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

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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 $C(CH_3)_2Ph$ 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 recrystallisastion. 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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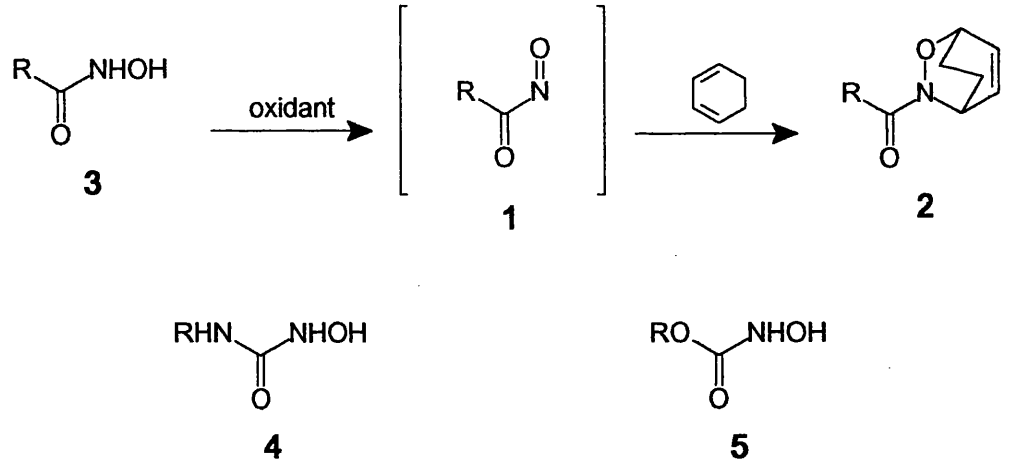
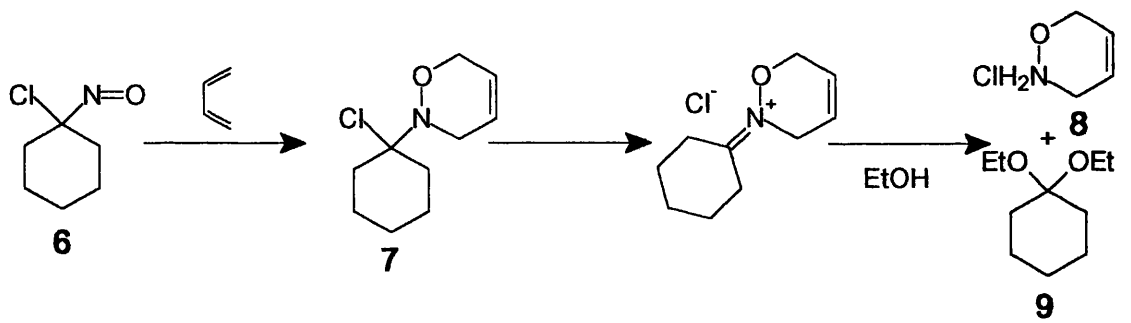
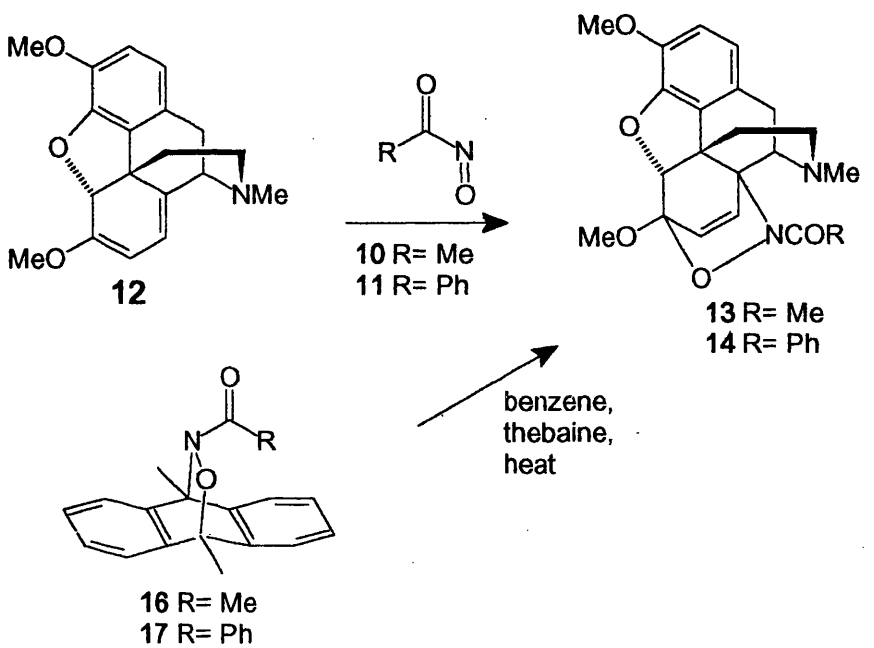


Scheme 1.



Scheme 2.



Scheme 3.

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 α-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. α-chloronitroso compounds *e.g.* α-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 α-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?

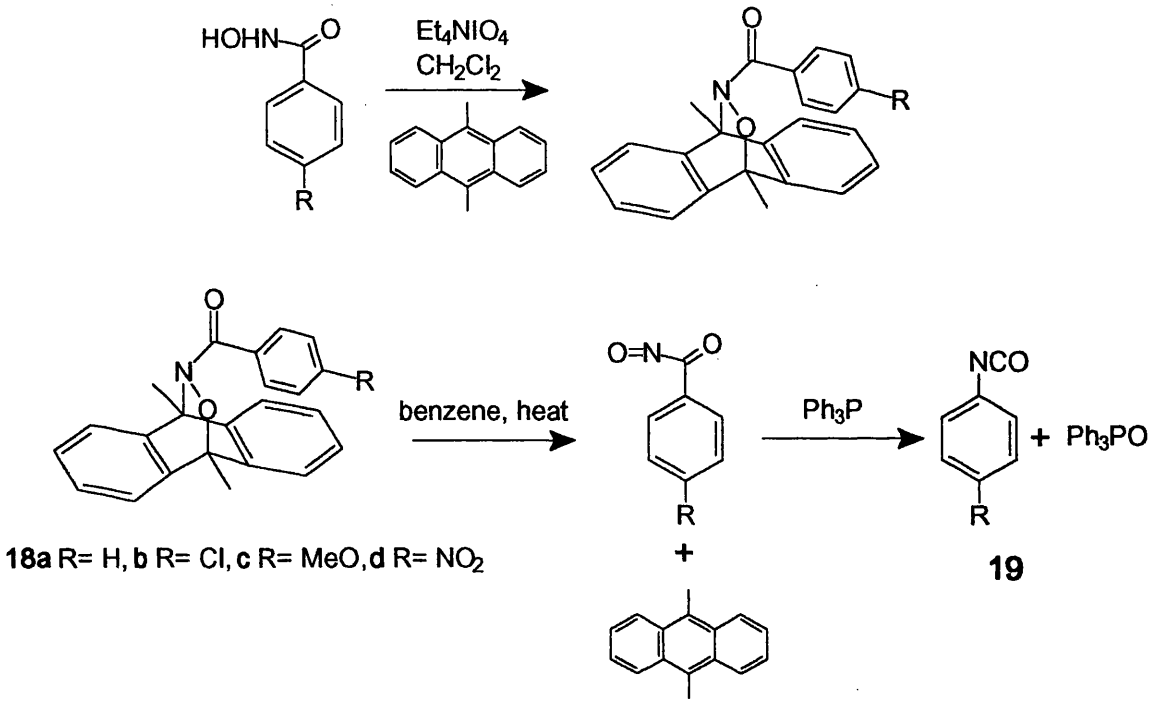
As the name suggests, these compounds have a nitroso group next to a carbonyl group and due to the electron withdrawing effect of the carbonyl group are very good dienophiles in hetero Diels-Alder reactions. They can react with a wide variety of dienes to form cycloadducts. Indeed, they are so reactive 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.

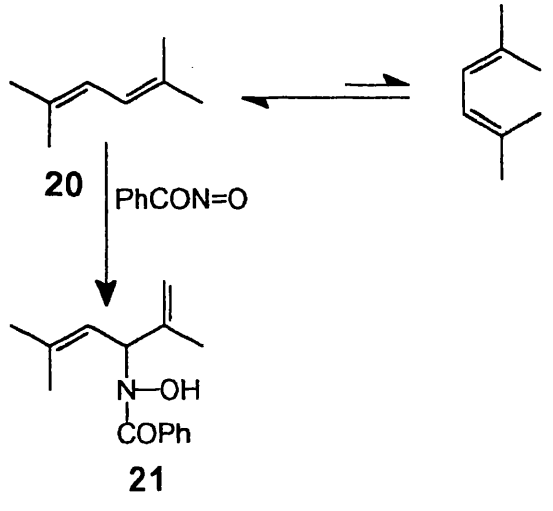
Hydroxamic acids can be oxidised in a variety of ways, the most common way is to use a periodate salt. The periodate can be present as either the sodium salt or since most of these reactions are carried out in non aqueous solvents, as an ammonium salt, which can be used as a phase transfer reagent. Ammonium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

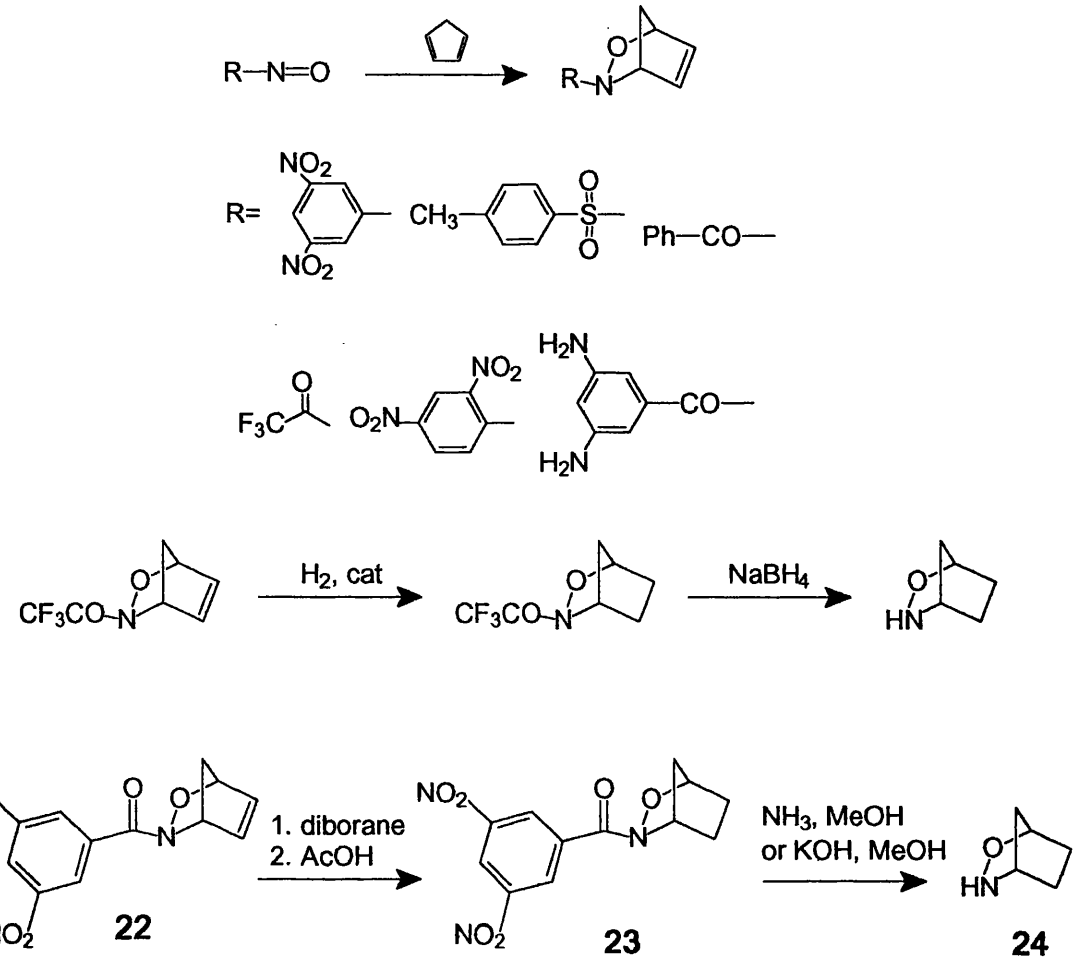


Scheme 4.

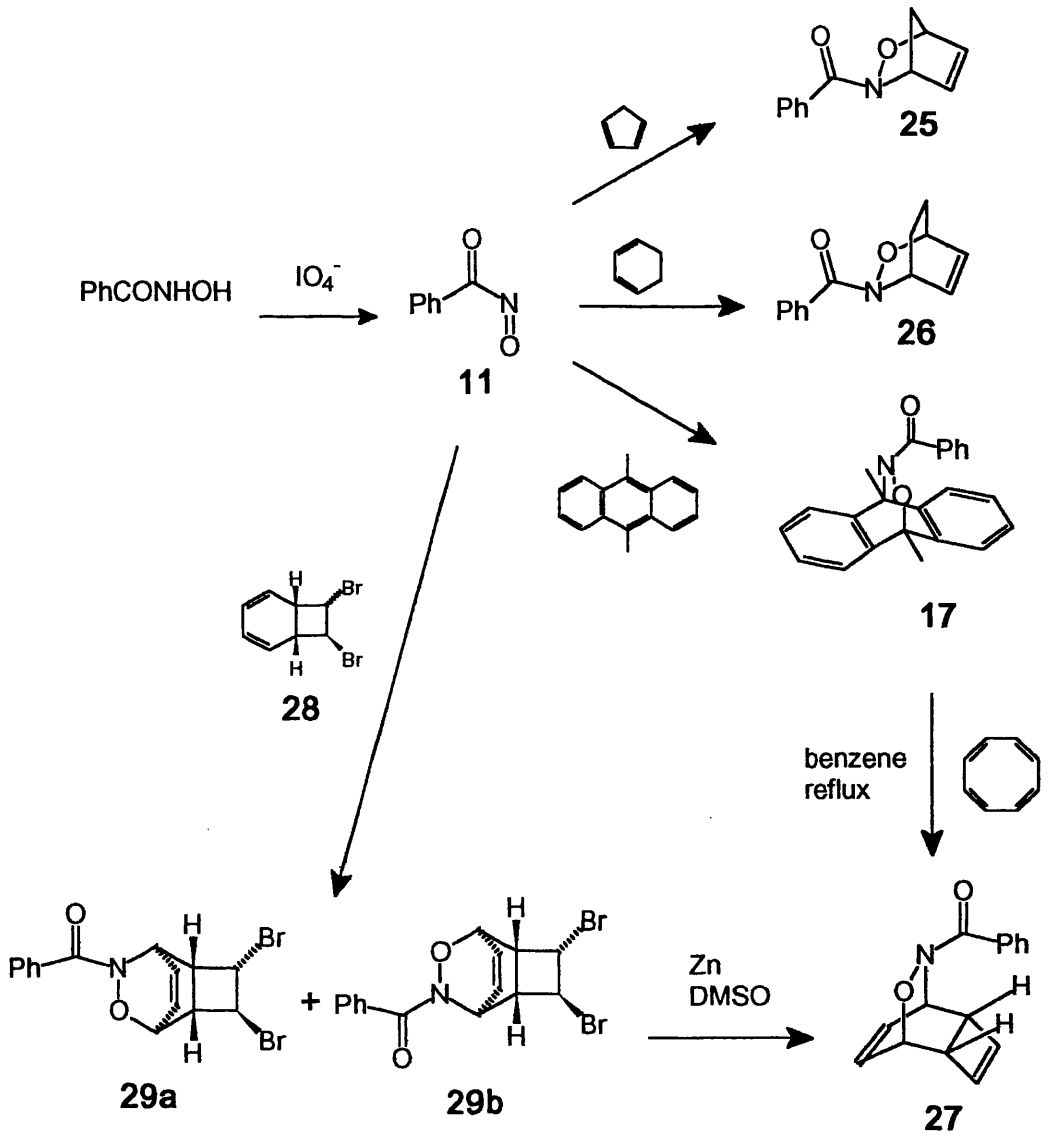


Scheme 5.

Section 1.1 Introduction to acylnitroso cycloadditions.



Scheme 6.



Scheme 7.

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[2] 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 dimethylanthracene 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.

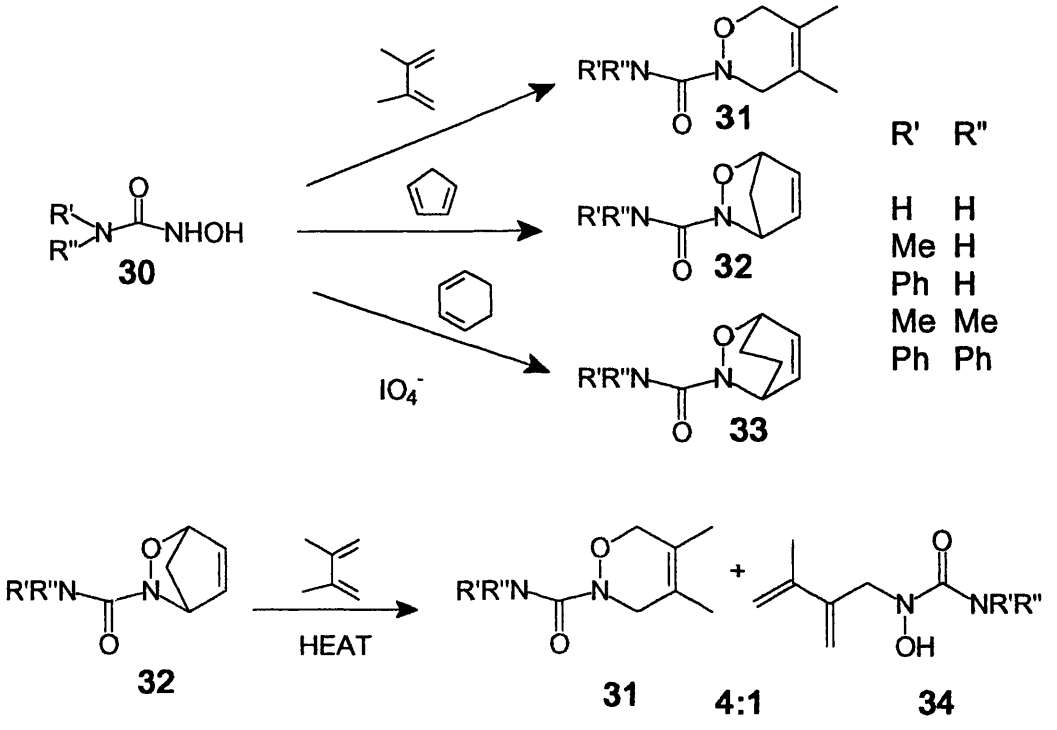
Further evidence for the presence of the acylnitroso compounds as intermediates came when Kirby *et al* heated the dimethylanthracene cycloadducts **18a-d** in the presence of triphenylphosphine resulting in the formation of the isocyanates **19a-d**. (Scheme 4).[3]

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**.

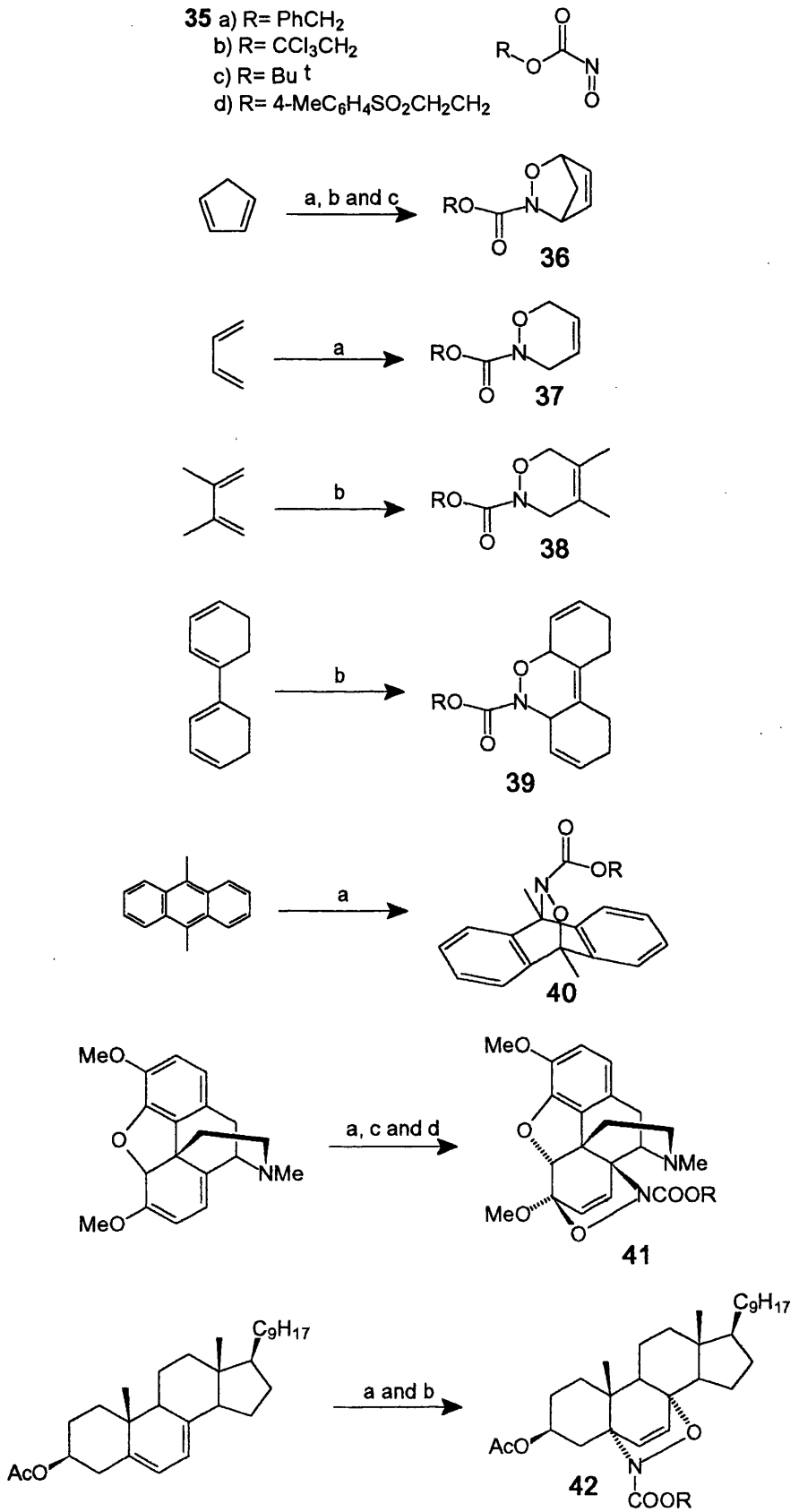
Just and Gutrone[4] have reported that a variety of dienophiles can react with cyclopentadiene to give the corresponding cycloadducts (Scheme 6). Hydrogenation of cycloadduct **22** gave oxazobicycloheptane **23** which was then hydrolysed under basic conditions to give the free amine **24**.

Kirby *et al*[5] 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.

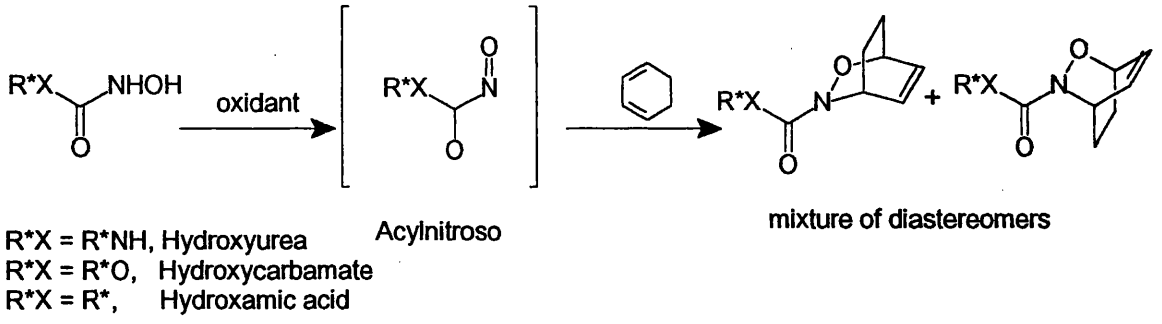


Scheme 8.


35 a) R= PhCH2
b) R= CCl3CH2
c) R= Bu t
d) R= 4-MeC6H4SO2CH2CH2
a, b and c
36
a
37
b
38
b
39
a
40
a, c and d
41
a and b
42

Scheme 9.

Section 1.1 Introduction to acylnitroso cycloadditions.



R*X = R*NH, Hydroxyurea
R*X = R*O, Hydroxycarbamate
R*X = R*, Hydroxamic acid

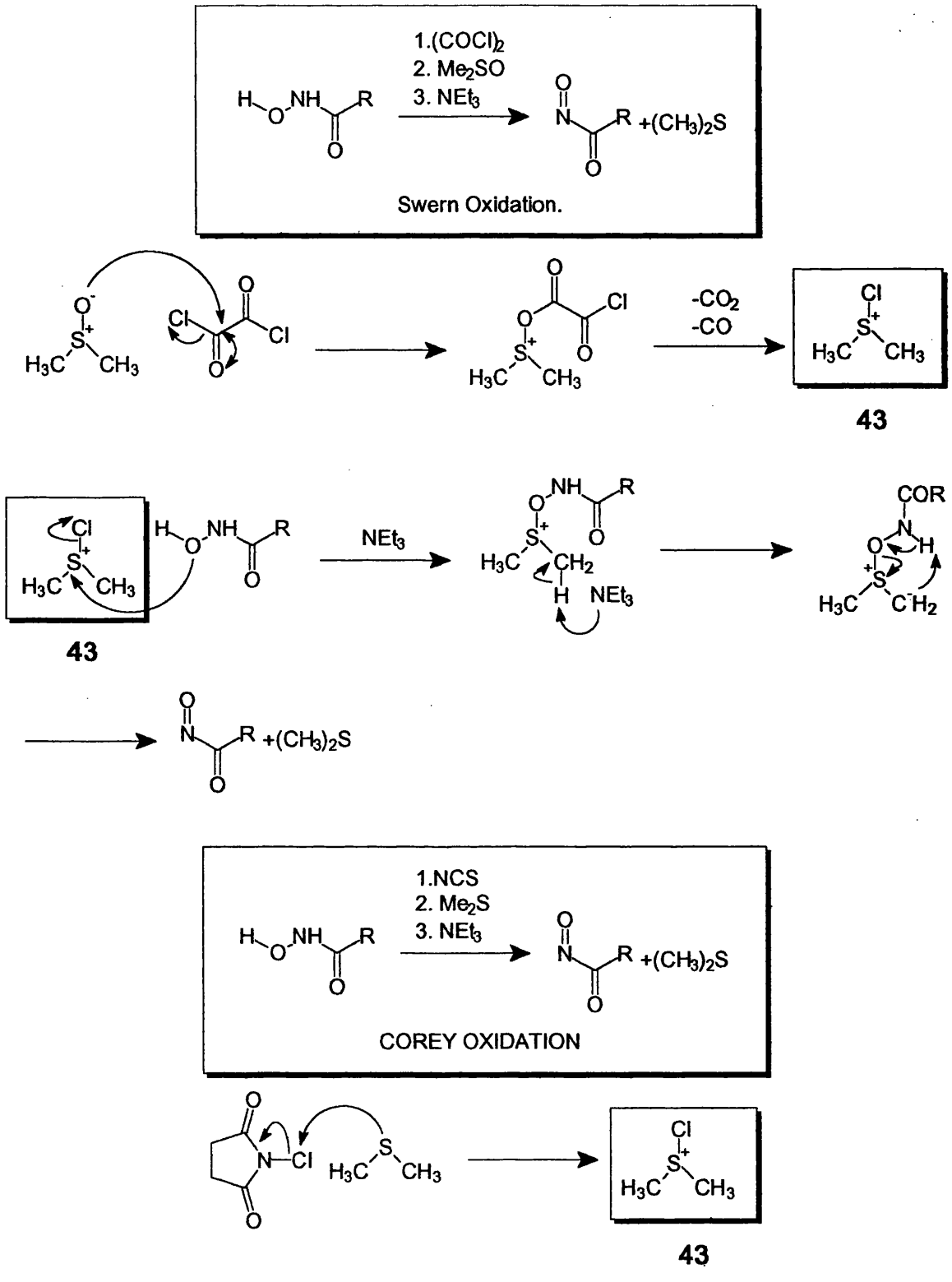
Scheme 10.

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*[7] 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 *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 **more** of the reaction proceeds *via* the lower energy transition state and **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.

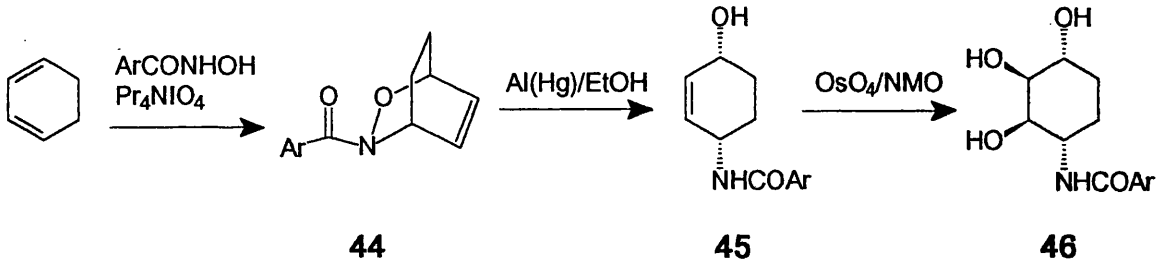
The Corey oxidation conditions can be used, *i.e.* *N*-chlorosuccinimide (NCS) and dimethyl sulfide or the Swern oxidation conditions *i.e.* dimethyl sulfoxide (DMSO) and oxalyl chloride (Scheme 11). In both of these methods, the triethylamine, which is added to


1.(COCl)2
2. Me2SO
3. NEt3
+(CH3)2S
Swern Oxidation.
-CO2
-CO
43
NEt3
43
1.NCS
2. Me2S
3. NEt3
+(CH3)2S
COREY OXIDATION
43

Scheme 11.

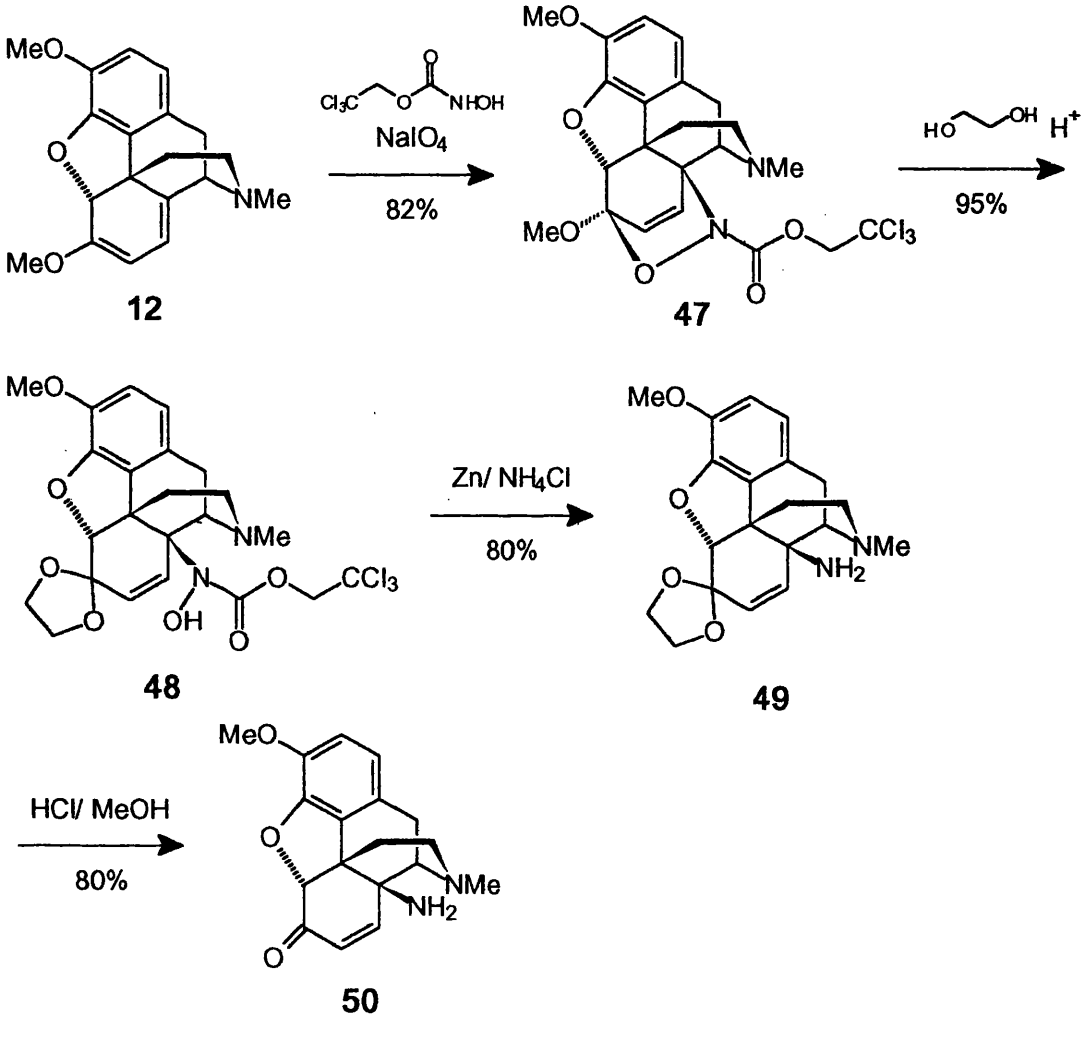
decompose the initially formed hydroxamic acid-sulfur compound, can be added very slowly using a syringe pump in an attempt to increase the diastereomeric induction.

Section 1.2 Use of acylnitroso derivatives in racemic synthesis.



44 **45** **46**

Scheme 12.



12 **47** **48** **49** **50**

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**

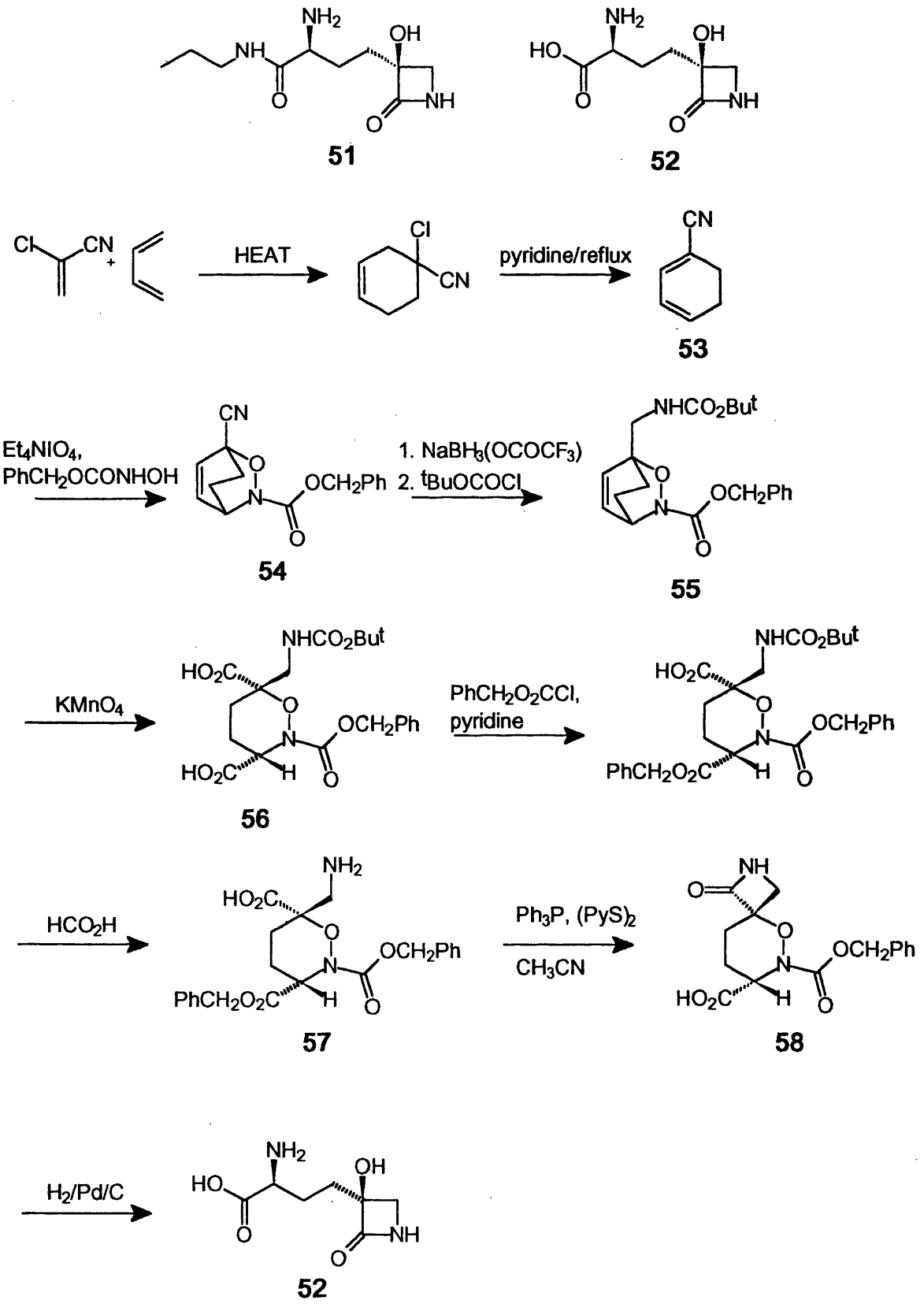
The first investigations into the synthetic utility of cycloadducts was carried out by Keck and Fleming[8] in which they investigated the synthesis of 1,4-aminoalcohol **45** (Scheme 12) which is an intermediate in the synthesis of lycoricidine **87** and other narcissus alkaloids. These alkaloids show 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.**

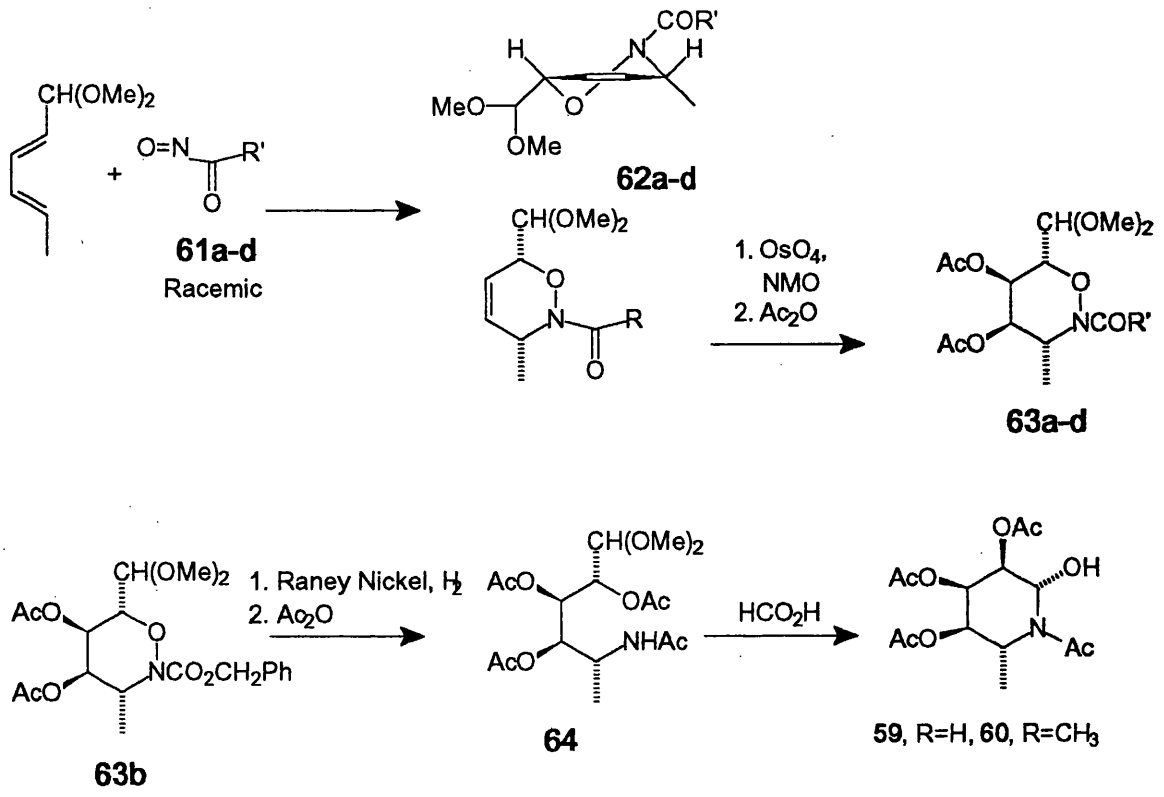
Kirby and McLean have prepared 14-β-aminocodeine **50**[9] from thebaine **12** using acylnitroso derivatives (Scheme 13). Trichloroethoxy acylnitroso dienophile reacted with thebaine to give the desired cycloadduct **47** as the only regioisomer in good yield. This was converted to the ethylene acetal **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 acylnitroso derivatives in racemic synthesis.



Scheme 14.

Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

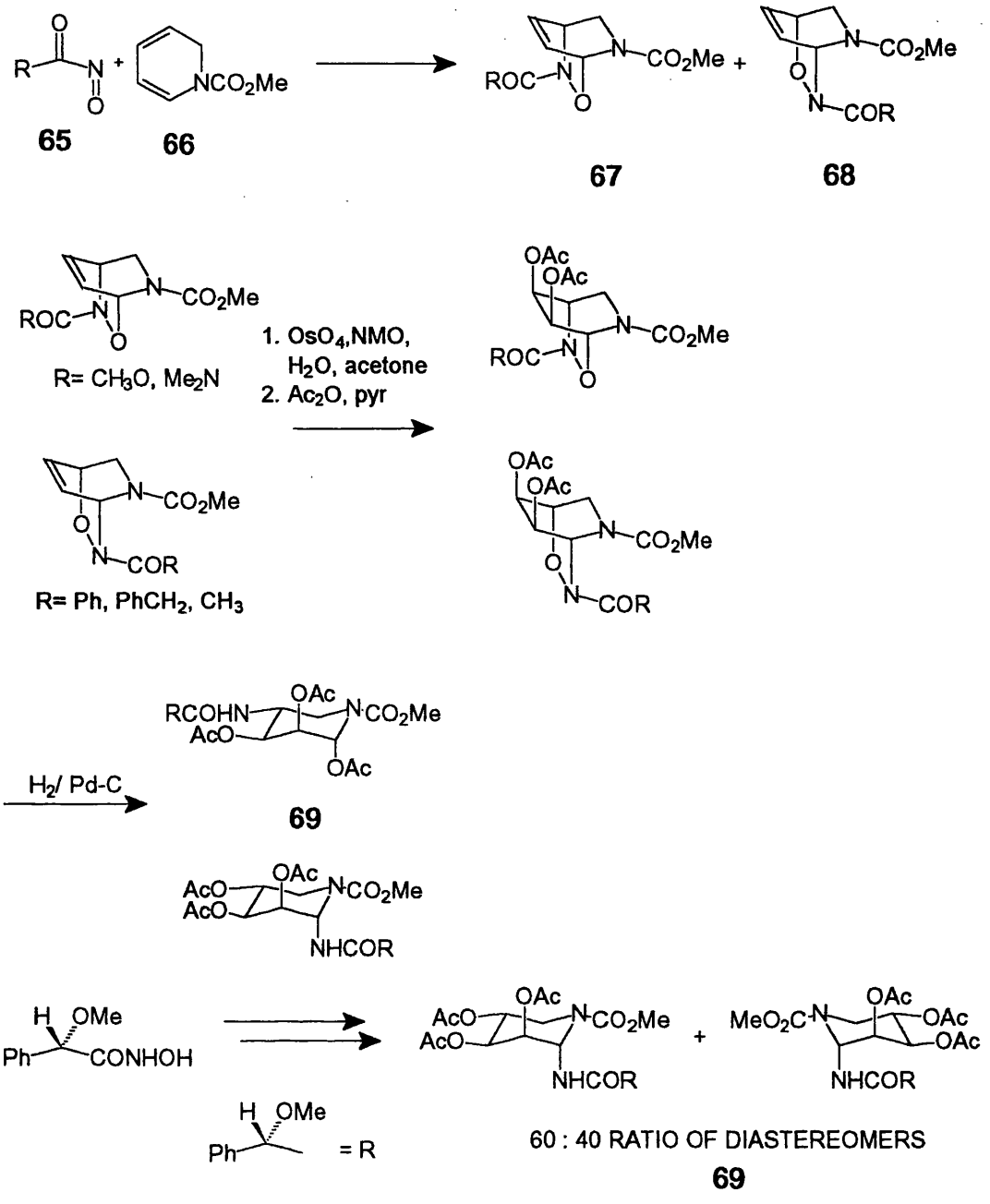


Scheme 15.

Table 1, Yields of cycloadducts **62** from acylnitroso dienophiles **61a-d**.

	R'	Total yield %
a	OMe	75
b	OCH_2Ph	85
c	CH_2Ph	40
d	Ph	23
e	NMe_2	<5

Section 1.2 Use of acylnitroso derivatives in racemic synthesis.



Scheme 16.

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

	R	Ratio **67: 68**	Yield %
a	Ph	0: 100	99
b	$PhCH_2$	0: 100	92
c	CH_3	0: 100	67
d	CH_3O	1:1	78
e	$PhCH_2O$	1: 1	100
f	Me_2N	3: 1	75
g	Ph-N=O	100: 0	80

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 β-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.

