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Protecting-Group-Free Total Synthesis of (±)-Subincanadine F

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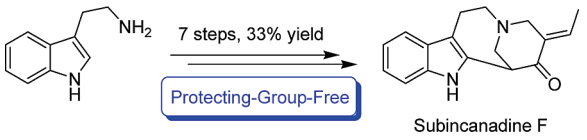


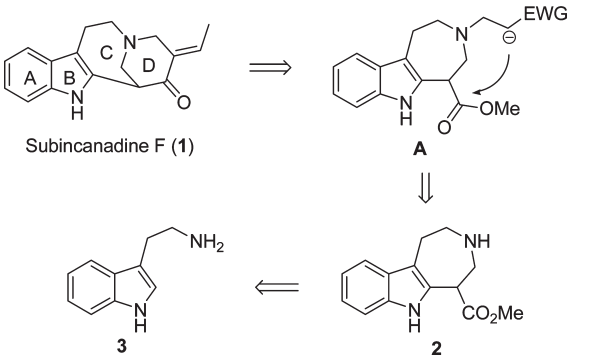
With chemoselective Dieckmann condensation as the key step, the protective-group-free total synthesis of (±)-subincanadine F was accomplished in 7 steps from the commercially available tryptamine in 33% overall yield.

While protective groups have found wide application in organic chemistry, protective-group-free synthesis is advantageous in shortening the reaction sequence and reducing the loss of material. The protective-group-free synthesis of complex natural products[1,2] has thus received increasing attention in the past few years and, in the meantime, imposes a significant challenge to synthetic organic chemists. Herein we report the protective-group-free synthesis of the indole alkaloid subincanadine F (**1**).

Subincanadine F was isolated (in 0.002% yield) from a Brazilian medicinal plant, *aspidosperma subincanum*, by Kobayashi and co-workers in 2002.[3] It possesses a unique 1-azabicyclo[4.3.1]decane skeleton. The preliminary biological evaluation revealed that subincanadine F exhibited potent cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 2.4 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 4.8 μg/mL) in vitro.[3] The synthesis of (±)-subincanadine F was recently reported by Zhai and coworkers starting from the 1-*p*-methoxybenzyl-protected tryptamine.[4] While their method was concise, it suffered from the low efficiency (28% yield) of the deprotection in the last step.[4] This aroused our interest in developing a protective-group-free strategy for the efficient synthesis of **1**.

Our approach to the target molecule was based on the retrosynthetic analysis shown in Scheme 1. We envisioned that the D ring of subincanadine F might be constructed via the Dieckmann condensation of intermediate **A**, which in turn could be generated from the tricyclic compound **2**.

SCHEME 1. Retrosynthetic Analysis



Kuehne et al. reported the three-step synthesis of compound **2** starting from tryptamine (**3**) and methyl chloropyruvate.[5] However, the second step, namely the skeletal rearrangement of chloromethyl tetrahydro-β-carboline (analogous to **4**) to the corresponding olefinic indoloazepine **5**, was operated in only moderate (67%) yield. We envisioned that switching the chloride to the corresponding bromide might enhance the efficiency of the rearrangement. Thus, the Pictet−Spengler condensation of tryptamine with bromopyruvate afforded the bromomethylated compound **4** in 78% yield, which was then subjected to treatment with pyridine at refluxing temperature. Indeed, the expected product **5** was achieved in a higher yield (87%). The subsequent reduction of **5** with $NaBH_3CN$ furnished **2** quantitatively (Scheme 2).

We then set out to construct the D ring of subincanadine F (Scheme 3). The reaction of **2** with methyl acrylate in methanol at room temperature (rt) gave the Michael addition product **6**. The Dieckmann condensation[6] of diester **6** was then explored. The prolonged treatment of **6** with an excess of *t*-BuOK in toluene[7] at rt failed to give the desired product **7** while most of the starting material remained unchanged. Switching the base to NaH did not help.[8] With lithium bis(trimethylsilyl)amide as the base and THF as the solvent,[9] the starting material underwent decomposition at rt. Finally, when **6** was treated with

