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Asymmetric Syntheses of 1-Deoxy-6,8a-di-*epi*-castanospermine and 1-Deoxy-6-*epi*-castanospermine

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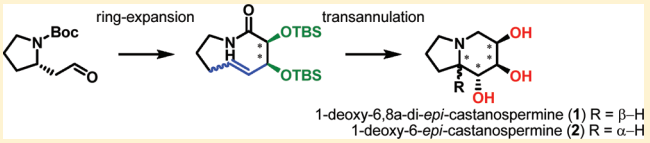
Supporting Information

ABSTRACT: Asymmetric syntheses of both 1-deoxy-6,8a-di-*epi*-castanospermine and 1-deoxy-6-*epi*-castanospermine, polyhydroxylated indolizidine alkaloids that act as selective glycosidase inhibitors, have been accomplished in seven steps. The key feature of our unique syntheses includes the stereoselective introduction of the C-3 and C-4 hydroxyl groups utilizing the aza-Claisen rearrangement-induced ring expansion of 1-acyl-2-alkoxyvinyl pyrrolidine and a substrate-controlled stereoselective transannulation of the resulting azoninone intermediate.



Over the past half century, studies on glycosidase inhibitors have been part of promising new drug-development programs.[1] Since nojirimycin, a natural glycosidase inhibitor, was isolated from a *Streptomyces* strain in 1966,[2] significant work on glycosidase inhibitors has been performed.[1] Glycosidase inhibitors exhibit diverse biological activities and have many types of beneficial effects, including anticancer, antidiabetic, antiobesity, antiviral, fungicidal, and insecticidal.[1] Among these glycosidase inhibitors, natural and non-natural polyhydroxylated indolizidine alkaloids, which structurally mimic bioactive carbohydrates, have attracted a great interest because of their potential to serve as pharmaceutical lead compounds (Figure 1).[3] In particular, castanospermine, a

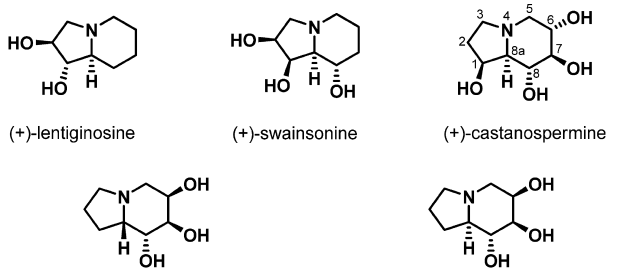


Figure 1. Polyhydroxylated indolizidines.

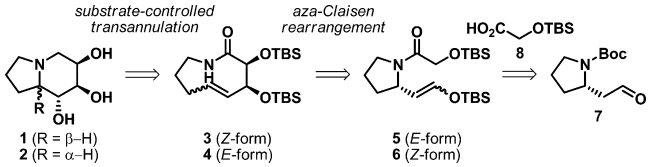
highly hydroxylated indolizidine alkaloid, inhibits many types of α- and β-D-glucosidases.[4] The selectivity and potency of the inhibition of glycosidases can be altered by modifying the five stereocenters.

1-Deoxy-6,8a-di-*epi*-castanospermine **1** is known to be a potent inhibitor of α-L-fucosidase, and 1-deoxy-6-*epi*-castanospermine **2** was shown to be an inhibitor of lysosomal α-mannosidase in a competitive manner.[4] Despite the excellent biological activities of these compounds, few syntheses of 1-deoxycastanospermines **1** and **2** have been reported.[5] The major challenge in their synthesis involved the elaboration of the four contiguous stereocenters that are compactly arranged. In this regard, these iminosugars have been considered as attractive targets in terms of both synthetic and medicinal chemistry.[6]

We have reported systematic studies on the ACR-induced stereoselective ring-expansions of lactams of various ring sizes and synthetic applications of this method.[7] However, there is a limit in synthetic application of the stereoselective ring-expansion of 5-membered azacycles. Our previous studies on the ACR-induced stereoselective ring-expansions of the 5-membered azacycles to yield the corresponding 9-membered lactams revealed that the mixed internal olefin geometries of the desired azoninone products consistently hindered the use of our synthetic strategy for the production of indolizidine alkaloids.[7c] Fortunately, we were able to overcome this poor olefin-geometry selectivity by using a substituent-controlled and microwave-assisted ACR of 1-acyl-2-alkoxyvinylpyrrolidine.

