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Synthesis of a trihydroxylated azepane from D-arabinose by way of an intramolecular alkene nitrone cycloaddition

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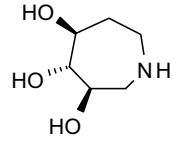
Abstract—The synthesis of 1,6-imino-1,5,6-trideoxy-L-*xylo*-hexitol, a trihydroxylated azepane, from D-arabinose was achieved by way of an intramolecular alkene nitrone cycloaddition. The final product as well as its bicyclic precursor, (3*R*,4*S*,5*S*)-3,4-dihydroxy-8-oxa-1-azabicyclo[3.2.1]octane, were evaluated as glycosidase inhibitors.

1. Introduction

Saturated nitrogen heterocycles mimicking carbohydrate structures are gaining widespread interest because of their potent and diverse biological activities: initially discovered for their properties as glycosidase inhibitors,[1] such iminosugars have been found to have activities, for example, on glycosyltransferases,[2] glycogen phosphorylases,[3] UDP-galactose mutase[4] and nucleoside-processing enzymes.[5] Since these enzymes are involved in numerous fundamental biological processes, these carbohydrate mimetics constitute leads for the development of new therapeutic agents in a wide range of diseases.[6]



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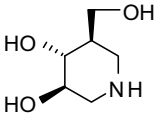

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While most iminosugars are pyrrolidine or piperidine derivatives, examples based on smaller as well as larger ring systems have been reported; in particular, polyhydroxylated azepanes[7] including seven-membered-ring homologues of nojirimycin[8] have been described by several groups, and we have disclosed recently the first example of an azocane-based iminosugar analogue.[9] Herein we report the synthesis of a new trihydroxylated azepane,[10] 1,6-imino-1,5,6-trideoxy-L-*xylo*-hexitol **1**, that is a ring-expanded isomer of isofagomine, **2**, by way of a methodology based on an internal 1,3-dipolar cycloaddition, as well as an evaluation of this seven-membered ring iminoalditol as a glycosidase inhibitor.

In previous studies, we have demonstrated the usefulness of the intramolecular cycloaddition of the oxime derived from an unsaturated sugar aldehyde for the synthesis of amino-cyclopentitols.[11] In this context, we have examined the feasibility of a synthesis of isofagomine **2** by way of an internal cycloaddition of an unsaturated nitrone. Isofagomine **2** is of interest as a powerful β-glucosidase inhibitor, but its synthesis remains lengthy and requires a chain-branching step.[12] As suggested by a strategic N,O-reconnection in **2** (Scheme 1), the resulting bicyclic structure **A** could be accessible by way of an intramolecular reaction of a methylene nitrone and an alkene (as in **B**). While intermolecular cycloadditions of methylene nitrones with terminal alkenes have been shown to proceed with the alternate regioselectivity (C–C bond formation at the terminal alkene carbon

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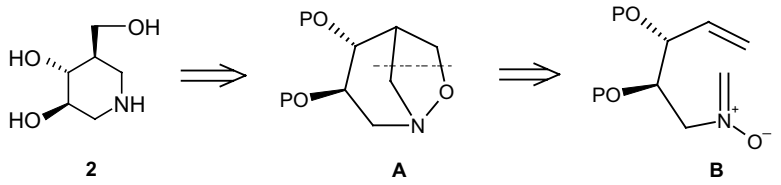


Scheme 1.

atom),[13] an example of intramolecular reaction in a related system[14] lent support to our idea. We therefore set out to explore this approach.

2. Results and discussion

The synthesis (Scheme 2) began with 5-deoxy-5-iodo-D-arabinofuranoside **3**, obtained in three steps and 63% yield from D-arabinose, as described by Ferrier and Haines.[15] Treatment of this compound with Zn in the presence of vitamin B_{12} as initiator[16] gave the 4,5-unsaturated pentose derivative **4** in 79% yield, and the aldehyde was rapidly converted into oxime **5**. Reduction of the oxime function with sodium cyanoborohydride led to the corresponding *N*-alkylated hydroxylamine **6**, which was then treated with gaseous formaldehyde under anhydrous conditions to form methylene nitrone **7**. This compound spontaneously cyclized to form a major bicyclic hydroxylamine, compound **8**, isolated in 56% yield. The ^{1}H and ^{13}C NMR data of this compound indicated unambiguously that it was the alternate regioisomer resulting from C–C bond connection at the terminal alkene carbon. The stereochemical assignments were established on the basis of its NMR parameters and extensive NOE studies (Fig. 1).

