Simple Total Syntheses of (+)-Castanospermine and (+)-6-Epicastanospermine Using Indium-Mediated Allylation

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Abstract: The indium-mediated allylation of α-aminoaldehyde **3** from D-glucono-δ-lactone provided the *syn*-aminoalcohol with excellent diastereoselectivity. *syn*-Aminoalcohol was easily applied to the total syntheses of the potent glycosidase inhibitors; (+)-castanospermine and (+)-6-epicastanospermine.

Keywords: (+)-castanospermine, (+)-6-epicastanospermine, indium-mediated allylation, (+)-cinchonine, glycosidase inhibitor

(+)-Castanospermine (**1**) and (+)-6-epicastanospermine (**2**) (Figure 1) are natural indolizidine alkaloids isolated from *Castanospermum australe*[1] and *Alexa leiopetala*.[2] These indolizidine alkaloids are a potent glycosidase inhibitor[3] with broad biological activities such as diabetes,[4] cancer,[5] and viral replication.[6] Thus, many synthetic strategies to target molecules (**1** and **2**) have been developed,[7] and the most practical route is starting from carbohydrate because of minimizing the need to create the requisite stereocenters. The efficiency of this approach to indolizidine alkaloids like castanospermine from carbohydrate would largely rely on how chiral induction of C-1 is carried out. Efficient, asymmetric methodology for manipulation of simple aminoaldehyde from carbohydrate into aminoalcohol is, therefore, of considerable merit. This key step has been accomplished through reduction of keto group,[8] Michael type reaction,[9] or aldol type reaction[10] because direct nucleophilic addition to aminoaldehyde does not give a high level of stereocontrol.[11] Although the above mentioned approaches have been proven as useful methods, they suffer from the disadvantage of either including non-stereoselective steps or have low overall yields owing to their tedious number of steps. Herein, we describe a highly diastereoselective synthesis of *syn*-aminoalcohol **4** via indium-mediated allylation in the presence of (+)-cinchonine as a chiral promoter.[12] *syn*-Aminoalcohol **4** was easily converted enantiomerically to pure (+)-castanospermine (**1**) and (+)-6-epicastanospermine (**2**).

Our approach to syntheses of **1** and **2** envisaged the use of *syn*-aminoalcohol **4**, which can be obtained from α-aminoaldehyde **3** via indium-mediated allylation in the presence of (+)-cinchonine with anticipation of a high selectivity and stereointegrity.

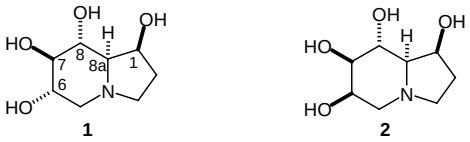
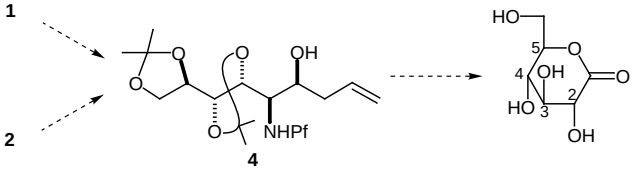


Figure 1 Target compounds **1** and **2**



Scheme 1 Retrosynthesis of target compounds **1** and **2**

In our retrosynthesis (Scheme 1), D-glucono-δ-lactone was chosen as the starting material with C2, C3, C4, and C5 being transferred into the C6, C7, C8, and C8a, respectively, in target molecules **1** and **2**. α-Aminoaldehyde **3** allows the introduction of C_2 unit for target compounds via an organometallic reagent (Scheme 2). We also anticipated the indium-mediated allylation in the presence of (+)-cinchonine to give the chiral *syn*-aminoalcohol **4** as the key intermediate of compounds **1** and **2**.

(+)-Castanospermine (1)

Our synthesis commenced with the synthesis of α-aminoaldehyde **3**, which was easily accessible via known procedures[8] from D-glucono-δ-lactone. We chose the 9-phenylfluoren-9-yl (Pf) group for protection of amine since this protecting group has been shown to inhibit deprotonation at the α-position of α-aminoaldehyde.[8] α-Aminoaldehydes having the Pf group are stable to Grignard reaction condition.[9] α-Aminoaldehyde **3** was treated with allylbromide and indium in the presence of (+)-cinchonine as a chiral promoter at –40 °C for 10 minutes to give *syn*-aminoalcohol **4** in a 50:1 ratio in 87% yield via a diastereoselective addition. As shown in Table 1, the optimum reaction conditions involved the use of (+)-cinchonine as a chiral promoter in THF. The *syn* diastereoselectivity of allylation could be explained by the chelation control model,[13] which concisely accommo-

