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Keywords

Synthesis, castanospermine

Disciplines

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Synthesis of Castanospermine

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Dedication: This paper is dedicated to E. J. Corey in the year of his 80th birthday.

Abstract: The diastereoselective synthesis of castanospermine is described in 11 synthetic steps from L-xylose. The borono-Mannich reaction between L-xylose, allylamine and (*E*)-styrene boronic acid gives a tetrahydroxy amine with the desired configurations for C-6, C-7, C-8 and C-8a in the target molecule. A novel pyrrolo[1,2-*c*]oxazol-3-one precursor was employed to allow for the control of π -facial diastereoselectivity in an osmium(VIII)-catalysed *syn*-dihydroxylation (DH) reaction. A regioselective ring-opening of the cyclic sulfate derivative of the resulting diol then secured the C-1 hydroxyl group of castanospermine with the correct configuration. A Mitsunobu cyclization then provided di-*O*-benzyl castanospermine and ultimately the final target alkaloid.

1. Introduction

The indolizidine alkaloid castanospermine **1** was first isolated from the seeds of *Castanospermum australe*¹ and then from the dry pods of *Alexa leiopetala*.² Castanospermine is a potent inhibitor of several glucosidases³ and has potential for the treatment of viral infections,⁴ cancers,⁵ and diabetes.⁶ In addition it shows anti-inflammatory⁷ and immunosuppressant⁸ properties. Recent *in vitro* studies have demonstrated that **1** was able to prevent mortality in mice infected with dengue virus.⁹ Because of its unique structure and biological activities many syntheses of castanospermine have been reported.¹⁰ As part of our program concerned with the synthesis of

polyhydroxylated indolizidine and pyrrolizidine alkaloids¹¹⁻¹⁹ we report here a 11-step synthesis of castanospermine from L-xylose. This synthesis demonstrates the versatility and flexibility of our earlier synthetic strategy for preparing polyhydroxyindolizidines.¹⁷

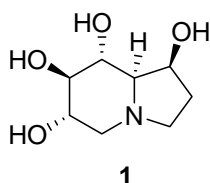
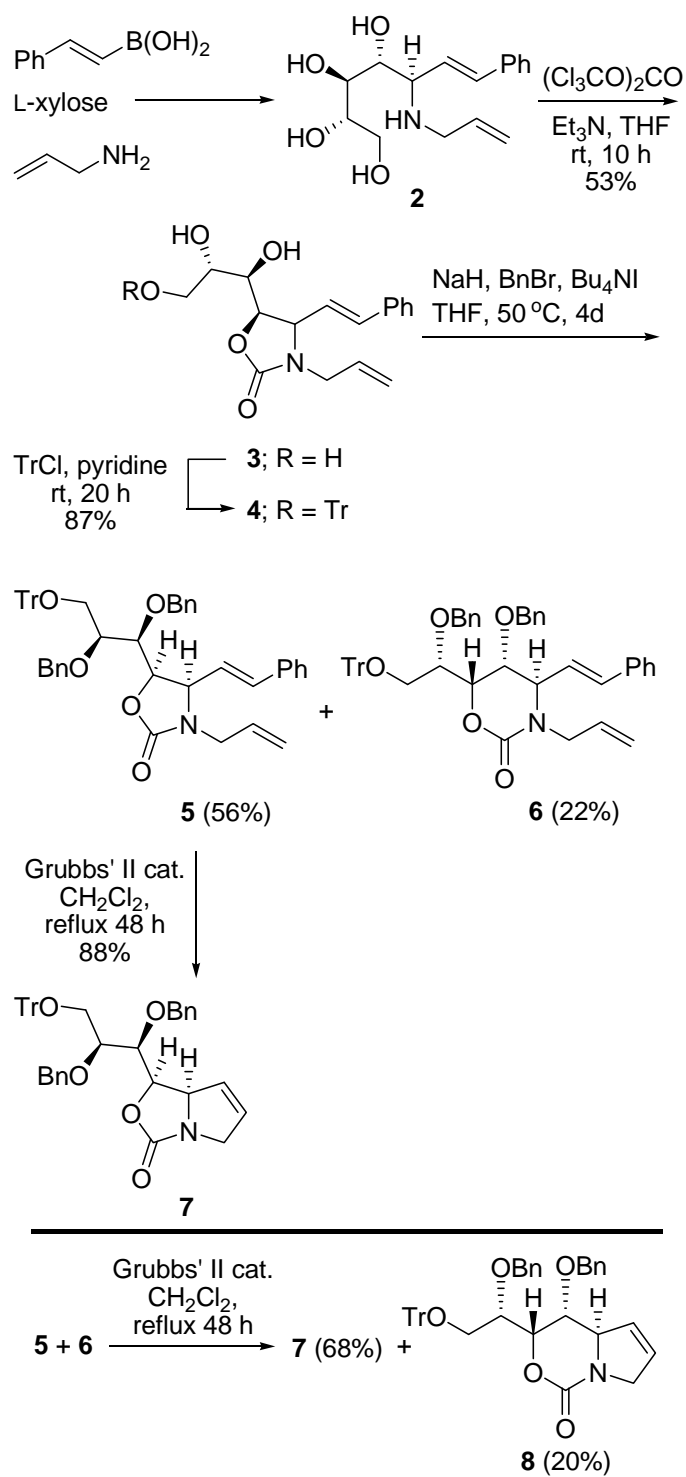


Figure 1. Structure of castanospermine (**1**).

2. Results and Discussion

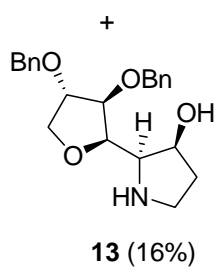
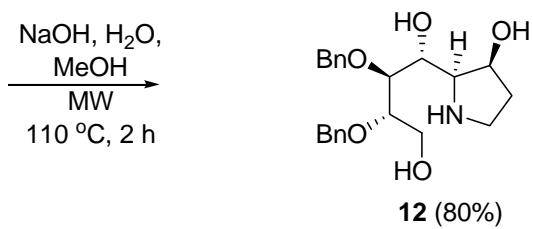
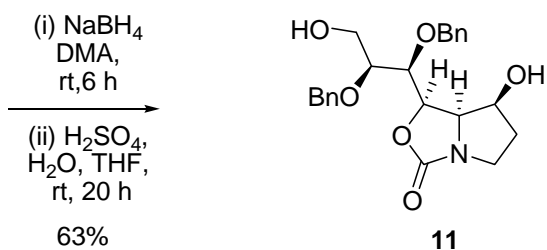
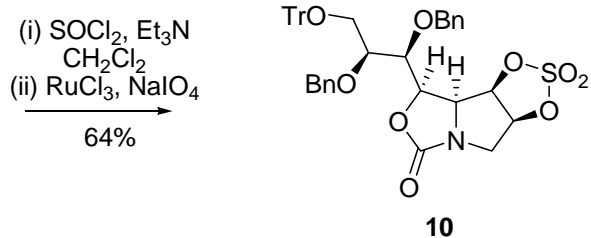
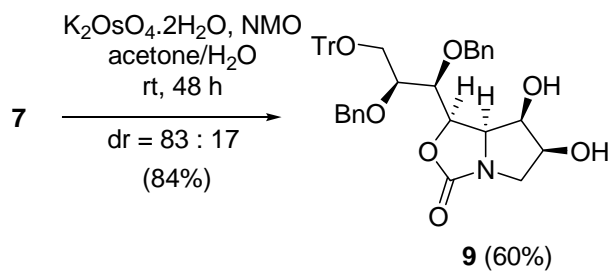
The known amino-tetraol **2**,¹⁷ obtained from the borono-Mannich reaction of L-xylose, allylamine and (*E*)-styrene boronic acid, was converted to oxazolidin-2-one **3** upon treatment with triphosgene under basic conditions (Scheme 1).^{13,14} The triol **4** was readily converted to its *O*-trityl derivative **4** in 87% yield under standard conditions.¹⁷ Under basic *O*-benzylation reaction conditions¹⁷ compound **4** gave a mixture of the corresponding di-*O*-benzyl-oxazolidin-2-one **5** and the oxazin-2-one **6** (Scheme 1). These could be separated by column chromatography to provide pure samples of **5** and **6** in yields of 56% and 22%, respectively, however this separation was difficult. Treatment of **5** with Grubbs' second generation ruthenium catalyst¹⁹ gave the pyrrolo[1,2-*c*]oxazol-3-one **7** in 88% yield. Alternatively, **7** could be more readily obtained by treating a mixture of **5** and **6** with Grubbs' second generation ruthenium catalyst followed by a relatively easier separation of **7** (68%) from the pyrrolo[1,2-*c*]oxazin-1-one **8** (20%) (Scheme 1).

