Asymmetric Synthesis from Pyridines: Use of New Chiral 1,4-Dihydropyridines in a Short Synthesis of 5,8-Disubstituted Indolizidine (+)-209B

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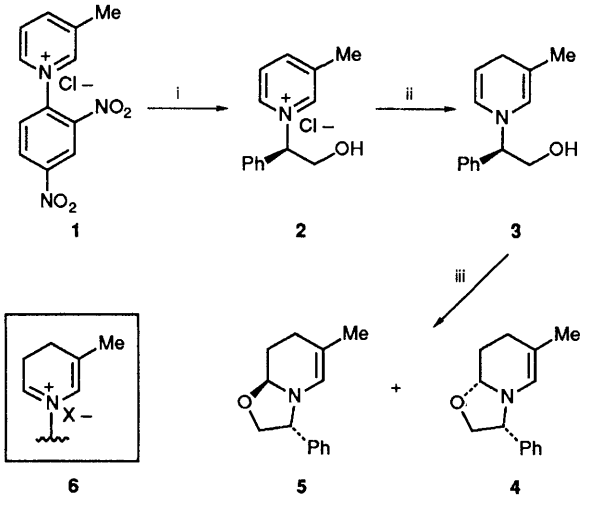
The synthetic potentiality of chiral oxazolidines, prepared from 3-picoline *via* a 1,4-dihydropyridine intermediate, has been illustrated by an expeditious route to the 5,8-disubstituted indolizidine alkaloid (+)-209B.

A simple approach to the synthesis of polysubstituted piperidines may be envisaged by successive regio-, stereo- and enantio-controlled introduction of substituents onto an appropriate pyridine nucleus. We have devised such a strategy[1] by using a 'Zincke–Koenig' reaction as the key step to an entry to pyridinium salts having a chiral carbon atom directly linked to the nitrogen of the pyridine ring. Starting from the salt **2**, we now report a convenient access to the 1,4-dihydropyridine (DHP) **3** which cyclized to the oxazolidines **4** and **5**, equivalents of a 3,4-dihydropyridinium salt **6** (Scheme 1). The interest of these intermediates for the construction of chiral 2,3,6-trisubstituted piperidines is illustrated by a short synthesis of the 5,8-disubstituted indolizidine alkaloid (+)-209B. A large number of such alkaloids occur in the skin extracts of neotropical dart-poison frogs (family Dendrobatidae)[2] and a synthesis of (−)-209B has recently been reported.[3]

Treatment of 3-picoline with 1 equiv. of 1-chloro-2,4-dinitrobenzene in acetone afforded in nearly quantitative yield the crystalline Zincke's salt **1** which was then refluxed with 1 equiv. of (*R*)-(−)-phenylglycinol in n-butanol for 4 h. The reaction mixture, after removal of butanol, was dissolved in H_2O and washed with CH_2Cl_2. Evaporation of the H_2O phase afforded the salt **2** as a viscous oil in 80–85% yield. Refluxing a two-phase system of Et_2O and an aqueous solution of the salt **2** containing $Na_2S_2O_4$ (2.5 mol dm^{-3}) and K_2CO_3 (2.5 mol dm^{-3}) for 1 h yielded in the Et_2O phase the desired 1,4-DHP **3** which was characterized by 200 MHz ^1H NMR and mass spectrometry. A similar 1,4-DHP intermediate was presumably involved in the reaction of phenylglycinol and glutaraldehyde in the presence of KCN.[4] This unstable compound **3** slowly isomerized in $CDCl_3$ solution to a mixture of the oxazolidines **4** and **5** along with appreciable decomposition. The kinetic product **5** was first formed and then equilibrated to the thermodynamically more stable oxazolidine **4**.[5] However, oxazolidine **4** was formed predominantly in an equilibrium mixture with **5** in the ratio 9 : 1 {$[\alpha]_D$ −275° (*c* 1.15, $CHCl_3$)} after filtration over alumina of a dilute solution of the crude 1,4-DHP **3** in n-C_5H_{12}–CH_2Cl_2 (1 : 3) (65% from **2**).

