A New Access to Polyhydroxylated Pyrrolidines from Epoxyaldehydes

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Abstract: Our approach relies on the stereocontrolled vinylation of a chiral α,β-epoxyimine derived from the corresponding aldehyde. Regioselective opening of the oxirane with carbonate anion allowed the formation of an oxazolidinone intermediate from which the glucosidase inhibitor 1,4-dideoxy-1,4-imino-D-glucitol (**14**) was synthesised. Direct cyclisation into a 2-vinyl-3,4-epoxypyrrolidine afforded a valuable intermediate for the preparation of synthetic azasugar analogues.

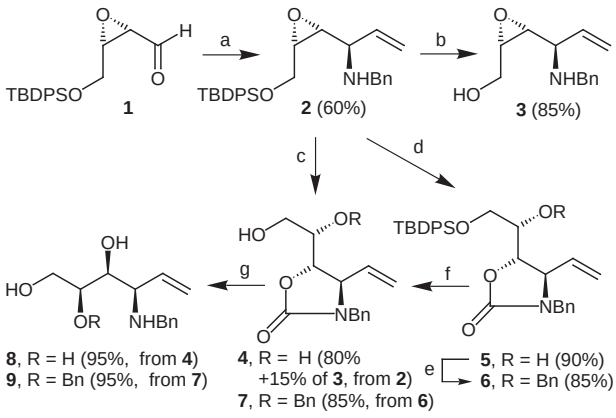
Key words: asymmetric synthesis, azasugars, epoxides, imines, 1,4-dideoxy-1,4-imino-D-glucitol

Polyhydroxylated pyrrolidines, piperidines, and their bicyclic congeners, indolizidines and pyrrolizidines, represent an important class of transition state analogue inhibitors of glycosidases and glycosyl transferases. Given the key role of carbohydrates in cellular recognition and signalling phenomena, these compounds represent useful biological tools for a better understanding of glycoconjugate function. Some of them have already found clinical application against HIV infection, cancer and diabetes,[1] but efforts are still required to create novel structures with improved potency and selectivity towards a target enzyme.

We and others have already demonstrated the versatility of epoxyaldehydes as chiral precursors in the enantioselective synthesis of various biologically relevant compounds.[2] We wish to report here how epoxyaldehydes can also constitute an efficient pathway towards azasugars.[3]

Our synthetic plan was the following: conversion of the α,β-epoxyaldehyde into the corresponding imine should allow incorporation of the nitrogen atom and, in turn, the creation of a third chiral centre via the stereocontrolled addition of an organometallic species. Direct access to the pyrrolidine series should then rely on intramolecular cyclisation onto the activated primary alcohol function. Regiocontrolled opening of the epoxide could finally afford a variety of substitution patterns, such as the *trans*-1,2-diol through hydrolytic cleavage. The epoxide moiety in itself could also represent an interesting structural variation of the parent glycosidase inhibitor.

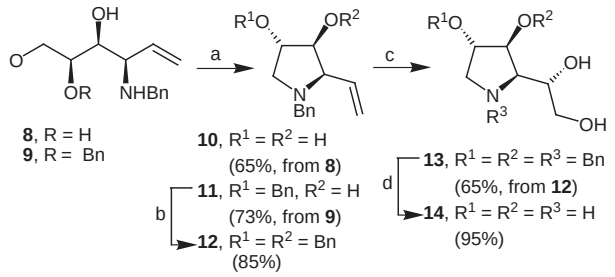
Readily available epoxyaldehyde **1** (3 steps, 70% global yield from commercially available *cis*-2-butene-1,4-diol) was chosen as the chiral precursor. Imine, formed after treatment with benzylamine in diethyl ether, reacted without being isolated with vinyl magnesium bromide in the presence of $Et_2O{\bullet}BF_3$ to afford exclusively the *anti* epoxy amine **2** in 60% isolated yield.[4] In an attempt to deprotect the primary hydroxyl group, treatment of the silyl ether **2** with HF/ pyridine followed by work up with sodium bicarbonate surprisingly yielded only 15% of the expected primary alcohol **3** along with 80% of another compound. Attribution of structure **4** to this product was based on the observation that spectroscopic data clearly indicated incorporation of CO_2 concomitant with epoxide ring opening. The presence of a 1,2-diol pattern was evidenced by ^{13}C NMR of the corresponding acetonide (quaternary carbon atom at δ 101.1 ppm characteristic of a dioxolane). Unfortunately, as a consequence of the presence of the vinyl substituant, the ^3J coupling constant of 7 Hz between the oxazolidinone protons could not be attributed to either a *cis* or *trans* relationship.[5] The regiocontrolled opening of the epoxide ring α to the amine resulting from the initial carbonatation of the amine was demonstrated by treatment of silyl ether **2** with potassium carbonate in THF. The reaction quantitatively provided the valuable intermediate **5**, which, upon desilylation, gave a product identical to diol **4**. The stereochemistry attributed to **4** was unambiguously proven by its transformation into 1,4-dideoxy-1,4-imino-D-glucitol hydrochloride (**14**), a known glucosidase inhibitor.[6a,d]



