DOCTOR OF PHILOSOPHY

Stereocontrolled Cyclopropane Synthesis

Huber, Florian Anton Martin

Award date:
1999

Awarding institution:
University of Wales, Bangor

Prifysgol Cymru · University of Wales

BANGOR

Stereocontrolled Cyclopropane Synthesis

A thesis submitted to the University of Wales
for the degree of Doctor of Philosophy

by

Florian Anton Martin Huber

August 1999

Dedicated to Michela and my parents.

Acknowledgements

First and foremost I wish to express my sincere thanks to my supervisor Professor Mark S. Baird for giving me the opportunity to undertake a Ph.D. and to work in his research group. I am extremely grateful for his help and encouragement throughout the last three years.

I would like to thank Dr. Juma'a Al-Dulayymi for his friendship, for his continual support and advice (and last but not least his excellent BBQs).

A special 'diolch' goes to my friend and colleague Pete Licence; further I would like to thank all my colleagues and friends within research group 101 (this includes also all "Russians", especially Slava Tverezovzky and Professor Ivan Bolesov).

I would like to thank Professor Rafael R. Kostikoff for his co-work and assistance in the attempted preparation of a novel propellane species.

Sincere thank goes to Mr. Evan Roberts for kindly supplying a chiral HPLC column, which provided excellent resolution.

Thanks also goes to all members of staff in the Department who have been very helpful; technicians: especially Eric Lewis, G. Griffiths, D. Williams, G. Davies, G. Connolly and G. Vickers; secretaries: B. A. Kinsella, H. Hughes and C. Naylor.

My thank is extended to the University of Wales, Swansea for the mass spectrometry service; further to I.H. Sadler from the University of Edinburgh for recording NOE difference spectra.

Finally I wish to thank Peboc Division - Eastman Chemical (UK) Limited for their financial support which made this Ph.D. possible.

TABLE OF CONTENTS

List of abbreviations

ACC	1-amino-1-cyclopropanecarboxylic acid
BSA	sodium bis[trimethylsilyl]amide
Cat.	catalyst
CEFNO	carbethoxyformonitrile oxide
1,3-DC	1,3-dipolar cycloaddition
diphos	1,2-bis(diphenylphosphino)ethane
DIPT	diisopropyl tartrate
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ether	diethyl ether
FMO	frontier molecule orbitals
FVT	flash vacuum thermolysis
GLC	gas liquid chromatography
h	hour(s)
HIV	human immunodeficiency virus
HOMO	highest occupied molecule orbital
HPLC	high performance liquid chromatography
HSV	herpes simplex virus
LD_{50}	lethal dose fifty: the amount of a toxic agent (as a poison, virus, or radiation) that is sufficient to kill 50% of a population of animals usually within a certain time
LDA	Lithium diisopropylamide
LG	leaving group
LUMO	lowest occupied molecule orbital
MAO	monoamine oxidase
MCPA	methylenecyclopropane acetic acid
mGluRs	metatropic glutamate receptors
min	minutes
(m)mol	(m)mole
mol.equiv.	mole / molar equivalents
n-BuLi	n-butyllithium
NCS	*N*-chlorosuccinimide

NOE	nuclear Overhauser effect
petrol	petroleum ether
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTC	phase transfer catalysis
r.t.	room temperature
TDBS	*tert*-butyldiphenylsilanyl
TEAB	tetraethylammonium bromide
THF	tetrahydrofuran
TLC	thin layer chromatography

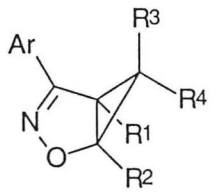
Abstract

This thesis consists of two major parts: **Part I** is about the application of the 1,3-dipolar cycloaddition reaction in the stereocontrolled synthesis of cyclopropanes; **Part II** explores the chemistry of *gem*-dibromocyclopropanes.

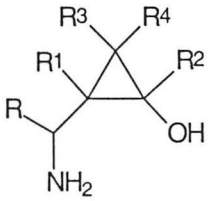
Part I:

1,3-Dipolar cycloaddition (1,3-DC) reactions of cyclopropenes to nitrile oxides gave access to a range of bicyclic systems (**i**), containing an isoxazoline moiety. Reduction of those compounds with lithium aluminium hydride afforded amino cyclopropanol species (**ii**) with 100 % diastereoselectivity.

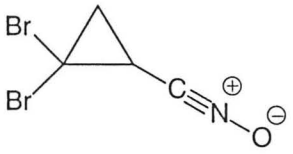
Two novel nitrile oxides, one dipole (**iii**) derived from 2,2-dibromocarboxylic acid, the other (**iv**) derived from (*S*)-(-)-ethyl lactate were prepared. Their asymmetric induction potential and their properties were tested upon reaction with cyclopropenes and acetylenic dipolarophiles.



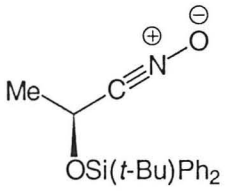
i



ii



iii

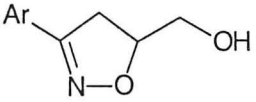


iv

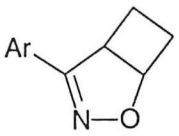
Catalytic asymmetric 1,3-DC reaction of a nitrile oxide to allyl alcohol provided enantiomerically pure isoxazoline (**v**). It served as a precursor for the synthesis of a novel optically active amino cyclopropanol species of type (**ii**). Transformation of the side chain of isoxazoline (**v**) was achieved *via* a Swern oxidation and subsequent Grignard addition.

The scope and generality of the catalytic asymmetric 1,3-DC reaction was investigated using a range of different substituted allylic alcohols. The catalytic asymmetric 1,3-DC reaction was also tested upon a nitrile imine.

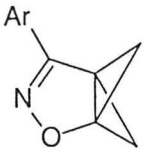
The syntheses of the strained bicycle (**vi**) and tricycle (**vii**) were attempted.



v



vi

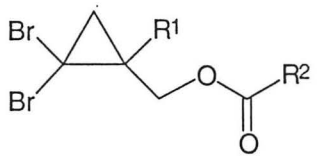


vii

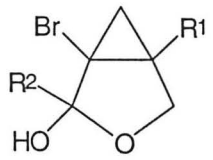
Part II:

Reaction of 2-acyloxymethyl (**viii**) or 2-acylaminomethyl-1,1-dibromocyclopropanes with methyllithium at –90 °C led to selective bromine-lithium exchange and intramolecular cyclisation to give a 1-bromo-3-oxa (**ix**) or 1-bromo-3-aza-bicyclo[3.1.0]-hexanol with high diasteroselectivity.

Gem-dibromocyclopropanes, derived from the cycloaddition of cyclopropenes to 2,2-dibromocyclopropylformonitrile oxide (**iii**) were treated with methyllithium at room temperature and it was found that only mono-reduction products were formed.



viii



ix

1. Introduction

1.1. Structure, energy and strain of three-membered carbocycles[1]

1.1.1. Bonding and bond angles in cyclopropanes[2] and cyclopropenes[3]

Cyclopropane

Cyclopropane is unique among carbocycles in both its properties and reactions.[4] It has played a special role in the development of an understanding of the nature of carbon-carbon bonds. Cyclopropane has a great deal of angle strain, since a 60° angle represents a large departure from the tetrahedral angle of 109.5°. For a normal carbon atom, one *s* and three *p* orbitals are hybridised to give four approximately equivalent sp^3 orbitals, each containing about 25 % s character. However for a cyclopropane carbon atom, the four hybrid orbitals are far from being equivalent. The two orbitals directed to the outside bonds have more s character than a normal sp^3 orbital, while the two orbitals involved in the ring bonding have less, because the more *p*-like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. This additional *p* character relieves some of the strain. The external orbitals have about 33 % *s* character, so that they are approximately sp^2 orbitals, while the internal orbitals have about 17 % *s* character, so they may be called approximately sp^5 orbitals.[5] Each of the three carbon-carbon bonds of cyclopropane is therefore formed by overlap of two sp^5 orbitals. Molecular calculations show that such bonds are not completely σ in character. In normal carbon-carbon bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. In cyclopropane however, the electron density is directed away from the ring. **Figure 1** shows the direction of orbital overlap;[6] the angle (marked θ) is 21°. Molecular orbital calculations also show that the maximum electron densities of the carbon-carbon σ orbitals are bent away from the ring with θ = 9.4°.[7] Thus the bonds in cyclopropane are called *bent bonds*, and are intermediate in character between σ and π.

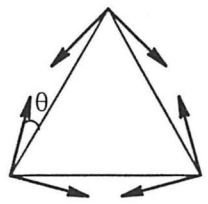
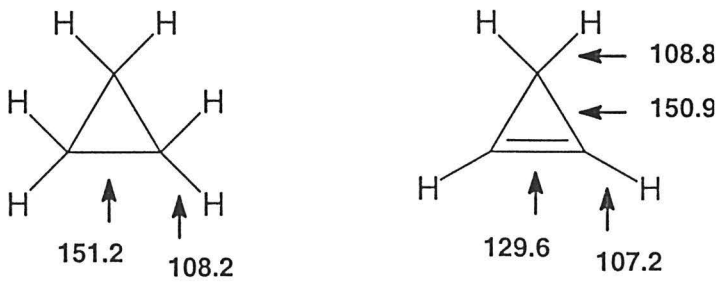


Figure 1

Cyclopropanes always have shorter carbon-carbon bonds than open chain alkanes (**Figure 2**). The short bonds in cyclopropanes are readily explained in terms of the bent bonds. The true length lies along the curved path that is significantly longer than the distance between the carbons.

The C-H bonds in cyclopropanes are shorter than those in most alkanes, and this is probably related to their high s character. The bond lengths and angles are similar to those found in alkenes. As a consequence, the C-H bonds in cyclopropane have properties similar to ethene. The C-H bond dissociation energy is 456 kJ/mol, much greater than that for the CH_2 group of propane (406 kJ/mol) and close to that of ethene (460 kJ/mol).



bond lengths in pm

Figure 2

Cyclopropenes[3]

Cyclopropene represents the smallest unsaturated cyclic molecule. The C(1)-C(2)-C(3) angle[8] is 51° and the C(1)-C(3)-C(2) angle is 64.5°. The highly strained nature of cyclopropanes results in a deviation of the hybridisation of the alkene carbons from the sp^2 hybridisation characteristic of open chain and large ring alkenes. Analysis of structural data of a variety of cyclopropene derivatives has led to the conclusion that the alkene carbon atoms use $sp^{1.19}$ hybrid orbitals in bonding to substituents and $sp^{2.68}$ hybrids to the σ-framework.[9]

Cyclopropenes have shorter carbon-carbon bonds than open chain alkenes. The bond lengths of cyclopropene itself are shown in **Figure 2**. Although the cyclopropene is more strained than cyclopropane, due to the lack of two hydrogens it has none of the eclipsing strain present in cyclopropane.

1.1.2. Energy and strain of small carbocycles[10]

Quantitative analysis of strain

The theory of strain in small rings dates back as early as 1885 when Adolf von Baeyer proposed that compounds with three- and four-membered rings would be less stable because of the deviation in bond angles from the normal tetrahedral values.[11] Although bond angle distortion is one of the major factors of strain, there are also other contributions to the strain of a molecule.[10]

The total strain in a molecule originates from:

(1) Bond length distortion

(2) Bond angle distortion

(3) Torsional strain

(4) Non-bonded interactions

(5) Energy changes due to rehybridisation

Chemical consequences of strain[10]

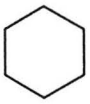
One might reasonably expect that increased strain would lead to increased reactivity. This is, however, not always the case. Factors that must be considered include the location of the activated complex along the reaction co-ordinate and the strain energies of the compounds that are formed as products or reaction intermediates. If the activated complex resembles the reactants, little of the strain energy would be released in the rate-determining step, and there would be little rate acceleration. Similarly, if the products or intermediates have large strain energies, there would be little driving force to help accelerate the reaction.

Strain energies[1,10]

The strain energy of a molecule is the difference between the observed heat of formation and that expected for a strain-free molecule. One might, for example, consider cyclohexane as a strain-free model. Its heat of formation is -123.4 kJ/mol, which is equivalent to -20.6 kJ/mol per methylene group. Cyclopropane, with three methylene groups, would be expected to have ΔH_f = -61.7 kJ/mol. The observed ΔH_f = +53.3 kJ/mol. The difference between these values, 115.0 kJ/mol, is the strain energy.

The heat of formation and the strain energies of some selected examples are given in **Table 1** below. Cyclopropene exhibits almost twice the strain energy of cyclopropane. If the double bond is located outside the ring as in case of methylenecyclopropane, the strain energy is considerable lower than that of cyclopropene. The last example given in the table is [1.1.1]propellane. It is among the most highly strained of hydrocarbons.

Table 1. Experimentally determined heats of formation (ΔH_f) and calculated strain energies (SE)

							
ΔH_f (25 °C) kJ/mol	+53.3	+28.4	-77.2	-123.4	+62.6	+47.9	+84.0
SE kJ/mol	115.0	110.9	25.9	0	218.8	171.1	406.7

1.2. Biologically active cyclopropanes and cyclopropenes: natural products and synthetic analogues of natural products[12]

Cyclopropane containing compounds, due to their unusual bonding and inherent ring strain are of great general interest, particularly to organic and bioorganic chemists. A growing number of naturally occurring cyclopropane derivatives are known to constitute the basic framework of active compounds present in animals, plants and micro-organisms, or to be generated transiently in primary and secondary metabolisms.[13] Also many insecticides and synthetic drugs include a cyclopropane in their structure. Naturally occurring or non-natural cyclopropane containing compounds are widely used to probe the mechanisms of biological processes.

Some of the various biological properties affected by a cyclopropane ring have become clear only very recently. They mainly range from:

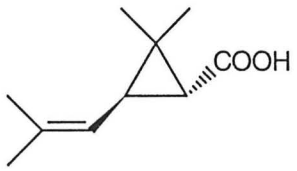
- enzyme inhibitions (e.g.: MAO, amino acid, amino acid decarboxylase, peptidase)
- insecticidal, antifungal, phytotoxic and herbicidal activities
- plant growth and fruit ripening controls
- hormonal activities (antiestrogens)
- neurochemical activities
- antibiotic, antimicrobial and antiviral (HSV, HIV) activities
- gluconeogenesis inhibition (hypoglycaemia)
- antimycotic properties
- carcinogenic or antitumoral properties
- metastatic and antimetastatic activities

1.2.1. Natural products containing cyclopropanes or cyclopropenes

Some examples of natural products are listed below. They are classified according to their functional groups.

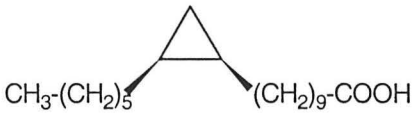
Cyclopropanecarboxylic acids

The *trans*-chrysanthemic acid **1** is an essential compound of naturally occurring pyrthrin esters, which are present in the flower of *Chrysanthenum cincerariaefolium* and have a defence function in these plants.[14] Very effective as an antifeedant for herbivores, it presents a broad spectrum as an insect repellent.



1

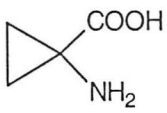
Cyclopropane containing fatty acids are found in bacterial membranes. Thus lactobacillic acid **2** has been isolated from *Lactobacillus arabinosus*,[15] *Brucella abortus* and *B. melitensis*.[16]



2

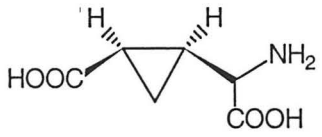
Aminocyclopropanecarboxylic acids

1-Amino-1-cyclopropanecarboxylic acid (ACC) **3** is a common constituent in apple, pear, grapefruit and many other plant tissues.[17] It is the immediate biosynthetic precursor of ethylene, the phytohormone that initiates and regulates many aspects of plant growth, including germination, inhibition, senescence, ripening of fruits, and is engaged in the metabolism of the plants.[18]

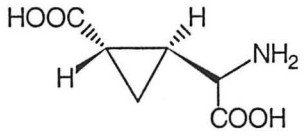


3

(*Z*)- and (*E*)-3,4-Methanoglutamic acid **4** represent conformationally constrained glutamate analogues that have been isolated from *Aesculus parviflora.*[19] The syntheses of the four diastereomers of **4** have been reported.[20] (*E*)-**4** exhibited neurochemical activities, thus it was found to be an isoform-selective agonist for group II metatropic glutamate receptors (mGluRs).[21] As a pharmacological tool this amino acid has played an important role in further understanding the functions and coupling mechanisms in mGluRs in the last few years.[22,23]

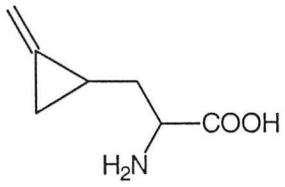


(*Z*)-(2S,3S,4R)-**4**



(*E*)-(2S,3S,4S)-**4**

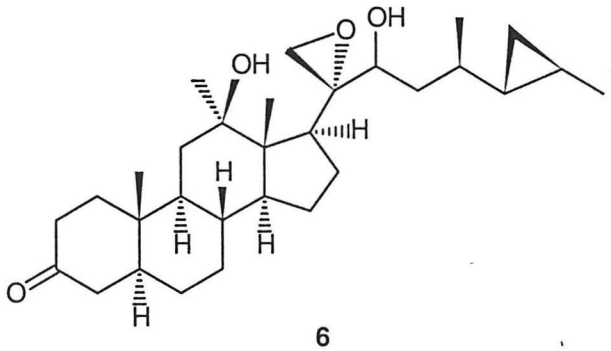
3-(2-Methylenecyclopropyl)alanine (hypoglycine A) **5** was isolated from the *ackee* (Jamaica) and *isin* (Nigeria) fruit of *Blighia sapida.*[24,25] Ingestion of unripe *ackee* fruits or seeds causes hypoglycaemia (lowering the blood sugar level), commonly known as 'Jamaican vomiting sickness'. The illness usually affects children and occasionally undernourished adults and is believed to have caused around 5,000 deaths in Jamaica between 1886-1950.[26] The LD_{50} value is 0.3 mmol per kg for hypoglycine A compared to 8 mmol per kg for (*S*)-tryptophan (the most toxic previously known amino acid). Gluconeogenesis is strongly inhibited so that the organisms run out of glucose when their glycogen reserves are exhausted.[27]



5

Steroids

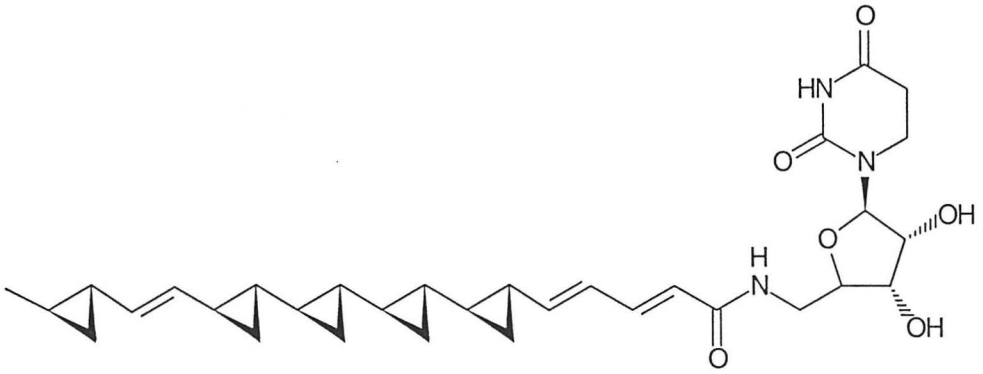
The marine cyclopropyl steroid, Aragusterol A **6** possesses potent antitumoral activity. It was isolated from the sponge of the genus *Xestospongia* on the coral reef of Aragusuku Island (Japan).[28]



6

Polycyclopropane

FR-900848 **7** is a natural product isolated from the fermentation broth of *Streptoverticillium fervens*. It shows potent, in vitro selective activity against filamentous fungi as *Aspergilus niger* and *Mucor rouxaianus*, but it is essentially inactive against non-filamentous fungi such as *Candida albicans*, yeasts and Gram-positive and negative bacteria.[29] Structurally the molecule is remarkable since it is endowed with five cyclopropanes, four of which are contiguous.



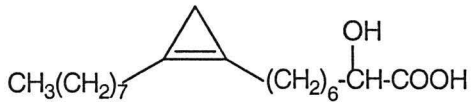
7

Cyclopropene fatty acids[12]

Four cyclopropene fatty acids have been reported in nature, sterculic acid **8**, malvalic acid **9**, (*R*)-2-hydroxysterculic acid **10**, and the very unusual sterculynic acid **11**,[30] which contains both cyclopropene and terminal alkyne groups. The hydroxy-acid is believed to be an intermediate in the metabolic conversion of **8** into **9**. The acetylenic acid **11** has only been isolated once, although a synthesis has been reported.[31] The

widespread presence of sterculic acid **8** and malvalic acid **9** as glycerides in the seed oils of a variety of plants has been known for many years. The biological effects of cyclopropene fatty acids range from slowed growth or genital system malfunctions in chickens, rats and mice, to liver cancer in synergy with aflatoxins in rainbow trout. Cyclopropene fatty acids also modify lipid protein and carbohydrate metabolisms and affect mixed hepatic oxidase systems.[32]

8 n = 7
9 n = 6



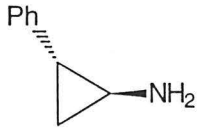
10

11

1.2.2. Non-natural products containing cyclopropanes

Cyclopropylamine

Trans-2-phenylcyclopropylamine (tranylcypramine) **12** is a potent inhibitor of the mitochondrial flavoenzyme monoamine oxidase (MAO), and an efficient albeit dangerous tranquillising drug.[33] Analogous cyclopropylamines provide suicide substrates for MAO.

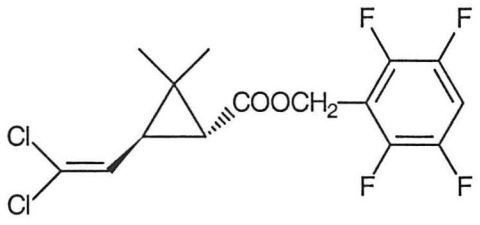


12

Esters of cyclopropanecarboxylic acids

Synthetic ester analogues of crysanthemic acid **1** have widely been used as insecticides for many decades. These derivatives (pyrethroids) show high insecticidal activity with low mammalian toxicity.[14,34] Various structural modifications gave material with enhanced stability and insecticidal activity for a wide range of insect pests. One of the latest pyrethroid agents developed is Transfluthrin® **13**.[35] In regard to

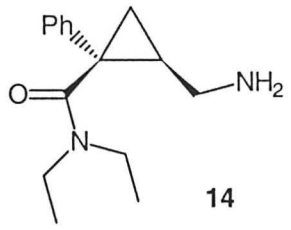
its structure, toxicology and principle of action on insects' nerves, Transfluthrin is regarded as one of the fastest acting pyrethroids with low persistency. Low quantities are exceptionally powerful against hygiene, health and material pests in the indoor environment.



(1*R*)-*trans*-**13**

Cyclopropanecarboxylic acid amide

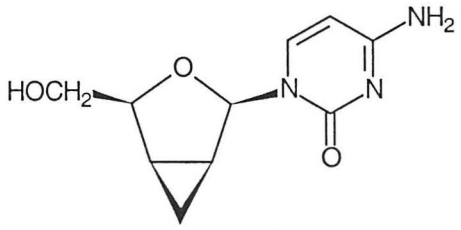
(Z)-2-Aminomethyl-1-phenyl-cyclopropanecarboxylic acid diethylamide **14** is a new drug whose INN is Milnacipran®. Milnacipran is a powerful antidepressant, which specifically inhibits the re-uptake of serotonin and noradrenaline.[36] Both its racemic and asymmetric synthesis have been reported.[37,38]



14

Cyclopropyl nucleosides

2',3'-Dideoxy nucleosides such as **15** containing a cyclopropane ring fused to the sugar portion have shown antiviral activity. The stereocontrolled synthesis of **15** has been achieved recently.[39]



15

1.3. Synthesis of cyclopropanes and cyclopropenes

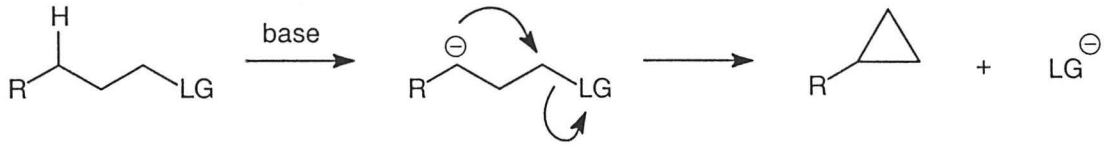
1.3.1. Racemic synthesis of cyclopropanes[40,41]

There are many methods for the preparation of cyclopropanes, some of which are illustrated below.

1.3.1.1. From a C_3 building block

1,3-Elimination of HX

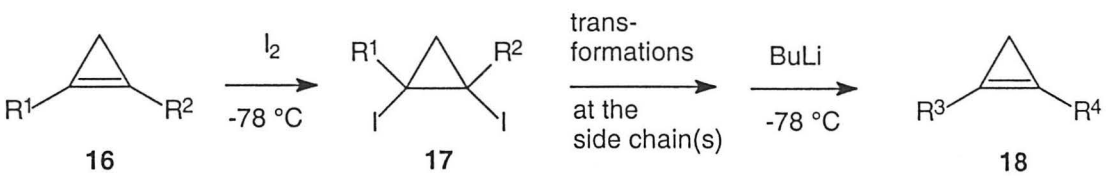
A convenient and general synthesis of cyclopropanes is *via* intramolecular S_N2 displacement of a suitable leaving group (LG) from the γ-carbon of a substrate bearing a carbanion at the α-carbon atom (**Scheme 1**). The leaving group is usually a tosylate or a halogen. R could be an ester,[42] ketone[43] or nitrile;[44] preferably it should be a functional group that is able to stabilise the carbanion.



Scheme 1

From Cyclopropenes[45]

Cyclopropanes can be generated from cyclopropenes by reactions such as addition of hydrogen, organometallic reagents, heteronucleophiles, electrophiles or radicals. An example of an electrophilic addition is the reaction of cyclopropene **16** with iodine (**Scheme 2**).[45]



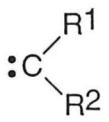
Scheme 2

A mixture of *cis*- and *trans*-1,2-diiodocyclopropane **17** is obtained. The cyclopropane species may readily be deiodinated to regenerate the cyclopropene **18**. Thus iodination represents an effective way to protect the cyclopropene species.[46]

Cyclopropenes are also known to undergo [2+2], [4+2] and [3+2] cycloaddition reactions, which lead to a variety of cyclopropanes.[45] The 1,3-dipolar cycloaddition of nitrile oxides to cyclopropenes will be described in detail in **Chapter 1.4.4.**

1.3.1.2. Combination of C_2 and C_1 building blocks

Cyclopropanation of carbon-carbon double bonds with carbenes and carbenoids

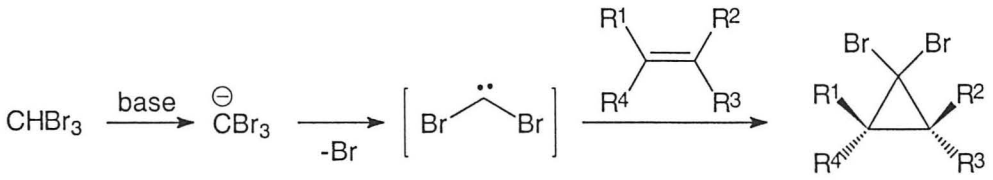


$R^1 = R^2 = H$ methylene

$R^1 = R^2$ or $R^1 \neq R^2$: H, alkyl, alkenyl, aryl, acyl, alkoxy, halogen

Carbenes are generally electrophilic and will react with olefins to form cyclopropanes.[47] The simplest carbene $:CH_2$ is usually called methylene. Major sources of carbenes are diazo compounds (diazomethane, diazoacetates) and haloforms ($CHCl_3$, $CHBr_3$). Diazo compounds form the carbene by photolytic or thermal decomposition processes. Especially vinyl-, acyl- and alkoxycarbenes are prepared in this way.

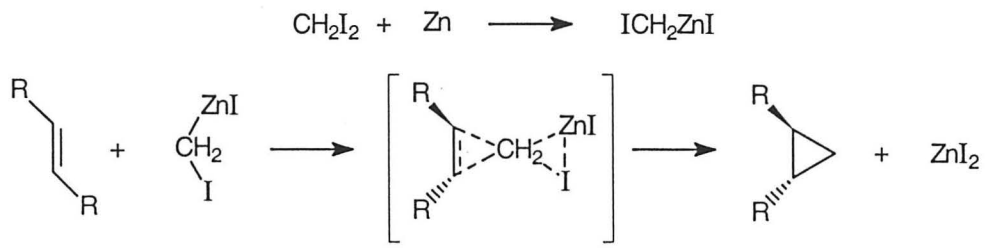
The generation of dihalocarbenes[48,49] is usually accomplished by reaction of the haloform with a strong base under Phase Transfer Catalysis (PTC) conditions.[50] Dibromocarbene addition to alkenes,[51] leading to *gem*-2,2-dibromocyclopropanes, was widely applied throughout this thesis (**Scheme 3**, see also **Chapter 1.5.**).



Scheme 3

Simmons-Smith reaction

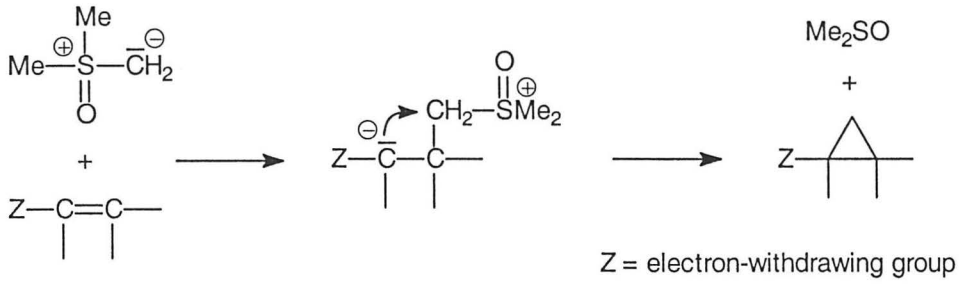
Since the discovery of Simmons and Smith[52] that simple alkenes undergo cyclopropanation at the double bond with a mixture of diiodomethane and zinc-copper couple, intensive use of this reagent has been made in preparative organic chemistry. The reaction of alkenes with the 'zinc reagent' is stereospecific with regard to the correlation of alkene configuration and product stereochemistry.[53] (Iodomethyl)zinc iodide, the product of the initial reaction of diiodomethane and zinc metal was proposed to be the active cyclopropanation reagent.[53] A three-centred transition structure was proposed to account for the observed stereoselectivities (**Scheme 4**).



Scheme 4

Cyclopropanation of Michael acceptors with ylides

Double bond compounds that can undergo a Michael addition can be converted into cyclopropane derivatives with sulfur ylides.[54] Among the most common of these is dimethyloxosulfonium methylide (**Scheme 5**).[55]



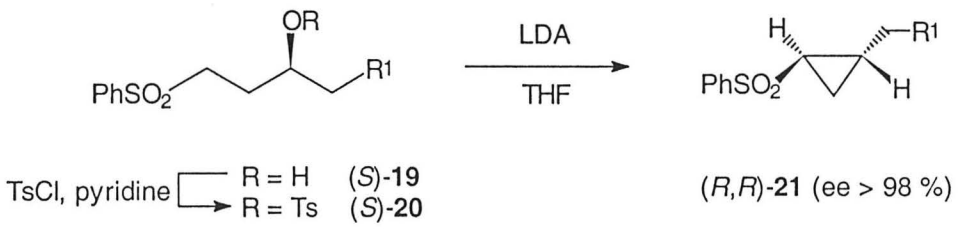
Scheme 5

1.3.2. Synthesis of enantiomerically pure cyclopropanes

1.3.2.1. Asymmetric synthesis

Active substrate - one or more chiral centres are present

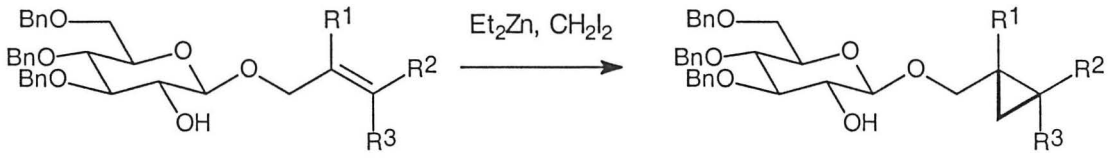
A wide range of optically active compounds have been used in the synthesis of enantiomerically pure cyclopropane derivatives; among them are sugar derivatives,[56] epoxides,[57] γ-heterosubstituted α,β-unsaturated esters[58] and alcohols,[59] 1,2-dioxines,[60] amino acid[61] and alcohol derivatives.[62] For the latter case an example is given below (**Scheme 6**). Enantiomerically pure alcohol **19** is obtained from a ketone by Bakers' yeast reduction. 1,3-Elimination of the tosylate **20** provides the cyclopropane species **21**.



Scheme 6

Active substrate - chiral auxiliary

3,4,6-Tri-*O*-benzyl-D-glucose was found to be an efficient and practical auxiliary for the asymmetric cyclopropanation of a variety of substituted allylic alcohols (**Scheme 7**).[63] This methology was applied to the stereoselective synthesis of the natural product coronamic acid.[64]



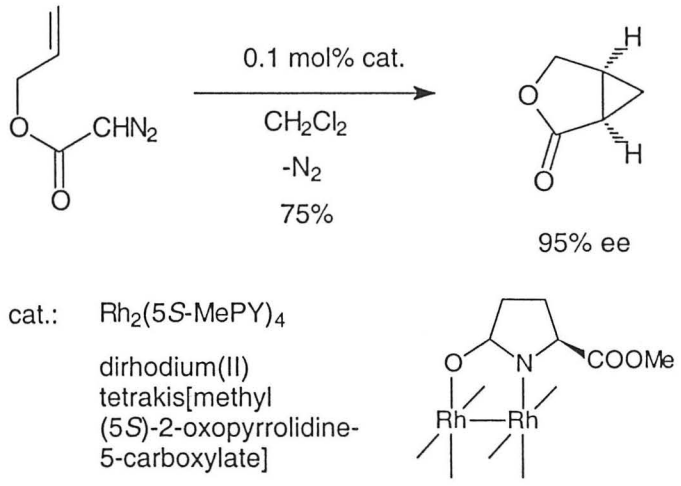
Scheme 7

Another example of a successful natural product synthesis, which applied a chiral auxiliary, is the stereocontrolled synthesis of dictyopterene B.[65] The key step is a highly stereocontrolled 1,3-elimination reaction of an ester derivative derived from (1*R*)-(+)-camphor.[57]

Active catalyst – enantioselective cyclopropanation reactions based on carbenoids *via* decomposition of diazoesters with chiral metal complexes[66,67]

As mentioned above diazocarbonyl compounds, such as diazoesters and diazoamides provide an efficient route to generate carbenes. In the presence of chiral catalysts the cyclopropanation occurs with moderate to high enantioselectivity. The catalyst consists of a metal - usually copper,[68] ruthenium[69] or rhodium[70] - and a chiral ligand, which is complexed to it. In intermolecular cyclopropanations copper-based catalysts gave the best results, whereas for intramolecular cyclopropanations rhodium based catalysts were usually employed.

In the latter case, especially chiral dirhodium(II) carboxamides proved to be very effective and optical purities of up to 95 % ee were reported.[71] One Example - the enantioselective synthesis of a lactone - is outlined in **Scheme 8**. In the catalyst system the dirhodium core is surrounded by four bridging amide ligands (the drawing shows only one ligand).

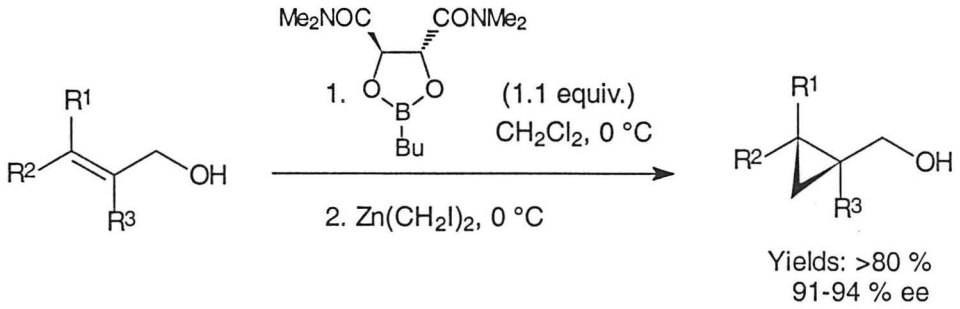


Scheme 8

Active catalyst – enantioselective cyclopropanation reactions based on carbenoids *via* decomposition of dihalomethanes with chiral metal complexes (enantioselective Simmons-Smith reaction)

An important route to enantiomerically pure cyclopropane derivatives is based on the Simmons-Smith reaction.[52] Since 1992 a range of chiral catalysts for this reaction has emerged.[72,73,74] Charette *et al.* reported the application of an amphoteric, bifunctional, chiral dioxoborolane ligand derived from (*R*,*R*)-(+)-*N*,*N*,*N'*,*N'*-tetramethyltartaric acid diamide.[75] It was shown to be an efficient chiral controller for

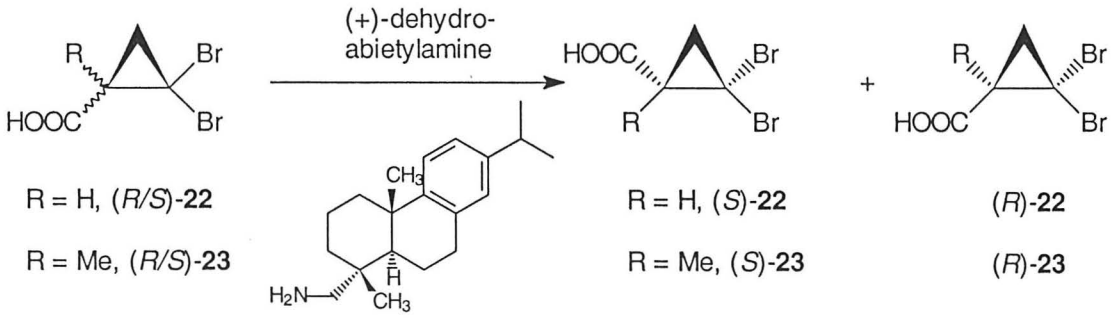
the enantioselective conversion of allylic alcohols to substituted cyclopropylmethanols in both high yields and enantiomeric excesses (**Scheme 9**).[75, 76]



Scheme 9

1.3.2.2. Resolution - conversion into diastereomers

Recently enantiomerically pure dihalocyclopropane derivatives have become accessible on a large scale.[77] The racemic 2,2-dibromocyclopropanecarboxylic acids **22**, **23** were resolved by treatment with dehydroabietylamine (**Scheme 10**).



Scheme 10

1.3.3. Racemic synthesis of cyclopropenes[78]

1.3.3.1. From a C_3 building block

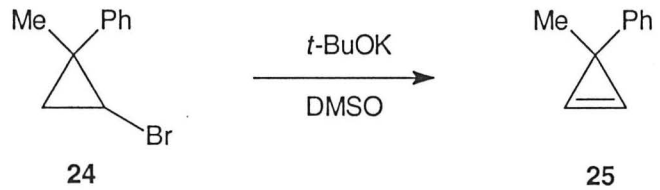
Cyclopropenes are generated from C_3 building blocks by following methods:

- from cyclopropenylium salts[79]
- nitrogen extrusion of 3*H*-pyrazoles[81]
- by transformation from other cyclopropenes[83]
- elimination reactions
- isomerisation of methylenecyclopropanes[80]
- rearrangement of allenes[82]
- ring contraction reactions (from 4-, 5-, 6-membered rings)[84]

Elimination reactions play an especially important role in the synthesis of cyclopropenes on a preparatively useful laboratory scale. Elimination reactions can be classified, according to the atoms where the elimination occurs, as 1,1- 1,2- and 1,3-eliminations respectively. Three examples of elimination reactions are outlined below:

1,2-Elimination from cyclopropanes – dehydrohalogenation

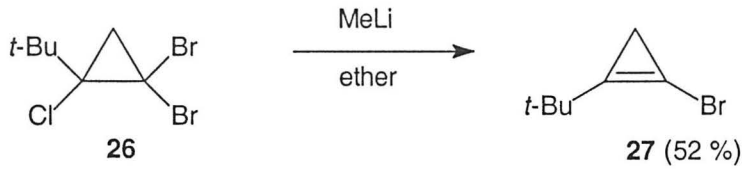
The dehydrohalogenation of a monohalocyclopropane is a generally applicable procedure. A range of disubstituted cyclopropenes (e.g. **25** in **Scheme 11**) has been prepared by this method.[85]



Scheme 11

1,2-Elimination from cyclopropanes – dehalogenation

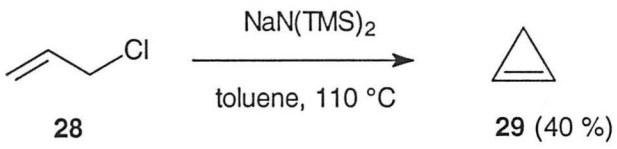
The elimination of halogen by reaction with alkyllithium occurs rapidly at -90 to 20 °C for 1,1-dibromides with a halogen at C-2 giving monohalocyclopropenes (e.g. **27** in **Scheme 12**).[86]



Scheme 12

1,1-Elimination and cyclisation of propylidenes - dehydrohalogenation of allylic halides

The elimination of hydrogen chloride from an allylic alcohol provides one of the most effective routes to simple alkylcyclopropenes, and to cyclopropene **29** itself (**Scheme 13**).[87]



Scheme 13

1.3.3.2. Combination of C_2 and C_1 building blocks

Reactions of triple-bond systems with Carbenes or Equivalents

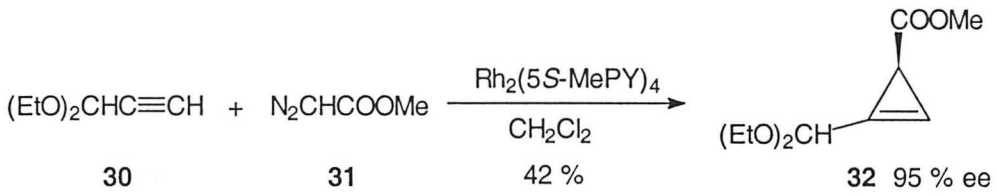
The addition of carbenes or equivalents to alkynes leads to the formation of cyclopropenes.[88] An example is given in **Chapter 1.3.4**. (**Scheme 14**, next page).

1.3.4. Synthesis of enantiomerically pure cyclopropenes

Compared to the large number of publications of enantiomerically pure cyclopropanes there are only a few examples of enantiomerically pure cyclopropenes reported in the literature.[89,90,91] Two syntheses are described below.

Addition of an alkoxycarbonylcarbene to an alkyne

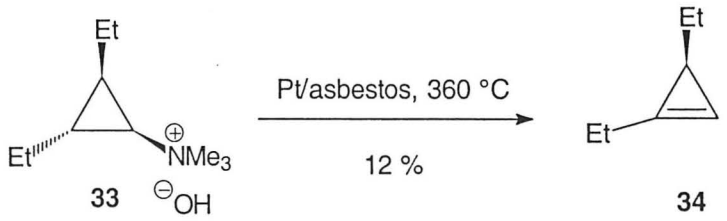
Intermolecular addition of methyl diazoacetate **31** to the alkyne **30** in the presence of a chiral catalyst (dirhodium(II) carboximate) gave the cyclopropene **32** in high optical purity (**Scheme 14**).[90]



Scheme 14

Synthesis from a cyclopropane

Deamination of a quaternary ammonium salt provided the original route to cyclopropene, this method has been applied to the synthesis of the optically active cyclopropene **34** (**Scheme 15**).[91]



Scheme 15

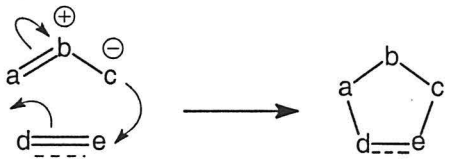
1.4. 1,3-Dipolar cycloaddition reactions and the transformation of cycloadducts

1.4.1. General aspects of 1,3-dipolar cycloaddition reactions

The addition of a 1,3-dipole to an alkene for the synthesis of five-membered rings is a classical reaction in organic chemistry. 1,3-Dipolar cycloaddition (1,3-DC) reactions are used for the preparation of molecules of fundamental importance for both academia and industry.

The history of 1,3-dipoles goes back to Curtius, who in 1883 discovered diazoacetic ester.[92] Five years later his younger colleague Buchner studied the reaction of diazoacetic ester with α,β-unsaturated esters and described the first 1,3-DC reaction. In 1893, he suggested that the product of the reaction of methyl diazoacetate and methyl acrylate was 1-pyrazoline and that the isolated 2-pyrazole was formed by rearrangement of the 1-pyrazole.[93] Five years later nitrones and nitrile oxides were discovered by Beckmann, and Werner and Buss, respectively.[94] The Diels-Alder reaction was found in 1928,[95] and the synthetic value of this reaction soon became obvious. The chemistry of the 1,3-DC reaction has thus evolved for more than 100 years, and a variety of different 1,3-dipoles have been discovered.[96] However, only a few dipoles found general application in synthesis during the first 70 years after the discovery of diazoacetic ester. Two well known exceptions were ozone and diazo compounds.[97] The general application of 1,3-dipoles in organic chemistry was first established by the systematic studies by Huisgen in the 1960s.[98] At the same time the new concept of conservation of orbital symmetry developed by Woodward and Hoffmann, appeared.[99] Their work was a milestone for the understanding of the mechanism of concerted cycloaddition reactions. On the basis of the concept by Woodward and Hoffmann, Houk *et al.* have further contributed to our present understanding and ability to predict relative reactivity and regioselectivity of the 1,3-DC reactions.[100]

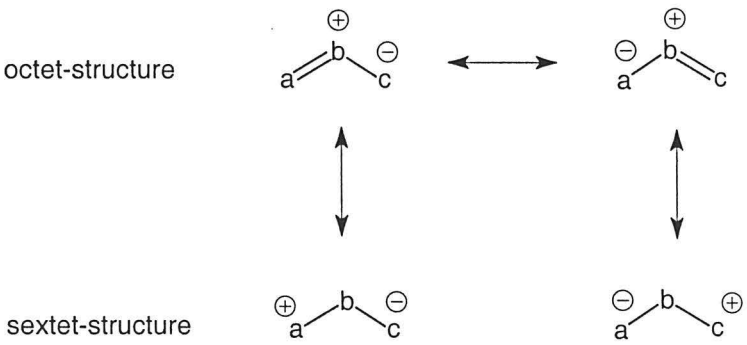
A 1,3-dipole is defined as an *a-b-c* structure and is portrayed by a dipolar structure as outlined in **Scheme 16**.[96,101] The dipole undergoes only cycloadditions of the ring-size classification 3+2 → 5.



Scheme 16

Basically 1,3-dipoles can be divided into two different types: the allyl type and the propargyl/allenyl type (**Figure 3**). The allyl type is characterised by four electrons in the three parallel p_z orbitals-perpendicular to the plane of the dipole and the 1,3-dipole is bent. Two resonance structures in which the three centres have an electron octet, and two structures in which the three centres *a* or *c* has an electron sextet, can be drawn. The central atom *b* can be nitrogen, oxygen, or sulfur. The propargyl/allenyl type has an extra π orbital located in the plane orthogonal to the allenyl type molecular orbital (MO), and the former orbital is therefore not directly involved in the resonance structures and reactions of the dipole. The propargyl/allenyl type is linear and the central atom *b* is limited to nitrogen. The three sextet resonances that also can be drawn are omitted in **Figure 3**.

Allyl type



Propargyl/allenyl type

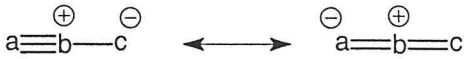


Figure 3

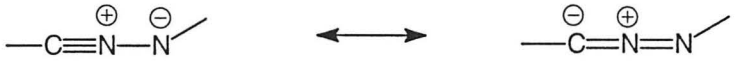
The 1,3-dipoles consist mainly of elements from main group IV, V and VI. Since the parent 1,3-dipoles consist of elements from the second row, and considering the above limitations on the central atom of the dipole, a limited number of structures can be formed by permutations of nitrogen, carbon, and oxygen. Hence, 12 dipoles of the allyl type and 6 dipoles of the propargyl/allenyl type are obtained. A few selected examples of both groups of dipoles are given in **Table 2**.

Table 2. Selected examples of 1,3-dipoles

⇨ A. Propargyl-Allenyl Type

Nitrile Ylides

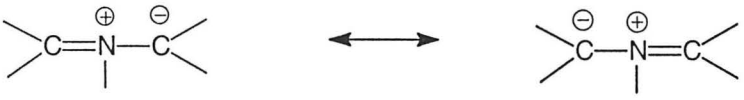
Nitrile Imines



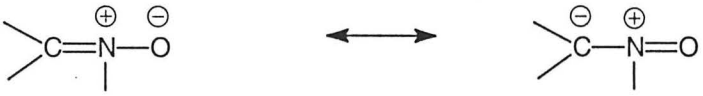
Nitrile Oxides

⇨ B. Allyl Type

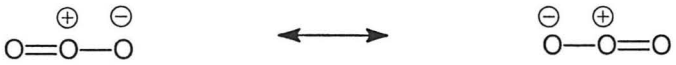
Azomethine Ylides



Nitrones



Ozone

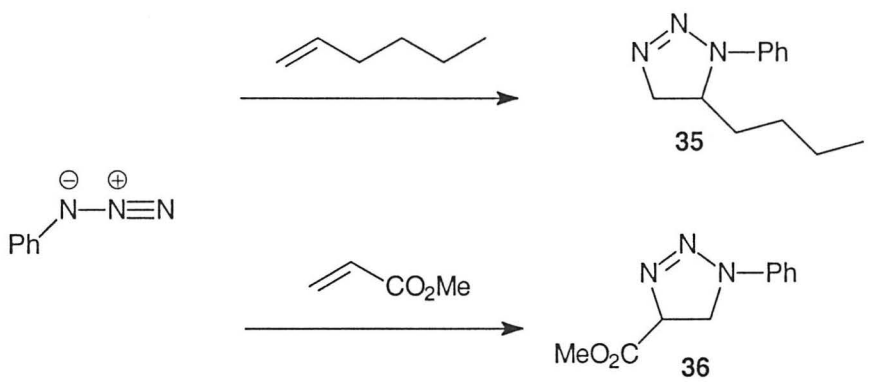


The 1,3-DC reaction involves 4 π electrons from the dipole and 2 π electrons from the dipolarophile (alkene or alkyne). 1,3-DC reactions are, according to the Woodward-Hoffmann rules,[99] $[_{\pi}4_s + {}_{\pi}2_s]$ reactions. The three p_z orbitals of the 1,3-dipole and the two p_z orbitals of the alkene both combine suprafacially.

It is generally agreed that 1,3-dipolar cycloadditions are concerted, like Diels-Alder reactions. This is borne out by their high regio- and stereoselectivities, among other factors.[96,102] The transition state of the concerted 1,3-DC reactions is thus controlled by the frontier molecule orbitals (FMO) of the substrates. Some 1,3-DC

reactions are controlled mainly by the HOMO (dipole) - LUMO (dipolarophile) interaction and others by the LUMO (dipole) - HOMO (dipolarophile) interaction. The smaller the energy gap between the controlling orbitals the faster the reaction. However, most 1,3-DC reactions fall into a third class in which both the HOMO (dipole) – LUMO (dipolarophile) and the LUMO (dipole) – HOMO (dipolarophile) interactions may be important. The controlling interaction in these cases depends on the nature of the dipolarophile and the electronic nature of the substituents on the dipole. These reactions can be accelerated by both electron-donating and electron-withdrawing substituents in either component. This change in orbital control from HOMO (dipole) to LUMO (dipole) or *vice versa* from one reaction to another of a particular dipole may have consequences for the regioselectivities of the reactions. Regioselectivities are controlled by the magnitudes of the atomic orbital coefficients in the orbitals concerned; the atoms in each component with the largest coefficients interact.[121]

For example, reaction of phenyl azide with 1-hexene, which is a LUMO (dipole) – HOMO (dipolarophile) interaction, gives mainly the 1-phenyl-5-butyltriazoline (**35**), but with methyl acrylate the 1-phenyl-4-carboxylic ester (**36**) is obtained (**Scheme 17**). The reaction is now HOMO (dipole) to LUMO (dipolarophile) controlled, because of the lowering of the energies of the frontier orbitals of the dipolarophile by the ester group, with a change in the relative magnitudes of the atomic orbital coefficients in the interacting frontier orbitals of the two components.[103] In some reactions electronically preferred orientations may be disfavoured by steric effects.



Scheme 17

As well as being regioselective, 1,3-DC reactions are highly stereoselective. Numerous examples have shown that the stereochemistry of substituents on the double

bond of the dipolarophile is retained in the adducts. Apparent exceptions have been shown to be due to isomerisation either before or after the cycloaddition.[104]

When two chiral centres are created in the cycloaddition, one arising from each reactant, diastereomeric products may be formed by way of *endo* and *exo* transition states, but it is not always easy to predict the stereochemical course of the reactions. The outcome depends on the interplay of two generally opposing forces in the transition state – attractive π-orbital overlap of unsaturated substituents favouring an *endo* transition state, and repulsive Van der Waals steric interactions favouring an *exo* transition state. Frequently mixtures of diastereomers are obtained.

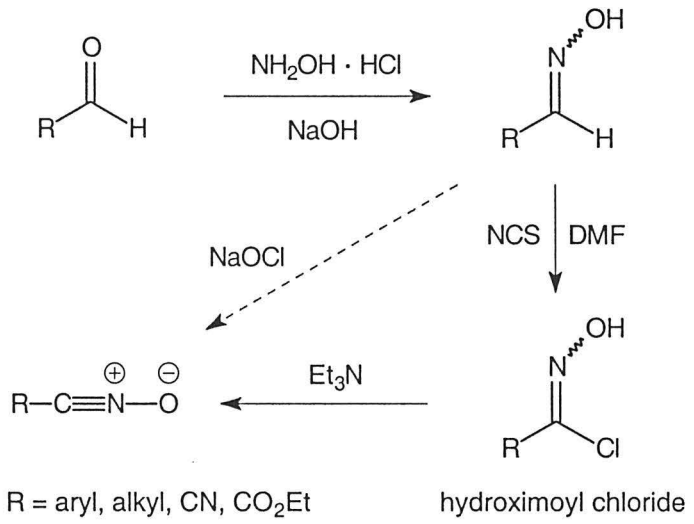
1.4.2. Nitrile oxides

Preparation of nitrile oxides

Nitrile oxides are 1,3-dipoles of the propargyl/allenyl type and they are among the most reactive species in organic synthesis.[96] Nitrile oxides are usually prepared *in situ* and not isolated. Generated in the presence of a dipolarophile they form the cycloadduct directly, often in high yield.

Two general methods have been used for their preparation - dehydrochlorination of hydroximoyl chloride (**method 1**) and dehydration of primary nitroalkanes (**method 2**).

Method 1: Dehydrochlorination of hydroximoyl chloride (Scheme 18)

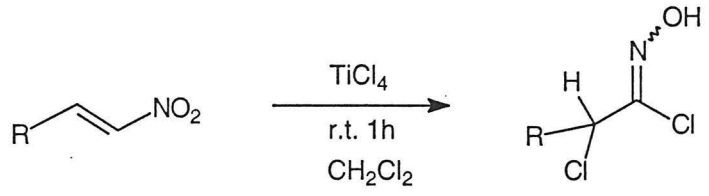


Scheme 18

Aldoximes are readily available from the corresponding aldehydes. Using an aqueous sodium hypochlorite solution, the nitrile oxide can be obtained in one step directly from the aldoxime.[105] Moriya *et al.* describe a similar direct approach, using *tert*-butyl hypochlorite and bis(tributyltin) oxide.[106]

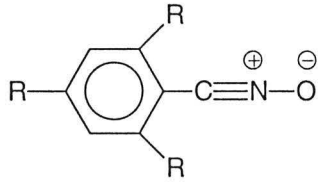
However the more common route to the nitrile oxide follows a two step procedure: the first step is the chlorination of the aldoxime with *N*-chlorosuccinimide (NCS) in DMF, which affords the nitrile oxide precursor, hydroximinoyl chloride.[107] In a second step, the nitrile oxide is generated upon treatment with triethylamine.[108,109]

Recently Kulkarni has developed a new route to the precursor hyroximoyl chloride by reacting titanium tetrachloride with nitroalkenes (**Scheme 19**).[110]

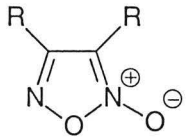


Scheme 19

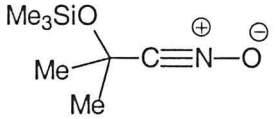
Nitrile oxides are unstable compounds and generally not isolated. Exceptions are 2,4,6-trimethylbenzonitrile oxide (**37**) and 2,4,6-trimethoxybenzonitrile oxide (**38**), which can be isolated as a crystalline solids and are indefinitely stable at ambient temperature.



37 R = Me
38 R = OMe



39



40

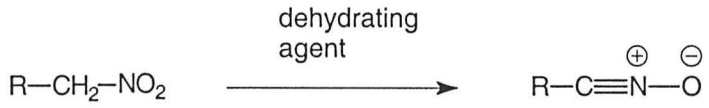
Nitrile oxides have a high tendency to dimerise to furoxans (= furazane 2-oxide) (**39**). In the absence of a dipolarophile, or if the reactivity of the dipolarophile is too low, the formation of the furoxan becomes the predominant reaction. The rate of formation also depends on the nature of the dipole:[111] bulky aryl derivatives of nitrile oxides are less prone to dimerisation than alkyl nitrile oxides. Barrow *et al.* reported an example of reduced dimerisation of alkyl nitrile oxides by protecting 2-oxopropanenitrile oxide as its 1,3-dithiane derivative.[112]

Furoxans have generally been regarded as stable "dead-end" side products from nitrile cycloaddition. However it is known that nitrile oxides can be regenerated from furoxans by thermolytic cycloreversion. Although this method is not generally applicable due to the vigorous reaction conditions (temperatures from 250 ° to 500 °C) that usually must be employed, Curran and Fenk[113] have shown that bis(2-(trimethylsilyl)oxy)prop-2-yl)furoxan affords the corresponding nitrile oxide **40** on

heating in benzene at 165 °C, and that the nitrile oxide give good yields with mono-, di- and tri- substituted alkenes under these conditions.

Over the past ten years furoxans themselves became the centre of attention due to their biological activity.[114] Recently, it was shown that furoxan derivatives are able to increase the level of cytosolic cyclic GMP in human platelets[115] and to activate rat liver soluble guanylate cyclase, in the presence of thiol cofactors.[116] This behaviour can be explained by the finding that furoxan can release nitric oxide (NO) when treated with thiols under physiological conditions. NO is an important physiological mediator in cardiovascular, immune, central, and peripheral nervous systems. These results prompted the synthesis of many new furoxan derivatives and the study of their pharmacological activities.[117]

Method 2: Dehydration of primary nitroalkanes

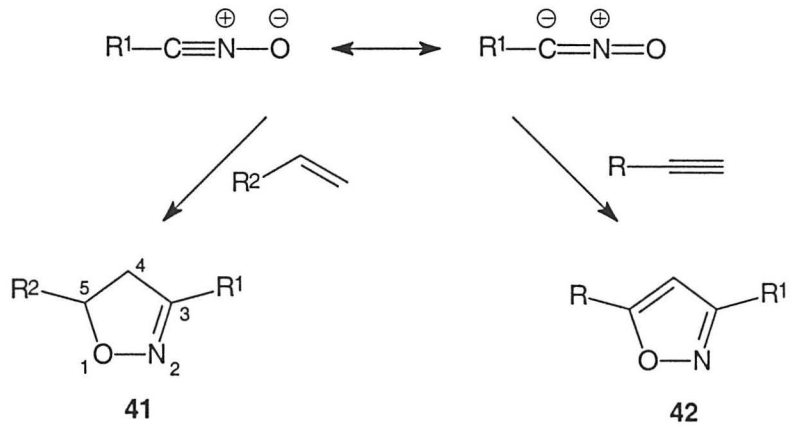


Scheme 20

The second important route for the generation of nitrile oxides is *via* dehydration of primary nitro compounds (**Scheme 20**, R = alkyl and aryl). This reaction was first described by Mukaiyama in 1960, using arylisocyanates as dehydrating agents.[118] This original procedure suffers limitations because it requires heating to ca. 80 °C, leading sometimes to low yields of products due to nitrile oxide dimerisation. Since then a range of dehydration agents has been found, which allows the conversion to nitrile oxides under mild reaction conditions. Di-*tert*-butyl dicarbonate in the presence of 0.1 molar equivalents of 4-methylaminopyridine (DMAP) was reported to be successful.[119] Alternative reagents for the dehydration include the Burgess reagent, DAST, acetic anhydride, oxalyl chloride and phosphorus oxychloride (all used with triethylamine).[120] Reagents such as DCC, thionyl chloride, triphenylphosphine oxide/triflic anhydride and butyltin oxide reportedly failed.[120]

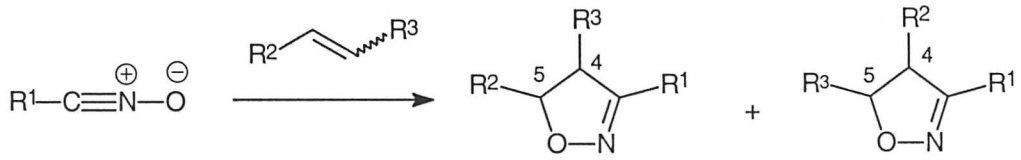
Preparation of isoxazolines and their transformations

The 1,3-DC reaction of nitrile oxides with alkenes provides a straightforward access to 2-isoxazolines **41** and the reports on synthetic application of this reaction are numerous.[111,121,122] Acetylenic dipolarophiles give isoxazoles **42** (**Scheme 21**).



Scheme 21

Nitrile oxides react with terminal alkenes, as shown in **Scheme 21**, to give the 5-isomer of the isoxazoline, i.e. the nitrile oxide carbon attacks the terminal carbon of the alkene. The 1,3-DC reaction of 1,2-substituted alkenes can give rise to two regioisomers of the 2-isoxazoline, each as a pair of enantiomers in which the relative configuration between the 4 and 5-substituents is determined from the geometry (*E* or *Z*) of the alkene (**Scheme 22**). The regioselectivity depends, as mentioned above, on the electronic and steric nature of the substituents.

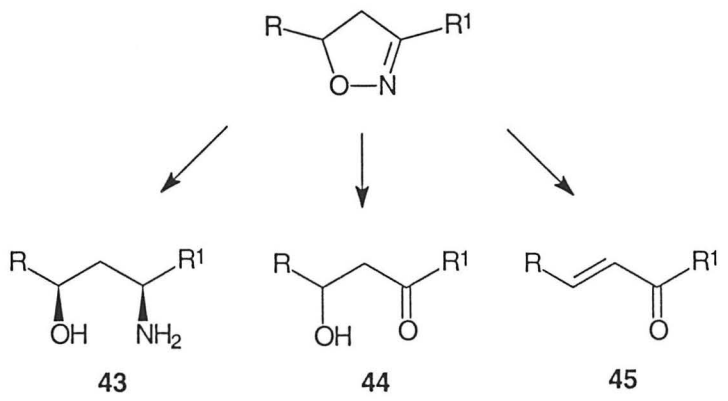


Scheme 22

In the literature, the reaction of nitrile oxides with a wide range of dipolarophiles is described; among them are cyclopropenes (see **Chapter 1.3.4**), unsaturated ferrocene derivatives,[123] fullerenes,[124,125] and highly fluorinated dipolarophiles.[126] Solid-phase 1,3-DC reactions were carried out with either the dipole[127] or the dipolarophile[128] attached to the resin.

The 1,3-DC reaction of nitrile oxides to olefinic and acetylenic dipolarophiles is a good method for the preparation of 2-isoxazolines and isoxazoles, but the real value of the reaction in synthesis lies in the access it provides to acyclic compounds by cleavage of the isoxazoline ring.

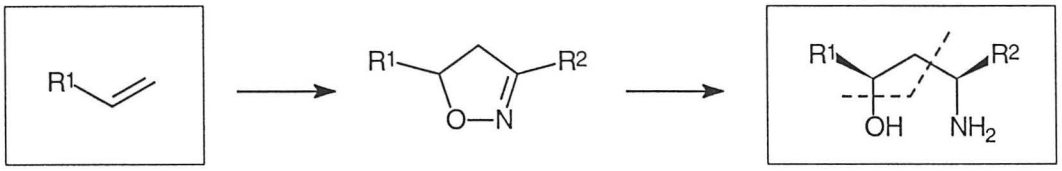
Since the initial cycloadditions are usually highly regio- and stereo-selective, the sequence of reactions – cycloaddition, manipulation of functional groups and ring cleavage of the isoxazoline - provides a valuable stereocontrolled route to a variety of acyclic compounds including γ-aminoalcohols **43**, βγ-hydroxyketones **44**[129,130] and αβ-unsaturated ketones **45** (**Scheme 23**).[121,131]



Scheme 23

Reduction of the isoxazoline ring - preparation of γ-aminoalcohols

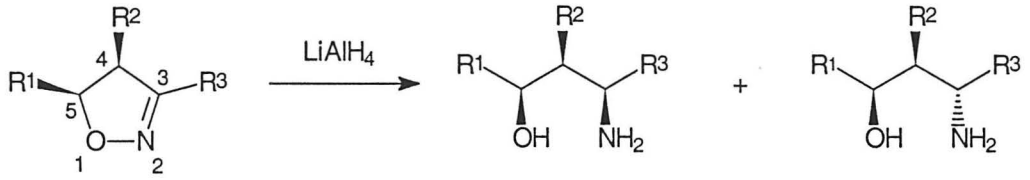
One conversion that will be described here in detail, is the reductive cleavage of 2-isoxazoline that leads to the formation of γ-aminoalcohols. Overall the reaction sequence cycloaddition - reduction represents a regio- and stereoselective hydroxy-α-aminoalkyl addition to an olefinic double bond (**Scheme 24**).



Scheme 24

The choice of the reducing agent is crucial for the extent of stereoselectivity in the isoxazoline ring cleavage step. Studies by Jäger *et al.*[132] found that lithium aluminium hydride was superior to other reducing systems such as, e.g. Na-Hg,

Na/ethanol or $Me_2S{\cdot}BH_3$ with respect to stereoselectivity and yield. Diastereoselectivities with ratios up to 95:5 were observed, depending on the nature of the substituent and its position. Some selected examples are given in **Scheme 25** below. 5-Substituents in isoxazoline **46** lead to greater steric hindrance than do 4-substituents, i.e. 1,3- exceeds 1,2-asymmetric induction (**Scheme 25**).



46 *syn*-**47** *anti*-**47**

R^1	R^2	R^3	*syn*/*anti* ratio of **47**	yield (%)
Me	H	Me	85:15	74
Ph	H	Ph	95:5	98
H	Me	Ph	69:31	82
CH_2OH	H	Me	37:63	69

Scheme 25

With alkyl or other non co-ordinating substituents at C-4 or C-5 of the isoxazoline ring, addition takes place *anti* (*trans*) to the substituents to give the *syn*-1,3-aminoalcohol **47**. Hydroxyl or hydroxymethyl substituents, on the other hand, direct the attack of the lithium aluminium hydride to the *syn* face of the C=N bond to give predominantly the *anti* aminoalcohol. This latter stereoselectivity has found application in the synthesis of amino sugars, amino acids and amino polyols.[121,133]

Due to the versatility of the reaction sequence cycloaddition/ring cleavage for the construction of chiral compounds, the demand for asymmetric versions of this reaction has increased over the last 20 years.

1.4.3. Asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides[134]

The development of 1,3-DC reactions has in recent years entered a new stage as control of the stereochemistry in the addition step is now the major challenge. The stereochemistry of the 1,3-DC reaction can be controlled by either choosing the appropriate substrates or controlling the reaction by a metal complex acting as a catalyst.

Compared with the development of the asymmetric metal-catalysed carbo- and hetero-Diels Alder reactions, the development of the analogous approach to asymmetric 1,3-DC reactions is several years behind. Probably the most important aspect of the 1,3-DC reaction is to control diastereo- and enantioselectivity.

Asymmetric synthesis can be achieved by the use of:

① **Chiral dipolarophiles (chiral alkenes)**
② **Intramolecular 1,3-DC reactions of nitrile oxides (INOC)**
③ **Chiral dipoles (chiral nitrile oxides)**
④ **Metal-catalysed reactions**

Several publications on asymmetric 1,3-DC reactions of nitrile oxides with alkenes have appeared. The majority of the reactions described involves optically active alkenes or are intramolecular reactions. However during the last 5 years the application of metal catalysts in this reaction for control of the stereochemistry has been described.

Asymmetric synthesis *via* chiral dipoles and metal-catalysed reactions will be discussed later in the individual introductions of the Results and Discussion, **Chapters 2.3.** and **2.4.**

Chiral Alkenes

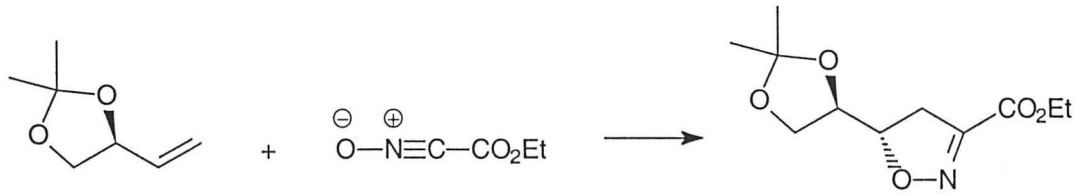
Contrary to the small number of publications dealing with 1,3-DC reactions of chiral nitrile oxides with alkenes several research groups have applied optically active alkenes in these reactions. The description of reactions of the several different types of chiral alkenes is divided in two major parts:

i. Alkenes in which the chiral centre is located vicinal to the double bond, which includes allylic alcohols, allylic amines, and chiral vinyl sulfoxides.

ii. Derivatives in which the chiral centre is located two or more bonds from the alkene moiety, which includes vinyl ethers, metalla complexes, chiral auxiliaries attached to acrylamides.

i. The chiral centre is located vicinal to the double bond (one example is given):

As a crucial step in the synthesis of optically pure 2-deoxy-D-ribose, Kozikowski *et al.* reported the 1,3-DC reaction between (*S*)-isopropylidene-3-buten-1,2-diol (**48**) (derived from glyceraldehyde) and carbethoxyformonitrile oxide (CEFNO) (**49**).[135] The reaction proceeds with fair selectivity, and the isoxazoline **50** is obtained as the major isomer with 60 % de (**Scheme 26**).



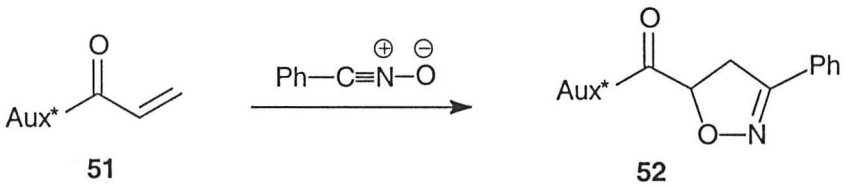
48 **49** **50**

Scheme 26

By the application of other nitrile oxides selectivities of up to 86 % de were observed in the reaction with **48**.[136] Reactions of nitrile oxides with alkenes similar to **48** have also been investigated by others.[137]

ii. The chiral centre is located two or more bonds from the alkene moiety:

Beside chiral vinyl ethers and metalla complexes, the most important representatives of this group are α,β-unsaturated carbonyl compounds, containing a chiral auxiliary that is linked to the alkene *via* an ester or amide. The majority of 1,3-DC reactions of nitrile oxide with this type of alkene involves acryl derivatives, probably due to the lack of regioselectivity in reactions of β-substituted derivatives such as crotonates or cinnamates. Extensive studies were performed by Curran *et al.*[138] as well as others[139,140,141,142] on the application of chiral auxiliaries attached to the nitrogen atom of α,β-unsaturated amides **51** in 1,3-DC reactions, and this approach has been developed to be one of the most effective methods for the synthesis of isoxazolines with high optical purity (**Scheme 27**). Curran *et al.* have applied *N*-acryloylbornane-10,2-sultam (**53**) (**Figure 4**) as the auxiliary for the preparation of natural products such as (+)-hepialone and (-)-pestalotin.[138,143]



Scheme 27

Figure 4 shows the acrylamides, which give the highest diastereomeric excesses, with the publishing author and the year of publication.

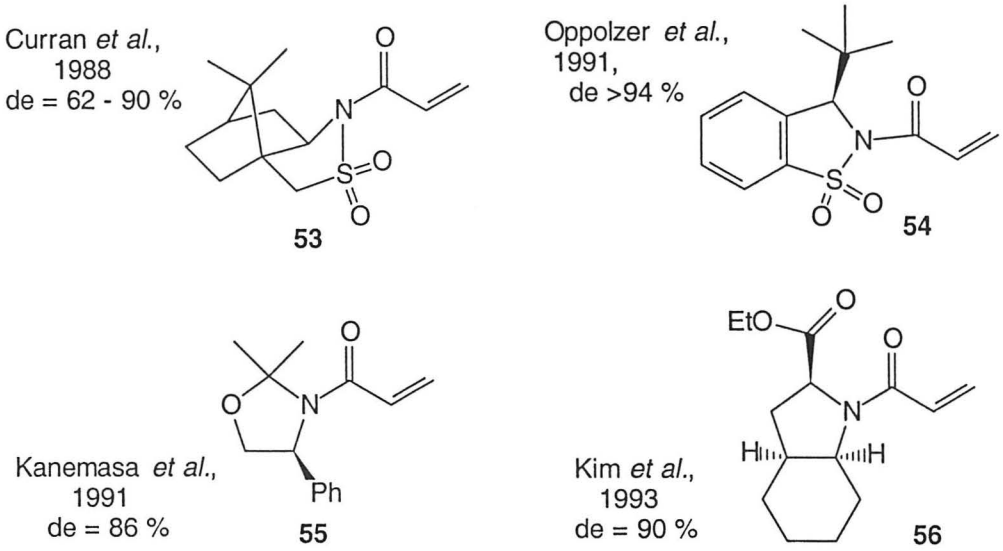
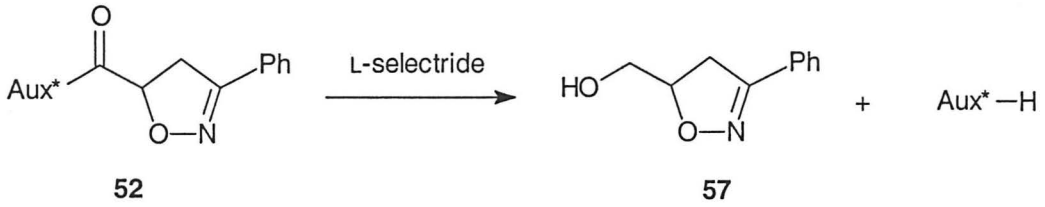


Figure 4

In most cases the different acrylamides have been applied in the 1,3-DC reaction with benzonitrile oxide, and the relative efficiency of the chiral auxiliaries in the reaction with the same nitrile oxide can thus be compared.

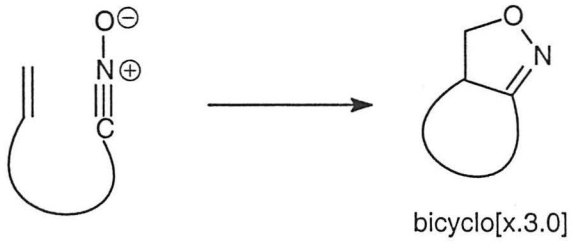
The optical active isoxazolines **52** were converted into isoxazolinylmethanol **57** by reaction with L-selectride and the chiral auxiliaries could be recovered (**Scheme 28**)



Scheme 28

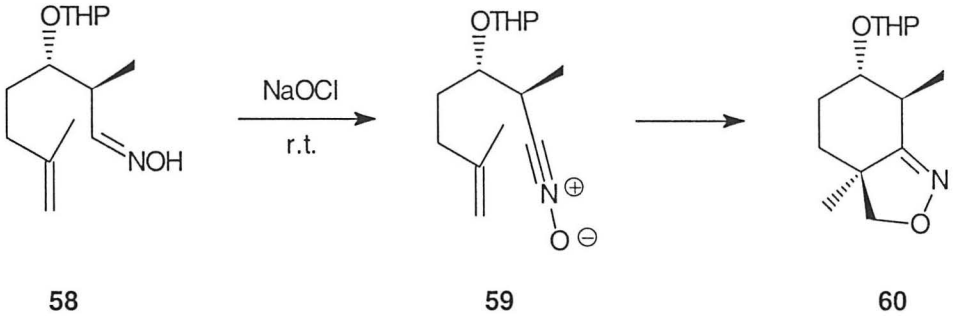
Intramolecular Reactions

The intramolecular 1,3-DC of nitrile oxides, often abbreviated INOC, with alkenes is an effective tool for the construction of bi- and polycyclic isoxazolines.[134] Due to the rigid linear structure of the nitrile oxide the reaction of alkenylnitrile oxides usually gives bicyclo[x.3.0] derivatives for x = 3-5 (**Scheme 29**).



Scheme 29

Like other intramolecular reactions it is easier to control the stereoselectivity than in the intermolecular counterpart. The chiral centre(s) controlling the diastereoselectivity of the reaction can be located outside the bicyclic isoxazoline formed or in the resulting ring. An example of the latter case is the enantioselective total synthesis of the natural product (+)-cassiol reported by Shishido *et al.*[144] (**Scheme 30**). The key-step in the synthesis was the INOC reaction of a 6-alkenylnitrile oxide: the oxime **58** was treated with aqueous sodium hypochlorite and base to generate the nitrile oxide **59**, which reacted to give the bicycle **60** as the sole product in 88 % yield with 100 % de.

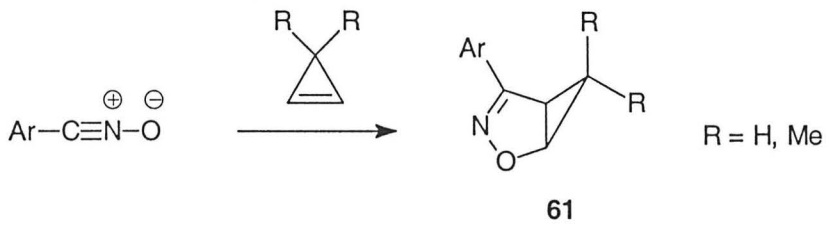


Scheme 30

1.4.4. 1,3-Dipolar cycloaddition reactions of nitrile oxides to cyclopropenes

The 1,3-DC reaction of cyclopropenes provides one route for the synthesis of cyclopropanes. The cyclopropene π-bond acts as a dipolarophile for a range of 1,3-dipoles. Today many examples of 1,3-DC reactions to cyclopropenes are known; the list of 1,3-dipoles includes diazoalkanes, azides, nitrile imines, azomethine ylides, pyridazinium *N*-ylides and nitrile oxides.[45]

Until early 1970 only reactions with diazo compounds and azides had been described. In 1973 Visser *et al.* reported the first 1,3-DC reaction involving nitrile oxides. Cyclopropene itself and 3,3-dimethylcyclopropene were reacted with arylcarbonitrile oxides (**Scheme 31**) to give 2-oxa-3-azabicyclo[3.1.0]hex-3-enes **61**.[145]

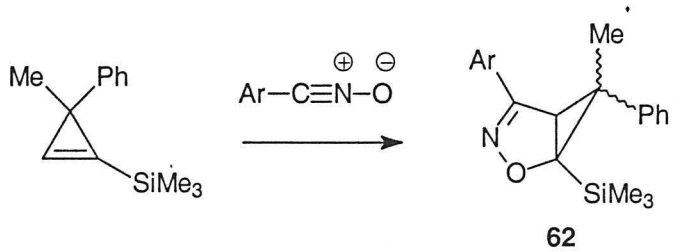


Scheme 31

Since then many examples of cycloadducts derived from nitrile oxides and various substituted cyclopropenes have been published. A range of aromatic and aliphatic nitrile oxides, prepared *in situ* by reaction of the corresponding hydroximoyl chloride with triethylamine, underwent cycloaddition with 1,3,3-trimethylcyclopropene.[45] With aromatic nitrile oxides higher yields were obtained than with aliphatic species. This is due to the fact that aromatic nitrile oxides are more stable and therefore less prone to dimerisation.

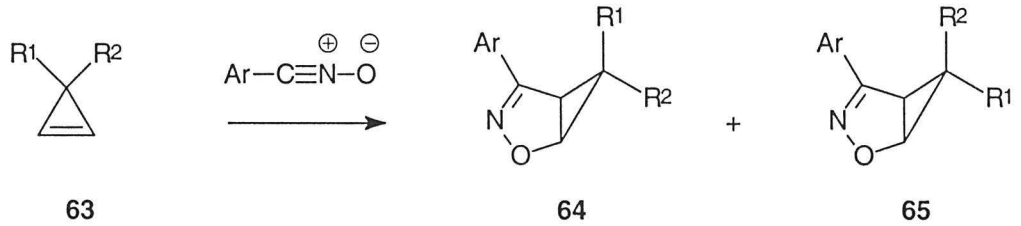
Research at Bangor applied (diisopropoxyphosphoryl)nitrile oxides in the 1,3-DC reaction with functionalised cyclopropenes and cycloadducts were obtained in moderate to good yield.[146]

Cycloaddition to 1-trimethylsilylcyclopropenes and to alkyl cycloprop-1-ene-1-carboxylates occurred with high regioselectivity, e.g. **62** in **Scheme 32**.



