Ring-selective Syntheses of Homochiral Oxepanes and Tetrahydropyrans from Carbohydrates *via* Intramolecular Nitrone or Nitrile Oxide Cycloadditions

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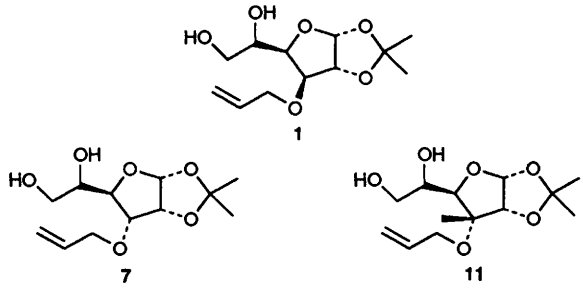
Intramolecular 1,3-dipolar cycloadditions of nitrones formed from 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-pentodialdofuranoses afford oxepanes or tetrahydropyrans selectively whereas the intramolecular cycloadditions of nitrile oxides derived from the same aldehydes give exclusively tetrahydropyrans.

O-Heterocycles occur widely in nature[1] and are important targets for synthesis, *e.g.* hemibrevetoxin B[2] and zoapatanol.[3] Collins[4] and then Bhattacharjya[5,6] have reported the use of intramolecular nitrone cycloaddition[7,8] (INC) of *O*-allyl-nitrones derives from D-glucose to construct *O*-heterocycles. We recently described[9] a facile method of preparing five- and six-membered carbocycles *via* an INC reaction and here we describe our investigation into the ring-selective syntheses of homochiral oxepanes or tetrahydropyrans involving an INC or an intramolecular nitrile oxide cycloaddition (INOC).[7,8]

The results obtained from the INC reactions are shown in Table 1. The vicinal diol moiety in 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose **1** was oxidatively cleaved[10] with sodium metaperiodate to give the corresponding aldehyde **2** which immediately reacted with *N*-methyl hydroxylamine in refluxing aqueous ethanol to give a mixture of two products in a ratio of *ca.* 11 : 1, readily separable by chromatography. The NMR of the major product displayed, a highfield methylene carbon resonance at δ_C 26.5 (DEPT) and a pair of highfield geminally coupled (12.4 Hz) proton resonances at δ_H 2.39 (m) and 2.60 (d), were assigned to the oxepane **3** (Table 1).† The minor product showed two methylene carbon resonances at δ_C 65.4 and 67.2 (DEPT), attributable to two oxygen-substituted methylene carbons, and was consistent with the tetrahydropyran structure **4**. The oxepanoisoxazolidine **3** may be rationalised to arise from the cycloaddition *via* the *Z*-nitrone-



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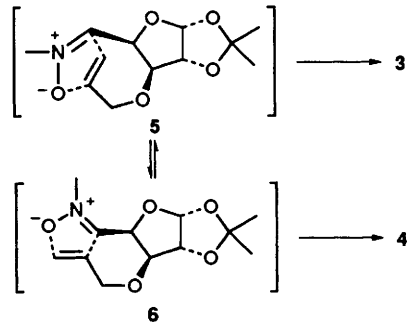
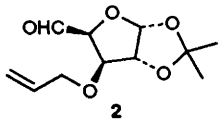
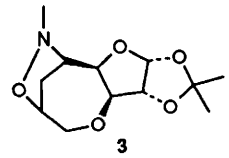
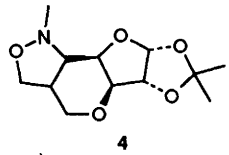
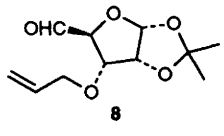
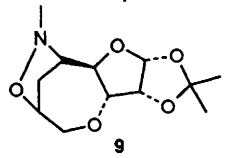
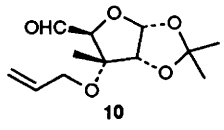
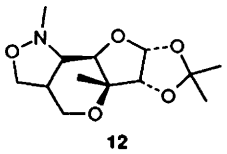


5 **6**

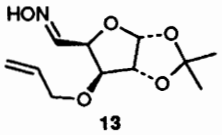
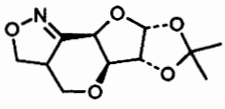
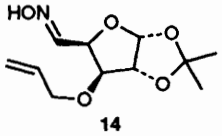
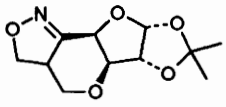
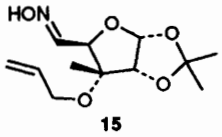
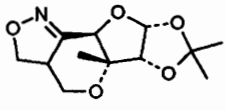
Fig. 1 Transition states for the INC of the nitrone derived from aldehyde **2**, leading to either oxepane **3** or tetrahydropyran **4**.

