Pergamon

Tetrahedron Letters, Vol. 37, No. 47, pp. 8573-8576, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01959-4

Synthesis of a Deoxynojirimycin Analogue from Castanospermine

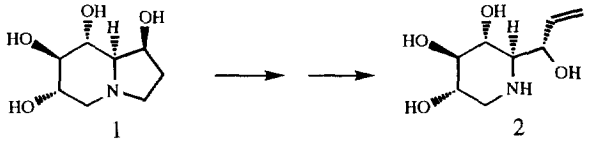
John B. Bremner[a]*, Brian W. Skelton[b], Reginald J. Smith[c], Gregory J. Tarrant[a], and Allan H. White[b]

a. Department of Chemistry, University of Wollongong, NSW, Australia, 2522.
b. Department of Chemistry, University of Western Australia, Nedlands, WA ,Australia 6907
c. Phytex Australia Pty Ltd, Sydney, NSW, Australia

Abstract: Ring cleavage of 1,6-*O,O-bis*-*t*-butyldimethylsilylcastanospermine **3** with methyl chloroformate followed by deprotection with tetrabutylammonium fluoride gave (1S,6S,7R,8R,8aR)-1-(2'-chloroethyl)-1,5,6,7,8,8a-hexahydro-6,7,8-trihydroxy-3*H*-furo[3,4-*a*]pyridin-3-one **5**. Refluxing **5** with potassium *t*-butoxide, followed by the addition of NaOH and futher refluxing yielded the deoxynojirimycin analogue (1'S,2R,3R,4R,5S)-2-(1'-hydroxy-2'-propenyl)-piperidine-3,4,5-triol **2**.

Castanospermine **1**, and a range of other polyhydroxy alkaloids, have attracted much interest due to the fact that they are potent inhibitors of a variety of glycosidases[1]. All the synthetic efforts carried out on **1** so far have focussed on its stereoisomers and analogues[2-5]. The only published work to date on the ring modification of castanospermine has been on the ring contraction to form australine[3] and a ring rearrangement[4].

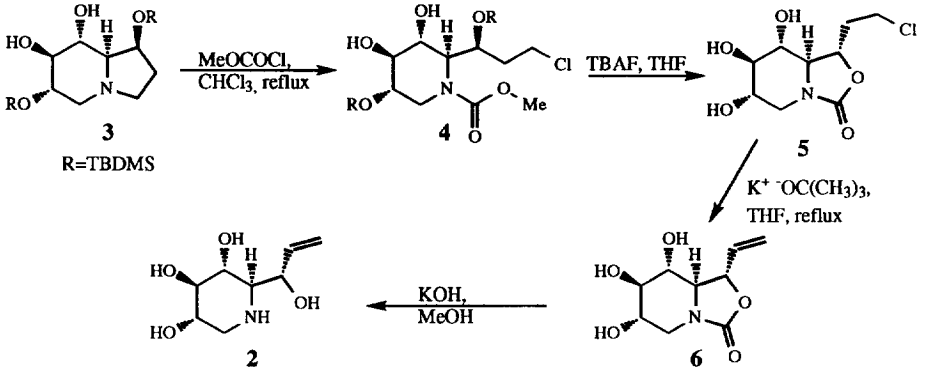
Our work has involved the development of new azasugars derived from ring cleavage modification of castanospermine with a long term goal of obtaining new, selective and potent glycosidase inhibitors. Herein we report the synthesis of (1'S,2R,3R,4R,5S)-2-(1'-hydroxy-2'-propenyl)-piperidine-3,4,5-triol **2** from castanospermine.



