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Iminosugars from α,β-epoxyamides. Part 2: Synthetic approach to hydroxylated pyrrolidine and azepane derivatives

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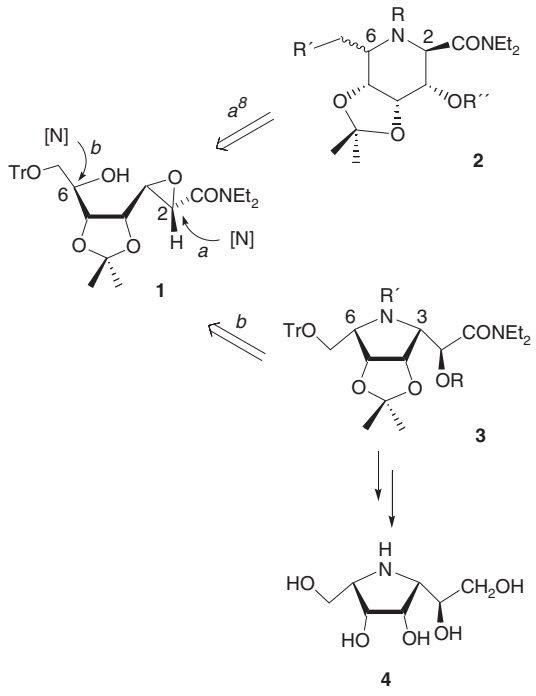
Abstract—This paper describes a new synthetic route towards hydroxylated pyrrolidines and azepane derivatives starting from chiral epoxyamides. The alternate transformations on a ribose derivative α,β-epoxyamide permit the construction of five or seven member rings leading to different precursors of homoiminosugars.

Homoiminosugars, or iminosugars with an additional hydroxymethyl group, have received considerable attention in the last few years because of their remarkable biological activities.[1] Among their useful properties is their greater selectivity in biological assays in comparison to their iminosugar homologues.[2] As a result of their potential therapeutic applications, more efficient synthesis and/or more selective compounds have been investigated and many synthetic[1–3] and natural[4–7] homoiminosugars have been identified.

We have reported in a recent communication[8] a synthetic approach to homoiminosugar derivatives from α,β-epoxyamides.[9] Two strategies (a and b) were planned starting from the epoxyamide **1**[9a] (Scheme 1), and the formation of piperidine derivatives was described.[8]

In this paper, we report the development of the second retrosynthetic alternative (b) with the formation of pyrrolidine derivatives of the type depicted by **3**. These compounds are aza-C-glycosides[10] and can be considered as precursors or derivatives of homoiminosugars. Thus, the deprotection and functional group interconversion of **3** could afford (inter alia) 2,5-dideoxy-2,5-imino-D-*glycero*-D-*galacto*-heptitol **4**. Polyhydroxylated alkaloids with analogous structures have recently been isolated from plants.[11]



Scheme 1.

With a view to broadening the utility of the epoxyamide **1**, we have reanalysed our retrosynthetic route leading to hydroxylated azepane derivatives **5** (Scheme 2). In a

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✠ Recently deceased. In memoriam.

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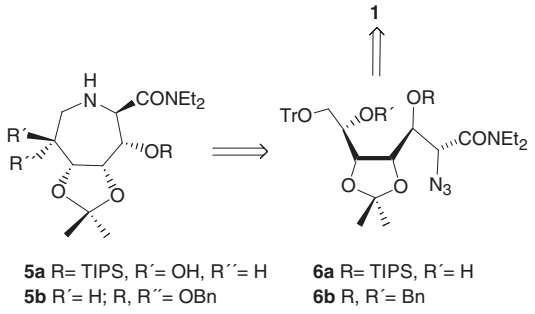
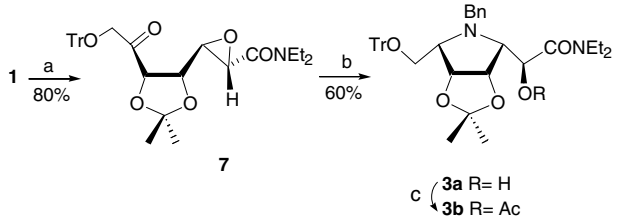


Scheme 2.

