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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

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 key step

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Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

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 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 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 broad spectrum of biological activities has led to the spurt of

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 later one is known for α -L-fucosidase inhibitors activity.⁵ To the best of our knowledge, so far only one asymmetric method is available in 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 in some racemic and asymmetric approaches^{14c-f}.

Azetidin-2-ones or β -lactams are an important class of organic compound having a wide range of biological activities. In addition to their medicinal values, β -lactams have served as a valuable synthons for synthesis of various natural products.¹⁵ As a part of our ongoing research program on 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*-castanoepermine (**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.

Result 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 intramolecular cyclization reaction. Compound **14** which would have all the required stereocentres can be synthesised from the β -lactam **11**.

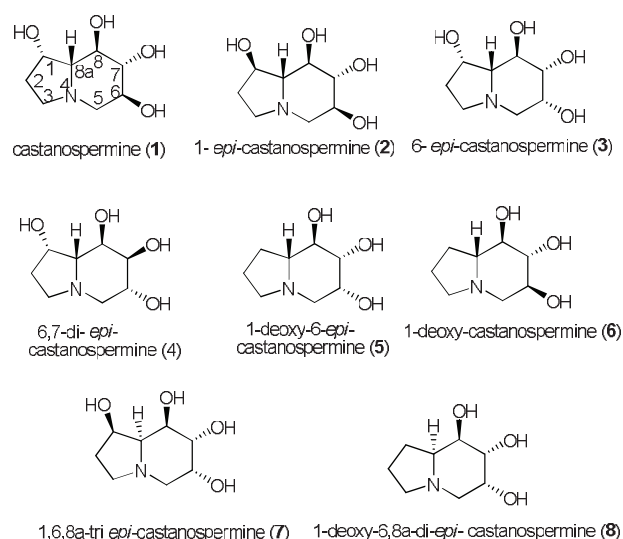
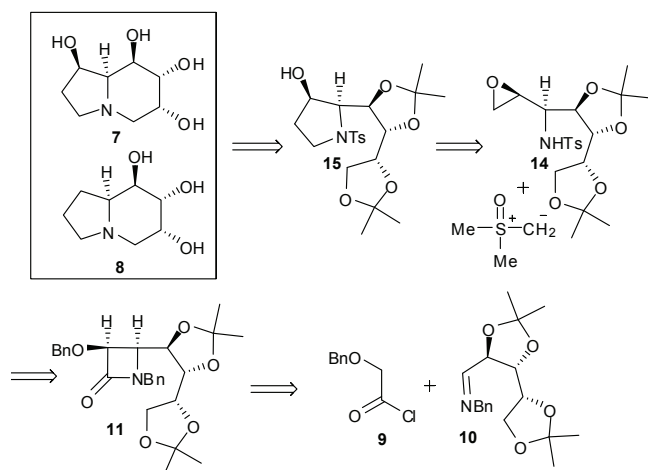


Fig. 1 Polyhydroxylated indolizidines

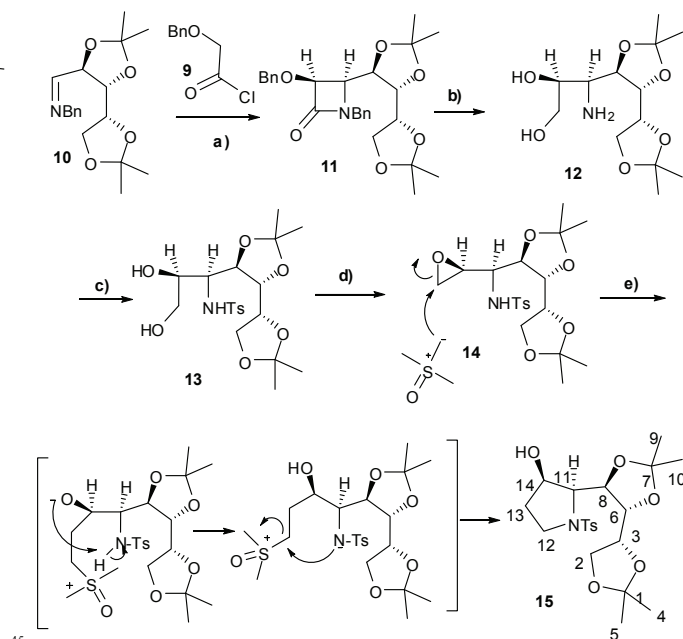


5 **Scheme 1** Retrosynthetic analysis of 1,6,8a-tri-epi-castanospermine (**7**) and 1-deoxy-6,8a-di-epi-castanospermine (**8**).

