ChemInform Abstract: Divergent Total Synthesis of 1,6,8a-Tri-epi-castanospermine (Ia) and 1-Deoxy-6,8a-di-epi-castanospermine (Ib) from Substituted Azetidin-2-one (β-Lactam), Invol...

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Divergent total synthesis of 1,6,8a-tri-*epi*-castanospermine and 1-deoxy-6,8a-di-*epi*-castanospermine from substituted azetidin-2-one (β-lactam), involving a cascade sequence of reactions as a key step†‡

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A divergent, short, and novel total synthesis of 1,6,8a-tri-*epi*-castanospermine (**7**) and 1-deoxy-6,8a-di-*epi*-castanospermine (**8**) has been developed *via* a common precursor, **15**, obtained from D-mannitol derived β-lactam. The key step involves a one pot cascade sequence of trimethyl sulfoxonium ylide based cyclization of epoxy sulfonamide **14** *via* epoxide ring opening, one carbon homologation followed by intramolecular cyclization.

Introduction

Polyhydroxylated alkaloids containing cyclic amines are found among various natural resources, including plants and microorganisms.[1] They have gained much attention over the past few decades owing to their glycosidase inhibitor activity.[2] Castanospermine (**1**)[3] and its analogues (**2–8**)[4] which represent polyhydroxylated indolizidine alkaloids have received considerable interest over the years, mainly due to their therapeutic potential in the treatment of various diseases such as diabetes,[5] obesity,[6] cancer,[7] viral infections,[8,9] and HIV-1.[10] The subtle variation of stereocentres of castanospermine (**1**), resulting in a broad spectrum of biological activities, has led to the spurt in publications dealing with the synthesis of various stereoisomers of castanospermine (**1**).[11,12] Amongst all possible stereoisomers of castanospermine (**1**), one of the least explored isomers in terms of their synthesis are 1,6,8a-tri-*epi*-castanospermine (**7**) and 1-deoxy-6,8a-di-*epi*-castanospermine (**8**) although the latter one is known for α-L-fucosidase inhibitor activity.[5] To the best of our knowledge, at present only one asymmetric method is available in the literature towards the synthesis of 1-*O*-ethyl derivative of 1,6,8a-tri-*epi*-castanospermine (**7**),[13a] whereas 1-deoxy-6,8a-di-*epi*-castanospermine (**8**) has been synthesised by some racemic[14a,b] and asymmetric approaches (Fig. 1).[14c–f]

Azetidin-2-ones or β-lactams are an important class of organic compounds having a wide range of biological activities. In addition to their medicinal value, β-lactams have served as valuable synthons for the synthesis of various

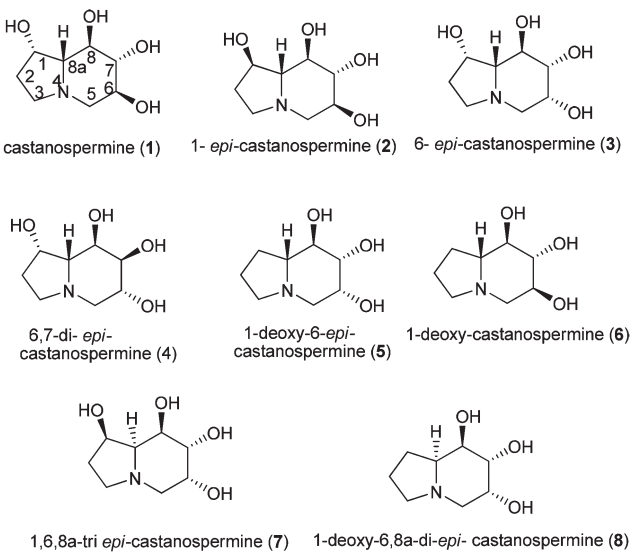

Fig. 1 Polyhydroxylated indolizidines.

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† Dedicated to Prof. Ganesh Pandey on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds, single crystal X-ray data for compound **15**. CCDC 939342. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00948g

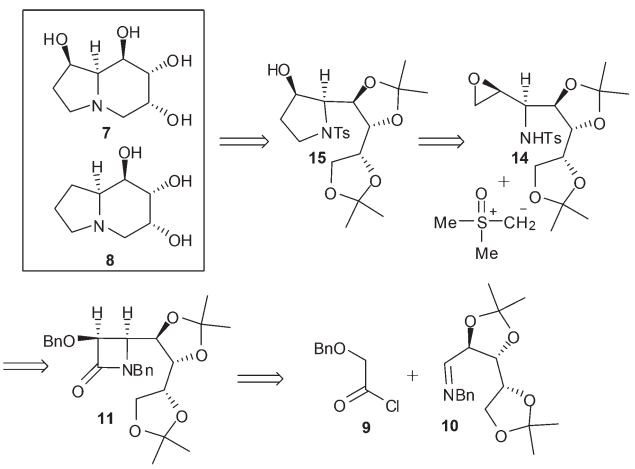
natural products.[15] As a part of our ongoing research program about the application of azetidin-2-ones as a synthon,[16] we therefore embarked on the development of an entirely new and versatile strategy for the synthesis of 1,6,8a-tri-*epi*-castanospermine (**7**) and 1-deoxy-6,8a-di-*epi*-castanospermine (**8**), starting from a suitably substituted β-lactam (**11**). To the best of our knowledge so far β-lactam has not been used in the synthesis of these alkaloids.

Results and discussion

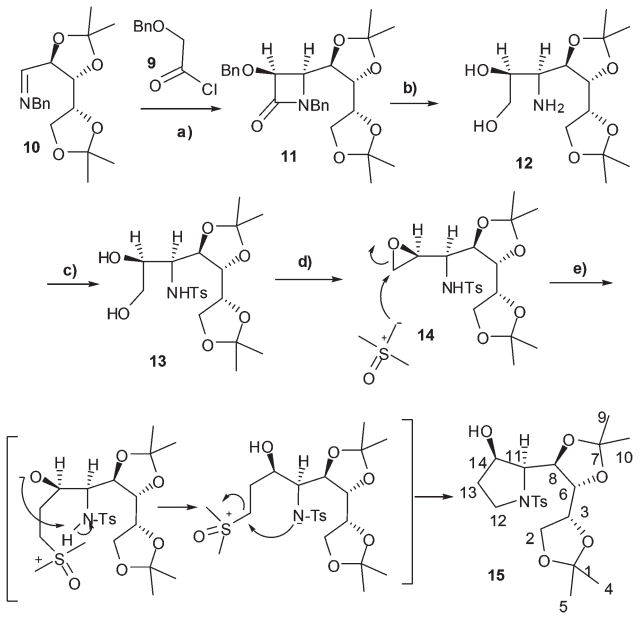
Our retrosynthetic plan is depicted in Scheme 1. We envisioned that the advanced intermediate **15** could serve as a common precursor for the synthesis of both **7** and **8**. This could in turn be obtained from a domino sequence of epoxide ring opening of **14** by trimethyl sulfoxonium ylide, followed by an intramolecular cyclization reaction. Compound **14** which would have all the required stereocentres can be synthesised from the β-lactam **11**.

