JOC*Note*

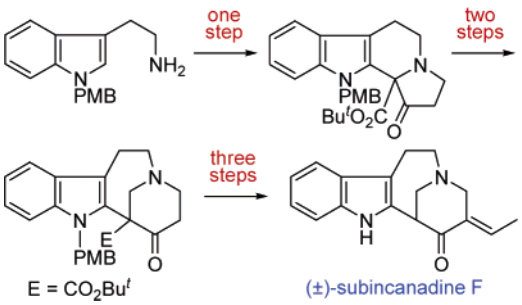
Total Synthesis of Indole Alkaloid (±)-Subincanadine F via SmI_2-Mediated Ring Opening and Bridge-Forming Mannich Reaction

Peng Gao,[†,‡] Yanqin Liu,[†] Lei Zhang,[†,§] Peng-Fei Xu,[‡] Shaowu Wang,[§] Yong Lu,[∥] Mingyuan He,[∥] and Hongbin Zhai*,[†,‡]

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China 200032, State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou, Gansu, China 730000, Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui, China 41000, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, Shanghai, China 200062

zhaih@mail.sioc.ac.cn

Received August 19, 2006



The first total synthesis of (±)-subincanadine F, a bioactive indole alkaloid structurally featuring a 1-azabicyclo[4.3.1]-decane unit, has been realized from 1-(*para*-methoxybenzyl)-tryptamine in six steps. The bridge-containing tetracyclic framework of subincanadine F was efficiently assembled by a SmI_2-mediated ring opening followed by an acid-mediated Mannich reaction. In addition, the tetracyclic ketoester **6**, a key intermediate potentially useful for synthesizing structurally related indole alkaloids as well, was obtained in one step from α,β-diketoester **5**.

Because of their remarkable pharmacological activities, indole alkaloids have been an attractive and rewarding source for developing new drug entities.[1] From 2002 to 2005, subincanadines A−G (**1a**−**c**, **2a**,**b**, **3**, and **1d**; Figure 1) were isolated by Kobayashi and co-workers from the barks of the Brazilian medicinal plant *Aspidosperma subincanum* Mart.[2] Among these intriguing polycyclic compounds was subincanadine F (**3**),

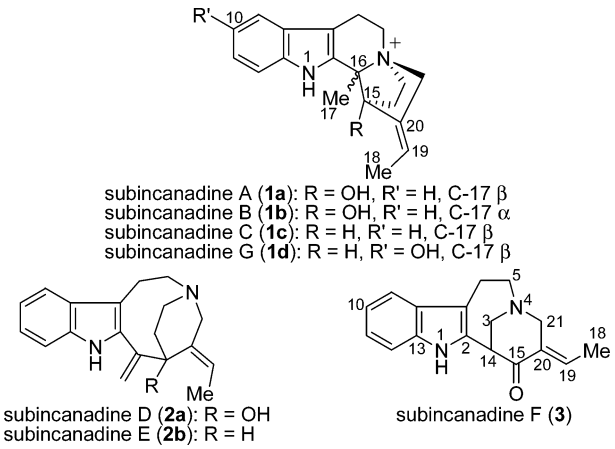


FIGURE 1. Subincanadines A−G.

featuring a 1-azabicyclo[4.3.1]decane framework, which displayed prominent in vitro cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 2.4 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 4.8 μg/mL) on the basis of the preliminary biological experiments.[2] There is rising interest in the assembly of the subincanadine family of alkaloids because of their unique structural characteristics and impressive pharmacological activity.[3]

In this paper, we wish to report a concise synthesis of (±)-subincanadine F (**3**), featuring the construction of the tetracyclic core by SmI_2-mediated ring opening and bridge-forming Mannich reactions as key steps. As shown in Scheme 1, the synthesis commenced from 1-(*para*-methoxybenzyl)tryptamine (**4**), a known intermediate[4] obtainable in one step from commercially available tryptamine. A reaction of **4** with α,β-diketoester **5**[5] (140 mol %) in acetonitrile at room temperature for 8 h afforded in a 75% yield the tetracyclic ketoester **6** as a yellow solid. The generation of **6** presumably results from the initial N-alkylation and iminium ion formation followed by Pictet−Spengler-type cyclization as depicted in Scheme 2.[6] The present one-pot procedure for the tetracycle assembly, involving the sequential D/C ring construction promoted by HCl generated in situ, is advantageous, concise, and practical.