Scheme 1 Reagents and conditions: a) i) $C_6H_5NH_2$, 4 Å MS, Et_2O, rt, ii) $Et_2O{\cdot}BF_3$, -78 °C to -40 °C, then $CH_2CHMgBr$, THF/Et_2O, -78 °C to rt b) TBAF supported on SiO_2, THF, rt c) HF-pyridine, THF/pyridine, rt; then aq. $NaHCO_3$ d) K_2CO_3, THF/H_2O/pyridine, rt e) Bn-Br, NaH, *n*-Bu_4NI, THF, rt f) TBAF supported on SiO_2, THF, rt g) LiOH, dioxane/H_2O, reflux.

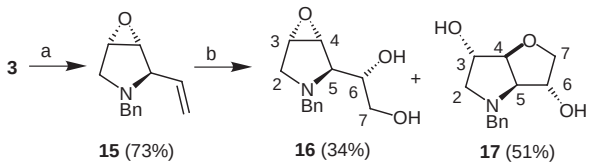
To this end, oxazolidinone **4** was first saponified to afford the amino triol **8** quantitatively and this was then smoothly cyclised in its unprotected form by means of the Appel

reaction.[7] The vinyl pyrrolidine **10** thus obtained, unfortunately, proved to be inert to osmium catalysed dihydroxylation conditions. In order to avoid possible participation of an osmate intermediate we decided to partially protect the diol moiety in **10**. Benzyl ether **6** was thus prepared from intermediate **5**, which presents three suitably discriminated hydroxyl groups. After desilylation, hydrolysis of the cyclic carbamate produced amino diol **9** that underwent facile cyclisation into vinyl pyrrolidine **11**. But, the reluctance of the latter to provide the desired dihydroxylation product (no reaction after one week at 70 °C in 4:1 dioxane/water) prompted us to submit its fully benzylated congener **12** to the same osmium catalysed reaction. Gratifyingly, this afforded the expected dihydroxylated derivative **13** as a single stereoisomer in 65% isolated yield.[8] Final hydrogenolysis of the benzyl groups was accomplished in acidic medium to afford polyhydroxylated pyrrolidine **14** as its hydrochloride. Compound **14** gave physical and structural data essentially identical to those reported for 1,4-dideoxy-1,4-imino-D-glucitol hydrochloride as judged by ^1H and ^{13}C NMR, mass, and α_D.[9] This represents the first synthesis of **14** that does not rely on the use of a sugar lactone[6b,e] or another carbohydrate-derived chiral precursor.[6a,d,c]



Scheme 2 Reagents and conditions: a) Ph_3P, CCl_4, Et_3N, DMF, rt b) BnBr, NaH, *n*-Bu_4NI, THF, rt c) NMO, OsO_4, dioxane/H_2O, 60 °C d) 4 bars H_2, 10% Pd/C, MeOH/ 1.2 N HCl.

In order to confirm the utility of our approach, we then studied the viability of the epoxy analogues of polyhydroxylated pyrrolidines **13** and **14**. Clean desilylation of **2** with TBAF supported on SiO_2 afforded the alcohol **3** that could be smoothly cyclised to vinyl pyrrolidine **15**. When treated with a catalytic amount of OsO_4 at 60 °C in dioxane/water, the latter gave in 83% yield, a reproducible 60:40 mixture of two isomeric dihydroxylated products.[10] The major diastereomer surprisingly suffered a rearrangement with opening of the oxirane ring (as evidenced by the absence of the two characteristic CH signals at δ 58-60 ppm in ^{13}C NMR spectra). A favoured 5-*exo* mode cyclisation[11] involving the primary hydroxyl group could explain formation of the proposed fused tetrahydrofuran structure **17**.[12] The minor product corresponded to one of the expected diastereomers **16**, which thus represents the epoxy analogue of dihydroxylated pyrrolidine **13**. Compound **16** constitutes a valuable intermediate for further transformation, via epoxide opening, into novel azasugar analogues. In addition, it will be interesting to evaluate biological activity of epoxypyrrolidine **16** (or its debenzylated form[13]) towards glycosidases. It is noteworthy that an epoxide-containing analogue of mannostatin A acts as a potent, active site directed, irreversible inactivator of α-mannosidase.[14]



Scheme 3 Reagents and conditions: a) Ph_3P, CCl_4, Et_3N, DMF, rt b) NMO, OsO_4, dioxane/H_2O, 60 °C.