Table 1 Syntheses of oxepanes and/or tetrahydropyrans *via* INC

Precursor	Product	mp/°C	$[\alpha]_D^a$	Yield[b]/%
 **2**	 **3** +  **4**	77–77.5 104–105	−54.2 −67.7	64 6
 **8**	 **9**	192	+60.0	96
 **10**	 **12**	129–131	−22.3	70

[a] All optical rotations were measured in $CHCl_3$. [b] Isolated yield.

Table 2 Syntheses of tetrahydropyrans *via* INOC

Precursor	Products	mp/°C	$[\alpha]_D^a$	Yield[b]/%
 **13**	 **16**	124–125	+17.1	86
 **14**	 **17**	185–186.5	−160.6	65
 **15**	 **18**	173–174	−16.1	61

[a] All optical rotations were measured in $CHCl_3$. [b] Isolated yield.

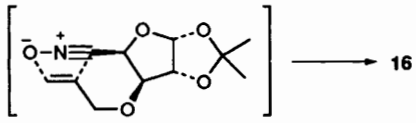


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Fig. 2 Transition state for the INOC of oxime **13**, leading to the tetrahydropyran **16**

S-cis-allyl ether transition state **5** whereas the pyranoisoxazolidine **4** from the cycloaddition *via* the *E*-nitrone-*S-trans*-allyl ether transition state **6** (Fig. 1).‡ Since *Z*- and *E*-nitrones are known to interconvert under the reaction condtions,[11] we assume that the product ratio was dependent only on the respective transition state energies. The observation that the oxepane **3** was formed in high selectivity (*ca.* 11 : 1) led to the conclusion that the *Z*-nitrone-*S-cis*-allyl ether transition state **5** was energetically more favourable.

In a similar manner, glycol cleavage oxidation[10] of 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-allofuranose **7**, followed by immediate treatment of the liberated aldehyhde **8** with *N*-methyl hydroxylamine furnished the oxepane **9** as the sole product (Table 1). The ring size of **9** was evident from NMR spectral analysis. In this case, the cycloaddition is believed to proceed also through a *Z*-nitrone-*S-cis*-allyl ether transition state similar to **5**.

Although INC of both β-allyloxy aldehydes **2** and **8** gave oxepanes selectively, introduction of a methyl substituent at the β-position altered the ring-selectivity from oxepane to tetrahydropyran. Thus, treatment of the aldehyde **10**, formed from the glycol fission of 3-*O*-allyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose **11**, with *N*-methyl hydroxylamine afforded the tetrahydropyran **12** as the only isolable cycloadduct (Table 1). We believe that the methyl substituent caused steric interaction with the *Z*-nitrone moiety in the transition state similar to **5** and thus the alternative *E*-nitrone-*S-trans*-allyl ether transition state took preference, furnishing exclusively the tetrahydropyran ring **12**.

On the other hand, the INOC of the oximes derived from aldehydes **2**, **8** and **10**, exhibited excellent selectivity towards tetrahydropyran formation. Thus, aldehydes **2**, **8** and **10** were converted into the respective oximes **13**, **14** and **15** under standard conditions (NH_2OH, Na_2CO_3, EtOH). The nitrile oxides were then generated *in situ* from the biphasic oxidation of the oximes (**13**, **14** and **15**) with NaOCl in dichoromethane–triethylamine[12] and underwent INOC to give only cycloadducts **16**, **17**, and **18**, respectively (Table 2). The ring size of all the cycloadducts was assigned as tetrahydropyran by ^{13}C (DEPT) NMR spectral analyses. Examination with molecular models indicated that maximum overlap of orbitals could only be achieved in the *S-trans*-allyl ether transition state for each cycloaddition (*e.g.* the transition state **19** is illustrated in Fig. 2 for the INOC of **13**), thus leading to the exclusive formation of the tetrahydropyran ring system.

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Footnotes

† All new compounds gave satisfactory analytical and spectral data.
‡ Molecular models show that the other two possible transition states involving a *Z*-nitrone-*S-trans*-allyl ether conformation and a *E*-nitrone-*S-cis*-allyl ether conformation do not appear to have favourable orbital overlap during cycloaddition.

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