DOI: 10.1002/ejoc.201000202

Asymmetric Total Synthesis of (+)-6-*epi*-Castanospermine by the Stereoselective Formation of a *syn,anti* Acetylenic 2-Amino-1,3-diol Stereotriad

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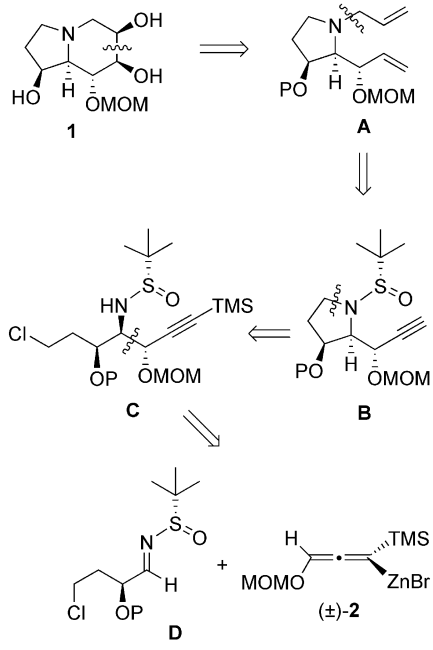
Keywords: Alkaloids / Zinc / Asymmetric synthesis / Chiral auxiliaries / Sulfinylimines

The asymmetric total synthesis of (+)-6-*epi*-castanospermine (**1**) is described herein. In this synthesis the diastereoselective addition of a racemic allenylzinc reagent to an enantiopure α-alkoxy-*tert*-butylsulfinylimine is the key step and is followed by the formation of a piperidine ring by ring-closing metathesis and subsequent *syn*-dihydroxylation of an alkene.

Introduction

The addition of allenylzinc reagent (±)-**2** to enantiopure *tert*-butylsulfinylimines offers a highly efficient access to enantiopure acetylenic amino alcohol units[1] and has already proven useful for the synthesis of several natural products bearing an *anti* 1,2-amino alcohol moiety.[2] Recently we reported the addition of (±)-**2** to enantiopure α-alkoxylated sulfinylimines, which led to the formation of acetylenic 2-amino-1,3-diol stereotriads (*anti*,*anti* and *syn*,*anti*), a unit that is widespread in natural products.[3] As a first illustration of its synthetic potential, we envisioned applying this reaction to the synthesis of the polyhydroxylated alkaloid (+)-6-*epi*-castanospermine (**1**).[4] This natural product, extracted from the pod seeds of *Castanospermum australe*, has been thoroughly studied for its biological properties, such as its potency to inhibit α-glycosidases.[5] We planned to synthesize **1** from intermediate **A** by ring-closing metathesis and subsequent stereoselective *syn*-dihydroxylation of the resulting internal alkene (Scheme 1). Intermediate **A** could be prepared by the semi-hydrogenation of the C–C triple bond of compound **B** followed by acidic removal of the *tert*-butylsulfinyl auxiliary and subsequent allylation of the nitrogen atom. The formation of **B** could be envisaged from *syn*,*anti*-2-*tert*-butylsulfinylamido 1,3-diether **C** by intramolecular substitution of the chlorine atom and desilylation of the acetylenic position. The addition of racemic allenylzinc reagent (±)-**2** to chiral α-alkoxy-sulfinylimine **D** should allow the stereoselective formation of key intermediate **C**.



Scheme 1. Proposed retrosynthesis of (+)-6-*epi*-castanospermine (**1**).

Results and Discussion

Our synthesis started with the preparation of α-(*p*-methoxybenzyloxy)-*tert*-butylsulfinylimine **3** (Scheme 2) as the chiral starting material required by our retrosynthesis. This compound could be obtained from protected triol **4**, itself prepared in four steps from (*S*)-malic acid following a known, non-epimerizing procedure.[6] Tosylation of the

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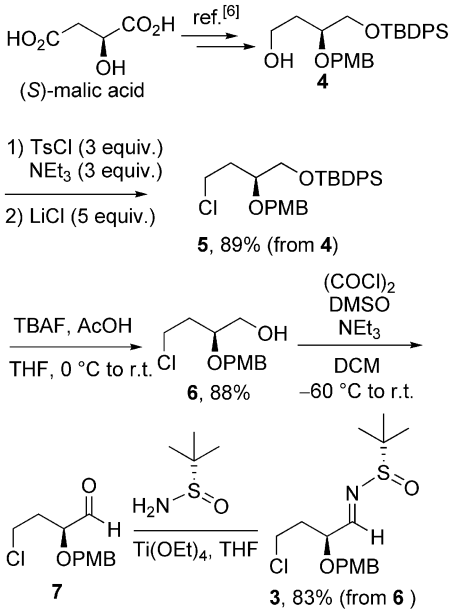
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000202.

