Tetrahedron Letters, Vol.31, No.30, pp 4321-4324, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

AN EFFICIENT, HIGHLY STEREOSELECTIVE SYNTHESIS OF (+)-CASTANOSPERMINE

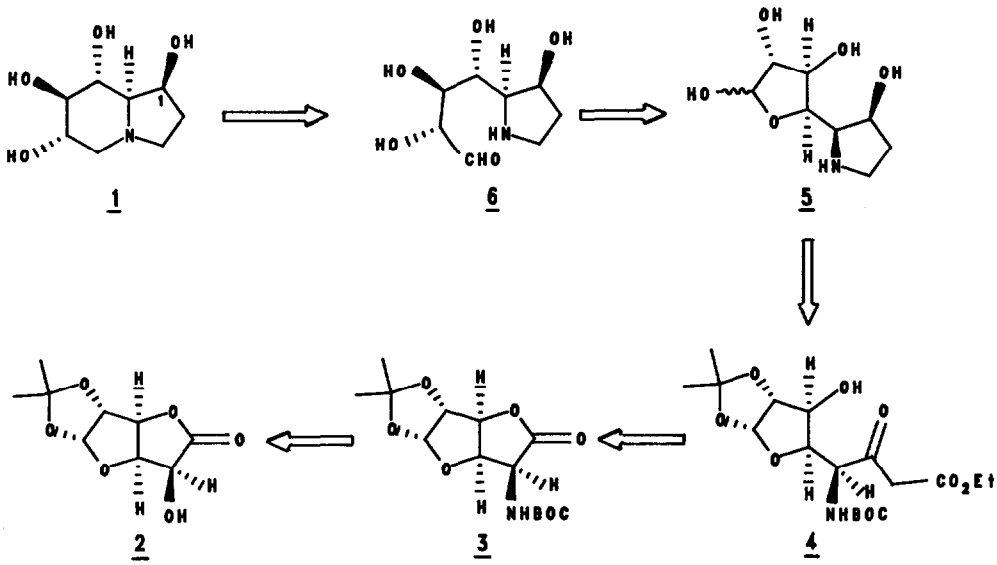
Peter B. Anzeveno*, Paul T. Angell, Laura J. Creemer and Michael R. Whalon

Merrell Dow Research Institute, 9550 N. Zionsville Rd
Indianapolis, IN 46268

Summary: An efficient, highly stereoselective synthesis of (+)-castanospermine (1) has been achieved from 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (2).

(+)-Castanospermine (1), a polyhydroxylated, indolizidine alkaloid isolated from *Castanospermum australe*[1] and *Alexa leiopetala*[2], is a potent inhibitor of several glycohydrolases[3] and shows promising antidiabetic[4], anticancer[5], antiviral[6], and anti-AIDS[7] activities. As part of an in-house program on glycohydrolase inhibition, several derivatives of 1 were chosen for further biological study. As a result, we required an efficient synthesis of 1 which would be readily amenable to scale-up.

The reported castanospermine (1) syntheses[8] are quite lengthy (⩾ 14 steps) and/or non-stereoselective, with yields ranging from less than 0.5% to 19%. In this letter, we describe a synthesis which is both short (10 steps) and highly stereoselective, giving 1 in 13% overall yield.



Scheme 1

Our retrosynthetic analysis of 1 is shown above (Scheme 1). The choice of this strategy was influenced by our recent nojirimycin synthesis[9], during which we had developed an efficient conversion of

starting glucuronolactone **2** to N-BOC-amino-desoxy-glucuronolactone **3**, an intermediate which includes four of the five chiral centers of castanospermine (**1**) in the desired configuration. The only stereocenter, then, that would require our attention was C-1. This was to be established by reduction of the ketone carbonyl of intermediate keto-ester **4**. Given the many stereoselective carbonyl reducing agents available[10], we expected to find a method that would give the desired (S)-alcohol selectively.

