A Concise, Enantioselective Synthesis of Castanospermine

No-Soo Kim, Jong-Ryoo Choi, and Jin Kun Cha*,†

Department of Chemistry, University of Alabama, Tuscaloosa, Alabama 35487

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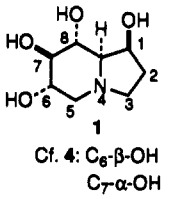
A stereoselective synthesis of the polyhydroxy indolizidine alkaloids castanospermine (1) and 6,7-diepicastanospermine (4) has been achieved starting from the readily available alcohol 8. Subsequent Sharpless asymmetric epoxidation, followed by the azide displacement of the tosyl group gave the epoxy azide 12. The asymmetric dihydroxylation of 12 with $(DHQ)_2$–PHAL gave the triol 13 in good diastereoselectivity. Alcohol protection, followed by reductive double cyclization of the resulting epoxy azide 17 gave 5-indolizidinone 18, which was then uneventfully converted to 1. On the other hand, the use of $(DHQD)_2$–PHAL in the dihydroxylation of 12 provided a stereoselective preparation of 4.

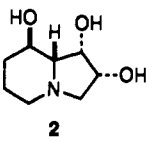
Polyhydroxylated indolizidine alkaloids continue to attract considerable attention due to their well-established function as glycosidase inhibitors and as inhibitors of glycoprotein processing.[1] Castanospermine (1), swainsonine (2), and deoxynojirimycin (3) in particular have also found use in anticancer, antiviral, and antiretroviral research.[2] For example, castanospermine has been shown to inhibit the infectivity of retroviruses, especially the human immunodeficiency virus (HIV).[3,4]

The high profile of castanospermine has resulted in a spate of syntheses of 1 and analogs.[5] Development of general synthetic methods which embody considerable flexibility for the construction of other stereoisomers and analogs continues to be important to probe structure–activity correlations. Toward this end we have developed a concise, enantioselective synthesis of castanospermine (1) and 6,7-diepicastanospermine (4).[6]



1

Cf. 4: C_6-β-OH
C_7-α-OH



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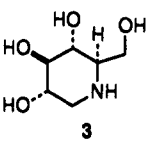

3

Results and Discussion

In our retrosynthetic analysis we envisaged that a conceptually appealing approach to castanospermine would arise from aziridine 5 through the diastereoselective dihydroxylation, followed by intramolecular ring-opening of the aziridine by the carboxyl group and concomitant lactam formation (Scheme I). The aziridine 5 in turn should be available stereoselectively by the intramolecular azide-diene cycloaddition methodology independently developed by Hudlicky and Pearson.[7-10] Alternatively, the double cyclization of the epoxy amine derived from azide 9 would provide an expedient entry to castanospermine.[11]

The latter synthetic approach was readily reduced to practice with excellent stereocontrol, as outlined in Scheme II. The requisite diene 7 was prepared in 41% overall yield by the use of iterative Horner–Emmons–Wittig reactions, starting from the known and readily available lactol 10.[9c,12] Not surprisingly, epoxidation of 7 with

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(10) The intramolecular 1,3-dipolar cycloaddition of azido diene 6 took place with complete diastereoselectivity to provide aziridine 5. Subsequent elaborations of the latter toward 1 and related structural analogs are currently in progress.