Our unified synthetic strategy for the 1-deoxycastanospermines **1** and **2** is outlined in Scheme 1. The final alkaloid

Scheme 1. Retrosynthetic Analysis



products **1** and **2** are accessible from the azoninones **3** and **4** bearing (*Z*)- or (*E*)-olefins via substrate-controlled stereoselective transannulations. The 9-membered lactams **3** and **4**

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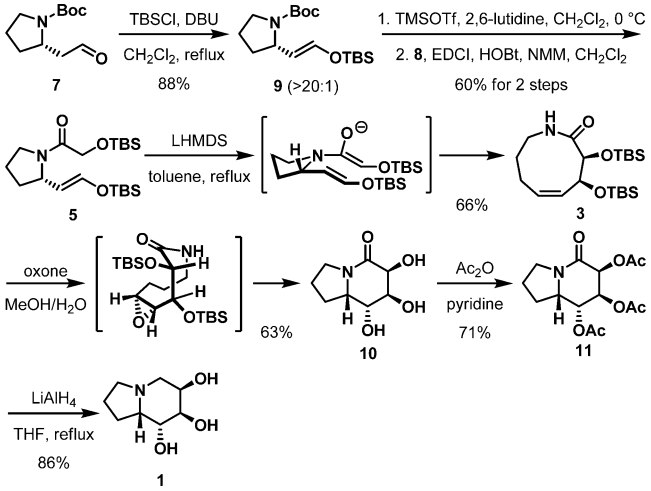
can be stereoselectively constructed through a ring-expansion ACR of the *N*-acyl-α-alkoxyvinylpyrrolidines **5** and **6**.[7] The appropriate aza-Claisen precursor could be obtained by the selective formation of the (*E*)- or (*Z*)-silyl enol ether[7d,8] followed by a facile amidation with the protected glycolic acid **8**. The change in the olefin-geometry of the ACR precursor effectively provides stereochemical diversity of the azoninone intermediate through the corresponding substrate-induced transition state.[7] The optically active aldehyde **7** was expected to be derived from commercially available L-proline.[9]

The synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine **1** (Scheme 2) commenced with the preparation of the (*E*)-silyl

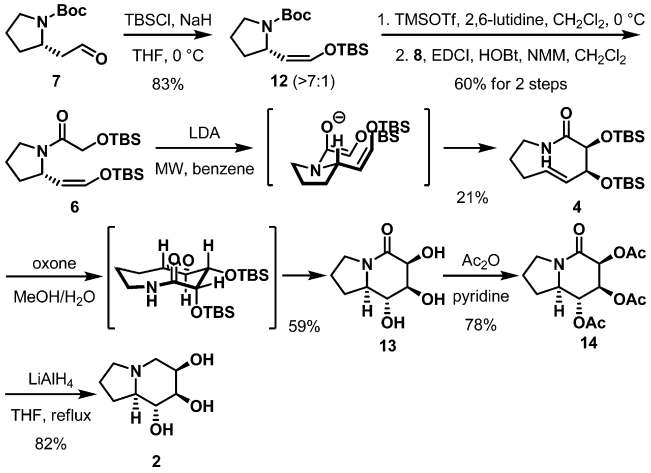
Scheme 2. Synthesis of 1-Deoxy-6,8a-di-*epi*-castanospermine 1



