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Ring-selective synthesis of *O*-heterocycles from acyclic 3-*O*-allyl-monosaccharides via intramolecular nitrone–alkene cycloaddition

Tony K. M. Shing* and Yong-Li Zhong

Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong

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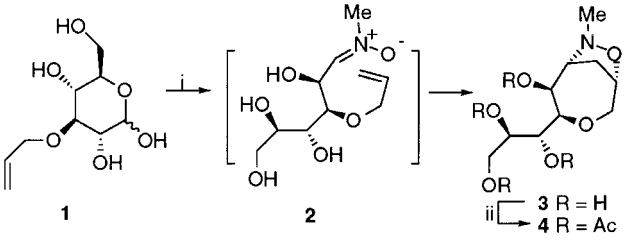
Abstract—Intramolecular 1,3-dipolar cycloadditions of nitrones formed from 3-*O*-allyl-D-glucose and D-altrose (both with *threo*-configuration at C-2,3) afford oxepanes selectively whereas the same reactions of nitrones derived from 3-*O*-allyl-D-allose and D-mannose (both with *erythro*-configuration at C-2,3) give tetrahydropyrans selectively.

1. Introduction

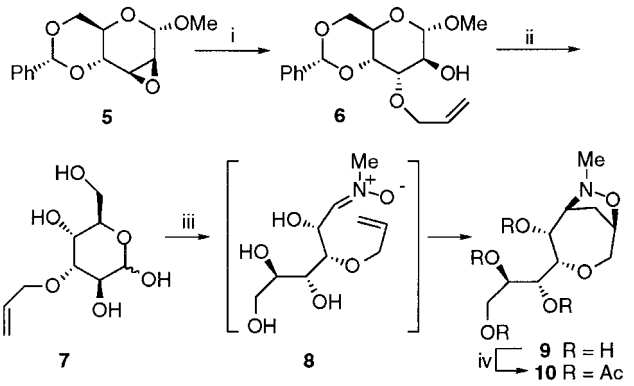
Cyclic and polycyclic ethers occur widely in marine organisms, especially in red algae and dinoflagellates.[1] Brevetoxin B[2] and ciguatoxin[3] are two examples of polycyclic ether comprising of fused tetrahydropyran and oxepane rings, and are selective activators of voltage-sensitive sodium channels in nerves, heart, and muscle.[4] We are interested in the use of intramolecular nitrone–alkene cycloaddition[5] (INAC) reactions for the construction of these bioactive *O*-heterocycles. The INAC reactions of *O*-allylnitrones derived from D-glucose to construct *O*-heterocycles was first reported by Collins,[6] then by Bhattacharjya,[7] and by our research group.[8] Actually, the application of INAC reactions to sugar derivatives was first described 28 years ago by Tronchet[9] to produce furanose isoxazolidines. Recently, INAC reactions have gained popularity among synthetic chemists and its applications in organic synthesis have flourished.[10] However, the stereochemical course of the INAC reactions is not well understood. In this article, we report in detail 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. A preliminary account of this work was recently reported.[11]

2. Results and discussion

Treatment of 3-*O*-allyl-D-glucose (**1**)[7] or 3-*O*-allyl-D-altrose (**7**) (obtainable from methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**5**)[12] via sequential epoxide opening with sodium allyl oxide and acidic hydrolysis in 55% overall yield) with *N*-methyl hydroxylamine in refluxing aqueous ethanol followed by acetylation afforded exclusively oxepane tetraacetate **4** or **10**, respectively (Schemes 1 and 2). The constitution and stereochemistry of **4** and **10** were confirmed by X-ray crystallographic analyses.[11]



Scheme 1. (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. (i) $CH_2{=}CHCH_2OH$, Na, reflux, 90%; (ii) 30% HCl(aq), reflux, 24 h, 60%; (iii) MeNHOH.HCl, $NaHCO_3$, 80% EtOH (aq), reflux, 48 h; (iv) Ac_2O, DMAP, pyridine CH_2Cl_2, rt, 6 h, 55% overall from **7**.

* Corresponding author. Tel.: +852-2609 6344; fax: +852-2603 5057; e-mail: tonyshing@cuhk.edu.hk

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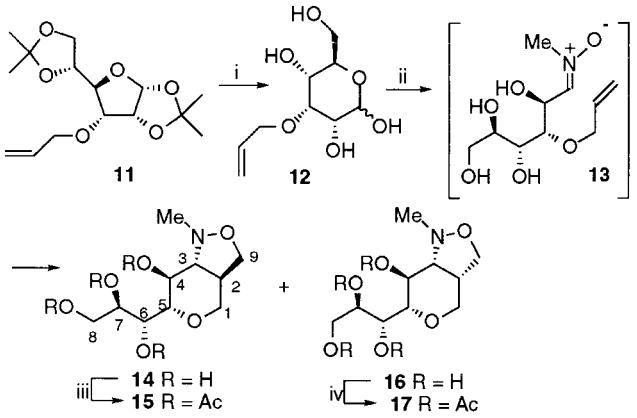
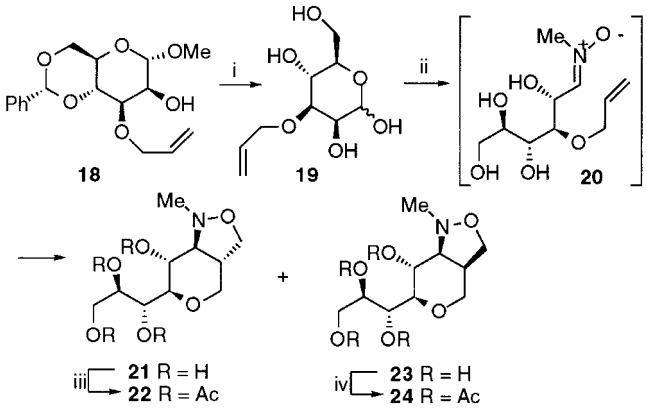


Scheme 3. (i) 30% HCl(aq), reflux, 24 h, 70%; (ii) MeNHOH.HCl, $NaHCO_3$ 80% EtOH(aq), reflux, 48 h; (iii) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 24 h, 8% overall from **10**; (iv) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 24 h, 33% overall from **10**.