† Shanghai Institute of Organic Chemistry.
‡ Lanzhou University.
§ Anhui Normal University.
∥ East China Normal University.

(1) (a) Atta-ur-Rahman; Basha, A. *Indole Alkaloids*; Harwood Academic: Amsterdam, The Netherlands, 1997. (b) Wright, C. W.; Phillipson, J. D. *Phytother. Res.* **1990**, *4*, 127.

(2) (a) Kobayashi, J.; Sekiguchi, M.; Shimamoto, S.; Shigemori, H.; Ishiyama, H.; Ohsaki, A. *J. Org. Chem.* **2002**, *67*, 6449. (b) Ishiyama, H.; Matsumoto, M.; Sekiguchi, M.; Shigemori, H.; Ohsaki, A.; Kobayashi, J. *Heterocycles* **2005**, *66*, 651.

(3) (a) Liu, Y.; Luo, S.; Fu, X.; Fang, F.; Zhuang, Z.; Xiong, W.; Jia, X.; Zhai, H. *Org. Lett.* **2006**, *8*, 115. (b) Suzuki, K.; Takayama, H. *Org. Lett.* **2006**, *8*, 4605.

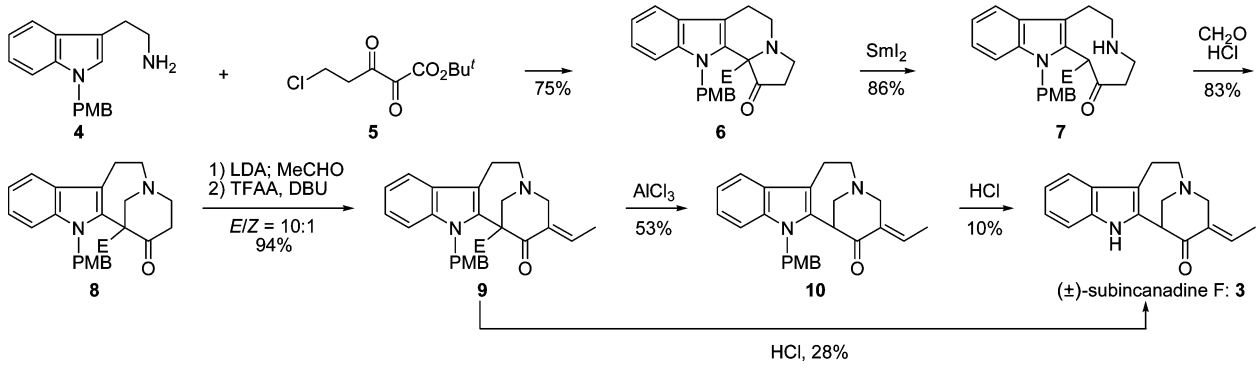
(4) Guengoer, T.; Malabre, P.; Teulon, J. M. *Synth. Commun.* **1994**, *24*, 2247.

(5) Wasserman, H. H.; Kuo, G.-H. *Tetrahedron* **1992**, *48*, 7071.

(6) Wasserman and co-workers once reported the efficient synthesis of an analogue of **6** (where the indolic nitrogen was unprotected), which consisted of the initial preparation of a crystalline vinyl tricarbonyl monohydrate from **5** via dehydrohalogenation with a saturated aqueous bicarbonate solution, followed by sequential Michael addition/intramolecular aminal formation/Pictet−Spengler cyclization in the presence of boron trifluoride etherate in dichloromethane at −78 °C. However, a less satisfactory yield (approximately 18%) for the tetracycle formation was observed when Wasserman's two-step protocol was applied to tryptamine. For Wasserman's two-step protocol, see: (a) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371. (b) Wasserman, H. H.; Parr, J. *Acc. Chem. Res.* **2004**, *37*, 687.

