Asymmetric total synthesis of 1-deoxy-7,8-di-*epi*-castanospermine†

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An efficient, stereocontrolled synthesis of (6*S*,7*S*,8*S*,8a*R*)-6,7,8-trihydroxyindolizidine (alias 1-deoxy-7,8-di-*epi*-castanospermine) (**14**) has been developed, which exploits an asymmetric vinylogous Mukaiyama aldol reaction (VMAR) between *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)-pyrrole (**1**) and 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) to construct the initial pyrrolidine building block **3**, and an ene-ene ring closing metathesis reaction (RCM) (**9** to **10**) to install the indolizidine skeleton. The synthetic sequence was 13 steps, proceeding in 19.5% overall yield. The configurational and conformational structure of **14** was ascertained unambiguously and confronted to previously published assignments of ***rac*-14** and ***ent*-14**.

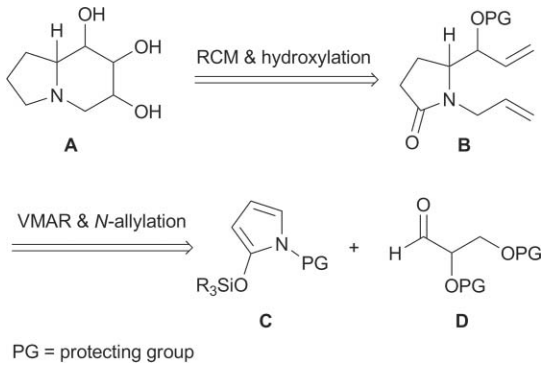
Introduction

Aza-fused bicyclic alkaloids having indolizidine ring systems are important core structures in organic and bioorganic chemistry due to their occurrence in many biologically active compounds of terrestrial and marine sources such as bacteria, fungi, higher plants, vertebrates, and invertebrates.[1] Accordingly, the motifs of these alkaloids have been the targets of many synthetic efforts, with novel racemic and enantioselective syntheses designed and implemented.[2]

Pursuing our investigations on the asymmetric synthesis of densely functionalized nitrogen heterocycles exploiting pyrrole-based dienoxy silane synthons,[3] we describe herein the construction of (6*S*,7*S*,8*S*,8a*R*)-6,7,8-trihydroxyindolizidine (alias 1-deoxy-7,8-di-*epi*-castanospermine) (**14**), featuring, as a key step, an ene-ene ring closing metathesis reaction (RCM).[4,5]

At present, three reports exist dealing with the preparation of structures related to **14**; a RCM-based racemic route to ***rac*-14** by Quintard *et al.*,[6] and two asymmetric syntheses of ***ent*-14** by Ding *et al.*[7] and Richardson *et al.*,[8] respectively. Discrepancies in the reported assignments and poor characterization of the respective targets forced us to develop an alternative, reliable access to **14** and provide a firm, unambiguous characterization of its structure.

To suggest a new asymmetric route to indolizidine systems of type **A** (Scheme 1), we envisioned that cyclization to the azabicycle skeleton would be feasible on terminal diolefinic substrates of type **B** *via* RCM, while we thought the requisite building block **B** would originate from a vinylogous Mukaiyama aldol reaction (VMAR) between silyloxy pyrrole **C** and a suitable chiral nonracemic α-hydroxyaldehyde **D**.[3,9] Thus, we started to investigate the feasibility of this synthesis plan.



Scheme 1 Retrosynthesis of a generic indolizidine **A** featuring VMAR and RCM as key manoeuvres.

Results and discussion

We began exploiting the d_4 vinylogous nucleophile *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)pyrrole (**1**), which was effectively coupled to the popular three-carbon chiral synthon 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**), to furnish crystalline (5*R*,1′*S*,2′*R*)-configured 5,1′-*syn*-1′,2′-*anti* lactam **3** as the sole detectable stereoisomer in a 80% isolated yield (Scheme 2).[10]

Next, to elaborate lactam **3** into diolefin **9** as requested for the RCM cyclization, a seven-step sequence was adopted, encompassing (1) double bond saturation, (2) 1′-OH protection, (3) 2′,3′-*O*-isopropylidene deblocking, (4,5) 2′,3′-deoxygenation *via* mesylation, and (6,7) swapping the *N*-Boc protection for an allyl group. Thus, working on 6.4 mmol scale, unsaturated lactam **3** was exposed to nickel boride ($NaBH_4/NiCl_2$)[11] to furnish a saturated pyrrolidinone, which was directly protected as TBS-ether **4** (TBSOTf/2,6-lutidine; 93% yield over two steps). Then, by subjecting **4** to 70% aqueous acetic acid, selective fragmentation of the acetonide blockage occurred, giving rise to free diol **5**, which was soon elaborated to olefin **7** by mesylation to **6** and NaI-driven

