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Synthesis of castanospermine

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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)-catalyzed *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** (Fig. 1) was first isolated from the seeds of *Castanospermum australe*[1] and then later from the dry pods of *Alexa leiopetala*.[2] Castanospermine is a potent inhibitor of several glucosidases[3] and has potential for the treatment of viral infections,[4] cancers,[5] and diabetes.[6] In addition it shows anti-inflammatory[7] and immunosuppressant[8] 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 alkaloids[11–19] 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]

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 conditions[17] compound **4** gave a mixture of the corresponding di-*O*-benzyl-oxazolidin-2-one **5** and 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 catalyst[19] gave the pyrrolo[1,2-*c*]oxazol-3-one **7** in 88% yield. Alternatively, **7** could be more readily obtained by treating a mixture

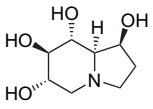

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Figure 1. Structure of castanospermine (**1**).

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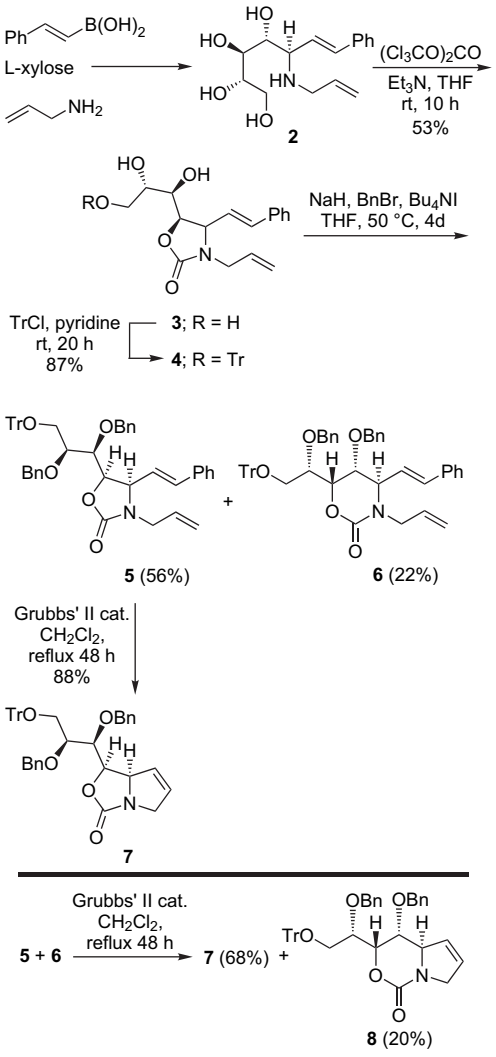
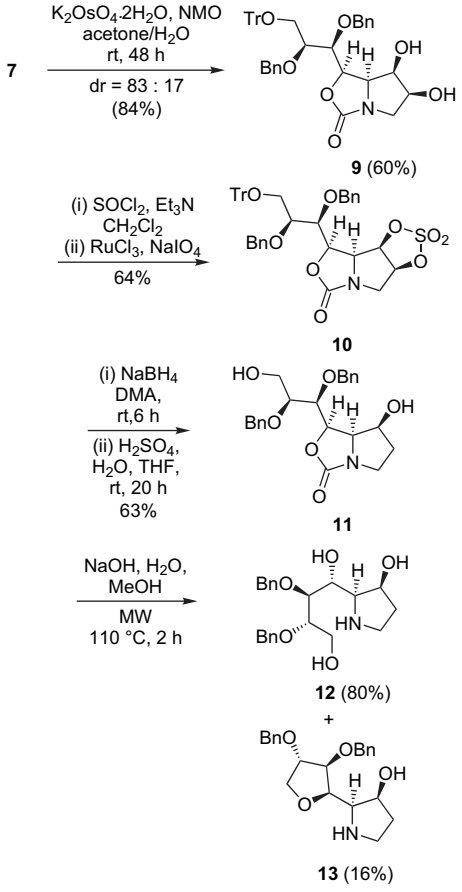
of **5** and **6** with Grubbs' second generation ruthenium catalyst followed by a relatively easier separation of **7** (68%) from the pyrrolo[1,2-*c*]oxazin-1-one **8** (20%) (Scheme 1).



