadiene adduct 131a had the 1S,4R stereochemistry. These observations are consistent with the mode of addition proposed by
Section 1.3 Chiral auxiliaries and diastereomeric induction.

\[
\begin{align*}
\text{137} & \xrightarrow{1. \text{ClCO}_2\text{Me}} \text{134}\text{e} \\
& \xrightarrow{2. \text{NH}_2\text{OH}} \ \text{136}
\end{align*}
\]

\[\text{134a} \quad \text{134b} \quad \text{134c} \quad \text{134d} \quad \text{134e}\]

\[\text{134a-e} \xrightarrow{\text{Pr}_2\text{NiO}_4} \text{133a-e} \xrightarrow{\text{138a-e}} \text{139a-e}\]

\[\begin{align*}
\text{140a} & \\
\text{140b}
\end{align*}\]

Scheme 28.

Table 8. Cycloaddition of acylnitroso dienophiles 133a-e with cyclohexadiene at room temperature.

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>Ratio</th>
<th>de %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>133a</td>
<td>3.2</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>133b</td>
<td>5.2</td>
<td>68</td>
<td>83</td>
</tr>
<tr>
<td>133c</td>
<td>4.5</td>
<td>64</td>
<td>79</td>
</tr>
<tr>
<td>133d</td>
<td>3.3</td>
<td>54</td>
<td>86</td>
</tr>
<tr>
<td>133e</td>
<td>1.5</td>
<td>20</td>
<td>81</td>
</tr>
</tbody>
</table>
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Kirby and Nazeer, allowing for the fact that a (R)-mandeloylnitroso dienophile was used by Procter et al.

Section 1.3.3.c

The group of Defoin has also investigated the stereoselectivity of the cycloadditions of the (R)-dienophile 123 and cyclohexadiene (Scheme 26). They have also investigated the role of hydrogen bonding and have carried out independent studies using the (R)-mandeloylnitroso dienophile 123a and its O-methyl ether 123b. The oxidation of the hydroxamic acids was carried out with periodate in chloroform at 0°C or at room temperature and the acylnitroso dienophiles were trapped with cyclohexadiene to give adducts 129&130a&b. (Table 7). Their results showed that dienophile 123b was less stereoselective than dienophile 123a and also that trapping the dienophiles at room temperature led to lower ratios of diastereomers.

To determine the absolute stereochemistry of cycloaddition, they synthesised the minor methylated cycloadduct 130b from (+)-1R,4S-oxazine 119 [αD = +24.0°] and methylated mandeloyl chloride. Direct coupling of the (+)-oxazine 119 with (R)-mandelic acid in the presence of dicyclohexylcarbodiimide gave the minor cycloadduct 130b (Scheme 27). This meant that the major diastereomer 130a had the opposite absolute configuration in the oxazine moiety, i.e. 1S,4R. Thus these results agree with those reported earlier by Kirby and Nazeer and by Procter et al.

Section 1.3.4 The use of chiral auxiliaries based on proline.

Defoin et al. have investigated a series of chiral auxiliaries based on (S)-proline (Scheme 28). They aimed to investigate whether greater stereoselectivity was obtained by attaching the acylnitroso derivative directly to the ring 133a-d or to the side chain 133e. They also investigated the role of hydrogen bonding by comparing the stereoselection of the primary alcohol 133a to that of the methoxy compound 133b.

In preparing hydroxyureas 134a-c, they used hydroxycarbamate 135 to prepare them from the corresponding prolines. They found that this reagent gave better yields than using phosgene/ hydroxylamine. However in preparing hydroxyurea 134d, they treated the corresponding amine with phosgene to form the chloroformate which was then treated with O-benzylhydroxylamine to give the benzyl-protected hydroxyurea. This was converted into the hydroxyurea 134d by catalytic hydrogenation. This method was used since either
heating or acidic conditions caused the hydroxyurea to undergo intramolecular cyclisation forming cyclic urea 136. The formation of hydroxamic acid 134e was achieved by the reaction of carboxylic acid 137 with methyl chloroformate to form the mixed anhydride which then reacted with hydroxylamine to give hydroxyurea 134e in excellent yield.

Dienophiles 133a-e were generated at room temperature, using tetrapropylammonium periodate in chloroform as the oxidising agent (Scheme 28), and trapped with cyclohexadiene to form cycloadducts 138a-e and these results are summarised in Table 8.

The diastereomeric excesses of cycloadducts 138a-e obtained were moderate, the best being d.e. 68% with nitrosoformamide dienophile 133b which was improved to d.e. 76% when the reaction was carried out at -78°C.

Defoin et al attribute these low diastereomeric excesses, in comparison to the pyrrolidine derivative 156 of Ghosez et al discussed below, to a lack of "stiffness" in the acylnitroso derivative. In dienophile 133e σ-bond rotation about the C2-C=O bond leads a number of possible reacting conformations some of which may result in low or even opposite stereoselectivities. In dienophiles 133a-d, the derived acylnitroso compounds are amides and therefore rotation about the N-C=O bond is slower. Therefore, the conformation of dienophiles 133a-d is more restricted than that of dienophile 133e and this may explain the higher diastereomeric excesses observed for the former in comparison with dienophile 133e.

They determined the absolute stereochemistry of the major adducts by synthesising each of the major diastereomers 138a-e from the known chiral oxazine 119 [of absolute configuration IR, 4S]. This means that the major adducts 138a-e must also have the same absolute configuration in the oxazine moiety, i.e. IR, 4S. For example adduct 138e was synthesised in 92% yield by coupling oxazine 119 and carboxylic acid 137 with dicyclohexylcarbodiimide (DCC) and triethylamine.

It was noted that dienophile 133a with a hydroxymethyl side chain gave cycloadducts with lower diastereomeric excesses than the dienophile 133b with a methoxy methyl side chain (Scheme 28) leading the authors to suggest that not only did H-bonding play no part in the transition state for this chiral auxiliary but that this finding contradicted the suggestion by Kirby and Nazeer that H-bonding was important in the mandelylnitroso dienophile 123a. However since H-bonding in dienophile 133b would involve either an 8-membered
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 29.

Table 9. Cycloadditions of acynitroso derivatives RCONO 142a-g with diene 141 at 0°C in chloroform. (Defoin et al26).

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>d.r. 143: 144</th>
<th>d.e. %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>NMe₂</td>
<td>11.5</td>
<td>84</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>OMe</td>
<td>3.2</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>c</td>
<td>OCOCH₂Ph</td>
<td>2.7</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>2.6</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>e</td>
<td>OCH₂CH₂SiMe₃</td>
<td>2.3</td>
<td>40</td>
<td>76</td>
</tr>
<tr>
<td>f</td>
<td>Me</td>
<td>2</td>
<td>34</td>
<td>62</td>
</tr>
<tr>
<td>g</td>
<td>CH₂Ph</td>
<td>1.3</td>
<td>12</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 10. The effect of temperature and solvent on the cycloaddition between PhCH₂OCONO 142c and the diene 141. (Defoin et al26).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>T/ °C</th>
<th>d.r.</th>
<th>d.e. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>toluene</td>
<td>0</td>
<td>2.1</td>
<td>36</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>0</td>
<td>2.7</td>
<td>46</td>
</tr>
<tr>
<td>MeOH</td>
<td>40</td>
<td>2.4</td>
<td>42</td>
</tr>
<tr>
<td>MeOH</td>
<td>0</td>
<td>2.8</td>
<td>48</td>
</tr>
<tr>
<td>MeOH</td>
<td>-20</td>
<td>3.8</td>
<td>58</td>
</tr>
<tr>
<td>MeOH</td>
<td>-78</td>
<td>4.3</td>
<td>62</td>
</tr>
</tbody>
</table>
ring involving the nitroso group 140a or a 7-membered ring involving the carbonyl group 140b, it is hardly surprising that no beneficial effect was observed. In contrast, dienophile 123a can adopt a favourable 6-membered H-bonded ring 128a.

Section 1.3.5 The use of chiral dienes to achieve diastereomeric induction.

Defoin et al. have also investigated the use of chiral diene 141 in the hetero Diels-Alder reaction of the acylnitroso derivatives of various hydroxamic acids (Scheme 29). As before, the hydroxamic acids were oxidised with periodate in chloroform at 0°C to give the dienophiles 142a-g which were trapped in situ with the diene. A mixture of cycloadducts 143a-g and 144a-g was formed and analysed using NMR spectroscopy to determine the relative ratios of the four possible diastereomers (Table 9).

All of the reactions proceeded in good yield and gave a mixture of only two diastereomers 143 & 144 out of a possible four, i.e. only one regioisomer was formed, the meta regioisomer. This was the only regioisomer formed due to steric interactions between the large glutamate amide group of the diene and the R group of the dienophile. Using this chiral diene led to a d.e. of 84% with acylnitroso dienophile 142a and a d.e. of 46% with benzyl-C-nitrosoformate 142c.

Since the benzyl group can be easily removed with catalytic hydrogenation, they investigated the effect of temperature and solvent on the cycloaddition between benzyl-C-nitrosoformate 142c and the diene 141 to try and increase the diastereoselection (Table 10). It was found that the diastereoselection of the cycloaddition was increased from d.e. 46% to d.e. 62% by generating and trapping the dienophile at -78°C in methanol.

The absolute stereochemistry of the major cycloadducts 143 was determined by X-ray crystallography and found to have the stereochemistry shown, with both chiral centres having the S-configuration. The transition state proposed by the authors to explain these results, involves diene 141 (with the amide of the γ-lactam coplanar and in a s-trans conformation with respect to the butadienyl moiety) reacting with the dienophile in an endo manner. This leads to the best overlap of the π-orbitals of the amide and the diene. The approach of the acylnitroso compound was in an endo manner from the less hindered top face (Scheme 29). This proposed transition state accounts for the observed stereochemistry. It was discovered that both the glutamate residue and the benzyl formate could be easily
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 30.
**Section 1.3** Chiral auxiliaries and diastereomeric induction.

![Chemical structures](image)

Scheme 31.
removed by catalytic hydrogenation, although with loss of chirality, resulting in the formation of the meso pyrrolidine.

**Section 1.3.6a** The use of C$_2$-symmetry; pyrrolidine derivatives.

The groups of Ghosez and Defoin have both investigated the reactions of acylnitroso dienophiles based on chiral auxiliaries with C$_2$ symmetry e.g. based on chiral pyrrolidines.

Defoin et al$^{27}$ have used the chiral dienophiles 146 and 150 derived from two chiral hydroxamic acids 145 and 149 in hetero Diels-Alder reactions with cyclohexadiene (Scheme 30). The two dienophiles are of opposite chirality and helicity and so were expected to give chiral oxazines of opposite chirality. Acylnitroso derivatives 146 and 150 were generated from the corresponding hydroxamic acids by oxidation with periodate in chloroform at room temperature and trapped with cyclohexadiene forming single cycloadducts in >98% d.e.. Dimethylpyrrolidine dienophile 146 formed cycloadduct 147 with cyclohexadiene in 81% yield, with only 1% of the minor diastereomer. Reaction with the siloxydiene 72 at 0°C gave cycloadduct 148 as the only regioisomer in 50% yield with a d.e. of >98% (Scheme 30). The tricyclic pyrrolidine dienophile 150 was trapped with cyclohexadiene forming cycloadduct 151 in 90% yield with no trace of the minor cycloadduct, i.e. as the sole product.

The absolute stereochemistry of siloxy cycloadduct 148 was determined by X-ray crystallography and was found to be as shown. The absolute stereochemistry of cyclohexadiene adducts 147 and 151 was determined by independently synthesising them from (IR,4S)-chiral oxazine 119 (Scheme 31). Reaction of oxazine 119 with phosgene gave carbamoyl chloride 154 which reacted with chiral pyrrolidines 152 and 153 to give cycloadducts 147 and 151b. It was found when tricyclic pyrrolidine 153 was used, the minor cycloadduct 151b was formed, thus implying that the cycloadduct formed in the cycloaddition had the opposite absolute stereochemistry in the oxazine moiety, i.e. 1S, 4R. In contrast, dimethyl pyrrolidine 152 gave the major cycloadduct 147 on reaction with carbamoyl chloride 154, thus implying that the cycloadduct formed in the cycloaddition had the IR,4S stereochemistry in the oxazine moiety.

**Section 1.3.6b**

Ghosez and Gouverneur$^{28}$ have investigated the cycloadditions of dienophile 156, based on the C$_2$-symmetric pyrrolidine chiral hydroxamic acid 155, with cyclohexadiene,
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 32.
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 33.
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 34.

Table 11. Cycloadditions of dienophile 169 with various dienes at -78°C, oxidised under the Swern conditions. (Martin et al.26)

<table>
<thead>
<tr>
<th>diene</th>
<th>product</th>
<th>d.e. %</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="170" alt="Image" /></td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td><img src="171" alt="Image" /></td>
<td>&gt;95</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td><img src="172" alt="Image" /></td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td><img src="173" alt="Image" /></td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td><img src="174" alt="Image" /></td>
<td>95</td>
<td>65</td>
</tr>
</tbody>
</table>
Section 1.3 Chiral auxiliaries and diastereomeric induction.

cycloheptadiene and cyclopentadiene (Scheme 32). They oxidised hydroxamic acid 155 with
tetraethylammonium periodate in chloroform to form acylnitroso dienophile 156 which gave
cycloadducts 157-9 with high diastereoselectivity (d.e. >87%) when trapped with
cyclopentadiene, cyclohexadiene and cycloheptadiene respectively.

The major diastereomer of cyclohexadiene adduct 158 was reduced with sodium
amalgam to give the amidoalcohol 160 and the relative stereochemistry was then
determined by X-ray crystallography. Since the absolute configuration of the pyrrolidine
ring was already known the absolute stereochemistry of the oxazine ring was determined to
be 1S,4R.

Section 1.3.7 The use of sultam 163 as a chiral auxiliary.

Ghosez et al²⁹ have also reported the cycloadditions of a dienophile 164 based on
D-bornane-10,2-sultam 163 (Scheme 33). The nitroso dienophile 162 did not undergo the
hetero Diels-Alder reaction, probably since the lack of an electron withdrawing group such
as a chlorine or carbonyl made it insufficiently reactive. However the acylnitroso dienophile
164 did undergo hetero Diels-Alder reactions, and was trapped with cyclopentadiene and
cyclohexadiene to give the cycloadducts 165&166 respectively. Each of these cycloadduct
were formed as single diastereomers, with d.e. of >98% in both cases. Both cyclohexadiene
adduct 166 and cyclopentadiene adduct 165 had the 1R,4S absolute configuration in the
oxazine moiety which was determined when both of the major adducts were independently
synthesised from the known 1R,4S oxazine 119, via chlorocarbamate 154.

Section 1.3.8 The use of Oppolzer's chiral alcohol 167 as a chiral auxiliary.

Martin et al⁶⁹ have investigated the Diels-Alder reactions of the dienophile 169 (Scheme
34) which was generated from hydroxycarbamate 168 by oxidation. This hydroxycarbamate
is based on the chiral alcohol 167 investigated by Oppolzer⁴¹ as a chiral auxiliary, both
enantiomers of which are available. Alcohol 167 was converted to hydroxycarbamate 168 in
93% yield, using triphosgene and hydroxylamine.

When acylnitroso derivative 169 was generated using Et₄NIO₂ at -20°C, it reacted with
various substituted cyclohexadienes to give the expected cycloadducts in diastereomeric
ratios of 8:14:1. This stereoselection was improved by oxidising with DMSO and oxalyl
chloride at -78°C to form dienophile 169. The use of this oxidation method gave the
expected cycloadducts 170-4 in good yield and in d.e. of more than 90% (Table 11).
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 35.
Section 1.3 Chiral auxiliaries and diastereomeric induction.

To determine the absolute configuration, the major cyclohexadiene adduct 170 was hydrolysed with base giving the known chiral 1R,4S-oxazine 119 [α_D = +24.4°]. The chiral alcohol 167 was recovered in 85% yield from this reaction.

Section 1.3.9 Double asymmetric induction

One example exists in the literature of the use of double asymmetric induction to achieve stereoselection in the cycloadditions of acylnitroso derivatives. Defoin et al have investigated the cycloadditions of the chiral diene 141 and two chiral dienophiles generated from the hydroxamic acids 122a and 134b (Scheme 35).

The theory behind double asymmetric induction states that when the two stereocontrolling effects complement each other, a matched pair is obtained, resulting in increased stereoselection. When the two stereocontrolling effects compete with each other a mismatched pair is obtained which gives reduced stereoselection.

To investigate double asymmetric induction, the chiral dienophiles 133b and 123a used were derived from proline and mandelic acid respectively. The chiral diene 141 used was the (S)-enantiomer (Table 12).

When the (S)-dienophiles were generated from (S)-hydroxamic acids, this resulted in an almost total lack of diastereoselectivity, i.e. a mismatched pair. However when (R)-acylnitroso dienophile 133b was used, this showed the diastereoselection increasing from 68% with cyclohexadiene to 96% with the chiral diene 141, i.e. a matched pair. Unfortunately, the (R)-mandeloylnitroso dienophile 123a had its diastereoselectivity reduced from 58-75% with cyclohexadiene to 46% with chiral diene 141. Therefore, only dienophile 133b was observed to give increased stereoselection by forming a matched pair with diene 141.

The absolute stereochemistry of the major products was determined by X-ray crystallography and was found to be as shown. To explain this stereochemistry, the following transition state was postulated, involving the diene reacting in the anti form, as before, and the dienophile reacting in the s-cis state, also as before, leading to the observed stereochemistry with the assumption of an endo approach of the diene.
Table 12. Double asymmetric induction, cycloaddition between chiral acyl nitroso dienophiles and chiral diene 141 at 0°C. (Streith et al. 119).

<table>
<thead>
<tr>
<th>R*CO-N=O absolute configuration</th>
<th>de % (cyclohexadiene)</th>
<th>d.r. 143:144</th>
<th>d.e. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>129 R</td>
<td>58-75</td>
<td>2.77</td>
<td>46</td>
</tr>
<tr>
<td>123 S</td>
<td></td>
<td>1.2</td>
<td>10</td>
</tr>
<tr>
<td>133 R</td>
<td>68</td>
<td>49</td>
<td>96</td>
</tr>
<tr>
<td>133 S</td>
<td></td>
<td>1.1</td>
<td>4</td>
</tr>
</tbody>
</table>

Scheme 36.
Section 1.3.10 Imidazolidinone 175 as a chiral auxiliary.

Orena et al.\textsuperscript{33} have investigated the use of the chiral imidazolidin-2-one 175 as a chiral auxiliary in the asymmetric Diels-Alder reaction of acylnitroso dienophiles (Scheme 36). The enantiopure imidazolidin-2-one 175 can be prepared as either enantiomer from either (-)- or (+)-ephedrine, which are both readily available. Hydroxyurea 177 was prepared by deprotonating imidazolidin-2-one 175 with butyllithium and treating the resulting anion with phosgene to form carbamoyl chloride derivative 176. Treatment with hydroxylamine gave hydroxyurea 177 in good yield.

Attempts to oxidise hydroxyurea 177 with tetrabutylammonium periodate to dienophile 178 at both -60°C and -20°C failed. However, dienophile 178 could be generated by oxidising hydroxyurea 177 at -78°C using oxalyl chloride and DMSO. The dienophile was then trapped \textit{in situ} with either cyclopentadiene or cyclohexadiene forming cycloadducts 179 or 180 respectively as mixtures of diastereomers. Both cycloadducts were formed in good yield and the ratio of diastereomers formed was determined by both \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy to be approximately 9:1. The two diastereomeric mixtures formed in the reaction could be separated by column chromatography on silica.

The absolute stereochemistry of the major cyclohexadiene adduct 180a was determined by removal of the chiral auxiliary with lithium hydroxide and hydrogen peroxide. Subsequent acidification with hydrochloric acid gave oxazine 118, [\(\alpha_P = -24.7^\circ\), \(c=1\), \(\text{CHCl}_3\)]. Comparison of the optical rotation with the literature value showed that the oxazine moiety must have the (\textit{IS}, 4\textit{R}) absolute stereochemistry.

Section 1.3.11 Use of amino acids as chiral auxiliaries.

Ritter and Miller\textsuperscript{34} have investigated the use of amino acids as chiral auxiliaries in the hetero Diels-Alder reactions of acylnitroso derivatives (Scheme 37). Hydroxamic acids 181a-f were made in good yield by treating the \(N\)-protected methyl esters of valine, alanine and phenylalanine with a solution of excess hydroxylamine in THF. The dienophiles 182a-f were generated from the corresponding hydroxamic acids by oxidation with tetrabutylammonium periodate in methanol and trapped \textit{in situ} with cyclopentadiene forming a mixture of diastereomers 183\&184a-f. The cycloadducts 183\&184a-f were formed (Table 13) in 75-90% yield and the ratio of diastereomers formed was measured by HPLC and found to be d.r. 4:1 for valine based dienophile 182a and d.r. 3:1 for the alanine
Section 1.3 Chiral auxiliaries and diastereomeric induction.

Scheme 37.

Table 13. Cycloadditions between dienophiles 182a-f and cyclopentadiene. (Ritter and Miller*)

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>R</th>
<th>P</th>
<th>Yield %</th>
<th>d.r. 183: 184</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (L)-valine</td>
<td>1Pr</td>
<td>Cbz</td>
<td>85</td>
<td>1: 4</td>
</tr>
<tr>
<td>b (L)-alanine</td>
<td>Me</td>
<td>Cbz</td>
<td>90</td>
<td>1: 3</td>
</tr>
<tr>
<td>f (L)-alanine</td>
<td>Me</td>
<td>Boc</td>
<td>78</td>
<td>1: 3</td>
</tr>
<tr>
<td>c (D)-alanine</td>
<td>Me</td>
<td>Cbz</td>
<td>78</td>
<td>3: 1</td>
</tr>
<tr>
<td>d (L)-phenylalanine</td>
<td>CH₂Ph</td>
<td>Cbz</td>
<td>79</td>
<td>1: 2</td>
</tr>
<tr>
<td>e (L, D)-phenylalanine</td>
<td>CH₂Ph</td>
<td>Cbz</td>
<td>75</td>
<td>-</td>
</tr>
</tbody>
</table>
Section 1.3 Chiral auxiliaries and diastereomeric induction.

based dienophile 182c. The mixtures of diastereomers 183&184a-f were separated by column chromatography on silica.

Acylnitroso dienophile 182c was also generated by heating the dimethylanthracene adduct 185 in refluxing benzene and was trapped in situ with cyclohexadiene. The cyclohexadiene adduct 186 was formed in this reaction as a 1.6:1 mixture of diastereomers. These diastereomers could also be separated by chromatography on silica.

The stereochemistry of the major cyclohexadiene cycloadduct 186 was determined by X-ray crystallography. Since the absolute stereochemistry of the chiral auxiliary was known to be R, then the absolute stereochemistry of the cycloadduct was determined to be as shown 186, i.e. (1S, 4R) in the oxazine moiety. This stereochemistry was assumed to be the same for cyclopentadiene adducts 183a-f.

The lower diastereoselectivities observed for dienophiles 182a-f when compared with α-hydroxy dienophile 123a derived from mandelic acid suggest that the hydrogen bonding in dienophiles 182a-f is not as great as in dienophile 123a.

Although these chiral dienophiles gave only moderate stereoselection, they have some advantages. One advantage is that the amino acids on which they are based are readily and cheaply available as either enantiopure enantiomer. Also the chiral auxiliary may sometimes be part of the desired product and so not discarded.
Section 1.4 The use of chiral acylnitroso dienophiles in chiral synthesis.

Scheme 38.

Table 14. Effect of temperature and method of oxidation (A. with Et$_4$NIO$_4$ and B. with NCS and DMSO) on the diastereomeric excesses of the cycloaddition between acylnitroso dienophile 156 and 2-azadienes 188a-c.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Oxidation</th>
<th>T/ °C</th>
<th>d.e. %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>A</td>
<td>-25</td>
<td>59</td>
<td>68</td>
</tr>
<tr>
<td>a</td>
<td>Me</td>
<td>B</td>
<td>-78</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>A</td>
<td>0</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>B</td>
<td>-78</td>
<td>94</td>
<td>62</td>
</tr>
<tr>
<td>c</td>
<td>PhCH$_2$</td>
<td>A</td>
<td>-25</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>c</td>
<td>PhCH$_2$</td>
<td>B</td>
<td>-65</td>
<td>93</td>
<td>65</td>
</tr>
</tbody>
</table>
Section 1.4 The use of chiral acyl nitroso dienophiles in chiral synthesis.

Scheme 39.
Section 1.4.1 Synthesis of enantiomerically pure amino acids using pyrrolidine based acylnitroso derivatives.

Ghosez and Gouverneur have used acylnitroso dienophile 156 generated from pyrrolidine based hydroxyurea 155 in the synthesis of several enantiomerically pure amino acids\(^3\) (Scheme 38). They used as the dienophile, 2-azadienes 188a-c which were made from the corresponding acid chlorides (RCH₂COCI). The method of synthesis used gave exclusively E,Z azadienes 188a-c. It was found that although the 2-azadienes did not react with less reactive α-chloronitroso dienophiles, they reacted well with acylnitroso dienophiles. Attempts to oxidise the hydroxamic acids with periodate proved slow at low temperatures and also led to degradation of the diene. These problems were overcome by using the Corey oxidation conditions (NCS, dimethylsulphide and triethylamine) at −78°C. The cycloadditions gave the major product 189a-c in \(\approx 70\%\) yields and with diastereomeric excesses of 85-95%.

Cleavage of the oxazine bond was achieved with either molybdenum hexacarbonyl or sodium amalgam to give amide 190. After purification and acid hydrolysis of the chiral auxiliary, (S)-amino acids were obtained in 70-80% yield from the cycloadducts 189a-c and in d.e. of >98%.

Section 1.4.2 The synthesis of mannostatin A 193.

King and Ganem have used a mandeloxy nitroso dienophile 123a to synthesise mannostatin A 193\(^3\), a glycosidase inhibitor (Scheme 39). (R)-Mandeloxy nitroso dienophile 123a, was generated by oxidation of hydroxamic acid 122a with periodate at 0°C and trapped with 1-methylthio cyclopentadiene 194 to give as the major product cycloadduct 195 in 30-35% yield and as a 2.6:1 mixture of diastereomers, which could be separated by chromatography. Attempts to dihydroxylate adduct 195 directly with osmium tetroxide did not work. Catalytic osmylation gave sulfoxides and sulfones, while stoichiometric amounts of osmium tetroxide gave α-ketoamide 196. After cleavage of the oxazine bond of the cycloadduct with aluminium amalgam and protection as the acetate to give 197, dihydroxylation with osmium tetroxide in pyridine gave a 20:1 mixture of isomers with the desired isomer 198 as the major product. Hydrolysis of the amide and the acetate protecting groups with methanolic hydrochloric acid gave the desired product 193.
Section 1.4 The use of chiral acyl nitroso dienophiles in chiral synthesis.

Scheme 40.

Table 15, Yield of the cycloaddition of the haloacetonides 201.

<table>
<thead>
<tr>
<th>Halogen</th>
<th>R</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cl</td>
<td>OCH₂Ph</td>
</tr>
<tr>
<td>b</td>
<td>Br</td>
<td>OCH₂Ph</td>
</tr>
<tr>
<td>c</td>
<td>Br</td>
<td>CH₃</td>
</tr>
</tbody>
</table>
Section 1.4 The use of chiral acyl nitroso dienophiles in chiral synthesis.

\[ \text{205 } R=\text{OH, narciclasine} \]
\[ \text{87 } R=\text{H, lycoricide} \]

\[ \text{88 } \text{pancratistatin} \]

\[ \text{92} \]

\[ \text{200} \]

\[ \text{Br} \]
\[ \text{RCONHOH} \]
\[ \text{Bu}_4\text{NIO}_4 \]
\[ \text{CH}_2\text{Cl}_2 \]

\[ \text{206 a } R=\text{CBz, 74\%} \]
\[ \text{b } R=\text{Br-piperonyl, 80\%} \]

\[ \text{1. } \text{Al(Hg), THF, 91\%} \]
\[ \text{2. } \text{ClSiMe}_2\text{Pr}^\text{i}, \text{Im, CH}_2\text{Cl}_2, 98\% \]

\[ \text{206a} \]

\[ \text{207} \]

\[ \text{1. } \text{BuLi, THF, -78\%} \]
\[ \text{2. } \text{ClSiMe}_2\text{Pr}^\text{i}, \text{Im, CH}_2\text{Cl}_2, 98\% \]

\[ \text{208} \]

\[ \text{1. } \text{Pd(OAc)}_2, \text{Ti(OAc)}_2, \text{PHOS, anisole, 27\%} \]
\[ \text{2. } \text{Pd-C, EtOH, cyclohexene, 99\%} \]

\[ \text{209} \]

\[ \text{F}_3\text{CCO}_2\text{H} \]
\[ \text{85\%} \]

\[ \text{87} \]

Scheme 41.


Section 1.4.3 Synthesis of aminocyclitols.

Hudlicky and Olivo have developed a route to the synthesis of aminocyclitols37 based on the cycloaddition between the chiral bromo and chloro cyclohexadiene acetonides 200 and acylnitroso dienophiles (Scheme 40). Mutant strains of *Pseudomonas putida* produce the halodiols 199, as single enantiomers, from the corresponding halobenzenes in what is now a commercial process. Chiral acetonide 200 can be easily made by the acid catalysed reaction of the diol with acetone.

The cycloadditions between the acylnitroso derivatives of benzyloxyhydroxamic acid and acetohydroxamic acid lead to the corresponding cycloadducts 201a&b in 50% yield. In both cases, the cycloadducts were the only products formed and there was no trace of either the other regioisomer or enantiomer *i.e.* the reactions were completely regioselective and stereoselective. After reductive cleavage of the oxazine bond of 201 with aluminium amalgam which also led to dehalogenation, deprotection and reduction of the double bond, the conduramidine A-1 204 was formed. The oxazine bond was also cleaved with tributyltin hydride and AIBN resulting in the formation of the aminoketone 202. This would allow further investigation into the use of selective hydrogenation of the ketone to give other epimeric aminocyclitols.

Section 1.4.5 Synthesis of (+)-lycoricidine.