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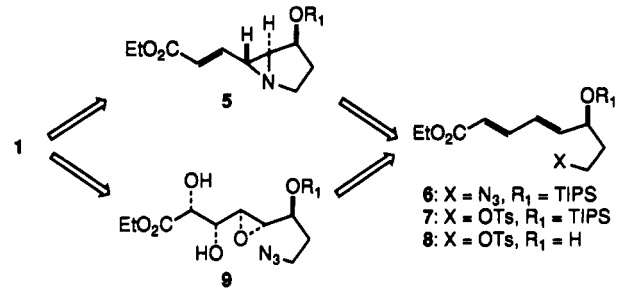
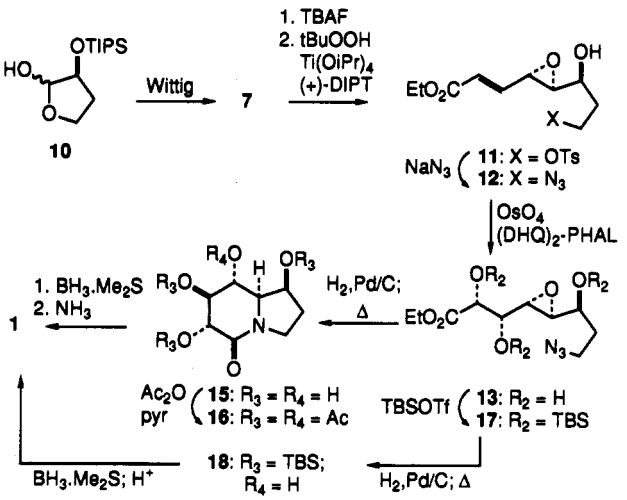
0022-3263/93/1958-7096$04.00/0

Scheme I



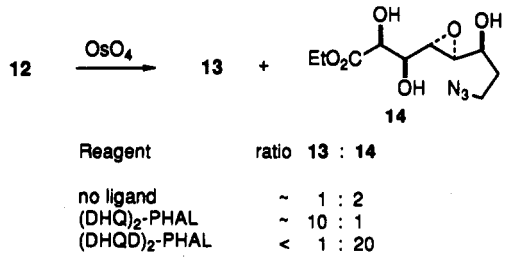
Scheme II



mCPBA was nonstereoselective, affording a chromatographically inseparable 1:1 mixture of the two diastereomeric epoxides. However, the desired *erythro* epoxidation could be achieved with complete stereocontrol by means of the Sharpless epoxidation.[13] Thus, the triisopropylsilyl (TIPS) protecting group was first removed with n-Bu_4NF (THF, 0 °C, 0.5 h) to give alcohol 8 (91%). The asymmetric epoxidation of 8 using (+)-diisopropyl tartrate then afforded the *erythro* epoxide 11, as a single isomer, in 81–90% yield. Subsequent treatment with NaN_3 (DMF, room temperature, 14 h) gave azide 12 in 73% yield.[14]

Our attention was next turned to the introduction of the *threo* dihydroxy groups at the C(6) and C(7) positions (castanospermine numbering) by osmylation. Guided by Kishi's empirical rule,[15] we were cognizant that the stereoselective preparation of the requisite *syn*-epoxy diol **13** would impose the "mismatched" diastereocontrol.[16] We anticipated that the Sharpless asymmetric dihydroxylation[17] would override the directing effect of the epoxy group to afford stereoselectively the desired diol **13**, since the inherent diastereoselectivity by the epoxy group in osmylation would be less dominant than that dictated by other allylic oxygen substituents. The inherent diastereoselectivity of olefin **12** was ~2:1 as gleaned from dihydroxylation with OsO_4 alone (Scheme III). In the event, the pivotal dihydroxylation with $(DHQ)_2$-PHAL[18] proceeded with ~10:1 diastereoselectivity to afford the desired product **13**. The effect of matching substrate diastereoselectivity with catalyst enantioselectivity was also examined: with $(DHQD)_2$-PHAL[18] as ligand, triol **14** was obtained virtually as a single isomer.

Scheme III



The double cyclization of **13** to indolizidine **15** was accomplished without incident by reduction of the azide functionality (H_2, 10% Pd/C, EtOH or Ph_3P–H_2O), followed by heating of the resulting crude amine in refluxing ethanol. To facilitate the isolation and full characterization, indolizidine **15** was converted into the corresponding tetraacetate **16** in 13% overall yield from **12**. Finally, reduction of lactam **16** with BH_3·Me_2S, followed by global deprotection, afforded (+)-**1** in 55% yield. The physical and spectral data of synthetic (+)-**1** were identical with those of an authentic sample of natural (+)-castanospermine.[19]

The overall efficiency of the double cyclization process was enhanced by isolating the osmylation product **13** as the tris-TBS derivative **17** (in 42% yield). The reductive cyclization of the latter to **18** was then achieved in 54% yield. Subsequent reduction with BH_3·Me_2S, followed by global deprotection with TFA gave (+)-**1** in 71% yield. Similarly, the azido epoxide **14** was converted to (+)-6,7-diepicastanospermine (**4**).

