ASYMMETRIC INDUCTION IN 1,3-DIPOLAR CYCLOADDITION USING CHIRAL NITRONES

BY

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ABSTRACT

NAME: Basem Abdel Hamid Moosa
TITLE: Asymmetric Induction In 1,3-Dipolar Cycloaddition Using Chiral Nitrones

MAJOR: Chemistry
DATE: 2010

This thesis describes the development of methods for the preparation of chiral racemic substituted cyclic and a cyclic nitrones. This has been accomplished by the following points.

In chapter 3, the diastereoselectivity in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)norephedrine-derived methylenenitrone has been investigated. The stereochemical analysis of the addition products (i.e. isoxazolidines) has been carried out by X-ray, NMR and chemical conversions. The NMR spectra of the isoxazolidines at low temperatures indicated the presence of either a single or a predominant invertomer. The stereochemistry of the invertomers and nitrogen inversion barriers are determined using complete line-shape analysis and their dependence on solvent is discussed.

In chapter 4, a study of the stereo- and face-selectivity of the cycloaddition reactions of several mono- and disubstituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide has been carried out. The addition reactions have displayed a very high degree of face selectivity (13-48:1). Use of dimethyl methylenemalonate as a protective group in nitrone cycloaddition reactions has been demonstrated. The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer which leads to the formation of synthetically important second-generation cyclic aldonitrones via peracid oxidation. One interesting finding was that treatment of the cycloadducts with two equivalents of peracid afforded the cyclic N-hydroxy lactams, presumably via further oxidation of the aldonitrones. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

In chapter 5, the cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be
highly stereo- as well as face-selective. In solution, the 6/5 fused bicyclic cycloadducts remain solely as the cis-fused invertomers in order to accommodate the bulky tertiary substituent 2-hydroxy-2-propyl in the equatorial orientation. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones. The stereo- and face-selectivity of the cycloaddition reactions of these second-generation nitrones bearing substituents at C(4) and C(6) have been briefly examined.

In chapter 6, One interesting finding was that treatment of the first generation nitrone i.e., 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide or 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide, with mercury(II) oxide afforded novel bicyclic nitrones, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxides, whose cycloaddition reactions were briefly examined.

In chapter 7, the cycloaddition reaction of 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide with butyl vinyl ether was used as a key step in the short stereoselective racemic synthesis of ladybird beetle alkaloid 2-epicalvine. The cycloadduct on quartenization with 2-bromoethanol followed by ring opening and lactonization afforded the natural product in a single pot reaction.
هذه الدراسة تصف عدة طرق لتحضير مركبات الجيل الثاني من الأنثوديترونتنات الحلقية (Chiral) ذات المزيج الراسمي (Racemic) بواسطة الفوق أسيد (Racemic) للنواتن. 

1- دراسة الانهائية الوجيه و الانتقائية الفرعية لتفاعلات الأضلاع الحلقيات المتنوعة لمجموعة من المركبات أحادية و ثنائية الألكينات بواسطة النتروين الميليكي مشتق المورفين. 

2- دراسة الانتماء الوجيه والانتقائية الفرعية لتفاعلات الأضلاع الحلقيات المتنوعة لمجموعة من الألكينات الأحادية والثنائية مع تأكيد أظهرت تفاعلات الانتماء كثيفة بشكل دائم على هيئة الشكل (cis- isomer). 

3- دراسة تفاعلات الأضلاع الحلقيات لمركب (2-heptadecyl-4,3,6,5,4,3 dibromide - 2). أوكسيد أظهرت تفاعلات الأضلاع كثيفة بشكل دائم على هيئة الشكل (cis-fused invertomers) اللاموجة الأردة المفتوحة على هيئة الشكل (tertiary substituent). 

4- دراسة الانتماء الوجيه والانتقائية الفرعية لتفاعلات الأضلاع الحلقيات المتنوعة لمجموعة من المركبات أحادية والثنائية. 

5- دراسة مركبات الدهون المدرجة في الفلستك. 

ABBREVIATION
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D$</td>
<td>Specific rotation at $\lambda = 599.6$ nm</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>CI</td>
<td>Chair Inversion</td>
</tr>
<tr>
<td>CM</td>
<td>Cross Metathesis</td>
</tr>
<tr>
<td>CN(R,S)</td>
<td>Chiral Ncyanomethyloxazolidine</td>
</tr>
<tr>
<td>DC</td>
<td>dipolar cycloaddition</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethyl AminoPyridine</td>
</tr>
<tr>
<td>DMD</td>
<td>Dimethylidioxirane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium DiisopropylAmide</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>m.p</td>
<td>Melting point</td>
</tr>
<tr>
<td>$m/z$</td>
<td>Mass- to- charge ratio</td>
</tr>
<tr>
<td>MCPBA</td>
<td>m-Chloroperbenzoic Acid</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NI</td>
<td>Nitrogen Inversion</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
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</table>

XXIII
<table>
<thead>
<tr>
<th>Abbreviation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Part per million</td>
</tr>
<tr>
<td>p-tosic acid</td>
<td>p-toluene sulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
<tr>
<td>tRNA</td>
<td>Transfer Ribonucleic Acid</td>
</tr>
<tr>
<td>$\Delta G^#$</td>
<td>Free energy of activation</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Chemical Shift</td>
</tr>
</tbody>
</table>
CHAPTER 1

1.1 Introduction

The 1,3-dipolar cycloaddition (DC) is a reaction where two organic compounds, a dipolarophile, 1, and a 1,3-dipole (or ylide), 2, combine to form a five membered heterocycle 3 (Scheme 1). The reaction is related to Diels- Alder reaction where a diene and a dienophile form a six membered ring. From simple starting materials, the 1,3-dipolar cycloaddition reaction can furnish very complex heterocycles, containing multiple stereogenic centers. Therefore, this reaction is often used as a key step in the syntheses of many natural products and pharmaceuticals. After its discovery in 1888, with diazoacetic ester as the 1,3- dipole, various other 1,3-dipoles have been used in this type of reaction. [1, 2].

![Scheme 1](image)

The 1,3-dipole, also known as an ylide, bears a positive and a negative charge distributed over three atoms and has $4\pi$ electrons. The most common atoms incorporated in the 1,3-dipole are nitrogen, carbon, oxygen or sulfur. Representative examples of some 1,3-dipoles are shown in (Scheme 2) [2], These are devided into two groups; the allyl anion type which has a bent structure and the propargyl/allenyl anion type with a linear structure. Each of these dipoles has four resonance structures as exemplified for the nitrone. The ylide can, depending on the nature of the 1,3-dipole, exist in an equilibrium.
between an $E$-form and a $Z$-form. This can have consequences for the diastereoselectivity in reactions with dipolarophiles

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing $2\pi$ electrons. Like, $\alpha,\beta$- unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily (Scheme 3). It must be noted, however, that other $2\pi$- moieties such as carbonyls and imines also can undergo cycloaddition with dipoles. The alkene moiety can be mono-, di-, tri- or even tetrasubstituted (only monosubstituted ones are shown here). However, mostly due to steric factors, tri- and tetrasubstituted ones often display very low reactivity in reactions with dipoles [3].
1.2 Mechanism of DC

The 1,3-dipolar cycloaddition reaction of a 1,3-dipole with a dipolarophiles involves an interaction between the $4\pi$ electrons of the dipole/ylide and the $2\pi$ electrons of the dipolarophiles. The reaction mostly proceeds in a concerted manner, which means that all bonds are created simultaneously, but not necessarily to the same extent at a certain time. Consequently, the stereochemistry of the dipolarophile is conserved in the final product. This is exemplified in (Scheme 4), where trans-2-butene (8) reacts with the hypothetical dipole furnishing exclusively trans-product. Starting from the cis isomer of butene (8) will thus yield the cis isomer product [4].
If, on the other hand, the reaction proceeds *via* a two-step mechanism, the stereochemistry of the starting dipolarophile is not necessarily conserved throughout the whole reaction. This is exemplified in (Scheme 4), where trans-2- butene (8) reacts with the dipole in a two-step fashion furnishing the diastereomer cis-9 via isomerisation of the starting dipolarophile.

Depending on the nature of the dipole and the dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a LUMO (dipolarophile)- HOMO (dipole)- or a LUMO (dipole)-HOMO (dipolarophile) interaction but in some cases a combination of both interactions is involved. An example of a LUMO (dipolarophile)-HOMO (dipole) controlled reaction is depicted in Scheme 5. The approach of the dipole (e.g. 10) to the dipolarophile (e.g. 11) can occur in an *endo* or *exo* mode resulting in two diastereomeric
endo/exo cycloadducts, endo-12 and exo-12, respectively. An overview over both these approaches is depicted in (Scheme 5) where the endo approach is stabilised by small secondary π-orbital interactions, contributing to the endo/exo selectivity of the reaction [5].

![Scheme 5](image)

However, other factors such as steric ones can have a major influence on this endo/exo selectivity and can often override this stabilizing effect. Moreover, depending on the substitution pattern of the ylide, this can exist in equilibrium between a Z-form and an
E-form. Reaction of each of these isomers with a dipolarophile, gives rise to
diastereomeric cycloadducts, provided that the approach of these (endo or exo) is the same.
This is exemplified in Scheme 6 where ylides $E$-13 and $Z$-13 react with the dipolarophile
11 via an exo-approach furnishing diastereomeric cycloadducts $trans$-$14$ and $cis$-$14$
respectively. The $cis/trans$ nomenclature for the description of the stereochemistry of the
cycloadducts is thus often used instead of the $exo/endo$ one to avoid confusion when ylides
existing as an equilibrating mixture of $Z/E$ isomers are used [6-10].

![Scheme 6.](image)

1.3 Nitrones

1,3-Dipolar cycloaddition reactions offer one of the most versatile synthetic routes
to five-membered heterocycles, and the reactions of nitrone dipoles play an important part
in the history of cycloaddition reactions. These particular dipolar cycloaddition reactions can be considered as concerted but asynchronous \( [4\pi - 2\pi] \) suprafacial processes and the reactions allow creation of up to three contiguous carbon stereocentres in a single step. In any nitrone–alkene cycloaddition reaction, two pairs of regioisomeric and diastereoisomeric products can result and these arise from the nitrone and alkene approaching each other in either of two regiochemical senses, and in either an endo- or an exo-fashion Scheme 5. Therefore, much effort has focussed on the development of regioselective and stereoselective nitrone–alkene cycloaddition reactions [9-11]. Nitrones have been used in numerous studies of asymmetric 1,3-dipolar cycloadditions. In general, nitrones are relatively stable species and do not need to be prepared in situ. Nitrones could be generated or prepared by two main methods (Oxidative and non-oxidative methods).

1.3.1. Oxidative Methods

1.3.1.1 Oxidation of imines

Oxidation of imines leads to oxaziridines which can be rearranged to nitrones. Different types of oxidant could be used in this type of reaction such as MCPBA (m-chloroperbenzoic acid), Oxone (potassiumperoxymonosulfate), DMD (dimethyldioxirane), methyl (trifluoromethyl) dioxirane and peroxides like hydrogen peroxide and tert-butyldihydroperoxide. Oxidation of 3,4-dihydroisoquinoline (15) with Oxone initially leads to the formation of oxaziridine (16) which is easily transformed into the corresponding 3,4 dihydroisoquinoline N-oxide (17) upon treatment with catalytic amounts of p-toluenesulfonic acid (Scheme 7) [20-24].
1.3.1.2 Oxidation of amines

Oxidation of secondary amines into nitrones has been extensively studied and a variety of well-known efficient oxidants and catalysts which can be employed in this process are available. Catalytic oxidation by hydrogen peroxide at room temperature is carried out by using sodium tungstate (Scheme 8).

C-Phenyl-N-phenylsulfonyloxaziridine (19) (Davis reagent) is also used as an oxaziridine type oxidant. The use of this reagent in oxidation of diazepine (18), give the corresponding nitrones (21) in quantitative yields (Scheme 9) [25-32].
1.3.1.3 Oxidation of hydroxylamines

The mildest oxidation method of nitrone formation seems to be *via* oxidation of the corresponding hydroxylamines (22) containing one or more protons at α-C. In this reaction, air, H₂O₂, MCPBA, oxides of different metals (MnO₂, PbO₂, HgO, Ni₂O₃, etc.) can be used as oxidants. The resulting nitroxyl radicals (23) undergo a disproportionation reaction (Scheme 10), and with an excess of the oxidant, give nitrones (24) as the reaction products [33,34].

In a mechanistic study of oxidation of N-benzyl-N-alkyl hydroxylamines, with HgO and p-benzoquinone, it has been proposed on the basis of intra- and intermolecular
kinetic isotope effects that, initially, there takes place a one-electron transfer from a nitrogen atom to the oxidant, with a subsequent proton abstraction. Oxidation of cyclic and acyclic hydroxylamines with yellow mercuric oxide appears to proceed with high regioselectivity. Regioselectivity is determined by the electronic nature of the substituents. The oxidative regioselectivity of MnO$_2$ is comparable to that of HgO, but due to its lower toxicity, it has been proposed to use MnO$_2$ rather than HgO.

**1.3.1.4 Oxidation of bicyclic isoxazolidines**

Oxidative ring opening of isoxazolidines leads to nitrones. Thus, bicyclic isoxazolidines (25) and (26), treated with MCPBA, afford nitrones (27), (28), (29), and (30) (Scheme 11). Conformational analysis has confirmed the key role of the nitrogen lone pair with respect to regioselectivity of the reaction and of the intramolecular kinetic deprotonation of the intermediate oxoammonium derivative. Similar oxidative ring opening occurs in other bi- and tricyclic isoxazolidines upon treatment with MCPBA [35,36].

![Scheme 11](image)
1.3.2 Non-Oxidative Methods

1.3.2.1 Condensation of secondary hydroxylamines with carbonyl compounds

Condensation of N-monosubstituted hydroxylamines with carbonyl compounds is used as a direct synthesis of many acyclic nitrones. The condensation is carried out under mild conditions; this allows the synthesis of various nitrones to proceed without affecting functional groups. Thus, condensation of various aromatic, heteroaromatic, and aliphatic aldehydes with alkylhydroxylamines makes it possible to synthesize a variety of N-alkynitrones [37-39].

The main building block of PEDC (33) (1-phenyl-2-[(S)-1-aminoethyl]-N,N -diethylcyclopropanecarboxamide), a potent NDMA (N-methyl-D-aspartic acid) receptor antagonist of a cyclopropane structure, N-benzyl-C-cyclopropyl nitrone(32) was generated in quantitative yield by condensation of asymmetric cyclopropylcarbaldehyde (31) with N-benzylhydroxylamine hydrochloride in CH₂Cl₂ (Scheme 12) [40,41].

![Scheme 12.](image)

The synthesis of optically active nitrones (36) was carried out by an aldol reaction of aldehydes (34), catalyzed by L- proline, with carbonyl activated compounds (35) and by an in situ reaction with N-alkylhydroxylamines (Scheme 13), (Table 1) [42].
Table 1. Formation of optically active functionalized β-hydroxy-nitrones 36 by reaction of aldehydes 34 with activated carbonyl compounds 35 and substituted N-alkyl hydroxylamine hydrochloride in the presence of L-proline as the catalyst.

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>CO₂Et</td>
<td>Bu</td>
<td>95</td>
<td>77</td>
</tr>
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<td>Et</td>
<td>CO₂Et</td>
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</tr>
<tr>
<td>i-Pr</td>
<td>CO₂Et</td>
<td>Bn</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Allyl</td>
<td>CO₂Et</td>
<td>Bu</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td>Me</td>
<td>CF₃</td>
<td>Bu</td>
<td>95</td>
<td>91</td>
</tr>
</tbody>
</table>
1.3.2.2 Synthesis from oximes

Alkylation of oximes at the nitrogen atom with various reagents seems to be one of the easiest and convenient methods for synthesizing nitrones. The significant advantage of this method is that there is no need to use oxidants. Electron poor alkenes, resulting from the activation of electron-accepting groups and action of electrophiles or metal ions as catalysts, are used as the most available alkylating agents. The reaction known as Grigg's nitrone formation, involving formal Michael addition is widely used. In most cases, the resulting nitrones quickly enter into a specific 1,3-cycloaddition reaction. Similar transformations are observed in the reactions of oximes with alkynes. Therefore, Grigg's reaction, which seems very effective in using the sequence of oxime-nitrone-products and 1,3-dipolar cycloaddition, can hardly be considered as an overall synthetic approach to nitrones [43-47]. However, under certain conditions, the resulting nitrones can be isolated. Thus, the reaction of indol-oxime (37) with methyl acrylate, methyl vinyl ketone, acrylonitrile, and acrylamide gives indol-nitrones (38) (Scheme 14).

\[ \text{R} = \text{a) COOCH}_3, \text{ b) COCH}_3, \text{ c) CN, d) CONH}_2 \]

Scheme 14.
Bromocyclization of $\gamma,\delta$-unsaturated oximes (39) affords the corresponding bromomethylpyrrolidine-N-oxides (40) (Scheme 15). Reversal of steps, that is addition of Br/OH to the C=C bond of the unsaturated aldehyde (41) first, followed by oximation, opens access to six-membered nitrones (43) (Scheme 16) [48].

![Scheme 15.](image)

1.3.2.3 Synthesis from nitro compounds

Nitrones can be obtained in good yields from the addition of benzyl and allyl Grignard reagents to aryl- and alkyl nitro compounds. This reaction proceeds chemoselectively; carbonyl groups and other reactive electrophilic groups are not affected by the reaction conditions. Double bond stereochemistry is determined by the nature of the
employed Grignard reagent. Benzylmagnesium halides give exclusively Z-isomers of nitrones (47) and (48), whereas 2-butenylmagnesium chloride gives nonconjugated Z-nitrones with the predominance of E-isomers in the conjugated nitrone (174) (Scheme17) [49-51].

1.4 Asymmetric induction in nitrone cycloaddition

Asymmetric Induction describes the preferential formation in a chemical reaction of one enantiomer or diastereomer over the other as a result of the influence of a chiral feature present in the substrate, reagent, and catalyst. The addition of a nitrone to an alkene or alkyne is a prominent transformation in organic synthesis. Over the past two decades the intense study of enantioselective 1,3-dipolar cycloaddition methodologies has provided organic chemists with the tools necessary to synthesize a variety of chiral heterocycles in highly enantio-enriched forms. Over the years a variety of chiral Lewis acids have been
evaluated for dipolar cycloadditions. The most successful of these have employed copper, silver, nickel, aluminum, zinc, and lanthanide Lewis acids, generally in combination with one of the privileged classes of chiral ligands such as the bisoxazolines, BINAPs, and Pyboxs. Chiral copper(I) and (II) salts figure prominently in the development of enantioselective 1,3-dipolar cycloaddition reactions (Scheme 18) [52-54].

All of the enantioselective reactions described so far have involved catalysts composed of enantiomerically pure ligands coordinated to various metal-salts. Those catalysts often have to be used under dry conditions under an inert atmosphere. A more easily managed, metal-free catalyst gives operational and economical advantages over the ones containing metals. Therefore, organocatalysis has become a very active research field at present. Organocatalysts are often low molecular weight compounds readily available from inexpensive starting materials. They can in general be reused in a convenient manner. Because organocatalysts do not contain any heavy metals, they are, in general, more environmentally friendly than most chiral Lewis acid catalysts. Moreover, organocatalysed reactions can often be conducted under air and even in wet solvents [55,56].
A milestone in the field of organocatalysis is the development of the enantioselective Robinson annulation of triketones of type 58 catalysed by proline (Scheme 19). Thus, in the presence of this naturally occurring amino acid (i.e. proline), such triketones undergo Robinson annulation to give chiral nonracemic bicycles 59, which, after dehydration, furnish compounds of type 60. This approach has opened a new route for enantioselective syntheses of steroids and other natural products such as taxol [57,58].
Since the discovery of the proline catalyzed Robinson annulation reaction discussed above, organocatalysis has become a rapidly growing research area in organic chemistry. In the field of 1,3-dipolar cycloaddition reactions, MacMillan et al. have been the first to explore organocatalysis. They have developed a general protocol for the enantioselective syntheses of isoxazolidines from nitrones of type 61 and \(\alpha,\beta\)-unsaturated aldehydes 62 catalysed by the phenylalanine derived organocatalyst (Scheme 20) [59,60].

Scheme 20.

1.5 Application of nitrone cycloaddition reaction

The impact of dipolar cycloaddition reactions in the area of heterocyclic synthesis is in many ways comparable to that of Diels–Alder reactions on carbocyclic synthesis. In fact, the availability of various classes of dipoles and dipolarophiles has allowed a greater
degree of versatility. The discovery of new dipolar species was followed by applications of their reactions in targeted syntheses. Even though all dipolar cycloaddition reactions are, in principle, closely related processes, their applications are seldom discussed together in the chemical literature. The main reason for this anomaly is the vast variety of heterocyclic systems produced in such reactions. Discussions on heterocyclic synthesis generally follow a product-class-based approach. Although convenient, such an approach fails to address the underlying similarities of the various processes involved. There has been no concerted attempt to categorize various dipolar cycloadditions used in the synthesis of natural products, apart from an excellent book edited by Padwa. Because the total syntheses of various natural products and other bioactive substances via asymmetric 1,3-dipolar cycloaddition reactions of nitrones are numerous, only a few examples will be presented here [61-63].

![Image of chemical structures](image)

**Figure 1.**

Caprio et. al. synthesized trans-2-Substituted-3-hydroxypiperidines to form the core structure of a diverse range of alkaloids of biological interest, such as the antimalarial alkaloid (+)-febrifugine *via* nitrene cycloaddition of (S)-3-benzyloxy-3,4,5,6-tetrahydropyridine N-oxide from L-glutamic acid (Scheme 21) [64].
Isoxazolidines are structural key moieties in many bioactive substances and herbicides. Because they are also easily ring opened to the corresponding aminoalcohols, they can serve as attractive building blocks for the construction of other natural products and bioactive substances. Isoxazolidines are also building blocks for the preparation of chiral ligands which are used in enantioselective transformations [60-63].

N-O bond cleavage in isoxazolidines is a very important reaction as it can be transformed to many intermediates which are useful in several total syntheses. Three

Scheme 21. Reagent and condition: (i) PhMe, reflux, 24 h, 67 48%, 68 18%; (ii) Zn, HOAc, reflux, 5 h, 53%; (iii) BOC₂O, Et₃N, CH₂Cl₂, 20 h, 80%; (iv) Dess-Martin periodinane, pyridine, CH₂Cl₂, 2 h, quant.; (v) 6 M HCl(aq), reflux, 40 min, 67%.
different reactions for N-O bond cleavage are mentioned in the literature. The first reaction is the normal reduction using any reducing agent such as Zn/HOAc, LiAlH₄ (Scheme 21) [64]. The second reaction is MCBPA ring opening to produce the second generation of nitrones (Scheme 11) [35, 36]. The last reaction is a quaternization of the isoxazolidines by means of any alkyl halides (Scheme 22). The importance of these three reactions is its application in synthesis by the liberation of the masked functionality in the resulting isoxazolidines [65].

![Scheme 22](image_url)
CHAPTER 2

2.1 Literature Review

Nitrones are very useful tools in the construction of structurally complex molecules and particularly biologically active nitrogen-containing compounds. The cyclic nitrones, in the absence of $E \leftrightarrow Z$ isomerization enjoy a higher degree of stereoselectivity in compare to its acyclic counterpart. Various types of methods in the literature described the preparation of cyclic nitrones, including the oxidation of cyclic amines, hydroxylamines, imines, intramolecular condensation of $\omega$-hydroxylaminocarbonyl derivatives, and cyclization of $\omega$-unsaturated oximes.²

Six-membered cyclic nitrones are considered as an attractive building block for a natural product synthesis. The natural product SB-219383, isolated from a Micromonospora sp. NCIMB 40684, is a potent and selective inhibitor of bacterial tyrosyl tRNA synthetase (YRS) and as such is a potential lead for new antibacterial agents. SB-219383 contains a unique bicyclic hydroxyamino sugar moiety (Figure 2).

![Figure 2.](image-url)
Both indolizidine and quinolizidine alkaloids [66] contain the piperidine ring, this is why it's very useful to start with this type of ring as a starting material. Many studies have been done on a substituted 3,4,5,6-tetrahydropyridine 1-oxide. So, it's worth to mention some of these studies according to the pattern of substitution on the ring.

### 2.1.1 2-Substituted tetrahydropyridine N-oxide

Extensive works on this class of nitrone were mentioned in the literature. Nitrone 76 is prepared by an oxidation of the corresponding amine (75) in presence of a tungsten catalyst (Scheme 23) [67-69].

![Scheme 23](image)

Some of these nitrones (78, 79) are generated by peracid induced ring opening of the cycloaddition products (77) (Scheme 24) [17].

![Scheme 24](image)
2.1.2 3-Substituted tetrahydropyridine N-oxide

Substitution at C-3 of the tetrahydropyridine N-oxide has been mentioned in the literature [25]. Nitrone (81) is prepared by an oxidation of corresponding hydroxylamine (Scheme 25). Different types of substitution products on the ring have been synthesized and a cycloaddition reaction was done to examine the regio- and stereoselectivity of the adducts (83-85) [70-72].

\[
\text{Scheme 25.}
\]

2.1.3 4-Substituted tetrahydropyridine N-oxide

Only two studies on six-membered nitrone containing a substituent farthest from the nitrone moiety, i.e., at the C(4) position have been reported [73,74]. The recent study reports the kinetic and stereoselectivity of the addition reaction of a C(4)-substituted cyclic nitrone (86) with various alkenes.
2.1.4 5-Substituted tetrahydropyridine N-oxide

Also, few studies on six-membered nitrones (88, 89) containing a substituent at the C(5) position have been reported [75].

2.1.5 6-Substituted tetrahydropyridine N-oxide

Cycloaddition reactions involving 6-substituted 3,4,5,6-tetrahydropyridine 1-oxides (90-92) and alkenes are reported to give single cycloadducts in a regio-, face-, and stereo-selective manner [76,77].
There have been much interest in the asymmetric synthesis of isoxazolidines using 1,3-dipolar cycloaddition reaction. Intermolecular nitrone olefin cycloaddition reactions leading to optically active isoxazolidines have been carried out by several workers using chiral starting material (nitrone or alkene or both) and by metal-catalyzed reactions. Several groups have also reported a reaction of alkenyl nitrone leading to optically active products (Schemes 8-11).

Nitrones (93), bearing 1-phenylethyl substituent at the nitrogen atom and with different substituents at the carbon atom, have been subjected to 1,3-DC reactions with styrene (94) [33b,c]. The reactions proceed to give a mixture of the exo and endo isomers in ratios between 68:32 to 87:13 Scheme 26.

The chiral group can be located at the carbon atom. Brandi et al, have studied the nitrone cycloaddition of chiral α,β-dialkoxy nitrones (95) with vinylphosphine oxide (96a,b). The reaction of (96a) gave a 65:14 mixture of the endo: exo isomers. The endo isomer was formed with a high diastereofacial selectivity of 94% de. However, the reaction with (96b) proceeded to form (97b) with a high degree of endo selectivity with diastereofacial selectivity of 96% de (Scheme 27) [78].
Kanemasa et al. [79] studied the reaction of allylic alcohols with nitrones in the presence of Mg(II) salts, ZnBr$_2$, TiCl$_2$(OiPr)$_2$, or BF$_3$.Et$_2$O. The reaction of the following nitrone (97) with allyl alcohol afforded the cis and trans isomers in a ratio of 44:56. In the presence of 1 equiv MgBr$_2$.Et$_2$O the cis isomer (98) is obtained as the sole product (Scheme 28). In recent years, the asymmetric nitrene cycloaddition reactions involving the intramolecularly H-bonded nitrene (Scheme 29) is receiving increasing attention owing to its efficacy in transferring chirality to the newly created stereocenter at C(4) and C(5) of the cycloadducts isoxazolidines [79].

Scheme 27.
Scheme 28.

Scheme 29.
2.2. Objectives

After examining the precedent literature on DC, the objectives of the proposed study were outlined under (i)-(ix).

i) Synthesis and stereochemical analysis of some norephedrine-derived isoxazolidines (Scheme 30).

![Scheme 30.]

ii) Synthesis of 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide (107) and its stereochemistry of cycloaddition to various alkenes (Scheme 31).

![Scheme 31.]

iii) Synthesis of novel bicyclic nitron (111) and its stereochemistry of cycloaddition to various alkenes (Scheme 32).
iv) Study of conformational equilibria in cycloaddition product isoxazolidines (113) to shed light on the composition of peracid induced ring opening to obtain second generation aldo-(115) and keto-nitrones (116) (Scheme 33).
v) Stereochemistry of cycloaddition of second generation aldonitrones (115) to various alkenes (Scheme 34).

vi) Conversion of tricyclic adducts (112) to bicyclic adduct (108) to investigate the possible reversal of stereochemistry in the addition of the mono-(109) and bicyclic nitrone (111) (Scheme 35).
vii) Study the effect of the bulkier tertiary substituent at C(4) on the *cis-trans* ratio of the cycloadducts and second-generation aldonitrones *via* peracid induced ring opening of the cycloadducts (Scheme 36).

![Scheme 36.](image)

viii) Due to the high stereoselectivity of the cycloaddition reaction, and as an application in the synthesis of natural product, the total synthesis of epi-calvine (123) will be attempted using the reaction scheme as outlined (Scheme 37).

![Scheme 37.](image)

ix) Use of $^1$H, $^{13}$C NMR spectroscopy, elemental analyses, mass spectrometry, and X-ray crystallography to characterize the synthetic products.
CHAPTER 3

Synthesis and stereochemical analysis of some norephedrine-derived isoxazolidines

Summary:

The diastereoselectivity in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)-norephedrine-derived methylenenitrone has been investigated. The stereochemical analysis of the addition products (i.e. isoxazolidines) has been carried out by X-ray, NMR and chemical conversions. The NMR spectra of the isoxazolidines at low temperatures indicated the presence of either a single or a predominant invertomer. The stereochemistry of the invertomers and nitrogen inversion barriers are determined using complete line-shape analysis and their dependence on solvent is discussed.

3.1 Introduction

1,3-Dipolar cycloaddition reaction of nitrones is the best chemical template for the construction of isoxazolidine ring; efficient incorporation of multiple stereocentres makes it an efficient key step in the synthesis of a great many natural products of biological interest [2]. In recent years, focus has been shifted towards asymmetric nitrone cycloaddition reactions, the efficiency of which very much depends on the ability of the chiral auxiliary to effectively transfer chirality to the newly created stereocenters [2]. Even though the nitrone cycloaddition reactions of C,N-disubstituted nitrones have been studied in great detail [2], the chemistry of chiral (or even achiral) N-substituted nitrones (i.e. methylenenitrones) has only been investigated to a limited extent [80]. Here we report, for
the first time, the stereochemical features associated with the cycloaddition of a norephedrine-derived chiral methylenenitrole 124 (Scheme 38) with several mono- and 1,1-disubstituted alkenes. The study would reflect the scope and limitations associated with the addition reactions of this important and readily accessible optically pure methylenenitrole. The NMR spectroscopy is utilized to examine the nitrogen inversion process and determine the configuration of the cycloadducts (isoxazolidines).
3.2 Results and Discussion

Each nitrono (124)-alkene cycloaddition with 129 (or 130) proceeded regiospecifically to afford a separable mixture of diastereomeric isoxazolidines 127 and 128 (or 131 and 132), the compositions of which are given in (Schemes 38 and 39).