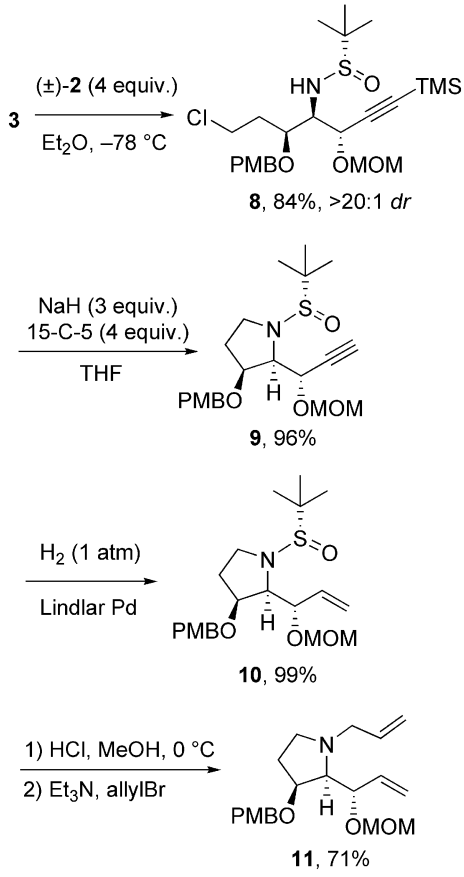
hydroxy group in **4** and subsequent substitution of the resulting tosylate by a chloride anion gave chloride **5** in 89% yield over the two steps. The silyl ether was then cleaved under acidic conditions to give alcohol **6** in 88% yield. This alcohol was oxidized under Swern conditions to give the crude aldehyde **7**, which was immediately engaged in a condensation reaction with enantiopure (*S*)-*tert*-butylsulfinamide[2a,7] under mild conditions to prevent epimerization of such aldehydes. This afforded the desired enantiopure *tert*-butylsulfinylimine **3** as a single diastereomer in 83% yield over the two steps (Scheme 2).



Scheme 2. Synthesis of sulfinylimine **3**.

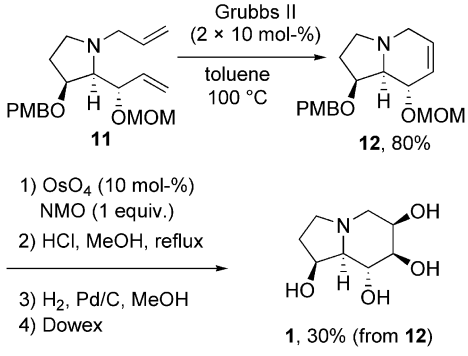
We then examined the reaction of α-alkoxy-*tert*-butylsulfinylimine **3** with racemic allenylzinc (±)-**2** derived from methoxymethyl 3-(trimethylsilyl)prop-2-ynyl ether. Under the reported conditions[3] the anticipated enantiopure *syn*,*anti*-2-*tert*-butylsulfinylamido 1,3-diether **8** was obtained by kinetic resolution of racemic (±)-**2** in 84% yield as a single diastereomer. The key intermediate **8** was then treated with excess NaH in the presence of 15-crown-5, which resulted in the intramolecular substitution of the chlorine atom. Under these conditions, desilylation of the acetylenic position occurred to afford pyrrolidine **9** in 96% yield. Semi-hydrogenation of **9** using the Lindlar palladium catalyst gave **10** in near quantitative yield. The latter was then submitted to a one-pot procedure comprising the selective acidic removal of the sulfinyl auxiliary in MeOH at 0 °C followed by allylation of the resulting secondary amine with allyl bromide in the presence of triethylamine to give *N*-allylamine **11** in 71% overall yield (Scheme 3).

At this stage we envisioned the formation of the hexahydroindolizine core by ring-closing metathesis of **11**. Several conditions had to be tested as metathesis reactions involving basic tertiary amines are known to be troublesome.[8] The best results were obtained by heating the *N*-



Scheme 3. Stereotriad and pyrrolidine ring formation.

allylamine at 100 °C in toluene in the presence of Grubbs II catalyst[9] (2 × 10 mol-% over 4 h), which led to the total conversion of the starting material into the desired **12**, which was obtained in an isolated yield of 80% (Scheme 4).

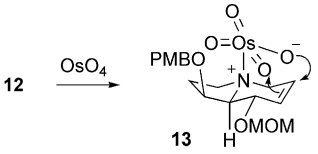


Scheme 4. Synthesis of **1** from *N*-allylamine **11**.