The required β-lactam **11** in turn can be obtained from D-mannitol derived imine **10**.

To this end, the required β-lactam **11** was prepared in high yield using [2 + 2] cycloaddition reaction of ketene (generated *in situ* from benzyloxy acetyl chloride **9**) and imine **10** (derived from D-mannitol)[17] (Scheme 2). The β-lactam **11** had all the required stereocentres and their stereochemistry was confirmed by the single crystal structure obtained at a later stage of synthesis (*vide infra*). **11** was then treated with lithium aluminium hydride in refluxing THF, leading to opening of the ring, which was then subjected to reductive hydrogenolysis using 10% Pd/C in the presence of hydrogen at atmospheric pressure giving diol **12**. The diol **12** being very polar and relatively unstable in nature was immediately subjected to selective tosylation of primary amine giving **13** in 67% yield over three steps. In order to prepare the proposed epoxy amine **14**, the primary hydroxyl group of **13** was first regioselectively tosylated



Scheme 1 Retrosynthetic analysis of 1,6,8a-tri-*epi*-castanospermine (**7**) and 1-deoxy-6,8a-di-*epi*-castanospermine (**8**).



Scheme 2 Synthesis of hydroxyl pyrrolidine (**15**). (a) Et_3N, CH_2Cl_2, −20 to 25 °C, 65%; (b) (i) $LiAlH_4$, THF, 0 °C, reflux 4–6 h; (ii) H_2/Pd–C (10%), EtOAc, 1 atm, rt, 12 h; (c) TsCl, K_2CO_3, DCM–H_2O (1 : 1), rt, 3 h, 67% over three steps; (d) (i) TsCl, Bu_2SnO (cat.), Et_3N, CH_2Cl_2, 0 °C to rt 4 h; (ii) K_2CO_3, CH_3CN, rt, 10 h, 88.5%, over two steps. (e) NaH, $(CH_3)_3SOI$, DMSO, 85 °C, 24 h, 77%.

under Martinelli's protocol[18] using catalytic Bu_2SnO in the presence of Et_3N in dichloromethane at room temperature. The resulting ditosyl compound upon treatment with K_2CO_3 in CH_3CN at room temperature produced the required epoxy amine **14** in 88.5% yield over two steps. With epoxy amine **14** in hand, we proceeded to the key step of pyrrolidine ring construction. This was achieved by heating **14** (85 °C) in DMSO in the presence of NaH and trimethyl sulfoxonium iodide, which resulted in the formation of the desired hydroxy pyrrolidine **15** in 77% yield as a white crystalline solid (m.p. 151–153 °C). The reaction is believed to proceed *via* a cascade sequence of epoxide ring opening by *in situ* generated ylide, followed by proton abstraction and subsequent ring closure by nitrogen.[19]

At this stage the single crystal analysis of **15** revealed that the hydrogen attached to C_{14}, C_{11}, and C_8 were on the same side, thus confirming the required stereochemistry (Fig. 2).

After successfully installing the required stereocentres, along with construction of the pyrrolidine ring, we turned our attention to the completion of synthesis of 1,6,8a-tri-*epi*-castanospermine **7** (Scheme 3). The N-detosylation of **15** was successfully achieved under Birch reduction conditions (Na–liq. NH_3) giving **16**. Other methods for deprotection such as Na–Hg, Mg/MeOH, or Na/naphthalene for the detosylation of **15** were found to be either unsuccessful or low yielding. The resulting crude amine was immediately protected as a Cbz group to give carbamate **16** in 85% yield over two steps. Furthermore, the terminal acetonide group in **16** was first deprotected by stirring it in CH_3COOH–MeOH–H_2O (6 : 3 : 1) to obtain triol **17**. The primary hydroxy group of **17** was tosylated

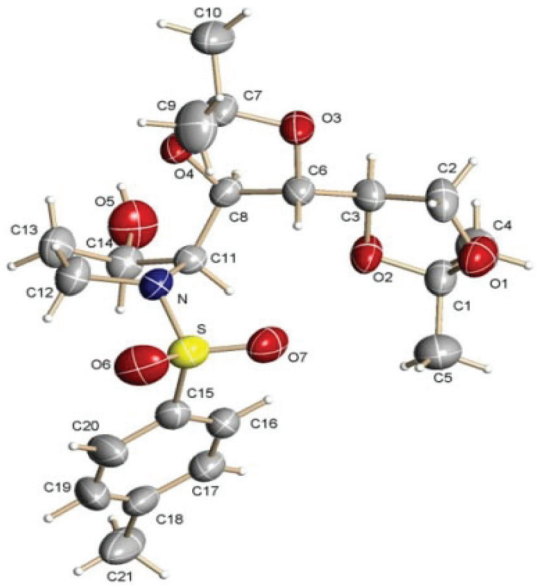
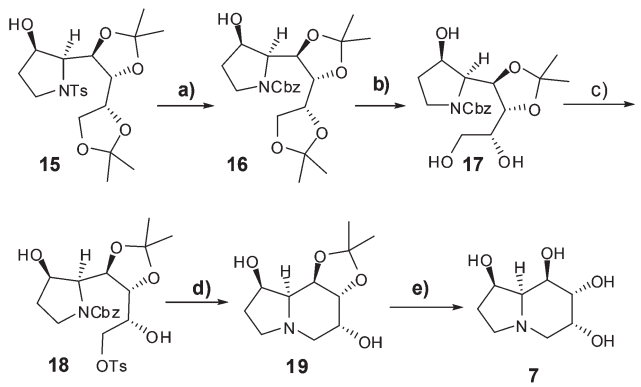


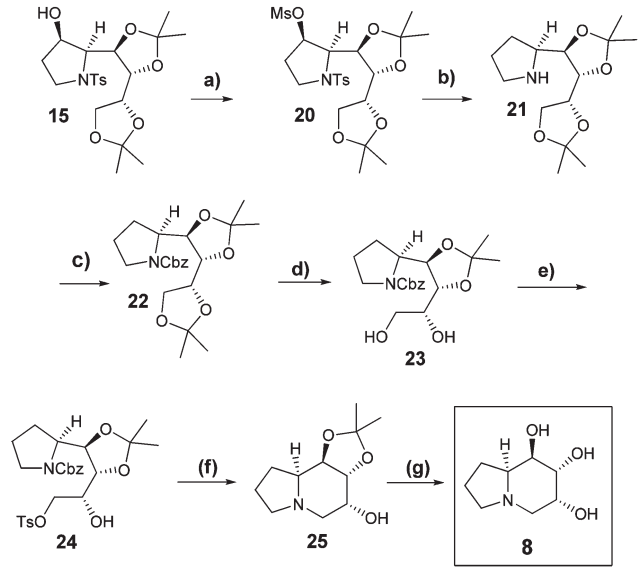
Fig. 2 ORTEP diagram of **15** (ellipsoids are drawn at 40% probability).



