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# The Chemistry of Castanospermine, Part V[1]: Synthetic Modifications at *C*-1 and *C*-7

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Abstract: New selective derivatisation of castanospermine has allowed the synthesis of analogues selectively modified at *C*-1 or *C*-7.

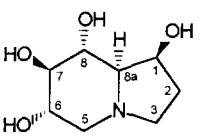

Castanospermine **1** is a polyhydroxy alkaloid which occurs in the seeds of the Australian legume *Castanospermum australe*[2] and the pods of *Alexa leiopetala*[3]. It is one of an array of polyhydroxy alkaloids from plant sources that have been found to be potent glycosidase inhibitors, and to have further wide ranging biological effects[4]. Castanospermine is a potent inhibitor of glucosidases[5] including lysosomal and glycoprotein processing enzymes[6]. The diverse and alluring array of biological activity that has been ascribed to castanospermine has indicated potential utility in the treatment of viral infections[7], cancer[8], malaria[9] and diabetes[10]. As a consequence, total syntheses of castanospermine and a number of stereoisomers and analogues have been the subjects of a variety of publications[11]. We have engaged in the synthesis of novel castanospermine analogues and derivatives looking for compounds with improved biological activity and selectivity[1,12-14]. We present here our results on the synthesis of castanospermine derivatives selectively modified at *C*-1 or *C*-7 along with selected biological results.

## RESULTS AND DISCUSSION

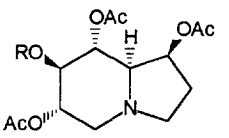
Synthesis of Derivatives Modified at *C*-7

We have previously shown that 1,6,8-tri-*O*-acetylcastanospermine **2** is available, albeit as the minor product, from selective deacetylation of tetra-*O*-acetylcastanospermine **3**[12]. This tri-acetate **2** has proved useful for the synthesis of a number of derivatives.

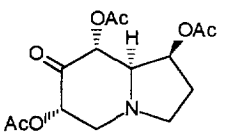
Swern oxidation of tri-acetate **2** successfully afforded the 7-keto derivative **4**. This was in contrast to our previous attempts to effect similar oxidations at *C*-6 or *C*-8 all of which gave either recovered starting material or no discrete products[1,12]. The ketone **4** was moderately stable and could be stored in the freezer for extended periods. When treated with *ca* 2 equivalent of methylmagnesium chloride in tetrahydrofuran, ketone **4** gave the 7-*epi*-7-*C*-methyl triacetate **5** in 43% yield, as well as a mixture of




**1**




**2 R = H**
**3 R = Ac**

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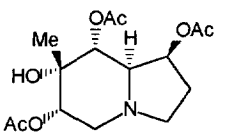


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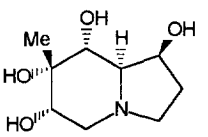
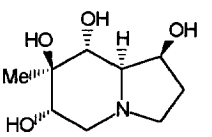



**6**

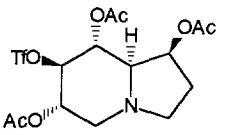



**7**

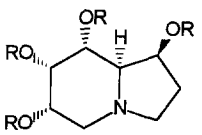
partially deacetylated products. Full deacetylation of this mixture (NaOMe/MeOH) afforded 7-*epi*-7-*C*-methylcastanospermine **6** (15%) (also available by deacetylation of **5**) as well as 7-*C*-methylcastanospermine **7** (26%). The 7-*epi* stereochemistry of the major products, which was confirmed by x-ray crystallography of **6** (Figure 1), results from attack by the Grignard reagent on the less hindered face of ketone **4**. The minor products, with castanospermine stereochemistry, are only formed in partially deacetylated form. Possibly, deacetylation occurs prior to Grignard addition and a complex between *O*-6 or *O*-8 and the reagent delivers the reagent from the lower, more hindered face.

The triflate ester **8** was readily available from alcohol **2** and when treated with dry triethylammonium acetate in acetonitrile it afforded the 7-*epi*-tetraacetate **9**. Deacetylation of this (NaOMe/MeOH) gave 7-*epi*-castanospermine **10**. Similarly, in the presence of tetrabutylammonium fluoride, the triflate **8** generated the 7-*epi*-7-fluoro compound **11**. Deacetylation afforded 7-deoxy-7-*epi*-7-fluorocastanospermine **12**. The stereochemistry at *C*-7 of compounds **9-12** was readily established by consideration of their $^1$H n.m.r. spectra. In compounds with 'castanospermine' stereochemistry H-7 is

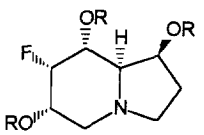
diaxial to both H-6 and H-8 and appears as a triplet (J ≅ 10 Hz). In 7-*epi*-castanospermine compounds H-7 is equatorial and appears as a broad singlet or narrow multiplet (J < 3 Hz). Base treatment (NaOMe, MeOH/THF) of the triflate **8** provided only the 6,7-anhydro compound **13**, which on acetylation gave diacetate **14**. The corresponding 7,8-anhydro derivative **15** was not observed.



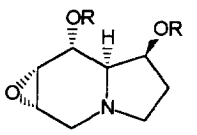

**8**



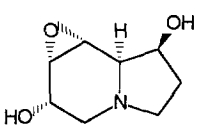

**9 R = Ac**
**10 R = H**



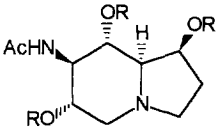

**11 R = Ac**
**12 R = H**



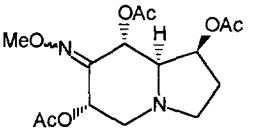

**13 R = H**
**14 R = Ac**



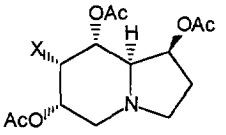

**15**



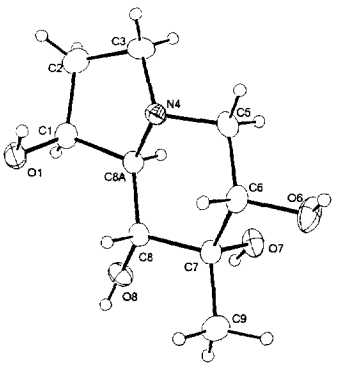

**16 R = H**
**18 R = Ac**




**17**




**19**

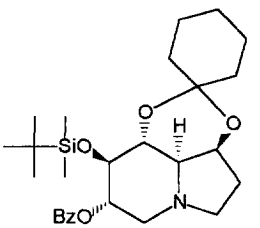



Ortep drawing of **6**

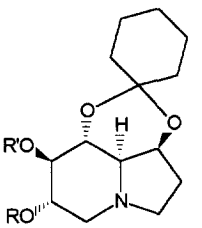
**FIGURE 1**

Castanospermine analogues with C-7 *epi* stereochemistry were thus readily available *via* triflate **8**, but a route to C-7 substituted compounds with castanospermine stereochemistry was required. 7-Acetamido-7-deoxycastanospermine **16** was prepared in low yield by reduction of the *O*-methyl oxime **17** of ketone **4**, acetylation to per-acetate **18**, and de-*O*-acetylation. A more general route to such compounds would be potentially offered by compound **19**, where X is a leaving group. Refluxing triflate **8** in acetone

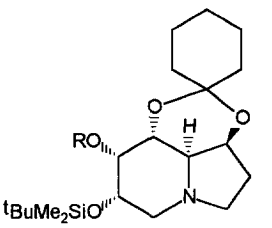
with sodium iodide readily gave **19** (X=I), but reaction of this compound with nucleophiles did not lead to discreet products. Attempts to prepare **19** (X=OMs) by reduction of ketone **4** followed by mesylation were confounded by removal and migration of the acetate groups during reduction. We have previously reported that debenzoylation of the 6-benzoate **20**, under basic conditions, afforded a 1:1 mixture of the 6- and 7-silyl ethers **21** and **22**[12]. These can be separated by chromatography and the unwanted isomer re-equilibrated in base so that multi-gram quantities of the 6-silyl ether **21** are available. This compound provided a route to the target **19** (*vide infra*).



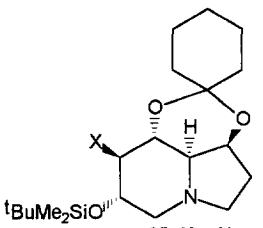

**20**



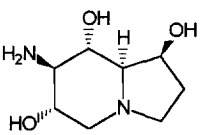

**21** R = $SiMe_2{}^tBu$, R' = H
**22** R = H, R' = $SiMe_2{}^tBu$



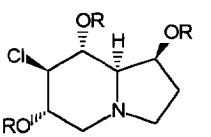

**23** R = H
**24** R = Ms




**25** X = $N_3$
**26** X = $NH_2$



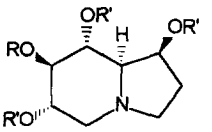

**27**

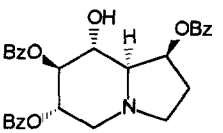



**28** R = Ac
**29** R = H

Oxidation/reduction of **21** gave the 7-*epi* compound **23** where the 7-OH was selectively available for substitution. Mesylation generated 7-mesylate **24** which suffered nucleophilic displacement with inversion by azide ion to give 7-azide **25**. Reduction ($H_2$, Pd/C) of the azide gave amine **26** and deprotection of this by acid hydrolysis followed by treatment with base resin afforded 7-amino-7-deoxycastanospermine **27**. Attempts to effect a displacement on mesylate **24** with chloride ion only led to rearrangement products. However when mesylate **24** was converted into the triacetate **19** (X=OMs), (by sequential desilylation, acid hydrolysis and acetylation), subsequent treatment with lithium chloride in DMF led to the 7-chloro-castanospermine derivative **28**. Deacetylation (NaOMe/MeOH) successfully afforded 7-chloro-7-deoxycastanospermine **29** without apparent formation of epoxides.

