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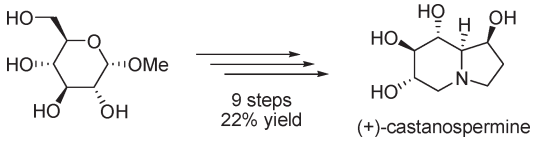
A Concise Synthesis of Castanospermine by the Use of a Transannular Cyclization

Thomas Jensen, Mette Mikkelsen, Anne Lauritsen, Thomas L. Andresen, Charlotte H. Gotfredsen, and Robert Madsen*

Department of Chemistry, Building 201, Technical University of Denmark, DK-2800 Lyngby, Denmark

rm@kemi.dtu.dk

Received September 11, 2009



A nine-step synthesis of (+)-castanospermine has been accomplished in 22% overall yield from methyl α-D-glucopyranoside. The key transformations involve a zinc-mediated fragmentation of benzyl-protected methyl 6-iodoglucopyranoside, ring-closing olefin metathesis, and strain-release transannular cyclization to afford the indolizidine skeleton of the natural product.

The indolizidine alkaloid (+)-castanospermine was first isolated in 1981 from the seeds of the Australian legume *Castanospermum australe*.[1] It is structurally related to D-glucose and is a powerful inhibitor of both mammalian and plant α- and β-glucosidases.[2] The complexation to a β-glucosidase has been studied by X-ray crystallography, and the natural product was shown to bind in a distorted boat conformation.[3] The alkaloid is also a potent antiviral agent,[4] and the 6-butanoyl analogue is currently undergoing clinical trials for treatment of hepatitis C.[5] As a result, (+)-castanospermine has been the target of a number of total syntheses starting from either a carbohydrate,[6] tartaric/malic acid,[7] or an achiral substrate via an enantioselective approach.[8] The shortest synthesis is an eight-step route from 2,5-dihydrofuran where an asymmetric tandem [4 + 2]/[3 + 2] cycloaddition serves as the key step.[8d] All other syntheses of the natural product have used more than 10 synthetic steps.

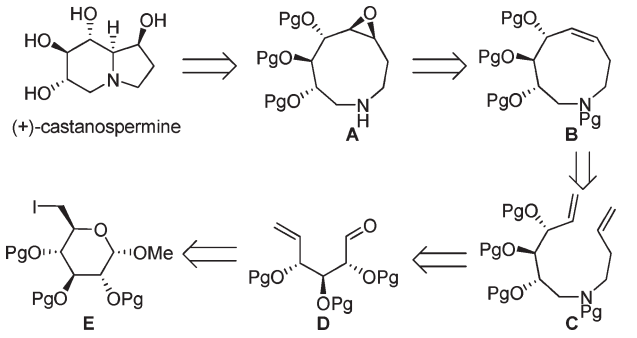


FIGURE 1. Retrosynthesis for (+)-castanospermine.

The rings in the indolizidine system are usually formed in two separate steps. We envisioned using a transannular cyclization[9] from epoxide **A** to form the azabicycle in one step (Figure 1). The epoxide would arise from a diastereoselective epoxidation of the nine-membered cycloalkene **B**, which would be prepared by ring-closing metathesis from diene **C**. The latter can originate from reductive amination of unsaturated aldehyde **D** which is available by zinc-mediated fragmentation of methyl 6-deoxy-6-iodo-α-D-glucopyranoside. Herein, we describe a nine-step synthesis of (+)-castanospermine from methyl α-D-glucopyranoside by the use of a medium-ring metathesis reaction and a transannular cyclization as the pivotal steps.