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 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 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** 67% yield over three steps. In order to prepare the proposed epoxy amine **14**, the primary hydroxyl group of **13** was first regioselectively tosylated under Martinelli's protocol¹⁸ using catalytic Bu_2SnO in the presence of Et_3N in dichloromethane at room temperature. Resulting ditosyl compound upon treatment with K_2CO_3 in CH_3CN at room temperature produced 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 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



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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) $\text{H}_2/\text{Pd-C-10\%}$, EtOAc , 1 atm, rt, 12 h, (c) TsCl , K_2CO_3 , $\text{DCM:H}_2\text{O}$ (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 hrs., ii) K_2CO_3 , CH_3CN , rt, 10 hrs, 88.5%, over two steps. (e) NaH, $(\text{CH}_3)_3\text{SOI}$, DMSO, 85 °C, 24 h, 77%.

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

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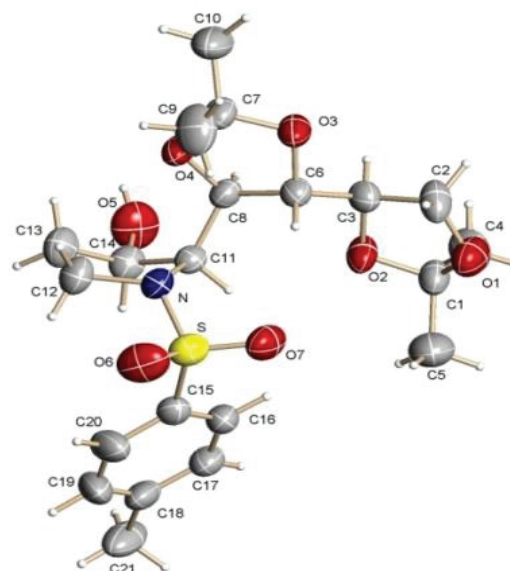
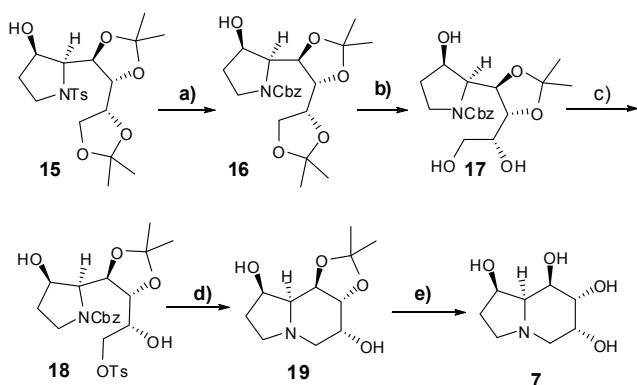


Fig. 2 ORTEP diagram of **15**, (Ellipsoid are drawn at 40% probability)