When castanospermine was treated with dibutyltin oxide (toluene, reflux, azeotropic removal of water) followed by 2,2,2-trichloroethylchloroformate (3 equiv.) only the 1,6,8-tricarbonate **30** was formed in high yield. This was readily apparent from the $^1H$ n.m.r. spectrum of **30** where H-1,6 and 8 were deshielded by acylation. In contrast, when benzoyl chloride was used in place of the chloroformate, the




**31**

**30** R = H, R' = $CO_2CH_2CCl_3$
**32** R = $COC(CH_3)_3$, R' = $CO_2CH_2CCl_3$
**33** R = $COC(CH_3)_3$, R' = H

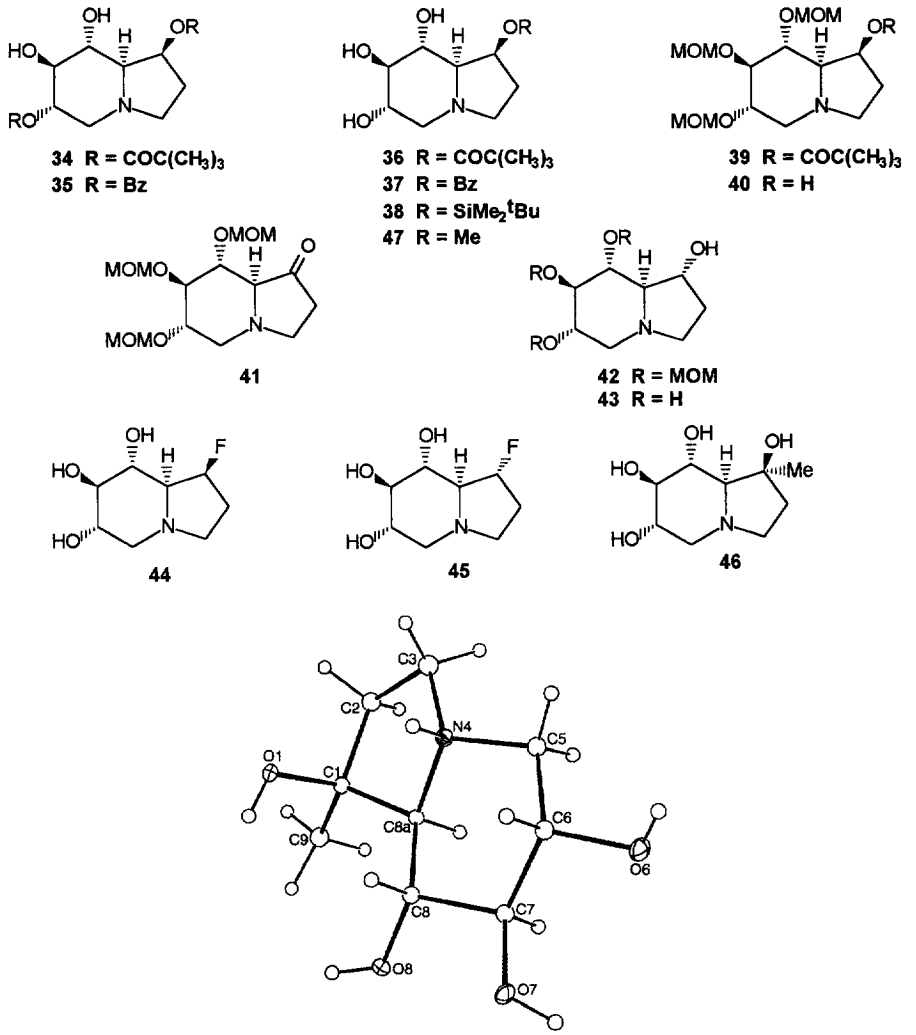
major product was the 1,6,7-tribenzoate **31**[1]. Pivaloylation of the tricarbonate **30** gave pivalate **32** which was deprotected (Zn/HOAc) to 7-*O*-pivaloylcastanospermine **33**.

Synthesis of Derivatives Modified at *C*-1

Initial attempts to prepare either 1-mono-*O*- or 6,7,8-tri-*O*-protected-castanospermine derivatives directly were unsuccessful. However the 1,6-di-*O*-acyl derivatives **34** and **35** were readily available under the same conditions used to prepare the 1,6,7-triester **31**[1], but using fewer equivalents of acyl halide. Basic solvolysis of these 1,6-diesters **34** or **35** caused an initial isomerisation to a mixture of 1,6-, 1,7-, and 1,8-diesters which then solvolyzed selectively affording the 1-*O*-monoesters **36** and **37**, respectively.

Subsequently we discovered that direct silylation of castanospermine [$(Bu_3Sn)_2O$, toluene, reflux, $Bu_4NBr$, $^tBuMe_2SiCl$] affords only 1-*O*-$^t$butyldimethylsilylcastanospermine **38**. This is a surprising result since analogous acylation reactions have given rise to 6-*O*-acyl derivatives selectively[12]. Others have recently reported organotin ether-assisted silylations of polyols which showed selectivities different to those obtained from the corresponding acylation or alkylation reactions[15]. The ready accessibility of **38** makes it a useful synthon for chemical derivatisation at *C*-1. We have utilized here the monopivalate **36** for such reactions as this selective silylation reaction was discovered later.

Monopivalate **36** was fully protected as the tri-*O*-(methoxymethyl) derivative **39** and then treatment with lithium aluminium hydride afforded 6,7,8-tri-*O*-(methoxymethyl)-castanospermine **40** in 85% overall yield. Attempted base catalyzed solvolysis (NaOMe, MeOH, reflux) of **39** failed to remove the pivalate ester. Swern oxidation of **40** gave the unstable ketone **41** which was immediately reduced ($LiAlH_4$, THF, -78°C) to give a 3:1 ratio of the 1-*epi*-compound **42** and starting material **40**. Acid hydrolysis of **42** followed by chromatography with an alkaline eluant afforded 1-*epi*-castanospermine **43** [1(R), 6(S), 7(R), 8(R), 8a(R)-tetrahydroxyoctahydroindolizidine]. The 1-*epi*-compound **42** on exposure to diethylaminosulfur trifluoride with subsequent acid hydrolysis and deionization with base resin gave 1-deoxy-1-fluorocastanospermine **44**. Similarly, the same treatment applied to alcohol **40** afforded 1-deoxy-1-*epi*-1-fluorocastanospermine **45**. The stereochemistry at *C*-1 of these deoxyfluoro compounds **44** and **45** is inferred from their method of synthesis as the $^1$H n.m.r. spectra do not provide unambiguous assignments.




Ortep drawing of **46**.HCl

**FIGURE 2**

Reaction of ketone **41** with methylmagnesium chloride followed by acid hydrolysis and chromatography with an alkaline eluant furnished a single adduct, 1-*C*-methylcastanospermine **46**. The stereochemistry of this branched derivative **46** was established by x-ray crystallography of its hydrochloride salt (Figure 2), The methyl ether **47** was readily prepared by methylation (NaH, THF, $Me_2SO_4$) of the

alcohol **40** and then acid hydrolysis. There was no significant methylation of the nitrogen under these conditions.

## BIOLOGICAL RESULTS

Several of the derivatives of castanospermine modified at *C*-1 or *C*-7 were tested for their inhibition of human liver glycosidases as described previously[5(iii)] (Table 1). Castanospermine **1**, the parent compound, is a potent inhibitor of all forms of α- and β-glucosidase in human liver. It has been shown previously that the *C*-1 hydroxy group of castanospermine is an important structural feature for this inhibition because 1-deoxycastanospermine is only a very weak inhibitor of the α- and β-glucosidases[5(iii)]. The importance of the stereochemistry at *C*-1 of castanospermine was confirmed by the inhibitory properties of the derivatives modified at *C*-1. Inversion of configuration to form 1-*epi*-castanospermine **43** abolished the inhibitory properties as did substitution of fluorine for the hydroxy group in 1-deoxy-1-fluorocastanospermine **44**. Interestingly, 1-deoxy-1-*epi*-1-fluorocastanospermine **45** retained weak

**Inhibition of Human Liver Glycosidases by Castanospermine Analogues Modified at *C*-1 and *C*-7**

| COMPOUND | | α-glucosidase % inhibition at 1mM | β-glucosidase % inhibition at 1mM |
|---|---|---|---|
| Castanospermine | **1** | 100 | 96 |
| 1-*epi*- | **43** | 0 | 0 |
| 1-deoxy-1-fluoro- | **44** | 0 | 0 |
| 1-deoxy-1-*epi*-1-fluoro- | **45** | 51 | 0 |
| 1-*C*-methyl- | **46** | 97 | 16 |
| 1-*O*-methyl- | **47** | 31 | 0 |
| 1-*O*-benzyl- | **37** | 1 | 39 |
| 1-*O*-pivaloyl- | **36** | 0 | 13 |
| 7-*epi*- | **10** | 92 | 27 |
| 7-*C*-methyl- | **7** | 38 | 0 |
| 7-*epi*-7-*C*-methyl- | **6** | 42 | 0 |
| 7-deoxy-7-*epi*-7-fluoro- | **12** | 50 | 0 |
| 7-*O*-pivaloyl- | **33** | 37 | 0 |

**TABLE 1**

inhibition of α-glucosidase. The addition of a methyl group to give 1-*C*-methylcastanospermine **46** had virtually no effect on the inhibition of α-glucosidase. Methylation (**47**), benzoylation (**37**) and pivaloylation (**36**) at *C*-1 abolished inhibition of both α- and β-glucosidase except for very weak inhibition of α-glucosidase and β-glucosidase by **47** and **37**, respectively.

The correct stereochemistry at *C*-7 is essential for inhibition of β-glucosidase but not so important for inhibition of α-glucosidase. In fact 7-*epi*-castanospermine **10**, which is inactive towards β-glucosidase, retains almost complete activity towards α-glucosidase. All the other derivatives modified at *C*-7, **6**, **7**, **12** and **33** were weak inhibitors of α-glucosidase but had no effect on β-glucosidase.

These results show that the structural criteria for inhibition of β-D-glucosidase are more rigorous than for α-D-glucosidase. An unsubstituted *C*-1 hydroxy group of the configuration found in castanospermine is necessary for the inhibition of both enzymes. Although the correct configuration of the *C*-7 hydroxy group is essential for inhibition of β-glucosidase, α-glucosidase was inhibited weakly by several analogues modified at *C*-7. The hexose corresponding to 7-*epi*-castanospermine **10** is D-altrose, which does not occur in mammalian cells. This may explain the lack of specificity at *C*-7 of castanospermine derivatives for inhibition of α-glucosidase.