In conclusion, we have developed an efficient method for preparing castanospermine and stereoisomers. Our synthesis further underscores the usefulness of the Sharpless asymmetric epoxidation and dihydroxylation in natural product synthesis.

Experimental Section[20]

Ethyl (6*S*)-6-(Triisopropylsiloxy)-8-[(*p*-toluenesulfonyl)oxy]-(*E*,*E*)-2,4-octadienoate (7). To a solution of (4*S*)-4-(triisopropylsiloxy)-6-[(*p*-toluenesulfonyl)oxy]-(*E*)-2-hexenal (750 mg, 1.7 mmol) in dry benzene (20 mL) was added (carbethoxymethylene)triphenylphosphorane (1.19 g, 3.4 mmol). The reaction mixture was heated at 55 °C for 1.5 h. After removal of the solvent, the resulting crude product was purified by flash column chromatography on silica gel using 8:1 hexane–EtOAc as eluent to give 765 mg (89%) of **7** as a colorless liquid: $[\alpha]^{25}_D$ = −11.5° (*c* 0.46, $CDCl_3$); IR (film) 1715 (s), 1366 (s), 1178 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.99 (br s, 21 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.85–1.99 (m, 2 H), 2.45 (s, 3 H), 4.03–4.08 (m, 1 H), 4.12–4.16 (m, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 4.46 (dt, J = 5.9, 6.1 Hz, 1 H), 5.83 (d, J = 15.4 Hz, 1 H), 5.94 (dd, J = 6.1, 15.4 Hz, 1 H), 6.19 (dd, J = 11.0, 15.4 Hz, 1 H), 7.18 (dd, J = 11.0,

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(14) Azide displacement of the tosyl group in the corresponding TIPS-protected tosylate **7** was achieved in nearly quantitative yield.
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15.4 Hz, 1 H), 7.34 (d, J = 8.2 Hz, 2 H), 7.77 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 12.3 (3C), 14.3, 18.0 (6C), 21.6, 37.2, 60.4, 66.7, 69.4, 121.9, 127.9 (2C), 129.8, 133.1, 143.3, 143.8, 144.8, 166.8; HRMS(M^+) calcd 510.2473 for $C_{26}H_{42}O_6SSi$, found 510.2471.

Ethyl (6*S*)-6-Hydroxy-8-[(*p*-toluenesulfonyl)oxy]-(*E*,*E*)-2,4-octadienoate (8). To a solution of **7** (1.15 g, 2.25 mmol) in 30 mL of THF was added 2.3 mL of tetrabutylammonium fluoride at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and quenched with water. The product mixture was extracted twice with EtOAc, and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvents were evaporated *in vacuo*, and the resulting crude product was purified by flash column chromatography on silica gel using 2:1 hexane–EtOAc to give 726 mg (91%) of **8** as a colorless liquid: $[\alpha]^{25}_D$ = +10.1° (*c* 0.63, $CDCl_3$); IR (film) 3510 (w), 1710 (s), 1368 (s), 1182 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.27 (t, J = 7.1 Hz, 3 H), 1.81–1.90 (m, 2 H), 2.43 (s, 3 H), 4.06–4.10 (m, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.22–4.24 (m, 1 H), 4.38 (br m, 1 H), 5.83 (d, J = 15.3 Hz, 1 H), 6.00 (dd, J = 6.0, 15.3 Hz, 1 H), 6.29 (dd, J = 11.0, 15.3 Hz, 1 H), 7.18 (dd, J = 11.0, 15.3 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.2, 21.6, 35.8, 60.4, 67.0, 67.8, 122.0, 127.8, 128.0, 129.9, 132.8, 143.2, 143.3, 144.9, 166.8; HRMS(M^+) calcd 354.1140 for $C_{17}H_{22}O_6S$, found 354.1137.