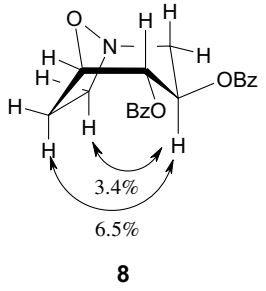
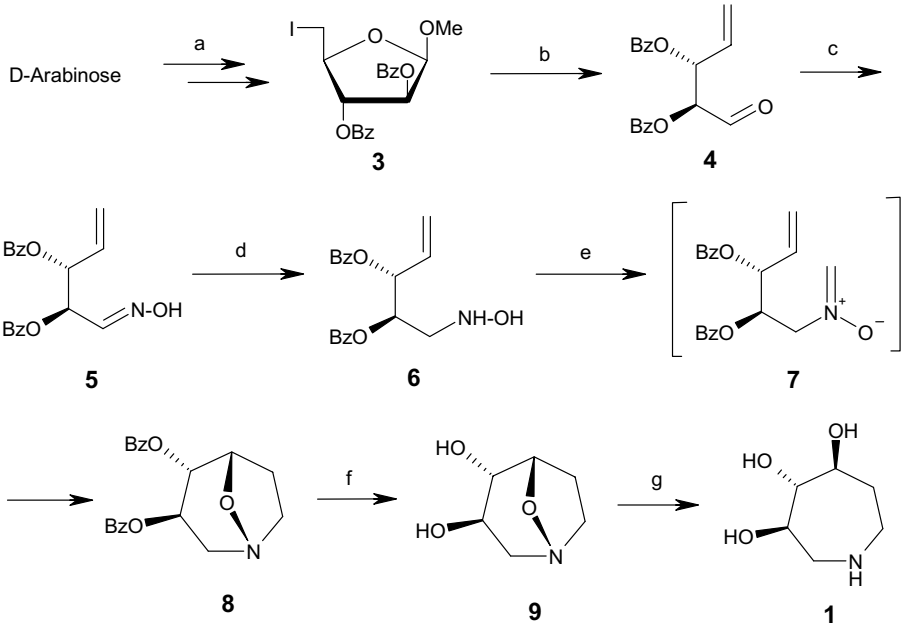


Figure 1. NOE correlations in **8**.

The constitution and stereochemistry of the main cycloaddition product **8** are consistent with a mechanism involving a chair-like transition state structure carrying two equatorial substituents, and controlled by C–C bond formation to the less substituted end of the alkene (Fig. 2). This approach therefore does not provide the carbon skeleton of isofagomine, but the isomeric azepane ring system.

Compound **8** was debenzoylated under Zemplén conditions to provide the unusual bicyclic iminosugar analogue **9**. The N–O linkage was then cleaved by



Scheme 2. Reagents and conditions: (a) Ref. 15; (b) Zn, NH_4Cl, vitamin B_{12}, MeOH, rt, 79%; (c) $NH_2OH{\cdot}HCl$, pyridine, EtOH, 60 °C, 87%; (d) $NaBH_3CN$, HCl, pH 3–4, MeOH, −5 °C; (e) HCHO, toluene, Na_2SO_4, 0 °C then reflux, 56% (over the two steps); (f) MeONa, MeOH, rt, 81%; (g) H_2, Pd/C, MeOH, rt, 99%.

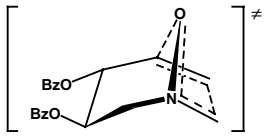


Figure 2. Proposed transition state structure.