Scheme 3 Synthesis of 1,6,8a-tri-*epi*-castanospermine (**7**). Reagents and conditions: (a) (i) Na/liq. NH_3, −78 °C, 1 h; (ii) aq. K_2CO_3, CbzCl, CH_2Cl_2, 0 °C to rt, 30 min, 85% over two steps; (b) CH_3COOH–MeOH–H_2O (3 : 2 : 1), reflux, 5 h, 75%; (c) Et_3N, TsCl, Bu_2SnO (cat.), CH_2Cl_2, 0 °C, 2 h, 90%; (d) H_2, Pd–C (10%), NaOAc, rt, 12 h, (e) Dowex 50W-X8, THF–H_2O (3 : 1) reflux 12 h, 90% over two steps.

regioselectively to afford **18** in 90% yield. The –NCbz deprotection and cyclization was performed *via* catalytic hydrogenation (Pd/C, 10%) in the presence of sodium acetate in MeOH giving the desired product **19**. The reaction mixture was then filtered through a pad of celite and concentrated. To the residue was then added THF–H_2O (3 : 1) and acidic Dowex 50W-X8, and the mixture was heated for 12 hours, giving the target molecule **7** in 90% yield over two steps.

After successfully completing the total synthesis of 1,6,8a-tri-*epi*-castanospermine **7**, we focused our efforts towards **8** from the common intermediate **15**. Mesylation of the free hydroxyl moiety of **15** produced **20**, which upon LAH reduction led to the deoxygenation at C_{14} position. To our delight, LAH reduction also led to the N-detosylation in the same pot,



Scheme 4 Synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine (**8**): (a) MsCl, Et_3N, cat. DMAP, DCM, 0 °C, 1 h, 91%; (b) LAH, THF, reflux, 5 h; (c) aq. K_2CO_3, CbzCl, DCM–H_2O (1 : 1), 0 °C to rt, 1 h, 82% over two steps; (d) CH_3COOH–MeOH–H_2O (6 : 3 : 1), reflux, 5 h, 77%; (e) Et_3N, TsCl, Bu_2SnO (cat.), CH_2Cl_2, 0 °C, 2 h, 88%; (f) H_2, Pd–C (10%), NaOAc, MeOH, rt, 12 h; (g) Dowex 50W-X8, THF–H_2O (3 : 1), reflux 12 h, 86% over two steps.

affording **21**, which was immediately subjected to Cbz protection, delivering **22** in 85% yield over two steps. Compound **22** was easily converted into target molecule **8** (Scheme 4) following a similar sequence of steps as those described above for the synthesis of **7** (Scheme 3, from **16** to **7**). The spectral data and specific rotation of **8** $[\alpha]_D^{27}$ = +23.6 (c = 0.90, MeOH) were in excellent agreement with the reported values {$[\alpha]_D^{27}$ +23.5 (c = 0.90, MeOH)}.[14f]

Conclusions

In conclusion, we have demonstrated a new and flexible approach for the syntheses of 1,6,8a-tri-*epi*-castanospermine **7** and 1-deoxy-6,8a-di-*epi*-castanospermine **8** from D-mannitol triacetonide derived β-lactam. The key features of this approach include the construction of hydroxyl pyrrolidine **15** from epoxy amine using trimethyl sulfoxonium ylide.

Experimental

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin and co-workers' method.[20] CH_3CN, CH_2Cl_2, and triethylamine were distilled over CaH_2 and stored over molecular sieves and KOH, respectively. THF was distilled from sodium benzophenone ketyl. Solvents used for chromatography were distilled at their

respective boiling points according to known procedures. Petroleum ether used in the column had a boiling range of 60–80 °C. All commercial reagents were obtained from Sigma–Aldrich and Lancaster Chemical Co. (U.K.). MsCl was distilled before use. The progress of the reactions was monitored by TLC, performed on aluminium sheets precoated with silica gel 60 (Merck, 230–400 mesh). Compounds were visualized by heating after dipping in an alkaline solution of $KMnO_4$ and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in aqueous H_2SO_4 (250 mL). Column chromatography was performed on silica gel (100–200 for all compounds and 230–400 mesh for **7** and **8**). Typical syringe and cannula techniques were used to transfer air and moisture-sensitive reagents. All melting points were recorded with Thermonik and Büchi melting-point instruments. IR spectra were recorded with Perkin-Elmer 599-B IR and 1620 FT-IR spectrometers. ^{1}H NMR spectra were recorded with Bruker ACF 200, AV 400 and DRX 500 instruments operating at 200, 400 and 500 MHz, respectively, by using deuterated solvents. Chemical shifts are reported in ppm, proton coupling constants (J) are reported as absolute values in Hz, and multiplicity is given as follows: br., broad; s, singlet; d, doublet; t, triplet; dt, doublet of triplets; ddd, doublet of doublet of doublet; m, multiplet. ^{13}C NMR spectra were recorded with Bruker ACF 200, AV 400 and DRX 500 instruments operating at 50, 100 and 125 MHz, respectively. Optical rotations were recorded at 27 °C in a 1 dm cell. Mass spectra were recorded with a PE SCIEX API QSTAR pulsar spectrometer (LC-MS), an automated GC-MS with a solid-probe facility mass spectrometer. X-ray data were collected at T = 296 K with a SMART APEX CCD single crystal X-ray diffractometer by using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. The structures were solved by direct methods using SHELXTL.[21] All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (SHELXTL) was used for structure solution and full matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97. Microanalysis data were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyser.

Compound 11

A solution consisting of benzyloxy acetyl chloride **9** (5.6 mL, 38 mmol) in dichloromethane (100 mL) was added dropwise to a stirred solution containing imine **10** (9.6 g, 30 mmol), triethyl amine (10.58 mL, 76 mmol) in dichloromethane (200 mL) at −20 °C. The reaction mixture was stirred overnight at room temperature, washed with saturated sodium bicarbonate solution (100 mL), brine (100 mL), dried and evaporated to give the crude product, which was purified by column chromatography in 20% ethyl acetate–petroleum ether to give **11** (9.13 g, 65%) as a white solid. m.p.: 114–116 °C (from MeOH), $[\alpha]_D^{27}$ +12.5 (c 1.2 in $CHCl_3$); Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 2.99. Found: C, 69.32, H, 7.15; N, 3.12. IR: (ν_{max}, $CHCl_3$): 3054, 2950, 1741, 1598, 1480 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.37–7.27 (10H, m), 4.94 (1H, d, J = 11.4 Hz), 4.92 (1H, d, J = 14.9 Hz), 4.70 (1H, d, J = 11.4 Hz), 4.65 (1H, d, J = 4.99 Hz), 4.16–4.01 (3H, m), 3.85–3.79 (3H, m), 3.70 (1H, dd, J = 6.8, 5.1 Hz), 1.37 (3H, s), 1.29 (3H, s), 1.21 (6H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 167.44, 136.79, 135.52, 128.87, 128.64, 128.44, 128.18, 128.08, 127.66, 110.07, 109.29, 80.85, 79.13, 78.28, 75.60, 73.07, 65.53, 57.70, 45.02, 27.42, 26.99, 26.11, 25.22. MS: m/z = 468 (M + 1).