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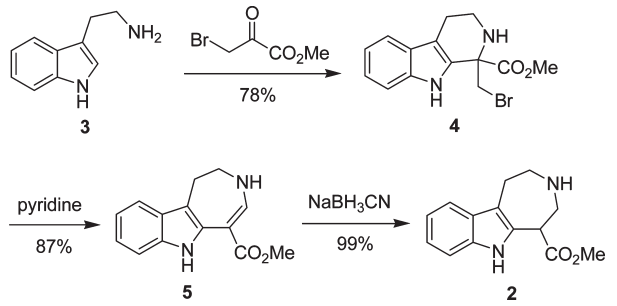
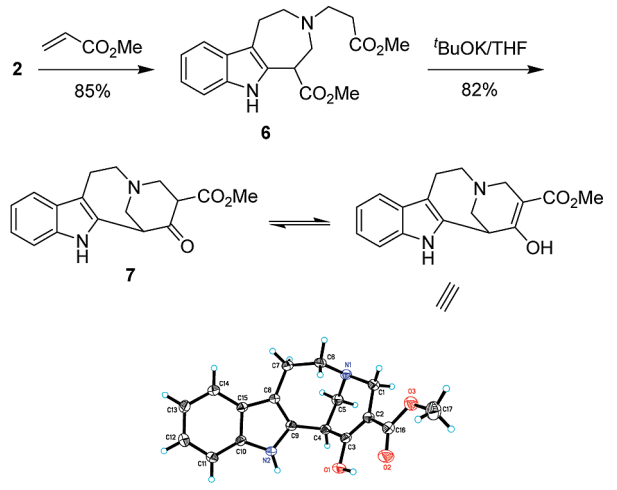
SCHEME 2. Improved Synthesis of 2



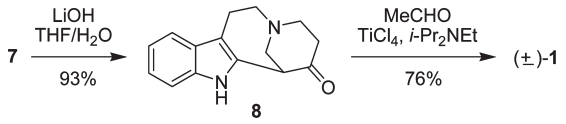
SCHEME 3. Construction of the D Ring of 1



2 equiv of *t*-BuOK in THF at rt, we were pleased to find that the reaction proceeded smoothly and cleanly, and the expected condensation product **7** was isolated in 82% yield, whose structure was unambiguously established by its X-ray diffraction experiments. The excellent chemoselectivity in the above Dieckmann condensation should be attributed to the steric control because the alternative condensation via the attack of the tertiary C-5 carbanion would require the generation of a sterically congested quaternary carbon center. Compound **7** existed in the enol form in the solid state. In a solution, the equilibrium between the enol form and the ketone form was observed as indicated by ^{13}C NMR.

With the key intermediate **7** in hand, we set out to complete the synthesis of subincanadine F (Scheme 4). Thus, the treatment of **7** with lithium hydroxide in aqueous THF solution at reflux afforded the deesterification product **8** in high yield.[10] The last step was the aldol reaction with acetaldehyde followed by dehydration. Several experimental conditions were screened. With lithium diisopropylamide or bis(trimethylsilyl)-amide as the base,[11] the reaction of **8** with acetaldehyde provided the aldol addition product in a low yield. Switching the base to *t*-BuOK increased the efficiency of the aldol reaction and, after the subsequent dehydration with methanesulfonyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene, the product **1** was obtained in 45% yield via two steps. Finally, with the

SCHEME 4. Completion of the Total Synthesis of 1



choice of $TiCl_4$ as the Lewis acid and ethyldiisopropylamine as the base,[12,13] the condensation of **8** with acetaldehyde proceeded smoothly at low temperature (−78 °C). By warming the reaction mixture to rt, the final product **1** was directly achieved in 76% yield in a one-step procedure (Scheme 4). An excellent (*E*)-selectivity was observed in the above process while the corresponding (*Z*)-isomer could not be detected. The spectra of **1** thus obtained were identical with those reported in the literature.[3,4,14]

In summary, the indole alkaloid (±)-subincanadine F was synthesized in 7 steps starting from the commercially available tryptamine with an overall yield of 33%. The exquisite design and careful implementation made this method straightforward, highly efficient, and protective-group-free. Moreover, the chemoselective Dieckmann condensation to construct the bicyclic [4.3.1]-skeleton should find more application in the synthesis of related natural products.

