SHORT SYNTHESIS OF (±)-TACAMONINE BY THE INTRAMOLECULAR DOUBLE MICHAEL REACTION#

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Abstract — The racemate of tacamonine (**1**), an indole alkaloid of pseudovincamine type, was synthesised in short steps *via* the intramolecular double Michael reaction of the unsaturated amide (**3**).

Tacamonine (**1**) is an indole alkaloid, isolated from *Tabernaemontana eglandulosa.*[1] Considerable synthetic efforts have been made due to its structural similarity to the pharmacologically important ebrunamine-vincamine alkaloids.[2–4] Here we would like to communicate a short synthesis of (±)-tacamonine (**1**) by employing the intramolecular double Michael reaction.[5]

The substrate (**3**) of the key reaction was synthesised from the dihydro-β-carboline hydrochloride (**2**) (Scheme 1). Thus, reaction of **2** and 2-ethylacryloyl chloride[6] in the presence of triethylamine in a mixture of dimethylformamide and tetrahydrofuran at 0 °C,[7] followed by Wittig reaction, provided the unsaturated amide (**3**)[8] in 40 % overall yield. The intramolecular double Michael reaction of **3** was carried out by the treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of triethylamine in 1,2-dichloroethane at room temperature for 5 days. Two separable indolo[2,3-*a*]quinolizines (**4**)[8] and (**5**)[8] were obtained in 19% and 16% yields, respectively. Reduction of **4** with borane-tetrahydrofuran complex in tetrahydrofuran gave **6**[8] in 40% yield, while **7**[8] was produced from **5** in 56% yield by the same treatment. The NMR spectra of the products were similar to those of the authentic compounds.[3b-d] Furthermore, the structure of **7** was confirmed by X-Ray analysis of its hydrochloride (Figure 1).[9]

Since **6** had been converted into (±)-tacamonine (**1**) by Lounasmaa and coworkers,[3b-d] a short formal synthesis of **1** was accomplished.

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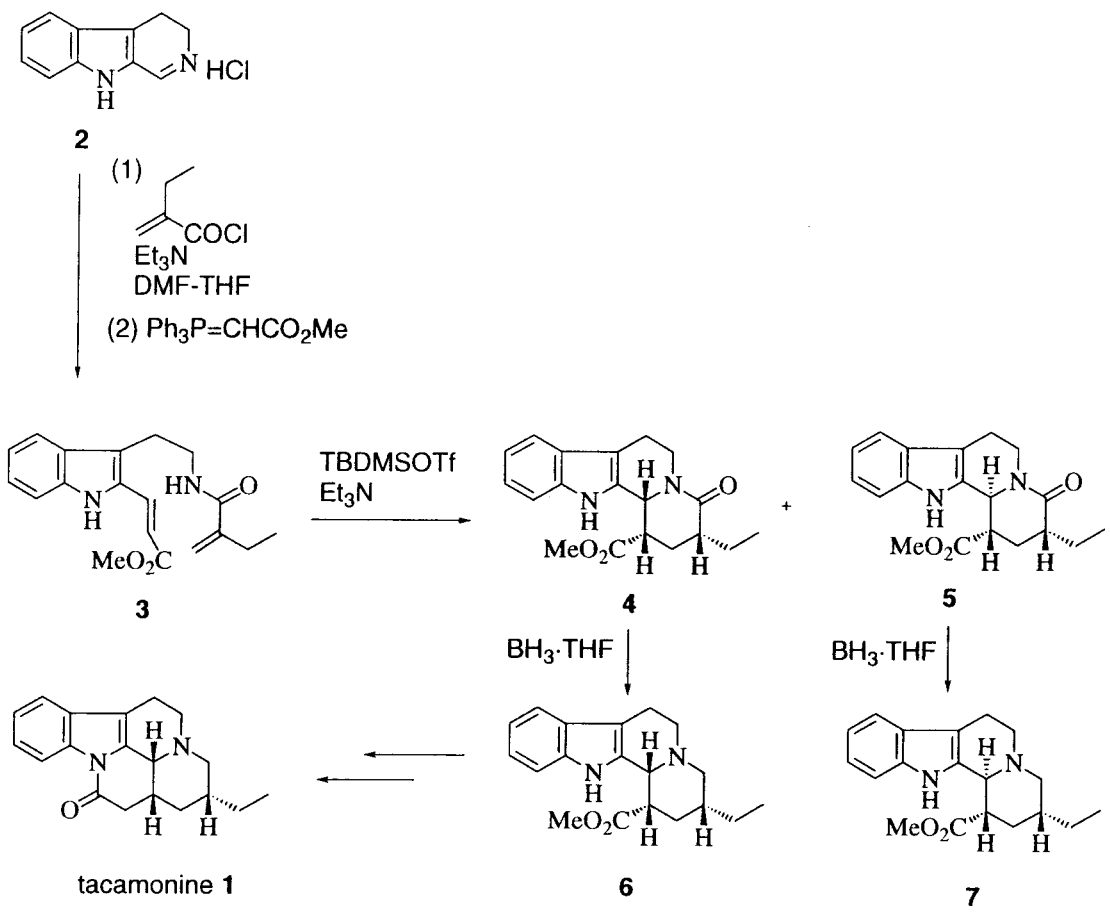
#Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.