enol ether **9** (>20:1) by a reaction of aldehyde **7**[9] with DBU in the presence of TBSCl.[7d,8a] Selective Boc-deprotection of **9** with TMSOTf and 2,6-lutidine followed by the amidation of the resulting amine with **8** afforded the ACR precursor **5**. With the desired amide **5** in hand, we executed the ACR of **5** under our standard ACR conditions.[7] Azoninone **3** bearing an internal (*Z*)-olefin and two *sec*-alcohol units was stereoselectively obtained in high yield. The coupling constant between the two olefinic protons of **3** (J = 11.7 Hz) was indicative of a *cis*-relationship. The selective production of the desired product as a single diastereomer was likely due to the ACR of **5** only through a boatlike transition state induced by the two bulky silyloxy substituents, which preferentially occupied pseudoequatorial positions. To the best of our knowledge, the stereoselective formation of azoninone via an amide enolate-induced ACR has not been reported previously.[10] After extensive attempts to perform the pivotal transannular ring-contraction of lactam **3** under various conditions, we finally obtained indolizidine **10** through the effective Oxone-induced transannulation[11] of **3** and the concomitant TBS-deprotection. We did not observe any regio- or diastereomers. The exclusive formation of the desired isomer is explained by the initial epoxide formation, which spontaneously underwent the regio- and stereoselective ring-opening by the amide nitrogen. The exposure of triol **10** to Ac_2O and the global reduction of the resulting amide **11** with LAH produced 1-deoxy-6,8a-di-*epi*-castanospermine **1**.[12] Because the amide reduction of triol **10** did not proceed under various conditions, protection of the triols as acetates was inevitable. The physical and spectral data of the synthetic product were consistent with those of the reported product.[5a,f]

The synthesis of 1-deoxy-6-*epi*-castanospermine **2** commenced with the stereoselective preparation of the (*Z*)-silyloxyvinyl pyrrolidine **12** from aldehyde **7** (Scheme 3). The

Scheme 3. Synthesis of 1-Deoxy-6-*epi*-castanospermine 2



treatment of aldehyde **7** with TBSCl in the presence of NaH provided largely the (*Z*)-silyl enol ether **12** (>7:1),[8b,c] which was separable from the (*E*)-stereoisomer by chromatography. Selective Boc-deprotection of **12** with TMSOTf in the presence of 2,6-lutidine and the subsequent amidation of the resulting amine with acid **8** afforded the ACR precursor **6**. Unfortunately, our initial attempts to achieve the ACR of **6** under a variety of previously used ACR conditions[7] were not successful. However, this reluctant ACR of **6** proceeded under microwave-assisted conditions.[13] Only azoninone **4** (J = 16.8 Hz) with an internal (*E*)-olefin was obtained, although the yield was not satisfactory. The reaction seemed to proceed through a chairlike transition state, and the low yield is likely due to the instability of the (*Z*)-silyl enol ether under the ACR conditions. Again, the stereoselective transannulation of **4**[14] by Oxone treatment provided the corresponding indolizidine **13**,[11] which was then subjected to acetylation of the three hydroxyl groups. The global reduction of **14** with LAH afforded 1-deoxy-6-*epi*-castanospermine **2**. The synthetic product proved to be identical in all respects with the authentic alkaloid.[5a,b]

In conclusion, we have achieved the highly concise syntheses of 1-deoxy-6,8a-di-*epi*-castanospermine **1** (13% overall yield) and 1-deoxy-6-*epi*-castanospermine **2** (4% overall yield) in only seven steps from the known aldehyde **7**. The key features of our syntheses include the stereoselective construction of the indolizidine backbone with the two silyloxy groups utilizing the ACR-induced ring-expansion of the (*E*)- and (*Z*)-1-acyl-2-alkoxyvinylpyrrolidines and the stereoselective transannulation of the resulting azoninone. It should be noted that the azoninone bearing an internal (*E*)-olefin could be prepared by microwave-accelerated ACR of the labile *N*-acyl-(*Z*)-silyloxyvinylpyrrolidine. Our syntheses seem to be quite efficient in terms of excellent asymmetric induction, high versatility, low number of steps and simple manipulations. Considering a variety of approaches for triggering the transannular reaction, our synthetic route can also be widely applicable to the syntheses of other highly functionalized indolizidine alkaloids.