Experimental Section

Methyl 1-(Bromomethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylate (4). A mixture of tryptamine hydrochloride (9.80 g, 50 mmol), methyl bromopyruvate (7.2 mL, 60 mmol), and decolorizing charcoal (0.5 g) in anhydrous MeOH (120 mL) was heated at reflux for 18 h under argon atmosphere. The resulting mixture was cooled to rt, filtered, and concentrated under reduced pressure to about 20 mL, and then diluted with water (150 mL). Concentrated ammonium hydroxide was added slowly until the aqueous phase became strongly basic. The resulting mixture was filtered and the filtrate was rinsed with 5 mL of ether. Recrystallization from acetone/water afforded 7.27 g of yellow crystalline product **4**. On concentration under reduced pressure, a further 5.30 g of product **4** was obtained. Yield 78%; mp 138−140 °C; IR (KBr) ν (cm^{-1}) 3387, 3285, 3054, 2951, 1729, 1604, 1457, 1434, 1295, 1254, 1137, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 2.76 (2H, t, J = 5.4 Hz), 3.22 (2H, t, J = 5.4 Hz), 3.63 (1H, d, J = 9.9 Hz), 3.85 (3H, s), 4.10 (1H, d, J = 9.9 Hz), 7.10 (1H, t, J = 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz), 7.36 (1H, d, J = 8.1 Hz), 7.51 (1H, d, J = 7.8 Hz), 8.31 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 39.1, 40.5, 53.3, 62.6, 111.2, 112.3, 118.8, 119.8, 122.9, 126.5, 128.3, 136.1, 171.7; ESI-MS m/z 323 (M^+ + H); HRMS calcd for $C_{14}H_{16}BrN_2O_2$ (M + H) 323.0395, found 323.0389.

(*E*)-Methyl 1,2,3,6-Tetrahydroazepino[4,5-*b*]indole-5-carboxylate (5). The solution of **4** (7.27 g, 22.6 mmol) in pyridine (25 mL) was refluxed under argon atmosphere for 15 min. After cooling to rt, the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water (3 × 30 mL), and then dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with petroleum−ethyl acetate (1:1, v:v) as the eluent to give the

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(14) Kobayashi et al. characterized subincanadine F in the salt form with trifluoroacetic acid (TFA). See the Supporting Information for the ^1H and ^{13}C NMR spectra of free subincanadine F and its TFA salt.

pure **5** as a yellow solid. Yield 4.74 g (87%); mp 148−149 °C (lit.[5] mp 138−139 °C).

Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (2). To a stirred slurry of compound **5** (4.34 g, 18 mmol) in glacial acetic acid (40 mL) was added sodium cyanoborohydride (3.17 g, 50 mmol) in small portions over the period of 2 h. Concentrated hydrochloric acid was added slowly into the reaction mixture, with cooling, until the gas evolution ceased. The reaction mixture was then concentrated under reduced pressure. The residue was poured onto ice and basified with ammonium hydroxide. The aqueous solution was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After the removal of the solvent, the expected product **2** was obtained as a yellow solid. Yield 4.30 g (99%); mp 153−154 °C (lit.[5] mp 138−139 °C).

Methyl 3-(3-Methoxy-3-oxopropyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (6). Methyl acrylate (2.70 mL, 29.0 mmol) was added into the solution of **2** (6.00 g, 24.6 mmol) in MeOH (80 mL) at rt. The mixture was stirred at rt for 12 h and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with petroleum−ethyl acetate (1:1, v:v) as the eluent to give pure **6** as a yellow oil. Yield 6.90 g (85%); IR (KBr) ν (cm^{-1}) 3389, 3054, 2951, 2833, 1731, 1608, 1464, 1338, 1210, 1162, 1022, 745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (2H, t, J = 7.2 Hz), 2.85−3.17 (7H, m), 3.36 (1H, dd, J = 7.2, 13.2 Hz), 3.69 (3H, s), 3.77 (3H, s), 4.04 (1H, d, J = 6.3 Hz), 7.07−7.17 (2H, m), 7.28 (1H, d, J = 7.5 Hz), 7.47 (1H, d, J = 7.5 Hz), 8.36 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 32.7, 45.5, 51.6, 52.3, 53.3, 55.6, 57.3, 110.7, 113.9, 118.0, 119.3, 121.6, 128.5, 131.9, 134.8, 172.4, 173.0; EIMS m/z (rel intensity) 330 (M^+, 56), 271 (5), 257 (55), 215 (67), 202 (65), 183 (31), 156 (100), 116 (91); HRMS calcd for $C_{18}H_{22}N_2O_4$ (M) 330.1580, found 330.1580.