The requisite starting material for the reductive fragmentation was prepared in two steps from cheap and commercially available methyl α-D-glucopyranoside. Treatment with iodine and triphenylphosphine gave 6-iodopyranoside **2** which was separated from triphenylphosphine oxide by reversed-phase column chromatography (Scheme 1).[10] Initially, we attempted to perform the fragmentation−amination sequence with the

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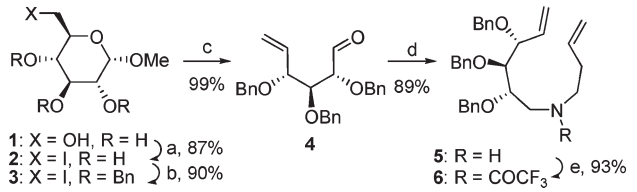
Published on Web 10/26/2009 DOI: 10.1021/jo9019495

SCHEME 1[a]



[a]Reagents and conditions: (a) I_2, PPh_3, imidazole, THF, 65 °C; (b) Bn-OC(NH)CCl_3, TfOH, *p*-dioxane, 22 °C; (c) Zn, THF/H_2O, ultrasound, 40 °C; (d) homoallylamine, 4 Å molecular sieves, AcOH, $NaCNBH_3$, THF, 0−22 °C; (e) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C.

unprotected 6-iodopyranoside **2**, but this approach was hampered by difficult isolation procedures for the highly polar intermediates. Therefore, we settled for a strategy relying on benzyl protection of **2**. The hydroxy groups were protected smoothly under acidic conditions utilizing an excess of benzyl trichloroacetimidate. The attained tribenzyl ether **3** was sonicated in the presence of activated, powdered zinc to furnish unsaturated aldehyde **4**. The aldehyde could easily be purified by the use of silica gel chromatography without epimerization of the α-stereocenter. However, upon standing, this stereocenter epimerized readily even when the compound was stored in the freezer; hence, in practice the crude aldehyde was used directly in the subsequent step.

We attempted to perform the reductive amination as a one-pot sequence where **4** was formed with zinc in the presence of $NaCNBH_3$ or $NaBH(OAc)_3$, homoallyl amine,[11] and acetic acid. Unfortunately, these experiments only provided the desired amine **5** in a moderate yield along with reduced aldehyde and epimerized amine. Thus, we decided to perform the zinc-mediated fragmentation and the reductive amination in two separate steps. After some experimentation, it was found that employing $NaCNBH_3$ as the reducing agent in the presence of an excess of homoallyl amine and powdered 4 Å molecular sieves in THF furnished the desired amine in 89% yield. Careful adjustment to pH 7−8 using acetic acid and allowing for complete formation of the imine before adding $NaCNBH_3$ proved to be crucial in order to avoid epimerization and direct reduction of the aldehyde. Amine **5** was readily converted into the corresponding trifluoroacetamide **6** by treatment with trifluoroacetic anhydride in the presence of triethylamine.

With diene **6** in hand, we set out to identify reaction conditions that would furnish the nine-membered (*Z*)-alkene **7** efficiently. Initial experiments with Grubbs' second-generation catalyst revealed that ring-closing metathesis had to be performed under highly dilute conditions in refluxing benzene or toluene. When the reaction was performed at more than 1.0 mM concentration of diene **6** the homodimer was the predominant product. Furthermore, reactions conducted at ambient temperature or at 40 °C in CH_2Cl_2 under highly dilute conditions (0.2 mM) did not afford any reaction and the starting material could be isolated quantitatively. Therefore we decided to screen several metathesis catalysts (Table 1) for this crucial reaction. Surprisingly, neither Grubbs' first generation catalyst **9** nor the ruthenium indylidene catalyst **10**[12] afforded any of the desired product (Table, entry 1 and 2). Gratifyingly, the more reactive ruthenium carbene complexes endowed with an *N*-heterocyclic carbene ligand provided the desired product in moderate to good yield (entries 3−6).

A byproduct in all these reactions was the 8-membered *N*-heterocycle, which likely results from ruthenium-catalyzed isomerization of the electron-rich terminal double bond in **6** followed by elimination of propene instead of ethylene during the ring closure.[13] Grubbs' catalyst **12** proved to be the best catalyst, providing the desired product in 71% yield along with only 9% of the byproduct. When **12** was added in a dropwise manner over 20 h alkene **7** was obtained in 78% yield (entry 7). Attempts to run the reaction at a higher concentration, adding Ti(O-*i*-Pr)$_4$ or BHT let to a decreased yield of **7** (entries 8−10). In addition, when 10 mol % of **12** was used or when performing the reaction in refluxing toluene the yield dropped significantly (entry 11 and 12).