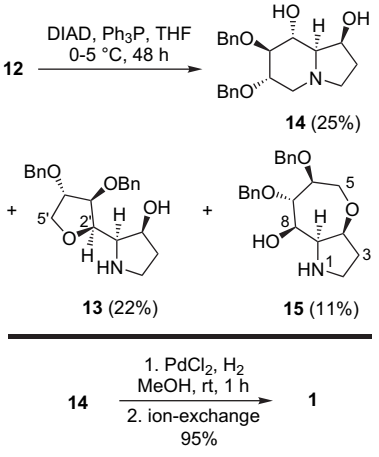
Scheme 1.

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, osmium(VIII)-catalyzed *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 tetraoxide ($RuCl_3$, $NaIO_4$).[13,22] Regioselective reductive ring-opening of **10** with sodium borohydride[10f] in dimethylacetamide (DMA) at rt for 6 h followed by acid hydrolysis of the resulting adduct gave the diol **11** in 63% yield in



Scheme 2.

which the *O*-trityl group had also been cleaved (Scheme 2). Base catalyzed 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** as shown in Scheme 3. The most likely mechanism for the formation of **13** as shown in Scheme 3 is



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.[23]

Attempts to cyclize the amino-triol **12** under Appel cyclization reaction conditions ($Ph_3P/CBr_4/Et_3N$)[24] were unsuccessful and a complex mixture of products resulted. Treatment of **12** under Mitsunobu reaction conditions[25] produced the desired indolizidine product **14** in 25% yield along with the furan **13** (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 δ 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 $[\alpha]_D^{27}$ +82 (*c* 1.2, H_2O) also agreed with that reported (lit.[1] $[\alpha]_D^{24}$ +79.7 (*c* 0.93, H_2O)). This sample was also identical to an authentic sample by TLC analysis.[27]

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)-catalyzed *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

4.1. General

General methods were as described previously.[12,13] All ^1H NMR spectra were performed at 500 MHz and all ^{13}C NMR (DEPT) spectra at 125 MHz in $CDCl_3$ 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.

*4.1.1. (4R,5R)-3-Allyl-5-((1R,2S)-1,2,3-trihydroxypropyl)-4-((E)-2-phenyl-vinyl)-1,3-oxazolidin-2-one (**3**) and its 1,3-dioxolan-2-onyl derivative, (4R,5R)-3-allyl-5-(((4S)-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 (3×100 mL). The combined organic extracts were dried ($MgSO_4$) 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). $[\alpha]_D^{27}$ −10 (*c* 4.5, MeOH). Mp 141 °C. IR ν_{max}/cm^{-1} 3550, 2950, 2914, 1737, 1447, 1094, 1041. MS (ESI+) *m/z* 320 ($M+H^+$, 100%). ^1H NMR (CD_3OD) δ 3.57 (1H, dd, *J*=11.3, 6.3 Hz, H3′), 3.60 (1H, app. ddt, *J*=15.7, 6.7, 1.3 Hz, H1‴), 3.65 (1H, dd, *J*=11.3, 5.3 Hz, H3′), 3.73 (1H, m, H2′), 3.83 (1H, app. t, *J*=4.3 Hz, H1′), 4.01 (1H, app. ddt, *J*=15.7, 4.7, 1.7 Hz, 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, H3‴), 5.22 (1H, dd, *J*=17.5, 1.0 Hz, H3‴), 5.79 (1H, m, H2‴), 6.38 (1H, dd, *J*=16.0, 9.5 Hz, H1″), 6.70 (1H, d, *J*=16.0 Hz, 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×Ar–CH), 129.4 (Ar–CH), 129.7 (2×Ar–CH), 133.4 (CH), 137.2 (C), 138.5 (CH), 159.8 (CO).