Hudlicky and Olivo38 have also used the bromo cyclohexadiene acetonide 200 in a synthesis of (+)-lycoricidine 87 (Scheme 41). Benzylnitrosoformate and dienophile 92 were trapped with diene 200 to give the adducts 206a&b were obtained in good yield, with no other regioisomer or enantiomer present. Reductive cleavage with aluminium amalgam gave amidoalcohols 207a&b. Unfortunately over reduction of cycloadduct 207b, led to the partial loss of the aryl bromine, necessary for the cyclisation reaction. This meant that amidoalcohol 207a had to be used and this was deprotonated with butyllithium and then treated with 2-bromopiperonyl chloride to give 208. This was cyclised in a modified Heck reaction to give 209, in 27% yield, which after deprotection gave the product 87. The byproducts of the cyclisation reaction were mainly desilylated and acetylated starting material which was recyclised bringing the overall yield of 87 to 70-80%.
Section 2.0 Aims and Strategy.

Scheme 42.
Section 2.0 Aims and Strategy.

As can be seen from Section 1.3, a wide variety of chiral auxiliaries attached to acylanitroso groups have been used to investigate asymmetric induction in the cycloaddition of acylanitroso dienophiles with dienes (Scheme 42). These chiral auxiliaries have resulted in a wide range of stereoselectivities ranging from low to excellent. The chiral auxiliaries (Scheme 42) have fallen into three classes:-

1. carboxylic acids, e.g. mandelic acid 121, which have been converted into hydroxamic acids.
2. amines, e.g. the pyrrolidine derivatives 152, 153 and 155 or the sultam 163, which have been converted into $N$-hydroxyureas and subsequently $C$-nitrosoformamides.
3. alcohols which have been converted into $N$-hydroxycarbamates and hence $C$-nitrosoformates, e.g. the nitroso derivative of the Oppolzer auxiliary 167.

Since Kirby and Nazeer, had observed good to excellent diastereomeric induction in the cycloaddition between the mandeloylnitroso dienophile 123a and cyclohexadiene, up to a 10:1 ratio of diastereomers at -78°C, we wanted to investigate further the hydrogen bonding which we believed was responsible for the high degree of diastereomeric induction. Our aim was to investigate the cycloadditions of $C$-nitrosoformamides e.g. 234 and 248 which were derived from hydroxyureas. We hoped that we could obtain intramolecular hydrogen bonding in these dienophiles with a 5-membered ring of hydrogen bonding between the NH and the nitroso group (Scheme 42). It was hoped that this hydrogen bonding would increase the rigidity of the dienophile (expected for an amide rather than an ester) and so lead to greater stereoselection in the cycloaddition reaction. This would be achieved by greater conformational rigidity resulting in greater differentiation of the two conformations of the nitroso group and hopefully we predict increasing the amount of the *anti* conformation.

Rotation about the NH-CO or O-CO bond results in both faces of the dienophile being exposed to the diene and hence a reduction in stereoselection. The rate of rotation about the O-CO bond in the nitrosoformates would be much faster than the rate of rotation about the NH-CO bond of nitrosoformamides even at low temperatures and there would also be no hydrogen bonding. Our strategy was to see if $C$-nitrosoformamides, due to their slower rotation about the NH-CO bond would have higher diastereoselectivities in cycloadditions in comparison to the more freely rotating $C$-nitrosoformates. By elucidation of the absolute or relative stereochemistry of the cycloadditions, our assumption that the dienophile prefers to react in the *anti* conformation could also be tested.
Two possible drawbacks to this idea were that:

1. The 5-membered hydrogen bonded ring of a C-nitrosoformamide could be less favoured than the 6-membered ring of α-hydroxy dienophile 123a and so contribute less to the overall conformation.

2. The hydroxyurea and the derived C-nitrosoformamide dienophiles are further from the chiral centre than the hydroxamic acid and the derived nitrosocarbonyl groups and so there is more flexibility and opportunity for rotation of the dienophile which could lead to reduced stereoselection. The highly stereoselective C-nitrosoformamide dienophiles in the literature all have the amide nitrogen embedded in a ring system and so have much less flexibility. However, high stereoselectivity had been obtained for C-nitrosoformate dienophile 169.

The dienophiles chosen were based on 1,2-\textit{trans}-cyclohexanes. These were chosen since both the nitrosoformate or nitrosoformamide groups and the bulky blocking groups occupied equatorial positions. Due to their large size, both these groups were locked into these conformations. It was also hoped that the presence of the bulky group would result in the approach to one face of the nitroso group being more hindered than the other and so result in diastereoselection.

Phenylmenthol 210 and \textit{trans}-phenylcyclohexanol 211 have both been used as chiral auxiliaries before in other reactions with high stereoselectivity, \textit{e.g.} Diels-Alder reaction\textsuperscript{39} and it was hoped that using them as chiral auxiliaries would lead to good stereoselection.

It was also hoped that by increasing the size of the bulky group, that the stereoselection of the reaction would be increased. It was planned to investigate the cycloaddition reaction with dienophiles with differently sized bulky groups ranging from phenyl to phthaloyl and phenyldimethyl with the aim of increasing the stereoselectivity of the reaction. With this in mind, the dienophiles 234, 238, 248, 271\& 292 were synthesised and their cycloadditions investigated.
Section 2.1 \(\text{N-cyclohexyl-C-nitrosoformate.}\)

Scheme 43.

Section 2.1.1 Synthesis of hydroxyurea 213.

To investigate the transformation of an amine into a hydroxyurea, cyclohexylamine 212 was converted into hydroxyurea 213 (Scheme 43). When cyclohexylamine 212 was added slowly to a chilled solution of phosgene in toluene, it was found that the corresponding carbamoyl chloride formed rapidly and that the reaction was complete within one hour. Triethylamine was used to neutralise the hydrochloric acid produced by the reaction avoiding the formation of cyclohexylamine hydrochloride salt which would reduce the yield of product based on starting amine. The amination of the carbamoyl chloride with chilled aqueous hydroxylamine solution gave hydroxyurea 213 in good yield.
Section 2.1.2 Cycloadditions of cyclohexyl dienophile 214.

Since hydroxyurea 213 and acyl nitroso dienophile 214 are achiral, the resulting cycloadducts with prochiral dienes e.g. cyclopentadiene and cycloheptadiene were formed without chiral induction as racemates. Although there was no stereoselection, the reactions of this dienophile were of interest firstly to check that the desired cycloadditions would occur and secondly to interpret the NMR spectra of the simplest cycloadducts.

Section 2.1.3 Generation of cyclohexyl dienophile 214.

A typical procedure for generating the acyl nitroso dienophile and trapping it in situ with periodate was to dissolve tetraethylammonium periodate and excess diene in a mixture of ethanol and dichloromethane. The solution was chilled to 0°C and magnetically stirred. The hydroxamic acid derivative 213 was then dissolved in ethanol and dichloromethane and added slowly to the chilled solution of diene and oxidant, which then turned yellow. The solution was then stirred for an hour at 0°C and then concentrated under reduced pressure. The residue was redissolved in dichloromethane and washed with sodium thiosulphate to remove the periodate and iodine and then washed with brine. The organic layer was then dried and concentrated to give the crude product. The dienophile was trapped in situ at 0°C with both cyclopentadiene and cycloheptadiene to form adducts 215 and 216, respectively in good yields.

Section 2.1.4 NMR spectra of cycloadducts 216 and 215.

It is interesting to note the major differences in the NMR spectra between the two cycloadducts. In the ¹H NMR spectra the major difference is the chemical shift of the bridgehead hydrogens. In cyclopentadiene adduct 215, the two bridgehead proton signals are coincidental and are downfield in comparison with those of the cycloheptadiene adduct 216 which are well separated, by over 0.2 ppm. Another difference is in the chemical shifts of the methylene carbon(s) of the oxazine bridge. In the ¹³C spectrum of the cyclopentadiene adduct the bridging methylene resonates at δ 48.3, due to the more strained bicyclic heptene ring system, whilst in the less strained bicyclic octene ring system of the cycloheptadiene adduct the two bridging carbons resonate at δ 23.8 and 19.8. This ring strain also affects the chemical shift of the two bridgehead carbons; in the cyclopentadiene adduct they resonate downfield in comparison to the cycloheptadiene adduct.
Scheme 44.

Scheme 45.

Scheme 46.
Section 2.2 N-(trans-2-Phenylcyclohexyl)-C-nitrosoformamide.

Scheme 47.

Section 2.2.1 (±)-trans-2-phenylcyclohexyl-N'-hydroxyurea 225.

The synthesis of the racemic hydroxyurea 225 was examined and a retro synthetic route is shown in Scheme 44. This synthetic route involves the known carboxylic acid 221 as an intermediate. This acid was synthesised in racemic form by Verbitt and Price\textsuperscript{40} who also resolved the (+)-acid 221 as a single enantiomer. The racemic acid has also been synthesised by Ansell and Clements\textsuperscript{41} and Ropp and Cognier\textsuperscript{42}. The acid was a useful intermediate since the initially formed mixture of cis and trans esters 219\&227 could be epimerised with base, thereby giving predominantly the desired thermodynamically more stable trans compound 219, in which both substituents are in equatorial positions. It would have been possible to resolve the acid 221, if necessary following the procedure of Verbitt and Price\textsuperscript{40}, by fractional crystallisation from methanol of the salt formed by treatment of the acid with (−)–α-phenylethylamine. Acidification would give the (+)-acid 221.

Section 2.2.2 Synthesis of (±)-trans-2-phenylcyclohexyl-N'-hydroxyurea 225.

Scheme 45 outlines the synthetic route used to make the desired racemic hydroxyurea 225. 1-Phenylbutadiene 218 was made by the Wittig reaction between cinnamaldehyde 217
Section 2.2 \(N\)-(trans-2-Phenylcyclohexyl)-C-nitrosoformamide.

and methylenetriphenylphosphonium ylid, following the procedure of Wittig and Schoellkopf.\(^{43}\) Two alterations were made to their procedure. Firstly, methyltriphosphonium iodide was used instead of the methyltriphosphonium bromide. This change was made since it was easier to handle the liquid iodomethane b.p. 42-43\(^\circ\)C rather than the gaseous bromomethane b.p. 4\(^\circ\)C. Thus, the reaction could be carried out in a stoppered flask rather than a pressure vessel. The second change was to use THF instead of diethyl ether because of its higher boiling point.

The methyltriphosphonium salt was made by mixing triphenylphosphine and iodomethane in toluene. After stirring the mixture overnight, the product precipitated out as a white solid which was filtered off and dried to give the pure material in 90% yield. Methyltriphosphonium iodide and THF were added to the flame-dried apparatus under an atmosphere of nitrogen and the stirred suspension was chilled to 0\(^\circ\)C. A solution of n-butyllithium was then added slowly to deprotonate the insoluble methyltriphosphonium salt and form a yellow orange solution of the methylenetriphenylphosphonium ylid. After the mixture was stirred and warmed to room temperature, cinnamaldehyde was slowly added. This resulted in a green solution and the formation of a precipitate of triphenylphosphine oxide. After the addition of the aldehyde, the solution was stirred at room temperature for 30 minutes, before being heated to reflux for 2 hours. The solution was then left to cool overnight before work-up and distillation gave the desired product 218.

1-Phenylbutadiene 218 was then heated neat in excess ethyl acrylate at 100\(^\circ\)C for 24 hours. The ensuing Diels-Alder reaction gave the cyclohexene 219 (Scheme 46). The crude product was found to be a mixture of the trans and cis isomers 219& 227 The more stable trans ester 219 was formed by equilibration in refluxing methanolic sodium methoxide. Samples of the reaction mixture were treated in this way for 4, 8 and 12 hours and, after epimerisation, the ester was hydrolysed to carboxylic acid 220 with aqueous sodium hydroxide. NMR spectroscopy showed that there was still some of the cis-acid after 4 hours of epimerisation but that after 8 hours only the trans-acid was present. To ensure that the epimerisation reaction went to completion, the ester was heated to reflux overnight in methanolic sodium methoxide then hydrolysed to give the trans-acid 220, with no trace of
the cis isomer. Acid 220 was then catalytically hydrogenated at atmospheric pressure to give trans-carboxylic acid 221, which was purified by recrystallisation.

The next stage of the synthesis was to form acyl azide 223 which underwent a Curtius rearrangement when heated to form isocyanate 224. Isocyanate 224 then reacted with hydroxylamine to give hydroxyurea 225. Following the procedure of Arnold and Richardson, acid chloride 222 was formed (Scheme 45) from cyclohexylcarboxylic acid 221 by heating to reflux for 30 minutes in thionyl chloride. The thionyl chloride was removed under a vacuum. Toluene was added and then evaporated under a vacuum to remove any excess thionyl chloride. Acid chloride 222 was then dissolved in aqueous acetone (1:1), chilled and treated with aqueous sodium azide. The solution was stirred for 15 minutes at 0°C, and then acyl azide 223 was extracted with dichloromethane. The extract was dried and the solvent partially evaporated. Toluene was then added and the solution was heated to reflux for 4 hours to ensure full conversion of acyl azide 223 into the isocyanate. Since the isolation of the acyl azide was undesirable due to the explosive nature of these compounds, it was important to know that all of the acyl azide had been converted into the isocyanate. IR spectroscopy showed a strong band at 2140 cm\(^{-1}\) due to the azide group and the progress of the rearrangement was followed by the disappearance of this strong band at 2140 cm\(^{-1}\) and the appearance of a strong band at 2260 cm\(^{-1}\) due to the isocyanate group. Isocyanate 224 was obtained in good yield after distillation. A solution of isocyanate 224 in dichloromethane was added to a slight excess of chilled aqueous hydroxylamine solution following the procedure of Hurdl which was then stirred overnight to give hydroxyurea 225. The latter had a carbonyl stretching band at 1640 cm\(^{-1}\), which was not present in the isocyanate 224. (±)-Hydroxyurea 225 was recrystallised to give the pure product.

**Section 2.2.3 Cycloaddition reactions of C-nitrosoformamide 234.**

The cycloadditions of racemic nitrosoformamide dienophile 234 derived from (±)-hydroxyurea 225 were then investigated. The aim was to determine the effect of temperature on the diastereomeric excesses generated in the reaction. The oxidant initially used to generate acyl nitroso dienophile 234 was tetraethylammonium periodate. This was made by neutralising tetraethylammonium hydroxide with periodic acid in water and is a white solid that is soluble in both water and organic solvents. At -78°C it is not very soluble
in chlorinated solvents e.g. dichloromethane and chloroform although it does dissolve when ethanol is added. Most of the cycloadditions were carried out in a 1:1 mixture of ethanol and dichloromethane, which ensured that both the ammonium periodate and the hydroxamic acid dissolved fully even at -78°C.

A typical reaction involved dissolving a slight excess of tetraethylammonium periodate and excess diene in a mixture of ethanol and dichloromethane at the desired reaction temperature. The reactions at 0°C were carried out with an ice filled cooling bath and at -78°C using a dry-ice and acetone cooling bath. The hydroxyurea 225 dissolved in ethanol and dichloromethane was then added dropwise to the stirred oxidant and diene over a period of 20 to 30 minutes. After being stirred for an hour, the solution was evaporated. The work-up consisted of washing a dichloromethane solution of the residue with sodium thiosulphate solution and then brine. The organic layer was dried and evaporated to give the crude product.

The ratio of diastereomers present in the crude product was measured by NMR spectroscopy. 200 MHz NMR spectra showed that several corresponding protons and carbons in each diastereomer had different chemical shifts. Although in the \(^1\)H spectrum, some of the chemical shifts were either almost identical or overlapped, the signals for the bridgehead and olefinic protons of the oxazine moiety and the urea NH protons were sufficiently separated to use the integration of these signals to measure the ratio of diastereomers present in the crude product. In the \(^13\)C spectra, there were more pairs of signals which allowed many more measurements to be taken and averaged to give a more accurate estimate of the ratio of the two diastereomers although the signal intensities may not be strictly proportional to the amounts of each diastereomer (Table 16). For simplicity, it was assumed that diastereomeric carbons would have similar relaxation times, which may not always be true, and that the greater number of measurements would give a better average value for the ratio. The ratio was estimated by measuring the height of the signals with a ruler. These results are summarised in Table 16.

**Section 2.2.4 Cyclopentadiene cycloadducts 232a&b.**

As can be seen, when the dienophile 234 was trapped with cyclopentadiene, the adducts 232a and 232b were formed in good to excellent yields. These adducts were formed as a
mixture of racemic diastereomers 232a\&b, and the ratio of diastereomers in the crude product was determined using NMR spectroscopy. The ratio could be measured from both the 1H and the 13C NMR spectra. In the 1H NMR spectrum, the ratio was independently determined by the relative integrations of the olefinic signals and of the bridgehead protons. The olefinic proton signals were well separated, with those of the minor adduct occurring at δ 6.17 and 6.26 ppm whereas the corresponding olefinic signals of the major adduct 232a occurred at δ 5.34 and 5.45 ppm. One snag was that the signals from the major diastereomer 232a also overlapped with those from the NH protons in both diastereomers, and so the ratio had to be calculated carefully. The two bridgehead protons of each diastereomer gave 2 fairly sharp singlets, which could be integrated. In the 13C NMR spectra, there were many more pairs of signals, especially those of the two bridgeheads, the olefinic and the aromatic carbons.

From these results, which are shown in Table 16, it can be seen that within the limits of experimental error, that lowering the temperature of the reaction from 0°C to -78°C brought no improvement in the ratio of diastereomers 232a\&b; both reaction temperatures gave d.r. ≈3:1. It was known from previous experiments, that the Diels-Alder reaction proceeded at -78°C but that the rate of the peridate oxidation at lower temperatures depended on the particular hydroxamic acid. To see if the similar ratios were caused by very slow formation of the dienophile at -78°C, with the bulk of the oxidation occurring on warming, the temperature of the reaction mixture was kept at -78°C at first for 4 hours and then overnight. However this did not affect the ratio of diastereomers obtained. The Corey oxidation conditions using NCS and DMSO were tried, but this too did not improve the diastereomeric ratio. When the Swern oxidation conditions, oxaly chloride and DMSO, at -78°C were used to generate 234 an improved d.r. of 4.7:1 was obtained. This is close to the predicted theoretical d.r. (based on d.r. 3:1 at 0°C). This would appear to indicate that the peridate oxidation is very slow at -78°C and that the bulk of the dienophile is generated when the solution warms up.

The mixture of the cyclopentadiene adducts 232a\&b was purified by chromatography on an alumina column, eluted with dichloromethane. This not only purified the cycloadduct but separated the two diastereomers, and a sample of the more polar major adduct 232a was
obtained as a single diastereomer. This was further purified by recrystallisation and an X-ray structure was obtained and is discussed in Section 2.9.

Section 2.5.5 Cyclohexadiene cycloadducts 239a and 233b.

When nitrosoformamide dienophile 234 was trapped with cyclohexadiene, the racemic cyclohexadiene adducts 233a&b were formed in good yield. The crude product contained both of the possible diastereomers 233a&b, and the relative ratios of the two diastereomers were measured using NMR spectroscopy (Table 16).

In the $^1$H NMR spectrum, the ratio of the adducts present in the crude product was determined by the relative integrals of the signals for the olefinic protons and also the bridgehead protons. In the $^{13}$C NMR spectra, the ratios of diastereomeric carbons were measured and averaged to give an average value as described above.

A slight increase in the ratio of diastereomers 233a&b from d.r. 2.4:1 to d.r. 2.9:1 was observed when the periodate oxidation was carried out at -78°C compared with 0°C. For some reason, when the oxidation was carried out under the Swern conditions as described above, the desired cycloadducts 233a&b were not isolated.

The adducts 233a&b were purified as above by chromatography on alumina, which resulted in their separation. A sample of the major adduct 233a was recrystallised and an X-ray structure was obtained. This is discussed in Section 2.9.
### Table 16. Results of the cycloaddition between acylnitroso dienophile 234 and cyclopentadiene and cyclohexadiene.

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>T/ °C (time)</th>
<th>Diene</th>
<th>Oxidant</th>
<th>d.r. (^{1}H)</th>
<th>d.r. (^{13}C)</th>
<th>mean d.r.</th>
<th>d.e. %</th>
<th>Yield % crude (pure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure](Ph</td>
<td>0</td>
<td>C(_2)H(_6)</td>
<td>Et(_4)NIO(_4)</td>
<td>3.06</td>
<td>2.76</td>
<td>2.9</td>
<td>49</td>
<td>111 (83)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78</td>
<td>C(_2)H(_6)</td>
<td>Et(_4)NIO(_4)</td>
<td>2.93</td>
<td>3.29</td>
<td>3.1</td>
<td>51</td>
<td>93 (82)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78 2 hrs</td>
<td>C(_2)H(_6)</td>
<td>Et(_4)NIO(_4)</td>
<td>3.29</td>
<td>3.17</td>
<td>3.2</td>
<td>52</td>
<td>109 (72)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78 24 hrs</td>
<td>C(_2)H(_6)</td>
<td>Et(_4)NIO(_4)</td>
<td>3.11</td>
<td>2.99</td>
<td>3.1</td>
<td>51</td>
<td>83 (-)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78</td>
<td>C(_2)H(_6)</td>
<td>Me(_2)S/NCS</td>
<td>2.5</td>
<td>2.78</td>
<td>2.6</td>
<td>43</td>
<td>82 (-)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78</td>
<td>C(_2)H(_6)</td>
<td>DMSO+ (COCl)(_2)</td>
<td>4.66</td>
<td>4.69</td>
<td>4.7</td>
<td>65</td>
<td>92 (92)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>0</td>
<td>C(_6)H(_4)</td>
<td>Et(_4)NIO(_4)</td>
<td>2.49</td>
<td>2.42</td>
<td>2.4</td>
<td>41</td>
<td>88 (72)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78 4 hrs</td>
<td>C(_6)H(_4)</td>
<td>Et(_4)NIO(_4)</td>
<td>3.24</td>
<td>2.86</td>
<td>3</td>
<td>50</td>
<td>73 (-)</td>
</tr>
<tr>
<td>![Chemical Structure](Ph</td>
<td>-78</td>
<td>C(_6)H(_4)</td>
<td>DMSO+ (COCl)(_2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-^a</td>
</tr>
</tbody>
</table>

^a no adduct isolated
Section 2.3 \((\pm)-(\text{trans}-2\text{-phenylcyclohexyl})\text{-C-nitrosoformate}\).

Scheme 48.

**Section 2.3.1 Synthesis of \((\pm)\text{-trans-2-phenylcyclohexyl hydroxycarbamate 237.}\)**

As discussed earlier, it was hoped that the C-nitrososformamides might exist predominantly in a hydrogen bonded conformation and that rotation about the amidic N-C=O single bond would be slower than about the related C-nitrosoformate O-C=O ester link. To test for any effects of these differences, the cycloadditions of the C-nitrosoformate dienophile 238 was compared with those of the structurally similar C-nitrosoformamide 234.

Since the only difference between the two dienophiles is the substitution of an oxygen atom for a nitrogen atom, it was hoped to investigate the effects on stereoselectivity of both the different rotational speed and also any hydrogen bonding.

Phenyl cyclohexanol 236 has been used as a chiral auxiliary by Whitesell, who has obtained excellent diastereoselectivities in Diels-Alder reactions and alkylations.\(^{49}\) The racemic cyclohexanol has been resolved by selective hydrolysis of the acetate using pig liver esterase.\(^{49}\)

The synthesis of the hydroxycarbamate 237 proceeded easily (Scheme 48). The first stage was to make \(\text{trans-phenylcyclohexanol 236}\) following the procedure of Huynh\(^{49}\) using a cuprate controlled Grignard reaction. Phenyl magnesium bromide was stirred with 10%
Section 2.3 (\(\pm\)-(trans-2-Phenylcyclohexyl)-C-nitrosoformate.

cuprous iodide at -30°C in dry THF for 5 minutes before cyclohexene oxide 235 was added. The cuprous iodide ensured that only the \(\text{trans}\) alcohol 236 was formed. Workup and distillation gave the phenylcyclohexanol 236 in excellent yield, as a low melting solid. Distillation removed the biphenyl by-product formed by coupling of phenyl magnesium bromide and bromobenzene. Cyclohexanol 236 was converted into hydroxycarbamate 237, firstly by treatment of the alcohol with phosgene to form the chloroformate. This reaction was followed by TLC and found to be slower than the equivalent reaction to form a chlorocarbamate from an amine. Although the alcohol did not react with the hydrochloric acid produced by the reaction, it was found that the reaction proceeded faster if triethylamine was present to neutralise the hydrochloric acid. The reaction was judged to be complete after about 4 hours, and the chloroformate was stirred overnight with hydroxylamine hydrochloride, sodium carbonate and a drop of water. After work up, the crude product was chromatographed on silica to give the racemic hydroxycarbamate 237 in 49% yield as a white solid. The remainder of the crude product was the starting alcohol 236. It is interesting to note that, due to the greater electron withdrawing effect of the hydroxycarbamate group, the \(\text{CHO}\)C proton \(\delta\) 4.88 resonates downfield from the corresponding \(\text{CHNHCO}\) proton \(\delta\) 3.77 in the hydroxy urea 225. The same effect was seen in the \(^{\text{13}}\text{C}\) NMR spectra; \(\delta\) 65.4 for \(\text{CHO}\text{C}\) of 237 and \(\delta\) 52.8 for \(\text{CHNHCO}\) of 225.

Section 2.3.2 Cyclodadditions of the racemic dienophile 238.

The (\(\pm\))-hydroxycarbamate 237 was oxidised as before to generate the racemic nitrosoformate dienophile 238 which was trapped \textit{in situ} with either cyclopentadiene or cyclohexadiene to give the expected crude products which on examination by NMR spectroscopy proved to be mixtures of diastereomers 239a&b and 240a&b. The cyclodadditions with both dienes proceeded in good yield. The relative ratios of the two diastereomers formed with each diene were determined using NMR spectroscopy as described previously.

Both the \(^{1}\text{H}\) and \(^{\text{13}}\text{C}\) NMR spectra showed separate signals for each diastereomer and both were used to estimate the relative ratio of diastereomers in the crude product of each cyclodaddition. The \(^{\text{13}}\text{C}\) NMR spectra proved more useful, but see earlier \textit{caveat} concerning similar relaxation times for diastereomeric carbons, since they showed more pairs of signals which could be measured and averaged to obtain a more accurate estimate of the ratios of
diastereomers produced. Especially useful were the bridgehead carbons, the two olefinic carbons and the two tertiary cyclohexyl carbons, all of which appeared as separate peaks. In the $^1$H NMR spectra, the analysis was complicated by the overlap of the CHOCO signal and one of the olefinic signals and also by the fact that the signals due to each diastereomer were not as well separated and tended to overlap either partially or completely. This made the analysis more difficult in comparison to the corresponding adducts obtained from the nitrosoformamide 234. The results are shown in Table 17.

**Section 2.3.3 Cyclopentadiene adduct 239a&b.**

The NMR spectrum of the crude product from cyclopentadiene revealed that it was a mixture of the diastereomers 239a&b. In the $^1$H NMR, all of the equivalent signals from the two diastereomers overlapped either partially or completely and so their ratio could not be determined. In the $^{13}$C NMR spectrum, each diastereomer gave a separate set of signals from which the ratio of diastereomers was calculated.

It was found that the major 239a and minor 239b of the cyclopentadiene adduct could be separated by column chromatography on silica eluted with ethyl acetate and light petrol. The major diastereomer 239a was eluted first. Recrystallisation removed the final traces of the minor diastereomer and gave a sample of the major diastereomer 239a. The relative stereochemistry of this adduct was determined by X-ray crystallography (see Section 2.9).

**Section 2.3.4 Cyclohexadiene adduct 240a&b.**

Unlike cyclopentadiene adduct 239a&b, for cyclohexadiene adduct 240, both the $^1$H NMR spectra and the $^{13}$C NMR spectra could be used to determine the ratios of diastereomers formed in the cycloaddition. These results are summarised in Table 17. The crude product of the reaction was then purified by column chromatography. It was found that the major and minor diastereomers of cyclohexadiene adduct 240a& a could not be separated by column chromatography on silica eluted with ethyl acetate and light petrol, as both diastereomers were eluted simultaneously. The major diastereomer 240a could however be fractionally recrystallised from ethyl acetate and light petroleum. It was also found that when the crude product was chromatographed on an alumina column eluted with light petroleum and ethyl acetate the two diastereomers could be separated. The major diastereomer 240a was further purified by fractional recrystallisation as above to give a
single diastereomer. The relative stereochemistry of this adduct was determined by X-ray crystallography (see Section 2.9).

**Section 2.3.5 Results.**

From these results (Table 17) it can be seen that the best diastereomeric induction was obtained when nitrosoformate 238 was generated by Swern oxidation at \(-78^\circ\text{C}\), d.r. 5.45 for cyclopentadiene adduct 239 and d.r. 7.17 for cyclohexadiene adduct 240. This resulted in almost twice as much of the major diastereomers 239a and 240a in comparison to oxidation with periodate at \(-78^\circ\text{C}\), d.r. 3.5 approximately for both adducts. When the periodate oxidation is used to generate dienophile 238, there is little or no improvement in stereoselection of the cycloadditions when the temperature of the reaction is lowered from 0°C to \(-78^\circ\text{C}\). This would seem to indicate that the periodate oxidation of the hydroxycarbamate to nitrosoformate 238 proceeds very slowly at \(-78^\circ\text{C}\) and that the bulk of reaction does not occur at \(-78^\circ\text{C}\) but instead as the solution slowly warms to room temperature. Both of these observations are similar to the results obtained for nitrosoformamide dienophile 234. Thus the best diastereomeric excesses were d.e. 69% for the cyclopentadiene adduct 239 and d.e. 75% for the cyclohexadiene adduct 240 when the hydroxycarbamate 237 was oxidised under the aforementioned Swern conditions, *i.e.* DMSO and oxalyl chloride.