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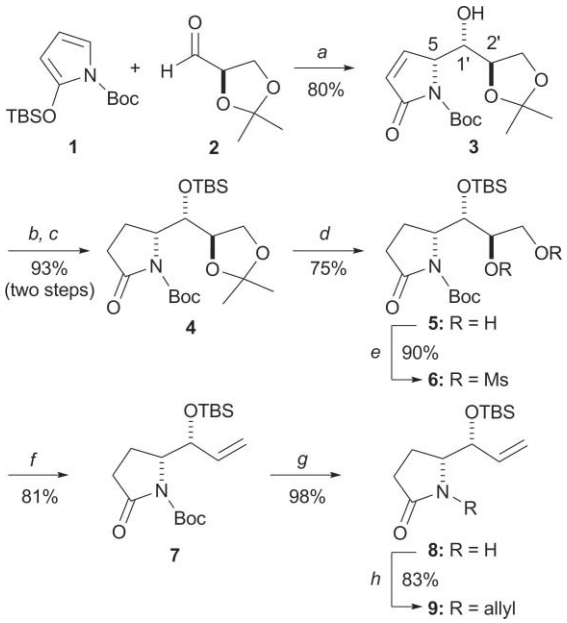
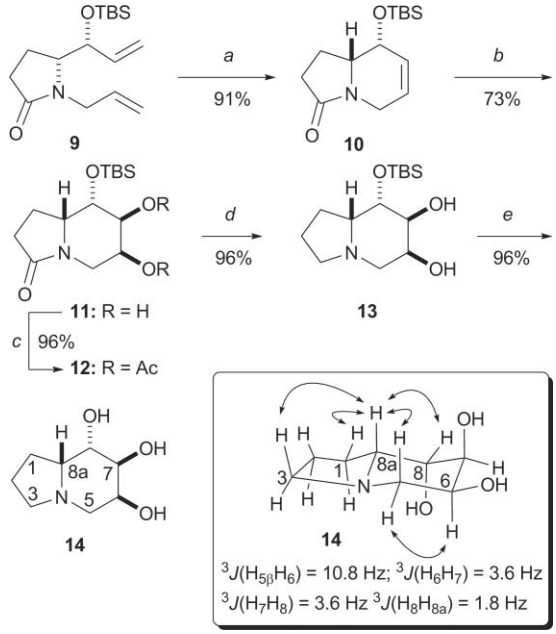
† Electronic supplementary information (ESI) available: NMR comparison Tables S1–S4 for compounds **13**, **13**·BH_3, ***ent*-13**, ***rac*-13**, **14**, ***ent*-14** and ***rac*-14**, and copies of ^1H, ^{13}C, and ^{11}B NMR spectra of compounds **6–14**. See DOI: 10.1039/b924721a



Scheme 2 Synthesis of diolefin precursor **9**. *Reagents and conditions*: (*a*) $SnCl_4$, Et_2O, –80 °C; (*b*) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C; (*c*) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (*d*) aq AcOH, rt; (*e*) MsCl, pyridine, 0 °C; (*f*) NaI, DME, reflux; (*g*) CAN, CH_3CN, reflux; (*h*) allylBr, n-$Bu_4N{\cdot}HSO_4$, CH_2Cl_2, NaOH, rt.



Scheme 3 Completion of the synthesis of indolizidine **14**. *Reagents and conditions*: (*a*) Grubbs II cat., CH_2Cl_2, reflux; (*b*) OsO_4, NMO, acetone, H_2O, rt; (*c*) Ac_2O, pyridine, rt; (*d*) $BH_3{\cdot}$DMS, THF, reflux, then 10% Pd/C, MeOH, rt; (*e*) TBAF, THF, rt. The inset depicts a stereodrawing of **14** with double headed arrows showing diagnostic nOe's between indicated hydrogen atoms.

deoxygenation.[12] These manoeuvres allowed us to obtain olefin **7** cleanly, in a good 55% yield over three steps. Finally, the second olefin substituent was appended to pyrrolidine nitrogen by Boc excision to **8** (CAN, MeCN), followed by *N*-allylation to deliver the requisite diolefin **9** in 81% yield over two steps.

In the past few years, the use of RCM to assemble heterocyclic systems from acyclic or cyclic diolefins has increased enormously, as a result of the alkylidene ruthenium and molybdenum catalysts developed by Grubbs, Schrock, and Hoveyda.[4] Thus, prompted by the easy with which diolefin **9** was created, we applied, as planned, RCM to complete the azabicycle motif of the indolizidine target **14** (Scheme 3).

The cyclization reaction of **9** was performed with a Grubbs' second generation catalyst in CH_2Cl_2, which furnished pure unsaturated bicycle **10** in a respectable 91% isolated yield. A further advance in the synthesis involved a diastereocontrolled *cis*-dihydroxylation of the double bond within **10** (OsO_4-NMO) to install the requisite oxygen functionalities at C6 and C7 carbons, which occurred exclusively at the β face of the double bond, giving rise to diol **11** that, upon acetylation, delivered crystalline indolizidinone **12** in a 70% yield over two steps. The stereochemistry of **12** was secured as shown by extensive ^{1}H and ^{13}C NMR investigations including ^{1}H-^{1}H coupling constant measurements, and was further supported by its spectral identity with the known racemic counterpart ***rac*-12**.[6]

With ready access to protected triol **12** secured, we opted to reduce all the carbonyl functionalities present in the molecule in one pot, and this was attained by exposing **12** to ten molar excess $BH_3{\cdot}$DMS complex in refluxing THF, as suggested by Quintard in his original report.[6] That our borane reduction had indeed delivered indolizidine free base **13** puzzled us, given the marked disagreement between our data and the optical and spectroscopic properties reported by Ding for the enantiomer of **13** [referred as (6*R*,7*R*,8*R*,8a*S*)-8-(*tert*-butyldimethylsilyloxy)-6,7-dihydroxyindolizidine (**12b**) in the original report] and fair matching to NMR data for racemic **13**, as reported by Quintard [referred as (±)-8-(*tert*-butyldimethylsilyloxy)-1-deoxy-6,8a-di-*epi*-castanospermine (**14**) in the original report].