Scheme 4. (i) 30% HCl(aq), reflux, 24 , 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**.

On the other hand, the similar reaction of 3-*O*-allyl-D-allose (**12**) (obtainable from acidic hydrolysis of diacetonide **11**[13]) or 3-*O*-allyl-D-mannose (**19**) (from acidic hydrolysis of acetal **18**[14]) with *N*-methyl hydroxylamine gave THP tetraacetates **15** and **17**or **22** and **24**, respectively (Schemes 3 and 4). The ring size (by COSY and HMQC) and the stereochemistry (by *J* and NOESY) of the cycloadducts **15**, **17**, and **24** were assigned by NMR spectroscopic techniques and those of **22** were corroborated by an X-ray[11] crystallographic analysis.

The above results may be rationalized as follows. Resubjection of the respective cycloadducts **3**, **9**, **14**, **16**, **21**, and **23** 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[15] showed that the E_{steric} of the pyranoisoxazolidine (e.g. **14**) is roughly 8–10 kcal mol^{-1} more stable than the corresponding oxepanoisoxazolidine. On the basis of the above findings and since

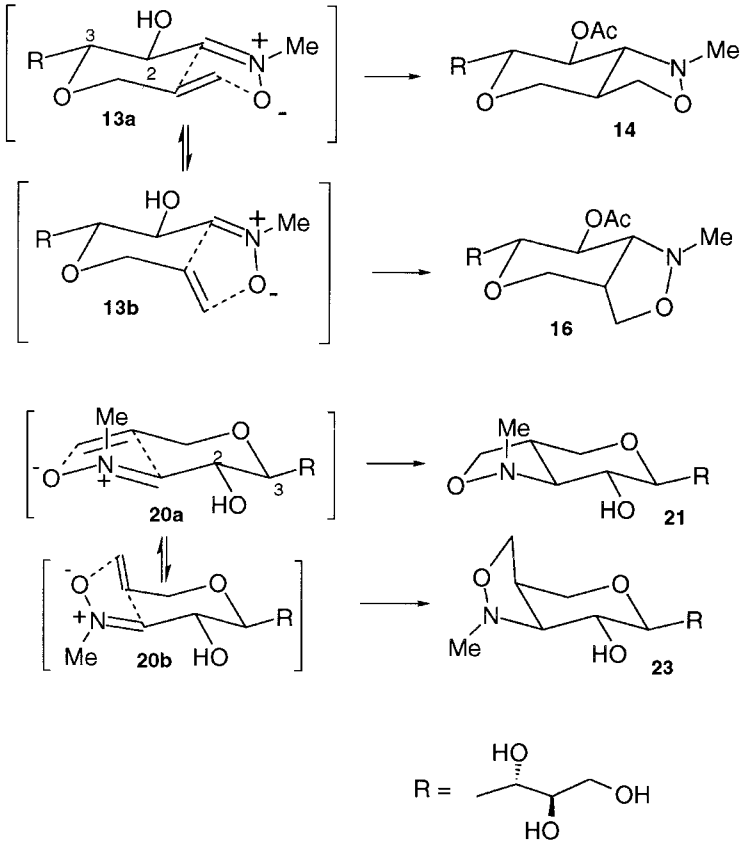


Figure 1.

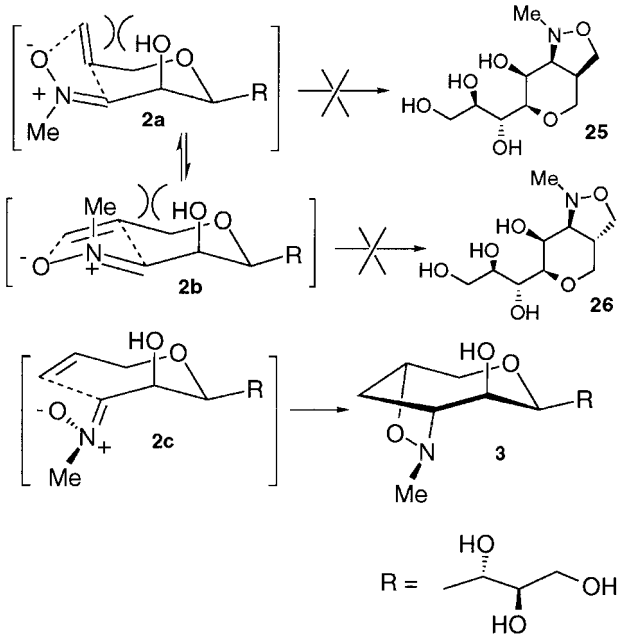


Figure 2.