**Table 17. Results of the cycloaddition between nitrosoformate dienophile 238 and cyclopentadiene and cyclohexadiene.**

<table>
<thead>
<tr>
<th></th>
<th>T/°C (time)</th>
<th>Diene</th>
<th>Oxid*</th>
<th>d.r. (^1\text{H})</th>
<th>d.r. (^13\text{C})</th>
<th>average d.r.</th>
<th>d.e. % crude (pure)</th>
<th>yield % pure</th>
</tr>
</thead>
<tbody>
<tr>
<td>239</td>
<td>0</td>
<td>C(_5)H(_6)</td>
<td>Et(_2)NIO(_4)</td>
<td>-</td>
<td>6.21</td>
<td>6.21</td>
<td>45</td>
<td>167 (98)</td>
</tr>
<tr>
<td></td>
<td>-78</td>
<td>C(_5)H(_6)</td>
<td>Et(_2)NIO(_4)</td>
<td>-</td>
<td>3.6</td>
<td>3.6</td>
<td>56</td>
<td>106 (98)</td>
</tr>
<tr>
<td></td>
<td>-78</td>
<td>C(_6)H(_6)</td>
<td>DMSO+ (COCl)(_2)</td>
<td>-</td>
<td>5.45</td>
<td>5.45</td>
<td>69</td>
<td>102 (-)</td>
</tr>
<tr>
<td>240</td>
<td>0</td>
<td>C(_6)H(_6)</td>
<td>Et(_2)NIO(_4)</td>
<td>2.43</td>
<td>3.3</td>
<td>2.87</td>
<td>48</td>
<td>79 (51)</td>
</tr>
<tr>
<td></td>
<td>-78</td>
<td>C(_6)H(_6)</td>
<td>Et(_2)NIO(_4)</td>
<td>3.33</td>
<td>3.68</td>
<td>3.51</td>
<td>57</td>
<td>140 (54)</td>
</tr>
<tr>
<td></td>
<td>-78</td>
<td>C(_6)H(_6)</td>
<td>DMSO+ (COCl)(_2)</td>
<td>6.67</td>
<td>7.67</td>
<td>7.17</td>
<td>75</td>
<td>115 (92)</td>
</tr>
</tbody>
</table>
Section 2.4 \textit{trans}-2-(nitrosocarbonyl)-phenylcyclohexane.

Scheme 49.

Section 2.4.1

With a supply of (±)-\textit{trans}-2-phenylcyclohexanecarboxylic acid 221, it was a simple matter to make (±)-hydroxamic acid 241 and so it seemed logical to investigate the cycloadditions of the derived racemic acylnitroso derivative 242. Two factors were
Section 2.4 *trans*-2-(nitrosocarbonyl)-phenylcyclohexane.

expected to lead to greater diastereomeric induction for the dienophile 242 when compared to the C-nitrosoformamide dienophile 234 and C-nitrosoformate dienophile 238.

i The acylnitroso group in 242 is closer to the chiral auxiliary and so should be better shielded by the phenyl group and

ii The acylnitroso group is directly attached to the cyclohexane ring and so there will be less opportunity for conformations arising from rotation about single bonds *i.e.* greater conformational rigidity. To test these predictions, the cycloadditions of dienophile 242 were investigated.

The hydroxamic acid 241 was made in good yield by treating acid chloride 222 with aqueous hydroxylamine. The product was shown to be the desired (±)-*trans*-hydroxamic acid 241 as follows. The $^1$H NMR spectrum in (CD$_3$)$_2$SO showed the presence of D$_2$O exchangeable signals at δ 10.24 and 8.55 due to the CONHOH group. The compound also gave a red colour with ethanolic ferric chloride.

As before, hydroxamic acid 241 was oxidised with periodate, at both 0°C and -78°C, to give acylnitroso dienophile 242. The dienophile was trapped as before *in situ* with either cyclopentadiene or cyclohexadiene to give the corresponding adducts 244 or 243. Both the cyclopentadiene and the cyclohexadiene adducts were formed in good yields (71% and 93% respectively, after chromatography).

Section 2.4.2 Cyclopentadiene adduct 244

The crude product from cyclopentadiene appeared to be a 1:1 mixture of the diastereomers 244a&b when examined by NMR spectroscopy. The crude product was chromatographed on both silica and alumina to try and separate the two diastereomers. However, as with the cyclohexadiene adduct 243 only one substance was isolated, which had identical NMR spectra to that of the crude product.

Section 2.4.3 Cyclohexadiene adduct 243a&b

The $^1$H NMR spectrum of the crude product 243a&b showed all of the expected signals of the adducts, but the signals of both diastereomers coincided. The two bridgehead protons resonated at δ 5.05 and 4.65 as broad singlets. The signals due to the two α-cyclohexane protons overlapped at δ 2.8. However, in the $^{13}$C spectrum most carbons gave pairs of signals of equal intensity, which appeared to indicate that a 1:1 mixture of diastereomers
Section 2.4 trans-2-(nitroso carbonyl)-phenyl cyclohexane.

had been formed. The crude product was chromatographed on both silica and alumina in an attempt to separate the two diastereomers. However, only one compound was isolated, and this had NMR spectra identical with those of the crude material. The purified product was then recrystallised from ethyl acetate and light petroleum and again the NMR spectra of the recrystallised product were unchanged.

Section 2.4.4 Interpretation of cyclopentadiene and cyclohexadiene results.

There are two possible explanations for the two sets of signals in the NMR spectra of 243 and 244 at 25°C.

i That the crude product consists of a 1:1 mixture of diastereomers and the cycloaddition proceeds with 0% d.e. The broadened spectra are due to a little signal broadening due to slow amide rotation or

ii That there is only one diastereomer present in the crude product and that the cycloaddition proceeds with 100% d.e.. This would mean that two rotamers give rise to two sets of signals.

We attempted to try and provide evidence for one or other of these explanations and carried out 1H NMR experiments at -50°C and +50°C in addition to the 25°C NMR experiments. The 1H NMR spectra of both adducts 244a&b and 243a&b are temperature dependent and can be summarised as follows. As the temperature of the NMR spectra experiment falls the 1H NMR spectra become sharper. Also there is no change in the 1H and 13C NMR of both adducts when they are purified by chromatography, on either alumina or silica, and by recrystallisation. These methods of purification separated the diastereomeric mixtures of the corresponding adducts 232a&b & 233a&b and 239a&b and 240a&b of the nitrosoformamide and nitrosoformate dienophiles 234 and 238.

The best explanation is that a 1:1 mixture of diastereomers is formed in both cycloadditions. Restricted rotation giving rise to two sets of spectra has not been observed, both in research in the Kirby group nor reported for various nitroso carbonyl adducts in the literature. Presumably, in all other examples at least, one rotamer is more stable for each diastereomer, since we would not expect rapid interconversion at normal spectrometer temperature. The 1H NMR spectra were measured at various temperatures since some of the signals were broader than usual and it was just possible that 2 rotamers of a single cycloadduct were present with rotation just beginning to be detectable in the spectra.
Section 2.4 *trans*-2-(nitrosocarbonyl)-phenylcyclohexane.

However, sharp spectra were not produced at either the higher temperature (+50°C) (although this is not a great temperature increase) or at the lower temperature (-50°C). Presumably, the changes in the NMR spectra are due to an increase in the rate of amide rotation with temperature, *i.e.* there is no evidence that a single diastereomer is present as two rotamers in equal amounts. Although the varying temperature NMR experiments do not exclude this, we did not observe 2 spectra collapsing into 1 spectrum, *i.e.* coalescence of the two sets of signals did not occur.

Section 2.4.5 Model compounds.

In an attempt to get more evidence for this phenomenon of restricted rotation, three model compounds were made.

Since 2,3-dimethylbutadiene is not a prochiral diene, no chiral centres are formed during the cycloaddition of the diene and a chiral dienophile. Thus although the adduct formed will be chiral, this will be due to the presence of the chiral auxiliary *i.e.*, only one product will be formed. With the racemic dienophile 242, the adduct 245 will be formed as a racemate. This means that if two sets of signals are observed in either the 1H or 13C NMR spectrum of this compound they can only be due to restricted rotation and not the presence of two diastereomers. The adduct 245 was made in the usual manner in 33% yield, after chromatography and recrystallisation. The 13C NMR spectrum of the recrystallised sample was complicated and showed pairs of signals which could be attributed to two rotamers. This is in contrast to the 13C NMR spectrum, room temperature, of the dimethylbutadiene adduct of dienophile 234 generated from hydroxyurea 225 which is a nicely behaved spectrum with only one set of signals visible, *i.e.* no sign of restricted rotation.

The second and third model compounds were amides. Dimethylamide 246 was made in good yield by treating acid chloride 222 with aqueous dimethylamine. The NMR spectra of a recrystallised sample of amide 246 showed no sign of restricted rotation. In the 1H NMR spectrum, the two amide methyl signals appeared as a sharp singlet at δ 2.55. In the 13C NMR spectra, they appeared as two quartets of equal intensity.

Piperonyl amide 247 was made in quantitative yield by treating acid chloride 222 with piperidine and again, there was no sign of restricted rotation. The room temperature 13C NMR spectra was well resolved with every signal present and no sign of any splitting.
The model compounds showed that there was no sign of restricted rotation at room temperature for the simpler dimethylamide 246 and piperonylamide 247. The dimethylbutadiene adduct 245 showed signs of restricted rotation, perhaps due to the fact that it is larger than the two amides.

**Section 2.4.6 Stereochemistry.**

Although the evidence appeared to point to a 1:1 mixture of diastereomers, it was decided to obtain an X-ray structure of cycloadduct 243 (see fig 1). The X-ray structure of 243 showed that both the bridging CH₂-CH₂ bond and the olefinic bond of the oxazine were indistinguishable in length from one another, *i.e.* there were two diastereomers present in the crystal in a 1:1 ratio. Thus the X-ray structure showed that the cycloaddition proceeded in a non stereoselective manner to give a 1:1 mixture of two cycloadducts. It was assumed that this was also the case for cyclopentadiene cycloadduct 244.

This would seem to suggest that for dienophile 242 that either there is no distinction between the *endo* and *exo* cycloaddition of the diene or that the dienophile can react equally well in both the *cis* and the *trans* conformation of the acylnitroso group, which results in the lack of stereoselectivity.
Fig 1. X-ray structure of 243.

\(^1\)H NMR shows apparently a 1:1 mixture of diastereomers. Bond lengths essentially the same (c.f. 1.33 and 1.54 for double and single bonds, respectively). Note also N now nearly planar, i.e. it could be average of two pyramidal forms.
Scheme 2.5 N-(trans-2-phthaloylaminocyclohexyl)-C-nitrosoformamide

\[
\begin{align*}
250 & \xrightarrow{\text{toluene, heat}} 252 \\
& \xrightarrow{\text{AcOH, heat}} 253 \\
248 & \xrightarrow{\text{ClCO}_2\text{Et, NEt}_3, \text{MeCN, CHCl}_3} 254 \\
250 & \xrightarrow{\text{CHCl}_3, \text{heat}} 252 \\
252 & \xrightarrow{\text{Cl}_2\text{CO, NEt}_3, \text{toluene}} 255 \\
252 & \xrightarrow{\text{Me}_3\text{SiNHSiMe}_3, \text{THF}} 258 \\
& \xrightarrow{\text{MeOH}} 249
\end{align*}
\]

Scheme 50.

\[
\begin{align*}
260 & \xrightarrow{\text{H}_2\text{C-NH}_2, \text{EtOH, reflux}} 261 \\
& \xrightarrow{R-\text{NH}_2} R-\text{NH}_2 + 262
\end{align*}
\]

Scheme 51.
Scheme 52.

Scheme 53.

Scheme 54.
Section 2.5.1

Since moderate diastereoselectivity was observed for the cycloadditions between the
dienophiles generated from trans-phenylcyclohexyl-N'-hydroxyurea 225 and the related
trans-phenylcyclohexyl-hydroxycarbamate 237 with either cyclopentadiene or
cyclohexadiene, it was anticipated that increasing the size of the bulky R group would
improve the diastereoselection. The use of the phthaloyl group was investigated since being
bicyclic, it is larger than a phenyl group and so should shield more of one face of the
acylnitroso derivative relative to the smaller phenyl group. It was also hoped that as both
groups are planar aromatic groups, they would have similar orientations in space. It was
hoped that combining these factors would lead to greater stereoselection in the
cycloadditions of this dienophile 248 prepared from (±)-trans-1,2-diaminocyclohexane 250,
which is available in racemic and optically active forms and so if desired, a single
enantiomer of the dienophile could be easily prepared.

Since the phthaloyl group is a polar group, many phthaloyl derivatives are relatively
insoluble in non-polar organic solvents. This proved to be the case with the very polar
hydroxyurea 249 which was only soluble in more polar solvents e.g. dimethyl sulphoxide
and ethanol.

Section 2.5.2 Synthesis of (±)trans-2-phthaloylaminocyclohexyl hydroxyurea 249.

A possible synthetic route to hydroxyurea 249 is shown (Scheme 50), involving the
synthesis of phthaloyl amine 252 from diaminocyclohexane 250. Treatment of 252 with
phosgene should give chloroformate 255, which when treated with hydroxylamine should
form the desired hydroxyurea 249. However the synthesis did not proceed as planned and
had to be altered.

When (±)-diaminocyclohexane 250 reacted with phthalic anhydride 251 in toluene under
Dean and Stark conditions, according to the procedure of Bose et al 31, a white insoluble
precipitate formed immediately and this did not disappear even after prolonged refluxing.
This solid was presumed to be zwitterion 264 (Scheme 52). In an attempt to dissolve this
solid and to complete the imide formation, the reaction was carried out in different solvents,
for example in chloroform following the procedure of Sasaki et al 32, but again this led to an
insoluble precipitate with no sign of the desired product. When the reaction was carried out in dimethyl sulfoxide it was found that, although no precipitate formed, there was also no sign of the expected product.

When the reaction was carried out in refluxing acetic acid, a product was obtained, but this proved to be the N-acetylated derivative 253 of 252. It was also of note that the diphthaloylated amine was also formed and, in an attempt to reduce this, phthalic anhydride was added slowly to a slight excess of diamine 250 in the hope that the phthalic anhydride 251 would mainly react with diamine 250 to form mono-phthaloylated amine 252 and not with already mono-phthaloylated amine, which would lead to the formation of the undesired diphthaloylated amine. When the reaction was carried out in pyridine, the initially formed precipitate did disappear after refluxing overnight and the desired product 252 was obtained, although in low yield. When attempts were made to scale up this reaction, it was found that a large amount of phthaloyl amine 252 could not be made, in this way, since the desired product was obtained in low yields.

It was decided to use the phthaloylating agent N-ethoxycarbonylphthalimide33 254. This was made in good yield by adding ethyl chloroformate to phthalimide and triethylamine in acetonitrile and chloroform. When carbamate 254 was slowly added to a slight excess of diamine 250 in chloroform and the mixture was stirred overnight, the phthaloyl amine 252 was formed in good yield. A by-product of the reaction was the water soluble and low boiling ethyl carbamate 266 which was removed by a combination of water washing and evaporation under vacuum. It was found that this route could be used to prepare 5g quantities of the desired amine 252.

The formation of hydroxyurea 249 from amine 252 also proved to be troublesome. It was found that the original plan of treating amine 252 with phosgene to form chloroformate 255 followed by treatment with hydroxylamine did not result in the formation of the desired hydroxyurea 249. This was perhaps due to the nucleophilicity of the hydroxylamine, a good nucleophile, with the phthaloyl group. If the hydroxylamine attacks one of the imide carbonyls, then it can form the amide and further attack will result in loss of the phthaloyl group. Indeed methylamine has been used to remove phthaloyl groups,34 with a reaction time of 5 minutes to cleave the cyclic imide 260 to the amide 261 and 2.5 hours to remove the phthaloyl group completely (Scheme 51). Another problem, found later when the
hydroxyurea 249 was synthesised, is that the hydroxyurea formed is very insoluble and so it is difficult to separate the hydrochloride salts and the mixture of products formed in the reaction.

Due to these reasons, another method was tried (Scheme 53). This involved treating ethyl carbamate 267, formed in the reaction between ethyl chloroformate and phthaloyl amine 252, with hydroxylamine solution. It was hoped that the carbamate would undergo nucleophilic attack from hydroxylamine forming the desired hydroxyurea 249 with loss of ethanol. Ethyl carbamate 267 was treated with hydroxylamine in both methanol and a mixture of dichloromethane and water. However, the starting material was recovered in both cases.

Treatment of amine 252 with phosgene lead to the isolation of chloroformate 255. When this was treated with methanol, the expected methyl carbamate was generated. It was decided to use a protected hydroxylamine, which would be more reactive than hydroxylamine towards the chloroformate and would also avoid the need for aqueous alkaline conditions. The hydroxylamine derivative chosen was \(N,O\)-bis(trimethylsilyl)hydroxylamine 259. Ghosez and Gouverneur used this compound in their synthesis of sultam 161 from the corresponding chloroformate\(^{29}\). This hydroxylamine was chosen because:-

i. it is a liquid which is soluble in non-polar organic solvents,

ii. it is volatile and so can be easily removed and

iii. it is easy to make from hydroxylamine.

Three literature methods were found for the synthesis of this compound.

\[
\begin{align*}
\text{NH}_2\text{OH}.\text{HCl} + (\text{Me}_3\text{Si})_2\text{NH} & \text{ in THF} \quad \text{ref. 55} \\
\text{NH}_2\text{OH}.\text{HCl} + (\text{Et})_2\text{NH} + \text{ClSiMe}_3 & \text{ in THF} \quad \text{ref. 56} \\
\text{NH}_2\text{OH}.\text{HCl} + \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2 + \text{ClSiMe}_3 & \text{ in CH}_2\text{Cl}_2 \quad \text{ref. 57}
\end{align*}
\]

The first method\(^{25}\) involved the reaction between hexamethyldisilazane (HMDS) and hydroxylamine hydrochloride in tetrahydrofuran. HMDS acts both as a base to neutralise the hydroxylamine hydrochloride and the HCl formed in the reaction and as a silylating agent. However no product was isolated from this reaction. The second method\(^{26}\) involved the neutralisation of hydroxylamine hydrochloride with diethylamine and then the addition
of two equivalents of trimethylsilyl chloride to the free hydroxylamine. Although this was tried several times, each time the desired hydroxylamine 259 was not isolated. The third method tried was that of Bottaro et al., which involved the neutralisation of hydroxylamine hydrochloride with ethylenediamine in dichloromethane, followed by addition of trimethylsilyl chloride. The resulting mixture was stirred at room temperature for 24 hours. The diamine hydrochloride salt was very insoluble in dichloromethane and so precipitated out and was removed by filtration. Distillation gave the desired product 259 in good yield.

When chloroformate 255 was treated with the silylated hydroxylamine 259 in THF, the desired silylated hydroxyurea was formed rapidly and was isolated by evaporation of the solution. It was deprotected by heating to reflux overnight in methanol to give the desired hydroxy urea 249.

Section 2.5.3 Cycloadditions of the nitrosoformamide dienophile 248.

The racemic dienophile 248 was generated as before with tetraethylammonium periodate in ethanol-dichloromethane at 0°C and at -78°C, and as previously, trapped in situ with either cyclopentadiene or cyclohexadiene to give the cycloadducts 256a&b and 257a&b respectively. The dienophile 248 was also generated at -78°C using the Swern oxidation conditions and trapped with cyclopentadiene to give the cycloadducts 256a&b. As before, the ratios of the diastereomers 256a&b in the crude product were measured by NMR spectroscopy.

Results of the cycloaddition of the dienophile 248

Table 18. Cycloaddition of dienophile 248 with cyclopentadiene and cyclohexadiene, ratios and yields of cycloadducts 256 and 257.

<table>
<thead>
<tr>
<th>Cycloadduct formed</th>
<th>T/°C</th>
<th>Diene</th>
<th>Oxidant</th>
<th>d.r. ^1^H</th>
<th>d.r. ^13^C</th>
<th>Yield % crude (purified)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /></td>
<td>0</td>
<td>C₅H₆</td>
<td>Et₄NIO₄</td>
<td>1</td>
<td>1</td>
<td>93 (72)</td>
</tr>
<tr>
<td></td>
<td>-78</td>
<td>C₅H₆</td>
<td>Et₄NIO₄</td>
<td>1</td>
<td>1</td>
<td>99 (54)</td>
</tr>
<tr>
<td>256</td>
<td>-78</td>
<td>C₅H₆</td>
<td>DMSO+(COCl)₂</td>
<td>1</td>
<td>1</td>
<td>82 (-)</td>
</tr>
</tbody>
</table>
### Table 2.5 N-(trans-2-phthaloylaminocyclohexyl)-C-nitrosoformamide

<table>
<thead>
<tr>
<th>Cycloadduct formed</th>
<th>T/°C</th>
<th>Diene</th>
<th>Oxidant</th>
<th>d.r. $^1$H</th>
<th>d.r. $^{13}$C</th>
<th>Yield % crude (purified)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0</td>
<td>C$_6$H$_5$</td>
<td>Et$_4$NIO$_4$</td>
<td>1</td>
<td>1</td>
<td>107 (48)</td>
</tr>
<tr>
<td>257</td>
<td>-78</td>
<td>C$_6$H$_5$</td>
<td>Et$_4$NIO$_4$</td>
<td>1</td>
<td>1</td>
<td>108 (42)</td>
</tr>
</tbody>
</table>

The results of the cycloadditions are presented in Table 18. As can be seen, there is no diastereoselectivity for dienophile 248 and that both of the diastereomers were formed in equal amounts within experimental error.

### Section 2.5.3.a Analysis of the results

#### Cyclopentadiene adduct 256

The NMR spectra of the crude cyclopentadiene adduct 256 showed that two diastereomers 256a&b were formed and that within experimental error, they were formed in a 1:1 ratio, *i.e.* there was no diastereomeric induction in the cycloaddition reaction. The signals of each diastereomer were well separated in both the $^1$H and the $^{13}$C NMR spectra. In the $^1$H NMR spectra, each set of olefinic protons was well separated and appeared as a pair of multiplets. The amide protons also gave two distinct signals although since they overlapped, they were useless for determination of d.e.. A separate signal could be seen for each of the four bridgehead protons of the two diastereomers. In the $^{13}$C NMR spectra, almost every carbon atom appeared as a pair of signals.

The crude product was purified using column chromatography on silica, as before, and the two diastereomers 256a&b were shown to separate under these conditions. Both were crystalline solids which were soluble in chloroform, although the hydroxyurea 249 was very insoluble. The NMR spectra of each of these adducts showed that almost complete separation of the diastereomers had been achieved. By comparison of the two sets of spectra, it could be seen that they were indeed different diastereomers with the olefinic, bridgehead and NH protons of one diastereomer occurring downfield relative to those of the other diastereomer.
Section 2.5 \(N\)-(trans-2-phthaloylaminocyclohexyl)-C-nitrosoformamide

Swern oxidation with DMSO and \((\text{COCl})_2\).

The dienophile 248 was generated as before with DMSO and \((\text{COCl})_2\), the Swern oxidation conditions, at \(-78^\circ\text{C}\) and was trapped with cyclopentadiene to form the adducts 256a\&b. This experiment also produced a 1:1 ratio of diastereomers. This result is not too surprising since, if there is little difference in the activation energies of the two diastereomeric reactions at 0°C then it follows that at \(-78^\circ\text{C}\) or even lower temperatures, little improvement in diastereoselection will be obtained.

Section 2.5.3.b Cyclohexadiene adducts 257a\&b

The NMR spectra of the crude product of the cycloaddition between the dienophile 248 and cyclohexadiene showed that, as with the cyclopentadiene adducts 256, the two possible diastereomers were formed in equal amounts. Signals for the olefinic protons of one diastereomer coincided and appeared downfield of the corresponding signals of the other diastereomer, which were separated by c.a. 0.75 ppm. The two NH signals were not fully separated. In the \(\text{^13C}\) NMR, pairs of signals could be seen corresponding to both diastereomers.

The crude product was purified by column chromatography on alumina, but only one spot was seen by TLC and so the purified product remained a mix of diastereomers 257a\&b.

Section 2.5.4 Stereochemistry of the cycloaddition.

The reaction proceeds with no stereoselection and both possible diastereomers are formed in equal amounts when dienophile 248 is trapped with both cyclopentadiene and cyclohexadiene. The only difference between dienophiles 248 and 234 is that the phenyl group in the latter is replaced with a phthaloyl amino group. The absence of diastereomeric induction with the former dienophile must be related to this difference. This loss of diastereoselectivity could be have at least three possible explanations :-

i. The phthaloyl group might not have the same orientation in dienophile 248 as the phenyl group in 234 and therefore might not be as effective in shielding one face of the nitroso group.

ii. The orbitals of the phenyl group and the acylnitroso group may interact and hold the acylnitroso group in dienophile 234 in a fixed conformation until it reacts with the
diene. These interactions may not be as great when the phenyl group is replaced with the phthaloylamino group and so the conformation of the acynitroso group in \textbf{248} is less rigidly defined.

iii. Since the phthaloyl group is larger and has a larger \( \pi \) system, it is possible that it also interacts with the diene leading to less differentiation between \textit{endo} and \textit{exo} attack and hence to less stereocontrol.

It is likely that more than one of the above explanations are true and that the effects act in concert. But whatever the explanation, there is no stereocontrol observed for the cycloadditions of dienophile \textbf{248} with cyclopentadiene and cyclohexadiene.
Section 2.6 (±)-2-Phthaloylaminocyclohexyl C-nitrosoformate.

\[
\begin{align*}
\text{235} \xrightarrow{\text{NH}_3(aq)} & \text{268} \xrightarrow{\text{CH}_3\text{CO}_2\text{H}} \text{269} \\
\text{i \text{Cl}_2\text{CO}, \text{NE}_3} \quad \text{ii \text{TMSNHOTMS}} & \text{270} \\
\text{271} \text{272a&b, 1:1 mixture of diastereomers} \\
\text{273a&b, 1:1 mixture of diastereomers} \\
\text{Scheme 55.}
\end{align*}
\]

Section 2.6.1 Synthesis of (±)-trans-Phthaloylaminocyclohexyl hydroxycarbamate 270.

As phthaloyl hydroxyurea 249 had already been synthesised and the cycloadditions of the derived nitrosoformamide dienophile 248 with cyclopentadiene and cyclohexadiene had been investigated, the cycloadditions of nitrosoformate dienophile 271 were of interest. Fortunately, the synthesis of the racemic-\textit{N}-hydroxycarbamate 270 proved far easier than that of the \textit{N}-hydroxyurea 249. (Scheme 55).
Section 2.6 (+)-2-Phthaloylamino cyclohexyl C-nitrosoformate.

trans-2-Aminocyclohexanol 268 was easily made by stirring cyclohexene oxide in concentrated aqueous ammonia at room temperature for 3-4 days. The desired racemic amino alcohol 268 precipitated out and was easily separated by evaporation of the solution under reduced pressure. The trans-amino alcohol 268 was formed in 87% yield. The melting point of the product 62-64°C, agreed with the literature value 

\[ \text{m.p. 107-8°C} \]

whereas the cis-amino alcohol has m.p. 107-8°C. The amino alcohol 268 was then treated with phthalic anhydride to form trans-2-phthaloylamino cyclohexanol 269. Two methods of phthaloylation were tried. The first was to treat amino alcohol 268 with phthalic anhydride in refluxing acetic acid for 30 minutes; this gave the desired product 269 in 52% yield. The second method was to reflux amino alcohol 268 and phthalic anhydride in toluene in a Dean and Stark apparatus for 3 hours. This gave the desired product 269 in 66% yield. Since the starting material was an amino alcohol and not a diamine, there were no problems in forming phthaloyl alcohol 269 with phthalic anhydride. That the trans-phthaloyl amino alcohol 269 was formed and not the cis-isomer was indicated by the 'H NMR spectrum of the product. This showed two signals at \( \delta \) 4.28 and 4.00 due to the CHOH and CHNPhth respectively. Both of these signals were doublets of triplets with a triplet coupling of 10.2 Hz. In trans-phthaloylamino cyclohexanol 269, both the hydroxy and the phthaloylamino groups are in equatorial positions and the corresponding trans hydrogens are axial. These couple with each other and the axial protons of the neighbouring methylene groups to give triplets. Since the dihedral angle is \( \sim 180^\circ \), according to the Karplus equation this coupling approaches its maximum value. The vicinal coupling of 10.2 Hz is consistent with an axial-axial cyclohexane coupling (9-13 Hz) rather than an equatorial-axial coupling (cis) (2-5 Hz).

The phthaloylamino alcohol was then converted into N-hydroxycarbamate 270. Treatment with phosgene gave the chloroformate which reacted with bis-silylhydroxylamine 259 to give the silylated hydroxycarbamate. This was desilylated with methanol to give the desired racemic hydroxycarbamate 270. The deprotection proved to be more difficult than for the corresponding hydroxyurea, since some starting material was recovered after stirring overnight in methanol. However, complete conversion was brought about by overnight heating to reflux in methanol.
Section 2.6.2 Cycloadditions of C-nitrosoformate 271.

Attempts to form acylnitroso dienophile 271 by oxidation of hydroxycarbamate 270 with tetraethylammonium periodate proved difficult. The previous method of slow addition of the hydroxycarbamate to a dichloromethane-ethanol solution of periodate and diene led to phthaloylaminocyclohexanol 269 as the major product. The desired cycloadducts were however, formed by adding the periodate slowly to a stirred solution of the diene and the hydroxycarbamate in dichloromethane at 0°C. The dienophile 271 could also be generated at -78°C using Swern oxidation conditions of dimethyl sulfoxide and oxalyl chloride in dichloromethane (Scheme 55). These results are summarised in Table 19.

Results.

Table 19, Ratios of the diastereomeric adducts formed by trapping dienophile 271 with cyclopentadiene and cyclohexadiene at 0°C and -78°C.

<table>
<thead>
<tr>
<th>Cycloadduct formed</th>
<th>T/°C</th>
<th>Diene</th>
<th>Oxidant</th>
<th>d.r.</th>
<th>Yield % Crude (purified)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td>0</td>
<td>C₅H₆</td>
<td>Et₄NIO₄</td>
<td>1:1</td>
<td>113 (87)</td>
</tr>
<tr>
<td>272a&amp;b</td>
<td>-78</td>
<td>C₅H₆</td>
<td>DMSO + (COCl)₂</td>
<td>1:1</td>
<td>97 (-)</td>
</tr>
<tr>
<td><img src="image2" alt="Image" /></td>
<td>0</td>
<td>C₆H₄</td>
<td>Et₄NIO₄</td>
<td>1:1</td>
<td>93 (-)</td>
</tr>
<tr>
<td>273a&amp;b</td>
<td>-78</td>
<td>C₆H₄</td>
<td>DMSO + (COCl)₂</td>
<td>1:1</td>
<td>89 (-)</td>
</tr>
</tbody>
</table>

Section 2.6.3 Cyclopentadiene adduct 272a&b.

