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The Chemistry of Castanospermine, Part IV[1]: Synthetic Modifications at *C*-8

Richard H Furneaux, Graeme J Gainsford, Jennifer M Mason and Peter C Tyler*

Industrial Research Limited
P O Box 31310
Lower Hutt
New Zealand

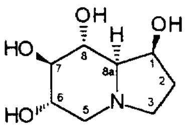
Oliver Hartley and Bryan G Winchester

Institute of Child Health
University of London
30 Guilford Street
London WC1N 1EH
UK

Abstract: New methods for the selective functionalisation of castanospermine has enabled the synthesis of analogues and derivatives selectively modified at C-8.

INTRODUCTION

Castanospermine **1**, has generated considerable interest over the past few years because of the varied biological activities that have been ascribed to it. It was first isolated from the seeds of the Australian legume *Castanospermum australe*[2] and then also from *Alexa leiopetala*.[3] Castanospermine is one of a collection of polyhydroxyalkaloid glycosidase inhibitors isolated from plant sources, which have wide ranging biological effects.[4] Swainsonine **2**, for example, is a potent and specific inhibitor of lysosomal and glycoprotein processing α-mannosidases,[5] while deoxynojirimycin **3** is a glucosidase inhibitor and also inhibits glycoprotein processing enzymes.[6] Castanospermine is a potent inhibitor of



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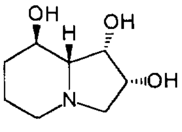

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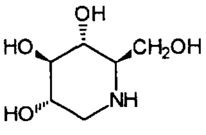

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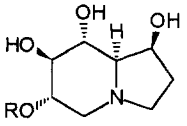
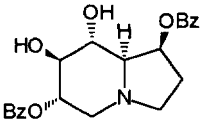
glucosidases[7] including lysosomal and glycoprotein processing enzymes.[8] Its biological activity has indicated potential utility in the treatment of viral infections,[9] cancers,[10] malaria[11] and diabetes.[12] The total synthesis of castanospermine and a number of its stereoisomers and analogues has been the subject of a variety of publications.[13] We have been engaged in a systematic programme to study the chemistry of castanospermine with the intention of synthesizing novel analogues and derivatives that might offer improved activity and selectivity in their biological effects.[1,14,15] We chose to start from castanospermine isolated from the *Castanospermum australe* seeds,[12] rather than to engage in total synthesis. A previous paper concentrated on the chemistry at *C*-6,[14] and here we present our results on attempted synthetic modifications at *C*-8. Parts of this work have been reported in a communication.[15] Selected biological results are presented here.

RESULTS AND DISCUSSION

In order to perform chemistry at *C*-8, castanospermine needed to be selectively protected at the 1,6,7-positions. We have used organotin ether derivatives of castanospermine previously to successfully carry out selective manipulations.[14] Thus use of bis(tributyltin) oxide has allowed the synthesis of 6-*O*-monoesters **4** in high yields. However attempts to use this method to obtain tri-*O*-acylated castanospermine derivatives were unsuccessful. With an excess of benzoyl chloride only a mixture of the 6-benzoate **4a** and the 1,6-dibenzoate **5** were obtained. On the other hand, when dibutyltin oxide was used, tri-esters of castanospermine were readily available, and the 1,6,7- and 1,6,8-tribenzoates **6** and **7**



4 (a) R = COC_6H_5
(b) R = $CO(CH_2)_2CH_3$
(c) R = $CO_2CH_2C_6H_5$



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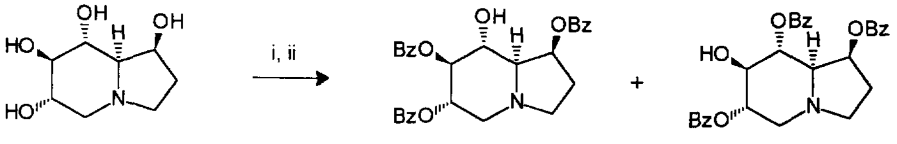


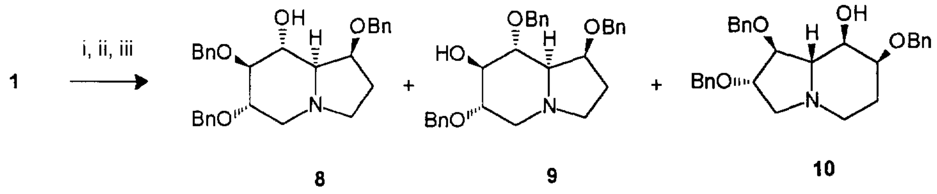
6 **7**

Reagents: i, Bu_2SnO, toluene, reflux; ii, BzCl, toluene, -10°C to RT.

SCHEME 1

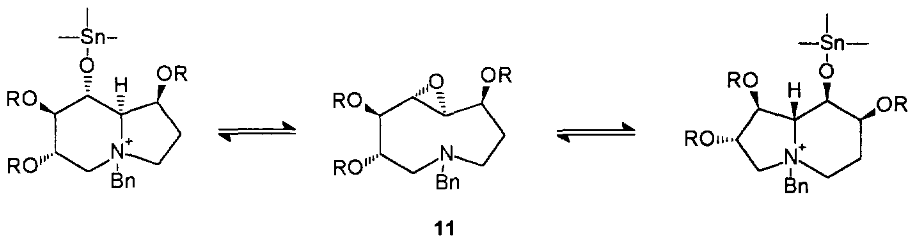
were formed in a 4:1 ratio in 75% yield (Scheme 1). The 1,6,7-tribenzoate **6** proved useful for the synthesis of new analogues *vide infra*.

Attempts were then made to prepare tri-*O*-benzylcastanospermine derivatives in a similar fashion, as the benzyl ether protecting groups would be more stable than benzoate esters under some conditions. When the product obtained from treating castanospermine with 2 equivalents of dibutyltin oxide in refluxing toluene was allowed to react with benzyl bromide and tetrabutylammonium bromide in the usual way,[16] the nitrogen of the castanospermine moiety was quickly quaternised by benzyl bromide. A slow reaction then took place in refluxing toluene to give mixtures mainly of tribenzylated isomers. After work-up, the parent amines were released from their quaternised state using LiSPr (or NaSMe) in dimethylsulfoxide, and this afforded the 1,6,7-tri-*O*-benzyl derivative **8** (contaminated with a little of the corresponding 1,6,8-isomer **9**) as well as a rearranged tribenzyl ether **10** (Scheme 2). Presumably the rearranged material is produced *via* the transient amine epoxide **11** which can suffer intramolecular opening by the nitrogen to give either the starting castanospermine derivative or the rearranged material in an equilibrium reaction (Scheme 3). The ratio of products **8** and **10** varied somewhat depending on the concentration of reagents and the amount of benzyl bromide added, but conditions were found that reproducibly afforded a 50% yield of 1,6,7-tri-*O*-benzylcastanospermine **8** and 15% of the rearranged product **10**.



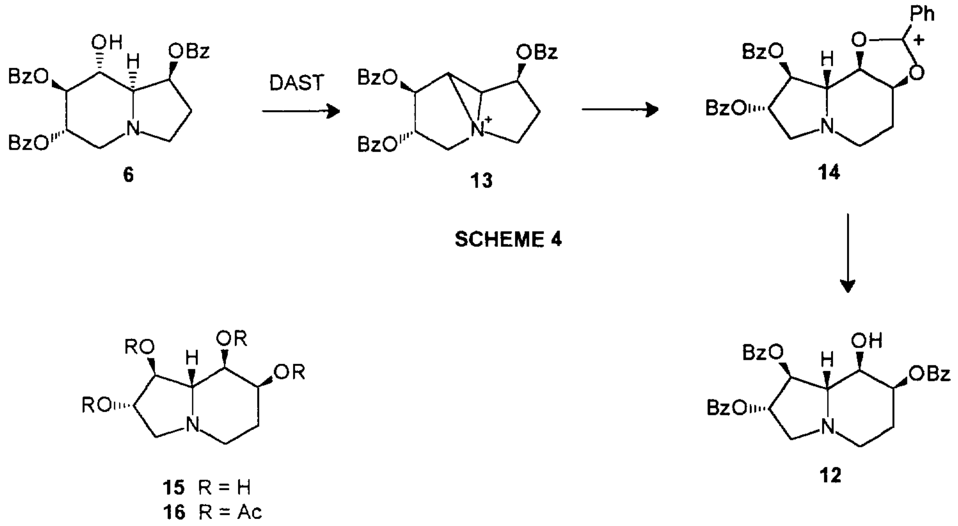
Reagents: i, Bu_2SnO, toluene, reflux 2h; ii, add Bu_4NBr, BnBr, reflux 3d; iii, LiSPr, DMSO.