Since the nitrono is optically pure, the isoxazolidines differ only in the configuration of the C(5) substituents. The nitrono 124 is expected to assume the conformation as depicted in Scheme 38. The planar nitrono functionality is in Ha-eclipsed conformation 127 having Me and PhCHOH on the α- and β-faces, respectively. The J_{ab} value of 5.5 Hz, corresponding to a torsional angle of 40.5° as determined by Karplus rule, supports the gauche orientation between Ha and Hb. Since both the faces of the dipole, in the vicinity of N, have substituents, addition reaction does not offer any clear cut face selectivity. Sterically favored α-exo (R) or β-exo (R) mode of attack may happen with equal ease thereby giving the isoxazolidines 127 and 128 in almost equal yields (Scheme 38).
Since the addition reaction of methyl acrylate (129c) was found to have a preference to give the isoxazolidine 128c by an $\alpha$-exo (CO$_2$Me) mode of approach (Scheme 38), the major adduct in the addition reaction of methyl methacrylate (130) was similarly assigned the configuration of 132 obtained by a similar $\alpha$-exo (CO$_2$Me) mode of attack (Scheme 39). However, in the absence of X-ray analysis (owing to difficulty in

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>$^{13}$C NMR Chemical Shifts of compounds Studied in CDCl$_3$ at -40°C</td>
</tr>
<tr>
<td>Compound</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>127a</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>128a</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>127b</td>
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<td>128b</td>
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<td>127c</td>
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<td>128c</td>
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<td>127d</td>
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<tr>
<td>128d</td>
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<td></td>
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<tr>
<td>131</td>
</tr>
<tr>
<td>132</td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Absolute configuration of the chiral centers as defined in Schemes 38 and 39.

C(5) Me at <sup>b</sup>22.82, <sup>c</sup>24.29, <sup>d</sup>22.95 ppm

getting crystalline material), the configuration of the adduct could not be confirmed.
During the course of the structural investigation of the isomeric isoxazolidines, it was observed that the isoxazolidines were present either as a single invertomer or an equilibrating mixture of two invertomers in a ~80:20 ratio at lower temperatures in CDCl₃. Slow nitrogen inversion in most of the isoxazolidines has been observed to give broadened peaks in ¹H and ¹³C spectra recorded at ambient temperature. On lowering the temperature, the spectral lines became sharper and showed two distinct forms of the compound. Around -10°C, the ¹H NMR spectra of these compounds showed well separated signals for the two invertomers. Integration of the relevant peaks gives the population trends in these systems. The ¹³C chemical shifts were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in (Table 2).

The nitrogen inversions barriers were determined using NMR band shape analysis. The proton spectra were used in the calculation of barriers in all compounds. The complete band shape analysis yielded the rate constants and the free energy of activation using Eyring equation. The activation parameters ΔHₚ and ΔSₚ were calculated from plots of ln(k/T) vs. 1/T. It is well known [5] that NMR band shape fitting frequently gives rather large but mutually compensating errors in ΔHₚ and ΔSₚ and as such their values are not reported here. However, band shape fitting is viewed as a method of getting rather accurate values of ΔGₚ (probably within ± 0.3 kJ/mol) in the vicinity of the coalescence temperature. The ΔGₚ values calculated at 0°C are reported in Table 3, along with the invertomer ratios and ΔGₒ values.
Both the cis-1,3-dimethylcyclopentane and cis-1,3-dimethylcyclohexane are known [81] to be more stable than their trans counterparts by an enthalpy difference of 2.3 kJ/mol and 7.1 kJ/mol, respectively. The slight preference for the cis isomer in cyclopentane may be attributed to the disposition of the substituents in the pseudoequatorial orientations. The 2,5-disubstituted isoxazolidines, however, have been found to have a slight preference
for the trans-invertomers \[82\]; shortened bond lengths due to the presence of two heteroatoms are expected to augment the steric congestion between the cis substituents. The conformation of 5-membered ring system is indeed very complex to elucidate with some certainty. The complexity arises from the fact that changing the size of the substituent may lead to change in conformation (half chair/envelope/near planar) and the flap of the envelope. Earlier works \[82\] on 2,5-disubstituted isoxazolidines revealed the trans-invertomer as the major isomer. The 2-methyl-, 2-isopropyl-, and 2-\text{t}butyl-5-\text{t}butyldimethylsiloxy methyl isoxazolidines were found to have the trans- and cis-invertomers in a ratio of \(53:47\), \(55:45\) and \(63:37\), respectively. The compounds studied in this work are sterically similar to the 2-isopropyl isoxazolidines since they also contain a secondary alkyl substituent at the 2-position (Scheme 38).

To confirm the stereochemistry, adducts \(128\text{b}\) and \(128\text{c}\) were subjected to X-ray crystallographic analysis; the ORTEP representations are shown in (Figures 7 and 8). The stereochemistry of the methyl acrylate adducts \(127\text{c}\) and \(128\text{c}\) were then correlated to allyl alcohol adducts \(127\text{d}\) and \(128\text{d}\) by conversions of the former isomers to the later by reduction with lithium aluminum hydride. It has been observed that the minor isomers (\(127\text{b}, 128\text{c}\)) in the addition reactions of styrene or methyl acrylate always eluted first during the silica gel chromatography. As a result, in the addition reaction of 1-hexene, adduct eluted first was given the configuration of \(127\text{a}\). The X-ray analyses revealed the existence of both the adducts \(128\text{b}\) and \(128\text{c}\) in the cis invertomeric form. The chemical shift difference between the isomers for a particular ring carbon is generally less than 1 ppm for most carbons and as such the C-13 shifts are not very sensitive to the difference
in the isomeric configurations (Table 2). This is not surprising in view of the fact that the five-membered ring does not have the well-defined conformation of six-membered systems. However, one striking difference in the $^{13}$C chemical shift values of CH$_3$C=N was observed; the signals for the major invertomers appeared at $\delta$ 10.7 ± 0.2 ppm, while the minor signal appeared at $\delta$ 6.8 ± 0.9. The C-3 and C-OH of the major invertomers invariably appeared downfield and upfield, respectively, in compare to the minor

<table>
<thead>
<tr>
<th>Isoxazolidine</th>
<th>CH$_3$C=N</th>
<th>PhCHO</th>
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<tbody>
<tr>
<td></td>
<td>Major$^b$</td>
<td>Minor$^c$</td>
</tr>
<tr>
<td></td>
<td>$\delta$ (ppm)</td>
<td>$\delta$ (ppm)</td>
</tr>
<tr>
<td>127a</td>
<td>0.81</td>
<td>1.00</td>
</tr>
<tr>
<td>128a</td>
<td>0.81</td>
<td>Overlapped</td>
</tr>
<tr>
<td>127b</td>
<td>0.85</td>
<td>1.09</td>
</tr>
<tr>
<td>128b</td>
<td>0.94</td>
<td>1.02</td>
</tr>
<tr>
<td>127c</td>
<td>0.78</td>
<td>−$^b$</td>
</tr>
<tr>
<td>127c$^c$</td>
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<tr>
<td>128c</td>
<td>0.84</td>
<td>0.95</td>
</tr>
<tr>
<td>128c$^c$</td>
<td>0.80</td>
<td>1.01</td>
</tr>
<tr>
<td>127d</td>
<td>0.85</td>
<td>−$^b$</td>
</tr>
<tr>
<td>128d</td>
<td>0.88</td>
<td>1.00</td>
</tr>
<tr>
<td>131</td>
<td>0.73</td>
<td>−$^b$</td>
</tr>
<tr>
<td>132</td>
<td>0.80</td>
<td>0.94</td>
</tr>
</tbody>
</table>

$^a$overlapped. $^b$No minor invertomer. $^c$in CD$_3$OD
invertomers (Table 2). The benzylic proton NMR signals for all the major invertomers appeared downfield than the PhCHO of the minor invertomers (Table 4). The methyl protons in CH₂C=N of the major and minor invertomers appeared upfield and downfield, respectively, in all the compounds studied. Similar trend in the chemical shift values of PhCHO and CH₂C=N protons (Table 3) and the CH₂C=N, C-3 and C-OH carbons (Table 1) between the major and minor invertomers strongly suggest the similarity in the configuration among all the major invertomers (or among all the minor invertomers). As supported by X-ray analyses, all the dominant or sole nitrogen invertomers are believed to have the identical configuration of (R), (S), and (R) at the three chiral centers at benzylic C, exocyclic C attached to nitrogen, and N, respectively.

X-ray analyses revealed that the proton in exocyclic CH-N is anti to the nitrogen lone pair as depicted in (Scheme 40); the arrangement will have the lower number of gauche interactions (two in these cases) around the C-N bond. The protons in the exocyclic CH-N and PhCHO are not in expected anti dispositions; the torsional angle between them is found to be 63.3° in 128c as a result of their gauche orientations (Scheme 40 and Figure 8). Similar orientation is observed in the ORTEP diagram of 128b (Figure 7).

Such an orientation will lead to a very low coupling constant (J ≈ 1.5 Hz) between these protons as calculated using Karplus equation. The appearance of PhCHO proton of both the invertomers as a singlet (i.e. J ≈ 0 Hz) in the ¹H NMR spectrum in CDCl₃ or CD₃OD confirmed the gauche orientation between these protons in solution as well as solid state. Such an orientation may be helpful in establishing intramolecular H-bond between the OH and nitrogen lone pair as depicted in (Scheme 40). The sum of Van der
Waal radii of H,N is known to be 2.75 Å, while the observed distance of 2.44 Å in 128c (Figure 8) suggest the presence of intramolecular H-bond.

A look at the Newman projections (Scheme 40) revealed that the Me and C-3 are in the gauche conformations in the major invertomers, while they remain anti in the minor invertomers. We cannot offer a rationale, at this stage, for the considerable upfield shift by ~4 ppm for the methyl carbons in the methyl/C-3 anti-oriented minor invertomers.
The question remains: why are the (R),(S),(R)-diastereomers more stable than their corresponding (R),(S),(S)-invertomers? It may be the result of an energetically favourable orientation of the groups around C-N having the larger substituent (PhCHOH) in gauche
orientation with the ring ‘O’ in the major invertomer. The Newman projections also reveals that the ‘OH’ in the major invertomers is also capable of forming H-bond with the ring ‘O’, while this is not possible with the minor form. The special stability imparted by the (R),(S),(R) arrangement does not mind the substituent at C-5 to be trans or cis-oriented. Note that while the 2,5 substituents in 127(a-d) remain trans oriented in the major invertomers, the cis remains the stable form for the corresponding isoxazolidines 128(a-d). The isoxazolidines 127c and 127d remained exclusively in the (R),(S),(R) configurations; the presence of the minor invertomers could not be detected. Presumably, the pseudoaxial orientation of the CO$_2$Me is better tolerated in (R),(S),(R) invertomer for its smaller size as a result of the sp$^2$-hybridized carbon. It is worth mentioning that the C(5)-CH$_2$OH in the exclusive invertomer of 127d may gain additional stability as a result of intramolecular H-bonding with the nitrogen as depicted in (Scheme 40).

The most interesting display of isomeric stability is found with the isoxazolidines 131 and 132; while the former exists exclusively in the (R),(S),(R) form, the later remains in the (R),(S),(R) and R),(S),(S) forms in a respective ratio of 63:37 (Scheme 41, Table 3). The C(5)Me carbon of (R),(S),(R)-7, (R),(S),(S)-131, and (R),(S),(R)-132 appeared at δ22.82, 22.95, and 24.29 ppm, respectively; the similarity in the chemical shift values of the former two invertomers indicates the similar environments of the methyl group such as its cis orientation with the N(2) substituents. The extra stability enjoyed by the (R),(S),(R)-131 invertomer could be attributed to the pseudoequatorial orientation of the bulkier substituents at C(5) and N(2), while the smaller CO$_2$Me is pseudoaxially-oriented.
The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines [83,84]. Experimental and calculated spectra for one of the isoxazolidines (127b) are shown in (Figure 8). The inversion barriers hover around 59 kJ/mol for most of the isoxazolidines (Table 3). The similar barriers were expected since the steric requirements to attain the sp^2 hybridized transition state (through which the nitrogen inversion occurs) remains more or less similar as the substituents in the immediate vicinity of nitrogen remains the same in all the isoxazolidines. An increase in the inversion barrier in in isoxaolidines in CD_3OD is attributed to the extra energy required for breaking of H-bonding prior to inversion [84]. However, the inversion in the current compounds in CDCl_3 also involves the breaking of the intramolecular H-bonding.
As a result the inversion barrier remains similar in hydrogen bonding solvent CD₃OD and non protic CDCl₃ for the compound 128c (Table 3).

The solvent effects provided the additional support for the assigned stereochemistry. In methanol, the intramolecular H-bonding is disrupted; the steric bulk of the solvation shell of the nitrogen lone pair increases in hydrogen-bonding solvents. This should diminish the preference for the 127-trans- and 128-trans invertomers in CD₃OD since the steric bulk of the salvation lone pair salvation shell would interfere with the C(5) substituents (Scheme 3). This is exactly what is observed: the isoxazolidine trans-127c remained as the sole invertomer in CDCl₃ while in CD₃OD the 127-trans/cis ratio becomes 83:17 (Table 3). For the isoxazolidine 128c the trans/cis ratio of 21:79 in CDCl₃ is decreased to 13:87 in CD₃OD.

3.3 Experimental

3.3.1 General.

All m.p.s are uncorrected. I.r. spectra were recorded on a Perkin Elmer 16F PC FTI.r spectrometer. Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Paraformaldehyde, 1-hexene, styrene, allyl alcohol, methyl acrylate, methyl methacrylate, (-) norephedrine from Fluka were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. MgBr₂ was freshly prepared by reaction of Mg with 1,2-dibromoethane. All reactions were carried out under N₂.
The $^{13}$C and variable temperature $^1$H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm$^3$ solutions in CDCl$_3$ and CD$_3$OD with TMS as internal standard. Multiplicities of the carbons were determined using DEPT experiments. X-ray crystallographic analysis was carried out on a Bruker-AXS Smart Apex system equipped with graphite-monochromatized Mo-K$\alpha$ radiation ($\lambda = 0.71073$ Å). Optical rotations were measured in a JASCO (P-2000) polarimeter. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N).

3.3.2 Hydroxylamine 126.

Chiral hydroxylamine 126 was prepared from (−) norephedrine in 38% yield using procedure as described [85]. The compound 126 was not fully characterized in the previous reports. M.p. 79-80°C (ether-hexane); $\alpha$D$^{23}$ −26.3 (c 2.00, methanol). (Found: C, 64.5; H, 7.7; N, 8.3. C$_9$H$_{13}$NO$_2$ requires C, 64.65; H, 7.84; N, 8.38 %); $\nu_{\max}$ (KBr) 3480, 3270, 3239, 3081, 3055, 3025, 2974, 2933, 2897, 2877, 2795, 1488, 1442, 1380, 1350, 1314, 1243, 1200, 1140, 1092, 1070, 1049, 1034, 988, 942, 914, 890, 850, 736 and 691 cm$^{-1}$; $\delta$(CDCl$_3$, +25°C) : 0.85 (3H, d, J 6.7 Hz), 3.24 (1H, dq, J 2.8, 6.7 Hz), 5.17 (1H, d, J 2.8 Hz), 5.54 (2H, br, NHOH), 7.31 (5H, m); $\delta$(CDCl$_3$, +25°C) 10.25, 62.70, 71.93, 125.92 (2C), 127.21, 128.26 (2C), 141.37.

3.3.3 Nitrone 124.

Prepared via condensation of hydroxylamine 126 with paraformaldehyde, was not isolated (vide infra). But a crude $^1$H NMR spectrum revealed the following signals
attributed to the nitrone: δH(CDCl₃, +20°C) : 1.36 (3H, d, J 6.8 Hz), 4.10 (1H, m), 5.42 (1H, d, J 5.5 Hz), 6.38 (1H, d, J 7.1 Hz; CH=N), 6.54 (1H, d, J 7.1 Hz; CH=N), 7.35 (5H, m). However, the nitrone functionality accounted for only 20% of the product mixture as indicated by the integration of the olefinic protons of the nitrone functionality versus the aromatic protons. The complicated spectra indicated the involvement of several compounds (e.g. 124-A, 124-B, etc) under equilibration with nitrone 124 as outlined in (Scheme 38).

3.3.4. Cycloaddition of nitrone 124 with 1-hexene (129a).

To a solution of hydroxylamine 126 (670 mg, 4.0 mmol) in toluene (10 cm³) was added paraformaldehyde (200 mg, 6.7 mmol) and 1-hexene (3 cm³). The mixture was stirred using a magnetic stir bar in the closed vessel under N₂ at 105°C for 12 h. After removal of the solvent the residual mixture was chromatographed over silica using ether/hexane mixture as eluant to give pure isomer 127a followed by a mixture of the adducts 127a and 128a as a colourless liquid. The combined yield of the cycloadducts was found to be 89%. Spectral analysis adducts revealed the presence of 127a/128a in a ratio of 50:50, respectively, as determined by integration and peak heights of C(5)H signals.

127a: [α]²³_D = -8.5 (c 0.946, methanol); m/z 156 [M⁺-107 (PhCHOH)]; (Found: C, 72.8; H, 9.5; N, 5.2. C₁₆H₂₅NO₂ requires C, 72.97; H, 9.57; N, 5.32 %); νmax (neat) 3517, 3214, 3061, 3027, 2956, 2930, 2859, 1495, 1451, 1379, 1332, 1231, 1198, 1097, 1067, 999, 878, 750 and 702 cm⁻¹; δH(CDCl₃, +20°C) : 0.81 (3H, m), 0.91 (3H, t, J 7.0 Hz) 1.15-2.00 (7H, m), 2.36 (1H, m), 2.50-3.50 (4H, m), 4.13 (1H, m), 5.20 (1H, apparent s), 7.30 (5H, m).
The $^1$H NMR spectrum in CDCl$_3$ at -40°C revealed the presence of two invertomers in a 83:17 ratio as determined by integration of several proton signals.

Major invertomer: $\delta$H(CDCl$_3$, -40°C) : 0.81 (3H, d, J 6.4 Hz), 0.92 (3H, t, J 7.0 Hz) 1.15-1.55 (5H, m), 1.72 (1H, m), 1.93 (1H, m), 2.39 (1H, m), 2.83 (1H, m), 2.90 (1H, m), 3.26 (1H, m), 3.98 (1H, br, OH), 4.20 (1H, quint, J 6.3 Hz), 5.26 (1H, d, J 3.0 Hz), 7.35 (5H, m); $\delta$C(CDCl$_3$, -40°C) 10.88, 14.26, 22.72, 28.42, 33.90, 35.13, 52.32, 65.68, 72.59, 76.75, 125.96 (2C), 126.73, 127.89 (2C), 140.94.

Minor invertomer: The minor invertomer has the following non-overlapping signals: $\delta$H(CDCl$_3$, -40°C) 1.00 (3H, d, J 6.5 Hz), 3.05 (1H, m), 3.51 (1H, m), 4.05 (1H, quint, J 6.9 Hz), 5.14 (1H, d, J 5.2 Hz); $\delta$C(CDCl$_3$, -40°C) 7.12, 14.21, 22.77, 28.24, 33.81, 34.23, 52.06, 67.26, 74.81, 77.50, 125.71 (2C), 126.84, 127.99 (2C), 141.24.

128a: The second fraction was contaminated with a minor amount of 127a. The following signals were attributed to 128a. The $^1$H NMR spectrum in CDCl$_3$ at -40°C revealed the presence of two invertomers in a 89:11 ratio as determined by integration of benzylic proton signals. (Found: C, 72.7; H, 9.4 ; N, 5.2. C$_{16}$H$_{25}$NO$_2$ requires C, 72.97; H, 9.57; N, 5.32 %); m/z 156 [M$^+$-107 (PhCHOH)]; $\nu_{max}$ (neat) 3424, 3062, 3027, 2958, 2929, 2858, 1494, 1452,1379, 1336, 1197, 1097, 1020, 999, 911, 751, 731 and 702 cm$^{-1}$.

Major invertomer: $\delta$H(CDCl$_3$, -40°C) : 0.81 (3H, d, J 6.3 Hz), 0.87 (3H, t, J 6.7 Hz), 1.15-2.00 (7H, m), 2.40 (1H, m), 2.60 (1H, m), 2.91 (1H, m), 3.33 (1H, m), 4.05 (1H, m), 4.22 (1H, br, OH), 5.35 (1H, d, J 2.5 Hz), 7.35 (5H, m); $\delta$C(CDCl$_3$, -40°C) 10.75, 14.25,
22.82, 28.26, 33.61, 34.56, 53.13, 68.02, 72.31, 77.48, 126.15 (2C), 126.69, 127.87 (2C), 141.22.

Minor invertomer: The minor invertomer has the following non-overlapping signals: δH(CDCl3, -40°C) 5.00 (1H, d, J 5.0 Hz). δC(CDCl3, -40°C) 7.42, 12.54, 22.72, 28.40, 33.83, 34.24, 51.87, 65.93, 73.96, 74.38, 125.63 (2C), 126.95, 128.25 (2C), 141.00.

3.3.5. Cycloaddition of nitrone 124 with styrene (129b).

To a solution of the hydroxylamine 126 (670 mg, 4.0 mmol) in toluene (10 cm³) was added paraformaldehyde (200 mg, 6.7 mmol) and styrene (3 cm³). The mixture was stirred using a magnetic stir bar in the closed vessel under N2 at 90°C for 6 h. After removal of the solvent and excess styrene the residual mixture was chromatographed over silica using 9:1 ether/hexane mixture as eluant to give pure isomer 127b followed by a mixture of the adducts 127b and 128b. Continued elution afforded the pure adduct 127b. The combined yield of the cycloadducts was found to be 89%. Spectral analysis adducts revealed the presence of 127/128 in a ratio of 40:60, respectively, as determined by integration of several non overlapping signals of the C(5)H and Me doublets.

Minor isomer 127b: Mp 65-66°C (ether-pentane); m/z 176 [M+107 (PhCHOH)]; [α]D 23 +37.1 (c 0.488, methanol). (Found: C, 76.1; H, 7.5; N, 4.8. C18H21NO2 requires C, 76.30; H, 7.47; N, 4.94 %.) νmax (KBr) 3423, 3081, 3055, 3025, 2984, 2948, 2897, 2831, 1595, 1488, 1447, 1437, 1380, 1334, 1299, 1278, 1197, 1105, 1094, 1023, 1013, 916, 885, 854, 798, 752 and 696 cm⁻¹.
The $^1$H NMR spectrum in CDCl$_3$ at -40°C revealed the presence of two invertomers in a 88:12 ratio as determined by integration of several proton signals.

Major invertomer: $\delta$H(CDCl$_3$, -40°C) : 0.85 (3H, d, J 6.4 Hz), 2.38 (1H, m), 2.82 (1H, m), 2.96 (2H, m), 3.44 (1H, m), 3.62 (1H, OH), 5.27 (1H, apparent t, J 7.2 Hz), 5.43 (1H, s), 7.35 (10H, m); $\delta$C(CDCl$_3$, -40°C) 10.73, 37.48, 53.02, 66.31, 72.44, 77.57, 125.67 (2C), 125.88 (2C), 126.81, 127.48, 127.99 (2C), 128.54(2C), 140.71, 142.57.

Minor invertomer: The minor invertomer has the following non-overlapping signals: $\delta$H(CDCl$_3$, -40°C) 1.09 (3H, d, J 6.4 Hz), 3.18 (1H, m), 3.70 (1H, m), 5.07 (1H, apparent t, J 7.2 Hz), 5.22 (1H, s); $\delta$C(CDCl$_3$, -40°C) 6.44, 36.97, 52.38, 66.71, 75.68, 78.95, 125.75 (2C), 126.60 (2C), 126.75, 127.00, 128.05 (2C), 128.44 (2C), 140.34, 141.01.

Major isomer 128b: Mp 74-75°C (ether-pentane); m/z 176 [M$^+$-107 (PhCHOH)]; $[\alpha]_{D}^{23}$ −17.8 (c 0.386, methanol); (Found: C, 76.2; H, 7.3; N, 5.0. C$_{18}$H$_{21}$NO$_2$ requires C, 76.30; H, 7.47; N, 4.94 %); $\nu_{\max }$ (KBr) 3375, 3029, 2980, 2937, 2851, 1603, 1493, 1450, 1381, 1367, 1341, 1327, 1284, 1241, 1204, 1156, 1096, 1043, 1001, 944, 919, 880, 823, 753 and 699 cm$^{-1}$.

The $^1$H NMR spectrum in CDCl$_3$ at -40°C revealed the presence of two invertomers in a 87:13 ratio as determined by integration of Me doublets.

Major invertomer: $\delta$H(CDCl$_3$, -40°C) 0.94 (3H, d, J 6.7 Hz), 2.15 (1H, m), 2.74 (2H, m), 3.02 (1H, m), 3.47 (1H, m), 4.49 (1H, s, OH), 5.06 (1H, m), 5.43 (1H, s), 7.35 (10H, m);
\[ \delta C(CDCl_3, -40^\circ C) \quad 10.65, 36.93, 53.90, 68.15, 71.98, 78.77, 125.99 \text{ (2C)}, 126.69, 126.76 \text{ (2C)}, 127.88, 127.93 \text{ (2C)}, 128.39 \text{ (2C)}, 140.79, 141.44. \]

Minor invertomer: The minor invertomer has the following non-overlapping signals: \[ \delta H(CDCl_3, -40^\circ C) \quad 1.02 \text{ (3H, d, } J 6.5 \text{ Hz)}. \delta C(CDCl_3, -40^\circ C) \quad 7.45, 37.51, 52.54, 65.99, 74.70, 78.85, 125.68 \text{ (2C)}, 125.88, 126.08 \text{ (2C)}, 127.05, 128.09 \text{ (2C)}, 128.52 \text{ (2C)}, 140.79, 141.44. \]

### 3.3.6 Cycloaddition of nitron 124 with methyl acrylate (129c).

A mixture of the hydroxylamine 126 (670 mg, 4.0 mmol) and paraformaldehyde (200 mg, 6.7 mmol) in chloroform (15 cm\(^3\)) was stirred using a magnetic stir bar in a closed vessel under N\(_2\) at 65°C for 2 h. Methyl acrylate (2 cm\(^3\)) was then added to the resulting nitron solution (at 25°C) and stirring was continued at 60°C for 24 h. After removal of the solvent and excess alkene, the residual mixture was chromatographed over silica using 9:1 hexane/ether mixture as eluant to give the minor isomer 127c (417 mg). Continued elution afforded the pure sample of the major isomer 128c (580 mg). Adducts 127c and 128c were thus formed in a ratio of 42:58, respectively. The \(^1\)H NMR analysis of the crude cycloadducts also supported the ratio obtained from the chromatographic separation. The combined yield of the cycloadducts was found to be 94%.

Minor isomer 127c: Mp 68-69°C (ether-pentane); m/z 158 \([M^+ -107 \text{ (PhCHOH)}] \); \([\alpha]_{D}^{23} \approx -48.3 \text{ (c 0.425, methanol)}\); (Found: C, 63.2; H, 7.1; N, 5.2. C\(_{14}\)H\(_{19}\)NO\(_4\) requires C, 63.38; H, 7.22; N, 5.28 %.). \( \nu_{\text{max}} \) (KBr) 3485 (sharp), 3061, 2986, 2958, 2847, 1746, 1496, 1451, 1430, 1380, 1337, 1286, 1205, 1177, 1086, 1026, 1003, 812, 752 and 705 cm\(^{-1}\).
Sharp $^1$H NMR signals at room temperature indicated the presence of a single invertomer: $\delta$(CDCl$_3$, +25°C) : 0.78 (3H, d, J 6.7 Hz), 2.48-2.70 (3H, m), 2.92 (1H, m), 3.32 (1H, m), 3.57 (1H, s, OH), 3.80 (3H, s), 4.63 (1H, dd, J 3.9, 9.7 Hz), 5.38 (1H, s), 7.33 (5H, m). The spectrum at -40°C remained similar to that at +25°C. $\delta$(CDCl$_3$, -40°C) 11.07, 32.90, 51.63, 52.73 (OMe), 65.79, 72.03, 73.38, 125.69 (2C), 126.80, 128.01 (2C), 140.25, 173.87.

In CD$_3$OD (-40°C) the $^1$H NMR spectrum revealed several nonoverlapping minor signals indicating the major/minor invertomers of 127c in a ratio of 83:17. The CH$_3$ doublets appeared at $\delta$0.77 (major, d, J = 6.7 Hz) and $\delta$1.02 (minor, d, J = 6.1 Hz). The benzylic proton appeared at $\delta$5.38 (major, s) and $\delta$5.17 (minor, s).

Major isomer 128c: Mp 60-61°C (ether-pentane); m/z 158 [M$^-$-107 (PhCHOH)]; [\(\alpha\)]$^D_{23}$ -26.4 (c 0.872, methanol); (Found: C, 63.3; H, 7.1; N, 5.2. C$_{14}$H$_{19}$NO$_4$ requires C, 63.38; H, 7.22; N, 5.28 %).) $\nu_{\text{max}}$(KBr) 3543 (sharp), 3081, 2990, 2942, 2908, 2869, 1754, 1492, 1453, 1434, 1409, 1378, 1349, 1328, 1284, 1262, 1198, 1088, 1061, 996, 964, 949, 877, 854, 795, 763 and 706 cm$^{-1}$.

The $^1$H NMR spectrum in CDCl$_3$ at -40°C revealed the presence of two invertomers in a 79:21 ratio as determined by integration of several proton signals.

Major invertomer: $\delta$(CDCl$_3$, -40°C) : 0.84 (3H, d, J 6.7 Hz), 2.39 (1H, m), 2.66 (1H, m), 2.89 (1H, m), 3.11 (1H, m), 3.31 (1H, m), 3.75 (1H, s, OH), 3.83 (3H, s), 4.64 (1H, dd, J 5.8, 9.2 Hz), 5.45 (1H, s), 7.37 (5H, m); $\delta$(CDCl$_3$, -40°C) 10.48, 32.98,
51.78, 52.67 (OMe), 66.92, 71.68, 75.09, 125.84 (2C), 126.70, 127.95 (2C), 141.09, 172.47.

Minor invertomer: The non overlapping $^1$H signals at $\delta$(CDCl$_3$, -40°C) 0.95 (3H, d, J 6.7 Hz), 5.18 (1H, s); $\delta$(CDCl$_3$, -40°C) 5.14, 32.18, 50.59, 52.79 (OMe), 64.46, 74.05, 76.20, 125.66 (2C), 127.00, 128.06 (2C), 140.57, 173.33.

In CD$_3$OD (-40°C) the $^1$H NMR spectrum revealed several nonoverlapping minor signals indicating the major/minor invertomers of 128c in a ratio of 87:13. The CH$_3$ doublets appeared at $\delta$0.80 (major, d, J = 6.7 Hz) and $\delta$1.01 (minor, d, J = 6.1 Hz). The benzyl protons appeared at $\delta$5.47 (major, s) and $\delta$5.17 (minor, s).

3.3.7. Lithium aluminium hydride reduction of cycloadducts methyl acrylate adducts (127c, 128c) to allyl alcohol adducts (127d, 128d).

