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A concise stereoselective synthesis of (+)-1-deoxy-6-*epi*-castanospermine

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ABSTRACT

A concise stereoselective synthesis of (+)-1-deoxy-6-*epi*-castanospermine has been developed through stereoselective approach from the chiral precursor *R*-Glycidol. The key steps in the synthesis involve Grignard reaction through Weinreb amide, followed by Sharpless dihydroxylation and stereoselective reduction of imine assigned the required stereochemical feature of indolizidine azasugar (+)-1-deoxy-6-*epi*-castanospermine.

Indolizidine alkaloids possessing azabicyclic structure are widely spread in nature and embrace a wide range of structural and stereochemical feature. Polyhydroxy indolizidine alkaloids (+) Castanospermine (**1**), (+) Swainsonine (**2**), (+) Letigenosine (**3**) etc. are the important natural azasugars found in many plants and showed a wide range of biological activities (Fig. 1). Castanospermine (**1**) was first isolated from the seeds of *Castanospermum australe*[1] and showed potent glycosidase inhibitory activity,[2] the rigid bicyclic structure of this molecule is suggested for their potent biological activity.[3] As the study progresses Castanospermine (**1**), 1-deoxy Castanospermine (**4**), and their stereoisomers are evaluated in various forms of biological activity which includes antiviral,[4] anticancer,[5] antidiabetics, antiobesity[6] etc. Among those isomers (−)-1-deoxy-6-*epi*-castanospermine (**6**) found lysosomal α-mannosidase inhibitory activity in a competitive way.[2b] Though this compound has shown excellent biological activity, there are only few syntheses reported in the literature for chirally pure 1-deoxy-6-*epi*-castanospermine. The placement of four different stereo centers in a continuous manner makes these syntheses challenging.

Richardson and co-workers have reported the synthesis of (−)-1-deoxy-6-*epi*-castanospermine (**6**) from derivative of β-D-fructopyranoside.[7] Meyers et al. synthesized (+)-1-deoxy-6-*epi*-castanospermine (**5**) from 1,3-cyclohexane dione and (*S*)-Phenyl glycinol.[8] Suh and coworkers reported the synthesis of **6** from *N*-acyl-α-alkoxyvinylpyrrolidines via aza-Claisen rearrangemt.[9] The racemic synthesis of 1-deoxy-6-*epi*-castanospermine is reported by John and co-workers from the hetero-Diels–Alder adduct of diethyl 2-nitrosoacrylate.[10] Herewith we disclosed the novel and concise stereoselective approach toward the synthesis of (+)-1-deoxy-6-*epi*-castanospermine (**5**) starting from (*R*)-Glycidol.

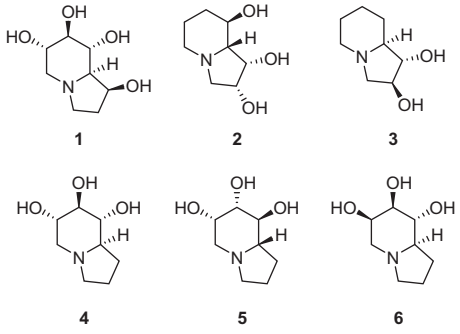

Figure 1. Naturally occurring and synthetic analogue of polyhydroxy indolizidine.

The retro synthetic design for the asymmetric synthesis of (+)-1-deoxy-6-*epi*-castanospermine (**5**) is depicted in Scheme 1. The

