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# The Chemistry of Castanospermine, Part II:[1] Synthesis of Deoxyfluoro Analogues of Castanospermine

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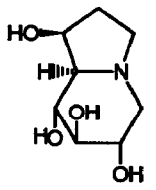
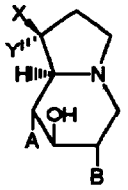
**Abstract:** The deoxyfluorocastanospermine compounds (4), (5), (6) and (7) were prepared from castanospermine *via* the novel partially protected intermediates (8), (9), (11), (13) and (17).

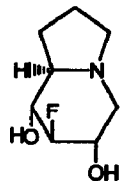
Castanospermine (1), a plant derived polyhydroxy alkaloid[2,3], is a potent inhibitor of a number of mammalian and insect glycosidases[4]. The biological activity ascribed to castanospermine of anti-viral[5], -cancer[6], -malarial[7], and -diabetes[8] properties is thought to be as a result of its glycosidase inhibitory properties. This diverse array of potentially useful activities has stimulated considerable interest in the synthesis of castanospermine and its stereoisomers and analogues[9].



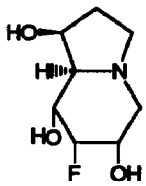
(1)



(2) X=OH, Y=H, A=OH, B=F
(4) X=F, Y=H, A=B=OH
(5) X=H, Y=F, A=B=OH
(6) X=OH, Y=H, A=F, B=OH



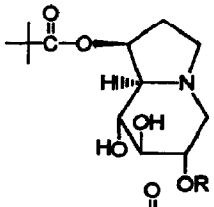
(3)



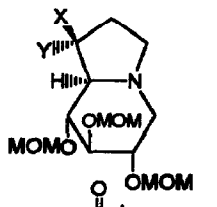
(7)

We have been pursuing a program of synthesizing castanospermine analogues with a view to improving the potency and selectivity of some of its biological properties[1]. As part of this work we were interested in synthesizing some deoxyfluoro analogues of castanospermine. So far the only known deoxyfluorocastanospermine derivatives are the 6-deoxy-6-fluoro-[1,10] and the 1,7-dideoxy-7-fluoro-[11] compounds (2) and (3). We present here syntheses of 1-deoxy-1-fluorocastanospermine (4), its *C*-1 epimer (5), 8-deoxy-8-fluorocastanospermine (6), and 7-deoxy-7-*epi*-7-fluorocastanospermine (7) from castanospermine *via* the novel and potentially very useful partially protected derivatives (8), (9), (11), (13) and (17). Biological results for these compounds will be reported elsewhere.

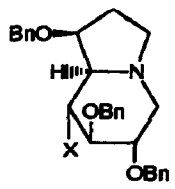
While only a few examples of selective protection procedures for castanospermine have been reported[8(c),12], we have found that high yields (80%-95%) of 6-*O*-acylated derivatives are available directly by treating tributylstannylated castanospermine with acyl halides in cold toluene[1]. In a similar way, when the solution obtained by treating castanospermine with 2 equivalents of dibutyltin oxide in refluxing toluene (with removal of water) was cooled to -10°C and treated with 2 equivalents of pivaloyl chloride only the 1,6-dipivalate (8)[13] was obtained. This could be isolated in 75% yield if desired, while in this case the crude product was treated directly with KCN in refluxing methanol to saponify selectively the 6-pivalate. The reaction was monitored by t.l.c. and stopped when almost all the dipivalate (8) was consumed. Chromatography then afforded the 1-*O*-pivalate (9)[13] in 63% overall yield. The three hydroxy groups were protected as methoxymethyl ethers ($^iPr_2NEt$, MOM Br, toluene 90°C) and the resulting tri-MOM derivative (10) was treated with $LiAlH_4$ in ether to give the alcohol (11)[13] in 85% yield from (9). Normal base catalysed solvolysis of the pivalate ester (10) (NaOMe/MeOH, reflux) was ineffective.



