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# Synthesis of (R)-(-)-O-Methyljoubertiamine

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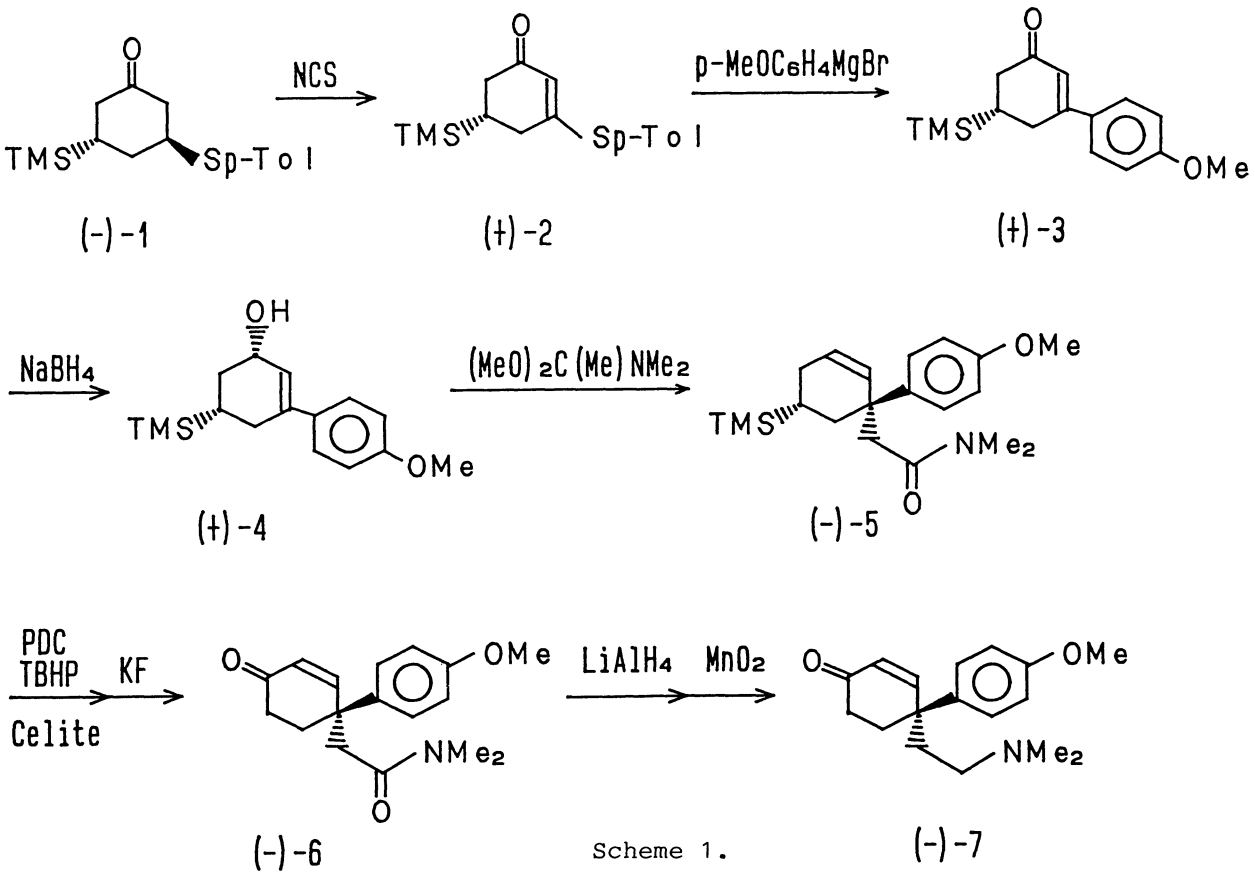
The title compound was synthesized by utilizing [3,3]sigmatropic rearrangement of 3-substituted 2-cyclohexenol derivative for the construction of optically active quaternary carbon center.

(R)-(-)-O-Methyljoubertiamine (**7**) is a minor alkaloid isolated from Sceletium species in 1981.[1] Several reports on the synthesis of racemic **7** are known,[2] but no synthetic report on optically active one has appeared. In this paper we will report a short step synthesis of (R)-(-)-**7**.

Our synthetic strategy involves the stereoselective reduction of the chiral cyclohexenone derivative **3** to the corresponding chiral 2-cyclohexenol derivative **4**, which chirality is utilized for the construction of optically active quaternary carbon center by the chirality transfer via [3,3]sigmatropic rearrangement (Scheme 1). The synthesis was started with the oxidation of optically pure (-)-**1**[3] with N-chlorosuccimide (NCS) in $CCl_4$ at 0 °C and the vinylsulfide (+)-**2** [mp 99.5-100 °C, $[\alpha]_D^{21}$+102.8°(c 1.00, $CHCl_3$)] was obtained in 72% yield. The reaction of p-methoxyphenylmagnesium bromide in the presence of CuI gave the enone (+)-**3** [mp 81.0-81.5 °C, $[\alpha]_D^{25}$+81.4°(c 1.02, $CHCl_3$)] in 66% yield.[4] Reduction of (+)-**3** with sodium borohydride at 0 °C followed by chromatographical purification gave diastereomerically pure (+)-**4**, which homogeneity was confirmed by $^{13}$C-NMR, as a crystalline product in 96% yield [88%, after recrystallization from hexane, mp 119.5-120.0 °C, $[\alpha]_D^{19}$+84.5°(c 1.50, $CHCl_3$)]. Among the methods[5] for the [3,3]sigmatropic rearrangement of (+)-**4** examined, Eschenmoser method[5a] with N,N-dimethylacetamide dimethyl acetal (140 °C, 2 h, in xylene) gave the best result and the expected (-)-**5** [mp 96.5-97.0 °C, $[\alpha]_D^{23}$-63.7°(c 0.60, $CHCl_3$)] was obtained in 70% yield, whereas Ireland method[5b] gave dehydrated product in 80% yield and Johnson method[5c] gave rearranged product only in a poor (28%) yield. Allylic oxidation with pyridinium dichromate-t-butyl hydroperoxide-celite (PDC-TBHP-celite)[6] at rt for 12 h followed by treatment with KF gave (-)-**6** [viscous oil, $[\alpha]_D^{23}$-47.7°(c 2.25, $CHCl_3$)] in 39% yield [66% based on consumed (-)-**5**]. Reduction of (-)-**6** with $LiAlH_4$ and subsequent oxidation with $MnO_2$[2a] gave (-)-**7** [oil $[\alpha]_D^{22}$-68.4°(c 1.40, MeOH)][7] in 65% yield.




Scheme 1.

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7) Lit.[1] $[\alpha]_D^{25}$ -51°(c 1.45, MeOH).

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