The NMR spectra of the crude product of the cycloaddition of dienophile 271 with cyclopentadiene showed that the two possible diastereomers 272a&b were formed in equal amounts, i.e. there was no diastereoselectivity in this reaction. The method of oxidation used to form dienophile 271 made no difference within experimental error to the ratio of diastereomers formed; both the periodate oxidation at 0°C and the Swern oxidation conditions at -78°C gave a 1:1 mixture of diastereomers, although for both dienes, the Swern oxidation conditions gave a higher yield of the cycloadducts with no formation of phthaloylamino alcohol 269. In contrast, the periodate oxidation conditions gave alcohol 269 as the major product; this was also the case when dienophile 271 was trapped with
cyclohexadiene. The signals attributable to diastereomers 272a&b were both well separated in both the 1H and the 13C NMR spectra and these signals were used to show that the two diastereomers were formed in equal amounts.

The 1H NMR spectrum of the mixture of the cyclopentadiene adducts 272a&b was temperature dependent. As the temperature increased, so the resolution of the signals increased. In the 13C NMR spectrum, pairs of signals of equal height due to the two diastereomers were observed, although they were very close in chemical shift.

The crude product was purified by column chromatography on silica eluted with ethyl acetate and light petroleum. However, this did not separate the two diastereomers and the purified product was still 1:1 mixture of diastereomers 272a&b. The two diastereomers were separated by column chromatography on alumina eluted with dichloromethane. The 1H NMR spectrum of the less polar fraction 272a showed that the two diastereomers were fully separated. The CHOCO and CHNPhht protons gave doublets of triplets with no sign of the other diastereomer and the 13C NMR spectrum showed only one set of signals.

**Section 2.6.4 Cyclohexadiene adduct 273a&b.**

The NMR spectra of the crude product, formed when dienophile 271 was trapped with cyclohexadiene, showed that both diastereomers 273a&b were formed as a 1:1 mixture. This was the case whether dienophile 271 was generated at 0°C using periodate as the oxidant or, in an attempt to improve the diastereoselection, at -78°C using the Swern oxidation conditions.

In the 1H NMR spectrum of the crude product, the olefinic protons of the two diastereomers 273a&b coincided in a broad multiplet and the two bridgehead protons of both isomers overlapped as a broad singlet, with a slight upfield shoulder. In the 13C NMR spectrum, pairs of signals of equal intensity could be seen for most signals, although the separation was small.

The crude product 273a&b was purified by column chromatography on alumina eluted with dichloromethane-light petroleum. This resulted in the separation of the two diastereomers 273a&b. In both the 1H and the 13C NMR spectra of the less polar diastereomer, there was no sign of any other diastereomer. The more polar diastereomer was obtained contaminated with the other diastereomer.
Section 2.6.5 Stereochemistry of the cycloadditions.

As for the related nitrosoformamide dienophile 248 generated from hydroxyurea 249, C-nitrosoformate dienophile 271 showed no stereoselectivity in the cycloadditions with cyclopentadiene and cyclohexadiene, since both cycloadducts were formed in equal amounts. Even generating and trapping the dienophile at -78°C led to both diastereomers of both cycloadducts being formed in equal amounts. Again, this is not too surprising since if the activation energies are the same, the relative rates will be independent of temperature.

To confirm the lack of diastereoselectivity, the two sets of diastereomers 272a&b and 273a&b formed by trapping dienophile 271 with cyclopentadiene and cyclohexadiene were separated by chromatography on alumina eluted with dichloromethane.
Section 2.7 C-nitrosoformamide derivatives of bornylamines.
Section 2.7.1 C-nitrosoformamide derivatives of bornylamines.

Many chiral auxiliaries in the literature are based on camphor 274 and so we decided to prepare C-nitrosoformamides 278 and 281, derived from iso-bornylamine 276 and bornylamine 279. If the cycloadditions of these dienophiles with cyclopentadiene and cyclohexadiene resulted in substantial asymmetric induction, then a comparison with the C-nitrosoformates derived from exo-borneol and endo-borneol could be made. The cycloadditions of the dienophiles derived from both the exo and endo hydroxyureas 277 and 282 were investigated.

Section 2.7.2 Synthesis and cycloadditions of dienophile 281.

A sample of the endo-bornylamine 279 was converted into the endo-hydroxyurea 280, in 45% yield, by treatment with phosgene and then aqueous hydroxylamine as previously. The endo-acylnitroso dienophile 281 was formed in the usual manner by oxidation of the hydroxyurea 280 with tetraethylammonium periodate at both 0°C and -78°C. The dienophile 281 was trapped in situ with cyclohexadiene and the corresponding mixture of cycloadducts 282a&b was obtained in moderate yield. At both reaction temperatures, the $^{13}$C NMR spectra showed that the signals due to each diastereomer were of equal intensity and so the cycloadduct 282a&b were formed as a 1:1 mixtures of diastereomers within experimental error, i.e. with no diastereomeric induction at all.

Section 2.7.3 Synthesis and cycloadditions of dienophile 278.

(±)-exo-bornylamine 276 was synthesised from racemic camphor oxime 275, which was formed in good yield by treating camphor with hydroxylamine in aqueous ethanol 59. Attempts were made to hydrogenate the oxime 275 to give the exo-bornylamine 276. Morris et al 60 carried out the reaction in the presence of 1 equivalent of concentrated hydrochloric acid, so that as the amine was converted to the hydrochloride salt as it formed to prevent poisoning of the catalyst. Catalytic hydrogenation with platinum oxide in ethanol at room temperature and atmospheric pressure in the presence of 1 equivalent of hydrochloric acid, following the method of Morris et al 60, did not give the desired bornylamine 276. Catalytic hydrogenation at higher pressures and temperatures in the presence of acetic acid was tried, but did not give the desired product 276; instead starting material was recovered. Unfortunately, since the bomb was made from stainless steel,
concentrated hydrochloric acid could not be used. The exo-bornylamine 276 was formed by treating the oxime with sodium borohydride in the presence of an excess of nickel chloride, following the method of Ipaktschi.\(^41\) This gave the desired exo-bornylamine 276, in moderate yield after purification, which separated the bornylamine from the nickel metal formed in the reaction. The hydroxyurea 277 was then formed, in moderate yield, in the usual manner with phosgene and aqueous hydroxylamine.

**Section 2.7.4 Cycloadditions of the dienophile 278.**

The acylnitroso derivative 278 was formed in the usual manner by oxidation of the hydroxyurea 277 at both 0°C and -78°C with tetraethylammonium periodate. The dienophile 278 was trapped *in situ* with cyclopentadiene and cyclohexadiene and the corresponding mixtures of cycloadducts 283a&b and 284a&b were obtained in moderate yield. As before in the case of the endo-dienophile 281, at both temperatures, the \(^{13}\)C NMR spectrum showed that the cycloadducts were formed as a 1:1 mixture of diastereomers, *i.e.* with no stereoselection.

Since both the *exo* and *endo* nitrosoformamide dienophiles gave no stereoselection, the corresponding C-nitrosoformate dienophiles were not made. This low stereoselection could be due to the flexibility of the hydroxyurea, as described earlier (Section 1.3). The camphor based chiral auxiliary 161 used by Ghosez\(^{29}\) is a more rigid structure, with the sulphonyl holding the hydroxyurea firmly in position. The camphor based dienophile 169 of Miller\(^{30}\) has a larger shielding group, a \(t\)-butyl ether, which is also closer to the acylnitroso group than the methyl of the bornylamines.
Scheme 2.8 8-phenylmenthyl-C-nitrosoformate.

![Chemical Reaction Diagram]

Scheme 57.
Section 2.8 8-phenylmenthyl-C-nitrosoformate.

Scheme 58.

Section 2.8.1 Introduction.

In Section 2.3, the acylnitroso dienophile 238 derived from trans-2-phenylcyclohexanol 236 was described. Moderate diastereoselectivities in the reactions of this dienophile with cyclopentadiene and cyclohexadiene were observed. To investigate whether a larger group on the cyclohexane ring than a phenyl group would improve the stereoselectivity, we decided to employ the chiral auxiliary 8-phenylmenthol 288. This compound was originally synthesised by Corey and Ensley\textsuperscript{62} and to make it, we followed the procedure of Ort\textsuperscript{63}. This employs the route briefly described by Corey but gives full details of the separation of 8-phenylmenthol 288 from the minor diastereomer 289. This is achieved by fractionally crystallising the chloroacetate derivative 290 from the crude mixture of chloroacetate diastereomers. The major chloroacetate was then hydrolysed to give enantiomerically and diastereomerically pure 8-phenylmenthol 288. The corresponding acrylate 295 of dieneophile 292, \textit{i.e.} -N=O replaced with -C=C, gives an e.e. 90\% in forming the Diels-Alder cyclopentadiene cycloadduct 296 and e.e. 90\% in the formation of butadiene cycloadduct 297, in the presence of Lewis acids (Scheme 58)\textsuperscript{64,65}.

Section 2.8.2. Synthesis of hydroxycarbamate 291.

The starting material for the synthesis of the 8-phenylmenthol was (\textit{R})-pulegone 285 which was bought from Aldrich as the 80\% technical grade. This was added slowly to a stirred solution of 10\% copper (I) iodide and phenylmagnesium bromide, in THF at -20°\textdegree C. The solution was stirred and allowed to warm to room temperature overnight. After
work-up, the crude phenylmenthone which was formed as a 1:1 mixture of diastereomers 286 and 287 was refluxed in ethanolic potassium hydroxide for 3 hours. The base removed the acidic proton α to the carbonyl group forming the more substituted enolate which on reprotonation formed the thermodynamically more stable trans-8-phenylmenthone 286. This equilibration converted most of the kinetically formed cis-product 287 into the desired trans-product 286. However, after equilibration there was still 13% of the cis-phenylmenthone 287 present in the equilibrium mixture, which is the theoretical amount. After purification, which removed the Grignard-coupling by-product biphenyl, phenylmenthone was obtained in 70% yield as a mixture of diastereomers 286&287. No attempt was made to separate the diastereomers and the mixture was dissolved in propanol and added to a stirred dispersion of sodium in refluxing toluene. After work-up and distillation the 8-phenylmenthol was obtained as a 87:13 mixture of the two epimers 288 and 289 in 70% yield. A chilled solution of the two diastereomers of 8-phenylmenthol in dichloromethane was treated with chloroacetyl chloride in the presence of N,N'-dimethylaniline. After heating to reflux and work-up, the chloroacetate derivatives of both epimers were obtained in good yield as a white crystalline solid. Two fractional recrystallisations from ethanol gave the diastereomerically pure major chloroacetate 290 in 43% yield overall. This was hydrolysed in ethanolic potassium hydroxide to give the diastereomerically pure 8-phenylmenthol 288.

8-Phenylmenthol 288 was added to phosgene in toluene in the presence of triethylamine at 0°C to form the chloroformate which was then treated with aqueous hydroxylamine solution. After work-up, and chromatography, hydroxycarbamate 291 was obtained in 69% yield as a thick gum. The 1H and 13C spectra of the hydroxycarbamate showed that only one product was formed, with no sign of the other diastereomer.

Section 2.8.3 Cycloadditions of 8-phenylmenthyl-C-nitrosoformate 292.

Attempts to generate acylnitroso derivative 292 from hydroxycarbamate 291 by oxidation with periodate in dichloromethane and ethanol at 0°C and -78°C, in the presence of cyclopentadiene and cyclohexadiene, led to very little of the desired cycloadducts being formed. Instead the major product isolated was 8-phenylmenthol 291 which was identified by TLC and also by the appearance of a peak at δ 3.52 (CHOH) in the 1H NMR spectra and peaks at δ 72.9 (CHOH) and δ 54.08 (CMe2Ph) in the carbon spectra. These peaks are
identical to those in 8-phenylmenthol. The phenylmenthol was probably formed by decomposition of the C-nitrosoformate dienophile.

The acylnitroso compound 292 was formed by oxidising hydroxycarbamate 291 with DMSO and oxalyl chloride, the Swern oxidation conditions, at -78°C and was trapped in situ with both cyclopentadiene and cyclohexadiene, as before, to give the cycloadducts 293a&b and 294a&b respectively in 59% and 64% yields after chromatography.

Section 2.8.4 Cyclopentadiene adduct 293a&b.

The crude cycloadduct mixtures were analysed as before using NMR spectroscopy and it was found that both the cyclopentadiene 293a&b and cyclohexadiene 294a&b adducts were formed as a mixture of diastereomers (Table 20).

From the NMR spectra of cyclopentadiene adducts 293a&b it was found that the ratio of diastereomers formed in the reaction was 7.1:1. The 1H NMR spectrum, showed a d.r. of 8.6:1, which was measured from the signals observed for the olefinic protons and the bridgehead protons. The 13C NMR spectrum showed that the ratio was 5.6:1 and since this was calculated using more measurements, this is probably more accurate (but see earlier caveat). The two diastereomers were separated by chromatography on silica gel. The less polar fraction contained the minor diastereomer 293b as a 1:1 mixture with the major diastereomer. The more polar major diastereomer 293a was obtained as a single diastereomer. This product was shown to be the major diastereomer by comparing the chemical shifts with those of the crude mixture. The major diastereomer 293a was initially obtained as a thick gum which solidified when kept in air.

Section 2.8.5 Cyclohexadiene adduct 294a&b.

The crude product from cyclohexadiene was shown to be a mixture of diastereomers 294a&b (d.r. 6.1:1) from the 13C NMR spectrum, although the signals were not as well separated as those of the cyclopentadiene adducts. In the 1H NMR spectrum, the two diastereomers gave coincidental signals and the only sign of the minor diastereomer was a slight shoulder on the olefinic signal. Chromatography on silica gel gave only one fraction and this was shown to be a mixture of diastereomers 294a&b (d.r. 6.1:1), i.e. no enrichment, from the 13C spectrum. Only some of the signals of the minor diastereomer 294b were visible. In the 1H spectrum of the purified material, only the shoulder of the
minor diastereomer on the olefinic signal could be seen. When the purified material was recrystallised from hexane to give a sample of the major diastereomer 294a, the shoulders in the $^1$H spectra disappeared as did the signals in the $^{13}$C NMR spectrum due to 294b. An X-ray structure of 294a was obtained and this is discussed in Section 2.9.

Table 20. Cycloadducts of dienophile 292* trapped with cyclopentadiene and cyclohexadiene.

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>Diene</th>
<th>$^1$H ratio</th>
<th>$^{13}$C ratio</th>
<th>Average</th>
<th>de %</th>
<th>Yield %, crude (pure)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="293" alt="Image" /></td>
<td>C$_5$H$_6$</td>
<td>8.62</td>
<td>5.6</td>
<td>7.11</td>
<td>75</td>
<td>91(82)</td>
</tr>
<tr>
<td><img src="294" alt="Image" /></td>
<td>C$_6$H$_8$</td>
<td>-</td>
<td>6.15</td>
<td>6.15</td>
<td>72</td>
<td>88(59)</td>
</tr>
</tbody>
</table>

* formed from 291 oxidation with (COCl)$_2$ and DMSO at -78°C, in CH$_2$Cl$_2$.

It is to be noted that the d.e. of these two cycloadditions are not as good as those of the acrylate 295.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

![Reaction Scheme]

Scheme 59.
Section 2.9 Discussion of diastereoselectivities in acyl nitroso cycloadditions.

Scheme 60.
Section 2.9 Stereocontrol using chiral auxiliaries.

Section 2.9.1 Stereochemistry of published cycloadditions.

Kirby and Nazeer\textsuperscript{32} (Scheme 59), Defoin \textit{et al}\textsuperscript{33} (Scheme 60) and Procter \textit{et al}\textsuperscript{34}(Scheme 60) have all investigated the cycloadditions of acylnitroso derivatives 123a\&b derived from (R)- and (S)-mandelic acid, respectively.

To determine the absolute stereochemistry of the cycloaddition, Kirby and Nazeer acetylated and purified the major cyclohexadiene cycloadduct 124a of (S)-dienophile 123a (Scheme 59). This was then cleaved with methoxide to give chiral oxazine 119 of known absolute configuration\textsuperscript{19} 1R,4S.

The absolute configuration of the oxazine moiety of the major cycloadduct, \textit{i.e.} 1R,4S, is that expected if:-

i) the dienophile reacts mainly in the hydrogen bonded form 128a,

ii) the cycloaddition is mainly \textit{endo} and

iii) the diene adds selectively to the face of the nitroso group \textit{anti} to the phenyl group.

The authors argue that the alternatively hydrogen bonded forms 128b\&c would be less stable than 128a since:

i) 6-membered, H-bonded rings are generally favoured over 5-membered rings

ii) 128b which would give the observed result, has unfavourable dipole-dipole repulsions, expected for the \textit{syn} NO and CO groups which disfavour this conformation and

iii) in conformer 128c, steric repulsion between the NO and CO groups raise the energy and so disfavour this conformer. In summary, the most likely conformation 128a gives the expected stereochemistry.

Procter \textit{et al} have carried out independent studies\textsuperscript{34} (Scheme 60), using the mandeloyl nitroso dienophiles 123a\&b derived from (R)-mandelic acid. They confirmed the absolute stereochemistry of the major cyclohexadiene adduct 129a (Scheme 60) by hydrolysing it with hydrochloric acid to give chiral oxazine 118 with absolute stereochemistry 1S,4R. Further they showed by X-ray crystallography that the major cyclopentadiene adduct 131a
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

either

\[ \text{A} \quad -5.45 \text{ KJ/MOL} \]

or

\[ \text{B} \quad -2.54 \text{ KJ/MOL} \]

\[ \text{C} \quad -1.75 \text{ KJ/MOL} \]

Scheme 61.
also had the $IS,4R$ stereochemistry. These observations are consistent with the mode of addition $128a$ proposed by Kirby and Nazeer$^{22}$, allowing for the fact that a $(R)$-mandeloyl dienophile was used by Procter et al.

Using the $(R)$-dienophile $123a$, the group of Defoin have also independently investigated the stereoselectivity of the cycloadditions of $123a$ with cyclohexadiene. The absolute stereochemistry of cycloaddition, was determined by synthesising the methylated minor cycloadducts $130b$ from $(+)-IR,4S$-oxazine $119$ [$\alpha_0 = +24.0^\circ$] and mandeloyl chloride (Scheme 60). This shows that the major diastereomer $129a$ has the opposite $IS,4R$ absolute configuration in the oxazine moiety. Thus these results agree with those reported earlier by Kirby and Nazeer$^{22}$ and by Procter et al.$^{24}$.

There has been some debate over the actual conformation of the transition state and in particular whether the H-bonding involves a 6 membered ring with the nitroso group anti to the carbonyl group $128a$ as postulated by both Kirby and Nazeer and also by Procter and Procter or if a 5 membered ring with the nitroso and carbonyl groups syn to each other is formed $(R)$-$128b$ as suggested by Defoin et al.

In all cases, the $\alpha$-hydroxy dienophile $123a$ produced a larger diastereomeric induction than the $\alpha$-methoxy dienophile $123b$, thus implying that there is a hydrogen bonding effect in the transition state, although the larger size of the methoxy group compared with the hydroxyl group could also cause this effect.

Procter et al have carried out molecular modelling on the acynitroso dienophile $123a^{66}$ (Scheme 61). These calculations predict not only that the conformation with the nitroso anti to the carbonyl group is more stable than the corresponding syn conformation by 11.7 kJ/mol but also that two of the three lowest energy conformations possess hydrogen bonding between the OH and nitroso groups. These two anti-carbonyl-nitroso 6-membered hydrogen bonded conformations would both produce the major cycloadduct $129a$, assuming that the diene approaches in an endo manner from the less hindered side of the nitroso group. Whilst the third most stable conformation having the hydrogen bond between the carbonyl group and the OH in a 5-membered ring, would produce the opposite cycloadduct $130a$, i.e. the minor cycloadduct, assuming that the diene again approaches in an endo manner from the less hindered side.
Section 2.9 Discussion of diastereoselectivities in acyl nitroso cycloadditions.

\[
\begin{align*}
133a & : \text{CH}_2\text{OH}^- \quad 133b & : \text{CH}_2\text{OMe}^- \\
133c & : \text{CHNHPh}^- \\
133d & : \text{CO}_2\text{Me}^- \\
133e & : \text{CO}_2\text{But}^- \\
\end{align*}
\]

\[
\begin{array}{c}
\text{d.e. \%} \\
52 \\
\text{\%} \\
89 \\
68 \\
64 \\
54 \\
20 \\
83 \\
79 \\
86 \\
81 \\
\end{array}
\]

\[
\begin{align*}
& \xrightarrow{\text{COC}_2\text{NE}_3} \\
\text{133} & \rightarrow \text{138} \\
\text{119} & \quad + \\
\end{align*}
\]

\[
\begin{align*}
\text{syn} & : 133 \\
\text{anti} & : 133 \\
140a & : \\
140b & : \\
139 & : \\
\end{align*}
\]

Scheme 62.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 63.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Defoin has postulated the 5-membered ring hydrogen bonded transition state (R)-128b in which the nitroso group is syn to the carbonyl group. Again endo cycloaddition as shown would produce the observed stereochemistry.

Defoin et al\textsuperscript{32} have investigated a series of chiral auxiliaries based on (S)-proline (Scheme 62). Defoin et al attribute the lower diastereomeric excesses, in comparison to the pyrrolidine dienophiles 156, 146 & 150 discussed below, to a lack of "stiffness" in the acylnitroso derivative. In the dienophile 133e σ-bond rotation about the C2-C=O bond leads to a number of possible reacting conformations some of which may result in low or even opposite stereoselectivities. In the dienophiles 133a-d the higher diastereomeric excesses observed may result from slower rotation about the N-C=O bond leading to fewer conformations of these dienophiles in comparison to the dienophile 133e.

To determine the absolute stereochemistry of the cycloaddition, each of the major diastereomers 138a–e was synthesised from the known IR,4S-oxazine 119, proving that the major adducts 138a–e must have this absolute configuration in the oxazine moiety. Assuming that the attack of the diene occurred via an endo transition state then to give the observed major diastereomer the dienophile 133a–e must react in a syn conformation and not in the anti conformation (Scheme 62). Usually the more stable conformation is with the polar groups in a anti arrangement, however, in this particular example, steric interactions between the nitroso and R groups raise the energy of this conformation so favouring the syn conformation.

The groups of Ghosez and Defoin have both investigated the reactions of acylnitroso dienophiles based on chiral auxiliaries with C\textsubscript{2} symmetry based on chiral pyrrolidines.

Defoin et al\textsuperscript{37} have used the chiral dienophiles 146 and 150 in hetero Diels-Alder reactions with cyclohexadiene (Scheme 63). Since the two dienophiles are of opposite chirality and helicity they were expected to give opposing diastereoselectivities.

The absolute stereochemistry of the cyclohexadiene adducts 147 and 151a was determined by independently synthesising them from (IR,4S)-chiral oxazine 119 (Scheme 63). Treatment of tricyclic pyrrolidine 153 with chlorocarbamate 154 gave minor cycloadduct 151b, which was not actually produced in the cycloaddition; hence the only cycloadduct formed in the cycloaddition 151 had the IS,4R absolute stereochemistry in the
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 64.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 65.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

oxazine moiety. Similar treatment of dimethyl pyrrolidine 152 gave the major cycloadduct 147, i.e. 1R,4S absolute stereochemistry in the oxazine moiety.

Assuming that the diene approaches dienophiles 146&150 in an endo manner then the rationalisation for this stereocontrol is that in the transition state (Scheme 63) the dienophile adopts a syn conformation and that the diene approaches from the top face to give the observed stereochemistry. Since tricyclic pyrrolidine 150 has opposite helicity, the opposite sense of diastereomeric induction is observed in cycloadduct 151.

Ghosez and Gouverneur23 have investigated the cycloadditions of the C2 symmetric dienophile 156 with cyclohexadiene, cycloheptadiene and cyclopentadiene (Scheme 64).

The absolute stereochemistry of the oxazine moiety of the major diastereomer of cyclohexadiene adduct 158 was determined from the X-ray structure of the reduced amido alcohol 160 to be 1S,4R. This stereochemistry was explained by postulating that in the transition state (Scheme 64) the acylnitroso group adopts the cis/syn conformation rather than a trans/anti conformation. Approach of the diene from the top, less hindered face in an endo manner results in the observed stereochemistry.

Ghosez et al29 have also reported the cycloadditions of a dienophile 164 based on D-bornane-10,2-sultam 161 (Scheme 65). Both the cyclohexadiene adduct 166 and the cyclopentadiene adduct 165 were formed as single diastereomers, d.e. >98% in both cases. The cyclohexadiene adduct had the 1R,4S absolute configuration in the oxazine moiety, determined by independent synthesis of 166 from the known 1R,4S-oxazine 119, via chlorocarbamate 154.

Conformational analysis showed that of the two syn conformers 164a and 164b are respectively 19.7 and 34.5 kcal/mol more stable than the syn-anti and the anti-anti conformers. In the preferred transition state 164a, the diene approaches in an endo manner giving the observed stereochemistry, even although this transition state is 1.3 kCal/mol higher in energy than the alternative exo approach 164b which does not give the observed stereochemistry. However, the exo transition state 164b is disfavoured by steric interactions between the diene and the SO2.

Martin et al20 have investigated the Diels-Alder reactions of nitrosoformate 169 which gave excellent diastereoselectivities with a range of cyclohexadienes (Scheme 66).
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 66.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 67.
Section 2.9 Discussion of diastereoselectivities in acyl nitroso cycloadditions.

![Chemical structures and reactions](image)

Scheme 68.

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>R</th>
<th>P</th>
<th>Yield %</th>
<th>d.r. 183: 184</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (L)-valine</td>
<td>^Pr</td>
<td>Cbz</td>
<td>85</td>
<td>1: 4</td>
</tr>
<tr>
<td>b (L)-alanine</td>
<td>Me</td>
<td>Cbz</td>
<td>90</td>
<td>1: 3</td>
</tr>
<tr>
<td>f (L)-alanine</td>
<td>Me</td>
<td>Boc</td>
<td>78</td>
<td>1: 3</td>
</tr>
<tr>
<td>c (D)-alanine</td>
<td>Me</td>
<td>Cbz</td>
<td>78</td>
<td>3: 1</td>
</tr>
<tr>
<td>d (L)-phenylalanine</td>
<td>CH₂Ph</td>
<td>Cbz</td>
<td>79</td>
<td>1: 2</td>
</tr>
<tr>
<td>e (L, D)-phenylalanine</td>
<td>CH₂Ph</td>
<td>Cbz</td>
<td>75</td>
<td>-</td>
</tr>
</tbody>
</table>
To determine the absolute configuration, the major cyclohexadiene adduct 170a, was hydrolysed with base to give the known chiral 1R,4S-oxazine 119 [$\alpha_D = +24.4^\circ$].

Although the authors gave no explanation for the stereochemical outcome (Scheme 66), the stereochemistry of the major cycloadduct suggests that the diene reacts with the dienophile in an endo manner (via syn conformer 169a) approaching the nitroso group from the less hindered rear face. A similar endo approach of the diene to anti conformer 169b would not give the observed stereochemistry.

Orena et al.\(^3\) have investigated the cycloadditions of chiral dienophile 178 (Scheme 67).

The absolute stereochemistry of the major cyclohexadiene adduct 179a was determined by cleavage of the chiral auxiliary with lithium hydroxide and hydrogen peroxide. Acidification with hydrochloric acid gave the known 1S, 4R-oxazine 118, [$\alpha_D = -24.7^\circ$, c=1, CHCl\(_3\)].

Molecular modelling predicted that the most stable conformer of the dienophile would have the two carbonyl groups anti to one another. Rotation of the nitroso group revealed that the optimum conformation was anti, syn conformer 178a, which was more stable than anti, anti conformer 178b by 2.9 kcal/ mol, presumably due to steric crowding in the latter conformer. It was calculated that at -78°C, the relative populations of the two conformers would be 99.8: 0.2 respectively, although the minor conformation could react faster with the diene.

If it is assumed that the diene attacks in an endo manner from the less hindered top face, i.e. anti to the phenyl group then only the anti, syn conformer 178a, will give the observed stereochemistry.

Ritter and Miller\(^{34}\) have investigated the cycloadditions of acylnitroso dienophiles based on amino acids (Scheme 68). These reacted with cyclopentadiene and cyclohexadiene with poor stereoselectivity. The absolute stereochemistry of major cyclopentadiene adduct 183c was determined by X-ray crystallography to be IS, 4R-oxazine moiety.

Assuming that the diene attacks dienophile 182c in an endo manner from the least hindered rear face, i.e. anti to the methyl group, then the dienophile must react in the anti-6-membered hydrogen bonded ring conformation 187 shown, to give the observed stereochemistry of the major diastereomer. The lower diastereoselectivities observed for the
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 69, showing the predicted cycloadducts from the cycloadditions of dienophiles 234, 238 & 292 with cyclopentadiene and cyclohexadiene.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

dienophiles 182a-f, c.f. mandelo-dienophile 123a suggest that either the hydrogen bonding effect in dienophiles 182a-f is not as great as in dienophile 123a or that dienophiles 182a-f are less rigid than dienophile 123a.

Section 2.9.2 Predicted stereochemistry of the cycloadditions in this work.

The stereochemistry of the cycloadditions was predicted as shown in Scheme 69. The racemic dienophiles 234& 238 were drawn with the same absolute stereochemistry as 8-phenylmenthol derived dienophile 292. Since the nitrosoformate and nitrosoformamide dienophiles 238 and 234 were racemic, only the relative stereochemistry could be predicted. The stereochemistry of the major diastereomers obtained by reaction of dienophiles 234, 238 or 292 with either cyclopentadiene or cyclohexadiene was predicted by making three assumptions about the transition state and the conformation of the dienophile. These three assumptions were:-

i) the diene would add to the dienophile in an endo manner

ii) that the diene would attack the dienophile from the less hindered face of the nitroso group and

iii) that the nitrosocarbonyl group of the dienophile would react mainly in the anti conformer rather than the syn conformer, due to dipole-dipole repulsion between the carbonyl and nitroso groups.

