REVIEW

# 1,3-Dipolar cycloaddition reactions of carbohydrate derived nitrones and oximes

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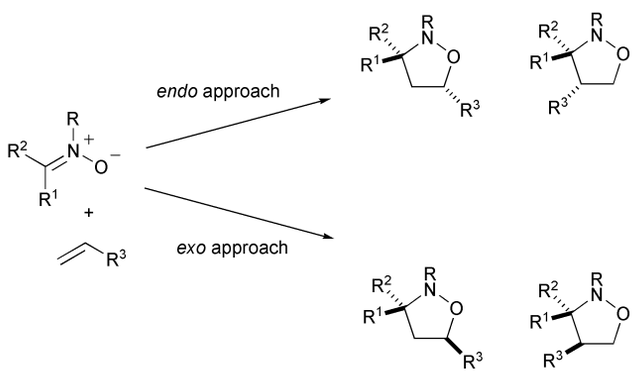
This review aims to summarise key features of the synthesis and 1,3-dipolar cycloaddition reactions of carbohydrate derived nitrones and oximes, allowing access to isoxazolines and isoxazolidines. An alternative approach to these targets, which involves the reaction of non-carbohydrate dipoles with carbohydrate derived alkenes, is also described.



## 1 1,3-Dipolar cycloaddition reactions of nitrones: a general introduction

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.[1] These particular dipolar cycloaddition reactions can be considered as concerted but asynchronous [4π + 2π] 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 1). Therefore




**Scheme 1**

much effort has focussed on the development of regioselective and stereoselective inter- and intramolecular nitrone–alkene cycloaddition reactions.

The isoxazolidine products of the dipolar cycloaddition reactions can be converted to many useful compounds, including 1,3-amino alcohols and 1,3-keto alcohols. Nitrones that are derived from, or tethered to, carbohydrates have proved particularly useful for stereoselective entry to stereochemically complex carbocycles and heterocycles.[2] The hydroxy groups of the carbohydrates also offer the opportunity for temporarily appending a range of non-carbohydrate ligands. Moreover, the recent resurgence of interest in carbohydrates and their derivatives has raised the profile of such functionalised targets within the chemical and biological communities.[3]

Whilst this review will only consider 1,3-dipolar cycloaddition reactions of nitrones, it is also worth noting their use for asymmetric entry to nitrogenated compounds, *via* the addition of nucleophiles to chiral nitrones.[4]

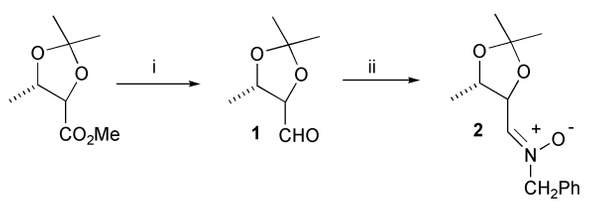
## 2 Synthesis of carbohydrate derived oximes and nitrones

Whilst entry to oximes is generally restricted to the condensation of aldehydes or ketones with hydroxylamines, several methods exist for the preparation of nitrones. These include the condensation between a carbonyl compound and an

*N*-substituted hydroxylamine,[5] *N*-alkylation of oximes,[6] oxidation of *N*,*N*-dialkylhydroxylamines,[7] imines[8] and amines,[9] and the zinc mediated reduction of nitroalkanes and nitroarenes, in the presence of aldehydes.[10] The first two methods have been found most useful for the synthesis of carbohydrate derived nitrones, and are therefore discussed in more detail below.

### 2.1 Synthesis of nitrones from aldehydes or ketones *via* condensation with *N*-monosubstituted hydroxylamines

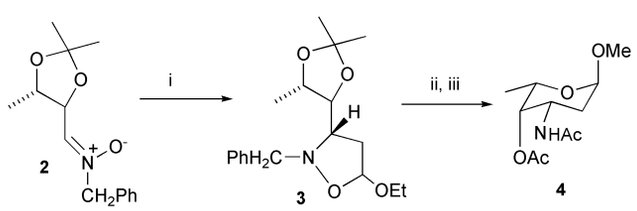
One of the most versatile routes to carbohydrate derived nitrones involves the condensation of *N*-monosubstituted hydroxylamines with aldehydes or ketones. Subsequent treatment with a mild base then affords the required nitrone. Whilst aldehydes react readily with *N*-monosubstituted hydroxylamines at room temperature, the less reactive ketones invariably require heating or longer reaction times. This can sometimes hamper their utility within synthetic strategies. A useful example of aldonitrone formation is illustrated in Scheme 2




**Scheme 2** *Reagents and conditions*: i) DIBAL-H, $Et_2O$, −78 °C, 90%; ii) NBnNHOH·HCl, $CaCl_2$, ether, 2 h, 0 °C, 90%.

where condensation of aldehyde **1** with *N*-benzylhydroxylamine affords *N*-benzyl nitrone **2**, exclusively as the *Z*-isomer, in 93% yield.[11] Due to the high reactivity of the aldehyde, this reaction proceeds readily at room temperature.

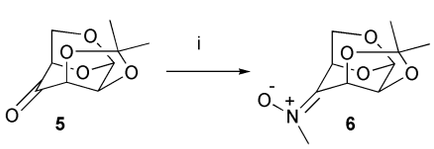
The utility of the nitrone **2** for subsequent formation of isoxazolidines is exemplified in Scheme 3 where treatment with




**Scheme 3** *Reagents and conditions*: i) ethyl vinyl ether, 72 °C, 36 h, 93%; ii) 10% HCl in MeOH, $Pd(OH)_2$, $H_2$ 50 psi, 48 h, iii) $Ac_2O$, pyridine, DMAP, 25 °C, 24 h, 74% from (**2**).

excess ethyl vinyl ether afforded the corresponding heterocycle **3**, in an excellent yield of 93%. This reaction illustrates the ability of the nitrone to add to the alkene with high diastereofacial selectivity, *via* the *endo* transition state. The diastereomerically pure isoxazolidine then provided entry to the methyl pyranoside **4**, *via* a series of reactions involving cleavage of the N–O bond under reductive conditions.

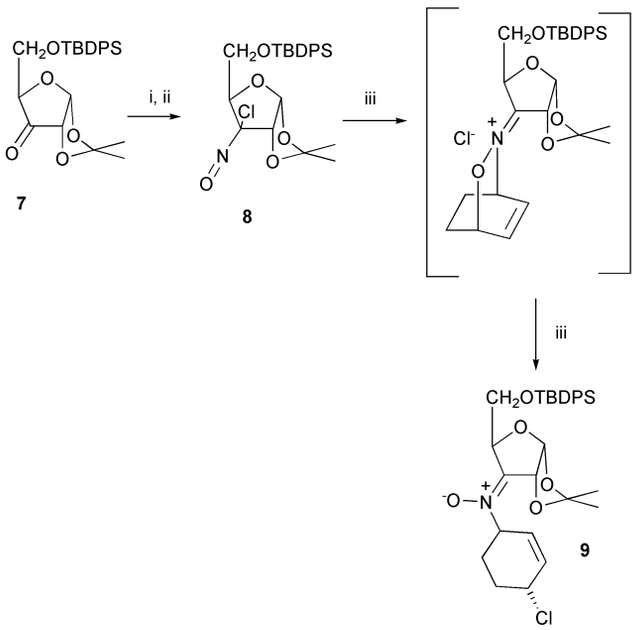
Alonso *et al.*[12] have also described the formation of carbohydrate derived ketonitrones *via* reaction of *N*-methylhydroxylamine with 4-oxomannopyranose **5** (Scheme 4). For example,




**Scheme 4** *Reagents and conditions*: i) MeNHOH·HCl, pyridine, 0 °C, 5 h, 97%.

the *N*-methyl nitrone **6** could be isolated in good yield, and this proved of use for accessing a range of functionalised isoxazolidines (*vide infra*).

Interestingly, if carbohydrate ketone **7** was treated with hydroxylamine hydrochloride in the presence of *tert*-butyl hypochlorite, the α-chloronitroso compound **8** was isolated in good yield. Subsequent reaction with a diene such as cyclohexa-1,3-diene then allowed entry to the corresponding nitrone **9** in 69% yield (Scheme 5).[13]

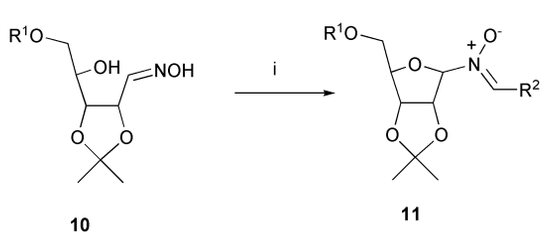



**Scheme 5** *Reagents and conditions*: i) $NH_2OH$·HCl, $NaHCO_3$, EtOH, $H_2O$; ii) *t*-BuOCl, DCM, 69% overall from D-xylose; iii) cyclohexa-1,3-diene, $CHCl_3$, 0 °C, 69%.

In this reaction sequence, the nitrone **9** was not the intended product but its formation was observed by altering the solvent to a non-nucleophilic and non-coordinating solvent. In this case the chloride ion attacked carbon, displacing oxygen, to generate the nitrone **9**.

### 2.2 Condensation of carbonyl compounds with carbohydrate based oximes

An alternative approach for entry to carbohydrate derived nitrones involves initial conversion of the carbohydrate derived aldehydes and ketones to the respective oximes. Oximes have also been formed *via* reaction of the open chain aldehyde tautomer of reducing sugars with hydroxylamine hydrochloride. Subsequent treatment with an alkylating agent, an aldehyde or a Michael acceptor then affords the required nitrone. For example oxime **10**, upon condensation with an aldehyde, generated nitrone **11**, *in situ* (Scheme 6).[14]



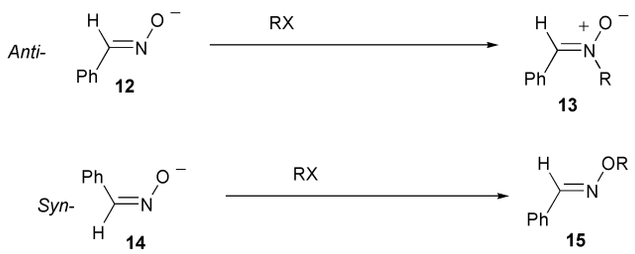

**Scheme 6** *Reagents and conditions*: i) $R^2CHO$.

This approach has the advantage that a variety of alkylating agents can be incorporated within this strategy allowing access to a diverse array of derivatives, as illustrated below.

### 2.3 Alkylation of oximes

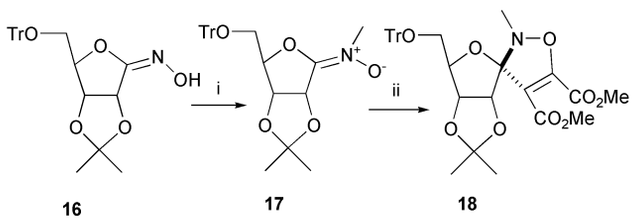
Alkylation of oximes offers a useful method for entry to nitrones. The nitrogen lone pair on the oxime is considered to

be more nucleophilic than the oxygen lone pairs, however, mixtures of *N*-alkylated and *O*-alkylated products often still result.[15] As a general rule, it has been reported that aldehyde-derived oximes often favour nitrone formation[16a] whereas ketone derived oximes generally favour *O*-alkylation.[16b] Studies on the alkylation of oxime salts[16b] have concluded that electron-withdrawing groups markedly promote alkylation on the oxygen of *p*,*p*′-disubstituted benzophenone oximes, whereas treatment of benzophenone oximes with neat benzyl bromide heavily favoured *N*-alkylation. The geometry of the oxime affects the stereoselectivity of the subsequent nitrone forming reaction, with *anti*-aryloximes **12** affording nitrones **13**, whereas *syn*-aryloximes **14** favour the formation of the oxime ethers **15** (Scheme 7).[15a]




**Scheme 7**

One useful example that has exemplified nitrone generation *via N*-methylation of a carbohydrate derived oxime **16**, using methyl trifluoromethanesulfonate, is illustrated in Scheme 8.[17]



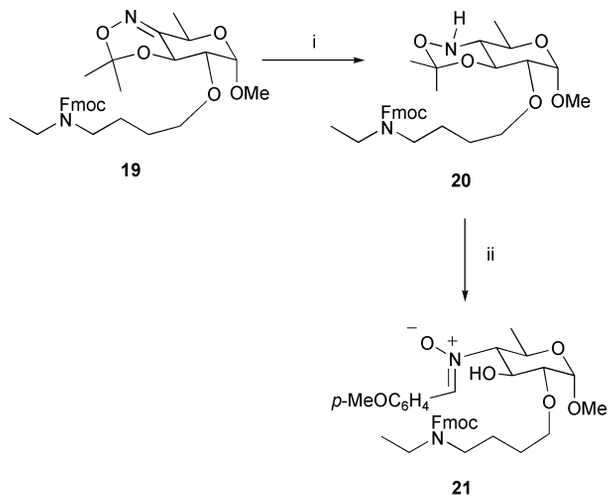

**Scheme 8** *Reagents and conditions*: i) MeOTf, $Et_3N$, $CHCl_3$, room temp.; ii) DMAD, −78 °C then room temp., 99%.

In many cases the nitrones are not isolated but trapped *in situ* to afford isoxazolines in a one-pot process. Thus addition of dimethyl acetylenedicarboxylate (DMAD) to the *in situ* generated nitrone **17** afforded one-pot entry to the isoxazoline **18**, in a highly stereoselective manner.

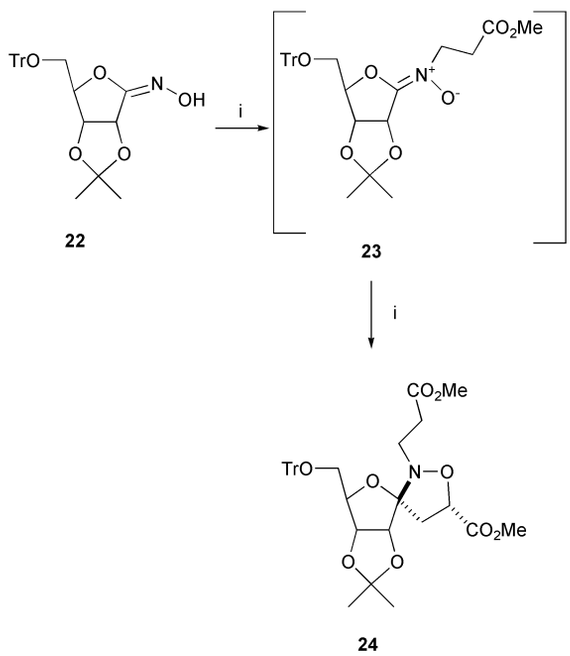
An interesting variant of this reaction has seen the synthesis of a carbohydrate derived nitrone of use for entry to a novel analogue of the calicheamicin $\gamma_1^I$ and esperamicin $A_{1B}$ oligosaccharides.[18] In this case, the required nitrone **21** was accessed *via N*-condensation of a cyclic hydroxylamine **20** with *p*-methoxybenzaldehyde (Scheme 9). Nitrone **21** was not incorporated within a cycloaddition strategy but was instead utilised as an acceptor within glycosidation reactions with a series of trichloroacetimidate donors.