To clarify this matter, we deeply investigated the exact nature of protected indolizidine **13** in our hands, and soon discovered that the product, which was isolated in a homogeneous state after silica gel chromatography, was indeed a stable amine-borane complex, not a free base. Examination of the ^{11}B NMR spectrum of this material clearly revealed a broad resonance at –9.25 ppm, which was definitely attributed to a tertiary amine-borane complex. Thus, the mild protocol introduced by Couturier[13] to cleave amine-borane complexes, was here adopted to liberate indolizidine **13** (treatment with 10% Pd on carbon in methanol). Here, free base **13** was obtained as a glassy solid by simple filtration and solvent evaporation in a 96% yield for the entire treatment. At this point, the chiro-optical and ^{13}C NMR data for **13** matched those reported by Ding for the enantiomer of **13** {**13**: $[\alpha]_D^{20}$ –10.1 (*c* 1.9, MeOH); ***ent*-13**:[7] $[\alpha]_D^{20}$ +13.1 (*c* 0.96, MeOH)}, whilst profound disagreement remained with the data reported by Quintard for ***rac*-13**. In this latter case, we surmised that published ***rac*-13** was probably a borane complex, since an almost exact match between our data for **13·BH$_3$** and those reported for ***rac*-13** was attained (see electronic supplementary information for details, Tables S1 and S2†).

Now, all that remained to complete the journey was a simple desilylation, that was carried out by exposing **13** to TBAF, avoiding any acidic treatment. After quenching the reaction with aqueous methanol and silica gel chromatographic purification,

1-deoxy-7,8-di-*epi*-castanospermine (**14**) was obtained in a 96% yield, which corresponded to a 19.5% global yield for the entire linear sequence of 13 steps from pyrrole **1**.

As expected, the specific optical rotation of **14** matched well the value reported in the literature for its enantiomer, though opposite in sign {**14**: $[\alpha]_D^{20}$ −26.0 (*c* 1.1, MeOH) *vs.* ***ent*-14**:[7] $[\alpha]_D^{20}$ +23.5 (*c* 0.90, MeOH); ***ent*-14**:[8a] $[\alpha]_D^{25}$ +23 (MeOH)}.

An attentive comparison of ^{1}H and ^{13}C NMR data for **14** in our hands with those reported for ***ent*-14**[7] and ***rac*-14**[6] was made. ^{1}H NMR data are quite similar for **14** and ***ent*-14**, with integrals, multiplicity of resonances and coupling constants largely consistent. ^{13}C NMR data is an excellent match for the two molecules and all δCH_2 and CH values support the assignment (see electronic supplementary information for details, Tables S3 and S4†). Regrettably, both the proton and carbon NMR resonances of ***rac*-14**, as reported by Quintard, proved different from those reported by us and Ding for **14** and ***ent*-14**; and this suggests that structure ***rac*-14** (compound **15** in the original paper) is misassigned.

Conclusions

In summary, we have devised an asymmetric total synthesis of (6*S*,7*S*,8*S*,8a*R*)-6,7,8-trihydroxyindolizidine (alias 1-deoxy-7,8-di-*epi*-castanospermine) (**14**). The protocol required 13 steps starting from pyrrole **1** and proceeded in 19.5% overall yield. Key steps included a diastereocontrolled VMAR to assemble the initial chiral building block **3**, and a highly productive RCM (**9** to **10**) to install the bicyclic skeleton of **14**. With the configurational structure of **14** (and **13**) firmly established, new light was cast on the rather obscure corners of previously published characterization of related ***rac*-13** and ***rac*-14** counterparts.

Experimental section

General methods

All anhydrous solvents were dried and freshly distilled before use according to literature procedures. All moisture sensitive reactions were carried out under a positive pressure of nitrogen or argon. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} precoated plates (Merck) with visualization under short-wavelength UV light or by dipping the plates with molybdate reagent (aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate) followed by heating. Flash chromatography was performed on 63–200 μm silica gel (Merck) using the indicated solvent mixtures. Direct infusion ESI-MS spectra were recorded on API 150EX apparatus (Applied Biosystems). Melting points were determined with an optical thermomicroscope Optiphot2-Pol (Nikon) and are uncorrected. Optical rotations were measured using a Perkin-Elmer model 341 polarimeter at ambient temperature using a 100-mm cell with a 1-mL capacity and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Microanalytical Laboratory of the University of Parma. IR Spectra were recorded on a Jasco FT/IR-300E apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Avance 300 (Bruker), Avance 400 (Bruker), Mercury Plus MP-400 (Varian), or 600 INOVA (Varian) NMR spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) with TMS ($CDCl_3$) and CD_2HOD resonance peaks set at 0.0 and 3.31 ppm, respectively. Peak assignments were performed using conventional 1D and 2D-NMR experiments, such as COSY, NOESY and HSQC sequences. ^{11}B NMR spectra were recorded on 600 INOVA (Varian) spectrometer operating at 192 MHz. Chemical shifts (δ) are reported in parts per million (ppm) referred to external $BF_3{\cdot}OEt_2$ ($CDCl_3$).