In the event, homologation of **3**[9] (**Scheme 2**) by treatment with EtOAc and LDA gave a 97% yield of syrupy hemiketal **7**[11] as a single epimer at C-6. The trans relationship of the carbamate and acetate moieties was determined by NOE studies (magnetic coupling of H-5 to both H's 7 and 7' was observed).

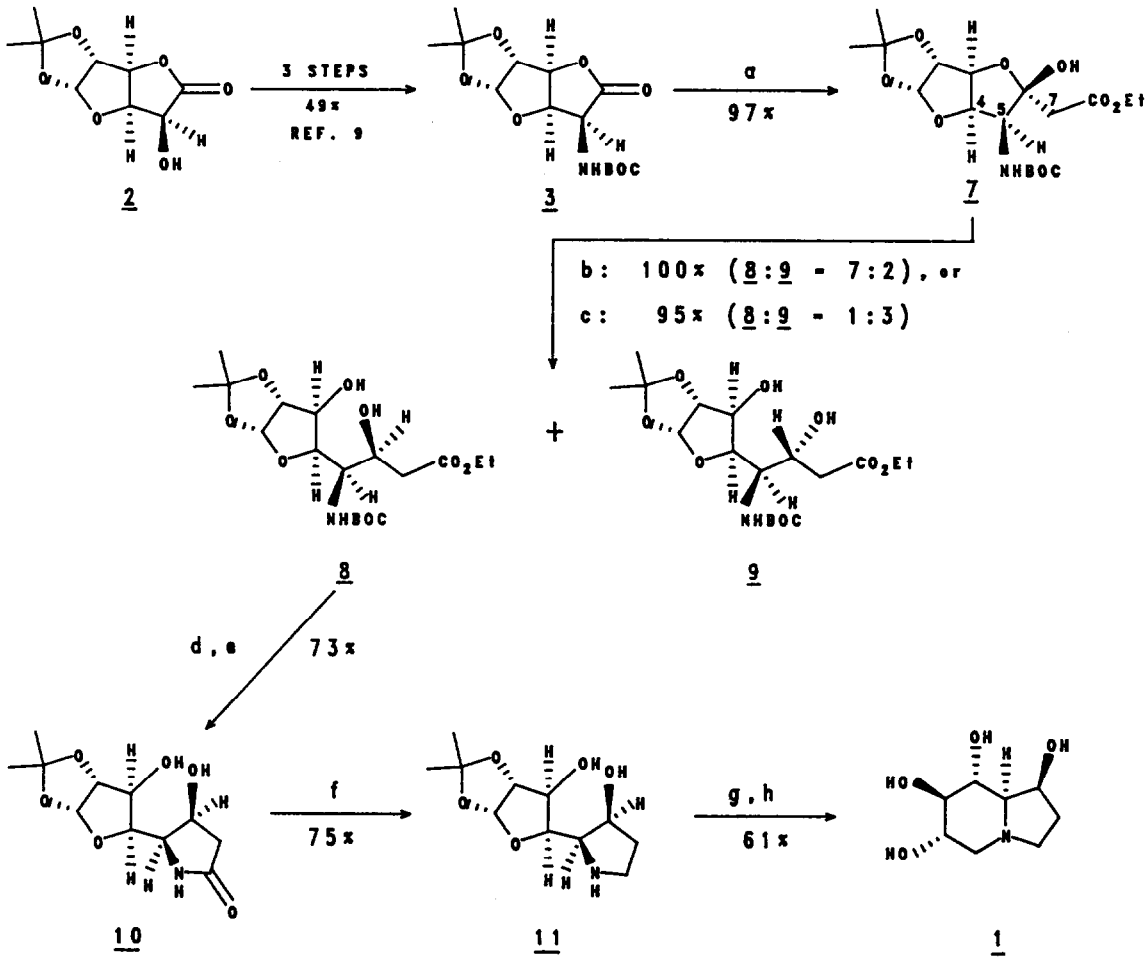
Reduction of **7** by a variety of borohydride, aluminohydride, borane and alane reagents gave rise to product mixtures containing both diastereomeric amino-diols **8** (5R,6S (desired))[12] and **9** (5R,6R), with **9** predominating by 3 to 4-fold (HPLC). Both products were crystalline and could easily be separated by flash chromatography over silica gel. This high diastereoselectivity may be due to some coordination of the reducing agent with the oxygen functions of keto-ester **4** (in equilibrium with **7**), *e.g.* as depicted in Fig. 1. Conversely, catalytic hydrogenation of **7** over PtO_2 in EtOAc at 45-50 psi gave reproducible 7:2 mixtures of **8** and **9**, from which **8** could be isolated in 79% yield after chromatography. This preference can be rationalized by assuming that the favored reaction conformer of keto-ester **4** is that pictured in Fig. 2, and that hydrogen transfer takes place, for the most part, from the direction opposite to the sterically demanding *tert*-butyl carbamate group.