*4.1.2. (4R,5R)-3-Allyl-5-((1R,2S)-1,2-dihydroxy-3-(triphenylmethyloxy)-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 (3×80 mL). The combined organic phases were washed with saturated $CuSO_4$ (3×90 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 ν_{max}/cm^{-1} 3401, 3053, 3027, 2914, 1731, 1448, 1070. MS (ESI+) *m/z* 579 ($M+NH_4^+$, 100%); HRMS (ESI+) calcd for $C_{36}H_{35}NO_5Na$ ($M+Na^+$) 584.2413, found 584.2419. ^1H NMR δ 2.57 (1H, br d, *J*=5.0 Hz, OH1′), 2.82 (1H, br d, *J*=5.5 Hz, OH2′), 3.18 (1H, dd, *J*=10.0, 5.5 Hz, H3′), 3.31 (1H, dd, *J*=9.5, 5.0 Hz, H3′), 3.54 (1H, dd, *J*=15.5, 7.5 Hz, H1‴), 3.90 (1H, br t, *J*=4.0 Hz, H2′), 3.96 (1H, br d,

J=3.5 Hz, H1′), 4.11 (1H, dd, J=15.8, 6.5 Hz, 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, H3‴), 5.21 (1H, dd, J=10.3, <1 Hz, H3‴), 5.74 (1H, m, H2‴), 6.32 (1H, dd, J=16.0, 9.5 Hz, H1″), 6.61 (1H, d, J=15.5 Hz, 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×Ar–CH), 132.1 (CH), 135.6 (Ar–C), 137.6 (CH), 143.7 (Ar–C), 157.2 (CO).

*4.1.3. (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-oxazinan-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.

Compound **5**: $[\alpha]_D^{26}$ +52 (c 3.2, $CHCl_3$). IR ν_{max}/cm^{-1} 3058, 3027, 2945, 2873, 1752, 1450, 1070. MS (ESI+) m/z 764 (M+Na$^+$, 85%); HRMS (ESI+) calcd for $C_{50}H_{47}NO_5Na$ (M+Na$^+$) 764.3351, found 764.3378. ^{1}H NMR (300 MHz) δ 3.32 (1H, dd, J=16.0, 7.5 Hz, H1‴), 3.39 (1H, dd, J=9.5, 5.0 Hz, H3′), 3.44 (1H, dd, J=10.0, 5.0 Hz, H3′), 3.58 (1H, app. t, J=8.0 Hz, H4), 3.75 (1H, m, H2′), 4.01 (1H, dd, J=7.5, 3.3 Hz, H1′), 4.08 (1H, app. dd, J=16.0, 4.5 Hz, 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, H3‴), 5.15 (1H, d, J=10.0 Hz, 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 (CH_2), 59.4 (CH), 60.6 (CH_2), 70.7 (CH_2), 74.3 (CH_2), 74.4 (CH), 76.6 (CH), 77.2 (CH), 77.4 (CH), 86.6 (C), 117.7 (CH_2), 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).

Compound **6**: $[\alpha]_D^{26}$ +37 (c 1.2, $CHCl_3$). MS (ESI+) m/z 764 (M+Na$^+$, 100%); HRMS (ESI+) calcd for $C_{50}H_{47}NO_5Na$ (M+Na$^+$) 764.3352, found 764.3364. ^{1}H 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, CH_2Ph), 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, CH_2Ph), 4.60–4.52 (1H, m, H1‴), 4.70 (1H, d, J=11.4 Hz, CH_2Ph), 4.84 (1H, d, J=11.4 Hz, CH_2Ph), 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 (CH_2), 57.9 (CH), 62.2 (CH), 71.6 (CH_2), 73.2 (CH), 73.9 (CH_2), 77.6 (CH), 79.3 (CH), 86.5 (C), 118.0 (CH_2), 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).

*4.1.4. (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**)*

*4.1.4.1. 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 CH_2Cl_2 (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.

*4.1.4.2. 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 CH_2Cl_2 (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.

Compound **7**: $[\alpha]_D^{25}$ +13 (c 4.5, $CHCl_3$). IR ν_{max}/cm^{-1} 3063, 3027, 2945, 2868, 1696, 1125, 1070, 1029. MS (ESI+) m/z 660 (M+Na$^+$, 43%); HRMS (ESI+) calcd for $C_{42}H_{39}NO_5Na$ (M+Na$^+$) 660.2726, found 660.2712. ^{1}H 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, CH_2Ph), 4.58 (1H, d, J=11.0 Hz, CH_2Ph), 4.64 (1H, d, J=11.5 Hz, CH_2Ph), 4.71 (1H, d, J=11.5 Hz, CH_2Ph), 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). ^{13}C NMR δ 54.7 (CH_2), 62.5 (CH_2), 67.0 (CH), 72.6 (CH_2), 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).