Z- and *E*-nitrones are known to interconvert under the reaction conditions,[16] it is reasonable to assume that the product 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 chair-like transition-state conformations that afford THPs. The observation that the THPs **14**, **16**, **21** and **23** were formed exclusively led to the conclusion that the transition-states **13a** and **13b**; **20a** and **20b** (with substituents at C-2,3 occupying pseudoequatorial positions

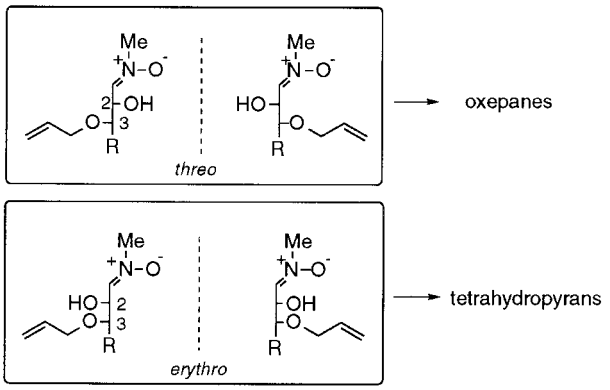
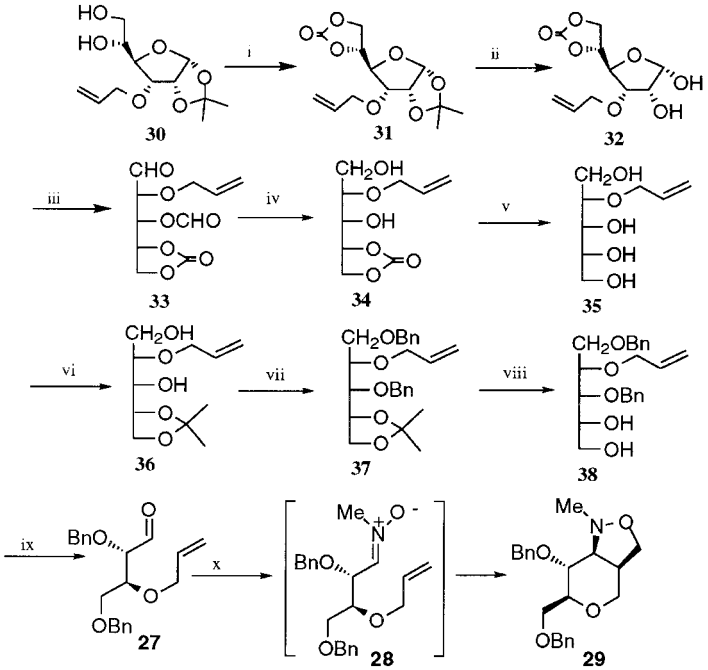


Figure 3.

and hence free from 1,3-diaxial interactions) were energetically more favorable than the transition-states that led to the corresponding oxepanes (Fig. 1). In addition, these transition-states **13a** and **13b**; **20a** and **20b** may also be stabilized by a vinylogous anomeric effect[17] ($\sigma_{C-OH} \rightarrow \pi^*_{C=N}$ stabilization). Examination with molecular models indicates that orbital overlap for cycloaddition appears to be more effective via *Z*-nitrone-*S*-*cis*-allyl ether transition-states **13b** and **20b** than via *E*-nitrone-*S*-*trans*-allyl ethers **13b** and **20a**, respectively. On the other hand, a similar chair-like 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 **25** or **26** was not observed (Fig. 2). 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 oxepanoisoxazolidine **9** from 3-*O*-allyl-D-altrose (**7**) can be rationalized in a similar manner.



Scheme 5. (i) MeOCOCl, TEA, CH_2Cl_2; (ii) 90% aq. TFA; (iii) $NaIO_4$, dioxane–water; (iv) $NaBH_4$, MeOH–H_2Ov, MeOH, NaOMe; (iv) acetone, CSA, (vii) BnBr, NaH, THF; (viii) 90% aq. TFA; (ix) $NaIO_4$, dioxane–water; AcOH, CH_2Cl_2; (x) MeNHOH.HCl, $NaHCO_3$, 80% aq. EtOH.

3. Conclusion

Since the chirality at C-4,5 is the same in all the four 3-*O*-allyl-D-hexoses **1**, **7**, **12**, and **19**, 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 predominantly, and the ring selectivity is independent of the substituent R (see Fig. 3).

This conclusion is supported by the observation that 3-*O*-allyl-2,4-di-*O*-benzyl-aldehydo-L-erythrose (**27**) (with *erythro*-configuration at C-2,3) on reaction with *N*-methyl hydroxylamine gave exclusively pyran cycloadduct **29** in 88% yield (Scheme 5). This example also provides evidence that hydrogen bonding may not have significant effect on the stereoselectivity of the INAC reactions. The aldehyde **27** was prepared in nine steps from 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-allofuranose (**30**)[8] by standard transformations as shown in Scheme 5.

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 active investigation and will be reported in due course.

4. Experimental

Melting points were measured in °C and uncorrected. IR spectra were recorded on an FT-IR spectrophotometer as neat films on KBr plates. Optical rotations were obtained at 589 nm. ^{1}H NMR spectra were measured at either 250 or 500 MHz. ^{13}C NMR spectra were obtained at 62.9 MHz. 2D NMR spectra were measured at 500 MHz. Elemental analyses were performed at either the Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China, or the MEDAC Ltd., Department of Chemistry, Brunel University, UK. Mass spectra were obtained using EI or FAB techniques. All reactions were monitored by analytical TLC performed on Merck aluminum precoated plates of silical gel 60 F_{254} with detection by spraying with 5% w/v dodecamolybdophosphoric acid in ethanol and subsequent heating. All columns were packed wet using E. Merck silica gel 60 (230–400 mesh) as the stationary phase and eluted using the flash chromatographic technique. THF was distilled from sodium benzophenone ketyl under a nitrogen atmosphere.