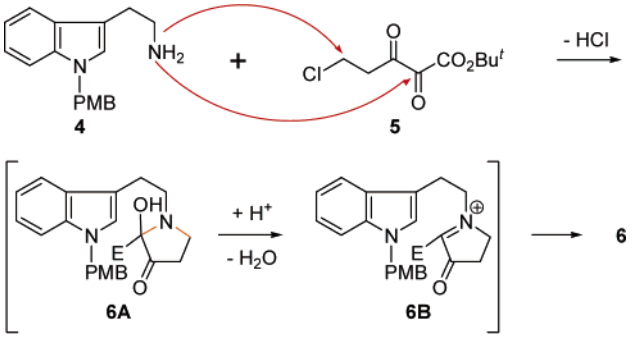
10.1021/jo061724h CCC: $33.50
Published on Web 11/14/2006

SCHEME 1. Synthesis of (±)-Subincanadine F (3)[a]



[a] E = $CO_2{}^t$Bu, TFAA = trifluoroacetic anhydride, PMB = *para*-methoxybenzyl.

SCHEME 2. Formation of 6[a]



[a] E = $CO_2{}^t$Bu.

We envisaged that the tetracyclic core of subincanadine F could be easily accessed from ketoester **6** by skeletal reorganization. The central theme of this strategy was based on the disconnection of the C/D ring conjunction of **6** followed by insertion of a one-carbon linker at the breakup points. To our delight, the samarium diiodide mediated ring-opening[7] of **6** furnished the 6/5/9 tricycle **7** in an 86% yield. Exposure of **7** to formalin (i.e., aqueous formaldehyde solution, 37%) in the presence of hydrochloric acid for 1 h led to the tetracycle **8** in an 83% yield. Thus, the tetracyclic 1-azabicyclo[4.3.1]decane framework of subincanadine F was constructed in three steps from **4**.

The (*E*)-ethenyl group adjacent to the ketone carbonyl in **3** would ideally be introduced at the stage of **8** since the presence of PMB and $CO_2{}^t$Bu could block the corresponding reactive sites that would otherwise interfere with the desired transformations.[8] Treatment of **8** with LDA followed by MeCHO[9] at −78 °C furnished the expected aldol condensation products (presumably containing four stereoisomers), and the dehydration of which with TFAA/DBU/DMAP[10] generated enone **9** (as a pair of geometric isomers of close R_f values, E/Z = 10:1) in an excellent combined yield (94%).

Considerable endeavors were then devoted to the remaining tasks for the synthesis of subincanadine F, that is, the removal of $CO_2{}^t$Bu and PMB. Reaction of **9** with $AlCl_3$ in benzene at room temperature for 4 h selectively furnished the decarboxylation product **10** in only a moderate yield (53%), which represented the optimum result obtained for this particular transformation under various experimental conditions. PMB deprotection could not be realized in reasonable yields by treating **10** with a Lewis acid ($AlCl_3$,[11] $TiCl_4$, or $F_3B{\cdot}OEt_2$), a protic acid (TFA[12] or $HClO_4$[13]), an oxidizing agent (DDQ[14] or CAN), a base (LDA[15]), or with the $Pd(OAc)_2/Et_3SiH/Et_3N$[16] reagent system. Finally, heating **9** in 0.5 M hydrochloric acid under reflux for 4 h resulted in full deprotection, and (±)-subincanadine F (**3**) was produced in a 28% yield.[17] For comparison, a lower yield (10%) for **3** was observed when the same conditions were applied to the decarboxylation product **10**. The TFA salt[18] of subincanadine F (**3**) displayed spectral data in full consistence with those reported in the literature.[2a]

In summary, the first total synthesis of (±)-subincanadine F (**3**), a bioactive indole alkaloid structurally featuring a 1-azabicyclo[4.3.1]decane unit, has been accomplished in six

(7) For a SmI_2-mediated reaction, see: Katritzky, A. R.; Wang, J.; Henderson, S. A. *Heterocycles* **1998**, *48*, 1567.