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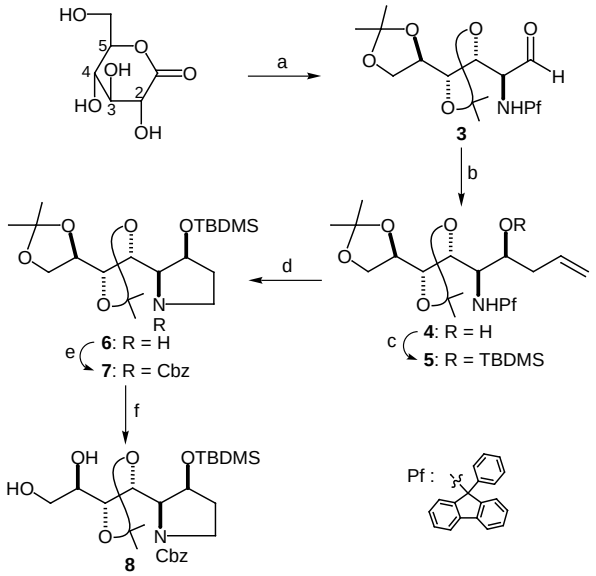
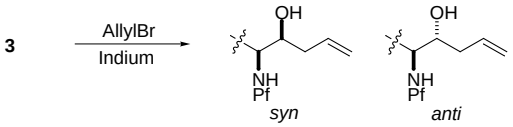
dates favored formation of the *syn*-aminoalcohol (Figure 2). Fortunately, each diastereomeric allylic alcohol obtained by the allylation could be isolated in pure form by column chromatography. The stereochemistry of product **4** was deduced from NOE experiment of final product **2**.



Scheme 2 a) Ref.[7]; b) AllylBr, In, (+)-cinchonine, THF, –78 °C; c) TBDMSCl, Imidazole, DMF, r.t.; d) O_3, CH_2Cl_2, –78 °C, 10% $Pd(OH)_2$, H_2, EtOH, r.t.; e) CbzCl, K_2CO_3, CH_2Cl_2, 0 °C; f) Dowex 50W-X8, 90% MeOH, r.t.

Table 1 Stereoselective Allylation of Aminoaldehyde with Allylbromide[a]



Entry	Chiral promoter	Condition[b]	Ratio[c] (*syn*/*anti*)	Yield (%)[d]
1	None	THF	2:1	70
2	None	THF–H_2O (3:1)	3:1	75
3	(+)-cinchonine	THF	50:1	87
4	(+)-cinchonine	THF–hexane (3:1)	1:1	75
5	(–)-cinchonidine	THF	1:2	80

[a] All experiments were performed at least in duplicate.
[b] The solution of allylbromide was heated to reflux with indium prior to reaction. The mixture was cooled prior to introduction of the aldehyde.
[c] The ratio was determined by ^1H NMR analysis of the reaction mixtures.
[d] Isolated yield.

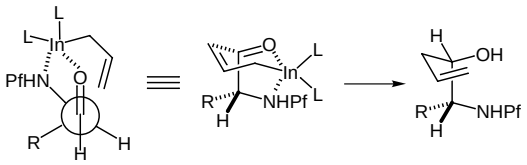


Figure 2

The secondary hydroxy group of **4** was easily protected with TBDMSCl, to give silylate **5** in 98% yield. The terminal olefin group in **5** should be cleaved for the formation of five-membered ring in castanospermine. The compound **5** was ozonized with anticipation of the aldehyde product, but this reaction kept running directly to intramolecular amination to give corresponding hemiaminal **15**, which was used in the next step without a further purification (Figure 3).

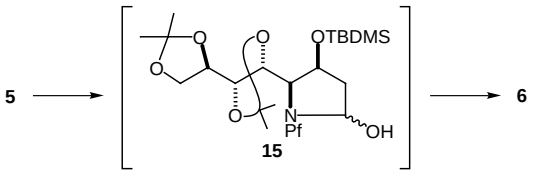
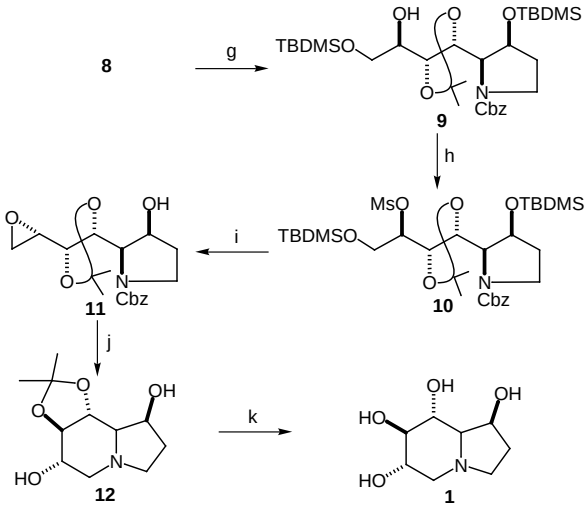