Table 1. IC_{50} values for of **9** and **1** in assays of various glycosidases[a]

Enzyme	IC_{50} (μM)	
	9	**1**
α-Glucosidase (rice)	(40.4)	(47.8)
β-Glucosidase (almond)	(8.2)	250
α-Galactosidase (coffee beans)	(0)	350
β-Galactosidase (bovine liver)	(42.4)	420
α-Mannosidase (rat epididymis)	(0)	(49.2)
β-Mannosidase (rat epididymis)	(0)	(13.4)
α-L-Fucosidase (bovine epididymis)	(13.8)	59

[a] Values in brackets are % inhibition of enzyme activity at 1000 μM.

hydrogenolysis, to afford 1,6-imino-1,5,6-trideoxy-L-*xylo*-hexitol **1**.

The potential of **9** and **1** as glycosidase inhibitors was examined towards a panel of glycosidases (Table 1). Compound **9** was found to be only very weakly active (40% inhibition of two enzymes at 1 mM concentration: α-glucosidase (rice) and bovine β-galactosidase). The trihydroxylated azepane **1** however exhibited an interesting activity towards bovine α-L-fucosidase (IC_{50} 59 μM) as well as, to a lesser extent, towards other glycosidases.

3. Conclusion

In conclusion, it was shown that the intramolecular 1,3-dipolar cycloaddition of a N-methylene nitrone derived from a 4,5-unsaturated pentose gave the bicyclic 8-oxa-1-azabicyclo[3.2.1]octane ring system by formation of the C–C bond to the less substituted carbon of the alkene. The resulting bicyclic product serves as a precursor of a trihydroxylated azepane, a compound that exhibits interesting activities as α-L-fucosidase inhibitor.

4. Experimental

4.1. General methods

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a positive pressure of argon. Anhydrous solvents were prepared by standard protocols and were freshly distilled. All reactions were monitored by TLC on 0.2 mm Merck silica gel plates ($60F_{254}$) using UV light, ethanol–sulfuric acid (10:1) solution or 2% phosphomolybdic acid solution as developing agent. Flash column chromatography was performed on Merck silica gel 60 (0.036–0.063 mm). Optical rotations were determined at 20–25 °C using a Perkin–Elmer polarimeter (model 41) and specific rotation values are given in 10^{-1} deg $cm^2\ g^{-1}$. NMR spectra were recorded on Bruker AVANCE DPX 250 and DRX 400 spectrometers with either TMS or residual protic solvent as internal reference. IR spectra were recorded on Perkin–Elmer TF PARAGON 1000 PC spectrophotometer. Mass spectra were recorded under ion spray conditions on a Perkin–Elmer SCIEX API 300 spectrometer at the Institut de Chimie Organique et Analytique, University of Orléans. Accurate masses were recorded under positive-ion electrospray on a Finnigan MAT 900 XLT high-resolution mass spectrometer.

4.2. 2,3-Di-*O*-benzoyl-4,5-dideoxy-D-*threo*-pent-4-enose 4

To a stirred solution of vitamin B_{12} (37 mg, 27 μmol) in methanol (85 mL) were successively added zinc dust (3.00 g, 46 mmol) and ammonium chloride (2.50 g, 46 mmol). The mixture was stirred for 10 min and a solution of compound **3**[15] (2.22 g, 4.6 mmol) in methanol (5 mL) was added. After 90 min, the mixture was filtered on Celite and the solvent removed under reduced pressure. Column chromatography (light petroleum–ethyl acetate; 5:1 then 3:1) provided aldehyde **4** (1.18 g, 79%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3472, 1740, 1601, 1452, 1242, 1106, 709; δ_H (250 MHz, $CDCl_3$) 9.70 (s, 1H, H-1), 8.20–8.00 (m, 4H, ArH), 7.70–7.30 (m, 6H, ArH), 6.14 (m, 1H, $J_{3,4}$ 6.0, $J_{3,2}$ 3.8, H-3), 6.04 (ddd, 1H, $J_{3,4}$ 6.0, $J_{4,5Z}$ 17.0, $J_{4,5E}$ 10.3, H-4), 5.58 (d, 1H, $J_{3,2}$ 3.8, H-2), 5.55 (d, 1H, $J_{4,5Z}$ 17.0, H-5_Z), 5.41 (d, 1H, $J_{4,5E}$ 10.3, H-5_E); δ_C (62.9 MHz, $CDCl_3$) 195.3 (C-1), 165.8 (C=O), 165.2 (C=O), 133.9 (CH), 133.7 (CH), 131.2 (CH), 130.1 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.3 (C), 128.8 (C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 120.2 (C-5), 78.8, 72.4 (C-2, C-3); *m/z* 325 $[M+H]^+$.