Compound **8**: $[\alpha]_D^{27}$ +67 (c 5.15, $CHCl_3$). IR ν_{max}/cm^{-1} 3052, 3027, 2924, 2863, 1685, 1105, 1096. MS (ESI+) m/z

660 ($M+Na^+$, 42%); HRMS (ESI+) calcd for $C_{42}H_{39}NO_5$ (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, CH_2Ph), 4.52 (1H, dd, J=9.8, 1.5 Hz, H4a), 4.57 (1H, d, J=11.5 Hz, CH_2Ph), 4.59 (1H, d, J=11.5 Hz, CH_2Ph), 4.60 (1H, d, J=11.5 Hz, CH_2Ph), 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). ^{13}C NMR δ 55.4 (CH_2), 63.0 (CH), 63.1 (CH_2), 72.5 (CH_2), 73.1 (CH_2), 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).

*4.1.5. (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%, dr=83:17). The isomers were separated using 2% MeOH/CH_2Cl_2 as an eluent on a silica gel column (1 cm diameter×30 cm long) to give the pure compound **9** (894 mg, 60%) and 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/CH_2Cl_2).

Compound **9**: $[\alpha]_D^{27}$ +43 (*c* 3.5, $CHCl_3$). 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 $C_{42}H_{42}NO_7$ ($M+H^+$) 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, CH_2Ph), 4.64 (1H, dd, J=7.5, 6.0 Hz, H1), 4.71 (1H, d, J=11.0 Hz, CH_2Ph), 4.73 (1H, d, J=12.0 Hz, CH_2Ph), 4.76 (1H, d, J=11.0 Hz, CH_2Ph), 7.44–7.18 (25H, m, Ar). ^{13}C NMR δ 50.6 (CH_2), 62.6 (CH_2), 64.6 (CH), 70.8 (CH), 72.3 (CH_2), 74.1 (CH), 75.0 (CH_2), 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).

Compound 6,7-di-*epi*-**9**: $[\alpha]_D^{24}$ +24 (*c* 1.2, $CHCl_3$). IR ν_{max}/cm^{-1} 3412, 3058, 3027, 2930, 1731, 1447, 1095, 1053. MS (ESI+) *m/z* 694 ($M+Na^+$, 100%); HRMS (ESI+) calcd for $C_{42}H_{42}NO_7$ ($M+H^+$) 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, CH_2Ph), 4.53 (1H, d, J=11.0 Hz, CH_2Ph), 4.70 (1H, d, J=11.5 Hz, CH_2Ph), 4.71 (1H, d, J=11.5 Hz, CH_2Ph), 4.83 (1H, app. t, J=7.5 Hz, H1), 7.44–7.14 (m, 25H, Ar). ^{13}C NMR δ 52.7 (CH_2), 62.2 (CH_2), 63.5 (CH), 70.0 (CH), 71.4 (CH), 72.5 (CH_2), 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).

*4.1.6. (3aR,3bS,4R,8aS)-Tetrahydro-4-((1S,2S)-1,2-bis(benzyloxy)-3-triphenylmethoxy)-propyl)-2,2-dioxide,5H,4H-1,3,2-dioxathiolo[3,4]pyrrolo[1,2-c]oxazol-6-one (**10**)*

To a solution of **9** (1.207 g, 1.80 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2 (3×100 mL). The combined extracts were washed with brine and dried ($MgSO_4$) 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 $CCl_4/CH_3CN/H_2O$ (2:3:2, v/v/v) then $NaIO_4$ (1.539 g, 7.12 mmol) and $RuCl_3\cdot 3H_2O$ (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 ($MgSO_4$). 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. $[\alpha]_D^{27}$ +30.6 (*c* 7.5, $CHCl_3$). IR ν_{max}/cm^{-1} 3050, 3020, 2935, 2850, 1761, 1349, 1173, 1075. MS (ESI–) *m/z* 732 ($M-H^+$, 100%); HRMS (ESI+) calcd for $C_{42}H_{39}NO_9SNa$ ($M+Na^+$) 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×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 (25×Ar–CH), 137.0 (Ar–C), 137.5 (Ar–C), 143.5 (3×Ar–C), 159.0 (CO).