Intermediate **12** was then subjected to *syn*-dihydroxylation using 10 mol-% of OsO_4 in the presence of 1 equiv. of NMO as co-oxidant.[10] The resulting product was engaged in the next steps without purification, that is, acidic cleavage of the MOM group in MeOH at reflux followed by hydrogenolysis of the PMB moiety on Pd/C (Scheme 4). This synthetic sequence afforded (+)-6-*epi*-castanospermine (**1**) as the sole product after ion-exchange chromatography in an

overall isolated yield of 30% from **12** (three steps). (+)-6-*epi*-Castanospermine (**1**) thus obtained exhibited spectroscopic and physical data in good agreement with those reported in the literature {$[\alpha]_D^{20}$ = +6 (*c* = 0.84, MeOH);[4d,4g] $[\alpha]_D^{20}$ = +2.2 (*c* = 0.7, MeOH)}.[4d,4g]

This allowed us to confirm the stereoselectivity of the *syn*-dihydroxylation step, which can be rationalized through intermediate **13** in which the lone pair of the nitrogen atom of **12** adopts a *trans* configuration and directs the addition by complexation with OsO_4 (Scheme 5).[11]



Scheme 5. Possible origin of the stereoselectivty in the *syn*-dihydroxylation of **12**.

Conclusions

We have accomplished the total synthesis of (+)-6-*epi*-castanospermine (**1**) in 8.5% overall yield from (*S*)-4-(*tert*-butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)butan-1-ol (**4**), readily available from cheap (*S*)-malic acid. Our synthesis uses the highly diastereoselective addition of a racemic allenylzinc bromide to an enantiopure α-chiral Ellman *tert*-butylsulfinylimine to obtain an acetylenic *syn-anti* 2-amino-1,3-diol stereotriad synthon. This method could be applied to a variety of polyhydroxylated alkaloids and further efforts in this direction will be reported in due course.

Experimental Section

General: Experiments involving organometallic compounds were carried out in dried glassware under a positive pressure of dry N_2. Liquid nitrogen was used as a cryoscopic fluid. A four-necked, round-bottomed flask equipped with an internal thermometer, a septum cap, a nitrogen inlet, and a mechanical stirrer was used. Anhydrous solvents were distilled to remove stabilizers and dried with a double column purification system. Zinc bromide (98%) was melted under dry N_2 and, immediately after cooling to room temperature, was dissolved in anhydrous Et_2O. All other reagents and solvents were of commercial quality and were used without further purification. ^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer. Chemical shifts are reported in δ relative to an internal standard of residual chloroform (δ = 7.27 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR). IR spectra were recorded with a diamond ATR spectrometer. High-resolution mass spectra (HRMS) were obtained with a Finnigan MAT 95 spectrometer (accuracy: 4 ppm).

(–)-(*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)butyl 4-Methylbenzenesulfonate (4a): NEt_3 (1.41 mL, 10.10 mmol) and tosyl chloride (1.93 g, 10.10 mmol) were added to a solution of (*S*)-4-(*tert*-butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)butan-1-ol (**4**;[6] 1.57 g, 3.40 mmol) in DCM (25 mL). The mixture was then stirred overnight at room temperature and quenched with DCM (75 mL) and saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous phase was extracted with DCM (50 mL). The organic layers were gathered, dried with $MgSO_4$, and the solvent evaporated. The resulting crude product was purified by flash chromatography on silica gel (10:90 to 30:70 Et_2O/pentane) to afford the title product (1.96 g, 93%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.1 Hz, 2 H, Ts), 7.67–7.60 (m, 4 H, SiAr), 7.45–7.36 (m, 6 H, SiAr), 7.32 (d, *J* = 13.4 Hz, 2 H, Ts), 7.12 (d, *J* = 8.6 Hz, 2 H, PMP), 6.84 (d, *J* = 8.6 Hz, 2 H, PMP), 4.51 (AB system, *J* = 10.9 Hz, 1 H, C*H*$_2$PMP), 4.20 (AB system, *J* = 10.9 Hz, 1 H, C*H*$_2$PMP), 4.18–4.10 (m, 2 H, 4-H), 3.82 (s, 3 H, OMe), 3.68–3.60 (m, 3 H, 1-H, 3-H), 2.43 (s, 3 H, Ts), 2.02–1.94 (m, 1 H, 2-H), 1.85–1.77 (m, 1 H, 2-H), 1.05 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 144.8, 135.7, 133.3, 133.2, 130.6, 129.9, 129.5, 128.1, 127.9, 113.9, 75.5, 72.2, 67.7, 65.7, 55.4, 31.6, 26.9, 21.8, 19.3 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2857, 1612, 1513, 1463, 1427, 1359, 1246, 1175, 1097, 1033, 925, 814, 742, 702, 633, 613 cm^{-1}. $[\alpha]_D^{20}$ = –22.1 (*c* = 1.11, $CHCl_3$). HRMS (ESI): calcd. for $C_{35}H_{42}O_6NaSSi$ [M + Na]$^+$ 641.2364; found 641.2361.