Scheme 32

Bolesov *et al.*[147] studied extensively the 1,3-DC reaction of 3,3-disubstituted cyclopropenes with aromatic nitrile oxides. Unsymmetrically substituted cyclopropenes **63** afforded the two diastereomers **64** and **65** with a high degree of stereoselectivity (**Scheme 33**); the major product showed an *endo* orientation of the methyl group. The two stereoisomeric adducts **64,65** could easily be separated by column chromatography on silica gel. Some selected examples are given in **Scheme 33** below.



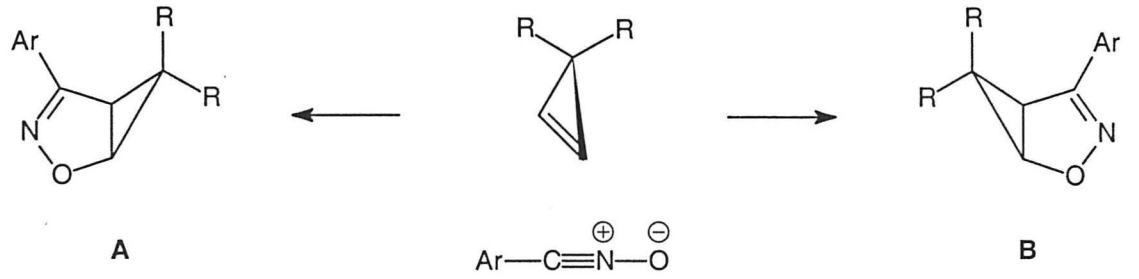
R^1	R^2	Ar	Yield (%)	
			64	**65**
Me	Ph	Ph	59	7
Me	Ph	4-$NO_2C_6H_4$	75	17
Me	4-$MeOC_6H_4$	Ph	81	11

Scheme 33

Both diastereomers were assigned in the ^{1}H NMR spectrum; it was established that the *endo*-methyl group showed an upfield shift in comparison with the *exo*-methyl group.

Although the 1,3-DC reactions occurred with high diastereoselectivity it has to be noted here that the cycloaddition always provides the cycloadduct as a pair of enantiomers. Unsymmetrically 3,3-disubstituted cyclopropenes **63** give in total four stereoisomers: two diastereomers **64,65** and each as a pair of enantiomers (**Scheme 33**, only one possible enantiomer is shown). In case of symmetrically 3,3-disubstituted

cyclopropenes two stereoisomers are obtained: a pair of enantiomers **A** and **B** as shown in **Scheme 34**.



Scheme 34

There is an alternative way to draw the two enantiomers **A** and **B:** the cyclopropane ring can be drawn up or down the plane of the isoxazoline ring (**Figure 5**). Generally only one of the two possible enantiomers is shown for reasons of simplicity.

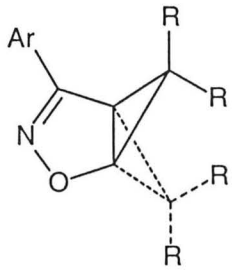
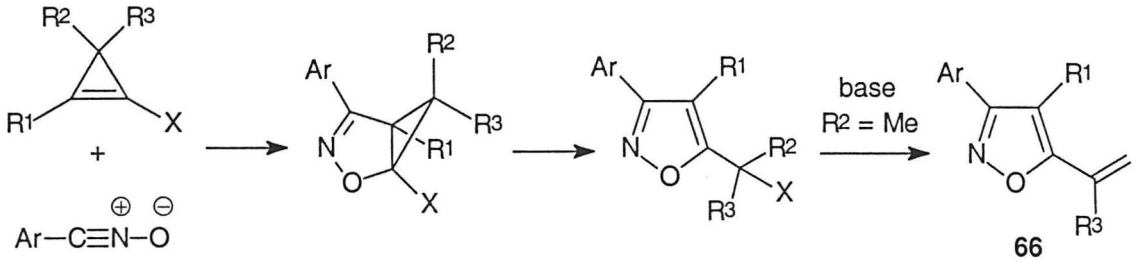


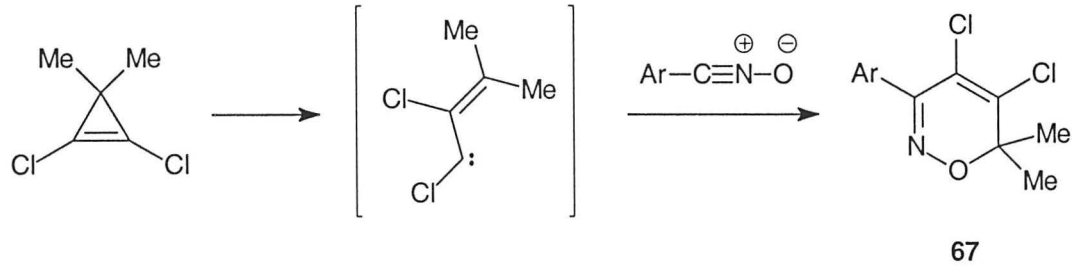
Figure 5

In the examples discussed so far the cyclopropene reacted with the nitrile oxide to give stable bicyclic products. 1-Halocyclopropenes and 1,2-dihalocyclopropenes however underwent more complex reactions involving ring opening reactions of either the cyclopropene (prior to the cycloaddition) or the cyclopropane moiety (after the cycloaddition).[148] In the latter case, e.g. 5-alkenyl-4-alkyl-3-arylisoxazole **66** (**Scheme 35**, R^2 = Me) were formed.



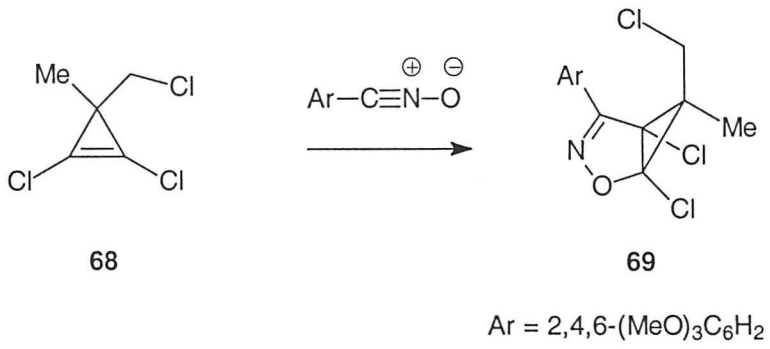
Scheme 35

An example where the cyclopropene ring opened prior to the reaction with nitrile oxide is outlined below: 1,2-dichloro-3,3-dimethylcyclopropene rearranged first to a vinylcarbene species, which then underwent an unusual cyclisation with the dipole, affording the 1,2-oxazine **67** (**Scheme 36**).



Scheme 36

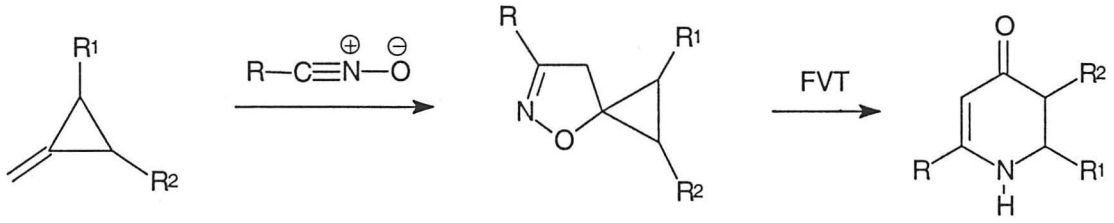
An exception to above observed reactivity was seen with 1,2-dichloro-3-chloromethyl-3-methylcyclopropene **68**. The 1,3-DC reaction occurred faster than the ring opening of the cyclopropene and the bicyclic product **69** (*exo*-methyl) was formed with high stereoselectivity (**Scheme 37**).



Scheme 37

Cycloaddition of methylenecyclopropanes

Methylenecyclopropanes **70** represent a group of strained molecules that are closely related to cyclopropenes. The double bond is located outside the three-membered ring. It undergoes 1,3-DC reactions regioselectively with a range of nitrile oxides to form spirocyclic compounds of type **71** (**Scheme 38**).



70 **71** **72**

Scheme 38

Those compounds are valuable synthetic intermediates for the preparation of pyridone derivatives. Flash vacuum thermolysis (FVT) rearranges the spirocyclic compound **71** to 5,6-dihydro-4-pyridones **72**.[149] This strategy was, e.g. successfully applied to the total synthesis of azasteroids.[150]

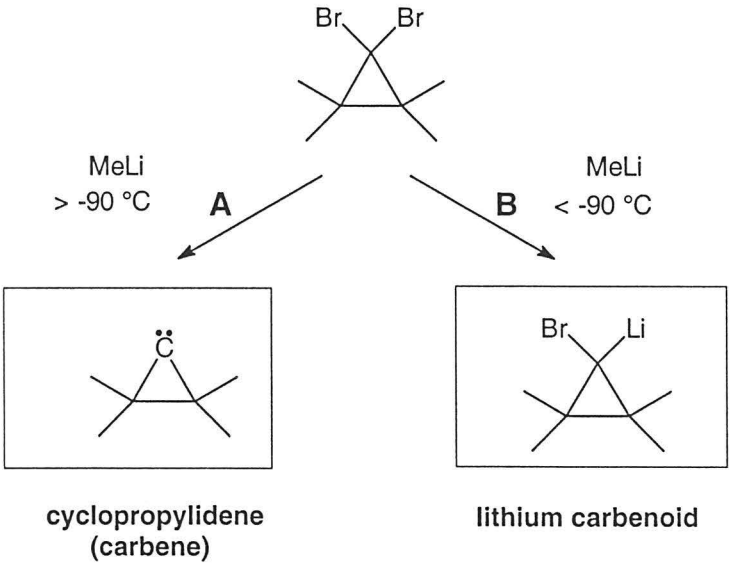
1.5. Chemistry of *gem*-dibromocyclopropanes

1,1-Dibromocyclopropanes are versatile synthetic building blocks for the preparation of a wide range of cyclopropane derivatives. Bromines in 1,1-dibromocyclopropanes are more reactive than for example chlorides in the corresponding 1,1-dichloro derivatives. The most convenient method for the preparation of 1,1-dibromocyclopropanes consists of the addition of dibromocarbene to an alkene (see **Chapter 1.3.1.2.**).[48-51]

1,1-Dibromocyclopropanes can undergo a vast variety of reactions. First the reaction with alkyllithium is described.

1.5.1. Reactions of *gem*-dibromocyclopropanes with alkyllithium

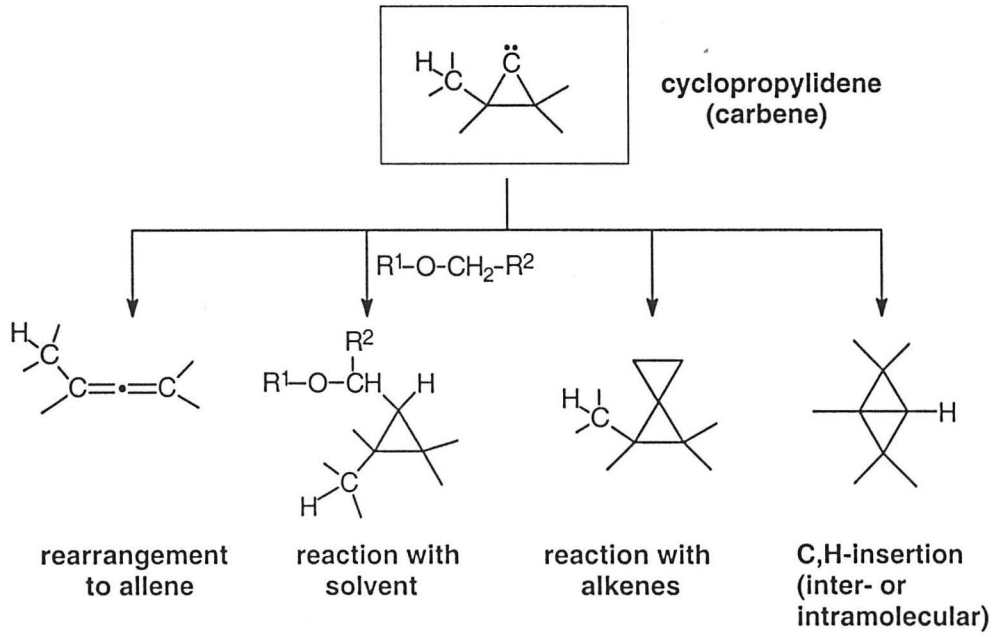
Gem-dibromocyclopropanes can react with alkyllithium (e.g. methyllithium) to form either a carbene (pathway **A**)[49] or a lithium carbenoid (pathway **B**)[151] (**Scheme 39**). Which pathway is followed depends on the reaction conditions applied (temperature) and on substituents of the cyclopropane. Below temperatures of -90 °C the cyclopropyl-lithium (lithium carbenoid) species is stable, less low temperatures may give rise to the formation of a cyclopropylidene (carbene) species. Both species are generated *in situ*. The reactions, which they can undergo, are outlined on the next page.



Scheme 39

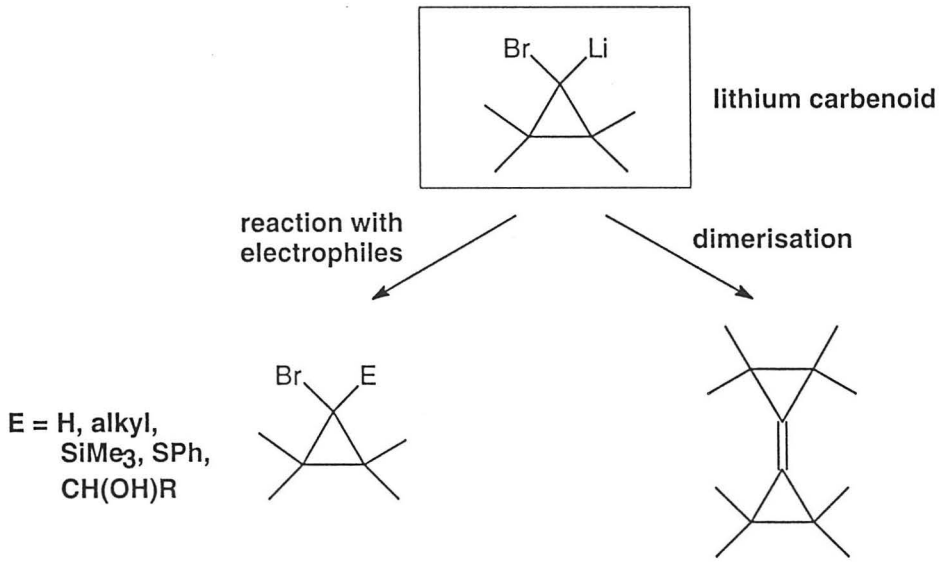
Reactions of the cyclopropylidene[49]

The formed cyclopropylidene species may rearrange to allenes, it can undergo reaction with alkenes, or it can react with the solvent. Quite often insertion reactions take place as well. The C,H-insertion can occur inter- or intramolecularly (**Scheme 40**).



Scheme 40

Reactions of the lithium carbenoid



Scheme 41

Lithiocyclopropanes (carbenoids) are formed from *gem*-dibromocyclopropanes by bromine-lithium exchange. The metallorganic species is a versatile intermediate as it can be trapped with a wide range of electrophiles[152] such as aldehydes, ketones, esters, carbon dioxide, trimethylsilyl chloride, phenyl disulfide, methyl iodide[153] (alkylation) or water (**Scheme 41**). In the latter case the overall reaction – replacement of a halogen with a hydrogen – represents a reduction. Alkyllithium/H^+ is only one among many reducing agents (see below: **Chapter 1.5.2.**).

In the absence of electrophiles the lithiocyclopropane species can also undergo a dimerisation reaction to form bicyclopropylidenes (**Scheme 41**). The exact mechanism is still unclear.[154] It was reported that the addition of $CuCl_2$ in conjunction with butyllithium enhanced the yield of the dimers.[155]

1.5.2. Reductions of *gem*-dihalocyclopropanes

Reduction is probably the cyclopropane transformation most frequently studied and most often utilised in organic synthesis. *Gem*-dihalocyclopropanes can undergo both monoreduction and direduction and yield the corresponding monohalocyclopropanes and cyclopropanes, respectively. The synthesis of monohalocyclopropanes *via* reduction of dihalocyclopropanes is much more efficient than the direct synthesis by addition of monohalocarbene to alkene, because there is not any particularly good source of **:**CHBr available.

The list of reducing agents[156] includes Bu_3SnH, $NaBH_4$, Mg, various transition metals, Zn/acetic acid/EtOH, $LiAlH_4$, RedAl, diethyl phosphonate/Et_3N and, alkyllithium. Electrochemical methods have been applied as well.[157] Recently a new convenient reduction method has been reported, which employed EtMgBr together with catalytic amounts of $Ti(O\mathit{i}Pr)_4$.[158]

2. Results and Discussion

Part I

1,3-Dipolar cycloaddition (DC) reactions

2.1. Aim

The aim of the first part of this thesis was to investigate the applicability of the 1,3-dipolar cycloaddition (DC) reaction to the stereocontrolled synthesis of cyclopropanes. A range of cycloadducts was prepared from nitrile oxides and dipolarophiles (alkenes, cyclopropenes) and subsequently converted into novel cyclopropanes.

At an early stage of the research project the products were obtained in racemic form (**Chapter 2.2.**). Later the focus was put on the synthesis of enantiomerically pure cyclopropanes (**Chapter 2.4.**).

2.2. 1,3-DC reactions of nitrile oxides to cyclopropenes and reductive cleavage of isoxazolines

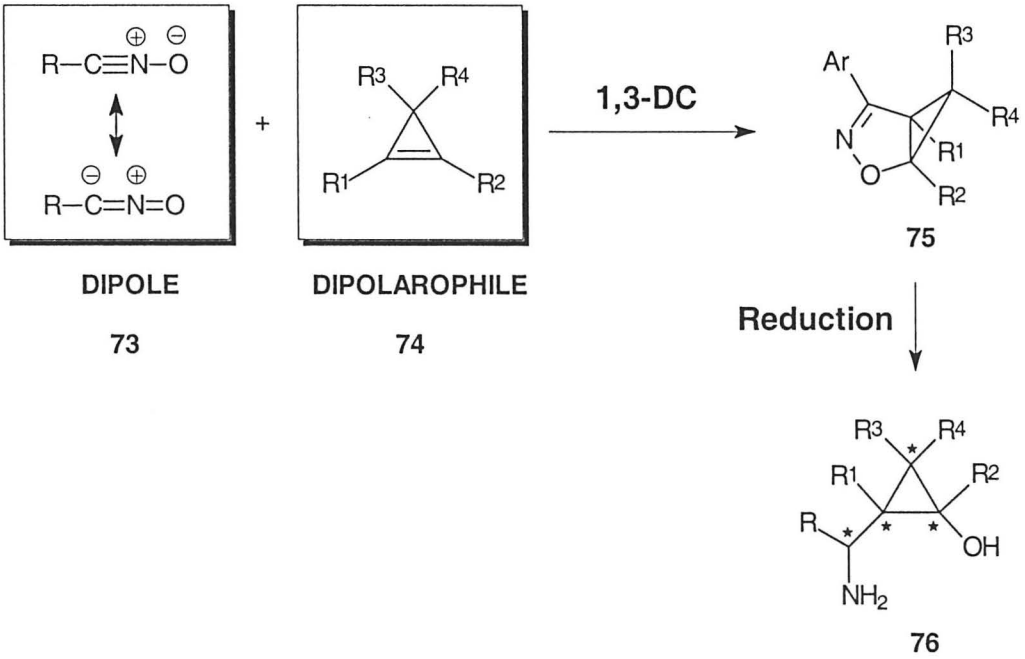
2.2.1. Introduction

General concept

A synthesis of novel cyclopropanol derivatives (**76**) was devised, involving a two-step procedure (**Scheme 42**):

- 1,3-Dipolar cycloaddition (1,3-DC) to cyclopropenes
- Reduction of the derived heterocyclic compound

Cyclopropenes **74** are known to undergo 1,3-DC reactions with nitrile oxides **73**.[45,147] Bicyclic systems **75**, containing an isoxazoline moiety, are formed. Isoxazolines can be subjected to ring cleavage, affording a range of acyclic compounds as outlined in **Chapter 1.3.2.** This chapter describes a study of reductions of the bicyclic ring system, using $LiAlH_4$ as an effective reagent for cleaving the isoxazoline ring in a highly diastereoselective manner. The potential in this cyclopropanol synthesis lies in the fact that theoretically in just two steps up to four new stereocentres are created (compound **76**; the number of stereocentres depends on the substitution pattern of the cyclopropene).



Scheme 42

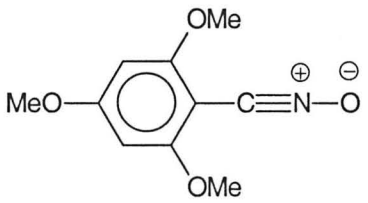
2.2.2. Discussion

1,3-Dipolar cycloaddition of cyclopropenes to nitrile oxides afforded several, differently substituted cycloadducts. The reduction of those cycloadducts is the main topic in this chapter, which is split into three parts, according to three different nitrile oxides that were used in the cycloaddition step:

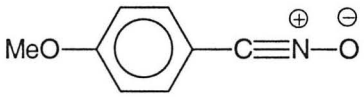
i. 2,4,6-Trimethoxybenzonitrile oxide (**38**)

ii. 4-Methoxybenzonitrile oxide (**77**)

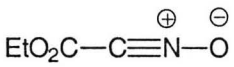
iii. Carbethoxyformonitrile oxide (CEFNO) (**49**)[135]



38



77

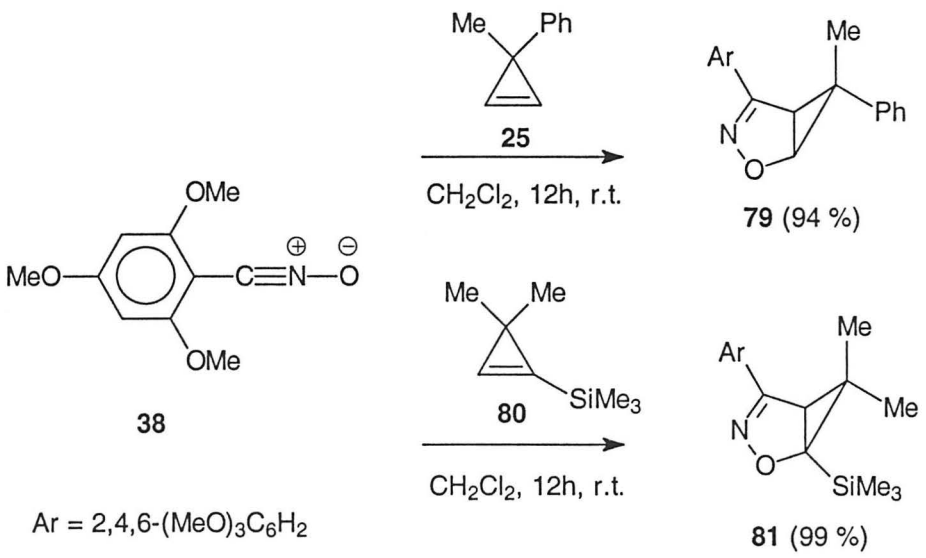


"CEFNO"

49

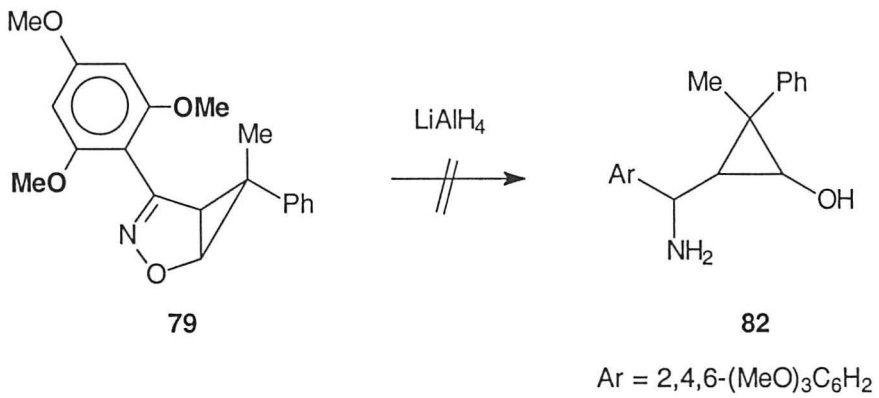
2.2.2.1. Attempted reduction of cycloadducts, derived from 2,4,6-trimethoxybenzonitrile oxide

The stable 2,4,6-trimethoxybenzonitrile oxide **38**[98] was the first dipole to be chosen for the cycloaddition reactions. It was treated with a slight excess of the dipolarophile 3-methyl-3-phenylcyclopropene (**25**) [the preparation of this cyclopropene is described in the introduction, **Chapter 1.3.3.**] in dichloromethane at room temperature. After 12 hours the solvent was removed and the bicycle **59** was obtained in 94 % yield (**Scheme 43**, next page). The 1,3-DC reaction proceeded very cleanly and no further purification was required. 6-Methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (**79**) was formed with complete stereoselectivity; only the diastereomer in which the methyl group occupied the *endo*-position was formed [the *endo*/*exo* assignment will be explained on a similar compound later in this chapter]. 3,3-Dimethyl-1-trimethylsilylcyclopropene (**80**) underwent cycloaddition in analogous manner to give regioselectively the bicycle **81** in 99 % yield.



Scheme 43

Reduction of bicycle **79**, in order to cleave the isoxazoline moiety but keeping the cyclopropane ring intact, was expected to be straightforward. Based on the high diastereoselectivities reported in the literature,[132] $LiAlH_4$ was chosen as the reducing agent. The cycloadduct was added to a suspension of $LiAlH_4$ in diethyl ether at room temperature. Although an excess (2 mol.equiv.) of $LiAlH_4$ was employed and the mixture was refluxed for 24 hours, conversion to the cyclopropanol **82** was not observed (**Scheme 44**); only starting material **79** was recovered. Probably the methoxy groups in position C-2 and C-6 of the aromatic ring (highlighted in bold in **Scheme 44**) were too bulky and prevented the hydride attack.

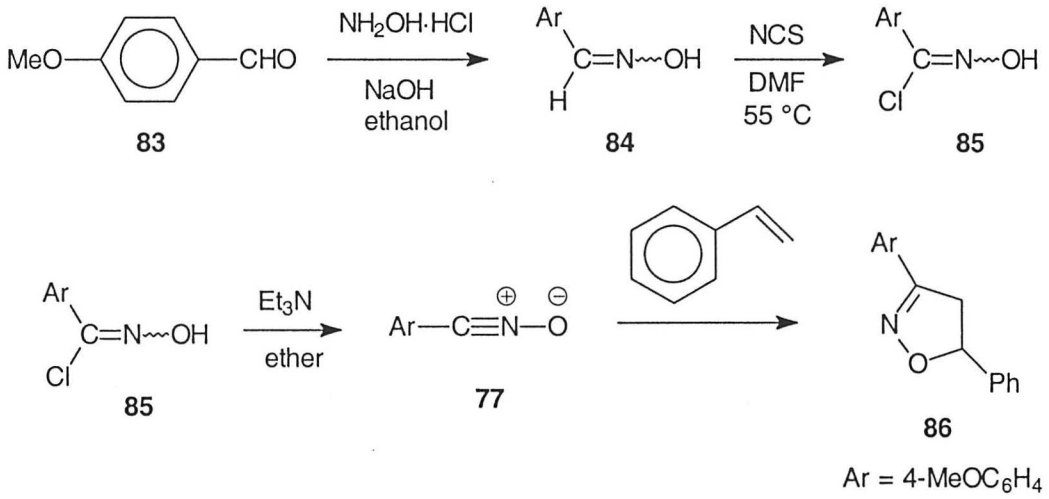


Scheme 44

2.2.2.2. Reduction of cycloadducts derived from 4-methoxybenzonitrile oxide

Reduction of 3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (86)

To test the reducing agent and to become familiar with this type of reduction, the model compound 3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**86**) was prepared by a 1,3-DC reaction of 4-methoxybenzonitrile oxide (**77**)[107,159] in ether with an excess of styrene. The dipole **77** was generated *in situ* from the corresponding *N*-hydroxy benzimidoyl chloride **85** upon treatment with triethylamine (**Scheme 45**). The precursor **85** was prepared from the oxime **84,** which in turn was prepared from commercially available *p*-anisaldehyde **83**; for both conversions standard methods were used.[107]

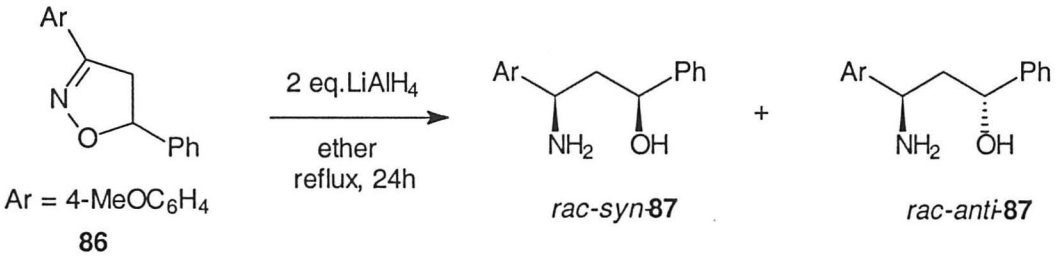


Scheme 45

The cycloadduct **86** was treated with 2 mol.equiv. of $LiAlH_4$ and the mixture was refluxed for 24 hours. The compound underwent reductive ring cleavage as expected. Due to the high polarity of the aminoalcohol **87** extractive isolation of the product was avoided. An alternative work-up procedure was followed [this work-up procedure was used for all $LiAlH_4$ reductions described in this thesis]: drops of a saturated aqueous Na_2SO_4 solution were added to the reaction mixture until no further reaction with excess of $LiAlH_4$ was observed. To the white-grey suspension dichloromethane and a small amount of anhydrous $MgSO_4$ were added. The suspension was filtered through a layer of anhydrous $MgSO_4$ and a clear solution was obtained. The

solvent was removed to give the crude product 3-amino-3-(4-methoxyphenyl)-1-phenyl-propan-1-ol (**87**), in 85 % yield with good diastereoselectivity.

1,3-Asymmetric induction of the phenyl substituent led to a *syn* to *anti* ratio of 93 to 7 (**Scheme 46**). Diastereomeric ratios were generally calculated by comparing integrals of protons in the ^{1}H NMR spectra. The observed ratio for **67** is close to the ratio 95:5 reported in the literature for the analogous compound 3-amino-1,3-diphenyl-propan-1-ol (see also **Chapter 1.3.2.**).[132] The *syn/anti* configurations were assigned on comparison with the ^{1}H and ^{13}C NMR signals reported for analogous compounds.[132]



reducing system	ratio *syn/anti*	yield **67** (%)
$LiAlH_4$	93 : 7	85 (crude product)
$NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH	31 : 69	79 (recryst. from EtOAc)

Scheme 46

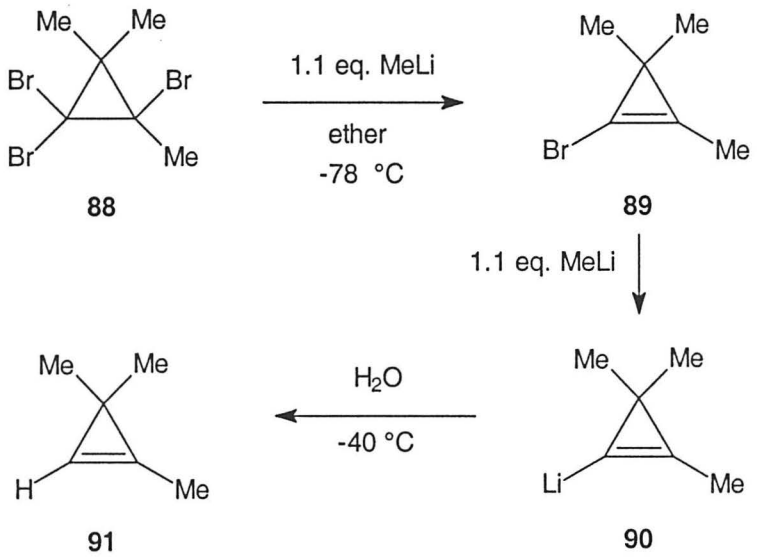
To be able to characterise the minor *anti* diastereomer by NMR the cycloadduct was subjected to reduction by a nickel chloride/sodium borohydride system.'[160] Now asymmetric induction was low and the diastereomeric ratio changed in favour of the *anti* isomer of **87** (**Scheme 46**). The diastereomers were not separated from each other.

Preparation of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (73)

Having successfully carried out the reduction of the cycloadduct **86**, derived from styrene and nitrile oxide **77**, the less sterically demanding dipole 4-methoxybenzonitrile oxide (**77**) was also used in the 1,3-DC reaction to 1,3,3-trimethylcyclopropene (**91**).

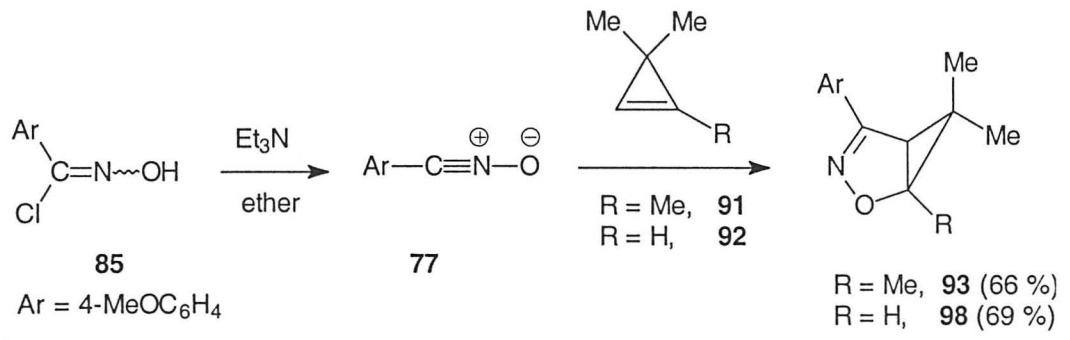
The cyclopropene was generated prior to the cycloaddition by treating 1,2,2-tribromo-1,3,3-trimethylcyclopropane with 2.2 mol.equiv. of methyllithium at -78 °C for 10 minutes followed by quenching with water at -40 °C. The first equivalent of

methyllithium leads to dehalogenation of the cyclopropane, forming the monohalocyclo-propene **89**. A second equivalent of methyllithium gives the cyclopropene **90** *via* a bromine lithium exchange, which is then converted into the cyclopropene **91** by protonation during the aqueous work-up (**Scheme 47**).



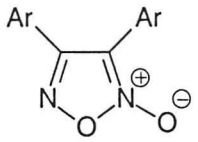
Scheme 47

The ethereal solution of 1,3,3-trimethylcyclopropene (**91**) was combined with an ether solution of the nitrile oxide precursor **85**. Triethylamine was added dropwise at -15 °C and then the mixture was stirred at room temperature for 24 h. The cycloadduct 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**93**) was formed in 66 % yield (**Scheme 48**, R = Me). The NMR spectrum of this type of compounds will be discussed in detail in **Chapter 2.3.2.**



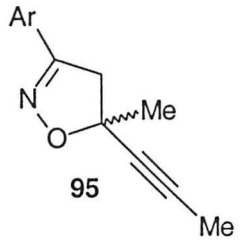
Scheme 48

Two minor by-products were also isolated in this cycloaddition reaction: the first was bis(4-methoxyphenyl)furoxan (**94**), formed upon dimerisation of the nitrile oxide **77**. The second by-product 3-(4-methoxyphenyl)-5-methyl-5-prop-1-ynyl-4,5-dihydro-isoxazole (**95**) is derived from the monohalocyclopropene **89**, which means that **89** was not entirely converted into its lithium species **90** upon treatment with methyllithium. This cyclopropene species **89** ring opened and underwent rearrangement prior to the cycloaddition with the nitrile oxide; a possible reaction mechanism is discussed by Li who studied the 1,3-DC reactions of mono- and dihalocyclopropenes to nitrile oxides.[148]



94

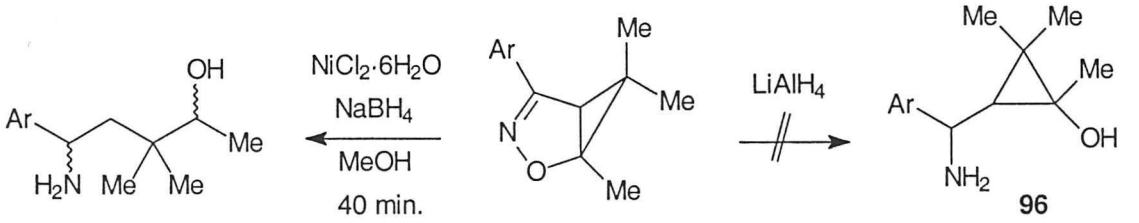
Ar = 4-$MeOC_6H_4$



95

Reduction of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (93)

The cycloadduct **93** was subjected to $LiAlH_4$ reduction (96 hours reflux) but surprisingly again no conversion to the cyclopropanol **96** was observed and only starting material **93** was recovered. The alternative reducing system nickel chloride/sodium borohydride was also applied. It was possible to cleave the isoxazoline ring; however the cyclopropane ring was broken too and the acyclic δ-aminoalcohol **97** was obtained as mixture of diastereomers (62:38) in 70 % yield (**Scheme 49**). It is not clear if the cyclopropane ring cleavage is caused by the reducing agent or by the work-up conditions that employed an aqueous solution of NH_3.[105]



97 (62:38, 70 %)

93

96

Ar = 4-$MeOC_6H_4$

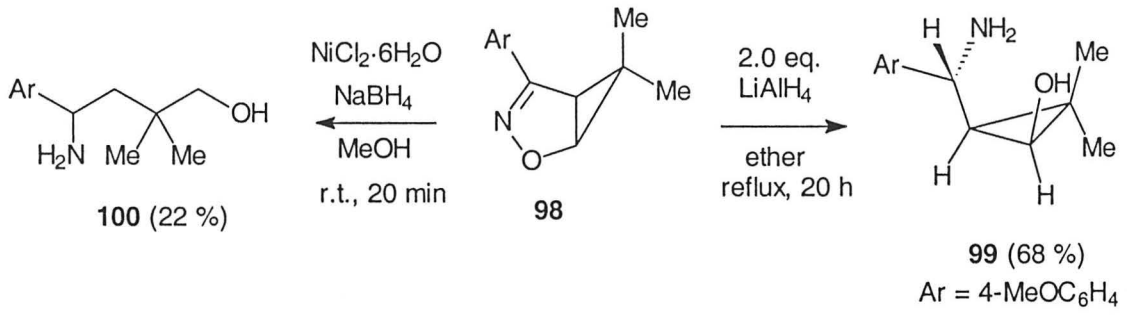
Scheme 49

Preparation of 4-(4-methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (98) and its reductive cleavage

To diminish steric hindrance further, the cycloadduct **98** was prepared from the disubstituted 3,3-dimethylcyclopropene (**92**) in 69 % yield (**Scheme 48**, R = H). The cyclopropene in turn was prepared using a procedure analogous to the one described above for 1,3,3-trimethylcyclopropene (**91**).

This time the reduction of the cycloadduct **98** with $LiAlH_4$ was successfully and the desired product, 3-[amino(4-methoxyphenyl)methyl]-2,2-dimethylcyclopropanol **99** was formed in 68 % yield (**Scheme 50**). The NMR spectrum of **99** showed only one set of signals; thus the reduction proceeded with 100 % diastereoselectivity. NMR data for this type of cyclopropane will be given in **Chapter 2.3.2.** The stereochemistry of **99** and related compounds will be discussed in detail at the end of this chapter.

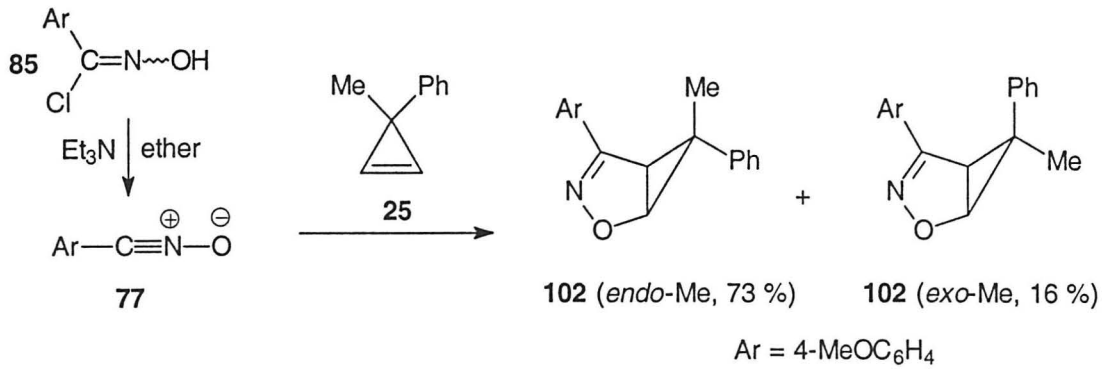
The same cycloadduct was also subjected to reduction with nickel chloride/sodium borohydride. Again both ring systems were cleaved and the acyclic compound **100** was obtained in low yield (**Scheme 50**).



Scheme 50

Preparation of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (102)

4-Methoxybenzonitrile oxide (**77**) was also reacted with the unsymmetrically disubstituted 3-methyl-3-phenylcyclopropene (**25**). The cycloaddition reaction gave rise to two stereoisomers (*endo*- and *exo*-methyl **102**) in ratio 85:15 in favour of the *endo*-methyl isomer. Both isomers could easily be separated by column chromatography on silica. The *endo* and *exo* isomers were isolated in 73 % and 16 % yield respectively (**Scheme 51**, next page).

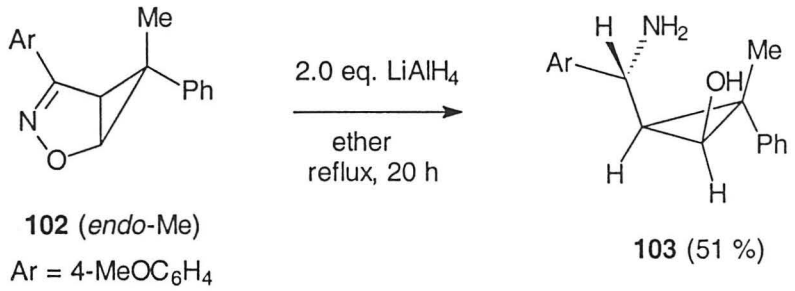


Scheme 51

In the NMR spectrum the two diastereomers were easy to distinguish. The stereochemical assignment was based on the chemical shift difference of the methyl group being either in *endo* or *exo* position. The *endo*-methyl group showed a signal at 1.24 ppm in the ^{1}H NMR whereas the *exo*-methyl group appeared downfield at 1.44 ppm. In the ^{13}C NMR the *endo*-methyl group gave a signal at 12.6 ppm, the *exo*-methyl group appeared at 24.7 ppm. The chemical shifts were in good agreement with those of closely related systems reported in the literature.[147]

Reduction of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (102) with $LiAlH_4$

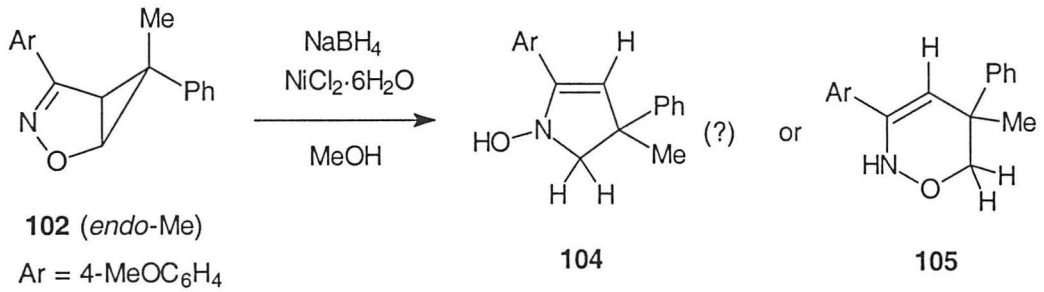
Only the major *endo*-methyl isomer of **102** was subjected to reduction. $LiAlH_4$ reduction again proceeded smoothly and with excellent stereocontrol. Crystalline 3-[amino(4-methoxyphenyl)methyl]-2-methyl-2-phenylcyclopropanol (**103**) was isolated as a single diastereomer in 51 % yield. (**Scheme 52**). The compound showed one set of signals in the NMR spectrum. The stereochemistry of **103** will be discussed at the end of this chapter.



Scheme 52

Reduction of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (102) with nickel chloride/sodium borohydride

The reduction of **102** with nickel chloride/sodium borohydride did provide a white solid compound, though this could not be identified. **Scheme 53** shows two possible structures, **104** and **105** that fit closest to the observed spectroscopic data.



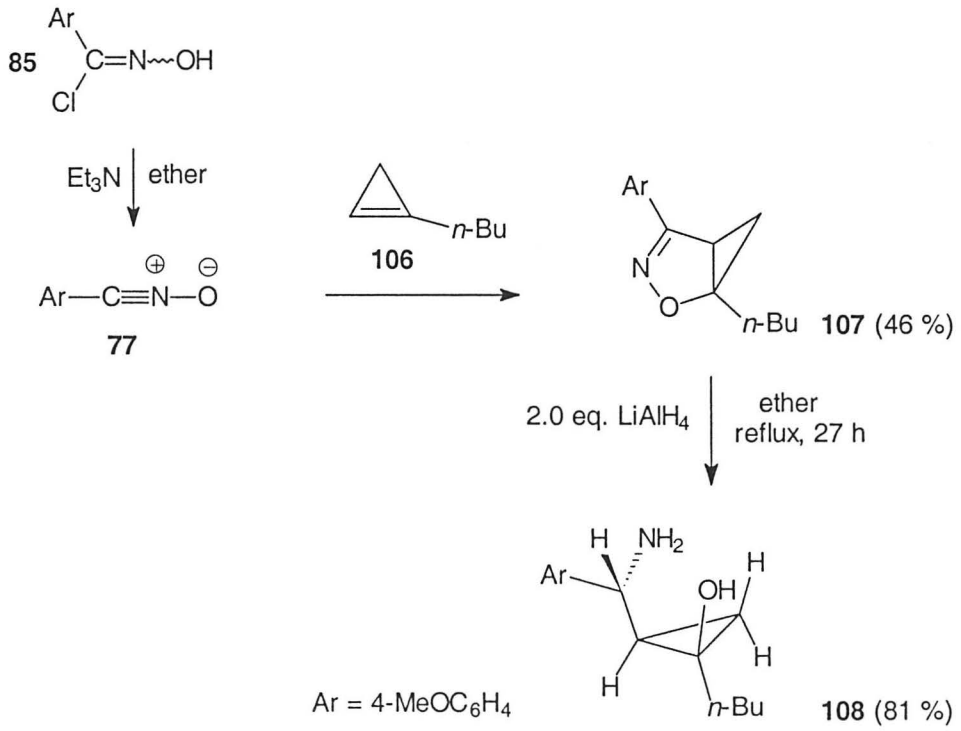
Scheme 53

Both structures have the molecular formula of $C_{18}H_{19}NO_2$, which was established by the mass spectrum (M^+ 218) and CHN analysis. The infrared spectrum was inconclusive as to whether an OH or NH group was present. The presence of an olefinic proton is supported both by the ^{13}C NMR with a signal at 99.9 ppm and by ^1H NMR with a singlet at 5.80 ppm. Two doublets in the ^1H NMR at 3.21 ppm and 3.30 ppm with a coupling constant of 17 Hz could correspond for a CH_2 group next to a chiral centre. However the chemical shift of this CH_2 group in the ^{13}C NMR shows a value of 48.1 ppm, which seems to somewhat low for a position next to a heteroatom such as nitrogen (in case of **104**) or oxygen (in case of **105**). No literature data were available for both compounds or closely related systems [literature search was carried out using the Beilstein database].

Preparation of 1-butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (87) and its reductive cleavage

The cycloadduct **107** was prepared from 4-methoxybenzonitrile oxide (**77**) and the 1-monosubstituted 1-butylcyclopropene (**106**) in 46 % yield (**Scheme 54**). The cyclo-propene in its turn was prepared prior to the cycloaddition reaction using a procedure analogous to the one described above for 1,3,3-trimethylcyclopropene (**91**).

1-Butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**107**) was reduced with $LiAlH_4$ and the corresponding cyclopropanol (**108**) was obtained in good yield. The NMR spectrum of **107** and that of a similar system will be discussed in **Chapter 2.3.2.**



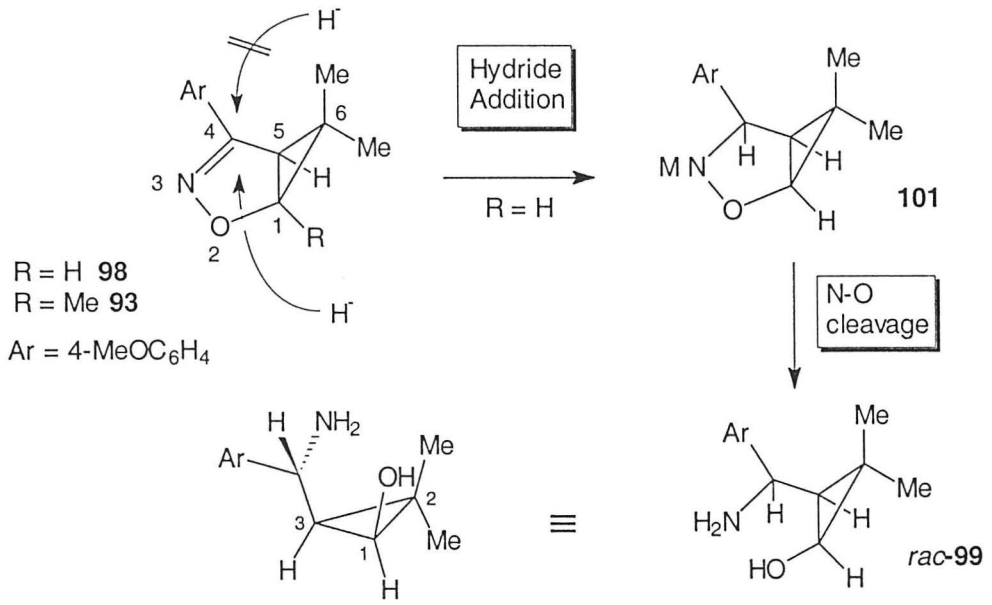
Scheme 54

Stereochemistry and pathway of the $LiAlH_4$ reduction

The replacement of the methyl group with a hydrogen at the C-1 position of the bicycle caused an extraordinary change of reactivity - from no reaction at all in case of bicycle **93** (R = Me) to a smooth reduction as observed with bicycle **98** (R = H).

Scheme 55 shows a very simplified model of the hydride attack (it omits the complexation of the lithium and aluminium atoms to the nitrogen and oxygen atoms). In both cases hydride attack from above the isoxazoline ring plane is prevented by the cyclopropane ring and the methyl groups at C-6. The steric hindrance of the methyl group at C-1 in bicycle **93,** which suppresses the reduction is less obvious. Probably this methyl group, together with the two methyl groups at C-6, forces the aromatic ring system (at C-4) into a conformation that increases the steric hindrance to such an extent that the reduction does not occur.

Compound **107** (see previous page) represents an example, where a bicycle is cleaved, despite bearing a substituent at C-1 [n-butyl group at C-1]. This becomes possible due to the absence of substituents at C-6 in that molecule. Hydride attack to the N=O bond now occurs from below the isoxazoline plane analogous to bicycle **98**.



Scheme 55

The bicyclic system **98** (**Scheme 55**) reacts with the hydride stepwise. In a first step, the hydride selectively attacks from below the isoxazoline plane to form a isoxazolidine intermediate (**101**) (M = metal), which in a second step undergoes N-O

ring cleavage. This gives rise to a single diastereomer, 3-[amino(4-methoxyphenyl)methyl]-2,2-dimethylcyclopropanol (**99**) in which the two functional groups, OH and the α-aminoalkyl group, are in *cis* position to each other. The structure drawn shows only one of the two enantiomers that are present (the previous cycloaddition step does not show any enantiofacial selectivity; as mentioned in the introduction all cycloadducts are obtained as a pair of enantiomers).

Final confirmation about the correct stereochemistry of the products of these reductions came from a single x-ray crystal structure determination of the cyclopropanol **103** (**Figure 6** below). The methyl, the hydroxy and the α-aminoalkyl group in the cyclopropane are all in *cis* position relative to each other. The x-ray crystal structure also confirmed the assignment of the cycloadduct **102** with regard of its *endo/exo* orientation [The x-ray crystal structure shows the opposite enantiomer to the drawing in above **Scheme 52**; it arises from the reduction of the cycloadduct with the cyclopropane ring facing down].

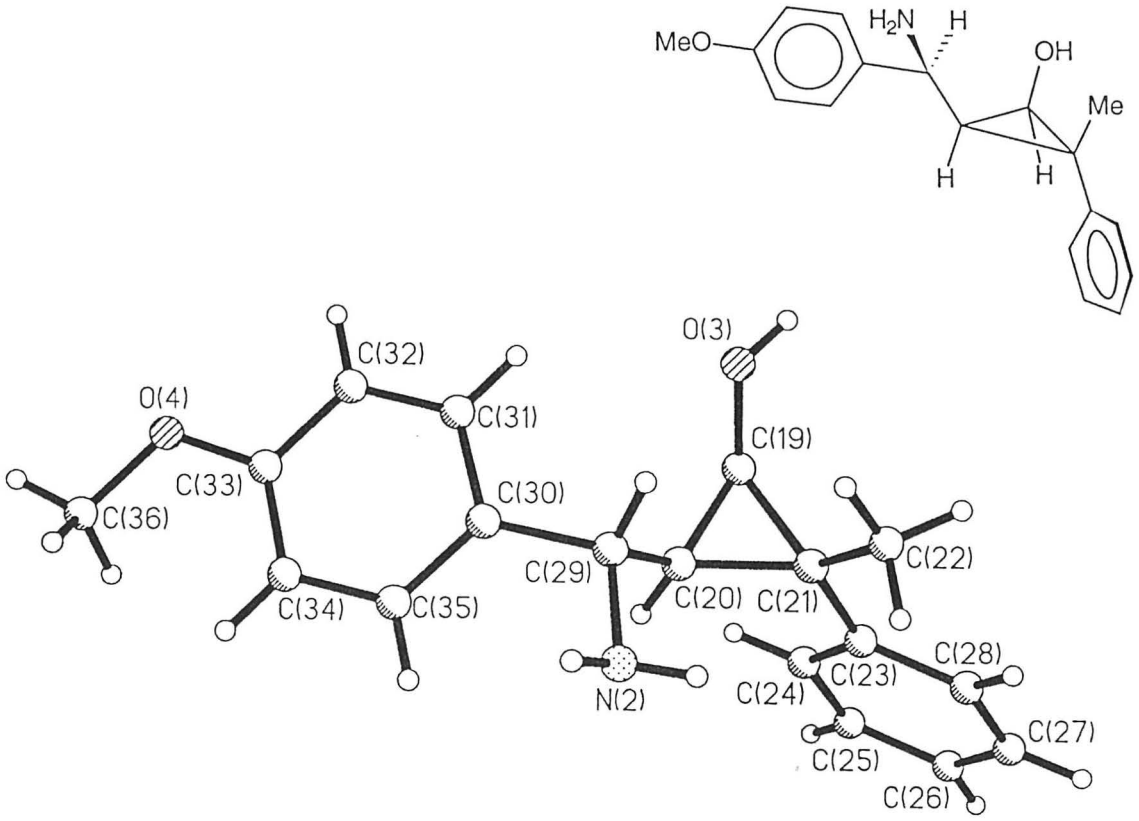
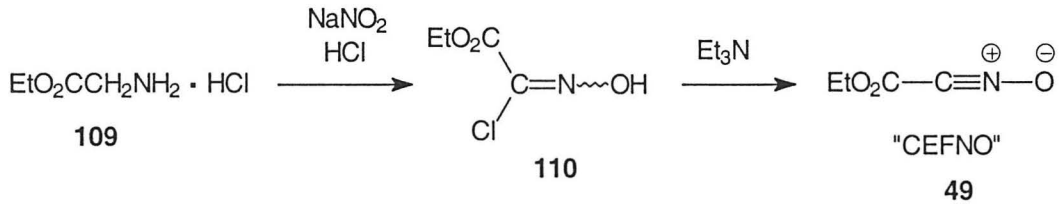


Figure 6. X-ray crystallographic structure of *rac*-3-[(amino(4-methoxyphenyl)-methyl]-2-methyl-2-phenylcyclopropanol (103)

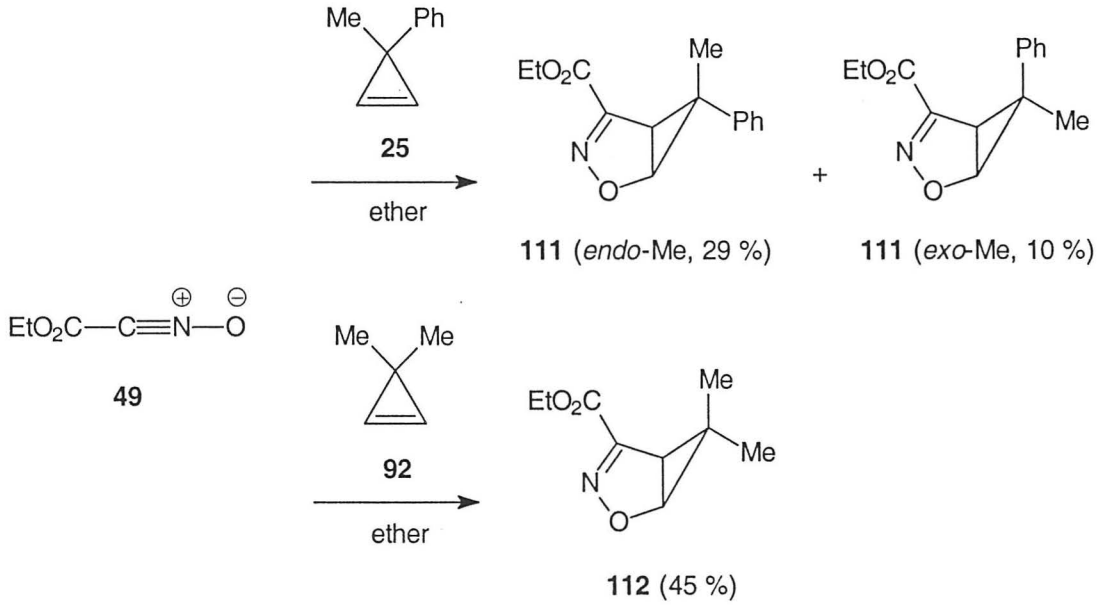
2.2.2.3. Reduction of cycloadducts, derived from carbethoxyformonitrile oxide (CEFNO)

The third nitrile oxide that was used in the cycloaddition reactions was carbethoxyformonitrile oxide (CEFNO) (**49**).[135] It is an interesting type of dipole because of the functional group present. Its precursor, ethyl chlorooximidoacetate (**110**), is commercially available but also can be prepared easily in one step by nitrosation of glycine ethyl ester hydrochloride (**109**) (**Scheme 56**).[135]



Scheme 56

CEFNO (**49**) was generated *in situ* upon treatment with triethylamine in the presence of the cyclopropene. The reaction of CEFNO with 3-methyl-3-phenylcyclopropene (**25**) gave rise to two diastereomers (*endo*- and *exo*-methyl-**111**) in ratio 75:25 in favour for the *endo*-methyl isomer (**Scheme 57**).

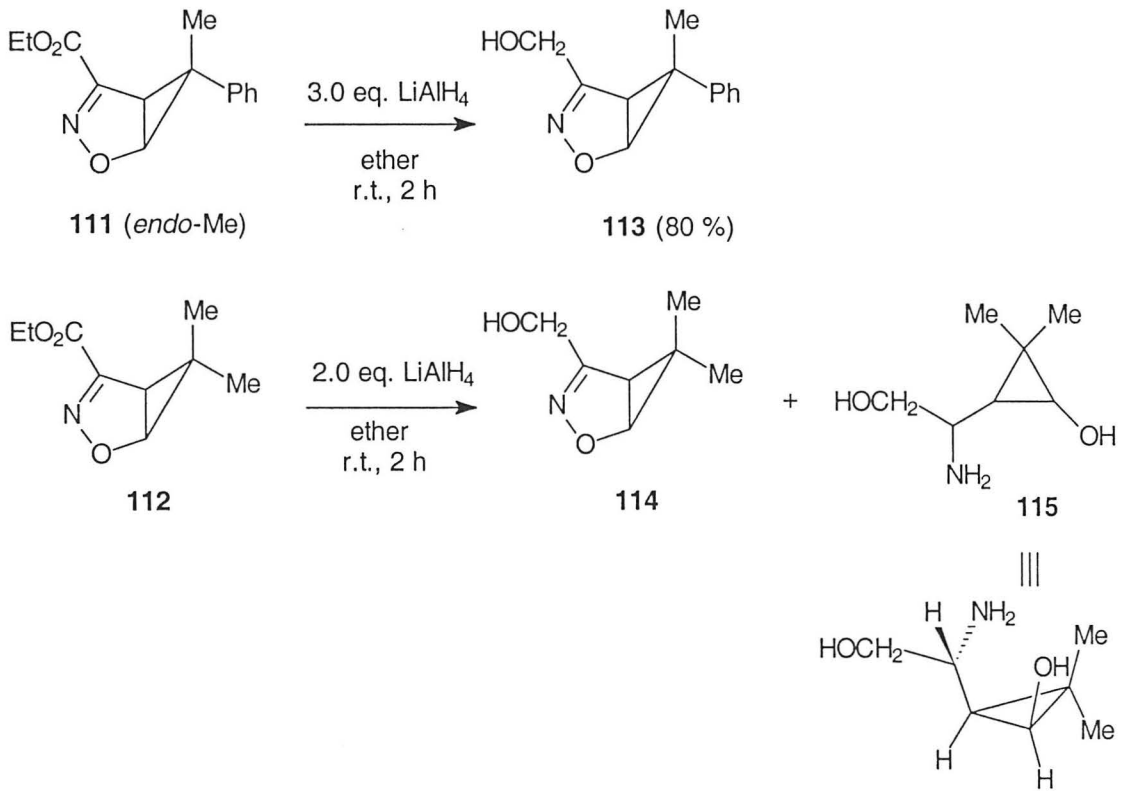


Scheme 57

Both isomers were separated by column chromatography on silica. The *endo* and *exo* isomers were isolated in 29 % and 10 % yield respectively. The chemical shift difference of the *endo*/*exo* isomers in the ^{1}H NMR was similar to the one observed with compound **102**. The *endo*-methyl group showed a signal at 1.18 ppm while the *exo*-methyl group appeared at 1.38 ppm.

A second cycloadduct **112** was prepared upon reaction with 3,3-dimethylcyclopropene (**92**) in 45 % yield.

Cycloadduct *endo*-methyl **111** and cycloadduct **112** were both subjected to reduction with excess $LiALH_4$ for 2 hours (**Scheme 58**). The two compounds showed a considerable difference in rate. While after 2 hours **111** only showed reduction of the ester to the alcohol group (compound **113**), the less hindered bicycle **112** was mostly further reduced to the ring opened diol-amino species **115** (the alcohol **114** was only a minor product). The NMR showed one set of signals; thus **115** was formed as a single diastereomer. Compound **115** represents a very polar type of compound, difficult to isolate in pure form. Only a small part (14 %) was isolated as colourless crystalline solid.



Scheme 58

Summary

All the above described products, derived from the cycloadditions and reductions are summarised in the following tables, **Table 3** and **Table 4.**

Table 3

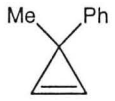
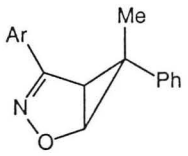
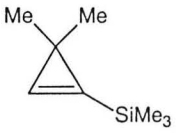
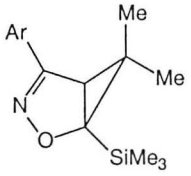
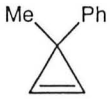
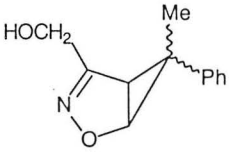
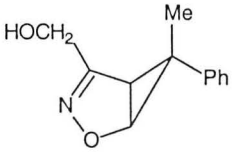
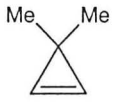
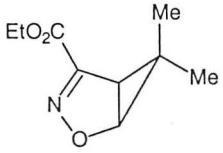
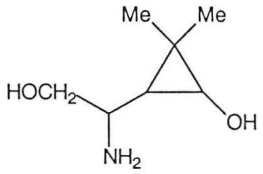
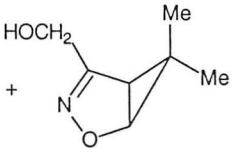
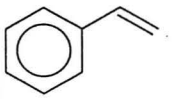
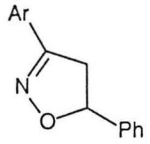
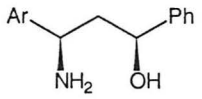
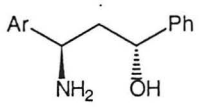
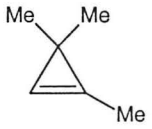
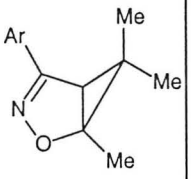
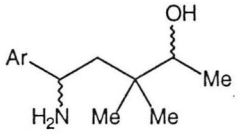
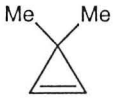
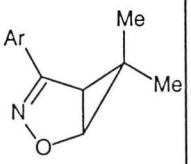
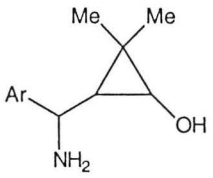
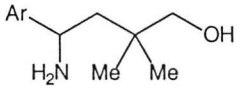
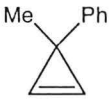
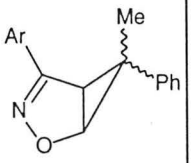
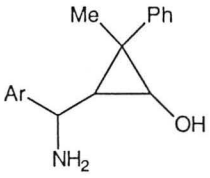
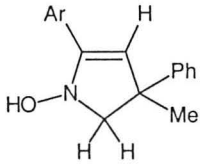
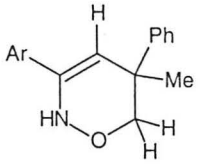
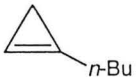
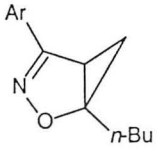
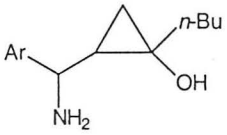
entry	cyclopropene	cycloadduct	reduction with $LiAlH_4$
dipole 2,4,6-$(MeO)_3C_6H_2$-CNO (**38**) Ar = 2,4,6-$(MeO)_3C_6H_2$			
1	 **25**	 **79** (94 %)	no conversion observed
2	 **80**	 **81** (99 %)	—
dipole EtO_2C-CNO (CEFNO) (**49**)			
3	 **25**	 *endo/exo*-Me **111** (29 % / 10 %)	 **113** (80 %)
4	 **92**	 **112** (45 %)	 **115** +  **114**

Table 4

entry	cyclopropene	cycloadduct	reduction with $LiAlH_4$	reduction with $NaBH_4$
dipole 4-$MeOC_6H_4$-CNO (**77**) Ar = 4-$MeOC_6H_4$				
1		 **86** (85 %)	 *syn*-**87** +  *anti*-**87** *syn/anti* ratio depends on reducing reagent	
2	 **91**	 **93** (66 %)	no conversion was observed	 **97** (70 %)
3	 **92**	 **98** (69 %)	 **99** (68 %)	 **100** (22 %)
4	 **25**	 *endo* / *exo*-Me **102** (73 % / 16 %)	 **103** (68 %)	 or  **104** or **105**
5	 **106**	 **107** (46 %)	 **108** (81 %)	—

2.2.3. Conclusion

The cycloaddition-reduction sequence has been shown to provide a straightforward access to novel cyclopropanol species. Multiple stereocentres can be built up with this short reaction sequence. As an extension of this work the chemistry of these species requires investigation.

The right choice of reducing agent is vital to give complete stereocontrol without ring opening the cyclopropane moiety. $LiAlH_4$ proved to be a mild reagent that cleaves the isoxazoline ring with 100 % diastereoselectivity.

The steric influence of substituents at C-4 (choice of dipole) and at C-1 and C-6 (choice of cyclopropene) of the bicyclic adduct has to be considered as a possible limiting factor. If the substituents at C-4 were too bulky or three substituents occupied positions 6,6' and 1, reduction was not observed. Substitution of a methyl group with phenyl can slow down the rate considerably as shown with the bicycles derived from carbethoxyformonitrile oxide (CEFNO). The reduction of an ester group proved to be much faster than the reductive ring cleavage of the isoxazoline ring.

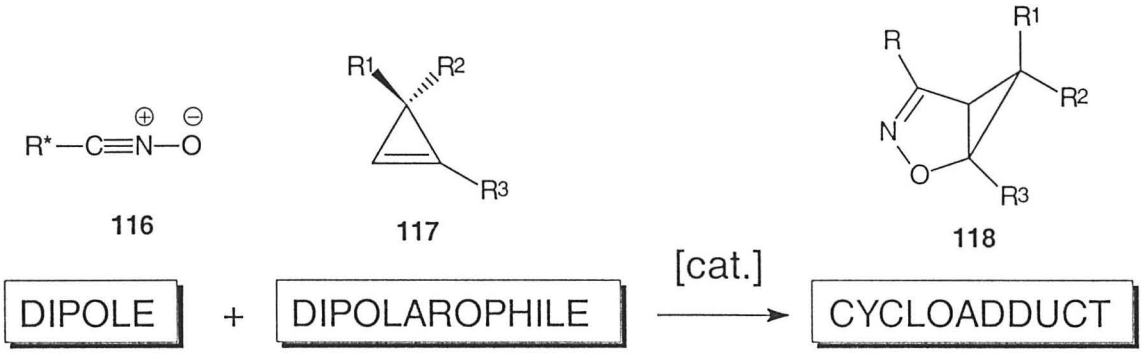
Although the cyclopropanols **99**, **103**, **108** and **115** were obtained as single diastereomers, they were all racemic compounds because the cycloaddition step does not exhibit any enantiofacial control. The attempt to prepare those cycloadducts enantioselectively is the topic of the next chapters.

2.3. Chiral dipoles

2.3.1. Introduction

Having shown in the previous chapter that reduction of bicycles, derived from nitrile oxides and cyclopropenes occurred with 100 % diastereoselectivity, the aim was now to apply this methodology to enantiomerically pure cycloadducts in order to obtain functionalised optical active cyclopropanols.

Asymmetric synthesis generally can be achieved by using either a chiral substrate (dipole or dipolarophile) or an active catalyst.



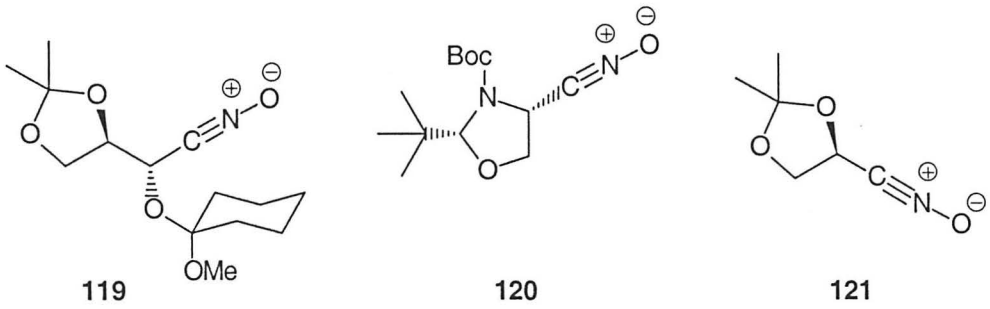
Scheme 59

The general aspects of asymmetric 1,3-dipolar cycloaddition reactions including the application of chiral alkenes and intramolecular strategies have already been discussed in the introduction, **Chapter 1.4.3.** In this specific case, in order to obtain bicycles such as **118** the dipolarophile has to be a cyclopropene (**Scheme 59**).

Chiral cyclopropenes (such as **117** with $R^1 \neq R^2 \neq R^3$) would probably be the most efficient and direct way to synthesise those types of cycloadducts enantiomerically pure, however unfortunately access to chiral cyclopropenes is limited. There is no general route to the preparation of chiral cyclopropenes (see also introduction, **Chapter 1.3.4.**). Our attention was therefore drawn first to chiral dipoles (chiral nitrile oxides, **116**) and later to the application of a chiral catalyst system.

Chiral nitrile oxides

Only a few reports have described the application of optically active nitrile oxides in the 1,3-DC reactions.[161] Three literature examples of chiral nitrile oxides are shown in **Scheme 60**.

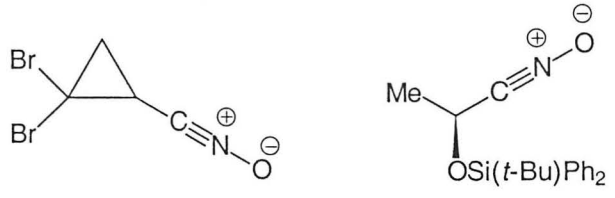


Scheme 60

Kozikowski *et al.* described the application of a glyceraldehyde-derived nitrile oxide **119**.[162] In the reaction with (*Z*)-2-butene a diastereomeric excess of 49 % was achieved. In a more recent work Kim *et al.* demonstrated that by the concomitant application of the chiral nitrile oxide **120** and a chiral alkene, selectivities of up to 84 % de were observed.[163] A similar approach by Paton *et al.*, involving both a chiral nitrile oxide (**121**) and a chiral sugar derivative afforded cycloadducts in 74 % de.[164]

2.3.2. Discussion

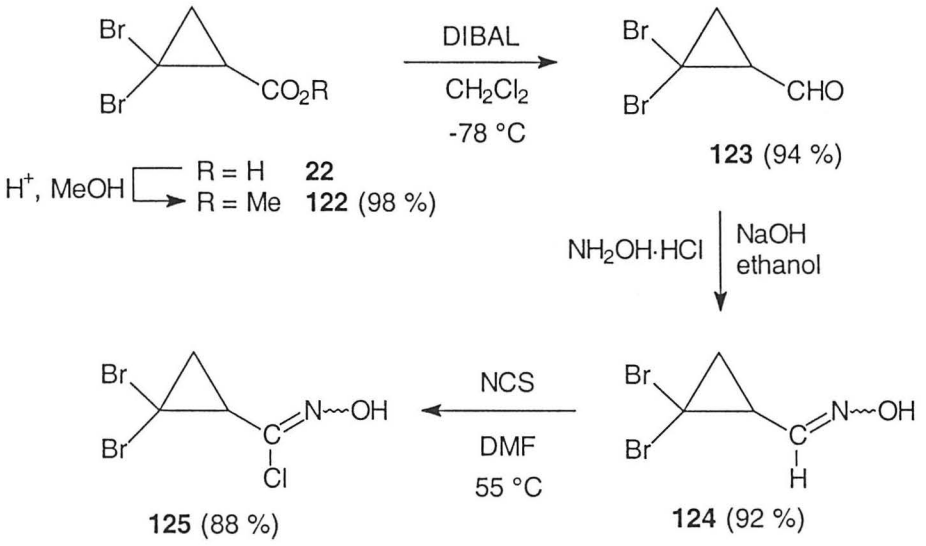
Two novel nitrile oxides, one dipole (**126**) derived from 2,2-dibromocarboxylic acid, the other (**139**) derived from (*S*)-(-)-ethyl lactate were prepared. Their asymmetric induction potential and their properties (stability and reactivity) were tested upon reaction with cyclopropenes and acetylenic dipolarophiles.



2.3.2.1. 2,2-Dibromocyclopropylformonitrile oxide (126)

Preparation of nitrile oxide precursor, *N*-hydroxy-2,2-dibromocyclopropyl-methanimidoyl chloride (125)

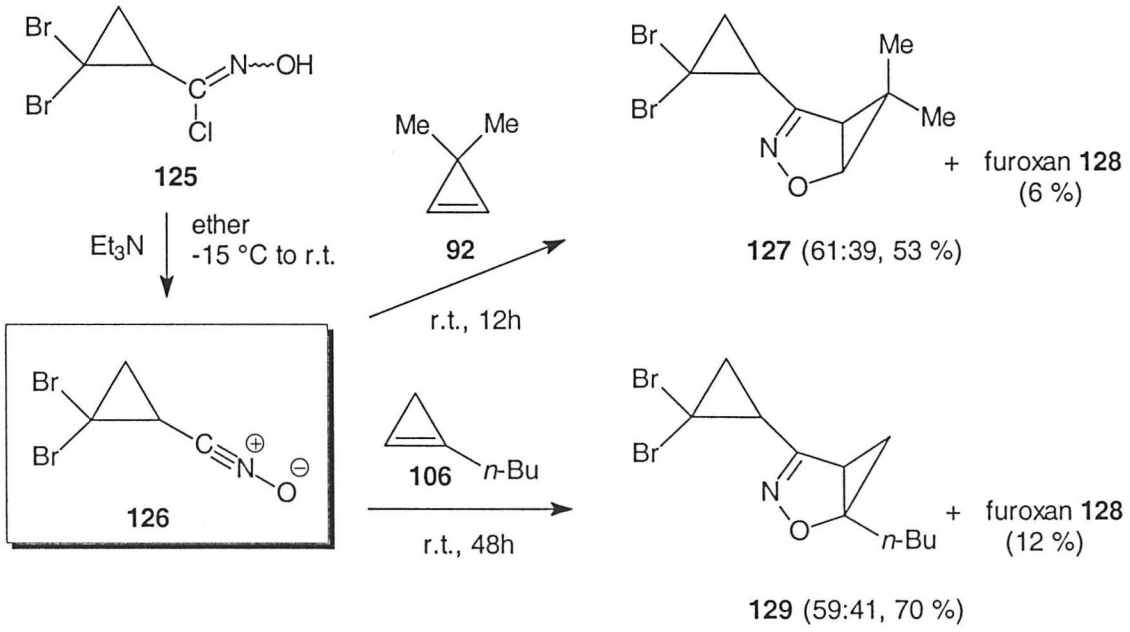
The nitrile oxide precursor **125** was obtained as shown in **Scheme 61**. The synthesis started from 2,2-dibromocyclopropanecarboxylic acid (**22**) that is now available in enantiomerically pure form (see **Chapter 1.3.2.2.**; the preparation of the acid will be outlined in **Chapter 3.1.2.1.**).[77] For the initial nitrile oxide synthesis however racemic material was used. The acid **22** was esterified with methanol in the presence of catalytic amounts of sulphuric acid in nearly quantitative yield. Ester **122** was reduced with diisobutyl aluminium hydride at –78 °C. Temperature control was important to avoid reduction to the corresponding alcohol. The aldehyde **123** was converted into the corresponding oxime **124** and *N*-chloro-oxime **125** by standard methods.[107] The oxime proved to be unstable; it decomposed at room temperature within 24 hours. Immediate conversion of the oxime into its chloro species **125** was therefore necessary. *N*-Hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (**125**) could be stored in a freezer without any change for several months.



Scheme 61

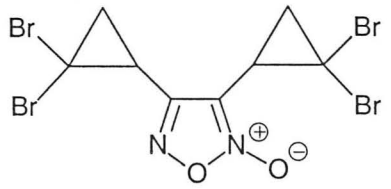
Reaction of 2,2-dibromocyclopropylformonitrile oxide (126) with cyclopropenes

The nitrile oxide **126** was generated *in situ* in ether upon treatment with triethylamine at -15 °C in presence of 1.1 mol.equiv. of the cyclopropenes **92** and **106** respectively (**Scheme 62**). The reaction mixture was allowed to warm to room temperature and stirred for several hours. Generation of the nitrile oxide was indicated by the formation of a triethylammonium chloride precipitate. The cycloadducts **127** and **129** respectively were obtained as oils in moderate yields.



Scheme 62

In both reactions a mixture of diastereomers was obtained (see drawings in **Figure 7**, next page). Although by TLC the diastereomers appeared as two separate spots close together, attempts to separate them by column chromatography failed. In both cases a by-product was isolated that was identified as a furoxan species (**128**) formed by dimerisation of the nitrile oxide. It was also obtained as a diastereomeric mixture.



128

The observed asymmetric inductions for cycloadducts **127** and **129** were disappointingly low, both reactions gave rise to a diastereomeric ratio of about 60:40. The molecule has in total three stereocentres; in the cycloaddition step two new stereocentres were generated. As the nitrile oxide **126** was used in its racemic form, both diastereomers are present as a pair of enantiomers, which gives a total of four stereoisomers. The isomers are illustrated for cycloadduct **129** in **Figure 7** below. There are two three-membered rings present in the molecule, the rings can show up (**u**) or down (**d**); the pair of enantiomers are uu/dd and ud/du respectively.