1 2

The protection of all four hydroxyls of castanospermine as the *t*-butyldimethylsilyl ethers failed. Treatment of castanospermine with TBDMSCl gave a mixture of four compounds. Of the four compounds one isomer was isolated pure. $^1H,^1H$ COSY experiments in d_6 DMSO confirmed this compound to be 1,6-*O,O*-bis-*t*-butyldimethylsiloxy-castanospermine **3**[6,7]. Refluxing **3** with methyl chloroformate in chloroform resulted in the ring cleaved product **4**[8] in 80% yield. The dehydrohalogenation of **4** with potassium *t*-butoxide failed to yield any olefin. However after treatment of **4** with tetrabutylammonium fluoride (TBAF) to give **5**[9] (78%), followed by dehydrohalogenation with potassium *t*-butoxide, the furopyridinone **6**[10] was obtained in good yield. Other derivatives of the 3*H*-furo[3,4-*a*]pyridin-3-one skeleton have been reported previously, for example in the synthesis of deoxynojirimycin[11], α-homogalactostatin[12] and its 1,*N*-anhydro derivative[12], but different routes were employed to the one described here.

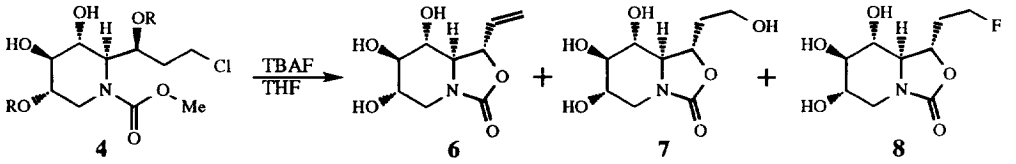
The overall yield of **6** was increased by not separating the mixture obtained from the protection of castanospermine with TBDMSCl. Carrying this mixture through the two steps described for **3** gave **5** in an overall yield of 44% from castanospermine. Dehydrohalogenation of **5** then gave **6** in 88% yield.



3 **4** **5** **6** **2**

Structural elucidation of **4**, **5** and **6** was based on a series of 2D NMR experiments [(^{1}H,^{1}H COSY and ^{1}H, ^{13}C COSY (HMQC or HETCOR and HMBC)]. The deoxynojirimycin analogue **2**[13] was formed from **5** (93% yield) in a one pot reaction involving dehydrohalogenation followed by base hydrolysis. Similar *O*- and *N*-protected but epimeric analogues of deoxynojirimycin have been synthesised before as part of the total synthesis of castanospermine epimers based on sugar precursors[2,14]. A double-bond reduced derivative of **2**, has also been prepared[15] in a multi-step route from a sugar derivative.

Prolonged treatment of **4** with TBAF resulted in a further mixture of compounds. This mixture was separated by HPLC to give three pure compounds. Structural determination of these compounds by NMR revealed that compound **6** was formed as well as the hydroxy substituted derivative **7**[16] and the new fluoro substituted analogue **8**[17]. The percentage yields of these compounds determined by ^{1}H NMR on the reaction mixture after the removal of the excess TBAF by ion exchange, were **6** 17%, **7** 67%, and **8** 16%. The unequivocal confirmation of the structure and stereochemistry of **8**, was forthcoming from a single crystal X-ray structure determination[18]. The structure obtained is shown in Figure **1** and non-hydrogen atom parameters are given in Table **1**. The molecule adopts a flattened chair conformation in the six membered ring and a *gauche* conformation in the fluoroethyl side chain.



4 **6** **7** **8**

The formation of **7** and **8** is due to OH^- and F^- exchange of the chlorine in **5**. The hydroxide ions most likely originate from traces of water in the TBAF solution in THF. The formation of **6** is via base (F^- or OH^-) promoted dehydrohalogenation of **5**.

The availability of **2** and the presence of the double bond affords further derivatisation possibilities for structure-glycosidase inhibition studies[19].

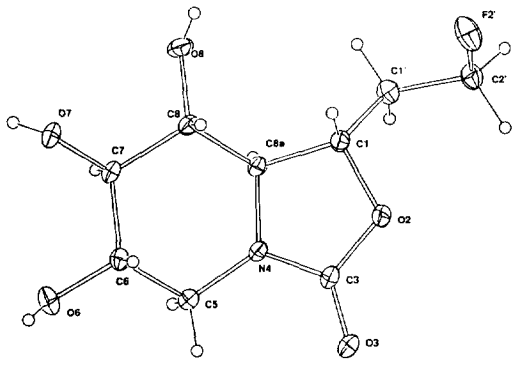


Figure 1: Structure of **8** with the molecule projected normal to the heterocyclic skeleton; 20% thermal ellipsoids are shown for the non-hydrogen atoms, together with skeletal and substituent numbering. Hydrogen atoms have arbitrary radii of 0.1 *Å*