Conventional treatment of BOC-amino-diol **8** with either TFA or HCl gave poor yields of deprotected amine. Fortunately, **8** could be effectively deprotected by treatment with formic acid.[13] The resulting amino ester cyclized during purification over Dowex 1X2 basic ion exchange resin, affording crystalline lactam **10** in 73% yield. LAH reduction of **10** gave a 75% yield of furanose-pyrrolidine **11**, which upon treatment with 90% TFA at 0°C, followed by catalytic hydrogenation over Pt on carbon, gave (+)-castanospermine (**1**) in 61% yield from **11**. This was identical to an authentic sample of natural **1** by comparison of its ^1H (300 MHz) and ^{13}C NMR spectra, mass spectrum, optical rotation and melting point.

Carrying BOC-amino-diol **9** through the same series of reactions as described for **8** gave (-)-1-epicastanospermine[8a,c] (35% from **9**).

Acknowledgments: The authors thank Dr. John C. Huffman of the Indiana University Department of Chemistry-Molecular Structure Center, Bloomington,

Scheme 2



Conditions: (a) EtOAc (3.0 equiv), LDA (3.0 equiv), THF, -78°C, 2.5 h; (b) H_2 (45-50 psi), PtO_2, EtOAc, 20 h; (c) $NaBH_4$ (0.5 equiv), EtOH, 0°C, 1h; (d) HCO_2H (98%), CH_2Cl_2, 0-5°C (2h) then 25°C (6h); (e) Dowex 1X2 (OH-) resin, H_2O; (f) LAH (5.0 equiv), THF, reflux, 20h; (g) CF_3CO_2H (90%), 25°C, 20h; (h) H_2 (50 psi), 5% Pt on C, H_2O, 20h.

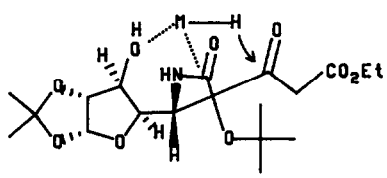


Fig. 1

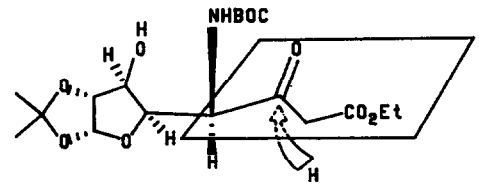


Fig. 2

IN, for X-ray analysis of amino-diol **8** and Dr. Paul S. Liu of MDRI-Cincinnati for samples of (+)-castanospermine (**1**) and (-)-1-epicastanospermine.