(–)-(*S*)-*tert*-Butyl[4-chloro-2-(4-methoxybenzyloxy)butoxy]diphenylsilane (5): LiCl (2.12 g, 50.00 mmol) was added to a solution of **4a** (6.46 g, 10.00 mmol) in acetone (100 mL) and the mixture was heated at reflux for 60 h. It was then allowed to cool to room temperature and filtered through Celite (washed with DCM), extracted with DCM, and the solvents were evaporated. The crude product was then purified by flash chromatography over silica gel (5:95 Et_2O/pentane) to afford **5** (4.63 g, 96%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.9 Hz, 4 H, SiAr), 7.49–7.43 (m, 6 H, SiAr), 7.27 (d, *J* = 8.8 Hz, 2 H, PMP), 6.91 (d, *J* = 8.8 Hz, 2 H, PMP), 4.66 (AB system, *J* = 11.1 Hz, 1 H, C*H*$_2$PMP), 4.46 (AB system, *J* = 11.1 Hz, 1 H, C*H*$_2$PMP), 3.84 (s, 3 H, OMe), 3.83–3.80 (m, 2 H, 1-H), 3.73–3.67 (m, 3 H, 2-H, 4-H), 2.07–2.04 (m, 2 H, 3-H), 1.14 (s, 9 H, Si*t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 135.7, 133.5, 130.8, 129.9, 129.6, 127.9, 113.9, 76.4, 72.4, 65.9, 55.4, 41.9, 35.2, 27.0, 19.3 ppm. IR (neat): $\tilde{\nu}$ = 2857, 1612, 1512, 1463, 1427, 1301, 1247, 1173, 1110, 1075, 1035, 822, 740, 701, 660, 613 cm^{-1}. $[\alpha]_D^{20}$ = –43.7 (*c* = 1.06, $CHCl_3$). HRMS (ESI): calcd. for $C_{28}H_{35}O_3ClNaSi$ [M + Na]$^+$ 505.1936; found 505.1930.

(–)-(*S*)-4-Chloro-2-(4-methoxybenzyloxy)butan-1-ol (6): AcOH (107 μL, 0.50 mmol) and TBAF (1 M in THF, 1.88 mL, 1.88 mmol) were added to a solution of **5** (900 mg, 1.88 mmol) in THF (20 mL) at 0 °C. The mixture was then stirred overnight at room temperature and quenched with water (25 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 × 50 mL). The organic phases were then gathered, dried with $MgSO_4$, and the solvent evaporated. Purification of the crude product by flash chromatography over silica gel (40:60 to 80:20 Et_2O/pentane) afforded **6** (403 mg, 88%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.3 Hz, 2 H, PMP), 6.81 (d, *J* = 8.8 Hz, 2 H, PMP), 4.50 (AB system, *J* = 11.2 Hz, 1 H, C*H*$_2$PMP), 4.45 (AB system, *J* = 11.2 Hz, 1 H, C*H*$_2$PMP), 3.72 (s, 3 H, OMe), 3.69–3.63 (m, 2 H, 1-H, 2-H), 3.58–3.52 (m, 2 H, 4-H), 3.46–3.41 (m, 1 H, 1-H), 2.28 (br. s, 1 H, OH), 2.04–1.96 (m, 1 H, 3-H), 1.88–1.79 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 130.3, 129.6, 114.0, 76.3, 72.0, 63.7, 55.4, 41.7, 34.4 ppm. IR (neat): $\tilde{\nu}$ = 2935, 1612, 1512, 1463, 1301, 1245, 1174, 1031, 819, 726, 638 cm^{-1}. $[\alpha]_D^{20}$ = –42.0 (*c* = 1.06, $CHCl_3$). HRMS (ESI): calcd. for $C_{12}H_{17}O_3ClNa$ [M + Na]$^+$ 267.0758; found 267.0759.

(+)-(*S*,*E*)-*N*-[(*S*)-4-Chloro-2-(4-methoxybenzyloxy)butylidene]-2-methylpropane-2-sulfinamide (3): A solution of DMSO (2.10 mL, 29.10