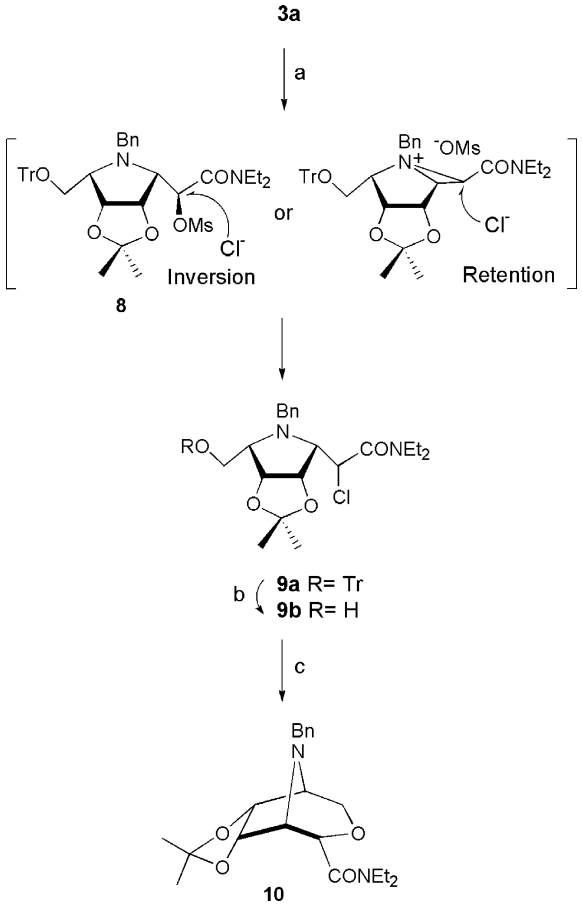
previous communication, we have mentioned the azepane **5a** as a side product in the formation of a piperidine derivative from precursor **6a**.[8] Now, we present an alternative synthesis of azepane **5b** as the sole product, starting with the introduction of an azide at C-2 of **1**, followed by the protection of the free hydroxyls to give **6b**.

For the synthesis of pyrrolidines, our strategy was based on the introduction of an amino precursor at C-6, according to the retrosynthetic analysis. In order to avoid a nucleophilic attack of the epoxide, an oxidation of the C-6 hydroxyl was envisaged to obtain a carbonyl group which should compete to attract the nucleophile. Indeed, the pyrrolidine **3a** could be obtained in only two steps from the epoxyamide **1** (Scheme 3), that is, five steps from D-ribose. Oxidation of the hydroxyl group was performed with dimethyl sulfoxide and acetic anhydride giving **7**. Other methods employed (PCC or Swern oxidations) gave lower yields. The ketone **7** was condensed with benzyl amine and the resulting imine reduced with $NaBH_3CN$ in one pot, giving the isomer **3a** through a regioselective and stereospecific intramolecular epoxide opening. It is to be noted that the nucleophilic attack at C-3 in the epoxyamide is due to a 5-*exo* intramolecular cyclisation process. In the intermolecular processes, we have always observed the nitrogen attack at C-2.[8,12] The high stereoselectivity observed in the formation of **3a** could be attributed to the approach of the hydride from the less hindered face (β) in a favoured conformation to start the cyclisation. In deprotected substrates, it has been reported that the opposite stereoselectivity was observed in a similar reductive amination reaction.[13] The NMR data of **3a** and its acetate **3b** were consistent with the presence of a pyrrolidine ring with (*S*) configuration at C-6.[14] The complete connectivity of the carbon and hydrogen atoms was ascertained by 2D NMR experiments.

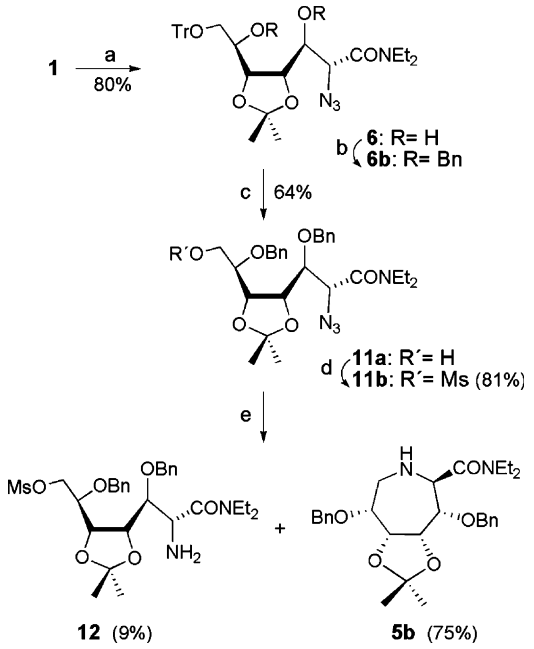
Another structural confirmation of **3a** was made with the formation of the bicyclic compound **10** that could only be formed by the *syn* disposition of the substituents at C-3 and C-6 (Scheme 4). The chloride **9a** was obtained by reaction of **3a** with mesyl chloride: the initially formed mesylated derivative **8** was spontaneously transformed into the chloride **9a** (^{13}C NMR: δ 52.6 ppm, C-2). The introduction of the chlorine in **9a** was confirmed by high resolution X-ray photoelectron spectroscopy. No rearrangement was observed[15] from the possible nitrogen-assisted retention of configuration at C-2 (Scheme 4). Selective de-O-tritylation of **9a** into **9b** (80%) and subsequent displacement of the chloride in basic medium afforded **10** in 66% yield. This transformation could be followed by ^1H NMR using CD_3OD as the solvent (disappearance of the peaks 4.67 (d, H-2), 4.70 (t, H-5) and 4.86 (t, H-4) of product **9b** and appearance of 4.7–4.9 (m, H-4,5) of product **10**). The absolute configuration at C-2 could not be determined from the NMR data.



