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Synthesis of chiral oxepanes and pyrans by 3-*O*-allylcarbohydrate nitrone cycloaddition (3-OACNC)

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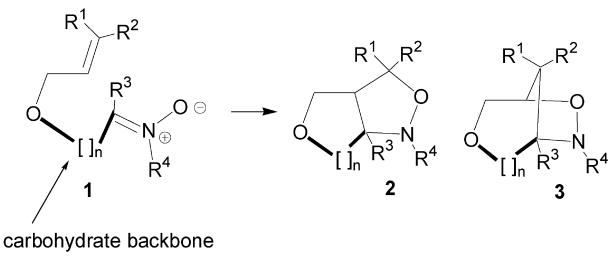
Abstract—3-*O*-Allylcarbohydrate nitrone cycloaddition (3-OACNC) furnished pyran and oxepane derivatives from 3-*O*-allyl hexose *N*-benzyl nitrones and 3-*O*-allyl furanoside-5-aldehyde *N*-benzyl/methyl nitrones. The regioselectivity of 3-OACNC was found to depend on the following factors (a) the structural nature of the nitrone (b) substitution and stereochemistry at 3-C of the carbohydrate backbone (c) substitution at the terminus of the *O*-allyl moiety. Oxepanes or pyrans obtained from a particular set of a hexose nitrone and the corresponding furanoside nitrone were converted to enantiomeric cyclic ethers through degradation. A mixture of an oxepane and a pyran was formed in the intramolecular oxime olefin cycloaddition (IOOC) of a 3-*O*-allylcarbohydrate derived oxime.

1. Introduction

The profound influence of chirality on the biological activity of drugs and related substances[1] has made the preparation of enantiomerically pure compounds an impulsive engagement for the synthetic chemist. Among the various methods employed for this purpose, the use of a suitable chiral pool is an important way of constructing the chiral framework of the target compound.[2] The unequivocal supremacy of carbohydrates in this regard has been demonstrated in the plethora of examples of synthesis of different classes of chiral molecules from carbohydrates.[2] In 1990 we[3] and others[4] disclosed a simple and efficient strategy for the synthesis of chiral cyclic ethers, which constitute the frameworks of a large number of biologically active naturally occurring compounds such as marine toxins,[5] zoapatanol,[6] sepholenol,[7] laurencin,[8] and many others. The strategy is based on the intramolecular 1,3-dipolar cycloaddition of a nitrone **1** which has a cyclic or an acyclic carbohydrate backbone bearing an *O*-allyl group, the vinyl moiety of which serves as the dipolarophile (Scheme 1). The cycloaddition can lead to a fused isoxazolidine **2** or a bridged isoxazolidine **3** or both. An interesting feature of the structures of the isoxazolidines **2** and **3** is that they incorporate a cyclic ether ring, which inherits parts of the carbohydrate backbone as well as the allyl moiety. Two new asymmetric centers are formed by the cycloaddition at the ring juncture of the isoxazolidine and the ether moiety. The size of the chiral cyclic ether core in **2** or **3** is dependent on (i) *n*, i.e. the number of intervening carbon atoms between the nitrone functionality and the *O*-allyl group and (ii) the regioselectivity of the reaction, because the bridged isoxazolidine **3** contains an ether ring, which is one carbon atom larger than the fused isoxazolidine **2**. Therefore it is understandable that these two factors can make the cycloaddition strategy a potentially important method for the synthesis of cyclic ether skeletons of various ring sizes. As evident from Scheme 1, cycloaddition of both aldo- and ketonitrones are possible, and consequently cyclic ether skeletons of ring sizes 5–7 have been synthesized from carbohydrate derivatives having *O*-allyl moieties and aldo- and ketonitrone functionalities at different positions of cyclic and acyclic carbohydrate scaffolds.[3,4,9–20] These examples involved nitrones represented by **1**, in



Scheme 1. The OACNC strategy.

Keywords: chiral oxepanes; pyrans; carbohydrates; nitrone cycloaddition; OACNC.

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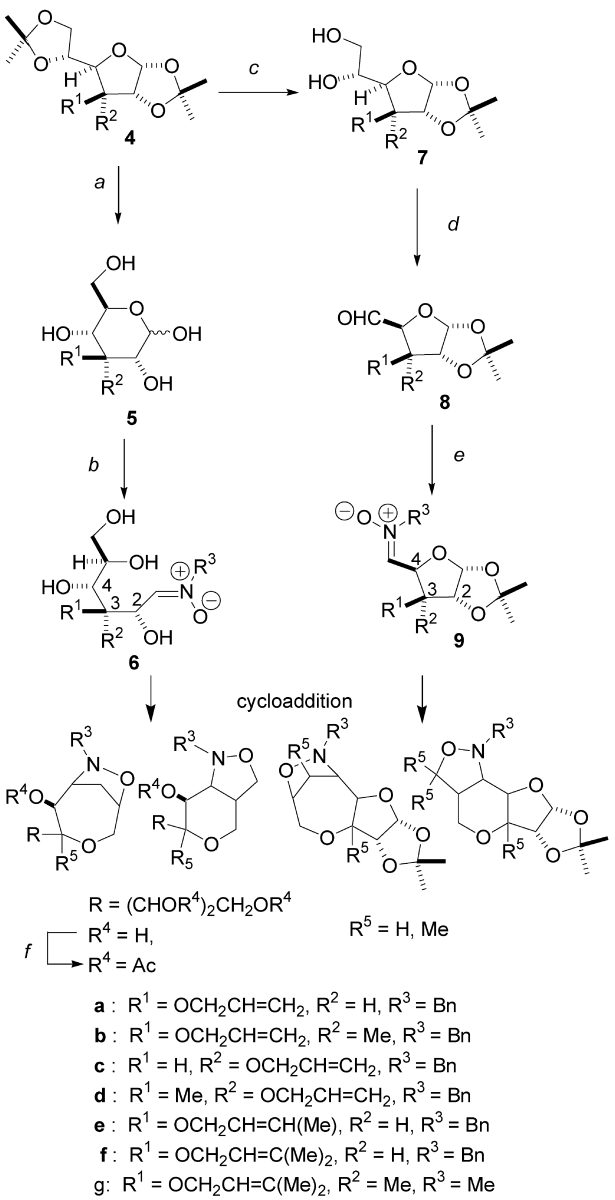
which n=1, 2 and 3, and cyclic ethers of ring sizes 5 (fused isoxazolidines from n=1), 6 (fused isoxazolidines from n=2) and 7 (fused isoxazolidines from n=3, and bridged isoxazolidines from n=2) were obtained. Preliminary work on *O*-allyl carbohydrate nitrone cycloaddition (OACNC) involving carbohydrate scaffolds containing two intervening carbon atoms between the nitrone and the *O*-allyl moiety has demonstrated the usefulness of this reaction for the synthesis of pyrans and oxepanes.[3,4,9–13,19] Herein we describe in detail the work reported earlier in preliminary communications[3,11,14] and some new results involving the effect of stereochemical and structural change in the 3-*O*-allylcarbohydrate nitrone cycloaddition (3-OACNC). An application of the closely related intramolecular oxime olefin cycloaddition (IOOC) to a 3-*O*-allyl carbohydrate derived oxime is also described at the end.

2. Results and discussion

Two types of structurally related 3-*O*-allyl carbohydrate nitrones, 3-*O*-allylhexose nitrones **6** and 3-*O*-allylfuranoside-5-aldehyde nitrones **9** (Scheme 2), were studied in this work. The difference in the flexibility of the carbohydrate backbones in **6** and **9** is noteworthy, since **9** is less flexible than **6** due to the presence of a structural constraint in the form of the isopropylidene furanoside ring. This structural dissimilarity turned out to be responsible for the difference in the regioselectivity of the 3-OACNC of the two types of nitrones. Another interesting and important structural feature of **6** and **9** is that the configurations of the stereocenters 2-C, 3-C and 4-C in both of them are identical, because they are derived from the same precursor through reactions, which do not affect the aforementioned stereocenters. The precursor hexoses **5** and the furanoside-5-aldehydes **8** required for generating the two classes of nitrones were prepared from the corresponding 1,2:5,6-diisopropylidene-3-*O*-allyl furanosides **4** via straightforward transformations shown in Scheme 2. 1,2:5,6-Diisopropylidene-α-D-glucose (**10**)[21] was converted via the ketone **11**[22,23] to **12**,[24] **13**[25] and **14**,[26] and subsequent allylation[27] of **10** and **12-14** in the presence of tetrabutylammonium bromide in CH_2Cl_2–water (Scheme 3) provided the *O*-allyl derivatives **4**, which, as evident from their ^{1}H NMR spectra, were sufficiently pure to be used directly for the next steps without any further processing. Preparation of the 3-*O*-allyl hexoses **5** required a single hydrolytic treatment of **4** with 4% aqueous H_2SO_4, and the corresponding 3-*O*-allyl furanoside aldehydes **8** were prepared from **4** via stepwise removal of the 5,6-isopropylidene group by treatment with 75% aqueous AcOH followed by oxidation of the resulting diols **7** with $NaIO_4$ (Scheme 2). The intermediates **5**, **7** and **8** were used without purification for the next steps. All the nitrones were generated by treatment of **5** or **8** with BnNHOH[28] or MeNHOH (for **9g**), and underwent cycloaddition in situ. The cycloaddition of the furanside-5-aldehyde nitrones **9** except **9g** was performed in benzene, whereas that of **9g** was effected in aqueous ethanol. Attempted cycloaddition of the hexose nitrones in benzene was unsuccessful, probably due to sluggish nitrone formation, and starting materials were recovered after reaction. So the reactions were first attempted in ethanol, and in the cases of unsuccessful reactions giving back



Scheme 2. *Reagents*: (*a*) 4% H_2SO_4–H_2O, 25°C. (*b*) BnNHOH, EtOH or CF_3CH_2OH, reflux. (*c*) 75% AcOH–H_2O, 25°C. (*d*) $NaIO_4$, MeOH–H_2O, 0–25°C. (*e*) BnNHOH, benzene, 4 Å mol. sieves, reflux (for **9a-f**); MeNHOH·HCl, $NaHCO_3$, 80% aq. EtOH, reflux (for **9g**). (*f*) Ac_2O, pyridine, 0°C.

starting materials, CF_3CH_2OH was used as the solvent. The tetrahydroxy products obtained from **6** were isolated as the corresponding acetates. The structural assignment of the carbohydrate derived cycloadducts, particularly the stereochemistry of the newly formed centers 4-C and 5-C in the pyranoisoxazolidines **A** (Fig. 1) proved to be problematic. In most of the cases analysis of the relevant

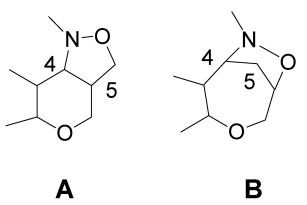
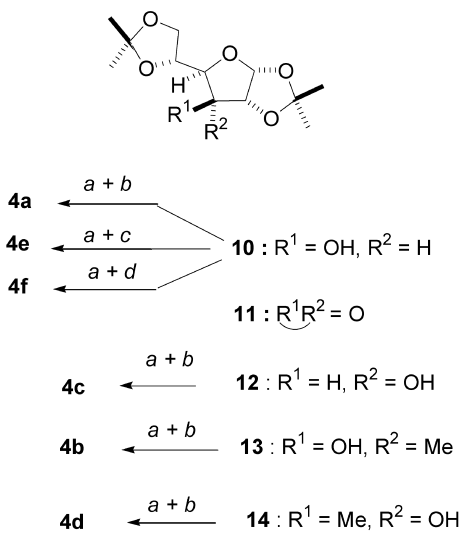


Figure 1. Pyran and oxepane skeletons from 3-OACNC.



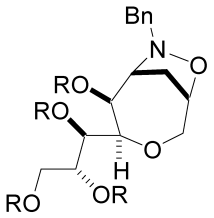
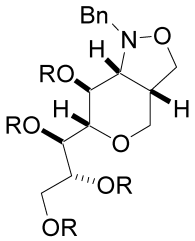
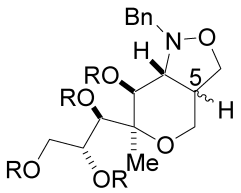
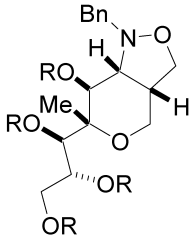
Scheme 3. *Reagents*: (*a*) Bu_4NBr, 50% aq. NaOH, CH_2Cl_2, 25°C. (*b*) Allyl bromide. (*c*) *trans*-Crotyl bromide. (*d*) Prenyl bromide.

^1H, ^1H coupling constants derived after decoupling experiments led to the assignment of the stereochemistry. However, the information about the skeletal nature of the product, whether a pyran or an oxepane, was easily established by the ^1H and ^{13}C NMR spectral characteristics of the product. The appearance of a one-proton multiplet in the vicinity of δ 3 in the ^1H NMR spectra due to 5-H and a methine carbon signal near δ 40.0 in the ^{13}C NMR spectra due to 5-C in **A** is a good indication of the formation of a fused isoxazolidine skeleton. The bridged isoxazolidine **B** (Fig. 1) incorporating an oxepane skeleton is characterized by the appearance of a set of a one-proton doublet and a one-proton multiplet near δ 2.5 due to 5-H_A and 5-H_B and a relatively high field methylene carbon signal near δ 30.0 due to 5-C in the ^{13}C NMR spectra. The bicyclo[4.2.1] system in **B** has one of the bridge methylene protons (5-H) making dihedral angles of approximately 90° with the adjacent bridgehead protons, and this results in the appearance of a simple or a poorly coupled doublet for this proton in the ^1H NMR spectrum of **B**.