### 2.4 Synthesis of nitrones *via* reaction with Michael acceptors

*N*-Alkylation of oximes can also be achieved *via* reaction of the oximes with Michael acceptors. In such cases the possibility exists to perform a subsequent intermolecular cycloaddition reaction between the nitrone and a further equivalent of the Michael acceptor, which this time acts as the dipolarophile.[19] The generation of cyclic nitrones by the intramolecular conjugate addition of unsaturated oximes was first reported by Grigg *et al*. as a 1,3-azaprotio cyclotransfer reaction.[19] An example of use for preparing carbohydrate derived spiro-isoxazolidines involves reaction of oxime **22** with methyl acrylate to yield nitrone **23**. Subsequent *in situ* reaction with methyl acrylate then yields the isoxazolidine **24** in 85% yield[17] (Scheme 10).



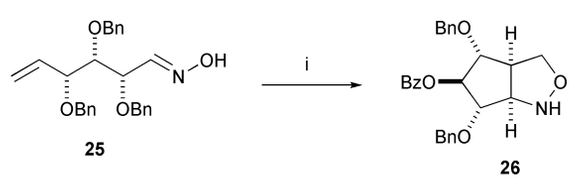

**Scheme 9** *Reagents and conditions*: i) $NaBH_3CN$, $BF_3{\cdot}OEt_2$, −30 °C, 86%; ii) 0.3 M HCl in MeOH–water then *p*-$MeOC_6H_4CHO$, toluene, 82%




**Scheme 10** *Reagents and conditions*: i) methyl acrylate, −78 °C to room temp., 85%.

### 2.5 Synthesis of nitrones *via* 1,2-prototropic shift of oximes

The use of oximes in oxime olefin cycloaddition[20] reactions has been well established but remains poorly exploited in the field of carbohydrate chemistry. However, a recent example has been reported that involved thermolysis of the oxime carbohydrate **25** by heating at reflux in toluene for 15 hours, to produce the cycloadduct **26** in quantitative yield (Scheme 11).[21]




**Scheme 11** *Reagents and conditions*: i) toluene, reflux, 15 h, 100%.

It was suggested that the reaction occurred *via* a 1,2-prototropic shift, with the oxime and olefin lying *exo* and the benzyl ethers being positioned in pseudoequatorial positions (Fig. 1).

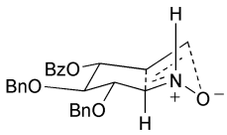
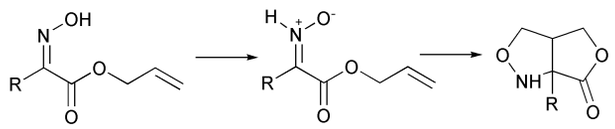


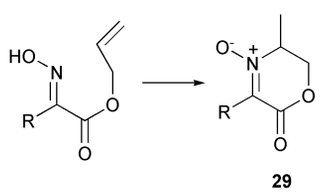
**Fig. 1**

The reaction was performed with a variety of sugar derived oximes to probe the versatility of the cycloaddition. It was concluded that the oxime geometry may have a defining influence on reactivity,[22] as demonstrated by the reaction of ω-alkenyl oximes. Such systems may form nitrones in two possible ways. Firstly an acyclic NH nitrone **27** could prevail, *via* tautomerism of the oxime, as evidenced by the formation of the intramolecular cycloadduct **28** (Scheme 12).



**Scheme 12**

Alternatively, cyclic nitrone **29** could form, *via* an intramolecular cycloaddition reaction of the oxime by a so termed "1,3-azaprotio cyclotransfer" process (Scheme 13).



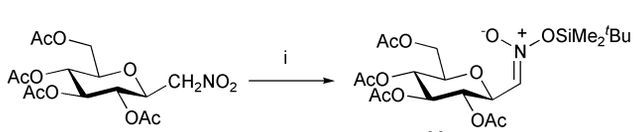
**Scheme 13**

It has been reported that *Z*-oximes generally react *via* the corresponding acyclic NH nitrone, to form isoxazolidines whilst *E*-oximes afford the alternative cyclic nitrone derivatives.

The oxime intermediates required for the above strategies are generally accessed by condensation of carbonyl compounds with hydroxylamine. However an alternative method for synthesising carbohydrate derived oximes has been reported[23] that involves the selective deacylation of furanoid and pyranoid enol esters using 3–3.5 molar equivalents of hydroxylamine hydrochloride. The intermediate ketones that are generated are not isolated, but reacted directly, *in situ*, with the excess hydroxylamine to form the corresponding oximes. This reaction is considered of use due to the ability to selectively cleave an enol ester in the presence of a normal ester functional group.

### 2.6 Miscellaneous preparations of nitrones

The methods of nitrone formation described so far are relatively well established procedures. It is also worth noting some less common procedures that offer entry to a wider choice of nitrone derivatives. For example, silyl nitronates have been prepared from nitroalkanes[24] by reaction with silyl chlorides. Martin *et al.* applied this methodology for the synthesis of carbohydrate derived silyl nitronates such as **30**[25] (Scheme 14).



**Scheme 14** *Reagents and conditions*: i) *t*-BuMe$_2$SiCl, DBU, DCM, 95%.

It was anticipated that treatment of the silyl nitronates with a catalytic amount of fluoride ion, and subsequent addition of aldehydes, would afford the corresponding chain-extended nitro sugars. However, only trace amounts of the desired product were formed in this way from silyl nitronate **30**. Better yields could, however, be obtained when the nucleophilic carbon atom was sufficiently remote from the cyclic carbohydrate moiety.[25]

Spirocyclic carbohydrate derived nitrone **33**[26] has also been accessed by exposure of the dioxime **32** to silica gel. Dioxime **32** was itself prepared from hemiacetal **31** by treatment with excess hydroxylamine hydrochloride in propanol, at reflux. In this way, nitrone **33** was obtained in 50% yield from hemiacetal **31** (Scheme 15).

In another example a chiral nitrone was obtained by treating an enamine **34** with the oxalate salt of *N*-((*S*)-1-phenylethyl)hydroxylamine **35**.[27] The chiral nitrone thus formed was a key intermediate in an enantioselective [3 + 2] intramolecular nitrone cycloaddition, to afford isoxazolidine precursors **36** to acosamine which is of intense interest as a sugar fragment in the anthracycline antibiotics (Scheme 16).

In a final example, hydroxylamine **37**, prepared in six steps from D- or L-fructose, has been used in the generation of the novel nitrone **38**[28] (Scheme 17).

Nitrone **38** proved of use for determining the configurations of the stereocentres of the hydroxy amino sugar fragments of esperamicin A.

## 3 Physical and spectroscopic properties of nitrones[29]

Carbohydrate derived nitrones are often crystalline in nature and they exhibit marked polarity. Their IR spectra generally display an intense band at around 1613 cm$^{-1}$, which is probably due to the vibration of the C=N functional group, and this band is generally more pronounced than for the corresponding oxime. One further intense absorption is observed at around 1183 cm$^{-1}$, and this band, which is absent in the IR spectra of the corresponding oximes, is attributed to the vibration of the $N^+$–$O^-$ functional group. Nitrones often display UV absorptions at 238–251 nm. NMR studies have also illustrated that the nitrones generally exist in the more stable *Z*-conformations.

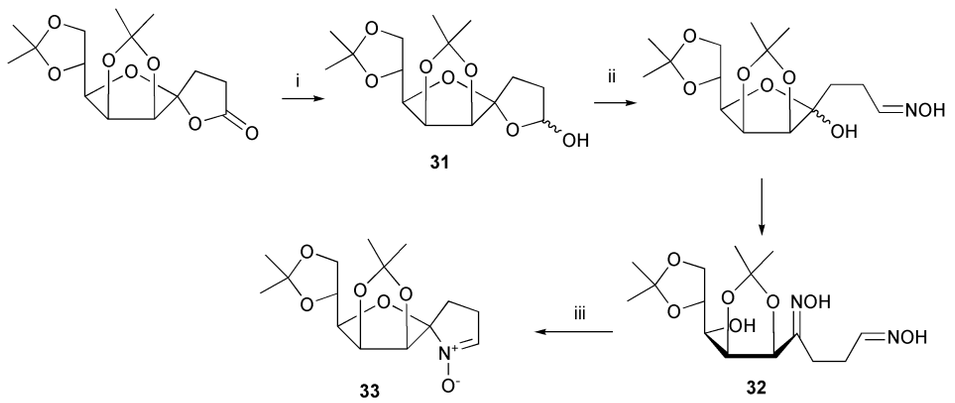
## 4 1,3-Dipolar cycloaddition reactions of carbohydrate derived nitrones and oximes

### 4.1 Intramolecular reactions

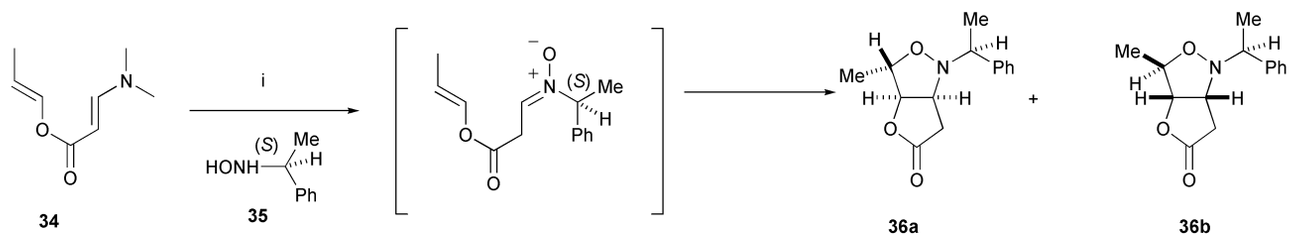
Intramolecular olefin–nitrone cycloaddition (commonly referred to as INC) reactions provide a simple method for the construction of carbocycles and heterocycles of different ring-sizes.[30] As such, dipolar cycloaddition reactions of nitrones have been incorporated within the total synthesis of natural products, and their analogues. For example, the total synthesis of Taxol and its derivatives has attracted much recent interest, and it has been reported that entry to the fully functionalised taxane CD ring can be achieved *via* an intramolecular carbohydrate derived aldonitrone cycloaddition reaction.[31] However, integration of cycloaddition reactions of the less reactive ketonitrones has proved more challenging. Synthetically important examples of both strategies are provided below.

#### 4.1.1 Intramolecular aldonitrone reactions

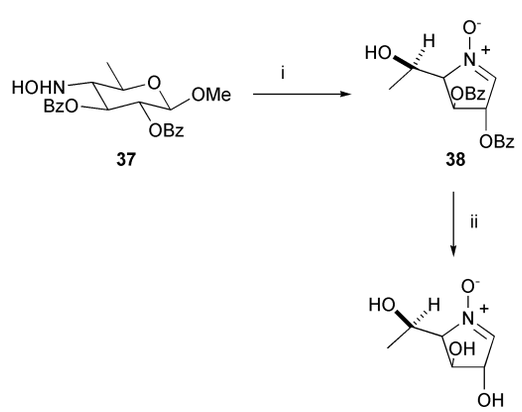
*4.1.1.1 Reactions of sugar aldonitrones containing an O-allyl moiety.* Bhattacharjya *et al.*[32] and others[33] have reported some intramolecular reactions of sugar aldonitrones with β-*O*-allyl moieties, which allow asymmetric entry to enantiopure cyclic ether heterocycles such as tetrahydrofurans, pyrans and oxepanes. For example 3-*O*-allyl-D-(+)-glucose **39**, on heating with *N*-benzylhydroxylamine, afforded an isoxazolidine which was subsequently treated with acetic anhydride to effect *O*-acetylation (Scheme 18).[32a,b] The structure of compound **40** was confirmed by X-ray crystallographic analysis.



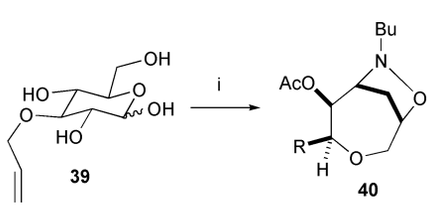
**Scheme 15** *Reagents and conditions*: i) DIBAL-H, −78 °C, $Et_2O$, 88%; ii) excess $NH_2OH$, PrOH, reflux.; iii) column chromatography on silica gel.



**Scheme 16** *Reagents and conditions*: i) xylene, reflux, 68% over 2 steps, **36a** : **36b** 82 : 18.



**Scheme 17** *Reagents and conditions*: i) $BCl_3$, DCM, 100%; ii) NaOH, MeOH, 100%.

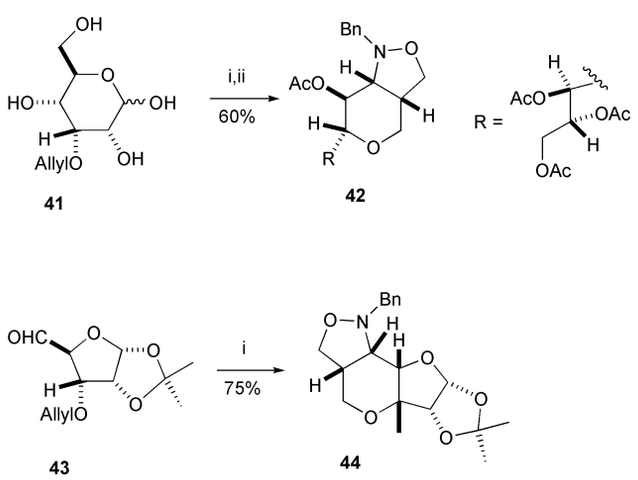


R = -CH(OAc)-CH(OAc)-$CH_2$OAc

**Scheme 18** *Reagents and conditions*: i) $PhCH_2NHOH$ then $Ac_2O$, pyridine, 55–60%.

The significant biological activity of naturally occurring oxepanes, for example zoapatanol[34] is of current interest in the area of reproductive medicine. Later publications by Bhattacharjya *et al.*[32c,d] have extended this methodology to allow synthesis of enantiomerically pure pyrans from 3-*O*-allylallose (Scheme 19). By manipulation of the starting material, a range of enantiomerically pure pyran and oxepane derivatives have been readily prepared (Table 1).