Scheme 3. Reagents and conditions: (a) DMSO, Ac_2O, 24 h; (b) $BnNH_2$, $ZnCl_2$, $NaBH_3CN$, EtOH, 7 h; (c) Ac_2O, py, 48 h.



Scheme 4. Reagents and conditions: (a) MsCl, py, 24 h; (b) TFA, $CDCl_3$, 55 min; (c) CD_3ONa/CD_3OD, 72 h.



Scheme 5. Reagents and conditions: (a) NaN_3, AcOH, DMF; (b) BnBr, NaH, TBAI, THF, several days; (c) 5% TFA in CH_2Cl_2; (d) MsCl, py, 0 °C, 15 h; (e) (i) Ph_3P, CH_2Cl_2, 17 h, (ii) H_2O, K_2CO_3, 48 h.

In order to synthesise azepane derivatives, the azido group was stereoselectively introduced in **1** and the hydroxyls benzylated giving, after 6 days at rt, a mixture of **6b** (31%) and monobenzylated product that could be isolated and further rebenzylated. Hydrolysis of the trityl group, mesylation, then reduction of the azido group afforded the acyclic amine **12** and subsequent cyclisation gave the azepane **5b**. The structural assignments were consistent with the NMR data (Scheme 5).[16]

The present syntheses of **3a**, **3b** and **5b** from the D-ribo derivative **1** have demonstrated the utility of α,β-epoxyamides in the formation of hydroxylated pyrrolidines and azepanes.[17] To summarise, we have reported an efficient methodology for the preparation of iminosugar derivatives with different ring sizes, combining functional group transformations and regioselective epoxide openings. Use of the above strategy for the preparation of additional iminosugars, utilising different monosaccharide starting materials, is under way in our laboratory and will be reported in due course.

Acknowledgements

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14. Selected data for **3a** and **3b**. Compound **3a**. ^{1}H NMR ($CDCl_3$): δ 4.93 (dd, $J_{5,6} = 6.4$, H-5), 4.70 (dd, $J_{4,5} = 5.2$, H-4), 4.57 (d, $J_{2,3} = 5.3$, H-2), 2.75 (m, H-6), 2.68 (m, $J_{3,4} = 6.3$, H-3). ^{13}C NMR ($CDCl_3$): δ 80.6 (C-5), 78.7 (C-4), 67.7 (C-2), 67.6 (C-3), 66.4 (C-6). HRMS: calcd for $C_{40}H_{47}N_2O_5$ (MH^+) 635.3485, found 635.3457. Compound **3b**. ^{1}H NMR ($CDCl_3$): δ 5.51 (d, $J_{2,3} = 8.2$, H-2), 4.72 (dd, $J_{4,5} = 6.0$, H-4), 4.60 (dd, $J_{5,6} = 6.2$, H-5), 3.06 (dd, $J_{3,4} = 4.6$, H-3), 2.73 (m, H-6). ^{13}C NMR ($CDCl_3$): δ 79.5 (C-5), 78.8 (C-4), 69.2 (C-2), 65.7 (C-3), 65.1 (C-6).
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16. Selected data for **5b**. ^{1}H NMR ($CDCl_3$): δ 4.50 (H-4, H-5), 4.05 (H-2), 3.50 (H-3), 3.20 (H-6), 3.10 (H-7,7′). ^{13}C NMR ($CDCl_3$): δ 83.1 (C-3), 80.3 (C-6), 75.6 (C-4, C-5), 56.2 (C-2), 44.5 (C-7).
17. Yields are given after product purification and are not optimised. The deprotection of the products is under way in our laboratory and will be reported in a full account of our work.