mmol) in DCM (6 mL) was added dropwise to a solution of oxalyl chloride (1.25 mL, 14.60 mmol) in DCM (33 mL) at –60 °C. After 5 min at –60 °C a solution of alcohol **6** (3.24 g, 13.20 mmol) in DCM (13 mL) was added. The mixture was then stirred for 30 min at –60 °C and NEt_3 (9.20 mL, 66.00 mmol) was added. After stirring for 15 min at –60 °C, the mixture was allowed to reach room temperature and water (75 mL) was added. The phases were separated and the aqueous layer extracted with DCM (3 × 75 mL). The organic layers were collected and washed with saturated aqueous NH_4Cl (200 mL) and water (200 mL), dried with Na_2SO_4, and the solvents evaporated in vacuo. The crude aldehyde **7** was dissolved in THF (60 mL) and $Ti(OEt)_4$ (7.00 mL, 33.00 mmol) and (*S*)-*tert*-butanesulfinamide (1.76 g, 14.50 mmol) were added. The mixture was then stirred for 15 h and quenched with saturated aqueous NaCl (60 mL) and EtOAc (60 mL) under vigorous stirring. After stirring for 10 min, the mixture was filtered through Celite and washed with EtOAc. The filtrate was then transferred to a separating funnel and washed with saturated aqueous NaCl (60 mL). The organic phase was then dried with Na_2SO_4 and the solvents were removed in vacuo. Purification of the crude product by flash chromatography over silica gel (25:75 to 50:50 Et_2O/pentane) afforded **3** (3.81 g, 83% over two steps) as a pale-yellow oil that crystallized upon cooling to 4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 4.6 Hz, 1 H, 1-H), 7.27 (d, *J* = 8.8 Hz, 2 H, PMP), 6.90 (d, *J* = 8.5 Hz, 2 H, PMP), 4.65 (d, *J* = 10.7 Hz, 1 H, C*H*$_2$PMP), 4.48–4.41 (m, 2 H, C*H*$_2$PMP, 2-H), 3.82 (s, 3 H, OMe), 3.76–3.64 (m, 2 H, 4-H), 2.21–2.06 (m, 2 H, 3-H), 1.24 [s, 9 H, S(O)*t*Bu] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 159.7, 129.9, 129.4, 114.1, 76.8, 72.3, 57.1, 55.4, 40.7, 35.8, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 2959, 1613, 1513, 1456, 1363, 1302, 1247, 1174, 1079, 1032, 910, 820, 730, 658 cm^{-1}. $[\alpha]_D^{20}$ = +63 (*c* = 1.24, $CHCl_3$). HRMS (ESI): calcd. for $C_{16}H_{24}O_3NClNaS$ $[M + Na]^+$ 368.1058; found 368.1068.

(+)-(*S*)-*N*-[(3*S*,4*R*,5*S*)-7-Chloro-5-(4-methoxybenzyloxy)-3-(methoxymethoxy)-1-(trimethylsilyl)hept-1-yn-4-yl]-2-methylpropane-2-sulfinamide (8): TMEDA (0.66 mL, 4.40 mmol) followed by *s*BuLi (1.3 M in cyclohexane/hexane, 33.80 mL, 44.00 mmol) were added to a solution of [3-(methoxymethoxy)prop-1-ynyl]trimethylsilane (8.36 mL, 44.00 mmol) in Et_2O (360 mL) at –78 °C. After stirring for 1 h at –78 °C, $ZnBr_2$ (1 M in Et_2O, 44.00 mL, 44.00 mmol) was added to the pale-orange solution, which turned a pale yellow. After 20 min at –78 °C imine **3** (3.81 g, 11.00 mmol) in Et_2O (44 mL) was added. The reaction was monitored by TLC and quenched after 1 h with 1 M aqueous HCl (360 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 × 360 mL). The organic layers were gathered and washed with saturated aqueous $NaHCO_3$ (350 mL), water (350 mL), and brine (350 mL), and dried with $MgSO_4$. The solvents were then removed in vacuo and the crude product was purified by flash chromatography on silica gel (40:60 to 50:50 Et_2O/pentane) to afford **8** (4.78 g, 84%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.8 Hz, 2 H, PMP), 6.85 (d, *J* = 8.8 Hz, 2 H, PMP), 4.91 (d, *J* = 6.8 Hz, 1 H, OC*H*$_2$OCH$_3$), 4.60–4.52 (m, 3 H, C*H*$_2$PMP, OC*H*$_2$OCH$_3$), 4.35 (d, *J* = 7.2 Hz, 1 H, 5-H), 4.22–4.17 (m, 2 H, 1-H, 2-H), 3.78 (s, 3 H, ArOMe), 3.71–3.57 (m, 2 H, 4-H), 3.38 (s, 3 H, OCH$_2$OC*H*$_3$), 3.36–3.34 (m, 1 H, NH), 2.30–2.23 (m, 1 H, 3-H), 2.14–2.06 (m, 1 H, 3-H), 1.22 [s, 9 H, S(O)*t*Bu], 0.14 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 130.3, 129.3, 113.9, 102.6, 94.6, 92.8, 73.5, 72.5, 68.7, 61.8, 56.5, 56.3, 55.3, 41.8, 34.4, 23.0, –0.2 ppm. IR (neat): $\tilde{\nu}$ = 2957, 1613, 1514, 1464, 1363, 1302, 1248, 1173, 1153, 1068, 1023, 920, 842, 759, 731 cm^{-1}. $[\alpha]_D^{20}$ = +27.2 (*c* = 1.62, $CHCl_3$). HRMS (ESI): calcd. for $C_{24}H_{40}O_5NClNaSSi$ $[M + Na]^+$ 540.1977; found 540.1987.