Applying each of the three conditions above to the dienophiles modeled on 292 resulted in the same relative configurations for the oxazine moiety i.e. 15, 4R since dienophiles 238 and 292 differ only in the nature of the R-group and dienophile 234 is a nitrosoformamide.

Section 2.9.3 Actual stereochemistry of the cycloadditions.

As stated in Section 2.9.2., the stereochemistry of the major diastereomers was predicted making three assumptions about the transition state and the conformation of the dienophile. The stereochemistry of the major cycloadducts actually obtained were determined using X-ray crystallography (figs 2-4). These structures are shown in schematic form (Schemes 70-72). Note that since dienophiles 234 and 238 were racemic the relative stereochemistry is shown. Dienophile 292 was a single enantiomer, so in this case, the stereochemistry shown is the absolute stereochemistry.
Fig 2. X-ray structures of the major cyclopentadiene adduct 239a and the major cyclohexadiene adduct 240a of nitrosoformate dieneophile 238.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 70, showing the predicted and observed cycloadducts from the cycloadditions between nitrosoformate 238 and cyclohexadiene and also cyclopentadiene.
Fig 3. X-ray structures of the major cyclopentadiene adduct 232a and the major cyclohexadiene adduct 233a of nitrosoformamide dieneophile 234.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Prediction

Observed

297 → 232b, predicted major diastereomer

232a, X-Ray structure

299

234

Prediction

Observed

300 → 233b, predicted major diastereomer

233a, X-Ray structure

301

302

Scheme 71, showing the predicted and observed cycloadducts from the cycloadditions between nitrosoformamide dienophile 234 and cyclohexadiene and cyclopentadiene.
Fig 4. X-ray structure of the major cyclohexadiene adduct 294a of nitrosoformate dieneophile 292.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

Scheme 72, Predicted 294b and observed 294a cycloadducts from the cycloaddition between 8-phenylmenthol derived dienophile 292 and cyclohexadiene.
These results showed, that in the cycloadditions of nitrosoformate dienophile 238 (Scheme 70) with cyclopentadiene and cyclohexadiene to give 239a and 240a respectively, the predicted and observed relative stereochemistry match, *i.e.* the relative stereochemistry is as predicted in Section 2.9.2 *IS, 4R*. For nitrosoformamide 234 (Scheme 71), cycloadducts 232& 233, and nitrosoformate 292 (Scheme 72), cyclohexadiene adduct 294, it can be seen that the predicted and the observed stereochemistry are different, *i.e.* *IR, 4S* is observed.

These results appear not to be due to differences in the conformations adopted by nitrosoformate dienophiles and nitrosoformamide dienophiles, since the 8-phenylmenthol derived dienophile 292 appears *not* to react *via* the predicted *anti* conformation whilst the nitrosoformate dienophile 238 *does* react *via* the expected *anti* conformation. The reason for the differences lies in the transition states of the reaction and implies that the three assumptions made above are not always valid. In all of the cycloadditions in the literature, the diene was assumed to approach the dienophile from the less hindered face of the nitroso group, *i.e.* away from the bulky group, although the degree of preference for this approach depends on the effectiveness of the chiral auxiliary used, giving varied diastereomeric induction. This assumption appears correct and can be regarded as true for this discussion. It is also assumed that the diene approaches the dienophile in an *endo* manner rather than an *exo* manner. Although this may or may not be true, the very large stereoselectivities observed for some of the cycloadditions, suggests that in most cases at least the diene must approach the dienophile exclusively in one orientation.

From the survey of the literature (Table 21), it can be seen that for all of the chiral dienophiles, the diastereoselectivity of the cycloaddition falls as the distance between the nitroso group and the chiral centre(s) increases. An exception to this is for nitrosoformamide dienophile where the N' nitrogen is incorporated into a ring system, *e.g.* pyrrolidines 146, 150 & 156 and the sultam 164 based dienophiles. This eliminates rotation of between the chiral centre and the N' nitrogen and can also influence the conformation of the carbonyl group in relation to the chiral auxiliary and so reduce rotation about the N'-CO bond. This fixing of the carbonyl group will in turn affect the conformation of the nitroso group and so reduce the total number of conformations available to these dienophiles. This gives more stiffness to the dienophile and may help to keep it in a preferred conformation.
Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.

increasing the diastereoselectivity of the reaction. Although a minor energetically disfavoured conformation may react faster than the preferred lowest energy conformation e.g. dienophile 164. This may explain why the dienophiles based on cyclic chiral auxiliaries tend to have the highest diastereoselectivities. The only acyclic dienophile to gave good stereoselectivity is the mandeloylnitroso dienophile 123a. This is believed to be due to hydrogen bonding leading a more rigidly defined reacting conformer 128a. This hydrogen bonding would appear not to be as great in the case of the amino acid based dienophiles 182 since the diastereoselectivity is far lower.

These examples point to the major factor controlling stereoselectivity being the conformation of the dienophile. Assuming that the diene reacts in an endo manner with the diene, this means that nitrosomformate 238 must react mainly via anti conformation 295 or 296 and that the dienophiles 234 and 292 must react mainly via syn conformations, i.e. 299&302 and 303.
Section 2.9 Discussion of diastereoselectivities in acynitroso cycloadditions.

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>Diene</th>
<th>Oxidant/ T°C</th>
<th>syn/anti</th>
<th>d.e. %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
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<td>C₅H₅</td>
<td>A/ -78</td>
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<td>82</td>
<td>71</td>
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<td>A/ -78</td>
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<td></td>
<td>C₆H₄</td>
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<td>anti</td>
<td>75</td>
<td>-</td>
</tr>
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<td>238</td>
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<td>B/ -78</td>
<td>anti</td>
<td>69</td>
<td>102</td>
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<td>B/ -78</td>
<td>anti</td>
<td>75</td>
<td>92</td>
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<tr>
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<td>syn</td>
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<td>59</td>
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<td>88</td>
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<td>A/ -78</td>
<td>syn</td>
<td>&gt;99</td>
<td>90</td>
</tr>
<tr>
<td>164</td>
<td>C₅H₅</td>
<td>A/ -78</td>
<td>syn</td>
<td>&gt;98</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>C₆H₄</td>
<td>A/ -78</td>
<td>syn</td>
<td>&gt;98</td>
<td>94</td>
</tr>
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<td>A/ -78</td>
<td>syn</td>
<td>98</td>
<td>81</td>
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<tr>
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<td>syn</td>
<td>91</td>
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</tr>
<tr>
<td>182c</td>
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<td>A/ -78</td>
<td>syn</td>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 21, Summary of diastereoselectivities and conformations of various dienophiles. Oxidation A, IO₄⁻; B, Swern oxidation.
NMR spectra were recorded with a Bruker WP 200 spectrometer (¹H, 200 MHz, ¹³C, 50 MHz) in CDCl₃ solution unless otherwise stated, calibrated with either internal TMS or with deuterium lock and run by Mr J. Gall or Mr J. McIver. 90 MHz spectra were recorded with a Perkin-Elmer R-32 (¹H, 90 MHz) spectrometer. All J values are in Hz. IR spectra were recorded with either Perkin-Elmer 580 or 257 spectrometers. Mass spectra were obtained by EI at 70 eV with AEI MS 12 and MS 9 spectrometers. TLC was carried out on Merck silica gel GF₂₅₄ plates and visualised using UV light and/or iodine bath. For hydroxamic acids, the plate was sprayed with ethanolic FeCl₃ and heated to give a purple, red colour. Dry column chromatography employed Merck silica HF₂₅₄, the solvent flow being assisted with a water pump. Organic solutions were dried over anhydrous magnesium sulfate and concentrated on a Buchi rotary evaporator. Light petroleum refers to the fraction b.p. 40-60°C. Melting points were recorded on a Kofler and Hoch hotplate microscope. Optical rotations were measured on AA-100 auto-digital polarimeter. X-ray structures were obtained by Ali Ashgar Torabi and Dr K.W. Muir.

**Methyltriphenylphosphine iodide.**

\[
\text{Ph₃P + MeI} \xrightarrow{\text{toluene}} \text{Ph₃PCH₃I}
\]

To a stirred solution of triphenylphosphine (16.91 g, 64.47 mmol) in toluene (50 ml) was added neat methyl iodide (9.14 g, 4.0 ml, 64.47 mmol) with stirring. A white precipitate immediately formed. After being stirred overnight at room temperature, the slurry was filtered and the precipitate was dried under a vacuum to give methyltriphenylphosphonium iodide (23.64 g, 90%) as a white solid, which was used without further purification.

1-Phenylbuta-1,3-diene 218.

\[
\begin{array}{ccc}
\text{Ph} & \xrightarrow{\text{Ph₃PCH₃I, BuLi, THF}} & \text{Ph}
\end{array}
\]

217

A suspension of methyltriphenylphosphonium iodide (23.64 g, 58.51 mmol) in dry THF (70 ml) was stirred in a flame dried three necked flask fitted with reflux condenser, subaseal and magnetic stirrer bar, under a nitrogen atmosphere. Butyllithium (1.5M, 37.9 ml, 56.93 mmol) was added slowly to give a yellow orange solution which was stirred at room temperature for a further hour. After the stirred solution was cooled to 0°C,
temperature for a further hour. After the stirred solution was cooled to 0°C, cinnamaldehyde 217 (7.51 g, 7.1 ml, 56.93 mmol) was added slowly to give a green suspension. This mixture was stirred for 1 hour at 0°C, then heated to reflux for 2 hours and then left stirring overnight at room temperature. The mixture was then filtered and water (200 ml) was added to the filtrate and the layers separated. The aqueous layer was extracted with ether (3 x 100 ml). The organic layers were combined, washed with brine, dried, and concentrated. The residue was taken up in light petroleum (250 ml) and filtered to remove triphenylphosphine oxide. The filtrate was then concentrated to give the crude product, which was then distilled (b.p. 86-88°C, 20 Torr) to give diene 218 as a colourless oil (4.67 g, 67%) (identical to lit., 45).

(Found: M+, 130.0784. C_{10}H_{10} requires M, 130.0782); δ_H 7.21-7.47 (5H, m, Ph), 6.85 (1H, m), 6.56 (2H, m), 5.85 (1H, m) and 5.22 (1H, m); δ_C 137.18 (d), 137.09 (s), 132.85 (d), 129.60 (d), 128.61 (d, 2xCH), 127.64 (d), 126.44 (d, 2xCH) and 117.66 (t); m/z 130 (M+, 70%), 129 (78), 128 (42), 127 (18), 115 (38), 74 (66), 59 (100) and 51 (12).

(+)-Ethyl 2-phenylcyclohex-3-ene 1-carboxylate 219.

In a round bottomed flask fitted with condenser and drying tube, 1-phenylbutadiene 218 (4.67 g, 35.92 mmol) was heated with excess ethyl acrylate (6.94 g, 7.52 ml, 69.48 mmol) and two crystals of 2,6-di-t-butyl-4-methylphenol at 100°C for 24 hours. After the solution was concentrated, the residue was distilled (b.p. 112°C, 0.9 Torr) to give 219 as a mixture of isomers, colourless oil (6.03 g, 73%).

ν_max/ cm⁻¹ (thin film) 3980bm, 3030m and 1730s (C=O); δ_H (unequilibrated) 7.18-7.32 (5H, m, aromatic), 5.70-5.95 (2H, br m, olefinic), 3.88-4.05 (3H, m, CH₂CH₂ &CH₂CO₂Et), 2.93 (0.5H, m, CHPh), 2.60 (0.5H, m, CHPh), 1.81-2.27 (4H, m, cyclohexyl CH₂) and 1.11 (3H, t, J 7.1, CH₃CH₂); δ_C 174.85 (s), 173.36 (s), 143.73 (s), 140.02 (s), 129.39 (d), 129.29 (d), 128.10 (d), 127.83 (d), 127.64 (d), 127.61 (d), 127.28 (d), 127.16 (d), 126.66 (d), 126.32 (d), 125.76 (d), 59.87 (t), 59.65 (t), 48.32 (d), 44.81 (d), 44.07 (d), 42.46 (d), 25.27 (t), 24.31 (t), 24.07 (t), 18.75 (t) and 13.82 (q); m/z
230 (M⁺, 13%), 157 (32), 156 (100), 155 (30), 154 (13), 153 (11), 141 (15), 130 (20), 129 (36), 128 (26), 115 (37), 91 (59), 79 (14), 78 (10), 77 (25), 51 (13), 39 (11), 29 (23), 28 (46) and 27 (14).

(±)-trans-2-Phenyl-1-cyclohex-3-ene-1-carboxylic acid 220.

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Et} \quad \text{i NaOMe/ MeOH} \quad \text{ii KOH/H}_2\text{O} \\
\text{219} & \quad \rightarrow \\
\text{Ph} & \quad \text{CO}_2\text{H} \quad \\
220
\end{align*}
\]

Sodium metal (3.40 g, 147.8 mmol) was dissolved in dry methanol (60 ml) to form a solution of sodium methoxide in which ester 219 (6.03 g, 26.2 mmol) was heated to reflux overnight. Then sodium hydroxide (3.44 g, 86 mmol) in water (20 ml) was added and the mixture was heated to reflux for a further 2 hours. The solution was cooled and extracted with ether (2 x 50 ml). The aqueous layer was then acidified with hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The combined dichloromethane fractions were washed with brine, dried and concentrated to give the acid 220 as light yellow crystals (4.18 g, 79%), m.p. 100-4°C (ethyl acetate and light petroleum) (identical to lit., 45).

(Found: M⁺, 202.0977. C₁₃H₁₄O₂ requires M, 202.0994); \( \nu_{max} / \text{cm}^{-1} (\text{KBr disc}) \) 1705 (C=O); \( \delta_H \) 11.2-11.6 (0.98H, br m, CO₂H), 7.17 (5 H, m, aromatic), 5.78 (1H, m, olefinic), 5.55 (1H, dt, J 2.1 & 10.1, olefinic), 3.66 (1H, dt, J 2.7 & 8.8, CHCO₂H), 2.53 (1H, dt, J 3.2 & 8.8, CHPh) and 1.68-2.14 (4H, m, CH₂ of ring); \( \delta_C \) 181.81 (s, C=O) 143.69 (s), 129.23 (d, Ph), 128.48 (d, 2xCH Ph), 128.11 (d, 2xCH Ph), 126.97 (d, olefinic), 126.72 (d, olefinic), 48.12 (d, CHCO₂H), 43.52 (d, CHPh), 25.13 (t) and 24.04 (t); \( m/z \) 202 (40), 157 (31), 156 (93), 155 (17), 142 (12), 141 (27), 130 (72), 129 (100), 128 (67), 127 (22), 117 (10), 116 (16), 115 (95), 103 (13), 102 (18), 92 (11), 91 (87), 89 (15), 79 (32), 78 (32), 77 (64), 76 (13), 65 (25), 63 (24), 55 (12), 53 (13), 52 (14), 51 (53), 45 (12), 41 (14), 39 (46), 28 (23), 27 (30) and 18 (14).

(±)-2-trans-Phenylcyclohexane-1-carboxylic acid 221.

\[
\begin{align*}
\text{220} & \quad \text{H}_2/\text{PtO} \quad \text{EtOH} \\
\text{221}
\end{align*}
\]
The acid 220 (4.18 g, 20.69 mmol) was dissolved in ethanol (50 ml) in a round bottomed flask with magnetic stirrer and platinum oxide (50 mg) was added. The solution was then hydrogenated at atmospheric pressure and room temperature. After the calculated amount of hydrogen was absorbed, the solution was filtered through Celite and concentrated to give acid 221 (4.22 g, 100%) as white crystals, m.p. 105-107°C (ethyl acetate and light petroleum)(identical to lit., 42).

ν̃max/cm⁻¹ (KBr disc) 3030, 2860, 2940 and 1705 (C=O); δH 10.8-11.4 (1H, br s, CO₂H), 7.12 (5H, m, aromatic), 2.60 (1H, dt, J 3.5 & 11.4, CHCO₂H), 2.46 (1H, dt, J 3.4 & 11.3, CHPh) and 1.19-2.0 (8H, m, CH₂ of cyclohexane); δC 181.36 (s, C=O), 144.41 (s), 128.34 (d, 2xCH), 127.18 (d, 2xCH), 126.38 (d), 49.71 (d, CHCO₂H), 45.90 (d, CHPh), 34.21 (t), 30.25 (t), 26.09 (t) and 25.23 (t); m/z 204 (M⁺, 47%), 186 (22), 158 (57), 144 (18), 129 (38), 117 (82), 115 (56), 104 (45), 91 (100), 77 (36), 65 (24), 55 (23) and 39 (43).

(+)-trans-2-Phenylcyclohexane-1-isocyanate 224.

[Diagram of the synthesis process]

To acid 221 (1.50 g, 7.35 mmol) in a round bottomed flask with magnetic stirrer bar and condenser was added thionyl chloride (6.56 g, 4.0 ml, 55.13 mmol). After the solution was stirred for 30 min at room temperature, the solution was heated to reflux for 1 hour and then concentrated. Toluene (10 ml) was added to the residue and the solution was concentrated. This was repeated twice to remove excess thionyl chloride. This gave the product 222 as white crystals.

Acid chloride 222 was dissolved in acetone-water (1:1) (20 ml). Sodium azide (1.53 g, 23.53 mmol) was added and the solution was stirred for 10 minutes. Acyl azide 223 was extracted with ether (3 x 50 ml), dried and added to toluene (100 ml). The solution was concentrated to approximately 100 ml and then heated to reflux in toluene for 2 hours, the reaction being followed by infrared spectroscopy. When all of the acyl azide 223 was converted to the isocyanate 224, the solution was then concentrated and distilled (b.p. 90°C/ 0.3 Torr, Kugelrohr) to give isocyanate 224 (1.20 g, 81%), as a colourless oil.
\( \nu_{\text{max}} \text{ cm}^{-1} (\text{CHCl}_3) \) 2260s (NCO); \( \delta_1 \) 7.12-7.30 (5H, m, Ph), 3.41 (1H, dt, \( J \) 4.0 & 10.7, \text{CHNCO}), 2.40 (1H, dt, \( J \) 3.5 & 11.1, CHPh) and 1.11-2.07 (8H, m, cyclohexane); \( \delta_C \) 143.20 (s), 128.66 (d, 2xCH Ph), 127.47 (d, 2xCH Ph), 127.03 (d, CH Ph), 58.81 (d, \text{CHNCO}), 52.62 (d, CHPh), 35.52 (t), 33.81 (t), 25.72 (t) and 25.07 (t).

\((\pm)-\text{trans-2-Phenylcyclohexane-1-N,N'-hydroxyurea 225.}\)

Isocyanate 224 (1.20 g, 5.88 mmol) was dissolved in dichloromethane (20 ml) and added slowly to an ice cold solution of hydroxylamine hydrochloride (1.23 g, 17.65 mmol) and sodium carbonate (1.87 g, 17.65 mmol) in water (20 ml). The mixture was stirred overnight and the two layers separated. The organic layer was extracted with 1 M sodium hydroxide and the aqueous layers combined, acidified and extracted with dichloromethane (3 x 50 ml). The organic layers were then combined, dried and concentrated to give hydroxyurea 225 (1.01 g, 72%) as a crystalline solid, m.p. 128-130°C (ethyl acetate and light petroleum).

(Found: C, 66.57; H, 7.81; N, 11.97; \( M^+ \), 234.1353. \( C_{13}H_{14}N_2O_2 \) requires C, 66.66; H, 7.69; N, 11.96; \( M \), 234.1368); \( \nu_{\text{max}} \text{ cm}^{-1} (\text{CHCl}_3) \) 1660m (C=O) and 1550s; \( \delta_1 \) 7.14 (5H, m, Ph), 5.69 (2H, d, \( J \) 8.8, NHCONHOH, \( D_2\)O exchange), 3.77 (1H, br m, CHNHCONHOH), 2.39 (1H, br m, CHPh) and 1.23-2.14 (8H, m, cyclohexane); \( \delta_C \) 161.37 (s, C=O), 143.52 (s), 128.42 (d, 2xCH), 127.51 (d, 2xCH), 126.44 (d), 52.84 (d, CHNHCONHOH), 50.80 (d, CHPh), 34.97 (t), 34.33 (t), 26.06 (t) and 25.38 (t); m/z 204 (M+, 6%), 201 (14), 158 (73), 130 (17), 117 (34), 115 (28), 103 (13), 91 (100), 77 (25) and 56 (19).

\((\pm)-3\text{-[trans-2-Phenylcyclohexylaminocarbonyl]-3-SR-2-oxa-3-azabicyclo[2.2.1]hept-5-ene 232.}\)
General Procedure A at 0°C
In a round bottomed flask with a magnetic stirrer, cyclopentadiene (0.26 g, 0.32 ml, 3.88 mmol) and tetraethylammonium periodate (0.32 g, 0.97 mmol) were dissolved in ethanol-dichloromethane (1:1) (15 ml) and chilled to 0°C. Hydroxyurea 225 (0.17 g, 0.74 mmol) in ethanol-dichloromethane (1:1) (15 ml) was added dropwise over 40 min. The solution was stirred for a further hour, concentrated and then redissolved in dichloromethane (50 ml). The solution was washed with dilute sodium thiosulphate solution and water, dried and concentrated. End of General procedure A. This gave cycloadduct 232a&b (0.24 g, 111%, d.r. 2.9:1). 0.13 g was then chromatographed on alumina eluted with dichloromethane to give the major diastereomer 232a (0.04 g) (Rf 0.41) as a crystalline solid, m.p. 144°C (ethyl acetate and light petroleum) and a mixture of the major and minor diastereomers 232a&b (0.05 g) (Rf 0.50) as white solids.

This experiment was repeated following General Procedure A at -78°C, with hydroxyurea 225 (0.21 g, 0.90 mmol) all other quantities as above. The reaction mixture was stirred for 2 hours at -78°C and then allowed to warm to room temperature. Crude product 232a&b (0.29 g, 109%, d.r. 3.2:1) was chromatographed on alumina eluted with dichloromethane to give the major 232a and minor 232b diastereomers as white solids (0.19 g, 73%).

General Procedure B, Swern Oxidation
In a flame dried round bottomed flask with side arm and magnetic stirrer bar under nitrogen, oxaly chloride (0.75 ml, 1.47 mmol, 2.0 M) in dichloromethane was chilled to -78°C. Dimethyl sulfoxide (0.23 g, 0.20 ml, 2.95 mmol) was then added in dichloromethane (1 ml) and the solution was stirred for 5 minutes. Then hydroxyurea 225 (0.30 g, 1.27 mmol) in dichloromethane (1 ml) was then added and the reaction mixture was stirred for a further 15 min. Then cyclopentadiene (0.14 g, 0.18 ml, 2.18 mmol) in dichloromethane (1 ml) was added. Triethylamine (0.94 ml, 6.70 mmol) in dichloromethane (5 ml) was added via a syringe pump over 1 hour at -78°C. The solution was kept at -78°C for a further 2 hours and allowed to warm to room temperature overnight. It was then dissolved in dichloromethane (25 ml) and washed with saturated brine. The organic layer was dried and concentrated to give cycloadduct 232a&b (0.35g, 92%, d.r. 4.68:1). End of General procedure B.
The crude product was chromatographed on silica eluted with ethyl acetate-light petroleum (4:1) to give the product (0.35 g, 92%) as a mixture of diastereomers 232a&amp;b (R<sub>r</sub> 0.33). (Found: C, 72.20; H, 7.30; N, 9.25. C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> requires C, 72.48; H, 7.38; N, 9.39); ν<sub>max</sub>/cm<sup>-1</sup> (CHCl<sub>3</sub>) 1662s (C=O) and 1512s (C=C); δ<sub>η</sub> (Major cycloadduct) 7.04-7.24 (5H, m, Ph), 5.45 (1H, m, olefin), 5.34 (2H, m, olefin and NH (5.29)), 4.82 (2H, s, bridgehead), 3.79 (1H, ddt, J=3.8, 9.0 & 11.1, CHNHCO), 2.15 (1H, dt, J=3.3 & 11.4, CHPh) and 1.04-2.08 (10H, m, ring protons); δ<sub>c</sub> (Major cycloadduct) 161.71 (s, C=O), 143.81 (s, aromatic), 133.73 (d), 130.28 (d), 128.18 (d, 2xCH), 127.74 (d, 2xCH), 126.23 (d), 83.49 (d), 65.26 (d), 52.18 (d), 51.18 (d), 47.90 (t, CH<sub>2</sub> of adduct), 35.41 (t), 34.20 (t), 26.02 (t) and 25.26 (t); δ<sub>η</sub> (Minor cycloadduct) 7.16 (5H, m, Ph), 6.26 (1H, m, olefin), 6.17 (1H, m, olefin), 5.42 (1H, s, NH), 4.93 (2H, s, bridgehead), 3.78 (1H, m, CHNHCO), 2.30 (1H, m, CHPh) and 1.04-2.20 (10H, m, ring protons); δ<sub>c</sub> (Minor cycloadduct) 161.90 (s, C=O), 143.57 (s, Ph), 134.95 (d), 132.21 (d), 128.39 (d, 2xCH), 127.35 (d, 2xCH), 126.38 (d), 83.37 (d), 65.29 (d), 52.86 (d), 50.51 (d), 47.92 (t, CH<sub>2</sub> of adduct), 35.33 (t), 34.38 (t), 26.07 (t) and 25.32 (t); m/z 219 (1.9%), 201 (31), 158 (12), 130 (44), 117 (47), 104 (39), 91 (100), 77 (32), 44 (48), 56 (33) and 39 (62).

(±)-3-[trans-2-Phenylcyclohexylaminocarbonyl]-(1-SR)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 233.

225

233

Followed General Procedure A at 0°C, using cyclohexadiene (0.35 g, 0.41 ml, 4.35 mmol), tetraethylammonium periodate (0.31 g, 0.96 mmol), hydroxyurea 225 (0.20 g, 0.87 mmol), to give the crude product 233a&amp;b (0.24 g, 92%, d.r. 2.5:1). This was then chromatographed on alumina eluted with dichloromethane-light petroleum (4:1) to give (0.195 g, 72%) total product. Major diastereomer 233a (R<sub>r</sub> 0.48), was separated from minor diastereomer 233b (R<sub>r</sub> 0.42), as a white crystalline solid, m.p. 180°C (ethyl acetate and light petroleum).

This experiment was repeated following General Procedure A at -78°C, hydroxyurea 225 (0.21 g, 0.88 mmol), other weights as above. This gave after workup, the crude product 233a&amp;b (0.20 g, 73%, d.r. 2.4:1).
This experiment was repeated following General Procedure B at -78°C using, oxalyl chloride (0.75 ml, 1.47 mmol, 2.0 M), dimethyl sulfoxide (0.23 g, 0.20 ml, 2.95 mmol), hydroxyurea 225 (0.32 g, 1.35 mmol), cyclohexadiene (0.17 g, 0.20 ml, 2.10 mmol) and triethylamine (0.94 ml, 6.70 mmol) to give the crude product 233a&b (0.29g, 67%). This was chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) to give the major diastereomer 233a (R<sub>t</sub> 0.49) (0.19g, 45%) and a mixture of minor diastereomer 233b (R<sub>t</sub> 0.40) and major diastereomer 233a (R<sub>t</sub> 0.49) (0.07g, 17%).

(Found: C, 73.05; H, 7.47; N, 8.92; M<sup>+</sup>, 312.1843. C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> requires C, 73.08; H, 7.69; N, 8.97; M, 312.1838); v<sub>max</sub> cm<sup>-1</sup> (CHCl<sub>3</sub>) 1662m (C=O) and 1512m (C=C); δ<sub>H</sub> (Major adduct) 7.05-7.24 (5H, m, aromatic), 5.81 (1H, dt, J 1.4 & 6.6, 1 olefinic proton), 5.55 (2H, m, NH (5.47 ppm) and 1 olefinic proton), 4.58 (1H, m, bridgehead), 4.26 (1H, m, bridgehead), 3.78 (1H, ddt, J 3.8, 8.3 & 11.4, (CH/Ph)), 2.25 (1H, dt, J 3.3 & 11.4, CH/Ph) and 0.97-2.32 (12H, m, ring protons and adduct methines); δ<sub>C</sub> (Major adduct) 161.96 (s, C=O), 143.82 (s), 131.03 (d), 129.14 (d), 128.22 (d), 127.67 (d), 126.16 (d), 70.09 (d), 52.50 (d), 51.13 (d), 50.39 (d), 35.23 (t), 34.15 (t), 26.11 (t), 25.25 (t), 23.89 (t) and 19.56 (t); δ<sub>H</sub> (Minor adduct) 7.14 (5H, m, aromatic), 6.42 (2H, m, olefin), 5.60 (1H, br s, NHCO), 4.74 (1H, m, bridgehead), 4.51 (1H, m, bridgehead), 3.87 (1H, m, CH/Ph) and 1.04-2.49 (13H, m, cyclohexane and adduct methines); δ<sub>C</sub> (Minor adduct) 161.90 (s), 143.80 (s), 131.01 (d), 130.43 (d), 128.37 (d), 127.35 (d), 126.30 (d), 70.07 (d), 50.53 (d), 52.49 (d), 35.64 (t), 34.54 (t), 26.10 (t), 25.37 (t), 23.43 (t) and 19.67 (t); m/z 312 (M<sup>+</sup>, 9%), 201 (16), 158 (12), 117 (18), 11 (72), 104 (10), 91 (78) and 79 (100).

(±)-2-[trans-2-Phenylcyclohexylaminocarbonyl]-(1-SR)-1-oxa-2-aza-4, 5-dimethylcyclohex-4-ene 306.

Following General Procedure A at 0°C, using 2, 3-dimethylbutadiene (0.36 g, 0.50 ml, 4.43 mmol), tetraethylammonium periodate (0.43 g, 1.34 mmol) and hydroxy urea 225 (0.21 g, 0.89 mmol), gave the crude product (0.28 g, 99%). This was chromatographed on silica
eluted with light petroleum-ethyl acetate (85:15) to give cycloadduct 306 (Rf 0.25) (0.13 g, 46%).