Scheme 1



Based on our previous work,^{13,14,19} and that of Parsons,^{20,21} we expected that the *syn*-dihydroxylation (DH) of **7** would furnish the corresponding diol with the desired stereochemistry for the synthesis of the target alkaloid. In the event, the osmium(VIII)-catalysed *syn*-DH of **7** furnished the desired diol **9** accompanied by 17% of its diastereomeric diol in 84% yield after purification of the crude reaction mixture by column chromatography (Scheme 2). Separation of this mixture by further column chromatography gave diastereomerically pure **9** in 60% yield and 6,7-di-*epi*-**9** in 16% yield. The diol **9** was then converted to the cyclic sulfate **10** in 64% overall yield by first treatment with thionyl chloride under basic conditions to give the corresponding cyclic sulfite followed by oxidation at sulfur with catalytic ruthenium tetroxide (RuCl₃, NaIO₄).^{13,22} Regioselective reductive ring-opening of **10** with sodium borohydride^{10(f)} in dimethylacetamide (DMA) at rt for 6 h followed by acid hydrolysis of the resulting adduct gave the diol **11** in 63% yield in which the *O*-trityl group had also been cleaved (Scheme 2). Base catalysed hydrolysis of the oxazolidinone ring of **11** under microwave irradiation conditions gave the pyrrolidine **12** in 80% yield which was readily separated from the unexpected cyclized product, the furan derivative **13** (16% yield). **We have not unequivocally proved the structure of 13.** However this compound is also produced as a byproduct from the Mitsunobu reaction of **12** in Scheme 3. The most likely mechanism for the formation of **13** in the latter reaction is shown in Scheme 3 via initial activation of the primary hydroxyl. We therefore speculate that **13** arises from **11** (Scheme 2) via cyclization of the incipient alkoxide ion that is generated from collapse of the initial tetrahedral intermediate formed from addition of hydroxide ion to the carbonyl group of the oxazolidinone moiety of **11**. This incipient alkoxide intermediate then attacks the carbon of the terminal methylene of the side chain to displace hydroxide ion and give the furan ring.

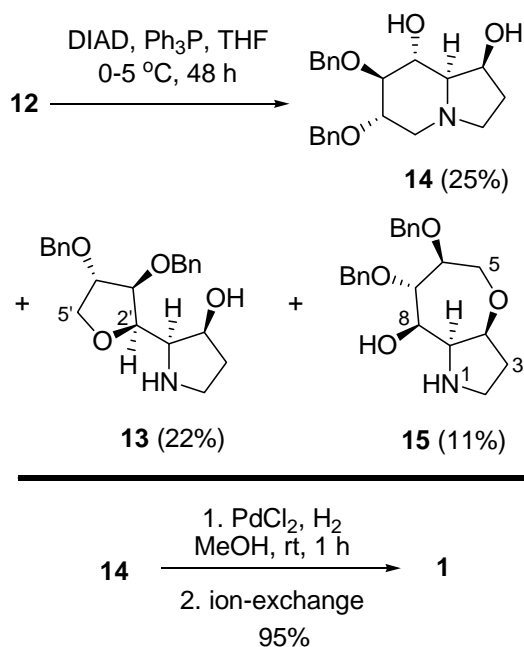
Scheme 2



Attempts to cyclize the amino-triol **12** under Appel cyclization reaction conditions ($\text{Ph}_3\text{P}/\text{CBr}_4/\text{Et}_3\text{N}$)²³ were unsuccessful and a complex mixture of products resulted. Treatment of **12** under Mitsunobu reaction conditions²⁴ produced the desired indolizidine product **14** in 25% yield along with the furan **13**²⁵ (22% yield) and the oxepino[3,2-*b*]pyrrole **15** (11% yield) (Scheme 3). These three isomeric compounds were readily distinguished by ^{13}C and HMBC NMR experiments. The structure of the indolizidine **14** was clear from the relatively upfield ^{13}C NMR methylene resonances at δ 54.2 (C-5) and 52.0 (C-2) for the methylenes directly attached to nitrogen. While the downfield methylene resonances at δ 72.0 (C-5') and δ 72.2 (C-5) in **13** and **15**, respectively were consistent with methylenes directly attached to oxygen in a ring system. HMBC NMR experiments on **13** demonstrated a 3-bond correlation between C-2' and H-5', such a correlation between the analogous carbon (C-8) and proton (H-5) in **15** would not be expected as this would represent a 4-bond correlation.

Debenzylation of **14** under hydrogenolysis conditions using PdCl_2/H_2 ²⁶ gave castanospermine **1** in 95% yield after ion-exchange chromatography (Scheme 3). The ^1H and ^{13}C NMR spectral data of this compound matched very closely to that reported in the literature.¹ The optical rotation of this compound $[\alpha]_{\text{D}}^{27} + 82$ (*c* 1.2, H_2O) also agreed with that reported (lit.¹ $[\alpha]_{\text{D}}^{24} + 79.7$ (*c* 0.93, H_2O)). This sample was also identical to an authentic sample by TLC analysis.²⁷

Scheme 3



3. Conclusions

In conclusion we have successfully developed a diastereoselective synthesis of castanospermine in 11 synthetic steps from L-xylose using the borono-Mannich reaction to give a tetrahydroxy amine with the desired configurations for C-6, C-7, C-8 and C-8a in the target molecule. A novel pyrrolo[1,2-*c*]oxazol-3-one precursor was employed to allow for the control of π -facial diastereoselectivity in an osmium(VIII)-catalysed *syn*-dihydroxylation (DH) reaction. A regioselective ring-opening of the cyclic sulfate derivative of the resulting diol then secured the C-1 hydroxyl group of castanospermine with the correct configuration. A Mitsunobu cyclization then provided di-*O*-benzyl castanospermine and ultimately the final target alkaloid. This synthesis further demonstrates the versatility and flexibility of our earlier synthetic strategy for preparing polyhydroxyindolizidines.¹⁷

4. Experimental

General methods were as described previously.^{12,13} All ¹H NMR spectra were performed at 500 MHz and all ¹³C NMR (DEPT) spectra at 125 MHz in CDCl₃ solution, unless otherwise noted. NMR assignments are based on COSY, DEPT and HSQC NMR experiments and sometimes HMBC and NOESY experiments. IR spectra were determined as neat samples. Petrol refers to petroleum spirit bp 40-60 °C.