2.1. 3-OACNC of the acyclic hexose nitrones 6a-d

The earlier published[3,11,14] results of the 3-OACNC of the acyclic hexose nitrones **6a-d** are summarized in Table 1. The nitrone **6a** derived from 3-*O*-allyl glucose (**5a**) afforded the tetrahydroxy oxepanoisoxazolidine **15**, which was isolated as the tetraacetate **16** in 45–55% yields. The stereochemistry and the absolute configuration of **16** had earlier been established by X-ray crystallographic analysis.[3] Recently Shing et al. reported the exclusive formation of the *N*-methyl analog of **16** in the cycloaddition of the *N*-methyl analog of **6a** following the same strategy.[10] Treatment of **5b** with BnNHOH in EtOH did not result in the formation of any nitrone and the starting material remained unchanged. However, the cycloaddition could be achieved in CF_3CH_2OH resulting in the exclusive formation of an inseparable mixture of the diastereomeric pyran derivatives **18a** and **18b** in 57% yield via the nitrone **6b**. The exclusive formation of the pyran skeleton was again observed in the cycloaddition of **6c**. The product obtained was assigned the structure **20** on the basis of ^1H NMR coupling

Table 1. 3-OACNC of hexose nitrones

Nitrone[a]	Product[b]	Yield (%)	Nitrone[a]	Product[b]	Yield (%)
6a	 **15** : R = H **16** : R = Ac	45–55	**6c**	 **19** : R = H **20** : R = Ac	80
6b	 **17a** : R = H, 5-H, β **17b** : R = H, 5-H, α **18a** : R = Ac, 5-H, β **18b** : R = Ac, 5-H, α	57[c]	**6d**	 **21** : R = H **22** : R = Ac	60

[a] Ethanol was used as solvent for **6a** and **6c**, whereas 2,2,2-trifluoroethanol was used for **6b** and **6d**.
[b] Products were isolated as acetates.
[c] 1:1-Mixture of diastereomers; structures were based on analysis of enriched mixtures.

constants, which were otherwise incompatible with any alternative stereochemistry of the ring-juncture carbon atoms. The assigned stereochemistry of **20** is in agreement with the results obtained by Shing et al. who reported the cycloaddition of the corresponding *N*-methyl nitrone, and obtained in 33% yield the *N*-methyl analog of **20** with the same stereochemistry as obtained by us, along with a diastereomeric *trans*-fused product in 8% yield.[10] As observed with **5b**, treatment of the hexose **5d** with BnNHOH in EtOH under reflux for 24 h failed to afford any product, and the starting material was recovered unchanged. Formation of the nitrone **6d** and its concomitant cycloaddition could be achieved in CF_3CH_2OH leading to the exclusive formation of the pyranoisoxazolidine **22**.

The results cited in Table 1 indicates that formation of a bridged isoxazolidine, i.e. an oxepane skeleton was observed only in the case of the acyclic nitrone **6a**. Similar observation in the cases of the *N*-methyl analogs of **6a** and **6c** led Shing et al. to suggest, on the basis of the stability of the pyran and oxepane transition states that the regioselectivity in these cases is determined by the relative stereochemistry of 2-C and 3-C of the nitrones.[10] According to these authors, a *threo*-2-C, 3-C stereochemistry in a nitrone such as **6a**, favors the formation of an oxepane, whereas an *erythro* stereochemistry as in **6c** results in the formation of a pyran. However, with the introduction of a substituent at 3-C as in **6b** and **6d**, the situation becomes more complex, and a straightforward explanation of the regioselectivity based on the stereochemistry of 2-C and 3-C becomes untenable. In order to get some idea about the relative stability of the transition states involved in the cycloaddition of **6b** and **6d**, relative energies of the probable pyran and oxepane transition states were computed (vide Section 4), and are shown along with the corresponding products in Figure 2. As seen from the results cited in Figure 2, the formation of a mixture of the diastereomeric pyrans **17a** and **17b** from **6b** was in agreement with the corresponding pyran T.S.s **23c** (−128.7 kcal/mol) and **23d** (−127.9 kcal/mol), which are significantly lower in energy than the oxepane T.S. **23a** (−44.3 kcal/mol) and **23b** (−113.8 kcal/mol). A steric interaction between CH_3 and the developing isoxazolidine ring or the bridge methylene raises the energy of **23a** and **23b** considerably. A similar steric situation for **6d** makes the oxepane T.S. **23e** (−118.2 kcal/mol) less likely than the pyran T. S. **23f** (−130.6 kcal/mol) corresponding to the observed product **21**. The other pyran T.S.s **23g** (−128.4 kcal/mol) and **23h** (−120.4 kcal/mol) have higher energies than that of **23f**, and the corresponding products were not observed. The above results will serve as a guideline for any application of the OACNC strategy to the synthesis of natural products

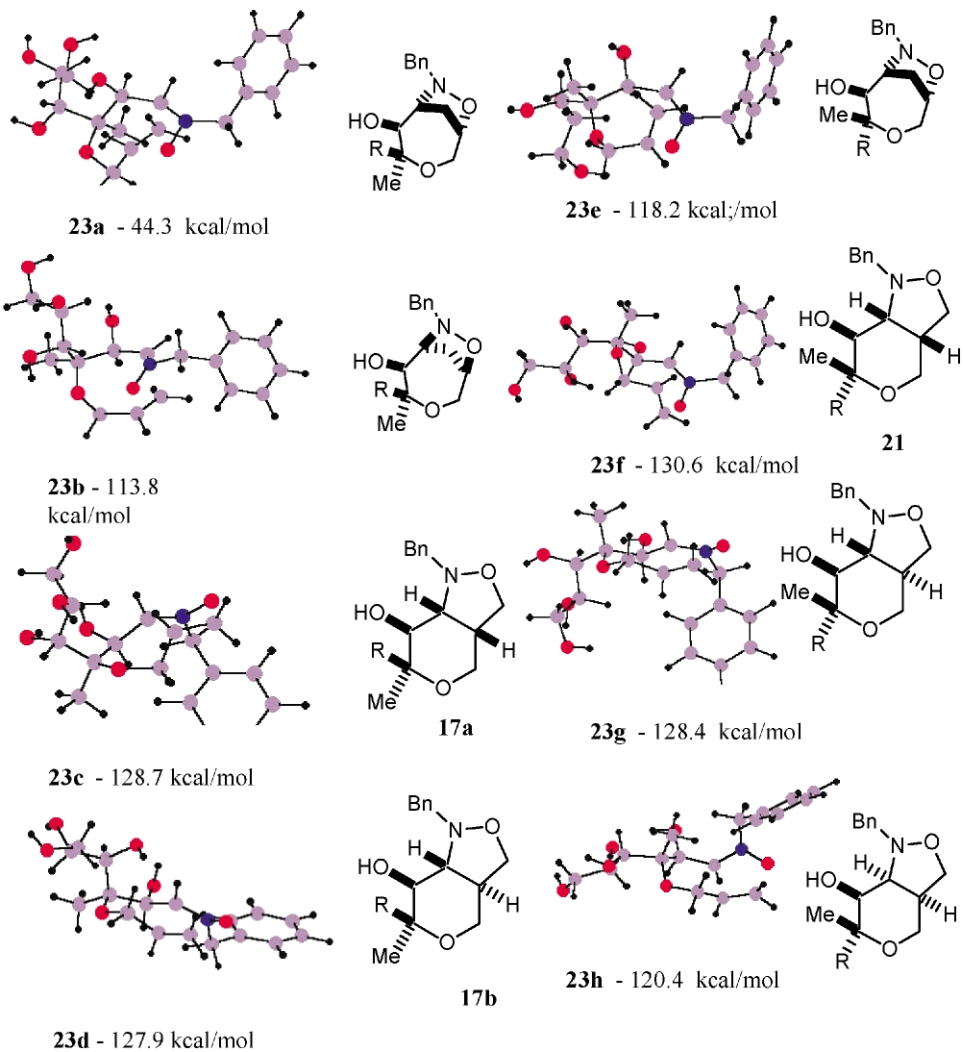
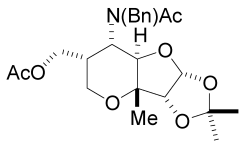


Figure 2. Probable transition state structures in the cycloaddition of **6b** and **6d**, and the corresponding products.

incorporating cyclic ether moieties. As an example, our attempts to synthesize zoapatanol[29] (**24**) having a quaternary C-methyl via the nitrones **6b** and **6d** were foiled due to the failure to prepare any oxepane derivative by their cycloadditions.

2.2. 3-OACNC of the furanoside-5-aldehyde nitrones 9a-d and 9g

The results of the earlier reported 3-OACNC of the furanoside-5-aldehyde nitrones **9a-d**,[11,14] as well as an investigation of the cycloaddition of **9g**, the *N*-methyl analog of the nitrone **9b**, are presented in Table 2. In our preliminary communication the cycloaddition of the nitrone **9a** was reported to furnish the oxepane derivative **25** in 56% yield.[11] However later work revealed the presence of an additional compound, which was characterized as the pyran derivative **26** isolated in less than 5% yield by repeated chromatography of the material obtained after crystallization of **25**. Formation of a similar mixture of the *N*-methyl analogs of **25** and **26** in the cycloaddition of the *N*-methyl analog of **9a** has also been reported by others.[12] The cycloaddition of the nitrone **9b** afforded the oxepane derivative **27** as the only isolable compound in 50% yield. The reaction was accompanied by the formation of unidentified aromatic byproducts. The β-orientation of the bridge CH_2 in **27** was indicated by its NOESY spectrum, which revealed cross-peaks between the doublet at δ 5.83 due to the anomeric proton of the furanoside ring and the doublet due to one of the bridge CH_2 protons at δ 2.62 (Fig. 3). The alternative structure with an α-orientation of the bridge CH_2 is not expected to give rise to an observable NOE between the two protons. Recently the cycloaddition has been carried out by using the corresponding *N*-methyl nitrone **9g** in order to avoid the formation of aromatic impurities, which complicated the product profile of the cycloaddition of **9b**. Treatment of **8b** with MeNHOH·HCl in aqueous ethanol in the presence of $NaHCO_3$ resulted in the formation of the oxepane **27a** (38%), which is the *N*-methyl analog of **27**, along with a mixture (30%) of three pyran derivatives, **27b-d** (Table 2). The ^{1}H NMR spectral behavior of **27a** was found to be closely similar to that of **27**, and the bridge methylene was assigned β-orientation. However, the stereochemistry of the pyran derivatives **27b-d** remained unestablished, because the individual compounds could not be separated from the mixture. Cycloaddition of the furanoside nitrone **9c** furnished exclusively the oxepane derivative **28** in 73% yield. The result was also in agreement with the observations of Shing et al. who reported the exclusive formation of the *N*-methyl analog of **28** from the *N*-methyl analog of the nitrone **9c**.[12] An observed NOE between the doublet of doublets at δ 3.81 due to 3-H and the doublet at δ 2.11 due to one of the bridge methylene protons established the α-orientation of the bridge methylene in **28** (Fig. 3). A similar stereochemical outcome was observed with pyranoside nitrones in which the *O*-allyl and the nitrone moieties are trans to each other.[4] The change of orientation of the bridge methylene from β in **25** and **27** to α in **28** indicated that the facility of approach of the nitrone moiety in the cycloadditions of **9a**, **9b** and **9c** is determined by the orientation of the *O*-allyl moiety. In contrast to the behavior of the above three nitrones, the nitrone **9d**, which is the 3-C epimer of **9b**, gave exclusively the pyran derivative **29** in 75% yield. The stereochemistry of the isoxazolidine ring fusion in **29** was established by the analysis of the relevant ^{1}H coupling constants in **30** which was obtained by the cleavage of the isoxazolidine ring in **29** by $LiAlH_4$ followed by acetylation. The coupling constants $J_{3,4}$=12.3 Hz, $J_{4,5}$=4.0 Hz, $J_{5,6A}$=3.0 Hz, and $J_{5,6B}$=2.8 Hz are only compatible with the structure **30**, which also leads to the assigned stereochemistry of 4-C and 5-C in **29**.



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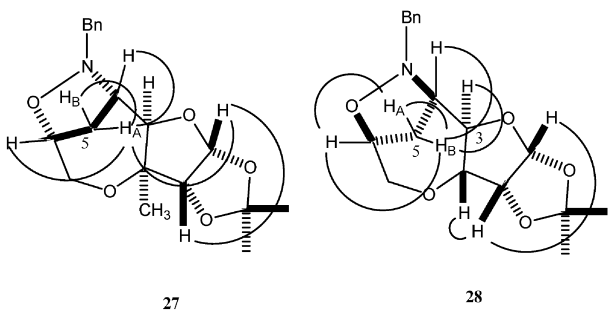
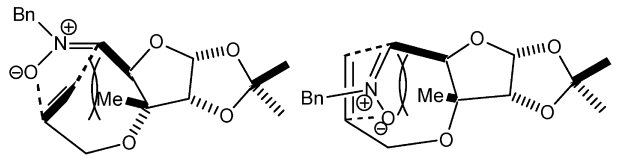
The results cited in Table 2 point to the fact that availability of oxepane skeleton is more probable from the furanoside-5-aldehyde nitrones **9a-d** than from the acyclic nitrones **6a-d**. Although a straightforward explanation of this difference is not possible, it is apparent that the difference in the structural nature of the two types of nitrones is responsible for the observed difference in behavior. The acyclic nitrones **6a-d** have a flexible backbone, whereas **9a-d** have a rather rigid backbone incorporating the 1,2-isopropylidene furanoside ring. Recently, molecular mechanics calculations have been used to explain the regioselectivity of similar *O*-allylcarbohydrate nitrone cycloadditions.[9a] So, the minimum-energy conformations of all the probable products from **9a-d** were calculated. In the cases of the cycloaddition of **9a**, **9c** and **9d**, formation of the major products was in agreement with the results of the calculations, because the calculated energies of the major products were lower than those of the other products. The oxepanes **25** (−34.3 kcal/mol), **28** (−30.5 kcal/ mol) and the pyran **29** (−25.8 kcal/mol) were found to be 0.4–16.3 kcal/mol lower in energy than the other probable products. In the case of the nitrone **9b** or **9g**, the energy values were found to be inconsistent with the observed results, although the formation of more than one pyran was indicated by nearly identical energies of three probable pyran structures. The validity of the computed structures was checked in one case by calculating the coupling constant $J_{4,5}$ in the minimum energy conformation of **29**, and the calculated value 9.9 Hz agreed well with the observed value of 8.2 Hz. The proposed transition state structures **31a** and **31b** for the formation of probable oxepanes from **9d** point to substantial steric interaction between CH_3 and the methylene bridge in **31a** or the isoxazolidine ring in **31b**. The *Z*-nitrone-*S*-*cis* allyl ether pyran transition state **32** is, however, free from such interactions.