$\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl$_3$): 1662 m (C=O) and 1512 m (C=C); $\delta_{\text{H}}$ 7.03-7.25 (5H, m, Ph), 5.37 (1H, d, J 8.3, NHCO), 3.28-4.05 (5H, m, 2xCH$_2$ of oxazine and CHNHCOC), 3.83 (1H, dt, J 3.5 & 9.0, CHNHCOC), 2.35 (1H, dt, J 3.4 & 9.0, CPh), 1.14-2.44 (12H, m, cyclohexane and oxazine methines), 1.32 (3H, s, CH$_3$) and 1.49 (3H, s, CH$_2$); $\delta_{C}$ 157.71 (s, C=O), 143.84 (s, Ph), 128.40 (d, 2xCH$_2$Ph), 127.50 (d, 2xCH$_3$ Ph), 126.34 (d, Ph), 122.19 (s, 2 olefins), 70.35 (t, CH$_2$ of oxazine), 52.91 (d, CHNHCOC), 50.95 (d, CPh), 47.23 (t, CH$_2$ of oxazine), 35.28 (t), 34.55 (t), 26.17 (t), 25.35 (t), 15.22 (q, CH$_3$ of oxazine) and 13.58 (q, CH$_3$ of oxazine).

$(\pm)$-trans-2-Phenylcyclohexan-1-ol 236.

Magnesium turnings (1.85 g, 77.08 mmol) were placed in a flame dried three necked flask fitted with septa, magnetic stirrer bar and condenser under an atmosphere of nitrogen. Bromobenzene (1.0 ml) in THF (20 ml) was added and when the reaction had started, the remainder of the bromobenzene (10.09 g, 6.76 ml, 64.24 mmol) in THF (100 ml) was added at such a rate as to maintain a controlled reflux. The solution was left stirring for 1 hour at room temperature. After being cooled to -30°C, cuprous iodide (1.22 g, 6.42 mmol) was added and the mixture was stirred for 5 minutes. Then cyclohexene oxide 235 (6.30 g, 6.5 ml, 64.24 mmol) was added, the solution was allowed to warm to 0°C and stirred for a further 2 hours at 0°C. Then dilute hydrochloric acid (40 ml) was added followed by ethyl acetate (50 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The organic layers were combined, dried and concentrated to give cyclohexanol 236 which was distilled (b.p. 150°C/1 Torr, Kugelrohr) to give cyclohexanol 236 as a white solid (11.14 g, 98%), m.p. 52-54°C (light petroleum)(identical to lit., 30).

$\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl$_3$): 3063, 3018, 2936, 2860s, 2401 m and 1603 m; $\delta_{\text{H}}$ 7.18-7.42 (5H, m, Ph), 3.63 (1H, dt, J 4.3 & 9.9, CH/OH), 2.42 (1H, dt, J 2.9 & 10.8, CPh) and 1.29-2.12 (9H, m, cyclohexane and OH); $\delta_{C}$ 143.35 (s), 128.68 (d, 2xCH$_2$), 127.90 (d, 2xCH$_3$), 126.74 (d), 74.32 (d, CH/OH), 53.15 (d, CPh), 34.41 (t), 33.31 (t), 26.03 (t) and 25.04 (t); m/z 176 (M$, 36\%$, 158 (10), 143 (11), 130 (45), 117 (33), 104 (42), 98 (19), 91 (100), 77 (25), 65 (19) and 57 (16).
Section 3 Experimental

(±)-trans-2-Phenylcyclohexane-1-(N'-hydroxycarbamate) 237.

A solution of cyclohexanol 236 (2.07 g, 11.76 mmol) and triethylamine (1.30 g, 1.81 ml, 12.94 mmol) in toluene (5 ml) was added dropwise to a solution of phosgene in toluene (12.5%, 6.40 g, 6.74 ml, 12.94 mmol) and stirred for 4 hours until there was no sign of cyclohexanol 236 by TLC. Then hydroxylamine hydrochloride (1.23 g, 17.64 mmol) and sodium carbonate (1.87 g, 17.64 mmol) and water (0.2 ml) were added and the solution stirred overnight. The solution was filtered and concentrated to give the crude 237 which was then chromatographed on silica eluted with ethyl acetate-light petroleum (3:1) to give hydroxycarbamate 237 (R_f 0.21, red with ethanolic ferric chloride spray) as a white solid (1.36, 49%), m.p. 96-98°C (ethyl acetate and light petroleum).

(Found: M^-H_2O, 217.1109. C_{13}H_{17}NO_2 requires M^-H_2O, 217.1103; vmax cm^-1 (CHCl_3) 1737s (C=O); δ_H 7.16 (5H, m, Ph), 6.86 (2H, br s, NHOH), 4.88 (1H, dt, J 4.5 & 10.4, CHOCO), 2.64 (1H, dt, J 3.4 & 11.3 CHPh) and 0.84-2.18 (8H, m, cyclohexane); δ_C 158.94 (s, C=O), 142.84 (s), 128.39 (d, 2xCH), 127.39 (d, 2xCH), 126.46 (d), 77.96 (d, CHOCO), 49.57 (CHPh), 34.27 (t), 32.36 (t), 25.70 (t) and 24.64 (t); m/z 217 (1.3%), 176 (19), 159 (44), 130 (26), 117 (23), 91 (100) and 81 (18).

(±)-3-[trans-2-Phenylcyclohexyloxy carbonyl]-1-(1-SR)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene 239.

Following General Procedure A at 0°C, using cyclopentadiene (0.24 g, 0.30 ml, 3.62 mmol), tetraethylammonium periodate (0.28 g, 0.87 mmol) and hydroxy carbamate 237 (0.17 g, 0.72 mmol), gave the crude cycloadduct 239a&b (0.36 g, 167%, d.r. 2.6:1). The crude product was then chromatographed on silica eluted with ethyl acetate-light petroleum (20 ml fractions increasing the ethyl acetate concentration by 10% each time) to give minor
diastereomer 239b (R<sub>f</sub> 0.63, ethyl acetate-light petroleum (3:1)) (0.04 g, 17%) and the major diastereomer 239a (R<sub>f</sub> 0.45, ethyl acetate-light petroleum (3:1)) (0.18 g, 81%) as a crystalline solid, m.p. 117-119°C (ethyl acetate and light petroleum). This experiment was repeated following General Procedure A at -78°C, using hydroxycarbamate 237 (0.22 g, 0.93 mmol) with all other quantities as above. This gave after work up the crude product 237 (0.30 g, 106%, d.r. 3.6:1), which was chromatographed on silica to give (0.19 g, 68%) of both 239a&b.

Followed General Procedure B at -78°C, using oxalyl chloride (0.75 ml, 1.47 mmol, 2.0 M), dimethyl sulfoxide (0.23 g, 0.20 ml, 2.95 mmol), hydroxy carbamate 237 (0.30 g, 1.28 mmol), cyclohexadiene (0.16 g, 0.19 ml, 2.03 mmol) and triethylamine (0.65 ml, 6.70 mmol) to give the crude cycloadduct 239a&b (0.39 g, 105%, d.r. 5.4:1). (Found: C, 72.15; H, 7.03; N, 4.62; M<sup>+</sup> -C<sub>4</sub>H<sub>8</sub>O, 217.1114. C<sub>11</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub> requires C, 72.24; H, 7.02; N, 4.68; M<sup>+</sup> -C<sub>4</sub>H<sub>8</sub>O, 217.1103); ν<sub>max</sub>/cm<sup>-1</sup> (CHCl<sub>3</sub>) 1737s (C=O); δ<sub>δ</sub> (Major diastereomer) 7.26 (5H, m, Ph), 6.00 (1H, m, olefin), 5.05 (1H, s, bridgehead), 4.82 (1H, dt, J 4.4 & 10.6, CHOCO), 4.72 (1H, br s, olefin), 4.61 (1H, s, bridgehead), 2.69 (1H, dt, J 3.5 & 11.4, CHPh) and 1.20-2.26 (10H, m, cyclohexane); δ<sub>δ</sub> (Major diastereomer) 159.02 (s, C=O), 143.55 (s, Ph), 133.40 (d, olefin), 131.69 (d, olefin), 128.50 (d, 2xCH), 127.55 (d, 2xCH), 126.52 (d), 83.47 (d, bridgehead), 78.19 (d, CHOCO), 65.43 (d, bridgehead), 49.92 (d, CHPh), 47.68 (t, CH<sub>2</sub> of adduct), 34.25 (t), 32.19 (t), 25.73 (t) and 24.56 (t); δ<sub>δ</sub> (Minor diastereomer) 134.12 (d), 132.54 (d), 128.14 (d), 127.39 (d), 126.26 (d), 77.38 (d), 65.04 (d), 49.75 (d), 34.19 (t), 25.98 (t) and 24.68 (t); m/z 217 (M<sup>+</sup>-82, 0.3%), 176 (2), 159 (32), 117 (11) and 91 (100).

(±)-3-[trans-2-Phenylcyclohexyloxy carbonyl]-(1SR)-2-oxa-3-azabicyclo[2.2.2]oct-5-en e 240.
as a mixture of diastereomers 240a\&b (0.05 g, 51%). Fractional recrystallisation gave the major diastereomer as a white crystalline solid, m.p. 133-134°C (ethyl acetate and light petroleum).

This experiment was repeated, following General Procedure A at -78°C, using hydroxycarbamate 237 (0.20 g, 0.85 mmol) with all other quantities as above, to give the crude cycloadduct 240a\&b (0.37 g, 140%, d.r. 3.5:1), which was chromatographed on alumina eluted with light petroleum-ethyl acetate (4:1) (Rf 0.49) to give the product 240a\&b (0.144 g, 54%).

This experiment was repeated, following General Procedure B at -78°C, using oxalyl chloride (0.75 ml, 1.47 mmol, 2.0 M), dimethyl sulfoxide (0.23 g, 0.20 ml, 2.95 mmol), hydroxy carbamate 237 (0.32 g, 1.35 mmol), cyclohexadiene (0.16 g, 0.19 ml, 2.03 mmol) and triethylamine (0.65 ml, 6.70 mmol) to give the crude product 240a\&b (0.49g, 115%, d.r. 7.2:1) which was chromatographed on silica eluted with light petroleum-ethyl acetate (3:2) (Rf 0.66) to give the product 240a\&b (0.39g, 92%), m.p. 133-134°C (ethyl acetate and light petroleum).

(Found: C, 71.87; H, 7.40; N, 4.25; M+, 313.1698. C<sub>19</sub>H<sub>17</sub>NO<sub>5</sub> requires C, 72.84%; H, 7.35%; N, 4.47; M+, 313.1678); ν<sub>max</sub> cm<sup>-1</sup> (CHCl<sub>3</sub>) 1740s; δ<sub>gg</sub> (Major diastereomer) 7.15-7.34 (5H, m, Ph), 6.20 (1H, m, olefin), 5.33 (1H, br s, olefin), 4.87 (1H, dt, J 4.4 & 10.5, CHOOC), 4.60 (1H, m, bridgehead), 4.32 (1H, d, J 3.9, bridgehead), 2.69 (1H, dt, J 3.4 & 11.4, CHPh) and 1.17-2.26 (12H, m, ring protons); δ, 158.39 (s, C=O), 143.51 (s), 131.05 (d, olefin), & 130.59 (d, olefin), 128.39 (d, 2xCH), 127.52 (d, 2xCH), 126.53 (d), 77.90 (d, CHOOC), 70.46 (d, bridgehead), 50.76 (d, bridgehead), 50.04 (d, CHPh), 34.36 (t), 32.29 (t), 25.77 (t), 24.62 (t), 23.42 (t) and 20.06 (t), m/z 313 (M+, 3%), 159 (40), 117 (11), 91 (100), 81 (18) and 79 (19).

(±)-2-trans-Phenylcyclohexane-1-hydroxamic acid 241.

![Chemical Reaction](image)

To acid 221 (0.95 g, 4.66 mmol) in a round bottomed flask with magnetic stirrer bar and condenser was added thionyl chloride (6.56 g, 4.0 ml, 55.13 mmol). After stirring for 30 min at room temperature, the solution was refluxed for 1 hour and then concentrated. Toluene (10 ml) was added to the residue and the solution was concentrated. This was
repeated twice to remove excess thionyl chloride. This gave the acid chloride 222 as white crystals which were immediately dissolved in dichloromethane (15 ml) and added dropwise to a chilled solution of hydroxylamine hydrochloride (0.93 g, 13.38 mmol) and potassium carbonate (1.90 g, 13.77 mmol) in water (10 ml). After the solution was stirred for 1 hour at 0°C, it was neutralised with dilute hydrochloric acid and the layers separated. The organic layer was dried and concentrated to give hydroxamic acid 241 (0.84 g, 82%), m.p. 141°C (ethyl acetate and light petroleum).

(Found: C, 71.01; H, 7.81; N, 6.35; M', 219.1259. C13H17NO2 requires C, 71.23; H, 7.76; N, 6.39; M, 219.1259); ν_max/cm⁻¹ (KBr disc) 1628 (C=O); δH ((CD)₂SO) 10.24 (1H, s) & 8.55 (1H, s) NHOH, 7.08-7.26 (5H, m, aromatic), 2.75 (1H, br dt, CHCONH), 2.75 (1H, dt, J 3.1 & 12.0, CPh) and 1.30-2.50 (8H, m, cyclohexane); δH 9.05 (1H, br m, NHOH), 6.97-7.13 (5H, m, aromatic), 2.60 (1H, dt, J 3.4 & 11.4, CHCONHOH), 2.39 (1H, dt, J 3.4 & 11.4, CPh) and 1.20-2.24 (8H, m, cyclohexane); δC ((CD)₂SO) 181.30 (s, C=O), 170.85 (s), 145.28 (s), 128.16 (d, 2xCH), 127.40 (d, 2xCH), 125.98 (d), 46.27 (d, CHCONH), 45.03 (d, CPh), 34.98 (t), 30.70 (t), 26.03 (t) and 25.29 (t); δC 181.20 (s, C=O), 144.48 (s), 128.36 (d, 2xCH), 127.61 (d, 2xCH), 124.39 (d), 49.76 (d, CHCONHOH), 45.95 (d, CPh), 34.25 (t), 30.28 (t), 26.11 (t) and 25.26 (t); m/z 219(M⁺, 7%), 187 (15), 159 (38), 129 (8), 117 (18), 104 (7), 91 (100) and 81 (19).

(+/−)-3-[trans-2-Phenylcyclohexylcarbonyl]-(1-SR)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene 244.

Followed General Procedure A at 0°C using cyclopentadiene (1.20 g, 1.5 ml, 11.82 mmol), tetraethylammonium periodate (0.45 g, 1.40 mmol) and hydroxamic acid 241 (0.20 g, 0.89 mmol) to give the crude product 244 (0.32 g, 126%, d.r. 1:1). This was then chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) to give the product 244a & b (R₂, 0.49), as thin needles (0.18 g, 71%), m.p. 105°C (ethyl acetate and light petroleum).

(Found: C, 75.72; H, 7.61; N, 4.92; M⁺, 283.1572. C₁₃H₁₇NO₂ requires C, 76.32; H, 7.42; N, 4.94; M, 283.1572); ν_max/cm⁻¹ (CHCl₃) 1650 s (C=O), δH 7.03-7.20 (5H, m, Ph), (6.36 (0.5H, br s) & 6.23 (0.5H, br s), olefin), 5.72 (0.5H, br s) & 5.66 (0.5H, br s), olefin), 5.04 (2H, s, 2 bridgehead
Section 3 Experimental

(2H, s, 2 bridgehead CH), 2.79 (2H, br s, CHPh and CHCO) and 1.14-1.92 (10H, m, ring protons); δ C 145.09 (s), 136.32 & 135.51 (d), 133.16 & 131.23 (d), 128.08 & 127.86 (d, 2 x CH), 126.07 & 125.91 (d), 84.31 & 83.87 (d, CH bridgehead), 61.32 (d, CH bridgehead), 47.97 (t, CH₂ of adduct), 47.84 (d), 45.39 (d), 34.19 (t), 30.40 (t), 27.83 (t), 26.07 (t), 25.58 (t) and 25.48 (t); m/z 283 (M⁺, 2.3%), 159 (30), 117 (14), 91 (100) and 66 (18).

(±)-3-[trans-2-Phenylcyclohexylcarbonyl]-1-SR)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 243.

![Chemical Structure](image)

General procedure A at 0°C was followed using cyclohexadiene (1.26 g, 1.5 ml, 15.77 mmol), tetraethylammonium periodate (0.45 g, 1.40 mmol), hydroxamic acid 241 (0.20 g, 0.90 mmol) to give the crude cycloadduct 243. The product was chromatographed on alumina eluted with dichloromethane-light petroleum (3:2) to give the product 243a&b (Rf 0.14) (0.25 g, 93%, d.r. 1:1) as thin needles, m.p. 125°C (ethyl acetate and light petroleum). General Procedure B was followed using oxalyl chloride (0.75 ml, 1.47 mmol, 2.0 M), dimethyl sulfoxide (0.23 g, 0.20 ml, 2.95 mmol), hydroxamic acid 241 (0.29 g, 1.34 mmol), cyclohexadiene (0.16 g, 0.20 ml, 2.00 mmol) and triethylamine (1.0 ml, 7.14 mmol), to give the crude product 243a&b (0.31 g, 78%, d.r. 1:1). This was chromatographed on silica eluted with light petroleum-ethyl acetate (65:35) to give the purified product 243a&b (Rf 0.34) (0.14 g, 35%, d.r. 1:1) as thin needles, m.p. 125°C (ethyl acetate and light petroleum). (Found: C, 76.88; H, 7.67; N, 4.67; M⁺, 297.1735. C₁₉H₂₃NO₂ requires C, 76.77; H, 7.74; N, 4.71; M⁺, 297.1729); υ max/cm⁻¹ (CHCl₃) 1625m, 1612m, 1437m, δ H 7.01-7.19 (5H, m, Ph), 6.39 (1H, m, olefin), 5.96 (1H, m, olefin), 4.97 (1H, br s, bridgehead), 4.53 (1H, br s, bridgehead), 2.77-3.00 (2H, br m, CH₃ & CH₂CO) and 0.99-2.11 (12H, m, ring protons); δ C, 175.38 & 171.77 (s, C=O), 145.35 & 145.08 (s, Ph), 132.42 & 132.33 (d, CH olefin), 131.58 & 129.98 (d, CH olefin), 127.96 & 127.89 & 127.71 & 127.65 (d, 2xCH, Ph), 126.00 & 125.78 (d, CH Ph), 71.67 (d, CH bridgehead), 45.84 & 45.79 & 45.59 & 44.92 (d), 34.71 & 34.21 (t), 30.04 & 28.74 (t), 26.22 (t), 25.62 & 25.50 (t), 23.64 & 22.67 (t, CH₃ of adduct) and 21.36 & 20.53 (t, CH₂ of adduct); m/z 297 (M⁺, 9%), 218 (17), 159 (58), 91 (100), 81 (18) and 79 (15).
(±)-2-[trans-2-Phenylcyclohexylcarbonyl]-1-(1-SR)-1-oxa-2-aza-4,5-dimethylcyclohex-4-ene 245.

Followed General Procedure A at 0°C, using 2, 3-dimethylbutadiene (0.37 g, 0.52 ml, 4.56 mmol), tetraethylammonium periodate (0.38 g, 1.87 mmol), hydroxamic acid 241 (0.20 g, 0.91 mmol) to give the crude product. This was then chromatographed on silica eluted with ethyl acetate-light petroleum (3:1) (Rf 0.71) to give cycloadduct 245 as a gum (0.09 g, 33%).

(Found: M+ , 299.1885. C19H25NO2 requires M, 299.1885); δH 7.12 (5H, m, Ph), 3.59-4.08 (2H, m, 2xCH of oxazine), 0.80-2.91 (16H, m, ring protons), 1.37 (3H, s, CH3 of oxazine) and 1.47 (3H, s, CH3 of oxazine); δC 175.03 & 173.51 (s, C=O), 144.83 & 143.79 (s, Ph), 128.16 & 128.05 (d, 2xCH, Ph), 127.33 & 127.17 (d, 2xCH, Ph), 126.13 & 125.90 (d, CHPh), 122.14 & 121.45 (s, olefin), 73.03 (t, CH2 of oxazine), 59.60 & 58.18 (t, CH2 of oxazine), 50.08 (d, CHCO), 46.58 & 45.14 (d, CHPh), 34.01 & 33.57 (t), 29.97 & 29.87 (t), 25.86 & 25.44 (t), 25.15 & 25.04 (t), 15.02 (q, CH3 of oxazine) and 13.73 & 13.47 (q, CH3 of oxazine); m/z 299 (M+ , 9.3%), 232 (14.7), 158 (67), 130 (14), 117 (20), 104 (10) and 91 (100).

(±)-N,N-Dimethyl-trans-2-phenylcyclohexanecarboxamide 246.

The acid 221 (0.51 g, 2.50 mmol) was added to thionyl chloride (5 ml) and heated to reflux for 2 hours. The solution was then concentrated and taken up in toluene and reconcentrated to remove excess thionyl chloride. The acid chloride 222 was dissolved in chloroform (5 ml) and chilled to 0°C. It was then added dropwise to an excess of dimethylamine solution and stirred for 45 minutes. Then dichloromethane (40 ml) was added and the solution was
washed with 1 M hydrochloric acid (2 x 25 ml). The organic layer was washed with brine, dried and concentrated to give amide 246 (0.52 g, 90%), m.p. 75-76°C (ethyl acetate and light petroleum).

(Found: C, 77.73; H, 8.94; N, 6.07; M*, 231.1623. C18H16NO requires C, 77.92; H, 9.09; N, 6.06; M, 231.1623); νmax/cm⁻¹ (CHCl₃) 1624s (C=O); δ_H 7.03 (5H, m, Ph), 2.55-2.79 (8H, m, 2xCH₃ & 2xCH₂), 2.55 (6H, s, 2xCH₂) and 1.05-1.77 (6H, m, ring protons); δ_C 174.68 (s, C=O), 144.95 (s), 128.00 (d, 2xCH), 127.22 (d, 2xCH), 126.08 (d), 46.30 (d CH₂Ph & CHCO), 36.83 (q), 35.12 (q), 33.16 (t), 29.73 (t), 26.07 (t) and 25.50 (t); m/z 231 (M⁺, 45%), 202 (8), 176 (10), 158 (21), 130 (17), 115 (23), 91 (100) and 72 (52).

(±)-N,N-Pentamethylene-trans-2-phenylcyclohexanecarboxamide 247.

![Chemical Structure](image)

The acid 221 (0.51 g, 2.50 mmol) was added to excess thionyl chloride (5.0 ml), and the solution was stirred at room temperature for 30 min and then heated to reflux for 2 hours. The solution was then concentrated, taken up in toluene and reconcentrated to remove excess thionyl chloride. The acid chloride was dissolved in chloroform (5 ml), chilled to 0°C and piperidine (0.53 g, 0.6 ml, 6.25 mmol) was added slowly. The solution was stirred for 45 minutes. Then washed with 1 M hydrochloric acid (2 x 25 ml). The organic layer was dried and concentrated to give amide 247 (0.67 g, 99%), m.p. 104-5°C (ethyl acetate and light petroleum).

(Found: C, 79.62; H, 9.25; N, 5.39; M*, 271.1937. C₁₈H₁₉NO requires C, 79.70; H, 9.22; N, 5.17; M, 271.1937); νmax/cm⁻¹ (CHCl₃) 1612s (C=O); δ_H 7.18 (5H, m, Ph), 3.60 (1H, br m, CHNH), 2.65-3.3 (5H, m, 2xCH₂ of piperidine ring & CHPh) and 0.75-2.1, (14H, m, ring protons); δ_C 173.04 (s, C=O), 145.20 (s), 128.17 (d, 2xCH), 127.53 (d, 2xCH), 126.09 (d), 46.47 (t), 46.34 (d, CHCO), 46.07 (d, CH₂Ph), 42.57 (t), 33.24 (t), 30.21 (t), 26.24 (t), 26.15 (t), 25.67 (t), 25.50 (t) and 24.48 (t); m/z 271 (M⁺, 38), 180(12), 158 (20), 129 (13), 115 (22), 91 (100) and 69 (32).
(±)-trans-1-Phthaloylamino-2-aminocyclohexane 252.

To a stirred solution of trans-1,2-diaminocyclohexane 250 (0.45 g, 3.95 mmol) in pyridine (50 ml), was added dropwise phthalic anhydride (0.54 g, 3.65 mmol) in pyridine (10 ml). The resulting solution was refluxed overnight, then concentrated and dried under vacuum. Chromatography on silica eluted with ethyl acetate-light petroleum (1:1) gave the product 252 (0.41 g, 43%), m.p. 130-135°C (ethyl acetate-light petroleum).

υmax/ cm⁻¹(KBr disc) 3380, 2930m, 2850m, 1760m and 1700s; δH 7.71 & 7.62 (4H, m, aromatic), 3.70 (1H, dt, J 3.7 & 11.4, CHNH₂), 3.31 (1H, dt, J 3.9 & 10.8, CHNPhth) and 1.04-2.13 (10H, m, ring protons); δC 168.64 (s, C=O), 133.75 (d), 131.79 (s), 123.01 (d), 58.45 (d, CHNH₂), 50.74 (d, CHNPhth), 36.63 (t), 29.21 (t), 25.56 (t) and 25.03 (t); m/z 244 (M⁺, 0.5%), (130 (7), 104 (11), 97 (100), 76 (15) and 56 (100).

(±)-trans-1-Phthaloylaminocyclohexane-2-methylamide 253.

To a stirred solution of trans-1,2-diaminocyclohexane 250 (0.68 g, 5.96 mmol) in acetic acid, was added a solution of phthalic anhydride (0.88 g, 5.96 mmol) in acetic acid (20 ml), this was heated to reflux for 20 minutes, then concentrated and chromatographed on silica eluted with ethyl acetate. This gave acetate 253 (Rₗ 0.20) (0.46 g, 31%), m.p. 213-5°C (ethyl acetate, light petroleum).

(Found: C, 66.75; H, 6.55; N, 9.77. C₁₆H₁₄N₂O₄ requires C, 67.13; H, 6.29; N, 9.79); υmax/ cm⁻¹(KBr disc) 3950, 3030, 2860, 1770m, 1725s, 1620 and 1470; δH 7.79 (2H, m, aromatic), 7.70 (2H, m, aromatic), 6.00 (1H, d, J 9.1, NHCOCH₃), 4.55 (1H, dt, J 4.0 & 10.4, CHNHCOCH₃), 3.96 (1H, dt, J 3.4 & 11.6, CHNPhth), 1.22-2.66 (8H, m, ring protons) and 1.73 (s, 3H, CH₃); δC 169.59 (s,
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2xC=O OF phthaloyl, 168.51 (s, C=O OF COCH₃), 133.79 (d), 131.63 (s), 122.97 (d), 54.83 (d, CHNHAc), 49.34 (d, CHNPth), 32.84 (t), 28.47 (t), 25.31 (t), 24.50 (t) and 22.99 (q); m/z 286 (M⁺, 7%), 243 (40), 227 (39), 160 (19), 139 (100), 104 (26), 96 (39), 80 (22), 76 (27) and 56 (69).

*N-Ethoxycarbonylphthalimide 254.*

![Chemical structure of 254](image)

To a stirred suspension of phthalimide (9.08 g, 61.77 mmol) and triethylamine (6.53 g, 9.06 ml, 64.69 mmol) in acetonitrile (50 ml), was added dropwise a solution of ethyl chloroformate (7.02 g, 6.18 ml, 64.69 mmol) in chloroform (50 ml). The solution was stirred at room temperature for 4 hours, chloroform (100 ml) was added and the solution was washed with water (3x50 ml). The organic layer was dried and concentrated to give the product 254 as white crystals (11.49g, 85%), m.p. 80°C (lit., 80°C (ethyl acetate, light petroleum) (identical to lit., 53).

δH 7.81 (4H, dm, Ph), 4.41 (2H, q, J 7.1, CH₂CH₂) and 1.37 (3H, t, J 7.1, CH₂CH₂); δc 163.71 (s, 2xC=O), 148.37 (s), 135.31 (d), 130.99 (s), 124.37 (d), 64.00 (t) and 14.03 (q); m/z, 147 (M⁺72, 3%), 75 (100), 47 (21) and 28 (7).

(±)-trans-1-Phthaloylamino-2-aminocyclohexane 252.

![Chemical structure of 250](image)

To a stirred solution of diaminocyclohexane (7.50 g, 65.79 mmol) in THF (30 ml), was added dropwise a solution of *N*-ethoxycarbonylphthalimide 254 (10.35 g, 47.26 mmol) in THF (25 ml). The solution was stirred overnight, then concentrated and taken up in chloroform (75 ml). It was then washed with water (3 x 50 ml), then the organic layer was dried and concentrated. The crude product was then recrystallised twice from THF and light
petroleum to remove ethylcarbamate, to give phthaloylamine 252 (6.85 g, 59%), m.p. 135°C (ethyl acetate-light petroleum).

\[ \text{HNO}_2\text{HCl} \rightarrow \text{Si} \quad \text{NH} \quad \text{O} \quad \text{Si} \]

\[ \text{ClSi(CH}_3\text{)}_3 \quad \text{(H}_2\text{NCH}_2\text{)}_2 \quad \text{CH}_2\text{Cl}_2 \]

To a stirred suspension of hydroxylamine hydrochloride (7.00 g, 100.72 mmol) in dry dichloromethane (80 ml), was added ethylenediamine (9.08 g, 101.1 ml, 151.08 mmol) and the mixture was stirred overnight in a stoppered flask. A condenser was then fitted and trimethylsilyl chloride (21.88 g, 25.6 ml, 108.66 mmol) was added over 30 minutes. The flask was then stoppered and stirred for a further 24 hours then the mixture was filtered and concentrated to give the crude product. This was distilled (b.p. 74-79°C / 92 Torr) to give 259 as a colourless oil (12.33 g, 69%) (identical to lit., \(^{35}\)).

\[ \text{HNO}_2\text{HCl} \rightarrow \text{ClSi(CH}_3\text{)}_3 \quad \text{(H}_2\text{NCH}_2\text{)}_2 \quad \text{CH}_2\text{Cl}_2 \]

To a stirred solution of phosgene in toluene (12.5%, 0.27 g, 1.4 ml, 2.69 mmol) at 0°C was added a solution of phthaloylcylohexylamine 252 (0.60 g, 2.46 mmol) and triethylamine (0.40 g, 0.55 ml, 3.93 mmol) in toluene (10 ml). After the mixture was stirred for 1 hour at
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0°C, the solution was concentrated and taken up in dry THF (5 ml).