Compound 13

A solution of benzyloxy β-lactam **11** (23.25 g, 50 mmol) in THF (60 mL) was added dropwise to a suspension of $LiAlH_4$ (4.75 g, 125 mmol) in THF (100 mL) at 0 °C over a period of 15 min. The ice bath was removed and the reaction mixture was allowed to stir for 4–6 h under reflux conditions and then cooled to 0 °C again and subsequently quenched by saturated aqueous solution of sodium sulfate. The white precipitate was filtered through a sintered funnel, and the filtrate was washed with ethyl acetate. Solvent was removed under reduced pressure to obtain a colourless oil (20.1 g), which was subsequently dissolved in freshly distilled EtOAc (100 mL). 10% Pd/C (2.0 g) was added to it and the mixture was allowed to stir under a hydrogen balloon for 12 h. The mixture was filtered over celite and the primary amine **12** was obtained as a colorless oil (11.3 g). Compound **12** was found to be highly polar and relatively unstable at room temperature. Thus the resulting amine was dissolved in DCM (40 mL) and an aqueous solution of K_2CO_3 (5.89 g, 42 mmol) in H_2O (40 mL) was added dropwise over a period of 10 min at room temperature. To the resulting solution, tosyl chloride (7.98 g, 42 mmol) was added portionwise under stirring. The reaction mixture was allowed to stir for an additional 3 h, then washed successively with water (20 mL) and brine (20 mL), dried over sodium sulphate and was concentrated to dryness. The crude product was chromatographed (50% ethyl acetate–petroleum ether) to give the desired product **13** (15.0 g, 67% yield over three steps) as a white sticky solid. $[\alpha]_D^{27}$ −13.5 (c 1.5 in $CHCl_3$): Anal. Calcd for $C_{20}H_{31}NO_6$: C, 53.92; H, 7.01; N, 3.14. Found: C, 53.85, H, 7.14; N, 3.24. IR (ν_{max}, $CHCl_3$) 3450, 3293, 1599, 1066, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 7.78 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 4.12–4.01 (1H, m), 3.98–3.62 (8H, m), 2.42 (3H, s), 1.46 (3H, s), 1.36 (3H, s), 1.28 (3H, s), 1.23 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 143.77, 137.79, 129.71, 129.61, 127.30, 127.04, 110.13, 109.81, 80.49, 77.73, 76.81, 71.11, 68.07, 62.90, 54.01, 26.78, 26.68, 26.08, 25.01, 21.52. MS: m/z = 446 (M + 1).

Compound 14

To a solution of **13** (8.0 g, 17.9 mmol) in DCM (100 mL) were added n-Bu_2SnO (180 mg, 0.72 mmol), p-toluenesulfonyl chloride (3.7 g, 1.96 mmol) and triethyl amine (3.5 mL, 19.6 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for an additional 2 h. It was then filtered through a small pad of celite and the filtrate was concentrated under reduced pressure to obtain the crude product (10 g), which was further dissolved in CH_3CN

(150 mL), and K_2CO_3 (3.45 g, 25.04 mmol) was added to it in four portions at room temperature. The reaction mixture was allowed to stir at the same temperature for 6 h. After completion of the starting material (as monitored by TLC), the mixture was passed through a pad of celite and the filtrate was concentrated to give the crude product which was purified by column chromatography (25% ethyl acetate–pet. ether) to obtain **14** (6.0 g, 88.5% over two steps) as a colorless oil. $[\alpha]_D^{27}$ −5.65 (*c* 0.5 in $CHCl_3$): Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28. Found: C, 56.24; H, 6.79; N, 3.31. IR (ν_{max}, $CHCl_3$): 3449, 2987, 1629, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.77 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 5.75 (1H, d, J = 9.8 Hz), 4.11 (1H, dd, J = 8.7, 5.8 Hz), 3.90–3.77 (4H, m), 3.61 (1H, dd, J = 7.75, 2.98 Hz), 3.19–3.18 (1H, m), 2.76 (1H, dd, J = 4.93, 2.63 Hz), 2.65 (1H, dd, J = 5.11, 4.17 Hz), 2.41 (3H, s), 1.48 (3H, s), 1.39 (3H, s), 1.34 (3H, s), 1.24 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.51, 138.19, 129.69, 126.95, 110.42, 109.55, 79.94, 77.72, 76.46, 68.18, 51.55, 50.11, 43.02, 26.79, 26.63, 26.08, 25.26, 21.01. MS: m/z = 428 (M + 1).

Compound 15

NaH (60% mineral oil, 0.7 g, 17.55 mmol) was placed in a flame dried flask and then DMSO (30 mL) was added. To this was added trimethyl sulfoxinium iodide (3.86 g, 17.55 mmol) at room temperature. The reaction mixture was then stirred for an additional 30 min until the bubbling of the milky white suspension ceased. A solution of epoxy amine **14** (5.0 g, 11.7 mmol) in DMSO (10 mL) was added dropwise to the reaction mixture and then the reaction mixture was heated at 80 °C for 20 h. The mixture was then cooled and diluted with 100 mL of water and extracted with ethyl acetate (5 × 150 mL). The organic layer was washed with aqueous sodium thiosulfate (50 mL), brine (50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the product was purified by column chromatography (40% ethyl acetate–pet. ether) to obtain **15** (4.0 g, 77%) as a white crystalline solid. m.p.: 151–153 °C (from $CHCl_3$); $[\alpha]_D^{27}$ +9.8 (*c* 0.6 in $CHCl_3$): Anal. Calcd for $C_{21}H_{31}NO_7S$: C, 57.12; H, 7.08; N, 3.17. Found: C, 57.18; H, 6.99; N, 3.33. IR (ν_{max}, $CHCl_3$): 3393, 1598, 1372, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.74 (2H, d, J = 8.19 Hz), 7.30 (2H, d, J = 8.19 Hz), 4.69–4.64 (1H, m), 4.20–4.13 (3H, m), 4.01–3.95 (2H, m), 3.81 (1H, dd, J = 5.83, 3.80 Hz), 3.64–3.54 (1H, m), 3.38 (1H, ddd, J = 11.68, 7.28, 4.27 Hz), 2.43 (3H, s), 1.86–1.72 (2H, m), 1.46 (3H, s), 1.39 (3H, s), 1.41 (3H, s), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.91, 133.71, 129.72, 127.87, 109.96, 109.74, 81.63, 78.55, 76.89, 73.21, 67.49, 60.98, 47.07, 33.62, 27.35, 26.76, 26.57, 26.5, 25.47, 21.58. MS: m/z = 464 (M + Na).

