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Total Synthesis of the *Aspidosperma* Alkaloid (±)-Subincanadine F via a Titanium-Mediated Intramolecular Nucleophilic Acyl Substitution Strategy

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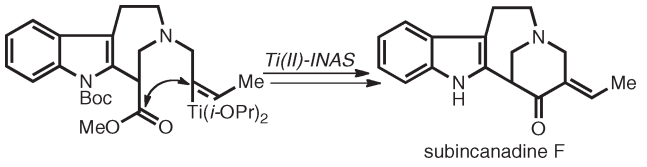
Received August 11, 2010



The total synthesis of the bridge-fused *Aspidosperma* indole alkaloid (±)-subincanadine F has been accomplished in seven steps. The synthetic utility of a titanium-mediated intramolecular nucleophilic acyl substitution (INAS) reaction for the construction of the bridge-fused ring system was demonstrated.

In 2002, Kobayashi and co-workers reported the isolation, structure determination, and preliminary biological properties of subincanadine F (**1**, Figure 1), one member of a family of monoterpenoid indole alkaloids obtained in minute quantities from the barks of the Brazilian medicinal plant *Aspidosperma subincanum* Mart.[1] In vitro pharmacological evaluations of subincanadine F (**1**) revealed cytotoxic activities against murine lymphocytic leukemia (L1210) and human epidermoid carcinoma (KB) cell lines with IC_{50} values of 2.4 and 4.8 μg/mL, respectively.

Among the rich and diverse families of monoterpenoid indole alkaloids,[2] subincanadine F stands out as being the only known member to feature a 1-azabicyclo[4.3.1]decane bridge-fused system. Though a biogenetic mechanism rationalizing the origins of this framework has yet to be fully elucidated, one postulate put forth by Kobayashi involves a three-carbon metabolic degradation of a stemmadenine-type precursor (cf. **4**, Figure 1), the proposed biosynthetic forerunner of the subincanadines.[1a] The structural considerations presented by subincanadine F (**1**), together with its biological properties, invited us to initiate efforts directed toward its total synthesis. We also viewed the ring system of **1** as grounds on which to advance further methods for the construction of bridge-fused azabicyclic scaffolds for projected extrapolation onto broader classes of alkaloid natural products. In this Note, we describe the outcome of these initiatives.

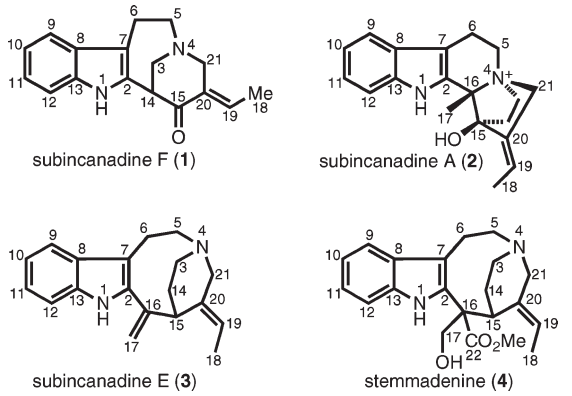
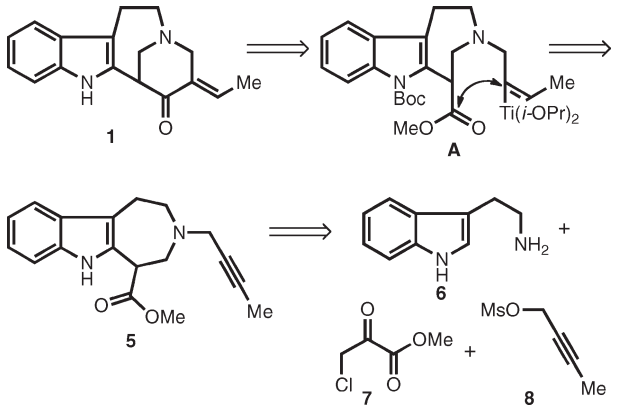


FIGURE 1. Representative members of the subincanadine class of indole alkaloids and stemmadenine.