SCHEME 2



SCHEME 3

With the tribenzoate **6** and tribenzyl ether **8** readily available, efforts were made to prepare derivatives selectively modified at *C*-8. Treatment of the 1,6,7-tribenzoate **6** with diethylaminosulfur



SCHEME 4

trifluoride (DAST) afforded a single product, but n.m.r. analysis showed that it did not contain fluorine, and suggested the product was **12** (Scheme 4). Evidently treatment with DAST converts the *C*-8 hydroxyl into a leaving group and displacement with participation by the ring nitrogen gives the aziridinium ion **13**. Rather than being attacked by fluoride ion, **13** undergoes a further rearrangement with participation by the *C*-1 benzoate group to give the benzoxonium ion **14** which is hydrolysed on work-up affording **12**. The rearranged material **12** has the same ring system and stereochemistry as the rearrangement product **10** obtained in the benzylation - even though they are thought to arise *via* quite different mechanisms. This was confirmed by deprotecting **12** (NH_4OH/MeOH) and **10** (H_2, Pd/C, HOAc) to the same parent

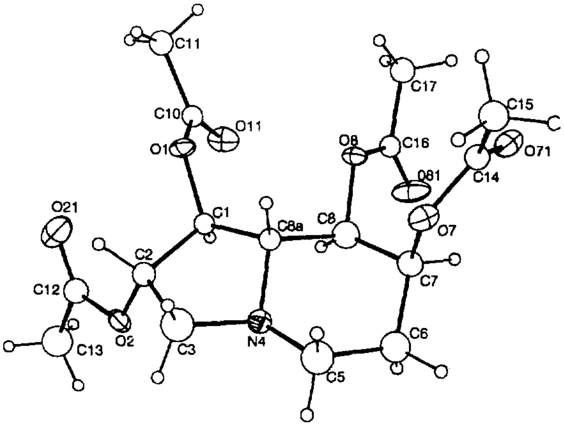
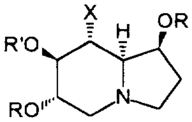
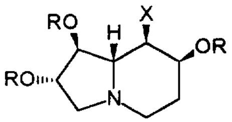


FIGURE 1



17 X = OMs, R,R' = Bz
18 X = OBz, R = Bz, R' = Ms
19 X = N_3, R,R' = Bz
21 X = NH_2, R,R' = Bz
23 X = NH_2, R,R' = H
24 X = NHAc, R,R' = H
26 X = OCS-imidazole, R,R' = Bz
27 X = H, R,R' = Bz
28 X = H, R,R' = H



20 X = N_3, R = Bz
22 X = NH_2, R = Bz
25 X = NHAc, R = H

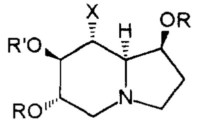
tetrahydroxyoctahydroindolizidine **15** which was isolated as its tetraacetate **16**. An x-ray crystal structure of **16** (Figure 1) confirmed its structure.

The participation by nitrogen when attempting substitution of the C-8 hydroxyl group with DAST is consistent with observations made previously by us with reactions at C-6 of castanospermine derivatives[14], and by others with analogous ring systems.[17,18]

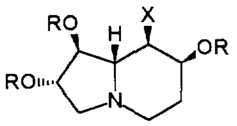
Mesylation of the mixture of **6** and **7** gave mesylates **17** and **18** which were more readily separable than their parent alcohols. Treatment of the 8-*O*-mesyl derivative **17** with sodium azide in warm hexamethylphosphoric triamide afforded the product **19** of displacement with *retention* of configuration as well as the rearranged material **20** in a 1.3:1 ratio. Presumably the aziridinium ion **13** is an intermediate and this is attacked by azide ion at either *C*-8 or *C*-8a of the parent molecule. These isomeric azides could be separated by chromatography but in practice it was easier to first reduce the mixture (H_2, Pd/C) to the more readily separated amines **21** and **22**. Saponification of **21** gave 8-amino-8-deoxycastanospermine **23**, while *N*-acetylation prior to saponification afforded the corresponding *N*-acetate **24**, and also the rearranged material **25** from **22**.

Deoxygenation at C-8 of the 1,6,7-tribenzoate **6** was achieved by conversion to its imidazolethiocarbamate **26** and subsequent reduction with tributyltin hydride to give the 8-deoxy derivative **27**. Saponification then afforded 8-deoxycastanospermine **28**. The success of this deoxygenation sequence was a little surprising, as analogous attempts to reduce *C*-6 imidazolethiocarbamates resulted only in regeneration of the parent alcohol.[19]

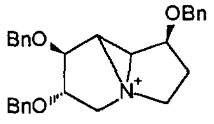
Since DAST treatment of alcohol **6** did not result in any fluorinated products, attempts were made to effect displacements on mesylate **17** with fluoride ions, but without success. Either starting material was returned or degradation occurred under all conditions tried. Consequently attention was turned to the tribenzyl ether **8**. Treatment of this alcohol with DAST gave the product of displacement with *retention* of configuration **29** and rearranged material **30** in a ratio of ~2:3. Clearly participation of the nitrogen was occurring again and the aziridinium ion **31** was the intermediate. Because this intermediate **31** can be



29 X = F, R = Bn
32 X = F, R = H
34 X = OMs, R = Bn
35 X = CN, R = Bn
38 X = CH_2OH, R = Bn
39 X = CH=NH, R = Bn
40 X = CH_2NH_2, R = Bn
41 X = CO_2Me, R = Bn
43 X = CHO, R = Bn
45 X = CH_2F, R = Bn
46 X = $OCOC(CH_3)_3$, R = Bn
47 X = $OCOC(CH_3)_3$, R = H
48 X = OMe, R = Bn
50 X = OMe, R = H



30 X = F, R = Bn
33 X = F, R = H
36 X = CN, R = Bn
37 X = OMs, R = Bn
49 X = OMe, R = Bn
51 X = OMe, R = H



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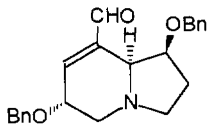

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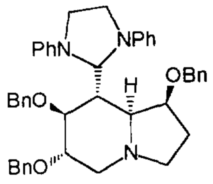

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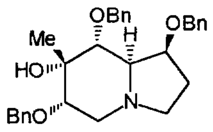

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formed from either the tribenzyl ether **8** or the rearrangement material **10** produced during the benzylation, it didn't matter whether **8** or **10** or a mixture thereof was treated with DAST, the same product ratio of **29** and **30** was formed in the same yield. Hydrogenolysis of **29** gave 8-deoxy-8-fluorocastanospermine **32** while **30** afforded the interesting fluorinated octahydroindolizidine triol **33**.

The tribenzyl mesylate **34** was readily available from **8** and when it was treated with potassium cyanide in warm dimethylsulfoxide the two expected nitrile products **35** and **36** were obtained in ~2:3 ratio. Again, because the aziridinium ion **31** is an intermediate, either of the mesylates **34** or **37**, or a mixture of the two, can be used to the same effect. The nitrile **35** was made with the intention of converting it to the 8-*C*-hydroxymethyl derivative **38**. However, attempts to selectively reduce nitrile **35** to the imine **39** were unsuccessful. Using diisobutylaluminium hydride at -70°C the imine **39** was reduced faster to the amine **40** than it was formed. Thus with 1 equiv. of DIBAH a mixture of starting nitrile **35** and amine **40** was formed. Using excess DIBAH, **40** was the only product and was isolated in 91% yield. Other reducing agents [$Li(EtO)_3AlH$, or $\mathrm{Li^tBu^iBu_2AlH}$] also failed to produce any of the desired imine **39**. Attempts to solvolyse the nitrile **35** in acidic methanol (HCl, MeOH, reflux) to give the methyl ester **41** afforded either no reaction or, eventually, only degradation, and attempts at basic hydrolysis (NaOH, EtOH, reflux) gave the same result. Raney nickel in the presence of sodium hypophosphite in pyridine/acetic acid/water is known to reductively hydrolyse nitriles to the corresponding aldehydes.[20] When these conditions were applied to nitrile **35**, however, only a low yield of product was obtained which had n.m.r. data consistent with it being the elimination product **42**. In order to stabilise the desired aldehyde **43** in the reaction mixture, the reaction was repeated in the presence of 1,2-dianilinoethane. Then the dianilino-adduct **44** was obtained, but it was too unstable to be conveniently purified by chromatography and it was directly hydrolysed to the aldehyde **43** and then reduced to **38**. While this method did give access to the *C*-8-hydroxymethyl-substituted material, the yield from nitrile **35** was only 19% and the yield of **35** from alcohol **8** was only ~20%. Considerable efforts were made to improve these yields, but without success. Treatment of alcohol **38** with DAST afforded the fluoromethyl substituted castanospermine **45**.

The preparation of a lipophilic 8-*O*-monoester of castanospermine was of interest. The 1,6,7-tribenzyl ether **8** was converted into the 8-*O*-pivalate **46** (Me_3CCOCl, pyr, 70°C), which on hydrogenolysis (Pd/C, H_2, HOAc) afforded 8-*O*-pivaloylcastanospermine **47**. Attempts to prepare 8-*O*-methyl ethers from either the tribenzoate **6** or the tribenzyl ether **8** resulted only in preferential formation of the N^+-methyl salts before any *O*- methylation. If the benzylation product mixture described in Scheme 2 was used, prior to dequaternisation, then *O*-methylation was successful (NaH, MeI, DMSO) and subsequent dequaternisation (NaSPr, DMSO) afforded the castanospermine methyl ether **48** as well as the rearranged material **49**. Hydrogenolysis of these gave 8-*O*-methylcastanospermine **50** and its analogue **51**.