Compound 16

To a round bottom flask, fitted with a cold finger condenser (acetone/solid CO_2), containing **15** (0.3 g, 0.68 mmol) was introduced ammonia *ca.* 100 mL at −78 °C. Small pieces of sodium were added to the stirring solution until the solution became persistently dark blue. After 30 min, the reaction mixture was quenched by the addition of solid NH_4Cl, and allowed to stir until all ammonia had evaporated. The remaining solid was filtered through a sintered funnel and washed with ethyl acetate three times. Evaporation of solvent under reduced pressure gave 0.18 g of product. This crude product was immediately dissolved in CH_2Cl_2 (10 mL). To the solution was added aq. K_2CO_3 (1.24 g, 9 mmol) in 2 mL water and the mixture was cooled in an ice bath. To this stirred biphasic solution was added dropwise a solution of benzylchloroformate (0.85 mL, 6 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture was allowed to stir at room temperature for 30 minutes. The organic phase was washed with brine, and evaporated. The residue was chromatographed on silica gel (40% ethyl acetate–pet. ether) to give **16** (0.24 g, 85%) over two steps as a colourless oil. $[\alpha]_D^{27}$ +3.88 (*c* 0.5 in $CHCl_3$); Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.72; H, 7.53; N, 3.41; IR (ν_{max}, $CHCl_3$); 3453, 2986, 1699, 1412 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.30 (5H, m), 5.13 (2H, s), 4.41–4.24 (1H, m), 4.16–4.14 (5H, m), 3.48–3.45 (2H, m), 2.39 (1H, d, J = 8.51 Hz), 2.20–2.16 (1H, m), 2.03–1.99 (1H, m), 1.37 (3H, s), 1.35 (3H, s), 1.33 (3H, s), 1.30 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.94, 136.58, 128.44, 128.04, 109.54, 109.28, 77.46, 71.54, 67.26, 67.09, 66.38, 58.89, 44.31, 32.25, 27.22, 26.53, 26.01, 25.14. MS: m/z = 422 (M + 1).

Compound 17

A solution of **16** (1.28 g, 3 mmol) containing acetic acid (6 mL), methanol (3 mL), and water (1 mL) was heated at reflux temperature for 4 h. The reaction mixture was cooled to 0 °C and then solid sodium bicarbonate was added until all acetic acid was neutralized. The reaction mixture was extracted with ethyl acetate (100 mL), washed with water (50 mL), and the organic layer was dried over sodium sulphate and evaporated. Purification of the residue by column chromatography (40% acetone–petroleum ether) gave **17** (0.85 g, 75%) as a colourless oil. $[\alpha]_D^{27}$ −13.56 (*c* 1.5 in $CHCl_3$); Anal. Calcd for $C_{19}H_{27}NO_7$: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.75; H, 7.22; N, 3.59; IR (ν_{max}, $CHCl_3$) 3417, 2985, 1682, 1417 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.35 (5H, bs), 5.13 (2H, s), 4.43–4.31 (m, 2H), 4.30–4.21 (2H, m), 3.84–3.79 (2H, m), 3.50–3.43 (2H, m), 2.44 (1H, d, J = 10.36 Hz), 2.29–2.05 (2H, m), 1.38 (3H, s), 1.30 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 156.68, 136.01, 128.51, 128.22, 127.82, 108.80, 79.34, 75.75, 73.36, 71.58, 67.64, 65.09, 58.94, 44.12, 32.58, 27.09, 26.45. MS: m/z = 382 (M + 1).

Compound 18

To a solution of **17** (0.8 g, 2.09 mmol) in DCM (15 mL) were added catalytic *n*-Bu_2SnO (50 mg), *p*-toluenesulfonyl chloride (0.48 g, 2.5 mmol) and triethyl amine (1.0 mL, 7.31 mmol) at 0 °C. The reaction mixture was allowed to attain room temperature and was stirred for an additional 2 h. The reaction mixture was filtered through a small pad of celite and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography using 30% ethyl acetate–pet. ether to obtain **18** (0.95 g, 84%) as a colourless oil. $[\alpha]_D^{27}$ +7.67 (*c* 1.1 in $CHCl_3$); Anal. Calcd for

$C_{26}H_{33}NO_9S$: C, 58.30; H, 6.21; N, 2.62. Found: C, 58.27; H, 6.26; N, 2.57; IR (ν_{max}, $CHCl_3$) 3402, 2985, 1674, 1115 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.86 (2H, d, J = 8.5 Hz), 7.39–7.29 (7H, m), 5.21–5.06 (2H, m), 4.20–4.15 (1H, m), 3.85–3.66 (4H, m), 3.48–3.46 (1H, m), 3.43 (1H, dt, J = 6.30, 3.27 Hz), 3.42–3.41 (2H, m), 2.41 (3H, s), 2.22–2.01 (2H, m), 1.34 (3H, s), 1.27 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 156.86 144.56, 136.12, 132.82, 129.66, 128.53, 128.05, 108.93, 80.19, 77.19, 74.02, 71.93, 71.36, 67.37, 58.42, 43.71, 33.13, 27.02, 26.47, 21.58. MS: m/z = 536 (M + 1).

1,6,8a-Tri-*epi*-castanospermine (7)

A mixture of **18** (0.1 g, 0.18 mmol), sodium acetate (0.073 g, 0.9 mmol) and 10% Pd/C (20 mg) in methanol (1.5 mL) was hydrogenated at atmospheric pressure for 10 h. The catalyst was filtered, methanol was evaporated and the residue was dissolved in DCM. The organic layer was washed with water and brine, and dried over sodium sulfate. Solvent was removed and the crude product **19** obtained was dissolved in THF–H_2O (3 : 1) and refluxed overnight with Dowex 50W-X8 (50 mg). The reaction mixture was filtered and washed with MeOH. The remaining residue was eluted with 2 N NH_3 solution. The NH_3 solution was evaporated to give the crude product, which was purified by column chromatography (MeOH–EtOAc 10%) to obtain 1,6,8a-tri-*epi*-castanospermine **7** (19 mg, 90%) as a colorless oil. $[\alpha]_D^{27}$ −60.34 (c 0.7 in $CHCl_3$); Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.81; H, 7.95; N, 7.43; IR (ν_{max}, neat) 3434, 1403, 1265 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ: 4.59–4.56 (m, 1H), 4.26 (1H, dd, J = 3.92, 1.64 Hz), 4.13–4.10 (1H, m), 3.89 (1H, t, J = 7.21, 3.42 Hz), 3.14 (1H, t, J = 17.24, 8.9 Hz), 3.06 (1H, dd, J = 10.6, 4.91 Hz), 2.44–2.36 (1H, m), 2.28–2.25 (3H, m), 1.75–1.69 (1H, m). ^{13}C NMR (D_2O, 100 MHz) δ: 71.95, 69.38, 69.25, 65.01, 63.25, 51.89, 51.25, 32.91. MS m/z = 190 (M + 1).