Zhai and co-workers previously used a bridge-forming Mannich reaction to construct the C(3−14) bond of **1**,[3] while Li and co-workers employed a Dieckmann cyclization for C(15−20).[4] Each synthetic route, however, required a late-stage aldol condensation to install the (*E*)-*exo*-ethenyl appendage.[5] We envisioned that both the C(15−20) bond and the (*E*)-ethenyl moiety could be fashioned simultaneously through a titanium-mediated intramolecular nucleophilic acyl substitution (INAS) reaction. Specifically, 6-*exo*-*trig* ring-closure of an organotitanium species (cf. **A**, Scheme 1) onto the ester function at C(15) would afford the complete fused ring system of subincanadine F (**1**). Such an organotitanium intermediate[6,7] could be derived from the in situ complexation of alkyne **5** with a low-valent titanium reagent

SCHEME 1. Retrosynthetic Analysis of Subincanadine F

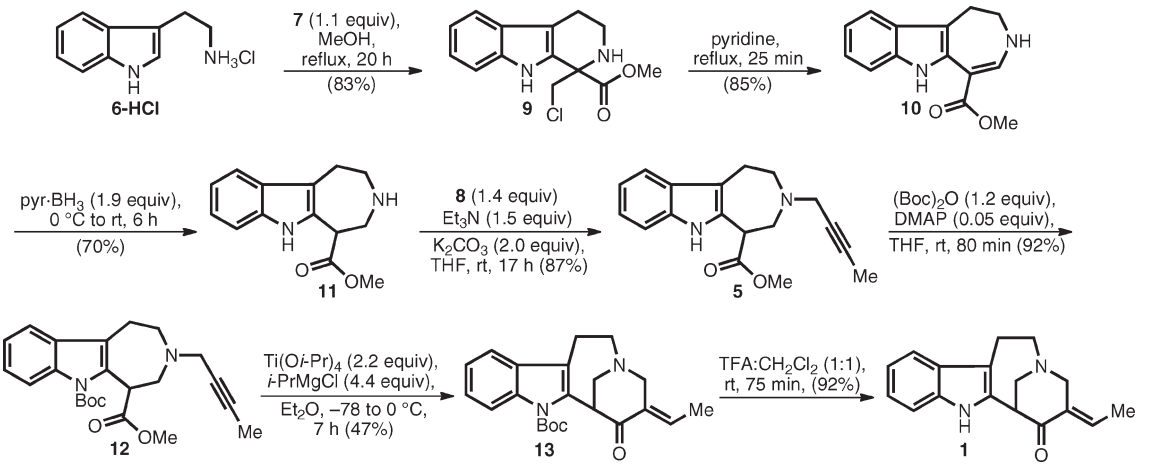


(1) (a) Kobayashi, J.; Sekiguchi, M.; Shimamoto, S.; Shigemori, H.; Ishiyama, H.; Ohsaki, A. *J. Org. Chem.* **2002**, *67*, 6449–6445. (b) Ishiyama, H.; Matsumoto, M.; Sekiguchi, M.; Shigemori, H.; Ohsaki, A.; Kobayashi, J. *Heterocycles* **2005**, *66*, 651–658.

(2) (a) Saxton, J. E. The Aspidospermine Group. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Supplement to Vol. 25, Part 4 of *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: New York, 1994; pp 357−436. (b) Sapi, J.; Massiot, G. The Strychnos Alkaloids. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Supplement to Vol. 25, Part 4 of *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: New York, 1994; pp 279−355.

Published on Web 09/16/2010 DOI: 10.1021/jo1015823

SCHEME 2. Total Synthesis of Subincanadine F



generated from Ti(O*i*-Pr)$_4$ and 2 equiv of *i*-PrMgCl. Importantly, such a strategy would directly furnish an *exo*-ethenyl group having the requisite (*E*) geometry about the trisubstituted C(19−20) bond, thereby obviating the need for its late-stage installation.