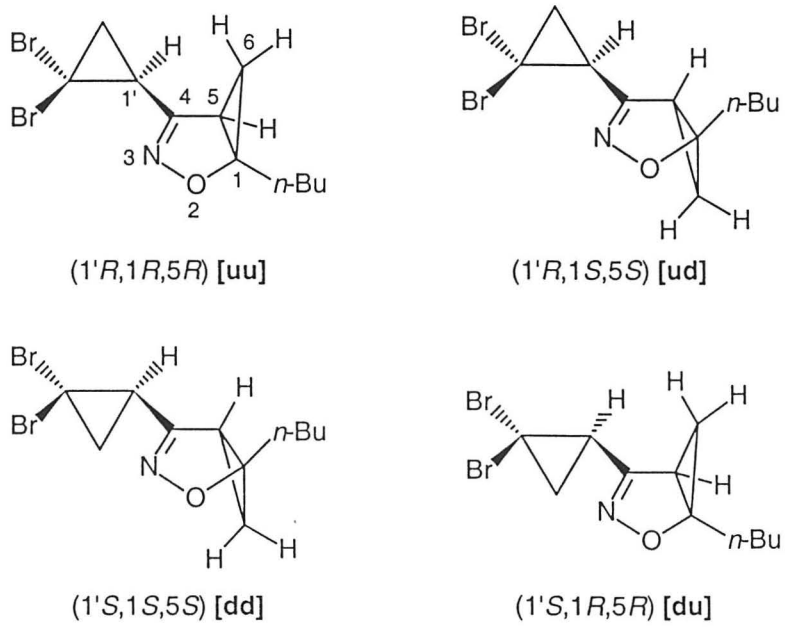


Figure 7

NMR data of cycloadducts 129 and 107

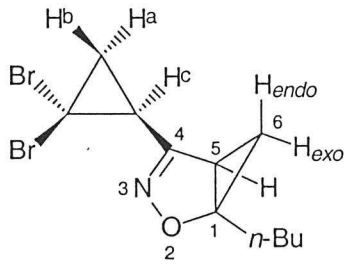
The ^{1}H and ^{13}C NMR data of cycloadduct **129** are given in **Table 5** and **Table 6** on the following pages. It also includes the data of the analogous compound **107** that has an aromatic system at C-4 of the bicyclic system (instead the cyclopropane moiety). The focus in the tables is on the two three-membered ring systems present in **129**; the data of the *n*-butyl group are omitted in this table.

All protons on the ring systems could be assigned by the size of their coupling constants. Generally, in cyclopropanes the *cis*-coupling constants have bigger values than the *trans* ones, which is opposite to alkenes.[165] For the protons in *endo*/*exo* position at C-6 of the bicycle additionally the chemical shift difference allows identification of whether the orientation is *exo* or *endo*: H_{endo}-6 generally appears at higher field

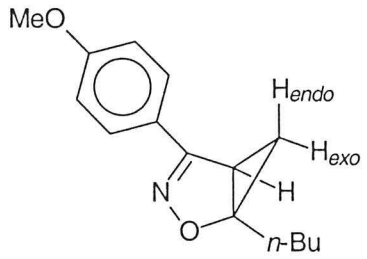
compared with H_{exo}-6. As mentioned above cycloadduct **129** was obtained as a mixture of diastereomers (59:41). Data for both diastereomers are given in the table. The chemical shifts of the isomers are close, with the exception of H_{endo}-6 (chem. shift difference, 0.10 ppm) and H^c (difference, 0.18 ppm). Those two protons are most affected by the position that the two three-membered rings are taking relative to each other - facing up and/or down in the corresponding diastereomeric structures. (uu/ud, etc., see **Figure 7**).

The chemical shifts of the CH_2 group in the "isolated" cyclopropane are in a region of 2.04 to 2.17 ppm while the CH_2 group of the three-membered ring in the bicycle gives values of 0.47 to 1.10 ppm. The values around 2 ppm are due to the electronic effect of the C=N bond and for similar environments, e.g. for the nitrile oxide precursor **125**, similar chemical shifts are observed.

Table 5. ^{1}H data of cycloadducts 129 and 107



129



107

^{1}H NMR	δ_H ($CDCl_3$; coupling constants in Hz)		
atom	**129** (major isomer)	**129** (minor isomer)	**107**
H_{endo}-6	0.47 (J_{trans} 3.7, J_{gem} 5.5)	0.57 (J_{trans} 3.7, J_{gem} 5.5)	0.51 (J_{trans} 3.9, J_{gem} 5.2)
H_{exo}-6	1.01 (J_{gem} 5.5, J_{cis} 9.5)	1.00 (J_{gem} 5.5, J_{cis} 9.5)	1.10 (J_{gem} 5.2, J_{cis} 9.3)
H-5	2.29 (J_{trans} 3.7, J_{cis} 9.5)	2.36 (J_{trans} 3.7, J_{cis} 9.5)	2.59 (J_{trans} 3.9 J_{cis} 9.3)
H^a	2.04 (J_{gem} 7.8, J_{cis} 10.1)	2.05 (J_{gem} 7.8, J_{cis} 10.2)	—
H^b	2.17 ($J_{trans} = J_{gem}$ 7.8)	2.15 ($J_{trans} = J_{gem}$ 7.8)	—
H^c	2.69 (J_{trans} 7.8, J_{cis} 10.1)	2.51 (J_{trans} 7.8, J_{cis} 10.2)	—

Table 6. ^{13}C NMR data of cycloadducts 129 and 107

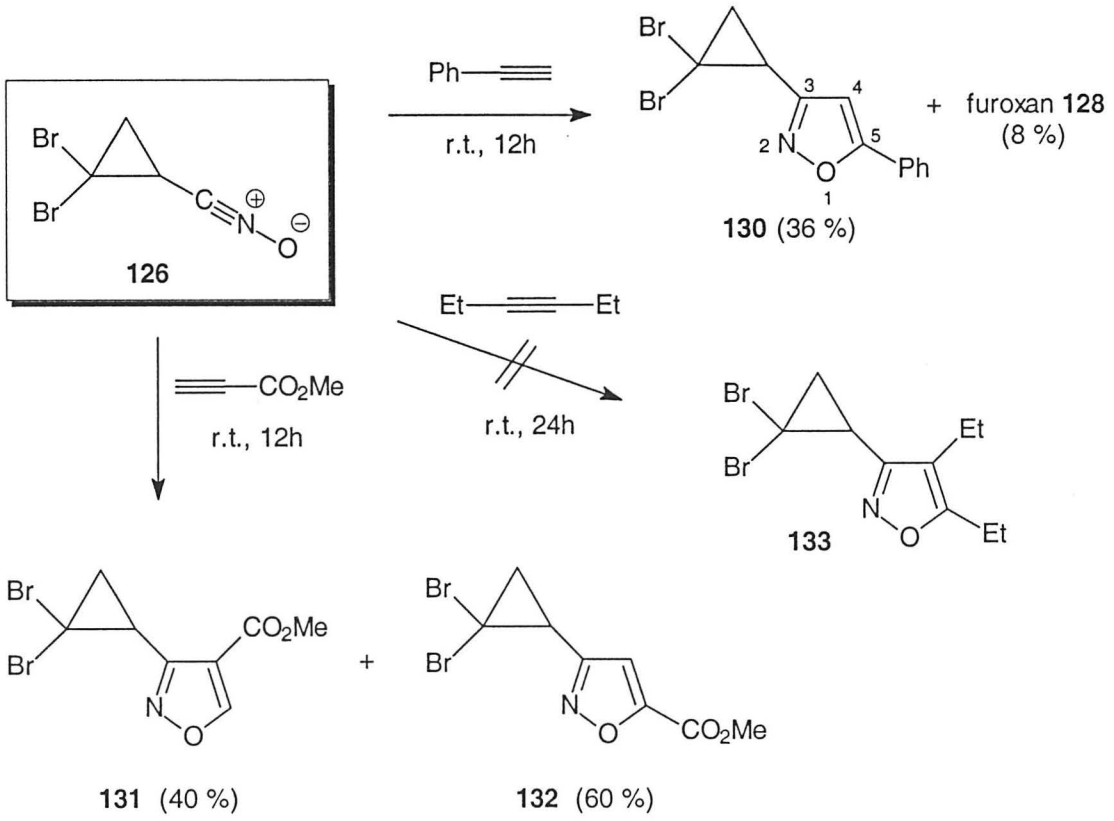
^{13}C NMR	δ_C ($CDCl_3$)		
atom	**129** (major isomer)	**129** (minor isomer)	**107**
C-6	12.0	11.2	12.2
C-5	29.1	29.8	29.1
C-1	77.3	76.8	75.3
C-4	160.8	159.8	161.4
CBr_2 (cyclopropane)	24.2	24.6	—
CH_2 (cyclopropane)	27.0	27.9	—
CH (cyclopropane)	30.6	30.5	—

The chemical shifts of the three-membered ring in the bicycle of compound **129** have comparable values to the one of the analogous compound **107** that has an aromatic system at C-4. This is the case for both the proton and the carbon NMR. The only exception is H-5 in the ^{1}H NMR, which appears in bicycle **107** at lower field relative to compound **129**: 2.59 ppm for **107**, compared with 2.36 ppm for **129**.

Reaction of nitrile oxide 126 with alkynes

The reactivity of this novel nitrile oxide species was also tested by reacting it with three alkynes (**Scheme 63**). The nitrile oxide was generated as above *in situ* and in the presence of the dipolarophile. Generally, the reaction of nitrile oxides with acetylenic dipolarophiles leads to the formation of isoxazole derivatives.

In a first attempt the nitrile oxide **126** was treated with 1 mol.equiv. of the dipolarophile phenylacetylene. The cycloadduct 3-(2,2-dibromocyclopropyl)-5-phenylisoxazole (**130**) was obtained as a crystalline solid in only 19 % yield. The dimerisation product bis(2,2-dibromocyclopropyl)furoxan **128** had become the major product in this cycloaddition reaction with 33 % yield. This competing reaction could be suppressed by employing a large excess (4 mol.equiv.) of phenylacetylene. The furoxan was now formed in 8 % only, however the yield of **130** did not improve dramatically (36 % isolated yield compared with 19 % above).



Scheme 63

In both reactions the isoxazole **130** was formed regioselectively. Only the 5-substituted isomer was present. In contrast the cycloaddition reaction of nitrile oxide **126** with methyl propiolate gave rise to two regioisomers, 4-substituted **131** and 5-substituted **132**, in ratio 40:60. Again a 1:4 ratio of dipole to dipolarophile was employed and the two isomers were isolated in quantitative yield. The formation of furoxan **128** was not observed in this case.

The regioselectivies are controlled by frontier molecule orbital (FMO) interactions and these depend on the electronic nature both of the dipole and the dipolarophile (see also introduction, **Chapter 1.3.1.**). The regioisomers were distinguished on the basis of their ^{1}H NMR spectra. The aromatic isoxazole proton showed a 2 ppm chemical shift difference being either at C-4 or C-5 of the isoxazole ring system: in isomer **131** (ester group in position 4) the aromatic proton is next to the oxygen atom and is shifted downfield to 8.93 ppm, while in **132** (ester group in position 5) the signal of this proton appears at 6.92 ppm. In comparison compound **130** with the phenyl group at C-5 gave a signal for the aromatic proton at C-4 at 6.52 ppm.

The third alkyne species to be employed was 3-hexyne. No cycloaddition reaction between the alkyne and dipole **126** occurred. Only the nitrile oxide dimerisation product bis(2,2-dibromocyclopropyl)furoxan **128** was formed in 42 % yield.

Conclusion

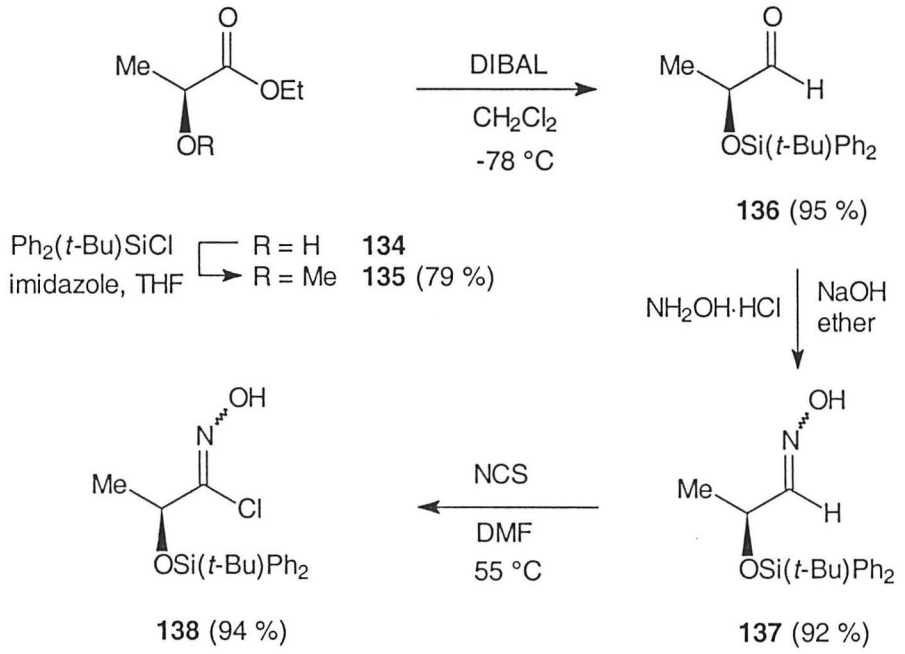
Overall, this novel nitrile oxide **126** proved to have a high tendency to dimerise, which led to low yields of the desired products. Even more important however, the asymmetric inductions observed (20 % de) were far too low to justify synthesising this nitrile oxide in enantiomerically pure form.

The products **127**, **129** and **130**, derived from the cycloaddition with 3,3-dimethylcyclopropene, 1-butylcyclopropene and phenylacetylene were also subjected treatment with methyllithium, this will be described in **Chapter 3.2.**

2.3.2.2. (*S*)-2-(*tert*-Butyldiphenylsilanyloxy)propionitrile oxide (139)

Preparation of nitrile oxide precursor, *N*-hydroxy-(*S*)-2-(*tert*-butyldiphenyl-silanyloxy)propanimidoyl chloride (138)

Due to the limitations observed with the above nitrile oxide, a second chiral dipole was prepared, this time in enantiomerically pure form. Commercially available ethyl (*S*)-(-)-lactate **134** was the starting material of this nitrile oxide synthesis, which is outlined in **Scheme 64**.



Scheme 64

The alcohol function of ethyl lactate **134** was protected with the sterically demanding *tert*-butyldiphenylsilyl group, following an Organic Synthesis procedure.[166] Reduction to the aldehyde **136** was carried out according to literature,[167] using diisobutyl aluminium hydride at low temperature (-78 °C); only the solvent was altered, *n*-hexane was substituted with dichloromethane.

The next step, formation of the oxime proved to be unsuccessful under standard conditions, which usually employ hydroxylamine hydrochloride (1.1 mol.equiv.), excess sodium hydroxide (2.5 mol.equiv.) and ethanol/water.[107] Under these basic conditions the silyl ether was found to hydrolyse readily.[168]

Alternative conditions are described in literature for the analogous compound (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal, employing hydroxylamine hydrochloride, methanol/water and pyridine as the base.[169]

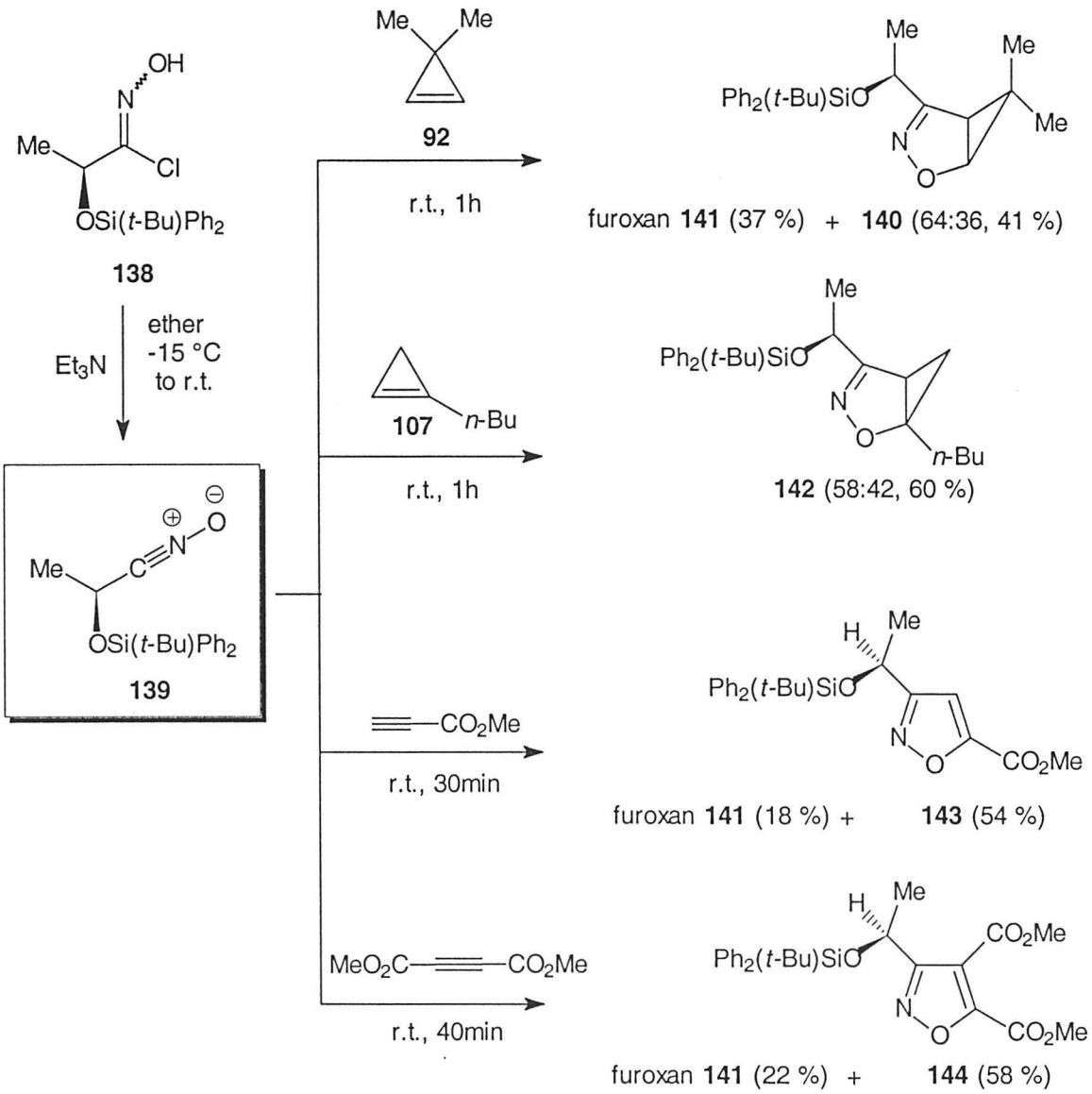
To avoid the use of pyridine, the procedure that employs sodium hydroxide was modified. The amount of hydroxylamine hydrochloride was increased to 3 mol.equiv. while the molar amount of sodium hydroxide was only raised to 2.8 equivalents. This corresponds to 0.9 mol.equiv. with respect to hydroxylamine hydrochloride; sufficient base to form an excess of salt free hydroxylamine. This leads to a pH around 8, keeping the silyl protecting group intact. Ethanol/water was substituted by ether/water. The two-phase system was stirred vigorously and the progress of the reaction was monitored by TLC and GLC. To bring the reaction to completion enough ethanol was added to give a single layer and the mixture was stirred for an additional short period. Extractive work-up afforded the oxime **137** as a mixture of *E*/*Z* isomers (66:34) in 92 % yield.

The final step to the nitrile oxide precursor **138**, chlorination of the oxime under standard conditions,[107] could be carried out without encountering any problems. *N*-Hydroxy-(*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanimidoyl chloride (**138**) was prepared in 94 % yield. The overall yield over 4 steps from ethyl lactate was 65 %.

Reaction of (*S*)-2-(*tert*-butyldiphenylsilanyloxy)propionitrile oxide (139) with dipolarophiles

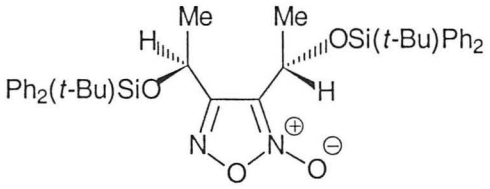
The nitrile oxide **139** was generated *in situ* in ether upon treatment with triethylamine at -15 °C in the presence of the cyclopropenes **92** and **107** (1.1 mol.equiv. each), respectively (**Scheme 65**). The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The cycloadducts **140** and **142** respectively were obtained as oils in moderate yields.

Mixtures of diastereomers were obtained in both cases. The extent of asymmetric induction was again very low. The diastereoselectivities were similar to the one observed with the previously discussed nitrile oxide **126**; the "best" result gave cycloadduct **140** with a ratio of 64:36. No attempts were made to separate the diastereomers.



Scheme 65

As observed with other cycloaddition reactions a furoxan species was formed as a by-product. In this specific case the furoxan **141** is optically active as it is derived from enantiomerically pure nitrile oxide **139** (both chiral centres are in (*S*)-configuration).



141 $[\alpha]_D^{26}$ = -36° (c 1.0, $CHCl_3$)

The cycloaddition reaction of **139** to 3,3-dimethylcyclopropene **92** afforded the furoxan in 37 % yield. This is in sharp contrast to the cycloaddition reaction with the other cyclopropene **107**, which surprisingly proceeded without any formation of the furoxan species.

The nitrile oxide **139** was also subjected to cycloaddition with two acetylenic dipolarophiles and two novel optically active isoxazole derivatives were obtained. In both reactions only 1.0 mol.equiv. of the alkyne was used, which might explain the low yields of product and the presence of the furoxan in about 20 % yield. Contrary to the above dipole, 2,2-dibromocyclopropylformonitrile oxide (**126**), the reaction of (*S*)-2-(*tert*-butyldiphenylsilanyloxy)propionitrile oxide (**139**) with methyl propiolate was completely regioselective. The C-5 substituted cycloadduct **143** was the sole product. In the ^{1}H NMR **143** showed a singlet for the aromatic proton at 6.98 ppm. The compound's optical rotation, $[\alpha]_D^{26}$ of -79.1° (c 1.0, $CHCl_3$) was close to the one of the related cycloadduct **144**, which bears an additional ester group at C-4; **144** exhibited an $[\alpha]_D^{26}$ of -72.8° (c 1.0, $CHCl_3$).

2.2.3. Conclusion

Two precursors of novel chiral nitrile oxides had been successfully prepared. However the cycloaddition reactions of the corresponding 2,2-dibromocyclopropyl formonitrile oxide (**126**) and (*S*)-2-(*tert*-butyldiphenylsilanyloxy)propionitrile oxide (**139**) to cyclopropenes showed only low asymmetric inductions. Moreover the yields were only moderate and in most cases furoxans were formed as by-products.

Thus the chiral dipoles did not provide a synthetic route to enantiomerically pure 2-oxa-3-azabicyclo[3.1.0]hex-3-enes. No attempts were made to reduce the diastereomeric mixtures to aminoalcohols.

2.4. Synthesis of a novel enantiomerically pure cyclopropanol derivative *via* a metal-catalysed asymmetric 1,3-DC reaction

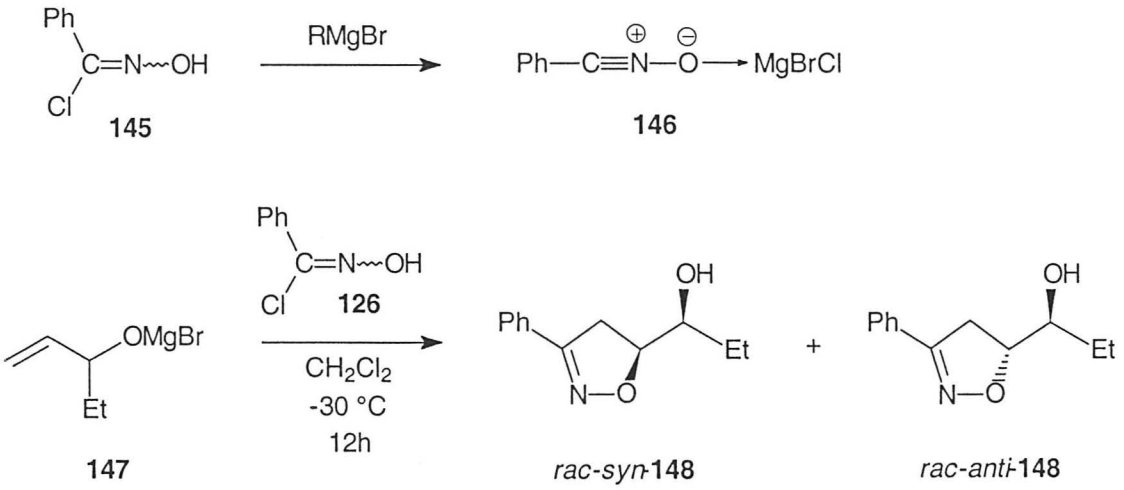
2.4.1. Introduction

This introduction deals with the aspect of asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides that has not been discussed yet - application of a metal based chiral catalyst system. First however, metal-catalysis in 1,3-DC reactions of nitrile oxides is described briefly in general.

Metal-catalysed 1,3-DC reactions of nitrile oxides[134]

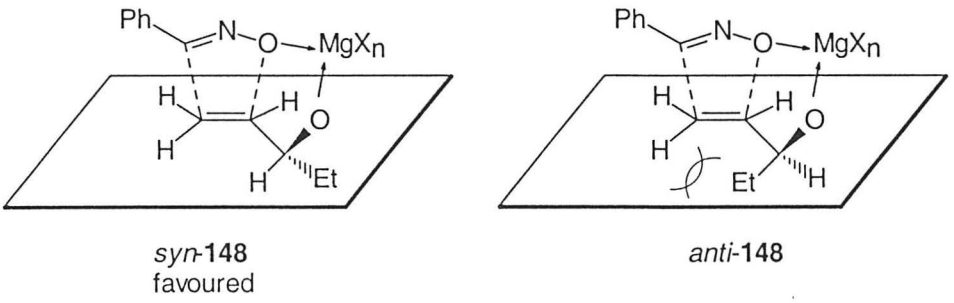
Compared to reactions of related dipoles such as nitrones, only a few publications have appeared on metal-assisted or metal-catalysed 1,3-DC reactions of nitrile oxides. Some of the obstacles for controlling the stereoselectivity with metal complexes are (i) most nitrile oxides are very reactive short-lived species that must be generated *in situ*, (ii) in the two general procedures for the generation of nitrile oxides, bases such as triethylamine are used, which may destroy the catalyst, and (iii) the nitrile oxide have low-lying FMOs and therefore attempts to use the traditional activation of α,β-unsaturated carbonyl compound with Lewis acids would probably fail.

At least one of these obstacles was overcome by Kanemasa *et al.*[170,171] Instead of using amines for the generation of the nitrile oxide they applied alkylmagnesium bromide or alkoxymagnesium bromide (**Scheme 66**).



Scheme 66

The nitrile oxide is smoothly generated at low temperature under these conditions probably co-ordinated to the magnesium salt. In the reaction of chiral allylic alcohols with nitrile oxides generated by the conventional method, low diastereoselectivity is mostly obtained; however when the magnesium alkoxide is mixed with hydroximoyl chloride **145**, the resulting nitrile oxide reacts with the alkene to give **146** with a *syn* selectivity of up to 98 %. It is proposed that the *syn* selectivity and also the rate accelerations observed are due to chelation *via* the metal salt. Of the two transition states *syn*-**148** and *anti*-**148,** the former is favoured since steric repulsion between the substituent at the chiral centre and the allylic proton is to be expected (**Figure 8**).[113] In reactions of 1,2-disubstitued alkenes of allylic alcohols this approach also offers an excellent control of the regioselectivity (see also **Chapter 2.5.2.**).[114,172]



syn-**148**
favoured

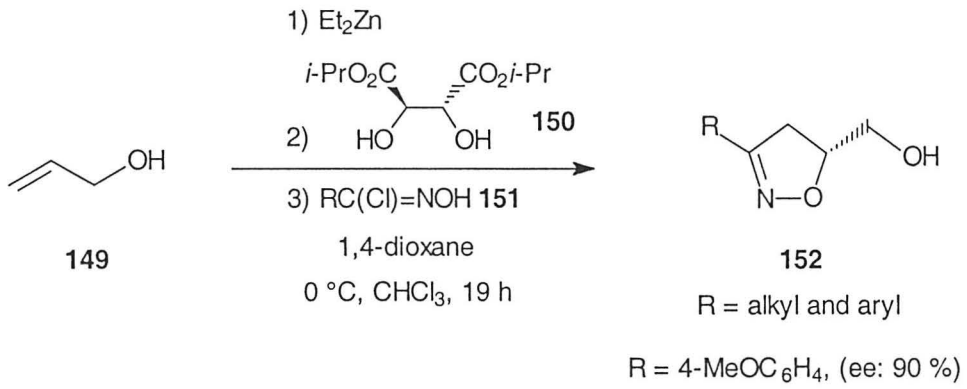
anti-**148**

Figure 8

Asymmetric metal-catalysed 1,3-DC reaction of nitrile oxides

Ukaji *et al.* applied a related approach to the first and so far only asymmetric metal-catalysed 1,3-DC reaction of nitrile oxides with alkenes.[173] Upon treatment of allyl alcohol **149** with diethylzinc and (*R*,*R*)-diisopropyl tartrate (DIPT) (**150**), followed by the addition of diethylzinc and substituted hydroximoyl chlorides **151**, the (*R*)-2-isoxazolines **152** are formed with excellent enantioselectivities of up to 96 % ee.[173] The (*S*)-enantiomers of **152** are also accessible by using the corresponding (*S*,*S*)-DIPT. Optically active 2-isoxazolines **152** had been prepared before; several methods have reported the synthesis *via* cycloaddition of nitrile oxide to acrylic derivatives. However those methods still required introduction and removal of chiral auxiliaries on the olefinic acceptor (see also introduction **Chapter 1.3.3.**).[173]

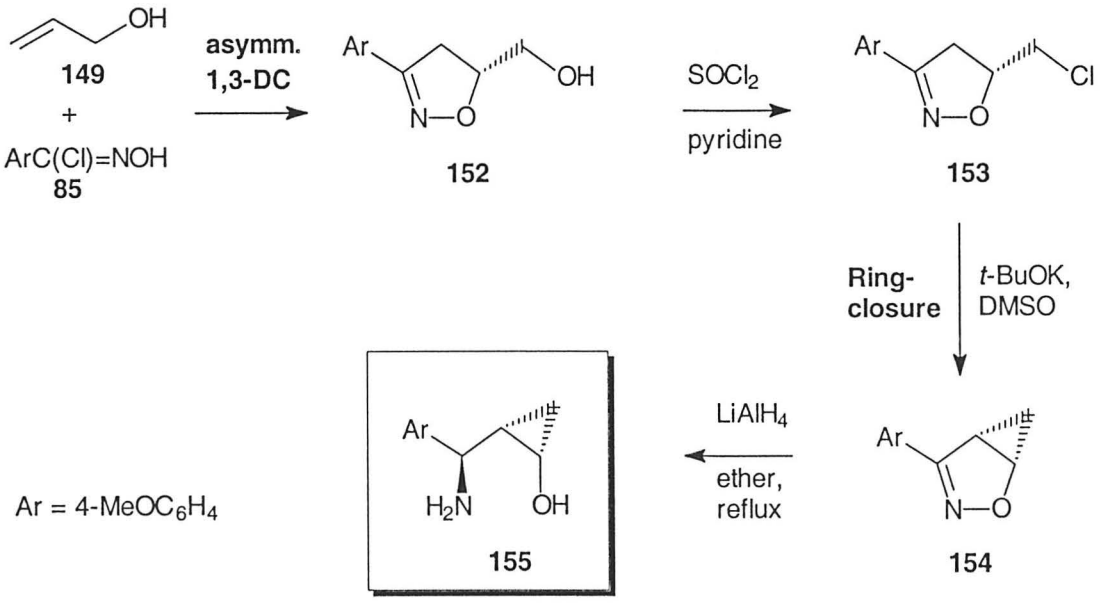
In an extension of this work Ukaji *et al.* developed a catalytic version of the reaction in which the chiral ligand DIPT **150** was applied at a concentration of 20 mole %.[174] Despite the reduction of the amount of the chiral ligand, similar high enantioselectivities were obtained in this work. The addition of a small amount of 1,4-dioxane proved to be crucial for the enantioselectivity of the reaction. The catalytic version of this asymmetric metal-catalysed 1,3-DC reaction is outlined in **Scheme 67**.



Scheme 67 (Ukaji 1996)

2.4.2. Discussion

Based on Ukaji's catalytic asymmetric 1,3-DC reaction of nitrile oxides to allyl alcohol[174] a synthetic route was proposed that should lead to a novel optically active cyclopropanol derivative (**155**) (**Scheme 68**). In the previous chapters the synthetic pathway was such that first the three-membered ring (cyclopropene) was formed and secondly the 1,3-DC reaction took place, affording a bicyclic compound. Now the same bicyclic system (**155**) should be accessed by the opposite order, the 1,3-DC reaction first (**149/85** to **152**) and subsequently the building up of the three-membered ring system (ring-closure, **153** to **154**).



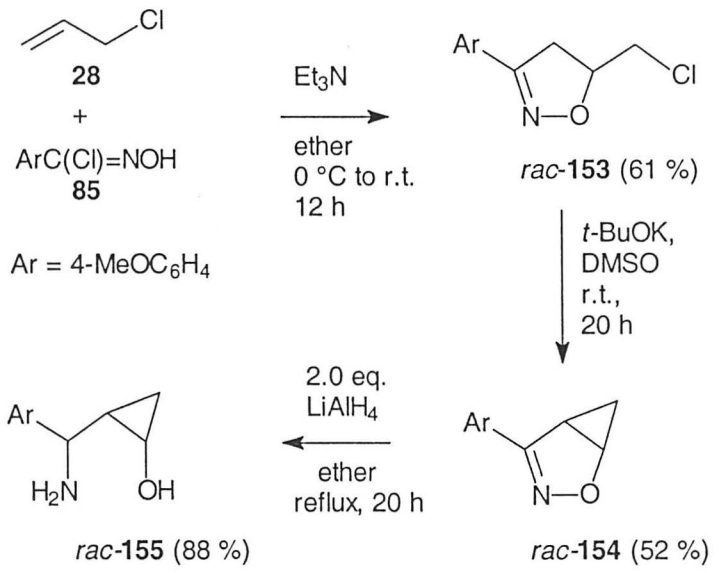
Scheme 68

Asymmetric cycloaddition provides optically active [3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**152**). The following steps, conversion into the chloride **153**[175] and base induced ring closure to bicycle **154**[176] are both reported in literature for racemic material and with Ar = phenyl. In the latter reference there are also some unsuccessful attempts described to cleave the heterocyclic ring *via* hydrogenation or by treatment with base. However complicated mixtures of products were obtained and none of the products was identified.[176]

The interesting question now was, in the absence of substituents at the cyclopropane moiety, to what extent the three-membered ring would induce diastereofacial selectivity and whether the formed cyclopropanol species would be stable under the reaction conditions that employ $LiAlH_4$ as reducing agent.

Racemic synthesis of 2-[amino(4-methoxyphenyl)methyl]cyclopropan-1-ol (155)

A racemic synthesis of the cyclopropanol **136** was carried out in order to test the reduction step and also to provide racemic compounds that could serve as standards for "chiral" HPLC analysis. The cycloaddition reaction of allyl chloride (**28**) to *N*-hydroxy-4-methoxybenzimidoyl chloride (**85**) provided direct access to chloromethylisoxazolidine **153** (**Scheme 69**). Treatment of **153** with potassium *tert*-butoxide in anhydrous dimethyl sulfoxide (DMSO) afforded the bicycle **154**. The amount of solvent (DMSO) had to be kept as low as possible to facilitate the extractive work-up (which ultimately influenced the yield). When the reaction was carried out on a bigger scale, potassium *tert*-butoxide was added in small portions under an inert atmosphere and the reaction temperature was kept below 40 °C during the addition. In the final step the bicycle **154** was subjected to reduction with $LiAlH_4$. Racemic cyclopropanol **155** was formed as a single diastereomer in 88 % yield.



Scheme 69

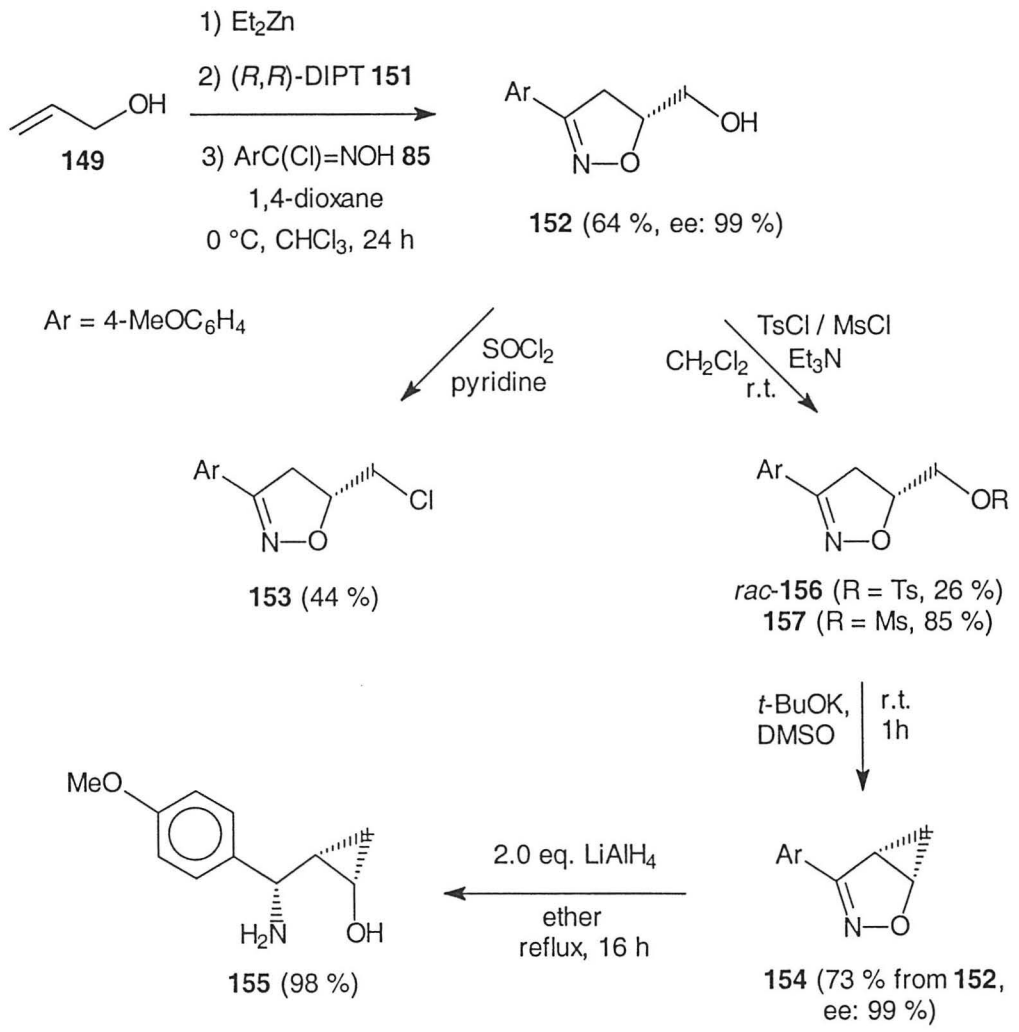
Synthesis of enantiomerically pure 2-[amino(4-methoxyphenyl)methyl]cyclopropan-1-ol (155)

Following the success of the racemic synthesis, the synthesis was repeated with enantiomerically pure starting material **152**. Enantiomerically pure [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**152**) was prepared according to Ukaji's procedure (**Scheme 67**; see also **Scheme 70**, next page).[174] Allyl alcohol (**149**) was treated with 1.2 molar amounts of diethylzinc, 0.2 molar amounts of (*R*,*R*)-DIPT, and 1.0 molar amounts of hydroximoyl chloride **85** successively in chloroform at 0 °C. When the reaction was carried out on a 2.7 mmol scale (with respect of allyl alcohol), the product **152** was isolated by extractive work-up. Purification by column chromatography on silica afforded crystalline **152** in 68 % yield with the selectivity of 97 % ee [In comparison, the original literature procedure[174] is described on a 0.5 mmol scale (with respect of allyl alcohol), purification was carried out by TLC on silica affording the isoxazoline in 98 % yield with 90 % ee].

When the procedure was repeated on a ten times larger scale (27 mmol), the work-up procedure was altered, due to the poor solubility of **152**. The reaction mixture was quenched with a few drops of saturated aqueous NH_4Cl. The mixture was filtered through a layer of anhydrous $MgSO_4$ and a clear solution (I) was obtained. Washing the filter residue four times with hot ethyl acetate gave solution (II). The solutions were concentrated (separately) and the residues recrystallised from ethyl acetate. Solution (I) yielded 14 % (80 % ee), solution (II) yielded 64 % (99 % ee) (total yield 78 %).

Even in polar solvents enantiomerically pure **152** only dissolves slowly. For the $[\alpha]_D$ analysis the solvent methanol had to be heated to dissolve the compound completely. The value of the specific optical rotation was higher than the one reported in literature; an $[\alpha]_D^{30}$ of -140° (c 0.4, MeOH) was obtained (lit. $[\alpha]_D^{25}$ = -120° (c 0.4, MeOH)). The absolute configuration of **152** is established to be *R*.[173] The optical yields were determined by direct HPLC (Daicel Chiracel OD) analysis. Racemic material of **133** was prepared as a standard for the HPLC (= reference compound) by using conventional conditions - generating the nitrile oxides with triethylamine (*rac*-**152**, 57 % yield).

Isoxazoline **152** with 97 % ee was treated with thionyl chloride and the mixture was refluxed in pyridine for 6 hours (**Scheme 70**).[175] Despite these rather harsh reaction conditions it had little effect on the stereochemistry. HPLC analysis showed an optical purity of 94 % for the formed chloromethylisoxazoline **153**. However due to the low yield of 44 %, this route was not pursued further. Other transformations like tosylation and mesylation were tested. Tosylation of racemic compound **152** was not very successful, only 26 % of the corresponding tosylate **156** were isolated. The main product (56 % yield) of this conversion, which employed toluene-4-sulfonyl chloride was found to be chloromethylisoxazoline **153**.



Scheme 70

In contrast, treatment of enantiomerically pure **152** (ee 99 %) with methanesulfonyl chloride[177] afforded the mesylate **157** as the sole product in good yield (85 % after recrystallisation). A stepwise addition of the reagent was found to be most effective. First 0.6 mol.equiv. of methanesulfonyl chloride were added at room temperature to **152**

in dichloromethane in the presence of an equimolar amount of triethylamine. The reaction mixture was stirred for 20 minutes [after the first addition starting material was detected, even when an excess (1.2 -1.5 mol.equiv.) of methanesulfonyl chloride was used in the first place]. After the second addition (further 0.6 mol.equiv. of triethylamine and methanesulfonyl chloride) and an additional 20 minutes, TLC showed full conversion. The optically active mesylate **157** gave an $[\alpha]_D^{26}$ of –137.6° (c 1.0, $CHCl_3$). In the ^1H NMR the methyl of the mesylate group gave a singlet at 3.07 ppm; in the ^{13}C NMR the same group appeared at 37.8 ppm.

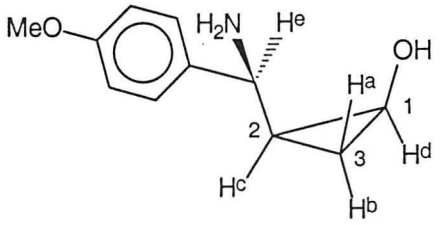
The mesylate proved to be good leaving group in the next step of the synthesis, the 1,3-elimination reaction to bicycle **154**. The reaction time of 20 hours, as used above for racemic chloromethylisoxazoline **153** is not necessarily required. The potassium *tert*-butoxide induced elimination occurred very fast and it was found that full conversion was achieved already within 1 hour. Crude mesylate **157** could be used directly for the elimination step and an overall yield of 73 % was obtained (two steps, from **152** to **154**). As the stereochemistry is fixed at C-5 of the isoxazoline ring - *R* configuration in the present case - only the product with the cyclopropane ring facing backwards can be formed (**Scheme 70**). In the newly formed molecule, 4-(4-methoxyphenyl)-2-oxa-3-aza-bicyclo[3.1.0]hex-3-ene (**154**) are now two stereocentres present, both possess the *S* configuration. HPLC analysis of **154** confirmed the unchanged optical purity of 99 % ee.

Reduction of the bicycle **154** with $LiAlH_4$ gave enantiomerically pure (1*S*,2*S*)-2-[(*S*)-amino(4-methoxyphenyl)methyl]cyclopropan-1-ol (**155**) in good yield. As already observed with the racemic compound, the reduction proceeded with 100 % diastereoselectivity. Thus the cyclopropane moiety proved to be a very effective tool in the control of the stereochemistry.

Interestingly, the sign of the optical rotation of the chiral compounds changed with the reduction step. While the bicycle **154** gave an $[\alpha]_D^{26}$ of -154.6° (c 1.0, $CHCl_3$) the cyclopropanol **155** showed an $[\alpha]_D^{18}$ of +65.5° (c 0.4, MeOH).

The NMR data of **155** are summarised in **Table 7** on the next page.

Table 7. NMR data of cyclopropanol 155



^{1}H NMR			^{13}C NMR	
atom	multiplicity	δ_H ($CDCl_3$; coupling constants in Hz)	atom	δ_C ($CDCl_3$)
H^a	dt	0.56 (*J* 3.3, 6.7)	C-3	10.6
H^b	td	0.76 (*J* 6.7, 9.2)	C-2	24.0
H^c	tdd	0.94 (*J* 6.7, 7.0, 9.2)	$CH\text{-}NH_2$	49.8
H^d	dt	3.45 (*J* 3.3, 6.7)	C-1	52.9
H^e	d	3.91 (*J* 7.0)	OCH_3	55.2
OCH_3	s	3.74	aromatic C	113.8, 127.3, 138.4, 158.5
aromatic H	m	6.81-6.85 (2H) and 7.28-7.32 (2H)		

The multiplicity of the signals, together with the size of the coupling constants and the chemical shifts allowed a complete assignment of all the protons in the ^{1}H NMR spectrum. Due to the similar size of coupling constants, the multiplicity of the signals was simplified. For example, for H^c in theory 16 lines of a "dddd" multiplicity are expected; it however appeared as a "tdd". H^c showed a coupling constant of 7.0 Hz to H^e and a J_{cis} of 9.2 Hz to H^b. The third coupling constant observed had a value of 6.7 Hz, which served as a J_{trans} in the coupling to H^a but also as a J_{cis} in the coupling to H^d. Also the other protons H^a, H^b and H^d showed 6 lines according to a "dt" instead of 8 lines for the theoretical "ddd".

In the ^{13}C NMR the signals were assigned by analogy and similarities in trends of those of other cyclopropanols, obtained in **Chapter 2.2.**

2.5. Scope of the catalytic asymmetric 1,3-DC reaction of nitrile oxides to allylic alcohols

2.5.1. Introduction

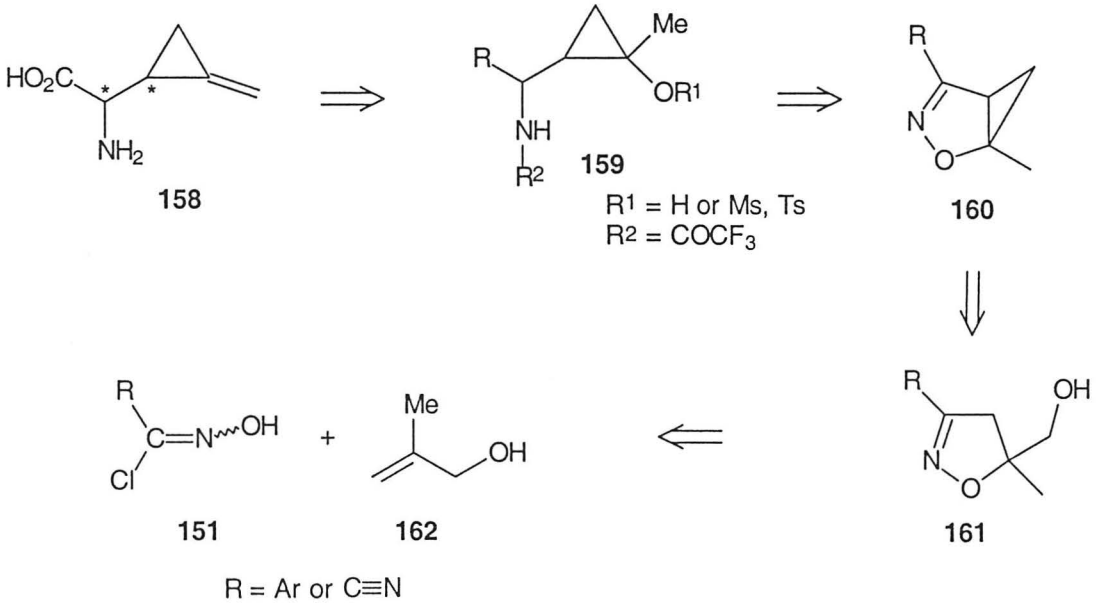
In the previous chapter the application of Ukaji's catalytic asymmetric 1,3-DC reaction was shown by synthesising a novel cyclopropanol derivative. Cyclopropanols have a high tendency to undergo ring opening reactions in the presence of heat, bases, acids or nucleophiles.[178,179] Racemic cyclopropanols bearing a substituent in the α-position (= at C-1) of the three-membered ring are now accessible in one step *via* the Kulinkovich reaction[180,181] (see also **Chapter 1.2.1**). This type of cyclopropanol is more stable than the one with a hydrogen at the α-position. Thus it can undergo transformations, both at the substituent and at the alcohol functionality without cyclopropane ring cleavage, e.g. the alcohol group was brominated using standard bromination conditions.[182] The novel cyclopropanol **155** does not bear any substituents in α-position of the cyclopropane ring. So far the reactivity of these cyclopropanols has not been investigated widely.

The question that arose was how to introduce substituents into the cyclopropane ring system for (a) reasons of stability and (b) with respect to a potential application in natural product synthesis. This was required to occur without loss of optical activity. In theory introduction of substituents can be done either in the cycloaddition step, choosing the proper allylic alcohol, or in a later stage by modifying the heterocycle formed.

For instance, a stereoselective approach to α-(methylenecyclopropyl)glycine **158** was envisioned.[183] This amino acid represents a lower homologue of hypoglycine A (see **Chapter 1.2.1.**); it had been found in the seeds of the *Sapindacea* family[19] and exhibited a significant biological activity by causing hypoglycaemic symptoms in mice and rats.[184] So far **158** had only been prepared in its racemic form. The proposed retrosynthetic route is outlined in **Scheme 71**.

Exomethylene groups are known to be formed *via* elimination reactions of tosylates or mesylates.[149] The acid function in **158** should be accessible by oxidation of the aromatic ring system - if the R group in **159** is aryl. Alternatively, in case R is a nitrile functionality the acid should be obtained by hydrolysis. The cyclopropanol species **159** (R^1 = H) should be available from **161** by the ring closure and reduction

sequence that was applied in the previous chapter. Isoxazoline **161** itself should be built up stereoselectively by an asymmetric 1,3-DC reaction of a nitrile oxide (derived from the precursor **151**) and the methyl substituted allyl alcohol **162**.



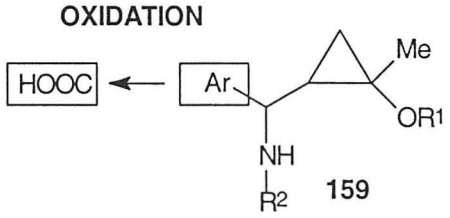
Scheme 71

However Ukaji's asymmetric 1,3-DC reaction was originally only described for allyl alcohol.[173] In order to prepare a variety of substituted isoxazolines enantiomerically pure, a range of different substituted allylic alcohols was tested in the asymmetric 1,3-DC reaction. This will form the main part of the following discussion.

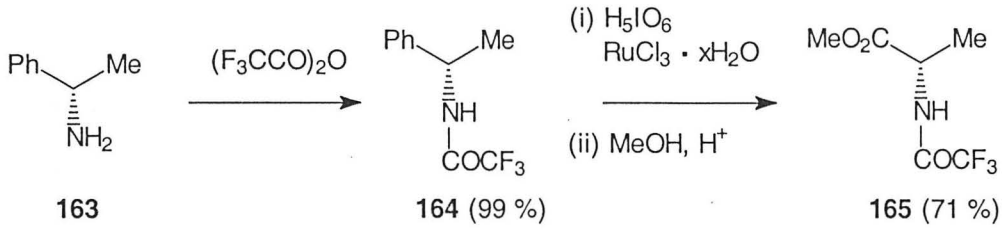
2.5.2. Discussion

2.5.2.1. Oxidation of the model compound (*S*)-(-)-α-methylbenzylamine

A preliminary experiment was carried out to prove the practicability of the oxidation step (**159** to **158**) in the proposed retrosynthesis of α-(methylenecyclopropyl)glycine **158** (R = aryl, **Scheme 71**),



(*S*)-(-)-α-Methylbenzylamine (**163**) served as model compound in this oxidation of an aromatic ring system to an acid. The right choice of the protecting group on the amine is vital for the success of the oxidation as was demonstrated in the total synthesis of 3,4-methanoproline. [185] The amine **163** was protected by trifluoroacetylation to give **164**[186] in quantitative yield (**Scheme 72**).



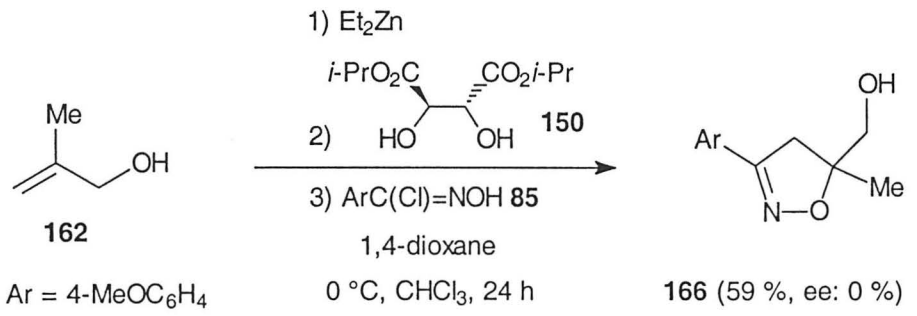
Scheme 72

The phenyl group of **164** was then successfully oxidised with ruthenium trichloride hydrate in the presence of periodic acid.[187] The crude acid was directly converted into its methyl ester **165**[188] that was isolated in 71 % yield. The transformation occurred without loss of optical purity, the analytical data corresponded with those of the literature.[189]

Next, attention was turned to the other part of the retrosynthesis, the 1,3-dipolar cycloaddition step.

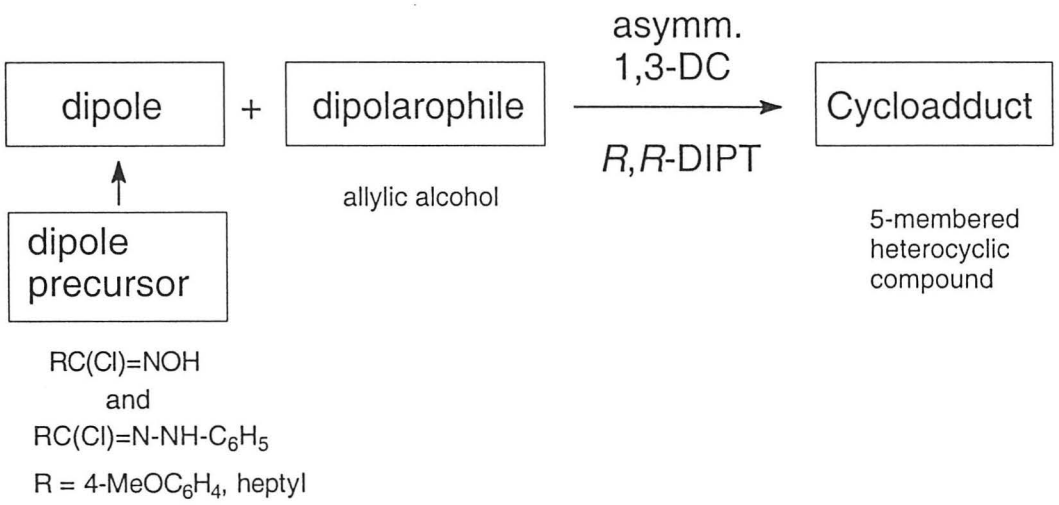
2.5.2.2. Introduction of substituents by 1,3-DC reactions

2-Methyl-2-propen-1-ol (**162**) was subjected to a catalytic asymmetric 1,3-DC reaction, applying conditions identical to those described in the previous chapter for allyl alcohol (**Scheme 73**). The cycloadduct **166** was obtained in 59 % yield. Its optical purity was determined by direct HPLC analysis (Daicel Chiracel OD) but disappointingly both enantiomers were found to be present in equal ratio (= 0 % ee).



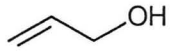
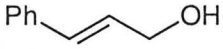
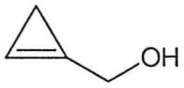
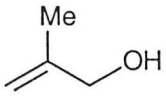
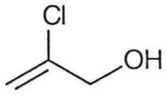
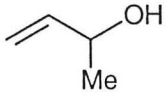
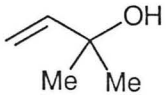
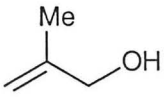
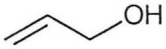
Scheme 73

Due to this negative result, synthesis of optical active amino acid **158** was no longer pursued. The scope of the catalytic asymmetric 1,3-DC reaction was investigated instead. A range of allylic alcohols was tested; two nitrile oxide precursors (R = 4-$MeOC_6H_4$/heptyl) and one nitrile imine precursor were employed; see general **Scheme 74**. The results of those cycloaddition reactions are summarised in **Table 8**.



Scheme 74

Table 8. 1,3-DC reactions of nitrile oxides/imines to allylic alcohols

allylic alcohol	cyclo -add.	% yield racemic. cycloadd.	asymmetric 1,3-DC				
			entry	T °C	% yield	% ee	comments
dipole precursor 4-$MeOC_6H_4C(Cl)=NOH$ (**85**)							
 **149**	**152**	57	1 2 3 4	0 0 r.t. -70	68 64 76 95	97 99 93 79	2.7 mmol scale 27 mmol scale
 **167**	**168**	80	5	0	56	0	
 **169**	**170/ 171**	48	6	-65	56	0	
 **172**	**173**	75	7	0	22	22	
 **162**	**166**	77	8* 9 10* 11*	0 -70 0 0	59 73 12 62	0 0 0 5	1.0 mol.eq. DIPT stoichiometry altered
 **174**	**176**	51	12	0	33	-	
 **177**	**179a**	80	13	0	60	8/10	
 **180**	**181**	79	14	0	49	0	
dipole precursor $CH_3(CH_2)_6C(Cl)=N\text{-}OH$ (**182**)							
 **162**	**183**	18	15	0	56	11	
dipole precursor 4-$MeOC_6H_4C(Cl)=N\text{-}NH\text{-}C_6H_5$ (**189**)							
 **149**	**190**	86	16	0	11	0	

*....see **Table 9**

General comments to Table 8

The order in **Table 8** is (a) according to the dipole precursors employed and (b) follows the substitution pattern of the allylic alcohols: unsubstituted alcohols first, followed by terminal substituted allylic alcohols, then alcohols with substituents in C-2 and C-1 position.

Asymmetric 1,3-DC conditions according to Ukaji *et al.* were applied[174](1.0 mol.equiv. allylic alcohol, 1.2 mol.equiv. Et_2Zn, 0.2 mol.equiv. *R,R*-DIPT, 1.0 mol.equiv. nitrile oxide precursor, 1.5 mol.equiv. 1,4-dioxane; 24 hours at 0 °C in $CHCl_3$; this method is referred later in this chapter simply as "chiral method"; any modifications are discussed in detail below.

R,R-Diisopropyl tartrate (*R,R*-DIPT) was employed in catalytic amounts (0.2 mol.equiv.) with the exception of entries 10 and 11 (for details see **Table 9** below).

Additionally all compounds were prepared under racemic conditions - generation of the dipole with triethylamine (referred later as "racemic method"). The yields of those reactions are given in the 3rd column of **Table 8**. The cycloadducts prepared in this manner served as reference compounds in the "chiral" HPLC analysis.

All yields and enantiomeric excesses given are after purification; compounds prepared by the racemic method were purified by recrystallisation, the cycloadducts obtained by the chiral method were usually purified by column chromatography on silica.

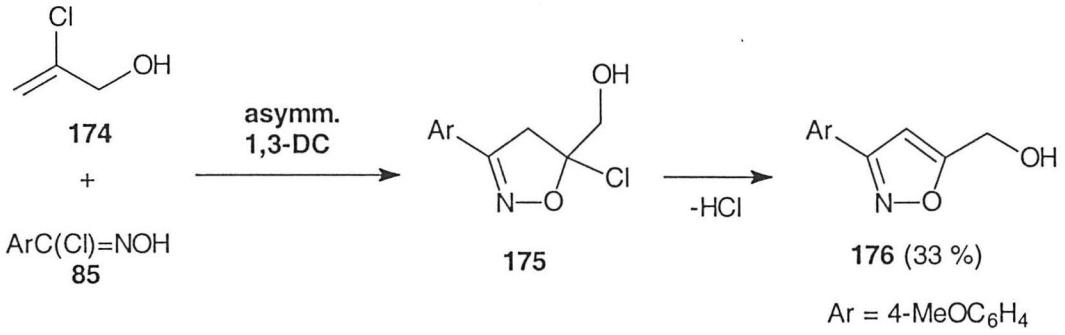
For all compounds the optical yields were determined by direct HPLC analysis (Daicel Chiracel OD) with exception of entry 15 where the cycloadduct was analysed as its benzoate derivative; the HPLC retention times are summarised in **Table 17** in the **Appendix**.

With exception of the parent isoxazoline **152**, all other cycloadducts were new compounds and were therefore fully characterised. However, for most cases the literature describes closely related compounds, i.e. instead of the 4-methoxyphenyl group the compounds are bearing, e.g. a phenyl group at C-3.

Optical yields of the cycloaddition reactions

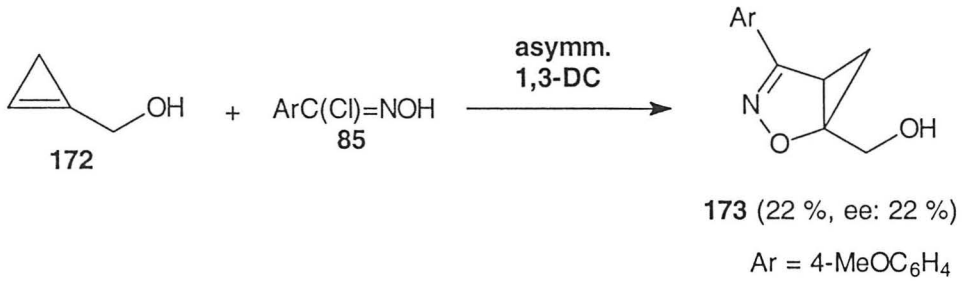
In strong contrast to the parent allyl alcohol none of the tested allylic alcohols gave isoxazolines that exhibited any considerable enantiomeric excess. Most products were optically inactive; among them were products derived from 3-buten-1-ol (homoallyl alcohol) (**167**; entry 5), (*E*)-cinnamyl alcohol (**169**; entry 6), 2-methyl-3-buten-2-ol (**180**; entry 14), and the already mentioned 2-methyl-2-propen-1-ol (**162**; entries 8-10).

2-Chloro-2-propen-1-ol (**174**) did not afford any chiral cycloadduct, only the aromatic isoxazole **176** was isolated (entry 12). The racemic method provided the same product.[176] The isoxazole is formed from the unstable isoxazoline **175** by hydrogen chloride elimination (**Scheme 75**). The ^{1}H NMR gave a signal for the aromatic proton at 6.45 ppm and in the absence of a chiral centre the $C\underline{H}_2OH$ appeared as a singlet at 4.74 ppm.



Scheme 75

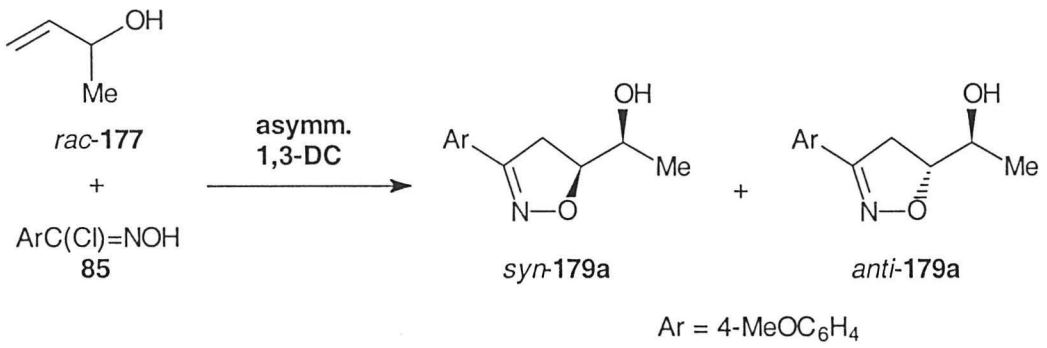
Only a few cycloadducts showed a small differentiation in the enantiomeric ratio. The "highest" value was obtained for cyclopropenemethanol (**172**)[190] with disappointingly 22 % ee, which corresponds to an enantiomeric ratio of 61:39 (entry 7; **Scheme 76**).



Scheme 76

In addition the chemical yield was only 22 %. Cyclopropenemethanol (**172**) had been prepared prior to the cycloaddition by treatment of (1,2,2-tribromocyclopropyl)methanol with methyllithium according to literature.[190] By applying this cyclopropene derivative in the cycloaddition reaction, a 2-oxa-3-azabicyclo[3.1.0]-hex-3-ene system is formed directly (the cyclopropane moiety is formed in the cycloaddition step, contrary to above where ring closure to the cyclopropane was achieved by elimination of a mesylate group; compare also the cycloaddition reactions in **Chapter 2.2.2.**).

The asymmetric cycloaddition reaction of racemic 3-buten-2-ol (**177**) was more complex because it additionally gave rise to two diastereomers, *syn* and *anti* **179a** in ratio 69:31, in favour of the *syn* isomer (entry 13; **Scheme 77**). Both diastereomers could be separated by column chromatography on silica and were fully characterised. The *anti* isomer exhibited an enantiomeric excess of 10 %, while the *syn* isomer gave 8 % ee. The product **179a** will be mentioned again in **Chapter 2.6.** where it was obtained by an alternative route.



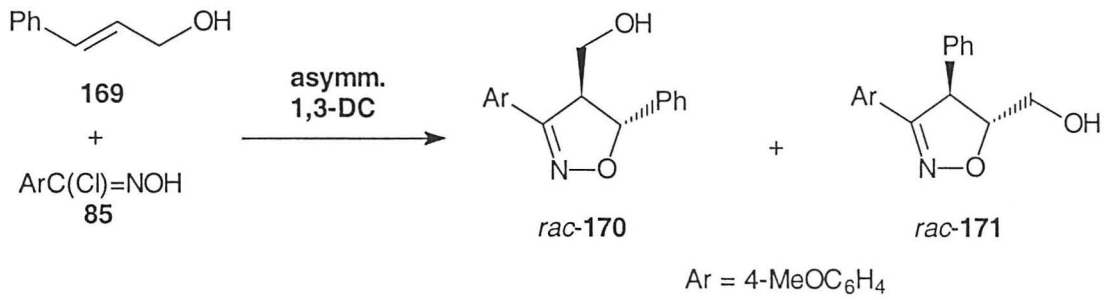
Scheme 77

Modification of reaction conditions - temperature alterations

The catalytic asymmetric 1,3-DC reaction of allyl alcohol (**149**) with nitrile oxide **77** (derived from precursor **85**) was repeated using different temperature conditions. Carrying out the reaction at -70 °C for 24 hours increased the chemical yield of cycloadduct **152** to 95 %; the enantiomeric excess however dropped to 79 % ee (entry 4). The reaction run at room temperature did have a much smaller effect on the stereoselectivity, an optical yield of 93 % was achieved (with a chemical yield of 76 %; entry 3).

In the reaction of 2-methyl-2-propen-1-ol (**162**), low temperature had the same positive effect on the chemical yield, now 74 % compared with 56 % for the same reaction at 0 °C, however again no asymmetric induction was observed (entry 9).

In case of (*E*)-cinnamyl alcohol (**169**) the reaction was only carried out at low temperature (-65 °C) and it gave rise to two regioisomers, 4-substituted isoxazole **170** and 5-substituted **171** in ratio 67:33 (entry 6 and **Scheme 78**). The two isomers were not separable by column chromatography, and they were isolated in a combined yield of 56 %. Neither of the regioisomers showed any enantiomeric excess. In comparison, the racemic method provided a similar isomeric ratio in comparable yield. As the allylic alcohol was used in its *E* form, all the products were obtained as 4,5-*trans*-2-isoxazolines. The outcome of the asymmetric cycloaddition with respect to regioselectivity was not surprisingly. Kanemasa *et al.* already had demonstrated the poor regioselectivity in the cycloaddition of nitrile oxides generated by reagents such as *n*-butyllithium, triethylaluminium and diethylzinc.[171] In contrast they achieved total regiocontrol by using alkyl- or alkoxymagnesium bromide. The observed analytical data of **170** and **171** were in complete agreement with the analogous compounds (R = Ph), reported by above authors.[170]

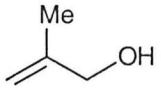


Scheme 78

Modification of reaction conditions - alterations of stoichiometry (see also entries 10 and 11 of Table 8)

The asymmetric 1,3-DC reaction of nitrile oxide **77** (derived from precursor **85**) to 2-methyl-2-propen-1-ol (**162**) was repeated using altered stoichiometric conditions as outlined in **Table 9**. The first entry of **Table 9** represents the molar amounts in the standard catalytic asymmetric 1,3-DC reaction. Entry 2 of **Table 9** corresponds to the reaction in which DIPT is employed as a chiral auxiliary.[173] Both reactions did not give any enantiomeric excess. In another attempt (entry 3 of **Table 9**) all the reagents with the exception of allylic alcohol were used in a threefold excess in comparison with the standard procedure in entry 1. However this change in stoichiometry did not have much impact on the enantioselectivity, and only 5 % ee was detected.

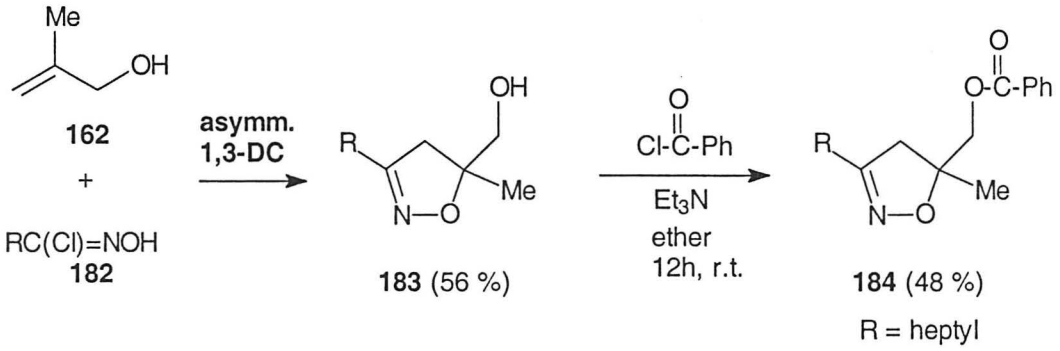
Table 9

entry		ArC(Cl)=NOH	Et_2Zn	DIPT	Dioxane	% ee of **166**
1	1.0	1.0	1.2	0.2	1.5	0
2	1.0	1.1	2 × 1.1	1.0	-	0
3	1.0	3	3	0.6	4.5	5

Modification of dipole - application of an aliphatic nitrile oxide

Rather than relying on the results of one type of nitrile oxide (precursor) - so far an aromatic species had been used - an alkyl nitrile oxide (precursor) was tested too. The precursor hydroximoyl chloride **182** (R = heptyl) was prepared from the oxime[191] using standard methods,[107] which in its turn was prepared from commercially available octanal. Ukaji *et al.* reported the successful application of this nitrile oxide precursor in the catalytic asymmetric 1,3-DC reaction to allyl alcohol.[174] Hence the reaction with allyl alcohol was not carried out and the substituted allyl alcohol **162** was chosen to be tested directly instead. The chiral method afforded the cycloadduct **183** in 56 % yield (entry 15 of **Table 8**, and **Scheme 79** below) while the racemic method yielded 18 % only. Generally the racemic method provided better yields than its chiral analogue. A possible explanation for the opposite outcome in this specific case might be in the stability of the starting material **182**: in the chiral method freshly prepared hydroximoyl

chloride **182** was used while for the racemic method the precursor had been stored for several weeks in a freezer.

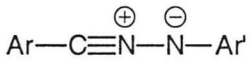


Scheme 79

The optical yield of the isoxazoline **183** was determined indirectly by HPLC analysis of its benzoate derivative **184**. The aromatic group was introduced in the system to get a good UV-detection in the HPLC analysis. The enantiomeric excess found did not exceed 11 %.

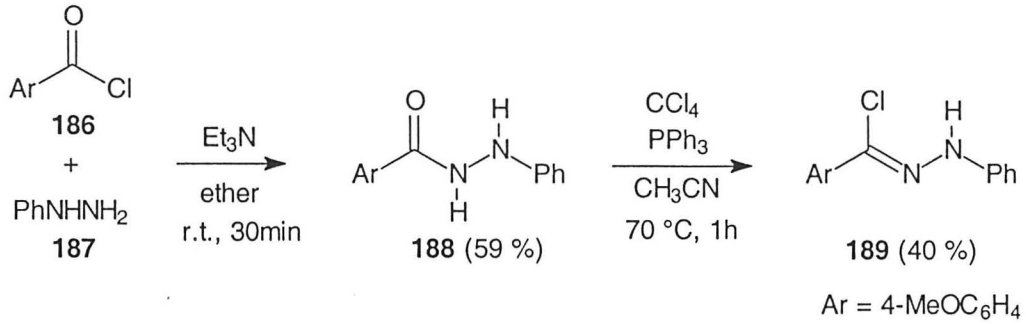
Modification of dipole - application of an nitrile imine

So far the asymmetric 1,3-DC reaction of nitrile oxides to allylic alcohols has been described. As already mentioned earlier, Ukaji *et al.* had extended their method successfully to the 1,3-DC reaction of nitrones to allyl alcohol.[198] Now it was decided to test the method on a different dipole system - a nitrile imine.



As with the nitrile oxide, this dipole is of the propargyl/allenyl type and is linear. The 1,3-DC reaction of nitrile imines with alkenes leads to the formation of 2-pyrazolines. Only very few studies have been performed in the field of asymmetric 1,3-DC reactions involving nitrile imines.[134] Bis(trityl)nitrile imine, e.g. was found to undergo a diastereoselective 1,3-DC reaction with a chiral alkene and a 2-pyrazoline was formed with a diastereomeric excess of 50 %.[192]

First the preparation of the nitrile imine precursor shall be discussed briefly (**Scheme 80**).

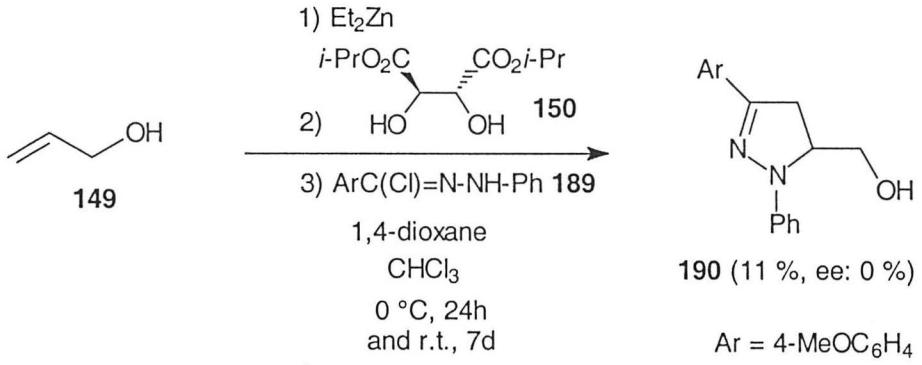


Scheme 80

Commercially available *p*-anisoyl chloride (**186**) was treated with phenylhydrazine (**187**) in ether in the presence of triethylamine.[193] The corresponding 1-(4-methoxybenzoyl)-2-phenylhydrazine (**188**) was obtained in 59 % yield. For the second step, the conversion of **188** to the nitrile imine precursor **189,** two methods are known. The older method by Pechmann and Seeberger from 1894 uses phosphorus pentachloride followed by 3 mol.equiv. of phenol.[194] To make it applicable for bigger scale reactions the procedure was slightly modified by Huisgen *et al.* in 1962.[104] The second method by Wolkoff from 1975 employs triphenylphosphine and carbon tetrachloride in acetonitrile.[195] In the original procedure the reaction is carried out at

room temperature for 6 hours. Under those conditions however no conversion at all was observed for **188**. Consequently the reaction temperature was raised to 70 °C and now within 1 hour no starting material was left. The reaction was cooled, crystallisation was initiated by scratching and the product, hydrazonyl chloride **189**[196,197] was simply filtered off. Recrystallisation afforded **189** in 40 % yield. The low yield was due to the fact that not all of **189** was isolated; additional product was present as a mixture together with triphenylphosphonium oxide.

Treatment of **189** with triethylamine (racemic method) or diethylzinc (chiral method) generated *in situ* the nitrile imine, which underwent cycloaddition with allyl alcohol. While the racemic method gave the heterocycle **190** in 86 % yield, the chiral method only afforded 11 % despite a prolonged reaction time (entry 16 of **Table 8**, and **Scheme 81**). In the latter case no asymmetric induction was observed. Perhaps the chiral method would need an additional activation by a Lewis acid as applied in the asymmetric 1,3-DC reaction of nitrones.[198]



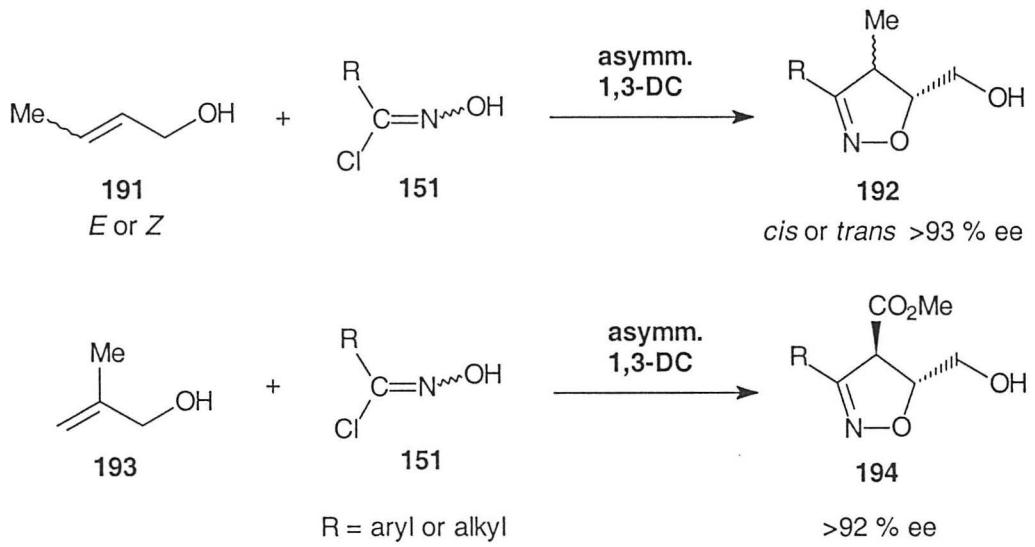
Scheme 81

2.5.3. Conclusion

The scope of the catalytic asymmetric 1,3-dipolar cycloaddition reaction of nitrile oxides to allylic alcohols was investigated. A wide range of alcohols was tested. Only poor enantioselectivities were obtained or in many cases no enantiomeric excess at all was observed. Modification of reaction conditions such as temperature and stoichiometry proved to have little effect upon the enantiomeric excess. Thus this method suffers strong limitations regarding substituents at the allylic alcohol system.

Ukaji's asymmetric 1,3-DC reaction was originally only described for allyl alcohol.[174] Very recently however, the same author reported an extension of his own work by applying dipolarophiles such as (*E*)- and (*Z*)-2-buten-1-ol (**191**) and ethyl (*E*)-4-hydroxy-2-butenoate (**193**) in the cycloaddition (**Scheme 82**).[199] This publication was not available when the experimental work was carried out that is described in this chapter. In both cases (*R,R*)-DIPT was used as chiral auxiliary, i.e. stoichiometric amounts of DIPT, and the cycloadducts were obtained with high optical yields (> 92 %). The catalytic asymmetric 1,3-DC reaction of alcohol **193**, which employed 0.2 mol.equiv. of DIPT, still afforded **194** with an enantiomeric excess of 84 %.