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EXPERIMENTAL SECTION

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air- and moisture-sensitive reactions were performed under argon atmosphere. Flash column chromatography was performed using silica gel of 230−400 mesh with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates. Optical rotations were measured with a digital polarimeter at ambient temperature using 100 mm cell of 2 mL capacity. Infrared spectra were recorded on a FT-IR spectrometer. Mass spectra were obtained with a GC−MS instrument. The ^{1}H and ^{13}C NMR spectra were recorded on 300, 400, or 500 MHz spectrometers as solutions in the indicated solvent. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

(*S*,*E*)-*tert*-Butyl 2-(2-(*tert*-Butyldimethylsilyloxy)vinyl)-pyrrolidine-1-carboxylate (9). To a solution of the aldehyde **7** (1.17 g, 5.49 mmol) in CH_2Cl_2 (50 mL) were added TBSCl (2.23 g, 14.8 mmol, ca. 10%) and DBU (8.2 mL, 54.9 mmol) at ambient temperature. After being stirred for 12 h at 40 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane =1: 10) to afford 1.58 g (88%) of the (*E*)-silyl enol ether **9** as a colorless oil: $[\alpha]_D^{24}$ −7.10 (*c* 1.00, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 2958, 2931, 2884, 2859, 1698, 1663, 1473, 1391, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.31 (brs, 1H), 4.86 (dd, 1H, *J* = 11.8, 8.0 Hz), 4.16 (brs, 1H), 3.29 (brs, 2H), 1.99−1.71 (m, 2H), 1.85−1.54 (m, 2H), 1.40 (s, 9H), 0.87 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4, 142.0, 112.0, 78.7, 55.2, 45.8, 32.9, 28.5, 28.5, 28.5, 25.6, 25.6 25.6, 22.9, 18.2, −5.3, −5.3; LR-MS (FAB+) *m*/*z* 328 (M + H$^+$); HR-MS (FAB+) calcd for $C_{17}H_{34}NO_3Si$ (M + H$^+$) 328.2308, found 328.2316.

(*S*,*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-(2-(2-(*tert*-butyldimethylsilyloxy)vinyl)pyrrolidin-1-yl)ethanone (5). To a solution of the (*E*)-silyl enol ether **9** (100 mg, 305 μmol) in CH_2Cl_2 (10 mL) were added 2,6-lutidine (71 μL, 610 μmol) and TMSOTf (83 μL, 458 μmol) at 0 °C. After being stirred for 1 h at ambient temperature, the reaction mixture was quenched with MeOH and then concentrated in vacuo. This crude mixture was used for the next step without further purification. To a solution of the crude amine and the acid **8** (87.2 mg, 458 μmol) in CH_2Cl_2 (5 mL) were added 1-hydroxybenzotriazole hydrate (45.4 mg, 336 μmol), 4-methylmorpholine (74 μL, 671 μmol), and EDCI (87.8 mg, 458 μmol) at ambient temperature. After being stirred for 14 h at the same temperature, the reaction mixture was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to afford 73.1 mg (60%) of the amide **5** as white solid: mp 62−64 °C; $[\alpha]_D^{25}$ −23.5 (*c* 1.03, MeOH); FT-IR (thin film, neat) ν_{max} 2954, 2930, 2885, 2858, 1666, 1471, 1425, 1362, 1338 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz, mixture of rotamers) δ 6.45 (m, 1H), 6.47 (m), 4.96 (dd, 1H, *J* = 11.9, 8.5 Hz), 4.87 (dd), 4.41 (m, 1H), 4.54 (m), 4.24 (s, 2H), 4.33 (m), 3.50−3.41 (m, 2H), 3.56−3.48 (m), 2.05−1.83 (m, 2H), 2.16−2.07 (m), 1.91−1.74 (m, 2H), 1.69−1.66 (m), 0.92 (m, 18H), 0.16 (s, 3H), 0.13 (s, 3H), 0.11 (m, 6H); ^{13}C NMR (CD_3OD, 75 MHz, mixture of rotamers) δ 172.9/172.0, 144.8/145.3, 112.9/112.3, 64.8/65.4, 57.4/57.7, 48.2/47.3, 36.0/33.2, 27.2/27.2, 27.2/27.2, 27.2/27.2, 26.9/29.9, 26.9/26.9, 26.9/26.9, 23.4/25.8, 20.2/20.1, 19.9, −4.3, −4.3, −4.4, −4.4; LR-MS (FAB+) *m*/*z* 400 (M + H$^+$); HR-MS (FAB+) calcd for $C_{20}H_{42}NO_3Si_2$ (M + H$^+$) 400.2703, found 400.2702.