N-(*tert*-Butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (**1**) was prepared from pyrrole according to a described protocol.[14] 2,3-*O*-Isopropylidene-D-glyceraldehyde (**2**) was prepared from D-mannitol according to an optimized protocol.[15]

Synthetic procedures

(1′*S*,4″*R*,5*R*)-1-(*tert*-Butyloxycarbonyl)-5-[(2,2-dimethyl-1,3-dioxolan-4-yl)hydroxymethyl]-1,5-dihydropyrrol-2-one (3). To a solution of pyrrole **1** (TBSOP, 2.50 g, 8.45 mmol) in anhydrous Et_2O (50 mL) under argon atmosphere, was added protected D-glyceraldehyde **2** (1.43 g, 10.98 mmol) and the resulting mixture was cooled to −80 °C. $SnCl_4$ (0.1 M solution in Et_2O, 1.10 mL, 10.98 mmol), cooled to the same temperature, was then added dropwise to the stirring solution, and the reaction was allowed to proceed for 5 h at −80 °C. The reaction mixture was then quenched at the same temperature with water (30 mL) and solid $NaHCO_3$ (2.7 g). After reaching room temperature, the mixture was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under vacuum to furnish a crude residue, which was purified by flash chromatography (EtOAc/hexanes, 60 : 40). Pure lactam **3** was obtained (2.12 g) in 80% yield as a white solid: mp 138–140 °C; $[\alpha]_D^{20}$ +197.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 6.3, 2.1 Hz, 1H), 6.13 (dd, J = 6.3, 1.5 Hz, 1H), 4.81 (ddd, J = 5.7, 2.4, 2.4 Hz, 1H), 4.09 (ddd, J = 6.0, 5.7, 3.9 Hz, 1H), 4.01 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 3.94 (dd, J = 8.1, 6.0 Hz, 1H), 3.86 (dd, J = 8.1, 6.0 Hz, 1H), 3.63 (d, J = 3.9 Hz, 1H), 1.57 (s, 9H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 150.9, 148.2, 126.9, 109.2, 83.8, 75.6, 72.6, 66.4, 65.6, 28.0 (3C), 26.4, 25.1. MS (ESI) calcd for $C_{15}H_{24}NO_6$ $[M+H]^+$:314.16; found: 314.1. Anal. calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47; found: C, 57.40; H, 7.36; N, 4.35.

(1′*S*,4″*R*,5*R*)-1-(*tert*-Butyloxycarbonyl)-5-[(*tert*-butyldimethylsilanyloxy)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]pyrrolidin-2-one (4). A solution of lactam **3** (2.00 g, 6.38 mmol) in absolute methanol (60 mL) was cooled to 0 °C and treated with $NiCl_2{\cdot}6H_2O$ (0.38 g, 1.60 mmol). The resulting mixture was stirred at the same temperature for 10 min before adding $NaBH_4$ (0.12 g, 3.19 mmol). After 30 min, further portion of $NaBH_4$ (0.06 g, 1.60 mmol) was added and the reaction was allowed to stir for additional 15 min. The reaction was then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatographic purification of crude residue (EtOAc/hexanes, 60 : 40) afforded a saturated lactam intermediate (1.96 g, 98%) as a white solid: mp 102–105 °C; $[\alpha]^{D}_{20}$ −60.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (ddd, J = 7.7, 5.9, 1.9 Hz, 1H), 4.09 (m, 2H), 3.98 (m, 1H), 3.75 (dd, J = 6.0, 6.0 Hz, 1H), 2.70 (ddd, J = 17.7, 12.1, 9.1 Hz, 1H), 2.39 (ddd, J = 17.7, 8.7, 2.2 Hz, 1H), 2.16 (m, 2H), 1.75 (bs, 1H), 1.54 (s, 9H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 151.7, 109.4, 83.6, 77.7, 74.5, 66.8, 60.4, 32.0, 28.0 (3C), 26.6, 25.1, 21.7.

To a stirred solution of this lactam intermediate (1.90 g, 6.1 mmol) in anhydrous CH_2Cl_2 (12 mL), cooled to 0 °C, were added 2,6-lutidine (2.13 mL, 18.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.55 mL, 6.71 mmol) under argon atmosphere. After being stirred at room temperature for 24 h, the reaction was quenched by addition of distilled water and 5% citric acid aqueous solution until neutralization. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexanes, 80 : 20) to give pure lactam **4** (2.50 g, 95%) as a pale yellow oil: $[\alpha]^{D}_{20}$ +38.1 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (ddd, J = 9.2, 3.7, 1.3 Hz, 1H), 4.10 (dd, J = 8.5, 3.7 Hz, 1H), 4.07 (dd, J = 8.0, 5.9 Hz, 1H), 3.95 (ddd, J = 8.5, 6.1, 6.1 Hz, 1H), 3.71 (dd, J = 8.1, 6.2 Hz, 1H), 2.57 (ddd, J = 17.8, 11.5, 9.8 Hz, 1H), 2.38 (ddd, J = 17.8, 10.3, 2.0 Hz, 1H), 2.16 (m, 1H), 1.98 (m, 1H), 1.52 (s, 9H), 1.30 (s, 3H), 1.26 (s, 3H), 0.85 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 149.8, 109.8, 82.3, 75.2, 71.1, 68.6, 60.2, 31.8, 29.4, 28.0 (3C), 26.2, 25.4 (3C), 24.9, 17.6, –4.2, –5.0. MS (ESI) calcd for $C_{21}H_{40}NO_6Si$ $[M+H]^+$:430.26; found: 430.3. Anal. calcd for $C_{21}H_{39}NO_6Si$: C, 58.71; H, 9.15; N, 3.26; found: C, 58.85; H, 9.30; N, 3.20.

