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First total synthesis of (±)-tangutorine

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Abstract—The first total synthesis of the novel indole alkaloid, tangutorine **1** was performed in seven steps from 7,8-dihydroquinoline-5(6*H*)-one **2**.

In 1999, Duan and colleagues reported the isolation of a new biogenetically interesting indole alkaloid, tangutorine **1** from the leaves of *Nitraria tangutorum*.[1] So far, this novel compound is the only known natural product containing the benz[*f*]indolo[2,3-*a*]quinolizidine unit (Fig. 1).

The structure of tangutorine was originally reported by Duan et al.[1] based on spectral and crystallographic analyses. In their paper the ORTEP structure of tangutorine corresponded with the spectral data. Their results indicated, however, a discrepancy between the ORTEP structure and the structural formula given. According to the ORTEP structure the H-3/H-19 relationship was *cis* and H-3/H-20 *trans*. The chemical shifts given for H-3 (3.54 ppm) and C-6 (22.2 ppm) were typical for a structure with a *trans* C/D ring juncture.

The basic ring system of tangutorine **1** was recently synthesized in our laboratory.[2] We proved definitely that the H-3α stereochemistry in the structural formula of the original paper of Duan et al.[1] should be H-3β, which corresponds with the original crystallographic data. The NMR spectral data of our model compound also confirmed the stereochemistry shown in the ORTEP structure.

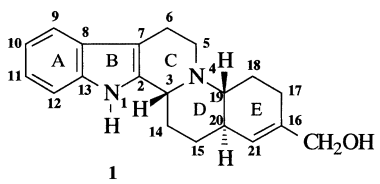

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Figure 1.

In addition to our synthesis of the basic ring system of tangutorine, only a few approaches to the benz[*f*]indolo[2,3-*a*]quinolizidine skeleton have been reported in the literature.[3–9] We now report the first total synthesis of tangutorine **1** starting from 7,8-dihydroquinoline-5(6*H*)-one **2**.

7,8-Dihydroquinoline-5(6*H*)-one **2** was prepared in two steps starting from 1,3-cyclohexanedione.[10] Reaction of **2** with dimethyl carbonate containing a catalytic amount of methanol under reflux for 3 h gave compound **3** (yield 90%). Alkylation of ester **3** with tryptophyl bromide afforded salt **4** in 90% yield. Treatment of this salt with sodium dithionite in a water–methanol solution for 18 h at room temperature in the presence of sodium bicarbonate gave a 95% yield of compound **5**. Cyclization in HCl–MeOH for 3 days afforded the two isomers of compound **6**[11] in 65% yield. Reduction with sodium borohydride in glacial acetic acid for 5 h gave an inseparable mixture of isomers of compound **7a**[12] (50%). Dehydration[13] was carried out through the mesyl intermediate **7b** with DBU to afford compound **8**[14] (15%). Finally, the ester group was reduced at room temperature for 4 h with lithium aluminum hydride in THF to give (±)-tangutorine **1**[15] in 90% yield (Scheme 1).

The spectral data (MS, ^{1}H and ^{13}C NMR) of tangutorine **1**[15] obtained correspond to those in the original paper of Duan et al.[1] The chemical shifts of H-3 and C-6 measured are characteristic for compounds in an all *trans* conformation, thus confirming the stereochemistry of tangutorine as presented by Berner et al.[2]

Keywords: natural products; indole alkaloids; benz[*f*]indolo[2,3-*a*]-quinolizidine.

