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Stereoselective synthesis of (+)-(8*R*,8a*R*)-perhydro-8-indolizidinol

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ABSTRACT

A highly stereoselective total synthesis of (+)-(8*R*,8a*R*)-perhydro-8-indolizidinol is described. Key steps involved in this synthesis are diastereoselective zinc allylation, azido-olefin cyclization and reductive amination followed by cyclization which effectively constructed the indolizidine ring. This contributes a unique approach to the synthesis of indolizidine alkaloids that offers the advantages of brevity and relatively high overall yields.

Nitrogen-containing heterocycles are widespread in medicinal chemistry due to the fact that many natural and synthetic biologically active compounds share this common architectural feature.[1] Polyhydroxy indolizidine frame work (Fig. 1) represents one of the major classes of alkaloids,[2] which exhibits intriguing molecular structures featuring a N-bridgehead bicyclic ring system. These systems have received much attention in recent years. Many of the synthetic and natural indolizidines have displayed important biological activities which can find a variety of applications in the field of pharmaceuticals and material science.[3e–h] The structural diversity and pharmacological activities of these alkaloids, as well as the limited amounts available from natural sources have stimulated considerable synthetic effort in this area.[3i–r] Discovery and synthesis of new classes of heterocycles, especially if the synthetic methodology is modular and reliable, are always a welcome addition as they offer routes to new substrates which may possess advantageous therapeutic activities or chemical reactivity.[3a–d]

In continuation of our ongoing studies on the synthesis of bioactive natural products,[4] we became interested in various indolizidine alkaloids.

In this Letter, we report a new approach for the stereoselective synthesis of (+)-(8*R*,8a*R*)-perhydro-8-indolizidinol **4** as shown in Scheme 1, which makes use of azido-olefin cyclization and reductive amination followed by cyclization as key steps in the overall synthetic sequence. To date only one synthesis is reported on hydroxyindolizidine **4**, which features SmI_2 mediated reductive carbon–nitrogen cleavage reaction as a crucial step for the construction of indolizine ring.[5]

In an earlier study from our laboratory, we had demonstrated the versatility of allylation (Keck allylation and Marouka allylation) and Grubb's cross metathesis reactions for the synthesis of the putative piperidine alkaloids.[4a,c] Our retro synthetic strategy for the present synthesis relies on the azido-olefin cyclization, reductive amination followed by cyclization starting from the mannitol diacetonide (Scheme 1).

As shown in Scheme 1, initial disconnection of **4** revealed fragment **6**, which could be subjected to reductive amination followed by cyclization to realize the target molecule. The key step in this synthesis would utilize one-pot intramolecular hydroboration–cycloalkylation of the azido-olefin. The brevity of this analysis along with the structural simplicity of the precursors makes this route attractive for implementation.

The total synthesis based on the above mentioned plan was initiated with mannitol diacetonide (**13**) which can be readily prepared from D-mannitol. Compound **12** was synthesized from mannitol diacetonide by following the literature procedure in an overall yield of 73% in a three step sequence.[6] Tosyl ester **12** was

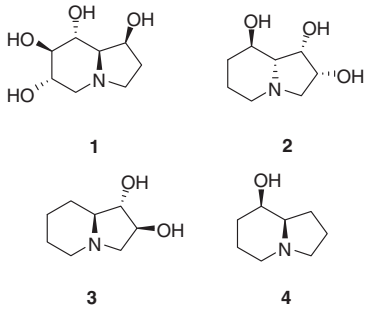

Figure 1. Representative examples of indolizidine alkaloids.

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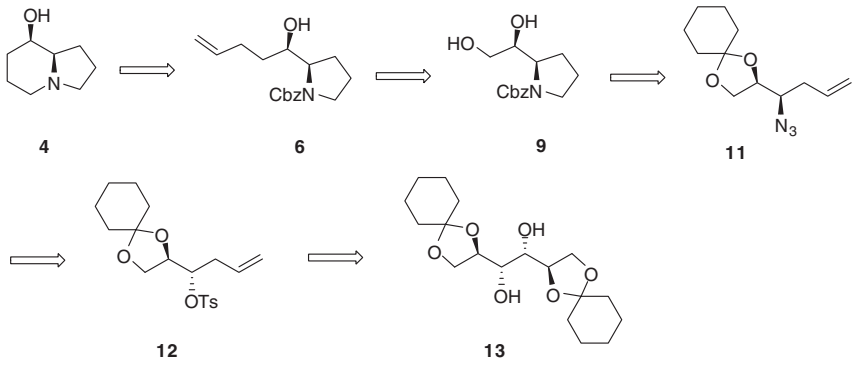