## X-RAY CRYSTALLOGRAPHY

*Compound 6.* $C_9H_{17}NO_4$, orthorhombic, space group $P2_12_12_1(18)$[16], a=5.6276(2), b=12.115(6), c=14.9649(8) Å, V=1020.28(8) Å$^3$, z=4, $D_c$=1.323 g.cm$^{-3}$, T=291 K, Cu Kα radiation (λ=1.54056 Å), μ=8.30 cm$^{-1}$. Picker FACS-1 diffractometer, 914 independent reflections measured ($3^0<2\theta<120^0$), of which 874 had $I_{net}>2.5\sigma(I_{net})$. Absorption correction, by Gaussian method[17], minimum, maximum transmission 0.234, 0.584. Solved by direct methods and refined onto $F_0$; R, $R_w$ of 0.028, 0.039.[17] All hydrogens located and refined with isotropic thermal parameters. Secondary extinction was refined, coefficient 0.67(14).[17] Absolute configuration determined by complete sphere data collection[18]. Final maximum shift/error 0.001 and Δρ excursions -0.13 to 0.11 e/Å$^3$.

*Compound 46.HCl.* $C_9H_{18}NO_4Cl$, monoclinic, space group $P2_1$ (4)[16], a=8.028(2), b=9.679(3), c=8.025(3) Å, β=117.49(2)°, V=553.2(3)Å$^3$, Z=2, $D_c$ 1.439 g.cm$^{-3}$, T=140K, Mo Kα radiation (λ=0.71073Å), μ=3.41cm$^{-1}$. Nicolet R3m diffractometer, 1144 independent reflections measured ($4<2\theta\leq52^\circ$), of which 1002 "observed" reflections had $I_{net}>2\sigma(I_{net})$. No absorption correction. Solved by direct methods[19] and refined on $F_o^2$ using all data to give R(observed) 0.034, $wR_2$ (all data, on $F_o^2$) 0.070.[20] Absolute configuration not determined. All hydrogens located and refined with isotropic thermal

parameters; thermal parameters for hydrogens H3, H7, H8 and H8a constrained to 1.2 times their corresponding parent atom. Final maximum shift/error 0.001 and $\Delta\rho$ excursions -0.25 to 0.22 e/Å$^3$.

The independent molecules (Figures 1 and 2) are hydrogen bonded though somewhat differently in both crystals: in **6** hydroxyl protons on O7, O8 and O1 bind to adjacent molecule oxygen or nitrogen atoms (O1-H10...O8 1.95(4)Å, O8-H8O...O1 1.98(4)Å, O7-H7O...N4 2.15(4)Å) while in **46**.HCl the proton on N4 and hydroxyl protons on O6, O7 and O8 couple with adjacent molecule oxygens and the chloride ion (O7-H7...O1 1.99(6) Å, O6-H6...O7 2.06(5) Å, N4-H4N...Cl 2.28(4) Å, O8-H8O...Cl 2.33(6) Å). The five membered rings (C1-C3, N4, C8a) differ in their degree of twist from an envelope conformation, with C8a the "flap" atom (Q 0.415, 0.448 Å and $\phi$ 348°, 309° for **6**, **46**.HCl respectively[21] dihedral angles C8a-C1-C2-C3, C5-N4-C3-C2 -31.9, -16.1 and 141.4, 161.8° respectively). The fused six-membered rings have regular chair conformations with, for example, N4, C6, C7 and C8a rigorously planar and atoms C5, C8 -0.708(3), 0.650(3) Å from the plane in **6**; the $\sigma$, Q and q(z) values (0°, 0.63, 0.0 Å for ideal chair)[21] are 7.1, 4.0°; 0.62, 0.58; 0.08, 0.04 Å respectively for **46**.HCl, **6**. The different five membered ring conformations correspond to a bending away of the C1 and C2 atoms in **46**.HCl consistent with the close proximity of the (hydrogen bonded) chloride anion, and the additional hydrogen bonding at O1 in **6**, where both hydrogen atom and lone pair are involved. There are no abnormal bonding distances or angles[22]

## EXPERIMENTAL

N.m.r. spectra were recorded on a Bruker AC-300 instrument at 300 MHz or 75 MHz ($^{13}$C) in $CDCl_3$ solution unless specified. In solvents other than $D_2O$, internal TMS was used as a reference. High resolution accurate mass determinations were performed on a VG70-250S mass spectrometer under chemical ionization conditions using isobutane or ammonia as the ionizing gas. Melting points were determined on a Reichert hot stage microscope and are uncorrected. Elemental analyses were performed by the Otago University Microanalytical Laboratory, Dunedin. Aluminium backed silica gel sheets (Merck or Reidel de Haen) were used for thin layer chromatography. Column chromatography was performed on silica gel (230-400 mesh, Merck). Chromatography solvents were distilled prior to use. Castanospermine was obtained as described previously[12].

*(1S, 6S, 8R, 8aR)-1,6,8-triacetoxyoctahydroindolizidin-7-one* ***4***. A solution of oxalyl chloride in dichloromethane (1.2 ml, 2.0 M) was added to a stirred solution of DMSO (0.206 ml, 2.6 mmol) in dichloromethane (2 ml) at <-50°C. After 5 min 1,6,8-tri-*O*-acetylcastanospermine **2**[12] (0.7 g, 2.2mmol) in dichloromethane (5 ml) was added slowly so that the solution temperature did not rise above -60°C. After 10 min triethylamine (1.5 ml, 5 eq) was added and the reaction mixture was allowed to warm to room temperature. Extractive work-up (dichloromethane - water) and column chromatography [ethyl acetate -

hexanes (2:1)] gave the title compound **7** (0.52 g, 74%). M.p. 147.5-148.5 (ethyl acetate - hexanes). Accurate mass: calc. for $C_{14}H_{20}NO_7$ ($MH^+$) 314.1240; obs. 314.1242. $^1H$ n.m.r. ($C_6D_6$) 5.69 (d J=10.6 H-8) 5.40 (dd J=7.0, 11.0 H-6) 5.30 (m H-1) 2.96 (dd J=7.0, 10.1 H-5) 2.64 (m H-3) 2.14 (dd J=5.0, 10.5 H-8a) 1.99 (t J=10.6 H-5') 1.85 (3H s acetate) 1.74-1.84 (7H m H-2, acetate) 1.52-1.72 (2H m H-2', H-3'). $^{13}C$ n.m.r ($C_6D_6$) 197.3 C-7; 169.6, 169.6, 168.7 acetate; 73.0 C-6, C-8; 71.9 C-1; 69.9 C-8a; 53.6 C-5; 51.4 C-3; 32.1 C-2; 20.5, 20.1 acetate.

*1,6,8-Tri-O-acetyl-7-*epi*-7-C-methyl-castanospermine* **5**, *7-*epi*-7-C-methyl-castanospermine* **6** *and 7-C-methyl-castanospermine* **7**. Ethereal methylmagnesium chloride (2.0 M, 9 ml) was added to a cooled (ice bath), stirred solution of ketone **4** (3 g, 9.6 mmol) in tetrahydrofuran (100 ml). An exothermic reaction occurred, causing the temperature of the reaction to rise to approximately 20°C. Celite and then water were added to the reaction mixture and the whole filtered through a plug of Celite which was washed with methanol and dichloromethane. The solvents were removed under reduced pressure and chromatography of the residue [ethyl acetate - hexanes (2:1)] gave title triacetate **5** (1.35 g, 43%). Accurate mass: calc. for $C_{15}H_{24}NO_7$ ($MH^+$) 330.1552; obs. 330.1572. $^1H$ n.m.r. δ 5.35 (m H-1) 5.07 (t J=9.9 H-8) 4.94 (dd J=5.0, 10.4 H-6) 3.22 (m H-3) 3.12 (dd J=5.0, 9.9 H-5) 2.67 (dd J=4.4, 9.9 H-8a) 2.42 (t J=10.2 H-5') 2.24-2.37 (2H m H-2, H-3') 2.13, 2.10, 2.04 (3H each, s, acetate) 1.82 (m H-2') 1.17 (3H s $CH_3$). $^{13}C$ n.m.r. δ 170.9, 169.9, 169.8 acetate; 73.3 C-6; 72.5 C-7; 71.5, 71.5 C-1, C-8; 64.5 C-8a; 51.9 C-3; 50.0 C-5; 31.3 C-2; 22.5 $CH_3$; 21.2, 20.9, 20.8 acetate. Further elution with dichloromethane-methanol-ammonium hydroxide (25%) (10:4:1) gave a fraction containing a mixture of partially deacetylated Grignard adducts. This material was taken up in methanolic sodium methoxide and stirred at room temperature for 1 hr. The solvent was removed under reduced pressure and chromatography [dichloromethane-methanol-ammonium hydroxide (25%) (5:4:1)] gave first 7-*epi*-7-*C*-methyl-castanospermine **6** (0.30 g, 15%) (see below) and then 7-*C*-methyl-castanospermine 7 (0.50 g, 26%). M.p. 204-208°C (MeOH). Accurate mass; calc. for $C_9H_{18}NO_4$ ($MH^+$) 204.1235; obs. 204.1245. $^1H$ n.m.r. ($D_2O$) 4.18 (m H-1) 3.48 (2H m H-6, H-8) 2.98 (2H m H-3, H-5) 2.06 - 2.39 (4H m H-2, H-3', H-5', H-8a) 1.61 (m H-2') 0.93 (3H s $CH_3$). $^{13}C$ n.m.r. ($D_2O$) 79.6 C-7; 74.8 C-6; 73.6 C-8; 72.0 C-8a; 71.8 C-1; 55.6, 54.1 C-3, C-5; 34.9 C-2; 14.7 $CH_3$.

*7-Epi-7-C-methyl-castanospermine* **6**. A solution of 1,6,8- tri-*O*-acetyl-7-*epi*-7-*C*-methylcastanospermine **5** (1.35 g, 4.1 mmol) in methanol (30 ml) was basified with sodium methoxide (1%) in methanol, and stirred at room temperature overnight. The solution was then passed through a short column of cation exchange resin (Dowex X-8, $NH_4^+$ form) and the column eluted with more methanol. Evaporation of the solvent and recrystallisation from methanol gave the title compound. Further material could be recovered by silica gel chromatography of the mother liquors [dichloromethane-methanol-ammonium hydroxide (25%) (5:4:1)] to give a total yield of 0.57 g (62%) of **6**. M.p. 222 - 224°C. Accurate mass: calc. for $C_9H_{18}NO_4$ ($MH^+$) 204.1235; obs. 204.1238. $^1H$ n.m.r.