(4*R*,5*R*)-3-Allyl-5-((1*R*,2*S*)-1,2,3-trihydroxypropyl)-4-((*E*)-2-phenyl-vinyl)-1,3-oxazolidin-2-one (3) and its 1,3-dioxolan-2-onyl derivative, (4*R*,5*R*)-3-allyl-5-(((4*S*)-1,3-dioxolan-2-onyl)-hydroxymethyl)-4-((*Z*)-2-phenylvinyl)-1,3-oxazolidin-2-one.

To a solution of the amino alcohol **2**¹⁷ (4.560 g, 15.56 mmol) in dry THF (400 mL) was added triethylamine (4.3 mL, 31.13 mmol) and then triphosgene (1.390 g, 4.68 mmol). The mixture was stirred at rt for 10 h, followed by the evaporation of all volatiles *in vacuo*. The residue was suspended in water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried (MgSO₄) and filtered then concentrated *in vacuo* to give a yellow solid. Chromatography of the crude product and eluting with 90-100% EtOAc/petrol and then 2% MeOH/EtOAc gave compound **3** as a white crystalline solid (2.65 g, 53%, *R*_f = 0.20, 2% MeOH/EtOAc). [α]_D²⁷ -10 (*c* 4.5, MeOH). Mp

141 °C. IR $\nu_{\max}/\text{cm}^{-1}$ 3550, 2950, 2914, 1737, 1447, 1094, 1041. MS (ESI+) m/z 320 ($\text{M}+\text{H}^+$), 100%. ^1H NMR (CD_3OD) δ 3.57 (1H, dd, $J = 11.3, 6.3$ Hz, $\text{H3}'$), 3.60 (1H, app. ddt, $J = 15.7, 6.7, 1.3$ Hz, $\text{H1}''''$), 3.65 (1H, dd, $J = 11.3, 5.3$ Hz, $\text{H3}'$), 3.73 (1H, m, $\text{H2}'$), 3.83 (1H, app. t, $J = 4.3$ Hz, $\text{H1}'$), 4.01 (1H, app. ddt, $J = 15.7, 4.7, 1.7$ Hz, $\text{H1}''''$), 4.61 (1H, app. t, $J = 9.0$ Hz, H4), 4.83 (1H, dd, $J = 8.5, 4.0$ Hz, H5), 5.20 (1H, dd, $J = 10.0, 1.5$ Hz, $\text{H3}''''$), 5.22 (1H, dd, $J = 17.5, 1.0$ Hz, $\text{H3}''''$), 5.79 (1H, m, $\text{H2}''''$), 6.38 (1H, dd, $J = 16.0, 9.5$ Hz, $\text{H1}''$), 6.70 (1H, d, $J = 16.0$ Hz, $\text{H2}''$), 7.36 (5H, m, Ar-H). ^{13}C NMR (CD_3OD) δ 45.5 (CH_2), 62.6 (CH), 64.1 (CH_2), 70.9 (CH), 73.3 (CH), 78.9 (CH), 118.3 (CH), 124.2 (CH), 127.9 ($2\times\text{Ar-CH}$), 129.4 (Ar-CH), 129.7 ($2\times\text{Ar-CH}$), 133.4 (CH), 137.2 (C), 138.5 (CH), 159.8 (CO).

(4R,5R)-3-Allyl-5-((1R,2S)-1,2-dihydroxy-3-(triphenylmethoxy)-propyl)-4-((E)-2-phenylvinyl)-1,3-oxazolidin-2-one (4).

To a solution of oxazolidinone **3** (2.42 g, 7.59 mmol) in anhydrous pyridine (40 mL) was added trityl chloride (3.17 g, 11.38 mmol). The mixture was stirred for 20 h at rt. The reaction was quenched with water (60 mL) then extracted with diethyl ether (3 x 80 mL). The combined organic phases were washed with saturated CuSO_4 (3 x 90 mL) and brine (90 mL), dried (MgSO_4) and evaporated to give a yellow oil that was purified by column chromatography (30-50% EtOAc/petrol) to give compound **4** as a white foamy solid (3.68 g, 87%, $R_f = 0.20$, 30% EtOAc/petrol). $[\alpha]_D^{27} -18$ (c 4.4, CHCl_3). IR $\nu_{\max}/\text{cm}^{-1}$ 3401, 3053, 3027, 2914, 1731, 1448, 1070. MS (ESI+) m/z 579 ($\text{M}+\text{NH}_4^+$, 100%) ; HRMS (ESI+) calcd for $\text{C}_{36}\text{H}_{35}\text{NO}_5\text{Na}$ ($\text{M}+\text{Na}^+$) 584.2413, found 584.2419. ^1H NMR δ 2.57 (1H, br.d, $J = 5.0$ Hz, $\text{OH1}'$), 2.82 (1H, br.d, $J = 5.5$ Hz, $\text{OH2}'$), 3.18 (1H, dd, $J = 10.0, 5.5$ Hz, $\text{H3}'$), 3.31 (1H, dd, $J = 9.5, 5.0$ Hz, $\text{H3}'$), 3.54 (1H, dd, $J = 15.5, 7.5$ Hz, $\text{H1}''''$), 3.90 (1H, br. t, $J = 4.0$ Hz, $\text{H2}'$), 3.96 (1H, br. d, $J = 3.5$ Hz, $\text{H1}'$), 4.11 (1H, dd, $J = 15.8, 6.5$ Hz, $\text{H1}''''$), 4.46 (1H, app. t, $J = 9.3$ Hz, H4), 4.55 (1H, dd, $J = 8.8, 3.8$ Hz, H5), 5.18 (1H, dd, $J = 17.3, 1.0$ Hz, $\text{H3}''''$), 5.21 (1H, dd, $J = 10.3, <1$ Hz, $\text{H3}''''$), 5.74 (1H, m, $\text{H2}''''$), 6.32 (1H, dd, $J = 16.0, 9.5$ Hz, $\text{H1}''$), 6.61 (1H, d, $J = 15.5$ Hz, $\text{H2}''$),

7.39-7.19 (20H, m, Ar). ^{13}C NMR δ 44.8 (CH_2), 61.1 (CH), 64.4 (CH_2), 69.9 (CH), 71.0 (CH), 77.3 (CH), 87.2 (C), 118.7 (CH), 123.0 (CH), 127.1-129.0 ($20\times\text{Ar-CH}$), 132.1 (CH), 135.6 (Ar-C), 137.6 (CH), 143.7 (Ar-C), 157.2 (CO).

