Total Synthesis of (−)-Indolizidine 239CD

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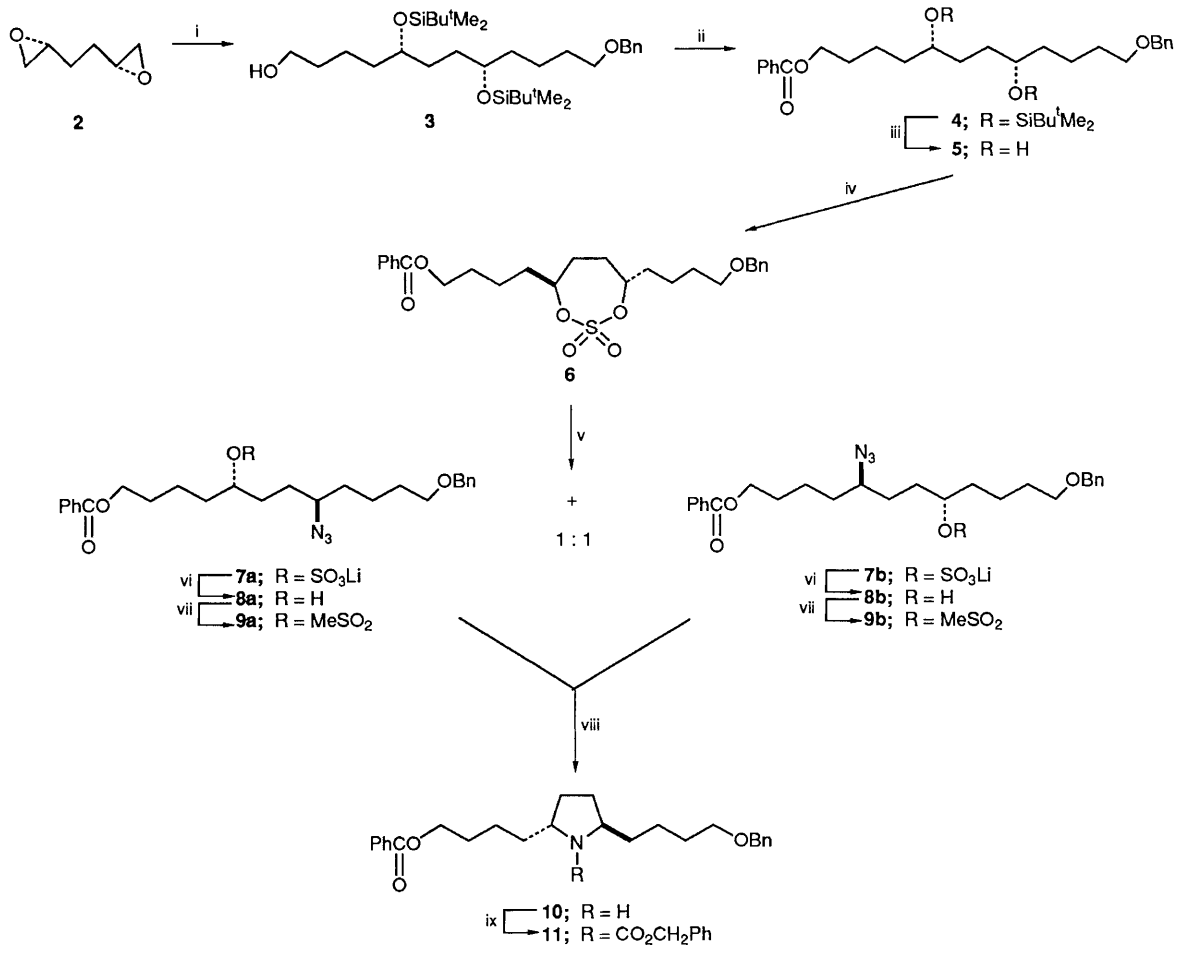
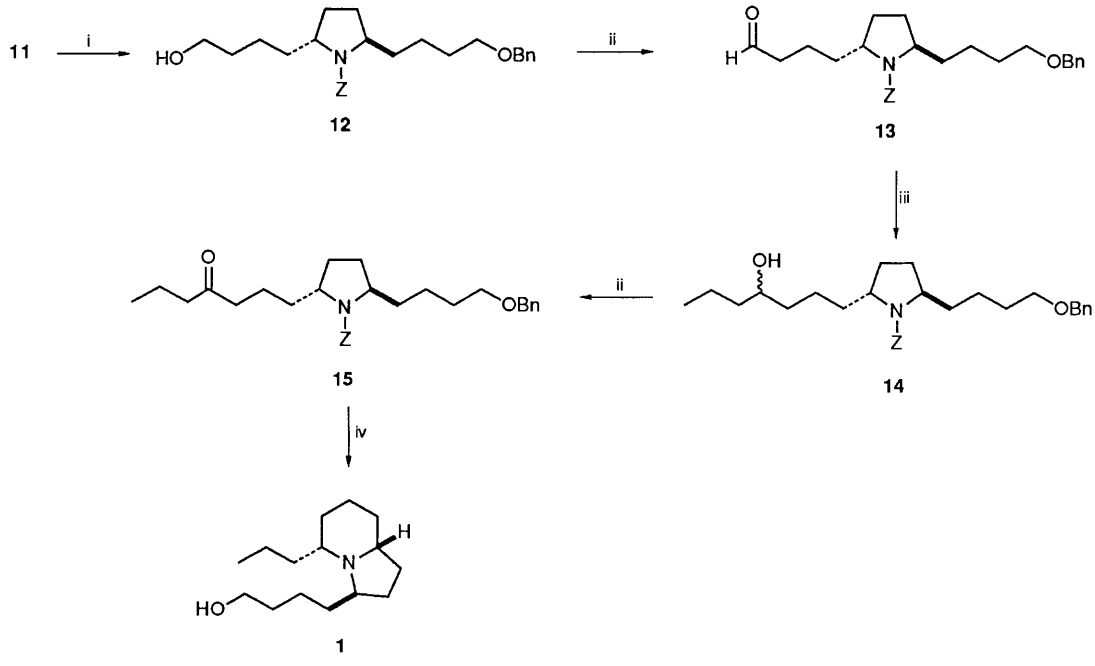
The first total synthesis of enantiomerically pure (−)-indolizidine **239CD** starting from the (*R,R*)-diepoxide building block **2** is described, which confirms its gross structure and absolute stereostructure.