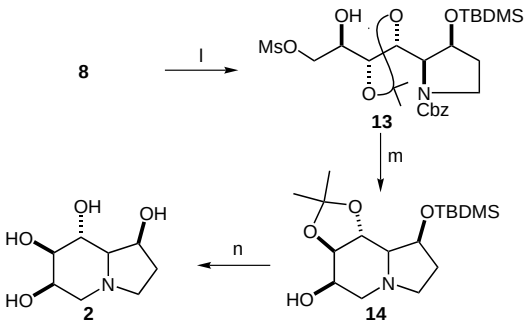
Figure 3

Catalytic hydrogenolysis of hemiaminal **15** over palladium hydroxide in EtOH cleaved Pf group, and subsequently produced pyrrole **6** in 63% yield from **5**. The observed one-pot cyclization probably curtailed two steps in our scheme. The pyrrole **6** was protected with benzyl chloroformate (CbzCl) in quantitative yield. For regioselective hydrolysis of the terminal *O*-isopropylidene group in diisopropylidene **7** under acidic condition, Dowex 50W-X8 was treated with **7** in 90% MeOH to give diol **8** in 93% yield.



Scheme 3 g) TBDMSCl, Imidazole, CH_2Cl_2, r.t.; h) MsCl, Et_3N, CH_2Cl_2, 0 °C; i) TBAF, K_2CO_3, THF, r.t.; j) H_2, 10% Pd/C, NaOAc, MeOH, 60 °C; k) Dowex 50W-X8, THF–H_2O (3:1), reflux

The primary hydroxy group of **8** was highly selectively protected with TBDMSCl to give **9**, and the secondary hydroxy group of **9** was mesylated to give compound **10** in 92% yield. To prepare (+)-castanospermine (**1**) from the well-designed intermediate **10**, all that was required was the inversion of the C3′ hydroxy group. The inversion of stereochemistry at C3′ in **11** was accomplished by epoxidation. The TBDMS group of **10** was deprotected with tetrabutylammonium fluoride (TBAF) in THF at room temperature and then treated with K_2CO_3 in MeOH to give epoxide **11** in 90% yield. Hydrogenolysis of epoxide **11** in the presence of 10% Pd/C and NaOAc removed the Cbz group and led to highly selective 6-membered intramolecular cyclization to give indolizidine **12** in 65% yield. (+)-Castanospermine (**1**) was easily obtained by treatment of **12** with Dowex 50W-X8 in THF–H_2O (3:1) in nearly quantitative yield without the necessity of additional ion-exchange chromatography. The spectral and physical properties of (+)-castanospermine (**1**) matched those reported in the literature {$[\alpha]_D^{20}$ +79.8 (*c* 0.90, H_2O); lit.,[14] $[\alpha]_D^{20}$ +79.7 (*c* 1.06, H_2O)} (Scheme 3).



Scheme 4 l) MsCl, Et_3N, CH_2Cl_2, –40 °C; m) 10% Pd/C, H_2, MeOH, NaOAc, r.t.; n) Dowex 50W-X8, THF–H_2O (3:1), reflux.

(+)-6-Epicastanospermine (2)

Diol **8** was treated with mesylchloride under CH_2Cl_2 at –40 °C for 5 minutes to give monomesylate **13** selectively in 86% yield (based on 68% conversion). The longer reaction time results in a diminution of selectivity. Monomesylate **13** was hydrogenated in the presence of 10% Pd/C and NaOAc to remove Cbz group, and led to direct intramolecular cyclization to give indolizidine **14** in 85% yield. Indolizidine **14** was protected with acid-sensitive groups and was refluxed with Dowex 50W-X8 in 90% MeOH for 5 hours and filtered. The filterate was washed with MeOH, and then eluted with 3 N NH_3 solution to afford enantiomerically pure (+)-6-epicastanospermine (**2**) in 90% yield (Scheme 4). The physical properties and the ^1H and ^{13}C spectral data of (+)-6-epicastanospermine (**2**) matched with those reported in the literature {$[\alpha]_D^{20}$ +2.8 (*c* 1.00, H_2O); lit.,[8] $[\alpha]_D^{20}$+2.2 (*c* 0.70, MeOH)}. The relative stereochemistry of the target molecules **1** and **2** were determined from 2D NOESY experiment. Strong NOE cross peaks were observed only between H1–H8a in compound **1**, and between H1–H8a and H6–H7 in compound **2**.

We have prepared (+)-castanospermine (**1**) and (+)-6-epicastanospermine (**2**) through highly diastereoselective indium-mediated allylation. The developed synthetic route should be valuable for the total synthesis of indolizidine alkaloids as like swainsonine and lentiginosine.

