Acyclic Stereodifferentiation: Selective Construction of Tetrahydropyran/Oxepane via Intramolecular Nitrone−Alkene Cycloaddition of Acyclic 3-*O*-Allylmonosaccharides†

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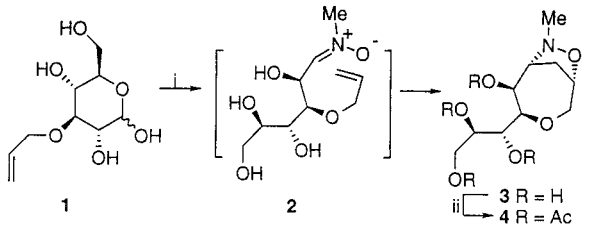
Recently, the intramolecular nitrone−alkene cycloaddition (INAC) reactions[1] have gained popularity among the synthetic chemists and its applications in organic synthesis have flourished.[2] We are interested in the use of INAC reactions for the construction of bioactive *O*-heterocycles that occur widely in nature[3] and are challenging synthetic targets, e.g., ciguatoxin,[4] isolaurepinnacin,[5] and zoapatanol.[6] However, the stereochemical course of the INAC reactions is not well understood. In this paper, we demonstrate for the first time that the stereochemical outcome of the INAC reactions of nitrones derived from 3-*O*-allyl-D-hexoses is dependent only on the relative configuration at C-2,3, and thus, 3-*O*-allyl-D-glucose and -D-altrose (both with *threo*-configuration at C-2,3) afford oxepanes selectively whereas 3-*O*-allyl-D-allose and -D-mannose (both with *erythro*-configuration at C-2,3) give tetrahydropyrans (THPs) selectively.

Treatment of 3-*O*-allyl-D-glucose (**1**)[7] or 3-*O*-allyl-D-altrose (**5**)[8] with *N*-methylhydroxylamine in refluxing aqueous ethanol followed by acetylation afforded exclusively oxepane tetraacetate **4** or **8**, respectively (Schemes 1 and 2). The constitution and the stereochemistry of **4** and **8** were confirmed by X-ray crystallographic analyses. On the other hand, the similar reaction of 3-*O*-allyl-D-allose (obtainable from acidic hydrolysis of diacetonide **9**[10]) or 3-*O*-allyl-D-mannose (from acidic hydrolysis of acetal **16**[11]) with *N*-methylhydroxylamine gave THP tetraacetates **13** and **15** or **20** and **22**, respectively (Schemes 3 and 4). The ring size (by COSY and HMQC) and the stereochemistry (by *J* and NOESY) of the cycloadducts **13**, **15**, and **22** were assigned by NMR spectroscopic techniques, and those of **20** were corroborated by X-ray crystallographic analysis.

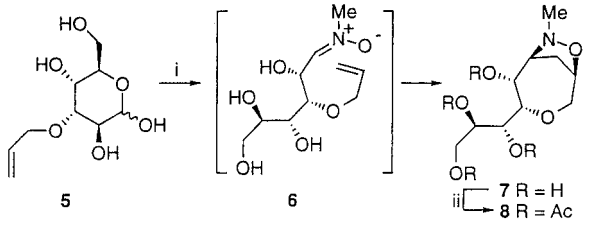
Scheme 1[a]



1 2

[a] Keys: (i) MeNHOH·HCl, $NaHCO_3$, 80% EtOH(aq), reflux, 48 h; (ii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 6 h, 53% overall from **1**.

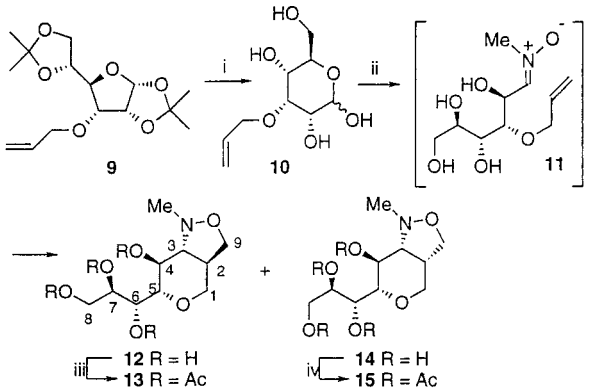
Scheme 2[a]



5 6

[a] Keys: (i) MeNHOH·HC l, $NaHCO_3$, 80% EtOH(aq), reflux, 48 h; (ii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 6 h, 55% overall from **5**.