With access to **7**, we started to investigate conditions for installing the epoxide and mediating the transannular cyclization. Initially cyclononene **7** was treated with excess *m*-CPBA in CH_2Cl_2, and even though the reaction provided one major product as judged by ^{1}H NMR, the reaction was sluggish and all efforts to purify the epoxide led to decomposition. Attempts to buffer the reaction with $NaHCO_3$ or NaH_2PO_4 were largely unsuccessful and the addition of KF to complex *m*-chlorobenzoic acid decreased the reaction rate markedly. Luckily, after some experimentation it was found that the in situ generated dioxirane of 1,1,1-trifluoroacetone cleanly converted **7** into the desired epoxide (more than 80% of the desired diastereomer as judged by ^{1}H NMR of the crude reaction mixture). The crude product was used directly in the next step to avoid decomposition of the acid-labile epoxide during workup. Before identifying optimal reaction conditions, a range of different bases and solvents such as Na_2CO_3, K_2CO_3, LiOH, NaOH, MeOH, EtOH, and THF were investigated for the key *N*-deprotection/transannular cyclization. In the event, treating the crude epoxide with 2 equiv of water and 20 equiv of KO-*t*-Bu in Et_2O at 0 °C and allowing the reaction mixture to reach room temperature furnished indolizidine **15** in 44% yield over the two steps along with 15% of the strained byproduct **16** (Scheme 2). The structure of the latter was assigned by 2D NMR spectroscopy.

Finally indolizidine **15** was deprotected by hydrogenolysis using H_2 over Pd/C to afford (+)-castanospermine in almost quantitative yield. Physical and spectral data for the synthetic material were found to be consistent with those for the natural product.[1]

In conclusion, we have developed a concise synthesis of enantiopure (+)-castanospermine. The synthesis comprises no more than nine steps from methyl α-D-glucopyranoside and provides the natural product in 22% overall yield. The key steps are a zinc-mediated reductive fragmentation of **3**, a challenging ruthenium-catalyzed ring-closing metathesis reaction of diene **6**, and a strain-driven *N*-deprotection/transannular cyclization cascade. This synthesis further underscores the effectiveness of employing a zinc-fragmentation

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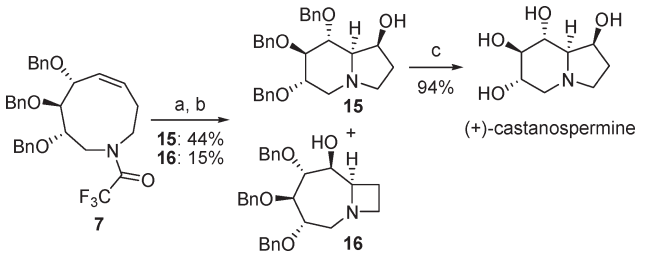
SCHEME 2[a]



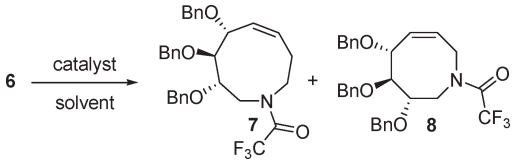
[a]Reagents and conditions: (a) CF_3COCH_3, Oxone, $NaHCO_3$, Na_2EDTA, CH_3CN/H_2O, −10 to 0 °C; (b) KO-*t*-Bu, H_2O, Et_2O, 0−22 °C; (c) H_2, Pd/C, HCl, MeOH, 22 °C.

ring-closing metathesis sequence in the development of highly efficient synthetic routes from carbohydrates.