Table 1 Non-hydrogen atom parameters for **8**

atom	x	y	z	Ueq Å^2
C(1)	0.6208(1)	0.7821(2)	0.6843(3)	0.0297(5)
C(1')	0.6863(2)	0.9180(3)	0.7048(3)	0.0365(6)
C(2')	0.6591(2)	1.0205(3)	0.8419(3)	0.0420(7)
F(2')	0.5683(1)	1.0786(2)	0.8143(2)	0.0598(5)
O(2)	0.6170(1)	0.6950(2)	0.8349(2)	0.0388(5)
C(3)	0.6257(1)	0.5439(3)	0.8029(2)	0.0319(6)
O(3)	0.6183(1)	0.4455(2)	0.9079(2)	0.0432(5)
N(4)	0.6451(1)	0.3685(2)	0.4236(3)	0.0316(6)
C(5)	0.6531(2)	0.3742(3)	0.5689(3)	0.0352(6)
C(6)	0.5869(2)	0.3685(2)	0.4236(3)	0.0316(6)
O(6)	0.6079(1)	0.2336(2)	0.3348(2)	0.0451(5)
C(7)	0.6012(1)	0.5089(3)	0.3164(2)	0.0300(5)
O(7)	0.5328(1)	0.5053(2)	0.1885(2)	0.0377(5)
C(8)	0.5892(2)	0.6599(2)	0.4075(2)	0.0297(6)
O(8)	0.6155(1)	0.7855(2)	0.3080(2)	0.0417(5)
C(8a)	0.6518(2)	0.6641(2)	0.5573(2)	0.0287(5)

Acknowledgments: Support of this work by an Australian Postgraduate Award (Industry) through the Australian Research Council and Phytex Australia Pty Ltd to G. J. T. is gratefully acknowledged together with help from Dr J. Carver (University of Wollongong) in setting up the HMQC and HMBC NMR experiments.

REFERENCES AND NOTES.

1. Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.
2. Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045, and references therein.
3. Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131, and references therein.
4 Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1994**, *35*, 3143.
5 Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1995**, *36*, 3055.
6. All new compounds gave spectral data consistent with the proposed structures.
7. Compound **3**. ^{1}H ^{1}H COSY (d_6 DMSO) correlations were observed between 8-OH - H8 and also 7-OH - H7. (MS M$^+$, 1.25%; Calcd. for $C_{20}H_{43}NO_4Si_2$: 417.2731, found: 417.2735).
8. Compound **4**. mp. 187-190°C from $CHCl_3$. ^{1}H NMR ($CDCl_3$) δ: 4.35 (ddd, *J* = 5.3, 5.3, 11.7Hz, H1'), 4.23 (dd, *J* = 3.5, 6.35Hz, H1), 4.04 (d, *J* = 14Hz, H6), 3.82-3.62 (m, H3, H4, H5, H3', OMe), 3.28 (dd, *J* = 1.8, 14.4Hz, H6), 2.04 (ddd, *J* = 5.5, 7.0, 12.5Hz, H2'); ^{13}C NMR δ: 157.6 (N$\underline{C}O_2$Me), 71.9, 71.6, 69.7, 69.5 (C1'), 60.7 (C2), 52.7 (OMe), 43.3 (C6), 40.8 (C2), 36.9 (C2'), 26.0 (C($\underline{C}H_3)_3$) 25.8 (C($\underline{C}H_3)_3$), 18.3 ($\underline{C}(CH_3)_3$) 18.0 ($\underline{C}(CH_3)_3$) and -4.4, -4.6, -4.7, -4.9 ($Si(CH_3)_2$); MS m/z 512 (M$^+$, 0.05%), 454 (M-C$(CH_3)_3^+$, 19.5%; Calcd. for $C_{22}H_{46}{}^{35}ClNO_6Si_2$ 454.1848, found: 454.1841), 322 (13.5), 304 (14.75), 172 (17), 73 (100); IR (KBr), 1667cm^{-1}.
9. Compound **5**. mp. 150-152°C from CH_3OH. ^{1}H NMR (D_2O) δ: 4.79 (m, H1,), 3.89 (dd, *J* = 5.9, 13.1Hz, H5), 3.74 (dd, *J* = 5.5, 6.7Hz, $\underline{CH}_2Cl$,), 3.65-3.36 (m, H8a, H8, H7, H6), 2.86 (dd, *J* =