Many attempts were made to oxidise alcohols **6** and **8** to the corresponding ketones so that further analogues could be prepared. However, all attempts either returned starting material unchanged or resulted in complete decomposition. In one instance, Swern oxidation of a sample of **8** was attempted which had a small amount of the isomeric alcohol **9** in it. The reaction was not worked up but an excess of methyl magnesium chloride was added. A product was isolated which had NMR characteristics consistent with it being the adduct **52**, or its *C*-7 epimer, derived from oxidation of the minor impurity. Nothing else discrete was obtained. Similar problems have been observed when attempting oxidations at C-6.[14]

The chemistry presented here provides new protecting group methodology that has allowed the synthesis of a number of castanospermine derivatives and analogues by manipulation at *C*-8.

BIOLOGICAL RESULTS

Several of the derivatives of castanospermine, modified at *C*-8, were tested for their inhibition of human liver glycosidases as described previously[7(iii)] (Table 1). The parent compound, castanospermine **1**, inhibits all the forms of α- and β-D-glucosidases in human liver. Removal of the hydroxyl group at *C*-8 to give 8-deoxycastanospermine **28** almost abolishes this inhibitory activity, indicating that this hydroxyl group is important in recognition of substrate by these enzymes. Similarly substitution of the *C*-8 hydroxyl by an amino group to give 8-amino-8-deoxycastanospermine **23** abolishes inhibition. Replacement of the OH group with fluorine (8-deoxy-8-fluorocastanospermine **32**) decreases but does not completely abolish

Inhibition of human liver glycosidases by castanospermine and C-8 derivatives at 1 mM concentration

Compound	Activities Inhibited	% at 1 mM
1	Lysosomal α-glucosidase	100
	neutral α-glucosidase	97
	lysosomal β-glucosidase	96
	cytosolic β-glucosidase	90
28	weak inhibition of all glucosidases	
23	None	0
32	lysosomal β-galactosidase	55
	lysosomal α-glucosidase	32
50	lysosomal α-glucosidase	91
	neutral α-glucosidase	66
	lysosomal β-glucosidase	13
	cytosolic β-glucosidase	47
47	lysosomal α-glucosidase	90
	β-hexosaminidase	29
15	lysosomal α-glucosidase	71
	neutral α-glucosidase	39
	cytosolic β-glucosidase	51
	lysosomal β-galactosidase	74
	lysosomal β-xylosidase	66
33	lysosomal α-glucosidase	91
	lysosomal β-galactosidase	55
25	lysosomal β-glucosidase	30

Table 1

the inhibition of α- and β-D-glucosidases. Methylation of the hydroxyl group to give 8-*O*-methylcastanospermine **50** does not affect the α-glucosidase activities as much as it does the β-glucosidase, confirming the observation that β-hexosidases generally show more stringent requirements for inhibition. The lipophilic 8-*O*-pivaloylcastanospermine **47** initially appeared to retain the ability to inhibit α- and β-glucosidase. However, analysis of the enzyme reaction mixture by t.l.c. showed that the ester was hydrolysed by enzymic activity in the liver extract to castanospermine, which would inhibit the enzymes. The specificities of inhibition of the *C*-8 derivatives of castanospermine are consistent with previous studies. The rearranged tetrahydroxyoctahydroindolizidine **15** was a moderately good inhibitor of α- and β-glucosidase and also of β-D-galactosidase and β-D-xylosidase. Its 8-deoxy-8-fluoro derivative **33** was also a good inhibitor of α-glucosidase and β-galactosidase, whereas the 8-acetamido-8-deoxy derivative **25** retained only weak inhibitory activity towards β-glucosidase. The structural basis of the inhibitory pattern of the rearranged compound and its two derivatives is not readily apparent in terms of aza-furanose or aza-pyranose analogues.

X-RAY SINGLE CRYSTAL ANALYSIS

Compound **16**, $C_{16}H_{23}NO_8$, orthorhombic space group $P2_12_12_1$(19)[21], a=8.665(3), b=13.912(4), c=15.108(5) Å, V=1821.2(10) $Å^3$, z=4, D_c=1.303g.cm^{-3}, T=291K, Mo Kα radiation (λ=0.71073 Å), μ=1.05cm^{-1}. Nicolet R3m diffractometer, 1473 independent reflections measured (4°‹2θ‹49°) of which 522 had I_{net}›3σ(I_{net}). No absorption correction. Solved by direct methods[22] and refined on F using observed data[23] to R, R_w 0.058, 0.052. Absolute configuration not determined. All hydrogens included in calculated positions (C-H, 0.95Å), with two group isotropic thermal parameters for methyl, and fused ring hydrogen atoms. Final maximum shift/error was 0.07 and Δρ excursions 0.26 to -0.29 e/$Å^3$.

The independent molecules (Figure 1) only have Van der Waal contacts, with closest contacts H5(C5)....H15(C15), and O71....H2(C2) at 2.35, and 2.52 Å respectively. The six-membered ring is close to the ideal cyclohexane chair form (Q 0.56Å, q_3 0.05Å, θ 5.3° compared with 0.63, 0.05Å, 0° for ideal[24]), with atoms N4, C5, C7, C8 coplanar and C6, C8a being -0.62, 0.70Å out of this plane. The five membered ring is in a distorted envelope (Q 0.46Å, ø 9.5°) with the flap atom C8a being 0.62Å above the mean plane of C1, C2, C3 and N4. There are no significant deviations from expected bond lengths and angles[25].

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 ionisation conditions using isobutane or ammonia as the ionising gas. Melting points were determined on a Reichert hot stage microscope and are uncorrected. Elemental analyses were performed by the Campbell 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[14]. Tetrahydrofuran was distilled from sodium/benzophenone under argon and dichloromethane was distilled from calcium hydride before use. All other chemicals were commercially available and were used without further purification.

1,6,7-Tri-O-benzoylcastanospermine ***6*** *and 1,6,8-tri-O-benzoylcastanospermine 7.* A suspension of castanospermine (15 g) and dibutyltin oxide (39.5 g, 2 equiv.) in toluene (800 ml) was heated under reflux with azeotropic removal of water for 2 h. The resulting clear solution was cooled to -70°C under argon and benzoyl chloride (27.9 ml, 3 equiv.) was added slowly with stirring maintaining the reaction temperature ≤ -60°C. The solution was then stirred and slowly allowed to warm to room temperature overnight, then it was concentrated to dryness. The residue was dissolved in acetonitrile (500 ml) and washed with petroleum ether (x3). The acetonitrile phase was concentrated to dryness, redissolved in toluene (600 ml), and washed with 2 M aqueous ammonium hydroxide. The resultant emulsion was filtered through celite, and then the organic phase was processed as usual to give 37 g of crude product. Chromatography afforded 29.9 g (75%) of a 4:1 mixture of the tribenzoates **6** and 7. Further chromatography (EtOAc/$CHCl_3$/Petroleum Ether 1:2:2) gave pure samples of each. For the 1,6,7-tribenzoate **6**: Accurate mass, calc. for $C_{29}H_{28}NO_7$ (MH^+) 502.1866, obs. 502.1865. ^{1}H n.m.r. δ 8.1-7.9 (6H, m, Ar), 7.6-7.3 (9H, m, Ar), 5.62 (1H,m, H-1), 5.52 (1H, t, J= 9.4 Hz, H-7), 5.38 (1H, dt, J= 9.9, 5.4 Hz, H-6), 3.87 (1H, t, J= 9.1 Hz, H-8), 3.60 (1H, dd, H-5), 3.45 (1H, s, OH), 3.35 (1H, dt, H-3), 2.54-2.12 (5H, m, H-2, 2', 3', 5', 8a). ^{13}C n.m.r. δ 167.6, 166.7, 165.8, 74.4, 72.0, 70.9, 68.4, 53.3, 51.8 and 31.2. For the 1,6,8-tribenzoate 7: accurate mass, calc. for $C_{29}H_{28}NO_7$ (MH^+) 502.1866, obs. 502.1880. ^{1}H n.m.r. ($CDCl_3$) δ 8.1-7.9 (6H, m, Ar), 7.6-7.3 (9H, m, Ar), 5.59 (1H, t, J=9.4 Hz, H-8), 5.52 (1H, m, H-1), 5.37 (1H, dt, J=5.3, 9.9 Hz, H-6), 3.97 (1H, t, J=9.3 Hz, H-7), 3.56 (1H, dd, H-5), 3.28 (1H, dd, H-3), 2.98 (1H, s, OH), 2.65 (1H, dd, J=5.0, 9.7 Hz, H-8a), 2.83 (1H, m, H-2), 2.38-2.23 (2H, m, H-3',5'), 2.03 (1H, m, H-2'). ^{13}C n.m.r. δ 166.8, 166.4, 166.2, 76.8, 73.8, 73.1, 72.3, 68.5, 53.3, 52.4, 32.6.