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(8) The *S* stereochemistry was attributed to the newly formed stereocenter in **13** by analogy with the work of R.C. Bernotas: see ref. 6c.

(9) α_D - 25.3° (c, 0.8 in H_2O). This value is in agreement with those reported in the literature (α_D - 27° (c, 1 in H_2O)[6a]; α_D - 28.1° (c, 0.4 in H_2O)[6b]; α_D - 25° (c, 0.3 in H_2O)[6d]) considering the 95% ee of our starting epoxy-alcohol.

(10) **Compound 16:** ^{1}H RMN (400 MHz, $CDCl_3/CD_3OD$): δ 7.35 - 7.25 (5H, m, Ph,); 3.89 (2H, ABq, J = 12.9 Hz, C*H*$_2$Ph) δa - δb = 28 Hz; 3.88 (1H, d, J = 2.8 Hz, H-4); 3.70 (1H, d, J = 2.8 Hz, H-3); 3.58 - 3.53 (3H, m, H-6, 2H-7); 3.26 (1H, d, J = 6.8 Hz, H-5); 3.07 (2H, ABq, J = 13.6 Hz, H-2) δa -δb = 58.4 Hz. ^{13}C RMN (100 MHz, $CDCl_3/CD_3OD$): δ 138.69 (C arom.); 129.56 (CH arom.); 129.06 (CH arom.); 128.04 (CH arom.); 70.52 (C-6); 68.64 (C-5); 65.25 (C-7); 64.46 (*C*H$_2$Ph); 59.85 (C-4); 58.05 (C-3); 54.19 (C-2). SM (CI, NH_3) MH^+ 236. α_D +1.4° (c, 0.5 in $CHCl_3$).
Compound 17: ^{1}H RMN (400 MHz, $CDCl_3/CD_3OD$): δ 7.35 - 7.24 (5H, m, Ph); 4.49 (1H, dd, J = 6.6 and 3.0 Hz, H-4); 4.12 (1H, m, H-3); 3.99 (1H, m, H-6); 3.93 (1H, dd, J = 9.6 and 3.2 Hz, H-7); 3.78 (1H, dt, J = 10.0 and 0.8 Hz, H-7); 3.75 (2H, ABq, J = 12.4 Hz, C*H*$_2$Ph) δa -δb = 122.0 Hz; 3.28 (1H, d, J = 6.4 Hz, H-5); 3.14 (1H, dd, J = 9.6 and 6.4 Hz, H-2); 2.30 (1H, t, J = 8.4 Hz, H-2). ^{13}C RMN (100 MHz, $CDCl_3/CD_3OD$): δ 138.20 (C arom.); 129.37 (CH arom.); 128.82 (CH arom.); 127.84 (CH arom.); 89.78 (C-4); 75.70 (C-3); 75.45 (C-6); 75.23 (C-5); 74.31 (C-7); 59.68 (C-2); 59.58 (*C*H$_2$Ph). SM (CI, NH_3) MH^+ 236. α_D - 1.2° (c, 0.9 in $CHCl_3$).

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(12) This structure is in full agreement with all spectral data (1D ^{1}H and ^{13}C NMR; COSY, HMQC and long range HMQC 2D experiments). Relative stereochemistry at C-6 is based on 1D dpgse NOE experiment: a strong NOE is observed between H-4 and H-5, whereas a comparatively weak NOE is observed between H-5 and H-6, as well as between H-4 and H-3. For an example of related cyclisation concomitant with osmium catalysed dihydroxylation of a vinyl pyrrolidine see: Lin, G.-Q.; Shi, Z.-C. *Tetrahedron* **1997**, *53*, 1369-1382.

(13) In preliminary attempts (atmospheric pressure H_2, 10% Pd/C, EtOH or 4 bars H_2, 10% Pd/C, AcOEt) hydrogenolytic debenzylation of epoxypyrrolidine **16** yielded a complex reaction mixture.

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