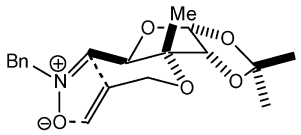


27 **28**

Figure 3. NOE in **27** and **28**.



31a 31b



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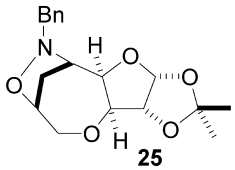
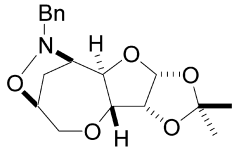
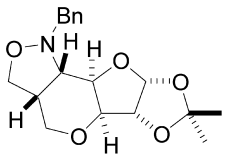
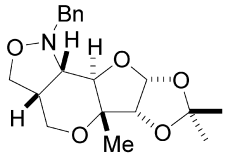
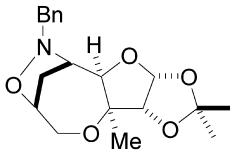
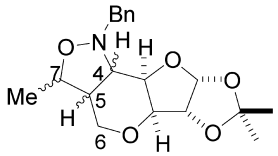
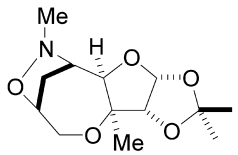
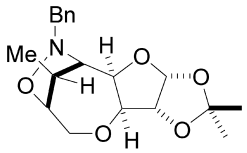
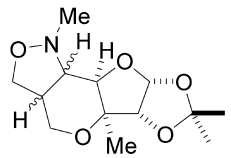
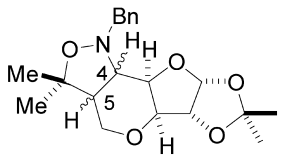
2.3. Influence of substitution at the allyl terminus on the regioselectivity

The above discussion on the dependence of 3-OACNC on 3-C stereochemistry and substitution as well as the structural nature of the carbohydrate framework of the nitrones clearly indicated the importance of steric interaction in the transition states of the cycloadditions. The involvement of this steric effect was also apparent in the behavior of nitrones **9e** and **9f** bearing substitutents at the allyl terminus, and the results of their cycloaddition are presented in Table 2. Unlike the nitrone **9a**, which gave the oxepane **25** as the preponderant product, the 3-*O*-*trans*-crotyl nitrone[30] **9e** gave the pyran derivatives **33** (17%) and **34** (34%) along with the oxepane **35** (11%) (Table 2). The

Table 2. 3-OACNC of furanoside-5-aldehyde nitrones

Nitrone[a]	Product	Yield (%)[b]	Nitrone[a]	Product	Yield (%)[b]
9a	 **25**	56	**9c**	 **28**	73
	 **26**	<5	**9d**	 **29**	75
9b	 **27**	50	**9e**	 **33** : Me, 4-H, 5-H - β **34** : Me, 4-H, 5-H - α	17, 34
9g	 38 **27a**	38		 **35**	11
	 **27b, 27c, 27d** (mix. of three pyrans)	30[c]	**9f**	 **36** : 4-H, 5-H - β **37** : 4-H - β, 5-H - α.	42, 28

[a] Nitrones except **9g** were generated by heating the respective aldehydes with *N*-benzyl hydroxylamine in benzene, and **9g** was prepared by using MeNHOH·HCl in aq. EtOH in the presence of $NaHCO_3$.
[b] Yields were based on chromatographically pure compounds.
[c] Combined yields of **27b-d** (13:12:5) based on ^{1}H NMR integration.

observation of a quartet at δ 3.09 in the ^{1}H NMR spectrum of **35** due to the bridge methine proton as well as a peak at δ 36.6 in the ^{13}C NMR spectrum due to the bridge methine carbon atom was a fair indication of the oxepane skeleton in **35**. The bridge -CH(CH$_3$)- in **35** was assigned the β-orientation in analogy with **25**. The structures of the pyrans **33** and **34** were based on the analysis of the $J_{4,5}$, $J_{5,6'}$, and $J_{5,6''}$. Any *trans*-fused structure was ruled out, because $J_{4,5}$ for either of these compounds was less than expected for *trans*-diaxial vicinal protons. The *trans* relationship of 5-H and 7-H in **33** and **34** was the stereochemical consequence of the dipolar cycloaddition, in which the *trans* geometry of the crotyl system is retained in the products. The comparison of yields of **35** and **25** from **9e** and **9a**, respectively, suggested increased steric crowding in the oxepane T. S. for **35**. The steric effect was expected to be more in the cycloaddition of **9f** having the dimethylallyl group. It was indeed the case, because a diastereomeric mixture (3:2) of the pyran derivatives **36** and **37** was exclusively obtained from this reaction. The presence of a *trans*-fused isoxazolidine ring in **37** was evident from its ^{1}H NMR spectrum, which exhibited a doublet of triplets due to 5-H with $J_{4,5}$=$J_{5,6A}$=11.3 Hz and $J_{5,6B}$=3.1 Hz. Recently the cycloadditions of the *N*-methyl analogs of **9e** and **9f** were reported.[31] In striking contrast to our observation, no oxepane was formed from the *N*-methyl analog of **9e**. The cycloaddition of the *N*-methyl analog of **9f**, however, furnished the *N*-methyl analogs of **36** and **37** in agreement with our results.[31] It has been demonstrated recently that the formation of oxepane skeleton is also discouraged when the allyl moiety is incorporated in a ring.[32] The 3-OACNC of the furanoside nitrones described above is expected to find application in the preferential synthesis of six and seven-membered cyclic ethers through the tuning of the regioselectivity by substitution at the allyl terminus.

2.4. Synthesis of enantiomeric oxepanes and pyrans

A comparison of the hexose nitrones **6** and the furanoside nitrones **9** revealed that the sequences 1C–2C–3C–4C in **6** and 5C–4C–3C–2C in **9** have a 'pseudoenantiomeric'[33] relationship with each other as exemplified by **6a/9a** in Figure 4. Consequently, if a particular ether ring system is formed from a set comprising a nitrone **6** and its pseudoenantiomeric counterpart **9** (i.e. both having identical R^1 and R^2 in Scheme 2), the domains specified by the sequences 1C–2C–3C–4C in the transition state of the cycloaddition of **6** and 5C–4C–3C–2C in that of **9** are pseudoenantiomeric. As a result, the new centers in the cyclic ethers formed after cycloaddition of **6** and **9** will also be pseudoenantiomerically related to each other. The results presented in the Tables 1 and 2 show that this pseudoenantiomeric relationship exists between **16/25** obtained from **6a/9a** and **22/29** from **6d/9d**. A practical utility of this phenomenon, which was earlier demonstrated[11,14] through the expedient conversion of some of the products to enantiomeric cyclic ether derivatives, is outlined in Schemes 4 and 5. The oxepanoisoxazolidine **16** on deacetylation with sodium in methanol gave the tetrahydroxy compound **15**. Oxidation of **15** with $NaIO_4$ to the aldehyde **38** followed by reduction with $NaBH_4$ to the diol **39** and subsequent acetylation afforded the diacetate **40** (Scheme 4). In a similar route the oxepanoisoxazolidine **25** was converted to the diacetate **45** (Scheme 4) through the sequence of reactions involving deprotection with aqueous H_2SO_4 to the diol **42** followed by oxidation with $NaIO_4$ to **43**, reduction with $NaBH_4$ to **44** and acetylation. The oxepanoisoxazolidine diacetates **40** and **45** were found to be enantiomeric as evident from their physical characteristics and spectral behavior. As the precursors **16** and **25** were both prepared from the common diisopropylidene derivative **4a**, the above conversions also constituted an enantiodivergent synthesis of **40** and **45** from **4a**. Scheme 5 shows the analogous conversions of the pyranoisoxazolidines **22** and **29** to the enantiomeric diacetates **49** and **53** by following identical routes described above for the oxepane derivatives. The degradative scheme also demonstrates the use of the isopropylidene furanoside moiety as a precursor of chiral, disubstituted two-carbon units.[34] It is worthy of mention that the enantiomeric progenitors in the above enantiodivergent syntheses are the hydroxyaldehydes **38/43** and **47/51**, which are potentially useful for generating other enantiomeric compounds. As examples, the oxepane derivatives **38** and **43** could be converted to the enantiomeric conjugated aldehydes **41** and **46** (Scheme 4), respectively, albeit in poor yields by dehydration procedures involving treatment with *p*-toluenesulfonic acid or *p*-toluenesulphonyl chloride in the presence of pyridine (Scheme 4). The presence of the conjugated aldehyde moieties makes these compounds potentially amenable to skeletal elaboration for the construction of other chiral ring systems.

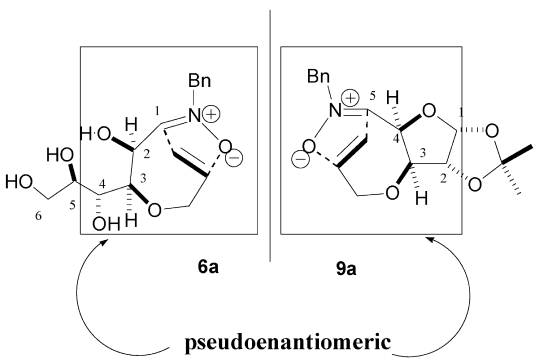
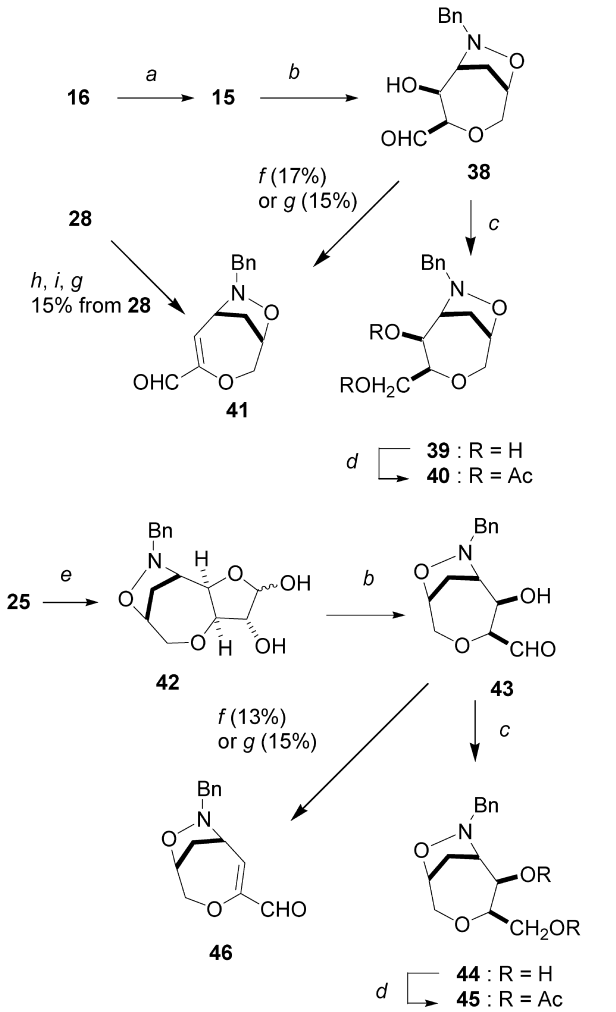


Figure 4. Pseudoenantiomerism of nitrones **6a** and **9a**.

Apart from the synthetic utility, the above degradative procedure also helped in the chemical intercorrelation of the cycloadducts. The assigned stereochemistry of the bridge methylene of **28** was confirmed by its correlation with **16**, when both **16** and **28** were found to give the aldehyde **41** (Scheme 4). Similarly, the formation of **46**, the enantiomer of **41**, from **25** led to the confirmation of the stereochemistry of the bridge methylene in **25**.

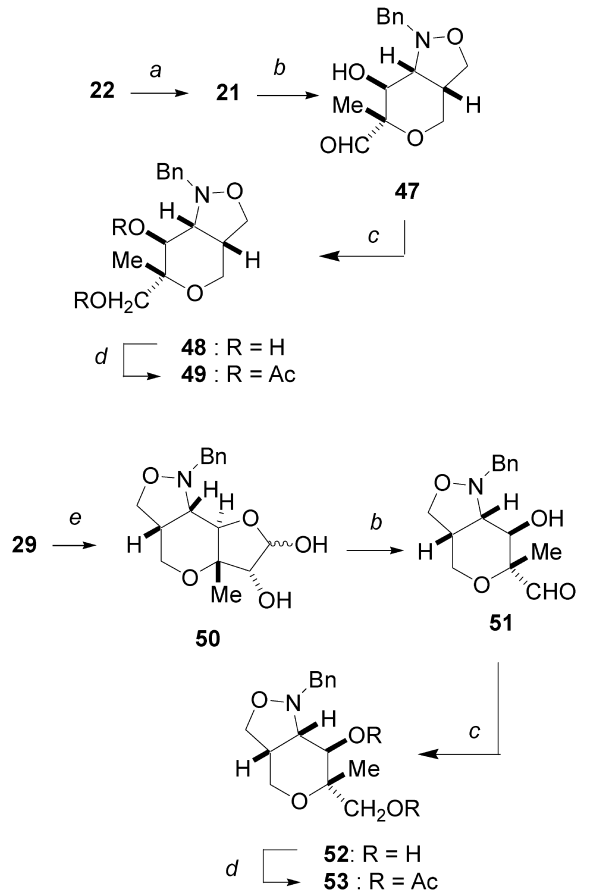
The isoxazolidine rings in **16**, **25** and **44** were cleaved by means of transfer hydrogenation[4] using 10% Pd–C in the presence of cyclohexene giving rise to **54**, **55** and **56**, respectively (Scheme 6). The tetrasubstituted oxepane **56** illustrates the synthetic potential of the 3-OACNC strategy by way of incorporating a three-carbon unit 5C–6C–7C derived from the allyl moiety as well two chiral centers (2-C and 3-C) derived from D-glucose, and two new chiral centers (4-C and 6-C) created in the cycloaddition process.



