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# A Fast Assembly of Pentacyclic Benz[*f*]indolo[2,3-*a*]quinolizidine Core by Tandem Intermolecular Formal Aza-[3 + 3] Cycloaddition/Pictet−Spengler Cyclization: A Formal Synthesis of (±)-Tangutorine

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**Abstract:** We have described a concise construction of the pentacyclic benz[*f*]indolo[2,3-*a*]quinolizidine intermediate **3** (with an overall yield of 54% for three steps), featuring a tandem intermolecular formal aza-[3 + 3] cycloaddition/Pictet−Spengler cyclization. The present work can be considered as a formal synthesis of *β*-carboline alkaloid (±)-tangutorine. Our strategy disclosed herein constitutes a new effective general synthetic approach toward the indoloquinolizidine family of alkaloids.

*Nitraria tangutorum* L., available in the Northwest region of China, is among the approximately 15 species comprising the genus *Nitraria* (*Zygophyllaceae*). The leaves of this species have long been prescribed in traditional Chinese medicine (TCM) as antispasmodic, antineuropathic, and antiarrhythmic agents. Che and colleagues disclosed in 1999 the isolation from the leaves of *N. tangutorum* L. and structural determination of (±)-tangutorine (**1**, Chart 1), a novel benz[*f*]indolo[2,3-*a*]-quinolizidine alkaloid.[1] As the sole known *β*-carboline natural product of this type, tangutorine has emerged as an attractive target for synthetic organic chemists.[2] Jokela[2a,b] accomplished the first total synthesis of **1** starting from 7,8-dihydroquinoline-5(6*H*)-one, by taking advantage of the classic Pictet−Spengler cyclization strategy commonly employed in constructing monoterpenoid indole alkaloids. More recently, Hsung and coworkers[2c] published a novel and practical synthesis of **1**, featuring an intramolecular formal aza-[3 + 3] cycloaddition,[3] as well as a Heck coupling for establishing the C2−C3 bond. Because the indolo[2,3-*a*]quinolizidine-type natural products might be derived biosynthetically from tryptophan, the commercially available tryptamine was chosen as the starting point for the stereoselective route.[2c]

**CHART 1**

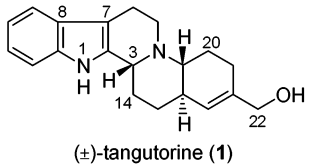
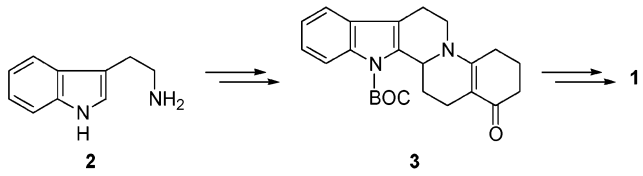
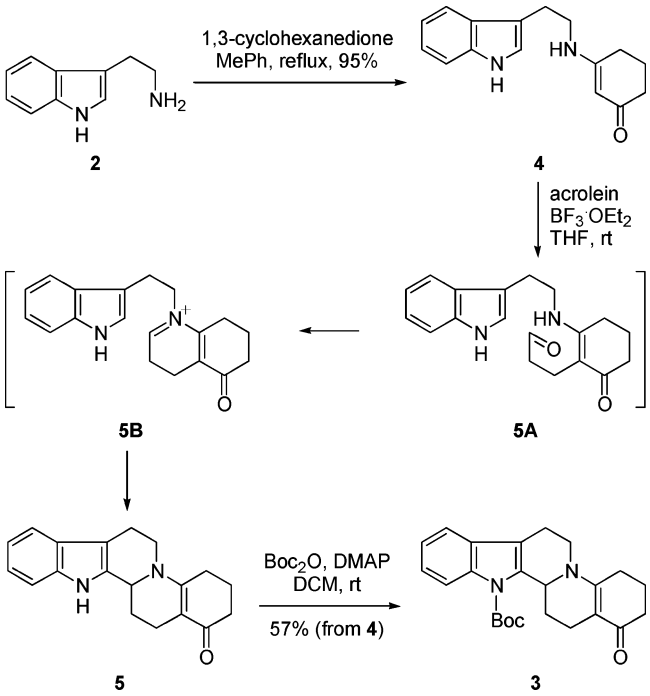



**CHART 2**




**SCHEME 1. Synthesis of Intermediate 3**




We noticed that in Hsung's synthesis[2c] considerable endeavor (11 steps) was devoted to constructing the key pentacyclic Boc-protected intermediate **3**, from which tangutorine (**1**) was obtained in another eight steps (Chart 2).