Compound 20

To a solution of **15** (0.5 g, 1.13 mmol) in DCM (4 mL) were added Et_3N (0.39 mL, 2.8 mmol) and methanesulfonyl chloride (0.13 mL, 1.7 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature and was subsequently quenched with saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was concentrated and the residue was chromatographed on silica gel (30% EtOAc–petroleum ether) to give **20** (0.54 g, 91%) as a colorless oil. $[\alpha]_D^{27}$ −13.13 (c 0.6 in $CHCl_3$); Anal. Calcd for $C_{22}H_{33}NO_9S_2$: C, 50.85; H, 6.40; N, 2.70. Found: C, 50.81; H, 6.55; N, 2.64; IR (ν_{max}, $CHCl_3$) 1597, 1353 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (2H, d, J = 8.19 Hz), 7.34 (2H, d, J = 8.2 Hz), 4.47–4.43 (1H, m), 4.27–4.14 (4H, m), 4.12–4.07 (1H, m), 3.95 (1H, dd, J = 7.54, 5.83 Hz), 3.51 (1H, ddd, J = 12.80, 9.91, 2.89 Hz), 3.31 (1H, dt, J = 11.04, 8.46 Hz), 2.99 (3H, s), 2.44 (3H, s), 2.33–2.31 (1H, m), 2.07–2.03 (1H, m), 1.54 (3H, s), 1.42 (3H, s), 1.37 (6H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.33, 134.52, 130.12, 127.25, 110.18, 109.76, 77.37, 77.24, 76.94, 76.00, 67.76, 59.72, 45.70, 38.38, 29.20, 27.34, 26.38, 26.12, 25.41, 21.56. MS: m/z = 520 (M + 1).

Compound 22

To a suspension of LAH (0.18 g, 4.8 mmol) in THF (5 mL) was added a solution of **20** (0.5 g, 0.96 mmol) in THF (2 mL) at 0 °C and refluxed while stirring for 5 h. The reaction mixture was quenched with aq. sodium sulfate, extracted with ethyl acetate (5 × 15 mL) and solvent was removed under reduced pressure to give **21** (0.26 g). The crude **21** (0.26 g, 0.96 mmol) was dissolved in DCM (3 mL) containing aq. solution of K_2CO_3 (0.4 g, 2.89 mmol). CbzCl (0.2 mL, 1.4 mmol) was added to it at 0 °C. The reaction mixture was stirred at the same temperature for another 30 minutes. The organic layer was then washed with water (1 × 5 mL) and brine (1 × 5 mL). Solvent was removed under reduced pressure and residue was purified by column chromatography (15% ethyl acetate–pet. ether) to yield **22** (0.32 g, 82% over two steps) as a colourless oil. $[\alpha]_D^{27}$ −12.96 (c 1.3 in $CHCl_3$); Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.22; H, 7.61; N, 3.54; IR (ν_{max}, $CHCl_3$) 1597, 1353 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.38–7.34 (5H, m), 5.20–5.12 (2H, m), 4.27–3.98 (5H, m), 3.62–3.42 (2H, m), 2.04–2.01 (2H, m), 2.0–1.85 (2H, m), 1.35 (12H, bs). ^{13}C NMR ($CDCl_3$, 100 MHz shows a mixture of rotamers, values for major peaks are written) δ: 155.95, 136.90, 128.46, 127.89, 127.79, 127.67, 109.52, 109.45, 81.99, 77.99, 77.24, 76.83, 66.45, 57.69, 47.42, 27.29, 26.87, 26.86, 26.24, 25.27. MS: m/z = 406 (M + 1).

Compound 23

A solution of **22** (0.81 g, 2 mmol) in acetic acid (4 mL), methanol (2 mL) and water (0.75 mL) was heated at reflux temperature for 4–6 h. The reaction mixture was cooled to 0 °C and then solid sodium bicarbonate was added until all of the acetic acid was neutralized. The reaction mixture was extracted with ethyl acetate (50 mL), washed with water (20 mL), and the organic layer was dried over sodium sulphate and evaporated. Purification of the residue by column chromatography (30%, acetone–petroleum ether) gave **23** (0.53 g, 72%) as a colourless oil. $[\alpha]_D^{27}$ −31.52 (c 1.25 in $CHCl_3$); Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.42; H, 7.53; N, 3.79. IR (ν_{max}, $CHCl_3$) 3418, 2934, 1674, 1417 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.34 (5H, bs), 5.12 (2H, s), 4.24 (1H, d, J = 6.90 Hz), 4.01 (1H, d, J = 7.2 Hz), 3.98 (1H, dd, J = 8.7, 1.7 Hz), 3.75–3.72 (m, 2H), 3.63–3.55 (m, 3H), 3.53 (1H, dt, J = 11.21, 3.20 Hz), 2.02 (1H, bs), 2.01–1.98 (1H, m), 1.83–1.82 (2H, m), 1.81–1.79 (1H, m), 1.34 (3H, s), 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.99, 136.35, 128.50, 128.13, 127.78, 108.21, 83.92, 76.06, 73.22, 67.51, 65.51, 57.93, 47.70, 29.01, 26.92, 26.52, 24.10. MS: m/z = 366 (M + 1).

Compound 24

To a solution of **23** (0.5 g, 1.36 mmol) in DCM (8 mL) were added catalytic n-Bu_2SnO (25 mg), p-toluenesulfonyl chloride (0.28 g, 1.49 mmol) and triethyl amine (0.66 mL, 4.76 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for an additional 2 h. The reaction mixture was filtered through a small pad of celite and the

filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography using (30% ethyl acetate–pet. ether) to obtain **24** (0.62 g, 88%) as a colorless oil. $[\alpha]_D^{27}$ −11.44 (*c* 0.7 in $CHCl_3$); Anal. Calcd for $C_{26}H_{33}NO_8S$: C, 60.10; H, 6.40; N, 2.70. Found: C, 60.25; H, 6.40; N, 2.74; IR (ν_{max}, $CHCl_3$) 3364, 2986, 1673, 1417 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (2H, d, J = 8.55 Hz), 7.37–7.29 (7H, m), 5.13 (1H, dd, J = 20.12, 12.44 Hz), 4.86 (1H, d, J = 9.95 Hz), 4.21–4.19 (2H, m), 4.06 (1H, dd, J = 10.17, 3.45 Hz), 3.89 (1H, dd, J = 8.81, 1.70 Hz), 3.71 (1H, t, J = 8.5 Hz), 3.62 (1H, t, J = 8.89 Hz), 3.52 (1H, dd, J = 18.15, 8.31 Hz), 3.40 (1H, dt, J = 10.73, 2.91 Hz), 2.40 (3H, s), 2.12–2.24 (1H, m), 2.05–1.92 (2H, m), 1.83–1.76 (1H, m), 1.68 (1H, s), 1.29 (3H, s), 1.23 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.92, 144.49, 136.45, 133.15, 129.65, 129.56, 128.52, 127.98, 127.01, 108.29, 84.22, 74.30, 72.23, 71.49, 67.61, 57.81, 47.57, 28.76, 26.86, 26.52, 24.16, 21.60; MS: m/z = 520 (M + 1).