Ethyl (4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-8-[(*p*-toluenesulfonyl)oxy]-(*E*)-2-octenoate (11). A mixture of titanium tetraisopropoxide (0.7 mL, 2.4 mmol), (+)-diisopropyl L-tartrate (0.57 mL, 2.75 mmol), and 0.45 g of 4-Å molecular sieves was stirred in 10 mL of anhydrous CH_2Cl_2 at −23 °C for 0.5 h. To this mixture was added alcohol **8** (697 mg, 1.97 mmol) with 14 mL of CH_2Cl_2 at −30 °C. After the resulting mixture was stirred at −23 °C for 0.5 h, *tert*-butylhydroperoxide (2.2 mL; 3.0 M in 2,2,4-trimethylpentane) was added. The resulting mixture was stirred at −23 °C overnight and filtered through a Celite pad. The filtrate was diluted with ethyl acetate and washed with aqueous saturated Na_2SO_4 solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel using 2:1 hexane–EtOAc to give 585 mg (81–90%) of epoxide **11** as a white solid: mp 94–95 °C; $[\alpha]^{25}_D$ = −25.3° (*c* 0.66, $CDCl_3$); IR (film) 3382 (w), 1711 (s), 1361 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.31 (t, J = 7.1 Hz, 3 H), 1.79 (m, 1 H), 2.00 (br s, 1 H, O*H*), 2.05 (m, 1H), 2.48 (s, 3 H), 2.95 (dd, J = 2.1, 2.5 Hz, 1 H), 3.52 (dd, J = 2.1, 7.2 Hz, 1 H), 4.01 (br m, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 4.17–4.27 (m, 2 H), 6.13 (d, J = 15.7 Hz, 1 H), 6.66 (dd, J = 7.2, 15.7 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.2, 21.6, 32.4, 52.5, 60.7, 62.6, 64.7, 66.4, 124.6, 127.9, 129.9, 132.8, 143.2, 145.0, 165.4.

Ethyl (4*S*,5*S*,6*S*)-8-Azido-4,5-epoxy-6-hydroxy-(*E*)-2-octenoate (12). A solution of epoxide **11** (611 mg, 1.65 mmol) in 10 mL of DMF was stirred with 536 mg of sodium azide at rt for 14 h. The reaction mixture was diluted with 40 mL of ethyl acetate, washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of solvents *in vacuo* afforded 380 mg of the crude product. Purification by flash column chromatography on silica gel using 2:1 hexane–EtOAc as eluent gave 292 mg (73%) of azide **12** as a yellow oil: $[\alpha]^{25}_D$ = −35.7° (*c* 0.68, $CDCl_3$); IR (film) 3470 (w), 2099 (s), 1718 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 1.71 (m, 1 H), 1.83 (m, 1 H), 2.56 (s, 1 H, O*H*), 2.97 (dd, J = 2.0, 2.7 Hz, 1 H), 3.48 (dd, J = 6.1, 7.2 Hz, 2 H), 3.54 (dd, J = 2.0, 7.2 Hz, 1 H), 3.95 (br m, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 6.12 (d, J = 15.7 Hz, 1 H), 6.65 (dd, J = 7.2, 15.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.0, 32.2, 47.5, 52.7, 60.6, 62.8, 65.9, 124.3, 143.4, 165.5.

