Synthesis of Tangutorine

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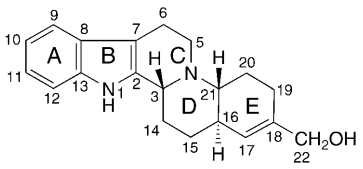
Tangutorine (**1**) in the racemic form has been assembled from tryptamine and aldehyde **3**. The synthetic design was based on uncovering a hidden symmetry in the nontryptamine portion of the norketone **2**. A five-step process with an overall yield of 7% was developed in which **2** was transformed into the target molecule *via* a *Vilsmeier–Haack* reaction and two reduction steps.

Introduction. – From the leaves of the Chinese medicinal plant *Nitraria tangutorum* L., the racemic pentacyclic indole alkaloid tangutorine (**1**) was isolated by *Duan et al.* [1] in 1999[2]). Until the present time, **1** is the only known natural product of intriguing biogenetic origin bearing the benz[*f*]indolo[2,3-*a*]quinolizidine unit [2]. Its synthesis has been accomplished by three groups [3–5]. Thus, *Jokela* and co-workers constructed the skeleton from tryptophyl bromide and a tetrahydroquinoline derivative [3], while *Hsung* and co-workers employed a formal intramolecular aza-[3+3]-cycloaddition to bring about a simultaneous closure of both *C* and *D* rings [4]. The report of *Zhai* features a tandem enamide alkylation and *Pictet–Spengler* cyclization [5], and an *N-tert*-butoxycarbonyl group was introduced to obtain an intermediate in *Hsung*'s synthesis.



Results and Discussion. – During the past several years, we have engaged in a synthetic program aiming at the elaboration of natural products while considering the exploitation of molecular symmetry, whether apparent or hidden, in the design [6][7]. For a synthesis of **1**, an apparent precursor is **2**, and the nontryptamine portion is readily accessible from a symmetric 3-(1,3-dioxocyclohex-2-yl)propanal. Alterna-

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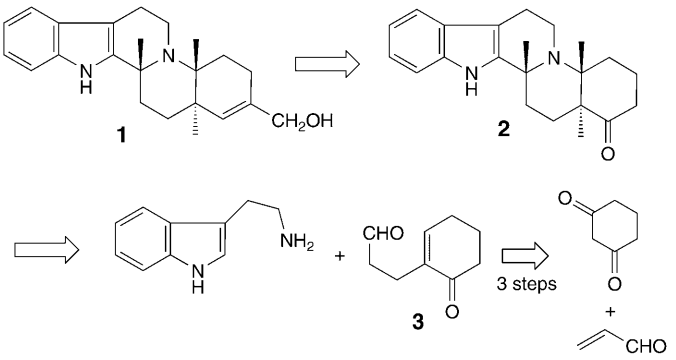
[2]) In this work, the stereochemical formula was misrepresented. The X-ray crystallographic plot of **1** clearly indicates that H(3) and H(15) are *cis* to one another.

Scheme 1



tively, the diketo aldehyde can be replaced by the cyclohexenone 3 (*Scheme 1*). The latter compound is available from the reaction of cyclohexa-1,3-dione with acrolein in three steps [8].

When tryptamine and aldehyde **3** were submitted to a *Pictet–Spengler* reaction [9], the initial product underwent an intramolecular *Michael* addition to afford a pentacyclic compound **2**. However, due to the difficulty in its purification, direct conversion into an *N*-Boc derivative was performed. In other words, **4** was obtained in 31% yield over two steps. The spectral characteristics of **4** were in total agreement with those reported previously by *Hsung*, and at this point, the formal synthesis of tangutorine (**1**) was complete. Since five more steps were required for eventual achievement of the alkaloid, we felt that there was room for improvement. Our independent pursuit in introducing the allylic alcohol subunit involved treatment of **4** with the *Vilsmeier–Haack* reagent ($POCl_3$/DMF) to generate the β-chloro α,β-unsaturated aldehyde **5** [10], $NaBH_4$ reduction, and dechlorination with Na-Naphthalenide [11] or Li-Naphthalenide, see [12], which was attended by spontaneous removal of the *N*-Boc group to furnish tangutorine (**1**) (*Scheme 2*). Its spectral characteristics were in total agreement with those found ealier[3]).

In summary, starting from tryptamine, we have synthesized tangutorine **1** in five steps in an overall yield of 7%. Our approach is the shortest among the presently known syntheses.