1,6,7-Tri-O-benzylcastanospermine ***8*** *and 1,2,7-tri-O-benzyl-1(R),2(S),7(S),8(R),8a(R) -tetrahydroxyoctahydroindolizidine* ***10***. A suspension of castanospermine (10 g, 0.053 mol.) and dibutyltin oxide (26.4 g, 2 equiv.) in toluene (1500 ml) was heated under reflux with azeotropic removal of water for 2 h. Benzyl bromide (50 ml, 8 equiv.) and tetrabutylammonium bromide (17 g, 1 equiv.) were added to the resulting solution and the mixture was heated under reflux under argon for 3 days. The solution was concentrated to dryness, and the residue was dissolved in acetonitrile (~800 ml) and then washed (x2) with petroleum ether. The acetonitrile solution was concentrated to dryness and the residue subjected to short column chromatography on silica gel. Elution first with ethyl acetate removed excess benzyl bromide and then with $CHCl_3$/EtOAc/MeOH (5:2:2 v/v/v) gave the products as their benzyl bromide salts along with tetrabutylammonium bromide. This mixture was dissolved in dry DMSO (100 ml), containing 1-propanethiol (9.0 ml, 0.1 mole) and to this lithium hydride (0.8 g, 0.1 mole) was added slowly with stirring. After stirring for 3 h, water (10 ml) was added carefully. Then the mixture was partitioned between toluene (500 ml) and water (1500 ml). The organic layer was washed again with water and then dried ($MgSO_4$) and concentrated. Chromatography of the residue (EtOAc/petroleum ether 1:4, 1:2, then 1:1 v/v) afforded first the castanospermine derivative **8** (12.3 g, 50%) followed by the rearranged material **10** (3.76 g, 15%). For 1,6,7-tri-*O*-benzylcastanospermine **8**: accurate mass, calc. for $C_{29}H_{34}NO_4$ (MH^+) 460.2488, obs. 460.2480. ^1H n.m.r. δ 7.38 - 7.23 (15H, m, Ar), 5.02 and 4.76 (1H each, d, AB, $PhCH_2$), 4.66 (2H, s, $PhCH_2$), 4.62 and 4.46 (1H each, d, AB, $PhCH_2$), 4.08 (1H, m, H-1), 3.90 (1H, t, J=9.2 Hz, H-8), 3.76 (1H, dt, J=5.1, 10.0 Hz, H-6), 3.40 - 3.31 (2H, m, H-5,7), 3.14 (1H, m, H-3), 2.20 - 1.92 (5H, m, H-2, 2′, 3′, 5′, 8a). ^{13}C n.m.r. δ 86.8, 79.0, 77.2, 75.3, 72.7, 71.5, 71.3, 69.3, 54.6, 52.3, 31.1. For the rearranged product **10** : accurate mass, calc. for $C_{29}H_{34}NO_4$ (MH^+) 460.2488, obs. 460.2482. ^1H n.m.r. δ 7.34 - 7.24 (15 H, m, Ar), 4.69-4.41 (6 H, m, $PhCH_2$), 3.95 - 3.90 (2H, m, H-1,2), 3.82 (1H, d, J=2.8 Hz, H-7), 3.63 (1H, dt, J=3.1, 9.5 Hz, H-8), 3.10 (1H, d, J=10.3 Hz, H-3), 2.72 - 2.68 (1H, m, H-5), 2.57-2.52 (2H, m, H-3′ and OH or H-8a), 2.39 - 2.31 (2H, m, H-5′ and OH or H-8a), 2.02 - 1.98 (1H, m, H-6), 1.79 - 1.67 (1H, m, H-6′). ^{13}C n.m.r. δ 89.3, 82.5, 75.8, 73.5, 72.1, 71.3, 71.2, 68.0, 57.9, 46.2, 27.3.

*1,2,7-Tri-O-benzoyl-1(R),2(S),7(S),8(R),8a(R)-tetrahydroxyoctahydroindolizidine **12**.*

A solution of 1,6,7-tri-*O*-benzoylcastanospermine **6** (1.7 g) in dry dichloromethane (40 ml) was stirred in an ice bath while diethylaminosulfur trifluoride (1.02 ml, 2.25 mol. equiv.) was added. After 1 h in the cold bath the solution was washed with aq sodium bicarbonate, dried ($MgSO_4$) and concentrated. Chromatography (EtOAc/$CHCl_3$/petroleum ether 1:2:2 v/v/v) of the residue afforded the title compound **12** (0.885 g, 52%). Accurate mass calc. for $C_{29}H_{28}NO_7$ (MH^+) 502.1866, obs. 502.1870. ^1H n.m.r. δ 8.1 (6H, m, Ar), 7.6 - 7.3 (9H, m, Ar), 5.62 - 5.50 (3H, m, H-1,2,7), 4.12 - 4.01 (1H, m, H-8), 3.27 (1H, d, H-3), 3.09 (2H, dd, H-3′, OH), 2.90 - 2.84 (1H, m, H-5), 2.77 (1H, dd, H-8a), 2.54 (1H, dt, H-5′) 2.11 - 1.97 (2H, m, H-6,6′). ^{13}C n.m.r. δ 82.0, 78.0, 71.9, 71.1, 67.6, 58.5, 46.1, 29.0.

*1,2,7,8-Tetra-O-acetyl-1(R),2(S),7(S),8(R),8a(R)-tetrahydroxyoctahydroindolizidine **16**. (A) From tribenzyl ether **10**.* A solution of tribenzyl ether **10** (0.5 g) in acetic acid (10 ml) was stirred with 20% $Pd(OH)_2$/C (0.2 g) in an atmosphere of hydrogen for 16 h. The solids and solvent were removed and the residue was stirred in pyridine/acetic anhydride overnight. Removal of the solvents and chromatography of the residue gave title compound **16** (0.25 g). Accurate mass, calc. for $C_{16}H_{24}NO_8$(MH^+) 358.1502, obs. 358.1502. ^1H n.m.r. δ 5.38 (1H, dd, J=2.9, 5.8 Hz, H-7), 5.15 (1H, dd, J=2.5, 7.6 Hz, H-1), 5.01 (1H, m, H-2), 4.90 (1H, dd, J=3.0, 10.1 Hz, H-8), 3.04 (1H, d, J=11.0 Hz, H-3), 2.86 - 2.76 (2H, m, H-3′,5), 2.59 (1H, dd, J=7.7, 10.1 Hz, H-8a), 2.40 (1H, dt, H-5′), 2.11, 2.09, 2.08, 1.94 (4 x 3H, s, OAc), 2.04 - 1.82 (2H, m, H-6,6′). ^{13}C n.m.r. δ 170.7, 170.0, 169.7, 169.3, 80.2, 77.1, 72.7, 67.6, 63.7, 58.6, 45.9, 28.8, 21.1, 21.0, 20.9, 20.7. *(B) From tribenzoate ester **12**.* A solution of tribenzoate **12** (70 mg) in methanol was adjusted to pH~11 with aqueous ammonium hydroxide and then allowed to stand at room temperature for 3 days. It was then concentrated to dryness, and the residue was partitioned between water and chloroform. The aqueous layer was evaporated and the residue was stirred in pyridine/acetic anhydride overnight. The solvents were removed and chromatography of the residue gave 45 mg of material identical by ^{1}H and ^{13}C n.m.r. spectroscopy with that described in procedure (A) above.

*1,6,8-Tri-O-benzoyl-7-O-methanesulfonylcastanospermine **18** and 1,6,7-tri-O-benzoyl-8-O-methanesulfonylcastanospermine **17**.* A solution of 5.0 g of the mixture of tribenzoates **6** and **7** described above, in pyridine (50 ml), was mixed with methanesulfonyl chloride (3.5 ml) and the solution was stored at room temperature overnight. Toluene was added and the solution was washed (x2) with water, dried ($MgSO_4$) and evaporated. Chromatography (EtOAc/$CHCl_3$/petroleum ether 1/2/4 v/v/v) gave first the 7-mesylate **18** (0.75 g). Accurate mass, calc. for $C_{30}H_{30}NO_9S$ (MH^+) 580.1641, obs. 580.1616. ^{1}H n.m.r. δ 8.14 - 7.89 (6H, m, Ar), 7.60 - 7.36 (9H, m, Ar), 5.84 (1H, t, H-8), 5.54 - 5.46 (2H, m, H-1,6), 5.14 (1H, t, H-7), 3.67 (1H, dd, H-5), 3.30 (1H, dd, H-3), 2.74 (3H, s, CH_3), 2.70 (1H, dd, H-8a), 2.54 (1H, m, H-2), 2.41 - 2.28 (2H, m, H-3',5'), 2.08 - 1.97 (1H, m, H-2'). ^{13}C n.m.r. δ 82.1, 72.6, 70.4, 68.6, 68.3, 53.0, 51.9, 38.9, 32.5. Further elution afforded the 8-mesylate **17** (3.8 g). Accurate mass, calc. for $C_{30}H_{30}NO_9S$ (MH^+) 580.1641, obs. 580.1642. ^{1}H n.m.r. δ 8.16 - 7.94 (6H, m, Ar), 7.62 - 7.35 (9H, m, Ar), 5.71 (1H, t, H-7), 5.61 (1H, m, H-1), 5.44 (1H, dt, H-6), 5.36 (1H, t, H-8), 3.66 (1H, dd, H-5), 3.37 - 3.30 (1H, m, H-3), 2.77 (3H, s, CH_3) 2.67 (1H, dd, H-8a), 2.62 - 2.51 (1H, m, H-2), 2.46 - 2.29 (2H, m, H-3',5'), 2.09 - 1.99 (1H, m, H-2'). ^{13}C n.m.r. δ 74.6, 74.4, 72.7, 71.1, 68.5, 52.9, 51.9, 38.8, 32.3.