Ethyl (2*R*,3*S*,4*S*,5*S*,6*S*)-8-Azido-4,5-epoxy-2,3,6-trihydroxyoctanoate (13). To a solution of azide **12** (120.9 mg, 0.5 mmol) in a 1:1 mixture (3 mL) of water–*tert*-butyl alcohol were added sequentially 495 mg (1.5 mmol) of potassium ferricyanide, 207 mg (1.5 mmol) of potassium carbonate, 19.5 mg (0.125 mmol) of $(DHQ)_2$-PHAL, 3.7 mg (0.1 mmol) of potassium osmate dihydrate, and 48 mg (0.5 mmol) of methanesulfonamide. The resulting mixture was stirred at rt for 12 h, and 5 mg of sodium metabisulfite was then added. After the mixture was stirred for additional 40 min, it was filtered through Celite, Florisil, and $MgSO_4$. The filter cake was thoroughly rinsed with CH_2Cl_2/methanol (20:1). The combined filtrates were concentrated and purified by flash column chromatography on silica gel using 20:1 CH_2Cl_2–methanol as eluent to give 84.5 mg of triol **13** contaminated with methanesulfonamide: IR (film) 3410 (m), 2103 (s), 1743 (s), 1327 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.31 (t, J = 7.2 Hz, 3 H), 1.75 (m, 1 H), 1.88 (m, 1 H), 3.06 (dd, J = 2.3, 2.6 Hz, 1 H), 3.35 (dd, J = 2.3, 3.9 Hz, 1 H), 3.48 (dd, J = 6.1, 7.2 Hz, 2 H), 3.86–3.93 (m, 1 H), 3.96 (br s, 1 H), 4.28 (q, J = 7.2 Hz, 2 H), 4.32 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.1, 32.4, 47.6, 55.6, 57.3, 62.4, 66.2, 70.9, 72.6, 172.3.

(1*S*,6*R*,7*S*,8*R*,8a*R*)-1,6,7,8-Tetraacetoxy-5-oxoindolizidine (16). To a solution of 84 mg of the crude triol **13** (as obtained from the previous step; contaminated with methanesulfonamide) in ethanol (2.5 mL) was added 10% of Pd/C (10 mg). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 6 h, and filtered through Celite. The filter cake was washed twice with ethanol. After the filtrate was refluxed for 10 h, the solvent was removed *in vacuo* to provide the crude lactam **15**.

The crude lactam **15** was then dissolved in 2 mL of pyridine and 1 mL of acetic anhydride. The resulting mixture was stirred for 20 h. The solvents were removed *in vacuo*. Purification by flash column chromatography on silica gel using 10:1 CH_2Cl_2–methanol as eluent yielded 38 mg of the tetraacetoxy lactam **16** (13% overall yield from **12**): $[\alpha]^{25}_D$ = +84.8° (*c* 0.46, $CHCl_3$); IR (film) 1754 (s), 1748 (s), 1673 (s), 1371 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.02 (s, 3 H), 2.05 (s, 3 H), 2.08 (s, 3 H), 2.12 (s, 3 H), 2.01–2.21 (m, 2 H), 3.63–3.69 (m, 2 H), 3.85 (dd, J = 3.1, 9.7 Hz, 1 H, H-8a), 4.99 (d, J = 8.8 Hz, 1 H, H-6), 5.30 (dd, J = 9.7, 10.3 Hz, 1 H, H-8), 5.45 (dd, J = 3.1, 3.2 Hz, 1 H, H-1), 5.57 (dd, J = 8.8, 10.3 Hz, 1 H, H-7); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 20.5, 20.6, 20.9, 29.5, 29.7, 43.7, 61.4, 65.7, 70.9, 71.7, 72.5, 163.2, 169.2, 169.9, 170.0, 170.3.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetraacetoxyindolizidine (Castanospermine Tetraacetate). To a solution of lactam **16** (8.0 mg, 22 μmol) in 2 mL of anhydrous THF was added at 0 °C 71 μL of a 2.0 M borane–dimethyl sulfide complex solution in THF. The reaction mixture was stirred at rt for 3 days and quenched with 0.5 mL of water. After 1 h, the mixture was extracted four times with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography using 4:1 CH_2Cl_2–EtOAc as eluent to give 4.2 mg (55%) of castanospermine tetraacetate: $[\alpha]^{25}_D$ = +42.7° (*c* 0.08, $CHCl_3$); IR (film) 1753 (s), 1742 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.85 (m, 1 H, H-2), 1.97 (s, 3 H), 2.01 (s, 6 H), 2.04 (s, 3 H), 1.98–2.11 (m, 1 H, H-5′), 2.24 (m, 1 H, H-2′), 2.32 (dd, $J_{8a,1}$ = 4.5 Hz, $J_{8a,8}$ = 9.4 Hz, 1 H, H-8a), 2.34 (m, 1 H, H-3′), 3.22 (ddd, J = 2.0, 8.4, 8.9 Hz, 1 H, H-3), 3.39 (dd, J = 4.7, 10.9 Hz, 1 H, H-5), 5.06–5.09 (m, 2 H, H-6 and H-7), 5.21 (t, 1 H, J = 9.4 Hz, H-8), 5.36 (ddd, $J_{1,8a}$ = 4.5 Hz, $J_{1,2}$ = 1.6 Hz, $J_{1,2'}$ = 7.1 Hz, 1 H, H-1); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 20.6, 20.7, 20.8, 21.0, 31.6, 51.9, 52.9, 68.2, 68.5, 70.2, 71.1, 75.2, 169.6, 169.9, 170.4, 170.5.