127d: To a stirred solution of 127c (120 mg, 0.45 mmol) in ether (15 cm$^3$) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1 g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$), concentrated, and purified by silica gel chromatography using a 95:5 CH$_2$Cl$_2$/methanol as the eluant to give 127d as a colorless liquid (100 mg, 94%), $\left[\alpha\right]^{23}_D$ -38.7 (c 1.53, methanol); m/z 130 [M$^+$-107 (PhCHOH)]; (Found: C, 65.6; H, 7.8; N, 5.7. C$_{13}$H$_{19}$NO$_3$ requires C, 65.80; H, 8.07; N, 5.90 %.); $\nu$$_{max}$. 
(neat) 3402, 3060, 3027, 2981, 2940, 1494, 1450, 1380, 1334, 1236, 1199, 1097, 1041, 993, 859, 807, 736 and 703 cm\(^{-1}\).

Sharp \(^1\)H NMR signals at room temperature indicated the presence of a single invertomer. The spectrum at -40°C remained similar to that at +25°C.

Single invertomer: \(\delta\)H(CDCl\(_3\), -40°C) 0.85 (3H, d, J 6.4 Hz), 2.13 (1H, m), 2.30 (1H, m), 2.72 (1H, m), 2.81 (1H, m), 3.22 (1H, m), 3.72 (2H, m), 4.37 (1H, m), 4.75 (1H, broad, OH), 4.89 (1H, broad, OH), 5.43 (1H, s), 7.35 (5H, m).

\(\delta\)C (CDCl\(_3\), -40°C) 10.36, 29.44, 53.03, 63.60, 67.30, 71.71, 77.47, 125.86 (2C), 126.73, 127.94 (2C), 141.40.

128d: Adduct 128c was reduced with LiAlH\(_4\) using procedure as described above to give 128d (95%) as a colorless liquid; \([\alpha]^{23}_D\) -18.4 (c 1.58, methanol); m/z 130 [M\(^+\)-107 (PhCHOH)]; (Found: C, 65.5; H, 7.9; N, 5.8. C\(_{13}\)H\(_{19}\)NO\(_3\) requires C, 65.80; H, 8.07; N, 5.90%); \(v_{\max}\). (neat) 3286, 2982, 2880, 1494, 1451, 1381, 1336, 1198, 1041, 999, 887, 829, 751 and 703 cm\(^{-1}\).

The \(^1\)H NMR spectrum in CDCl\(_3\) at -40°C revealed the presence of two invertomers in a 84:16 ratio as determined by integration of several proton signals.

Major invertomer: \(\delta\)H(CDCl\(_3\), -40°C) 0.88 (3H, d, J 6.7 Hz), 1.85 (1H, m), 2.33 (1H, m), 2.44 (1H, m), 2.87 (1H, m), 3.37 (1H, m), 3.64 (1H, m), 3.81 (1H, m), 4.41 (2H, m, including an OH), 4.87 (1H, broad s, OH), 5.42 (1H, s), 7.35 (5H, m); \(\delta\)C(CDCl\(_3\), -40°C) 10.62, 30.03, 53.64, 64.29, 67.98, 71.61, 77.67, 125.99 (2C), 126.71, 127.91 (2C), 141.08.
Minor invertomer: The minor invertomer has the non overlapping $^1$H signals at:
\[ \delta_{\text{H(CDCl}}_3, -40^\circ \text{C}} 1.00 \,(3\text{H, d, } J 6.4 \text{ Hz}), 5.02 \,(1\text{H, s}); \delta_{\text{C(CDCl}}_3, -40^\circ \text{C}} 7.37, 29.26, 52.26, 63.84, 66.09, 74.72, 78.07, 125.67 \,(2\text{C}), 127.13, 128.09 \,(2\text{C}), 140.85.

3.3.8. Cycloaddition of nitrone 124 with allyl alcohol (129d).

To a solution of the hydroxylamine 126 (670 mg, 4.0 mmol) in toluene (10 cm$^3$) was added paraformaldehyde (200 mg, 6.7 mmol) and allyl alcohol (3 cm$^3$). The mixture was stirred using a magnetic stir bar in the closed vessel under N$_2$ at 90°C for 12 h. After removal of the solvent the residual mixture was chromatographed over silica using 98:2 dichloromethane/methanol mixture as eluant to give a non separable mixture of adducts 127d and 128d as a colourless liquid (0.80 g, 84%). Spectral analysis revealed the presence of 127d/128d in a ratio of 50:50.

3.3.9. Cycloaddition of nitrone 124 with allyl alcohol (129d) in the presence of MgBr2.

To a solution of hydroxylamine 126 (167 mg, 1.0 mmol) in dichloromethane (20 cm$^3$), was added paraformaldehyde (34 mg, 1.13 mmol) and the mixture was stirred in a closed vessel under N$_2$ at 65°C for 2 h. Thereafter, the solution was cooled to room temperature and the volume of the solution was reduced to 5 cm$^3$ by gently blowing N$_2$ at 40°C. This process is expected to remove moisture (H$_2$O) by evaporation along with CH$_2$Cl$_2$. Then MgBr$_2$ (184 mg, 1.0 mmol) was added to the solution. The resulting suspension was stirred at 20°C for 15 min after which allyl alcohol (129d) (4.0 mmol) was added. The reaction mixture was then stirred at 65°C in the closed vessel under N$_2$ for 48 h. After the elapsed time, the reaction mixture was cooled to room temperature and was
taken up in 10% K$_2$CO$_3$ (20 cm$^3$) and extracted with CH$_2$Cl$_2$ (3 × 20 cm$^3$). The combined organic layers were dried (Na$_2$SO$_4$), concentrated and purified by silica gel chromatography using 98:2 dichloromethane/methanol mixture as eluent to give a non-separable mixture of isomers 127d and 128d as a colourless liquid (190 mg, 80%). The ratio of 127d and 128d was found to be 50:50, respectively, as determined by $^1$H NMR spectroscopic analysis (vide supra). The Lewis acid catalyzed 129a-c cycloaddition thus failed to improve the diastereoselectivity of the addition reaction.

3.3.10. Cycloaddition of nitrone 124 with methyl methacrylate (130).

A mixture of the hydroxylamine 126 (670 mg, 4.0 mmol) and paraformaldehyde (200 mg, 6.7 mmol) in chloroform (15 cm$^3$) was stirred using a magnetic stir bar in the closed vessel under N$_2$ at 65°C in a closed vessel for 2 h. Methyl methacrylate (130) (2 cm$^3$) was then added to the resulting nitrone solution (at 25°C) and stirring was continued at 60°C for 24 h. After removal of the solvent and excess alkene, the residual mixture was chromatographed over silica using 9:1 hexane/ether mixture as eluant to give the minor isomer 131 (371 mg). Continued elution afforded the pure sample of the major isomer 132 (690 mg). Adducts 131 and 132 were thus formed in a ratio of 35:65, respectively. The $^1$H NMR integration of the benzylic proton signals (CDCl$_3$, +25°C) of the crude cycloadducts at $\delta$ 5.39 (minor) and 5.26 (major) also supported the ratio obtained from the chromatographic separation. The combined yield of the cycloadducts was found to be 95%.

131: Single invertomer: Mp 78-79°C (ether-pentane); m/z 172 [M$^+$-107 (PhCHOH)]; $[\alpha]^{23}_D$ $-70.8$ (c 0.267, methanol). (Found: C, 64.3; H, 7.4; N, 4.9.
C_{15}H_{21}NO_{4} \text{ requires C, 64.50; H, 7.58; N, 5.01 \%.) \; \nu_{\text{max}} (\text{KBr}) 3502 (\text{very sharp}), 3059, 2994, 2955, 2882, 2840, 1738, 1499, 1449, 1409, 1383, 1341, 1279, 1232, 1201, 1126, 1070, 1023, 1002, 971, 933, 906, 848, 818, 752 and 706 cm}^{-1}; \delta H(\text{CDCl}_{3}, +25^\circ \text{C}) : 0.73 (3H, d, J 6.7 Hz), 1.56 (3H, s), 2.13 (1H, ddd, J 2.1, 9.1 12.7 Hz), 2.60 (1H, m), 2.84 (1H, td, J 8.7, 12.6 Hz), 2.91 (1H, dq, J 2.9, 6.6 Hz), 3.29 (1H, dt, J 2.1, 8.7 Hz), 3.58 (1H, s, OH), 3.80 (3H, s), 5.39 (1H, br s), 7.33 (5H, m). Identical $^1$H NMR spectrum was obtained at -40°C. $\delta C(\text{CDCl}_{3}, -40^\circ \text{C})$ 10.80, 22.82, 39.13, 52.50, 52.89 (OMe), 65.81, 71.90, 81.11, 125.70 (2C), 126.73, 127.96 (2C), 140.31, 176.31.

132: Mp 49-50°C (ether-pentane); m/z 172 [M$^+$-107 (PhCHOH)]; $[\alpha]^{23}_D +13.5$ (c 0.942, methanol); (Found: C, 64.4; H, 7.6; N, 4.9. C_{15}H_{21}NO_{4} \text{ requires C, 64.50; H, 7.58; N, 5.01 \%.) \; \nu_{\text{max}} (\text{KBr}) 3408, 2999, 2948, 2854, 1741, 1495, 1450, 1383, 1316, 1278, 1203, 1147, 1099, 1064, 1032, 988, 926, 871, 756 and 705 cm}^{-1}.

The 1H NMR spectrum in CDCl$_3$ at -40°C revealed the presence of two invertomers in a 63:37 ratio as determined by integration of several proton signals.

**Major invertomer:** \delta H(\text{CDCl}_{3}, -40^\circ \text{C}) : 0.80 (3H, d, J 6.7 Hz), 1.57 (3H, s), 2.26 (1H, m), 2.71 (1H, m), 2.83-3.25 (2H, m), 3.34 (1H, m), 3.67 (1H, s, OH), 3.84 (3H, s), 5.39 (1H, s), 7.37 (5H, m); \delta C(\text{CDCl}_{3}, -40^\circ \text{C}) 10.55, 24.29, 39.02, 52.08, 52.94 (OMe), 66.31, 72.06, 82.17, 125.82 (2C), 126.69, 127.92 (2C), 141.04, 174.73.

**Minor invertomer:** The invertomer has the following non overlapping 1H signals at \delta H(\text{CDCl}_{3}, -40^\circ \text{C}) 0.94 (3H, d, J 6.7 Hz), 2.11 (1H, m), 1.55 (3H, s), 3.98 (1H, s, OH),
5.21 (1H, s); δC(CDCl₃, -40°C) 4.00, 22.95, 38.10, 51.06, 52.90 (OMe), 64.06, 76.91, 81.63, 125.60 (2C), 126.90, 128.04 (2C), 140.64, 176.01.

Inversion barrier calculations. Simulations of exchange-affected proton spectra for all compounds were carried out using a computer program AXEX⁸⁶, corresponding to a two non coupled sites exchange with unequal populations. The following signals were utilized: 127a (or 128a), benzyl protons at δ5.26 (major, s) and δ5.14 (minor, s); 128a (or 127a), benzyl protons at δ5.35 (major, s) and δ5.00 (minor, s); 127b: (CDCl₃), CH₃ doublets appeared at δ0.85 (major) and δ1.09 (minor); 128b: (CDCl₃), CH₃ doublets appeared at δ0.94 (major) and δ1.02 (minor); 127c: (CD₃OD), CH₃ doublets appeared at δ0.77 (major) and δ1.02 (minor); 128c: (CDCl₃), benzyl protons at δ5.45 (major, s) and δ5.18 (minor, s); 128c: (CD₃OD), methyl doublets at δ0.80 (major) and δ1.01 (minor); 128d: (CDCl₃), benzyl protons at δ5.42 (major, s) and δ5.02 (minor, s); 132: (CDCl₃), benzyl protons at δ5.39 (major, s) and δ5.21 (minor, s).

Simulations of exchange affected triplets were carried out by modifying the two-site exchange program [87]. The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange. Simulations of exchange affected doublet of doublets were carried out by modifying the two-site exchange program. The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange.
CHAPTER 4

Peracid induced ring opening of some hexahydro-2H-isoxazol [2, 3-a] pyridines to second-generation cyclic aldonitrone

Summary:

A study of the stereo- and face-selectivity of the cycloaddition reactions of several mono- and disubstituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide has been carried out. The addition reactions have displayed a very high degree of face selectivity (13-48:1). Use of dimethyl methylenemalonate as a protective group in nitrone cycloaddition reactions has been demonstrated. The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer which leads to the formation of synthetically important second-generation cyclic aldonitrone via peracid oxidation. One interesting finding was that treatment of the cycloadducts with two equivalents of peracid afforded the cyclic N-hydroxy lactams, presumably via further oxidation of the aldonitrone. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

4.1 Introduction

1,3-Dipolar cycloaddition reaction of nitrones with alkenes has become an important tool in the synthesis of natural products [2]. The efficacy of these additions lies on the remarkable selectivity in the incorporation of multiple stereocenters in a single step [2]. The cyclic nitrones have been shown to exhibit greater stereoselectivity and reactivity compared to their acyclic counterparts as a result of the former existing in the E
form [2, 88]. The pyrrolidine- and piperidine-based alkaloids, which are widespread in nature, can be accessed through the cycloaddition reaction of five- and six-membered cyclic nitrones, respectively [2]. Nitrones generated by peracid-induced ring opening of the cycloaddition products derived from cyclic nitrones marked the beginning of the utilization of the second-generation of cyclic nitrones (Scheme 40) [89]. However, the proper utilization of these second-generation nitrones has been hampered by the lack of selectivity [90] in the oxidation process in the 6/5-fused isoxazolidines 133 (R1=H), where the major or sole trans invertomer leads to the synthetically less important ketonitrone 135 either as the major or sole product. Orientation of the nitrogen lone pair, and the \textit{trans/cis} invertomer ratio dictate the regiochemical outcome of the oxidation process. The higher activation barrier to nitrogen inversion mett principle [91] to apply; as such the \textit{trans} and \textit{cis} invertomers in a ratio of x:y afford ($\Delta G^\#$, ~70 kJ/mol)6b than the oxidation process does not permit the Curtin-Ham the keto- and aldo-nitrones, respectively, in a similar ratio. However, the corresponding 5/5-fused isoxazolidines 136, which exist only as the \textit{cis}-invertomers, give aldonitrones 137 exclusively (Scheme 42) [72].
Note that the 6/5-fused isoxazolidines 133 (R1=H) remain in the trans-form as the major or sole invertomer (Scheme 42). In our continuing efforts to generate the synthetically important aldonitrones 134 in greater proportions, we realized that the proportion of the cis-invertomer has to be increased at the expense of its trans counterpart. Attachment of an ester functionality (R1 = CO₂R) via its sp² hybridized carbon at C(5) in
did bring about a moderate change in the composition favouring the cis invertomer A as a result of the equatorially-oriented CO₂R group [73] We anticipated that a C(5) substituent attached through a sp³ hybridized carbon (having a larger steric size than its sp² counterpart) would motivate the ring further in the direction of the cis-invertomer A. Hence we report, for the first time, the face- and stereo-selectivity of cycloaddition of a new cyclic nitrone 140 (Scheme 43) having a hydroxymethyl substituent at C(4) with various alkenes. The invertomer analysis and peracid-induced ring opening of the resultant cycloadducts may lead to the second-generation cyclic aldonitrones (Scheme 42) more selectively. The study would give an opportunity to examine the face selectivity associated with cycloaddition of the second-generation nitrones 4,6-disubstitued-3,4,5,6-tetrahydropyridine 1-oxides 134.
4.2 Results and Discussion

The synthesis of nitrone 140 is outlined in (Scheme 43). It was presumed at the outset that preparation of the nitrone by direct oxidation of the secondary amine 138 will be a trivial matter. However, we were unable to obtain the nitrone by the procedure of Murahashi et al.[92] using hydrogen peroxide oxidation mediated by selenium dioxide either in acetone or methanol. The oxidation process gave a complicated mixture of products (presumably a mixture of 139, 140, and other products), which upon treatment with NaBH₄ afforded the hydroxylamine 139. The required nitrone 140 was then prepared by mercury(II) oxide oxidation of 139 (Scheme 43).
Next, we pursued the addition reaction of nitrone 140 with various alkenes. The addition of monosubstituted alkene 1-hexene (141a) was found to be stereo-, as well as highly face-selective; a mixture of diasteromers 142a and 144a was obtained in a ~13:1 ratio. The configuration of the major adduct 142a was based on the sterically favourable exo approach (Scheme 43) of the Bu group from the less hindered face (i.e. α face) of the nitrone, while the β-exo approach of the alkene afforded the adduct 144a. We are unable to detect the formation of the stereoisomers 143a and 145a arising from the α-endo and β-endo mode of approach, respectively, by the alkene. Likewise, the addition reaction with styrene (141b) led to the formation of the cycloadducts 142b-145b in a ratio of 93:5:2:~0, thereby ascertaining again the highly face selective (98:2) nature of the cycloadditions. Such a high selectivity is surprising since the C(4)-CH₂OH group imparting the facial difference is positioned at the furthest point from the nitrone functionality in 140. The face selectivity of the nitrone 140 was found to be better than a nitrone containing C(4)-CO₂Bu group (attached to the ring through a sp² carbon) [73]. In order to confirm the stereochemistry of the cycloadducts, the compounds 146, 147a, and 147b having known configurations [73], were converted into 142b, 144a and 144b, respectively (Scheme 43).

The addition of disubstituted alkenes methyl crotonate (148) and methyl methacrylate (153) to the nitrone 140 also demonstrated very high face selectivity (97:3) in each case (Scheme 44). In both cases, the major adducts (i.e. 149 and 154) were obtained via α-exo (Me) approach. The stereochemistry is based on the precedent in the literature [73, 18] - the major adducts were obtained via an endo-oriented methoxycarbonyl group in the transition state as a result of a favourable secondary orbital interaction.
In order to study the effect of increasing the steric bulk of the C(4) substituent in nitrone 140, the nitrone was first protected by reacting with dimethyl methylenemalonate (158) to give a regioisomeric mixture of 159a and 160a which upon silylation afforded 159b and 160b (Scheme 45). Similar electronic controlled reversal in the regioselections are known [72] in the addition reaction of the highly electron deficient alkene 158. The nitrone functionality is protected in the sense that the cycloadducts derived from the highly electron deficient alkene readily undergo cycloreversion to the starting reactants [72].
Thus upon thermolysis at 90°C, either 159b or 160b was changed to a mixture of 159b and 160b in an equilibrium ratio of 3:1.
Table 5

$^{13}$C NMR Chemical Shifts of compounds Studied in CDCl$_3$ at +25°C

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Invertomer$^c$</th>
<th>C-2</th>
<th>C-3</th>
<th>C-3a</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>via $\alpha$-mode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>142a {</td>
<td>cis-A</td>
<td>88</td>
<td>77.3</td>
<td>35.4</td>
<td>59.4</td>
<td>28.1</td>
<td>32.5</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>12</td>
<td>76.1</td>
<td>40.1</td>
<td>61.2</td>
<td>30.1</td>
<td>34.0</td>
<td>25.6</td>
</tr>
<tr>
<td>142b {</td>
<td>cis-A</td>
<td>90</td>
<td>78.9</td>
<td>38.8</td>
<td>59.9</td>
<td>28.3</td>
<td>32.6</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>10</td>
<td>77.7</td>
<td>43.2</td>
<td>61.7</td>
<td>30.1</td>
<td>34.0</td>
<td>25.7</td>
</tr>
<tr>
<td>143b {</td>
<td>cis-A</td>
<td>84</td>
<td>81.7</td>
<td>38.3</td>
<td>60.7</td>
<td>28.4</td>
<td>33.0</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>16</td>
<td>78.9</td>
<td>44.2</td>
<td>62.5</td>
<td>29.8</td>
<td>33.9</td>
<td>25.7</td>
</tr>
<tr>
<td>149</td>
<td>trans-C</td>
<td>65</td>
<td>75.2</td>
<td>57.1</td>
<td>62.9</td>
<td>27.1</td>
<td>33.6</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>cis-A</td>
<td>35</td>
<td>75.7</td>
<td>56.7</td>
<td>62.4</td>
<td>26.5</td>
<td>32.7</td>
<td>26.0</td>
</tr>
<tr>
<td>150</td>
<td>cis-A Solo</td>
<td>80.2</td>
<td>54.4</td>
<td>46.4</td>
<td>27.4</td>
<td>32.9</td>
<td>27.2</td>
<td>52.3</td>
</tr>
<tr>
<td>145 {</td>
<td>cis-A</td>
<td>80</td>
<td>84.3</td>
<td>39.6</td>
<td>59.9</td>
<td>27.9</td>
<td>32.6</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>20</td>
<td>80.0</td>
<td>44.9</td>
<td>61.6</td>
<td>29.5</td>
<td>33.7</td>
<td>25.3</td>
</tr>
<tr>
<td>159b</td>
<td>trans-C Solo</td>
<td>71.8</td>
<td>67.0</td>
<td>71.6</td>
<td>29.3</td>
<td>38.3</td>
<td>27.3</td>
<td>54.5</td>
</tr>
<tr>
<td>160b {</td>
<td>cis-A</td>
<td>84</td>
<td>87.0</td>
<td>38.1</td>
<td>60.3</td>
<td>27.7</td>
<td>32.7</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>16</td>
<td>83.3</td>
<td>42.7</td>
<td>61.7</td>
<td>29.7</td>
<td>33.3</td>
<td>25.3</td>
</tr>
<tr>
<td>162 {</td>
<td>cis-A</td>
<td>84</td>
<td>78.8</td>
<td>38.9</td>
<td>60.0</td>
<td>28.3</td>
<td>32.7</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>16</td>
<td>77.7</td>
<td>43.3</td>
<td>61.9</td>
<td>30.2</td>
<td>33.8</td>
<td>25.6</td>
</tr>
<tr>
<td>168a {</td>
<td>cis-A</td>
<td>83</td>
<td>77.3</td>
<td>35.3</td>
<td>59.1</td>
<td>28.3</td>
<td>29.5</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>17</td>
<td>76.1</td>
<td>40.0</td>
<td>61.0</td>
<td>30.4</td>
<td>30.5</td>
<td>25.8</td>
</tr>
<tr>
<td>168b {</td>
<td>cis-A</td>
<td>88</td>
<td>78.8</td>
<td>38.8</td>
<td>59.7</td>
<td>28.3</td>
<td>29.6</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>trans-C</td>
<td>12</td>
<td>77.7</td>
<td>43.1</td>
<td>61.6</td>
<td>30.5</td>
<td>30.5</td>
<td>25.9</td>
</tr>
<tr>
<td><strong>via $\beta$-mode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>144a</td>
<td>trans- F Solo</td>
<td>76.6</td>
<td>39.8</td>
<td>65.7</td>
<td>32.1</td>
<td>38.7</td>
<td>27.9</td>
<td>53.9</td>
</tr>
<tr>
<td>144b</td>
<td>trans- F Solo</td>
<td>78.2</td>
<td>42.8</td>
<td>66.2</td>
<td>32.1</td>
<td>38.6</td>
<td>27.9</td>
<td>54.0</td>
</tr>
<tr>
<td>156</td>
<td>trans- F Solo</td>
<td>80.5</td>
<td>44.6</td>
<td>66.1</td>
<td>31.6</td>
<td>38.4</td>
<td>27.5</td>
<td>54.1</td>
</tr>
</tbody>
</table>

$^c$Refers to invertomer A, C or F in Scheme 44.
When the thermolysis was carried out in the presence of styrene, the intervening nitrone 161 was trapped by undergoing stereoselective cycloaddition to give a mixture of adducts 162-165 in a ratio of 94:3:3:0. The exercise has thus demonstrated a suitable way to protect a nitrone functionality and also paved the way to examine the effect of changing the substituent C(4)-CH₂OH in 8 to C(4)-CH₂OSiBuMe₂ in 161 on the stereoselection and composition of nitrogen invertomers of the cycloadducts (vide infra).

The presence of −N−O− moiety in an organic molecule has a distinctive place in conformational analysis [84]; oxygen being next to nitrogen raises the barrier to nitrogen inversion to such an extent that the individual invertomers can be identified by NMR spectroscopy [83]. Orientation of the nitrogen lone pair with respect to the bridgehead hydrogen and the trans-/cis-fused invertomer ratio dictate the regiochemical outcome of the peracid oxidation process leading to the second-generation nitrones (vide supra) (Scheme 42). Therefore, the proper utilization of these second-generation nitrones requires prior information on the stereochemistry of the ring fusion. we have examined the conformational aspects as well as composition of the nitrogen invertomers by NMR spectroscopy. The ¹³C chemical shifts in CDCl₃ were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in (Table 4).
Scheme 45.
At ambient temperature, the $^1$H and $^{13}$C NMR spectra of these compounds show well separated signals for the two invertomers in CDCl$_3$. Integration of the relevant peaks gives the population trends in these systems (Table 4, 3rd column).

For the 6/5 fused carbocyclic compound 166, the $\Delta G^0$ value of 2.09 kJ/mol at 25°C favours the trans- over the cis-fused isomer (Scheme 46) [93]. Both 167 (the heterocyclic counterpart of 166), and its derivatives having substituents at the 2-, 3- and an ester group at the 5- position are also reported to favour, in most cases, the trans invertomers [83,93]. The currently prepared major isoxazolidines, obtained by $\alpha$-mode of attack, can, in principle, exist in three different chair conformations: the cis-fused pair A and B and the trans isomer C (Scheme 46). While the cis pair is in rapid equilibrium by chair inversion (CI), one of the cis conformers B is converted into the trans invertomer C by a relatively slow nitrogen inversion process (NI). The NMR spectra, both $^1$H and $^{13}$C, for some of the compounds show peaks due to two distinct isomers, a major and a minor invertomer. With respect to the six-membered ring, both cis-fused A and trans-fused C has one axial substituent at C(3a) and C(5), respectively, while cis-fused B has two energetically destabilizing axial substituents at C(5) and N. As such the major cycloadducts, obtained by an $\alpha$-mode of attack, are expected to remain as A and/or C. For the reasons discussed above, the minor isoxazolidines, obtained by $\beta$-mode of attack, should have an overwhelming preference for the trans-fused invertomer F since it is free of any destabilizing axial group. The conformer D having two axial substituents is anticipated to be the least favoured. Note that our objective is to have the isoxazolidines exist as the cis-fused invertomer in order to get the desired second-generation aldonitrone s via peracid oxidation (vide supra). While this may not be achieved in the case of the trans-fused
inertomer F, the overwhelmingly predominant cycloaddition products (via an α-mode of attack), is, however, expected to be in the desired cis-form A.

\[
\begin{align*}
\text{Major Adducts} & \quad (\text{via } \alpha\text{-mode of attack}) \\
A & \quad (\text{cis-fused}) \\
\text{Favoured} & \\
B & \quad (\text{cis-fused}) \\
C & \quad (\text{trans-fused}) \\
\end{align*}
\]

\[
\begin{align*}
\text{Minor Adducts} & \quad (\text{via } \beta\text{-mode of attack}) \\
D & \quad (\text{cis-fused}) \\
E & \quad (\text{cis-fused}) \\
F & \quad (\text{trans-fused}) \\
\text{Favoured} & \\
\end{align*}
\]

Scheme 46.

Isoxazolidine 146 (Scheme 43) has been shown to exist in a cis-A/trans-C ratio of 55:45 (Scheme 46) [94]. A comparison between compound 146 and 142b (Scheme 43), both having a phenyl group at C(2), may be helpful in identifying the stereochemistry of the ring fusion in the latter. Since the axially disposed CH$_2$OH substituent at C(5) of 142b, being larger in size than the ester substituent in 146, is expected to destabilize its trans 142-C as well as cis 142-B conformers; the relative proportion of cis-10b-A is anticipated to increase in compare to that of compound 146 (Scheme 46). As evident from Table 4, this is indeed the case; the cis-A isomer becomes the overwhelmingly major invertomer
for all the cycloadducts obtained via $\alpha$-mode of attack, except 159b (Scheme 45) which would be destabilized in cis-A as a result of placement of an axially-oriented tertiary sustituent (akin to a t-butyl group) at C3a. The correctness of the assignment of the configuration is based on the rationale detailed in the subsequent discussion.

The C(2)H of the cis invertomers of 6/5-fused isoxazolidines is known to appear at higher frequency compared to its trans invertomers [94,95]. This is indeed found to be the case for the current compounds in CDCl$_3$; the C(2)H of the cis-A invertomers invariably appeared at higher frequency compared to their trans-C isomers (Scheme 46). The axially disposed C(3a)H of trans-C, as expected, appeared at lower frequency in comparison to the corresponding equatorially disposed proton of cis-A (See Experimental). The axial substituent at C(3a) of the cis conformer A will have $\gamma$-gauche interactions with C(5) and C(7) and as such these carbon signals are expected to be shielded in comparison to the trans-C as is evident from Table 4. In cis-A all the carbons appeared at lower frequency except C-2 and C-6.

Where only one invertomer is observed as in the cases of 144a, 144b, 156, 159b (the minor products obtained via $\beta$-mode of attack), the C(2), C(3), C(3a) and C(7) chemical shifts match those of the trans-C invertomers, and we can therefore conclude that these compounds exist almost exclusively in the trans-F conformation (Scheme 44) (Table 4). The presence of 1,3-diaxial interaction exclude the participation of conformer cis-D in the equilibration process (Scheme 46). In the absence of D & E equilibration, the stabilization arising out of entropy gain will be lost; as such the all equatorial trans-invertomer F is expected to be overwhelmingly favoured over cis-E.
To get an idea about the magnitude of nitrogen inversion barriers in these compounds, 142b was selected as a representative example. The nitrogen inversion barrier, $\Delta G^\#$, was determined to be 71.3 kJ/mol for a major to minor inversion at 35°C in toluene-$d_8$. Simulations of exchange-affected proton spectra, corresponding to two non-coupled sites exchange with unequal populations, were carried out as described elsewhere [95]. For 142b in toluene-$d_8$, the C(2)H signals at $\delta$5.42 (major, dd, J 1.7, 4.9 Hz) and 5.28 ppm (minor) in a 83:17 ratio at $+30^\circ$C were utilized. For such a high free energy of activation barrier, the extremely fast peracid oxidation process (presumably with a lower activation barrier) is not expected to follow the Curtin-Hammett principle [81]; as such the trans and cis invertomers in a ratio of x:y should afford the keto- and aldo-nitrones, respectively, in a similar ratio. In order to ascertain the correctness of the assignment of the configuration of the invertomers, we carried out the peracid induced ring opening of isoxazolidines 168a and 168b (Scheme 47). The isoxazolidine 168a, having the cis and trans invertomers in a 83:17 ratio, on treatment with m-chloroperbenzoic acid (MCPBA) gave a mixture of the aldo- (169a) and keto-nitrone (170a) in a 80:20 ratio. For the corresponding ring opening reaction of the isoxazolidine 168b, having the cis and trans invertomers in a 88:12 ratio, a mixture of the aldo- (169b) and keto-nitrone (170b) in a ratio of 82:18 was obtained. It is indeed gratifying to see the ratio in favour of the synthetically more useful second-generation aldonitrones. One interesting finding was that the treatment of the isoxazolidines 168 with two equivalents of MCPBA at $-40^\circ$C afforded the N-hydroxyamides 171, presumably via further oxidation of the aldonitrones with peracid as shown in (Scheme 47). The formation of amide thus paves the way to obtain acyclic
compounds from the cyclic piperidine system via hydrolysis of the amide functionality in 171.