*N,O*-bis(trimethylsilyl)hydroxylamine 259 (0.44 g, 2.50 mmol) was added and the solution was stirred for 30 min at room temperature under nitrogen. Then methanol (5 ml) was added and the solution left stirring over night. The solution was then concentrated to give hydroxyurea 249 (0.42 g, 56%).

\[\nu_{\text{max}}/\text{cm}^{-1} (\text{KBr disc}) 2936\text{m}, 1771\text{m} \text{ and } 1709\text{s (C=O); } \delta_{\text{H}} ((\text{CD}_2)\text{SO}) 8.51 (1\text{H}, \text{br s, NHOH}), 8.14 (1\text{H}, \text{br s, NHOH}), 7.86 (4\text{H}, \text{s, aromatic}), 6.30 (1\text{H}, \text{d, J} 9.1, \text{NHOH}), 4.25 (1\text{H}, \text{m, CHNHC}O), 4.06 (1\text{H}, \text{m, CHNPth}) \text{ and } 1.19-2.57 (8\text{H}, \text{m, cyclohexane); } \delta_{\text{C}} ((\text{CD}_2)\text{SO}) 167.89 (\text{S, C=O of NPhth}), 160.82 (\text{s, C=O of urea}), 134.34 (\text{d}), 131.50 (\text{s}), 123.02 (\text{d}), 54.21 (\text{d, CHNCONHOH}), 48.60 (\text{d, CHNPth}), 32.57 (\text{t}), 28.61 (\text{t}), 24.95 (\text{t}) \text{ and } 24.84 (\text{t}); m/z 303 (M^+, 2%), 270 (13), 186 (35), 160 (40), 148 (100), 130 (56) \text{ and } 104 (58).

*\((\pm)-3\text{-trans-2-Phthaloylaminocyclohexylaminocarbonyl}2\text{-oxa-3-azabicyclo[2.2.1]hept-5-ene 256a&b.}\)

Followed General Procedure A at 0°C, using cyclopentadiene (0.52 g, 0.65 ml, 7.92 mmol), tetraethylammonium periodate (0.28 g, 0.90 mmol) and hydroxy urea 249 (0.24 g, 0.79 mmol) to give the crude product 256a&b (0.27g, 93%, d.r. 1:1). This was then chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) to give two products, (0.07g, 24%, \(R_f 0.58\)) & (0.14g, 48%, \(R_f 0.47\)), m.p. 147-9°C(ethyl acetate). This experiment was repeated following General Procedure A at -78°C, using hydroxyurea 249 (0.31 g, 1.01 mmol) with all other quantities as above. This gave crude product 256a&b (0.37 g, 99%, d.r. 1:1), which was chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) to give the product 256a&b (0.20 g, 54%). This experiment was repeated following General Procedure B at -78°C, using oxalyl chloride (0.75 ml, 1.47 mmol, 2.0 M), dimethyl sulfoxide (0.23 g, 0.2 ml, 2.95 mmol), hydroxyurea 249 (0.41 g, 1.36 mmol), cyclopentadiene (0.13 g, 0.16 ml, 1.98 mmol) and triethylamine (1.00 ml, 7.13 mmol) to give the crude product 256a&b (0.41g, 82%, d.r. 1:1).
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(Found C, 65.62; H, 5.71; N, 11.32; $M^+$, 367.1508. C$_{20}$H$_{27}$N$_2$O$_4$ requires C, 65.39; H, 5.72; N, 11.44; $M$, 367.1532), $\nu_{max}$/ cm$^{-1}$ (CHCl$_3$) 1712s (C=O); More polar fraction (R$_f$ 0.47), $\delta_{\eta}$ 7.86 & 7.70 (4H, m, aromatic), 5.84 (1H, m, olefinic), 5.46 (1H, d, $J$ 9.8, NHCO), 5.17 (1H, m, olefinic), 5.03 (1H, s, bridgehead), 4.80 (1H, s, bridgehead), 4.37 (1H, dd, $J$ 4.1 & 11.0, CH(NHCO)), 3.82 (1H, dd, J 3.0 & 10.5, CH(Nphth)), 2.45 (1H, dt, $J$ 3.6 & 13.0, ringproton) and 1.14-2.18 (10H, m, ring protons); $\delta_{C}$ 161.55 (s, C=O of urea), 134.00 (d, aromatic), 133.88 (d, aromatic), 132.01 (d), 131.41 (s), 123.19 (d), 123.02 (d), 83.55 (d), 64.69 (d), 54.92 (d, CH(NHCO)), 49.22 (d, CH(Nphth)), 48.36 (t, CH$_2$ of adduct), 33.48 (t), 28.76 (t), 25.33 (t) and 24.66 (t); Less polar fraction (R$_f$ 0.58), $\delta_{\eta}$ 7.83 & 7.72 (4H, m, aromatic), 6.29 (1H, m, olefinic), 6.15 (1H, m, olefinic), 5.56 (1H, d, $J$ 8.9, NHCO), 5.07 (1H, s, bridgehead), 4.92 (1H, s, bridgehead), 4.31 (1H, m, CH(NHCO)), 3.82 (1H, m, CH(Nphth)), 2.42 (m) and 1.22-2.17 (10H, m, ring protons); $\delta_{C}$ 168.45 (s, C=O of phthaloyl), 162.21 (s, C=O of urea), 134.93 (d, aromatic), 133.80 (d, aromatic), 131.82 (s), 131.56 (d), 123.19 (d), 83.59 (d), 65.15 (d), 54.34 (d, CH(NHCO)), 50.14 (d, CH(Nphth)), 48.15 (t, CH$_2$ of adduct), 33.44 (t), 28.91 (t), 25.35 (t) and 24.65 (t); $m/z$ 367 ($M^+$, 0.4%), 270 (30), 242 (9), 186 (40), 160 (24), 148 (100), 130 (23), 123 (41) and 104 (20).

(±)-3-[[trans-2-Phthaloylaminocyclohexylaminocarbonyl]2-oxa-3-azabicyclo[2.2.2]oct-5-ene 257a&b.

Following General Procedure A at 0°C, using cyclohexadiene (0.53 g, 0.63 ml, 6.66 mmol), tetraethylammonium periodate (0.55 g, 1.72 mmol) and hydroxy urea 249 (0.40 g, 1.32 mmol) to give the crude product (0.50, 99%, d.r. 1:1). This was then chromatographed on alumina eluted with ethyl acetate-light petroleum (1:1) to give 257a&b ($R_f$ 0.39) (0.31 g, 62%).

This experiment was repeated following General Procedure A at -78°C, using hydroxyurea 249 (0.24 g, 0.80 mmol) with all other quantities as above. This gave the crude product 257a&b (0.33 g, 107%, d.r. 1:1) which was chromatographed on alumina eluted with ethyl acetate-light petroleum (1:1) to give total product 257a&b ($R_f$ 0.39) (0.13 g, 42%), m.p. 163-5 °C (ethyl acetate).
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(Found: C, 65.04; H, 6.32; N, 9.91 (+C₂H₅OH); M⁺, 381.1688. C₂rH₂₂N₂O₄ requires C, 64.64; H, 6.79; N, 9.84 (+C₂H₅OH); M⁺, 381.1688); νmax/cm⁻¹ (CHCl₃) 1712s (C=O); Both diastereomers, δH 7.76 & 7.63 (4H, m, aromatic (both)), (6.32 (1H, ddd, J 1.9, 5.9 & 8.0) & 6.24 (1H, ddd, J 2.1, 5.8 & 8.1) 2 olefins of A), 5.89 (1H, ddd, J 1.9, 6.0 & 8.1, 1x olefin of B), 5.65 (1H, d, J 8.8, (1x NHCO), 5.60 (1H, d, J 9.5, 1x NHCO), 5.25 (1H, ddd, J 1.4, 5.9 & 8.1, 1x olefin of B), 4.59 (1H, m, 1x bridgehead), 4.47 (3H, m, 3X bridgeheads), 3.93 (1H, dt, J 4.4 & 12.0, CHNHCO), 3.76 (1H, dt, J 3.4 & 11.7, (CHNHCO), 2.35 (2H, m) and 1.06-1.96 (12H, m, ring protons); δC 171.09 & 168.29 (s, C=O of phthaloyl), 161.81 & 161.55 (s, C=O of urea), 133.69 (d, aromatic), 131.94 (d, olefin), 131.70 (s, aromatic), 130.90 (d, olefin), 130.10 & 130.16 (d, 2xCH, ar), 123.03 & 122.87 (d), 70.14 & 70.09 (d, bridgehead), 54.91 & 54.24 (d, CHNHCO), 49.96 & 49.91 (d, bridgehead), 49.82 & 49.18 (d, CHNPhth), 33.44 & 33.23 (t), 28.85 & 28.58 (t), 25.27 & 24.58 (t), 23.75 & 23.46 (t) and 19.57 & 19.48 (t); m/z 381 (M⁺, 4.8%), 270 (26), 186 (38), 160 (33), 148 (100), 130 (26) and 123 (35).

(±)-trans-2-Aminocyclohexan-1-ol 268.

Ammonium hydroxide (33%, 60 ml) was added to cyclohexene oxide 235 (5.00 g, 51.02 mmol) in a round bottomed flask and the solution was stirred for 4 days. The solution was then extracted with dichloromethane (3 x 50 ml). The organic layers were combined and dried and concentrated to give the product 268 as white crystals (5.10 g, 87%), m.p. 62-64°C (ethyl acetate, light petroleum) (lit., 68°C for trans; 107-8°C for cis).

δH 2.81 (3H, br s, amino and hydroxyl protons) and 1.02-3.38 (8H, m, cyclohexane); δC 75.64 (d, CHO), 57.00 (d, CHNH₂), 34.50 (t), 33.85 (t), 25.05 (t) and 24.79 (t).

(±)-trans-2-Phthaloylaminocyclohexan-1-ol 269.
trans-2-Aminocyclohexan-1-ol 268 (1.0 g, 8.69 mmol) and phthalic anhydride (1.54 g, 10.40 mmol) were heated to reflux in glacial acetic acid (10 ml) for 35 min and then concentrated to give the crude product. This was chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) to give phthaloylcyclohexanol 269 (Rf 0.43) as white crystals (1.12 g, 52%), m.p. 172°C (ethyl acetate, light petroleum).

(Found: C, 68.58; H, 6.02; N, 5.77; M+, 245.1046. C_{14}H_{15}NO_{3} requires C, 68.57; H, 6.12; N, 5.71; M+, 245.1052); ν_{max} / cm^{-1} (CHCl_{3}) 1700s(C=O); δ_{H} 7.67 (4H, m, aromatic hydrogens), 4.26 (1H, dt, J =4.5 & 10.2, CHOH), 3.94 (1H, dt, J=3.8 & 10.2, CHNPhth), 2.42 (1H, s, OH (disappears with D_{2}O)) and 1.31- 2.15 (8H, bm, ring protons); δ_{C} 168.88 (s, 2xC=O), 133.80 (d, 2xCCH), 131.9 (s), 123.09 (d, 2xCCH), 69.51 (d, CHOH), 57.46 (d, CHNPhth), 35.36 (t), 28.89 (t), 25.30 (t) and 24.40 (t); m/z 245 (M+, 2%), 186 (14), 174 (19), 160 (26), 148 (19), 130 (19), 104 (16) and 98 (100).

(±)-trans-2-Phthaloylaminocyclohexane-1-(N-hydroxycarbamate) 270.

![Chemical structures](269_270.png)

To a stirred solution of phosgene (12.5 %, 0.24 g, 1.31 ml, 2.41 mmol) at 0°C, was added dropwise, a solution of cyclohexanol 269 (0.59 g, 2.41 mmol) and triethylamine (0.24 g, 0.34 ml, 2.41 mmol) in toluene (10 ml). This solution was stirred for 1 hour at 0°C and for a further hour at room temperature. N, O-bis(trimethylsilyl)hydroxylamine 259 (0.55 g, 3.13 mmol) was added under a nitrogen atmosphere. The solution was stirred for 1 hour at room temperature, concentrated, taken up in ethyl acetate (20 ml), filtered and concentrated. Then methanol (15 ml) was added and the solution was stirred overnight at room temperature. The solution was then concentrated to give hydroxycarbamate 270 (0.38 g, 52%).

(Found: M+-CHNO_{2}, 245.1040. C_{14}H_{15}NO_{3} requires M-CHNO_{2}, 245.1052); ν_{max} / cm^{-1} (KBr disc) 3312m and 1708s (C=O); δ_{C} 8.26 (2H, br s, NH=OH), 7.38 (4H, m, aromatic), 4.97 (1H, dt, J 4.5 & 10.4, CHOOC), 3.75 (1H, dt, J 3.3 & 11.6, CHNPhth) and 0.95-2.00 (8H, m, ring protons); δ_{C} 167.63 (s), 157.44 (s), 133.70 (d), 131.40 (s), 122.77 (d), 71.90 (d, CHOOC), 53.31 (d, CHNPhth), 31.85 (t), 28.45 (t), 24.65 (t) and 23.54 (t); m/z 245 (2%), 228 (89), 186 (16), 174 (10), 160 (100), 148 (88) and 130 (43).
(±)-3-[trans-2-Phthaloylaminocyclohexyloxycarbonyl]2-oxa-3-azabicyclo[2.2.1]hept-5-ene 272a&b.

Following General Procedure A at 0°C, using cyclopentadiene (0.28 g, 0.35 ml, 4.24 mmol), hydroxycarbamate 271 (0.23 g, 0.78 mmol) and tetraethylammonium periodate (0.27 g, 0.84 mmol), (ethanol-dichromethane 1:25) used, gave the crude product 272a&b (0.31 g, 113%, d.r. 1:1). This was then chromatographed on silica eluted with ethyl acetate-light petroleum (3:2) to give 272a&b (Rₗ 0.47) (0.25 g, 87%) as a white solid. The two diastereomers were separated by chromatography on alumina eluted with dichloromethane (Rₗ 0.70 and Rₗ 0.62), m.p. 125-8 °C (ethyl acetate).

Following General Procedure B at -78°C, using oxaly chloride (0.75 ml, 1.47 mmol, 2.0 M), dimethyl sulfoxide (0.23 g, 0.2 ml, 2.95 mmol), hydroxycarbamate 270 (0.40 g, 1.32 mmol), cyclopentadiene (0.13 g, 0.16 ml, 1.98 mmol) and triethylamine (0.94 ml, 6.70 mmol) to give the crude product 272a&b (0.47 g, 97%, d.r. 1:1). The crude product was chromatographed on alumina eluted with dichloromethane to separate the two diastereomers 272a&b (Rₗ 0.70 and Rₗ 0.63).

(Found: C, 65.78; H, 5.72; N, 6.99; M⁺, 368.1372. C₃₆H₅₀N₅O₂ requires C, 65.21; H, 5.43; N, 7.61; M, 368.1372), ν_max/cm⁻¹ (CHCl₃) 1712 (C=O); δ_H 7.76 (2H, m, aromatic), 7.65 (2H, aromatic), 5.85 (2H, br d, olefin), 5.86 (2H, s, T=318K), 5.29 (1H, dt, J 4.8 & 10.4, CHOOC), 4.98 (1H, s, bridgehead), 4.74 (1H, s, bridgehead), 4.12 (1H, dt, J 4.1 & 10.4, CHNPhth) and 1.00-2.42 (10H, m, ring protons), δ_C (less polar diastereomer) 167.92 (s), 158.72 (s), 134.17 (d), 133.85 (d), 132.71 (d), 131.81 (s), 123.05 (d), 83.45 (d, bridgehead), 73.66 (d, CHOOC), 64.72 (d, bridgehead), 53.64 (d, CHNPhth), 47.93 (t, CH₂ of adduct), 31.61 (t), 28.39 (t), 24.92 (t) and 23.73 (t); δ_C (More polar diastereomer) 167.76 (s), 157.91 (s), 133.89 (d), 133.47 (d), 132.51 (d), 131.41 (s), 122.92 (d), 83.26 (d, bridgehead), 73.47 (d, CHOOC), 64.63 (d, bridgehead), 53.33 (d, CHNPhth), 47.86 (t, CH₂ of adduct), 31.49 (t), 28.28 (t), 24.79 (t) and 23.63 (t); m/z 368 (M⁺, 0.1%), 228 (38), 186 (16), 174 (13), 160 (86), 148 (84), 130 (57), 104 (31) and 98 (87).
(±)-3-[trans-2-Phthaloylaminocyclohexyloxy carbonyl]2-oxa-3-azabicyclo[2.2.2]oct-5-ene 273a&b.

Followed General Procedure A at 0°C, using cyclohexadiene (0.30 g, 0.38 ml, 3.79 mmol), hydroxy carbamate 270 (0.23 g, 0.76 mmol) and tetraethylammonium periodate (0.26 g, 0.81 mmol) and ethanol-dichloromethane (1:25) to give the crude product 273a&b (0.27 g, 93%, d.r. 1:1). The crude product was chromatographed on alumina eluted with dichloromethane-light petroleum (7:3) to separate the two diastereomers 273a (Rf 0.71) (0.09 g, 35%) m.p. 163-5°C (ethyl acetate) and 273b (Rf 0.63) (0.02 g, 8%).

Followed General Procedure B at -78°C, using oxalyl chloride (0.75 ml, 1.47 mmol, 2.0 M), DMSO (0.23 g, 0.20 ml, 2.95 mmol), hydroxy carbamate 270 (0.41 g, 1.34 mmol), cyclohexadiene (0.54 g, 0.65 ml, 6.70 mmol) and triethylamine (0.94 ml, 6.70 mmol) to give the crude product 273a&b (0.46 g, 89%, d.r. 1:1).

(Found C, 65.82; H, 5.61; N, 7.18; M, 382.1531. C_{21}H_{22}N_{2}O_{3} requires C, 65.96; H, 5.75; N, 7.32; M, 382.1529); υ_{max}/cm^{-1} (CHCl₃) 1712m (C=O); δ_{1H} (Less polar diastereomer, at 333K) 7.82 (2H, m, aromatic), 7.71 (2H, m, aromatic), 6.05 (2H, m, olefin), 5.32 (1H, dt, J 4.9 & 10.5, CHOOCO), 4.54 (1H, m, bridgehead), 4.44 (1H, m, bridgehead), 4.19 (1H, dt, J 4.1 & 10.4, CHNPht) and 1.17-2.49 (12H, m, ring protons); (at 298K, as above except) 5.97 (2H, br s, 2x olefin) and 4.47 (2H, m, 2x bridgeheads); δ_{C} (Less polar diastereomer) 168.00 (s, C=O), 133.74 (d, 2XCH, aromatic), 131.94 (s, aromatic), 131.67 (d, olefin), 131.23 (d, olefin), 123.03 (d, 2XCH, aromatic), 73.56 (d, CHOOCO), 70.57 (d, bridgehead), 53.83 (d, CHNPht), 49.90 (d, bridgehead), 31.69 (t), 28.40 (t), 25.00 (t), 23.80 (t), 23.38 (t, CH₂ of adduct) and 20.05 (t, CH₂ of adduct); δ_{C} (More polar diastereomer) 167.76 (s), 157.91 (s), 133.89 (d), 133.47 (d), 132.51 (d), 131.41 (s), 122.92 (d), 83.26 (d), 73.47 (d), 64.63 (d), 53.33 (d), 47.86 (t), 31.49 (t), 28.28 (t), 24.79 (t) and 23.63 (t); m/z 382 (M⁺, 2.2%), 228 (97), 160 (87), 148 (100), 130 (37), 98 (40) and 81 (59).
Camphoroxime 275.

Camphor 274 (4.12 g, 27.10 mmol), hydroxylamine hydrochloride (3.65 g, 52.52 mmol) and sodium acetate (4.13 g, 50.37 mmol) were heated to reflux in water-ethanol (60 ml) (5:1) for 1 hour. The solution was then cooled and extracted with dichloromethane (2x50 ml). The organic layer was dried, concentrated and recrystallised to give the product 275 (3.82 g, 84%), m.p. 110-116°C (ethanol) (m.p. 118°C (ethanol) lit., 67).

υmax/ cm⁻¹ (CHCl₃) 3020s, 2966m, 2401m and 1736m (C=O); δH 9.24 (1H, br s, NOH), 0.84-2.55 (7H, m, ring protons), (0.73 (3H, s, CH₃), (0.84 (3H, s, CH₃) and 0.93 (3H, s, CH₃)); δC 169.82 (s), 51.79 (s), 48.24 (s), 43.63 (d), 33.07 (t), 32.53 (t), 27.17 (t), 19.38 (q), 18.45 (q) and 11.03 (q); m/z, 167 (M⁺, 47), 152(-CH₃, 22), 150(-OH, 21) and 134 (47).

exo-Bornylamine 276.

Oxime 275 (3.82 g, 22.87 mmol) and nickel(II) chloride hexahydrate (11.04 g, 45.75 mmol) were dissolved in methanol (50 ml) and the solution was cooled with stirring to -30°C. Then sodium borohydride (8.69 g, 222.74 mmol) was added over 20 minutes. The black mixture was allowed to warm to room temperature and concentrated. It was taken up in light petroleum (100 ml), filtered through Celite and concentrated to give the product 276 (1.74 g, 49.7%) (identical to lit., 61).

υmax/ cm⁻¹ (KBr disc, free amine) 3500, 3000 and 2500; δH (hydrochloride salt) 8.21 (3H, br s, NH₂), 0.90-2.15 (8H, ring protons), 1.12 (3H, s, CH₃), 1.08 (3H, s, CH₃) and 0.81 (3H, s, CH₃); δC (hydrochloride salt) 58.4 (d, CH₂NH₂), 48.1 (s), 47.2 (s), 44.7 (d), 46.2 (t), 36.0 (t), 26.6 (t), 20.6 (q), 20.04 (q) and 12.0 (q); m/z (free amine), 153 (M⁺, 23%), 136 (22), 121 (16), 110 (14) 108 (40) and 95 (100).
exo-Camphor-1-N,N'-hydroxyurea 277.

exo-bornylamine 276 (0.86 g, 5.62 mmol) was dissolved in toluene (10 ml) and triethylamine (0.85 g, 1.2 ml, 8.43 mmol) was added. This solution was added slowly to a stirred solution of phosgene in toluene (12.5%, 0.72 g, 6.4 ml, 7.31 mmol) at 0°C. After 1 hour at 0°C, this solution was added slowly to an ice cold solution of hydroxylamine hydrochloride (1.17 g, 16.86 mmol) and sodium carbonate (2.00 g, 18.9 mmol) in water (50 ml). After the solution was stirred for 1 hour, the two layers were separated and the organic layer dried and concentrated to give the product 277 (0.54 g, 45%) as a gum.

δH 6.7-7.6 (2H, br s, NHOOH), 5.97 (1H, d, J 9.4, NHCO), 3.67 (1H, m, CHNHCO), 0.73-1.92 (8H, ring protons), 0.76 (3H, s, CH3), 0.77 (3H, s, CH3) and 0.85 (3H, s, CH3); δc 162.02 (s, C=O), 56.91 (d), 46.89 (s), 45.86 (s), 44.77 (d), 39.04 (t), 35.79 (t), 27.38 (t), 20.93 (q), 20.44 (q) and 11.68 (q).

endo-Camphor-1-N,N'-hydroxyurea 280.

A solution of endo-Bornylamine 279 (0.50 g, 2.62 mmol) and triethylamine (0.40 g, 0.55 ml, 3.93 mmol) in toluene (10 ml) was added slowly to phosgene in toluene (12.5%, 2.70 g, 2.96 ml, 3.41 mmol) at 0°C. After being stirred for 1 hour at 0°C, this solution was added slowly to an ice cold solution of hydroxylamine hydrochloride (0.86 g, 12.37 mmol) and sodium carbonate (3.24 g, 30.56 mmol) in water (50 ml). After an hour, the two layers were separated and the organic layer dried and concentrated to give the product 280 (0.59 g, 106%) as a gum.

δH 7.54 (1H, br s, NHOOH), 6.06 (1H, d, J 9.3, NHCO), 3.99 (1H, br m, CHNHCO), 0.73-2.20 (9H, m, ring protons), 0.73 (3H, s, CH3), 0.80 (3H, s, CH3) and 0.86 (3H, s, CH3); δc 160.07 (s, C=O),
54.06 (d), 49.30 (s), 47.94 (s), 44.73 (d), 37.31 (t), 28.17 (t), 27.71 (t), 19.78 (q), 18.55 (q) and 13.48 (q); m/z, 212 (M⁺, 6%), 136 (29), 121 (29) and 95 (100).

[exo-2-Bromylaminocarbonyl]-{1-SR}-2-oxa-3-azabicyclo[2.2.1]hept-5-ene 283.

Followed General Procedure A at 0°C, using cyclopentadiene (0.36 g, 0.45 ml, 5.45 mmol), tetraethylammonium periodate (0.52 g, 1.63 mmol) and hydroxyurea 277 (0.23 g, 1.08 mmol) to give the crude product 283a&b (0.23 g, 75%, d.r. 1:1). This was then chromatographed on alumina eluted with light petroleum-ethyl acetate (7:3) to give 283a (Rₜ 0.61) and 283b Rₜ 0.56 (0.12 g, 40%).

δₜ (both diastereomers) 6.30 (2H, m, olefin), 5.61 (1H, br d, NHCO), 5.10 (1H, s, bridgehead), 5.07 (1H, bridgehead), 3.61 (1H, dt, J 5.0 & 9.3, CHNHCO), 0.54-2.16 (12H, m, ring proton) and 0.8 (m, 6xCH₃); δc 161.82 (s), 134.96 & 134.63 (d), 131.52 & 131.31 (d), 83.61 (d), 65.10 (d), 56.96 & 56.90 (d), 48.30 (t), 46.77 (s), 44.69 (d), 39.44 & 38.68 (t), 35.72 & 35.46 (t), 26.88 (t), 20.19 & 20.04 (q), 19.94 (q) and 11.86 & 11.61 (q).

[exo-2-Bromylaminocarbonyl]-{1-SR}-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 284.

Followed General Procedure A at 0°C, using cyclohexadiene (0.22 g, 0.26 ml, 2.73 mmol), tetraethylammonium periodate (0.38 g, 1.82 mmol) and hydroxyurea 277 (0.19 g, 0.91 mmol) to give the crude product 284a&b (0.25 g, 94%, d.r. 1:1). This was then chromatographed on silica eluted with ethyl acetate to give 284a&b (Rₜ 0.47).

δₜ (Both diastereomers) 6.42 (2H, m, olefin), 5.76 (1H, d, J 8.8, NHCO), 4.81 (1H, m, bridgehead), 4.58 (1H, m, bridgehead), 3.62 (1H, m, CHNHCO), 0.67-2.29 (22H, m, ring protons), 0.67 (3H, s, CH₃), 0.74& 0.76 (3H, s, CH₃) and 0.80& 0.85 (3H, s, CH₃); δc 161.83 (s, C=O), 132.16 & 131.90
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(d), 130.06 & 129.94 (d), 70.34 & 70.31 (d), 56.92 & 56.84 (d, CHNCO), 50.35 & 50.16 (d), 48.50 & 48.29 (s), 46.81 & 46.76 (s), 44.69 (d), 39.44 & 38.72 (t), 35.70 & 35.50 (t), 26.90 (t), 23.89 & 23.83 (t), 20.21 & 20.03 (q), 19.90 & 19.86 (t) and 11.78 & 11.57 (q).

[endo-Bornylaminocarbonyl]-(1-SR)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 282.

Following General Procedure A at 0°C, using cyclohexadiene (0.14 g, 0.16 ml, 1.71 mmol), tetraethylammonium periodate (0.14 g, 0.45 mmol) and hydroxyurea 280 (0.08 g, 0.34 mmol) gave the crude product 282a & b (0.09 g, 87%, d.r. 1:1). This was then chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) to give 282a & b (Rf 0.46).

δH 6.43 (2H, m, olefin), 5.77 (1H, br s, NHCO), 4.83 (1H, m, bridgehead), 4.64 (1H, m, bridgehead), 3.98 (1H, m, CHNCO), 0.67–2.32 (22H, m, ring protons), 0.67 (3H, s, CH3), 0.78 (3H, s, CH3) and 0.85 (3H, s, CH3); δC 162.48 (s, C=O), 132.09 (d), 130.17 & 129.96 (d), 70.43 & 70.36 (d), 54.05 (d), 50.47 & 50.10 (d), 49.48 & 49.38 (s), 47.99 & 47.86 (s), 44.83 (d), 37.91 & 37.22 (t), 28.29 & 28.19 (t), 27.79 (t), 23.98 & 23.87 (t), 20.00 & 19.88 (t), 19.82 (q), 18.54 (q) and 13.48 (q).

Cyclohexyl-N,N'-hydroxyurea 213.

Cyclohexylamine 212 (0.62 g, 0.72 ml, 6.32 mmol) in toluene (10 ml) was added dropwise to a solution of phosphene in toluene (20%, 3.60 ml, 4.14 mmol) at 0°C and stirred for an hour at 0°C. Then hydroxylamine hydrochloride (0.46 g, 6.62 mmol) and sodium carbonate (3.40 g, 32.07 mmol) in toluene (20 ml) and water (40 ml) were added and the solution was stirred for an at 0°C. The layers were separated and the organic layer was washed with 2 M
sodium hydroxide solution (2x25 ml). The combined basic layers were acidified and extracted with ethyl acetate (3x60 ml). The combined organic layers were dried and concentrated to give hydroxyurea 213 (0.50g, 80%) as a gum.

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{CHCl}_3) 1720 (\text{C=O}) ; \delta_H (\text{CDCl}_3, 90 \text{ MHz}) 7.1 (2H, \text{br s}, \text{NHOH}), 5.8 (1H, \text{br d}, \text{NHCO}), 3.5 (1H, m, \text{CHNHC}O) \text{ and } 0.8-2.0 (10H, m, \text{ring protons}) ; m/z, 158 (M^+, 2.4\%), 142 (3), 126 (21) \text{ and } 83 (100).

3-[Cyclohexylaminocarbonyl]-\{1SR\}-2-oxa-3-azabicyclo[2.2.1]hept-5-ene 215.