The physical and spectral data of synthetic castanospermine tetraacetate were identical with those of an authentic sample obtained from peracetylation (Ac_2O–pyr) of natural **1**: $[\alpha]^{25}_D$ = +43.8° (*c* 0.32, $CHCl_3$).

(+)-Castanospermine (1). Castanospermine tetraacetate (1.6 mg, 4 μmol) was treated with 0.5 mL of 20% aqueous NH_3 for 12 h. Removal of solvents *in vacuo* furnished 0.79 mg (93%) of **1** as a white solid. Their physical and spectroscopic data (vide infra) were found to be identical with those of natural castanospermine.

Ethyl (2*R*,3*S*,4*S*,5*S*,6*S*)-8-Azido-4,5-epoxy-2,3,6-tris(*tert*-butyldimethylsiloxy)octanoate (17). To a solution of azide **12** (66 mg, 0.27 mmol) in a 1:1 solution (1.5 mL) of water–*tert*-butyl alcohol were added sequentially 287 mg (0.81 mmol) of potassium ferricyanide, 120 mg (0.81 mmol) of K_2CO_3, 12 mg (0.067 mmol) of $(DHQ)_2$-PHAL, 4.1 mg (0.11 mmol) of potassium osmate dihydrate, and 27.5 mg (0.27 mmol) of methanesulfonamide. The resulting mixture was stirred at room temperature for 16 h, diluted with ether, and stirred with $MgSO_4$ at 0 °C for additional 0.5 h. The reaction mixture was filtered through Celite, Florisil, and $MgSO_4$. The filter cake was thoroughly rinsed with

CH_2Cl_2/methanol (20:1). The combined filtrates were concentrated *in vacuo* to provide 81 mg of the crude product.

The crude product was then treated with 0.23 mL of pyridine and 0.43 mL of *tert*-butyldimethylsilyl triflate in 2.5 mL of anhydrous CH_2Cl_2 at 0 °C. The resulting mixture was stirred for additional 4 h and at rt for 10 h. The mixture was then diluted with 20 mL of CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using 20:1 hexane–EtOAc as eluent to give 67 mg (40%) of **17**: $[\alpha]^{25}_D$ = −15.2° (*c* 0.58, $CHCl_3$); IR (film) 2098 (s), 1746 (m), 1255 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.06 (s, 12 H), 0.10 (s, 3 H), 0.11 (s, 3 H), 0.87 (s, 9 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.80 (m, 2 H), 2.90 (t, *J* = 2.1 Hz, 1 H), 3.12 (dd, *J* = 2.1, 6.6 Hz, 1 H), 3.40 (dt, *J* = 7.6, 12.3 Hz, 1 H), 3.49 (m, 2 H), 4.02 (m, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.19 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.2 (2 C), −5.1, −4.8, −4.6, −4.5, 14.2, 18.0, 18.3, 25.6, 25.7, 25.8, 33.2, 47.6, 54.7, 58.3, 60.8, 66.5, 74.8, 76.1, 171.0.