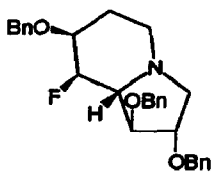

(8) R=C(O)$^t$Bu
(9) R=H



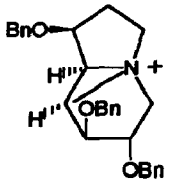

(10) X=OC(O)$^t$Bu, Y=H
(11) X=OH, Y=H
(12) X=H, Y=OH



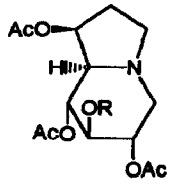

(13) X=OH
(14) X=F



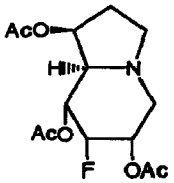

(15)




(16)




(17) R=H
(18) R=Tf




(19)

These readily available di- and mono-pivalates (8) and (9) and the mono-ol (11) are expected to be useful intermediates for the synthesis of castanospermine analogues.

A solution of alcohol (11) and triethylamine (5 eq) in dichloromethane was treated with diethylaminosulfur trifluoride (DAST) (1.5 eq) and the crude product was deprotected with 20% conc. HCl in MeOH affording 1-deoxy-1-*epi*-1-fluorocastanospermine (5)[13] in 63% yield. Swern oxidation of alcohol (11) (TFAA, DMSO, $CH_2Cl_2$, $Et_3N$) followed by reduction ($LiAlH_4$, THF, -70°C) gave a separable 1:3 mixture of the two epimeric alcohols (11) and (12)[13] respectively. This new alcohol (12) was treated with DAST and then deprotected as above to give 1-deoxy-1-fluorocastanospermine (4)[13], in 46% yield. The stereochemistries of the deoxyfluoro compounds (4) and (5) are inferred by their method of synthesis as the NMR data is not unequivocal.

A 1,6,7-protected castanospermine derivative was required to prepare the 8-deoxy-8-fluoro-compound (6). Benzylation of castanospermine [$Bu_2SnO$ (2 eq), $Bu_4NBr$ (1 eq) BnBr (8 eq), toluene, reflux 3d] afforded, after dequaternisation (LiSPr, DMSO), 1,6,7-tri-*O*-benzylcastanospermine (13)[13] in 50% yield contaminated with small amounts of the corresponding 1,6,8-tribenzyl ether. A more detailed examination of this reaction will be reported later including the characterisation of other by-products that were obtained under certain conditions.The alcohol (13) is another intermediate that will be useful for the synthesis of castanospermine analogues.

Treatment of this alcohol (13) with DAST in dichloromethane gave the 8-deoxy-8-fluoro compound (14)[13] with retention of configuration as well as the rearranged material (15)[13] in a 1:1.7 ratio in 44% yield. The aziridinium ion (16) is presumably an intermediate in the formation of these two products. Participation by the nitrogen atom in this way is analogous to the behaviour observed when attempting displacements at *C*-6[1]. Hydrogenolysis of tribenzyl ether (14) (Pd/C, EtOH, $H_2$) then gave 8-deoxy-8-fluorocastanospermine (6)[13] in 73% yield. That the DAST product (14) was the result of displacement with retention was evident from the NMR data of (6). H-8 was a doublet of triplets ($J_{H,F}$= 51Hz, $J_{7,8}$=$J_{8,8a}$= 9Hz) implying that H-8 was still axial.

The 7-deoxy-7-*epi*-7-fluorocastanospermine (7) was prepared from 1,6,8-tri-*O*-acetylcastanospermine (17)[1] *via* formation of the triflate (18) ($Tf_2O$, py, $CH_2Cl_2$), and then displacement with fluoride ion ($Bu_4NF$, $CH_3CN$) affording the tri-acetate (19)[13] in 65% yield. The NMR data for (19) showed that $J_{6,7}$ and $J_{7,8}$ were very small (~ 1Hz) indicating that displacement with inversion had occurred. Deacetylation (NaOMe, MeOH) then gave the desired deoxyfluoro derivative (7)[13] in 80% yield.