Both allopyranose **41** and allofuranose **43** derivatives react to afford pyran derivatives **42** and **44** respectively. However, removal of the C-3 methyl group (entries 1 and 2) gave rise to two different types of cycloadducts with the allopyranose generating the pyran, whilst the furanose derivative afforded the oxepane. The same difference in regioselectivity was observed

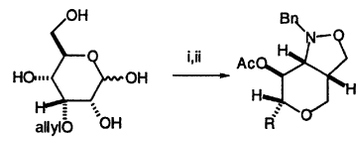
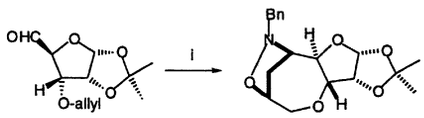
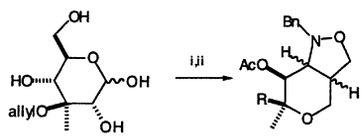
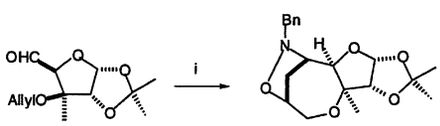


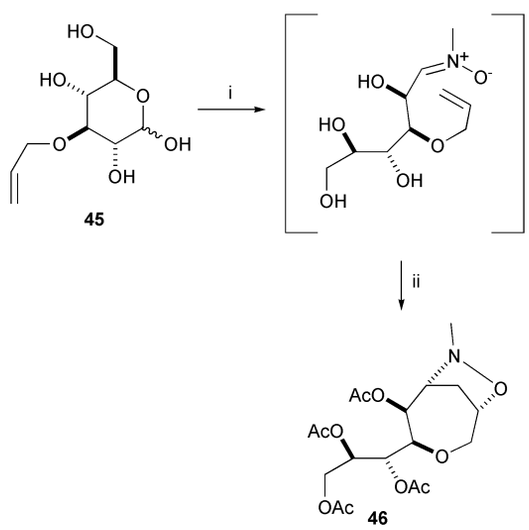
**Scheme 19** *Reagents and conditions*: i) BnNHOH; ii) $Ac_2O$, pyridine.

for glucopyranose (entry 3) which forms the pyran as a mixture of diastereomers in a 1:1 ratio, whilst furanose (entry 4) again affords the oxepane. When 3-*O*-cyclohexenylfuranoside-5-aldehydes were converted to the corresponding aldonitrones, this methodology allowed diastereoselective entry to tetrahydropyran-fused cyclohexane ring systems, with six asymmetric centres.

In similar studies Collins *et al.*[35] and Shing *et al.*[36] employed *O*-allyl nitrones derived from glucose to allow entry to oxygenated heterocycles using INC and intramolecular nitrile oxide cycloaddition (termed INOC) reactions. INOC reactions of a variety of oximes derived from *O*-allylglucose demonstrated excellent selectivity and 3-*O*-allyl-D-hexoses have been used extensively in intramolecular nitrone alkene cycloaddition (termed INAC) reactions. The stereochemical outcome of the INAC reactions derived from these sugars is dependent on the relative configuration of the stereocentres at C-2 and C-3.[37] The underlying rule for these reactions is that D-glucose and D-altrose (*i.e.* both with *threo*-configuration at C-2 and C-3) selectively afford oxepanes, whereas D-allose and D-mannose (both with *erythro*-configuration at C-2 and C-3) exclusively afford tetrahydropyrans. For example treatment of 3-*O*-allyl-D-glucose **45** or 3-*O*-allyl-D-altrose **47** with *N*-methylhydroxylamine in aqueous ethanol at reflux gave, after acetylation, the

**Table 1**

| Entry | Reaction | Yield (%) |
|---|---|---|
| 1 |  | 80 |
| 2 |  | 73 |
| 3 |  | 57 |
| 4 |  | 50 |



**Scheme 20** *Reagents and conditions*: i) MeNHOH·HCl, $NaHCO_3$, 80%, aq. EtOH, reflux, 48 h; ii) $Ac_2O$, DMAP, pyridine, DCM, rt, 6 h, 53% overall from **45**.

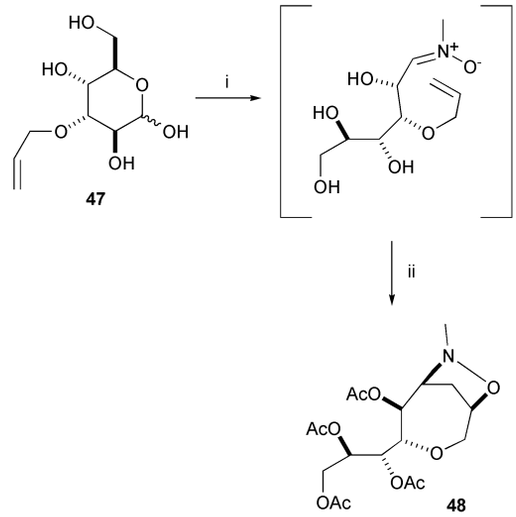
oxepane tetraacetates **46** and **48** respectively (Schemes 20 and 21).

In contrast, 3-*O*-allyl-D-allose **49** and 3-*O*-allyl-D-mannose **53** allowed entry to nitrones **50** and **54** respectively, leading exclusively to tetrahydropyrans **51** and **52** and **55** and **56** (Schemes 22 and 23).

Resubmitting the deacetylated cycloadducts to the reaction conditions for a further 56 hours did not alter the product mixture thus hinting at a kinetically controlled reaction. It was proposed that the tetrahydropyrans were formed *via* a chair transition-state conformation (Fig. 2).

When the substituents at C-2 and C-3 occupy pseudoequatorial positions minimal 1,3-diaxial interaction occurs. Conversely, formation of an oxepane **58** results from the transition state **57** which has minimal 1,3-diaxial interaction; consequently, transition states **59** and **61** are disfavoured resulting in no formation of the tetrahydropyrans **60** and **62** (Fig. 3).

Further work involving intramolecular cycloaddition reactions of *O*-allyl carbohydrate nitrones has produced fused isoxazolidines as the exclusive products (Scheme 24).[32d]



**Scheme 21** *Reagents and conditions*: i) MeNHOH·HCl, $NaHCO_3$, 80%, aq. EtOH, reflux, 48 h; ii) $Ac_2O$, DMAP, pyridine, DCM, rt, 6 h, 55% overall from **47**.

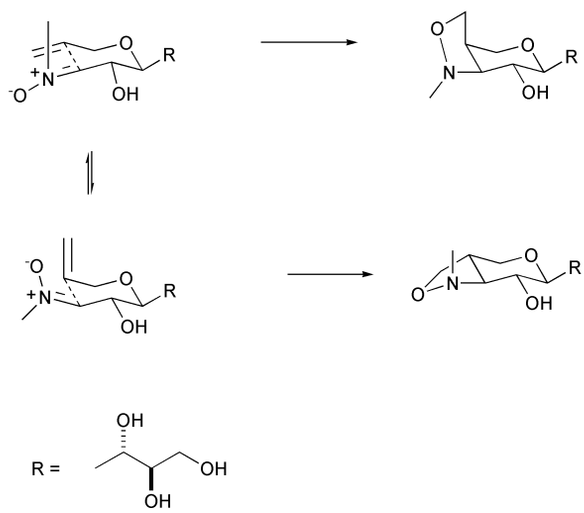


**Fig. 2**

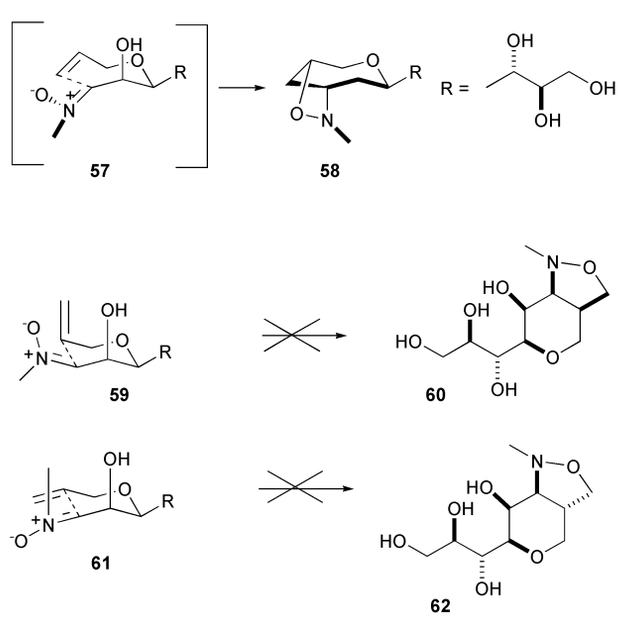
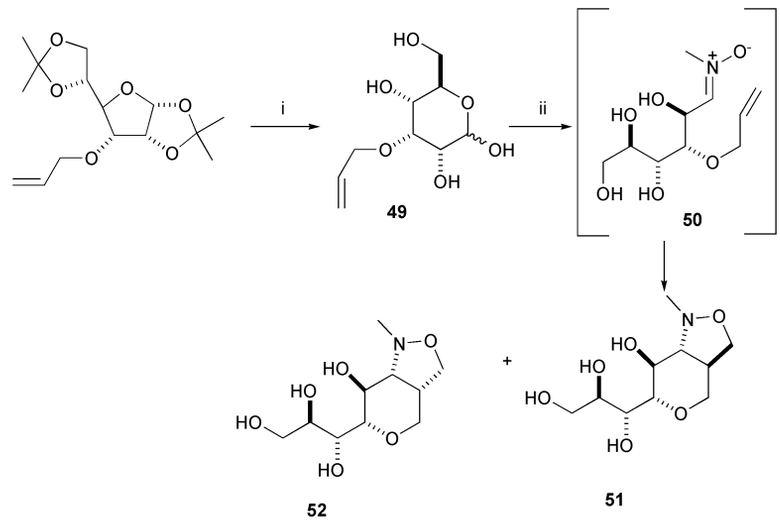
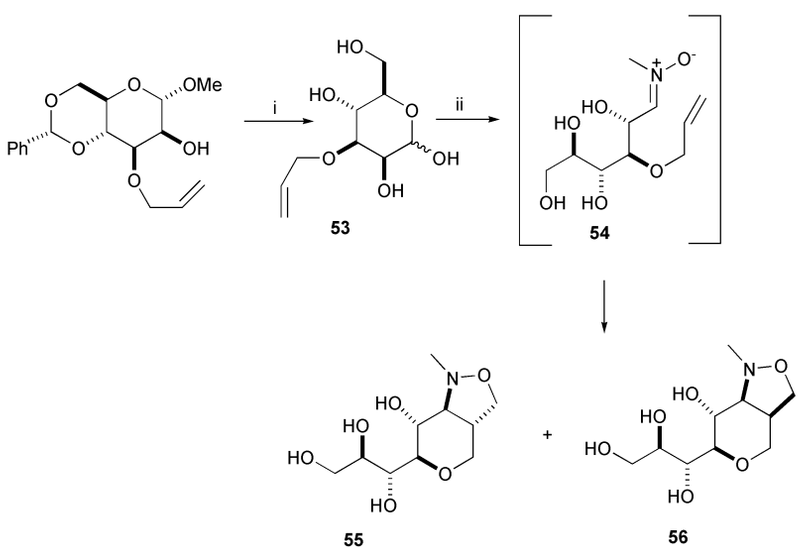


**Fig. 3**

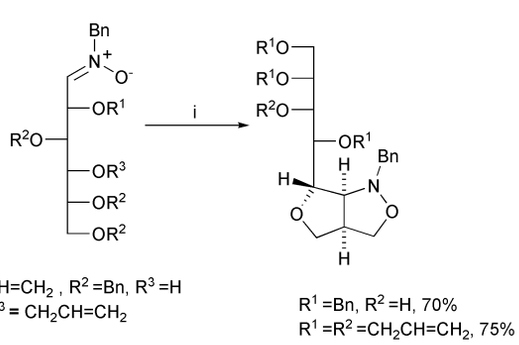
Kinetic control again operates in these reactions to allow preferential formation of the chiral five-membered tetrahydrofurans, in preference to six- and seven-membered cyclic ethers.



**Scheme 22** *Reagents and conditions*: i) 30% HCl, reflux, 24 h, 70%; ii) MeNHOH·HCl, $NaHCO_3$, 80%, aq. EtOH.



**Scheme 23** *Reagents and conditions*: i) 30% HCl, reflux, 24 h, 66%; ii) MeNHOH·HCl, $NaHCO_3$, 80%, aq. EtOH.



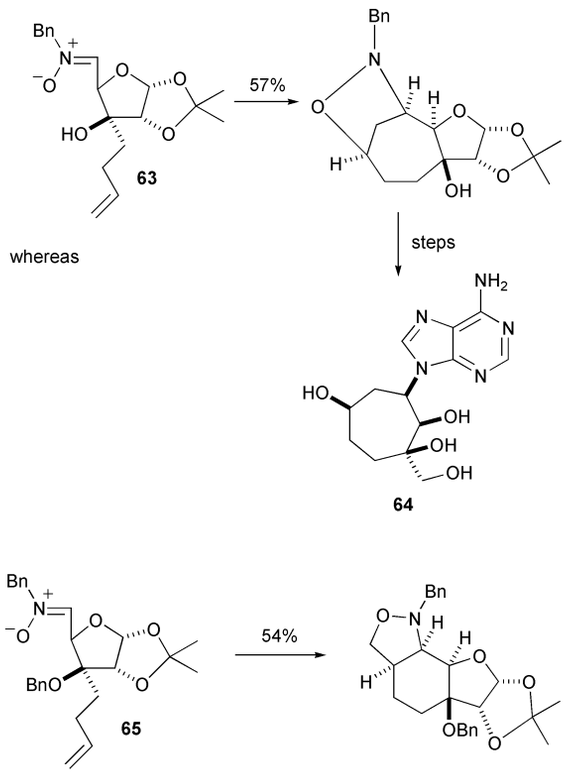

**Scheme 24** *Reagents and conditions*: i) ethanol, reflux.

Chiral pyranobenzene- and oxepanobenzene-derived, and furylpyran and oxepane systems have also been accessed by the application of intramolecular nitrone and nitrile oxide cycloaddition reactions of carbohydrate derivatives.[38] Such strategies have proved of use for accessing the skeletal frameworks of natural products such as forskolin,[39] sipophenol A[40] and lasalocid A.[41] Studies have also been reported concerning the synthesis of various inositols and pseudo-sugars using intramolecular aldonitrone cycloaddition reactions of alkenyl nitrones derived from *O*-allylated sugar based aldehydes.[42]

Bhattacharjya and co-workers have also demonstrated that the presence or absence of a hydroxy group at C-3 can influence the formation of isomeric cyclisation products that differ in ring size. Thus it was generally found that the furanose aldonitrones **63** bearing a free hydroxy at C-3 afforded larger cycloadducts than those generated from the analogous compounds **65** bearing an alkoxy substituent at C-3.[43] The isoxazolofuranocarbocyclic derivatives obtained in this way have been further elaborated to afford carbocyclic nucleoside analogues **64** with varying ring-sizes and stereochemistry (Scheme 25).[43a]

The synthesis of chiral six and seven-membered nitrogen heterocycles has also been achieved *via* *N*-allyl carbohydrate nitrone cycloadditions.[44] Degradation of the carbohydrate framework, or reductive cleavage of the N–O bond, allowed entry to substituted amines. Interestingly, the regioselectivity of the cycloaddition reaction could be controlled by changing the substituent on the nitrogen atom of the *N*-allyl moiety. This allowed selective entry to piperidines or azepanes in good to excellent yield. Introduction of a tether unit containing a 1,2-disubstituted aromatic moiety between a heteroatom attached to a carbohydrate scaffold, and the allyl moiety, allowed the same workers to generate chiral ten to twelve-membered nitrogen and oxygen heterocycles, fused to isoxazoline rings (Scheme 26).[45]

Alternatively, enantiopure pyranoisoxazole and oxepinoisoxazole analogues can be prepared from carbohydrate derivatives *via* the corresponding nitrile oxides.[41b,46] This has allowed entry to benzopyrans, benzooxepines and functionalised tetrahydrofurans.[42c]




**Scheme 25**

*4.1.1.2 Preparation of isoxazoline carbocycles.* Intramolecular cycloaddition reactions of carbohydrate derived nitrones have been exploited by Mandal *et al.* in their synthesis of isoxazoline carbocycles.[47] Initial treatment of diacetone glucose ketone **70** with allylmagnesium bromide afforded alcohol **71**. Aqueous acetic acid was then employed to selectively open the 5,6-isopropylidene acetal to give triol **72**. Oxidative cleavage of the vicinal diol unit thus formed using sodium metaperiodate in aqueous ethanol afforded aldehyde **73**, which reacted readily with *N*-benzylhydroxylamine to give the nitrone **74** (Scheme 27).

