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Asymmetric synthesis of novel polyhydroxylated derivatives of indolizidine and quinolizidine by intramolecular 1,3-dipolar cycloaddition of *N*-(3-alkenyl)nitrones†

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Reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-1,5-pentadialdo-α-D-xylofuranose with *N*-(1,1-dimethylbut-3-enyl)-hydroxylamine followed by intramolecular 1,3-dipolar cycloaddition yields 7-oxa-1-azabicyclo[2.2.1]heptane derivative 4, which is easily converted into novel polyhydroxylated quinolizidine 6 and indolizidine 8.

Polyhydroxylated derivatives of indolizidine and quinolizidine (frequently named as azasugars) are powerful glycosidase inhibitors and potential therapeutics.[1] Consequently, these compounds are targets of intensive synthetic studies.

Many syntheses of azasugars use derivatives of natural sugars as starting materials.[1] Based on our experience in intramolecular 1,3-dipolar cycloaddition of *N*-(3-alkenyl)nitrones[2,3] we envisaged that this reaction, proceeding with high regio- and diastereoselectivity,[4] might be a useful tool for conversion of sugar dialdehydes, with one carbonyl group masked, into bicyclic azasugars **E** (Fig. 1).

We reasoned that the nitrone **C**, attained from the protected cyclic or acyclic sugar dialdehydes **A** and *N*-homoallylhydroxylamine **B**, (a sugar ring in Fig. 1 is symbolised by the dashed bow) might undergo intramolecular 1,3-dipolar cycloaddition to give the **7**-oxa-1-azabicyclo[2.2.1]heptane derivative **D** with high stereoselectivity induced by the sugar moiety.‡ Subsequent unmasking of the carbonyl function, which could be combined with a modification of the sugar residue (*e.g.* shortening of the carbon skeleton by a diol cleavage), followed by hydrogenolysis of the N–O bond accompanied by intramolecular reductive amination would complete the synthesis of the target derivative **E**.

We describe herein the transformation of the cyclic sugar dialdehyde 1,2-*O*-isopropylidene-1,5-pentadialdo-α-D-xylofuranose **1**,[5] readily available from α-D-glucose, into the novel polyhydroxylated quinolizidine **6** and indolizidine **8**, possessing a tertiary carbon at an α position to nitrogen, to illustrate the usefulness of the proposed method for the bicyclic azasugar preparation (Scheme 1).

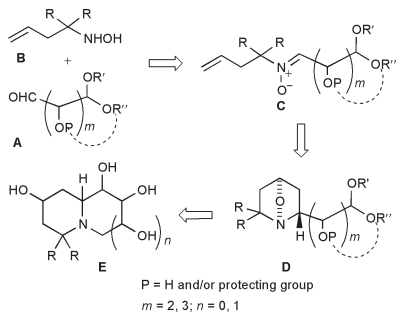
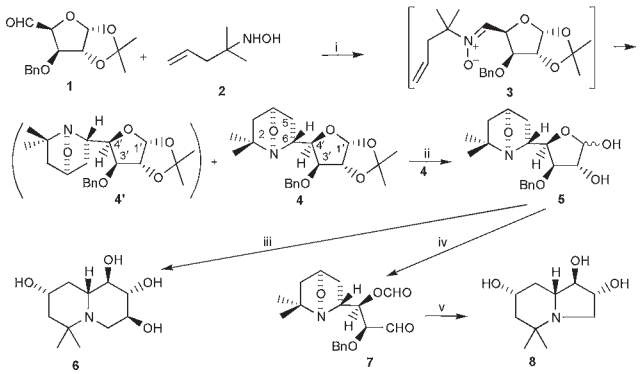


Fig. 1 General approach for asymmetric synthesis of bicyclic azasugars **E** by intramolecular 1,3-dipolar cycloaddition of *N*-(3-alkenyl)nitrones.

† Electronic supplementary information (ESI) available: configurational assignment of the adduct **4** and experimental details of preparation and characterisation of **6** and **8**. See http://www.rsc.org/suppdata/cc/b1/b101057n/



Scheme 1 *Reagents and conditions*: i, toluene, argon, 85–90 °C, 43 h, 52%; ii, 5% HCl aq., rt, 2 d, 96%; iii, H_2 (10 bar), Raney-Ni, MeOH, 75–80 °C, 21 h, 70% based on **4**; iv, $NaIO_4$, MeOH–H_2O, 0 °C; v, H_2 (10 bar), Raney-Ni, MeOH, rt, 24 h then 45 °C, 24 h, 55% based on **4**.