(1*S*,6*R*,7*S*,8*R*,8a*R*)-8-Hydroxy-1,6,7-tris(*tert*-butyldimethylsiloxy)-5-oxoindolizidine (18). To a solution of **17** (60.4 mg, 0.05 mmol) in ethanol (2 mL) was added 10% of Pd/C (10 mg). The reaction mixture was stirred under a hydrogen atmosphere at rt for 7 h and filtered through Celite. The filter cake was washed twice with ethanol. After the filtrate was refluxed for 13 h, the solvent was removed *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel using 10:1 hexane–EtOAc as eluent to give 28.8 mg of oxoindolizidine **18** (54%): $[\alpha]^{25}_D$ = +50.2° (*c* 1.02, $CHCl_3$); IR (film) 3340 (w), 1657 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.11 (s, 3 H), 0.12 (s, 6 H), 0.13 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 1.87–1.92 (m, 2 H, H-2 and H-2′), 2.02 (d, *J* = 5.6 Hz, 1 H, O*H*), 3.52–3.60 (m, 3 H, H-3, H-3′ and H-8a), 3.80 (dt, $J_{8,7} = J_{8,OH}$ = 5.6 Hz, $J_{8,8a}$ = 8.3 Hz, 1 H, H-8), 3.87 (dd, $J_{7,6}$ = 5.1 Hz, $J_{7,8}$ = 5.6 Hz, 1 H, H-7), 3.99 (d, *J* = 5.1 Hz, 1 H, H-6), 4.49 (m, 1 H, H-1); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.0, −4.7, −4.4 (3C), −4.2, 18.0, 18.1, 18.3, 25.7, 25.9, 26.0, 32.7, 42.9, 64.8, 71.4, 76.2, 78.5, 168.1; HRMS($M^+ - CH_3$) calcd 530.3153 for $C_8H_{15}NO_4$, found 530.3144.

(1*S*,6*S*,7*S*,8*R*,8a*R*)-8-Hydroxy-1,6,7-tris(*tert*-butyldimethylsiloxy)indolizidine. A solution of lactam **18** (25 mg, 0.05 mmol) in 2 mL of anhydrous THF was treated at 0 °C with 0.14 mL of a 2.0 M solution of borane–dimethyl sulfide complex. The reaction mixture was stirred at rt for 2 days, and carefully quenched with water (0.3 mL) at 0 °C. The product was then extracted with $CHCl_3$ (5 × 6 mL), and the combined organic extracts were dried over $MgSO_4$. After the solvents were removed under reduced pressure, the concentrate was purified by flash column chromatography on silica gel using 20:1 hexane–EtOAc to yield 13.6 mg of silylated castanospermine as a colorless oil, along with 5.8 mg of its borane complex (total 79% yield): $[\alpha]^{25}_D$ = +38.1° (*c* 0.43, $CHCl_3$); IR (film) 2929 (s), 1253 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.08 (s, 6 H), 0.09 (s, 6 H), 0.11 (s, 3 H), 0.13 (s, 3 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.92 (s, 9 H), 1.73∼1.81 (m, 1 H, H-2), 1.82 (dd, $J_{8a,1}$ = 5.1 Hz, $J_{8a,8}$ = 9.0 Hz, 1 H, H-8a), 1.90 (d, *J* = 3.3 Hz, 1 H, O*H*), 1.91 (dd, $J_{5',6}$ = 10.0 Hz, $J_{5',5}$ = 10.8 Hz, 1 H, H-5′), 2.04 (app q, *J* = 8.8 Hz, 1 H, H-3′), 2.20 (m, 1 H, H-2′), 3.07 (m, 1 H, H-3), 3.10 (dd, $J_{5,6}$ = 5.0 Hz, $J_{5,5'}$ = 10.8 Hz, 1 H, H-5), 3.37 (dd, $J_{7,6}$ = 8.4 Hz, $J_{7,8}$ = 9.0 Hz, 1 H, H-7), 3.63 (dt, $J_{8,OH}$ = 3.3 Hz and $J_{8,6} = J_{8,7}$ = 9.0 Hz, 1 H, H-8), 3.72 (ddd, $J_{6,5}$ = 5.0 Hz, $J_{6,7}$ = 8.4 Hz, $J_{6,5'}$ = 10.0 Hz, 1 H, H-6), 4.30 (m, 1 H, H-1); ^{13}C NMR ($CDCl_3$, 90 MHz) δ −5.0, −4.5, −4.2, −4.0, −3.5, −3.0, 18.2, 18.4, 25.9, 26.2 (2 C), 35.2, 52.6, 57.8, 70.8, 71.7, 71.9, 72.3, 81.4.