Scheme 1. Retro synthetic analysis of (+)-(8*R*,8a*R*)-perhydro-8-indolizidinol.

then converted into its corresponding azide **11** using standard conditions (NaN_3, DMF, 70 °C) with 70% yield.[7]

With the chiral azide **11** in hand, our efforts were directed towards the construction of the pyrrolidine ring. For this purpose, we have used an intramolecular hydroboration–cycloalkylation of the azido-olefin **11**, which has been used for the synthesis of pyrrolidinone and piperidine derivatives.[8] Thus, chiral azide **11** was treated with an excess of freshly prepared dicyclohexylborane followed by hydrolysis with methanol to afford pyrrolidine intermediate **10**. This one-pot sequence proceeded by hydroboration of the double bond of **11** and subsequent formation of a boron nitrogen bond between the azide and the trialkylborane to afford the cyclic azide borane complex intermediate **I**. Finally, migration of the borane methylene group to N-1 of **I** proceeds with a ring contraction and concomitant loss of nitrogen (Scheme 2). Reaction mixture was diluted with ether and washed with 1 N HCl to yield corresponding hydrochloride salt. Aqueous layer was basified with $NaHCO_3$ and treated with Cbz-Cl to yield Cbz-protected amine **10** in good yield.

Having successfully accomplished the synthesis of key intermediate **10**, we then shifted our focus to investigate the general applicability of this strategy for the synthesis title compound **4.** Thus, cyclohexylidine group in compound **10** was deprotected with aqueous TFA to yield diol **9** in moderate yield (62%).[9] Selective protection of diol **9** was achieved with TsCl, Bu_2SnO, DCM and Et_3N in 3 h to give **8** with 85% yield.[10] The formation of monoprotected diol **8** was further determined by the ^1H NMR spectrum which showed the presence of a singlet at δ 2.43. Subsequent conversion of **8** to the corresponding epoxide with NaH, THF at 0 °C in 30 min yielded **7** (94%).[11] Absence of tosyl group in ^1H NMR and the presence of epoxide protons (δ 2.4–2.52, m, 1H and δ 2.57–2.73, m, 1H) confirmed epoxide product **7**. Treatment of epoxide **7** with allyl magnesium bromide in the presence of CuI in THF at −40 °C afforded secondary alcohol **6** in excellent yield. The presence of olefinic signal at δ 5.98–5.59 (m, 1H) confirmed hydroxy pyrrolidine compound **6**. Further, ozonolysis of hydroxy compound **6** was smoothly carried out in dry DCM at −78 °C to obtain aldehyde (immediately converted to hemiacetal) without further purification subjected to reduction with $NaBH_4$ to yield diol **5** in good yield. Diol **5** was converted into monotosylated compound **5a** using TsCl, Bu_2SnO, DCM and Et_3N.[10] Finally, reductive amination followed by cyclization of compound **5a** in hydrogenation conditions to afford hydroxy indolizidine alkaloid **4** in excellent yield with properties consistent with literature values[5] (Scheme 3). All the intermediate compounds were well characterized by IR, NMR and mass spectral techniques.[12]

In conclusion, we have developed an efficient stereoselective protocol for the preparation of hydroxyindolizidine alkaloid **4** by employing diastereoselective allylation, azido-olefin cyclization and reductive amination followed by cyclization. This general synthetic route demonstrates its versatility towards the synthesis of highly functionalized indolizidines and also paves the way for the structurally related analogues. On the basis of the route described herein, further work towards preparation of the library of hydroxyindolizidine alkaloids for biological analysis is in progress in our laboratory.