We constructed intermediate **5**, an N_b-butynyl derivative of Kuehne's indoloazepine **11** (Scheme 2),[8] from tryptamine (**6**), methyl chloropyruvate (**7**), and butynyl mesylate **8**, by using a modification of Kuehne's protocol.[8] Thus, Pictet−Spengler condensation of **6** and **7**[9] provided (chloromethyl)-tetrahydro-β-carboline adduct **9** (Scheme 2), which was briefly heated in refluxing pyridine to effect clean rearrangement with ring expansion to give indoloazepine ester **10**. Reduction of the olefin in **10** with pyridine−borane complex furnished its saturated congener **11**.

Alkylation of the azepine nitrogen in **11** (Scheme 2) was achieved by using butynyl mesylate **8**[10] and a Et_3N/K_2CO_3 base mixture to give butynyl amine **5**, which after protection of the indole nitrogen provided key intermediate **12** for subsequent use in the titanium-mediated INAS reaction. After a survey of reaction parameters, the intramolecular process was best conducted under the general conditions described by Sato and co-workers involving addition of 2.2 equiv of Ti(O*i*-Pr)$_4$ and 4.4 equiv of *i*-PrMgCl to a solution of alkyne **12** in Et_2O at −78 °C, followed by a period at −50 °C. Gradual warming to 0 °C over several hours resulted in cyclization to give the bridge-fused tetracyclic ketone **13** in 47% yield; the remaining material balance consisted of ∼20% unreacted alkyne **12** and an N_b-butenyl derivative from quenching of unreacted organotitanium species **A** (Scheme 1). Removal of the Boc group in **13** furnished (±)-subincanadine F (**1**) in 92% yield, with spectral characteristics in agreement with those reported.

In summary, the total synthesis of subincanadine F (**1**) was accomplished in seven steps from tryptamine. Access to the unusual 1-azabicyclo[4.3.1]decane ring system was gained through a titanium-mediated ring-closing strategy employing N_b-butynyl indoloazepine ester **12** as a key intermediate. These studies underscore the emerging utility of low-valent titanium methodologies in organic synthesis and further applications in the context of alkaloid natural products are anticipated. Efforts toward the total synthesis of additional members of this structurally interesting class of indole alkaloids are currently in progress.

Experimental Section

Methyl 1-(Chloromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylate (9). A solution of tryptamine hydrochloride (18.3 g, 93.0 mmol) and methyl chloropyruvate (14.6 g, 106.9 mmol) in MeOH (365 mL) was heated at reflux for 20 h. The cooled reaction mixture was concentrated and diluted with H_2O (270 mL). Slow addition of concentrated NH_4OH (pH >10) gave a crude solid that was filtered, rinsed with Et_2O, and recrystallized from acetone to afford **9** (24.7 g, 83% yield) as a yellow solid: mp 138−140 °C (lit.[8] mp 137−139 °C); IR (neat) 3369, 2958, 2869, 1708, 1460, 1447, 1431, 1270, 1215, 1151, 1088, 1026, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 4.20 (d, J = 10.8 Hz, 1H), 3.84 (s, 3H), 3.75 (d, J = 10.8 Hz, 1H), 3.23 (dd, J = 2.6, 5.6 Hz, 1H), 3.22 (dd, J = 1.4, 5.6 Hz, 1H), 2.77 (t, J = 5.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.2, 128.3, 126.6, 122.8, 119.7, 118.7, 112.4, 111.2, 63.2, 53.2, 50.4, 40.4, 21.9; HRMS *m*/*z* calcd for $[(C_{14}H_{15}N_2O_2Cl) + H]^+$ 279.0900, found 279.0894.