Scheme 4. *Reagents*: (*a*) Na, MeOH, 0–25°C, 80%. (*b*) $NaIO_4$, MeOH–H_2O, 25°C. (*c*) $NaBH_4$, EtOH, 0–25°C, 70% (for **39** from **15**), 62% (for **44** from **42**). (*d*) Ac_2O, pyridine, 25°C, 60% (for **40**), 56% (for **45**). (*e*) 4% H_2SO_4–CH_3CN-H_2O, 25°C, 80%. (*f*) TsOH, benzene, reflux. (*g*) TsCl, pyridine, 60°C. (*h*) 4% H_2SO_4–CH_3CN–H_2O, 25°C. (*i*) $NaIO_4$, MeOH–H_2O, 25°C.

2.5. Intramolecular oxime olefin cycloaddition (IOOC) of 3-*O*-allyl furanoside aldehyde oxime

Although in this study nitrones were generated by reaction of *N*-benzyl or *N*-methyl hydroxylamine and an aldehyde, it appeared worthwhile to investigate whether the intramolecular oxime olefin cycloaddition (IOOC)[35] could be performed on any of the carbohydrate derivatives described above, because involvement of NH-nitrones is well established in this reaction.[36] With this objective in view, the oxime **57**[37] derived from the aldehyde **8a** was heated in toluene in a sealed tube at 180°C for 5 h resulting in an intractable mixture. The same reaction was performed at 140°C and the ^1H NMR spectrum of the product did indicate the formation of cycloadducts, albeit in a very poor yield. However, cycloaddition performed at 120–130°C for an extended period of time (20 h) afforded a relatively cleaner mixture, benzoylation of which followed by repeated chromatography of the product yielded the oxepane **59** (30%) and the pyran **61** (15%), which are the *N*-benzoyl derivatives of the primary products **58** and **60**, respectively. The structures of **59** and **61** were established on the basis of

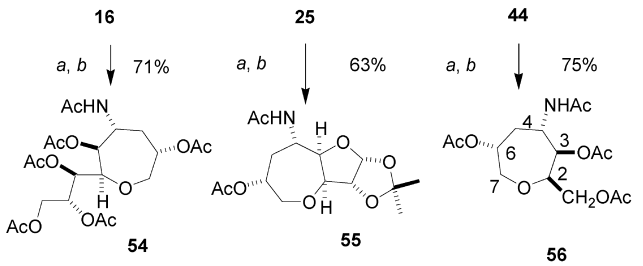


Scheme 5. *Reagents*: (*a*) Na, MeOH, 25°C, 75%. (*b*) $NaIO_4$, MeOH H_2O, 25°C. (*c*) $NaBH_4$, EtOH, 25°C, 47% (for **48** from **21**), 56% (for **52** from **50**). (*d*) Ac_2O, pyridine, 25°C, 61% (for **49**), 77% (for **53**). (*e*) 4% H_2SO_4–CH_3CN–H_2O, 25°C, 70%.

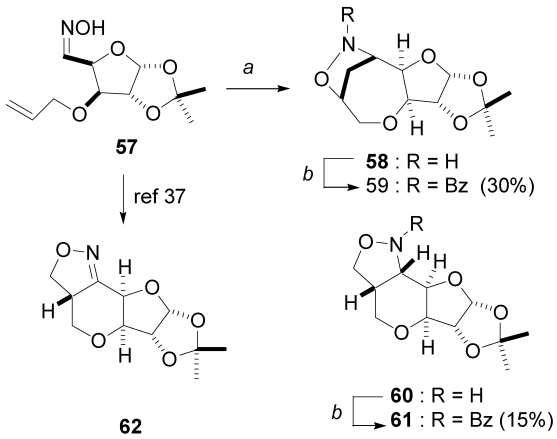
^1H and ^{13}C NMR spectral data, which had resemblance to those of the corresponding *N*-benzyl derivatives **25** and **26**. The result of the IOOC was significant, because the pyran skeleton was formed in a higher yield than that observed in the case of the cycloaddition of the corresponding *N*-benzyl nitrone **9a** (Scheme 7). Interestingly the oxime **57** can serve as the precursor for a pyran system simply by switching to intramolecular nitrile oxide cycloaddition, because the nitrile oxide generated from **57** was reported by us and others to give exclusively the pyranoisoxazoline **62**.[12,37]

3. Conclusion

3-*O*-Allyl carbohydrate nitrone cycloaddition (3-OACNC) has been established as an efficient and operationally simple



Scheme 6. *Reagents*: (*a*) Pd–C (10%), cyclohexene, alcohol, reflux. (*b*) Ac_2O, pyridine, 0–25°C.



Scheme 7. *Reagents*: (*a*) toluene, 120–130°C, sealed tube, 20 h. (*b*) PhCOCl, pyridine, 0–25°C.

method for the synthesis of chiral pyrans and oxepanes. It has been demonstrated in the work that the regioselectivity of the cycloaddition depends on (a) the skeletal nature of the carbohydrate backbone of the nitrone (b) substitution at 3-C (c) stereochemistry at 3-C (d) substitution at the allyl terminus of the *O*-allyl moiety. The utility of the cycloaddition lies in the easy access to complex oxepane and pyran ring systems with diverse substitutional and stereochemical patterns. In specific cases enantiomeric oxepanes and pyrans were synthesized from the same precursor. The regioselective features of the 3-OACNC will provide some guidelines, which will be useful for the future application of the cycloaddition methodology to synthesis of natural products incorporating oxepane and pyran skeletons. The *O*-allylcarbohydrate nitrone cycloaddition (OACNC) promises to be an important strategy for the synthesis of chiral cyclic ethers.[38–40] The emergence of the OACNC strategy for chiral cyclic ethers has led to the development of similar approaches for chiral cyclic amines, and several six- and seven-membered cyclic amines have been reported recently.[41,42]

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field stength. High resolution NMR spectra were recorded at the CAS Instrumentation Centre, Chemistry Department, Calcutta University. Elemental analyses were performed at the Regional Sophisticated Instrumentation Centre, Lucknow and Indian Association for the Cultivation of Science, Kolkata. Reactions were monitored by thin layer chromatography using Merck 60 F_{254} precoated silica gel plate (No. 1.05554). Organic extracts were dried over anhydrous sodium sulphate. For routine column chromatography 60–120 mesh silica gel (SRL, India) and for flash chromatography 230–400 mesh silica gel (Merck, grade 60) were used. Solvents were distilled and dried immediately prior to use. Unless otherwise mentioned petroleum ether refers to a fraction boiling between 60 and 80°C. Room temperature refers to 25°C.

4.2. Computational method

For all the compounds the conformational space was first scanned using molecular mechanics calculations with MM+ force field, using a sequence of dihedral angle driving (where necessary), molecular dynamics (simulated annealing) and optimization. Short listed low energy conformations were optimized with semiempirical PM3 parameterization. The neighborhoods of low energy conformations were scanned by large numbers of molecular dynamics and optimization cycles.

For TS determination, PM3 semiempirical method was used for all calculations. Two step linear search (from ≥4.90 Å C–C bond distance) was performed with interval of 0.003 Å (first step) until it reached 2.05 Å (approx.). Thereafter, a grid search with C–O bond distance, keeping the C–C bond distance fixed, was performed at 0.003 intervals, which located a change of sign in reaction gradient. Then refined line search at 0.001 Å intervals identified a tentative TS, the structure with the highest heat of formation. This was optimized using TS option and removing the C–C distance constraint. The output structure converging from the optimization was taken as the right TS. Finally TS was confirmed by obtaining only one negative frequency using force option of MOPAC and by vibration Multimedia Component using Review [a molecular visualization, Multimedia Component and analyser for Windows 3 by J.J. Gosper, 1996]. Search starting from TS, along with the eigenvector corresponding to the negative frequency, led on one side to reactants; on the other side, it led to the product.

4.3. General procedure for the preparation of 3-*O*-allyl carbohydrate derivatives

To a solution of the 1,2:5,6-diisopropylidene monosaccharide (1 mmol) and allyl bromide or crotyl bromide or prenyl bromide (1.5 mmol) in CH_2Cl_2 (10 mL) was added 50% aqueous NaOH solution (10 mL) and the mixture was stirred vigorously. Tetrabutylammonium bromide (0.035 g, 0.1 mmol) was then added to this mixture and stirring was continued until the disappearance of the starting material as indicated by TLC. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried and evaporated. The crude product containing residual PTC was chromatographed over neutral Al_2O_3 using hexane–$CHCl_3$ (1:1) as eluent and the syrupy product was dried under vacuum. The products were essentially pure as evident from their ^{1}H NMR spectra. **4a** was prepared by literature procedure.[43] Reaction time, yield and spectral data of **4b-f** are given separately for respective compounds.

4.3.1. 1,2:5,6-Di-*O*-isopropylidene-3-*C*-methyl-3-*O*-allyl-α-D-glucofuranose (4b). 16 h; 91%; $[\alpha]_D^{25}$=(6.3 (*c* 1.05, $CHCl_3$); MS (EI) *m/z* 314 (M^+), 299 (M^+-15); IR (neat) ν 1646 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.36 (s, 3H), 1.44 (s, 6H), 1.52 (s, 3H), 3.88–4.44 (m, 7H), 5.04–5.40 (m, 2H), 5.72–6.08 (m, 1H), 5.84 (d, *J*=4 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (CH_3), 25.2 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 63.9 (CH_2), 66.9 (CH_2), 72.8 (CH), 83.2 (CH), 83.9 (q), 84.4 (CH), 104.6 (CH), 108.5 (q), 111.7 (q), 115.3 (CH_2), 134.9 (CH).

4.3.2. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-allyl-α-D-allofuranose (4c). 2 h; 95%; $[\alpha]_D^{25}$=+118.2 (*c* 0.29, $CHCl_3$); MS (EI) *m/z*300 (M^+), 285 (M^+-15); IR (neat) ν 1645 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.40 (br s, 6H), 1.48 (s, 3H), 1.60 (s, 3H), 3.48–4.52 (m, 7H), 4.64 (t, *J*=4 Hz, 1H), 5.16–5.48 (m, 2H), 5.76–6.24 (m, 1H), 5.80 (d, *J*=4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7 (CH_3), 25.8 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 64.6 (CH_2), 71.0 (CH_2), 74.4 (CH), 77.2 (CH), 77.4 (CH), 77.5 (CH), 103.3 (CH), 109.1 (q), 112.3 (q), 117.4 (CH_2), 134.2 (CH).

4.3.3. 1,2:5,6-Di-*O*-isopropylidene-3-*C*-methyl-3-*O*-allyl-α-D-allofuranose (4d). 16 h; 90%; $[\alpha]_D^{25}$=+61.5 (*c* 0.24, $CHCl_3$); MS (EI) *m/z*314 (M^+), 299 (M^+-15); IR (neat) ν 1645 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.36 (br s, 6H), 1.44 (s, 3H), 1.56 (s, 3H), 3.96–4.20 (m, 6H), 4.24 (d, *J*=4 Hz, 1H), 5.08–5.40 (m, 2H), 5.70 (d, *J*=4 Hz, 1H), 5.76–6.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (CH_3), 25.3 (CH_3), 26.5 (2×CH_3), 26.9 (CH_3), 65.4 (CH_2), 67.0 (CH_2), 73.6 (CH), 80.9 (CH), 82.0 (q), 84.0 (CH), 103.6 (CH), 109.1 (q), 112.8 (q), 115.6 (CH_2), 135.4 (CH).

4.3.4. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-crotyl-α-D-glucofuranose (4e). 2 h; 95%; $[\alpha]_D^{25}$=−26.3 (*c* 1.25, $CHCl_3$); MS (EI) *m/z* 315 (M^++1), 299 (M^+-15); IR (neat) ν 1672 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.52 (s, 3H), 1.64–1.76 (m, 3H), 3.96–4.44 (m, 7H), 4.56 (d, *J*=4 Hz, 1H), 5.44–5.84 (m, 2H), 5.92 (d, *J*=4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7 (CH_3), 25.3 (CH_3), 26.1 (CH_3), 26.69 (CH_3), 26.74 (CH_3), 65.8 (CH_2), 67.2 (CH_2), 72.4 (CH), 80.9 (CH), 81.1 (CH), 82.8 (CH), 105.1 (CH), 108.8 (q), 111.6 (q), 126.9 (CH), 129.8 (CH).

4.3.5. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-prenyl-α-D-glucofuranose (4f). 2 h; 90%; $[\alpha]_D^{25}$=−22.6 (*c* 1.18, $CHCl_3$); MS (EI) *m/z* 328 (M^+), 313 (M^+-15); IR (neat) ν 1674 cm^{-1}; ^1H NMR (100 MHz) δ 1.28 (s, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 3.90 (d, *J*=2 Hz, 1H), 3.96–4.40 (m, 6H), 4.52 (d, *J*=4 Hz, 1H), 5.36 (m, 1H), 5.90 (d, *J*=4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7 (CH_3), 25.1 (CH_3), 25.5 (CH_3), 25.9 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 66.7 (CH_2), 67.0 (CH_2), 72.2 (CH), 80.6 (CH), 81.0 (CH), 82.7 (CH), 105.0 (CH), 108.5 (q), 111.3 (q), 120.4 (CH), 137.3 (q).