*4.1.7. (7S,7aR)-1-((1S,2S)-1,2-Bis(benzyloxy)-3-hydroxypropyl)-tetrahydro-7-hydroxypyrrolo[1,2-c]oxazol-3(1H)-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 (3×30 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, CH_2Ph), 4.79 (1H, d, *J*=11.0 Hz, CH_2Ph), 4.94 (1H, dd, *J*=7.0, 5.0 Hz, H1), 7.33 (10H, m, Ar–H). ^{13}C NMR δ 34.5 (CH_2), 43.8 (CH_2), 61.1 (CH_2), 67.2 (CH), 70.1 (CH), 72.3 (CH_2), 74.5 (CH_2), 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).

*4.1.8. (2S,3S)-2-((1R,2S,3S)-2,3-Bis(benzyloxy)-1,4-dihydroxybutyl)-pyrrolidin-3-ol (**12**) and (2R,3S)-2-((2R,3S,4S)-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 (4×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give a semisolid. The pure products were obtained by column chromatography (10:1:0.5 EtOAc/MeOH/NH_4OH), which gave the desired compound **12** (49 mg, 80%, R_f=0.33, 10:1:0.5 EtOAc/MeOH/NH_4OH), as a clear oil, and product **13** (10 mg, 16%, R_f=0.44, 10:1:0.5 EtOAc:MeOH:NH_4OH) as a white solid.

Compound **12**: $[\alpha]_D^{27}$ +32 (*c* 7.5, $CHCl_3$). MS (ESI+) *m/z* 388 ($M+H^+$, 100%); HRMS (ESI+) calcd for $C_{22}H_{30}NO_5$ ($M+H^+$) 388.2128, found 388.2128. ^1H NMR (CD_3OD) 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, CH_2Ph), 4.63 (1H, d, *J*=11.0 Hz, CH_2Ph), 4.77 (1H, d, *J*=11.5 Hz, CH_2Ph), 4.81 (1H, dd, *J*=9.0, 7.5 Hz, H1′), 4.83 (1H, d, *J*=10.5 Hz, CH_2Ph), 7.37 (10H, m, Ar–H). ^{13}C NMR (CD_3OD) δ 34.8 (CH_2), 43.2 (CH_2), 65.4 (CH), 66.3 (CH_2), 69.4 (CH), 71.5 (CH_2), 74.6 (CH), 74.9 (CH_2), 76.8 (CH), 78.9 (CH), 127.8–128.5 (10×Ar–CH), 138.0 (Ar–C), 138.4 (Ar–C).

Compound **13**: $[\alpha]_D^{28}$ +21 (*c* 9.4, $CHCl_3$). IR ν_{max}/cm^{-1} 3450, 3057, 3027, 2930, 2868, 1614, 1454, 1096, 1073. MS (ESI+) *m/z* 370 ($M+H^+$, 100%); HRMS (ESI+) calcd for $C_{22}H_{28}NO_4$ ($M+H^+$) 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, CH_2Ph), 4.54 (1H, d, *J*=12.0 Hz, CH_2Ph), 4.57 (1H, *J*=12.0 Hz, CH_2Ph), 4.61 (1H, d, *J*=11.5 Hz, CH_2Ph), 7.39 (10H, m, Ar–H). ^{13}C NMR ($CDCl_3$) δ 35.4 (CH_2, C4), 44.7 (CH_2, C5), 65.5 (CH, C2), 71.6 (C4′–OCH_2Ph), 72.0 (CH_2, C5′), 72.5 (C3′–OCH_2Ph), 73.4 (CH, C3), 83.0 (CH, C4′), 83.3 (CH, C2′), 86.1 (CH, C3′), 137.4 (Ar–C), 137.6 (Ar–C).