(*E*)-Methyl 1,2,3,6-Tetrahydroazepino[4,5-*b*]indole-5-carboxylate (10). A solution of tetrahydro-β-carboline **9** (4.18 g, 15.0 mmol) in pyridine (23 mL) was heated at reflux for 25 min. After removal of pyridine, the residue was taken up in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and concentrated to afford **10** (3.08 g, 85% yield) as a brown solid that was sufficiently pure for further use. An analytical sample obtained by flash chromatography (SiO_2, 50:50:1 EtOAc:hexanes:Et_3N) gave the title compound as a yellow crystalline solid: mp 152−153 °C (lit.[4]

(3) Gao, P.; Liu, Y.; Zhang, L.; Xu, P.; Wang, S.; Lu, Y.; He, M.; Zhai, H. *J. Org. Chem.* **2006**, *71*, 9495–9498.
(4) Chen, P.; Cao, L.; Li, C. *J. Org. Chem.* **2009**, *74*, 7533–7535.
(5) A model study toward subincanadine F was recently reported: Solé, D.; Bennasar, M.-L.; Jiménez *Synlett* **2010**, 944–946.
(6) For reviews, see: (a) Kulinkovich, O. G. *Pure Appl. Chem.* **2000**, *72*, 1715–1719. (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.
(7) (a) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984–6990. (b) Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208–2216. (c) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753–775.
(8) Kuehne, M. E.; Bohnert, J. C.; Bornmann, W. G.; Kirkemo, C. L.; Kuehne, S. E.; Seaton, P. J.; Zebovitz, T. C. *J. Org. Chem.* **1985**, *50*, 919–924. A larger excess of pyridine−borane complex, delivered in two stages at temperatures between 0 °C and rt over longer reaction times, best promoted complete reduction of **10** to **11**. Chromatographic purification of **11** was preferred over the reported trituration/recrystallization method.
(9) Speciale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 4361–4365.
(10) Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Aust. J. Chem.* **1988**, *41*, 1201–1208.

mp 148−149 °C); IR (neat) 3449, 3354, 1641, 1592, 1433, 1291, 1249, 1136, 1065, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.11 (td, J = 1.0, 7.1 Hz, 1H), 7.07 (td, J = 0.8, 7.2 Hz, 1H), 5.23 (br s, 1H), 3.80 (s, 3H), 3.49 (q, J = 4.4 Hz, 2H), 3.12 (t, J = 4.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 145.9, 134.2, 131.7, 127.8, 120.4, 118.7, 116.3, 110.5, 109.3, 92.7, 51.2, 45.6, 26.5; HRMS m/z calcd for $[(C_{14}H_{14}N_2O_2) + H]^+$ 243.1134, found 243.1129.

Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (11). To a solution of azepine **10** (3.08 g, 12.7 mmol) in formic acid (10 mL) at 0 °C was added pyridine−borane (1.48 mL 14.8 mmol). After being stirred at rt for 2.5 h, the reaction mixture was cooled to 0 °C and a second portion of pyridine−borane (0.90 mL, 9.00 mmol) was added. After an additional 3.5 h at rt, the reaction mixture was cooled to 0 °C, diluted with 10% HCl, and stirred for 30 min. The mixture was basified with concentrated NH_4OH, extracted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (SiO_2, 90:10:1 CH_2Cl_2:MeOH:NH_4OH) afforded **11** (2.18 g 70% yield) as a yellow solid: mp 135−137 °C (lit.[8] mp 138−139 °C); IR (neat) 1724, 1461, 1434, 1337, 1238, 1209, 1158, 1008, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 3.84 (dd, J = 2.8, 4.8 Hz, 1H), 3.71 (s, 3H), 3.59 (dd, J = 4.7, 13.8 Hz, 1H), 3.30 (ddd, J = 3.1, 5.5, 13.1 Hz, 1H), 3.23 (dd, J = 2.9, 13.7 Hz, 1H), 2.98−2.87 (m, 3H), 2.45 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 134.8, 131.7, 128.3, 121.3, 118.9, 117.9, 113.9, 110.5, 52.0, 50.2, 49.4, 47.5, 27.4; HRMS m/z calcd for $[(C_{14}H_{16}N_2O_2) + H)]^+$ 245.1290, found 245.1290.

