AN IMPROVED SYNTHESIS OF (+)-HELIOTRIDINE

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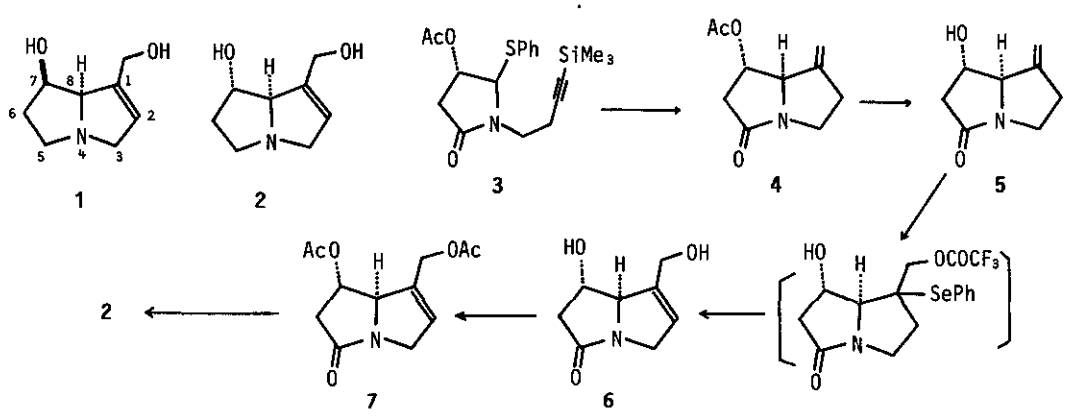
Abstract —— An alternative synthesis of (+)-heliotridine was achieved from 7-hydroxy-1-methylene-hexahydro-3H-pyrrozin-5-one, through conversion of exo-methylene to allylic alcohol part.

The challenging structures and diverse biological activity of pyrrolizidine alkaloids[1] containing $\Delta^{1,2}$-unsaturated dihydroxynecine base[2] such as retronecine (**1**)[3] and heliotridine (**2**)[1,3a,4] have stimulated a great deal of interest in their synthesis. Due to their intriguing chemical structures and their characteristic pharmacological activities, unsaturated dihydroxypyrrolizidine alkaloids are attractive synthetic targets. As an extention of the previous work,[5] we investigated an alternative synthesis of (+)-heliotridine from 7-acetoxy-1-methylene-hexahydropyrrolizin-3H-5-one (**4**),[4d,5] which was obtained through the radical cyclization by the use of **3**. Our approach to **2** involves an effective conversion of exo-methylene group at 1-position to the allylic alcohol part. The results of our studies[6] are described in this paper. Conversion of **5**, obtained by hydrolysis of **4**, to **6** was effectively carried out as described in detail in the experimental section. Trifluoroacetoxy phenylselenylation of **5** by treatment with phenylselenyl trifluoroacetate,[7] formed from silver trifluoroacetate and phenylselenyl chloride, followed by hydrolysis with $NaHCO_3$ and oxidation with 30 % hydrogen peroxide yielded **6**. Acetylation of **6** with acetic anhydride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine afforded the diacetate (**7**), the spectral data of which are identi cal in all respects with those of the literature.[5] For the further confirmation of these structures, **7** was reduced with lithium aluminum hydride to yield (+)-heliotridine (**2**),[3a,4d] $[\alpha]_D^{28}$=+29.0 (c 0.1, MeOH), (lit.,[3a] $[\alpha]_D^{25}$=+30.3° (c 1.6,

MeOH)), which was identified by direct comparison with an authentic sample of (+)-heliotridine donated by Professor Chamberlin, Department of Chemistry, University of California, Irvine.



EXPERIMENTAL

^{1}H nmr spectra (in $CDCl_3$) were taken with a Varian EM-390 (90 MHz) and Bruker AM-400 instrument (400 MHz). Mass spectra (ms) were recorded with Hitachi RMU-7L spectrometer at 70 eV.

(7S,8R)-7-Hydroxy-1-methylene-hexahydro-3H-pyrrolizin-5-one (5) —— A mixture of **4** (1 g, 5.1 mmol) , MeOH (6 ml) and 20 % K_2CO_3 (6 ml) was stirred for 4 h at room temperature. The mixture was extracted with CH_2Cl_2 and then $CHCl_3$. The combined extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with $CHCl_3$-MeOH (98:2) afforded **5** (780 mg, 99% yield)) as an oil, ^{1}H nmr ($CDCl_3$) δ 2.43-2.78 (4H, m), 2.83-3.19 (1H, m), 3.87 (1H, dq, J=6, 6 Hz), 4.17-4.53 (2H, m), 5.09 (1H, broad s), 5.19 (1H, broad s). Ms m/z 153 (M^+)

(7S,8R)-7-Hydroxy-1-hydroxymethyl-5,6,7,8-tetrahydro-3H-pyrrolizin-5-one (6) —— To a mixture of silver trifluoroacetate (641 mg, 2.8 mmol) and tetrahydrofuran (6 ml) was added phenylselenyl chloride (459 mg, 2.4 mmol). To this solution was added a solution of **5** (360 mg, 1.95 mmol) in tetrahydrofuran (3 ml) at -10°C. After addition, the mixture was stirred at room temperature for 2 h. The mixture was extracted with ether. The extract was evaporated after removal of the insoluble precipitate by filtration. A mixture of the resulting residue, MeOH (7.5 ml), H_2O (2.5 ml) and $NaHCO_3$ (323 mg) was stirred at room temperature for 2

h and was extracted with CH_2Cl_2. The extract was evaporated. To a solution of the remaining residue in tetrahydrofuran (2 ml) was added 0.3 ml of 30 % H_2O_2 under ice-cooling. After the stirring had been continued at the same temperature for 10 min, the mixture was further stirred at room temperature for 2.5 h. The solvent was removed and the resulting residue was chromatographed on silica gel. Elution with MeOH-ethyl acetate (1:2) afforded **6** (244 mg, 74 % yield) as an oil, ^1H nmr ($CDCl_3$) δ 2.41-2.88 (2H, m), 2.98-3.30 (1H, m), 3.81-3.44 (1H, m), 4.21-4.44 (4H, m), 5.23 (1H, broad s, OH), 5.60 (1H, s), electron impact ms did not give M^+, CI ms m/z 170 (M^++1).

(7S,8R)-7-Acetoxy-1-acetoxymethyl-5,6,7,8-tetrahydro-3H-pyrrolizin-5-one (7) —— To a mixture of **6** (169 mg, 1 mmol), triethylamine (150 mg, 1.5 mmol), 4-dimethylaminopyridine and CH_2Cl_2 (2 ml) was added acetic anhydride (216 mg, 2 mmol) at room temperature under stirring. After the stirring had been continued for 2 h, the mixture was diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 5 % $NaHCO_3$ and dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on silica gel (hexane-ethyl acetate, 1:1) to give **7** (235 mg, 93 % yield) as an oil, the spectroscopic data of which were identical with those of the authentic sample appeared in the literature.[4d]

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