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

Heinrich Rüeger and Michael Benn*

Department of Chemistry, The University, Calgary, Alberta, Canada, T2N 1N4

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 (-)-
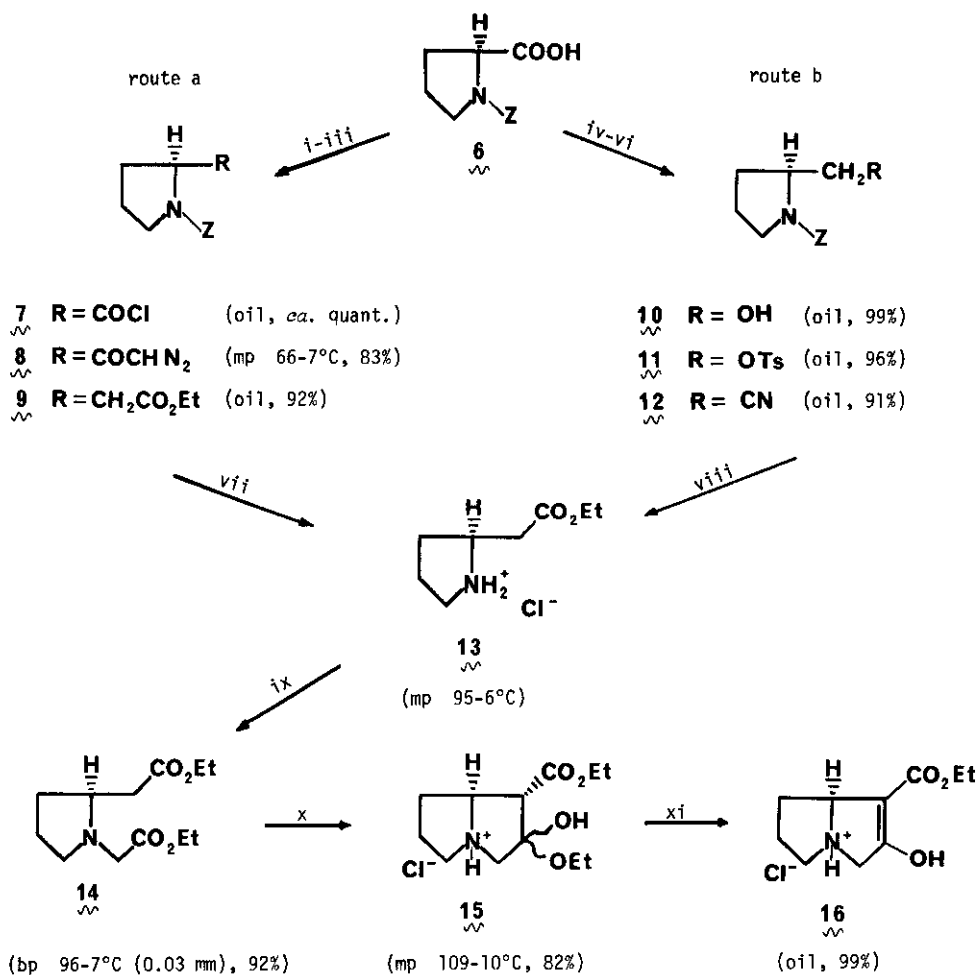supinidine.