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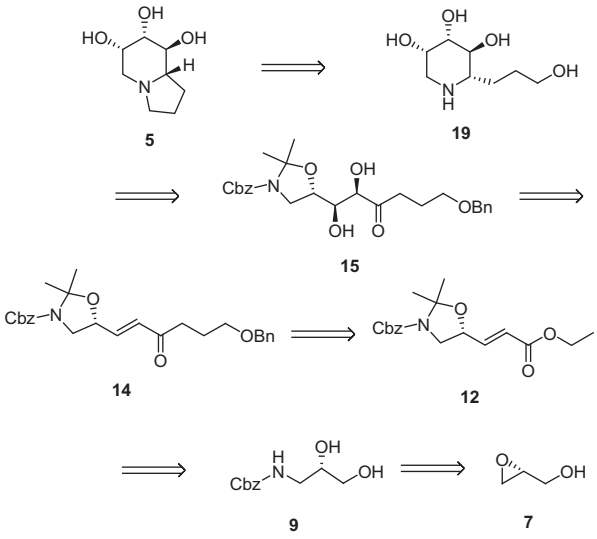
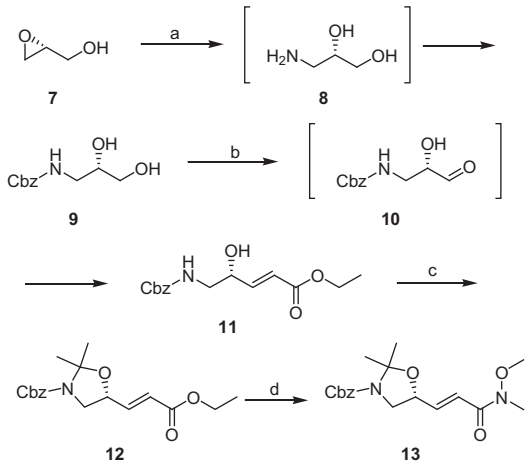


Scheme 1. Retro synthetic analysis.



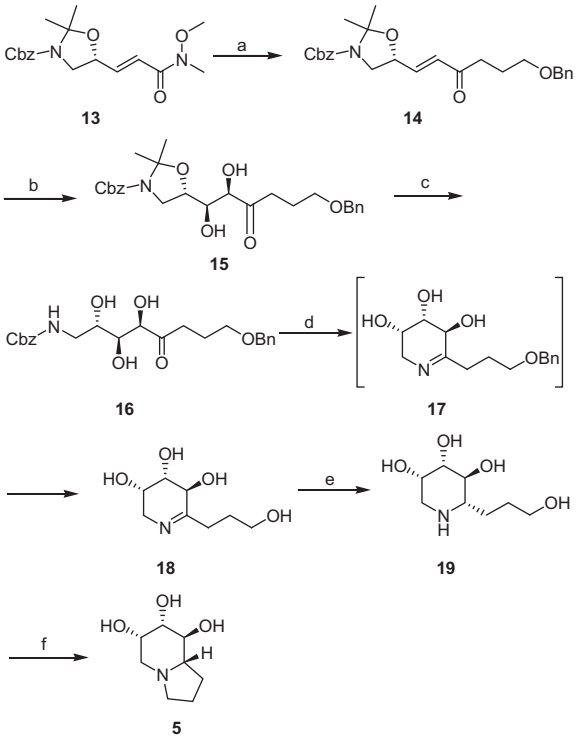
Scheme 2. Reagents and conditions: (a) (i) Aq ammonia, 0 °C, 24 h (ii) CbzCl, THF–water, $NaHCO_3$, 0 °C, 70% (two step); (b) (i) TCCA/TEMPO, EA, 5 °C, (ii) Ph_3-PCH=CHCOOEt, DCM, rt, 3 h, 50% (two step); (c) acetone–2,2′ DMP, Cat. $BF_3{\cdot}Et_2O$, rt, 1 h, 86%; (d) $HCl{\cdot}NH(OCH_3)CH_3$, *i*-PrMgCl, −20 to −15 °C, 1 h, 83%.