These results are not in contrast to the work carried out in this thesis, because those allylic alcohols were not tested. It suggests that only a few selected examples are efficient substrates, presumably only allylic alcohols with substituents in the terminal alkene position.



Scheme 82

2.6. Introduction of substituents by transformations of the isoxazoline system without ring cleavage or by transformations of the side chain

2.6.1. Introduction

1,3-DC reactions of nitrile oxides to allyl alcohol provided a range of different substituted isoxazoline derivatives. However with exception of the parent isoxazolinylmethanol **152** none of the cycloadducts could be obtained in enantiomerically pure form. The idea was therefore to introduce substituents after the cycloaddition step by transforming the optically active parent heterocycle. This needed be done without cleaving the isoxazoline ring.

Transformations at C-4 of the heterocycle and at the side chain (**Figure 9**) have been reported in literature.[130] The only reaction that is known to take place at C-5 of the isoxazoline and at the same time keeps the ring system intact, is the aromatisation to isoxazole.[200]

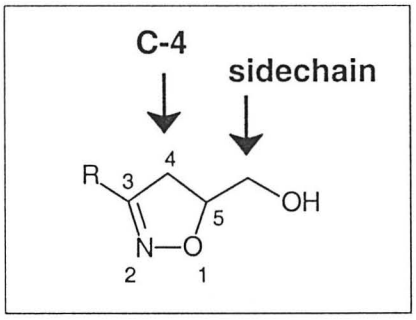
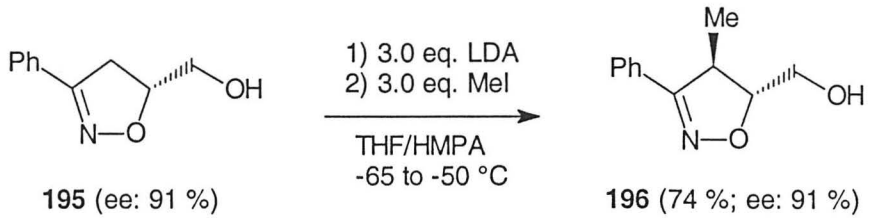


Figure 9

Transformation at C-4 of isoxazoline

Isoxazolines with an hydroxymethyl group at C-5 can be substituted regio- and stereoselectively at C-4. In most cases the alcohol function is protected as a silyl ether or as an actetal. A strong base removes the proton at C-4 to form the carbanion, which is trapped with reagents such as methyl iodide or methyl chloroformate.[201] For deprotonation usually lithium diisopropylamide (LDA) is used.[136] The reaction is normally carried out in THF, quite often in the presence of HMPA. To avoid ring cleavage the reaction temperature has to be kept below -60 °C. Alkylation of the isoxazoline occurs *anti* to the C-5 substituent and provides the product as a single

diastereomer.[136] In many cases the isoxazolines are used in their racemic form, however in a recent publication by Ukaji *et al.* methylation is described for the optical active (*R*)-isoxazolinylmethanol **195** (**Scheme 83**).[199] As the alcohol function was not protected, the reagents were used in a threefold excess. The reaction proceeded with complete diastereoselectivity and **196** was obtained in 74 % yield.



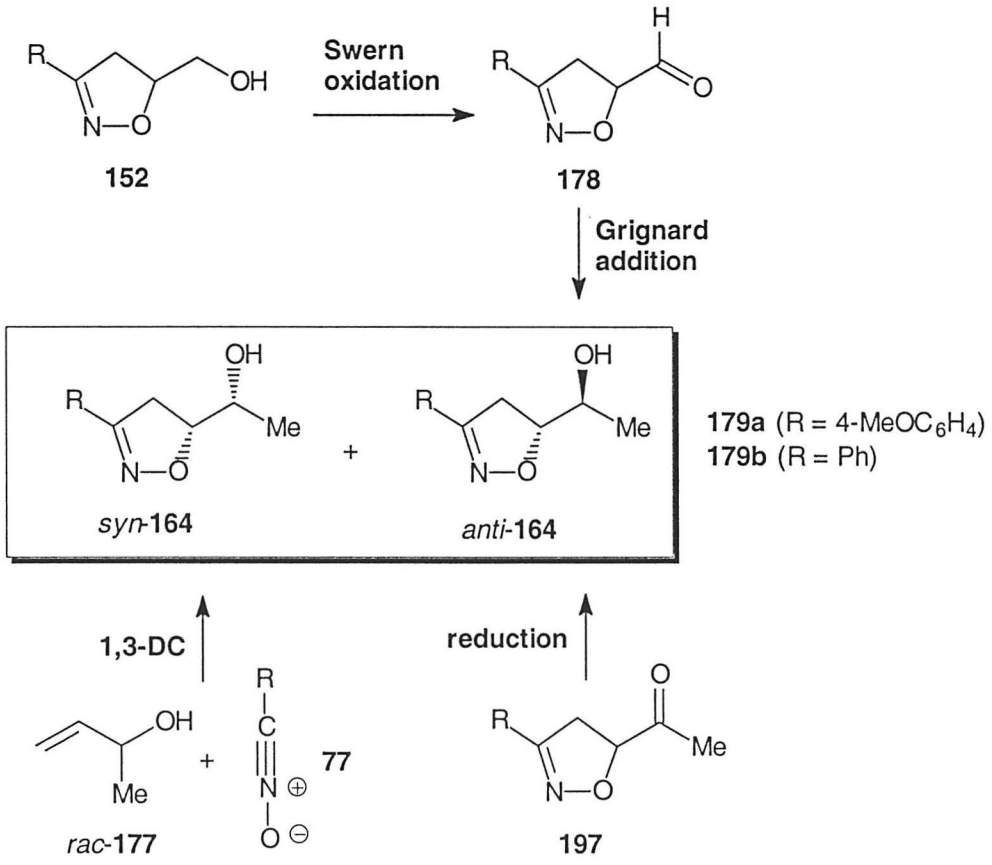
Scheme 83

Transformation of the side chain of isoxazolines

Curran *et al.* described the transformation of the side chain of racemic isoxazolinylmethanols in detail.[130] In order to introduce alkyl substituents they applied an Ireland Norbeck procedure.[202] Swern oxidation of the alcohol function in **152** generated the aldehyde **178** (**Scheme 84**, next page). This aldehyde decomposed readily if isolated. Therefore after the oxidation but prior to any work-up the mixture was treated with a five-fold excess of Grignard reagent. In case of R = Ph and using methylmagnesium bromide they obtained the corresponding racemic *syn* and *anti* isoxazoline **179b** in 60 % yield with a *syn/anti* ratio of 17:83. The best results gave an isoxazoline with a *tert*-butyl group at C-3 and by using cyclohexyl-magnesium chloride as Grignard reagent. A *syn/anti* ratio of 4:96 was achieved.

The *syn/anti* isoxazoline **179** can also be prepared by alternative methods. For example diastereoselective reduction of 5-acyl-2-isoxazoline **197** gave the product, however with reversed *syn/anti* ratio. L-Selectride was found to be the most effective reducing agent and in case of **179b** (R = Ph) a *syn/anti* ratio of 98:2 is reported. 5-Acyl-2-isoxazoline **197** in its turn is readily available by 1,3-DC reactions of nitrile oxides to α,β-unsaturated ketones.

The third strategy was the already discussed 1,3-DC reaction of a nitrile oxide to 3-buten-2-ol (see **Chapter 2.5.2.**; R = 4-$MeOC_6H_4$).



Scheme 84

2.6.2. Discussion

To obtain compounds complementary to the ones prepared *via* the 1,3-DC reaction of nitrile oxide **77** (R = 4-$MeOC_6H_4$) to 3-buten-2-ol (**177**), the above described strategy *via* Swern oxidation/Grignard addition was applied to enantiomerically pure [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**152**). After the first step, the oxidation under standard Swern conditions, and prior to the addition of the Grignard reagent, the procedure by Curran *et al.*[130] quotes: "the reaction mixture was warmed *briefly* to 25 °C and was then cooled to -78 °C". It has to be noted here that it is important to monitor the progress of reaction at this point - to control by TLC whether there is any starting material left; this can result in stirring at 25 °C for one hour if necessary. Longer reaction times should be avoided due to the instability of the formed aldehyde **178**. After the addition of five mol.equiv. of methylmagnesium bromide the isoxazoline **179a** (R = 4-$MeOC_6H_4$) was obtained in 48 % yield as a mixture of diastereomers (*syn*/anti-**179a**). The diastereomers were not

separated by column chromatography. The diastereoselectivity was slightly smaller than the one observed for the analogous racemic compound **179b** (R = Ph), reported in literature:[74] a *syn/anti* ratio of 23:77 was observed, compared with the 17:83 ratio from literature.

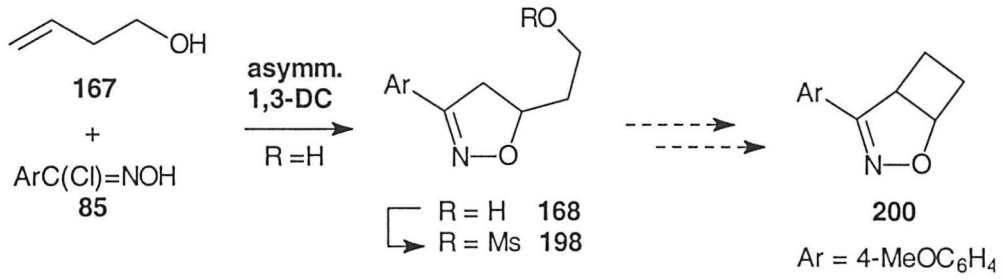
In the ^{1}H NMR spectrum the proton at the stereocentre of the side chain is the one that exhibits the biggest chemical shift difference between the two isomers: in the *syn* isomer the signal is at 3.76 ppm while in the *anti* isomer the signal is at 4.09 ppm. The characteristic methyl group appears as a doublet, with signals at 1.26 ppm for the *syn* and at 1.19 ppm for the *anti* isomer. The *syn/anti* assignment of **179a** was based on the ^{1}H NMR data by comparing them with those of compound **179b**.[74]

The analytical data for **179a**, obtained *via* this route were identical to the one obtained by the cycloadditive route. The difference in the two routes lies in the *syn/anti* ratios and in the optical purity of the products. The asymmetric 1,3-DC reaction of nitrile oxide **77** to 3-buten-2-ol (**177**) described in the previous chapter had afforded the opposite *syn/anti* ratio (69:31). The isomers had been obtained with extremely low optical yields (10 % ee each) while the complementary route could employ enantiomerically pure starting material and both diastereomers were now optical active. The stereocentre at C-5 of the isoxazoline **179a** is fixed with *R* configuration, consequently the newly formed stereocentres in the side chain showed *R* configuration for the *syn* isomer and *S* configuration for the *anti* isomer.

2.7. Attempted preparation of 4-(4-methoxyphenyl)-2-oxa-3-aza-bicyclo[3.2.0]hept-3-ene

2.7.1. Introduction

The asymmetric 1,3-DC reaction of nitrile oxide **77** to homoallyl alcohol (**167**) (**Scheme 85**) was discussed in **Chapter 2.5.2.**; it failed to give any asymmetric induction.



Scheme 85

Racemic isoxazolinylethanol **168** was taken further to its mesylate derivative **198.** Upon treatment with a strong base, the analogous, one CH_2 unit shorter isoxazolinylmethyl mesylate **157** had formed an 2-oxa-3-azabicyclo[3.1.0]hex-3-ene system *via* an 1,3-elimination. In order to extend the methodology, the preparation of 4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.2.0]hept-3-ene (**200**) was attempted *via* an 1,4-elimination from isoxazolinylethyl mesylate (**198**).

The preparation of this type of bicycle was reported by Bianchi *et al.* in 1970.[203] They achieved the synthesis by a direct 1,3-DC reaction of a nitrile oxide to cyclobutene. Alternatively they prepared the bicycle (Ar = Ph, 4-BrB_6H_4, 3-$NO_2C_6H_4$) by selective hydrogenation from a 2-oxa-3-azabicyclo[3.2.0]hep-3,6-diene. This latter system in turn was prepared from cyclooctatetraene by a reaction sequence that involved two cycloaddition reactions and a thermal decomposition.[203]

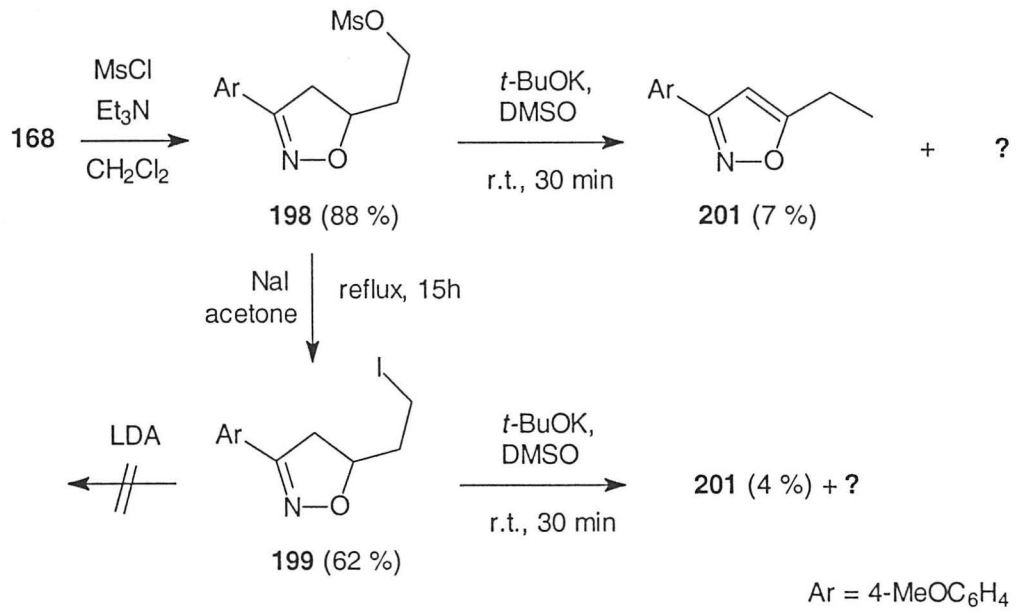
2.7.2. Discussion

The mesylate **198** was prepared by applying the same condition, which had been used in **Chapter 2.4.** for an analogous system. It was isolated in 88 % yield. In a first

attempt the mesylate was treated with potassium *tert*-butoxide in anhydrous dimethyl sulfoxide (DMSO) (**Scheme 86**). Extractive work-up gave an unidentified mixture, which showed a complex ^{1}H NMR spectrum. Purification by column chromatography afforded several fractions. Traces of isoxazolinylmethanol, formed by hydrolysis of the mesylate, were found in the last fraction. The first fraction, a colourless oil gave a clean ^{1}H NMR spectrum, thus it could be identified as 5-ethyl-3-(4-methoxyphenyl)isoxazole (**201**). Beside the signals for the 4-methoxyphenyl group, the ^{1}H NMR spectrum showed a singlet at 6.21 ppm for the isoxazole proton, a triplet at 1.31 ppm for the methyl group and a quartet at 2.79 ppm for the CH_2 group. Isoxazole **201** was present only as a minor component in 7 %, none of the other fraction was identified. There was no evidence that the bicycle **200** was formed in this reaction.

To exclude hydrolysis of the mesylate as a possible side reaction, the mesylate was then converted into the iodide **199** under Finkelstein conditions.[204] When the iodide was subjected to the same conditions as above, potassium *tert*-butoxide in anhydrous DMSO, the outcome of this reaction was comparable. A mixture of products was obtained. After separation by column chromatography only **201** could be identified as minor product in 4 % yield.

In a final attempt the iodide was treated with 2 mol.equiv. of LDA at low temperature. A yellow oil was obtained, which gave a complicated ^{1}H NMR spectrum. No product was isolated or identified.

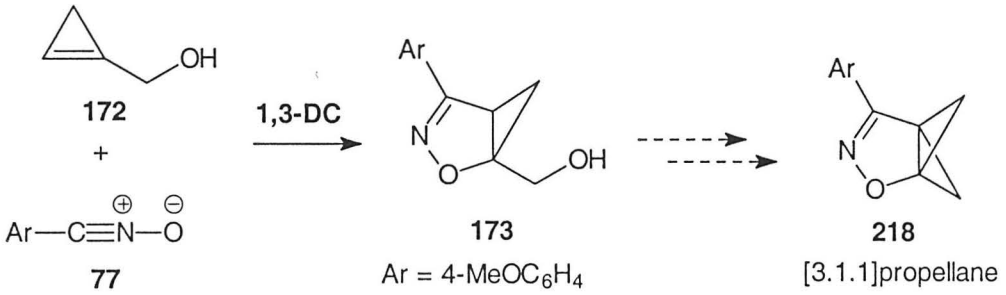


Scheme 86

2.8. Attempted synthesis of a [3.1.1]propellane.[205]

2.8.1. Introduction

The 1,3-DC reaction of 4-methoxybenzonitrile oxide (**77**) to cyclopropene-methanol **172** had provided the bicycle **173**. This compound was thought to be a potential precursor to a [3.1.1]propellane system (**Scheme 87**). Small ring propellanes are highly strained hydrocarbons and they have attracted much attention over the past 20 years.

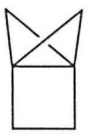


Scheme 87

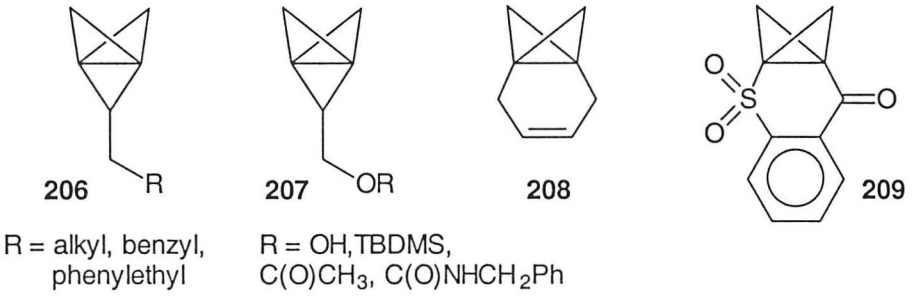
Small ring [n.1.1]propellanes

Propellanes are tricyclic systems, in which three rings are conjoined in a single carbon-carbon bond. The definition of propellanes disregards that conjoining bond and merely gives the additional number of atoms forming a particular ring. If there are two cyclopropane rings present the compound is named [n.1.1]propellane. The third ring is of ring size n + 2; in this introduction only numbers of n = 1 to 4 are considered. The parent systems are shown in **Table 10**.

Table 10. Parent [n.1.1]propellanes

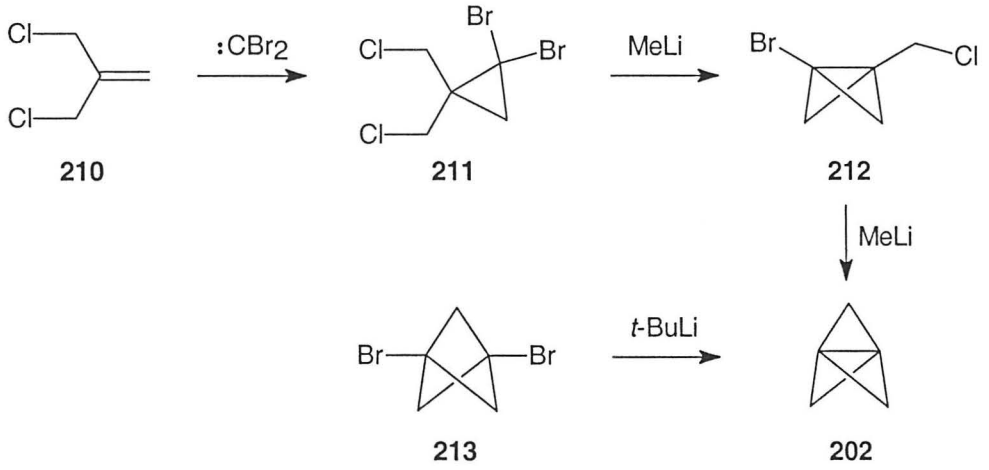
n 1	2	3	4
			
202[206]	**203**[207]	**204**[208]	**205**[209]

The smallest possible system is the [1.1.1]propellane (**202**). It is among the most highly strained hydrocarbons known. The strain of the propellane systems has consequences upon their reactivity and stability. Many small ring propellanes are unstable at room temperature; in some cases they could be isolated only in a nitrogen matrix at low temperature. However there are also stable [n.1.1]propellanes known, for example alkyl substituted [1.1.1]propellanes **206**,[210] derivatives of hydroxymethyl-[1.1.1]propellane **207**,[211] [4.1.1]propell-3-ene (**208**)[212] and [4.1.1]propellane **209**.[213] The latter is a crystalline solid with a m.p. of 181-182 °C.



Synthesis of small ring [n.1.1]propellanes[214]

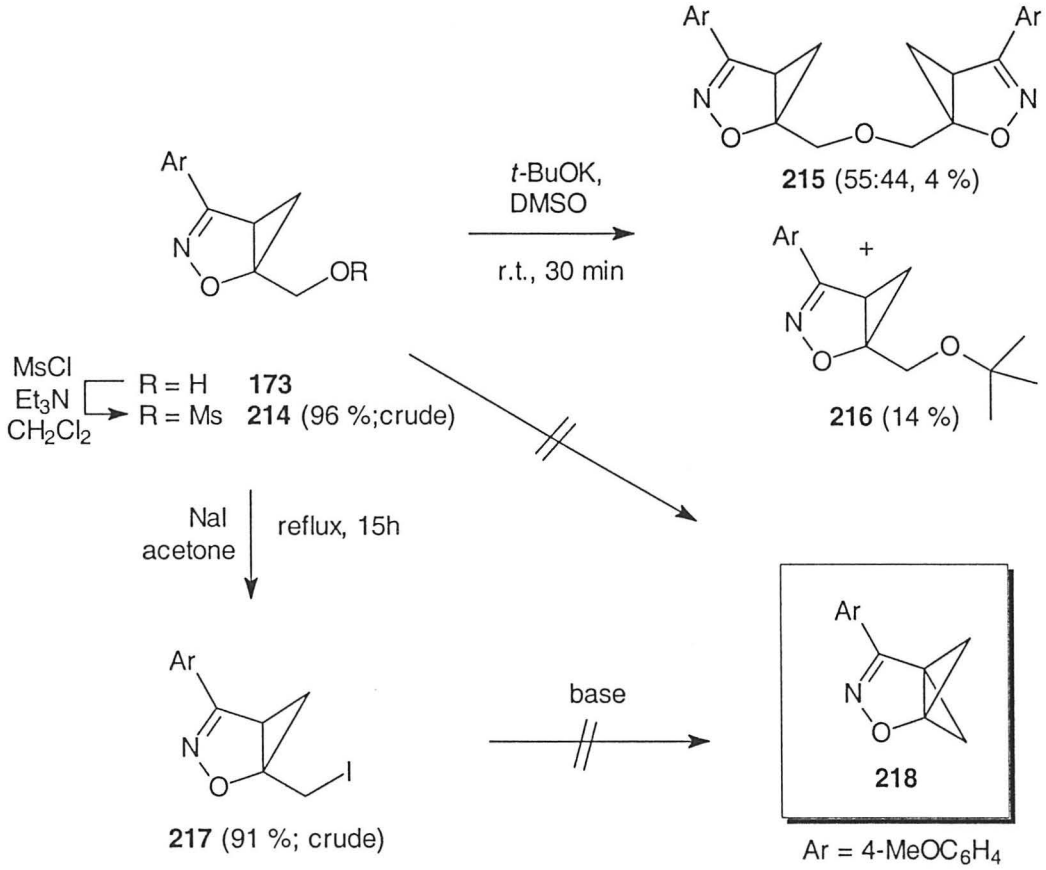
The most convenient method for the preparation of [n.1.1]propellanes is outlined on the example of the [1.1.1] species (**202**) (**Scheme 88**). It involves dibromocarbene addition to 3-chloro-2-chloromethylprop-1-ene (**210**) followed by 1,3-debromochlorinations of the resulting 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (**211**).[214] In an alternative approach the central carbon-carbon bond is formed in the last step.



Scheme 88

2.8.2. Discussion

Racemic [4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methan-ol (**173**) had been prepared by the 1,3-DC reaction of 4-methoxybenzonitrile oxide **77** to cyclopropenemethanol in 74 % yield. The bicycle **173** was converted into its mesylate **214** by applying the same conditions, which had been successfully used in **Chapter 2.4.** In a first attempt to achieve ring closure to tricyclic system **218**, crude mesylate was treated with potassium *tert*-butoxide in anhydrous dimethyl sulfoxide (DMSO) (**Scheme 89**).



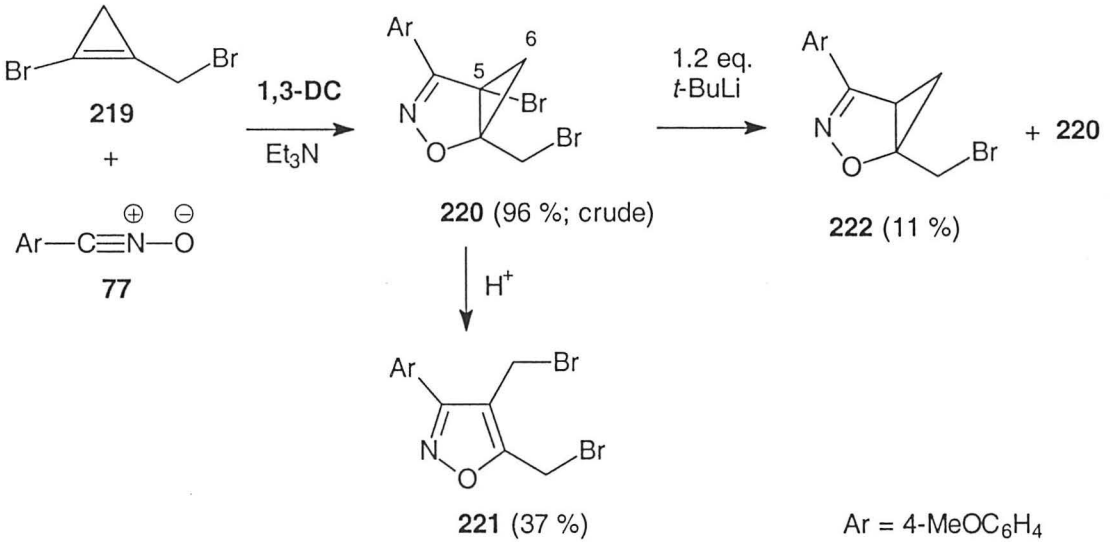
Scheme 89

A mixture of compounds was obtained. Purification by column chromatography led to the isolation of two compounds. Both were ether species. The major product **216**, isolated in 14 % yield, was derived from nucleophilic displacement of the mesylate **214** by *tert*-butoxide. A second, minor compound **215** was isolated in 4 % yield as a mixture of diastereomers in ratio 55:45. This latter ether was formed by nucleophilic attack of

the alcoholate of **173** to mesylate **214**. There was no evidence for the formation of the desired product, the [3.1.1]propellane **218**.

Thus the mesylate leaving group was converted into the iodide **217** by applying Finkelstein conditions. Ring-closure to **218** was then attempted by subjecting the iodide species to treatment with several base systems. While reaction with LDA did not lead to any conversion at all, other strong bases such as sodium bis[trimethylsilyl]amide (BSA), methyllithium, *n*-butyllithium, or *tert*-butyllithium afforded complex mixtures. In none of the cases could any product be identified. Again there was no evidence that the propellane **218** was formed in these reactions.

Above attempts had failed to give the [3.1.1]propellane therefore a different bicycle was prepared that could serve as a propellane precursor. This new bicycle **220** additionally had a bromine at the C-5 position. It was prepared *via* a 1,3-DC reaction of 4-methoxybenzonitrile oxide (**77**) to 1-bromo-2-bromomethylcyclopropene (**219**) (**Scheme 90**). The cyclopropene in its turn had been prepared from 1,2,2-tribromo-1-bromomethylcyclopropane prior to the cycloaddition reaction.[190]



Scheme 90

The bicycle **220** proved to be very unstable. Once isolated its colour changed from yellow to a deep green-blue within a few minutes. Under slightly acidic conditions it readily converted into 4,5-bis(bromomethyl)-3-(4-methoxyphenyl)isoxazole (**221**). Thus when crude **220** was subjected to purification by column chromatography on silica, complete conversion to **221** was observed. The acidity of a $CDCl_3$ solution was

enough to trigger the transformation. After 24 hours the ^{1}H NMR showed a ratio **220** to **221** of about 1:1 and after 48 hours no **220** could be detected anymore. The ^{1}H NMR spectrum of **220** showed a doublet at 1.46 ppm for H_{endo}-6, a doublet at 1.76 ppm for H_{exo}-6 (with a J_{gem} of 7.1 Hz) and two more doublets for the CH_2Br group at 3.75 ppm and 3.98 ppm. Compound **221** lacked of any stereocentre thus the two CH_2Br groups appeared as singlets at 4.38 ppm and 4.54 ppm respectively.

Due to the acid sensitivity, the product was used crude for the next step, the attempt to prepare the propellane *via* a 1,3-dehalogenation. Bicycle **220** was treated with *tert*-butyllithium at -50 °C and then quenched with water. Work-up gave a mixture of compounds. In the ^{1}H NMR the main compound could be identified as "reduced" bicycle **222** (**Scheme 90**). Further there was still a large amount of starting material **220** present.

The fact that the bromine at C-5 had been replaced by a proton suggested that an anion species at C-5 had been formed, however no ring-closure to the propellane took place. The crude reaction mixture was purified by column chromatography on silica. Pure 1-bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**222**) and pure (**221**) were isolated (all unreacted starting material **220** had been converted into isoxazole **221** on silica).

3. Results and Discussion

Part II

Chemistry of *gem*-Dibromocyclopropanes

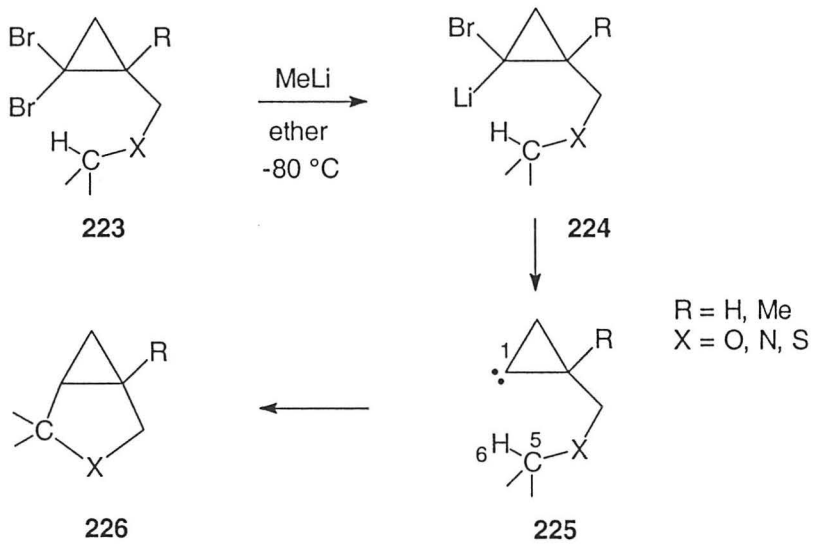
3.1. Intramolecular trapping of esters and amides by 1-lithio-1-bromocyclopropanes

3.1.1. Introduction

As already outlined in the introduction (**Chapter 1.5.**) the fate of a *gem*-dibromo species upon treatment with methyllithium depends on the reaction conditions applied and on substituents of the cyclopropane.

Reactions *via* a carbene intermediate

1,1-Dibromocyclopropanes can react with methyllithium by lithium-bromide exchange followed by elimination of lithium bromide to produce a carbene intermediate. Insertion into CH bonds is a unique reaction of carbenes and it is of considerable synthetic potential.[215,216] In the presence of monocyclic ethers,[217] sulfides and amines[185] of the general structure **1** insertion occurs exclusively at the CH bond adjacent to the heteroatom and 5,6-related to the carbenic carbon (1,5-insertion) (**Scheme 91**).

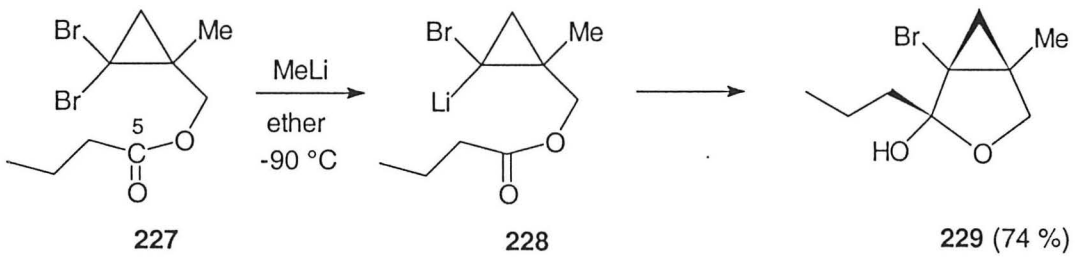


Scheme 91

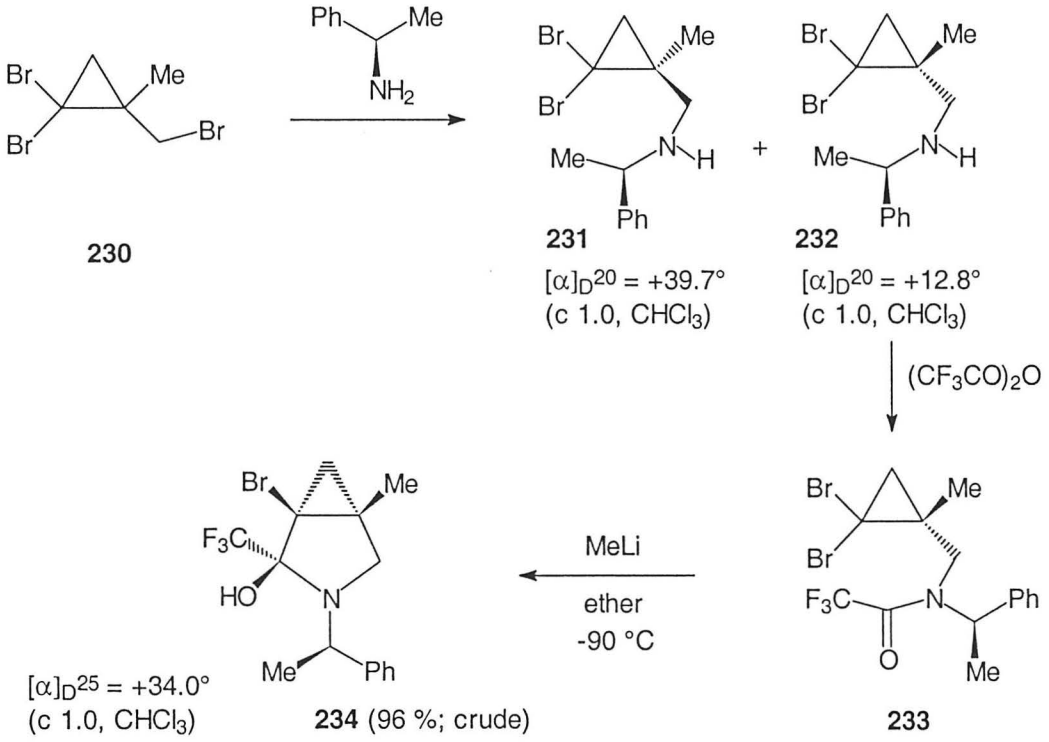
This type of transformation was the keystep in the total synthesis of the natural product 3,4-methanoproline.[185] Insertion occurred with a high degree of stereoselectivity and the final product was obtained as a single enantiomer.

Reactions *via* a carbenoid intermediate

If no hydrogen is available at C-5 other reactions become dominant. In the presence of a carbonyl group (ester or amide functionality) the lithiocyclopropane **228** can be trapped intramolecularly as research at Bangor recently demonstrated (**Scheme 92**).[218] Viacheslav V. Tverezovzky investigated two examples of stereoselective cyclisation reactions.[219] In the first case the ester **227** gave the hemiacetal 1-bromo-5-methyl-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**7**) in 74 % yield (**Scheme 92**). A second bicyclic system **234** was obtained in enantiomerically pure form from the amide **233** (**Scheme 93**).[218,219]



Scheme 92

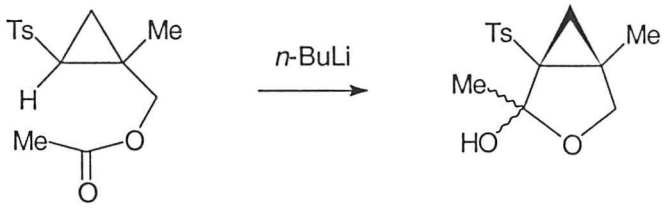


Scheme 93

Enantiomerically pure amide **233** was prepared from the corresponding amine **232** upon treatment with trifluoroacetic anhydride. The amine **232** in turn was prepared from the bromide **230**[185] with (*R*)-(+)-α-methylbenzylamine (**Scheme 93**). Two diastereomers **231** and **232** formed, which were separated by column chromatography on silica. The optical rotation of the stereoisomer **232** - $[\alpha]_D^{20}$ of +12.8° (c 1.0, $CHCl_3$) was close to the one of a sample derived from enantiomerically pure (*S*)-(-)-2,2-dibromo-1-methylcyclopropane-carboxylic acid ($[\alpha]_D^{20}$ of +11.9° (c 1.0, $CHCl_3$)).[219]

The systematic study of this cyclisation reaction was the main subject of the second part of this thesis and will be outlined in detail in the discussion part (**Chapter 3.1.2.**).

Although this appears to be the first example of such a cyclisation by reaction of 1,1-dibromides with an alkyllithium, it is known that the sulphone **13** (Ts = tosyl) reacts with *n*-butyllithium by proton removal from C-1 followed by cyclisation to give the hemiacetal **236** (**Scheme 94**).[220]



235 **236** (50 %)

Scheme 94

A similar system was formed when 2-(hydroxymethyl)cyclopropyl phenyl sulfide **237** was treated first with an excess of *n*-butyllithium and then with dimethylformamide to give the bicycle **238** (**Scheme 95**).[221]

237 **238** (61 %)

Scheme 95

In both cases the stereocentre of the (hemi)-acetal was not defined, probably a mixture of diastereomers had been obtained.

3.1.2. Discussion

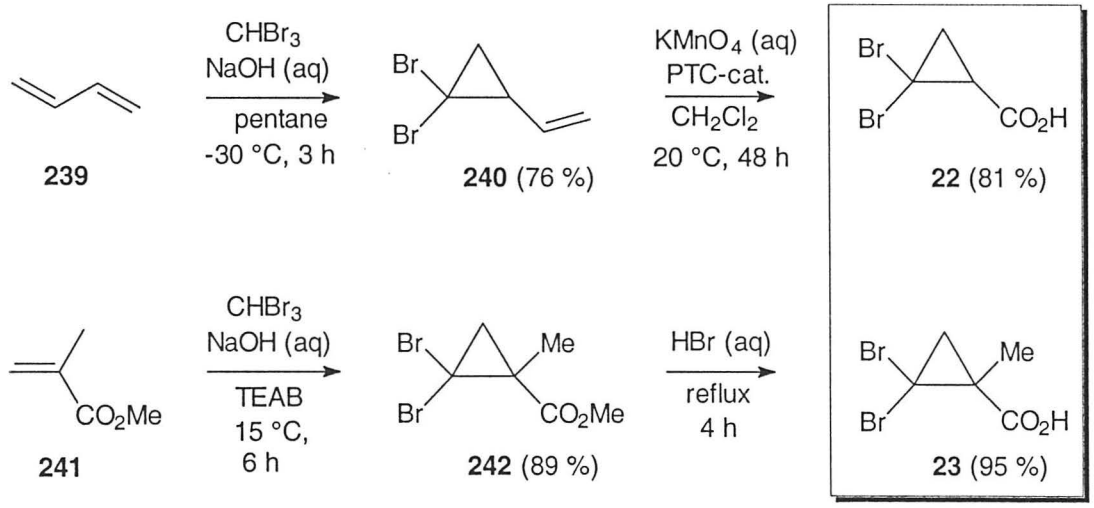
3.1.2.1. Preparation of starting material (esters) for intramolecular cyclisation reactions

For the systematic investigation of the novel intramolecular cyclisation reaction a range of esters, analogous to structure **227** in **Scheme 92** were prepared. The synthesis of those esters is divided into 3 steps:

- Preparation of 2,2-dibromocyclopropanecarboxylic acid (**22**) and its methyl analogue **23**.
- Preparation of (2,2-dibromocyclopropyl)methanol **245** and its methyl analogue **246**.
- Preparation of esters.

Preparation of 2,2-dibromocyclopropanecarboxylic acid (22) and its methyl analogue 23

Two types of cyclopropanecarboxylic acids - **22** and **23** - were prepared according to literature procedures.[77,185] The synthetic pathway is outlined in **Scheme 96**.



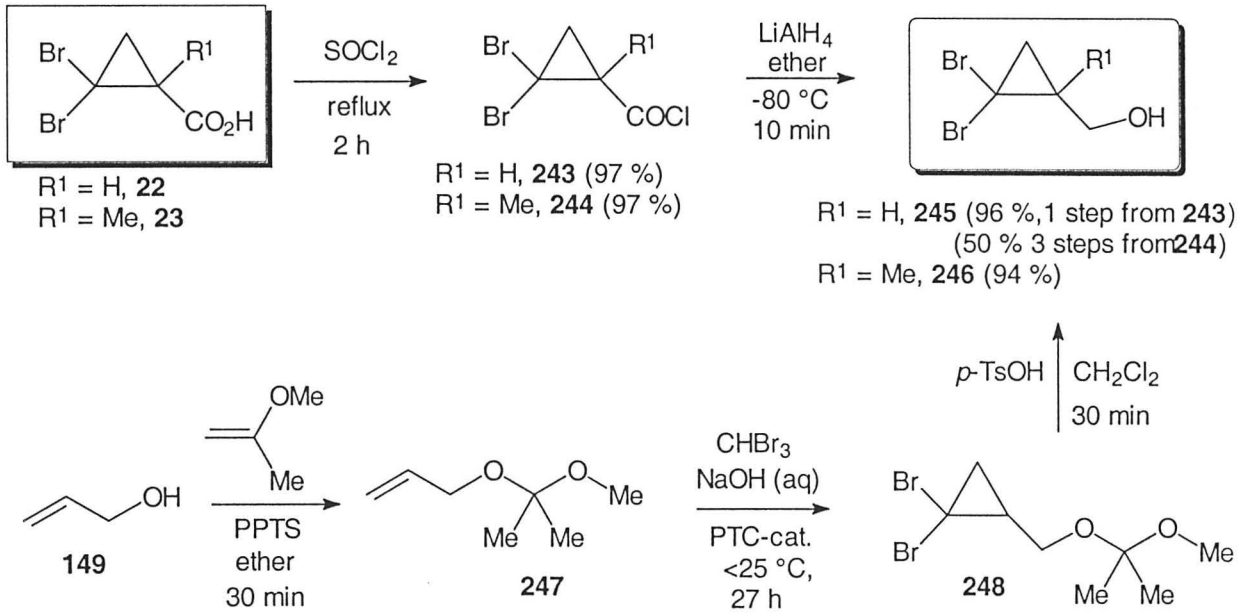
Scheme 96

2,2-Dibromo-1-methylcyclopropanecarboxylic acid **23** is readily prepared by the reaction of methyl methacrylate **241** with bromoform and aqueous sodium hydroxide in the presence of a phase transfer catalyst;[222] subsequent acid hydrolysis leads to the formation of the desired product (**Scheme 96**). The analogous acid **22** cannot be

obtained efficiently by the dihalocyclopropanation of methyl acrylate under phase transfer conditions because of further reaction, presumably initiated by removal of the proton adjacent to the acid group.[223] However, addition of dibromocarbene to 1,3-butadiene leads readily to the vinylcyclopropane **240**, which could be oxidised to the acid **22** with potassium permanganate (**Scheme 96**).[77]

As mentioned in the introduction (**Chapter 1.3.2.2.**) both acids, **22** and **23** are now available in enantiomerically pure form by a resolution procedure that was developed at Bangor.[77] For this particular synthesis however racemic material was used.

Preparation of (2,2-Dibromocyclopropyl)methanol 245 and its methyl analogue 246



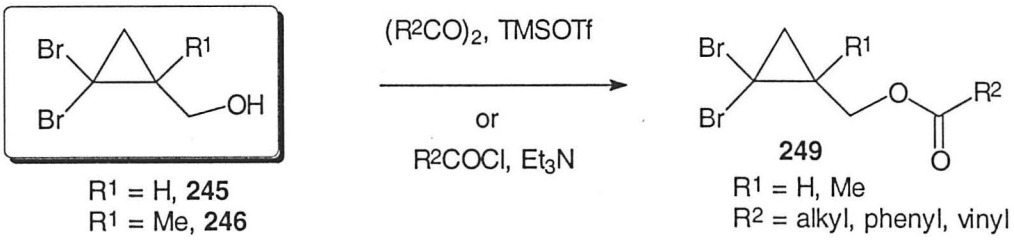
Scheme 97

The acids **22,23** were converted into the corresponding acid chlorides by reaction with thionyl chloride, and those were reduced to the alcohols **245,246** (**Scheme 97**).[185]

Racemic alcohol **245** (R^1 = H) was also prepared by an alternative route. Allyl alcohol **149** was protected with 2-methoxypropene in the presence of pyridinium *p*-toluenesulfonate (PPTS).[224] The protected alcohol **247** was converted to the cyclopropane **248** with bromoform and aqueous sodium hydroxide in the presence of a phase transfer catalyst. After removal of the protecting group under acidic conditions the alcohol **245** was obtained in 50 % yield (overall yield from allyl alcohol and after

distillation of the crude product). The dihalocyclopropanation of **247** was also carried out under ultrasonic conditions according to a general procedure by U.H. Brinker.[225] However a complex mixture of compounds was obtained and its separation failed.

Preparation of esters of general structure 249 (Scheme 98)



Scheme 98

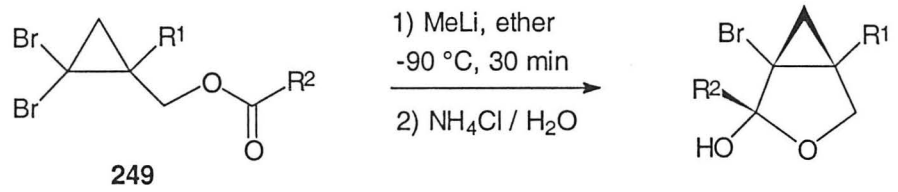
A range of esters of general structure **249** (**Scheme 98**) was prepared by standard esterification methods. Esters with R^2 = methyl, trifluoromethyl and *n*-propyl were made from the alcohols **245,246** by treatment with the corresponding acid anhydride in the presence of trimethylsilyl trifluoromethane sulfonate as catalyst.[226] The benzoates (R^2 = Ph) and acrylates (R^2 = vinyl) were prepared upon treatment with acid chloride in presence of triethylamine. All products are listed in **Table 11**. The esters prepared with acid anhydride were generally very clean and did not require any further purification. Esterification with acid chloride gave only low to moderate yields but no attempts were made to optimise the reaction. The yields given for the benzoate (**253**, **257**) and acrylate (**254**, **258**) are after purification by column chromatography on silica.

Table 11. Yields of various esters

R^2	R^1 = H ester (yield)	R^1 = Me ester (yield)
Me	**251** (86 %)	**256** (88 %)
n-Pr	**252** (92 %)	**227** (93 %)
Ph	**253** (62 %)	**257** (52 %)
Vinyl	**254** (35 %)	**258** (44%)
CF_3	**255** (88 %)	-

3.1.2.2. Intramolecular cyclisation reactions of esters

Reaction of esters **249** with a slight excess of methyllithium at -90 °C for 30 min. followed by quenching with ammonium chloride either at low temperature or after warming to 0 °C led to the hemiacetals **250** (**Scheme 99**).



R1 = H, Me
R2 = alkyl, phenyl, vinyl

Scheme 99

All products of the intramolecular trapping are summarised in **Table 12**. Individual examples are discussed in detail below.

Table 12. Reactions of esters with methyllithium in diethyl ether at –90 °C

	$R^1 = H$		$R^1 = Me$	
R^2	**ester**	**product**	**ester**	**Product**
Me	**251**	**259** (90 %) + **245** (10 %)	**256**	**266** (60 %)
n-Pr	**252**	**261** (46 %)	**227**	**229** (74 %)
Ph	**253**	**263** (64 %)	**257**	**267** (82 %)
Vinyl	**254**	**265** (39 %)	**258**	**268** (86 %)
CF_3	**255**	**245** (90 %)	-	-

The formation of products **250** apparently involves a lithium-bromine exchange in **249** and cyclisation of the derived lithiocyclopropane by intramolecular attack at the ester group. It is not clear whether the initial exchange leads stereoselectively to the *syn*-lithio-ester, or whether a more complex process occurs in which the two isomeric lithiobromides are formed and equilibrate but only one isomer cyclises. Nonetheless, no products of intermolecular trapping of the *anti*-lithio ester have been observed. Neither

was there any evidence for the formation of products derived from cyclopropylidene intermediates (e.g. allenes).

In case of the trifluoroacetic acid ester **255** (R^1 = H, R^2 = CF_3) no cyclisation at all took place, the ester was nearly quantitatively hydrolysed to the alcohol **245**. Thus nucleophilic attack of methyllithium at the ester carbonyl was much faster than lithium-halogen exchange. When the reaction was carried out with the acetic acid ester **251** (R^1 = H, R^2 = Me) only 10 % hydrolysed product was observed. The main product was the hemiacetal **259**, which was isolated in 55 % yield. All other reactions did not afford any hydrolysis products.

Stereochemistry of hemiacetals

Remarkably the intramolecular cyclisation reaction was highly stereoselective. A single diastereomer was isolated in each case after chromatography; minor signals in the crude mixture could not be assigned with certainty to a second isomer. Due to the use of racemic esters as starting materials, all products were obtained as pairs of enantiomers.

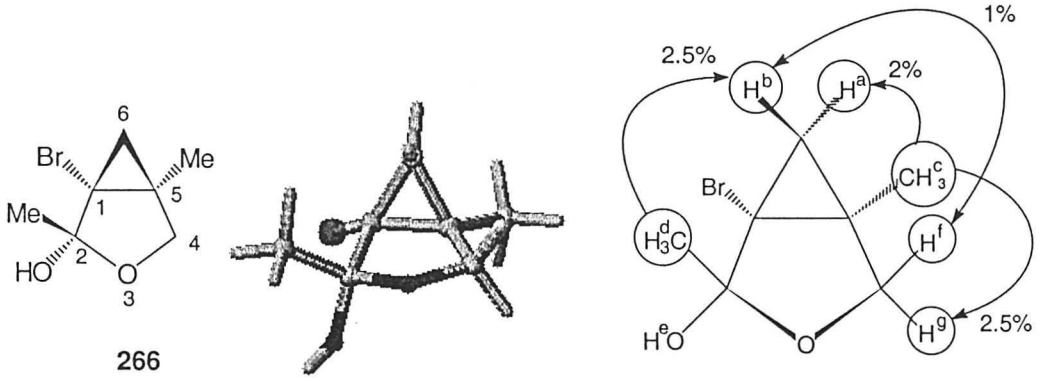
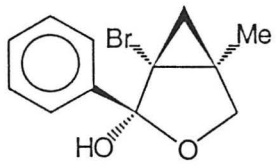


Figure 10

The stereochemistry at C-2 of the hemiacetal **266** (R^1 = R^2 = Me) was assigned as that with the methyl group *endo* to the cyclopropane on the basis of an NOE effects (**Figure 10**). The NOE study established:

- reciprocal enhancements (1 %) of H^b and H^f (but not H^a and H^g) located these protons as *endo*
- enhancement of H^b on irradiation CH^d_3, only possible if both groups are *endo*
- H^a and H^g both enhanced by irradiation of methyl CH^c_3 -this locates both protons *exo*

The stereochemistry of other products was assigned by analogy with this. Final confirmation about the correct stereochemistry came from a single x-ray crystal structure determination of the hemiacetal **267** (R^1 = Me, R^2 = Ph). As predicted the phenyl group on the hemiacetal centre lies *endo* to the cyclopropane moiety (see **Figure 11.** below).



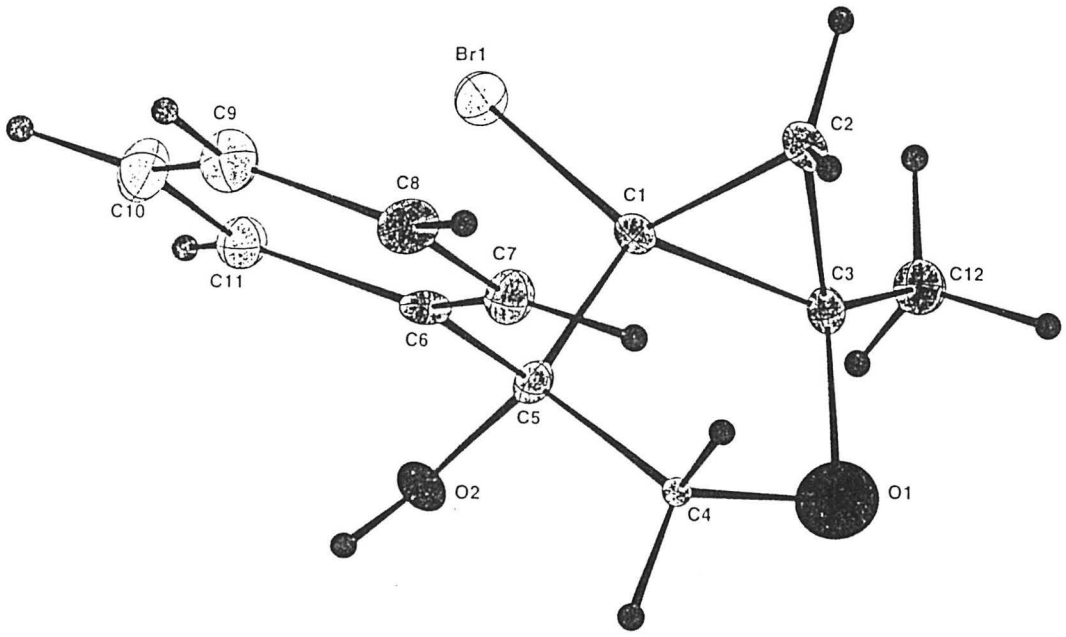
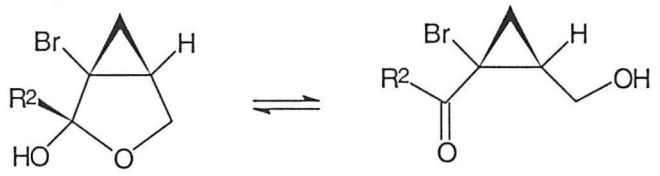


Figure 11. X-ray crystallographic structure of *rac*-1-Bromo-5-methyl-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol (267)

<u>Note:</u> this X-ray crystallographic structure is not correct as the atoms 'C4' and 'O1' are in the wrong place (these atoms should be interchanged); comments to the refinement of atom C4: "Atom C4 is disordered over 3 sites, only the major component (under 50 %) occupancy) is shown in the figure. These atoms could not be made anisotropic".

Equilibrium of hemiacetals (R^1 =H)

In the cases of the hemiacetals **229**, **266**, **267** (R^1 = Me, see **Table 12**) the NMR spectra in deuterochloroform showed only the presence of the cyclic form. However, for the analogous hemiacetals **259**, **261**, **263** (R^1 = H) the ^{1}H NMR spectra in deuterated solvents were more complicated and could be interpreted in terms of an equilibrium between the hemiacetals **259**, **261**, **263** and the keto-alcohols **260**, **262**, **264** (**Scheme 100**). The observed ratios between those two species are summarised in **Table 13** below.



R^2 = Me, **259** R^2 = Me, **260**

R^2 = *n*-Pr, **261** R^2 = *n*-Pr, **262**

R^2 = Ph, **263** R^2 = Ph, **264**

Scheme 100

Table 13. Equilibrium hemiacetal / keto-alcohol in various deuterated solvents

R^2	compound	solvent	ratio* hemiacetal : keto-alcohol
Me	**259 / 260**	$CDCl_3$	81 : 19
		benzene-d_6	84 : 16
n-Pr	**261 / 262**	$CDCl_3$	58 : 42
		toluene-d_8	67 : 33
Ph	**263 / 264**	$CDCl_3$	43 : 57
		CD_3OD	58 : 42
		toluene-d_8	100 : 0

*ratios measured after 1 hour in deuterated solvent

Generally the equilibrium was on the side of the hemiacetals, with one exception: compound **263** (R^2 = Ph) in deuterochloroform showed more of the keto-

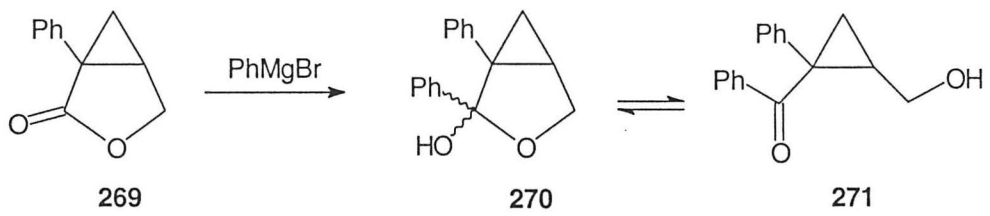
alcohol than the hemiacetal present. Surprisingly, in deuterated toluene the same compound **263** did not show any equilibrium at all. Thus the equilibrium depends on:

- structural properties of the hemiacetal - substituents on the hemiacetal centre (R^2 either Me, *n*-Pr or Ph) and group R^1 on the cyclopropane ring (whether there is a methyl group or only a proton)
- properties of solvent (polarity and acidity)

The reversibility of this equilibrium was tested with compound **263** (R^2 =Ph). The compound was first dissolved in deuterated methanol and showed a ratio of 58 : 42 in the ^{1}H NMR spectrum (the NMR spectrum of **263** is discussed in detail below). The solvent was evaporated and the same sample was dissolved in deuterated toluene. Now only signals of the hemiacetal were present in the ^{1}H NMR spectrum. The solvent was evaporated and the spectrum was recorded once again in deuterated methanol. An almost identical ratio of hemiacetal to keto-alcohol to that above was observed.

When samples of **259**, and **261** in deuterochloroform were re-measured after one or more days, the NMR spectrum became highly complex. It was not clear whether the compounds simply decomposed or if there were also the formation of other hemiacetal diastereomers (stereoisomers with the opposite configuration on the hemiacetal carbon).

In the literature, a similar equilibrium has been reported in closely related acetals **270**.[227] The bicyclic system was obtained from reaction of the lactone **269** with phenylmagnesium bromide (**Scheme 101**). The authors quoted a ratio hemiacetal to keto-alcohol of 25 to 75 in deuterated methanol.

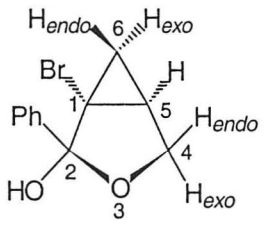


Scheme 101

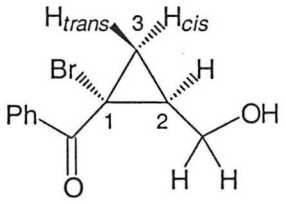
NMR spectra of the hemiacetal 263 and the keto-alcohol 264

The ^{1}H NMR data of the hemiacetal 1-bromo-2-phenyl-3-oxabicyclo[3.1.0]-hexan-2-ol (**263**) and the keto-alcohol (1-bromo-2-hydroxymethylcyclopropyl)phenyl-methanone (**264**) are listed in **Table 14**.

Table 14. ^{1}H NMR data of compounds 263 and 264



263



264

hemiacetal			keto-alcohol		
atom	multi-plicity	δ_H (CD_3OD; coupling constants in Hz)	atom	multi-plicity	δ_H (CD_3OD; coupling constants in Hz)
H_{endo}-6	dd	1.03 (*J* 5.1, 6.0)	H_{cis}-3	dd	1.46 (*J* 6.6, 9.9)
H_{exo}-6	dd	1.10 (*J* 6.0, 8.4)	H_{trans}-3	dd	1.70 (*J* 6.6, 7.4)
H-5	ddd	2.07 (*J* 2.9, 5.1, 8.4)	H-2	ddd	2.24 (*J* 6.6, 7.4, 9.9)
H_{endo}-4	d	3.86 (*J* 8.5)	CH_2O	d	3.43 (*J* 6.6)
H_{exo}-4	dd	4.30 (*J* 2.9, 8.5)			
aromatic H	m	7.30-7.40 (3H) and 7.59-7.65 (2H)	aromatic H	m	7.38-7.56 (3H) and 8.07-8.11 (2H)

In the hemiacetal **263** the coupling pattern is less complicated than one might expect at the first glance. The *endo* proton at C-4 only shows a doublet and not a "dd" multiplicity. The explanation for this observation is that the vicinal coupling constant is zero. This is due to the torsion angle between H_{endo}-4 and H-5, which is close to 90 degree.

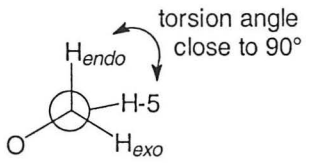


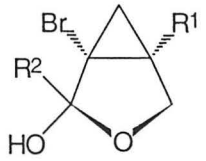
Table 15. ^{13}C NMR data of compounds 263 and 264

hemiacetal		keto-alcohol	
atom	δ_C (CD_3OD)	atom	δ_C (CD_3OD)
C-6	19.7	**C-3**	18.9
C-5	27.8	**C-2**	34.3
C-1	42.1	**C-1**	35.0
C-4	67.8	CH_2O	61.6
C-2	104.6	aromatic C	129.6, 131.3, 134.8, 136.8
aromatic C	127.9, 129.0, 129.6, 141.0	CO	195.2

The ^{13}C NMR data of hemiacetal **263** and keto-alcohol **264** are summarised in **Table 15**. The three carbon atoms of the cyclopropane are highlighted bold. Only the CH_2 group of the cyclopropane moiety has a comparable chemical shift. The carbon C-2 of hemiacetal **263** appears at 104.6 ppm. In the ring-opened structure **264** this carbon has carbonyl functionality and gives a signal at 195.2 ppm.

Comparison of hemiacetals R^1 = H with the analogous hemiacetals R^1 = Me

The products of intramolecular trapping of esters were divided into 2 groups (see **Table 12** above). One set of products was with a methyl group (R^1 = Me) at the cyclopropane moiety, the other one without (R^1 =H) (see general structure **250**).

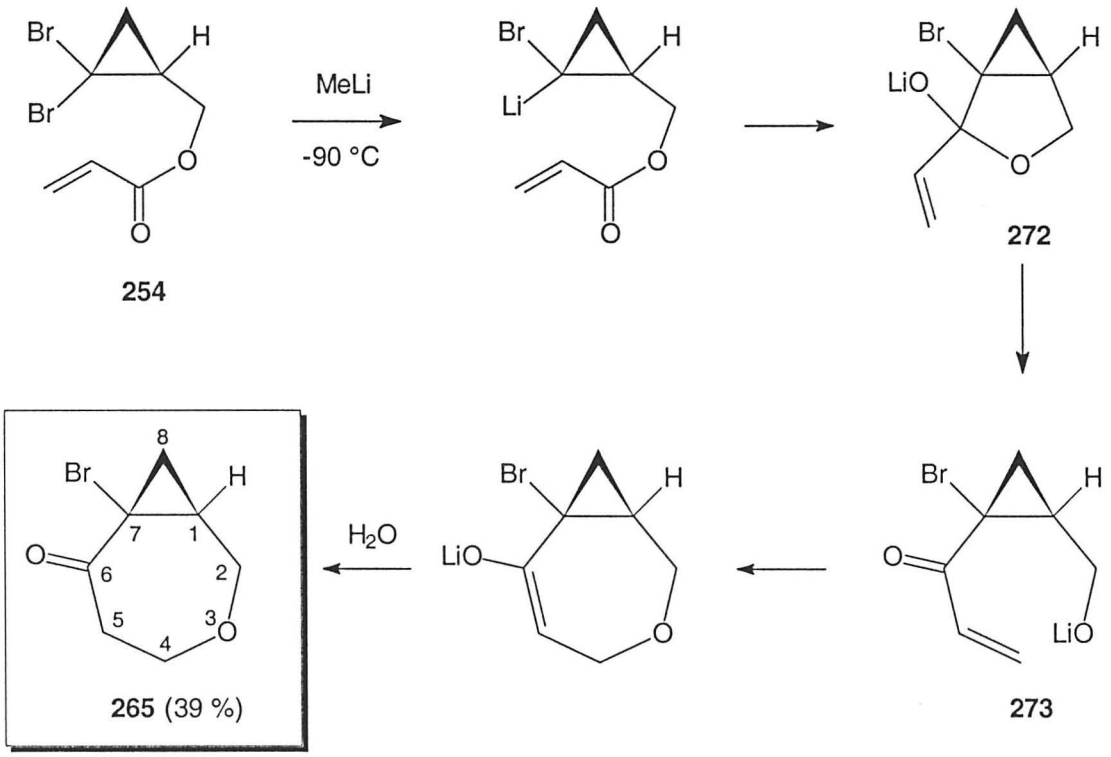


250

R1 = H or Me

This methyl group was of vital influence in this reaction. As already outlined above only the hemiacetals with R^1 = H showed the equilibrium with the keto-alcohol. Generally the reactions of esters with the methyl substituent proceeded in a cleaner manner, thus giving a somewhat higher yield. In the 'methyl' series no hydrolysis product was observed. The most significant difference was in the reaction of acrylates **254** and **258** with methyllithium. The ester **258** with the methyl group gave the expected

product, the hemiacetal **268**. The reaction of ester **254** with methyllithium followed a rather different course, leading to the bicyclic ketone **265** as the sole product (**Scheme 102**).



Scheme 102

This may be explained in terms of initial formation of a hemiacetal species **272** as above followed by ring-opening to a keto-alcohol **273** and recyclisation by attack of the alcoholate at the β-position of the derived α,β-unsaturated ketone.

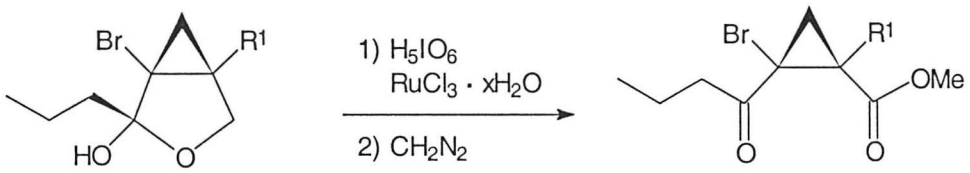
The bicyclic ketone **265** exhibited an unusual double carbonyl peak with maxima at 1711 and 1692 cm^{-1}. In the ^{13}C NMR the carbonyl carbon gave a signal at 199.3 ppm. Peaks at 67.2 ppm and 69.7 ppm are signals of a CH_2 group next to the ring-oxygen, but is was not possible to assign which of them was C-2 and which C-4. In the ^{1}H NMR all protons could be assigned due to their coupling constants. The two CH_2 groups at C-4 and C-5 gave for each proton a 'ddd' multiplicity with signals at 2.04 ppm, 2.28 ppm (H-5 each) and at 2.69 ppm, 3.20 ppm (H-4 each). Contrary to above hemiacetal system, both H-2 protons gave a 'dd' multiplicity due to an altered torsion angle (bigger ring size: seven-membered instead of five-membered ring; torsion angle ≠ 90° thus vicinal coupling constant ≠ zero).

3.1.2.3. Reaction of hemiacetals

The hemiacetals, which have been obtained by intramolecular trapping of esters were reacted further to give ring-opened products. Following transformations were carried out:

Oxidation of the hemiacetal system

1-Bromo-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**261**) and its methyl analogue **7** were oxidatively[187] ring-opened to the corresponding 2-bromo-2-butyrylcyclo-propanecarboxylic acids, which were isolated as their methyl esters (**274** and **275**, **Scheme 103**).



R^1 = H, **261**
R^1 = Me, **229**

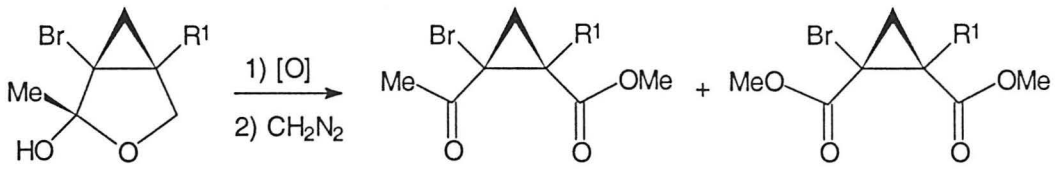
R^1 = H, **274** (66 %)
R^1 = Me, **275** (72 %)

Scheme 103

In each case catalytic amounts of ruthenium trichloride were employed. The active oxidising agent ruthenium tetroxide is formed *in situ* upon reaction with periodic acid.[187] With hemiactal **229** the oxidation was carried out, both with 2 mol.equiv. and with 14 mol.equiv. of periodic acid. Using 2 mol.equiv. gave a higher yield of **275** (72 %) than using a large excess of the acid (52 % yield).

The ^{13}C NMR spectra gave correct signals for the ester carbonyl in the region of 170 ppm and for the ketone at 200 ppm.

1-Bromo-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (**259**) and 1-bromo-2,5-dimethyl-3-oxabicyclo[3.1.0]hexan-2-ol (**266**) were also subjected to ruthenium tetroxide oxidation. Now in each case the oxidation of the hemiacetal afforded two products. The major products were the keto-esters **276** and **278** – compounds analogous to the one observed above. A second set of compound were formed, which was identified as a diesters **277** and **279** (**Scheme 104**). The mechanism for this oxidation-product is unclear.



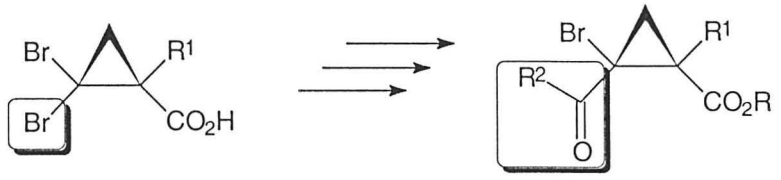
R^1 = H, **259** R^1 = H, **276** (57 : 43) R^1 = H, **277**

R^1 = Me, **266** R^1 = Me, **278** (58 : 42) R^1 = Me, **279**

Scheme 104

In both cases the ratio keto-ester to diester was roughly the same – about 60 to 40, as determined by GLC [the assignment of the retention times was based on GC/MS spectra]. In neither case was the mixture separated. Diester **279** and keto-esters **276, 278** are new compounds, while diester **277**[228] is a known compound.

If 2,2-dibromocyclopropanecarboxylic acid is regarded as one of the starting points of the synthesis, the overall transformation achieved, is a stereoselective acylation (the acyl group is *cis* to the ester group) (**Scheme 105**).



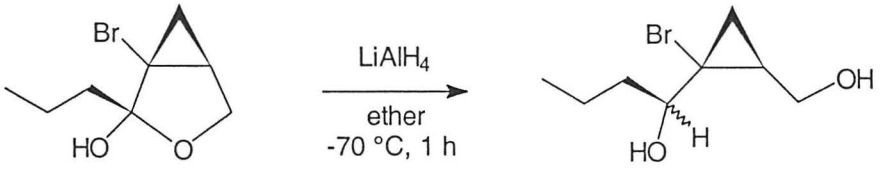
R^1 = H, Me

R^2 = Me, *n*-Pr
R = Me

Scheme 105

Reduction of the hemiacetal system

Reduction of the hemiacetal **261** with lithium aluminium hydride in ether was not stereoselective, leading to a mixture of isomeric diols **280, 281** (**Scheme 106**).



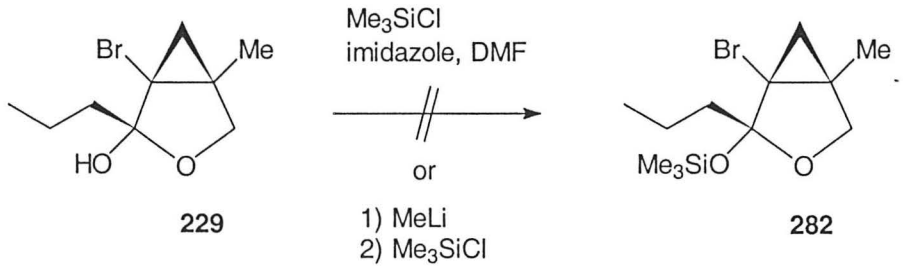
261 **280/281** (50:50; in total: 74 %)

Scheme 106

The two diastereomers could be separated by column chromatography on silica. One diastereomer (**280**) was obtained as a white solid, the other (**281**) as colourless oil.

Attempted protection of hemiacetal 229 with trimethylsilyl chloride

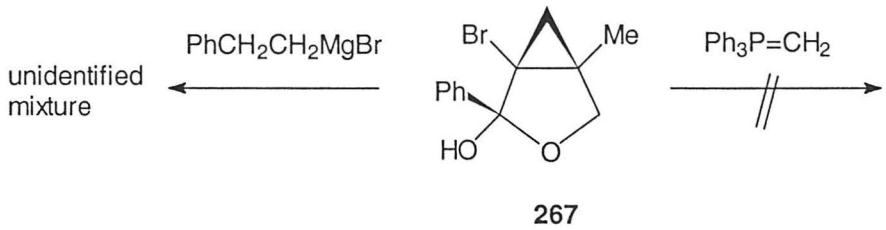
Attempts were made to protect the hemiacteal **229** with a trimethylsilyl group (structure **282** in **Scheme 107**). Common silylation conditions (trimethylsilyl chloride imidazole, DMF)[168] were employed. The reaction time was extended up to 72 hours, but upon work-up only starting material (80 %) was recovered. Thus alternative conditions were used in a second attempt. The hemiacetal **229** was treated with methyllithium at low temperature in order to generate an anion. Trimethylsilyl chloride was added to the reaction mixture. However after work-up, again only starting material (70 %) was isolated.



Scheme 107

Attempted reaction of hemiacetal 267 with Grignard and Wittig reagents

To the hemiacetal **267** was added 2.0 mol.equiv. of the Grignard reagent[229] 2-phenylethylmagnesium bromide (**Scheme 108**). The reaction gave a mixture, which could not be identified. The same hemiacetal was also subjected to addition of a simple Wittig reagent. No reaction at all took place, the starting material was quantitatively recovered.



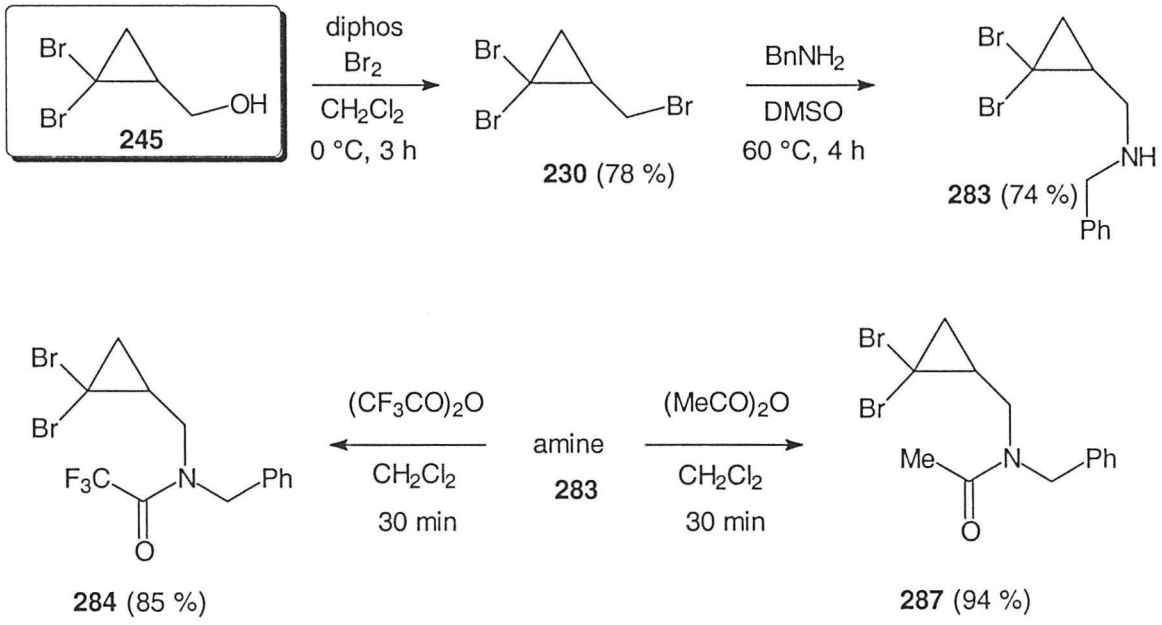
Scheme 108

3.1.2.4. Preparation of amides and their intramolecular trapping

Not only ester can be trapped intramolecularly by 1-lithio-1-bromocyclopropanes but also amides. One example was already given above in the introduction (amide **233**, **Scheme 93**, **Chapter 3.1.1.**). Two more examples shall be discussed here. First the preparation of the amides is described.

Preparation of amides

The amides **284** and **287** were obtained as shown in **Scheme 109**. The synthesis started from alcohol **23**, which was converted into the corresponding bromide **8** with 1,2-bis(diphenylphosphino)ethane and bromine.[185] Reaction with benzylamine gave the amine **62**. The amine was treated either with trifluoroacetic anhydride or acetic anhydride to give the amides **63** and **66** respectively. In each case these compounds showed the signals for two rotamers about the amide bond by ^{1}H and ^{13}C NMR spectroscopy.



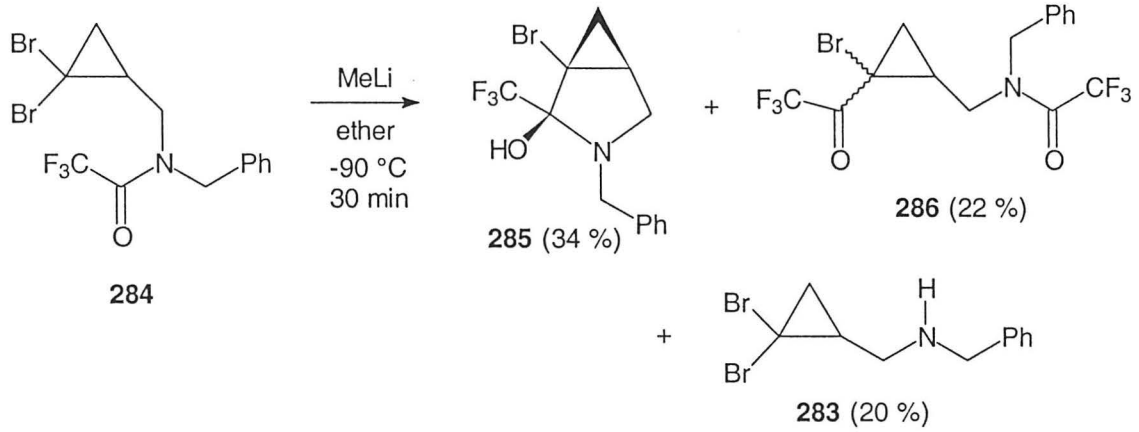
Scheme 109

Intramolecular cyclisation reactions of amides

It has to be emphasised here again that only racemic compounds were used in the trapping reactions. Contrary to the amide **233** mentioned in the introduction, the amides **284** and **287** are without a methyl group at the cyclopropane ring. Once more this methyl group proved to be important for the reactivity behaviour shown in the intramolecular trapping reaction. While the earlier mentioned amide **233** gave a single product - hemiaminal **234**, the reactions of the non-methylated amides gave a mixture of products.

Amide **284** was treated with methyllithium under the same conditions that were applied for the intramolecular trapping of esters. A mixture of three compounds was obtained. The expected hemiaminal **285** was formed only in 34 % yield (**Scheme 110**).

In the ^{1}H NMR spectrum, the hemiaminal **285** exhibited similar coupling patterns to the analogous hemiacetals. The vicinal coupling constant of H_{endo}-4 was zero, thus only a doublet was observed; the signal appeared at 2.94 ppm and showed only the geminal coupling constant (9.0 Hz) from coupling with H_{exo}-4. In the ^{13}C NMR, the carbon at the hemiaminal centre (= C-2) appeared as a quartet (*J* 30.3 Hz) at 90.3 ppm due to CF coupling. The trifluoromethyl group also gave a quartet (*J* 288.9 Hz) at 124.1 ppm.