(+)-(2*R*,3*S*)-1-[(*S*)-*tert*-Butylsulfinyl]-3-(4-methoxybenzyloxy)-2-[(*S*)-1-(methoxymethoxy)prop-2-ynyl]pyrrolidine (9): 15-Crown-5 (5.47 mL, 27.70 mmol) and NaH (60% dispersion in mineral oil, 1.46 g, 36.90 mmol) were added to a solution of **8** (4.78 g, 9.20 mmol) in THF (270 mL) at 0 °C. The mixture was then stirred at room temperature for 36 h and cautiously quenched with saturated aqueous NH_4Cl (45 mL). The resulting mixture was then extracted with EtOAc (3 × 45 mL) and the combined organic layers were washed with brine (45 mL) and dried with $MgSO_4$. The solvents were then evaporated and purification of the crude product by flash chromatography on silica gel (80:20 Et_2O/pentane) afforded **9** (3.60 g, 96%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H, PMP), 6.88 (d, *J* = 8.6 Hz, 2 H, PMP), 4.91 (d, *J* = 6.8 Hz, 1 H, OC*H*$_2$OCH$_3$), 4.60–4.52 (m, 2 H, OC*H*$_2$OCH$_3$, C*H*OCH$_2$OCH$_3$), 4.52 (AB system, *J* = 11.5 Hz, 1 H, C*H*$_2$PMP), 4.45 (AB system, *J* = 11.5 Hz, 1 H, C*H*$_2$PMP), 4.17 (q, *J* = 6.9 Hz, 1 H, 3-H), 3.92 (dd, *J* = 7.0, 4.2 Hz, 1 H, 2-H), 3.81 (s, 3 H, ArOMe), 3.78–3.74 (m, 1 H, 5-H), 3.36 (s, 3 H, OCH$_2$OC*H*$_3$), 3.07–3.01 (m, 1 H, 5-H), 2.47 (d, *J* = 2.0 Hz, 1 H, C≡C*H*), 2.28–2.19 (m, 1 H, 4-H), 2.01–1.93 (m, 1 H, 4-H), 1.25 [s, 9 H, S(O)*t*Bu] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 130.2, 129.2, 114.0, 94.4, 81.5, 78.1, 75.9, 72.0, 70.9, 66.5, 58.7, 56.0, 55.4, 39.4, 30.9, 24.4 ppm. IR (neat): $\tilde{\nu}$ = 2952, 1612, 1513, 1464, 1360, 1301, 1246, 1174, 1150, 1090, 1029, 949, 820 cm^{-1}. $[\alpha]_D^{20}$ = +73.2 (*c* = 1.00, $CHCl_3$). HRMS (ESI): calcd. for $C_{21}H_{31}O_5NNaS$ $[M + Na]^+$ 432.1815; found 432.1809.

(+)-(2*R*,3*S*)-1-[(*S*)-*tert*-Butylsulfinyl]-3-(4-methoxybenzyloxy)-2-[(*S*)-1-(methoxymethoxy)allyl]pyrrolidine (10): Lindlar catalyst (5 wt.-% on calcium carbonate, 6.00 g, 20 wt.-%) and 3,6-dithia-1,8-octanediol (0.06 g, 4 wt.-%) were added to a solution of alkyne **9** (1.51 g, 3.69 mmol) in hexane (110 mL) and acetone (5.5 mL). The flask was then flushed three times with H_2 and the mixture was stirred for 48 h at room temperature. It was then filtered through Celite, washed with EtOAc, and the solvents were evaporated. Purification of the crude product by flash chromatography on silica gel (80:20 to 90:10 Et_2O/pentane) afforded alkene **10** (1.50 g, 99%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H, PMP), 6.88 (d, *J* = 8.6 Hz, 2 H, PMP), 5.88 (ddd, *J* = 17.8, 10.3, 7.6 Hz, 1 H, C*H*=CH$_2$), 5.34–5.26 (m, 2 H, CH=C*H*$_2$), 4.67 (AB system, *J* = 6.6 Hz, 1 H, OC*H*$_2$OCH$_3$), 4.55 (AB system, *J* = 6.6 Hz, 1 H, OC*H*$_2$OCH$_3$), 4.47 (s, 2 H, C*H*$_2$PMP), 4.32 (dd, *J* = 7.7, 4.2 Hz, 1 H, C*H*OCH$_2$OCH$_3$), 4.16 (q, *J* = 7.0 Hz, 1 H, 3-H), 3.95 (dd, *J* = 7.0, 4.4 Hz, 1 H, 2-H), 3.81 (s, 3 H, ArOMe), 3.76–3.70 (m, 1 H, 5-H), 3.35 (s, 3 H, OCH$_2$OC*H*$_3$), 2.88–2.82 (m, 1 H, 5-H), 2.01–1.95 (m, 1 H, 4-H), 1.22 [s, 9 H, S(O)*t*Bu] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 136.1, 130.4, 129.3, 119.5, 114.0, 94.1, 78.5, 77.4, 72.0, 71.3, 58.7, 55.7, 55.4, 39.0, 31.0, 24.5 ppm. IR (neat): $\tilde{\nu}$ = 2932, 1612, 1513, 1465, 1360, 1301, 1247, 1173, 1149, 1064, 1031, 918, 820 cm^{-1}. $[\alpha]_D^{20}$ = +51 (*c* = 1.00, $CHCl_3$). HRMS (ESI): calcd. for $C_{21}H_{33}O_5NNaS$ $[M + Na]^+$ 434.1972; found 434.1965.

