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TOTAL SYNTHESIS OF (±)-DECARBOMETHOXYNAUCLECHINE

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Summary: Both diastereoisomers of (±)-decarbomethoxynauclechine (I) have been synthesized, but stereochemical assignments cannot be made unequivocally.

An alkaloid isolated from Nauclea latifolia in very small amounts (1 mg) has been assigned[1,2] structure I, corresponding to decarbomethoxynauclechine but of undefined stereochemistry, mainly on the basis of its mass spectrum and analogy with nauclechine.[3] We have now synthesized, in racemic form, both diastereoisomers of formula I. Isomer A, mp 219-220°C (decomp.), and isomer B, mp 218-221°C (prior phase change, 213°C), give very similar mass spectra, the mass spectrum of the natural alkaloid (presumably optically active), mp 222°C, is also similar, and where differences are observed, they may arise from differences in operating conditions. The most distinctive spectroscopic difference between isomers A and B is seen in the 400 MHz ^{1}H nmr spectra of their O-acetyl derivatives: the C-3 proton of acetyl-A appears at τ 6.07, while that of acetyl-B is at τ 5.96, and both show similar couplings (10 and 0 Hz) to vicinal protons; the C-19 proton of acetyl-A appears at τ 3.36 with J values of 9 and 1.5 Hz, while that of acetyl-B is at τ 4.09 with J values of 5.5 and 2 Hz However, because of the nature of the flexible seven-membered ring, it is not possible to make unequivocal configurational assignments to the isomers on the basis of these data.

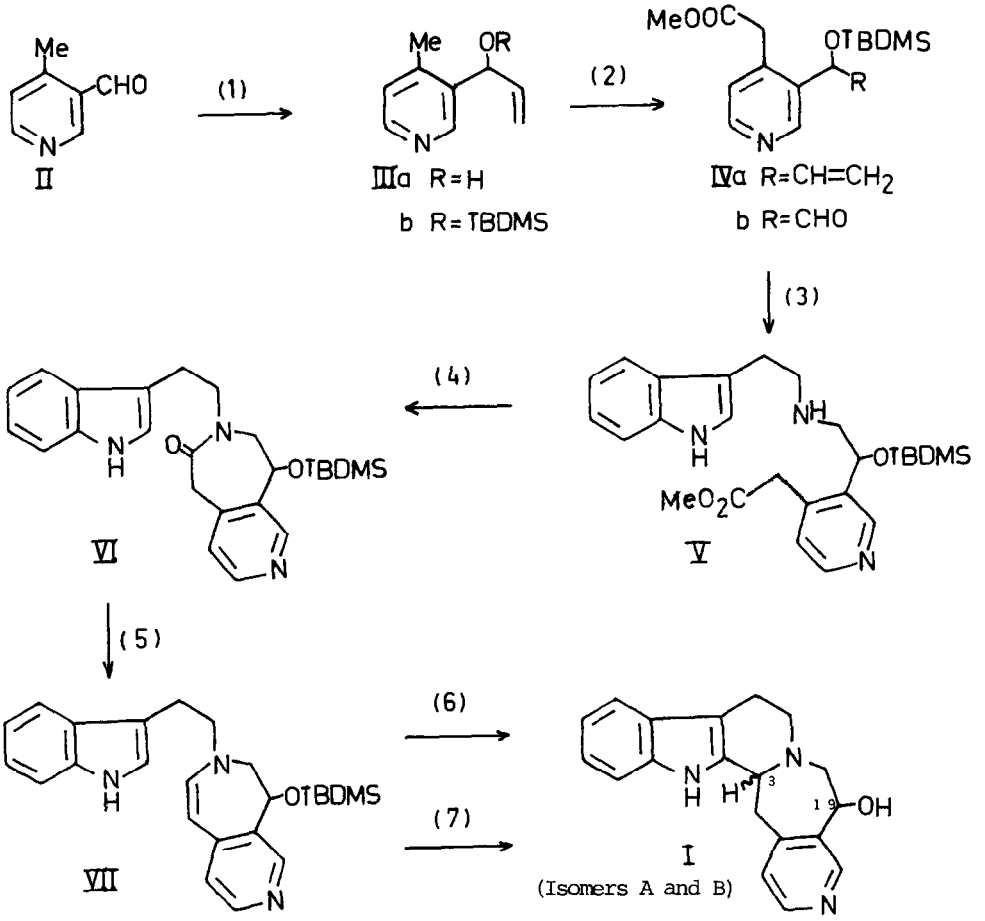
In our synthetic route, 4-methylnicotinaldehyde (II)[4] was converted to IVa by standard procedures outlined in the Chart; we found that the vinyl substituent provided the best form of a protected aldehyde during these operations. Careful ozonolysis of IVa provided the unstable aldehyde IVb, which was converted to V by reductive coupling with tryptamine; for preparative purposes,