(1′*S*,2′*R*,5*R*)-1-(*tert*-Butyloxycarbonyl)-5-[1-(*tert*-butyldimethylsilanyloxy)-2,3-dihydroxypropyl]pyrrolidin-2-one (5). Protected lactam **4** (2.40 g, 5.59 mmol) was dissolved in 70% aqueous acetic acid (45 mL) and the resulting solution was allowed to react at room temperature. The reaction was monitored by TLC and judged complete after 6 h. The solution was extracted with CH_2Cl_2, the organic extract was washed twice with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and $NaHCO_3$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography with EtOAc (100%) affording pure diol **5** (1.63 g, 75%) as a white solid: mp 118–120 °C; $[\alpha]^{D}_{20}$ +45.4 (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (ddd, J = 9.0, 4.0, 2.1 Hz, 1H), 4.05 (dd, J = 8.0, 4.0 Hz, 1H), 3.75 (dd, J = 10.7, 3.0 Hz, 1H), 3.62 (m, 1H), 3.52 (dd, J = 10.7, 6.3 Hz, 1H), 3.24 (bs, 2H), 2.64 (ddd, J = 18.2, 10.3, 10.3 Hz, 1H), 2.38 (ddd, J = 18.1, 10.3, 2.9 Hz, 1H), 1.9–2.2 (m, 2H), 1.51 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 150.2, 82.9, 71.8, 70.2, 64.3, 60.0, 31.8, 28.0 (3C), 25.6 (3C), 17.7, 17.4, –4.3, –5.1. MS (ESI) calcd for $C_{18}H_{36}NO_6Si$ $[M+H]^+$:390.23; found: 390.2. Anal. calcd for $C_{18}H_{35}NO_6Si$: C, 55.50; H, 9.06; N, 3.60; found: C, 55.43; H, 9.10; N, 3.75.

(1′*S*,2′*R*,5*R*)-1-(*tert*-Butyloxycarbonyl)-5-[1-(*tert*-butyldimethylsilanyloxy)-2,3-bis(methanesulfonyloxy)propyl]pyrrolidin-2-one (6). To a stirring solution of diol **5** (1.50 g, 3.85 mmol) in dry pyridine (33 mL) cooled to 0 °C, methanesulfonyl chloride (1.49 mL, 19.25 mmol) was added dropwise under argon atmosphere. The reaction was monitored by TLC and judged complete after 6 h. The solution was then concentrated under vacuum to leave an oily residue which was diluted with distilled water and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a residue which was subjected to flash chromatographic purification (EtOAc/hexanes, 70 : 30). Pure compound **6** (1.89 g, 90%) was obtained as a pale yellow oil: $[\alpha]^{D}_{20}$ +26.1 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (ddd, J = 5.6, 4.8, 2.4 Hz, 1H), 4.62 (dd, J = 12.0, 2.4 Hz, 1H), 4.48 (dd, J = 5.6, 5.6 Hz, 1H), 4.45 (dd, J = 12.0, 4.8 Hz, 1H), 4.36 (ddd, J = 8.4, 5.6, 2.8 Hz, 1H), 3.12 (s, 3H), 3.07 (s, 3H), 2.67 (ddd, J = 18.4, 10.0, 9.6 Hz, 1H), 2.50 (ddd, J = 18.4, 9.6, 3.6 Hz, 1H), 2.05–2.22 (m, 2H), 1.56 (s, 9H), 0.91 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 149.9, 83.7, 77.4, 70.2, 67.9, 58.6, 38.6, 37.4, 31.2, 28.1 (3C), 25.7 (3C), 18.5, 18.0, –4.4, –4.9. MS (ESI) calcd for $C_{20}H_{40}NO_{10}S_2Si$ $[M+H]^+$:546.19; found: 546.2. Anal. calcd for $C_{20}H_{39}NO_{10}S_2Si$: C, 44.02; H, 7.20; N, 2.57; found: C, 44.10; H, 7.05; N, 2.40.

(1′*R*,5*R*)-1-(*tert*-Butyloxycarbonyl)-5-[1-(*tert*-butyldimethylsilanyloxy)allyl]pyrrolidin-2-one (7). To a solution of protected compound **6** (1.80 g, 3.30 mmol) in 1,2-dimethoxyethane (100 mL) sodium iodide (3.90 g, 26.05 mmol) was added, and the resulting mixture was allowed to react at reflux for 4 h. The mixture was concentrated and the residue was diluted with 10% aqueous $Na_2S_2O_3$ solution and extracted with $CHCl_3$ (3×). The organic extracts were washed with water (25 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave a yellow oily residue. Purification by flash chromatography (EtOAc/hexanes, 20 : 80) gave pure compound **7** (0.95 g, 81%) as a colourless oil: $[\alpha]^{D}_{20}$ +4.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, J = 17.2, 10.4, 5.6 Hz, 1H), 5.26 (ddd, J = 17.2, 1.6, 1.6 Hz, 1H), 5.15 (ddd, J = 10.4, 1.6, 1.6 Hz, 1H), 4.57 (m, 1H), 4.15 (ddd, J = 9.6, 4.8, 1.6 Hz, 1H), 2.39 (ddd, J = 18.0, 10.4, 9.6 Hz, 1H), 2.29 (ddd, J = 18.0, 10.4, 2.8 Hz, 1H), 2.09 (m, 1H), 1.89 (m, 1H), 1.50 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 150.0, 135.6, 117.8, 83.0, 72.1, 61.2, 32.2, 28.1 (3C), 25.7 (3C), 18.1, 17.1, –4.6, –4.9. MS (ESI) calcd for $C_{18}H_{34}NO_4Si$ $[M+H]^+$:356.23; found: 356.2. Anal. calcd for $C_{18}H_{33}NO_4Si$: C, 60.81; H, 9.36; N, 3.94; found: C, 60.63; H, 9.45; N, 3.80.