($D_2O$) 4.36 (m H-1) 3.51 (2H m H-6, H-8) 3.05 (m H-3) 2.93 (dd J=5.8, 10.5 H-5) 1.99 - 2.30 (4H m H-2, H-3', H-5', H-8a) 1.65 (m H-2') 1.32 (3H s $CH_3$). $^{13}C$ n.m.r. ($D_2O$) 76.4 C-7; 74.0, 73.0 C-6, C-8; 72.6 C-1; 70.0 C-8a; 55.3 C-5; 54.5 C-3; 34.9 C-2; 23.7 $CH_3$.

*1,6,7,8-Tetra-O-acetyl-7-epi-castanospermine* **9**. A solution of 1,6,8-tri-*O*-acetylcastanospermine[12] **2** (0.6 g, 1.9 mmol) and pyridine (1.0 ml, 6.5 eq) in dichloromethane (10 ml) was cooled to -50°C and then treated with triflic anhydride (0.64 ml, 3.8 mmol, 2eq). After 30 min stirring at -30 to -50°C the reaction mixture was warmed to 0°C, quenched with water and then extracted with aqueous HCl (1M), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), filtered through a plug of silica gel and evaporated to dryness. Triethylammonium acetate tetrahydrate (0.8 g, 3.1 mmol, 1.6 eq) was dried by dissolving it in acetonitrile and evaporating the solution to dryness and then it and the crude triflate were stirred together in acetonitrile for 1h. The reaction mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. Chromatography (hexanes:ethyl acetate 1:1) gave the title compound **9** (0.41 g, 1.1 mmol, 62%) as an oil. Accurate mass: calc. for $C_{16}H_{24}NO_8$ ($MH^+$) 358.1502; obs. 358.1510. 1H n.m.r. ($C_6D_6$) δ 5.93 (m H-7) 5.44 (m H-1) 5.37 (dd J=2.8, 10.2 H-8) 5.08 (ddd J=2.8, 5.0, 10.6 H-6) 2.93 (dd J=5.1, 9.9 H-5) 2.71 (m H-3) 2.46 (dd J=4.8, 10.2 H-8a) 2.27 (t J=10.2 H-5') 1.63-1.81 (11H m H-2, H-3', acetate) 1.59 (4H m H-2', acetate). $^{13}C$ n.m.r. δ 170.6, 170.2, 169.7, 169.6 acetate; 71.4, 68.6, 68.2, 67.0, 63.5 C-1, C-6, C-7, C-8, C-8a; 53.0, 49.6 C-3, C-5; 31.2 C-2; 21.1, 20.9, 20.9, 20.7 acetate.

*7-Epi-castanospermine* ***10***. A solution of tetraacetate **9** (0.1 g, 0.28 mmol) in methanol was basified (pH 12) with sodium methoxide, stirred at room temperature overnight, and passed through a column of cation exchange resin (Dowex X-8) in the ammonium salt form. The solvents were removed under reduced pressure and chromatography of the residue [dichloromethane-methanol-ammonia (25%, aq.) 5:4:1] gave the title compound **10** (0.037 g, 0.20 mmol, 71%) which was further purified by crystallisation from aqueous acetone. M.p. 200-205°C (dec). Accurate mass: calc. for $C_8H_{16}NO_4$ ($MH^+$) 190.1082; obs. 190.1079. $^1H$ n.m.r. ($D_2O$) δ 4.37 (m H-1) 4.06 (t J=2.84 H-7) 3.78 (2H m H-6, H-8) 3.06 (m H-3) 2.91 (dd J=5.0, 10.5 H-5) 2.20 (4H m H-2, H-3', H-5', H-8a) 1.69 (m H-2'). $^{13}C$ n.m.r. ($D_2O$) 74.0 C-1; 72.0 C-7; 70.4, 69.4 C-6, C-8; 68.3 C-8a; 57.1 C-3; 54.1 C-5; 34.9 C-2.

*1,6,8-Tri-O-acetyl-7-deoxy-7-epi-7-fluorocastanospermine* ***11***. This was prepared from 1,6,8-tri-*O*-acetylcastanospermine **2** (2.0 g, 6.3 mmol) by the method described above for 1,6,7,8-tetra-*O*-acetyl-7-*epi*-castanospermine **9** but using 4 equivalents of tetraethylammonium fluoride as the nucleophile, affording **11** (1.3 g, 4.1 mmol, 65%). M.p. 111-112°C (EtOAc - hexanes). Accurate mass: calc. for $C_{14}H_{21}FNO_6$ ($MH^+$) 318.1353; obs. 318.1338. $^1H$ n.m.r. δ 5.38 (m H-1) 5.12-4.89 (3H m H-6, H-7, H-8) 3.23 (m H-3) 3.15 (dd J=5.2, 9.9 H-5) 2.63 (dd J=4.5, 10.1 H-8a) 2.44 (t J=10.1 H-5' ) 2.24-2.38 (2H m H-2, H-3' ) 2.11, 2.08, 2.03 (3H each s acetate)

1.83-1.90 (m H-2'). $^{13}$C n.m.r. δ 170.5, 169.9 acetate; 88.1 (d J=184.0 C-7) 71.4, 63.1 C-1, C-8a; 69.2 (d J=16.7), 67.6 (d J=15.9) C-6, C-8; 51.8 C-3; 48.8 C-5; 31.3 C-2.

*7-Deoxy-7-epi-7-fluorocastanospermine* **12**. The triacetate **11** (1.25 g, 3.9 mmol) was deacetylated as described for compound **9**. Column chromatography [dichloromethane-methanol (4:1)] gave the title compound **12** (0.60 g, 3.2 mmol, 81%). M.p. 188-193°C (EtOAc - MeOH). Accurate mass calc. for $C_8H_{15}FNO_3$ ($MH^+$) 192.1036; obs. 192.1028. $^1$H n.m.r. ($D_2O$) 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, 10.6Hz, H-5), 2.23(4H, m, H-2,3',5',8a), 1.67(1H, m, H-2'). $^{13}$C n.m.r. δ 95.6(d, J=177 Hz, C-7), 71.5 (C-1), 69.4(d, J=18 Hz, C-6 or C-8), 68.6 (C-8a), 68.4(d, J=17 Hz, C-6 or C-8), 53.8 (C-3), 53.6 (C-5), 34.8 (C-2).

*6,7-Anhydro-7-epi-castanospermine* **13** *and 1,8-di-O-acetyl-6,7-anhydro-7-epi-castanospermine* **14**. 1,6,8-Tri-*O*-acetylcastanospermine (5.0 g, 15.9 mmol) was converted to the 7-triflate as described in the synthesis of compound **9**. The crude triflate was dissolved in tetrahydrofuran (10 ml), diluted with methanol (50 ml) and basified with sodium methoxide. After stirring at room temperature overnight, the solvents were removed under reduced pressure and the residue chromatographed [dichloromethane-methanol-ammonium hydroxide (25%) (20:4:1)] to give the title compound **13**. M.p. 157-161°C (EtOAc - MeOH). Accurate mass: calc. for $C_8H_{14}NO_3$ ($MH^+$) 172.0974; obs. 174.0970. $^1$H n.m.r. ($D_2O$) δ 4.33 (m H-1) 4.18 (dd J=9.5, 1.7 H-8) 3.53 (2H m H-6, H-7) 3.27 (dd J=4.9, 13.7 H-5) 2.99 (m H-3) 2.42 (d J-13.6 H-5') 2.00 - 2.27 (3H m H-2, H-3', H-8a) 1.55 (m H-2'). $^{13}$C n.m.r. ($D_2O$) δ 72.2, 68.4, 67.7 C-1, C-8, C-8a; 59.3, 57.5 C-6, C-7; 54.5, 52.6 C-3, C-5; 34.7 C-2. A sample was acetylated in pyridine - acetic anhydride to give **14**. Accurate mass: calc. for $C_{12}H_{18}NO_5$ ($MH^+$) 256.1185; obs. 256.1174. $^1$H n.m.r. ($C_6D_6$) 5.55 (dd J=1.9, 9.5 H-8) 5.43 (m H-1) 3.31 (bs H-6) 2.79 (2H m H-5, H-7) 2.69 (m H-3) 2.49 (dd J=5.2, 9.4 H-8a) 2.16 (d J=12.8 H-5' ) 1.79, 1.77 (3H each s acetate) 1.72 (m H-2) 1.50 (2H m H-3', H-2'). $^{13}$C n.m.r. ($CDCl_3$) 170.4, 170.4 acetate; 71.9, 68.6, 61.7 C-1, C-8, C-8a; 53.6, 53.4 C-6, C-7; 52.7, 50.5 C-3, C-5; 30.8 C-2; 21.1, 21.0 acetate.

*(1S,6S,8R,8aR)-1,6,8-Triacetoxyoctahydroindolizidin-7-one O-methyl oxime* **17**. A solution of ketone **4** (2.0 g, 6.3 mmol) and methoxyamine hydrochloride (0.80 g, 9.6 mmol, 1.5 eq) in pyridine (30 ml) was heated to 60°C for 2 h. Extractive work up (dichloromethane - aqueous sodium hydrogen carbonate) followed by column chromatography (ethyl acetate - hexanes 2:1) gave the title compound **17** (1.9 g, 5.6 mmol, 88%) as a mixture of isomers in 1:1 ratio. Two crystallisations from hexanes - ethyl acetate gave a pure sample of one of the isomers. M.p. 124 - 129°C. Accurate mass; calc. for $C_{15}H_{23}N_2O_7$ ($MH^+$) 343.1505; obs.343.1509. $^1$H n.m.r. δ 6.11 (d J=7.6 H-8) 5.56 (dd J=4.3, 6.7 H-6) 5.35 (m H-1) 3.89 (3H s $OCH_3$) 3.60 (dd J=6.8, 12.0) 3.20 (m H-3) 2.84 (dd J=5.0, 7.5 H-8a) 2.58 (dd J=4.4, 11.9 H-5') 2.37 (2H m H-2, H-3') 2.12, 2.10, 2.03 (3H each, s, acetate)

1.87 (m H-2'). $^{13}$C n.m.r. δ 170.5, 169.6, 169.3 acetate; 149.3 C-7; 72.5 C-1; 69.1 C-6; 66.7 C-8a; 62.8 $OCH_3$ 62.3 C-8; 55.6 C-5; 52.0 C-3; 31.6 C-2; 21.2, 20.9, 20.7 acetate.