(3*S*,4*S*,*Z*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-3,4,8,9-tetrahydro-1*H*-azonin-2(7H)-one (3). To a solution of the amide **5** (1.53 g, 3.83 mmol) in toluene (60 mL) was added lithium bis(trimethylsilyl)-amide (11.5 mL, 11.5 mmol, 1.0 M in hexanes) at 120 °C. After stirring for 15 h at the same temperature, the reaction mixture was quenched with H_2O at ambient temperature. The aqueous layer was extracted with EtOAc (2 × 70 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc: n-hexane =1: 10) to afford 1.01 g (66%) of the azoninone **3** as white solid: mp 81−83 °C; $[\alpha]_D^{26}$ −10.1 (*c* 1.01, MeOH); FT-IR (thin film, neat) ν_{max} 3409, 2954, 2930, 2858, 1686, 1515, 1472, 1362 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 6.89 (d, 1H, *J* = 11.2 Hz), 5.53 (m, 1H), 5.27 (dd, 1H, *J* = 11.6, 6.7 Hz), 4.57 (d, 1H, *J* = 6.4 Hz), 4.20 (s, 1H), 4.03 (m, 1H), 3.03 (m, 1H), 2.00−1.82 (m, 2H), 1.73 (m, 2H), 0.92 (s, 18H), 0.15 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.9, 135.0, 131.9, 81.3, 76.2, 41.3, 31.9, 27.3, 27.3, 27.3, 27.1, 27.1, 27.1, 27.0, 20.0, 20.0, −3.6, −3.7, −3.7, −4.1; LR-MS (FAB+) *m*/*z* 400 (M + H$^+$); HR-MS (FAB+) calcd for $C_{20}H_{42}NO_3Si_2$ (M + H$^+$) 400.2703, found 400.2715.

(6*S*,7*S*,8*R*,8a*S*)-6,7,8-Trihydroxyhexahydroindolizin-5(1*H*)-one (10). To a solution of the azoninone **3** (897 mg, 2.24 mmol) in MeOH (30 mL) and H_2O (10 mL) were added Oxone (3.44 g, 11.2 mmol) at ambient temperature. After being stirred for 60 h at the same temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1: 10) to afford 264 mg (63%) of the triol **10** as colorless and foamy solid: $[\alpha]_D^{26}$ −83.1 (*c* 1.04, MeOH); FT-IR (thin film, neat) ν_{max} 3378, 2889, 1623, 1484, 1326 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 4.18 (d, 1H, *J* = 3.7 Hz), 4.13 (d, 1H, *J* = 4.2 Hz), 4.02 (dd, 1H, *J* = 4.6, 2.6 Hz), 3.90 (m, 1H), 3.42 (dd, 2H, *J* = 8.8, 5.5 Hz), 2.04−1.87 (m, 2H), 1.95−1.79 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.3, 72.9, 69.6, 69.6, 60.6, 46.7, 28.1, 24.3; LR-MS (FAB+) *m*/*z* 188 (M + H$^+$); HR-MS (FAB+) calcd for $C_8H_{14}NO_4$ (M + H$^+$) 188.0923, found 188.0911.

