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Total synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine and formal synthesis of pumiliotoxin-251D

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ABSTRACT

A concise and efficient synthesis of (6*R*,7*S*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **2** is described. The synthesis employs cross metathesis in building the key intermediate **9** and is used effectively in constructing indolizidine skeleton for the total synthesis of 1-deoxy-7, 8a-di-*epi*-castanospermine and also for the bicyclic framework of pumiliotoxin 251D **12**, **13**. The indolizidine skeleton is achieved in one pot sequence of transformations such as deprotection of Cbz group, reduction of double bond, and cyclization. The configurational and conformational structures of compound **10** are unambiguously confirmed by X-ray analysis.

Aza fused indolizidine bicyclic alkaloids are widely distributed in microorganisms, vertebrates, higher invertebrates, and plants.[1,2] These bicyclic core structures being biologically active have drawn attention of synthetic organic chemists to develop a concise and efficient strategy.[1,3] The naturally occurring polyhydroxylated indolizidine alkaloids such as (+)-castanospermine **1** and their analogues **2**, **3** have been reported to exhibit glycosidase inhibition activity,[4] and they are also known to display potential antitumor, antiviral, and immunomodulating activities (Fig. 1). Similarly, the structurally related alkaloids of pumiliotoxin **4** (Fig. 1) have been isolated and characterized from the neotropical frogs of family 'Dendrobadidae'.[5] These alkaloids are known to act as chemical defense agents against predators and have a high pharmacological activity on nerve and muscle.[6] Though several reports of racemic and enantioselective syntheses of 1-deoxy-8a-*epi*-castanospermine stereoisomers exist,[7] there are discrepancies in the reported assignments and characterization. This prompted us to synthesize 1-deoxy-7,8a-di-*epi*-castanospermine diastereomer **2**. Herein, we wish to report a short and practical synthesis as a general synthetic route to 1-deoxy-7,8a-di-*epi*-castanospermine **2** and bicyclic frameworks of pumiliotoxin 251D (**12**, **13**). Compound **9** was effectively used as a common key intermediate for the syntheses of **2**, **12,** and **13** in this approach.

(2*S*)-*N*-Cbz-pyrrolidine-2-carboxaldehyde **7** was prepared in two steps from *N*-Cbz-L-proline **5**. Compound **5** was coupled with *N*,*O*-dimethylhydroxylamine hydrochloride to give the corresponding Weinreb amide **6** in 92% yield, which on reduction with lithium aluminium hydride (LAH) led to the formation of the corresponding aldehyde **7** in 90% yield. The addition of vinyl magnesium bromide to aldehyde **7** afforded an inseparable mixture of diastereomeric alcohol **8** in 70% yield (Scheme 1).

Olefin metathesis of acyclic or cyclic olefins using alkylidene ruthenium and molybdenum catalysts[8] plays a pivotal role in the synthesis of heterocyclic framework. Thus olefin **8** was subjected to cross metathesis approach to arrive at the key intermediate **9** (Scheme 1).

The cross metathesis of **8** and methyl acrylate was performed with Grubbs' second generation catalyst (G-II) in toluene at room temperature and gave the expected *E*-isomer **9** predominantly (E/Z 20:1) in an excellent yield of 92%. Then compound **9** upon dihydroxylation[9] using OsO_4 and NMO resulted in the formation of a mixture of lactones owing to the alkaline condition of the

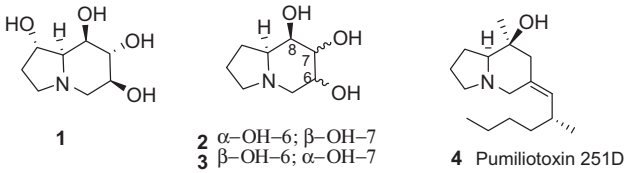

Figure 1. Polyhydroxylated indolizidine alkaloids and pumiliotoxin 251 D.

