Pergamon

Tetrahedron Letters 42 (2001) 747–749

TETRAHEDRON LETTERS

A short and efficient synthesis of 1-deoxy-castanospermine and 1-deoxy-8a-*epi*-castanospermine

Nitin T. Patil, Jayant N. Tilekar and Dilip D. Dhavale*

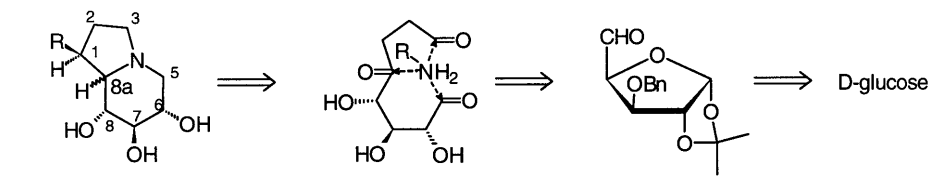
Department of Chemistry, Garware Research Centre, University of Pune, Pune 411 007, India

Received 25 August 2000; revised 9 November 2000; accepted 15 November 2000

Abstract—A new route for the synthesis of 1-deoxy-castanospermine **2** and 1-deoxy-8a-*epi*-castanospermine **3** has been developed via a sequential triple reductive amination process of a suitably protected D-*gluco*-oct-5-ulo-1,8-dialdose, which was easily prepared by three carbon homologation of readily available α-D-*xylo*-pentodialdose using an appropriate Grignard reagent followed by oxidation.

The synthesis of polyhydroxylated indolizidine alkaloids such as castanospermine **1** and 1-deoxy-castanospermine **2** is a fascinating area of research.[1,2] Due to their promising glycosidase inhibitory activity, these compounds are potential chemotherapeutic agents for the treatment of diabetes, obesity, cancer and AIDS.[3] Amongst various stereoisomers of castanospermine, the structural assignment of 1-deoxy-8a-*epi*-castanospermine **3** was in doubt.[4,5] As a part of our continuing efforts in the synthesis of polyhydroxylated piperidine alkaloids,[6] we are now reporting the synthesis of 1-deoxy-castanospermine **2** and 1-deoxy-8a-*epi*-castanospermine **3**. As per our visualisation (Scheme 1), the synthesis of **2** or **3** involves the sequential triple reductive amination of a suitably protected D-*gluco*-oct-5-ulo-1,8-dialdose. The addition of the requisite three carbon Grignard reagent to the readily available α-D-*xylo*-pentodialdose **4** followed by oxidation would give an easy access to D-*gluco*-oct-5-ulo-1,8-dialdose.

The reaction of α-D-*xylo*-pentodialdose[6a] **4** with the Grignard reagent prepared from magnesium and 2-(2-bromoethyl)-1,3-dioxolane in THF, afforded a diastereomeric mixture of the C5-carbinols which was

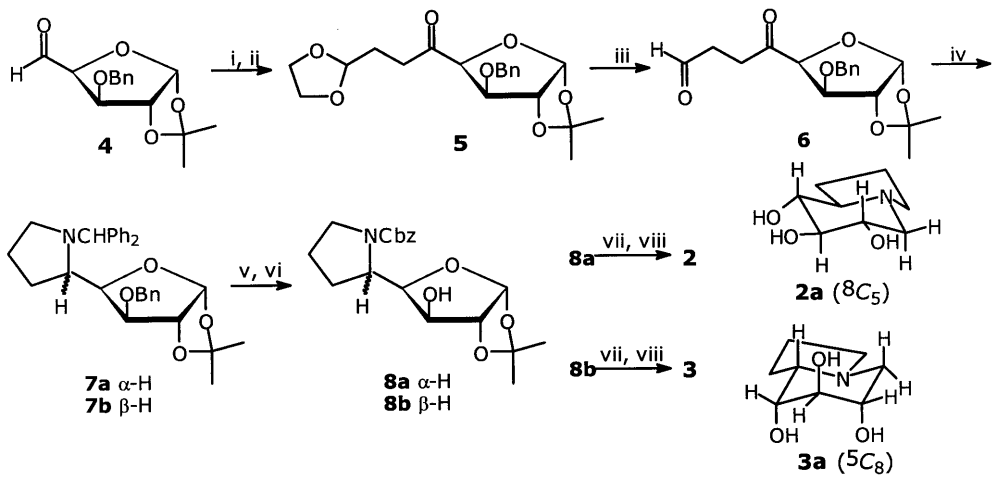


1 R = OH, α-H; **2** R = H, α-H
3 R = H, β-H

Scheme 1.