Next, we explored the cycloaddition reaction of the second-generation nitrones 169 and 170 with the alkenes 141. Under the reaction conditions, the ketonitrone remained inactive while the aldonitrone 169 afforded the cycloadducts 172 and 173 (Scheme 48). While the aldonitrone 169a afforded 172a and 173a in a 2:1 ratio, the corresponding ratio for 172b and 173b was found to be 1:1.5. For the addition of 1-hexene (141a) the face
selectivity is thus dictated by the steric influence of the substituent at C(6) so as to force the alkene to approach from the β-face of the nitrone, while styrene (141b) prefers to approach the nitrone from its α-face. The face selectivity is modest in these additions; however, we are unable to rationalize the difference in the face selectivity observed in the addition reactions of these two alkenes. The stereochemistry of these addition reactions were confirmed by chemical conversion into the ring opened products by cleaving the N-O bond of the cycloadducts with zinc/acetic acid. The NMR spectra of the amine 178 (C_{20}H_{39}NO_{4}), obtained from adduct 173a, confirmed its symmetric nature; as expected the \(^{13}\)C NMR spectrum revealed the presence of 12 carbon signals, whereas the isomeric 2,6-trans substituted amine 177, obtained from adduct 172a, displayed 18 different carbon signals as a result of its unsymmetrical nature. (In the unsymmetrical amine the signals at δ14.1 and 22.8 ppm belonged to two carbons in each case). The nonseparable mixture of adducts 172b and 173b upon hydrolysis was converted into a separable mixture of compounds 174 and 175. The N-O bond cleavage of 175 afforded the symmetrical cis amine 180, while 174 led to the unsymmetrical \(\textit{trans}\) amine 179.
Finally, we explored the face selectivity in the cycloaddition of the aldonitrone \textbf{169a} with 1,1-disubstituted alkene, methyl methacrylate (153). To our surprise, the addition was found to be highly face selective; adduct \textbf{176} and a nonseparable mixture of three minor adducts were obtained in a ratio of 88:12. The stereochemistry of the adduct was based on the approach of the alkene from the $\beta$-face of the nitrone to give 2,6-$\textit{trans}$ substituted adduct \textbf{176}. The assignment of stereochemistry was based on the observed stereochemistry of the addition reaction of the second-generation nitrones \textbf{169} to 1-hexene and styrene. In both cases the 3a,7-$\textit{trans}$ substituted adducts \textbf{172a} and \textbf{174} were found to have two invertomers, whereas the 3a,7-$\textit{cis}$ substituted adducts \textbf{173a} and \textbf{175} gave sharp NMR signals and revealed the presence of a single invertomer in each case. The major
adduct 176 in the nitrone 169a-methylmethacrylate addition reaction was also found to have a single invertomer and as such was assigned the 3a,7-\textit{trans} configuration. The conformational analysis revealed that while the adduct 142a remained as a mixture of two invertomers A and C in a ratio of 88:12 (\textit{vide supra}), the presence of two axial groups in A and B forces the 3a,7-\textit{cis}-substituted adduct 173a to remain exclusively in the invertomeric form of 173a-C (Scheme 49). While the adduct 144a remained exclusively in the invertomeric form of 144a-C (\textit{vide supra}), the 3a,7-\textit{cis}-substituted adduct 172a remained in the invertomeric forms of 172a-B and 172a-C in a ratio of 28:72 (See experimental). The presence of 172a-B in sizable proportion is justified even though it has two axial groups; the additional gauche interaction between C(7)R and N-O in 172a-C is absent in the conformer 172a-B, thereby encouraging its presence.
A systematic study of the stereochemistry associated with the cycloaddition of a C(4)-substituted and second-generation C(4),(6)-disubstituted six-membered cyclic nitrones has been carried out for the first time. The remarkable exo/endo- and face-selectivity observed in our study reflects the scope inherent in these important cycloaddition reactions. The study suggests that a bulkier tertiary substituent at C(4) may freeze the invertomer exclusively in the cis-fused form and thus would lead to the exclusive formation of the synthetically important second-generation aldonitrones via peracid induced ring opening of the cycloadducts.
4.3 Experimental

4.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer. $^1$H and $^{13}$C NMR spectra were measured in CDCl$_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Piperidine 4-carboxylic acid, 1-hexene, styrene, methyl methacrylate, methyl crotonate, m-chloroperbenzoic acid, from Fluka Chemie AG (Buchs, Switzerland) were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N$_2$. 4-Piperidinemethanol (138) was prepared from methyl ester of piperidine 4-carboxylic acid as described [73]. Dimethyl methylenemmalonate was prepared using the literature procedure [92].

4.3.2. $N$-hydroxy-4-Piperidinemethanol (139)

To a stirring solution of amine 138 (15 g, 130 mmol) with methanol (200 mL) in presence of selenium dioxide (0.7 g) at 0°C under N$_2$ was added dropwise a 30% H$_2$O$_2$ solution (18.5 g, 163 mmol) in 15 min. The mixture was then stirred at 20°C for 8 h. Sodium borohydride (2 g, 54 mmol) was added to the above mixture and stirring continued for 2 h. After removal of the solvent, the residual mixture was taken up in saturated K$_2$CO$_3$ solution (40 mL) and extracted with CH$_2$Cl$_2$/MeOH (9:1) (4×50 mL). The combined organic layers was dried (Na$_2$SO$_4$), concentrated and the residual liquid was purified by
chromatography over silica using 1:1 ether/methanol mixture as eluant to give the hydroxylamine 139 as a white solid (10.2 g, 60%). $m/z$ 131 [$M^+$]; mp 103-104°C (methanol-ether). (Found: C, 54.8; H, 9.9; N, 10.6. C₆H₁₃NO₂ requires C, 54.94; H, 9.99; N, 10.68 %); $\nu_{\text{max}}$ (KBr) 3226, 2963, 2911, 2856, 2830, 1656, 1480, 1446, 1383, 1276, 1242, 1133, 1103, 1037 and 996 cm⁻¹; $\delta_H$ (500 MHz, 9:1 CDCl₃/CD₃OD, +25°C) 3.42-3.28 (4H, m, C₂-HₐHₑ, C₆-HₐHₑ and CH₂O), 2.50-2.44 (2H, m, C₂-HₐHₑ, C₆-HₐHₑ), 1.81-1.31 (5H, m, C₃-H₂, C₄-H, C₅-H₃); $\delta_C$ (500 MHz, 9:1 CDCl₃/CD₃OD, +25°C) 66.6 (2C), 58.1, 37.2, 28.2 (2C). The hydroxylamine was partially soluble in CDCl₃, but soluble in a CDCl₃/CD₃OD mixture.

4.3.3. 4-Hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide (140)

To a solution of the hydroxylamine (5.24 g, 40 mmol) in EtOH or MeOH (50 mL) was added yellow HgO (18.0 g, 84 mmol) and the mixture was stirred using a magnetic stir bar at 35°C for 2 h or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and MgSO₄. The bed was washed with liberal excess of ethanol. The formation of the nitrone was assumed quantitative for the percent yield calculation in the subsequent cycloaddition reactions. $\delta_H$ (500 MHz, CD₃OD +25°C) 7.34-7.33 (1H, m), 3.87-3.72 (2H, m, C₆-H₂), 3.57-3.45 (2H, m, CH₂O), 2.66-2.56 (1H, m, C₃-HₐHₑ), 2.30-2.20 (1H, m, C₃-HₐHₑ), 2.11-2.03 (1H, m, C₅-HₐHₑ), 1.97-1.87 (1H, m, C₄-H), 1.83-1.71 (1H, m, C₅-HₐHₑ); $\delta_C$ (500 MHz, CD₃OD, +25°C) 143.6, 65.6, 57.7, 32.3, 29.5, 26.2. The nitrone can not be purified further since upon concentration it undergoes dimerization and other side reactions.

4.3.4. Reaction of nitrone 140 with 1-hexene (141a)
A solution of nitrone (10 mmol) in EtOH (40 mL) containing 1-hexene (141a) (6 mL) was heated at 90°C for 24 h under N₂ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give 142a containing minor amount of 144a. Continued elution gave a pure sample of the major adduct 142a as a colourless liquid. The minor diastereomer 144a was obtained in the pure form after repeated chromatography of the fraction containing the mixture of 142a and 144a. The combined yield of the cycloadducts was found to be (1.67 g, 78%).

The C(2) of the major adduct 142a appeared at 4.38 (major invertomer) and 4.02 ppm (minor invertomer). The overlapping C(2)H signal for the isomer 144a appeared at 4.06 ppm. The complete ¹H NMR analysis of the C(2)H of crude and the separated fraction revealed the ratio of the isomers 142a-145a as 93:~0:7:~0, respectively.

4.3.4.1 Major Diastereomer 142a

(Found: C, 67.4; H, 10.7; N, 6.5. C₁₂H₂₃NO₂ requires C, 67.57; H, 10.87; N, 6.57 %); νmax (neat) 3352, 2954, 2925, 2858, 1455, 1379, 1260, 1100, 1037, 963, and 765 cm⁻１. The major and minor invertomer at 25 °C was found to be in a ratio of 88:12 as determined by integration of the C(2)H at δ4.38 (major) and 4.02 (minor) ppm.

4.3.4.1.1. Major invertomer of 142a

δH (500 MHz, CDCl₃, 25 °C) 4.42-4.34 (1H, m, C₂-H), 3.66-3.58 (1H, m, C₃a-H), 3.49-3.41 (2H, m, CH₂OH), 3.08 (1H, td, J 3.2, 10.4 Hz, C₇-H₆aHc), 2.92 (1H, br, OH), 2.68 (1H, ddd, J 2.5, 10.3, 12.8 Hz, C₇-H₆bHc), 2.35 (1H, dt, J 9.5, 11.9 Hz, C₃-H₆aHb), 2.00 -1.20 (12H, m, (CH₂)₃, C₃-H₆bHb, C₄-H₂, C₅-H, C₆-H₂), 0.90 (3H, t, J 6.8 Hz, Me); δC
4.3.4.1.2. Minor invertomer 142a

Minor invertomer has the following non-overlapping signals: \( \delta_H \) (500 MHz, CDCl\(_3\), 25 °C) 4.07-3.97 (1H, m, C2-H), 3.64-3.60 (2H, m, CH\(_2\)OH), 3.33-3.27 (1H, m, C3a-H), 2.61-2.51 (1H, m, C7-H\(_a\)H\(_e\)), 2.04-1.94 (1H, m, C3-H\(_a\)H\(_b\)); \( \delta_C \) (500 MHz, CDCl\(_3\), 25 °C) 76.1, 67.2, 65.7, 53.9, 39.8, 38.7, 35.0, 32.1, 28.0, 27.9, 22.7, 14.0.

4.3.4.2. Minor diastereomer 144a

The sharp proton and carbon signals at +25 °C or -30 °C indicated the presence of a single invertomer. Colourless liquid (Found: C, 67.7; H, 10.9; N, 6.5. C\(_{12}\)H\(_{23}\)NO\(_2\) requires C, 67.57; H, 10.87; N, 6.57%).); \( \nu_{\text{max}} \) (neat) 3386, 2928, 2859, 1460, 1379, 1259, 1099, 1049, 1017, 898, and 779 cm\(^{-1}\); \( \delta_H \) (500 MHz, CDCl\(_3\), +25 °C) 4.10-4.02 (1H, m, C2-H), 3.56-3.46 (2H, m, CH\(_2\)O), 3.51-3.43 (1H, m, C3a-H), 2.56-2.46 (1H, m, C7-H\(_a\)H\(_e\)), 2.30-2.20 (1H, m, C7-H\(_a\)H\(_e\)), 2.02-1.20 (13H, m, (CH\(_2\)\(_3\)), C3-H\(_2\), C4-H\(_2\), C5-H, C6-H\(_a\)H\(_e\), OH), 1.14 (1H, q, J 12.2 Hz, C6-H\(_a\)H\(_e\)), 0.90 (3H, t, J 6.8 Hz, Me); \( \delta_C \) (500 MHz, CDCl\(_3\), +25 °C) 76.6, 67.2, 65.7, 53.9, 39.8, 38.7, 35.0, 32.1, 28.0, 27.9, 22.7, 14.0.

4.3.5. Reaction of nitrone 140 with styrene (141b)

A solution of nitrone 140 (10 mmol) in EtOH (40 mL) containing styrene (4 mL) was heated at 90 °C for 4 h under N\(_2\) in a closed vessel. After removal of the solvent and excess alkene, the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give 142b containing minor amount of 144b. Continued elution gave a pure sample of the major adduct 142b as
white crystals. Finally, a fraction containing 142b and 143b was obtained; repeated chromatography enriched the fraction to a ratio of 4:96 for the isomers 142b/143b. The combined yield of the cycloadducts was found to be (1.98 g, 85%). The fraction containing the mixture of 142b and 144b was crystallized to separate the major adduct 142b, while the mother liquor upon repeated chromatography gave the minor adduct 144b.

A careful 1H NMR (CDCl3, -40° C) analysis of the crude reaction mixture and the separated fractions revealed the presence of the isomers 142b-144b in a ratio of 93:5:2~0, respectively. The C(2) of the major adduct 142b appeared at δ 5.39 (major invertomer) and 5.02 ppm (minor invertomer). The corresponding proton for the isomer 143b appeared at δ 5.23(1H, apparent t, J 8.5 Hz). The C(2)H signal for the isomer 144b appeared as a dd (J 4.0, 9.8 Hz) at δ 5.05 ppm.

4.3.5.1. Major Diastereomer 142b

Mp 104–105 °C (ether-dichloromethane); m/z 233.1 [M+]; (Found: C, 72.0; H, 8.1; N, 5.9. C14H19NO2 requires C, 72.07; H, 8.21; N, 6.00 %); νmax (KBr) 3406, 2925, 2844, 1450, 1380, 1308, 1253, 1090, 1052, 955, 768, 701, and 630 cm⁻¹. The major and minor invertomer at 25 °C was found to be in a ratio of 90:10 as determined by integration of the C(2)H. (The ratio becomes 93:7 at -40 °C).

4.3.5.1.1. Major invertomer of 142b

δH (500 MHz, CDCl3, +25 °C) 7.44-7.24 (5H, m, Ph), 5.39 (1H, dd, J 3.7 and 9.8 Hz, C2-H), 3.88-3.80 (1H, m, C3a-H), 3.54-3.42 (2H, m, CH3OH), 3.26-3.18 (1H, td, J 3.3, 10.4 Hz, C7-HaHb), 2.82 (1H, ddd, J 2.2, 10.6, 12.8 Hz, C7-HaHb), 2.70 (1H, q, J 11.2 Hz, C3-HaHb), 2.50 (1H, br, OH), 2.05 -1.60 (5H, m, C3-HaHb, C4-H2, C5-H, C6-
H$_2$H$_2$), 1.38-1.24 (1H, m, C6-H$_b$H$_c$); $\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 142.3, 128.4 (2C), 127.6, 126.4 (2C), 78.9, 67.1, 59.9, 49.4, 38.8, 32.6, 28.3, 27.6.

4.3.5.1.2. Minor invertomer of 142b.

Minor invertomer has the following non-overlapping signals: $\delta$$_H$ (500 MHz, CDCl$_3$, +25°C) $\delta$ 5.06-4.98 (1H, m, C2-H; at -40 °C the signal becomes a dd ($J$ 4.2, 9.6 Hz)), 3.70-3.62 (2H, m, CH$_2$OH), 3.39-3.31 (1H, m, C3a-H), 2.38-2.26 (1H, m C3-H$_a$H$_b$); $\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 141.6, 128.3 (2C), 127.7, 126.7 (2C), 77.7, 63.2, 61.7, 51.1, 43.2, 34.0, 30.1, 25.7.

4.3.5.2. Minor diastereomer 143b

We were unable to obtain the distereomer 143b in pure form even after repeated chromatography. Finally, a fraction containing adduct 143b along with minor amount (~4%) of the isomer 142b was analyzed. The proton and carbon signals at 25 °C or -40 °C indicated the presence of two invertomers for 143b in a 84:16 ratio as indicated by the C(2)H (CDCl$_3$, -40°C) at $\delta$ 5.28 (1H, t, $J$ 8.5 Hz) and 5.10 (1H, t, $J$ 8.4 Hz). The invertomer ratio becomes 80:20 at + 25 °C. Colorless liquid; (Found: C, 71.9; H, 8.3; N, 6.1. C$_{14}$H$_{19}$NO$_2$ requires C, 72.07; H, 8.21; N, 6.00%). $\nu_{max}$ (neat) 3336, 2921, 2859, 1448, 1355, 1279, 1258, 1094, 1034, 961, 756, 700, and 673 cm$^{-1}$.

4.3.5.2.1. Major Invertomer of 143b

$\delta$$_H$ (500 MHz, CDCl$_3$, 25 °C) 7.52-7.20 (5H, m, Ph), 5.24 (1H, t, $J$ 8.5 Hz, C2-H), 3.90-3.78 (1H, m, C3a-H), 3.53-3.41 (2H, m, CH$_2$OH), 3.27 (1H, td, $J$3.7, 11.0 Hz, C7-H$_a$H$_c$), 2.73 (1H, t, $J$ 12.2 Hz, C7-H$_a$H$_c$), 2.59-2.47 (1H, m, C3-H$_a$H$_b$), 2.38 (1H, q, $J$ 12.2
Hz, C3-HaHb), 2.09 (1H, apparent d, J 14.6 Hz, C6-HaHc), 1.85-1.57 (4H, m, C4-Ha, C5-H, OH), 1.31 (1H, apparent q, J 12.2 Hz, C6-HaHc); δC (500 MHz, CDCl3, +25 °C) 143.2, 128.3 (2C), 127.1, 125.6 (2C), 81.7, 67.3, 60.7, 52.0, 38.3, 33.0, 28.4, 27.7.

4.3.5.2.2. Minor Invertomer of 143b

δC (500 MHz, CDCl3, +25 °C) 143.2, 128.3 (2C), 127.1, 125.6 (2C), 78.9, 63.6, 62.5, 51.3, 44.2, 33.9, 29.8, 25.7.

4.3.5.3. Minor diastereomer 144b

Colourless liquid; (Found: C, 71.8; H, 8.0; N, 5.8. C14H19NO2 requires C, 72.07; H, 8.21; N, 6.00 %). The signals were sharp; the 1H spectrum revealed the presence of a single invertomer. \( \nu_{\text{max}}(\text{neat}) \) 3356, 2921, 2849, 1449, 1364, 1324, 1260, 1099, 1051, 1011, 948, 912, 760, 730 and 699 cm\(^{-1}\); δH (500 MHz, CDCl3, +25 °C) 7.47-7.23 (5H, m, Ph), 5.05 (1H, dd, J 4.9, 9.8 Hz, C2-H), 3.54 (3H, m, C3a-H, CH2OH), 2.68 (1H, apparent t, J 9.8 Hz, C7-HaHc), 2.60-2.50 (1H, m C7-HaHc), 2.37 (1H, q, J 11.0 Hz, C3-HaHb), 2.23-2.15 (1H, m, C3-HaHb), 2.08 (1H, d, J 12.2 Hz, C4-HaHc), 2.01-1.89 (2H, m, C4-HaHc, OH), 1.76-1.64 (1H, m, C5-H), 1.48 (1H, dq, J 3.7, 13.4 Hz, C6-HaHc), 1.21 (1H, q, J 12.2 Hz, C6-HaHc); δC (500 MHz, CDCl3, +25 °C) 141.6, 128.4 (2C), 127.8, 126.7 (2C), 78.2, 66.9, 66.2, 54.0, 42.8, 38.6, 32.1, 27.9.

4.3.6. Lithium aluminium hydride reduction of ester cycloadduct 146 to 142b

To a stirred solution of ester adduct 146 of known configuration\(^9\) (100 mg, 0.33 mmol) in ether (15 mL) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1
g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH₂Cl₂. The organic layer was dried (Na₂SO₄), concentrated, and purified by silica gel chromatography using a 95:5 CH₂Cl₂/methanol as the eluant to give 142b as a white solid (71 mg, 92%), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.5.

4.3.7. Lithium aluminium hydride reduction of ester cycloadduct 147a to 144a

A sample of adduct 147a was reduced with LiAlH₄ using procedure as described in Section 3.6 to give 144a as a colourless liquid (93% yield), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.2.

4.3.8. Lithium aluminium hydride reduction of ester cycloadduct 147b to 144b

A sample of adduct 147b was reduced with LiAlH₄ using procedure as described in Section 4.3.6 to give 144b as a colourless liquid (90% yield), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.5.3.

4.3.9. Reaction of nitrone 140 with methyl crotonate (148)

A solution of nitrone 140 (5.0 mmol) in EtOH (20 mL) containing methyl crotonate (148) (4 mL) was heated at 90 °C for 10 h under N₂ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was purified by chromatography over silica using 95:5 ether/methanol as eluant to give a non-separable mixture of adducts 149-151 as a colourless liquid (0.974 g, 85%). We were unable to separate the isomers even after repeated chromatography. (Found: C, 57.5; H, 8.2; N, 6.0.)
C$_{11}$H$_{19}$NO$_4$ requires C, 57.63; H, 8.35; N, 6.11 %; $\nu_{\text{max}}$ (neat) 3380, 2929, 2855, 1730, 1439, 1392, 1379, 12.97, 1265, 1203, 1179, 1113, 1090, and 1029 cm$^{-1}$.

A careful $^1$H NMR (CDCl$_3$, -40$^\circ$ C) analysis of the crude reaction mixture and the separated fractions revealed the presence of the isomers 149-151 in a respective ratio of 81:16:3. The C(2) of the major adduct 149 appeared at $\delta$4.50 (quint, $J$ 5.8 Hz, major invertomer) and 5.01 ppm (quint, $J$ 6.1 Hz, minor invertomer) in a 65:35 ratio. The ratio becomes 60:40 at +25$^\circ$ C. The corresponding proton of the isomers 150 and 151 appeared at $\delta$4.41 (qd, $J$ 6.5, 8.9 Hz, single invertomer), and 4.29 (quint, $J$ 6.1 Hz, single invertomer). The CO$_2$Me singlets of the 149 appeared at $\delta$3.75 (major invertomer), and 3.79 (minor invertomer) and that of 150 appeared at 3.77 ppm. The C(2)Me (CDCl$_3$, +25$^\circ$ C) signal for the isomer 149, 150 and 151 appeared at $\delta$1.33 (d, $J$ 6.4 Hz), 1.50 (d, $J$ 6.4 Hz), and 1.44 (d, $J$ 6.4 Hz), respectively.

4.3.9.1. Major invertomer of major diastereomer 149

$\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 172.1, 75.2, 64.5, 62.9, 57.1, 52.3, 51.3, 33.6, 27.1, 25.2, 19.3.

4.3.9.2. Minor invertomer of major diastereomer 149

$\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 173.6, 75.7, 66.6 (CH$_2$O), 62.4, 56.7, 51.8 (OMe). 48.6, 32.7, 26.5, 26.0, 19.5.

4.3.9.3. Minor diastereomer 150

A single invertomer. $\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 171.8, 80.2, 66.6 (CH$_2$O), 64.0, 54.4, 52.8, 52.3, 33.0, 27.4, 27.2, 22.7.
4.3.10. Reaction of nitrone 140 with methyl methacrylate (153)

A solution of nitrone 140 (5.0 mmol) in EtOH (20 mL) containing methylmethacrylate (153) (4 mL) was heated at 50°C for 6 h under N₂ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give 157 containing minor amount 154. Continued elution afforded 22 along with minor amounts of 156 and 157. The first fraction was rechromatographed to obtain 157 as a colourless liquid. Adduct 154 was obtained from the second fraction as white crystals by crystallization. The mother liquor contained a mixture of 154-157. The combined yield of the cycloadducts was found to be (1.05 g, 92%). The ¹³C (CDCl₃, -40°C) spectrum of the crude mixture revealed the presence of C(2) of the major and minor invertomers of 154 at δ84.2 and 79.8 ppm in a 80:20 ratio. The corresponding signal for the isomer 157 appeared as a sole invertomer at 80.33, while the signals at δ84.8 and 80.6 in a respective ratio of 65:35 were assigned to C(2) of the major and minor invertomers of 156. The ratio, as approximated, by analysis of ¹³C and ¹H of the crude as well as the separated fraction revealed the presence of 154, 156 and 157 in ratio of 92:5:3, respectively. We were unable to obtain a pure sample of the minor isomer 156 even after repeated chromatography.

4.3.10.1 Major Diastereomer 154

The major and minor invertomer at 25°C was found to be in a ratio of 80:20 as determined by integration of several non overlapping signals (the ratio remains the same at
-40 °C). Mp 72-73 °C (ether-dichloromethane); m/z 229 [M⁺]; (Found: C, 57.5; H, 8.3; N, 6.1. C₁₁H₁₉NO₄ requires C, 57.62; H, 8.35; N, 6.11%); νₘₐₓ (KBr) 3337, 3234, 2953, 2926, 2862, 1746, 1727, 1454, 1442, 1370, 1255, 1127, 1183, 1086, 1026, 980, 962, 770, and 631 cm⁻¹.

4.3.10.1.1. Major inveromer of 154

δ_H (500 MHz, CDCl₃, +25 °C) 3.78 (3H, s, COMe), 3.69-3.61 (1H, m, C3a-H), 3.53-3.42 (2H, m, CH₂OH), 3.16 (1H, d, J 7.5 Hz, C7-H₃H₂), 2.87 (1H, t, J 11.7 Hz, C7-H₃H₂), 2.68 (1H, t, J 10.0 Hz, C3a-H), 2.10-1.50 (6H, m, C3-H₃H₂, C4-H₂, C5-H, C6-H₃H₂, OH), 1.49 (3H, s, Me), 1.35-1.19 (1H, m, C6-H₃H₂); δ_C (CDCl₃, +25 °C) 175.5, 84.3, 67.1, 59.9, 52.7, 50.2, 39.6, 32.6, 27.9, 27.5, 25.7.

4.3.10.1.2. Minor invertomer of 154

Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, CDCl₃, +25°C): δ 3.39-3.30 (1H, m, C3a-H), 2.64-2.53 (1H, m, C7-H₃H₂), 2.50-2.35 (1H, m, C7-H₃H₂), 2.18-2.07 (1H, m, C3-H₃H₂); δ_C (CDCl₃, +25 °C) 175.5, 80.0, 63.3, 61.6, 52.7, 51.2, 44.9, 33.7, 29.5, 25.3, 24.8.

4.3.10.2 Minor Diastereomer 157

Colourless liquid. (Found: C, 57.4; H, 8.2; N, 5.9. C₁₁H₁₉NO₄ requires C, 57.62; H, 8.35; N, 6.11%). The ¹H spectrum revealed the presence of a single invertomer. νₘₐₓ (neat) 3350, 2924, 2853, 1730, 1445, 1373, 1260, 1210, 1142, 1040, and 986 cm⁻¹; δ_H (500 MHz, CDCl₃, +25 °C) 3.77 (3H, s, COMe), 3.58-3.46 (3H, m, C3a-H, CH₂OH), 2.58-2.48 (1H, m, C7-H₃H₂), 2.47-2.35 (2H, m, C7-H₃H₂, OH), 2.20-2.12 (1H, m, C3-H₃H₂), 2.07-1.97 (1H, m, C3-H₃H₂), 1.92-1.82 (1H, m, C5-H), 1.73-1.60 (2H, m, C4-H₃H₂, C6-
1.50 (3H, s, Me), 1.48-1.40 (1H, m, C4-HaHb), 1.16 (1H, q, J 11.9 Hz, C6-HcHd); δC (500 MHz, CDCl3, +25 °C) 175.6, 80.5, 67.2, 66.1, 54.1, 52.6, 44.6, 38.4, 31.6, 27.5, 24.7.

4.3.11. Reaction of nitrone 140 with dimethyl methylenemalonate (158) and conversion of cycloadducts 159a and 160a to silylated ethers 159b and 160b

A solution of nitrone 140 (10 mmol) in methanol (40 mL) was reacted with dimethylmethylenemalonate (158) (1.73 g, 12 mmol) at 20 °C for 1 h. After removal of the solvent by blowing a gentle stream of N2, the residual liquid was dried under vacuum to a constant weight (3 g). Extensive decomposition happened during silica gel chromatography to separate and purify the cycloadducts 159a and 160a. As such, the crude products were silylated using the following procedure. To a solution of the crude adducts 159a and 160a (~10 mmol) in DMF (25 mL) was added imidazole (2.7 g, 40 mmol). A solution of t-butyldimethylsilyl chloride (2.1 g, 14 mmol) in DMF (10 mL) was added dropwise to the above mixture at 0°C over a period of 15 min. the reaction mixture, after stirring at 0 °C for 1 h, was allowed to warm to 20°C and stirring continued for an additional 4 h. The mixture was taken up in ether (50 ml) and washed with water (3×50 mL). The organic layer was dried over (MgSO4), concentrated and the residual liquid was chromatographed over silica gel using hexane/ether as the eluent to give 159b as a white solid. Continued elution afforded a mixture of 159b and 160b, and finally, the isomer 160b as a colourless liquid. The approximate ratio of 159b and 160b was found to be 3:1. The overall yield for the two steps was determined to be (3.18 g, 82%).

4.3.11.1. Major Diastereomer 159b
Both the $^1$H and $^{13}$C NMR spectra in CDCl$_3$ revealed the presence of a single
invertomer. Mp 45-46°C (ether/hexane); (Found: C, 55.7; H, 8.5; N, 3.6. C$_{18}$H$_{33}$NO$_6$Si
requires C, 55.79; H, 8.58; N, 3.61%).; v$_{\text{max}}$ (KBr) 2953, 2927, 2855, 1741, 1460, 1435,
1257, 12.05, 1104, 1005, 836, and 776 cm$^{-1}$; $\delta$$_H$ (500 MHz, CDCl$_3$, +25 °C) 4.56 (1H, d, $J$
8.8 Hz, C2-$^a$H$_a$H$_b$), 4.21 (1H, d, $J$ 8.8 Hz, C2-$^a$H$_a$H$_b$), 3.78 ( 3H, s, CO$+$Me), 3.77 ( 3H, s,
CMe$_3$), 3.53-3.48 (1H, m, C3a-$^a$H), 3.47-3.42 (2H, m, CH$_2$OSi), 2.88 (1H, dd, $J$ 2.4, 11.7
Hz, C7-$^a$H$_a$H$_e$), 2.50 (1H, ddd, $J$ 2.9, 9.5, 12.3 Hz, C7-$^a$H$_a$H$_e$), 2.12 (1H, apparent d, $J$ 13.1
Hz, C4-$^a$H$_a$H$_b$), 1.83 (1H, apparent d, $J$ 14.0 Hz, C6-$^a$H$_a$H$_e$), 1.68-1.60 (1H, m, C5-$^a$H), 1.41
(1H, dq, $J$ 4.0, 12.5 Hz, C4-$^a$H$_a$H$_b$), 1.03 (1H, q, $J$ 11.9 Hz, C6-$^a$H$_a$H$_e$), 0.87 (9H, s, CMe$_3$),
0.031 (6H, s, CMe$_3$); $\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 170.2, 168.9, 71.8, 71.6, 67.0, 54.5,
53.3, 52.9, 52.8, 38.3, 29.3, 27.3, 25.9 (3C), 18.3, (-) 5.4 (2C).

