

A CONVENIENT SYNTHESIS OF (±)-RETRONECINE

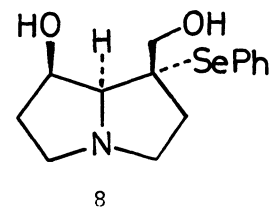
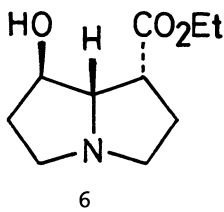
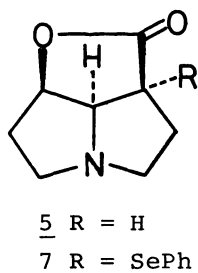
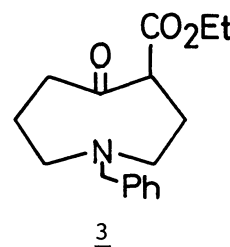
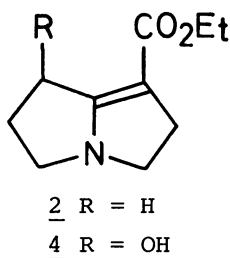
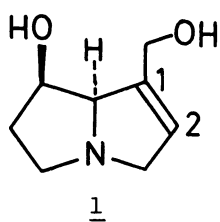
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Retronecine (1), the necine base of physiologically active pyrrolizidine alkaloids was synthesized in racemic form from ethyl 2,3,5,6-tetrahydro-1H-pyrrolizine-7-carboxylate (2) in five steps.

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 compounds⁴⁾ 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 2⁵⁾ 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).



The enolate was reacted with $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$ ⁸⁾ (-78 °C, 20 min) to afford the desired γ -hydroxy- α, β -unsaturated ester 4⁶⁾ (unstable and colorless oil, 52% yield after purification^{9a)}). γ -Hydroxylation of the enolate with $\text{O}_2\text{-P(OEt)}_3$ 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 6⁶⁾ (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 7⁶⁾ (colorless oil, 21% yield after purification^{9b)}). Reduction of the selenide 7 with LiAlH_4 (-10 °C, 2 h, THF) yielded the diol 8⁶⁾ (amorphous solid, 95% yield after purification^{9c)}). Final conversion of the diol 8 into retronecine (1) was accomplished by the procedure reported by Robins¹²⁾: oxidation of the diol 8 with 30% $\text{H}_2\text{O}_2\text{-AcOH}$ (room temp., 1.5 h) and subsequent elimination of the selenoxide afforded (\pm)-retronecine (1)⁶⁾, mp 128.5-129.5 °C (acetone)¹³⁾ (53% yield after purification^{9d)}). The spectral properties (IR, ¹H-NMR and mass) and chromatographic mobility of synthetic retronecine (1) were identical to those of natural specimen.

Acknowledgments: Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research, No. 57540303 to H. N.) is gratefully acknowledged. One of the authors (H. N.) would like to express his deep gratitude to Takeda Science Foundation for financial support.

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- 9) By thin layer chromatography on: a) SiO_2 with $\text{CH}_2\text{Cl}_2\text{-EtOAc}$ (3:1); b) Al_2O_3 with EtOAc; c) Al_2O_3 with $\text{CHCl}_3\text{-MeOH-conc. NH}_4\text{OH}$ (200:20:0.5); d) Al_2O_3 with $\text{CHCl}_3\text{-MeOH-conc. NH}_4\text{OH}$ (10:1:0.03).
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(Received November 16, 1982)