After extended reaction times, *in situ* cycloaddition resulted to give a mixture of isoxazolidines **75** and **76**. It was noted that the solvent used in the cyclisation affected the regioselectivity of the reaction. Non-polar aprotic solvents (benzene/toluene) afforded **75** and **76** in 1.6 : 1 ratio, whereas polar aprotic solvents (DMF, DMSO, $CH_3Cl$) reversed the ratio to 1 : 4. In the presence of ethanol, methanol or *tert*-butyl alcohol the isoxazolidine **76** was again the major product. If nitrone **77** was instead utilised in the reaction, only one mode of attack was observed (Scheme 28).

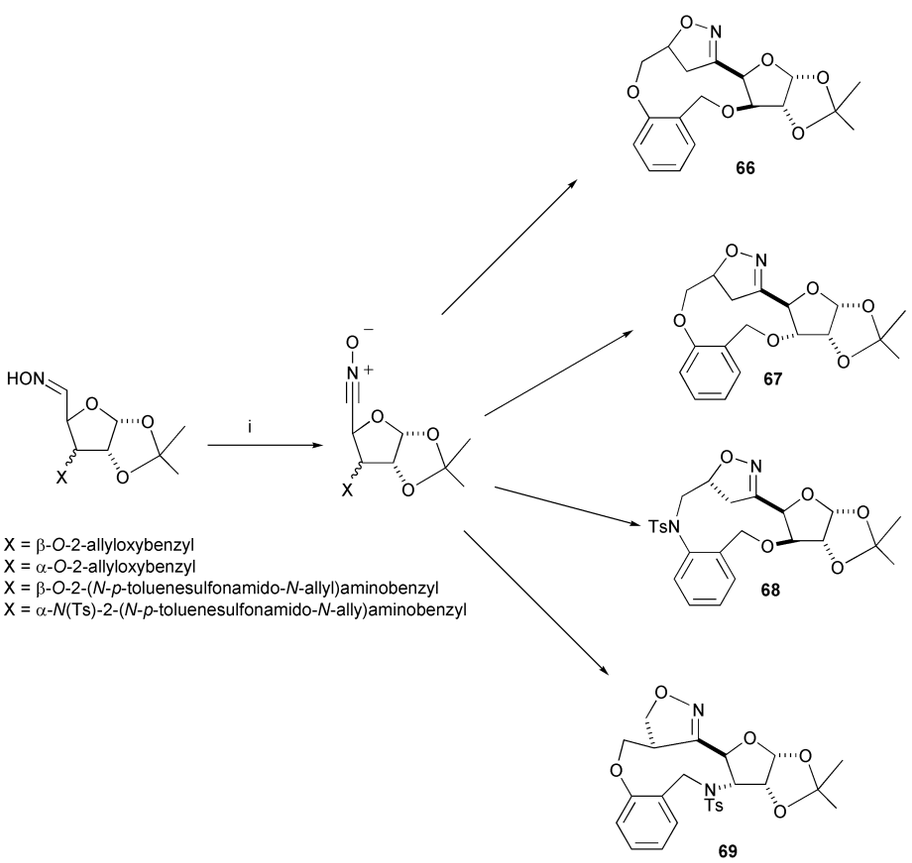
A further use of intramolecular nitrone cycloaddition reactions has been reported by Shing *et al.*[48] in their synthesis of functionalised cyclopentanes and cyclohexanes. Such derivatives were prepared from D-ribose and D-mannose respectively. Thus cyclopentane **80** was obtained by intramolecular reaction of nitrone **78**, itself generated by reaction with *N*-methylhydroxylamine. The isoxazolidine **79** was obtained as a single diastereoisomer, in 94% yield (Scheme 29).

A similar route allowed entry to the cyclohexane **81** (Scheme 30).

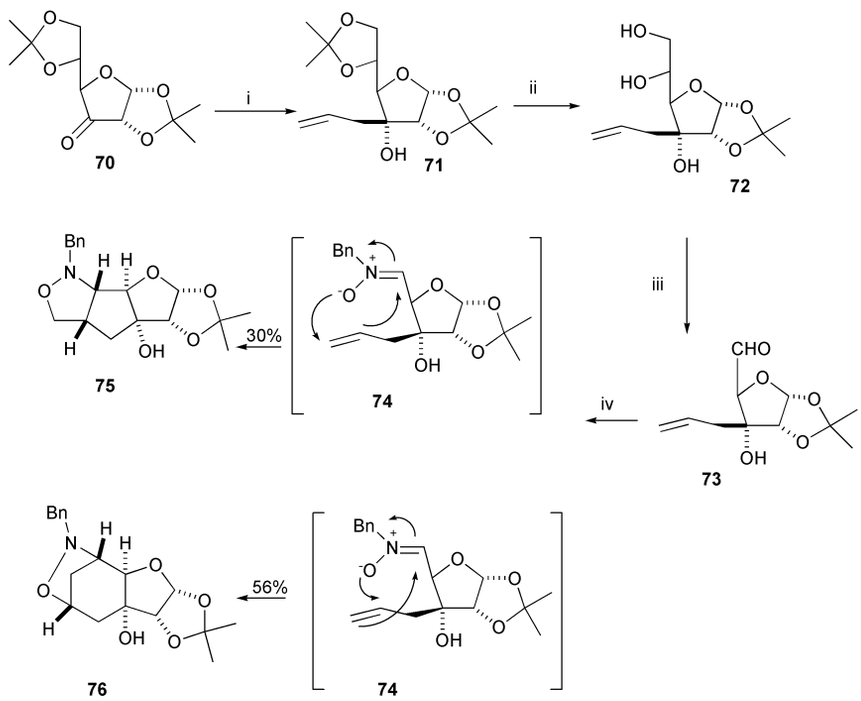
A number of carbocyclic carbohydrate analogues, of use as inhibitors of the carbohydrate processing enzymes, have been prepared *via* intramolecular cycloaddition reactions.[49] For example, Farr *et al.*[50] employed an intramolecular nitrone cycloaddition as the key step in the synthesis of carbocycle **82** and related compounds (Scheme 31), which have potential inhibitory properties against the α-mannosidase enzymes.

This cycloaddition methodology was extended to incorporate cycloaddition reactions of nitrile oxide and oxime derivatives of the same sugar.[50b]

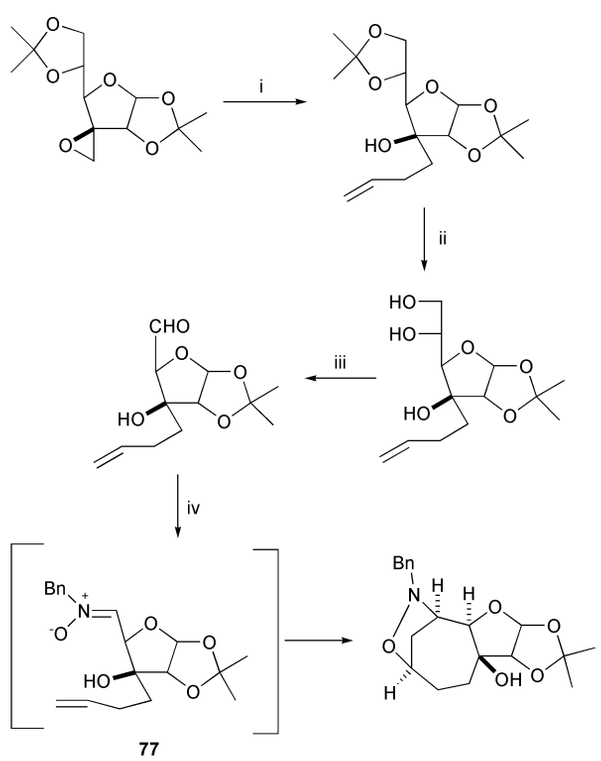
The enantiospecific total synthesis of β-glucosidase inhibitor cyclophellitol **86**[51] has also been achieved from oxime **84** which is made *via* treatment of carbohydrate




**Scheme 26** *Reagents and conditions*: i) chloramine-T hydrate, EtOH, reflux, 8 h, 50% **66**, 62% **67**, 35% **68**, 70% **69**.



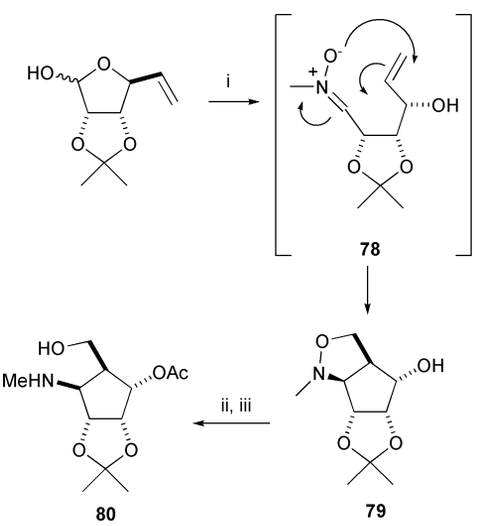
**Scheme 27** *Reagents and conditions*: i) $CH_2$=$CH_2CH_2MgBr$, THF, 0 °C, 2 h then reflux, 1 h, 8%; ii) $H_2O$–HOAc (2 : 3), 60 °C, 1 h, $NaIO_4$ (1.2 eq.), aq. EtOH, rt, 1 h, 95%; iii) $NaIO_4$ (1.2 eq.), aq. EtOH, rt, 1 h; iv) $PhCH_2NHOH$ (1.3 eq.), EtOH, rt, 20 h, 86% total yield.



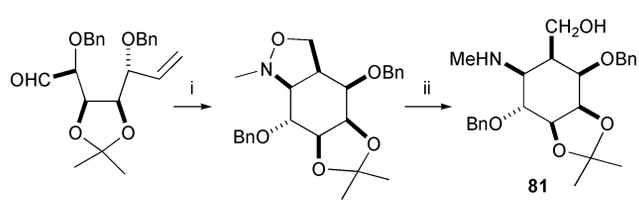
**Scheme 28** *Reagents and conditions*: i) $CH_2$=$CH_2CH_2MgBr$, THF, 0 °C, 2 h then reflux, 1 h, 72%; ii) $H_2O$–HOAc (2 : 3), 60 °C, 1 h, 79%; iii) $NaIO_4$ (1.2 eq.), aq. EtOH, rt, 1 h; iv) $PhCH_2NHOH$ (1.3 eq.), EtOH, rt, 12 h, 98%.

precursor **83** with hydroxylamine hydrochloride and pyridine (Scheme 32).

Treatment of the oxime **84** with sodium hypochlorite generated the nitrile oxide, which underwent the intramolecular cycloaddition reaction to form the isoxazoline **85** as the only product. Isoxazoline **85** proved a key intermediate in the synthesis of the highly functionalised cyclohexane **86** (Scheme 32) which has previously been isolated from a culture filtrate of mushroom (*Phellinus* sp.) and is believed to have activity against HIV.



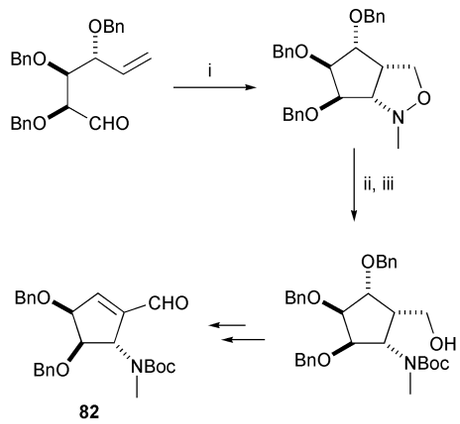
**Scheme 29** *Reagents and conditions*: i) MeHNOH·HCl, $NaHCO_3$, aq. EtOH, reflux, 94%; ii) $Ac_2O$, pyridine, 85%; iii) $Pd(OH)_2$, EtOH–AcOH, 75%.



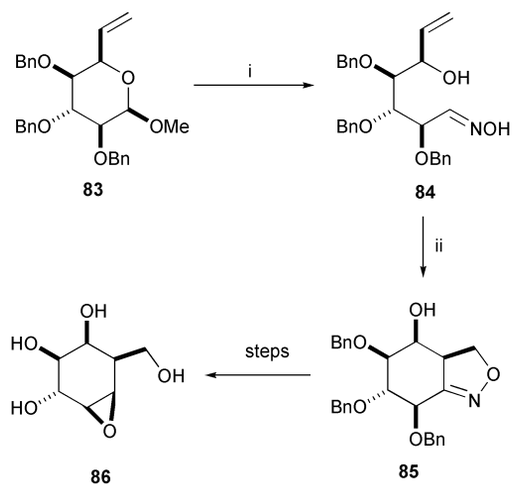
**Scheme 30** *Reagents and conditions*: i) MeHNOH·HCl, $NaHCO_3$, aq. EtOH, 65%; ii) $Pd(OH)_2$, EtOH–AcOH 60%.

The asymmetric synthesis of chiral, densely functionalised cycloheptanes from carbohydrates has also been achieved using a 7-alkenyl tethered *N*-benzyl nitrone[52] (Scheme 33).

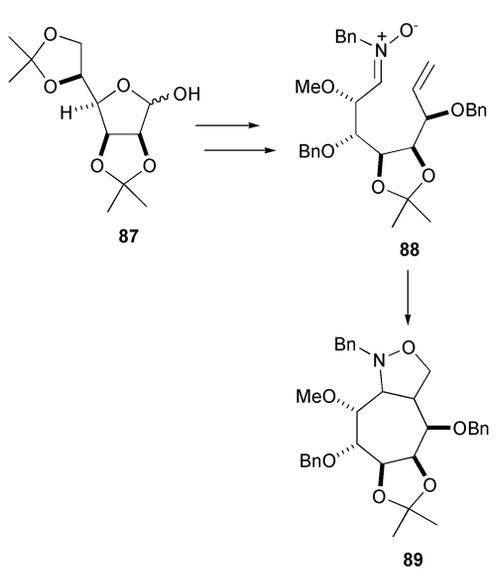
The nitrone **88**, derived from 2,3:5,6-bis-*O*-isopropylidene-α-D-mannofuranose **87**, was employed in a simple sequence of steps to give the isoxazolidine **89**. The success of the reaction was thought to result from the presence of the 1,3-dioxolane ring at the C-3 and C-4 positions, since this reduces the degrees of conformational freedom in the transition state.