Experimental Section

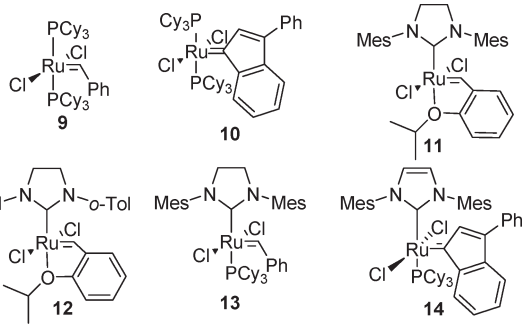
***N*-But-3-enyl-((2*S*,3*S*,4*R*)-2,3,4-tris(benzyloxy)hex-5-enyl)-amine (5).** The iodide **3**[10] (2.0 g, 3.75 mmol) was dissolved in a mixture of THF (16.9 mL) and H_2O (1.88 mL), Zn (2.46 g, 37.6 mmol) was added, and the flask was immersed into a sonication apparatus preheated to 40 °C. The solution was sonicated for 60 min upon which TLC revealed full conversion of the starting material. The suspension was filtered through a plug of Celite using Et_2O (50 mL). Saturated aqueous $NaHCO_3$ (25 mL) was added to the filtrate, the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a pale yellow viscous oil which was purified by flash chromatography (heptane/EtOAc = 9:1 → 4:1) to afford aldehyde **4** as a colorless oil (1.55 g, 99%). The oil was used directly in the next step since the aldehyde epimerizes when stored in the freezer. To a solution of the aldehyde (1.55 g, 3.71 mmol) and homoallyl amine[11] (2.64 g, 37.1 mmol) in THF (65.6 mL) were added activated 4 Å powdered molecular sieves (7.43 g) followed by AcOH (2.75 mL) in a dropwise manner until pH = 7−8. The suspension was cooled to 0 °C, and after stirring for 30 min, $NaCNBH_3$ (1.17 g, 18.6 mmol) was added in one portion and the mixture was allowed to warm to 21 °C. The reaction was stirred for 14 h and then quenched by addition of saturated aqueous $NaHCO_3$ (25 mL). The mixture was filtered and the filter cake washed with EtOAc (3 × 50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale yellow oil. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 9:1) to afford **5** (1.56 g, 89% over two steps) as a colorless oil: R_f = 0.23 (CH_2Cl_2/MeOH = 9:1); $[\alpha]^{21}_D$ −39.4 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.22 (m, 15H), 5.86 (ddd, *J* = 14.0, 9.9, 7.6 Hz, 1H), 5.62 (ddt, *J* = 13.8, 10.3, 7.0 Hz, 1H), 5.31−5.19 (m, 2H), 4.98 (ddd, *J* = 13.8, 3.0, 1.3 Hz, 1H), 4.95−4.91 (m, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.00 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.79 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.55 (t, *J* = 5.0 Hz, 1H), 2.69 (dd, *J* = 12.4, 5.0 Hz, 1H), 2.59 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.06 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 138.1, 136.0, 135.5, 128.2, 128.1, 127.8, 127.5, 118.5, 116.2, 82.0, 80.3, 78.6, 74.7, 73.1, 70.4, 49.4, 48.7, 33.8; IR (neat) 3088, 3065, 3029, 2976, 2863, 1496, 1454, 1392, 1351, 1330, 1306, 1207, 1088, 1067, 996, 917, 734, 697 cm^{-1}; HRMS (ESI+) calcd for $C_{31}H_{37}NO_3Na$ ($[M + Na]^+$) 494.2666, found 494.2647.

TABLE 1. Optimization of the Key Ring-Closing Metathesis Reaction



entry	catalyst (20 mol %)	solvent	*T* (°C)	[**6**] (mM)	% yield (**7**)[a]	% yield (**8**)[a]
1	**9**	PhH	80	0.2		
2	**10**	PhH	80	0.2		
3	**11**	PhH	80	0.2	52	16
4	**12**	PhH	80	0.2	71	9
5	**13**	PhH	80	0.2	63	11
6	**14**	PhH	80	0.2	59	10
7	**12**[b]	PhH	80	0.5	78	7
8	**12**	PhH	80	1.0	51	12
9[c]	**12**	PhH	80	0.5	73	8
10[d]	**12**	PhH	80	0.5	69	13
11	**12**[e]	PhH	80	0.5	52	5
12	**12**	PhMe	110	0.5	41	18

[a]Yield of isolated product. [b]Catalyst added over 20 h. [c]With 30 mol % of ($Ti(O\text{-}i\text{-}Pr)_4$ as additive. [d]With 30 mol % of BHT as additive. [e]10 mol % catalyst added over 20 h.



