Asymmetric Synthesis of 1-Deoxy-8,8a-di-*epi*-castanospermine

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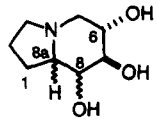
We recently reported the asymmetric syntheses of 1-deoxycastanospermine (**1**) and a diastereomer that was originally thought to be 1-deoxy-8a-*epi*-castanospermine (**2**).[1] However, during the course of subsequent investigations directed toward the synthesis of other derivatives of **1**, we discovered that the compound we had previously assigned as being **2** was in fact the diastereomeric 1-deoxy-8-*epi*-castanospermine (**3**).[2] We now report the details of these findings together with a description of the synthesis of the related analogue 1-deoxy-8,8a-di-*epi*-castanospermine (**4**).

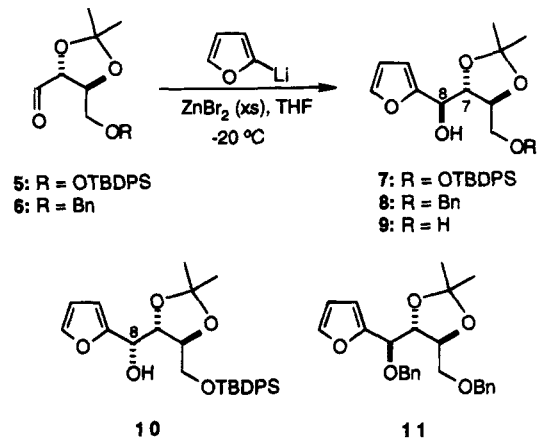


1: α-H; α-OH
2: β-H; α-OH
3: α-H; β-OH
4: β-H; β-OH

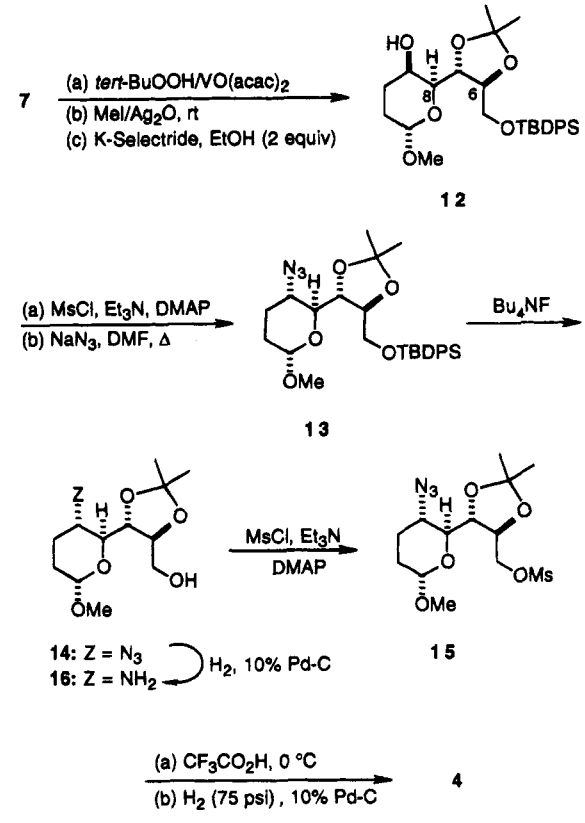
One of the key steps in our approach to hydroxylated indolizidines involved the stereoselective addition of 2-furyllithium to the silyl-protected aldehyde **5** in the presence of $ZnBr_2$ to give what was originally assigned to be **10**, which has the *S*-configuration at C(8) (castanospermine numbering) (Scheme 1). This stereochemical assignment was based upon the eventual conversion of the major product of this addition into synthetic 1-deoxycastanospermine (**1**) that was identical to an authentic sample. Since the absolute stereochemistry at C(8) in **1** corresponds to that found in **10**, the assignment of the *S*-configuration to the major adduct seemed reasonable at the time. That something was wrong with this conclusion was first revealed when we prepared 1-deoxy-8,8a-di-*epi*-castanospermine (**4**) from an intermediate that had been previously converted into **1** (*vide infra*).[1]

We then reexamined the stereochemistry of this key reaction by correlating the major products of the additions of 2-furyllithium to **5** and **6**. Mukaiyama had previously observed that the latter reaction proceeded with >98% diastereoselectivity to provide **8**.[3] Thus, removal (*n*-Bu_4NF, THF, 0 °C) of the silyl protecting group from the major adduct of the addition of 2-furyllithium to **5** followed by exhaustive *O*-benzylation (NaH, BnBr, DMF, −70 → 25 °C) of **9** gave the dibenzyl ether **11**, which was identical with an authentic sample prepared independently from **8**. Thus, the stereochemistry of the addition of 2-furyllithium to **5** and **6** occur with the same diastereofacial selectivity to give the *R*-adducts **7** and **8**, respectively.