As a result of our interest in efficiently assembling structurally complex and biologically active natural products, we recently embarked on a novel expeditious three-step synthesis of the pentacycle **3**, the useful intermediate for constructing tangutorine (**1**). As outlined in Scheme 1, our synthetic strategy for constructing **3** relied

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(1) For the isolation of tangutorine, see: Duan, J.-A.; Williams, I. D.; Che, C.-T.; Zhou, R.-H.; Zhao, S.-X. *Tetrahedron Lett.* **1999**, *40*, 2593.

(2) For the previous syntheses of tangutorine, see: (a) Putkonen, T.; Tolvanen, A.; Jokela, R. *Tetrahedron Lett.* **2001**, *42*, 6593. (b) Putkonen, T.; Tolvanen, A.; Jokela, R.; Caccamese, S.; Parrinello, N. *Tetrahedron* **2003**, *59*, 8589. (c) Luo, S.; Zificsak, C. A.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709.

(3) For intramolecular formal aza-[3 + 3] cycloaddition, see: (a) Wei, L.-L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516; *Angew. Chem.* **2001**, *113*, 1564. For intermolecular formal aza-[3 + 3] cycloaddition, see: (b) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J. *Org. Lett.* **2000**, *2*, 1161. (c) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10435.

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upon combining the three basic components: tryptamine (**2**), 1,3-cyclohexanedione, and acrolein. Heating tryptamine with 1 equiv of 1,3-cyclohexanedione in refluxing toluene for 1 h brought on complete condensation to afford ketoenamine **4** as colorless crystals in 95% yield. Despite its high polarity, this compound was found to be slightly soluble in tetrahydrofuran (THF). Next, a solution of ketoenamine **4** and freshly distilled acrolein (2.5 equiv) in THF was subjected to a boron trifluoride diethyl etherate promoted tandem intermolecular formal aza-[3 + 3] cycloaddition/Pictet−Spengler cyclization. Indeed, the pentacycle **5** with the newly formed B and C rings was produced after the reaction proceeded at room temperature for 18 h. Note that sufficiently slow introduction of $BF_3{\cdot}OEt_2$ to the system was crucial to this transformation. The reaction sequence presumably consisted of (i) the initial intermolecular formal aza-[3 + 3] cycloaddition, via the enamine-to-acrolein Michael addition (generating **5A**) followed by dehydrative iminium formation (generating **5B**), and (ii) the subsequent Pictet−Spengler cyclization. For the aza-[3 + 3] cycloaddition, a head-to-tail orientation is assumed with regard to the carbonyl groups of vinylogous amides and acrolein. The regioselectivity that we adopted is coincident with those reported previously by Hickmott,[4] Greenhill,[5] and Stille[6] but is opposite of the head-to-head orientation proposed by Hsung.[3c] Either regiochemistry should be possible,[7] and appropriate mechanistic studies remain to be conducted to reveal the exact reaction pathway.

The intermediate **5** was not sufficiently soluble in most common organic solvents, which posed an obstacle in the substance purification while ensuring reasonably high yield. Therefore, the pentacycle **5**, as a crude product, was directly treated with excess di-*tert*-butyl dicarbonate ($Boc_2O$) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane at room temperature to realize the Boc protection at the indolyl nitrogen. The addition of $Boc_2O$ in batches was found to be vital in achieving better conversion (see Experimental Section). The key pentacyclic benz[*f*]indolo[2,3-*a*]quinolizidine intermediate **3** (shown in Hsung's synthesis of (±)-tangutorine[2c]) was obtained as a colorless oil in a combined yield of 57% for the last two steps (i.e., the tandem reaction and the Boc protection step). The physical properties and the spectroscopic data of **3** were in agreement with those reported in the literature.[2c]