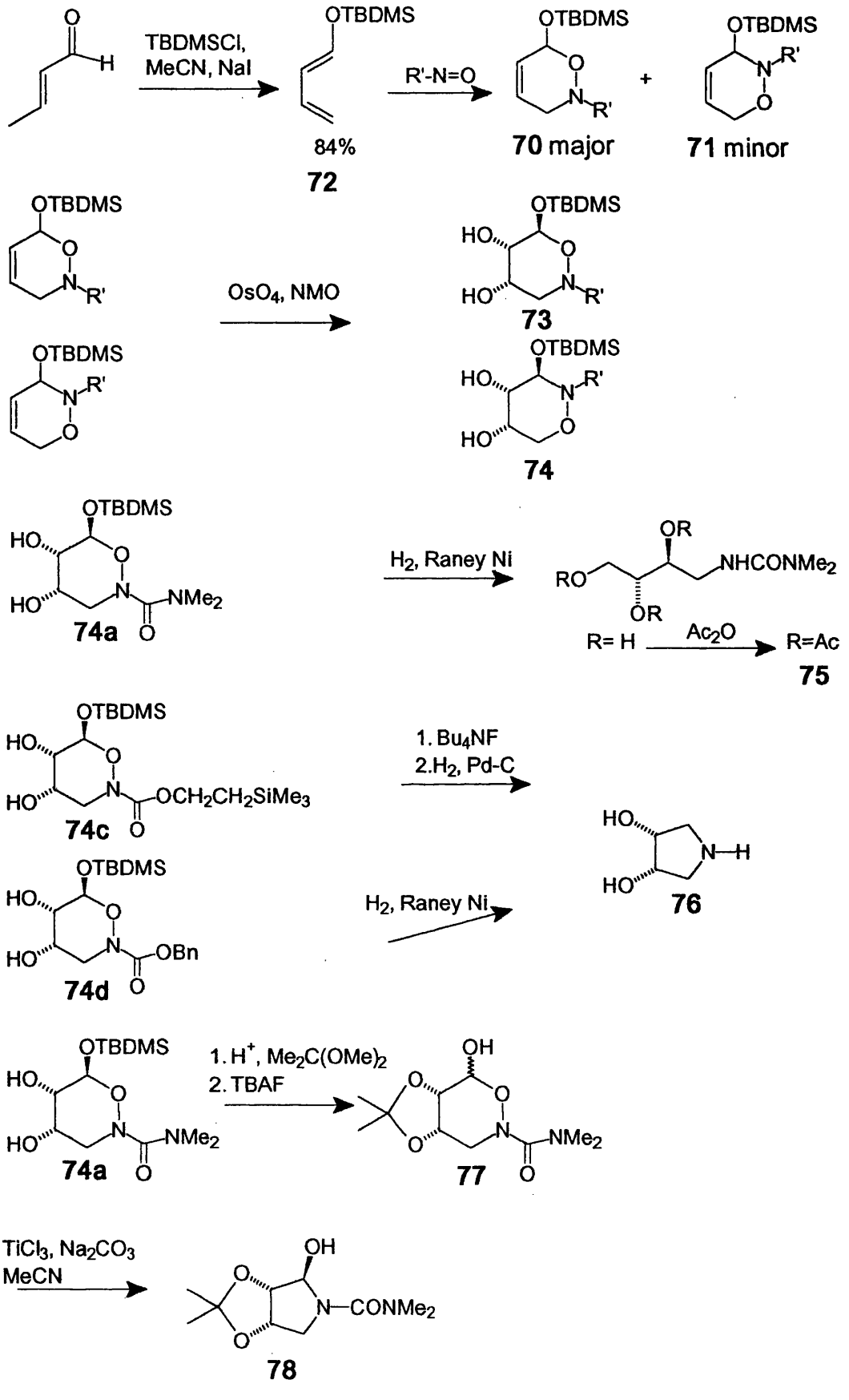
Section 1.2.5a Synthesis of aminodeoxyribose **59** and aminodideoxyallose **60** derivatives

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 disfavouring 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[12] **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.



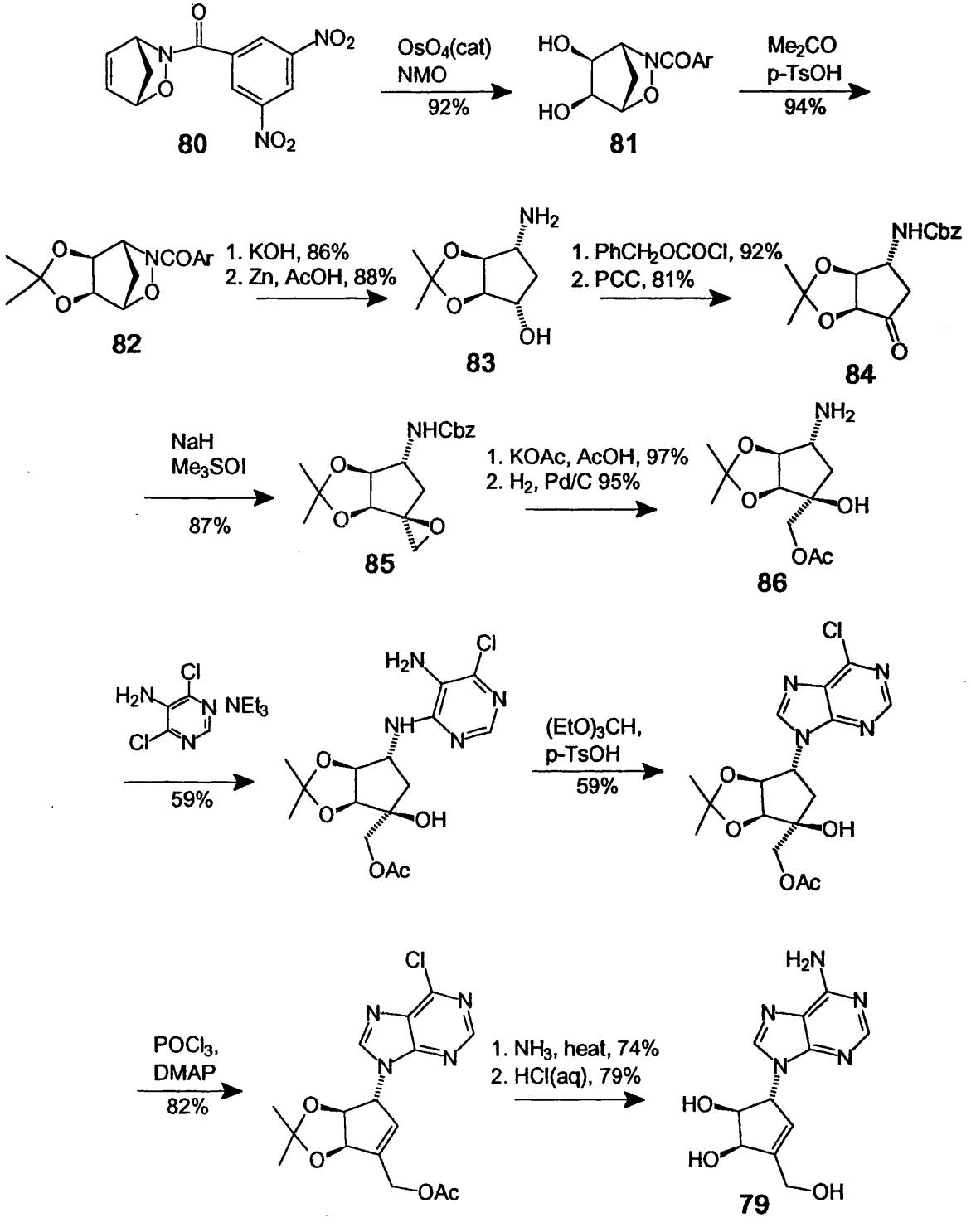
Scheme 17.

Section 1.2 Use of acylnitroso derivatives in racemic synthesis.

Table 3, Yields of **70&71** from different acylnitroso dienophiles.

	R'	Ratio **70**: **71**	Yield %
a	$CONMe_2$	100 :0	85
b	COPh	2.3: 1	66
c	$CO_2(CH_2)_2SiMe_3$	3: 1	97
d	CO_2CH_2Ph	1.5: 1	93
e	CO_2Me	1: 1	68
f	$COCH_2Ph$	1: 1	56
g	COMe	1: 1	79
h	SO_2Ph	100: 0	50
i	Ph	4: 1	100

Section 1.2 Use of acylnitroso 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 $PhCH_2$) gave only meta adducts **68a-c** whilst **65d&e** (R= OMe or OCH_2Ph) 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 16) 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

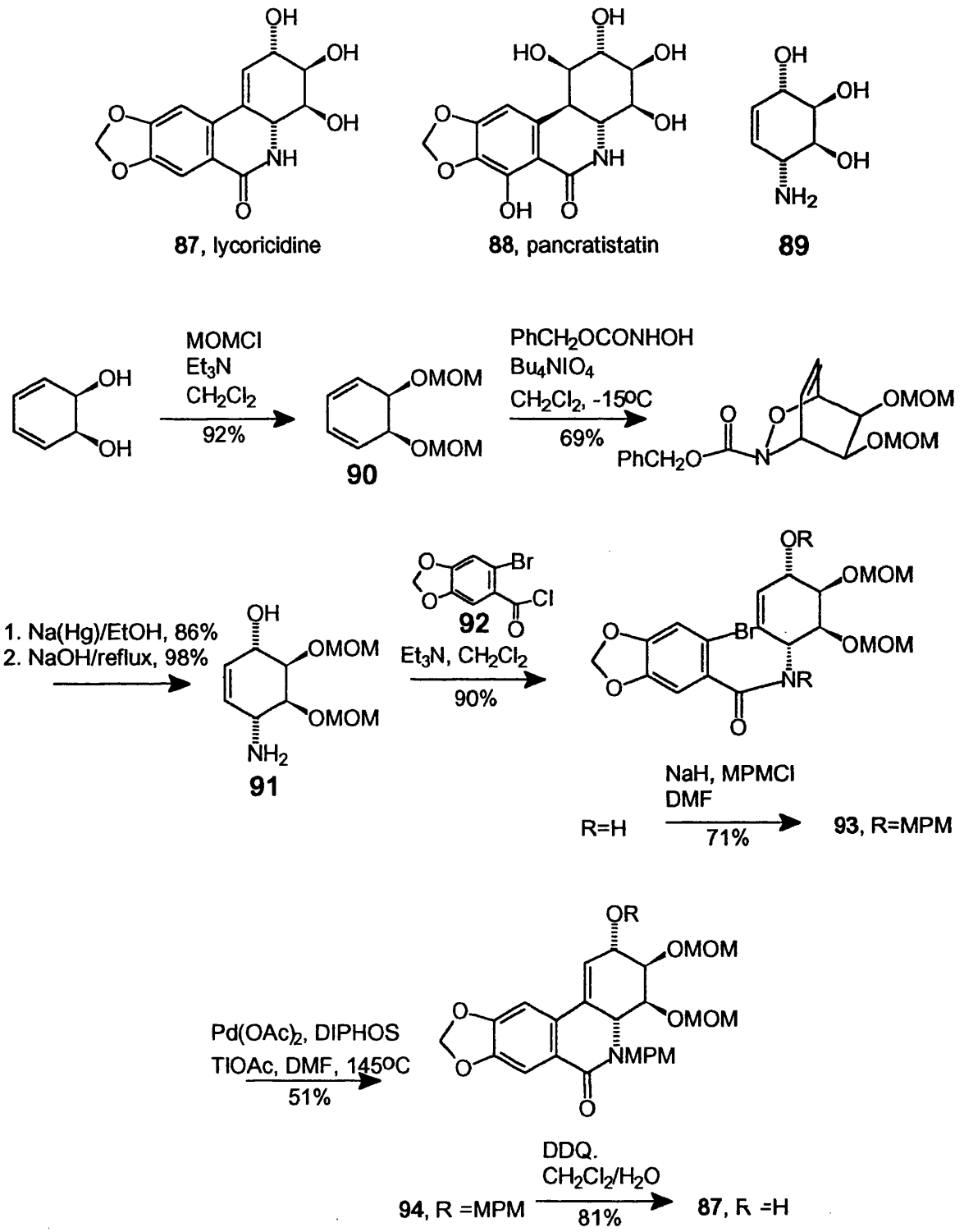
For the erythritol and erythrose series[13] (Scheme 17) the cycloadducts **70& 71** from the reaction of various dienophiles and 1-siloxy diene **72** were formed in the usual way. It was found that the ratio of regioisomers formed varied according to the R substituent on the dienophile, for example R= $CONMe_2$ and SO_2Ph 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 R' 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**.

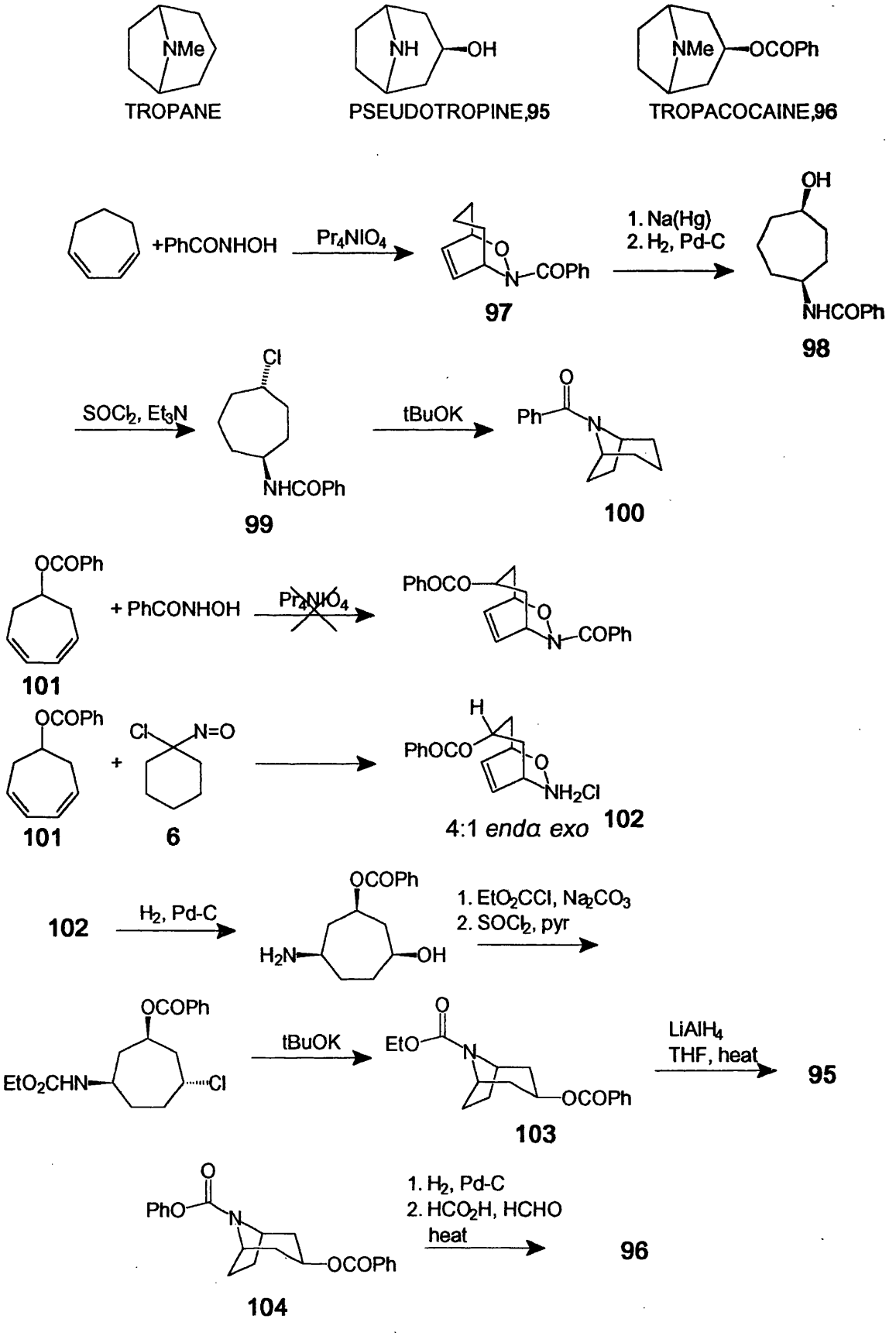
Retey *et al*, have investigated the synthesis, of neplanocin A[14] **79**, a carbacyclic analogue of adenosine which has antitumour activity (Scheme 18). They used as a starting material, the cycloadduct of 3,5-dinitrophenyl nitrosocarbonyl and cyclopentadiene, **80**. Dihydroxylation gave **81** as 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 Tso[15] 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 benzylnitrosoformate 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

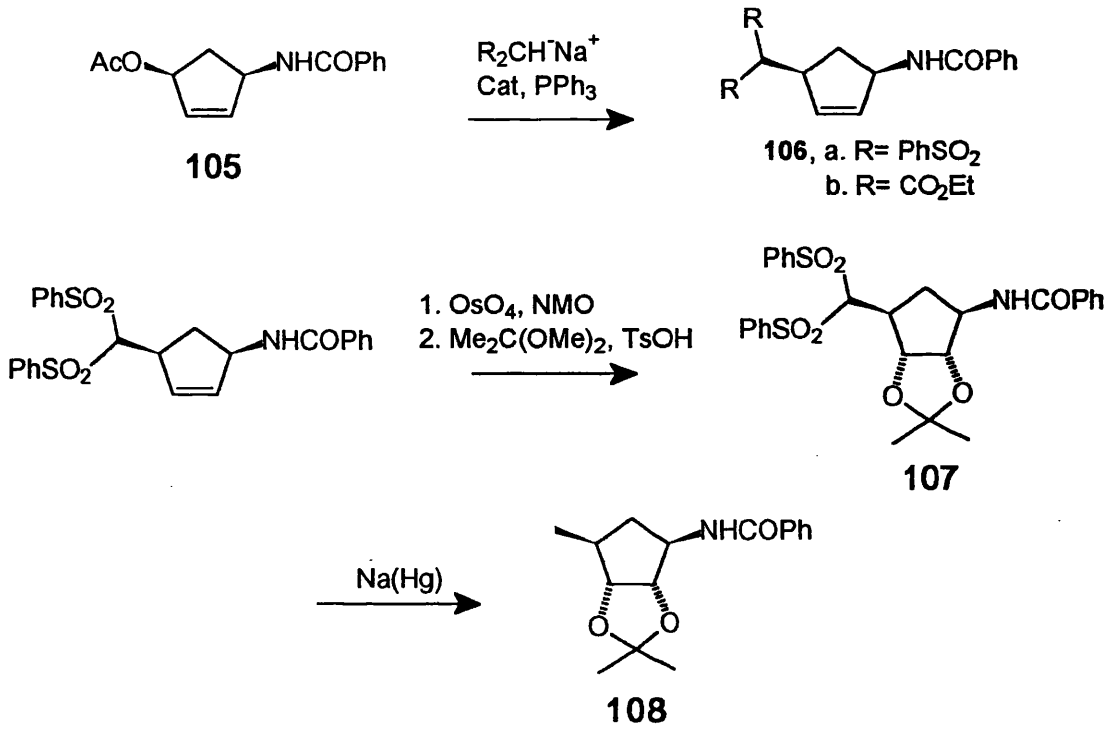
Kibayashi *et al*[16] have developed a synthesis for tropane alkaloids based on the hetero Diels-Alder reaction of acylnitroso derivatives (Scheme 20).

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**.

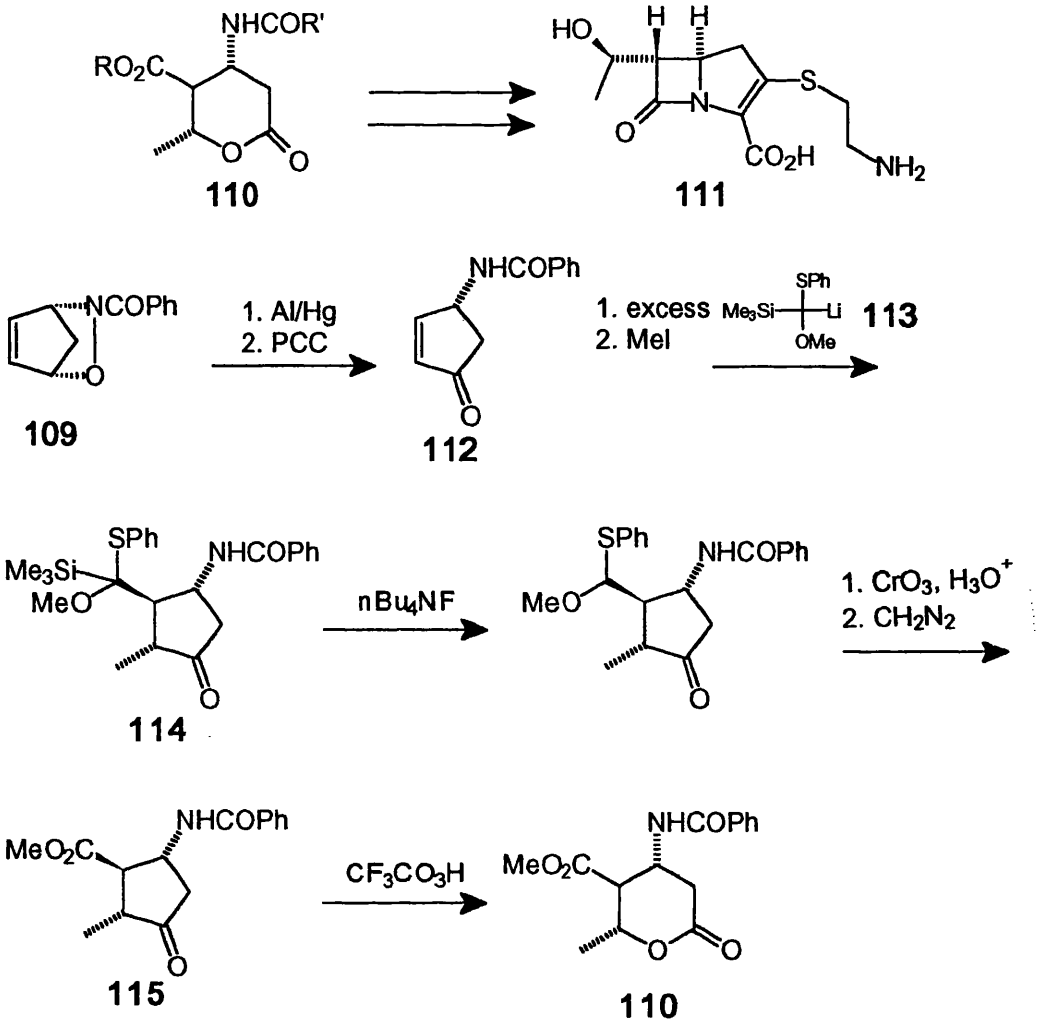
This method was slightly altered to synthesise pseudotropane **95** and tropacocaine **96**, since the phenacylnitroso dienophile did not form the expected cycloadduct with the cycloheptadiene **101**. Instead, the cycloaddition between 1-chloro-1-nitrosocyclohexane **6** and cycloheptadiene **101** 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 acylnitroso 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 nucleosides[17] (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 4. Yields of the reaction between the acetate **105** and anions catalysed by various catalysts.

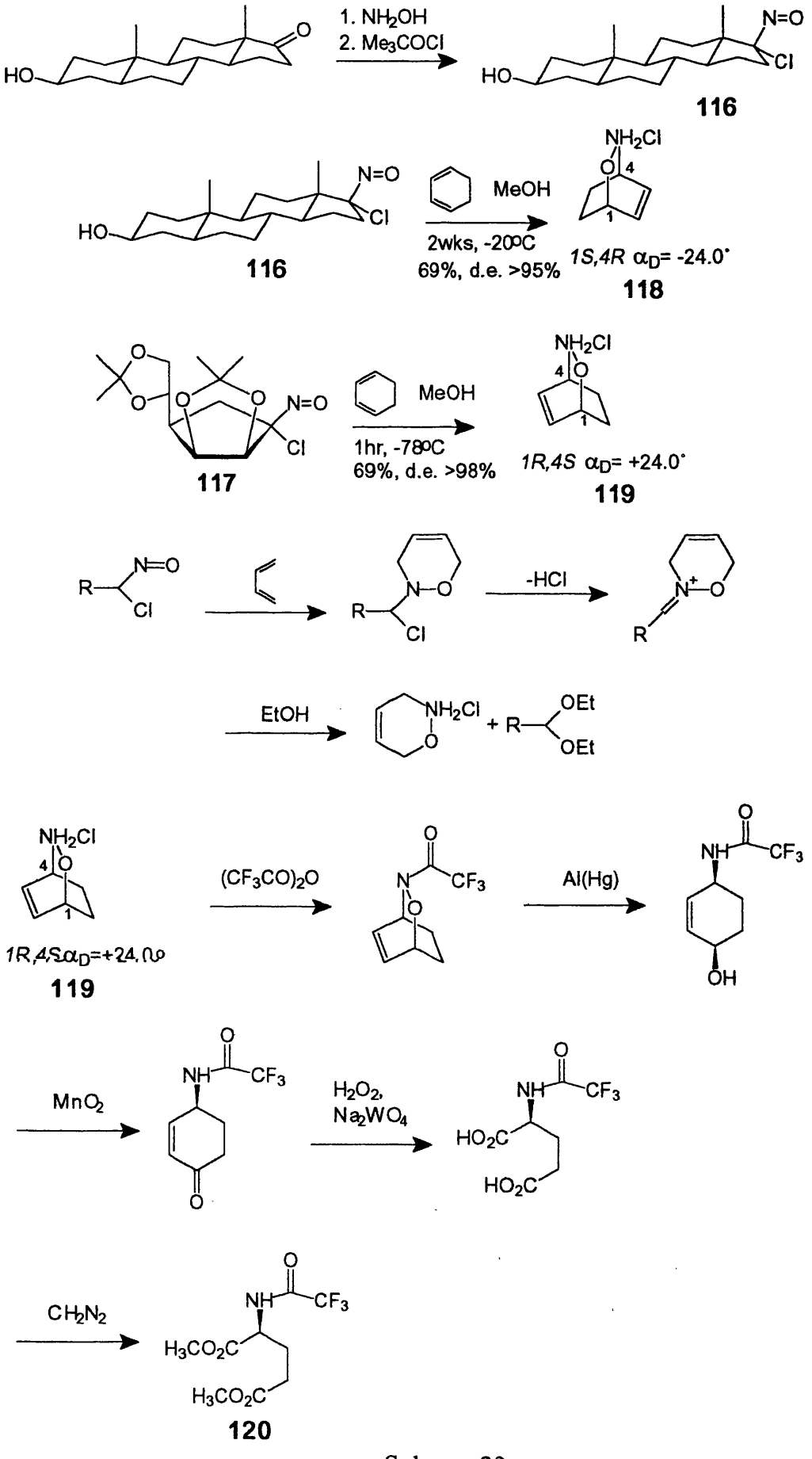
R_2CH^-	Catalyst	Yield of **106** (%)
$(PhSO_2)_2CH^-$	$Pd(Ph_3P)_4$	62
$(PhSO_2)_2CH^-$	$Pd(OAc)_2/Ph_3P$	88
$(PhSO_2)_2CH^-$	$Pd(Ph_3P)_2Cl_2$	81
$(EtO_2C)_2CH^-$	$Pd(Ph_3P)_4$	80
$(EtO_2C)_2CH^-$	$Pd(dba)_2$/dppe	68
$(EtO_2C)_2CH^-$	Pt(cod)/dppe	48

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 al*[18] 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 acylnitroso 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 acylnitroso 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 :-

d.e.= (a-b) / (a+b) where a and b are the relative amounts of A and B in the mixture.

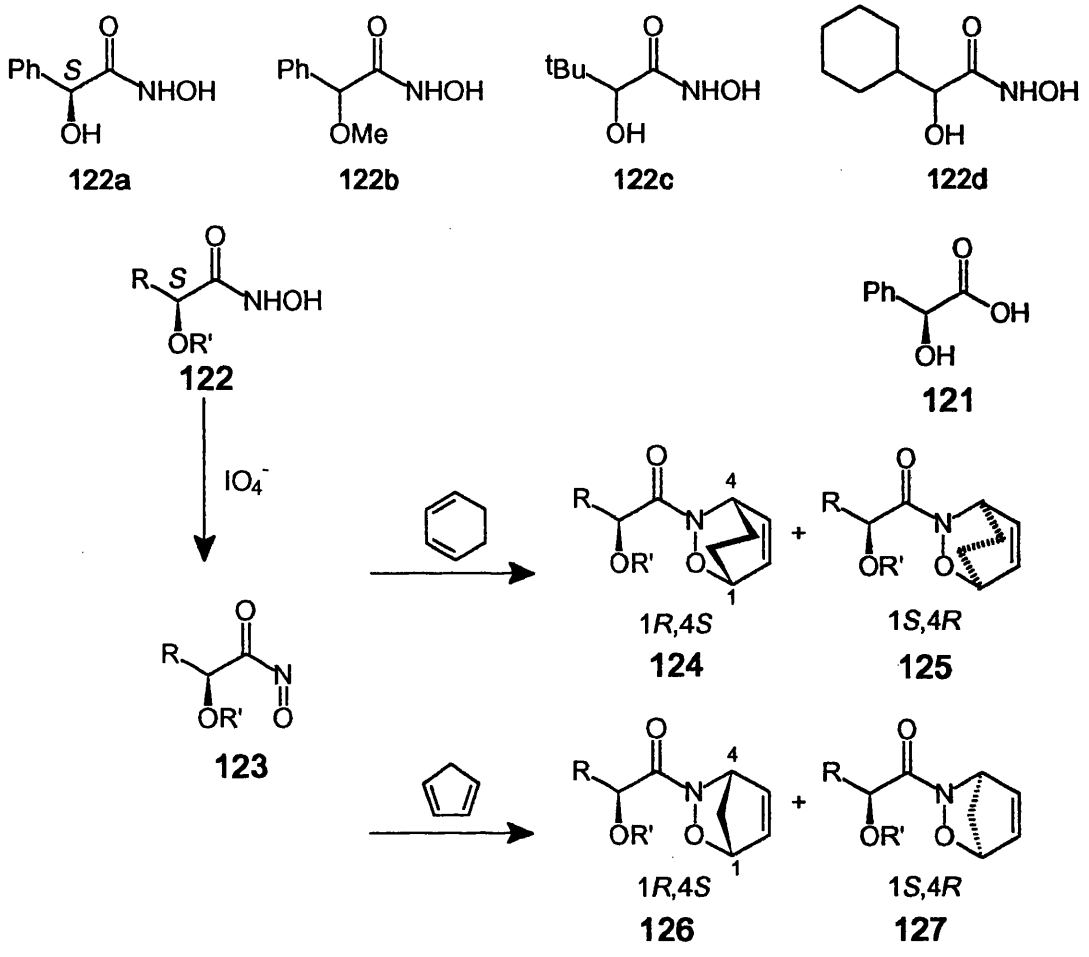
The diastereomeric excess is usually expressed as a percentage. The closer this ratio is to 100% then the more stereoselective the reaction is. If d.e.= 100% then only product A is formed whereas if d.e.= 0% then A and B are formed in equal amounts, *i.e.* with no stereocontrol whatsoever.

The relative amounts of the diastereomers can be measured by NMR spectroscopy, both ^{13}C and ^{1}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 α-chloronitroso dienophiles.

Kresze *et al* (Scheme 23), investigated the cycloadditions with cyclohexadiene of the chiral α-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

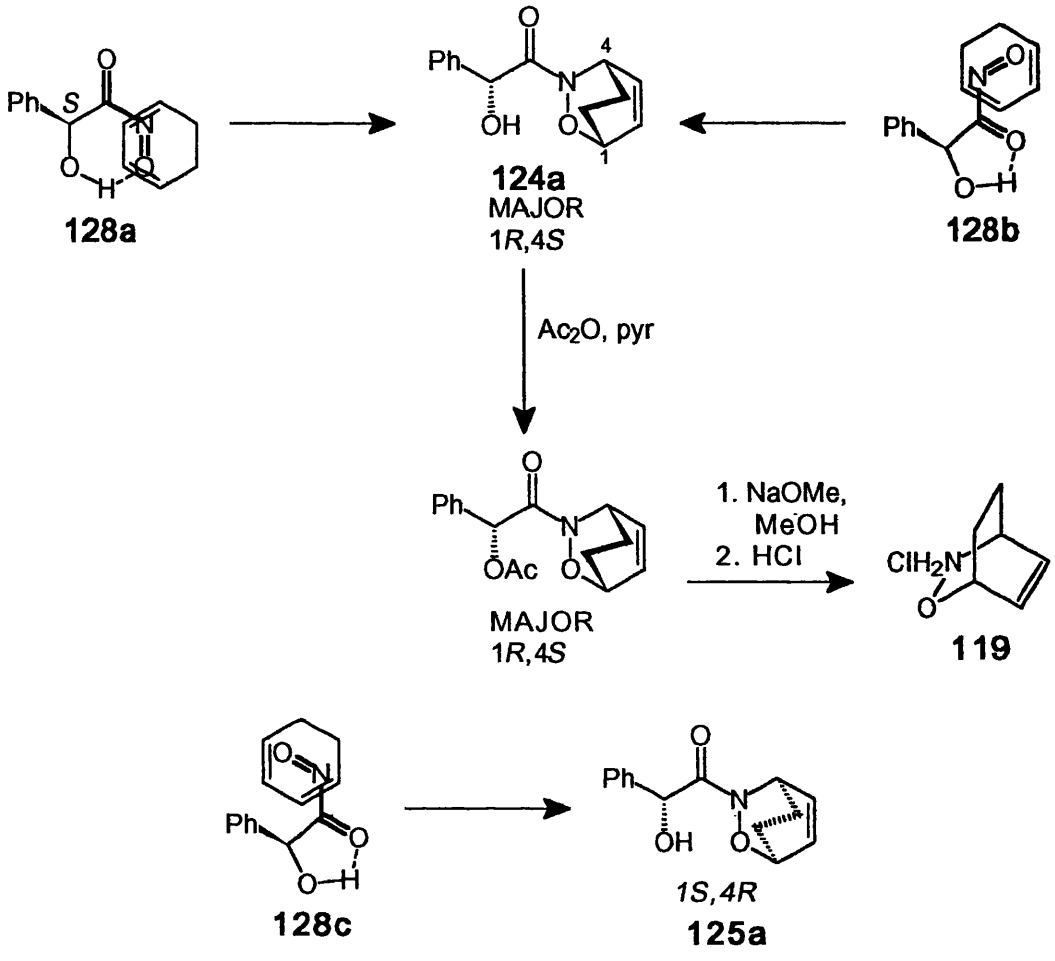
Section 1.3 Chiral auxiliaries and diastereomeric induction.



Scheme 24.

Table 5. Cycloadditions of acylnitroso dienophiles **123a-d** (Kirby and Nazeer[22]).

	R	OR'	T/ °C	cyclopentadiene		cyclohexadiene	
				d.r.	Yield %	d.r	Yield %
123a	Ph	OH	0	5.1	68	3.5	55
123b	Ph	OMe	0	2.6	65	2.1	59
123c	Bu^t	OH	0	3.4	75	4.6	58
123d	$c\text{-}C_6H_{11}$	OH	0	3.6	80	2.5	55
123a	Ph	OH	-78	10	71	6.1	53
123b	Ph	OMe	-78	3.5	63	3.3	54
123c	Bu^t	OH	-78	10	70	11	60
123d	$c\text{-}C_6H_{11}$	OH	-78	6.3	83	5.1	56


Ph
S
O
N
O
H
128a
Ph
OH
O
N
O
4
1
124a
MAJOR
1R,4S
N
O
Ph
O
O
H
128b
Ac2O, pyr
Ph
OAc
O
N
O
MAJOR
1R,4S
1. NaOMe,
MeOH
2. HCl
ClH2N
O
119
O
N
Ph
O
O
H
128c
Ph
OH
O
N
O
1S,4R
125a

Scheme 25.

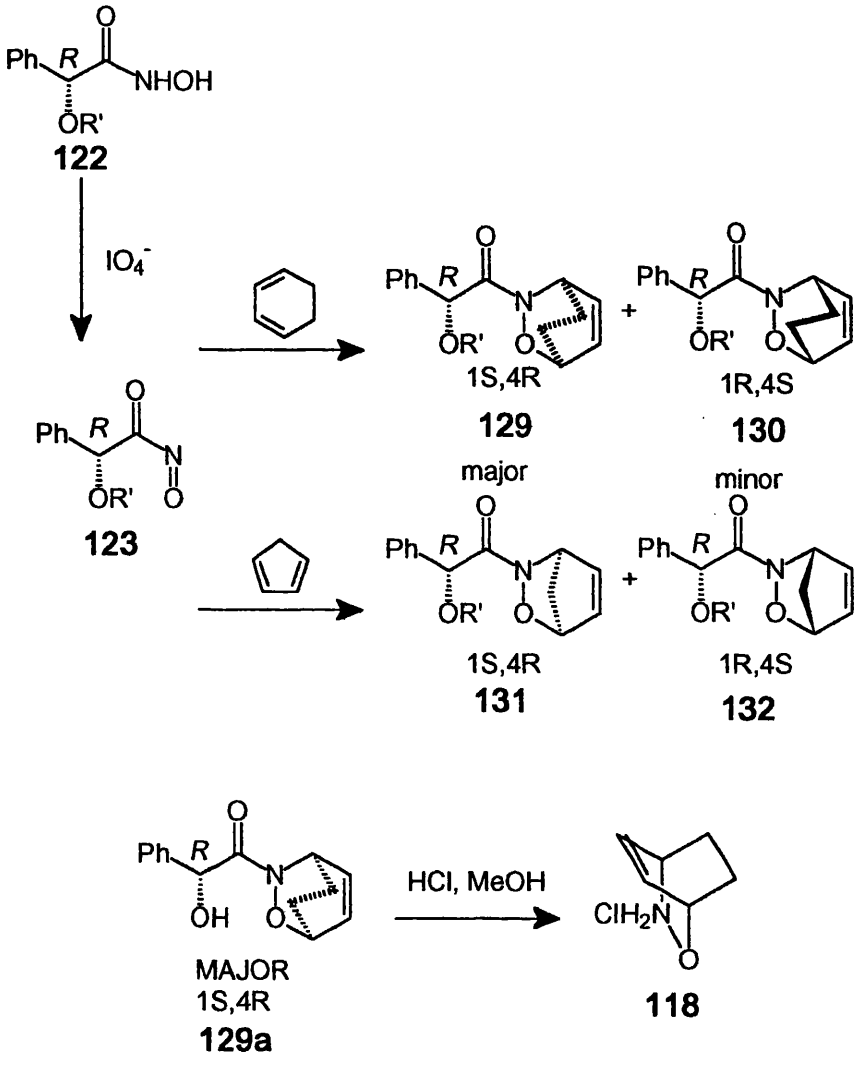
essentially as single diastereomers and were solvolysed *in situ* to give single enantiomers **118** and **119**. Optical rotation measurements on the oxazine hydrochlorides showed that the e.e. of both reactions was >98%. The absolute stereochemistry of oxazine **118** was determined by conversion into a chiral amide and determining the relative stereochemistry by *X*-ray crystallography.[20] However the initially reported absolute configuration proved to be incorrect and the correct configuration, *1R, 4S*, was established when the enantiomer **119** was converted into amide **120** which was compared with a sample prepared from L-glutamic acid.[21] Hence oxazine **118**, $[\alpha_D]$ = -24.0°, 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[22] (Scheme 24), Defoin *et al*[23] (Scheme 26) and Procter *et al*[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 α 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 α-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



Scheme 26.

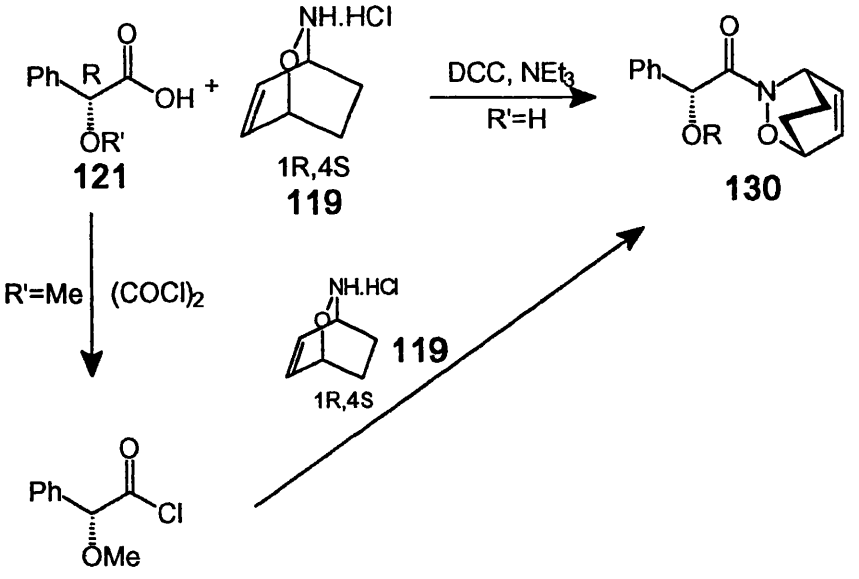
Table 6. Cycloadditions of *(R)*-mandeloylnitroso dienophiles **123a&b** with cyclohexadiene and cyclopentadiene. (Procter *et al*[24])

	R	OR'	diene	Oxid^n	Solvent	T/°C	d.r.	d.e. %	Yield %
a	Ph	OH	C_5H_6	Et_4NIO_4	MeOH	-78	7	75	70
a	Ph	OH	C_6H_8	Et_4NIO_4	MeOH	-78	7	75	50
b	Ph	OMe	C_5H_6	$NaIO_4$	EtOAc, H_2O	25	4	60	67
b	Ph	OMe	C_5H_6	Et_4NIO_4	MeOH	-50	5.4	69	75
b	Ph	OMe	C_5H_6	$(COCl)_2$/DMSO	CH_2Cl_2	-78	5.4	69	80

Table 7. Cycloadditions of *(R)*-mandeloylnitroso dienophiles **123a&b** with cyclohexadiene. (Defoin *et al*[23]).

	R	OR'	Diene	T/ °C	d.r.	de %	yield %
a	Ph	OH	C_6H_8	20	2.2	42	67
a	Ph	OH	C_6H_8	0	3.2	52	-
b	Ph	OMe	C_6H_8	20	1.4	16	67

Section 1.3 Chiral auxiliaries and diastereomeric induction.



Scheme 27.

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.

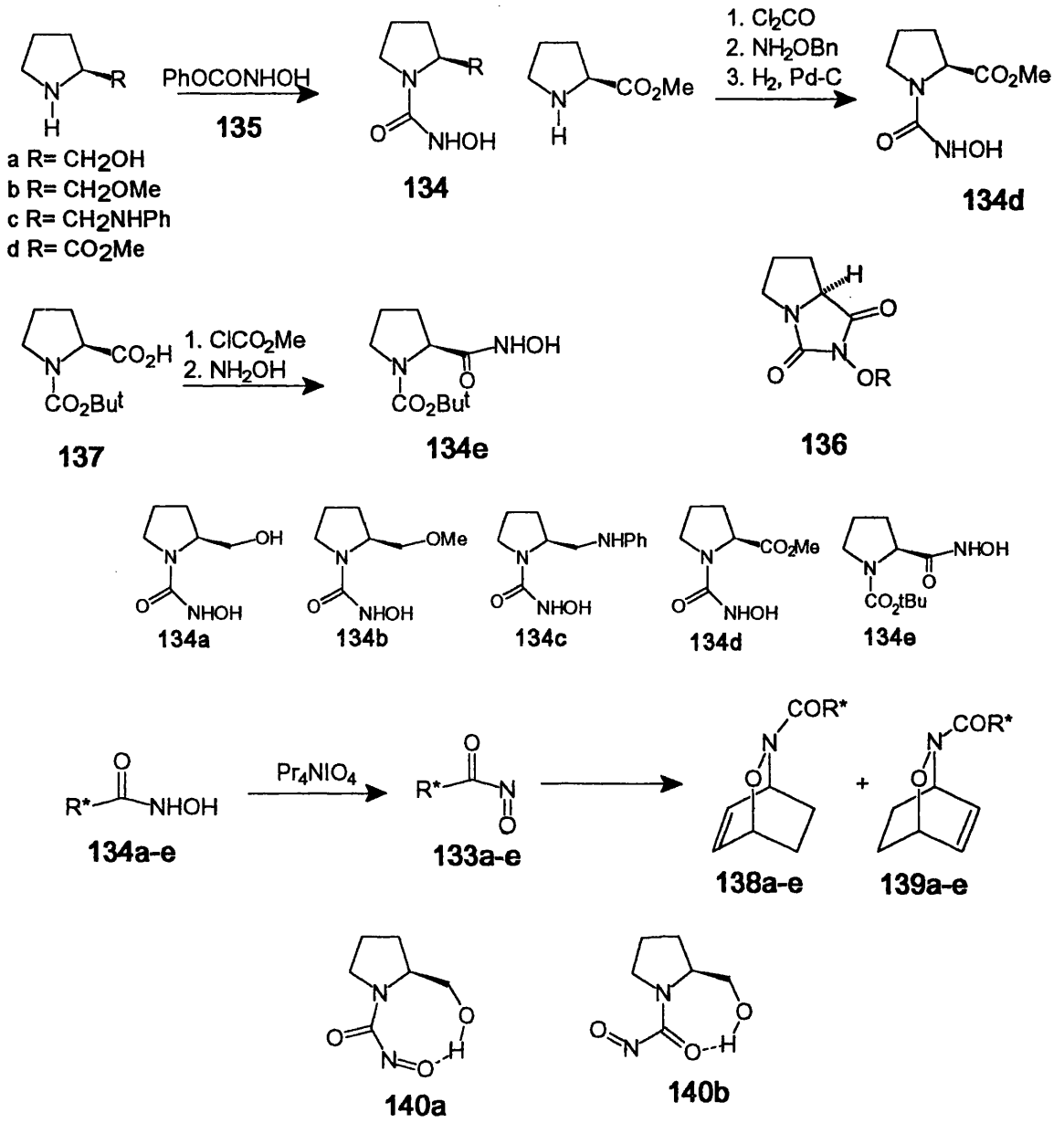
As expected, in all cases higher stereoselectivity was observed when the reaction was carried out at -78°C than at 0°C and the α-methoxy dienophile **123b** gave consistently lower ratios (approx. 3:1) than the α-hydroxy dienophile **123a** with both dienes (approx. 5:1 or greater). This supported the 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 studies[24] (Scheme 26) using mandeloylnitroso dienophiles **123a&b** derived from (*R*)-mandelic acid. They have trapped the acylnitroso 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



Scheme 28.

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

Dienophile	Ratio	de %	Yield %
133a	3.2	52	89
133b	5.2	68	83
133c	4.5	64	79
133d	3.3	54	86
133e	1.5	20	81

Kirby and Nazeer,[22] 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[23] (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** [α_D= +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[22] and by Procter *et al*[24].

Section 1.3.4 The use of chiral auxiliaries based on proline.

Defoin *et al*[25] 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.

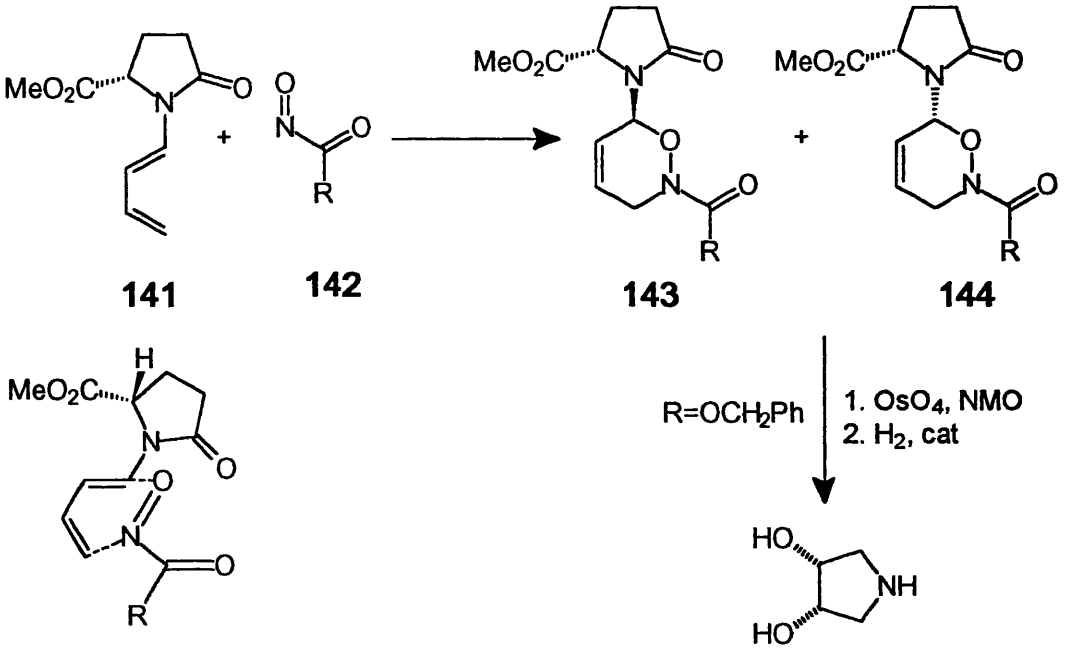
Dienophiles **133a-e** were generated at room temperature, using tetrapropylammonium periodate in chloroform as the oxidising agent (Scheme 28), and trapped with cyclohexadiene to form cycloadducts **138&137 a-e** and these results are summarised in Table 8.