Keywords: alkaloids; indolizidine; enzyme inhibitors; Grignard reaction.
* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02103-1



Scheme 2. Reagents and conditions: i, Mg, 2-(2-bromoethyl)-1,3-dioxolane (1.2 equiv.), Et_2O, −78°C to rt, 6 h, 90%. ii, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C to rt, 4 h, 92%. iii, 80% aq. acetic acid, 70°C, 2 h, 80%. iv, Ph_2CHNH_2 (1.1 equiv.), AcOH (1.1 equiv.), $NaCNBH_3$ (2.5 equiv.), MeOH, −78°C to rt, 12 h, 95%. v, 10% Pd/C, H_2, MeOH, 80 Psi, 20 h. vi, CbzCl (1.1 equiv.), $NaHCO_3$, EtOH–H_2O (8:2), 2 h, 85%. vii, TFA–H_2O (3:2), rt, 2 h. viii, 10% Pd/C, H_2, MeOH, 80 Psi, 90%.

directly subjected to Swern oxidation to give **5**† in 92% yield (Scheme 2). Selective deprotection of the acetal functionality (80% AcOH) afforded 1,2-*O*-isopropylidene-3-*O*-benzyl-D-*gluco*-oct-5-ulo-1,8-dialdose **6**.[7]

Treatment of **6** with aminodiphenylmethane, in the presence of sodium cyanoborohydride and acetic acid in methanol gave an inseparable diastereomeric mixture of **7a** and **7b** in the ratio of 45:55. In the subsequent step, hydrogenolysis gave a mixture of the amino alcohols which was directly reacted with CbzCl in ethanol and 5,6,7,8-tetradeoxy-5,8-(*N*-benzoxycarbonylimino)-1,2-*O*-isopropylidene-α-D-*gluco*-oct-1,4-furanose **8a** and its C5-epimer β-L-*ido*-oct-1,4-furanose **8b** were isolated by chromatographic purification in 38% and 47% yield, respectively.[8] The specific rotation† of **8a** was found to be in agreement with that reported[2b] however, **8b** was independently characterised by spectral and analytical data.† Treatment of **8a** with TFA–H_2O followed by hydrogenation gave 1-deoxy-castanospermine **2**. Analogously, reaction of **8b** with TFA–H_2O followed by hydrogenation afforded 1-deoxy-8a-*epi* castanospermine **3** in good yield. The rotation, spectral and analytical data† for **2** and **3** were found to be in good agreement with those reported.[9]

The coupling constant $J_{8,8a}$ is important in the determination of the configuration at C8a while, the conformation of **3** could be determined by the coupling constant values between H5, H6, H7, and H8. The initial geometry in the precursor **8b** ensures that, in the product **3** the substituents at C6, C7 and C7, C8 should be *trans*. The comparison of ^1H NMR spectra of **2** and **3** revealed the downfield shift of all the protons in **3** with respect to the corresponding protons in **2** (Table 1). This is indicative of *equatorial* orientation of these protons in **3** as against *axial* as noted for **2**. In this case of **3** H6 appeared as a broad singlet at δ 4.55 while H7 and H8 were found to be accidentally equivalent and showed broad singlet at δ 4.42. This indicated that $J_{6,7}$ and $J_{8,8a}$ are small values ($W_H \sim 5$ Hz) suggestive of the *equatorial* orientation of these protons. The small value of $J_{8,8a}$ along with the *axial* orientation of C8-OH, suggests that the C8a substituent is *equatorial* with the C8a(*S*) configuration accounting for the structure of 1-deoxy-8a-*epi*-castanospermine **3**. This observation is

