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A CONVENIENT SYNTHESIS OF (±)-RETRONECINE

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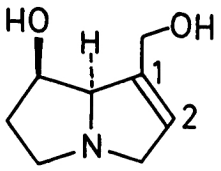
Retronecine (1), the necine base of physiologically active pyrrolizidine alkaloids was synthesized in racemic form from ethyl 2,3,5,6-tetrahydro-1H-pyrrolizine-7-carboxylate (2) in five steps.

Pyrrolizidine alkaloids containing retronecine (1) as the necine base are known to exhibit remarkable hepatotoxic and, in certain cases, carcinogenic properties.[1] The presence of a double bond between C-1 and C-2 in retronecine (1) was shown to be responsible for these physiological activities.[2] Recently synthetic efforts towards retronecine (1) have increasingly been made, culminating in the total synthesis of 1.[3] In this communication we wish to disclose a new, convenient synthesis of retronecine (1) in racemic form.

The published behaviors of enolates derived from β-dialkylamino-α,β-unsaturated carbonyl compounds[4] prompted us to examine γ-hydroxylation of the enolate generated from the unsaturated ester 2 as the key step of the synthesis. The known unsaturated ester 2[5] was obtained in high yield by a modification of Leonard's procedure[5a]: catalytic hydrogenation (Pd/C, room temp., 40 min, EtOH) of the readily available keto ester 3[5a] prepared from ethyl γ-iodobutyrate and benzylamine gave the unsaturated ester 2[6,7] (unstable, colorless oil, 96% yield). The unsaturated ester 2 was converted into the corresponding enolate on treatment with lithium diisopropylamide (LDA) (-78 °C, 100 min, THF).



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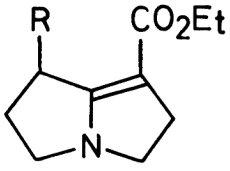
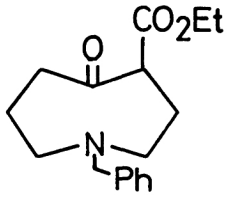


2 R = H
4 R = OH



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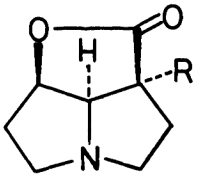
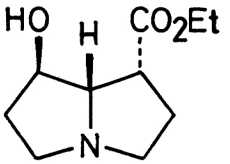


5 R = H
7 R = SePh



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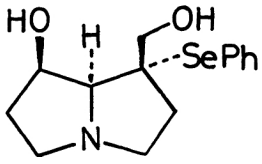

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The enolate was reacted with $MoO_5 \cdot Py \cdot HMPA$[8] (-78 °C, 20 min) to afford the desired γ-hydroxy-α,β-unsaturated ester 4[6] (unstable and colorless oil, 52% yield after purification[9a]). γ-Hydroxylation of the enolate with O_2-$P(OEt)_3$[10] also gave the desired compound 4 in relatively low yield (33%). Catalytic hydrogenation of the hydroxy ester 4 (PtO_2, room temp., 3 h, MeOH) gave the tricyclic lactone 5[6,11] [colorless oil, 44% yield after purification[9b], mp of the hydrochloride, 225 °C (decomp) (MeOH-ether)] and a hydroxy ester 6[6] (colorless oil, 26% yield after purification[9b]). Phenylselenylation of the lactone 5 using LDA and diphenyldiselenide (-50 °C, 90 min, THF-HMPA) afforded the selenide 7[6] (colorless oil, 21% yield after purification[9b]). Reduction of the selenide 7 with $LiAlH_4$ (-10 °C, 2 h, THF) yielded the diol 8[6] (amorphous solid, 95% yield after purification[9c]). Final conversion of the diol 8 into retronecine (1) was accomplished by the procedure reported by Robins[12]: oxidation of the diol 8 with 30% H_2O_2-AcOH (room temp., 1.5 h) and subsequent elimination of the selenoxide afforded (±)-retronecine (1)[6], mp 128.5-129.5 °C (acetone)[13] (53% yield after purification[9d]). The spectral properties (IR, ^{1}H-NMR and mass) and chromatographic mobility of synthetic retronecine (1) were identical to those of natural specimen.

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6) The IR, ^{1}H-NMR and mass spectral data of this compound were in accord with the structure assigned. Satisfactory microanalyses or exact mass spectral data were obtained for this compound.

7) Since this compound showed purity more than 95% by ^{1}H-NMR spectrum, it was used for the next reaction without further purification.

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9) By thin layer chromatography on: a) SiO_2 with CH_2Cl_2-EtOAc (3:1); b) Al_2O_3 with EtOAc; c) Al_2O_3 with $CHCl_3$-MeOH-conc.NH_4OH (200:20:0.5); d) Al_2O_3 with $CHCl_3$-MeOH-conc.NH_4OH (10:1:0.03).

10) a) J. N. Gardner, F. E. Carlon, and O. Gnoj, J. Org. Chem., 33, 3294 (1968).
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11) Viscontini has also synthesized this compound by different, somewhat longer route.[14] Our procedure to obtain this compound is much more convenient than that reported by Viscontini and his coworker.

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13) Lit. mp 130 °C[3a]; mp 129-130 °C[3c].

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