*7-Acetamido-1,6,8-tri-O-acetyl-7-deoxycastanospermine 18.* A stirred solution of oxime **17** (9.3 g, 27.2 mmol) in tetrahydrofuran (200 ml) was cooled in an ice - water bath and then lithium aluminium hydride (2.5 g, 66 mmol) was added in portions so that the temperature of the reaction mixture did not exceed 40°C. After stirring at room temperature for 4 hr the suspension was heated to reflux and held there for 36 h and then cooled, quenched with the minimum quantity of water and concentrated to dryness under reduced pressure. The residue was taken up in pyridine (100 ml) and acetic anhydride (100 ml), stirred at room temperature for 24 h and concentrated under reduced pressure. Filter aid was added to the residue and the whole was suspended in ethyl acetate and filtered through a pad of filter aid which was washed exhaustively with more ethyl acetate. The solvent was removed under reduced pressure and chromatography of the residue [ethyl acetate - hexanes (2:1), ethyl acetate] gave the title compound **18** (1.1 g, 3.1 mmol, 11%). M.p. 193- 194°C (EtOAc - hexanes). Accurate mass: calc. for $C_{16}H_{25}N_2O_7$ ($MH^+$) 357.1662; obs. 357.1659. $^1$H n.m.r. δ 6.87 (d J=9.5 -NH) 5.32 (m H-1) 5.01 (t J=9.9 H-8) 4.90 (td J=5.1, 10.3 H-6) 4.09 (q J=10.1 H-7) 3.27 (dd J=5.1, 10.3 H-5) 3.11 (m H-3) 2.32 (2H m H-2, H-8a) 2.19 (q H-3') 2.04 (m H-5') 1.95, 1.91, 1.89, 1.82 (3H each, s acetate) 1.70 (m H-2'). $^{13}$C n.m.r. δ 170.8, 170.6, 170.4, 170.1 acetate; 71.2, 70.1, 68.6, 68.7 C-1, C-6, C-8, C-8a; 55.6 C-7; 53.7, 52.0 C-3, C-5; 31.3 C-2; 23.1 N-acetate; 20.8, 20.7, 20.6 acetate.

*7-Acetamido-7-deoxycastanospermine 16.* A solution of tetra-acetate **18** (1.1 g, 3.1 mmol) in methanol (10 ml) was basified with sodium methoxide and stirred at room temperature overnight. Removal of the solvent under reduced pressure and chromatography of the residue [dichloromethane - methanol - ammonium hydroxide (25%) (5:4:1)] gave the title compound **16** (0.30 g, 1.3 mmol, 55%). M.p. 200°C (dec.) (EtOAc - MeOH). Accurate mass: calc. for $C_{10}H_{19}N_2O_4$ ($MH^+$) 231.1345; obs. 231.1341. $^1$H n.m.r. ($D_2O$) δ 4.51 (m H-1) 3.74 (3H m H-6, H-7, H-8) 3.43 (2H m H-3, H-5) 2.34-2.68 (4H m H-2, H-3', H-5', H-8a) 2.06 (3H s acetate) 1.83 (m H-2'). $^{13}$C n.m.r. ($D_2O$) δ 177.9 acetate, 74.4, 71.3, 70.3, 69.0 C-1, C-6, C-8, C-8a; 62.0 C-7; 57.6, 54.4 C-3, C-5; 34.6 C-2; 24.9 acetate. A portion of amide **16** was deacetylated (aqueous NaOH (1M), overnight) to give a compound identical (t.l.c. and $^1$H n.m.r.) with amine **27**.

*1,6,8-Tri-O-acetyl-7-epi-7-O-mesylcastanospermine 19.* Tetrabutylammonium fluoride (1M in THF, 6 ml, 1 eq) was added to a solution of mesylate **24** (2.7 g, 5.9 mmol) in THF (20 ml). After stirring for 10 min the solution was partitioned between dichloromethane and water. The organic phase was concentrated to dryness and the residue was taken up in trifluoroacetic acid (8 ml) and water (2 ml) and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue stirred with acetic anhydride (25 ml) and pyridine (25 ml) for 24 h. Extractive work - up (dichloromethane - 10% aq. $K_2CO_3$) and column

chromatography [ethyl acetate-hexanes (1:1, 2:1)] gave the title compound **19** (1.4 g, 3.6 mmol, 60%). Accurate mass: calc. for $C_{15}H_{24}NO_9S$ ($MH^+$) 394.1172; obs. 394.1161. $^1H$ n.m.r. δ 5.36 (m H-1) 5.19 (m H-7) 5.08 (2H m H-6, H-8) 3.23 (m H-3) 3.15 (dd J=5.1, 10.3 H-5) 3.09 (3H s $CH_3$) 2.64 (dd J=4.6, 10.2 H-8a) 2.45 (t J=10.5 H-5') 2.34 (2H m H-2, H-3') 2.10, 2.07, 2.03 (3H each s acetate) 1.84 (m H-2'). $^{13}C$ n.m.r. δ 170.4, 169.7, 169.4 acetate; 77.4, 71.3, 67.9, 66.5, 63.0 C-1, C-6, C-7, C-8, C-8a; 51.7, 49.0 C-3, C-5; 38.7 $CH_3$; 31.1 C-2; 21.0, 20.8, 20.7 acetate.

*6-O-$^t$Butyldimethylsilyl-1,8-O-cyclohexylidenecastanospermine* ***21.*** The title compound was synthesised as a 1:1 mixture with 7-*O*-t-butyldimethylsilyl-1,8-*O*-cyclohexylidenecastanospermine **22** by debenzoylation of 6-*O*-benzoyl-7-*O*-t-butyldimethylsilyl-1,8-*O*-cyclohexylidenecastanospermine **20**, as described previously[12]. Additional quantities of the required 6-*O*-silyl compound could be formed by base catalysed isomerisation of the 7-*O*-silyl compound. Thus a methanolic solution of 7-*O*-$^t$butyldimethylsilyl-1,8-*O*-cyclohexylidenecastanospermine **22** was made basic with sodium methoxide and stirred at room temperature overnight. The solvent was removed under reduced pressure and the resulting 1:1 mixture of 6-*O*-silyl and 7-*O*-silyl compounds was separated by column chromatography. A total yield of 60% of the title compound **21** could be obtained after three recycles.

*6-O-$^t$Butyldimethylsilyl-1,8-O-cyclohexylidene-7-epi-castanospermine* ***23.*** A stirred solution of dimethyl sulfoxide (1.3 ml, 18.3 mmol, 2 eq) in dichloromethane (30 ml) was held under argon below -50°C whilst oxalyl chloride (1.5 ml, 17.3 mmol, 1.9 eq) was added. After 20 min a solution of alcohol **21** (3.2 g, 9.1 mmol) in dichloromethane (30 ml) was added and then triethylamine (6 ml, excess) after a further 20 min. The solution was allowed to warm slowly to 0°C, ethanol (150 ml) was then added and the solution recooled to -30°C. Sodium borohydride (1.5 g, excess) was added and the mixture allowed to come to room temperature over several hours. Most of the solvent was removed under reduced pressure and the residue was subjected to extractive work - up (dichloromethane - aqueous sodium hydrogen carbonate). Column chromatography (ethyl acetate-hexanes 1:1 and 2:1) then gave the title compound **23** (2.7 g, 7.0 mmol, 84%) and starting alcohol **21** (0.42 g, 1.1 mmol, 13%). For **23**, accurate mass: calc. for $C_{20}H_{38}NO_4Si$ ($MH^+$) 384.2570; obs. 384.2556. $^1H$ n.m.r. δ 4.40 (m H-1) 3.99 (s H-7) 3.84 (ddd J=2.7, 5.6, 10.5 H-6) 3.63 (dd J=2.0, 10.6 H-8) 3.39 (dd J=6.9, 10.6 H-8a) 2.90 (2H m H-3, H-5) 2.70 (2H m H-3', H-5') 2.28 (s -OH) 2.10 (m H-2) 1.78 (m H-2') 1.29-1.56 (10H m cyclohexylidene) 0.80 (9H s TBDMS) 0.00, -0.01 (3H each s TBDMS). $^{13}C$ n.m.r. δ 101.1 cyclohex. quat. 80.0 C-7; 70.7 C-1; 66.3 C-6; 63.6 C-8; 56.4 C-8a; 48.7, 48.7 C-3, C-5; 32.8 C-2; 37.5, 34.3, 25.2, 23.2, 22.9 cyclohex.; 25.6, 18.0, -4.76, -4.90 TBDMS.

*6-O-$^t$Butyldimethylsilyl-1,8-O-cyclohexylidene-7-epi-7-O-mesylcastanospermine* ***24.*** A solution of 7-*epi*-alcohol **23** (2.12 g, 5.5 mmol) and mesyl chloride (0.64 ml, 1.5 eq) in pyridine (20 ml) was stirred at room temperature

overnight. Extractive work - up and column chromatography of the residue [hexanes-ethyl acetate (1:1)] gave the title compound **24** (2.0 g, 4.3 mmol, 79%). Accurate mass: calc. for $C_{21}H_{40}NO_6SiS$ ($MH^+$) 462.2345; obs. 462.2347. $^1H$ n.m.r. δ 4.94 (s H-7) 4.43 (m H-1) 3.91 (ddd J=2.6, 5.4, 10.6 H-6) 3.71 (d J=10.6 H-8) 3.29 (dd J=6.9, 10.6 H-8a) 5.31 (3H s Me) 2.71-2.94 (4H m H-3, H-3', H-5, H-5') 2.14 (m H-2) 1.80 (m H-2') 1.33-1.53 (10H m cyclohexylidene) 0.81 (9H s TBDMS) 0.03, 0.00 (3H each s TBDMS). $^{13}C$ n.m.r. δ 101.3 cyclohex. quat. 82.2 C-7; 70.8 C-1; 63.9 61.9 C-6, C-8; 57.5 C-8a; 49.3, 48.6 C-3, C-5; 39.2 Me; 32.6 C-2; 37.5, 34.5, 25.0, 23.0, 22.8 cyclohex.; 25.6, 18.1, -4.96, -5.08 TBDMS.