† Selected physical data for **5**: thick liquid, $[\alpha]_D = -69.30$ (*c* 0.92, $CHCl_3$); ν_{max} (Nujol) 1718 cm^{-1} δ_H ($CDCl_3$, 300 MHz): 1.32 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.85–2.03 (2H, m, CH_2), 2.70–2.85 (2H, m, CH_2), 3.70–3.98 (4H, m, CH_2), 4.27 (1H, d, *J* 3.6 Hz, H-2), 4.46 (1H, d, *J* 11.7 Hz, OCH_2Ph), 4.57 (1H, d, *J* 11.7 Hz, OCH_2Ph), 4.59 (1H, d, *J* 3.7 Hz, H-3), 4.67 (1H, d, *J* 3.7 Hz, H-4), 4.88 (1H, t, *J* 4.5 Hz, H-8), 6.06 (1H, d, *J* 3.6 Hz, H-1), 7.18–7.40 (5H, m, ArH). δc ($CDCl_3$, 75 MHz): 26.2, 26.7, 26.8, 34.5, 64.8, 72.3, 81.7, 83.6, 85.3, 103.3, 105.8, 112.2, 127.6, 127.9, 128.4, 136.8, 207.5. Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found C, 63.70; H, 6.70. For **8a**: thick liquid; $[\alpha]_D = +29.00$ (*c* 0.56, $CHCl_3$); ν_{max} (Neat) 3366, 1675 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.31 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.84–2.05 (3H, m, H-6/H-7), 2.09–2.15 (1H, m, H-6/H-7), 3.38–3.45 (2H, m, N-CH_2), 3.80 (1H, dd, *J* = 10.2, 1.8 Hz, H-4), 4.02 (1H, d, *J* 1.8 Hz, H-3), 4.14 (1H, dt, *J* 10.2, 6.2 Hz, H-5), 5.26 (1H, bs, exchanges with D_2O, OH), 4.59 (1H, d, *J* 3.7 Hz, H-2), 5.14 (2H, ABq, *J* 12.5 Hz, OCH_2Ph), 5.90 (1H, d, *J* 3.7 Hz, H-1), 7.26–7.38 (5H, m, ArH). δc ($CDCl_3$, 75 MHz): 23.0, 26.1, 27.1, 28.2, 48.8, 59.9, 68.1, 73.9, 81.0, 85.0, 105.2, 112.3, 128.0, 128.4, 129.1, 136.0, 157.1. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93. Found: C, 62.68; H, 6.81. For **8b**: thick liquid; $[\alpha]_D = -72.27$ (*c* 0.44, $CHCl_3$); ν_{max} (Neat) 3390, 1693 cm^{-1}; δ_H (300 MHz): 1.30 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.82–1.94 (2H, m, H-6/H-7), 1.96–2.20 (2H, m, H-6/H-7), 3.42–3.58 (2H, m, NCH_2), 4.0 (1H, t, *J* = 3.0 Hz, H-4), 4.13 (1H, d, *J* = 2.9 Hz, H-3), 4.26–4.34 (1H, m, H-5), 4.48 (1H, d, *J* = 3.6 Hz, H-2), 5.13 (2H, ABq, *J* = 12.3 Hz, OCH_2Ph), 5.87 (1H, d, *J* = 3.6 Hz, H-1), 7.24–7.42 (5H, m, ArH). δc (75 MHz): 23.6, 26.1, 26.7, 29.7, 47.2, 55.5, 67.5, 75.7, 84.0, 85.0, 104.5, 111.2, 127.8, 128.0, 128.4, 136.3, 158.7. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93. Found C, 62.80; H, 6.79. For **2** mp: 176–178°C (reported 178–181°C)[2b], $[\alpha]_D = +50.10$ (*c* 0.7, MeOH) [reported +50.6 (*c* 0.2, MeOH)].[2b] For **3**: semisolid; $[\alpha]_D = +23.0$ (*c* 0.72, MeOH) [reported +22.5 (*c* 1.13, MeOH)[5a–b]]; ν_{max} (KBr) 3360–3250 cm^{-1} (broad band); δ_H (300 MHz, pyridine-d_5+D_2O): 1.72–2.00 (3H, m, H-1/H-2), 2.22–2.40 (1H, m, H-1/H-2), 2.84–3.00 (1H, m, H-3), 3.44 (1H, bd, *J* = 12.3 Hz, H-5), 3.49–3.67 (2H, m, H-8a and H-3), 3.69 (1H, bd, *J* = 12.3 Hz, H-5), 4.42 (2H, bs, H-7 and H-8), 4.55 (1H, bs, H-6). δc (125 MHz, pyridine-d_5): 21.1, 24.5, 54.7, 55.5, 64.6, 70.5, 70.7, 70.9. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73. Found C, 55.80; H, 9.02.