All non-aqueous reactions were carried out under an inert N_2 atmosphere. THF was distilled from Na/benzophenone whereas Et_3N, 2,2-dimethoxypropane, DMF, and CH_2Cl_2 were distilled from CaH_2. All reactions were monitored by TLC with commercially available glass-backed plates. Column chromatography was carried out using 230–400 mesh silica gel. Final solution before the removal of solvent was washed with brine and dried over anhyd Na_2SO_4. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured downfield relative to TMS on a Brucker AW-500 spectrometer in $CDCl_3$ unless otherwise noted (δ in ppm). HREIMS were obtained on a JEOLJMS-700 mass spectrometer. Optical rotations were measured on a Perkin-Elmer polarimeter 343 and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

2-[(9-Phenylfluoren-9-yl)-amino]-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannose (3)

This compound was prepared as described in literature;[8] $[\alpha]_D^{20}$ +16.9 (*c* 0.49, $CHCl_3$).

IR (neat): 1720, 3305 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.09, 1.18, 1.25, 1.27 (4 s, 12 H), 2.83 (m, 1 H), 3.45 (br s, 1 H), 3.72–3.83 (m, 3 H), 3.93 (dd, *J* = 7.0, 5.0 Hz, 1 H), 4.02 (m, 1 H), 7.19–7.63 (m, 13 H), 9.27 (d, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 25.2, 25.6, 25.7, 62.1, 66.5, 71.7, 77.3, 80.5, 108.7, 108.9, 118.9, 119.1, 124.1, 124.6, 125.2, 126.3, 126.8, 126.9, 127.2, 127.5, 127.8, 139.6, 139.7, 143.1, 147.8, 147.9, 200.1.

Anal. Calcd for $C_{31}H_{33}NO_5$: C, 74.5; H, 6.6; N, 2.8. Found: C, 74.4; H, 6.7; N, 2.7.

(1*S*)-1-Allyl-2-[(9-phenylfluoren-9-yl)-amino]-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol (4)

Allylbromide (0.98 g, 7.61 mmol) was added to an In suspended solution (0.26 g, 2.28 mmol) in THF (20 mL) and then the reaction mixture was stirred vigorously till it became clear at reflux to which then was added (+)-cinchonine (0.88 g, 3.04 mmol) at r.t. To the reaction mixture was added compound **3** (0.76 g, 1.52 mmol) at –78 °C and then stirred for 2 h. The reaction mixture was filtered and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc, 15:1) to give compound **4** (0.72 g, 87%) as a solid; mp 115–116 °C, $[\alpha]_D^{20}$ +182.8 (*c* 2.00, $CHCl_3$).

IR (neat): 1636, 2997, 3078, 3509 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.05 (s, 3 H), 1.16 (s, 3 H), 2.25 (m, 1 H), 2.40 (m, 1 H), 2.56 (s, 1 H), 3.19 (m, 1 H), 3.33 (t, *J* = 8.0 Hz, 1 H,), 3.42 (dd, *J* = 8.5, 2.0 Hz, 1 H), 3.66 (dd, *J* = 8.5, 5.0 Hz, 1 H), 3.73 (t, *J* = 6.5 Hz, 1 H), 3.81 (dd, *J* = 8.5, 6.5 Hz, 1 H), 4.96 (m, 1 H), 5.03 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.63 (m, 1 H), 7.19–7.70 (m, 13 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.3, 26.6, 27.5, 38.9, 54.9, 67.5, 71.3, 72.5, 77.7, 78.1, 83.3, 109.4, 109.6, 117.1, 120.4, 120.5, 125.6, 126.3, 126.6, 127.5, 128.1, 128.2, 128.6, 128.7, 136.1, 140.6, 141.3, 145.9, 149.3, 152.1.

Anal. Calcd for $C_{34}H_{39}NO_5$: C, 75.4; H, 7.3; N, 2.6. Found: C, 75.3; H, 7.2; N, 2.5.

(1*S*)-1-Allyl-1-*O*-*t*-butyldimethylsilyl-2-[(9-phenylfluoren-9-yl)-amino]-2-deoxy-3,4;5,6-di-*O*-isopro-pylidene-D-mannitol (5)
To a solution of **4** (2.20 g, 4.06 mmol) in anhyd DMF (20 mL) were added imidazole (0.69 g, 10.15 mmol) and TBDMSCl (0.91 g, 6.09 mmol) at r.t. After stirring for 6 h, sat. $NaHCO_3$ (60 mL) was added and the mixture was extracted with EtOAc (5 × 20 mL). The combined extract was evaporated, and the residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give compound **5** (2.61 g, 98%) as a solid; mp 73–74 °C, $[\alpha]_D^{20}$ +70.3 (*c* 2.0, $CHCl_3$).

