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A short synthesis of (+)-hygrine

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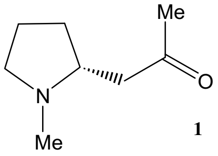
Abstract

The synthesis of the alkaloid hygrine in a series of six steps starting from readily available proline *N*-methyl derivative (**5**) is described.

Keywords: Hygrine; Alkaloid; Dess–Martin periodinane

Hygrine (**1**) is an alkaloid present in coca leaves as well as in a variety of other plants. It has been the subject of several biological and pharmacological studies,[1] especially since it is known that hygrine is the precursor of hyoscyamine and scopolamine, both compounds are used in the preparation of a vast number of pharmaceutical products; consequently, there is an increased interest in the development of synthetic routes to this alkaloid in order to investigate structure–activity relationship. Hygrine (**1**) has been prepared previously[2] by rather lengthy and tedious synthetic routes. We now present an exceptionally simple synthesis route which provides **1** in good overall yield (Scheme 1); As a result, our approach presents an advantage over a recently published synthesis of hygrine.[3]



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Thus, treatment of the readily available **5**[4] with DIBAL-H in CH_2Cl_2 at −30 °C afforded aldehyde **4**. This product, without further purification, was then reacted with (methoxymethyl)triphenylphosphonium bromide and with KO-*t*-Bu/THF to generate a methyl vinyl ether. The subsequent acid hydrolysis of the vinyl ether provided the homologated aldehyde **3**; treatment of this compound with methyl magnesium bromide afforded **2** in a mixture 2.5:1 (hygroline:pseudohygroline). Finally, the transformation of **2** to hygrine **1** was carried out by the Dess–Martin[5] periodinane procedure; the final product was then purified with flash column chromatography (hexane–AcOEt = 6:4) and its identification was accomplished by comparison of the obtained data with those previously described in the literature.[2,3] All the analytical data are in agreement with the values reported for the optically pure compound, included: bp 87–88 °C (23 mm); (lit.:[2c,5] bp 83–84 °C (21 mm)); hygrine·HCl[6] $[\alpha]_D$ +34.0 ($c = 0.5$, H_2O); (lit.[3] $[\alpha]_D$ +34.5 ($c = 0.5$, H_2O)).

Thus, an efficient 6-step synthesis of hygrine was accomplished in 35% overall yield.

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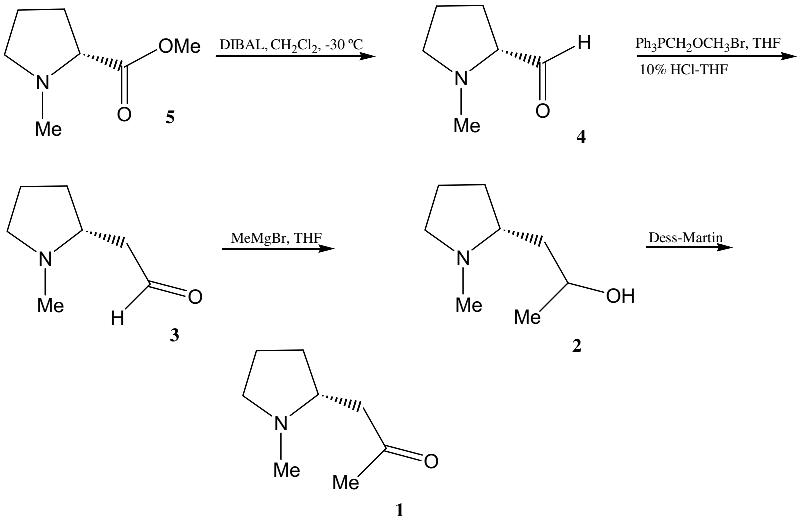

Scheme 1.

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References and notes

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3. Lee, J.-H.; Jeong, B.-S.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *J. Org. Chem.* **2006**, *71*, 6690.
4. Commercially available. It is also easily synthesized from proline by treatment with $SOCl_2$/MeOH, and subsequent addition of MeI and NaH.
5. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
6. Hygrine was readily transformed into its hydrochloride salt for comparison with the literature data of the same compound (see Ref. 3).