(4R,5R)-3-Allyl-5-((1S,2S)-1,2-bis(benzyloxy)-3-(triphenylmethoxy)-propyl)-4-((E)-2-phenylvinyl)-1,3-oxazolidin-2-one (5), and (4R,5R,6S)-3-allyl-5-(benzyloxy)-6-((S)-1-(benzyloxy)-2-(triphenylmethoxy)-ethyl)-4-((E)-2-phenylvinyl)-1,3-oxazin-2-one (6).

To a solution of **4** (4.403 g, 7.85 mmol) in dry THF (50 mL) was added 40% NaH in mineral oil (1.20 g, 19.62 mmol). After H_2 evolution had ceased (15 min), benzyl bromide (7.5 mL, 62.79 mmol) and tetrabutylammonium iodide (444 mg, 1.18 mmol) were added. The mixture was stirred for 24 h at rt, then treated with methanol (10 mL) and triethylamine (6 mL) and stirred for 15 min. All volatiles were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 , filtered through a pad of celite, followed by further washings of the solids with CH_2Cl_2 . The filtrate was washed with water and brine and then dried (MgSO_4) and concentrated to give a yellow oil. The residue was purified by column chromatography (20-40% EtOAc/petrol) to yield two compounds, **5** as a yellow oil (3.258 g, 56%) and **6** as a yellow oil (1.299 g, 22%). Because of the similar polarity of the products (R_f of **5** = 0.60 and R_f of **6** = 0.55 in 40% EtOAc/petrol), they were used in the subsequent RCM reaction step without separation.

5: $[\alpha]_{\text{D}}^{26} +52$ (*c* 3.2, CHCl_3). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3058, 3027, 2945, 2873, 1752, 1450, 1070. MS (ESI+) *m/z* 764 ($\text{M} + \text{Na}^+$, 85%), HRMS (ESI+) calcd for $\text{C}_{50}\text{H}_{47}\text{NO}_5\text{Na}$ ($\text{M} + \text{Na}^+$) 764.3351, found 764.3378. ^1H NMR (300 MHz) δ 3.32 (1H, dd, $J = 16.0, 7.5$ Hz, $\text{H1}''''$), 3.39 (1H, dd, $J = 9.5, 5.0$ Hz, $\text{H3}'$), 3.44 (1H, dd, $J = 10.0, 5.0$ Hz, $\text{H3}'$), 3.58 (1H, app. t, $J = 8.0$ Hz, H4), 3.75 (1H, m, $\text{H2}'$), 4.01 (1H, $J =$ dd, 7.5, 3.3 Hz, $\text{H1}'$), 4.08 (1H, app. dd, $J = 16.0, 4.5$ Hz, $\text{H1}''''$), 4.13 (1H, d, $J = 12.0$ Hz, CH_2Ph), 4.60 (1H, d, $J = 11.4$ Hz, CH_2Ph), 4.65 (1H, d, $J = 12.0$ Hz, CH_2Ph), 4.79 (1H, app. t, $J = 7.4$ Hz, H5), 4.85 (1H, d, $J = 11.1$ Hz, CH_2Ph), 5.06 (1H, d, $J = 17.0$ Hz, $\text{H3}''''$), 5.15 (1H, d, $J = 10.0$ Hz, $\text{H3}''''$), 5.63

(1H, m, H2'''), 5.93 (1H, d, $J = 15.5$ Hz, H2''), 5.99 (1H, dd, $J = 16.0, 9.0$ Hz, H1''), 7.35-7.09 (30H, m, Ar). ^{13}C NMR δ 43.8 (CH₂), 59.4 (CH), 60.6 (CH₂), 70.7 (CH₂), 74.3 (CH₂), 74.4 (CH), 76.6 (CH), 77.2 (CH), 77.4 (CH), 86.6 (C), 117.7 (CH₂), 121.0 (CH), 126.1-128.7 (30×Ar-CH) 131.9 (CH), 134.5, (Ar-C), 136.8 (CH), 137.4 (Ar-C), 137.7 (Ar-C), 143.2 (3 × Ar-C), 156.8 (CO).

6: $[\alpha]_{\text{D}}^{26} +37$ (c 1.2, CHCl₃). MS (ESI+) m/z 764 (M+Na⁺, 100%) HRMS (ESI+) calc. for C₅₀H₄₇NO₅Na (M+Na⁺) 764.3352, found 764.3364. ^1H NMR (300 MHz) δ 2.92 (1H, dd, $J = 10.7, 2.9$ Hz, H2'), 3.34 (1H, app. ddt, $J = 15.5, 7.7, 1.1$ Hz, H1'''), 3.45 (1H, app. t, $J = 1.8$ Hz, H5), 3.57 (1H, d, $J = 10.8$ Hz, CH₂Ph), 3.70 (1H, dd, $J = 10.5, 1.8$ Hz, H2'), 3.90 (1H, app dt, $J = 7.8, 1.8$ Hz, H1'), 4.08 (1H, app. dt, $J = 6.3, 1.7$ Hz, H4), 4.24 (1H, d, $J = 11.1$ Hz, CH₂Ph), 4.60-4.52 (1H, m, H1'''), 4.70 (1H, d, $J = 11.4$ Hz, CH₂Ph), 4.84 (1H, d, $J = 11.4$ Hz, CH₂Ph), 4.93 (1H, dd, $J = 7.8, 1.5$ Hz, H6), 5.12 (1H, dd, $J = 10.2, 1.5$ Hz, H3'''), 5.16 (1H, dd, $J = 17.4, 1.5$ Hz, H3'''), 5.77 (1H, m, H2'''), 5.93 (1H, dd, $J = 15.9, 6.3$ Hz, H1''), 6.54 (1H, dd, $J = 15.9, 1.5$ Hz, H2''), 7.57-7.06 (30H, m, Ar). ^{13}C NMR δ 50.0 (CH₂), 57.9 (CH), 62.2 (CH), 71.6 (CH₂), 73.2 (CH), 73.9 (CH₂), 77.6 (CH), 79.3 (CH), 86.5 (C), 118.0 (CH₂), 125.2 (CH), 127.2-129.1 (30×Ar-CH), 132.9 (CH), 134.1 (CH), 135.7 (Ar-C), 137.2 (Ar-C), 138.8 (Ar-C), 143.6 (3 × Ar-C), 153.2 (CO).

(1R,7aR)-1-((1S,2S)-1,2-Bis(benzyloxy)-3-(triphenylmethoxy)propyl)-1,7a-dihydropyrrolo[1,2-c]oxazol-3(5H)-one (7), and (3S,4R,4aR)-4-(benzyloxy)-3-((S)-1-(benzyloxy)-2-(triphenylmethoxy)-ethyl)-4,4a-dihydro-3H-pyrrolo[1,2-c] [1,3]oxazin-1(7H)-one (8).

Method 1: Synthesis of 7 from pure 6.

Grubbs' II catalyst (105.2 mg, 0.124 mmol) was added to a solution of oxazolidinone **6** (918.8 mg, 1.240 mmol) in dry CH₂Cl₂ (150 mL) under nitrogen. The mixture was heated at reflux for 48 h, followed by cooling to rt and then removal of the solvent *in vacuo* to give a brown oil. The residue was purified by column chromatography (20-50% EtOAc/petrol) to give compound **7** (695.1 mg, 88%, $R_f = 0.26$, 30% EtOAc/petrol) as a white foamy solid.