*8-Azido-1,6,7-tri-O-benzoyl-8-deoxycastanospermine **19** and 8-azido-1,2,7-tri-O-benzoyl-1(R),2(S), 7(S),8(R),8a(R) - trihydroxyoctahydroindolizidine **20**.* A solution of 1,6,7-tri-*O*-benzoyl-8-*O*-methanesulfonylcastanospermine **17** (2.0 g) in hexamethylphosphoric triamide (30 ml) containing sodium azide (1.12 g, 5 equiv.) was heated at 80°C for 2 h. Toluene was added and the mixture was washed with water (x3), dried ($MgSO_4$) and evaporated. Chromatography (EtOAc/CH_2Cl_2/petroleum ether 1/15/15 v/v/v) gave first the castanospermine azide **19** (1.01 g), then the rearranged azide **20** (0.75 g). For **19**: accurate mass, calc. for $C_{29}H_{27}N_4O_6$ (MH^+) 527.1931, obs. 527.1890. ^{1}H n.m.r. δ 8.12 - 7.94 (6H, m, Ar), 7.63 - 7.35 (9H, m, Ar) 5.63 - 5.52 (2H, m, H-1,7), 5.45 (1H, dt, J=5.0, 9.8 Hz, H-6), 4.06 (1H, t, J=10.0 Hz, H-8), 3.63 (1H, dd, J=5.1, 10.5 Hz, H-5), 3.28 (1H, m, H-3), 2.60 (1H, m, H-2), 2.43 - 2.31 (3H, m, H-3',5',8a), 2.09 - 1.97 (1H, m, H-2'). ^{13}C n.m.r. δ 75.6, 73.5, 71.2, 68.8, 60.3, 53.0, 52.1, 32.5. For **20**: accurate mass, calc. for $C_{29}H_{27}N_4O_6$ (MH^+) 527.1931, obs. 527.1914. ^{1}H n.m.r. δ 8.14 - 8.10 (6H, m, Ar), 7.64 - 7.36 (9H, m, Ar), 5.72 - 5.65 (2H, m, H-1,7), 5.42 (1H, dd, J=2.7, 6.2 Hz, H-2), 3.47 (1H, dd, J=2.8, 10.2 Hz, H-8), 3.26 (1H, d, J=11.1 Hz, H-3), 3.12 - 3.03 (2H, m, H-3',8a), 2.89 (1H, dd, H-5), 2.53 (1H, t, H-5'), 2.19 - 1.97 (2H, m, H-6,6'). ^{13}C n.m.r. δ 81.3 (C-1), 77.6 (C-2), 70.3 (C-7), 63.6 (C-8a), 62.1 (C-8), 59.1 (C-3), 46.0 (C-5), 29.3 (C-6).

8-Amino-1,6,7-tri-O-benzoyl-8-deoxycastanospermine 21 and 8-amino-1,2,7-tri-O-benzoyl- 1(R),2(S),7(S),8(R),8a(R)-trihydroxyoctahydroindolizidine 22. The mesylate **17** (3.0 g) was treated with sodium azide in hexamethylphosphoric triamide and worked up as described above. The crude product was stirred in ethyl acetate/ethanol (~1:6 v/v 100 ml) with 20% $Pd(OH)_2/C$ (0.5 g) in a hydrogen atmosphere for 24 h. The solids and solvent were removed and chromatography (CH_2Cl_2/acetone 20/1 v/v) of the residue afforded first the castanospermine amine **21** (1.22 g) followed by the rearranged material **22** (0.85 g). For **21**: accurate mass, calc. for $C_{29}H_{29}N_2O_6$ (MH^+) 501.2026, obs. 501.2039. ^1H n.m.r. δ 8.12 - 7.91 (6H, m, Ar), 7.62 - 7.32 (9H, m, Ar), 5.68 (1H, m, H-1), 5.45 (1H, dt, J=5.0, 9.7 Hz, H-6), 5.36 (1H, t, J=9.5 Hz, H-7), 3.63 (1H, dd, J=4.8, 10.2 Hz, H-5), 3.34 (1H, t, J=9.5 Hz, H-8), 3.29 (1H, m, H-3), 2.57 - 2.47 (1H, m, H-2), 2.36 - 2.26 (3H, m, H-3′,5′,8a), 2.10 - 1.99 (1H, m, H-2′). ^{13}C n.m.r. δ 78.5, 73.6, 72.5, 71.5, 53.5, 52.1, 51.2, 32.0. For **22**: accurate mass, calc. for $C_{29}H_{29}N_2O_6$ (MH^+) 501.2026, obs. 501.2016. ^1H n.m.r. δ 8.12 - 8.05 (6H, m, Ar), 7.63 - 7.42 (9H, m, Ar), 5.67 (1H, dd, J=2.6, 7.7 Hz, H-1), 5.43 - 5.40 (2H, m, H-2, 7), 3.26 (1H, d, J=11.1 Hz, H-3), 3.18 (1H, dd, J=2.9, 9.8 Hz, H-8), 3.03 (1H, dd, H-3′), 2.89 (1H, dd, H-5), 2.63 (1H, dd, J=7.8, 9.8 Hz, H-8a), 2.49 (1H, dt, H-5′), 2.14 - 1.94 (2H, m, H-6,6′). ^{13}C n.m.r. δ 81.9, 78.4, 73.2, 68.6, 59.1, 55.0, 46.7, 29.7.

8-Amino-8-deoxycastanospermine 23. A solution of 8-amino-1,6,7-tri-*O*-benzoyl-8-deoxycastanospermine **21** (0.60 g) in methanol (20 ml) was adjusted to pH ~ 10 with methanolic sodium methoxide. The resulting solution was stored overnight at room temperature and then evaporated. Chromatography of the residue (CH_2Cl_2/MeOH/conc. aq NH_3 5/4/1 v/v/v) afforded title compound **23** (0.214 g). Accurate mass, calc. for $C_8H_{17}N_2O_3$ (MH^+) 189.1239, obs. 189.1237. ^1H n.m.r. (D_2O) (HOD δ 4.91) 4.50 (1H, m, H-1), 3.73 (1H, dt, J=5.0, 10.2 Hz, H-6), 3.43 (1H, t, J=9.7 Hz, H-7), 3.32 (1H, dd, J=5.1, 10.9 Hz, H-5), 3.22 - 3.08 (2H, m, H-3,8), 2.49 - 2.16 (4H, m, H-2,3′,5′,8a), 1.88 - 1.78 (1H, m, H-2′). ^{13}C n.m.r. (D_2O) δ 79.5 (C-7), 73.0 (C-6), 72.5 (C-8a), 72.0 (C-1), 57.9 (C-5), 54.2 (C-3), 53.7 (C-8), 36.0 (C-2).

8-Acetamido-8-deoxycastanospermine 24. A solution of 8-amino-1,6,7-tri-*O*-benzoyl-8-deoxycastanospermine **21** (0.56 g) in pyridine and acetic anhydride (10 ml, 1:1 v/v) was allowed to stand at room temperature for 3 h and then concentrated to dryness. A solution of the residue in methanol was adjusted to pH ~ 10-11 with methanolic sodium methoxide and left overnight at room temperature. The solution was evaporated and then chromatography (CH_2Cl_2/MeOH/conc. aq. NH_3 6/3/0.5 v/v/v) afforded material contaminated with benzoic acid. An aqueous solution of this was treated with base resin (Amberlyst A26, CO_3^{2-} form) in water and then filtered and evaporated to give title compound **24** (0.215 g). Accurate mass, calc. for $C_{10}H_{19}N_2O_4$ (MH^+) 231.1345, obs. 231.1333. ^1H n.m.r. (D_2O) (HOD δ 4.67) δ 4.03 (1H, s, H-1), 3.63 (1H, t, H-8), 3.53 (1H, dt, H-6), 3.28 (1H, t, H-7), 3.09 (1H, dd, H-5), 3.00 (1H, m, H-3), 2.20 - 1.94 (4H, m, H-2,3′,5′,8a), 1.90 (3H, s, OAc), 1.64 - 1.52 (1H, m, H-2′). ^{13}C n.m.r. (D_2O) δ 177.9 (C=O), 78.6 (C-7), 73.7 (C-8a), 73.0 (C-6), 72.2 (C-1), 57.5 (C-5), 54.2 (C-3), 52.9 (C-8), 33.8 (C-2), 24.6 (Ac).

8-Acetamido-1(R),2(S),7(S),8(R),8a(R)-trihydroxyoctahydroindolizidine 25. A solution of 8-amino-1,2,7-tri-*O*-benzoyl- 1(R),2(S),7(S),8(R),8a(R)-trihydroxyoctahydroindolizidine **22** (0.48 g) in pyridine/acetic anhydride (10 ml 1:1 v/v) was allowed to stand at room temperature for 4 h, and then was evaporated to dryness. A solution of the residue in methanol was adjusted to pH ~ 11 with sodium methoxide and allowed to stand at room temperature overnight. After evaporation, chromatography of the residue (CH_2Cl_2/MeOH 3:1) gave material contaminated with some benzoic acid. This was treated with base resin (Amberlyst A26 CO_3^{2-} form) in water, then filtered and evaporated to give title compound **25** (0.188 g). Accurate mass, calc. for $C_{10}H_{19}N_2O_4$ (MH^+) 231.1345, obs. 231.1356. ^1H n.m.r. (D_2O) (HOD δ 4.68) δ 3.92-3.89 (1H, m, H-2), 3.86 (1H, dd, H-7), 3.75 (1H, dd, H-8), 3.67 (1H, dd, H-1), 2.72 (1H, d, H-3), 2.61 (1H, dt, H-5), 2.54 (1H, dd, H-3′), 2.27 - 2.20 (1H, m, H-5′), 2.14 (1H, dd, H-8a), 1.87 (3H, s, Ac), 1.69 (2H, m, H-6,6′). ^{13}C n.m.r. (D_2O) δ 176.7 (C=O), 85.0 (C-1), 79.3 (C-2), 69.0 (C-7), 67.6 (C-8a), 62.3 (C-3), 56.2 (C-8), 48.4 (C-5), 33.2 (C-6), 24.8 (CH_3).