**Scheme 31** *Reagents and conditions*: i) MeNHOH, MeOH, heat, 81%; ii) Zn, HOAc; iii) $(Boc)_2O$, 87%.



**Scheme 32** *Reagents and conditions*: i) HCl, aq. dioxane, 80 °C, 12 h then $NH_2OH$, pyridine, 25 °C, 1 h. 80%; ii) NaOCl, 70%.



**Scheme 33**

Consequently, it was observed that heating nitrone **90** at reflux in chlorobenzene did not afford an isoxazolidine and only led to regeneration of the aldehyde (Fig. 4).

Carbohydrate isoxazolidine **91** also proved of use as a precursor to epoxide **92**,[53] a key intermediate in a recent synthetic route to prostaglandin F2α.[54] An intramolecular nitrone cycloaddition reaction was utilised to generate the required isoxazolidine **91** (Scheme 34).

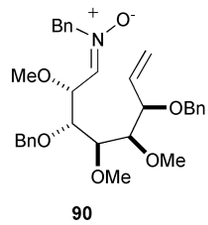
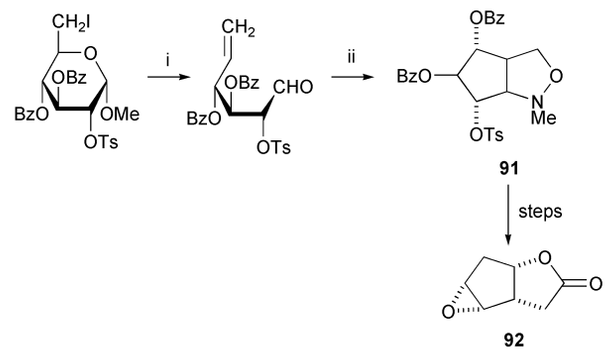
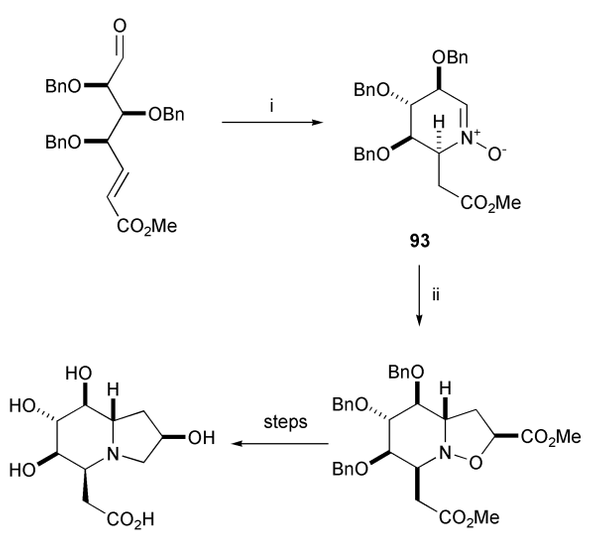


**Fig. 4**



**Scheme 34** *Reagents and conditions*: i) Zn, EtOH reflux; ii) NHMeHCl, pyridine, EtOH, 73%.

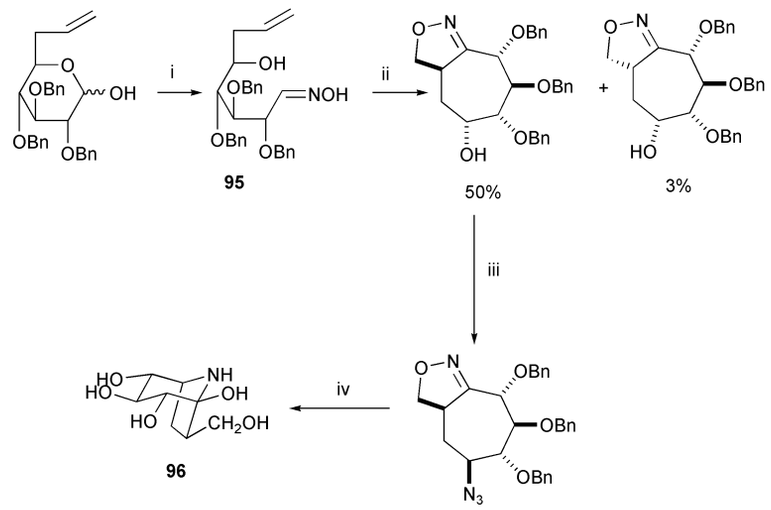
In further examples the enantiospecific total syntheses of (−)-allosamizoline[55] and shikimic acid have also been achieved using intramolecular aldonitrone cyclisation reactions.[56] D-Glucosamine was used as the starting material in the former synthesis, which involved an intramolecular cycloaddition of a nitrile oxide to an olefin as the main step. In a further example, a cyclic nitrone **93**, prepared from D-xylose *via* intramolecular conjugate addition of the oxime, has also proved of use for accessing a trihydroxyindolizidine derivative **94**[57] which bears structural similarity to natural products such as swainsonine and castanospermine (Scheme 35).



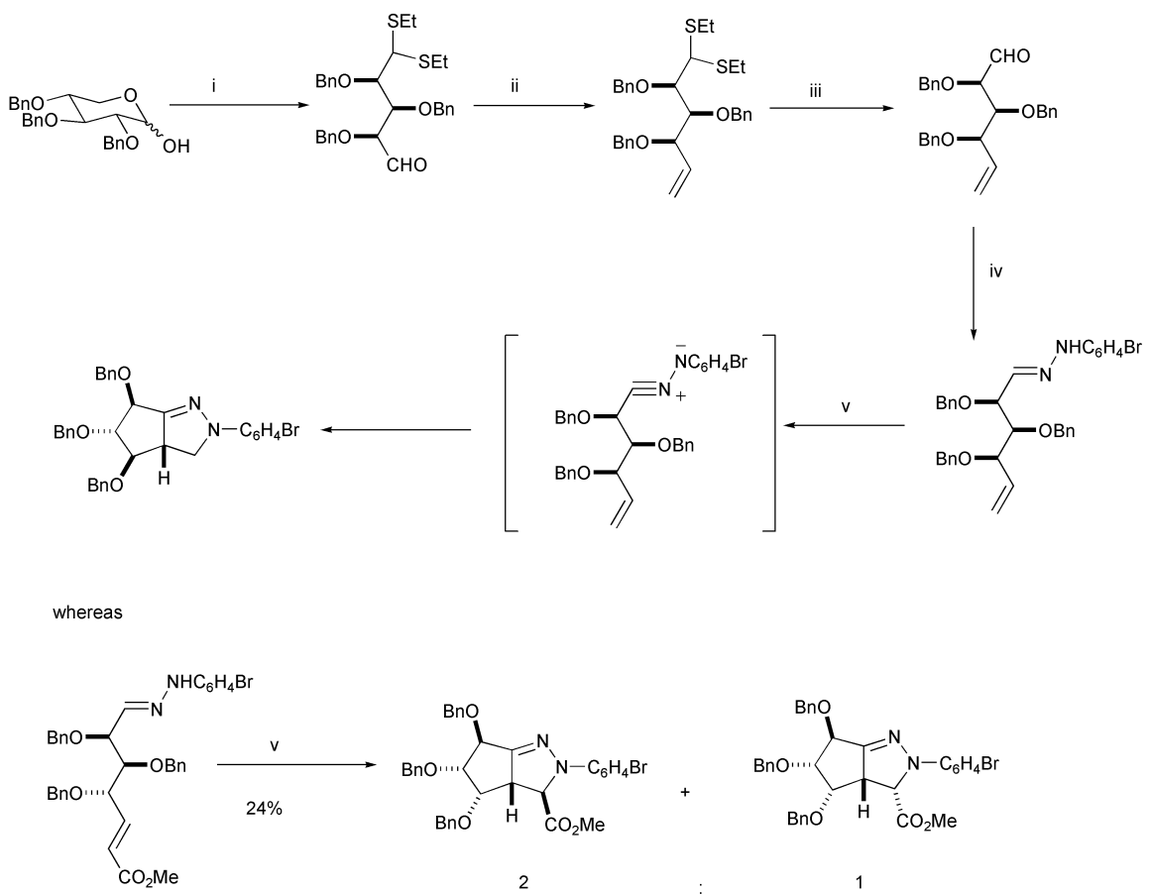
**Scheme 35** *Reagents and conditions*: i) $H_2NOH$, EtOH–$H_2O$, rt; ii) methyl acrylate, 36%.

Swainsonine and castanospermine are of current interest due to their anti-tumour properties. Interestingly, daunosamine and acosamine, which are also considered of importance as potential anti-tumour agents and antibiotics, have also been synthesised *via* diastereoselective intramolecular nitrone olefin cyclisations.[58]

In one final example, the oxime **95**, derived from D-glucose, has been employed in a nitrile oxide intramolecular cycloaddition reaction resulting in the formation of a seven-membered



**Scheme 36** *Reagents and conditions*: i) $NH_2OH{\cdot}HCl$, 94%; ii) 1.75 M aq. NaOCl; iii) $ZnN_6{\cdot}2py$, $PPh_3$–isopropyl azodicarboxylate couple, 79%; iv) Pd, 80% aq. acetic acid, 80%.



**Scheme 37** *Reagents and conditions*: i) EtSH, HCl then PCC, 58%; ii) $Ph_3P{=}CH_2$; iii) NBS, $CdCO_3$, 25%; iv) *p*-Br-$C_6H_4NHNH_2$; v) NBS–$Me_2S$ then $Et_3N$, 30%

ring system[59] (Scheme 36). This proved of use for entry into the enantiomerically pure hydroxymethylcalystegine **96**, an alkaloid of the tropane family.

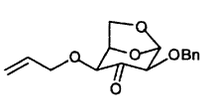
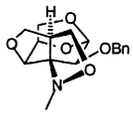
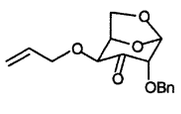
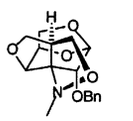
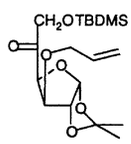
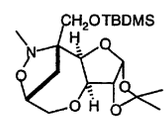
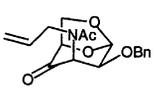
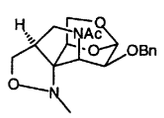
Analogous intramolecular cycloaddition reactions of carbohydrate derived nitrilimines containing an alkene functionality have also been reported, allowing entry to cyclopentapyrazole derivatives.[60] Molecular modelling and experimental results have illustrated that nitrilimines having the D-ribo, L-arabino or D-xylo stereotriads in the tethering chain preferentially afford (3α*S*)-products. In contrast, introduction of a prochiral centre into the nitrilimine, by methoxycarbonyl substitution on the alkene, results in the formation of diastereomeric mixtures of cycloadducts (Scheme 37).

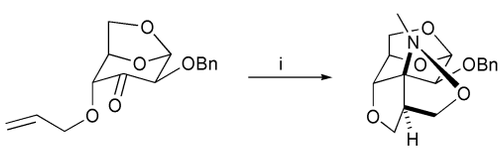
Stereochemical studies of the analogous intermolecular cycloaddition reactions have also been presented.[61]

### 4.1.2 Intramolecular ketonitrone reactions

As mentioned before, there are far fewer reports in the literature of cycloaddition reactions of ketonitrones. However, their development is of interest for the generation of complex molecular frameworks. One report that neatly illustrates this has appeared from Alonso *et al.*[12] and this work allows the synthesis of a number of isoxazolidines in moderate yield from *N*-methyl ketonitrone derived sugar analogues (Scheme 38).

**Table 2**

| Entry | Starting material | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  | 77 |
| 2 |  |  | 65 |
| 3 |  |  | 69 |
| 4 |  |  | 52 |



**Scheme 38** *Reagents and conditions*: i) MeNHOH·HCl, pyridine, rt to 45–65 °C, 5 h, 78%.

This approach has allowed entry to a range of carbohydrates that possess nitrogen substituted quaternary centres (Table 2).

From the results, it was evident that tethering the dipolarophile to the sugar hydroxy groups afforded cycloadducts with good stereocontrol. When the α-C-4 hydroxy group was utilised the C-3 stereogenic centre was formed exclusively as the (*S*)-configuration. However, employing the β-C-4 hydroxy group (entries 1 and 2) affords the isomeric C-3 (*R*)-cycloadducts. Entries 3 and 4 demonstrate the extension of this methodology for the formation of alternative isomeric carbohydrate heterocycles.

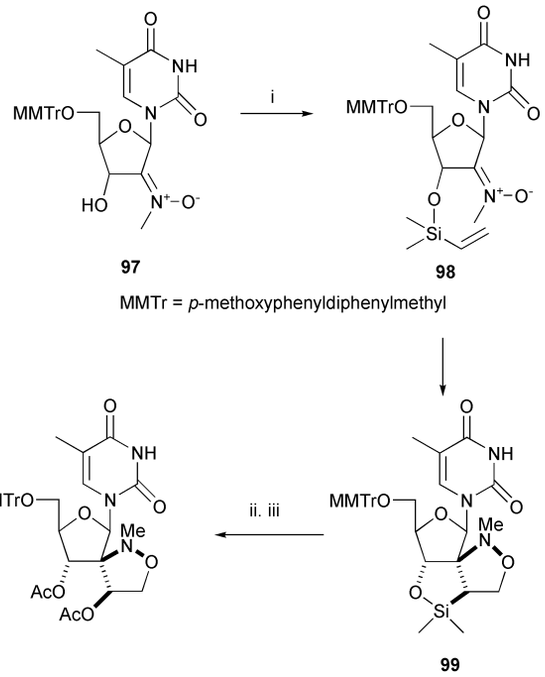
An additional example of an intramolecular ketonitrone cycloaddition for the synthesis of isoxazolidines employs a silyl ether tethered alkene **98** allowing access to tricyclic spiro-isoxazolidines **99** (Scheme 39).[62]

Nitrone **97** was converted to the silyl nitrone **98** using a suitable vinyl chlorosilane. *In situ* cycloaddition reaction, *via* the *endo*-transition state, then afforded the silicon containing heterocycle **99** and this could be readily deprotected using Tamao oxidation conditions.[63] Interaction between the nitrone oxygen, the terminal carbon of the alkene, and the C-2 carbon, with the carbon α to the terminal carbon of the alkene, results in formation of the *cis*-fused isoxazolidines **99**.