Scheme 1



Scheme 2

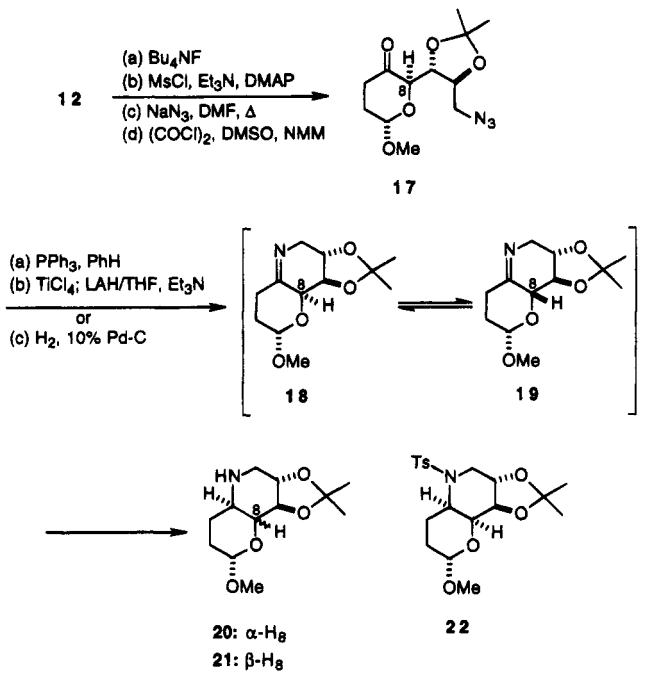


The conversion of **7** into the hydropyran intermediate **15** follows the same route that was outlined in our earlier report, but the relative stereochemistry of the centers in the hydropyran ring of the intermediates leading from **7** to **15** have the configurations depicted in Scheme 2 rather than the diastereomeric ones that were previously assigned.[1] The present assignments were unequivocally verified by the X-ray analysis of the amino alcohol **16**.[4] Hydrolysis of the acetonide and acetal moieties of **15** followed by reduction of the azide group and cyclization of the intermediate amino mesylate then gave 1-deoxy-

(1) Martin, S. F.; Chen, H.-J.; Yang, C.-P. *J. Org. Chem.* **1993**, *58*, 2867.
(2) Paulsen, H.; Matzke, M.; Orthen, B.; Nuck, R.; Reutter, W. *Liebigs Ann. Chem.* **1990**, 953.
(3) (a) Mukaiyama, T.; Yuki, Y.; Suzuki, K. *Chem. Lett.* **1982**, 1169. (b) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.
(4) The author has deposited atomic coordinates for compounds **16** and **22** with the Cambridge Crystallographic Data Centre. These coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

0022-3263/95/1960-0276$09.00/0

Scheme 3



8,8a-di-*epi*-castanospermine (**4**). If the azide was reduced to an amino group *prior* to the hydrolysis step, **4** was not detected in the reaction mixture.[1] Although we were not able to obtain an authentic sample of **4**, the splitting patterns and coupling constants for the protons on C(5), C(6), C(7), C(8) and C(8a) correlate closely to those reported by Gallagher for 8,8a-di-*epi*-castanospermine.[5] However, our ^1H and ^{13}C NMR data for **4** do not correspond to those reported by Chan;[6] we have no explanation for this discrepancy since our assignment seems secure with the X-ray structure of **16**.