(6*S*,7*S*,8*R*,8a*S*)-5-Oxooctahydroindolizine-6,7,8-triyl Triacetate (11). To a solution of the triol **10** (264 mg, 1.41 mmol) in pyridine (30 mL) was added acetic anhydride (1.3 mL, 14.1 mmol) at ambient temperature. After stirring for 12 h at the same temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc: n-hexane =1: 3 to 1: 1) to afford 313 mg (71%) of the triacetate **11** as a pale yellow oil: $[\alpha]_D^{26}$ −130 (*c* 1.05, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3481, 2977, 2939, 2891, 1754, 1662, 1459, 1372, 1332 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.55 (m, 1H), 5.46 (m, 1H), 5.30 (m, 1H), 3.91 (d, 1H, *J* = 10.7 Hz), 3.52 (m, 2H), 2.11 (s, 3H), 2.07 (s, 6H), 2.00−1.84 (m, 2H), 1.88−1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 169.2, 169.2, 163.3, 67.5, 66.3, 66.2, 57.2, 44.6, 27.1, 22.1, 20.6, 20.6, 20.5; LR-MS (FAB+) *m*/*z* 314 (M + H$^+$); HR-MS (FAB+) calcd for $C_{14}H_{20}NO_7$ (M + H$^+$) 314.1240, found 314.1241.

1-Deoxy-6,8a-di-*epi*-castanospermine (1). To a solution of lithium aluminum hydride (157 mg, 4.15 mmol) in THF (10 mL) was slowly added a solution of the triacetate **11** (130 mg, 415 μmol) in THF (10 mL) at 0 °C. After being for 12 h at 60 °C, the reaction mixture was quenched with H_2O and NaOH (10%). The resulting mixture was dried over $MgSO_4$ at 0 °C and filtered under reduced pressure. The organic layer was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:10) to afford 61.8 mg (86%) of 1-deoxy-6,8a-di-*epi*-castanospermine **1** as a colorless solid: mp 127−129 °C; $[\alpha]_D^{25}$ 23.3 (*c* 0.950, MeOH); FT-IR (thin film, neat) ν_{max} 3365, 2922, 2822, 1647, 1464 cm^{-1}; ^{1}H NMR (D_2O, 500 MHz) δ 3.92 (m, 1H), 3.83 (s, 2H), 3.00 (m, 1H), 2.97 (m, 1H), 2.71 (m, 1H), 2.42 (m, 2H), 1.80−1.69 (m, 2H), 1.74−1.57 (m, 2H); ^{13}C NMR (D_2O, 100 MHz) δ 72.2, 69.6, 66.5, 64.8, 55.0, 53.2, 24.4, 22.6; LR-MS (FAB+) *m*/*z* 174 (M + H$^+$); HR-MS (FAB+) calcd for $C_8H_{16}NO_3$ (M + H$^+$) 174.1130, found 174.1130.

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(*S*,*Z*)-*tert*-Butyl 2-(2-(*tert*-Butyldimethylsilyloxy)vinyl)-pyrrolidine-1-carboxylate (12). To a solution of sodium hydride (940 mg, 23.5 mmol, 60% dispersion in paraffin liquid) in THF (10 mL) was slowly added a solution of the aldehyde **7** (833 mg, 3.91 mmol) in THF (30 mL) and TBSCl (2.95 g, 19.6 mmol) at −78 °C. After being stirred for 1 h at ambient temperature, the reaction mixture was quenched with H_2O and then extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:10) to afford 1.06 g (83%) of the (*Z*)-silyl enol ether **12** as a colorless oil: $[\alpha]_D^{23}$ 33.5 (*c* 1.00, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3037, 2957, 2930, 2884, 2859, 2712, 1698, 1657, 1473, 1462, 1392, 1364, 1343, 1321 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.07 (d, 1H, *J* = 5.7 Hz), 4.62 (m, 1H), 4.46 (brs, 1H), 3.33 (m, 2H), 2.08−1.77 (m, 2H), 1.80 (m, 2H), 1.40 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 137.7, 113.4, 78.6, 52.6, 46.1, 33.5, 28.5, 28.5, 28.5, 25.5, 25.5 25.5, 23.6, 18.2, −5.3, −5.6; LR-MS (FAB+) *m*/*z* 328 (M + H^+); HR-MS (FAB+) calcd for $C_{17}H_{34}NO_3Si$ (M + H^+) 328.2308, found 328.2303.

