Total synthesis of (±)-quinolizidine 207I, an alkaloid from *Mantella baroni*, a Madagascan mantelline frog

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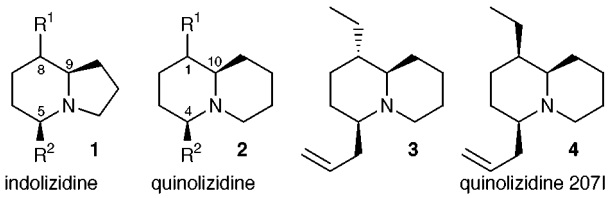
The first synthesis of quinolizidine 207I was achieved by a totally stereocontrolled approach starting from a 9-azabicyclo[3.3.1]nonane derivative, thus establishing the exceptional axial stereochemistry of the ethyl group at position 1.

Several alkaloids of the indolizidine **1** and quinolizidine **2** series have been isolated from the skin of certain poisonous frogs and



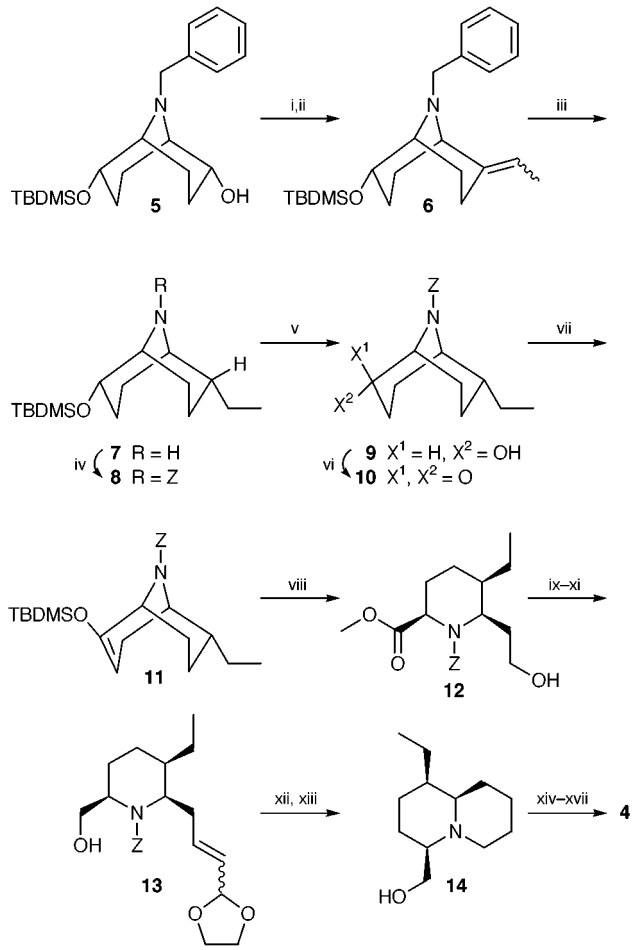
toads.[1] While the structures of the 5,8-disubstituted indolizidines are well-known and have in some cases been confirmed by synthesis,[2] the 1,4-disubstituted quinolizidine are a relatively new class of alkaloids. They have been isolated in minute quantities, and their structure determined mainly on the basis of GC-FTIR and GC-MS: the presence of significant Bohlmann bands[3] in the FTIR spectra shows that the hydrogens at position 4 and 10 are *cis*, but does not provide any information on the relative configuration at position 1, which is only tentative and must be confirmed by synthesis.

One of these alkaloids, quinolizidine 207I, was assigned structure **3** for which a total synthesis was reported in 1997 by Momose and co-workers.[4] However the synthetic material was found to be different from the natural one. Quinolizidine 207I was then reassigned the epimeric structure **4**, the first example of a 1,4-disubstituted quinolizidine with an axial 1-substituent.

We report herein the first synthesis of (±)-**4** (Scheme 1). In this totally stereocontrolled approach, the three asymmetric centres were introduced at an early stage by the use of a *pseudo*-pelletierine derivative **5**. Furthermore, this synthesis is formally enantioselective: because of the C_2 symmetry of the diol precursor of this synthon, it may safely be expected that the enantiomers of this diol as well as all the intermediates obtained in this synthesis will not undergo racemization at any point.