(+)-(2*R*,3*S*)-1-Allyl-3-(4-methoxybenzyloxy)-2-[(1*S*)-(methoxymethoxy)allyl]pyrrolidine (11): HCl (4 M in 1,4-dioxane, 5.60 mL, 22.30 mmol) was added to a solution of sulfinamide **10** (1.84 g, 4.46 mmol) in MeOH (90 mL) at 0 °C. After stirring for 1 h at 0 °C, NEt_3 (9.30 mL, 67.00 mmol) was added followed by allyl bromide (1.00 mL, 11.20 mmol). The resulting mixture was stirred at room temperature for 48 h, quenched with 33% NH_3/NH_4Cl saturated solution (90 mL). and extracted with EtOAc (3 × 180 mL). The combined organic layers were washed with brine (90 mL), dried with $MgSO_4$, and the solvents evaporated. Purification of the crude product by flash chromatography on silica gel (50% Et_2O/pentane) afforded *N*-allylamine **11** (1.12 g, 71%) as a colorless oil. ^1H NMR

(400 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.6 Hz, 2 H, PMP), 6.87 (d, J = 8.6 Hz, 2 H, PMP), 6.04 (ddd, J = 17.3, 10.7, 6.6 Hz, 1 H, NCH_2CH=CH_2), 5.94–5.84 (m, 1 H, $CHCH$=CH_2), 5.29 (m, 1 H, $CHCH$=CH_2), 5.22 (m, 1 H, NCH_2CH=CH_2), 5.15 (dd, J = 17.1, 1.1 Hz, 1 H, $CHCH$=CH_2), 5.07 (d, J = 10.1 Hz, 1 H, NCH_2CH=CH_2), 4.67 (AB system, J = 6.7 Hz, 1 H, OCH_2OCH_3), 4.61 (AB system, J = 6.7 Hz, 1 H, OCH_2OCH_3), 4.51 (d, J = 11.6 Hz, 1 H, CH_2PMP), 4.40–4.35 (m, 2 H, OCH_2OCH_3, CH_2PMP), 4.10 (q, J = 6.0 Hz, 1 H, 3-H), 3.81 (s, 3 H, ArOMe), 3.61 (dd, J = 13.6, 5.0 Hz, 1 H, NCH_2CH=CH_2), 3.36 (s, 3 H, OCH_2OCH_3), 3.15 (ddd, J = 9.6, 7.2, 4.0 Hz, 1 H, 5-H), 2.85 (dd, J = 13.8, 7.9 Hz, 1 H, NCH_2CH=CH_2), 2.78 (dd, J = 6.6, 3.9 Hz, 1 H, 5-H), 2.24 (q, J = 7.4 Hz, 1 H, 2-H), 1.97–1.82 (m, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 137.3, 136.0, 130.7, 129.3, 116.5, 116.3, 113.6, 94.7, 79.4, 77.5, 70.9, 70.0, 58.6, 55.5, 55.2, 50.8, 30.1 ppm. IR: $\tilde{\nu}$ = 2881, 1613, 1513, 1441, 1354, 1301, 1246, 1149, 1112, 1034, 915, 820 cm^{-1}. $[\alpha]_D^{20}$ = +61.5 (c = 0.97, $CHCl_3$). HRMS (ESI): calcd. for $C_{20}H_{30}O_4N$ $[M + H]^+$ 348.2169; found 348.2163.