N,N-But-3-enyl-((2*S*,3*S*,4*R*)-2,3,4-tris(benzyloxy)hex-5-enyl)-trifluoroacetamide (6). Amine **5** (1.13 g, 2.30 mmol) was dissolved in CH_2Cl_2 (24.0 mL), Et_3N (1.0 mL, 727 mg, 7.2 mmol) was added, and the solution was cooled to 0 °C. Trifluoroacetic anhydride (680 μL, 1.0 g, 4.8 mmol) was added in a dropwise manner, and the reaction was stirred for 30 min at 0 °C. The mixture was diluted with CH_2Cl_2 (50 mL) and quenched with saturated aqueous $NaHCO_3$ (25 mL) at 0 °C. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (heptane/EtOAc = 98:2 → 95:5) to afford **6** (1.26 g, 93%) as a viscous colorless oil: R_f = 0.41 (heptane/EtOAc = 7:3); $[\alpha]^{21}_D$ −52.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer δ 7.34−7.14 (m, 15H), 5.90 (ddd, *J* = 17.3, 10.4, 7.9 Hz, 1H), 5.72−5.46 (m, 1H), 5.32 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.29−5.21 (m, 1H), 5.06−4.91 (m, 2H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.15 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.06 (ddd, *J* = 8.6, 5.0, 3.4 Hz, 1H), 3.77 (dd, *J* = 13.9, 3.4 Hz, 1H), 3.52−3.29 (m, 4H), 2.19 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ major rotamer 157.1 (q, J_{CF} = 35.6 Hz), 138.1, 138.1, 138.0, 135.1, 133.3, 128.4,

128.4, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.6, 119.3, 117.8, 116.4 (q, J_{CF} = 288 Hz), 80.7, 80.2, 76.0, 73.9. 73.8, 70.6, 48.8, 48.6, 32.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ major rotamer −69.43 (s, 3F); minor rotamer −68.34 (s, 3F); IR (Neat) 3089, 3067, 3032, 2910, 2871, 1687, 1454, 1252, 1206, 1144, 1122, 1089, 1072, 735, 698 cm^{-1}; HRMS (ESI+) calcd for $C_{33}H_{36}F_3NO_4Na$ ([M + Na]$^+$) 590.2489, found 590.2472.

(3*S*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-1-trifluoroacetyl-1-azacyclonon-6-ene (7). Diene **6** (100 mg, 0.185 mmol) was dissolved in benzene (370 mL, 0.5 mM). The solution was degassed by sonication (5 min under a positive flow of Ar) and heated to 80 °C. Catalyst **12** (21 mg, 0.037 mmol) was dissolved in benzene (20 mL) and added to the mixture in a dropwise manner over 20 h by the use of a syringe pump. After being stirred for an additional 4 h, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford a dark green oil. The crude oil was purified by flash chromatography (heptane/EtOAc = 98:2 → 95:5) to afford **7** (78 mg, 78%) as a colorless oil which crystallized upon standing: R_f = 0.18 (heptane/EtOAc = 9:1); $[\alpha]^{21}_D$ +33.8 (*c* 1.6, $CHCl_3$); mp 76−77 °C (heptane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ major rotamer 7.46−7.13 (m, 15H), 5.93−5.84 (m, 1H), 5.72 (t, *J* = 10.0 Hz, 1H), 4.87 (d, *J* = 11.1 Hz, 1H), 4.83 (d, *J* = 10.7 Hz, 1H), 4.70 (t, *J* = 11.3 Hz, 2H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.38−4.27 (m, 1H), 4.05 (ddd, *J* = 9.3, 6.7, 2.9 Hz, 1H), 3.93 (dd, *J* = 14.0, 2.7 Hz, 1H), 3.90−3.81 (m, 1H), 3.66 (dd, *J* = 8.4, 6.7 Hz, 1H), 3.41 (dd, *J* = 13.9, 9.1 Hz, 1H), 3.07−2.76 (m, 1H), 2.55−2.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ major rotamer 158.7 (q, J_{CF} = 35.4 Hz), 138.6, 138.5, 138.1, 133.7, 129.0, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 118.1, 116.2 (q, J_{CF} = 288 Hz), 114.3, 84.5, 78.1, 75.0, 74.6, 73.3, 70.6, 51.9, 48.5, 27.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ major rotamer −69.6 (s, 3F); minor rotamer −67.9 (s, 3F); IR (Neat) 3090, 3062, 3031, 2929, 2900, 2871, 1692, 1454, 1205, 1144, 1093, 1068, 736, 698 cm^{-1}; HRMS (ESI+) calcd for $C_{31}H_{32}F_3NO_4Na$ ([M + Na]$^+$) 562.2176, found 562.2152.