(8) Wiemer's protocol of ketone carbonyl O-phosphorylation/1,3-phosphorus shift rearrangement/Horner−Wadsworth−Emmons reaction was explored on the indolic *N*-benzyl analogue (rather than *N*-PMB) of **8**. While the enol phosphonate was easily accessible (LDA; $ClP(O)(OEt)_2$), the action of LDA (200 mol %) could not effect the 1,3-phosphorus shift rearrangement. Because of this unsuccessful attempt, a different α-ethenylation strategy was utilized for the PMB-protected ketone **8**. For Wiemer's protocol, see: (a) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185. (b) An, Y.-Z.; Wiemer, D. F. *J. Org. Chem.* **1992**, *57*, 317. (c) Baker, T. J.; Wiemer, D. F. *J. Org. Chem.* **1998**, *63*, 2613. For an application of Wiemer's protocol in total synthesis, see: (d) Sudau, A.; Munch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315.

(9) The anhydrous acetaldehyde (as a solution in ether) was prepared as follows: Acetaldehyde (40 wt. % solution in water) was extracted with ether. The combined ether layers were dried (Na_2SO_4) at low temperature and then distilled with a Vigreux column to afford an anhydrous acetaldehyde solution in ether in which the mole ratio of MeCHO to Et_2O was discovered to be 1:3 on the basis of the ^{1}H NMR spectrum.

(10) For dehydration of aldols with TFAA/DBU/DMAP, see: (a) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179. (b) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469. (c) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498.

(11) (a) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152. (b) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, *9*, 738.

(12) Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem. Soc.* **2000**, *122*, 6382.

(13) Miki, Y.; Hachiken, H.; Yanase, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2213.

(14) Miki, Y.; Hachiken, H.; Kashima, Y.; Sugimura, W.; Yanase, N. *Heterocycles* **1998**, *48*, 1.

(15) Suzuki, H.; Tsukuda, A.; Kondo, M.; Aizawa, M.; Senoo, Y.; Nakajima, M.; Watanabe, T.; Yokoyama, Y.; Murakami, Y. *Tetrahedron Lett.* **1995**, *36*, 1671.

(16) Wen, S.-J.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2721.

steps starting from 1-(*para*-methoxybenzyl)tryptamine (**4**). On the basis of the overall synthetic efficiency, the current route to (±)-subincanadine F constitutes a general method for rapid synthesis of a number of indole alkaloids with similar structures. The bridge-containing tetracyclic framework of subincanadine F was efficiently assembled by a SmI_2-mediated ring opening followed by an acid-mediated Mannich reaction. The tetracyclic ketoester **6**, a key intermediate, is a potential substrate for synthesizing structurally related indole alkaloids.

Experimental Section

Compound 6. To a solution of **4** (345 mg, 1.23 mmol) in acetonitrile (10 mL) was added dropwise a solution of **5** (380 mg, 1.72 mmol) in acetonitrile (10 mL) at rt. The mixture was stirred at rt for 8 h, neutralized with a saturated aqueous $NaHCO_3$ solution, concentrated, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (petroleum ether/EtOAc, 8:1) to afford **6** (412 mg, 75%) as a yellow solid: mp 52−53 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H), 2.38 (dd, J = 18.0, 6.3 Hz, 1H), 2.66−2.82 (m, 2H), 3.10−3.51 (m, 5H), 3.75 (s, 3H), 5.45 (d, J = 17.1 Hz, 1H), 5.60 (d, J = 17.1 Hz, 1H), 6.73−6.87 (m, 4H), 6.93−7.00 (m, 1H), 7.03−7.13 (m, 2H), 7.51−7.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.5, 27.7, 36.8, 43.6, 44.3, 49.1, 55.2, 72.3, 83.1, 110.7, 111.3, 113.7, 118.3, 119.2, 122.4, 126.8, 127.2, 127.3, 130.3, 137.6, 158.3, 168.2, 206.8; MS (ESI) 347 (57), 447 (M + H, 100), 469 (M + Na, 27). HRMS (ESI): (M + H) calcd for $C_{27}H_{31}N_2O_4$, 447.2284; found, 447.2278.