1,6,7-Tri-O-benzoyl-8-deoxycastanospermine 27. A solution of 1,6,7-tri-*O*-benzoylcastanospermine **6** (2.4 g) in dry toluene (80 ml) containing thiocarbonyldiimidazole (4 g) was heated at 80°C for 3 h. The solvent was removed and a chloroform solution of the residue was washed with 1M aq NaOH, water (x2), dried ($MgSO_4$) and evaporated. Chromatography gave 1,6,7-tri-*O*-benzoyl-8-*O*-imidazolethiocarbonylcastanospermine **26** (1.8 g). ^1H n.m.r. δ 8.12 - 7.84 (7H, m, Ar), 7.61 - 7.27 (10H, m, Ar), 6.94 (1H, s, Ar), 6.42 (1H, t, H-8), 5.82 (1H, t, H-7), 5.64 - 5.56 (2H, m, H-1,6), 3.71 (1H, dd), 3.39 (1H, t), 2.89 (1H, dd) 2.57 - 2.41 (3H, m), 2.12 - 2.03 (1H, m). ^{13}C n.m.r. δ 182.2, 165.9, 165.7, 165.6, 76.5, 75.4, 72.1, 70.6, 68.2, 53.0, 51.8, 32.1. This material was dissolved in toluene (60 ml), tributyltin hydride (1.5 equiv.) and a little azobisisobutyronitrile were added and the solution was heated at 90°C for 1 h. The toluene was removed, the residue dissolved in acetonitrile and this solution was washed with petroleum ether (x3), and then evaporated. Chromatography of the residue afforded title compound **27** (0.86 g, 36% overall). Accurate mass, calc. for $C_{29}H_{28}NO_6$ (MH^+) 486.1917, obs. 486.1922. ^1H n.m.r. δ 8.09 - 7.90 (6H, m, Ar), 7.58 - 7.28 (9H, m, Ar), 5.56 - 5.48 (2H, m, H-1,6), 5.37 (1H, dt, H-7), 3.65 (1H, dd, H-5), 3.25 (1H, t, H-3), 2.57 - 2.35 (3H, m, H-2,8,8a), 2.31 - 2.21 (2H, m, H-3′,5′), 2.12 - 1.89 (2H, m, H-2′,8′). ^{13}C n.m.r. δ 74.4, 73.6, 71.5, 65.3, 53.7, 51.9, 32.2, 29.1.

*8-Deoxycastanospermine **28**.* A solution of 1,6,7-tri-*O*-benzoyl-8-deoxycastanospermine **27** (0.60 g) in methanol (60 ml) containing conc. aq NH_4OH (10 ml) was heated at 50°C for 48 h, and then evaporated to dryness. Chromatography (CH_2Cl_2/EtOAc/MeOH 5:1:3 v/v/v) afforded title compound **28** (0.16 g). Accurate mass calc. for $C_8H_{16}NO_3$ (MH^+) 174.1130, obs. 174.1137. ^1H n.m.r. (D_2O) (HOD δ 4.57) δ 3.99 - 3.94 (1H, m, H-1), 3.31 - 3.22 (2H, m, H-6,7), 2.93 (1H, dd), 2.76 (1H, dt), 2.13 - 1.99 (1H, m), 1.92 - 1.83 (2H, m), 1.77 - 1.70 (2H, m), 1.45 - 1.34 (1H, m), 1.26 - 1.14 (1H, m). ^{13}C n.m.r. (D_2O) δ 76.1, 74.1, 73.7, 69.5, 58.1, 54.0, 35.6, 33.1.

*1,6,7-Tri-O-benzyl-8-deoxy-8-fluorocastanospermine **29** and 1,2,7-tri-O-benzyl-8-fluoro-1(R),2(S),7(S), 8(R),8a(R)-trihydroxyoctahydroindolizidine **30**.* A solution of either 1,6,7-tri-*O*-benzylcastanospermine **8** or 1,2,7-tri-*O*-benzyl-1(R),2(S),7(S),8(R),8a(R)-tetrahydroxyoctahydroindolizidine **10**, or a mixture of the two, in dry dichloromethane (15 ml per g) was stirred while diethylaminosulfur trifluoride (1.5 equiv.) was added. The solution was stirred for 2 days and then washed with 0.5 M aqueous sodium hydroxide, water, dried ($MgSO_4$) and concentrated. Chromatography (EtOAc/petroleum ether 1:4, 1:2 v/v) gave first the castanospermine derivative **29** (~16-20% yield) followed by the rearranged material **30** (~26 - 30% yield). For **29**: accurate mass, calc. for $C_{29}H_{33}NO_3F$ (MH^+) 462.2444, obs. 462.2455. ^{1}H n.m.r. δ 7.43 - 7.23 (15H, m, Ar), 4.97 - 4.50 (7H, m, $PhCH_2$, H-8), 4.07 (1H, m, H-1), 3.72 (1H, dt, J=5.1, 9.4 Hz, H-6), 3.60 (1H, dt, J=8.8 Hz, $J_{H,F}$ 15.3 Hz, H-7), 3.25 (1H, m, H-5), 3.15 (1H, dt, H-3), 2.33 - 1.91 (5H, m, H-2,2',3',5',8a). ^{13}C n.m.r. δ 90.3 ($J_{C,F}$ 176 Hz), 85.0 ($J_{C,F}$ 16.5 Hz), 77.9 ($J_{C,F}$ 10.5 Hz), 76.6, 74.9, 73.2, 71.4, 69.8 ($J_{C,F}$ 25.1 Hz), 54.4, 52.2, 31.0. For **30**: accurate mass, calc. for $C_{29}H_{33}NO_3F$ (MH^+) 462.2444, obs. 462.2456. ^{1}H n.m.r.

δ 7.41 - 7.24 (15H, m, Ar), 4.79 - 4.41 (7H, m, $PhCH_2$, H-8), 4.01 - 3.85 (3H, m, H-1,2,7), 3.06 (1H, d, H-3), 2.83 (1H, m, H-8a), 2.71 - 2.61 (2H, m, H-3',5), 2.47 (1H, dt, H-5'), 1.93 - 1.70 (2H, m, H-6,6'). ^{13}C n.m.r. δ 94.1 ($J_{C,F}$ 184 Hz), 88.3, 83.1, 73.7 ($J_{C,F}$ 16 Hz), 72.2, 71.8, 71.3, 65.5 ($J_{C,F}$ 25 Hz), 57.8, 45.8, 28.9 ($J_{C,F}$ 6 Hz).

8-Deoxy-8-fluorocastanospermine 32. A solution of 1,6,7-tri-*O*-benzyl-8-deoxy-8-fluorocastanospermine **29** (0.67 g) in ethanol (50 ml) containing conc. HCl (1 ml) was stirred with 20% $Pd(OH)_2/C$ (0.2 g) in a hydrogen atmosphere for 2 days. Removal of the solids and solvent followed by elution of the residue in water through a base resin (Amberlyst A26 OH^- form) column gave title compound **32** (0.203 g, 73%). Accurate mass, calc. for $C_8H_{15}NO_3F$ (MH^+) 192.1036, obs. 192.1027. ^{1}H n.m.r. (D_2O) (HOD δ 4.81) δ 4.45 (1H, dt, J=9.1 Hz, $J_{H,F}$ 50.8 Hz, H-8), 4.41 (1H, m, H-1), 3.65 - 3.53 (2H, m, H-6,7), 3.16 - 3.03 (2H, m, H-3,5), 2.39 - 2.03 (4H, m, H-2,3',5',8a), 1.87 - 1.64 (1H, m, H-2'). ^{13}C n.m.r. (D_2O) δ 92.6 ($J_{C,F}$ 174 Hz), 79.8 ($J_{C,F}$ 17.5 Hz), 72.5 ($J_{C,F}$ 9.9 Hz), 72.0, 71.9 ($J_{C,F}$ 24 Hz), 57.9, 54.3, 35.5.