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 *1R,4S*]. This means that the major adducts **138a-e** must also have the same absolute configuration in the oxazine moiety, *i.e. 1R,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 mandeloylnitroso dienophile **123a**. However since H-bonding in dienophile **133b** would involve either an 8-membered



Scheme 29.

Table 9. Cycloadditions of acylnitroso derivatives RCONO **142a-g** with diene **141** at 0°C in chloroform. (Defoin *et al*[26]).

	R	d.r. **143: 144**	d.e. %	Yield %
a	NMe_2	11.5	84	70
b	OMe	3.2	52	63
c	$OCOCH_2Ph$	2.7	46	80
d	Ph	2.6	44	70
e	$OCH_2CH_2SiMe_3$	2.3	40	76
f	Me	2	34	62
g	CH_2Ph	1.3	12	58

Table 10. The effect of temperature and solvent on the cycloaddition between $PhCH_2OCONO$ **142c** and the diene **141**. (Defoin *et al*[26]).

Solvent	T/ °C	d.r.	de %
toluene	0	2.1	36
CH_2Cl_2	0	2.7	46
MeOH	40	2.4	42
MeOH	0	2.8	48
MeOH	-20	3.8	58
MeOH	-78	4.3	62

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**.

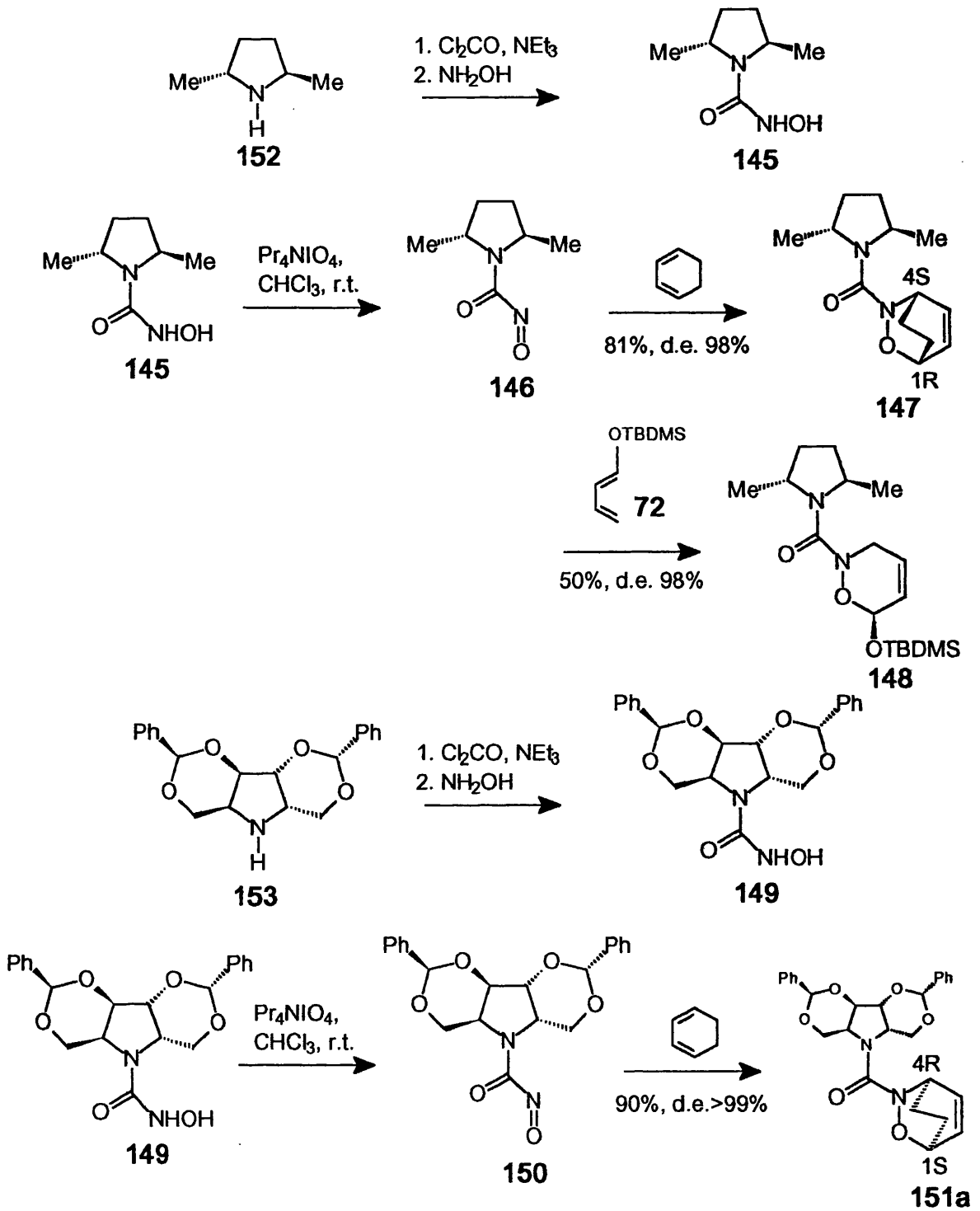
Section 1.3.5 The use of chiral dienes to achieve diastereomeric induction.

Defoin *et al*[26] 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 generate 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).

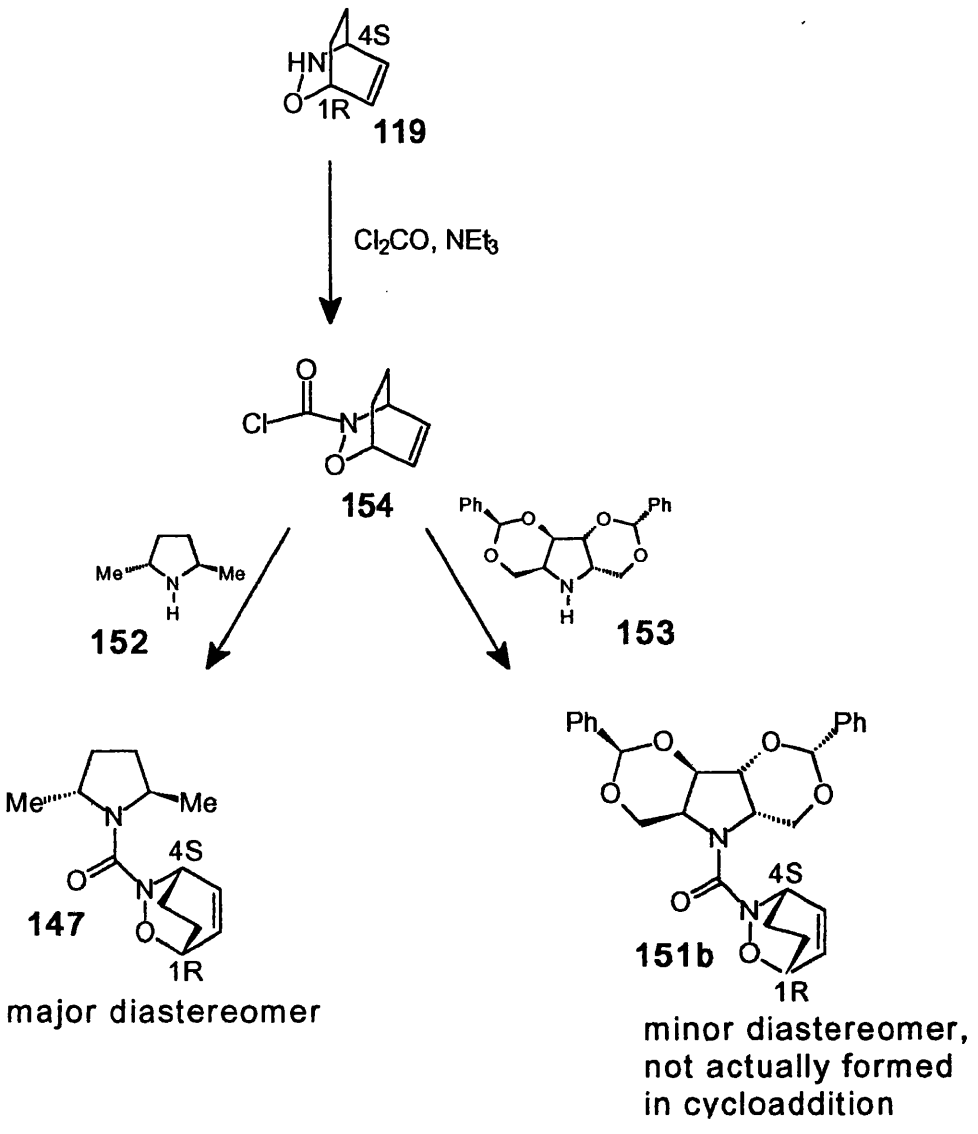
All of the reactions proceeded in good yield and gave a mixture of only **two** diastereomers **143&144** out of a possible four, *i.e.* only one regioisomer was formed, the meta regioisomer. This was the only regioisomer formed due to steric interactions between the large glutamate amide group of the 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


1. Cl_2CO, NEt_3
2. NH_2OH
152
145
Pr_4NIO_4,
$CHCl_3$, r.t.
146
81%, d.e. 98%
4S
1R
147
OTBDMS
72
50%, d.e. 98%
148
153
149
90%, d.e.>99%
4R
1S
150
151a

Scheme 30.


4S
HN
O
1R
119
Cl2CO, NEt3
O
Cl
N
O
154
Ph
O
O
O
Ph
N
H
153
Me
N
H
Me
152
Me
N
Me
4S
O
N
147
O
1R
major diastereomer
Ph
O
O
O
Ph
O
N
4S
O
N
151b
O
1R
minor diastereomer,
not actually formed
in cycloaddition

Scheme 31.

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

Section 1.3.6.a The use of C_2-symmetry; pyrrolidine derivatives.

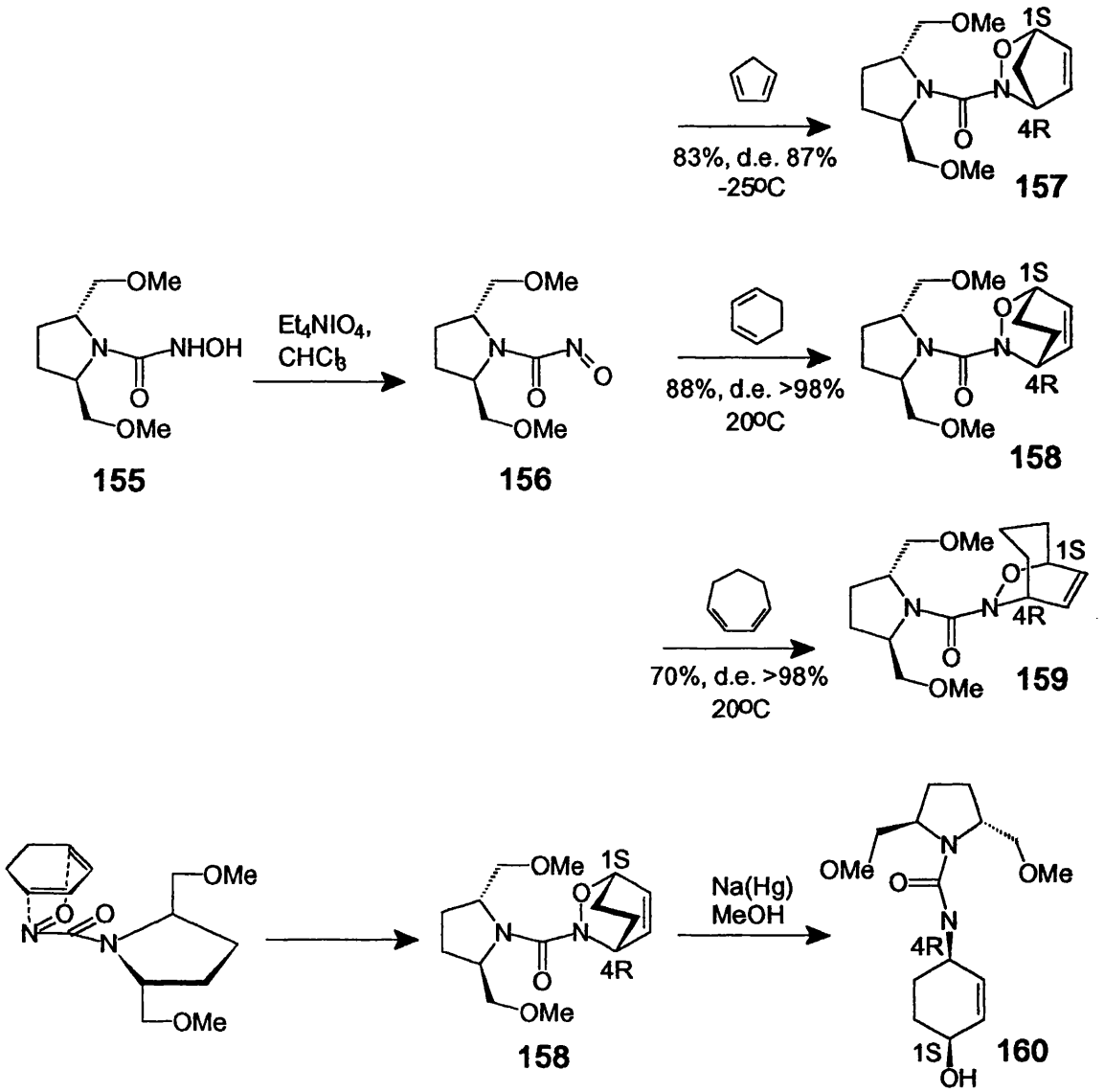
The groups of Ghosez and Defoin have both investigated the reactions of acylnitroso dienophiles based on chiral auxiliaries with C_2 symmetry *e.g.* based on chiral pyrrolidines.

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** [32] 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.

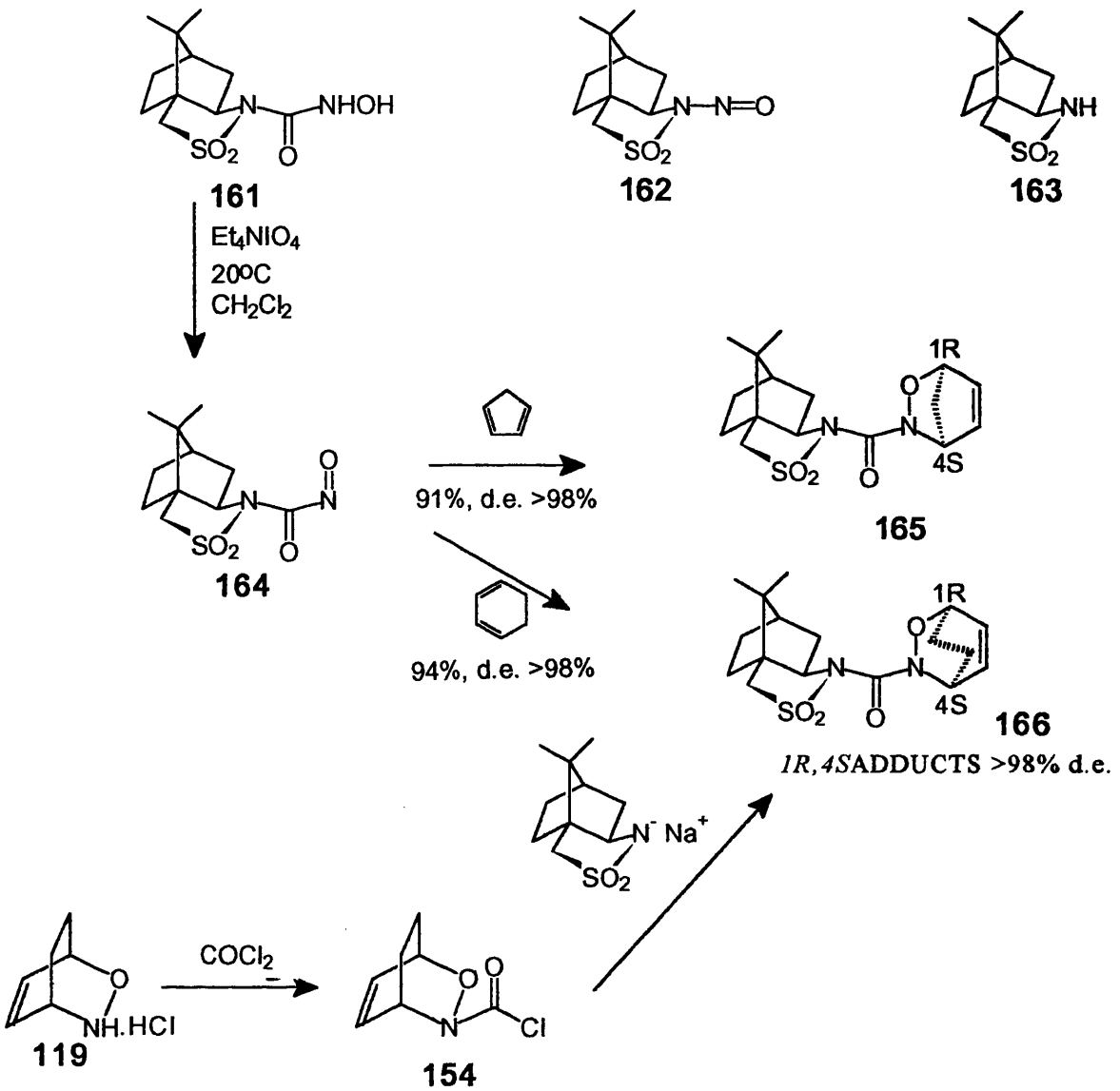
The absolute stereochemistry of siloxy cycloadduct **148** was determined by *X*-ray crystallography and was found to be as shown. The absolute stereochemistry of cyclohexadiene adducts **147** and **151** was determined by independently synthesising them from (*1R,4S*)-chiral oxazine **119** (Scheme 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 *1R,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,

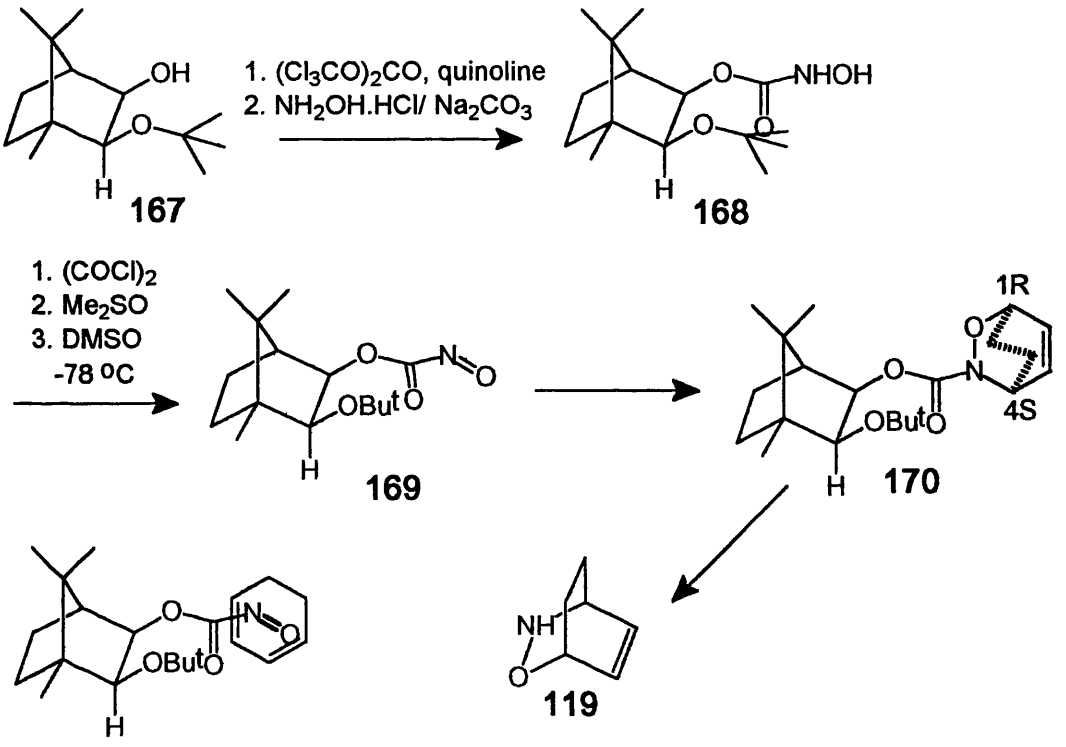

OMe
1S
O
N
N
4R
O
OMe
83%, d.e. 87%
-25°C
157
OMe
NHOH
O
OMe
155
Et4NIO4,
CHCl3
OMe
N
N
O
O
OMe
156
88%, d.e. >98%
20°C
158
OMe
1S
O
N
N
4R
O
OMe
159
70%, d.e. >98%
20°C
OMe
O
O
N
N
OMe
OMe
1S
O
N
N
4R
O
OMe
158
Na(Hg)
MeOH
OMe
N
OMe
O
N
4R
1S
OH
160

Scheme 32.


NHOH
SO2
O
161
Et4NIO4
20°C
CH2Cl2
N—N=O
162
NH
163
164
91%, d.e. >98%
94%, d.e. >98%
1R
4S
165
166
1R,4S ADDUCTS >98% d.e.
N⁻ Na⁺
COCl2
NH.HCl
119
Cl
154

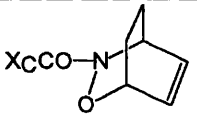
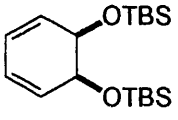
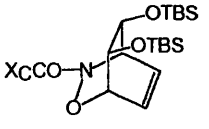
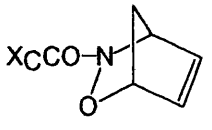
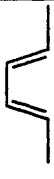
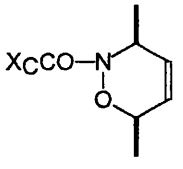
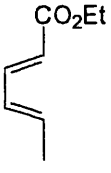
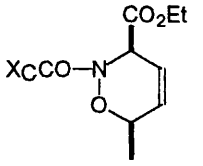
Scheme 33.

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*[80]).

diene	product		d.e. %	yield %
		**170**	95	93
		**171**	>95	62
		**172**	91	89
		**173**	96	94
		**174**	95	65

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*.

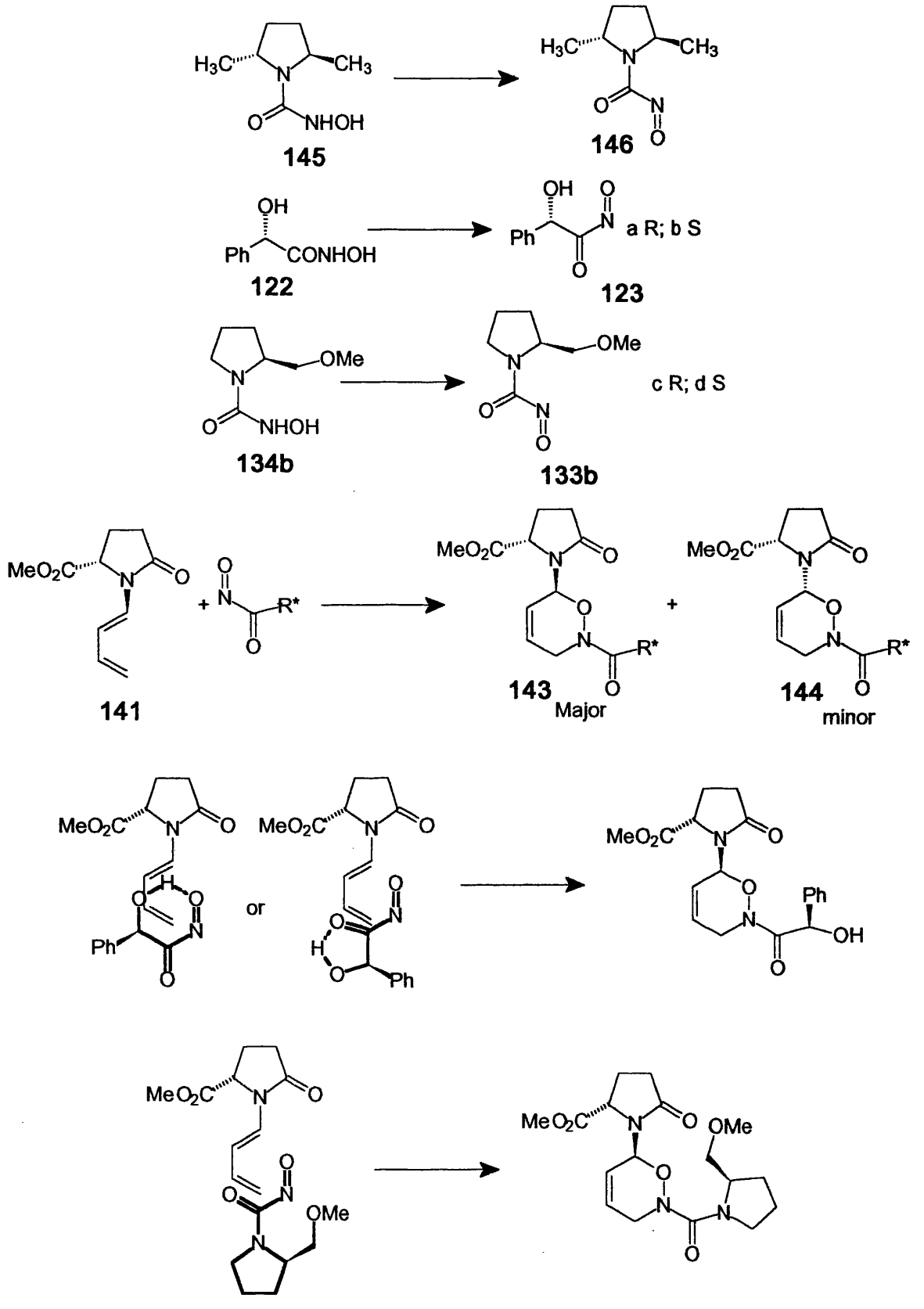
Section 1.3.7 The use of sultam **163** as a chiral auxiliary.

Ghosez *et al*[29] 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 al*[30] 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 Oppolzer[31] 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 Et_4NIO_4 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).



Scheme 35.

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**[32] 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.

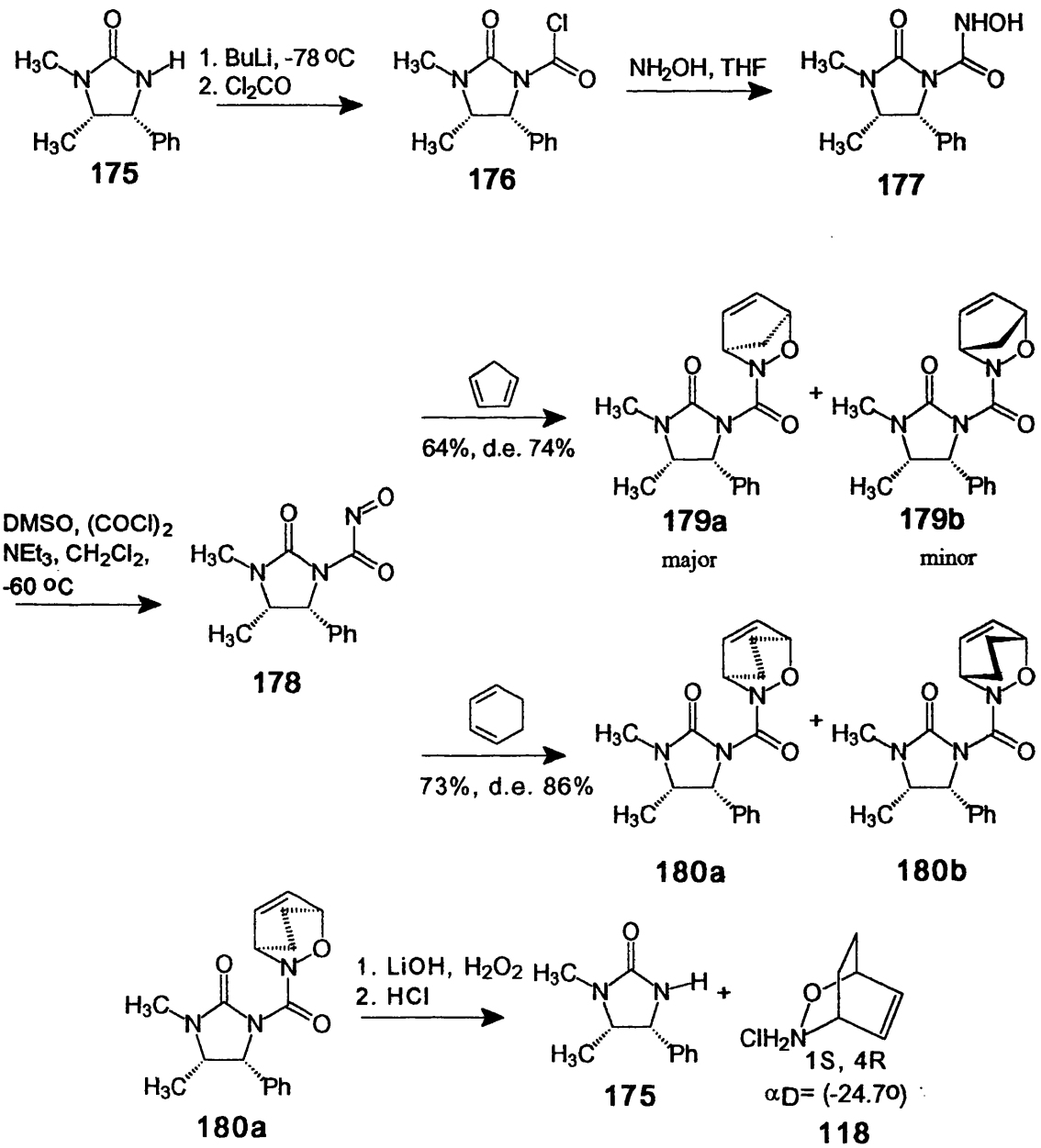
To investigate double asymmetric induction, the chiral dienophiles **133b** and **123a** used were derived from proline and mandelic acid respectively. The chiral diene **141** used was the (*S*)-enantiomer (Table 12).

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 acylnitroso dienophiles and chiral diene **141** at 0°C. (Streith *et al*[32]).

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



Scheme 36.

Section 1.3.10 Imidazolidinone 175 as a chiral auxiliary.

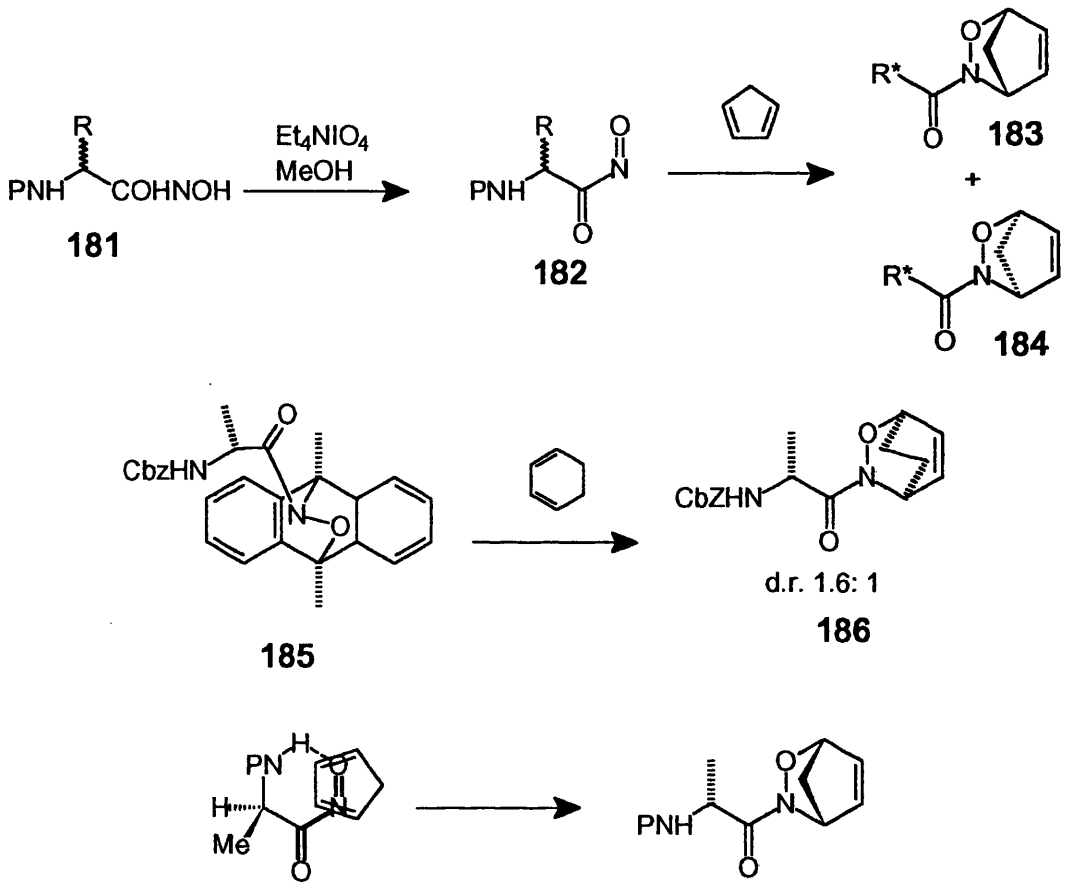
Orena *et al*[33] have investigated the use of the chiral imidazolidin-2-one **175** as a chiral auxiliary in the asymmetric Diels-Alder reaction of acylnitroso dienophiles (Scheme 36). The enantiopure imidazolidin-2-one **175** can be prepared as either enantiomer from either (-)- or (+)-ephedrine, 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 *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 ^{1}H and ^{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**, [α_D= -24.7°, c=1, $CHCl_3$]. Comparison of the optical rotation with the literature value showed that the oxazine moiety must have the (*1S, 4R*) absolute stereochemistry.

Section 1.3.11 Use of amino acids as chiral auxiliaries.

Ritter and Miller[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 *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



Scheme 37.

Table 13. Cycloadditions between dienophiles **182a-f** and cyclopentadiene. (Ritter and Miller[34])

	Amino acid	R	P		Yield %	d.r. **183: 184**
a	(*L*)-valine	^{i}Pr	Cbz	*S*	85	1: 4
b	(*L*)-alanine	Me	Cbz	*S*	90	1: 3
f	(*L*)-alanine	Me	Boc	*S*	78	1: 3
c	(*D*)-alanine	Me	Cbz	*R*	78	3: 1
d	(*L*)-phenylalanine	CH_2Ph	Cbz	*S*	79	1: 2
e	(*L, D*)-phenylalanine	CH_2Ph	Cbz	*R, S*	75	-

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

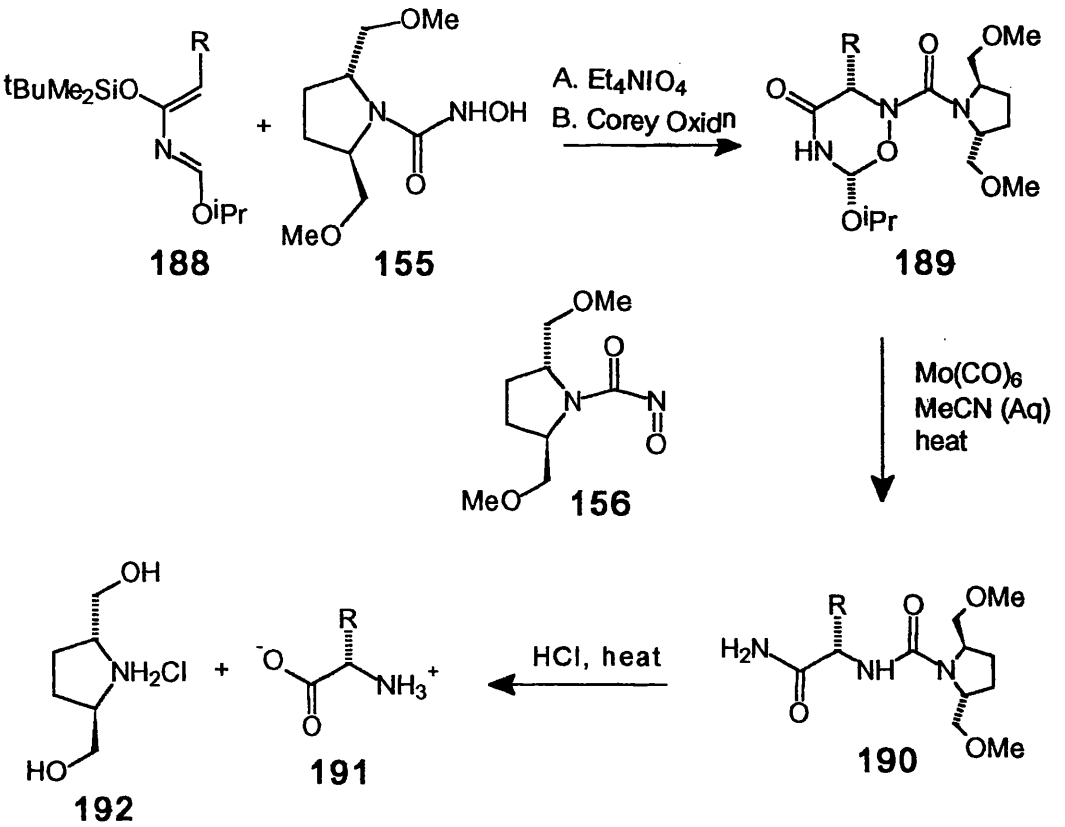
Acylnitroso dienophile **182c** was also generated by heating the dimethylanthracene adduct **185** in refluxing benzene and was trapped *in situ* with cyclohexadiene. The cyclohexadiene adduct **186** was formed in this reaction as a 1.6:1 mixture of diastereomers. These diastereomers could also be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

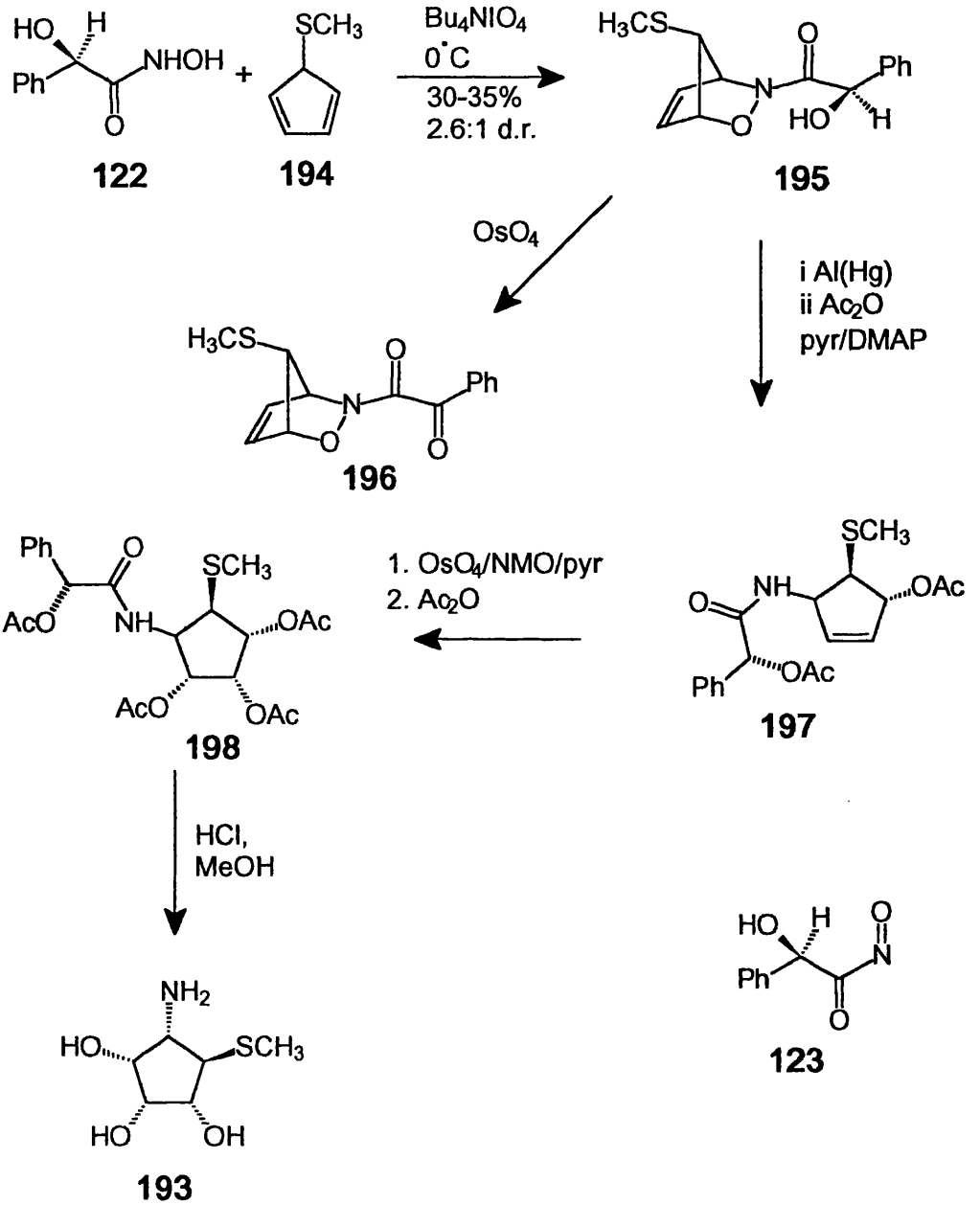


Scheme 38.

Table 14. Effect of temperature and method of oxidation (A. with Et_4NIO_4 and B. with NCS and DMSO) on the diastereomeric excesses of the cycloaddition between acylnitroso dienophile **156** and 2-azadienes **188a-c**.

	R	Oxidation	T/ °C	d.e. %	Yield %
a	Me	A	-25	59	68
a	Me	B	-78	90	72
b	Ph	A	0	84	68
b	Ph	B	-78	94	62
c	$PhCH_2$	A	-25	90	70
c	$PhCH_2$	B	-65	93	65

Section 1.4 The use of chiral acylnitroso dienophiles in chiral synthesis.



Scheme 39.

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

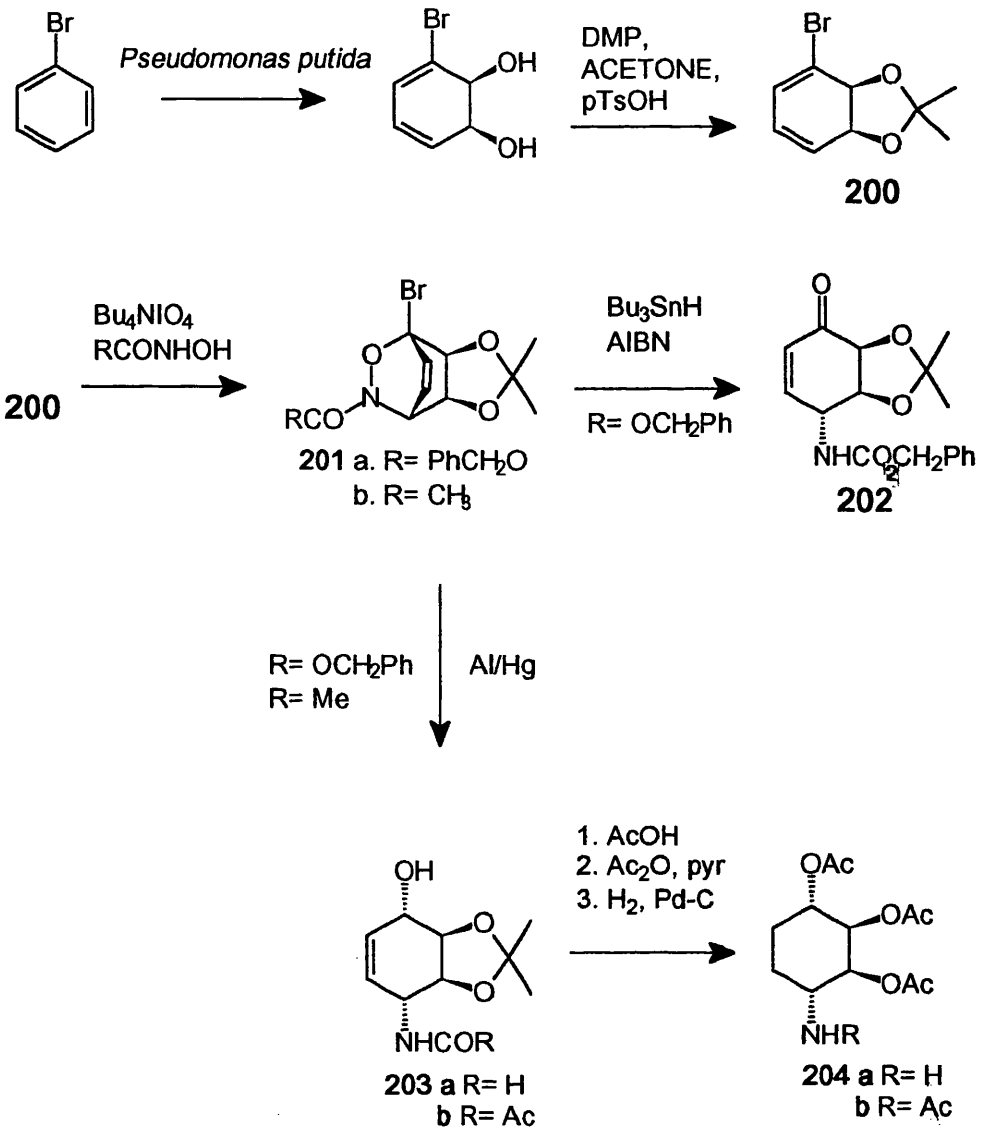
Ghosez and Gouverneur have used acylnitroso dienophile **156** generated from pyrrolidine based hydroxyurea **155** in the synthesis of several enantiomerically pure amino acids[35] (Scheme 38). They used as the dienophile, 2-azadienes **188a-c** which were made from the corresponding acid chlorides (RCH_2COCl). 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, dimethylsulfide and triethylamine) at –78°C. The cycloadditions gave the major product **189a-c** in ≈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 mandeloylnitroso dienophile **123a** to synthesise mannostatin A **193**[36], a glycosidase inhibitor (Scheme 39). (*R*)-Mandeloylnitroso 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 acylnitroso dienophiles in chiral synthesis.

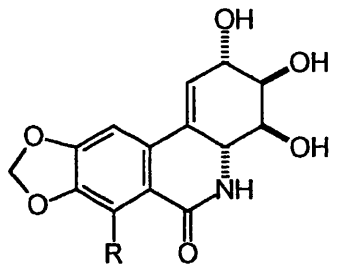


Scheme 40.

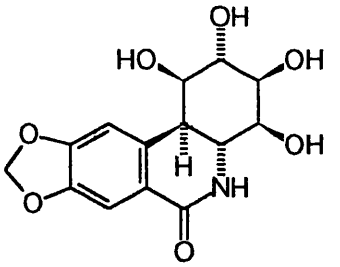
Table 15, Yield of the cycloaddition of the haloacetonides **201**.