4.1. General procedure A for the preparation of 3-*O*-allyl-pyranose by acidic hydrolysis

A solution of the acetal protected sugar derivative (2.0 mmol) in 30% aqueous HCl (5 mL) was heated under reflux for 24 h. The reaction mixture was cooled and the solvent was removed in vacuo. The residue was chromatographed on silica gel to give the 3-*O*-allyl-pyranose.

4.2. General procedure B for INAC reactions

Sodium hydrogen carbonate (218 mg, 2.6 mmol) was added to a solution of the 3-*O*-allyl-pyranose (220 mg, 1.0 mmol) and *N*-methyl hydroxylamine hydrochloride (217 mg, 2.6 mmol) in 80% aqueous EtOH (10 mL) and the resultant mixture was heated under reflux for 48 h. The cooled solution was concentrated to give a yellow syrup that was immediately used in the next stage without purification. Acetic anhydride (0.6 mL, 6 mmol), pyridine (1 mL, 12 mmol), DMAP (cat.) and CH_2Cl_2 (5 mL) were added to the syrup. After being stirred for 6 h, the mixture was evaporated to dryness and the residue was chromatographed on silica gel to give the cycloadduct peracetate.

4.3. General procedure C for INAC reactions

Sodium hydrogen carbonate (218 mg, 2.6 mmol) was added to a solution of the aldehyde (1.0 mmol) and *N*-methyl hydroxylamine hydrochloride (217 mg, 2.6 mmol) in CH_3CN (10 mL) and the resultant mixture was heated under reflux for 7 h. The reaction mixture was filtered and the filtrate was extracted with $CHCl_3$ (3×15 mL). The combined extracts were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$) and filtered. The filtrate was concentrated to a yellow syrup that was chromatographed on silica gel to give the cycloadduct.

4.3.1. [1*S*-[1α,4α(1*R,2*R**),5α,6α]]-1-(5-Acetyloxy-7-methyl-3,8-dioxa-7-azabicyclo[4.2.1]non-4-yl)-1,2,3-propanetriol triacetate (4).** INAC reaction of 3-*O*-allyl-D-glucose (**1**)[7] according to procedure B followed by flash chromatography [EtOAc–hexane (3:1)] afforded oxepane **4** in 53% yield as colorless prisms: mp 145°C; R_f 0.33 [EtOAc–hexane (3:1)]; $[\alpha]^{25}_D$=+95.5 (*c* 1.0, $CHCl_3$); IR (neat) 1744, 1372, 1224, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (3H, s), 2.12 (6H, s), 2.20 (3H, s), 2.28–2.45 (1H, m), 2.55 (1H, d, *J*=12.5 Hz), 2.67 (3H, s), 3.45–3.52 (2H, m), 3.63 (1H, dd, *J*=7.4, 1.0 Hz), 4.04 (1H, d, *J*=7.4 Hz), 4.22 (2H, dq, *J*=11.9, 5.0 Hz), 4.60 (1H, dd, *J*=7.5, 2.8 Hz), 5.03–5.10 (2H, m), 5.38 (1H, dd, *J*=7.5, 3.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6 (2C), 20.9 (2C), 27.1, 46.5, 61.1, 65.3, 69.4, 71.9, 72.4, 73.2, 74.7, 78.6, 169.7, 169.9, 170.4, 170.6; EIMS *m/z* (relative intensity) 417 (M^+, 2), 43 (CH_3CO^+, 100). Anal. Calcd for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.36. Found: C, 51.69; H, 6.56; N, 3.33.

4.3.2. Methyl 3-*O*-Allyl-4,6-*O*-benzylidene-α-D-altropyranoside (6). Sodium metal (250 mg, 10.9 mmol) was added to allyl alcohol (5 ml) at 0°C very slowly and the resulting mixture was stirred for 0.5 h. Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**5**)[12] (168 mg, 0.64 mmol) was added to the mixture, which then was heated under reflux for 6 h. The reaction mixture was cooled to room temperature and saturated NH_4Cl (5 mL) was added. The mixture was extracted with $CHCl_3$ (3×30 mL). The combined extracts were washed with saturated aqueous NH_4Cl (20 mL), dried with MgSO4 and filtered. The filtrate was concentrated to a yellow syrup and chromatographed on silica gel to give allyl ether **6** (187 mg, 90%) as pale yellow crystals: mp 74°C; R_f 0.46 [Et_2O–hexane (1:1)]; $[\alpha]^{25}_D$=+67.9 (*c* 0.9, $CHCl_3$); IR (neat) 3450, 1650, 1460, 1380, 1138, 1044, 1017 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 2.01 (1H, d, J=5.8 Hz), 3.42 (3H, s), 3.71–3.81 (1H, m), 3.88 (1H, t, J=2.9 Hz), 3.96–4.01 (2H, m), 4.21 (1H, ddt, J=13.5, 6.1, 1.3 Hz), 4.28–4.37 (3H, m), 4.59 (1H, s), 5.17 (1H, dq, J=10.5, 1.3 Hz), 5.29 (1H, dq, J=19.0, 1.3 Hz), 5.55 (1H, s), 5.87–5.96 (1H, m), 7.30–7.50 (5H, m); ^{13}C NMR ($CDCl_3$) δ 55.6, 58.5, 69.3, 70.2, 72.4, 74.8, 77.0, 101.9, 102.2, 116.9, 126.1 (2C), 128.2 (2C), 129.0, 135.0, 137.6; EIMS *m/z* (relative intensity) 322 (M^+, 0.3), 41 (CH_2=$CHCH_2^+$, 100). Anal. Cacld for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.26; H, 6.72.