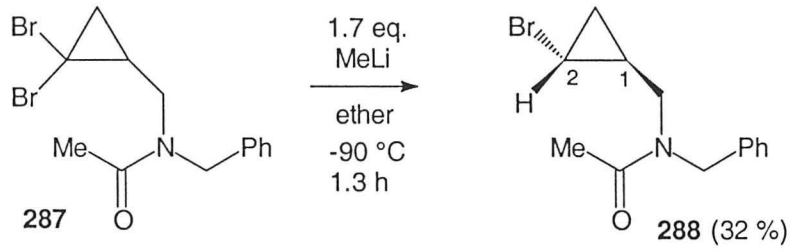


Scheme 110

Two other products were identified as hydrolysed amine **283** (20 %) and the keto-amide **286** (22 %). The latter compound is derived from an intermolecular reaction of the lithiocyclopropane of **284** with another molecule of **284**. It is not clear whether

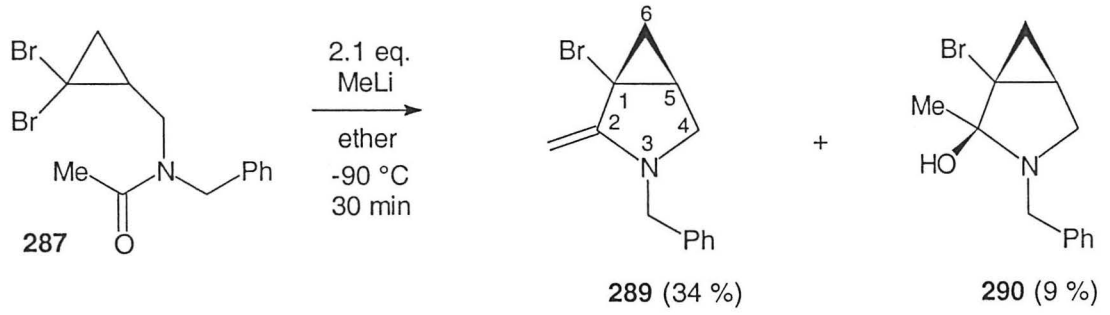
the trifluoroacetyl group in **286** is *cis* or *trans* with regard of the amide function. Analogous to **284,** compound **286** was present as a mixture of two rotamers about the amide bond by ^{1}H and ^{13}C NMR. In the ^{13}C NMR the two carbonyl groups present appeared as quartets (*J* 39 Hz each) due to CF coupling; the major rotamer of **286** gave a signal for the amide carbonyl at 157.8 ppm and for the ketone at 184.7 ppm.

The last compound that was tested for intramolecular trapping was the amide **287** (**Scheme 111**). It was treated at low temperature (-90 °C) with 1.3 mol.equiv. of methyllithium. After 45 minutes starting material was still found to be present and thus more methyllithium was added (in total 1.7 mol.equiv.). Work-up gave the mono-bromide **288** (32 %) and despite the excess of methyllithium used, starting material was recovered as well (23 %). The reduction was stereoselective, only the isomer with the bromine group *trans* to the substituent at C-1 was formed. The stereochemistry was established by ^{1}H NMR, where H-2 showed two *trans* (*J* 3.8 Hz each) and only one *cis* (*J* 7.4 Hz) coupling constant. The compound showed the signals for two rotamers about the amide bond by ^{1}H and ^{13}C NMR.



Scheme 111

The same amide **287** was also reacted with 2.1 mol.equiv. of methyllithium at low temperature for 30 minutes and now additional products were formed (**Scheme 112**).



Scheme 112

The crude ^{1}H NMR indicated four compounds to be present: some starting material **287**, traces of mono-reduced **288**, some hemiaminal **290** and a new bicyclic compound **289** (**Scheme 112**). After purification by column chromatography on silica bicycle **289** (34 %) was isolated together with some hemiaminal **290** (9 %).

The bicyclic compound **289** was identified as an enamine species. It is formally formed from the hemiaminal **290** by loss of H_2O. The methylene group of the enamine showed two singlets in the ^{1}H NMR spectrum at 3.82 ppm and 4.02 ppm and two ^{13}C signals at 75.5 (C=$\underline{C}H_2$) and 154.1 (C-2); these values are very close to those reported for *N*-alkyl-2-methylenetetrahydropyrrole.[230] The enamine decomposed over several days at room temperature in $CDCl_3$ to unidentified products.[231]

It remains unclear why the increase of the molar amount of methyllithium from 1.7 to 2.1 had such a big effect on the formation of products. To exclude experimental errors the reactions were repeated but the outcome was the same.

3.1.3. Conclusion

Reaction of 2-acyloxymethyl or 2-acylaminomethyl-1,1-dibromocyclopropanes with methyllithium at –90 °C led to the stereoselective formation of bicyclic compounds (hemiacetals and hemiaminals). The synthesis was carried out with racemic compounds. However optically pure compounds are easily accessible if the starting material is derived from enantiomerically pure 2,2-dibromocyclopropanecarboxylic acid and its 1-methyl analogue.

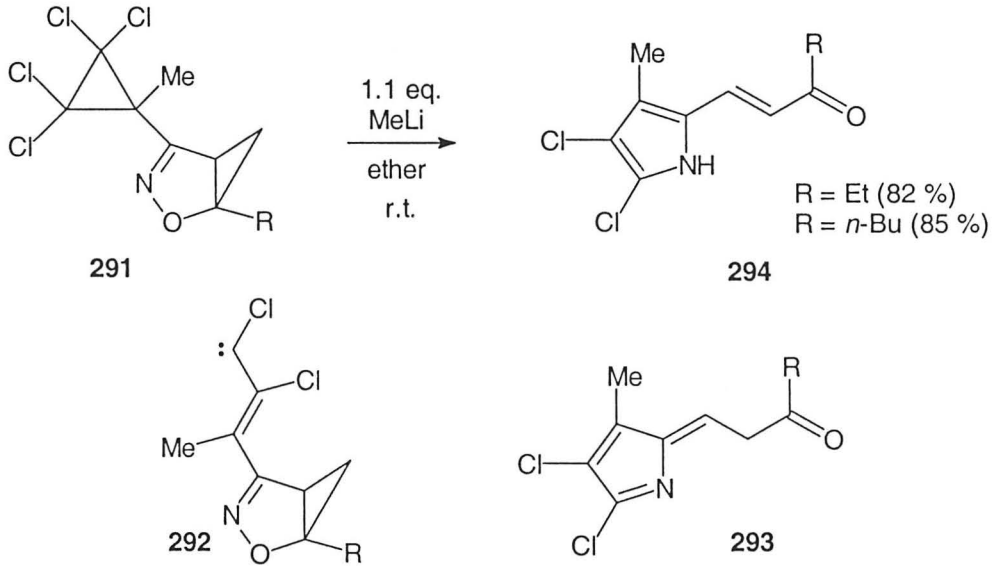
A methyl group at the cyclopropane ring proved to play an important role in the outcome of the reaction and the stability of the products. In the absence of this methyl group more complex reactions took place and other products than hemiacetals or hemiaminals were observed (e.g. formation of a seven-membered ring or an enamine species).

Transformation of hemiacetals were also briefly investigated. Reductions and oxidations led to ring-opened products. Other reactions such as addition of Grignard and Wittig reagents or protection of the hydroxy-group of the hemiacetal were unsuccessfully attempted. Thus in order to exploit the intramolecular cyclisation reactions fully, further work would be needed to look into those transformations in greater detail.

3.2. Reaction of cycloadducts derived from 2,2-dibromocyclopropylformonitrile oxide with methyllithium

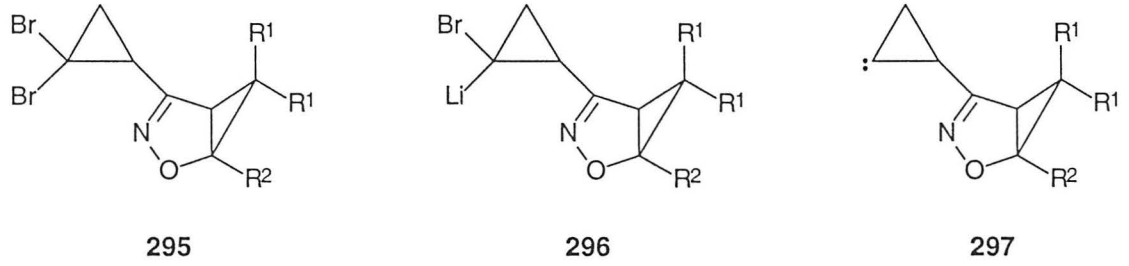
3.2.1. Introduction

Recently an unusual rearrangement of isoxazoline derivatives to 2-alkenoylpyrroles was reported.[232] Cyclopropane **291** was treated with methyllithium at room temperature and pyrroles **294** were obtained (**Scheme 113**). The reaction may be explained in terms of the formation of a vinylcarbene species **292**. The carbene cyclises to a methylenepyrrole **293**, which may rearrange to the corresponding pyrrole through a prototropic shift.



Scheme 113

Earlier in this thesis (**Chapter 2.3.2.1.**) the synthesis of products of type **295** was reported. These dibromocyclopropanes are derived from the cycloaddition of cyclopropenes to 2,2-dibromocyclopropylformonitrile oxide **126**.

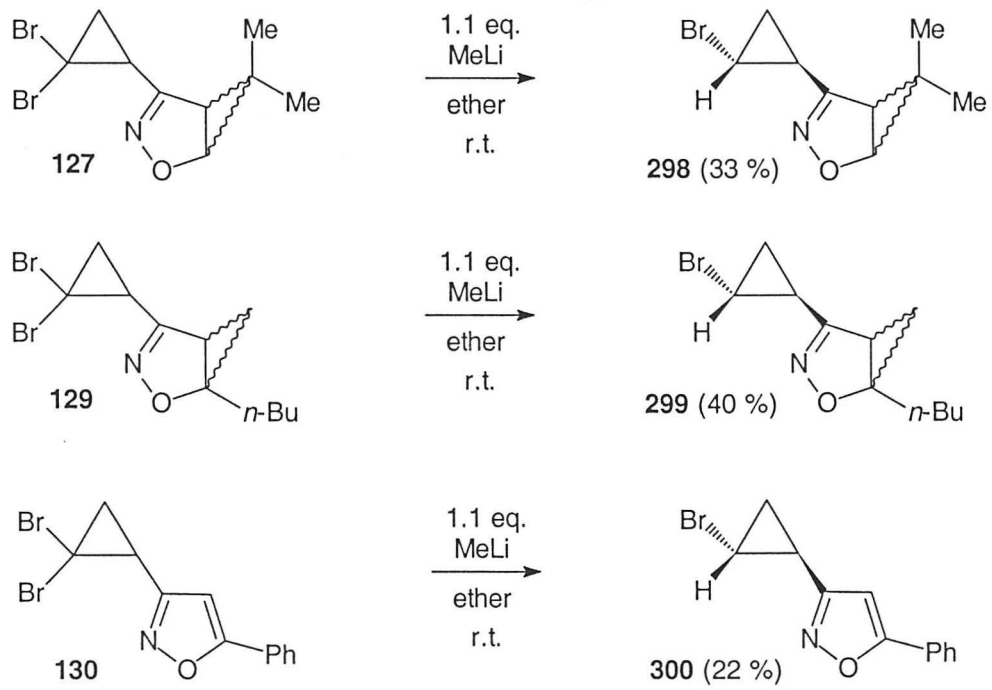


The interesting question now was, what would happen if the dibromo species **295** was treated with methyllithium at room temperature. Would the lithiocyclopropane **296** or the corresponding carbene **297** be formed and would any kind of rearrangement take place?

Three examples of reactions of dibromocycloclopropanes with methyllithium were studied and are outlined in the discussion part.

3.2.2. Discussion

Cyclopropanes **127**, **129** and **130** were treated with methyllithium in ether at room temperature for a period of 10 to 30 minutes (**Scheme 114**). The reaction mixtures were quenched with water at 0 °C and the crude products were purified by column chromatography on silica. The yields obtained were generally low; in all cases only mono-reduced compounds were formed. No products derived from a carbene species (e.g. allenes) nor from any rearrangements were observed. Compounds **127** and **129** were each employed as mixtures of diastereomers (see **Chapter 2.3.2.1.**) thus the products **298** and **299** were obtained as diastereomeric mixtures.



Scheme 114

In all three cases (**298**, **299** and **300**) the reduction of the dibromocyclopropane species was stereoselective: only the isomer with the bromine group *trans* to the substituent at the cyclopropane ring was formed. The stereochemistry was established by ^{1}H NMR by the size of the coupling constants. For example the proton H-CBr of the major diastereomer of **298** showed two *trans* (*J* 3.4, 4.6 Hz) and only one *cis* (*J* 7.5 Hz) coupling constant. The chemical shifts of the mono-reduced compounds in the ^{1}H and ^{13}C NMR were consistent with the data of the starting cycloadducts (see **Chapter 2.3.2.1.**).

4. Summary of Part I and Part II

Summary

This thesis described the stereocontrolled synthesis of novel cyclopropanes. Two different synthetic approaches were chosen.

In **Part 1** of the thesis, the synthetic concept was based on 1,3-dipolar cycloaddition reactions. Reduction of cycloadducts, derived from cyclopropenes and nitrile oxides, led to the stereoselective formation of cyclopropanols with three or four stereocentres. A drawback of the synthesis was that these compounds were all racemic compounds because the cycloaddition step did not exhibit any enantiofacial control. Thus routes to enantiomerically pure cyclopropanes were investigated. Two chiral nitrile oxides were tested in the cycloaddition reaction, but only low asymmetric induction was observed. The catalytic asymmetric 1,3-dipolar cycloaddition of a nitrile oxide to allyl alcohol was successfully applied to the synthesis of a novel optically active cyclopropanol species. Attempts to extent the methodology to other allylic alcohols (thus introducing substituents) failed. Overall the enantioselective synthesis of cyclopropanes *via* the 1,3-dipolar cycloadditions proved to be not generally applicable.

Part 2 of this thesis explored the chemistry of *gem*-dibromocyclopropanes. A highly stereoselective synthesis of bicyclic hemiacetals (hemiaminals) was achieved *via* an intramolecular cyclisation reaction of a lithio-cyclopropane and an ester (amide) group. Several examples demonstrated the general applicability of this reaction. However in order to exploit this reaction fully, the transformations of these bicycles to cyclopropane derivatives would require investigation in greater detail.

5. Appendix to Results and Discussion

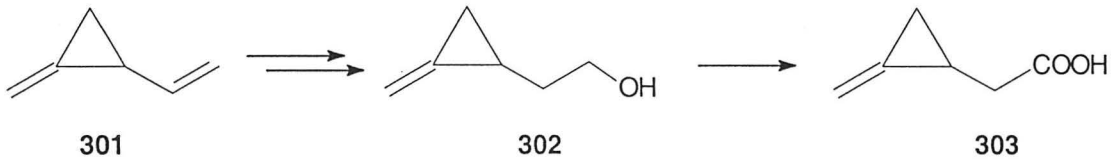
Chemistry of 1-methylene-2-vinylcyclopropane

5.1. Introduction

The final topic of this thesis moves away from stereocontrolled synthesis and puts a small hydrocarbon in the centre of attention: 1-methylene-2-vinylcyclopropane (**301**) (left structure in **Scheme 115**). In methylenecyclopropanes[184] such as **301** the double bond is located outside the three-membered ring, thus those molecules are less strained than related cyclopropenes (see introduction, **Chapter 1.1.2.).**

The synthesis of 1-methylene-2-vinylcyclopropane (**301**) was first published by Shields *et al.* in 1968.[233] Research on this molecule mainly concentrated on rearrangement reactions. At about 80 °C 1-methylene-2-vinylcyclopropane undergoes a thermal rearrangement to 3-methylene cyclopentene.[234,234,235] Palladium(0) catalysed cycloaddition reactions were also carried out with **301.**[236,237] Apart from this, the chemistry of **301** was not investigated extensively.

The reason for being interested in this cyclopropane was the idea that **301** could be a starting material for the synthesis of 2-(2-methylenecyclopropyl)ethanol **302**[238] (**Scheme 115**). Compound **302** is the direct precursor of methylenecyclopropaneacetic acid (MCPA) **303**. MCPA is a strong inhibitor of fatty acid oxidation[12] and recently several derivatives were shown to be potent inhibitors of root galling induced by the nematode pest *Meloidogyne incognita.*[239]

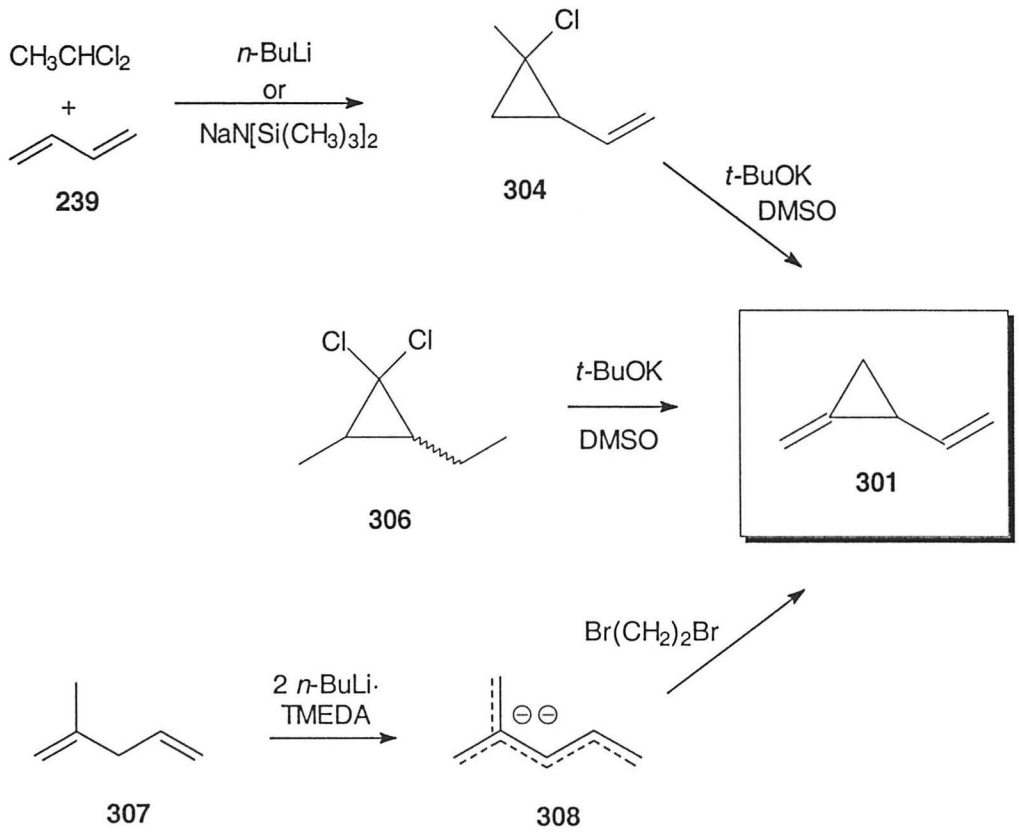


Scheme 115

Synthesis of 1-methylene-2-vinylcyclopropane

Three methods of preparation are known in literature. Arora *et al.*[240] converted 1,3-butadiene **239** into 2-chloro-2-methyl-1-vinylcyclopropane **303** (**Scheme 116**, next page) The yield depends on the base used, in case of *n*-BuLi yields were about 40 %, sodium-bis[trimethylsilyl]amide gave yields at about 80 %. Treatment of **303** with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) gave 1-methylene-2-vinylcyclopropane **301.** The authors claimed that they had obtained 1-methylene-2-vinylcyclopropane (**301**) in 98 % yield and with 99 % purity (determined by GLC).

In a similar reaction reported by Shields *et al* 1-methylene-2-vinylcyclopropane (**301**) was obtained in 62 % yield from 1,1-dichloro-2-ethyl-3-methylcyclo-propane **305**.

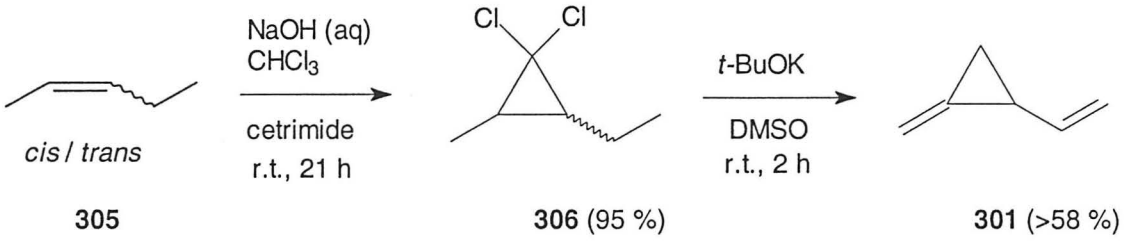


Scheme 116

A different approach was published by Bahl *et al.*[241] (**Scheme 116**). In a first step the 2-methylenepentadienyl dianion **308** was prepared by reacting a *n*-butyllithium-tetramethylethylene-diamine (TMEDA) complex with 2-methyl-1,4-pentadiene **307**. Crystallisation time varied from 2 to 4 weeks and yields of 30 to 40 % (isolated dianion) were achieved. The dianion was isolated in order to determine the amount of reagent necessary for the subsequent step, the treatment of the dianion with 1,2-dibromoethane. This reaction gave **301** in quantitative yield.

5.2. Discussion

1-Methylene-2-vinylcyclo-propane **301** was prepared according to the procedure of Shields *et al.*[241] (see above). The synthesis is outlined here in greater detail (**Scheme 117**).



Scheme 117

Starting from a *cis / trans* isomer mixture of pent-2-ene the cyclopropane **306** was obtained by phase transfer catalysis (PTC) in high yield (95 %). Treatment of **306** with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) gave 1-methylene-2-vinylcyclo-propane (**301**).

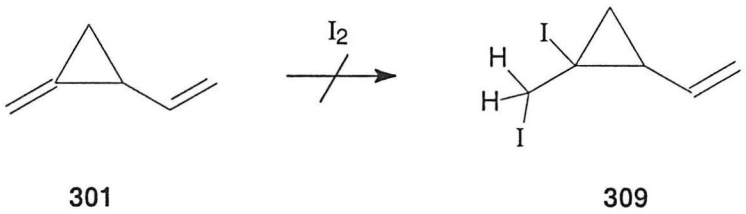
The reaction mixture was extracted with high boiling petrol (b.p.: 240 to 260 °C) and the organic layers were washed with water to remove tertiary butanol and DMSO. The volatile product was distilled off from the solvent and pure product **301** was collected (58 % yield). This isolation method is simpler than the procedure described in literature,[241] where preparative GLC was necessary to obtain pure 1-methylene-2-vinylcyclopropane.

Attempted synthesis of 2-(2-methylenecyclopropyl)ethanol

Conversion of 1-methylene-2-vinylcyclo-propane **301** into 2-(2-methylenecyclo-propyl)ethanol **302** was attempted *via* a hydroboration/oxidation reaction.

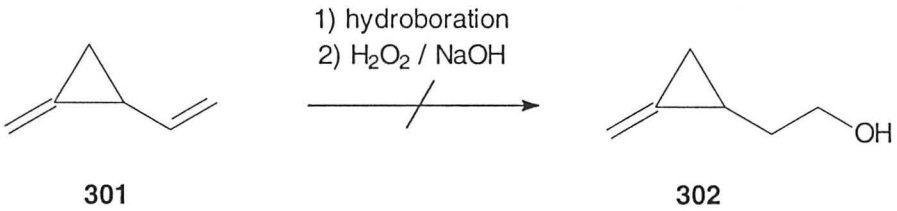
First 1-methylene-2-vinylcyclopropane was treated with iodine in order to protect the methylene group (**Scheme 118**). Protection of the methylene group was thought to be necessary because of the possible interference of this group in the hydroboration reaction. Treatment with iodine is a common method of protecting the double bond in cyclopropenes (see **Chapter 1.3.1.1.**).[46] Similar reactivity was expected with the *exo*-methylene group. However formation of the protected product **309** was not

observed and the ^{1}H-NMR showed a complicated, un-interpretable spectrum. The mixture formed was not stable and decomposed, releasing iodine.



Scheme 118

Now hydroboration-reactions were carried out directly with 1-methylene-2-vinylcyclo-propane **301**, on a small scale and using two different types of reagents, 9-BBN and chiral isopinocampheylborane ($IPCBH_2$) respectively (**Scheme 119**). These reagents are bulky molecules, therefore it was expected that steric hindrance would favour the attack on the vinyl group rather than on the methylene group. Both reaction mixtures were analysed by GLC, but a common product could not be detected. No product could be isolated or identified by ^{1}H-NMR. Further attempts were not undertaken to obtain the alcohol **302** from **301**.



Scheme 119

Studies of reactivity of 1-methylene-2-vinylcyclopropane - attempted trapping of the anion of 301

In order to investigate the reactivity of 1-methylene-2-vinylcyclopropane, several experiments of treating **301** with a strong base and trapping the methylenevinylcyclopropane-anion with different electrophiles were carried out (see **Table 16**).

It was expected that **301** would show similar properties to the analogous methylenecyclopropane.[242] Metalation of methylenecyclopropane with *n*-butyllithium in THF afforded methylenecyclopropyllithium, which reacted with carbonyl electrophiles to produce alcohols in good yields.[244] When diethyl ether was substituted for THF, the rate of deprotonation was significantly reduced.

In case of 1-methylene-2-vinylcyclopropane (**301**), reaction with a strong base (LDA, *n*-BuLi) in diethyl ether did not lead to any trapping with different electrophiles (entries 1-4 of **Table 16**). This suggested that an anion species of **301** was not formed since reacting **301** with *n*-BuLi and quenching the solution with CO_2 afforded valeric acid in moderate yield.

Table 16. Reaction of 1-methylene-2-vinylcyclopropane with strong base and subsequent treatment with electrophiles

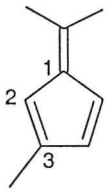
entry	solvent	base	electrophile	comments
1	ether	LDA	TMSCl	no conversion observed
2	ether	LDA	acetone	no conversion observed
3	ether	LDA	CO_2	no conversion observed
4	ether	*n*-BuLi	CO_2	formation of valeric acid
5	THF	LDA	acetone	mixture in GLC
6	THF	LDA	CO_2	mixture in GLC
7	THF	*n*-BuLi	CO_2	solid
8	THF	*n*-BuLi	cyclohexanone	mixture in GLC
9	THF	*n*-BuLi	acetone	isolation of 3-methyl-6,6-dimethylfulvene

Subsequent reactions were therefore carried out in THF (entries 5-9). 1-methylene-2-vinylcyclopropane was treated with LDA in THF and the reaction mixture was quenched with acetone or CO_2 gas. The GLC indicated a mixture of compounds; in

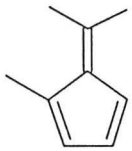
neither case was any product isolated or identified (entries 5, 6). Using *n*-BuLi as a base instead of LDA and upon treatment with CO_2 gas, a solid was isolated (entry 7). The solid was almost insoluble in ether and partially soluble in $CHCl_3$. Purification by column chromatography and recrystallisation were not possible. The NMR was recorded using as well $CDCl_3$ as d-acetone, but both spectra were very complicated and no product could be identified (entry 7).

In another experiment *n*-BuLi / cyclohexanone were employed. Two column chromatographic separations were performed on the obtained mixture; different fractions were collected and analysed by NMR but again a product could not be identified (entry 8).

In a final attempt, the system THF / *n*-BuLi / acetone was tested (entry 9, **Table 16**). Again a mixture was obtained. This time however, a product could be isolated by column chromatography. The compound was identified as 5-isopropylidene-2-methylcyclopenta-1,3-diene **310**. The NMR spectrum also showed traces of its regioisomer **311** to be present.



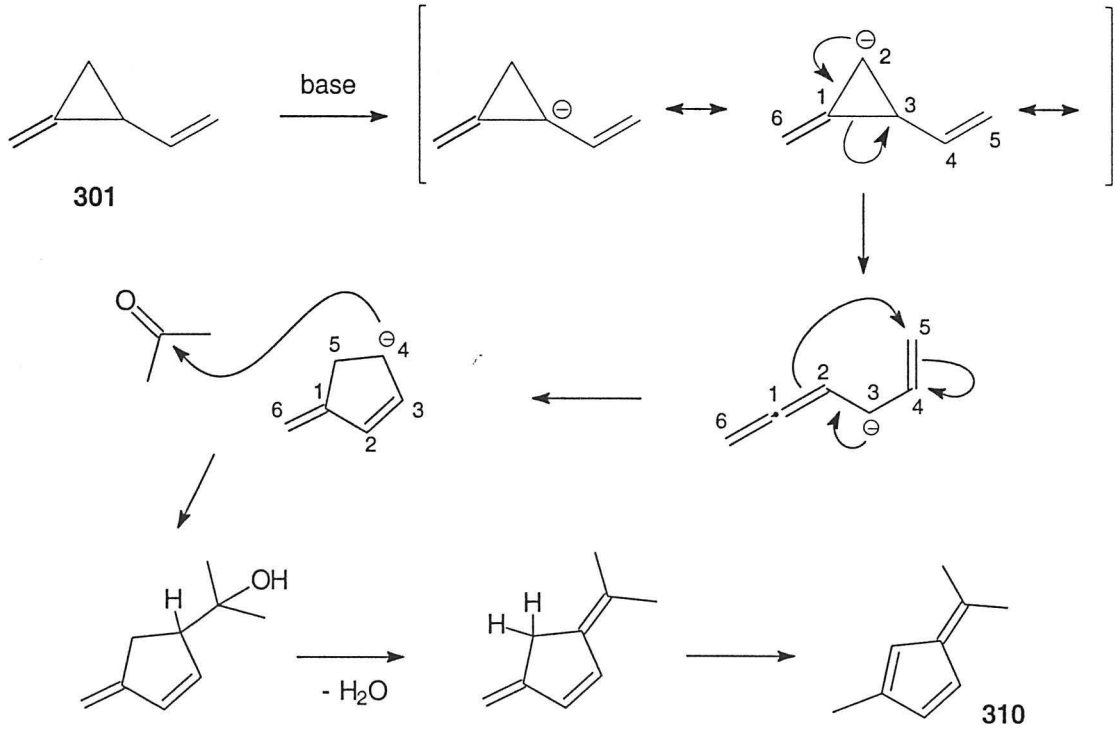
310



311

The ^{1}H NMR of the main compound **88** gave a singlet at 2.08 ppm (methyl group at the ring), two singlets at 2.14 and 2.15 ppm (6H; isopropylidene group) and three multiplets at 6.18, 6.34 and 6.50 ppm respectively. Those values were close to the one reported in literature,[243] where this fulvene species was prepared from methylcyclopentadiene and acetone in the presence of potassium hydroxide.[243,244]

One possible reaction mechanism for the transformation of 1-methylene-2-vinylcyclopropane **301** into the fulvene **310** is outlined in **Scheme 120** (next page).



Scheme 120

1-Methylene-2-vinylcyclopropane **301** was treated with *n*-butyllithium. An anion species was formed, which underwent a fast rearrangement to the 3-methylene-cyclopentene anion. This anion was trapped with acetone to give an alcohol. A conjugated double bond system is formed by the loss of water and in a final step the molecule isomerises to the more stable trimethyfulvene **310**.

The yield of the isolated product was about 13 %. Other products than fulvene were not identified. Signals of **310** were now also identified in the ^{1}H-NMR spectrum of a previous experiment, where acetone was used as well for trapping the anion (entry 5 of **Table 16**).

6,6-Dialkyl- and 6,6-diarylfulvenes are known to be air-sensitive, thermally unstable and very susceptible to autoxidation and polymerisation.[245,246] This may explain the low yield of product isolated.

5.3. Conclusion

The highly volatile hydrocarbon 1-methylene-2-vinylcyclopropane was successfully prepared. Attempts to protect the *exo*-methylene group with iodine failed. The conversion of the vinyl group into an alcohol functionality was neither successful.

Several experiments of treating 1-methylene-2-vinylcyclopropane with a strong base and trapping the methylenevinylcyclopropane anion with different electrophiles were carried out. The trapping experiments were unsuccessful with one exception: using *n*-butyllithium in THF and acetone as the electrophile, 5-isopropylidene-2-methylcyclopenta-1,3-diene was obtained in low yield.

6. Experimental

6.1. General experimental details

Reagents were obtained from commercial suppliers (Aldrich, Lancaster) and were used without further purification unless otherwise stated. Solvents were purified when necessary using the methods suggested in "Purification of Laboratory Chemicals" by D.D Perrin, W.L.F. Armarego and D.R. Perrin.[247] In particular dichloromethane was distilled over calcium hydride, diethyl ether, 1,4-dioxane and tetrahydrofuran over sodium wire. Chloroform was washed with water and dried with phosphorus pentoxide. Petroleum ether was of boiling point 40 - 60 °C unless otherwise stated.

Reactions requiring anhydrous conditions were performed using oven dried glassware (160 °C) cooled under a stream of dry nitrogen or argon; the experiments were conducted under a positive atmosphere of one of these gases. Organic solutions were dried over anhydrous magnesium sulfate, and, unless stated, were evaporated at 14 mmHg. Yields quoted are for purified compounds unless otherwise stated. Any ratios given are calculated by comparing integrals of protons in the ^{1}H NMR spectra unless otherwise stated.

All new compounds were homogenous by TLC or by GLC. GLC was conducted using a Carlo Erba HRGC 5300 (F.I.D., on a capillary column).

TLC was performed using Aldrich silica plates coated with silica gel 60 (F254). Compounds were visualised by examination under an ultraviolet source, by exposure to iodine vapour or by contact with phosphomolybdic acid hydrate (2 % solution in ethanol) followed by heating to 180 °C. Column chromatography was conducted with Fisher Scientific Silica Gel 60 under medium pressure.

Melting points are uncorrected. Infrared spectra were obtained as KBr discs or as liquid films on a Perkin Elmer 1600 FTIR spectrometer. Low resolution mass spectra were obtained on a Finnigan 8430 spectrometer. Accurate mass measurements refer to ^{79}Br and ^{35}Cl isotopes unless stated and were obtained from the Swansea Mass Spectrometry Service. Microanalyses were performed on a Carlo Erba Model 1106 CHN analyser.

NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a Bruker AC250 at 250 MHz for protons, at 62.9 MHz for carbons and in the later case were either broad-band or gated decoupled.

Important note about the use of numbers in the assignment of the NMR spectra: If there is any ring system (mono or bicyclic) present,[i] only the ring-atoms will be labelled with numbers [in case of two separate ring systems, only the larger ring will be numbered]. All other groups / substituents in the molecule are labelled either by their name or elemental symbols.

When a NOE difference spectra was obtained from the Edinburgh University Ultra High Field NMR Service, conditions were as follows: recorded on a Bruker 360 MHz spectrometer, a total of 512 scans per FID, interleaved in blocks of 32 each with 4 'dummy scans', using Bruker program NOEMULT.AU; irradiation period: 7 s; 90 degree pulse, FID acquisition time: 2 s; sample stationary. Data were processed with 1 Hz line broadening.

HPLC was performed on a Milton Roy system (solvent delivering system: consta Metric 3000; variable wavelength detector: spectro Monitor 3100) with a Hewlett-Packard 3392A integrator; the chiral column used was a Chiracel OD from Daicel Chemical Industries, 0.46×25 cm; conditions for the HPLC were as follows: solvent mixture: 2-propanol / hexane 2 %, 5 % and 10 % respectively (see **Table 17**); pressure: 30 psi; flowrate: 0.80 ml/min, UV-detection: 254 nm; concentration of sample 5-10 mg / 1l solvent. The retention times of all tested compounds are given in **Table 17** in the **Appendix**.

i Aryl groups are not considered here.

6.2. Experiments

6.2.1. Experiments of Part I. (1,3-Dipolar cycloaddition reactions)

EXPERIMENT 1

***N*-Hydroxy-4-methoxybenzimidoyl chloride (85)**

Since this nitrile oxide precursor was widely used throughout this thesis, the procedure is described in full.[107]

To a stirred solution of 4-methoxybenzaldehyde oxime (15 g, 0.099 mol) in DMF (90 ml) was added about one-fifth of solid NCS (in total 13.9 g, 0.104 mol). The solution was carefully heated to 50-55 °C (heating gun) to initiate the reaction. Once the reaction began the temperature was kept at about 55 °C by the rate of addition of the rest of the NCS (added in small portions). Stirring was continued for 10 min and the solution was poured into four volumes of ice water. The mixture was extracted with ether (3 × 80 ml). The combined ether extracts were washed with water (3 × 200 ml) and dried. The solvent was removed to give crude crystalline *N-hydroxy-4-methoxy-benzimidoyl chloride* (**85**) (18.4 g, 100 %). The nitrile oxide precursor prepared in this manner did not require further purification for the cycloaddition reactions.

The analytical data of **85** were identical to those reported.[159]

EXPERIMENT 2

6-Methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (79)

A solution of 2,4,6-trimethoxybenzonitrile oxide[148,248] (438 mg, 2.1 mmol) in dry dichloromethane (10 ml) was added to a solution of 3-methyl-3-phenylcyclopropene (300 mg, 2.3 mmol) in dry dichloromethane (5 ml) and the reaction was stirred for 12 h. The solvent was removed and a colourless oil was obtained. Storage in the freezer overnight afforded crystalline *6-methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**79**) (670 mg, 94 %).

White solid, m.p. 104-106 °C.

Found: C 70.79, H 6.22, N 4.20. $C_{20}H_{21}NO_4$ requires: C 70.78, H 6.24, N 4.13.

δ_H 1.33 (3H, s, CH_3), 3.18 (1H, d, J 5.6 Hz, H-5), 3.88 (6H, s, 2× OCH_3), 3.89 (3H, s, OCH_3), 5.01 (1H, d, J 5.6 Hz, H-1), 6.22 (2H, s, CH, aromatic), 7.22-7.41 (5H, m, aromatic).

δ_C 13.3 (CH_3), 20.8 (C-6), 45.0 (C-5), 55.4 (OCH_3), 55.9 (OCH_3), 73.4 (C-1), 90.8 (CH, aromatic), 100.6, 126.3, 127.9, 128.6, 144.0, 153.6, 160.0 (all aromatic C), 162.6 (C-4).

ν_{max} 3008 s, 2929 s, 2839 s, 1604 s, 1500 s, 1459 s, 1413 s, 1344 s, 1226 s, 1205 s, 1156 s, 1134 s, 1068 s, 1034 s, 1015 s, 1002 s, 992 s, 920 m, 846 s, 755 s, 700 s, 627 s, cm^{-1}.

m/z, % 340, 3; 339, 3 (M^+); 311, 23; 310, 24; 309, 11; 308, 10; 281, 9; 280, 9; 265, 5; 192, 88; 193, 100; 165, 11; 146, 27; 117, 12.

EXPERIMENT 3

6,6-Dimethyl-4-(2,4,6-trimethoxyphenyl)-1-trimethylsilanyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (81)

A solution of 2,4,6-trimethoxybenzonitrile oxide[148,248] (407 mg, 1.9 mmol) in dry dichloromethane (10 ml) was added to a solution of 3,3-dimethyl-1-trimethylsilylcyclopropene (300 mg, 2.1 mmol) in dry dichloromethane (5 ml) and the reaction was stirred for 12 h. The solvent was removed and a pale yellow oil was obtained. Storage in the freezer for about one week afforded crystalline *6,6-dimethyl-4-(2,4,6-trimethoxyphenyl)-1-trimethylsilanyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**81**) (675 mg, 99 %).

White solid, m.p. 69-70 °C.

Found: C 61.81, H 7.78, N 4.03. $C_{18}H_{27}NO_4Si$ requires: C 61.86, H 7.79, N 4.01.

δ_H 0.17 (9H, s, $Si(CH_3)_3$), 0.97 (3H, s, CH_3), 1.14 (3H, s, CH_3), 2.41 (1H, s, H-5), 3.77 (6H, s, 2× OCH_3), 3.80 (3H, s, OCH_3), 6.11 (2H, s, CH, aromatic).

δ_C -1.2 ($Si(CH_3)_3$), 14.9 (CH_3), 17.2 (C-6), 23.0 (CH_3), 49.0 (C-5), 55.4 (OCH_3), 55.9 (OCH_3), 90.9 (CH, aromatic), 101.4, 152.3, 159.7 (all aromatic C), 162.1 (C-4).

ν_{max} 2954 m, 1613 s, 1586 s, 1459 s, 1413 s, 1344 m, 1252 m, 1226 s, 1208 s, 1158 s, 1130 s, 1038 w, 930 w, 873 m, 839 s, 812 m, 638 m cm^{-1}.

m/z, % 349, 6 (M^+); 334, 14; 306, 14; 290, 100; 266, 100; 248, 100; 219; 38; 193, 16;157, 16; 141, 20; 113, 11; 73, 31.

EXPERIMENT 4

4-(4-Methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (93)

i. Generation of cyclopropene: methyllithium (7.54 ml, 1.5 M) was added dropwise to a stirred solution of 1,2,2-tribromo-1,3,3-trimethylcyclopropane[249] (1.73 g, 5.4 mmol) in dry ether (15 ml) at -78 °C. The mixture was allowed to reach room temperature and was cooled again to -40 °C. The reaction mixture was quenched with water (5 ml), extracted with ether (3 × 10 ml) and the combined organic layers were dried.

ii. Cycloaddition reaction: *N*-hydroxy-4-methoxybenzimidoyl chloride (1 g, 5.4 mmol) was dissolved in the above ethereal solution (containing 1,3,3-trimethylcyclopropene) and the mixture was cooled to -15 °C. A solution of triethylamine (0.75 ml, 5.4 mmol) in dry ether (10 ml) was added dropwise; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 24 h and then washed with hydrochloric acid (2 %, 20 ml) and water (2 × 30 ml). After drying the organic layer and removing the solvent, the mixture was purified by column chromatography over silica (petrol - ether, 3:1) to give *4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**93**) (820 mg, 66 %) as the main product and as a by-product *3-(4-methoxyphenyl)-5-methyl-5-prop-1-ynyl-4,5-dihydroisoxazole* (**95**) together with a small amount of *bis(4-methoxyphenyl)furoxan* (**94**) (a beige solid, in total 136 mg, compounds not separated).

Main product (**93**):

White solid, m.p. 77-79 °C.

Found: C 72.95, H 7.46, N 6.29. $C_{14}H_{17}NO_2$ requires: C 72.70, H 7.41, N 6.06.

δ_H 0.85 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.64 (3H, s, CH_3), 2.27 (1H, s, H-5), 3.81 (3H, s, OCH_3), 6.86-6.92 (2H, m, aromatic), 7.58-7.63 (2H, m, aromatic).

δ_C 13.6 (CH_3), 14.0 (CH_3), 17.0 (C-6), 21.7 (CH_3), 41.8 (C-5), 55.3 (OCH_3), 79.9 (C-1), 114.0, 122.9, 128.5, 158.4 (all aromatic C), 161.0 (C-4).

ν_{max} 3003 w, 2934 m, 2837 w, 1609 s, 1584 m, 1515 s, 1459 s, 1427 s, 1420 s, 1361 m, 1255 s, 1176 s, 1109 m, 1030 s, 903 s, 876 s, 842 s, 821 s, 736 w cm^{-1}.

m/z, % 231, 10 (M^+); 216, 40; 188, 100; 173, 23; 133, 64; 83,73; 43, 37.

By-product **95**:

δ_H 1.67 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.23 (1H, d, J 16.3 Hz, first of H-4), 3.52 (1H, d, J 16.3 Hz, second of H-4), 3.87 (3H, s, OCH_3), 6.85-6.9 (2H, m, aromatic), 7.53-7.58 (2H, m, aromatic).

δ_C 3.8 (C≡C-$\underline{C}H_3$), 27.8 (CH_3), 48.68 (C-4), 55.3 (OCH_3), 79.9 (C-5), 80.3 (C≡C), 81.4 (C≡C), 114.1, 122.2, 128.1, 156.9 (all aromatic C), 161.1 (C-3).

m/z, % 229, 100 (M^+).

EXPERIMENT 5

4-(4-Methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (98)

i. Generation of cyclopropene: methyllithium (29.6 ml, 1.5 M) was added dropwise to a stirred solution of 1,1-dibromo-3-chloro-2,2-dimethylcyclopropane[250] (5.3 g, 0.020 mol) in dry ether (15 ml) at -78 °C. The mixture was allowed to reach room temperature and was cooled again to -40 °C. The reaction mixture was quenched with water (5 ml), extracted with ether (3 × 10 ml) and the combined organic layers were dried.

ii. Cycloaddition reaction: *N*-hydroxy-4-methoxybenzimidoyl chloride (3 g, 0.016 mol) was dissolved in the above ethereal solution (containing 3,3-dimethylcyclopropene) and the mixture was cooled to -15 °C. Triethylamine (2.25 ml, 0.016 mol) was added dropwise; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 30 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 20 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 2.5:1) to give *4-(4-methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**98**) (2.42 g, 69 %). *Bis(4-methoxyphenyl)furoxan* (**94**) (260 mg, 10 %) was isolated as a by-product.

White solid, m.p. 63-64 °C.

Found: C 71.51, H 6.93, N 6.63. $C_{13}H_{15}NO_2$ requires: C 71.87, H 6.96, N 6.45.

δ_H 0.91 (3H, s, CH_3), 1.18 (3H, s, CH_3), 2.27 (1H, d, J 5.6 Hz, H-5), 3.84 (3H, s, OCH_3), 4.64 (1H, d, J 5.6 Hz, H-1), 6.91-6.96 (2H, m, aromatic), 7.64-7.68(2H, m, aromatic).

δ_C 12.7 (CH_3), 13.4 (C-6), 22.5 (CH_3), 39.5 (C-5), 55.3 (OCH_3), 74.4 (C-1), 114.1, 122.4, 128.8, 158.0 (all aromatic C), 161.1 (C-4).

ν_{max} 3032 w, 2956 m, 2870 m, 2839 m, 1607 s, 1585 m, 1515 s, 1462 s, 1421 s, 1303 s, 1253 s, 1175 s, 1116 m, 1030 s, 999 s, 869 s, 851 s, 834 s, 758 w cm^{-1}.

m/z, % 217, 16 (M^+); 188, 46; 134, 35; 133, 100; 103, 13; 81, 13.

EXPERIMENT 6

4-(4-Methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (102)

Triethylamine (1.46 ml, 10.5 mmol) was added dropwise to a stirred solution of *N*-hydroxy-4-methoxybenzimidoyl chloride (1.94 g, 10.5 mmol) and 3-methyl-3-phenylcyclopropene (1.50 g, 11.5 mmol) in dry ether (20 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 6 h and then treated with hydrochloric acid (2 %, 15 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 15 ml) and the combined organic layers were dried. The solvent was removed to give crude *4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**102**) as a mixture of *endo* and *exo* isomers (ratio *endo*-Me to *exo*-Me, 85:15). The mixture was separated by column chromatography on silica gel (petrol - ether, 3:1 to 1:5).

Major isomer, *endo*-Me (**102**) (2.13 g, 73 %):

White solid, m.p. 95 °C.

Found: C 77.28, H 6.04, N 5.25. $C_{18}H_{17}NO_2$ requires: C 77.40, H 6.13, N 5.01.

δ_H 1.24 (3H, s, CH_3), 3.25 (1H, d, J 5.8 Hz, H-5), 3.87 (3H, s, OCH_3), 5.07 (1H, d, J 5.8 Hz, H-1), 6.95-7.00 (2H, m, aromatic), 7.27-7.42 (5H, m, aromatic), 7.73-7.77 (2H, m, aromatic).

δ_C 12.6 (CH_3), 21.1 (C-6), 40.9 (C-5), 55.4 (OCH_3), 74.5 (C-1), 114.2, 122.1, 126.7, 126.8, 128.8, 128.9, 143.0, 158.3 (all aromatic C), 161.4 (C-4).

ν_{max} 3046 w, 2934 w, 2833 w, 1608 s, 1584 m, 1515 s, 1498 s, 1463 m, 1420 s, 1370 s, 1251 s, 1177 s, 1023 s, 1004 s, 994 s, 868 s, 847 s, 808 s, 759 s, 748 s, 696 s cm^{-1}.

m/z, % 279, 3 (M^+); 264, 2; 250, 11; 146, 42; 145, 100; 133, 27; 131, 25; 117, 11; 103, 10; 91; 10; 77, 10.

Minor isomer, *exo*-Me (**102**) (480 mg, 16 %):

White solid, m.p. 122 °C.

Found: C 77.28, H 6.06, N 5.07. $C_{18}H_{17}NO_2$ requires: C 77.40, H 6.13, N 5.01.

δ_H 1.44 (3H, s, CH_3), 3.14 (1H, d, J 5.5 Hz, H-5), 3.85 (3H, s, OCH_3), 5.02 (1H, d, J 5.5 Hz, H-1), 6.89-6.95 (2H, m, aromatic), 7.16-7.27 (5H, m, aromatic), 7.64-7.70 (2H, m, aromatic).

δ_C 24.4 (C-6), 24.7 (CH_3), 40.7 (C-5), 55.3 (OCH_3), 73.7 (C-1), 114.1, 122.3, 127.1, 128.4, 128.7, 129.5, 137.0, 158.1 (all aromatic C), 161.0 (C-4).

ν_{max} 3039 w, 3011 w, 2966 w, 2938 w, 2842 w, 1608 s, 1582 m, 1514 s, 1498 m, 1458 s, 1444 s, 1377 s, 1303 s, 1252 s, 1176 s, 1021 s, 858 s, 839 s, 824, 766 m, 704 s cm^{-1}.

m/z, % 279, 22 (M^+); 264, 4; 250, 43; 146, 54; 145, 100; 133, 23; 131, 24; 117, 13; 115, 12; 103, 7.

EXPERIMENT 7

1-Butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (107)

i. Generation of cyclopropene: methyllithium (8.8 ml, 1.5 M) was added dropwise to a stirred solution of 1,1,2-tribromo-2-butylcyclopropane[251] (2.0 g, 6.0 mmol) in dry ether (15 ml) at -78 °C. The mixture was allowed to reach room temperature and was cooled again to -40 °C. The reaction mixture was quenched with water (5 ml), extracted with ether (3 × 10 ml) and the combined organic layers were dried.

ii. Cycloaddition reaction: *N*-hydroxy-4-methoxybenzimidoyl chloride (970 mg, 6.0 mmol) was dissolved in the above ethereal solution (containing 1-butylcyclopropene) and the mixture was cooled to -15 °C. Triethylamine (0.83 ml, 6.0 mmol) was added dropwise; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 20 ml) to dissolve

the precipitate. The aqueous layer was extracted with ether (3 × 20 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 2.5:1) to give *1-butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**107**) (585 mg, 46 %). *Bis(4-methoxyphenyl)furoxan* (**94**) (95 mg, 12 %) was isolated as a by-product.

White solid, m.p. 53-54 °C.

Found: C 72.97, H, 7.84, N 5.78. $C_{15}H_{19}NO_2$ requires: C 73.44, H 7.81, N 5.71.

δ_H 0.51 (1H, dd, J 3.9, 5.2 Hz, H_{endo}-6), 0.93 (3H, t, J 7.2 Hz, CH_3), 1.10 (1H, dd, J 5.2, 9.3 Hz, H_{exo}-6), 1.33-1.60 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.85-2.12 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.59 (1H, dd, J 3.9, 9.3 Hz, H-5), 3.85 (3H, s, OCH_3), 6.91-6.96 (2H, m, aromatic), 7.68-7.73 (2H, m, aromatic).

δ_C 12.2 (C-6), 14.0 (CH_3), 22.5 (CH_2), 28.4 (CH_2), 29.1 (C-5), 31.3 (CH_2), 55.3 (OCH_3), 75.3 (C-1), 114.0, 122.7, 128.5 (all aromatic C); 161.4 and 162.1 (C-4 and aromatic C).

ν_{max} 3056 w, 2957 s, 2935 s, 2856 m, 1608 s, 1584 w, 1517 s, 1459 m, 1426 s, 1397 m, 1309 m, 1254s, 1175 m, 1110 m, 1029 s, 920 m, 883 s, 828 s, 606 w cm^{-1}.

m/z, % 245, 5 (M^+); 161, 11; 160, 100; 133, 6; 106, 4; 77, 10; 57, 18.

EXPERIMENT 8

6-Methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylic acid ethyl ester (111)

A solution of triethylamine (0.29 ml, 2.1 mmol) in dry ether (5 ml) was added dropwise to a stirred solution of ethyl 2-chloro-2-(hydroximino)acetate[135] (317 mg, 2.1 mmol) and 3-methyl-3-phenylcyclopropene (300 mg, 2.3 mmol) in dry ether (15 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 24 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed to give crude *6-methyl-6-phenyl-2-oxa-3-aza-bicyclo[3.1.0]hex-3-ene-4-carboxylic acid ethyl ester* (**111**) as a mixture of *endo* and *exo* isomers (ratio *endo*-Me to *exo*-Me, 75:25). The mixture was separated by column chromatography on silica gel (petrol - ether, 3:1).

Major isomer, *endo*-Me (**111**) (150 mg, 29 %), colourless oil:

Found $[M+NH_4]^+$: 263.1402. $C_{14}H_{15}NO_3 + NH_4$ requires: 263.1396.

δ_H 1.18 (3H, s, CH_3), 1.41 (3H, t, J 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 3.31 (1H, d, J 5.6 Hz, H-5), 4.40 (2H, q, J 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 5.17 (1H, d, J 5.6 Hz, H-1), 7.23-7.41 (5H, m, aromatic).

δ_C 13.2 (CH_3), 14.1 ($CO_2CH_2\underline{C}H_3$), 19.8 (C-6), 39.4 (C-5), 62.3 ($CO_2\underline{C}H_2CH_3$), 77.0 (C-1), 127.1, 128.9, 141.6 (all aromatic C), 153.4 (C=O), 160.2 (C-4).

ν_{max} 3060 w, 2983 m, 2936 w, 1741 s, 1721 s, 1601 w, 1558 m, 1497 m, 1446 m, 1384 m, 1258 s, 1221 s, 1127 s, 1051 m, 993 s, 904 m, 889 m, 779 s, 756 s, 700 s cm^{-1}.

m/z (CI, NH_4^+), % 263, 25 $[M+NH_4]^+$; 246, 10 $[MH]^+$; 218, 100; 201, 18; 146, 51; 145, 70.

Minor isomer, *exo*-Me (**111**) (50 mg, 10 %), colourless oil:

An accurate mass spectrum was not obtained.

δ_H 1.31 (3H, t, J 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.38 (3H, s, CH_3), 3.20 (1H, d, J 5.4 Hz, H-5), 4.30 (2H, q, J 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 5.11 (1H, d, J 5.4 Hz, H-1), 7.18-7.36 (5H, m, aromatic).

δ_C 14.0 ($CO_2CH_2\underline{C}H_3$), 22.8 (C-6), 24.2 (CH_3), 39.6 (C-5), 62.0 ($CO_2\underline{C}H_2CH_3$), 75.8 (C-1), 127.4, 128.7, 129.6, 136.4 (all aromatic C), 153.6 (C=O), 160.5 (C-4).

ν_{max} 3060 w, 2981 w, 2927 w, 1742 s, 1721 s, 1558 m, 1497 m, 1445 m, 1382 w, 1261 s, 1181 s, 1118 s, 1009 m, 896 m, 766 m, 702 s cm^{-1}.

m/z, % 216, 16 (M^+-CH_3CH_2); 146, 33; 145, 100; 131, 25; 117, 15; 115, 19; 103, 12; 91, 8; 77, 12.

EXPERIMENT 9

6,6-Dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylic acid ethyl ester (112)

Triethylamine (2.76 ml, 0.020 mol) was added dropwise to a stirred solution of ethyl 2-chloro-2-(hydroximino)acetate (3 g, 0.020 mol) and 3,3-dimethylcyclopropene [prepared from 1,1-dibromo-3-chloro-2,2-dimethylcyclopropane (6.5 g, 0.025 mol) and methyllithium (36.3 ml, 1.5 M) as described in Exp. 6] in ether at -15 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 30 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 20 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 2.5:1) to give a colourless oil, *6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylic acid ethyl ester* (**112**) (1.62 g, 45 %).

An accurate mass spectrum was not obtained.

δ_H 0.84 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.36 (3H, t, J 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 2.73 (1H, d, J 5.5 Hz, H-5), 4.33 (2H, q, J 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.74 (1H, d, J 5.5 Hz, H-1).

δ_C 11.8 (C-6), 12.7 (CH_3), 14.0 ($CO_2CH_2\underline{C}H_3$), 21.9 (CH_3), 38.5 (C-5), 62.0 ($CO_2\underline{C}H_2CH_3$), 77.1 (C-1), 153.0 (C=O), 160.4 (C-4).

ν_{max} 2984 m, 2960 m, 2933 m, 2874 w, 1723 s, 1557 m, 1381 m, 1262 s, 1204 s, 1121 s, 1050 m, 1000 s, 896 s, 823 m, 779 s cm^{-1}.

m/z, % 183, 1 (M^+); 168, 2; 156, 4; 154, 3; 138, 6; 126, 15; 110, 15; 96, 7; 84, 39; 83, 79; 82, 100; 55, 48; 41, 37.

EXPERIMENT 10

Attempted reduction of 6-methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (79) with $LiAlH_4$

A solution of 6-methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (270 mg, 0.8 mmol) in dry THF (10ml) was added to a suspension of $LiAlH_4$ (49 mg, 1.3 mmol) in dry ether (8 ml). The mixture was refluxed for 24 h.

Standard work-up procedure for $LiAlH_4$ reactions:

Drops of a saturated aqueous Na_2SO_4 solution were added to above mixture until no further reaction with the excess of $LiAlH_4$ was observed. To the white-grey suspension dichloromethane (15ml) (or alternatively ethyl acetate) and a small amount of anhydrous $MgSO_4$ were added. The suspension was filtered through a layer of anhydrous $MgSO_4$ and a clear solution was obtained. The solvent was removed under vacuum to give the crude product.

In the present experiment conversion to an amino alcohol was not observed, only starting material (243 mg, 90 %) was recovered.

EXPERIMENT 11

3-Amino-3-(4-methoxyphenyl)-1-phenyl-propan-1-ol (87)

11a) Reduction of 3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (86) with $LiAlH_4$

A solution of 3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (300 mg, 1.2 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (90 mg, 2.4 mmol) in dry ether (10 ml). The mixture was refluxed for 24 h and worked up as is Exp. 10. *3-Amino-3-(4-methoxyphenyl)-1-phenyl-propan-1-ol* (**87**) (260 mg, 85 %) was obtained as a mixture of diastereomers (ratio *syn* to *anti*, 93:7); further purification was not required. The diastereomers were not separated. The *anti* isomer was obtained in enriched form by reduction with $NaBH_4$ (see 11b)).

Mixture of isomers; ratio *syn* to *anti*, 93 to 7:

White solid, m.p. 97-98 °C.

Found: C 74.42, H 7.57, N 5.32. $C_{13}H_{19}NO_2$ requires: C 74.68, H 7.44, N 5.44.

NMR data of major diastereomer (*syn*):

δ_H 1.87-2.03 (2H, m, 2 × H-2), 3.82 (3H, s, OCH_3), 4.15 (1H, m, H-3), 5.02 (1H, m, H-1), 6.88-6.92 (2H, m, aromatic), 7.19-7.23 (2H, m, aromatic), 7.26-7.44 (5H, m, aromatic).

δ_C 46.5 (C-2), 55.3 (OCH_3), 56.4 (C-3), 75.1 (C-1), 114.1, 125.6, 126.5, 127.1, 128.3, 139.1, 145.0, 158.7 (all aromatic C).

ν_{max} (mixture) 3339 m, 3274 m, 3098 br. s, 2915 m, 2830 m, 1609 m, 1512 s, 1459 m, 1243 s, 1177 m, 1033 s, 989 m, 834 m, 709 m, 560 m cm^{-1}.

m/z, % (mixture) 258, 1; 257, 0.5 (M^+); 150, 2; 137, 9; 136, 100; 134, 4; 109, 7; 77, 5.

11b) Reduction of 3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (86) with $NaBH_4$

$NaBH_4$ (224 mg, 5.9 mmol) was added portionwise to a stirred solution of 3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (300 mg, 1.2 mmol) and $NiCl_2 \cdot 6H_2O$ (563 mg, 2.4 mmol) in methanol (50 ml) at -20 °C under nitrogen and the mixture was stirred for 15 min.

Work-up: methanol was removed under reduced pressure, NH_3 (aqueous solution , *d* 0.88, 40 ml) and dichloromethane (40 ml) were added carefully, and the black mixture was stirred under air until the organic layer became almost clear (about 20 min). The aqueous layer was extracted with dichloromethane (3 × 40 ml), the combined organic layers were dried and the solvent was removed. The residue was recrystallised from ethyl acetate to give *3-amino-3-(4-methoxyphenyl)-1-phenyl-propan-1-ol* (**87**) (240 mg, 79 %) as a mixture of diastereomers (ratio *syn* to *anti*, 31:69).

NMR data of *syn* isomer: see 11a)

NMR data of *anti* isomer:

δ_H 2.07-2.12 (2H, m, 2 × H-2), 3.82 (3H, s, OCH_3), 4.13 (1H, dd, J 4.6, 7.2 Hz, H-3), 4.93 (1H, dd, J 4.6, 6.1 Hz, H-1), 6.88-6.92 (2H, m, aromatic), 7.19-7.23 (2H, m, aromatic), 7.26-7.44 (5H, m, aromatic).

δ_C 45.4 (C-2), 52.7 (C-3), 55.3 (OCH_3), 71.9 (C-1), 114.0, 125.7, 126.9, 128.2 (2 peaks), 137.4, 144.9 158.7 (all aromatic C).

EXPERIMENT 12

Attempted reduction of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (93) with $LiAlH_4$

A solution of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (300 mg, 1.3 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (59 mg, 1.6 mmol) in dry ether (8 ml). The mixture was refluxed for 72 h. TLC did not show

any conversion; more $LiAlH_4$ (133 mg) was added and the mixture was refluxed for further 24 h. Work-up as is Exp. 10 gave only starting material (**93**).

EXPERIMENT 13

5-Amino-5-(4-methoxyphenyl)-3,3-dimethylpentan-2-ol (97)

$NaBH_4$ (131 mg, 3.4 mmol) was added portion wise to a stirred solution of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (160 mg, 0.7 mmol) and $NiCl_2 \cdot 6H_20$ (329 mg, 1.4 mmol) in methanol (30 ml) at -20 °C under nitrogen. After 5 min the mixture was allowed to reach room temperature and stirring was continued for 40 min. The work-up was carried as in Exp. 11b). The residue was passed over a short column of silica gel, eluting with ether, to give a pale yellow oil, *5-amino-5-(4-methoxyphenyl)-3,3-dimethylpentan-2-ol* (**97**) (115 mg, 70 %) as a mixture of two diastereomers (ratio, 62:38).

M^+ was not observed.

NMR data, major diastereomer:

δ_H 0.98 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.09 (3H, d, 6.4 Hz, CH_3), 1.69 (1H, dd, J 10.0, 12.5 Hz, first of H-4), 1.98 (1H, br. s, OH), 2.07 (1H, dd, J 7.2, 12.5 Hz, second of H-4), 3.14 (1H, q, J 6.4 Hz, H-2), 3.84 (3H, s, OCH_3), 4.34 (1H, dd, J 7.2, 10.0 Hz, H-5), 6.88-6.92 (2H, m, aromatic), 7.30-7.34 (2H, m, aromatic).

δ_C 14.9 (CH_3), 20.5 (C-1), 25.7 (CH_3), 42.0 (C-3), 51.7 (C-4), 55.3 (OCH_3), 58.5 (C-5), 63.2 (C-2), 113.8, 127.2, 139.4, 158.2 (all aromatic C).

NMR data, minor diastereomer:

δ_H 1.00 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.13 (3H, d, 6.4 Hz, CH_3), 1.62 (1H, dd, J 8.4, 12.9 Hz, first of H-4), 1.98 (1H, br. s, OH), 2.06 (1H, dd, J 8.4, 12.9 Hz, second of H-4), 2.96 (1H, q, J 6.4 Hz, H-2), 3.84 (3H, s, OCH_3), 4.18 (1H, t, J 8.4 Hz, H-5), 6.88-6.92 (2H, m, aromatic), 7.30-7.34 (2H, m, aromatic).

δ_C 15.6 (CH_3), 24.5 (C-1), 27.8 (CH_3), 40.3 (C-3), 50.0 (C-4), 55.3 (OCH_3), 59.6 (C-5), 63.8 (C-2), 113.7, 127.7, 136.9, 156.1 (all aromatic C).

ν_{max} (mixture) 2955 s, 2867 w, 2834 w, 1611 m, 1584 w, 1511 s, 1462 m, 1366 w, 1301 m, 1244 s, 1179 m, 1125 w, 1038 m, 828 m cm^{-1}.

m/z, % (mixture) 220, 12 (M^+-OH); 219, 28; 218, 17; 176, 19; 163, 100; 162, 75; 161, 73; 148, 16; 134, 16; 121, 15; 91, 8; 77, 8.

EXPERIMENT 14

3-[Amino(4-methoxyphenyl)methyl]-2,2-dimethylcyclopropanol (99)

A solution of 4-(4-methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (550 mg, 2.5 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (192 mg, 5.1 mmol) in dry ether (10 ml). The mixture was refluxed for 20 h. Work-up was carried out as is Exp. 10 and the residue was recrystallised from ether / petrol to give *3-[amino(4-methoxyphenyl)methyl]-2,2-dimethylcyclopropanol* (**99**) (380 mg, 68 %).

White solid, m.p. 102-103 °C.

Found: C 70.51, H 8.84, N 6.50. $C_{13}H_{19}NO_2$ requires: C 70.56, H 8.65, N 6.33.

δ_H 0.77 (1H, dd, J 6.8, 10.1 Hz, H-3), 1.03 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.78 (3H, br. s, NH_2 and OH), 3.08 (1H, d, J 6.8 Hz, H-1), 3.77 (3H, s, OCH_3), 3.89 (1H, d, J 10.1 Hz, C<u>H</u>-NH_2), 6.82-6.86 (2H, m, aromatic), 7.31-7.34 (2H, m, aromatic).

δ_C 13.3 (CH_3), 19.1 (C-2), 26.4 (CH_3), 35.7 (C-3), 50.6 (CH-NH_2), 55.3 (OCH_3), 57.9 (C-1), 113.9, 127.5, 138.2, 158.5 (all aromatic C).

ν_{max} 3351 w, 3295 w, 3126 br. s, 2950 s, 16101 s, 1581 s, 1512 s, 1461 m, 1343 m, 1303 s, 1272 s, 1248 s, 1178 s, 1148 s, 1038 s, 1005 m, 951 s, 831 s, 781 w, 542 m cm^{-1}.

m/z, % 204, 12 (M^+-OH); 175, 58; 149, 46; 136, 100; 134, 34; 121, 10; 109, 12; 58, 5.

EXPERIMENT 15

4-Amino-4-(4-methoxyphenyl)-2,2-dimethylbutan-1-ol (100)

$NaBH_4$ (348 mg, 9.2 mmol) was added portionwise to a stirred solution of 4-(4-methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (400 mg, 1.8 mmol) and $NiCl_2 \cdot 6H_20$ (875 mg, 3.7 mmol) in methanol (50 ml) at -15 °C. After 5 min the mixture was allowed to reach room temperature and stirring was continued for 20 min. Work-up as in Exp. 11b) gave a yellow oil (337 mg). The residue was purified by column chromatography on silica gel (petrol - ether, 2.5:1 to ether only) to give a pale yellow oil, *4-amino-4-(4-methoxyphenyl)-2,2-dimethylbutan-1-ol* (**100**) (90 mg, 22 %).

M^+ (223) was not observed.

δ_H 1.16 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.54 (1H, dd, J 9.8, 12.5 Hz, first of H-3), 1.96 (1H, dd, J 7.1, 12.5 Hz, second of H-3), 2.10 (1H, br. s, OH), 2.80 (1H, d, J 10.2 Hz, first of H-1), 2.93 (1H, d, J 10.2 Hz, second of H-1), 3.82 (3H, s, OCH_3), 4.26 (1H, dd, J 7.1, 9.8 Hz, H-4), 6.86-6.90 (2H, m, aromatic), 7.29-7.33 (2H, m, aromatic).

δ_C 27.9 (CH_3), 28.7 (CH_3), 39.5 (C-2), 50.0 (C-3), 55.2 (OCH_3), 61.1 (C-1), 62.0 (C-4), 113.7, 127.5, 137.0, 158.4 (all aromatic C).

ν_{max} 3342 br. m, 2952 s, 2865 w, 2834 w, 1611 m, 1585 w, 1513 s, 1464 m, 1365 w, 1300 m, 1245 s, 1179 m, 1037 m, 830 m cm^{-1}.

m/z, % 203, 3; 202, 28; 201, 42; 200, 33; 186, 5; 171, 8; 158, 14; 146, 45; 145, 100; 133, 19; 131, 9; 118, 10; 116, 10; 96, 7; 89, 8; 75, 6.

EXPERIMENT 16

3-[Amino(4-methoxyphenyl)methyl]-2-methyl-2-phenylcyclopropanol (103)

A solution of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (390 mg, 1.4 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (90 mg, 2.8 mmol) in dry ether (10 ml). The mixture was refluxed for 20 h. Work-up was carried out as is Exp. 10 and the residue was recrystallised from ethyl acetate to give *3-[amino(4-methoxyphenyl)methyl]-2-methyl-2-phenylcyclopropanol* (**103**) (200 mg, 51 %).

White solid, m.p. 116-120 °C.

Found: C 76.32, H 7.72, N 5.08. $C_{18}H_{21}NO_2$ requires: C 76.30, H 7.47, N 4.94.

δ_H 1.45 (1H, dd, J 7.1, 10.1 Hz, H-3), 1.63 (3H, s, CH_3), 1.98 (3H, br. s, NH_2 and OH), 3.64 (1H, d, J 7.1 Hz, H-1), 3.82 (3H, s, OCH_3), 4.16 (1H, d, J 10.1 Hz, C<u>H</u>-NH_2), 6.87-6.92 (2H, m, aromatic), 7.16-7.35 (5H, m, aromatic), 7.41-7.45 (2H, m, aromatic).

δ_C 13.8 (CH_3), 28.3 (C-2), 36.6 (C-3), 50.4 (CH-NH_2), 55.3 (OCH_3), 58.0 (C-1), 114.0, 125.9, 127.2, 127.7, 128.4, 137.6, 147.0, 158.7 (all aromatic C).

ν_{max} 3418 br. s, 3145 br. s, 3057 m, 2931 m, 1609 m, 1579 m, 1512 s, 1459 m, 1444 m, 1247 s, 1182 m, 1154 m, 1034 s, 956 m, 830 m, 765 m, 701 s cm^{-1}.

m/z, % 266, 1 (M^+-OH); 237, 28; 149, 41; 136, 100; 134, 22; 57, 20; 43, 18.

EXPERIMENT 17

Reduction of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (102) with $NaBH_4$

$NaBH_4$ (271 mg, 7.2 mmol) was added portionwise to a stirred solution of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (400 mg, 1.4 mmol) and $NiCl_2 \cdot 6H_20$ (681 mg, 2.9 mmol) in methanol (50 ml) at -35 °C. After 5 min the mixture was allowed to reach room temperature and stirring was continued for 10 min. Work-up as in Exp. 11b) gave a yellow oil (295 mg). The oil was treated with ether; a white precipitate formed and was filtered off. The compound (**102**) (65 mg) could not be identified.

Unidentified compound, Rf (ether): 0.38.

White solid, m.p. 160-162 °C.

Found: C 78.12, H 6.81, N 4.92. $C_{18}H_{19}NO_2$ requires: C 76.84, H 6.81, N 4.98.

δ_H 1.32 (3H, s, CH_3), 3.21 (1H, d ?, J 17.7 Hz), 3.30 (1H, d ?, J 16.2 Hz), 3.84 (3H, s, OCH_3), 5.8 (1H, s, C=C-H ?), 6.92-6.96 (2H, m, aromatic), 7.18-7.36 (5H, m, aromatic), 7.84-7.88 (2H, m, aromatic).

δ_C 20.3 (CH_3), 48.1 (CH_2), 51.2 (q?), 55.3 (OCH_3), 99.9 (C=<u>C</u>-H), 114.0, 126.2, 126.3, 127.3, 128.4, 129.5, 147.4, (all aromatic C), 162.1 (q), 170.8 (q).

ν_{max} 3440 br. w, 3078 br. s, 2986 w, 2962 w, 2836 w, 1610 m, 1572 m, 1516 s, 1444 m, 1333 s, 1313 m, 1256 s, 1177 s, 1151 m, 1122 s, 1097 m, 1058 s, 1034 s, 981 m, 832 s, 760 m, 697 s, 593 w cm^{-1}.

m/z, % 281, 42; 266, 27; 263, 25; 248, 18; 236, 23; 221, 15; 204, 9; 176, 28; 164, 68; 162, 68; 134, 100; 121, 39; 115, 25; 103, 23; 91, 28; 77, 40.

EXPERIMENT 18

2-[Amino(4-methoxyphenyl)methyl]-1-butylcyclopropanol (108)

A solution of 1-butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (400 mg, 1.6 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (124 mg, 3.3 mmol) in dry ether (10 ml). The mixture was refluxed for 27 h. Work-up as is Exp. 10 gave a yellow oil, *2-[amino(4-methoxyphenyl)methyl]-1-butylcyclopropanol* (**108**) (330 mg, 81 %); further purification was not required.

M^+ was not observed.

δ_H 0.68 (1H, dd, J 5.7, 9.5 Hz, H_{cis}-3), 0.78 (1H, dd, J 5.7, 6.2 Hz, H_{trans}-3), 0.84 (3H, t, J 7.1 Hz, CH_3), 0.93 (1H, ddd, J 5.8, 6.2, 9.5 Hz, H-2), 1.24-1.53 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.68 (3H, br. s, NH_2 and OH), 3.77 (3H, s, OCH_3), 4.06 (1H, d, J 5.8 Hz, $C\underline{H}$-NH_2), 6.83-6.87 (2H, m, aromatic), 7.29-7.32 (2H, m, aromatic).

δ_C 14.1 (CH_3), 15.4 (C-3), 22.6 (CH_2), 27.8 (CH_2), 28.9 (C-2), 38.5 (CH_2), 53.2 (CH-NH_2), 55.3 (OCH_3), 58.7 (C-1), 114.0, 127.2, 138.6, 158.6 (all aromatic C).

ν_{max} 3340 br. s, 2956 s, 2931 s, 1612 m, 1513 s, 1464 m, 1301 w, 1246 s, 1178 m, 1108 w, 1037 m, 829 m cm^{-1}.

m/z, % 233, 10; 232, 33 (M^+-OH); 189, 35; 176, 19; 162, 8; 147, 100; 136, 83; 121, 20; 102, 37; 91, 21; 85, 15; 77, 18; 57, 33.

EXPERIMENT 19

[6-(4-Methoxyphenyl)-6-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]methanol (113)

A solution of *endo* 6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylic acid methyl ester (**113**) (60 mg, 0.24 mmol) in dry ether (5 ml) was added to a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in dry ether (5 ml). The mixture was refluxed for 2 h. Work-up as in Exp. 11b) gave pure *[6-(4-methoxyphenyl)-6-methyl-2-oxa-3-aza-bicyclo[3.1.0]hex-3-en-4-yl]methanol* (**113**) (40 mg, 80 %).

The compound was not fully characterised.

δ_H 1.21 (3H, s, CH_3), 2.99 (1H, br. s, OH), 3.02 (1H, d, J 5.5 Hz, H-5), 4.51 (2H, s, CH_2OH), 4.98 (1H, d, J 5.5 Hz, H-1), 7.20-7.40 (5H, m, aromatic).

δ_C 12.8 (CH_3), 20.5 (C-6), 40.8 (C-5), 58.1 (CH_2OH), 74.7 (C-1), 126.3, 128.7, 142.4 (all aromatic C), 160.4 (C-4).

EXPERIMENT 20

3-(1-Amino-2-hydroxyethyl)-2,2-dimethylcyclopropanol (115)

$LiAlH_4$ (414 mg, 10.9 mmol) was added in small portions to a solution of 6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylic acid methyl ester (**112**) (1 g, 5.4 mmol) in dry ether (50 ml). The mixture was stirred for 2 h at room temperature. Drops of a saturated aqueous Na_2SO_4 solution were added to the above mixture until no further reaction with the excess of $LiAlH_4$ was observed. The suspension was filtered through a layer of anhydrous $MgSO_4$ and a clear solution (I) was obtained. Washing the filter residue with ethyl acetate (2 × 15 ml) gave solution (II). Solution (I) was concentrated to give a crude mixture of *3-(1-amino-2-hydroxyethyl)-2,2-dimethylcyclopropanol* (**115**) and *[6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]methanol* (**114**) (ratio, 71:29; in total 400 mg). The mixture was not separated.

Solution (II) was left standing overnight and crystals were formed which were identified as pure **115** (110 mg, 14 %).

^{1}H NMR of (**114**):

δ_H 0.85 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.41 (1H, d, J 5.5 Hz, H-5), 4.32 (2H, s, CH_2OH), 4.52 (1H, d, J 5.5 Hz, H-1).

Isolated compound (**115**):

Colourless crystals , m.p. 109-111 °C.

Found: C 58.08, H 10.41, N 9.83. $C_7H_{15}NO_2$ requires: C 57.90, H 10.41, N 9.65.

δ_H (CD_3OD) 0.40 (1H, dd, J 7.0, 10.2 Hz, H-3), 1.04 (3H, s, CH_3), 1.21 (3H, s, CH_3), 2.88 (1H, ddd, J 4.5, 7.2 , 10.2 Hz, C<u>H</u>-NH_2), 3.10 (1H, d, J 7.0 Hz, H-1), 3.43 (1H, dd, J 7.2, 10.3 Hz, first H of C<u>H</u>$_2$OH), 3.67 (1H, dd, J 4.5, 10.3 Hz, second H of C<u>H</u>$_2$OH), 4.90 (4H, br. s, 2 × OH and NH_2).

δ_C (CD_3OD) 14.3 (CH_3), 19.9 (C-2), 27.3 (CH_3), 32.4 (C-3), 50.5 (CH-NH_2), 58.8 (C-1), 68.3 (CH_2OH).

ν_{max} 3376 br. s, 3319 s, 3263 s, 3086 br s, 2973 br. s, 2688 br.s, 1601 s, 1459 s, 1418 s, 1332 s, 1254 m, 1196 s, 1146 s, 1043 s, 978 s, 893 s, 863 s, 709 s, 667 s, 520 s cm^{-1}.

m/z, % 146, 3 (M^++1); 116, 9; 114, 18; 99, 10; 97, 10; 81, 26; 60, 100; 58, 30; 43, 58.5

EXPERIMENT 21

2,2-Dibromocyclopropanecarbaldehyde oxime (124)

To a mixture of 2,2-dibromocyclopropanecarbaldehyde (5.8 g, 0.025 mol) in water (20 ml), ethanol (20 ml), and ice (20 ml) was added hydroxylamine hydrochloride (1.94 g, 0.028 mol). Sodium hydroxide (2.54 g, 50% solution, 0.064 mol) was added with stirring. Enough ice to keep the temperature at 25-30 °C was added. The mixture was stirred for 1 h, acidified with hydrochloric acid (10 %) to pH 5 and extracted with ether (2 × 100 ml). The combined ether extracts were dried and the solvent was removed to give crude *2,2-dibromocyclopropanecarbaldehyde oxime* (**124**) (5.69 g, 92 %) as a mixture of *E* and *Z* isomers (ratio 50:50). The oxime was used without further purification for the next step, the conversion to the hydroximoyl chloride (Exp. 22).

Beige solid, unstable at room temperature, m.p. 57-67 °C.

CHN analysis was not obtained; compound decomposed.

δ_H *E/Z* mixture: 1.75 (1H, t, J 7.5 Hz, H_{trans}-3), 1.83 (1H, t, J 7.5 Hz, H_{trans}-3), 2.07 (1H, dd, J 7.5, 10.4 Hz, H_{cis}-3), 2.14 (1H, dd, J 7.5, 10.4 Hz, H_{cis}-3), 2.49 (1H, td, J 7.5, 10.4 Hz, H-1), 3.08 (1H, td, J 7.5, 10.4 Hz, H-1), 6.53 (1H, d, J 7.5 Hz, CH=N), 7.23 (1H, d, J 7.5 Hz, CH=N).

δ_C *E/Z* mixture: 23.61 (C-2), 23.64 (C-2), 25.3 (C-1), 28.3 (C-3), 29.4 (C-3), 29.9 (C-1), 149.3 (CH=N), 150.4 (CH=N).

ν_{max} 3242 br. s, 3090 s, 2977 s, 2899 m, 1654 m, 1428 s, 1343 s, 1216 m, 1167 m, 1102 s, 1051 m, 1016 s, 965 s, 920 s, 852 m, 693 s cm^{-1}.

m/z, % 226, 5 (M^+-OH); 201, 3; 199, 5; 164, 34; 162, 42; 145, 17; 119, 18; 117, 11; 83, 100; 64, 15; 55, 33; 44, 16.

EXPERIMENT 22

N-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (125)

2,2-Dibromocyclopropanecarbaldehyde oxime (**125**) (5.46 g, 0.022 mol) in DMF (30 ml) was reacted with NCS (3.00 g, 0.022 mol), using a procedure analogous to the one described in Exp. 1. Crude *N-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride* (**125**) (5.46 g, 88 %) was obtained. The nitrile oxide precursor prepared in this manner did not require further purification for the cycloaddition reactions.

White-grey solid, m.p. 75-77 °C.

Found: C 18.13, H 1.53, N 4.85. $C_4H_4Br_2ClNO$ requires: C 17.32, H 1.45, N 5.05 (it was not possible to obtain a better value for carbon in the CHN analysis).

δ_H 2.03 (1H, dd, J 7.7, 10.0 Hz, H_{cis}-3), 2.22 (1H, t, J 7.7 Hz, H_{trans}-3), 2.65 (1H, dd, J 7.7, 10.0 Hz, H-1), 8.59 (1H, br. s, OH).

δ_C 23.0 (C-2), 27.9 (C-3), 35.7 (C-1), 137.8 (CCl=N).