	Halogen	R	Yield, %
a	Cl	OCH_2Ph	54
b	Br	OCH_2Ph	52
c	Br	CH_3	51

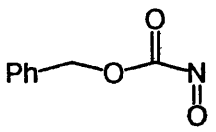
Section 1.4 The use of chiral acylnitroso dienophiles in chiral synthesis.

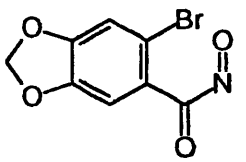


205 R=OH, narciclasine
87 R=H, lycoricidine

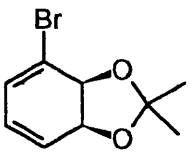


88 pancratistatin



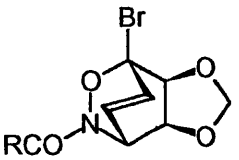


92



200

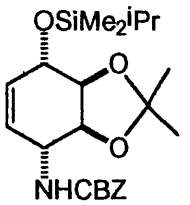
RCONHOH
Bu_4NIO_4
CH_2Cl_2



206 a R= CBz, 74%
b R= Br-piperonoyl, 80%

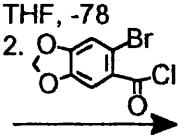
206a

1. Al(Hg), THF, 91%
2. $ClSiMe_2Pr^i$, Im, CH_2Cl_2, 98%

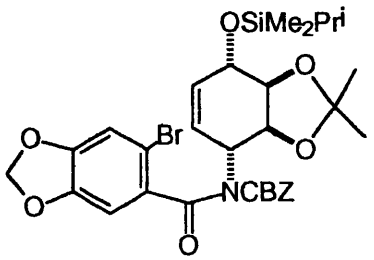


207

1. BuLi, THF, -78
2.

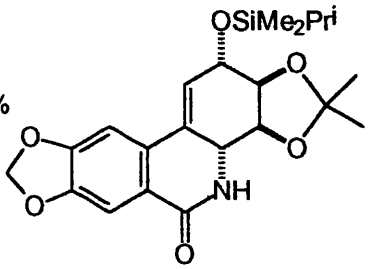


78%



208

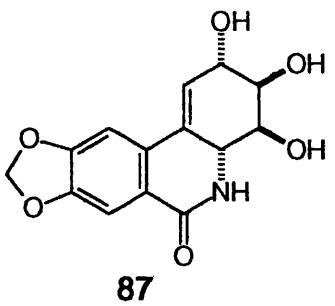
1. $Pd(OAc)_2$, Tl(OAc) DIPHOS, anisole, 27%
2. Pd-C, EtOH, cyclohexene, 99%



209

F_3CCO_2H

85%



87

Scheme 41.

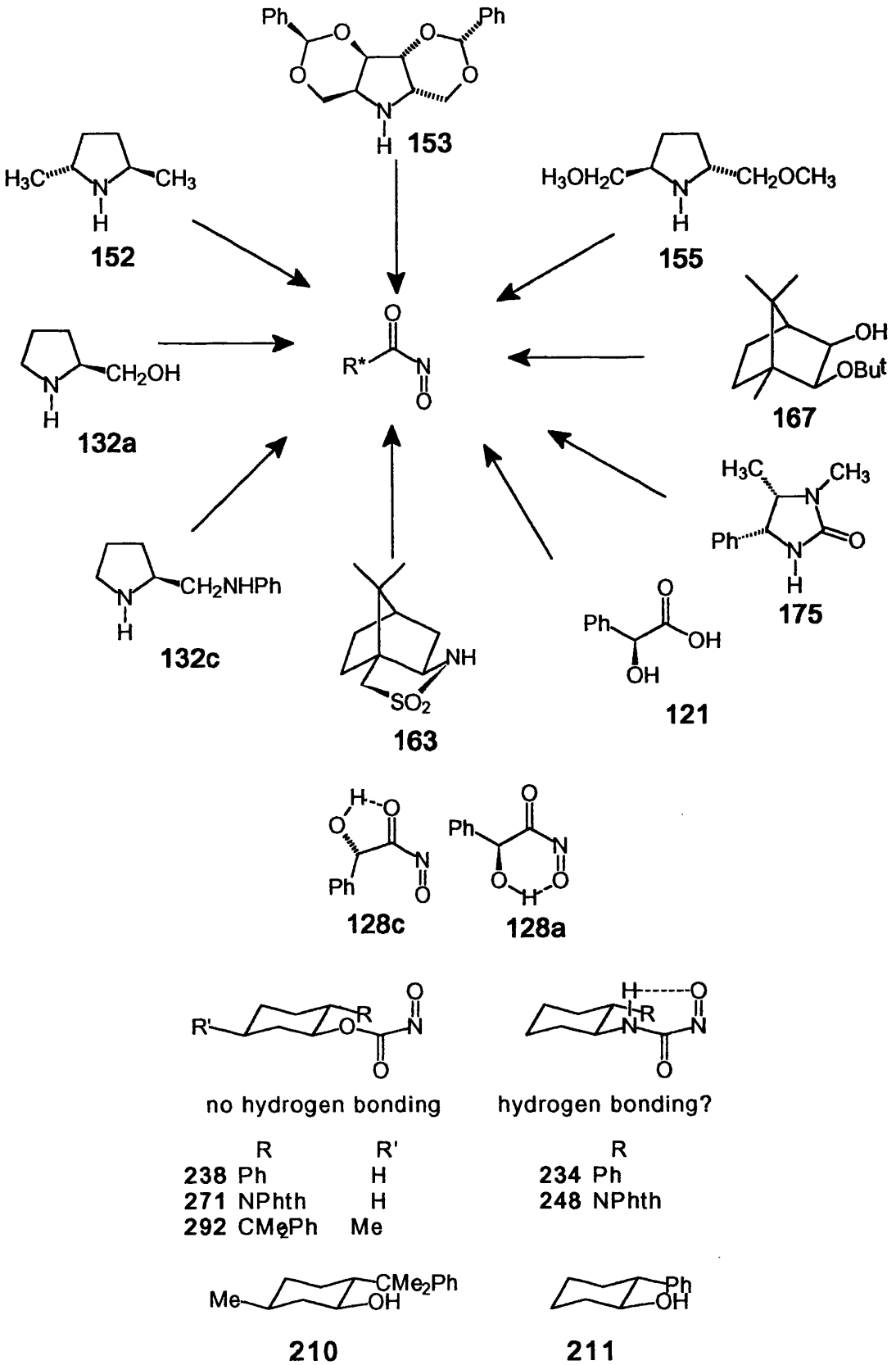
Section 1.4.3 Synthesis of aminocyclitols.

Hudlicky and Olivo have developed a route to the synthesis of aminocyclitols[37] 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 conduramine 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 Olivo[38] 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%.


153
152
155
132a
167
175
132c
163
121
128c
128a
no hydrogen bonding
hydrogen bonding?
R R'
238 Ph H
271 NPhth H
292 CMe2Ph Me
R
234 Ph
248 NPhth
210
211

Scheme 42.

As can be seen from Section 1.3, a wide variety of chiral auxiliaries attached to acylnitroso groups have been used to investigate asymmetric induction in the cycloaddition of acylnitroso 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.

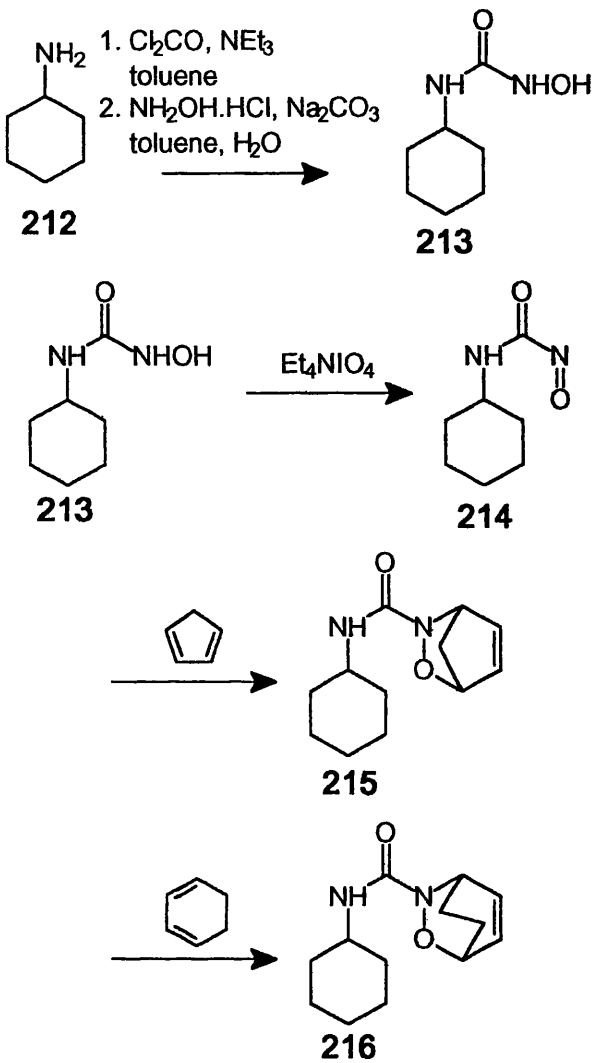
Two possible drawbacks to this idea were that:-

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 amidic 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-*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 *trans*-phenylcyclohexanol **211** have both been used as chiral auxiliaries before in other reactions with high stereoselectivity, *e.g.* Diels-Alder reaction[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.



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.

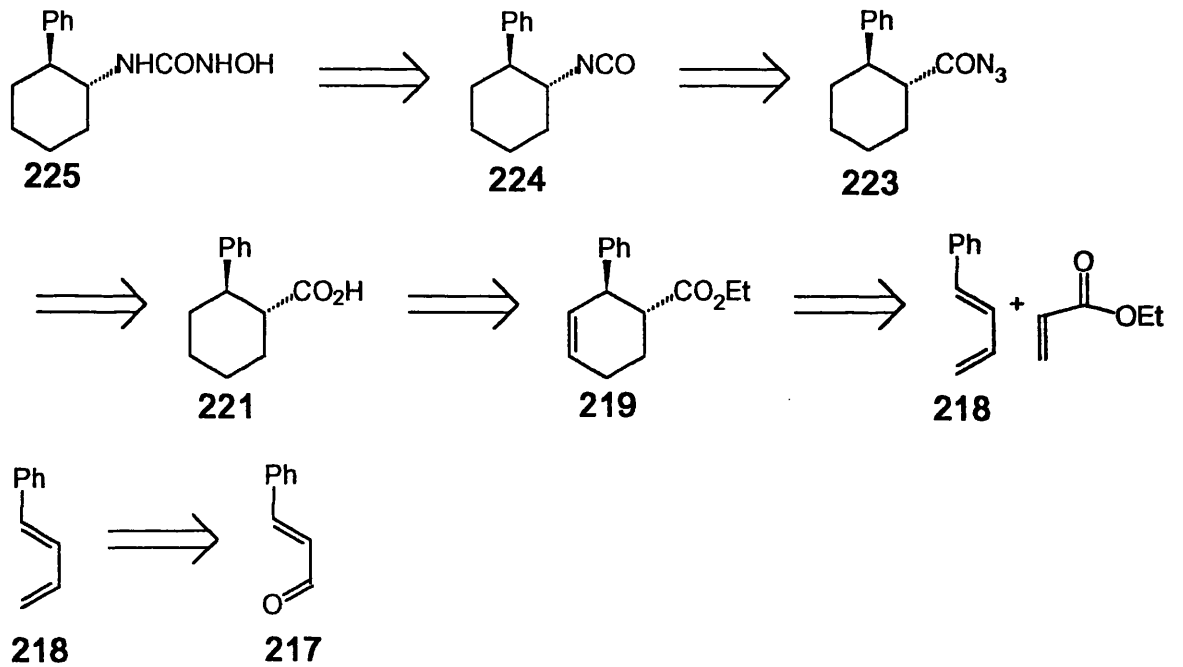
Since hydroxyurea **213** and acylnitroso dienophile **214** are achiral, the resulting cycloadducts with prochiral dienes *e.g.* cyclopentadiene and cyclohexadiene were formed without chiral induction as racemates. Although there was no stereoselection, the reactions of this dienophile were of interest 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.

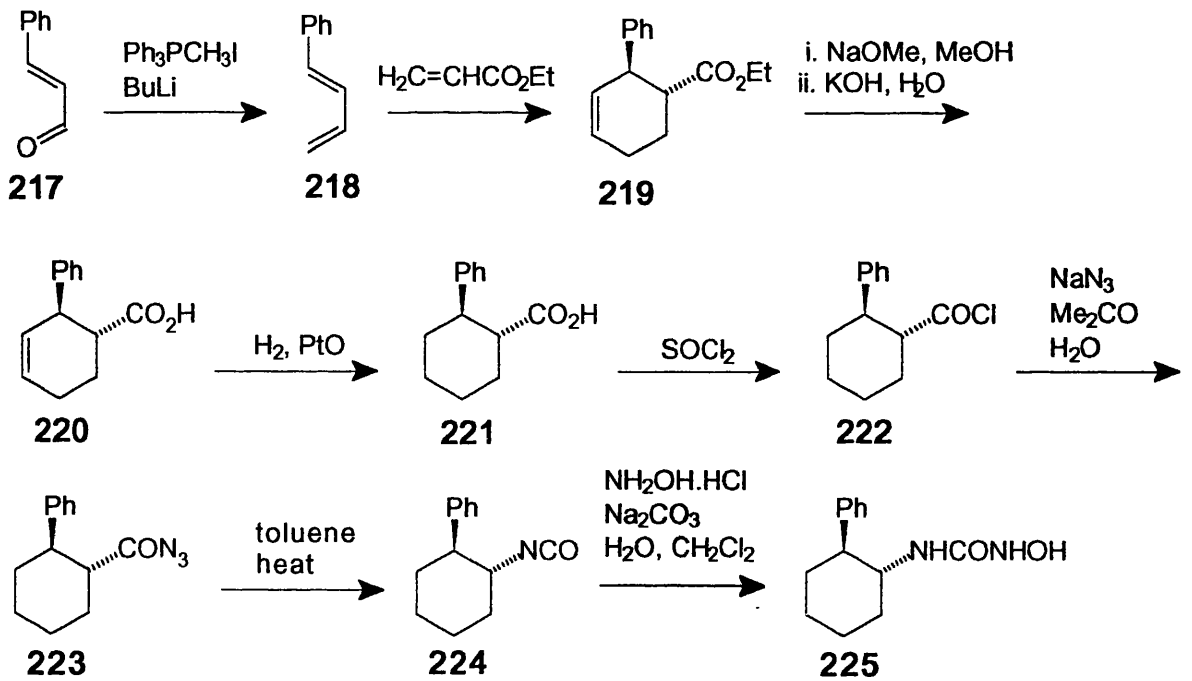
A typical procedure for generating the acylnitroso dienophile and trapping it *in situ* with periodate was to dissolve tetraethylammonium periodate and excess diene in a mixture of ethanol and dichloromethane. The solution was chilled to 0°C and magnetically stirred. The hydroxamic acid derivative **213** 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 cyclohexadiene to form adducts **215** and **216**, respectively in good yields.

Section 2.1.4 NMR spectra of cycloadducts 216 and 215.

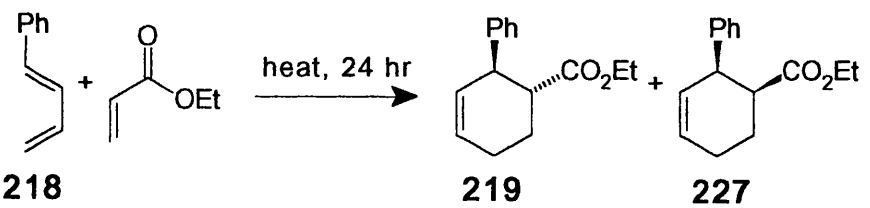
It is interesting to note the major differences in the NMR spectra between the two cycloadducts. In the ^{1}H NMR spectra the major difference is the chemical shift of the bridgehead hydrogens. In cyclopentadiene adduct **215**, the two bridgehead proton signals are coincidental and are downfield in comparison with those of the cyclohexadiene 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 ^{13}C 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 cyclohexadiene 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 cyclohexadiene adduct.



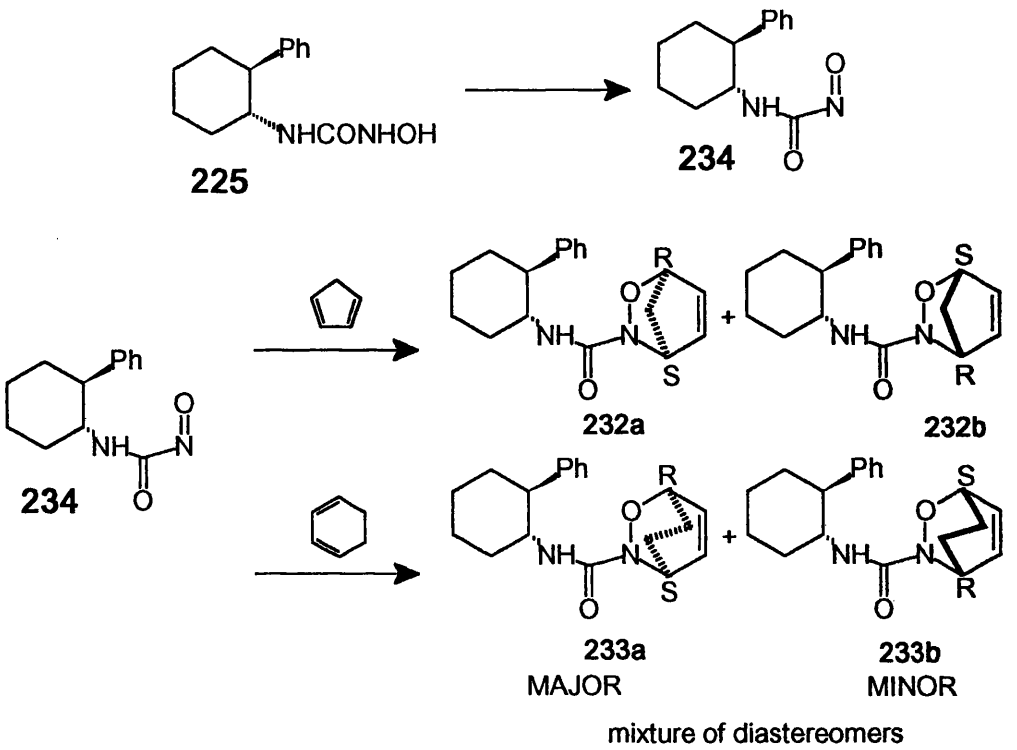
Scheme 44.



Scheme 45.



Scheme 46.



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 [40] who also resolved the (+)-acid **221** as a single enantiomer. The racemic acid has also been synthesised by Ansell and Clements [41] and Ropp and Cogner[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[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**

and methylenetriphenylphosphonium ylid, following the procedure of Wittig and Schoellkopf.[43] Two alterations were made to their procedure. Firstly, methyltriphenylphosphonium iodide was used instead of the methyltriphenylphosphonium bromide. This change was made since it was easier to handle the liquid iodomethane b.p. 42-43°C rather than the gaseous bromomethane b.p. 4°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 methyltriphenylphosphonium 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. Methyltriphenylphosphonium iodide and THF were added to the flame-dried apparatus under an atmosphere of nitrogen and the stirred suspension was chilled to 0°C. A solution of n-butyllithium was then added slowly to deprotonate the insoluble methyltriphenylphosphonium 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°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**.[44] Isocyanate **224** then reacted with hydroxylamine to give hydroxyurea **225**.[45] Following the procedure of Arnold and Richardson,[44] acid chloride **222** was formed (Scheme 45) from cyclohexylcarboxylic acid **221** by heating to reflux for 30 minutes in thionyl chloride.[46, 47] 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 Hurd[45] 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 ^{1}H and the ^{13}C NMR spectra. In the ^{1}H 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 ^{13}C 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 periodate 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, oxalyl 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 periodate 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.

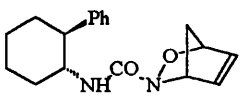
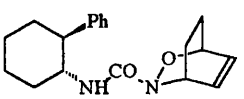
When nitrosoformamide dienophile **234** was trapped with cyclohexadiene, the racemic cyclohexadiene adducts **233a&b** were formed in good yield. The crude product contained both of the possible diastereomers **233a&b**, and the relative ratios of the two diastereomers were measured using NMR spectroscopy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

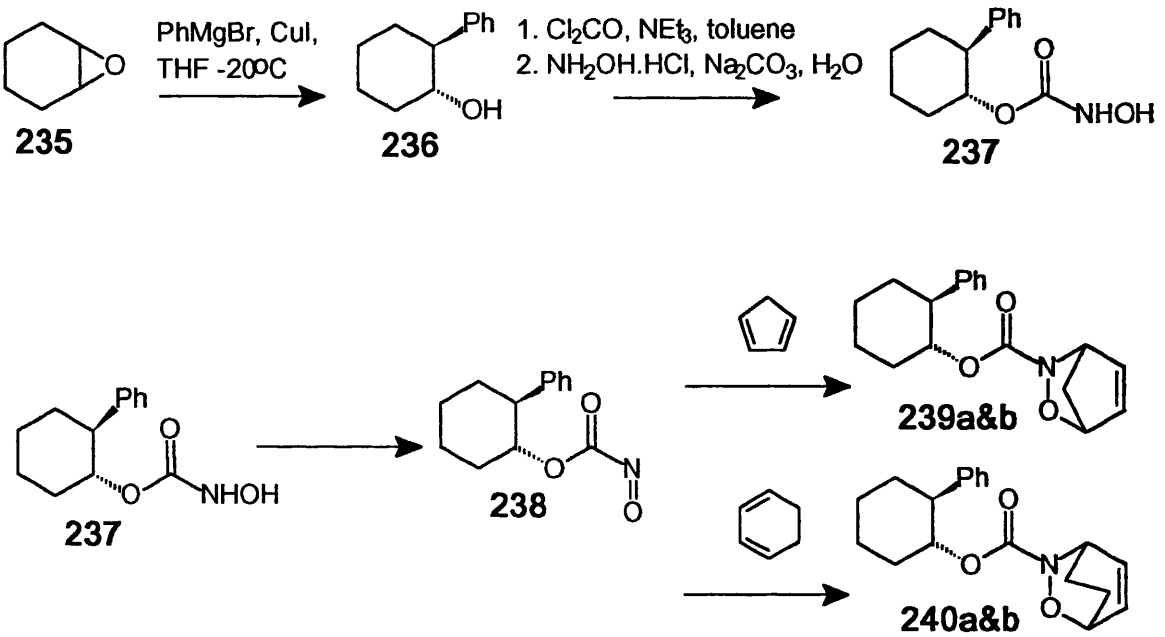
A slight increase in the ratio of diastereomers **233a&b** from d.r. 2.4:1 to d.r. 2.9:1 was observed when the periodate oxidation was carried out at -78°C compared with 0°C. For some reason, when the oxidation was carried out under the Swern conditions as described above, the desired cycloadducts **233a&b** 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.

Cycloadduct	T/ °C (time)	Diene	Oxidant	d.r. ^1H	d.r. ^{13}C	mean d.r.	d.e. %	Yield % crude (pure)
 **232**	0	C_5H_6	Et_4NIO_4	3.06	2.76	2.9	49	111 (83)
	-78	C_5H_6	Et_4NIO_4	2.93	3.29	3.1	51	93 (82)
	-78 2 hrs	C_5H_6	Et_4NIO_4	3.29	3.17	3.2	52	109 (72)
	-78 24 hrs	C_5H_6	Et_4NIO_4	3.11	2.99	3.1	51	83 (-)
	-78	C_5H_6	Me_2S/NCS	2.5	2.78	2.6	43	82 (-)
	-78	C_5H_6	DMSO+ $(COCl)_2$	4.66	4.69	4.7	65	92 (92)
 **233**	0	C_6H_8	Et_4NIO_4	2.49	2.42	2.4	41	88 (72)
	-78 4 hrs	C_6H_8	Et_4NIO_4	3.24	2.86	3	50	73 (-)
	-78	C_6H_8	DMSO+ $(COCl)_2$	-	-	-	-	-[a]

[a] no adduct isolated



Scheme 48.

Section 2.3.1 Synthesis of (±) *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.[48] 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 *trans*-phenylcyclohexanol **236** following the procedure of Huynh[50] using a cuprate controlled Grignard reaction. Phenyl magnesium bromide was stirred with 10%

cuprous iodide at -30°C in dry THF for 5 minutes before cyclohexene oxide **235** was added. The cuprous iodide ensured that only the *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 C*H*OCO proton δ 4.88 resonates downfield from the corresponding C*H*NHCO δ 3.77 in the hydroxy urea **225**. The same effect was seen in the ^{13}C NMR spectra; δ 65.4 for *CH*OCO of **237** and δ 52.8 for *CH*NHCO of **225**.

Section 2.3.2 Cycloadditions of the racemic dienophile 238.

The (±)-hydroxycarbamate **237** was oxidised as before to generate the racemic nitrosoformate dienophile **238** which was trapped *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 cycloadditions 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}H and ^{13}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 cycloaddition. The ^{13}C NMR spectra proved more useful, but see earlier *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 C*H*OCO 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.

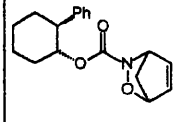
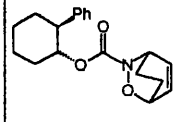
Unlike cyclopentadiene adduct **239a&b**, for cyclohexadiene adduct **240**, both the ^{1}H NMR spectra and the ^{13}C NMR spectra could be used to determine the ratios of diastereomers formed in the cycloaddition. These results are summarised in Table 17. The crude product of the reaction was then purified 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

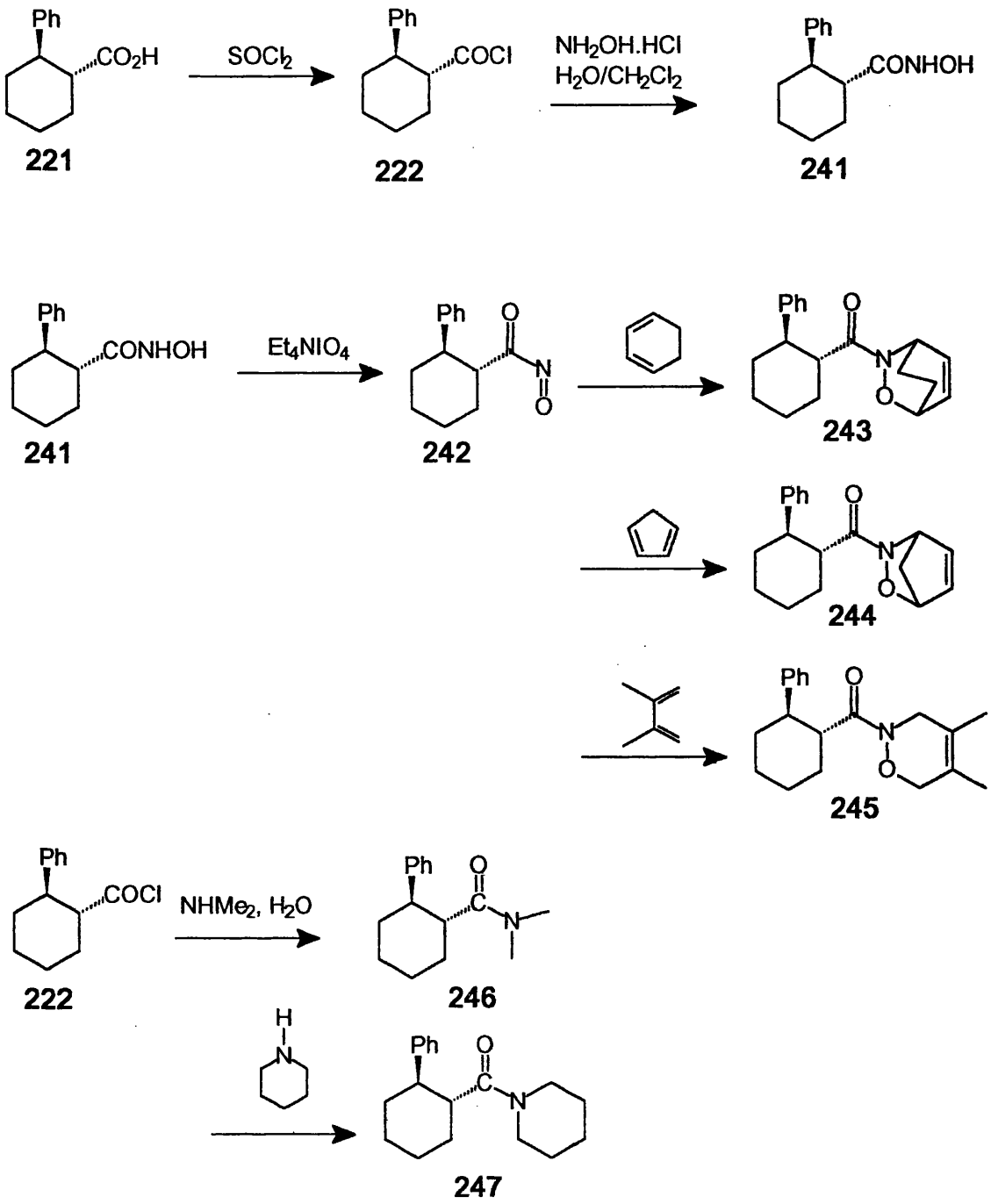
single diastereomer. The relative stereochemistry of this adduct was determined by *X*-ray crystallography (see Section 2.9).

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°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°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°C. This would seem to indicate that the periodate oxidation of the hydroxycarbamate to nitrosoformate **238** proceeds very slowly at -78°C and that the bulk of reaction does not occur at -78°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.

	T/°C (time)	Diene	Oxid[n]	d.r. ^{1}H	d.r. ^{13}C	average d.r.	d.e. %	yield % crude (pure)
 **239**	0	C_5H_6	Et_4NIO_4	-	2.61	2.61	45	167 (98)
	-78	C_5H_6	Et_4NIO_4	-	3.6	3.6	56	106 (98)
	-78	C_5H_6	DMSO+ $(COCl)_2$	-	5.45	5.45	69	102 (-)
 **240**	0	C_6H_8	Et_4NIO_4	2.43	3.3	2.87	48	79 (51)
	-78	C_6H_8	Et_4NIO_4	3.33	3.68	3.51	57	140 (54)
	-78	C_6H_8	DMSO+ $(COCl)_2$	6.67	7.67	7.17	75	115 (92)



Scheme 49.

Section 2.4.1

With a supply of (±)-*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

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 $(CD_3)_2SO$ showed the presence of D_2O 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

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 ^{1}H NMR experiments at -50°C and +50°C in addition to the 25°C NMR experiments. The ^{1}H 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 ^{1}H NMR spectra become sharper. Also there is no change in the ^{1}H and ^{13}C 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 nitrosocarbonyl 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 ^{1}H 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.

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 ^{1}H or ^{13}C 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 ^{13}C 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 ^{13}C 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 ^{1}H NMR spectrum, the two amide methyl signals appeared as a sharp singlet at δ 2.55. In the ^{13}C 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 ^{13}C 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 CH_2-CH_2 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.

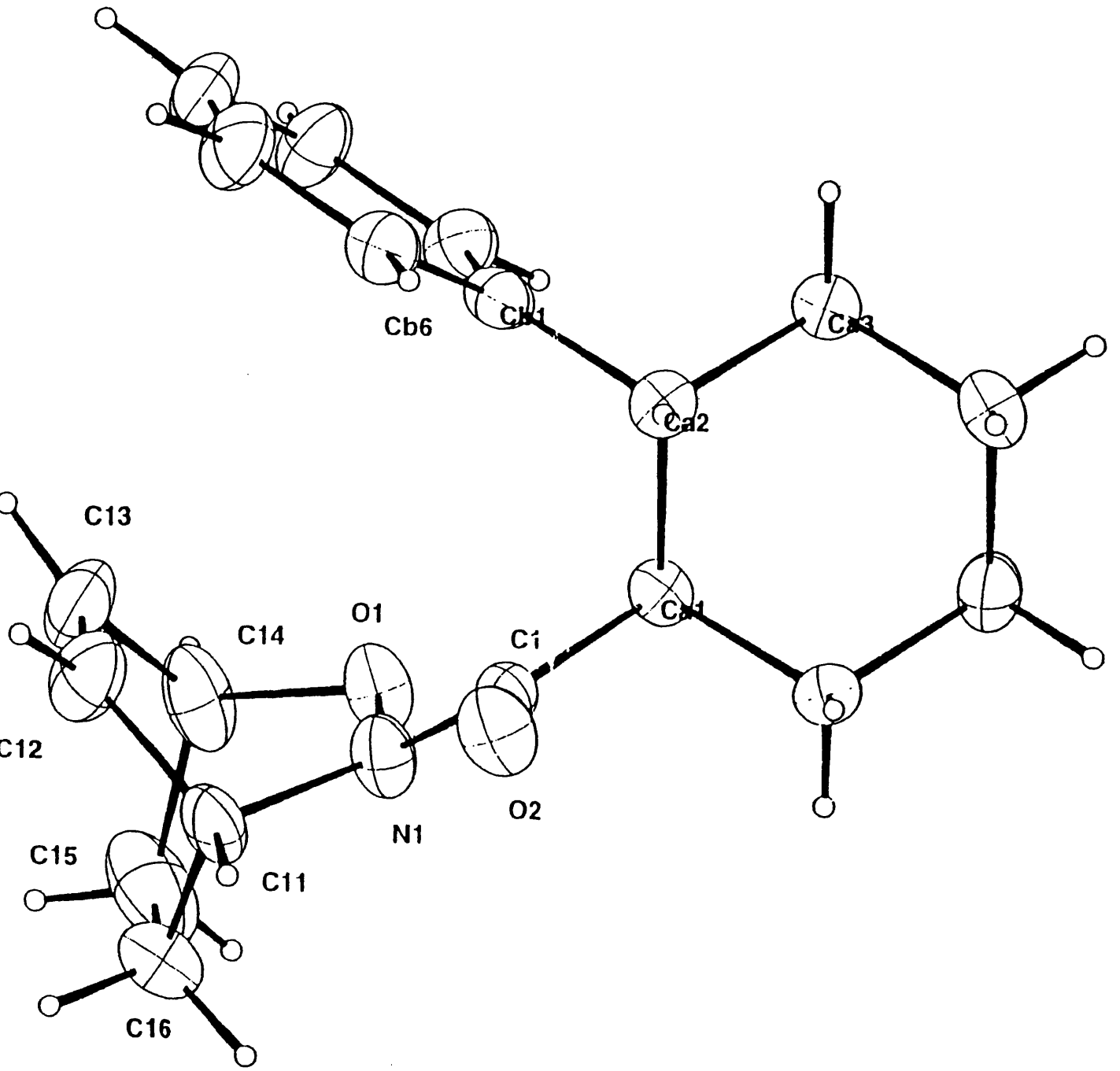
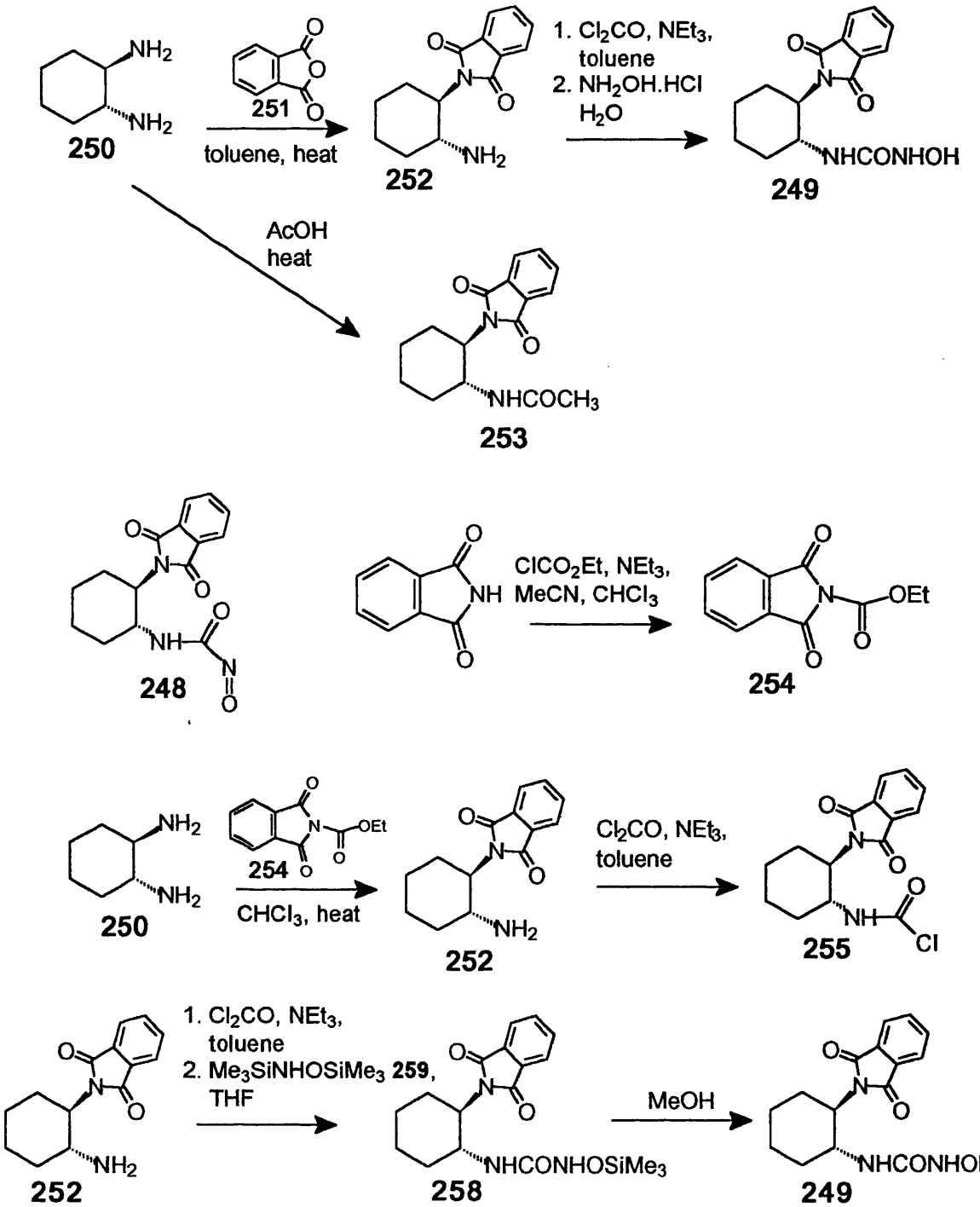
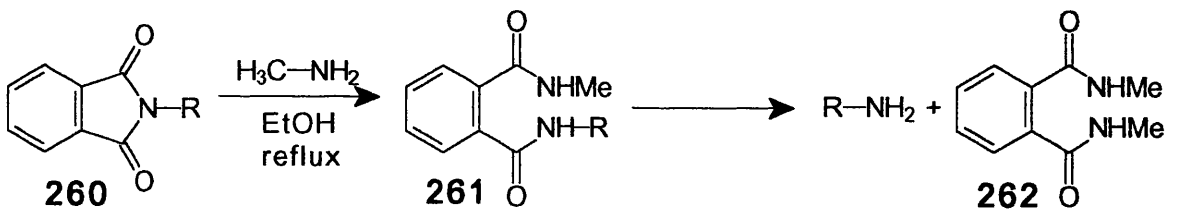


Fig 1. *X*-ray structure of **243**.

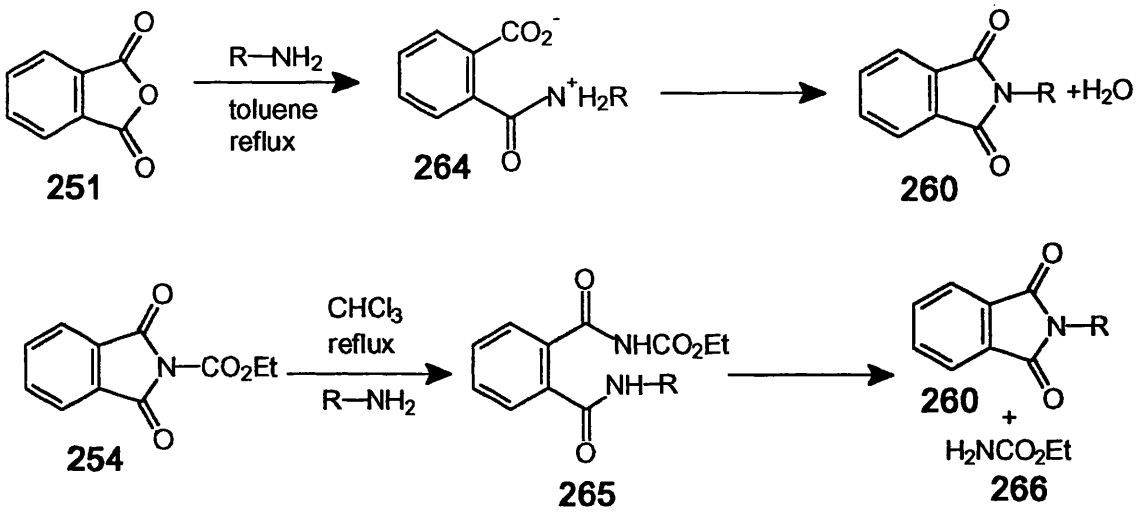
^{1}H NMR shows apparently a 1:1 mixture of diastereomers. Bond lengths essentially the same (*c.f.* 1.33 and 1.54 for double and single bonds, respectively). Note also N now nearly planar, *i.e.* it could be average of two pyramidal forms.



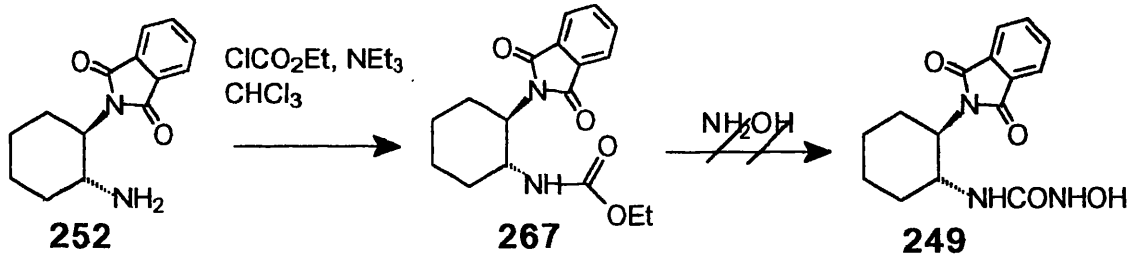
Scheme 50.



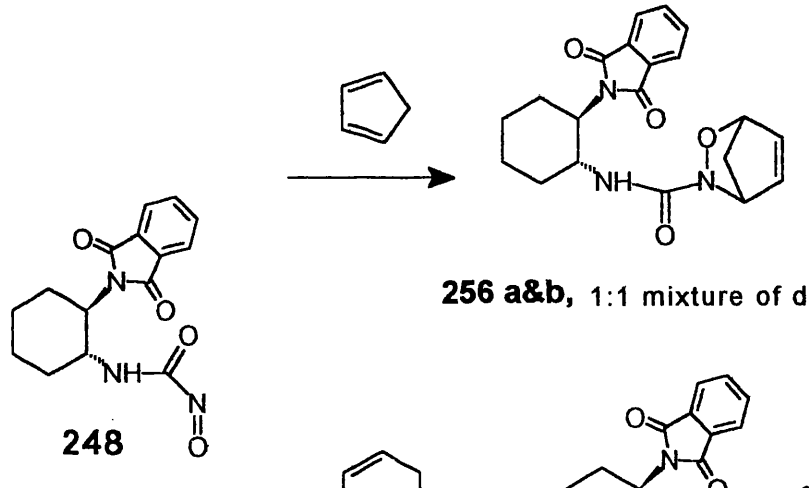
Scheme 51.



Scheme 52.



Scheme 53.



256 a&b, 1:1 mixture of diastereomers

257a&b, 1:1 mixture of diastereomers

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* [51], 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* [52], 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*-ethoxycarbonylphthalimide[53] **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,[54] 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.

$NH_2OH.HCl + (Me_3Si)_2NH$ in THF ref. 55

$NH_2OH.HCl + (Et)_2NH + ClSiMe_3$ in THF ref. 56

$NH_2OH.HCl + H_2NCH_2CH_2NH_2 + ClSiMe_3$ in CH_2Cl_2 ref. 57

The first method[55] 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[56] 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*[57], 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.

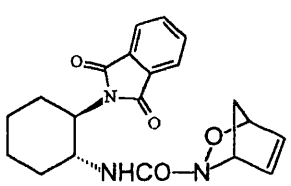
When chloroformate **255** was treated with the silylated hydroxylamine **259** in THF, the desired silylated hydroxyurea was formed rapidly and was isolated by evaporation of the solution. It was deprotected by heating to reflux overnight in methanol to give the desired hydroxy urea **249**.

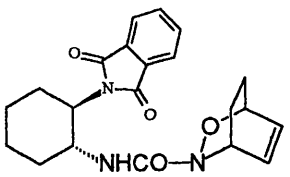
Section 2.5.3 Cycloadditions of the nitrosoformamide dienophile **248**.

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**.

Cycloadduct formed	T/°C	Diene	Oxidant	d.r. ^{1}H	d.r. ^{13}C	Yield % crude (purified)
	0	C_5H_6	Et_4NIO_4	1	1	93 (72)
	-78	C_5H_6	Et_4NIO_4	1	1	99 (54)
256	-78	C_5H_6	DMSO+ $(COCl)_2$	1	1	82 (-)

Cycloadduct formed	T/°C	Diene	Oxidant	d.r. ^{1}H	d.r. ^{13}C	Yield % crude (purified)
	0	C_6H_8	Et_4NIO_4	1	1	107 (48)
257	-78	C_6H_8	Et_4NIO_4	1	1	108 (42)

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.

Swern oxidation with DMSO and $(COCl)_2$.