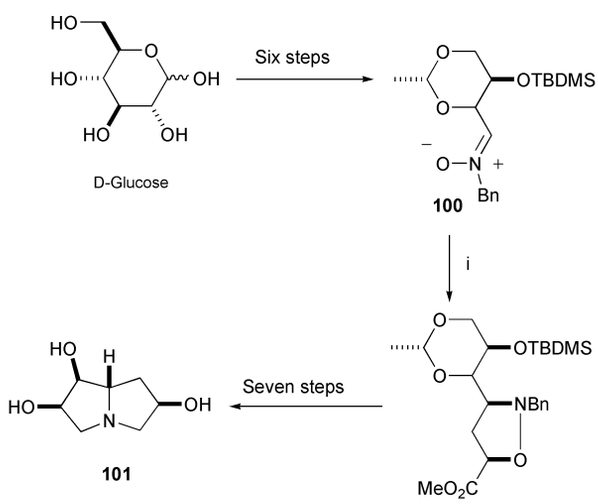
### 4.2 Intermolecular reactions of nitrones

#### 4.2.1 Intermolecular reactions of carbohydrate derived aldonitrones

Intermolecular cycloaddition reactions of carbohydrate derived nitrones are far less prevalent in the chemical literature than intramolecular examples. Some excellent results have, however, been achieved using both protected[64] and unprotected carbohydrate derived nitrones.[65] For example, the D-erythrose derived nitrone **100** has been shown to react with methyl acrylate to afford the enantiomerically and diastereomerically pure trihydroxylated pyrrolizidine **101** in an overall yield of 12% (Scheme 40).



**Scheme 39** *Reagents and conditions*: i) vinyldimethylchlorosilane, pyridine, 0–5 °C, 18 h, 70%; ii) $H_2O_2$, KF, $KHCO_3$, MeOH, THF, 91%; iii) 80% AcOH–$H_2O$, 40 °C, 1 h, 58%.



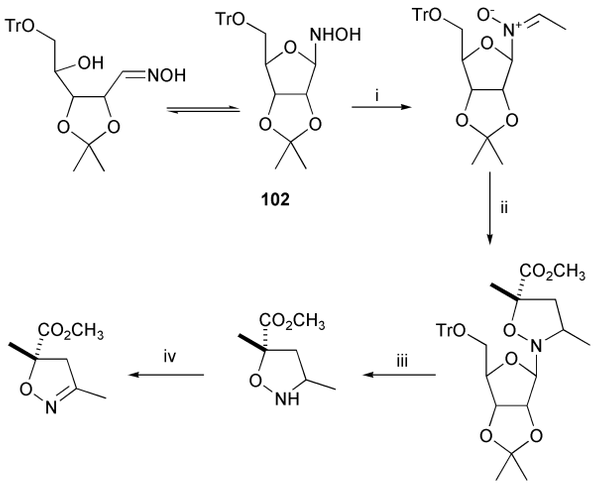
**Scheme 40** *Reagents and conditions*: i) methyl acrylate in toluene, 4 h at 110 °C, 88%.

Reports have also been forthcoming from Vasella[14] who has developed stereoselective syntheses of diastereomeric isoxazolidine-ribosides *via* reactions of hydroxylamines, for example **102**, with aldehydes, in the presence of dipolarophiles such as methyl methacrylate (Scheme 41).

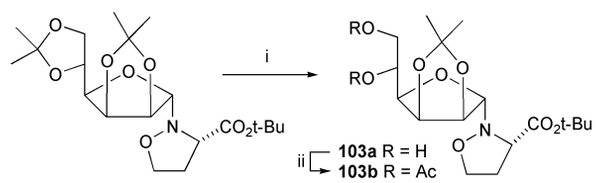
The rationale for the stereoselectivity is based on a combination of the kinetic anomeric effect and the relative importance of *exo versus endo* approach of the dipolarophile. Moreover, the presence of a bulky trityl group was not found to adversely effect the selectivity of the reaction. This work was further extended to allow the asymmetric synthesis of a new proline analogue.[66] Thus the *N*-glycosylisoxazolidines **103** and **104** were prepared by reacting *N*-glycosyl-*C*-alkoxycarbonyl nitrones, obtained *in situ* from 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime and *tert*-butyl glyoxylate, with ethylene[67] (Scheme 42).

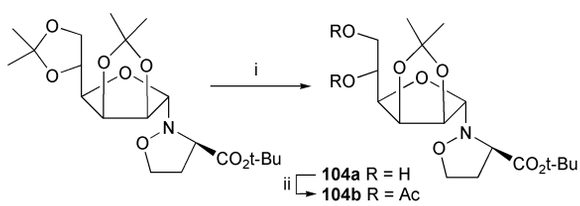
The diastereomeric isoxazolidines **103a** and **104a** were not separated but instead utilised for entry to the 5-oxaproline esters **105** *via* glycosidic cleavage of the *N*-glycosylisoxazolidines, followed by benzyloxycarbonylation (Scheme 43).

In a similar fashion, Vasella and Voeffray later applied this principle to the synthesis of derivatives of captopril **106**,[67] for

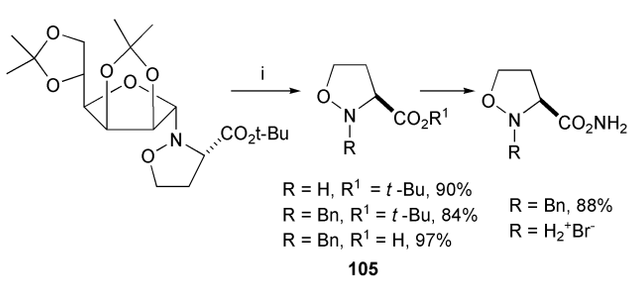


**Scheme 41** *Reagents and conditions*: i) acetaldehyde; ii) methyl methacrylate, 93%; iii) $H^+$, MeOH, 79%; iv) *N*-chlorosuccinimide, rt, 66%.





**Scheme 42** *Reagents and conditions*: i) $HCO_2H$, rt, 4 min. **103a** + **104a** 46%; ii) $Ac_2O$, pyr **103b** + **104b** 41%.



**Scheme 43** *Reagents and conditions*: i) MeOH, HCl, 6 h., room temp.

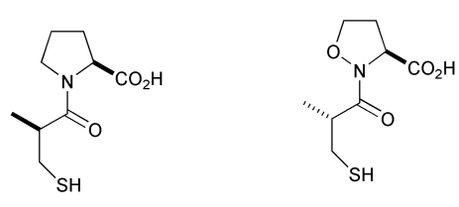


**Fig. 5**

example compound **107**, as potential inhibitors of the angiotensin-converting enzyme (ACE) (Fig. 5). In these cases a ribose derived oxime was utilised as the cycloaddition precursor.

Vasella and Voeffray neatly demonstrated the versatility and usefulness of these intermolecular nitrone cycloadditions in the synthesis of 1-deoxynojirimycin **114**.[68] Reaction of oxime **108** with *tert*-butyl glyoxylate (OHC-$CO_2Bu^t$) generated the nitrone which reacted with furan to give the isoxazolidine **109**. Osmium tetraoxide oxidation followed by protection of the resultant diols gave the isopropylidene compound **111** which was converted into the hydroxyester **112**. Benzoylation and lactonisation afforded derivative **113** which allowed subsequent entry to 1-deoxynojirimycin **114** in an overall yield of 19.5% (Scheme 44).

The promising results afforded by Vasella's chiral sugar derived nitrones have also been incorporated within the synthesis of (2*S*)-4-oxopipecolic acid, an unusual amino acid, as reported by Brandi *et al.*[69] Kibayashi *et al.* have also reported the total asymmetric syntheses of (+)-negamycin **115** and (−)-3-epinegamycin **116** *via* enantioselective intermolecular 1,3-dipolar cycloaddition reactions.[70] (+)-Negamycin is of interest due to its ability to inhibit both Gram-negative and Gram-positive bacteria (Fig. 6).

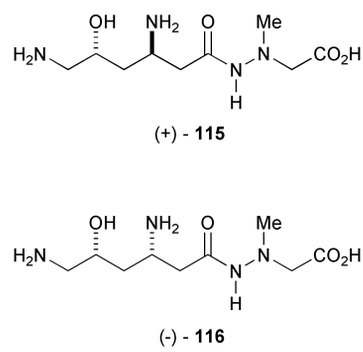


**Fig. 6**

*N*-Glycosyl nitrones **117** have also served as versatile building blocks in the preparation of modified nucleosides including α-D- and β-D-isoxazolidinylthymidines.[71] A number of chiral auxiliaries have been incorporated within the nitrone, including ribofuranose derived auxiliaries. The carbohydrate chiral auxiliary was easily incorporated within the nitrone **117** prior to the cycloaddition reaction, and was easily removed at the end of the synthesis, under mild acidic conditions. This afforded the *N*,*O*-nucleoside **120**, unsubstituted at the nitrogen atom. The diastereoselectivity of the cycloaddition process was high when the carbohydrate derived aldonitrone was employed, and the results obtained were interpreted in terms of an "*O-endo*" transition state model that assumed that the *E*-isomer of the nitrone was the more reactive form (Scheme 45).[72]

### 4.2.2 Intermolecular reactions of carbohydrate derived ketonitrones

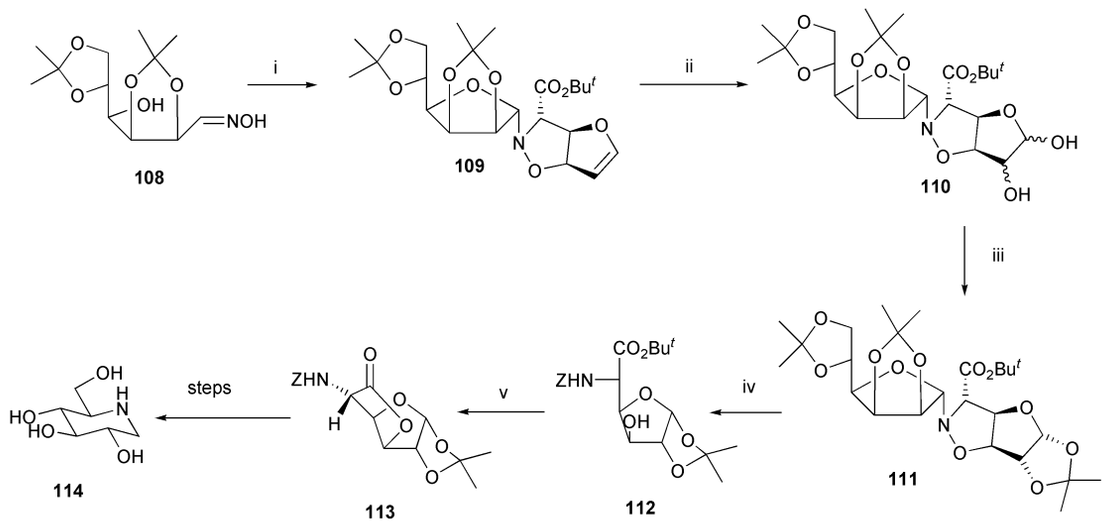
The utility of the more hindered carbohydrate derived ketonitrones within intermolecular cycloaddition reactions is even less widespread in the literature than for carbohydrate derived aldonitrones. One early example reported the addition of *N*-methyl ketonitrones **121** to phenylacetylene to generate the isoxazoline **122** and aziridine **123**[73] (Scheme 46) although no yields were reported for these transformations.

In a more recent study the reaction of sugar ketonitrone **124** with benzyl vinyl ether was reported to afford two isoxazolidines **125** and **126** in a 6 : 1 ratio in 73% overall yield[12] (Scheme 47).

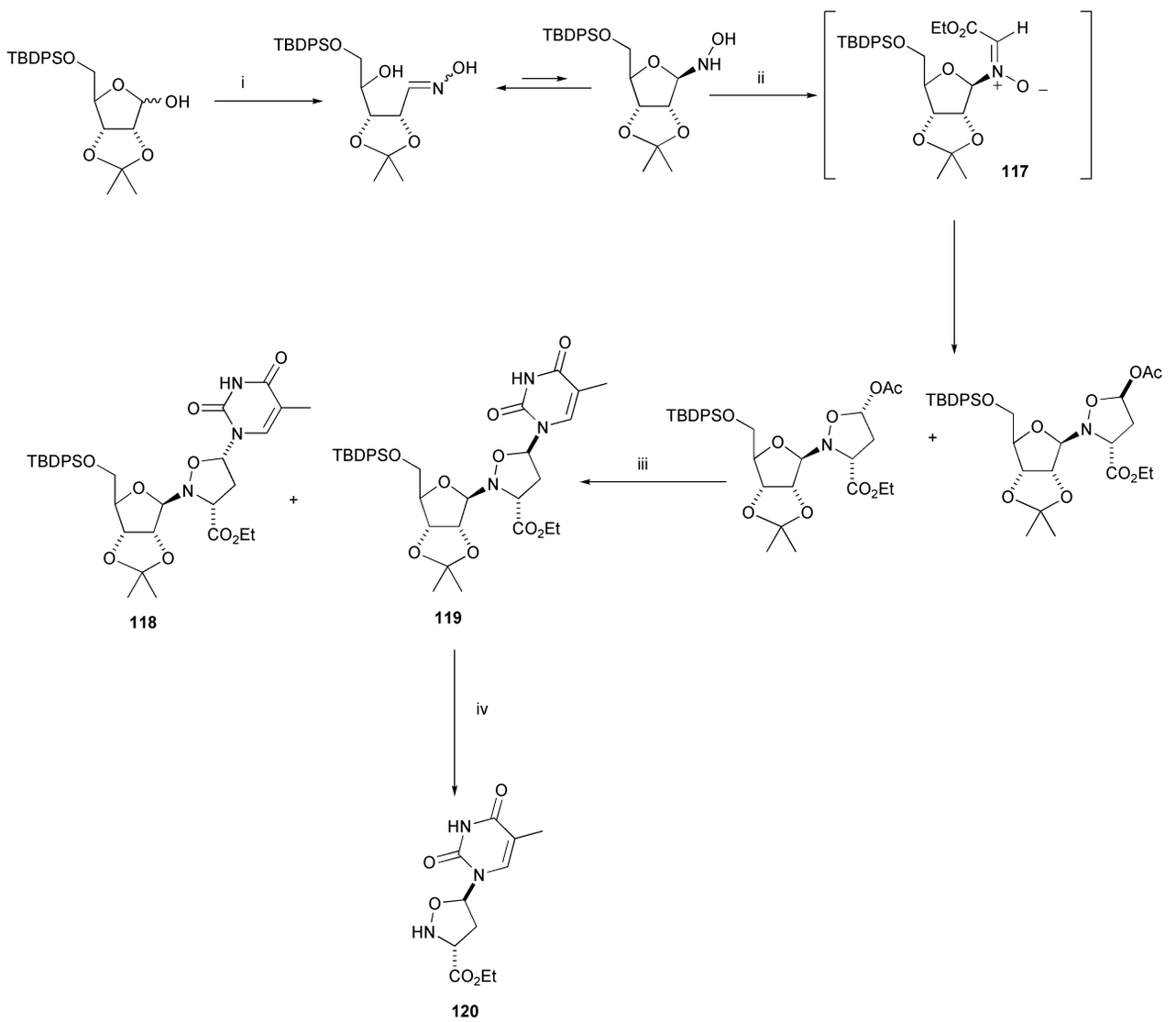
The fact that only a limited number of intermolecular ketonitrone cycloaddition reactions have been reported to date does, however, suggest that such reactions are of more limited use in synthetic strategies.