(+)-(1*S*,8*S*,8a*R*)-1-(4-Methoxybenzyloxy)-8-(methoxymethoxy)-1,2,3,5,8,8a-hexahydroindolizine (12): Grubbs II catalyst (212 mg, 0.25 mmol) was added to a solution of *N*-allylamine **11** (823 mg, 2.40 mmol) in toluene (140 mL) and the mixture was heated at 100 °C. After 2 h, a second portion of the catalyst (212 mg, 0.25 mmol) was added and the mixture was heated at reflux for an additional 2 h. The mixture was then allowed to cool to room temperature and the solvents were evaporated. Purification of the residue by flash chromatography on silica gel (50–70% EtOAc/cyclohexane) afforded **12** (601 mg, 80%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.6 Hz, 2 H, PMP), 6.84 (d, J = 8.8 Hz, 2 H, PMP), 5.82–5.75 (m, 2 H, 6-H, 7-H), 4.73 (d, J = 6.6 Hz, 1 H, OCH_2OCH_3), 4.66–4.62 (m, 2 H, OCH_2OCH_3, 8-H), 4.54 (AB system, J = 11.4 Hz, 1 H, CH_2PMP), 4.33 (AB system, J = 11.4 Hz, 1 H, CH_2PMP), 4.17–4.13 (m, 1 H, 1-H), 3.78 (s, 3 H, ArOMe), 3.44 (d, J = 16.9 Hz, 1 H, 5-H), 3.35 (s, 3 H, OCH_2OCH_3), 3.28–3.23 (m, 1 H, 3-H), 2.70 (d, J = 16.4 Hz, 1 H, 5-H), 2.24–2.15 (m, 2 H, 3-H, 8a-H), 2.10–2.03 (m, 1 H, 2-H), 1.98–1.90 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 130.5, 129.4, 128.1, 126.6, 113.6, 96.7, 76.9, 72.3, 70.3, 68.5, 55.4, 55.3, 53.0, 52.3, 29.4 ppm. IR: $\tilde{\nu}$ = 2935, 1613, 1514, 1442, 1301, 1248, 1147, 1123, 1036, 990, 915, 821, 692 cm^{-1}. $[\alpha]_D^{20}$ = +75.0 (c = 0.11, $CHCl_3$). HRMS (ESI): calcd. for $C_{18}H_{26}O_4N$ $[M + H]^+$ 320.1856; found 320.1846.

(+)-(1*S*,6*R*,7*R*,8*R*,8a*R*)-Octahydroindolizine-1,6,7,8-tetraol [(+)-6-*epi*-Castanospermine] (1): OsO_4 (2.5 wt.% in *tert*-butyl alcohol, 225 μL, 0.02 mmol) followed by NMO (28 mg, 0.24 mmol) was added to a solution of **12** (70 mg, 0.22 mmol) in a mixture of acetone (2.1 mL) and water (0.1 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and quenched with Na_2SO_3 (1 g). After stirring for 1 h of at room temp., the solvents were evaporated in vacuo and the resulting mixture was filtered through a short pad of silica gel (eluting with 10% MeOH/EtOAc). The solvents were evaporated and the crude product was used in the next step without further purification.

HCl (4 M in 1,4-dioxane, 210 μL, 0.85 mmol) was added to a solution of crude product (30 mg, 0.09 mmol) in MeOH (5 mL) and the mixture was heated at reflux for 2 h. The solvents were then evaporated and the residue was taken up in MeOH (5 mL) and Pd/C (10 wt.-% on calcium carbonate, 30 mg) was added. The flask was purged with H_2 (×3) and the mixture was stirred overnight at room temp. under H_2 (1 atm). It was then filtered through Celite and the filtrate was evaporated. The residue was passed through a Dowex 50WX-8 column (eluted with water followed by 1 M NH_3). The collected product was then passed through a Dowex 1X2–400 column (OH^- form, eluted with MeOH and then water) to afford **1** (10 mg, 30% over three steps) as a colorless viscous oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.43–4.40 (m, 1 H, 1-H), 4.02 (dd, J = 5.0, 3.1 Hz, 1 H, 6-H), 3.90 (t, J = 9.6 Hz, 1 H, 8-H), 3.56 (dd, J = 9.6, 3.5 Hz, 1 H, 7-H), 3.16–3.08 (m, 2 H, 3-H, 5-H), 2.39–2.33 (m, 1 H, 2-H), 2.30 (dd, J = 12.5, 1.8 Hz, 1 H, 5-H), 2.17 (q, J = 9.1 Hz, 1 H, 3-H), 1.94 (dd, J = 9.6, 4.4 Hz, 1 H, 8a-H) 1.75 (dtd, J = 14.3, 9.0, 2.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 77.3, 73.6, 72.1, 70.8, 69.2, 57.2, 53.6, 34.6 ppm. $[\alpha]_D^{20}$ = +6 (c = 0.84, MeOH) {ref.[4d,4g] $[\alpha]_D^{20}$ = +2.2 (c = 0.7, MeOH)}. HRMS (ESI): calcd. for $C_8H_{16}O_4N$ $[M + H]^+$ 190.1074; found 190.1075.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **4a**, **5**, **6**, **8**, **9**, **10**, **11** and **12**.

Acknowledgments

We are grateful to the Centre National de la Recherche Scientifique (CNRS) and GlaxoSmithKline for a Ph. D. grant (to J. L.).

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Received: February 15, 2010
Published Online: April 8, 2010