IR (neat): 1648, 2590, 2935, 3070 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.21 (s, 3 H), 0.95 (s, 9 H), 1.40 (d, *J* = 4.5 Hz, 6 H), 1.44 (d, *J* = 10 Hz, 6 H), 2.17 (m, 1 H), 2.45 (s, 1 H), 3.12 (m, 1 H), 3.32 (dd, *J* = 8.5, 5.0 Hz, 1 H), 3.73 (m, 2 H), 3.78 (t, *J* = 8.0 Hz, 1 H), 3.92 (m, 1 H), 4.44 (m, 1 H), 5.06 (m, 2 H), 5.73 (m, 1 H), 7.35–7.89 (m, 13 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.0, 25.4, 25.9, 26.2, 26.7, 27.5, 38.8, 55.8, 65.3, 72.8, 75.7, 76.4, 80.9, 108.4, 108.8, 116.4, 120.0, 125.7, 126.2, 127.0, 127.8, 128.0, 128.2, 128.3, 128.4, 136.7, 140.1, 141.0, 145.6, 150.0 and 150.8.

Anal. Calcd for $C_{40}H_{53}NO_5Si$: C, 73.2; H, 8.1; N, 2.1. Found: C, 73.2; H, 8.1; N, 2.2

(1′*R*,2′*S*,3′*R*,3*S*)-2-(1′,2′,3′,4′-*O*-Di-isopropylidene-1′,2′,3′,4′-tetrahydroxy butyl)-3-*O*-*t*-butyldimethylsilyl-3-hydroxypyrrolidine (6)
A solution of **5** (2.61 g, 3.98 mmol) in MeOH (30 mL) was ozonized at –78 °C until the solution turned blue, then the residual ozone was removed with N_2 gas. Then dimethylsulfide (0.87 mL, 11.94 mmol) was added, and the reaction mixture was allowed to warm to r.t. (12 h). The solvent was evaporated to give corresponding hemiaminal **12**, the remaining residue was directly hydrogenated with 10% $Pd(OH)_2/C$ (0.03 g) in EtOH (30 mL) for 10 h, and the mixture was filtered and the solvent was evaporated. The residue was chromatographed on silica gel (CH_2Cl_2–acetone, 10:1) to give the compound **6** (1.01 g, 63%) as an oil; $[\alpha]_D^{20}$+37.9 (*c* 2.0, $CHCl_3$).

IR (neat): 2983, 3354 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.81 (s, 9 H), 1.27 (m, 9 H), 1.36 (s, 3 H), 1.69 (m, 1 H), 1.82 (m, 1 H), 2.84 (m, 2 H), 3.10 (m, 1 H), 3.90 (m, 3 H), 4.04 (m, 2 H), 4.24 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.0, –4.7, 18.2, 25.4, 25.8, 26.4, 27.1, 27.4, 35.7, 44.6, 67.1, 67.3, 72.8, 77.3, 77.8, 80.8, 109.1, 109.7.

Anal. Calcd for $C_{20}H_{39}NO_5Si$: C, 59.8; H, 9.8; N, 3.5. Found: C, 59.9; H, 9.7; N, 3.4.

(1′*R*,2′*S*,3′*R*,3*S*)-2-(1′,2′,3′,4′-*O*-Di-isopropylidene-1′,2′,3′,4′-tetrahydroxy butyl)-3-(*O*-*t*-butyl dimethylsilyl)-3-hydroxy-*N*-(benzyloxycarbonyl)-pyrrolidine (7)
To a solution of pyrrolidine **6** (1.01 g, 2.51 mmol) in CH_2Cl_2 (10 mL) was added aq K_2CO_3 (1.05g, 7.68 mmol) and the mixture was cooled in an ice-bath. To this stirred mixed-phase solution was added dropwise a solution of benzylchloroformate (0.73 mL, 5.12 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at r.t. for 30 min. The organic phase was washed with brine, and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc, 6:1) to give compound **7** (1.21 g, 90%) as an oil; $[\alpha]_D^{20}$ +15.1 (*c* 2.0, $CHCl_3$).

IR (neat): 1698, 2942 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.94 (s, 9 H), 1.16–1.37 (m, 12 H), 1.92 (m, 1 H), 2.05 (m, 1 H), 3.28–3.35 (m, 2 H), 3.77 (m, 2 H), 3.97 (m, 2 H), 4.15 (m, 1 H), 4.29 (m, 2 H), 5.00 (m, 1 H), 5.11 (m, 1 H), 7.17–7.30 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.1, –5.0, –4.8, 18.2, 25.4, 25.8, 26.4, 27.0, 27.2, 31.2, 31.9, 43.2, 43.3, 59.0, 60.3, 66.9, 67.0, 67.8, 72.2, 72.9, 76.8, 79.5, 80.5, 109.4, 127.9, 128.0, 128.3, 128.5, 136.7, 155.7.

Anal. Calcd for $C_{28}H_{45}NO_7Si$: C, 62.8; H, 8.5; N, 2.6. Found: C, 62.7; H, 8.4; N, 2.6.

