Hydroxy-directed Ketone Reduction. Application to the Synthesis of (+)-8,8a-Diepicastanospermine

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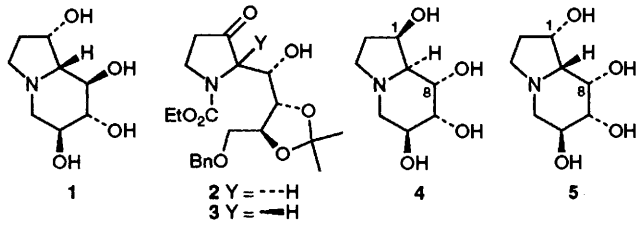
Reduction of heterocyclic-derived aldol adducts **2** and **3** using $NaBH(OAc)_3$ is stereoselective and proceeds *via* a hydroxy-directed mechanism to give **6** and **7**, respectively, thereby complementing the stereoselectivity available with $NaBH_4$; a synthesis of (+)-8,8a-diepicastanospermine **11** from diol **6** is described.

Polyhydroxylated indolizidines, exemplified by castanospermine **1**,[1] have attracted interest as potential regulators of oligosaccharide metabolism. As a result, a variety of strategies have been developed that have led to syntheses of both the natural products themselves as well as stereoisomers and related structural analogues.[2]

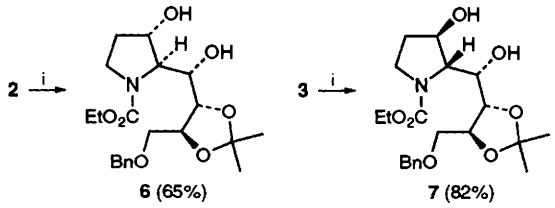
Our studies in this area have focused on the aldol strategy based on the C-2 enolate of *N*-substituted pyrrolidin-3-one, which is summarised below.[3] Using this chemistry, two major aldol components **2** and **3** have been characterised and subsequently converted to 1,8,8a-triepicastanospermine **4** and 8-epicastanospermine **5**, respectively; a key step in each case being the introduction of the C-1 OH (indolizidine numbering) by stereoselective reduction of the pyrrolidin-3-one ketone of **2** and **3**.[4] This was accomplished efficiently using either $NaBH_4$ or Bu^i_2AlH, with hydride approach taking place exclusively from the less hindered face of the heterocyclic ring.



Achieving this reduction step in a stereochemically complementary fashion, that is from the more hindered face of the five-membered ring, was an attractive proposition since this would enable a *single* aldol adduct to be selectively manipulated to provide *two* isomeric polyhydroxylated indolizidines. This introduces a divergent element into the underlying aldol strategy and the realisation of this goal, using a hydroxy-directed reduction, is now described.

The use of directed reduction of acyclic β-hydroxyketones in the stereoselective synthesis of 1,3-diols has found widespread use[5] but the application of this methodology to cyclic variants is less well-established.[6] Using standard conditions, reduction of aldol adduct **2** with $NaBH(OAc)_3$[7] gave the *syn*-1,3-diol **6** in 65% yield. Similarly, reduction of **3** gave the *anti*-1,3-diol **7** in 82% yield (Scheme 1).

In both cases, reduction was highly selective with no other diol isomer being detected. It should also be appreciated that

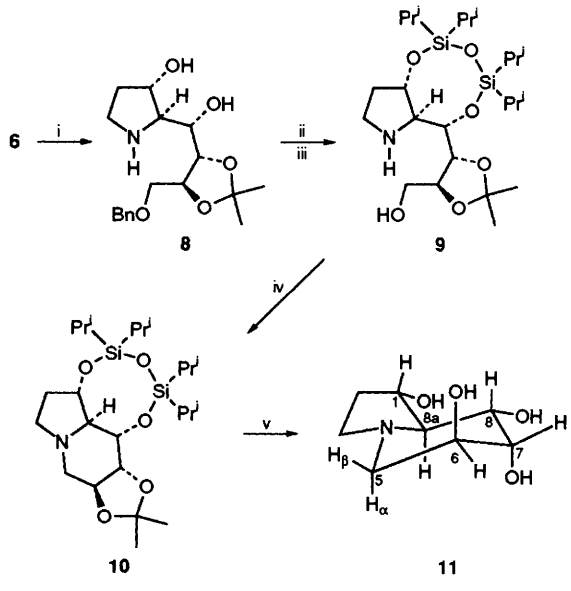


Scheme 1 *Reagents and conditions*: i, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, room temp.