Methyl 6-Oxo-1,2,4,5,6,7-hexahydro-3,7-methano-8*H*-azonino-[5,4-*b*]indole-5-carboxylate (7). Potassium *tert*-butoxide (896 mg, 8.0 mmol) was added into the solution of **6** (1.31 g, 3.9 mmol) in THF (40 mL) at 0 °C under argon atmosphere. The mixture was allowed to warm to rt and then stirred for 12 h. The resulting solution was then concentrated under reduced pressure and the residue was dissolved in water (20 mL). CH_2Cl_2 (20 mL) was added and the aqueous layer was then acidified with HCl (1 M) until the pH was close to 2. Saturated aqueous $NaHCO_3$ solution was introduced until the pH of the aqueous phase reached about 7. The resulting mixture was extracted with CH_2Cl_2/MeOH (5:1, v:v). The combined organic extracts were dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with CH_2Cl_2−MeOH (10:1, v:v) as the eluent to give **7** as a yellow solid. Yield 955 mg (82%); mp 176−177 °C; IR (KBr) ν (cm^{-1}) 3292, 2914, 2846, 1708, 1655, 1604, 1455, 1435, 1314, 1263, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75−2.89 (13H, m), 7.06−7.20 (2H, m), 7.28 (1H, d, J = 7.5 Hz), 7.44 (1H, d, J = 7.5 Hz), 8.19 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) (enol form) δ 22.7, 37.9, 47.7, 50.9, 51.7, 55.8, 95.9, 110.8, 113.8, 117.9, 119.6, 121.7, 128.5, 134.5, 134.9, 168.0, 171.6; ESI-MS 299 ($M^+ + H$); HRMS calcd for $C_{17}H_{19}N_2O_3$ ($M + H$) 299.1396, found 299.1390. The structure was further confirmed by its X-ray diffractional analysis.

6-Oxo-1,2,4,5,6,7-hexahydro-3,7-methano-8*H*-azonino[5,4-*b*]-indole (8). Lithium hydroxide monohydrate (305 mg, 7.2 mmol) was added into the solution of **7** (721 mg, 2.4 mmol) in THF (48 mL) and H_2O (24 mL). The mixture was refluxed for 24 h. After cooling to rt, the resulting solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with CH_2Cl_2−MeOH (10:1, v:v) as the eluent to give the pure product **8** as a yellow solid. Yield 540 mg (93%); mp 122−123 °C; IR (KBr) ν (cm^{-1}) 3294, 2918, 2852, 1702, 1460, 1339, 1172, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (1H, dd, J = 3.6, 14.4 Hz), 2.72−2.77 (1H, m), 3.06−3.12 (2H, m), 3.39−3.52 (5H, m), 3.61 (1H, s), 3,71 (1H, d, J = 13.8 Hz), 7.09−7.19 (2H, m), 7.25 (1H, d, J = 7.8 Hz), 7.49 (1H, d, J = 7.8 Hz), 8.18 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 39.5, 51.1, 55.1, 55.5, 55.9, 110.9, 113.3, 118.3, 119.8, 122.5, 129.2, 132.4, 135.5, 208.0; ESI-MS m/z 241 ($M^+ + H$); HRMS calcd for $C_{15}H_{17}N_2O$ ($M + H$) 241.1341, found 241.1335.

(±)-Subincanadine F (1). A solution of **8** (120 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to −78 °C and $TiCl_4$ (0.60 mL, 0.60 mmol, 1.0 M solution in CH_2Cl_2) was added. The mixture was stirred at −78 °C for 5 min and diisopropylethylamine (115 μL, 0.70 mmol) was added slowly. The mixture was stirred at −78 °C for an additional 30 min and anhydrous acetaldehyde (0.36 mL, 0.97 mmol, 2.7 M solution in CH_2Cl_2) was added dropwise. The resulting mixture was stirred at −78 °C for 2 h and then at rt for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with CH_2Cl_2−MeOH (10:1, v:v) as the eluent to give the pure product **1** as a yellow oil. Yield 101 mg (76%).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**−**8** and X-ray crystal data of **7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.