4.3. 2,3-Di-*O*-benzoyl-4,5-dideoxy-D-*threo*-pent-4-enose oxime 5

A stirred solution of aldehyde **4** (220 mg, 0.68 mmol), pyridine (165 μL, 2.03 mmol) and hydroxylamine hydrochloride (141 mg, 2.03 mmol) in ethanol (5 mL) was heated at 60 °C for 45 min. After cooling, the ethanol was removed under reduced pressure and the residue taken up in diethyl ether and washed with water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. Column chromatography (light petroleum–ethyl acetate; 4:1) provided oxime **5** (200 mg, 87%) as a colourless, oily, 7:3 mixture of *E* and *Z* isomers, ν_{max} (thin film)/cm^{-1} 3428, 1731, 1601, 1452, 1257, 1107, 946, 711; δ_H (250 MHz, $CDCl_3$) 9.60 (br s, 0.3H, OH_Z), 9.30 (br s, 0.7H, OH_E), 8.18–7.95 (m, 4H, ArH), 7.70–7.30 (m, 7.7H, ArH, H-1_E), 6.86 (d, 0.3H, $J_{1,2}$ 5.8, H-1_Z), 6.47 (dd, 0.3H, $J_{1,2}$ 5.8, $J_{2,3}$ 4.4, H-2_Z), 6.15–5.90 (m, 2.7H, H-2_E, H-3, H-4), 5.60–5.30 (m, 2H, 2 × H-5); δ_C (62.9 MHz, $CDCl_3$) 165.5 (C=O), 165.4 (C=O), 147.0 (C-1_Z), 146.2 (C-1_E), 133.6 (CH), 133.5 (CH), 133.4 (CH), 131.5, 131.4 (C-4_E, C-4_Z), 130.0 (CH), 129.9 (CH), 129.7 (C), 129.6 (C), 129.4 (C), 129.3 (C), 128.7 (CH), 128.6 (CH), 120.5 (C-5_E), 119.9 (C-5_Z), 73.9 (C-3_E), 73.7 (C-3_Z), 71.7 (C-2_E),

68.2 (C-2$_Z$); *m/z* 362 $[M+Na]^+$, 357 $[M+NH_4]^+$, 340 $[M+H]^+$; HRMS: found: MH^+, 340.1187. ($C_{19}H_{17}NO_5$ requires *m/z* 340.1185).

4.4. 2,3-Di-*O*-benzoyl-1,4,5-trideoxy-1-hydroxylamino-D-*threo*-pent-4-enitol 6

Sodium cyanoborohydride (60 mg, 0.95 mmol) was added at −5 °C to a stirred solution of oxime **5** (124 mg, 0.36 mmol) and a few drops of methyl orange indicator in dry methanol (3 mL) under nitrogen. A solution of hydrochloric acid in methanol (6 M) was added dropwise to keep the solution pink (pH 3). The solution was stirred for 30 min and quenched with aqueous sodium hydroxide (20%) and then poured into ice brine. The aqueous suspension was extracted at 0 °C with dichloromethane (2×) and the organic phase dried over $MgSO_4$, filtered and the solvent removed in vacuo. The hydroxylamine **6** was used in the next step without further purification.

