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Novel Synthesis of Castanospermine and 1-Epicastanospermine

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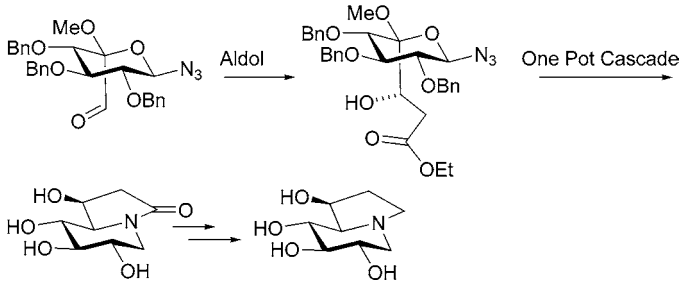
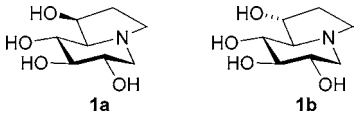
ABSTRACT



Polyhydroxylated indolizidines have potential for treatment of HIV, hepatitis C and HSV infection, multiple sclerosis, angiogenesis, cancer, and diabetes. A new synthetic approach to the title compounds from a 5-*C*-methoxypyranosyl azide has been developed. The route incorporates the aldol reaction and a novel catalytic reductive amination cascade to generate the indolizidine ring.

Castanospermine **1a** is a bioactive naturally occurring polyhydroxylated indolizidine, first isolated from seeds of *Castanospermum australe*.[1] It and closely related congeners have shown considerable potential as antiviral agents for the treatment of HIV,[2] hepatitis C,[3] and HSV-1[4] infections. They also have potential for inhibition of progression of multiple sclerosis,[5] angiogenesis, cancer,[6] and diabetes.[7] The development of new synthetic routes to castanospermine enable the production of novel analogues for biological studies, and a number of syntheses of **1** have been developed.[8] Herein we present a novel synthesis of castanospermine **1a** and 1-epicastanospermine **1b** from methyl α-D-glucopyranoside.



We have recently reported a general synthesis of iminosugars from 5-*C*-methoxypyranosyl azides (e.g., production of **3** from **2**).[9] We were interested to investigate extending the catalytic reductive amination cascade reaction used for

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(8) For selected syntheses of **1a** and **1b**, see: (a) Tyler, P. C.; Winchester, B. G. In *Iminosugars as Glycosidase Inhibitors*; Stuetz, A., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1999; pp 125−156. (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625. (c) Somfai, P.; Marchand, P.; Torsell, S.; Lindstrom, U. M. *Tetrahedron* **2003**, *59*, 1293. (c) Zhao, H.; Mootoo, D. R. *J. Org. Chem.* **1996**, *61*, 6762. (d) Kim, J. H.; Woo, D.; Lee, J. H.; Lee, B. W.; Park, K. H. *Synthesis* **2003**, 2473. (e) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887. (f) Grassberger, V.; Berger, A.; Dax, K.; Fechter, M.; Gradnig, G.; Stuetz, A. E. *Liebigs Ann. Chem.* **1993**, 379. (g) Mulzer, J.; Dehmlow, H.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1992**, *57*, 3194. (h) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165. (i) Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617.

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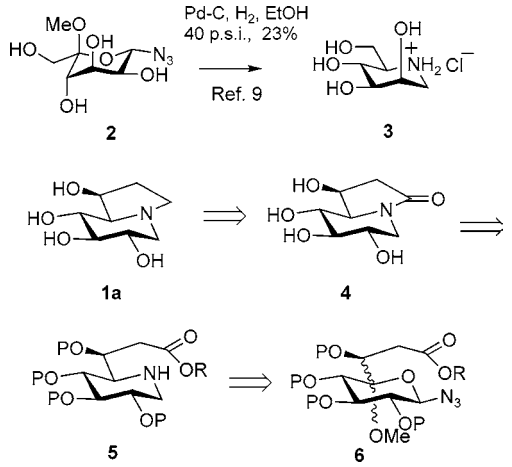
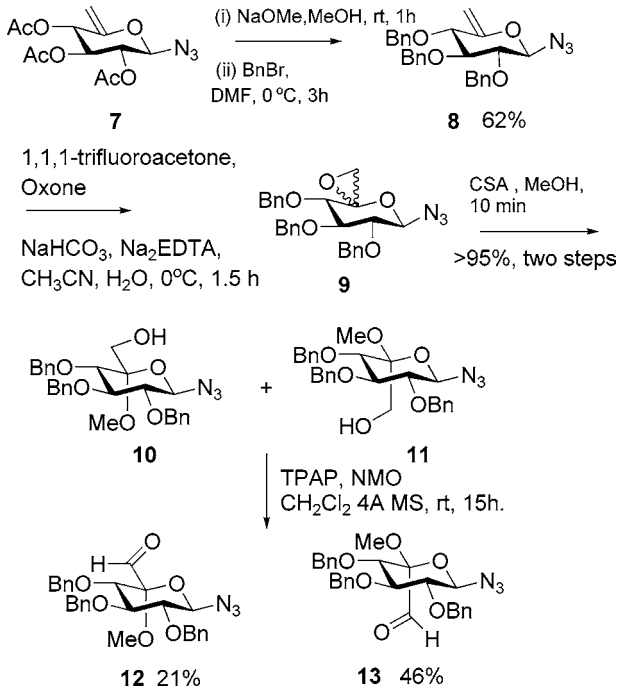
preparation of piperidine **3** to generate the indolizidine ring system (Scheme 1). It was envisaged that the piperidine **5** generated from 5-*C*-methoxypyranosyl azide **6** would undergo an additional cyclization and give the indolizidinone **4**, which would be subsequently converted to **1a**.