### 4.3 Intermolecular reactions between carbohydrate derived dipolarophiles and non-carbohydrate nitrones or nitrile oxides

Alternative entry to carbohydrate derived isoxazolines and isoxazolidines can be achieved *via* the complementary reactions




**Scheme 44** *Reagents and conditions*: i) OHC–$CO_2t$-Bu, furan, 38%; ii) $OsO_4$, 52%; iii) acetone, $H^+$, 77%; iv) $H_2$, Pt, then, ZCl, 69%; v) intramolecular esterification, 97%.



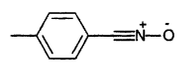
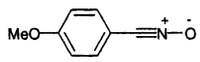
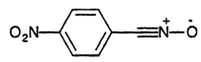
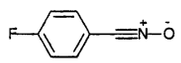
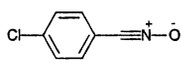
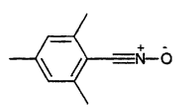

**Scheme 45** *Reagents and conditions*: i) $NH_2OH{\cdot}HCl$, py, rt, 1 h, 98%; ii) vinyl acetate, ethyl glyoxylate, 60 °C, 14 h, 95%; iii) bis(trimethylsilyl)-acetamide (BSA), thymine, $Me_3SiOTf$, MeCN, reflux, 1 h, 24% **118**, 59% **119**; iv) 3.7% HCl in EtOH, rt, 3 h, 60%.

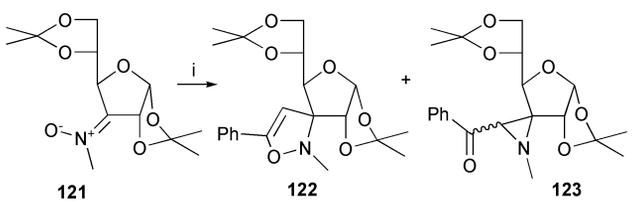
of carbohydrate derived alkenes with non-carbohydrate based nitrile oxides or nitrones. An early example is the cycloaddition of stable nitrile oxides with terminal unsaturated sugars **127**, leading to the expected isoxazolines[74] (Scheme 48).

A similar sugar dipolarophile **128** was also found to undergo highly regio- and stereoselective cycloaddition reactions with numerous arylnitrile oxides[75] (Scheme 49).

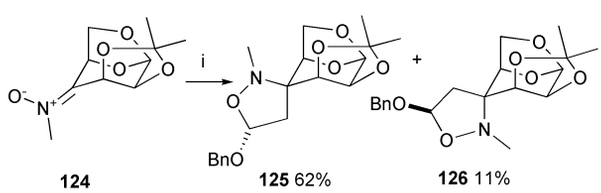
Purification employing column chromatography resulted in the isolation of the *anti* adduct in 51% yield. The nature of the nitrile oxides apparently had no effect on the diastereo-

**Table 3**

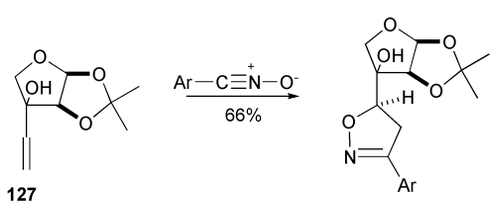
| Entry | Nitrile oxide | Yield (%) |
|---|---|---|
| 1 |  | 65 |
| 2 |  | 55 |
| 3 |  | 58 |
| 4 |  | 65 |
| 5 |  | 52 |
| 6 |  | 51 |



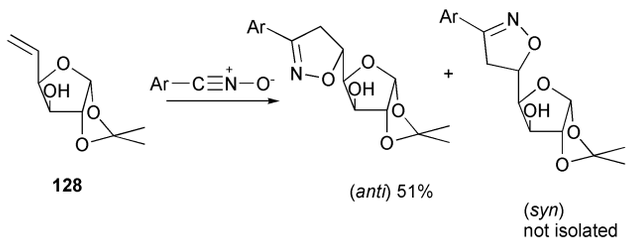
**Scheme 46** *Reagents and conditions*: i) phenylacetylene, heat.



**Scheme 47** *Reagents and conditions*: i) $BnOCHCH_2$, benzene, heat, 3 Å mol sieves.



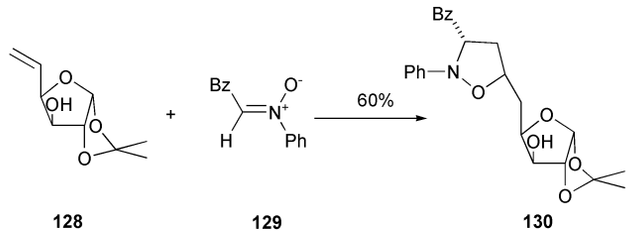
**Scheme 48**



**Scheme 49**

selectivity of the cycloaddition as changing the steric or electronic properties of the nitrile oxide still resulted in the isolation of the *anti* adduct as the predominant product (Table 3).

Nitrile oxides have also been reported to react with 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose to produce mainly *anti* adducts.[76] Al-Timari *et al.*[77] employed the achiral nitrone **129** in a cycloaddition with the same sugar alkene derivative **128** (Scheme 50) and found that this reaction again proceeded with *anti* selectivity to afford cycloadduct **130** as the major product.



**Scheme 50**

If hex-5-enopyranosides or pent-4-enofuranosides were instead employed in the intermolecular nitrile oxide cycloaddition, spiro-isoxazolines were produced in good to excellent yields.[78] These intermediates have proved of use as precursors to densely functionalised six- and five-membered carbocycles, *via* reductive opening of the heterocyclic ring and spontaneous intramolecular aldol-like condensation (Scheme 51). This transformation has offered complementary methodology for entry to aminocyclitols, carbasugars and inositols to that proposed by Ferrier.[79]

Various *O*-silylnitronates **132** have also been reported to react with sugar alkenes *e.g.* **131** to afford enantiomerically pure *N*-silyloxyisoxazolidines **133** and **134** that have been easily transformed into isoxazolines **135** and **136** (Scheme 52).[80]

Although four possible isomeric cycloaddition products could result, only **133** and **134** were observed by $^1$H NMR analysis of the crude reaction mixture. Thus the cycloaddition methodology was considered to be regiospecific and highly diastereoselective. *N*-Silyloxyisoxazolidines **133** and **134** were not isolated but were instead converted into **135** and **136** in 60% yield in a ratio of 92 : 8 respectively.

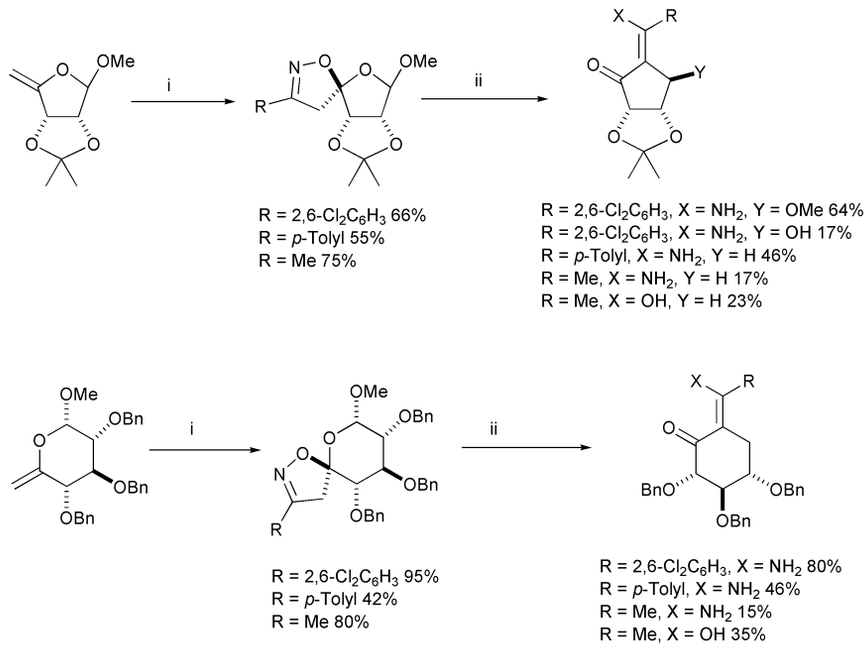
Carbohydrate derived alkenes have also proved of use as key intermediates in the synthesis of a number of natural products. Thus the reaction of a nitrile oxide with the carbohydrate derived alkene **137** was a key step in the synthesis of amino sugars, including D-lividosamine **139**.[81] In this example the nitrile oxide was generated *in situ* from nitroalkane **138** *via* the procedure of Mukaiyama (Scheme 53).[82]

Subsequently, the stereoselective synthesis of aminodeoxyfuranosides was developed by employing 3-bromoisoxazolines **141** as precursors to β-hydroxy esters **142**.[83] The 3-bromoisoxazoline was itself formed from alkene **140** *via* treatment with BrCNO. Treatment of the bromoisoxazoline **141** with base afforded the 3-methoxyisoxazoline which under hydrogenolysis–hydrolysis conditions was transformed to the β-hydroxy ester **142** (Scheme 54).

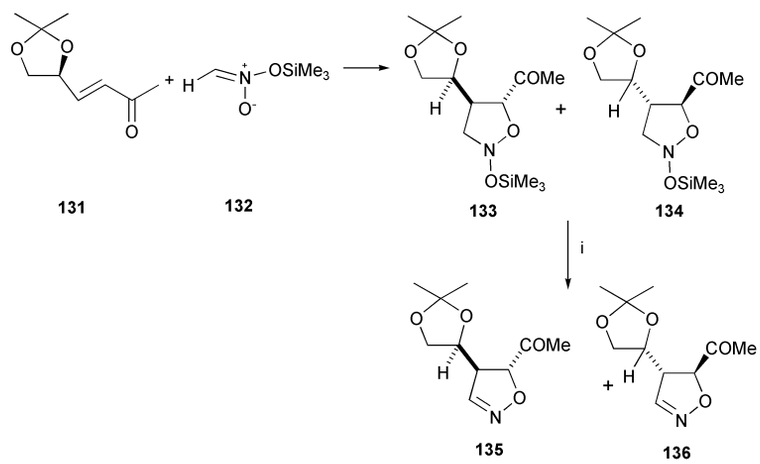
An alternative approach that utilises isoxazolidines in the preparation of deoxysugars has also been disclosed by Deshong and Leginus.[84]

α,β-Unsaturated carbohydrate lactones **143** have also proved of use as dipolarophiles in the 1,3-cycloaddition reactions with nitrones[85] (Scheme 55). Thus a regiospecific reaction of nitrone **144** with α,β-unsaturated sugar lactone **143** afforded a mixture of two diastereomeric sugar lactones **145** and **146** in a total yield of 80%. It was postulated that nitrone approach to the unsaturated lactone must occur exclusively *trans* with respect to the existing ring substituent with the *exo* transition state being more energetically favoured than the *endo*. Disappointingly, cycloaddition of a benzonitrile oxide with α,β-unsaturated sugar lactone **147** showed no such stereocontrol resulting in the formation of all four isomeric products (Scheme 56).

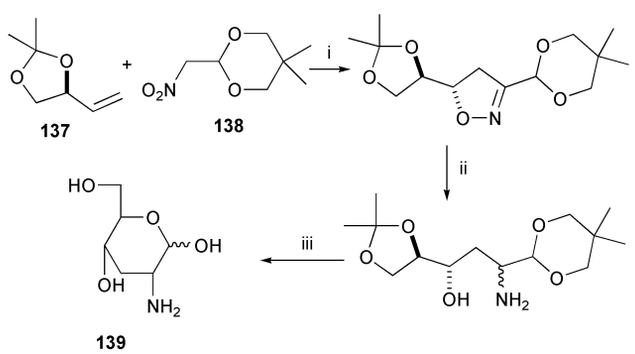
In another example, however, levoglucosenone **148** underwent a highly selective cycloaddition reaction with benzonitrile oxide (Scheme 57).[86] Dehydrochlorination of benzohydroximoyl chloride generated the benzonitrile oxides. An excess of



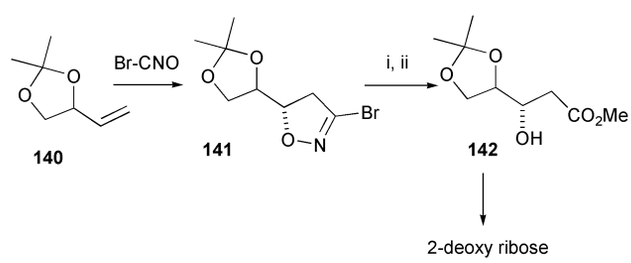

**Scheme 51** *Reagents and conditions*: i) 2,6-$Cl_2C_6H_3CNO$ or *p*-$MeC_6H_4CH{=}NOH$, NCS, $Et_3N$ or $EtNO_2$, PhNCO, $Et_3N$; ii) Raney Ni, $MgSO_4$, $H_2$, MeOH–$MeCO_2H$.



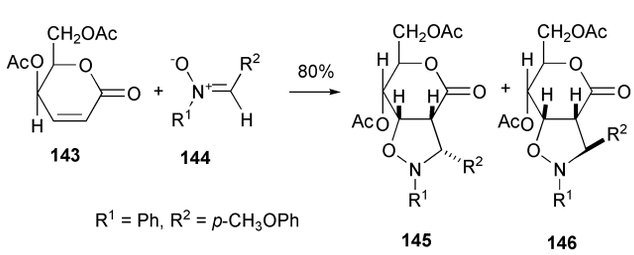

**Scheme 52** *Reagents and conditions*: i) *p*-TsOH, ether, 1 h, rt, 60%.




**Scheme 53** *Reagents and conditions*: i) PhNCO, $Et_3N$, 53%; ii) $LiAlH_4$; iii) 6 M HCl.

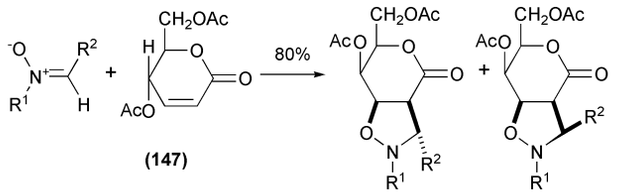


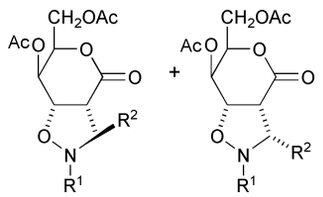

**Scheme 54** *Reagents and conditions*: i) MeOLi; ii) $H_2$, Ra-Ni, 79%.



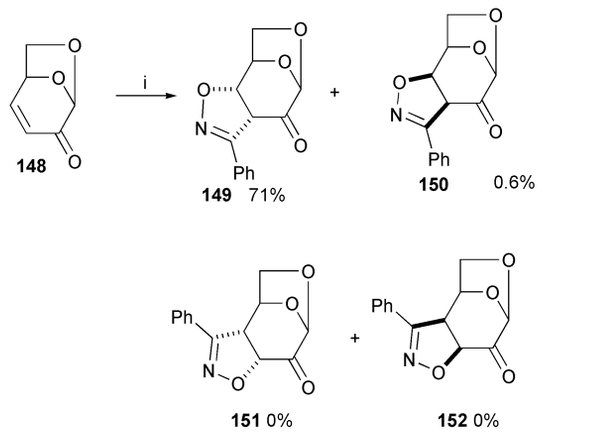

**Scheme 55**

the dipolarophile was utilised to minimise the competing dimerisation of the nitrile oxide. The major cycloadduct was identified as **149**, and the minor **150**, whilst cycloadducts **151** and **152** were not detected. Whilst the two regioisomers **149** and **151** could be considered to result from approach of the 1,3-dipole to the lower face of the alkene double bond, **150** and **152** would result from attack of the upper face. Thus it was concluded that the reaction was regiospecific with high facial selectivity, attack of the dipole occurring from the less hindered lower face. In a similar fashion, *C*,*N*-diphenyl nitrone and *N*-benzyl-*C*-phenyl nitrone reacted with levoglucosenone **148** to afford isoxazolidines **153** and **154** (Fig. 7).[65]



Scheme 56




**Scheme 57** *Reagents and conditions*: i) benzonitrile oxide, generated *in situ* by dehydrochlorination of benzohydroxyimoyl chloride, $Et_3N$, heat.