We have recently developed a facile access[5] to this new molecule from cycloocta-1,5-diene by modification of Ganter's approach to related systems.[6] Swern oxidation of **5** followed by a Wittig reaction afforded **6** in 90% yield, as a 1/9 mixture of *Z* and *E* isomers. Although easily separated by column chromatography, this mixture was directly hydrogenated in MeOH with 10% palladium on (wet) charcoal to give the debenzylated amine **7** as a single epimer, of *endo* stereochemistry, as will be proved at the quinolizidine stage. The amine was then protected with BnO_2CCl and the alcohol function liberated with HF to give **9** (82% yield from **6**). In order to open the bicyclic skeleton, this alcohol was oxidised (Swern) and converted to the silyl enol ether **11**. Treatment with O_3 gave the piperidine **12** after reduction and esterification (52% from **9**). Two carbons were added to the alcoholic chain by classical methods, and **13** was obtained (72% from **12**) as a mixture of isomers, after reduction of the methyl ester with Super-Hydride®. After hydrolysis of the dioxolane, hydrogenation with Pd/C removed the carbamate function and at the same time reduced both the double bond and the intermediate imine to yield **14** (69% from **13**). At this stage, the axial stereochemistry of the ethyl side-chain was determined from the coupling constant of the protons at positions 1 and 10, thus establishing the *endo* stereochemistry of this substituent in **7**. Target molecule **4**[7] was then obtained in 25% yield from **14** through two Wittig reactions. The total yield from **5** for this 17-step synthesis is 6.8%.

A sample of this molecule has been analysed at NIH-NIDDK: it had an FTIR spectrum identical in all respects with the natural product and it co-chromatographed with it on the achiral GC column that had produced the best separations in this series.



Scheme 1 *Reagents and conditions*: i, Swern oxidation (93%); ii, Ph_3EtPBr, Bu^tOK, THF (98%); iii, H_2, Pd/C 10% (wet), MeOH; iv, ZCl, K_2CO_3, acetone; v, HF 40%, MeCN (82% in 3 septs); vi, Swern oxidation (81%); vii, KH, THF, TBDMSCl (88%); viii, O_3, MeOH–CH_2Cl_2, then $NaBH_4$, then CH_2N_2 (71%); ix, Swern oxidation (81%); x, [$Ph_3PCH_2CH(OCH_2CH_2O)$] Br, Bu^tOK, THF (95%); xi, Super-Hydride®, THF, 0 °C (94%); xii, THF, HCl (1.2 M) (89%); xiii, H_2, Pd/C 10%, MeOH–H_2O (78%); xiv Swern oxidation (75%); xv, ($Ph_3PCH_2OCH_3$)Cl, Bu^tOK, THF (83%); xvi, THF, HCl (4 M); xvii, Ph_3MePBr, Bu^tOK, THF (41% in 2 steps).

Furthermore, the synthetic racemate can be separated on a chiral column, and the natural compound co-chromatographed with one of the synthetic enantiomers.

Because this synthesis is totally stereocontrolled, it establishes the relative configuration of the three epimeric centres: structure **4** can thus definitely be assigned to natural quinolizidine 207I. Since, as said before, this synthesis is formally enantioselective, resolution of an intermediate at an early stage should determine the absolute configuration of the natural product. Work along these lines is in progress.

The strategy used here is general and may provide an easy access not only to other natural (R^1 = Me or Pr) or unnatural quinolizidines **2**, but also to similar natural (R^1 = Me, Et or Pr) or unnatural indolizidines **1**. Syntheses following this approach should make possible a systematic exploration of the unknown pharmacological properties of these two series.

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7 *Selected data* for **4**: δ_H(400 MHz, $CDCl_3$) 0.88 (t, *J* 7.5, 3H; CH_3), 1.20–1.83 (m, 14H), 1.85–1.93 (m, 1H, CH), 1.97 (ddd, *J* 11.4, 2.6, 2.6, 1H; CH), 2.12–2.22 (m, 1H; CH), 2.44 (ddddd, *J* 14.2, 6.5, 3.2, 1.6, 1.6, 1H; CH), 3.32–3.38 (m, 1H; CH), 5.02–5.09 (m, 2H; CH_2), 5.85 (dddd, *J* 17.0, 10.3, 7.5, 6.7, 1H; CH); δ_C(100 MHz, $CDCl_3$) 12.45, 18.40, 24.99, 26.20, 26.26, 27.13, 31.01, 38.27, 40.56, 53.00, 64.13, 66.66, 115.88, 136.16.

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