8-Fluoro-1(R),2(S),7(S),8(R),8a(R)-trihydroxyoctahydroindolizidine 33. A solution of 1,2,7-tri-*O*-benzyl-8-fluoro-1(R),2(S),7(S),8(R) 8a(R)-trihydroxyoctahydroindolizidine **30** (0.7 g) in ethanol (30 ml) containing conc. HCl (1 ml) was stirred in the presence of 20% $Pd(OH)_2/C$ (0.3 g) in a hydrogen atmosphere for 24 h. The solids and solvent were removed and an aqueous solution of the residue was passed through a base resin (Amberlyst A26 OH^- form) column affording title compound **33** (0.25 g, 86%). Accurate mass, calc. for $C_8H_{15}NO_3F$ (MH^+) 192.1036, obs. 192.1038. ^{1}H n.m.r. (D_2O) (HOD δ 4.75) δ 4.47 (1H, ddd, $J_{H,F}$= 47.1 Hz, $J_{8,8a}$=9.8 Hz, $J_{7,8}$=3 Hz, H-8), 4.21 (1H, dd, J=3.1, 8.0 Hz, H-7), 4.04 (1H, m, H-2), 3.91 (1H, dd, J=3.2, 7.9 Hz, H-1), 2.81 (1H,d, J=11.0 Hz, H-3), 2.72 - 2.60 (2H, m, H-3',5), 2.48 (1H, m, H-8a), 2.28 (1H, m, H-5'), 1.85 - 1.64 (2H, m, H-6,6'). ^{13}C n.m.r. (D_2O) δ 96.1 ($J_{C,F}$ 177 Hz, C-8), 84.7 (C-1), 79.0 (C-2), 68.3 ($J_{C,F}$ 16.7 Hz, C-7), 67.2 ($J_{C,F}$ 24.0 Hz, H-8a), 62.3 (C-3), 47.8 (C-5), 32.0 ($J_{C,F}$ 6.3 Hz, C-6).

1,6,7-Tri-O-benzyl-8-C-cyano-8-deoxycastanospermine 35 and 1,2,7-tri-O-benzyl-8-C-cyano-1(R),2(S), 7(S),8(S),8a(R)-trihydroxyoctahydroindolizidine 36. A solution of either 1,6,7-tri-*O*-benzylcastanospermine **8** or 1,2,7-tri-*O*-benzyl-1(R),2(S),7(S),8(R),8a(R)-tetrahydroxyoctahydroindolizidine **10** or a mixture thereof, in dry dichloromethane (~10 ml per g) was treated with triethylamine (5 eq.) and methanesulfonyl chloride (2 eq.) until t.l.c. indicated complete conversion to the corresponding mesylate(s). The solution was washed (x2) with water and processed as usual. The residue, in dry dimethylsulfoxide (~10 ml per g) containing potassium cyanide (~7 eq.) was heated at 90°C for 1 h. Toluene (~30 ml per g) was added to the cooled solution and it was washed (x2) with water, dried ($MgSO_4$) and concentrated. Chromatography (EtOAc/petroleum ether 1:3, 1:2 v/v) gave first the castanospermine nitrile **35** (~18-22%) followed by the rearranged material **36** (~30-36%). For **35**: accurate mass, calc. for $C_{30}H_{33}N_2O_3$ (MH^+) 469.2491, obs. 469.2485. ^{1}H n.m.r. δ 7.44 - 7.25 (15H, m, Ar), 4.96, 4.89 (1H each, AB, $PhCH_2$), 4.68, 4.62 (1H each, AB, $PhCH_2$), 4.58, 4.44 (1H each, AB, $PhCH_2$), 4.10 (1H, m, H-1), 3.62 (2H, m, H-6,7), 3.29 (1H, dd, J=4.1, 11.0 Hz, H-5), 3.11 (1H, dt, H-3), 3.06 (1H, t, J 10.6 Hz, H-8), 2.25 - 1.93 (5H, m, H-2,2′,3′,5′,8a). ^{13}C n.m.r. δ 119.1 (CN), 81.8 (C-7), 78.9 (C-6), 77.2 (C-1), 75.8, 72.8, 71.5 (OCH_2Ar), 68.3 (C-8a), 54.2 (C-5), 52.2 (C-3), 33.7 (C-8), 30.4 (C-2). For **36**: accurate mass, calc. for $C_{30}H_{33}N_2O_3$ (MH^+) 469.2491, obs. 469.2479. ^{1}H n.m.r. δ 7.40 - 7.23 (15H, m, Ar), 4.69 - 4.39 (6H, m, $PhCH_2$), 3.97 (1H, s, H-7), 3.90 (1H, d, J=5.1 Hz, H-2), 3.81 (1H, d, J=4.5 Hz, H-1), 3.06 (1H, d, J=10.5 Hz, H-3), 2.86 - 2.70 (3H, m, H-5,8,8a), 2.55 (1H, dd, J=5.8, 10.5 Hz, H-3′), 2.47 (1H, dt, H-5′), 2.05 - 1.57 (2H, m, H-6,6′). ^{13}C n.m.r. δ 118.8 (CN), 89.0 (C-1), 81.4 (C-2), 71.7 (C-7), 72.5, 71.6, 71.5 ($PhCH_2$), 63.1 (C-8a), 57.6 (C-3), 45.9 (C-5), 37.4 (C-8), 27.1 (C-6).

*8-C-Aminomethyl 1,6,7-tri-O-benzyl-8-deoxycastanospermine **40**.* A solution of 1,6,7-tri-*O*-benzyl-8-*C*-cyano-8-deoxycastanospermine **35** (1.28 g) in dry dichloromethane (25 ml) was stirred at -70°C under argon while diisobutylaluminium hydride (1.22 ml, 2.5 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature, and then quenched carefully with ethanol, and poured onto water. The mixture was filtered through celite, and then the organic phase was processed normally. Chromatography (EtOAc/$CHCl_3$/MeOH 5:2:1 v/v/v) gave title compound **40** (1.18 g, 91%). Accurate mass, calc. for $C_{30}H_{37}N_2O_3$ (MH^+) 473.2804, obs. 473.2804. ^{1}H n.m.r. δ 7.38 - 7.19 (15H, m, Ar), 4.99, 4.69 (1H each, AB, $PhCH_2$), 4.66 (2H, s, $PhCH_2$), 4.58, 4.26 (1H each, AB, $PhCH_2$), 3.99 (1H, m, H-1), 3.81 (1H, dt, H-6), 3.44 - 3.35 (2H, m, H-5,7), 3.13 (1H, m, H-3), 2.87, 2.67 (1H each, dd AB, CH_2N), 2.12 - 1.83 (6H, m, H-2,2′,3′,5′,8,8a). ^{13}C n.m.r. δ 81.8 (C-7), 81.0 (C-6), 77.2 (C-1), 74.6, 72.3, 70.5 ($PhCH_2O$), 68.6 (C-8a), 54.7 (C-5), 52.6 (C-3), 41.8 (C-8), 40.0 (CH_2NH_2), 30.1 (C-2).

*1,6,7-Tri-O-benzyl-8-deoxy-8-C-hydroxymethylcastanospermine **38**.* Sodium hypophosphite (6.5 g) was added to a solution of 1,6,7-tri-*O*-benzyl-8-*C*-cyano-8-deoxycastanospermine **35** (2.6 g) in pyridine and acetic acid (100 ml, 1:1 v/v) and, when it had fully dissolved, 1,2-dianilinoethane (6.5 g) was added. The solution was stirred at room temperature while Raney nickel (4-5 spatulas) was added. After stirring overnight more Raney nickel was added and after a further 3-4 h t.l.c. examination indicated the starting nitrile had been consumed. The mixture was filtered, the solids washed with ethanol and the filtrate was partitioned between chloroform and water. The organic phase was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated. The residue was dissolved in dichloromethane/acetone 2:1 v/v (60 ml) and toluenesulfonic acid (22 g) was added. After 20 mins the mixture was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated. The residue was immediately dissolved in methanol (50 ml) and treated with sodium borohydride (1.2 g). After stirring overnight the mixture was partitioned between chloroform and water. The organic phase was dried ($MgSO_4$) and evaporated. Chromatography then afforded title compound **38** (0.51 g, 19%). Accurate mass, calc, for $C_{30}H_{36}NO_4$ (MH^+) 474.2644, obs. 474.2630. ^1H n.m.r. δ 7.35 - 7.24 (15H, m, Ar), 4.99, 4.70 (1H each, AB, $PhCH_2$), 4.67 (2H, s, $PhCH_2$), 4.58, 4.25 (1H each, AB, $PhCH_2$), 3.99 (1H, m, H-1), 3.82 (1H, dt, H-6), 3.67 (1H, dd, H-9), 3.57 (1H, dd, H-9′), 3.47 - 3.36 (2H, m, H-5,7), 3.15 (1H, m, H-3), 2.16 - 1.85 (6H, m, H-2,2′,3′,5′,8,8a). ^{13}C n.m.r. δ 81.5 (C-7), 80.8 (C-6), 77.3 (C-1), 74.7, 72.4, 70.5 ($PhCH_2$), 68.2 (C-8a), 61.3 (C-9), 54.7 (C-5), 52.5 (C-3), 41.9 (C-8), 30.1 (C-2).