Table 1. Comparison of ^{1}H NMR spectra of **2** and **3**

	H5a	H5e	H6	H7	H8	H8a
2	2.30 (t) $J_{5a,5e}=J_{5a,6a}=10.5$ Hz	3.43 (dd) $J_{5e,6a}=5.2$ Hz	4.33 (ddd) $J_{6,7}=8.6$ Hz	3.91 (t) $J_{7,8}=8.6$ Hz	3.86 (t) $J_{8,8a}=8.6$ Hz	2.94 (dt) $J_{8a,1a}=8.6$ Hz $J_{8a,1e}=2.0$ Hz
3	3.44 (bd) $J_{5a,5e}=12.3$ Hz	3.69 (bd) $J_{5a,5e}=12.3$ Hz	4.55 (bs, 1H)	4.42 (bs, 2H)		3.49–3.67 (m, 2H)

further supported by the observed two doublets at δ 3.44 and 3.69 ($J_{5e,5a}=12.3$ Hz) for the protons H5a and H5e wherein, the absence of $J_{5a,6e}$ and $J_{5e,6e}$ is suggestive of the fact that H6 is *equatorial* and bisecting the H5 protons. Based on those data the conformation assigned for **3** was $^5C_8$ while that of **2** was $^8C_5$ as shown in **3a** and **2a**, respectively.

In conclusion, we have demonstrated an efficient method for the synthesis of 1-deoxy-castanospermine **2** and 1-deoxy-*8a-epi*-castanospermine **3**. The easy availability of the chiral starting materials, mild reaction conditions and good yields make the route attractive and indicate that it could operate on a gram scale.

Acknowledgements

We gratefully acknowledge the financial support from BRNS, Mumbai. NTP is thankful to CSIR, New Delhi for JRF.

References

1. (a) For a review, see: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. (b) Denmark S. E.; Herbert B. *J. Org. Chem.* **2000**, *65*, 2887 and references cited therein.
2. (a) Yoda, H.; Nakajima, T.; Takabe, K. *Synlett* **1997**, 911; (b) Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron* **1988**, *44*, 6143; (c) Martin, S. F.; Chen, H.-J.; Yang, C.-P. *J. Org. Chem.* **1993**, *58*, 2867; (d) Izquierdo, I.; Plaza, M. T.; Robles, R.; Rodriguez, C.; Ramirez, A.; Mota, A. J. *Eur. J. Org. Chem.* **1999**, *64*, 1269.
3. (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, pp. 1–54; (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.
4. Martin and co-workers claimed the synthesis of **3** however, the subsequent paper from the same group stated that the compound reported was not **3** but its diastereomer namely 1-deoxy-8-*epi*-castanospermine. (a) Martin, S. F.; Chen, H.; Yang, C-P. *J. Org. Chem.* **1993**, *58*, 2867. (b) Martin, S. F.; Chen, H.; Lynch, V. M. *J. Org. Chem.* **1995**, *60*, 276.
5. The other report by Denis and Chan also described the synthesis of **3**. Nevertheless, in their paper, the characterisation of structure for 1-deoxy-8a-*epi*-castanospermine, based on ^{1}H NMR analysis, was doubtful (a) Denis, Y. S.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*, 3078. Only recently they have revised their stereochemical assignment for **3** (b) Denis, Y. S.; Chan, T.-H. *Can. J. Chem.* **2000**, 78, 776
6. (a) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1719; (b) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482; (c) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M. D.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475.
7. At this stage, compound **6** was reacted with TFA–H_2O to cleave the acetal as well as the 1,2-acetonide groups and the product obtained was subjected to one pot triple reductive amination to get indolizidine ring skeleton. This process, however, gave complex mixture of products.
8. The assignment of stereochemistry at C5 was made by comparison of ^{1}H NMR data of **8a** and **8b** and confirmed by conversion of **8a** to known compound **2**.
9. Although, our rotation value and ^{13}C NMR data of **3** match with that reported by Denis and Chan,[5a,b] there is a discrepancy in the ^{1}H NMR data probably due to solvent shift. Denis and Chan reported the ^{1}H NMR of **3** in methanol-d_4. It may be noted that methanol-d_4 itself shows two signals at δ 3.31 and 4.80, which obscure the signals due to compound **3**. In addition, exchange of HC-OH protons of **3**, with methanol-d_4, also gives signal at δ 4.84 due to HDO.