(1′*R*,2′*S*,3′*R*,3*S*)-2-(1′,2′-*O*-Isopropylidene-1′,2′,3,4-tetrahydroxy butyl)-3-*O*-*t*-butyl-dimethylsilyl-3-hydroxy-*N*-(benzyloxycarbonyl)-pyrrolidine (8)
To a solution of compound **7** (1.21 g, 2.26 mmol) in 90% MeOH was added Dowex 50W-X8 resin (400 mg). The reaction mixture was stirred for 18 h at r.t., then filtered and the solvent was evaporated. The crude residue was chromatographed on silica gel (hexane–EtOAc, 2:1) to give compound **8** (1.04 g, 93%) as an oil; $[\alpha]_D^{20}$ +20.6 (*c* 2.0, $CHCl_3$).

IR (neat): 1686, 2942, 3442 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.81 (s, 9 H), 1.24–1.31 (m, 6 H), 1.87 (m, 1 H), 2.08 (m, 1 H), 3.37 (m, 2 H), 3.53–3.61 (m, 3 H), 4.01 (m, 1 H), 4.18–4.34 (m, 4 H), 4.98–5.07 (m, 2 H), 7.16–7.28 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.1, –4.9, 18.2, 25.8, 27.0, 27.2, 32.2, 43.9, 64.1, 67.2, 72.6, 73.5, 76.8, 78.1, 79.3, 109.3, 128.2, 128.5, 136.5.

Anal Calcd for $C_{25}H_{41}NO_7Si$: C, 60.6; H, 8.3; N, 2.8. Found: C, 60.5; H, 8.4; N, 2.8.

(1′*R*,2′*S*,3′*R*,3*S*)-2-(1′, 2′-*O*-Isopropylidene-4′-*O*-*t*-butyldimethylsilyl-1′,2′,3′,4′-tetrahydroxy-butyl)-3-*O*-*t*-butyldimethylsilyl-3-hydroxy-*N*-(benzyloxycarbonyl)-pyrrolidine (9)
To a solution of diol **8** (1.04 g, 2.10 mmol) in CH_2Cl_2 (10 mL) were added imidazole (0.37 g, 5.45 mmol) and TBDMSCl (0.54 g, 3.36 mmol) at r.t. After stirring the mixture for 1 h, sat. $NaHCO_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was concentrated and the residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give compound **9** (1.27 g, 99%) as an oil; $[\alpha]_D^{20}$ +10.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 1704, 2950, 3489 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 12 H), 0.83 (s, 18 H), 1.18–1.37 (m, 6 H), 1.90 (br s, 1 H), 2.12 (m, 1 H), 3.31 (m, 1 H), 3.39 (m, 2 H), 3.50 (m, 1 H), 3.73 (m, 1 H), 4.09 (m, 1 H), 4.23–4.33 (m, 3 H), 5.10 (d, *J* = 12.4 Hz, 1 H), 5.11 (d, *J* = 12.2 Hz, 1 H), 4.32 (m, 1 H), 7.31 (m, 5 H).

^{13}C NMR(125 MHz, $CDCl_3$): δ = –5.3, –5.0, 18.2, 18.3, 25.8, 25.9, 27.0, 43.4, 64.9, 74.3, 77.3, 109.3, 127.9, 128.4, 136.9, 155.7.

Anal. Calcd for $C_{31}H_{55}NO_7Si_2$: C, 61.0; H, 9.1; N, 2.3. Found; C, 61.0; H, 9.1; N, 2.3.

(1′*R*,2′*S*,3′*R*,3*S*)-2-(1′, 2′-*O*-Isopropylidene-3′-*O*-methanesulfonyl-4′-*O*-*t*-butyldimethylsilyl-1′,2′,3′,4′-tetrahydroxybutyl)-3-*O*-*t*-butyldimethylsilyl-3-hydroxy-*N*-(benzyloxycarbonyl)-pyrrolidine (10)
To a solution of compound **9** (1.27 g, 2.08 mmol) in THF (8 mL) were added Et_3N (0.63 mL, 4.58 mmol) and methanesulfonyl chloride (0.19 mL, 2.50 mmol) at 0 °C. The reaction mixture was stirred for 20 min at r.t., and was then quenched with sat. $NaHCO_3$ (30 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL). The organic layer was concentrated and the residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give compound **10** (1.32 g, 92%) as an oil; $[\alpha]_D^{20}$ +28.3 (*c* 1.0, $CHCl_3$).

IR (KBr): 1697, 2960 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 12 H), 0.82 (s, 18 H), 1.29 (s, 3 H), 1.37 (s, 3 H), 1.85–1.94 (m, 2 H), 3.03 (s, 3 H), 3.39 (m, 3

H), 3.72 (m, 1 H), 3.95 (m, 1 H), 4.24–4.32 (m, 2 H), 4.60 (m, 2 H), 5.05 (m, 2 H), 7.27 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.4, –5.1, 18.4, 25.8, 26.0, 27.1, 32.5, 38.9, 44.0, 61.9, 62.5, 67.2, 72.1, 77.3, 83.8, 109.9, 128.0, 128.5, 128.7, 136.7, 156.6.