In summary, we have described a concise construction of the pentacyclic benz[*f*]indolo[2,3-*a*]quinolizidine intermediate **3** (with an overall yield of 54% over three steps), featuring a tandem intermolecular formal aza-[3 + 3] cycloaddition/Pictet−Spengler cyclization. The present work can be considered as a formal synthesis of $\beta$-carboline alkaloid (±)-tangutorine, since **3** could be manipulated to give rise to **1** in eight more steps.[2c] Our strategy disclosed herein constitutes a new effective general synthetic approach toward the indoloquinolizidine family of alkaloids.

## Experimental Section

**General Methods.** Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ ($^1$H at 300 MHz and $^{13}$C at 75 MHz) using TMS as the internal standard. Column chromatography was performed on silica gel. Dichloromethane was distilled over calcium hydride under $N_2$. THF and toluene were distilled over sodium benzophenone ketyl under $N_2$.

**3-[2-(1*H*-3-Indolyl)ethylamino]-2-cyclohexen-1-one (4).** A mixture of tryptamine (5.00 g, 31.2 mmol) and 1,3-cyclohexanedione (3.50 g, 31.2 mmol) in toluene (170 mL) was refluxed under $N_2$, and the reaction reached completion within 1 h as judged by TLC analysis. After the reaction mixture was allowed to cool to room temperature, the solid mass was collected by filtration and the product in the mother liquor was subjected to recrystallization. The two crops of the solid were combined and washed with a small amount of petroleum ether to give **4** (7.54 g, 95%) as colorless crystals: mp 158−160 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.93−2.00 (m, 2H), 2.25 (t, $J$ = 6.0 Hz, 2H), 2.34 (t, $J$ = 6.5 Hz, 2H), 3.08 (t, $J$ = 6.6 Hz, 2H), 3.46 (dd, $J$ = 12.0, 6.6 Hz, 2H), 4.44 (br s, 1H), 5.25 (s, 1H), 7.07 (d, $J$ = 2.4 Hz, 1H), 7.16 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.25 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.42 (dt, $J$ = 7.8, 0.9 Hz, 1H), 7.60 (dt, $J$ = 7.8, 0.6 Hz, 1H), 8.19 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 22.3, 24.2, 29.2, 37.1, 43.5, 95.2, 112.0 (possibly corresponding to two carbons, C-3 and C-7 of indole moiety), 118.7, 118.9, 121.6, 123.5, 127.7, 136.8, 165.1, 195.1. MS (ESI): *m*/*z* (% relative intensity) 255 (M + H$^+$, 100). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.29; H, 7.20; N, 11.07.