Scheme 3[a]



[a] Key: (i) 30% HCl(aq), reflux, 24 h, 70%; (ii) MeNHOH·HCl, $NaHCO_3$, 80% EtOH(aq), reflux, 48 h; (iii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 24 h, 8% overall from **10**; (iv) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 24 h, 33% overall from **10**.

The above results may be rationalized as follow. Resubjection of the respective cycloadducts **3**, **7**, **12**, **14**, **19**, and **21** to the INAC reaction conditions for 56 h did not cause any change, and the cycloadducts were recovered essentially in quantitative yields, thus hinting at a kinetically controlled reaction. The molecular mechanics calculations according to the MM2 force field of Allinger[12] showed that the E_{steric} of the pyranoisoxazolidine (e.g., **12**) is roughly 8−10 kcal mol^{-1} more stable than the corresponding oxepanoisoxazolidine. On the basis of the above findings and since (*Z*)- and (*E*)-nitrones are known to interconvert under the reaction conditions,[13] it is reasonable to assume that the product

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† Dedicated to Professor J. K. Sutherland on the occasion of his 65th birthday.

‡ Researchers who performed the X-ray analysis of which inquiries should be directed to T.C.W.M.

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(8) Obtained from methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[9] via sequential epoxide opening with sodium allyl oxide and acidic hydrolysis in 54% overall yield.

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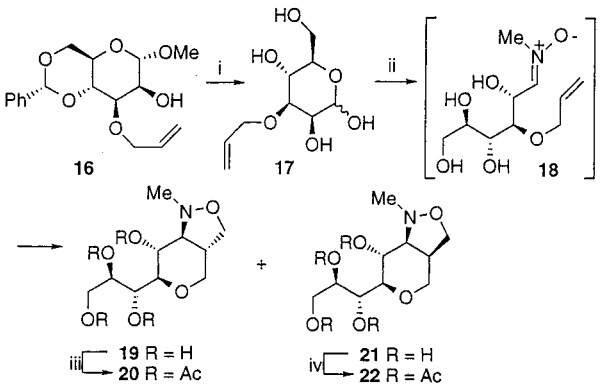
Scheme 4[a]



[a] Key: (i) 30% HCl(aq), reflux, 24 h, 66%; (ii) MeNHOH·HCl, $NaHCO_3$, 80% EtOH(aq), reflux, 48 h; (iii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 24 h, 8% overall from **17**; (iv) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 24 h, 37% overall from **17**.

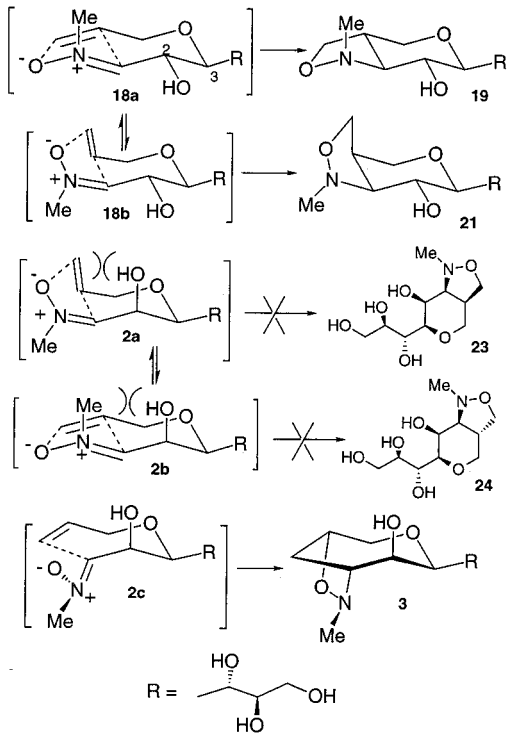


Figure 1.

selectivity of the INAC reactions was dependent only on the respective transition-state energies.