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13. All compounds gave satisfactory $^1H$, $^{13}C$ NMR and accurate mass spectra.
For (4): $MH^+$ Calc. for $C_8H_{15}FNO_3$ requires 192.1036; obs. 192.1030. $^1H$ NMR ($D_2O$) δ 5.02 (1H, m, $J_{H,F}$ = 52.6 Hz, H-1), 3.43 - 3.34 (2H, m, H-6,8), 3.11 (1H, t, H-7), 3.01 - 2.88 (2H, m, H-3,5), 2.24 - 1.67 (5H, m, H-2, 2′, 3′, 5′, 8a).
For (5): $MH^+$ Calc. for $C_8H_{15}FNO_3$ requires 192.1036; obs. 192.1036. $^1H$ NMR ($D_2O$) δ 4.94 (1H, m, $J_{H,F}$ = 55.9 Hz, H-1), 3.50 - 3.41 (1H, m, H-6), 3.22 and 3.16 (1H each, t, H-7,8), 3.01 (1H, dd, H-5), 2.78 (1H, t, H-3), 2.51 (1H, dd, H-3′), 2.29 (1H, ddd, $J_{H,F}$ = 25 Hz, H-8a), 2.19 - 2.03 (2H, m, H-2, 5′), 1.94 - 1.76 (1H, m, $J_{H,F}$ = 31 Hz, H-2′).
For (6): $MH^+$ Calc. for $C_8H_{15}FNO_3$ requires 192.1036; obs. 192.1027. $^1H$ NMR ($D_2O$) δ 4.44 (1H, dt, $J_{H,F}$ = 51 Hz, H-8), 4.40 (1H, m, H-1), 3.65 - 3.53 (2H, m, H-6, 7), 3.16 - 3.03 (2H, m, H-3, 5), 2.38 - 2.21 (3H, m, H-2, 3′,8a), 2.06 (1H, t, H-5′), 1.73 - 1.63 (1H, m, H-2′).
For (7): $MH^+$ Calc. for $C_8H_{15}NO_5F$ requires 192.1036, obs. 192.1028. $^1H$ NMR ($D_2O$) δ 4.9 (1H, d, H-7) 4.35 (1H, m, H-1), 3.88, 3.78 (1H each, m, H-6, 8) 3.06 (1H, m, H-3) 2.98 (1H, dd, J=5.5, 10.6 Hz, H-5) 2.23 (4H, m, H-2, 3′, 5′, 8a) 1.67 (1H, m, H-2′).
For (8): $MH^+$ Calc. for $C_{18}H_{32}NO_6$ requires 358.2230; obs. 358.2246. M.P. 235-242°C. $^1H$ NMR ($CDCl_3$) δ 5.24 (1H, m, H-1), 4.87 (1H, dt, J=5.2, 9.7 Hz, H-6), 3.56 (1H, dt, J=2.8, 9.0 Hz, H-7), 3.45 (1H, d, J=2.5 Hz, OH), 3.38 (1H, dt, J=2.4, 9.0 Hz, H-8), 3.28 (1H, dd, J=5.2, 10.3 Hz, H-5), 3.18 (1H, dt, H-3), 2.80 (1H, d, J=2.9 Hz, OH), 2.36-2.26 (1H, m, H-2), 2.17 (1H, dd, H-3′), 2.09 (1H, dd, J=4.3, 9.1 Hz, H-8a), 1.99 (1H, t, H-5′), 1.93-1.85 (1H, m, H-2′), 1.24 and 1.22 (2 x 9H, $(CH_3)_3C$).
For (9): $MH^+$ Calc. for $C_{13}H_{24}NO_5$ requires 274.1654; obs. 274.1646. M.P.120-122°C. $^1H$ NMR ($CDCl_3$) δ 5.23 (1H, m, H-1), 3.70 (1H, m, H-6), 3.40 and 3.35 (1H each, t, J=8.7 Hz, H-7, 8), 3.25-3.14 (2H, m, H-3,5), 2.35 - 2.28 (1H, m), 2.16 (1H, dd), 2.06 (1H, m), 1.99 (1H,t), 1.88 - 1.77 (1H, m), 1.22 (9H, s, $(CH_3)_3C$).

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