(*S*,*Z*)-2-(*tert*-Butyldimethylsilyloxy)-1-(2-(2-(*tert*-butyldimethylsilyloxy)vinyl)pyrrolidin-1-yl)ethanone (6). To a solution of the (*Z*)-silyl enol ether **12** (1.53 g, 4.67 mmol) in CH_2Cl_2 (30 mL) were added 2,6-lutidine (1.1 mL, 9.34 mmol) and TMSOTf (1.3 mL, 7.01 mmol) at 0 °C. After being stirred for 2 h at ambient temperature, the reaction mixture was quenched with MeOH and then concentrated in vacuo. This crude mixture was used for next step without further purification. To a solution of the crude amine and the acid **8** (1.33 g, 7.01 mmol) in CH_2Cl_2 (50 mL) were added 1-hydroxybenzotriazole hydrate (695 mg, 5.14 mmol), 4-methylmorpholine (1.1 mL, 10.3 mmol), and EDCI (1.34 g, 7.01 mmol) at ambient temperature. After being stirred for 18 h at the same temperature, the reaction mixture was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to afford 1.12 g (60%) of the amide **6** as a colorless oil: $[\alpha]_D^{20}$ 90.2 (*c* 0.100, MeOH); FT-IR (thin film, neat) ν_{max} 2954, 2930, 2885, 2857, 1667, 1650, 1462, 1426, 1342 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 6.33 (d, 1H, *J* = 5.6 Hz), 4.56 (dd, 1H, *J* = 9.1, 5.8 Hz), 4.32 (s, 2H), 3.47 (m, 2H), 2.15 (m, 1H), 2.00−1.81 (m, 2H), 1.93−1.74 (m, 2H), 0.96 (s, 9H), 0.91 (s, 9H), 0.19 (s, 6H), 0.09 (s, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 172.8, 141.6, 112.4, 64.3, 53.5, 48.0, 35.7, 27.2, 27.2, 27.2, 26.9, 26.9, 26.9, 24.0, 20.2, 19.9, −4.2, −4.3, −4.3, −4.6; LR-MS (FAB+) *m*/*z* 400 (M + H^+); HR-MS (FAB+) calcd for $C_{20}H_{42}NO_3Si_2$ (M + H^+) 400.2703, found 400.2702.

(3*S*,4*S*,*E*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-3,4,8,9-tetrahydro-1*H*-azonin-2(7*H*)-one (4). To a solution of the amide **6** (56.6 mg, 142 μmol) in benzene (60 mL) was added lithium diisopropylamide (142 μL, 284 μmol, 2.0 M in THF). The reaction mixture and a magnetic bar were sealed in the reaction vessel of a Discover monomode microwave apparatus (CEM) and irradiated for 1.5 h at 150 °C. The reaction mixture was quenched with H_2O at ambient temperature. The aqueous layer was extracted with EtOAc (2 × 70 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:10) to afford 11.9 mg (21%) of the azoninone **4** as a pale yellow oil: $[\alpha]_D^{21}$ 20.2 (*c* 0.825, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3428, 3394, 2953, 2928, 2857, 2739, 2710, 1736, 1686, 1651, 1514, 1470, 1409, 1389, 1362, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.07 (d, 1H, *J* = 8.4 Hz), 5.55 (m, 1H), 5.44 (dd, 1H, *J* = 16.8, 8.1 Hz), 4.26 (dd, 1H, *J* = 8.3, 3.2 Hz), 4.15 (d, 1H, *J* = 3.3 Hz), 3.72−2.93 (m, 2H), 2.20 (m, 2H), 1.94−1.50 (m, 2H), 0.89 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 175.0, 131.8, 131.1, 79.6, 77.5, 40.0, 29.3, 28.1, 26.3, 26.3, 26.3, 25.9, 25.9, 25.9, 18.6, 18.5, −4.3, −4.4, −4.4, −5.4; LR-MS (FAB+) *m*/*z* 400 (M + H^+); HR-MS (FAB+) calcd for $C_{20}H_{42}NO_3Si_2$ (M + H^+) 400.2703, found 400.2701.