(1′*R*,5*R*)-5-[1-(*tert*-Butyldimethylsilanyloxy)allyl]pyrrolidin-2-one (8). To a stirring solution of compound **7** (0.9 g, 2.53 mmol) in CH_3CN (50 mL) was added ceric ammonium nitrate (CAN, 0.28 g, 0.51 mmol) and the resulting mixture was allowed to react at reflux overnight. The reaction was then quenched by sequential addition of saturated aqueous solutions of $NaHCO_3$ (10 mL) and NH_4Cl (10 mL) and extracted with EtOAc (3×). The combined organic layers were dried with $MgSO_4$, and concentrated under vacuum to furnish a crude residue, which was purified by flash chromatography (EtOAc/hexanes, 80 : 20). Pure compound **8** (0.63 g, 98%) was obtained as a yellow glassy solid: $[\alpha]^{D}_{20}$ –9.2 (*c* 3.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (bs, 1H), 5.72 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.28 (ddd, J = 17.2, 1.6, 1.2 Hz, 1H), 5.21 (ddd, J = 10.4, 1.2, 0.8 Hz, 1H), 3.88 (dddd, J = 6.8, 6.8, 1.2, 0.8 Hz, 1H), 3.54 (ddd, J = 7.6, 6.8, 6.0 Hz, 1H), 2.35 (ddd, J = 17.2, 9.6, 6.4 Hz, 1H), 2.29 (ddd, J = 17.2, 8.8, 7.6 Hz, 1H), 2.08 (dddd, J = 12.8, 8.4, 7.6, 6.4 Hz, 1H), 1.78 (dddd, J = 13.2, 9.6, 7.6, 6.0 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 137.2, 117.8, 77.9, 58.9, 30.1, 25.8 (3C), 22.9, 18.0, –4.1, –4.9. MS (ESI) calcd for $C_{13}H_{26}NO_2Si$ $[M+H]^+$:256.17; found: 256.2. Anal. calcd for $C_{13}H_{25}NO_2Si$: C, 61.13; H, 9.87; N, 5.48; found: C, 61.30; H, 9.70; N, 5.55.

(1′*R*,5*R*)-1-Allyl-5-[1-(*tert*-butyldimethylsilanyloxy)allyl] pyrrolidin-2-one (9). Alkene **8** (0.60 g, 2.35 mmol) was dissolved in 20 mL of CH_2Cl_2 and treated with 13 mL of an aqueous solution

of NaOH (40%). To the resulting mixture were sequentially added allyl bromide (0.81 mL, 9.4 mmol) and *n*-$Bu_4N{\cdot}HSO_4$ (0.4 g, 1.18 mmol). The mixture was stirred at room temperature for 2 h; then further portions of allyl bromide (0.81 mL, 9.4 mmol) and *n*-$Bu_4N{\cdot}HSO_4$ (0.4 g, 1.18 mmol) were added. The reaction was judged complete after 4 h, quenched with water, and extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatographic purification (EtOAc/hexanes, 80 : 20) afforded pure *N*-allyl compound **9** (0.58 g, 83%) as a yellow glassy solid: $[\alpha]^D_{20}$ +10.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66–5.78 (m, 2H), 5.29 (ddd, J = 17.2, 2.0, 1.6 Hz, 1H), 5.14–5.22 (m, 3H), 4.36 (dddd, J = 15.2, 4.8, 1.6, 1.6 Hz, 1H), 4.33 (m, 1H), 3.62 (ddd, J = 8.4, 4.4, 2.8 Hz, 1H), 3.51 (ddd, J = 15.2, 8.0, 0.8 Hz, 1H), 2.30 (ddd, J = 17.2, 9.2, 9.2 Hz, 1H), 2.21 (ddd, J = 17.2, 10.4, 3.6 Hz, 1H), 1.83–2.23 (m, 2H), 0.86 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 135.6, 132.8, 118.2, 117.4, 72.1, 61.3, 44.3, 30.2, 25.7 (3C), 18.6, 18.1, –4.6, –5.0. MS (ESI) calcd for $C_{16}H_{30}NO_2Si$ $[M+H]^+$:296.20; found: 296.2. Anal. calcd for $C_{16}H_{29}NO_2Si$: C, 65.03; H, 9.89; N, 4.74; found C, 65.20; H, 9.80; N, 4.65.

(8*R*,8a*R*)-8-(*tert*-Butyldimethylsilanyloxy)-1,2,8,8a-tetrahydroindolizin-3(5*H*)-one (10). To a solution of compound **9** (0.54 g, 1.83 mmol), in anhydrous CH_2Cl_2 (30 mL) under argon atmosphere, (IMes)(PCy_3)Cl_2Ru=CHPh (Grubbs catalyst 2nd generation, 0.15 g, 0.18 mmol) was added and the resulting mixture was allowed to react at reflux for 2 h. The reaction was quenched with $NaHCO_3$ saturated aqueous solution (15 mL) and extracted with CH_2Cl_2 (3×). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/hexanes, 80 : 20) affording pure bicyclic compound **10** (0.44 g, 91%) as a white glassy solid: $[\alpha]^D_{20}$ –13.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dddd, J = 10.0, 5.6, 2.4, 2.0 Hz, 1H), 5.85 (ddd, J = 10.0, 2.8, 2.2 Hz, 1H), 4.40 (ddd, J = 18.8, 2.4, 2.4 Hz, 1H), 4.05 (m, 1H), 3.68 (ddd, J = 8.4, 3.2, 3.2 Hz, 1H), 3.51 (bd, J = 18.8 Hz, 1H), 2.50 (ddd, J = 17.6, 10.4, 8.0 Hz, 1H), 2.34 (m, 1H), 2.00–2.18 (m, 2H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 127.3, 127.1, 65.7, 58.5, 40.2, 30.4, 25.8 (3C), 19.7, 18.0, –3.9, –4.7. MS (ESI) calcd for $C_{14}H_{26}NO_2Si$ $[M+H]^+$:268.17; found: 268.1. Anal. calcd for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.24; found C, 62.75; H, 9.30; N, 5.17.