*7-Azido-6-O-$^t$butyldimethylsilyl-1,8-O-cyclohexylidene-7-deoxycastanospermine* ***25.*** A solution of the 7-mesylate **24** (0.50 g, 1.1 mmol) and sodium azide (0.30 g, 4.2 eq) in DMSO (8 ml) was heated at 80°C overnight. Extractive work - up and column chromatography of the residue [hexanes-ethyl acetate (2:1)] gave the title compound **25** (0.28 g, 0.69 mmol, 62%) as a white solid. Accurate mass: calc. for $C_{20}H_{37}N_4O_3Si$ ($MH^+$) 409.2635; obs. 409.2641. $^1H$ n.m.r. δ 4.41 (m H-1) 3.59 (ddd J=5.3, 8.8, 10.2 H-6) 3.53 (t J=10.4 H-8) 3.20 (dd J=8.8, 10.6 H-7) 3.00 (dd J=5.3, 13.9 H-5) 2.85 (2H m H-3, H-8a) 2.65 (2H m H-3', H-5') 2.12 (m H-2) 1.82 (m H-2') 1.23-1.62 (10H m cyclohexylidene) 0.81 (9H s TBDMS) -0.09, -0.14 (3H each s TBDMS). $^{13}C$ n.m.r. δ 101.5 cyclohex. quat.; 70.7 C-1; 69.3 C-7; 68.8 C-6; 64.9 C-8; 64.0 C-8a; 54.0 C-5; 49.1 C-3; 33.0 C-2; 36.8, 34.6, 25.3, 23.1, 23.0 cyclohex.; 25.7, 18.0, -4.7, -4.7 TBDMS.

*7-Amino-6-O-$^t$butyldimethylsilyl-1,8-O-cyclohexylidene-7-deoxycastanospermine* ***26.*** A solution of azide **25** (0.27 g, 0.66 mmol) in ethanol (30 ml) was stirred with palladium - on - carbon (10% Pd, 50 mg) under hydrogen (1 atm) overnight. The solids and solvent were removed and column chromatography of the residue [hexanes - ethyl acetate (2:1)] gave the title compound **26** (0.20 g, 0.52 mmol, 79%). Accurate mass: calc. for $C_{20}H_{39}N_2O_3Si$ ($MH^+$) 383.2730; obs. 383.2747. $^1H$ n.m.r. δ 4.39 (m H-1) 3.57 (ddd J=5.1, 8.6, 10.4 H-6) 3.46 (t J=10.3 H-8) 2.84-2.98 (3H m H-3, H-5, H-8a) 2.84-2.98 (3H m H-3', H-5', H-7) 2.11 (m H-2) 1.60-2.04 (3H m H-2', $NH_2$) 1.24-1.55 (10H m cyclohexylidene) 0.81 (9H s TBDMS) 0.04, 0.00 (3H each s TBDMS). $^{13}C$ n.m.r. δ 100.7 cyclohex. quat.; 70.7 C-1; 70.7 C-6; 65.5 C-8; 63.2 C-8a; 59.2 C-7; 53.2, 49.1 C-3, C-5; 32.9 C-2; 37.0, 34.7, 25.3, 23.1, 23.0 cyclohex.; 25.6, 18.0, -4.3, -4.6 TBDMS.

*7-Amino-7-deoxycastanospermine* ***27.*** A solution of protected amine **26** (0.47 g, 1.2 mmol) in trifluoroacetic acid (4 ml) and water (1 ml) was stirred at room temperature for a week. The solvents were removed under reduced pressure and the residue was taken up in water, passed through a column of anion exchange resin Amberlyst A-26 ($OH^-$ form), concentrated again and chromatographed on silica gel [dichloromethane-methanol-ammonium hydroxide (25%) (5:4:1)] to give the title compound **27**. M.p. 215-220 °C (dec) (MeOH). Accurate mass: calc. for $C_8H_{17}N_2O_3$ ($MH^+$) 189.1239; obs. 189.1240. $^1H$ n.m.r. ($D_2O$) δ 4.53 (m H-1) 3.65 (2H m H-6, H-8) 3.30 (dd

J=4.9, 10.7 H-5) 3.20 (m H-3) 2.76 (t J=9.6 H-7) 2.28-2.48 (2H m H-2, H-3') 2.02-2.20 (2H m H-5', H-8a) 1.80 (m H-2'). $^{13}$C n.m.r. ($D_2O$) δ 74.3, 72.5, 72.2, 71.3 C-1, C-6, C-8, C-8a; 63.4 C-7; 58.8, 54.3 C-3, C-5; 35.2 C-2.

*1,6,8-Tri-O-acetyl-7-chloro-7-deoxycastanospermine* ***28***. A solution of mesylate **19** (0.8 g, 2.0 mmol) and lithium chloride (0.8 g, excess) in DMF (10 ml) was heated at 115°C for 3 days. Extractive work - up (dichloromethane - 10% aq. $K_2CO_3$) and column chromatography [ethyl acetate-hexanes (1:1)] gave the title chloride **28** (0.42 g, 1.26 mmol, 62%) as a pale yellow solid. Accurate mass: calc. for $C_{14}H_{21}NO_6{}^{35}Cl$ ($MH^+$) 334.1057; obs. 334.1044. $^1$H n.m.r. δ 5.37 (m H-1) 5.31 (t J=989 H-8) 5.12 (td J=5.2, 10.1 H-6) 3.78 (t J=10.1 H-7) 3.43 (dd J=5.2, 10.6 H-5) 3.23 (m H-3) 2.19-2.39 (3H m H-2, H-3', H-8a) 2.11, 2.07, 2.06 (3H each, s acetate) 2.03 (m H-5') 1.85 (m H-2'). $^{13}$C n.m.r. δ 170.7, 169.7, 169.2 acetate; 72.1 C-6; 71.0 C-1; 69.7 C-8; 69.5 C-8a; 63.4 C-7; 54.2 C-5; 51.9 C-3; 31.6 C-2; 20.8, 20.7, 20.7 acetate.

*7-Chloro-7-deoxy-castanospermine* ***29***. A solution of triacetate **28** (0.39 g, 1.2 mmol) in methanol (10 ml) was basified with sodium methoxide and stirred overnight at room temperature. Evaporation of the solvent under reduced pressure and column chromatography [dichloromethane-methanol-ammonium hydroxide (25%) (5:4:1)] gave the title compound **29** (0.22 g, 1.1 mmol, 90%). M.p. 164-169°C (MeOH). Accurate mass: calc. for $C_8H_{15}NO_3{}^{35}Cl$ ($MH^+$) 208.0740; obs. 208.0737. $^1$H n.m.r. ($D_2O$) δ 4.17 (m H-1) 3.52 (2H m H-6, H-8) 3.41 (t J=9.4 H-7) 3.00 (dd J=5.0, 11.0 H-5) 2.85 (m H-3) 2.08 (m H-2) 1.98 (q J=8.9 H-3) 1.86 (t J=10.5 H-5') 1.80 (dd J=4.2, 9.3 H-8a) 1.47 (m H-2'). $^{13}$C n.m.r. ($D_2O$) δ 74.4 C-8a; 73.4 C-6; 72.9 C-7; 72.3 C-8; 72.1 C-1; 58.7 C-5; 53.9 C-3; 35.1 C-2.

*1,6,8-Tris-O-(2,2,2-trichloroethoxycarbonyl)-castanospermine* ***30***. A suspension of castanospermine (2.0 g) and dibutyltin oxide (5.3 g) in toluene (100 ml) was heated under reflux with azeotropic removal of water for 2 h. The clear solution was cooled to -10°C and 2,2,2-trichloroethylchloroformate (4.4 ml, 3 equiv.) was added slowly with stirring. The solution was allowed to warm to room temperature and stirred for 2 days, then the solvent was evaporated. A solution of the residue in acetonitrile was washed with petroleum ether (x2) and then concentrated to dryness affording a white solid. Recrystallisation from ethyl acetate/petroleum ether gave 7.13 g (94%) of title compound **30** m.p. 135-136°C. Accurate mass: calc. for $C_{17}H_{19}{}^{35}Cl_7{}^{37}Cl_2NO_{10}$; 715.8147, obs. 715.8152. $^1$H n.m.r. δ 5.30 (1H, m, H-1), 5.06 (1H, t, H-8), 4.91 (1H, dt, H-6), 4.85-4.63 (6H, m, $OCH_2CCl_3$), 3.81 (1H, dt, H-7), 3.45 (1H, dd, H-5), 3.28 (1H, m, H-3), 2.65 (1H, d, OH), 2.45-2.26 (3H, m, H-2, 3',8a), 2.21 (1H, t, H-5'), 2.08-1.99 (1H, m, H-2'). $^{13}$C n.m.r. δ 153.7, 153.6, 153.5, 94.4, 94.3, 94.3, 77.2, 77.2, 77.1, 77.0, 76.9, 75.3, 74.9, 67.9, 52.3, 51.5, 31.6.

*7-O-Pivaloylcastanospermine* ***33***. A solution of 1,6,8-tris-*O*-(2,2,2-trichloroethoxycarbonyl)-castanospermine **30** (1.2 g) in pyridine (10 ml) and pivaloyl chloride (1.5 ml) was heated at 75°C for 4 days. Toluene was added and the solution was washed with water (x3) and processed as usual.

Chromatography (EtOAc/petroleum ether 1:4) gave *7-O-pivaloyl-1,6,8-tris-O-(2,2,2-trichloroethoxycarbonyl)-castanospermine* **32** (1.18 g). $^1$H n.m.r. δ 5.30 (1H, m, H-1), 5.26, 5.17 (1H each, t, H-7,8), 5.03 (1H, dt, H-6), 4.84-4.61 (6H, m, $OCH_2CCl_3$) 3.46 (1H, dd, H-5), 3.30 (1H, t, H-3), 2.57-2.28 (4H, m, H-2, 3',5',8a), 2.13-1.99 (1H, m, H-2'). $^{13}$C n.m.r. δ 177.3, 153.4, 153.2, 152.9, 94.3, 94.0, 93.9, 77.0, 76.9, 76.8, 76.7, 74.7, 73.7, 73.0, 67.8, 52.2, 51.4, 38.9, 31.5, 26.9. This material (0.86 g) in acetic acid (20 ml) was stirred with zinc dust (3 g) at room temperature for 4 h, then the solids and solvent were removed and chromatography ($CHCl_3$/EtOAc/MeOH 5:2:1) of the residue gave title compound **33** (0.31 g). Accurate mass: calc. for $C_{13}H_{24}NO_5$ 274.1654, obs. 274.1641. $^1$H n.m.r. (DMSO) δ 4.40 (1H, t, H-7), 3.95 (1H, m, H-1), 3.38-3.23 (2H, m, H-6,8), 2.86-2.78 (2H, m, H-3,5), 1.97-1.36 (5H, H-2,2',3',5', 8a), 0.98 (9H, s, $(CH_3)_3C$). $^{13}$C n.m.r. δ 178.6, 81.9, 74.2, 70.5, 69.8, 68.3, 58.3, 53.2, 35.0, 28.6.