4.4. General procedure for the OACNC of 3-*O*-allyl hexoses

A mixture of the 3-*O*-allyldiisopropylidene carbohydrate derivative (3 mmol) and 4% aqueous H_2SO_4 (20 mL) was stirred at room temperature for 18 h. The resulting solution was then stirred with $CaCO_3$ (2 g) for 2 h. The reaction mixture was filtered and the residue was repeatedly washed with methanol. The combined filtrate and washings were evaporated under reduced pressure. The residual syrupy material was treated with a minimum volume of water and filtered in order to remove some insoluble material. The residue was washed with methanol and the combined filtrate and washings was concentrated to give the 3-*O*-allyl pyranose derivative as syrup. A mixture of this material and BnNHOH (0.39 g, 3.2 mmol) in the appropriate solvent (10 mL; ethanol for **5a**,**5c** and CF_3CH_2OH for **5b** and **5d**) was stirred at 25°C for 30 min and then heated under reflux until the TLC of the reaction mixture indicated the disappearance of the hexose. The residue obtained after concentrating and drying the mixture was dissolved in pyridine (5 mL), and acetic anhydride (4 mL, 0.042 mol) was added at 0°C. The reaction mixture was kept at room temperature for 14 h. The solution was poured into ice-water (25 mL), extracted with $CHCl_3$, washed with water and dried. After removal of solvent, the residual syrup was purified by column chromatography over silica gel using the eluent mentioned below for individual isoxazolidine tetra-acetate derivatives.

4.4.1. (3*R*,4*S*,5*R*,8*S*)-4-Acetoxy-2-aza-2-benzyl-1,6-dioxa-5-[(1*S*,2*R*)-1,2,3-triacetoxy]propylbicyclo[4.2.1]-nonane (16). On elution with $CHCl_3$–CH_3OH (99:1) **16** (45–55%) was obtained as a sticky liquid, which solidified on standing. Recrystallization from ether gave the oxepanoisoxazolidine **16** as white needles, mp 165–166°C; $[\alpha]_D$=(108 (*c* 0.45, $CHCl_3$); MS (CI) *m/z* 494 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.10 (s, 3H), 2.10 (m, 1H), 2.50 (d, *J*=12 Hz, 1H), 3.45 (d, *J*=14 Hz, 1H), 3.57 (dd, *J*=14, 4 Hz, 1H), 3.65 (m, 1H), 3.78 (d, *J*=14 Hz, 1H), 3.92 (d, *J*=14 Hz, 1H), 4.00 (d, *J*=8 Hz, 1H), 4.11 (dd, *J*=12 Hz, 1H), 4.23 (dd, *J*=12, 6 Hz, 1H), 4.51 (br d, *J*=8 Hz, 1H), 4.92 (d, *J*=4 Hz, 1H), 4.97 (m, 1H), 5.28 (dd, *J*=8, 4 Hz, 1H),7.2–7.3 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.6 (q), 20.9 (q), 27.7 (t), 61.0 (t), 62.7 (t), 63.1 (d), 69.5 (d), 71.8 (d), 72.4 (d), 73.1 (t), 74.8 (d), 78.9 (d), 127.5 (d), 128.3 (d), 128.8 (d), 136.7 (s), 169.6 (s), 169.8 (s), 170.3 (s), 170.5 (s). Anal. calcd for $C_{24}H_{31}NO_{10}$: C, 58.41; H, 6.33; N, 2.84. Found: C, 58.63; H, 6.02; N, 3.09.

4.4.2. (3a*S*,6*R*,7*S*,7a*R*)-7-Acetoxy-1-benzyl-6-methyl-6-[(1*S*,2*R*)-1,2,3-triacetoxy]propyl-1,3,3a,6,7,7a-hexahydro-4*H*-pyrano[4,5-*c*]isoxazole (18a) and (3a*R*,6*R*,7*S*,7a*R*)-7-acetoxy-1-benzyl-6-methyl-6-[(1*S*,2*R*)-1,2,3-triacetoxy]propyl-1,3,3a,6,7,7a-hexahydro-4*H*-pyrano-[4,5-*c*]isoxazole (18b). The crude product was chromatographed over silica gel using EtOAc–petroleum ether (1:4) as eluent to give **18a** and **18b** as a 1:1 mixture (57%) of diastereomers. Attempted separation of the two isomers by flash chromatography resulted in two samples, which were enriched in one isomer or the other. Only the ^1H NMR signals, which could be assigned to the respective diastereomers are cited.

Compound **18a**. MS (EI): *m/z* 507 (M+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H), 2.16 (s, 3H), 3.02 (m, 1H), 3.23 (dd, *J*=4.0, 9.5 Hz, 1H), 3.45 (t, *J*=7.8, 8.0 Hz,1 H), 3.73 (dd, *J*=7, 11 Hz, 1H), 3.82 (d, *J*=11 Hz, 1H), 3.96 - 4.05 (m, 3H), 4.42 (dd, *J*=12.4, 2.5 Hz, 1H), 5.22 (m, 1H), 5.22 (d, *J*=4 Hz, 1H), 5.61 (d, *J*=6.2 Hz, 1H), 7.20–7.40 (m, 5H).

Compound **18b**. ^1H NMR (300 MHz; $CDCl_3$) δ 1.38 (s, 3H), 1.63 (s, 3), 1.97 (s, 3H), 1.98 (s, 3H), 2.02 (s, 3H), 3.22 (m, 1H), 3.29 (t, *J*=8.4 Hz, 1H), 3.58 (dd, *J*=7.8, 12.3 Hz, 1H), 3.72 (dd, *J*=4.7, 8.3 Hz, 1H), 3.82 (d, *J*=12.9 Hz, 1H), 4.19 (t, *J*=8.3 Hz, 1H), 4.52 (dd, *J*=12.1, 2.1 Hz, 1H), 4.98 (d,

J=8.4 Hz, 1H), 5.25 (m, 1H), 5.30 (m, 1H), 5.61 (d, J=6.2 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$, contains additional peaks due to the other isomer) δ 20.4, 20.6, 21.1, 41.0, 41.6, 60.0, 60.7, 61.3, 61.6, 62.1, 62.5, 62.6, 64.1, 67.9, 68.1, 69.7, 70.6, 70.8, 70.9, 72.6, 73.3, 75.3, 76.7, 127.1, 128.1, 128.5, 128.8, 137.2, 169.4, 169.9, 172.3.

4.4.3. (3a*S*,6*S*,7*S*,7a*R*)-7-Acetoxy-1-benzyl-6-[(1*S*,2*R*)-1,2,3-triacetoxy]propyl-1,3,3a,6,7,7a-hexahydro-4*H*-pyrano[4,5-*c*]isoxazole (20). The crude product was chromatographed over silica gel using EtOAc–petroleum ether (1:1) as eluent to afford **20** (80%) as a viscous oil, which was recrystallized from ether, mp 120–121°C, $[\alpha]_D$=−25 (c 0.8, $CHCl_3$); MS (EI) m/z 493 (M^+); IR (KBr) 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.98 (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 3.02 (m, 1H), 3.16 (t, J=7.4 Hz, 1H), 3.43 (dd, J=3.3, 9.3 Hz, 1H), 3.71 (dd, J=9.0, 3.3 Hz, 1H), 3.73–3.75 (m, 2H), 4.08 (m, 2H), 4.16 (dd, J=12.3, 6.2 Hz, 1H), 4.28 (dd, J=9.3, 7.6 Hz, 1H), 4.37 (dd, J=12.3, 2.4 Hz, 1H), 4.98 (dd, J=9.5, 7.5 Hz, 1H), 5.25 (dd, J=6.4, 3.3 Hz, 1H), 5.34 (m, 1H), 7.25–7.36 (m, 5H). ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.4 (q), 20.6 (q), 39.9 (d), 59.7 (t), 62.0 (t), 64.9 (t), 65.8 (d), 67.5 (d), 68.6 (t), 69.3 (d), 69.7 (d), 77.6 (d), 127.4 (d), 128.1 (d), 128.7 (d), 136.5 (s), 169.1 (s), 169.3 (s), 169.4 (s), 170.4 (s). Anal. calcd for $C_{24}H_{31}NO_{10}$: C, 58.35; H, 6.34. Found: C, 58.55; H, 6.29.

4.4.4. (3a*S*,6*S*,7*S*,7a*R*)-7-Acetoxy-1-benzyl-6-methyl-6-[(1*S*,2*R*)-1,2,3-triacetoxy]propyl-1,3,3a,6,7,7a-hexahydro-4*H*-pyrano[4,5-*c*]isoxazole (22). The crude product was chromatographed over silica gel using EtOAc–petroleum ether (2:3) as eluent to afford **22** (60%) which was recrystallized from ether- petroleum ether. mp 123–124°C, $[\alpha]_D$=−2.1 (c 4.25, $CHCl_3$); IR (KBr) 1741 cm^{-1}; MS (EI) m/z 507 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 3.01 (m, 1H), 3.18 (dd, J=8.2, 7.6 Hz, 1H), 3.73 (d, J=12.8 Hz, 1H), 3.78–3.90 (m, 3H), 4.05–4.11 (m, 2H), 4.31 (dd, J=9.6, 7.6 Hz, 1H), 4.54 (dd, J=12.3, 2.5 Hz, 1H), 5.17 (d, J=8.4 Hz, 1H), 5.23 (d, J=4.8 Hz, 1H), 5.49 (m, 1H), 7.23–7.36 (m, 5H). ^{13}C NMR (25 MHz, $CDCl_3$) δ 14.2 (q), 20.3 (q), 20.4 (q), 20.6 (q), 39.3 (d), 58.5 (t), 60.0 (t), 62.5 (t), 63.2 (d), 68.1 (d), 69.0 (t), 69.6 (d), 73.3 (d), 76.4 (s), 127.2 (d), 128.2 (d), 128.7 (d), 136.7 (s), 168.9 (s), 169.5 (s), 170.3 (s). Anal. calcd for $C_{25}H_{33}NO_{10}$: C, 59.15; H, 6.56; N, 2.76. Found: C, 59.25; H, 6.45; N, 2.59.

4.5. General procedure for the OACNC of 3-*O*-allylfuranoside-5-aldehydes

A solution of the 3-*O*-allyl diisopropylidene derivatives (3 mL) in aqueous AcOH (75%, 20 mL) was stirred for 14 h at 25°C. The reaction mixture was then evaporated and the residue was coevaporated with dry toluene. The oil thus obtained was chromatographed over silica gel using EtOAc as the eluent and the diol **7** obtained as a syrupy liquid was dried under vacuum and used for the next step without any further purification.

Compound **7b**. MS (EI) m/z 274 (M^+), 259; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 3.80–4.10 (m, 6H), 4.42 (d, J=4 Hz, 1H), 5.12–5.38 (m, 2H), 5.72–6.10 (m, 2H). *Compound* **7c**. MS (EI) m/z 245 (M^+-15); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.56 (s, 3H), 3.68–4.36 (m, 7H), 4.64 (t, 1H), 5.20–5.40 (m, 2H), 5.82 (d, J=4 Hz, 1H), 5.84–6.19 (m, 1H). *Compound* **7d**. MS (EI) m/z 275 (M^++1), 259; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 6H), 1.56 (s, 3H), 3.56–4.04 (m, 5H), 4.13 (d, J=6 Hz, 1H), 4.30 (d, J=4 Hz, 1H), 5.12–5.36 (m, 2H), 5.70 (d, J=4 Hz, 1H), 5.78–6.16 (m, 1H). *Compound* **7e**. MS (EI) m/z 273 (M^+-1); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.48 (s, 3H), 1.72 (d, J=6 Hz, 3H), 2.04 (bm, 1H), 2.68 (d, J=6 Hz, 1H), 3.60–4.36 (m, 7H), 4.52 (d, J=4 Hz, 1H), 5.68 (m, 2H), 5.92 (d, J=4 Hz, 1H). *Compound* **7f**. MS (EI) m/z 288 (M^+), 287, 273; ^{1}H NMR (100 MHz, $CDCl_3$); δ 1.32 (s, 3H), 1.48 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 3.68–4.20 (m, 7H), 4.60 (d, J=4 Hz, 1H), 5.40 (m, 1H), 6.00 (d, J=4 Hz, 1H).

To a solution of the above diol (1 mmol) in CH_3OH (10 mL) was added dropwise at 0°C a solution of $NaIO_4$ (1.2 mmol) in water (10 mL). The solution was allowed to warm upto 25°C and stirring was continued for 2 h. After filtration of the reaction mixture, the filtrate was concentrated. Extraction with $CHCl_3$ and evaporation of the solvent afforded the aldehyde, which was used immediately without further purification. *Compound* **8a**. IR (neat)1738, 1643 cm^{-1}. *Compound* **8b**. IR (neat) 1735, 1646 cm^{-1}. *Compound* **8c**. IR (neat) 1738,1645 cm^{-1}. *Compound* **8d**. IR (neat) 1738,1646 cm^{-1}. **8e**. IR (neat) 1741 cm^{-1}. *Compound* **8f**. IR (neat) 1730 cm^{-1}.

A solution of the crude aldehyde (1 mmol) and BnNHOH (0.15 g, 1.2 mmol) in benzene (6 mL) was stirred in the presence of 3 Å molecular sieves (1 g) at 25°C for 1 h, and then heated at reflux until the TLC of the reaction mixture indicated the disappearance of the aldehyde. After cooling down to 25°C, the reaction mixture was filtered and washed with benzene. The combined filtrate and the washings were evaporated to afford the crude product, which was purified by column chromatography using eluents cited below for individual isoxazolidines. Generation of **9g** is described below in the procedure for **27a**-**d**.

4.5.1. (2a*S*,2b*R*,4*R*,5*R*,5a*S*,7a*R*)-2-Benzyl-2b,4,5,5a-tetrahydro-2-aza-1,6-dioxa-4,5-isopropylidenedioxyfuro-[2′,3′:4,5]bicyclo[4.2.1]nonane (25) and (3a*R*,5a*S*,6*R*,7*R*,8a*R*,8b*S*)-1-benzyl-1,3,3a,5a,6,7,8a,8b-octahydro-6,7-isopropylidenedioxy-4*H*-furo[2′,3′:3,2]pyrano[4,5-*c*]isoxazole (26). Elution with $CHCl_3$ gave **25** (56%) as a white solid, which was crystallized from $CHCl_3$–petroleum ether as white flakes, mp 126–127°C; $[\alpha]_D^{28}$=−100.8 (c 1.0, $CHCl_3$); MS (EI) m/z 333 (M^+), 160, 132, 123, 91, 69; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.46 (s, 3H), 2.34 (m, 1H), 2.64 (d, J=12 Hz, 1H), 3.56–3.84 (m, 3H), 3.70 (d, J=12 Hz, 1H), 4.08 (brs, 1H), 4.12 (d, J=12 Hz, 1H), 4.42 (d, J=4 Hz, 1H), 4.62 (br d, J=10 Hz, 1H), 5.86 (d, J=4 Hz,1H), 7.32 (br s, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 25.9 (q), 26.5 (q), 26.9 (t), 62.0 (t), 62.5 (d), 72.3 (t), 78.3 (d), 79.5 (d), 82.3 (d), 84.4 (d), 104.1 (d), 111.5 (s), 127.5 (d), 128.4 (d), 129.0 (d), 136.7 (s). Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.96; N, 4.21. Found: C, 64.82; H, 7.17; N, 4.22.