4.3.11.2. Minor Diastereomer 160b

(Found: C, 55.6; H, 8.5; N, 3.5. C$_{18}$H$_{33}$NO$_6$Si requires C, 55.79; H, 8.58; N, 3.61%).; The $^{13}$C NMR
spectrum revealed the presence of two invertomers in a 84:16. $v_{\text{max}}$
(neat) 2954, 2928, 2855, 1766, 1754, 1746, 1738, 1731, 1470, 1462, 1454, 1434, 1251,
1203, 1135, 1108, 1083, 1044, 1005, 837, and 776 cm$^{-1}$; $\delta$$_H$ (500 MHz, CDCl$_3$, +25 °C)
3.28-3.83 (10H, m, including several CO$_2$Me singlets), 2.30-2.90 (2H, m), 1.50-2.03 (5H,
m), 0.87 (9H, s, CMe$_3$), 1.29-1.15 (1H, m, C6-$^a$H$_a$H$_e$), 0.034 (3H, s, Me), 0.031 (3H, s, Me).

4.3.11.2.1. Major invertomer of 160b

$\delta$$_C$ (500 MHz, CDCl$_3$, +25 °C) 170.3, 168.9, 87.0, 67.1, 60.3, 53.3 (2C), 50.9,
38.1, 32.7, 27.7, 27.6, 25.9 (3C), 18.3, (-) 5.4 (2C).

4.3.11.2.2. Minor invertomer of 160b
δC (500 MHz, CDCl₃, +25 °C) 170.3, 168.9, 83.3, 63.5, 61.7, 53.3, 52.7, 51.4, 42.7, 33.3, 29.5, 25.9 (3C), 25.3, 18.3, (-) 5.4 (2C).

4.3.12. Thermolysis of 159b in toluene-d₆

A solution of the adduct 159b (20 mg) in toluene-d₆ was thermolyzed at 90°C. After 30 min of heating the ratio of 159b and 160b became 77:23, while the ratio became 72:28 after 2 h at 90°C and thereafter remained unchanged. The CO₂Me of 159b appeared at δ3.29 and 3.35 ppm, while that of 160b appeared at 3.32 and 3.39 ppm. The C(3a) proton of the 160b appeared at δ3.70, while the C(2) Hs appeared at 4.83 (1H, d, J 8.6 Hz), 4.20 (1H, J 8.6 Hz).

4.3.13. Thermolysis of 159b in toluene in the presence of styrene (141b)

A solution of 159b (400 mg, 1.03 mmol), styrene (1.5 mL) in toluene (5 mL) was stirred under N₂ at 100°C overnight. After removal of the solvent and excess alkene, residual liquid was chromatographed over silica gel using hexane/ether as the eluent to give 163 as a white solid. Continued elution afforded a mixture of 163-165. The yield was found to be 83% (0.297 g). The crude mixture revealed the presence of three adducts as revealed by the presence of C(2)H of 162 at δ5.40 (major invertomer) and 5.02 (minor invertomer), 164 at 5.23 (1H, t, J 8.7 Hz, major invertomer) and 5.10 (minor invertomer, overlapping), and 165 at 5.10.

In order to determine the structure and composition of 163-165, a portion of the above crude adducts was hydrolyzed with 5:1 MeOH/HCl at 20°C (10 min) to 142b-145b. ³H NMR (CDCl₃, -30°C) analysis of the crude hydrolyzed products revealed the presence
of three isomers **142b-144b**, hence **163-165**, in a ratio of 94:3:3 as indicated by integration of the C(2)H signals as described (Section 4.3.5).

### 4.3.13.1. Major adduct 163

Mp. 80-81°C (ether-pentane); (Found: C, 68.9; H, 9.4; N, 3.9. C_{20}H_{33}NO_2Si requires C, 69.11; H, 9.57; N, 4.03%); ν_{max} (KBr) 2928, 2888, 2855, 1459, 1386, 1361, 1253, 1115, 1077, 1044, 1006, 834, 763, 703 and 661 cm^{-1}. The major and minor invertomer at 25 °C was found to be in a ratio of 86:14 as determined by integration of the C(2)H. (The ratio becomes 93:7 at -40 °C).

#### 4.3.13.1.1. Major invertomer 163

δ_{H} (500 MHz, CDCl_{3}, 25 °C) 7.37-7.25 (5H, m, Ph), 5.40 (1H, dd, J 3.6, 9.8 Hz, C2-H), 3.85-3.75 (1H, m, C3a-H), 3.51-3.41 (2H, m, CH_{2}OSi), 3.26-3.20 (1H, m, C7-H_{a}H_{e}), 2.83 (1H, ddd, J 2.6, 10.4, 13.1 Hz, C7-H_{a}H_{e}), 2.73 (1H, dt, J 10.0, 11.9 Hz, C3-H_{a}H_{b}), 1.50-2.00 (5H, m, C3-H_{a}H_{b}, C4-H_{2}, C5-H, C6-H_{a}H_{e}), 1.32-1.20 (1H, m, C6-H_{a}H_{e}), 0.89 (9H, s, CMe_{3}), 0.03 (6H, s, Me_{2}); δ_{C} (500 MHz, CDCl_{3}, 25 °C) -5.4 (2C), 18.3, 25.9 (3C), 27.7, 28.3, 32.7, 38.9, 49.5, 60.0, 67.5, 78.8, 126.4 (2C), 127.5, 128.4 (2C), 142.5.

#### 4.3.13.1.2. Minor invertomer 163

δ_{H}(500 MHz, CDCl_{3}, 25°C). Minor invertomer has the following non-overlapping signals: δ5.02 (1H, dd, J 4.3 and 9.0 Hz) , C2-H, broad dd at 25°C became sharp at -40°C), 3.58-3.52 (1H, m, C3a-H), 3.33-3.27 (2H, m); δ_{C} (500 MHz, CDCl_{3}, 25 °C) 142.3, 128.4 (2C), 127.6, 126.8 (2C), 77.7, 63.8, 61.9, 51.2, 43.3, 33.8, 30.2, 25.6, 25.9 (3C), 15.0, -5.4 (2C).

### 4.3.14. Conversion 142a into its acetate 168a
The cycloadduct 142a (1.28 g, 6.0 mmol) in CH₂Cl₂ (10 mL) was treated with acetic anhydride (3 mL) at 25 °C for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using ether as eluant to give 168a as a colourless liquid (1.46 g, 95%). (Found: C, 65.9; H, 9.8; N, 5.4. C₁₄H₂₅NO₃ requires C, 65.85; H, 9.87; N, 5.49 %). νₑₑₑ max (neat) 2955, 2929, 2857, 1742, 1454, 1366, 1244, 1036, and 963 cm⁻¹. The ¹H NMR spectrum revealed the presence of two invertomers in a ratio of 83:17.

4.3.14.1. Major invertomer of 168a

δ_H (500 MHz, CDCl₃, +25 °C) 4.43-4.37 (1H, m, C2-H), 3.92 (2H, ABX, J 6.4, 10.7 Hz, CH₂OAc), 3.60 (1H, app. quint, J 5.8 Hz, C3a-H), 3.11 (1H, td, J 3.4, 10.4 Hz, C7-HₐHₑ), 2.69 (1H, ddd, J 2.6, 10.4, 12.9 Hz, C7-HₐHₑ), 2.33 (1H, dt, J 9.4, 11.9 Hz, C3-HₐHₑ), 2.06 (3H, s, COMe), 2.00-1.80 (2H, m, C3-HₐHₑ, C5-H), 1.78-1.68 (2H, m, C4-HₐHₑ, C6-HₐHₑ), 1.63-1.53 (1H, m, C4-HₐHₑ), 1.55-1.45 (1H, m, C6-HₐHₑ), 1.43-1.23 (6H, m, (CH₃)₃Me), 0.90 (3H, t, J 7.0 Hz, Me); δ_C (500 MHz, CDCl₃, +25 °C) 171.0, 77.3, 68.3, 59.1, 48.8, 35.3, 35.2, 29.5, 28.3, 28.1, 27.6, 22.7, 20.9, 14.0.

4.3.14.2. Minor invertomer of 168a

δ_H (CDCl₃, +25 °C) Non overlapping signals at 4.13-4.09 (2H, m, CH₃OAc), 4.06-4.01 (1H, m, C2-H), 3.32-3.26 (1H, m, C3a-H), 2.62-2.54 (1H, m), 2.03 (3H, s, COMe); δ_C (500 MHz, CDCl₃, +25 °C) 173.8, 76.1, 65.0, 61.0, 50.7, 40.0, 34.9, 30.5, 30.4, 28.0, 25.8, 22.7, 21.1, 4.0.

4.3.15. Conversion 142b into its acetate 168b
The cycloadduct 142b (1.40 g, 6.00 mmol) in toluene (10 mL) was treated with acetic anhydride (1 mL) at 70°C for 3 h. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 60:40 hexane/ether as eluant to give 168b as white crystals (1.58 g, 96%). Mp 97-98 °C (hexane/ether); m/z 275 [M⁺]; (Found: C, 69.6; H, 7.6; N, 5.0. C₁₆H₂₁NO₃ requires C, 69.79; H, 7.69; N, 5.09 %); νmax (KBr) 3028, 2952, 2919, 2854, 1741, 1456, 1366, 1245, 1035, 946, 903, 765, 708, 670, and 644 cm⁻¹. The major and minor invertomers of 168b at 25 °C was found to be in a ratio of 88:12 as determined by integration of the C(2)H.

4.3.15.1. Major invertomer of 168b

δH (500 MHz, CDCl₃, 25 °C) 7.37-7.25 ( 5H, m, Ph) , 5.41 ( 1H, dd, J 3.7 and 9.8 Hz, C2-H) , 3.95 ( 2H, ABX, J 6.1, 6.4, 10.7Hz, CH₂OAc), 3.88-3.83 (1H, m, C3a-H), 3.24 (1H, td, J 3.4, 10.4 Hz, C7-HaHb) , 2.84 (1H, ddd, J 2.5, 10.4, 12.8 Hz, C7-HaHb), 2.73 (1H, app. q, J 11.6 Hz, C3-HaHb), 2.07 (3H, s, COMe), 1.75-2.15 (5H, m, C3-HaHb, C4-H₂, C5-H, C6-HaHb), 1.40 (1H, dq, J 2.2, 12.2 Hz, C6-HaHb); δC (500 MHz, CDCl₃, +25 °C) 171.0, 145.2, 128.5 (2C), 127.6, 126.4 (2C), 78.8, 68.2, 59.7, 49.1, 38.8, 29.6, 28.3, 27.6, 20.9.

4.3.15.2. Minor invertomer of 168b

Minor invertomer has the following non-overlapping signals: δH (500 MHz, CDCl₃, 25 °C) 5.02 (1H, dd, J 3.9 and 8.8 Hz, C2-H), 4.14 (2H, d, J 7.9 Hz, CH₂OAc), 3.42-3.37 (1H, m, C3a-H), 2.67-2.57 (1H, m), 2.33 (1H, app q, J 10.4 Hz), 1.74-1.65 (1H, m); δC (500 MHz, CDCl₃, 25 °C) 171.0, 141.5, 128.5 (2C), 127.9, 126.7 (2C), 77.7, 64.9, 61.6, 50.9, 43.1, 30.5 (2C), 25.9, 20.9.
4.3.16. MCPBA oxidation of adduct 168a to nitrones 169a and 170a. Cycloaddition of 169a with 1-hexene (141a)

To a stirred solution of the cycloadduct 168a (3.0 mmol) in dichloromethane (30 mL) at 20°C was added MCPBA (3.0 mmol) in one portion. After 30 m at 20 °C the organic layer was washed with 5% NaHCO₃ solution (3×10 mL). The combined aqueous layers were re-extracted with CH₂Cl₂ (3×25 mL). The combined organic layers was dried (Na₂SO₄), concentrated to give a mixture of the aldonitrone 169a and keto-nitrone 170a in a ratio of 80:20, respectively, as a pale yellow liquid in almost quantitative yield. A small portion of the solution was concentrarated for ¹H NMR analysis which revealed the aldonitrone 169a having the following characteristic signals at δ7.18 (1H, t, J 3.5 Hz, CH=N), 4.24 (1H, m, =NCH), 2.08 (3H, s), 0.90 (3H, t, J 7.0 Hz). The Ketonitrone 170a has the following nonoverlapping signals at δ3.00 (1H, dd, J 9.6, 13.1 Hz), 2.17 (3H, s).

After exchanging CH₂Cl₂ with toluene (15 mL), the above solution of nitrones was treated with 1-hexene (141a) (5 mL) at 75°C for 48 h. After removal of the solvent and excess alkene, the residual mixture was separated by chromatography over silica gel using 1:1 hexane/ether as eluant to give the minor cycloadduct 173a as a colourless liquid (220 mg, 21%). Continued elution afforded the major isomer 172a also as a colourless liquid (423 mg, 40%). Finally, elution with 90:10 ether/methanol afforded the un-reacted ketonitrone 170a as a colourless liquid.
4.3.16.1. Major cycloadduct 172a

(Found: C, 67.3; H, 10.2; N, 3.8. C\textsubscript{20}H\textsubscript{37}NO\textsubscript{4} requires C, 67.57; H, 10.49; N, 3.94\%). \(\nu\text{max} \text{ (neat)}\ 3440, 2918, 2850, 1743, 1467, 1451, 1427, 1371, 1254, 1121, 1039, 901, 782, \text{ and } 732 \text{ cm}^{-1}.\) The ratio of the invertomers by \(^{13}\text{C}\) was estimated to be 85:15.

4.3.16.1.1. Major invertomer of 172a

\(\delta\text{H} \ (500 \text{ MHz, CDCl}_3, -40^\circ\text{C})\ 5.48 \ (1\text{H, br s, O}\text{H}), 4.13-4.05 \ (1\text{H, m, C2-H}), 3.95-3.83 \ (2\text{H, m, CH}_3\text{OAc}), 3.85-3.78 \ (1\text{H, m, C3a-H}), 3.74-3.66 \ (1\text{H, m, C7-CH}_2\text{CHO}), 3.57-3.49 \ (1\text{H, m, C7-H}), 2.10 \ (3\text{H, s, COMe}), 1.10-2.05 \ (21\text{H, m}), 0.91 \ (6\text{H, two overlapping t, } J 7.0 \text{ Hz, CH}_2\text{Me, CH}_2\text{Me}); \delta\text{C} \ (500 \text{ MHz, CDCl}_3, -40^\circ\text{C})\ 171.7, 75.3, 70.0, 68.6, 54.2, 53.0, 40.9, 36.3, 35.9 \ (2\text{C}), 29.0, 28.6, 28.5, 28.1, 26.9, 22.8, 22.6, 21.2, 14.3, 14.2.

4.3.16.1.2. Minor invertomer of 172a

Minor invertomer has the following nonoverlapping signals: \(\delta\text{C} \ (500 \text{ MHz, CDCl}_3, -40^\circ\text{C})\ 76.2, 68.0, 54.5, 39.3, 36.8, 34.9, 33.5, 32.8, 32.5, 30.3, 30.0, 27.9, 22.7.

4.3.16.2. Minor cycloadduct 173a

The \(^1\text{H}\) spectrum revealed the presence of a single invertomer. (Found: C, 67.4; H, 10.3; N, 3.8. C\textsubscript{20}H\textsubscript{37}NO\textsubscript{4} requires C, 67.57; H, 10.49; N, 3.94 \%). \(\nu\text{max} \text{ (neat)}\ 3430, 2954, 2927, 2858, 1742, 1466, 1451, 1370, 1237, 1036, 788 \text{ and } 733 \text{ cm}^{-1}; \delta\text{H} \ (500 \text{ MHz, CDCl}_3, 25 \ ^\circ\text{C})\ 3.80-4.15 \ (4\text{H, m, C2-H, CH}_3\text{OAc, C3a-H}), 2.98-2.90 \ (1\text{H, m, C7-H}), 2.48-2.36 \ (1\text{H, m, C3-CH}_2\text{H}_5), 2.05 \ (3\text{H, s, COMe}), 1.20-2.00 \ (21\text{H, m}), 0.90 \ (6\text{H, two overlapping t, } J 7.0 \text{ Hz, CH}_2\text{Me, CH}_2\text{Me}); \delta\text{C} \ (500 \text{ MHz, CDCl}_3, +25 \ ^\circ\text{C})\ 171.1, 75.9,
68.4, 65.2, 61.0, 58.4, 40.1, 39.8, 37.4, 34.8, 31.3, 31.2, 29.9, 27.9 (2C), 22.7, 22.6, 20.9, 14.1, 14.0.

4.3.16.3. ketonitrone 170a

(Found: C, 61.7; H, 9.4; N, 5.2. C_{14}H_{25}NO_4 requires C, 61.97; H, 9.29; N, 5.16%); ν_{\text{max}} (neat) 3366, 2955, 2929, 2858, 1738, 1446, 1367, 1245, 1193, 1150, and 1041 cm\(^{-1}\), δ_H (500 MHz, CDCl\(_3\), +25 °C) 6.13 (1H, Br OH), 4.05 (2H, app. d, J 6.1 Hz, CH\(_2\)OAc), 3.96 (1H, m, CHOH), 3.96-3.84 (2H, m, C6-H\(_2\)), 3.04 (1H, dd, J 9.7, 12.9 Hz, C6-CH\(_a\)H\(_b\)CHOH), 2.73-2.57 (1H, m, C6-CH\(_{a}\)H\(_b\)CHOH), 2.36 (1H, app d, J 11.9 Hz, C3-H\(_a\)H\(_b\)), 2.28-2.20 (1H, m, C3-H\(_a\)H\(_b\)), 2.09 (3H, s, COMe), 1.20-1.90 (9H, m), 0.91 (3H, t, J 6.7 Hz, Me); δ_C (500 MHz, CDCl\(_3\), +25 °C) 170.8, 148.5, 71.8, 66.5, 57.0, 40.0, 38.4, 33.6, 30.0, 27.7, 25.7, 22.7, 20.8, 14.1.

4.3.17. MCPBA oxidation of adduct 168a to nitrone 169a and 170a. Cycloaddition of 169a with methyl methacrylate (153)

The mixture of nitrone 169a and 170a (prepared by MCPBA oxidation of 168a (1.0 mmol) as described in Section 4.3.16) in CH\(_2\)Cl\(_2\) (10 mL) was treated with methyl methacrylate (1.0 mL) and the mixture was stirred at 20°C for overnight. The ketonitrone was unreactive under these conditions. After removal of the solvent and excess alkene, the residual liquid was separated by chromatography over silica gel using 97:3 ether/methanol as eluant to give the first fraction as a nonseparable mixture of three isomers as a colorless liquid (48 mg, 8.7%). Continued elution gave the second fraction containing the major adduct 176 as a colourless liquid (353 mg, 63%). Analysis of the first fraction revealed the presence three isomers as indicated by the \(^1\)H NMR spectrum which displayed C(2) methyl...
singlets at $\delta$ 1.45, 1.46 and 1.49 ppm in an approximate ratio of 1.5:1:1. The acetyl singlets appeared at 2.01, 2.02 and 2.03 ppm and the CO$_2$Me singlets appeared at 3.71, 3.74 and 3.75 ppm. The ratio of 176 and the combined minor isomers was thus found to be 88:12.

4.3.17.1. Major adduct 176

(Found: C, 61.3; H, 8.9; N, 3.7. C$_{10}$H$_{33}$NO$_6$ requires C, 61.43; H, 8.95; N, 3.77%). $\nu_{\text{max}}$ (neat) 3445, 2953, 2931, 2858, 1742, 1738, 1732, 1462, 1454, 1446, 1434, 1371, 1242, 1150, 1121, 1038 and 982 cm$^{-1}$. The major and minor invertomers of 176 at -40 °C was found to be in a ratio of 72:28 as determined by integration of several proton signals.

4.3.17.1.1. Major Invertomer of 176

$\delta$$_H$ (500 MHz, CDCl$_3$, -40 °C) 5.00 (1H, Br OH), 3.82 (3H, s, CO$_2$Me), 3.96-3.78 (4H, m, CH$_2$OAc, C7-CH$_2$CHO, C3a-H), 3.65-3.55 (1H, m, C7-H), 2.11 (3H, s, COMe), 1.90-2.50 (5H, m), 1.50 (3H, s, C2-Me), 1.00-1.75 (10H, m), 0.91 (3H, t, J 6.7 Hz, CH$_2$Me); $\delta$$_C$ (500 MHz, CDCl$_3$, -40 °C) 173.8, 171.5, 80.5, 70.0, 68.3, 54.7, 53.1 (2C), 45.7, 36.6, 35.9, 32.1, 28.9, 28.4, 27.2, 25.9, 22.8, 21.2, 14.3.

4.3.17.1.2. Minor Invertomer of 176

The $^1$H NMR (500 MHz, CDCl$_3$, -40 °C) revealed the following nonoverlapping signals at: 3.79 (3H, s, CO$_2$Me), 2.89-2.82 (1H, m), 2.09 (3H, s, COMe), 1.42 (3H, s, C2-Me); $\delta$$_C$ (500 MHz, CDCl$_3$, -40 °C) 175.8, 171.5, 79.8, 71.2, 68.3, 56.2, 55.5, 53.1, 44.3, 37.8, 35.9, 31.2, 30.0, 28.4, 27.8, 24.7, 22.6, 21.2, 14.3.

4.3.18. MCPBA oxidation of adduct 168a to lactam 171a
To a stirred solution of the cycloadduct 168a (128 mg, 0.5 mmol) in dichloromethane (10 mL) at -40°C was added MCPBA (1.1 mmol) in one portion. The reaction mixture was then stirred 10 min each at -40°C, -20°C, 0°C and 20 min at 20°C. The organic layer was then washed with 5% NaHCO₃ solution (3×10 mL). The combined aqueous layers were re-extracted with CH₂Cl₂ (3×25 mL). The combined organic layers was dried (Na₂SO₄), concentrated and the residual mixture was purified by chromatography over silica gel using 90:10 ether/methanol as eluant to give the lactam 171a as a liquid (110 mg, 77%). The crude spectrum revealed the presence of ketonitrone 170a (~15%). However, the ketonitrone 170a was not separated in this case. 171a: m/z 288 [M⁺+I]; (Found: C, 58.4; H, 8.6; N, 4.8. C₁₄H₂₅NO₅ requires C, 58.52; H, 8.77; N, 4.87 %); ν_max (KBr) 3380, 2954, 2930, 2870, 1743, 1642, 1632, 1468, 1454, 1416, 1371, 1315, 1246, 1046 and 731 cm⁻¹, δ_H (500 MHz, CDCl₃, +25 °C) 4.11-4.04 (1H, m, C₆-H), 4.03-3.94 (2H, m, CH₂OAc), 3.92-3.84 (1H, m, C₆-CH₂CHO), 2.57 (1H, dd, J 5.3, 17.2 Hz, C₃-HₐHₖ), 2.44-2.34 (1H, m, C₆-CH₂H₆CHO), 2.23 (1H, dd, J 10.2, 17.2 Hz, C₃-HₐHₖ), 2.07 (3H, s, COMe), 1.99-1.90 (2H, m, C₆-CH₄H₅CHO, C₄-H), 1.89-1.78 (1H, m, C₅-HₕHₜ), 1.75-1.65 (1H, m, C₅-HₕHₜ), 1.54-1.28 (6H, m, (CH₂)₃), 0.91 (3H, t, J 7.0 Hz, Me); δ_C (500 MHz, CDCl₃, +25 °C) 170.8, 163.7, 69.2, 66.6, 55.6, 41.2, 37.4, 33.6, 31.3, 28.5, 27.7, 22.6, 20.7, 14.0.

4.3.19. MCPBA oxidation of adduct 168b to nitrones 169b and 170b. Cycloaddition of 169b with styrene (141b) to cycloadducts 172b and 173b

To a stirred solution of the cycloadduct 168b (3.0 mmol) was oxidized with MCPBA using procedure as described in Section 3.16 to give in dichloromethane (30 mL)
at 20ºC was added MCPBA (3.0 mmol) in one portion. After 30 min at 20 ºC the organic layer was washed with 5% NaHCO₃ solution (3×10 mL). The combined aqueous layers were re-extracted with CH₂Cl₂ (3×25 mL). The combined organic layers was dried (Na₂SO₄), concentrated to give a mixture of the aldonitrone 169b and keto-nitrone 170b in a ratio of 82:18, respectively, as determined by ¹H NMR integration of several proton signals. A small portion of the solution was concentrated for ¹H NMR analysis which revealed the aldonitrone 169b having the following characteristic signals at δ7.19 (1H, t, J 3.5 Hz, CH=N), 4.09 (1H, m, =NCH), 2.06 (3H, s), 3.97 (2H, d, J 61 Hz, CH₂O), 5.05 (1H, dd, J 3.6, 7.4 Hz). The NMR spectra of the ketonitrone 170b are described later.

After exchanging the solvent CH₂Cl₂ with toluene (15 mL), the above solution of nitrones was treated with styrene (141b) (5 mL) at 60ºC for 48 h. After removal of the solvent and excess alkene, the residual mixture was analysed by ¹H NMR analysis which revealed the presence of two cycloadducts 172b and 173b as well as the unreacted ketonitrone 170b. The 172b/173b was found to be in a ratio of 40:60 as determined by integration of several proton signals at δ3.16 (1H, m, major 173b), 4.15 (2H, AB, CH₂O, major 173b), 3.90 (2H, d, CH₂O, minor 172b). The crude mixture of adducts were purified by chromatography over silica gel using 3:2 hexane/ether as eluant to give a nonseparable mixture of the cycloadducts 172b and 173b (in a ratio of 40:60) as a colourless liquid (830 mg, 70%). TLC analysis in several solvents revealed the nonseparability of the adducts by silica gel chromatography. The adduct mixture was not analyzed further, instead it was hydrolyzed by NaOH to a separable mixture of isomers 174 and 175 (See section 4.3.20). Finally, elution with 80:20 ether/methanol afforded the unreacted ketonitrone 170b as a white solid (122 mg, 14%).
4.3.19.1. ketonitrone 38b

Mp 98-99°C (CH₂Cl₂-pentane), m/z 274 [M⁺-OH]; (Found: C, 65.8; H, 7.3; N, 4.7. C₁₆H₂₁NO₄ requires C, 65.96; H, 7.27; N, 4.81%). ν max (KBr) 3146, 2953, 2919, 2857, 1735, 1615, 1485, 1448, 1419, 1363, 1243, 1187, 1144, 1056, 1030, 990, 915, 882, 834, 766 and 709 cm⁻¹, δ H (500 MHz, CDCl₃, +25 °C) 7.30 (6H, Ph, O H), 5.17 (1H, dd, J 3.1, 8.0 Hz, PhCHO), 3.92-3.82 (4H, m, CH₂OAc, C6-H₂), 3.04 (1H, dd, J 2.2, 13.2 Hz, C2-CH₃H₆CHO), 2.94 (1H, dd, J 7.7, 13.2 Hz, C2-CH₃H₆CHO), 2.41 (1H, dd, J 5.5, 19.5 Hz, C3-H₆H₅), 2.13-2.03 (1H, m, C3-H₆H₅), 2.05 (3H, s, COMe), 2.02-1.90 (1H, m, C4-H), 1.70 (1H, dd, J 9.7, 19.5 Hz, C5-H₆H₅), 1.67-1.55 (1H, m, C5-H₆H₅); δ C (500 MHz, CDCl₃, +25 °C) 170.6, 148.1, 144.3, 128.3 (2C), 127.3, 125.1 (2C), 73.7, 66.1, 56.7, 42.6, 33.9, 29.6, 25.3, 20.7.

4.3.20. Conversion of 172b and 173b into 174 and 175 by hydrolysis with NaOH

A solution of 172b and 173b, in a ratio of 40:60, (800 mg, 2.02 mmol) in methanol (5 mL) containing NaOH (100 mg, 2.5 mmol) was stirred at 20 °C for 10 min. The reaction was over as indicated by TLC experiment (silica, ether). The reaction mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers was dried (Na₂SO₄) and concentrated and the residual liquid was separated by chromatography over silica gel using ether as eluant to give 175 as a white solid (310 mg). Continued elution gave a mixture of adducts 174 and 175 (132 mg) and finally the pure adduct 174 (200 mg). The total yield of the hydrolyzed adducts were found to be (642 mg, 90%). The ratio of the hydrolyzed adducts 174 and 175 were found to be similar to the
ratio of the starting acetylated adducts $172b$ and $173b$ as revealed by the $^1$H NMR of the crude mixture.

**4.3.20.1. Minor diasteromer 174**

Colourless liquid; $m/z$ 353 [$M^+$]; (Found: C, 74.5; H, 7.5; N, 3.9. C$_{22}$H$_{27}$NO$_3$ requires C, 74.76; H, 7.70; N, 3.96%). $\nu_{\text{max}}$ (neat) 3354, 3062, 3030, 2919, 1603, 1493, 1452, 1367, 1307, 1043, 952, 911, 858, 788, 700 cm$^{-1}$. The major and minor invertomers of 174 at -40°C was found to be in a ratio of 87:13 as determined by integration of the benzylic proton signals.

**4.3.20.1.1. Major invertomer of 174**

$\delta$H (500 MHz, CDCl$_3$, -40 °C) 7.37-7.21 (10H, m, Ph, Ph), 6.75 (1H, br, OH), 5.12-5.06 (2H, m, C2-H, PhCHOH), 3.75-3.65 (1H, m, C3a-H), 3.64-3.54 (1H, m, C7-H), 3.50-3.40 (2H, m, CH$_2$OH), 2.56-2.40 (4H, m, C3-H$_2$, C7-CH$_2$H$_5$CHO, OH), 1.92-1.80 (1H, m, C5-H), 1.74 (1H, apparent d, $J$ 14.0 Hz, C7-CH$_2$H$_5$CHO), 1.63 (1H, apparent d, $J$ 13.2 Hz, C4-H$_a$H$_e$), 1.55 (1H, dt, $J$ 5.2, 13.2 Hz, C6-H$_a$H$_e$), 1.22 (1H, apparent q, $J$ 12.2 Hz, C4-H$_a$H$_c$), 1.15 (1H, apparent d, $J$ 12.2 Hz, C6-H$_a$H$_c$); $\delta$C (500 MHz, CDCl$_3$, -40 °C) 144.0, 143.3, 128.5 (2C), 128.2 (2C), 127.4, 126.6, 125.4 (2C), 125.3 (2C), 76.3, 72.2, 67.4, 54.9, 53.3, 44.4, 38.7, 32.1, 28.6, 26.6.

**4.3.20.1.2. Minor invertomer of 174**

Minor invertomer of 174 has the following nonoverlapping signals: $\delta$H (500 MHz, CDCl$_3$, -40 °C) 4.90 (1H, m, C2-H), 4.88-4.80 (1H, m, PhCHOH), 3.92-3.84 (2H, m, C3a-H, C7-H), 3.01-2.89 (2H, m, C3-H$_2$), 2.46-2.38 (1H, m, C7-CH$_2$H$_5$CHO), 2.30-2.20
(1H, m, C7-CHaHbCHO), 1.10-1.00 (1H, m, C6-HaHc); δC (500 MHz, CDCl3, -40 °C) 73.8, 66.5, 57.0, 42.4, 33.3, 33.0.

4.3.20.2. Major diasteromer 175

m/z 353 [M⁺]; mp 125-126 °C (ether-pentane). (Found: C, 74.8; H, 7.8; N, 3.9. C22H27NO3 requires C, 74.76; H, 7.70; N, 3.96%). νmax (KBr) 3280, 3181, 3029, 2906, 1485, 1452, 1380, 1306, 1242, 1206, 1037, 910, 859, 799, 760, 699, 624, and 556 cm⁻¹.

