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

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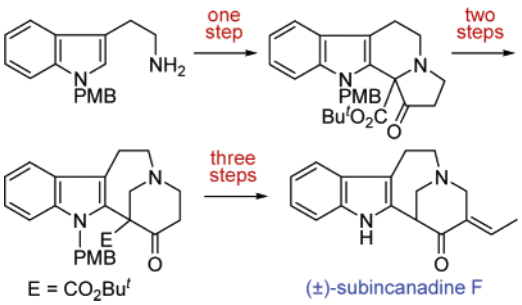


The first total synthesis of (±)-subincanadine F, a bioactive indole alkaloid structurally featuring a 1-azabicyclo[4.3.1]-decane unit, has been realized from 1-(*para*-methoxybenzyl)-tryptamine in six steps. The bridge-containing tetracyclic framework of subincanadine F was efficiently assembled by 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**),

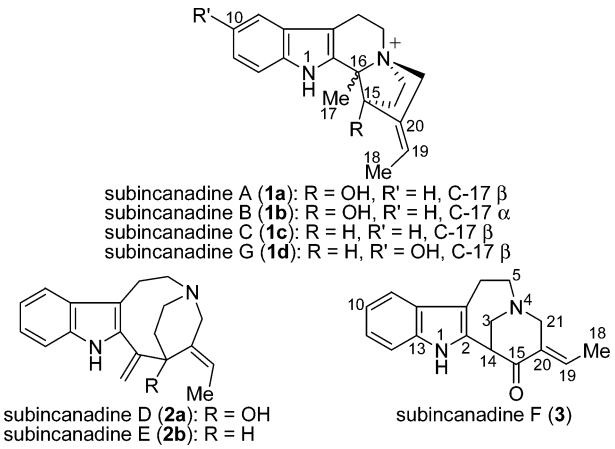


**FIGURE 1.** Subincanadines A−G.

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.

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(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.

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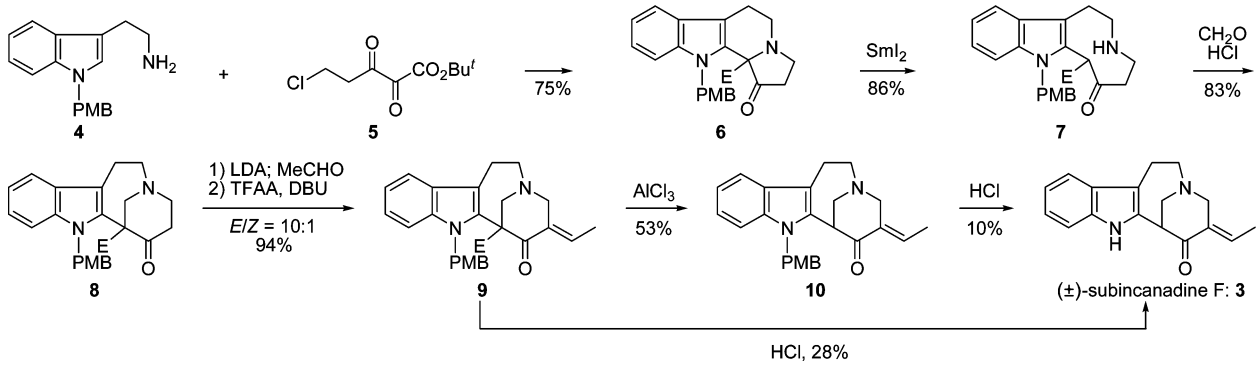
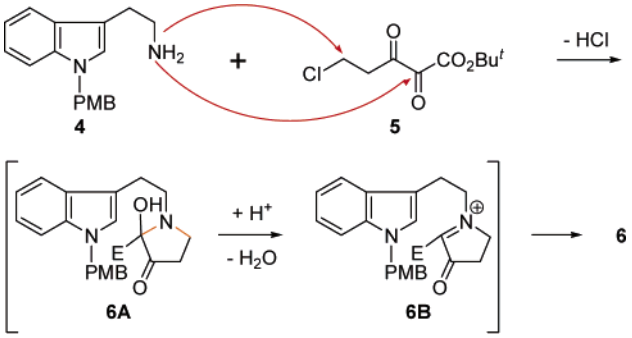
**SCHEME 1. Synthesis of (±)-Subincanadine F (3)[a]**




[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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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 $\mu$L, 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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).

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**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.

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