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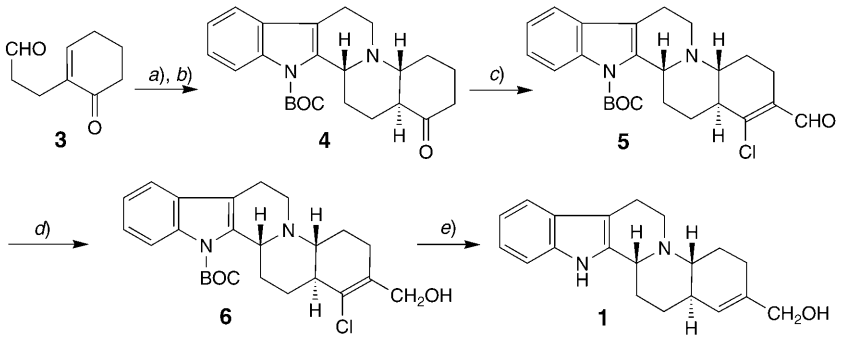
Experimental Part

General. Column chromatography (CC): *Merck* silica-gel (70–230 mesh). TLC: *Merck* silica-gel *60* F_{254} plates. M.p.: *Laboratory Devices*; uncorrected. IR Spectra: *Bio-Rad FTS 165* and *Digilab FTS 3100*;

[3]) The last 3 steps were originally developed by Dr. E. Gorobets in 2001–2002, after he obtained compound **4** in a different and less efficient way. We did not report this work earlier because we thought that a diastereomer was generated. The use of different solvent systems to record the NMR spectra misled us very badly.

Scheme 2



a) TFA, CH_2Cl_2, 0° to r.t., overnight. *b*) $(BOC)_2O$, DMAP (cat.), CH_2Cl_2; 31% (two steps). *c*) $POCl_3$, DMF, $CHCl_3$, r.t.; 47%. *d*) $NaBH_4$, EtOH, 93%; *e*) Na-Naphthalenide, THF, 0°, 2 h; 52%.

in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian Unity-300* and *Unity-500*; $CDCl_3$ unless otherwise indicated; δ in ppm, J in Hz. EI-MS: *Trio-2000* and *Jeol SX-102A*; at 70 eV, unless otherwise indicated. All reactions were conducted under N_2. For drying of org. solns. during workup of reactions, Na_2SO_4 was used.

3-(6-Oxocyclohex-1-en-1-yl)propanal (**3**). Prepared according to [7] from 1,3-cyclohexadione and acrolein in *ca.* 50% yield. IR: 1670, 1720 (C=O). ^1H-NMR: 1.86–1.93 (*m*, 2 H); 2.24–2.35 (*m*, 4 H); 2.41–2.52 (*m*, 4 H); 6.71 (*t*, $J=3.9$, 1 H); 9.65 (*t*, $J=1.5$, 1 H). ^{13}C-NMR: 22.71 (*t*); 22.79 (*t*); 25.83 (*t*); 38.22 (*t*); 42.56 (*t*); 137.73 (*s*); 146.62 (*d*); 199.12 (*s*); 210.86 (*d*).

*tert-Butyl (4a*RS*,12b*RS*,14a*RS*)-2,3,4,4a,6,7,12b,13,14,14a-Decahydro-1-oxoindolo[2′,3′:3,4]pyrido[1,2-*a*]-12(1*H*)-carboxylate* (**4**). A slow addition of a soln. of tryptamine (0.32 g, 2.18 mmol) in CH_2Cl_2 (10 ml) to an ice-cold soln. of aldehyde **3** (0.30 g, 1.97 mmol) in anh. CH_2Cl_2 (5 ml) was followed by a soln. of TFA (0.52 g, 4.53 mmol) in CH_2Cl_2 (5 ml) during 10 min. The mixture was kept for 1 h, gradually warmed up to r.t. overnight, and poured into an ice-cold 5% $NaHCO_3$-soln. (50 ml). Workup involved layer separation, extraction with CH_2Cl_2, rewashing of the org. soln. with aq. $NaHCO_3$ and brine. Drying and concentration *in vacuo* gave a product (**2**), which was directly treated with $(Boc)_2O$ (0.50 g, 2.29 mmol), DMAP (0.02 g, 0.02 mmol) in CH_2Cl_2 (10 ml) at r.t. overnight. After washing the reaction mixture with brine, the layers were separated. Drying and evaporation *in vacuo* were followed by chromatography (eluent gradient: AcOEt/hexane) to give **4** (0.31 g, 31%). M.p.: 108–110°. R_f (AcOEt/hexane 1:1) 0.15. IR: 2977, 2933, 2862 (C–H), 1723, 1701 (C=O), 1450, 1351, 1314. ^1H-NMR (500 MHz): 1.54–1.75 (*m*, 3 H); 1.61 (*s*, 9 H); 1.88–2.11 (*m*, 5 H); 2.22–2.43 (*m*, 3 H); 2.72–2.76 (*m*, 2 H); 2.95 (*dt*, $J=11.1$, 3.3, 1 H); 2.96–3.04 (*m*, 2 H); 4.32 (*d*, $J=9$, 1 H); 7.14–7.24 (*m*, 2 H); 7.50 (*d*, $J=7.5$, 1 H); 8.11 (*d*, $J=7.5$, 1 H). ^{13}C-NMR: 21.92 (*t*); 23.30 (*t*); 24.37 (*t*); 25.14 (*t*); 28.15 (*q*); 29.78 (*t*); 36.80 (*t*); 41.38 (*t*); 47.80 (*d*); 58.21 (*d*); 66.95 (*d*); 83.62 (*s*); 114.60 (*s*); 115.64 (*d*); 117.69 (*d*); 122.49 (*d*); 123.81 (*d*); 128.95 (*s*); 136.39 (*s*); 136.55 (*s*); 149.85 (*s*); 211.12 (*s*). EI-MS: 395 (3.3), 394 (16.8, M^+), 339 (5.0), 338 (27.2), 337 (100), 294 (13.5). HR-MS: 394.2249 ($C_{24}H_{30}N_2O_3^+$; calc. 394.2256).