Scheme 1

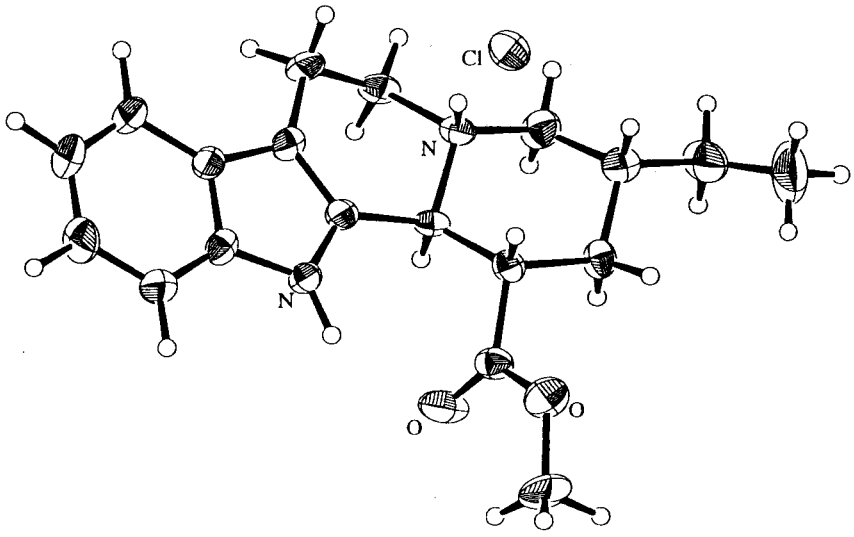


Figure1 Molecular Structure of the Hydrochloride of **7**.

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4. It was observed by using our synthetic sample that the IC_{50} values of (±)-**1** against muscarine M 1, M 2 and M3 receptors were 10 μg/mL, 0.9 μg/mL and 10 μg/mL.
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8. Selected spectral data for **3**: δ_H (300 MHz, $CDCl_3$) 1.04 (3H, t, J = 7.3 Hz), 2.28 (2H, q, J = 7.3 Hz), 3.16 (2H, t, J = 6.6 Hz), 3.62 (2H, t, J = 6.6 Hz), 3.82 (3H, s), 5.21 and 5.50 (each 1H, s), 6.26 (1H, d, J = 16.0 Hz), 7.12–7.67 (4H, m), 7.78 (1H, d, J = 16.0 Hz), 8.82 (1H, br s); for **4**: δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, J = 7.4 Hz,), 2.70– 2.93 (4H, m) 3.84 (3H, s), 5.02 (1H, br s), 7.03–7.11 (2H, m), 7.25 (1H, d, J = 7.9 Hz), 7.43 (1H, d, J = 7.7 Hz), 8.34 (1H, br s); for **5**: δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, J = 7.5 Hz), 1.48–1.60 (2H, m), 1.74-1.78 (1H, m), 1.94-2.05 (1H, m), 2.19–2.29 (2H, m), 2.67 (1H, t, J = 7.3 Hz), 2.71–2.90 (3H, m) 3.85 (3H, s), 5.04 (1H, d, J = 9.9 Hz), 7.03-7.11 (2H, m), 7.24 (1H, d, J = 8.0 Hz), 7.42 (1H, d, J = 7.7 Hz), 8.34 (1H, br s, NH); for **6**: δ_H (300 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.5 Hz), 1.10–1.15 (2H, m), 3.83 (3H, s), 5.09 (1H, br s), 7.15–7.22 (2H, m), 7.35 (1H, d, J = 7.9 Hz), 7.50 (1H, d, J = 7.5 Hz), 7.99 (1H, br s); for **7**: δ_H (300 MHz, $CDCl_3$) 0.98 (3H, t, J = 7.5 Hz), 1.20-1.28 (2H, m), 3.72 (3H, s), 4.43 (1H, d, J = 12 Hz), 7.03–7.21 (2H, m), 7.31 (1H, d, J = 7.9 Hz), 7.52 (1H, d, J = 7.5 Hz), 8.02 (1H, br s).
9. Crystal data for **7**·HCl: $C_{19}H_{25}N_2O_2Cl$, orthorhombic, $P2_12_12_1$, a = 12.186 (2), b = 22.020 (3), c = 6.788 (2) Å, V = 1821.5 (5) $Å^3$, Z = 4, μ (MoKa) = 2.23 cm^{-1}, Dc = 1.27 g/cm^3, F000 = 744, R, Rw = 0.070, 0.031 for 922 observed reflections with $I > 1.5\sigma(I)$.

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