Stereocontrolled Synthesis of a Trihydroxylated Indolizidine Alkaloid, 1-Deoxycastanospermine

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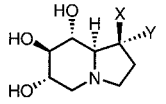
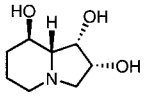
Abstract: An efficient and novel process is described for the asymmetric synthesis of *(6S,7R,8R,8aR)*-6,7,8-trihydroxyindolizidine alkaloid, 1-deoxycastanospermine in 22% overall yield based on the C_2-imide featuring the completely stereoselective reduction of an α-hydroxypyrrolidine intermediate elaborated through asymmetric deoxygenation of a quaternary α-hydroxylactam.

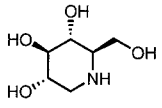
In recent years, due to their ability to act as competitive inhibitors of glycosidases and of glycoprotein processing, polyhydroxylated indolizidine alkaloids have attracted considerable attention, exhibiting various degrees of potency and specificity.[1] Noteworthy members among this class of compounds are castanospermine (**1**), swainsonine (**3**) and deoxynojirimycin (**4**) and these have also found use in anticancer, antiviral and antiretroviral research.[2] Of all these molecules, **1** has been shown to inhibit replication of human immunodeficiency virus (HIV)[3] and is of particular interest in connection with chemotherapeutic intervention in the treatment of AIDS. The diverse array of potentially useful activities make it an inviting target for synthesis.[4] In particular the preparation of unnatural epimers and other structural analogs of **1** has genarated much interest since the biological activity of these molecules varies substantially with the number, position and stereochemistry of the hydroxy groups into the indolizidine skeleton.[5] In this communication we wish to report our novel synthetic strategy based on the completely stereoselective reduction of an α-hydroxypyrrolidine which has led to the total synthesis of 1-deoxycastanospermine (**2**).



1: Castanospermine, X = OH, Y = H
2: 1-Deoxycastanospermine, X = Y = H



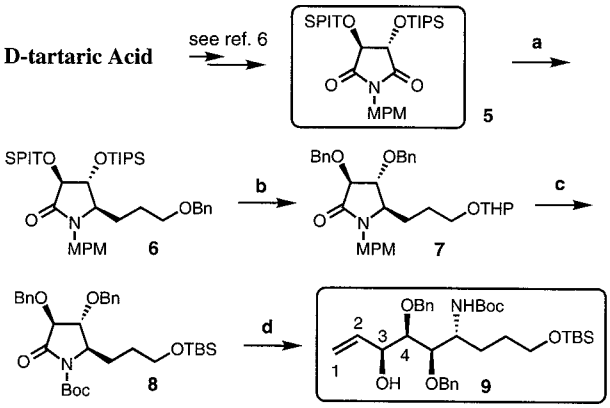
3: Swainsonine



4: Deoxynojirimycin

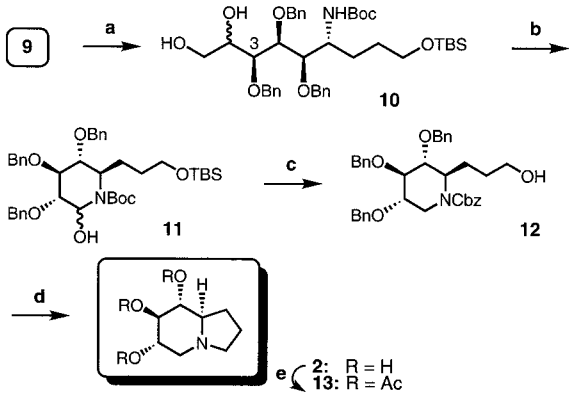
C_2-imide **5** with *N-p*-methoxybenzyl (MPM) group obtained from D-tartaric acid was treated with Grignard reagent followed by the reductive deoxgenation according to our reported process,[6] leading to the homochiral lactam **6** predominantly (95:5) (Scheme 1). After exchange of the protecting group in **6** to benzyl and THP ethers, **7** thus obtained was transformed into the *N*-Boc lactam **8** ($[\alpha]D^{18}$-44.0° (c 3.41, MeOH)) in high yield. Then, nucleophilic addition of the second Grignard reagent (vinylmagnesium bromide) to **8** easily afforded the labile quaternary α-hydroxypyrolidine,[7] which was successively submitted to the reduction with $NaBH_4$[8] in the presence of $CeCl_3$ to give the desired *(3S)*-stereoisomer **9** ($[\alpha]D^{19}$+14.1° (c 3.24, MeOH)) as a sole product[9] (determined by HPLC using Daicel Chiralpak AD).

As shown in Scheme 2, the olefinic part in **9** was cleavaged via dihydroxylation after benzyl-protection to lead to the cyclized α-hydroxypiperidine (azasugar) derivative **11**. Interestingly, it became apparent that Lewis-acid induced deoxgenation[6,7] of **11** cleanly resulted



Scheme 1. Reagents and conditions: (a) 1, $BnO(CH_2)_3MgBr$, THF, -78 - 0 °C; 2, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 96% (2 steps); (b) 1, Pd (black), 4.4% HCOOH-MeOH; 88%; 2, DHP, cat. *p*-TsOH, MeOH, CH_2Cl_2; 97%; 3, Bu_4NF, THF, quant.; 4, BnBr, Ag_2O, CH_3COOEt; 99%; (c) 1, cat. *p*-TsOH, MeOH; 77%; 2, CAN, CH_3CN-H_2O (9:1); 81%; 3, TBSCl, imidazole, DMAP, DMF; 72%; 4, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; quant.; (d) 1, vinylmagnesium bromide, THF, -78 °C; 2, $NaBH_4$-$CeCl_3$, MeOH, -18 °C; 86% (2 steps).

in the direct preparation of the *N*- and *O*-deprotected piperidine which was in turn isolated as the Cbz-derivative **12** ($[\alpha]D^{16}$-0.98° (c 3.13, MeOH)) in quantitative yield. Finally, **12** was subjected to the tandem reactions of mesylation and cyclization followed by the simultaneous debenzylation with Pd (black) to complete the total synthesis of 1-deoxycastanospermine **2**[5a,c] in reasonably high yield. The structure was characterized after derivatization to the known triacetate **13**, $[\alpha]D^{22}$+40.5° (c 0.31, $CHCl_3$) [lit. $[\alpha]D$+40.7° (c 0.3, $CHCl_3$)][5a] whose physical data were completely identical with the reported values.[5a]



Scheme 2. Reagents and conditions: (a) 1, BnBr, Ag_2O, CH_3COOEt; 87%; 2, OsO_4, NMO, acetone-H_2O (1:1); 88%; (b) $NaIO_4$, Et_2O-H_2O (1:1); 95%; (c) 1, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; 99%; 2, CbzCl, $NaHCO_3$, CH_2Cl_2; 99%; (d) 1, MsCl, Et_3N, CH_2Cl_2; 2, Pd (black), 4.4% HCOOH-MeOH; 99% (2 steps); (e) Ac_2O, Et_3N, CH_2Cl_2; 80%.

In summary, an efficient and novel synthetic pathway to 1-deoxycastanospermine has been established in 22% overall yield from C_2-symmetrical imide based on the stereoselective reduction of α-hydroxypyrrolidine.

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References and Notes

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After detailed investigations, the best result was observed under the conditions as shown in the text. The absolute configuration of the generated stereogenic center was assigned based on the spectral data of synthetic (+)-**2** and triacetate (+)-**13**.