1-deoxy-6-*epi*-castanospermine (**5**) could be obtained by Mitsunobu cyclization of 1-deoxy homonojirimycin derivative (**19**). The compound **19** could be synthesized from **15** by global deprotection and in situ reductive amination reaction. The dihydroxylated compound **15** could be easily obtained from **14** by Sharpless dihydroxylation. The *trans* α,β unsaturated ketone could be obtained from **14** via Weinreb amide and Grignard reaction. The protected *trans* α,β unsaturated ester **12** could be obtained from **9** by selective oxidation, Wittig reaction, and protection of *N*-Cbz and free allylic hydroxyl group. *N*-Cbz glycidine **9** could be obtained as per literature procedure from *R*-Glycidol (**7**) and ammonia followed by *N*-Cbz protection.

The synthesis of (+)-1-deoxy-6-*epi*-castanospermine (**5**) began using commercially viable enantiomerically pure (*R*)-Glycidol (**7**). Thus reaction of (*R*)-Glycidol and ammonia was carried out at 0 °C for 24 h to form 2-amino glycidine **8** which was in situ protected with CbzCl in the presence of sodium bicarbonate to provide **9**.[11] The *trans* α,β-unsaturated ester **11** was obtained by selective oxidation[12a] and Wittig reaction as per our previous reported protocol with 50% yield.[12] The acetonide protection of amide and allylic hydroxy of **11** was carried out in acetone–2,2′ DMP mixture by using catalytic $BF_3{\cdot}Et_2O$ with 86% yield of **12**. The Weinreb amide **13** was synthesized from α,β-unsaturated ester **12** using Bourdox reaction condition at −20 to −15 °C with 83% yield[13] (Scheme 2).

The next reaction which was needed Grignard substrate, 3-benzyloxy-1-bromopropanol was prepared starting from 1,3-propane diol as per literature protocol.[14] The 3-benzyloxy Magnesium bromide was prepared freshly from 3-benzyloxy-1-bromopropanol with Mg in dry THF at ambient temperature. When the Grignard reaction of 3-benzyloxy Magnesium bromide attempted on **13** in THF, the reaction rate was too slow. Even the excess mol equiv of Grignard substrate or at elevated temperature failed to achieve the satisfactory yield, conversion was less than 20%. When reaction solvent switched to diethyl ether at 0–30 °C, the reaction was completed in 1 h and the required product **14** was isolated with 81% yield. The required stereochemistry in dihydroxylation was achieved by Sharpless dihydroxylation reaction with AD-mix-α at 0 °C to afford **15** with 75% yield.[15] The reaction was highly stereoselective and the other isomer was observed very less (98% de) which was separated by column chromatography.

To construct the piperidine skeleton we followed the cascade approach for deprotection and cyclization as per the literature procedure. The deprotection of acetonide by using catalytic *p*-TSA in methanol, followed by *N*-Cbz deprotection, cyclization and reductive amination using $H_2/Pd/C$[16] or $H_2/Pd(OH)_2/C$[17] along with aqueous HCl. But in our study this cascade approach failed to get desired product and ended up with mixtures of isomers, therefore we proceed in a stepwise approach. First the acetonide was deprotected with catalytic *p*-TSA in methanol and after the usual work up the crude **16** was taken for next conversion. Next, the deprotection of *N*-Cbz, cyclization, and reductive amination was carried out



Scheme 3. Reagents and conditions: (a) (i) 1-((3-bromopropoxy)methyl)benzene, Mg, dry THF; (ii) diethyl ether, 0–30 °C, 1 h, 81%; (b) AD mix α, $Ke_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, $NaHCO_3$, OsO_4, *t*-BuOH–water, 0 °C, 18 h, 75%; (c) *p*-TSA, MeOH, rt, 16 h; (d) H_2, $Pd(OH)_2/C$, methanol, rt, 8 h then 2 N HCl, rt, 12 h, 75% (two steps); (e) $NaBH_3CN$, acetic acid, methanol, rt, 30 h; (f) PPh_3, DIED, pyridine 0 °C, 3 h, 43% (two steps).