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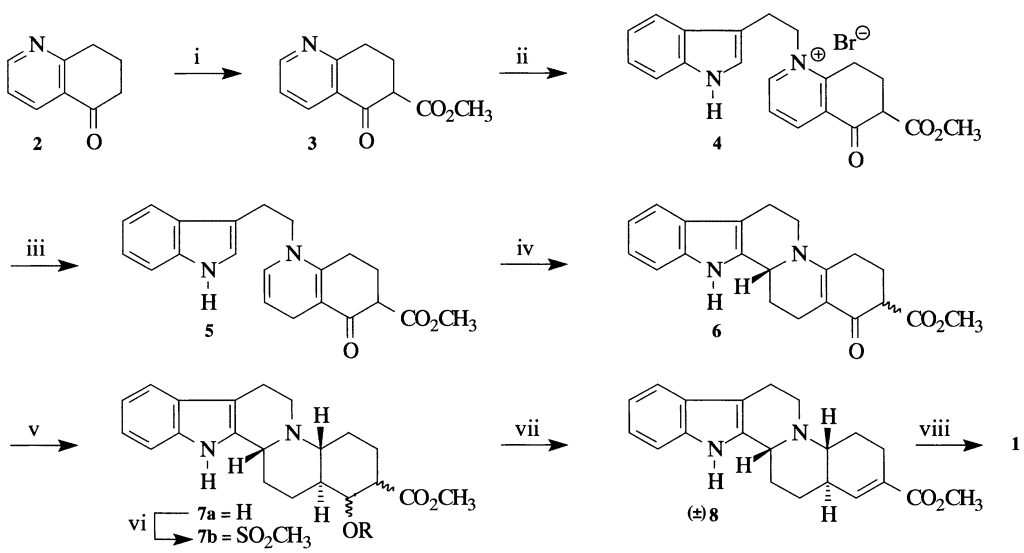

Scheme 1. (i) $(MeO)_2CO$, NaH, MeOH, reflux, 3 h; (ii) tryptophyl bromide, Et_2O, 100°C; (iii) $Na_2S_2O_4$, $NaHCO_3$, MeOH, H_2O, rt, 18 h; (iv) HCl–MeOH, rt, 65 h; (v) $NaBH_4$, CH_3COOH, rt, 5 h; (vi) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h; (vii) DBU, 100°C, 2 h; (viii) $LiAlH_4$, THF, rt, 4 h.

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11. Selected spectral data of the two isomers of compound **6**: ^1H NMR ($CDCl_3$, 400 MHz): 4.59, 4.54 (1H, br s, $J=11$ Hz, H-3), 3.69 (2×3H, s, $-CO_2C\underline{H}_3$), 3.36 (2×1H, m, H-16). ^{13}C NMR ($CDCl_3$, 100 MHz): 188.5, 187.8 (C-21), 172.2, 171.8 ($-\underline{C}O_2CH_3$), 159.8, 159.3 (C-19), 106.6, 106.4 (C-20), 54.6 (C-3), 52.2, 52.1 ($-CO_2\underline{C}H_3$), 51.4, 50.2 (C-16), 45.3, 45.0 (C-5), 22.2 (C-6). MS (m/z): 350 (M^+, 100%), 291, 263, 235, 169, 156.
12. Mass spectral data of compound **7a**: MS (m/z): 354 (M^+), 353, 336, 277, 170, 169 (100%).
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14. Selected spectral data of compound **8**: ^1H NMR ($CDCl_3$, 400 MHz): 6.68 (1H, br s, H-21), 3.75 (3H, s, $-CO_2C\underline{H}_3$), 3.50 (1H, br d, $J=11$ Hz, H-3). ^{13}C NMR ($CDCl_3$, 100 MHz): 167.6 ($-\underline{C}O_2CH_3$), 141.9 (C-16), 129.2 (C-21), 64.0 (C-19), 60.5 (C-3), 51.7 ($-CO_2\underline{C}H_3$), 45.6 (C-5), 40.6 (C-20), 22.0 (C-6). MS (m/z): 336 (M^+), 170 (100%).
15. Selected spectral data of compound **1**: ^1H NMR ($CDCl_3$, 400 MHz): 5.41 (1H, s, H-21), 4.04 (2H, br s, $-C\underline{H}_2OH$), 3.51 (1H, br d, $J=11$ Hz, H-3). ^{13}C NMR ($CDCl_3$, 100 MHz): 136.7 (C-16), 126.0 (C-21), 66.5 ($-\underline{C}H_2OH$), 65.1 (C-19), 60.6 (C-3), 45.5 (C-5), 39.6 (C-20), 22.7 (C-6). MS (m/z): 308 (M^+), 170 (100%).