Since the stereochemistry at C(8) in **7** is *R*, the question arises of how 1-deoxycastanospermine could have arisen from **7**. To resolve this issue, we reexamined the reductions of the azido ketone **17**, the preparation of which has been previously described (Scheme 3).[1] Catalytic hydrogenation of **17** afforded a single product that was determined to be **20** based upon the single crystal X-ray analysis of the derived tosylamide **22**.[4] The amine **20** was then transformed into 1-deoxy-8-*epi*-castanospermine (**3**), not 1-deoxy-8a-*epi*-castanospermine (**2**) as originally reported. Although we were unable to secure an authentic sample of **3**, its ^1H and ^{13}C NMR spectra in D_2O were identical to those reported by Paulsen for its enantiomer ***ent*-3**.[2] On the other hand, when **17** was treated with triphenylphosphine in refluxing benzene followed by hydride reduction, a mixture of **20** and **21** was obtained in a ratio of 1:4.4.[1] The structure assigned to **21** was verified by its subsequent conversion [H_3O^+; H_2 (70 psi), 10% Pd–C, MeOH] into a sample of synthetic 1-deoxycastanospermine (**1**) that was identical to an authentic sample.[7]

The preceding experiments revealed that epimerization at C(8) occurred at some stage during the sequential processing of **17** with triphenylphosphine and a hydride reducing reagent. Because of limited quantities of material, we were unable to examine the timing of this deleterious event completely, but a preliminary experiment indicated that the imine **18** could suffer equilibration at C(8). For example, examination of the ^1H NMR spectrum of the crude reaction mixture obtained upon treatment of **17** with triphenylphosphine in refluxing benzene suggested that a mixture (ca. 1:2) of the two imines **18** and **19** was present in the reaction medium. Low energy conformations of **18** and **19**, which were identified using a Monte-Carlo search and minimized with the MM2* force field (MacroModel, Ver 4.5), were found to have comparable stabilities.[8,9]

Experimental Section[10]

L-*arabino*-Octa-5,7-dienitol, 5,8-anhydro-6,7-dideoxy-2,3-*O*-(1-methylethylidene)- (9). A solution of **7** (33 mg, 0.07 mmol) in THF (1 mL) containing *n*-Bu_4NF (1.0 M in THF, 70 μL, 0.07 mmol) was stirred at 0 °C for 15 min. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography eluting with CH_2Cl_2/EtOAc (1:1) to give the diol **9** (12 mg, 74%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.42 (m, 1 H), 6.37–6.35 (complex m, 2 H), 4.86 (d, *J* = 4.7 Hz, 1 H), 4.22–4.15 (complex m, 2 H), 3.62 (dd, *J* = 11.6, 2.7 Hz, 1 H), 3.44 (br d, *J* = 11.6 Hz, 1 H), 2.95 (br s, 1 H), 2.38 (br s, 1 H), 1.42 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 142.3, 110.4, 109.5, 107.6, 78.7, 78.5, 67.9, 62.5, 27.1, 26.9; IR (CCl_4) ν 3607, 3384 cm^{-1}; mass spectrum (CI) *m/z* 228.1004 ($C_{11}H_{16}O_5$ requires 228.0998), 211 (base), 185.

L-*arabino*-Octa-5,7-dienitol, 5,8-anhydro-6,7-dideoxy-1,4-di-*O*-benzyl-2,3-*O*-(1-methylethylidene)- (11). To a solution of NaH (1.6 mg of a 60% dispersion in mineral oil, 0.04 mmol) in DMF (0.2 mL) was added a solution of **9** (5 mg, 0.02 mmol) in DMF (0.5 mL) at −70 °C. The solution was stirred for 1 h, whereupon BnBr (4.2 μL, 0.04 mmol) was added. After stirring for 40 min at −70 °C, the solution was warmed to rt and quenched by adding H_2O (1 drop). The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexane/EtOAc (6:1) to give **11** (4 mg, 50%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (br s, 1 H), 7.33–7.23 (complex m, 10 H), 6.39–6.35 (complex m, 2 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 4.53 (d, *J* = 13.3 Hz, 2 H), 4.44 (d, *J* = 6.0 Hz, 1 H), 4.33 (d, *J* = 12.0 Hz, 1 H), 4.26–4.15 (complex m, 2 H), 3.66 (dd, *J* = 10.4, 2.7 Hz, 1 H), 3.52 (dd, *J* = 10.4, 6.2 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 137.6, 128.4, 128.3, 127.9, 127.7, 127.5, 110.3, 110.1, 109.7, 78.8, 78.2, 75.1, 73.4, 71.3, 70.8, 27.2, 26.9; IR (CCl_4) ν 3066, 2989, 1497 cm^{-1}; mass spectrum (CI) *m/z* 408.1935 ($C_{25}H_{28}O_5$ requires 408.1937), 393, 301 (base), 243.