Compound 7. A suspension of samarium powder (1.47 g, 9.75 mmol) and I_2 (1.90 g, 7.50 mmol) in dry THF (75 mL) was stirred vigorously under N_2 at rt for 30 min. During that course of time, the color of the reaction mixture changed from purple to yellow-brown to green and finally to Prussian blue. The mixture was then refluxed for 1 h to give a solution of SmI_2 in THF (0.1 M). To a solution of **6** (200 mg, 0.448 mmol) in THF (20 mL) was added dropwise a solution of SmI_2 (0.10 M in THF, 16 mL, 1.6 mmol) at rt. The mixture was stirred at rt for 3 h, quenched with a saturated aqueous $NaHCO_3$ solution, filtered, concentrated, and extracted with $CHCl_3$/*i*-PrOH (4:1). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (CH_2Cl_2/EtOAc, 2.5:1) to afford **7** (173 mg, 86%) as a colorless viscous oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H), 1.79 (td, J = 12.9, 3.9 Hz, 1H), 1.91 (dt, J = 12.2, 4.6 Hz, 1H), 2.46−2.72 (m, 3H), 3.02−3.19 (m, 2H), 3.32−3.45 (m, 1H), 3.75 (s, 3H), 5.00 (d, J = 16.5 Hz, 1H), 5.23 (d, J = 16.5 Hz, 1H), 6.77 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.08−7.22 (m, 2H), 7.28 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 28.7, 35.9, 46.1, 46.8, 49.0, 55.2, 82.1, 96.4, 109.9, 113.8, 115.0, 118.4, 118.7, 121.5, 127.6, 128.1, 130.2, 132.0, 136.4, 158.7, 171.6, 180.4; MS (ESI) 449 (M + H, 100). HRMS (ESI): (M + H) calcd for $C_{27}H_{33}N_2O_4$, 449.2440; found, 449.2435.

Compound 8. A solution of **7** (173 mg, 0.386 mmol) in EtOH (12 mL) was acidified with 12 M hydrochloric acid to pH 3−7, and formalin (containing 37 wt % CH_2O, 75 μL, 1.0 mmol) was added. The mixture was stirred at rt for 1 h, neutralized with a saturated aqueous $NaHCO_3$ solution, concentrated, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (petroleum ether/EtOAc, 3:1) to afford **8** (147 mg, 83%) as a white solid: mp 152−154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 2.04 (d, J = 1.2 Hz, 1H), 2.47−2.62 (m, 1H), 2.92 (dt, J = 11.3, 4.0 Hz, 1H), 3.10−3.34 (m, 3H), 3.34−3.48 (m, 1H), 3.57 (d, J = 14.7 Hz, 1H), 3.67−3.80 (m, 1H), 3.74 (s, 3H), 4.42 (dd, J = 14.7, 3 Hz, 1H), 5.28 (s, 2H), 6.75 (s, 4H), 6.89−6.97 (m, 1H), 7.02−7.15 (m, 2H), 7.55−7.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 27.8, 35.1, 48.2, 52.9, 53.9, 55.0, 56.0, 65.9, 82.4, 111.0, 113.6, 115.7, 118.0, 119.1, 122.2, 127.1, 127.4, 129.5, 130.8, 136.9, 158.2, 168.4, 203.7; MS (ESI) 461 (M + H, 100), 483 (M + Na, 28). HRMS (ESI): (M + H) calcd for $C_{28}H_{33}N_2O_4$, 461.2440; found, 461.2435.

Compound 9. A solution of LDA in hexanes (1.9 M, 1.8 mL, 3.4 mmol) was diluted with THF (20 mL) and cooled to −78 °C. A solution of **8** (752 mg, 1.63 mmol) in THF (5 mL) was then added dropwise via a syringe. After the mixture was stirred at −78 °C for 1 h, a solution of anhydrous acetaldehyde in ether[9] {CH_3-CHO:Et_2O = 1:3 (mole ratio), 1.8 mL, 4.9 mmol} was added at −78 °C. The mixture was stirred at −78 °C for 1 h, quenched with a saturated aqueous $NaHCO_3$ solution, concentrated, and extracted with $CHCl_3$/*i*-PrOH (4:1). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford the crude aldol as a yellow oil, which was used without further purification for the next step.