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 race-
mic 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 func-
tion, 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 (+)-trache-
lanthamidine, 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.
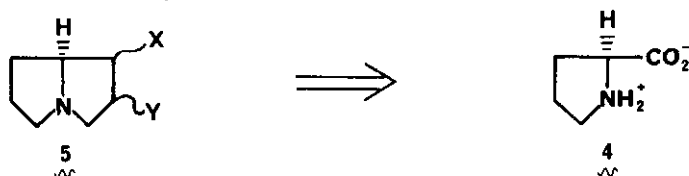
Guided by the Geissman-Waiss synthesis of (±)-retronecine[3], we decided to gain entry to the
pyrrolizidine system by Dieckmann cyclisation of the diester 14. Of crucial importance was the
homologation of the acid side-chain of (S)-proline without loss of chirality. Using commercially
available N-Cbz-(S)-proline (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 race-
misation[4], whereas the Arndt-Eistert route was more questionable in this regard). In fact, both
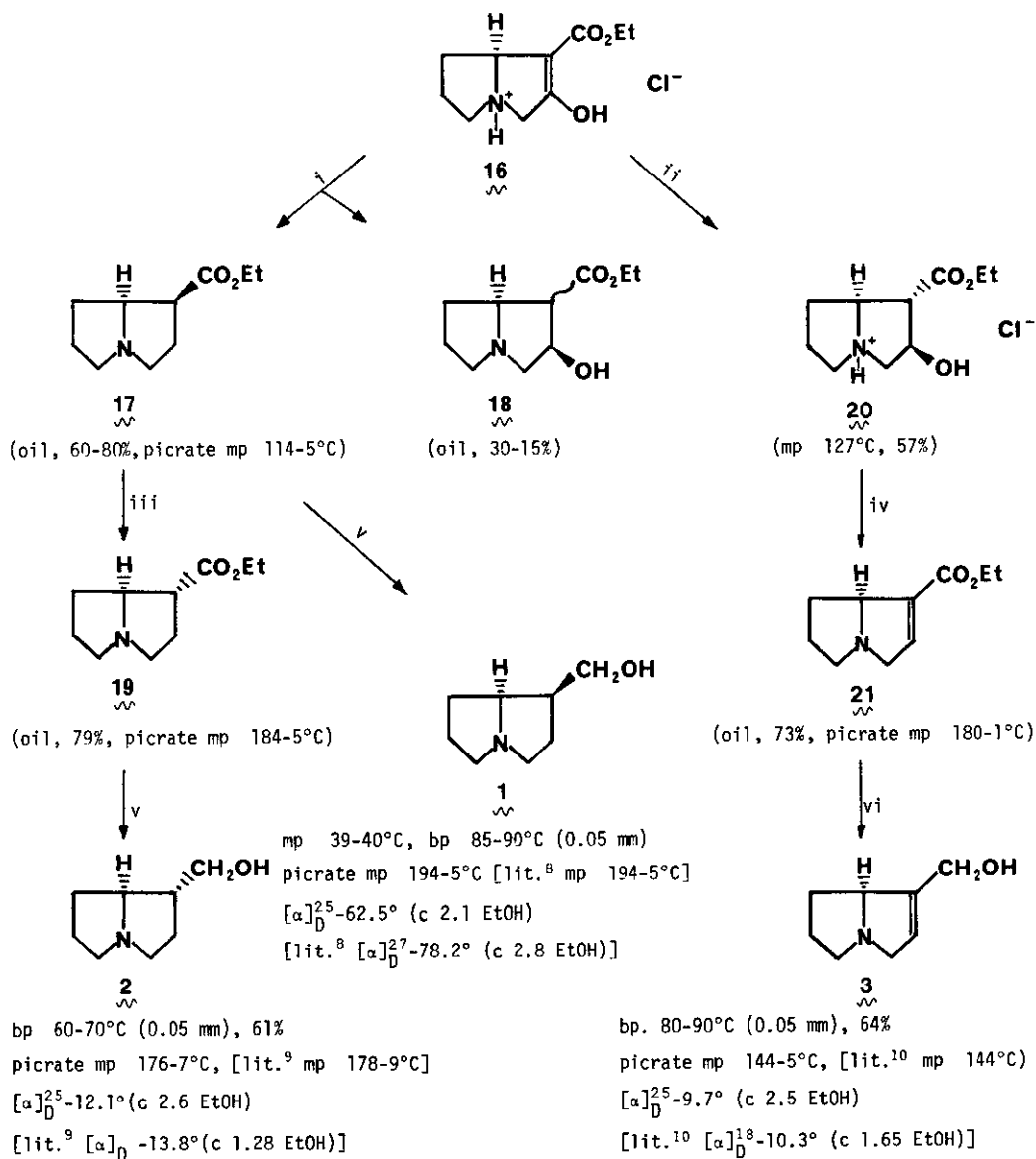
<center>Scheme I</center>

route a   (structure **6**)   route b

7 R = COCl   (oil, *ca.* quant.)   **10** R = OH   (oil, 99%)

8 R = COCHN$_2$ (mp 66-7°C, 83%)   **11** R = OTs (oil, 96%)

9 R = CH$_2$CO$_2$Et (oil, 92%)   **12** R = CN   (oil, 91%)

13 (mp 95-6°C)

14 (bp 96-7°C (0.03 mm), 92%)   **15** (mp 109-10°C, 82%)   **16** (oil, 99%)

(i) (COCl)$_2$, DMF cat.; (ii) CH$_2$N$_2$; (iii) Ag$_2$O, EtOH; (iv) BH$_3$·Me$_2$S; (v) TsCl, Py; (vi) NaCN, DMSO; (vii) Pd-C/H$_2$; (viii) (a) HCl/EtOH, (b) H$_2$O, (c) HCl/EtOH; (ix) BrCH$_2$CO$_2$Et/Na$_2$CO$_3$; (x) NaOEt; (xi) AcOH/H$_2$O.

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

16

17
(oil, 60-80%, picrate mp 114-5°C)

18
(oil, 30-15%)

20
(mp 127°C, 57%)

19
(oil, 79%, picrate mp 184-5°C)

21
(oil, 73%, picrate mp 180-1°C)

1
mp 39-40°C, bp 85-90°C (0.05 mm)
picrate mp 194-5°C [lit.[8] mp 194-5°C]
$[\alpha]_D^{25}$ -62.5° (c 2.1 EtOH)
[lit.[8] $[\alpha]_D^{27}$ -78.2° (c 2.8 EtOH)]

2
bp 60-70°C (0.05 mm), 61%
picrate mp 176-7°C, [lit.[9] mp 178-9°C]
$[\alpha]_D^{25}$ -12.1° (c 2.6 EtOH)
[lit.[9] $[\alpha]_D$ -13.8° (c 1.28 EtOH)]

3
bp. 80-90°C (0.05 mm), 64%
picrate mp 144-5°C, [lit.[10] mp 144°C)
$[\alpha]_D^{25}$ -9.7° (c 2.5 EtOH)
[lit.[10] $[\alpha]_D^{18}$ -10.3° (c 1.65 EtOH)]

(i) Rh/Al$_2$O$_3$ 5%, 30-50 psi, AcOH/H$_2$O 1:1; (ii) NaBH$_3$CN/H$_2$O; (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.

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