α-L-*talo*-Octopyranoside, methyl 4-amino-2,3,4-trideoxy-6,7-*O*-(1-methylethylidene)- (16). A mixture of **14** (15 mg, 0.05 mmol) and Pd/C (10%) (5 mg) in absolute MeOH (0.2 mL) was shaken under an atmosphere of H_2 (70 psi) overnight at rt. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (10:1) to give **16** (13 mg, 90%) as a white solid, mp 120–121 °C (EtOAc/hexane). A single crystal for X-ray analysis was obtained by dissolution in a minimum volume of EtOAc and placing this solution in a chamber saturated with hexane: ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, *J* = 2.9 Hz, 1 H), 4.10 (ddd, *J* = 7.7, 4.9, 4.5 Hz, 1 H), 3.90 (t, *J* = 7.7 Hz, 1 H), 3.80 (dd, *J* = 11.5, 4.9 Hz, 1 H), 3.76 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.43 (dd, *J* = 9.2, 7.7 Hz, 1 H), 3.35 (s, 3 H), 2.76 (td, *J* = 9.2, 4.1 Hz, 1 H), 1.90 (br s, 1 H), 1.80–1.74 (complex m, 2 H), 1.73–1.68 (m, 1 H), 1.65–1.55 (m, 1 H),

(5) Thompson, S. H. J.; Subramanian, R. S.; Roberts, J. K.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc. Chem. Commun.* **1994**, 933.

(6) St-Denis, Y.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*, 3078. We thank Professor T.-H. Chan for providing copies of his ^1H NMR spectra of his samples of **3** and **4**.

(7) We thank Professor A. C. Richardson (Kings College London) for copies of the ^1H NMR spectra of 1-deoxycastanospermine and Dr. Norton Peet (Marion Merrell Dow) for an authentic sample of 1-deoxycastanospermine for comparison.

(8) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(9) We thank Dr. Kyle S. Knight for performing these calculations.

(10) With the exceptions of the new procedures reported herein, the synthetic procedures used to effect all transformations are identical to those described previously.[1]

1.43 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.5, 97.5, 80.9, 80.7, 75.0, 63.6, 54.8, 51.7, 29.1, 27.3, 27.1, 26.9; IR ($CHCl_3$) ν 3593, 3444, 3383, 3314 cm^{-1}; mass spectrum (CI) m/z 262.1640 ($C_{12}H_{23}NO_5$ + H requires 262.1654), 258, 230 (base).

1-Deoxy-8,8a-di-*epi*-castanospermine (4). A solution of **15** (11.2 mg, 0.03 mmol) in THF (0.1 mL) and 90% CF_3CO_2H (0.5 mL) was stirred for 3 h at 0 °C, and the volatiles were removed under reduced pressure. The residue was dissolved in MeOH (0.5 mL) containing 10% Pd–C (3.8 mg), and the mixture was shaken under an atmosphere of H_2 (75 psi) for 14 h at rt. Solid K_2CO_3 (ca 100 mg) and CH_2Cl_2 (ca 3 mL) were added, and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (1:1) to give **4** (4.4 mg, 83%) as a white semisolid: ^{1}H NMR (500 MHz, pyridine-d_5) δ 5.10–4.90 (br s, 3 H), 4.54 (t, J = 3.1 Hz, 1 H), 4.38 (dt, J = 3.1, 2.2 Hz, 1 H), 4.28 (dd, J = 9.5, 3.1 Hz, 1 H), 3.16 (dd, J = 11.3, 2.2 Hz, 1 H), 2.99 (td, J = 8.3, 1.5 Hz, 1 H), 2.94 (dd, J = 11.3, 2.2 Hz, 1 H), 2.71 (td, J = 9.5, 6.5 Hz, 1 H), 2.24–2.17 (complex m, 2 H), 1.80–1.64 (complex m, 2 H), 1.62–1.52 (m, 1 H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 73.2, 73.1, 71.8, 63.9, 54.4, 54.1, 29.5, 26.1; ^{1}H NMR (CD_3OD) (500 MHz) δ 3.82–3.78 (complex m, 2 H), 3.61 (dd, J = 10.0, 2.4 Hz, 1 H), 3.00 (td, J = 9.0, 2.4 Hz, 1 H), 2.85 (dd, J = 11.8, 1.1 Hz, 1 H), 2.48 (dd, J = 11.8, 1.2 Hz, 1 H), 2.26 (td, J = 10.0, 6.4 Hz, 1 H), 2.18 (t, J = 9.0 Hz, 1 H), 2.06–1.97 (m, 1 H), 1.82–1.66 (complex m, 2 H), 1.57–1.48 (m, 1 H); ^{13}C NMR (125 MHz) δ 73.1, 72.8, 71.8, 63.8, 55.0, 54.1, 29.1, 21.7; mass spectrum (CI) m/z 174.1128 ($C_8H_{15}NO_3$ + H requires 174.1130), 174 (base), 156, 113.