(6*S*,7*S*,8*R*,8a*R*)-6,7,8-Trihydroxyhexahydroindolizin-5(1*H*)-one (13). To a solution of the azoninone **4** (104 mg, 260 μmol) in MeOH (6 mL) and H_2O (2 mL) was added Oxone (400 mg, 1.30 mmol) at ambient temperature. After being stirred for 24 h at the same temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:10) to afford 28.7 mg (59%) of the triol **13** as pale yellow solid: mp 78−80 °C; $[\alpha]_D^{22}$ 16.3 (*c* 1.10, MeOH); FT-IR (thin film, neat) ν_{max} 3384, 2975, 2919, 2886, 1652, 1480, 1461, 1391, 1340 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 4.21 (d, 1H, *J* = 3.8 Hz), 3.90 (t, 1H, *J* = 3.8 Hz), 3.53 (m, 1H), 3.49 (m, 1H), 3.44−3.34 (m, 2H), 2.37−1.93 (m, 2H), 1.89−1.71 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 171.8, 77.6, 77.0, 71.6, 62.7, 47.1, 33.7, 24.8; LR-MS (FAB+) *m*/*z* 188 (M + H^+); HR-MS (FAB+) calcd for $C_8H_{14}NO_4$ (M + H^+) 188.0923, found 188.0921.

(6*S*,7*S*,8*R*,8a*R*)-5-Oxooctahydroindolizine-6,7,8-triyl Triacetate (14). To a solution of the triol **13** (70.0 mg, 374 μmol) in pyridine (10 mL) was added acetic anhydride (0.3 mL, 3.74 mmol) at ambient temperature. After stirring for 13 h at the same temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3 to 1:1) to afford 91.4 mg (78%) of the triacetate **14** as a pale yellow oil: $[\alpha]_D^{24}$ 21.9 (*c* 1.31, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3482, 2956, 2888, 1751, 1692, 1447, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.49 (d, 1H, *J* = 4.0 Hz), 5.38 (t, 1H, *J* = 3.5 Hz), 4.83 (dd, 1H, *J* = 8.0, 3.0 Hz), 3.58 (m, 2H), 3.50 (m, 1H), 2.27−1.91 (m, 2H), 2.14 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 169.5, 169.5, 163.1, 73.9, 72.1, 68.3, 58.2, 45.2, 31.9, 22.9, 20.8, 20.7, 20.6; LR-MS (FAB+) *m*/*z* 314 (M + H^+); HR-MS (FAB+) calcd for $C_{14}H_{20}NO_7$ (M + H^+) 314.1240, found 314.1237.

1-Deoxy-6-*epi*-castanospermine (2). To a solution of lithium aluminum hydride (41.4 mg, 1.09 mmol) in THF (5 mL) was added a solution of the triacetate **14** (34.0 mg, 109 μmol) in THF (5 mL) at 0 °C. After being stirred for 8 h at 60 °C, the reaction mixture was quenched with H_2O and NaOH (10%). The resulting mixture was dried over $MgSO_4$ at 0 °C and filtered under reduced pressure. The organic layer was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1:10) to afford 15.5 mg (82%) of 1-deoxy-6-*epi*-castanospermine **2** as a colorless solid: mp 123−125 °C; $[\alpha]_D^{23}$ −25.2 (*c* 0.250, MeOH); FT-IR (thin film, neat) ν_{max} 3364, 2924, 2853, 2809, 1745, 1660, 1648, 1567, 1412, 1339 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 3.96 (brs, 1H), 3.49 (t, 1H, *J* = 9.1 Hz), 3.43 (dd, 1H, *J* = 9.5, 3.5 Hz), 3.04 (dd, 1H, *J* = 12.7, 2.4 Hz), 2.93 (m, 1H), 2.26 (d, 1H, *J* = 12.6 Hz), 2.17 (q, 1H, *J* = 9.2 Hz), 1.97 (m, 2H), 1.75 (m, 2H), 1.50 (m, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 75.9, 73.6, 69.8, 68.4, 55.8, 53.9, 28.2, 21.8; LR-MS (FAB+) *m*/*z* 174 (M + H^+); HR-MS (FAB+) calcd for $C_8H_{16}NO_3$ (M + H^+) 174.1130, found 174.1128.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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