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A STEREOSELECTIVE SYNTHESIS OF *dl*-3-EPIULEINE

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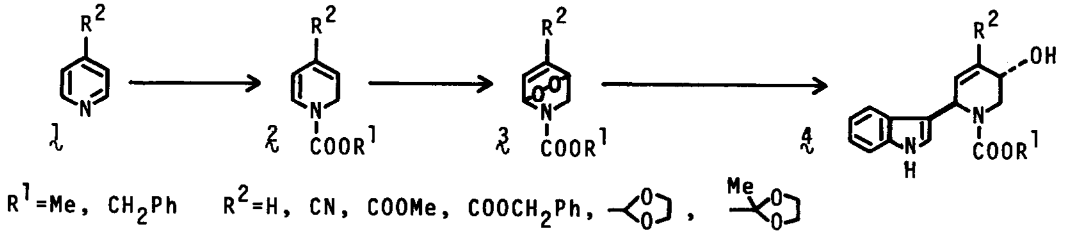
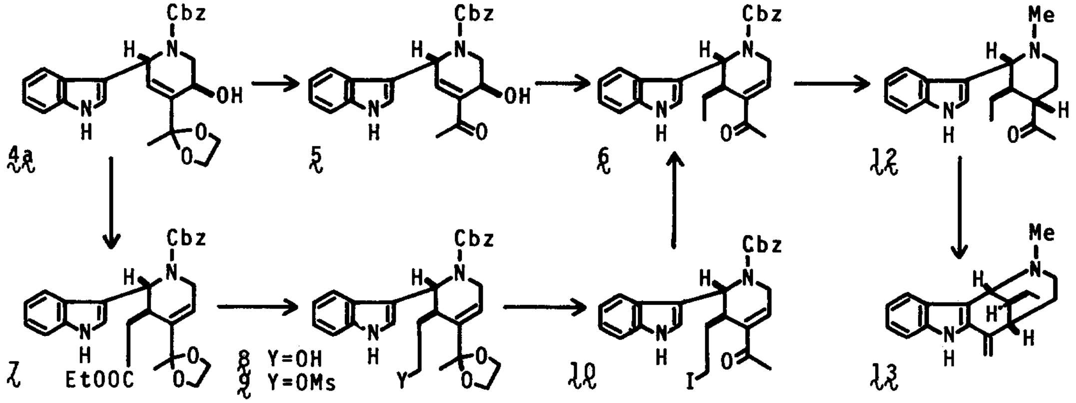
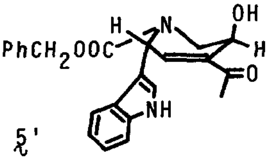
Summary: A stereoselective synthesis of an indole alkaloid, 3-epiuleine, in racemic form is described. The key step involved is the ethylation of readily accessible compound 5 with Et_2CuLi.

Previously, we reported a new method to condense indole with substituted dihydropyridine derivatives (2) by utilizing a $SnCl_2$ effected ring-opening reaction of endoperoxides (3).[1] The condensation products (4) seemed to be useful starting materials for the synthesis of indole alkaloids, and we wish to describe here a stereoselective synthesis of *dl*-3-epiuleine[2] (13) starting from one of the condensation products (4a).



The enone (5), mp 179-181° (decomp.), obtained in 89% yield by refluxing 4a in acetone in the presence of p-TsOH, was treated with Et_2CuLi in THF-Et_2O to give an enone (6), mp 112-113.5°, with an ethyl substituent, in 60% yield as the sole product. The trans relationship between ethyl and indolyl groups in 6





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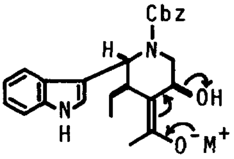

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was clarified by an alternative synthesis of this compound by way of a stereochemically definite compound 7, mp 159-160°, which was obtained in 25% yield by the modified Claisen rearrangement[3] of 4a [$MeC(OEt)_3$, Me_3CCOOH, DMF, 120°, 26 hr]. The alcohol (8), obtained by $LiAlH_4$ reduction of 7 (95% yield), was mesylated to 9 (88% yield), which was then converted to an iodide (10), mp 135-136° (decomp.), by warming with NaI in DMF (90°, 30 min, 63% yield). Catalytic hydrogenation over 10% Pd-C in dimethoxyethane in the presence of Et_3N was an effective condition only for the hydrogenolysis of the iodine group in 10, producing 6 in 79% yield.

Conformation of the compound 5 was tentatively assumed to be as shown by 5'. Et_2CuLi approached to the enone system exclusively from the opposite side of indole, which was situated in the pseudo-axial configuration, and the reaction was completed by elimination of the hydroxyl group adjacent to the enolate anion as illustrated in formula 11.

The compound 6 was hydrogenated over 10% Pd-C in MeOH in the presence of CH_2O, followed by the treatment with NaOMe in MeOH in order to stabilize the MeCO function, to obtain 12 in 59% yield. Final step of the synthesis was achieved by refluxing 12 in $CHCl_3$ in the presence of p-TsOH, and the product 13, obtained in 32% yield, was proved to be identical with the authentic sample of *dl*-3-epiuleine (mixed mp, ms, ir, ^1H- and ^{13}C-nmr spectra).

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