10.6, 13.1Hz, H5), 2.2 (m, $C\underline{H}_2CH_2Cl$); ^{13}C NMR δ: 158.9 (C3), 77.8 (C1), 77.6 (C7), 69.6 (C8), 63.0 (C8a), 45.1 (C5), 41.3 ($\underline{C}H_2Cl$), 38.1 ($\underline{C}H_2CH_2Cl$); MS m/z 251, 253 (M^+ $^{35}Cl/^{37}Cl$, 0.5%; Calcd. for $C_9H_{14}{}^{35}ClNO_5$ 251.0561, found: 251.0586), 179 (13.5), 1158 (60), 118 (100). IR (KBr), 1726cm^{-1}.

10. Compound **6**. ^1H NMR (D_2O) δ: 6.04 (ddd, *J* = 6.8, 10.5, 13.4Hz, $C\underline{H}=CH_2$), 5.54 (ddd, *J* = 1, 1, 17.1Hz, $CH=C\underline{H}_2$), 5.44 (ddd, *J* = 0.9, 0.9, 10.5Hz, $CH=C\underline{H}_2$) 5.03 (m, H1), 3.93 (dd, *J* = 5.9, 12.9Hz, H5,), 3.66-3.53 (m, H8a, H8 and H6), 3.44 (dd, *J* = 9.27, 9.27Hz, H7), 2.90 (dd, *J* = 10.6, 13.1Hz, H5); ^{13}C NMR δ: 158.6 (C3), 134.6 ($\underline{C}H=CH_2$), 120.4 ($CH=\underline{C}H_2$), 80.4 (C1), 77.5 (C7), 73.5 (C8), 69.2 (C6), 63.1 (C8a), 44.8 (C5); MS m/z 215 (M^+, 6%; Calcd. for $C_9H_{13}NO_5$ 215.0794, found: 215.0794), 171 (30), 112 (20), 82 (100).
11. Rudge, A. J.; Collins, I.; Holmes, A. B.; Baker, R. *Angewandte Chemie (Int .Ed.)* **1994,** *33*, 2320.
12. Martin, O. R.; Xie, F.; Liu, L. *Tetrahedron Lett.* **1995,** *36*, 4027.
13. Compound **2**. mp. 179-183°C from EtOH/CH_3CN. ^1H NMR (D_2O) δ: 5.92 (ddd, *J* = 4.6,10.8, 17.2Hz, $C\underline{H}=CH_2$), 5.50 (ddd, *J* = 1.2, 1.2, 17.2Hz, $CH=C\underline{H}_2$), 5.39 (ddd, *J* = 1.2, 1.2, 10.8Hz, $CH=C\underline{H}_2$), 4.71 (m, H1'), 3.74 (m, H3), 3.70 (dd, *J* = 7.1, 7.1Hz, H2), 3.50 (dd, *J* = 9.28, 9.28Hz, H4), 3.41 (dd, 5.13 and 12.57Hz, H6), 3.17 (dd, *J* = 2.1, 10.4Hz, H2) and 2.91 (dd, *J* = 11.5, 11.5Hz, H6), ^{13}C NMR δ: 137.2 ($\underline{C}H=CH_2$), 119.0 ($CH=\underline{C}H_2$), 77.7 (C4) 69.7 (C3), 68.6 (C5), 67.9 (C1'), 63.0 (C2), 47.6 (C6); MS m/z 189 (M^+, 2.5%; Calcd. for $C_8H_{15}NO_4$ 189.1001, found: 189.1008), 171 (6), 132 (100), 114 (18), 86 (34), 72 (65), 60 (90).
14 Burgess, K.; Chaplin, D. A. *Tetrahedron Lett.* **1992,** *33*, 6077.
15. Berger, A.; Dax, K.; Gradnig, G.; Grassberger, V.; Stütz, A.E.; Ungerank, M.; Legler, G.; Bause, E. *Bioorg.Med.Chem.Lett.*, **1992**, 2, 27.