Scheme 1. Synthesis of 1-Deoxymannojirimycin **3** and Retrosynthetic Analysis of **1a**



The synthesis commenced from the 6-deoxyhex-5-enopyranoside **7**, prepared from methyl α-D-glucopyranoside in five steps (69%) as previously described.[9b] The acetate groups were removed, and benzyl protecting groups were introduced to give **8**. Oxidation using methyl(trifluoromethyl)dioxirane generated in situ[10] gave a 1.7:1 mixture of epoxides **9**.[11] Treatment of the epoxides with methanol in the presence of camphorsulfonic acid gave a mixture of 5-*C*-methoxy-D-glucopyranosyl azide **10** and 5-*C*-methoxy-L-idopyranosyl azide **11**. This mixture was oxidized to aldehydes **12** and **13** using the method of Ley and Griffith.[12] The aldehydes were separated using chromatography,[13] and the configurations assigned to **12** and **13** were determined using 1D NOE spectroscopy. An NOE enhancement was observed for H-3 on irradiation of the aldehyde proton for **13**, with no enhancement observed for H-4. An NOE enhancement was observed for H-4 of **12** on irradiation of its aldehyde proton with no enhancement observed for H-3 (Figure 1).The aldol reaction of **13** was next investigated. Reaction of ethyl acetate at −78 °C with LDA generated the desired enolate, which on reaction with **13** gave a mixture of diastereoisomeric alcohols **14** and **15**; these were separated using silica gel

Scheme 2



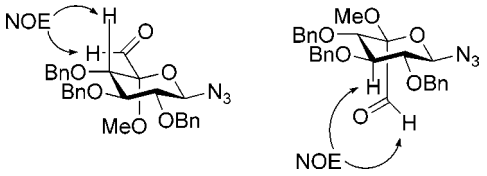
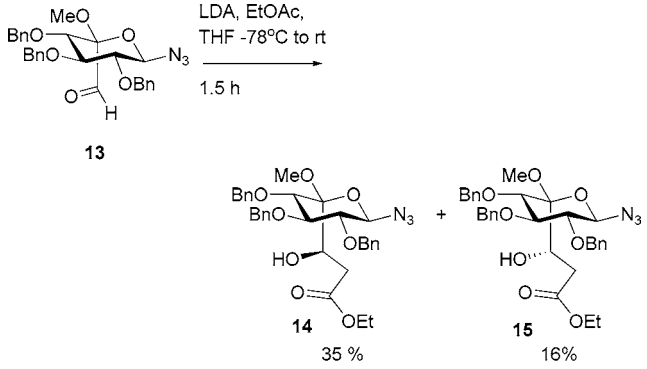


Figure 1. Assignment of the configuration of **12** and **13**

Scheme 3



(9) (a) Tosin, M.; O'Brien, J.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 3353. (b) McDonnell, C.; Cronin, L.; O'Brien, J. L. *J. Org. Chem.* **2004**, *69*, 3565.

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(11) (a) Enright, P. M.; O'Boyle, K. M.; Murphy, P. V. *Org. Lett.* **2000**, *2*, 3929. (b) Enright, P. M.; Tosin, M.; Nieuwenhuyzen, M.; Cronin, L.; Murphy, P. V. *J. Org. Chem.* **2002**, *67*, 3733.