4.3.3. 3-*O*-Allyl-D-altrose (7). Acidic hydrolysis of compound **6** according to procedure A followed by flash chromatography [MeOH–$CHCl_3$ (1:3)] afforded hemiacetal **5** in 60% yield as a pale yellow syrup: R_f 0.37 [MeOH–$CHCl_3$ (1:3)]. 3-*O*-Allyl-D-altrose (**5**) was immediately used in the next step.

4.3.4. [1*R*-[1α,4α(1*R,2*R**),5α,6α]]-1-(5-Acetyloxy-7-methyl-3,8-dioxa-7-azabicyclo[4.2.1]non-4-yl)-1,2,3-propanetriol triacetate (10).** INAC reaction of 3-*O*-allyl-D-altrose (**7**) according to procedure B followed by flash chromatography (EtOAc) afforded oxepane tetraacetate **10** in 55% yield as colorless prisms: mp 99–99.5°C; R_f 0.34 (EtOAc); $[\alpha]^{25}_D$=−29.9 (*c* 0.9, $CHCl_3$); IR (neat) 1750, 1390, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (3H, s), 2.08 (6H, s), 2.09 (3H, s), 2.35–2.45 (1H, m), 2.55 (1H, d, J=12.4 Hz), 2.67 (3H, s), 3.45 (1H, dd, J=6.4, 4.9 Hz), 3.67 (2H, brs), 4.08–4.16 (2H, m), 4.38 (1H, dd, J=12.0, 3.8 Hz), 4.63 (1H, bd, J=8.1 Hz), 4.91 (1H, d, J=4.6 Hz), 5.13 (1H, dd, J=10.2, 2.0 Hz), 5.38 (1H, ddd, J=10.2, 3.8, 2.1 Hz); ^{13}NMR ($CDCl_3$) δ 20.7, 20.8, 20.9 (2C), 27.3, 46.5, 62.5, 65.5, 69.1, 70.0, 70.9, 72.6, 74.1, 79.0, 169.7, 170.1, 170.6 (2C); EIMS *m/z* (relative intensity) 417 (M^+, 3), 43 (CH_3CO^+, 100). Anal. Cacld for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.36. Found: C, 51.77; H, 6.54; N, 2.99.

4.3.5. 3-*O*-Allyl-D-allopyranose (12). Acidic hydrolysis of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**11**)[13] according to procedure A followed by flash chromatography [MeOH–$CHCl_3$ (1:3)] afforded hemiacetal **12** in 70% yield as a sticky white solid: R_f 0.33 [MeOH–$CHCl_3$ (1:3)]. The product was immediately used in the next step.

4.3.6. [3a*R*-[3aα,6α(1*R,2*R**),7β,7aα]]-1-[7-(Acetyloxy)-hexahydro-1-methyl-3*H*-pyrano[4,3-c]isoxazol-6-yl]-1,2,3-propanetriol triacetate (15) and [3a*S*-[3aα,6α(1*R**,2*R**),7β,7aα]]-1-[7-(acetyloxy)hexahydro-1-methyl-3*H*-pyrano-[4,3-c]isoxazol-6-yl]-1,2,3-propanetriol triacetate (17).** INAC reaction of 3-*O*-allyl-D-allose (**12**) according to procedure B followed by flash chromatography [EtOAc–hexane (3:1)] afforded syrupy tetraacetates **15** and **17** in 8 and 33% yield, respectively.

For **15**: R_f 0.38 [EtOAc–hexane (3:1)]; $[\alpha]^{25}_D$=+12.6 (*c* 1.2, $CHCl_3$); IR (neat) 1744, 1400, 1225, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (3H, s), 2.02 (3H, s), 2.07 (3H, s), 2.12 (3H, s), 2.67 (3H, s, N–CH_3), 2.87–2.98 (1H, m, H-2), 3.27 (1H, dd, J=5.1, 3.9 Hz, H-3), 3.50 (1H, d, J=8.2 Hz, H-9a), 3.57 (1H, t, J=11.4 Hz, H-1eq), 3.95 (1H, dd, J=11.4, 7.0 Hz, H-1ax), 3.98 (1H, dd, J=8.2, 5.0 Hz, H-9b), 4.06 (1H, dd, J=10.3, 3.2 Hz, H-5ax), 4.14 (1H, dd, J=12.4, 7.5 Hz, H-8a), 4.46 (1H, dd, J=12.4, 2.4 Hz, H-8b), 5.11 (1H, dd, J=10.3, 3.9 Hz, H-4ax), 5.19 (1H, ddd, J=7.5, 4.6, 2.4 Hz, H-7), 5.37 (1H, dd, J=4.6, 3.2 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 20.7 (4C), 45.1, 47.2, 62.4, 66.3, 66.4, 66.7, 69.4, 70.2, 70.6, 73.4, 169.8 (4C); EIMS *m/z* (relative intensity) 417 (M^+, 13), 43 (CH_3CO^+, 100). Anal. Cacld for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.36. Found: C, 52.11; H, 6.71; N, 3.02.