The borane complex can be converted to the silylated castanospermine by treatment with dilute aqueous HCl. Most conveniently, however, a mixture of the silylated castanospermine and its borane complex were directly converted into **1** without further separation.

(+)-Castanospermine (1). A mixture of trisilylated castanospermine (9.5 mg, 18 μmol) and the corresponding borane complex (4.6 mg) in 2.0 mL of CH_2Cl_2 was treated with 1.0 mL of 9:1 CF_3CO_2H/H_2O. The reaction mixture was stirred at rt for 2.5 days. Removal of solvents under reduced pressure gave the trifluoroacetic acid salt of **1**: ^1H NMR (D_2O, ref 4.67, 360 MHz) δ 1.96 (m, 1 H, H-2), 2.40 (m, 1 H, H-2′), 2.89 (t, *J* = 11.5 Hz, 1 H, H-5′), 3.06–3.14 (m, 2 H, H-3′ and H-8a), 3.43 (t, *J* = 9.2 Hz, 1 H, H-7), 3.59 (dd, *J* = 5.0, 11.5 Hz, 1 H, H-5), 3.65–3.74 (m, 3 H, H-3, H-6 and H-8), 4.54 (dd, $J_{1,8a}$ = 3.1, $J_{1,2'}$ = 5.4 Hz, 1 H, H-1).

The crude product was dissolved in 0.5 mL of H_2O and then subjected to anion-exchange chromatography (Dowex 1-X8) to afford 4.5 mg (90%) of castanospermine: mp 207–210 °C dec (lit.[3a] mp 212–215 °C dec); $[\alpha]^{25}_D$ = +77.8° (*c* 0.16, H_2O) {lit.[3a] $[\alpha]^{25}_D$ = +79.7° (*c* 0.93, H_2O)}; ^1H NMR (D_2O, ref 4.67, 360 MHz) δ 1.61 (ddt, $J_{2,1}$ = 1.4 Hz, $J_{2,3} = J_{2,3'}$ = 8.9 Hz, $J_{2,2'}$ = 13.9 Hz, 1 H, H-2), 1.93 (dd, $J_{8a,1}$ = 4.4 Hz, $J_{8a,8}$ = 9.2 Hz, 1 H, H-8a), 1.97 (t, *J* = 10.9 Hz, 1 H, H-5′), 2.12 (app q, *J* = 8.9 Hz, 1 H, H-3′), 2.23 (dddd, $J_{2',3}$ = 2.3 Hz, $J_{2',1}$ = 6.8 Hz, $J_{2',3'}$ = 8.9 Hz, $J_{2',2}$ = 13.9 Hz, 1 H, H-2′), 2.99 (dt, $J_{3,2'}$ = 2.0 Hz, $J_{3,2} = J_{3,3'}$ = 8.9 Hz, 1 H, H-3), 3.08 (dd, $J_{5,6}$ = 5.0 Hz, $J_{5,5'}$ = 10.9 Hz, 1 H, H-5), 3.22 (t, *J* = 9.2 Hz, 1 H, H-7), 3.50 (t, *J* = 9.2 Hz, 1 H, H-8), 3.52 (ddd, $J_{6,5}$ = 5.0 Hz, $J_{6,7}$ = 9.2 Hz and $J_{6,5'}$ = 10.9 Hz, 1 H, H-6), 4.30 (ddd, $J_{1,2}$ = 1.4 Hz, $J_{1,8a}$ = 4.4 Hz, $J_{1,2'}$ = 6.8 Hz, 1 H, H-1); ^{13}C NMR (D_2O, 90 MHz) δ 35.4, 54.3, 58.0, 71.6, 72.3, 72.8, 74.1, 81.7; HRMS (M^+) calcd 189.1001 for $C_8H_{15}NO_4$, found 189.0995.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of **1**, **7**, **8**, **11**, **12**, **13**, **16–18**, and castanospermine tetraacetate (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.