The dienophile **248** was generated as before with DMSO and $(COCl)_2$, the Swern oxidation conditions, at -78°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°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 ^{13}C 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 phthaloylamino 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 :-

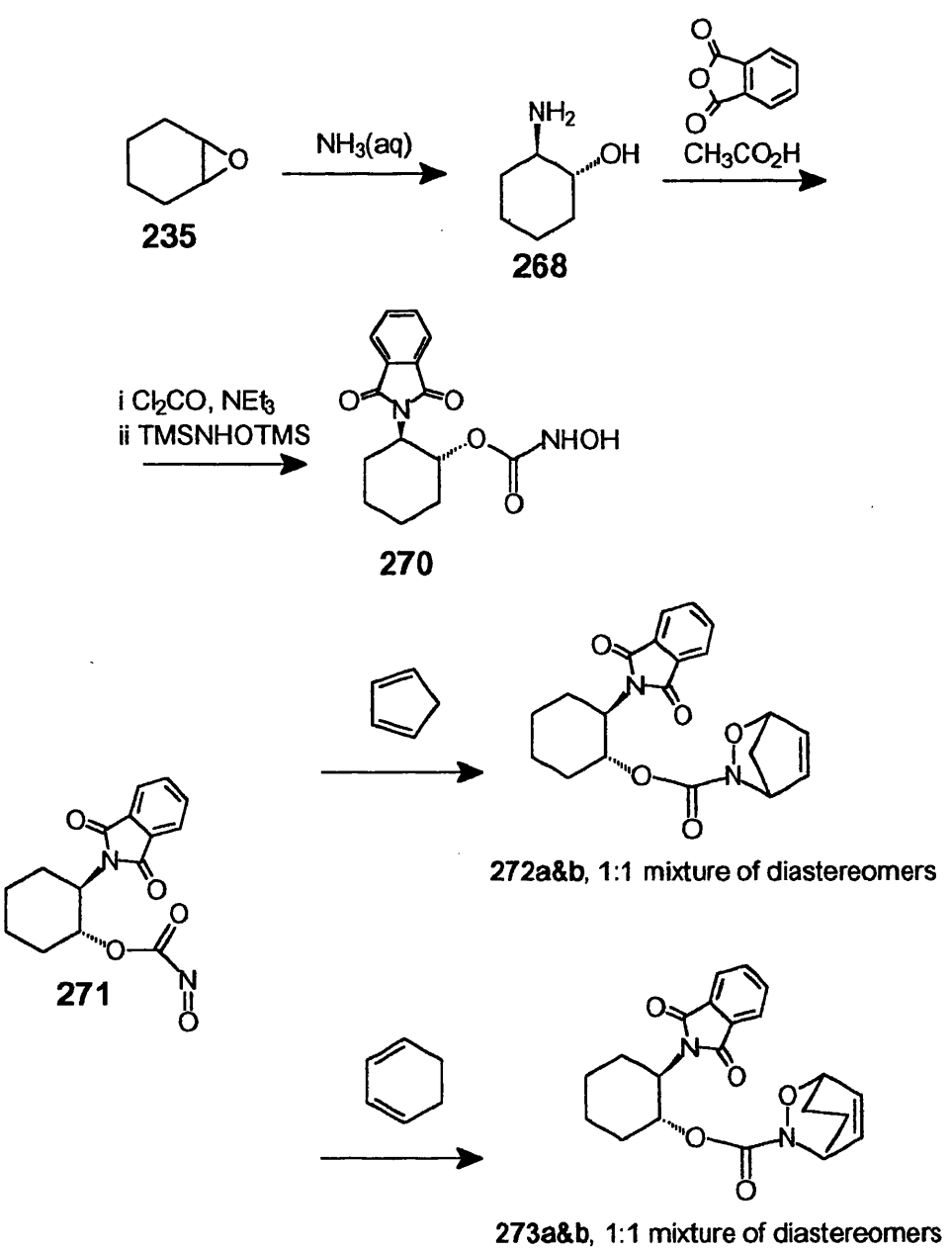
i. The phthaloyl group might not have the same orientation in dienophile **248** as the phenyl group in **234** and therefore might not be as effective in shielding one face of the nitroso group.

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 acylnitroso group in **248** is less rigidly defined.

iii. Since the phthaloyl group is larger and has a larger π system, it is possible that it also interacts with the diene leading to less differentiation between *endo* and *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 **248** with cyclopentadiene and cyclohexadiene.



Scheme 55.

Section 2.6.1 Synthesis of (±)-*trans*-Phthaloylaminocylohexyl 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-*N*-hydroxycarbamate **270** proved far easier than that of the *N*-hydroxyurea **249**. (Scheme 55).

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 [58], (68°C whereas the *cis*-aminoalcohol has m.p. 107-8°C. The amino alcohol **268** was then treated with phthalic anhydride to form *trans*-2-phthaloylaminocyclohexanol **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*-phthaloylamino alcohol **269** was formed and not the *cis*-isomer was indicated by the ^{1}H NMR spectrum of the product. This showed two signals at δ 4.28 and 4.00 due to the C*H*OH and C*H*NPhth respectively. Both of these signals were doublets of triplets with a triplet coupling of 10.2 Hz. In *trans*-phthaloylaminocyclohexanol **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 ~180°, 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).

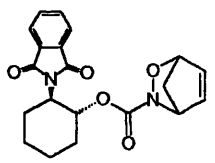
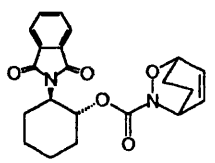
The phthaloylamino alcohol was then converted into *N*-hydroxycarbamate **270**. Treatment with phosgene gave the chloroformate which reacted with *bis*-silylhydroxylamine **259** to give the silylated hydroxycarbamate. This was desilylated with methanol to give the desired racemic hydroxycarbamate **270**. 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.

Cycloadduct formed	T/°C	Diene	Oxidant	d.r.	Yield % Crude (purified)
 **272a&b**	0	C_5H_6	Et_4NIO_4	1:1	113 (87)
	-78	C_5H_6	DMSO + $(COCl)_2$	1:1	97 (-)
 **273a&b**	0	C_6H_8	Et_4NIO_4	1:1	93 (-)
	-78	C_6H_8	DMSO + $(COCl)_2$	1:1	89 (-)

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 ^{1}H and the ^{13}C NMR spectra and these signals were used to show that the two diastereomers were formed in equal amounts.

The ^{1}H 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 ^{13}C 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 ^{1}H NMR spectrum of the less polar fraction **272a** showed that the two diastereomers were fully separated. The C*H*OCO and C*H*NPhtht protons gave doublets of triplets with no sign of the other diastereomer and the ^{13}C 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.

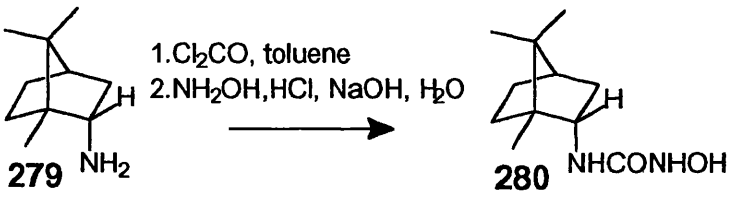
In the ^{1}H NMR spectrum of the crude product, the olefinic protons of the two diastereomers **273a&b** coincided in a broad multiplet and the two bridgehead protons of both isomers overlapped as a broad singlet, with a slight upfield shoulder. In the ^{13}C NMR spectrum, pairs of signals of equal intensity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

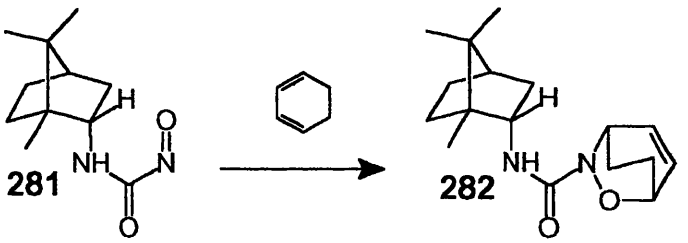
The crude product **273a&b** was purified by column chromatography on alumina eluted with dichloromethane-light petroleum. This resulted in the separation of the two diastereomers **273a&b**. In both the ^{1}H and the ^{13}C NMR spectra of the less polar diastereomer, there was no sign of any other diastereomer.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

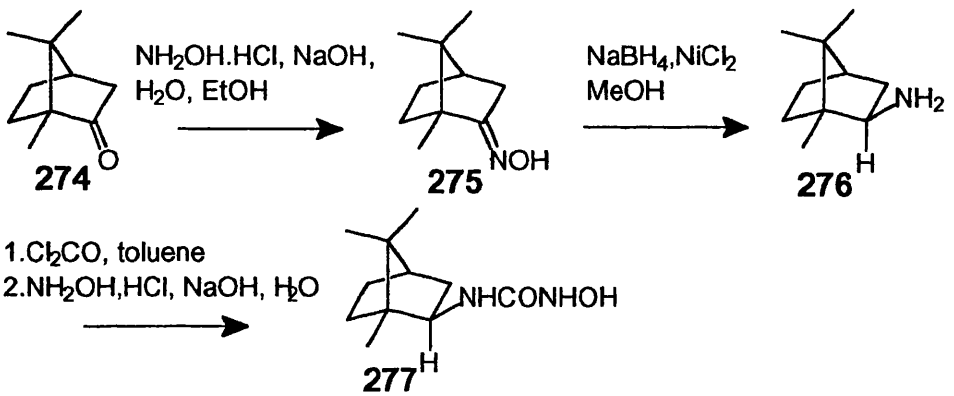
Section 2.6.5 Stereochemistry of the cycloadditions.

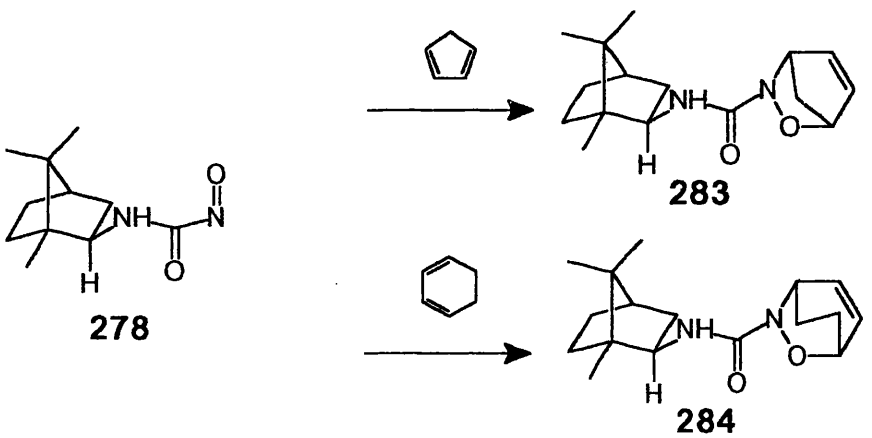
As for the related nitrosoformamide dienophile **248** generated from hydroxyurea **249**, *C*-nitrosoformate dienophile **271** showed no stereoselectivity in the cycloadditions with cyclopentadiene and cyclohexadiene, since both cycloadducts were formed in equal amounts. Even generating and trapping 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.


1.Cl2CO, toluene
2.NH2OH,HCl, NaOH, H2O
279
NH2
280
NHCONHOH


281
NH
O
N
O
282
NH
N
O


NH2OH.HCl, NaOH,
H2O, EtOH
NaBH4,NiCl2
MeOH
274
O
275
NOH
276
NH2
H
1.Cl2CO, toluene
2.NH2OH,HCl, NaOH, H2O
277
NHCONHOH
H


278
NH
O
N
O
H
283
NH
N
O
O
H
284
NH
N
O
O
H

Scheme 56.

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**.

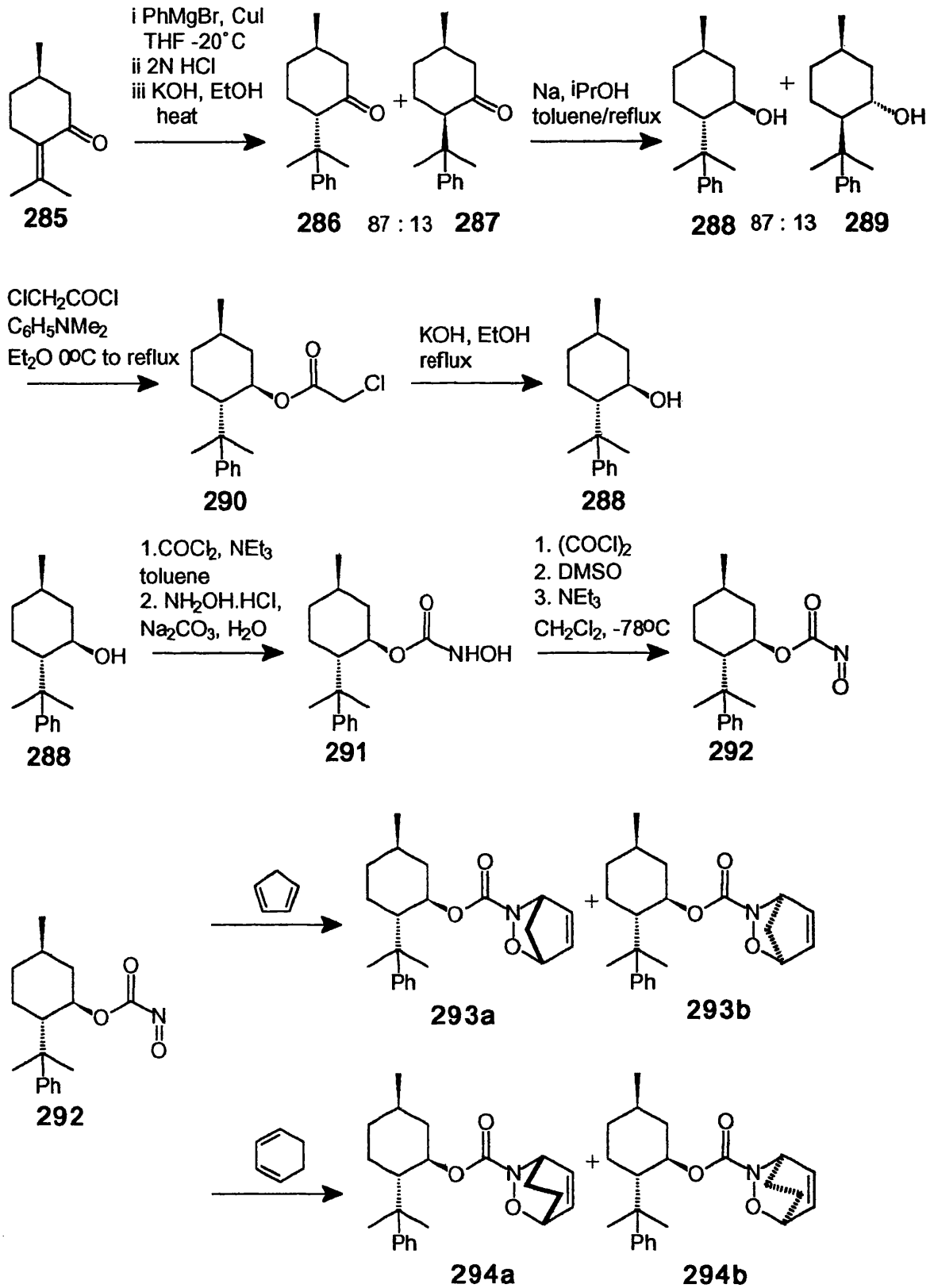
(±)-*exo*-bornylamine **276** was synthesised from racemic camphor oxime **275**, which was formed in good yield by treating camphor with hydroxylamine in aqueous ethanol [59]. Attempts were made to hydrogenate the oxime **275** to give the *exo*-bornylamine **276**. Morris *et al* [60] carried out the 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.[61] 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.

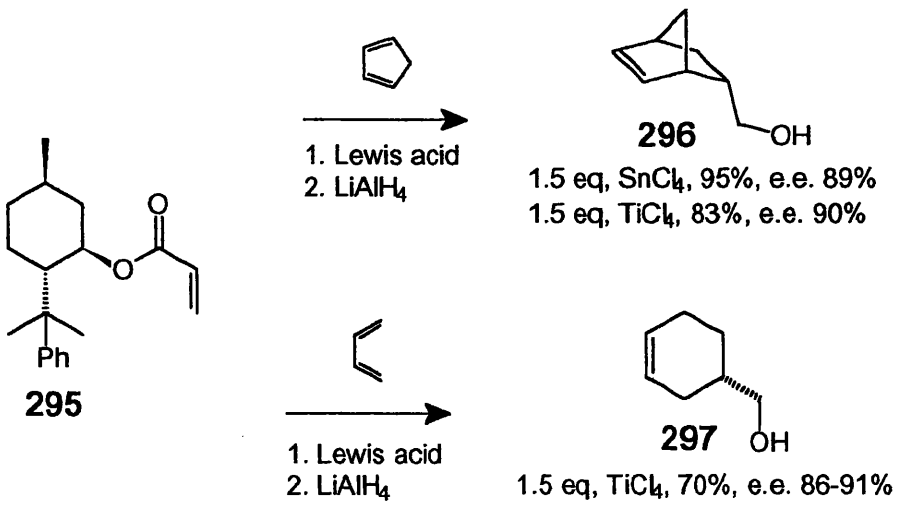
Section 2.7.4 Cycloadditions of the dienophile **278**.

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.


i PhMgBr, CuI
THF -20°C
ii 2N HCl
iii KOH, EtOH
heat
Na, iPrOH
toluene/reflux
285
286 87 : 13 287
288 87 : 13 289
ClCH2COCl
C6H5NMe2
Et2O 0°C to reflux
KOH, EtOH
reflux
290
288
1.COCl2, NEt3
toluene
2. NH2OH.HCl,
Na2CO3, H2O
1. (COCl)2
2. DMSO
3. NEt3
CH2Cl2, -78°C
288
291
292
292
293a
293b
294a
294b

Scheme 57.



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[62] and to make it, we followed the procedure of Ort[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**, *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)[64,65].

Section 2.8.2. Synthesis of hydroxycarbamate 291.

The starting material for the synthesis of the 8-phenylmenthol was (*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°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 ^{1}H and ^{13}C 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 (C*H*OH) in the ^{1}H NMR spectra and peaks at δ 72.9 (*CH*OH) and δ 54.08 (*C*Me$_2$Ph) 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).

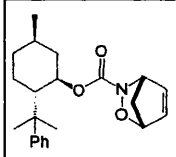
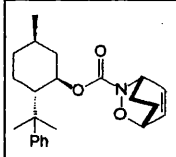
From the NMR spectra of cyclopentadiene adducts **293a&b** it was found that the ratio of diastereomers formed in the reaction was 7.1:1. The ^{1}H NMR spectrum, showed a d.r. of 8.6 :1, which was measured from the signals observed for the olefinic protons and the bridgehead protons. The ^{13}C NMR spectrum 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 ^{13}C NMR spectrum, although the signals were not as well separated as those of the cyclopentadiene adducts. In the ^{1}H 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 ^{13}C spectrum. Only some of the signals of the minor diastereomer **294b** were visible. In the ^{1}H 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.

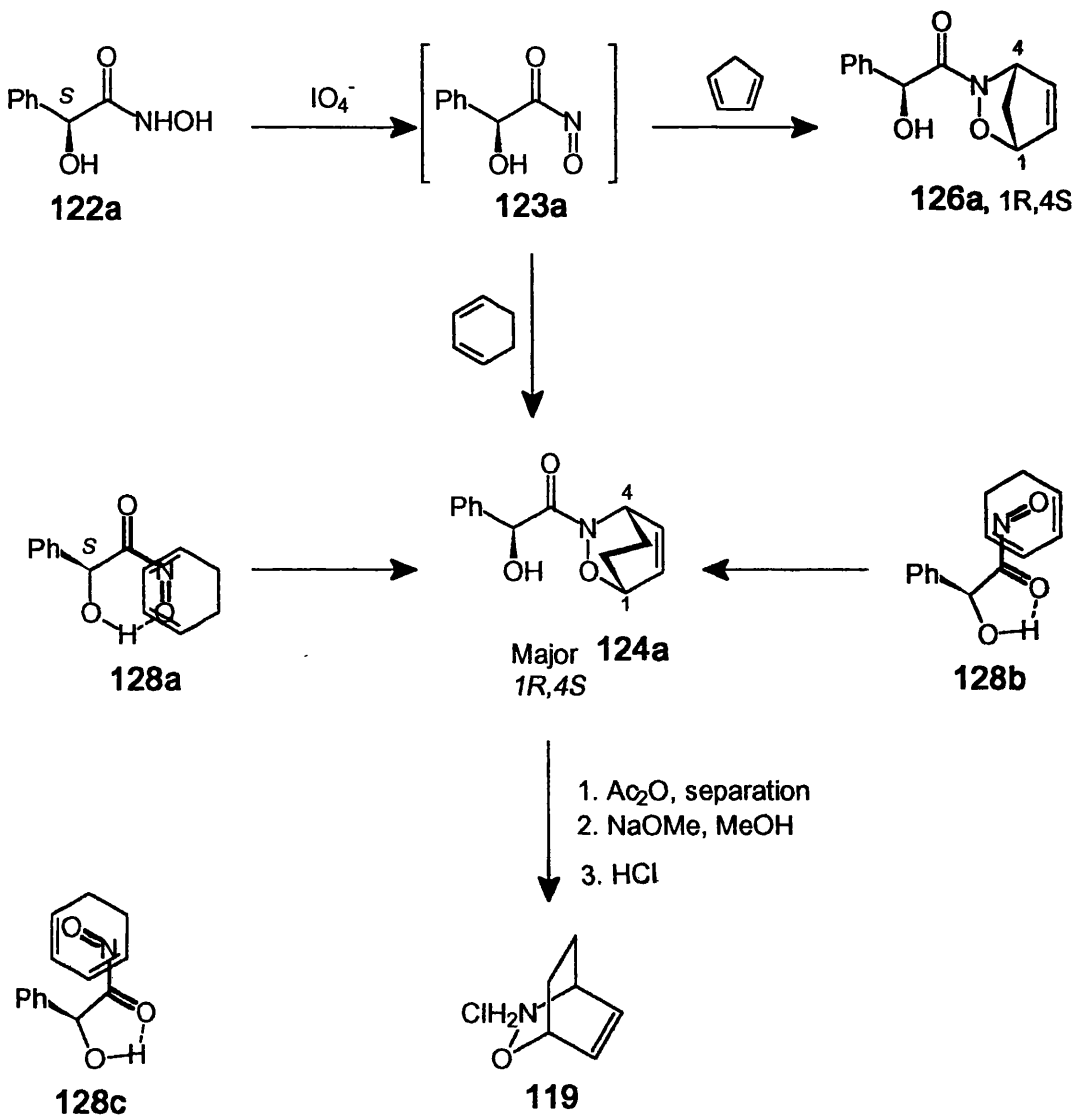
Table 20. Cycloadducts of dienophile **292**[a] trapped with cyclopentadiene and cyclohexadiene.

Cycloadduct	Diene	^{1}H ratio	^{13}C ratio	Average	de %	Yield %, crude (pure)
 **293**	C_5H_6	8.62	5.6	7.11	75	91(82)
 **294**	C_6H_8	-	6.15	6.15	72	88(59)

[a] formed from **291** oxidation with $(COCl)_2$ and DMSO at -78°C, in CH_2Cl_2.

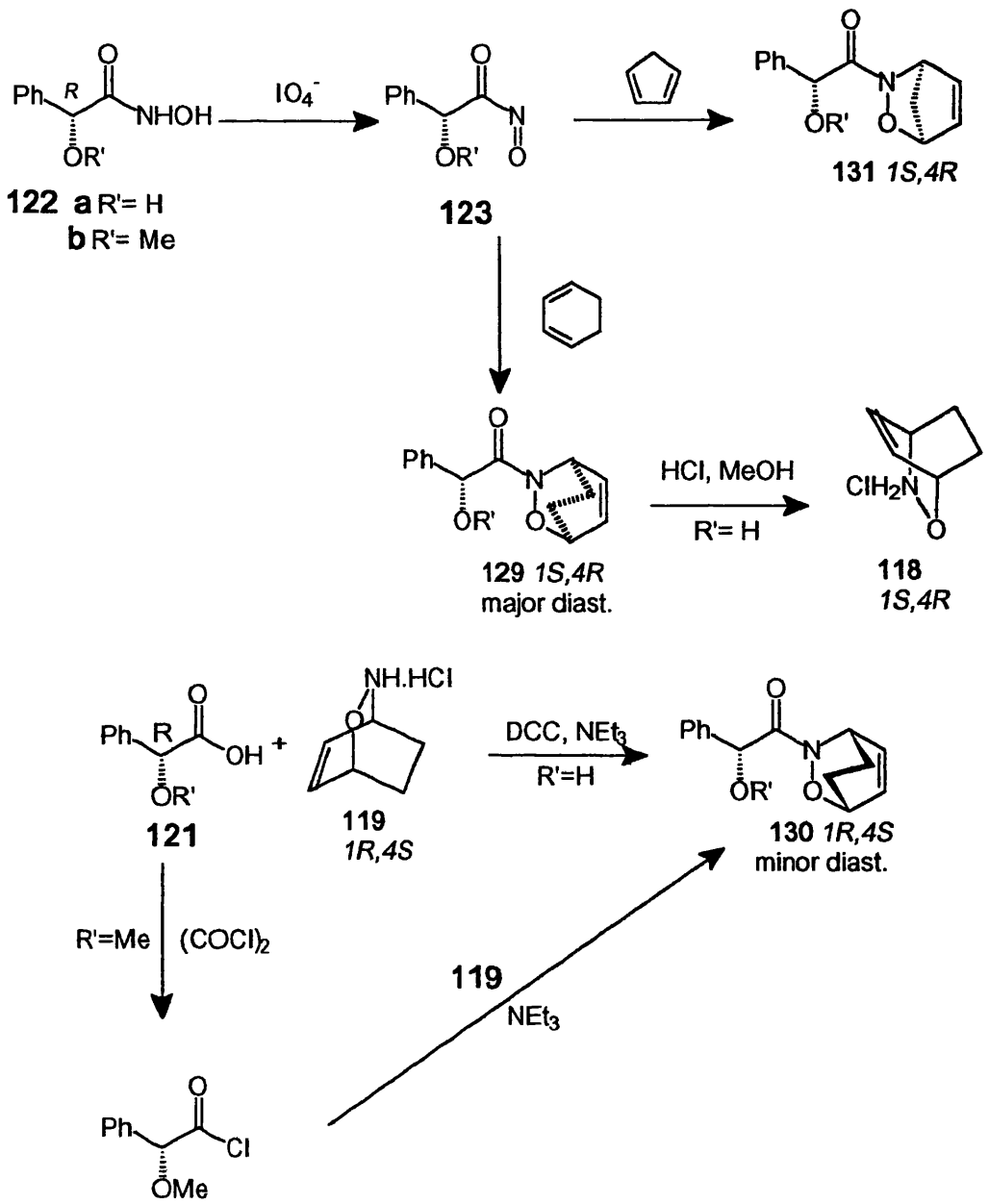
It is to be noted that the d.e. of these two cycloadditions are not as good as those of the acrylate **295**.

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



Scheme 59.

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



Scheme 60.

Section 2.9 Stereocontrol using chiral auxiliaries.

Section 2.9.1 Stereochemistry of published cycloadditions.

Kirby and Nazeer[22] (Scheme 59), Defoin *et al*[23] (Scheme 60) and Procter *et al*[24](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[19] *1R,4S*.

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

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

ii) the cycloaddition is mainly *endo* and

iii) the diene adds selectively to the face of the nitroso group *anti* to the phenyl group.

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

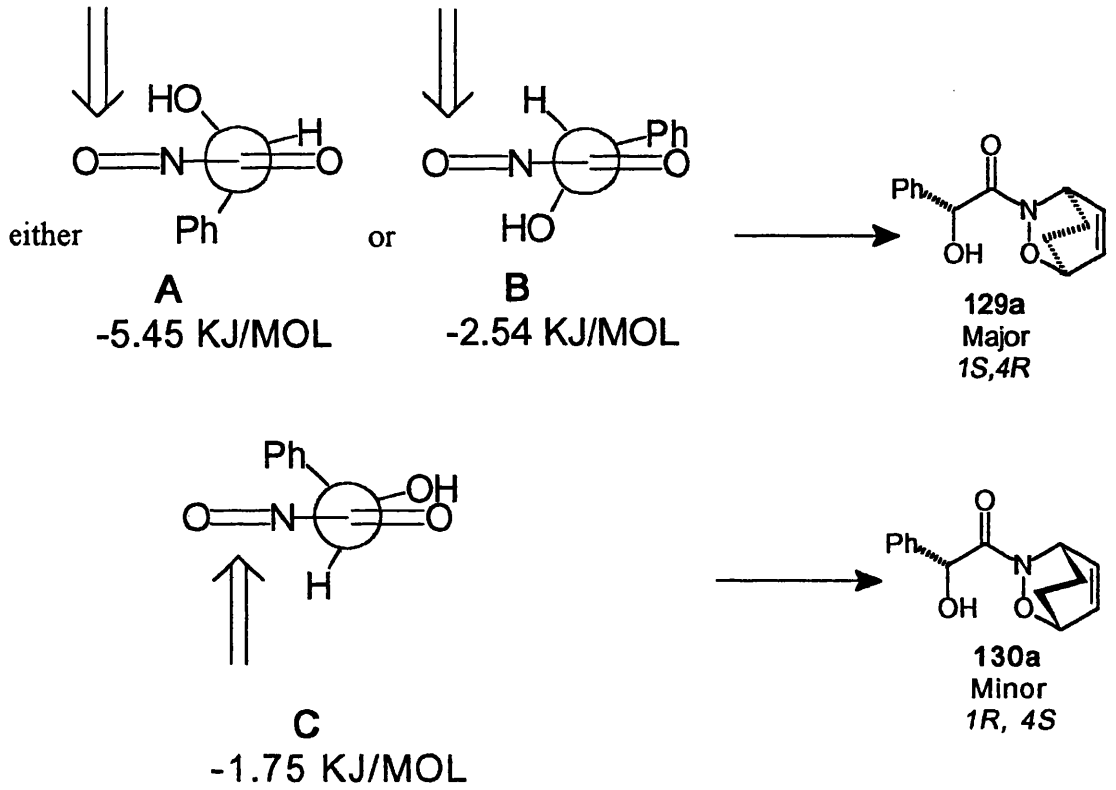
i) 6-membered, H-bonded rings are generally favoured over 5-membered rings

ii) **128b** which would give the observed result, has unfavourable dipole-dipole repulsions, expected for the *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 *et al* have carried out independent studies[24] (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.



Scheme 61.

also had the *1S,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.*

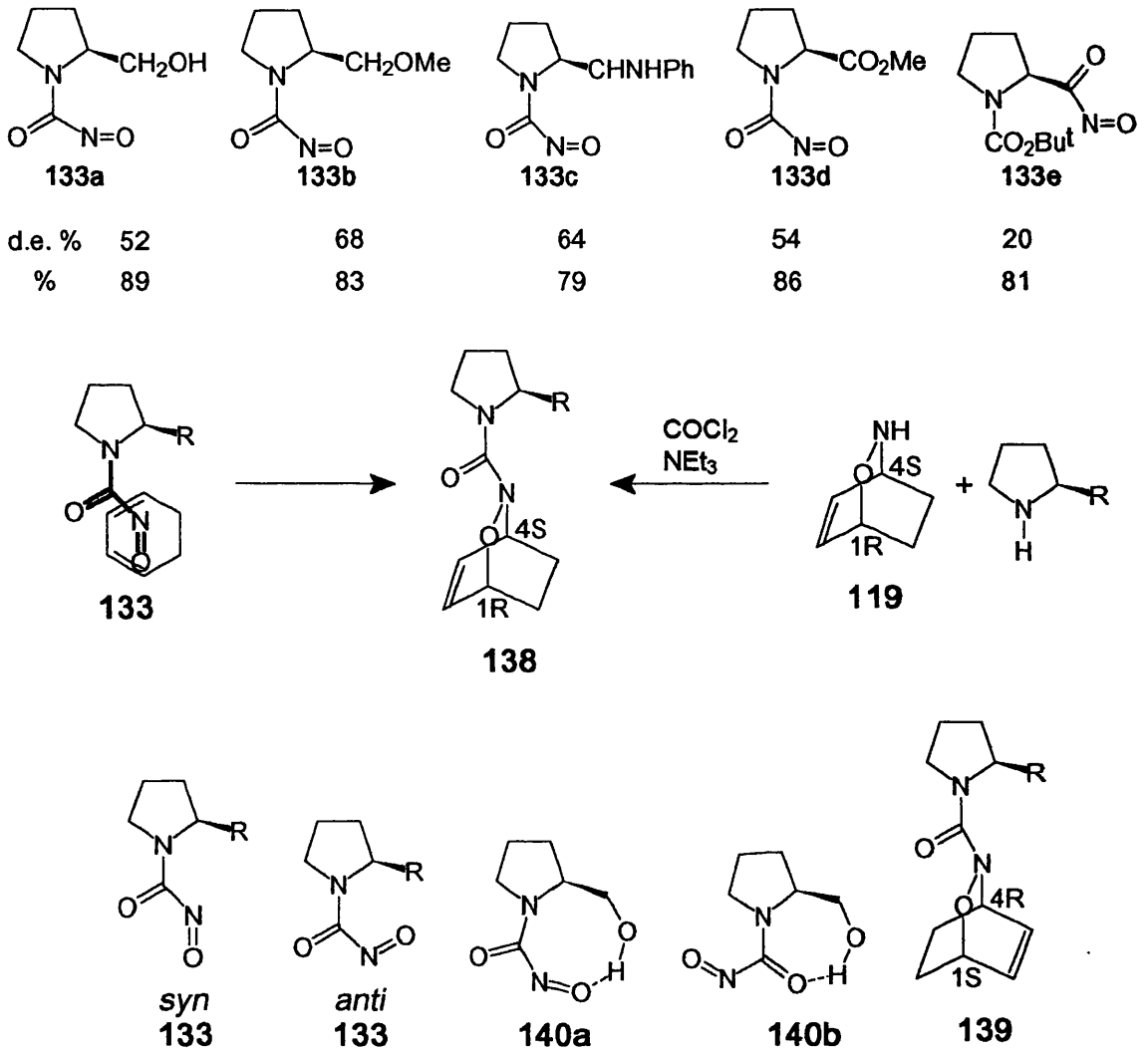
Using the (*R*)-dienophile **123a**, the group of Defoin have also independently investigated the stereoselectivity of the cycloadditions of **123a** with cyclohexadiene. The absolute stereochemistry of cycloaddition, was determined by synthesising the methylated **minor** cycloadducts **130b** from (+)-*1R,4S*-oxazine **119** [α_D= +24.0°] and mandeloyl chloride (Scheme **60**). This shows that the major diastereomer **129a** has the opposite *1S,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 α-hydroxy dienophile **123a** produced a larger diastereomeric induction than the α–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.

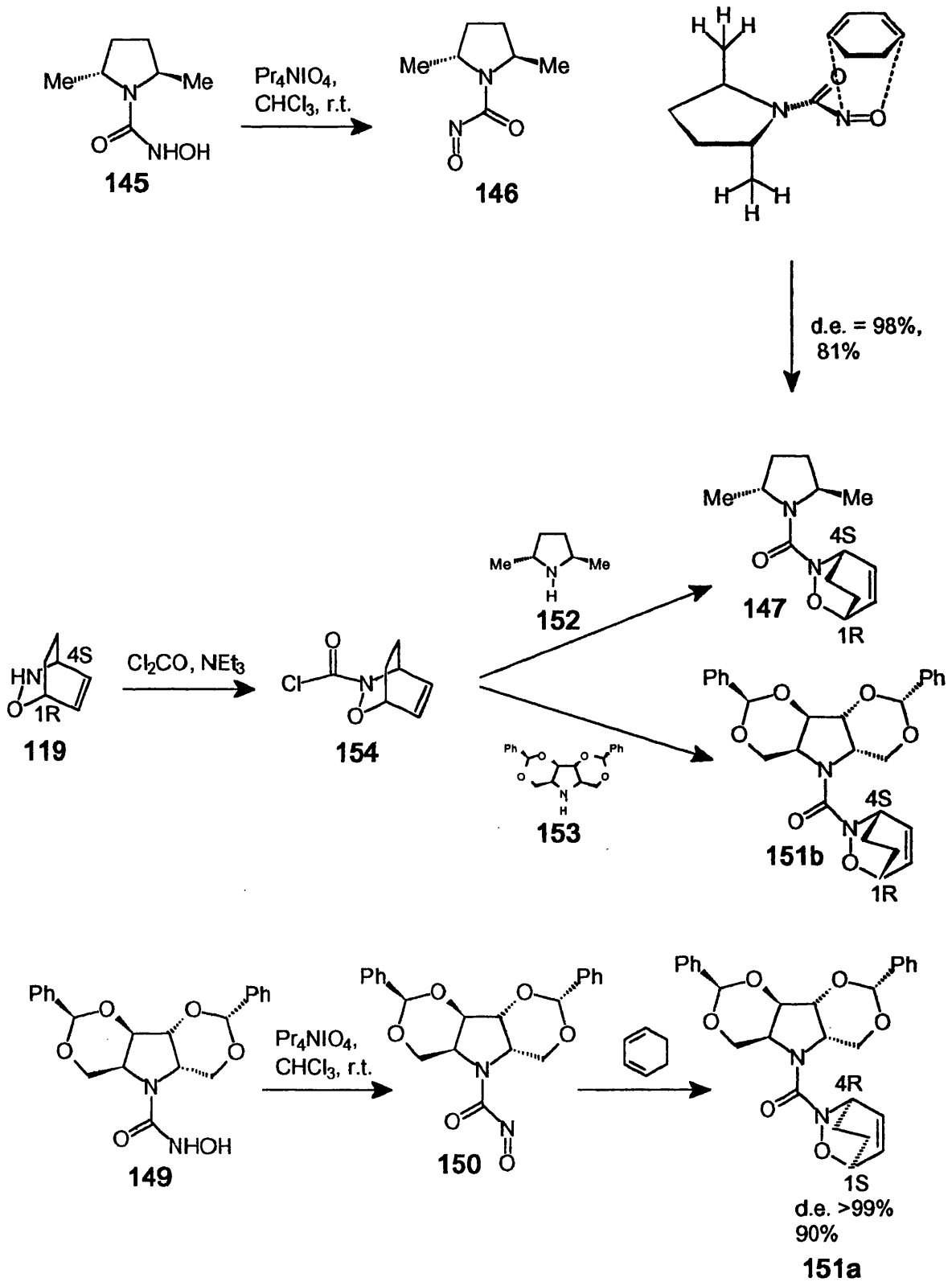
Procter *et al* have carried out molecular modelling on the acylnitroso dienophile **123a**[66] (Scheme 61). These calculations predict not only that the conformation with the nitroso *anti* to the carbonyl group is more stable than the corresponding *syn* conformation by 11.7 kJ/mol but also that two 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 acylnitroso cycloadditions.



Scheme 62.

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



Scheme 63.

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*[25] 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**.

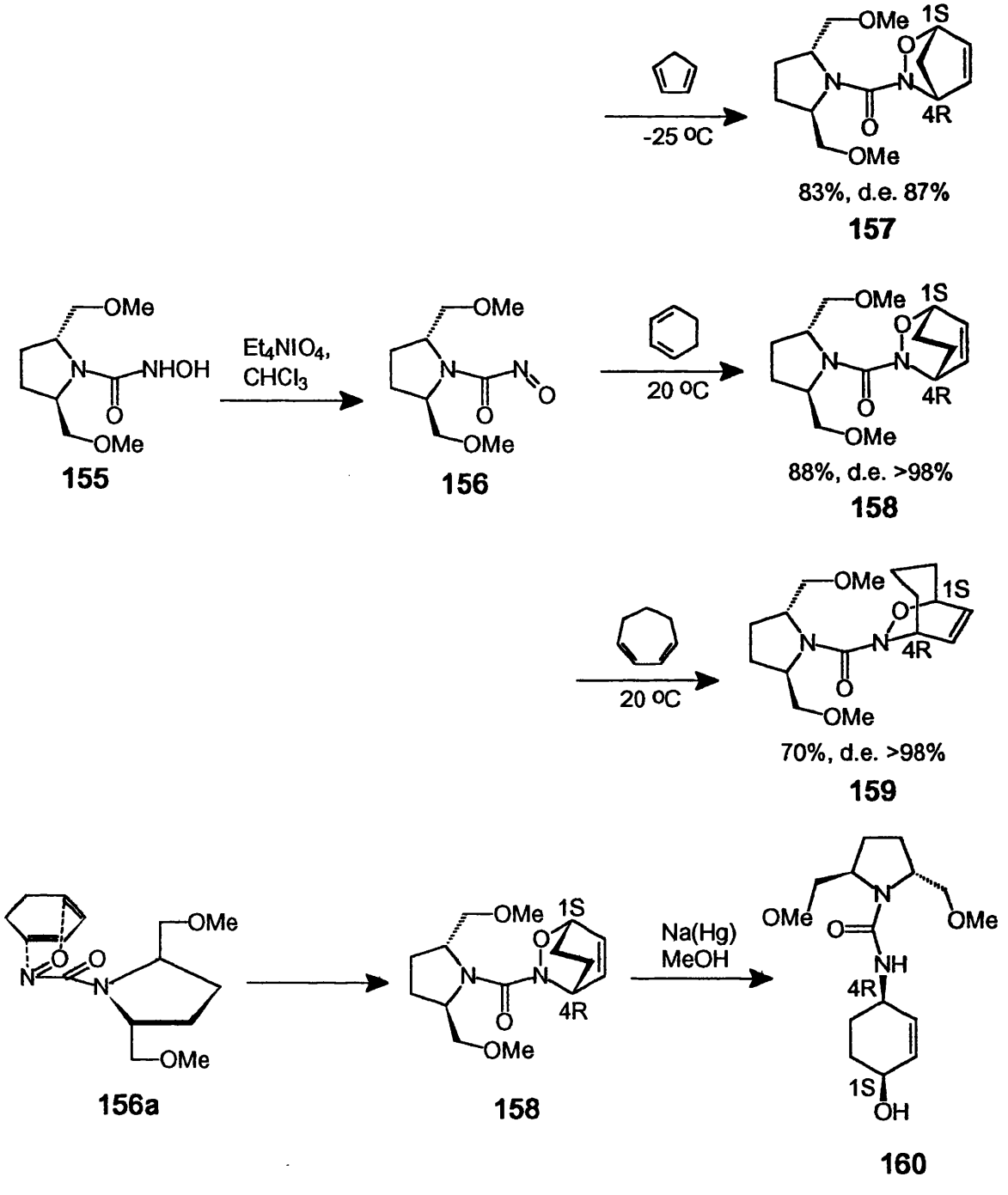
To determine the absolute stereochemistry of the cycloaddition, each of the major diastereomers **138a-e** was synthesised from the known *1R,4S*-oxazine **119**, proving that the major adducts **138a-e** must have this absolute configuration in the oxazine moiety. Assuming that the attack of the diene 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_2 symmetry based on chiral pyrrolidines.

Defoin *et al*[27] 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.

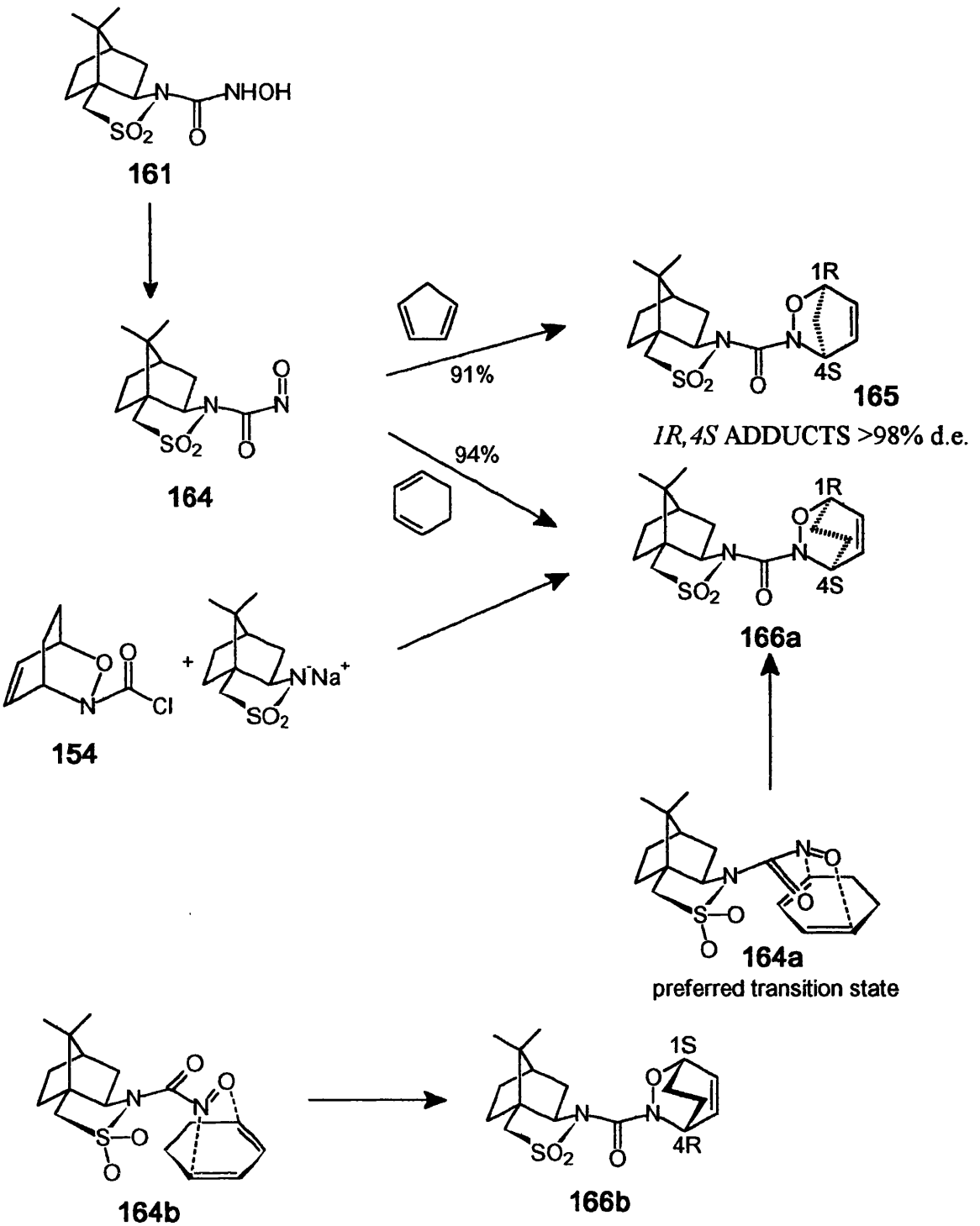
The absolute stereochemistry of the cyclohexadiene adducts **147** and **151a** was determined by independently synthesising them from (*1R,4S*)-chiral oxazine **119** (Scheme 63). Treatment of tricyclic pyrrolidine **153** with chlorocarbamate **154** gave minor cycloadduct **151b**, which was not actually produced in the cycloaddition; hence the only cycloadduct formed in the cycloaddition **151** had the *1S,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.

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 Gouverneur[28] have investigated the cycloadditions of the C_2 symmetric dienophile **156** with cyclohexadiene, cycloheptadiene and cyclopentadiene (Scheme 64).

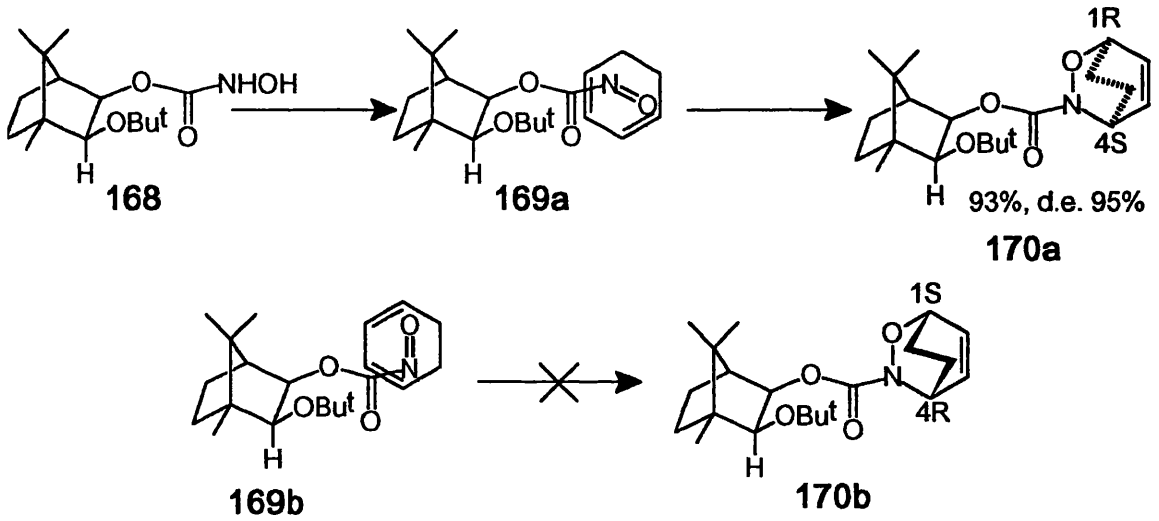
The absolute stereochemistry of the oxazine moiety of the major diastereomer of cyclohexadiene adduct **158** was determined from the X-ray structure of the reduced amido alcohol **160** to be *1S,4R*. This stereochemistry was explained by postulating that in the transition state (Scheme 64) the acylnitroso 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 al*[29] 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 SO_2.