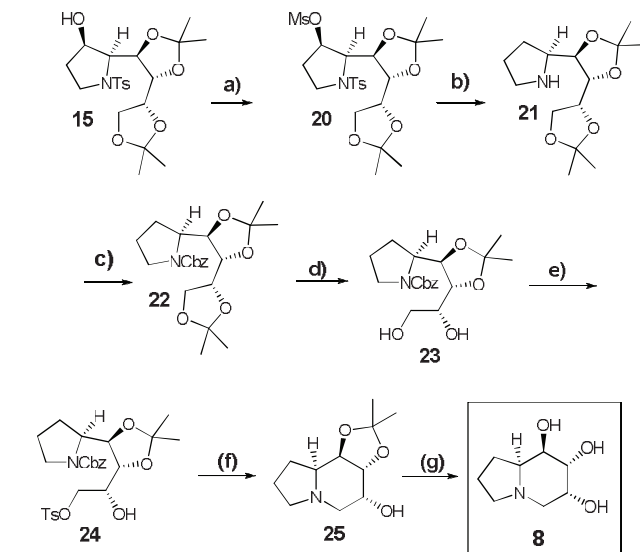
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After successfully installing the required stereocentres, along with construction of pyrrolidine ring we turned our attention for the completion of synthesis of 1,6,8a-tri-*epi*-castanospermine **7** (Scheme 3). The *N*-detosylation of **15** was successfully achieved under Birch reduction conditions (Na/Liq. NH₃) giving **16**. Other methods for deprotection such Na-Hg, Mg/MeOH, or Na/naphthalene for the detosylation of **15** were found either unsuccessful or low yielding. The resulting crude amine was immediately protected as 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 CH₃COOH/MeOH/H₂O (6:3:1) to obtain triol **17**. The primary hydroxy group of **17** was tosylated 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**. Reaction mixture was then filtered through a pad of celite and concentrated. To the residue was then added THF:H₂O (3:1) and acidic Dowex 50W-X8 and the mixture was heated for 12 hours gave the target molecule **7** in 90% yield over two steps.



Scheme-3 Synthesis of 1,6,8a-tri-*epi*-castanospermine (**7**) Reagents and conditions: a) i) Na/Liq NH₃, -78 °C, 1 h; ii) aq. K₂CO₃, CbzCl, CH₂Cl₂, 0 °C to rt, 30 min, 85% over two steps; b) CH₃COOH/MeOH/H₂O, (3:2:1), reflux, 5 h, 75%; c) Et₃N, TsCl, Bu₂SnO (cat), CH₂Cl₂, 0 °C, 2 h, 90%; d) H₂, Pd-C-10%, NaOAc, rt, 12 h, e) Dowex 50W-X8, THF:H₂O, (3:1) reflux 12 h, 90% 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 C14 Position. To our delight, LAH reduction also led to the *N*-detosylation in the same pot affording **21** which was immediately subjected for Cbz protection delivering **22** in 85% yield over two steps. Compound **22** was easily converted into target molecule **8** (Scheme 4) following the similar sequence of steps as described above for synthesis of **7** (Scheme 3, from **16-7**). The spectral data and specific rotation of **8** [α]_D²⁷ = +23.6 (c = 0.90, MeOH) were in excellent agreement with the reported values { $[\alpha]_D^{27}$ +23.5 (c = 0.90, MeOH)}.^{14f}



Scheme 4 Synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine (**8**) (a) MsCl, Et₃N, cat. DMAP, DCM, 0 °C, 1 h, 91%; (b) LAH, THF, reflux, 5 h; (c) aq K₂CO₃, CbzCl, DCM:H₂O (1:1), 0 °C to rt, 1 h, 82% over two steps; (d) CH₃COOH/MeOH/H₂O, (6:3:1), reflux, 5 h, 77%; (e) Et₃N, TsCl, Bu₂SnO (cat), CH₂Cl₂, 0 °C, 2 h, 88%; (f) H₂, Pd/C-10%, NaOAc, MeOH, rt, 12 h; g) Dowex 50W-X8, THF-H₂O (3:1), reflux 12 h, 86% over two steps.

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.

Experiment

All reactions requiring anhydrous conditions were performed under a positive pressure of argon by 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 CH₃CN, CH₂Cl₂, and triethylamine were distilled over CaH₂ 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 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 KMnO₄ and (NH₄)₆Mo₇O₂₄ (6.25 g) in aqueous H₂SO₄ (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. ¹H NMR spectra were

recorded with Bruker ACF 200, AV 400 and DRX 500 instruments operating at 200, 400 and 500 MHz, respectively by using deuteriated 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), automated GC-MS with a solid-probe facility mass spectrometer. Auto-concept instrument with ionization by electron impact, achieved at an ionization potential of 70 eV. X-ray data was collected at $T = 296$ K with a SMART APEX CCD singlecrystal X-ray diffractometer by using Mo- $K\alpha$ radiation ($\lambda = 0.7107$ 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 fullmatrix least-squares refinement on F^2 . Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out by using SHELXL-97. Microanalysis data were obtained by using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser.