1,6,7-Tri-O-benzyl-8-deoxy-8-C-fluoromethylcastanospermine 45. A solution of 1,6,7-tri-*O*-benzyl-8-deoxy-8-*C*-hydroxymethylcastanospermine **38** (0.40 g) in dry dichloromethane (10 ml) was cooled to 0°C and diethylaminosulfur trifluoride (0.22 ml) was added with stirring, then the solution was stirred at room temperature for 4 h and washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated. Chromatography (EtOAc/petroleum ether 1:2 v/v) of the residue gave title compound **45** (0.12 g, 30%). Accurate mass, calc. for $C_{30}H_{35}NO_3F$ (MH^+) 476.2601, obs. 476.2619. ^1H n.m.r. δ 7.34 - 7.18 (15H, m, Ar), 5.03 - 4.23 (7H, m, 3x $PhCH_2$, H-9,9′), 4.03 (1H, m, H-1), 3.79 (1H, dt, H-6), 3.55 (1H, t, H-7), 3.38 (1H, dd, H-5), 3.15 (1H, m, H-3), 2.19 (6H, m, H-2,2′,3′,5′,8,8a). ^{13}C n.m.r. δ 80.7 ($J_{C,F}$ 166 Hz, C-9), 80.6 (C-6), 79.9 ($J_{C,F}$ 2.5 Hz, C-7), 76.8 (C-1), 75.3, 72.3, 70.3 ($PhCH_2$), 66.8 (C-8a), 54.6 (C-5), 52.4 (C-3), 41.2 ($J_{C,F}$ 17.5 Hz, C-8), 30.1 (C-2).

1,6,7-Tri-O-benzyl-8-O-pivaloylcastanospermine 46. A solution of 1,6,7-tri-*O*-benzylcastanospermine **8** (1.6 g) in pyridine (20 ml) and pivaloyl chloride (2.5 ml) was heated at 70°C for 30 h. The solution was coevaporated with toluene, the residue dissolved in chloroform, washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated. Chromatography afforded the title compound **46** (1.2 g, 63%). Accurate mass calc. for $C_{34}H_{42}NO_5$ (MH^+) 544.3063, obs. 544.3046. ^1H n.m.r. δ 7.35 - 7.21 (15H, m, Ar), 5.49 (1H, t, H-8), 4.91, 4.60 (1H each, AB, $PhCH_2$), 4.62 (2H, s, $PhCH_2$), 4.43, 4.32 (1H, each, AB, $PhCH_2$), 3.90 (1H, m, H-1), 3.84 (1H, dt, H-6), 3.49 (1H, t, H-7), 3.32 (1H, dd, H-5), 3.18 (1H, dt, H-3), 2.22 - 1.97 (5H, m, H-2,2′,3′,5′,8a), 1.11 (9H, s, $C(CH_3)_3$). ^{13}C n.m.r. δ 176.1, 85.5, 78.5, 76.8, 74.5, 72.9, 71.2, 70.1, 69.2, 54.7, 52.3, 38.7, 30.3, 27.1.

8-O-Pivaloylcastanospermine 47. A solution of 1,6,7-tri-*O*-benzyl-8-*O*-pivaloylcastanospermine **46** (1.2 g) in acetic acid (30 ml) was shaken with 20% $Pd(OH)_2/C$ (0.8 g) under hydrogen at 45 psi for 24 h. The solids and solvent were removed and chromatography of the residue ($CHCl_3$/EtOAc/MeOH 5:2:1 v/v/v) afforded title compound **47** (0.45 g, 74%). Accurate mass, calc. for $C_{13}H_{24}NO_5$ (MH^+) 274.1654, obs. 274.1655. ^1H n.m.r. δ 4.81 (1H, t, H-8), 4.36 (3H, s, OH), 4.01 (1H, bs, H-1), 3.80 (1H, dt, H-6), 3.52 (1H, t, H-7), 3.27 - 3.18 (2H, m, H-3,5), 2.19 - 1.83 (5H, m, H-2,2′,3′,5′,8a), 1.23 (9H, s, $C(CH_3)_3$). ^{13}C n.m.r. δ 180.3, 77.5, 71.9, 71.0, 70.6, 69.8, 55.6, 51.9, 39.2, 32.2, 27.1.

1,6,7-Tri-O-benzyl-8-O-methylcastanospermine 48 and 1,2,7-tri-O-benzyl-8-O-methyl-1(R),2(S),7(S),8(R),8a(R)-tetrahydroxyoctahydroindolizidine 49. Castanospermine (2 g) was benzylated as described for the preparation of **8** and **10** above, but the product, prior to dequaternisation, was dissolved in dry DMSO (20 ml) and stirred with sodium hydride (80%, 0.8 g) and methyl iodide (2.0 ml) overnight. 1-Propanethiol (3.8 ml) was added followed carefully by sodium hydride (80%, 1.2 g). The mixture was stirred at room temperature overnight, carefully quenched with water, and then partitioned between chloroform and water. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. Chromatography of the residue (EtOAc/petroleum ether 1:6, 1:4, 1:2 v/v) afforded first the castanospermine methyl ether **48** (2.2 g, 44%) followed by the rearranged material **49** (1.53 g, 30%). For the castanospermine derivative **48**: accurate mass, calc. for $C_{30}H_{36}NO_4$ (MH^+) 474.2644, obs. 474.2635. ^1H n.m.r. δ 7.40 - 7.22 (15H, m, Ar), 4.94 and 4.81 (1H each, AB, $PhCH_2$), 4.65 (2H, AB, $PhCH_2$), 4.59 and 4.38 (1H each, AB, $PhCH_2$), 4.10 (1H, m, H-1), 3.68 (1H, m, H-6), 3.62 (1H, t, J=9.0 Hz, H-7 or H-8), 3.54 (3H, s, OCH_3), 3.43 (1H, t, J= 9.0 Hz, H-7 or H-8), 3.27 (1H, dd, J=4.8, 10.4 Hz, H-5), 3.15 (1H, dt, H-3), 2.18 - 1.82 (5H, m, H-2,2',3',5',8a). ^{13}C n.m.r. δ 87.6, 78.9, 78.5, 77.3, 75.4, 72.8, 71.6, 70.5, 60.3, 54.5, 52.4, 30.0. For the rearranged product **49**: ^1H n.m.r. δ 7.40 - 7.23 (15H, m, Ar), 4.73 - 4.39 (6H, m, $PhCH_2$), 3.97 (1H, m, H-7), 3.92 and 3.86 (2H, d, H-1,2), 3.36 (3H, s, OCH_3), 3.19 (1H, dd, J=2.6, 9.8 Hz, H-8), 3.04 (1H, d, J=10.2 Hz, H-3), 2.72 - 2.60 (3H, m, H-3',5,8a), 2.50 (1H, dt, H-5'), 1.94 - 1.84 (1H, m, H-6), 1.71 - 1.60 (1H, m, H-6'). ^{13}C n.m.r. δ 88.2, 83.1, 83.0, 71.5, 71.2, 71.2, 70.8, 66.0, 57.5, 56.6, 45.9, 27.8.

8-O-Methylcastanospermine ***50***. A solution of 1,6,7-tri-*O*-benzyl-8-*O*-methylcastanospermine **48** (2.2 g) in acetic acid (50 ml) was shaken with 20% $Pd(OH)_2/C$ (0.5 g) under hydrogen at 40 psi for 2 days. The solids and solvent were removed and the residue was dissolved in water and eluted through a base resin (Amberlyst A-26 OH^- form) column. The eluate was concentrated to dryness affording title compound **50** (0.80 g, 85%). Accurate mass, calc. for $C_9H_{18}NO_4$ (MH^+) 204.1236, obs. 204.1234. ^1H n.m.r. (D_2O) (HOD δ 4.89) δ 4.45 (1H, m, H-1), 3.73 - 3.63 (1H, m, H-6), 3.66 (3H, s, OCH_3), 3.50 - 3.41 (2H, m, H-7,8), 3.22 (1H, dd, J=5.1, 10.8 Hz, H-5), 3.14 (1H, dt, J=2.0, 9.3 Hz, H-3), 2.44 - 1.75 (5H, m, H-2,2',3',5',8a). ^{13}C n.m.r. (D_2O) δ 81.3, 81.2, 73.2, 72.8, 72.4, 62.1, 58.0, 54.1, 35.9.

8-O-Methyl-1(R),2(S),7(S),8(R),8a(R)-tetrahydroxyoctahydroindolizidine ***51***. A solution of tribenzyl ether **49** (1.5 g) in acetic acid (30 ml) was shaken with 20% $Pd(OH)_2/C$ (0.5 g) under hydrogen at 40 psi for 3 days. The solids and solvent were removed and the residue was dissolved in water and eluted through a base resin (Amberlyst A 26 OH^- form) column. Concentration of the eluant afforded 0.75 g of material which was further purified from a minor contaminant by chromatography (EtOAc/MeOH/$CHCl_3$ 1:2:5 v/v/v) to give title compound **51**. Accurate mass, calc. for $C_9H_{18}NO_4$ (MH^+) 204.1236, obs. 204.1241. ^1H n.m.r. (D_2O) (HOD δ 4.70) δ 4.20 (1H, m, H-7), 3.92 (1H, m, H-2), 3.77 (1H, dd, J=2.9, 7.8 Hz, H-1), 3.26 (3H, s, OCH_3), 3.17 (1H, dd, J=2.6, 10.1 Hz, H-8), 2.70 (1H, d, J=11.0 Hz, H-3), 2.58 - 2.50 (2H, m, H-3',5), 2.24 - 2.11 (2H, m, H-5',8a), 1.75 - 1.53 (2H, m, H-6,6'). ^{13}C n.m.r. (D_2O) δ 85.1, 84.8, 79.0, 68.1, 65.7, 62.2, 58.4, 48.2, 32.1.

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