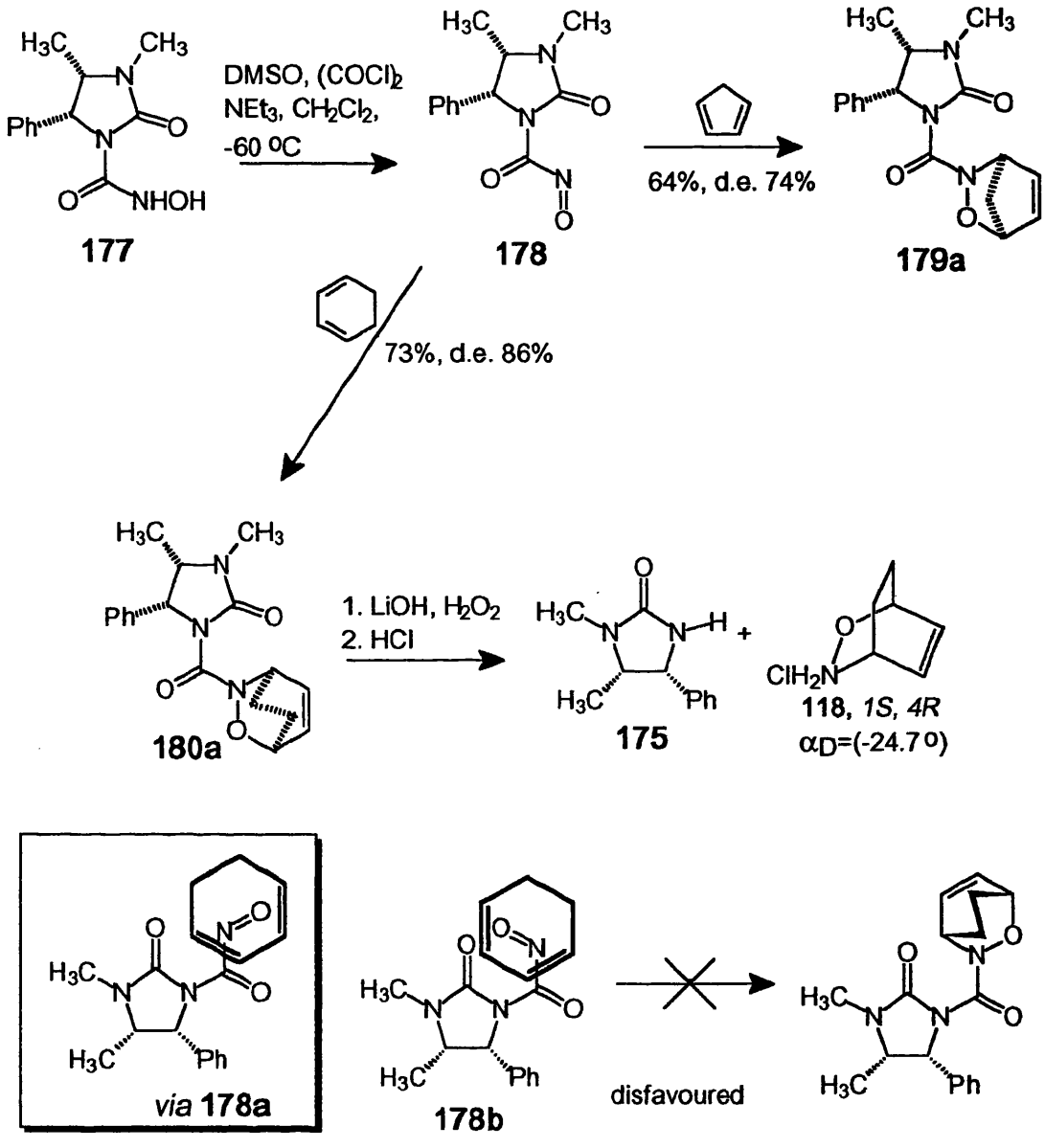
Martin *et al*[30] have investigated the Diels-Alder reactions of nitrosoformate **169** which gave excellent diastereoselectivities with a range of cyclohexadienes (Scheme 66).

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



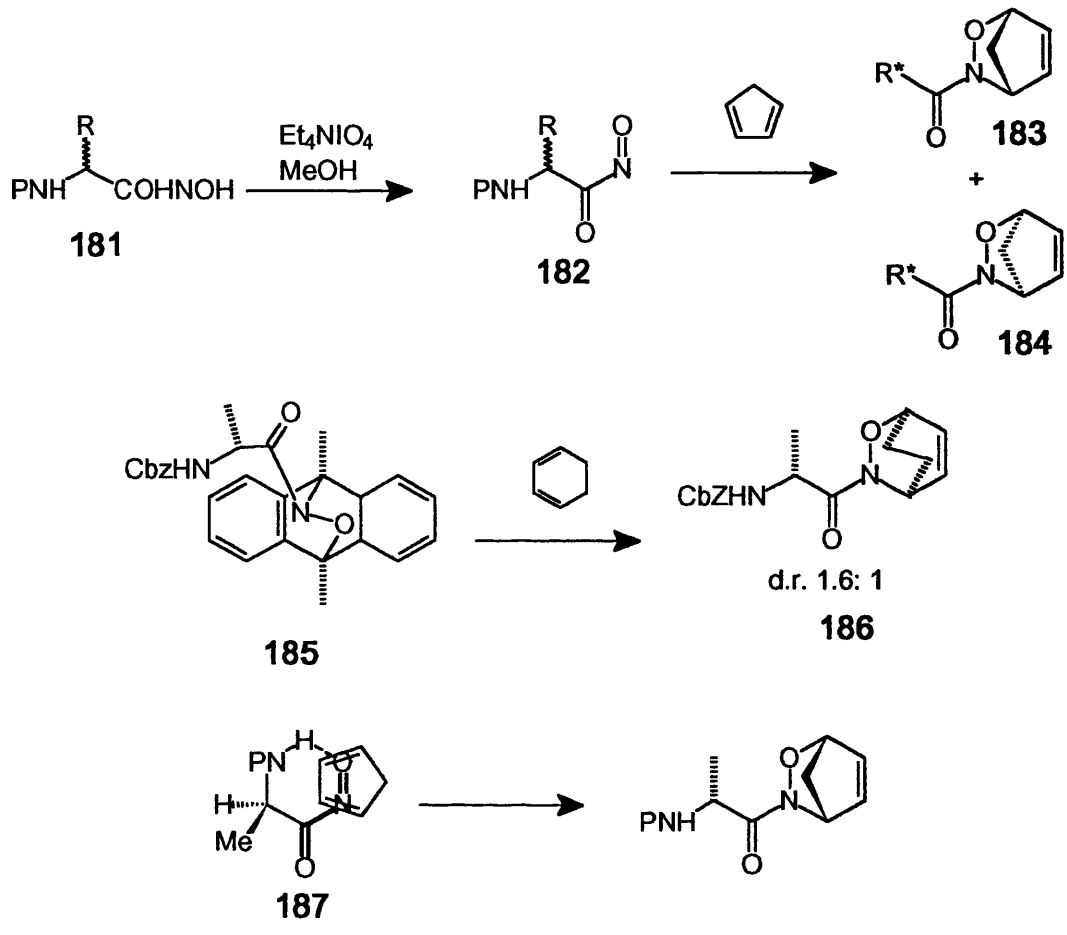
Scheme 66.

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



Scheme 67.

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



Scheme 68.

	Amino acid	R	P		Yield %	d.r. **183: 184**
a	(*L*)-valine	^{i}Pr	Cbz	*S*	85	1: 4
b	(*L*)-alanine	Me	Cbz	*S*	90	1: 3
f	(*L*)-alanine	Me	Boc	*S*	78	1: 3
c	(*D*)-alanine	Me	Cbz	*R*	78	3: 1
d	(*L*)-phenylalanine	CH_2Ph	Cbz	*S*	79	1: 2
e	(*L, D*)-phenylalanine	CH_2Ph	Cbz	*R, S*	75	-

To determine the absolute configuration, the major cyclohexadiene adduct **170a**, was hydrolysed with base to give the known chiral *1R,4S*-oxazine **119** [α_D=+24.4°].

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*[33] 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**, [α_D= -24.7° , c=1, $CHCl_3$].

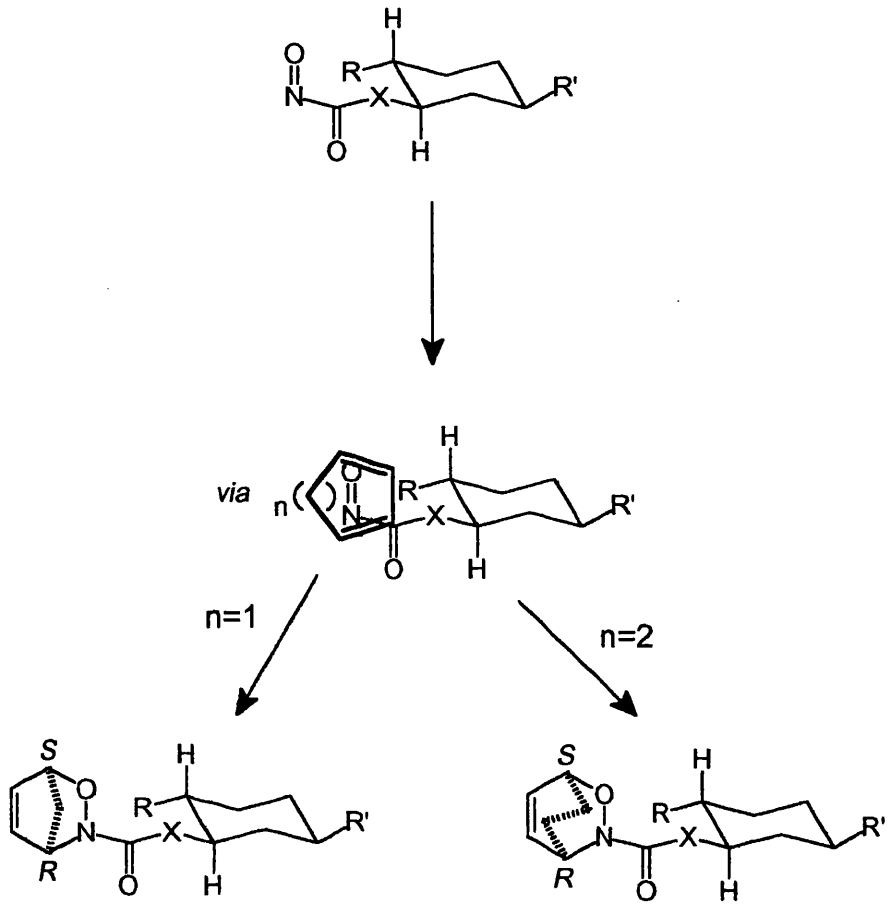
Molecular modelling predicted that the most stable conformer of the dienophile would have the two carbonyl groups *anti* to one another. Rotation of the nitroso group revealed that the optimum conformation was *anti, syn* conformer **178a**, which was more stable than *anti, anti* conformer **178b** 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 *1S, 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.



R	R'	X	Dienophile	Diene	Cycloadduct	Prediction
Ph	H	NH	**234**	C_5H_6	**232b**	✖
Ph	H	NH	**234**	C_6H_8	**233b**	✖
Ph	H	O	**238**	C_5H_6	**239a**	✔
Ph	H	O	**238**	C_6H_8	**240a**	✔
$PhMe_2C$	Me	O	**292**	C_6H_8	**294b**	✖

Scheme 69, showing the predicted cycloadducts from the cycloadditions of dienophiles **234, 238 & 292** with cyclopentadiene and cyclohexadiene.

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. 1S, 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.

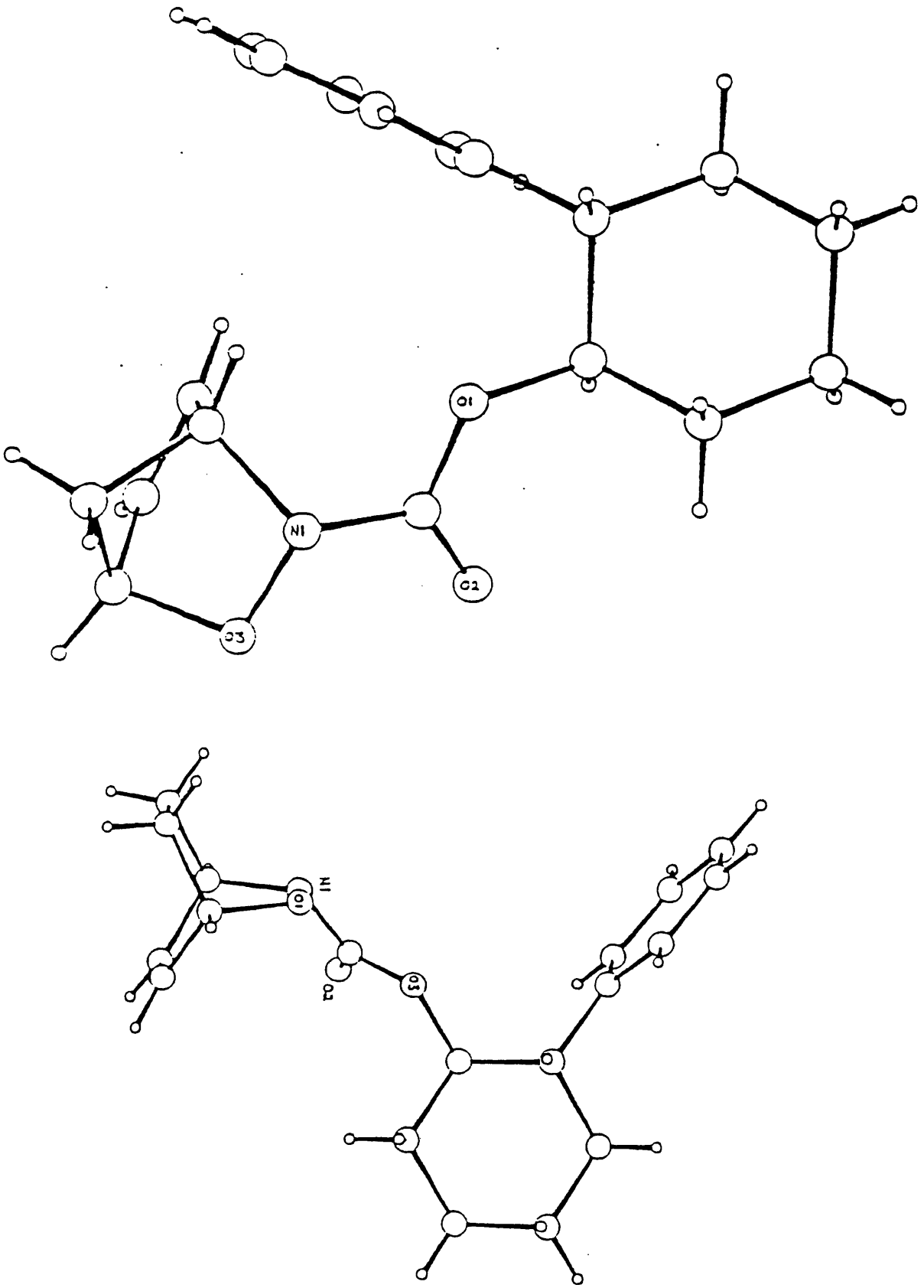
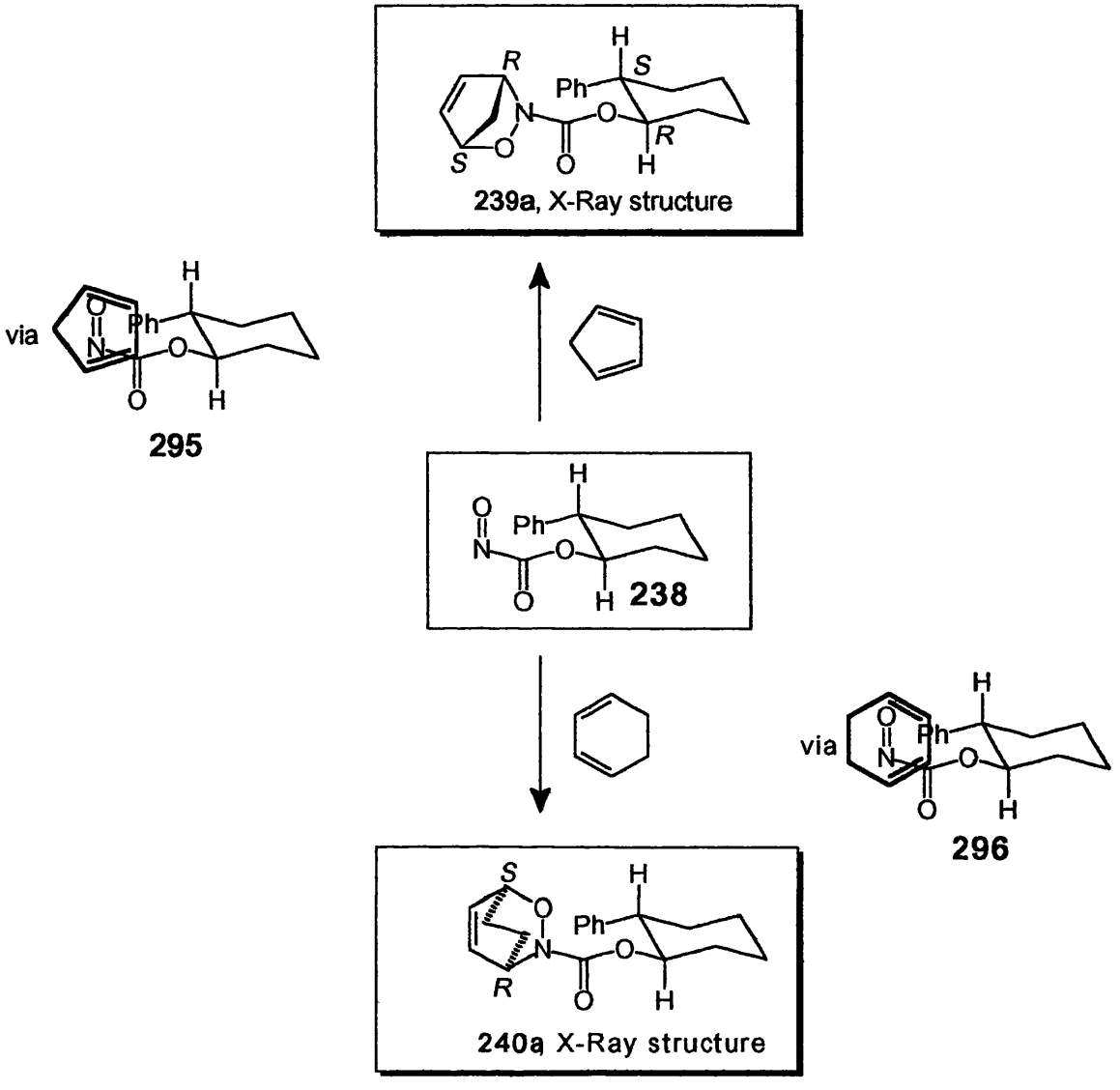


Fig 2. *X*-ray structures of the major cyclopentadiene adduct **239a** and the major cyclohexadiene adduct **240a** of nitrosoformate dieneophile **238**.

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.

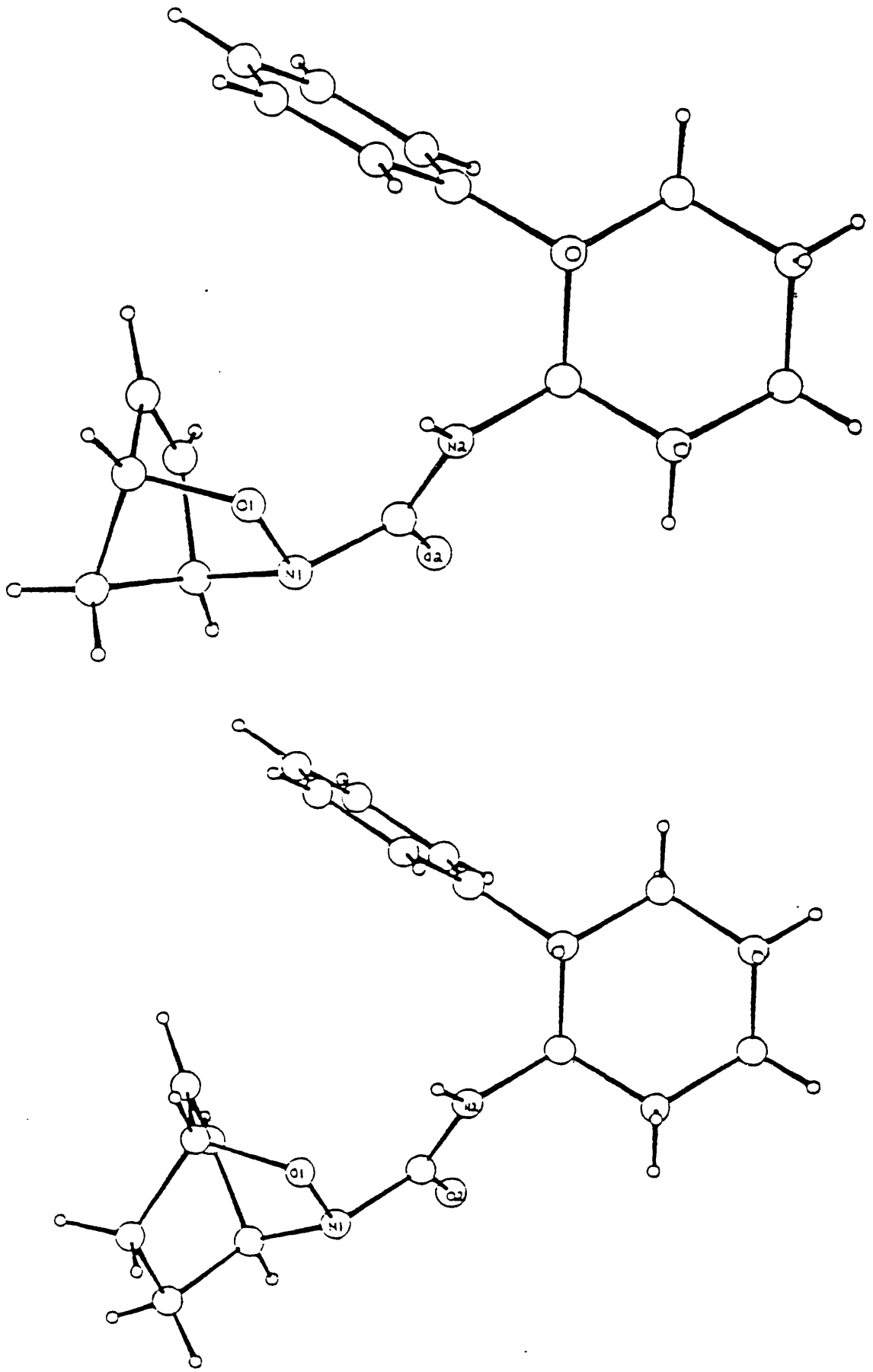
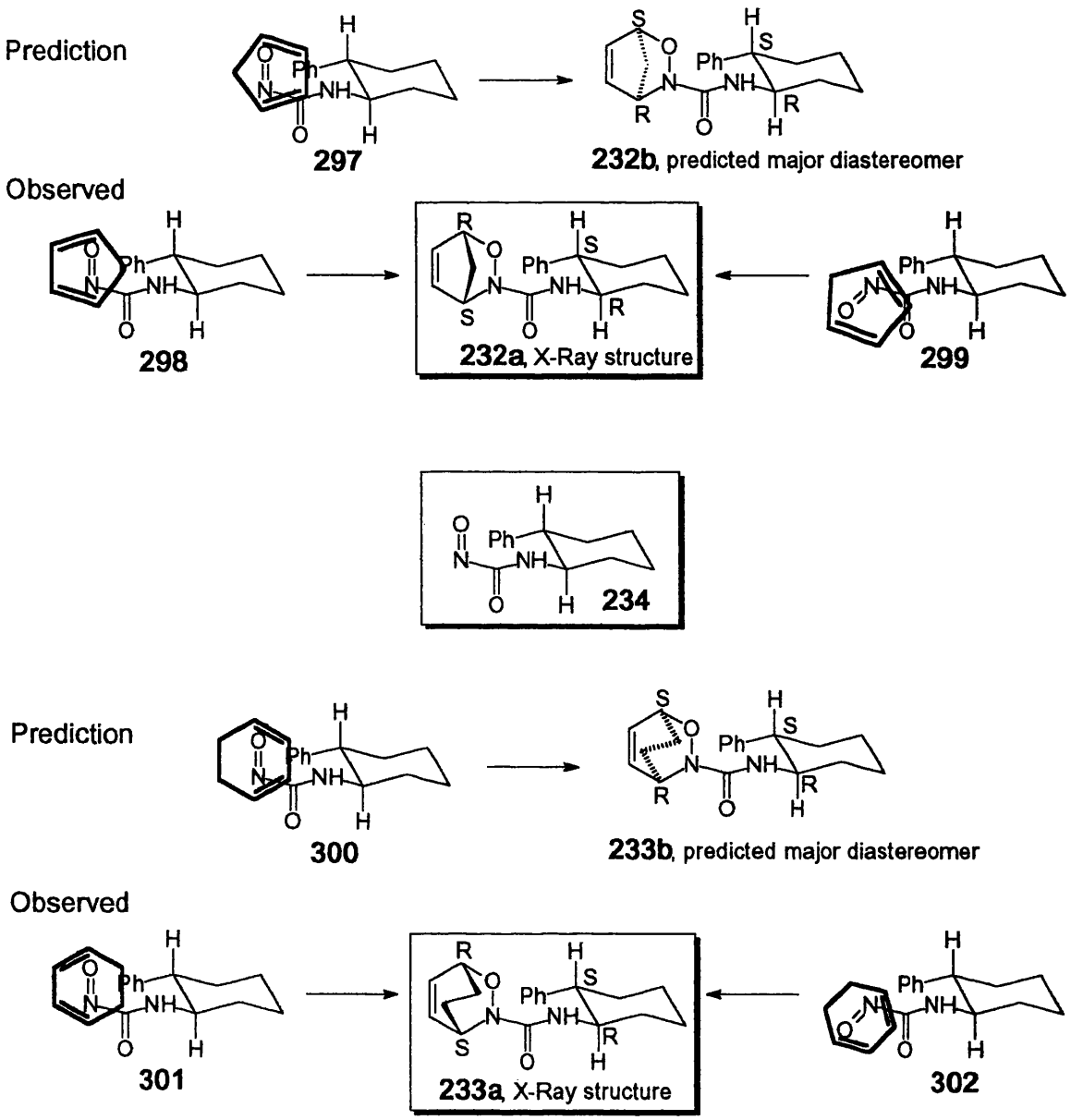


Fig 3. *X*-ray structures of the major cyclopentadiene adduct **232a** and the major cyclohexadiene adduct **233a** of nitrosoformamide dieneophile **234**.

Section 2.9 Discussion of diastereoselectivities in acylnitroso cycloadditions.



Scheme 71, showing the predicted and observed cycloadducts from the cycloadditions between nitrosoformamide dienophile **234** and cyclohexadiene and cyclopentadiene.

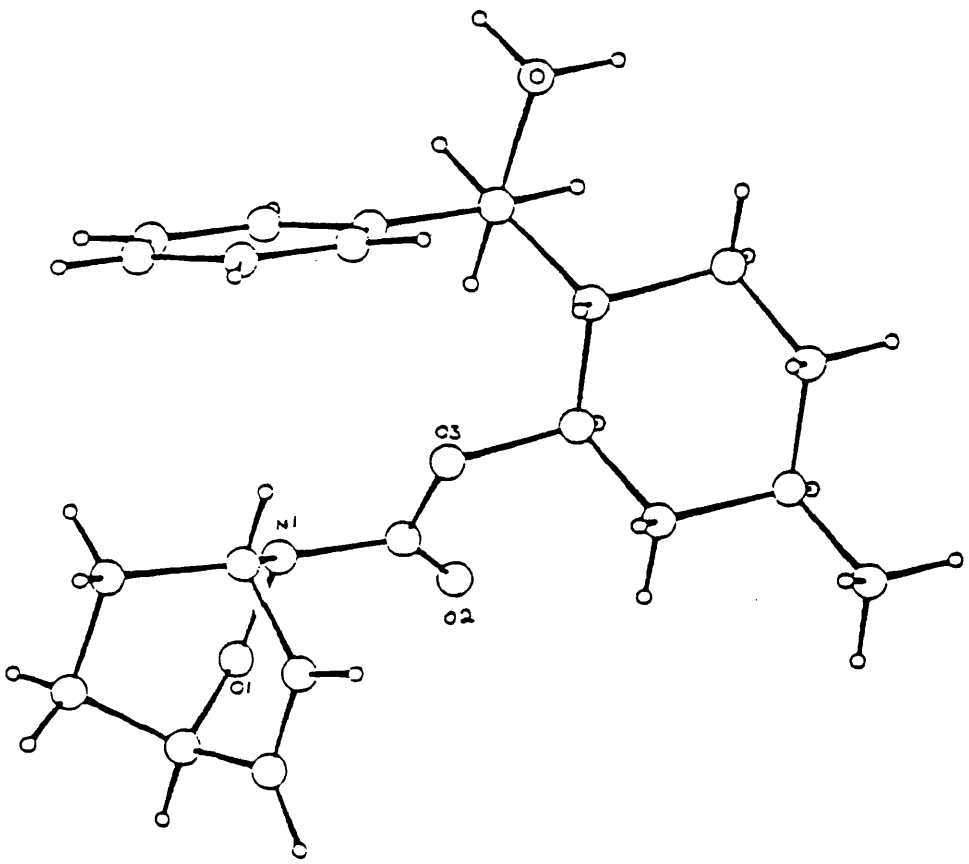
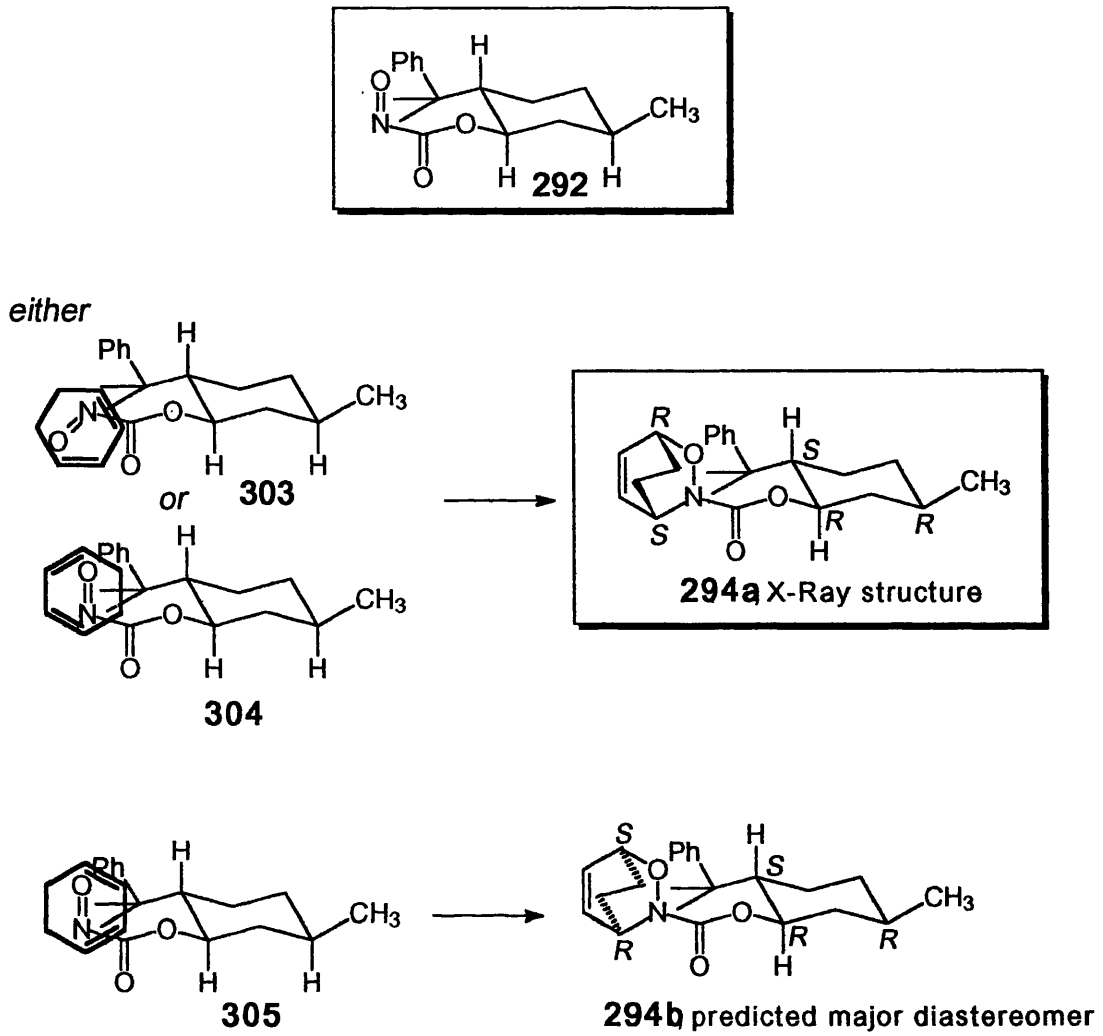


Fig 4. *X*-ray structure of the major cyclohexadiene adduct **294a** of nitrosoformate dieneophile **292**.

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 *1S, 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. 1R, 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

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 diasteroselectivities. 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 nitrosoformate **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**.

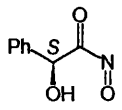
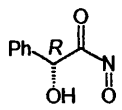
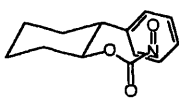
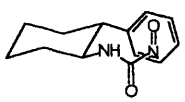
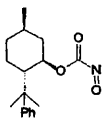
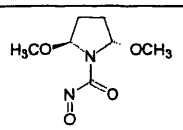
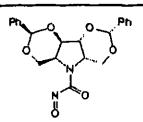
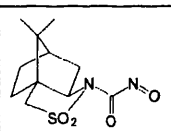
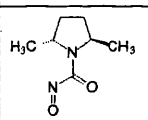
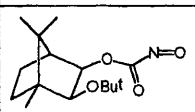
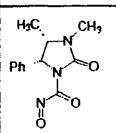
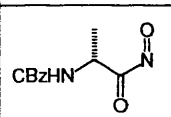
	Dienophile	Diene	Oxidant/ T°C	*syn/ anti*	d.e. %	Yield %
123a		C_5H_6	A/ -78	*anti*	82	71
		C_6H_8	A/ -78	*anti*	72	53
123		C_5H_6	A/ -78	*anti*	75	70
		C_6H_8	A/ -78	*anti*	75	-
238		C_5H_6	B/ -78	*anti*	69	102
		C_6H_8	B/ -78	*anti*	75	92
234		C_5H_6	B/ -78	*syn*	65	92
		C_6H_8	A/ -78	*syn*	50	73
292		C_5H_6	B/ -78	*syn*	75	82
		C_6H_8	B/ -78	*syn*	72	59
156		C_5H_6	A/ -78	*syn*	87	83
		C_6H_8	A/ -78	*syn*	>98	88
150		C_6H_8	A/ -78	*syn*	>99	90
164		C_5H_6	A/ -78	*syn*	>98	91
		C_6H_8	A/ -78	*syn*	>98	94
146		C_6H_8	A/ -78	*syn*	98	81
169		C_5H_6	A/ -78	*syn*	91	89
		C_6H_8	A/ -78	*syn*	95	93
178		C_5H_6	A/ -78	*syn*	74	64
		C_6H_8	A/ -78	*syn*	86	73
182c		C_5H_6	A/ -78	*syn*	50	90

Table 21, Summary of diastereoselectivities and conformations of various dienophiles. Oxidation A, IO_4^-; B, Swern oxidation.

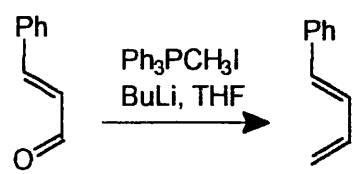
NMR spectra were recorded with a Bruker WP 200 spectrometer (^1H, 200 MHz; ^{13}C, 50 MHz) in $CDCl_3$ solution unless otherwise stated, calibrated with either internal TMS or with deuterium lock and run by Mr J. Gall or Mr J. McIver. 90 MHz spectra were recorded with a Perkin-Elmer R-32 (^1H, 90 MHz) 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 GF_{254} plates and visualised using UV light and/or iodine bath. For hydroxamic acids, the plate was sprayed with ethanolic $FeCl_3$ and heated to give a purple, red colour. Dry column chromatography employed Merck silica HF_{254}, 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.

$$Ph_3P + MeI \xrightarrow{\text{toluene}} Ph_3PCH_3I$$

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 (23.64g, 90%) as a white solid, which was used without further purification.

1-Phenylbuta-1,3-diene **218.**



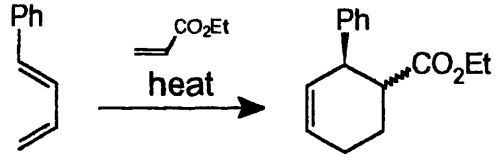
217 **218**

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 (4.67g, 67%) (identical to lit., [43]).

(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.**



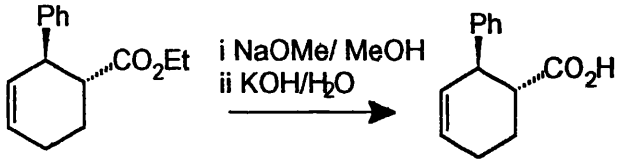
218 **219**

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%).

υ_{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, CH_2CH_3 &$CHCO_2Et$), 2.93 (0.5H, m, CHPh), 2.60 (0.5H, m, CHPh), 1.81-2.27 (4H, m, cyclohexyl CH_2) and 1.11 (3H, t, J 7.1, CH_2CH_3); 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).

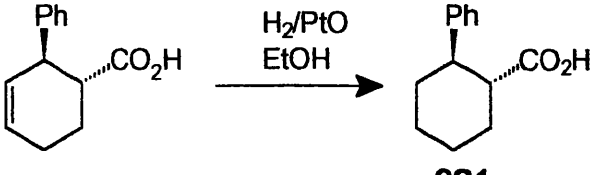
(±)-*trans*-2-Phenyl-1-cyclohex-3-ene-1-carboxylic acid **220.**



219 **220**

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., [42]). (Found: M^+, 202.0977. $C_{13}H_{14}O_2$ requires M, 202.0994); υ_{max}/ cm^{-1} (KBr disc) 1705 (C=O); δ_H 11.2-11.6 (0.98H, br m, CO_2H), 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, $CHCO_2H$), 2.53 (1H, dt, J 3.2 & 8.8, $CHPh$) and 1.68-2.14 (4H, m, CH_2 of ring); δ_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, $CHCO_2H$), 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**.

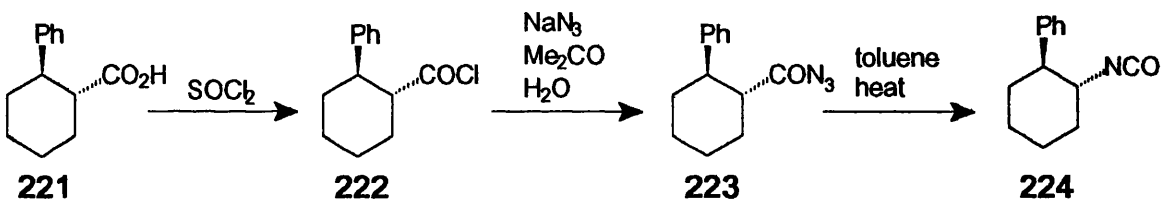


220 **221**

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]).

υ_{max}/ cm^{-1} (KBr disc) 3030, 2860, 2940 and 1705 (C=O); δ_H 10.8-11.4 (1H, br s, CO_2H), 7.12 (5H, m, aromatic), 2.60 (1H, dt, *J* 3.5 & 11.4, C*H*CO_2H), 2.46 (1H, dt, *J* 3.4 & 11.3, C*H*Ph) and 1.19-2.0 (8H, m, CH_2 of cyclohexane); δ_C 181.36 (s, C=O), 144.41 (s), 128.34 (d, 2xCH), 127.18 (d, 2xCH), 126.38 (d), 49.71 (d, *CH*CO_2H), 45.90 (d, *CH*Ph), 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**.



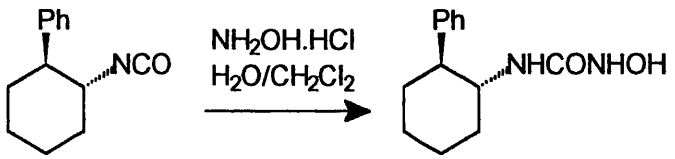
221 **222** **223** **224**

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.

υ_{max}/ cm^{-1} ($CHCl_3$) 2260s (NCO); δ_H 7.12-7.30 (5H, m, Ph), 3.41 (1H, dt, *J* 4.0 & 10.7, C*H*NCO), 2.40 (1H, dt, *J* 3.5 & 11.1, C*H*Ph) and 1.11-2.07 (8H, m, cyclohexane); δ_C 143.20 (s), 128.66 (d, 2x*CH* Ph), 127.47 (d, 2x*CH* Ph), 127.03 (d, CH Ph), 58.81 (d, *CH*NCO), 52.62 (d, *CH*Ph), 35.52 (t), 33.81 (t), 25.72 (t) and 25.07 (t).

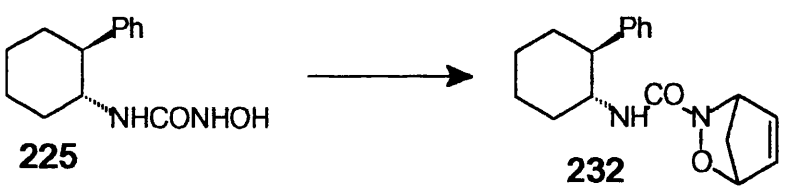
(±)-*trans*-2-Phenylcyclohexane-1-N,N'-hydroxyurea **225.**



224 **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. $C_{13}H_{18}N_2O_2$ requires C, 66.66; H, 7.69; N, 11.96; *M*, 234.1368); υ_{max}/ cm^{-1} ($CHCl_3$) 1660m (C=O) and 1550s; δ_H 7.14 (5H, m, Ph), 5.69 (2H, d, *J* 8.8, N*H*CONHOH, D_2O exchange), 3.77 (1H, br m, C*H*NHCONHOH), 2.39 (1H,br m, C*H*Ph) and 1.23-2.14 (8H, m, cyclohexane); δ_C 161.37 (s, C=O), 143.52 (s), 128.42 (d, 2xCH), 127.51 (d, 2xCH), 126.44 (d), 52.84 (d, *CH*NHCONHOH), 50.80 (d, *CH*Ph), 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).

(±)-3-[*trans*-2-Phenylcyclohexylaminocarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **232.**



225 **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) (R_f 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) (R_f 0.50) as white solids.

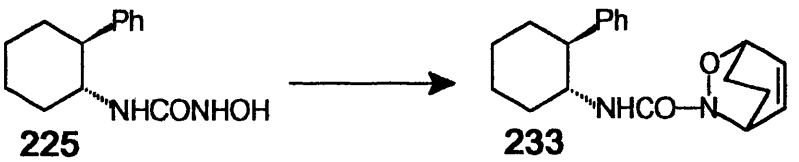
This experiment was repeated following General Procedure A at -78°C, with hydroxyurea **225** (0.21 g, 0.90 mmol) all other quantities as above. The reaction mixture was stirred for 2 hours at -78°C and then allowed to warm to room temperature. Crude product **232a&b** (0.29 g, 109%, d.r. 3.2:1) was 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[30].

In a flame dried round bottomed flask with side arm and magnetic stirrer bar under nitrogen, oxalyl 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 (0.35g, 92%) as a mixture of diastereomers **232a&b** (R_f 0.33). (Found: C, 72.20; H, 7.30; N, 9.25. $C_{18}H_{22}N_2O_2$ requires C, 72.48; H, 7.38; N, 9.39); υ_{max}/ cm^{-1} ($CHCl_3$) 1662s (C=O) and 1512s (C=C); δ_H (Major cycloadduct) 7.04-7.24 (5H, m, Ph), 5.45 (1H, m, olefin), 5.34 (2H, m, olefin and N*H* (5.29)), 4.82 (2H, s, bridgehead), 3.79 (1H, ddt, *J* 3.8, 9.0 & 11.1, C*H*NHCO), 2.15 (1H, dt, *J* 3.3 & 11.4, C*H*Ph) and 1.04-2.08 (10H, m, ring protons); δ_C (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_2 of adduct), 35.41 (t), 34.20 (t), 26.02 (t) and 25.26 (t); δ_H (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, C*H*NHCO), 2.30 (1H, m, C*H*Ph) and 1.04-2.20 (10H, m, ring protons); δ_C (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_2 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**.

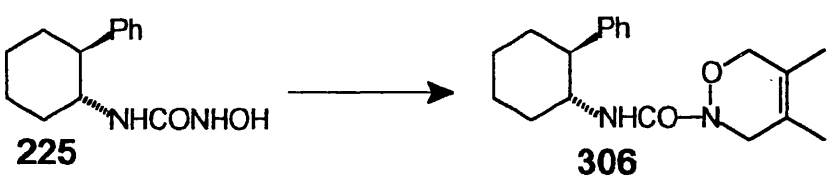


Followed General Procedure A at 0°C, using cyclohexadiene (0.35 g, 0.41 ml, 4.35 mmol), tetraethylammonium periodate (0.31 g, 0.96 mmol), hydroxyurea **225** (0.20 g, 0.87 mmol), to give the crude product **233a&b** (0.24 g, 92%, d.r. 2.5:1). This was then chromatographed on alumina eluted with dichloromethane-light petroleum (4:1) to give (0.195g, 72%) total product. Major diastereomer **233a** (R_f 0.48), was separated from minor diastereomer **233b** (R_f 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&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_f 0.49) (0.19g, 45%) and a mixture of minor diastereomer **233b** (R_f 0.40) and major diastereomer **233a** (R_f 0.49) (0.07g, 17%).
(Found: C, 73.05; H, 7.47; N, 8.92; M^+, 312.1843. $C_{19}H_{24}N_2O_2$ requires C, 73.08; H, 7.69; N, 8.97; *M*, 312.1838); υ_{max}/ cm^{-1} ($CHCl_3$) 1662m (C=O) and 1512m (C=C); δ_H (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, (C*H*NHCO), 2.25 (1H, dt, *J* 3.3 & 11.4, C*H*Ph) and 0.97- 2.32 (12H, m, ring protons and adduct methines); δ_C (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_H (Minor adduct) 7.14 (5H, m, aromatic), 6.42 (2H, m, olefin), 5.60 (1H, br s, N*H*CO), 4.74 (1H, m, bridgehead), 4.51 (1H, m, bridgehead), 3.87 (1H, m, C*H*NHCO) and 1.04- 2.49 (13H, m, cyclohexane and adduct methines); δ_C (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^+, 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.**

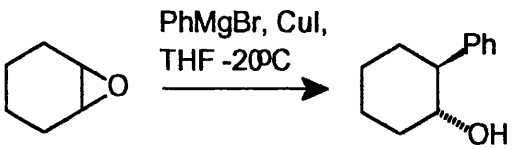


Following General Procedure A at 0°C, using 2, 3-dimethylbutadiene (0.36 g, 0.50 ml, 4.43 mmol), tetraethylammonium periodate (0.43 g, 1.34 mmol) and hydroxy urea **225** (0.21 g, 0.89 mmol), gave the crude product (0.28 g, 99%). This was chromatographed on silica

eluted with light petroleum-ethyl acetate (85:15) to give cycloadduct **306** (R_f 0.25) (0.13 g, 46%).