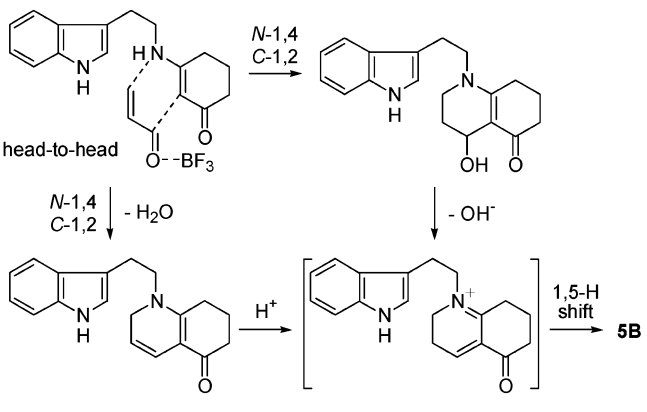
**11-(*tert*-Butoxycarbonyl)-2,3,4,5,6,11b,12,13-octahydro-1-oxo-11*H*-4b,11-diazaindeno[2,1-*a*]phenanthrene (3).** To a solution of **4** (762 mg, 3.00 mmol) in dry THF (65 mL) was added freshly distilled acrolein (0.50 mL, 7.5 mmol) under $N_2$. A solution of $BF_3{\cdot}OEt_2$ (0.46 mL, 3.6 mmol) in THF (5 mL) was added over 10 min, and the resulting mixture was stirred at room temperature for 18 h. The reaction was complete as judged by TLC analysis. Evaporation of the volatiles gave the crude cyclization product of **5** as a solid, which could be used directly for the next reaction. An analytical sample of **5** was obtained by recrystallization (MeOH/MeCOMe/petroleum ether, 3/20/3.5) as colorless crystals: mp 205−207 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.67 (tdd, $J$ = 11.9, 11.6, 2.7 Hz, 1H), 1.85−1.90 (m, 1H), 1.94−2.02 (m, 1H), 2.23 (t, $J$ = 11.9 Hz, 1H), 2.45−2.55 (m, 3H), 2.61−2.75 (m, 2H), 2.77−2.96 (m, 3H), 3.47 (td, $J$ = 12.8, 3.8 Hz, 1H), 4.48 (d, $J$ = 11.7 Hz, 1H), 4.98 (d, $J$ = 8.4 Hz, 1H), 7.02 (t, $J$ = 7.4 Hz, 1H), 7.11 (t, $J$ = 7.5 Hz, 1H), 7.37 (d, $J$ = 7.8 Hz, 1H), 7.45 (d, $J$ = 7.5 Hz, 1H), 11.08 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 18.1, 21.1, 21.7, 26.7, 27.3, 31.0, 47.9, 56.4, 106.4, 107.4, 111.8, 118.5, 119.4, 121.9, 126.5, 133.5, 136.8, 169.8, 184.7. MS (ESI): *m*/*z* (% relative intensity) 293 (M + H$^+$, 100).

(4) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 2112.

(5) (a) Greenhill, J. V.; Mohamed, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1411. (b) Chaaban, J.; Greenhill, J. V.; Ramli, M. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 3120. (c) Greenhill, J. V.; Moten, M. A. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 287. (d) Heber, D.; Berghaus, Th. *J. Heterocycl. Chem.* **1994**, *31*, 1353.

(6) (a) P. Benovsky, G. A. Stephenson, J. R. Stille, *J. Am. Chem. Soc.* **1998**, *120*, 2493. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (c) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673. (d) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319.

(7) Intermediate **5B** could be alternatively formed by adopting a head-to-head orientation with regard to the carbonyl groups of vinylogous amides and acrolein. See the following:



Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.13; H, 6.84; N, 9.70.

To a suspension of the above-mentioned crude **5** in dry dichloromethane (190 mL) were added $Boc_2O$ (1.96 g, 8.98 mmol) and DMAP (146 mg, 1.20 mmol). After the mixture was stirred at room temperature for 18 h, the second batch of $Boc_2O$ (1.31 g, 6.00 mmol) was added. The resulting mixture was stirred for another 20 min, and TLC analysis revealed the completion of the reaction. Evaporation of the solvent resulted in a residue, which was chromatographed (EtOAc/petroleum ether, gradient, 1/1 to 1/0) to give **3** (0.67 g, 57%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.30−1.52 (m, 1H), 1.60 (s, 9H), 1.43−1.65 (m, 1H), 1.89−2.02 (m, 2H), 2.22−2.34 (m, 3H), 2.40−2.59 (m, 2H), 2.64−2.70 (m, 3H), 3.11−3.20 (m, 1H), 4.12 (d, $J$ = 13.2 Hz, 1H), 4.76 (d, $J$ = 10.5 Hz, 1H), 7.19 (t, $J$ = 7.2 Hz, 1H), 7.26 (t, $J$ = 7.2 Hz, 1H), 7.37 (d, $J$ = 7.5 Hz, 1H), 8.11 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 20.3, 21.5, 22.3, 27.3, 27.9, 29.2, 35.1, 42.9, 55.7, 84.1, 107.2, 115.3, 116.6, 117.7, 122.7, 124.3, 128.0, 134.8, 136.7, 149.6, 158.7, 194.2. MS (ESI): $m/z$ (% relative intensity) 393 ($M + H^+$, 100), 337 (20), 293 (10). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.55; H, 7.01; N, 7.11.

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