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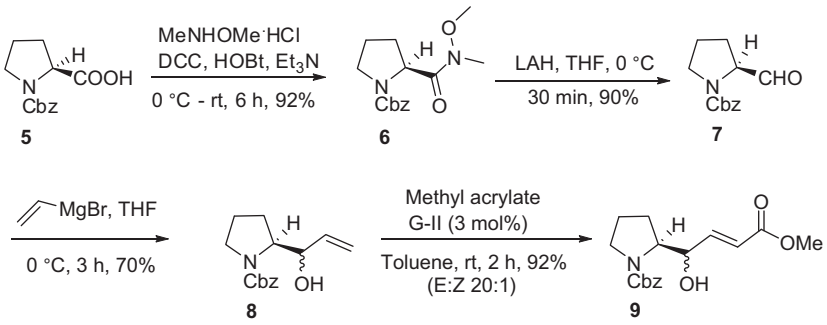
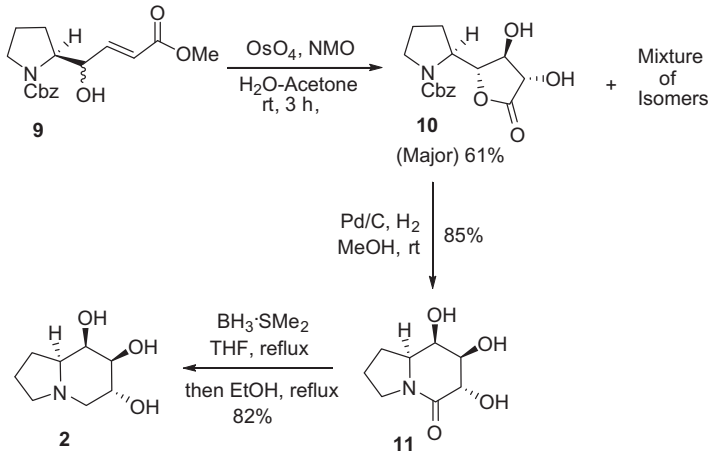


Scheme 1. Synthesis of key intermediate **9**.



Scheme 2. Synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine.

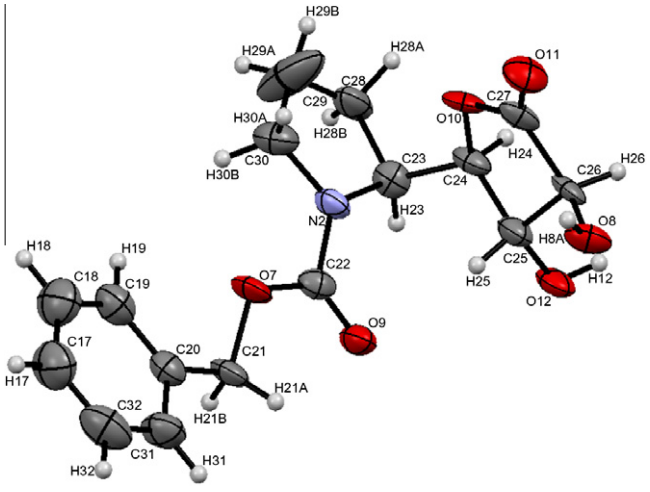


Figure 2. Molecular structure of lactone **10** by X-ray analysis (ORTEP diagram; ellipsoids are drawn at 50% probability).

reaction. The mixture was purified by column chromatography and lactone **10** was isolated in major amount (61% yield) as a white solid (Scheme 2). The molecular structure of **10** was confirmed by single-crystal X-ray analysis.[10] This gave the exclusive evidence for the stereochemistry of hydroxyl groups (Fig. 2).

Compound **10** under hydrogenolysis condition with Pd/C, H_2 deprotected the benzyloxycarbonyl (Cbz) group followed by the facile and rapid cyclization in one pot to give aza fused lactam: indolizidinone **11** in 85% yield. This on reduction with BH_3·DMS complex[7f,11] in THF gave the desired final compound 1-deoxy-7,8a-di-*epi*-castanospermine **2** in 82% yield (Scheme 2).

It is important to note that in contrast to the usual practice,[11] we successfully reduced the amide bond without protecting any of the hydroxyl groups thus minimizing the extra two steps in the route. After completion of reaction it was refluxed with EtOH to avoid the formation of amine-borane complex. Thus, the synthesis of (6*R*,7*S*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **2** was accomplished in a total of 7 steps with an overall yield of 23%. ^{1}H and ^{13}C NMR data for compound **2** do not match with the spectral data reported by Chan et al.[7a] However, the data of its enantiomer reported by Martin et al.[7c] and Pandey et al.[7d] were in close agreement with the spectral data of **2**. Specific rotation of compound **2** was in close agreement with that of its enantiomer (for **2**, obs: $[\alpha]_D^{25}$ −30 *c* 0.5, MeOH; its enantiomer $[\alpha]_D^{27}$ +26.1 *c* 0.45, MeOH).[7d] Our assignment is further supported by the X-ray crystal structure of compound **10**.