References and Notes

1. Hohenschutz, L.D.; Bell, E.A.; Jewess, P.J.; Leworthy, D.P.; Pryce, R.J.; Arnold, E., Clardy, J. *Phytochemistry* **1981**, *20*, 811.
2. Nash, R.J.; Fellows, L.E.; Dring, J.V.; Stirton, C.H.; Carter, D.; Hegarty, M.P.; Bell, E.A. *Phytochemistry* **1988**, *27*, 1403.
3. (a)Saul, R.; Chambers, J.P.; Molyneux, R.J.; Elbein, A.D. *Arch. Biochem Biophys.* **1983**, *221*, 593. (b) Pan, Y.T.; Hori, H.; Saul, R.; Sanford, B.A.; Molyneux, R.J.; Elbein, A.D. *Biochemistry*, **1983**, *22*, 3975. (c) Campbell, B.C.; Molyneux, R.J.; Jones, K.C. *J. Chem. Ecol.* **1987**, *13*, 1759. (d) Szumilo T.; Kaushal, G.; Elbein, A.D. *Arch. Biochem. Biophys.* **1986**, *247*, 261.
4. (a) Rhinehart, B.L.; Robinson, K.M.;Payne, A.J.; Wheatly, M.E.; Fisher, J.L.; Liu, P.S.; Cheng, W. *Life Sci.* **1987**, *41*, 2325. (b) Trugnan, G.; Rousset, M.; Zweibaum, A. *Febs Lett.* **1986**, *195*, 28.
5. Humphries, M.J.; Matsumoto, K.; White, S.L; Olden, K. *Cancer Res.* **1986**, *46*, 5215.
6. Sunkara, P.S.; Bowlin, T.L.; Liu, P.S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*,206.
7. (a) Tyms, A.S.; Berrie, E.M.;Ryder, T.A.; Nash, R.J.; Hegarty, M.P.; Taylor, D.L.; Moberley, M.A.; Davis, J.M.; Bell, E.A.; Jeffries, D.J.; Taylor-Robinson, D.; Fellows, L.E. *Lancet* **1987**, *ii*, 1026. (b) Gruters, R.A.; Neefjes, J.J.; Tersmette M.; de Coede, R.E.Y.; Tulp, A.; Huisman, H.G.; Miedema, F.; Ploegh, H.L. *Nature* **1987**, *330*, 74 (c) Walker. B.D.; Kowalski, M.; Goh, W.C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W.A.; Sodroski, J. *Proc. Natl. Acad. Sci.* USA **1987**, *84*, 8120.
8. (a) Setio, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617. (b) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492. (c) Bernotas, R.B.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165. (d) Reymond, J.-L.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 705.
9. Anzeveno, P.B.; Creemer L.J. *Tetrahedron Lett.* **1990**, *31*, 2085.
10. For reviews of recent work, see: (a) Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V. *J. Org. Chem.* **1987**, *52*, 5406. (b) Midland, M.M. "Asymmetric Synthesis"; Morrison, J.D., Ed.; Academic: New York, **1983**; Vol. 2, Chapter 2. (c) Grandbois, E.R.; Howard, S.I.; Morrison, J.D. "Asymmetric Synthesis"; Morrison, J.D., Ed.; Academic: New York, 1983; Vol. 2, Chapter 3. (d) Haubenstock, H. *Top. Stereochem.* **1983**, *14*, **231**. (e) Ap Simon, J.W.; Lee Collier, T. *Tetrahedron* **1986**, *42*, **5157**.
11. All new compounds reported were fully characterized by ^{1}H and ^{13}C NMR, IR and mass spectrometry. Each gave satisfactory analytical data (C,H,N). Physical data: **7**, oil, $[\alpha]_D^{25}$ = +10.7° (c 2.3, $CHCl_3$); **8**, mp 102-104°C, $[\alpha]_D^{25}$ = + 21.8° (c 2.3, $CHCl_3$); **8a**, mp 149-150°C, $[\alpha]_D^{25}$ = +34.8° (c 2.0, $CHCl_3$); **9**, mp 263-265°C, $[\alpha]_D^{25}$ = -39.3° (c 0.67, H_2O); **10**, mp 223-225°C, $[\alpha]_D^{25}$ = -5.0° (c 0.32, H_2O)
12. The structure of amino-diol **8** was confirmed both by X-ray analysis and by its conversion to **1**.
13. Halpern, B.; Nitecki, D.E. *Tetrahedron Lett.* **1967**, 3031.

(Received in USA 2 May 1990)