Methyl 3-(But-2-ynyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (5). A mixture of azepine **11** (920 mg, 3.77 mmol), but-2-ynyl methanesulfonate (**8**, 782 mg, 5.27 mmol), K_2CO_3 (1.04 g, 7.53 mmol), and Et_3N (0.79 mL, 5.65 mmol) in THF (21 mL) was stirred at rt for 17 h. The reaction mixture was partitioned between Et_2O and H_2O and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated, and the residue was purified by flash chromatography (SiO_2, 65:35:1 hexanes:EtOAc:Et_3N) to afford **5** (971 mg, 87% yield) as a light yellow oil: IR (thin film) 3399, 2950, 2916, 2360, 2340, 1729, 1462, 1434, 1240, 1161, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1 H), 4.04 (dd, J = 2.3, 7.0 Hz, 1H), 3.76 (s, 3H), 3.49 (q, J = 2.2 Hz, 2H), 3.30 (dd, J = 7.1, 12.9 Hz, 1H), 3.14 (dd, J = 2.4, 12.9 Hz, 1H), 2.97−2.88 (m, 4H), 1.81 (t, J = 2.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 134.7, 132.0, 128.4, 121.5, 119.3, 118.0, 113.7, 110.7, 80.5, 74.4, 56.8, 55.3, 52.4, 49.2, 45.6, 24.4, 3.4; HRMS m/z calcd for $[(C_{18}H_{20}N_2O_2) + H]^+$ 297.1603, found 297.1607.

6-*tert*-Butyl 5-Methyl-3-(but-2-ynyl)-2,3,4,5-tetrahydroazepino-[4,5-*b*]indole-5,6(1*H*)-dicarboxylate (12). To a solution of the alkylated azepine **11** (328 mg, 1.11 mmol) in THF were added Boc_2O (290 mg, 1.33 mmol) and DMAP (6.8 mg, 0.055 mmol). The reaction mixture was stirred at rt for 80 min and concentrated. Purification of the residue by flash chromatography (SiO_2, 67:33:1 hexanes:EtOAc:Et_3N) gave **12** (402 mg, 92% yield) as a yellow solid: mp 35−37 °C; IR (thin film) 2976, 2904, 2826, 2362, 2341, 1721, 1455, 1358, 1324, 1141, 1030, 845, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.25 (td, J = 1.4, 7.2 Hz, 1H), 7.21 (td, J = 1.2, 7.2 Hz, 1H), 4.92 (dd, J = 2.4, 5.2 Hz, 1H), 3.70 (s, 3H), 3.60 (ddd, J = 1.0, 5.3, 13.2 Hz, 1H), 3.43 (q, J = 2.2 Hz, 2H), 3.08 (dt, J = 4.3, 12.1 Hz, 1H), 3.00 (ddd, J = 2.2, 5.1, 15.7 Hz, 1H), 2.91−2.82 (m, 2H), 2.65 (ddd, J = 2.2, 11.7, 11.7 Hz, 1H), 1.80 (t, J = 2.3 Hz, 3H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 150.6, 135.5, 134.4, 129.7, 123.9, 122.4, 121.1, 117.9, 115.6, 83.9, 80.3, 74.3, 56.5, 54.1, 52.0, 49.5, 46.0, 28.1 (3C), 23.8, 3.4; HRMS m/z calcd for $[(C_{23}H_{28}N_2O_4) + H]^+$ 397.2127, found 397.2130.