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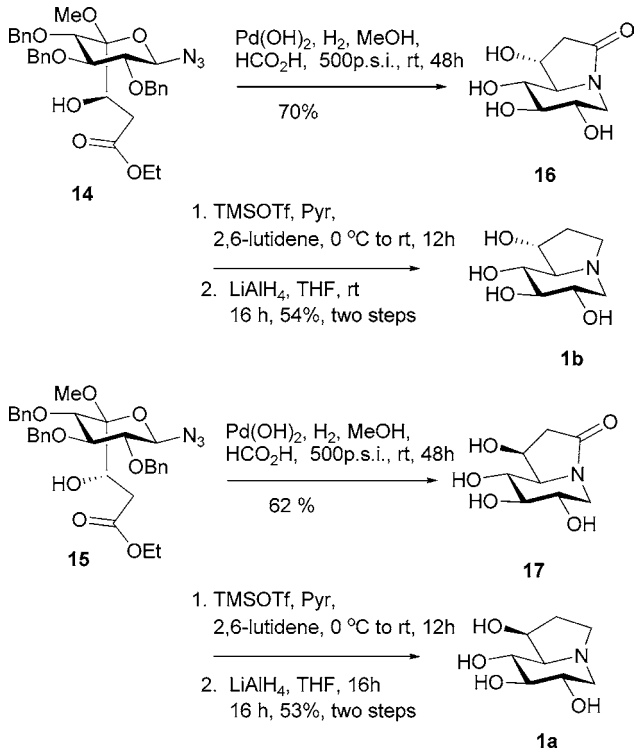
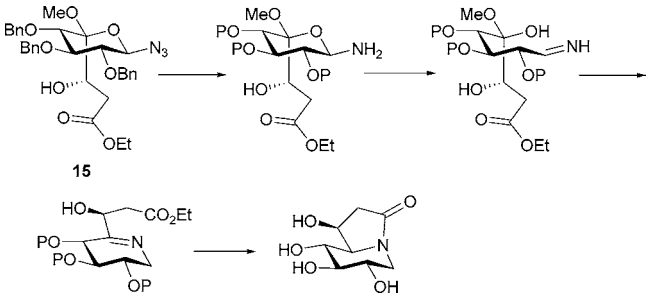
(13) **Oxidation to 12 and 13.** To a mixture of **10** and **11** (1.6 g, 3.2 mmol) in dry CH_2Cl_2 (35 mL) were added activated 4 Å molecular sieves (0.1 g) and *N*-methylmorpholine *N*-oxide (NMO, 0.56 g, 4.8 mmol). After 30 min of stirring at room temperature under nitrogen, tetra-*n*-propylammonium perruthenate (TPAP, 0.11 g, 0.31 mmol) was added, and the mixture was stirred overnight and then filtered through Celite. Filtration through a short column of silica gel, eluting with CH_2Cl_2 gave **13** (0.74 g, 46%). Further elution with EtOAc gave **12** (0.33 g, 21%) as a clear oil.

Scheme 4



chromatography with **14** being eluted first. The one-pot reductive indolizidine ring generating cascade reaction was then investigated and, gratifyingly, succeeded in a highly stereoselective manner for both substrates **14** and **15**, giving lactams **16** (70%) and **17**[14] (62%), respectively.[15] Reduction of **16** and **17** was achieved by protection of the hydroxyl groups as trimethylsilyl ethers and subsequent reaction using $LiAlH_4$ in THF, giving 1-epicastanospermine **1b** and (+)-castanospermine **1a**, respectively.[16] Indolizidine **1a** was converted to its per-*O*-acetate, which was subjected to chromatographic purification, and subsequent deacetylation gave a sample of **1a** of higher purity. This sample was found to have ^1H and ^{13}C NMR spectroscopic data[17] identical to those previously reported[18] and to those of an authentic sample. Similarly **1b** was found to have spectroscopic data identical to those reported in the literature.[19] A possible sequence of intermediates explaining the formation of the lactam **17** is shown in Scheme 5. This involves reduction of

Scheme 5



azide group to give a pyranosylamine, which ring opens to an acyclic imine. Further reductive cyclization gives a cyclic imine, which is reduced in situ to give **5**, and subsequent cyclization gives lactam **17**.

In summary, a new strategy for the synthesis of polyhydroxylated indolizidines and related lactams has been demonstrated and should be amenable to the synthesis of further analogues. A wider investigation of the aldol reaction from the view of generating analogues for biological evaluation as well as improving stereoselectivity would seem appropriate next studies. In addition aldehydes such as **13** could have more wide application as synthetic intermediates to novel iminosugars and indolizidines.

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Supporting Information Available: Full experimental details and ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We repeated the previously reported synthesis of **17** from castanospermine and the NMR spectroscopic data of the two samples were identical. See: Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Carbohydr. Res.* **2004**, *339*, 1747.

(15) **Preparation of 17.** Azide **15** (110 mg, 0.186 mmol), $Pd(OH)_2$ (30 mg), and formic acid (0.82 mL) were added to MeOH (60 mL), and the mixture was stirred in a Parr reactor in an atmosphere of hydrogen (500 psi) for 48 h. The suspension was then filtered through Celite, washing first with MeOH and then water; the combined filtrate was evaporated to dryness in vacuo; and the residue was purified using silica gel chromatography (4:1 EtOAc/MeOH) to give **17** (23 mg, 62%).

(16) The removal of the TMS protecting groups is facile and occurs during the workup after reduction.

(17) **^1H NMR data for 1a:** δ (300 MHz, D_2O) 4.41 (ddd, 1H, *J* 6.8, *J* 4.6, *J* 1.5), 3.61 (m, 1H, H-6), 3.60 (t, 1H, *J* 9.6), 3.32 (t, 1H, *J* 9.1), 3.18 (dd, 1H, *J* 10.8, *J* 5.1), 3.08 (dt, 1H, *J* 9.1, *J* 2.1), 2.33 (dddd, 1H, *J* 14.8, *J* 8.1, *J* 7.3, *J* 2.2), 2.21 (q, 1H, *J* 9.2), 2.06 (t, 1H, *J* 10.7), 2.02 (dd, 1H, *J* 9.8, *J* 4.4), 1.17 (dddd, 1H, *J* 14.2, *J* 8.7, *J* 8.7, *J* 1.8).

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