4.5. (3*R*,4*S*,5*S*)-3,4-Dibenzoyloxy-8-oxa-1-azabicyclo-[3.2.1]octane 8

Gaseous formaldehyde, prepared from paraformaldehyde by heating a flask containing the solid with a flame, was bubbled into a solution of crude hydroxylamine **6** in dry toluene (8 mL) under nitrogen at 0 °C containing anhydrous sodium sulfate (500 mg). The mixture was stirred for 45 min at 0 °C and then heated at reflux for 24 h. On cooling, the mixture was filtered through a pad of Celite and the solvent was removed in vacuo. The residue was purified by flash column chromatography (light petroleum–ethyl acetate; 1:1) to provide bicyclic compound **8** (73 mg, 56% over two steps) as a yellow solid; $[\alpha]_D = -147$ (*c* 1.05, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1728, 1601, 1452, 1276, 1108, 709; δ_H (400 MHz, C_6D_6) 8.17 (d, 2H, ArH), 8.10 (d, 2H, ArH), 7.10–7.00 (m, 6H, ArH), 5.81 (dd, 1H, $J_{4,5}$ 4.2, $J_{4,3}$ 9.0, H-4), 5.60 (ddd, 1H, $J_{3,2eq}$ 6.6, $J_{3,2ax}$ 10.0, $J_{4,3}$ 9.0, H-3), 4.67 (dd, 1H, $J_{5,4}$ 4.2, $J_{5,6eq}$ 7.5, H-5), 3.40 (dd, 1H, $J_{2ax,2eq}$ 13.9, $J_{3,2ax}$ 10.0, H-2ax), 3.28 (dd, 1H, $J_{3,2eq}$ 6.6, $J_{2eq,2ax}$ 13.9, H-2eq), 3.00 (ddd, 1H, $J_{7eq,6eq}$ 11.3, $J_{7eq,6ax}$ 5.5, $J_{7eq,7ax}$ 16.9, H-7eq), 2.66 (ddd, 1H, $J_{7ax,6eq}$ 4.2, $J_{7ax,6ax}$ 9.2, $J_{7ax,7eq}$ 16.9, H-7ax), 2.04 (ddd, 1H, $J_{6ax,6eq}$ 14.5, $J_{6ax,7ax}$ 9.2, $J_{6ax,7eq}$ 5.5, H-6ax), 1.64 (m, 1H, $J_{6ax,6eq}$ 14.5, $J_{6eq,7ax}$ 4.2, $J_{6eq,7eq}$ 11.3, $J_{6eq,5}$ 7.5, H-6eq); δ_C (100.6 MHz, C_6D_6) 165.8 (C=O), 165.2 (C=O), 133.0 (CH), 132.9 (CH), 132.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 75.5 (C-5), 72.8 (C-4), 67.2 (C-3), 58.6 (C-2), 52.6 (C-7), 29.8 (C-6); *m/z* 376 $[M+Na]^+$, 354 $[M+H]^+$; HRMS found: MH^+, 354.1340 ($C_{20}H_{19}NO_5$ requires *m/z* 354.1341). Selected NOE data: irradiation of H-7eq enhances H-7ax (25.1%), H-6eq (6.1%); irradiation of H-7ax enhances H-7eq (27.2%), H-3 (6.5%), irradiation of H-6ax enhances H-6eq (23.6%), H-7ax (4.1%), H-3 (9.5%); irradiation of H-6eq enhances H-6ax (26.5%), H-7eq (6.4%), H-5 (8.3%); irradiation of H-5 enhances H-6eq (4.3%), H-4 (10.0%); irradiation of H-4 enhances H-5 (9.0%), H-2ax (2.6%); irradiation of H-3 enhances H-2eq (4.5%), H-7ax (3.4%), H-6ax (6.5%); irradiation of H-2ax enhances H-2eq (8.9%), H-4 (5.0%); irradiation of H-2eq enhances H-7ax (4.3%), H-2ax (20.2%) and H-3 (7.8%) (Fig. 2).

