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A simple and efficient synthesis of (±)-mesembrine ☆

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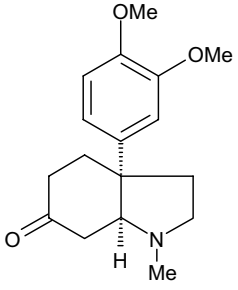
Abstract—A simple and efficient synthesis of (±)-mesembrine **1** is described employing double Michael addition and as the key step in 18% overall yield.

1. Introduction



(-)-Mesembrine 1

The selectium alkaloids, isolated from the Mesembryanthemaceae family, have continued to interest synthetic organic chemists as attractive molecular targets[1–3] of which (−)-mesembrine **1** is a naturally occurring serotonin uptake inhibitor.[4] The main challenge in the synthesis of this octahydroindole alkaloid and other members of the mesembrine family lies in the construction of the benzylic quaternary center.[5–15] A variety of approaches have been delineated for the construction of this molecule. Our quest for forming C–C bonds under aqueous conditions led us to the development of a very mild and efficient method for the synthesis of an intermediate to a potent antidepressant.[16] In this communication, we describe the construction of the quaternary center employing a double Michael strategy by a mild protocol. Accordingly, Michael addition of 3,4-dimethoxyphenyl acetonitrile **2** to methyl acrylate **3** using aqueous 10% NaOH solution and a phase transfer catalyst furnished diester **4**. The diester **4** formed crashes out of the aqueous medium. Thus, the reaction is performed under the aqueous medium and the product formed is just filtered off and then crystallized from ethyl acetate. Thus, this is a completely green step devoid of any organic solvents in the reaction as well as work-up. Alternatively, diester **4** can also be obtained efficiently (99%) using Triton-B as a catalyst in refluxing acetonitrile. Dieckmann condensation gave a β-ketoester, which exists in the enol form **5**, which upon Krapcho's demethoxycarbonylation yielded a ketone[17] **6**. The keto group was protected as a 2,2-dimethyl-1,3-dioxane **7** with 2,2-dimethyl-1,3-propanediol using PPTS as a catalyst in refluxing benzene in a Dean–Stark apparatus. The cyano group was then reduced with DIBAL-H to give the aldehyde **8** in quantitative yield. Aldehyde **8** was then homologated via a one carbon Wittig reaction, hydroboration followed by oxidative work up then gave alcohol **10**. Alcohol **10** was converted into its mesyl ester, which on treatment with 40% aqueous methylamine in a sealed tube afforded a secondary amine **11**. The free amine was protected as its carbamate **12**. The dioxane **12** was deprotected in acetone–water mixture in the presence of 1–2 drops of H_2SO_4 to give the ketone **13**. This was converted into its silyl enol ether **14**, followed by bromination with NBS to give the α-bromoketone **15**. Since the bromo compound **15** was found to be unstable it was immediately subjected to the next reaction. Accordingly, treatment of **15** with Li_2CO_3 and LiBr in

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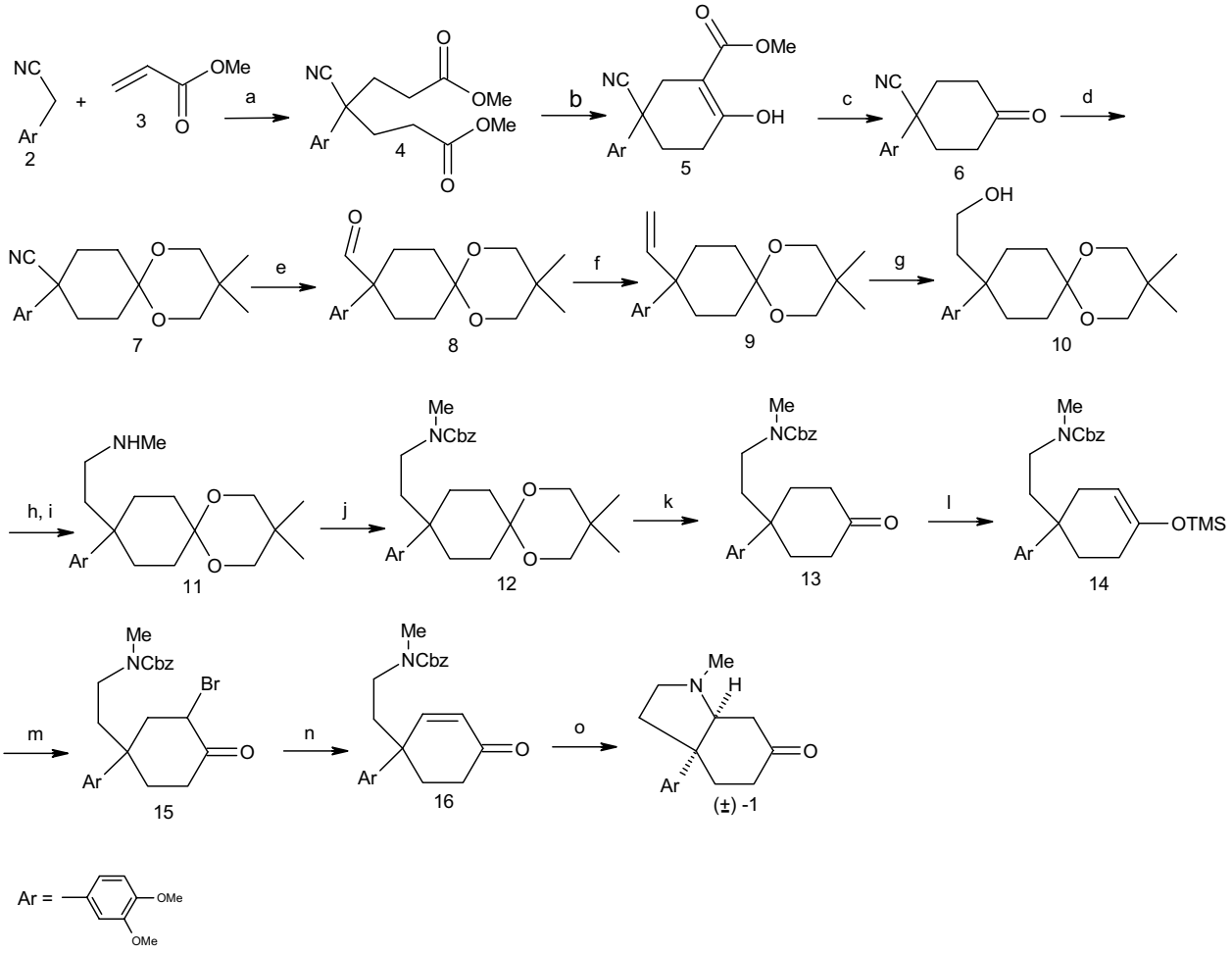