ν_{max} 3293 br. s, 3092 s, 2924 s, 1707 w, 1632 s, 1432 s, 1361 s, 1212 m, 1172 w, 1136 s, 1098 s, 1040 s, 993 s, 927 s, 862 s, 710 s, 672 s, 617 s cm^{-1}.

m/z, % 235, 8; 233, 12 (M^+-"44"); 231, 6; 198, 33; 196, 23; 119, 34; 117, 100; 51, 11; 44, 23.

EXPERIMENT 23

1-Butyl-4-(2,2-dibromocyclopropyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (129)

Triethylamine (0.29 ml, 2.7 mmol) was added dropwise to a stirred solution of *N*-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (580 mg, 2.1 mmol) and 1-butylcyclopropene [prepared from 1,1,2-tribromo-2-butylcyclopropane (960 mg, 2.9 mmol) and methyllithium (3.97 ml, 1.5 M) as described in Exp. 7] in ether at -15 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 48 h and then treated with hydrochloric acid (2 %, 20 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 20 ml) and the combined organic layers were dried. The solvent was removed to give crude *1-butyl-4-(2,2-dibromocyclopropyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**129**) as a mixture of two diastereomers (ratio a to b, 41:59). The mixture was partially separated by column chromatography on silica gel (petrol - ether, 2:1); yellow oil, total yield: 490 mg (70 %); *bis(2,2-dibromocyclopropyl)furoxan* (**128**) (55 mg, 12 %) was isolated as a by-product (full analytical data of **128** are given in Exp. 27).

M^+ was not observed.

NMR data, diastereomer a (minor isomer, fraction 1):

δ_H 0.57 (1H, dd, J 3.7, 5.5 Hz, H_{endo}-6), 0.89 (3H, t, J 7.1 Hz, CH_3), 1.00 (1H, dd, J 5.5, 9.5 Hz, CH, H_{exo}-6), 1.30-1.52 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.80-2.01 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.05 (1H, dd, J 7.8, 10.2 Hz, H_{cis} of cyclopropyl CH_2), 2.15 (1H, t, J 7.8 Hz, H_{trans} of cyclopropyl CH_2), 2.36 (1H, dd, J 3.7, 9.5 Hz, H-5), 2.51 (1H, dd, J 7.8, 10.2 Hz, H cyclopropyl).

δ_C 11.2 (C-6), 13.9 (CH_3), 22.4 (CH_2), 24.6 (CBr_2), 27.9 (CH_2, cyclopropyl), 28.3 (CH_2), 29.8 (C-5), 30.5 (CH, cyclopropyl), 31.2 (CH_2), 76.8 (C-1), 159.8 (C-4).

NMR data, diastereomer b (major isomer):

δ_H 0.47 (1H, dd, J 3.7, 5.5 Hz, H_{endo}-6), 0.87 (3H, t, J 7.1 Hz, CH_3), 1.01 (1H, dd, J 5.5, 9.5 Hz, H_{exo}-6), 1.29-1.49 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.69-1.99 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.04 (1H, dd, J 7.8, 10.1 Hz, CH, H_{cis} of cyclopropyl CH_2), 2.17 (1H, t, J 7.8 Hz, H_{trans} of cyclopropyl CH_2), 2.29 (1H, dd, J 3.7, 9.5 Hz, H-5), 2.69 (1H, dd, J 7.8, 10.1 Hz, H cyclopropyl).

δ_C 12.0 (C-6), 13.9 (CH_3), 22.4 (CH_2), 24.2 (CBr_2), 27.0 (CH_2, cyclopropyl), 28.3 (CH_2), 29.1 (C-5), 30.6 (CH, cyclopropyl), 31.2 (CH_2), 77.3 (C-1), 160.8 (C-4).

ν_{max} (mixture) 2956 s, 2932 s, 2870 m, 1611m, 1466 m, 1432 s, 1410 s, 1168 w, 1107 m, 1055 m, 968 m, 944 m, 881 m, 649 m cm^{-1}.

m/z, % (mixture) 258, 3; 256, 6 (M^+-Br); 201, 5; 199, 10; 177, 2; 173,7; 93, 11; 85, 98; 57, 100; 55, 37.

EXPERIMENT 24

4-(2,2-Dibromocyclopropyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (127)

Triethylamine (2.0 ml, 0.014 mol) was added dropwise to a stirred solution of *N*-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (4.0 g, 0.014 mol) and 3,3-dimethylcyclopropene [prepared from 1,1-dibromo-3-chloro-2,2-dimethylcyclopropane (4.76 g, 0.018 mol) and methyllithium (26.6 ml, 1.5 M) as described in Exp. 6] in ether at -15 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 30 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 30 ml) and the combined organic layers were dried. The solvent was removed to give crude *4-(2,2-dibromocyclopropyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**127**) as a mixture of two diastereomers (ratio, 61:39). The mixture was purified by column chromatography on silica gel (petrol - ether, 2:1), when a semi-solid **127** (2.36 g, 53 %) was obtained. The two diastereomers were not separated.

Found: C 32.87, H, 3.22, N 4.76. $C_{15}H_{19}NO_2$ requires: C 34.98, H. 3.59, N 4.53 (**127** was purified by column chromatography for a second time, however it was not possible to obtain a better value for carbon in the CHN analysis).

NMR data, major diastereomer:

δ_H 0.91 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.04 (1H, dd, J 7.8, 10.2 Hz, H_{cis} of cyclopropyl CH_2), 2.15 (1H, t, J 7.8 Hz, H_{trans} of cyclopropyl CH_2), 2.40 (1H, d, J 5.5 Hz, H-5), 2.61 (1H, dd, J 7.8, 10.2 Hz, H cyclopropyl), 4.60 (1H, d, J 5.5 Hz, H-1).

δ_C 12.9 (C-6), 13.0 (CH_3), 22.2 (CH_3), 23.9 (CBr_2), 27.0 (CH_2, cyclopropyl), 28.9 (CH, cyclopropyl), 40.5 (C-5), 75.3 (C-1), 157.0 (C-4).

NMR data, minor diastereomer:

δ_H 0.91 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.98 (1H, t, J 7.8 Hz, H_{trans} of cyclopropyl CH_2), 2.11 (1H, dd, J 7.8, 10.5 Hz, H_{cis} of cyclopropyl CH_2), 2.41 (1H, d, J 5.5 Hz, H-5), 2.58 (1H, dd, J 7.8, 10.5 Hz, H cyclopropyl), 4.59 (1H, d, J 5.5 Hz, H-1).

δ_C 13.6 (C-6), 13.7 (CH_3), 22.4 (CH_3), 23.9 (CBr_2), 28.8 (CH_2, cyclopropyl), 29.0 (CH, cyclopropyl), 40.9 (C-5), 75.5 (C-1), 156.5 (C-4).

ν_{max} (mixture) 3090 w, 3050 s, 2958 s, 2926 s, 2871 s, 1613 s, 1567 m, 1466 s, 1454 s, 1428 s, 1398 s, 1378 s, 1293 m, 1213 m, 1108 s, 1096 s, 1001 s, 906 m, 864 s, 733 m, 680 s, 641 s cm^{-1}.

m/z, % (mixture) 294, 2 (M^+ - CH_3); 199, 16; 121, 13; 102, 17; 95, 21; 94, 17; 84, 63; 83, 100; 56, 35; 55, 63.

Bis(2,2-dibromocyclopropyl)furoxan (**128**) (210 mg, 6 %) was isolated as a by-product.

EXPERIMENT 25

3-(2,2-Dibromocyclopropyl)-5-phenylisoxazole (130)

Triethylamine (0.34 ml, 2.4 mmol) was added dropwise to a stirred solution of *N*-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (620 mg, 2.2 mmol) and phenylacetylene (1.0 ml, 8.9 mmol) in dry ether (10 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *3-(2,2-dibromocyclopropyl)-5-phenylisoxazole* (**130**) (275 mg, 36 %).

White solid, m.p. 77-79 °C.

Found: C 42.22, H 2.53, N 4.17. $C_{12}H_9Br_2NO$ requires: C 42.02, H 2.64, N 4.08.

δ_H 2.25 (2H, d, J 9.1 Hz, 2H of cyclopropyl CH_2,), 2.94 (1H, t, J 9.1 Hz, H cyclopropyl), 6.52 (1H, s, H-4), 7.43-7.79 (5H, m, aromatic).

δ_C 25.0 (CBr_2), 27.7 (CH, cyclopropyl), 27.9 (CH_2, cyclopropyl), 99.7 (C-4), 125.8, 127.5, 129.0, 130.3 (all aromatic C); 161.3 (C-3), 170.3 (C-5).

ν_{max} 3125 w, 1611 m, 1591 m, 1573 s, 1500 m, 1448 s, 1421 s, 1284 w, 1110 m, 1066 m, 1034 m, 1010 m, 944 m, 809 m, 768 s, 693 s, 659 s cm^{-1}.

m/z, % 264, 41; 262, 37 (M^+-Br); 236, 12; 234, 10; 201, 7; 199, 20; 197, 9; 184, 14; 183, 83; 182, 10; 155, 100; 154, 62; 105, 43; 77, 54.

An unidentified mixture, together with some dimer *bis(2,2-dibromocyclopropyl)furoxan* (**128**) (in total 280 mg) was also isolated.

EXPERIMENT 26

3-(2,2-Dibromocyclopropyl)isoxazole-4-carboxylic acid methyl ester (131) and 3-(2,2-dibromocyclopropyl)isoxazole-5-carboxylic acid methyl ester (132)

Triethylamine (0.35 ml, 2.5 mmol) was added dropwise to a stirred solution of *N*-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (630 mg, 2.3 mmol) and methyl propiolate (0.81 ml, 9.1 mmol) in dry ether (15 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and a mixture of two regioisomers in ratio 39:61 was obtained. Separation by column chromatography on silica gel (petrol - ether, 5:1) gave pure *3-(2,2-dibromocyclopropyl)isoxazole-4-carboxylic acid methyl ester* (**131**) (298 mg, 40 %) and *3-(2,2-dibromocyclopropyl)isoxazole-5-carboxylic acid methyl ester* (**132**) (440 mg, 60 %).

Minor isomer (**131**):

White solid, m.p. 52 – 54 °C.

Found: C 29.81, H 1.98, N 4.574. $C_8H_7Br_2NO_3$ requires: C 29.57, H 2.17, N 4.31.

δ_H 2.19 (1H, dd, J 7.9, 10.0 Hz, H_{cis} of cyclopropyl CH_2), 2.39 (1H, t, J 7.9 Hz, H_{trans} of cyclopropyl CH_2), 3.13 (1H, dd, J 7.9, 10.0 Hz, H cyclopropyl), 3.95 (3H, s, CO_2CH_3), 8.93 (1H, s, H-4).

δ_C 24.6 (CBr_2,), 26.9 (CH, cyclopropyl), 26.9 (CH_2, cyclopropyl), 52.3 ($CO_2\underline{C}H_3$), 114.5 (C-4), 158.8 (C=O), 161.2 (C-3), 163.6 (C-5).

ν_{max} 3117m, 3009 w, 2953 m, 1730 s, 1594 s, 1496 s, 1437 s, 1418 s, 1347 s, 1314 s, 1290 s, 1228 s, 1210 s, 1125 s, 1051 s, 854 m, 804 s, 779 s, 736 w, 675 s cm^{-1}.

m/z, % 328, 3; 326, 6; 324, 3 (M^+ + 1); 294, 7; 246, 30; 244, 35; 214, 65; 212, 57; 199, 10; 186, 87; 184, 100; 165, 18; 158, 11; 117, 8; 107, 11.

Major isomer (**132**):

White solid, m.p. 87 °C.

Found: C 29.66, H 2.16, N 4.44. $C_8H_7Br_2NO_3$ requires: C 29.57, H 2.17, N 4.31.

δ_H 2.20 (1H, t, J 8.0 Hz, H_{trans} of cyclopropyl CH_2), 2.27 (1H, dd, J 8.0, 10.1 Hz, H_{cis} of cyclopropyl CH_2), 2.95 (1H, dd, J 8.0, 10.1 Hz, H cyclopropyl), 3.95 (3H, s, CO_2CH_3), 6.92 (1H, s, H-4).

δ_C 23.7 (CBr_2), 27.3 (CH, cyclopropyl), 28.1 (CH_2, cyclopropyl), 53.0 ($CO_2\underline{C}H_3$), 109.5 (C-4); 156.9, 160.4 and 161.0 (C=O, C-5 and C-3).

ν_{max} 3131 m, 3092 w, 3011 w, 2952 w, 1717 s, 1477 s, 1436 m, 1419 m, 1322 m, 1297 s, 1239 s, 1093 s, 1046 m, 1001 s, 933 m, 914 m, 867 m, 806 m, 772 m, 670 s cm^{-1}.

m/z, % 268, 2; 266, 4; 264, 3 (M^+-CO_2CH_3); 246, 18; 244, 21; 218, 33; 216, 31; 201, 12; 199, 30; 197, 16; 190, 45; 188, 40; 186, 81; 184, 100; 165, 29; 106, 76; 93, 39; 78, 38; 59, 76.

EXPERIMENT 27

Reaction of *N*-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride with 3-hexyne

Triethylamine (0.25 ml, 1.8 mmol) was added dropwise to a stirred solution of *N*-hydroxy-2,2-dibromocyclopropylmethanimidoyl chloride (500 mg, 1.8 mmol) and 3-hexyne (0.24 ml, 2.1 mmol) in dry ether (15 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 24 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and residue was purified by column chromatography on silica gel

(petrol - ether, 2:1) to give two diastereomers of the dimer *bis(2,2-dibromocyclopropyl)furoxan* (**128**) (in total 183 mg, 42 %). The cycloadduct derived from the reaction with 3-hexyne was not observed.

Diastereomer a:

White solid, m.p. 130-133 °C.

Found: C 20.56, H 1.42, N 5.77. $C_8H_6Br_4N_2O_2$ requires: C 19.95, H 1.26, N 5.81.

δ_H 2.32 (1H, dd, J 7.9, 10.2 Hz), 2.35 (1H, dd, J 7.9, 10.4 Hz), 2.49 (1H, t, J 7.9 Hz), 2.60 (1H, t, J 7.9 Hz), 2.78 (1H, dd, J 7.9, 10.4 Hz), 2.97 (1H, dd, J 7.9, 10.2 Hz).

δ_C 22.2 (2 × CBr_2), 23.8 (CH), 26.2 (CH_2), 26.3 (CH_2), 26.6 (CH), 112.6 ($C=N^+$), 155.3 (C=N).

ν_{max} 3007 w, 1655 m, 1605 s, 1474 s, 1391 s, 1318 m, 1213 m, 1126 m, 1097 s, 1059 s, 1009 s, 943 m, 923 m, 874 m, 812 s, 758 m, 725 m, 700 s, 678 s, 614 s cm^{-1}.

m/z, % 483, 2; 482, 1 (M^+); 305, 27; 262, 19; 243, 30; 213, 52; 199, 43; 183, 49; 162, 95; 160, 87; 132, 59; 102, 100; 76, 49; 75, 63; 52, 65.

Diastereomer b:

White solid, m.p. 139-141 °C.

Found: C 20.51, H 1.39, N 5.94. $C_8H_6Br_4N_2O_2$ requires: C 19.95, H 1.26, N 5.81.

δ_H 2.32 (1H, dd, J 7.9, 10.4 Hz), 2.37 (1H, dd, J 7.9, 10.4 Hz), 2.46 (1H, t, J 7.9 Hz), 2.65 (1H, t, J 7.9 Hz), 2.74 (1H, dd, J 7.9, 10.4 Hz), 2.78 (1H, dd, J 7.9, 10.4 Hz).

δ_C 22.3 (CBr_2), 23.1 (CBr_2), 24.7 (CH), 26.4 (CH_2), 26.7 (CH_2), 26.8 (CH), 113.1 ($C=N^+$), 154.4 (C=N).

ν_{max} 3091 w, 3026 w, 1608 s, 1477 s, 1396 m, 1308 m, 1221 w, 1096 s, 1062 m, 1015 m, 924 m, 818 m, 710 m, 676 s, 587 m, 576 m cm^{-1}.

m/z, % 483, 1 (M^++1); 403, 2; 305, 20; 262, 16; 243, 24; 213, 35; 199, 28; 183, 44; 181, 44; 162, 42; 132, 40; 102, 100; 76, 43; 75, 53; 52, 37.

EXPERIMENT 28

(*S*)-2-(*tert*-Butyldiphenylsilanyloxy)propanaldoxime (137)

To a mixture of (*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanal (1.79 g, 5.7 mmol) in water (15 ml) and ether (20 ml) was added hydroxylamine hydrochloride (1.19 g, 17.2 mmol). Sodium hydroxide (640 mg, 50% solution, 16.0 mmol) was added with stirring at 0 °C. The two phase mixture was stirred vigorously for 3 h at room temperature, monitored by GLC and TLC. To bring the reaction to completion ethanol (20 ml) was added to obtain a single layer, and the mixture was stirred for further 30 min. Ether (20 ml) was added to separate the layers. The aqueous layer was extracted with ether (2 × 20 ml), the combined ether extracts were dried and the solvent was removed to give a colourless oil, *(S)-2-(tert-butyldiphenylsilanyloxy)propanaldoxime* (**137**) (5.69 g, 92 %), as a mixture of *E* and *Z* isomers (ratio, 66:34). The oxime was used without further purification for the next step, the conversion to the hydroximoyl chloride (Exp. 29).

$[\alpha]_D^{19}$ = - 28.7° (c 1.0, $CHCl_3$).

Found $[MH]^+$: 328.1733. $C_{19}H_{25}NO_2Si$ + H requires: 328.1732.

NMR data, major isomer:

δ_H 1.05 (9H, s, $C(CH_3)_3$), 1.23 (3H, d, J 6.4 Hz, CH_3), 4.39 (1H, quintet, J 6.4 Hz, H-2), 7.37 (1H, d, 6.4 Hz, H-1), 7.32-7.71 (10H, m, aromatic).

δ_C 19.1 ($\underline{C}(CH_3)_3$), 22.0 (C-3), 26.9 ($C(\underline{C}H_3)_3$), 67.3 (C-2), 127.6, 129.7, 133.4, 133.8, 135.8 (all aromatic C), 154.0 (C-1).

NMR data, minor isomer:

δ_H 1.07 (9H, s, $C(CH_3)_3$), 1.24 (3H, d, J 6.4 Hz, CH_3), 5.01 (1H, dq, J 5.4, 6.4 Hz, H-2), 6.81 (1H, d, 5.4 Hz, H-1), 7.32-7.71 (10H, m, aromatic), 7.81 (1H, br s, OH).

δ_C 19.1 ($\underline{C}(CH_3)_3$), 20.6 (C-3), 26.9 ($C(\underline{C}H_3)_3$), 63.7 (C-2), 127.6, 129.7, 133.4, 133.8, 135.7 (all aromatic C), 156.2 (C-1).

ν_{max} (mixture) 3284 br. s, 3071 m, 2959 s, 2930 s, 2893 s, 2858 s, 1960 w, 1892 w, 1823 w, 1736 w, 1659 w, 1589 m, 1472 s, 1428 s, 1370 m, 1111 s, 998 m, 938 m, 822 s, 740 s, 701 s, 613 s cm^{-1}.

m/z (mixture; CI, NH_4^+), % 328, 2 $[MH]^+$; 299, 6; 270, 100 (M^+-C_4H_9); 250, 43; 216, 22; 199, 61.

EXPERIMENT 29

N-Hydroxy-(*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanimidoyl chloride (138)

(*S*)-2-(*tert*-Butyldiphenylsilanyloxy)propanaldoxime (**137**) (1.63 g, 4.5 mmol) in DMF (15 ml) was reacted with NCS (660 mg, 4.5 mmol), using a procedure analogous to the one described in Exp. 1. Crude *N-hydroxy-(S)-2-(tert-butyldiphenylsilanyloxy)propan-imidoyl chloride* (**138**) (1.69 g, 94 %) was obtained. The nitrile oxide precursor prepared in this manner did not require further purification for the cycloaddition reactions.

$[\alpha]_D^{27}$ = - 36.3° (c 1.0, $CHCl_3$).

M^+ was not observed.

δ_H 1.08 (9H, s, $C(CH_3)_3$), 1.33 (3H, d, J 6.3 Hz, CH_3), 4.57 (1H, q, J 6.3 Hz, H-2), 7.32-7.72 (10H, m, aromatic), 8.27 (1H, s, OH).

δ_C 19.3 ($\underline{C}(CH_3)_3$), 21.8 (C-3), 26.8 ($C(\underline{C}H_3)_3$), 70.3 (C-2), 127.6, 127.7, 129.9, 132.9, 133.5, 135.7, 135.8 (all aromatic C), 144.5 (C-1).

ν_{max} 3284 br. s, 3071 m, 2959 s, 2932 s, 2893 m, 2858 s, 1960 w, 1890 w, 1823 w, 1729 w, 1635 m, 1590 w, 1472 w, 1428 s, 1372 m, 1180 m, 1113 s, 977 s, 938 s, 822 m, 740 s, 702 s cm^{-1}.

m/z, % 326, 39 (M^+-^{35}Cl); 306, 40; 305, 25; 304, 100; 283, 24; 217, 20; 157, 30; 135, 28; 75, 18.

EXPERIMENT 30

1-Butyl-4-[1-(*tert*-butyldiphenylsilanyloxy)ethyl]-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (142)

Triethylamine (0.19 ml, 1.4 mmol) was added dropwise to a stirred solution of *N*-hydroxy-(*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanimidoyl chloride (500 mg, 1.4 mmol) and 1-butylcyclopropene [prepared from 1,1,2-tribromo-2-butylcyclopropane (509 mg, 1.5 mmol) and methyllithium (2.2 ml, 1.5 M) as described in Exp. 7] in ether at -20 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 1 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined

organic layers were dried. The solvent was removed to give crude *1-butyl-4-[1-(tert-butyldiphenylsilanyloxy)ethyl]-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**142**) as a mixture of two diastereomers (ratio, 58:42). The mixture was purified by column chromatography on silica gel (petrol - ether, 5:1). The two diastereomers were not separated, and a colourless oil (351 mg, 60 %) was obtained.

Found $[MH]^+$: 422.2512 $C_{26}H_{35}NO_2Si$ + H requires: 422.2515.

NMR data, major diastereomer:

δ_H 0.31 (1H, dd, J 3.8, 5.1 Hz, H_{endo}-6), 0.93 (3H, t, J 6.9 Hz, CH_3), 0.95 (1H, dd, J 5.1, 9.5 Hz, H_{exo}-6), 1.07 (9H, s, $C(CH_3)_3$), 1.36 (3H, t, J 6.5 Hz, $CHC\underline{H}_3$), 1.38-1.47 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.69-2.00 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.44 (1H, dd, J 3.8, 9.5 Hz, H-5), 4.69 (1H, q, J 6.5 Hz, $C\underline{H}CH_3$), 7.35-7.68 (10H, m, aromatic).

δ_C 11.8 (C-6), 14.0 (CH_3), 19.3 ($\underline{C}(CH_3)_3$), 22.5 (CH_2), 22.7 ($CH\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$), 27.8 (C-5), 28.4 (CH_2), 28.6 (CH_2), 31.3 (CH_2), 65.5 ($\underline{C}HCH_3$), 74.7 (C-1), 127.7, 129.8, 133.0, 133.8, 135.8 (all aromatic C), 166.3 (C-4).

NMR data, minor diastereomer:

δ_H 0.17 (1H, dd, J 3.8, 5.1 Hz, H_{endo}-6), 0.93 (3H, t, J 6.9 Hz, CH_3), 0.95 (1H, dd, J 5.1, 9.5 Hz, H_{exo}-6), 1.07 (9H, s, $C(CH_3)_3$), 1.33 (3H, t, J 6.5 Hz, $CHC\underline{H}_3$), 1.38-1.47 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.69-2.00 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.39 (1H, dd, J 3.8, 9.5 Hz, H-5), 4.77 (1H, q, J 6.5 Hz, $C\underline{H}CH_3$), 7.35-7.68 (10H, m, aromatic).

δ_C 11.7 (C-6), 14.0 (CH_3), 19.3 ($\underline{C}(CH_3)_3$), 22.3 ($CH\underline{C}H_3$), 22.4 (CH_2), 26.9 ($C(\underline{C}H_3)_3$), 28.4 (CH_2), 28.6 (C-5), 31.2 (CH_2), 65.8 ($\underline{C}HCH_3$), 74.7 (C-1), 127.7, 129.8, 133.0, 133.8, 135.8 (all aromatic C), 166.3 (C-4).

ν_{max} (mixture) 3071 m, 2957 s, 2931 s, 2856 s, 1960 w, 1891 w, 1824 w, 1736 w, 1663 w, 1590 m, 1472 m, 1213 s, 1188 m, 956 m, 875 m, 822 m, 702 s cm^{-1}.

m/z, % (mixture) 422, 0.003 (M^+); 364, 21; 283, 25; 281, 23; 280, 100; 239, 19; 197, 19; 181, 18; 135, 55; 85, 18; 75, 15; 57, 25.

EXPERIMENT 31

6,6-Dimethyl-4-[1-(*tert*-butyldiphenylsilanyloxy)ethyl]-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (140)

Triethylamine (0.19 ml, 1.4 mmol) was added dropwise to a stirred solution of *N*-hydroxy-(*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanimidoyl chloride (500 mg, 1.4 mmol) and 3,3-dimethylcyclopropene [prepared from 1,1-dibromo-3-chloro-2,2-dimethylcyclopropane (400 mg, 1.5 mmol) and methyllithium (2.2 ml, 1.5 M) as described in Exp. 6] in ether at -15 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 1 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 3:1). The first fraction gave crystalline dimer, *bis[(1S,1'S)-1-(tert-butyldiphenylsilanyloxy)-ethyl]furoxan* (**141**) (165 mg, 37 %), the second fraction afforded a colourless oil, *6,6-dimethyl-4-[1-(tert-butyldiphenylsilanyloxy)ethyl]-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**140**) (222 mg, 41 %) as a mixture of two diastereomers (ratio, 64:36).

Dimer, bis[(1*S*,1'*S*)-1-(*tert*-butyldiphenylsilanyloxy)ethyl]furoxan (**141**):

White solid, m.p. 85-87 °C.

$[\alpha]_D^{26}$ = -36.0° (c 1.0, $CHCl_3$).

Found: C 69.90, H 7.13, N 4.22. $C_{38}H_{46}N_2O_4Si_2$ requires: C 70.11, H 7.12, N 4.30.

δ_H 0.99 (9H, s, $C(CH_3)_3$), 1.03 (9H, s, $C(CH_3)_3$), 1.41 (3H, d, J 6.5 Hz, $CHC\underline{H}_3$), 1.48 (3H, d, J 6.5 Hz, $CHC\underline{H}_3$), 4.72 (1H, q, J 6.5 Hz, $C\underline{H}CH_3$), 4.92 (1H, q, J 6.5 Hz, $C\underline{H}CH_3$), 7.23-7.68 (20H, m, aromatic).

δ_C 19.1 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$), 20.3 ($CH\underline{C}H_3$), 22.4 ($CH\underline{C}H_3$), 26.8 (2 × $C(\underline{C}H_3)_3$), 63.3 ($\underline{C}HCH_3$), 65.1 ($\underline{C}HCH_3$), 117.1 ($C=N^+$), 127.7, 127.8, 127.9, 129.9, 130.0, 130.1, 132.3, 132.5, 133.2, 135.3, 135.7, 135.8 (all aromatic C), 159.3 (C=N).

ν_{max} 3071 w, 2957 m, 2932 s, 2893 m, 2858 s, 1960 w, 1891 w, 1831 w, 1735 w, 1609 s, , 1472 s, 1417 s, 1373 m, 1330 m, 1153 m, 1098 s, 1046 m, 954 s, 936 s, 824 s, 790 m, 747 s, 702 s, 617 s, 503 s cm^{-1}.

m/z, % 594, 26 (M^+-C_4H_9); 593, 68; 311, 90; 283, 40; 265, 13; 239, 34; 199, 29; 197, 41; 179, 20; 135, 100; 75, 25.

Main product **140**:

Found $[MH]^+$: 394.2209. $C_{24}H_{31}NO_2$ + H requires: 394.2202.

NMR data, major diastereomer:

δ_H 0.82 (3H, s, CH_3), 1.07 (9H, s, $C(CH_3)_3$), 1.08 (3H, s, CH_3), 1.25 (3H, d, J 6.4 Hz, $CHC\underline{H}_3$), 2.53 (1H, d, J 5.5 Hz, H-5), 4.48 (1H, d, J 5.5 Hz, H-1), 4.68 (1H, q, J 6.4 Hz, $C\underline{H}CH_3$), 7.35-7.68 (10H, m, aromatic).

δ_C 12.5 (C-6), 13.2 (CH_3), 19.4 ($\underline{C}(CH_3)_3$), 22.5 (CH_3), 22.6 ($CH\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$), 38.6 (C-5), 65.1 ($\underline{C}HCH_3$), 74.1 (C-1), 127.7, 129.8, 132.9, 133.8, 135.8 (all aromatic C), 162.3 (C-4).

NMR data, minor diastereomer:

δ_H 0.82 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.07 (9H, s, $C(CH_3)_3$), 1.25 (3H, d, J 6.4 Hz, $CHC\underline{H}_3$), 2.49 (1H, d, J 5.5 Hz, H-5), 4.49 (1H, d, J 5.5 Hz, H-1), 4.76 (1H, q, J 6.4 Hz, $C\underline{H}CH_3$), 7.35-7.68 (10H, m, aromatic).

δ_C 12.5 (C-6), 13.1 (CH_3), 19.4 ($\underline{C}(CH_3)_3$), 22.4 ($CH\underline{C}H_3$), 22.5 (CH_3), 26.8 ($C(\underline{C}H_3)_3$), 38.8 (C-5), 65.8 ($\underline{C}HCH_3$), 74.2 (C-1), 127.6, 129.8, 132.9, 133.8, 135.8 (all aromatic C), 163.2 (C-4).

ν_{max} (mixture) 3071 m, 3048 m, 2930 s,2892 s, 2858 s, 1962 w, 1891 w, 1824 w, 1736 w, 1658 w, 1590 s, 1471 s, 1427 s, 1372 s, 1110 s, 1001 s, 955 s, 842 s, 822 s, 774 s, 741 s, 703 s, 609 s cm^{-1}.

m/z, % (mixture; CI, NH_4^+) 394, 9 $[MH]^+$;366, 12; 336, 100; 308, 61; 299, 50; 283, 32; 269, 25; 227, 20; 199, 65; 181, 21; 138, 18; 135, 40.

EXPERIMENT 32

3-[(1*S*)-1-(*tert*-Butyldiphenylsilanyloxy)ethyl]isoxazole-5-carboxylic acid methyl ester (143)

Triethylamine (0.23 ml, 1.7 mmol) was added dropwise to a stirred solution of *N*-hydroxy-(*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanimidoyl chloride (600 mg, 1.7 mmol) and methyl propiolate (0.15 ml, 1.7 mmol) in dry ether (10 ml) at -10 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 30 min and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by

column chromatography on silica gel (petrol - ether, 5:1) to give *bis[(1S,1'S)-1-(tert-butyldiphenylsilanyloxy)ethyl]furoxan* (**141**) (94 mg, 18 %; see Exp. 31) and a colourless oil *3-[(1S)-1-(tert-butyldiphenylsilanyloxy)ethyl]isoxazole-5-carboxylic acid methyl ester* (**143**) (370 mg, 54 %).

$[\alpha]_D^{26}$ = -79.1° (c 1.0, $CHCl_3$).

M^+ was not observed.

δ_H 1.05 (9H, s, $C(CH_3)_3$), 1.39 (3H, d, J 6.4 Hz, $CHC\underline{H}_3$), 3.95 (3H, s, CO_2CH_3), 5.18 (1H, q, J 6.4 Hz, $C\underline{H}CH_3$), 6.98 (1H, s, H-4), 7.31-7.67 (10H, m, aromatic).

δ_C 19.1 ($\underline{C}(CH_3)_3$), 24.4 ($CH\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$), 52.8 ($CO_2\underline{C}H_3$), 64.6 ($\underline{C}HCH_3$), 107.6 (C-4), 127.7, 129.9, 132.7, 133.4, 135.7 (all aromatic C), 156.6 (C-5), 159.9 (C-3), 168.6 (C=O).

ν_{max} 3136 w, 3072 m, 2956 s, 2931 s, 2893 s, 2858 s, 1962 w, 1893 w, 1746 s, 1588 s, 1472 s, 1428 s, 1372 m, 1310 s, 1288 s, 1210 s, 1111 s, 1030 m, 1001 s, 949 s, 911 s, 822 s, 770 m, 741 s, 702 s, 612 s cm^{-1}.

m/z, % 353, 23; 352, 100 (M^+-C_4H_9); 225, 4; 213, 11; 197, 3; 183, 15.

EXPERIMENT 33

3-[(1*S*)-1-(*tert*-Butyldiphenylsilanyloxy)ethyl]isoxazole-4,5-dicarboxylic acid dimethyl ester (144)

Triethylamine (0.23 ml, 1.7 mmol) was added dropwise to a stirred solution of *N*-hydroxy-(*S*)-2-(*tert*-butyldiphenylsilanyloxy)propanimidoyl chloride (600 mg, 1.7 mmol) and dimethyl acetylenedicarboxylate (0.20 ml, 1.7 mmol) in dry ether (10 ml) at -10 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 40 min and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *bis[(1S,1'S)-1-(tert-butyldiphenylsilanyloxy)ethyl]furoxan* **141** (120 mg, 22 %; see Exp. 31) and *3-[(1S)-1-(tert-butyldiphenylsilanyloxy)ethyl]isoxazole-4,5-dicarboxylic acid dimethyl ester* (**144**) (448 mg, 58 %).

$[\alpha]_D^{26}$ = -72.8° (c 1.0, $CHCl_3$).

m.p. 94-95 °C.

Found: C 64.11, H 6.27, N 3.21. $C_{25}H_{29}NO_6Si$ requires: C 64.22, H 6.25, N 3.00.

δ_H 1.02 (9H, s, $C(CH_3)_3$), 1.45 (3H, d, J 6.5 Hz, $CHC\underline{H}_3$), 3.82 (3H, s, CO_2CH_3), 3.97 (3H, s, CO_2CH_3), 5.18 (1H, q, J 6.5 Hz, $C\underline{H}CH_3$), 7.27-7.67 (10H, m, aromatic).

δ_C 19.1 ($\underline{C}(CH_3)_3$), 23.6 ($CH\underline{C}H_3$), 26.8 ($C(\underline{C}H_3)_3$), 52.7 ($CO_2\underline{C}H_3$), 53.3 ($CO_2\underline{C}H_3$), 64.9 ($\underline{C}HCH_3$), 115.0 (C-4), 127.6, 127.7, 129.9, 132.6, 133.3, 135.7 (all aromatic C), 156.6 (C-5); 159.1 and 161.2 (C=O and C-3), 165.9 (C=O).

ν_{max} 3075 m, 2956 s, 2859 s, 1961 w, 1893 w, 1745 s, 1609 m, 1472 s, 1428 s, 1309 s, 1271 s, 1210 s, 1176 s, 1127 s, 1106 s, 1048 s, 1013 m, 949 s, 822 s, 778 m, 741 s, 703 s, 612 s cm^{-1}.

m/z, % 411, 34; 410, 100 (M^+-C_4H_9); 338, 20; 270, 6; 235, 10; 214, 17; 213, 84; 183, 29; 181, 17; 135, 9; 104, 8; 44, 11.

EXPERIMENT 34[173,174]

Enantiomerically pure compound:

[(5*R*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (152)

General procedure A (chiral cycloaddition reaction):

To a $CHCl_3$ (6 ml) solution of allylic alcohol (2.7 mmol) was added diethylzinc (1.2 mol.equiv., 1.1 M in toluene or 1.0 M in hexane) at 0 °C under an argon atmosphere and the mixture was stirred for 10 min. To the solution, a $CHCl_3$ (6 ml) solution of (*R*,*R*)-DIPT (0.2 mol.equiv.) was added and the mixture was stirred for 1 h. A $CHCl_3$ (6 ml) solution of hydroximoyl chloride (nitrile oxide precursor) (1.0 mol.equiv.) and 1,4-dioxane (1.5 mol.equiv.) was added, and the resulting solution was stirred for 24 h at 0 °C. A saturated aqueous solution of NH_4Cl was added, followed by hydrochloric acid (2 %). The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ethyl acetate, 1:1) to give *2-isoxazoline*.

a) In the present case allyl alcohol (0.18 ml, 2.7 mmol) was reacted with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol) to give *[(5R)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol* (**152**) (379 mg, 68 %) with 97 % ee.

b) When the procedure was repeated on a ten times larger scale (27 mmol) the work-up procedure was altered, due to the poor solubility of the product **152**, as follows: after stirring the reaction for 24 h, the reaction mixture was quenched with a few drops of a saturated aqueous NH_4Cl solution. The mixture was filtered through a layer of anhydrous $MgSO_4$ and a clear solution (I) was obtained. Washing the filter residue with hot ethyl acetate (4 × 70 ml) gave solution (II). The solutions were concentrated (separately) and the residue recrystallised from ethyl acetate. Solution (I) yielded 14 % (80 % ee), solution (II) yielded 64 % (99 % ee) (total yield 78 %).

The reaction was also repeated using modified reaction conditions:

c) Stirring for 24 h at room temperature gave a yield of 76 % (93 % ee).

d) Stirring for 24 h at -70 °C gave a yield of 95 % (79 % ee).

Full analytical data are given here because in the original literature[173,174] only the $[\alpha]_D$ is given.

$[\alpha]_D^{30}$ = + 140° (c 0.4, MeOH) (lit.[116]: $[\alpha]_D^{25}$ = + 120° (c 0.4, MeOH)).

White crystalline solid; m.p. 155-157 °C.

Found: C 64.32, H 6.64, N 6.81. $C_{11}H_{13}NO_3$ requires: C 63.76, H 6.32, N 6.76.

δ_H 1.89 (1H, br. s, OH), 3.23 (1H, dd, J 7.9, 16.5 Hz, first of H-4), 3.36 (1H, dd, J 10.5, 16.5 Hz, second of H-4), 3.64 (1H, dd, J 4.7, 12.1 Hz, first H of $C\underline{H}_2OH$), 3.81 (3H, s, OCH_3), 3.83 (1H, dd, J 3.2, 12.1 Hz, second H of $C\underline{H}_2OH$), 4.82 (1H, dddd, J 3.2, 4.7, 7.9, 10.6 Hz, H-5), 6.86-6.90 (2H, m, aromatic), 7.55-7.59 (2H, m, aromatic).

δ_C (CD_3OD) 37.9 (C-4), 56.1 (OCH_3), 64.4 (CH_2OH), 83.0 (C-5), 115.5, 123.7, 129.6, 158.4 (all aromatic C), 163.0 (C-3).

ν_{max} 3361 br. s, 3304 m, 2938 m, 1611 s, 1520 s, 1463 m, 1445 m, 1414 m, 1364 s, 1313 m, 1296 m, 1263 s, 1183 s, 1106 m, 1053 s, 957 m, 929 s, 904 s, 833 s, 813 s, 708 m, 646 m cm^{-1}.

m/z, %207, 100 (M^+); 176, 68; 148, 27; 121, 56; 92, 13; 77, 23.

Retention times of **152** obtained by the chiral HPLC are given in **Table 17** (**Appendix**).

Racemic compound:

[(5*RS*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (152)

Racemic compound of **152** was prepared as a standard for the HPLC.

General procedure B (racemic cycloaddition reaction):

Triethylamine (2.7 - 2.8 mmol) was added dropwise to a stirred solution of hydroximoyl chloride (nitrile oxide precursor) (2.7 mmol) and allylic alcohol (3.2 - 5.4 mmol) in dry ether (20 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2 %, 10 ml) to dissolve the precipitate. The aqueous layer was extracted with ethyl acetate (3 × 10 ml) and the combined organic layers were dried. The solvent was removed and the residue was recrystallised from ethyl acetate / petrol to give racemic *2-isoxazoline*.

In some cases an alternative work-up procedure was used: after stirring for 12 h the precipitate of triethylammonium chloride was filtered off; removal of the solvent gave the adduct which was recrystallised from ethyl acetate / petrol.

e) In the present case allyl alcohol (1.1 ml, 16.2 mmol) was reacted with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 13.5 mmol) to give *[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol* (**152**) (1.6 g, 57 %).

White crystalline solid; m.p. 133-135 °C.

All other analytical data of **152** were identical to those given for the enantiomerically pure compound (see above).

EXPERIMENT 35

Enantiomerically pure compound:

(5*R*)-5-Chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (153)

By conversion of alcohol into chloride:

A solution of [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**153**) (200 mg, 0.96 mmol) and thionyl chloride (0.7 ml, 9.6 mmol) in pyridine (10 ml) was stirred for 6 h at 100 °C. Excess thionyl chloride was removed by flash distillation, dichloromethane (20 ml) and hydrochloric acid (2 %, 20 ml) were added and the aqueous layer was extracted with dichloromethane (2 × 20 ml). The combined organic layers were washed with hydrochloric acid (2 %, 2 × 40 ml) and water (1 × 40 ml). The organic layer was dried and the solvent was removed. The crude product was purified by column chromatography on silica gel (petrol only to petrol - ether, 1:1) to give *(5R)-5-chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole* (**153**) (96 mg, 44 %).

$[\alpha]_D^{26}$ = -50.4° (c 0.4, $CHCl_3$).

White solid; m.p. 83-85 °C.

Found: C 58.59, H 5.21, N 6.37. $C_{11}H_{12}ClNO_2$ requires: C 58.54, H 5.36, N 6.21.

δ_H 3.29 (1H, dd, J 6.4, 16.9 Hz, first of H-4), 3.37 (1H, dd, J 10.3, 16.9 Hz, second of H-4), 3.54 (1H, dd, J 7.6, 11.2 Hz, first H of CH_2Cl), 3.69 (1H, dd, J 4.4, 11.2 Hz, second H of CH_2Cl), 3.82 (3H, s, OCH_3), 4.94 (1H, dddd, J 4.4, 6.4, 7.6, 10.3 Hz, H-5), 6.89-6.93 (2H, m, aromatic), 7.58-7.62 (2H, m, aromatic).

δ_C 38.8 (C-4), 44.8 (CH_2Cl), 55.3 (OCH_3), 79.5 (C-5), 114.1, 121.5, 128.3, 155.7 (all aromatic C), 161.2 (C-3).

ν_{max} 3004 m, 2866 m, 2914 m, 2838 w, 1609 s, 1598 s, 1566 m, 1517 s, 1460 s, 1420 s, 1360 s, 1311 s, 1291 m, 1255 s, 1180 s, 1111 m, 1040 s, 1021 s, 961 w, 911 s, 887 s, 836 s, 816 s, 677 s, 608 s, 538 s cm^{-1}.

m/z, % 227, 26; 225, 70 (M^+); 176, 62; 148, 33; 133, 13; 132, 121, 100; 107, 13; 92, 28; 77, 50; 63, 18.

Racemic compound:

(5*RS*)-5-Chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (153)

By cycloaddition reaction:

The general procedure B (Exp. 34) was used to react allyl chloride (0.33 ml, 4.05 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (250 mg, 1.35 mmol), yielding *(5RS)-5-chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole* (**153**) (185 mg, 61 %).

White solid; m.p. 69-70 °C.

All other analytical data of **153** were identical to those given for the enantiomerically pure compound (see above).

EXPERIMENT 36

[(5*RS*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl tosylate (156)

A solution of [(5*RS*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**156**) (1.0 g, 4.8 mmol) and toluene-4-sulfonyl chloride (2.76 g, 14.5 mmol) in pyridine (10 ml) was stirred for 12 h at room temperature. Pyridine was removed by flash distillation, ethyl acetate (20 ml) and citric acid (10 %, 20 ml) were added and the aqueous layer was extracted with ethyl acetate (2 × 20 ml). The combined organic layers were washed with citric acid (10 %, 40 ml) and water (1 × 40 ml). The organic layer was dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol only to petrol - ether, 1:1) to give unreacted *toluene-4-sulfonyl chloride* (840 mg), *(5RS)-5-chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole* (**153**) (610 mg, 56 %) [see Exp. 36] and *[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl tosylate* (**156**) (447 mg, 26 %).

156, white solid, m.p. 120-122 °C.

Found: C 59.84, H 5.26, N 4.14. $C_{18}H_{19}NO_5S$ requires: C 59.82, H 5.30, N 3.88.

δ_H 2.42 (3H, s, $SO_2C_6H_4C\underline{H}_3$), 3.20 (1H, dd, J 6.7, 16.8 Hz, first of H-4), 3.41 (1H, dd, J 10.5, 16.8 Hz, second of H-4), 3.83 (3H, s, OCH_3), 4.05 (1H, dd, J 5.8, 10.5 Hz, first H of CH_2O), 4.15 (1H, dd, J 4.8, 10.5 Hz, second H of CH_2O), 4.88 (1H, dddd, J 4.8, 5.8, 6.7, 10.5 Hz, H-5), 6.89-6.93 (2H, m, aromatic), 7.31-7.35

(2H, m, aromatic), 7.52-7.56 (2H, m, aromatic), 7.76-7.80 (2H, m, aromatic).

δ_C 21.6 ($SO_2C_6H_4\underline{C}H_3$), 37.5 (C-4), 55.3 ($OCH_3$), 69.2 ($CH_2O$), 77.1 (C-5), 114.1, 121.3, 127.9, 128.3, 129.9, 132.4, 145.2, 155.7 (all aromatic C), 161.2 (C-3).

ν_{max} 2975 w, 2936 w, 2840 w, 1608 s, 1594 s, 1516 s, 1459 m, 1423 m, 1331 s, 1309 m, 1254 s, 1195 s, 1173 s, 1096 m, 1033 m, 1014 m, 967 s, 907 s, 837 s, 816 s, 692 s, 576 m, 554 s cm^{-1}.

m/z, % 361, 15 (M^+); 176, 100; 160, 10; 147, 18; 134, 8; 132, 8; 121, 21; 107, 4; 91, 20; 77, 10; 65, 7.

EXPERIMENT 37

[(5*R*)-3-(4-Methoxyphenyl)-4,5-dihydro-isoxazol-5-yl]methyl mesylate (157)

Methanesulfonyl chloride (0.03 ml, 0.43 mmol, 0.6 mol.equiv.) was added to a solution of [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**157**) (150 mg, 0.72 mmol) and triethylamine (0.06 ml, 0.43 mmol, 0.6 mol.equiv.) in dichloromethane (5 ml). The mixture was stirred for 20 min at room temperature. More triethylamine (0.06 ml, 0.43 mmol, 0.6 mol.equiv.) and methanesulfonyl chloride (0.03 ml, 0.43 mmol, 0.6 mol.equiv.) were added [a total of 1.2 mol.equiv. of MsCl and base were used]. After stirring for additional 20 min water (10 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 15 ml). The combined organic layers were washed with water (1 × 30 ml), dried and the solvent was removed. The residue was recrystallised from ethyl acetate / petrol to give *[(5R)-3-(4-methoxyphenyl)-4,5-dihydro-isoxazol-5-yl]methyl mesylate* (**157**) (175 mg, 85 %).

$[\alpha]_D^{26}$ = -137.6° (c 1.0, $CHCl_3$).

Colourless crystals, m.p. 160-161 °C.

Found: C 50.36, H 5.14, N 5.02. $C_{12}H_{15}NO_5S$ requires: C 50.52, H 5.30, N 4.91.

δ_H 3.07 (3H, s, SO_2CH_3), 3.25 (1H, dd, J 7.0, 16.8 Hz, first of H-4), 3.46 (1H, dd, J 10.8, 16.8 Hz, second of H-4), 3.83 (3H, s, OCH_3), 4.32 (1H, dd, J 4.9, 11.4 Hz, first H of CH_2O), 4.37 (1H, dd, J 4.1, 11.4 Hz, second H of CH_2O), 4.97 (1H, dddd, J 4.1, 4.9, 7.0, 10.8 Hz, CH-O), 6.89-6.93 (2H, m, aromatic), 7.56-7.69 (2H, m, aromatic).

δ_C 37.2 (C-4), 37.8 (SO_2CH_3), 55.4 (OCH_3), 69.5 (CH_2O), 77.5 (C-5), 114.2, 121.2, 128.3, 156.0 (all aromatic C), 161.4 (C-3).

ν_{max} 3029 m, 2974 w, 2939 m, 1607 s, 1594 s, 1517 s, 1458 s, 1422 s, 1320 s, 1254 s, 1110 m, 1035 m, 1004 s, 972 s, 907 s, 875 s, 834 s, 817 s, 782 m, 746 m, 608 m cm^{-1}.

m/z, % 285, 42 (M^+); 176, 100; 160, 9; 148, 18; 147, 20; 134, 10; 132, 11; 107, 7; 92, 11; 77, 17.

EXPERIMENT 38

Enantiomerically pure compound:

(1*S*,5*S*)-4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (154)

Potassium *tert*-butoxide (1.62 g, 14.5 mmol) was added in small portions to a solution of methanesulfonic acid (5*R*)-3-(4-methoxyphenyl)-4,5-dihydro-isoxazol-5-ylmethyl ester (1.38 g, 4.8 mmol) [crude ester **157**, prepared from chiral alcohol **152** (1.0 g, 4.8 mmol) as described in Exp. 37, was used] in anhydrous dimethyl sulfoxide (15 ml) at room temperature. After stirring the mixture for 1 h, water (30 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 30 ml). The combined organic layers were washed with water (2 × 80 ml), dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ethyl acetate, 3:1) to give *(1S,5S)-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**154**) (670 mg, 73 % over two steps).

$[\alpha]_D^{26}$ = -154.6° (c 1.0, $CHCl_3$).

White solid, m.p. 107-109 °C.

Found: C 69.58, H 5.86, N 7.59. $C_{11}H_{11}NO_2$ requires: C 69.83, H 5.86, N 7.40.

δ_H 0.43 (1H, ddd, J 2.2, 3.8, 5.5 Hz, H_{endo}-6), 1.04 (1H, dt, J 5.5, 9.2 Hz, H_{exo}-6), 2.84 (1H, ddd, J 3.8, 5.5, 9.2 Hz, H-5), 3.83 (3H, s, OCH_3), 4.99 (1H, dt, J 2.2, 5.5 Hz, H-1), 6.91-6.95 (2H, m, aromatic), 7.70-7.74 (2H, m, aromatic).

δ_C 8.0 (C-6), 25.9 (C-5), 55.3 (OCH_3), 63.9 (C-1), 114.1, 121.6, 128.7 (all aromatic C); 161.2 and 161.3 (aromatic C and C-4).

ν_{max} 3058 w, 2964 w, 2839 m, 1608 s, 1584 s, 1517 s, 1463 m, 1425 s, 1377 s, 1308 s, 1249 s, 1189 s, 1178 s, 1113 s, 1081 s, 1028 s, 975 s, 936 s, 871 s, 848 s, 823 s, 790 s, 665 m, 603 s, 532 s cm^{-1}.

m/z, % 189, 25 (M^+); 160, 100; 134, 10; 115, 5; 107, 7; 103, 6; 92, 13; 77, 17; 64, 10.

Racemic compound:

(1RS,5RS)-4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (154)

(5*RS*)-5-Chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**153**) (2.5 g, 0.011 mol) was treated with potassium *tert*-butoxide (3.73 g, 0.033 mmol) as above. The crude product was recrystallised from ether /petrol to give *(1RS,5RS)-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**154**) (1.09 g, 52 %)

Attempted ring-closure with alkyllithium: a 1.4 M solution of *n*-butyllithium in hexane (1.74 ml, 2.4 mmol) was added dropwise to a stirred solution of (5*RS*)-5-chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**153**) (500 mg, 2.2 mmol) in dry ether (20 ml) at -78 °C. The mixture was allowed to reach room temperature and was cooled again to -40 °C. The reaction mixture was quenched with water (5 ml) and extracted with ether (3 × 10 ml). The combined organic layers were dried and the solvent was removed to give a white solid, which was identified as starting material **153** (220 mg, 44 %). The crude ^{1}H NMR showed only traces of *4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**154**).

White solid, m.p. 82-83 °C.

All other analytical data of **154** were identical to those given for the enantiomerically pure compound (see above).

EXPERIMENT 39

(1*S*,2*S*)-2-[(*S*)-Amino(4-methoxyphenyl)methyl]cyclopropan-1-ol (155)

A solution of (1*S*,5*S*)-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (100 mg, 0.53 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (40 mg, 1.06 mmol) in dry ether (10 ml) and the mixture was refluxed for 16 h. Work-up as is Exp. 10 gave *(1S,2S)-2-[(S)-amino(4-methoxyphenyl)methyl]cyclopropan-1-ol* (**155**) (100 mg, 98 %).

$[\alpha]_D^{26}$ = +65.5.6° (c 0.4, MeOH).

Found: C 68.17, H 8.13, N 7.19. $C_{11}H_{15}NO_2$ requires: C 68.37, H 7.82, N 7.25.

White solid, m.p. 80-83 °C.

δ_H 0.56 (1H, dt, J 3.3, 6.7 Hz, H_{cis}-3 (relative to H-1)), 0.76 (1H, td, J 6.7, 9.2 Hz H_{trans}-3 (relative to H-1)), 0.94 (1H, tdd, J 6.7, 7.0, 9.2 Hz, H-2), 2.60 (3H, br. s, NH_2 and OH), 3.45 (1H, dt, J 3.3, 6.7 Hz, H-1), 3.74 (3H, s, OCH_3), 3.91 (1H, d, J 7.0 Hz, C<u>H</u>-NH_2), 6.81-6.85 (2H, m, aromatic), 7.28-7.32 (2H, m, aromatic).

δ_C 10.6 (C-3), 24.0 (C-2), 49.8 (CH-NH_2), 52.9 (C-1), 55.2 (OCH_3), 113.8, 127.3, 138.4, 158.5 (all aromatic C).

ν_{max} 3340 br. s, 2999 s, 2934 s, 2836 s, 1667 m, 1614 s, 1514 s, 1462 s, 1305 m, 1252 s, 1177 s, 1108 m, 1035 s, 834 s, 732 m cm^{-1}.

m/z, % 177, 10; 176, 67 (M^+-OH); 173, 25; 158, 13; 149, 37; 147, 100; 136, 53; 134, 99; 121, 23; 109, 18; 91, 21; 77, 18.

EXPERIMENT 40

(2*S*)-2-(2,2,2-Trifluoroacetylamino)propionic acid methyl ester (165)

2,2,2-Trifluoro-*N*-[(1*S*)-1-phenylethyl]acetamide (**164**) (600 mg, 2.9 mmol) was dissolved in carbon tetrachloride (5 ml) and acetonitrile (5 ml). Water (7.5 ml), periodic acid (9.4 g, 41.3 mmol) and ruthenium trichloride hydrate (31 mg, 0.05 mol.equiv.) were added to the above solution. The mixture was refluxed for 3 h. Water (10 ml) was added, the mixture was extracted with ethyl acetate (3 × 25 ml), and the combined organic layers were washed with water (2 × 50 ml) and dried. The solvent was removed, the residue was dissolved in methanol (10 ml) and 3 drops of concentrated sulfuric acid

were added. After 4 h at reflux methanol was removed and the residue was dissolved in dichloromethane (20 ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 ml) and water (1 × 10 ml) and then dried. The solvent was removed to give *(2S)-2-(2,2,2-trifluoroacetylamino)propionic acid methyl ester* (**165**) (416 mg, 71 %) as a colourless oil.

The analytical data of **165** were identical to those reported.[188]

EXPERIMENT 41

[(5*RS*)-3-(4-Methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (166)

a) The general procedure A (Exp. 34) was used to react 2-methyl-2-propen-1-ol (0.23 ml, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding *[(5RS)-3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]methanol* (**166**) (352 mg, 59 %) with 0 % ee.

The reaction was repeated using modified reaction conditions (b-d):

b) Stirring for 24 h at -70 °C gave **166** in 73 % yield (0 % ee).

c) Change of the molar amounts used [2-methyl-2-propen-1-ol (1 mol.equiv., unchanged), Et_2Zn (3 instead of 1.2 mol.equiv.), *R,R*-DIPT (0.6 instead of 0.2 mol.equiv.), 1,4-dioxane (4.5 instead of 1.5 mol.equiv.), *N*-hydroxy-4-methoxybenzimidoyl chloride (3 instead of 1 mol.equiv.)] afforded **166** in 62 % yield (5 % ee).

d) A stoichiometric amount of (*R,R*)-DIPT (1 mol.equiv.) was used and the general procedure A (Exp. 34) was altered as follows: after stirring the reaction mixture for 1 h, a $CHCl_3$ (6 ml) solution of hydroximoyl chloride (1.1 mol.equiv.) and an additional amount of diethylzinc (another 1.1 mol.equiv.) were added successively [no 1,4-dioxane was used]. The resulting mixture was stirred for 24 h at 0 °C. Work-up afforded **166** in 12 % yield (0 % ee).

Racemic compound **166** as a standard for the HPLC was prepared as follows:

e) The general procedure B (Exp. 34) was used to react 2-methyl-2-propen-1-ol (0.23 ml, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding **166** (457 mg, 77 %).

White solid, m.p. 94-95 °C.

Found: C 65.36, H 6.46, N 6.32. $C_{12}H_{15}NO_3$ requires: C 65.11, H 6.83, N 6.33.

δ_H 1.40 (3H, s, CH_3), 2.97 (1H, d, J 16.5 Hz, first of H-4), 3.44 (1H, d, J 16.5 Hz, second of H-4), 3.55 (1H, d, J 12.0 Hz, first H of $C\underline{H}_2OH$), 3.70 (1H, d, J 12.0 Hz, second H of $C\underline{H}_2OH$), 3.81 (3H, s, OCH_3), 6.86-6.90 (2H, m, aromatic), 7.54-7.58 (2H, m, aromatic).

δ_C 22.6 (CH_3), 42.1 (C-4), 55.3 (OCH_3), 67.1 (CH_2OH), 87.0 (C-5), 114.0, 122.2, 128.0, 156.5 (all aromatic C), 160.9 (C-3).

ν_{max} 3356 br. s, 2954 m, 2835 m, 1611 s, 1518 s, 1456 m, 1425 m, 1362 s, 1307 m, 1261 s, 1172 s, 1044 s, 1024 s, 931, 909 s, 828 s, 806 m, 787 m, 661 m cm^{-1}.

m/z, % 221, 50 (M^+); 190, 46; 148, 100; 133, 10; 121, 29; 77, 16.

EXPERIMENT 42

[3-(4-Methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-4-yl]methanol (170) and [3-(4-methoxyphenyl)-4-phenyl-4,5-dihydroisoxazol-5-yl]methanol (171)

a) The general procedure A (Exp. 34) with a modified reaction temperature (24 h at –65 °C instead of 0 °C) was used to react cinnamyl alcohol (361 mg, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol) yielding a mixture of two regioisomers, *[3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazol-4-yl]methanol* (**170**) and *[3-(4-methoxyphenyl)-4-phenyl-4,5-dihydroisoxazol-5-yl]methanol* (**171**) (in total 425 mg, 56 %; 0 % ee for both isomers; ratio 67:33; the isomers were not separated by column chromatography).

b) The general procedure B (Exp. 34) was used to react cinnamyl alcohol (361 mg, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol) yielding a mixture of two regioisomers, (**170**) and (**171**) (in total 368 mg, 48 %; ratio, 66:35; the isomers were not separated by column chromatography).

Analytical data of mixture:

Found: C 71.36, H 6.19, N 4.89. $C_{17}H_{17}NO_3$ requires: C 72.07, H 6.05, N 4.94.

NMR data, major isomer (**170**):

δ_H 2.33 (1H, br. s, OH), 3.82 (3H, s, OCH_3), 3.76-3.92 (2H, m, H-4 and first H of $C\underline{H}_2OH$, together with peaks of isomer B), 4.00 (1H, dd, J 3.5, 10.5 Hz, second H of $C\underline{H}_2OH$), 5.74 (1H, d, J 4.0 Hz, H-5), 6.86-6.93 (2H, m, aromatic), 7.25-7.40 (5H, m, aromatic), 7.62-7.66 (2H, m, aromatic).

δ_C 55.3 (OCH_3), 59.4 (C-4), 62.0 (CH_2OH), 85.5 (C-5), 114.3, 121.0, 125.3, 128.5, 128.7, 129.3, 141.3, 156.6 (all aromatic C), 161.1 (C-3).

NMR data, minor isomer (**171**):

δ_H 1.80 (1H, br. s, OH), 3.76 (3H, s, OCH_3), 3.76-3.92 (2H, m, CH_2OH, together with peaks of isomer A), 4.59 (1H, ddd, J 3.8, 4.4, 5.9 Hz, H-5), 4.69 (1H, d, J 5.9 Hz, H-4), 6.76-6.80 (2H, m, aromatic), 7.25-7.40 (5H, m, aromatic), 7.50-7.54 (2H, m, aromatic).

δ_C 55.2 (OCH_3), 55.9 (C-4), 63.2 (CH_2OH), 90.2 (C-5), 114.0, 120.9, 127.7, 127.9, 128.9, 129.0, 139.0, 158.3 (all aromatic C), 160.8 (C-3).

The IR and mass spectrum of the mixture were not recorded.

EXPERIMENT 43

[4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methanol (173)

a) The general procedure A (Exp. 34) was used to react cyclopropene-1-methanol [prepared from 1,1,2-tribromocyclopropane-2-methanol (4.2 g, 0.0136 mol) and methyllithium (29.9 ml, 1.5 M) in a procedure analogous to the one described in Exp. 6] with *N*-hydroxy-4-methoxybenzimidoyl chloride (1.8 g, 0.0097 mol), yielding *[4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methanol* (**173**) (470 mg, 22 %) with 22 % ee.

b) The general procedure B (Exp. 34) was used to react cyclopropene-1-methanol [prepared from 1,1,2-tribromocyclopropane-2-methanol (4.2 g, 0.0136 mol) and methyllithium (29.9 ml, 1.5 M) in a procedure analogous to the one described in Exp. 6] with *N*-hydroxy-4-methoxybenzimidoyl chloride (2.29 g, 0.0124 mol), yielding **173** (2.03 g, 75 %).

Racemic compound:

White solid, m.p. 98-99 °C.

Found: C 65.51, H 6.05, N 6.44. $C_{12}H_{13}NO_3$ requires: C 65.74, H 5.98, N 6.39.

δ_H 0.60 (1H, dd, J 4.0, 5.5 Hz, H_{endo}-6), 1.26 (1H, dd, J 5.5, 9.5 Hz, H_{exo}-6), 2.48 (1H, br. s, OH), 2.82 (1H, dd, J 4.0, 9.5 Hz, H-5), 3.76 (1H, d, J 13.3 Hz, first H of $C\underline{H}_2OH$), 3.82 (3H, s, OCH_3), 4.35 (1H, d, J 13.3 Hz, second H of $C\underline{H}_2OH$), 6.88-6.92 (2H, m, aromatic), 7.65-7.68 (2H, m, aromatic).

δ_C 11.2 (C-6), 28.7 (C-5), 55.3 (OCH_3), 62.3 (CH_2OH), 76.2 (C-1), 114.1, 121.6, 128.6 (all aromatic C); 161.3 and 161.9 (aromatic C and C-4).

ν_{max} 3417 br. s, 3267 br. s, 3052 m, 2923 m, 1610 s, 1586 m, 1517 s, 1468 m, 1427 s, 1388 s, 1309 s, 1255 s, 1176 s, 1111 m, 1054 s, 1044 s, 1027 s, 978 s, 930 m, 900 m, 974 m, 844 s, 822 s, 653 m cm^{-1}.

m/z, % 220, 14 (M^++1); 189, 3; 160, 100; 133, 24; 107, 11; 92, 12; 86, 28; 77, 30.

EXPERIMENT 44

[3-(4-Methoxyphenyl)isoxazol-5-yl]methanol (176)

a) The general procedure A (Exp. 34) was used to react 2-chloro-2-propen-1-ol (0.21 ml, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding *[3-(4-methoxyphenyl)isoxazol-5-yl]methanol* (**176**) (185 mg, 33 %).

b) The general procedure B (Exp. 34) was used to react 2-chloro-2-propen-1-ol (0.43 ml, 5.4 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol). The crude product was purified by column chromatography on silica gel (petrol - ethyl acetate, 3:1) yielding **176** (280 mg, 51 %).

White solid, m.p. 97-98 °C.

Found: C 64.64, H 5.28, N 6.76. $C_{11}H_{11}NO_3$ requires: C 64.38, H 5.40, N 6.83.

δ_H 3.81 (3H, s, OCH_3), 4.74 (2H, s, CH_2OH), 6.45 (1H, s, H-4), 6.89-6.94 (2H, m, aromatic), 7.63-7.69 (2H, m, aromatic).

δ_C 55.3 (OCH_3), 56.4 (CH_2OH), 99.8 (C-4), 114.3, 122.4, 128.2 (all aromatic C); 161.0, 162.0 and 171.7 (aromatic C, C-3 and C-5).

ν_{max} 3356 br. s, 2918 m, 2837 m, 1612 s, 1527 s, 1465 m, 1446 s, 1431 s, 1366 s, 1297 m, 1260 s, 1178 s, 1083 s, 1062 m, 1028 s, 984 s, 919 s, 842 s, 803 m, 723 m, 607 m cm^{-1}.

m/z, % 205, 58 (M^+); 174, 100; 146, 77; 131, 5; 119, 5; 103,3; 92, 7; 77, 12.

EXPERIMENT 45

2-[(5*RS*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]propan-2-ol (181)

a) The general procedure A (Exp. 34) was used to react 2-methyl-3-buten-2-ol (0.28 ml, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding *2-[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]propan-2-ol* (**181**) (313 mg, 49 %) with 0 % ee.

b) The general procedure B (Exp. 34) was used to react 2-methyl-3-buten-2-ol (0.56 ml, 5.4 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding *2-[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]propan-2-ol* (**181**) (499 mg, 79 %).

White solid, m.p. 95-96 °C.

Found: C 66.40, H 7.16, N 6.06. $C_{13}H_{17}NO_3$ requires: C 66.36, H 7.28, N 5.95.

δ_H 1.20 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.92 (1H, br. s, OH), 3.23 (1H, dd, J 10.7, 16.6 Hz, first of H-4), 3.33 (1H, dd, J 9.1, 16.6 Hz, second of H-4), 3.81 (3H, s, OCH_3), 4.52 (1H, dd, J 9.1, 10.7 Hz, H-5), 6.86-6.91 (2H, m, aromatic), 7.55-7.61 (2H, m, aromatic).

δ_C 24.7 (CH_3), 26.2 (CH_3), 35.8 (C-4), 55.3 (OCH_3), 71.1 ($\underline{C}(CH_3)_2$-OH), 87.3 (C-5), 114.0, 122.0, 128.1, 156.7 (all aromatic C), 161.0 (C-3).

ν_{max} 3350 br. s, 2974 s, 2954 m, 2840 m, 1608 s, 1517 s, 1466 s, 1421 s, 1356 s, 1299 s, 1244 s, 1180 s, 1161 s, 1044 s, 1021 s, 963 s, 912 s, 832 s, 813 s, 641 m, 612 s cm^{-1}.

m/z, % 235, 28 (M^+); 220, 2; 202, 3; 177, 4; 149, 50; 134, 100; 121, 9; 92, 6; 77, 9; 59, 48.

EXPERIMENT 46

***syn/anti*-1-[3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol (179a)**

By cycloaddition reaction:

a) The general procedure A (Exp. 34) was used to react 3-buten-2-ol (0.23 ml, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol). Crude *1-[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol* (**179a**) was obtained as a mixture of two diastereomers (ratio *syn* to *anti*, 69:31). The mixture was partially separated by column chromatography on silica gel (petrol - ethyl acetate, 3:1 to 1:1): fraction 1: *anti* isomer, fraction 2: mixture of both isomers, fraction 3: *syn* isomer; total yield: 355 mg (60 %); *anti*: 10 % (ratio 1*S*,5*R* to 1*R*,5*S* was 55 : 45); *syn*: 8 % ee (ratio 1*R*,5*R* to 1*S*,5*S* was 54 : 46).

b) The general procedure B (Exp. 34) was used to react 3-buten-2-ol (0.47 ml, 5.4 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding **179a** (499 mg, 79 %); ratio *syn* to *anti*, before recrystallisation from EtOAc / petrol: 54:46, after recryst. 58:42.

(1SR)-1-[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol (*anti*-**179a**):

White solid, m.p. 87-91 °C.

Found: C 65.05, H 6.54, N 6.19. $C_{12}H_{15}NO_3$ requires: C 65.14, H 6.83, N 6.33.

δ_H 1.19 (3H, d, J 6.5 Hz, CH_3), 2.47 (1H, br. s, OH), 3.18 (1H, dd, J 10.9, 16.6 Hz, first of H-4), 3.36 (1H, dd, J 8.7, 16.6 Hz, second of H-4), 3.81 (3H, s, OCH_3), 4.09 (1H, dq, J 3.4, 6.5 Hz, C<u>H</u>-OH), 4.59 (1H, ddd, J 3.4, 8.7, 10.9 Hz, H-5), 6.85-6.90 (2H, m, aromatic), 7.55-7.60 (2H, m, aromatic).

δ_C 18.1 (CH_3), 34.5 (C-4), 55.3 (OCH_3), 67.1 (CH-OH), 84.8 (C-5), 114.0, 121.9, 128.2, 156.6 (all aromatic C), 161.0 (C-3).

ν_{max} 3391 br. s, 2979 m, 2843 m, 1609 s, 1518 s, 1470 s, 1461 s, 1361 s, 1292 s, 1259 s, 1174 s, 1062 s, 1020 s, 908 s, 893 s, 823 s, 632 m, 571 m cm^{-1}.

m/z, %221, 97 (M^+); 176, 56; 149, 30; 148, 30; 134, 100; 121, 77; 92, 15; 77, 35.

(1RS)-1-[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol (*syn*-**179a**):

White solid, m.p. 111-112 °C.

Found: C 64.92, H 6.68, N 6.23. $C_{12}H_{15}NO_3$ requires: C 65.14, H 6.83, N 6.33.

δ_H 1.26 (3H, d, J 6.4 Hz, CH_3), 2.33 (1H, br. s, OH), 3.12 (1H, dd, J 7.6, 16.6 Hz, first of H-4), 3.35 (1H, dd, J 10.6, 16.6 Hz, second of H-4), 3.76 (1H, dq, J 5.6, 6.4 Hz, C<u>H</u>-OH), 3.81 (3H, s, OCH_3), 4.53 (1H, ddd, J 5.6, 7.6, 10.6 Hz, H-5), 6.87-6.92 (2H, m, aromatic), 7.55-7.60 (2H, m, aromatic).

δ_C 18.9 (CH_3), 37.2 (C-4), 55.3 (OCH_3), 69.1 (CH-OH), 84.4 (C-5), 114.0, 121.7, 128.2, 156.5 (all aromatic C), 161.0 (C-3).

ν_{max} 3371 br. s, 2982 m, 2935 m, 1609 s, 1517 s, 1420 s, 1352 m, 1308 m, 1253 s, 1182 m, 1079 m, 1958 m, 1040 s, 1020 s, 902 s, 835 s cm^{-1}.

m/z, % 221, 100 (M^+); 176, 53; 149, 34; 148, 32; 134, 91; 121, 78; 92, 24; 77, 39.

By Swern oxidation & Grignard addition (use of enantiomerically pure starting material):

c) To a stirred solution of oxalyl chloride (0.13 ml, 1.5 mmol) in THF (2 ml) at -78 °C was added dimethyl sulfoxide (0.12 ml, 1.6 mmol). The solution was warmed to -35 °C for 5 min and then recooled to -78 °C. A solution of [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (150 mg, 0.72 mmol) in THF (5 ml) was added to the reaction mixture which was then warmed to -35 °C and, after 15 min, treated with triethylamine (0.50 ml, 3.6 mmol). The cooling bath was removed and the reaction mixture was stirred at room temperature until no starting material was left (monitored by TLC). The vigorously stirred mixture was cooled to -78 °C and methylmagnesium bromide (3.6 ml, 1.0 M in butyl ether) was added dropwise. It was stirred at -78 °C for 30 min, and then allowed to warm to room temperature over a period of 3 h. Ethanol (2 ml) was added cautiously, followed by a saturated aqueous solution of NH_4Cl (10 ml) and hydrochloric acid (2 %, 15 ml). The aqueous layer was extracted with ethyl acetate (3 × 25 ml) and the combined organic layers were dried. The solvent was removed to give the crude product as a mixture of two diastereomers: *(1R)-1-[(5R)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol* (*syn*-**179a**) and *(1S)-1-[(5R)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol* (*anti*-**179a**) (ratio *syn* to *anti*, 23:77). The mixture was purified by column chromatography on silica gel (petrol - ether, 2:1); the two diastereomers were not separated; total yield of **179a** (77 mg, 48 %).

The ^1H NMR spectrum was identical to the ones obtained from the cycloaddition reactions (see above).

EXPERIMENT 47

2-[(5*RS*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol (168)

a) The general procedure A (Exp. 34) was used to react 3-buten-1-ol (0.23 ml, 2.7 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding *2-[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol* (**168**) (335 mg, 56 %) with 0 % ee.

b) The general procedure B (Exp. 34) was used to react 3-buten-1-ol (0.46 ml, 5.4 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol), yielding *2-[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol* (**168**) (475 mg, 80 %).

White solid, m.p. 114-116 °C.

Found: C 65.48, H 6.81, N 6.52. $C_{12}H_{15}NO_3$ requires: C 65.14, H 6.83, N 6.33.

δ_H 1.81-2.05 (2H, m, $C\underline{H}_2CH_2OH$), 2.24 (1H, br. s, OH), 3.03 (1H, dd, J 7.9, 16.5 Hz, first of H-4), 3.41 (1H, dd, J 10.2, 16.5 Hz, second of H-4), 3.80 (3H, s, OCH_3), 3.83 (2H, t, J 6.1 Hz, $CH_2C\underline{H}_2OH$), 4.86 (1H, dtd, J 4.9, 7.9, 10.2 Hz, H-5), 6.85-6.91 (2H, m, aromatic), 7.54-7.58 (2H, m, aromatic).

δ_C 37.7 (C-4), 40.6 ($\underline{C}H_2CH_2OH$), 55.3 (OCH_3), 59.6 ($CH_2\underline{C}H_2OH$), 79.0 (C-5), 114.0, 122.0, 128.1, 156.4 (all aromatic C), 160.9 (C-3).

ν_{max} 3315 br. s, 2940 s, 2835 s, 1611 s, 1597 s, 1519 s, 1465 m, 1420 s, 1356 s, 1307 s, 1253 s, 1180 s, 1109 m, 1041 s, 907 s, 830 s, 605 s cm^{-1}.

m/z, % 222, 100 (M^++1); 176, 93; 149, 17; 134, 24; 121, 30; 77, 24.

EXPERIMENT 48

[(5*RS*)-3-Heptyl-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (183)

a) The general procedure A (Exp. 34) was used to react 2-methyl-2-propen-1-ol (0.95 ml, 11.3 mmol) with *N*-hydroxyoctanimidoyl chloride (2 g, 11.3 mmol), yielding *[(5RS)-3-heptyl-5-methyl-4,5-dihydroisoxazol-5-yl]methanol* (**183**) (1.34 g, 56 %) as a colourless oil.

The optical yield was determined by HPLC analysis of its benzoic acid ester derivative **184**, see below.

b) The general procedure B (Exp. 34) was used to react 2-methyl-2-propen-1-ol (2.28 ml, 27.2 mmol) with *N*-hydroxyoctanimidoyl chloride (1.2 g, 6.8 mmol). The crude product was purified by column chromatography on silica gel (petrol - ethyl acetate, 1:1), yielding **183** (265 mg, 18 %) as a colourless oil.

Racemic compound:

Found $[MH]^+$: 214.1807. $C_{12}H_{23}NO_2$ + H requires: 214.1807.

δ_H 0.83 (3H, t, J 6.3 Hz, CH_3), 1.24-1.29 (8 H, m, 4 × CH_2), 1.29 (3H, s, CH_3), 1.50 (2H, quintet, J 7.4 Hz, CH_2), 2.26 (2H, t, J 7.4 Hz, CH_2), 2.54 (1H, d, J 17.0 Hz, first of H-4), 3.00 (1H, d, J 17.0 Hz, second of H-4), 3.42 (1H, d, J 11.9 Hz, first H of $C\underline{H}_2OH$), 3.60 (1H, d, J 11.9 Hz, second H of $C\underline{H}_2OH$).

δ_C 14.0 (CH_3), 22.5 (CH_3), 22.6, 26.3, 27.9, 28.9, 29.1, 31.6 (all CH_2), 44.0 (C-4), 67.2 (CH_2OH), 87.8 (C-5), 159.8 (C-3).

ν_{max} 3395 br. s, 2927 s, 2856 s, 1726 w, 1626 w, 1456 m, 1434 m, 1377 m, 1056 s, 890 m, 805 w, 724 w cm^{-1}.

m/z (CI, NH_4^+), % 214, 100 $[MH]^+$; 182, 82; 140, 12; 129, 10.

[(5*RS*)-3-Heptyl-5-methyl-4,5-dihydroisoxazol-5-yl]methyl benzoate (184)

Benzoyl chloride (0.09 ml, 0.76 mmol) was added to a stirred solution of [(5*RS*)-3-heptyl-5-methyl-4,5-dihydroisoxazol-5-yl]methanol (155 mg, 0.73 mmol; from Exp. 58a) and triethylamine (0.11 ml, 0.76 mmol) in dry ether (5 ml); triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and the precipitate was filtered off. The solvent was removed and the crude product was purified by column chromatography on silica gel (petrol - ether, 5:1 to ether only) to give *[(5RS)-3-heptyl-5-methyl-4,5-dihydroisoxazol-5-yl]methyl benzoate* (**184**) (110 mg, 48 %, 11 % ee).

The reaction was repeated on the same scale (this time using racemic alcohol from Exp. 58b) yielding **184** (120 mg, 52 %).

Racemic compound:

White solid, m.p. 26-27 °C.

Found $[MH]^+$: 318.2070. $C_{19}H_{27}NO_3$ + H requires: 318.2069.

δ_H 0.84 (3H, t, J 6.6 Hz, CH_3), 1.20-1.33 (8 H, m, 4 × CH_2), 1.47 (3H, s, CH_3), 1.47-1.53 (2H, m, CH_2, peak partially underneath peak of CH3), 2.30 (2H, t, J 7.4 Hz, CH_2), 2.70 (1H, d, J 17.1 Hz, first of H-4), 2.96 (1H, d, J 17.1 Hz, second of H-4), 4.30 (2H, s, CH_2OH), 7.38-7.69 (3H, m, aromatic), 7.99-8.15 (2H, m, aromatic).

δ_C 14.0 (CH_3), 22.5 (CH_3), 23.1, 26.4, 27.9, 28.9, 29.2, 31.6 (all CH_2), 45.3 (C-4), 68.5 (CH_2O), 83.6 (C-5), 128.4, 129.7, 133.2 (all aromatic C), 158.8 (C-3), 166.3 (CO).

ν_{max} 2927 s, 2856 s, 1724 s, 1602 m, 1451 s, 1435 m, 1376 s, 1314 s, 1276 s, 1176 s, 1114 s, 1070 s, 1027 s, 886 m, 712 s cm^{-1}.

m/z (CI, NH_4^+), % 318, 35 $[MH]^+$; 182, 100; 105, 14.

EXPERIMENT 49

[5-(4-Methoxyphenyl)-2-phenyl-3,4-dihydro-2*H*-pyrazol-3-yl]methanol (190)

a) The general procedure A (Exp. 34) with modified reaction time (24 h at 0 °C and additionally 1 week at room temperature) was used to react allyl alcohol (0.18 ml, 2.7 mmol) with *N*-phenyl-4-methoxybenzhydrazonyl chloride (700 mg, 2.7 mmol), yielding *[5-(4-methoxyphenyl)-2-phenyl-3,4-dihydro-2H-pyrazol-3-yl]methanol* (**190**) (83 mg, 11 %) with 0 % ee.

b) The general procedure B (Exp. 34) was used to react allyl alcohol (1.8 ml, 27.0 mmol) with *N*-phenyl-4-methoxybenzhydrazonyl chloride (700 mg, 2.7 mmol). The crude product was purified by column chromatography on silica gel (petrol - ether, 1:1), yielding **190** (650 mg, 86 %).

White-yellow solid, m.p. 112-113 °C.

Found: C 72.76, H 6.46, N 10.11. $C_{17}H_{18}N_2O_2$ requires: C 72.32, H 6.43, N 9.92.

δ_H 1.97 (1H, br. s, OH), 3.24 (1H, dd, J 6.1, 17.1 Hz, CH), 3.38 (1H, dd, J 11.3, 17.1 Hz, CH), 3.72 (1H, dd, J 3.2, 11.4 Hz, CH-OH), 3.81 (3H, s, OCH_3), 3.85 (1H, dd, J 4.9, 11.4 Hz, CH-OH), 4.40 (1H, dddd, J 3.2, 4.9, 6.1, 11.3 Hz, CH-O), 6.80-6.90 (3H, m, aromatic), 7.15-7.29 (4H, m, aromatic), 7.62-7.67 (2H, m, aromatic).

δ_C 36.1 (CH_2), 55.3 (OCH_3), 61.4 (CH-N), 62.6 (CH_2OH),113.3, 113.9, 119.2, 125.3, 127.3, 129.2, 145.5, 149.1 (all aromatic C), 160.2 (C=N).