The *N*-homoallylhydroxylamine **2**, necessary for the preparation of **4**, was obtained from the aluminium amalgam reduction of 4-methyl-4-nitropent-1-ene (readily accessible from palladium(0)-catalysed *C*-allylation of 2-nitropropane[6]).[3] The aldehyde **1** heated with **2** in toluene, under argon, gave *N*-(3-alkenyl)nitrone **3** (Scheme 1), which *in situ* underwent intramolecular 1,3-dipolar cycloaddition. Although the possibility exists for formation of two adducts **4** and **4′**, we separated only one diastereoisomer **4** in 52% yield.§ Its structure was determined from ^{1}H NMR spectra and molecular modelling (AM1). The coupling constant between H_6 and $H_{4'}$ was very helpful for configurational assignment; the value of this constant, $^3J_{6,4'}$ = 9.9 Hz, is characteristic for protons in an antiperiplanar arrangement. Molecular modelling revealed that only for the adduct **4** did the lowest energy minimum correspond to the conformation in which H_6 and $H_{4'}$ are antiperiplanar.

The conversion of **4** into quinolizidine **6** was straightforward. Removal of isopropylidene protection by acidic hydrolysis gave cleanly the derivative **5**, which was hydrogenated in the presence of Raney-nickel to afford directly the quinolizidine **6** in 70% yield based on **4**. The structure of **6** from its ^{1}H NMR spectrum is consistent with the structure of **4**. Thus the heterobicyclic system adopts a structure close to *trans*-decaline and all hydroxy groups occupy equatorial positions.

The preparation of the indolizidine **8** was also easy. In this case the carbon skeleton of **5** was cut down by sodium periodate 1,2-diol cleavage to give the aldehyde **7**, which also without purification was hydrogenated in the presence of the nickel catalyst to yield **8** in 55% yield, based on **4**.

In conclusion, it has been shown that the intramolecular 1,3-dipolar cycloaddition of *N*-(3-alkenyl)nitrones, obtained from *N*-homoallylhydroxylamines and sugar dialdehydes, is very useful for the synthesis of polyhydroxylated derivatives of both quinolizidine and indolizidine. Further studies on improve-

ment and extension of this approach for the synthesis of bicyclic azasugars are in progress.

Notes and references

‡ To our best knowledge the intramolecular 1,3-dipolar cycloaddition reaction of *N*-(3-alkenyl)nitrones, obtained from non-racemic chiral aldhydes, has never been investigated.

§ All new compounds were fully characterised by ^{1}H and ^{13}C NMR, IR spectroscopy, high resolution mass spectrometry and optical rotation. Compound **4**: The aldehyde **1**[5] (0.58 g, 2.09 mmol) and the hydroxylamine **2**[3] (obtained from 0.50 g, 4.0 mmol of 4-methyl-4-nitropent-1-ene) were heated in toluene (4 cm^3), under argon, at 85–90 °C for 43 h. Chromatographic purification (silica gel, hexane–ethyl acetate, 5 : 1 → 2 : 1, v/v) furnished **4** (0.38 g, 52%) as white crystals, mp 91–92 °C (hexane); δ_H (500 MHz, $CDCl_3$): 1.12 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.24 (d, *J* 11.3 Hz, 1H, H_{3en}) 1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.66 (dd, *J* 11.8, 7.8 Hz, 1H, H_{5en}), 1.75 (ddd, *J* 11.3, 5.4, 2.5 Hz, 1H, $H_{3'}$), 1.99 (m, 1H, $H_{5'}$), 3.86 (ddd, *J* 9.9, 7.8, 3.9 Hz, 1H, H_6), 4.07 (dd, *J* 9.9, 3.1 Hz, 1H, $H_{4'}$), 4.22 (d, *J* 3.1 Hz, 1H, $H_{3'}$), 4.59 (d, *J* 3.9 Hz, 1H, $H_{2'}$), 4.67 (AB, Δ 0.06, *J* 11.8 Hz, 2H, CH_2Ph), 4.83 (t, *J* 5.3 Hz, 1H, H_4), 5.88 (d, *J* 3.9 Hz, 1H, $H_{1'}$), 7.2–7.37 (m, 5H, C_6H_5); δ_C (50 MHz, $CDCl_3$): 24.43, 26.25, 26.70, 31.27, 36.81, 46.86, 57.41, 65.82, 72.21, 81.76, 82.64, 83.25, 104.70, 111.49, 127.64, 127.71, 128.37; ν cm^{-1}: 3068, 3032, 2980, 1452, 1372, 1076; HRMS *m*/*z* calc. for $C_{20}H_{26}NO_5$ $(M\text{-}CH_3)^+$ 360.1811, found 360.1791; $[\alpha]_D^{20}$ −40.5 (*c* 0.4, CH_2Cl_2).

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