Anal. Calcd for $C_{32}H_{57}NO_9SSi_2$: C, 55.9; H, 8.4; N, 2.0. Found; C, 55.8; H, 8.4; N, 2.0.

(1′*R*,2′*S*,3′*S*,3*S*)-2-(3′,4′-Anhydro-1′,2′-*O*-isopropylidene-1′,2′-dihydroxybutyl)-3-hydroxy-*N*-(benzyloxycarbonyl)-pyrrolidine (11)

To a solution of **10** (1.32 g, 1.91 mmol) in THF (8 mL) was added TBAF in 1 M THF (4.20 mL) and stirred for 2 h at r.t. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was concentrated and added to K_2CO_3 (0.5 g) in MeOH (8 mL). The mixture was stirred for 30 min at r.t., and was quenched with sat. $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 15 mL). The organic phase was evaporated and chromatographed on silica gel (hexane–EtOAc, 10:1) to give compound **11** (0.62 g, 90%) as an oil; $[\alpha]_D^{20}$ +51.4 (*c* 2.0, $CHCl_3$).

IR (KBr): 1648, 2937, 3465 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.44 (s, 3 H), 2.03 (m, 2 H), 2.71 (m, 2 H), 2.90 (s, 1 H), 3.36 (m, 1 H), 3.48–3.63 (m, 2 H), 4.07 (m, 1 H), 4.28 (t, *J* = 12.5 Hz, 1 H,), 4.44–4.49 (m, 2 H), 5.11 (s, 2 H), 7.32 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4, 27.1, 32.5, 44.5, 44.7, 51.3, 61.3, 67.2, 72.6, 77.5, 77.9, 78.2, 109.7, 127.9, 128.2, 128.6, 136.4, 156.0.

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.8; H, 6.9; N, 3.9. Found; C, 62.8; H, 6.9; N, 3.8.

7,8-*O*-Isopropylidene-(+)-castanospermine (12)

A mixture of epoxide **11** (0.62 g, 1.71 mmol), NaOAc (0.45 g) and 10% Pd/C (0.03 g) in MeOH (8 mL) was hydrogenated at 60 °C for 6 h. After the reaction mixture was filtered with Celite, the filtrate was concentrated. The remaining residue was chromatographed on silica gel (CH_2Cl_2–acetone, 3:1) to give compound **12** (0.25 g, 65%) as an oil; $[\alpha]_D^{20}$ +40.1 (*c* 0.4, $CHCl_3$).

IR (KBr): 1678, 2956, 3455, cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 1.42 (s, 3 H), 1.43 (s, 3 H), 1.91 (m, 1 H), 2.00 (m, 1 H), 3.12–3.15 (m, 2 H), 3.21–3.31 (m, 1 H), 3.80 (dd, *J* = 12.9, 5.4 Hz, 1 H), 3.97 (dd, *J* = 12.9, 3.2 Hz, 1 H), 4.26 (t, *J* = 5.8 Hz, 1 H), 4.50 (m, 2 H), 4.80 (m, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 26.7, 27.9, 28.0, 39.3, 45.8, 62.4, 68.9, 74.5, 76.7, 80.8, 84.7, 111.6.

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.6; H, 8.4; N, 6.1. Found: C, 57.6; H, 8.3; N, 6.1.

(+)-Castanospermine (1)

To a solution of **12** (0.25 g, 1.09 mmol) in THF–H_2O (3:1) was added Dowex 50W-X8 (200 mg) and the solution was refluxed overnight. The reaction mixture was filtered, and washed with MeOH. The remaining residue was eluted with 2 N NH_3 solution. The NH_3 solution was evaporated to give compound **1** (0.19 g, 92%) as a solid; mp 203–205 °C (decomp.), $[\alpha]_D^{20}$ +79.8 (*c* 0.9, H_2O).

IR (KBr): 1658, 2980, 3484 cm^{-1}.

^{1}H NMR (500 MHz, D_2O): δ = 1.69 (m, 1 H), 2.15–2.17 (m, 2 H), 2.26–2.33 (m, 2 H), 3.14 (m, 1 H), 3.20 (dd, *J* = 11, 5.0 Hz, 1 H), 3.29 (t, *J* = 9.1 Hz, 1 H), 3.54–3.60 (m, 2 H), 4.38 (m, 1 H).

^{13}C NMR (125 MHz, D_2O): δ = 32.9, 51.9, 55.2, 68.8, 69.6, 70.0, 71.7, 78.9.

MS (FAB): *m*/*z* = 211.92 (M + Na).

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.8; H, 8.0; N, 7.4. Found: C, 50.7; H, 7.9; N, 7.4.