(6*S*,7*S*,8*S*,8a*R*)-8-(*tert*-Butyldimethylsilanyloxy)-6,7-dihydroxyhexahydroindolizin-3(5*H*)-one (11). To a solution of compound **10** (0.38 g, 1.42 mmol) in 15 mL of acetone/H_2O (9 : 1), 4-methylmorpholine *N*-oxide (NMO, 0.25 g, 2.13 mmol) and OsO_4 (2.5% in *t*-BuOH, 4 mL, 0.28 mmol) were added. The resulting mixture was stirred at room temperature for 6 h, then quenched by addition of $Na_2S_2O_3$ saturated aqueous solution (15 mL). After concentration under reduced pressure, the residue was dissolved in 10 mL of water and extracted with EtOAc (3×). The organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum providing an oily crude residue, which was subjected to flash chromatographic purification (EtOAc–MeOH, 95 : 05). Pure diol **11** was obtained (0.31 g, 73%) as a white solid: mp 166–169 °C; $[\alpha]^D_{20}$ –11.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (dd, J = 12.4, 6.4 Hz, 1H), 3.9–4.0 (m, 3H), 3.83 (dd, J = 3.6, 2.0 Hz, 1H), 2.89 (dd, J = 12.0, 11.6 Hz, 1H), 2.58 (bs, 2H), 2.43 (ddd, J = 17.2, 10.4, 7.2 Hz, 1H), 2.33 (ddd, J = 16.8, 10.4, 5.2 Hz, 1H), 2.03 (m, 1H), 1.85 (m, 1H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 72.0, 71.8, 64.0, 55.3, 40.2, 31.0, 25.7 (3C), 18.3, 17.8, –4.6, –5.0. MS (ESI) calcd for $C_{14}H_{28}NO_4Si$ $[M+H]^+$:302.18; found: 302.2. Anal. calcd for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65; found C, 55.85; H, 9.15; N, 4.50.

(6*S*,7*S*,8*S*,8a*R*)-8-(*tert*-Butyldimethylsilanyloxy)-6,7-diacetoxyhexahydroindolizin-3(5*H*)-one (12). To a solution of diol **11** (0.30 g, 1.00 mmol) in pyridine (20 mL), acetic anhydride (2.8 mL, 30.0 mmol) was added and the reaction was stirred at room temperature for 6 h. The solution was concentrated under vacuum and the residue was subjected to flash chromatographic purification (EtOAc, 100%). Pure compound **12** (0.37 g, 96%) was obtained as a white solid: mp 133–135 °C; $[\alpha]^D_{20}$ –2.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (film on NaCl disk): 2921, 2852, 1749, 1687, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (dd, J = 3.6, 3.6 Hz, 1H), 5.13 (ddd, J = 11.6, 6.0, 2.8 Hz, 1H), 4.18 (dd, J = 12.4, 6.0 Hz, 1H), 3.86 (ddd, J = 9.2, 4.0, 2.0 Hz, 1H), 3.78 (dd, J = 4.4, 2.0 Hz, 1H), 3.00 (dd, J = 12.4, 11.6 Hz, 1H), 2.46 (ddd, J = 17.2, 10.0, 6.8 Hz, 1H), 2.36 (ddd, J = 17.2, 10.4, 5.2 Hz, 1H), 2.14 (s, 3H), 2.03 (m, 1H), 2.01 (s, 3H), 1.89 (m, 1H), 0.92 (s, 9H), 0.20 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 169.7, 169.5, 70.2, 69.8, 64.6, 55.8, 37.9, 30.7, 25.6 (3C), 20.9, 20.7, 18.4, 17.8, –4.8, –5.2. MS (ESI) calcd for $C_{18}H_{32}NO_6Si$ $[M+H]^+$:386.20; found: 386.1. Anal. calcd for $C_{18}H_{31}NO_6Si$: C, 56.08; H, 8.10; N, 3.63; found C, 56.00; H, 8.16; N, 3.55.