ν_{max} 3452 br. s, 2932 m, 1597 s, 1498 s, 1394 s, 1336 m, 1257 s, 1178 s, 1125 m, 1068 m, 1032 m, 954 w, 834 s, 749 s, 694 m cm^{-1}.

m/z, % 282, 55 (M^+); 251, 100; 236, 8; 208, 4; 148, 4; 104, 5; 91, 5; 77, 11.

EXPERIMENT 50

2-[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethyl mesylate (198)

2-[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethanol (545 mg, 2.46 mmol) was reacted with methanesulfonyl chloride (in total 0.22 ml, 2.95 mmol), using a procedure analogous to the one described in Exp. 37. Recrystallisation from ether / petrol gave *2-[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethyl mesylate* (**198**) (650 mg, 88 %).

White solid, m.p. 93-94 °C.

Found: C 52.21, H 5.57, N 4.83. $C_{13}H_{17}NO_5S$ requires: C 52.16, H 5.72, N 4.68.

δ_H 2.09 (2H, "q", J 6.4 Hz, $C\underline{H}_2CH_2OSO_2CH_3$), 3.00 (3H, s, OSO_2CH_3), 3.01 (1H, dd, J 6.8, 16.5 Hz, first of H-4), 3.47 (1H, dd, J 10.4, 16.5 Hz, second of H-4), 3.82 (3H, s, OCH_3), 4.40 (2H, 2 × t, J 6.4 Hz, $CH_2C\underline{H}_2OSO_2CH_3$), 4.86 (1H, tdd, J 6.4, 6.8, 10.4 Hz, H-5), 6.88-6.92 (2H, m, aromatic), 7.55-7.59 (2H, m, aromatic).

δ_C 34.7 (C-4), 37.0 (SO_2CH_3), 40.4 ($\underline{C}H_2CH_2O$), 55.3 (OCH_3), 66.7 ($CH_2\underline{C}H_2O$), 76.6 (C-5), 114.1, 121.7, 128.1, 156.1 (all aromatic C), 161.0 (C-3).

ν_{max} 3024 w, 2969 w, 2845 w, 1608 s, 1518 s, 1466 m, 1442 m, 1342 s, 1260 s, 1170 s, 1008 s, 989 s, 910 s, 837 s, 824 s, 603 m cm^{-1}.

m/z, % 299, 48 (M^+); 176, 100; 148, 10; 134, 21; 121, 23; 77, 10; 70, 11.

EXPERIMENT 51

5-(2-Iodoethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (199)

Crude 2-[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethyl mesylate (1.55 g, 5.2 mmol) and sodium iodide (2.3 g, 15.5 mmol) were refluxed in acetone (50 ml) for 15 h. The reaction mixture was filtered to give a clear solution. Acetone was removed and the residue was dissolved in dichloromethane (40 ml). The organic layer was washed with a saturated aqueous solution of sodium thiosulfate (1 × 30 ml), with water (1 × 30 ml) and then dried. The solvent was removed and the residue was recrystallised from ether /petrol to give *5-(2-iodoethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole* (**199**) (1.06, 62 %).

Yellow-white solid, m.p. 96-99 °C.

Found: C 43.63, H 4.19, N 4.32. $C_{12}H_{14}INO_2$ requires: C 43.52, H 4.26, N 4.23.

δ_H 2.03-2.31 (2H, m, $C\underline{H}_2CH_2I$), 2.93 (1H, dd, J 7.1, 16.5 Hz, first of H-4), 3.29 (2H, dd, J 6.4, 7.7 Hz, $CH_2C\underline{H}_2I$), 3.44 (1H, dd, J 10.3, 16.5 Hz, second of H-4), 3.82 (3H, s, OCH_3), 4.79 (1H, dddd, J 4.3, 7.1, 7.8, 10.4 Hz, CH-O), 6.88-6.92 (2H, m, aromatic), 7.56-7.59 (2H, m, aromatic).

δ_C 0.9 ($CH_2\underline{C}H_2I$), 39.2 (C-4), 40.0 ($\underline{C}H_2CH_2I$), 55.3 (OCH_3), 80.3 (C-5), 114.1, 121.9, 128.2, 156.0 (all aromatic C), 161.1 (C-3).

ν_{max} 2910 w, 2835 w, 1612 s, 1596 m, 1519 s, 1422 m, 1359 m, 1307 m, 1253 s, 1203 m, 1180 s, 1042 m, 1020 m, 912 m, 886 m, 830 s cm^{-1}.

m/z, % 331, 100 (M^+); 204, 2; 176, 38; 148, 18; 132, 7; 121, 34; 92, 6; 77, 14.

EXPERIMENT 52

Attempted synthesis of 4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.2.0]hept-3-ene (200)

a) Potassium *tert*-butoxide (731 mg, 2.2 mmol) was added in small portions to a solution 2-[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]ethyl mesylate (650 mg, 6.5 mmol) in anhydrous dimethyl sulfoxide (7 ml) at room temperature. After stirring the mixture for 30 min, water (5 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 15 ml). The combined organic layers were washed with water (1× 40

ml) and dried. The solvent was removed to give an unidentified mixture, which was purified by column chromatography on silica gel (petrol - ethyl acetate, 1:1). Only a minor compound (fraction 1) was identified as *5-ethyl-3-(4-methoxyphenyl)isoxazole* (**201**) (30 mg, 7 %). The rest (128 mg) was not identified.

5-Ethyl-3-(4-methoxyphenyl)isoxazole (**201**), colourless oil:

Found M^+: 203.0952. $C_{12}H_{13}NO_2$ requires: 203.0946.

δ_H 1.31 (3H, t, J 7.6 Hz, $CH_2\underline{C}H_3$), 2.79 (2H, q, J 7.6 Hz, $\underline{C}H_2CH_3$), 3.83 (3H, s, OCH_3), 6.21 (1H, s, H-4), 6.92-6.96 (2H, m, aromatic), 7.69-7.73 (2H, m, aromatic).

δ_C 11.7 (CH_3), 20.3 (CH_2), 55.3 (OCH_3), 98.0 (C-4), 114.2, 121.9, 128.1 (all aromatic C); 160.8 and 161.9 (aromatic C and C-3), 175.1 (C-5).

ν_{max} 2976 m, 2937 m, 2838 w, 1614 s, 1575 m, 1529 s, 1456 m, 1431 s, 1395 m, 1297 m, 1253 s, 1177 s, 1114 w, 1031 s, 948 w, 909 m, 838 s, 804 m cm^{-1}.

m/z, % 203, 63 (M^+); 174, 100; 146, 50; 132, 8; 77, 8; 57, 8.

b) 5-(2-Iodoethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (180 mg, 0.54 mmol) in anhydrous dimethyl sulfoxide (5 ml) was reacted with potassium *tert*-butoxide (183 mg, 1.63 mmol) as above. Only *5-ethyl-3-(4-methoxyphenyl)isoxazole* (**201**) (4 mg, 4 %) was isolated.

c) Lithium diisopropylamide (LDA) was prepared by adding *n*-BuLi (2.7 ml, 1.6 M in hexane, 4.3 mmol) dropwise to a solution of diisopropylamine (0.48 ml, 3.6 mmol) in dry ether (5 ml) at 0° C. The mixture was stirred at 0° C for 30 min, then added to a solution of 5-(2-iodoethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (500 mg, 1.5 mmol) in dry ether (5 ml) at -80° C. After 10 min the mixture was allowed to reach 0 °C and kept at this temperature for 1 h. The reaction mixture was quenched with hydrochloric acid (2 %, 5 ml) and extracted with ether (3 × 15 ml). The combined organic layers were dried and the solvent was removed to give a yellow oil. The crude ^1H NMR gave a complicated spectrum; no product was isolated or identified.

EXPERIMENT 53

[4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl mesylate (214)

[4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methanol (1.09 g, 5.0 mmol) was reacted with methanesulfonyl chloride (in total 0.46 ml, 6 mmol), using a procedure analogous to the one described in Exp. 37, yielding crude [*4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl mesylate* (**214**) (1.42 g, 96 %).

White solid, m.p. 125-126 °C (recrystallised from ethyl acetate).

Found: C 52.49, H 5.11, N 4.73. $C_{13}H_{14}NO_5S$ requires: C 52.52, H 5.09, N 4.71.

δ_H 0.76 (1H, dd, J 4.2, 5.8 Hz, H_{endo}-6), 1.40 (1H, dd, J 5.8, 9.6 Hz, H_{exo}-6), 2.99 (1H, dd, J 4.2, 9.6 Hz, H-5), 3.10 (3H, s, SO_2CH_3), 3.83 (3H, s, OCH_3), 4.46 (1H, d, J 13.0 Hz, first H of CH_2O), 4.91 (1H, d, J 13.0 Hz, second H of CH_2O), 6.91-6.94 (2H, m, aromatic), 7.65-7.69 (2H, m, aromatic).

δ_C 12.2 (C-6), 30.0 (C-5), 38.1 (SO_2CH_3), 55.4 (OCH_3), 69.4 (CH_2O), 76.8 (C-1), 114.2, 121.0, 128.7 (all aromatic C); 161.5 and 161.6 (aromatic C and C-4).

ν_{max} 3053 m, 2957 m, 1608 s, 1584 m, 1518 s, 1464 m, 1427 m, 1369 s, 1331 s, 1310 m, 1254 s, 1170 s, 1114 m, 1048 m, 1023 s, 969 s, 935 s, 914 s, 869 s, 845 s, 818 m, 808 m, 757 m, 687 w, 607 m cm^{-1}.

m/z, % 297, 5 (M^+); 161, 9; 160, 100; 133, 84; 107, 6; 92, 4; 79, 8; 77, 10.

EXPERIMENT 54

Reaction of [4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl mesylate with potassium *tert*-butoxide (attempted synthesis of 4-(4-methoxyphenyl)-2-oxa-3-azatricyclo[3.1.1.0^{1,5}]hept-3-ene (218))

A solution of [4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl mesylate (300 mg, 1.0 mmol) in anhydrous dimethyl sulfoxide (10 ml) was added to a suspension of potassium *tert*-butoxide (340 mg, 3.0 mmol) in dimethyl sulfoxide (10 ml). After stirring the mixture for 4 h at room temperature, water (10 ml) was added and the aqueous layer was extracted with ether (5 × 10 ml). The combined organic layers were washed with water (3 × 40 ml) and dried. The solvent was removed to give a mixture, which was purified by column chromatography on silica gel (petrol - ether, 1:1). Two compounds were isolated and identified: *4-(4-methoxyphenyl)-1-(tert-butoxymethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**216**) (38 mg, 14 %) and *bis[[4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl] ether* (**215**) (8 mg, 4 %; as a mixture of diastereomers, ratio 55:44).

4-(4-Methoxyphenyl)-1-(tert-butoxymethyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**216**):
White solid, m.p. 70 °C.
Found: C 70.15, H 7.74, N 5.20. $C_{16}H_{21}NO_3$ requires: C 69.79, H 7.69, N 5.09.

δ_H 0.55 (1H, dd, J 4.0, 5.3 Hz, H_{endo}-6), 1.21 (9H, s, $C(C\underline{H}_3)_3$), 1.30 (1H, dd, J 5.3, 9.4 Hz, H_{endo}-6), 2.75 (1H, dd, J 4.0, 9.4 Hz, H-5), 3.83 (3H, s, OCH_3), 3.85 (1H, d, J 11.0 Hz, first H of CH_2O), 3.89 (1H, d, J 11.0 Hz, second H of CH_2O), 6.90-6.94 (2H, m, aromatic), 7.68-7.72 (2H, m, aromatic).

δ_C 10.8 (C-6), 27.4 ($C(\underline{C}H_3)_3$), 28.8 (C-5), 55.34 (OCH_3), 61.0 (CH_2O), 73.4 ($\underline{C}(CH_3)_3$), 74.7 (C-1), 114.0, 121.9, 128.6 (all aromatic C); 161.1 and 161.6 (aromatic C and C-4).

ν_{max} 3051 w, 2984 w, 1607 s, 1515 s, 1459 m, 1425 m, 1389 s, 1365 s, 1307 m, 1301 m, 1252 s, 1199 m, 1180 s, 1086 s, 1027 s, 927 s, 872 m, 838 s, 819 m, 768 m, 606 w cm^{-1}.

m/z, % 275, 6 (M^+); 189, 3; 161, 10; 160, 100; 134, 5; 133, 5; 107, 5; 92, 5; 77, 7; 57, 23.

Bis[[4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl] ether (**215**):

Beige solid.

Found: C 68.44, H 6.06, N 6.67. $C_{24}H_{24}N_2O_5$ requires: C 68.56, H 5.75, N 6.66.

NMR data, major diastereomer:

δ_H 0.60 (2 × 1H, dd, J 3.9, 5.5 Hz, H_{endo}-6), 1.33 (2 × 1H, dd, J 5.5, 9.5 Hz, H_{exo}-6), 2.86 (2 × 1H, dd, J 3.9, 9.5 Hz, H-5), 3.83 (2 × 3H, s, OCH_3), 3.97 (2 × 1H, d, J 12.6 Hz, first H of CH_2O), 4.18 (2 × 1H, d, J 12.6 Hz, second H of CH_2O), 6.90-6.94 (2 × 2H, m, aromatic), 7.67-7.71 (2 × 2H, m, aromatic).

δ_C 11.4 (2 × C-6), 29.4 (2 × C-5), 55.3 (2 × OCH_3), 70.5 ($H_2\underline{C}$-O-$\underline{C}H_2$), 74.6 (2 × C-1), 114.1, 121.6, 128.6 (all aromatic C); 161.2 and 161.5 (2 × aromatic C and 2 × C-6).

NMR data, minor diastereomer:

δ_H 0.60 (2 × 1H, dd, J 3.9, 5.5 Hz, H_{endo}-6), 1.29 (2 × 1H, dd, J 5.5, 9.5 Hz, H_{exo}-6), 2.83 (2 × 1H, dd, J 3.9, 9.5 Hz, H-5), 3.82 (2 × 3H, s, OCH_3), 4.02 (2 × 1H, d, J 12.6 Hz, first H of CH_2O), 4.25 (2 × 1H, d, J 12.6 Hz, second H of CH_2O), 6.88-6.92 (2 × 2H, m, aromatic), 7.66-7.70 (2 × 2H, m, aromatic).

δ_C 11.4 (2 × C-6), 29.3 (2 × C-5), 55.3 (2 × OCH_3), 70.5 ($H_2\underline{C}$-O-$\underline{C}H_2$), 74.7 (2 × C-1), 114.1, 121.6, 128.6 (all aromatic C); 161.2 and 161.5 (2 × aromatic C and 2 × C-4).

ν_{max} (mixture) 2934 w, 2837 w, 1609 s, 1585 m, 1516 s, 1459 m, 1424 m, 1369 s, 1301 m, 1252 s, 1176 s, 1112 s, 1026 s, 931 s, 912 m, 873 m, 832 s, 764 w, 608 m, 528 m cm^{-1}.

m/z, % (mixture) 220, 1; 218, 1 (M^+-$C_{12}H_{12}NO_2$); 202, 3; 201, 6; 160, 100; 133; 55; 103, 10, 90, 11; 77, 10.

EXPERIMENT 55

1-Iodomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (217)

[4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-en-1-yl]methyl mesylate (1.02 g, 3.4 mmol) and sodium iodide (1.54 g, 10.3 mmol) were refluxed in acetone (50 ml) for 16 h. The reaction mixture was filtered to give a clear solution. Acetone was removed and the residue was dissolved in dichloromethane (30 ml). The organic layer

was washed with a saturated aqueous solution of sodium thiosulfate (1 × 20 ml), with water (1 × 20 ml) and then dried. The solvent was removed to give crude *5-(2-iodoethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole* (**217**) (1.04, 91 %).

Yellow-brown solid, m.p. 105-106 °C (recrystallised from ethyl acetate /petrol).

Found: C 44.18, H 3.66, N 4.26. $C_{12}H_{12}INO_2$ requires: C 43.79, H 3.67, N 4.26.

δ_H 0.99 (1H, dd, J 4.3, 5.5 Hz, H_{endo}-6), 1.46 (1H, dd, J 5.5, 9.6 Hz, H_{exo}-6), 2.79 (1H, dd, J 4.3, 9.6 Hz, H-5), 3.53 (1H, d, J 11.5 Hz, first H of CH_2I), 3.83 (1H, d, J 11.5 Hz, second H of CH_2I), 3.83 (3H, s, OCH_3), 6.90-6.94 (2H, m, aromatic), 7.66-7.70 (2H, m, aromatic).

δ_C 4.3 (CH_2I), 16.6 (C-6), 34.7 (C-5), 55.4 (OCH_3), 75.2 (C-1), 114.1, 121.4, 128.6 (all aromatic C); 161.3 and 161.4 (aromatic C and C-4).

ν_{max} 3019 w, 2965 w, 2923 w, 2847 w, 1607 s, 1515 s, 1423 s, 1386 m, 1337 m, 1304 m, 1249 s, 1176 s, 1025 s, 976 m, 938 m, 901 m, 883 s, 832 s, 742 w, 605 m cm^{-1}.

m/z, % 329, 6 (M^+); 202, 4; 160, 100; 133, 7; 107, 7; 92, 8; 86, 8; 84, 8; 77, 10.

EXPERIMENT 56

Treatment of 1-iodomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (217) with a range of different bases (attempted synthesis of 4-(4-methoxyphenyl)-2-oxa-3-azatricyclo[3.1.1.0^{1,5}]hept-3-ene (218))

1-Iodomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**217**) was treated with a range of different bases (a-e):

a) **217** (250 mg, 0.76 mmol) was treated with LDA (2.4 mol.equiv.), using a procedure analogous to the one described in Exp. 52c. The mixture was stirred for 16 h at room temperature, but no reaction took place and only starting material was detected.

b) **217** (100 mg, 0.3 mmol) and sodium bis[trimethylsilyl]amide (0.8 ml, 0.8 mmol, 1.0 M in THF) were refluxed in dry THF (5 ml) for 12 h. The reaction mixture was quenched with water (5 ml) and extracted with ether (3 × 5 ml).The combined organic layers were dried and the solvent was removed to give a orange oil; this showed a complicated mixture in the ^{1}H NMR spectrum, which could not be identified.

c) A 1.5 M solution of methyllithium in ether (0.19 ml, 0.29 mmol) was added dropwise to a solution of **217** (80 mg, 0.24 mmol) in dry THF (5 ml) at -50 °C. The mixture was allowed to reach room temperature and was stirred for 3 h. A few drops of water were added, the mixture was filtered through a layer of anhydrous $MgSO_4$ and a clear solution was obtained. The solvent was removed to give an orange oil. The crude ^1H NMR spectrum gave a complicated spectrum; no product was isolated or identified.

d) **217** (80 mg, 0.24 mmol) was treated with *n*-butyllithium (0.18 ml, 0.29 mmol, 1.6 M solution of in hexane) as above under c). Again no product was isolated or identified.

e) A 1.0 M solution of *tert*-butyllithium in pentane (0.9 ml, 0.9 mmol) was added dropwise to a solution of **217** (100 mg, 0.3 mmol) in dry THF (7 ml) at -50 °C. The mixture was warmed to 0 °C over 1 h, quenched with water (4 ml) and extracted with ether (3 × 5 ml). The combined organic layers were dried and the solvent was removed to give a yellow oil, which was purified by column chromatography on silica gel (petrol - ether, 1:1). No product was identified.

EXPERIMENT 57

5-Bromo-1-bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (220) and (4,5-bis(bromomethyl)-3-(4-methoxyphenyl)isoxazole (221)

i. Generation of cyclopropene: methyllithium (3.3 ml, 4.89 mmol, 1.5 M in ether) was added dropwise to a stirred solution of 1,2,2-tribromo-1-bromomethylcyclopropane (1.5 g, 4.04 mmol) in dry ether (20 ml) at -78 °C. The mixture was allowed to reach room temperature and was cooled again to -40 °C. The reaction mixture was quenched with water (5 ml), extracted with ether (3 × 10 ml) and the combined organic layers were dried.

ii. Cycloaddition reaction: *N*-hydroxy-4-methoxybenzimidoyl chloride (682 mg, 3.67 mmol) was dissolved in the above ethereal solution (containing 1-bromo-2-bromomethylcyclopropene) and the mixture was cooled to -15 °C. Triethylamine (0.56 ml, 4.04 mmol) was added dropwise, triethylammonium chloride precipitated and the mixture was stirred at room temperature for 14 h. The precipitate was filtered off, the solution was washed with water (3 × 10 ml) and dried. The solvent was removed to give crude *5-bromo-1-bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**220**) (1.29, 96 %). The oily product was not stable; it changed colour from yellow

to a deep green-blue within a few minutes. In a solution in $CDCl_3$, conversion into *4,5-bis(bromomethyl)-3-(4-methoxyphenyl)isoxazole* (**221**) was observed (after 1 day ratio **220** to **221** was about 1:1; after 2 days, no **220** was left).

Only the ^1H NMR spectrum of **220** was recorded:

δ_H 1.46 (1H, d, J 7.1 Hz, H_{endo}-6), 1.76 (1H, d, J 7.1 Hz, H_{exo}-6), 3.75 (1H, d, J 12.2 Hz, first H of CH_2Br), 3.82 (3H, s, OCH_3), 3.98 (1H, d, J 12.2 Hz, second H of CH_2Br), 6.92-6.96 (2H, m, aromatic), 7.73-7.77 (2H, m, aromatic).

For analytical purposes 110 mg of crude **220** were subjected to column chromatography on silica gel (petrol - ether, 1:1). The isolated solid was identified as pure **221** (41 mg, 37 %) (complete conversion by silica gel).

4,5-Bis(bromomethyl)-3-(4-methoxyphenyl)isoxazole (**221**):

Yellow-brown solid, m.p. 78-82 °C.

Found M^+: 358.9162. $C_{12}H_{11}Br_2NO_2$ requires: 358.9157.

δ_H 3.83 (3H, s, OCH_3), 4.38 (2H, s, CH_2Br), 4.54 (2H, s, CH_2Br), 7.00-7.04 (2H, m, aromatic), 7.65-7.69 (2H, m, aromatic).

δ_C 16.8 (CH_2Br), 19.7 (CH_2Br), 55.4 (OCH_3), 113.6 (C-4), 114.6, 120.0, 129.6 (all aromatic C); 161.2 and 161.8 (aromatic C and C-3); 166.3 (C-5).

ν_{max} 3017 w, 2969 w, 2844 w, 1612 s, 1508 m, 1435 s, 1294 s, 1253 s, 1174 s, 1023 s, 918 m, 839 s, 769 m, 680 m cm^{-1}.

m/z, % 363, 8; 361, 20; 359, 7 (M^+); 319, 1; 317, 5; 315, 3; 284, 1; 283, 11; 282, 100; 280, 61; 236, 16; 173, 14; 159, 27; 133, 67; 103, 13; 92, 17; 90, 19; 77, 21.

EXPERIMENT 58

Treatment of 5-bromo-1-bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo-[3.1.0]hex-3-ene with *tert*-butyllithium (attempted synthesis of 4-(4-methoxy-phenyl)-2-oxa-3-azatricyclo[3.1.1.0^{1,5}]hept-3-ene (218))

A 1.7 M solution of *tert*-butyllithium in pentane (1.96 ml, 3.3 mmol) was added dropwise to a solution of crude *5-bromo-1-bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**220**) (1.0 g, 2.7 mmol) in dry ether (20 ml) at -50 °C. The mixture was allowed to reach 10 °C and after 30 min was cooled again to -50 °C. Water (5 ml) was added, the aqueous layer was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried. The solvent was removed to give a 1:1 mixture of unreacted starting material **220** and *1-bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**222**). Purification by column chromatography on silica gel (petrol - ether, 1:1) gave pure **221** (90 mg, 9 %; again full conversion of **220** on silica to **221**, see Exp. 57) and **222** (87 mg, 11 %).

1-Bromomethyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**222**):
Yellow brown solid, m.p. 101-102 °C.
Found M^+: 281.0053. $C_{12}H_{12}BrNO_2$ requires: 281.0051.

δ_H 0.88 (1H, dd, J 4.3, 5.5 Hz, H_{endo}-6), 1.45 (1H, dd, J 5.5, 9.6 Hz, H_{exo}-6), 2.88 (1H, dd, J 4.3, 9.6 Hz, H-5), 3.71 (1H, d, J 11.9 Hz, first H of CH_2Br), 3.83 (3H, s, OCH_3), 4.03 (1H, d, J 11.9 Hz, second H of CH_2Br), 6.90-6.94 (2H, m, aromatic), 7.66-7.70 (2H, m, aromatic).

δ_C 15.0 (C-6), 31.8 (CH_2Br), 32.6 (C-5), 55.4 (OCH_3), 74.7 (C-1), 114.2, 121.3, 128.7 (all aromatic C), 161.4 (2 peaks: aromatic C and C-4).

ν_{max} 2932 w, 2836 w, 1609 s, 1517 s, 1428 m, 1389 m, 1310 m, 1252 s, 1176 m, 1112 m, 1024 s, 894 s, 8484 m, 824 s, 637 w, 530 w cm^{-1}.

m/z, % 283, 37; 281, 41 (M^+); 202, 39; 161, 99; 160, 100; 134, 82; 133, 99; 107, 61; 103, 41; 92, 63; 90, 42; 77, 99; 64, 38; 63, 33; 55, 80.

6.2.2. Experiments of Part II (Chemistry of *gem*-dibromocyclopropanes)

EXPERIMENT 59

(2,2-Dibromocyclopropyl)methanol (245)[252]

a) 3-(1-Methoxy-1-methylethoxy)propene (11.5 g, 0.088 mol) [prepared from allyl alcohol (10 g, 0.172 mol) as described][224] was added to a mixture of bromoform (15.8 ml, 0.177 mol), dichloromethane (50 ml), *n*-hexadecyltrimethylammonium bromide (1.5 g) [phase transfer-catalyst; common name: cetrimide] and four drops of triethylamine. The mixture was stirred vigorously and sodium hydroxide (35 g, 0.883 mol) in water (35 ml) was added slowly, keeping the temperature below 25 °C. After 27 h at 20 °C a brine solution (120 ml) was added and the mixture was extracted with dichloromethane (4 × 120 ml). The combined organic layers were dried and the solvent was removed. Petrol (150 ml) was added to the residue and the mixture was filtered through a layer of celite. The filter cake was washed with ether (50 ml). Removal of the solvent from the filtrate followed by distillation of unreacted bromoform at 30-40 °C at 0.5 mmHg gave crude, already largely deprotected alcohol **245** as brown oil.
To make sure that all 1,1-dibromo-2-(1-methoxy-1-methyl-ethoxymethyl)cyclopropane (**245**) was deprotected, the oil was dissolved in dichloromethane (50 ml), water (25 ml) and *p*-toluenesulfonic acid (1g) were added. After stirring for 30 min the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined organic layers were washed with water (1 × 100 ml) and dried. After removal of the solvent the residue was purified by distillation to give *(2,2-dibromocyclopropyl)methanol* (**245**) (10.2 g, 50 %); b.p. 82 °C at 0.3 mmHg.

The analytical data of **245** were identical to those reported.[252]

b) The reaction was repeated under ultrasonic conditions:
In a round-bottom flask, with a reflux condenser connected to a nitrogen inlet, were placed powdered sodium hydroxide (24.8 g, 0.620 mol), a solution of 3-(1-methoxy-1-methylethoxy)propene [prepared from allyl alcohol (6 g, 0.103 mol) as described in the literature][224] in dichloromethane (40 ml). The flask was immersed into the water bath of

an ultrasonic cleaner (47 kHz, 160 W) *ca.* 0.5 cm above the bottom and positioned right above the horn. The level of the water bath was set to be the same as the dichloromethane solution inside the flask. After adding cetrimide (0.5 g) and bromoform (18.5 ml, 0.207 mol), the reaction mixture was sonicated for 4 h. The reaction mixture was treated with celite and then filtered through a layer of celite.
GLC showed a series of peaks, among them also the product **245**. In an attempt to prepurify the mixture, the solvent was removed, ether / petrol (3:1) was added and the solution was filtered through a layer of silica. However GLC still indicated a complex mixture of compounds. The solvent was removed again and the residue, a brown liquid, was subjected to a distillation. Before the b.p. was reached the liquid decomposed to a black tarry mixture. It was not possible to isolate any product.

EXPERIMENT 60

2,2-Dibromocyclopropylmethyl trifluoroacetate (255)

General procedure C (esterification with anhydride):

A solution of alcohol (1 mmol) in dichloromethane (5 ml) was treated with the corresponding anhydride (1.1 - 2 mmol) at 0 °C, followed by addition of trimethylsilyl trifluoromethanesulfonate (3 mol %). The reaction upon completion (TLC) was treated with a saturated aqueous solution of $NaHCO_3$, and the aqueous phase was extracted with dichloromethane (10 ml). The organic extracts were washed with aqueous $NaHCO_3$ (3 × 15 ml) and water, dried and the solvent evaporated. Generally, the products were very clean and did not require any further purification.

In the present case (2,2-dibromocyclopropyl)methanol (1.0 g, 4.35 mmol) was reacted with trifluoroacetic anhydride (0.67 ml, 4.78 mmol), yielding *2,2-dibromocyclopropyl-methyl trifluoroacetate* (**255**) (1.5 g, 88 %) as a colourless liquid.

Found M^+: 325.8588. $C_6H_5Br_2F_3O_2$ requires: 325.8588.

δ_H 1.57 (1H, t, J 7.4 Hz, H_{trans}-3), 1.95 (1H, dd, J 7.4, 10.4 Hz, H_{cis}-3), 2.09 (1H, dddd, J 6.5, 7.4, 7.5, 10.4 Hz, H-1), 4.45 (1H, dd, J 7.5, 11.7 Hz, first H of CH_2O), 4.52 (1H, dd, J 6.5, 11.7 Hz, second H of CH_2O).

δ_C 23.1 (C-2), 27.0 (C-3), 28.0 (C-1), 69.2 (CH_2OH), 114.3 (q, J_{CF} 285 Hz, CF_3), 157 (q, J_{CF} 43 Hz, CO).

ν_{max} 1789 s, 1368 s, 1333 m, 1226 s, 1168 s, 1108 s, 959 m, 775 m, 730 s, 689 s cm^{-1}.

m/z, % 328, 1; 326, 2; 324, 1 (M^+); 214, 41; 212, 100; 210, 37; 201, 9; 199, 13; 197, 9; 188, 10; 186, 22; 184, 10; 133, 23; 131, 26; 69, 93; 51, 29.

EXPERIMENT 61

2,2-Dibromocyclopropylmethyl acetate (251)

The general procedure C (Exp. 60) was used to react (2,2-dibromocyclopropyl)methanol (0.6 g, 2.61 mmol) with acetic anhydride (0.27 ml, 2.87 mmol), yielding *2,2-dibromocyclopropylmethyl acetate* (**251**) (0.61 g, 86 %) as a colourless liquid.

Found M^+: 271.8871. $C_6H_8Br_2O_2$ requires: 271.8871.

δ_H 1.44 (1H, t, J 7.4 Hz, H_{trans}-3), 1.84 (1H, dd, J 7.4, 10.4 Hz, H_{cis}-3), 1.97 (1H, dddd, J 5.8, 7.4, 8.2, 10.4 Hz, H-1), 2.11 (1H, s, CH_3), 4.05 (1H, dd, J 8.2, 11.9 Hz, first H of CH_2O), 4.28 (1H, dd, J 5.9, 11.9 Hz, second H of CH_2O).

δ_C 20.9 (CH_3), 24.8 (C-2), 26.8 (C-3), 28.9 (C-1), 65.8 (CH_2O), 170.8 (CO).

ν_{max} 2953 w, 1742 s, 1438 w, 1369 s, 1235 s, 1109 m, 1036 s, 687s cm^{-1}.

m/z, % 272, 0.5; 272, 1; 270, 0.5 (M^+); 214, 6; 212, 8; 210, 5; 201, 9; 133, 5; 86, 14; 43, 100.

EXPERIMENT 62

2,2-Dibromocyclopropylmethyl butyrate (252)

The general procedure C (Exp. 60) was used to react (2,2-dibromocyclopropyl)methanol (2.2 g, 9.6 mmol) with butyric anhydride (1.72 ml, 10.5 mmol), yielding *2,2-dibromocyclopropylmethyl butyrate* (**252**) (2.63 g, 92 %) as a colourless liquid.

Found M^+: 299.9184. $C_8H_{12}Br_2O_2$ requires: 299.9184.

δ_H 0.97 (3H, t, J 7.4 Hz, CH_3), 1.45 (1H, t, J 7.4 Hz, H_{trans}-3), 1.69 (2H, sextet, J 7.4 Hz, $CH_2C\underline{H}_2CH_3$), 1.84 (1H, dd, J 7.4, 10.4 Hz, H_{cis}-3), 1.99 (1H, dddd, J 5.9, 7.4, 8.2, 10.4 Hz, H-1), 2.34 (2H, t, J 7.4 Hz, $C\underline{H}_2CH_2CH_3$), 4.05 (1H, dd, J 8.2, 11.9 Hz, first H of CH_2O), 4.29 (1H, dd, J 5.9, 11.9 Hz, second H of CH_2O).

δ_C 13.6 (CH_3), 18.4 ($CH_2\underline{C}H_2CH_3$), 24.8 (C-2), 26.8 (C-3), 29.0 (C-1), 36.0 ($\underline{C}H_2CH_2CH_3$) 65.5 (CH_2O), 173.4 (CO).

ν_{max} 2965 m, 2875 w, 1739 s, 1459 w, 1364 w, 1380 w, 1250 w, 1176 s, 1107 m, 1047 w, 955 w, 686 m cm^{-1}.

m/z, % 302, 0.5; 300, 1; 298, 0.5 (M^+); 214, 2; 212, 6; 210, 3; 133, 5; 131, 5; 114, 10; 71, 100.

EXPERIMENT 63

2,2-Dibromocyclopropylmethyl benzoate (253)

Benzoyl chloride (0.56 ml, 4.8 mmol) was added to a stirred solution of (2,2-dibromocyclopropyl)methanol (1.0 g, 4.3 mmol) and triethylamine (0.67 ml, 4.8 mmol) in dry ether (10 ml); triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and the precipitate was filtered off. The solvent was removed and the crude product was purified by column chromatography on silica gel (petrol - ether, 3:1) to give *2,2-dibromocyclopropylmethyl benzoate* (**253**) (900 mg, 62 %) as a colourless oil.

Found M^+: 333.9027. $C_{11}H_{10}Br_2O_2$ requires: 333.9027.

δ_H 1.56 (1H, t, J 7.5 Hz, H_{trans}-3), 1.91 (1H, dd, J 7.5, 10.4 Hz, H_{cis}-3), 2.15 (1H, dddd, J 6.0, 7.5, 8.2, 10.4 Hz, H-1), 4.32 (1H, dd, J 8.2, 12.0 Hz, first H of CH_2O), 4.58 (1H, dd, J 6.0, 12.0 Hz, second H of CH_2O), 7.44-7.64 (3H, m, aromatic), 8.08-8.12 (2H, m, aromatic).

δ_C 24.7 (C-2), 27.0 (C-3), 29.1 (C-1), 66.2 (CH_2O), 128. 4, 129.7, 133.2 (all aromatic C), 166.23 (CO).

ν_{max} 3063 w, 2952 w, 1722 s, 1602 w, 1451 m, 1341 m, 1314 m, 1270 s, 1176 m, 1111 s, 1070 m, 1026 m, 711 s, 687 m cm^{-1}.

m/z, % 336, 2; 334, 4; 332, 2 (M^+); 148, 8; 105, 100; 77, 28.

EXPERIMENT 64

2,2-Dibromocyclopropylmethyl acrylate (254)

Acryloyl chloride (0.78 ml, 9.6 mmol) was added to a stirred solution of (2,2-dibromocyclopropyl)methanol (1.6 g, 7.7 mmol) and triethylamine (1.58 ml, 11.3 mmol) in dry ether (40 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 2 h and then treated with hydrochloric acid (2 %, 35 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 40 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *2,2-dibromocyclopropylmethyl acrylate* (**254**) (700 mg, 35 %) as a colourless oil.

Found M^+: 283.8871, $C_{11}H_{10}Br_2O_2$ requires: 283.8871.

δ_H 1.48 (1H, t, J 7.5 Hz, H_{trans}-3), 1.86 (1H, dd, J 7.5, 10.4 Hz, H_{cis}-3), 2.04 (1H, dddd, J 6.0, 7.5, 8.2, 10.4 Hz, H-1), 4.16 (1H, dd, J 8.2, 12.0 Hz, first H of CH_2O), 4.38 (1H, dd, J 6.0, 12.0 Hz, second H of CH_2O), 5.89 (1H, dd, J 1.5, 10.4 Hz, H_b vinyl), 6.17 (1H, dd, J 10.4, 17.3 Hz, H_a vinyl), 6.47 (1H, dd, J 1.5, 17.3 Hz, H_c vinyl).

δ_C 24.7 (C-2), 26.9 (C-3), 28.9 (C-1), 65.9 (CH_2O), 128.0 (CH, vinyl), 131.5 (CH_2, vinyl), 165.9 (CO).

ν_{max} 2953 m,1728 s, 1634 s, 1444 m, 1409 s,1394 s, 1341 m, 1294 s, 1269 s, 1185 s, 1109 s, 1058 s, 985 s, 809 s, 689 s cm^{-1}.

m/z, % 286, 0.5; 284, 2; 282, 0.5 (M^+); 214, 20; 212, 47; 210, 25; 133, 20; 131, 29; 98, 100; 70, 44.

EXPERIMENT 65

2,2-Dibromo-1-methylcyclopropylmethyl acetate (256)

The general procedure C (Exp. 60) was used to react (2,2-dibromo-1-methylcyclopropyl)methanol (1.7 g, 6.97 mmol) with acetic anhydride (0.72 ml, 7.67 mmol), yielding *2,2-dibromo-1-methylcyclopropylmethyl acetate* (**256**) (1.75 g, 88 %) as a colourless liquid.

Found M^+: 285.9027. $C_7H_{10}Br_2O_2$ requires: 285.9027.

δ_H 1.45 (3H, s, CH_3), 1.49 (1H, d, J 7.7 Hz, first of H-3), 1.65 (1H, d J 7.7 Hz, second of H-3), 2.12 (3H, s, CH_3CO), 4.08 (1H, d, J 11.6 Hz, first H of CH_2O), 4.34 (1H, d, J 11.6 Hz, second H of CH_2O).

δ_C 20.9 (2 × CH_3), 29.7 (C-1), 32.8 (C-3), 34.4 (C-2), 70.2 (CH_2O), 170.8 (CO).

ν_{max} 2993 m, 2968 m, 2933 m, 1738 s, 1459 s, 1431 s,1387s, 1378 s, 1364 s, 1246 s, 1162 m, 1036 s, 989 s, 851 m, 696 s cm^{-1}.

m/z, % 288, 0.1; 286, 0.2; 284, 0.1 (M^+); 246, 2; 244, 4; 242, 2; 228, 8; 226, 15; 224, 7; 147, 8; 145, 7; 100, 100; 72, 13; 66, 20; 65, 25.

EXPERIMENT 66[219]

2,2-Dibromo-1-methylcyclopropylmethyl butyrate (227)

The general procedure C (Exp. 60) was used to react (2,2-dibromo-1-methylcyclopropyl)methanol (12.2 g, 50 mmol) with butyric anhydride (15.8 g, 100 mmol). Excess butyric anhydride was removed *in vacuo* (3 mmHg, 80 °C) and flash distillation of the residue at 140 °C and 0.3 mmHg gave *2,2-dibromo-1-methylcyclopropylmethyl butyrate* (**227**) 14.62 g, 46.5 mmol, 93 %) as a colourless liquid.

Found M^+: 313.9340. $C_{12}H_{12}Br_2O_2$ requires: 313.9340.

δ_H 0.96 (3H, t, J 7.4 Hz, CH_3), 1.45 (3H, s, CH_3), 1.49 (1H, t, J 7.7 Hz, first of H-3), 1.65 (1H, d, J 7.7 Hz, second of H-3), 1.68 (2H, qt, J 7.4, 7.5 Hz, $CH_2C\underline{H}_2CH_3$), 2.35 (2H, t, J 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 4.08 (1H, d, J 11.6 Hz, first H of CH_2O), 4.34 (1H, d, 11.6 Hz, second H of CH_2O).

δ_C 13.6 (CH_3), 18.4 ($CH_2\underline{C}H_2CH_3$), 20.9 (CH_3), 28.4 (C-1), 32.7 (C-3), 34.4 (C-2), 35.9 ($\underline{C}H_2CH_2CH_3$) 69.9 (CH_2O), 173.1 (CO).

ν_{max} 3077 w, 2966 s, 2934 s, 2875 m, 1738 s, 1461 s, 1431 m, 1380 m, 1356 m, 1303 m, 1282 m, 1254 s, 1173 br. s, 1090 s, 1044 s, 996 s, 852 w, 750 w, 695 s cm^{-1}.

m/z, % 316, 0.1; 314, 0.2; 312, 0.1 (M^+); 228, 1; 226, 2; 224, 1; 128, 16; 71, 100; 65, 12.

EXPERIMENT 67

2,2-Dibromo-1-methylcyclopropylmethyl benzoate (257)

Benzoyl chloride (2.86 ml, 24.6 mmol) was added to a stirred solution of (2,2-dibromo-1-methylcyclopropyl)methanol (3.0 g, 12.3 mmol) and triethylamine (3.42 ml, 24.6 mmol) in dry ether (40 ml); triethylammonium chloride precipitated. The mixture was refluxed for 24 h and then the precipitate was filtered off. The solvent was removed and the crude product was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *2,2-dibromo-1-methylcyclopropylmethyl benzoate* (**257**) (2.22 g, 52 %) as a colourless oil.

Found M^+: 347.9184. $C_{12}H_{12}Br_2O_2$ requires: 347.9184.

δ_H 1.57 (3H, s, CH_3), 1.58 (1H, d, J 7.7 Hz, first of H-3), 1.78 (1H, d, J 7.7 Hz, second of H-3), 4.35 (1H, d, J 11.6 Hz, first H of CH_2O), 4.65 (1H, d, 11.6 Hz, second H of CH_2O), 7.45-7.64 (3H, m, aromatic), 8.09-8.13 (2H, m, aromatic).

δ_C 21.1 (CH_3), 28.8 (C-1), 33.0 (C-3), 34.3 (C-2), 70.7 (CH_2O), 128.5, 129.7, 129.8, 133.2 (all aromatic C), 166.3 (CO).

ν_{max} 2992 w, 2964 w, 2931 w, 1721 s, 1602 w, 1451 m, 1386 w, 1314 m, 1270 s, 1175 m, 1115 s, 1070 m, 1026 m, 973 m, 710 s cm^{-1}.

m/z, %348, 1 (M^+); 162, 11; 105, 100; 77, 35.

EXPERIMENT 68

2,2-Dibromo-1-methylcyclopropylmethyl acrylate (258)

Acryloyl chloride (0.90 ml, 11.0 mmol) was added to a stirred solution of (2,2-dibromo-1-methylcyclopropyl)methanol (2.5 g, 10.2 mmol) and triethylamine (2.86 ml, 20.5 mmol) in dry ether (40 ml) at 0 °C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 2 h and then treated with hydrochloric acid (2 %, 35 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3 × 40 ml) and the combined organic layers were dried. The solvent was removed and the residue was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *2,2-dibromo-1-methylcyclopropylmethyl acrylate* (**258**) (1.33 g, 44 %) as a colourless oil.

Found M^+: 297.9027. $C_8H_{10}Br_2O_2$ requires: 297.9027.

δ_H 1.44 (3H, s, CH_3), 1.48 (1H, d, J 7.7 Hz, first of H-3), 1.65 (1H, d, J 7.7 Hz, second of H-3), 4.15 (1H, d, J 11.7 Hz, first H of CH_2O), 4.41 (1H, d, 11.7 Hz, second H of CH_2O), 5.85 (1H, dd, J 1.5, 10.3 Hz, H_b vinyl), 6.15 (1H, dd, J 10.3, 17.3 Hz, H_a vinyl), 6.44 (1H, dd, J 1.5, 17.3 Hz, H_c vinyl).

δ_C 20.9 (CH_3), 28.6 (C-1), 32.9 (C-3), 34.3 (C-2), 70.2 (CH_2O), 128.0 (CH, vinyl), 131.4 (CH_2, vinyl), 165.6 (CO).

ν_{max} 2993 w, 2966 w, 2933 w, 1727 s, 1634 m, 1458 m, 1407 s, 1384 m, 1295 s, 1268 s, 1185 s, 1058 s, 1033 m, 985 s, 808 m, 695 s cm^{-1}.

m/z, % 300, 1; 298, 2; 296, 1 (M^+); 228, 16; 226, 32; 224, 19; 188, 8; 186, 14; 184, 8; 147, 22; 145, 18; 112, 100; 107, 16.

EXPERIMENT 69

Reaction of 2,2-dibromocyclopropylmethyl trifluoroacetate (255) with methyllithium (ester hydrolysis)

A 1.5 M solution of methyllithium in ether (0.61 ml, 0.97 mmol) was added dropwise to a solution of 2,2-dibromocyclopropylmethyl trifluoroacetate (**255**) (300 mg, 0.92 mmol) in dry ether (15 ml) at -90 °C. The solution was stirred for 30 min at -90 °C then warmed to 0 °C over a period of 30 min and quenched with a saturated aqueous solution of NH_4Cl (5 ml). The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed to give *(2,2-dibromocyclopropyl)methanol* (**245**) (190 mg, 90 %).

The analytical data of **245** were identical to those reported.[252]

EXPERIMENT 70

1-Bromo-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (259)

A 1.5 M solution of methyllithium in ether (1.13 ml, 1.70 mmol) was added dropwise to a solution of 2,2-dibromocyclopropylmethyl acetate (**251**) (420 mg, 1.54 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 45 min at -90 °C and was then

allowed to warm to -75 °C. A saturated aqueous solution of NH_4Cl (5 ml) was added and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give a mixture of *1-bromo-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**259**) (55 %) and *(2,2-dibromocyclopropyl)-methanol* (**245**) (10 %) (it was not possible to separate the two compounds; in total 200 mg were isolated as a colourless oil; the individual yields were calculated on basis of the ratio found in the ^{1}H NMR spectrum; ratio **259** to **245**, 83:17)

1-Bromo-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (**259**):

M^+ was not observed.

ν_{max} 3389 br. s, 2991m, 2939 m, 2884 m, 1698 m, 1430 m, 1382 m, 1361 m, 1328 m, 1252 m, 1214 m, 1160 s, 1093 s, 1044 s, 976 s, 949 s, 869 m, 791 m cm^{-1}.

m/z, % 177, 27; 175, 38 (M^+-OH); 131, 2; 53, 16; 43, 100.

In the NMR solution additionally an equilibrium between the hemiacetal 1-bromo-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (**259**) and the keto-alcohol 1-(1-bromo-2-hydroxymethylcyclopropyl)ethanone (**260**) was observed; ratio (**259**) to (**260**) in $CDCl_3$, 81:19; in benzene-d_6, 84:16.

NMR data, hemiacetal (**259**):

δ_H 0.97 (1H, dd, J 5.0, 5.7 Hz, H_{endo}-6), 1.19 (1H, dd, J 5.7, 8.4 Hz, H_{exo}-6), 1.48 (3H, s, CH_3), 1.96 (1H, ddd, 2.8, 5.0, 8.4 Hz, H-5), 2.90 (1H, s, OH), 3.67 (1H, d, J 8.6 Hz, H_{endo}-4), 4.13 (1H, dd, J 2.8, 8.6 Hz, H_{exo}-4).

δ_C (benzene-d_6) 18.5 (C-6), 21.2 (CH_3), 25.3 (C-5), 39.6 (C-1), 65.9 (C-4), 103.7 (C-2).

NMR data, keto-alcohol (**260**):

δ_H 2.13 (1H, m, H-2), 2.57 (3H, s, CH_3), 3.34 (1H, dd, J 9.1, 12.0 Hz, one H of CH_2O), all other peaks underneath alcohol (**x**) peaks.

δ_C (benzene-d_6) 22.5 (C-3), 30.0 (CH_3), 37.0 (C-2), 37.4 (C-1), 59.8 (CH_2O), CO peak too weak, not detected.

EXPERIMENT 71

1-Bromo-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (261)

A 1.5 M solution of methyllithium in ether (1.22 ml, 1.83 mmol) was added dropwise to a solution of 2,2-dibromocyclopropylmethyl butyrate (**252**) (500 mg, 1.67 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 1 h at -90 °C and quenched with water (5 ml). The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give *1-bromo-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**261**) (170 mg, 46 %).

White solid, m.p. 51-53 °C.

Found: M^+, 220.0099. $C_8H_{13}BrO_2$ requires: 220.0099.

Found: C 43.87, H 5.95. $C_8H_{13}BrO_2$ requires: C 43.46, H 5.93.

ν_{max} 3362 br. s, 2959 s, 2932 s, 2874 m, 1696 w, 1458 m, 1408 m, 1338 m, 1240 m, 1151 s, 1110 s, 1070 m, 1046 s, 1002 s, 973 s, 945 s, 882 s, 710 m, 484 m cm^{-1}.

m/z, % 222, 5; 221, 3, 220, 3 (M^+); 205, 60; 203, 66; 179, 41; 177, 30; 134, 24; 99, 20; 97, 16; 71, 42; 69, 20; 53, 100.

In the NMR solution, an equilibrium between the hemiacetal 1-bromo-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**261**) and the keto-alcohol 1-(1-bromo-2-hydroxymethylcyclopropyl)butan-1-one (**262**) was observed; ratio (**261**) to (**262**) in $CDCl_3$, 58:42; in toluene-d_8, 67:33.

NMR data, hemiacetal (**261**):

δ_H 0.94 (3H, t, J 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.03 (1H, dd, J 4.8, 6.0 Hz, H_{endo}-6), 1.22 (1H, dd, J 6.0, 8.5 Hz, H_{exo}-6), 1.45 - 1.85 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.92 (1H, ddd, 2.8, 4.8, 8.5 Hz, H-5), 2.67 (1H, s, OH), 3.66 (1H, d, J 8.6 Hz, H_{endo}-4), 4.13 (1H, dd, J 2.8, 8.6 Hz, H_{exo}-4).

δ_C (toluene-d_8) 15.4 (CH_3), 17.9 ($CH_2\underline{C}H_2CH_3$), 19.4 (C-6), 25.9 (C-5), 38.6 ($\underline{C}H_2CH_2CH_3$), 40.6 (C-1), 66.6 (C-4), 105.2 (C-2).

NMR data, keto-alcohol (**262**):

δ_H 0.92 (3H, t, J 7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.45 (1H, dd, J 6.0, 9.8 Hz, H_{cis}-3), 1.70 (2H, sextet, J 7.3 Hz, $CH_2C\underline{H}_2CH_3$), 1.80 (1H, dd, J 6.0, 8.0 Hz, H_{trans}-3), 2.13 (1H, dddd, J 5.1, 8.0, 8.9, 9.8 Hz, H-2), 2.87 (1H, td, J 7.3, 17.9 Hz, $C\underline{H}_2CH_2CH_3$), 2.98 (1H, td, J 7.3, 17.9 Hz, $C\underline{H}_2CH_2CH_3$), 3.39(1H, dd, J 8.9, 12.0 Hz, first H of CH_2O), 3.82 (1H, dd, J 5.1, 12.0 Hz, second H of CH_2O).

δ_C (toluene-d_8) 14.4 ($CH_2CH_2\underline{C}H_3$), 18.7 ($CH_2\underline{C}H_2CH_3$), 22.6 (C-3), 37.7 (C-2), 38.9 (C-1), 44.4 ($\underline{C}H_2CH_2CH_3$), 60.6 (CH_2O), 204.6 (CO).

EXPERIMENT 72

1-Bromo-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol (263)

A 1.5 M solution of methyllithium in ether (0.72 ml, 1.09 mmol) was added dropwise to a solution of 2,2-dibromocyclopropylmethyl benzoate (**253**) (300 mg, 0.90 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 40 min, keeping the temperature below -80 °C. Water (5 ml) was added and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give *1-bromo-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**263**) (146 mg, 64 %).

White solid, m.p. 139-141 °C.

Found: C 51.91, H 4.27. $C_{11}H_{11}BrO_2$ requires: C 51.79, H 4.35.

ν_{max} 3360 br. s, 3091 m, 2948 m, 2887 s, 1451 m, 1411 s, 1333 m, 1240 s, 1222 s, 1145 s, 1092 s, 1077 s, 1056 s, 1045 s, 1017 s, 1000 s, 954 s, 932 m, 884 s, 785 m, 762 s, 705 s cm^{-1}.

m/z, % 256, 9; 254, 4 (M^+); 239, 4; 237, 4; 175, 12; 134, 25; 132, 17; 105, 100; 77, 42; 53, 77.

In the NMR solution, an equilibrium between the hemiacetal 1-bromo-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol (**263**) and the keto-alcohol (1-bromo-2-hydroxymethylcyclopropyl)phenylmethanone (**264**) was observed; ratio (**263**) to (**264**) in $CDCl_3$, 43:57; in CD_3OD, 58:42; in toluene-d_8, 100:0.

NMR data, hemiacetal (**263**):

δ_H (CD_3OD) 1.03 (1H, dd, J 5.1, 6.0 Hz, H_{endo}-6), 1.10 (1H, dd, J 6.0, 8.4 Hz, H_{exo}-6), 2.07 (1H, ddd, 2.9, 5.1, 8.4 Hz, H-5), 3.86 (1H, d, J 8.5 Hz, H_{endo}-4), 4.30 (1H, dd, J 2.9, 8.5 Hz, H_{exo}-4), 7.30-7.40 (3H, m, aromatic), 7.59-7.65 (2H, m, aromatic).

δ_C (CD_3OD) 19.7 (C-6), 27.8 (C-5), 42.1 (C-1), 67.8 (C-4), 104.6 (C-2), 127.9, 129.0, 129.6, 141.0 (all aromatic C).

NMR data, keto-alcohol (**264**):

δ_H (CD_3OD) 1.46 (1H, dd, J 6.6, 9.9 Hz, H_{cis}-3), 1.70 (1H, dd, J 6.6, 7.4 Hz, H_{trans}-3), 2.24 (1H, ddd, 6.6, 7.4, 9.9 Hz, H-2), 3.43 (2H, d, J 6.6 Hz, CH_2O) 7.38 - 7.56 (3H, m, phenyl), 8.07 - 8.11 (2H, m, phenyl).

δ_C (CD_3OD) 18.9 (C-3), 34.3 (C-2), 35.0 (C-1), 61.6 (CH_2O), 129.6, 131.3, 134.8, 136.8 (all aromatic C), 195.2 (CO).

EXPERIMENT 73

7-Bromo-3-oxabicyclo[5.1.0]octan-6-one (265)

A 1.5 M solution of methyllithium in ether (0.96 ml, 1.39 mmol) was added dropwise to a solution of 2,2-dibromocyclopropylmethyl acrylate (**254**) (330 mg, 1.16 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 50 min, keeping the temperature below -80 °C. Water (5 ml) and a saturated aqueous solution of NH_4Cl (5 ml) were added. The aqueous layer was extracted with ether (2 × 10 ml), the combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 2:1) to give *7-bromo-3-oxa-bicyclo[5.1.0]octan-6-one* (**265**) (92 mg, 39 %).

White solid, m.p. 29-31 °C.

Found M^+: 203.9786. $C_7H_9BrO_2$ requires : 203.9786.

δ_H (benzene-d_8) 1.21 (1H, dd, J 5.8, 9.1 Hz, H_{exo}-8), 1.40 (1H, dddd, J 2.5, 4.3, 7.7, 91 Hz, H-1), 1.49 (1H, dd, J 5.8, 7.7 Hz, H_{endo}-8), 2.04 (1H, ddd, J 4.3, 10.6, 13.5 Hz, first of H-5), 2.28 (1H, ddd, J 2.3, 5.0, 13.5 Hz, second of H-5), 2.69 (1H, ddd, J 2.3, 10.6, 12.4 Hz, first of H-4), 3.20 (1H, ddd, J 4.3, 5.0, 12.4 Hz, second

of H-4), 3.21 (1H, dd, J 2.5, 13.6 Hz, first of H-2), 3.28 (1H, dd, J 4.3, 13.6 Hz, second of H-2).

δ_C (benzene-d_8) 23.2 (C-8), 29.8 (C-1), 42.3 (C-7), 43.2 (C-5), 67.2 (C-4 or C-2), 69.7 (C-2 or C-4), 199.3 (C-6).

ν_{max} 2937 w, 2862 m, 1711 m, 1692 s, 1463 w, 1440 w, 1389 w, 1294 m, 1261 m, 1166 m, 1141 s, 1034 m, 966 w, 904 m, 845 w cm^{-1}.

m/z, % 206, 5; 204, 4 (M^+); 178, 5; 176, 12; 148, 9; 146, 10; 133, 10; 125, 70; 97, 18; 69, 75, 53, 100.

EXPERIMENT 74

1-Bromo-2,5-dimethyl-3-oxabicyclo[3.1.0]hexan-2-ol (266)

A 1.5 M solution of methyllithium in ether (1.37 ml, 2.06 mmol) was added dropwise to a solution of 2,2-dibromo-1-methylcyclopropylmethyl acetate (**256**) (490 mg, 1.70 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 1 h, keeping the temperature below -80 °C, and was then warmed to 0 °C over a period of 30 min. A saturated aqueous solution of NH_4Cl (5 ml) was added and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 2:1) to give unreacted starting material (**256**) (60 mg) and a colourless oil, *1-bromo-2,5-dimethyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**266**) (186 mg, 52 % [or 60 % if recovered starting material **256** is subtracted from original amount]).

Found M^+: 205.9942. $C_7H_{10}Br_2O_2$ requires: 205.9942.

δ_H 0.89 (1H, d, J 5.9 Hz, H_{exo}-6), 1.10 (1H, d, J 5.9 Hz, H_{endo}-6), 1.35 (3H, s, CH_3), 1.50 (3H, s, *endo*-CH_3, hemiacetal), 3.14 (1H, broad, OH), 3.72 (1H, d, J 8.4 Hz, H_{endo}-4), 3.88 (1H, d, J 8.4 Hz, H_{exo}-4).

NOE difference spectra of **266** were recorded; Conditions used to record the spectra, are given in the **Chapter 6.1.** (general experimental details). The results of those experiments are discussed in **Chapter 3.1.2.2.**

δ_C 15.2 (CH_3), 21.9 (*endo*-CH_3 at C-2), 23.8 (C-6), 28.1 (C-5), 47.4 (C-1), 70.8 (C-4), 104.5 (C-2).

ν_{max} 3397 br. s, 2954 m, 2933 m, 2878 m, 1446 m, 1389 m, 1315 m, 1212 m, 1171 s, 1077 s, 997 s, 952 s, 883 s, 807 m, 754 m cm^{-1}.

m/z, % 208, 2; 206, 2 (M^+); 193, 21; 191, 20; 175, 6; 173, 4; 151, 12; 149, 11; 148, 13; 146, 10; 127, 16; 67, 100.

EXPERIMENT 75

1-Bromo-5-methyl-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (229)

A 1.5 M solution of methyllithium in ether (22.3 ml, 33.4 mmol) was added to a solution of 2,2-dibromo-1-methylcyclopropylmethyl butyrate (**227**) (10.00 g, 31.8 mmol) in dry ether (150 ml) at -90 °C over a period of 5 min. The solution was stirred for 30 min at -90 °C then warmed to 0 °C for 30 min and a saturated aqueous solution of NH_4Cl (50 ml) was added. The water layer was extracted with ether (2 x 50 ml) and the combined organic layers were dried. The solvent was removed to give crude *1-bromo-5-methyl-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**229**) (7.75 g, 99 %). For analytical purposes 1.14 g of crude **229** were purified by column chromatography on silica gel (petrol - ether, 1:1) yielding 840 mg (74 %) of pure **229**.

White solid, m.p. 49-51 °C.

Found M^+: 234.0255. $C_9H_{15}BrO_2$ requires: 234.0255.

Found: C 46.45, H 6.50. $C_9H_{15}BrO_2$ requires: C 45.98, H 6.43.

δ_H 0.91 (1H, d, J 6.0 Hz, first of H-6), 0.96 (3H, t, J 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.18 (1H, d, J 6.0 Hz, second of H-6), 1.35 (3H, s, CH_3), 1.40-1.95 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 2.65 (1H, s, OH), 3.73 (1H, d, J 8.4 Hz, first of H-4), 3.88 (1H, d, J 8.4 Hz, second of H-4).

δ_C 14.4 ($CH_2CH_2\underline{C}H_3$), 15.2 (CH_3), 16.7 ($CH_2\underline{C}H_2CH_3$), 23.9 (C-6), 27.3 (C-5), 38.1 ($\underline{C}H_2CH_2CH_3$), 47.2 (C-1), 70.7 (C-4), 105.4 (C-2).

ν_{max} 3425 br. s, 2961 s, 2931 s, 2873 s, 1456 s, 1390 s, 1315 m, 1294 m, 1267 m, 1245 m, 1162 s, 1127 m, 1103 m, 1086 m, 1039 s, 1011 s, 954 s, 909 m, 880 m, 859 m, 804 m, 755 m cm^{-1}.

m/z, % 236, 6; 234, 8 (M^+), 193, 29; 191, 41; 179, 6; 177, 6; 148, 12; 146, 12; 111, 41; 86, 26; 84, 43; 71, 42; 67, 100; 43, 58; 41, 90.

EXPERIMENT 76

1-Bromo-5-methyl-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol (267)

A 1.5 M solution of methyllithium in ether (2.77 ml, 3.60 mmol) was added dropwise to a solution of 2,2-dibromo-1-methylcyclopropylmethyl benzoate (**257**) (1.0 g, 2.87 mmol) in dry ether (25 ml) at -90 °C. The solution was stirred for 20 min at -90 °C and quenched with a saturated aqueous solution of NH_4Cl (10 ml). The aqueous layer was extracted with ether (2 × 15 ml). The combined organic layers were dried and the solvent was removed. The residue was recrystallised from ethyl acetate to give *1-bromo-5-methyl-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**267**) (631 mg, 82 %).

White solid, m.p. 140-142 °C.

Found: C 53.63, H 4.90. $C_{12}H_{13}BrO_2$ requires: C 53.55, H 4.87.

δ_H 0.81 (1H, d, J 6.2 Hz, first of H-6), 1.17 (1H, d, J 6.2 Hz, second of H-6), 1.39 (3H, s, CH_3), 3.92 (1H, d, J 8.4 Hz, first of H-4), 4.05 (1H, d, J 8.4 Hz, second of H-4), 7.33-7.36 (3H, m, aromatic), 7.62-7.65 (2H, m, aromatic).

δ_C 15.6 (CH_3), 23.8 (C-6), 28.6 (C-5), 48.1 (C-1), 71.2 (C-4), 104.2 (C-2), 126.2, 128.5, 128.8, 139.4 (all aromatic C).

ν_{max} 3354 s, 2966 m, 2931 m, 2876 s, 1448 s, 1411 s, 1323 m, 1275 s, 1165 s, 1071 s, 1015 s, 954 s, 920 s, 878 s, 768 s, 752 s, 702 s, 655 s, 596 m cm^{-1}.

m/z, % 270, 5; 268, 3 (M^+), 253, 4; 251, 5; 162, 12; 148, 18; 115, 15; 105, 30; 77, 100; 65, 32; 51, 32.

EXPERIMENT 77

1-Bromo-5-methyl-2-vinyl-3-oxabicyclo[3.1.0]hexan-2-ol (268)

A 1.3 M solution of methyllithium in ether (0.65 ml, 0.84 mmol) was added dropwise to a solution of 2,2-dibromo-1-methylcyclopropylmethyl acrylate (**258**) (200 mg, 0.67 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 40 min, keeping the temperature below -80 °C. A saturated aqueous solution of NH_4Cl (5 ml) was added and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column

chromatography on silica gel (petrol - ether, 1:5) to give *1-bromo-5-methyl-2-vinyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**268**) (100 mg, 68 %).

White solid, m.p. 60-63 °C.

It was not possible to obtain good CHN values of **268**. An accurate mass was not recorded because the low resolution mass spectrum showed peaks close to (215/217) that did not seem to correspond to the compound (M^+ should be 219; see data given below); however the compound was pure by NMR and the chemical shifts were in full agreement to the ones observed with analogous compounds.

δ_H 1.44 (3H, s, CH_3, cyclopropane), 1.48 (1H, d, J 7.7 Hz, first of H-6), 1.65 (1H, d, J 7.7 Hz, second of H-6), 4.15 (1H, d, J 11.7 Hz, first of H-4), 4.41 (1H, d, 11.7 Hz, second of H-4), 5.85 (1H, dd, J 1.5, 10.3 Hz, H_b vinyl), 6.15 (1H, dd, J 10.3, 17.3 Hz, H_a vinyl), 6.44 (1H, dd, J 1.5, 17.3 Hz, H_c vinyl).

δ_C 20.9 (CH_3), 28.6 (C-5), 32.9 (C-6), 34.3 (C-1), 70.2 (C-4), 128.0 (CH, vinyl), 131.4 (CH_2, vinyl), 165.6 (C-2).

ν_{max} 3340 br. s, 2962 m, 2885 m, 1724 w, 1419 m, 1389 w, 1214 m, 1176 s, 1088 m, 1044 s, 1021 m, 983 s, 954 m, 039 s, 880 m, 803 m, 760 m, 681 m, 502 m cm^{-1}.

m/z, % 221, 4; 220, 5; 219, 5 (M^+); 218, 7; 217, 40; 215, 60; 203, 25; 201, 37; 137, 98; 108, 84; 67, 52; 55, 100; 53, 53.

EXPERIMENT 78

2-Bromo-2-butyrylcyclopropanecarboxylic acid methyl ester (274)

1-Bromo-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**261**) (100 mg, 0.45 mmol) was dissolved in carbon tetrachloride (2 ml) and acetonitrile (2 ml). Water (3 ml), periodic acid (1.5 g, 6.56 mmol) and ruthenium trichloride hydrate (5 mg, 0.05 mol.equiv.) were added to above solution. The mixture was refluxed for 12 h. Water (5 ml) was added, the mixture was extracted with ether (3 × 10 ml), the combined organic layers were washed with water (2 × 20 ml) and dried. The volume was reduced to about 6 ml and a solution of diazomethane in ether was added. The solvent and excess diazomethane were removed. The residue was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *2-bromo-2-butyrylcyclopropanecarboxylic acid methyl ester* (**274**) (74 mg, 66 %) as a colourless oil.

M^+ was not observed.

δ_H 0.90 (3H, t, J 7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.61 (2H, sextet, J 7.3 Hz, $CH_2C\underline{H}_2CH_3$), 1.62 (1H, dd, J 7.0, 9.4 Hz, H_{cis}-3), 2.12 (1H, t, J 7.0 Hz, H_{trans}-3),), 2.45 (1H, dd, J 7.0, 9.4 Hz, H-2), 2.55 (1H, td, J 7.3, 17.8 Hz, first H of $C\underline{H}_2CH_2CH_3$), 2.89 (1H, td, J 7.3, 17.8 Hz, second H of $C\underline{H}_2CH_2CH_3$), 3.68 (1H, s, OCH_3).

δ_C 13.5 ($CH_2CH_2\underline{C}H_3$), 17.2 ($CH_2\underline{C}H_2CH_3$), 21.9 (C-3), 31.8 (C-1), 37.4 (C-2), 41.7 ($\underline{C}H_2CH_2CH_3$), 52.5 (OCH_3), 168.9 (CO, ester), 200.1 (CO, ketone).

ν_{max} 2963 s, 2877 m, 1732 s, 1439 s, 1373 s, 1273 m, 1207 s, 1181 s, 1141 s, 1066 m, 1009 m, 936 m, 915 m, 840 w, 733 s cm^{-1}.

m/z, % 222, 56; 220, 6 (M^+-CO); 205, 2; 203, 2; 169, 9; 149, 7; 98, 7; 81, 9; 71, 57; 59, 23; 55, 19; 43, 100.

EXPERIMENT 79

2-Bromo-2-butyryl-1-methylcyclopropanecarboxylic acid methyl ester (275)

1-Bromo-5-methyl-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**229**) (200 mg, 0.85 mmol) was dissolved in carbon tetrachloride (2 ml) and acetonitrile (2 ml). Water (3 ml), periodic acid (2.8 g, 12.3 mmol) and ruthenium trichloride hydrate (9 mg, 0.05 mol.equiv.) were added to above solution. The mixture was refluxed for 12 h. Water (5 ml) was added, the mixture was extracted with ether (3 × 10 ml), the combined organic layers were washed with water (2 × 20 ml) and dried. The solvent was removed to give *2-bromo-2-butyryl-1-methylcyclopropanecarboxylic acid* (**275a**). The ^1H NMR of the crude acid was not very clean and attempts to purify the acid failed. Crude acid was therefore dissolved in ether (10 ml) and a solution of diazomethane in ether was added. The solvent and excess diazomethane were removed. The residue was purified by column chromatography on silica gel (petrol - ether, 5:1) to give *2-bromo-2-butyryl-1-methylcyclopropanecarboxylic acid methyl ester* (**275**) (116 mg, 52 %) as a colourless oil.

The reaction was also carried out using only 2 mol.equiv. of periodic acid. This improved the yield to 72 %.

Found M^+: 262.0205. $C_{10}H_{15}BrO_3$ requires: 262.0205.

δ_H 0.98 (3H, t, J 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 1.26 (1H, d, J 6.5 Hz, first of H-3), 1.63 (2H, sextett, J 7.4 Hz, $CH_2C\underline{H}_2CH_3$), 1.68 (3H, s, CH_3), 2.41 (1H, d, J 6.5 Hz, second of H-3), 2.60 (1H, td, J 7.4, 17.8 Hz, first H of $C\underline{H}_2CH_2CH_3$), 2.92 (1H, td, J 7.4, 17.8 Hz, second H of $C\underline{H}_2CH_2CH_3$), 3.68 (1H, s, OCH_3).

δ_C 13.6 ($CH_2CH_2\underline{C}H_3$), 17.3 ($CH_2\underline{C}H_2CH_3$), 19.9 (CH_3), 27.9 (C-3), 33.0 (C-1), 41.9 ($\underline{C}H_2CH_2CH_3$), 47.1 (C-2), 52.5 (OCH_3), 176.4 (CO, ester), 201.6 (CO, ketone).

ν_{max} 2963 m, 2876 w, 1732 s, 1456 m, 1436 m, 1386 w, 1363 w, 1303 s, 1199 s, 1166 s, 1091 w, 1059 w, 1012 w, 889 w cm^{-1}.

m/z, % 264, 16; 262, 17 (M^+), 233, 6; 203, 9; 183, 100; 175, 10; 173, 10; 124, 11; 71, 33; 53, 17.

EXPERIMENT 80

2-Acetyl-2-bromocyclopropanecarboxylic acid methyl ester (276) and 1-bromocyclopropane-1,2-dicarboxylic acid dimethyl ester (277)

1-Bromo-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (**259**) (100 mg, 0.52 mmol) was dissolved in carbon tetrachloride (2 ml) and acetonitrile (2 ml). Water (3 ml), periodic acid (1.6 g, 7.25 mmol) and ruthenium trichloride hydrate (5 mg, 0.05 mol.equiv.) were added to the above solution. The mixture was refluxed for 12 h. Water (5 ml) was added, the mixture was extracted with ether (3 × 10 ml), the combined organic layers were washed with water (2 × 20 ml) and dried. The volume was reduced to about 10 ml and a solution of diazomethane in ether was added. The solvent and excess diazomethane were removed to give a mixture of *2-acetyl-2-bromocyclopropanecarboxylic acid methyl ester* (**276**) and *1-bromocyclopropane-1,2-dicarboxylic acid dimethyl ester* (**277**) (98 mg in total, compounds not separated, ratio by GLC, **276** to **277**, 57:43).

An IR spectrum of the mixture was not recorded.

The analytical data of **277** were identical to those reported.[228]

2-Acetyl-2-bromocyclopropanecarboxylic acid methyl ester (**276**):

δ_H 1.64 (1H, dd, J 6.7, 9.6 Hz, H_{cis}-3), 2.12 (1H, dd, J 6.7, 7.3 Hz, H_{trans}-3), 2.39 (3H, s, CH_3), 2.47 (1H, dd, J 7.3, 9.6 Hz, H-2), 3.68 (1H, s, OCH_3).

δ_C 27.4 (CH_3), 21.9 (C-3), 31.8 (C-1), 37.6 (C-2), 52.5 (OCH_3), 169.1 (CO, ester), 197.7 (CO, ketone).

m/z, % (GC/MS) 207, 0.5; 205, 0.5 (M^+-CH_3); 191, 7; 189, 13; 163, 24; 141, 100; 99, 67; 82, 18; 59, 20; 53, 19.

EXPERIMENT 81

2-Acetyl-2-bromo-1-methylcyclopropanecarboxylic acid methyl ester (278) and 1-bromo-2-methylcyclopropane-1,2-dicarboxylic acid dimethyl ester (279)

1-Bromo-2,5-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-ol (**266**) (180 mg, 0.87 mmol) was dissolved in carbon tetrachloride (2 ml) and acetonitrile (2 ml). Water (3 ml), periodic acid (2.77 g, 12.17 mmol) and ruthenium trichloride hydrate (9 mg, 0.05 mol.equiv.) were added to above solution. The mixture was refluxed for 12 h. Water (5 ml) was added, the mixture was extracted with ether (3 × 10 ml), the combined organic layers were washed with water (2 × 20 ml) and dried. The volume was reduced to about 10 ml and a solution of diazomethane in ether was added. The solvent and excess diazomethane were removed to give a mixture of *2-acetyl-2-bromo-1-methylcyclopropanecarboxylic acid methyl ester* (**278**) and *1-bromo-2-methylcyclopropane-1,2-dicarboxylic acid dimethyl ester* (**279**) (194 mg in total, compounds not separated, ratio by GLC, **278** to **279**, 58:42).

IR of mixture (selected peaks):

ν_{max} 1789 m, 1735 s cm^{-1}.

2-Acetyl-2-bromo-1-methylcyclopropanecarboxylic acid methyl ester (**278**):

δ_H 1.21 (1H, d, J 6.6 Hz, first of H-3), 1.63 (3H, s, CH_3), 2.34 (1H, d, J 6.6 Hz, second of H-3), 2.39 (3H, s, CH_3), 3.64 (1H, s, OCH_3).

δ_C 19.8 (CH_3), 27.4 (CH_3), 27.9 (C-3), 33.2 (C-1), 46.7 (C-2), 52.6 (OCH_3), 170.9 (CO, ester), 199.4 (CO, ketone).

m/z, % (GC/MS) 235, 0.1;(M^+); 221, 0.1; 205, 5; 177, 8; 176, 13; 175, 13; 174, 8; 155, 100; 96, 37; 53, 33.

1-Bromo-2-methylcyclopropane-1,2-dicarboxylic acid dimethyl ester (**279**):

δ_H 1.26 (1H, d, J 6.6 Hz, first of H-3), 1.58 (3H, s, CH_3), 2.33 (1H, d, J 6.6 Hz, second of H-3), 3.63 (3H, s, OCH_3), 3.71 (1H, s, OCH_3).

δ_C 19.4 (CH_3), 28.4 (C-3), 31.9 (C-2), 38.8 (C-1), 52.6 (OCH_3), 53.4 (OCH_3), 168.1 (CO, ester), 171.0 (CO, ester).

m/z, % (GC/MS) 252, 6; 250, 3 (M^+); 221, 23; 220, 18; 219, 24; 218, 31; 192, 40; 190, 23; 175, 20; 171, 100, 139, 25; 112, 30; 111, 30; 83, 33; 69, 25; 59, 44; 53, 84.

EXPERIMENT 82

1-(1-Bromo-2-hydroxymethylcyclopropyl)butan-1-ol (280/281)

A solution of 1-bromo-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**261**) (60 mg, 0.27 mmol) in dry ether (8 ml) was added dropwise to a suspension of $LiAlH_4$ (23 mg, 6.0 mmol) in dry ether (8 ml) at -80 °C. The mixture was stirred for 1 h at -70 °C and was then allowed to warm to room temperature. Work-up was carried out as is Exp. 10 and the residue was purified by column chromatography on silica gel (petrol - ether, 1:5) to give two diastereomers of *1-(1-bromo-2-hydroxymethylcyclopropyl)butan-1-ol* (**280/281**) (in total 45 mg, 74 %).

Diastereomer a, **280** (fraction 1; 20 mg):

White solid, m.p. 72 °C.

Found: C 43.52, H 6.83. $C_8H_{15}BrO_2$ requires: C 43.07, H 6.78.

δ_H 0.81 (1H, t, J 6.7 Hz, H_{trans}-3), 0.93 (3H, t, J 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 1.42 (2H, sextet, J 7.4 Hz, $CH_2C\underline{H}_2CH_3$), 1.44 (1H, dd, J 6.7, 9.6 Hz, H_{cis}-3), 1.61-1.80 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.91 (1H, dddd, J 5.8, 6.7, 9.6, 10.9 Hz, H-2), 3.10 (1H, t, 6.6 Hz, C$\underline{H}$OH), 3.27 (1H, dd, 10.9, 12.1 Hz, first H of $C\underline{H}_2OH$), 4.04 (1H, dd, 5.8, 12.1 Hz, second H of $C\underline{H}_2OH$).

δ_C 14.1 ($CH_2CH_2\underline{C}H_3$), 18.6 ($CH_2\underline{C}H_2CH_3$), 20.1 (C-3), 29.4 (C-2), 38.4 ($\underline{C}H_2CH_2CH_3$), 43.9 (C-1), 63.0 (CH_2OH), 74.7 (CHOH).

ν_{max} 3320 br. s, 2953 s, 2913 m, 2868 m, 1464 m, 1376 m, 1332 s, 1268 w, 1166 m, 1145 m, 1111 s, 1080 s, 1028 s, 969 m, 840 m, 628 m cm^{-1}.

m/z, % 207, 100; (M^+-OH); 128, 46; 127, 53; 85, 48; 55, 25.

Diastereomer b, **281** (colourless oil; 25 mg; fraction 2):

M^+ was not observed.

δ_H 0.92 (3H, t, J 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.0 (1H, t, J 7.0 Hz, H_{trans}-3), 1.39 (1H, dd, J 7.0, 9.9 Hz, H_{cis}-3), 1.43-1.58 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.60-1.78 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.89 (1H, ddd, J 7.0, 7.3, 9.9 Hz, H-2), 3.18 (1H, dd, 3.5, 9.0 Hz, C$\underline{H}$OH), 3.65 (1H, dd, 7.3, 11.6 Hz, first H of $C\underline{H}_2OH$), 3.71 (1H, dd, 7.0, 11.6 Hz, second H of $C\underline{H}_2OH$).

δ_C 14.0 ($CH_2CH_2\underline{C}H_3$), 18.9 ($CH_2\underline{C}H_2CH_3$), 20.0 (C-3), 30.3 (C-2), 39.0 ($\underline{C}H_2CH_2CH_3$), 45.2 (C-1), 61.5 (CH_2OH), 74.7 (CHOH).

ν_{max} 3354 br. s, 2959 s, 2872 s, 1640 w, 1445 m, 1380 m, 1313 m, 1256 m, 1158 m, 1108 m, 1074 m, 1036s, 900 w, 744 w cm^{-1}.

m/z, % 207, 0.4; 205, 0.8 (M^+-OH); 181, 3; 179, 5; 163, 17; 137, 16; 107, 15; 81, 23; 73, 16; 69, 16; 53, 46; 43, 100.

EXPERIMENT 83

Attempted protection of 1-bromo-5-methyl-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (229) with trimethylsilyl chloride

a) Trimethylsilyl chloride (0.06 ml, 0.47 mmol) was added to a stirred mixture of 1-bromo-5-methyl-2-propyl-3-oxabicyclo[3.1.0]hexan-2-ol (**229**) (100 mg, 0.42 mmol) and imidazole (35 mg, 0.51 mmol) in dry DMF (5ml). After 72 h water (10 ml) was added and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were washed with water (2 × 15 ml), dried and the solvent was removed. Only starting material **229** (80 mg, 80 %) was recovered.

b) A 1.5 M solution of methyllithium in ether (0.31 ml, 0.47 mmol) was added dropwise to a solution of 1-bromo-5-methyl-2-propyl-3-oxa-bicyclo[3.1.0]hexan-2-ol (**229**) (100 mg, 0.42 mmol) in dry ether (10 ml) at -80 °C. After 10 min, trimethylsilyl chloride (0.06 ml, 0.47 mmol) was added and the mixture was allowed to warm to room temperature. After 30 min, water (5 ml) was added and the aqueous layer was extracted

with ether (2 × 8 ml). The combined organic layers were dried and the solvent was removed. Only starting material **229** (70 mg, 70 %) was recovered.

The reaction was repeated with an extended reaction time: after the addition of trimethylsilyl chloride the reaction mixture was stirred for 12 h at room temperature. Work-up as above afforded again only starting material (70 %).