16. Compound **7**. ^1H NMR (D_2O) δ: 4.65 (m, H1), 3.86 (dd, J = 5.98, 13.06Hz, H5), 3.74 (dd, J = 6.72, 6.72Hz, $C\underline{H}_2OH$), 3.60-3.30 (m, H6, H7, H8, H8a), 2.84 (dd, 10.49, 12.94Hz, H5), 1.99 (m, $C\underline{H}_2CH_2OH$), ^{13}C NMR δ: 159.1 (C9), 78.0 (C7), 77.9 (C4), 73.8 (C5), 69.6 (C3), 63.2 (C2), 58.5 (C2'), 45.1 (C6), 37.9 (C1'); MS ES$^+$ m/z MNa^+ 256.1 (100), MH^+ 234.0 (20%), EI m/z 215 (4), 172 (M^+ -$C_2H_5O_2$, 100% Calcd. for $C_7H_{10}NO_4$ 172.0610, found: 172.0601), 158 (62), 143 (98), 70 (75).
17. Compound **8**. mp. 208-210°C from CH_3OH. ^1H NMR (D_2O) δ: 4.81-4.74 (m, H1, $C\underline{H}_2F$), 4.66 (dd, *J* = 6.1, 6.1Hz, $C\underline{H}_2F$), 3.93 (dd, *J* = 5.9, 13.1Hz, H5), 3.62 (m, H6) 3.53 (m, H8a, H8) 3.44, (m, H7), 2.91 (dd, *J* = 10.7, 13.2Hz, H5) 2.27 (ddd, *J* = 5.4, 6.1, 6.2Hz, H1') and 2.20 (m, H1'), ^{13}C NMR δ: 159.0 (C3), 82.0 (d, *J* = 159.6Hz, $\underline{C}H_2F$), 77.8 (C7) 77.3 (d, *J* = 4.4Hz, C1), 73.7 (C8), 69.6 (C6), 63.1 (C8a), 45.1 (C5), 36.1 (d, *J* = 18.9Hz, $\underline{C}H_2CH_2F$); MS m/z 235 (M^+, 0.31%; Calcd. for $C_9H_{14}FNO_5$ 235.0856, found: 235.0855), 163 (10), 132 (12), 102 (100).
18. Structure determination of **8**: $C_9H_{14}FNO_5$ *M* = 235.1, Orthorhombic, *P*2,2,2, (No. 19), *a* = 14.118(3), *b* = 8.690(3), *c* =8.315(4) A, *V* = 1020 Å^3. D_c(Z = 2) = 1.53 g.cm^{-1}, *F*(000) = 496. Final *R* = 0.037, *Rw* = 0.041 for 1493 'observed' ($I > 3\sigma(I)$) diffractometer reflections out of 1707 unique measured to $2\theta_{max} = 60^0$ Chirality was adopted from the chemistry (monochromatic Mo *K*α radiation, $\lambda = 0.7107_3$ Å; μ_{Mo} = 0.8 cm^{-1}; specimen: 0.42 x 0.55 x 0.55mm). *T* =295 K. Anisotropic thermal parameters were refined for C, N, O, F; $(x, y, z, Uiso)_H$ were also refined. Full molecular geometries, hydrogen and thermal parameters and structure factor amplitudes have been deposited at the Cambridge Crystallographic Data Center.
19. Glycosidase inhibition studies on **2** revealed the compound was inactive as an inhibitor for amyloglucosidase, α- and β-glucosidase, α- and β-mannosidase, and α- and β-galactosidase; we thank Prof. A. Elbein, Uni. of Arkansas, USA for these results and Dr. R. Molyneux for helpful discussions. In contrast, the double-bond reduced derivative of **2** shows[15] strong α-glucosidase inhibitory activity.

(*Received in UK* 14 *August* 1996; *revised* 1 *October* 1996; *accepted* 4 *October* 1996)