*tert-Butyl (4a*RS*,12b*RS*,14a*RS*)-1-Chloro-2-formyl-4,4a,6,7,12b,13,14,14a-octahydroindolo[2′,3′:3,4]pyrido[1,2-*a*]quinoline-12(3*H*)-carboxylate* (**5**). A soln. of **4** (0.31 g, 0.78 mmol) in $CHCl_3$ (6.0 ml) was added during 30 min to an ice-cooled soln. of freshly distilled $POCl_3$ (0.80 g, 5.2 mmol) in anh. DMF (0.56 g, 7.6 mmol) and $CHCl_3$ (2.0 ml). The mixture was stirred at r.t. overnight, diluted with CH_2Cl_2 (15 ml), successively washed with H_2O, 5% $NaHCO_3$, and brine, dried, and concentrated *in vacuo*. Column chromatography (SiO_2; hexane/AcOEt 9:1 → 1:9) to give unreacted **4** (0.10 g) and **5** (0.11 g, 47% based on reacted **4**) as a thick oil. R_f (AcOEt/hexane 1:1) 0.6. IR: 2971, 2932, 2863 (C–H), 1724, 1679 (C=O), 1613, 1454, 1357, 1322, 1244, 1154. ^1H-NMR: 1.45–1.84 (*m*, 3 H); 1.65 (*s*, 9 H); 1.98–2.02 (*m*, 1 H); 2.14–2.23 (*m*, 2 H); 2.52–2.76 (*m*, 5 H); 2.95–3.02 (*m*, 3 H); 4.56 (*d*, $J=11.1$, 1 H); 7.20–7.28 (*m*, 2 H); 7.38–7.40 (*m*, 1 H); 8.11 (*d*, $J=7.8$, 1 H); 10.20 (*s*, 1 H). ^{13}C-NMR: 21.91 (*t*); 23.91 (*t*); 25.89

(*t*); 26.15 (*t*); 28.19 (*q*); 29.52 (*t*); 36.39 (*t*); 40.21 (*d*); 58.02 (*d*); 64.73 (*d*); 83.66 (*s*); 114.66 (*s*); 115.76 (*d*); 117.83 (*d*); 122.59 (*d*); 123.93 (*d*); 129.00 (*s*); 133.34 (*s*); 136.21 (*s*); 136.26 (*s*); 149.87 (*s*); 153.44 (*s*); 191.44 (*d*). EI-MS: 442 (8), 441 (7), 440 (26, M^+), 412 (5), 383 (58), 356 (23), 339 (15), 214 (70), 170 (78). HR-MS: 440.1858 ($C_{25}H_{29}ClN_2O_3^+$; calc. 440.18687).