Method 2: Synthesis of 7 and 8 from a mixture of 6 and 7.

Grubbs' II catalyst (199 mg, 0.234 mmol) was added to a solution of the mixture of **6** and **7** (2.383 g, 3.22 mmol), obtained above from **4**, in dry CH₂Cl₂ (350 mL) under nitrogen. The mixture was heated at reflux for 48 h, followed by cooling to rt and then removal of the solvent *in vacuo* to give a brown oil. The residue was purified by column chromatography (20-50% EtOAc/petrol) to give compound **7** (1.403 g, 68%, *R_f* = 0.26, 30% EtOAc/petroleum ether) as a white foamy solid, and **8** (412.4 mg, 20%, *R_f* = 0.07, 30% EtOAc/petrol) as a white foamy solid.

7: [α]_D²⁵ +13 (*c* 4.5, CHCl₃). IR $\nu_{\max}/\text{cm}^{-1}$ 3063, 3027, 2945, 2868, 1696, 1125, 1070, 1029. MS (ESI+) *m/z* 660 (M+Na⁺, 43%), HRMS (ESI+) calcd for C₄₂H₃₉NO₅Na (M+Na⁺) 660.2726, found 660.2712. ¹H NMR δ 3.43 (1H, dd, *J* = 10.0, 4.8 Hz, H3'), 3.52 (1H, dd, *J* = 10.0, 5.0 Hz, H3'), 3.66-3.61 (1H, m, H5), 3.69-3.70 (2H, m, H1', H2'), 4.04-4.08 (1H, m, H7a), 4.22-4.27 (1H, m, H5), 4.35 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.58 (1H, d, *J* = 11.0 Hz, CH₂Ph), 4.64 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.71 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.77 (1H, dd, *J* = 8.0, 6.0 Hz, H1), 5.65 (1H, app. dd, *J* = 6.0, 1.0 Hz, H6), 5.84 (1H, app. dd, *J* = 6.0, 1.5 Hz, H7), 7.43-7.12 (25H, m, Ar).

¹³C NMR δ 54.7 (CH₂), 62.5 (CH₂), 67.0 (CH), 72.6 (CH₂), 74.6 (CH), 77.1 (CH), 78.3 (CH), 79.0 (CH), 87.4 (C), 126.2 (CH), 127.4-128.8 (25×Ar-CH), 131.7 (CH), 138.1(Ar-C), 138.2 (Ar-C), 144.0 (3 × Ar-C), 162.2 (CO).

8: [α]_D²⁷ +67 (*c* 5.15, CHCl₃). IR $\nu_{\max}/\text{cm}^{-1}$ 3052, 3027, 2924, 2863, 1685, 1105, 1096. MS (ESI+) *m/z* 660 (M+Na⁺, 42%), HRMS (ESI+) calcd for C₄₂H₃₉NO₅ (M⁺) 637.2828, found 637.2811. ¹H NMR δ 3.51 (1H, dd, *J* = 10.0, 7.0 Hz, H2'), 3.54 (1H, dd, *J* = 10.0, 6.0 Hz, H2'), 3.60 (1H, dd, *J* = 10.0, 6.0 Hz, H4), 3.86 (1H, ddd, *J* = 7.2, 6.0, 1.5 Hz, H1'), 4.03 (1H, ddt, *J* = 16.0, 4.5, 1.5 Hz, H7), 4.40 (1H, ddt, *J* = 16.0, 4.5, 1.5 Hz, H7), 4.45 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.52 (1H, dd, *J* = 9.8, 1.5 Hz, H4a), 4.57 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.59 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.60 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.61 (1H, dd, *J* = 6.0, 1.0 Hz, H3), 5.84 (2H, br. m, H5, H6), 7.43-7.20 (25H, m, Ar). ¹³C NMR δ 55.4

(CH₂), 63.0 (CH), 63.1 (CH₂), 72.5 (CH₂), 73.1 (CH₂), 74.3 (CH), 75.4 (CH), 75.6 (CH), 87.7 (C), 127.3-128.9 (25×Ar-CH), 127.9 (HC=CH), 137.3 (Ar-C), 138.4 (Ar-C), 144.2 (3 ×Ar-C), 152.1 (CO).

(1R,6S,7R,7aR)-1-((1S,2S)-1,2-Bis(benzyloxy)-3-(triphenylmethoxy)propyl)-tetrahydro-6,7-dihydroxypyrrolo[1,2-c]oxazol-3(1H)-one (9) and (1R,6R,7S,7aR)-1-((1S,2S)-1,2-bis(benzyloxy)-3-(triphenylmethoxy)-propyl)-tetrahydro-6,7-dihydroxypyrrolo[1,2-c]oxazol-3(1H)-one (6,7-di-*epi*-9).

To a solution of **7** (1.403 g, 2.203 mmol) in acetone (13.2 mL) and water (8.8 mL) was added potassium osmate dihydrate (57 mg, 0.15 mmol) and 4-morpholine *N*-oxide (516 mg, 4.41 mmol). The mixture was stirred at rt for 48 h followed by evaporation of all the volatiles to give a black oil. Purification by column chromatography (70–90% EtOAc/petrol) gave a mixture of diastereoisomeric dihydroxy products, **9** and **6,7-di-*epi*-9**, as a white foamy solid (1.242 g, 84%, d.r. = 83 : 17). The isomers were separated using 2% MeOH/CH₂Cl₂ as an eluent on a silica gel column (1 cm diameter × 30 cm long) to give the pure compound **9** (894 mg, 60%) and compound **6,7-di-*epi*-9** (248 mg, 16%) (*R_f* of **9** = 0.33 and *R_f* of **6,7-di-*epi*-9** = 0.27, 2% MeOH/CH₂Cl₂).

9: [α]_D²⁷ +43 (*c* 3.5, CHCl₃). IR ν_{\max} /cm⁻¹ 3411, 3058, 3027, 2914, 2848, 1734, 1445, 1093, 1055

MS (ESI+) *m/z* 694 (M+Na⁺, 100%) HRMS (ESI+) calcd for C₄₂H₄₂NO₇ (M+H⁺), 672.2961 found 672.3005. ¹H NMR δ 2.57 (br, OH), 2.94 (1H, dd, *J* = 8.0, 2.0 Hz, H7a), 3.40 (1H, dd, *J* = 10.5, 4.8 Hz, H3'), 3.36 (1H, dd, *J* = 11.5, 8.0 Hz, H5), 3.29 (1H, dd, *J* = 11.5, 7.5 Hz, H5), 3.54-3.55 (2H, m, H3', H7), 3.76, dd, *J* = 9.5, 5.0 Hz, H2'), 4.14 (1H, m, H6), 4.32 (1H, dd, *J* = 6.0, 4.5 Hz, H1'), 4.41 (1H, d, *J* = 12.0 Hz, CH₂Ph), 4.64 (1H, dd, *J* = 7.5, 6.0 Hz, H1), 4.71 (1H, d, *J* = 11.0 Hz, CH₂Ph), 4.73 (1H, d, *J* = 12.0 Hz, CH₂Ph), 4.76 (1H, d, *J* = 11.0 Hz, CH₂Ph), 7.44-7.18 (25H, m, Ar). ¹³C NMR δ 50.6 (CH₂), 62.6 (CH₂), 64.6 (CH), 70.8 (CH), 72.3 (CH₂), 74.1 (CH), 75.0 (CH₂), 76.6 (CH), 76.6 (CH), 77.4 (CH), 87.4 (C), 127.5-129.0 (25×Ar-CH), 137.2 (Ar-C), 138.0 (Ar-C), 144.0 (3 × Ar-C), 162.1 (CO).