We propose that the INAC reactions generally prefer to proceed through chairlike transition-state conformations that afford THPs. The observation that the THPs **19** and **21** were formed exclusively led to the conclusion that the transition states **18a** and **18b** (with substituents at C-2,3 occupying pseudoequatorial positions and hence free from 1,3-diaxial interactions) were energetically more favorable than the transition states that led to the corresponding oxepanes (Figure 1). In addition, these transition states **18a** and **18b** may also be stabilized by a vinylogous anomeric effect[14] ($\sigma_{COH} \rightarrow \pi^*_{C=N}$ stabilization) as suggested by a reviewer. Examination with molecular models indicates that orbital overlap for cycloaddition appears to be more

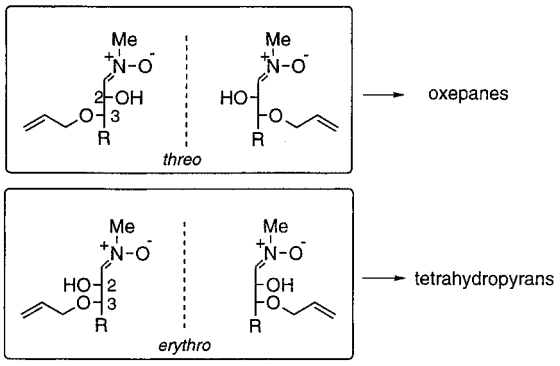
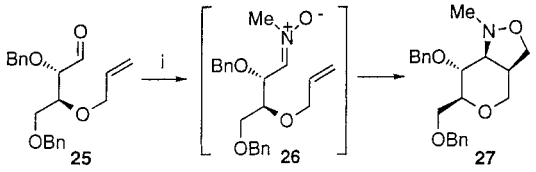


Figure 2.

Scheme 5[a]



[a] Key: (i) MeNHOH·HCl, $NaHCO_3$ in 80% EtOH(aq), reflux, 7 h, 70% or in CH_3CN, reflux, 7 h, 88%.

effective via (*Z*)-nitrone-*S*-*cis*-allyl ether transition state **18b** than via (*E*)-nitrone-*S*-*trans*-allyl ether **18a**. On the other hand, a similar chairlike transition state for the INAC reaction of **1** would incur 1,3-diaxial interactions in either conformation **2a** or **2b** and the respective THP cycloadduct **23** or **24** was not observed (Figure 1). No vinylogous anomeric effect is expected in **2a** or **2b** because there is no efficient orbital overlap between the HO−C σ bond and the C=N π bond. The alternative transition state **2c** that led to oxepane **3** is energetically more favorable in this case. The exclusive formation of pyranoisoxazolidines **12** and **13** from 3-*O*-allyl-D-allose (**10**) and oxepanoisoxazolidine **7** from 3-*O*-allyl-D-altrose (**5**) can be rationalized in a similar manner.

Since the chirality at C-4,5 is the same in all four 3-*O*-allyl-D-hexoses **1**, **5**, **10**, and **17**, the observed stereoselectivity should only be dependent on the *relative* stereochemistry at C-2,3. We conclude that nitrones derived from 3-*O*-allyl sugars having *threo*-configuration at C-2,3 would give oxepanoisoxazolidines, whereas those having *erythro*-configuration at C-2,3 would afford pyranoisoxazolidines preponderantly, and the ring selectivity is independent of the substituent R (see Figure 2). This conclusion is supported by the observation that 3-*O*-allyl-2,4-di-*O*-benzylaldehydo-L-erythrose (**25**) (with *erythro*-configuration at C-2,3) on reaction with *N*-methylhydroxylamine gave exclusively pyran cycloadduct **27** in 88% yield (Scheme 5). This example also provides evidence that hydrogen bonding may not have a significant effect on the stereoselectivity of the INAC reactions.

The yields of the INAC reactions involving unprotected sugar derivatives are moderate, and the remaining materials from the reactions are degradation products. The problem of decomposition could be alleviated by masking the hydroxy groups as benzyl ethers. The INAC reactions of the corresponding benzyl-protected sugar derivatives are under investigation and will be reported in a full paper.

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Supporting Information Available: Experimental details and characterization data and X-ray structural data for **4**, **8**, and **20** (6 pages).

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