(6*S*,7*S*,8*S*,8a*R*)-8-(*tert*-Butyldimethylsilanyloxy)-6,7-dihydroxyindolizidine (13). To a stirred solution of compound **12** (0.28 g, 0.73 mmol) in dry THF (25 mL) $BH_3{\cdot}$DMS (2.0 M solution in THF, 3.6 mL, 7.3 mmol) was added under argon atmosphere, and the resulting mixture was refluxed for 4 h. The reaction was then cooled to room temperature, quenched by careful addition of water, and extracted with Et_2O and EtOAc. The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* affording a crude residue which was purified by flash chromatography (EtOAc/hexanes, 40 : 60). Pure borane complex **13·BH$_3$** (0.21 g, 96%) was obtained as a colourless glassy solid: $[\alpha]^D_{20}$ +32.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (m, 2H, H6 and H8), 3.71 (m, 1H, H7), 3.53 (m, 1H, C6-OH), 3.46 (m, 1H, H8a), 3.26 (dd, J = 13.7, 6.0 Hz, 1H, H5), 3.19 (m, 1H, H3), 3.11 (m, 1H, H3′), 2.98 (dd, J = 13.7, 3.7 Hz, 1H, H5′), 2.63 (bd, J = 5.6 Hz, 1H, C7-OH), 2.30 (m, 1H, H1), 2.04 (m, 1H, H2), 1.87 (m, 2H, H1′ and H2′), 2.4–1.6 (m, 3H, BH_3), 0.90 (s, 9H, C(CH_3)$_3$), 0.15 (s, 3H, CH_3), 0.13 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC-based) δ 70.7 (C8), 69.6 (C7), 67.1 (C8a), 65.4 (C6), 63.0 (C3), 55.1 (C5), 25.6 (3C, C(CH_3)$_3$), 24.1 (C1), 20.3 (C2), 17.8 (C(CH$_3$)$_3$), –4.8 (CH$_3$), –5.1 (CH$_3$); ^{11}B NMR (192 MHz, $CDCl_3$) δ –9.25 (bs, 50% line width = 161.0 Hz, ^{1}H decoupled; 306.0 Hz, not decoupled).

Borane complex **13·BH$_3$** (0.21 g, 0.70 mmol) was dissolved in MeOH (20 mL) and 10% palladium on carbon (15 mg, 2 mol%) was added. The resulting heterogeneous mixture was stirred overnight at room temperature, then the catalyst was filtered off and the filtrate was concentrated under reduced pressure affording free base **13** (0.2 g, quant.) as a colourless glassy solid: $[\alpha]^D_{20}$ –10.1 (*c* 1.9, MeOH); lit.,[7] $[\alpha]^D_{20}$ +13.1 (*c* 0.96, MeOH) for ***ent*-13**; IR ν_{max} (film on NaCl disk): 3355, 2931, 2854, 1457, 1257, 1079 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.20 (ddd, J = 10.8,

4.2, 3.0 Hz, 1H, H6), 3.97 (dd, J = 3.0, 3.0 Hz, 1H, H8), 3.80 (dd, J = 3.6, 3.6 Hz, 1H, H7), 3.4–3.7 (bs, 2H, OH), 3.23 (m, 1H, H3α), 3.14 (dd, J = 10.8, 4.2 Hz, 1H, H5α), 2.75 (m, 1H, H8a), 2.53 (dd, J = 10.8, 10.8 Hz, 1H, H5β), 2.41 (m, 1H, H3β), 1.93 (m, 1H, H2), 1.84 (m, 2H, H1 and H2′), 1.57 (m, 1H, H1′), 0.96 (s, 9H, C(CH_3)$_3$), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, HSQC-based) δ 71.7 (C6), 70.2 (C8), 66.0 (C7), 61.5 (C8a), 53.5 (C3), 52.3 (C5), 25.9 (3C, C(CH_3)$_3$), 23.7 (C1), 21.4 (C2), 18.3 (C(CH_3)$_3$), –4.8 (CH_3), –4.9 (CH_3). MS (ESI) calcd for $C_{14}H_{30}NO_3Si$ [M+H]$^+$:288.20; found: 288.2. Anal. calcd for $C_{14}H_{29}NO_3Si$: C, 58.49; H, 10.17; N, 4.87; found C, 58.61; H, 10.11; N, 4.94.

(6*S*,7*S*,8*S*,8a*R*)-6,7,8-Trihydroxyindolizidine (alias 1-Deoxy-7,8-di-*epi*-castanospermine) (14). To a stirred solution of **13** (200 mg, 0.70 mmol) in THF (8 mL) n-Bu_4NF (TBAF, 1.0 M solution in THF, 0.7 mL, 0.70 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with aq MeOH and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc–MeOH/~28% aq NH_3, 85 : 15 : 4) furnishing pure indolizidine **14** (116 mg, 96%) as a colourless glassy solid: $[\alpha]^D_{20}$ –26.0 (c 1.1, MeOH); lit.,[7] $[\alpha]^D_{20}$ +23.5 (c 0.90, MeOH) for ***ent*-14**; lit.,[8a] $[\alpha]^D_{25}$ +23 (MeOH) for ***ent*-14**; IR ν_{max} (film on NaCl disk): 3425, 2090, 1643, 1072 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 4.00 (ddd, J = 11.4, 5.4, 3.6 Hz, 1H, H6), 3.86 (dd, J = 3.6, 3.6 Hz, 1H, H7), 3.74 (dd, J = 3.0, 1.8 Hz, 1H, H8), 3.00 (m, 1H, H3α), 2.90 (dd, J = 10.2, 5.4 Hz, 1H, H5α), 2.53 (m, 1H, H8a), 2.32 (dd, J = 10.8, 10.8 Hz, 1H, H5β), 2.22 (ddd, J = 9.0, 9.0, 8.4 Hz, 1H, H3β), 1.76–1.86 (m, 3H, H2α, H2β and H1α), 1.67 (m, 1H, H1β); ^{13}C NMR (75 MHz, CD_3OD, HSQC-based) δ 72.6 (C6), 70.1 (C8), 67.2 (C7), 62.8 (C8a), 54.8 (C3), 54.0 (C5), 24.4 (C1), 22.5 (C2). MS (ESI) calcd for $C_8H_{16}NO_3$ [M+H]$^+$:174.11; found: 174.1. Anal. calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; found C, 55.58; H, 8.66; N, 8.20.

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