6,7-di-epi-9: $[\alpha]_{\text{D}}^{24} +24$ (*c* 1.2, CHCl₃). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3412, 3058, 3027, 2930, 1731, 1447, 1095, 1053. MS (ESI+) *m/z* 694 (M+Na⁺, 100%). HRMS (ESI+) calcd for C₄₂H₄₂NO₇ (M+H⁺), 672.2961 found 672.3020. ¹H NMR δ 2.49 (1H, br, OH), 3.08 (1H, dd, *J* = 12.8, 1.8 Hz, H5), 3.34 (1H, dd, *J* = 9.0, 7.0 Hz, H7a), 3.44 (1H, dd, *J* = 10.0, 5.5 Hz, H3'), 3.53 (1H, dd, *J* = 10.0, 5.0 Hz, H3'), 3.81 (1H, dd, *J* = 13.0, 5.5 Hz, H5), 3.83 (1H, m, H7), 3.96 (1H, dd, *J* = 8.0, 3.5 Hz, H1'), 4.08-4.09 (2H, m, H2', H6), 4.41 (1H, d, *J* = 12.0 Hz, CH₂Ph), 4.53 (1H, d, *J* = 11.0 Hz, CH₂Ph), 4.70 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.71 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.83 (1H, app. t, *J* = 7.5 Hz, H1), 7.44-7.14 (m, 25H, Ar). ¹³C NMR δ 52.7 (CH₂), 62.2 (CH₂), 63.5 (CH), 70.0 (CH), 71.4 (CH), 72.5 (CH₂), 74.7 (CH), 76.2 (CH), 76.8 (CH), 77.2 (CH), 87.7(C), 127.5-129.1 (25×Ar-CH), 137.2 (Ar-C), 137.8 (Ar-C), 143.7 (3 × Ar-C), 161.0 (CO).

(3aR, 3bS, 4R, 8aS)-Tetrahydro-4-((1S,2S)-1,2-bis(benzyloxy)-3-triphenylmethoxy)-propyl)-2,2-dioxide,5H,4H-1,3,2-dioxathiol[3,4]pyrrolo[1,2-*c*]oxazol-6-one (10).

To a solution of **9** (1.207 g, 1.80 mmol) in dry CH₂Cl₂ (40 mL) was added triethylamine (4 mL, 28.78 mmol) and thionyl chloride (0.2 mL, 2.70 mmol). The mixture was stirred for 48 h at rt, and then water (50 mL) was added to the mixture. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined extracts were washed with brine and dried (MgSO₄) then evaporated under reduced pressure to give a brown foamy solid. The crude cyclic sulfite was used for the next step without further purification. The crude obtained above was dissolved in 50 mL of a solution of CCl₄/CH₃CN/H₂O (2 : 3 : 2, v/v/v) then NaIO₄ (1.539 g, 7.12 mmol) and RuCl₃·3H₂O (23.5 mg, 0.09 mmol) were added. The mixture was stirred for 3 h at rt and then diluted with diethyl ether (80 mL). The organic layer was filtered through a pad of celite. The filtrate was washed with brine and dried (MgSO₄). The solvent was removed *in vacuo* then purified by column chromatography (30-70% EtOAc/petrol) to give compound **10** (849 mg, 64%, *R*_f = 0.49, 50% EtOAc/petrol) as a white foamy solid. $[\alpha]_{\text{D}}^{27} +30.6$ (*c* 7.5, CHCl₃). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3050, 3020, 2935, 2850, 1761, 1349, 1173, 1075. MS

(ESI-) m/z 732 ($M-H^+$, 100%) HRMS (ESI+) calcd for $C_{42}H_{39}NO_9Na$ ($M+Na^+$) 756.2243, found 756.2297. 1H NMR δ 3.15 (1H, dd, $J = 15.0, 5.5$ Hz, H8) 3.30 (1H, dd, $J = 7.0, 3.5$ Hz, H3b), 3.50-3.55 (2H, m, 2 x H3'), 3.56-3.60 (1H, m, H2'), 4.13 (1H, dd, $J = 14.5, 1.0$ Hz, H8), 4.26 (1H, dd, $J = 9.5, 4.0$ Hz, H1'), 4.29 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.54 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.58 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.80 (1H, dd, $J = 5.5, 3.5$ Hz, H3a), 4.84 (1H, d, $J = 11.5$ Hz, CH_2Ph), 5.03-5.05 (2H, m, H4, H8a), 7.31 (25H, m, Ar-H). ^{13}C NMR δ 50.2 (CH_2), 61.5 (CH_2), 63.5 (CH), 72.3 (CH_2), 74.3 (CH_2), 74.9 (CH), 77.0 (CH), 77.8 (CH), 83.6 (CH), 84.3 (CH), 87.8 (C), 127.3-129.0 (25xAr-CH), 137.0 (Ar-C), 137.5 (Ar-C), 143.5 (3xAr-C), 159.0 (CO).

(7*S*,7*aR*)-1-((1*S*,2*S*)-1,2-Bis(benzyloxy)-3-hydroxypropyl)-tetrahydro-7-hydroxypyrrolo[1,2-*c*]oxazol-3(1*H*)-one (11).

To a solution of **10** (689 mg, 0.940 mmol) in anhydrous *N,N*-dimethylacetamide (2.5 mL) was added $NaBH_4$ (62 mg, 1.410 mmol). The reaction was stirred under nitrogen at rt for 6 h, then the *N,N*-dimethylacetamide was removed under reduced pressure and the residue was suspended in THF (30 mL). Water (1 mL) followed by concentrated H_2SO_4 (0.5 mL) was added, and the suspension became a clear solution. The solution was stirred for 48 h at rt followed by the addition of water (20 mL). The mixture was extracted with EtOAc (3 x 30 mL) and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (5-10% MeOH/EtOAc) to give compound **11** (248 mg, 63%, $R_f = 0.40$, 8% MeOH/EtOAc) as a white foamy solid. $[\alpha]_D^{28} +19$ (c 16.6, $CHCl_3$). IR ν_{max}/cm^{-1} 3426, 3050, 2950, 2840, 1732, 1075, 1052. MS (ESI+) m/z 414 ($M+H^+$, 100%). HRMS (ESI+) calcd for $C_{23}H_{28}NO_6$ ($M+H^+$) 414.1917, found 414.1926. 1H NMR δ 1.74 (1H, dddd, $J = 13.5, 10.0, 10.0, 3.5$ Hz, H6), 1.93 (1H, ddd, $J = 13.5, 8.0, 2.0$ Hz, H6), 3.11 (1H, br. d, $J = 9.5$ Hz, H7a), 3.14 (1H, dd, $J = 7.5, 2.0$ Hz, H5), 3.68 (1H, m, H5), 3.78-3.81 (2H, m, H2', H3'), 3.89 (1H, dd, $J = 11.0, 3.5$ Hz, H3'), 3.93 (1H, app. br. s, H7), 4.20 (1H, app. t, $J = 4.5$ Hz, H1'), 4.54 (1H, d, $J = 12.0$ Hz, CH_2Ph), 4.72 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.75 (1H, d, $J = 11.0$

Hz, CH₂Ph), 4.79 (1H, d, *J* = 11.0 Hz, CH₂Ph), 4.94 (1H, dd, *J* = 7.0, 5.0 Hz, H1), 7.33 (10H, m Ar-H).
¹³C NMR δ 34.5 (CH₂), 43.8 (CH₂), 61.1 (CH₂), 67.2 (CH), 70.1 (CH), 72.3 (CH₂), 74.5 (CH₂), 76.4 (CH), 76.7 (CH), 77.7 (CH), 128.4-129.0 (10×Ar-CH) 137.0 (Ar-C), 137.8 (Ar-C), 162.9(CO).