*1,6-Di-O-benzoylcastanospermine* ***35***. A suspension of castanospermine (1.5 g) and dibutyltin oxide (3.95 g, 2 equiv.) in toluene (40 ml) was heated under reflux with azeotropic removal of water for 2 h. The resulting solution was cooled to -10°C and benzoyl chloride (2.03 ml, 2.2 equiv.) was added dropwise, then the solution was allowed to warm to room temperature overnight. The solution was concentrated, the residue was partitioned between chloroform and 2M aqueous ammonium hydroxide and the organic phase was dried and evaporated to dryness. Chromatography of the residue afforded title compound **35** ( 75%). Recrystallised from ethanol it had m.p. 206-208°C. Anal. calc. for $C_{22}H_{23}NO_6$: C, 66.47; H, 5.84; N, 3.53. Found: C, 66.40; H, 5.86; N, 3.27. $^1$H n.m.r. δ 8.24-8.18(4H ,m ,Ar), 7.76-7.42(6H, m, Ar), 5.69(1H, m, H-1), 5.31(1H, dt, J=5.2, 9.7Hz, H-6), 3.91(1H, t, J=9.1Hz, H-7), 3.77(2H, t, J=9.1Hz, H-8, OH), 3.63(1H, dd, J=5.2, 10.3Hz, H-5), 3.44(1h, dt, J=2.3, 8.6Hz, H-3), 3.10(1H, s, OH), 2.63-2.23(5H, m, H-2,2',3',5',8a). $^{13}$C n.m.r. δ 167.8, 166.3, 133.6, 133.2, 130.1, 130.0, 129.8, 129.5, 128.6, 128.4, 76.7(C-7), 74.6(C-1), 72.9(C-6), 71.4(C-8a), 70.0(C-8), 53.4(C-5), 51.9(C-3), 31.2(C-2).

*1-O-Pivaloylcastanospermine* ***36***. A suspension of castanospermine (30 g) and dibutyltin oxide (78.7 g, 2 equiv.) in toluene (800 ml) was heated under reflux with azeotropic removal of water for 2 h. The resulting solution was cooled to 0°C and pivaloyl chloride (43 ml, 2.2 equiv.) was added slowly with stirring. The solution was then allowed to warm to room temperature overnight. 2 M Aqueous ammonium hydroxide (1 L) was added, the mixture was shaken and then filtered through celite. The solids were washed with ethyl acetate and the organic phases were combined, dried ($MgSO_4$) and evaporated. The syrupy residue (56 g) was mostly *1,6-di-O-pivaloylcastanospermine* ***34***. A small amount purified by chromatography had m.p. 235-242°C (EtOH). Accurate mass: calc. for $C_{18}H_{32}NO_6$ 358.2230, obs. 358.2246. $^1$H n.m.r. δ 5.24 (1H, m, H-1), 4.87 (1H, dt, H-6), 3.56 (1H, t, H-7), 3.38 (1H, t, H-8), 3.28 (1H, dd, H-5), 3.18 (1H, dt, H-3), 2.36-2.26 (1H, m, H-2), 2.17 (1H, dd, H-3'), 2.09 (1H, dd, H-8a), 1.99 (1H, t, H-5'), 1.93-1.85(1H, m, H-2'), 1.24, 1.22 (9H each, $(CH_3)_3C$). $^{13}$C n.m.r. δ 180.3, 178.3, 76.7, 73.6,

71.9, 71.2, 69.8, 53.2, 51.8, 39.0, 38.9, 31.0, 27.2, 27.1. A solution of this material in methanol (400 ml) containing potassium cyanide (2 g) was heated under reflux and progress of the reaction was monitored carefully by t.l.c. After 1 h, dichloromethane (400 ml) was added and the solution was filtered through a pad of silica gel. The filtrate was evaporated to dryness and chromatography of the residue (36 g) ($CHCl_3$/MeOH/EtOAc 10:1:4) afforded title compound **36** (27.4 g, 63%) with m.p. 120-122°C (ethyl acetate/petroleum ether). Accurate mass: calc. for $C_{13}H_{24}NO_5$ ($MH^+$) 274.1654, obs. 274.1646. $^1$H n.m.r. δ 5.23 (1H, m, H-1), 3.70 (1H, dt, H-6), 3.40, 3.35 (1H each, t, 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, $(CH_3)_3C$). $^{13}$C n.m.r. δ 179.8, 79.4, 73.4, 71.3, 70.2, 69.4, 56.1, 52.1, 38.9, 31.3, 27.2.

*1-O-Benzoylcastanospermine 37.* A solution of 1,6-di-*O*-benzoylcastanospermine **35** (1.0 g) in methanol containing 10% conc. aqueous ammonia (40 ml) was allowed to stand at room temperature for 2 h, and then evaporated to dryness. Chromatography ($CHCl_3$/EtOAc/MeOH 5:2:1) of the residue afforded title compound **37** (0.57 g, 77%). Accurate mass: calc. for $C_{15}H_{20}NO_5$ ($MH^+$) 294.1341, obs. 294.1342. $^1$H n.m.r. (DMSO-$d_6$) δ 7.80 (2H, d, Ar), 7.50 (1H, t, Ar), 7.38 (2H, t, Ar), 5.16 (1H, t, H-1), 4.74 (1H, d, OH), 4.69 (2H, d, OH), 3.37 (1H, dt, H-8), 3.32-3.22 (1H, m, H-6), 2.90-2.82 (3H, m, H-3,5,7), 2.25-2.15 (1H, m, H-2), 1.90 (1H, t, H-3′), 1.82 (1H, dd, H-8a), 1.66 (1H, t, H-5′), 1.58-1.47 (1H, m, H-2′). $^{13}$C n.m.r. δ 166.7, 134.6, 131.8, 130.6, 130.1, 81.0, 75.0, 72.3, 71.7, 70.5, 58.3, 53.3, 33.4.

*1-O-$^t$Butyldimethylsilylcastanospermine 38.* A suspension of castanospermine (5.0 g) in toluene (250 ml) containing bis(tributyltin) oxide (27 ml, 2 equiv.) was heated under reflux with azeotropic removal of water for 2 h. Tetrabutylammonium bromide (6.8 g, 0.8 equiv.) and $^t$butyldimethylsilyl chloride (7.15 g, 1.8 equiv.) were added and the solution was heated under reflux for 3 h, then further $^t$butyldimethylsilyl chloride (1.0 g) was added and reflux was continued for another 1 h. The solvent was removed and the residue was dissolved in 1% aq. acetonitrile (300 ml) and washed with petroleum ether (x4). The acetonitrile phase was concentrated to dryness and chromatography (EtOAc, to EtOAc/MeOH 20:1) of the residue gave title compound **38** (6.18 g, 77%) with m.p. 178-180°C. $^1$H n.m.r. δ 4.32(1H, m, H-1), 3.69-3.57(2H, m, H-6,8), 3.24(1H, t, J=8.9Hz, H-7), 3.11(1H, dd, J=4.9, 10.6 Hz, H-5), 3.02(1H, t, J=7.6 Hz, H-3), 2.16-1.64(5H, m, H-2,2',3',5',8a), 0.81(9H,s), 0.01(6H,s). $^{13}$C n.m.r. δ 80.4(C-7), 71.8(C-1), 71.6(C-8a), 70.4(C-6), 69.7(C-8), 56.3(C-5), 52.3(C-3), 35.0(C-2), 26.1, 18.4, -4.6, -4.7. A sample acetylated overnight in pyridine/acetic anhydride/4-dimethylaminopyridine afforded 1-*O*-$^t$butyldimethylsilyl-6,7,8-tri-*O*-acetylcastanospermine with m.p. 122-123°C (aq. ethanol). Anal. calc. for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.22; N, 3.26. Found: C, 56.07; H, 8.30; N, 3.24. $^1$H n.m.r. δ 5.25(1H, t, J=9.0Hz, H-8), 5.15-5.02(2H, m, H-6,7), 4.31(1H, m, H-1), 3.37(1H, dd, J=4.6, 10.1Hz, H-5), 3.18(1H, t, J=7.1Hz, H-3), 2.27-1.77(5H, m, H-2,2',3',5',8a), 2.02, 2.02, 1.99(3H each, s). $^{13}$C n.m.r. δ 170.9, 169.8,

169.3, 76.2(C-7), 70.6(C-1), 70.2(C-6), 70.0(C-8a), 69.3(C-8), 53.2(C-5), 52.2(C-3), 35.1(C-2), 25.8, 21.1, 20.8, 20.7, 17.9, -4.8, -5.0.

*6,7,8-Tri-O-(methoxymethyl)-castanospermine 40.* Diisopropylethylamine (65 ml) and then bromomethyl methyl ether (25 g) were added to a warm solution of 1-*O*-pivaloylcastanospermine **36** (10.0 g) in dry toluene (250 ml), and the mixture was heated with stirring at 80°C for 2 h, cooled, and the solution was decanted. The residual solids were crushed and extracted (x2) with warm toluene. The combined toluene solutions were washed with water (x2), dried ($MgSO_4$) and evaporated. The residue was dissolved in dry ether (200 ml) and stirred at room temperature while lithium aluminium hydride (1.0 g) was added. After stirring for 1 h the reaction mixture was quenched carefully with ethyl acetate, acetone and then water. The solids were removed, washed with ethyl acetate, and the combined filtrates concentrated to dryness. Chromatography (EtOAc) gave title compound **40** (10.0 g, 85%). Accurate mass: calc. for $C_{14}H_{28}NO_7$ ($MH^+$) 322.1866, obs. 322.1869. $^1$H n.m.r. δ 4.97-4.68 (6H, m, $OCH_2O$), 4.33 (1H, m, H-1), 3.88 (1H, d, OH), 3.71 (1H, dt, H-6), 3.63, 3.50 (1H each, t, H-7,8) 3.47, 3.43, 3.36 (3H each, s, $OCH_3$), 3.35 (1H, m, H-5), 3.16 (1H, m, H-3), 2.30-1.79 (5H, m, H-2,2′,3′,5′,8a). $^{13}$C n.m.r. δ 99.2, 98.2, 97.1, 83.4, 78.1, 77.9, 71.8, 70.3, 56.0, 56.0, 55.6, 55.1, 52.4, 32.5.