Earlier Gallagher[12d] and Nubbemyer[12i,j] have reported the synthesis of pumiliotoxin 251D **4** using indolizidine bicyclic frameworks (**12–14**) as key intermediates (Fig 3).

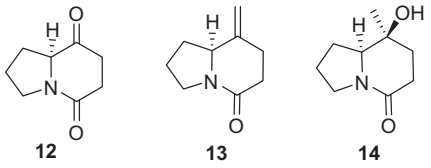
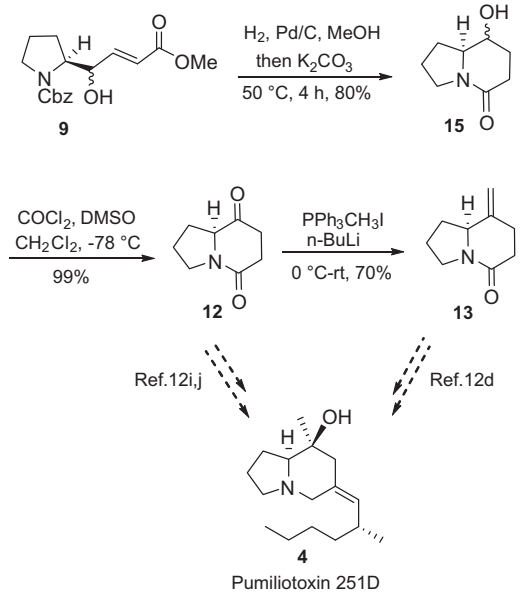


Figure 3. Key intermediates of pumiliotoxin 251D



Scheme 3. Formal synthesis of pumiliotoxin 251D.

Encouraged by this we planned to utilize effectively olefin **9** for the synthesis of the compounds **12** and **13** (Scheme 3). Compound **9** on treatment with Pd/C, H_2 in MeOH, followed by the addition of K_2CO_3 gave the corresponding alcohol **15** in 80% yield. It is striking to note that the sequence of transformations viz. deprotection of benzyloxycarbonyl (Cbz) group, reduction of double bond, and facile cyclization takes place in one pot. Subsequently, alcohol **15** upon Swern oxidation, gave indolizidinedione **12** in almost quantitative yield of 99%. Thus compound **12** was obtained in an overall yield of 42% in 6 steps. Spectral data for compound **12** were in close agreement with the reported values (obs: $[\alpha]_D^{20}$ −243, *c* 1.56, $CHCl_3$ lit.[12i,j] $[\alpha]_D^{20}$ −245, *c* 1.56, $CHCl_3$).

Finally when compound **12** was subjected to Wittig olefination afforded bicyclic lactam **13** in 70% yield. Spectral data for compound **13** were in close agreement with the reported values (Obs: $[\alpha]_D^{20}$ −99.6, *c* 1.2, $CHCl_3$; lit.[12d] $[\alpha]_D^{20}$ −98.3 *c* 1.2, $CHCl_3$). While both the compounds **12** and **13** have been explored earlier as key intermediates for the synthesis of pumiliotoxin 251D,[12d,i,j] it is evident that **13** is a more viable and an efficient precursor of pumiliotoxin 251D than **12**, as the conversion of **12** to the corresponding tertiary alcohol **14** was diastereoselectively poor (1:1.9).[12i,j] But the conversion of bicyclic lactam **13** to the corresponding tertiary alcohol **14** was highly diastereoselective (10:1).[12d] Also in comparison with the reported procedures,[12] synthesis routes to **12** and **13** described in this Letter are shorter and better yielding.

In summary, we have developed a concise and convenient total synthesis of (*6R*,*7S*,*8R*, *8aS*)-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **2**. This procedure requires a total of 7 steps starting from *N*-Cbz-L-Proline **5** and proceeded in overall 23% yield. X-ray analysis of **10** established its unambiguous structural determination, which in turn confirmed the configurational structure of **2**. In addition, the formal synthesis of pumiliotoxin 251D was accomplished in a total of 6 or 7 steps starting from **5** in an overall 30% yield. Olefin **9** resulting from cross metathesis was used as a common key intermediate for both the syntheses.

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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.2012.08.061.

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