For **17**: R_f 0.30 [EtOAc–hexane (3:1)]; $[\alpha]^{25}_D$=+11.3 (*c* 1.0, $CHCl_3$); IR (neat) 1744, 1372, 1225, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (3H, s), 2.10 (6H, s), 2.16 (3H, s), 2.63 (3H, s, N–CH_3), 2.98–3.08 (2H, m), 3.53 (1H, dd, J=8.4, 3.9 Hz, H-5ax), 3.65 (1H, t, J=7.5 Hz, H-9a), 3.71 (1H, dd, J=12.5, 3.0 Hz, H-1ax), 3.95 (1H, d, J=12.5 Hz, H-1eq), 4.17 (1H, dd, J=7.5, 5.0 Hz, H-9b), 4.19 (1H, dd, J=12.0, 6.0 Hz, H-8a), 4.36 (1H, dd, J=12.0, 2.0 Hz, H-8b), 4.94 (1H, dd, J=8.4, 7.5 Hz, H-4ax), 5.31 (1H, d, J=3.9 Hz, H-6), 5.36 (1H, dt, J=6.0, 2.0 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.6 (2C), 20.8, 40.0, 43.5, 62.0, 64.5, 67.1, 67.9, 68.2, 69.5, 70.0, 77.5, 169.3, 169.4, 169.6, 170.4; EIMS *m/z* (relative intensity) 417 (M^+, 2.3), 43 (CH_3CO^+, 100). Anal. Cacld for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.36. Found: C, 51.70; H, 6.68; N, 3.23.

4.3.7. 3-*O*-Allyl-D-mannose (19). Acidic hydrolysis of methyl 3-*O*-allyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**18**)[14] according to procedure A followed by flash chromatography [MeOH–$CHCl_3$ (1:3)] afforded hemiacetal **19** in 66% yield as a sticky white solid: R_f 0.37 [MeOH–$CHCl_3$ (1:3)]. The product was immediately used in the next step.

4.3.8. [3a*S*-[3aα6β (1*R,2*R**),7α,7aβ]]-1-[7-(Acetyloxy)-hexahydro-1-methyl-3*H*-pyrano[4,3-c]isoxazol-6-yl]-1,2,3-propanetriol triacetate (22) and [3a*R*-[3aα,6β (1*R**,2*R**),7α,7aβ]]-1-[7-(acetyloxy)hexahydro-1-methyl-3*H*-pyrano[4,3-c]isoxazol-6-yl]-1,2,3-propanetriol triacetate (24).** INAC reaction of 3-*O*-allyl-D-mannose (**19**) according to procedure B followed by flash chromatography [EtOAc–hexane (3:1)] afforded **22** in 8% yield as colorless prisms and **24** in 37% yield as a white solid.

For **22**: mp 95–96°C; R_f 0.35 [EtOAc–hexane (3:1)]; $[\alpha]^{20}_D$=−2.5 (*c* 0.4, $CHCl_3$); IR (neat) 2967, 2933, 2887, 1745, 1367, 1229, 1039 cm^{-1}; ^{1}H NMR?($CDCl_3$) δ 2.05 (3H, s), 2.07 (3H, s), 2.10 (6H, s), 2.47 (1H, dd, J=10.0, 9.5 Hz, H-3ax), 2.66 (3H, s, N–CH_3), 2.73 (1H, m, H-2ax), 3.38 (1H, t, J=11.0 Hz, H-1eq), 3.52 (1H, dd, J=9.0, 2.0 Hz, H-5ax), 3.63 (1H, dd, J=11.0, 6.8 Hz, H-1ax), 4.01 (1H, t, J=7.7 Hz, H-9a), 4.12 (1H, dd, J=12.5, 5.5 Hz, H-8a), 4.15 (1H, dd, J=7.7, 5.0 Hz, H-9b), 4.41 (1H, dd, J=12.5, 2.0 Hz, H-8b), 5.03 (1H, dd, J=10.0, 9.0 Hz, H-4ax), 5.28–5.38 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.3 (2C), 21.4, 21.7, 41.0, 47.1, 62.3, 65.2, 67.9, 69.4 (2C), 70.4, 79.1, 80.3, 166.5, 169.2, 170.1, 171.3; FABMS *m/z* (relative intensity) [$(M+H)^+$, 100]. Anal. Cacld for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.36. Found: C, 51.98; H, 6.71; N, 3.22.

For **24**: mp 82–83°C; R_f 0.33 [EtOAc–hexane (3:1)]; $[\alpha]^{25}_D$=+33.8 (*c* 1.0, $CHCl_3$); IR (neat) 2950, 2850, 1747, 1371, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (6H, s), 2.06 (6H, s), 2.60 (3H, s, N–CH_3), 3.07 (2H, m, H-2eq,

H-3ax), 3.43 (1H, dd, J=10.0, 2.0 Hz, H-5ax), 3.67 (1H, dd, J=13.0, 2.0 Hz, H-1ax), 3.76 (1H, t, J=7.4 Hz, H-9a), 4.04 (1H, dd, J=12.5, 6.5 Hz, H-8a), 4.08 (1H, d, J=13.0 Hz, H-1eq), 4.21 (1H, dd, J=9.6, 7.4 Hz, H-9b), 4.36 (1H, dd, J=12.5, 2.5 Hz, H-8b), 4.86 (1H, dd, J=10.0, 8.5 Hz, H-4ax), 5.21 (1H, dd, J=6.5, 2.0 Hz, H-6), 5.26 (1H, dq, J=6.5, 2.5 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 21.1 (4C), 40.9, 44.6, 62.9, 66.3, 66.5, 68.0, 68.3, 69.8, 70.8, 76.8, 169.9, 170.2, 170.6, 171.0; EIMS m/z (relative intensity) 417 (M^+, 85). Anal. Calcd for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.36. Found: C, 52.06; H, 6.74; N, 3.06.