*1(R), 6(S), 7(R), 8(R), 8a(R)-Tetrahydroxy-6,7,8-tri-O-(methoxymethyl)-octahydroindolizidine 42.* A solution of dry DMSO (1.1 ml) in dry dichloromethane (40 ml) was cooled to -70°C under argon and trifluoroacetic anhydride (1.75 ml) was added dropwise with stirring. After 10 min. a solution of 6,7,8-tri-*O*-(methoxymethyl)-castanospermine **40** (2.0 g) in dry dichloromethane (10 ml) was added slowly. The solution was stirred at -70°C for 20 min. and then triethylamine (6 ml) was added and the solution was allowed to warm to room temperature, then washed with water (x2), dried ($MgSO_4$) and evaporated. The residue was dissolved in dry tetrahydrofuran (30 ml), cooled to -70°C under argon, and lithium aluminium hydride (10 ml, 1.0 M in tetrahydrofuran) was added slowly with stirring. After 30 min. the cooling bath was removed and the mixture was quenched carefully with ethyl acetate, acetone and then water. The solids and solvent were removed and chromatography ($CH_2Cl_2$/acetone 4:1) of the residue gave starting material **40** (0.43 g) followed by title compound **42** (1.25 g). Accurate mass: calc. for $C_{14}H_{28}NO_7$ ($MH^+$) 322.1866, obs. 322.1878. $^1$H n.m.r. δ 4.88-4.67 (6H, m, $OCH_2O$), 4.23-4.15 (1H, m, H-1), 3.60 (1H, dt, H-6), 3.47, 3.39 (1H each, t, H-7,8), 3.43, 3.42, 3.37 (3H each, s, $OCH_3$), 3.21 (1H, dd, H-5), 2.94 (1H, dt, H-3), 2.47 (1H, dd, H-3′), 2.36-2.22 (1H, m, H-2), 2.10 (1H, t, H-5′), 1.99 (1H, dd, H-8a), 1.74-1.64 (1H, m, H-2′). $^{13}$C n.m.r. δ 99.2, 98.2, 97.1, 83.5, 83.0, 78.0, 75.2, 72.8, 56.1, 55.6, 55.5, 54.9, 51.4, 31.8.

*1(R), 6(S), 7(R), 8(R), 8a(R)-Tetrahydroxyoctahydroindolizidine 43.* A solution of [1(R),6(S),7(R),8(R),8a(R)]-tetrahydroxy-6,7,8-tri-*O*-(methoxymethyl)-octahydroindolizidine **42** (0.11 g) in methanol (10 ml) containing conc. HCl (1 ml) was allowed to stand at room temperature overnight and

then concentrated to dryness. Chromatography ($CH_2Cl_2$/MeOH/conc. aq. $NH_3$ 5:4:1) of the residue afforded title compound **43** (0.06 g). Accurate mass: calc. for $C_8H_{16}NO_4$ ($MH^+$) 190.1079, obs. 190.1082. $^1H$ n.m.r. ($D_2O$) (HOD δ 4.72) δ 4.19 (1H, m, H-1), 3.65-3.51 (1H, m, H-6), 3.26 (2H, t, H-7,8), 3.15 (1H, dd, H-5), 2.97 (1H, t, H-3), 2.76 (1H, dd, H-3′), 2.42-2.35 (2H, m, H-5′, 8a), 2.30-2.16 (1H, m, H-2), 1.69-1.61 (1H, m, H-2′). $^{13}C$ n.m.r. δ 80.4, 75.6, 74.9, 74.4, 71.2, 56.1, 53.5, 34.5.

*1-Deoxy-1-fluorocastanospermine* ***44***. Diethylaminosulfur trifluoride (2.0 ml) was added to a solution of [1(R),6(S),7(R),8(R),8a(R)]-tetrahydroxy-6,7,8-tri-*O*-(methoxymethyl)-octahydroindolizidine **42** (1.1 g) in dry dichloromethane (40 ml) containing triethylamine (4 ml) and the solution was allowed to stand at room temperature for 5 days, then washed with 5% aq. sodium carbonate, water, dried ($MgSO_4$) and evaporated. The crude product was dissolved in methanol (40 ml) containing 10 M HCl (8 ml) and the solution was left at room temperature for 16 h. The solvents were removed and the residue eluted through base resin (Amberlyst A26, $OH^-$ form) with water. Chromatography of the resulting material afforded title compound **44** (0.30 g, 46%). Accurate mass: calc. for $C_8H_{15}FNO_3$ ($MH^+$) 192.1036, obs. 192.1030. $^1H$ n.m.r. ($D_2O$) (HOD δ 4.60) 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). $^{13}C$ n.m.r. δ 95.1 ($J_{C,F}$ 178 Hz, C-1), 81.1 (C-7), 73.6 ($J_{C,F}$ 20 Hz, C-8a), 72.6 (C-6), 70.9 ($J_{C,F}$ 6 Hz, C-8), 57.5 (C-5), 53.7 (C-3), 33.4 ($J_{C,F}$ 23 Hz, C-2).

*1-Fluoro-1(R), 6(S), 7(R), 8(R), 8a(R)-trihydroxyoctahydroindolizidine* ***45***. Diethylaminosulfur trifluoride (1.0 ml) was added to a solution of 6,7,8-tri-*O*-(methoxymethyl)-castanospermine **40** (1.5 g) in dry dichloromethane (40 ml) containing triethylamine (3 ml). The solution was stirred at room temperature for 2 h, washed with 10% aqueous sodium carbonate, water, dried ($MgSO_4$) and evaporated. Chromatography (EtOAc/$CHCl_3$ 1:1) gave the major less polar product (1.1 g). This was dissolved in methanol (40 ml) containing 10 M HCl (8 ml) and the solution was stored at room temperature for 40 h, then concentrated to dryness. Chromatography ($CH_2Cl_2$/MeOH/conc. aq. $NH_3$ 5:4:1) afforded title compound **45** (0.564 g, 63%). Accurate mass: calc. for $C_8H_{15}FNO_3$ ($MH^+$) 192.1036; obs. 192.1036. $^1H$ n.m.r. ($D_2O$) (HOD δ 4.67) δ 4.94 (1H, m, $J_{H,F}$ 55.9 Hz, H-1), 3.46 (1H, ddd, H-6) 3.22, 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′). $^{13}C$ n.m.r. δ 98.0 ($J_{C,F}$ 175 Hz, C-1), 81.1 (C-7), 74.3 (C-8), 73.9 ($J_{C,F}$ 23 Hz, C-8a), 72.0 (C-6), 56.7(C-5), 53.0 (C-3), 33.3 ($J_{C,F}$ 22 Hz, C-2).

*1-C-Methylcastanospermine* ***46***. 6,7,8-Tri-*O*-(methoxymethyl)-castanospermine **40** (2.0 g) was oxidized under Swern conditions as described above for the preparation of the C-1 epimer **42**. The crude product after work up was dissolved in dry tetrahydrofuran (50 ml), cooled to -10°C, and methylmagnesium chloride (3 M in THF, 6 ml) was added dropwise with stirring. After 1 h saturated aqueous ammonium chloride was added and the mixture was extracted (x2) with chloroform. The organic extracts were

washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated. Chromatography ($CH_2Cl_2$/acetone 2:1) of the residue gave 1.52 g of a single major product. This material was dissolved in 20% conc. HCl in methanol (40 ml) and the solution was allowed to stand at room temperature for 24 h. The solvents were removed and chromatography ($CH_2Cl_2$/MeOH/conc. aq. $NH_3$ 6:3:0.5) of the residue afforded title compound **46** (1.1 g). The hydrochloride salt of this material when crystallized and recrystallized from ethanol had m.p. 205-208°C. Accurate mass: calc. for $C_9H_{18}NO_4$ ($MH^+$) 204.1236; obs. 204.1228. $^1$H n.m.r. ($D_2O$) (HOD δ 4.80) δ 3.86-3.79 (2H, m, H-6,8), 3.76-3.65 (2H, m, H-3,5), 3.55 (1H, t, H-7), 3.25 (1H, dt, H-3′), 3.17 (1H, d, H-8a), 3.04 (1H, t, H-5′), 2.37-2.12 (2H, m, H-2,2′), 1.56 (3H, s, $CH_3$). $^{13}$C n.m.r. δ 79.5 (C-7), 78.8 (C-1), 74.8 (C-8a), 69.9, 69.8 (C-6,8), 55.1 (C-5), 53.2 (C-3), 40.4 (C-2), 26.7 ($CH_3$).

*1-O-Methylcastanospermine 47.* Dimethylsulfate (0.5 ml) and then sodium hydride (0.22 g, 80%) were added to a stirred solution of 6,7,8-tri-*O*-(methoxymethyl)-castanospermine **40** (0.78 g) in dry tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 2 h. Methanol (2 ml) was added carefully and then the mixture was partitioned between chloroform and water. The organic phase was processed and the crude product was dissolved in acetic acid/water (9:1, 20 ml) and the solution was heated under reflux for 40 h. The solvents were removed and a solution of the residue in methanol was stirred with base resin (Amberlyst A21), then filtered and evaporated. Chromatography ($CH_2Cl_2$/MeOH 4:1) afforded title compound **47** (0.30 g). Accurate mass: calc. for $C_9H_{18}NO_4$ ($MH^+$) 204.1236; obs. 204.1227. $^1$H n.m.r. ($D_2O$) (HOD δ 4.67) δ 3.93 (1H, t, H-1), 3.55 (1H, t, H-7 or H-8), 3.51 (1H, dt, H-6), 3.26-3.14 (3H, m, H-3,5,7 or 8), 3.16 (3H, s, $OCH_3$), 2.51-2.37 (2H, m), 2.25 (1H, t), 2.15-2.04 (1H, m), 1.97-1.80 (1H, m). $^{13}$C n.m.r. δ 80.6, 80.5, 73.4, 71.7, 70.3, 58.8, 56.9, 54.4, 31.3.

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