(2*S*,3*S*)-2-((1*R*,2*S*,3*S*)-2,3-Bis(benzyloxy)-1,4-dihydroxybutyl)-pyrrolidin-3-ol (12) and (2*R*,3*S*)-2-((2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-tetrahydrofuran-2-yl)pyrrolidin-3-ol (13).

Compound **11** (65.4 mg, 0.16 mmol) was dissolved in MeOH (20 mL) and then a solution of NaOH (63.2 mg, 1.58 mmol) in water (5 mL) was added. The mixture was placed in a teflon tube with a 100 bar pressure cap, then heated in a CEM Discover microwave reactor with constant temperature heating at 110 °C for 2 h. After cooling the mixture was poured into water (50 mL), then extracted with EtOAc (4 x 30 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to give a semisolid. The pure products were obtained by column chromatography (10:1:0.5; EtOAc:MeOH:NH₄OH), which gave the desired compound **12** (49 mg, 80%, *R*_f = 0.33, 10:1:0.5 EtOAc:MeOH:NH₄OH), as a clear oil, and product **13** (10 mg, 16%, *R*_f = 0.44, 10:1:0.5 EtOAc:MeOH:NH₄OH) as a white solid.

12: [α]_D²⁷ +32 (*c* 7.5, CHCl₃). MS (ESI+) *m/z* 388 (M+H⁺, 100%), HRMS (ESI+) calcd for C₂₂H₃₀NO₅ (M+H⁺) 388.2128, found 388.2128. ¹H NMR (CD₃OD) δ 1.69 (1H, m, H4), 1.84 (1H, dd, *J* = 13.5, 8.0 Hz, H4), 2.71 (1H, dd, *J* = 7.5, 2.5 Hz, H2), 3.06 (1H, app. dt, *J* = 10.5, 2.0 Hz, H5), 3.54 (1H, ddd, *J* = 10.5, 9.5, 8.0 Hz, H5), 3.94 (1H, app. t, *J* = 2.5 Hz, H3), 4.00 (1H, app. dt, *J* = 6.0, 2.5 Hz, H3'), 4.21(1H, dd, *J* = 10.5, 6.0 Hz, H4'), 4.35 (1H, dd, *J* = 11.0, 5.5 Hz, H4'), 4.52 (1H, dd, *J* = 9.0, 2.5 Hz, H2'), 4.56 (1H, d, *J* = 12.0 Hz, CH₂Ph), 4.63 (1H, d, *J* = 11.0 Hz, CH₂Ph), 4.77 (1H, d, *J* = 11.5 Hz, CH₂Ph), 4.81 (1H, dd, *J* = 9.0, 7.5 Hz, H1'), 4.83 (1H, d, *J* = 10.5 Hz, CH₂Ph), 7.37 (10H, m, Ar-H).
¹³C NMR (CD₃OD) δ 34.8 (CH₂), 43.2 (CH₂), 65.4 (CH), 66.3 (CH₂), 69.4 (CH), 71.5 (CH₂), 74.6 (CH), 74.9 (CH₂), 76.8 (CH), 78.9 (CH), 127.8-128.5 (10×Ar-CH), 138.0 (Ar-C), 138.4 (Ar-C).

13: $[\alpha]_D^{28} +21$ (*c* 9.4, CHCl₃). IR $\nu_{\max}/\text{cm}^{-1}$ 3450, 3057, 3027, 2930, 2868, 1614, 1454, 1096, 1073. MS (ESI+) *m/z* 370 (M+H⁺, 100%). HRMS (ESI+) calcd for C₂₂H₂₈NO₄ (M+H⁺) 370.2018, found 370.2010. ¹H NMR δ 1.81 (1H, m, H4), 1.97 (1H, m, H4), 2.87 (1H,m, H5), 3.05 (1H, app. t, *J* = 5.0 Hz, H2), 3.21 (1H, m, H5), 3.90 (1H, dd, *J* = 10.5, 4.5 Hz, H5'), 4.08-4.01 (3H, m, H2', H4', H5'), 4.15 (1H, br d, *J* = 5.0 Hz, H3'), 4.23 (1H, m, H3), 4.50 (1H, d, *J* = 12.5 Hz, CH₂Ph), 4.54 (1H, d, *J* = 12.0 Hz, CH₂Ph), 4.57 (1H, *J* = 12.0 Hz, CH₂Ph), 4.61 (1H, d, *J* = 11.5 Hz, CH₂Ph), 7.39 (10H, m, Ar-H). ¹³C NMR (CDCl₃) δ 35.4 (CH₂, C4), 44.7 (CH₂, C5), 65.5 (CH, C2), 71.6 (C4'-OCH₂Ph), 72.0 (CH₂, C5'), 72.5 (C3'-OCH₂Ph), 73.4 (CH, C3), 83.0 (CH, C4'), 83.3 (CH, C2'), 86.1 (CH, C3'), 137.4 (Ar-C), 137.6 (Ar-C).

(1S,6S,7S,8R,8aS)-6,7-Bis(benzyloxy)-octahydroindolizine-1,8-diol (14) and (3aS,6S,7S,8R,8aS)-6,7-bis(benzyloxy)-octahydro-1H-oxepino-[3,2-*b*]pyrrol-8-ol (15).

To a solution of **12** (49.2 mg, 0.13 mmol) in dry THF (2 mL) was added triphenylphosphine (47 mg, 0.18 mmol) and diisopropyl azodicarboxylate (36 mg, 0.18 mmol) at 0 °C. The mixture was stirred at 0-5 °C for 12 h, then the volatiles were removed *in vacuo* to give an oil. The pure products were obtained by column chromatography (100% EtOAc and 8.4:1.4:0.2; EtOAc:MeOH:NH₄OH), which gave the major compound **14** (11.5 mg, 25%, *R*_f = 0.47, 8.4:1.4:0.2 EtOAc:MeOH:NH₄OH) as a clear oil and compound **13** (10 mg, 22% *R*_f = 0.15, 8.4:1.4:0.2 EtOAc:MeOH:NH₄OH or *R*_f = 0.44, 10:1:0.5 EtOAc:MeOH:NH₄OH), as a white solid, as well as compound **15** (5.0 mg, 11%, *R*_f = 0.27, 8.4:1.4:0.2 EtOAc:MeOH:NH₄OH) as a white solid.