4.3.9. 3-*O*-Allyl-5,6-carbonate-1,2-*O*-isopropylidene-α-D-allofuranose (31). Methyl chloroformate (0.7 mL, 9.1 mmol) was added to a solution of diol **30**[8] (0.5 g, 1.92 mmol) and TEA (0.7 mL, 9.1 mmol) in CH_2Cl_2 (5 mL) at 0°C. The reaction mixture was stirred for 3 h and the solvent was removed in vacuo. Et_2O (20 mL) was added and the mixture was filtered. The solvent was removed in vacuo and the residue was chromatographed on silica gel to give carbonate **31** (0.53 g, 97%) as colorless crystals: mp 72°C; $[\alpha]^{27}_D$=81.7 (c 1.2, $CHCl_3$); TLC [Et_2O–hexane (3:1)] R_f 0.32; IR (neat) 1801, 1168, 1085, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, s); 1.59 (3H, s); 3.77–3.81 (4H, m); 3.93–4.01 (1H, m); 4.19–4.28 (2H, m); 4.49 (2H, ddt, J=2.2, 4.0, 6.9 Hz); 4.67 (1H, t, J=3.85 Hz); 4.92–5.00 (2H, m); 5.23–5.37 (2H, m); 5.77 (1H, d, J=6.8 Hz); 5.84–6.00 (1H, m); MS m/z 271 (M^+–Me, 20.8), 43 ($C_3H_7^+$, 100). Anal. Cacld for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.58; H, 6.18.

4.3.10. 3-*O*-Allyl-5,6-carbonate-D-allofuranose (32). A solution of the acetonide **31** (445 mg, 1.55 mmol) in 90% TFA (3 mL) was stirred for 12 h. The acid was removed in vacuo and the residue was chromatographed on silica gel to give hemiacetal **32** (331 mg, 87%) as a colorless oil. TLC [EtOAc–hexane (3:1)] R_f 0.34. The product was used immediately in the next step.

4.3.11. 2-*O*-Allyl-4,5-carbonate-3*O*-formyl-D-ribose (33). $NaIO_4$ (4.6 g, 21 mmol) was added to a solution of **114** (1.2 g, 4.9 mmol) in 60% aqueous dioxane (70 mL). After stirring for 4 h at rt, the reaction mixture was filtered and concentrated to give **115** (0.95 g, 80%) as a yellow syrup. The product was immediately used in the next stage without further purification.

4.3.12. 2-*O*-Allyl-4,5-carbonate-D-ribitol (34). $NaBH_4$ (140 mg, 3.8 mmol) in H_2O (10 mL) was added to a solution of **33** (0.95 g, 3.9 mmol) in MeOH (10 mL) at 0°C. The mixture was stirred for 6 h at rt and saturated aqueous NH_4Cl (20 mL) was added slowly. The mixture was extracted with CH_2Cl_2 (3×40 mL). The combined extracts were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$) and filtered. The filtrate was concentrated to a yellow syrup and chromatographed on silica gel to give diol **34** (0.76 g, 90%) as colorless oil: $[\alpha]^{27}_D$=+19.3 (c 1.0, $CHCl_3$); TLC [EtOAc–hexane (2:1)] R_f 0.31; IR (neat) 3400, 1785, 1187, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.38–3.43 (1H, m); 3.65–3.89 (4H, m); 3.93–4.01 (1H, m); 4.10–4.24 (2H, m); 4.45 (1H, t, J=8.4 Hz); 4.58 (1H, t, J=8.4 Hz); 4.93–5.00 (1H, m); 5.20–5.35 (2H, m); 5.85 (1H, ddt, J=10.3, 17.2, 6.0 Hz); MS m/z 203 (M^+–Me, 13), 57 ($C_3H_5O^+$, 57.5). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.15; H, 6.49.

4.3.13. 2-*O*-Allyl-D-ribitol (35). NaOMe (cat. amt.) was added to a solution of **34** (1.1 g, 5.0 mmol) in MeOH (25 mL) and stirred for 1 h. The mixture was concentrated and the residue was chromatographed on silica gel to give **35** (0.96 g, 100%) as a sticky pale yellow solid: $[\alpha]^{25}_D$=+2.22 (c 0.9, MeOH); TLC [MeOH–$CHCl_3$ (1:3)] R_f 0.38; IR (neat) 3400, 2910, 1420, 1050 cm^{-1}; ^{1}H NMR (D_2O) δ 3.57–4.15 (7H, m); 4.13 (2H, dd, J=1.4, 6.0 Hz); 5.25 (1H, dq, J=10.3, 1.4 Hz); 5.33 (1H, dq, J=17.2, 1.4 Hz); 5.97 (1H, ddt, J=10.3, 17.2, 6.0 Hz); MS m/z 187 (5.4), 43 ($C_3H_7^+$, 100). Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 49.06; H, 8.11.

4.3.14. 2-*O*-Allyl-4,5-*O*-isopropylidene-D-ribitol (36). Camphorsulfonic acid (cat. amt.) was added to a solution of **35** (0.5 g, 2.6 mmol) in acetone (15 mL) and stirred for 1 h. NH_3 solution (four drops) was added and the solvent was removed in vacuo. The residue was chromatographed on silica gel to give acetonide **36** (370 mg, 61%) as a pale yellow syrup: $[\alpha]^{24}_D$=+18.0 (c 1.4, $CHCl_3$); TLC [EtOAc–hexane (2:1)] R_f 0.33; IR (neat) 3450, 2950, 1400, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, s); 1.43 (3H, s); 3.52 (1H, q, J=4.5 Hz); 3.73–4.24 (9H, m); 5.20–5.25 (1H, m); 5.26–5.34 (1H, m); 5.84–6.00 (1H, m); MS m/z 217 (M^+–Me, 10), 43 ($C_3H_7^+$, 100). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.06; H, 8.68.