The ¹H spectrum revealed the presence of a single invertomer. δH (500 MHz, CDCl3, 25 °C) 7.38-2.22 (10H, m, Ph, Ph), 5.11 (1H, dd, J 2.2, 10.2 Hz, C2-H), 5.07 (1H, dd, J 4.3, 9.5 Hz, PhCHOH), 4.36 (1H, br s, OH), 3.66 (2H, d, J 7.3 Hz, CH₂OH), 3.15-3.05 (1H, m, C7-H), 2.79-2.63 (1H, m, C3-HaHb), 2.35 (1H, apparent q, J 10.7 Hz, C3-HaHb), 1.70-2.30 (8H, m), 1.65 (1H, dt, J 5.1, 13.0 Hz, C6-HaHc); δC (500 MHz, CDCl3, 25 °C) 144.8, 141.4, 128.5 (2C), 128.2 (2C), 127.8, 127.0, 126.6 (2C), 125.7 (2C), 77.4, 71.3, 63.6, 61.8, 59.0, 43.0, 42.7, 34.6, 31.2, 29.6.

4.3.21. MCPBA oxidation of adduct 168b to lactam 171b

The cycloadduct 168b (0.5 mmol) was oxidized with MCPBA (1.1 mmol) using procedure as described in Section 3.18. Similar workup and chromatography afforded the lactam 171b as a white solid (115 mg, 75%). ¹H NMR revealed the presence of ketonitrone 168b (~15%). Mp 96-97°C (ether); m/z 307 [M⁺]; (Found: C, 62.4; H, 6.7; N, 4.5. C16H21NO5 requires C, 62.53; H, 6.89; N, 4.5%). νmax (KBr) 3136, 3025, 2942, 2922, 2883, 1740, 1622, 1492, 1454, 1418, 1365, 1342, 1243, 1225, 1181, 1123, 1085, 1045, 759, and 701 cm⁻¹; δH (500 MHz, CDCl3, +25 °C) 7.40-7.26 (5H, m, Ph), 5.03 (1H, d, J 6.5 Hz, PhCHO), 4.12-4.00 (1H, m, C6-H), 3.95 (2H, d, J 6.1 Hz, CH₂OAc), 2.56 (1H,
dd, J 5.0, 17.1 Hz, C3-HaHa), 2.38-2.24 (1H, m, C6-CHaHbCHO), 2.20 (1H, dd, J 10.4, 17.1 Hz, C3-HaHa), 2.20 (1H, overlapping m, C6-CHaHbCHO), 2.05 (3H, s, COMe), 1.85-1.75 (2H, m, C4-H, C5-HaHb), 1.45-1.35 (1H, m, C5-HaHb); δC (500 MHz, CDCl3, +25 °C) 170.8, 164.0, 144.2, 128.4 (2C), 127.4, 125.5 (2C), 71.51, 66.5, 55.8, 43.0, 33.6, 31.1, 28.2, 20.7.

4.3.22. Conversion of 172a to 177 by treatment with zinc and acetic acid

To a vigorously stirred solution of the adduct 172a (0.3 mmol) in acetic acid (2 mL) and water (2 mL) at 60 °C was added Zn (0.85 g) in two portions (ca. 5 min). The reaction mixture was stirred at 60°C for a total 30 min. The reaction mixture was decanted and the residual solid was washed with water (10 mL) and CH2Cl2 (20 mL). After basification (K2CO3), the aqueous layer was extracted with CH2Cl2 (3×20 mL). The organic layer was dried (Na2SO4), concentrated to give the amine 177 in almost quantitative yield as a solid. Mp 75-76°C (ether); (Found: C, 66.9; H, 10.8; N, 3.8. C20H39NO4 requires C, 67.19; H, 10.99; N, 3.92%).; νmax (neat) 3313, 2929, 2858, 1742, 1574, 1433, 1454, 1368, 1243, 1127, 1092, 1037, and 732 cm−1; δH (500 MHz, CDCl3, +25 °C) 4.0-3.0 (3H, br, NH, OHa, OH), 3.90 (1H, dd, BX of a ABX, J 6.1, 11.0 Hz, CHaHbOAc), 3.85 (1H, dd, AX of a ABX, J 6.4, 11.0 Hz, CHaHbOAc), 3.82-3.80 (2H, m, CHOH, CHOH), 3.59-3.47 (1H, m, C2-H), 3.21-3.08 (1H, m, C6-H), 2.20-2.10 (1H, m, C4-H), 2.08 (3H, s, COMe), 1.20-1.70 (20H, m), 0.90 (6H, two overlapping triplets, J 7.0 Hz, Me, Me); δC (500 MHz, CDCl3, +25 °C) 171.1, 69.8, 69.2, 68.2, 47.9, 45.6, 42.8, 37.4, 37.0, 36.2, 35.1, 34.0, 30.9, 28.3, 28.1, 22.8 (2C), 20.9,14.1 (2C).

4.3.23. Conversion of 173a to 178 by treatment with zinc and acetic acid
Using procedure as described in Section 4.3.22, the adduct 173a was converted into 178 as a solid in 95% yield. Mp 64-65°C (ether); (Found: C, 66.9; H, 11.2; N, 4.0; C₂₀H₃₉NO₄ requires C, 67.19; H, 10.99; N, 3.92 %.) νₘₐₓ (neat) 3351, 2928, 2858, 1742, 1645, 1632, 1573, 1555, 1452, 1370, 1246, 1128, and 1037 cm⁻¹; δ_H (500 MHz, CDCl₃, +25 °C) 4.18 (2H,d, J 7.9 Hz, CH₂OAc), 3.83-3.73 (2H, m, CHOH, CHOH), 3.06-2.94 (2H, m, C2-H, C6-H), 2.20-2.10 (1H, m, C4-H), 2.07 (3H, s, COMe), 1.20-1.60 (23H, m), 0.90 (6H, t, J 6.8 Hz, Me, Me); δ_C (CDCl₃, +25 °C) 171.2, 68.5 (2C), 65.3, 48.5 (2C), 42.8 (2C), 37.7 (2C), 32.5 (2C), 31.5, 28.0 (2C), 22.7 (2C), 21.0, 14.1 (2C).

4.3.24. Conversion of 174 to 179 by treatment with zinc and acetic acid

Using procedure as described in Section 4.3.22, the adduct 174 was converted into 179 as a solid in 95% yield. In the work up procedure, the aqueous layer was extracted with hot CHCl₃ instead of CH₂Cl₂ (as a result of poor solubility of the product). Mp 146-148°C (ether); (Found: C, 74.1; H, 8.1; N, 3.8. C₂₂H₂₉NO₃ requires C, 74.33; H, 8.22; N, 3.94%); νₘₐₓ (KBr) 3320, 3054, 3020, 2928, 2907, 2853, 1490, 1448, 1365, 1351, 1218, 1144, 1115, 1094, 1067, 1022, 914, 881, 853, 786, 760, 749, and 701 cm⁻¹; δ_H (500 MHz, 9:1 CDCl₃/CD₃OD, 25 °C) 7.37-7.24 (10H, m, Ph, Ph), 4.94 (1H, dd, J 3.4, 8.6 Hz, PhCHOH), 4.98 (1H, dd, J 4.3, 6.1 Hz, PhCHOH), 3.35 (3H, a two proton d, J 6.1 Hz, CH₂OH, and an overlapping 1H, m, C2-H), 3.19-3.11 (1H, m, C6-H), 2.71 (4H, br, OHs, NH), 2.37 (1H, ddd, J 4.2, 10.4, 14.6 Hz, C2-CH₃CHO), 1.90-1.75 (2H, m C2-CH₃CHO, C6-CH₃CHO), 1.72-1.65 (2H, m, C6-CH₃CHO, C4-H), 1.59-1.53 (1H, m, C5-CH₃Hb), 1.51-1.47 (1H, m C5-CH₃Hb), 1.18 (1H, dt, J 5.5, 12.8 Hz, C3-CH₃Hb), 0.83 (1H, q, J 12.5 Hz, C3-HbHb); δ_C (500 MHz, 9:1 CDCl₃/CD₃OD, 25°C) 145.1, 144.9,
128.4 (2C), 128.4 (2C), 127.1, 127.1, 125.6 (2C), 125.6 (2C), 72.1, 70.5, 67.8, 48.2, 45.8, 45.3, 37.7, 36.2, 33.9 (2C).

4.3.25. Conversion of 175 to 180 by treatment with zinc and acetic acid

Using procedure as described in Section 4.3.22, the adduct 175 was converted into 180 as a solid in 90% yield. In the work up procedure, the aqueous layer was extracted with hot CHCl₃ instead of CH₂Cl₂ (as a result of poor solubility of the product). Mp 199-200°C (ether); (Found: C, 74.2; H, 8.0; N, 3.9. C₂₂H₂₉NO₃ requires C, 74.33; H, 8.22; N, 3.94%).; ν_max (KBr) 3311, 3171, 2931, 2884, 2718, 1450, 1388, 1332, 1262, 1205, 1119, 1063, 1037, 987, 914, 878, 827, 788, 759, and 702 cm⁻¹; δ_H (500 MHz, 9:1 CDCl₃/CD₃OD, 25 °C) 7.38-7.32 (10H, m, Ph, Ph), 4.88 (2H, dd, J 4.3, 8.0 Hz, PhCHOH, PhCHOH), 4.00 (4H, br s, OHs and NH), 3.55 (2H, d, J 7.6 Hz, CH₂OH), 2.95-2.82 (2H, m, C2-H, C6-H), 2.08-2.00 (1H, m, C4-H), 1.72-1.68 (4H, m, C3-CHO, C6-CH₂CHO, ), 1.64 (2H, apparent d, J 13.5 Hz, C3-HₐHₑ, C5-HₐHₑ), 1.41 (2H, dt, J 5.2, 13.5 Hz, C3-HₐHₑ, C5-HₐHₑ); δ_C (500 MHz, 9:1 CDCl₃/CD₃OD, 25 °C) 144.5 (2C), 128.1 (4C), 127.0 (2C), 125.4 (4C), 70.8 (2C), 62.7, 48.1 (2C), 44.7 (2C), 34.4, 32.6 (2C).
CHAPTER 5

Regioselective transformation of 6/5-fused bicyclic isoxazolidines to second-generation cyclic aldonitrones

Summary:

The cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be highly stereo- as well as face-selective. In solution, the 6/5 fused bicyclic cycloadducts remain solely as the cis-fused invertomers in order to accommodate the bulky tertiary substituent 2-hydroxy-2-propyl in the equatorial orientation. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones. The stereo- and face-selectivity of the cycloaddition reactions of these second-generation nitrones bearing substituents at C(4) and C(6) have been briefly examined.

5.1 Introduction

The efficacy of 1,3-Dipolar cycloaddition reaction of cyclic nitrones lies on the remarkable selectivity in the incorporation of multiple stereocenters in a single step [1,2]. The pyrrolidine- and piperidine-based alkaloids, which are widespread in nature, can be accessed through the cycloaddition reaction of the parent five- 181 and six-membered cyclic nitrones, or the second-generation aldonitrones 183 and 184, respectively (Scheme 50) [89]. The five-membered aldonitrones 183 can be accessed regiospecifically by peracid-induced ring opening of the bicyclic isoxzolidines 181 (nitrone (1)-alkene cycloaddition products). It has been suggested that the orientation of the nitrogen lone pair in 182 dictates the formation of the N-oxide intermediate on the β-face of the nitrone; the
subsequent ring opening leads the C(2)-O- to abstract the nearby Hb immediately, thereby leading to the exclusive formation of the aldonitrones 183 [77a]. However, the proper utilization of the second-generation six-membered aldonitrones 185 has been severely hampered by the lack of selectivity for the oxidation process in 6/5-fused isoxazolidines 184a,b (R1=H) (Table in Scheme 1), where the synthetically less important ketonitrones 186a,b are obtained as the major products. While the geometric compulsion makes sure that the 5/5-ring system in 182 remains cis-fused, its corresponding 6/5 ring system in cycloadducts 184 exists in three different conformations/configurations: the cis pair A and B, in rapid equilibrium by chair inversion (CI), and its trans inveromer C, in a relatively slow equilibrium with cis inveromer B by nitrogen inversion process (NI). It has been suggested that the higher activation barrier to nitrogen inversion (ΔG**, ~70 kJ/mol) [90a] than the oxidation process does not permit the Curtin-Hammett principle91 to apply; as such the inveromer ratio reflects the ratio of the products keto- and aldo-nitrones. While the cis inveromer leads to aldonitrones 185 via intermediate D, the trans inveromer affords the synthetically less important ketonitrones 186 via E. As evident from the Table included in the Scheme 48, the cycloadduct 184a having a cis/trans inveromer ratio of 24:76 afforded the aldo-185/keto-186 nitrones in an almost identical ratio of 23:77.9 Likewise, 184b having a cis/trans inveromer ratio of 22:78 affords the aldo-185/keto-186 nitrones in a similar ratio of 35:65 [7a].

Note that the placement of a substituent R1 at C(5) in cycloadducts 184 would favour the cis inveromer A at the expense of B and the trans inveromer C, both of which places the C(5)R1 in the unfavourable axial orientation. Exploring this idea, greater percentages of the aldonitrones 185 are obtained from peracid-induced oxidation of the
isoxazolidines 184c and 184d [73,97]. In our continuing endeavour to obtain the aldonitrones 185 regiospecifically, we intended to place at C(5) in 184 a very bulky substituent that would ascertain the exclusive presence of the invertomer A and exclude the C(5) axially-oriented R₁ in cis B and trans invertomer C. The current work describes our attempt to test the above proposition and confirm the mechanism of the peracid oxidation process.
181

\[
\begin{array}{c}
\text{182-} \text{cis-invertomer} \\
\text{(Exclusive)}
\end{array}
\]

183: Aldonitrome (Exclusive)

\[
\begin{array}{c}
\text{184-} \text{cis-invertomers} \\
\text{184: trans-invertomer}
\end{array}
\]

185: Aldonitrome

186: Ketonitrome

\[
\begin{array}{c}
\text{D} \\
\text{185: Aldonitrome}
\end{array}
\]

\[
\begin{array}{c}
\text{E} \\
\text{186: Ketonitrome}
\end{array}
\]

<table>
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<th>% Composition of nitrones (aldol-185/keto-186)</th>
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<tr>
<td>a, ( R_1 = R_2 = H )</td>
<td>24:76</td>
<td>23:77</td>
</tr>
<tr>
<td>b, ( R_1 = H; \ R_2 = \text{Ph} )</td>
<td>22:78</td>
<td>35:65</td>
</tr>
<tr>
<td>c, ( R_1 = \text{CO}_2\text{Bu}; \ R_2 = \text{Ph} )</td>
<td>55:45</td>
<td>52:48</td>
</tr>
<tr>
<td>d, ( R_1 = \text{CH}_2\text{OAc}; \ R_2 = \text{Ph} )</td>
<td>88:12</td>
<td>82:18</td>
</tr>
</tbody>
</table>

\text{Scheme 50.}
5.2 Results and Discussion

The synthesis of nitrone 192, having a bulky CMe$_2$OH at C(4) is outlined in (Scheme 51). Amine 190 upon hydrogen peroxide oxidation in the presence of sodium tungstate$^{96}$ in water afforded a mixture of nitrone 192 and hydroxylamine 191 which upon treatment with NaBH$_4$ afforded the hydroxylamine 191 in pure form. The required nitrone 192 was then prepared by mercury(II) oxide oxidation of 191.

Next, we pursued the addition reaction of nitrone 192 with various alkenes. The addition of monosubstituted alkene styrene 193a was found to be stereo-, as well as face-selective; a single adduct 194a was obtained in 80% yield. The $^1$H NMR analysis of the crude as well as purified product failed to reveal the presence of any minor isomer. Likewise, the addition reaction of 1-hexene 193b also afforded a single isomer 194b. The configuration of the adduct 194a and 194b was based on the sterically favourable exo approach (Scheme 51) of the Ph and Bu groups from the less hindered face (i.e. $\alpha$ face) of the nitrone.$^{97}$ Such a high selectivity is surprising since the C(4)-CMe$_2$OH group, imparting the facial difference, is positioned at the furthest point from the nitrone functionality in 192, yet a surprisingly high selectivity in the addition reactions were observed.

The addition of disubstituted alkenes methyl methacrylate (195) to the nitrone 192 also demonstrated a very high face- and stereoselectivity (Scheme 51); a nonseparable mixture of adducts 196 and 197 in a respective ratio of 95:5 was obtained. The major adduct 196 was obtained via $\alpha$-exo (Me) approach. The stereochemistry is based on the precedent literature [2a], the parent nitrone 3,4,5,6-tetrahydropyridine 1-oxide is known to
give major and minor adducts in a ratio of 96:4 as a result of a favourable secondary orbital interaction via an endo-oriented methoxycarbonyl group in the transition state.

Scheme 51.

Since the stereochemistry of the ring fusion dictates the regiochemical outcome of the peracid oxidation process leading to the second-generation nitrones (vide supra) (Scheme 50), we have examined the conformational aspects as well as composition of the
nitrogen invertomers (if any) by NMR spectroscopy. The presence of \( -\text{N}--\text{O}-- \) moiety in an organic molecule has a distinctive place in conformational analysis; [13-15] oxygen being next to nitrogen raises the barrier to nitrogen inversion to such an extent that the individual invertomers can be identified by NMR spectroscopy.\(^8\) At ambient temperature, the \(^1\)H and \(^{13}\)C NMR spectra of these cycloadducts show sharp signals indicating the presence of a single invertomer for each of the compounds 194a, 194b and 196 as well as their corresponding acetate derivatives 198-200 obtained by reacting the former compounds with acetic anhydride in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) (Scheme 52).

With respect to the six-membered ring, both cis-fused B and trans-fused C have the bulky CMe\(_2\)OH(Ac) substituent axially-oriented, while the tertiary group is equatorially oriented in cis-fused A. As such the major cycloadducts 194a, 194b and 196a, as well as their acetates 198-200, are expected to remain exclusively in the invertomeric form of cis-fused A. Note that for compound 184a, the parent 6/5 fused bicyclic isoxazolidine, a \( \text{cis/trans} \) ratio of 22:78 translates into a \( \Delta G^0 \) value (determined at -50 °C) of 2.11 kJ mol\(^{-1}\) favoring the 184a-trans-fused invertomer, while for a \( \text{cis/trans} \) ratio of 24:76 for cycloadduct 184b, \( \Delta G^0 \) value (determined at +25 °C) becomes 3.13 kJ mol\(^{-1}\) (Scheme 50). \(^1\)Butyl group is well known to have a conformational enthalpy (\( \Delta H^0 \)) difference of 21 kJ mol\(^{-1}\). Comparing cis-fused A of 194a with its trans-fused C, the bulky tertiary substituent CMe\(_2\)OH (akin to a \(^1\)butyl group) at C(5) is expected to destabilize the latter invertomer by an approximate \( \Delta H^0 \) of 21 kJ mol\(^{-1}\), thereby implying an overall free energy (\( \Delta G^0 \)) advantage of about 18 kJ mol\(^{-1}\) (i.e. 21-3.13) for the cis-invertomer. (Note that the entropy difference (\( \Delta S^0 \)) between the two invertomeric forms is assumed to be
zero since both the invertomers remain as dl-pairs and have no axis of rotation). Such an astronomical energy difference would predict the complete absence of the trans invertomer as far as NMR detection limit is concerned. That the stable invertomers have the configuration of cis-fused A as depicted in (Scheme 52) get further credence from $^1$H NMR spectroscopy. While the C(3a)H is equatorially oriented in cis-fused A, it is axially oriented in trans-fused C. The equatorially and axially oriented protons are known to appear at the chemical shift values of $\delta$ 3.8 and 3.3 ppm, respectively; the observed chemical shifts of $\sim\delta$ 3.8 for the current compounds thereby ascertain the equatorial orientation of the C(3a)H in the exclusive invertomer cis-fused A.

Assertion of the cis fusion of the ring juncture predicts that the synthesis of the desired second-generation aldonitrones regiospecifically may be achieved by the peracid oxidation process mentioned earlier. To our relief and delight, the isoxazolidines 198-200, on treatment with m-chloroperbenzoic acid (MCPBA) gave the aldonitrones 201-203 exclusively and in almost quantitative yields (Scheme 52). This is the first time a series of 6/5-fused isoxazolidines have been shown to generate the synthetically important aldonitrones regiospecifically.

The peracid oxidation was also carried out in protic solvent ethanol in the hope that it will be able to intercept the intermediate B to obtain its protonated species C which would then generate both the aldo- and ketonitrones by general base catalysed abstraction of the proton H$_a$ or H$_b$ and H$_c$, respectively (Scheme 53). The oxidation of 200 with MCPBA in methanol did indeed generate two nitrones 203 and 204 in a respective ratio of 80:20. While the general base catalyzed proton abstraction would favour the formation of more substituted ketonitrone 204, its formation as a minor isomer certifies a certain degree
of concertedness as depicted in intermediate A as well as a competitive abstraction of proton H₆ by RO⁻ in B versus the protonation leading to C. The nitrones are readily identified by the ¹H NMR spectral analysis. The nonoverlapping H_c, H_d and H_f of aldonitrone 203 appeared at δ4.21, 2.64 (1H, dd, J 10.2, 14.3 Hz), and 7.08, respectively, while for the ketonitrone 204, the H_g and H_h was displayed at δ 3.90, and H_i and H_j at 3.23 (d, J 13.6 Hz) and 2.74 (d, J 13.6 Hz) ppm.

Scheme 52.

194a, R¹ = Ph; R² = R³ = H  
194b, R¹ = Bu; R² = R³ = H  
196, R¹ = Me; R² = CO₂Me; R³ = H  
198, R¹ = Ph; R² = H; R³ = Ac  
199, R¹ = Bu; R² = H; R³ = Ac  
200, R¹ = Me; R² = CO₂Me; R³ = Ac

198  MCPPA  201
202
203

Scheme 52.
Next, we explored the cycloaddition reaction of the second-generation nitrone 201 with the alkene 183; a nonseparable mixture of three adducts in a respective ratio of 89:8:~1) was obtained in 91% yield (Scheme 53). The addition was thus found to be highly face selective. The stereochemistry of the major adduct was based on the approach of the alkene from the β-face of the nitrene to give C(3a),C(7)-trans substituted adduct 205; in the α-face approach, the CO$_2$Me group is expected to experience severe steric crowding in the transition state. The face selectivity is thus dictated by the steric influence of the substituent at C(6) so as to force the alkene to approach from the β-face of the nitrene whereby the smaller Hs at the unsubstituted end of the alkene are in a better position to negotiate with the steric encumbrance of C(4) substituent. The adduct 205 is expected to be equilibrating between the two invertomers in both of which the bulky tertiary substituent is placed at equatorial orientation. The $^1$H as well as $^{13}$C NMR spectra at ambient temperatures did indeed reveal broad signals.
For the addition reaction of styrene 183a with nitrone 201, a mixture of isomers 206 and 207 was obtained in a respective ratio of 1:3; the face selectivity is thus dictated by the steric influence of the β–substituent at C(4) so as to force the alkene to a preferable approach from the α-face of the nitrone. The endo-oriented H of styrene will have very little discomfort in compare to the endo-oriented carbomethoxy as far as the steric encumbrance of the α–oriented substituent at C(6) is concerned. The stereochemical analyses thus revealed that the mono- 183a and dissubstitued 185 alkenes prefer to
approach the $\alpha$- and $\beta$-face of the nitrone, respectively, and the experimental findings are rationalized in terms of the transition state structures depicted in (Scheme 54).

Scheme 54.

The stereochemistry of the addition reaction was confirmed by chemical conversion of 207 into the ring opened product 208 by cleaving the N-O bond of the cycloadducts with zinc/acetic acid. The NMR spectra of the amine 208 ($C_{26}H_{35}NO_4$),
obtained from adduct 207, confirmed its symmetric nature; as expected the $^{13}$C NMR spectrum revealed the presence of 13 carbon signals. The two benzylic protons appeared identical as displayed by a single signal at $\delta 4.96-4.94$ (2H, m); even the two phenyl rings appeared identical as displayed by three types of proton at $\delta 7.14$ (4H, d, J 7.3 Hz), 7.24 (4H, t, J 7.3 Hz), 7.14 (2H, t, J 7.3 Hz).

The study has confirmed the mechanism of the peracid induced ring opening of the isoxazolidine, and led to the synthetically important second-generation cyclic aldonitrones, for the first time, with a complete regioselectivity. The bulkier tertiary substituent at C(5) in the cycloadducts has, to our advantage, frozen the invertomer exclusively in the cis-fused form and thus led to the observed regioselectivity.

5.3 Experimental

5.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTIR spectrometer. $^1$H and $^{13}$C NMR spectra were measured in CDCl$_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). 4-methoxycarbonylpiperidine (187), 1-hexene, styrene, methyl methacrylate, m-chloroperbenzoic acid, from Fluka Chemie AG (Buchs, Switzerland) were used as
received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N₂.

**5.3.2. N-Benzyl-4-methoxycarbonylpiperidine (188)**

To a stirring solution of amine 187 (10 g, 70 mmol) in THF (50 mL) in the presence of triethyl amine (7 g) at 0°C was added benzyl bromide (13.2 g, 70 mmol) dropwise. After stirring at room temperature overnight, the mixture was taken up in water (20 mL) and extracted with CH₂Cl₂ (4×30 mL). The combined organic layers were dried (Na₂SO₄), concentrated and the residual liquid was distilled to give amine 188 as a colorless liquid (15.3 g, 94%), bp₀.1 mbarHg 104 °C; (Found: C, 71.9; H, 8.2; N, 5.8. C₁₄H₁₉NO₂ requires C, 72.07; H, 8.21; N, 6.00%); ν_max (neat) 3027, 2949, 2802, 2760, 1732, 1494, 1450, 1435, 1367, 1320, 1286, 1268, 1196, 1167, 1145, 1047, 1014, 983, 906, 738, and 699 cm⁻¹. δ_H 7.21-7.32 (5H, m), 3.67 (3H, s), 3.48 (2H, s), 2.85 (2H, apparent d, J 11.9 Hz), 2.29 (1H, tt, J 4.0, 11.0 Hz), 2.02 (2H, dt, J 2.3, 11.6 Hz), 1.89-1.84 (2H, m), 1.82-1.71 (2H, m); δ_C 175.7, 138.3, 129.1 (2C), 128.1 (2C), 126.9, 63.2, 52.8 (2C), 51.5, 41.0, 28.2 (2C).

**5.3.3. N-Benzyl-4-(2-hydroxy-2propyl)piperidine (189)**

To a stirring solution of amine 188 (10 g, 42 mmol) in THF (50 mL) at 0 °C was added dropwise a 3M solution of methyl magnesium bromide (30 mL, 90 mmol). The mixture was then stirred at room temperature for 6 h. After addition of a saturated solution of ammonium chloride (20 mL), the aqueous layer was extracted with CH₂Cl₂ (4×30 mL). The combined organic layers was dried (Na₂SO₄), concentrated and the residual liquid was
purified by chromatography over silica using 1:1 ether/methanol mixture as eluant to give the aminoalcohol 189 as a white solid (7.3 g, 75%). Mp 75-76°C (ether-pentane); (Found: C, 77.0; H, 10.1; N, 5.9. C₁₅H₂₅NO requires C, 77.21; H, 9.93; N, 6.00 %); vₚₑₚₑ (KBr) 3366, 2961, 2939, 2861, 2802, 2760, 1452, 1368, 1342, 1269, 1218, 1137, 1090, 997, 920, 759, 739, and 700 cm⁻¹. δₕ 7.32 -7.23 (5H, m), 3.49 (2H, s), 2.97 (2H, apparent d, J 11.6 Hz), 1.92 (2H, dt, J 2.3, 11.7 Hz), 1.72 -1.66 (2H, m), 1.39 (2H, dq, J 3.6, 12.5 Hz), 1.32-1.24 (2H, m), 1.17 (6H, s); δ c 138.0, 129.3 (2C), 128.1 (2C), 127.0, 72.4, 63.2, 54.0 (2C), 47.3, 26.9 (2C), 26.7 (2C).

5.3.4. 4-(2-hydroxy-2-propyl)piperidine (190)

The protected aminoalcohol 189 (10 g, 42 mmol) in ethanol (50 mL) containing Pd/C (1 g) was hydrogenated at 20 °C under 50 psi pressure for 3 h. The reaction mixture was filtered over celite and washed with ethanol (2×10 mL). After removal of the solvent, the residue was crystallized from acetone to give the pure aminoalcohol 190 as a white solid (4.3 g, 72%); mp 136-137°C (Lit.⁹₈ mp 135-137°C); vₚₑₚₑ (KBr) 3387, 2970, 2856, 1643, 1632, 1537, 1470, 1426, 1380, 1307, 1276, 1254, 1172, 1117, 915 and 818 cm⁻¹. δₕ 3.23 (2H, apparent d, J 12.2 Hz), 2.92 (2H, br s), 2.63 (2H, t, J 11.7 Hz), 1.79 (2H, apparent d, J 12.6 Hz), 1.46-1.28 (3H, m), 1.18 (6H, s); δ c 72.4, 47.6, 46.8 (2C), 27.7 (2C), 26.7(2C).

5.3.5. 4-(2-hydroxy-2-propyl)-N-hydroxypiperidine (191)

To a stirring solution of aminoalcohol 190 (10 g, 70 mmol) in water (100 mL) in the presence of sodium tungstate (0.8 g) at 0°C under N₂ was added dropwise a 30% H₂O₂
solution (18.5 g, 163 mmol) in 15 min. The mixture was then stirred at 20°C for 2 h. Solid sodium borohydride (2 g, 54 mmol) was added in portions to the above mixture and stirring continued for 1 h. The mixture was extracted with CH₂Cl₂ (4×50 mL). The combined organic layers was dried (Na₂SO₄), concentrated and the residual liquid was purified by chromatography over silica using 70:30 ether/methanol mixture as eluant to give the hydroxylamine 191 as a colorless liquid (8 g, 71%). (Found: C, 60.2; H, 10.6; N, 8.7. C₈H₁₇NO₂ requires C, 60.35; H, 10.76; N, 8.80%). νmax (neat) 3349, 2966, 2861, 2830, 1659, 1449, 1377, 1301, 1254, 1162, 1131, 1099, 1049, 921, 794, 733 cm⁻¹. δH 3.37-3.28 (2H, m), 2.47 (2H, t, J 10.5 Hz), 1.85-1.75 (2H, m), 1.50-1.37 (4H, m), 1.35-1.27 (1H, m), 1.17 (6H, s); δC 72.0, 58.6, 45.9, 27.1, 26.5 (C).

5.3.6. 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide (192)

To a solution of the hydroxylamine 191 (4.5 g, 28.2 mmol) in EtOH (50 mL) was added yellow HgO (12.0 g, 56.4 mmol) and the mixture was stirred at 20°C for 6 h or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and MgSO₄. The bed was washed with liberal excess of ethanol. The formation of the nitrone was assumed quantitative for the percent yield calculation in the subsequent cycloaddition reactions. However, the nitrone contained minor quantities of impurities and as such its elemental analysis was not carried out. νmax (neat) 3360, 2972, 2938, 1633, 1446, 1369, 1299, 1245, 1162, 1047, 950, 924, 790, 732 and 478 cm⁻¹. δH 7.18-7.15 (1H, m), 3.90-3.81 (2H, m), 2.55-2.48 (1H, m), 2.43-2.28 (2H, m), 2.13-2.10 (1H, m), 1.70-1.83 (2H, m), 1.25 (3H, s), 1.24 (3H, s); δC 137.0, 70.8, 58.2,
40.1, 27.3 (Me), 27.1, 26.9 (Me), 23.9. Assignment of the $^{13}$C chemical shifts was based on DEPT experiment results.