(3*S*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-1-trifluoroacetyl-1-azacyclooct-6-ene (8):. R_f = 0.20 (heptane/EtOAc = 9:1); $[\alpha]^{22}_D$ +23.9 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ major rotamer 7.39−7.19 (m, 15H), 5.89−5.58 (m, 2H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.37 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.13 (dd, *J* = 8.5, 5.6 Hz, 1H), 4.02 (d, *J* = 13.8 Hz, 1H), 3.82−3.65 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ major rotamer 157.0 (q, J_{CF} = 37.0 Hz), 138.3, 138.2, 137.8, 134.2, 128.3, 127.9, 127.7, 126.0, 116.4 (q, J_{CF} = 287 Hz), 83.5, 78.5, 77.3, 74.6, 72.8, 71.8, 47.2, 46.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ major rotamer −69.5 (s, 3F); minor rotamer −68.2 (s, 3F); IR (neat) 3088, 3063, 3031, 2924, 2870, 1692, 1497, 1454, 1206, 1184, 1143, 1100, 1028, 736, 697 cm^{-1}; HRMS (ESI+) calcd for $C_{30}H_{30}F_3NO_4Na$ ([M + Na]$^+$) 548.2020, found 548.2036.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1-Hydroxy-6,7,8-tris(benzyloxy)indolizidine (15). Oxone (114 mg, 0.185 mmol) and $NaHCO_3$ (24 mg, 0.286 mmol) were added to a solution of Na_2EDTA (186 μL, 0.4 mM in H_2O) and 1,1,1-trifluoroacetone (100 μL) in CH_3CN (500 μL) at −10 °C (MeOH/ice bath). Within 5 min of stirring, the suspension became pale yellow. Azacyclononene **7** (20 mg, 0.037 mmol) was dissolved in CH_3CN (500 μL) and added in a dropwise manner. The mixture was allowed to warm to 0 °C and stirred for 4 h upon which TLC revealed full consumption of **7**. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 2.5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was dissolved in Et_2O (7.4 mL), and the solution was cooled to 0 °C. H_2O (1.2 μL, 0.064 mmol) and KO-*t*-Bu (71 mg, 0.634 mmol) were added. After 30 min of stirring, the mixture was allowed to warm to room temperature and stirred for an additional 10 h. H_2O (2.5 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2.5 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated under reduced pressure. The crude oil was purified by preparative TLC (heptane/CH_2Cl_2/MeOH = 7:7:2) to afford **15** (7.6 mg, 44% over two steps) as a pale yellow oil: R_f = 0.4 (heptane/CH_2Cl_2/MeOH = 7:7:2); $[\alpha]^{21}_D$ +35.5 (*c* 0.96, CH_2Cl_2) (lit.[6i] $[\alpha]^{26}_D$ +36.4 (*c* 1.2, CH_2Cl_2)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.22 (m, 15H), 4.99 (d, *J* = 10.9 Hz, 1H), 4.87 (d, *J* = 11.6 Hz, 2H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.31−4.14 (m, 1H), 3.74−3.62 (m, 2H), 3.61−3.51 (m, 1H), 3.26 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.16−3.00 (m, 1H), 2.26−2.06 (m, 1H), 2.00 (t, *J* = 10.4, 1H), 1.94 (dd, *J* = 9.4, 3.6 Hz, 1H), 1.79−1.71 (m, 1H), 1.40 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8 (2C), 138.4, 128.5 (3C), 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 87.3, 79.2, 76.9, 75.6, 74.3, 72.9, 71.8, 70.7, 54.3, 51.6, 33.6; IR (Neat) 3450, 3088, 3063, 3030, 2925, 2855, 2812, 1713, 1678, 1606, 1497, 1454, 1400, 1167, 1135, 1097, 1068, 1028, 734, 697 cm^{-1}; HRMS (ESI+) calcd for $C_{29}H_{33}NO_4Na$ ([M + Na]$^+$) 482.2303, found 482.2293.