The mother liquor obtained after crystallization of **25** was concentrated and chromatographed repeatedly over silica

gel ($CHCl_3$–petroleum ether) giving a mixture enriched in **26** (<5%) as a sticky material, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.47 (s, 3H), 2.85 (m, 1H), 3.31 (d, *J*=6.3 Hz, 1H), 3.49–3.63 (m, 2H), 3.79 (dd, *J*=11.6, 6.3 Hz, 1H), 3.87 (s, 1H), 4.01 (s, 1H), 4.03–4.13 (m, 3H), 4.51 (d, *J*=3.6 Hz, 1H), 5.86 (d, *J*=3.6 Hz, 1H), 7.25–7.42 (m, 5H). Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.96. Found: C, 64.57; H, 6.92.

4.5.2. (2a*S*,2b*R*,4*R*,5*R*,5a*S*,7a*R*)-2-Benzyl-5a-methyl-2b,4,5,5a-tetrahydro-2-aza-1,6-dioxa-4,5-isopropylidenedioxyfuro[2′,3′:4,5]bicyclo[4.2.1]nonane (27). Elution with EtOAc–petroleum ether (1:4) afforded **27** (50%), which was crystallized from petroleum ether (40–60°C), mp 80–81°C. $[\alpha]_D^{25}=-66.8$ (*c* 0.5, $CHCl_3$); MS (EI) *m*/*z* 347 (M^+), 332; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.48 (s, 3H), 1.56 (s, 3H), 2.20 (ddd, *J*=12.3, 8.5, 6.8 Hz, 1H), 2.62 (d, *J*=12.3 Hz, 1H), 3.69 (dd, *J*=6.8, 4, 5 Hz, 1H), 4.54 (dd, *J*=8.5, 3.5 Hz, 1H) 3.44 (dd, *J*=13.6, 3.6 Hz, 1H), 3.76 (d, *J*=13.0 Hz, 1H), 3.85 (d, *J*=13.7 Hz, 1H), 3.89 (d, *J*=4.9 Hz, 1H), 4.06 (d, 1H), 4.13 (d, *J*=3.6 Hz, 1H), 5.83 (d, *J*=3.6 Hz, 1H), 7.25–7.42 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 12.8 (q), 26.3 (q), 26.6 (t), 27.0 (q), 63.1 (t), 63.4 (d), 68.0 (t), 78.9 (d), 81.2 (d), 85.2 (s), 88.1 (d), 103.6 (d), 111.6 (s), 128.2 (d), 128.6 (d), 129.5 (d), 137.1 (s). Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.66; H, 7.26; N, 4.04. Found: C, 65.51; H, 7.24; N, 4.00.

4.5.3. (2a*S*,2b*R*,4*R*,5*R*,5a*S*,7a*R*)-2-Methyl-5a-methyl-2b,4,5,5a-tetrahydro-2-aza-1,6-dioxa-4,5-isopropylidenedioxyfuro[2′, 3′:4,5]bicyclo[4.2.1]nonane (27a), (3a*R*/*S*,5a*S*,6*R*,7*R*,8a*R*,8b*R*/*S*)-1-methyl-5a-methyl-1,3,3a,5a,6,7,8a,8b-octahydro-6,7-isopropylidenedioxy-4*H*-furo[2′,3′:3,2]pyrano[4,5-*c*]isoxazole (27b-d). A mixture of the aldehyde **8b** (1 mmol) prepared as described before, MeNHOH·HCl (1 mmol), $NaHCO_3$ (3.3 mmol) in EtOH–water (4:1) (10 mL) was heated under reflux for 15 h. After removal of solvent, the residue was extracted with CH_2Cl_2. The extract on removal of solvent gave an oily residue, which was chromatographed over silica gel (EtOAc–petroleum ether, 95:5–70:30) affording four different fractions (total yield, 0.440 g). Further chromatography of these fractions over silica gel using EtOAc–petroleum ether in varying proportions gave the following compounds, of which only a part of **27a** could be isolated as a solid. Yields are based on the ^{1}H NMR integration of characteristic peaks due to the anomeric protons of the furanoside ring or *N*–Me. The NMR data for pyran **27b-d** were obtained from the spectra of enriched samples. Pyrans **27b-d** could not be purified to a level suitable for optical rotation measurement or microanalysis.

Compound **27a**. White needles, mp 133–135°C; 38%; $[\alpha]_D^{20}=62.1$ (*c* 0.62, $CHCl_3$); MS (EI) *m*/*z* 271 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 2.26–2.36 (m, 1H), 2.63 (d, *J*=11.7 Hz, 1H), 2.65 (s, 3H). 3.44 (dd, *J*=3.8, 13.5 Hz, 1H), 3.53 (dd, *J*=4.5, 6.6 Hz, 1H), 3.82 (d, *J*=13.5 Hz, 1H), 3.99 (d, *J*=4.2 Hz, 1H), 4.13 (d, *J*=3.5 Hz, 1H), 4.52 (dd, *J*=3.4, 8.5 Hz, 1H), 5.84 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 12.8 (CH_3), 26.2 (CH_2), 26.5 (CH_3), 27.2 (CH_3), 47.3 (CH_3), 66.4 (CH), 68.1 (CH_2), 78.9 (CH), 81.2 (CH), 85.2 (quaternary), 88.3 (CH), 103.7 (CH), 111.9 (quaternary). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.54; H, 7.81; N, 5.16. Found: C, 57.31; H, 8.09; N, 5.35.

The NMR spectral analysis of the following compounds was performed on enriched fractions obtained during chromatography.

Compound **27b**. 13% (based on ^{1}H NMR integration); ^{1}H NMR (300 MHz, $CDCl_3$; peaks assignable to **27b** in the mixture): δ 1.33 (s, 3H), 1.45 (s, 3H), 1.52 (s, 3H), 2.73 (s, 3H), 2.84 (m, 1H), 2.98 (dd, *J*=5.8, 1.6 Hz, 1H), 3.52 (dd, *J*=8.1, 1.7 Hz, 1H), 3.65 (dd, *J*=11.8, 6.6 Hz, 1H), 3.77 (t, *J*=11.5 Hz, 1H), 3.82 (d, *J*=2.0 Hz, 1H), 4.03 (dd, *J*=8.1, 6.1 Hz, 1H), 4.23 (d, *J*=3.6 Hz, 1H), 5.86 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (25 MHz, $CDCl_3$; peaks assignable to **27b** in the mixture) δ 14.1 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 38.8 (CH), 44.8 (CH_3), 60.5 (CH_2), 66.0 (CH), 67.3 (CH_2), 75.5 (CH), 79.7 (q), 87.2 (CH), 104.3 (CH), 111.9 (q).

Compound **27c**. 12% (based on ^{1}H NMR integration); MS (EI) *m*/*z* 271 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.35 (s, 3H), 1.51 (s, 3H), 2.32 (d, *J*=10.7 Hz, 1H), 2.78 (s, 3H), 2.96 (m, 1H), 3.59 (m, 2H), 3.99 (m, 2H), 4.10 (s, 1H), 4.23 (d, *J*=3.5 Hz, 1H), 5.93 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 40.2 (CH), 44.0 (CH_3), 64.0 (CH_2), 65.9 (CH_2), 70.3 (CH), 75.9 (CH), 82.2 (q), 85.6 (CH), 106.0 (CH), 112.1 (q).

Compound **27d**. 5% (based on ^{1}H NMR integration); MS (EI) *m*/*z* 271 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.49 (s, 3H), 2.78 (s, 3H), 2.87 (m, 1H), 2.99–3.03 (m, 1H), 3.70 (dd, *J*=11.9, 5.5 Hz, 1H), 3.80 (dd, *J*=11.9, 6.3 Hz, 1H), 3.92 (dd, *J*=11.9, 5.5 Hz, 1H), 4.12 (t, *J*=7.8 Hz, 1H), 4.16 (d, *J*=4.2 Hz, 1H), 4.24 (d, *J*=3.6 Hz, 1H), 5.87 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): (15.5 (CH_3), 26.9 (CH_3), 38.8 (CH), 45.7 (CH_3), 60.8 (CH_2), 62.0 (CH), 68.8 (CH_2), 76.3 (CH), 81.0 (q), 86.7 (CH), 104.5 (CH), 112.1 (q).

4.5.4. (2a*R*,2b*R*,4*R*,5*R*,5a*R*,7a*S*)-2-Benzyl-2b,4,5,5a-tetrahydro-2-aza-1,6-dioxa-4,5-isopropylidenedioxyfuro-[2′,3′:4,5]bicyclo[4.2.1]nonane (28). Elution with EtOAc–petroleum ether (1:1) afforded **28** (73%), which was crystallized from diethyl ether–petroleum ether, mp 119–120°C. $[\alpha]_D^{25}=(98.8$ (*c* 1.0, $CHCl_3$); MS (EI) *m*/*z* 333 (M^+), 318; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.58 (s, 3H), 2.11 (d, *J*=12.7 Hz, 1H), 2.38 (ddd, *J*=12.7, 9.2, 7.4 Hz, 1H), 3.67 (dd, *J*=12.9, 2.9 Hz, 1H), 3.77 (dd, *J*=7.4, 2.3 Hz, 1H), 3.81 (dd, *J*=9.3, 2.4 Hz, 1H), 3.85 (d, *J*=12.8 Hz, 1H), 3.88 (d, *J*=13.5 Hz, 1H), 4.07 (d, *J*=13.5 Hz, 1H), 4.10 (dd, *J*=9.3, 4.2 Hz, 1H), 4.54 (dd, *J*=9.2, 2.9 Hz, 1H), 4.57 (d, *J*=3.6 Hz, 1H), 5.81 (d, *J*=3.5 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 25.8 (q), 26.2 (q), 29.0 (t), 60.7 (d), 62.6 (t), 72.8 (t), 77.2 (d), 77.6 (d), 78.0 (d), 78.2 (d), 104.3 (d), 112.7 (s), 127.2 (d), 128.2 (d), 128.7 (d), 136.7 (s). Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.90. Found: C, 64.70; H, 7.12.

4.5.5. (3a*R*,5a*R*,6*R*,7*R*,8a*R*,8b*S*)-1-Benzyl-5a-methyl-1,3,3a,5a,6,7,8a,8b-octahydro-6,7-isopropylidenedioxy-4*H*-furo[2′,3′:3,2]pyrano[4,5-*c*]isoxazole (29). Elution with EtOAc–petroleum ether (1:10) afforded **29** (75%), which was crystallized from diethyl ether–petroleum ether,

mp 142–143°C. $[\alpha]_D^{25}=-56.4$ (*c* 1.0, $CHCl_3$); MS (EI) *m/z* 347 (M^+), 332; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.36 (s, 3H), 1.67 (s, 3H), 3.16 (m, 1H), 3.28 (dd, *J*=8.2, 9.9 Hz, 1H), 3.51 (dd, *J*=7.0, 8.5 Hz, 1H), 3.93–4.01 (m, 3H), 3.95 (d, *J*=13.9 Hz, 1H), 4.13 (d, *J*=14.0 Hz, 1H), 4.14 (t, *J*=8.5 Hz, 1H), 4.23 (d, *J*=3.5 Hz, 1H), 4.28 (d, *J*=9.9 Hz, 1H), 5.76 (d, *J*=3.5 Hz, 1H), 7.26–7.43 (m, 5H). ^{13}C NMR (25 MHz, $CDCl_3$) δ 18.8 (q), 26.0 (q), 26.4 (q), 41.1 (d), 60.2 (t), 63.7 (d), 64.4 (t), 68.0 (t). 74.2 (d), 78.0 (s), 82.6 (d), 105.0 (d), 113.3 (s), 127.1 (d), 128.1 (d), 128.8 (d), 137.1 (s). Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.66; H, 7.26; N, 4.04. Found C, 65.74; H, 7.30; N, 4.25.

4.5.6. (2*R*,3*R*,3a*R*,6*R*,7*S*,7a*R*)-6-Acetoxymethyl-7-(*N*-acetyl-*N*-benzyl)amino-2,3,3a,6,7,7a-hexahydro-2,3-isopropylidenedioxy-3a-methyl-5*H*-furo[3,2-*b*]pyran (30). To a suspension of $LiAlH_4$ (0.1 g, 2.6 mmol) in THF (10 mL), **29** (0.11 g, 0.3 mmol) was added in portions and the reaction mixture was heated to reflux for 24 h. After cooling to 0°C and dropwise addition of saturated ammonium chloride solution (5 mL) to destroy the excess $LiAlH_4$, the mixture was filtered and the filtrate was extracted with chloroform. Removal of solvent gave an oil, which was dissolved in pyridine (3 mL), and acetic anhydride (2 mL) was added at 0°C. The reaction mixture was allowed to warm upto room temperature and left overnight. Usual work up of the reaction mixture gave an oil, which was chromatographed over silica gel to yield a white solid. Recrystallization of the solid from diethyl ether–petroleum ether afforded **30** (0.07 g, 50%), mp 123–124°C. $[\alpha]_D^{25}=+12.4$ (*c* 0.55, $CHCl_3$); MS (EI) *m/z* 433 (M^+), 432, 418; IR (KBr) 2984, 2926, 1737, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.30 (s, 3H), 1.50 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.70 (m, 1H), 3.96 (dd, *J*=12, 3 Hz, 1H), 3.98 (d, *J*=12 Hz, 1H), 4.04 (dd, *J*=10.5, 9 Hz, 1H), 4.22 (dd, *J*=10.5, 3.5 Hz, 1H), 4.26 (d, *J*=3.5 Hz, 1H), 4.56 (d, *J*=17.4 Hz, 1H), 4.66 (d, *J*=17.4 Hz, 1H), 4.75 (dd, *J*=12.3, 4.0 Hz, 1H), 5.64 (d, *J*=3.5 Hz, 1H), 7.26–7.35 (m, 5H). ^{13}C NMR (25 MHz, $CDCl_3$) δ 15.4 (q), 20.7 (q), 23.0 (q), 25.9 (q), 26.2 (q), 38.6 (d), 50.7 (t), 55.1 (t), 61.6 (t), 63.4 (t), 70.8 (t), 80.2 (s), 82.5 (d), 104.1 (d), 113.3 (s), 126.4 (d), 127.0 (d), 128.4 (d), 137.4 (s), 170.4 (s), 172.7 (s). Anal. calcd for $C_{23}H_{31}NO_7$: C, 63.79; H, 7.22; N, 3.24. Found: C, 63.55; H, 7.31; N, 3.15.