υ_{max}/ cm^{-1} ($CHCl_3$) 1662m (C=O) and 1512m (C=C); δ_H 7.03-7.25 (5H, m, Ph), 5.37 (1H, d, *J* 8.3, N*H*CO), 3.28-4.05 (5H, m, 2xCH_2 of oxazine and C*H*NHCO), 3.83 (1H, dt, *J* 3.5 & 9.0, C*H*NHCO), 2.35 (1H, dt, *J* 3.4 & 9.0, C*H*Ph), 1.14-2.44 (12H, m, cyclohexane and oxazine methines), 1.32 (3H, s, CH_3) and 1.49 (3H, s, CH_3); δ_C 157.71 (s, C=O), 143.84 (s, Ph), 128.40 (d, 2xCH, Ph), 127.50 (d, 2xCH, Ph), 126.34 (d, Ph), 122.19 (s, 2 olefins), 70.35 (t, CH_2 of oxazine), 52.91 (d, *C*HNHCO), 50.95 (d, *C*HPh), 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).

(±)-*trans*-2-Phenylcyclohexan-1-ol **236**.

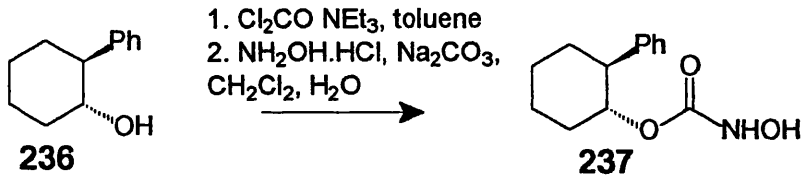


235 **236**

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 (11.14g, 98%), m.p. 52-54°C (light petroleum)(identical to lit., [50]).

υ_{max}/ cm^{-1} ($CHCl_3$) 3063, 3018, 2936, 2860s, 2401m and 1603m; δ_H 7.18-7.42 (5H, m, Ph), 3.63 (1H, dt, *J* 4.3 & 9.9, C*H*OH), 2.42 (1H, dt, *J* 2.9 & 10.8, C*H*Ph) and 1.29-2.12 (9H, m, cyclohexane and OH); δ_C 143.35 (s), 128.68 (d, 2xCH_2), 127.90 (d, 2xCH_2), 126.74 (d), 74.32 (d, *C*HOH), 53.15 (d, CHPh), 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).

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

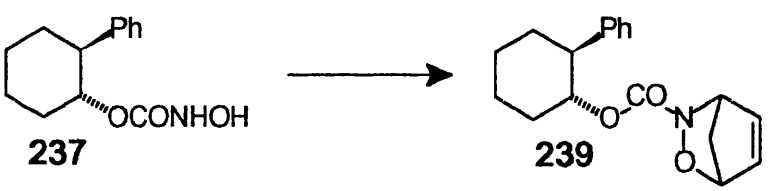


236 **237**

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. $C_{13}H_{15}NO_2$ requires M-H_2O, 217.1103); υ_{max}/ 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, *CH*OCO), 49.57 (*CH*Ph), 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-Phenylcyclohexyloxycarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **239.**



237 **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

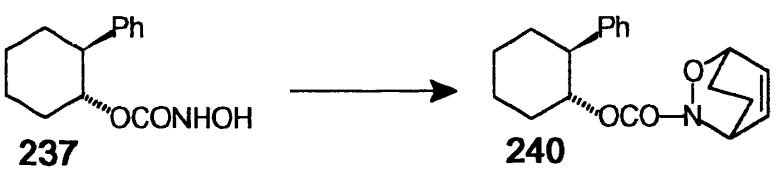
diastereomer **239b** (R_f 0.63, ethyl acetate-light petroleum (3:1)) (0.04 g, 17%) and the major diastereomer **239a** (R_f 0.45, ethyl acetate-light petroleum (3:1)) (0.18 g, 81%) as a crystalline solid, m.p. 117-119°C (ethyl acetate and light petroleum).

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^+ -C_5H_6O, 217.1114. $C_{18}H_{21}NO_3$ requires C, 72.24; H, 7.02; N, 4.68; M^+ -C_5H_6O, 217.1103); υ_{max}/ cm^{-1} ($CHCl_3$) 1737s (C=O); δ_H (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, C*H*OCO), 4.72 (1H, br s, olefin), 4.61 (1H, s, bridgehead), 2.69 (1H, dt, *J* 3.5 & 11.4, C*H*Ph) and 1.20-2.26 (10H, m, cyclohexane); δ_C (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, *CH*OCO), 65.43 (d, bridgehead), 49.92 (d, *CH*Ph), 47.68 (t, CH_2 of adduct), 34.25 (t), 32.19 (t), 25.73 (t) and 24.56 (t); δ_C (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^+-82, 0.3%), 176 (2), 159 (32), 117 (11) and 91 (100).

(±)-3-[*trans*-2-Phenylcyclohexyloxycarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **240**.



237 **240**

Followed General Procedure A at 0°C, using cyclohexadiene (0.08 g, 0.1 ml, 1.05 mmol), tetraethylammonium periodate (0.13 g, 0.40 mmol) and hydroxycarbamate **237** (0.08 g, 0.35 mmol) to give the crude adduct **240a&b** (0.086g, 79%, d.r. 2.9 :1) which was then chromatographed on silica eluted with ethyl acetate-light petroleum (1:1) (R_f 0.60) to give

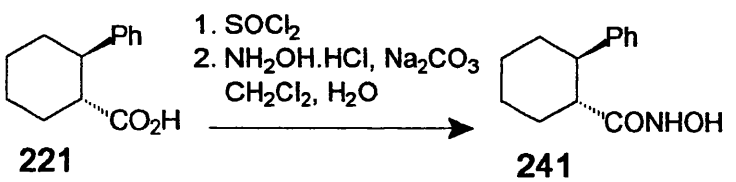
as a mixture of diastereomers **240a&b** (0.05 g, 51%). Fractional recrystallisation gave the major diastereomer as a white crystalline solid, m.p. 133-134°C (ethyl acetate and light petroleum).

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) (R_f 0.49) to give the product **240a&b** (0.144g, 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) (R_f 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*$^+$, 313.1696. $C_{19}H_{23}NO_3$ requires C, 72.84; H, 7.35; N, 4.47; *M*, 313.1678); υ_{max}/ cm^{-1} ($CHCl_3$) 1740s; δ_H (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, C*H*OCO), 4.60 (1H, m, bridgehead), 4.32 (1H, d, *J* 3.9, bridgehead), 2.69 (1H, dt, *J* 3.4 &11.4, C*H*Ph) and 1.17-2.26 (12H, m, ring protons); δ_C 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, *CH*OCO), 70.46 (d, bridgehead), 50.76 (d, bridgehead), 50.04 (d, *CH*Ph), 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**.



221 **241**

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 (0.93g, 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** (0.84g, 82%), m.p. 141°C (ethyl acetate and light petroleum).

(Found: C, 71.01; H, 7.81; N, 6.35; M^+, 219.1259. $C_{13}H_{17}NO_2$ requires C, 71.23; H, 7.76; N, 6.39; *M*, 219.1259); υ_{max}/ cm^{-1} (KBr disc) 1628 (C=O); δ_H($(CD_3)_2SO$) 10.24 (1H,s) & 8.55 (1H, s) N*H*O*H*, 7.08-7.26 (5H, m, aromatic), 2.75 (1H, br dt, C*H*CONHOH), 2.75 (1H, dt, *J* 3.1 & 12.0, C*H*Ph) and 1.30-2.50 (8H, m, cyclohexane); δ_H 9.05 (1H, br m, N*H*O*H*), 6.97-7.13 (5H, m, aromatic), 2.60 (1H, dt, *J* 3.4 & 11.4, C*H*CONHOH), 2.39 (1H, dt, *J* 3.4 & 11.4, C*H*Ph) and 1.20-2.24 (8H, m, cyclohexane); δ_C($(CD_3)_2SO$) 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, *CH*CONHOH), 45.03 (d, *CH*Ph), 34.98 (t), 30.70 (t), 26.03 (t) and 25.29 (t); δ_C 181.20 (s, C=O), 144.48 (s), 128.36 (d, 2xCH), 127.61 (d, 2xCH), 126.39 (d), 49.76 (d, *CH*CONHOH), 45.95 (d, *CH*Ph), 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.

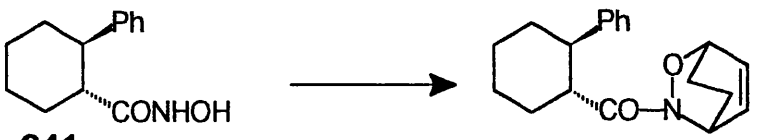
241 **244**

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** (0.32g, 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** (R_f 0.49), as thin needles (0.18g, 71%), m.p. 105°C (ethyl acetate and light petroleum).

(Found: C, 75.72; H, 7.61; N, 4.92; M^+, 283.1572. $C_{18}H_{21}NO_2$ requires C, 76.32; H, 7.42; N, 4.94; *M*, 283.1572); υ_{max}/ cm^{-1} ($CHCl_3$) 1650s (C=O); δ_H 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

(2H, s, 2 bridgehead CH), 2.79 (2H, br s, C*H*Ph and C*H*CO) 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, CH_2 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).

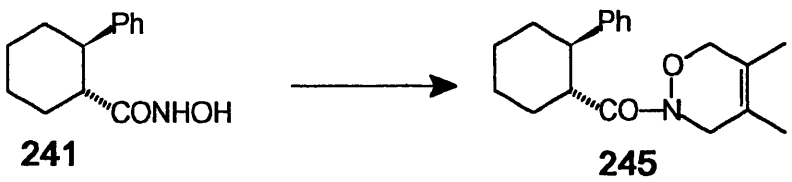
(±)-3-[*trans*-2-Phenylcyclohexylcarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **243**.



241 **243**

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** (R_f 0.14) (0.25g, 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** (R_f 0.34) (0.14g, 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. $C_{19}H_{23}NO_2$ requires C, 76.77; H, 7.74; N, 4.71; *M*, 297.1729); υ_{max}/ cm^{-1} ($CHCl_3$) 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, C*H*Ph & C*H*CO) 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 & 45.49 & 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, CH_2 of adduct) and 21.36 & 20.53 (t, CH_2 of adduct); *m/z* 297 (M^+, 9%), 218 (17), 159 (58), 91 (100), 81 (18) and 79 (15).

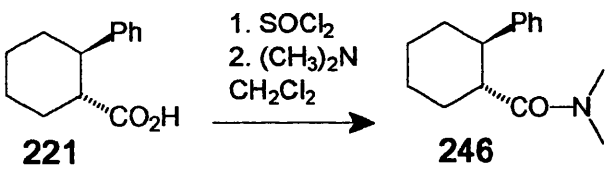
(±)-2-[*trans*-2-Phenylcyclohexylcarbonyl]-(*1-SR*)-1-oxa-2-aza-4,5-dimethylcyclohex-4-ene **245.**



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) (R_f 0.71) to give cycloadduct **245** as a gum (0.09g, 33%).

(Found: M^+, 299.1885. $C_{19}H_{25}NO_2$ requires M, 299.1885); δ_H 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, CH_3 of oxazine) and 1.47 (3H, s, CH_3 of oxazine); δ_C 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, CH Ph), 122.14 & 121.45 (s, olefin), 73.03 (t, CH_2 of oxazine), 59.60 & 58.18 (t, CH_2 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, CH_3 of oxazine) and 13.73 & 13.47 (q, CH_3 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.**

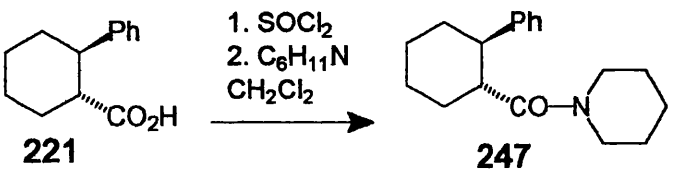


The acid **221** (0.51 g, 2.50 mmol) was added to thionyl chloride (5 ml) and heated to reflux for 2 hours. The solution was then concentrated and taken up in toluene and reconcentrated to remove excess thionyl chloride. The acid chloride **222** was dissolved in chloroform (5 ml) and chilled to 0°C. 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. $C_{15}H_{21}NO$ requires C, 77.92; H, 9.09; N, 6.06; M, 231.1623); υ_{max}/ cm-1 ($CHCl_3$) 1624s (C=O); δ_H 7.03 (5H, m, Ph), 2.55-2.79 (8H, m, 2xCH_3 & 2x*CH*), 2.55 (6H, s, 2xCH_3) 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 *CH*Ph & *CH*CO), 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.**

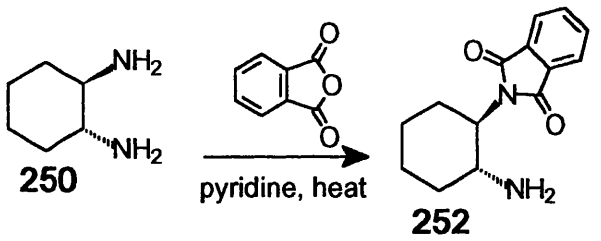


221 **247**

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. $C_{18}H_{25}NO$ requires C, 79.70; H, 9.22; N, 5.17; M, 271.1937); υ_{max}/ cm^{-1}($CHCl_3$) 1612s (C=O); δ_H 7.18 (5H, m, Ph), 3.60 (1H, br m, C*H*NH), 2.65-3.3 (5H, m, 2xCH_2 of piperidine ring & C*H*Ph) 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, CHPh), 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).

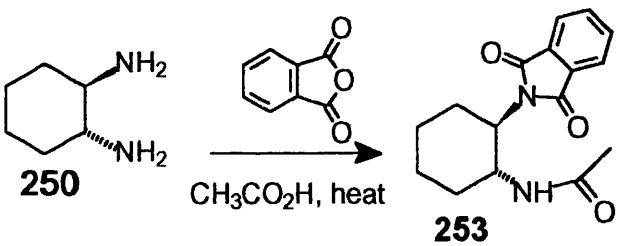
(±)-*trans*-1-Phthaloylamino-2-aminocyclohexane **252.**



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).

υ_{max}/ cm^{-1}(KBr disc) 3380, 2930m, 2850m, 1760m and 1700s; δ_H 7.71 & 7.62 (4H, m, aromatic), 3.70 (1H, dt, *J*3.7 & 11.4, C*H*NH_2), 3.31 (1H, dt, *J*3.9 & 10.8, C*H*NPhth) and 1.04-2.13 (10H, m, ring protons); δ_C 168.64 (s, C=O), 133.75 (d), 131.79 (s), 123.01 (d), 58.45 (d, C*H*NH_2), 50.74 (d, C*H*NPhth), 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.**

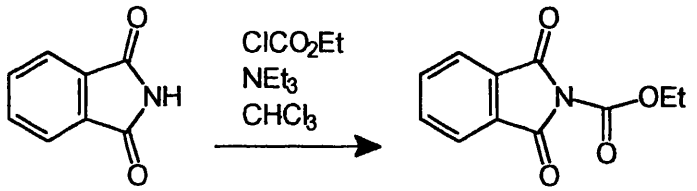


To a stirred solution of *trans*-1,2-diaminocyclohexane **250** (0.68 g, 5.96 mmol) in acetic acid, was added a solution of phthalic anhydride (0.88 g, 5.96 mmol) in acetic acid (20 ml), this was heated to reflux for 20 minutes, then concentrated and chromatographed on silica eluted with ethyl acetate. This gave acetate **253** (R_f 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. $C_{16}H_{18}N_2O_3$ requires C, 67.13; H, 6.29; N, 9.79); υ_{max}/ cm^{-1}(KBr disc) 3950, 3030, 2860, 1770m, 1725s, 1620 and 1470; δ_H 7.79 (2H, m, aromatic), 7.70 (2H, m, aromatic), 6.00 (1H, d, *J* 9.1, N*H*$COCH_3$), 4.55 (1H, dt, *J* 4.0 & 10.4, CHN*H*$COCH_3$), 3.96 (1H, dt, *J*3.4 & 11.6, C*H*NPhth), 1.22-2.66 (8H, m, ring protons) and 1.73 (s, 3H, CH_3); δ_C 169.59 (s,

2XC=O OF phthaloyl), 168.51 (s, C=O OF $COCH_3$), 133.79 (d), 131.63 (s), 122.97 (d), 54.83 (d, *C*HNHAc), 49.34 (d, *C*HNPhth), 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**.

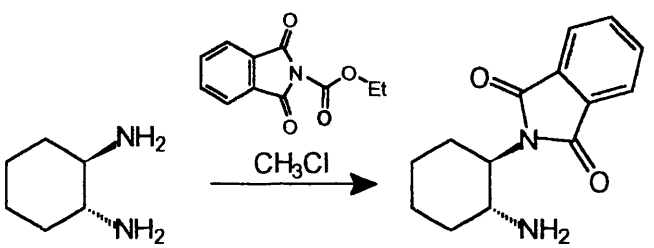


254

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.,[53a] 80 °C) (ethyl acetate, light petroleum) (identical to lit., [53]).

δ_H 7.81 (4H, dm, Ph), 4.41 (2H, q, *J* 7.1, CH_2CH_3) and 1.37 (3H, t, *J* 7.1, CH_2CH_3); δ_C 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**.



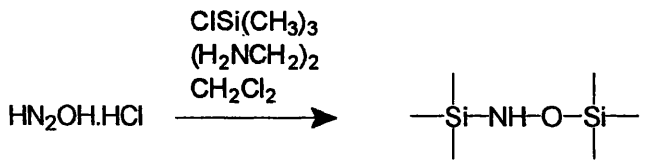
250 **252**

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** (6.85g, 59%), m.p. 135°C (ethyl acetate-light petroleum).

υ_{max}/ cm^{-1}(KBr disc) 3380, 2930m, 2850m, 1760m and 1700s; δ_H 7.71 & 7.62 (4H, m, aromatic), 3.70 (1H, dt, *J* 3.7 & 11.4, (C*H*NH$_2$), 3.31 (1H, dt, *J* 3.9 & 10.8, (C*H*NPhth) and 1.04-2.13 (10H, m, cyclohexane and amine); δ_C 168.64 (s, C=O), 133.75 (d), 131.79 (s), 123.01 (d), 58.45 (d, CHNH$_2$), 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).

N, O-bis(Trimethylsilyl)hydroxylamine **259.**

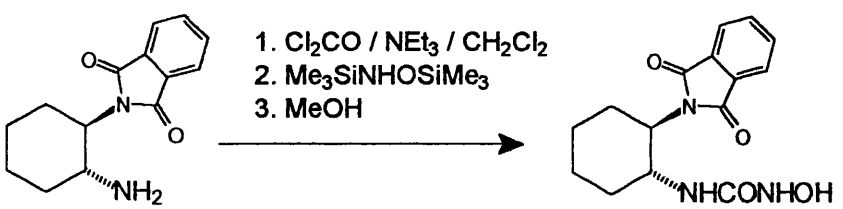


259

To a stirred suspension of hydroxylamine hydrochloride (7.00 g, 100.72 mmol) in dry dichloromethane (80 ml), was added ethylenediamine (9.08 g, 10.1 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 (12.33g, 69%) (identical to lit., [57]).

υ_{max}/ cm^{-1} ($CHCl_3$) 2925m and 1525w; δ_H 4.66 (1H, s, N*H*), 0.86 (9H, s, Si*Me*$_3$) and 0.11 (9H, s, SiMe$_3$); δ_C -2.12 (q, Si(CH$_3$)$_3$) and -1.01 (q, Si(CH$_3$)$_3$); *m/z* 177 (M$^+$, 9%), 162 (9), 146 (100), 130 (60), 100 (17) and 90 (32).

(±)-*trans*-1-Phthaloylaminocyclohexane-2-*(N,N'*-hydroxyurea) **249.**



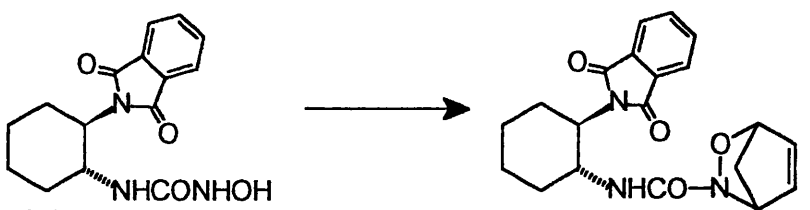
252 **249**

To a stirred solution of phosgene in toluene (12.5%, 0.27g, 1.4 ml, 2.69 mmol) at 0°C was added a solution of phthaloylcyclohexylamine **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

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%).

υ_{max}/ cm^{-1} (KBr disc) 2936m, 1771m and 1709s (C=O); δ_H ($(CD_3)_2SO$) 8.51 (1H, br s, N*H*OH), 8.14 (1H, br s, N*H*OH), 7.86 (4H, s, aromatic), 6.30 (1H, d, *J* 9.1, N*H*CO), 4.25 (1H, m, C*H*NHCO), 4.06 (1H, m, C*H*NPhth) and 1.19-2.57 (8H, m, cyclohexane); δ_C ($(CD_3)_2SO$) 167.89 (S, C=O of NPhth), 160.82 (s, C=O of urea), 134.34 (d), 131.50 (s), 123.02 (d), 54.21 (d, *C*HNHCONHOH), 48.60 (d, *C*HNPhth), 32.57 (t), 28.61 (t), 24.95 (t) and 24.84 (t); *m/z* 303 (M^+, 2%), 270 (13), 186 (35), 160 (40), 148 (100), 130 (56) and 104 (58).

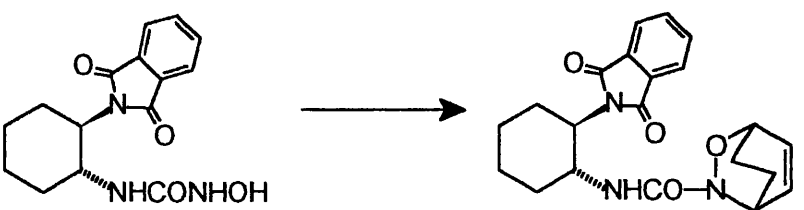
(±)-3-*[trans*-2-Phthaloylaminocyclohexylaminocarbonyl]2-oxa-3-azabicyclo[2.2.1]hept-5-ene **256a&b.**



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 actetate-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).

(Found C, 65.62; H, 5.71; N, 11.32; M^+, 367.1508. $C_{20}H_{21}N_3O_4$ requires C, 65.39; H, 5.72; N, 11.44; *M*, 367.1532); υ_{max}/ cm^{-1} ($CHCl_3$) 1712s (C=O); More polar fraction (R_f 0.47); δ_H 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, C*H*NHCO), 3.82 (1H, dd, *J* 3.0 & 10.5, C*H*NPhth), 2.45 (1H, dt, *J* 3.6 & 13.0, ringproton) and 1.14-2.18 (10H, m, ring protons); δ_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); δ_H 7.83 &7.72 (4H, m, aromatic), 6.29 (1H, m, olefinic), 6.15 (1H, m, olefinic), 5.56 (1H, d, *J* 8.9, N*H*CO), 5.07 (1H, s, bridgehead), 4.92 (1H, s, bridgehead), 4.31 (1H, m, C*H*NHCO), 3.82 (1H, m, C*H*NPhth), 2.42 (m) and 1.22-2.17 (10H, m, ring protons); δ_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.**



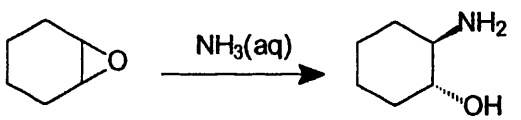
249 **257**

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 actetate-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).

(Found: C, 65.04; H, 6.32; N, 9.91 (+C_2H_5OH); M^+, 381.1688. $C_{21}H_{23}N_3O_4$ requires C, 64.64; H, 6.79; N, 9.84 (+C_2H_5OH); *M*, 381.1688); υ_{max}/ cm^{-1} ($CHCl_3$) 1712s (C=O); Both diastereomers; δ_H 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 N*H*CO), 5.60 (1H, d, *J* 9.5, 1x N*H*CO), 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, C*H*NHCO), 3.76 (1H, dt, *J* 3.4 & 11.7, (C*H*NHCO), 2.35 (2H, m) and 1.06-1.96 (12H, m, ring protons); δ_C 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, *CH*NHCO), 49.96 & 49.91 (d, bridgehead), 49.82 & 49.18 (d, *CH*NPhth), 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).

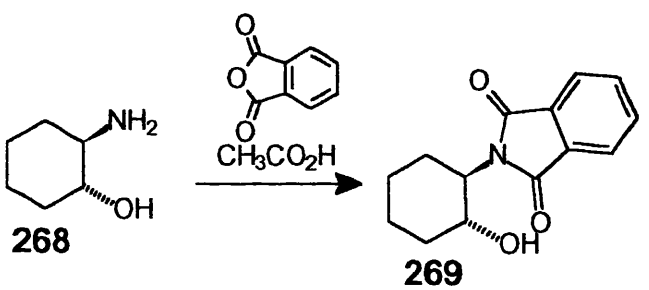
(±)-*trans*-2-Aminocyclohexan-1-ol **268.**



235 **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., [58] 68°C for *trans*; 107-8°C for *cis*). δ_H 2.81 (3H, br s, amino and hydroxyl protons) and 1.02-3.38 (8H, m, cyclohexane); δ_C 75.64 (d, *CH*OH), 57.00 (d, *CH*NH_2), 34.50 (t), 33.85 (t), 25.05 (t) and 24.79 (t).

(±)-*trans*-2-Phthaloylaminocyclohexan-1-ol **269.**

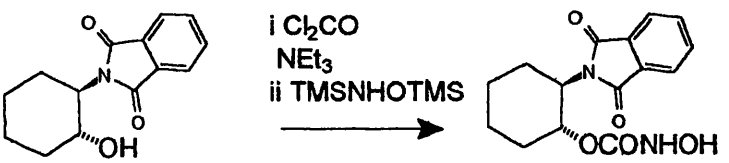


268 **269**

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** (R_f 0.43) as white crystals (1.12g, 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); υ_{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, C*H*OH), 3.94 (1H, dt, J=3.8 & 10.2, C*H*NPhth), 2.42 (1H, s, OH (disappears with D_2O)) and 1.31- 2.15 (8H, bm, ring protons); δ_C 168.88 (s, 2xC=O), 133.80 (d, 2xCH), 131.9 (s), 123.09 (d, 2xCH), 69.51 (d, *CH*OH), 57.46 (d, *CH*NPhth), 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.**

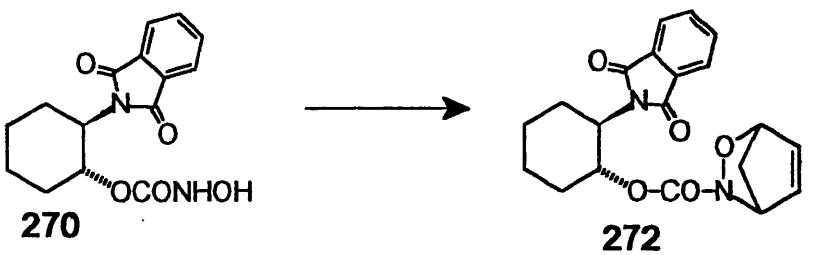


269 **270**

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); υ_{max}/ cm^{-1} (KBr disc) 3312m and 1708s (C=O); δ_H 8.26 (2H, br s, N*H*O*H*), 7.38 (4H, m, aromatic), 4.97 (1H, dt, J 4.5 & 10.4, C*H*OCO), 3.75 (1H, dt, J3.3 & 11.6, C*H*NPhth) 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, CHOCO), 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.**



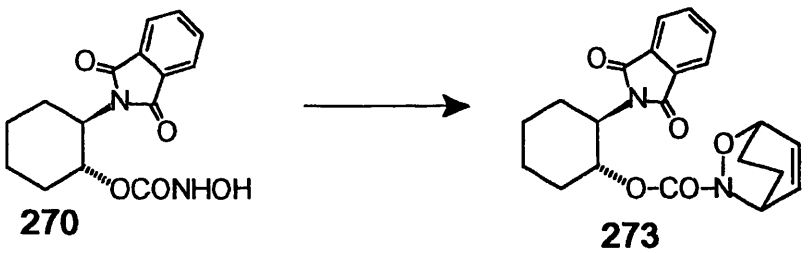
270 **272**

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-dichloromethane 1:25) used, gave the crude product **272a&b** (0.31g, 113%, d.r. 1:1). This was then chromatographed on silica eluted with ethyl acetate-light petroleum (3:2) to give **272a&b** (R_f 0.47) (0.25 g, 87%) as a white solid. The two diastereomers were separated by chromatography on alumina eluted with dichloromethane (R_f 0.70 and R_f 0.62), m.p. 125-8 °C (ethyl acetate).

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), 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** (0.47g, 97%, d.r. 1:1). The crude product was chromatographed on alumina eluted with dichloromethane to separate the two diastereomers **272a&b** (R_f 0.70 and R_f 0.63).

(Found: C, 65.78; H, 5.72; N, 6.99; M^+, 368.1372. $C_{20}H_{20}N_2O_5$ requires C, 65.21; H, 5.43; N, 7.61; *M*, 368.1372); υ_{max}/ cm^{-1} ($CHCl_3$) 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, C*H*OCO), 4.98 (1H, s, bridgehead), 4.74 (1H, s, bridgehead), 4.12 (1H, dt, *J* 4.1 & 10.4, C*H*NPhth) 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, *CH*OCO), 64.72 (d, bridgehead), 53.64 (d, CHNPhth), 47.93 (t, CH_2 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 (), 133.47 (d), 132.51 (d), 131.41 (s), 122.92 (d), 83.26 (d, bridgehead), 73.47 (d, *CH*OCO), 64.63 (d, bridgehead), 53.33 (d, *CH*NPhth), 47.86 (t, CH_2 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-Phthaloylaminocyclohexyloxycarbonyl]2-oxa-3-azabicyclo[2.2.2]oct-5-ene **273a&b.**



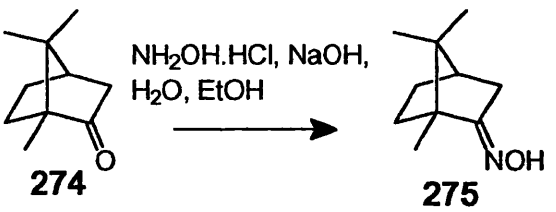
270 **273**

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** (0.27g, 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** (R_f 0.71) (0.09 g, 35%) m.p. 163-5°C (ethyl acetate) and **273b** (R_f 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), hydroxycarbamate **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** (0.46g, 89%, d.r. 1:1).

(Found C, 65.82; H, 5.61; N, 7.18; M^+, 382.1531. $C_{21}H_{22}N_2O_5$ requires C, 65.96; H, 5.75; N, 7.32; *M*, 382.1529); υ_{max}/ cm^{-1} ($CHCl_3$) 1712m (C=O); δ_H (Less polar diasteromer, 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, C*H*OCO), 4.54 (1H, m, bridgehead), 4.44 (1H, m, bridgehead), 4.19 (1H, dt, *J* 4.1 & 10.4, C*H*NPhth) 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, *CH*OCO), 70.57 (d, bridgehead), 53.83 (d, *CH*NPhth), 49.90 (d, bridgehead), 31.69 (t), 28.40 (t), 25.00 (t), 23.80 (t), 23.38 (t, CH_2 of adduct) and 20.05 (t, CH_2 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.**

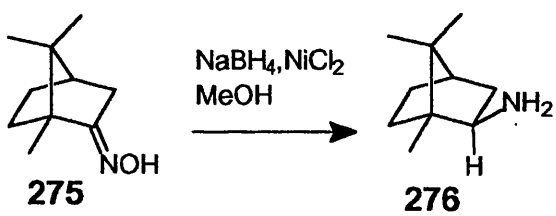


274 **275**

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** (3.82g, 84%), m.p. 110-116°C (ethanol) (m.p. 118 °C (ethanol) *lit.*, [67]).

υ_{max}/ cm^{-1} ($CHCl_3$) 3020s, 2966m, 2401m and 1736m (C=O); δ_H 9.24 (1H, br s, NO*H*), 0.84-2.55 (7H, m, ring protons), (0.73 (3H, s, CH_3), (0.84 (3H, s, CH_3) and 0.93 (3H, s, CH_3)); δ_C 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(-CH_3, 22)), 150(-OH, 21) and 134 (47).

exo-Bornylamine **276.**

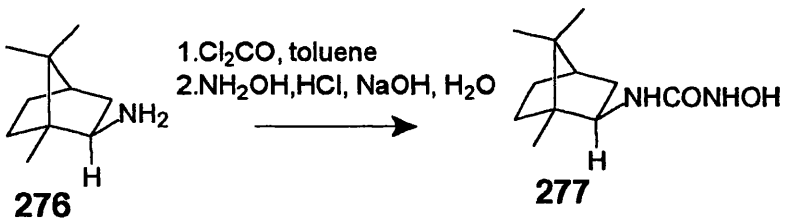


275 **276**

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** (1.74g, 49.7%) (identical to lit., [61]).

υ_{max}/ cm^{-1} (KBr disc, free amine) 3500, 3000 and 2500; δ_H (hydrochloride salt) 8.21 (3H, br s, N*H*$_3$), 0.90-2.15 (8H, ring protons), 1.12 (3H, s, CH_3), 1.08 (3H, s, CH_3) and 0.81 (3H, s, CH_3); δ_C (hydrochloride salt) 58.4 (d, *C*HNH$_3$), 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.**

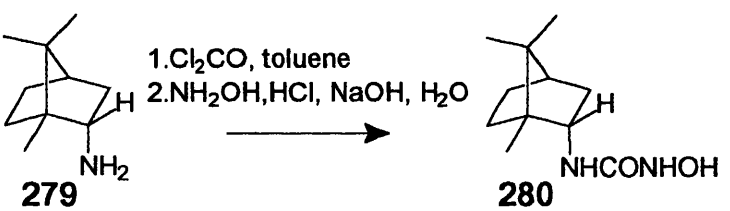


276 **277**

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 strirred 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.

δ_H 6.7-7.6 (2H, br s, N*H*O*H*), 5.97 (1H, d, *J* 9.4, N*H*CO), 3.67 (1H, m, CHNHCO), 0.73-1.92 (8H, ring protons), (0.76 (3H, s, CH_3), 0.77 (3H, s, CH_3) and 0.85 (3H, s, CH_3)); δ_C 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.**



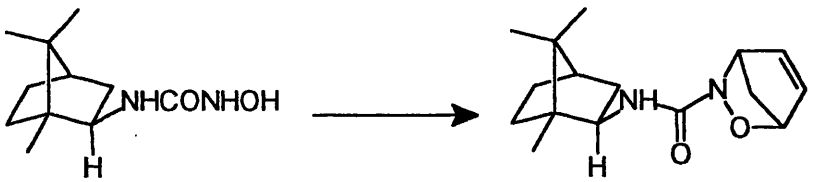
279 **280**

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.

δ_H 7.54 (1H, br s, N*H*O*H*), 6.06 (1H, d, *J* 9.3, N*H*CO), 3.99 (1H, br m, C*H*NHCO), 0.73- 2.20 (9H, m, ring protons), 0.73 (3H, s, CH_3), 0.80 (3H, s, CH_3) and 0.86 (3H, s, CH_3); δ_C 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-Bornylaminocarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **283.**

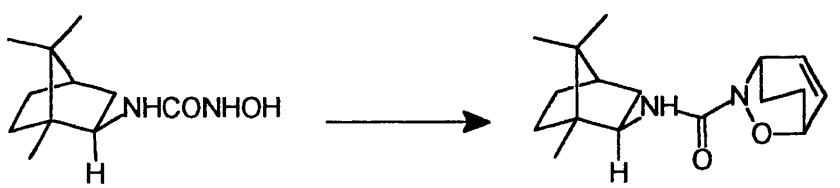


277 **283**

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** (R_f 0.61) and **283b** R_f 0.56) (0.12 g, 40%).

δ_H (both diastereomers) 6.30 (2H, m, olefin), 5.61 (1H, br d, N*H*CO), 5.10 (1H, s, bridgehead), 5.07 (1H, bridgehead), 3.61 (1H, dt, *J* 5.0 & 9.3, C*H*NHCO), 0.54-2.16 (12H, m, ring proton) and 0.8 (m, 6xCH_3); δ_C 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-Bornylaminocarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **284.**



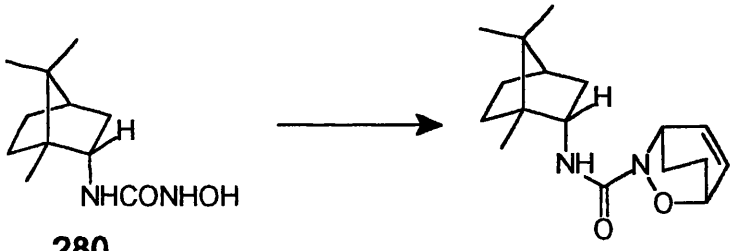
277 **284**

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** (R_f 0.47).

δ_H (Both diastereomers) 6.42 (2H, m, olefin), 5.76 (1H, d, *J* 8.8, N*H*CO), 4.81 (1H, m, bridgehead), 4.58 (1H, m, bridgehead), 3.62 (1H, m, C*H*NHCO), 0.67-2.29 (22H, m, ring protons), 0.67 (3H, s, CH_3), 0.74& 0.76 (3H, s, CH_3) and 0.80& 0.85 (3H, s, CH_3); δ_C 161.83 (s, C=O), 132.16 & 131.90

(d), 130.06 & 129.94 (d), 70.34 & 70.31 (d), 56.92 & 56.84 (d, *CH*NHCO), 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.**

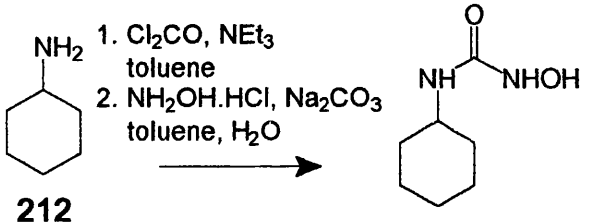


280 **282**

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** (R_f 0.46).

δ_H 6.43 (2H, m, olefin), 5.77 (1H, br s, N*H*CO), 4.83 (1H, m, bridgehead), 4.64 (1H, m, bridgehead), 3.98 (1H, m, C*H*NHCO), 0.67-2.32 (22H, m, ring protons), (0.67 (3H, s, CH_3), 0.78 (3H, s, CH_3) and 0.85 (3H, s, CH_3)); δ_C 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.**



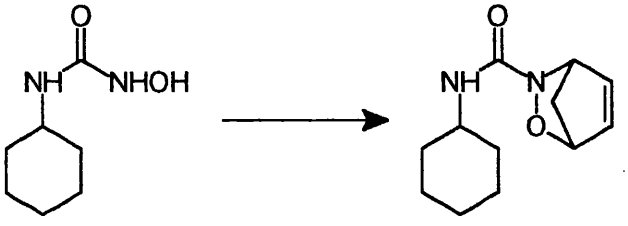
212 **213**

Cyclohexylamine **212** (0.62 g, 0.72 ml, 6.32 mmol) in toluene (10 ml) was added dropwise to a solution of phosgene 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.

υ_{max}/ cm^{-1} ($CHCl_3$) 1720 (C=O); δ_H ($CDCl_3$, 90 MHz) 7.1 (2H, br s, N*H*OH), 5.8 (1H, br d, N*H*CO), 3.5 (1H, m, C*H*NHCO) and 0.8-2.0 (10H, m, ring protons); *m/z*, 158 (M^+, 2.4%), 142 (3), 126 (21) and 83 (100).

3-[Cyclohexylaminocarbonyl]-(*1-SR*)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **215.**

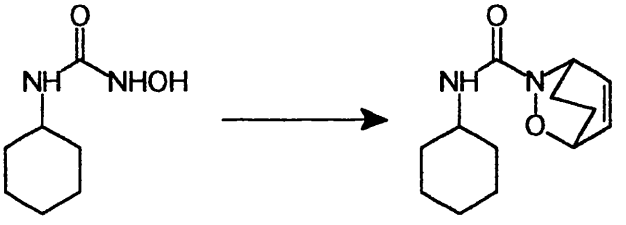


213 **215**

Following General Procedure A at 0°C, using cyclopentadiene (0.34 g, 0.42 ml, 5.09 mmol), tetraethylammonium 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.

υ_{max}/ cm^{-1} ($CHCl_3$) 1660 and 1512; δ_H 6.35 (2H, m, olefinics), 5.58 (1H, br d, N*H*CO), 5.16 (1H, s, bridgehead), 5.14 (1H, s, bridgehead), 3.55 (1H, m, C*H*NHCO) and 0.96-2.02 (12H, m, ring protons); δ_C 161.68 (s, C=O), 134.61 (d, olefin), 131.51 (d, olefin), 83.58 (d, bridgehead), 65.12 (d, bridgehead), 48.41 (d, *C*HNHCO), 48.30 (t, adduct), 33.43 (t), 32.95 (t), 25.38 (t) and 24.65 (t).

3-[Cyclohexylaminocarbonyl]-(*1SR*)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **216.**



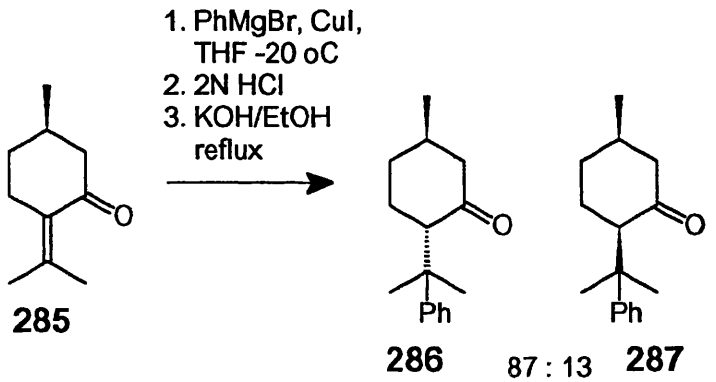
213 **216**

Followed General Procedure A at 0°C, using cyclohexadiene (0.20 g, 0.24 ml, 5.09 mmol), tetraethylammonium 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.

υ_{max}/ cm^{-1} ($CHCl_3$) 1660 and 1512; δ_H 6.42 (2H, m, olefinics), 5.62 (1H, d, *J* 8.0, N*H*CO), 4.83 (1H, m, bridgehead), 4.60 (1H, m, bridgehead), 3.49 (1H, m, C*H*NHCO) and 1.03-2.36 (14H, m, ring protons); δ_C 161.47 (s, C=O), 131.78 (d, olefin), 130.08 (d, olefin), 70.30 (d, 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).

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



285 **286** 87 : 13 **287**

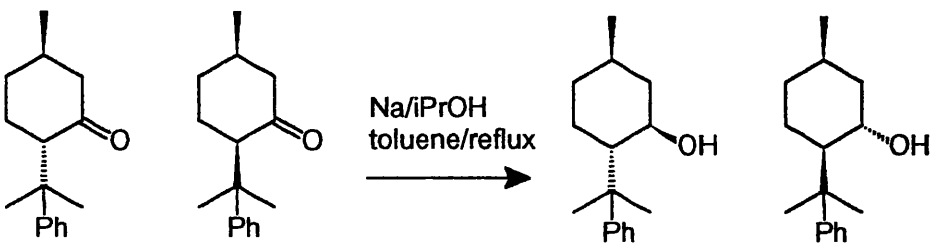
In a 250 ml flame dried three necked round bottomed flask fitted with a reflux condenser and a teflon coated magnetic stirrer bar under an atmosphere of nitrogen, was placed magnesium turnings (4.14g, 0.17 mol) and THF (20 ml). Bromobenzene (4 ml) was added to start the reaction, from bromobenzene (30.98g, 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 (3x50 ml). The organic layers were combined and washed with saturated sodium hydrogencarbonate 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., [63]). υ_{max}/ cm^{-1} ($CHCl_3$) 2958s and 1706s (C=O); δ_H 7.00-7.48 (5H, m, Ph), 0.82-2.71 (8H, m, ring protons), 0.90 (3H, d, *J* 6.9, CH_3CH *cis*), 0.95 (3H, d, *J* 6.0, CH_3CH *trans*), 1.40 (3H, s, $CPhCH_3$) and 1.46 (3H, s, $CPhCH_3$); δ_C (*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); δ_C (*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).

(*1RS, 2SR, 5R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol **288&289**.

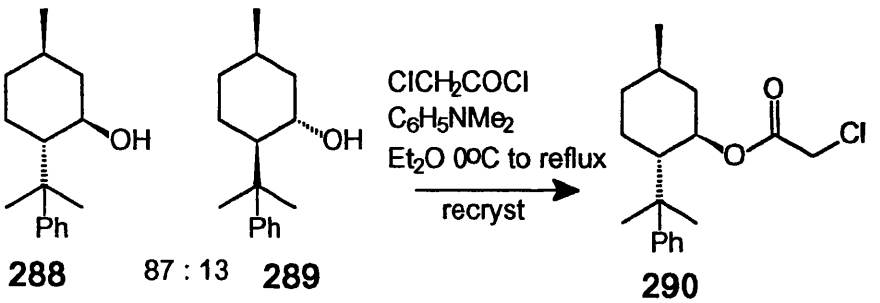


286 87 : 13 **287** **288** 87 : 13 **289**

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]).

(*1R, 2S, 5R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate **290.**

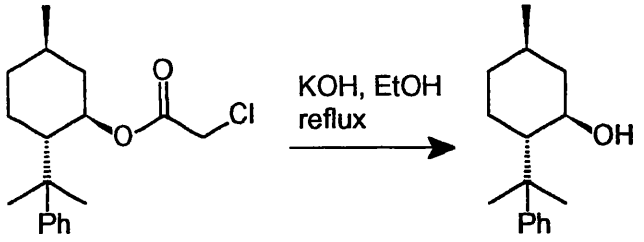


288 87 : 13 **289** **290**

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, $[\alpha]_D$=+18.9° (CCl_4, *c* 2.24) (lit [63], $[\alpha]_D$=+22.4° (CCl_4, *c* 2.29)) (identical to lit., [63]).