the stereochemistry of the newly formed diol is not determined by the stereochemistry of the existing hydroxy-bearing centre; this only acts to anchor and activate the borane reagent prior to delivery of hydride to the more hindered face of the pyrrolidine ring.†

With two new 1,3-diols available, we chose to illustrate the divergent nature of the aldol strategy by conversion of diol **6** to 8,8a-diepicastanospermine **11** (Scheme 2). Hydroxide-induced cleavage of the carbamate residue from **6** gave **8** in 76% yield. Protection of the 1,3-diol moiety, which was required prior to further elaboration,‡ with 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane[9] and then *O*-debenzylation gave amino alcohol **9** in 68% yield. Cyclisation to generate the indolizidine ring system was now straightforward and was carried out using CBr_4/PPh_3 to give the fully protected polyhydroxylated indolizidine **10**, which was then deprotected under acidic conditions. Following purification by ion exchange chromatography, 8,8a-diepicastanospermine **11** was isolated as a colourless glass in 56% yield from **9**§.

The ^1H and ^{13}C NMR spectra of **11** were assigned using COSY 45 and long range C–H correlation experiments and relative stereochemistry was confirmed using observed splittings of resonances in the ^1H NMR spectrum and NOE difference experiments.§ The indolizidine ring of **11**, which has a *trans* configuration between N (lone pair) and H-8a, adopts a conformation that places the C-6 and C-7 hydroxy groups in an axial orientation (assuming first-order analysis, $^3J_{6,7}$ 3.4, $^3J_{7,8}$ 3.4, $^3J_{8,8a}$ 10 Hz). We have also examined 8,8a-diepicastanospermine **11** (at levels up to 50 mol dm^{-3}) for its



Scheme 2 *Reagents and conditions*: i, KOH, MeOH, sealed tube, 120 °C; ii, pyridine, $ClSiPr^i_2OSiPr^i_2Cl$; iii, H_2, Pd/C, EtOAc; iv, Ph_3P, CBr_4, Pr^i_2NEt, THF, room temp., 3 h; v, 2 mol dm^{-3} HCl, 80 °C then Dowex 50W 8x-100

ability to inhibit viral replication in molt4 T-cells infected with HIV but this molecule is devoid of activity.

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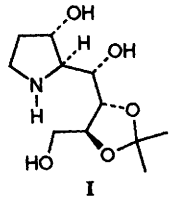
Footnotes

† The *syn* and *anti* aldol adducts derived from both cyclohexanone/PhCHO and cyclopentanone/PhCHO undergo reduction using $NaBH(OAc)_3$ with good (cyclohexyl series) to excellent (cyclopentyl series) levels of stereoselectivity.

‡ Use of the Markiewicz protecting group for the 1,3-diol function derived from **6** was essential to the success of the chemistry shown in Scheme 2; the corresponding 1,3-acetonide, a protecting group strategy that had been used for the synthesis of both **4** and **5**, was unstable. We were unable to achieve direct cyclisation of **I** and attempts to carry out a cyclisation of the fully deprotected variant (obtained from **I** by 1,2-acetonide cleavage under acidic conditions) also failed. Similar cyclisation reactions involving free polyhydroxylated precursors have, however, been described.[8]



I

§ 8,8a-Diepicastanospermine **11** (free base): $[\alpha]_D^{22}$ 14.8 (*c* 0.18, H_2O); δ_H (D_2O, 400 MHz) 4.30 (1H, ddd, *J* 9.1, 6.8, 3.9 Hz, H-1), 4.00 (1H, m, H-6), 3.93 (1H, t, *J* 3.4 Hz, H-7), 3.87 (1H, dd, *J* 10, 3.4 Hz, H-8), 3.05 (1H, td, *J* 8.4, 1.9 Hz, H-3β), 2.97 (1H, dd, *J* 12.6, 2.6 Hz, H-5β), 2.70 (2H, m, H-3α, H-5α), 2.48 (1H, br, t, *J* (*ca.*) 9 Hz, H-8a), 2.30 (1H, m, H-2), and 1.68 (1H, m, H-2); δ_C (D_2O, 127 MHz) 76.1 (C-1), 73.3 (C-7), 71.9 (C-6, C-8), 70.3 (C-8a), 54.6 (C-5), 54.0 (C-3) and 33.6 (C-2).

The following NOE experiments were conducted: irradiation of H-1 (enhancement of H-8 and H-2β); irradiation of H-8a (enhancement of H-3α, H-5α, H-2α); irradiation of H-5β (enhancement of H-5α, H-6, H-8a (three spin effect).

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