4.5.7. (3*R*,3a*R*,5a*S*,6*R*,7*R*,8a*R*,8b*S*)-1-Benzyl-6, 7-isopropylidenedioxy-3-methyl-1,3,3a,5a,6,7,8a,8b-octahydro-4*H*-furo[2′,3′:3,2]pyrano[4,5-*c*]isoxazole (33), (3*S*,3a*S*,5a*S*,6*R*,7*R*,8a*R*,8b*R*)-1-benzyl-6,7-isopropylidenedioxy-3-methyl-1,3,3a,5a,6,7,8a,8b-octahydro-4*H*-furo[2′,3′:3,2]-pyrano[4,5-*c*]isoxazole (34), (2a*S*,2b*R*,4*R*,5*R*,5a*S*,7b*R*,8*R*)-2-benzyl-8-methyl-2b,4,5,5a-tetrahydro-4,5-isopropylidenedioxy-furo[2′,3′:4,5]-bicyclo[4.2.1]nonane (35). The crude product obtained after the usual procedure of cycloaddition using **9e** yielded after chromatography over silica gel (10–30% EtOAc–petroleum ether) the following compounds, each of which was observed to have other diastereomers as contaminants; hence optical rotations of the samples were not measured.

Compound **33**. Yield, 17%; sticky material; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J*=6.3 Hz, 1H), 1.29 (s, 3H), 1.38 (s, 3H), 2.44 (m, 1H), 3.30 (d, *J*=6.2 Hz, 1H), 3.53 (t, *J*=11.2 Hz, 1H), 3.74–3.82 (m, 3H), 4.00 (d, *J*=1.8 Hz, 1H), 4.04 (d, *J*=13.9 Hz, 1H), 4.13 (d, *J*=13.9 Hz, 1H), 4.50 (d, *J*=3.7 Hz, 1H), 5.85 (d, *J*=3.7 Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 26.3, 26.6, 45.4, 60.7, 63.2, 63.5, 73.9, 75.8, 78.9, 83.8, 104.7, 111.7, 127.6, 128.4, 129.4, 136.6.

Compound **34**. Yield 34%; sticky material; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.29 (d, *J*=6.0 Hz, 3H), 1.39 (s, 3H), 2.06 (m, 1H), 3.32 (dd, *J*=8.0, 5.1 Hz, 1H), 3.68 (dd, *J*=12.4, 4.1 Hz, 1H), 3.78–3.83 (m, 4H), 4.37 (d, *J*=12.6 Hz, 1H), 4.44 (d, *J*=3.7 Hz, 1H), 5.89 (d, *J*=3.7 Hz, 1H), 7.23–7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 26.1, 26.7, 45.2, 62.6 (2×C), 65.0, 73.2, 74.8, 77.2, 84.1, 104.3, 111.7, 127.5, 128.4, 128.8, 137.1. Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25. Found: C, 65.37; H, 7.03.

Compound **35**. Yield, 11%; sticky material; ^1H NMR (300 MHz) δ 1.29 (s, 3H), 1.31 (d, *J*=7.3 Hz, 3H), 1.42 (s, 3H), 3.09 (q, *J*=7.2 Hz, 1H), 3.37 (d, *J*=4.62 Hz, 1H), 3.54 (d, *J*=13.3 Hz, 1H), 3.80 (dd, *J*=13.3, 5.1 Hz, 1H), 3.88 (bd, *J*=3.2 Hz, 1H), 4.07 (d, *J*=12.9 Hz, 1H), 4.12 (bs, 1H), 4.20 (d, *J*=5.1 Hz, 1H), 4.37 (d, *J*=12.9 Hz, 1H), 4.41 (d, *J*=3.7 Hz, 1H), 5.87 (d, *J*=3.6 Hz, 1H), 7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 36.6 (CH), 63.4 (CH_2), 69.3 (CH), 73.7 (CH_2), 78.5 (CH), 83.2 (CH), 84.1 (CH), 85.1 (CH), 104.9 (CH), 111.7 (quaternary C), 127.5 (CH), 128.5 (CH), 128.8 (CH), 137.4 (quaternary C).

4.5.8. (3a*R*,5a*S*,6*R*,7*R*,8a*R*,8b*S*)-1-Benzyl-3,3-dimethyl-1,3,3a,5a,6,7,8a,8b-octahydro-4*H*-furo[2′,3′:3,2]pyrano-[4,5-*c*]isoxazole (36) and (3a*R*,5a*S*,6*R*,7*R*,8a*R*,8b*R*)-1-benzyl-3,3-dimethyl-1,3,3a,5a,6,7,8a,8b-octahydro-4*H*-furo[2′,3′:3,2]pyrano[4,5-*c*]isoxazole (37). The crude material obtained from **9f** was chromatographed over silica gel using EtOAc–petroleum ether (1:1) to afford mixture of two products (70%). The two products were purified by further chromatography over silica gel followed by fractional crystallization affording **36** and **37** (3:2) as two diastereomers.

Compound **36**. 42%, mp 108–109°C. $[\alpha]_D^{25}=-52.9$ (*c* 0.27, $CHCl_3$); MS (EI) *m/z* 361 (M^+), 346; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.27 (s, 3H), 1.31 (s, 6H), 2.42 (m, 1H), 3.58 (dd, *J*=11.5, 12.0 Hz, 1H), 3.65 (dd, *J*=5.5, <2.0 Hz, 1H), 3.66 (d, *J*=1.9 Hz, 1H), 3.80 (dd, *J*=12.0, 5.1 Hz, 1H), 3.93 (d, *J*=1.6 Hz, 1H), 4.09 (d, *J*=13.4 Hz, 1H), 4.24 (d, *J*=13.4 Hz, 1H), 4.47 (d, *J*=3.6 Hz, 1H), 5.81 (d, *J*=3.6 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 21.7 (q), 26.0 (q), 26.6 (q), 29.7 (q), 45.6 (d), 63.7 (d), 63.9 (t), 64.1 (t). 73.7 (d), 76.7 (d), 80.3 (d), 83.6 (d), 104.2 (d), 111.5 (s), 127.4 (d), 128.3 (d), 128.7 (d), 136.8 (s). Anal. calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.54; N, 3.88. Found: C, 66.59; H, 7.37; N, 3.98.

Compound **37**. 28%, mp 154–155°C. $[\alpha]_D^{25}=+56.6$ (*c* 0.28, $CHCl_3$); MS (EI) *m/z* 361 (M^+), 346; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.25 (s, 3H), 1.38 (s, 3H), 1.60 (s, 3H), 2.64 (dt, *J*=11.3, 3.1 Hz, 1H), 2.86 (dd, *J*=11.3, 6.0 Hz, 1H), 3.36 (dd, *J*=11.3, 10.7 Hz, 1H), 3.76 (br s, 1H), 3.86 (dd, *J*=6.0, 4.0 Hz, 1H), 3.94 (dd, *J*=10.7, 3.3 Hz, 1H),

3.94 (d, J=13.2 Hz, 1H), 4.31 (d, J=13.2 Hz, 1H), 4.40 (d, J=3.5 Hz, 1H), 5.90 (d, J=3.5 Hz, 1H), 7.19–7.43 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 24.6 (q), 26.0 (q), 26.4 (q), 27.7 (q), 47.3 (d), 62.8 (t), 66.4 (t). 68.2 (d), 74.4 (d), 78.4 (s), 82.3 (d), 86.9 (d), 106.1 (d), 111.4 (s), 127.3 (d), 128.1 (d), 129.1 (d), 135.8 (s). Anal. calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.54; N, 3.88. Found: C, 66.18; H, 7.62; N, 3.65.

4.5.9. (3*R*,4*S*,5*R*,8*S*)-4-Acetoxy-2-aza-2-benzyl-1,6-dioxa-5-acetoxymethyl-bicyclo[4.2.1]nonane (40). To methanol (20 mL), cooled in ice, sodium (0.300 g, 13 mmol) was added with stirring. After the dissolution of sodium was complete, a solution of **16** (0.542 g, 1.1 mmol) in methanol (5 mL) was added in portions with stirring at 0°C and the stirring was continued for a further 4 h at 25°C. After concentration of the reaction mixture, a saturated ammonium chloride solution (20 mL) was added to the residue and extracted with chloroform. The organic layer was dried and evaporated to afford the tetrahydroxyisoxazolidine **15** (0.286 g, 80%) as a viscous liquid which was used without purification for the next step. To the above material in methanol (10 mL) at 25°C was added dropwise a solution of $NaIO_4$ (0.43 g, 0.2 mol) in water (10 mL) with stirring and the stirring was continued for 2 h. The reaction mixture was then extracted with chloroform and dried. Removal of solvent afforded the hydroxyaldehyde **38** as a colorless viscous liquid, which was immediately used for the next step. To a solution of this material in ethanol (12 mL) was added $NaBH_4$ (0.076 g, 2 mmol) in portions with stirring at 0°C and the mixture was stirred at 25°C for 3 h. Aqueous AcOH (1:1) was added to the reaction mixture and the excess acid was neutralized with solid $NaHCO_3$. The mixture was extracted with $CHCl_3$ and dried. Removal of solvent gave the diol **39** (0.163 g, 70% from **15**) as a syrup, which was dissolved in pyridine (4 mL). To this solution was added acetic anhydride (3 mL, 32 mmol) at 0°C and the reaction mixture was allowed to warm up to 25°C and left overnight. The mixture was poured into ice-water, extracted with diethyl ether, and the organic layer was dried. Removal of solvent afforded **40** (0.128 g, 60%) as a syrup, which solidified on standing, and was purified by recrystallization from diethyl ether.

Compound **40**. Mp 94–95°C; $[\alpha]_D^{25}$=(104.3 (*c* 0.23, $CHCl_3$). IR (KBr) 1738 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.10 (s, 3H), 2.04–2.44 (m, 1H), 2.58 (d, J=12 Hz, 1H), 3.56–3.72 (m, 3H), 3.82 (d, J=12 Hz, 1H), 3.96–4.32 (m, 3H), 4.04 (d, J=12 Hz, 1H), 4.64 (br d, J=8.0 Hz, 1H), 4.90 (d, J=6.0 Hz, 1H), 7.36 (br s, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.6 (q), 20.7 (q), 27.7 (t), 62.7 (t), 63.1 (d), 63.5 (t), 72.2 (d), 72.8 (t), 74.3 (d), 78.8 (d), 127.4 (d), 128.3 (d), 128.8 (d), 136.8 (s), 170.0 (s), 170.4 (s).

4.5.10. (3*S*,4*R*,5*S*,8*R*)-4-Acetoxy-2-aza-2-benzyl-1,6-dioxa-5-acetoxymethyl-bicyclo[4.2.1]nonane (45). A mixture of **25** (0.200 g, 0.6 mmol) and 4% H_2SO_4 in acetonitrile-water (10:1, 11.3 mL) was stirred at room temperature for 20 h and then stirred with solid calcium carbonate (2 g) for 3 h. After filtration the residue was washed successively with acetonitrile and $CHCl_3$. The combined filtrate and washings were concentrated. The crude product obtained was chromatographed over silica gel (EtOAc) to give the diol **42** (0.141 g, 80%) as a syrup, which was used without any purification for the next step. To a solution of the syrup in methanol-water (10 mL, 1:1), $NaIO_4$ (0.5 mmol) in water (5 mL) was added dropwise with stirring at 25°C. After the addition was over, stirring was continued for further 2 h. After removal of methanol, the residue was extracted with chloroform and the organic layer was washed with water, dried and evaporated to give the hydroxyaldehyde **43** as a viscous liquid which was used immediately for the next step. To a solution of this material in ethanol (4 mL), $NaBH_4$ (0.08 g, 2 mmol) was added at 0°C in portions with stirring. After the addition was over, stirring was continued for 3 h. The reaction mixture was then acidified with aqueous AcOH (1:1) followed by neutralization of the excess acid with solid $NaHCO_3$. Extraction with $CHCl_3$ and evaporation afforded the diol **44** (0.077 g, 62%), as a viscous liquid, which was dissolved in pyridine (1.5 mL) and treated with acetic anhydride (1 mL, 10.5 mmol) at 0°C. The reaction mixture was allowed to warm up to 25°C and left overnight. After pouring into ice-water, the mixture was extracted with $CHCl_3$ and washed with water. Removal of solvent gave a syrup, which was chromatographed over silica gel to give **45** (0.056 g, 56%) as white needles, mp 95–96°C (diethyl ether- petroleum ether); $[\alpha]_D^{25}$=−103.7 (*c* 0.27, $CHCl_3$); MS (EI) *m*/*z* 349 (M^+), 160, 123, 91, 69, 57. Anal. calcd for $C_{18}H_{23}NO_6$: C, 61.87; H, 6.64; N, 4.01. Found: C, 62.15; H, 6.37; N, 4.22.

The IR and ^{1}H NMR spectrum of **45** was identical with those of **40**.