4.6. (3*R*,4*S*,5*S*)-3,4-Dihydroxy-8-oxa-1-azabicyclo-[3.2.1]octane 9

A solution of sodium methoxide (produced from fresh sodium shavings) in methanol (1 mL) was added to a solution of bicyclic compound **8** (60 mg, 0.17 mmol) in methanol (0.5 mL) at 0 °C. The mixture was allowed to warm up to room temperature, stirred for 2 h, then neutralized with a mixture of AcOH and MeOH (1:3, v/v) and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH; 8:1) to provide bicyclic compound **9** (20 mg, 81%) as a white solid; $[\alpha]_D = -52$ (*c* 0.99, MeOH); ν_{max} (KBr)/cm^{-1} 3406, 1650, 1092; δ_H (250 MHz, CD_3OD) 4.34 (dd, 1H, $J_{5,4}$ 3.9, $J_{5,6eq}$ 7.3, H-5), 3.64 (ddd, 1H, $J_{3,2eq}$ 6.4, $J_{3,2ax}$ 10.0, $J_{4,3}$ 8.6, H-3), 3.55 (dd, 1H, $J_{4,5}$ 3.9, $J_{4,3}$ 8.6, H-4), 3.16–3.07 (m, 2H, H-7eq, H-7ax), 3.07 (dd, 1H, $J_{3,2eq}$ 6.4, $J_{2ax,2eq}$ 13.7, H-2eq), 2.88 (dd, 1H, $J_{3,2ax}$ 10.0, $J_{2eq,2ax}$ 13.7, H-2ax), 2.32 (m, 1H, $J_{6ax,6eq}$ 15.4, $J_{6ax,7eq}$ 7.3, $J_{6ax,7ax}$ 12.7, H-6ax), 2.08 (m, 1H, $J_{6ax,6eq}$ 15.4, $J_{6eq,7ax} = J_{5,6eq}$ 7.3, $J_{6eq,7eq}$ 12.7, H-6eq), δ_C (62.9 MHz, CD_3OD) 79.6 (C-5), 74.3 (C-4), 67.5 (C-3), 61.9 (C-2), 53.6 (C-7), 29.9 (C-6); *m/z* 146 $[M+H]^+$; HRMS found: MH^+, 146.0815 ($C_6H_{11}NO_3$ requires *m/z* 146.0817).

4.7. (3*R*,4*R*,5*S*)-3,4,5-Trihydroxyazepane 1

A solution of bicyclic compound **9** (12 mg, 83 μmol) in MeOH (2 mL) was hydrogenated in the presence of 10% Pd on carbon (spatula tip) at room temperature under atmospheric pressure of hydrogen for 24 h. The catalyst was removed by filtration through Celite and the filtrate concentrated in vacuo to give compound **1** (12 mg, 99%) as a colourless oil; $[\alpha]_D = +23.9$ (*c* 0.65, H_2O); δ_H (250 MHz, CD_3OD) 3.78–3.68 (m, 2H, H-3, H-5), 3.54 (dd, 1H, *J* 5.2, *J* 6.6, H-4), 3.25–3.14 (m, 1H, H-7), 3.06 (m, 2H, 2 × H-2), 2.93 (m, 1H, H-7), 1.96 (m, 2H, 2H-6), δ_C (62.9 MHz, CD_3OD) 80.1 (C-4), 74.1, 72.6 (C-5, C-3), 48.2 (C-2), 44.3 (C-7), 31.2 (C-6); *m/z* 148 $[M+H]^+$; HRMS found: MH^+, 148.0975 ($C_6H_{13}NO_3$ requires *m/z* 148.0973).

4.8. Enzymatic assays

The enzymes α-glucosidase (rice), β-glucosidase (sweet almond), α-galactosidase (coffee beans), β-galactosidase (bovine liver) and α-L-fucosidase (bovine epididymis) were purchased from Sigma Chemical Co. The rat epididymal fluid was purified from epididymis according to the method of Skudlarek et al.[17] The activity of rice α-glucosidase was determined using maltose as a substrate at pH 5.0. The released D-glucose was determined colorimetrically using Glucose B-test Wako (Wako Pure Chemicals Industries). Other glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as a substrate at the optimum pH of each enzyme. The reaction was stopped by adding 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

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