(1′*R*,2′*S*,3′*R*,3*S*)-2-(1′, 2′-*O*-Isopropylidene-4′-*O*-methansulfonyl-1′,2′,3′,4′-tetrahydroxybutyl)-3-*O*-*t*-butyldimethylsilyl-3-hydroxy-*N*-(benzyloxycarbonyl)-pyrrolidine (13)

To a solution of **8** (1.03 g, 2.09 mmol) in CH_2Cl_2 (10 mL) were added diluted Et_3N (0.32 mL, 2.30 mmol) in CH_2Cl_2 (5 mL) and diluted MsCl (0.18 mL, 2.3 mmol) in CH_2Cl_2 (5 mL) at –40 °C. The reaction mixture was stirred for 5 min at same temperature, and then sat. $NaHCO_3$ (50 mL) was added and extracted with CH_2Cl_2 (5 × 25 mL). The combined extract was evaporated, and the residue was chromatographed on silica gel (hexane–EtOAc, 3:1) to give compound **13** (1.03 g, 86%, based on 68% conversion) as an oil and starting material **8** (0.33 g); $[\alpha]_D^{20}$ +34.3 (*c* 1.5, $CHCl_3$).

IR (KBr): 1687, 2943, 3433 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.81 (s, 9 H), 1.22 (s, 3 H), 1.30 (s, 3 H), 1.87 (br s, 1 H), 2.06 (m, 1 H), 2.93 (s, 3 H), 3.38 (m, 2 H), 3.68 (br s, 1 H), 4.00 (m, 1 H), 4.11–4.22 (m, 3 H), 4.33 (m, 2 H), 5.00–5.08 (m, 2 H) and 7.16–7.28 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = – 5.1, –4.9, 18.2, 25.8, 27.0, 27.1, 37.5, 67.3, 71.8, 72.4, 72.7, 109.8, 128.2, 128.6 and 136.5.

Anal. Calcd for $C_{26}H_{43}NO_9SSi$: C, 54.4; H, 7.6; N, 2.4. Found: C, 54.4; H, 7.5; N, 2.5.

1-*O*-*t*-Butyldimethylsilyl-7,8-*O*-isopropylidene-(+)-6-epicastanspermine (14)

A mixture of **13** (1.00 g, 1.74 mmol), NaOAc (0.89 g, 10.8 mmol) and 10% Pd/C (50 mg) in MeOH (10 mL) was hydrogenated at atmospheric pressure for 10 h. The catalyst was filtered, the filtrate was refluxed for 2 h, and the reaction mixture was filtered, and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2–acetone, 10:1) to give compound **14** (0.51 g, 85%) as an oil; $[\alpha]_D^{20}$ +4.8 (*c* 1.5, $CHCl_3$).

IR (KBr): 1648, 2937, 3455 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.81 (s, 9 H), 1.36 (s, 6 H), 1.75 (s, 1 H), 2.03 (m, 1 H), 2.13 (m, 2 H), 2.21 (d, *J* = 12 Hz, 3 H), 2.34 (br s, 1 H), 3.06 (m, 1 H), 3.13 (dd, *J* = 12, 2.5 Hz, 1 H), 3.28 (dd, *J* = 9.5, 2.5 Hz, 1 H), 3.90 (t, *J* = 9.3 Hz, 1 H), 4.16 (s, 1 H), 4.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.0, –4.9, 18.4, 25.9, 26.6, 27.0, 35.1, 51.8, 55.7, 65.8, 70.3, 71.3, 71.4, 82.1, 110.2.

Anal. Calcd for $C_{17}H_{33}NO_4Si$: C, 59.4; H, 9.7; N, 4.1. Found: C, 59.5; H, 9.6; N, 4.0.

(+)-6-Epicastanospermine (2)

To a solution of **14** (0.51 g, 1.48 mmol) in THF–H_2O (3:1) was added Dowex 50W-X8 (200 mg) and refluxed overnight. The mixture was filtered, and washed with MeOH. The remaining residue was eluted with 2 N NH_3 solution. The NH_3 solution was evaporated to give compound **2** (0.25 g, 90%) as a solid, mp 203–206 °C (decomp.); $[\alpha]_D^{20}$ +2.8 (*c* 1.0, H_2O).

IR (KBr): 1648, 2940, 3394 cm^{-1}.

^{1}H NMR (500 MHz, D_2O): δ = 1.67 (m, 1 H), 1.95 (m, 1 H), 2.18 (m, 1 H), 2.26 (m, 2 H), 3.07 (m, 2 H), 3.47 (dd, *J* = 9.5, 3.0 Hz, 1 H,), 3.82 (m, 1 H), 3.94 (m, 1 H), 4.33 (m, 1 H).

^{13}C NMR(125 MHz, D_2O): δ = 33.0, 52.1, 55.6, 67.4, 69.1, 70.3, 72.1, 75.6.

MS: *m*/*z* = 189 (M^+).

HRMS–FAB: *m*/*z* [M] calcd for $C_8H_{15}NO_4$, 189.1001; found, 189.1003.

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