the conversion of IVa to V was carried through without isolation of intermediates: after IVa in dichloromethane-methanol at -40°C had been saturated with ozone, the solution obtained was placed under argon, treated with dimethyl sulfide, and allowed to warm up to room temperature; the solution was diluted with dichloromethane, washed with brine, stirred with excess anhydrous sodium sulfate, and tryptamine was added; after filtration, the solvent was removed and replaced with methanol under argon, sodium borohydride was added, the mixture was stirred for 17 hours and a standard work up provided intermediate V.

Lactamization of V, while preserving the protected alcohol function, proved to be a difficult step, and it was found that the cleanest conversion, albeit in only moderate yield, was achieved by heating V with anhydrous potassium carbonate in refluxing methanol.

We had previously experienced difficulty in carrying out the Bischler-Napieralski reaction on amides related to VI, so we carried out the next cyclization by a method reported recently[9] that effectively transforms the cyclization into a Pictet-Spengler process. diisobutylaluminum hydride reduction converted VI to enamine VII[10], which was cyclized by treatment with acid. The reduction appeared to stop when 50% of VI had reacted, but unchanged VI could be recovered and recycled, providing a satisfactory net conversion of VI to VII. When the cyclization of VII was completed in formic acid, and the silyl protecting group was subsequently removed, an excellent yield of tetracyclic product I was obtained; this was found to be a 3:1 mixture of isomers A and B, separable by chromatography. Alternatively, the cyclization was carried out in methanolic hydrogen chloride and, under these conditions, a separate deprotection step was unnecessary, and I could be isolated directly; however, the ratio of isomers was surprisingly different, with isomer B being the dominant product (1·5 A:B).

Our synthesis has thus provided both diastereoisomers of decarbomethoxynauclechine (I), but we are at present unable to assign unequivocally their stereochemistry or to provide a sound explanation for the difference in the ratio of isomers formed in the final step. The data available for the N. latifolia alkaloid[1,2] are not sufficient to prove the identity of the natural material with either of the synthetic products, but none of our data contradicts the previous structural proposal[1].



(1) II, H_2C=CHMgBr, THF, reflux, 30 min; H_2O → IIIa (73%). (Ref. 5).
IIIa, t-$BuMe_2SiCl$, imidazole, DMF, r.t., 15h → IIIb (73%). (Ref. 6).

(2) IIIb, LDA, THF, -78°C; $(MeO)_2CO$, -78°C to r.t.; H_2O → IVa (60%). (Ref. 7).
IVa, O_3, CH_2Cl_2-MeOH, -40°C; Me_2S, -40°C to r.t, 3h → IVb (Ref. 8).

(3) IVb, tryptamine, anhyd. Na_2SO_4, CH_2Cl_2, r.t., 1h;
$NaBH_4$, MeOH, r.t., 17h → V (50% from IVa).

(4) V, anhyd. K_2CO_3, MeOH, reflux, 18h → VI (40%).

(5) VI, DIBAH (4 eq.), THF, -78°C, 1h; aq. NH_4Cl, -78°C to r.t.
→ VII (84% conversion).

(6) VII, 90% HCOOH, r.t., 11h; n-Bu_4NF, THF, r.t., 1h → I (78%; 3:1 A.B).

(7) VII, 10% HCl in MeOH, r.t., 14h → I (65%; 1:5 A:B).

All isolable new compounds provided satisfactory ir, ^1H nmr, and high resolution mass spectra.

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10. ^{1}H nmr spectrum included one-proton doublets, J = 10 Hz, at τ 3.77 and 5.12.

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