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TOTAL SYNTHESIS OF (±)-OTONECINE, A NECINE BASE OF PYRROLIZIDINE ALKALOIDS

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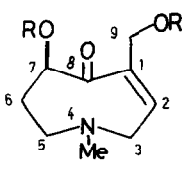
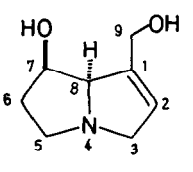
Abstract. *Otonecine (1), a representative necine base of hepatotoxic and carcinogenic pyrrolizidine alkaloids, was synthesized in racemic form from ethyl 1-hydroxy-2,3,5,6-tetrahydro-1H-pyrrolizine-7-carboxylate (5).*

Pyrrolizidine alkaloids containing otonecine (1) or retronecine (3) as the necine base are known to exhibit remarkable hepatotoxic and, in certain cases, carcinogenic properties:[1] otosenine (4)[2] and senkirkine[3] are the examples of pyrrolizidine alkaloids of otonecine type. 1,2-Unsaturation and esterification at C-9 in the necine base moiety of the alkaloids are the most important, structural requirements for these physiological activities.[4] While several groups including us reported the total synthesis of retronecine (3),[5] there seem to have been no reports of the synthetic studies on otonecine (1) in spite of its important physiological activities. Herein we wish to describe the first synthesis of otonecine (1) in racemic form.

We have chosen the known hydroxy ester 5 as the starting material, which was previously employed in our synthesis of (±)-retronecine (3).[5e] Michael addition of lithium thiophenolate to the α,β-unsaturated ester system in 5 (PhSH-THF, room temp., 2 h) afforded a tricyclic lactone 6[6] [mp 61-62 °C (benzene-hexane), 70%]. Treatment of the lactone 6 with mercuric diacetate (AcOH-H_2O, room temp. → 90 °C, 1 h) provided the hydroxy lactone 7[6] [mp 150 °C (dec.) ($CHCl_3$), 76%], which was converted to the corresponding methiodide 8[6] [mp 203 °C (dec.) (benzene-acetone), 95%] by the reaction with excess methyl iodide (acetone, reflux, 1 h). Treatment of the methiodide 8 with sodium hydride and phenylselenyl chloride (THF, room temp., 40 min.) gave the desired α-phyenylselenyl lactone 9[6] [mp 126-127 °C (benzene-hexane), 74%]. The crucial step in the present synthesis is the reduction of the lactone part in 9



1 R = H otonecine
2 R = Ac



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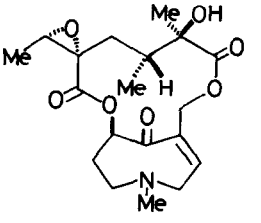
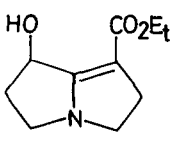


4 otosenine



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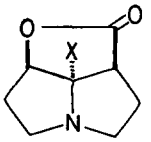
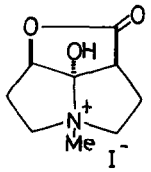


6 X = SPh
7 X = OH



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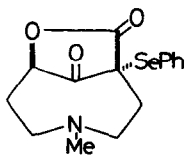

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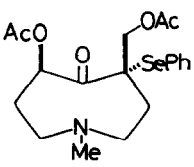

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in the presence of the phenylselenyl group, which is located alpha to the keto group and therefore readily undergoes reductive cleavage: addition of a variety of Lewis acids to the reducing system was found to be effective for the selective reduction of the lactone moiety in 9. Thus, reduction of 9 with diisobutylaluminum hydride in the presence of diethylaluminum chloride (toluene, 45 °C, 1 h) followed by acetylation[7] (Ac_2O-Py, room temp., 5 h) gave the desired diacetate 10[6] (colorless oil, ca. 17% overall yield after purification by preparative TLC on alumina with $CHCl_3$). Oxidation of the phenylselenyl group in 10 with 30% hydrogen peroxide (AcOH, room temp., 2 h) and subsequent elimination of the resulting phenylselenoxide afforded (±)-otonecine diacetate (2)[6] (colorless oil, 53% yield after purification by column chromatography on alumina with EtOAc), the spectral properties (IR, ^{1}H-NMR, and mass) of which were identical to those of authentic specimen derived from natural otonecine (1). Finally the methanolysis of the diacetate 10 (NaOMe-MeOH, room temp., 30 min.) afforded (±)-otonecine (1) (colorless oil, 90% yield after purification using the ion-exchange resin Amberlite IRC-50). Spectral properties (IR, ^{1}H-NMR, and mass) and chromatographic mobility of synthetic otonecine (1) were identical to those of natural specimen.

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6. Satisfactory IR, ^{1}H-NMR, mass, and exact mass spectral data were obtained for this compound.

7. The reduction product (a diol corresponding to the diacetate 10) was a very polar compound and difficult to handle, so that the product was isolated as the diacetate 10 after acetylation.

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