EXPERIMENT 84

Attempted reaction of 1-bromo-5-methyl-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol with Grignard and Wittig reagents

a) Attempted Grignard addition:

A 0.97 M solution of 2-phenylethylmagnesium bromide (0.56 ml, 0.55 mmol) in ether was added dropwise to a solution of 1-bromo-5-methyl-2-phenyl-3-oxabicyclo[3.1.0]-hexan-2-ol (**267**) (70 mg, 0.26 mmol) in dry THF (5 ml) at 0 °C. After 90 min sulfuric acid (2 ml 2 %) was added and the aqueous layer was extracted with ether (3 × 7 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give *1,4-diphenylbutane* (12 mg, 22 %), starting material **267** (36 mg, 51 %) and an unidentified mixture (13 mg).

b) Attempted Wittig reaction:

Methyltriphenylphosphonium bromide (204 mg, 0.57 mmol) was suspended in dry THF (5 ml), cooled to -78 °C and potassium *tert*-butoxide (64 mg, 0.57 mmol) was added. The stirred suspension was allowed to warm to room temperature. Change of the colour from white to deep yellow indicated the formation of the ylide. The solution was cooled again to -78 °C, 1-bromo-5-methyl-2-phenyl-3-oxabicyclo[3.1.0]hexan-2-ol (**267**) (70 mg, 0.26 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 12 h TLC showed only starting material present. Ether (15 ml) was added and the mixture was filtered through a layer of silica. The silica layer was washed with ether (2 x 10 ml) and the combined filtrates were evaporated. All of the starting material **267** (70 mg, 100 %) was recovered.

EXPERIMENT 85

N-Benzyl-*N*-(2,2-dibromocyclopropylmethyl)-2,2,2-trifluoroacetamide (284)

N-Benzyl-(2,2-dibromocyclopropylmethyl)amine (700 mg, 2.2 mmol) was dissolved in dichloromethane (30 ml) and trifluoroacetic anhydride (0.34 ml, 2.4 mmol) was added. After 30 min the volatiles were removed and the residue was dissolved in ether (30 ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 20 ml) and water (1 × 20 ml). The organic layer was dried and the solvent was removed to give a colourless oil, *N-benzyl-N-(2,2-dibromocyclopropylmethyl)-2,2,2-trifluoroacetamide* (**284**) (770 mg, 85 %) as a mixture of two rotamers (67:33).

Found M^{+}: 414.9217. $C_{13}H_{12}Br_2F_3NO$ requires: 414.9217.

NMR data, major rotamer:

δ_H 1.25 (1H, t, J 7.2 Hz, H_{trans}-3), 1.76 (1H, dd, J 7.2, 10.5 Hz, H_{cis}-3), 1.89 (1H, dddd, J 5.2, 6.5, 7.2, 10.5 Hz, H-1), 3.45 (1H, dd, J 6.5, 14.4 Hz, first H of CH_2N), 3.62 (1H, dd, J 5.2, 14.4 Hz, second H of CH_2N), 4.74 (1H, d, J 16.4 Hz, first H of $PhC\underline{H}_2N$), 4.87 (1H, d, J 16.4 Hz, second H of $PhC\underline{H}_2N$), 7.22-7.45 (5H, m, aromatic).

δ_C 25.5 (C-2), 27.5 (C-3), 28.4 (C-1), 48.8 (CH_2N), 51.2 (CH_2N), 116.5 (q, J_{CF} 288 Hz, CF_3), 127.2, 127.7, 129.1, 134.6 (all aromatic C), 157.5 (q, J_{CF} 39 Hz, CO).

NMR data, minor rotamer:

δ_H 1.35 (1H, t, J 7.2 Hz, H_{trans}-3), 1.76 (1H, dd, J 7.2, 10.5 Hz, H_{cis}-3), 1.89 (1H, dddd, J 5.2, 6.5, 7.2, 10.5 Hz, H-1), 3.60 (1H, dd, J 6.5, 14.4 Hz, first H of CH_2N), 3.62 (1H, dd, J 5.2, 14.4 Hz, second H of CH_2N), 4.71 (1H, d, J 15.1 Hz, first H of $PhC\underline{H}_2N$), 4.96 (1H, d, J 15.1 Hz, second H of $PhC\underline{H}_2N$), 7.22-7.45 (5H, m, aromatic).

δ_C 24.9 (C-2), 27.3 (C-3), 29.6 (C-1), 48.7 (CH_2N), 49.5 (CH_2N), 116.5 (q, J_{CF} 288 Hz, CF_3), 128.1, 128.4, 128.9, 135.0 (all aromatic C), 157.5 (q, J_{CF} 39 Hz, CO).

ν_{max} 3032 w, 2936 w, 1694 s, 1452 s, 1386 w, 1362 w, 1205 s, 1144 s, 1001 m, 740 m, 702 m cm^{-1}.

m/z, %417, 1; 415, 2; 413, 1 (M^{+}); 229, 2; 202, 5; 91, 100; 65; 4.

EXPERIMENT 86

N-Benzyl-*N*-(2,2-dibromocyclopropylmethyl)acetamide (287)

N-Benzyl-(2,2-dibromocyclopropylmethyl)amine (1.2 g, 3.8 mmol) was dissolved in dichloromethane (30 ml) and acetic anhydride (0.37 ml, 4.0 mmol) was added. After 90 min the volatiles were removed and the residue was dissolved in ether (40 ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 30 ml) and water (1 × 30 ml). The organic layer was dried and the solvent was removed to give *N-benzyl-N-(2,2-dibromocyclopropylmethyl)acetamide* (**287**) (1.28 g, 94 %) as a mixture of two rotamers (76:24).

Beige-brown solid, m.p. 63 °C.

Found: C 43.04, H 4.18, N 3.97. $C_{13}H_{15}Br_2NO$ requires: C 43.24, H 4.19, N 3.88.

NMR data, major rotamer:

δ_H 1.32 (1H, t, J 7.5 Hz, H_{trans}-3), 1.79 (1H, dd, J 7.5, 10.6 Hz, H_{cis}-3), 1.89-2.04 (1H, m, H-1, together with peaks of minor isomer), 2.22 (3H, s, CH_3), 3.28 (1H, dd, J 7.2, 14.3 Hz, first H of CH_2N), 3.93 (1H, dd, J 5.5, 14.3 Hz, second H of CH_2N), 4.77 (2H, s, Ph$C\underline{H}_2$N), 7.23-7.46 (5H, m, aromatic).

δ_C 21.7 (CH_3), 27.1 (C-2), 27.2 (C-3), 29.7 (C-1), 48.3 (CH_2N), 52.4 (CH_2N), 126.2, 127.7, 129.0, 136.6 (all aromatic C), 171.5 (CO).

NMR data, minor rotamer:

δ_H 1.32 (1H, t, J 7.5 Hz, H_{trans}-3), 1.78-1.85 (1H, m, H_{cis}-3, peaks underneath peaks H_{cis}-3 of major isomer), 1.89-2.04 (1H, m, H-1, together with peaks of major isomer), 2.31 (3H, s, CH_3), 3.38 (1H, dd, J 5.7, 15.5 Hz, first H of CH_2N), 3.63 (1H, dd, J 5.8, 15.5 Hz, second H of CH_2N), 4.68 (1H, d, J 15.1 Hz, first H of Ph$C\underline{H}_2$N), 4.89 (1H, d, J 15.1 Hz, second H of Ph$C\underline{H}_2$N), 7.23-7.46 (5H, m, aromatic).

δ_C 21.8 (CH_3), 25.6 (C-2), 27.7 (C-3), 29.7 (C-1), 48.3 (CH_2N), 49.9 (CH_2N), 127.4, 127.8, 128.6, 137.5 (all aromatic C), 170.6 (CO).

ν_{max} 3029 w, 2929 w, 1638 s, 1467 s, 1437 s, 1414 s, 1381 s, 1363 s, 1252 s, 1207 s, 1105 m, 980 m, 962 m, 730 s, 684 m cm^{-1}.

m/z, % 363, 2; 361, 5; 359, 2 (M^+); 188, 8; 175, 20; 174, 34; 146, 16; 120, 8; 106, 19; 91, 100, 65, 10.

EXPERIMENT 87

(1*S*, 2*S*, 5*R*)-1-bromo-5-methyl-3-[(1*R*)-1-phenylethyl]-2-trifluoromethyl-3-azabicyclo[3.1.0]hexan-2-ol (234)[219]

A 1.5 M solution of methyllithium in ether (0.44 ml, 0.66 mmol) was added to a solution of (*R*)-*N*-α-methylbenzyl-(*S*)-*N*-2,2-dibromo-1-methylcyclopropylmethyl)-amine (267 mg, 0.603 mmol) in dry ether (15 ml) at -90 °C for 5 min. The solution was stirred for 30 min at -90 °C then warmed to 0 °C for 30 min and a saturated aqueous solution of NH_4Cl (5 ml) was added. The water layer was extracted with ether (10 ml). The combined organic layers were evaporated to give crude (>85 % purity by NMR) *(1S, 2S, 5R)-1-bromo-5-methyl-3-[(1R)-1-phenylethyl]-2-trifluoromethyl-3-azabicyclo-[3.1.0]hexan-2-ol* (**234**), (208 mg, 95 %).

$[\alpha]_D^{25}$ +34.0° (c 1.0, $CHCl_3$).

Found M^+: 363.0446. $C_{15}H_{17}NBrOF_3$ requires: 363.0446.

δ_H 0.95 (1H, d, J 5.9 Hz, first of H-6), 1.20 (3H, s, CH_3), 1.36 (3H, d, J 7.1 Hz, $CH\underline{C}H_3$), 1.63 (1H, d, J 5.9 Hz, second of H-6), 2.60 (1H, d, J 8.6 Hz, first of H-4), 2.83 (1H, s, OH), 2.99 (1H, d, J 8.6 Hz, second of H-4), 4.60 (1H, q, J 7.1 Hz, $\underline{C}HCH_3$), 7.22-7.38 (5H, m, aromatic).

δ_C 17.5 (CH_3), 19.3 (CH_3), 24.7 (C-6), 25.5 (C-5), 46.1 (C-1), 50.8 (C-4), 52.6 (CH), 91.5 (q, J_{CF} 29.6 Hz, C-2), 124.2 (q, J_{CF} 289.6 Hz, CF_3), 127.3, 128.3, 128.6, 141.1 (all aromatic C).

ν_{max} 3548 m, 3350 br. w, 3031 m. 2977 s, 2931 s, 2850 m, 1693 m, 1495 m, 1454 s, 1388 m, 1166 br. s, 1068 s, 969 m, 762 m, 746 m, 700 s cm^{-1}.

m\z, % 365, 3; 363, 3 (M^+); 350, 17; 348, 22; 296, 18; 294, 18; 260, 10; 258, 10; 192, 12; 194, 12; 106, 17; 105, 100. 2.

EXPERIMENT 88

Reaction of *N*-benzyl-*N*-(2,2-dibromocyclopropylmethyl)-2,2,2-trifluoroacetamide (284) with methyllithium

A 1.35 M solution of methyllithium in ether (0.46 ml, 0.62 mmol) was added dropwise to a solution of *N*-benzyl-*N*-(2,2-dibromocyclopropylmethyl)-2,2,2-trifluoroacetamide (200 mg, 0.48 mmol) in dry ether (10 ml) at -90 °C. The solution was stirred for 30 min at -80 °C and was then quenched with a saturated aqueous solution of NH_4Cl (5 ml). The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give *3-benzyl-1-bromo-2-trifluoromethyl-3-azabicyclo[3.1.0]hexan-2-ol* (**285**) (55 mg, 34 %), *N-benzyl-N-[2-bromo-2-(2,2,2-trifluoroacetyl)cyclopropylmethyl]-2,2,2-trifluoroacetamide* (**286**) (45 mg, 22 %) and *N-benzyl-(2,2-dibromocyclopropylmethyl)amine* (**283**) (30 mg, 20 %).

3-Benzyl-1-bromo-2-trifluoromethyl-3-azabicyclo[3.1.0]hexan-2-ol (**285**):

Found M^+: 335.0133. $C_{13}H_{13}BrF_3NO$ requires: 335.0133.

δ_H 1.38 (1H, dd, J 5.9, 8.9 Hz, H_{exo}-6), 1.71 (1H, dd, J 5.0, 5.9 Hz, H_{endo}-6), 1.89 (1H, ddd, J 4.0, 5.0, 8.9 Hz, H-5), 2.94 (1H, d, J 9.0 Hz, H_{endo}-4), 3.02 (1H, dd, J 4.0, 9.0 Hz, H_{exo}-4), 3.27 (1H, s, OH), 3.54 (1H, d, J 14.5 Hz, first H of $C\underline{H}_2Ph$), 4.44 (1H, d, J 14.5 Hz, second H of $C\underline{H}_2Ph$), 7.24-7.39 (5H, m, aromatic).

δ_C 19.6 (C-6), 24.2 (C-5), 38.2 (C-1), 51.7 ($\underline{C}H_2Ph$), 52.1 (C-4), 90.3 (q, J_{CF} 30.3 Hz, C-2), 124.1 (q, J_{CF} 288.9 Hz, CF_3), 127.1, 128.0, 128.4, 138.4 (all aromatic C).

ν_{max} 3544 br s., 3030 w. 2920 w, 2851 m, 1682 w, 1455 m, 1364 m, 1182 s, 1150 s, 1076 m, 1035 m, 959 m, 742 m, 699 m cm^{-1}.

m\z, %337, 1; 335, 1 (M^+); 320, 1; 318, 1; 267, 22; 91, 100.

N-Benzyl-*N*-[2-bromo-2-(2,2,2-trifluoroacetyl)cyclopropylmethyl]-2,2,2-trifluoroacetamide (**286**); mixture of rotamers (77:23):

Found M^+: 430.9956. $C_{15}H_{12}BrF_6NO_2$ requires: 430.9956.

NMR data, major rotamer:

δ_H 1.52 (1H, dd, J 6.5, 9.7 Hz, H_{cis}-3), 1.72 (1H, dd, J 6.5, 8.4 Hz, H_{trans}-3), 2.22 (1H, dddd, J 6.7, 7.1, 8.4, 9.7 Hz, H-1), 3.05 (1H, dd, J 6.7, 14.5 Hz, first H of

CH_2N), 3.49 (1H, dd, J 7.1, 14.5 Hz, second H of CH_2N), 4.49 (1H, d, J 16.0 Hz, first H of $C\underline{H}_2Ph$), 4.68 (1H, d, J 16.0 Hz, second H of $C\underline{H}_2Ph$), 7.15-7.42 (5H, m, aromatic).

δ_C 24.6 (C-3), 28.4 (C-2), 34.5 (C-1), 44.4 (CH_2N), 51.7 (CH_2N), 115.5 (q, J_{CF} 291 Hz, CF_3), 116.4 (q, J_{CF} 288 Hz, CF_3), 127.5, 128.7, 129.2, 134.0 (all aromatic C), 157.8 (q, J_{CF} 39 Hz, CO, amide), 184.7 (q, J_{CF} 39 Hz, CO, ketone).

NMR data, minor rotamer:

δ_H 1.66 (1H, dd, J 6.6, 9.7 Hz, H_{cis}-3), 1.87 (1H, dd, J 6.6, 8.4 Hz, H_{trans}-3), 2.22 (1H, m, H-1), 3.06 (1H, peak underneath peak of major isomer, first H of CH_2N), 3.63 (1H, dd, J 4.5, 14.5 Hz, second H of CH_2N), 4.66 (2H, s, $C\underline{H}_2Ph$), 7.15-7.42 (5H, m, aromatic).

δ_C 25.3 (C-3), 29.9 (C-2), 35.1 (C-1), 44.1 (CH_2N), 49.8 (CH_2N), 115.5 (q, J_{CF} 291 Hz, CF_3), 116.4 (q, J_{CF} 288 Hz, CF_3), 127.8, 128.4, 129.1, 134.8 (all aromatic C), 157.8 (q, J_{CF} 39 Hz, CO, amide), 184.8 (q, J_{CF} 39 Hz, CO, ketone).

ν_{max} 3035 w, 1738 s, 1694 s, 1682 s, 1454 s, 1245 s, 1210 s, 1149 s, 1072 m, 999 m, 743 m, 702 s cm^{-1}.

m/z, % 433, 10; 431, 8 (M^+); 352, 10; 202, 18; 91, 100.

N-Benzyl-(2,2-dibromocyclopropylmethyl)amine (**283**) (hydrolysed product; used as starting material in Exp. 85 and Exp. 86):

The analytical data of **283** were identical to those reported.[185]

The reaction was repeated on a comparable scale and gave the same three products with yields as follows: **285** 37 %; **286** 18 % and **283** 28 %.

EXPERIMENT 89

Reaction of *N*-benzyl-*N*-(2,2-dibromocyclopropylmethyl)acetamide (287) with methyllithium

a) Reaction with 1.7 mol.equiv. of methyllithium:

A 1.35 M solution of methyllithium in ether (0.53 ml, 0.72 mmol, 1.3 mol.equiv.) was added dropwise to a solution of *N*-benzyl-*N*-(2,2-dibromocyclopropylmethyl)acetamide (200 mg, 0.55 mmol) in dry ether (10 ml) at -90 °C. After 45 min at -90 °C, TLC

showed starting material was still present and more methyllithium (0.15 ml; in total 1.7 mol.equiv.) was added. The solution was stirred for additional 40 min at -90 °C and was then quenched with a saturated aqueous solution of NH_4Cl (5 ml). The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:3) to give unreacted starting material **287** (45 mg, 23 %) and as a mixture of two rotamers (71:29) *N-benzyl-N-(2-bromocyclopropylmethyl)acetamide* (**288**) (50 mg, 32 % [or 36 % if recovered starting material **287** is subtracted from the original amount]).

Found M^+: 281.0415. $C_{13}H_{16}BrO$ requires: 281.0415.

NMR data, major rotamer:

δ_H 0.91 (1H, td, J 6.5, 7.4 Hz, H_{cis}-3 (relative to H-2)), 1.01 (1H, ddd, J 3.8, 6.5, 9.5 Hz, H_{trans}-3 (relative to H-2)), 1.38-1.47 (1H, m, H-1), 2.16 (3H, s, CH_3), 2.72 (1H, td, J 3.8, 7.4 Hz, H-2), 3.15 (1H, dd, J 8.2, 14.3 Hz, first H of CH_2N), 3.52 (1H, dd, J 6.2, 14.3 Hz, second H of CH_2N), 4.63 (2H, s, Ph$C\underline{H}_2N$), 7.18-7.41 (5H, m, aromatic).

δ_C 14.6 (C-3), 18.7 (C-1 or C-2), 21.2 (C-1 or C-2) 21.7 (CH_3), 47.4 (CH_2N), 52.0 (CH_2N), 126.2, 127.7, 129.0, 136.4 (all aromatic C), 171.2 (CO).

NMR data, minor rotamer:

δ_H 0.83 (1H, td, J 6.7, 7.5 Hz, H_{cis}-3 (relative to H-2)), 1.09 (1H, ddd, J 3.9, 6.7, 9.6 Hz, H_{trans}-3 (relative to H-2)), 1.38-1.47 (1H, m, H-1), 2.22 (3H, s, CH_3), 2.58 (1H, td, J 3.9, 7.6 Hz, H-2), 3.03 (1H, dd, J 8.0, 14.3 Hz, first H of CH_2N), 3.29 (1H, dd, J 6.0, 14.3 Hz, second H of CH_2N), 4.60 (1H, d, J 15.2 Hz, Ph$C\underline{H}_2N$), 4.85 (1H, d, J 15.2 Hz, Ph$C\underline{H}_2N$), 7.18-7.41 (5H, m, aromatic).

δ_C 14.5 (C-3), 17.9 (C-1 or C-2), 21.2 (C-1 or C-2) 21.7 (CH_3), 47.9 (CH_2N), 49.5 (CH_2N), 127.4, 127.7, 128.6, 137.1 (all aromatic C), 170.5 (CO).

ν_{max} 3062 w, 3028 m, 1926 m, 1650 s, 1470 s, 1422 s, 1384 s, 1359 s, 1251 s, 1036 m, 991 m, 733 s, 698 s cm^{-1}.

m/z, % 283, 7; 281, 4 (M^+); 202, 13; 174, 33; 160, 15; 148, 5; 146, 6; 120, 32; 91, 100; 65, 9.

b) Reaction with 2.2 mol.equiv. of methyllithium:

A 1.35 M solution of methyllithium in ether (2.25 ml, 3.04 mmol, 2.2 mol.equiv.) was added dropwise to a solution of *N*-benzyl-*N*-(2,2-dibromocyclopropylmethyl)acetamide (500 mg, 1.38 mmol) in dry ether (15 ml) at -90 °C. After 15 min at -90 °C and 15 min at -60 °C, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (5 ml). The aqueous layer was extracted with ether (2 × 15 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give *3-benzyl-1-bromo-2-methylene-3-azabicyclo[3.1.0]hexane* (**289**) (34 %). The compound was not completely pure, the NMR also showed signals of *3-benzyl-1-bromo-2-methyl-3-aza-bicyclo[3.1.0]hexan-2-ol* (**290**) (9 %) [in total 160 mg, ratio **289** to **290** 80:20].

3-Benzyl-1-bromo-2-methylene-3-azabicyclo[3.1.0]hexane (**289**):

Found M^+: 263.0310. $C_{13}H_{14}BrN$ requires: 263.0310.

δ_H 1.19 (1H, t, J 5.0 Hz, H_{endo}-6), 1.53 (1H, dd, J 5.0, 8.9 Hz, H_{exo}-6), 2.03 (1H, td, J 5.0, 8.9 Hz, H-5), 3.04 (1H, d, J 9.2 Hz, H_{endo}-4), 3.40 (1H, dd, J 5.0, 9.2 Hz, H_{exo}-4), 3.82 (1H, broad s, first H of C=C$\underline{H}_2$), 4.06 (1H, d, J 15.3 Hz, first H of C$\underline{H}_2$Ph), 4.07 (1H, broad s, second H of C=C$\underline{H}_2$), 4.25 (1H, d, J 15.3 Hz, second H of C$\underline{H}_2$Ph), 7.20-7.40 (5H, m, aromatic).

δ_C 23.4 (C-6), 24.6 (C-5), 34.2 (C-1), 50.8 (C-4 or $\underline{C}H_2$Ph), 52.1 (C-4 or $\underline{C}H_2$Ph), 75.5 (C=$\underline{C}H_2$), 127.0, 127.5, 128.5, 137.8 (all aromatic C), 154.1 (C-2).

ν_{max} 3568 w, 3085 m, 3062 m, 3028 s, 2999 m, 2875 s, 2838 s, 1948 w, 1877 w, 1810 w, 1644 s, 1604 m, 1495 s, 1495 s, 1453 s, 1356 s, 1301 s, 1217 m, 1180 s, 1129 s, 1080 m, 1039 m, 1010 m, 956 m, 912 m, 890 m, 735 s, 699 s cm^{-1}.

m/z, % 265, 14; 264, 39; 263, 19 (M^+); 262, 19; 184, 20; 182, 11; 91, 100; 65, 30.

NMR data of 3-benzyl-1-bromo-2-methyl-3-azabicyclo[3.1.0]hexan-2-ol (**290**):

δ_H 1.34 (1H, dd, J 4.4, 4.8 Hz, H_{endo}-6), 1.49 (3H, s, CH_3), 1.53 (1H, H_{exo}-6, peaks underneath peaks of **289**), 1.85 (1H, ddd, J 3.6, 4.4, 8.8 Hz, H-5), 2.76 (1H, d, J 8.8 Hz, H_{endo}-4), 2.88 (1H, dd, J 3.6, 8.8 Hz, H_{exo}-4), 3.57 (1H, d, J 14.6 Hz, first H of C$\underline{H}_2$Ph), 4.17 (1H, d, J 14.6 Hz, second H of C$\underline{H}_2$Ph), 7.20-7.40 (5H, m, aromatic).

δ_C 19.4 (C-6), 21.1 (CH_3), 23.4 (C-5), 50.4 (C-4 or $\underline{C}H_2Ph$), 50.5 (C-4 or $\underline{C}H_2Ph$), 126.8, 128.0, 128.2, (all aromatic C); quaternary carbons like C-1 and C-2 were not detected (signals too weak).

EXPERIMENT 90

4-(*trans*-2-Bromocyclopropyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (298)

A 1.5 M solution of methyllithium in ether (0.43 ml, 0.65 mmol) was added dropwise to a solution of 4-(2,2-dibromocyclopropyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (200 mg, 0.65 mmol) [a mixture of diastereomers was used; ratio, 64:36] in dry ether (10 ml) at room temperature. After 10 min the reaction mixture was cooled to 0 °C and water (5 ml) was added. The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 2:1) to give a white solid, *4-(trans-2-bromocyclopropyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**298**) (60 mg, 40 %) as a mixture of two diastereomers (ratio, 60:40).

Found: C 47.98, H 5.45, N 5.95. $C_9H_{12}NOBr$ requires: C 46.98, H 5.26, N 6.09.
It was not possible to obtain good CHN values of **298**; however the compound was pure by NMR and the chemical shifts were in full agreement to the ones observed with analogous compounds.
NMR data, major diastereomer:

δ_H 0.84 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.39 (1H, ddd, J 4.6, 6.4, 13.0 Hz, H_{trans} of cyclopropyl CH_2 (relative to BrC-H)), 1.55 (1H, td, J 6.4, 7.5 Hz, H_{cis} of cyclopropyl CH_2 (relative to BrC-H)), 2.12 (1H, ddd, J 3.4, 6.4, 13.0 Hz, H_{trans} cyclopropyl (relative to BrC-H)), 2.19 (1H, d, J 5.6 Hz, H-5), 3.01 (1H, ddd, J 3.4, 4.6, 7.5 Hz, BrC-H, cyclopropyl), 4.49 (1H, d, J 5.6 Hz, H-1).

δ_C 12.8 (CH_3), 13.0 (C-6), 16.6 (CH_2, cyclopropyl), 19.0 (CH, cyclopropyl), 19.7 (CH, cyclopropyl), 22.2 (CH_3), 40.0 (C-5), 74.4 (C-1), 158.9 (C-4).

NMR data, minor diastereomer:

δ_H 0.82 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.43 (1H, ddd, J 5.1, 6.4, 13.0 Hz, H_{trans} of cyclopropyl CH_2 (relative to BrC-H)), 1.55 (1H, td, J 6.4, 7.5 Hz, H_{cis} of

cyclopropyl CH_2 (relative to BrC-H)), 2.12 (1H, ddd, J 3.4, 6.4, 13.0 Hz, H_{trans} cyclopropyl (relative to BrC-H)), 2.17 (1H, d, J 5.6 Hz, H-5), 3.13 (1H, ddd, J 3.4, 5.1, 7.5 Hz, BrC-H, cyclopropyl), 4.49 (1H, d, J 5.6 Hz, H-1).

δ_C 12.8 (CH_3), 13.0 (C-6), 17.9 (CH_2, cyclopropyl), 18.1 (CH, cyclopropyl), 19.8 (CH, cyclopropyl), 22.2 (CH_3), 40.0 (C-5), 74.4 (C-1), 158.9 (C-4).

ν_{max} (mixture) 3031 w, 2955 s, 2926 m, 2870 m, 1582 w, 1456 m, 1437 m, 1401 s, 1378 m, 1233 s, 1117 m, 1049 s, 1030 s, 1001 s, 888 m, 831 s, 714 m cm^{-1}.

m/z, % (mixture) 214, 2, 212, 2; 199, 4; 182, 20; 155, 10; 127, 19; 86, 45; 84, 100, 71, 13; 57, 42.

EXPERIMENT 91

4-(*trans*-2-Bromocyclopropyl)-1-butyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (299)

A 1.5 M solution of methyllithium in ether (0.55 ml, 0.83 mmol) was added dropwise to a solution of 1-butyl-4-(2,2-dibromocyclopropyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (255 mg, 0.76 mmol) [a mixture of diastereomers was used; ratio a to b, 31:69] in dry ether (10 ml) at room temperature. After 30 min the reaction mixture was cooled to 0 °C and water (5 ml) was added. The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 1:1) to give *4-(trans-2-bromocyclopropyl)-1-butyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**299**) (65 mg, 33 %) as a mixture of two diastereomers (ratio a to b 42:58).

An accurate mass spectrum was not obtained.

NMR data, diastereomer a:

δ_H 0.32 (1H, dd, J 3.6, 5.3 Hz, H_{endo}-6), 0.87 (3H, t, J 7.1 Hz, CH_3), 0.93 (1H, dd, J 5.3, 9.3 Hz, CH, H_{exo}-6), 1.22-1.42 (5H, m, H_{trans} of cyclopropyl CH_2 (relative to BrC-H) together with 4H of $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (1H, td, J 6.4, 7.6 Hz, H_{cis} of cyclopropyl CH_2 (relative to BrC-H)), 1.64-1.95 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.04 (1H, dd, J 3.6, 9.3 Hz, H-5), 2.14 (1H, ddd, J 3.4, 6.4, 9.7 Hz, H_{trans} cyclopropyl (relative to BrC-H)), 3.15 (1H, ddd, J 3.4, 4.6, 7.6 Hz, BrC-H, cyclopropyl).

δ_C 11.6 (C-6), 13.9 (CH_3), 17.8 (CH_2, cyclopropyl), 18.3 (CH, cyclopropyl), 19.8 (CH, cyclopropyl), 22.4 (CH_2), 28.3 (CH_2), 29.6 (C-5), 31.1 (CH_2), 75.3 (C-1), 162.8 (C-4).

NMR data, diastereomer b:

δ_H 0.34 (1H, dd, J 3.6, 5.4 Hz, H_{endo}-6), 0.87 (3H, t, J 7.1 Hz, CH_3), 0.99 (1H, dd, J 5.4, 9.5 Hz, CH, H_{exo}-6), 1.22-1.42 (5H, m, H_{trans} of cyclopropyl CH_2 (relative to BrC-H) together with 4H of $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.57 (1H, td, J 6.4, 7.6 Hz, H_{cis} of cyclopropyl CH_2 (relative to BrC-H)), 1.68-1.98 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.05 (1H, dd, J 3.6, 9.5 Hz, H-5), 2.18 (1H, ddd, J 3.4, 6.4, 9.7 Hz, H_{trans} cyclopropyl (relative to BrC-H)), 3.07 (1H, ddd, J 3.4, 4.6, 7.6 Hz, BrC-H, cyclopropyl).

δ_C 11.6 (C-6), 13.9 (CH_3), 16.5 (CH_2, cyclopropyl), 19.0 (CH, cyclopropyl), 19.8 (CH, cyclopropyl), 22.4 (CH_2), 28.3 (CH_2), 29.4 (C-5), 31.1 (CH_2), 75.3 (C-1), 162.8 (C-4).

ν_{max} (mixture) 2956 s, 2932 s, 2870 m, 1611m, 1466 m, 1432 s, 1410 s, 1168 w, 1107 m, 1055 m, 968 m, 944 m, 881 m, 649 m cm^{-1}.

m/z, % (mixture) 260, 3; 258, 3 (M^+); 174, 20; 121, 20; 119, 15; 85, 100; 70, 18; 57, 62; 55, 26.

EXPERIMENT 92

3-(*trans*-2-Bromocyclopropyl)-5-phenylisoxazole (300)

A 1.5 M solution of methyllithium in ether (0.23 ml, 0.34 mmol) was added dropwise to a solution of 3-(2,2-dibromocyclopropyl)-5-phenylisoxazole (100 mg, 0.29 mmol) in dry ether (10 ml) at room temperature. After 20 min the reaction mixture was cooled to 0 °C and water (5 ml) was added. The aqueous layer was extracted with ether (2 × 10 ml). The combined organic layers were dried and the solvent was removed. The residue was purified by column chromatography on silica gel (petrol - ether, 2:1) to give a white solid, *3-(trans-2-bromocyclopropyl)-5-phenylisoxazole* (**300**) (22 mg, 29 %).

White solid, m.p. 73-75 °C.

Found M^+: 262.9946. $C_{12}H_{10}BrNO$ requires: 262.9941.

δ_H 1.57 (1H, ddd, J 4.7, 6.4, 9.7 Hz, H_{trans} of cyclopropyl CH_2 (relative to BrC-H)), 1.66 (1H, td, J 6.4, 7.6 Hz, H_{cis} of cyclopropyl CH_2 (relative to BrC-H)), 2.42 (1H, ddd, J 3.4, 6.4, 9.7 Hz, H_{trans} cyclopropyl (relative to BrC-H)), 3.22 (1H, ddd, J 3.4, 4.7, 7.6 Hz, BrC-H, cyclopropyl), 6.32 (1H, s, H-4), 7.43-7.74 (5H, m, aromatic).

δ_C 18.6 (CH, cyclopropyl), 18.7 (CH_2, cyclopropyl), 19.8 (CH, cyclopropyl), 98.1 (C-4), 125.8, 127.2, 129.0, 130.3 (all aromatic C), 163.3 (C-3), 170.1 (C-5).

ν_{max} 3128 w, 1613 m, 1574 m, 1501 m, 1449 s, 1427 s, 1242 m, 1074 m, 1048 m, 936 m, 913 m, 891 m, 809 m, 766 s, 691 s, 600 m cm^{-1}.

m/z, % 265, 19; 263, 27 (M^+); 184, 100; 156, 91; 105, 58; 77, 72.

6.2.3. Experiments of 'Appendix to Results and Discussion' (Chemistry of 1-methylene-2-vinylcyclopropane)

EXPERIMENT 93

1-Methylene-2-vinylcyclopropane (301)

The procedure for the preparation of this known compound is described in full because an alternative work-up procedure from that in the literature was applied.[241]

A 250 ml two-neck flask fitted with a condenser was charged with potassium *tert*-butoxide (22.0 g, 0.196 mol, 3 mol.equiv.) and anhydrous dimethyl sulfoxide (70 ml) under an atmosphere of argon. The suspension was heated to 60 °C and was then allowed to cool to room temperature. 1,1-Dichloro-2-ethyl-3-methylcyclopropane (**25**) (10 g, 0.065 mol) was added dropwise during 30 min, keeping the temperature between 35 and 37 °C (cooling with a water-bath). After 2 h stirring at room temperature the black reaction mixture was quenched with ice/water. High boiling petrol (75 ml, b.p.: 240 to 260 °C) was added, the aqueous layer was extracted with high boiling petrol (2 × 75 ml), the combined organic layers were washed with water (3 × 200 ml) and with a brine solution (1 × 200 ml). The product was removed from the solvent by flash distillation at 1 mm Hg and trapped by a cooling-bath (alcohol/liquid nitrogen) at -85 °C. Two fractions of product were collected. Flash distillation at room temperature (fraction 1) gave pure *1-methylene-2-vinylcyclopropane* (**301**) (3 g, 58 %). The second fraction was collected by heating the mixture to 50 °C and gave the product (**301**) together with about 30 % of the solvent (about 0.8 g).

The analytical data of **301** were identical to those reported.[241]

EXPERIMENT 94

Reaction of 1-methylene-2-vinylcyclopropane (301) with iodine

A solution of iodine (660 mg, 2.5 mmol, 1 mol.equiv.) in dry ether (10 ml) was added dropwise to a solution of 1-methylene-2-vinylcyclopropane (**301**) (200 mg, 2.5 mmol)

in dry ether (10 ml) at -78 °C under argon. The solution was allowed to warm to room temperature and stirred for 90 min. The reaction was quenched with aqueous sodium thiosulfate (30 ml, 20 %). A yellow liquid was isolated by extraction. NMR showed a complicated spectrum, which was not interpretable. The yellow liquid was not stable, it turned deeply red within a few hours probably due to the release of iodine.

EXPERIMENT 95

Attempted hydroboration of 1-methylene-2-vinylcyclopropane (301)

a) With 9-borabicyclo[3.3.1]nonane (9-BBN):

A solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in hexane (8.7 ml, 4.4 mmol, 0.5 M in hexane) was added dropwise to a stirred solution of 1-methylene-2-vinylcyclopropane (**301**) (350 mg, 4.4 mmol) in dry THF (10 ml) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (1.8 ml) was added at 0 °C, followed by the addition of sodium hydroxide (1.8 ml, 3 N), and hydrogen peroxide (1.8 ml, 30 % solution, 4 mol.equiv.). The mixture was stirred for additional 24 h. Extractive isolation with ether afforded a colourless oil (170 mg). The oil was subjected to column chromatography on silica, but no product could be identified by NMR.

b) With isopinocamphenylborane ($IPCBH_2$):

(1*R*)-(+)-α-Pinene (280 mg 2.0 mmol) in THF (2.5 ml) was treated with a cold (0 °C) solution of $BH_3{\cdot}SMe_2$ (2.0 mmol, 0.55 mol.equiv.) at 0 °C. The mixture was stirred for 30 min while warming up to room temperature. 1-Methylene-2-vinylcyclopropane (**301**) (300 mg, 3.7 mmol) in dry THF (2 ml) was added at 0 °C and the mixture was stirred for 20 h under an argon atmosphere. Water (0.44 ml) was added at 0 °C, followed by the addition of sodium hydroxide (0.89 ml, 3 N), and hydrogen peroxide (0.89 ml, 30 % solution). The mixture was stirred for additional 7.5 h. Extractive isolation with ether afforded a colourless oil (380 mg). No product could be identified by NMR.

EXPERIMENT 96

Treatment of 1-methylene-2-vinylcyclopropane (301) with strong bases and subsequent trapping with electrophiles

a) *n*-Butyllithium / acetone / THF:

A 1.6 M solution of *n*-butyllithium in hexane (6.5 ml, 10.5 mmol) was added to a solution of 1-methylene-2-vinylcyclo-propane (**301**) (760 mg, 9.5 mmol) in dry THF (15 ml) at -80 °C. The reaction was allowed to warm to room temperature and the mixture was stirred for 2 h. An excess of acetone (1.5 ml, 20.9 mmol) was added at -80 °C. The cooling bath was removed and the mixture was stirred for 12 h. The reaction mixture was quenched with water (10 ml) at -20 °C and extracted with ether (3 × 10 ml). The combined organic layers were washed with water (4 × 30 ml), dried and the solvent was removed. The residue, a yellow liquid (2.2 g), was purified by column chromatography on silica gel (petrol - ether, 6:1). Several fractions were analysed by ^{1}H NMR, but only the first fraction (150 mg) gave a clear spectrum. The compound was identified as *5-isopropylidene-2-methylcyclopenta-1,3-diene* (**310**) (150 mg, 13 %). The NMR spectrum also showed traces of its regioisomer, *5-isopropylidene-1-methylcyclopenta-1,3-diene* (**311**).

The analytical data of fulvene **310** was identical to those reported.[243]

b) *n*-Butyllithium / CO_2 / ether:

A 1.6 M solution of *n*-butyllithium in hexane (2.81 ml, 4.49 mmol) was added to a solution of 1-methylene-2-vinylcyclopropane (**301**) (300 mg, 3.74 mmol) in dry ether (5 ml) at -80 °C. The temperature was allowed to rise to -35 °C and CO_2 gas was bubbled through the solution for 20 min. The cooling bath was removed and addition was continued for another 10 min. The reaction mixture was quenched with water (5 ml) at – 20 °C. Extractive isolation with ether afforded a colourless liquid, which was identified as *valeric acid* (200 mg, 44 %).

c) *n*-Butyllithium / CO_2 / THF:

A solution of 1-methylene-2-vinylcyclopropane (**301**) (1.08 g, 0.013 mol) in dry THF (5 ml) was added to a solution of *n*-butyllithium (9.3 ml, 0.015 mol, 1.6 M in hexane) in THF (15 ml) at -10 °C. The reaction was warmed to 10 °C over 1 h and was kept at 10

°C for an additional 1 h. The solution was cooled to -10 °C and CO_2 was bubbled through it. The colour changed from intense red-black to yellow and the mixture turned to a thick suspension. Addition of CO_2 was continued for 20 min while the mixture was allowed to warm to room temperature. The reaction mixture was quenched with hydrochloric acid (2 %, 10 ml) at -20 °C. Extractive isolation with ether afforded a yellow solid which was not identified.

d) *n*-Butyllithium / cyclohexanone / THF:

A solution of 1-methylene-2-vinylcyclopropane (**301**) (1.5 g, 0.019 mol) in dry THF (5 ml) was added to a solution of *n*-butyllithium (79.3 ml, 0.012 mol, 1.6 M in hexane) in THF (15 ml) at -10 °C. The reaction was warmed to 10 °C over 1 h and was kept at 10 °C for an additional 1 h. The reaction mixture was cooled to -10 °C and a solution of cyclohexanone (1.2 ml, 0.012 mol) in THF (5 ml) was added. After 15 min the reaction was quenched with water (10 ml). Extractive isolation yielded a yellow oil, which was purified by column chromatography; several fractions were analysed by ^{1}H NMR, but the spectra were unclear and it was not possible to identify any product.

e) LDA / acetone / THF:

Lithium diisopropylamide (LDA) was prepared by adding *n*-butyllithium (2.6 ml, 1.6 M in hexane) dropwise to a solution of diisopropylamine (417 mg, 4.12 mmol) in dry THF (3 ml) at 0 °C under argon. The mixture was stirred at 0 °C for 30 min, then added to a solution of 1-methylene-2-vinylcyclopropane (**301**) (300 mg, 3.74 mmol) in dry THF (5 ml) at -80 C. The solution was warmed up to -40 °C and kept at this temperature for 1 h. An excess of acetone (0.65 ml, 11.23 mmol) was added and the cooling bath was removed. The mixture was stirred overnight. The reaction mixture was quenched with hydrochloric acid (2 %, 5ml) at -20 °C. Extractive isolation with ether afforded a yellow liquid. GLC showed a range of peaks, probably due the formation of different condensation products of acetone. No product was isolated or identified.

The reaction was repeated on the same scale, however this time the reaction mixture was treated with CO_2 gas. As above no product was isolated or identified.

7. References

References

1 (a) K.B. Wiberg, 'Introduction', pp 1-21, in *Methods of Organic Chemistry (Houben-Weyl)*, Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a.*
(b) K.B. Wiberg, 'Structures, energies and spectra of cyclopropanes', pp 1-16, in *The chemistry of the cyclopropyl group*, Ed. Z. Rappoport, John Wiley & Sons, New York, **1987**.

2 J. March, *Advanced organic chemistry*, 4th ed., Wiley-Interscience, New York, **1992**, pp 150-158.

3 B. Halton and M. Banwell, 'Cyclopropenes', pp 1223-1340, in *The chemistry of the Cyclopropyl group*, Ed. Z. Rappoport, John Wiley & Sons, New York, **1987**.

4 Armin de Meijere, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809.

5 F.J. Weigert, J.D. Roberts, *J. Am. Chem. Soc.* **1967**, *89*, 5962.

6 C. Coulson, W. Moffitt, *Philos. Mag.* **1949**, *40* ,1.

7 K.B. Wiberg, R.F.W. Bader, C.D.H. Lau, *J. Am. Chem. Soc.* **1987**, *109*, 985.

8 G.L. Gloss, *Adv. Alicyclic Chem.,* **1966**, *1*,53.

9 F.H. Allen, *Tetrahedron*, **1982**, *38*, 645.

10 K.B. Wiberg, *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 312.

11 A. von Baeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2278.

12 J. Salaün and M.S. Baird, *Current Medicinal Chemistry* **1995**, *2*, 511.

13 H.-W. Liu and C.T. Walsh, 'Biochemistry of the cyclopropyl group', pp 959-1025, in *The Chemistry of the Cyclopropyl Group*, Ed. Z. Rappoport, John Wiley & Sons, New York, **1987**.

14 J. H. Davies, 'The pyrethroids: an historical introduction', pp 1-41, in *The Pyrethroid Insecticides*, Ed. J.P. Leahey, Taylor & Francis, London; **1985**.

15 K. Hofmann, G.J. Marco and G.A. Jeffry, *J. Am. Chem. Soc.* **1958**, *80*, 5717.

16 J.F. Tocanne and R.G. Bergmann, *Tetrahedron* **1972**, *28*, 373.

17 (a) L.F. Burroughs, *Nature* (London) **1957**, *179*, 360.
(b) M.L. Vahatalo, A.I. Virtanen, *Acta Chem. Scand.* **1957**, *11*, 741.

18 M. Lieberman, *Ann. Rev. Plant Physiol.* **1979**, *30*, 533.

19 L. Fowden, A Smth, D.S Millington, R.C. Sheppard, *Phytochemistry* **1969**, *8*, 437.

20 (a) D. Ma, Z. Ma, *Tetrahedron Lett.* **1997**, *38*, 7599.

(b) K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ofune, *J. Org. Chem.* **1991**, *56*, 4167.

21 (a) S. Nakanishi, *Science* **1992**, *258*, 597.

(b) M.G. Moloney, *Natural Product Reports* **1998**, 205.

22 H. Kaba, Y. Hayashi, T. Higuchi, S. Nakanshi, *Science* **1994**, *265*, 262.

23 (a) T. Knopfel, R. Kuhn, H. Allgeier, *J. Med. Chem.* **1995**, *38*, 1417.

(b) T. Knopfel, F. Gasparini, *Drug Discovery Today* **1996**, *1*, 103.

24 (a) C.H. Hassall, K. Reyle, *Biochem. J.* **1955**, *60*, 334.

(b) J.N. Eloff, L. Fowden, *Phytochemistry* **1970**, *9*, 2423.

25 These african eatable fruits were introduced in Carribean islands and Florida by Captain Bligh. See: J.C. Mitchell "*The posthumous misfortune of captain Bligh of the Bounty: Hypoglyceamia from Blighia*" *Diabetes* **1974**, *23*, 919.

26 (a) L. Fowden, P.J. Lea, E.A. Bell, *The non protein amino acids of plants: Advances in Enzymology*. Ed. A. Merster, John Wiley & Sons, New York, **1979**, pp 117-175.

(b) H.S.A. Sherrat, *Trends in Pharmac. Sc.* **1986**, 186.

27 H. Osmundsen, D. Billington, J.R. Taylor, H.S.A. Sherrat, *Biochem. J.* **1978**, *170*, 337.

28 K. Iguchi, M. Fujita, H. Nagaoka, H. Mitome, Y. Yamada, *Tetrahedron Lett.* **1993**, *34*, 6277.

29 M. Yoshida, M. Ezaki, M. Hashimoto, M. Yamashita, N. Shigematsu, M. Okuhara, M. Kohsaka, K. Horikoshi, *J. Antibiot.* **1990**, *43*, 748.

30 A.W. Jeavans, C.Y. Hopkins, *Tetrahedron Lett.* **1968**, 2167.

31 M.S. Baird, C.M.Dale, W. Lytollis, M.J. Simpson, *Tetrahedron Lett.* **1992**, 1526.

32 A.A. Andrianaivorafehivola, E.M. Gaydou, L.H. Rahotovao, *Oleagineux* **1994**, *49*, 177.

33 R.B. Silverman, P.A. Zieske, *Biochem. Biophys. Res. Commun.* **1986**, *135*, 154.

34 M. Eliott, N.F. James, *Chem. Soc. Rev.* **1978**, *7*, 473.

35 (a) K. Naumann, *Pesticide Science* **1998**, *52*, 3.

(b) K.J. Mrusek, *Abstracts of Papers of the Am. Chem. Soc.* **1996**, *212*, 13.

36 P. Boyer, M. Briley, *Drugs of Today* **1998**, *34*, 709.

37 S. Shuto, S. Ono, Y. Hase, N. Kamiyama, and A. Matsuda, *Tetrahedron Lett.* **1996**, *37*, 641.

38 P. Viazzo, V. Alphand and R. Furstoss, *Tetrahedron Lett.* **1996**, *37*, 4519.

39 J.H. Hong, B.K. Chun and C.K. Chu, *Tetrahedron Lett.* **1998**, *39*, 225-228.

40 *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a, E17b.*

41 T. Tsuji and Shinya Nishida, 'Preparation of cyclopropyl derivatives', pp307-374 in *The chemistry of the cyclopropyl group*, Ed. Z. Rappoport; John Wiley & Sons, **1987**.

42 S.C. Bunce, R.A. Kent, *Org. Prep. Proced. Int.* **1974**, *6*, 193.

43 (a) G.W. Cannon, R.C. Ellis, J.R. Leal, *Org. Synth., Coll. Vol. IV* **1963**, 597.
(b) L. Fitjier, *Synthesis* **1977**, 189.

44 M.J: Schlatter, *Org. Synth., Coll. Vol. III* **1955**, 223, cf. p221.

45 M.S. Baird, 'Thermal Reactions', pp 114-198, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a.*

46 S. Hartmann. D.E. Minnikin, H.J. Romming, M.S. Baird, C. Ratledge, P.R. Wheeler, *Chemistry and Physics of Lipids* **1994**, *71*, 99.

47 W. Kirmse, *Carbene Chemistry*, 2nd ed., Academic Press, New York, **1971**.

48 R.R. Kostikov, A.P. Molchanov, A.F. Khlebnikov, *Russ. Chem. Rev.* **1989**, *58 (7)*, 654.

49 E. Dehmlov, 'Halogen-carbene', pp 1461-1627, in *Methoden der organischen Chemie* (*Houben-Weyl*), Ed. M. Regitz, Thieme Verlag, Stuttgart, **1989**, *Vol E19b.*

50 (a) E.V. Dehmlov, S.S. Dehmlov, *Phase Transfer Catalysis*, 3rd ed, VCH, Weinheim, **1993**.
(b) C.M. Starks, C.L. Liotta, M. Halpern, *Phase Transfer Catalysis*, Chapman Hall, New York, London, **1994**.

51 A. Jonczyk and M. Fedrynski, 'Dihalocarbenes or Equivalents', pp 589-734, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a.*

52 H.E. Simmons, R.D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256.

53 H.E. Simmons, T.L. Cairns, S.A. Vladuchick, C.M. Hoiness, *Org. React.* **1973**, *20*, 1-131.

54 M.V.R. Reddy, D.B.Reddy, P.V.R. Reddy, S. Vijayalakshmi, *Org. Prep. Proced. Int.* **1991**, *23*, 633.

55 E.J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353.

56 K-H. Altmann, R. Kesselring, E. Francotte, and G. Rihs, *Tetrahedron Lett.* **1994**, *35*, 2331.

57 (a) K. Okuma, Y. Tanaka, K. Yoshihara, A. Ezaki, G. Koda, H. Ohta, K. Hara and S. Kashimura, *J. Org. Chem.* **1993**, *58*, 5915.

(b) J.E. Baldwin, R. M. Adlington, D. Bebbington and A.T. Russel, *Tetrahedron Lett.* **1994**, *41*, 12015.

58 (a) A Krief and W. Dumont, *Tetrahedron Lett.* **1988**, *29*, 1083.

(b) A Krief, W. Dumont, P. Pasau and P. Lecomte, *Tetrahedron* **1989**, *45*, 3039.

(c) A. Krief, L. Provins, and A. Froidbise, *Tetrahedron Lett.* **1998**, *39*, 1437.

59 T. Morikawa, H. Sasaki, R. Hanai, A. Shibuya, and T. Taguchi, *J. Org. Chem.* **1994**, *59*, 97.

60 T.D. Avery, T.D. Haselgrove, T.J. Rathbone, D.K. Taylor and E.R.T. Tiekink, *J. Chem. Soc., Chem. Commun.* **1998**, 333.

61 C. Alcaraz and M. Bernabé, *Tetrahedron: Asymmetry* **1994**, *5*, 1221.

62 R. Tanikaga, N. Shibata and T. Yoneda, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2253.

63 (a) A.B. Charette, J.-F. Marcoux and B. Côté, *Tetrahedron Lett.* **1991**, *32*, 7215.

(b) A.B. Charette and B. Côté, *J. Am. Chem. Soc.* **1995**, *117*, 12721.

64 A.B. Charette, B. Côté, S. Monroc, and S. Prescott, *J. Org. Chem.* **1995**, *60*, 6888.

65 D. Dorsch, E. Kunz, G. Helmchen, *Tetrahedron Lett.* **1985**, *26*, 3319.

66 V.K. Singh, A. DattaGupta, G. Sekar, *Synthesis* **1997**, 137.

67 G. Maas, 'Transition Metal Catalysed Reactions', pp 444-495, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a.*

68 C. Pique, B. Fahndrich, A. Pfalz, *Synlett* **1995**, 491.

69 S.-B. Park, H. Nishiyama, K.J. Itoh, *J. Chem. Soc. Chem Commun.* **1994**, 1315.

70 (a) H.M.L. Davies, *Aldrichimica Acta* **1997**, *30*, 107.

(b) H.M.L. Davies, N. Kong, and M.R. Churchill, *J. Org. Chem.* **1998**, *63*, 6586.

71 (a) M.P. Doyle, *Aldrichimica Acta* **1996**, *29*, 3.

(b) M.P. Doyle, D.C. Forbes, *Chem. Rev.* **1998**, *98*, 911.

72 S. Kobayashi, H. Takahashi, M. Yoshioka, M. Ohno, *Tetrahedron Lett.* **1992**, *33*, 2575.

73 Y. Ukaji, K. Sada, and K. Inomata, *Chem. Lett.* **1993**, 1227.

74 S.E. Denmark, B.L. Christenson, S.P. O'Connor, *Tetrahedron Lett.* **1995**, *36*, 2219.

75 A.B. Charette, H. Juteau, *J. Am. Chem. Soc.* **1994**, *116*, 2651.

76 A.B. Charette, H. Juteau, H. Lebel, and C. Molinaro, *J. Am. Chem. Soc.* **1998**, *120*, 11943.

77 M.S. Baird, P. Licence, V.V. Tverezovsky, I.G. Bolesov, W. Clegg, *Tetrahedron* **1999**, *55*, 2773.

78 *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17d.*

79 R.A. Fiato, J.B. Williams, M.A. Battiste, Synthesis **1974**, 273.

80 E. Sternberg, P. Binger, *Tetrahedron Lett.* **1985**, *26*, 301.

81 R.J. Bushby, 'Cyclopropenes: Synthesis, From Five-Membered Rings by Elimination of Two Ring Atoms', pp 2749-2757, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17d.*

82 W.E. Billups, M.M. Haley, G.-A. Lee, *Chem. Rev.* **1989**, *89*, 1147.

83 M.S. Baird, 'Cyclopropenes: Synthesis, By Transformations of Other Cyclopropanes', pp 2759-2779, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17d.*

84 A.E. Feiring, J. Ciabattoni, *J. Am. Chem. Soc.* **1973**, *95*, 5266.

85 (a) N.V. Bovin, L.S. Surmina, *Zh. Org. Khim.* **1973**, *9*, 1888.
(b) N.V. Bovin, L.S. Surmina, N.I. Yakushkina, I.G. Bolesov, *Zh. Org. Khim.* **1979**, *15*, 954.

86 M.S. Baird, H.H. Hussain, W.J. Nethercott, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1845.

87 P. Binger, P. Wedemann, R. Goddard, and U.H. Brinker, *J. Org. Chem.* **1996**, *61*, 6462.

88 V. Dave, E.W. Warnhoff, *Org. React.* **1970**, *18*, 217.

89 (a) M.S. Baird, H.L. Fitton, W. Clegg and A. McCamley, *J. Chem. Soc. Perkin Trans 1* **1993**, 321.
(b) M.S. Baird, J.R. Al Dulayymi, unpublished results.

90 M.P. Doyle, M.N. Protopopova, P. Müller, D. Ené, *J. Am. Chem. Soc.* **1994**, *116*, 8492.

91 E.J. York, W. Dittmar, J.R. Stevenson, R.G. Bergman, *J. Am. Chem. Soc.* **1973**, *95*, 5680.

92 T. Curtius, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.

93 E. Buchner, M. Fritsch, A. Papendieck, H. Witter, *Liebigs Ann. Chem.* **1983**, *273*, 214.

94 E. Beckmann, *Ber. Dtsch. Chem. Ges.* **1890**, *236*, 3331.

95 O. Diels, K. Adler, *Liebigs Ann. Chem.* **1928**, *460*, 98.

96 R. Huisgen, *1,3-Dipolar Cycloaddition Chemistry*, Ed. A. Padwa; Wiley-Interscience, New York, **1984**, *Vol. 1*, p 1.

97 (a) E.K. Rideal, *Ozone*, Constable and Co. LTD, London, **1920**.

(b) D.S. Wolfman, G. Linstrumelle, C.F. Cooper, *The Chemistry of Diazonium and Diazo Groups*, John Wiley & Sons, New York, **1978**.

98 R. Huisgen, *Angew. Chem.* **1963**, *75*, 604.

99 (a) R.B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, **1970**.

(b) R.B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395.

100 (a) K.N. Houk, J. Sims, C.R. Watt, J.L. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7287.

(b) K.N: Houk, K. Yamaguchi, *1,3-Dipolar Cycloaddition Chemistry*, Ed. A. Padwa, Wiley, New York, **1984**, *Vol. 2*, p 407.

101 (a) A. Padwa in *Comprehensive Organic Synth*esis, Ed. B.M. Trost, I. Flemming, Pergammon Press, Oxford, **1991**, *Vol 4*, p 1069.

(b) P.A. Wade in *Comprehensive Organic Synth*esis, Ed. B.M. Trost, I. Flemming, Pergammon Press, Oxford, **1991**, *Vol 4*, p 1111.

102 (a) R. Huisgen and R. Weinberger, *Tetrahedron Lett.* **1985,** *26*, 5119.

(b) J.J.W. McDouall, M.A. Robb, U. Niazi, F. Bernardi and H.B. Schlegel, *J. Am. Chem. Soc.* **1987**, *109*, 4642.

103 (a) R. Huisgen, G.Szeimies, L. Möbius, *Chem. Ber.* **1966**, *99*, 475.

(b) P. Scheiner, *Tetrahedron* **1968**, *24*, 349.

104 R. Huisgen, M.Seidl, G. Wallbillich and H. Knupfer, *Tetrahedron* **1962**, *17*, 3.

105 S.K. Armstrong, S. Warren, E.W. Collington and A. Naylor, *Tetrahedron Lett.* **1991**, *32*, 4171.

106 O. Moriya, H. Takenaka, M. Iyoda, Y. Urata and T. Endo, *J. Chem. Soc., Perkin Trans. 1* **1994**, 413.

107 K.-C. Liu, B. R. Shelton, and R.K. Howe, *J. Org. Chem.* **1980**, *45*, 3916.

108 C. Grundmann and R. Richter, *J. Org. Chem.* **1968**, *33*, 476.

109 (a) H. Hassner, K.M.L. Rai, *Synthesis* **1989**, 57.

(b) J.N. Kim, E.K. Ryn, Synth. Commun. **1990**, *20*, 1373.

110 G. Kumaran and G. H. Kulkarni, *J. Org. Chem.* **1997**, *62*, 1516.

111 (a) C. Grundmann, P. Grünanger, *The Nitrile Oxides*, Springer Verlag, Berlin, **1971**.

(b) K.B.G. Torsell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH publishers, New York, **1988**.

112 S.J. Barrow and C.J. Easton, *Tetrahedron Lett.* **1997**, *38*, 2175.

113 D.P. Curran, C.J. Fenk, *J. Am. Chem. Soc.* **1985**, *107*, 6023.

114 A.M. Gasco, C. Cena, A. Di Stilo, G. Ermondi, C. Medana and A. Gasco, *Helv. Chim. Acta* **1996**, *79*, 1803

115 D. Ghigo, R. Heller, R. Calvino, P. Alessio, R. Fruttero, A. Gasco, A. Bosia, G. Pescarmona, *Biochem. Pharmocol.* **1992**, *43*, 1281.

116 M. Feelisch, K. Schönafinger, E. Noack, *Biochem. Pharmocol.* **1992**, *4,* 1149.

117 A. Gasco, R. Fruttero, G. Sorba, *Il Farmoco* **1996**, *51*, 617.

118 T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.* **1960**, 82, 5339-5342

119 Y. Basel, A. Hassner, *Synthesis* **1997**, 309.

120 N. Maugein, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **1997**, *38*, 1547.

121 W. Carruthers, *Cycloaddition reactions in organic synthesis* Tetrahedron organic Chemistry Series, Pergamon Press, Oxford, **1990,** *Vol. 8.*

122 (a) A.P. Kozikowski, A.K., *Acc. Chem. Res.* **1984**, *17*, 410.

(b) S. Kanemasa, O. Tsuge, Heterocycles **1990**, *30*, 719.

123 G.A. Shvekhgeimer and M. Litim, *Russian Chemical Bulletin* **1994**, 43, 136.

124 Hirsch, "*The Chemistry of the Fullerenes*", Thieme Verlag Stuttgart, **1994**.

125 M.S. Meier, *Tetrahedron* **1996**, *52*, 5043.

126 A. Studer and D.P. Curran, *Tetrahedron* **1997**, *53*, 6681.

127 B.B. Shankar, D.Y. Yang, S. Girton, and A.K. Ganguly, *Tetrahedron Lett.* **1998**, *39*, 2447.

128 (a) K.-H. Park, M.M. Olmstead, and M.J. Kurth, *J. Org. Chem.* **1998**, *63*, 6579.
(b) K.-H. Park, E. Abbate, S. Najdi, M.M. Olmstead, and M.J. Kurth, *J. Chem. Soc., Chem. Commun.* **1998**, 1679.

129 D.P. Curran, *J. Am. Chem. Soc.* **1983**, 5826.

130 D.P. Curran and J. Zhang, *J.Chem. Soc. Perkin Trans. 1* **1991**, 2613.

131 B.M. Trost, I. Flemming, *Comprehensive organic synthesis*, Pergammon Press, Oxford, **1991**, *Vol. 4*, pp1078; *Vol. 8*, p 392, p 644.

132 (a) V. Jäger, V. Buß, and W. Schwab, *Tetrahedron Lett.* **1978**, 3133.
(b) V. Jäger und V. Buß, *Liebigs Ann. Chem.* **1980**, 101.
(c) V. Jäger, V. Buß und W. Schwab, *Liebigs Ann. Chem.* **1980**, 122.

133 V. Jäger and I. Müller, *Tetrahedron Lett.* **1985**, *26*, 2997.

134 K.V. Gothelf and K.A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863.

135 (a) A.P. Kozikowski and M. Adamczyk, *J. Org. Chem.* **1983**, *48*, 366.
(b) A.P. Kozikowski and A.K. Gosh, *J. Am. Chem. Soc.* **1982**, *104*, 5788.

136 A.P. Kozikowski and A.K. Gosh, *J. Org. Chem.* **1984**, *49*, 2762.

137 (a) K.N. Houk, S.R. Moses, Y.-D. Wu, N.G. Rondan, V.Jäger, R. Schohe, and F.R. Fronczek, *J. Am. Chem. Soc.* **1984**, *106*, 3880.
(b) V. Jäger, R. Schohe, *Tetrahedron* **1984**, *40*, 2199.

138 (a) J.A. Stack, T.A. Heffner, S.J. Geib, D.P. Curran, *Tetrahedron* **1993**, *49*, 995.
(b) D.P. Curran, M.-H. Yoon, *Tetrahedron* **1997**, *53*, 1971.
(c) D. P. Curran, K.-S. Jeong, T.A. Heffner, and J. Rebek, Jr., *J. Am. Chem. Soc.* **1989**, *111*, 9238.
(d) D.P. Curran, B.H. Kim, J. Daugherty, and T. A. Heffner, *Tetrahedron Lett.* **1988**, *29*, 3555.

139 W. Oppolzer, A.J. Kingma and S. K. Pillai, *Tetrahedron Lett.* **1991**, *32*, 4893.

140 S. Kanemasa, K. Onimura, *Tetrahedron* **1992**, *48*, 8645.

141 Y.H. Kim, S.H. Kim and D.H. Park, *Tetrahedron Lett.* **1993**, *34*, 6063.

142 H. Waldmann, *Liebigs Ann. Chem.* **1990**, 1013.

143 D.P. Curran, T.A. Heffner, *J. Org. Chem.* **1990**, *55*, 4585.

144 O. Irie, Y. Fujiwara, H. Nemoto, K. Shishido, *Tetrahedron Lett.* **1996**, *37*, 9229.

145 J.P. Visser and P. Smael, *Tetrahedron Lett.* **1973**, 1139.

146 J.R. Al Dulayymi, M.S. Baird, V.A. Palov, and A. I. Kurdjukov, *Tetrahedron Lett.* **1996**, *26*, 8877.

147 I. G. Bolesov, A.V. Ignatchenko, N.V. Bovin, I.A. Prudchenko, L.S. Surmina, V.V. Plemenkov, P.V. Petrovskii, I.V. Romanov, and I.I. Mel'nik, *Zh. Org .Khim.* **1990**, *26*, 102. (*J. Org. Chem. USSR* **1990**, 87).

148 X. Li, Ph.D. Thesis, University of Bangor, **1995**.

149 A. Guarna, A. Brandi, F. De Sarlo, A. Goti, F. Pericciuoli, *J. Org. Chem.* **1988**, *53*, 2426.

150 C. Belle, A. Cardelli and A. Guarna, *Tetrahedron Lett.* **1991**, *32*, 6395.

151 K. Kitatani, T. Hiyama, and H. Nozaki, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3288.

152 (a) G. Köbrich, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 473.
(b)H. Taguchi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.* **1974**, *96*, 3010.

153 K. Kitatani, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1975**, *97*, 949.

154 M.G. Banwell, D.C.R. Hockless, R.W. Longmore and J.M. Walter, *Aust. J. Chem.* **1997**, *50*, 457.

155 M. Borer und M. Neuenschwander, *Helv. Chim. Acta* **1997**, *80*, 2486.

156 For an exhaustive list of references see: L.K. Sydnes, 'Substitution Reactions', pp 1255-1432, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17b*.

157 R. Wolf and E. Steckhan, *J. Electroanal. Chem.* **1981**, *130*, 367.

158 J.R. Al Dulayymi, M.S. Baird, I.G. Bolesov, V.V. Tveresovsky and M.Rubin, *Tetrahedron Lett.* **1996**, *37*, 8933.

159 J. N. Kim and E. K. Ryu, *J. Org. Chem.* **1992**, *57*, 6649.

160 S.K. Armstrong, E.W. Collington and S. Warren, *J. Chem. Soc., Perkin Trans. 1* **1994**, 515.

161 (a) K.N. Houk, S.R. Moses, Y.D. Wu, N.G. Rondan, V. Jäger, R. Schohe, F.R. Fronczek, *J. Am. Chem. Soc.* **1984**, *106*, 3880.
(b) K.E. Larsen, K.B.G. Torsell, *Tetrahedron* **1984**, *17*, 410.

162 A.P. Kozikowski, Y. Kitagawa, J.P. Springer, *J. Chem. Soc., Chem. Commun.* **1983**, 1460.

163 B.H. Kim, Y. J. Chung, G. Keum, J. Kim, K. Kim, Tetrahedron Lett. **1992**, *33*, 6811.

164 R.M. Paton and A.A. Young, *J. Chem. Soc., Perkin Trans. 1* **1997**, 629.

165 D.G. Morris, 'Nuclear magnetic resonance and infrared spectra of cyclopropanes and cyclopropenes', pp 101-172, in *The chemistry of the cyclopropyl group*, Ed. Z. Rappoport; John Wiley & Sons, **1987**.

166 3-(*S*)-[(tert-butyldiphenylsilyl)oxy]-2-butanone, *Org. Synth.* **1992**, *71*, 56.

167 S.K. Massad, L.D. Hawkins, D.C. Baker, *J. Org. Chem.* **1983**, *48*, 5180.

168 P.J. Kocienski, *Protecting Groups*, Thieme Verlag Stuttgart, **1994**.

169 M. Fredrickson, R. Grigg, Z. Rankovic, M. Thorton-Pett, J. Redpath, and R. Crossley, *Tetrahedron* **1995**, *51*, 6835.

170 S. Kanemasa, S. Kobayashi, M. Nishiuchi, H. Yamamoto, and E. Wada, *Tetrahedron Lett.* **1991**, *32*, 6367.

171 S. Kanemasa, M. Nishiuchi, A. Kamimura, and K. Hori, *J. Am. Chem. Soc.* **1994**, *116*, 2314.

172 S. Kanemasa, M. Nishiuchi, and E. Wada, *Tetrahedron Lett.* **1992**, *33*, 1357.

173 Y. Ukaji, K. Sada, and K. Inomata, *Chem. Lett.* **1993**, 1847 and references cited therein.

174 M. Shimizu, Y. Ukaji, and K. Inomata, *Chem. Lett.* **1996**, 455.

175 M.C. Ashraf, T.G. Burrowes and W.R. Jackson, *Aust. J. Chem.* **1976**, *29*, 2643.

176 T.G. Burrowes, W.R. Jackson, S. Faulks and I. Sharp, *Aust. J. Chem.* **1977**, *30*, 1855.

177 M.M. Hansen, C.F. Bertsch, A. R. Harkness, B.E, Huff, D.R. Hutchison, V.V. Khau, M.E. LeTourneau, M.J. Martinelli, J.W. Misner, B.C. Peterson, J.A. Rieck, K.A. Sullivan, and I.G. Wright, *J. Org. Chem.* **1998**, *63*, 775.

178 *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17c.*

179 A. Fadel, B. Karkour, J. Ollivier and J. Salaün, 'Efficient routes to optically active strained compounds', pp 493-494, *in Strain and its Implications in Organic Chemistry*, Ed. A. de Meijere, NATO ASI Series, **1989**, Vol. *273*.

180 L.R. Subramanian and K.-P. Zeller, 'Carbon-Substituted Methylene or Equivalents', pp 2685-308, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a.*

181 (a) O.G. Kulinkovich, S.V. Sviridov, D.A. Vasilevskii, T.S. Prityskaya, *Zh. Org. Khim.* **1989**, *25*, 2244.

(b) O.G. Kulinkovich, S.V. Sviridov, D.A. Vasilevskii, T.S. Prityskaya, *Synthesis* **1991**, 234.

182 A. de Meijere, S.I. Kozhushkov, T. Spaeth, and N.S. Zefirov, *J. Org. Chem.* **1993**, *58*, 502.

183 N. Kurowara and Y. Ohfune, *Tetrahedron Lett.* **1985**, *26*, 83.

184 A. Brandi and A. Goti, *Chem. Rev.* **1998**, *98*, 589.

185 V.V. Tverezovsky, M.S. Baird and I.G. Bolesov, *Tetrahedron* **1997**, *53*, 14773.

186 T. Kikukawa, M. Imaida, and A.Tai, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1954.

187 M.T. Nuñez and V.S. Martin, *J. Org. Chem.* **1990**, *55*, 1928.

188 L. Lepori, B. Koppenhoefer, *J. Phys. Chem.* **1994**, *98*, 6862.

189 F. Weygand und R. Geier, *Chem. Ber.* **1959**, *92*, 2099.

190 A.R. Al Dulayymi, J.R. Al Dulayymi, M.S.Baird, M.E.Gerrard, G. Koza, S.D. Harkins and E. Roberts, *Tetrahedron* **1996**, *52*, 3409.

191 R.M. Southam, M.C. Whiting, *J. Chem. Soc., Perkin Trans. 2* **1982**, 597.

192 J.-L. Fauré, R. Réau, M. W. Wong, R. Koch, C. Wentrup, and G. Bertrand, *J. Am. Chem. Soc.* **1997**, *119*, 2819.

193 W. R. Bowman, J.A.Forshaw, K.P. Hall, J.P. Kitchin, and A.W. Mott, *Tetrahedron* **1996**, *52*, 3961.

194 (a) H. v. Pechmann, L. Seeberger, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2121.
(b) H. v. Pechmann *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 320.

195 P. Wolkoff, *Can. J. Chem.* 1975, *53*, 1333.

196 H.V. Patel, K.A. Vyas, S.P. Pandey, P. S. Fernandes, *Tetrahedron* **1996**, *52*, 661.

197 G. Kaugars, E. Gemrich and V.L. Rizzo, *J. Agr. Food Chem.* **1973**, *21*, 647.

198 Y. Ukaji, K. Taniguchi, K. Sada, and K. Inomata, *Chem. Lett.* **1997**, 547.

199 Y. Yoshida, Y. Ukaji, S. Fujinami, and K. Inomata, *Chem. Lett.* **1998**, 1023.

200 E.V. Koroleva, F.A. Lakhvich, *Russ. Chem. Rev.* **1997**, *66* (1), 27.

201 M.J. Fray and E.J. Thomas, *Tetrahedron* **1984**, *40*, 673.

202 R.E. Ireland and D.W. Norbeck, *J. Org. Chem.* **1985**, *50*, 2198.

203 G. Bianchi, R. Gandolfi and P. Grünanger, *Tetrahedron* **1970**, *26*, 5113.

204 H. Finkelstein, Ber. **1910**, *43*, 1528.

205 D. Ginsburg, '[m.n.1]Propellanes', pp 1193-1222, in *The chemistry of the cyclopropyl group*, Ed. Z. Rappoport; John Wiley & Sons, **1987**.

206 (a) K.B. Wiberg, F.H. Walker, *J. Am. Chem. Soc.* **1982**, *104*, 5239.

(b) R.M. Jarret, L. Cusumano, *Tetrahedron Lett.* **1990**, *31*, 171.

207 K.B. Wiberg, F.H. Walker, W.E. Pratt, J. Michl, *J. Am. Chem. Soc.* **1983**, *105*, 3638.

208 (a) J. Fuchs, G. Szeimies, *Chem. Ber.* **1992**, *125*, 2517.

(b) P.G. Gassman, G.S. Proehl, *J. Am. Chem. Soc.* **1980**, *102*, 6862.

209 D.P.G. Hamon, V.C. Trenerry, J. Michl, *J. Am. Chem. Soc.* **1981**, *103*, 4962.

210 M.Werner, D.S. Stephenson, G. Szeimies, *Liebigs Ann.Org.Bioorg.Chem.* **1996**, 1705.

211 R. Klopsch, A.-D. Schlüter, *Tetrahedron* **1995**, *51*, 10491.

212 A.R. Al Dulayymi, J.R. Al Dulayymi and M.S.Baird, *Tetrahedron Lett.* **1997**, *38*, 6755.

213 Y. Gaoni, A. Tomazic, *J. Org. Chem.,* **1985**, *50*, 2948.

214 B. Zwanenburg and N. De Kimpe, '1,3-Elimination of Two Heteroatoms', pp 33-34, in *Methods of Organic Chemistry* (*Houben-Weyl*), Ed. A. de Meijere, Thieme Verlag, Stuttgart, **1997**, *Vol E17a.*

215 (a) M.S. Baird, *J. Chem. Soc., Chem. Commun.* **1971**, 1145.

(b) M.S. Baird, A.C. Kaura, *J. Chem. Soc., Chem. Commun.* **1976**, 356.

(c) M.S. Baird, *J. Chem. Res.* **1981**, 352.

216 (a) J. Arct and L. Skattebøl, *Acta Chem. Scand., Ser. B* **1982**, *36*, 593.

(b) L. Skattebøl, N.O. Nilsen, F. Myhren, *Acta Chem. Scand., Ser. B* **1986**, *40*, 782.

(c) L. Skattebøl, Y. Stenstrøm and M.-B. Stjerna, *Acta Chem. Scand., Ser. B* **1988**, *42*, 475.

217 I.G. Bolesov, V.V. Tverezovsky, Y.K. Grishin, *Zh. Org. Khim* **1997**, *33* (1), 135.

218 M.S. Baird, F.A.M. Huber, V.V. Tverezovsky and I.G. Bolesov, *Tetrahedron Lett.* **1998**, *39*, 9081.

219 V.V. Tverezovsky, personal communication.

220 Yehiel Gaoni, *J. Org. Chem.* **1982**, 2564.

221 B.M. Trost and P.L. Ornstein, *J. Org. Chem.* **1982**, *47*, 748.

222 (a) M.S. Baird and A.G.W. Baxter, *J. Chem. Soc., Perkin Trans. 1* **1979**, 2317.

(b) L.K. Sydnes, *Acta Chem. Scand., Ser. B* **1977**, *31*, 823.

223 M.S. Baird, M.E. Gerrard and R.J.G. Searle, *Tetrahedron Lett.* **1985**, 6353.

224 R. Menicagli, C. Malanga, M. Dell'Innocenti, and L. Lardicci, *J.Org. Chem.* **1987**, *52*, 5700.

225 U.H. Brinker, personal communication.

226 P.A. Procopiou, S.P.D. Baugh, S.S. Flack and G.G.A. Inglis, *J. Chem. Soc., Chem. Commun.* **1996**, 2625.

227 C. Berrier, B. Bonnaud, J.F. Patoiseau, D. Bigg, *Tetrahedron* **1991**, *47*, 9629.

228 (a) R.N. McDonald, R.R. Reitz, *J.Org.Chem.* **1972**, *37*, 2418.

(b) T. Saegusa,. *J.Org.Chem.* **1973**, 38, 2319.

229 B.M. Trost and P.L. Ornstein, *J. Org. Chem.* **1983**, *48*, 1131.

230 Y. Li and T.J. Marks, *J. Am. Chem. Soc.* **1996**, *118*, 9295.

231 K.S. Feldman and D.A. Mareska, *Tetrahedron Lett.* **1998**, *39*, 4781.

232 A.R. Al Dulayymi, M.S. Baird, and W. Clegg, *Tetrahedron Lett.* **1997**, *38*, 8271.

233 T.C. Shields, W.E. Billups, A.R. Lepley, *J. Am. Chem. Soc.* **1968**, *90*, 4749.

234 (a) J.C. Gilbert, J.R. Butler, *J. Am. Chem. Soc.* **1970**, *92*, 2168.

(b) J.C. Gilbert and D.P. Higley, *Tetrahedron Lett.* **1973**, *23*, 2075.

235 W.E. Billups, K.H. Leavell, E.S. Lewis, and S. Vanderpool, *J. Am. Chem. Soc.* **1973**, *95*, 8096.

236 Y. Inoue, T. Hibi, M. Satake, Y. Kawashima, H.Hashimoto, *Chemical Abstracts* **1982**, *96*, 720.

237 P. Binger, A. Germer, *Chem.Ber.* **1981**, *114*, 3325.

238 M.M. Kabat, J. Wicha, *Tetrahedron Lett.* **1991**, *32*, 4531.

239 J.T. Pechacek, T.M. Bargar, and M.R. Sabol, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2665.

240 S. Arora, P. Binger, *Synthesis*, **1974**, 801.

241 J.J. Bahl, R.B. Bates, W.A. Beavers, and N.S. Mills, *J. Org. Chem.* **1976**, *41*, 1620.

242 E.W. Thomas, *Tetrahedron Lett.* **1983**, *24*, 1467.

243 (a) W.B. Smith, S. Biesemeier, and D.L. Deavenport, *J. Org. Chem.* **1971**, *36*, 2853.

(b) J. Besancon, S. Top, J. Organomet. Chem. **1977**, *127*, 139.

244 K. Imafuku, K. Arai, *Synthesis* **1989**, 501.

245 G. Kresze und H.Goetz, *Chem. Ber.* **1957**, *90*, 2161.

246 K. Hafner, K. H. Häfner, C. König, M. Kreuder, G. Ploss, G. Schulz, E. Sturm and K.H. Vöpel, *Angew. Chem. internat. Edit.* **1963**, *2*, 123.

247 D.D. Perrin, W.L.F. Armarego and D.R. Perrin. "Purification of Laboratory Chemicals", Pergamon Press, Oxford, 3rd edition **1988**.

248 C. Grundmann, J.M. Dean. *J.Org. Chem.* **1965**, *30*, 2809.

249 M.S. Baird, H.H. Hussain, W. Nethercott, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1845.

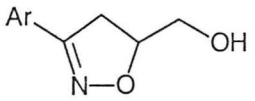
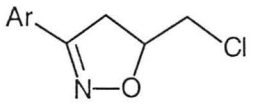
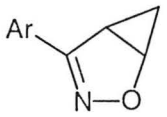
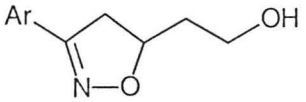
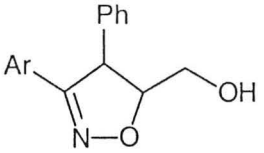
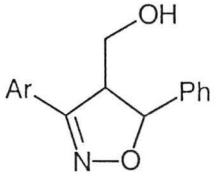
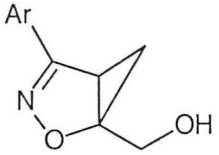
250 M.S. Baird, H.H. Hussain, *J. Chem. Res. Miniprint*, **1985**, 2061.

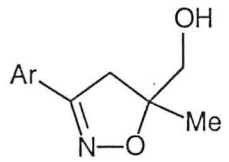
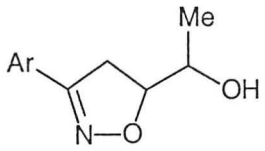
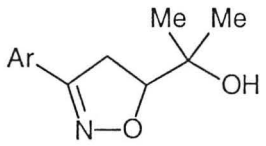
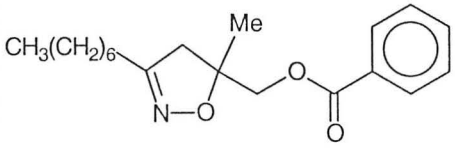
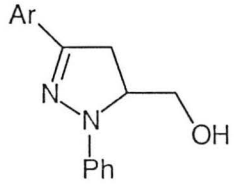
251 J.R. Al Dulayymi, M.S. Baird, M.J. Simpson, S. Nyman, G.R. Port, *Tetrahedron* **1996**, *52*, 12509.

252 D. Seyferth,V.A. Mai, J.Y.-P. Mui, and K.V. Darragh, *J.Org.Chem.* **1966**, *31*, 4079.

8. Appendix

Table 17. HPLC retention times of various heterocyclic compounds.

entry	compound	solvent mixture 2-propanol in *n*-hexane	t_R (min)
1	 **152**	10 %	25.5, 30
2	 **153**	5 %	21, 27.5
3	 **154**	10 %	14, 16
4	 **168**	10 %	37, 49.5
5	 **170**  **171**	5 %	36, 44 and 47, 49.5
6	 **173**	10 %	26, 35

entry	compound	solvent mixture 2-propanol in *n*-hexane	t_R (min)
7	 **166**	10 %	18, 24
8	 **179a**	10 %	19.5, 21; 25.5, 27
9	 **181**	10 %	16.5, 21.5
10	 **183**	2 %	11, 13.5
11	 **190**	10 %	18.5, 21.5