25 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 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), $[\alpha]_{\text{D}}^{27} +12.5$ (c 1.2 in CHCl_3), Anal. Calcd. For $\text{C}_{27}\text{H}_{33}\text{NO}_6$: 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} . ^1H 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 drop wise to a suspension of LiAlH_4 (4.75 g, 125 mmol) in THF (100 mL) at 0 °C over a period of 15 min. Ice bath was removed and reaction mixture was allowed to stir for 4-6 hrs under reflux condition and then cooled to 0 °C again and subsequently quenched by saturated aqueous solution of sodium sulfate. White precipitate was filtered through a sintered funnel, and the filtrate was washed with ethyl acetate. Solvent was removed under reduced pressure to obtain colourless oil (20.1 g) which was subsequently dissolved in freshly distilled EtOAc (100

mL). The Pd/C-10 % (2.0 g) was added to it and mixture was allowed to stir under hydrogen balloon for 12 hrs. The mixture was filtered over celite and primary amine **12** was obtained as colorless oil (11.3 g). The compound **12** was found highly polar and relatively unstable at room temperature. Thus the resultant amine was dissolved in DCM (40 mL) and an aqueous solution K_2CO_3 (5.89 in g, 42 mmol) in H_2O (40 mL) was added drop wise over a period of 10 min at room temperature. To the resultant solution, Tosyl chloride (7.98 g, 42 mmol) was added portion wise 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 white sticky solid. $[\alpha]_{\text{D}}^{27} -13.5$ (c 1.5 in CHCl_3): Anal. Calcd. For $\text{C}_{20}\text{H}_{31}\text{NO}_6$: 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} . ^1H 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 $n\text{-Bu}_2\text{SnO}$ (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 attain 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 obtained 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 same temperature for 6 h. After completion of starting material (as monitored by TLC), the mixture was passed through a pad of celite and filtrate was concentrated to give 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 colorless oil. $[\alpha]_{\text{D}}^{27} -5.65$ (c 0.5 in CHCl_3): Anal. Calcd. For $\text{C}_{20}\text{H}_{29}\text{NO}_7\text{S}$: 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 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 drop wise to reaction mixture and then reaction mixture was heated at 80 °C for 20 h. The mixture was then cooled and diluted with 100 mL of water and extracted by ethyl acetate (5 x 150 mL). The organic layer was washed with aqueous sodium thiosulfate (50 mL), brine (50 mL) and dried over sodium sulfate. Solvent was evaporated under reduced pressure and the product was purified by column chromatography (40% ethyl acetate-pet ether) to get **15** (4.0 g, 77%) as a white crystalline solid. m.p.: 151-153 °C (from CHCl₃); $[\alpha]_D^{27} +9.8$ (c 0.6 in CHCl₃). Anal. Calcd. For C₂₁H₃₁NO₇S: C, 57.12; H, 7.08; N, 3.17. Found: C, 57.18; H, 6.99; N, 3.33. IR (ν_{\max} , CHCl₃): 3393, 1598, 1372, 1091 cm⁻¹; ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 CO₂), 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 NH₄Cl, and allowed to stir until all ammonia had evaporated. The remaining solid was filtered through 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 CH₂Cl₂ (10 mL). To the solution was added aq K₂CO₃ (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 drop wise a solution of benzylchloroformate (0.85 mL, 6 mmol) in CH₂Cl₂ (5 mL), and reaction 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 (ethyl 40% 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 CHCl₃); Anal. Calcd. For C₂₂H₃₁NO₇: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.72; H, 7.53; N, 3.41; IR (ν_{\max} , CHCl₃): 3453, 2986, 1699, 1412, cm⁻¹; ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 under. The reaction mixture was cooled to 0 °C and 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), 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 colourless oil. $[\alpha]_D^{27} -13.56$ (c 1.5 in CHCl₃); Anal. Calcd. For C₁₉H₂₇NO₇: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.75; H, 7.22; N, 3.59; IR (ν_{\max} , CHCl₃) 3417, 2985, 1682, 1417, cm⁻¹; ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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*-Bu₂SnO (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 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 CHCl₃); Anal. Calcd. For C₂₆H₃₃NO₉S: C, 58.30; H, 6.21; N, 2.62. Found: C, 58.27; H, 6.26; N, 2.57; IR (ν_{\max} , CHCl₃) 3402, 2985, 1674, 1115, cm⁻¹; ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 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-H₂O (3:1) and refluxed over night with Dowex 50W-X8 (50 mg). The reaction mixture was filtered and washed with MeOH. The remaining residue was eluted with 2N NH₃ solution. The NH₃ 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 CHCl₃); Anal. Calcd. For C₈H₁₅NO₄: 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 (D₂O, 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). ¹³C NMR (D₂O, 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 Et₃N (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 NaHCO₃ (5 mL). The reaction mixture was extracted with EtOAc (3 x 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 CHCl₃); Anal. Calcd. For C₂₂H₃₃NO₉S₂: C, 50.85; H, 6.40; N, 2.70. Found: C, 50.81; H, 6.55; N, 2.64; IR (ν_{max}, CHCl₃) 1597, 1353, cm⁻¹. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 x 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 K₂CO₃ (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 x 5 mL) and brine (1 x 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 colourless oil. $[\alpha]_D^{27}$ -12.96 (c 1.3 in CHCl₃); Anal. Calcd. For C₂₂H₃₁NO₆: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.22; H, 7.61; N, 3.54; IR (ν_{max}, CHCl₃) 1597, 1353, cm⁻¹. ¹H NMR (CDCl₃, 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), 2.04-2.0 (2H, m), 2.0-1.85 (2H, m), 1.35 (12H, bs). ¹³C NMR (CDCl₃, 100 MHz) shows mixture of rotamers, value 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, 26.86, 26.87, 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 solid sodium bicarbonate was added until all acetic acid was neutralized. The reaction mixture was extracted with ethyl acetate (50 mL), washed with water (20 mL), 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 colourless oil. $[\alpha]_D^{27}$ -31.52 (c 1.25 in CHCl₃); Anal. Calcd. For C₁₉H₂₇NO₆: C, 62.45; H, 7.45; N, 3.83.