υ_{max}/ cm^{-1} ($CHCl_3$) 1754 (C=O) and 1185 (COC); δ_H 7.05-7.15 (5H, m, Ph), 4.64-4.77 (1H, dt, *J* 4.5 & 10.7, C*H*OCO), 3.04 and 3.43 ((AB doublet, 2H, *J* 15.0, CH_2Cl), 0.63-1.93 (8H, m, cyclohexane), 0.71 (3H, d, *J* 7.2, CH_3CH), 1.11 (3H, s, CPhCH_3) and 0.99 (3H, s, CPhCH_3); δ_C 166.48 (s), 151.70 (s), 127.97 (d), 125.24 (d), 125.09 (d), 75.74 (d), 50.19 (d), 41.43 (t), 40.75 (t), 39.36 (s), 34.34 (t), 31.21 (d), 29.80 (q), 26.12 (t), 22.57 (q) and 21.75 (q); *m/z*, 214 (M^+, 5%), 119 (100), 118 (16), 91 (32) and 41 (11).

(*1R, 2S, 5R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol **288.**

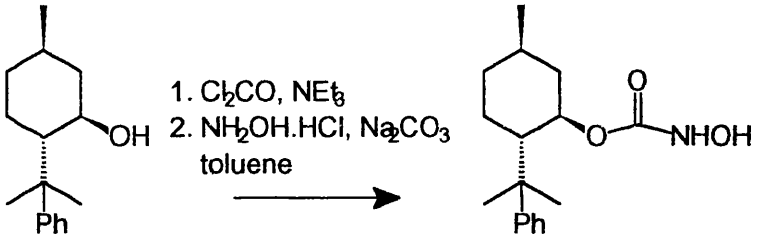


290 **288**

In a 500 ml round bottomed flask with a reflux condenser and a magnetic stirrer bar was placed phenylmenthol chloroacetate **290** (9.78g, 32 mmol) and sodium hydroxide (2.54g, 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 (3x50 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** (6.63g, 90%) as an oil, $[\alpha]_D$ = -24.1° (ethanol, *c* = 1.85), (lit., [63] $[\alpha]_D$ = -26.4° (ethanol, *c* = 1.97)).

υ_{max}/ cm^{-1} ($CHCl_3$) 3570 and 3420 (OH); δ_H 6.97-7.46 (5H, m, Ph), 3.34 (1H, dt, *J* 4.1 & 10.1, *CH*OH), 0.64-2.06 (8H, m, ring protons), 0.76 (3H, d, *J* 4.6, CH_3CH), 1.12 (3H, s, CPhCH_3) and 1.25 (3H, s, CPhCH_3); δ_C 151.31 (s), 128.41 (d), 125.77 (d), 72.89 (d), 54.09 (d, *CH*C(CH_3)$_2$Ph), 45.37 (t), 39.79 (s), 34.87 (t), 31.50 (d, *CH*CH_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'*-hydroxycarbamate) **291**.



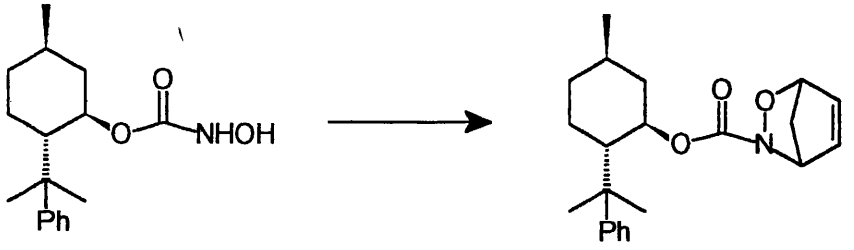
288 **291**

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_f 0.12) as a thick gum (3.15 g, 69%), α_D = -19.94° ($CHCl_3$, *c* = 1.62).

υ_{max}/ cm^{-1} ($CHCl_3$) 3412m, 2960m, 2926m and 1725s (C=O); δ_H 7.10 (5H, m, Ph), 6.16 (1H, br s, N*HOH*), 4.50 (1H, dt, *J* 4.4 & 10.7, C*H*OCO), 0.65-1.88 (8H, m, cyclohexane), 0.67 (3H, d, *J* 6.4, CHC*H*$_3$), 1.02 (3H, s, CPhC*H*$_3$) and 1.11 (3H, s, CPhC*H*$_3$); δ_C 158.55 (s), 152.30 (s), 127.85 (d), 125.41 (d), 124.76 (d), 76.24 (d, CHCO), 50.95 (d, *C*HC(CH$_3$)$_2$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^+-76; CH_2NO_3, 3), 120 (13), 119 (100), 118 (23), 105 (27), 91 (42) and 41 (15).

8-Phenylmenthyloxycarbonyl]-*(1-SR)*-2-oxa-3-azabicyclo[2.2.1]hept-5-ene **293a&b**.



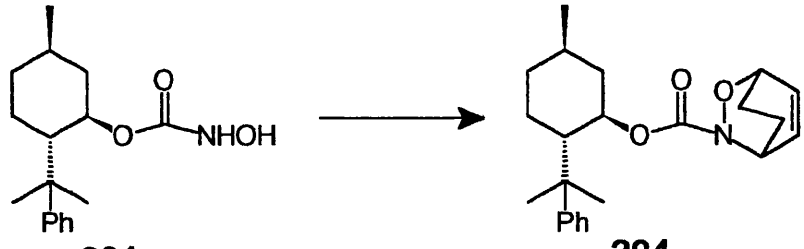
291 **293**

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&b** (0.52g, 91%, d.r. 7.1:1). This was chromatagraphed on silica eluted with light petroleum-ethyl acetate (85:15) to give a mixed fraction (0.14g, 24%) of both diastereomers **293a&b** (R_f 0.24 and R_f 0.19) in 1:1 ratio and the major diastereomer **293a** (R_f 0.19) (0.33g, 57%), m.p. 61-64°C (hexane), $[\alpha]_D$= -54.2° ($CHCl_3$, *c* 0.92). Total product **293a&b** (0.47g, 82%).

(Found: C, 74.42; H, 8.29; N, 4.02; *M*$^+$, 355.2170. $C_{22}H_{29}NO_3$ requires C, 74.36; H, 8.17; N, 3.94; *M*, 355.2147); υ_{max}/ cm^{-1} ($CHCl_3$) 2962s and 1720s (C=O); δ_H (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, C*H*OCO), 3.77 (1H, br s, 1 bridgehead H), 0.53-1.86 (10H, m, ringprotons), (0.63 (3H, d, *J* 6.4, CHC*H*$_3$), 0.98 (3H, s, CHC*H*$_3$) and 1.08 (3H, s, CHC*H*$_3$)); δ_C (Major diastereomer) 158.06 (s, C=O),

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, *CH*OCO), 64.18 (d, bridgehead), 50.91 (d, *CH*C(CH_3)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); δ_H(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, *CH*OCO), 0.67-1.95 (10H, m, ring protons), 0.75 (3H, d, *J* 5.0, CH*CH*$_3$), 1.21 (3H, s, CH*CH*$_3$) and 1.31 (3H, s, CH*CH*$_3$); δ_C 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, *C*HOCO), 64.61 (d), bridgehead), 50.28 (d, *CH*CMe$_2$Ph), 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-Phenylmenthyloxycarbonyl]-*(1-SR)*-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **294a&b.**



291 **294**

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, 3.33 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 chromatagraphed on silica eluted with light petroleum-ethyl acetate (4:1) to give the product **294a** (R_f 0.30) (0.33g, 59%), m.p. 90-91°C (hexane), $[\alpha]_D$= -25.2° ($CHCl_3$, *c* 1.26).

(Found: C, 74.97; H, 8.54; N, 3.88; *M*$^+$, 369.2287. $C_{23}H_{31}NO_3$ requires C, 74.80; H, 8.40; N, 3.79; *M*, 369.2304); υ_{max}/ cm^{-1} ($CHCl_3$) 2962m and 1720s (C=O); δ_H (major diastereomer) 7.20 (5H, m, Ph), 6.39 (2H, m, olefinic), 4.59 (2H, m, C*H*OCO & 1 bridgehead), 3.77 (1H, br s 1 bridgehead), 0.75-2.14 (21H, m, ring & CH_3 protons), 0.78 (3H, d, *J* 6.4, CH*CH*$_3$), 1.13 (3H, s, CPh*CH*$_3$), & 1.22 (3H, s, CPh*CH*$_3$); δ_H (minor diastereomer, observable signals) 1.16 (3H, s, CPh*CH*$_3$) and 1.20 (3H, s, CPh*CH*$_3$); δ_C (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, *CH*OCO), 70.75 (d, bridgehead), 50.73 (d, *CH*CMe$_2$Ph), 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); *m/z* 369 (M^+, 1.7%), 119 (63), 111 (27), 105 (100), 91 (35), 80 (10), 79 (31), 55 (17) and 41 (16).

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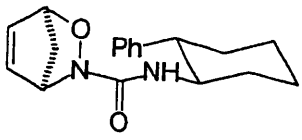

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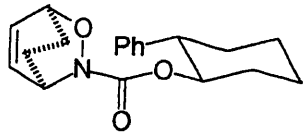

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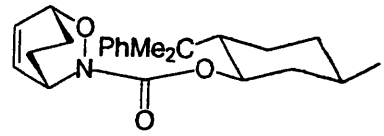

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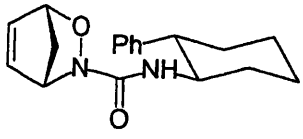
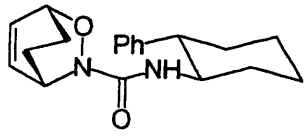
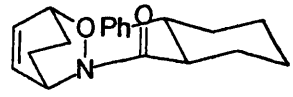


3, 239a



4, 240a



6, 243

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

	1	2		3	4	5	6
space group	$P2_1/a$	Cc		$P2_1/c$	$P2_1/c$	$P2_1$	$Pna2_1$
ϕ_1	-52.7(4)	-56.9(7)	-57.6(7)	-56.4(5)	-63.2(4)	-52.1(5)	-61.1(5)
ϕ_2	165.9(5)	-167.0(9)	-164.8(9)	14.3(6)	-158.9(7	-19.4(6)	169.9(7)
ϕ_3	40.8(4)	69.0(7)	70.6(7)	-36.7(5)	-68.7(4)	69.0(5)	-63.9(5)
C = C	1.288(8)	1.318(1)	1.300(11)	1.302(9)	1.305(7)	1.312(7)	1.390(8)
C – C	-	1.515(11)	1.504(10)	-	1.528(7)	1.515(8)	1.426(12)
ΣN	329	333	334	329	339	338	354

Notes:

1. The *trans* stereochemistry of the 1, 2-substituted cyclohexane ring is defined by the Ph-C-C-R torsion angle ϕ_1. 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 $\phi_1 \equiv -60^\circ$.
2. The O-N-C=O torsion angle ϕ_2 defines the relationship of the nitroso and carbonyl oxygen atoms.
3. The configuration of the dihydro-oxazine ring system is defined by torsion angle ϕ_3 = N-O-C-C_b where C_b 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 CH_2-CH_2 distances, where both CH_2 are derived from hexa-1, 3-diene.
5. ΣN is the sum of valency angles subtented at the oxazine nitrogen atom.

Table 3.1.2. Characteristics of the hydrogen bonds (Å) and angles (°) in 1 and 2

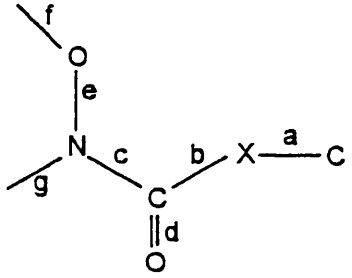
Compound	D-H...A	D-H	D...A	H...A	D-H...A
1	N(2)-H(2)...O(1)	0.96	2.593(4)	2.20	103
1	N(2)-H(2)...O(2^{i})	0.96	2.973(5)	2.15	143
2	N(21)-H(21)...O(11)	0.96	2.530(6)	2.09	106
2	N(22)-H(22)...O(12)	0.96	2.564(8)	2.01	105

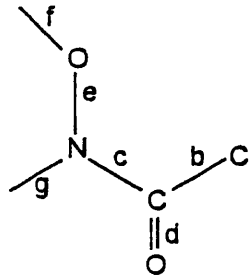
Symmetry code: (i); -x, 2-y, 1-z

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

	1	2		3	4	5	6
a	1.454(5)	1.461(10)	1.464(10)	1.462(6)	1.464(5)	1.452(6)	-
b	1.319(5)	1.332(10)	1.327(10)	1.316(7)	1.340(6)	1.340(6)	1.510(7)
c	1.410(5)	1.438(10)	1.417(10)	1.426(7)	1.385(6)	1.395(6)	1.342(6)
d	1.231(5)	1.227(10)	1.251(9)	1.202(7)	1.203(5)	1.192(6)	1.223(6)
e	1.455(5)	1.410(8)	1.426(8)	1.430(6)	1.428(5)	1.435(5)	1.437(5)
f	1.482(6)	1.461(9)	1.464(11)	1.486(7)	1.471(6)	1.471(6)	1.457(6)
g	1.507(6)	1.532(10)	1.500(10)	1.534(8)	1.474(6)	1.486(6)	1.469(6)

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





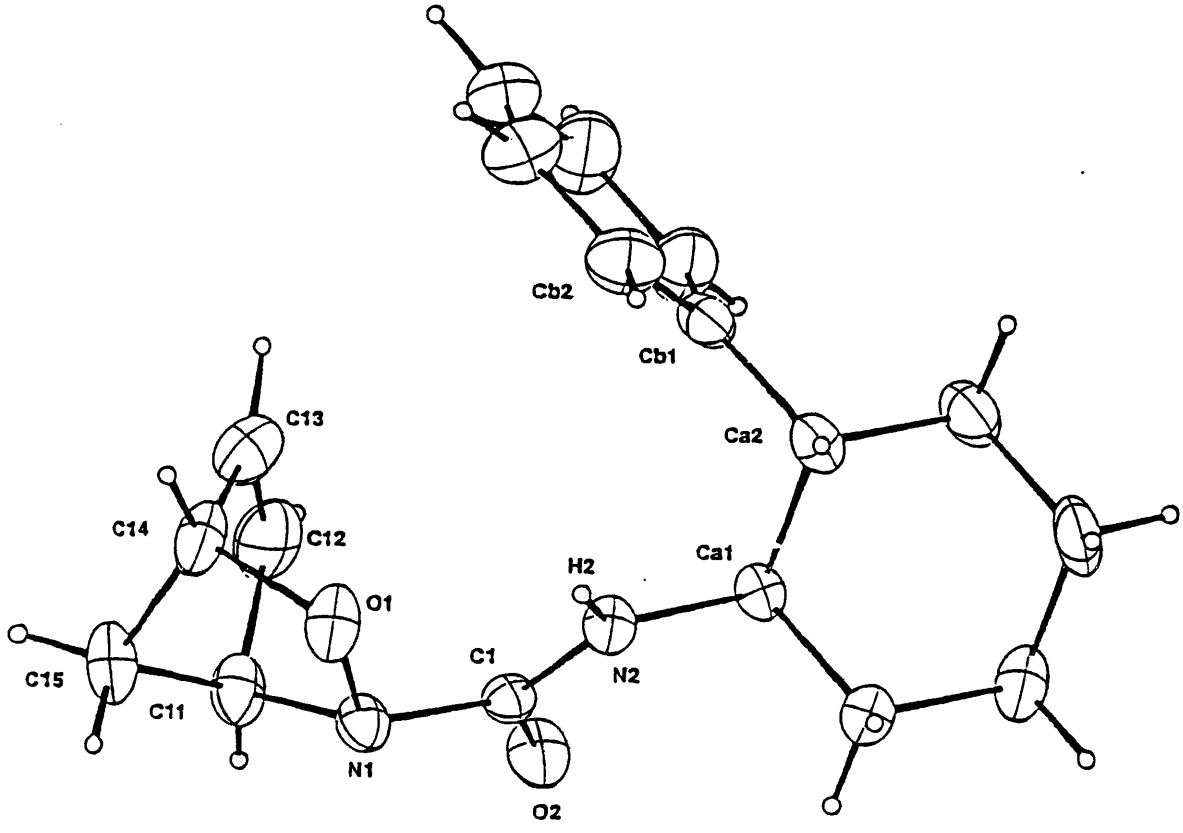


Figure 3.1.1

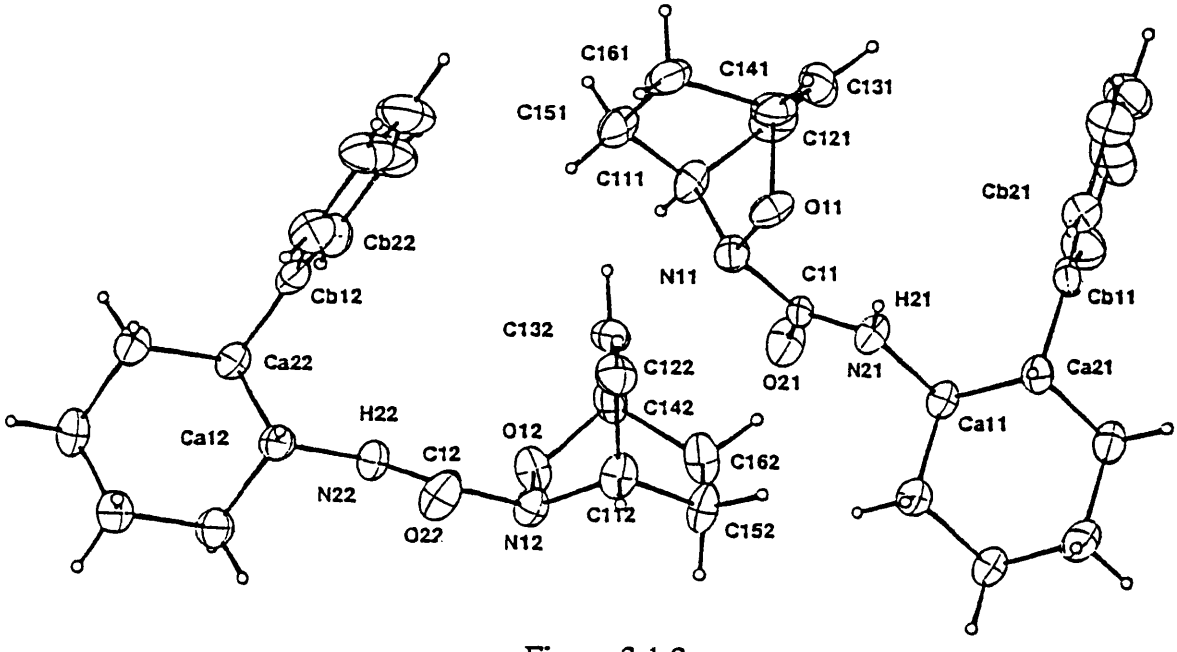


Figure 3.1.2

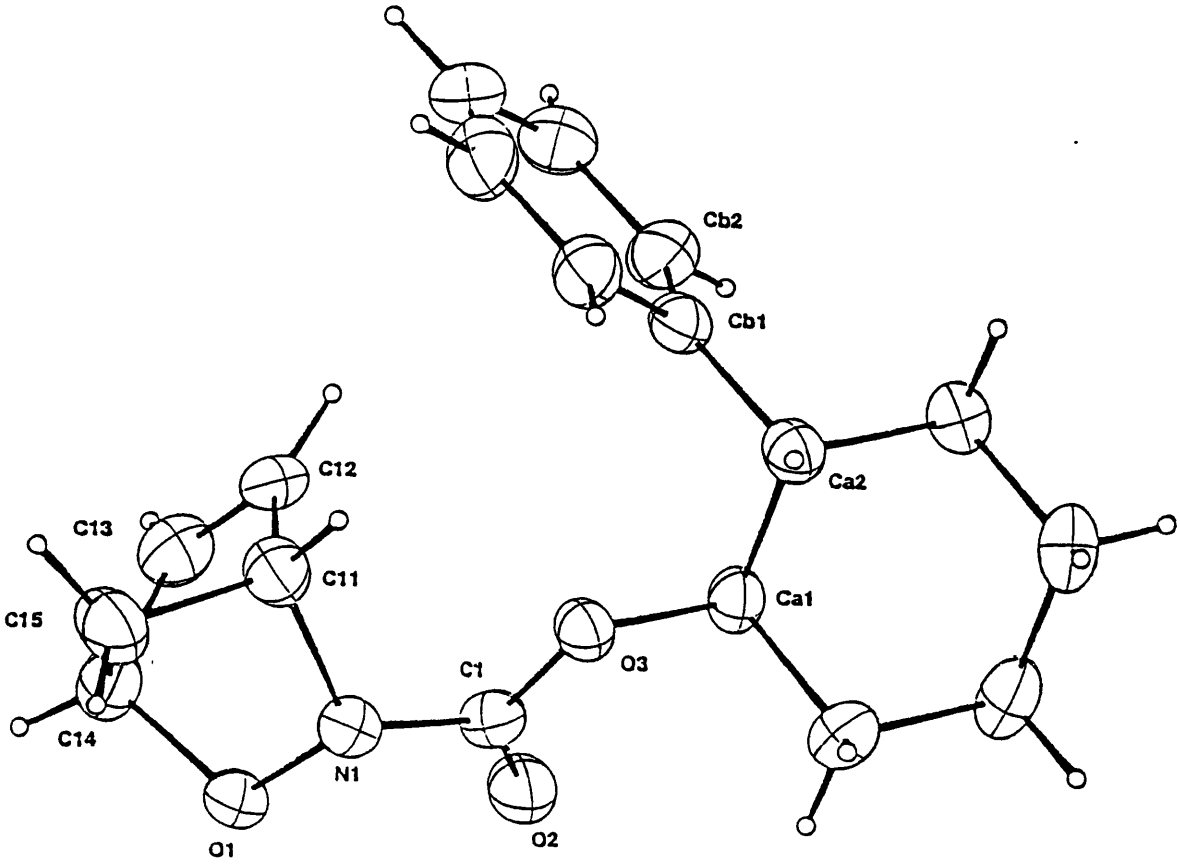


Figure 3.1.3

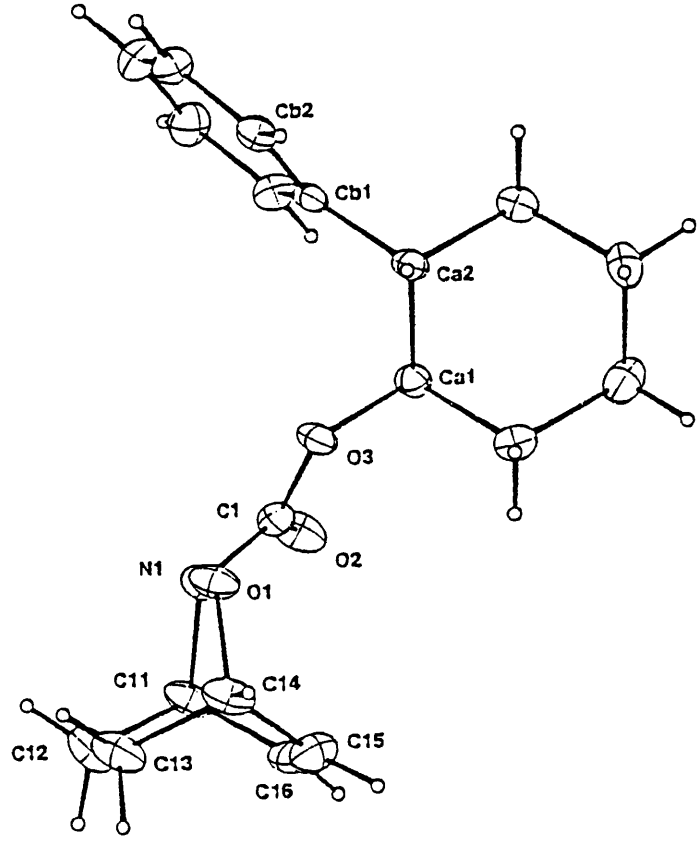


Figure 3.1.4

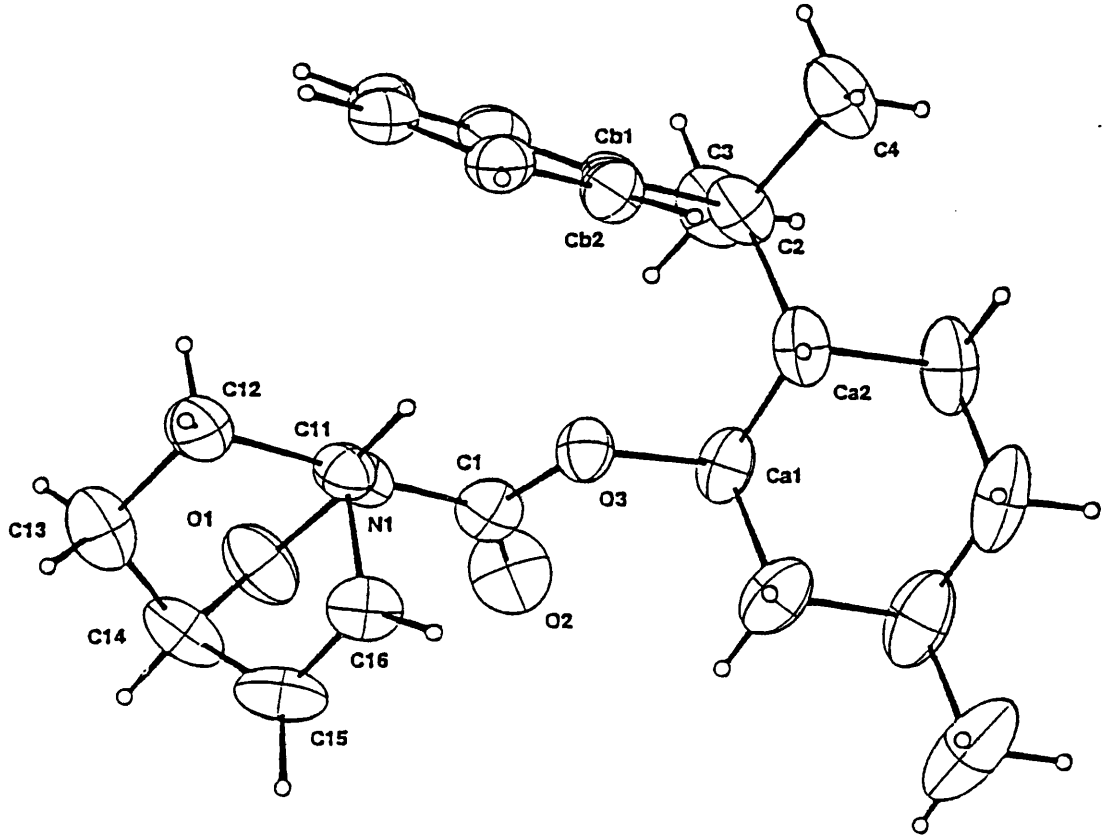


Figure 3.1.5

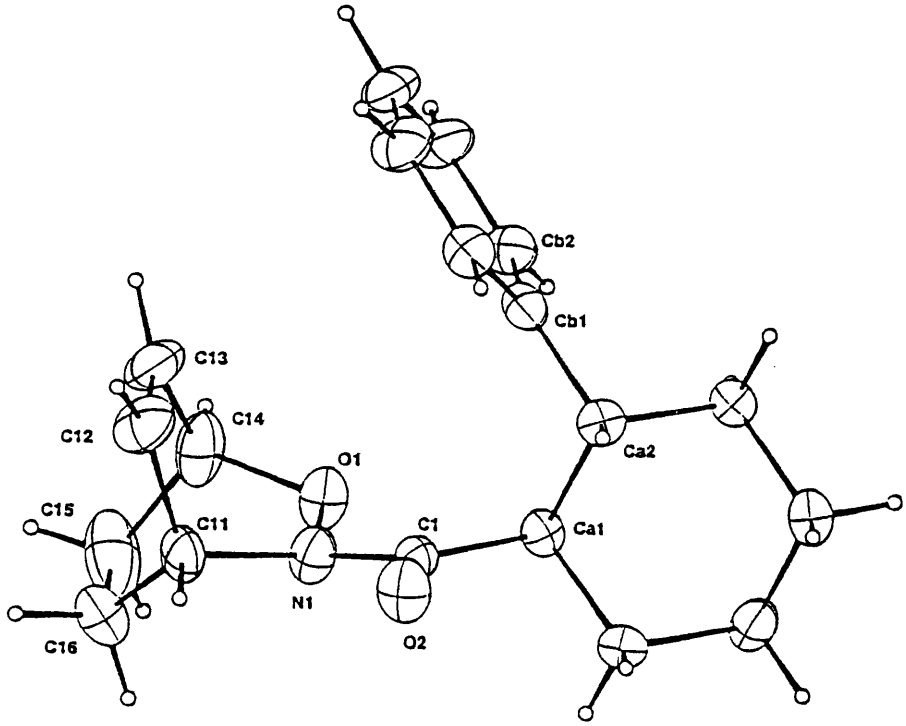


Figure 3.1.6

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 ($\Delta/\sigma>8$) 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 $\theta > 24.5°$ 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**

Formula	$C_{18}H_{22}N_2O_2$	$C_{19}H_{24}N_2O_2$
Formula wt	298.39	312.41
Crystal system	monoclinic	monoclinic
Space group	$P2_1/a$	Cc
a Å	10.157(2)	31.1495(18)
b Å	10.543(2)	5.5988(5)
c Å	15.617(2)	19.3637(15)
β °	107.085(14)	90.94(6)
V $Å^3$	1598.6(5)	3376.6(5)
Z	4	8
F(0 0 0)	640	1344
D calc g cm^{-3}	1.240	1.229
T K	295	295
Crystal colour and habit	colourless, needle	colourless, needle
Crystal size mm	0.38 x 0.20 x 0.15	0.54 x 0.29 x 0.15
Cell: reflections used θ range(°)	25 reflections 11.3<θ<20.9	15 reflections 5.4<θ<13.2
μ(Mo-Kα) cm^{-1}	0.76	0.75
Measured reflections	3821	5911
Unique reflections	3612	5909
Observed reflections $I \geq 3\sigma(I)$	1619	3251
θ range °	2.7 - 27.4	2.5 - 25.0
Miller indices h	-13 → 0	0 → 6
k	-13 → 0	-18 → 18
l	-19 → 20	-22 → 22
Decay in mean standard (%)	1.7	1.9
R_{int}	0.024	-
No. of parameters	200	414
R(F)	0.061	0.056
R_w (F)	0.078	0.071
S	2.9	2.4
$\Delta\rho_{max.}$ and $\Delta\rho_{min.}$ $eÅ^{-3}$	0.30 → -0.28	0.25 → -0.20
$\Delta/\sigma_{max.}$	0.024	0.023
Extinction coefficient	256(113)	588(97)

Table 3.1.5. Crystallographic details of the structure analyses of compounds **3** and **4**

Formula	$C_{18}H_{21}O_3N$	$C_{19}H_{23}O_3N$
Formula wt	299.37	313.40
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a Å	10.708(2)	15.640(6)
b Å	9.591(1)	9.819(4)
c Å	15.470(2)	11.324(8)
β °	95.129(14)	109.81(6)
V $Å^3$	1582.4(4)	1634.0(5)
Z	4	4
F(0 0 0)	640	672
D calc g cm^{-3}	1.257	1.272
T K	295	293
Crystal colour and habit	colourless block	colourless block
Crystal size mm	0.53 x 0.53 x 0.30	0.42 x 0.18 x 0.10
Cell: reflections used θ range(°)	25 reflections $11.5<\theta<18.2$	25 reflections $12.4<\theta<20.6$
μ(Mo-Kα) cm^{-1}	0.80	0.80
Measured reflections	2655	4659
Unique reflections	2549	2280
Observed reflections $I \geq 3\sigma(I)$	1161	1108
θ range °	3.0 - 24.5	2.7 - 27.4
Miller indices h	$-12 \rightarrow 12$	$-10 \rightarrow 10$
k	$0 \rightarrow 11$	$0 \rightarrow 12$
l	$0 \rightarrow 17$	$-16 \rightarrow 17$
Decay in mean standard (%)	50	1
R_{int}	0.055	0.038
No. of parameters	199	208
R(F)	0.066	0.045
R_w (F)	0.073	0.043
S	2.9	1.7
$\Delta\rho_{max.}$ and $\Delta\rho_{min.}$ $eÅ^{-3}$	$0.30 \rightarrow -0.29$	$0.19 \rightarrow -0.24$
$\Delta/\sigma_{max.}$	0.12	0.051

Table 3.1.6. Crystallographic details of the structure analyses of compounds **5** and **6**

Formula	$C_{23}H_{32}O_3N$	$C_{19}H_{23}O_2N$
Formula wt	370.5	297.4
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$Pna2_1$
a Å	6.0973(1)	21.1332(1)
b Å	20.1094(5)	12.7566(2)
c Å	9.1098(2)	5.9446(3)
β °	105.5(14)	-
V $Å^3$	1065.7(4)	1602.6(5)
Z	2	4
F(0 0 0)	402	640
D calc g cm^{-3}	1.154	1.232
T K	294	295
Crystal colour and habit	colourless plate	colourless plate
Crystal size mm	0.32 x 0.25 x 0.20	0.51 x 0.22 x 0.18
Cell: reflections used θ range(°)	25 reflections $8.3<\theta<18.1$	25 reflections $9.7<\theta<19.1$
μ(Mo-Kα) cm^{-1}	0.70	0.74
Measured reflections	3993	1544
Unique reflections	1934	1544
Observed reflections $I \geq 3\sigma(I)$	1047	894
θ range °	2.4 - 25.0	2.5 - 25.0
Miller indices h	$0 \rightarrow 7$	$0 \rightarrow 7$
k	$0 \rightarrow 23$	$0 \rightarrow 15$
l	$-10 \rightarrow 10$	$0 \rightarrow 25$
Decay in mean standard (%)	2	1.4
R_{int}	0.030	-
No. of parameters	243	198
R(F)	0.037	0.038
R_w (F)	0.034	0.042
S	1.8	1.6
$\Delta\rho_{max.}$ and $\Delta\rho_{min.}$ $eÅ^{-3}$	$0.10 \rightarrow -0.13$	$0.15 \rightarrow -0.16$
$\Delta/\sigma_{max.}$	0.033	0.091

Table 3.1.7. Atomic fractional coordinates and equivalent isotropic dispalcement parameters ($Å^2$) for compounds **1** - **6**

(a) compound **1**

Atom	x	y	z	U
O(1)	0.1041(3)	0.8712(3)	0.4637(2)	0.053
O(2)	0.2658(3)	0.7109(3)	0.3268(2)	0.054
N(1)	0.2083(3)	0.7895(3)	0.4457(2)	0.042
N(2)	0.0461(3)	0.7739(3)	0.3044(2)	0.040
C(1)	0.1747(4)	0.7578(4)	0.3541(2)	0.035
C(11)	0.3390(4)	0.8656(5)	0.4783(3)	0.053
C(12)	0.3232(6)	0.9733(5)	0.4162(3)	0.072
C(13)	0.2274(7)	1.0448(5)	0.4285(4)	0.076
C(14)	0.1813(5)	0.9878(5)	0.5008(3)	0.058
C(15)	0.3131(5)	0.9285(5)	0.5601(3)	0.064
C(A1)	0.0048(4)	0.7469(4)	0.2089(2)	0.042
C(A2)	-0.1071(4)	0.8388(4)	0.1569(2)	0.044
C(A3)	-0.1444(5)	0.8073(5)	0.0577(3)	0.062
C(A4)	-0.1887(6)	0.6704(5)	0.0375(3)	0.074
C(A5)	-0.0773(7)	0.5802(5)	0.0900(3)	0.078
C(A6)	-0.0401(5)	0.6106(4)	0.1900(3)	0.059
C(B1)	-0.0667(4)	0.9762(4)	0.1774(3)	0.046
C(B2)	-0.1289(5)	1.0472(5)	0.2289(3)	0.069
C(B3)	-0.0926(7)	1.1729(6)	0.2485(4)	0.085
C(B4)	0.0012(8)	1.2297(5)	0.2151(4)	0.089
C(B5)	0.0648(7)	1.1604(6)	0.1646(4)	0.093
C(B6)	0.0313(6)	1.0347(5)	0.1463(3)	0.072

(b) compound **2**

Atom	x	y	z	U
O(11)	0.2616	0.2023(8)	0.2258*	0.048
N(11)	0.2697(2)	-0.0118(11)	0.2621(3)	0.044
O(21)	0.3290(2)	-0.2325(10)	0.2978(3)	0.062
N(21)	0.3372(2)	0.1618(10)	0.2740(3)	0.046
C(11)	0.3147(2)	-0.0401(14)	0.2776(4)	0.039
C(111)	0.2521(2)	-0.2263(12)	0.2214(5)	0.046
C(121)	0.2742(3)	-0.2200(16)	0.1539(5)	0.065
C(131)	0.2715(3)	-0.0132(17)	0.1216(5)	0.068
C(141)	0.2444(3)	0.1529(15)	0.1566(4)	0.059
C(151)	0.2041(3)	-0.1741(13)	0.2103(4)	0.055
C(161)	0.1993(3)	0.0503(15)	0.1671(5)	0.063

C(A11)	0.3826(2)	0.1735(13)	0.2941(4)	0.047
C(A21)	0.4057(2)	0.3613(12)	0.2510(4)	0.042
C(A31)	0.4524(3)	0.3792(16)	0.2736(4)	0.061
C(A41)	0.4572(3)	0.4272(18)	0.3507(5)	0.078
C(A51)	0.4350(3)	0.2438(17)	0.3932(4)	0.073
C(A61)	0.3875(2)	0.2250(15)	0.3708(4)	0.059
C(B11)	0.4012(3)	0.3138(14)	0.1748(4)	0.047
C(B21)	0.3815(3)	0.4828(16)	0.1322(5)	0.061
C(B31)	0.3773(3)	0.4531(23)	0.0618(6)	0.092
C(B41)	0.3942(4)	0.2490(25)	0.0325(6)	0.101
C(B51)	0.4132(4)	0.0833(19)	0.0732(7)	0.087
C(B61)	0.4170(3)	0.1147(16)	0.1439(5)	0.069
O(12)	0.2110(2)	0.2375(7)	0.4780(4)	0.044
N(12)	0.2017(2)	0.4611(10)	0.5097(4)	0.044
O(22)	0.1429(2)	0.6890(9)	0.5380(3)	0.059
N(22)	0.1349(2)	0.2855(10)	0.5247(4)	0.042
C(12)	0.1575(2)	0.4866(13)	0.5242(4)	0.038
C(112)	0.2187(3)	0.6599(12)	0.4660(5)	0.047
C(122)	0.1963(3)	0.6475(15)	0.3990(5)	0.056
C(132)	0.2008(3)	0.4411(18)	0.3691(4)	0.065
C(142)	0.2276(3)	0.2722(14)	0.4084(5)	0.053
C(152)	0.2667(2)	0.6104(13)	0.4586(5)	0.054
C(162)	0.2726(3)	0.3783(15)	0.4199(5)	0.061
C(A12)	0.0898(2)	0.2792(13)	0.5446(4)	0.043
C(A22)	0.0660(2)	0.1013(12)	0.4992(4)	0.040
C(A32)	0.0188(3)	0.0857(14)	0.5217(4)	0.057
C(A42)	0.0149(3)	0.0295(15)	0.5975(5)	0.069
C(A52)	0.0389(3)	0.1974(17)	0.6414(4)	0.066
C(A62)	0.0855(2)	0.2167(15)	0.6206(4)	0.058
C(B12)	0.0696(2)	0.1605(13)	0.4242(4)	0.043
C(B22)	0.0900(3)	-0.0027(13)	0.3800(5)	0.053
C(B32)	0.0947(3)	0.0432(20)	0.3100(5)	0.086
C(B42)	0.0766(4)	0.2589(21)	0.2826(5)	0.091
C(B52)	0.0566(3)	0.4102(15)	0.3250(6)	0.071
C(B62)	0.0527(3)	0.3668(15)	0.3943(5)	0.061

*Fixed to defined origin

(c) compound **3**

Atom	x	y	z	U
O(1)	0.6475(4)	0.1601(4)	0.7630(2)	0.062
O(2)	0.8169(4)	0.1950(4)	0.8951(3)	0.070
O(3)	0.7017(3)	0.0634(4)	0.9795(2)	0.050
N(1)	0.6184(4)	0.1138(5)	0.8467(3)	0.052
C(1)	0.7255(5)	0.1279(5)	0.9078(4)	0.050
C(11)	0.5716(5)	-0.0360(6)	0.8307(4)	0.061
C(12)	0.6825(6)	-0.1169(6)	0.8092(4)	0.063
C(13)	0.7127(6)	-0.0712(7)	0.7346(4)	0.073

C(14)	0.6176(6)	0.0379(6)	0.7057(4)	0.067
C(15)	0.5011(7)	-0.0127(7)	0.7433(5)	0.077
C(A1)	0.8043(5)	0.0595(6)	1.0485(3)	0.049
C(A2)	0.7792(5)	-0.0661(6)	1.1048(3)	0.051
C(A3)	0.8805(6)	-0.0712(7)	1.1819(4)	0.065
C(A4)	0.8867(6)	0.0640(8)	1.2333(4)	0.074
C(A5)	0.9073(7)	0.1878(7)	1.1763(4)	0.079
C(A6)	0.8065(6)	0.1964(6)	1.0992(4)	0.070
C(B1)	0.7675(5)	-0.1992(6)	1.0529(3)	0.053
C(B2)	0.8717(5)	-0.2643(7)	1.0226(4)	0.069
C(B3)	0.8577(8)	-0.3844(8)	0.9739(5)	0.088
C(B4)	0.7436(10)	-0.4421(7)	0.9528(5)	0.096
C(B5)	0.6418(8)	-0.3807(9)	0.9819(5)	0.090
C(B6)	0.6532(6)	-0.2601(7)	1.0313(4)	0.068

(d) compound 4

Atom	x	y	z	U
O(1)	0.05406(19)	0.22346(33)	0.79740(26)	0.042
O(2)	0.2356(2)	0.1212(3)	0.7097(3)	0.052
O(3)	0.21591(19)	0.14715(30)	0.89671(29)	0.035
N(1)	0.0937(3)	0.1527(4)	0.7186(3)	0.033
C(1)	0.1874(3)	0.1420(5)	0.7710(5)	0.034
C(11)	0.0600(3)	0.2092(5)	0.5885(4)	0.040
C(12)	-0.0432(3)	0.1977(5)	0.5428(5)	0.052
C(13)	-0.0794(3)	0.2846(6)	0.6274(5)	0.055
C(14)	0.0019(3)	0.3414(5)	0.7302(4)	0.044
C(15)	0.0576(4)	0.4228(5)	0.6740(5)	0.053
C(16)	0.0878(3)	0.3546(6)	0.5974(5)	0.046
C(A1)	0.3142(3)	0.1614(5)	0.9588(4)	0.032
C(A2)	0.3373(3)	0.0964(4)	1.0877(4)	0.031
C(A3)	0.4380(3)	0.1237(5)	1.1628(4)	0.045
C(A4)	0.4613(3)	0.2739(5)	1.1709(5)	0.058
C(A5)	0.4361(4)	0.3356(5)	1.0407(6)	0.059
C(A6)	0.3361(3)	0.3109(5)	0.9659(5)	0.046
C(B1)	0.3181(3)	-0.0544(5)	1.0856(4)	0.028
C(B2)	0.2786(3)	-0.1094(5)	1.1677(4)	0.035
C(B3)	0.2670(3)	-0.2479(5)	1.1744(5)	0.044
C(B4)	0.2936(3)	-0.3352(5)	1.0990(5)	0.047
C(B5)	0.3314(3)	-0.2826(5)	1.0162(5)	0.046
C(B6)	0.3438(3)	-0.1439(5)	1.0093(4)	0.039

(e) compound 5

Atom	x	y	z	U
O(1)	0.5716(5)	0.6057	0.3125(4)	0.087
O(2)	0.4743(6)	0.4802(2)	0.2530(4)	0.091
O(3)	0.1018(5)	0.5053(2)	0.1595(3)	0.061
N(1)	0.3498(6)	0.5883(3)	0.2183(4)	0.062
C(1)	0.3227(10)	0.5195(3)	0.2185(5)	0.064
C(2)	-0.1673(8)	0.4648(3)	-0.1419(5)	0.071
C(3)	0.0484(8)	0.4412(3)	-0.1866(6)	0.092
C(4)	-0.3733(9)	0.4441(3)	-0.2749(6)	0.098
C(5)	-0.0842(15)	0.3126(4)	0.4380(10)	0.165
C(11)	0.1728(8)	0.6298(3)	0.2589(5)	0.060
C(12)	0.2387(10)	0.7017(3)	0.2418(5)	0.084
C(13)	0.4684(11)	0.7168(3)	0.3518(7)	0.100
C(14)	0.5520(9)	0.6532(3)	0.4322(6)	0.085
C(15)	0.3900(12)	0.6262(3)	0.5127(5)	0.094
C(16)	0.1856(8)	0.6154(3)	0.4224(5)	0.073
C(A1)	0.0381(8)	0.4356(3)	0.1420(6)	0.068
C(A2)	-0.1773(8)	0.4304(3)	0.0124(6)	0.071
C(A3)	-0.2475(9)	0.3565(3)	-0.0023(8)	0.106
C(A4)	-0.2655(13)	0.3291(3)	0.1530(10)	0.118
C(A5)	-0.0537(12)	0.3382(3)	0.2860(9)	0.109
C(A6)	0.0148(8)	0.4097(3)	0.2948(6)	0.084
C(B1)	-0.1754(8)	0.5403(3)	-0.1295(5)	0.060
C(B2)	-0.3422(8)	0.5708(3)	-0.0748(5)	0.065
C(B3)	-0.3630(9)	0.6386(3)	-0.0665(5)	0.071
C(B4)	-0.2165(11)	0.6795(3)	-0.1176(6)	0.079
C(B5)	-0.0486(10)	0.6506(4)	-0.1735(6)	0.084
C(B6)	-0.0312(8)	0.5825(3)	-0.1804(5)	0.070

(f) compound 6

Atom	x	y	z	U
O(1)	0.09481(15)	0.0445(3)	0.3204**	0.052
O(2)	0.0899(2)	0.2219(3)	-0.1269(7)	0.060
N(1)	0.0854(2)	0.0844(3)	0.0968(8)	0.051
C(1)	0.0890(2)	0.1884(3)	0.0659(9)	0.038
C(11)	0.0999(3)	0.0064(4)	-0.0774(10)	0.056
C(12)	0.1674(3)	-0.0221(5)	-0.0521(11)	0.066
C(13)	0.1791(3)	-0.0598(5)	0.1633(12)	0.077
C(14)	0.1210(3)	-0.0608(4)	0.3009(11)	0.069
C(15)	0.0717(4)	-0.1266(5)	0.1876(18)	0.108
C(16)	0.0603(3)	-0.0875(5)	-0.0336(17)	0.087
C(A1)	0.0861(2)	0.2606(3)	0.2670(9)	0.037
C(A2)	0.1469(2)	0.3263(3)	0.2763(9)	0.040
C(A3)	0.1424(2)	0.4089(3)	0.4612(10)	0.049
C(A4)	0.0841(2)	0.4775(3)	0.4347(10)	0.057

C(A5)	0.0248(2)	0.4126(3)	0.4297(11)	0.054
C(A6)	0.0280(2)	0.3312(3)	0.2422(10)	0.045
C(B1)	0.2060(2)	0.2597(3)	0.3022(9)	0.043
C(B2)	0.2175(2)	0.2032(4)	0.4960(10)	0.050
C(B3)	0.2718(2)	0.1449(4)	0.5181(11)	0.060
C(B4)	0.3165(2)	0.1434(4)	0.3534(12)	0.061
C(B5)	0.3059(2)	0.1975(4)	0.1571(11)	0.063
C(B6)	0.2511(2)	0.2553(4)	0.1325(9)	0.050

**Fixed to define origin