5*H*-1,3-Dioxolo[4,5-*d*]pyrano[3,2-*b*]pyridine, octahydro-8-methoxy-2,2-dimethyl-5-(toluenesulfonyl)-[3a*S*-(3aα,-5aβ,8β,9aβ,9bβ)]- (22). A solution containing **20** (2.0 mg, 0.008 mmol), Hünig base (4 μL, 0.02 mmol), and TsCl (2.0 mg, 0.01 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 48 h at rt. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography eluting with CH_2Cl_2/EtOAc (10:1) to yield **22** (1.4 mg, 45%) as a white solid, mp 159–160.5 °C. A single crystal for X-ray analysis was obtained by dissolution in a minimum volume of EtOAc and placing this solution in a chamber saturated with hexane: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2 H), 7.34 (d, J = 8.2 Hz, 2 H), 4.78 (d, J = 3.3 Hz, 1 H), 4.43 (dd, J = 10.2, 4.6 Hz, 1 H), 4.26 (t, J = 2.9 Hz, 1 H), 4.15 (ddd, J = 10.2, 9.4, 4.6 Hz, 1 H), 3.36 (s, 3 H), 3.12 (dd, J = 9.4, 2.9 Hz, 1 H), 2.68–2.63 (complex m, 2 H), 2.60 (t, J = 10.2 Hz, 1 H), 2.44 (s, 3 H), 2.20–2.13 (m, 1 H), 2.01–1.93 (m, 1 H), 1.53–1.48 (m, 1 H), 1.45 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 133.8, 129.9, 127.4, 111.3, 97.9, 80.2, 69.4, 65.3, 55.1, 54.8, 51.2, 26.8, 26.6, 25.0, 23.5, 21.5; IR ($CHCl_3$) ν 1350, 1165 cm^{-1}; mass spectrum (CI) m/z 398.1629 ($C_{19}H_{27}NO_6S$ + H requires 398.1637), 366, 340 (base).

1-Deoxy-8-*epi*-castanospermine (3): ^{1}H NMR (300 MHz, CD_3OD) δ 3.85–3.76 (complex m, 2 H), 3.25 (dd, J = 9.4, 3.2 Hz, 1 H), 3.13 (dd, J = 10.5, 5.2 Hz, 1 H), 3.02–2.97 (m, 1 H), 2.18–2.09 (complex m, 2 H), 1.89 (t, J = 10.5 Hz, 1 H), 1.90–1.67 (complex m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 78.0, 69.9, 69.4, 67.8, 57.7, 54.6, 25.3, 23.0; ^{1}H NMR (D_2O/CD_3CN) (500 MHz) δ 3.84 (dd, J = 3.5, 1.4 Hz, 1 H), 3.72 (ddd, J = 10.7, 9.6, 5.2 Hz, 1 H), 3.34 (dd, J = 9.6, 3.5 Hz, 1 H), 3.06 (dd, J = 10.7, 5.2 Hz, 1 H), 2.84 (td, J = 9.1, 2.7 Hz, 1 H), 2.14 (td, J = 8.3, 1.4 Hz, 1 H), 2.07 (t, J = 9.1 Hz, 1 H), 1.88(t, J = 10.7 Hz, 1 H), 1.72–1.60 (complex m, 4 H); ^{13}C NMR (125 MHz, D_2O/CD_3CN) δ 76.5, 69.0, 68.4, 66.6, 56.2, 53.6, 24.5, 22.2.

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Supplementary Material Available: Copies of ^{1}H NMR spectra of **3**, **4**, **9**, **11**, **16**, and **22** and ORTEP plots for **16** and **22** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS. See any current masthead page for ordering information.

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