14: $[\alpha]_D^{27} +71$ (*c* 2.5, CHCl₃). IR $\nu_{\max}/\text{cm}^{-1}$ 3360, 3000, 2940, 2868, 1662, 1091, 1075. MS (ESI+) *m/z* 370 (M+H⁺, 100%), HRMS (ESI+) calcd for C₂₂H₂₈NO₄ (M+H⁺) 370.1135, found 370.1130. ¹H NMR δ 1.74 (1H, m, H2), 1.85 (1H, dd, *J* = 10.0, 4.5 Hz, H8a), 1.94 (1H, app. t, *J* = 9.8 Hz, H5), 2.12 (1H, app. q, *J* = 9.0 Hz, H3), 2.33 (1H, m, H2), 3.08 (1H, app. dt, *J* = 9.0, 2.5 Hz, H3), 3.29 (1H, dd, *J* = 9.0, 5.5 Hz, H7), 3.34 (1H, app. t, *J* = 9.8 Hz, H5), 3.62 (1H, m, H6), 3.76 (1H, app. t, *J* = 9.5 Hz, H8),

4.30 (1H, m, H1), 4.62 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.66 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.87 (2H, br.s., CH_2Ph), 7.30 (10H, m, Ar-H). ^{13}C NMR δ 33.4 (CH_2 , C2), 52.0 (CH_2 , C3), 54.2 (CH_2 , C5), 69.4 (CH, C8), 69.8 (CH, C1), 72.5 ($\text{C7-OCH}_2\text{Ph}$), 72.8 (CH, C8a), 75.1 ($\text{C6-OCH}_2\text{Ph}$), 78.8 (CH, C8), 87.3 (CH, C7), 127.2-128.1 (10 \times Ar-CH), 138.4(Ar-C), 138.8(Ar-C).

15: $[\alpha]_{\text{D}}^{27} + 45$ (c 2.3, CHCl_3). IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3288, 2904, 2842, 1665, 1091, 1075. MS (ESI+) m/z 370 ($\text{M}+\text{H}^+$, 100%). ^1H NMR δ 1.89 (1H, m, overlapped with OH and NH, H3), 1.95 (1H, m, overlapped with OH and NH, H3), 2.93 (1H, m, H2), 3.15 (1H, m, H2), 3.35 (1H, dd, $J = 8.8, 3.8$ Hz, H8a), 3.83 (1H, dd, $J = 9.8, 1.8$ Hz, H5), 4.09-4.20 (4H, m, H5, H6, H7, H8), 4.47 (1H, m, H3a), 4.48 (1H, d, $J = 12.0$ Hz, CH_2Ph), 4.53 (1H, d, $J = 12.0$ Hz, CH_2Ph), 4.55 (1H, d, $J = 11.5$ Hz, CH_2Ph), 4.63 (1H, d, $J = 11.5$ Hz, CH_2Ph), 7.30 (10H, m, Ar-H). ^{13}C NMR δ 34.9 (CH_2 , C3), 44.9 (CH_2N , C2), 61.5 (CHN, C8), 71.7 (CH_2Ph), 72.2 (CH_2 , C5), 72.3 (CH_2Ph), 73.2 (CH, C3a), 80.3 (CH, C8), 81.9 (CH, C7), 82.5 (CH, C6), 127.9-128.8 (10 \times Ar-CH), 137.9 (Ar-C), 138.0 (Ar-C).

(1S,6S,7R,8R,8aS)-Octahydroindolizine-1,6,7,8-tetraol (castanospermine) (1)

The indolizidine **14** (6.4 mg, 0.173 mmol) was dissolved in methanol (1 mL), then PdCl_2 (2.4 mg, 0.013 mmol) was added. The mixture was stirred under an atmosphere of H_2 (balloon) for 1 h at rt, before the mixture was filtered through a plug of cotton wool. The filtrates were evaporated *in vacuo*, then the residue was dissolved in water (1 mL) and applied to a column of DOWEX-1-basic ion exchange resin. Elution with water (30 mL) followed by evaporation of the eluent *in vacuo* gave the title product castanospermine, **1**, (3.1 mg, 95%) as a colourless solid. Mp 206-208 °C (lit.¹ 212-215 °C). $[\alpha]_{\text{D}}^{27} + 82$ (c 1.2, H_2O) (lit.¹ $[\alpha]_{\text{D}}^{24} + 79.7$ (c 0.93, H_2O)). R_f 0.18 (96 : 4 EtOH: aqueous NH_3). ESI+ m/z 190 ($\text{M}+\text{H}^+$, 100%). ^1H NMR (D_2O , HOD ref. at 4.79 ppm) δ 1.72 (1H, dddd, $J_{2\beta,2\alpha} = 14$, $J_{2\beta,3\alpha} = 8.5$, $J_{2\beta,3\beta} = 8.5$, $J_{2\beta,1} = 1.8$, H2 β), 2.03 (1H, dd, $J_{8a,8} = 10$, $J_{8a,1} = 4.5$, H8a), 2.07 (1H, t, $J_{5\beta,5\alpha} = J_{5\beta,6} = 10.5$, H5 β), 2.23 (1H, q, $J_{3\beta,2\beta} = J_{3\beta,3\alpha} = J_{3\beta,2\alpha} = 9.5$, H3 β), 2.35 (1H, dddd, $J_{2\beta,2\alpha} = 14$, $J_{2\alpha,3\beta} =$

9.5, $J_{2\alpha,1} = 7.5$, $J_{2\alpha,3\alpha} = 2.5$, H2 α), 3.09 (1H, ddd, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 9$, $J_{3\alpha,2\alpha} = 2.5$, H3 α), 3.19 (1H, dd, $J_{5\alpha,5\beta} = 10.5$, $J_{5\alpha,6} = 5$, H5 α), 3.34 (1H, t, $J_{7,8} = J_{6,7} = 9.5$, H7), 3.61 (1H, t $J_{8,8a} = J_{8,7} = 9.5$, H8), 3.63 (1H, ddd, $J_{6,5\beta} = 10.5$, $J_{6,7} = 9.5$, $J_{6,5\alpha} = 5$, H6), 4.42 (1H, ddd, $J_{1,2\alpha} = 7$, $J_{1,8a} = 4.5$, $J_{1,2\beta} = 1.8$, H1). ^{13}C NMR (D₂O, internal reference, acetone at 30.89 ppm) δ 79.3 (CH, C7), 71.7 (CH, C8a), 70.4 (CH, C8), 69.9 (CH, C1), 69.2 (CH, C6), 55.7 (CH₂, C5), 51.8 (CH₂, C3), 33.0 (CH₂, C2).

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24. An alternative mechanism for the formation of **13** from the cyclization **11** (Scheme 2), may involve terminal alkoxide displacement of the carboxylate moiety of the cyclic carbamate. This would produce *2-epi-13*. The fact that the same compound **13** is produced in both Schemes 2 and 3 suggests that this alternative mechanism does not occur since the primary hydroxyl in **12** would be expected to be selectively activated under Mitsunobu cyclization conditions. We thank a referee for bringing this to our attention.
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GRAPHICAL ABSTRACT

Synthesis of Castanospermine

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