4.5.11. (3a*R*,6*R*,7*R*,7a*S*)-7-Acetoxy-1-benzyl-6-methyl-6-acetoxymethyl-1,3,3a,6,7,7a-hexahydro-4*H*-pyrano[4.5-*c*]isoxazole (53). The isoxazolidine **29** (0.350 g, 1 mmol) was subjected to the same procedure described above for the conversion of **25** to **45** via **50** (70%), **51** (70%) and **52** (80%) to give **53** (77%) as white needles, mp 118–119°C (diethyl ether); $[\alpha]_D^{25}$=(2.4 (*c* 0.75, $CHCl_3$); MS (EI) *m*/*z* 363 (M^+); IR (KBr) 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.96 (s, 3H), 2.08 (s, 3H), 3.08 (m, 1H), 3.21 (t, J=7.6, 8.5 Hz, 1H), 3.77 (d, J=12.9 Hz, 1H), 3.82–3.95 (m, 3H), 3.91 (d, J=11.8 Hz, 1H), 4.06 (d, J=11.8 Hz, 1H), 4.08 (d, 1H), 4.27 (dd, J=9.1, 9.0 Hz 1H), 5.10 (d, J=8.5 Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 15.0 (q), 20.7 (q), 39.9 (d), 59.2 (t), 60.6 (t), 63.1 (d), 67.3 (t), 68.0 (d), 68.8 (t), 74.4 (s), 127.4 (d), 128.2 (d), 128.7 (d), 136.9 (s), 169.3 (s), 170.5 (s). Anal. calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.94; N, 3.86. Found: C, 62.83; H, 7.21; N, 3.72.

4.5.12. (3a*S*,6*S*,7*S*,7a*R*)-7-Acetoxy-1-benzyl-6-methyl-6-acetoxymethyl-1,3,3a,6,7,7a-hexahydro-4*H*-pyrano[4.5-*c*]isoxazole (49). The isoxazolidine **22** (0.250 g, 0.5 mmol) was converted via **21** (75%), **47** (65%), and **48** (73%) to **49** (61%) by the procedure described above for **16** to **40**: $[\alpha]_D^{25}$=−2.4 (*c* 0.74, $CHCl_3$). The IR, and ^{1}H spectra of **49** were identical with those of **53**.

4.5.13. (3*R*,8*S*)-2-Aza-2-benzyl-1,6-dioxa-5-formyl-bicyclo[4.2.1]non-4-ene (41). *Method A*. To a solution of **38** (0.36 g, 1.4 mmol; prepared as described above in the preparation of **40**) in pyridine (3 mL) at 0°C was added with stirring TsCl (0.25 g, 1.3 mmol) under nitrogen atmosphere. The mixture was then stirred at 60°C for 3 h, poured into

crushed ice and extracted with CH_2Cl_2. After washing with water and drying, the organic layer was concentrated under vacuum to give an oil, which was purified by chromatography over silica gel (petroleum ether–$CHCl_3$, 1:2) to afford **41** (0.06 g 17%) as white flakes, mp 108–109°C; $[\alpha]_D^{25}$=(63.3 (*c* 0.39, $CHCl_3$); MS (EI): *m/z* 245 (M^+), IR (KBr): 1694 and 1633 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.74 (br m, 2H), 3.81–4.29 (m, 5H), 4.83 (br m, 1H), 5.91 (br d, *J*=4.8 Hz, 1H), 7.29–7.36 (m, 5H) and 9.17 (s, 1H); ^{13}C NMR (25 MHz, $CDCl_3$): δ 32.4 (br and weak, t), 59.8 (d), 60.9 (br, t), 76.4 (t), 77.2 (d), 126.2 (br and weak, d), 127.6 (d), 128.4 (d), 128.8 (d), 136.5 (s), 154.6 (s), 188.3 (d). Anal. calcd for $C_{14}H_{15}NO_3$, C, 68.56; H, 6.16; N, 5.71. Found C, 68.23; H, 6.03; N, 5.85.

Method B. A solution of **38** (0.18 g, 0.7 mmol) and TsOH (10 mg) in benzene (5 mL) was heated under reflux for 0.5 h. The mixture was washed with aq. $NaHCO_3$ solution and water, then evaporated to give a sticky residue, which was chromatographed over silica gel ($CHCl_3$–petroleum ether, 2:1) to afford **41** (0.053 g, 15%) as white flakes, mp 107–108°C. The material was identical in all respects with **41** obtained by Method A.

The oxepanoisoxazolidine **28** (0.330 g, 1 mmol) was converted to the respective hydroxyaldehyde (as described for **25** to **43** in the preparation of **45**), which was immediately subjected to Method A leading to the formation of **41** (5% from **28**), mp 107–108°C; $[\alpha]_D$=+61.1 (*c* 0.5, $CHCl_3$). The IR and ^1H NMR spectra of this sample were identical with those of **41** obtained from **38**.

4.5.14. (3*S*,8*R*)-2-Aza-2-benzyl-1,6-dioxa-5-formyl-bicyclo[4.2.1]non-4-ene (46). The oxepanoisoxazolidine **25** (0.650 g, 2 mmol) was converted to the hydroxyaldehyde **43** (0.328 g, 64%) as described above in the preparation of **45**. The conversion of **43** to **46** was carried out by both Methods A and B; yield, Method A, 0.015 g, 13% from 0.120 g of **43**. Method B, 0.028 g, 15% from 0.200 g of **43**; mp 108–109°C; $[\alpha]_D$=−59.1 (*c* 0.66, $CHCl_3$). The MS, IR and ^1H NMR spectra of **46** were identical with those of **41**.

4.6. N–O bond cleavage of the isoxazolidine derivatives, 16, 25, and 45. Preparation of 54, 55, and 56

A mixture of oxepanoisoxazolidine (0.46 mmol) in ethanol (15 mL), palladium–charcoal (10%) (0.4 g) and cyclohexene (1.5 mL) was stirred and heated to reflux for 10 h. The reaction mixture was cooled, filtered and washed with ethanol (10 mL). The combined filtrate was evaporated to dryness to give an oily residue. The crude oil in pyridine (2.5 mL) was treated with acetic anhydride (2 mL, 21 mmol) at 0°C, allowed to warm up to 25°C and left overnight. The reaction mixture was poured into ice-water (20 mL) and extracted with dichloromethane. The organic extract was washed with water and dried. After removal of solvent, the following products were obtained.

4.6.1. (2*R*,3*S*,4*R*,6*S*)-4-*N*-Acetylamino-3,6-diacetoxy-2-[(1*S*,2*R*)-1,2,3-triacetoxy]propyloxepane (54). The oxepanoisoxazolidine **16** was subjected to the above cleavage procedure and the crude solid obtained was washed thoroughly with diethyl ether and crystallized from ether to furnish **54** (71%) as white needles, mp 144–145°C. $[\alpha]_D^{25}$=−4.6 (*c* 0.74, $CHCl_3$); MS (EI) *m/z* 489 (M^+); IR (KBr) 1734, 1728, 1370, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 1.96 (s, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 3.42 (dd, *J*=10, 6 Hz, 1H), 3.92 (dd, *J*=10, 4 Hz, 1H), 4.06–4.14 (m, 2H), 4.22 (dd, *J*=12, 6 Hz, 1H), 4.40 (m, 1H), 4.84 (m, 1H), 5.04 (m, 1H), 5.36 (dd, *J*=8, 4 Hz, 1), 5.40 (dd, *J*=8, 6 Hz, 1H), 6.16 (d, *J*=8 Hz, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.5 (q), 20.8 (q), 23.1 (q), 33.3 (t), 49.1 (d), 61.3 (t), 69.4 (d), 70.0 (d), 70.8 (t), 71.2 (d), 73.0 (d), 77.6 (d), 169.2 (s), 169.4 (s), 169.7 (s), 170.4 (s). Anal. calcd for $C_{21}H_{31}NO_{12}$: C, 51.53; H, 6.38; N, 2.86. Found: C, 51.34; H, 6.15; N, 2.59.

4.6.2. (2*R*,3*R*,3a*S*,6*R*,8*S*,8a*R*)-6-Acetoxy-8-*N*-acetylamino-2,3-isopropylidenedioxy-furo[3,2-*b*]oxepane (55). The crude solid was purified by column chromatography over silica gel. Elution with ethylacetate–petroleum ether (1:3) gave a viscous liquid, which solidified on standing and was crystallized from EtOAc-hexane to yield **55** (63%) as white needles, mp 230–232°C (dec.). $[\alpha]_D^{28}$=+27.1 (*c* 0.45, $CHCl_3$); MS (EI) *m/z* 329 (M^+), 314; IR (KBr) 1734, 1657 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.48 (s, 3H), 1.84–2.30 (m, 2H), 3.40 (dd, *J*=12, 8 Hz, 1H), 4.04 (dd, *J*=12, 4 Hz, 1H), 4.16 (dq, *J*=4, 8, 8, 8 Hz, 1H), 4.50 (dd, *J*=4, 8 Hz, 1H), 4.60 (d, *J*=4 Hz, 1H), 5.08 (tt, *J*=8, 4 Hz, 1H), 5.82 (d, *J*=4 Hz, 1H), 6.04 (d, *J*=8 Hz, 1H). Anal. calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04. Found: C, 54.89; H, 7.18.

4.6.3. (2*S*,3*R*,4*S*,6*R*)-4-*N*-Acetylamino-3,6-diacetoxy-2-acetoxymethyloxepane (56). The crude solid was purified by column chromatography over silica gel. Elution with EtOAc–petroleum ether (1:3) gave a viscous liquid, which solidified on standing and was crystallized from $CHCl_3$–hexane to give **56** (75%) as colorless needles, mp 144–145°C. $[\alpha]_D^{25}$=+21.0 (*c* 1.0, $CHCl_3$); MS (FAB) *m/z* 368 (M^++Na), 346 (M^++H); IR (KBr) 1738, 1653 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.04 (s, 6H), 2.08 (s, 3H), 2.08 (m, 2H), 3.46 (dd, *J*=12, 8 Hz, 1H), 3.90–4.50 (m, 5H), 5.00–5.40 (m, 2H), 6.16 (br d, *J*=8 Hz, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.6 (2q), 20.8 (q), 23.2 (q), 33.7 (t), 49.3 (d), 62.1 (t), 71.1 (d), 71.7 (t), 73.8 (d), 78.1 (d), 169.3 (s), 169.5 (s), 170.1 (s), 170.4 (s). Anal. calcd for $C_{15}H_{23}NO_8$: C, 52.18; H, 6.72; N, 4.06. Found: C, 52.23; H, 6.84; N, 3.98.

4.6.4. Cycloaddition of 3-*O*-allyl carbohydrate oxime 57: (2a*S*,2b*R*,4*R*,5*R*,5a*S*,7b*R*)-2-benzoyl-2b,4,5,5a-tetrahydro-4,5-isopropylidenedioxy-furo[2′,3′:4,5]-bicyclo[4.2.1]nonane (59) and (3a*R*,5a*S*,6*R*,7*R*,8a*R*,8b*S*)-1-benzoyl-1,3,3a,5a,6,7,8a,8b-octahydro-4*H*-furo-[2′,3′:3,2]pyrano[4,5-*c*]isoxazole (61). A solution of the oxime **57** (50 mg) (prepared according to a known procedure[37]) in toluene (15 ml) was heated in a sealed tube at 120–130°C for 20 h. After concentrating the mixture, a solution of the residue in pyridine (5 mL) was treated with five drops of benzoyl chloride at 0°C and left at 25°C for 12 h. The mixture was poured into ice and extracted with CH_2Cl_2. The organic extract was washed with water, dried and concentrated to afford a deep brown syrupy liquid. Repeated chromatography of the above

material on silica gel using ether–petroleum ether (1:4) afforded a sticky residue, the TLC and ^{1}H NMR spectum of which revealed the presence of two compounds. Preparative TLC of this residue on silica gel using ether–petroleum ether (1:1) as the developing solvent afforded **59** (30%), the faster moving compound, as a colorless syrupy liquid; $[\alpha]_D^{25}=-118.2$ (*c* 0.67, $CHCl_3$); MS (EI) *m*/*z* 347 (M^+), 332; IR (KBr) 1656 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.53 (s, 3H), 2.10 (m, 1H), 2.72 (d, *J*=12.3 Hz, 1H), 3.75 (m, 2H), 4.14 (br s, 1H), 4.33 (br s, 1H), 4.48 (d, *J*=3.6 Hz, 1H), 4.66 (d, *J*=8.6 Hz, 1H), 5.09 (br m, 1H), 5.92 (d, *J*=3.6 Hz, 1H), 7.45 (m, 3H), 7.77 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1 (CH_3), 26.7 (CH_3), 28.4 (CH_2), 56.7 (CH), 72.4 (CH_2), 77.3 (CH), 80.8 (CH), 82.8 (CH), 84.2 (CH), 104.5 (CH), 112.0 (quaternary), 128.1 (CH), 129.0 (CH), 131.7 (CH), 132.8 (quaternary), 171.3 (quaternary). Anal. calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.04; N, 4.03. Found: C, 62.03; H, 6.31; N, 3.62.

The slower moving **61** (15%) was obtained as a colorless syrupy liquid; $[\alpha]_D^{25}=-198.8$ (*c* 0.50, $CHCl_3$); MS (EI) *m*/*z* 347 (M+), 332; IR (KBr): 1645 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.50 (s, 3H), 2.96 (m, 1H), 3.48 (t, *J*=11.4 Hz, 1H), 3.76 (d, *J*=8.4 Hz, 1H), 3.81 (dd, *J*=8.4, 4.2 Hz, 1H), 3.99 (dd, *J*=11.7, 6.0 Hz, 1H), 4.02 (br s, 1H), 4.53 (br s, 1H), 4.57 (d, *J*=3.6 Hz, 1H), 4.74 (d, *J*=6.3 Hz, 1H), 5.91 (d, *J*=3.6 Hz, 1H), 7.45 (m, 3H), 7.84 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3 (CH_3), 26.8 (CH_3), 37.0 (CH), 55.0 (CH), 64.6 (CH_2), 71.7 (CH_2), 73.3 (CH), 76.98 (CH), 84.1 (CH), 104.4 (CH), 112.1 (quaternary), 127.8 (CH), 129.5 (CH), 131.7 (CH), 133.0 (quaternary), 172.5 (quaternary C). Anal. calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.04; N, 4.03. Found: C, 62.62; H, 6.23; N, 4.04.

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