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ENANTIOSPECIFIC SYNTHESIS OF OPTICALLY ACTIVE NATURAL (+)-CONHYDRINE FROM (S,S)-TARTARIC ACID

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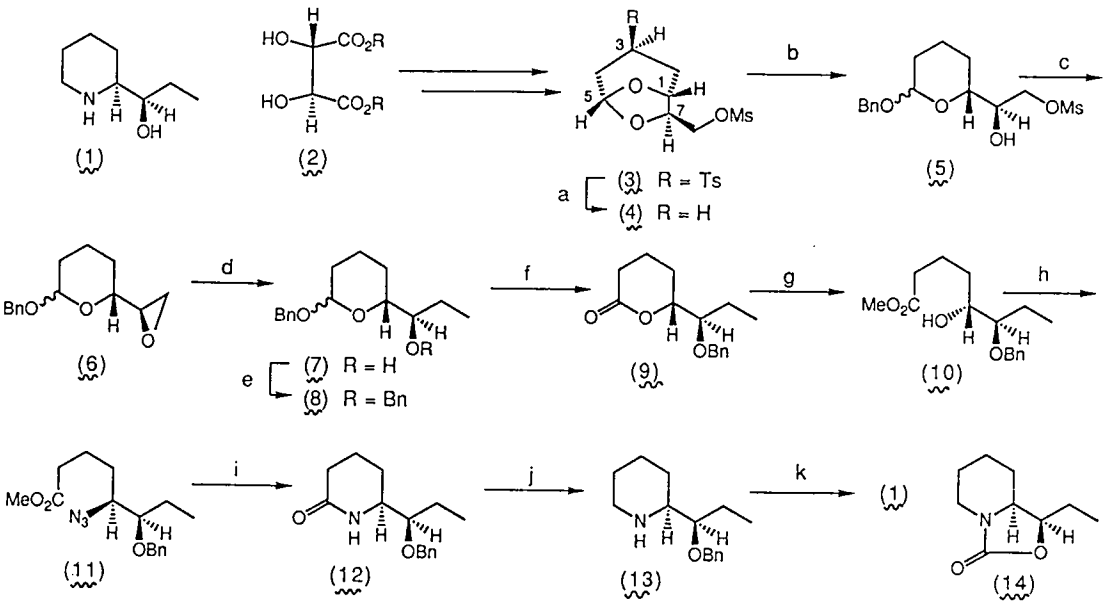
Summary: The first enantiospecific synthesis of (+)-conhydrine, one of the poisonous alkaloids of the hemlock was achieved via partial ring opening of 6,8-dioxabicyclo[3.2.1]-octane skeleton prepared from (S,S)-tartaric acid.

(+)-Conhydrine (1)[1] is one of the poisonous alkaloids of the hemlock, Conium maculatum, whose extracts were used in the ancient Greece for the execution of criminals. The structure of (+)-conhydrine including the absolute stereochemistry has been established as (2S)-((1'R)-hydroxypropyl)piperidine (1).[2] Although syntheses of optically active natural 1 by way of optical resolution of racemic 1 and of a synthetic intermediate 2-pyridylethylcarbinol have been reported,[3] there has been no enantiospecific synthesis of 1[4] starting with a configurationally defined chiral compound, that means synthetic verification of the structure of natural (+)-1. We wish to report here the first enantiospecific synthesis of natural (+)-1 from (S,S)-tartaric acid (2 R=H). The synthesis of (+)-1 described is featured by mild alcoholysis of 6,8-dioxabicyclo[3.2.1]octane skeleton prepared from 2 (R=H) and introduction of the nitrogen functionality with inversion of configuration of one of the hydroxyl groups.

(+)-(1R,5R,7R)-7-Mesyloxymethyl-6,8-dioxabicyclo[3.2.1]octane (4) ($[\alpha]_D^{20}$ +62.7° ($CHCl_3$)) was synthesized as an oil by reductive desulfurization of the 3-tosyl-derivative (3) (mp. 106-108 °C, $[\alpha]_D^{20}$ +49.6° ($CHCl_3$)) easily obtained in 54% overall yield from diethyl (S,S)-tartrate (2 R=Et) according to the reported method.[5] Although it has been known that unsubstituted 6,8-dioxabicyclo[3.2.1]octane is highly susceptible to polymerize in the presence of a Lewis acid such as BF_3-Et_2O,[6] we were very curious to open the 7-substituted bicyclic (4) by alcoholysis producing a pyranoid acetal of type (5). The desired partial ring opening was realized by treatment of 4 with benzyl alcohol in the presence of BF_3-Et_2O at the room temperature to lead to an acetal (5) in good yield (74%). Homologation with the Gilman's reagent on the terminal position of the epoxide (6) obtained by treatment of 5 with K_2CO_3, gave an alcohol (7). Protection of the alcohol as benzyl ether (8) followed by oxidation of the acetal portion on treatment successively with m-chloroperbenzoic acid (MCPBA) and Et_3N[5b] afforded a lactone (9) (IR $\nu_{C=O}$:1730 cm^{-1}). Methanolysis of 9 followed by the Mitsunobu type reaction of the ester-alcohol (10) using hydrazoic acid[7] gave an azido ester (11) ($[\alpha]_D^{20}$ +7.7° ($CHCl_3$); IR $\nu_{C=O}$ 1730, ν_{N_3} 2090 cm^{-1}). Cyclization of the intermediate amino ester obtained by reduction of 11 led to a lactam (12) ($[\alpha]_D^{20}$ +9.4° ($CHCl_3$); IR $\nu_{C=O}$ 1645 cm^{-1}) in 82% overall yield. Reduction of the lactam (12) with $LiAlH_4$ afforded O-benzylconhydrine (13) which was deprotected by hydrogenolysis to lead in 70% overall yield to (+)-conhydrine (1) as a crystal (mp. 119-121 °C; $[\alpha]_D^{20}$ +8.9° (EtOH)) (lit.[1a] mp. 121 °C; $[\alpha]_D^{18}$ +10.0° (EtOH)). The ^{1}H-NMR, ^{13}C-NMR, and IR spectra were identical with those for the authentic racemic 1.[4b,c]



(a) Na (10 equiv) / EtOH (10 equiv) / THF / -20°C / 2h (78 %) ; (b) $PhCH_2OH/BF_3$-Et_2O (2eq) / r.t. / 15h (74 %)
(c) K_2CO_3 / MeOH / 0°C / 0.5h (92 %) ; (d) Me_2CuLi / Et_2O / -5°C / 4h (90 %) ; (e) NaH / $PhCH_2Br$ / DME / r.t. / 15h (79 %)
(f) i) MCPBA / BF_3-Et_2O (cat.) / CH_2Cl_2 / r.t. / 2h ii) Et_3N / 0°C / 1.5h (75 %) ; (g) K_2CO_3/MeOH/0°C/2h (quant.)
(h) HN_3 / Ph_3P / DEAD / benzene / r.t. / 2h (75 %) ; (i) i) H_2 / Pd-black / MeOH ii) toluene / 120°C / 15h (82 %)
(j) $LiAlH_4$ / THF / r.t. / 0.5h (80 %) ; (k) H_2 / 5% Pd-C / EtOH / concd.HCl (cat.) (88 %)

The synthetic (+)-1 was converted by a known method [4b] into a oxazolidone derivative (14) which showed also identical spectral properties with those for the authentic racemic one ((±)-14) [4b] and which did not show any trace of the signals corresponding to the threo form ((±)-epi-14) [8] in the ^{1}H-NMR spectrum.

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References and Notes

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