1-Deoxy-6,8a-di-*epi*-castanospermine (8)

A mixture of **24** (0.21 g, 0.4 mmol), sodium acetate (0.16 g, 2.0 mmol) and 10% Pd/C (21 mg) in methanol (3.0 mL) was hydrogenated at atmospheric pressure for 10 h. The catalyst was filtered, methanol was evaporated and the residue was dissolved in DCM. The organic layer was washed with water and brine, and dried over sodium sulphate. The solvent was removed and the crude product **25** obtained was dissolved in THF–H_2O (3 : 1) and refluxed overnight with Dowex 50W-X8 (100 mg). The reaction mixture was filtered and washed with MeOH. The remaining residue was eluted with 2 N NH_3 solution. The NH_3 solution was evaporated to gave the crude product, which was purified by column chromatography (7%, MeOH–EtOAc) to obtain 1,6,8a-tri-*epi*-castanospermine **7** (0.06 g, 86%) over two steps as a colourless oil. $[\alpha]_D^{27}$ +23.6 (*c* 0.90 in MeOH) lit.[14f] {$[\alpha]_D^{27}$ +23.5 (*c* 0.90 in MeOH)}; Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; Found: C, 55.45; H, 8.68; N, 8.08; IR (ν_{max}, $CHCl_3$) 3336, 2956, 1673, 1081 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz) δ: 4.22 (1H, ddd, J = 10.02, 4.89, 3.21 Hz), 4.06 (1H, t, J = 3.27 Hz), 3.94 (1H, dd, J = 3.4, 1.6 Hz), 3.23–3.18 (1H, m), 3.11 (1H, dd, J = 10.12, 5.1 Hz), 2.77–2.69 (1H, m), 2.52 (1H, dd, J = 11.70, 10.63 Hz), 2.44–2.35 (1H, m), 2.04–1.96 (3H, m), 1.90–1.85 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ: 72.80, 70.31, 67.43, 63.02, 54.79, 54.18, 24.42, 22.65. MS: m/z = 174 (M + 1).

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References

1 (*a*) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139–165, and preceding reviews in the series; (*b*) J. P. Michael, *Beilstein J. Org. Chem.*, 2007, **3**, 27; (*c*) N. Asano, *Curr. Top. Med. Chem.*, 2003, **3**, 471–484; (*d*) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux and R. J. Nash, *Phytochemistry*, 2001, **56**, 265–295.

2 (*a*) G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319; (*b*) M. L. Sinnot, *Chem. Rev.*, 1990, **90**, 1171; (*c*) *Iminosugars as Glycosidase Inhibitors*, ed. S. G. Withers, M. Namchuk, R. Mosi and A. E. Stutz, 1999, pp. 188–206.

3 (*a*) L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold and J. Clardy, *Phytochemistry*, 1981, **20**, 811–814; (*b*) R. Saul, J. P. Chambers, R. J. Molyneux and A. D. Elbein, *Arch. Biochem. Biophys.*, 1983, **221**, 593–597; (*c*) Y. T. Pan, H. Hori, R. Saul, B. A. Sanford, R. J. Molyneux and A. D. Elbein, *Biochemistry*, 1983, **22**, 3976–3984; (*d*) R. Saul, J. J. Ghidoni, R. J. Molyneux and A. D. Elbein, *Proc. Natl. Acad. Sci. U. S. A.*, 1985, **82**, 93–97; (*e*) R. J. Nash, L. E. Fellows, J. V. Dring, C. H. Stirton, D. Carter, M. P. Hegarty and E. A. Bell, *Phytochemistry*, 1988, **27**, 1403–1406.

4 (*a*) B. D. Winchester, I. C. Di-Billo, A. C. Richardson, R. J. Nash, L. E. Fellows, N. G. Ramsden and G. Fleet, *Biochem. J.*, 1990, **269**, 227–231; (*b*) S. G. Pyne, *Curr. Org. Synth.*, 2005, **2**, 39–57.

5 (*a*) B. L. Rhinehart, K. M. Robinson, A. J. Payne, M. E. Wheatley, J. L. Fisher, P. S. Liu and W. Cheng, *Life Sci.*, 1987, **41**, 2325–2331; (*b*) G. Trugnan, M. Rousset and A. Zweibaum, *FEBS Lett.*, 1986, **195**, 28–32.

6 E. Truscheit, W. Frommer, B. Junge, L. Muller, D. D. Schmidt and W. Wingender, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 744–761.

7 (*a*) V. W. Sasak, J. M. Ordovas, A. D. Elbein and R. W. Berninger, *Biochem. J.*, 1985, **232**, 759–766; (*b*) P. B. Ahrens and H. J. Ankel, *Biol. Chem.*, 1987, **262**, 7575–7579; (*c*) J. W. Dennis, S. Laferte, C. Waghorne, M. L. Breitman and R. S. Kerbel, *Science*, 1987, **236**, 582–585; (*d*) G. K. Ostrander, N. K. Scribner and L. R. Rohrschneider, *Cancer Res.*, 1988, **48**, 1091–1094.

8 (*a*) E. J. Nichols, R. Manger, S. Hakomori, A. Herscovics and L. R. Rohrschneider, *Mol. Cell. Biol.*, 1985, **5**, 3467–3475; (*b*) P. S. Sunkara, T. L. Bowlin, P. S. Liu and A. Sjoerdsma, *Biochem. Biophys. Res. Commun.*, 1987, **148**, 206–210.

9 (*a*) R. A. Gruters, J. J. Neefjes, M. Tersmette, R. R. Y. de Goede, A. Tulp, H. G. Huisman, F. Miedema and H. L. Ploegh, *Nature*, 1987, **330**, 74–77; (*b*) B. D. Walker, M. Kowalski, W. C. Goh, K. Kozarsky, M. Krieger, C. Rosen, L. R. Rohrschneider, W. A. Haseltine and J. Sodroski, *Proc. Natl. Acad. Sci. U. S. A.*, 1987, **84**, 8120–8124; (*c*) R. Dagani, *Chem. Eng. News*, 1987, 25; (*d*) G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob and T. W. Rademacher,

FEBS Lett., 1988, **237**, 128–132; (*e*) Y. T. Pan, H. Hori, R. Saul, B. A. Stanford, R. J. Molyneux and A. D. Elbein, *Biochemistry*, 1983, **22**, 3975–3984; (*f*) B. C. Campbell, R. J. Molyneux and K. C. Jones, *J. Chem. Ecol.*, 1987, **13**, 1759–1770; (*g*) H. Hori, Y. T. Pan, R. J. Molyneux and A. D. Elbein, *Arch. Biochem. Biophys.*, 1984, **228**, 525–533; (*h*) A. D. Elbein, *CRC Crit. Rev. Biochem.*, 1984, **16**, 21–49; (*i*) A. M. Scofield, J. T. Rossiter, P. Witham, G. C. Kite, R. J. Nash and L. E. Fellows, *Phytochemistry*, 1990, **29**, 107–109.

10 (*a*) R. J. Molyneux, J. N. Roitman, G. Dunnheim, T. Szumilo and A. D. Elbein, *Arch. Biochem. Biophys.*, 1986, **251**, 450–457; (*b*) R. J. Nash, L. E. Fellows, A. Girdhar, G. W. J. Fleet, J. M. Peach, D. J. Watkin and M. P. Hegarty, *Phytochemistry*, 1990, **29**, 1356–1359; (*c*) G. W. J. Fleet, N. G. Ramsden, R. J. Molyneux and G. S. Jacob, *Tetrahedron Lett.*, 1988, **29**, 3603–3607; (*d*) G. W. J. Fleet, N. G. Ramsden, R. J. Nash, L. E. Fellows, G. S. Jacob, R. J. Molyneux, I. Bello Cenci di and B. Winchester, *Carbohydr. Res.*, 1990, **205**, 269–282.