Scheme 1. Reagents and conditions: (a) 10% aq NaOH, $TBAHSO_4$, 0 °C, 30 min, 76%; (b) NaH, DME, reflux, 3 h, 89%; (c) NaCl, H_2O, DMSO, 140 °C, 6 h, 87%; (d) $HOCH_2C(CH_3)_2CH_2OH$, PPTS, benzene, reflux, 3 h, 95%; (e) DIBAL-H, DCM, 0 °C, 30 min, 100%; (f) $Ph_3P^+CH_2I^-$, $NaNH_2$, Et_2O–THF (1:1), 0 °C, 10 min, 82%; (g) $BH_3{\cdot}Me_2S$, THF, 0 °C, then 30% H_2O_2, 30% NaOH, 75%; (h) Et_3N, $MeSO_2Cl$, DCM, 0 °C, 30 min, 100%; (i) 40% aq $MeNH_2$, THF–H_2O, in sealed tube, 80 °C, 2 h; (j) $ClCOOCH_2Ph$, K_2CO_3, 0 °C to rt, 4 h, 88%; (k) CH_3COCH_3–H_2O, 1–2 drops H_2SO_4, reflux, 24 h, 85%; (l) Et_3N, TMSCl, CH_3CN, reflux, 2 h, 100%; (m) NBS, THF, 0 °C, 10 min, 100%; (n) Li_2CO_3, LiBr, DMF, 110 °C, 2 h, 75%; (o) $BF_3{\cdot}OEt_2$, Me_2S, DCM, 0 °C to rt, 1 h, 95%.

DMF[18] smoothly afforded enone **16**. Deprotection of the carbamate was achieved with $BF_3{\cdot}OEt_2$ in the presence of Me_2S[19] to furnish the amine, which subsequently underwent facile intramolecular Michael addition[20,21] to obtain the target molecule **1** (Scheme 1). The spectral data of (±)-**1** thus obtained matched well with the reported data.[22]

2. Conclusion

In conclusion, we have demonstrated that (±)-mesembrine can be efficiently synthesized by double Michael addition under aqueous condition as the key step in 18% overall yield.

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22. Spectral data for (±)-mesembrine: IR ($CHCl_3$) 2959, 1716, 1519, 1254, 1217, 755, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05–2.18 (m, 4H), 2.23–2.29 (m, 1H), 2.34 (s, 3H), 2.35–2.42 (m, 2H), 2.62 (t, $J = 4.6$ Hz, 2H), 3.02 (t, $J = 3.7$ Hz, 1H), 3.15–3.23 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 6.81 (d, $J = 8.3$ Hz, 1H), 6.85 (dd, $J = 8.3$ Hz and $J = 2.0$ Hz, 1H), 6.87 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR 211.08, 149.43, 147.97, 140.02, 118.27, 111.54, 110.50, 70.46, 56.34, 56.16, 54.89, 47.84, 40.65, 40.24, 39.08, 36.35, 35.30; MS (EI) m/z 289 (M^+), 274, 254, 218, 204, 128, 91, 70, 59.