THE SYNTHESIS OF (-)-ISORETRONECANOL, (-)-TRACHELANTHAMIDINE, AND (-)-SUPINIDINE FROM (S)-PROLINE

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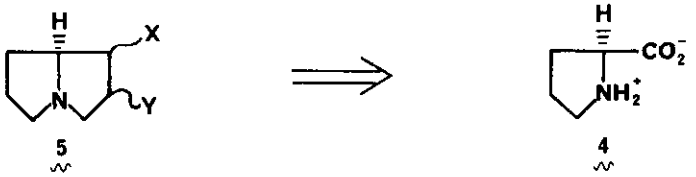
Abstract - Dieckmann cyclisation of (S)-N,2-di(carboethoxymethyl)pyrrolidine, made from (S)-proline, gave (8S)-1-carboethoxypyrrolizidin-2-one, which was then converted into (-)-isoretronecanol, (-)-trachelanthamidine, and (-)-supinidine.

Much effort has been spent on developing syntheses of the necine bases which characterise the pyrrolizidine alkaloids. However, so far as we are aware, these syntheses have all yielded racemic products, which required resolution, with two exceptions: Robins and Sakdarat's[1] preparation of the (+)-, and (-)-isomers of isoretronecanol (1), trachelanthamidine (2), and supinidine (3), all of better than 80% optical purity, from (2S,4R)-4-hydroxyproline (in which the hydroxyl function, as a formate ester, was used to control the stereochemistry of a catalytic hydrogenation, after which it was removed); and a recently described preparation by Takano *et al.*[2] of (+)-trachelanthamidine, of 33% optical purity, from an achiral precursor (using camphor-10-sulphonate to achieve chiral induction in a cyclisation).

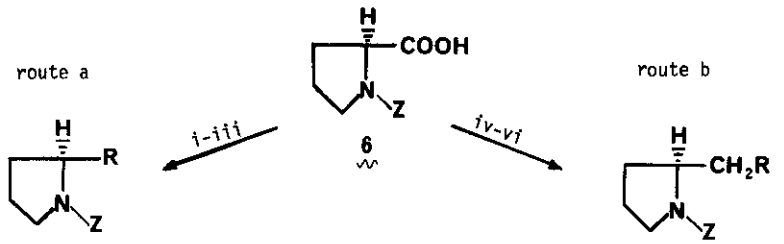
It appeared to us that (S)-proline might provide a convenient starting material for the chiral synthesis of (8α)-necine bases (e.g. 4 → 5) and we now report the successful application of this idea to the preparation of (-)-1, (-)-2, and (-)-3, all of high optical purity.



5 4

Guided by the Geissman-Waiss synthesis of (±)-retronecine[3], we decided to gain entry to the pyrrolizidine system by Dieckmann cyclisation of the diester 14. Of crucial importance was the homologation of the acid side-chain of (S)-proline without loss of chirality. Using commercially available N-Cbz-(S)-proline (6) we achieved this by two conventional procedures: (a) Arndt-Eistert homologation, and (b) a reduction-tosylation-cyanide displacement-ethanolysis sequence (see Scheme I). Of these, the second was felt to be safest, in terms of retention of chirality, (since borane-dimethyl sulphide reduction of α-amino acids is known to take place without racemisation[4], whereas the Arndt-Eistert route was more questionable in this regard). In fact, both