*4.1.9. (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/NH_4OH), which gave the major compound **14** (11.5 mg, 25%, R_f=0.47, 8.4:1:4.0.2 EtOAc/MeOH/NH_4OH) as a clear oil and compound **13** (10 mg, 22% R_f=0.15, 8.4:1:4.0.2 EtOAc/MeOH/NH_4OH or R_f=0.44, 10:1:0.5 EtOAc/MeOH/NH_4OH), 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/NH_4OH) as a white solid.

Compound **14**: $[\alpha]_D^{27}$ +71 (*c* 2.5, $CHCl_3$). IR ν_{max}/cm^{-1} 3360, 3000, 2940, 2868, 1662, 1091, 1075. MS (ESI+) *m/z* 370 ($M+H^+$, 100%); HRMS (ESI+) calcd for $C_{22}H_{28}NO_4$ ($M+H^+$) 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 (C7–OCH_2Ph), 72.8 (CH, C8a), 75.1 (C6–OCH_2Ph), 78.8 (CH, C8), 87.3 (CH, C7), 127.2–128.1 (10×Ar–CH), 138.4 (Ar–C), 138.8 (Ar–C).

Compound **15**: $[\alpha]_D^{27}$ +45 (*c* 2.3, $CHCl_3$). IR ν_{max}/cm^{-1} 3288, 2904, 2842, 1665, 1091, 1075. MS (ESI+) *m/z* 370 ($M+H^+$, 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×Ar−CH), 137.9 (Ar−C), 138.0 (Ar−C).

*4.1.10. (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 colorless solid. Mp 206−208 °C (lit.[1] 212−215 °C). $[\alpha]_D^{27}$ +82 (*c* 1.2, H_2O) (lit.[1] $[\alpha]_D^{24}$ +79.7 (*c* 0.93, H_2O)). R_f 0.18 (96:4 EtOH/aqueous NH_3). MS (ESI+) *m/z* 190 ($M+H^+$, 100%). ^{1}H NMR (D_2O, HOD ref. at 4.79 ppm) δ 1.72 (1H, dddd, $J_{2\beta,2\alpha}$=14 Hz, $J_{2\beta,3\alpha}$=8.5 Hz, $J_{2\beta,3\beta}$=8.5 Hz, $J_{2\beta,1}$=1.8 Hz, H2β), 2.03 (1H, dd, $J_{8a,8}$=10 Hz, $J_{8a,1}$=4.5 Hz, H8a), 2.07 (1H, t, $J_{5\beta,5\alpha}$= $J_{5\beta,6}$=10.5 Hz, H5β), 2.23 (1H, q, $J_{3\beta,2\beta}$=$J_{3\beta,3\alpha}$=$J_{3\beta,2\alpha}$= 9.5 Hz, H3β), 2.35 (1H, dddd, $J_{2\beta,2\alpha}$=14 Hz, $J_{2\alpha,3\beta}$=9.5 Hz, $J_{2\alpha,1}$=7.5 Hz, $J_{2\alpha,3\alpha}$=2.5 Hz, H2α), 3.09 (1H, ddd, $J_{3\alpha,3\beta}$= $J_{3\alpha,2\beta}$=9 Hz, $J_{3\alpha,2\alpha}$=2.5 Hz, H3α), 3.19 (1H, dd, $J_{5\alpha,5\beta}$= 10.5 Hz, $J_{5\alpha,6}$=5 Hz, H5α), 3.34 (1H, t, $J_{7,8}$=$J_{6,7}$=9.5 Hz, H7), 3.61 (1H, t, $J_{8,8a}$=$J_{8,7}$=9.5 Hz, H8), 3.63 (1H, ddd, $J_{6,5\beta}$=10.5 Hz, $J_{6,7}$=9.5 Hz, $J_{6,5\alpha}$=5 Hz, H6), 4.42 (1H, ddd, $J_{1,2\alpha}$=7 Hz, $J_{1,8a}$=4.5 Hz, $J_{1,2\beta}$=1.8 Hz, H1). ^{13}C NMR (D_2O, 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 (CH_2, C5), 51.8 (CH_2, C3), 33.0 (CH_2, C2).

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