(3*S*,4*R*,5*R*,6*S*,7*R*)-3,4,5-Tris(benzyloxy)-1-azabicyclo[5.2.0]nonan-6-ol (16):. R_f = 0.23 (heptane/CH_2Cl_2/MeOH = 7:7:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.25 (m, 15H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 11.3 Hz, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 3.77 (dd, *J* = 7.0, 2.7 Hz, 1H), 3.70−3.57 (m, 3H), 3.45 (t, *J* = 7.6, Hz, 1H), 3.30−3.19 (m, 1H), 3.10 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.04−2.93 (m, 1H), 2.46 (dd, *J* = 10.7, 8.9 Hz, 1H), 2.33−2.18 (m, 1H), 1.90−1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.5, 138.4, 128.4, 128.3 (2C), 127.9, 127.8, 127.7, 127.6, 127.5, 86.7, 86.4, 78.7, 75.8, 73.9, 73.6, 70.5, 66.2, 59.5, 50.8, 19.7; IR (neat) 3420, 3030, 2923, 2852, 1497, 1363, 1261, 1211, 1139, 1095, 734, 697 cm^{-1}; HRMS (ESI+) calcd for $C_{29}H_{33}NO_4Na$ ([M + Na]$^+$) 482.2303, found 482.2281.

(+)-Castanospermine. Tribenzyl ether **15** (23.7 mg, 0.0516 mmol) was dissolved in MeOH (7.1 mL). Pd/C (23 mg, 10% Pd) and concentrated HCl (78 μL) were added. The mixture was stirred under an H_2 atmosphere at room temperature for 48 h upon which TLC revealed full conversion of **15**. Amberlite IRA-400 (OH) (1.0 g) was added. After 2 h of stirring, the solution was filtered through a plug of Celite utilizing MeOH. The filtrate was concentrated under reduced pressure to provide (+)-castanospermine (9.2 mg, 94%) as a colorless oil that crystallized slowly. An analytical sample was prepared by recrystallization from EtOH: $[\alpha]^{21}_D$ +72.4 (*c* 0.22, H_2O) (lit.[1] $[\alpha]^{25}_D$ +79.7 (*c* 0.93, H_2O)); mp 209−213 °C dec (lit.[1] mp 212−215 °C dec); ^{1}H NMR (300 MHz, D_2O) δ 4.43−4.25 (m, 1H), 3.65−3.59 (m, 1H), 3.59 (t, *J* = 9.3 Hz, 1H), 3.32 (t, *J* = 9.1 Hz, 1H), 3.17 (dd, *J* = 10.8, 5.15 Hz, 1H), 3.08 (dt, *J* = 9.2, 2.1 Hz, 1H), 2.39−2.29 (m, 1H), 2.21 (q, *J* = 9.2 Hz, 1H), 2.04 (t, *J* = 10.7 Hz, 1H), 2.02 (dd, *J* = 9.8, 4.5 Hz, 1H), 1.71 (dddd, *J* = 13.8, 8.7, 8.5, 1.3 Hz, 1H); ^{13}C NMR (50 MHz, D_2O) δ 78.0, 70.4, 69.1, 68.6, 68.0, 54.4, 50.6, 31.7; HRMS (ESI+) calcd. for $C_8H_{15}NO_4Na$ ([M + Na]$^+$) 212.0894, found 212.0888.

Acknowledgment. We thank the Danish National Research Foundation for financial support.

Supporting Information Available: General methods, copies of NMR spectra, and NMR assignment of **16** and castanospermine. This material is available free of charge via the Internet at http://pubs.acs.org.