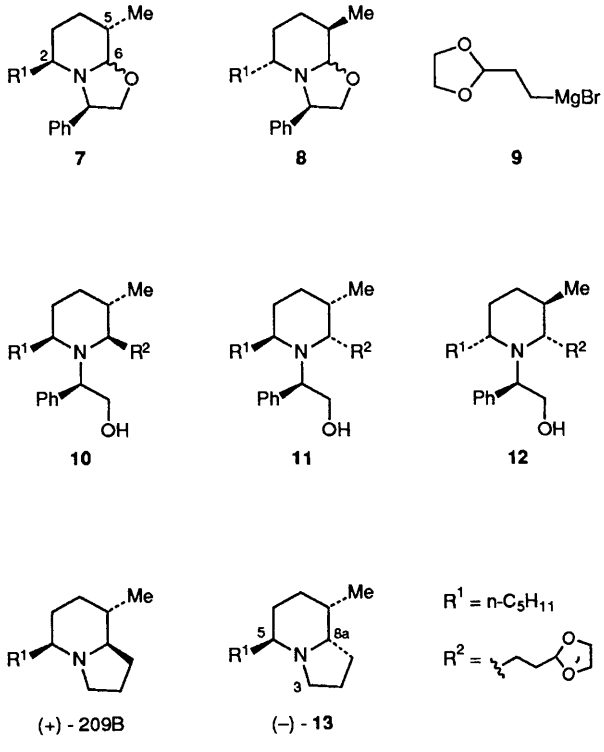
This oxazolidine mixture was treated with an excess of n-$C_5H_{12}MgBr$ in Et_2O at −78 °C for 2 h, then diluted with n-C_5H_{12}–CH_2Cl_2 (1 : 1) and filtered over alumina affording new oxazolidines **7** and **8** as an inseparable 3 : 1 mixture in 75% total yield. Noteworthy during this alkylation at C-2 by the opening of the oxazolidine ring in **4** and **5** is the concomitant recyclization to give oxazolidines **7** and **8** thereby not only activating the 6-position (undetermined stereochemistry) of the piperidine nucleus but also directing the stereochemistry of the 5-methyl group in a thermodynamically more favourable equatorial orientation. The crude mixture of **7** and **8** was then added to an excess of the Grignard reagent **9**[6] in tetrahydrofuran (THF). Flash chromatography of the reaction product on silica gel furnished compounds **10**, **11** and **12** whose ratio (5 : 3 : 2) in the mixture was estimated by HPLC.

The stereochemical assignment for each of these compounds could be established on the basis of the corresponding indolizidine structure subsequently elaborated. Thus, hydrogenation of the major isomer **10** (*ca.* 35% isolated yield) in an acidic medium directly furnished the indolizidine (+)-209B (80%). The salt (+)-209B·HCl crystallized as colourless needles (MeOH–EtOAc), m.p. 191 °C, $[\alpha]_D$ +54° (*c* 4, MeOH). The structure of the free base, colourless oil, $[\alpha]_D$ +98° (*c* 3, MeOH); {lit[3] (−)-209B, $[\alpha]_D$ −94.3° (*c* 1.85, MeOH)}, was confirmed by comparison with the literature data.[3] Similar reduction of the minor isomer **12** gave (−)-



1 2 3 6 5 4

Scheme 1 *Reagents and conditions*: i, Bu^nOH, (*R*)-(−)-phenylglycinol, reflux, 4 h; ii, $Na_2S_2O_4$ (2.5 mol dm^{-3}), K_2CO_3 (2.5 mol dm^{-3}), H_2O, Et_2O, 40 °C, 1 h; iii, filtration over alumina



7 8 9 10 11 12 (+) - 209B (−) - 13

209B, while the isomer **11** afforded the indolizidine (−)-**13** as a *colourless oil*, $[\alpha]_D$ −11° (*c* 0.66, MeOH), whose stereostructure was confirmed from the 200 MHz ^{1}H NMR spectrum which displayed characteristic signals for the protons at the 3, 5 and 8a positions.

This six-step synthesis of indolizidine (+)-209B from 3-picoline needed only one chromatographic separation with an overall yield of 8–10%.

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