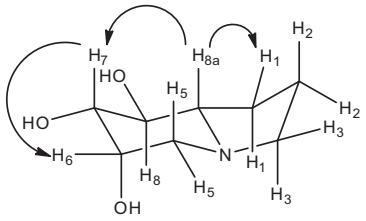


Figure 2. NOE effect of indolizidine **5**.

in $Pd(OH)_2$/C and 2 M HCl under hydrogen atmosphere, but we ended up with imine **18** with 75% yield. When we increased the concentration of HCl, the substrate was degraded and ended up with a complex mixture. Our different attempts to reduce the imine **18**, which include $Pd(OH)_2$ or Pd/C in neutral and basic condition ruled out to give the required product **19**. So finally the crude imine **18** was reduced with sodium cyanoborohydride in methanol and acetic acid which gave the required product **19**, the stereochemistry was confirmed at the final compound. The compound **19** was purified by acidic resin and immediately converted to the final product using the Mitsunobu's approach by intramolecular cyclization of secondary amine and primary hydroxyl.[18] The reaction was carried out with triphenyl phosphine and DIED at 0 °C for 3 h and the required product (+)-1-deoxy-6-*epi*-castanospermine (**5**) was isolated as a thick oil with 43% yield from crude **18** (Scheme 3). The spectral data of the isolated product **5** were comparable with the literature value,[19] $[\alpha]_D^{22} = +22.5°$ (*c* 0.05, MeOH), lit[7] $[\alpha]_D = +23°$ (MeOH) and enantiomer of **5** lit[9] $[\alpha]_D^{23} = -25.2°$ (*c* 0.25, MeOH).

The configuration and relative stereochemistry of the final indolizidine structure **5** were further confirmed by APT, HSQC, and COSY–NOESY tool. The strong NOE effect between H8a and H7, H8a and H1β indicates that H7 and H8a are same sides of the plane. Also NOE between H7 and H6 specifies that H6 and H7 are on the same side of the ring. Irradiation to H8a didn't enhance the intensity of H8, this indicates that H8 and H8a both are on the opposite side of the ring. The *trans* diaxial relation between H7 and H8 is revealed by the coupling constant $J_{7,8}$ value (9.3 Hz) while the small value of $J_{6,7}$ (3.4 Hz) suggested the *cis axial–equatorial* orientation (Fig. 2).

In conclusion, a new synthetic stereoselective approach for the construction of polyhydroxylated indolizidine, 1-deoxy-6-*epi*-castanospermine has been developed from readily accessible starting materials in moderate to good yields. The azabicyclic imino sugar synthesis involves many in situ conversions which includes Sharpless dihydroxylation, Grignard reaction, and asymmetric imine reduction. This synthetic approach can be useful to synthesize other polyhydroxy alkaloid analogues.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.080.

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19. *Spectral data of* **5**: ^{1}H NMR (400 MHz, D_2O): δ ppm 1.53 (m, 1H, H1β), 1.81 (m, 2H, H2α and H2β), 2.01 (m, 1H, H1α), 2.10 (m, 1H, H8a), 2.25 (q, *J* = 9.3 Hz, 1H, H3β), 2.39 (dd, *J* = 1.4 and 12.7 Hz, 1H, H5β), 3.0 (m, 1H, H5α), 3.10 (dd, *J* = 2.4 and 12.7 Hz, 1H, H3α), 3.46 (dd, *J* = 3.4 and 9.3 Hz, 1H, H7), 3.53 (t, *J* = 9.3 Hz, 1H, H8), 4.01 (br s, 1H, H6). ^{13}C NMR (100 MHz, D_2O): δ ppm 21.8, 28.1, 53.8, 55.8, 68.4, 69.7, 73.4, 75.8. IR (neat) cm^{-1}: 3020, 2400, 1423, 1215. HRMS (ESI): Calcd for $C_8H_{16}NO_3$ $(M+H)^+$ 174.1130, found 174.1128. $[\alpha]_D^{22} = +22.5°$ (*c* 0.05, MeOH).