In a recent communication,[1] we have reported the synthesis of pyrrolidine **197B** in optically active form, a new class of a naturally occurring alkaloid recently isolated[2] from the skin extracts of the Colombian poison-dart frog *Dendrobates histrionicus*. This synthesis demonstrates an efficient strategy for the construction of the *trans*-2,5-dialkylated pyrrolidine ring *via* cyclic sulphates utilizing a diepoxide building block. In our continuing interest in the chiral preparation of dendrobatid alkaloids,[1,3] we envisaged that the synthetic utility of this methodology would allow the possibility of preparing indolizi-



Scheme 1 *Reagents and conditions*: i, Ref. 1; ii, PhCOCl, 4-dimethylaminopyridine (DMAP), CH_2Cl_2; iii, Bu^n_4NF, THF; iv, $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, then $RuCl_3{\cdot}xH_2O$, $NaIO_4$, CCl_4–MeCN–H_2O; v, LiN_3, DMF; vi, aq. H_2SO_4, THF, room temp.; vii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; viii, H_2, Pd–C, MeOH; ix, $PhCH_2OCOCl$, 10% aq. K_2CO_3, CH_2Cl_2, 0 °C; Bn = $PhCH_2$



Scheme 2 *Reagents and conditions*: i, 1% KOH–MeOH, room temp.; ii, PDC, CH_2Cl_2; iii, PrMgBr, THF, 0 °C; iv, H_2, Pd–C, MeOH, then H_2, Pd–C, 2% HCl–MeOH; Z = $PhCH_2OC(:O)$–; Bn = $PhCH_2$

dine **239CD**, recently isolated[2] from *D. histrionicus* along with pyrrolidine **197B** and others. Indolizidine **239CD** has been characterized as 3-(4-hydroxybutyl)-5-propylindolizidine with the tentative absolute stereochemistry shown as formula **1**.[2,4] It has been reported to cause long-lasting locomotor difficulties and prostration after subcutaneous administration to mice.[5] We now describe a highly stereodefined total synthesis of the natural (−)-enantiomer of indolizidine **239CD 1** for the first time, establishing its gross structure and also its absolute stereostructure as shown.

Our approach to **1** (based on the reported tentative absolute stereostructure) began with the preparation of **3** by utilizing **2** according to the reported procedure.[1] As outlined in Scheme 1, **3** was converted to the diol **5**† in 81% overall yield *via* benzoylation followed by removal of the silyl protecting groups. Treatment of **5** with thionyl chloride and triethylamine, followed by a catalytic amount of RuO_4 (prepared from $RuCl_3$ and $NaIO_4$),[6] afforded the cyclic sulphate **6** in 82% overall yield. Subsequent treatment of **6** with LiN_3 in dimethylformamide (DMF) resulted in nucleophilic ring opening to given an inseparable 1 : 1 mixture of structural isomers **7a** and **7b**, which, without isolation, was immediately hydrolysed {aqueous H_2SO_4 in tetrahydrofuran (THF)} to yield a 1 : 1 mixture of **8a** and **8b** in 93% yield from **6**. The mixture of these isomers was converted to a 1 : 1 mixture of the corresponding mesylates **9a** and **9b** in 94% yield. Without separation, this mixture was hydrogenated over palladium on carbon to provide **10** as a single product, which was then transformed into the carbamate **11** in 76% yield.

Homologation of the *trans*-pyrrolidine **11** was performed as outlined in Scheme 2. The alcohol **12**, generated by alkaline hydrolysis of **11**, was oxidized {pyridinium dichromate (PDC), CH_2Cl_2} to give the aldehyde **13** (71% overall yield), which was treated with the Grignard reagent PrMgBr in THF to afford a diastereoisomeric mixture of the alcohols **14** in 86% yield. PDC oxidation of **14** gave the ketone **15**, which was hydrogenolysed over palladium on carbon in methanol then in 2% methanolic HCl to complete removal of the benzyl group to provide (−)-indolizidine **239CD 1** as a single isomer in 77% yield from **14**. The spectroscopic data (^{13}C NMR, mass and IR) of our synthetic **1** were found to be identical with those for the natural alkaloid[2] and its observed optical rotation {$[\alpha]_D^{26}$ −58.6° (*c* 0.21, MeOH)} was in good agreement with that reported[2] for the natural product {$[\alpha]_D$ − 52° (*c* 0.19, MeOH)}. These results provide clear evidence for the gross structure and absolute configuration of natural indolizidine **239CD** to be as shown by formula **1** as tentatively proposed.[2]

Thus we have demonstrated the first preparation of enantiomerically pure (−)-indolizidine **239CD** in a stereodefined manner *via* the *trans*-2,5-dialkylated pyrrolidine intermediate available from the diepoxide chiral synthon. This synthetic sequence can provide an efficient, versatile entry into other congeners, 3,5-disubstituted indolizidines **223AB** and **239AB**.[4]

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† All new compounds gave satisfactory spectral data and elemental analysis.

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