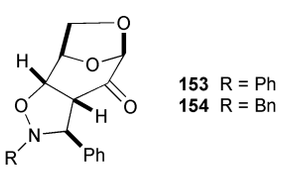


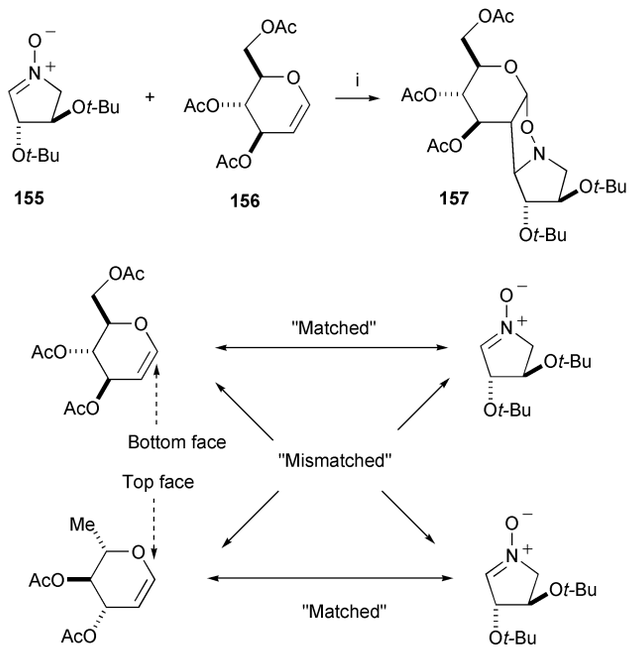

**Fig. 7**

In each case the dipole attacked the less hindered face of the dipolarophile, *anti* to the 1,6-anhydro bridge.

Finally, a number of glycals, for example glycal **156**, have been utilised as dipolarophiles in cycloaddition reactions with enantiopure substituted pyrroline *N*-oxides, derived from D-tartaric acid, L-tartaric acid and L-malic acid, such as *N*-oxide **155**.[87] Such reactions were of interest for providing efficient entry to stereodifferentiated tricyclic isoxazolidines **157**, of use as precursors to the pseudo-aza-*C*-disaccharide skeleton. These targets are currently being considered for selective inhibition of glycosidase enzymes.[88] In early reports this work was limited to include only stable nitrones, due to the forcing reaction conditions that were necessitated (100 °C, long reaction times, use of an excess of glycal **156**). However, a recent report has illustrated that the methodology can be extended by performing the reactions under increased pressures of 10 kbar.[89] Under these conditions, excellent diastereoselectivity was achieved to afford the *exo-anti* adducts, for example **157**, derived from "matched" interactions of the nitrones with the glycals.[87b] The stereoselectivity is believed to be controlled by the substituent on C-3 of the glycal **156**, as well as the *tert*-butoxy group adjacent to the nitrone double bond. Thus D-tartaric acid-derived nitrone and L-malic acid-derived nitrone approached the bottom face of the glucal, while L-tartaric acid-derived nitrone approached the top face of L-rhamnal and D-arabinal (Scheme 58).

**Table 4**

| | $R^3$ | $R^5$ | Global yield (%) |
|---|---|---|---|
| | Gal | Ph | 54 |
| | Gal | *p*-Anisyl | 72 |
| | Xyl | Ph | 48 |
| | Rib | Ph | 73 |
| | Ph | Gal | 78 |
| | Ph | Xyl | 66 |
| | Gal | Gal | 52 |
| | Xyl | Xyl | 51 |




**Scheme 58** *Reagents and conditions*: i) 10 kbar, toluene, 60 °C, 3 days, 100%.

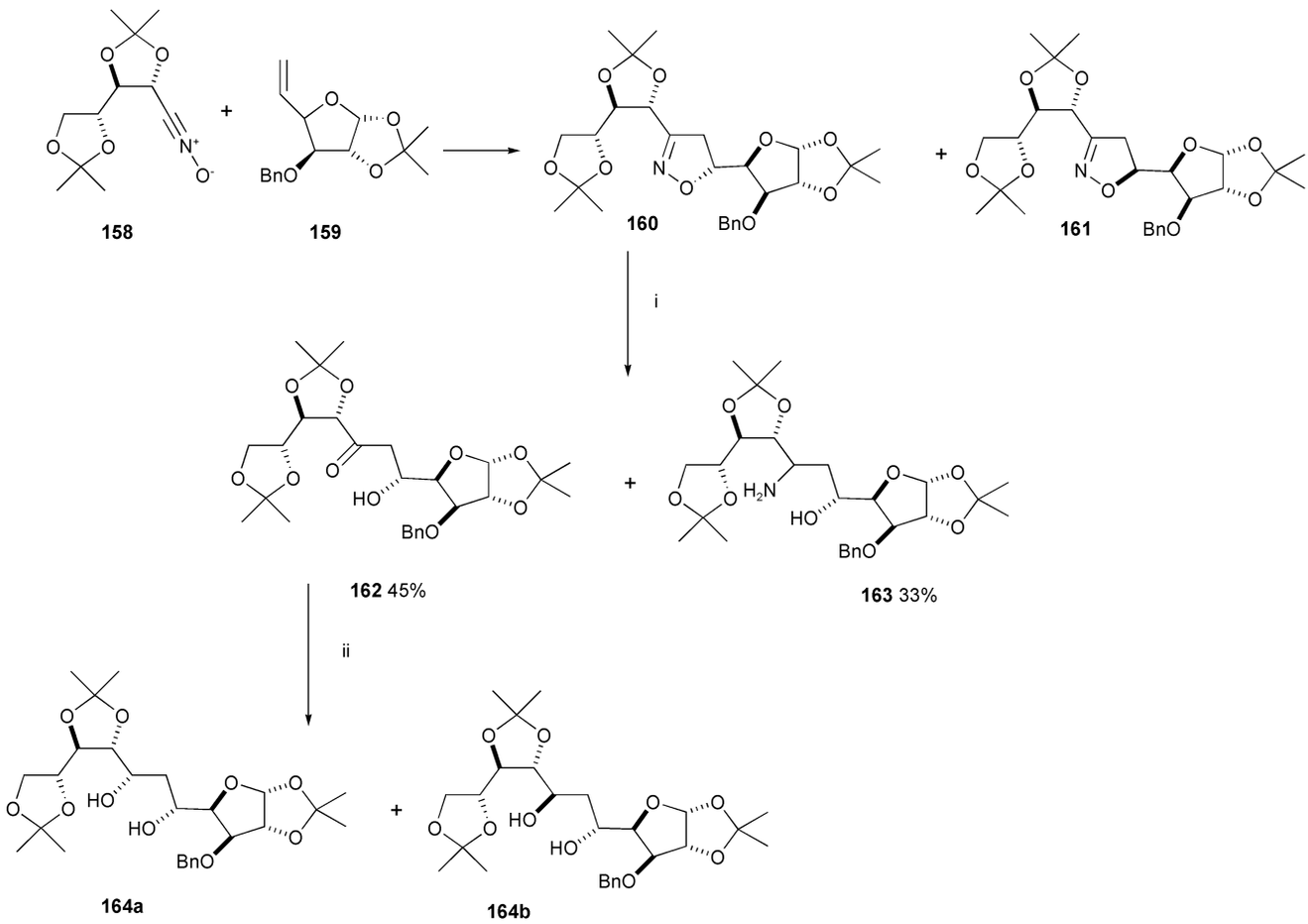
### 4.4 Intermolecular reactions between carbohydrate derived nitrones and carbohydrate derived alkenes

The reactions of carbohydrate derived nitrones with carbohydrate derived alkenes offer the potential of achieving highly stereoselective entry to isoxazoline targets *via* double asymmetric induction. Such a strategy has provided convenient entry to *C*-linked disaccharides and eleven-carbon monosaccharides (Scheme 59)[90] in an attempt to realise the synthesis of subunits of antibiotics such as hikizimycin (anthelmycin) and tunicamycin.[90a] Thus, reaction of carbohydrate derived nitrile oxide **158** with carbohydrate derived alkene **159** afforded a mixture of the isoxazolines **160** and **161** in a total yield of 61%. Unreacted alkene was also isolated. The ratio of **160** : **161** was found to be 89 : 11.

The isoxazoline **160** was converted to β-keto-alcohol **162** *via* reductive cleavage with Raney nickel, with the amino alcohol **163** also being produced in 33% yield as a by-product. The desired alcohol product **164** was formed by reduction of the ketone **162** with L-Selectride, with the alcohols being formed in the ratio of 97 : 3 for **164a** : **164b**.

Completely regioselective and stereospecific entry to 4,5-*trans*-4-nitroisoxazolidines **167** has also been achieved *via* the cycloaddition reactions of carbohydrate derived nitrones **165** with carbohydrate derived nitroolefins **166**. The *endo*/*exo* stereoselectivity was found to be dependent on the type of sugar derivatives used and worse selectivity was observed when non-carbohydrate derived nitrones or nitroolefins were employed (Scheme 60, Table 4).[91]

In general, it was observed that the *exo*/*endo* and/or the π-facial stereoselectivities were better for reactions of *C*-glycosyl nitrones than for those of sugar nitroalkenes (Fig. 8).




**Scheme 59** *Reagents and conditions*: i) $H_2$–Raney Ni, $H_3BO_3$, MeOH, $H_2O$, 45%; ii) $NaBH_4$ or L-Selectride, 98%.

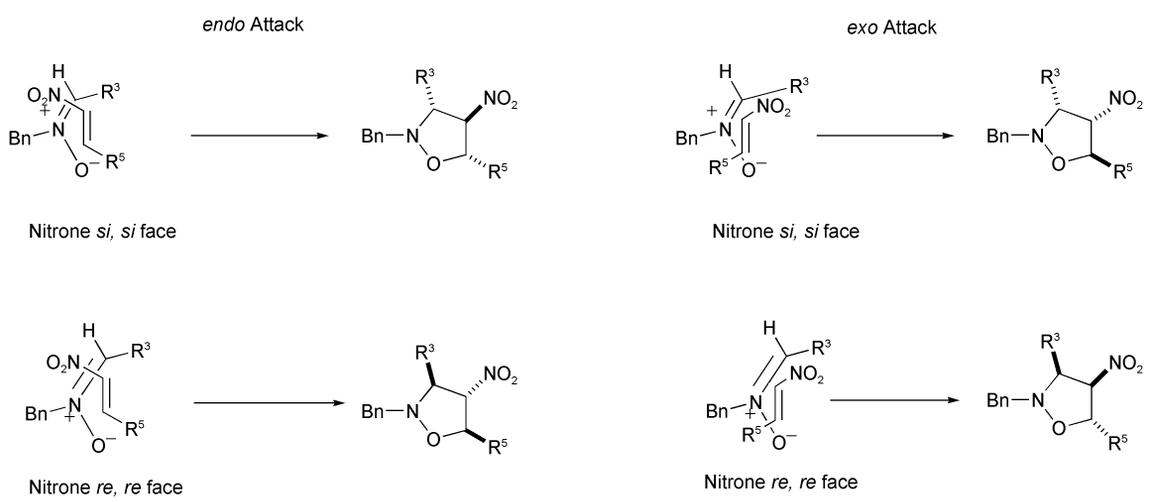
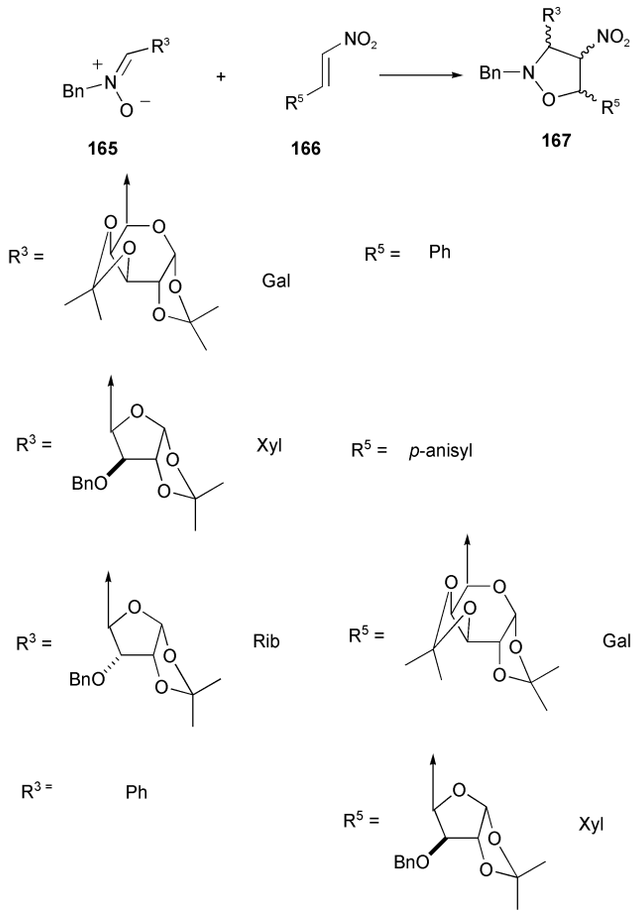



**Fig. 8**

## 5 Conclusions

This review has detailed the synthesis of 1,3-dipolar cycloaddition reactions of carbohydrate derived 1,3-dipoles. The possibility of utilising the carbohydrate moiety of the carbohydrate derived nitrones and alkenes as chiral auxiliaries has also been demonstrated, allowing highly stereoselective cycloaddition reactions to be performed. Further manipulation of the resultant isoxazolidines and isoxazolines has allowed synthesis of a wide range of key intermediates of use for the synthesis of natural products. Such targets have included enantiomerically pure pyran and oxepane derivatives, piperidine and azepane derivatives, and isoxazolidine carbocycles. Access to aminosugars including D-lividosamine, daunosamine, acosamine and various 2-deoxysugar derivatives has also been described. The potential of synthesising isoxazolidines with excellent stereocontrol, *via* double asymmetric induction, has been illustrated *via* the reaction of carbohydrate derived nitrones with carbohydrate derived alkenes.




**Scheme 60**

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