*tert-Butyl (4a*RS*,12b*RS*,14a*RS*)-1-Chloro-4,4a,6,7,12b,13,14,14a-octahydro-2-(hydroxymethyl)indolo[2′3′:3,4]pyrido[1,2-*a*]quinoline-12(3*H*)-carboxylate* (**6**). To a soln. of **5** (0.10 g, 0.22 mmol) in anh. EtOH (5 ml) was added $NaBH_4$ (0.08 g, 2.2 mmol) during 10 min. After another 10 min, a mixture of H_2O (5 ml) and CH_2Cl_2 (25 ml) was added. The org. layer was washed with H_2O, brine, and dried. Evaporation *in vacuo* followed by chromatography (SiO_2, AcOEt/hexane 75:25) to give **6** (0.09 g, 93%) as a very light yellow solid. R_f (AcOEt/hexane 75:25) 0.33. M.p.: 178–180° (dec.). IR: 3350 (O–H), 2975, 2931, 2861 (C–H), 1718 (C=O), 1479, 1378, 1315, 1249, 1160. ^{1}H-NMR: 1.30–1.93 (*m*, 4 H); 1.64 (*s*, 9 H); 2.08 (*d*, J = 13.6, 1 H); 2.22–2.46 (*m*, 4 H); 2.73–2.78 (*m*, 2 H); 2.89–2.97 (*m*, 3 H); 4.17 (*d*, J = 12.3, 1 H); 4.29 (*d*, J = 12.3, 1 H); 4.50 (*d*, J = 9.6, 1 H); 7.20–7.27 (*m*, 2 H); 7.37–7.40 (*m*, 1 H); 8.14 (*d*, J = 7.8, 1 H). ^{13}C-NMR: 21.92 (*t*); 25.87 (*t*); 27.01 (*t*); 28.04 (*t*); 28.23 (*q*); 30.19 (*t*); 36.42 (*t*); 38.31 (*d*); 58.10 (*d*); 63.10 (*t*); 65.19 (*d*); 83.63 (*s*); 114.62 (*s*); 115.78 (*d*); 117.83 (*d*); 122.57 (*d*); 123.89 (*d*); 129.08 (*s*); 131.70 (*s*); 133.16 (*s*); 136.34 (*s*); 136.49 (*s*); 149.92 (*s*). EI-MS: 442 (10, M^+), 385 (51), 341 (21), 305 (3), 270 (5), 241 (4), 214 (58), 170 (41), 168 (64). HR-MS: 442.2017 ($C_{25}H_{31}ClN_2O_3^+$; calc. 442.20253).

Tangutorine (=*4a*RS*,12b*RS*,14a*RS*)-3,4,4a,6,7,12,12b,13,14,14a-Decahydroindolo[2′3′:3,4]pyrido[1,2-*a*]pyrido[1,2-*a*]quinolin-2-ylmethanol*; **1**). To a suspension of Na wire (0.06 g, 2.6 mmol) in anh. THF (3 ml) was added a soln. of naphthalene (0.16 g, 1.25 mmol) in THF (3 ml). The mixture was sonicated until a persistent deep-green color appeared (*ca.* 10 min). After 1 h, it was cooled to 0° and treated with a soln. of **6** (0.06 g, 0.13 mmol) in THF (6 ml). Stirring was continued for 2 h, followed by cautious addition of H_2O (2 ml) to destroy excess Na. Workup involved dilution with CH_2Cl_2 (15 ml), washing with brine, drying, and evaporation *in vacuo.* Purification by CC (SiO_2; MeOH/CH_2Cl_2 10:90) afforded **1** (0.02 g, 52%) as colorless solid. R_f (10:90 MeOH/CH_2Cl_2) 0.10. M.p. 273–275° ([1]: 276–278°). IR: 3282 (NH, OH), 2924, 2854 (CH), 1666, 1454, 1051. ^{1}H-NMR (500 MHz, CD_3OD/$CDCl_3$ 5:95): 1.20–1.29 (*m*, 1 H); 1.40–1.49 (*m*, 1 H); 1.60–1.68 (*dq*, J = 12.8, 3.5, 1 H); 1.81–1.84 (*dd*, J = 12.8, 2.8, 1 H); 2.05–2.22 (*m*, 6 H); 2.35–2.38 (*m*, 1 H); 2.71 (br. *d*, J = 15, 1 H); 2.79–2.85 (*m*, 1 H); 3.46 (br. *d*, J = 11.5, 1 H); 3.55 (*m*, 1 H, overlapping with solvent peaks); 3.83 (*d*, J = 13.0, 1 H); 3.87 (*d*, J = 13.0, 1 H); 5.26 (br. *s*, 1 H); 6.93 (*t*, J = 7.5, 1 H); 6.99 (*t*, J = 7.5, 1 H); 7.20 (*d*, J = 7.5, 1 H); 7.34 (*d*, J = 7.5, 1 H). ^{13}C-NMR (CD_3OD/$CDCl_3$ 5:95): 21.40 (*t*); 25.59 (*t*); 25.90 (*t*); 28.87 (*t*); 30.69 (*t*); 38.62 (*d*); 45.08 (*t*); 60.62 (*d*); 64.99 (*d*); 65.57 (*t*); 106.91 (*s*); 110.73 (*d*); 117.72 (*d*); 118.76 (*d*); 120.92 (*d*); 125.25 (*d*); 126.68 (*s*); 134.78 (*s*); 136.14 (*s*); 136.48 (*s*). EI-MS: 309 (3), 308 (23, M^+), 307 (19), 170 (100), 169 (86), 144 (7). HR-MS: 308.1883 ($C_{20}H_{24}N_2O^+$; calc. 308.18902).

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