11 (*a*) I. Dragutan, V. Demonceau, A. Vosloo and C. M. Hermannus, *Curr. Org. Chem.*, 2013, **17**, 2721–2739; (*b*) E. G. Bowen and D. J. Wardrop, *Org. Lett.*, 2010, **12**, 5530–5533; (*c*) L. Cronin and P. U. Murphy, *Org. Lett.*, 2005, **7**, 2691–2693; (*d*) P. R. Sultane, A. R. Mohite and R. G. Bhat, *Tetrahedron Lett.*, 2012, **53**, 5856–5858; (*e*) G. Liu, T. J. Wu, Y. P. Ruan and P. Q. Huang, *Chem. – Eur. J.*, 2010, **16**, 5755–5758; (*f*) N. S. Karanjule, S. D. Markad, V. S. Shinde and D. D. Dhavale, *J. Org. Chem.*, 2006, **71**, 4667–4670; (*g*) S. H. Kang and J. S. Kim, *Chem. Commun.*, 1998, 1353–1354; (*h*) V. Zambrano, R. Gloria, R. Annamaria, P. Luigi, Z. Franca, C. Claudio, C. Giovanni and B. Lucia, *Org. Biomol. Chem.*, 2010, **8**, 1725–1730.

12 (*a*) B. Barbara, D. P. Vagner and B. C. B. Antonio, *J. Org. Chem.*, 2012, **77**, 9926–9931; (*b*) S. E. Denmark and E. A. Martinborough, *J. Am. Chem. Soc.*, 1999, **121**, 3046–3056; (*c*) T. Jensen, M. Mikkelsen, A. Lauritsen, T. L. Andresen, C. H. Gotfredsen and R. Madsen, *J. Org. Chem.*, 2009, **74**, 8886–8889; (*d*) N. S. Karanjule, S. D. Markad, S. V. Shinde and D. D. Dhavale, *J. Org. Chem.*, 2006, **71**, 4667–4670; (*e*) G. Pandey, S. G. Dumbre, S. Pal, M. I. Khan and M. Shabab, *Tetrahedron*, 2007, **63**, 4756–4761; (*f*) N. T. Patil, J. N. Tikekar and D. D. Dhavale, *J. Org. Chem.*, 2001, **66**, 1065–1074.

13 (*a*) P. Kefalas, H. P. Husson and D. S. Grierson, *Nat. Prod. Lett.*, 1993, **4**, 313–318; (*b*) W. H. Pearson and E. J. Hembre, *Tetrahedron Lett.*, 1993, **34**, 8221–8224.

14 For references covering the synthesis of 1-deoxy 6,8a-di-*epi* castanospermine, see: (*a*) F. Chevallier, E. Le. Grognec, I. Beaudet, F. Fliegel, M. Evain and J. P. Quintard, *Org. Biomol. Chem.*, 2004, **2**, 3128–3133; (*b*) A. T. Serafidou, E. G. Yioti and J. K. Gallos, *Eur. J. Org. Chem.*, 2013, 939–943; (*c*) N. Wang, L.-H. Zhang and X. S. Ye, *Org. Biomol. Chem.*, 2010, **8**, 2639–2649; (*d*) K. H. Aamlid, L. Hough and A. C. Richardson, *Carbohydr. Res.*, 1990, **202**, 117–129; (*e*) H. Yun, J. Kim, J. Sim, S. Lee, Y. T. Han, D. J. Chang, D.-D. Kim and Y.-G. Suh, *J. Org. Chem.*, 2012, **77**, 5389–5393; (*f*) H. Zhang, Y.-K. Ni, G. Zhao and Y. Ding, *Eur. J. Org. Chem.*, 2003, 1918–1922.

15 (*a*) A. R. Deshmukh, B. M. Bhawal, D. Krishnaswamy, V. V. Govande, B. A. Shinkre and A. Jayanthi, *Curr. Med. Chem.*, 2004, **14**, 1889–1920; (*b*) B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107**, 4437–4492; (*c*) I. Ojima and F. Delaloge, *Chem. Soc. Rev.*, 1997, **26**, 377–386; (*d*) B. Alcaide and P. Almendros, *Curr. Med. Chem.*, 2004, **11**, 1921–1949; (*e*) C. Palomo, F. Cabre and J. M. Ontoria, *Tetrahedron Lett.*, 1992, **33**, 4819–4822; (*f*) A. Kamath and I. Ojima, *Tetrahedron*, 2012, **68**, 10640–10664; (*g*) C. Palomo, J. M. Aizpurua, I. Ganboa and M. Oiardide, *Curr. Med. Chem.*, 2004, **11**, 1837–1872; (*h*) A. S. Kale, P. S. Sakle, V. K. Gumaste and A. R. A. S. Deshmukh, *Synthesis*, 2007, 2631–2636; (*i*) P. M. Chincholkar, A. S. Kale, V. K. Gumaste and A. R. A. S. Deshmukh, *Tetrahedron*, 2009, **65**, 2605–2609.

16 (*a*) D. K. Tiwari, A. Y. Shaikh, S. L. Pavase, V. K. Gumaste and A. R. A. S. Deshmukh, *Tetrahedron*, 2007, **63**, 2524–2534; (*b*) D. K. Tiwari, V. K. Gumaste and A. R. A. S. Deshmukh, *Synthesis*, 2005, 115–122; (*c*) G. Pandey and D. K. Tiwari, *Tetrahedron Lett.*, 2009, **50**, 3296–3298.

17 (*a*) B. K. Banik, M. S. Manhas and A. K. Bose, *J. Org. Chem.*, 1993, **58**, 307–309; (*b*) B. K. Banik, C. Mathur, D. R. Wagle, M. S. Manhas and A. K. Bose, *Tetrahedron*, 2000, **56**, 5603–5619.

18 M. J. Martinelli, N. K. Nayyar, E. D. Moher, U. P. Dhokte, J. M. Pawlak and R. Vaidyanathan, *Org. Lett.*, 1999, **1**, 447–450.

19 (*a*) D. M. Hodgson, M. J. Fleming, Z. Xu, C. Lin and S. J. Stanway, *Chem. Commun.*, 2006, 3226–3228; (*b*) J. M. Schomaker, S. Bhattacharjee, J. Yanj and B. Borhan, *J. Am. Chem. Soc.*, 2007, **129**, 1996–2003.

20 M. Ousmer, N. A. Bruan, C. Bavoux, M. Perrin and M. A. Ciufolini, *J. Am. Chem. Soc.*, 2001, **123**, 7534–7538, and references cited there in.

21 (*a*) G. M. Sheldrick, *SHELX-97, program for crystal structure solution and refinement*, University of Göttingen, Germany, 1997; (*b*) G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.