To a solution of the above-mentioned crude aldol in CH_2Cl_2 (25 mL) was added DMAP (20 mg, 0.16 mmol). After the solution was cooled to −42 °C, DBU (1.8 mL, 12 mmol) and trifluoroacetic anhydride (1.0 mL, 7.1 mmol) were sequentially added. After the solution was stirred at this temperature for 1 h, additional DBU (0.8 mL, 5 mmol) was added. The reaction mixture was warmed to rt and stirred at rt for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (petroleum ether/EtOAc, 3:1) to afford **9** (747 mg, 94% for the two steps from **8**) as a yellow solid: mp 75−77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (s, 9H), 1.77 (d, J = 7.2 Hz, 3H), 2.63−2.78 (m, 1H), 3.02−3.24 (m, 2H), 3.44−3.63 (m, 2H), 3.76 (s, 3H), 3.83 (d, J = 16.8 Hz, 1H), 3.96 (d, J = 16.8 Hz, 1H), 4.33 (d, J = 15.0 Hz, 1H), 5.46 (d, J = 17.3 Hz, 1H), 5.56 (d, J = 17.3 Hz, 1H), 6.70−7.02 (m, 8H), 7.52 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.0, 27.6, 49.3, 53.2, 53.5, 55.1, 56.9, 58.5, 82.8, 111.5, 113.4, 116.7, 117.8, 119.0, 121.9, 127.3, 127.6, 129.8, 131.9, 133.4, 136.5, 139.7, 158.2, 169.3, 193.2; MS (ESI) 387 (3), 487 (M + H, 100), 509 (M + Na, 17). HRMS (ESI): (M + H) calcd for $C_{30}H_{35}N_2O_4$, 487.2597; found, 487.2591.

Compound 10. To a suspension of anhydrous $AlCl_3$ (77 mg, 0.58 mmol) in benzene (3 mL) was added a solution of **9** (31 mg, 0.064 mmol) in benzene (2 mL). The mixture was stirred at rt for 4 h, quenched with a saturated aqueous $NaHCO_3$ solution, filtered, concentrated, and extracted with $CHCl_3$/*i*-PrOH (4:1). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (CH_2Cl_2/MeOH,

(17) Despite our extensive investigations, the transformation of **9** to **3** was achieved in a 28% yield. Nevertheless, this figure could amount to an average yield of 53% for each of the two operations considering the fact that both PMB and $CO_2{}^t$Bu were removed in the same step. The indolic nitrogen might not require protection under certain circumstances. In our case, however, indolic nitrogen protection proved to be necessary. Without indolic N protection, the corresponding intermediates are unstable, and the yield for the first step and the combined yield for the second and the third steps dropped to 50% and 10%, respectively (see Scheme 1). Electron-withdrawing groups (such as Ts and Boc) on indolic nitrogen would retard the Pictet−Spengler cyclization. We also found that no cyclization product could be isolated for the reaction of **5** and tryptamine with the indolic nitrogen protected with a bulky TBDPS group. In addition, if the 1-benzyltryptamine was employed instead of the 1-(*para*-methoxybenzyl)-tryptamine at the very beginning then the first five steps (reaching the counterpart of **9**, see Scheme 1) would have behaved essentially in the same manner. However, the overall yield for decarboxylation ($AlCl_3$, PhH, rt, 96%)[11] and debenzylation (excess LDA, THF, −42 °C to rt, 4%)[15] decreased to 3.8%.

(18) The ^{1}H and ^{13}C NMR spectroscopic data of the TFA salt of subincanadine F [rather than subincanadine F (as a free base) itself] was essentially identical with those for the so-called subincanadine F reported in the literature.[2a] This is presumably because of the presence of TFA in the eluent used for HPLC purification of subincanadine F by Kobayashi and co-workers.