Found: C, 62.42; H, 7.53; N, 3.79. IR (ν_{max}, CHCl₃) 3418, 2934, 1674, 1417, cm⁻¹. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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*-Bu₂SnO (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 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 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 CHCl₃); Anal. Calcd. For C₂₆H₃₃NO₈S: C, 60.10; H, 6.40; N, 2.70. Found: C, 60.25; H, 6.40; N, 2.74; IR (ν_{max}, CHCl₃) 3364, 2986, 1673, 1417, cm⁻¹. ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 residue was dissolved in DCM. The organic layer was washed with water and brine, and dried over sodium sulphate. Solvent was removed and the crude product **25** obtained was dissolved in THF-H₂O (3:1) and refluxed over night with Dowex 50W-X8 (100 mg). The reaction mixture was filtered and washed with MeOH. The remaining residue was eluted with 2N NH₃ solution. The NH₃ solution was evaporated to give 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 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 C₈H₁₅NO₃: C, 55.47; H, 8.73; N, 8.09; Found: C, 55.45; H, 8.68; N, 8.08; IR (ν_{max}, CHCl₃) 3336, 2956, 1673, 1081, cm⁻¹. ¹H NMR (CD₃OD, 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); ¹³C NMR (CD₃OD, 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).

Acknowledgments

The authors thank Department of Science and Technology, New Delhi, for financial support. The authors are grateful to the Director CSIR-NCL and CSIR-IICT for providing the necessary infrastructure. D. K. T. is grateful to Prof Ganesh Pandey, for his valuable suggestions.

Notes and references

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

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†Electronic Supplementary Information (ESI) available: [Copies of ¹H NMR and ¹³C NMR spectra for all compounds, Single crystal X-ray data for compound 15 are available in the supporting information].

20 See DOI: 10.1039/b000000x/

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