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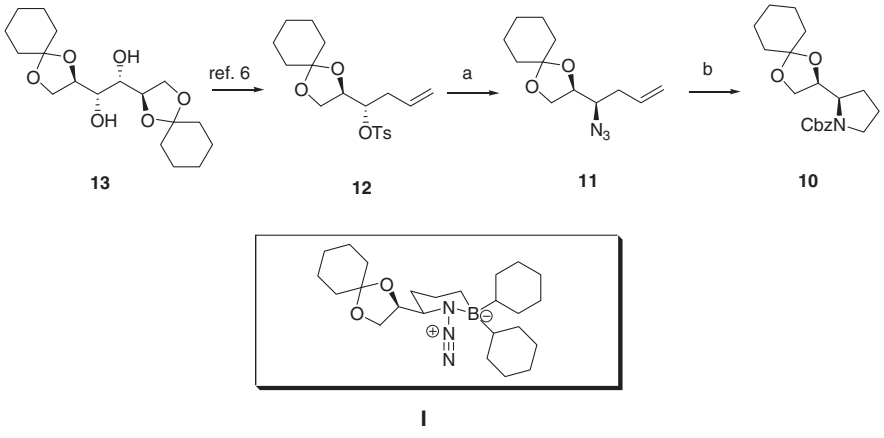
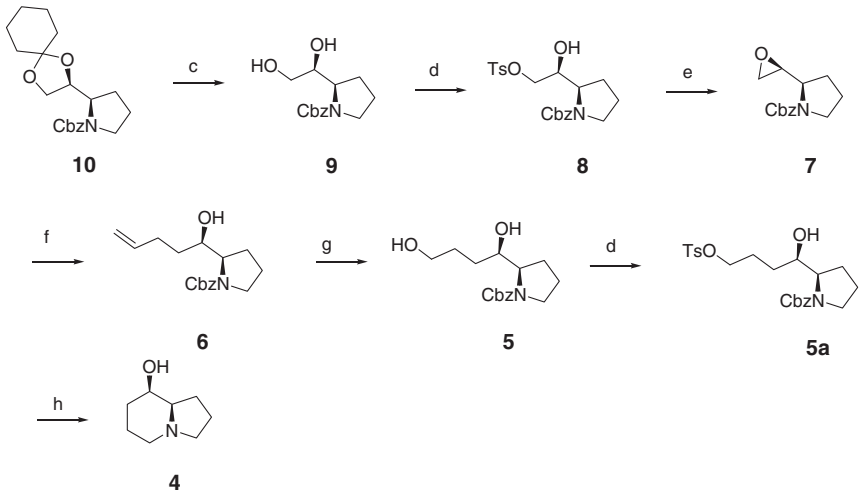


Scheme 2. Synthesis of key intermediate **10**. Reagents and conditions: (a) NaN_3, DMF, 70 °C, 6 h, 70%; (b) dicyclohexylborane, quenching with methanol, 1 N HCl, neutralization with $NaHCO_3$, Cbz-Cl, 70%.



Scheme 3. Synthesis of (+)-(8*R*,8a*R*)-perhydro-8-indolizidinol **4**. Reagents and conditions: (c) 90% aqueous TFA, 62%; (d) TsCl, Bu_2SnO, DCM, Et_3N, 85%; (e) NaH, THF, 0 °C, 30 min, 94%; (f) AllylMgBr, CuI, THF, −40 °C, 87%; (g) (i) O_3, DCM, −78 °C; (ii) $NaBH_4$, MeOH, 0 °C to rt, 63% (over two steps); (h) Pd/C (10%), H_2 (balloon), 70%.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.102.

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12. Spectral data of selected compounds: Compound **11**: Pale yellow oily liquid; $[\alpha]_D^{25}$ −10.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.71 (m, 1H), 5.23–5.06 (m, 2H), 4.13–4.02 (m, 1H), 4.02–3.92 (m, 1H), 3.78–3.69 (m, 1H), 3.2 (q, 1H, *J* = 6.4, 12.6 Hz), 2.29 (t, 2H, *J* = 6.7 Hz), 1.72–1.48 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.9, 118.8, 110.6, 78.0, 66.2, 62.9, 36.5, 35.4, 25.7, 24.4, 24.3; FABMS: *m*/*z* 238 $[M+1]^+$. Compound **10**: Pale yellow oily liquid; $[\alpha]_D^{25}$ +12 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.15 (m, 5H), 5.05 (m, 2H), 4.36–4.13 (m, 1H), 4.12–3.99 (m, 1H), 3.94–3.77 (m, 1H), 3.76–3.64 (m, 1H), 3.63–3.47 (m, 1H), 3.45–3.24 (m, 1H), 2.18–1.67 (m, 6H), 1.64–1.44 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 141.6, 128.5, 127.4, 127.0, 109.4, 78.0, 65.8, 64.9, 57.9, 47.7, 36.1, 35.2, 25.5, 24.2, 24.1; FABMS: *m*/*z* 346 $[M+1]^+$.
Compound **6**: Pale yellow oily liquid; $[\alpha]_D^{25}$ +58 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.17 (m, 5H), 5.98–5.59 (m, 1H), 5.3–4.78 (m, 4H), 3.98–3.74 (m, 1H), 3.7–3.19 (m, 3H), 2.43–1.30 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 138.5, 136.5, 128.3, 127.9, 114.7, 74.0, 67.1, 63.3, 47.0, 33.7, 29.6, 28.2, 24.1; FABMS: *m*/*z* 290 $[M+1]^+$.