4.3.15. 2-*O*-Allyl-1,3-di-*O*-benzyl-4,5-*O*-isopropylidene-D-ribitol (37). Sixty percent sodium hydride (150 mg, 3.8 mmol) was washed with hexane (3×10 mL) and dry THF (3 mL) was added. Diol **36** (255 mg, 1.1 mmol) and benzyl bromide (0.4 mL, 3.3 mmol) in THF (3 mL) was added slowly at 0°C. TBAI (cat. amt.) was added and heated to reflux for 3 h under nitrogen. Saturated aqueous NH_4Cl (10 mL) was added at 0°C and the mixture was extracted with $CHCl_3$ (3×10 mL). The combined extracts were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$) and filtered. The filtrate was concentrated to a yellow syrup and chromatographed on silica gel to give benzyl ether **37** (383 mg, 84%) as pale yellow syrup: $[\alpha]^{25}_D$=+22.4 (c 1.2, $CHCl_3$); TLC [Et_2O–hexane (1:5)] R_f 0.36; IR (neat) 2990, 2870, 1091, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, s); 1.41 (3H, s); 3.59–3.81 (4H, m); 3.89–4.27 (5H, m); 4.53 (2H, d, J=1.9 Hz); 4.70 (2H, s); 5.16 (1H, dd, J=1.5, 10.4 Hz); 5.30 (1H, dq, J=17.2, 1.6 Hz); 5.83–5.99 (1H, m); 7.25–7.33 (10H, m); MS m/z 412 (M^+, 0.1), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.75; H, 7.82.

4.3.16. 2-*O*-Allyl-1,3-di-*O*-benzyl-D-ribitol (38). A solution of the acetonide **37** (260 mg, 0.64 mmol) in 90% aqueous TFA (3 mL) was stirred for 3 h. The acid was removed in vacuo and the residue was chromatographed on silica gel to give diol **38** (171 mg, 72%) as colorless oil: $[\alpha]^{25}_D$=+19.8 (c 1.1, $CHCl_3$); TLC [EtOAc–hexane (3:2)]R_f 0.33; IR (neat) 3410, 2900, 1450, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.59–3.90 (6H, m); 4.01–4.24 (3H, m); 4.55 (2H, s); 4.61 (2H, d, J=3.1 Hz); 5.16–5.31 (2H, m); 5.82–5.98 (1H, m); 7.26–7.34 (10H, m); MS m/z 253

(M^+-H_2O, 2.2), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 70.61; H, 7.56.

4.3.17. 3-*O*-Allyl-2,4-di-*O*-benzyl-aldehydo-L-threose (27). $NaIO_4$ (1.0 g, 4.7 mmol) was added to a solution of the diol **38** (0.40 g, 1.07 mmol) in 60% aqueous dioxane (15 mL) and stirred for 3 h at rt. The reaction mixture was filtered and concentrated to give aldehyde **27** as a pale yellow syrup (0.3 g, 82%). The product was immediately used in the next stage without further purification.

4.3.18. [3a*R*-[3aα,6β,7α,7aβ]]-7-Benzyloxy-6-(benzyloxymethyl)hexahydro-1-methyl-3*H*-pyrano[4,3-c]isoxazole (29). INAC reaction of aldehyde **27** (0.3 g) according to procedure C followed by flash chromatography [EtOAc–hexane (3:1)] afforded THP **29** (278 mg, 88%) as colorless needles: mp 65–66°C; R_f 0.32 [Et_2O–hexane (3:1)]; $[\alpha]^{24}_D=-16.1$ (*c* 1.2, $CHCl_3$); IR (neat) 2860, 1410, 1106, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (3H, s, N–CH_3), 3.04 (1H, m, H-2eq), 3.18 (1H, t, *J*=7.3 Hz, H-3ax), 3.36 (1H, ddd, *J*=10.0, 5.5, 2.0 Hz, H-5ax), 3.46 (1H, dd, *J*=10.0, 7.3 Hz, H-4ax), 3.60 (1H, dd, *J*=10.8, 5.5 Hz, H-6a), 3.74 (1H, dd, *J*=12.3, 3.3 Hz, H-1ax), 3.77 (1H, dd, *J*=10.8, 2.0 Hz, H-6b), 3.79 (1H, dd, *J*=9.0, 7.3 Hz, H-7a), 4.06 (1H, bd, *J*=12.3 Hz, H-1eq), 4.24 (1H, dd, *J*=9.9, 7.3 Hz, H-7b), 4.52 (1H, d, *J*=11.2 Hz), 4.54 (1H, d, *J*=12.2 Hz), 4.59 (1H, d, *J*=12.2 Hz), 4.96 (1H, d, *J*=11.2 Hz), 7.20–7.35 (10H, m); ^{13}C NMR ($CDCl_3$) δ 40.1, 43.7, 64.7, 67.8, 69.9, 70.7, 73.2, 73.6, 74.0, 78.6, 127.1(2C), 127.4 (4C), 128.0 (4C), 138.0, 138.6; EIMS *m/z* (relative intensity) 278 ($M^+-C_7H_7$, 13), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.27; H, 7.30; N, 3.51.

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