N_a-Boc-subincanadine F (13). To a stirred solution of alkyne **12** (205 mg, 0.52 mmol) in Et_2O (7.0 mL) at rt was added Ti(O*i*-Pr)$_4$ (0.35 mL, 1.16 mmol). After the mixture was cooled to −78 °C, *i*-PrMgCl (2.0 M in THF, 1.13 mL, 2.26 mmol) was added. The reaction mixture was gradually warmed to −50 °C over 2 h, held at −50 °C for 1 h, then warmed to 0 °C over 1 h. After being stirred at 0 °C for 3 h, the reaction mixture was quenched with saturated $NaHCO_3$, filtered through Celite, washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (SiO_2, 68:25:7:1 EtOAc:CH_2Cl_2:MeOH:NH_4OH) gave **13** (90 mg, 47% yield) as a yellow oil: IR (thin film) 2983, 2929, 2362, 2337, 2151, 2013, 1725, 1680, 1610, 1454, 1358, 1327, 1249, 1138, 1115, 835, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 6.75 (q, J = 7.3 Hz, 1H), 5.04 (d, J = 4.6 Hz, 1H), 3.97 (m, 2H), 3.71 (d, J = 14.5 Hz, 1H), 3.62 (dd, J = 5.1, 14.6 Hz, 1H), 3.34 (m, 1H), 3.23 (ddd, J = 3.0, 5.7, 13.6 Hz, 1H), 2.98 (ddd, J = 3.0, 10.8, 16.7 Hz, 1H), 2.77 (ddd, J = 2.5, 5.5, 16.7 Hz, 1H), 1.78 (d, J = 7.3 Hz, 3H), 1.69 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 150.6, 136.0, 135.9, 135.7, 135.0, 129.1, 124.0, 122.2, 120.8, 117.7, 115.3, 84.1, 54.6, 51.8, 51.3, 44.7, 28.2 (3C), 23.1, 13.5; HRMS m/z calcd for $[(C_{22}H_{26}N_2O_3) + H]^+$ 367.2022, found 367.2027.

Subincanadine F (1). To a solution of **13** (34 mg, 0.093 mmol) in CH_2Cl_2 (1.3 mL) at rt was added TFA (1.3 mL). After 75 min, the reaction mixture was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (SiO_2, 63:29:8:1 EtOAc:CH_2Cl_2:MeOH:NH_4OH) to afford subincanadine F (**1**, 23 mg, 92% yield) as a yellow solid: mp 180 °C dec; IR (thin film) 3397, 2916, 2366, 2237, 1682, 1622, 1455, 1342, 1246, 1180, 1146, 967, 904, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.68 (q, J = 7.3 Hz, 1H), 4.06 (d, J = 16.7 Hz, 1H), 3.87 (d, J = 16.6 Hz, 2H), 3.72 (d, J = 13.8 Hz, 1H), 3.65−3.57 (m, 2H), 3.42−3.28 (m, 2H), 3.01 (ddd, J = 3.4, 10.6, 16.3 Hz, 1H), 2.85 (ddd, J = 3.1, 4.8, 16.4 Hz, 1H), 1.79 (d, J = 7.2 Hz, 3H); ^1H NMR (500 MHz, CD_3OD) δ 7.30 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.58 (q, J = 7.3 Hz, 1H), 4.10 (d, J = 16.5 Hz, 1H), 3.79 (d, J = 16.7 Hz, 1H), 3.61−3.50 (m, 1H), 3.28−3.34 (m, 2H), 3.16−3.27 (m, 2H), 2.95 (ddd, J = 3.2, 11.5, 16.4 Hz, 1H), 2.77 (ddd, J = 2.9, 4.4, 16.2 Hz, 1H), 1.77 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 135.8, 135.4, 135.3, 132.9, 128.5, 121.9, 119.4, 117.9, 114.2, 110.8, 55.8, 52.1, 50.6, 49.7, 23.4, 13.7; HRMS m/z calcd for $[(C_{17}H_{18}N_2O) + H]^+$ 267.1497, found 267.1497.

Acknowledgment. We gratefully acknowledge the University of Vermont for financial support. This work was also generously supported by the Vermont Genetics Network through Grant no. P20 RR16462 from the INBRE Program of the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). We thank Dr. Rakesh K. Kohli, Director of the Mass Spectrometry Center at the University of Pennsylvania, for obtaining high-resolution mass spectra.

Supporting Information Available: Characterization data and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.