40:1) to afford **10** (13 mg, 53%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (d, J = 7.5 Hz, 3H), 2.83−2.97 (m, 1H), 3.00−3.17 (m, 1H), 3.30−3.44 (m, 2H), 3.44−3.63 (m, 2H), 3.68−3.76 (m, 1H), 3.76 (s, 3H), 3.86 (d, J = 16.5 Hz, 1H), 4.08 (d, J = 16.5 Hz, 1H), 5.39 (d, J = 17.3 Hz, 1H), 5.66 (d, J = 17.3 Hz, 1H), 6.66 (q, J = 7.5 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 7.03−7.20 (m, 2H), 7.17−7.30 (m, 1H), 7.46 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 23.5, 29.4, 46.1, 50.6, 52.3, 55.3, 55.6, 109.7, 114.2, 114.3, 118.0, 119.3, 122.0, 127.0, 127.5, 130.2, 134.9, 135.1, 135.8, 136.6, 158.8, 194.6; MS (ESI) 387 (M + H, 100), 409 (M + Na, 6). HRMS (ESI):(M + H) calcd for $C_{25}H_{27}N_2O_2$, 387.2073; found, 387.2067.

(±)-Subincanadine F (3). (a) From 9. A mixture of **9** (46 mg, 0.094 mmol) and hydrochloric acid (0.48 M, 10 mL, 4.8 mmol) was heated at reflux for 4 h, cooled to rt, neutralized with an aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$/*i*-PrOH (4:1). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (CH_2Cl_2/EtOAc, 2:1) to afford **3** (7.0 mg, 28%) as a yellow oil.

(b) From 10. A mixture of **10** (30 mg, 0.078 mmol) and hydrochloric acid (0.5 M, 4 mL, 2 mmol) was heated at reflux for 4 h, cooled to rt, neutralized with an aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$/*i*-PrOH (4:1). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a residue. The residue was chromatographed (CH_2Cl_2/EtOAc, 2:1) to afford **3** (2 mg, 10%) as a yellow oil: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.85 (d, J = 7.2 Hz, 3H), 2.83−2.96 (m, 1H), 2.98−3.11 (m, 1H), 3.35−3.48 (m, 2H), 3.62−3.77 (m, 3H), 3.92 (d, J = 16.5 Hz, 1H), 4.23 (d, J = 16.5 Hz, 1H), 6.69 (q, J = 7.2 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H); MS (ESI) 267 (M + H, 100), 299 (M + MeOH + H, 10). HRMS (ESI): (M + H) calcd for $C_{17}H_{19}N_2O$, 267.1497; found, 267.1492. An analytical sample of **3**·TFA salt was prepared by reacting **3** and TFA (200 mol %) in CH_2Cl_2 at rt for 5 min followed by evaporation of the volatiles. The salt of **3**·TFA was obtained as a yellow amorphous solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.87 (d, J = 7.2 Hz, 3H), 3.06−3.28 (m, 2H), 3.47−3.66 (m, 1H), 3.66−3.90 (m, 1H), 3.96−4.12 (m, 2H), 4.05−4.23 (m, 1H), 4.34 (d, J = 15.9 Hz, 1H), 4.55 (d, J = 15.9 Hz, 1H), 6.95−7.06 (m, 1H), 7.02 (t, J = 7.4 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 14.2, 20.7, 45.5, 51.6, 51.7, 57.2, 112.1, 112.6, 118.7, 120.4, 123.2, 128.5, 128.7, 132.4, 137.4, 144.0, 189.7; MS (ESI) 267 (M + H, 100), 299 (M + MeOH + H, 15). HRMS (ESI): (M + H) calcd for $C_{17}H_{19}N_2O$, 267.1497; found, 267.1492 (note that the MS and HRMS data obtained for the salt were actually found to be essentially the same as those for the free amine).

Acknowledgment. We thank NSFC, STCSM ("Post-Venus" Program, No. 05QMH1416), and GCCP of ECNU for financial support. We are indebted to Prof. Zhiyu Liu of SIOC for enlightening discussions and kind assistance.

Supporting Information Available: Analytical data for **6**−**10** and **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO061724H