5.3.7. 2-Phenyl-5-(2-hydroxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (194a)

A solution of nitrone 192 (10 mmol) in EtOH (40 mL) containing styrene (193a) (5 mL) was heated at 90°C for 4 h under N$_2$ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was purified by chromatography over silica using 85:15 ether/methanol as eluant to give a single adduct 194a as a white solid (2.0 g, 80%). $^1$H NMR of the crude or the separated fraction failed to reveal the presence of any other minor isomers. $m/z$ 261 [$M^+$]; Mp 87-89°C (ether-pentane); (Found: C, 73.3; H, 8.7; N, 5.3. C$_{16}$H$_{23}$NO$_2$ requires C, 73.53; H, 8.87; N, 5.36%); $\nu_{\max}$ (neat) 3358, 2968, 2927, 2865, 1494, 1452, 1380, 1367, 1293, 1264, 1206, 1170, 1152, 1119, 1093, 952, 921, 758, 731, and 700 cm$^{-1}$; $\delta_{\mathrm{H}}$ 7.40-7.25 (5H, m), 5.40 (1H, dd, $J$ 3.8, 9.9 Hz), 3.92-3.85 (1H, m), 3.25 (1H, td, $J$ 3.4, 10.4 Hz), 2.83 (1H, ddd, $J$ 2.5, 10.4, 12.8 Hz), 2.75 (1H, dt, $J$ 10.0, 12.0 Hz), 2.05-1.70 (5H, m), 1.62-1.54 (1H, tt, $J$ 3.0, 12.0 Hz), 1.52-1.42 (1H, dq, $J$ 3.4, 12.8 Hz), 1.21 (3H, s), 1.20 (3H, s); $\delta_{\mathrm{C}}$ 142.3, 128.4 (2C), 127.6, 126.4 (2C), 78.8 (C-Ph), 72.1 (CMe$_2$), 60.2, 49.9, 40.8 (CMe$_2$), 38.8, 27.1 (Me), 27.0 (Me), 26.2, 25.8. Assignment of the $^{13}$C chemical shifts was based on DEPT experiment results.

5.3.8. 2-Butyl-5-(2-hydroxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (194b)

A solution of nitrone 192 (10 mmol) in EtOH (40 mL) containing 1-hexene (193b) (10 mL) was heated at 90°C for 20 h under N$_2$ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was purified by chromatography over
silica using 95:5 Dichloromethane/methanol as eluant to give only one adduct 194b as a colorless liquid (1.85 g, 75%). m/z 241 [M⁺]; mp 87-89°C (ether-pentane); (Found: C, 69.4; H, 11.1; N, 5.7. C₁₄H₂₇NO₂ requires C, 69.67; H, 11.27; N, 5.80%). v max (neat) 3397, 2958, 2927, 1666, 1454, 1379, 1369, 1291, 1265, 1210, 1140, 1098, 954, 926, and 761 cm⁻¹; δH 4.42-4.36 (1H, m), 3.64-3.58 (1H, m), 3.11 (1H, td, J 3.4, 10.4 Hz), 2.68 (1H, ddd, J 2.5, 10.2, 12.8 Hz), 2.36 (1H, dt, J 9.4, 11.9 Hz), 1.97-1.20 (13H, m), 1.19 (3H, s). 1.18 (3H, s), 0.90 (3H, t, J 7 Hz); δC 77.2, 72.1, 59.7, 49.6, 40.7, 35.35, 35.26, 28.1, 27.0 (2C), 26.3, 25.7, 22.7, 14.0.

5.3.9. Isomers of Methyl 2-methyl-5-(2-hydroxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine-2-carboxylate (196 and 197)

A solution of nitron 192 (10 mmol) in EtOH (40 mL) containing methyl methacrylate (195) (6 mL) was heated at 50°C for 3 h under N₂ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was separated by chromatography over silica using 95:5 DCM/methanol as eluant to give a nonseparable mixture of adducts 196 and 197 in a respective ratio of 95:5 as a colorless liquid (2.1 g, 83%). The presence of the minor adduct was revealed by the presence of a CO₂Me singlet at 3.75 ppm. Mp 128-129°C (ether-pentane); (Found: C, 60.5; H, 9.1; N, 5.3. C₁₃H₂₃NO₄ requires C, 60.68; H, 9.01; N, 5.44%). v max (neat) 3404, 2968, 2930, 2872, 1731, 1652, 1454, 1371, 1293, 1251, 1217, 1191, 1139, 1114, 1084, 987, 946, 920, 874, 738 and 667 cm⁻¹; δH 3.77 (3H, s), 3.79-3.74 (1H, m), 3.18 (1H, td, J 3.4,10.4 Hz), 2.90 (1H, t, J 12.5 Hz), 2.65 (1H, ddd, J 2.5, 10.7, 13.0), 2.00-1.93 (2H, m), 1.91-1.33 (1H, m), 1.79-1.71 (2H, m), 1.54 (1H, tt, J 3.0, 12.8 Hz), 1.50 (3H, s), 1.43-1.33 (1H, dq, J 3.4, 12.8 Hz),
1.19 (3H, s), 1.18 (3H, s); δC: 175.6, 84.2, 72.0, 60.3 (CHN), 52.6 (CO2Me), 50.8, 40.8 (CHCMe2), 39.6, 27.0 (2C, CMe2), 25.86 (2C), 25.75 (C-Me). Assignment of the 13C chemical shifts was based on DEPT experiment results.

5.3.10. 2-Phenyl-5-(2-acetoxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (198)

The cycloadduct 194a (1.10 g, 4.3 mmol) in toluene (20 mL) was treated with acetic anhydride (3 mL) and DMAP [4-(N,N-dimethylamino)pyridine] (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride, the residual liquid was purified by chromatography over silica gel using 1:1 ether/hexane as eluant to give the acetate 18 as a white solid (1.24 g, 95%). Mp 58-60°C (ether-pentane); (Found: C, 71.0; H, 8.1; N, 4.7. C18H25NO3 requires C, 71.26; H, 8.31; N, 4.62%); νmax (KBr) 2977, 2951, 2930, 2857, 1728, 1494, 1453, 1368, 1257, 1150, 1133, 1018, 949, 758, and 701 cm⁻¹; δH 7.37-7.25 (5H, m), 5.40 (1H, dd, J 3.8, 9.9 Hz), 3.93-3.80 (1H, m), 3.27 (1H, td, J 3.4,10.3 Hz), 2.84 (1H, ddd, J 2.7, 10.3, 12.8 Hz), 2.76 (1H, dt, J 10.1, 12.0 Hz), 2.23 (1H, tt, J 3.35, 12.3 Hz), 2.04 (1H, ddd, J 3.4, 7.6, 12.3 Hz), 1.98 (3H, s), 1.98-1.91 (1H, m), 1.88-1.91 (1H, m), 1.77-1.71 (1H, m), 1.52 (1H, dq, J 3.1, 12.8 Hz), 1.45 (3H, s), 1.43 (3H, s); δC: 170.5, 142.2, 128.5 (2C), 127.6, 126.4 (2C), 84.0 (CPh), 78.9 (CMe2CO), 60.0, 49.8, 38.8, 38.2 (CCMe2), 25.8, 25.5, 23.47 (CMe), 23.44 (CMe), 22.4 COCH3).

5.3.11. 2-Butyl-5-(2-acetoxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (199)

The cycloadduct 194b (1.30 g, 5.4 mmol) in toluene (10 mL) was treated with acetic anhydride (3 mL) and DMAP [4-(N,N-dimethylamino)pyridine] (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride the
residual liquid was purified by chromatography over silica gel using 80:20 ether-Hexanes as eluant to give the acetate 199 as a colourless liquid (1.30 g, 85%). \( m/z \) 283 [\( M^+ \)]; (Found: C, 67.6; H, 10.2; N, 4.8. \( C_{16}H_{29}NO_3 \) requires C, 67.81; H, 10.31; N, 4.94%); \( \nu_{\text{max}} \) (neat) 2955, 2930, 2858, 1729, 1454, 1431, 1368, 1256, 1222, 1153, 1134, 1018, 946, and 759 cm\(^{-1}\); \( \delta^H \) 4.43-4.36 (1H, m), 3.67-3.58 (1H, m), 3.11 (1H, td, \( J \) 3.4,10.40 Hz), 2.68 (1H, ddd, \( J \) 2.7, 10.4, 12.9 Hz), 2.36 (1H, dt, \( J \) 9.4, 11.9 Hz), 2.16 (1H, tt, \( J \) 4.0, 11.9 Hz), 1.97 (3H, s), 1.90-1.76 (2H, m), 1.73-1.55 (4H, m), 1.53-1.25 (5H, m), 1.43 (3H, s), 1.41 (3H, s), 0.90 (3H, t, \( J \) 7.0 Hz); \( \delta^C \) 170.5, 84.1, 77.3, 59.7, 49.6, 38.2, 35.34, 35.29, 28.2, 26.0, 25.5, 23.48, 23.42, 22.7, 22.4, 14.0.


The cycloadduct 196 (1.90 g, 7.4 mmol) in toluene (10 mL) was treated with acetic anhydride (3 mL) and DMAP (0.12 g, 1 mmol) at 70 °C for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 80:20 ether-hexanes as a eluant to give the acetate 200 as a colourless liquid (1.99 g, 90%). (Found: C, 60.0; H, 8.3; N, 4.6. \( C_{15}H_{25}NO_5 \) requires C, 60.18; H, 8.42; N, 4.68%); \( \nu_{\text{max}} \) (neat) 2959, 2951, 1730, 1454, 1370, 1255, 1192, 1137, 1116, 1086, 1019, 988, 947, 873, 757, and 608 cm\(^{-1}\). \( \delta^H \) 3.78 (3H, s), 3.80-3.75 (1H, m), 3.18 (1H, td, \( J \) 3.4,10.4 Hz), 2.87 (1H, t, \( J \) 12.5 Hz), 2.66 (1H, ddd, \( J \) 2.5, 10.7, 13.0), 2.11-2.02 (1H, m), 1.96 (3H, s), 1.70-1.63 (1H, m), 1.99-1.82 (3H, m), 1.50 (3H, s), 1.43 (3H, s), 1.41 (3H, s), 1.45-1.36 (1H, m); \( \delta^C \) 175.5, 170.4, 84.3, 83.8, 60.1 (CHN), 52.7(OMe),
Assignment of the $^{13}$C chemical shifts was based on DEPT experiment results.

5.3.13. 4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-2-phenyl-1-ethyl)-3,4,5,6-tetrahydropyridine 1-oxide (201)

To a stirred solution of the cycloadduct 198 (3.0 mmol) in dichloromethane (30 mL) at 20°C was added MCPBA (3.0 mmol) in one portion. After 30 min at 20 °C the organic layer was washed with 5% NaHCO$_3$ solution (3×10 mL). The combined aqueous layers was re-extracted with CH$_2$Cl$_2$ (3×25 mL). The combined organic layers was dried (Na$_2$SO$_4$), concentrated to give only the aldonitrone 201 as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. $\nu_{\text{max}}$ (neat) 3250, 2981, 2929, 1729, 1621, 1493, 1454, 1431, 1370, 1257, 1224, 1167, 1138, 1098, 1019, 914, 760, 733, and 703 cm$^{-1}$; $\delta$H 7.43-7.21 (5H, m), 7.21-7.17 (1H, m), 6.17 (1H, br s), 5.08-5.03 (1H, dd, $J$ 2.7, 6.4 Hz), 4.15-4.08 (1H, m), 2.55-2.45 (1H, m), 2.42-2.30 (3H, m), 2.03-1.98 (1H, m), 1.97 (3H, s), 1.88–1.82 (1H, m), 1.72-1.67 (1H, m), 1.46 (3H, s), 1.42 (3H, s); $\delta$C 170.1, 143.8, 137.5, 128.3 (2C), 127.0, 125.7 (2C), 82.2, 70.2, 63.1, 44.2, 34.4, 29.9, 27.0, 23.2, 23.1, 22.2.

5.3.14. 4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-1-hexyl)-3,4,5,6-tetrahydropyridine 1-oxide (202)

The cycloadduct 199 (3.0 mmol) was treated with MCPBA to generate the aldonitrone 202 as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. $\nu_{\text{max}}$ (neat) 3357, 2932,
2871, 1729, 1631, 1454, 1370, 1256, 1224, 1170, 1139, 1019, 921, 788, and 732 cm\(^{-1}\); \(\delta_H \)
7.16 (1H, t, \(J\) 3.8 Hz), 5.02 (1H, br s), 4.33-4.22 (1H, m), 3.92-3.78 (1H, m), 2.55-2.30
(4H, m), 2.10-1.90 (2H, m), 2.00 (3H, s), 1.88-1.80 (1H, m), 1.70-1.22 (6H, m), 1.50
(3H, s), 1.47 (3H, s), 0.91 (3H, t, \(J\) 7.0 Hz), \(\delta_C\) 170.2, 136.7, 82.4, 68.2, 63.7, 42.1, 36.5,

5.3.15. 4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-2-carbomethoxy-1-propyl)-3,4,5,6-
tetrahydropyridine 1-oxide (203)

The cycloadduct 200 (3.0 mmol) was treated with MCPBA to generate the aldonitrone 203 as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. \(\nu_{\text{max}}\) (neat) 3438, 2981
1728, 1713, 1644, 1631, 1554, 1537, 1516, 1452, 1371, 1256, 1137, 1020, 918, 732, 645
and 611 cm\(^{-1}\). \(\delta_H\) 7.09-7.06 (1H, m), 6.46 (1H, br s), 4.24-4.18 (1H, m), 3.75 (3H, s), 2.64
(1H, dd, \(J\) 10.2, 14.3 Hz), 2.58-2.25 (3H, m), 1.99 (3H, s), 2.02-1.77 (2H, m), 1.51 (3H, s), 1.50 (3H, s), 1.48 (3H, s), 1.54-1.37 (1H, m); \(\delta_C\) 176.2, 170.0, 137.5, 82.1, 73.2, 62.4, 52.4, 43.6, 34.7, 28.9, 26.8, 26.7, 23.2 (2C), 22.2.

5.3.16. Reaction of nitrone 201 with methylenecrylate (185)

The nitrone 201 [prepared by MCPBA oxidation of adduct 198 (1.0 mmol)] in CH\(_2\)Cl\(_2\) (10 mL) was treated with methyl methacrylate (185) (1.0 mL) and the mixture was stirred at 45ºC for overnight. After removal of the solvent and excess alkene, the residual liquid was purified by chromatography over silica gel using 9:1 ether/hexane as eluant to give a nonseparable mixture of three adducts (as indicated by the presence of three CO\(_2\)Me
singlets at δ3.77, 3.80 and 3.84 ppm in a respective ratio of 89:8:~1 as a colourless liquid (380 mg, 91%). The major adduct was assigned the stereochemistry of 205. (Found: C, 65.6; H, 7.7; N, 3.2. C_{23}H_{33}NO_{6} requires C, 65.85; H, 7.93; N, 3.34%). ν_{max} (neat) 3475, 2982, 2951, 2872, 1728, 1653, 1448, 1368, 1254, 1125, 1057, 1020, 936, 754, 700, 609 cm^{-1}; δ_{H} 7.40-7.23 (5H, m), 5.00 (1H, m), 3.77 (3H, s), 3.77-3.70 (2H, m), 2.43-2.20 (4H, m), 1.95 (3H, s), 1.98-1.22 (6H, m), 1.56 (3H, s), 1.37 (3H, s), 1.35 (3H, s); δ_{C} 174.2, 170.3, 144.6, 128.3 (2C), 126.9, 125.5 (2C), 84.1, 80.3, 72.6, 56.0, 54.8, 52.6, 46.2, 38.4 (2C), 27.5, 25.4 (2C), 23.14, 23.06, 22.4.

5.3.17. Reaction of nitrone 201 with styrene (193a)

The Nitrone 201 [prepared by MCPBA oxidation of adduct 198 (2.0 mmol)] in CH_{2}Cl_{2} (10 mL) was treated with styrene (2.0 mL) and the mixture was stirred at 45°C for overnight. After removal of the solvent and excess alkene, the residual liquid was separated by chromatography over silica gel using 7:1 ether/hexane as eluant to give the minor isomer 206 as a colorless liquid (90 mg). Continued elution gave a mixture of 206 and 207. Finally, the major adduct 207 was eluted as a colorless liquid. The total isolated yield was 82% and respective ratio of 206 and 207 was found to be 1:3.

5.3.17.1. Minor diastereomer 206.

(Found: C, 77.4; H, 7.7; N, 3.2. C_{26}H_{33}NO_{4} requires C, 73.73; H, 7.85; N, 3.31%). ν_{max} (neat) 3446, 3027, 2947, 2880, 1725, 1656, 1493, 1454, 1369, 1258, 1221, 1132, 1055, 1020, 946, 913, 759, 733 and 701 cm^{-1}; δ_{H} 7.40-7.20 (10H, m), 5.13-5.09 (1H, m), 5.06-5.02 (1H, m), 3.72-3.60 (2H, m), 2.50-2.28 (5H, m), 1.98 (3H, s), 1.75-1.22
(5H, m), 1.41 (3H, s), 1.38 (3H, s); δC 170.4, 144.6, 141.7, 128.5 (2C), 128.2 (2C), 127.4, 126.8, 125.6 (4C), 84.2, 76.5, 72.3, 56.3, 54.4, 44.6, 39.6, 38.4, 27.3, 25.2, 23.1 (2C), 22.4.

5.3.17.2. **Major distereomer: 207.**

(Found: C, 73.4; H, 7.6; N, 3.2. \(\text{C}_{26}\text{H}_{33}\text{NO}_4\) requires C, 73.73; H, 7.85; N, 3.31%); \(\nu_{\text{max}}\) (neat) 3429, 3064, 3026, 2945, 1726, 1451, 1367, 1253, 1136, 1018, 782, 753, and 698 cm\(^{-1}\); δH 7.40-7.20 (10H, m), 5.20-5.05 (2H, m), 4.60 (1H, br s), 3.41-3.32 (1H, m), 3.10-3.00 (1H, m), 2.50-1.40 (9H, m), 1.96 (3H, s), 1.52 (6H, s); δC 170.1, 144.7, 141.8, 128.4 (2C), 128.2 (2C), 127.8, 126.9, 126.4 (2C), 125.7 (2C), 84.3, 78.6, 71.5, 61.3, 59.2, 43.9, 43.6, 40.3, 29.7, 29.3, 24.8, 24.2, 22.6.

5.3.18. **Conversion of 207 to 208 by treatment with zinc and acetic acid**

To a vigorously stirred solution of the adduct 207 (0.3 mmol) in acetic acid (2 mL) and water (2 mL) at 60 °C was added Zn (0.85 g) in two portions (ca. 5 min). The reaction mixture was stirred at 60°C for a total 30 min. The reaction mixture was decanted and the residual solid was washed with water (10 mL) and \(\text{CH}_2\text{Cl}_2\) (20 mL). After basification (\(\text{K}_2\text{CO}_3\)), the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3×20 mL). The organic layer was dried (\(\text{Na}_2\text{SO}_4\)), concentrated to give the amine 208 in almost quantitative yield. (Found: C, 73.1; H, 8.0; N, 3.2. \(\text{C}_{26}\text{H}_{35}\text{NO}_4\) requires C, 73.38; H, 8.29; N, 3.29%); \(\nu_{\text{max}}\) (neat) 3410, 3297, 2978, 2858, 1737, 1444, 1373, 1254, 1221, 1113, 1058, 938, 754, 704, and 616 cm\(^{-1}\); δH (500 MHz, 9:1 CDCl\(_3\)/CD\(_3\)OD, 25 °C) 7.14 (4H, d, \(J\) 7.3 Hz), 7.24 (4H, t, \(J\) 7.3 Hz), 7.14 (2H, t, \(J\) 7.3 Hz), 4.96-4.94 (2H, m), 3.97 (3H, br, OHs and NH), 3.01-2.97 (2H, m), 2.02-1.38 (12 H, including a broad signal for OAc, m), 1.27( 6H, s); δC (500
MHz, 9:1 CDCl₃/CD₃OD, 25 °C) 169.7, 143.0 (2C), 128.4 (4C), 126.9 (2C), 125.4 (4C), 84.3, 70.6 (2C), 49.6 (2C), 41.8 (2C), 40.7, 30.2 (2C), 24.8 (2C), 21.8.
CHAPTER 6

Cycloaddition reaction of a novel class of nitrones: 1-Oxa-6-azabicyclo[3,2,1]-5-heptene 6-oxide

Summary:

One interesting finding was that treatment of the first generation nitrone i.e., 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide or 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide, with mercury(II) oxide afforded novel bicyclic nitrones, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxides, whose cycloaddition reactions were briefly examined.

6.1 Introduction

4-hydroxymethyl- and 4-(2-hydroxy-2-propyl)- substituents in the previous cyclic nitrones were our desire to study the effect of these substituents on the cis: trans ratio and then their effect on the second generation nitrone upon reacting the adducts with MCPBA. While the mercury(II) oxide oxidation of 139 and 181 in protic solvent ethanol afforded cleanly the monocyclic nitrone 140 and 182 respectively, the oxidation in aprotic solvent chloroform gave the novel bicyclic nitrone 209 and 210 in almost quantitative yield (Scheme 55).
Database searching indicated that this type of nitrones were novel and new. Also substructure search leads us to a novel type of natural product called SB-219383\cite{99} which is a tyrosyl tRNA synthetase inhibitor. SB-219383, isolated from fermentation of broth of a novel species of *Micromonospora sp.*, is the first member of new class of compounds having inhibitory activity against tyrosyl tRNA synthetase (IC$_{50}$ 2 nM). SB-219383 also exhibits moderate in vitro activity against some Gram positive bacteria \cite{100}. The relative stereochemical arrangement within the bicyclic moiety could be deduced from NMR experiments, while the relative stereochemistry between the amino acid $\alpha$-stereocentre and the ring system as well as the absolute configuration of this C-terminal amino acid remained elusive. Hamprecht *et.al.* \cite{101} synthesized four stereoisomeric analogues, to identify the correct stereostructure of the SB-219383, of SB-219383 (Scheme 53). The four stereoisomers were tested as an inhibitor of bacterial tyrosyl tRNA
synthetase. One of these isomers was found to be potent inhibitor with an IC$_{50}$ 1.2 nM, while the others are not. The proton NMR data for this potent isomer is almost identical (with the exception of the obvious differences resulting from the omission of the methylenoxy unit of SB-219383).

Scheme 53. (i) LiHMDS, Toluene, -78 oC to rt. (ii) HCl, H$_2$O, dioxane, 25oC. (iii) F$_3$CC(O)NMMeTMS, iPr$_2$EtN, pyridine, 25oC; BocTyrOSu, 60oC, MeOH, H$_2$O.
The objective of this work is to study the stereo-and face–selectivity of the cycloaddition reaction of this new class of bicyclic nitrones. Then, to study the relationship between the stereochemistry, in the addition reaction of the bicyclic nitrones $209$, $210$ and the monocyclic nitrones $140$, $192$. This cycloaddition protocol may have the potential application in the synthesis of piperidine alkaloids in which we can absolutely control the stereochemistry of the cycloaddition. However, this new tricyclic adducts can be considered as a cyclic N, O-acetal, in which the reactivity should be greatly enhanced due to the isoxazolidine ring. This special type of tricyclic adducts might react very easily with electrophiles as well as nucleophiles, so, it could be considered as a masked (or protected) piperidines.

6.2 Results and Discussion

The very idea of having a 4-hydroxymethyl substituent in the current cyclic nitrine was our desire to synthesize a nitrine with an unusual bicyclic system as shown in (Scheme 55) [97]. Surprisingly, mercury(II) oxide oxidation of $139$ and $181$ in aprotic solvent chloroform gave the novel bicyclic nitrone $209$ and $210$ in almost quantitative yield. The polar functionality of nitrine $140$ and $182$ is strongly solvated in ethanol; as a result, the internal aminalization of the nitrone moiety to the N-hydroxy compounds $211$ and $212$ is discouraged. In an aprotic solvent, further oxidation of the intermediates $211$ and $212$ led to the bicyclic nitrones $209$ and $210$.

Next, we pursued the addition reaction of nitrones $209$ and $210$ with various alkenes. The addition of monosubstituted alkene 1-hexene $141a$ and styrene $141b$ was found to be stereo-, as well as highly face-selective. A mixture of diasteromers $218a$ and $222a$ was obtained in a ~19:1 ratio. The configuration of the major adduct $218a$ was based on the
sterically favourable exo approach (Scheme 57) of the Bu group from the less hindered face (i.e. β face) of the nitrone, while the α-exo approach of the alkene afforded the adduct 222a. In order to confirm the stereochemistry of the cycloadducts, the compounds 218a,b which are the major adducts were converted into 144a,b in which the latter compounds have a known configuration (Scheme 58). It was surprising that the face selectivity is reversed. This is attributed to the big difference between the two faces of the bicyclic nitrones, in which the α-face contains seven membered ring while the β-face has a six membered ring. Next we did another cycloaddition reaction with a disubstituted alkene ( methylmethacrylate 153), at this stage we could not purify the adducts but the crude 1H-NMR showed two adducts. Then we decided to reduce the crude adducts with LiAlH4, hoping that we can purify the reduced products. This has been done according to (Scheme 58), we were able to separate two products in which we got the same results, that the major adduct was in agreement with the minor adduct from the previous work [97].

Next, nitrone 209 was reacted with methyl acrylate to study the face and stereoselectivity. It was surprising that the addition was α-exo( due the secondary orbital interaction it should be α-endo ). This means that the nitrone 209 can not accommodate any substituent to endo due to a steric effect. The cycloaddition also gave another regioisomer i.e 4-substituted isoxazolidine. To confirm the structure for the 5-isome of the methyl acrylate adduct x-ray crystal structure (Figure 9.) showed that the orientation of the CO2Me is exo and at C-5 of the isoxazolidine ring. Also, the piperidine ring is in the distorted chair conformation due the strain. One important properties of these cycloadducts is the very sharp signal in 1H-nmr which means the absence of any nitrogen process. This is due the strain in the tricyclic compounds i.e the strain prevents any inversion.
Figure 9. Molecular structure of compound 218c.
The last reaction is the cycloaddition of nitrone 210 with styrene 141b as an example to examine the face selectivity (Scheme 58). It was surprising that the major isomer was in agreement with the major isomer from the previous work. This is happened may be due to the effect of the two methyl groups in which they are increasing the crowdness of the α-face over the β-face of the nitrone 210 (Scheme 58).
Scheme 58.
Scheme 59.

Scheme 60.
6.3 Experimental

6.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTIR spectrometer. $^1$H and $^{13}$C NMR spectra were measured in CDCl$_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). 4-methoxycarbonylpiperidine (187), 1-hexene, styrene, methyl methacrylate, from Fluka Chemie AG (Buchs, Switzerland) were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N$_2$.

6.3.1. 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxide (209) (210).

To a solution of the hydroxylamine 181 or 139 (0.796 g, 5.0 mmol) in dry CHCl$_3$ (50 mL) was added yellow HgO (4.3 g, 20 mmol) and the mixture was stirred using a magnetic stir bar at 20°C for overnight or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and MgSO$_4$. After removal of the solvent, the bicyclic nitrone 210 was obtained as a solid in almost quantitative yield, while the bicyclic nitrone 209 was used directly. Mp 87-89°C of 210 (ether); (Found: C, 61.7; H, 8.3; N, 8.9. C$_8$H$_{13}$NO$_2$ requires C, 61.91; H, 8.44; N, 9.03%); $\nu_{\text{max}}$ (KBr) 3296, 2972, 2937, 1642, 1605, 1451, 1369, 1303, 1195, 1176, 1142, 1117, 1088, 1059, 1032, 963 and 899 cm$^{-1}$; $\delta$H (500 MHz, CDCl$_3$, +25°C) 6.82-6.79
(1H, m), 5.18 (1H, d, J 3.5 Hz), 2.66-2.48 (3H, m), 2.40-2.36 (1H, m), 2.21 (1H, d, J 12.3 Hz), 1.38 (3H, s), 1.30 (3H, s); δC (500 MHz, CDCl₃, +25°C) 130.2, 98.0, 85.3, 38.2, 34.5, 28.9, 28.6, 24.6.

6.3.2. Reaction of nitrone 209 with 1-hexene (141a)

To a stirring solution of the hydroxylamine 139 (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature for 6 h. The mixture was filtered over a bed of magnesium sulphate. The resulting solution was stirred at room temperature overnight after which 1-hexene 141a was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the adduct as a colorless liquid (0.25 g, 40%).

ν max (neat) 2928, 2871, 1448, 1379, 1303, 1221, 1062, 984, 908, 866, 788, 728 and 645 cm⁻¹. δH (500 MHz, CDCl₃, +25°C) 5.12- 5.11 (1H, d, J 5.5 Hz), 4.48- 4.43 (1H, m), 3.86-3.84 (1H, d, 8.3 Hz), 3.73-3.71 (1H, m), 3.57- 3.51 (1H, q, J 9.5 Hz), 2.45-2.40 (1H, m), 2.37-2.27 (1H, m), 2.17-2.11 (1H, m), 1.99-1.95 (1H, td, J 2.4, 14.0 Hz), 1.90-1.80 (3H, m), 1.57-1.50 (1H, m), 1.44-1.26 (5H, m), 0.89 (3H, t, J 7.1 Hz) ; δC (500 MHz, CDCl₃, +25°C) 93.1, 81.0, 72.2, 55.9, 41.6, 36.7, 35.5, 33.1, 30.4, 28.0, 22.7, 14.0.

6.3.3. Reaction of nitrone 209 with styrene (141b)

To a stirring solution of the hydroxylamine 139 (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature for
The mixture was filtered over a bed of magnesium sulphate. The resulting solution was stirred at room temperature overnight after which styrene 141b was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the adduct as white solid 218b Mp 116-118 °C (0.28 g, 45%). M+ 231.1; νmax (KBr disc) 2987, 2928, 2872, 1489, 1446, 1360, 1309, 1281, 1216, 1087, 1070, 1015, 978, 915, 830, 806, 761, 726, 695 and 674 cm⁻¹. δH (500 MHz, CDCl₃, +25°C) 7.35-7.23 (5H, m), 5.50-5.47 (1H, dd, J 4.6, 9.5 Hz), 5.25-5.24 (1H, dd, J 1.5, 4.6 Hz), 3.94-3.92 (2H, d, 8.2 Hz), 3.81-3.75 (1H, m), 2.75-2.68 (1H, q, J 10.7 Hz), 2.47-2.46 (1H, m), 2.23-2.12 (2H, m), 2.03-2.00 (1H, m), 1.94-1.91 (2H, m); δC (500 MHz, CDCl₃, +25°C) 143.0, 128.3 (2C), 127.4, 126.2 (2C), 93.2, 82.5, 72.4, 56.4, 45.1, 35.5, 33.1, 30.4.