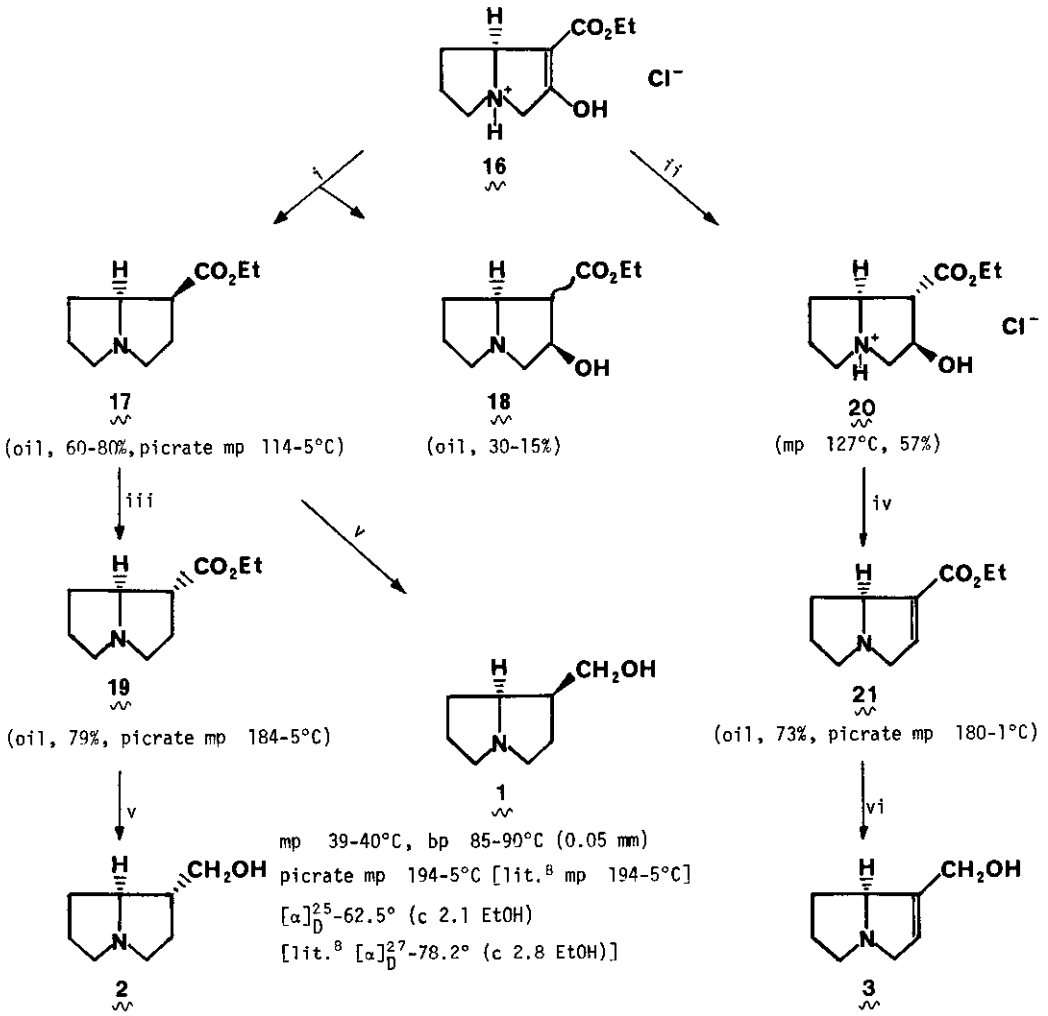
Scheme I



(i) $(COCl)_2$, DMF cat.; (ii) CH_2N_2; (iii) Ag_2O, EtOH; (iv) BH_3-Me_2S; (v) TsCl, Py; (vi) NaCN, DMSO; (vii) Pd-C/H_2; (viii) (a) HCl/EtOH, (b) H_2O, (c) HCl/EtOH; (ix) $BrCH_2CO_2Et/Na_2CO_3$; (x) NaOEt; (xi) $AcOH/H_2O$.

procedures gave optically pure[5] product, isolated as the crystalline hydrochloride 13 (70% from 6 by either route). This material was converted to the diester 14 and then cyclised under equilibrium control conditions[6] to give the desired pyrrolizidine keto-ester, which appears to exist predominately in the enol-form and which was isolated as 15 (75% from 13).

Scheme II



(i) Rh/Al_2O_3 5%, 30-50 psi, $AcOH/H_2O$ 1:1; (ii) $NaBH_3CN/H_2O$; (iii) NaOEt/EtOH; (iv) MsCl/NEt_3, Δ; (v) $LiAlH_4$; (vi) i-Bu$\frac{1}{2}$AlH.

The keto ester (16) was regenerated from 15 and then converted into 1, 2, and 3 as shown in Scheme II. Catalytic hydrogenations gave mixtures of 17 and 18, separated by column chromatography

(silica gel, $CHCl_3$-MeOH-NH_3 80:5:1→80:15:1). The *endo*-stereochemistry of 17 was confirmed by its ready epimerisation[7] to the more stable *exo*-isomer (19), and the LAH reduction of 17 to (-)-1, and 19 to (-)-2, whose identities were confirmed by comparison with lit. data for the natural bases[8,9,10]. As thus prepared these two bases had diastereomeric purities of ≥ 95%, and enantiomeric excesses of ≥ 80%.

Conversion of 18 to (-)-3 was carried out as described by Tufariello and Lee[11] for the (±)-system, or alternatively by the sodium cyanoborohydride reduction of 16, which proceeded slowly but stereospecifically to 20 (an intermediate like 18 of potential value for the preparation of 2-hydroxylated necines) and thence to (-)-3. By either process (-)-3 was obtained in a state of high optically purity, (≥ 88% e.e.).

In summary we have demonstrated the feasability of the chiral synthesis of some necine bases from (S)-proline illustrated by the chiral syntheses of (-)-isoretronecanol, (-)-trachelanthamidine, and (-)-supinidine.

ACKNOWLEDGEMENT

We are grateful for financial support of this work provided by the Alberta Heritage Foundation for Medical Research, and the Natural Sciences & Engineering Research Council of Canada.

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Received, 24th May, 1982