Following General Procedure A at 0°C, using cyclopentadiene (0.34 g, 0.42 ml, 5.09 mmol), tetrathylationmonium periodate (0.41 g, 1.28 mmol) and hydroxyurea 213 (0.16 g, 1.03 mmol) gave cycloadduct 215 (0.20 g, 87%) as a gum.

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{CHCl}_3) 1660 \text{ and } 1512 ; \delta_H 6.35 (2H, m, \text{olefins}), 5.58 (1H, \text{br d}, \text{NHCO}), 5.16 (1H, s, \text{bridgehead}), 5.14 (1H, s, \text{bridgehead}), 3.55 (1H, m, \text{CHNHCO}) \text{ and } 0.96-2.02 (12H, m, \text{ring protons}) ; \delta_C 161.68 (s, C=O), 134.61 (d, \text{olefin}), 131.51 (d, \text{olefin}), 83.58 (d, \text{bridgehead}), 65.12 (d, \text{bridgehead}), 48.41 (d, \text{CHNHCO}), 48.30 (t, \text{adduct}), 33.43 (t), 32.95 (t), 25.38 (t) \text{ and } 24.65 (t).

3-[Cyclohexylaminocarbonyl]-\{1SR\}-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 216.

Followed General Procedure A at 0°C, using cyclohexadiene (0.20 g, 0.24 ml, 5.09 mmol), tetrathylationmonium periodate (0.22 g, 0.61 mmol) and hydroxyurea 213 (0.08 g, 0.51 mmol) to give the crude product 216 (0.13 g, 113%) as a gum.

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{CHCl}_3) 1660 \text{ and } 1512 ; \delta_H 6.42 (2H, m, \text{olefins}), 5.62 (1H, d, J 8.0, \text{NHCO}), 4.83 (1H, m, \text{bridgehead}), 4.60 (1H, m, \text{bridgehead}), 3.49 (1H, m, \text{CHNHCO}) \text{ and } 1.03-2.36 (14H, m, \text{ring protons}) ; \delta_C 161.47 (s, C=O), 131.78 (d, \text{olefin}), 130.08 (d, \text{olefin}), 70.30 (d, \text{bridgehead}), 50.09 (d,
bridgehead), 48.42 (d, CHNHCO), 33.47 (t), 33.03 (t), 25.40 (t), 24.70 (t), 23.83 (t, bridge of adduct) and 19.98 (t, bridge of adduct).

**(2RS, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone 286.**

![Chemical Structure Diagram]

1. PhMgBr, CuI, THF -20 °C
2. 2N HCl
3. KOH/EtOH reflux

In a 250 ml flame dried three necked round bottomed flask fitted with a reflux condenser and a teflon coated magnetic stirrer bar under an atmosphere of nitrogen, was placed magnesium turnings (4.14g, 0.17 mol) and THF (20 ml). Bromobenzene (4 ml) was added to start the reaction, from bromobenzene (30.98g, 20.79 ml, 0.20 mol). Then the rest of the bromobenzene in THF (40 ml) was added at such a rate as to maintain reflux. The reaction mixture was heated to reflux for 1 hr, cooled to room temperature and further THF (40 ml) was added.

In a second 250 ml flame dried three necked round bottomed flask with a teflon coated stirrer bar and rubber septum under nitrogen, was placed copper(I) iodide (2.25g, 0.012 mol) in THF (25 ml). The Grignard solution of phenyl magnesium bromide was added via a cannula to the stirred suspension at -20°C. After the addition was complete, the solution was stirred at -20°C for 30 min. Then (R)-(−)-pulegone 285 (15.0g, 0.099 mol) in THF (20 ml) was added from a 100 ml pressure equilibrated dropping funnel to the dark green solution at -20°C over 2 hrs. The mixture was allowed to warm to room temperature overnight and then added to vigorously stirred ice cold 2N HCl (120 ml). The layers were separated and the aqueous layer was saturated with salt and extracted with ether (3×50 ml). The organic layers were combined and washed with saturated sodium hydrogen carbonate solution, dried and concentrated. The crude oily product 286 (27.29g) was used for equilibration without further purification.
Equilibration
A solution of crude phenylmenthone 286 (27.29g) in ethanol (225 ml) and water (30 ml) and potassium hydroxide (26.25g, 0.468 mol) was refluxed for 3 hrs. The solution was concentrated to ~75 ml and water (190 ml) was added. The aqueous layer was saturated with salt and extracted with ether (4x50 ml). The combined organic layers were dried and concentrated. The oily crude product was distilled to give phenyl menthone as a mixture of diastereomers 286&287 (15.78g, 69.5%), (b.p. 100-110°C/ 0.05 Torr) (identical to lit.: 6)). νmax/cm⁻¹(CHCl₃) 2958s and 1706s (C=O); δH 7.00-7.48 (5H, m, Ph), 0.82-2.71 (8H, m, ring protons), 0.90 (3H, d, J 6.9, CH₂CH₃ cis), 0.95 (3H, d, J 6.0, CH₂CH₃ trans), 1.40 (3H, s, CPh₂CH₂) and 1.46 (3H, s, CPh₂CH₂); δc (trans); 149.88 (s), 127.97 (d), 125.74 (d), 125.49 (d), 59.51 (d), 52.35 (t), 39.02 (s), 36.25 (d), 34.70 (t), 29.02 (t), 26.56 (q), 23.81 (q) and 22.31 (q); δc (cis); 149.37 (s), 125.88 (d), 125.60 (d), 59.66 (d), 50.27 (t), 39.47 (s), 32.18 (d), 31.25 (t), 27.23 (q), 24.85 (t), 23.95 (q) and 19.26 (q), m/z 230 (M⁺, 4%)., 119 (85), 112 (25), 91 (34), 74 (36), 59 (51.7), 45 (40), 43 (10), 41 (25) and 31 (100).


In a 500 ml, three necked round bottomed flask fitted with a reflux condenser and a magnetic stirrer bar was added sodium (4.56g, 0.20 mol) and toluene (100 ml). The solution was heated to reflux and stirred rapidly to give a fine dispersion of molten sodium. The phenylmenthone 286 (15.21g, 0.066 mol) in 2-propanol (11.90g, 0.20 mol) was added at such a rate as to maintain a controlled reflux. The reaction mixture was refluxed overnight and then cooled to 0°C, diluted with ether (50 ml) and carefully poured into ice water (100 ml). The organic layer was separated and the aqueous layer was saturated with salt and extracted with ether (3x70 ml). The combined organic layers were washed with saturated brine, dried and concentrated to give the crude product 288&289 (16.36g, 106%). This was
then distilled (b.p. 103-107°C at 0.01 Torr), to give the product 288&289, as a mixture of diastereomers, (10.74g, 70%) as an oil (identical to lit., 63).

\((IR, 2S, 5R)-5\text{-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl chloroacetate 290.}\)

To a three necked round bottomed flask fitted with reflux condenser and magnetic stirrer bar under nitrogen was added \(N, N\)-dimethylaniline (8.0g, 66 mmol) and 8-phenylmenthol 288&289 (15.34g, 66 mmol) in ether (30 ml). The stirred mixture was cooled to 0°C and a solution of chloroacetyl chloride (8.21g, 8.8 ml, 73 mmol) in ether (30 ml) was added at such a rate that the temperature remained at 0°C. The reaction mixture was stirred at 0°C for 1 hr and then allowed to warm to room temperature during which time the \(N,N\)-dimethylaniline hydrochloride precipitated. The mixture was then refluxed for 3 hrs and then concentrated. Water (30 ml) and dichloromethane (30 ml) were added to dissolve the white residue. The layers were separated and the organic layer washed with water (1x50 ml) and then sodium hydrogencarbonate solution (3x50 ml). The organic layer was then concentrated to give a viscous oil which crystallised when triturated with 90% aqueous ethanol. The crystals were filtered off to give chloroacetate 290 as a mixture of diastereomers (19.75g, 96%). Two fractional crystallisations from ethanol, gave enantiomerically and diastereomerically pure chloroacetate 290, (8.90g, 43%), m.p.

81-83°C, \([\alpha]_D^{20}=+18.9^\circ \text{ (CCl}_4, c \ 2.24)\) (lit 63, \([\alpha]_D=+22.4^\circ \text{ (CCl}_4, c \ 2.29)\) (identical to lit., 63).

\(\nu_{\text{max}} / \text{cm}^{-1} (\text{CHCl}_3) 1754 (\text{C}=\text{O}) \text{ and } 1185 (\text{COC}), \delta_2 \text{H} 7.05-7.15 (5\text{H}, \text{m, Ph}), 4.64-4.77 (1\text{H, dt, } J\text{ 4.5 & 10.7, CHOCO}), 3.04 \text{ and } 3.43 ((\text{AB doublet, } 2\text{H, } J\text{ 15.0, } \text{CH}_3\text{Cl}), 0.63-1.93 (8\text{H, m, cyclohexane}), 0.71 (3\text{H, d, } J\text{ 7.2, } \text{CH}_3\text{CH}), 1.11 (3\text{H, s, CPhCH}_2\text{)} \text{ and } 0.99 (3\text{H, s, CPhCH}_2\text{)} ; \delta_2 \text{C} 166.48 \text{ (s), } 151.70 \text{ (s), } 127.97 \text{ (d), } 125.24 \text{ (d), } 125.09 \text{ (d), } 75.74 \text{ (d), } 50.19 \text{ (d), } 41.43 \text{ (t), } 40.75 \text{ (t), } 39.36 \text{ (s), } 34.34 \text{ (t), } 31.21 \text{ (d), } 29.80 \text{ (q), } 26.12 \text{ (t), } 22.57 \text{ (q) and } 21.75 \text{ (q); } m/z, 214 (\text{M}^+, 5\%), 119 (100), 118 (16), 91 (32) \text{ and } 41 (11).
(IR, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol 288.

In a 500 ml round bottomed flask with a reflux condenser and a magnetic stirrer bar was placed phenylmenthol chloroacetate 290 (9.78 g, 32 mmol) and sodium hydroxide (2.54 g, 63 mmol) in ethanol-water (230 ml) (23:3). This solution was heated to reflux for 2 hrs. The solution was concentrated to ~50 ml and water (200 ml) and ether (100 ml) were added. The layers were separated and the aqueous layer saturated with salt and extracted with ether (3×50 ml). The organic layers were combined, dried and concentrated. Kugelrohr distillation (b.p. 105-115°C/0.01 Torr) of the oil gave phenyl menthol 288 (6.63 g, 90%) as an oil, \([\alpha]_D^{24} = -24.1^\circ\) (ethanol, \(c = 1.85\)), (lit., \(\delta^13 [\alpha]_D = -26.4^\circ\) (ethanol, \(c = 1.97\)).

\(\nu_{\text{max}}\) cm\(^{-1}\) (CHCl\(_3\)) 3570 and 3420 (OH); \(\delta_H\) 6.97-7.46 (5H, m, Ph), 3.34 (1H, d, J 4.1 & 10.1, CHOH), 0.64-2.06 (8H, m, ring protons), 0.76 (3H, d, J 4.6, CH\(_3\)CH), 1.12 (3H, s, CPhCH\(_3\)) and 1.25 (3H, s, CPhCH\(_3\)); \(\delta_C\) 151.31 (s), 128.41 (d), 125.77 (d), 72.89 (d), 54.09 (d, CHC(CH\(_3\))\(_2\)Ph), 45.37 (t), 39.79 (s), 34.87 (t), 31.50 (d, CHCH\(_3\)), 28.51 (q), 26.49 (t), 24.49 (q) and 22.04 (q); \(m/z\) 232 (M\(^+\), 2%), 119 (100), 118 (30), 105 (16), 91 (40) and 41 (17).

8-Phenylmenthol-1-\((N^\prime\)-hydroxy carbamate) 291.

To a stirred solution of phosgene in toluene (2.0 M, 1.86 g, 10.21 ml, mmol) at 0°C was added a solution of phenylmenthol 288 (3.63 g, 15.65 mmol) and triethylamine (1.90 g, 2.63 ml, 18.77 mmol) in toluene (15 ml). This solution was stirred for 1 hour at 0°C. Then hydroxylamine hydrochloride (3.26 g, 46.94 mmol), sodium carbonate (4.97 g, 46.94 mmol)
and water (15 ml) were added. The resulting mixture was stirred at 0°C for 1 hour then the layers were separated, the aqueous layer was saturated with salt and extracted with ethyl acetate (2x25 ml). The organic layers were combined, dried and concentrated to give the crude product 291. This was chromatographed on silica eluted with light petroleum-ethyl acetate (9:1) to give the desired product 291 (R<sub>r</sub> 0.12) as a thick gum (3.15 g, 69%), α<sub>D</sub> = -19.94° (CHCl<sub>3</sub>, c = 1.62).

υ<sub>max</sub> / cm<sup>-1</sup> (CHCl<sub>3</sub>): 3412m, 2960m, 2926m and 1725s (C=O); δ<sub>H</sub> 7.10 (5H, m, Ph), 6.16 (1H, br s, NHOH), 4.50 (1H, dt, J 4.4 & 10.7, CHOCO), 0.65-1.88 (8H, m, cyclohexane), 0.67 (3H, d, J 6.4, CHCH<sub>3</sub>), 1.02 (3H, s, CPhCH<sub>2</sub>) and 1.11 (3H, s, CPhCH<sub>3</sub>); δ<sub>C</sub> 158.55 (s), 152.30 (s), 127.85 (d), 125.41 (d), 124.76 (d), 76.24 (d, CHCO), 50.95 (d, CHC(CH<sub>3</sub>)<sub>2</sub>Ph), 41.67 (t), 39.37 (s), 34.40 (t), 31.18 (d), 28.93 (q), 26.21 (t), 23.10 (q) and 21.74 (q); m/z 230 (0.4%), 215 (M<sup>+</sup>-76; CH<sub>2</sub>NO<sub>3</sub>, 3), 120 (13), 119 (100), 118 (23), 105 (27), 91 (42) and 41 (15).

8-Phenylmethoxy carbonyl)-(-SR)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene 293a&amp;b.

![Chemical structure of 291 and 293](image)

Followed General Procedure B at -78°C, using oxalyl chloride (0.83 ml, 1.66 mmol, 2.0 M), dimethyl sulfoxide (0.26 g, 0.24 ml, 3.26 mmol), hydroxycarbamate 291 (0.45 g, 1.55 mmol), cyclopentadiene (0.31 g, 0.38 ml, 4.64 mmol) and triethylamine (1.06 ml, 7.56 mmol) to give the crude product 293a&amp;b (0.52g, 91%, d.r. 7:1:1). This was chromatographed on silica eluted with light petroleum-ethyl acetate (85:15) to give a mixed fraction (0.14g, 24%) of both diastereomers 293a&amp;b (R<sub>r</sub> 0.24 and R<sub>r</sub> 0.19) in 1:1 ratio and the major diastereomer 293a (R<sub>r</sub> 0.19) (0.33g, 57%), m.p. 61-64°C (hexane), [α]<sub>D</sub> = -54.2° (CHCl<sub>3</sub>, c 0.92). Total product 293a&amp;b (0.47g, 82%).

(Found: C, 74.42; H, 8.29; N, 4.02; M<sup>+</sup>, 355.2170. C<sub>22</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub> requires C, 74.36; H, 8.17; N, 3.94; M<sup>+</sup>, 355.2147); υ<sub>max</sub> / cm<sup>-1</sup> (CHCl<sub>3</sub>): 2962s and 1720s (C=O); δ<sub>H</sub> (Major diastereomer) 7.00-7.09 (5H, m, Ph), 5.96-6.15 (2H, dm, 2 olefinic protons), 4.90 (1H, br s, 1 bridgehead), 4.43 (1H, dt, J 4.2 & 10.7, CHOCO), 3.77 (1H, br s, 1 bridgehead H), 0.53-1.86 (10H, m, ringprotons), 0.63 (3H, d, J 6.4, CHCH<sub>3</sub>) 0.98 (3H, s, CHCH<sub>3</sub>) and 1.08 (3H, s, CHCH<sub>2</sub>)δ<sub>C</sub> (Major diastereomer) 158.06 (s, C=O),
Section 3 Experimental

151.68 (s), 134.04 (d, olefin), 132.60 (d, olefin), 127.83 (d, 2xCH), 125.45 (d, 2xCH), 124.74 (d), 83.37 (d, bridgehead), 76.78 (d, CHOCO), 64.18 (d, bridgehead), 50.91 (d, CHC(CH3)Ph), 47.84 (t), 41.57 (t), 39.61 (s), 34.50 (t), 31.13 (d), 27.36 (q), 26.60 (t), 25.51 (q) and 21.75 (q); δH (Minor diastereomer) 7.00-7.25 (5H, m, Ph), 6.31 (2H, br s, olefin), 5.13 (1H, br d, bridgehead), 4.84 (1H, s, bridgehead), 4.73 (1H, dt, J 4.3 & 10.6, CHOCO), 0.67-1.95 (10H, m, ring protons), 0.75 (3H, d, J 5.0, CHCH3), 1.21 (3H, s, CHCH3) and 1.31 (3H, s, CHCH3); δc 158.64 (s), 150.54 (s), 134.88 (d olefin), 133.20 (d olefin), 127.97 (d, 2xCH, Ph), 125.64 (d, 2xCH, Ph), 125.24 (d, Ph), 83.69 (d, bridgehead), 77.54 (d, CHOCO), 64.61 (d), bridgehead), 50.28 (d, CHCMe2Ph), 48.13 (t, adduct), 41.89 (t), 40.24 (s), 34.34 (t), 31.27 (d), 29.67 (q), 27.16 (t), 24.03 (q) and 21.71 (q); m/z 311 (M+, 0.1%), 119 (69), 106 (10), 105 (100), 91 (44), 66 (17), 55 (18), 41 (20) and 39 (11).

8-Phenylmenthylxocarbonyl[1R,2R]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 294a&b.

Followed General Procedure B at -78°C, using oxaly chloride (0.83 ml, 1.66 mmol, 2.0 M), dimethyl sulfoxide (0.26 g, 0.24 ml, 3.33 mmol), hydroxycarbamate 291 (0.44 g, 1.51 mmol), cyclohexadiene (0.36 g, 0.43 ml, 4.54 mmol) and triethylamine (1.06 ml, 7.56 mmol) to give the crude product 294a&b (0.49g, 88%, d.r. 6:1:1). This was chromatographed on silica eluted with light petroleum-ethyl acetate (4:1) to give the product 294a (R, 0.30) (0.33g, 59%), m.p. 90-91°C (hexane), [α]D = -25.2° (CHCl3, c 1.26).

(Found: C, 74.97; H, 8.54; N, 3.88; M', 369.2287. C26H35NO3, requires C, 74.80; H, 8.40; N, 3.79; M, 369.2304; νmax cm⁻¹ (CHCl3) 2962m and 1720s (C=O); δH (major diastereomer) 7.20 (5H, m, Ph), 6.39 (2H, m, olefinic), 4.59 (2H, m, CHOCO & 1 bridgehead), 3.77 (1H, br s 1 bridgehead), 0.75-2.14 (21H, m, ring & CH, protons), 0.78 (3H, d, J 6.4, CHCH3), 1.13 (3H, s, CPhCH3), & 1.22 (3H, s, CPhCH3); δc (minor diastereomer, observable signals) 1.16 (3H, s, CPhCH3) and 1.20 (3H, s, CPhCH3); δc (major diastereomer) 157.80 (s), 131.90 (d, olefin), 131.28 (d, olefin), 127.88 (d, 2xCH), 125.38 (d, 2xCH), 124.80 (d), 76.67 (d, CHOCO), 70.75 (d, bridgehead), 50.73 (d, CHCMe2Ph), 49.65 (d, bridgehead), 41.64 (t), 39.66 (s), 34.54 (t), 31.15 (d), 26.69 (t), 23.63 (t),
21.75 (q) and 20.13 (t); \textit{m/z} 369 (M⁺, 1.7%), 119 (63), 111 (27), 105 (100), 91 (35), 80 (10), 79 (31), 55 (17) and 41 (16).
References

References

which was corrected in H. Braun, R. Charles, G. Kresze, M. Sabuni and J. Winkler,
which was corrected in H. Braun, R. Charles, G. Kresze, M. Sabuni and J. Winkler,
1129.
32. A. Defoin, J. Pires, I. Tissot, T. Tschamber, D. Bur, M. Zehnder and J. Streith,
1994, 5, 1535.
References

### Table 3.1.1. Stereochemical parameters for compounds 1 - 6 (Å, °)

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<td>φ₂</td>
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<td>C - C</td>
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### Notes:

1. The *trans* stereochemistry of the 1, 2-substituted cyclohexane ring is defined by the Ph-C-C-R torsion angle φ₁. Compounds 1, 2, 3, 4 & 6 crystallise in achiral space groups. The enantiomers shown in Figures 3.1.1 - 3.1.6 and described here have φ₁ ≈ -60°.

2. The O-N-C=O torsion angle φ₂ defines the relationship of the nitroso and carbonyl oxygen atoms.

3. The configuration of the dihydro-oxazine ring system is defined by torsion angle φ₃ = N-O-C₁-C₆ where C₆ is a methylene carbon derived from the diene.

4. Each compound has a C=C double bond in the dihydro-oxazine ring. Here its length is compared with CH₂-CH₂ distances, where both CH₂ are derived from hexa-1, 3-diene.

5. ΣN is the sum of valency angles subtended at the oxazine nitrogen atom.
Table 3.1.2. Characteristics of the hydrogen bonds (Å) and angles (°) in 1 and 2

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<th>H...A</th>
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Symmetry code: (i); -x, 2-y, 1-z

Table 3.1.3. Selected bond lengths in the ONC(O)R unit of 1 - 6 (Å)*

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* In this table the bonds referred to by the letters a, b, c, d, e, f & g are defined as follows.
3.1.3 Experimental

Crystallographic data for 1 - 6 are summarised in Table 3.1.4 - 3.1.6. The fractional co-ordinates for non-hydrogen atoms for compounds 1 - 6 are given in Table 3.1.7. The experimental and computational procedures used have been described in Section 1. All structures were solved by direct methods (Sheldrick, 1985). For compound 1 eight reflections suspected of serious systematic error (Δ/σ>8) were excluded from the refinement. For 2 and 3 a full hemisphere (two asymmetric units) of data was collected. The crystal of 3 decomposed during the experiment and data with θ > 24.5° were excluded from the refinement because decomposition was substantial at high angles. The final full matrix least squares refinement on F included anisotropic displacement parameters for all elements except hydrogen. Additional material available in Volume 2 includes hydrogen atom co-ordinates and observed and calculated structure factors. All calculations were performed with the GX package (Mallinson & Muir, 1985).

Table 3.1.4. Crystallographic details of the structure analyses of compounds 1 and 2

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<td>90.946(6)</td>
</tr>
<tr>
<td>V Å³</td>
<td>1598.6(5)</td>
<td>3376.6(5)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>F(0 0 0)</td>
<td>640</td>
<td>1344</td>
</tr>
<tr>
<td>D calc g cm⁻³</td>
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<td>1.229</td>
</tr>
<tr>
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<td>295</td>
</tr>
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<td>colourless, needle</td>
</tr>
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<td>0.54 x 0.29 x 0.15</td>
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<tr>
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<td>15 reflections 5.4°&lt;θ&lt;13.2</td>
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<td>0 → 6</td>
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<td>-18 → 18</td>
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<td></td>
<td>-19 → 20</td>
<td>-22 → 22</td>
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<td>0.071</td>
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<td>S</td>
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<td>2.4</td>
</tr>
<tr>
<td>Δρ max. and Δρ min. eÅ⁻³</td>
<td>0.30 → -0.28</td>
<td>0.25 → -0.20</td>
</tr>
<tr>
<td>Δc/Δmax.</td>
<td>0.024</td>
<td>0.023</td>
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<tr>
<td>Extinction coefficient</td>
<td>256(113)</td>
<td>588(97)</td>
</tr>
<tr>
<td>Property</td>
<td>Compound 3</td>
<td>Compound 4</td>
</tr>
<tr>
<td>--------------------------------</td>
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<tr>
<td>Formula</td>
<td>C$<em>{18}$H$</em>{21}$O$_3$N</td>
<td>C$<em>{13}$H$</em>{22}$O$_3$N</td>
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<td>monoclinic</td>
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<td>P2$_1$/c</td>
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<td>15.640(6)</td>
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<tr>
<td>b Å</td>
<td>9.591(1)</td>
<td>9.819(4)</td>
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<tr>
<td>c Å</td>
<td>15.470(2)</td>
<td>11.324(8)</td>
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<tr>
<td>β °</td>
<td>95.129(14)</td>
<td>109.81(6)</td>
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<td>V Å$^3$</td>
<td>1582.4(4)</td>
<td>1634.0(5)</td>
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<td>4</td>
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<td>F(0 0 0)</td>
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<td>colourless block</td>
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<td>25 reflections 12.4&lt;θ&lt;20.6</td>
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<td>0.80</td>
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<td>1108</td>
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<td>2.7 - 27.4</td>
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<td>Miller indices</td>
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<td>-10 → 10</td>
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<tr>
<td>k</td>
<td>0 → 11</td>
<td>0 → 12</td>
</tr>
<tr>
<td>l</td>
<td>0 → 17</td>
<td>-16 → 17</td>
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<tr>
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<td>1</td>
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<td>208</td>
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<td>R(F)</td>
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<td>0.045</td>
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<tr>
<td>R$_{w}$ (F)</td>
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<td>0.043</td>
</tr>
<tr>
<td>S</td>
<td>2.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Δρ$<em>{max}$ and Δρ$</em>{min}$ eÅ$^{-3}$</td>
<td>0.30 → -0.29</td>
<td>0.19 → -0.24</td>
</tr>
<tr>
<td>Δρ/σ$_{max}$</td>
<td>0.12</td>
<td>0.051</td>
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Table 3.1.6. Crystallographic details of the structure analyses of compounds 5 and 6

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<tr>
<th>Property</th>
<th>Compound 5</th>
<th>Compound 6</th>
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<tr>
<td>Formula</td>
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<td>C$<em>{39}$H$</em>{32}$O$_3$N</td>
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<tr>
<td>Formula wt</td>
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<td>297.4</td>
</tr>
<tr>
<td>Crystal system</td>
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<td>orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2$_1$</td>
<td>Pna2$_1$</td>
</tr>
<tr>
<td>a Å</td>
<td>6.0973(1)</td>
<td>21.1332(1)</td>
</tr>
<tr>
<td>b Å</td>
<td>20.1094(5)</td>
<td>12.7566(2)</td>
</tr>
<tr>
<td>c Å</td>
<td>9.1098(2)</td>
<td>5.9446(3)</td>
</tr>
<tr>
<td>β °</td>
<td>105.5(14)</td>
<td>-</td>
</tr>
<tr>
<td>V Å$^3$</td>
<td>1065.7(4)</td>
<td>1602.6(5)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>F(0 0 0)</td>
<td>402</td>
<td>640</td>
</tr>
<tr>
<td>D calc g cm$^{-3}$</td>
<td>1.154</td>
<td>1.232</td>
</tr>
<tr>
<td>T K</td>
<td>294</td>
<td>295</td>
</tr>
<tr>
<td>Crystal colour and habit</td>
<td>colourless plate</td>
<td>colourless plate</td>
</tr>
<tr>
<td>Crystal size mm</td>
<td>0.32 x 0.25 x 0.20</td>
<td>0.51 x 0.22 x 0.18</td>
</tr>
<tr>
<td>Cell: reflections used θ range(*)</td>
<td>25 reflections 8.3&lt;θ&lt;18.1</td>
<td>25 reflections 9.7&lt;θ&lt;19.1</td>
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<td>μ(Mo-Kα) cm$^{-1}$</td>
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<td>Unique reflections</td>
<td>1934</td>
<td>1544</td>
</tr>
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<td>894</td>
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<td>2.4 - 25.0</td>
<td>2.5 - 25.0</td>
</tr>
<tr>
<td>Miller indices h</td>
<td>0 → 7</td>
<td>0 → 7</td>
</tr>
<tr>
<td>k</td>
<td>0 → 23</td>
<td>0 → 15</td>
</tr>
<tr>
<td>l</td>
<td>-10 → 10</td>
<td>0 → 25</td>
</tr>
<tr>
<td>Decay in mean standard (%)</td>
<td>2</td>
<td>1.4</td>
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<td>0.038</td>
</tr>
<tr>
<td>R$_{w}$(F)</td>
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<td>0.042</td>
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<tr>
<td>S</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Δρ$<em>{max}$ and Δρ$</em>{min}$ eÅ$^{-3}$</td>
<td>0.10 → -0.13</td>
<td>0.15 → -0.16</td>
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<tr>
<td>Δ/σ$_{max}$</td>
<td>0.033</td>
<td>0.091</td>
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Table 3.1.7. Atomic fractional coordinates and equivalent isotropic displacement parameters (Å\(^2\)) for compounds 1 - 6

(a) compound 1

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<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.1041(3)</td>
<td>0.8712(3)</td>
<td>0.4637(2)</td>
<td>0.053</td>
</tr>
<tr>
<td>O(2)</td>
<td>0.2658(3)</td>
<td>0.7109(3)</td>
<td>0.3268(2)</td>
<td>0.054</td>
</tr>
<tr>
<td>N(1)</td>
<td>0.2083(3)</td>
<td>0.7895(3)</td>
<td>0.4457(2)</td>
<td>0.042</td>
</tr>
<tr>
<td>N(2)</td>
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<td>0.7739(3)</td>
<td>0.3044(2)</td>
<td>0.040</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.1747(4)</td>
<td>0.7578(4)</td>
<td>0.3541(2)</td>
<td>0.035</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.3390(4)</td>
<td>0.8656(5)</td>
<td>0.4783(3)</td>
<td>0.053</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.3232(6)</td>
<td>0.9733(5)</td>
<td>0.4162(3)</td>
<td>0.072</td>
</tr>
<tr>
<td>C(13)</td>
<td>0.2274(7)</td>
<td>1.0448(5)</td>
<td>0.4285(4)</td>
<td>0.076</td>
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<tr>
<td>C(14)</td>
<td>0.1813(5)</td>
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<td>0.5008(3)</td>
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<tr>
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<td>0.9762(4)</td>
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(b) compound 2

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*Fixed to defined origin*

(c) compound 3
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(d) compound 4
(e) compound 5

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(f) compound 6

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**Fixed to define origin**