6.3.4. Reaction of nitrone 209 with methyl methacrylate (153)

A solution of nitrone 209 (3.0 mmol) in chloroform (20 mL) containing methylmethacrylate (153) (4 mL) was stirred at room temperature overnight under N₂ in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was not be able to be purified by chromatography. Then the mixture was taken to the LiAlH₄ reduction step (section 6.3.4.).

6.3.5. Reaction of nitrone 209 with methyl methacrylate (153)

To a stirring solution of the hydroxylamine 139 (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature for 6 h. The mixture was filtered over a bed of magnesium sulphate. The resulting solution
was stirred at room temperature for four hours after which methyl acrylate (2 ml) was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the first fraction which contains pure adduct 218d as a colorless liquid. Continued elution gave the second fraction which contains a pure cycloadducts 218c as white solid Mp 96-98 °C (0.28 g, 45%).

Compound 218d

$\nu_{\text{max}}$ (neat) 2947, 2883, 1741, 1439, 1277, 1206, 908, 726 and 674 cm$^{-1}$. $\delta$H (500 MHz, CDCl$_3$, +25°C) 5.02-5.01 (m, 1H), 4.36-4.32 (m, 1H), 3.97-3.95 (m, 1H), 3.80-3.78 (d, 1H, J= 8.5 Hz), 3.70-3.69 (m, 1H), 3.68 (s, 3H), 3.67-3.64 (m, 1H), 3.36-3.34 (m, 1H), 2.40-2.38 (m, 1H), 2.12-2.10 (m, 2H), 1.82-1.80 (m, 2H); $\delta$C (500 MHz, CDCl$_3$, +25°C) 172.9, 92.9, 72.2, 72.1, 60.2, 53.1, 51.9, 35.2, 32.6, 29.5.

Compound 218c

$\nu_{\text{max}}$ (KBr disc) 2949, 2885, 1740, 1438, 1276, 1203, 1068, 1029, 911, 726 and 698 cm$^{-1}$. $\delta$H (500 MHz, CDCl$_3$, +25°C) 5.05-5.03 (m, 1H), 4.83-4.80 (m, 1H), 3.76-3.72 (m, 1H), 3.68-3.66 (m, 1H), 3.65 (s, 3H), 3.55-3.53 (m, 1H), 2.52-2.50 (m, 1H), 2.39-2.37 (m, 1H), 2.28-2.25 (m, 1H), 2.14-2.10 (m, 1H), 1.98-1.94 (m, 1H), 1.79-1.75 (m, 2H); $\delta$C (500 MHz, CDCl$_3$, +25°C) 172.0, 92.4, 77.6, 72.1, 55.2, 51.8, 39.9, 34.7, 32.2, 29.7.
3.3.6. Lithium aluminium hydride reduction of cycloadducts 226 and 227 to 228 and 229

To a stirred solution of adducts 226 and 227 (from section 6.3.3) (100 mg, 0.33 mmol) in ether (15 mL) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1 g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$), concentrated, and purified by silica gel chromatography using a 85:15 ether/methanol as the eluant to give 228 as a colourless liquid (71 mg, 92%), then continuing elution gave 229 as a white liquid.

6.3.7. Lithium aluminium hydride reduction of cycloadduct 154 and 229

Major invertomer 229

$V_{max}$ (KBr disc) 3411, 2966, 2935, 2859, 1448, 1385, 1324, 1119, 1044, 975, 912, 793, and 730 cm$^{-1}$. $\delta$H (500 MHz, CDCl$_3$, +25°C) 3.78-3.75 (1H, m), 3.62-3.52 (2H, m), 3.42-3.41 (3H, m), 2.562.41 (2H, m), 2.04-1.99 (1H, m), 1.96-1.94 (2H, m), 1.88-1.83 (1H, m), 1.74-1.66 (2H, m), 1.57-1.53 (2H, m), 1.25 (3H, s), 1.23-1.93 (1H, m); $\delta$C (500 MHz, CDCl$_3$, +25°C) 23.0, 25.5, 29.8, 33.6, 42.6, 50.9, 62.2, 62.7, 66.6, 80.7.

Minor invertomer 229

$\delta$C (500 MHz, CDCl$_3$, +25°C) 24.5, 27.7, 28.4, 32.9, 37.4, 51.6, 59.3, 68.5, 70.1, 86.4.
6.3.8. Lithium aluminium hydride reduction of cycloadducts 218a,b to 144a,b

A sample of adduct 218a,b was reduced with LiAlH₄ using procedure as described above to give 144a,b as a colourless liquid (93% yield), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.4.2. and 4.3.5.3.

6.3.9. Reaction of nitrone 210 with styrene (141b)

To a stirring solution of the hydroxylamine 181 (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100 mg) in 10 min. The reaction mixture was then stirred at room temperature overnight. The mixture was filtered over a bed of magnesium sulphate. The resulting solution was stirred at room temperature overnight after which styrene 141b was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the adduct as yellow liquid 223a (0.28 g, 45%). νmax (neat) 2970, 2932, 2865, 1448, 1368, 1272, 1181, 1130, 1036, 1004, 907, 823, 727, 699 and 644 cm⁻¹. δH (500 MHz, CDCl₃, +25°C) 7.42-7.24 (5H, m), 5.23-5.20 (1H, m), 5.14-5.11 (1H,m), 4.02-3.97 (1H, m), 3.81-3.75 (1H, m), 2.43-2.41 (1H,m), 2.23-1.95 (4H, m), 1.61-1.56 (1H, m), 1.48 (3H, s), 1.25 (3H, s); δC (500 MHz, CDCl₃, +25°C) 140.8, 128.4 (2C), 127.7, 126.7 (2C), 90.1, 83.1, 78.5, 54.8, 44.9, 39.9, 32.9, 31.8, 29.3 (2C).

6.3.10. Lithium aluminium hydride reduction of cycloadduct 223 to 194b

A sample of adduct 223 was reduced with LiAlH₄ using procedure as described above to give 194a as a white solid (93% yield), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 5.3.7.
CHAPTER 7

A short stereoselective synthesis of racemic 2-epicalvine

Summary:

The cycloaddition reaction of 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide with butyl vinyl ether was used as a key step in the short stereoselective racemic synthesis of ladybird beetle alkaloid 2-epicalvine. The cycloadduct on quartenization with 2-bromoethanol followed by ring opening and lactonization afforded the natural product in a single pot reaction.

7.1 Introduction

Substituted piperidines are abundant in nature and many of these exhibit important biological activities. Particularly 2,6-disubstituted piperidines are one of the most common piperidine skeletons and have been the subject of intensive studies and synthetic efforts. One renowned example of this family is solenopsin A, the active ingredient in fire ants Solenopsis, which shows cytotoxic, hemolytic, necrotic, insecticidal, antibacterial, and antifungal activities [103]. Two examples of 2,6-disubstituted piperidines found in plants are lobeline from Indian tobacco (*Lobelia inflata*) [104] and dihydropinidine from pines, which was found later in the Mexican bean beetle (*Epilachna varivestis*) [105].
Ladybird beetles (*Coccinellidae*) are rarely exploited as food sources by predators, owing to toxic alkaloids produced in their hemolymph, which are released as yellow small droplets from their knee joints once they are disturbed or molested [106]. Calvine, a *cis-*2,6-disubstituted piperidine annulated with a seven-membered lactone, is the major alkaloid found in two ladybird beetles *Calvia 10-guttata* and *Calvia 14-guttata*. 2-Epicalvine, its corresponding trans-lactone was also found as the minor constituent (about 10%). Braekman et al. isolated the alkaloids in 1999 and determined their absolute configuration by enantioselective syntheses in 2000 [107].

![Figure 10](image1.png)

**Figure 10.**

![Figure 11](image2.png)

**Figure 11.**

### 7.1.1 Synthetic Strategies of Calvine

So far, four total synthesis syntheses of calvine have been reported. The first synthesis was done by Braekman *et al.* with CN(R,S) method as key step. Troin *et al.*
reported a formal synthesis, which involved an intramolecular Mannich reaction. The third is based on an olefin cross-metathesis (CM) reaction of a chiral homoallylamine and an enone. And the last report is based on the intramolecular Pd(II)-catalysed carbonylation of aminoalkenitol.

7.1.1.1 CN(R,S) Methodology

Husson and Royer developed a methodology known as CN(R,S), which based on a chiral Ncyanomethyloxazolidine intermediate. This method is flexible and allows the preparation of piperidines in both R- and S-configurations (Scheme 61) [108].

Condensation of glutaraldehyde 226 and phenyl glycinol 227 in the presence of KCN furnished the Ncyanomethyloxazolidine 228. Its deprotonation and alkylation affords 229, which after elimination of the cyano group gives the prochiral iminium 230.
Reduction and cleavage of the chiral moiety yield the piperidine 231. On the other hand, elimination of the cyano group from 228 yields the prochiral iminium ion 232, which reacts with a Grignard reagent to afford 233. Cleavage of the chiral moiety leads to 234, the enantiomer of 231. The method was successfully applied, for example to synthesize both configurations of coniine [109].

![Chemical structures](Image)

Scheme 62.

The total synthesis of calvine by Braekman et al. is outlined in (Scheme 62) [107]. The CN(R,S) method furnished the aminoalcohol 236 after decyanation by sodium in liquid ammonia. Reaction of 236 with 1-methoxy-1-trimethylsilyloxyethene in the presence of BF₃·OEt₂ led to piperidine 237 as single isomer [110]. Hydrogenolysis of the chiral appendage afforded the piperidine 238. Introduction of the ethylhydroxyl group was conducted by treating 238 with an excess of ethylene oxide in methanol, which resulted in a crude mixture containing calvine, epicalvine, methylester 239 (cis:trans 1:1). Subjecting the crude product mixture to the lactonization conditions in the presence of Amberlyst A15...
and molecular sieves in acetonitrile yielded calvine, epicalvine in 23, 20 yield, respectively. The major drawback of the synthesis is the hydroxyethylation reaction, which gave low yield and selectivity. However, it was essential to prepare both calvine and 2-epicalvine for determination of their structures.

7.1.1.2. Intramolecular Mannich Reaction

Troin et al. reported the synthesis of piperidine 247 from a chiral -aminoester 245 and hex-2- enal via Mannich-type reaction as shown in (Scheme 63) [111]. The preparation of the aminoester started from acid 240, which was transformed to the acylchloride. Treatment of the crude mixture with triethylamine and methyl triphenylphosphoranylidene acetate gave the conjugated allenic ester 242 via ketene intermediate 241 and subsequent Wittig reaction. Nucleophilic addition of (R)-methylbenzylamine provided an inseparable 3:1 Z/E mixture of chiral enaminoester 243. The Z-isomer, which was stabilized by intramolecular hydrogen bond, formed predominantly [112]. Reduction of the product with sodium acetoxyborohydride yielded amine 244 (dr 75:25), which was readily separated from its diastereomer. Hydrogenation led to the chiral aminoester 245, which reacted with hex-2-enal to give 246. Transformation of the dioxolane to dithiolane derivative followed by the reaction with Raney nickel furnished the piperidine 247. The synthetic route was lengthy and with moderate selectivity in the nucleophilic addition reaction.
7.1.1.3. Olefin cross-metathesis (CM) reaction of a chiral homoallylamine and an enone.

Blechert et.al. apply the sequential olefin cross-metathesis–reductive cyclization method to synthesize calvine[113]. In contrast to the synthesis of Braekman, he found it advantageous to introduce the hydroxyethyl group early in the synthesis to avoid the unselective hydroxyethylation( scheme 64). Compound 249 was prepared in two steps according to the procedure of Zibuck and Streiber [114]. The Jones oxidation yielded the desired enone 3 in 55% yield.
The homoallylamine 254 was prepared in six steps, starting from (R)-epichlorohydrine 250. Its conversion to pentyl Oxirane 251 was done by copper-catalyzed
oxirane opening with n-butyl magnesium chloride followed by oxirane formation in basic conditions [115]. The transformation of homoallylalcohol 252 to homoallylamine 254 was accomplished by tosylation, nucleophilic substitution, and introduction of the Cbz protecting group, yielding the homoallylamine 254.

CM between enone 249 and homoallylamine 254 was conducted in the presence of 7.5 mol% Hoveyda–Blechert ruthenium catalyst [Ru] [116] to afford exclusively the E-enone 255 in 70% yield. The catalyst was chosen as it shows higher reactivity and stability than the second generation Grubbs’ catalyst [117].

Reductive hydrogenation in isopropyl ether at 3 bar of hydrogen and 40 °C for three days followed by treatment with a slight excess of p-toluenesulfonic acid in refluxing benzene to afford neat calvine in 66% yield.

7.1.1.4. Intramolecular Pd(II)-catalysed carbonylation of aminoalkenitol

Szolcsanyi et. al. report a short racemic syntheses of the alkaloids calvine and epi-calvine featuring Pd(II)-catalysed aminocyclisation–lactonization [118] as a key step (Scheme 64).

Scheme 65. (i) CO (balloon), 0.1 equiv. PdCl2, 2equiv. CuCl2, 2 equiv. AcONa, dioxane, 40 °C, 7h, (55 %, 2.2:1)
After some experimentation, they identified the optimal catalytic system consisting of PdCl$_2$ as catalyst, excess CuCl$_2$ and AcONa as reoxidant and base, respectively. These reaction conditions which involved heating in dioxane under a CO atmosphere afforded racemic calvine rac-1 and epicalvine rac-2 in 55% combined yield and in the ratio 2.2:1 (Scheme 65).

It's worth to mention that all the reported syntheses, the cis-lactone (Calvine) is formed either as the predominant or sole isomer. So far, no stereoselective synthesis of the trans- lactone (2-epicalvine) has been reported. Also it's noted that the overall yield in the previous syntheses are very low. Herein, we report a concise stereoselective racemic synthesis of the alkaloid 2-epicalvine via nitrone cycloaddition reaction as a key step.

7.2 Results and Discussion

Nitrone (257)-butyl vinyl ether cycloaddition reaction at 50°C afforded a mixture of stereoisomers 258a and 258b in 92% yield in a respective ratio of 85:15 in a face selective manner; substituent at C(6) in cyclic nitrones are known to force alkenes to approach exclusively from its sterically favourable α-face (Scheme 66) [114]. Similar stereoselectivity is documented in the addition reaction of parent 5- or 6-membered cyclic nitrones with ethyl vinyl ether [119]. The trans stereochemistry of the substituents at C(3a) and C(7) in 258a or 258b is assured by the subsequent transformation of the cycloadducts to 2-epicalvine. In a single pot reaction, quaternization of adduct 258a with 2-bromoethanol to 259, followed by bromide catalyzed ring opening [120] to 260 and lactonization afforded the natural product 2-epicalvine in 46% yield and the uncyclised alcohol ester 260 (26% yield). Likewise, the adduct 258b was also converted into 2-
epicalvine, thereby confirming the trans relationship of the substituents. Note that the spectral analyses failed to detect the presence of the isomeric natural product calvine. However, when the above lactonization was repeated in refluxing toluene instead of benzene, a mixture of Calvine and 2-epicalvine was obtained in a respective ratio of 1:2 (56% yield) along with unicycled alcohol 260 (11%). At the higher temperature, isomerization happened via retro-Michael and Michael reactions involving β-amino ester functionalities [107]. In a separate experiment, the intermediate 260 was isolated and converted into 2-epicalvine by p-tosic acid catalyzed lactonization. The identity of the intermediate 260 was confirmed by its conversion to the known methyl ester 261 (Scheme 64) [107]. The methodology described above can be applied to incorporate and elaborate piperidine moiety so widespread in nature. Also note that this is the first stereoselective synthesis of the trans compound 2-epicalvine (all other reported syntheses led to the cis isomer 1).
Regiochemical complication associated with the generation of 6-substituted-3,4,5,6-tetrahydropyridine 1-oxide like 257 is a long standing problem and remains so at this stage [114a,122]. Our repeated attempts to generate the nitrone by mercury(II) oxide oxidation of 2-pentyl-N-hydroxypiperidine 263 resulted in a mixture of aldonitrone 257 and ketonitrone 264 in a respective ratio of 29:71 in almost quantitative yields (Scheme 67). Attempts to influence the abstraction of the C(6)H by carrying out the oxidation process using mercury(II) oxide or p-benzoquinone in CH₂Cl₂ in the presence of 1 equivalent of bulky base Et₃N or in solvent like t-butanol did not improve the ratio in favour of the desired aldonitrone 257. However, the regiochemical problem is partially solved by recycling the ketonitrone 264 to aldonitrone 257 via NaBH₄ reduction followed by mercury (II) oxide oxidation.
Scheme 67. 

7.3 Experimental

7.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTIR spectrometer. $^1$H and $^{13}$C NMR spectra were measured in CDCl$_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N$_2$. 
7.3.2. 2-pentyl-N-hydroxypiperidine 263

Prepared by dropwise addition of pentylmagnesium bromide (55 mmol) in ether (100 mL) to a solution of nitrone 262 [120a] (50 mmol) in (100 mL) at 20°C. After stirring for 1 h a saturated solution of NH₄Cl (100 mL) was added to the reaction mixture and extracted with diethyl ether (2 × 50 mL). Colourless liquid, 82%, bp₀.₈ mbarHg 100°C; υₘₚₙₙ (neat) 3210, 2935, 2853, 1455, 1377, 1355, 1260, 1229, 1177, 1103, 1064, 1035, 986, 949, 862, 828, 775 and 729 cm⁻¹; δH (500 MHz, CDCl₃, +25 °C) 7.24 (1H, br, OH), 3.30 (1H, apparent d, J 10.1 Hz), 2.49 (1H, ddd, J 3.0, 10.3, 13.1 Hz), 2.27-2.20 (1H, m), 2.04-1.95 (1H, m), 1.87-1.82 (1H, m), 1.75-1.50 (3H, m), 1.40-1.10 (9H, m), 0.89 (3H, t, J 7.0 Hz); δC (125 MHz, CDCl₃, +25 °C) 67.8, 59.7, 33.2, 32.3, 31.0, 25.9, 25.5, 23.8, 22.7, 14.1.

7.3.3. Reaction of nitrone 257 with butyl vinyl ether

A mixture of hydroxylamine 263 (3.80 g, 22 mmol) in CH₂Cl₂ (75 mL) and HgO oxidation (13 g, 60 mmol) was stirred at 0-10°C for 4h or until the TLC experiment (silica, ether) indicated the completion of the reaction. After filtering through a bed of MgSO₄, the solution of the nitrones 257 and 264 was reacted with butyl vinyl ether (15 mL) in a closed vessel at 55°C for overnight. Chromatography of the crude products over silica gel using 9:1 hexane /ether as eluant to give the minor isomer 258b (40 mg) as a colorless liquid. Continued elution gave a mixture of two adducts (650 mg) then finally the major adduct 258a as a colorless liquid (900 mg). The total isolated yield of adducts 258a and 258b was thus found to be 27% (92% based on the nitrone 257. Continued elution with 1:1 ether/methanol gave the ketonitrone 264 (2.5 g, 67%).
7.3.3.1. 2-butoxy-7-pentyl-hexahydro-2H-isoxazolo[2,3-a]pyridine 258a

\( \nu_{\text{max}} \) (neat) 2954, 2930, 2862, 1462, 1447, 1352, 1250, 1193, 1123, 1088, 943, 909, 849, 821 and 730 cm\(^{-1}\); \( \delta_{\text{H}} \) (500 MHz, CDCl\(_3\), +25 °C) 5.27 (1H, d, J 4.8 Hz), 3.74 (1H, td, J 6.7, 9.5 Hz), 3.77-3.67 (1H, m), 3.36 (1H, td, J 6.7, 9.2 Hz), 2.54-2.45 (1H, m), 2.40-2.30 (1H, m), 1.97-1.70 (5H, m), 1.54 (2H, quint, J 7.0 Hz), 1.52-1.46 (1H, m), 1.40-1.10 (11 H, m), 0.90 (3H, t, J 7.3 Hz), 0.88 (3H, t, J 7.0 Hz); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\), +25 °C) 102.5, 67.6, 60.9, 57.5, 37.4, 33.9, 32.1, 31.7, 28.8, 25.2 (2C), 22.6, 19.3, 18.6, 13.9 (2C).

7.3.3.2. 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide 264

mp 133-135 °C (Et\(_2\)O/CH\(_2\)Cl\(_2\)); \( \nu_{\text{max}} \) (KBr) 3415, 2955, 2931, 2869, 1656, 1630, 1448, 1379, 1333, 1282, 1248, 1195, 1150, 1068, 956 and 892 cm\(^{-1}\). \( \delta_{\text{H}} \) (500 MHz, CDCl\(_3\), +25 °C) 3.85-3.77 (2H, m), 2.57-2.50 (2H, apparent t, J 7.6 Hz), 2.46-2.40 (2H, m), 1.93 (2H, dquint, J 2.5, 6.1 Hz), 1.74 (2H, dquint, J 2.5, 6.1 Hz), 1.58-1.51 (2H, m), 1.38-1.30 (4H, m), 0.90 (3H, t, J 7.0 Hz); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\), +25 °C) 149.4, 58.0, 31.8, 31.5, 28.6, 24.1, 23.0, 22.3, 18.6, 13.8.

7.3.2. Reaction of cycloadducts 258a with 2-bromoethanol to form epi-calvine

A mixture of adduct 258a (2.0 mmol), 2-bromoethanol (2.3 mmol) in acetonitrile (10 cm\(^3\)) was refluxed under N\(_2\) for 24 h. After adding p-TsOH.H\(_2\)O (2.0 mmol), acetonitrile was exchanged with dry benzene (30 cm\(^3\)). The solution was then refluxed for a further 24 h. After removal of benzene the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (40 cm\(^3\)); the organic layer was washed with 5% K\(_2\)CO\(_3\) solution (15 cm\(^3\)). The aqueous layer
was re-extracted with CH$_2$Cl$_2$ (15 cm$^3$). The combined organic layers was dried, concentrated, and the residual liquid was chromatographed over silica using 9:1 ether/hexane to give the uncyclised alcohol 260 as a colorless liquid (160 mg, 26%). Continued elution with 95:5 ether/methanol saturated with NH$_3$ gave (±)-2-epicalvine (220 mg, 46%).

7.3.2.1. Epi-calvine

$\nu_{\text{max}}$ (neat) 2927, 2860, 1727, 1652, 1465, 1434, 1374, 1309, 1280, 1244, 1218, 1168, 1059, 1028, 939, 894, 743, and 596 cm$^{-1}$; $\delta$H (500 MHz, CDCl$_3$, +25 °C), 4.34 (1 H, dd, J 8.5, 13.3 Hz), 4.23 (1 H, dd, J 6.1, 13.3 Hz), 3.01 (1 H, dd, J 6.1, 14.6 Hz), 2.96 (1 H, dd, J 8.5, 14.6 Hz), 2.87 (1 H, apparent t, J 9.8 Hz), 2.75 (1 H, dd, J 9.8, 13.7 Hz), 2.78-2.72 (1 H, overlapping m), 2.53 (1 H, d, J 13.7 Hz), 1.70-1.10 (14 H, m), 0.89 (t, 3 H, J 7.0 Hz); $\delta$C (125 MHz, CDCl$_3$, +25 °C) 174.2, 68.5, 60.6, 54.8, 51.1, 42.9, 32.4, 31.9, 26.8, 26.7, 24.4, 22.5, 18.6, 13.9.

7.3.2.2 Compound 260

$\nu_{\text{max}}$(neat) 3424, 2954, 2923, 2859, 1727, 1463, 1381, 1352, 1288, 1258, 1176, 1118, 1058, and 727 cm$^{-1}$; $\delta$H (500 MHz, CDCl$_3$, +25 °C) 4.13-4.02 (2 H, m), 3.57 (1 H, ddd, J 3.7, 8.3, 11.8 Hz), 3.44 (1 H, td, J 4.6, 10.7 Hz), 3.45-3.37 (1 H, overlapping m), 3.12 (1 H, br OH), 2.81-2.68 (3 H, m), 2.59 (1 H, td, J 4.0, 13.4 Hz), 2.32 (1 H, dd, J 6.4, 15.0 Hz), 1.75-1.18 (14 H, m), 1.60 (2 H, quint, J 7.3 Hz), 1.38 (2 H, hext, J 7.3 Hz), 0.94 (3 H, t, J 7.3 Hz), 0.88 (3 H, t, J 7.3 Hz); $\delta$C (125 MHz, CDCl$_3$, +25 °C) 172.8, 64.4, 59.5, 54.5, 52.6, 47.1, 37.0, 32.9, 31.9, 30.6, 26.3, 25.5, 24.0, 22.6, 20.4, 19.1, 14.0, 13.7.
Conclusions

Scope and limitation with respect to asymmetric induction in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)norephedrine-derived methylenenitrone has been investigated.

The cycloaddition reactions of several mono- and disubstituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide have been found to be highly stereo- and face-selective. The addition reactions have displayed a very high degree of face selectivity (13-48:1). The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer which leads to the formation of synthetically important second-generation cyclic aldonitrones via peracid oxidation. The cycloadducts with two equivalents of peracid afforded the cyclic N-hydroxy lactams, presumably via further oxidation of the aldonitrones. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

Likewise, the cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be highly stereo- as well as face-selective. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones.

The treatment of the first generation nitrone i.e., 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide or 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide,
with mercury(II) oxide afforded novel bicyclic nitrones, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxides, whose cycloaddition reactions were briefly examined.

The cycloaddition reaction of 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide with butyl vinyl ether was used as a key step in the short stereoselective racemic synthesis of ladybird beetle alkaloid 2-epicalvine.

Overall, the work involved extensive investigation involving cycloaddition reactions of chiral nitrones. The results would indeed be useful in incorporation and elaboration of puiperidine alkaloids so widespread in nature.
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APPENDIX

$^1$H-NMR of 127a in CDCl$_3$ at 20°C

$^1$H-NMR of 127b in CDCl$_3$ at 20°C
$^1$H-NMR of 131 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 131 in CDCl$_3$ at 20°C
$^1$H-NMR of 128c in CDCl$_3$ at 20°C

$^1$H-NMR of 128d in CDCl$_3$ at 20°C
$^1$H-NMR of 127d in CDCl$_3$ at 20°C

$^{13}$C-NMR of 139 in CDCl$_3$ at 20°C
DEPT-NMR of 139 in CDCl$_3$ at 20°C

$^1$H-NMR of 155 in CDCl$_3$ at 20°C
$^{13}\text{C-NMR of 155 in CDCl}_3$ at 20°C

$^1\text{H-NMR of 154 in CDCl}_3$ at 20°C
$^1$H-NMR of 143b in CDCl$_3$ at 20°C

$^{13}$C-NMR of 143b in CDCl$_3$ at 20°C
$^1$H-NMR of 142b in CDCl$_3$ at 20°C

$^{13}$C-NMR of 142b in CDCl$_3$ at 20°C
$^1$H-NMR of 142a in CDCl$_3$ at 20°C

$^1$H-NMR of 160b in CDCl$_3$ at 20°C
$^{13}$C-NMR of 160b in CDCl$_3$ at 20°C

$^1$H-NMR of 162 in CDCl$_3$ at 20°C
$^1$H-NMR of 218b in CDCl$_3$ at 20°C

$^{13}$C-NMR of 218b in CDCl$_3$ at 20°C
$^{1}$H-NMR of 168a in CDCl$_3$ at 20°C

$^{13}$C-NMR of 168a in CDCl$_3$ at 20°C
$^1$H-NMR of 176 in CDCl$_3$ at 20°C

$^1$H-NMR of 170a in CDCl$_3$ at 20°C
DEPT-NMR of 168b in CDCl$_3$ at 20°C

$^{13}$C-NMR of 168b in CDCl$_3$ at 20°C
$^1$H-NMR of \textbf{168b} in CDCl$_3$ at 20°C

$^1$H-NMR of \textbf{172} in CDCl$_3$ at 20°C
$^{13}$C-NMR of 172 in CDCl$_3$ at 20°C

$^1$H-NMR of 173 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 173 in CDCl$_3$ at 20°C

$^1$H-NMR of 171b in CDCl$_3$ at 20°C
$^{13}$C-NMR of 171b in CDCl$_3$ at 20°C

$^1$H-NMR of 170b in CDCl$_3$ at 20°C
$^{13}$C-NMR of 170b in CDCl$_3$ at 20°C

$^1$H-NMR of 174 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 174 in CDCl$_3$ at 20°C

$^1$H-NMR of 175 in CDCl$_3$ at 20°C
$^1$H-NMR of 180 in CDCl$_3$ at 20°C

DEPT-NMR of 180 in CDCl$_3$ at 20°C
$^1$H-NMR of 179 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 179 in CDCl$_3$ at 20°C
DEPT-NMR of 179 in CDCl₃ at 20°C

¹³C-NMR of 177 in CDCl₃ at 20°C
$^{13}$C-NMR of 178 in CDCl$_3$ at 20°C

$^1$H-NMR of 178 in CDCl$_3$ at 20°C
$^1$H-NMR of 218a in CDCl$_3$ at 20°C

$^{13}$C-NMR of 218a in CDCl$_3$ at 20°C
DEPT-NMR of 218a in CDCl$_3$ at 20°C

$^1$H-NMR of 190 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 190 in CDCl$_3$ at 20°C

$^1$H-NMR of 191 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 191 in CDCl$_3$ at 20°C

$^1$H-NMR of 192 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 192 in CDCl$_3$ at 20°C

DEPT-NMR of 192 in CDCl$_3$ at 20°C
$^1$H-NMR of 194a in CDCl$_3$ at 20°C

$^{13}$C-NMR of 194a in CDCl$_3$ at 20°C
DEPT-NMR of 194a in CDCl₃ at 20°C

¹H-NMR of 196 in CDCl₃ at 20°C
$^{13}$C-NMR of 196 in CDCl$_3$ at 20°C

DEPT-NMR of 196 in CDCl$_3$ at 20°C
$^1$H-NMR of 194b in CDCl$_3$ at 20°C

$^{13}$C-NMR of 194b in CDCl$_3$ at 20°C
DEPT-NMR of 194b in CDCl₃ at 20°C

³¹H-NMR of 199 in CDCl₃ at 20°C
$^{13}$C-NMR of 199 in CDCl$_3$ at 20°C

$^1$H-NMR of 200 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 200 in CDCl$_3$ at 20°C

DEPT-NMR of 200 in CDCl$_3$ at 20°C
$^1$H-NMR of 202 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 202 in CDCl$_3$ at 20°C
$^1$H-NMR of 203 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 203 in CDCl$_3$ at 20°C
$^{1}$H-NMR of 201 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 201 in CDCl$_3$ at 20°C
$^1$H-NMR of 206 in CDCl$_3$ at 20°C

$^1$H-NMR of 205 in CDCl$_3$ at 20°C
$^1$H-NMR of 207 in CDCl$_3$ at 20°C

$^1$H-NMR of 208 in CDCl$_3$ at 20°C
$^{13}$C-NMR of 208 in CDCl$_3$ at 20°C

$^1$H-NMR of 258a in CDCl$_3$ at 20°C
$^1$H-NMR of 264 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 264 in CDCl$_3$ at 20°C
$^1$H-NMR of 260 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 260 in CDCl$_3$ at 20°C
$^1$H-NMR of 261 in CDCl$_3$ at 20°C

$^{13}$C-NMR of 261 in CDCl$_3$ at 20°C
$^1$H-NMR of 2-epicalvine in CDCl$_3$ at 20°C

$^{13}$C-NMR of 2-epicalvine in CDCl$_3$ at 20°C
VITA

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